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(54) **COMBINATIONS FOR CARDIOVASCULAR INDICATIONS**

(75) Inventors: **Bradley T. Keller**, Chesterfield, MO (US); **David B. Reitz**, Chesterfield, MO (US); **Joseph R. Schuh**, St. Louis, MO (US); **James A. Sikorski**, Des Peres, MO (US); **Samuel J. Tremont**, St. Louis, MO (US); **Rodney W. Lappe**, Chesterfield, MO (US)

Correspondence Address:
BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001 (US)

(73) Assignee: **G.D. SEARLE, LLC**, Chicago, IL

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(57) **ABSTRACT**

The present invention provides combinations of cardiovascular therapeutic compounds for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia and atherosclerosis. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesteryl ester transport protein (CETP) inhibitor, a fibric acid derivative, a nicotinic acid derivative, a microsomal triglyceride transfer protein inhibitor, a cholesterol abosrption antagonist, a phytosterol, a stanol, an antihypertensive agent, or others. Further combinations include a CETP inhibitor with a fibric acid derivative, a nicotinic acid derivative, a bile acid sequestrant, a microsomal triglyceride transfer protein inhibitor, a cholesterol abosrption antagonist, or others.

COMBINATIONS FOR CARDIOVASCULAR INDICATIONS

[0001] This application claims priority of U.S. provisional application Ser. No. 60/113,955 filed Dec. 23, 1998.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to methods of treating cardiovascular diseases, and specifically relates to combinations of compounds, compositions, and methods for their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as are associated with atherosclerosis, hypercholesterolemia, and other factors in coronary artery disease in mammals including hypertension. More particularly, the invention relates to ileal bile acid transporter (IBAT) inhibitors, cholesteryl ester transfer protein (CETP) activity inhibitors, fibric acid derivatives (fibrates), nicotinic acid derivatives, microsomal triglyceride transfer protein (MTP) inhibitors, cholesterol absorption antagonists, stanols, phytosterols, or antihypertensive agents.

[0004] 2. Description of Related Art

[0005] It is well-settled that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis. Numerous studies have demonstrated that a low plasma concentration of high density lipoprotein (HDL) cholesterol is a powerful risk factor for the development of atherosclerosis (Barter and Rye, *Atherosclerosis,* 121, 1-12 (1996)). HDL is one of the major classes of lipoproteins that function in the transport of lipids through the blood. The major lipids found associated with HDL include cholesterol, cholesteryl ester, triglycerides, phospholipids and fatty acids. The other classes of lipoproteins found in the blood are low density lipoprotein (LDL), intermediate density lipoprotein (IDL), and very low density lipoprotein (VLDL). Since low levels of HDL cholesterol increase the risk of atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of atherosclerosis and other diseases associated with accumulation of lipid in the blood vessels. These diseases include, but are not limited to, coronary heart disease, peripheral vascular disease, and stroke.

[0006] Atherosclerosis underlies most coronary artery disease (CAD), a major cause of morbidity and mortality in modern society. High LDL cholesterol (above about 180 mg/dl) and low HDL cholesterol (below 35 mg/dl) have been shown to be important contributors to the development of atherosclerosis. Other diseases or risk factors, such as peripheral vascular disease, stroke, and hypercholesterolaemia are negatively affected by adverse HDL/LDL ratios.

[0007] Interfering with the recirculation of bile acids from the lumen of the intestinal tract is found to reduce the levels of serum cholesterol in a causal relationship. Epidemiological data has accumulated which indicates such reduction leads to an improvement in the disease state of atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties,"*Biochimica et Biophysica Acta,* 1210, 255-287 (1994) discusses the biochemistry, physiology and known active agents surrounding bile acids and cholesterol.

[0008] Transient pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic circulation of bile acids in humans with an inherited lack of IBAT activity, as reported by Heubi, J. E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport", *Gastroenterology,* 83, 804-11 (1982).

[0009] In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al., "Intestinal Bile Acid Absorption"*The Journal of Biological Chemistry,* 268 (24), 18035-46 (1993).

[0010] In several individual patent applications, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents. The individual Hoechst patent applications which disclose such bile acid transport inhibiting compounds are each separately listed below.

[0011] R1. Canadian Patent Application No. 2,025,294.

[0012] R2. Canadian Patent Application No. 2,078,588.

[0013] R3. Canadian Patent Application No. 2,085,782.

[0014] R4. Canadian Patent Application No. 2,085,830.

[0015] R5. EP Application No. 0 379 161.

[0016] R6. EP Application No. 0 549 967.

[0017] R7. EP Application No. 0 559 064.

[0018] R8. EP Application No. 0 563 731.

[0019] Selected benzothiepines are disclosed in world patent application number WO 93/321146 for numerous uses including fatty acid metabolism and ccronary vascular diseases.

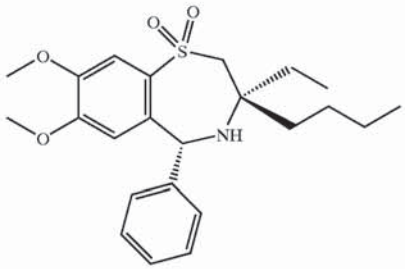
[0020] Other selected benzothiepines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed in application No. EP 508425. A French patent application, FR 2661676 discloses additional benzothiepines for use as hypolipaemic and hypocholesterolaemic agents. Furthermore, patent application no. WO 92/18462 lists other benzothiepines for use as hypolipaemic and hypocholesterolaemic agents. U.S. Pat. No. 5,994,391 (Lee et al.) Each of the benzothiepine hypolipaemic and hypocholesterolaemic agents described in these individual patent applications is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclobenzothiepine ring.

[0021] Further benzothiepines useful for the treatment of hypercholesterolemia arid hyperlipidemia are disclosed in

patent application no. PCT/US95/10863. More benzothiepines useful for the prophylaxis and treatment of hypercholesterolemia and hyperlipidemia as well as pharmaceutical compositions of such benzothiepines are described in PCT/US97/04076. Still further benzothiepines and compositions thereof useful for the prophylaxis and treatment of hypercholesterolemia and hyperlipidemia are described in U.S. application Ser. No. 08/816,065.

[0022] In vitro bile acid transport inhibition is disclosed to correlate with hypolipidemic activity in The Wellcome Foundation Limited disclosure of the Patent Application No. WO 93/16055 for "Hypolipidemic Benzothiazepine Compounds." That publication describes a number of hypolipidemic benzothiazepine compounds. Additional hypolipidemic benzothiazepine compounds (particularly 2,3,4,5-tetrahydrobenzo-1-thi-4-azepine compounds) are disclosed in Patent Application No. WO 96/05188. A particularly useful benzothiazepine disclosed in WO 96/05188 is the compound of formula B-2. Further hypolipidemic benzothiazepine compounds are described in Patent Application No. WO 96/16051.

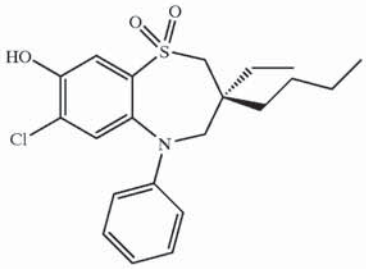
B-2



(3R,5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1-4-benzothiazepine 1,1-dioxide

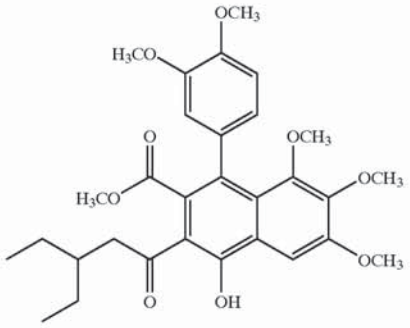
[0023] Other benzothiazepine compounds useful for control of cholesterol are 2,3,4,5-tetrahydrobenzo-1-thi-5-azepine IBAT inhibitor compounds described in PCT Patent Application No. WO 99/35135. Included in that description is the compound of formula B-7.

B-7



[0024] Further IBAT inhibitor compounds include a class of naphthalene IBAT inhibitor compounds, described by T. Ichihashi et al. in *J. Pharmacol. Exp. Ther.,* 284(1), 43-50 (1998). In this class, S-8921 (methyl 1-(3,4-dimethoxyphenyl)-3-(3-ethylvaleryl)-4-hydroxy-6,7,8-trimethoxy-2-naphthoate) is particularly useful. The structure of S-8921 is shown in formula B-20. Further naphthalene compounds or lignin derivatives useful for the treatment or prophylaxis of hyperlipidemia or atherosclerosis are described in PCT Patent Application No. WO 94/24087.

B-20



[0025] Another class of lipid-lowering drug is an antiobesity drug. An example of an antiobesity drug is orlistat. Orlistat is described in European Patent No. EP 0 129 748.

[0026] Inhibition of cholesteryl ester transfer protein (CETP) has been shown to effectively modify plasma HDL/LDL ratios, and is expected to check the progress and/or formation of certain cardiovascular diseases. CETP is a plasma protein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood (Tall, *J. Lipid Res.,* 34, 1255-74 (1993)). The movement of cholesteryl ester from HDL to LDL by CETP has the effect of lowering HDL cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile. Evidence of this effect is described in McCarthy, *Medicinal Res. Revs.,* 13, 139-59 (1993). Further evidence of this effect is described in Sitori, *Pharmac. Ther.,* 67, 443-47 (1995)). This phenomenon was first demonstrated by Swenson et al., (*J. Biol. Chem.,* 264, 14318 (1989)) with the use of a monoclonal antibody that specifically inhibits CETP. In rabbits, the antibody caused an elevation of the plasma HDL cholesterol and a decrease in LDL cholesterol. Son et al. (*Biochim. Biophys. Acta,* 795, 743-480 (1984)) describe proteins from human plasma that inhibit CETP. U.S. Pat. No. 5,519,001, herein incorporated by reference, issued to Kushwaha et al., describes a 36 amino acid peptide derived from baboon apo C-1 that inhibits CETP activity. Cho et al. (*Biochim. Biophys. Acta* 1391, 133-144 (1998)) describe a peptide from hog plasma that inhibits human CETP. Bonin et al. (*J. Peptide Res.,* 51, 216-225 (1998)) disclose a decapeptide inhibitor of CETP. A depspeptide fungal metabolite is disclosed as a CETP inhibitor by Hedge et al. in *Bioorg. Med. Chem. Lett.,* 8, 1277-80 (1998).

[0027] There have been several reports of non-peptidic compounds that act as CETP inhibitors. Barrett et al. (*J. Am. Chem. Soc.,* 188, 7863-63 (1996)) describe cyclopropane-containing CETP inhibitors. Further cyclopropane-containing CETP inhibitors are described by Kuo et al. (*J. Am.*

Chem. Soc., 117, 10629-34 (1995)). Pietzonka et al. (*Bioorg. Med. Chem. Lett.,* 6, 1951-54 (1996)) describe phosphonate-containing analogs of cholesteryl ester as CETP inhibitors. Coval et al. (*Bioorg. Med. Chem. Lett.,* 5, 605-610 (1995)) describe Wiedendiol-A and -B, and related sesquiterpene compounds as CETP inhibitors. Lee et al. (*J. Antibiotics,* 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (*Lipids,* 25, 216-220, (1990)) describe cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zilversmit (*J. Lipid Res.,* 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Connolly et al. (*Biochem. Biophys. Res. Comm.,* 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. describe 1,3,5-triazines as CETP inhibitors (*Bioorg. Med. Chem. Lett.,* 6, 919-22 (1996)). Bisgaier et al. (*Lipids,* 29, 811-8 (1994)) describe 4-phenyl-5-tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor. Additional triazole CETP inhibitors are described in U.S. patent application Ser. No. 09/153,360, herein incorporated by reference. Sikorski et al. disclosed further novel CETP inhibitors in PCT Patent Application No. WO 9914204.

[0028] Substituted 2-mercaptoaniline amide compounds can be used as CETP inhibitors and such therapeutic compounds are described by H. Shinkai et al. in PCT Patent Application No. WO 98/35937.

[0029] Some substituted heteroalkylamine compounds are known as CETP inhibitors. In European Patent Application No. 796846, Schmidt et al. describe 2-aryl-substituted pyridines as cholesterol ester transfer protein inhibitors useful as cardiovascular agents. One substituent at C_3 of the pyridine ring can be an hydroxyalkyl group. In European Patent Application No. 801060, Dow and Wright describe heterocyclic derivatives substituted with an aldehyde addition product of an alkylamine to afford 1-hydroxy-1-amines. These are reported to be β3-adrenergic receptor agonists useful for treating diabetes and other disorders. In Great Britain Patent Application No. 2305665, Fisher et al. disclose 3-agonist secondary amino alcohol substituted pyridine derivatives useful for treating several disorders including cholesterol levels and atherosclerotic diseases. In European Patent Application No. 818448 (herein incorporated by reference), Schmidt et al. describe tetrahydroquinoline derivatives as cholesterol ester transfer protein inhibitors. European Patent Application No. 818197, Schmek et al. describe pyridines with fused heterocycles as cholesterol ester transfer protein inhibitors. Brandes et al. in German Patent Application No. 19627430 describe bicyclic condensed pyridine derivatives as cholesterol ester transfer protein inhibitors. In PCT Patent Application No. WO 9839299, Muller-Gliemann et al. describe quinoline derivatives as cholesteryl ester transfer protein inhibitors.

[0030] Polycyclic compounds that are useful as CETP inhibitors are also disclosed by A. Oomura et al. in Japanese Patent No. 10287662. For example, therapeutic compounds having the structures C-1 and C-8 were prepared by culturing Penicillium spp.

[0031] Cycloalkylpyridines useful as CETP inhibitors are disclosed by Schmidt et al. in European Patent No. EP 818448. For example, the therapeutic compound having the structure C-9 is disclosed as being particularly effective as a CETP inhibitor.

[0032] Substituted tetrahydronaphthalene compounds useful as CETP inhibitors are described in PCT Patent Application No. WO 9914174. Specifically described in that disclosure as a useful CETP inhibitor is (8S)-3-cyclopentyl-1-(4-fluorophenyl)-2-[(S)-fluoro(4-trifluoromethylphenyl-)methyl]-8-hydroxy-6-spirocclobutyl-5,6,7,8-tetrahydronaphthalene.

[0033] Some 4--heteroaryl-tetrahydroquinolines useful as CETP inhibitors are described in PCT Patent Application No. WO 9914215. For example, that disclosure describes 3-(4-trifluoromethylbenzoyl)-5,6,7,8-tetrahydroquinolin-5-one as a useful CETP inhibitor.

[0034] In another approach to the reduction of total cholesterol, use is made of the understanding that HMG CoA reductase catalyzes the rate-limiting step in the biosynthesis of cholesterol (*The Pharmacological Basis of Therapeutics,* 9th ed., J. G. Hardman and L. E. Limberd, ed., McGraw-Hill, Inc., New York, pp. 884-888 (1996), herein incorporated by reference). HMG CoA reductase inhibitors (including the class of therapeutics commonly called "statins") reduce blood serum levels of LDL cholesterol by competitive inhibition of this biosynthetic step (M. S. Brown, et al., J. Biol. Chem, 253, 1121-28 (1978), herein incorporated by reference). Several statins have been developed or commercialized throughout the world. Mevastatin was among the first of the statins to be developed and it is described in U.S. Pat. No. 3,983,140 (herein incorporated by reference). Lovastatin, another important HMG CoA reductase inhibitor, is described in U.S. Pat. No. 4,231,938 (herein incorporated by reference). Simvastatin is described in U.S. Pat. No. 4,444,784 (herein incorporated by reference). Each of these HMG CoA reductase inhibitors contains a six-membered lactone function which apparently mimics the structure of HMG CoA in competition for the reductase. The HMG CoA reductase inhibitor class of cholesterol-lowering drugs is further exemplified by a group of drugs which contain 2,4-dihydroxyheptanoic acid functionalities rather than the lactone. One member of this group is pravastatin, described in U.S. Pat. No. 4,346,227 (herein incorporated by reference). Another HMG CoA reductase inhibitor which contains a 2,4-dihydroxyheptanoic acid group is fluvastatin, described in U.S. Pat. No. 5,354,772 (herein incorporated by reference). Warnings of side effects from use of HMG CoA reductase inhibitors include liver dysfunction, skeletal muscle myopathy, rhabdomyolysis, and acute renal failure. Some of these effects are exacerbated when HMG CoA reductase inhibitors are combined with fibrates or nicotinic acid.

[0035] Fibric acid derivatives comprise another class of drugs which have effects on lipoprotein levels. Among the first of these to be developed was clofibrate, disclosed in U.S. Pat. No. 3,262,850. Clofibrate is the ethyl ester of p-chlorophenoxyisobutyric acid. A widely used drug in this class is gemfibrozil, disclosed in U.S. Pat. No. 3,674,836. Gemfibrozil frequently is used to decrease triglyceride levels or increase HDL cholesterol concentrations (*The Pharmacological Basis of Therapeutics,* p. 893). Fenofibrate (U.S. Pat. No. 4,058,552) has an effect similar to that of gemfibrozil, out additionally decreases LDL levels. Ciprofibrate (U.S. Pat. No. 3,948,973) has similar effects to that of fenofibrate. Another drug in this class is bezafibrate (U.S. Pat. No. 3,781,328). Warnings of side effects from use of fibric acid derivatives include gall bladder disease

(cholelithiasis), rhabdomyolysis, and acute renal failure. Some of these effects are exacerbated when fibrates are combined with HmG CoA reductase inhibitors.

[0036] Probucol is a powerful antioxidant which has shown the ability to lower serum cholesterol levels and cause regression of xanthomas in patients having homozygous familial hypercholesterolemia (A. Yamamoto, et al., Am. J. Cardiol., 57, 29H-35H (1986)). However, treatment with probucol alone sometimes shows erratic control of LDL and frequent lowering of HDL (*The Pharmacological Basis of Therapeutics*, p. 891). Probucol is contraindicated for patients with progressive myocardial damage and/or ventricular arrhythmias.

[0037] A class of materials which operates by another mechanism to lower LDL cholesterol comprises bile acid sequestering agents. Such agents are typically anion exchange polymers administered orally to a patient. As the agent passes through the gut, anions of bile acids are sequestered by the agent and excreted. Such sequestering has been speculated to prevent reabsorption by the gut, for example the ileum, thereby preventing conversion of the bile acids into cholesterol. One such bile acid sequestering agent is cholestyramine, a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids. It is believed that cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their normal enterohepatic circulation. This effect is described by Reihnér et al., in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-COA reductase activity and low density lipoprotein receptor expression in gallstone patients", Journal of Lipid Research, 31, 2219-2226 (1990). Further description of this effect is found in Suckling et al. in "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine treatment", *Atherosclerosis,* 89, 183-90 (1991). This results in an increase in liver bile acid synthesis because of the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol levels.

[0038] Another bile acid sequestering agent is colestipol, a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane. Colestipol is described in U.S. Pat. No. 3,692,895. A frequent side effect of colestipol and of cholestyramine is gastric distress.

[0039] Additional bile acid sequestering agents are described in U.S. Pat. No. 5,703,188, assigned to Geltex Pharmaceuticals Inc. For example, one such bile acid sequestering agent is 3-methacrylamidopropyltrimethylammonium chloride copolymerized with ethylene glycol dimethacrylate to yield a copolymer.

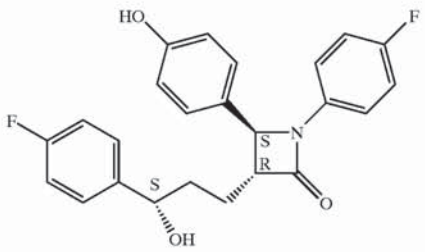
[0040] Yet another class materials proposed as bile acid sequestering agents comprises particles comprising amphiphilic copolymers having a crosslinked shell domain and an interior core domain (Patent application no. PCT/US 97/11610). Structures and preparation of such crosslinked amphiphilic copolymers are described in PCT/US97/11345. Such particles have been given the common name of "knedels" (K. B. Thurmond et al., J. Am. Chem. Soc., 118 (30), 7239-40 (1996)).

[0041] Nicotinic acid (niacin) is a B-complex vitamin reported as early as 1955 to act as a hypolipidemic agent (R. Altschl, et al., Arch. Biochem. Biophys., 54, 558-9 (1955)). It is sometimes used to raise low HDL levels and lower VLDL and LDL levels. Useful commercial formulations of nicotinic acid include Niacor, Niaspan, Nicobid, Nicolar, Slo-Niacin. Nicotinic acid is contraindicated for patients having hepatic dysfunction, active peptic ulcer, or arterial bleeding. Another compound in this class useful for cardiovascular indications is niceritrol (T. Kazumi et al., Curr. Ther. Res., 55, 546-51). J. Sasaki et al. (Int. J. Clin. Pharm. Ther., 33 (7), 420-26 (1995)) describes a reduction in cholesterol ester transfer activity by niceritrol monotherapy. Acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide, U.S. Pat. No. 4,002,750) is structurally similar to nicotinic acid and has antihyperlipidemic activity.

[0042] A study by Wetterau et al. (*Science,* 282, 751-54 (1998)) describes a number of alkylpiperidine compounds, isoindole compounds, and fluorene compounds useful for inhibiting microsomal triglyceride transfer protein (MTP inhibitors). Rodents and Watanabe-heritable hyperlipidemic rabbits treated with these compounds show decreased production of lipoprotein particles.

[0043] Cholesterol absorption antagonists may also be useful for the treatment of prophylaxis of cardiovascular diseases such as hypercholesterolemia or atherosclerosis. For example, azetidinones such as SCH 58235 ([3R-[3α(S*),4β]]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone) (formula A-1), described in *J. Med. Chem.,* 41(6), 973-980 (1998), are useful cholesterol absorption antagonists. SCH 58235 is further described by Van Heek et al. in *J. Pharmacol. Exp. Ther.,* 283(1), 157-163 (1997). Further azetidinone compounds useful for treatment or prophylaxis of cardiovascular disease are described in U.S. Pat. No. 5,767,115.

A-1



[3R-[3a(S*),4b]]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone

[0044] Phytosterols, and especially stanols have been shown to effectively inhibit cholesterol absorption from the gastrointestinal tract, and to negatively affect cholesterol synthesis. Phytosterols are expected to slow or inhibit the progress and formation of certain cardiovascular conditions, including hyperlipidemic conditions such as hypercholesterolemia and atherosclerosis. Stanols are 5α saturated derivatives of phytosterols. (Straub, U.S. Pat. No. 5,244,887). It has been suggested that phytosterols lower blood cholesterol levels by reducing the absorption of cholesterol from the intestine (Ling and Jones, "Minireview Dietary

Phytosterols: A Review of Metabolism, Benefits and Side Effects,"*Life Sciences,* 57 (3), 195-206 (1995)).

[0045] Sitostanol, clionastanol, 22,23-dihydrobrassicastanol, campestanol, and mixtures thereof contained in food additives intended to reduce cholesterol absorption from foods and beverages containing cholesterol are described by Straub in U.S. Pat. No. 5,244,887.

[0046] A beta-sitostanol fatty acid ester or fatty acid ester mixture which lowers cholesterol in serum is described by Miettinen et al. in U.S. Pat. No. 5,502,045.

[0047] A stanol composition containing in sitostanol and campestanol which effectively lowers serum cholesterol levels when incorporated into edibles is described by Wester et al. in WO 9806405.

[0048] A therapeutic composition of one or more oxysterols and a suitable carrier to inhibit cholesterol absorption from the diet is described by Haines in U.S. Pat. No. 5,929,062.

[0049] Cardiovascular disease is also caused or aggravated by hypertension. Hypertension is defined as persistently high blood pressure. Generally, adults are classified as being hypertensive when systolic blood pressure is persistently above 140 mmHg or when diastolic blood pressure is above 90 mmHg. Long-term risks for cardiovascular mortality increase in a direct relationship with persistent blood pressure (E. Braunwald, *Heart Disease,* 5th ed., W.B. Saunders & Co., Philadelphia, 1997, pp. 807-823). Various mechanisms have been advantageously exploited to control hypertension. For example, useful antihypertensive agents can include, without limitation, an andrenergic blocker, a mixed alpha/beta andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, an andrenergic stimulant, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a diuretic, or a vasodilator. A particularly useful antihypertensive agent is eplerenone (see, for example, U.S. Pat. No. 4,559,332). Eplerenone lowers blood pressure by functioning as a diuretic. Eplerenone was formerly called epoxymexrenone.

[0050] Some combination therapies for the treatment of cardiovascular disease have been described in the literature. Combinations of IBAT inhibitors with HMG CoA reductase inhibitors useful for the treatment of cardiovascular disease are disclosed in U.S. patent application Ser. No. 09/037,308 and in PCT Patent Application No. 98/40375.

[0051] A combination therapy of fluvastatin and niceritrol is described by J. Sasaki et al. (Id.). Those researchers conclude that the combination of fluvastatin with niceritrol "at a dose of 750 mg/day dose does not appear to augment or attenuate beneficial effects of fluvastatin."

[0052] L. Cashin-Hemphill et al. (J. Am. Med. Assoc., 264 (23), 3013-17 (1990)) describe beneficial effects of a combination therapy of colestipol and niacin on coronary atherosclerosis. The described effects include nonprogression and regression in native coronary artery lesions.

[0053] A combination therapy of acipimox and simvastatin shows beneficial HDL effects in patients having high triglyceride levels (N. Hoogerbrugge et al., J. Internal Med., 241, 151-55 (1997)).

[0054] Sitostanol ester margarine and pravastatin combination therapy is described by H. Gylling et al. (J. Lipid Res., 37, 1776-85 (1996)). That therapy is reported to simultaneously inhibit cholesterol absorption and lower LDL cholesterol significantly in non-insulin-dependent diabetic men.

[0055] Brown et al. (New Eng. J. Med., 323 (19), 1289-1339 (1990)) describe a combination therapy of lovastatin and colestipol which reduces atherosclerotic lesion progression and increase lesion regression relative to lovastatin alone.

[0056] Scott (PCT Patent Application No. WO 99/11260) describes combinations of atorvastatin (an HMG CoA reductase inhibitor) with an antihypertensive agent for the treatment of angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia, and symptoms of cardiac risk.

[0057] Egan et al. (PCT Patent Application No. WO 96/40255) describe a combination therapy of an angiotension II antagonist and an epoxy-steroidal aldosterone antagonist. The epoxy-steroidal aldosterone antagonist in the Egan application includes eplerenone.

[0058] The above references show continuing need to find safe, effective agents for the prophylaxis or treatment of cardiovascular diseases.

SUMMARY OF THE INVENTION

[0059] To address the continuing need to find safe and effective agents for the prophylaxis and treatment of cardiovascular diseases, combination therapies of cardiovascular drugs are now reported.

[0060] Among its several embodiments, the present invention provides a combination therapy comprising the use of a first amount of an IBAT inhibitor and a second amount of another cardiovascular therapeutic useful in the prophylaxis or treatment of hyperlipidemia or atherosclerosis, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. For example one of the many embodiments of the present invention is a therapeutic composition comprising first amount of an IBAT inhibitor and a second amount of a microsomal triglyceride transfer protein inhibitor (MTP inhibitor), wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor. In another embodiment, the IBAT inhibitor can be a benzothiazepine IBAT inhibitor. In still another embodiment, the IBAT inhibitor can be a naphthalene IBAT inhibitor.

[0061] The present invention further provides a therapeutic composition comprising a first amount of an IBAT inhibitor and a second amount of a cholesterol absorption antagonist, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

[0062] The present invention further provides a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of

an antihypertensive compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

[0063] In another embodiment, the present invention also includes a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antiobesity compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds. For example, the antiobesity compound can comprise orlistat. Orlistat is described in European Patent No. EP 0 129 748.

[0064] Among its several embodiments, the present invention further provides a combination comprising a first amount of an IBAT inhibitor and a second amount of another cardiovascular therapeutic useful in the prophylaxis or treatment of hyperlipidemia or atherosclerosis, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. For example one of the many embodiments of the present invention is a combination comprising therapeutic dosages of an IBAT inhibitor and a phytosterol. A preferred embodiment of the present invention is a combination comprising therapeutic dosages of a benzothiepine IBAT inhibitor and a phytosterol. In another preferred embodiment, the present invention embraces a combination comprising an IBAT inhibitor and a stanol.

[0065] A still further embodiment of the instant invention comprises the use of any of the cardiovascular combination therapies described herein for the prophylaxis or treatment of hypercholesterolemia or atherosclerosis.

[0066] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a microsomal triglyceride transfer protein inhibiting compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

[0067] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a cholesterol absorption antagonist compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

[0068] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antihypertensive compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount of the compounds.

[0069] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a phytosterol compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds. Preferably the phytosterol compound comprises a stanol.

[0070] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a microsomal triglyceride transfer protein inhibiting compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

[0071] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a cholesterol absorption antagonist compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

[0072] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of an antihypertensive compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

[0073] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a phytosterol compound in a second unit dosage form; and container means for containing said first and second unit dosage forms. Preferably the phytosterol compound comprises a stanol.

[0074] Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0075] The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

[0076] The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

a. Definitions

[0077] The following definitions are provided in order to aid the reader in understanding the detailed description of the present invention:

[0078] "Benzothiepine IBAT inhibitor" means an ileal bile acid transport inhibitor which comprises a therapeutic compound comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure or a 2,3,4,5-tetrahydro-1-benzothiepine 1-oxide structure.

[0079] "Benzothiazepine IBAT inhibitor" means an ileal bile acid transport inhibitor which comprises a therapeutic compound comprising a 2,3,4,5-tetrahydro-1-benzothi-4-azepine 1,1-dioxide structure or a 2,3,4,5-tetrahydro-1-benzothi-5-azepine 1,1-dioxide structure.

[0080] "Naphthalene IBAT inhibitor" means an ileal bile acid transport inhibitor which comprises a therapeutic compound comprising a substituted naphthalene structure.

[0081] "Nicotinic acid derivative" means a therapeutic compound comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions, and tautomers. Nicotinic acid derivatives include, for example, nicotinic acid (niacin), niceritrol, and acipimox.

[0082] A "phytosterol" means any steroid naturally or synthetically derived having about C_8 to about C_{10} carbon aliphatic side chains at position 17, and at least one alcoholic hydroxyl group (Miller-Keane, *Encyclopedia & Dictionary of Medicine, Nursing, & Allied Health,* 5th ed.). As used herein, the term "phytosterol" includes stanols.

[0083] "Stanol" means a class of phytosterols having a 5α-saturation.

[0084] "Combination therapy" means the administration of two or more therapeutic agents to treat a hypertensive condition or a hyperlipidemic condition, for example atherosclerosis and hypercholesterolemia. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single dosage form having a fixed ratio of active ingredients or in multiple, separate dosage forms for each inhibitor agent. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the hypertensive condition or the hyperlipidemic condition.

[0085] The phrase "therapeutically effective" is intended to qualify the combined amount of inhibitors in the combination therapy. This combined amount will achieve the goal of reducing or eliminating the hypertensive condition or the hyperlipidemic condition.

[0086] "Therapeutic compound" means a compound useful in the prophylaxis or treatment of a hypertensive condition or a hyperlipidemic condition, including atherosclerosis and hypercholesterolemia.

b. Combinations

[0087] The combinations of the present invention will have a number of uses. For example, through dosage adjustment and medical monitoring, the individual dosages of the therapeutic compounds used in the combinations of the present invention will be lower than are typical for dosages of the therapeutic compounds when used in monotherapy. The dosage lowering will provide advantages including reduction of side effects of the individual therapeutic compounds when compared to the monotherapy. In addition, fewer side effects of the combination therapy compared with the monotherapies will lead to greater patient compliance with therapy regimens.

[0088] Another use of the present invention will be in combinations having complementary effects or complementary modes of action. For example, IBAT inhibitors frequently lower LDL lipoprotein but also lower HDL lipoprotein. In contrast, CETP inhibitors raise HDL. A therapeutic combination of an IBAT inhibitor and a CETP inhibitor will, when dosages are optimally adjusted, lower LDL yet maintain or raise HDL.

[0089] Compounds useful in the present invention encompass a wide range of therapeutic compounds. IBAT inhibitors useful in the present invention are disclosed in patent application no. PCT/US95/10863, herein incorporated by reference. More IBAT inhibitors are described in PCT/US97/04076, herein incorporated by reference. Still further IBAT inhibitors useful in the present invention are described in U.S. application Ser. No. 08/816,065, herein incorporated by reference. More IBAT inhibitor compounds useful in the present invention are described in WO 98/40375, herein incorporated by reference. Additional IBAT inhibitor compounds useful in the present invention are described in U.S. application Ser. No. 08/816,065, herein incorporated by reference. IBAT inhibitors of particular interest in the present invention are shown in Table 1, as well as the diastereomers, enantiomers, racemates, salts, and tautomers of the IBAT inhibitors of Table 1.

TABLE 1

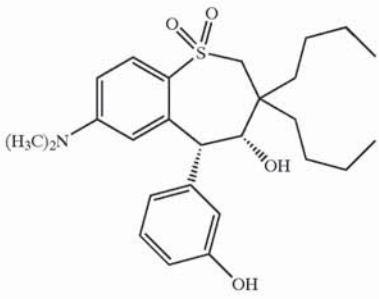
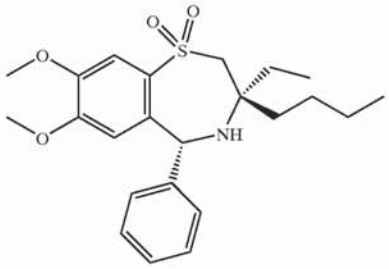
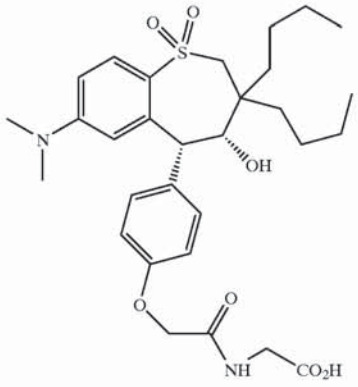
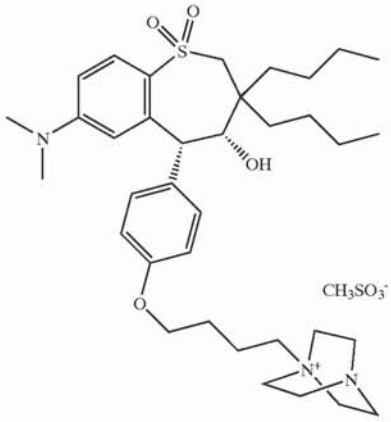
Compound Number	Structure
B-1	
B-2	
	(3R,5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1-4-benzothiazepine 1,1-dioxide
B-3	
B-4	

TABLE 1-continued

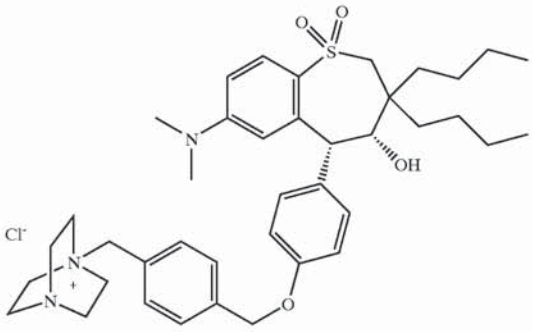
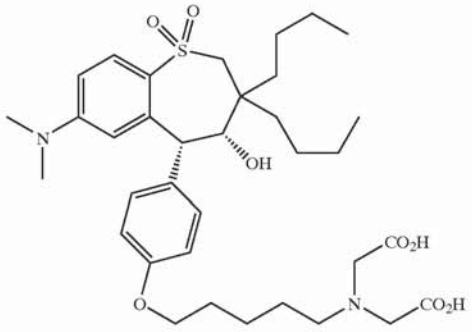
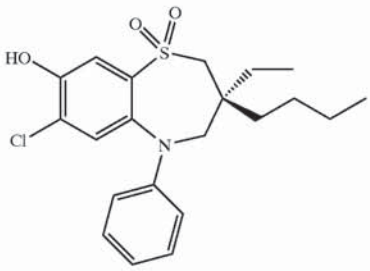
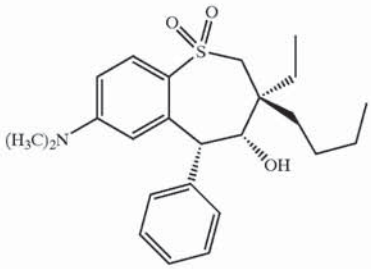
Compound Number	Structure
B-5	
B-6	
B-7	
B-8	

TABLE 1-continued

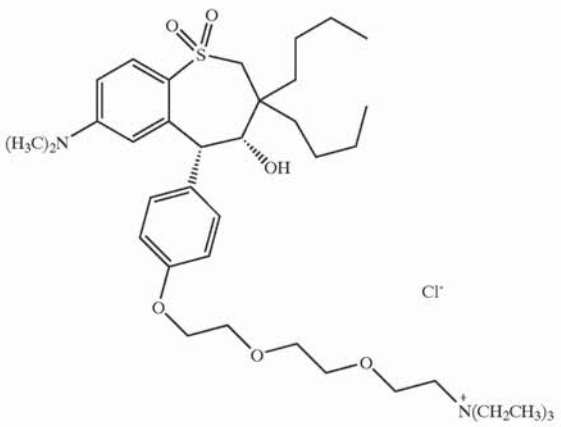
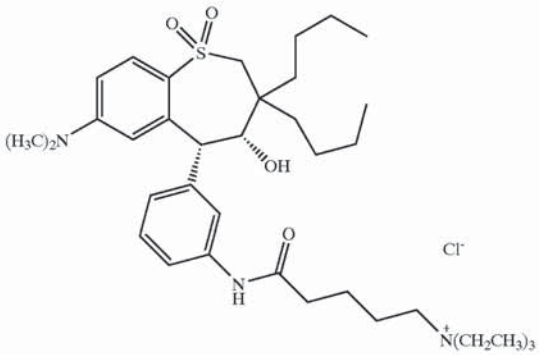
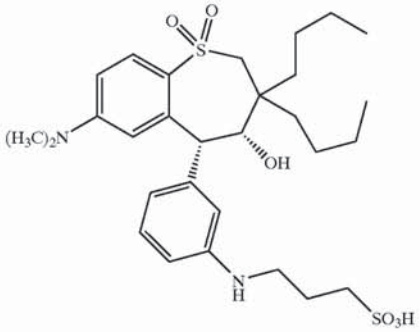
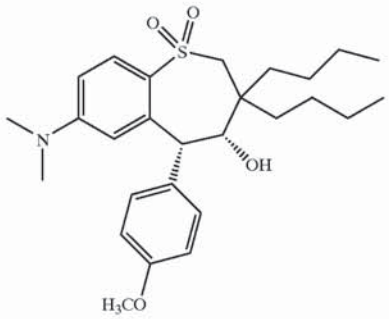
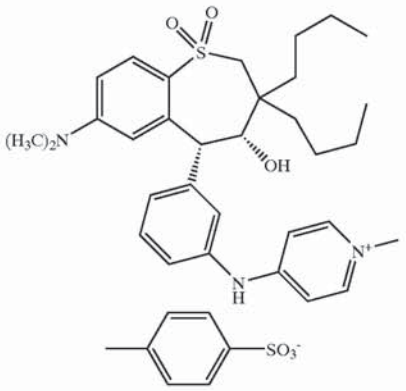
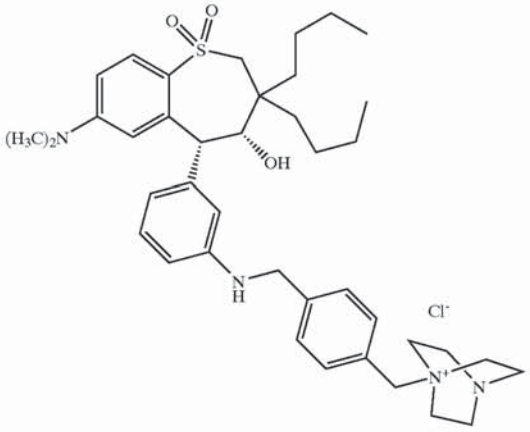
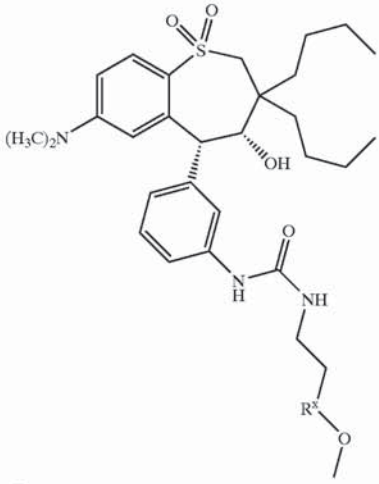
Compound Number	Structure
B-9	
B-10	
B-11	
B-12	

TABLE 1-continued

Compound Number	Structure
B-13	
B-14	
B-15	

R^x = 5000 formula weight polyethyleneglycol

TABLE 1-continued

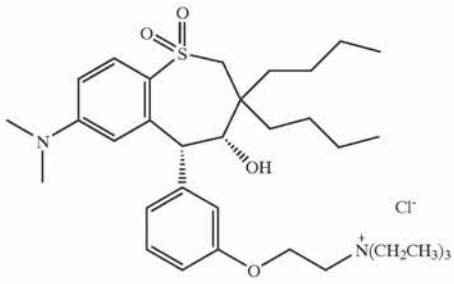
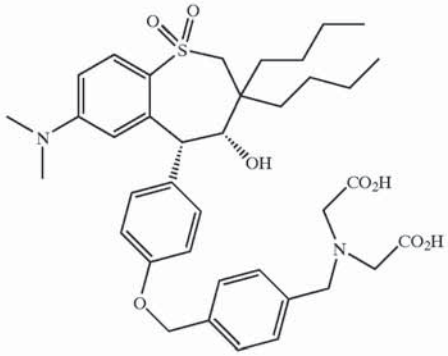
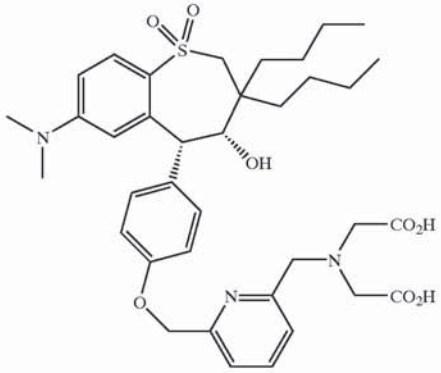
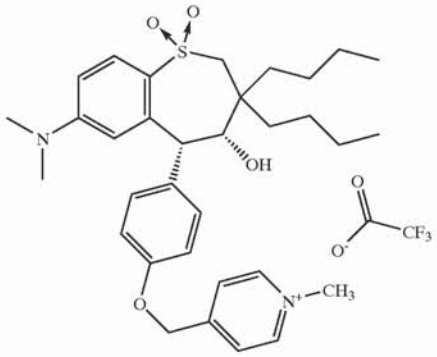
Compound Number	Structure
B-16	
B-17	
B-18	
B-19	

TABLE 1-continued

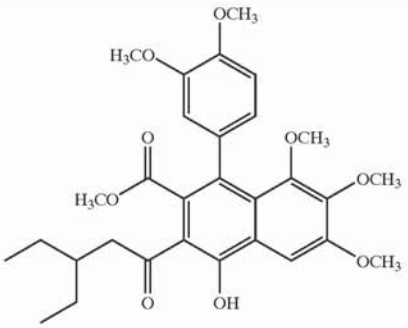
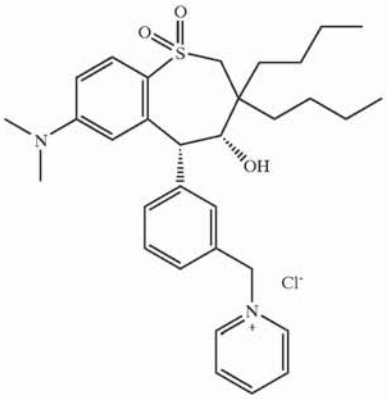
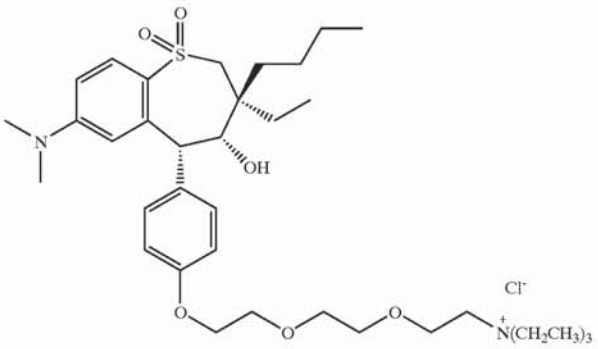
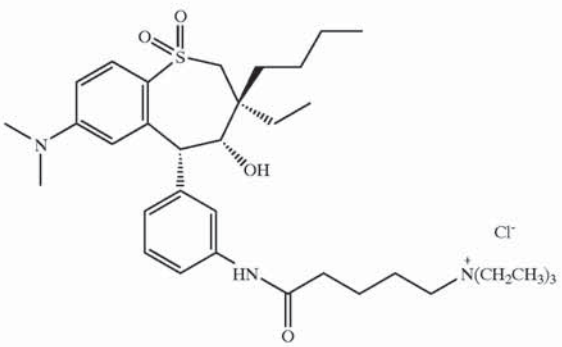
Compound Number	Structure
B-20	
B-21	
B-22	
B-23	

TABLE 1-continued

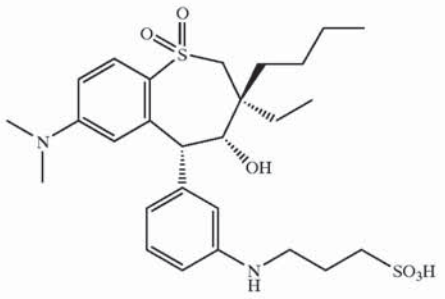
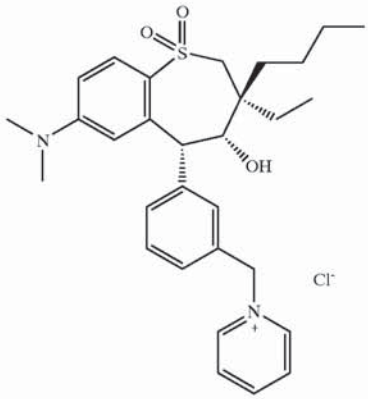
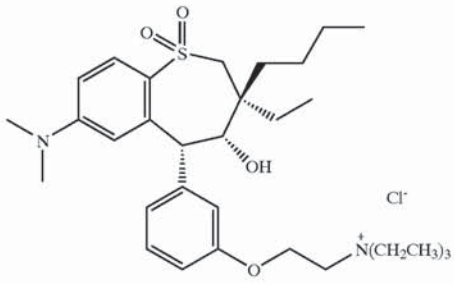
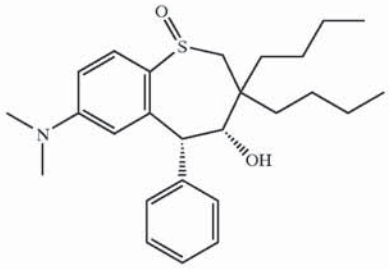
Compound Number	Structure
B-24	
B-25	
B-26	
B-27	

TABLE 1-continued

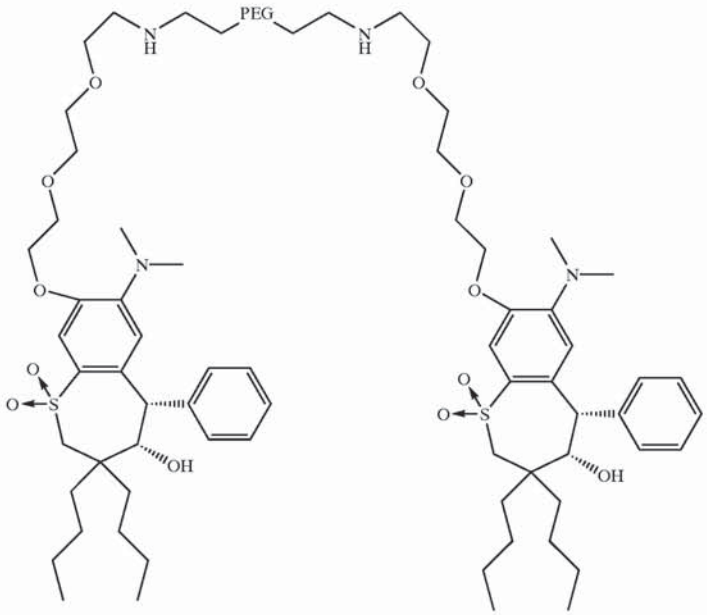
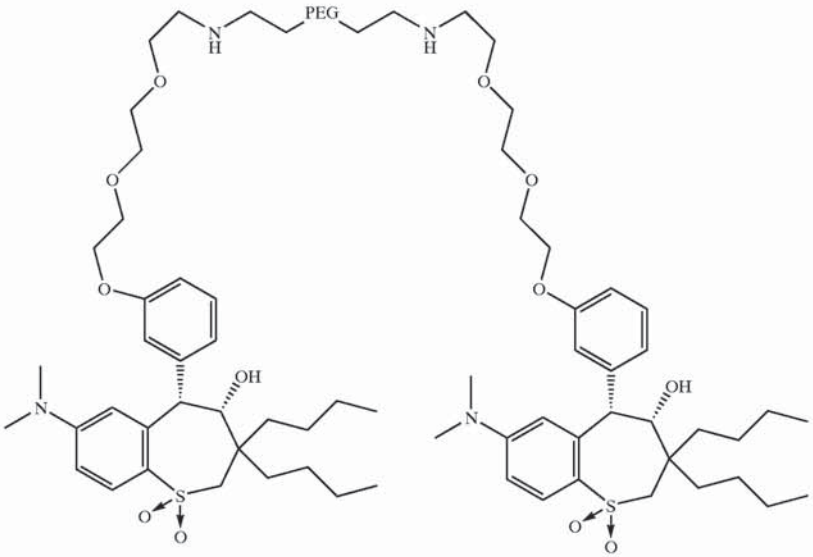
Compound Number	Structure
B-28	 PEG = 3400 molecular weight polyethylene glycol polymer chain
B-29	 PEG = 3400 molecular weight polyethylene glycol polymer chain

TABLE 1-continued

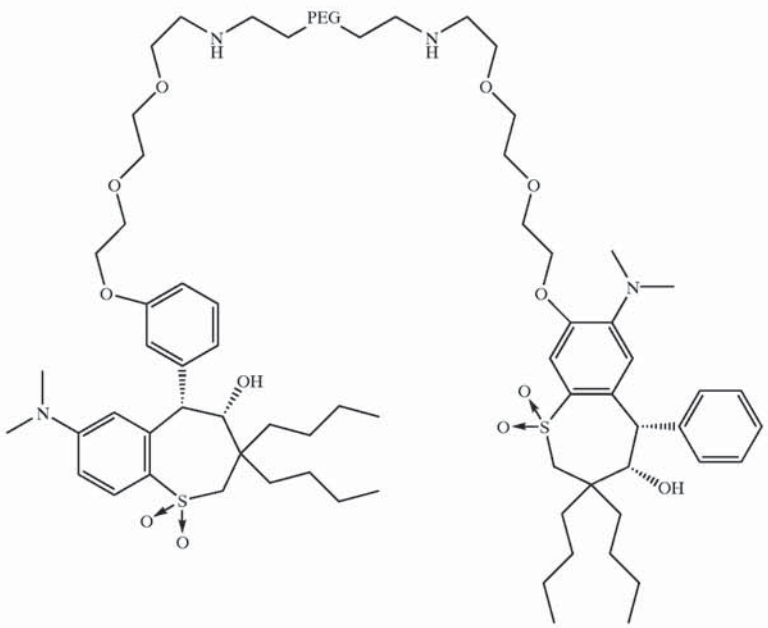
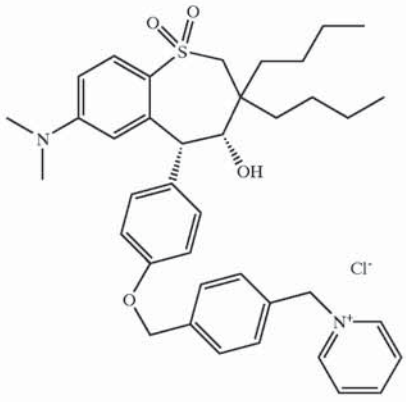
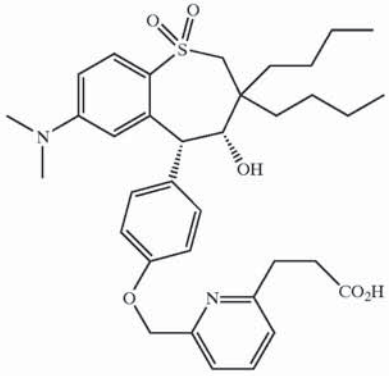
Compound Number	Structure
B-30	
	PEG = 3400 molecular weight polyethylene glycol polymer chain
B-31	
B-32	

TABLE 1-continued

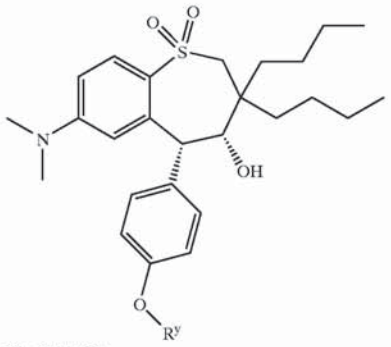
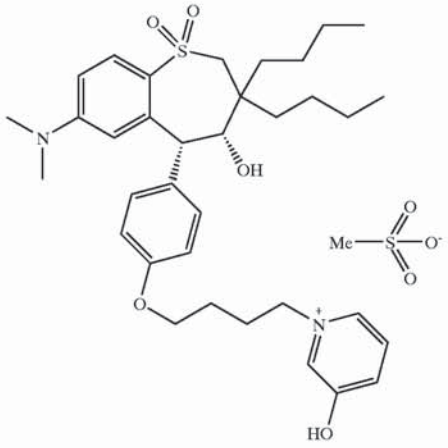
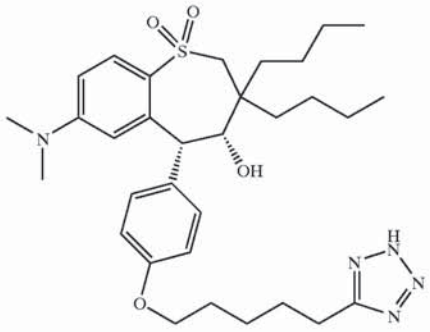
Compound Number	Structure
B-33	 R^y = PEG 1000
B-34	
B-35	

TABLE 1-continued

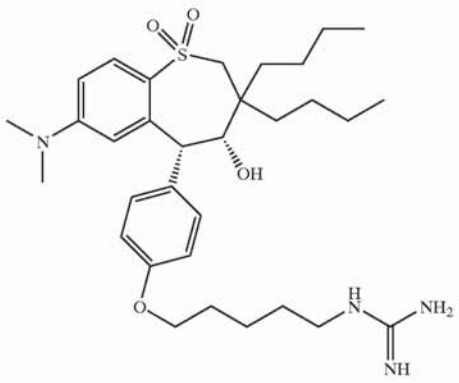
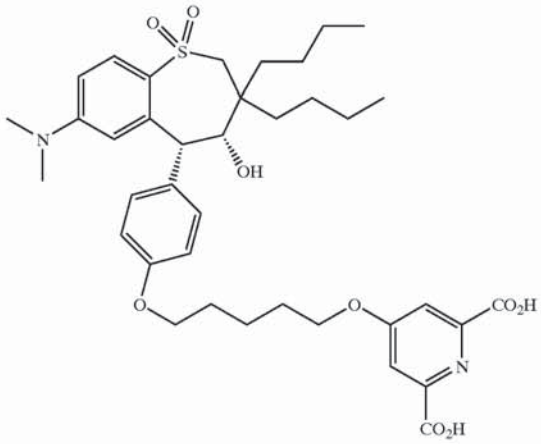
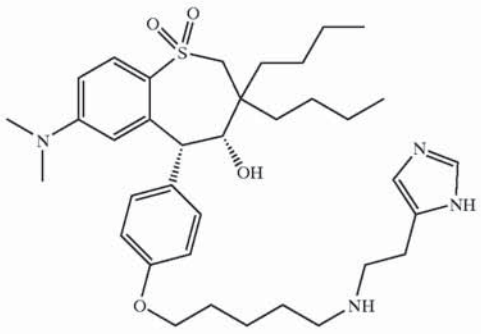
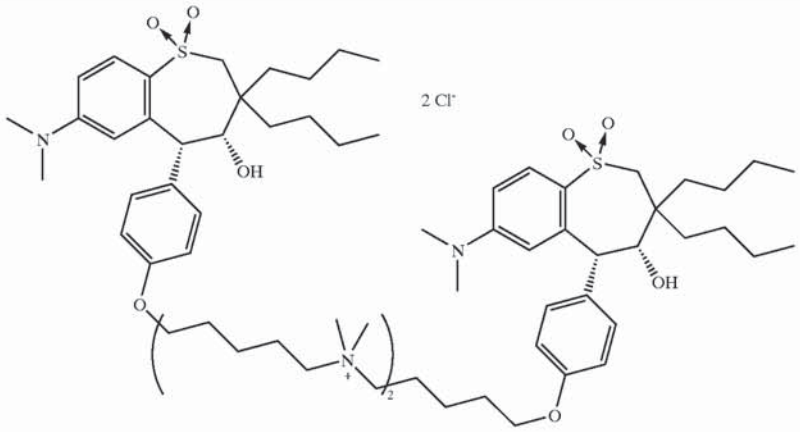
Compound Number	Structure
B-36	
B-37	
B-38	

TABLE 1-continued

Compound Number	Structure
B-39	

[0090] Individual CETP inhibitor compounds useful in the present invention are separately described in the following individual patent applications, each of which is herein incorporated by reference.

[0091] R9. U.S. patent application Ser. No. 60/101661.

[0092] R10. U.S. patent application Ser. No. 60/101711.

[0093] R11. U.S. patent application Ser. No. 60/101660.

[0094] R12. U.S. patent application Ser. No. 60/101664.

[0095] R13. U.S. patent application Ser. No. 60/101668.

[0096] R14. U.S. patent application Ser. No. 60/101662.

[0097] R15. U.S. patent application Ser. No. 60/101663.

[0098] R16. U.S. patent application Ser. No. 60/101669.

[0099] R17. U.S. patent application Ser. No. 60/101667.

[0100] R18. U.S. patent application Ser. No. 09/401, 916.

[0101] R19. U.S. patent application Ser. No. 09/405, 524.

[0102] R20. U.S. patent application Ser. No. 09/404, 638.

[0103] R21. U.S. patent application Ser. No. 09/404, 638.

[0104] R22. U.S. patent application Ser. No. 09/400, 915.

[0105] R23. U.S. Pat. No. 5,932,587.

[0106] R24. U.S. Pat. No. 5,925,645.

[0107] CETP inhibitor compounds of particular interest in the present invention are shown in Table 2.

TABLE 2

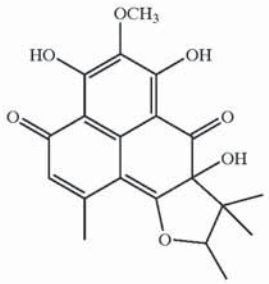
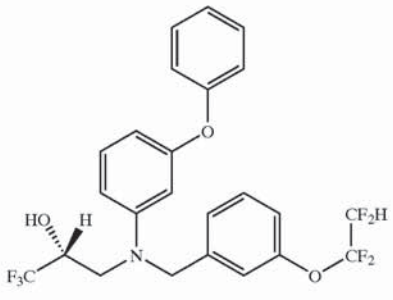
Compound Number	Structure
C-1	
C-2	

TABLE 2-continued

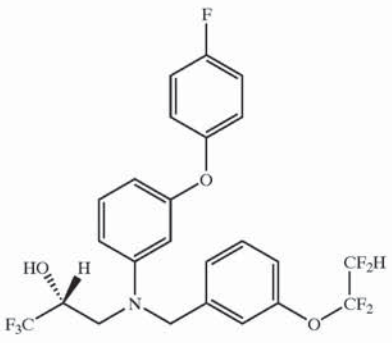
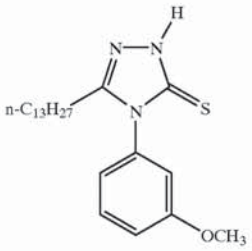
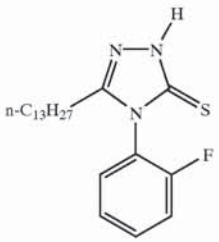
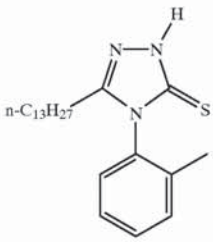
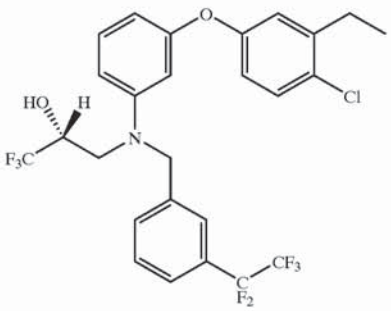
Compound Number	Structure
C-3	
C-4	
C-5	
C-6	
C-7	

TABLE 2-continued

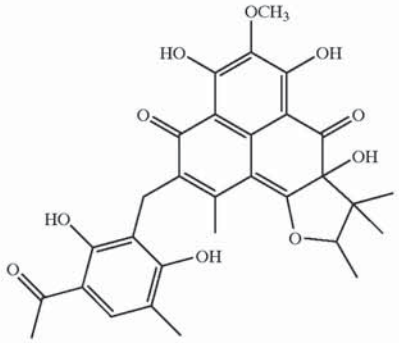
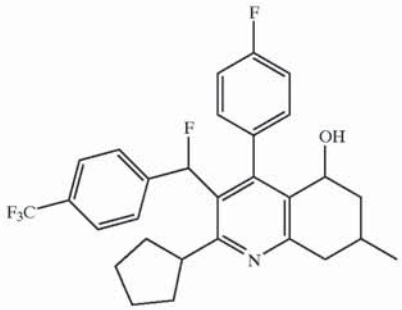
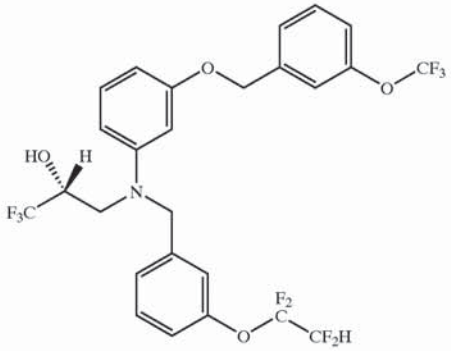
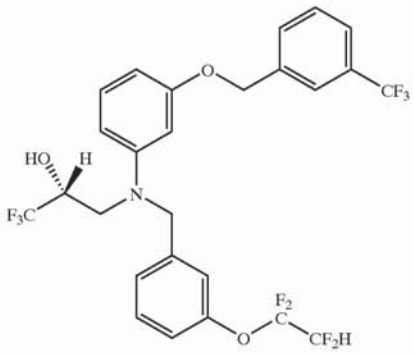
Compound Number	Structure
C-8	
C-9	
C-10	
C-11	

TABLE 2-continued

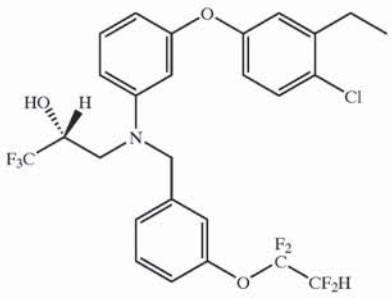
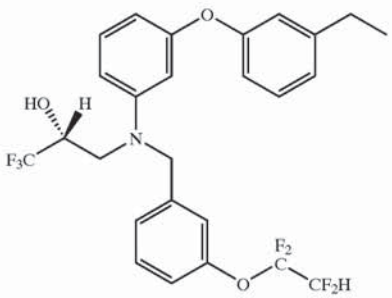
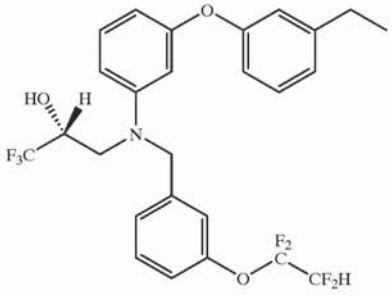
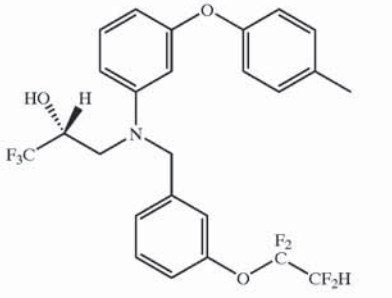
Compound Number	Structure
C-12	
C-13	
C-14	
C-15	

TABLE 2-continued

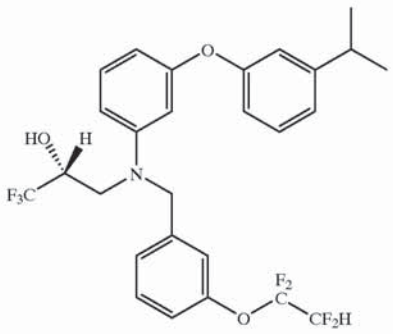
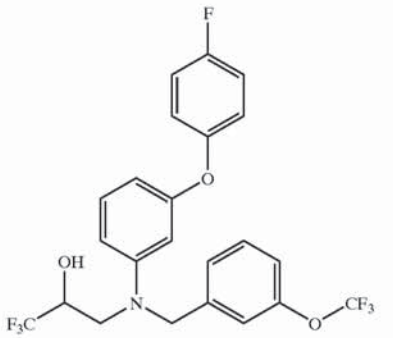
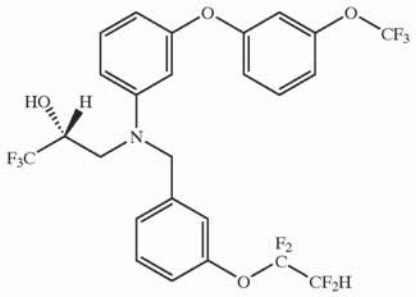
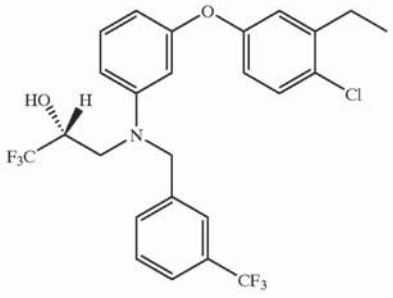
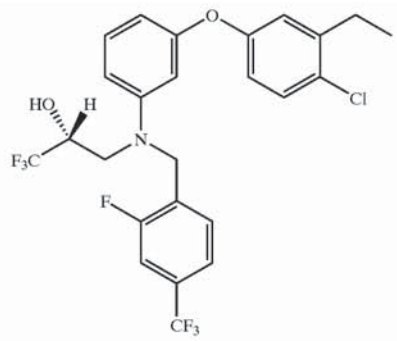
Compound Number	Structure
C-16	
C-17	
C-18	
C-19	

TABLE 2-continued

Compound Number	Structure
C-20	

[0108] Fibric acid derivatives useful in the combinations and methods of the present invention comprise a wide variety of structures and functionalities. Preferred fibric acid derivatives for the present invention are described in Table 4. The therapeutic compounds of Table 4 can be used in the present invention in a variety of forms, including acid form, salt form, racemates, enantiomers, zwitterions, and tautomers. The individual U.S. patents referenced in Table 4 are each herein incorporated by reference.

TABLE 4

Compound Number	Common Name	CAS Registry Number	U.S. Patent Reference for Compound Per Se
G-41	Clofibrate	637-07-0	3,262,850
G-70	Fenofibrate	49562-28-9	4,058,552
G-38	Ciprofibrate	52214-84-3	3,948,973
G-20	Bezafibrate	41859-67-0	3,781,328
G-78	Gemfibrozil	25182-30-1	3,674,836

[0109] MTP inhibitor compounds useful in the combinations and methods of the present invention comprise a wide variety of structures and functionalities. Some of the MTP inhibitor compounds of particular interest for use in the present invention are shown in Table 4b. The therapeutic compounds of Table 4b can be used in the present invention in a variety of forms, including acid form, salt form, racemates, enantiomers, zwitterions, and tautomers. Descriptions of the therapeutic compounds of Table 4b can be found in *Science,* 282, Oct. 23, 1998, pp. 751-754, herein incorporated by reference.

TABLE 4b

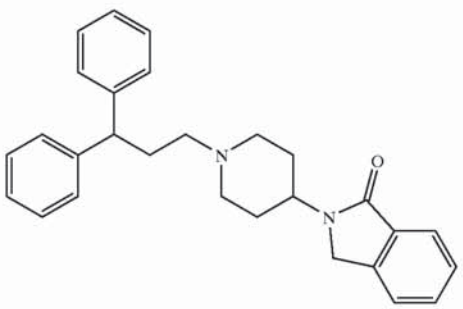
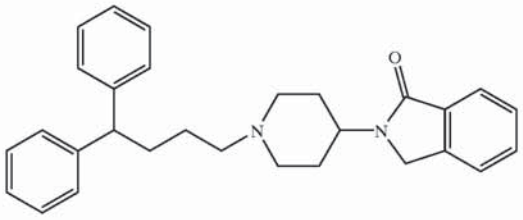
Compound Number	Structure
M-1	
M-2	

TABLE 4b-continued

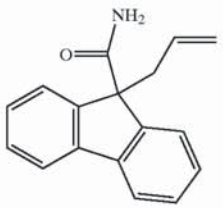
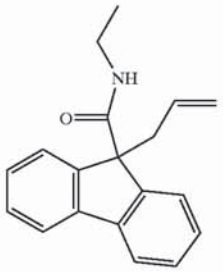
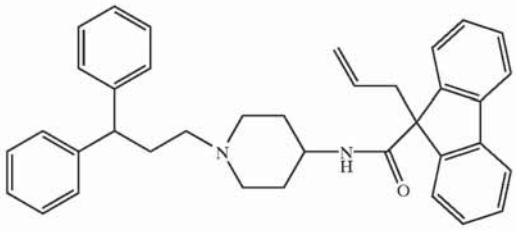
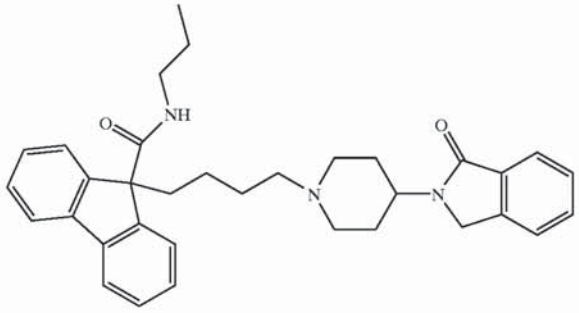
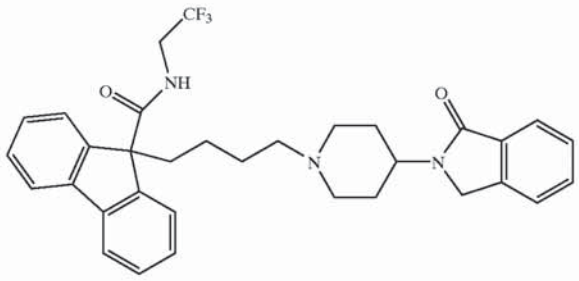
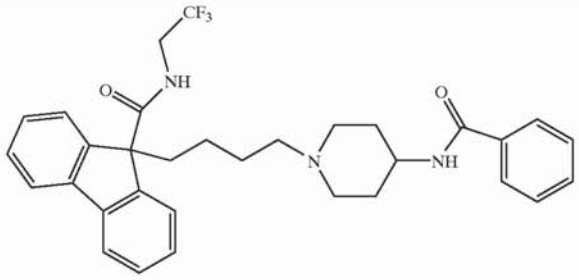
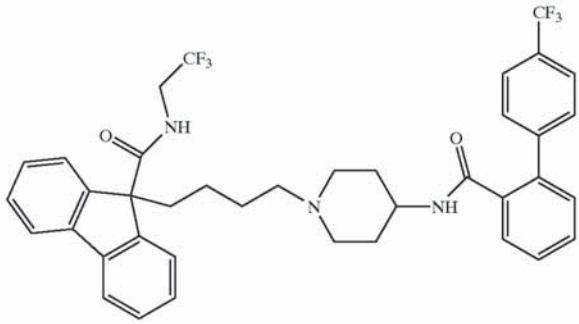
Compound Number	Structure
M-3	
M-4	
M-5	
M-6	
M-7	

TABLE 4b-continued

Compound Number	Structure
M-8	
M-9	

[0110] Cholesterol absorption antagonist compounds useful in the combinations and methods of the present invention comprise a wide variety of structures and functionalities. Some of the cholesterol absorption antagonist compounds of particular interest for use in the present invention are described in U.S. Pat. No. 5,767,115, herein incorporated by reference. Further cholesterol absorption antagonist compounds of particular interest for use in the present invention, and methods for making such cholesterol absorption antagonist compounds are described in U.S. Pat. No. 5,631,365, herein incorporated by reference. A particularly preferred cholesterol absorption antagonist for use in the combinations and methods of the present invention is SCH 58235 ([3R-[3α(S*),4β]]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone).

[0111] In another embodiment the present invention includes a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of a phytosterol compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds. A number of phytosterols are described by Ling and Jones in "Dietary Phytosterols: A Review of Metabolism, Benefits and Side Effects,"*Life Sciences,* 57 (3), 195-206 (1995). Without limitation, some phytosterols of particular use in the the combination of the present invention are shown in Table 4c. Phytosterols are also referred to generally by Nes (*Physiology and Biochemistry of Sterols*, American Oil Chemists' Society, Champaign, Ill., 1991, Table 7-2). Especially preferred among the phytosterols for use in the combination of the present invention are saturated phytosterols or stanols. Additional stanols are also described by Nes (Id.) and are useful in the combination of the present invention. In the combination of the present invention, the phytosterol preferably comprises a stanol. In one preferred embodiment the stanol is campestanol. In another preferred embodiment the stanol is cholestanol. In another preferred embodiment the stanol is clionastanol. In another preferred embodiment the stanol is coprostanol. In another preferred embodiment the stanol is 22,23-dihydrobrassicastanol. In another preferred embodiment the stanol is epicholestanol. In another Preferred embodiment the stanol is fucostanol. In another preferred embodiment the stanol is stigmastanol. In the combination of the present invention, the IBAT inhibitor is preferably a benzothiazepine IBAT inhibitor. In one preferred embodiment, the benzothiazepine IBAT inhibitor is compound B-2. In another preferred embodiment, the benzothiazepine IBAT inhibitor is compound B-7. In yet another preferred embodiment, the IBAT inhibitor is a benzothiepine IBAT inhibitor. Each of the following benzothiepine IBAT inhibitors represents a separate preferred embodiment of the present invention.

[0112] B-1.

[0113] B-3.

[0114] B-4.

[0115] B-5.

[0116] B-6.

[0117] B-8.

[0118] B-9.

[0119] B-10.

[0120] B-11.

[0121] B-12.

[0122] B-13.

[0123] B-14.

[0124] B-15.

[0125] B-16.

[0126] B-17.

[0127] B-18.

[0128] B-19.

[0129] B-21.

[0130] B-22.

[0131] B-23.

[0132] B-24.

[0133] B-25.

[0134] B-26.

[0135] B-27.

[0136] B-28.

[0137] B-29.

[0138] B-30.

[0139] B-31.

[0140] B-32.

[0141] B-33.

[0142] B-34.

[0143] B-35.

[0144] B-36.

[0145] B-37.

[0146] B-38.

[0147] B-39.

[0148] In yet another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor, for example, compound B-20.

TABLE 4c

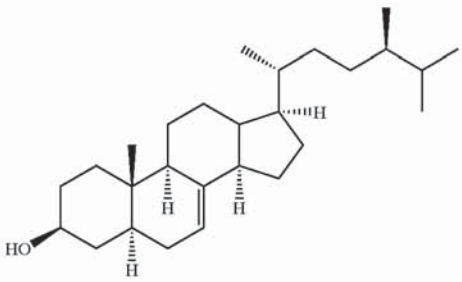
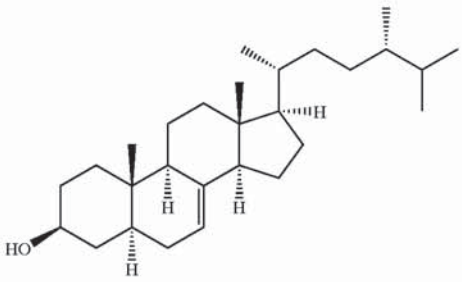
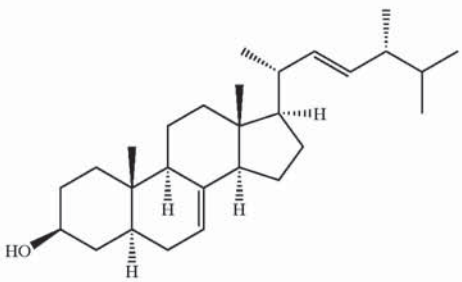
Compound No.	Compound Structure	Compound Name
P-1		Campesterol
P-2		22-Dihydrobrassicasterol
P-3		Brassicasterol

TABLE 4c-continued

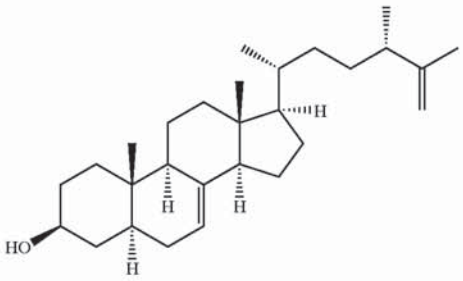
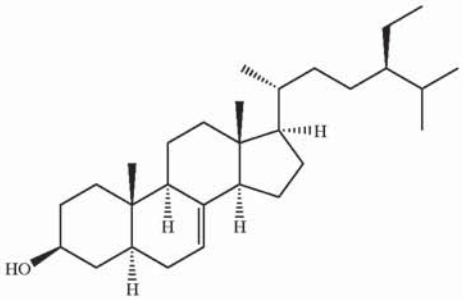
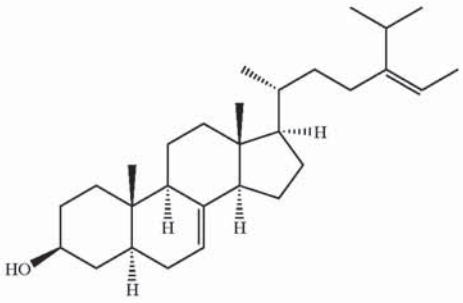
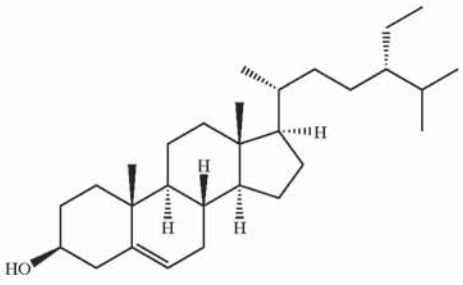
Compound No.	Compound Structure	Compound Name
P-4		Codisterol
P-5		β-sitosterol
P-6		α-sitosterol
P-7		γ-sitosterol

TABLE 4c-continued

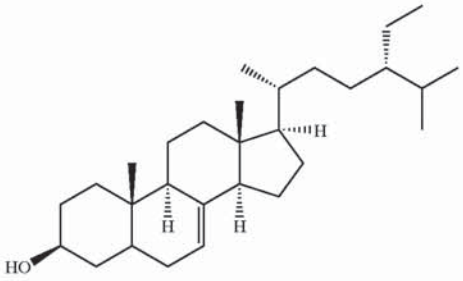
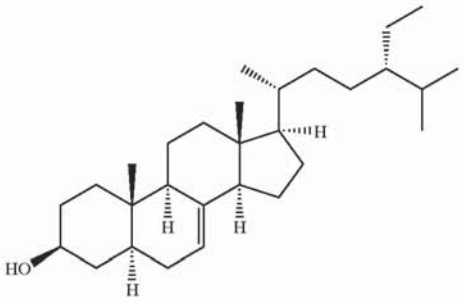
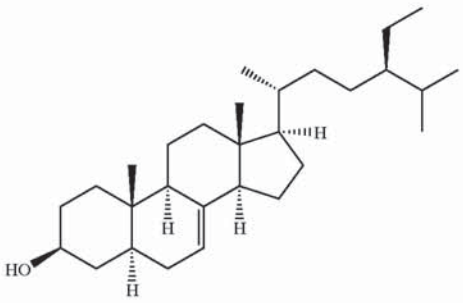
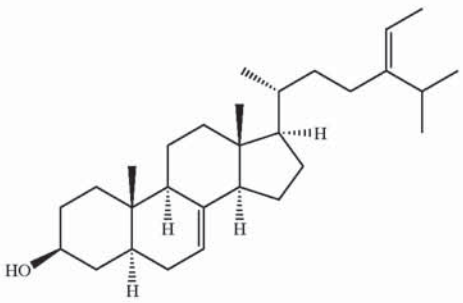
Compound No.	Compound Structure	Compound Name
P-8		Clionasterol
P-9		Poriferasterol
P-10		Stigmasterol
P-11		Isofucosterol

TABLE 4c-continued

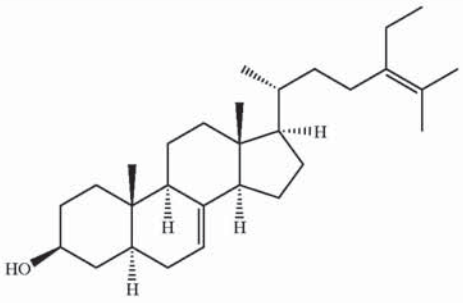
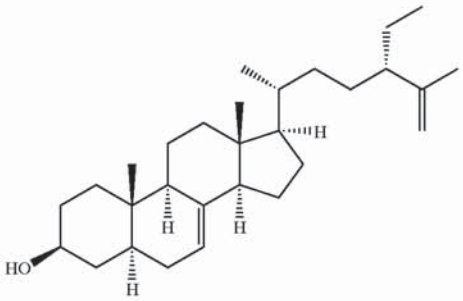
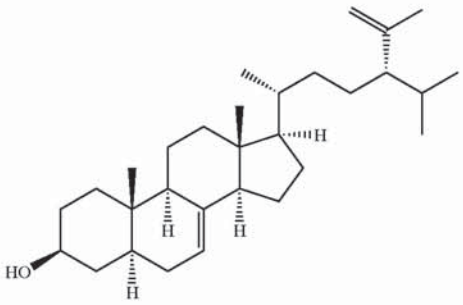
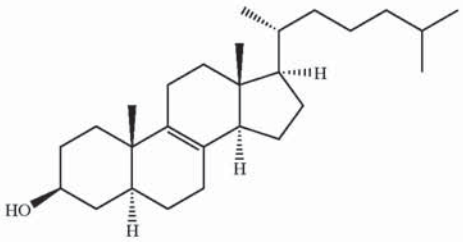
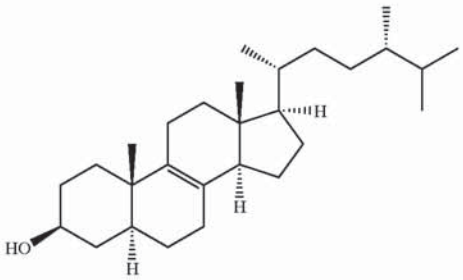
Compound No.	Compound Structure	Compound Name
P-12		Fucosterol
P-13		Clerosterol
P-14		Nervisterol
P-15		Lathosterol
P-16		Fungisterol

TABLE 4c-continued

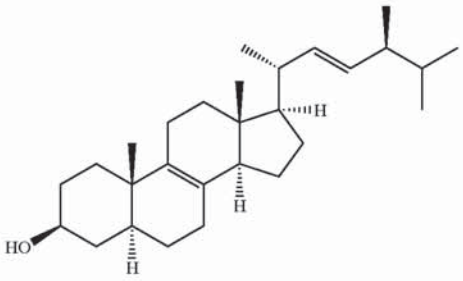
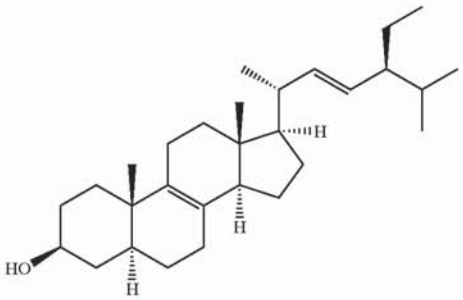
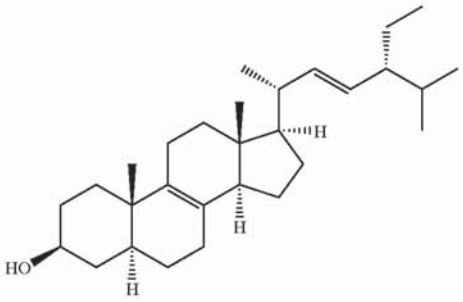
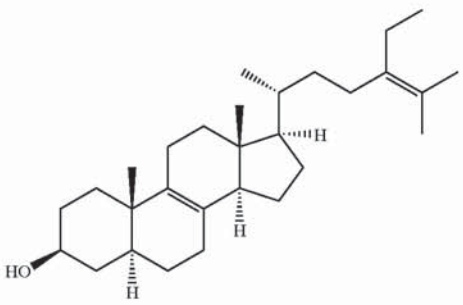
Compound No.	Compound Structure	Compound Name
P-17		Stellasterol
P-18		Spinasterol
P-19		Chondrillasterol
P-20		Peposterol

TABLE 4c-continued

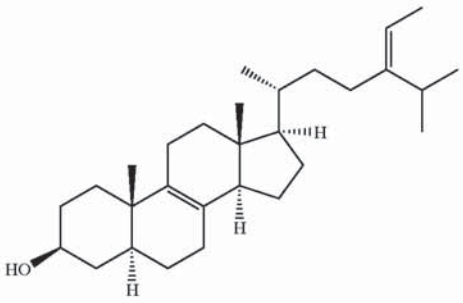
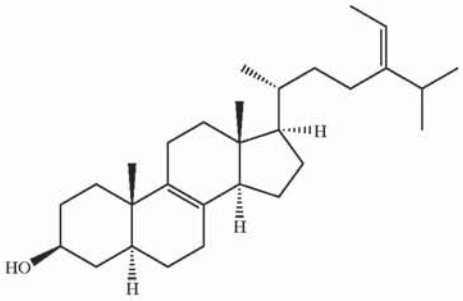
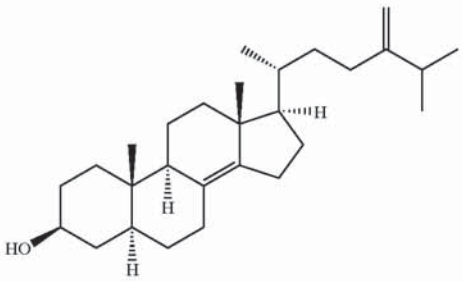
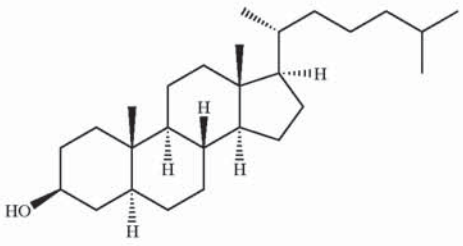
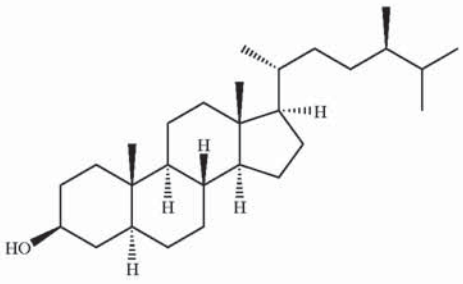
Compound No.	Compound Structure	Compound Name
P-21		Avenasterol
P-22		Isoavenasterol
P-23		Fecosterol
P-24		Cholestanol
P-25		Campestanol

TABLE 4c-continued

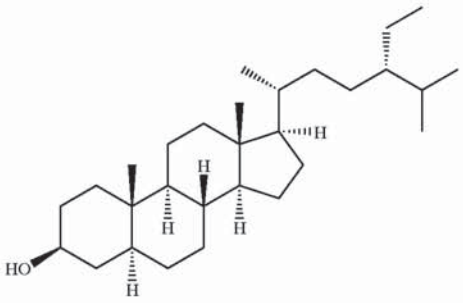
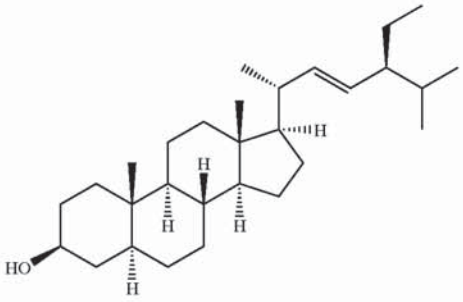
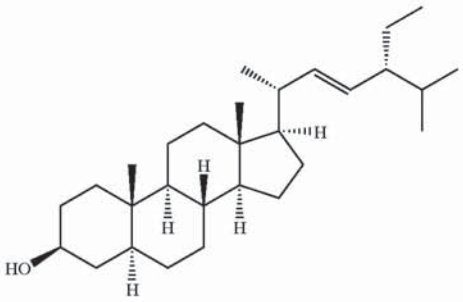
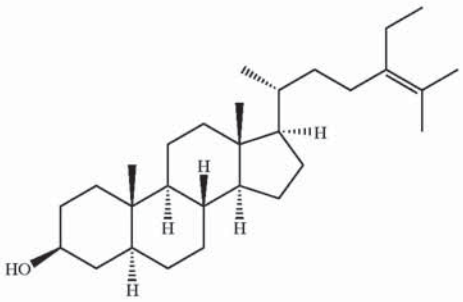
Compound No.	Compound Structure	Compound Name
P-26		24β-Ethylcholestanol
P-27		24α-Ethyl-22-dehydrocholestanol
P-28		24β-Ethyl-22-dehydrocholestanol
P-29		24-Ethyl-24(25)-dehydrocholestanol

TABLE 4c-continued

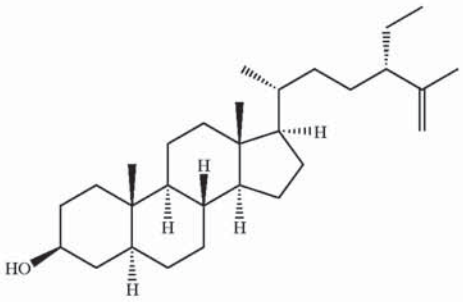
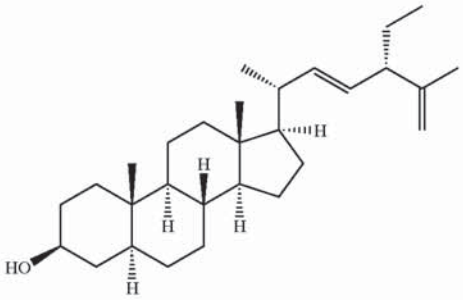
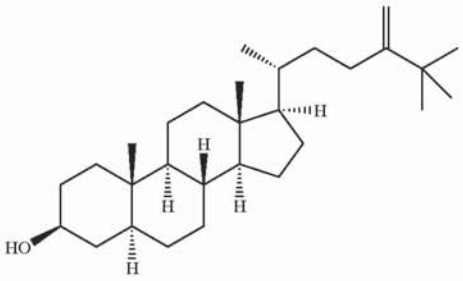
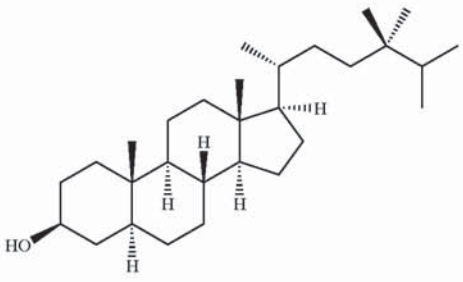
Compound No.	Compound Structure	Compound Name
P-30		24β-Ethyl-25-dehydrocholestanol
P-31		24β-Ethyl-22,25-bisdehydrocholestanol
P-32		24-Methylene-25-methylcholestanol
P-33		24,24-Dimethylcholestanol

TABLE 4c-continued

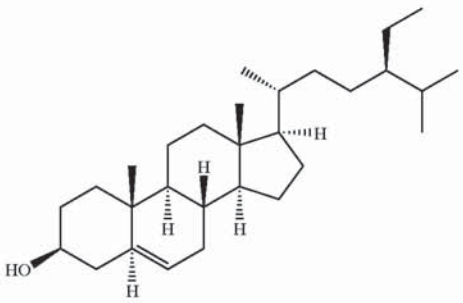
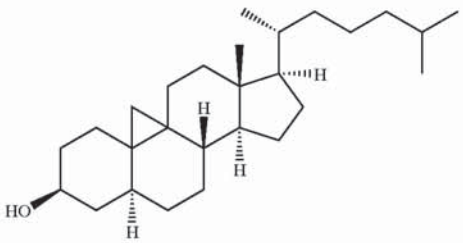
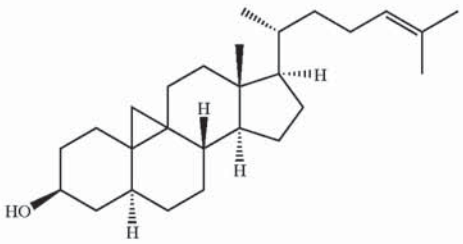
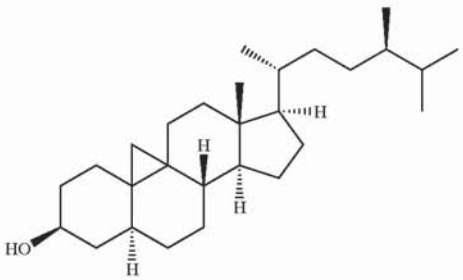
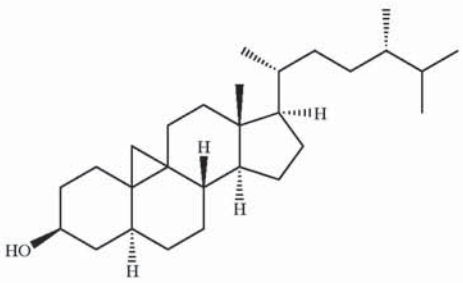
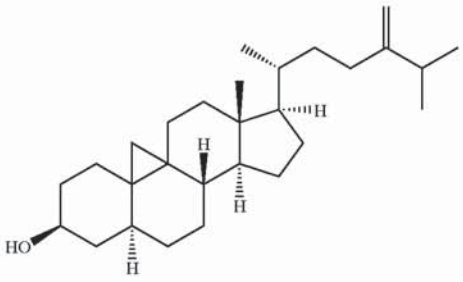
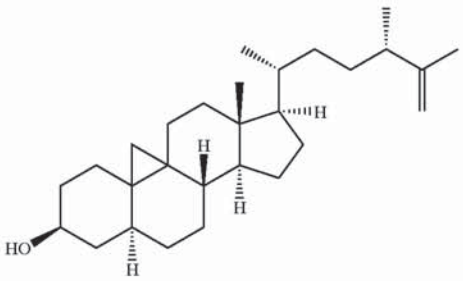
Compound No.	Compound Structure	Compound Name
P-34		24α-Ethylcholestan-3α-ol
P-35		Pollinastanol
P-36		24-Dehydropollinastanol
P-37		24-α-Methylpollinastanol
P-38		24-β-Methylpollinastanol

TABLE 4c-continued

Compound No.	Compound Structure	Compound Name
P-39		24-Methylenepollinastanol
P-40		24β-Methyl-25-dehydropollinastanol

[0149] In another embodiment the present invention encompasses a therapeutic combination of an IBAT inhibitor and an antihypertensive agent. Hypertension is defined as persistently high blood pressure. Generally, adults are classified as being hypertensive when systolic blood pressure is persistently above 140 mmHg or when diastolic blood pressure is above 90 mmHg. Long-term risks for cardiovascular mortality increase in a direct relationship with persistent blood pressure. (E. Braunwald, *Heart Disease,* 5th ed., W.B. Saunders & Co., Philadelphia, 1997, pp. 807-823.) Blood pressure is a function of cardiac output and peripheral resistance of the vascular system and can be represented by the following equation:

$$BP=CO\times PR$$

[0150] wherein BP is blood pressure, CO is cardiac output, and PR is peripheral resistance. (Id., p. 816.) Factors affecting peripheral resistance include obesity and/or functional constriction. Factors affecting cardiac output include venous constriction. Functional constriction of the blood vessels can be caused by a variety of factors including thickening of blood vessel walls resulting in diminishment of the inside diameter of the vessels. Another factor which affects systolic blood pressure is rigidity of the aorta (Id., p. 811.)

[0151] Hypertension and atherosclerosis or other hyperlipidemic conditions often coexist in a patient. It is possible that certain hyperlipidemic conditions such as atherosclerosis can have a direct or indirect affect on hypertension. For example, atherosclerosis frequently results in diminishment of the inside diameter of blood vessels. Furthermore, atherosclerosis frequently results in increased rigidity of blood vessels, including the aorta. Both diminished inside diameter of blood vessels and rigidity of blood vessels are factors which contribute to hypertension.

[0152] Myocardial infarction is the necrosis of heart muscle cells resulting from oxygen deprivation and is usually caused by an obstruction of the supply of blood to the affected tissue. For example, hyperlipidemia or hypercholesterolemia can cause the formation of atherosclerotic plaques which can cause obstruction of blood flow and thereby cause myocardial infarction. (Id., pp. 1185-1187.) Another major risk factor for myocardial infarction is hypertension. (Id., p. 815.) In other words, hypertension and hyperlipidemic conditions such as atherosclerosis or hypercholesterolemia work in concert to cause myocardial infarction.

[0153] Coronary heart disease is another disease which is caused or aggravated by multiple factors including hyperlipidemic conditions and hypertension. Control of both hyperlipidemic conditions and hypertension are important to control symptoms or disease progression of coronary heart disease.

[0154] Angina pectoris is acute chest pain which is caused by decreased blood supply to the heart. Decreased blood supply to the heart is known as myocardial ischemia. Angina pectoris can be the result of, for example, stenosis of the aorta, pulmonary stenosis, and ventricular hypertrophy. Some antihypertensive agents, for example amlodipine, control angina pectoris by reducing peripheral resistance.

[0155] It is now disclosed that a therapy which controls hypertension and which in combination controls hyperlipidemic conditions will reduce risk from cardiovascular disease or symptoms of heart disease, for example coronary heart disease, myocardial infarction, or angina pectoris. Therefore one embodiment of the present invention is directed to a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound

and a second amount of an antihypertensive agent compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

[0156] Some antihypertensive agents useful in the present invention are shown in Table 5, without limitation. A wide variety of chemical structures are useful as antihypertensive agents in the combinations of the present invention and the agents can operate by a variety of mechanisms. For example, useful antihypertensive agents can include, without limitation, an andrenergic blocker, a mixed alpha/beta andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, an andrenergic stimulant, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a diuretic, or a vasodilator. Additional hypertensive agents useful in the present invention are described by R. Scott in U.S. Patent Application No. 60/057,276 (priority document for PCT Patent Application No. WO 99/11260), herein incorporated by reference.

TABLE 5

Compound Number	Antihypertensive Classification	Compound Name	Dosage
N-1	andrenergic blocker	phenoxybenzamine	1–250 mg/day
N-2	andrenergic blocker	guanadrel	5–60 mg/day
N-3	andrenergic blocker	guanethidine	
N-4	andrenergic blocker	reserpine	
N-5	andrenergic blocker	terazosin	0.1–60 mg/day
N-6	andrenergic blocker	prazosin	0.5–75 mg/day
N-7	andrenergic blocker	polythiazide	0.25–10 mg/day
N-8	andrenergic stimulant	methyldopa	100–4000 mg/day
N-9	andrenergic stimulant	methyldopate	100–4000 mg/day
N-10	andrenergic stimulant	clonidine	0.1–2.5 mg/day
N-11	andrenergic stimulant	chlorthalidone	10–50 mg/day
N-12	andrenergic stimulant	guanfacine	0.25–5 mg/day
N-13	andrenergic stimulant	guanabenz	2–40 mg/day
N-14	andrenergic stimulant	trimethaphan	
N-15	alpha/beta andrenergic blocker	carvedilol	6–25 mg bid
N-16	alpha/beta andrenergic blocker	labetalol	10–500 mg/day
N-17	beta andrenergic blocker	propranolol	10–1000 mg/day
N-18	beta andrenergic blocker	metoprolol	10–500 mg/day
N-19	alpha andrenergic blocker	doxazosin	1–16 mg/day
N-20	alpha andrenergic blocker	phentolamine	
N-21	angiotensin converting enzyme inhibitor	quinapril	1–250 mg/day
N-22	angiotensin converting enzyme inhibitor	perindopril erbumine	1–25 mg/day
N-23	angiotensin converting enzyme inhibitor	ramipril	0.25–20 mg/day
N-24	angiotensin converting enzyme inhibitor	captopril	6–50 mg bid or tid
N-25	angiotensin converting enzyme inhibitor	trandolapril	0.25–25 mg/day
N-26	angiotensin converting enzyme inhibitor	fosinopril	2–80 mg/day
N-27	angiotensin converting enzyme inhibitor	lisinopril	1–80 mg/day
N-28	angiotensin converting enzyme inhibitor	moexipril	1–100 mg/day
N-29	angiotensin converting enzyme inhibitor	enalapril	2.5–40 mg/day
N-30	angiotensin converting enzyme inhibitor	benazepril	10–80 mg/day
N-31	angiotensin II receptor antagonist	candesartan cilexetil	2–32 mg/day
N-32	angiotensin II receptor antagonist	inbesartan	
N-33	angiotensin II receptor antagonist	losartan	10–100 mg/day
N-34	angiotensin II receptor antagonist	valsartan	20–600 mg/day
N-35	calcium channel blocker	verapamil	100–600 mg/day
N-36	calcium channel blocker	diltiazem	150–500 mg/day
N-37	calcium channel blocker	nifedipine	1–200 mg/day
N-38	calcium channel blocker	nimodipine	5–500 mg/day
N-39	calcium channel blocker	delodipine	
N-40	calcium channel blocker	nicardipine	1–20 mg/hr i.v.; 5–100 mg/day oral
N-41	calcium channel blocker	isradipine	
N-42	calcium channel blocker	amlodipine	2–10 mg/day
N-43	diuretic	hydrochlorothiazide	5–100 mg/day
N-44	diuretic	chlorothiazide	250–2000 mg bid or tid
N-45	diuretic	furosemide	5–1000 mg/day
N-46	diuretic	bumetanide	
N-47	diuretic	ethacrynic acid	20–400 mg/day

TABLE 5-continued

Compound Number	Antihypertensive Classification	Compound Name	Dosage
N-48	diuretic	amiloride	1–20 mg/day
N-49	diuretic	triameterene	
N-50	diuretic	spironolactone	5–1000 mg/day
N-51	diuretic	eplerenone	10–150 mg/day
N-52	vasodilator	hydralazine	5–300 mg/day
N-53	vasodilator	minoxidil	1–100 mg/day
N-54	vasodilator	diazoxide	1–3 mg/kg
N-55	vasodilator	nitroprusside	

[0157] Additional calcium channel blockers which are useful in the combinations of the present invention include, without limitation, those shown in Table 5a.

TABLE 5a

Compound Number	Compound Name	Reference
N-56	bepridil	U.S. Pat. No. 3,962,238 or U.S. Reissue No. 30,577
N-57	clentiazem	U.S. Pat. No. 4,567,175
N-58	diltiazem	U.S. Pat. No. 3,562,257
N-59	fendiline	U.S. Pat. No. 3,262,977
N-60	gallopamil	U.S. Pat. No. 3,261,859
N-61	mibefradil	U.S. Pat. No. 4,808,605
N-62	prenylamine	U.S. Pat. No. 3,152,173
N-63	semotiadil	U.S. Pat. No. 4,786,635
N-64	terodiline	U.S. Pat. No. 3,371,014
N-65	verapamil	U.S. Pat. No. 3,261,859
N-66	aranipine	U.S. Pat. No. 4,572,909
N-67	bamidipine	U.S. Pat. No. 4,220,649
N-68	benidipine	European Patent Application Publication No. 106,275
N-69	cilnidipine	U.S. Pat. No. 4,672,068
N-70	efonidipine	U.S. Pat. No. 4,885,284
N-71	elgodipine	U.S. Pat. No. 4,962,592
N-72	felodipine	U.S. Pat. No. 4,264,611
N-73	isradipine	U.S. Pat. No. 4,466,972
N-74	lacidipine	U.S. Pat. No. 4,801,599
N-75	lercanidipine	U.S. Pat. No. 4,705,797
N-76	manidipine	U.S. Pat. No. 4,892,875
N-77	nicardipine	U.S. Pat. No. 3,985,758
N-78	nifendipine	U.S. Pat. No. 3,485,847
N-79	nilvadipine	U.S. Pat. No. 4,338,322
N-80	nimodipine	U.S. Pat. No. 3,799,934
N-81	nisoldipine	U.S. Pat. No. 4,154,839
N-82	nitrendipine	U.S. Pat. No. 3,799,934
N-83	cinnarizine	U.S. Pat. No. 2,882,271
N-84	flunarizine	U.S. Pat. No. 3,773,939
N-85	lidoflazine	U.S. Pat. No. 3,267,104
N-86	lomerizine	U.S. Pat. No. 4,663,325
N-87	bencyclane	Hungarian Pat. No. 151,865
N-88	etafenone	German Patent No. 1,265,758
N-89	perhexiline	British Patent No. 1,025,578

[0158] Additional ACE inhibitors which are useful in the combinations of the present invention include, without limitation, those shown in Table 5b.

TABLE 5b

Compound Number	Compound Name	Reference
N-90	alacepril	U.S. Pat. No. 4,248,883
N-91	benazepril	U.S. Pat. No. 4,410,520

TABLE 5b-continued

Compound Number	Compound Name	Reference
N-92	captopril	U.S. Pat. Nos. 4,046,889 and 4,105,776
N-93	ceronapril	U.S. Pat. No. 4,452,790
N-94	delapril	U.S. Pat. No. 4,385,051
N-95	enalapril	U.S. Pat. No. 4,374,829
N-96	fosinopril	U.S. Pat. No. 4,337,201
N-97	imadapril	U.S. Pat. No. 4,508,727
N-98	lisinopril	U.S. Pat. No. 4,555,502
N-99	moveltopril	Belgian Patent No. 893,553
N-100	perindopril	U.S. Pat. No. 4,508,729
N-101	quinapril	U.S. Pat. No. 4,344,949
N-102	ramipril	U.S. Pat. No. 4,587,258
N-103	spirapril	U.S. Pat. No. 4,470,972
N-104	temocapril	U.S. Pat. No. 4,699,905
N-105	trandolapril	U.S. Pat. No. 4,933,361

[0159] Additional beta andrenergic blockers which are useful in the combinations of the present invention include, without limitation, those shown in Table 5C.

TABLE 5c

Compound Number	Compound Name	Reference
N-106	acebutolol	U.S. Pat. No. 3,857,952
N-107	alprenolol	Netherlands Patent Application No. 6,605,692
N-108	amosulalol	U.S. Pat. No. 4,217,305
N-109	arotinolol	U.S. Pat. No. 3,932,400
N-110	atenolol	U.S. Pat. No. 3,663,607 or 3,836,671
N-111	befunolol	U.S. Pat. No. 3,853,923
N-112	betaxolol	U.S. Pat. No. 4,252,984
N-113	bevantolol	U.S. Pat. No. 3,857,981
N-114	bisoprolol	U.S. Pat. No. 4,171,370
N-115	bopindolol	U.S. Pat. No. 4,340,641
N-116	bucumolol	U.S. Pat. No. 3,663,570
N-117	bufetolol	U.S. Pat. No. 3,723,476
N-118	bufuralol	U.S. Pat. No. 3,929,836
N-119	bunitrolol	U.S. Pat. Nos. 3,940,489 and 3,961,071
N-120	buprandolol	U.S. Pat. No. 3,309,406
N-121	butiridine hydrochloride	French Patent No. 1,390,056
N-122	butofilolol	U.S. Pat. No. 4,252,825
N-123	carazolol	German Patent No. 2,240,599
N-124	carteolol	U.S. Pat. No. 3,910,924
N-125	carvedilol	U.S. Pat. No. 4,503,067
N-126	celiprolol	U.S. Pat. No. 4,034,009
N-127	cetamolol	U.S. Pat. No. 4,059,622
N-128	cloranolol	German Patent No. 2,213,044
N-129	dilevalol	Clifton et al., Journal of Medicinal Chemistry, 1982 25, 670
N-130	epanolol	European Patent Publication Application No. 41,491
N-131	indenolol	U.S. Pat. No. 4,045,482
N-132	labetalol	U.S. Pat. No. 4,012,444
N-133	levobunolol	U.S. Pat. No. 4,463,176
N-134	mepindolol	Seeman et al., Helv. Chim. Acta, 1971, 54, 241
N-135	metipranolol	Czechoslovakian Patent Application No. 128,471
N-136	metoprolol	U.S. Pat. No. 3,873,600
N-137	moprolol	U.S. Pat. No. 3,501,769
N-138	nadolol	U.S. Pat. No. 3,935,267
N-139	nadoxolol	U.S. Pat. No. 3,819,702
N-140	nebivalol	U.S. Pat. No. 4,654,362
N-141	nipradilol	U.S. Pat. No. 4,394,382

TABLE 5c-continued

Compound Number	Compound Name	Reference
N-142	oxprenolol	British Patent No. 1,077,603
N-143	perbutolol	U.S. Pat. No. 3,551,493
N-144	pindolol	Swiss Patent Nos. 469,002 and 472,404
N-145	practolol	U.S. Pat. No. 3,408,387
N-146	pronethalol	British Patent No. 909,357
N-147	propranolol	U.S. Pat. Nos. 3,337,628 and 3,520,919
N-148	sotalol	Uloth et al., Journal of Medicinal Chemistry, 1966, 9, 88
N-149	sufinalol	German Patent No. 2,728,641
N-150	talindol	U.S. Pat. Nos. 3,935,259 and 4,038,313
N-151	tertatolol	U.S. Pat. No. 3,960,891
N-152	tilisolol	U.S. Pat. No. 4,129,565
N-153	timolol	U.S. Pat. No. 3,655,663
N-154	toliprolol	U.S. Pat. No. 3,432,545
N-155	xibenolol	U.S. Pat. No. 4,018,824

[0160] Additional alpha andrenergic blockers which are useful in the combinations of the present invention include, without limitation, those shown in Table 5d.

TABLE 5d

Compound Number	Compound Name	Reference
N-156	amosulalol	U.S. Pat. No. 4,217,307
N-157	arotinolol	U.S. Pat. No. 3,932,400
N-158	dapiprazole	U.S. Pat. No. 4,252,721
N-159	doxazosin	U.S. Pat. No. 4,188,390
N-160	fenspirlde	U.S. Pat. No. 3,399,192
N-161	indoramin	U.S. Pat. No. 3,527,761
N-162	labetalol	U.S. Pat. No. 4,012,444
N-163	naftopidil	U.S. Pat. No. 3,997,666
N-164	nicergoline	U.S. Pat. No. 3,228,943
N-165	prazosin	U.S. Pat. No. 3,511,836
N-166	tamsulosin	U.S. Pat. No. 4,703,063
N-167	tolazoline	U.S. Pat. No. 2,161,938
N-168	trimazosin	U.S. Pat. No. 3,669,968
N-169	yohimbine	Raymond-Hamet, J. Pharm. Chim., 19, 209 (1934)

[0161] Additional angiotensin II receptor antagonists which are useful in the combinations of the present invention include, without limitation, those shown in Table 5e.

TABLE 5e

Compound Number	Compound Name	Reference
N-170	candesartan	U.S. Pat. No. 5,196,444
N-171	eprosartan	U.S. Pat. No. 5,185,351
N-172	irbesartan	U.S. Pat. No. 5,270,317
N-173	losartan	U.S. Pat. No. 5,138,069
N-174	valsartan	U.S. Pat. No. 5,399,578

[0162] Additional vasodilators which are useful in the combinations of the present invention include, without limitation, those shown in Table 5F.

TABLE 5f

Compound Number	Compound Name	Reference
N-175	aluminum nicotinate	U.S. Pat. No. 2,970,082
N-176	amotriphene	U.S. Pat. No. 3,010,965
N-177	bamethan	Corrigan et al., Journal of the American Chemical Society, 1945, 67, 1894
N-178	bencyclane	Hungarian Patent No. 151,865
N-180	bendazol	J. Chem. Soc., 1968, 2426
N-181	benfurodil hemisuccinate	U.S. Pat. No. 3,355,463
N-182	benziodarone	U.S. Pat. No. 3,012,042
N-183	betahistine	Walter et al.; Journal of the American Chemical Society, 1941, 63, 2771
N-184	bradykinin	Hamburg et al., Arch. Biochem. Biophys., 1958, 76, 252
N-185	brovincamine	U.S. Pat. No. 4,146,643
N-186	bufeniode	U.S. Pat. No. 3,542,870
N-187	buflomedil	U.S. Pat. No. 3,895,030
N-188	butalamine	U.S. Pat. No. 3,338,899
N-189	cetiedil	French Patent No. 1,460,571
N-190	chloracizine	British Patent No. 740,932
N-191	chromonar	U.S. Pat. No. 3,282,938
N-192	ciclonicate	German Patent No. 1,910,481
N-194	cinepazide	Belgian Patent No. 730,345
N-195	cinnarizine	U.S. Pat. No. 2,882,271
N-197	citicoline	Kennedy et al., Journal of the American Chemical Society, 1955, 77, 250 or synthesized as disclosed in Kennedy, Journal of Biological Chemistry, 1956, 222, 185
N-198	clobenfural	British Patent No. 1,160,925
N-199	clonitrate	see Annalen, 1870, 155, 165
N-200	cloricromen	U.S. Pat. No. 4,452,811
N-201	cyclandelate	U.S. Pat. No. 2,707,193
N-203	diisopropylamine dichloroacetate	Neutralization of dichloroacetic acid with diisopropyl amine
N-204	diisopropylamine dichloroacetate	British Patent No. 862,248
N-205	dilazep	U.S. Pat. No. 3,532,685
N-206	dipyridamole	British Patent No. 807,826
N-207	droprenilamine	German Patent No. 2,521,113
N-208	ebumamonine	Hermann et al., Journal of the American Chemical Society, 1979, 101, 1540
N-209	efloxate	British Patent Nos. 803,372 and 824,547
N-210	eledoisin	British Patent No. 984,810
N-211	erythrityl tetranitrate	May be prepared by nitration of erythritol according to methods well-known to those skilled in the art. See e.g., Merck Index.
N-212	etafenone	German Patent No. 1,265,758
N-213	fasudil	U.S. Pat. No. 4,678,783
N-214	fendiline	U.S. Pat. No. 3,262,977
N-215	fenoxedil	U.S. Pat. No. 3,818,021 or German Patent No. 1,964,712
N-217	floredil	German Patent No. 2,020,464
N-218	flunarizine	German Patent No. 1,929,330 or French Patent No. 2,014,487
N-219	flunarizine	U.S. Pat. No. 3,773,939
N-220	ganglefene	U.S.S.R. Patent No. 115,905
N-221	hepronicate	U.S. Pat. No. 3,384,642
N-222	hexestrol	U.S. Pat. No. 2,357,985
N-223	hexobendine	U.S. Pat. No. 3,267,103
N-224	ibudilast	U.S. Pat. No. 3,850,941
N-225	ifenprodil	U.S. Pat. No. 3,509,164

TABLE 5f-continued

Compound Number	Compound Name	Reference
N-227	iloprost	U.S. Pat. No. 4,692,464
N-228	inositol niacinate	Badgett et al., Journal of the American Chemical Society, 1947, 69, 2907
N-229	isoxsuprine	U.S. Pat. No. 3,056,836
N-230	itramin tosylate	Swedish Patent No. 168,308
N-231	kallidin	Biochem. Biophys. Re& Commun., 1961, 6, 210
N-232	kallikrein	German Patent No. 1,102,973
N-233	khellin	Baxter et al., Journal of the Chemical Society, 1949, S 30
N-234	lidofiazine	U.S. Pat. No. 3,267,104
N-235	lomerizine	U.S. Pat. No. 4,663,325
N-236	mannitol hexanitrate	may be prepared by the nitration of mannitol according to methods well-known to those skilled in the art
N-237	medibazine	U.S. Pat. No. 3,119,826
N-238	moxisylyte	German Patent No. 905,738
N-239	nafronyl	U.S. Pat. No. 3,334,096
N-241	nicametate	Blicke & Jenner, J. Am. Chem. Soc., 64, 1722 (1942)
N-243	nicergoline	U.S. Pat. No. 3,228,943
N-245	nicofuranose	Swiss Patent No. 366,523
N-246	nimodipine	U.S. Pat. No. 3,799,934
N-247	nitroglycerin	Sobrero, Ann., 64, 398 (1847)
N-248	nylidrin	U.S. Pat. Nos. 2,661,372 and 2,661,373
N-249	papaverine	Goldberg, Chem. Prod. Chem. News, 1954, 17, 371
N-250	pentaerythritol tetranitrate	U.S. Pat. No. 2,370,437
N-251	pentifylline	German Patent No. 860,217
N-253	pentoxifylline	U.S. Pat. No. 3,422,107
N-254	pentrinitrol	German Patent No. 638,422-3
N-255	perhexilline	British Patent No. 1,025,578
N-256	pimefylline	U.S. Pat. No. 3,350,400
N-257	piribedil	U.S. Pat. No. 3,299,067
N-258	prenylamine	U.S. Pat. No. 3,152,173
N-259	propatyl nitrate	French Patent No. 1,103,113
N-260	prostaglandin El	may be prepared by any of the methods referenced in the Merck Index, Twelfth Edition, Budaved, Ed., New Jersey, 1996, p. 1353
N-261	suloctidil	German Patent No. 2,334,404
N-262	tinofedrine	U.S. Pat. No. 3,563,997
N-263	tolazoline	U.S. Pat. No. 2,161,938
N-264	trapidil	East German Patent No. 55,956
N-265	tricromyl	U.S. Pat. No. 2,769,015
N-266	trimetazidine	U.S. Pat. No. 3,262,852
N-267	trolnitrate phosphate	French Patent No. 984,523 or German Patent No. 830,955
N-268	vincamine	U.S. Pat. No. 3,770,724
N-269	vinpocetine	U.S. Pat. No. 4,035,750
N-270	viquidil	U.S. Pat. No. 2,500,444
N-271	visnadine	U.S. Pat. Nos. 2,816,118 and 2,980,699
N-272	xanthinol niacinate	German Patent No. 1,102,750 or Korbonits et al., Acta. Pharm. Hung., 1968, 38, 98

[0163] Additional diuretics which are useful in the combinations of the present invention include, without limitation, those shown in Table 5g.

TABLE 5g

Compound Nunber	Compound Name	Reference
N-273	acetazolamide	U.S. Pat. No. 2,980,679
N-274	althiazide	British Patent No. 902,658
N-275	amanozine	Austrian Patent No. 168,063
N-276	ambuside	U.S. Pat. No. 3,188,329
N-277	amiloride	Belgian Patent No. 639,386
N-278	arbutin	Tschb&habln, Annalen, 1930, 479, 303
N-279	azosemide	U.S. Pat. No. 3,665,002
N-280	bendroflumethiazide	U.S. Pat. No. 3,265,573
N-281	benzthiazide	McManus et al., 136th Am. Soc. Meeting (Atlantic City, September 1959). Abstract of Papers, pp 13-O
N-282	benzylhydro-chlorothiazide	U.S. Pat. No. 3,108,097
N-283	bumetanide	U.S. Pat. No. 3,634,583
N-284	butazolamide	British Patent No. 769,757
N-285	buthiazide	British Patent Nos. 861,367 and 885,078
N-286	chloraminophenamide	U.S. Pat. Nos. 2,809,194, 2,965,655 and 2,965,656
N-287	chlorazanil	Austrian Patent No. 168,063
N-288	chlorothiazide	U.S. Pat. Nos. 2,809,194 and 2,937,169
N-289	chlorthalidone	U.S. Pat. No. 3,055,904
N-290	clofenamide	Olivier, Rec. Trav. Chim., 1918, 37, 307
N-291	clopamide	U.S. Pat. No. 3,459,756
N-292	clorexolone	U.S. Pat. No. 3,183,243
N-293	cyclopenthiazide	Belgian Patent No. 587,225
N-294	cyclothiazide	Whitehead et al., Journal of Organic Chemistry, 1961, 26, 2814
N-295	disulfamide	British Patent No. 851,287
N-296	epithiazide	U.S. Pat. No. 3,009,911
N-297	ethacrynic acid	U.S. Pat. No. 3,255,241
N-298	ethiazide	British Patent No. 861,367
N-299	ethoxolamide	British Patent No. 795,174
N-300	etozolin	U.S. Pat. No. 3,072,653
N-301	fenquizone	U.S. Pat. No. 3,870,720
N-302	furosemide	U.S. Pat. No. 3,058,882
N-303	hydracarbazine	British Patent No. 856,409
N-304	hydrochlorothiazide	U.S. Pat. No. 3,164,588
N-305	hydroflumethiazide	U.S. Pat. No. 3,254,076
N-306	indapamide	U.S. Pat. No. 3,565,911
N-307	isosorbide	U.S. Pat. No. 3,160,641
N-308	mannitol	U.S. Pat. No. 2,642,462; or 2,749,371; or 2,759,024
N-309	mefruside	U.S. Pat. No. 3,356,692
N-310	methazolamide	U.S. Pat. No. 2,783,241
N-311	methyclothiazide	Close et al., Journal of the American Chemical Society, 1960, 82, 1132
N-312	meticrane	French Patent Nos. M2790 and 1,365,504
N-313	metochalcone	Freudenberg et al., Ber., 1957, 90, 957
N-314	metolazone	U.S. Pat. No. 3,360,518
N-315	muzolimine	U.S. Pat. No. 4,018,890
N-316	paraflutizide	Belgian Patent No. 620,829
N-317	perhexiline	British Patent No. 1,025,578
N-318	piretanide	U.S. Pat. No. 4,010,273
N-319	polythiazide	U.S. Pat. No. 3,009,911
N-320	quinethazone	U.S. Pat. No. 2,976,289
N-321	teclothiazide	Close et al., Journal of the American Chemical Society, 1960, 82, 1132
N-322	ticrynafen	U.S. Pat. No. 3,758,506
N-323	torasemide	U.S. Pat. No. 4,018,929
N-324	triamterene	U.S. Pat. No. 3,081,230
N-325	trichlormethiazide	deStevens et al., Experientia, 1960, 16, 113

TABLE 5g-continued

Compound Nunber	Compound Name	Reference
N-326	tripamide	Japanese Patent No. 73, 05,585
N-327	urea	Can be purchased from commercial sources
N-328	xipamide	U.S. Pat. No. 3,567,777

[0164] Many of the compounds useful in the present invention can have at least two asymmetric carbon atoms, and therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

[0165] Isomers may include geometric isomers, for example cis-isomers or trans-isomers across a double bond. All such isomers are contemplated among the compounds useful in the present invention.

[0166] The compounds useful in the present invention also include tautomers.

[0167] The compounds useful in the present invention as discussed below include their salts, solvates and prodrugs.

Dosages, Formulations, and Routes of Administration

[0168] The compositions of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of action in the body, for example in the ileum of a mammal, e.g., a human.

[0169] For the prophylaxis or treatment of the conditions referred to above, the compounds useful in the compositions and methods of the present invention can be used as the compound per se. Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, and alkaline earth salts such as magnesium and calcium salts.

[0170] The anions useful in the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from the above list.

[0171] The compounds useful in the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, consisting essentially of admixing the components.

[0172] These compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

[0173] The amount of compound which is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

[0174] In general, a total daily dose of an IBAT inhibitor can be in the range of from about 0.01 to about 1000 mg/day, preferably from about 0.1 mg to about 50 mg/day, more preferably from about 1 to about 10 mg/day.

[0175] A total daily dose of a fibric acid derivative can generally be in the range of from about 1000 to about 3000 mg/day in single or divided doses. Gemfibrozil or clinofibrate, for example, are frequently each administered separately in a 1200 mg/day dose. Clofibrate is frequently administered in a 2000 mg/day dose. Binifibrate is frequently administered in a 1800 mg/day dose.

[0176] Generally a total daily dose of probucol can be in the range of from about 250 to about 2000 mg/day, preferably about 500 to about 1500 mg/day, and more preferably still about 750 to about 1000 mg/day in single or divided doses.

[0177] Generally a total daily dose of a nicotinic acid derivative can be in the range of from about 500 to about 10,000 mg/day, preferably about 1000 to about 8000 mg/day, and more preferably still about 3000 to about 6000 mg/day in single or divided doses.

[0178] For a CETP inhibitor, a daily dose of about 0.01 to about 100 mg/kg body weight/day, and preferably between about 0.5 to about 20 mg/kg body weight/day, may generally be appropriate.

[0179] For stanols, a daily dose of about 1000 to about 4000 mg/kg body weight/day, preferably between about 500 to about 1500 mg/kg body weight/day, and more preferably between about 150 to about 600 mg/kg body weight/day will generally be appropriate.

[0180] For antihypertensive agents, the daily dose will vary depending on the specific mechanism of activity, the chemistry of the antihypertensive agent, and the patient. General dose ranges for specific antihypertensive agents are described in Table 5 or in the Biological Assays section.

[0181] For cholesterol absorption antagonists, a daily dose of about 0.001 to about 500 mg/kg body weight/day, preferably between about 0.05 to about 300 mg/kg body weight/

day, and more preferably between about 1 to about 200 mg/kg body weight/day will generally be appropriate.

[0182] For MTP inhibitors, a daily dose of about 0.001 to about 800 mg/kg body weight/day, preferably between about 0.01 to about 500 mg/kg body weight/day, more preferably between about 0.1 to about 300 mg/kg body weight/day, and more preferably still between about 1 to about 200 mg/kg body weight/day will generally be appropriate.

[0183] The daily doses described in the preceding paragraphs for the various therapeutic compounds can be administered to the patient in a single dose, or in proportionate multiple subdoses. Subdoses can be administered 2 to 6 times per day. Doses can be in sustained release form effective to obtain desired results.

[0184] In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

[0185] Oral delivery of the combinations of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. For some of the therapeutic compounds useful in the present invention (e.g., IBAT inhibitors or CETP inhibitors), the intended effect is to extend the time period over which the active drug molecule is delivered to the site of action (e.g., the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

[0186] The combinations of the present invention can be delivered orally either in a solid, in a semi-solid, or in a liquid form. When in a liquid or in a semi-solid form, the combinations of the present invention can, for example, be in the form of a liquid, syrup, or contained in a gel capsule (e.g., a gel cap). In one embodiment, when a CETP inhibitor is used in a combination of the present invention, the CETP inhibitor can be provided in the form of a liquid, syrup, or contained in a gel capsule.

[0187] When administered intravenously, the dose for an IBAT inhibitor can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight, more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight.

[0188] For a CETP inhibitor the intravenously administered dose can, for example, be in the range of from about 0.003 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.01 mg/kg body weight to about 0.75 mg/kg body weight, more preferably from about 0.1 mg/kg body weight to about 0.6 mg/kg body weight.

[0189] When administered intravenously, the dose for a fibric acid derivative can, for example, be in the range of from about 100 mg/kg body weight to about 2000 mg/kg body weight, preferably from about 300 mg/kg body weight to about 1000 mg/kg body weight, more preferably from about 400 mg/kg body weight to about 750 mg/kg body weight.

[0190] When administered intravenously, the dose for a nicotinic acid derivative can, for example, be in the range of from about 150 mg/kg body weight to about 3000 mg/kg body weight, preferably from about 300 mg/kg body weight to about 2000 mg/kg body weight, more preferably from about 500 mg/kg body weight to about 1000 mg/kg body weight.

[0191] The intravenously administered dose for probucol can, for example, be in the range of from about 50 mg/kg body weight to about 1500 mg/kg body weight, preferably from about 100 mg/kg body weight to about 1000 mg/kg body weight, more preferably from about 200 mg/kg body weight to about 750 mg/kg body weight.

[0192] The dose of any of these therapeutic compounds can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

[0193] Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

[0194] Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one therapeutic compound useful in the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent (s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

[0195] Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[0196] Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

[0197] Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[0198] Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly (e.g., Vaseline), lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 50% w/w of the composition, for example, from 0.5 to 2%.

[0199] Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35% preferably about 3% to 15%. As one particular possibility, the compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in *Pharmaceutical Research,* 3(6), 318 (1986).

[0200] In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

[0201] The solid dosage forms for oral administration including capsules, tablets, pills, powders, gel caps, and granules noted above comprise one or more compounds useful in the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate or solubilizing agents such as cyclodextrins. In the case of capsules, tablets, powders, granules, gel caps, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

[0202] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0203] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0204] Pharmaceutically acceptable carriers encompass all the foregoing and the like.

[0205] In combination therapy, administration of two or more of the therapeutic agents useful in the present invention may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular, or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropylmethyl cellulose, together with one or more of a lubricant, preservative, surface active or dispersing agent.

[0206] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. Capsules, tablets, etc., can be prepared by conventional methods well known in the art. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient or ingredients. Examples of dosage units are tablets or capsules. These may with advantage contain one or more therapeutic compound in an amount described above. For example, in the case of an IBAT inhibitor, the dose range may be from about 0.01 mg/day to about 500 mg/day or any other dose, dependent upon the specific inhibitor, as is known in the art.

[0207] The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. A suitable daily dose of each active therapeutic compound is one that achieves the same blood serum level as produced by oral administration as described above.

[0208] The therapeutic compounds may further be administered by any combination of oral/oral, oral/parenteral, or parenteral/parenteral route.

[0209] Pharmaceutical compositions for use in the treatment methods of the present invention may be administered in oral form or by intravenous administration. Oral admin-

istration of the combination therapy is preferred. Dosing for oral administration may be with a regimen calling for single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the day. The therapeutic compounds which make up the combination therapy may be administered simultaneously, either in a combined dosage form or in separate dosage forms intended for substantially simultaneous oral administration. The therapeutic compounds which make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step ingestion. Thus, a regimen may call for sequential administration of the therapeutic compounds with spaced-apart ingestion of the separate, active agents. The time period between the multiple ingestion steps may range from a few minutes to several hours, depending upon the properties of each therapeutic compound such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the therapeutic compound, as well as depending upon the effect of food ingestion and the age and condition of the patient. Circadian variation of the target molecule concentration may also determine the optimal dose interval. The therapeutic compounds of the combined therapy whether administered simultaneously, substantially simultaneously, or sequentially, may involve a regimen calling for administration of one therapeutic compound by oral route and another therapeutic compound by intravenous route. Whether the therapeutic compounds of the combined therapy are administered by oral or intravenous route, separately or together, each such therapeutic compound will be contained in a suitable pharmaceutical formulation of pharmaceutically-acceptable excipients, diluents or other formulations components. Examples of suitable pharmaceutically-acceptable formulations containing the therapeutic compounds for oral administration are given above.

Treatment Regimen

[0210] The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma or blood levels with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

[0211] Initial treatment of a patient suffering from a hyperlipidemic condition can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic disease condition has been controlled or eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for example, measuring serum LDL and total cholesterol levels by any of the methods well known in the art, to determine the effectiveness of the combination therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of each type of therapeutic compound are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the therapeutic compounds which together exhibit satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the hyperlipidemic condition.

[0212] A potential advantage of the combination disclosed herein may be reduction of the amount of any individual therapeutic compound, or all therapeutic compounds, effective in treating hyperlipidemic conditions such as atherosclerosis and hypercholesterolemia.

[0213] One of the several embodiments of the present invention provides a combination comprising the use of a first amount of an IBAT inhibitor and a second amount of another cardiovascular therapeutic useful in the prophylaxis or treatment of hyperlipidemia or atherosclerosis, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. For example one of the many embodiments of the present invention is a combination therapy comprising therapeutic dosages of an IBAT inhibitor and a CETP inhibitor. A preferred embodiment of the present invention is a combination therapy comprising therapeutic dosages of a benzothiepine IBAT inhibitor and a CETP inhibitor.

[0214] In another embodiment, the invention comprises a combination therapy comprising a first amount of an IBAT inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. Still another embodiment comprises a combination therapy comprising a first amount of an IBAT inhibitor and a second amount of a nicotinic acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this paragraph is preferably a benzothiepine IBAT inhibitor.

[0215] Alternatively, an embodiment of the present invention provides a combination which comprises a first amount of a CETP inhibitor and a second amount of another cardiovascular therapeutic, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. A preferred embodiment provides a combination comprising a first amount of a CETP inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. The invention is also embodied in a therapeutic composition comprising first amount of a CETP inhibitor and a second amount of a nicotinic acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. In the embodiments described in this paragraph, the CETP inhibitor is preferably the compound of formula C-1.

[0216] In another of its many embodiments, the present invention provides a combination comprising therapeutic dosages of an IBAT inhibitor and a phytosterol. In a preferred embodiment, the present invention provides a combination therapy comprising therapeutic dosages of a benzothiepine IBAT inhibitor and a phytosterol. In another preferred embodiment, the present invention provides a combination therapy comprising therapeutic dosages of an IBAT inhibitor and a stanol.

[0217] In another of its many embodiments, the present invention provides a combination comprising a first amount of an IBAT inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. In a preferred embodiment, the IBAT inhibitor is a benzothiepine IBAT inhibitor. In another preferred embodiment, the IBAT inhibitor is a benzothiazepine IBAT inhibitor. In yet another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor.

[0218] In another of its many embodiments, the present invention provides a combination comprising therapeutic dosages of an IBAT inhibitor and a cholesterol absorption antagonist. In a preferred embodiment, the present invention provides a combination therapy comprising therapeutic dosages of a benzothiepine IBAT inhibitor and a cholesterol absorption antagonist.

[0219] The embodiments of the present invention can comprise a combination therapy using two or more of the therapeutic compounds described or incorporated herein. The combination therapy can comprise two or more therapeutic compounds from different classes of chemistry, e.g., IBAT inhibitors can be therapeutically combined with CETP inhibitors. Therapeutic combinations can comprise more than two therapeutic compounds. For example, two or more therapeutic compounds from the same class of chemistry can comprise the therapy, e.g. a combination therapy comprising two or more IBAT inhibitors or two or more CETP inhibitors. In another embodiment the present invention provides a combination comprising two or more IBAT inhibitors or two or more stanols.

[0220] A further embodiment of the instant invention comprises the use of any of the cardiovascular combination therapies described herein for the prophylaxis or treatment of hypercholesterolemia or atherosclerosis.

[0221] The following non-limiting examples serve to illustrate various aspects of the present invention.

c. EXAMPLES

[0222] Table 6 illustrates examples of some of the many combinations of the present invention wherein the combination comprises a first amount of IBAT inhibitor and a second amount of a CETP inhibitor, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

TABLE 6

Example Number	Component 1	Component 2
1	B-1	C-1
2	B-1	C-2
3	B-1	C-3
4	B-1	C-4
5	B-1	C-5
6	B-1	C-6
7	B-1	C-7
8	B-1	C-8
9	B-1	C-9
10	B-1	C-10
11	B-1	C-11
12	B-1	C-12
13	B-1	C-13
14	B-1	C-14
15	B-1	C-15
16	B-1	C-16
17	B-1	C-17
18	B-1	C-18
19	B-1	C-19
20	B-1	C-20
21	B-2	C-1
22	B-2	C-2
23	B-2	C-3
24	B-2	C-4
25	B-2	C-5
26	B-2	C-6
27	B-2	C-7
28	B-2	C-8
29	B-2	C-9
30	B-2	C-10
31	B-2	C-11
32	B-2	C-12
33	B-2	C-13
34	B-2	C-14
35	B-2	C-15
36	B-2	C-16
37	B-2	C-17
38	B-2	C-18
39	B-2	C-19
40	B-2	C-20
41	B-3	C-1
42	B-3	C-2
43	B-3	C-3
44	B-3	C-4
45	B-3	C-5
46	B-3	C-6
47	B-3	C-7
48	B-3	C-8
49	B-3	C-9
50	B-3	C-10
51	B-3	C-11
52	B-3	C-12
53	B-3	C-13
54	B-3	C-14
55	B-3	C-15
56	B-3	C-16
57	B-3	C-17
58	B-3	C-18
59	B-3	C-19
60	B-3	C-20
61	B-4	C-1
62	B-4	C-2
63	B-4	C-3
64	B-4	C-4
65	B-4	C-5
66	B-4	C-6
67	B-4	C-7
68	B-4	C-8
69	B-4	C-9
70	B-4	C-10
71	B-4	C-11
72	B-4	C-12
73	B-4	C-13

TABLE 6-continued

Example Number	Component 1	Component 2
74	B-4	C-14
75	B-4	C-15
76	B-4	C-16
77	B-4	C-17
78	B-4	C-18
79	B-4	C-19
80	B-4	C-20
81	B-5	C-1
82	B-5	C-2
83	B-5	C-3
84	B-5	C-4
85	B-5	C-5
86	B-5	C-6
87	B-5	C-7
88	B-5	C-8
89	B-5	C-9
90	B-5	C-10
91	B-5	C-11
92	B-5	C-12
93	B-5	C-13
94	B-5	C-14
95	B-5	C-15
96	B-5	C-16
97	B-5	C-17
98	B-5	C-18
99	B-5	C-19
100	B-5	C-20
101	B-6	C-1
102	B-6	C-2
103	B-6	C-3
104	B-6	C-4
105	B-6	C-5
106	B-6	C-6
107	B-6	C-7
108	B-6	C-8
109	B-6	C-9
110	B-6	C-10
111	B-6	C-11
112	B-6	C-12
113	B-6	C-13
114	B-6	C-14
115	B-6	C-15
116	B-6	C-16
117	B-6	C-17
118	B-6	C-18
119	B-6	C-19
120	B-6	C-20
121	B-7	C-1
122	B-7	C-2
123	B-7	C-3
124	B-7	C-4
125	B-7	C-5
126	B-7	C-6
127	B-7	C-7
128	B-7	C-8
129	B-7	C-9
130	B-7	C-10
131	B-7	C-11
132	B-7	C-12
133	B-7	C-13
134	B-7	C-14
135	B-7	C-15
136	B-7	C-16
137	B-7	C-17
138	B-7	C-18
139	B-7	C-19
140	B-7	C-20
141	B-8	C-1
142	B-8	C-2
143	B-8	C-3
144	B-8	C-4
145	B-8	C-5
146	B-8	C-6

TABLE 6-continued

Example Number	Component 1	Component 2
147	B-8	C-7
148	B-8	C-8
149	B-8	C-9
150	B-8	C-10
151	B-8	C-11
152	B-8	C-12
153	B-8	C-13
154	B-8	C-14
155	B-8	C-15
156	B-8	C-16
157	B-8	C-17
158	B-8	C-18
159	B-8	C-19
160	B-8	C-20
161	B-9	C-1
162	B-9	C-2
163	B-9	C-3
164	B-9	C-4
165	B-9	C-5
166	B-9	C-6
167	B-9	C-7
168	B-9	C-8
169	B-9	C-9
170	B-9	C-10
171	B-9	C-11
172	B-9	C-12
173	B-9	C-13
174	B-9	C-14
175	B-9	C-15
176	B-9	C-16
177	B-9	C-17
178	B-9	C-18
179	B-9	C-19
180	B-9	C-20
181	B-10	C-1
182	B-10	C-2
183	B-10	C-3
184	B-10	C-4
185	B-10	C-5
186	B-10	C-6
187	B-10	C-7
188	B-10	C-8
189	B-10	C-9
190	B-10	C-10
191	B-10	C-11
192	B-10	C-12
193	B-10	C-13
194	B-10	C-14
195	B-10	C-15
196	B-10	C-16
197	B-10	C-17
198	B-10	C-18
199	B-10	C-19
200	B-10	C-20
201	B-11	C-1
202	B-11	C-2
203	B-11	C-3
204	B-11	C-4
205	B-11	C-5
206	B-11	C-6
207	B-11	C-7
208	B-11	C-8
209	B-11	C-9
210	B-11	C-10
211	B-11	C-11
212	B-11	C-12
213	B-11	C-13
214	B-11	C-14
215	B-11	C-15
216	B-11	C-16
217	B-11	C-17
218	B-11	C-18
219	B-11	C-19

TABLE 6-continued

Example Number	Component 1	Component 2
220	B-11	C-20
221	B-12	C-1
222	B-12	C-2
223	B-12	C-3
224	B-12	C-4
225	B-12	C-5
226	B-12	C-6
227	B-12	C-7
228	B-12	C-8
229	B-12	C-9
230	B-12	C-10
231	B-12	C-11
232	B-12	C-12
233	B-12	C-13
234	B-12	C-14
235	B-12	C-15
236	B-12	C-16
237	B-12	C-17
238	B-12	C-18
239	B-12	C-19
240	B-12	C-20
241	B-13	C-1
242	B-13	C-2
243	B-13	C-3
244	B-13	C-4
245	B-13	C-5
246	B-13	C-6
247	B-13	C-7
248	B-13	C-8
249	B-13	C-9
250	B-13	C-10
251	B-13	C-11
252	B-13	C-12
253	B-13	C-13
254	B-13	C-14
255	B-13	C-15
256	B-13	C-16
257	B-13	C-17
258	B-13	C-18
259	B-13	C-19
260	B-13	C-20
261	B-14	C-1
262	B-14	C-2
263	B-14	C-3
264	B-14	C-4
265	B-14	C-5
266	B-14	C-6
267	B-14	C-7
268	B-14	C-8
269	B-14	C-9
270	B-14	C-10
271	B-14	C-11
272	B-14	C-12
273	B-14	C-13
274	B-14	C-14
275	B-14	C-15
276	B-14	C-16
277	B-14	C-17
278	B-14	C-18
279	B-14	C-19
280	B-14	C-20
281	B-15	C-1
282	B-15	C-2
283	B-15	C-3
284	B-15	C-4
285	B-15	C-5
286	B-15	C-6
287	B-15	C-7
288	B-15	C-8
289	B-15	C-9
290	B-15	C-10
291	B-15	C-11
292	B-15	C-12

TABLE 6-continued

Example Number	Component 1	Component 2
293	B-15	C-13
294	B-15	C-14
295	B-15	C-15
296	B-15	C-16
297	B-15	C-17
298	B-15	C-18
299	B-15	C-19
300	B-15	C-20
301	B-16	C-1
302	B-16	C-2
303	B-16	C-3
304	B-16	C-4
305	B-16	C-5
306	B-16	C-6
307	B-16	C-7
308	B-16	C-8
309	B-16	C-9
310	B-16	C-10
311	B-16	C-11
312	B-16	C-12
313	B-16	C-13
314	B-16	C-14
315	B-16	C-15
316	B-16	C-16
317	B-16	C-17
318	B-16	C-18
319	B-16	C-19
320	B-16	C-20
321	B-17	C-1
322	B-17	C-2
323	B-17	C-3
324	B-17	C-4
325	B-17	C-5
326	B-17	C-6
327	B-17	C-7
328	B-17	C-8
329	B-17	C-9
330	B-17	C-10
331	B-17	C-11
332	B-17	C-12
333	B-17	C-13
334	B-17	C-14
335	B-17	C-15
336	B-17	C-16
337	B-17	C-17
338	B-17	C-18
339	B-17	C-19
340	B-17	C-20
341	B-18	C-1
342	B-18	C-2
343	B-18	C-3
344	B-18	C-4
345	B-18	C-5
346	B-18	C-6
347	B-18	C-7
348	B-18	C-8
349	B-18	C-9
350	B-18	C-10
351	B-18	C-11
352	B-18	C-12
353	B-18	C-13
354	B-18	C-14
355	B-18	C-15
356	B-18	C-16
357	B-18	C-17
358	B-18	C-18
359	B-18	C-19
360	B-18	C-20
361	B-19	C-1
362	B-19	C-2
363	B-19	C-3
364	B-19	C-4
365	B-19	C-5

TABLE 6-continued

Example Number	Component 1	Component 2
366	B-19	C-6
367	B-19	C-7
368	B-19	C-8
369	B-19	C-9
370	B-19	C-10
371	B-19	C-11
372	B-19	C-12
373	B-19	C-13
374	B-19	C-14
375	B-19	C-15
376	B-19	C-16
377	B-19	C-17
378	B-19	C-18
379	B-19	C-19
380	B-19	C-20
381	B-20	C-1
382	B-20	C-2
383	B-20	C-3
384	B-20	C-4
385	B-20	C-5
386	B-20	C-6
387	B-20	C-7
388	B-20	C-8
389	B-20	C-9
390	B-20	C-10
391	B-20	C-11
392	B-20	C-12
393	B-20	C-13
394	B-20	C-14
395	B-20	C-15
396	B-20	C-16
397	B-20	C-17
398	B-20	C-18
399	B-20	C-19
400	B-20	C-20

[0223] Table 8 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an IBAT inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

TABLE 8

Example Number	Component 1	Component 2
601	B-1	clofibrate
602	B-2	clofibrate
603	B-3	clofibrate
604	B-4	clofibrate
605	B-5	clofibrate
606	B-6	clofibrate
607	B-7	clofibrate
608	B-8	clofibrate
609	B-9	clofibrate
610	B-10	clofibrate
611	B-11	clofibrate
612	B-12	clofibrate
613	B-13	clofibrate
614	B-14	clofibrate
615	B-15	clofibrate
616	B-16	clofibrate
617	B-17	clofibrate
618	B-18	clofibrate
619	B-19	clofibrate
620	B-20	clofibrate

TABLE 8-continued

Example Number	Component 1	Component 2
621	B-1	fenofibrate
622	B-2	fenofibrate
623	B-3	fenofibrate
624	B-4	fenofibrate
625	B-5	fenofibrate
626	B-6	fenofibrate
627	B-7	fenofibrate
628	B-8	fenofibrate
629	B-9	fenofibrate
630	B-10	fenofibrate
631	B-11	fenofibrate
632	B-12	fenofibrate
633	B-13	fenofibrate
634	B-14	fenofibrate
635	B-15	fenofibrate
636	B-16	fenofibrate
637	B-17	fenofibrate
638	B-18	fenofibrate
639	B-19	fenofibrate
640	B-20	fenofibrate
641	B-1	ciprofibrate
642	B-2	ciprofibrate
643	B-3	ciprofibrate
644	B-4	ciprofibrate
645	B-5	ciprofibrate
646	B-6	ciprofibrate
647	B-7	ciprofibrate
648	B-8	ciprofibrate
649	B-9	ciprofibrate
650	B-10	ciprofibrate
651	B-11	ciprofibrate
652	B-12	ciprofibrate
653	B-13	ciprofibrate
654	B-14	ciprofibrate
655	B-15	ciprofibrate
656	B-16	ciprofibrate
657	B-17	ciprofibrate
658	B-18	ciprofibrate
659	B-19	ciprofibrate
660	B-20	ciprofibrate
661	B-1	bezafibrate
662	B-2	bezafibrate
663	B-3	bezafibrate
664	B-4	bezafibrate
665	B-5	bezafibrate
666	B-6	bezafibrate
667	B-7	bezafibrate
668	B-8	bezafibrate
669	B-9	bezafibrate
670	B-10	bezafibrate
671	B-11	bezafibrate
672	B-12	bezafibrate
673	B-13	bezafibrate
674	B-14	bezafibrate
675	B-15	bezafibrate
676	B-16	bezafibrate
677	B-17	bezafibrate
678	B-18	bezafibrate
679	B-19	bezafibrate
680	B-20	bezafibrate
681	B-1	gemfibrozil
682	B-2	gemfibrozil
683	B-3	gemfibrozil
684	B-4	gemfibrozil
685	B-5	gemfibrozil
686	B-6	gemfibrozil
687	B-7	gemfibrozil
688	B-8	gemfibrozil
689	B-9	gemfibrozil
690	B-10	gemfibrozil
691	B-11	gemfibrozil
692	B-12	gemfibrozil
693	B-13	gemfibrozil

TABLE 8-continued

Example Number	Component 1	Component 2
694	B-14	gemfibrozil
695	B-15	gemfibrozil
696	B-16	gemfibrozil
697	B-17	gemfibrozil
698	B-18	gemfibrozil
699	B-19	gemfibrozil
700	B-20	gemfibrozil

[0224] Table 10 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an IBAT inhibitor and a second amount of a nicotinic acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

TABLE 10

Example Number	Component 1	Component 2
901	B-1	nicotinic acid (niacin)
902	B-2	nicotinic acid (niacin)
903	B-3	nicotinic acid (niacin)
904	B-4	nicotinic acid (niacin)
905	B-5	nicotinic acid (niacin)
906	B-6	nicotinic acid (niacin)
907	B-7	nicotinic acid (niacin)
908	B-8	nicotinic acid (niacin)
909	B-9	nicotinic acid (niacin)
910	B-10	nicotinic acid (niacin)
911	B-11	nicotinic acid (niacin)
912	B-12	nicotinic acid (niacin)
913	B-13	nicotinic acid (niacin)
914	B-14	nicotinic acid (niacin)
915	B-15	nicotinic acid (niacin)
916	B-16	nicotinic acid (niacin)
917	B-17	nicotinic acid (niacin)
918	B-18	nicotinic acid (niacin)
919	B-19	nicotinic acid (niacin)
920	B-20	nicotinic acid (niacin)
921	B-1	niceritrol
922	B-2	niceritrol
923	B-3	niceritrol
924	B-4	niceritrol
925	B-5	niceritrol
926	B-6	niceritrol
927	B-7	niceritrol
928	B-8	niceritrol
929	B-9	niceritrol
930	B-10	niceritrol
931	B-11	niceritrol
932	B-12	niceritrol
933	B-13	niceritrol
934	B-14	niceritrol
935	B-15	niceritrol
936	B-16	niceritrol
937	B-17	niceritrol
938	B-18	niceritrol
939	B-19	niceritrol
940	B-20	niceritrol
941	B-1	acipimox
942	B-2	acipimox
943	B-3	acipimox
944	B-4	acipimox
945	B-5	acipimox
946	B-6	acipimox
947	B-7	acipimox
948	B-8	acipimox

TABLE 10-continued

Example Number	Component 1	Component 2
949	B-9	acipimox
950	B-10	acipimox
951	B-11	acipimox
952	B-12	acipimox
953	B-13	acipimox
954	B-14	acipimox
955	B-15	acipimox
956	B-16	acipimox
957	B-17	acipimox
958	B-18	acipimox
959	B-19	acipimox
960	B-20	acipimox

[0225] Table 13 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of a CETP inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

TABLE 13

Example Number	Component 1	Component 2
5601	C-1	clofibrate
5602	C-2	clofibrate
5603	C-3	clofibrate
5604	C-4	clofibrate
5605	C-5	clofibrate
5606	C-6	clofibrate
5607	C-7	clofibrate
5608	C-8	clofibrate
5609	C-9	clofibrate
5610	C-10	clofibrate
5611	C-11	clofibrate
5612	C-12	clofibrate
5613	C-13	clofibrate
5614	C-14	clofibrate
5615	C-15	clofibrate
5616	C-16	clofibrate
5617	C-17	clofibrate
5618	C-18	clofibrate
5619	C-19	clofibrate
5620	C-20	clofibrate
5621	C-1	fenofibrate
5622	C-2	fenofibrate
5623	C-3	fenofibrate
5624	C-4	fenofibrate
5625	C-5	fenofibrate
5626	C-6	fenofibrate
5627	C-7	fenofibrate
5628	C-8	fenofibrate
5629	C-9	fenofibrate
5630	C-10	fenofibrate
5631	C-11	fenofibrate
5632	C-12	fenofibrate
5633	C-13	fenofibrate
5634	C-14	fenofibrate
5635	C-15	fenofibrate
5636	C-16	fenofibrate
5637	C-17	fenofibrate
5638	C-18	fenofibrate
5639	C-19	fenofibrate
5640	C-20	fenofibrate
5641	C-1	ciprofibrate
5642	C-2	ciprofibrate
5643	C-3	ciprofibrate

TABLE 13-continued

Example Number	Component 1	Component 2
5644	C-4	ciprofibrate
5645	C-5	ciprofibrate
5646	C-6	ciprofibrate
5647	C-7	ciprofibrate
5648	C-8	ciprofibrate
5649	C-9	ciprofibrate
5650	C-10	ciprofibrate
5651	C-11	ciprofibrate
5652	C-12	ciprofibrate
5653	C-13	ciprofibrate
5654	C-14	ciprofibrate
5655	C-15	ciprofibrate
5656	C-16	ciprofibrate
5657	C-17	ciprofibrate
5658	C-18	ciprofibrate
5659	C-19	ciprofibrate
5660	C-20	ciprofibrate
5661	C-1	bezafibrate
5662	C-2	bezafibrate
5663	C-3	bezafibrate
5664	C-4	bezafibrate
5665	C-5	bezafibrate
5666	C-6	bezafibrate
5667	C-7	bezafibrate
5668	C-8	bezafibrate
5669	C-9	bezafibrate
5670	C-10	bezafibrate
5671	C-11	bezafibrate
5672	C-12	bezafibrate
5673	C-13	bezafibrate
5674	C-14	bezafibrate
5675	C-15	bezafibrate
5676	C-16	bezafibrate
5677	C-17	bezafibrate
5678	C-18	bezafibrate
5679	C-19	bezafibrate
5680	C-20	bezafibrate
5681	C-1	gemfibrozil
5682	C-2	gemfibrozil
5683	C-3	gemfibrozil
5684	C-4	gemfibrozil
5685	C-5	gemfibrozil
5686	C-6	gemfibrozil
5687	C-7	gemfibrozil
5688	C-8	gemfibrozil
5689	C-9	gemfibrozil
5690	C-10	gemfibrozil
5691	C-11	gemfibrozil
5692	C-12	gemfibrozil
5693	C-13	gemfibrozil
5694	C-14	gemfibrozil
5695	C-15	gemfibrozil
5696	C-16	gemfibrozil
5697	C-17	gemfibrozil
5698	C-18	gemfibrozil
5699	C-19	gemfibrozil
5700	C-20	gemfibrozil

[0226] Table 15 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of a CETP inhibitor and a second amount of a nicotinic acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

TABLE 15

Example Number	Component 1	Component 2
5901	C-1	nicotinic acid (niacin)
5902	C-2	nicotinic acid (niacin)
5903	C-3	nicotinic acid (niacin)
5904	C-4	nicotinic acid (niacin)
5905	C-5	nicotinic acid (niacin)
5906	C-6	nicotinic acid (niacin)
5907	C-7	nicotinic acid (niacin)
5908	C-8	nicotinic acid (niacin)
5909	C-9	nicotinic acid (niacin)
5910	C-10	nicotinic acid (niacin)
5911	C-11	nicotinic acid (niacin)
5912	C-12	nicotinic acid (niacin)
5913	C-13	nicotinic acid (niacin)
5914	C-14	nicotinic acid (niacin)
5915	C-15	nicotinic acid (niacin)
5916	C-16	nicotinic acid (niacin)
5917	C-17	nicotinic acid (niacin)
5918	C-18	nicotinic acid (niacin)
5919	C-19	nicotinic acid (niacin)
5920	C-20	nicotinic acid (niacin)
5921	C-1	niceritrol
5922	C-2	niceritrol
5923	C-3	niceritrol
5924	C-4	niceritrol
5925	C-5	niceritrol
5926	C-6	niceritrol
5927	C-7	niceritrol
5928	C-8	niceritrol
5929	C-9	niceritrol
5930	C-10	niceritrol
5931	C-11	niceritrol
5932	C-12	niceritrol
5933	C-13	niceritrol
5934	C-14	niceritrol
5935	C-15	niceritrol
5936	C-16	niceritrol
5937	C-17	niceritrol
5938	C-18	niceritrol
5939	C-19	niceritrol
5940	C-20	niceritrol
5941	C-1	acipimox
5942	C-2	acipimox
5943	C-3	acipimox
5944	C-4	acipimox
5945	C-5	acipimox
5946	C-6	acipimox
5947	C-7	acipimox
5948	C-8	acipimox
5949	C-9	acipimox
5950	C-10	acipimox
5951	C-11	acipimox
5952	C-12	acipimox
5953	C-13	acipimox
5954	C-14	acipimox
5955	C-15	acipimox
5956	C-16	acipimox
5957	C-17	acipimox
5958	C-18	acipimox
5959	C-19	acipimox
5960	C-20	acipimox

[0227] Any of the MTP inhibitor compounds described by Wetterau et al. (Id.) can be used in combinations of the present invention wherein the combination comprises a first amount of an ileal bile acid transporter inhibiting compound and a second amount of a MTP inhibitor wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypertensive condition effective amount of the compounds. The IBAT inhibitor

in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor. In another preferred embodiment, the IBAT inhibitor is a benzothiazepine IBAT inhibitor. In still another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor. The IBAT inhibitor can, without limitation, be any one or combination of the compounds listed in Table 1.

[0228] Table 17 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an ileal bile acid transporter inhibiting compound and a second amount of a cholesterol absorption antagonist wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, an anti-hypercholesterolemic condition effective amount, or an anti-hypertensive condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor. In another preferred embodiment, the IBAT inhibitor is a benzothiazepine IBAT inhibitor. In still another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor. The IBAT inhibitor can, without limitation, be any one or combination of the compounds listed in Table 1. Preferably the cholesterol absorption antagonist is an azetidinone compound, and more preferably the cholesterol absorption antagonist is compound A-1.

TABLE 16

Example Number	Compound 1	Compound 2
7001	B-1	A-1
7002	B-2	A-1
7003	B-3	A-1
7004	B-4	A-1
7005	B-5	A-1
7006	B-6	A-1
7007	B-7	A-1
7008	B-8	A-1
7009	B-9	A-1
7010	B-10	A-1
7011	B-11	A-1
7012	B-12	A-1
7013	B-13	A-1
7014	B-14	A-1
7015	B-15	A-1
7016	B-16	A-1
7017	B-17	A-1
7018	B-18	A-1
7019	B-19	A-1
7020	B-20	A-1
7021	B-21	A-1
7022	B-22	A-1
7023	B-23	A-1
7024	B-24	A-1
7025	B-25	A-1
7026	B-26	A-1
7027	B-27	A-1
7028	B-28	A-1
7029	B-29	A-1
7030	B-30	A-1
7031	B-31	A-1
7032	B-32	A-1
7033	B-33	A-1
7034	B-34	A-1
7035	B-35	A-1
7036	B-36	A-1
7037	B-37	A-1

TABLE 16-continued

Example Number	Compound 1	Compound 2
7038	B-38	A-1
7039	B-39	A-1

[0229] Table 21 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an ileal bile acid transporter inhibiting compound and a second amount of a cardiovascular therapeutic useful in the prophylaxis or treatment of hypertension, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, an anti-hypercholesterolemic condition effective amount, or an anti-hypertensive condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor. In another preferred embodiment, the IBAT inhibitor is a benzothiazepine IBAT inhibitor. In still another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor. The IBAT inhibitor can, without limitation, be any one or combination of the compounds listed in Table 1.

TABLE 21

Example Number	Compound 1	Compound 2
12000	amiloride	B-1
12001	amlodipine	B-1
12002	benazepril	B-1
12003	bumetanide	B-1
12004	candesartan cilexetil	B-1
12005	captopril	B-1
12006	carvedilol	B-1
12007	chlorothiazide	B-1
12008	chlorthalidone	B-1
12009	clonidine	B-1
12010	delodipine	B-1
12011	diazoxide	B-1
12012	diltiazem	B-1
12013	doxazosin	B-1
12014	enalapril	B-1
12015	eplerenone	B-1
12016	ethacrynic acid	B-1
12017	fosinopril	B-1
12018	furosemide	B-1
12019	guanabenz	B-1
12020	guanadrel	B-1
12021	guanethidine	B-1
12022	guanfacine	B-1
12023	hydralazine	B-1
12024	hydrochlorothiazide	B-1
12025	inbesartan	B-1
12026	isradipine	B-1
12027	labetalol	B-1
12028	lisinopril	B-1
12029	losartan	B-1
12030	methyldopa	B-1
12031	methyldopate	B-1
12032	metoprolol	B-1
12033	minoxidil	B-1
12034	moexipril	B-1
12035	nicardipine	B-1
12036	nifedipine	B-1
12037	nimodipine	B-1
12038	nitroprusside	B-1
12039	perindopril erbumine	B-1
12040	phenoxybenzamine	B-1

TABLE 21-continued

Example Number	Compound 1	Compound 2
12041	phentolamine	B-1
12042	polythiazide	B-1
12043	prazosin	B-1
12044	propranolol	B-1
12045	quinapril	B-1
12046	ramipril	B-1
12047	reserpine	B-1
12048	spironolactone	B-1
12049	terazosin	B-1
12050	trandolapril	B-1
12051	triameterene	B-1
12052	trimethaphan	B-1
12053	valsartan	B-1
12054	verapamil	B-1
12055	amiloride	B-2
12056	amlodipine	B-2
12057	benazepril	B-2
12058	bumetanide	B-2
12059	candesartan cilexetil	B-2
12060	captopril	B-2
12061	carvedilol	B-2
12062	chlorothiazide	B-2
12063	chlorthalidone	B-2
12064	clonidine	B-2
12065	delodipine	B-2
12066	diazoxide	B-2
12067	diltiazem	B-2
12068	doxazosin	B-2
12069	enalapril	B-2
12070	eplerenone	B-2
12071	ethacrynic acid	B-2
12072	fosinopril	B-2
12073	furosemide	B-2
12074	guanabenz	B-2
12075	guanadrel	B-2
12076	guanethidine	B-2
12077	guanfacine	B-2
12078	hydralazine	B-2
12079	hydrochlorothiazide	B-2
12080	inbesartan	B-2
12081	isradipine	B-2
12082	labetalol	B-2
12083	lisinopril	B-2
12084	losartan	B-2
12085	methyldopa	B-2
12086	methyldopate	B-2
12087	metoprolol	B-2
12088	minoxidil	B-2
12089	moexipril	B-2
12090	nicardipine	B-2
12091	nifedipine	B-2
12092	nimodipine	B-2
12093	nitroprusside	B-2
12094	perindopril erbumine	B-2
12095	phenoxybenzamine	B-2
12096	phentolamine	B-2
12097	polythiazide	B-2
12098	prazosin	B-2
12099	propranolol	B-2
12100	quinapril	B-2
12101	ramipril	B-2
12102	reserpine	B-2
12103	spironolactone	B-2
12104	terazosin	B-2
12105	trandolapril	B-2
12106	triameterene	B-2
12107	trimethaphan	B-2
12108	valsartan	B-2
12109	verapamil	B-2
12110	amiloride	B-3
12111	amlodipine	B-3
12112	benazepril	B-3
12113	bumetanide	B-3

TABLE 21-continued

Example Number	Compound 1	Compound 2
12114	candesartan cilexetil	B-3
12115	captopril	B-3
12116	carvedilol	B-3
12117	chlorothiazide	B-3
12118	chlorthalidone	B-3
12119	clonidine	B-3
12120	delodipine	B-3
12121	diazoxide	B-3
12122	diltiazem	B-3
12123	doxazosin	B-3
12124	enalapril	B-3
12125	eplerenone	B-3
12126	ethacrynic acid	B-3
12127	fosinopril	B-3
12128	furosemide	B-3
12129	guanabenz	B-3
12130	guanadrel	B-3
12131	guanethidine	B-3
12132	guanfacine	B-3
12133	hydralazine	B-3
12134	hydrochlorothiazide	B-3
12135	inbesartan	B-3
12136	isradipine	B-3
12137	labetalol	B-3
12138	lisinopril	B-3
12139	losartan	B-3
12140	methyldopa	B-3
12141	methyldopate	B-3
12142	metoprolol	B-3
12143	minoxidil	B-3
12144	moexipril	B-3
12145	nicardipine	B-3
12146	nifedipine	B-3
12147	nimodipine	B-3
12148	nitroprusside	B-3
12149	perindopril erbumine	B-3
12150	phenoxybenzamine	B-3
12151	phentolamine	B-3
12152	polythiazide	B-3
12153	prazosin	B-3
12154	propranolol	B-3
12155	quinapril	B-3
12156	ramipril	B-3
12157	reserpine	B-3
12158	spironolactone	B-3
12159	terazosin	B-3
12160	trandolapril	B-3
12161	triameterene	B-3
12162	trimethaphan	B-3
12163	valsartan	B-3
12164	verapamil	B-3
12165	amiloride	B-4
12166	amlodipine	B-4
12167	benazepril	B-4
12168	bumetanide	B-4
12169	candesartan cilexetil	B-4
12170	captopril	B-4
12171	carvedilol	B-4
12172	chlorothiazide	B-4
12173	chlorthalidone	B-4
12174	clonidine	B-4
12175	delodipine	B-4
12176	diazoxide	B-4
12177	diltiazem	B-4
12178	doxazosin	B-4
12179	enalapril	B-4
12180	eplerenone	B-4
12181	ethacrynic acid	B-4
12182	fosinopril	B-4
12183	furosemide	B-4
12184	guanabenz	B-4
12185	guanadrel	B-4
12186	guanethidine	B-4

TABLE 21-continued

Example Number	Compound 1	Compound 2
12187	guanfacine	B-4
12188	hydralazine	B-4
12189	hydrochlorothiazide	B-4
12190	inbesartan	B-4
12191	isradipine	B-4
12192	labetalol	B-4
12193	lisinopril	B-4
12194	losartan	B-4
12195	methyldopa	B-4
12196	methyldopate	B-4
12197	metoprolol	B-4
12198	minoxidil	B-4
12199	moexipril	B-4
12200	nicardipine	B-4
12201	nifedipine	B-4
12202	nimodipine	B-4
12203	nitroprusside	B-4
12204	perindopril erbumine	B-4
12205	phenoxybenzamine	B-4
12206	phentolamine	B-4
12207	polythiazide	B-4
12208	prazosin	B-4
12209	propranolol	B-4
12210	quinapril	B-4
12211	ramipril	B-4
12212	reserpine	B-4
12213	spironolactone	B-4
12214	terazosin	B-4
12215	trandolapril	B-4
12216	triameterene	B-4
12217	trimethaphan	B-4
12218	valsartan	B-4
12219	verapamil	B-4
12220	amiloride	B-5
12221	amlodipine	B-5
12222	benazepril	B-5
12223	bumetanide	B-5
12224	candesartan cilexetil	B-5
12225	captopril	B-5
12226	carvedilol	B-5
12227	chlorothiazide	B-5
12228	chlorthalidone	B-5
12229	clonidine	B-5
12230	delodipine	B-5
12231	diazoxide	B-5
12232	diltiazem	B-5
12233	doxazosin	B-5
12234	enalapril	B-5
12235	eplerenone	B-5
12236	ethacrynic acid	B-5
12237	fosinopril	B-5
12238	furosemide	B-5
12239	guanabenz	B-5
12240	guanadrel	B-5
12241	guanethidine	B-5
12242	guanfacine	B-5
12243	hydralazine	B-5
12244	hydrochlorothiazide	B-5
12245	inbesartan	B-5
12246	isradipine	B-5
12247	labetalol	B-5
12248	lisinopril	B-5
12249	losartan	B-5
12250	methyldopa	B-5
12251	methyldopate	B-5
12252	metoprolol	B-5
12253	minoxidil	B-5
12254	moexipril	B-5
12255	nicardipine	B-5
12256	nifedipine	B-5
12257	nimodipine	B-5
12258	nitroprusside	B-5
12259	perindopril erbumine	B-5

TABLE 21-continued

Example Number	Compound 1	Compound 2
12260	phenoxybenzamine	B-5
12261	phentolamine	B-5
12262	polythiazide	B-5
12263	prazosin	B-5
12264	propranolol	B-5
12265	quinapril	B-5
12266	ramipril	B-5
12267	reserpine	B-5
12268	spironolactone	B-5
12269	terazosin	B-5
12270	trandolapril	B-5
12271	triameterene	B-5
12272	trimethaphan	B-5
12273	valsartan	B-5
12274	verapamil	B-5
12275	amiloride	B-6
12276	amlodipine	B-6
12277	benazepril	B-6
12278	bumetanide	B-6
12279	candesartan cilexetil	B-6
12280	captopril	B-6
12281	carvedilol	B-6
12282	chlorothiazide	B-6
12283	chlorthalidone	B-6
12284	clonidine	B-6
12285	delodipine	B-6
12286	diazoxide	B-6
12287	diltiazem	B-6
12288	doxazosin	B-6
12289	enalapril	B-6
12290	eplerenone	B-6
12291	ethacrynic acid	B-6
12292	fosinopril	B-6
12293	furosemide	B-6
12294	guanabenz	B-6
12295	guanadrel	B-6
12296	guanethidine	B-6
12297	guanfacine	B-6
12298	hydralazine	B-6
12299	hydrochlorothiazide	B-6
12300	inbesartan	B-6
12301	isradipine	B-6
12302	labetalol	B-6
12303	lisinopril	B-6
12304	losartan	B-6
12305	methyldopa	B-6
12306	methyldopate	B-6
12307	metoprolol	B-6
12308	minoxidil	B-6
12309	moexipril	B-6
12310	nicardipine	B-6
12311	nifedipine	B-6
12312	nimodipine	B-6
12313	nitroprusside	B-6
12314	perindopril erbumine	B-6
12315	phenoxybenzamine	B-6
12316	phentolamine	B-6
12317	polythiazide	B-6
12318	prazosin	B-6
12319	propranolol	B-6
12320	quinapril	B-6
12321	ramipril	B-6
12322	reserpine	B-6
12323	spironolactone	B-6
12324	terazosin	B-6
12325	trandolapril	B-6
12326	triameterene	B-6
12327	trimethaphan	B-6
12328	valsartan	B-6
12329	verapamil	B-6
12330	amiloride	B-7
12331	amlodipine	B-7
12332	benazepril	B-7

TABLE 21-continued

Example Number	Compound 1	Compound 2
12333	bumetanide	B-7
12334	candesartan cilexetil	B-7
12335	captopril	B-7
12336	carvedilol	B-7
12337	chlorothiazide	B-7
12338	chlorthalidone	B-7
12339	clonidine	B-7
12340	delodipine	B-7
12341	diazoxide	B-7
12342	diltiazem	B-7
12343	doxazosin	B-7
12344	enalapril	B-7
12345	eplerenone	B-7
12346	ethacrynic acid	B-7
12347	fosinopril	B-7
12348	furosemide	B-7
12349	guanabenz	B-7
12350	guanadrel	B-7
12351	guanethidine	B-7
12352	guanfacine	B-7
12353	hydralazine	B-7
12354	hydrochlorothiazide	B-7
12355	inbesartan	B-7
12356	isradipine	B-7
12357	labetalol	B-7
12358	lisinopril	B-7
12359	losartan	B-7
12360	methyldopa	B-7
12361	methyldopate	B-7
12362	metoprolol	B-7
12363	minoxidil	B-7
12364	moexipril	B-7
12365	nicardipine	B-7
12366	nifedipine	B-7
12367	nimodipine	B-7
12368	nitroprusside	B-7
12369	perindopril erbumine	B-7
12370	phenoxybenzamine	B-7
12371	phentolamine	B-7
12372	polythiazide	B-7
12373	prazosin	B-7
12374	propranolol	B-7
12375	quinapril	B-7
12376	ramipril	B-7
12377	reserpine	B-7
12378	spironolactone	B-7
12379	terazosin	B-7
12380	trandolapril	B-7
12381	triameterene	B-7
12382	trimethaphan	B-7
12383	valsartan	B-7
12384	verapamil	B-7
12385	amiloride	B-8
12386	amlodipine	B-8
12387	benazepril	B-8
12388	bumetanide	B-8
12389	candesartan cilexetil	B-8
12390	captopril	B-8
12391	carvedilol	B-8
12392	chlorothiazide	B-8
12393	chlorthalidone	B-8
12394	clonidine	B-8
12395	delodipine	B-8
12396	diazoxide	B-8
12397	diltiazem	B-8
12398	doxazosin	B-8
12399	enalapril	B-8
12400	eplerenone	B-8
12401	ethacrynic acid	B-8
12402	fosinopril	B-8
12403	furosemide	B-8
12404	guanabenz	B-8
12405	guanadrel	B-8

TABLE 21-continued

Example Number	Compound 1	Compound 2
12406	guanethidine	B-8
12407	guanfacine	B-8
12408	hydralazine	B-8
12409	hydrochlorothiazide	B-8
12410	inbesartan	B-8
12411	isradipine	B-8
12412	labetalol	B-8
12413	lisinopril	B-8
12414	losartan	B-8
12415	methyldopa	B-8
12416	methyldopate	B-8
12417	metoprolol	B-8
12418	minoxidil	B-8
12419	moexipril	B-8
12420	nicardipine	B-8
12421	nifedipine	B-8
12422	nimodipine	B-8
12423	nitroprusside	B-8
12424	perindopril erbumine	B-8
12425	phenoxybenzamine	B-8
12426	phentolamine	B-8
12427	polythiazide	B-8
12428	prazosin	B-8
12429	propranolol	B-8
12430	quinapril	B-8
12431	ramipril	B-8
12432	reserpine	B-8
12433	spironolactone	B-8
12434	terazosin	B-8
12435	trandolapril	B-8
12436	triameterene	B-8
12437	trimethaphan	B-8
12438	valsartan	B-8
12439	verapamil	B-8
12440	amiloride	B-9
12441	amlodipine	B-9
12442	benazepril	B-9
12443	bumetanide	B-9
12444	candesartan cilexetil	B-9
12445	captopril	B-9
12446	carvedilol	B-9
12447	chlorothiazide	B-9
12448	chlorthalidone	B-9
12449	clonidine	B-9
12450	delodipine	B-9
12451	diazoxide	B-9
12452	diltiazem	B-9
12453	doxazosin	B-9
12454	enalapril	B-9
12455	eplerenone	B-9
12456	ethacrynic acid	B-9
12457	fosinopril	B-9
12458	furosemide	B-9
12459	guanabenz	B-9
12460	guanadrel	B-9
12461	guanethidine	B-9
12462	guanfacine	B-9
12463	hydralazine	B-9
12464	hydrochlorothiazide	B-9
12465	inbesartan	B-9
12466	isradipine	B-9
12467	labetalol	B-9
12468	lisinopril	B-9
12469	losartan	B-9
12470	methyldopa	B-9
12471	methyldopate	B-9
12472	metoprolol	B-9
12473	minoxidil	B-9
12474	moexipril	B-9
12475	nicardipine	B-9
12476	nifedipine	B-9
12477	nimodipine	B-9
12478	nitroprusside	B-9

TABLE 21-continued

Example Number	Compound 1	Compound 2
12479	perindopril erbumine	B-9
12480	phenoxybenzamine	B-9
12481	phentolamine	B-9
12482	polythiazide	B-9
12483	prazosin	B-9
12484	propranolol	B-9
12485	quinapril	B-9
12486	ramipril	B-9
12487	reserpine	B-9
12488	spironolactone	B-9
12489	terazosin	B-9
12490	trandolapril	B-9
12491	triameterene	B-9
12492	trimethaphan	B-9
12493	valsartan	B-9
12494	verapamil	B-9
12495	amiloride	B-10
12496	amlodipine	B-10
12497	benazepril	B-10
12498	bumetanide	B-10
12499	candesartan cilexetil	B-10
12500	captopril	B-10
12501	carvedilol	B-10
12502	chlorothiazide	B-10
12503	chlorthalidone	B-10
12504	clonidine	B-10
12505	delodipine	B-10
12506	diazoxide	B-10
12507	diltiazem	B-10
12508	doxazosin	B-10
12509	enalapril	B-10
12510	eplerenone	B-10
12511	ethacrynic acid	B-10
12512	fosinopril	B-10
12513	furosemide	B-10
12514	guanabenz	B-10
12515	guanadrel	B-10
12516	guanethidine	B-10
12517	guanfacine	B-10
12518	hydralazine	B-10
12519	hydrochlorothiazide	B-10
12520	inbesartan	B-10
12521	isradipine	B-10
12522	labetalol	B-10
12523	lisinopril	B-10
12524	losartan	B-10
12525	methyldopa	B-10
12526	methyldopate	B-10
12527	metoprolol	B-10
12528	minoxidil	B-10
12529	moexipril	B-10
12530	nicardipine	B-10
12531	nifedipine	B-10
12532	nimodipine	B-10
12533	nitroprusside	B-10
12534	perindopril erbumine	B-10
12535	phenoxybenzamine	B-10
12536	phentolamine	B-10
12537	polythiazide	B-10
12538	prazosin	B-10
12539	propranolol	B-10
12540	quinapril	B-10
12541	ramipril	B-10
12542	reserpine	B-10
12543	spironolactone	B-10
12544	terazosin	B-10
12545	trandolapril	B-10
12546	triameterene	B-10
12547	trimethaphan	B-10
12548	valsartan	B-10
12549	verapamil	B-10
12550	amiloride	B-11
12551	amlodipine	B-11

TABLE 21-continued

Example Number	Compound 1	Compound 2
12552	benazepril	B-11
12553	bumetanide	B-11
12554	candesartan cilexetil	B-11
12555	captopril	B-11
12556	carvedilol	B-11
12557	chlorothiazide	B-11
12558	chlorthalidone	B-11
12559	clonidine	B-11
12560	delodipine	B-11
12561	diazoxide	B-11
12562	diltiazem	B-11
12563	doxazosin	B-11
12564	enalapril	B-11
12565	eplerenone	B-11
12566	ethacrynic acid	B-11
12567	fosinopril	B-11
12568	furosemide	B-11
12569	guanabenz	B-11
12570	guanadrel	B-11
12571	guanethidine	B-11
12572	guanfacine	B-11
12573	hydralazine	B-11
12574	hydrochlorothiazide	B-11
12575	inbesartan	B-11
12576	isradipine	B-11
12577	labetalol	B-11
12578	lisinopril	B-11
12579	losartan	B-11
12580	methyldopa	B-11
12581	methyldopate	B-11
12582	metoprolol	B-11
12583	minoxidil	B-11
12584	moexipril	B-11
12585	nicardipine	B-11
12586	nifedipine	B-11
12587	nimodipine	B-11
12588	nitroprusside	B-11
12589	perindopril erbumine	B-11
12590	phenoxybenzamine	B-11
12591	phentolamine	B-11
12592	polythiazide	B-11
12593	prazosin	B-11
12594	propranolol	B-11
12595	quinapril	B-11
12596	ramipril	B-11
12597	reserpine	B-11
12598	spironolactone	B-11
12599	terazosin	B-11
12600	trandolapril	B-11
12601	triameterene	B-11
12602	trimethaphan	B-11
12603	valsartan	B-11
12604	verapamil	B-11
12605	amiloride	B-12
12606	amlodipine	B-12
12607	benazepril	B-12
12608	bumetanide	B-12
12609	candesartan cilexetil	B-12
12610	captopril	B-12
12611	carvedilol	B-12
12612	chlorothiazide	B-12
12613	chlorthalidone	B-12
12614	clonidine	B-12
12615	delodipine	B-12
12616	diazoxide	B-12
12617	diltiazem	B-12
12618	doxazosin	B-12
12619	enalapril	B-12
12620	eplerenone	B-12
12621	ethacrynic acid	B-12
12622	fosinopril	B-12
12623	furosemide	B-12
12624	guanabenz	B-12

TABLE 21-continued

Example Number	Compound 1	Compound 2
12625	guanadrel	B-12
12626	guanethidine	B-12
12627	guanfacine	B-12
12628	hydralazine	B-12
12629	hydrochlorothiazide	B-12
12630	inbesartan	B-12
12631	isradipine	B-12
12632	labetalol	B-12
12633	lisinopril	B-12
12634	losartan	B-12
12635	methyldopa	B-12
12636	methyldopate	B-12
12637	metoprolol	B-12
12638	minoxidil	B-12
12639	moexipril	B-12
12640	nicardipine	B-12
12641	nifedipine	B-12
12642	nimodipine	B-12
12643	nitroprusside	B-12
12644	perindopril erbumine	B-12
12645	phenoxybenzamine	B-12
12646	phentolamine	B-12
12647	polythiazide	B-12
12648	prazosin	B-12
12649	propranolol	B-12
12650	quinapril	B-12
12651	ramipril	B-12
12652	reserpine	B-12
12653	spironolactone	B-12
12654	terazosin	B-12
12655	trandolapril	B-12
12656	triameterene	B-12
12657	trimethaphan	B-12
12658	valsartan	B-12
12659	verapamil	B-12
12660	amiloride	B-13
12661	amlodipine	B-13
12662	benazepril	B-13
12663	bumetanide	B-13
12664	candesartan cilexetil	B-13
12665	captopril	B-13
12666	carvedilol	B-13
12667	chlorothiazide	B-13
12668	chlorthalidone	B-13
12669	clonidine	B-13
12670	delodipine	B-13
12671	diazoxide	B-13
12672	diltiazem	B-13
12673	doxazosin	B-13
12674	enalapril	B-13
12675	eplerenone	B-13
12676	ethacrynic acid	B-13
12677	fosinopril	B-13
12678	furosemide	B-13
12679	guanabenz	B-13
12680	guanadrel	B-13
12681	guanethidine	B-13
12682	guanfacine	B-13
12683	hydralazine	B-13
12684	hydrochlorothiazide	B-13
12685	inbesartan	B-13
12686	isradipine	B-13
12687	labetalol	B-13
12688	lisinopril	B-13
12689	losartan	B-13
12690	methyldopa	B-13
12691	methyldopate	B-13
12692	metoprolol	B-13
12693	minoxidil	B-13
12694	moexipril	B-13
12695	nicardipine	B-13
12696	nifedipine	B-13
12697	nimodipine	B-13

TABLE 21-continued

Example Number	Compound 1	Compound 2
12698	nitroprusside	B-13
12699	perindopril erbumine	B-13
12700	phenoxybenzamine	B-13
12701	phentolamine	B-13
12702	polythiazide	B-13
12703	prazosin	B-13
12704	propranolol	B-13
12705	quinapril	B-13
12706	ramipril	B-13
12707	reserpine	B-13
12708	spironolactone	B-13
12709	terazosin	B-13
12710	trandolapril	B-13
12711	triameterene	B-13
12712	trimethaphan	B-13
12713	valsartan	B-13
12714	verapamil	B-13
12715	amiloride	B-14
12716	amlodipine	B-14
12717	benazepril	B-14
12718	bumetanide	B-14
12719	candesartan cilexetil	B-14
12720	captopril	B-14
12721	carvedilol	B-14
12722	chlorothiazide	B-14
12723	chlorthalidone	B-14
12724	clonidine	B-14
12725	delodipine	B-14
12726	diazoxide	B-14
12727	diltiazem	B-14
12728	doxazosin	B-14
12729	enalapril	B-14
12730	eplerenone	B-14
12731	ethacrynic acid	B-14
12732	fosinopril	B-14
12733	furosemide	B-14
12734	guanabenz	B-14
12735	guanadrel	B-14
12736	guanethidine	B-14
12737	guanfacine	B-14
12738	hydralazine	B-14
12739	hydrochlorothiazide	B-14
12740	inbesartan	B-14
12741	isradipine	B-14
12742	labetalol	B-14
12743	lisinopril	B-14
12744	losartan	B-14
12745	methyldopa	B-14
12746	methyldopate	B-14
12747	metoprolol	B-14
12748	minoxidil	B-14
12749	moexipril	B-14
12750	nicardipine	B-14
12751	nifedipine	B-14
12752	nimodipine	B-14
12753	nitroprusside	B-14
12754	perindopril erbumine	B-14
12755	phenoxybenzamine	B-14
12756	phentolamine	B-14
12757	polythiazide	B-14
12758	prazosin	B-14
12759	propranolol	B-14
12760	quinapril	B-14
12761	ramipril	B-14
12762	reserpine	B-14
12763	spironolactone	B-14
12764	terazosin	B-14
12765	trandolapril	B-14
12766	triameterene	B-14
12767	trimethaphan	B-14
12768	valsartan	B-14
12769	verapamil	B-14
12770	amiloride	B-15

TABLE 21-continued

Example Number	Compound 1	Compound 2
12771	amlodipine	B-15
12772	benazepril	B-15
12773	bumetanide	B-15
12774	candesartan cilexetil	B-15
12775	captopril	B-15
12776	carvedilol	B-15
12777	chlorothiazide	B-15
12778	chlorthalidone	B-15
12779	clonidine	B-15
12780	delodipine	B-15
12781	diazoxide	B-15
12782	diltiazem	B-15
12783	doxazosin	B-15
12784	enalapril	B-15
12785	eplerenone	B-15
12786	ethacrynic acid	B-15
12787	fosinopril	B-15
12788	furosemide	B-15
12789	guanabenz	B-15
12790	guanadrel	B-15
12791	guanethidine	B-15
12792	guanfacine	B-15
12793	hydralazine	B-15
12794	hydrochlorothiazide	B-15
12795	inbesartan	B-15
12796	isradipine	B-15
12797	labetalol	B-15
12798	lisinopril	B-15
12799	losartan	B-15
12800	methyldopa	B-15
12801	methyldopate	B-15
12802	metoprolol	B-15
12803	minoxidil	B-15
12804	moexipril	B-15
12805	nicardipine	B-15
12806	nifedipine	B-15
12807	nimodipine	B-15
12808	nitroprusside	B-15
12809	perindopril erbumine	B-15
12810	phenoxybenzamine	B-15
12811	phentolamine	B-15
12812	polythiazide	B-15
12813	prazosin	B-15
12814	propranolol	B-15
12815	quinapril	B-15
12816	ramipril	B-15
12817	reserpine	B-15
12818	spironolactone	B-15
12819	terazosin	B-15
12820	trandolapril	B-15
12821	triameterene	B-15
12822	trimethaphan	B-15
12823	valsartan	B-15
12824	verapamil	B-15
12825	amiloride	B-16
12826	amlodipine	B-16
12827	benazepril	B-16
12828	bumetanide	B-16
12829	candesartan cilexetil	B-16
12830	captopril	B-16
12831	carvedilol	B-16
12832	chlorothiazide	B-16
12833	chlorthalidone	B-16
12834	clonidine	B-16
12835	delodipine	B-16
12836	diazoxide	B-16
12837	diltiazem	B-16
12838	doxazosin	B-16
12839	enalapril	B-16
12840	eplerenone	B-16
12841	ethacrynic acid	B-16
12842	fosinopril	B-16
12843	furosemide	B-16

TABLE 21-continued

Example Number	Compound 1	Compound 2
12844	guanabenz	B-16
12845	guanadrel	B-16
12846	guanethidine	B-16
12847	guanfacine	B-16
12848	hydralazine	B-16
12849	hydrochlorothiazide	B-16
12850	inbesartan	B-16
12851	isradipine	B-16
12852	labetalol	B-16
12853	lisinopril	B-16
12854	losartan	B-16
12855	methyldopa	B-16
12856	methyldopate	B-16
12857	metoprolol	B-16
12858	minoxidil	B-16
12859	moexipril	B-16
12860	nicardipine	B-16
12861	nifedipine	B-16
12862	nimodipine	B-16
12863	nitroprusside	B-16
12864	perindopril erbumine	B-16
12865	phenoxybenzamine	B-16
12866	phentolamine	B-16
12867	polythiazide	B-16
12868	prazosin	B-16
12869	propranolol	B-16
12870	quinapril	B-16
12871	ramipril	B-16
12872	reserpine	B-16
12873	spironolactone	B-16
12874	terazosin	B-16
12875	trandolapril	B-16
12876	triameterene	B-16
12877	trimethaphan	B-16
12878	valsartan	B-16
12879	verapamil	B-16
12880	amiloride	B-17
12881	amlodipine	B-17
12882	benazepril	B-17
12883	bumetanide	B-17
12884	candesartan cilexetil	B-17
12885	captopril	B-17
12886	carvedilol	B-17
12887	chlorothiazide	B-17
12888	chlorthalidone	B-17
12889	clonidine	B-17
12890	delodipine	B-17
12891	diazoxide	B-17
12892	diltiazem	B-17
12893	doxazosin	B-17
12894	enalapril	B-17
12895	eplerenone	B-17
12896	ethacrynic acid	B-17
12897	fosinopril	B-17
12898	furosemide	B-17
12899	guanabenz	B-17
12900	guanadrel	B-17
12901	guanethidine	B-17
12902	guanfacine	B-17
12903	hydralazine	B-17
12904	hydrochlorothiazide	B-17
12905	inbesartan	B-17
12906	isradipine	B-17
12907	labetalol	B-17
12908	lisinopril	B-17
12909	losartan	B-17
12910	methyldopa	B-17
12911	methyldopate	B-17
12912	metoprolol	B-17
12913	minoxidil	B-17
12914	moexipril	B-17
12915	nicardipine	B-17
12916	nifedipine	B-17

TABLE 21-continued

Example Number	Compound 1	Compound 2
12917	nimodipine	B-17
12918	nitroprusside	B-17
12919	perindopril erbumine	B-17
12920	phenoxybenzamine	B-17
12921	phentolamine	B-17
12922	polythiazide	B-17
12923	prazosin	B-17
12924	propranolol	B-17
12925	quinapril	B-17
12926	ramipril	B-17
12927	reserpine	B-17
12928	spironolactone	B-17
12929	terazosin	B-17
12930	trandolapril	B-17
12931	triameterene	B-17
12932	trimethaphan	B-17
12933	valsartan	B-17
12934	verapamil	B-17
12935	amiloride	B-18
12936	amlodipine	B-18
12937	benazepril	B-18
12938	bumetanide	B-18
12939	candesartan cilexetil	B-18
12940	captopril	B-18
12941	carvedilol	B-18
12942	chlorothiazide	B-18
12943	chlorthalidone	B-18
12944	clonidine	B-18
12945	delodipine	B-18
12946	diazoxide	B-18
12947	diltiazem	B-18
12948	doxazosin	B-18
12949	enalapril	B-18
12950	eplerenone	B-18
12951	ethacrynic acid	B-18
12952	fosinopril	B-18
12953	furosemide	B-18
12954	guanabenz	B-18
12955	guanadrel	B-18
12956	guanethidine	B-18
12957	guanfacine	B-18
12958	hydralazine	B-18
12959	hydrochlorothiazide	B-18
12960	inbesartan	B-18
12961	isradipine	B-18
12962	labetalol	B-18
12963	lisinopril	B-18
12964	losartan	B-18
12965	methyldopa	B-18
12966	methyldopate	B-18
12967	metoprolol	B-18
12968	minoxidil	B-18
12969	moexipril	B-18
12970	nicardipine	B-18
12971	nifedipine	B-18
12972	nimodipine	B-18
12973	nitroprusside	B-18
12974	perindopril erbumine	B-18
12975	phenoxybenzamine	B-18
12976	phentolamine	B-18
12977	polythiazide	B-18
12978	prazosin	B-18
12979	propranolol	B-18
12980	quinapril	B-18
12981	ramipril	B-18
12982	reserpine	B-18
12983	spironolactone	B-18
12984	terazosin	B-18
12985	trandolapril	B-18
12986	triameterene	B-18
12987	trimethaphan	B-18
12988	valsartan	B-18
12989	verapamil	B-18

TABLE 21-continued

Example Number	Compound 1	Compound 2
12990	amiloride	B-19
12991	amlodipine	B-19
12992	benazepril	B-19
12993	bumetanide	B-19
12994	candesartan cilexetil	B-19
12995	captopril	B-19
12996	carvedilol	B-19
12997	chlorothiazide	B-19
12998	chlorthalidone	B-19
12999	clonidine	B-19
13000	delodipine	B-19
13001	diazoxide	B-19
13002	diltiazem	B-19
13003	doxazosin	B-19
13004	enalapril	B-19
13005	eplerenone	B-19
13006	ethacrynic acid	B-19
13007	fosinopril	B-19
13008	furosemide	B-19
13009	guanabenz	B-19
13010	guanadrel	B-19
13011	guanethidine	B-19
13012	guanfacine	B-19
13013	hydralazine	B-19
13014	hydrochlorothiazide	B-19
13015	inbesartan	B-19
13016	isradipine	B-19
13017	labetalol	B-19
13018	lisinopril	B-19
13019	losartan	B-19
13020	methyldopa	B-19
13021	methyldopate	B-19
13022	metoprolol	B-19
13023	minoxidil	B-19
13024	moexipril	B-19
13025	nicardipine	B-19
13026	nifedipine	B-19
13027	nimodipine	B-19
13028	nitroprusside	B-19
13029	perindopril erbumine	B-19
13030	phenoxybenzamine	B-19
13031	phentolamine	B-19
13032	polythiazide	B-19
13033	prazosin	B-19
13034	propranolol	B-19
13035	quinapril	B-19
13036	ramipril	B-19
13037	reserpine	B-19
13038	spironolactone	B-19
13039	terazosin	B-19
13040	trandolapril	B-19
13041	triameterene	B-19
13042	trimethaphan	B-19
13043	valsartan	B-19
13044	verapamil	B-19
13045	amiloride	B-20
13046	amlodipine	B-20
13047	benazepril	B-20
13048	bumetanide	B-20
13049	candesartan cilexetil	B-20
13050	captopril	B-20
13051	carvedilol	B-20
13052	chlorothiazide	B-20
13053	chlorthalidone	B-20
13054	clonidine	B-20
13055	delodipine	B-20
13056	diazoxide	B-20
13057	diltiazem	B-20
13058	doxazosin	B-20
13059	enalapril	B-20
13060	eplerenone	B-20
13061	ethacrynic acid	B-20
13062	fosinopril	B-20

TABLE 21-continued

Example Number	Compound 1	Compound 2
13063	furosemide	B-20
13064	guanabenz	B-20
13065	guanadrel	B-20
13066	guanethidine	B-20
13067	guanfacine	B-20
13068	hydralazine	B-20
13069	hydrochlorothiazide	B-20
13070	inbesartan	B-20
13071	isradipine	B-20
13072	labetalol	B-20
13073	lisinopril	B-20
13074	losartan	B-20
13075	methyldopa	B-20
13076	methyldopate	B-20
13077	metoprolol	B-20
13078	minoxidil	B-20
13079	moexipril	B-20
13080	nicardipine	B-20
13081	nifedipine	B-20
13082	nimodipine	B-20
13083	nitroprusside	B-20
13084	perindopril erbumine	B-20
13085	phenoxybenzamine	B-20
13086	phentolamine	B-20
13087	polythiazide	B-20
13088	prazosin	B-20
13089	propranolol	B-20
13090	quinapril	B-20
13091	ramipril	B-20
13092	reserpine	B-20
13093	spironolactone	B-20
13094	terazosin	B-20
13095	trandolapril	B-20
13096	triameterene	B-20
13097	trimethaphan	B-20
13098	valsartan	B-20
13099	verapamil	B-20
13100	amiloride	B-21
13101	amlodipine	B-21
13102	benazepril	B-21
13103	bumetanide	B-21
13104	candesartan cilexetil	B-21
13105	captopril	B-21
13106	carvedilol	B-21
13107	chlorothiazide	B-21
13108	chlorthalidone	B-21
13109	clonidine	B-21
13110	delodipine	B-21
13111	diazoxide	B-21
13112	diltiazem	B-21
13113	doxazosin	B-21
13114	enalapril	B-21
13115	eplerenone	B-21
13116	ethacrynic acid	B-21
13117	fosinopril	B-21
13118	furosemide	B-21
13119	guanabenz	B-21
13120	guanadrel	B-21
13121	guanethidine	B-21
13122	guanfacine	B-21
13123	hydralazine	B-21
13124	hydrochlorothiazide	B-21
13125	inbesartan	B-21
13126	isradipine	B-21
13127	labetalol	B-21
13128	lisinopril	B-21
13129	losartan	B-21
13130	methyldopa	B-21
13131	methyldopate	B-21
13132	metoprolol	B-21
13133	minoxidil	B-21
13134	moexipril	B-21
13135	nicardipine	B-21

TABLE 21-continued

Example Number	Compound 1	Compound 2
13136	nifedipine	B-21
13137	nimodipine	B-21
13138	nitroprusside	B-21
13139	perindopril erbumine	B-21
13140	phenoxybenzamine	B-21
13141	phentolamine	B-21
13142	polythiazide	B-21
13143	prazosin	B-21
13144	propranolol	B-21
13145	quinapril	B-21
13146	ramipril	B-21
13147	reserpine	B-21
13148	spironolactone	B-21
13149	terazosin	B-21
13150	trandolapril	B-21
13151	triameterene	B-21
13152	trimethaphan	B-21
13153	valsartan	B-21
13154	verapamil	B-21
13155	amiloride	B-22
13156	amlodipine	B-22
13157	benazepril	B-22
13158	bumetanide	B-22
13159	candesartan cilexetil	B-22
13160	captopril	B-22
13161	carvedilol	B-22
13162	chlorothiazide	B-22
13163	chlorthalidone	B-22
13164	clonidine	B-22
13165	delodipine	B-22
13166	diazoxide	B-22
13167	diltiazem	B-22
13168	doxazosin	B-22
13169	enalapril	B-22
13170	eplerenone	B-22
13171	ethacrynic acid	B-22
13172	fosinopril	B-22
13173	furosemide	B-22
13174	guanabenz	B-22
13175	guanadrel	B-22
13176	guanethidine	B-22
13177	guanfacine	B-22
13178	hydralazine	B-22
13179	hydrochlorothiazide	B-22
13180	inbesartan	B-22
13181	isradipine	B-22
13182	labetalol	B-22
13183	lisinopril	B-22
13184	losartan	B-22
13185	methyldopa	B-22
13186	methyldopate	B-22
13187	metoprolol	B-22
13188	minoxidil	B-22
13189	moexipril	B-22
13190	nicardipine	B-22
13191	nifedipine	B-22
13192	nimodipine	B-22
13193	nitroprusside	B-22
13194	perindopril erbumine	B-22
13195	phenoxybenzamine	B-22
13196	phentolamine	B-22
13197	polythiazide	B-22
13198	prazosin	B-22
13199	propranolol	B-22
13200	quinapril	B-22
13201	ramipril	B-22
13202	reserpine	B-22
13203	spironolactone	B-22
13204	terazosin	B-22
13205	trandolapril	B-22
13206	triameterene	B-22
13207	trimethaphan	B-22
13208	valsartan	B-22

TABLE 21-continued

Example Number	Compound 1	Compound 2
13209	verapamil	B-22
13210	amiloride	B-23
13211	amlodipine	B-23
13212	benazepril	B-23
13213	bumetanide	B-23
13214	candesartan cilexetil	B-23
13215	captopril	B-23
13216	carvedilol	B-23
13217	chlorothiazide	B-23
13218	chlorthalidone	B-23
13219	clonidine	B-23
13220	delodipine	B-23
13221	diazoxide	B-23
13222	diltiazem	B-23
13223	doxazosin	B-23
13224	enalapril	B-23
13225	eplerenone	B-23
13226	ethacrynic acid	B-23
13227	fosinopril	B-23
13228	furosemide	B-23
13229	guanabenz	B-23
13230	guanadrel	B-23
13231	guanethidine	B-23
13232	guanfacine	B-23
13233	hydralazine	B-23
13234	hydrochlorothiazide	B-23
13235	inbesartan	B-23
13236	isradipine	B-23
13237	labetalol	B-23
13238	lisinopril	B-23
13239	losartan	B-23
13240	methyldopa	B-23
13241	methyldopate	B-23
13242	metoprolol	B-23
13243	minoxidil	B-23
13244	moexipril	B-23
13245	nicardipine	B-23
13246	nifedipine	B-23
13247	nimodipine	B-23
13248	nitroprusside	B-23
13249	perindopril erbumine	B-23
13250	phenoxybenzamine	B-23
13251	phentolamine	B-23
13252	polythiazide	B-23
13253	prazosin	B-23
13254	propranolol	B-23
13255	quinapril	B-23
13256	ramipril	B-23
13257	reserpine	B-23
13258	spironolactone	B-23
13259	terazosin	B-23
13260	trandolapril	B-23
13261	triameterene	B-23
13262	trimethaphan	B-23
13263	valsartan	B-23
13264	verapamil	B-23
13265	amiloride	B-24
13266	amlodipine	B-24
13267	benazepril	B-24
13268	bumetanide	B-24
13269	candesartan cilexetil	B-24
13270	captopril	B-24
13271	carvedilol	B-24
13272	chlorothiazide	B-24
13273	chlorthalidone	B-24
13274	clonidine	B-24
13275	delodipine	B-24
13276	diazoxide	B-24
13277	diltiazem	B-24
13278	doxazosin	B-24
13279	enalapril	B-24
13280	eplerenone	B-24
13281	ethacrynic acid	B-24

TABLE 21-continued

Example Number	Compound 1	Compound 2
13282	fosinopril	B-24
13283	furosemide	B-24
13284	guanabenz	B-24
13285	guanadrel	B-24
13286	guanethidine	B-24
13287	guanfacine	B-24
13288	hydralazine	B-24
13289	hydrochlorothiazide	B-24
13290	inbesartan	B-24
13291	isradipine	B-24
13292	labetalol	B-24
13293	lisinopril	B-24
13294	losartan	B-24
13295	methyldopa	B-24
13296	methyldopate	B-24
13297	metoprolol	B-24
13298	minoxidil	B-24
13299	moexipril	B-24
13300	nicardipine	B-24
13301	nifedipine	B-24
13302	nimodipine	B-24
13303	nitroprusside	B-24
13304	perindopril erbumine	B-24
13305	phenoxybenzamine	B-24
13306	phentolamine	B-24
13307	polythiazide	B-24
13308	prazosin	B-24
13309	propranolol	B-24
13310	quinapril	B-24
13311	ramipril	B-24
13312	reserpine	B-24
13313	spironolactone	B-24
13314	terazosin	B-24
13315	trandolapril	B-24
13316	triameterene	B-24
13317	trimethaphan	B-24
13318	valsartan	B-24
13319	verapamil	B-24
13320	amiloride	B-25
13321	amlodipine	B-25
13322	benazepril	B-25
13323	bumetanide	B-25
13324	candesartan cilexetil	B-25
13325	captopril	B-25
13326	carvedilol	B-25
13327	chlorothiazide	B-25
13328	chlorthalidone	B-25
13329	clonidine	B-25
13330	delodipine	B-25
13331	diazoxide	B-25
13332	diltiazem	B-25
13333	doxazosin	B-25
13334	enalapril	B-25
13335	eplerenone	B-25
13336	ethacrynic acid	B-25
13337	fosinopril	B-25
13338	furosemide	B-25
13339	guanabenz	B-25
13340	guanadrel	B-25
13341	guanethidine	B-25
13342	guanfacine	B-25
13343	hydralazine	B-25
13344	hydrochlorothiazide	B-25
13345	inbesartan	B-25
13346	isradipine	B-25
13347	labetalol	B-25
13348	lisinopril	B-25
13349	losartan	B-25
13350	methyldopa	B-25
13351	methyldopate	B-25
13352	metoprolol	B-25
13353	minoxidil	B-25
13354	moexipril	B-25

TABLE 21-continued

Example Number	Compound 1	Compound 2
13355	nicardipine	B-25
13356	nifedipine	B-25
13357	nimodipine	B-25
13358	nitroprusside	B-25
13359	perindopril erbumine	B-25
13360	phenoxybenzamine	B-25
13361	phentolamine	B-25
13362	polythiazide	B-25
13363	prazosin	B-25
13364	propranolol	B-25
13365	quinapril	B-25
13366	ramipril	B-25
13367	reserpine	B-25
13368	spironolactone	B-25
13369	terazosin	B-25
13370	trandolapril	B-25
13371	triameterene	B-25
13372	trimethaphan	B-25
13373	valsartan	B-25
13374	verapamil	B-25
13375	amiloride	B-26
13376	amlodipine	B-26
13377	benazepril	B-26
13378	bumetanide	B-26
13379	candesartan cilexetil	B-26
13380	captopril	B-26
13381	carvedilol	B-26
13382	chlorothiazide	B-26
13383	chlorthalidone	B-26
13384	clonidine	B-26
13385	delodipine	B-26
13386	diazoxide	B-26
13387	diltiazem	B-26
13388	doxazosin	B-26
13389	enalapril	B-26
13390	eplerenone	B-26
13391	ethacrynic acid	B-26
13392	fosinopril	B-26
13393	furosemide	B-26
13394	guanabenz	B-26
13395	guanadrel	B-26
13396	guanethidine	B-26
13397	guanfacine	B-26
13398	hydralazine	B-26
13399	hydrochlorothiazide	B-26
13400	inbesartan	B-26
13401	isradipine	B-26
13402	labetalol	B-26
13403	lisinopril	B-26
13404	losartan	B-26
13405	methyldopa	B-26
13406	methyldopate	B-26
13407	metoprolol	B-26
13408	minoxidil	B-26
13409	moexipril	B-26
13410	nicardipine	B-26
13411	nifedipine	B-26
13412	nimodipine	B-26
13413	nitroprusside	B-26
13414	perindopril erbumine	B-26
13415	phenoxybenzamine	B-26
13416	phentolamine	B-26
13417	polythiazide	B-26
13418	prazosin	B-26
13419	propranolol	B-26
13420	quinapril	B-26
13421	ramipril	B-26
13422	reserpine	B-26
13423	spironolactone	B-26
13424	terazosin	B-26
13425	trandolapril	B-26
13426	triameterene	B-26
13427	trimethaphan	B-26

TABLE 21-continued

Example Number	Compound 1	Compound 2
13428	valsartan	B-26
13429	verapamil	B-26
13430	amiloride	B-27
13431	amlodipine	B-27
13432	benazepril	B-27
13433	bumetanide	B-27
13434	candesartan cilexetil	B-27
13435	captopril	B-27
13436	carvedilol	B-27
13437	chlorothiazide	B-27
13438	chlorthalidone	B-27
13439	clonidine	B-27
13440	delodipine	B-27
13441	diazoxide	B-27
13442	diltiazem	B-27
13443	doxazosin	B-27
13444	enalapril	B-27
13445	eplerenone	B-27
13446	ethacrynic acid	B-27
13447	fosinopril	B-27
13448	furosemide	B-27
13449	guanabenz	B-27
13450	guanadrel	B-27
13451	guanethidine	B-27
13452	guanfacine	B-27
13453	hydralazine	B-27
13454	hydrochlorothiazide	B-27
13455	inbesartan	B-27
13456	isradipine	B-27
13457	labetalol	B-27
13458	lisinopril	B-27
13459	losartan	B-27
13460	methyldopa	B-27
13461	methyldopate	B-27
13462	metoprolol	B-27
13463	minoxidil	B-27
13464	moexipril	B-27
13465	nicardipine	B-27
13466	nifedipine	B-27
13467	nimodipine	B-27
13468	nitroprusside	B-27
13469	perindopril erbumine	B-27
13470	phenoxybenzamine	B-27
13471	phentolamine	B-27
13472	polythiazide	B-27
13473	prazosin	B-27
13474	propranolol	B-27
13475	quinapril	B-27
13476	ramipril	B-27
13477	reserpine	B-27
13478	spironolactone	B-27
13479	terazosin	B-27
13480	trandolapril	B-27
13481	triameterene	B-27
13482	trimethaphan	B-27
13483	valsartan	B-27
13484	verapamil	B-27
13485	amiloride	B-28
13486	amlodipine	B-28
13487	benazepril	B-28
13488	bumetanide	B-28
13489	candesartan cilexetil	B-28
13490	captopril	B-28
13491	carvedilol	B-28
13492	chlorothiazide	B-28
13493	chlorthalidone	B-28
13494	clonidine	B-28
13495	delodipine	B-28
13496	diazoxide	B-28
13497	diltiazem	B-28
13498	doxazosin	B-28
13499	enalapril	B-28
13500	eplerenone	B-28

TABLE 21-continued

Example Number	Compound 1	Compound 2
13501	ethacrynic acid	B-28
13502	fosinopril	B-28
13503	furosemide	B-28
13504	guanabenz	B-28
13505	guanadrel	B-28
13506	guanethidine	B-28
13507	guanfacine	B-28
13508	hydralazine	B-28
13509	hydrochlorothiazide	B-28
13510	inbesartan	B-28
13511	isradipine	B-28
13512	labetalol	B-28
13513	lisinopril	B-28
13514	losartan	B-28
13515	methyldopa	B-28
13516	methyldopate	B-28
13517	metoprolol	B-28
13518	minoxidil	B-28
13519	moexipril	B-28
13520	nicardipine	B-28
13521	nifedipine	B-28
13522	nimodipine	B-28
13523	nitroprusside	B-28
13524	perindopril erbumine	B-28
13525	phenoxybenzamine	B-28
13526	phentolamine	B-28
13527	polythiazide	B-28
13528	prazosin	B-28
13529	propranolol	B-28
13530	quinapril	B-28
13531	ramipril	B-28
13532	reserpine	B-28
13533	spironolactone	B-28
13534	terazosin	B-28
13535	trandolapril	B-28
13536	triameterene	B-28
13537	trimethaphan	B-28
13538	valsartan	B-28
13539	verapamil	B-28
13540	amiloride	B-29
13541	amlodipine	B-29
13542	benazepril	B-29
13543	bumetanide	B-29
13544	candesartan cilexetil	B-29
13545	captopril	B-29
13546	carvedilol	B-29
13547	chlorothiazide	B-29
13548	chlorthalidone	B-29
13549	clonidine	B-29
13550	delodipine	B-29
13551	diazoxide	B-29
13552	diltiazem	B-29
13553	doxazosin	B-29
13554	enalapril	B-29
13555	eplerenone	B-29
13556	ethacrynic acid	B-29
13557	fosinopril	B-29
13558	furosemide	B-29
13559	guanabenz	B-29
13560	guanadrel	B-29
13561	guanethidine	B-29
13562	guanfacine	B-29
13563	hydralazine	B-29
13564	hydrochlorothiazide	B-29
13565	inbesartan	B-29
13566	isradipine	B-29
13567	labetalol	B-29
13568	lisinopril	B-29
13569	losartan	B-29
13570	methyldopa	B-29
13571	methyldopate	B-29
13572	metoprolol	B-29
13573	minoxidil	B-29

TABLE 21-continued

Example Number	Compound 1	Compound 2
13574	moexipril	B-29
13575	nicardipine	B-29
13576	nifedipine	B-29
13577	nimodipine	B-29
13578	nitroprusside	B-29
13579	perindopril erbumine	B-29
13580	phenoxybenzamine	B-29
13581	phentolamine	B-29
13582	polythiazide	B-29
13583	prazosin	B-29
13584	propranolol	B-29
13585	quinapril	B-29
13586	ramipril	B-29
13587	reserpine	B-29
13588	spironolactone	B-29
13589	terazosin	B-29
13590	trandolapril	B-29
13591	triameterene	B-29
13592	trimethaphan	B-29
13593	valsartan	B-29
13594	verapamil	B-29
13595	amiloride	B-30
13596	amlodipine	B-30
13597	benazepril	B-30
13598	bumetanide	B-30
13599	candesartan cilexetil	B-30
13600	captopril	B-30
13601	carvedilol	B-30
13602	chlorothiazide	B-30
13603	chlorthalidone	B-30
13604	clonidine	B-30
13605	delodipine	B-30
13606	diazoxide	B-30
13607	diltiazem	B-30
13608	doxazosin	B-30
13609	enalapril	B-30
13610	eplerenone	B-30
13611	ethacrynic acid	B-30
13612	fosinopril	B-30
13613	furosemide	B-30
13614	guanabenz	B-30
13615	guanadrel	B-30
13616	guanethidine	B-30
13617	guanfacine	B-30
13618	hydralazine	B-30
13619	hydrochlorothiazide	B-30
13620	inbesartan	B-30
13621	isradipine	B-30
13622	labetalol	B-30
13623	lisinopril	B-30
13624	losartan	B-30
13625	methyldopa	B-30
13626	methyldopate	B-30
13627	metoprolol	B-30
13628	minoxidil	B-30
13629	moexipril	B-30
13630	nicardipine	B-30
13631	nifedipine	B-30
13632	nimodipine	B-30
13633	nitroprusside	B-30
13634	perindopril erbumine	B-30
13635	phenoxybenzamine	B-30
13636	phentolamine	B-30
13637	polythiazide	B-30
13638	prazosin	B-30
13639	propranolol	B-30
13640	quinapril	B-30
13641	ramipril	B-30
13642	reserpine	B-30
13643	spironolactone	B-30
13644	terazosin	B-30
13645	trandolapril	B-30
13646	triameterene	B-30

TABLE 21-continued

Example Number	Compound 1	Compound 2
13647	trimethaphan	B-30
13648	valsartan	B-30
13649	verapamil	B-30
13650	amiloride	B-31
13651	amlodipine	B-31
13652	benazepril	B-31
13653	bumetanide	B-31
13654	candesartan cilexetil	B-31
13655	captopril	B-31
13656	carvedilol	B-31
13657	chlorothiazide	B-31
13658	chlorthalidone	B-31
13659	clonidine	B-31
13660	delodipine	B-31
13661	diazoxide	B-31
13662	diltiazem	B-31
13663	doxazosin	B-31
13664	enalapril	B-31
13665	eplerenone	B-31
13666	ethacrynic acid	B-31
13667	fosinopril	B-31
13668	furosemide	B-31
13669	guanabenz	B-31
13670	guanadrel	B-31
13671	guanethidine	B-31
13672	guanfacine	B-31
13673	hydralazine	B-31
13674	hydrochlorothiazide	B-31
13675	inbesartan	B-31
13676	isradipine	B-31
13677	labetalol	B-31
13678	lisinopril	B-31
13679	losartan	B-31
13680	methyldopa	B-31
13681	methyldopate	B-31
13682	metoprolol	B-31
13683	minoxidil	B-31
13684	moexipril	B-31
13685	nicardipine	B-31
13686	nifedipine	B-31
13687	nimodipine	B-31
13688	nitroprusside	B-31
13689	perindopril erbumine	B-31
13690	phenoxybenzamine	B-31
13691	phentolamine	B-31
13692	polythiazide	B-31
13693	prazosin	B-31
13694	propranolol	B-31
13695	quinapril	B-31
13696	ramipril	B-31
13697	reserpine	B-31
13698	spironolactone	B-31
13699	terazosin	B-31
13700	trandolapril	B-31
13701	triameterene	B-31
13702	trimethaphan	B-31
13703	valsartan	B-31
13704	verapamil	B-31
13705	amiloride	B-32
13706	amlodipine	B-32
13707	benazepril	B-32
13708	bumetanide	B-32
13709	candesartan cilexetil	B-32
13710	captopril	B-32
13711	carvedilol	B-32
13712	chlorothiazide	B-32
13713	chlorthalidone	B-32
13714	clonidine	B-32
13715	delodipine	B-32
13716	diazoxide	B-32
13717	diltiazem	B-32
13718	doxazosin	B-32
13719	enalapril	B-32

TABLE 21-continued

Example Number	Compound 1	Compound 2
13720	eplerenone	B-32
13721	ethacrynic acid	B-32
13722	fosinopril	B-32
13723	furosemide	B-32
13724	guanabenz	B-32
13725	guanadrel	B-32
13726	guanethidine	B-32
13727	guanfacine	B-32
13728	hydralazine	B-32
13729	hydrochlorothiazide	B-32
13730	inbesartan	B-32
13731	isradipine	B-32
13732	labetalol	B-32
13733	lisinopril	B-32
13734	losartan	B-32
13735	methyldopa	B-32
13736	methyldopate	B-32
13737	metoprolol	B-32
13738	minoxidil	B-32
13739	moexipril	B-32
13740	nicardipine	B-32
13741	nifedipine	B-32
13742	nimodipine	B-32
13743	nitroprusside	B-32
13744	perindopril erbumine	B-32
13745	phenoxybenzamine	B-32
13746	phentolamine	B-32
13747	polythiazide	B-32
13748	prazosin	B-32
13749	propranolol	B-32
13750	quinapril	B-32
13751	ramipril	B-32
13752	reserpine	B-32
13753	spironolactone	B-32
13754	terazosin	B-32
13755	trandolapril	B-32
13756	triameterene	B-32
13757	trimethaphan	B-32
13758	valsartan	B-32
13759	verapamil	B-32
13760	amiloride	B-33
13761	amlodipine	B-33
13762	benazepril	B-33
13763	bumetanide	B-33
13764	candesartan cilexetil	B-33
13765	captopril	B-33
13766	carvedilol	B-33
13767	chlorothiazide	B-33
13768	chlorthalidone	B-33
13769	clonidine	B-33
13770	delodipine	B-33
13771	diazoxide	B-33
13772	diltiazem	B-33
13773	doxazosin	B-33
13774	enalapril	B-33
13775	eplerenone	B-33
13776	ethacrynic acid	B-33
13777	fosinopril	B-33
13778	furosemide	B-33
13779	guanabenz	B-33
13780	guanadrel	B-33
13781	guanethidine	B-33
13782	guanfacine	B-33
13783	hydralazine	B-33
13784	hydrochlorothiazide	B-33
13785	inbesartan	B-33
13786	isradipine	B-33
13787	labetalol	B-33
13788	lisinopril	B-33
13789	losartan	B-33
13790	methyldopa	B-33
13791	methyldopate	B-33
13792	metoprolol	B-33

TABLE 21-continued

Example Number	Compound 1	Compound 2
13793	minoxidil	B-33
13794	moexipril	B-33
13795	nicardipine	B-33
13796	nifedipine	B-33
13797	nimodipine	B-33
13798	nitroprusside	B-33
13799	perindopril erbumine	B-33
13800	phenoxybenzamine	B-33
13801	phentolamine	B-33
13802	polythiazide	B-33
13803	prazosin	B-33
13804	propranolol	B-33
13805	quinapril	B-33
13806	ramipril	B-33
13807	reserpine	B-33
13808	spironolactone	B-33
13809	terazosin	B-33
13810	trandolapril	B-33
13811	triameterene	B-33
13812	trimethaphan	B-33
13813	valsartan	B-33
13814	verapamil	B-33
13815	amiloride	B-35
13816	amlodipine	B-35
13817	benazepril	B-35
13818	bumetanide	B-35
13819	candesartan cilexetil	B-35
13820	captopril	B-35
13821	carvedilol	B-35
13822	chlorothiazide	B-35
13823	chlorthalidone	B-35
13824	clonidine	B-35
13825	delodipine	B-35
13826	diazoxide	B-35
13827	diltiazem	B-35
13828	doxazosin	B-35
13829	enalapril	B-35
13830	eplerenone	B-35
13831	ethacrynic acid	B-35
13832	fosinopril	B-35
13833	furosemide	B-35
13834	guanabenz	B-35
13835	guanadrel	B-35
13836	guanethidine	B-35
13837	guanfacine	B-35
13838	hydralazine	B-35
13839	hydrochlorothiazide	B-35
13840	inbesartan	B-35
13841	isradipine	B-35
13842	labetalol	B-35
13843	lisinopril	B-35
13844	losartan	B-35
13845	methyldopa	B-35
13846	methyldopate	B-35
13847	metoprolol	B-35
13848	minoxidil	B-35
13849	moexipril	B-35
13850	nicardipine	B-35
13851	nifedipine	B-35
13852	nimodipine	B-35
13853	nitroprusside	B-35
13854	perindopril erbumine	B-35
13855	phenoxybenzamine	B-35
13856	phentolamine	B-35
13857	polythiazide	B-35
13858	prazosin	B-35
13859	propranolol	B-35
13860	quinapril	B-35
13861	ramipril	B-35
13862	reserpine	B-35
13863	spironolactone	B-35
13864	terazosin	B-35
13865	trandolapril	B-35

TABLE 21-continued

Example Number	Compound 1	Compound 2
13866	triameterene	B-35
13867	trimethaphan	B-35
13868	valsartan	B-35
13869	verapamil	B-35
13870	amiloride	B-36
13871	amlodipine	B-36
13872	benazepril	B-36
13873	bumetanide	B-36
13874	candesartan cilexetil	B-36
13875	captopril	B-36
13876	carvedilol	B-36
13877	chlorothiazide	B-36
13878	chlorthalidone	B-36
13879	clonidine	B-36
13880	delodipine	B-36
13881	diazoxide	B-36
13882	diltiazem	B-36
13883	doxazosin	B-36
13884	enalapril	B-36
13885	eplerenone	B-36
13886	ethacrynic acid	B-36
13887	fosinopril	B-36
13888	furosemide	B-36
13889	guanabenz	B-36
13890	guanadrel	B-36
13891	guanethidine	B-36
13892	guanfacine	B-36
13893	hydralazine	B-36
13894	hydrochlorothiazide	B-36
13895	inbesartan	B-36
13896	isradipine	B-36
13897	labetalol	B-36
13898	lisinopril	B-36
13899	losartan	B-36
13900	methyldopa	B-36
13901	methyldopate	B-36
13902	metoprolol	B-36
13903	minoxidil	B-36
13904	moexipril	B-36
13905	nicardipine	B-36
13906	nifedipine	B-36
13907	nimodipine	B-36
13908	nitroprusside	B-36
13909	perindopril erbumine	B-36
13910	phenoxybenzamine	B-36
13911	phentolamine	B-36
13912	polythiazide	B-36
13913	prazosin	B-36
13914	propranolol	B-36
13915	quinapril	B-36
13916	ramipril	B-36
13917	reserpine	B-36
13918	spironolactone	B-36
13919	terazosin	B-36
13920	trandolapril	B-36
13921	triameterene	B-36
13922	trimethaphan	B-36
13923	valsartan	B-36
13924	verapamil	B-36
13925	amiloride	B-37
13926	amlodipine	B-37
13927	benazepril	B-37
13928	bumetanide	B-37
13929	candesartan cilexetil	B-37
13930	captopril	B-37
13931	carvedilol	B-37
13932	chlorothiazide	B-37
13933	chlorthalidone	B-37
13934	clonidine	B-37
13935	delodipine	B-37
13936	diazoxide	B-37
13937	diltiazem	B-37
13938	doxazosin	B-37

TABLE 21-continued

Example Number	Compound 1	Compound 2
13939	enalapril	B-37
13940	eplerenone	B-37
13941	ethacrynic acid	B-37
13942	fosinopril	B-37
13943	furosemide	B-37
13944	guanabenz	B-37
13945	guanadrel	B-37
13946	guanethidine	B-37
13947	guanfacine	B-37
13948	hydralazine	B-37
13949	hydrochlorothiazide	B-37
13950	inbesartan	B-37
13951	isradipine	B-37
13952	labetalol	B-37
13953	lisinopril	B-37
13954	losartan	B-37
13955	methyldopa	B-37
13956	methyldopate	B-37
13957	metoprolol	B-37
13958	minoxidil	B-37
13959	moexipril	B-37
13960	nicardipine	B-37
13961	nifedipine	B-37
13962	nimodipine	B-37
13963	nitroprusside	B-37
13964	perindopril erbumine	B-37
13965	phenoxybenzamine	B-37
13966	phentolamine	B-37
13967	polythiazide	B-37
13968	prazosin	B-37
13969	propranolol	B-37
13970	quinapril	B-37
13971	ramipril	B-37
13972	reserpine	B-37
13973	spironolactone	B-37
13974	terazosin	B-37
13975	trandolapril	B-37
13976	triameterene	B-37
13977	trimethaphan	B-37
13978	valsartan	B-37
13979	verapamil	B-37
13980	amiloride	B-38
13981	amlodipine	B-38
13982	benazepril	B-38
13983	bumetanide	B-38
13984	candesartan cilexetil	B-38
13985	captopril	B-38
13986	carvedilol	B-38
13987	chlorothiazide	B-38
13988	chlorthalidone	B-38
13989	clonidine	B-38
13990	delodipine	B-38
13991	diazoxide	B-38
13992	diltiazem	B-38
13993	doxazosin	B-38
13994	enalapril	B-38
13995	eplerenone	B-38
13996	ethacrynic acid	B-38
13997	fosinopril	B-38
13998	furosemide	B-38
13999	guanabenz	B-38
14000	guanadrel	B-38
14001	guanethidine	B-38
14002	guanfacine	B-38
14003	hydralazine	B-38
14004	hydrochlorothiazide	B-38
14005	inbesartan	B-38
14006	isradipine	B-38
14007	labetalol	B-38
14008	lisinopril	B-38
14009	losartan	B-38
14010	methyldopa	B-38
14011	methyldopate	B-38

TABLE 21-continued

Example Number	Compound 1	Compound 2
14012	metoprolol	B-38
14013	minoxidil	B-38
14014	moexipril	B-38
14015	nicardipine	B-38
14016	nifedipine	B-38
14017	nimodipine	B-38
14018	nitroprusside	B-38
14019	perindopril erbumine	B-38
14020	phenoxybenzamine	B-38
14021	phentolamine	B-38
14022	polythiazide	B-38
14023	prazosin	B-38
14024	propranolol	B-38
14025	quinapril	B-38
14026	ramipril	B-38
14027	reserpine	B-38
14028	spironolactone	B-38
14029	terazosin	B-38
14030	trandolapril	B-38
14031	triameterene	B-38
14032	trimethaphan	B-38
14033	valsartan	B-38
14034	verapamil	B-38
14035	amiloride	B-39
14036	amlodipine	B-39
14037	benazepril	B-39
14038	bumetanide	B-39
14039	candesartan cilexetil	B-39
14040	captopril	B-39
14041	carvedilol	B-39
14042	chlorothiazide	B-39
14043	chlorthalidone	B-39
14044	clonidine	B-39
14045	delodipine	B-39
14046	diazoxide	B-39
14047	diltiazem	B-39
14048	doxazosin	B-39
14049	enalapril	B-39
14050	eplerenone	B-39
14051	ethacrynic acid	B-39
14052	fosinopril	B-39
14053	furosemide	B-39
14054	guanabenz	B-39
14055	guanadrel	B-39
14056	guanethidine	B-39
14057	guanfacine	B-39
14058	hydralazine	B-39
14059	hydrochlorothiazide	B-39
14060	inbesartan	B-39
14061	isradipine	B-39
14062	labetalol	B-39
14063	lisinopril	B-39
14064	losartan	B-39
14065	methyldopa	B-39
14066	methyldopate	B-39
14067	metoprolol	B-39
14068	minoxidil	B-39
14069	moexipril	B-39
14070	nicardipine	B-39
14071	nifedipine	B-39
14072	nimodipine	B-39
14073	nitroprusside	B-39
14074	perindopril erbumine	B-39
14075	phenoxybenzamine	B-39
14076	phentolamine	B-39
14077	polythiazide	B-39
14078	prazosin	B-39
14079	propranolol	B-39
14080	quinapril	B-39
14081	ramipril	B-39
14082	reserpine	B-39
14083	spironolactone	B-39
14084	terazosin	B-39

TABLE 21-continued

Example Number	Compound 1	Compound 2
14085	trandolapril	B-39
14086	triameterene	B-39
14087	trimethaphan	B-39
14088	valsartan	B-39
14089	verapamil	B-39

[0230] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a microsomal triglyceride transfer protein inhibiting compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

[0231] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a cholesterol absorption antagonist compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

[0232] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antihypertensive compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount of the compounds.

[0233] In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a phytosterol compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds. Preferably the phytosterol compound comprises a stanol.

[0234] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a microsomal triglyceride transfer protein inhibiting compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

[0235] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a cholesterol absorption antagonist compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

[0236] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of an antihypertensive compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

[0237] In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a phytosterol compound in a second unit dosage form; and container means for containing said first and second unit dosage forms. Preferably the phytosterol compound comprises a stanol.

Biological Assays

[0238] The utility of the combinations of the present invention can be shown by the following assays. These assays are performed in vitro and in animal models essentially using procedures recognized to show the utility of the present invention.

[0239] In Vitro Assay of Compounds that Inhibit IBAT-mediated Uptake of [^{14}C]-Taurocholate (TC) in H14 Cells

[0240] Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are to be seeded at 60,000 cells/well in 96 well Top-Count tissue culture plates for assays run within in 24 hours of seeding, 30,000 cells/well for assays run within 48 hours, and 10,000 cells/well for assays run within 72 hours.

[0241] On the day of assay, the cell monolayer is gently washed once with 100 μl assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose+0.2% (w/v) fatty acid free bovine serum albumin-(FAF)BSA). To each well 50 μl of a two-fold concentrate of test compound in assay buffer is added along with 50 μl of 6 μM [^{14}C]-taurocholate in assay buffer (final concentration of 3 μM [^{14}C]-taurocholate). The cell culture plates are incubated 2 hours at 37° C. prior to gently washing each well twice with 100 μl 4° C. Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then to be gently washed once with 100 μl 4° C. PBS without (FAF)BSA. To each 200 μl of liquid scintillation counting fluid is to be added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

[0242] In Vitro Assay of Compounds that Inhibit uptake of [^{14}C]-Alanine

[0243] The alanine uptake assay can be performed in an identical fashion to the taurocholate assay, with the exception that labeled alanine is to be substituted for the labeled taurocholate.

[0244] In Vivo Assay of Compounds that Inhibit Rat Ileal Uptake of [^{14}C]-Taurocholate Into Bile

[0245] (See "Metabolism of 3α,7β-dihydroxy-7α-methyl-5β-cholanoic acid and 3α,7β-dihydroxy-7α-methyl-5β-cholanoic acid in hamsters" in *Biochimica et Biophysica Acta,* 833, 196-202 (1985) by Une et al., herein incorporated by reference.)

[0246] Male wistar rats (200-300 g) are to be anesthetized with inactin @100 mg/kg. Bile ducts are cannulated with a 10" length of PE10 tubing. The small intestine is exposed and laid out on a gauze pad. A canulae (⅛" luer lock, tapered female adapter) is inserted at 12 cm from the junction of the small intestine and the cecum. A slit is cut at 4 cm from this same junction (utilizing a 8 cm length of ileum). 20 ml of warm Dulbecco's phosphate buffered saline, pH 6.5 (PBS) is used to flush out the intestine segment. The distal opening is cannulated with a 20 cm length of silicone tubing (0.02" I.D.x0.037" O.D.). The proximal cannulae is hooked up to a peristaltic pump and the intestine is washed for 20 min with warm PBS at 0.25 ml/min. Temperature of the gut segment is to be monitored continuously. At the start of the experiment, 2.0 ml of control sample ([^{14}C]-taurocholate @ 0.05 mCi/ml with 5 mM non-radiolabeled taurocholate) is loaded into the gut segment with a 3 ml syringe and bile sample collection is begun. Control sample is infused at a rate of 0.25 ml/min for 21 min. Bile samples fractions will be collected every 3 minute for the first 27 minutes of the procedure. After the 21 min of sample infusion, the ileal loop is washed out with 20 ml of warm PBS (using a 30 ml syringe), and then the loop is washed out for 21 min with warm PBS at 0.25 ml/min. A second perfusion is to be initiated as described above but with test compound being administered as well (21 min administration followed by 21 min of wash out) and bile to be sampled every 3 min for the first 27 min. If necessary, a third perfusion will be performed as above that typically contains the control sample.

[0247] Measurement of Hepatic Cholesterol Concentration (Hepatic CHOL)

[0248] Liver tissue is to be weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant is separated and dried under nitrogen. The residue is to be dissolved in isopropanol and the cholesterol content will be measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A. et al., *Clin. Chem.,* 20, 470 (1974) (herein incorporated by reference).

[0249] Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL+LDL)

[0250] Total serum cholesterol (SER.CHOL) are to be measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, Va.); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) will be assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) will be assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL (VLDL+LDL) cholesterol concentrations will be calculated as the difference between total and HDL cholesterol.

[0251] Measurement of Hepatic Cholesterol 7-α-Hydroxylase Activity (7a-OHase)

[0252] Hepatic microsomes are to be prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material is resuspended in buffer and an aliquot will be assayed for cholesterol 7-α-hydroxylase activity by incubating for 5 minutes at 37° C. in the presence of NADPH. Following extraction into petroleum ether, the organic solvent is evaporated and the residue is dissolved in acetonitrile/methanol. The enzymatic product will be separated by injecting an aliquot of the extract onto a C_{18} reversed phase HPLC column and quantitating the eluted material using UV detection at 240 nm. (Reference: Horton, J. D., et al. (1994) J. Clin. Invest. 93, 2084).

[0253] Rat Gavage Assay

[0254] Male Wister rats (275-300 g) are to be administered IBAT inhibitors using an oral gavage procedure. Drug or vehicle (0.2% TWEEN 80 in water) is administered once a day (9:00-10:0 a.m.) for 4 days at varying dosages in a final volume of 2 mL per kilogram of body weight. (TWEEN 80 is a 20 molar polyethyleneoxide sorbitan monooleate surfactant manufactured by ICI Specialty Chemicals, Wilmington, Del., U.S.A.) Total fecal samples are collected during the final 48 hours of the treatment period and analyzed for bile acid content using an enzymatic assay as described below. Compound efficacy will be determined by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group.

[0255] Measurement of Fecal Bile Acid Concentration (FBA)

[0256] Total fecal output from individually housed rats is to be collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed. Approximately 0.1 gram is weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue is dissolved in methanol and the amount of bile acid present will be measured enzymatically using the 3α-hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (see Mashige, F. et al. *Clin. Chem.,* 27, 1352 (1981), herein incorporated by reference).

[0257] [^{3}H]taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

[0258] Rabbit Ileal brush border membranes are to be prepared from frozen ileal mucosa by the calcium precipitation method describe by Malathi et al. (*Biochimica Biophysica Acta,* 554, 259 (1979), herein incorporated by reference). The method for measuring taurocholate is essentially as described by Kramer et al. (*Biochimica Biophysica Acta,* 1111, 93 (1992), herein incorporated by reference) except the assay volume will be 200 μl instead of 100 μl. Briefly, at room temperature a 190 μl solution containing 2 μl [^{3}H]-taurocholate(0.75 μCi), 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 is incubated for 5 sec with 10 μl of brush border membrane vesicles (60-120 μg protein). The incubation is initiated by the addition of the BBMV while vortexing and the reaction is to be stopped by the addition of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2 μm pore) and an additional 5 ml wash with stop buffer.

[0259] Acyl-CoA; Cholesterol Acyl Transferase (ACAT)

[0260] Hamster liver and rat intestinal microsomes are to be prepared from tissue as described previously (*J. Biol.*

Chem., 255, 9098 (1980), herein incorporated by reference) and used as a source of ACAT enzyme. The assay will consist of a 2.0 ml incubation containing 24 μl Oleoyl-CoA (0.05 μCi) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 buffer containing 0.25% BSA and 200 μg of microsomal protein. The assay will be initiated by the addition of oleoyl-CoA. The reaction proceeds for 5 min at 37° C. and will be terminated by the addition of 8.0 ml of chloroform/methanol (2:1). To the extraction is added 125 μg of cholesterol oleate in chloroform methanol to act as a carrier and the organic and aqueous phases of the extraction are separated by centrifugation after thorough vortexing. The chloroform phase is to be taken to dryness and then spotted on a silica gel 60 TLC plate and developed in hexane/ethyl ether (9:1). The amount of cholesterol ester formed will be determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard Instaimager.

[0261] Dog Model for Evaluating Lipid Lowering Drugs

[0262] Male beagle dogs, obtained from a vendor such as Marshall farms and weighing 6-12 kg are fed once a day for two hours and given water ad libitum. Dogs may be randomly assigned to a dosing groups consisting of 6 to 12 dogs each, such as: vehicle, i.g.; 1 mg/kg, i.g.; 2 mg/kg, i.g.; 4 mg/kg, i.g.; 2 mg/kg, p.o. (powder in capsule). Intra-gastric dosing of a therapeutic material dissolved in aqueous solution (for example, 0.2% Tween 80 solution [polyoxyethylene mono-oleate, Sigma Chemical Co., St. Louis, Mo.]) may be done using a gavage tube. Prior to initiating dosing, blood samples may be drawn from the cephalic vein in the morning before feeding in order to evaluate serum cholesterol (total and HDL) and triglycerides. For several consecutive days animals are dosed in the morning, prior to feeding. Animals are to be allowed 2 hours to eat before any remaining food is removed. Feces are to be collected over a 2 day period at the end of the study and may be analyzed for bile acid or lipid content. Blood samples are also to be taken, at the end of the treatment period, for comparison with pre-study serum lipid levels. Statistical significance will be determined using the standard student's T-test with $p<0.05$.

[0263] Dog Serum Lipid Measurement

[0264] Blood is to be collected from the cephalic vein of fasted dogs in serum separator tubes (Vacutainer SST, Becton Dickinson and Co., Franklin Lakes, N.J.). The blood is centrifuged at 2000 rpm for 20 minutes and the serum decanted.

[0265] Total cholesterol may be measured in a 96 well format using a Wako enzymatic diagnostic kit (Cholesterol CII) (Wako Chemicals, Richmond, Va.), utilizing the cholesterol oxidase reaction to produce hydrogen peroxide which is measured calorimetrically. A standard curve from 0.5 to 10 μg cholesterol is to be prepared in the first 2 columns of the plate. The serum samples (20-40 μl, depending on the expected lipid concentration) or known serum control samples are added to separate wells in duplicate. Water is added to bring the volume to 100 μl in each well. A 100 μl aliquot of color reagent is added to each well and the plates will be read at 500 nm after a 15 minute incubation at 37 degrees centigrade.

[0266] HDL cholesterol may be assayed using Sigma kit No. 352-3 (Sigma Chemical Co., St. Louis, Mo.) which utilizes dextran sulfate and Mg ions to selectively precipitate LDL and VLDL. A volume of 150 μl of each serum sample is to be added to individual microfuge tubes, followed by 15 μl of HDL cholesterol reagent (Sigma 352-3). Samples are to be mixed and centrifuged at 5000 rpm for 5 minutes. A 50 μl aliquot of the supernatant is to be then mixed with 200 μl of saline and assayed using the same procedure as for total cholesterol measurement.

[0267] Triglycerides are to be measured using Sigma kit No. 337 in a 96 well plate format. This procedure will measure glycerol, following its release by reaction of triglycerides with lipoprotein lipase. Standard solutions of glycerol (Sigma 339-11) ranging from 1 to 24 μg are to be used to generate the standard curve. Serum samples (20-40 μl, depending on the expected lipid concentration) are added to wells in duplicate. Water is added to bring the volume to 100 μl in each well and 100 μl of color reagent was also added to each well. After mixing and a 15 minute incubation, the plates will be read at 540 nm and the triglyceride values calculated from the standard curve. A replicate plate is also to be run using a blank enzyme reagent to correct for any endogenous glycerol in the serum samples.

[0268] Dog Fecal Bile Acid Measurement

[0269] Fecal samples may be collected to determine the fecal bile acid (FBA) concentration for each animal. Fecal collections may be made during the final 48 hours of the study, for two consecutive 24 hour periods between 9:00 am and 10:00 am each day, prior to dosing and feeding. The separate two day collections from each animal are to be weighed, combined and homogenized with distilled water in a processor (Cuisinart) to generate a homogeneous slurry. About 1.4 g of the homogenate is to be extracted in a final concentration of 50% tertiary butanol/distilled water (2:0.6) for 45 minutes in a 37° C. water bath and centrifuged for 13 minutes at 2000×g. The concentration of bile acids (mmoles/day) may be determined using a 96-well enzymatic assay system (1,2). A 20 μl aliquot of the fecal extract is to be added to two sets each of triplicate wells in a 96-well assay plate. A standardized sodium taurocholate solution and a standardized fecal extract solution (previously made from pooled samples and characterized for its bile acid concentration) will also analyzed for assay quality control. Twenty-microliter aliquots of sodium taurocholate, serially diluted to generate a standard curve are similarly to be added to two sets of triplicate wells. A 230 μl reaction mixture containing 1M hydrazine hydrate, 0.1 M pyrophosphate and 0.46 mg/ml NAD is to be added to each well. A 50 μl aliquot of 3a-hydroxysteroid dehydrogenase enzyme (HSD; 0.8 units/ml) or assay buffer (0.1 M sodium pyrophosphate) are then added to one of the two sets of triplicates. All reagents may be obtained from Sigma Chemical Co., St. Louis, Mo. Following 60 minutes of incubation at room temperature, the optical density at 340 nm will be measured and the mean of each set of triplicate samples will be calculated. The difference in optical density±HSD enzyme is to be used to determine the bile acid concentration (mM) of each sample based on the sodium taurocholate standard curve. The bile acid concentration of the extract, the weight of the fecal homogenate (grams) and the body weight of the animal are to be used to calculate the corresponding FBA concentration in mmoles/kg/day for each animal. The mean FBA concentration (mmoles/kg/day) of the vehicle group is to be sub-

tracted from the FBA concentration of each treatment group to determine the increase (delta value) in FBA concentration as a result of the treatment.

[0270] Saponification and Extraction of Neutral Sterols in Hamster Feces

[0271] Generally, a sample of dried animal feces will be directly saponified with 0.3N KOH/Methanol for 1 hour. After saponification, the samples are filtered to remove solid matter. The samples are extracted twice with petroleum ether, and the extracts are combined and evaporated to dryness with heating under a stream of nitrogen gas. The sample can be analyzed by a Hewlett Packard Model 6890 GC with autosampler using a 50 meter HP-5 Ultra-2 capillary column, 0.33 um film thickness, 0.32 ID, 100:1 split ratio, and an FID detector.

[0272] For preparation of the saponified samples, each 0.25 gram sample of dried powdered feces is transferred to a labeled 20×150 millimeter screw top tube. Three milliliters of 0.3N KOH/MEOH (7.5 ml of 8N (45%) KOH qs 200 ml with HPLC grade methanol) and 25 microliters of 20 mg/ml 5-alpha Cholestane as the internal standard are added to the tubes. The tubes are tightly capped and vortexed. The tubes are placed in a Reacti-Therm heating block in a hood and heated at 70° C. for one hour with intermittent mixing.

[0273] For preparation of saponified standards, each standard stock is mixed with 3 milliliters of 0.3N KOH/MEOH and 25 microliters of 5-alpha Cholestane. The standards are capped, heated for one hour at 70 degrees C. and extracted. Standard 1 will include a combination of 40 microliters of 20 mg/ml Stocks of each of stigmasterol, coprostanol and beta-sitosterol. Standard 2 will be a combination of one microliter of 20 mg/ml cholesterol (0.04 ug/ul) and 5 microliters of 20 mg/ml sitostanol (0.2 ug/ul). Standard 3 will be a combination of 40 microliters of 20 mg/ml cholesterol (1.6 ug/ul) and 200 microliters of 20 mg/ml sitostanol (8.0 ug/ul).

[0274] For preparation of non-saponified standards, the standards are pipetted into one milliliter V-vials and 25 microliters of 5-alpha cholestane is added. The standards are evaporated to dryness in the Reacti-Therm heating block, removed from the block and allowed to cool. Methylene chloride (500 ul) is added. The extracts are mixed and filtered through the Whatman Anatop filters. Standard 1 will include the combination of 40 microliters of 20 mg/ml stocks of each stigmasterol, coprostanol and beta-sitosterol. Standard 2 will include the combination of 5 microliters of 20 mg/ml cholesterol (0.2 ug/ul) and 25 microliters of 20 mg/ml of sitostanol (1.0 ug/ul). Standard 3 will include the combination of 20 microliters of 20 mg/ml cholesterol (0.8 ug/ul) and 100 microliters of 20 mg/ml sitostanol (4.0 ug/ul). Standard 4 will include the combination of 80 microliters of 20 mg/ml cholesterol (3.2 ug/ul) and 300 microliters of 20 mg/ml sitostanol (12.0 ug/ul).

[0275] All tubes are removed from the heating blocks and cooled. Each saponified sample and standard is filtered through a Whatman Autovial Syingeless Filter Device, 0.45 um, PTFE (Teflon) membrane. Each tube is washed with 10 mL of petroleum ether, vortexed and combined in the filtering device. The plunger is pushed to collect the sample in a clean 50 mL glass tube. Additional petroleum ether (10 mL) is added to the sample in the 50 mL tube along with 2 mL of water. Each sample is vortexed at a moderate speed (mixing too fast will cause emulsions to form) for 20 seconds. After the layers separated, 2×7 mL of the petroleum ether phase is removed and transfered to 16×125 millimeter glass tubes. The samples are extracted one more time with the addition of 10 mL of petroleum ether and 8 mL are removed, combining the extracts of each sample. All tubes are evaporated to dryness under a stream of nitrogen gas at 70° C. The residue of each sample is quantitatively transferred to 1.5 mL glass conical vials using 3×0.5 mL washes of petroleum ether. The samples are once again evaporated to dryness. After the vials cool to room temperature, 500 microliters of methylene chloride are added. All samples and standards are filtered through Whatman Anotop 10 Plus (0.2 um, 10 mm) syringe filters. Sufficient filtrate (approximately 300 microliters) is collected into footed micro GC sample tubes. The footed micro tubes are placed in screw capped vials and tightened firmly. Analysis will be by the Hewlett Packard GC procedure.

[0276] CETP Activity Assay in Human Plasma (Tritiated Cholesteryl Ester)

[0277] Blood is to be obtained from healthy volunteers. Blood is collected in tubes containing EDTA (EDTA plasma pool). The EDTA human plasma pool previously stored at −20° C., is to be thawed at room temperature, and centrifuged for 5 minutes to remove any particulate matter. Tritiated HDL, radiolabeled in the cholesteryl ester moiety ([^{3}H]CE-HDL) as described by Morton and Zilversmit (*J. Biol. Chem.,* 256, 11992-95 (1981)), is to be added to the plasma to a final concentration of (25 μg/ml cholesterol). Inhibitor compounds are to be added to the plasma as follows: Equal volumes of the plasma containing the [^{3}H] CE-HDL (396 μl) are added by pipette into micro tubes (Titertube®, Bio-Rad laboratories, Hercules, Calif.). Compounds, usually dissolved as 20-50 mM stock solutions in DMSO, are to be serially diluted in DMSO (or an alternative solvent in some cases, such as dimethylformamide or ethanol). Four μl of each of the serial dilutions of inhibitor compounds or DMSO alone are then added to each of the plasma tubes. The tubes are immediately mixed. Triplicate aliquots (100 μl) from each plasma tube are then transferred to wells of 96-well round-bottomed polystyrene microtiter plates (Corning, Corning, N.Y.). Plates are sealed with plastic film and incubated at 37° C. for 4 hours. Test wells are to contain plasma with dilutions of inhibitor compounds. Control wells are to contain plasma with DMSO alone. Blank wells are to contain plasma with DMSO alone that are left in the micro tubes at 4° C. for the 4 hour incubation and are added to the microtiter wells at the end of the incubation period. VLDL and LDL are precipitated by the addition of 10 μl of precipitating reagent (1% (w/v) dextran sulfate (Dextralip50)/0.5 M magnesium chloride, pH 7.4) to all wells. The wells are mixed on a plate mixer and then incubated at ambient temperature for 10 min. The plates are then centrifuged at 1000×g for 30 min at 10° C. The supernatants (50 μl) from each well are then transferred to Picoplate™ 96 plate wells (Packard, Meriden, Conn.) containing 250:1 Microscint™-40 (Packard, Meriden, Conn.) The plates are heat-sealed (TopSeal™-P, Packard, Meriden, Conn.) according to the manufacturer's directions and mixed for 30 min. Radioactivity will be measured on a microplate scintillation counter (TopCount, Packard, Meriden, Conn.). IC_{50} values will be determined as the concentration of inhibitor compound inhibiting transfer of [^{3}H]CE from the supernatant [^{3}H]CE-HDL to the precipitated VLDL

and LDL by 50% compared to the transfer obtained in the control wells. The maximum percentage transfer (in the control wells) will be determined using the following equation:

$$\% \text{ Transfer} = \frac{[dpm_{blank} - dpm_{control}] \times 100}{dpm_{blank}}$$

[0278] The percentage of control transfer determined in the wells containing inhibitor compounds is determined as follows:

$$\% \text{ Control} = \frac{[dpm_{blank} - dpm_{test}] \times 100}{dpm_{blank} - dpm_{control}}$$

[0279] IC_{50} values will be calculated from plots of % control versus concentration of inhibitor compound.

[0280] CETP Activity In Vitro

[0281] The ability of compounds to inhibit CETP activity are assessed using an in vitro assay that measures the rate of transfer of radiolabeled cholesteryl ester ([^{3}H]CE) from HDL donor particles to LDL acceptor particles. Details of the assay are provided by Glenn et al. (Glenn and Melton, "Quantification of Cholesteryl Ester Transfer Protein (CETP): A) CETP Activity and B) Immunochemical Assay of CETP Protein,"*Meth. Enzymol.,* 263, 339-351 (1996)). CETP can be obtained from the serum-free conditioned medium of CHO cells transfected with a cDNA for CETP (Wang, S. et al. *J. Biol. Chem.* 267, 17487-17490 (1992)). To measure CETP activity, [^{3}H]CE-labeled HDL, LDL, CETP and assay buffer (50 mM tris(hydroxymethyl)aminomethane, pH 7.4; 150 mM sodium chloride; 2 mM ethylenediamine-tetraacetic acid; 1% bovine serum albumin) are incubated in a volume of 200 μl, for 2 hours at 37° C. in 96 well plates. LDL is differentially precipitated by the addition of 50 μl of 1% (w/v) dextran sulfate/0.5 M magnesium chloride, mixed by vortex, and incubated at room temperature for 10 minutes. The solution (200 μl) is transferred to a filter plate (Millipore). After filtration, the radioactivity present in the precipitated LDL is measured by liquid scintillation counting. Correction for non-specific transfer or precipitation is made by including samples that do not contain CETP. The rate of [^{3}H]CE transfer using this assay is linear with respect to time and CETP concentration, up to 25-30% of [^{3}H]CE transferred.

[0282] The potency of test compounds can be determined by performing the above described assay in the presence of varying concentrations of the test compounds and determining the concentration required for 50% inhibition of transfer of [^{3}H]CE from HDL to LDL. This value is defined as the IC_{50}. The ICSO values determined from this assay will be accurate when the IC_{50} is greater than 10 nM. In the case where compounds have greater inhibitory potency, accurate measurements of IC_{50} may be determined using longer incubation times (up to 18 hours) and lower final concentrations of CETP (<50 nM)

[0283] Inhibition of CETP Activity In Vivo

[0284] Inhibition of CETP activity by a test compound can be determined by administering the compound to an animal by intravenous injection or oral gavage, measuring the amount of transfer of tritium-labeled cholesteryl ester ([^{3}H]CE) from HDL to VLDL and LDL particles, and comparing this amount of transfer with the amount of transfer observed in control animals.

[0285] Male golden Syrian hamsters are to be maintained on a diet of chow containing 0.24% cholesterol for at least two weeks prior to the study. For animals receiving intravenous dosing, immediately before the experiment, animals are anesthetized with pentobarbital. Anesthesia is maintained throughout the experiment. In-dwelling catheters are to be inserted into the jugular vein and carotid artery. At the start of the experiment all animals will receive 0.2 ml of a solution containing [^{3}H]CE-HDL into the jugular vein. [^{3}H]CE-HDL is a preparation of human HDL containing tritium-labeled cholesteryl ester, and is prepared according to the method of Glenn et al. (*Meth. Enzymol.,* 263, 339-351 (1996)). Test compound is dissolved as a 80 mM stock solution in vehicle (2% ethanol: 98% PEG 400, Sigma Chemical Company, St. Louis, Mo., USA) and administered either by bolus injection or by continuous infusion. Two minutes after the [^{3}H]CE-HDL dose is administered, animals are to receive 0.1 ml of the test solution injected into the jugular vein. Control animals are to receive 0.1 ml of the intravenous vehicle solution without test compound. After 5 minutes, the first blood samples (0.5 ml) are taken from the carotid artery and collected in standard microtainer tubes containing ethylenediamine tetraacetic acid. Saline (0.5 ml) is injected to flush the catheter and replace blood volume. Subsequent blood samples are to be taken at two hours and four hours by the same method. Blood samples are mixed well and kept on ice until the completion of the experiment. Plasma is obtained by centrifugation of the blood samples at 4° C. The plasma (50 μl) is treated with 5 μl of precipitating reagent (dextran sulfate, 10 g/l; 0.5 M magnesium chloride) to remove VLDL/LDL. After centrifugation, the resulting supernatant (25 μl) containing the HDL will be analyzed for radioactivity using a liquid scintillation counter.

[0286] The percentage [^{3}H]CE transferred from HDL to LDL and VLDL (% transfer) will be calculated based on the total radioactivity in equivalent plasma samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals will be 20% to 35% after 4 hours.

[0287] Alternatively, conscious, non-anesthetized animals can receive an oral gavage dose of test compound as a suspension in 0.1% methyl cellulose in water. At a time determined for each compound at which plasma levels of the test substance reach their peak (C_{max}) after oral dosing, the animals are to be anesthetized wish pentobarbital and then dosed with 0.2 ml of a solution containing [^{3}H]CE-HDL into the jugular vein as described above. Control animals are to receive 0.25 ml of the vehicle solution without test compound by oral gavage. After 4 hours, the animals are to be sacrificed, blood samples are collected, and the percentage [^{3}H]CE transferred from HDL to LDL and VLDL (% transfer) is assayed as described above.

[0288] Alternatively, inhibition of CETP activity by a test compound can be determined by administering the compound to mice that have been selected for expression of human CETP (hCETP) by transgenic manipulation (hCETP mice) Test compounds can be administered by intravenous

injection, or oral gavage and the amount of transfer of tritium-labeled cholesteryl ester ([^{3}H]CE) from HDL to VLDL and LDL particles is determined, and compared to the amount of transfer observed in control animals. C57Bl/6 mice that are homozygous for the hCETP gene are to be maintained on a high fat chow diet, such as TD 88051, as described by Nishina et al. (*J Lipid Res.,* 31, 859-869 (1990)) for at least two weeks prior to the study. Mice are to receive an oral gavage dose of test compound as a suspension in 0.1% methyl cellulose in water or an intravenous bolus injection of test compound in 10% ethanol and 90% polyethylene glycol. Control animals are to receive the vehicle solution without test compound by oral gavage or by an intravenous bolus injection. At the start of the experiment all animals will receive 0.05 ml of a solution containing [^{3}H]CE-HDL into the tail vein. [^{3}H]CE-HDL will be a preparation of human HDL containing tritium-labeled cholesteryl ester, and is prepared according to the method of Glenn et al. (*Meth. Enzymol.,* 263, 339-351 (1996)). After 30 minutes, the animals are exsanguinated and blood collected in standard microtainer tubes containing ethylenediamine tetraacetic acid. Blood samples are mixed well and kept on ice until the completion of the experiment. Plasma will be obtained by centrifugation of the blood samples at 4° C. The plasma is separated and analyzed by gel filtration chromatography and the relative proportion of [^{3}H]CE in the VLDL, LDL and HDL regions will be determined.

[0289] The percentage [^{3}H]CE transferred from HDL to LDL and VLDL (% transfer) will be calculated based on the total radioactivity in equivalent plasma samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals will be 20% to 35% after 30 min.

[0290] Intestinal Cholesterol Absorption Assay

[0291] A variety of compounds are shown to inhibit cholesterol absorption from the intestinal tract. These compounds lower serum cholesterol levels by reducing intestinal absorption of cholesterol from both exogenous sources (dietary cholesterol) and endogenous cholesterol (secreted by the gall bladder into the intestinal tract).

[0292] In hamsters the use of a dual-isotope plasma ratio method to measure intestinal cholesterol absorption has been refined and evaluated as described by Turley et al. (J. Lipid Res. 35, 329-339 (1994), herein incorporated by reference).

[0293] Male hamsters weighing 80-100 g are to be given food and water ad libitum in a room with 12 hour alternating periods of light and dark. Four hours into the light period, each hamster is administered first an intravenous dose of 2.5 μCi of [1,2-^{3}H]cholesterol suspended in Intralipid (20%) and then an oral dose of [4-^{14}C]cholesterol in an oil of medium chain triglycerides (MCT). The i.v. dose is given by injecting a 0.4 ml volume of the Intralipid mixture into the distal femoral vein. The oral dose is given by gavaging a 0.6 ml volume of the MCT oil mixture introduced intragastrically via a polyethylene tube. After 72 hours the hamsters are bled and the amount of ^{3}H and ^{14}C in the plasma and in the original amount of label administered are determined by liquid scintillation spectrometry. The cholesterol absorption will be calculated based on the following equation:

[0294] Percent cholesterol absorbed=

$$\frac{\%\text{ of oral dose per ml of 72 hour plasma sample}}{\%\text{ of i.v. dose per ml of 72 hour plasma sample}} \times 100$$

[0295] Microsomal Triglyceride Transfer Protein (MTP) Assay

[0296] MTP can be purified from liver tissue or cultured cells (e.g. HepG2 cells) using standard methods as described by Ohringer et al. (Acta Crystallogr. D52, 224-225 (1996), herein incorporated by reference).

[0297] Subsequent analysis of MTP activity can be performed as described by Jamil et al. (Proc. Natl. Acad. Sci. 93, 11991-11995 (1996), herein incorporated by reference).

[0298] The basis of this assay is to measure the transfer of labeled triglycerides from a population of donor vesicles to a population of acceptor vesicles in the presence of MTP. Inhibitors of MTP can be evaluated by adding them to the mixture prior to the introduction of MTP. Donor vesicles are prepared by sonication of an aqueous mixture of egg phospholipids, cardiolipin, ^{3}H-labeled phospholipid and ^{14}C-labeled triglycerides. Acceptor vesicles are prepared by sonication of an aqueous mixture of egg phospholipids. The vesicle solutions are mixed together, with or without added MTP inhibitors, and MTP is added to initiate the transfer reaction. The assay is terminated after 60 minutes by addition of 0.5 ml of DE-52 cellulose followed by centrifugation to pellet the donor molecules. The amount of ^{3}H and ^{14}C in the pellet and in the original amount of label in the mixture are determined by liquid scintillation spectrometry. The lipid transfer rate will be calculated based on first order kinetics using the expression:

$$[S]=[S]_0 e^{-kt}$$

[0299] where $[S]_0$ and [S] are the fractions of ^{14}C label in the donor membrane pellet at times 0 and t, respectively, and the term k is the fraction of label transferred per unit time.

[0300] Plasma Lipids Assay in Rabbits

[0301] Plasma lipids can be assayed using standard methods as reported by J. R. Schuh et al., *J. Clin. Invest.,* 91, 1453-1458 (1993), herein incorporated by reference. Groups of male, New Zealand white rabbits are placed on a standard diet (100 g/day) supplemented with 0.3% cholesterol and 2% corn oil (Zeigler Bothers, Inc., Gardners, Pa.). Water is available ad lib. Groups of control and treated animals are killed after 1 and 3 months of treatment. Tissues are removed for characterization of atherosclerotic lesions. Blood samples are to be taken for determination of plasma lipid concentrations.

[0302] Plasma Lipids

[0303] Plasma for lipid analysis is to be obtained by withdrawing blood from the ear vein into EDTA-containing tubes (Vacutainer; Becton Dickenson & Co., Rutherford, N.J.), followed by centrifugal separation of the cells. Total cholesterol will be determined enzymatically, using the cholesterol oxidase reaction (C. A. Allain et al., *Clin. Chem.,* 20, 470-475 (1974), herein incorporated by reference). HDL cholesterol will also be measured enzymatically, after selec-

tive precipitation of LDL and VLDL by dextran sulfate with magnesium (G. R. Warnick et al., *Clin. Chem.,* 28, 1379-1388 (1982), herein incorporated by reference). Plasma triglyceride levels will be determined by measuring the amount of glycerol released by lipoprotein lipase through an enzyme-linked assay (G. Bucolo et al., *Clin. Chem.,* 19, 476-482 (1973), herein incorporated by reference).

[0304] Atherosclerosis

[0305] Animals are to be killed by pentobarbital injection. Thoracic aortas are rapidly removed, immersion fixed in 10% neutral buffered formalin, and stained with oil red O (0.3%). After a single longitudinal incision along the wall opposite the arterial ostia, the vessels are pinned open for evaluation of the plaque area. The percent plaque coverage is determined from the values for the total area examined and the stained area, by threshold analysis using a true color image analyzer (Videometric 150; American Innovision, Incl, San Diego, Calif.) interfaced to a color camera (Toshiba 3CCD) mounted on a dissecting microscope. Tissue cholesterol will be measured enzymatically as described, after extraction with a chloroform/methanol mixture (2:1) according to the method of Folch et al. (J. Biol. Chem., 226, 497-509 (1957), herein incorporated by reference).

[0306] In Vitro Vascular Response

[0307] The abdominal aortas are rapidly excised, after injection of sodium pentobarbital, and placed in oxygenated Krebs-bicarbonate buffer. After removal of perivascular tissue, 3-mm ring segments are cut, placed in a 37° C. muscle bath containing Krebs-bicarbonate solution, and suspended between two stainless steel wires, one of which is attached to a force transducer (Grass Instrument Co., Quincy, Mass.). Force changes in response to angiotensin II added to the bath will be recorded on a chart recorder.

[0308] Renal Hypertensive Rat Model

[0309] A combination therapy of an antihypertensive agent and an ileal bile acid transport inhibitor may be evaluated for blood pressure lowering activity in the renal-artery ligated hypertensive rat, a model of high renin hypertension. In this model, six days after litigation of the left renal artery, both plasma renin activity and blood pressure are elevated significantly (J. L. Cangiano et al, *J. Pharmacol. Exp. Ther.,* 206, 310-313 (1979)). Male Sprague-Dawley rats are instrumented with a radiotelemetry blood pressure transmitter for continuous monitoring of blood pressure. The rats are anesthetized with a mixture of ketamine-HCl (100 mg/kg) and acepromazine maleate (2.2 mg/kg). The abdominal aorta is exposed via a midline incision. Microvascular clamps are placed on the aorta distal to the renal arteries and the iliac bifurcation. The aorta is punctured with a 22-gauge needle and the tip of a catheter is introduced. The catheter, which is held in place by a ligature in the psoas muscle, is connected to a radiotelemetry blood pressure transmitter (Mini-Mitter Co., Inc., Sunriver, Oreg.). The transmitter is placed in the peritoneal cavity and sutured to abdominal muscle upon closing of the incision. Rats are housed singly above a radiotelemetry receiver and are allowed standard rat cho and water ad libitum. At least five days are allowed for recovery from surgery. Mean arterial pressure and heart rate are measured on a data recorder as is appropriate, such as a mini-computer. Data Data are sampled for 10 seconds at 200-500 Hz at 2.5 to 10 min intervals 24 hours per day. After collecting control data for 24 hours, the rats are anesthetized with methohexital (30 mg/kg, i.p.) and supplemented as needed. A midline abdominal incision is made, approximately 2 cm in length to expose the left kidney. The renal artery is separated from the vein near the aorta, with care taken not to tramatize the vein. The artery is completely ligated with sterile 4-O silk. The incision is closed by careful suturing of the muscle layer and skin. Six days later, when MAP is typically elevated by 50-70 mmHg, an antihypertensive agent or a combination with one or more cardiovascular therapeutic agents are administered by gavage each day for about 8 weeks. Single drug dosing is carried out using 20 and 200 mg/kg/day of the antihypertensive agent (for example, eplerenone) and 1, 3, 10, 30, and 100 mg/kg/day of the other cardiovascular therapeutic agent. Drug mixtures are obtained by administering a combination of a dose of 1, 3, 10, 30, or 100 mg/kg/day of the other cardiovascular therapeutic agent with a dose of either 20 or 200 mg/kg/day of the antihypertensive agent. Blood pressure lowering is monitored by the radiotelemetry system and responses with the compounds are compared to a response obtained in vehicle-treated animals. Plasma and urinary sodium and potassium levels are monitored as a measure of the effectiveness of the aldosterone blockade. Urine samples are collected overnight using metabolic cages to isolate the samples. Plasma samples are obtained by venous catheterization. Sodium and potassium are measured by flame photometry. Cardio fibrosis is determined by histological and chemical measurements of the excised hearts following perfusion fixation. Left and right ventricles are weighed, embedded, and sectioned. Subsequently, sections are stained with picrosirius red and the red staining collagen areas are quantitated by computerized image analysis. The apex of th heart is acid digested and the free hydroxyproline measured calorimetrically. It is expected that MAP will be significantly lowered toward normal pressures in the test animals, treated with the combination therapy and that the condition of myocardial fibrosis will be arrested or avoided.

[0310] Effect of an IBAT Inhibitor and an Antihypertensive Agent, Alone and in Combination, on the Treatment of Atherosclerosis

[0311] This study will be a prospective randomized evaluation of the effect of a combination of an IBAT inhibitor or a pharmaceutically acceptable salt thereof and an antihypertensive agent on the progression/regression of coronary and carotid artery disease. The study is used to show that a combination of an IBAT inhibitor or a pharmaceutically acceptable soft thereof and an antihypertensive agent is effective in slowing or arresting the progression or causing regression of existing coronary artery disease (CAD) as evidenced by changes in coronary angiography or carotid ultrasound in subjects with established disease.

[0312] This study will be an angiographic documentation of coronary artery diseasecarried out as a double-blind, placebo-controlled trial of a minimum of about 500 subjects and preferably of about 780 to about 1200 subjects. It is especially preferred to study about 1200 subjects in this study. Subjects will be admitted into the study after satisfying certain entry criteria set forth below.

[0313] Entry criteria: Subjects accepted for entry into this trial must satisfy certain criteria. Thus the subject

must be an adult, either male or female, aged 18-80 years of age in whom coronary angiography is clinically indicated. Subjects will have angiographic presence of a significant focal lesion such as 30% to 50% on subsequent evaluation by quantitative coronary angiography (QCA) in a minimum of one segment (non-PTCA, non-bypassed or non-MI vessel) that is judged not likely to require intervention over the next 3 years. It is required that the segments undergoing analysis have not been interfered with. Since percutaneous transluminal cardiac angioplasty (PTCA) interferes with segments by the insertion of a balloon catheter, non-PTCA segments are required for analysis. It is also required that the segments to be analyzed have not suffered a thrombotic event, such as a myocardial infarct (MI). Thus the requirement for non-MI vessels. Segments that will be analyzed include: left main, proximal, mid and distal left anterior descending, first and second diagonal branch, proximal and distal Left circumflex, first or largest space obtuse marginal, proximal, mid and distal right coronary artery. Subjects will have an ejection fraction of greater than 40% determined by catheterization or radionuclide ventriculography or ECHO cardiogram at the time of the qualifying angiogram or within the previous three months of the acceptance of the qualifying angiogram provided no intervening event such as a thrombotic event or procedure such as PTCA has occurred.

[0314] Generally, due to the number of patients and the physical limitations of any one facility, the study will be carried out at multiple sites. At entry into the study, subjects undergo quantitative coronary angiography as well as B-mode carotid artery ultrasonography and assessment of carotid arterial compliance at designated testing centers. This will establish baselines for each subject. Once admitted into the test, subjects are randomized to receive an antihypertensive agent (for example, eplerenone) or a pharmaceutically acceptable salt thereof (the dose is dependent upon the particular antihypertensive agent or salt thereof chosen) and placebo or antihyperlipidemic agent such as an IBAT inhibitor (50 mgs) and placebo or an antihypertensive agent or a pharmaceutically acceptable salt thereof (the dose is dependent upon the particular antihypertensive agent or salt thereof chosen) and IBAT inhibitor (50 mgs). It will be recognized by a skilled person that the free base form or other salt forms of antihypertensive agent or the free base form or other salt forms of the IBAT inhibitor may be used in this invention. Calculation of the dosage amount for these other forms of the IBAT inhibitor and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The amount of the antihypertensive agent may be varied as required. The amount of the IBAT inhibitor will be titrated down from 80 mg if it is determined by the physician to be in the best interests of the subject. The subjects are monitored for a one to three year period, generally three years being preferred. B-mode carotid ultrasound assessment of carotid artery atherosclerosis and compliance are performed at regular intervals throughout the study. Generally, six month intervals are suitable. Typically this assessment is performed using B-mode ultrasound equipment. However, a person skilled in the art may use other methods of performing this assessment coronary angiography is performed at the conclusion of the one to three year treatment period. The baseline and post-treatment angiograms and the intervening carotid artery B-mode ultrasonograms are evaluated for new lesions or progression of existing atherosclerotic lesions. Arterial compliance measurements are assessed for changes from baseline and over the 6-month evaluation periods.

[0315] The primary objective of this study is to show that the combination of an antihypertensive agent and an IBAT inhibitor reduces the progression of atherosclerotic lesions as measured by quantitative coronary angiography (QCA) in subjects with clinical coronary artery disease. QCA measures the opening in the lumen of the arteries measured.

[0316] The primary endpoint of the study is the change in the average mean segment diameter of the coronary artery tree. Thus, the diameter of an arterial segment is measured at various portions along the length of that segment. The average diameter of that segment is then determined. After the average segment diameter of many segments has been determined, the average of all segment averages is determined to arrive at the average mean segment diameter. The mean segment diameter of subjects taking the IBAT inhibitor or a pharmaceutically acceptable salt thereof and the antihypertensive agent or a pharmaceutically acceptable acid addition salt thereof will decline more slowly, will be halted completely, or there will be an increase in the mean segment diameter. These results will represent slowed progression of atherosclerosis, halted progression of atherosclerosis and regression of atherosclerosis, respectively.

[0317] The secondary objective of this study is that the combination of an antihypertensive agent and the IBAT inhibitor or a pharmaceutically acceptable salt thereof reduces the rate of progression of atherosclerosis in the carotid arteries as measured by the slope of the maximum intimal-medial thickness measurements averaged over 12 separate wall segments (Mean Max) as a function of time, more than does amlodipine or a pharmaceutically acceptable acid addition salt thereof or IBAT inhibitor or a pharmaceutically acceptable salt thereof alone. The intimal-medial thickness of subjects taking an IBAT inhibitor or a pharmaceutically acceptable salt thereof and amlodipine or a pharmaceutically acceptable acid addition salt thereof will increase more slowly, will cease to increase or will decrease. These results represent slowed progression of atherosclerosis, hafted progression of atherosclerosis and regression of atherosclerosis, respectively. Further, these results may be used to facilitate dosage determinations.

[0318] The utility of the compounds of the present invention as medical agents in the treatment of angina pectoris in mammals (e.g., humans) Is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below:

[0319] Effect of IBAT Inhibitor and an Antihypertensive Agent, Alone and in Combination, on the Treatment of Angina

[0320] This study will be a double blind, parallel arm, randomized study to show the effectiveness of an IBAT inhibitor or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in the treatment of symptomatic angina.

[0321] Entry criteria: Subjects are males or females between 18 and 80 years of age with a history of typical chest pain associated with one of the following objec-

tive evidences of cardiac ischemia: (1) stress test segment elevation of about one millimeter or more from the ECG; (2) positive treadmill stress test; (3) new wall motion abnormality on ultrasound; or (4) coronary angiogram with a significant qualifying stenosis. Generally a stenosis of about 30-50% is considered to be significant

[0322] Each subject is evaluated for about ten to thirty-two weeks. At least ten weeks are generally required to complete the study. Sufficient subjects are used in this screen to ensure that about 200 to 800 subjects and preferably about 400 subject are evaluated to complete the study. Subjects are screened for compliance with the entry criteria, set forth below, during a four week run in phase. After the screening criteria are met, subjects are washed out from their current ant-anginal medication and stabilized on a long acting nitrate such as nitroglycerine, isosorbide-5-mononitrate or isosorbide dinitrate. The term "washed out", when used in connection with this screen, means the withdrawal of current anti-anginal medication so that substantially all of the medication is eliminated from the body of the subject A period of eight weeks is preferably allowed for both the wash out period and for the establishment of the subject on stable doses of the nitrate. Subjects having one or two attacks of angina per week while on stable doses of long acting nitrate are generally permitted to skip the wash out phase. After subjects are stabilized on nitrates, the subjects enter the randomization phase provided the subjects continue to have either one or two angina attacks per week. In the randomization phase, the subjects are randomly placed into one of the four arms of the study set forth below. After completing the wash out phase, subjects in compliance with the entry criteria undergo twenty four hour ambulatory electrocardigram (ECG) such as Holter monitoring, exercise stress testing such as a treadmill and evaluation of myocardial perfusion using PET (photon emission tomography) scanning to establish a baseline for each subject. When conducting a stress test, the speed of the treadmill and the gradient of the treadmill can be controlled by a technician. The speed of the treadmill and the angle of the gradient are generally increased during the test. The time intervals between each speed and gradient Increase is generally determined using a modified Bruce Protocol.

[0323] After the baseline investigations have been completed, subjects are initiated on one of the following four arms of the study: (1) placebo; (2) IBAT inhibitor (about 1 mg to about 80 mg); (3) an antihypertensive agent (dose is dependent upon the particular antihypertensive agent chosen); or (4) a combination of the above doses of IBAT inhibitor and antihypertensive agent together. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the IBAT inhibitor may be used in this invention. Calculation of the dosage amount for these other forms of the IBAT inhibitor and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The subjects are then monitored for two to twenty four weeks.

[0324] After the monitoring period has ended subjects will undergo the following investigations: (1) twenty four hour ambulatory ECG, such as Holler monitoring, (2) exercise stress testing (e.g. treadmill using the modified Bruce Protocol); and (3) evaluation of myocardial perfusion using PET scanning. Patents keep a diary of painful ischemic events and nitroglycerine consumption. It is generally desirable to have an accurate record of the number of anginal attacks suffered by the patent during the duration of the test Since a patient generally takes nitroglycerin to ease the pain of an anginal attack, the number of times that the patient administers nitroglycerine provides a reasonably accurate record of the number of anginal attacks.

[0325] To demonstrate the effectiveness and dosage of the drug combination of this invention, the person conducting the test will evaluate the subject using the tests described. Successful treatment will yield fewer instances of ischemic events as detected by ECG, will allow the subject to exercise longer or at a higher intensity level on the treadmill, or to exercise without pain on the treadmill, or will yield better perfusion or fewer perfusion defects an ultrasound.

[0326] The utility of the compounds of the present invention as medical agents in the treatment of hypertension and hyperlipidemia in mammals (e.g., humans) suffering from a combination of hypertension and hyperlipidemia is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below,

[0327] Effect of an IBAT Inhibitor and an Antihypertensive Agent, Alone and in Combination, on the Treatment of Subjects Having Both Hypertension and Hyperlipidemia

[0328] This study will be a double blind, parallel arm, randomized study to show the effectiveness of an IBAT inhibitor or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in controlling both hypertension and hyperlipidemia in subjects who have mild, moderate, or severe hypertension and hyperlipidiemia

[0329] Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are used in this screen to ensure that about 400 to 800 subjects are evaluated to complete the study.

[0330] Entry criteria: Subjects are male or female adults between 18 and 80 years of age having both hyperlipidemia and hypertension. The presence of hyperlipidemia is evidenced by evaluation of the low density lipoprotein (LDL) level of the subject relative to certain positive risk factors. If the subject has no coronary heart disease (CHD) and has less than two positive risk factors, then the subject is considered to have hyperlipidemia which requires drug therapy if the LDL of the subject is greater than or equal to 190. If the subject has no CHD and has two or more positive risk factors, then the subject is considered to have hyperlipidemia which requires drug therapy if the LDL of the subject is greater than or equal to 160. If the subject has CHID, then the subject is considered to have hyperlipidemia if the LDL of the subject is greater than or equal to 130.

[0331] Positive risk factors include (1) male over 45, (2) female over 55 wherein the female is not undergoing hormone replacement therapy (HIRT), (3) family history of premature cardiovascular disease, (4) the subject is a current smoker, (5) the subject has diabetes, (6) an HDL of less than 45, and (7) the subject has hypertension. An HDL of greater than 60 is considered a negative risk factor and will offset one of the above mentioned positive risk factors. The

presence of hypertension is evidenced by a sitting diastolic blood pressure (BP) of greater than 90 or sitting systolic BP of greater than 140. All blood pressures are generally determined as the average of three measurements taken five minutes apart. Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, subjects are washed out from their current antihypertensive and lipid lowering medication and are placed on the NCEP ATP if Step 1 diet The NCEP ATP 11 (adult treatment panel, 2nd revision) Step I diet sets forth the amount of saturated and unsaturated fat which can be consumed as a proportion of the total caloric intake. The term "washed out' where used in connection with this screen, means the withdrawal of current antihypertensive and lipid lowering medication so that substantially all of the medication is eliminated from the body of the subject. Newly diagnosed subjects generally remain untreated until the test begins. These subjects are also placed on the NCEP Step I diet. After the four week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure and (2) fasting lipid screen. The fasting lipid screen determines baseline lipid levels in the fasting state of a subject Generally, the subject abstains from food for twelve hours, at which time lipid levels are measured. After the baseline investigations are performed subjects are started on one of the following: (1) a fixed dose of an antihypertensive agent, dose dependent upon the particular antihypertensive agent chosen; (2) a fixed dose of an IBAT inhibitor, generally about 1 to 80 mg; or (3) a combination of the above doses of the IBAT inhibitor and the antihypertensive agent together. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the IBAT inhibitor may be used in this invention. Calculation of the dosage amount for these other forms of the IBAT inhibitor and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. Subjects remain on these doses for a minimum of six weeks, and generally for no more than eight weeks. The subjects return to the testing center at the conclusion of the six to eight weeks so that the baseline evaluations can be repeated. The blood pressure of the subject at the conclusion of the study is compared with the blood pressure of the subject upon entry. The lipid screen measures the total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoB, VLDL (very low density lipoprotein) and other components of the lipid profile of the subject. Improvements in the values obtained after treatment relative to pretreatment values indicate the utility of the drug combination. The utility of the compounds of the present invention as medical agents in the management of cardiac risk in mammals (e.g., humans) at risk for an adverse cardiac event is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below.

[0332] Effects of an IBAT Inhibitor and an Antihypertensive Agent, Alone and in Combination, on Subjects at Risk of Future Cardiovascular Events

[0333] This study will be a double blind, parallel arm, randomized study to show the effectiveness of an IBAT inhibitor or a pharmaceutically acceptable salt thereof and an antihypertensive agent given in combination in reducing the overall calculated risk of future events in subjects who are at risk for having future cardiovascular events. This risk is calculated by using the Framingham Risk Equation. A subject is considered to be at risk of having a future cardiovascular event if that subject is more than one standard deviation above the mean as calculated by the Framingham Risk Equation. The study is used to evaluate the efficacy of a fixed combination of the IBAT inhibitor or a pharmaceutically acceptable salt thereof and the antihypertensive agent in controlling cardiovascular risk by controlling both hypertension and hyperlipidemia in patients who have both mild to moderate hypertension and hyperlipidemia.

[0334] Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are recruited to ensure that about 400 to 800 subjects are evaluated to complete the study.

[0335] Entry criteria: Subjects included in the study are male or female adult subjects between 18 and 80 years of age with a baseline five year risk which risk is above the median for the subject's age and sex, as defined by the Framingham Heart Study, which is an ongoing prospective study of adult men and women showing that certain risk factors can be used to predict the development of coronary heart disease. The age, sex, systolic and diastolic blood pressure, smoking habit, presence or absence of carbohydrate intolerance, presence or absence of left ventricular hypertrophy, serum cholesterol and high density lipoprotein (HDL) of more than one standard deviation above the norm for the Framingham Population are all evaluated in determining whether a patent is at risk for adverse cardiac event. The values for the risk factors are inserted into the Framingham Risk equation and calculated to determine whether a subject is at risk for a future cardiovascular event. Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, patients are washed out from their current antihypertensive and lipid lowering medication and any other medication which will impact the results of the screen. The patients are then placed on the NCEP ATP 11 Step I diet, as described above. Newly diagnosed subjects generally remain untreated until the test begins—These subjects are also placed on the NCEP ATP 11 Step 1 diet. After the four week wash out and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure; (2) fasting; (3) DPW screen; (4) glucose tolerance test; (5) ECG; and (6) cardiac ultrasound. These tests are carried out using standard procedures well known to persons skilled in the art The ECG and the cardiac ultrasound are generally used to measure the presence or absence of left ventricular hypertrophy.

[0336] After the baseline investigations are performed patents will be started on one of the following: (1) a fixed dose of an antihypertensive agent, dose dependent upon the particular antihypertensive agent chosen; (2) a fixed dose of an IBAT inhibitor (about 1 to 80 mg); or (3) the combination

of the above doses of the IBAT inhibitor and an antihypertensive agent. It will be recognized by a skilled person that the free base form or other salt forms of amlodipine besylate or the free base form or other salt forms of the IBAT inhibitor may be used in this invention. Calculation of the dosage amount for these other forms of the IBAT inhibitor and amlodipine besylate is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. Patients are kept on these doses and are asked to return in six to eight weeks so that the baseline evaluations can be repeated. At this time the new values are entered into the Framingham Risk equation to determine whether the subject has a lower, greater or no change in the risk of future cardiovascular event

[0337] The above assays demonstrating the effectiveness of amlodipine or pharmaceutically acceptable acid addition salts thereof and an IBAT inhibitor or pharmaceutically acceptable salts thereof in the treatment of angina pectoris, atherosclerosis, hypertension and hyperlipidemia together, and the management of cardiac risk, also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases. The following dosage amounts and other dosage amounts set forth elsewhere in this specification and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject and the presence of diseases, e.g., diabetes, in the subject. All doses set forth herein, and in the appendant claims, are daily doses.

[0338] By way of general example, in accordance with this invention, the below-listed antihypertensive agent may be administered in the following daily dosage amounts:

[0339] diltiazem, generally about 120 mg to about 480 mg;

[0340] verapamil, generally about 20 mg to about 48 mg;

[0341] felodipine, generally about 2.5 mg to about 40 mg;

[0342] isradipine, generally about 2.5 mg to about 40 mg;

[0343] lacidipine, generally about 1 mg to about 6 mg;

[0344] nicardipine, generally about 32 mg to about 120 mg;

[0345] nifedipine, generally about 10 mg to about 120 mg;

[0346] nimodipine, generally about 120 mg to about 480 mg;

[0347] nisoldipine, generally about 5 mg to about 80 mg;

[0348] nitrendipine, generally about 5 mg to about 20 mg;

[0349] benazepril, generally about 10 mg to about 80 mg;

[0350] captopril, generally about 50 mg to about 150 mg;

[0351] enalapril, generally about 5 mg to about 40 mg;

[0352] fosinopril, generally about 10 mg to about 80 mg;

[0353] lisinopril, generally about 10 mg to about 80 mg;

[0354] quinapril, generally about 10 mg to about 80 mg;

[0355] losartan, generally about 25 mg to about 100 mg;

[0356] valsartan, generally about 40 mg to about 640 mg;

[0357] doxazosin, generally about 0.5 mg to about 16 mg;

[0358] prazosin, generally about 1 mg to about 40 mg;

[0359] trimazosin, generally about 1 mg to about 20 mg;

[0360] arniloride, generally about 5 mg to about 20 mg; and

[0361] eplerenone, generally about 10 to about 150 mg.

[0362] It will be recognized by those skilled in the art that dosages for the above antihypertensive compounds must be individualized to each specific subject. This individualization will depend upon the medical history of the subject and whether the subject is concurrently taking other medications which may or may not interfere or have an adverse effect in combination with the above antihypertensives. Individualization is then achieved by beginning with a low dose of the compound and titrating the amount up until the desired therapeutic effect is achieved. In general, in accordance with this invention, the IBAT inhibitor is generally administered in a dosage of about 0.1 mg/day to about 500 mg/day. Preferably, the IBAT inhibitor is administered in a dosage of about 1 mg/day to about 100 mg/day.

[0363] Since the present invention relates to the treatment of diseases and conditions with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit includes two separate pharmaceutical compositions: an antihypertensive agent or a pharmaceutically acceptable salt thereof and an IBAT inhibi

tor or a pharmaceutically acceptable salt thereof. The kit includes container means for containing the separate compositions such as a divided bottle or a divided foil packet however, the separate compositions may also be contained within a single, undivided container. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

[0364] The examples herein can be performed by substituting the generically or specifically described therapeutic compounds or inert ingredients for those used in the preceding examples.

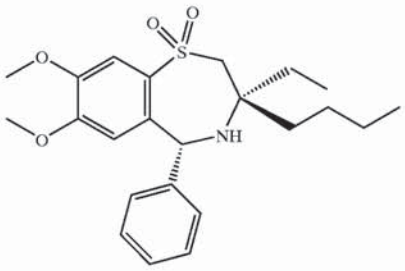
[0365] The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

What is claimed is:

1. A therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of a microsomal triglyceride transfer protein inhibiting compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

2. The therapeutic combination of claim 1 wherein the ileal bile acid transport inhibitor is a compound having the structure of formula B-2:

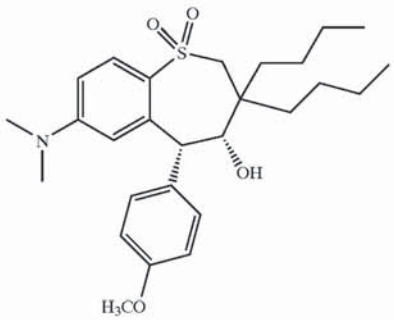
B-2



or an enantiomer or racemate thereof.

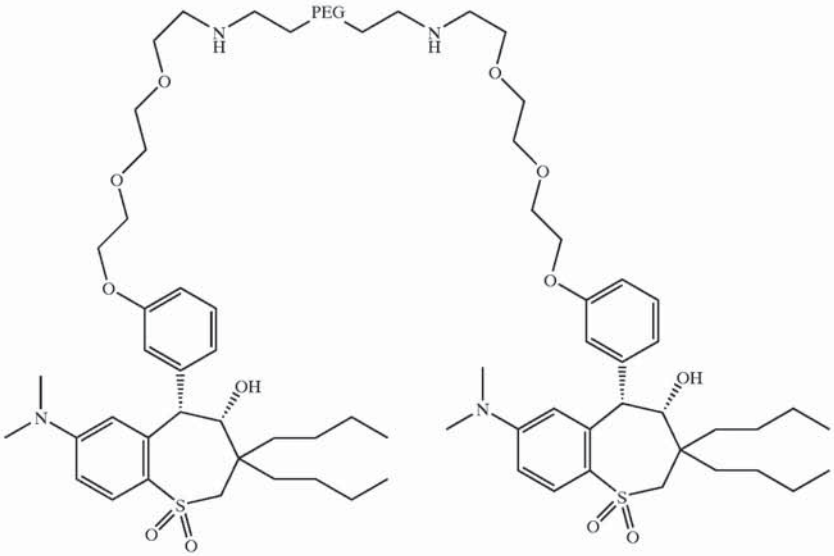
3. The therapeutic combination of claim 1 wherein the ileal bile acid transport inhibiting compound has the structure of formula B-12:

B-12



or an enantiomer or racemate thereof.

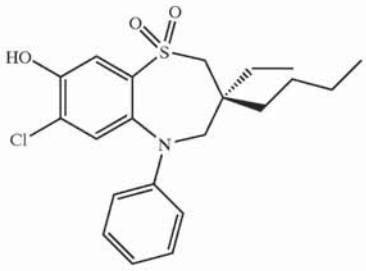
4. The therapeutic combination of claim 1 wherein the ileal bile acid transport inhibiting compound has the structure:



or an enantiomer or racemate thereof, wherein PEG is an about 3000 to about 4000 molecular weight polyethylene glycol polymer chain.

5. The therapeutic combination of claim 1 wherein the ileal bile acid transport inhibiting compound has the structure of formula B-7:

B-7



or an enantiomer or racemate thereof.

6. A therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of a cholesterol absorption antagonist compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

7. The combination of claim 6 wherein the cholesterol absorption antagonist compound comprises an azetidinone compound.

8. The combination of claim 7 wherein the cholesterol absorption antagonist compound comprises [3R-[3α(S*), 4β]]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone.

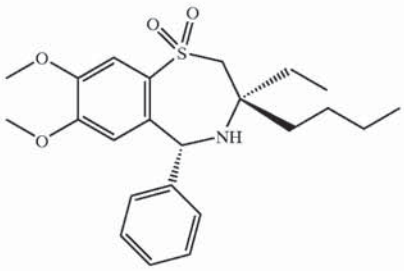
9. A therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antiobesity compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

10. The combination of claim 9 wherein the antiobesity compound comprises orlistat.

11. A therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antihypertensive compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, an anti-hypercholesterolemic condition effective amount, or an antihypertensive condition effective amount of the compounds.

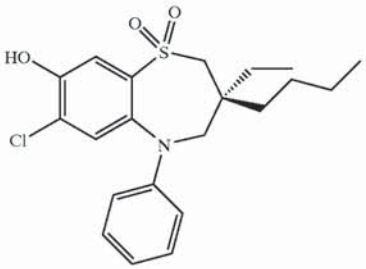
12. The combination of claim 11 wherein the ileal bile acid transport inhibiting compound comprises a benzothiazepine ileal bile acid transport inhibiting compound.

13. The combination of claim 12 wherein the benzothiazepine ileal bile acid transport inhibiting compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

14. The combination of claim 12 wherein the benzothiazepine ileal bile acid transport inhibiting compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

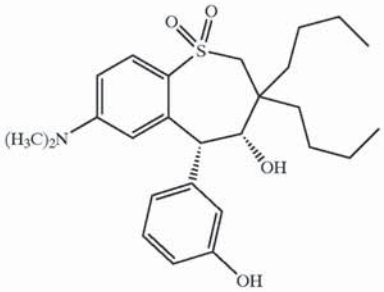
15. The combination of claim 11 wherein the antihypertensive compound comprises eplerenone.

16. The combination of claim 11 wherein the antihypertensive compound comprises spironolactone.

17. The combination of claim 11 wherein the antihypertensive compound comprises losartan or a salt thereof.

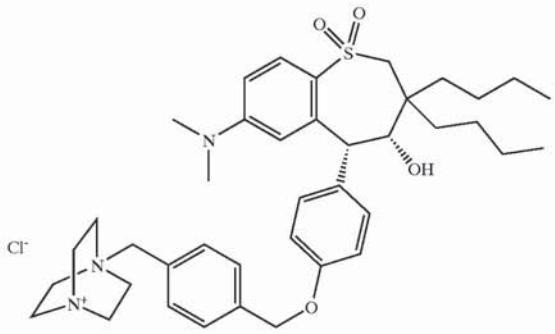
18. The combination of claim 11 wherein the ileal bile acid transport inhibiting compound comprises a benzothiepine ileal bile acid transport inhibiting compound.

19. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



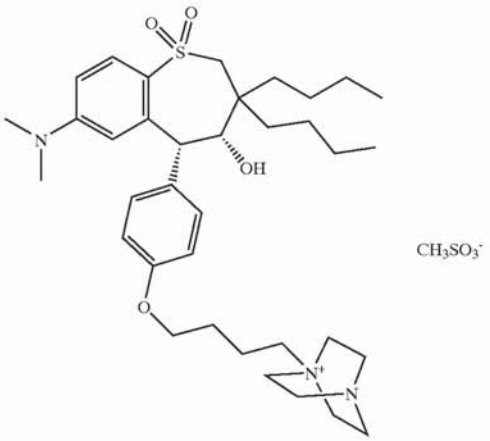
or a salt, an enantiomer or racemate thereof.

20. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



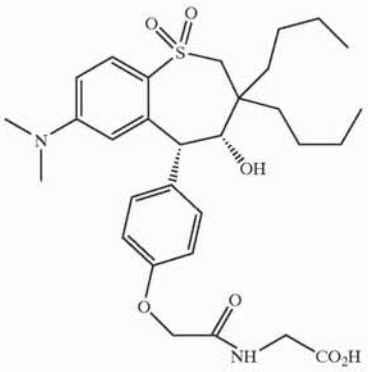
or a salt, an enantiomer, or racemate thereof.

21. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



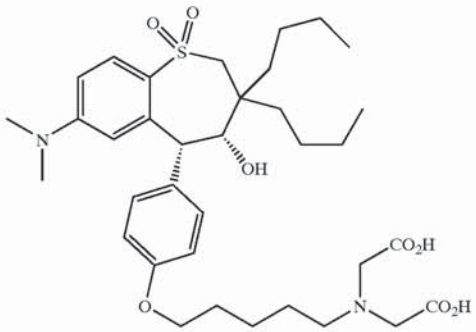
or a salt, an enantiomer, or a racemate thereof.

22. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



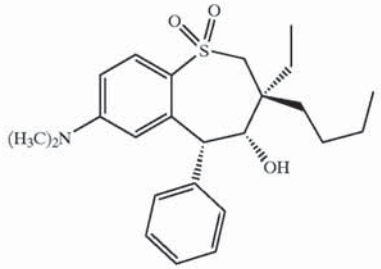
or a salt, an enantiomer, or a racemate thereof.

23. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



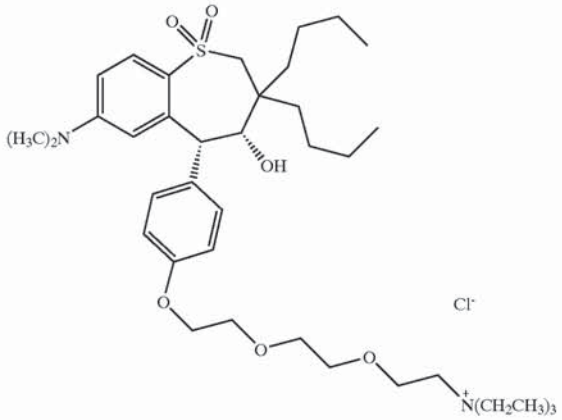
or a salt, an enantiomer, or a racemate thereof.

24. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



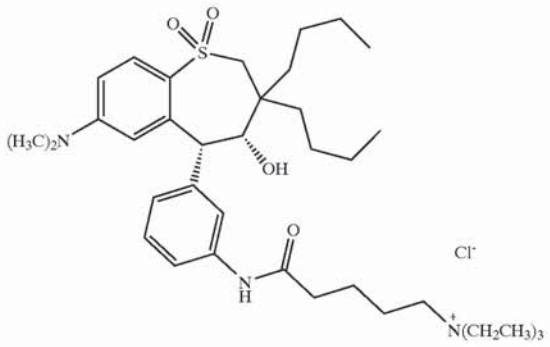
or a salt, an enantiomer, or a racemate thereof.

25. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



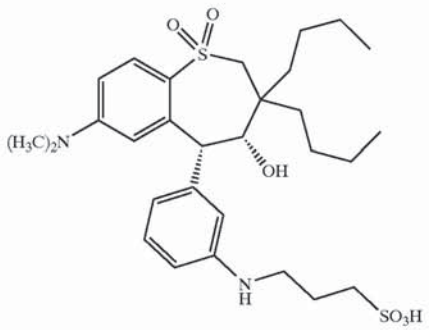
or a salt, an enantiomer, or a racemate thereof.

26. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



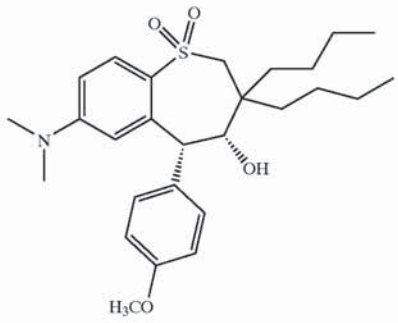
or a salt, an enantiomer, or a racemate thereof.

27. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



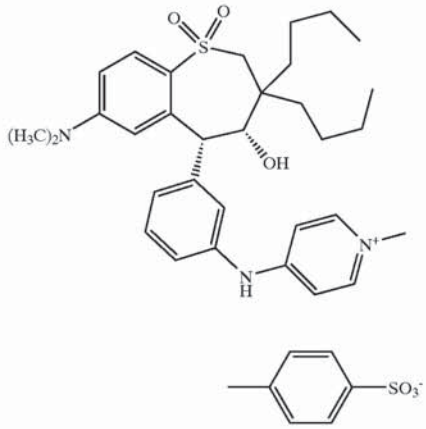
or a salt, an enantiomer, or a racemate thereof.

28. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



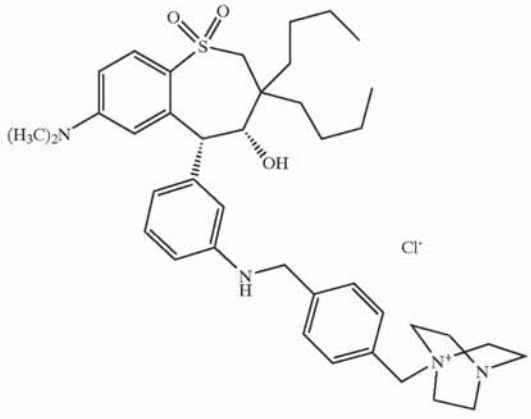
or a salt, an enantiomer, or a racemate thereof.

29. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



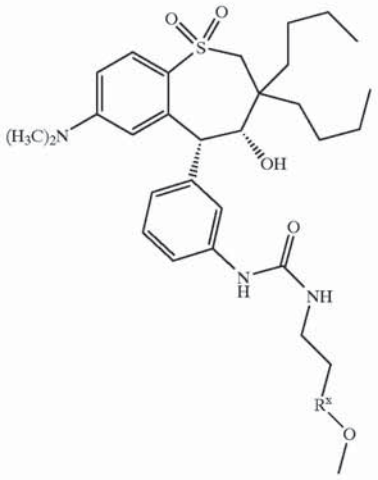
or a salt, an enantiomer, or a racemate thereof.

30. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



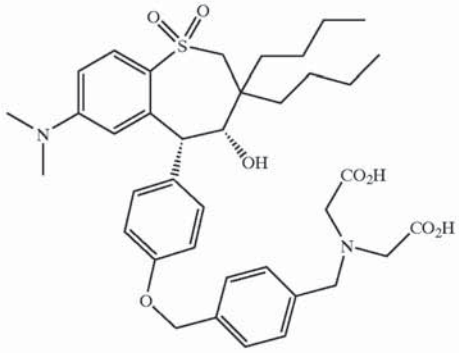
or a salt, an enantiomer, or a racemate thereof.

31. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



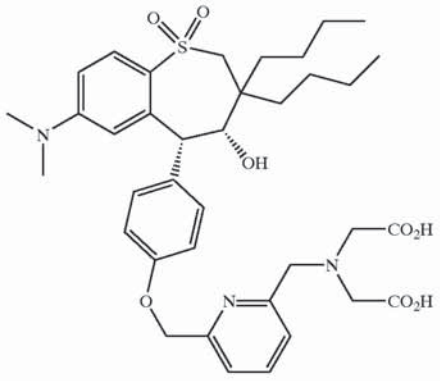
or salt, an enantiomer, or a racemate thereof wherein Rx is an about 4000 to about 6000 molecular weight polyethyleneglycol group.

32. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



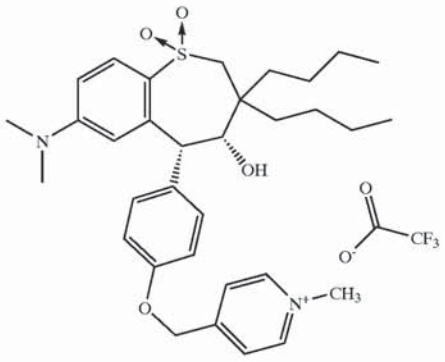
or a salt, an enantiomer, or a racemate thereof.

33. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



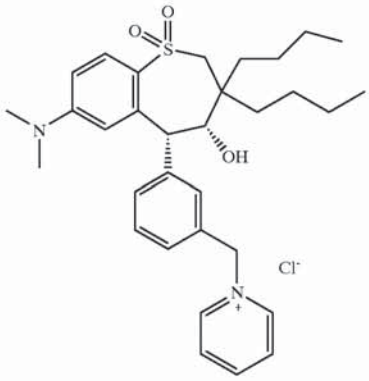
or a salt, an enantiomer, or a racemate thereof.

34. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



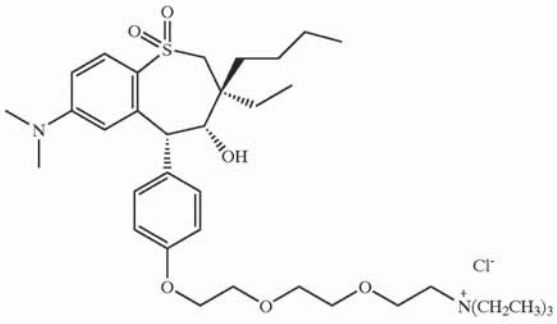
or a salt, an enantiomer, or a racemate thereof.

35. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



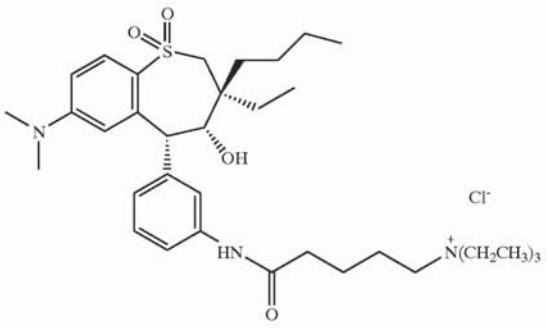
or a salt, an enantiomer, or a racemate thereof.

36. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



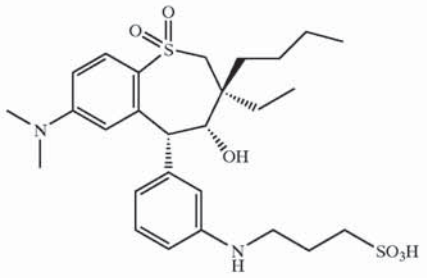
or a salt, an enantiomer, or a racemate thereof.

37. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



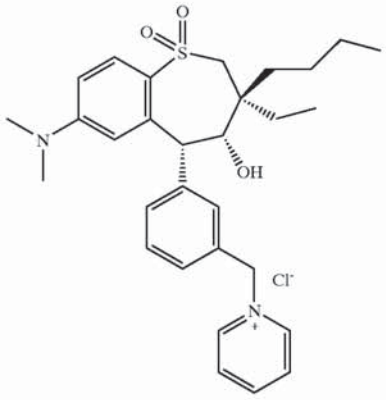
or a salt, an enantiomer, or a racemate thereof.

38. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



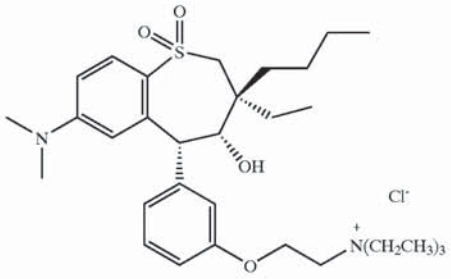
or a salt, an enantiomer, or a racemate thereof.

39. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



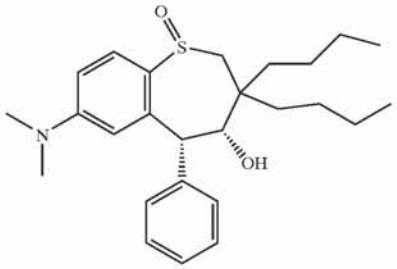
or a salt, an enantiomer, or a racemate thereof.

40. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



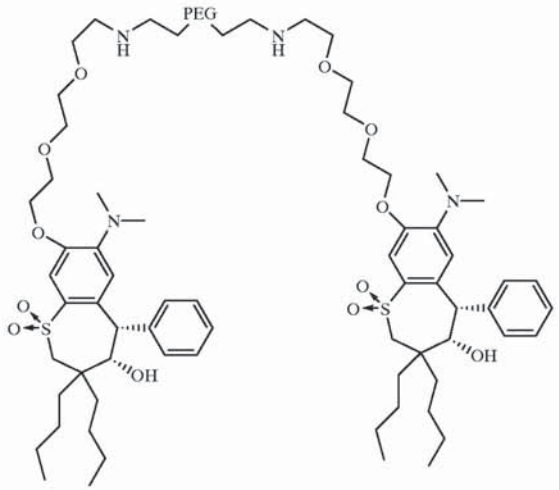
or a salt, an enantiomer, or a racemate thereof.

41. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



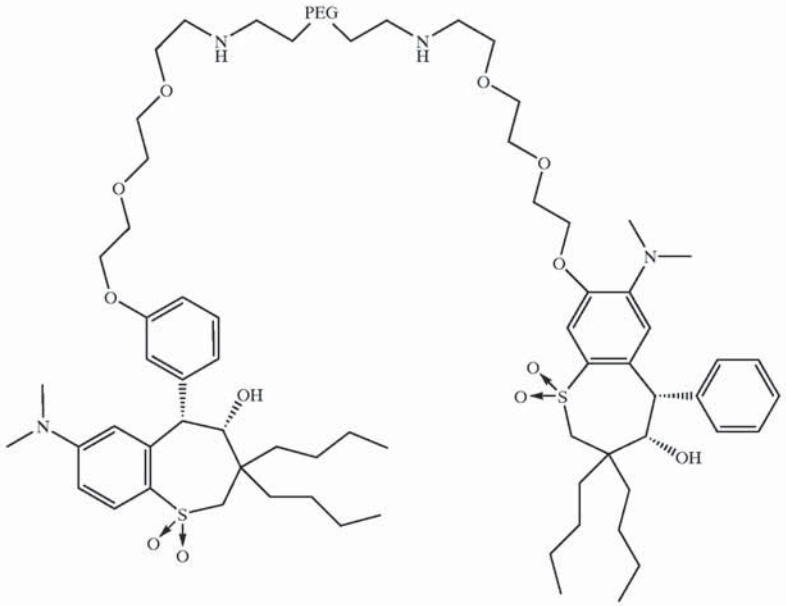
or a salt, an enantiomer, or a racemate thereof.

42. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



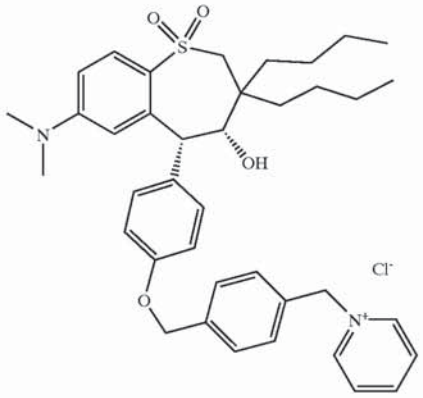
or a salt, an enantiomer, or a racemate thereof, wherein PEG is an about 3000 to about 4000 molecular weight polyethylene glycol polymer chain.

43. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



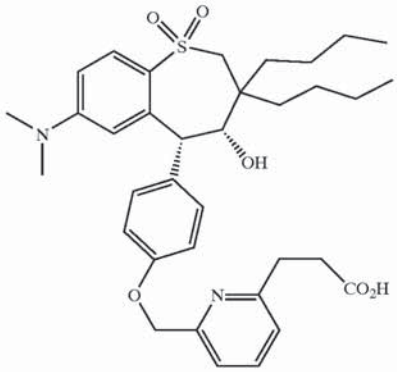
or a salt, an enantiomer, or a racemate thereof, wherein PEG is an about 3000 to about 4000 molecular weight polyethylene glycol polymer chain.

44. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



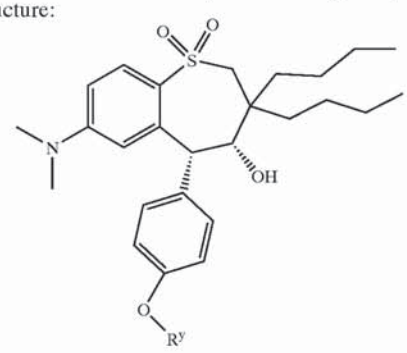
or a salt, an enantiomer, or a racemate thereof.

45. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



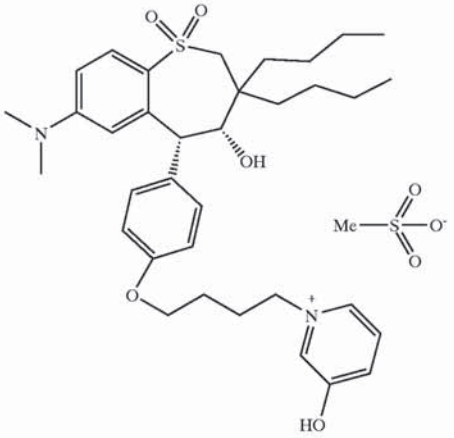
or a salt, an enantiomer, or a racemate thereof.

46. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



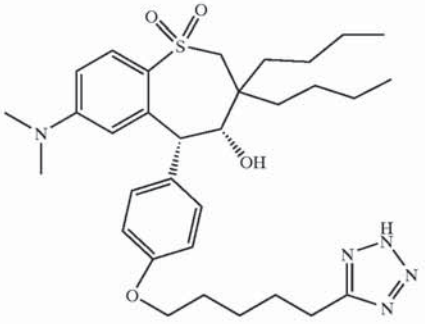
or a salt, an enantiomer, or a racemate thereof, wherein R^Y is an about 500 to about 1500 molecular weight polyethylene glycol polymer chain.

47. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



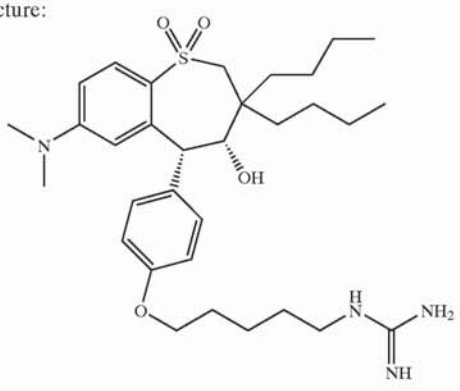
or a salt, an enantiomer, or a racemate thereof.

48. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



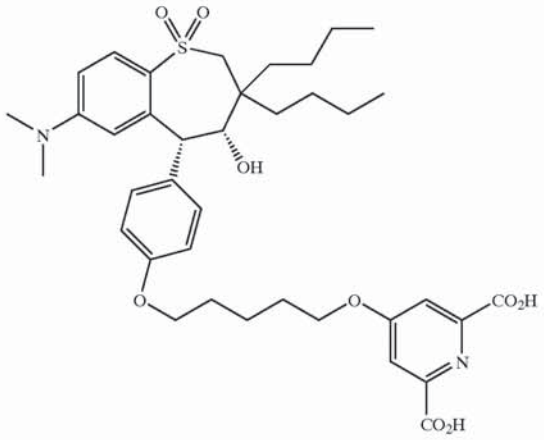
or a salt, an enantiomer, or a racemate thereof.

49. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



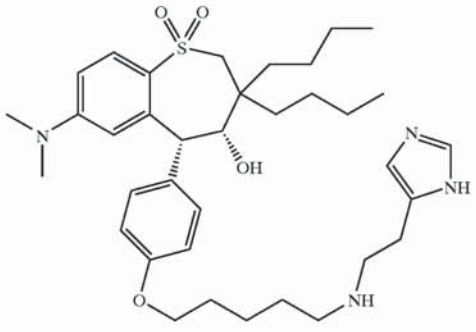
or a salt, an enantiomer, or a racemate thereof.

50. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



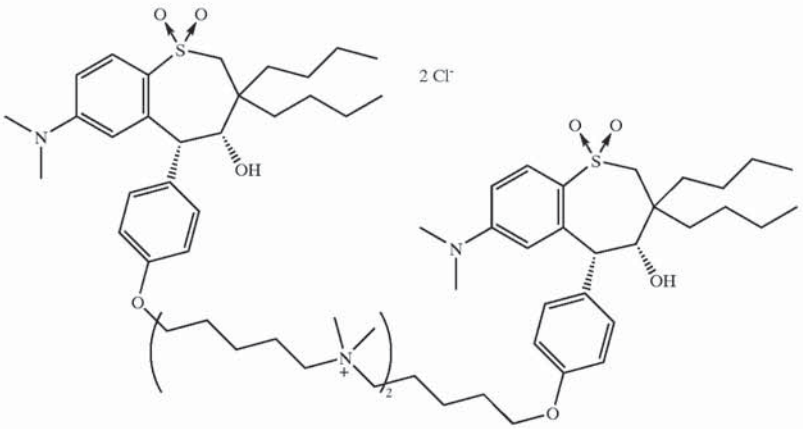
or a salt, an enantiomer, or a racemate thereof.

51. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

52. The combination of claim 18 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

53. A therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of a phytosterol compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

54. The combination of claim 54 wherein the phytosterol comprises a stanol.

55. The combination of claim 54 wherein the stanol is campestanol.

56. The combination of claim 54 wherein the stanol is cholestanol.

57. The combination of claim 54 wherein the stanol is clionastanol.

58. The combination of claim 54 wherein the stanol is coprostanol.

59. The combination of claim 54 wherein the stanol is 22,23-dihydrobrassicastanol.

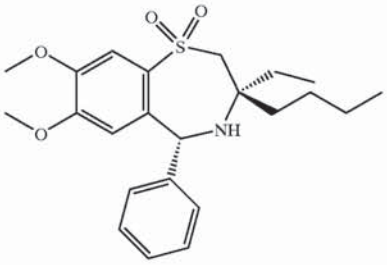
60. The combination of claim 54 wherein the stanol is epicholestanol.

61. The combination of claim 54 wherein the stanol is fucostanol.

62. The combination of claim 54 wherein the stanol is stigmastanol.

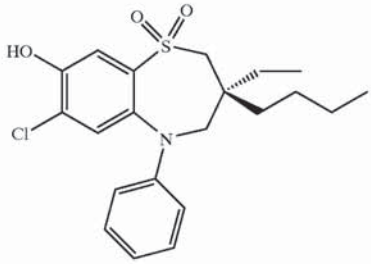
63. The combination of claim 53 wherein the ileal bile acid transport inhibitor compound comprises a benzothiazepine ileal bile acid transport inhibitor compound.

64. The combination of claim 63 wherein the ileal bile acid transport inhibitor compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

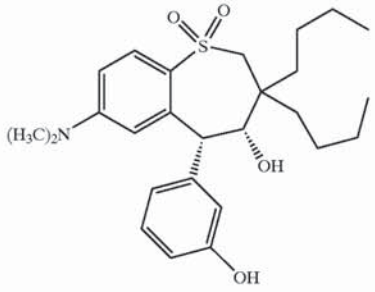
65. The combination of claim 63 wherein the benzothiazepine ileal bile acid transport inhibiting compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

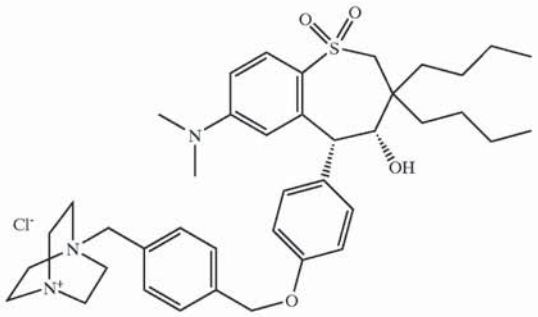
66. The combination of claim 53 wherein the ileal bile acid transport inhibiting compound comprises a benzothiepine ileal bile acid transport inhibiting compound.

67. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



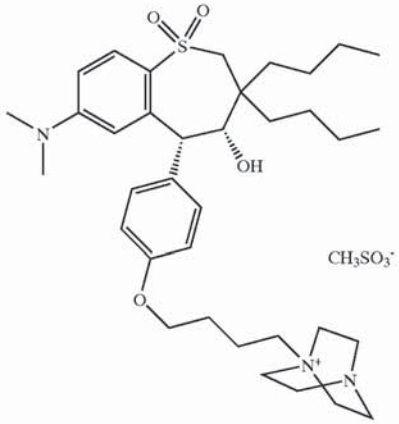
or a salt, an enantiomer or racemate thereof.

68. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



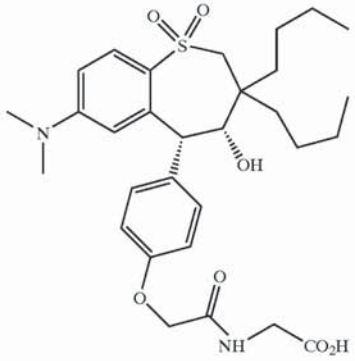
or a salt, an enantiomer, or racemate thereof.

69. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



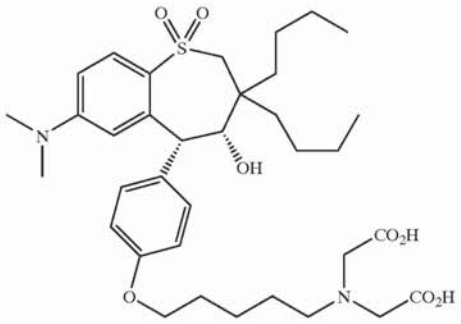
or a salt, an enantiomer, or a racemate thereof.

70. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



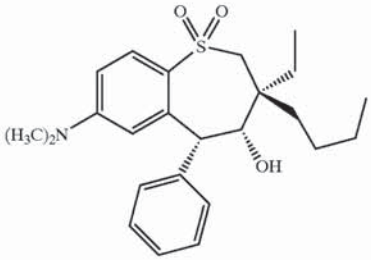
or a salt, an enantiomer, or a racemate thereof.

71. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



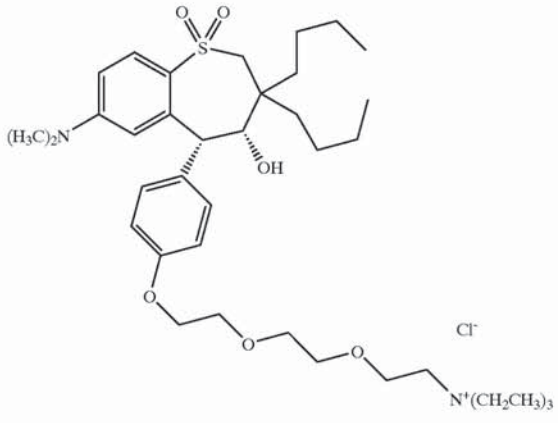
or a salt, an enantiomer, or a racemate thereof.

72. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



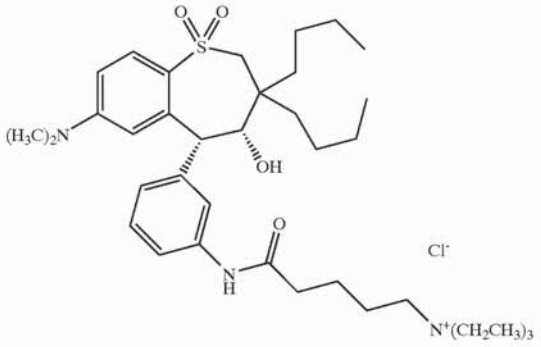
or a salt, an enantiomer, or a racemate thereof.

73. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



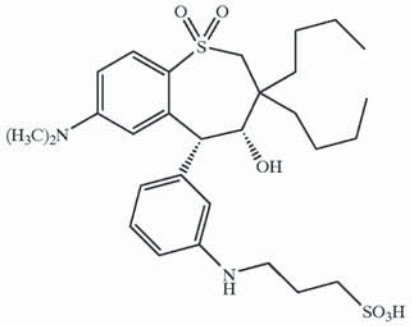
or a salt, an enantiomer, or a racemate thereof.

74. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



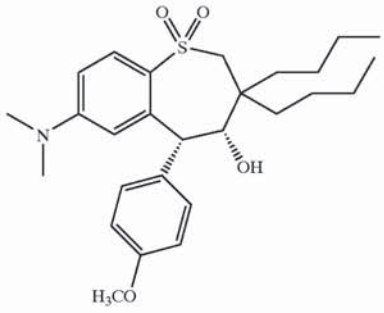
or a salt, an enantiomer, or a racemate thereof.

75. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



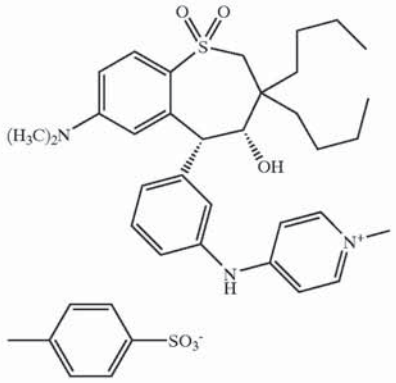
or a salt, an enantiomer, or a racemate thereof.

76. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



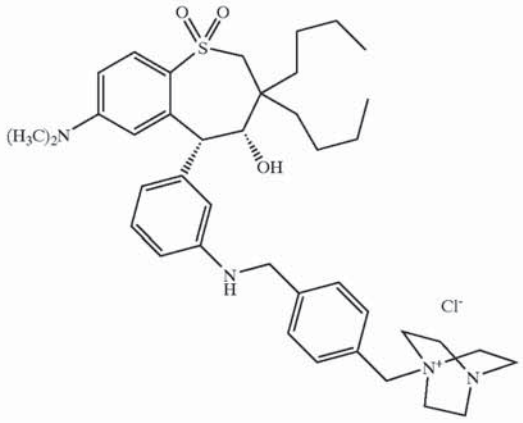
or a salt, an enantiomer, or a racemate thereof.

77. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



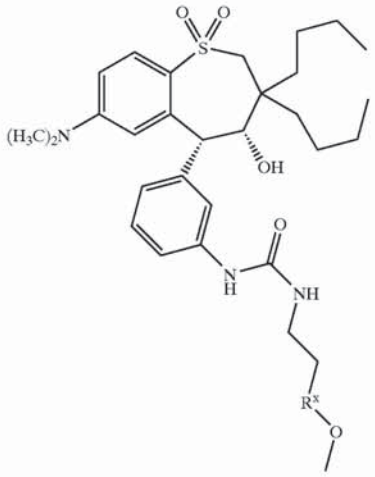
or a salt, an enantiomer, or a racemate thereof.

78. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



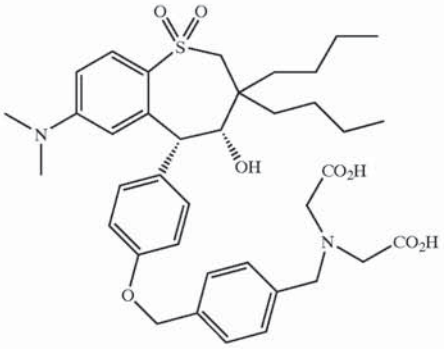
or a salt, an enantiomer, or a racemate thereof.

79. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



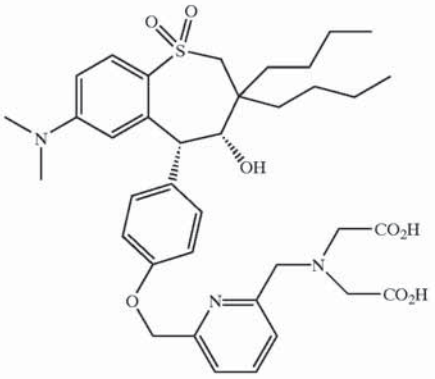
or salt, an enantiomer, or a racemate thereof wherein Rx is an about 4000 to about 6000 molecular weight polyethyleneglycol group.

80. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



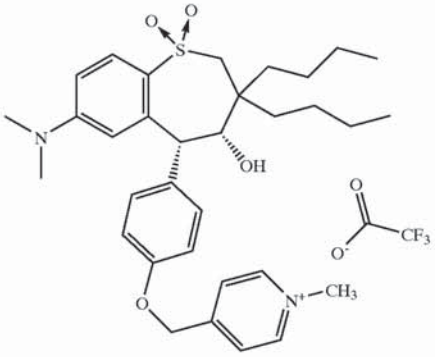
or a salt, an enantiomer, or a racemate thereof.

81. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



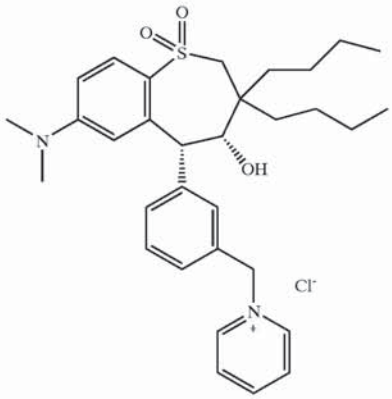
or a salt, an enantiomer, or a racemate thereof.

82. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



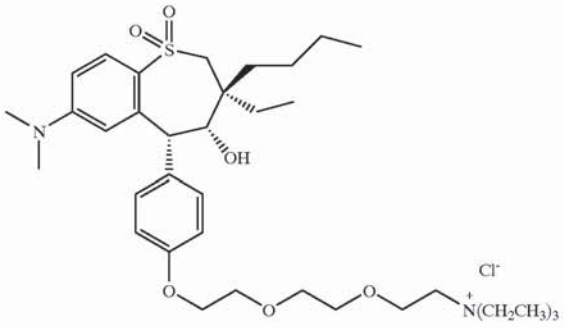
or a salt, an enantiomer, or a racemate thereof.

83. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



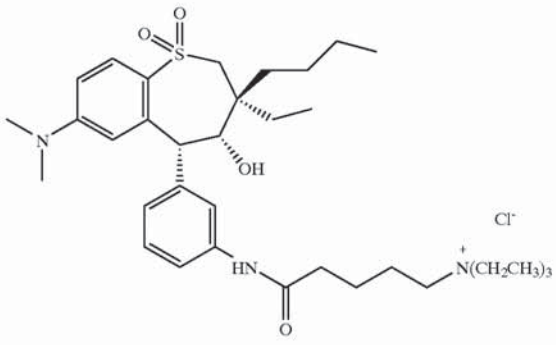
or a salt, an enantiomer, or a racemate thereof.

84. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



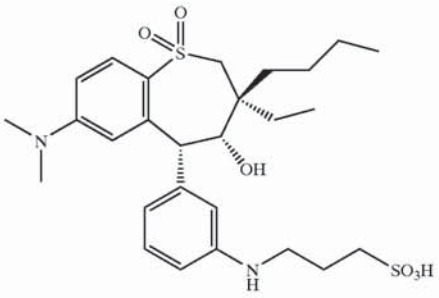
or a salt, an enantiomer, or a racemate thereof.

85. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



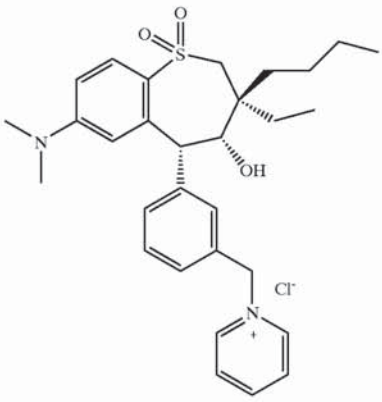
or a salt, an enantiomer, or a racemate thereof.

86. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



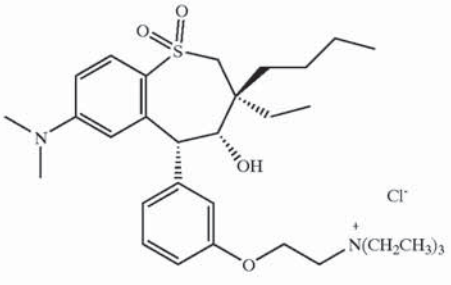
or a salt, an enantiomer, or a racemate thereof.

87. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



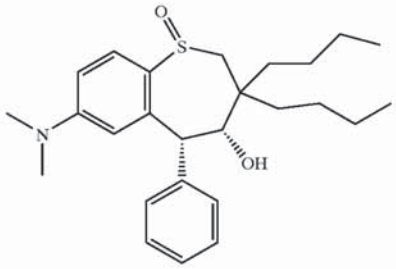
or a salt, an enantiomer, or a racemate thereof.

88. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



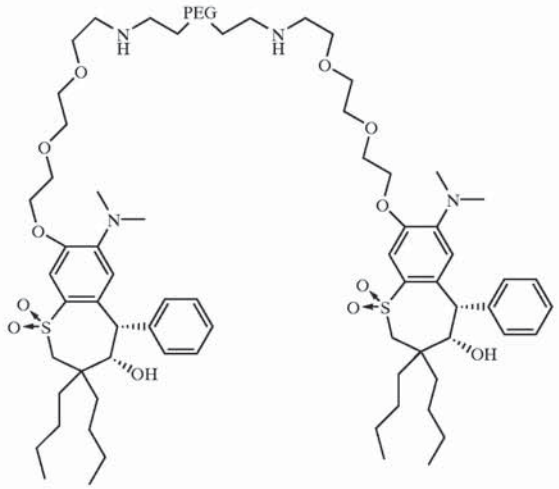
or a salt, an enantiomer, or a racemate thereof.

89. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



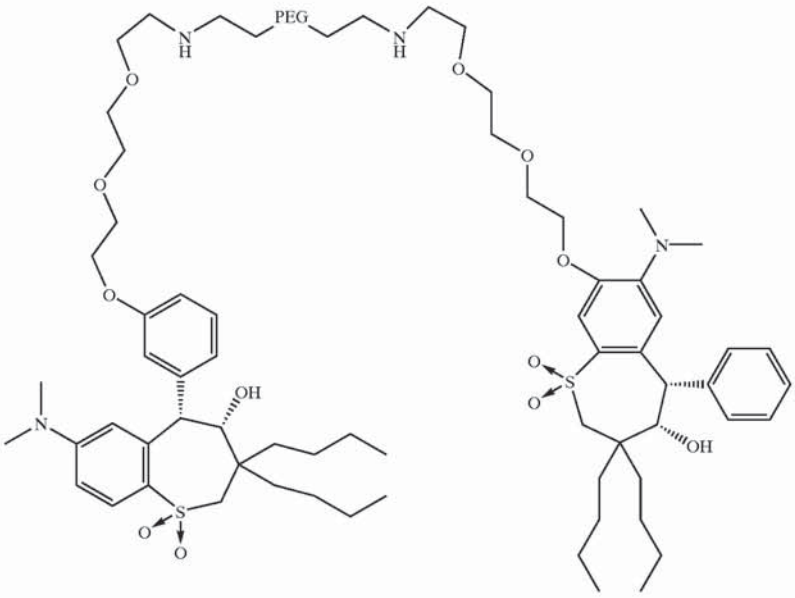
or a salt, an enantiomer, or a racemate thereof.

90. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



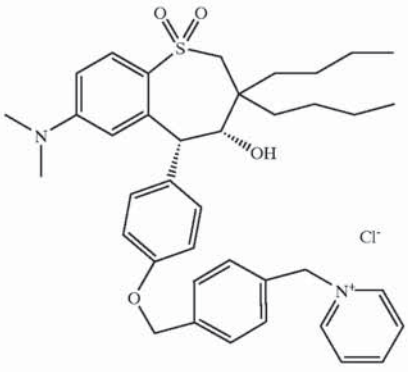
or a salt, an enantiomer, or a racemate thereof, wherein PEG is an about 3000 to about 4000 molecular weight polyethylene glycol polymer chain.

91. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



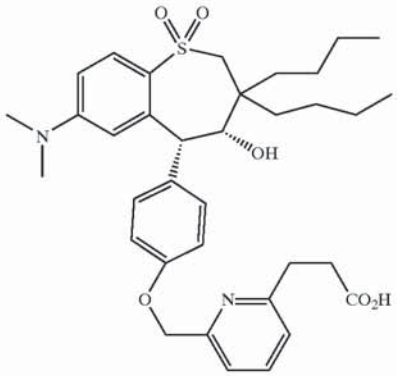
or a salt, an enantiomer, or a racemate thereof, wherein PEG is an about 3000 to about 4000 molecular weight polyethylene glycol polymer chain.

92. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



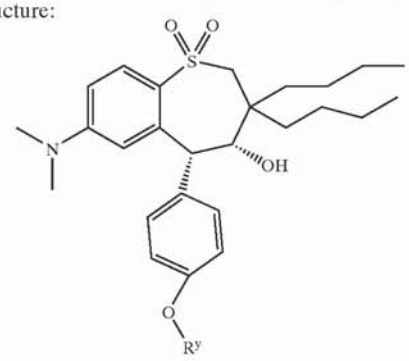
or a salt, an enantiomer, or a racemate thereof.

93. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



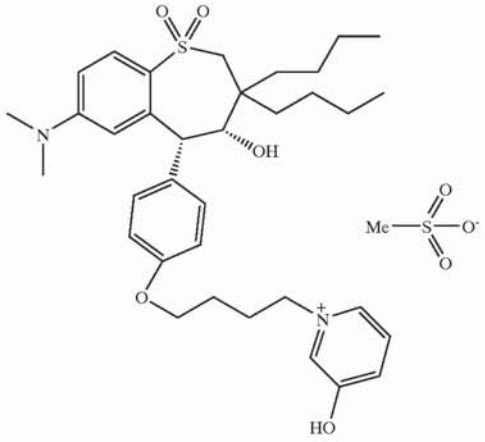
or a salt, an enantiomer, or a racemate thereof.

94. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



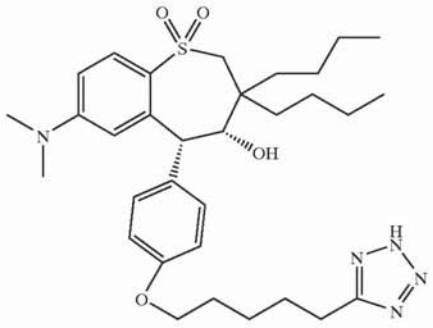
or a salt, an enantiomer, or a racemate thereof, wherein R^Y is an about 500 to about 1500 molecular weight polyethylene glycol polymer chain.

95. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



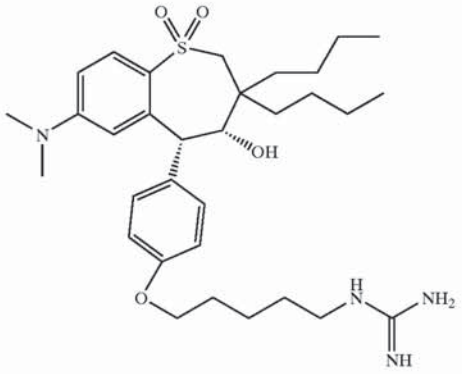
or a salt, an enantiomer, or a racemate thereof.

96. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



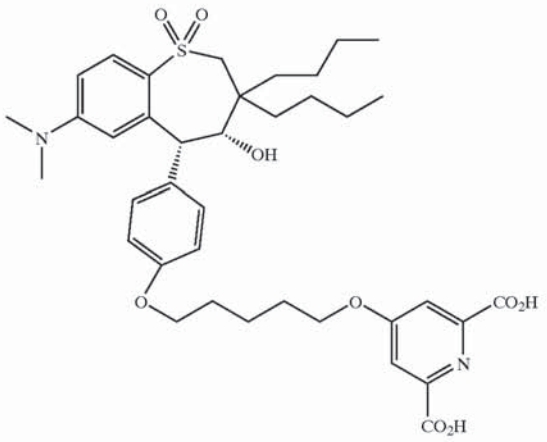
or a salt, an enantiomer, or a racemate thereof.

97. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



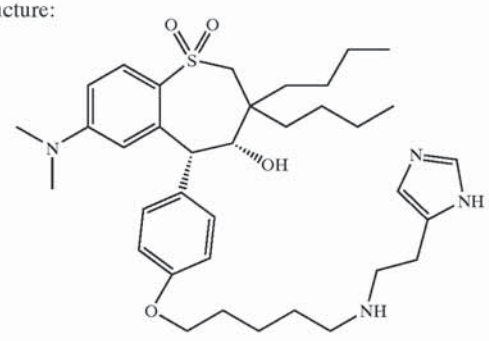
or a salt, an enantiomer, or a racemate thereof.

98. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



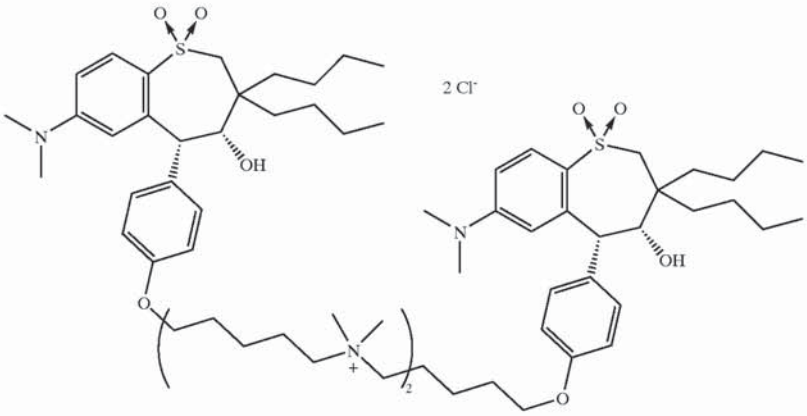
or a salt, an enantiomer, or a racemate thereof.

99. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

100. The combination of claim 66 wherein the benzothiepine ileal bile acid transport inhibiting compound has the structure:



or a salt, an enantiomer, or a racemate thereof.

101. The combination of claim 53 wherein the ileal bile acid transport inhibiting compound comprises a naphthalene ileal bile acid transport inhibiting compound.

102. A therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of probucol wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

103. The combination of claim 102 wherein the ileal bile acid transport inhibiting compound is a benzothiepine ileal bile acid transport inhibiting compound.

104. The combination of claim 102 wherein the ileal bile acid transport inhibiting compound is a benzothiazepine ileal bile acid transport inhibiting compound.

105. The combination of claim 102 wherein the ileal bile acid transport inhibiting compound is a naphthalene ileal bile acid transport inhibiting compound.

106. A method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a microsomal triglyceride transfer protein inhibiting compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

107. A method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a cholesterol absorption antagonist compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

108. A method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antihypertensive compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount of the compounds.

109. A method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a phytosterol compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

110. The method of claim 110 wherein the phytosterol compound comprises a stanol.

111. A kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a microsomal triglyceride transfer protein inhibiting compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

112. A kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a cholesterol absorption antagonist compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

113. A kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of an antihypertensive compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

114. A kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a phytosterol compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

115. The kit of claim 114 wherein the phytosterol compound comprises a stanol.

* * * * *