The present invention relates to certain novel bicyclic compounds, compositions comprising such bicyclic compounds and methods for using the Bicyclic compounds for treating or preventing a metabolic disorder, dyslipidemia, a cardiovascular disease, a neurological disorder, a hematological disease, cancer, inflammation, a respiratory disease, a gastroenterological disease, diabetes, a diabetic complication, obesity, an obesity-related disorder or non-alcoholic fatty liver disease. An illustrative bicyclic compound of the invention is shown below:
Published:

- with international search report (Art. 21(3))
BICYCLIC COMPOUNDS AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

The present invention relates to certain bicyclic compounds, compositions comprising such bicyclic compounds and methods for using the bicyclic compounds for treating or preventing a metabolic disorder, dyslipidemia, a cardiovascular disease, a neurological disorder, a hematological disease, cancer, inflammation, a respiratory disease, a gastroenterological disease, diabetes, a diabetic complication, obesity, an obesity-related disorder or non-alcoholic fatty liver disease.

BACKGROUND OF THE INVENTION

Niacin, commonly known as nicotinic acid, plays an important role in the production of several sex and stress-related hormones, particularly those made by the adrenal gland. It also plays a role in removing toxic and harmful chemicals from the body.

When taken in large doses, nicotinic acid increases the level of high density lipoprotein (HDL) in blood, and is sometimes prescribed for patients with low HDL, and at high risk of heart attack. Nicotinic acid is also used in the treatment of hyperlipidemia because it reduces very low density lipoprotein (VLDL), a precursor of low density lipoprotein (LDL) secretion from the liver, and inhibits cholesterol synthesis. Nicotinic acid has also been used to treat metabolic syndrome, but there are problems with the clinical use of nicotinic acid, including skin flushing and diarrhea, even with moderate doses.

International Publication No. WO 04/10368 describes combination therapies for the treatment of hypertension comprising the combination of an anti-obesity agent and an anti-hypertensive agent.

International Publication No. WO 05/000217 describes combination therapies for the treatment of dyslipidemia comprising the administration of a combination of an anti-obesity agent and an anti-dyslipidemic agent.


U.S. Patent Publication No. 2004/0122033 describes combination therapies for the treatment of obesity comprising the administration of a combination of an appetite suppressant and/or metabolic rate enhancers and/or nutrient absorption inhibitors.

U.S. Patent Publication No. 2004/0229844 describes combination therapies for treating atherosclerosis comprising the administration of a combination of nicotinic acid or another nicotinic acid receptor agonist and a DP receptor antagonist.

International Publication No. WO05/077950 describes xanthine derivatives which are agonists of the nicotinic acid receptor HM74A.

Despite the medicinal chemistry efforts directed to discovering NAR receptor modulators, their remains a need in the art for NAR agonists with improved efficacy and safety profiles. The present invention addresses this need.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides Compounds shown below in List 1, as well as pharmaceutically acceptable salts, solvates, esters and prodrugs thereof:
The compounds of List 1 are useful for treating or preventing a metabolic disorder, dyslipidemia, a cardiovascular disease, a neurological disorder, a hematological disease, cancer, inflammation, a respiratory disease, a gastroenterological disease, diabetes, a diabetic complication, obesity, an obesity-related disorder or non-alcoholic fatty liver disease (each being a "Condition") in a patient.

In another aspect, the invention provides methods for treating a Condition in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

In a further aspect, the invention provides compositions comprising an effective amount of one or more compounds of List 1 and a pharmaceutically acceptable carrier.
DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

A "patient" is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a non-human mammal, including, but not limited to, a monkey, dog, baboon, rhesus, mouse, rat, horse, cat or rabbit. In another embodiment, a patient is a companion animal, including but not limited to a dog, cat, rabbit, horse or ferret. In one embodiment, a patient is a dog. In another embodiment, a patient is a cat.

The term "impaired glucose tolerance" as used herein, is defined as a two-hour glucose level of 140 to 199 mg per dL (7.8 to 11.0 mmol) as measured using the 75-g oral glucose tolerance test. A patient is said to be under the condition of impaired glucose tolerance when he/she has an intermediately raised glucose level after 2 hours, wherein the level is less than would qualify for type 2 diabetes mellitus.

The term "impaired fasting glucose" as used herein, is defined as a fasting plasma glucose level of 100 to 125 mg/dL; normal fasting glucose values are below 100 mg per dL.

The term "obesity" as used herein, refers to a patient being overweight and having a body mass index (BMI) of 25 or greater. In one embodiment, an obese patient has a BMI of 25 or greater. In another embodiment, an obese patient has a BMI from 25 to 30. In another embodiment, an obese patient has a BMI greater than 30. In still another embodiment, an obese patient has a BMI greater than 40.

The term "obesity-related disorder" as used herein refers to: (i) disorders which result from a patient having a BMI of 25 or greater; and (ii) eating disorders and other disorders associated with excessive food intake. Non-limiting examples of an obesity-related disorder include edema, shortness of breath, sleep apnea, skin disorders and high blood pressure.

The term "metabolic syndrome" as used herein, refers to a set of risk factors that make a patient more susceptible to cardiovascular disease and/or type 2 diabetes. A patient is said to have metabolic syndrome if the patient simultaneously has three or more of the following five risk factors:
1) central/abdominal obesity as measured by a waist circumference of greater than 40 inches in a male and greater than 35 inches in a female;
2) a fasting triglyceride level of greater than or equal to 150 mg/dL;
3) an HDL cholesterol level in a male of less than 40 mg/dL or in a female of less than 50 mg/dL;
4) blood pressure greater than or equal to 130/85 mm Hg; and
5) a fasting glucose level of greater than or equal to 110 mg/dL.

The term "effective amount" as used herein, refers to an amount of a compound of List 1 and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a patient suffering from a Condition. When more than one compound of List 1 is present, or in the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term "alkyi," as used herein, refers to an aliphatic hydrocarbon group which may be straight or branched and which contains from about 1 to about 20 carbon atoms. In one embodiment, an alkyi group contains from about 1 to about 12 carbon atoms. In another embodiment, an alkyi group contains from about 1 to about 6 carbon atoms. Non-limiting examples of alkyi groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyi, isopentyi, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyi, aryl, cycloalkyl, -CN, -OH, -O-alkyi, -O-ary!, -alkylene-O-alkyi, alkylthio, -NH₂, -NH(alkyi), -N(alkyl)₂, -NH(cycloalkyl), -O-C(0)-alkyi, -O-C(0)-ary!, -O-C(0)-cycloalkyl, -C(O)OH and -C(0)O-alkyi. In one embodiment, an alkyi group is unsubstituted. In another embodiment, an alkyi group is linear. In another embodiment, an alkyi group is branched.

The term "alkenyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and contains from about 2 to about 15 carbon atoms. In one embodiment,
an alkenyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, -CN, -O-alkyl and -S(alkyl). In one embodiment, an alkenyl group is unsubstituted.

The term "aikynyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and contains from about 2 to about 15 carbon atoms. In one embodiment, an aikynyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an aikynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of aikynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyi. An aikynyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl. In one embodiment, an aikynyl group is unsubstituted.

The term "alkylene," as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkyne groups include -C\(_3\)H\(_4\)-, -CH\(_2\)CH\(_2\)-, -CH\(_2\)CH\(_2\)CH\(_2\)-, -CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-, -CH(CH\(_3\))CH\(_2\)CH\(_2\)- and -CH\(_2\)CH(CH\(_3\))CH\(_2\)-. In one embodiment, an alkyne group has from 1 to about 6 carbon atoms. In another embodiment, an alkyne group is branched. In another embodiment, an alkyne group is linear.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an aryl group contains from about 6 to about 10 carbon atoms. An aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. Non-limiting examples of aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is unsubstituted. In another embodiment, an aryl group is phenyl.
The term "cycloalkyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 3 to about 7 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 5 to about 7 ring atoms. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, norbornyl and adamantyl. A cycloalkyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. A cycloalkyl group may also have one of its ring carbon atoms substituted as a carbonyl group to form a cycloalkanoyl group (such as cyclobutanoyl, cyclopentanoyl, cyclohexanoyl, etc.). In one embodiment, a cycloalkyl group is unsubstituted.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. A heteroaryl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined via a ring carbon atom, and any nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which has been fused to a benzene ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thiophenyl, pyrimidinyl, pyridonyl (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl,imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinoliny1, imidazo1, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is unsubstituted. In another
embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a heteroaryl group is a 6-membered heteroaryl.

The term "heterocycloalkyi," as used herein, refers to a non-aromatic saturated monocyclic or multiciclic ring system comprising 3 to about 10 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S or N and the remainder of the ring atoms are carbon atoms. A heterocycloalkyi group can be joined via a ring carbon or ring nitrogen atom. In one embodiment, a heterocycloalkyi group has from about 5 to about 10 ring atoms. In another embodiment, a heterocycloalkyi group has 5 or 6 ring atoms. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any -NH group in a heterocycloalkyi ring may exist protected such as, for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyi groups are considered part of this invention. A heterocycloalkyi group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. The nitrogen or sulfur atom of the heterocycloalkyi can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyi rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyi, oxetanyl, thiomorpholinyl, thiazolodinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyi, lactam, lactone, and the like. A ring carbon atom of a heterocycloalkyi group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyi group is pyrroidonyl:

\[
\begin{align*}
\text{N} & \\
\text{O} & \\
\end{align*}
\]

In one embodiment, a heterocycloalkyi group is unsubstituted. In another embodiment, a heterocycloalkyi group is a 5-membered heterocycloalkyi. In another embodiment, a heterocycloalkyi group is a 6-membered heterocycloalkyi.

It should also be noted that tautomeric forms such as, for example, the moieties:
are considered equivalent in certain embodiments of this invention.

The term "ring system substituent," as used herein, refers to a substituent group attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkyl-aryl, -aryl-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, -OH, hydroxyalkyl, haloalkyl, -O-alkyl, -alkylene-O-alkyl, -O-aryl, -O-alkylene-aryl, acyl, aroyl, halo, nitro, -CN, -C(O)OH, -C(O)alkyl, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-alkylene-aryl, -C(=N-CN)NH2, -C(=NH)NH2, -C(=NH)-NH(alkyl), Y1Y2N-, YiY2N-alkyl-, Y1Y2NC(0)- and Y1Y2NSO2-, wherein Y1 and Y2 can be the same or different and are independently selected from the group consisting of hydrogen, aikyl, aryl, cycloalkyl, and -alkylene-aryl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylenedioxy, ethylenedioxy, -C(CH3)2- and the like which form moieties such as, for example:

"Halo" means -F, -Cl, -Br or -I. In one embodiment, halo refers to -Cl or -Br.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the aikyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include --CH2F, -CHF2, -CF3, -CH2Cl and -CCl3.
The term "hydroxyalkyl," as used herein, refers to an alky! group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with an -OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH and -CH₂CH(OH)CH₃.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of the compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of the compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene et al, Protective Groups in Organic Synthesis (1991), Wiley, New York.
When any variable (e.g., \(R^1, R^2, \text{etc.}\)) occurs more than one time in any constituent or in Formula I or II, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g., a drug precursor) that is transformed in vivo to yield a compound of List 1 or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of List 1 or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, \((C_1-C_8)\text{alkyl}, (C_2)\text{alkanoyloxy} , (C_{12})\text{alkanoyloxymethyl}, 1-(\text{alkanoyloxy})\text{ethyl} \text{having from 4 to 9 carbon atoms, 1-methyl-1-(\text{alkanoyloxy})-ethyl} \text{having from 5 to 10 carbon atoms, alkoxy carbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(Ci-C_2)alkylamino(C_{2-C_3})alkyl (such
as β-dimethylaminoethyl), carbamoyl-(Ci-C_2)alkyl, N,N-di (Ci-C_2)alkylcarbamoyl-(Ci-C_2)alkyl and piperidino-, pyrrolidine- or morpholino (C_2-C_3)alkyl, and the like.

Similarly, if a compound of List 1 contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (Ci-C_6)alkanoyloxyethyl, 1-methyl-1-(C_1-C_6)alkanoyloxyethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(Ci-C_6)alkoxycarbonylaminomethyl, succinoyl, (C-r C_6)alkanoyl, α-amino(Ci-C_4)alkyl, α-amino(CrC^alkylene-aryl), arylacyl and a-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(0)(OH)(2) or P(0)(OH)(2)alkyl or glycosyl (the radical resulting from the removal of a hydroxy group of the hemiacetal form of a carbohydrate), and the like.

If a compound of List 1 incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (CrC_2)alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural a-aminoacyl, —C(OH)C(0)OY wherein Y^1 is H, (Ci-C_5)alkyl or benzyl, —C(OY)^2 wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_5)alkyl, —C(0)(0)-alkyl, amino(C_1-C_6-Oaikyl), or mon-O— or di-N,N-(Ci-C_6)alkylaminoalkyl, —C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^6 is mono-N— or di-N,N-(C_1-Ce)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.
One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira et al, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder et al, AAPS PharmSciTechours., 5(1), article 12 (2004); and A. L. Bingham et al, Chem. Commun., 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The compounds of List lean form salts which are also within the scope of this invention. Reference to a compound of List 1 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of List 1 contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the compounds of the Formula I or II may be formed, for example, by reacting a compound of List 1 with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartrates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, choline, t-butyl amine, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy group of a hydroxy compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (for example, phenyl optionally substituted with, for example, halo, C<sub>1</sub>C<sub>1</sub>alkyl, or C<sub>1</sub>C<sub>4</sub>alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters.
The phosphate esters may be further esterified by, for example, a C-1-20 alcohol or reactive derivative thereof, or by a 2,3-di (Ce₂₄)acyl glycerol.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Stereochemically pure compounds may also be prepared by using chiral starting materials or by employing salt resolution techniques. Also, some of the compounds of List 1 may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of List 1 may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of List 1 incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present
invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^{15}$N, $^{18}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, and $^{36}$Cl, respectively.

Certain isotopically-labelled Compounds of Formulas (I) and (II) (e.g., those labeled with $^3$H and $^{14}$C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., $^3$H) and carbon-14 (i.e., $^{14}$C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

Isotopically labelled compounds of List 1 can generally be prepared using synthetic chemical procedures analogous to those disclosed herein for making the compounds of List 1, by substituting an appropriate isotopically labelled starting material or reagent for a non-isotopically labelled starting material or reagent.

Polymorphic forms of the compounds of List 1, and of the salts, solvates, hydrates, esters and prodrugs of the compounds of List 1, are intended to be included in the present invention.

The following abbreviations are used herein and have the following meanings: n-Bu is n-butyli, CDI is 1,1'-carbonyldiimidazole, dba is dibenzylideneacetone, DMF is $N,N$-dimethylformamide, DMSO is dimethylsulfoxide, EtOAc is ethyl acetate, EtOH is ethanol, HOAc is acetic acid, HPLC is high performance liquid chromatography, Me is methyl, NiS is N-iodosuccinimide, PBS is phosphate-buffered saline, Ph is phenyl, PPh$_3$ is triphenylphosphine and TFAA is trifluoroacetic acid.
Methods for Making the compounds of List 1

Methods useful for making the compounds of List 1 are set forth below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis. The starting materials and reagents depicted in the schemes and examples are either available from commercial suppliers such as Sigma-Aldrich (St. Louis, MO) and Acros Organics Co. (Fair Lawn, NJ), or can be prepared using methods well-known to those of skill in the art of organic synthesis.

One skilled in the art will recognize that the synthesis of compounds of List 1 may require the need for the protection of certain functional groups (i.e., derivatization for the purpose of chemical compatibility with a particular reaction condition). Suitable protecting groups for the various functional groups of the compounds of List 1 and methods for their installation and removal may be found in Greene et al., Protective Groups in Organic Synthesis, Wiley-Interscience, New York, (1999).

EXAMPLES

The following examples exemplify illustrative examples of compounds of the present invention and are not to be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

General Methods

The starting materials and reagents used in preparing compounds described are either available from commercial suppliers such as Aldrich Chemical Co. (Wisconsin, USA) and Acros Organics Co. (New Jersey, USA) or were prepared using methods well-known to those skilled in the art of organic synthesis. All commercially purchased solvents and reagents were used as received. LCMS analysis was performed using an Applied Biosystems API-100 mass spectrometer equipped with a Shimadzu SCL-10A LC column: Alttech platinum C18, 3 μm, 33 mm X 7 mm ID; gradient flow: 0 minutes, 10% CH₃CN; 5 minutes, 95% CH₃CN; 7 minutes, 95% CH₃CN; 7.5 minutes, 10% CH₃CN; 9 minutes, stop. Flash column chromatography was performed using Selecto Scientific flash silica gel, 32-63 mesh. Analytical and preparative TLC was performed using Anaitech Silica gel GF plates. Chiral HPLC was performed using a Varian PrepStar system equipped with a Chiralpak OD column (Chiral Technologies).
PREPARATIVE EXAMPLE 5

A suspension of 4-amino-pyridin-2-ol hydrochloride 5a (200 mg, 1.36 mmol) and methyl 3-oxoheptanoate 5b (324 mg, 2.05 mmol, 1.5 equiv) was heated to 170 °C for 1 h. The crude solid was cooled to room temperature and diluted with methanol. The suspension was stirred for 10 min, filtered, and triturated with methanol which upon drying gave the desired product 5 as a white powder.

PREPARATIVE EXAMPLE 21

To a stirred suspension of 5 (161 mg, 0.74 mmol) in 5 mL CH$_3$CN was added NBS (329 mg, 1.84 mmol, 2.5 equiv). The reaction was left to stir at room temperature overnight. After the reaction was complete, the mixture was filtered, triturated with CH$_2$Cl$_2$, and dried to yield the desired product 21 as a pale yellow powder.

PREPARATIVE EXAMPLE 22
To a stirred suspension of NaH (1.53 g, 38.14 mmol, 1.1 equiv) in 50 mL THF was added ethyl caproate 22a (5.73 mL, 34.67 mmol, 1.0 equiv) dropwise. The reaction was heated to 40 °C for 15 min followed by the dropwise addition of ethyl formate 22b (5.58 mL, 69.34 mmol, 2.0 equiv) and the heating was continued overnight, cooled to room temperature, and quenched by the addition of sat. NH₄Cl (20 mL). The mixture was extracted with Et₂O (2 x 30 mL), washed with brine, dried over Na₂SO₄, filtered and concentrated to yield crude 22c which was used without further purification.

A suspension of 4-amino-pyridin-2-ol hydrochloride 5a (1.14 g, 7.74 mmol) and Compound 22c (1.6 g, 9.29 mmol, 1.2 equiv) was heated to 170 °C for 1.5 h. The crude solid was cooled to room temperature and diluted with methanol. The suspension was stirred for 10 min, filtered, and triturated with methanol which upon drying gave the desired product 22 as a beige powder.

PREPARATIVE EXAMPLE 22

Mel (57.3 uL, 0.92 mmol) was added to a mixture of compound 2 (50.5 mg) and CS₂CO₃ (0.18 g) in DMF (1.0 mL) at room temperature. The mixture was heated at 50 °C overnight. The reaction was cooled and diluted with EtOAc and HCl (0.5 M). Organic phase was washes with water (3x), brine, dried (MgSO₄). Solvent was removed under reduced pressure and the residue was purified with preparatory TLC, eluted with hexane:EtOAc to give compound 34.

PREPARATIVE EXAMPLE 20
The mixture of butyl ketoester (1.04g, 6.6 mmol) and 4-aminonitric acid methyl ester (1g, 6.6 mmol) was heated to 150 °C for 4 hours. The reaction mixture was separated using silica gel flash column chromatography eluting with methanol/dichloromethane (v/v = 5/95) to give compound 20 (0.05g, 3%).

**PREPARATIVE EXAMPLE 38**

The mixture of the ketoester (0.55g, 3 mmol) and 4-aminonitric acid methyl ester (0.47g, 3 mmol) was heated to 150 °C for 2 hours. The reaction mixture was separated using silica gel flash column chromatography eluting with methanol/ dichloromethane (v/v = 3/97) to give compound 38 (0.02g, 2.5%).

**PREPARATIVE EXAMPLE 39**

The mixture of the ketoester (1.1g, 6 mmol) and 3-aminothiophene-2-methyl ester hydrochloride salt (0.5g, 3 mmol) was heated to 150 °C for 2 hours. The reaction mixture was separated using silica gel flash column chromatography eluting with dichloromethane to give compound 39 (0.2g, 23%).

**PREPARATIVE EXAMPLE 46**
Oxylyldiimidazole (0.141 g) was added to a solution of compound 28 (0.136 g) in benzene (3.0 mL) at room temperature. The mixture was heated at reflux for 2 hours. The reaction was cooled and diluted with EtOAc and HCl (0.5 M). Organic phase was washed with water, brine, dried (MgSO₄). Solvent was removed under reduced pressure and the residue was purified with Gilson reverse phase HPLC to give compound 46 and 47.

PREPARATIVE EXAMPLE 69

The mixture of the ketoester (0.78g, 6 mmol) and 3-arninothiophene-2-methyi ester hydrochloride salt (0.5g, 3 mmol) was heated to 150 °C for 3 hours. The reaction mixture was separated using silica gel flash column chromatography eluting with methanol/dichloromethane (v/v = 4/96) to give compound 69 (0.15g, 21%).

PREPARATIVE EXAMPLE 70

The mixture of compound 69 (0.11g, 0.46 mmol) in MeOH/H₂O (5 mL, v/v = 4/1) and NaOH (0.072g, 1.8 mmol) was stirred at room temperature for over night. The reaction mixture was acidified with 2N HCl. The precipitate was isolated to give compound 70 (0.18g, 100%).

Experimental part for compounds 3, 4, 13, and 72:

General procedure for the lactam formation and hydrolysis:

PREPARATIVE EXAMPLE 3

The ketoester and aniline were mixed in a 1:1 mole ratio and heated in a seal tube at 150°C over night. The reaction mixture was cooled to room temperature and purified by prep-TLC and eluted with mixture of MeOH:DCM 1:10; to give the desired product.

PREPARATIVE EXAMPLE 4
The cyanide compound was dissolved in 1,4-dioxane and water (1:1) and treated with KOH (4 eq). The reaction mixture was heated to reflux. The mixture was cooled to room temperature and the aqueous layer was acidified with 1N HCl (aq), and the precipitation was collected to give the desired product.

PREPARATIVE EXAMPLE 13

The cyanide compound was dissolved in ethylene glycol and water (1:1) and treated with KOH (4 eq). The resulting solution was heated at 150°C overnight. The mixture was cooled to room temperature and the aqueous layer was acidified with HCl (1N, aq). The precipitation was collected to give the desired product.

PREPARATIVE EXAMPLE 73

Compound 73 was prepared in a similar fashion as described in *Bioorganic & Medicinal Chemistry* 11(6), 1031, 2003, with a different ketoester.

General procedure for synthesizing compounds 83, 104, 105, 132, 134, 135, 138, 139, 140:

PREPARATIVE EXAMPLE 83

The compound 73 (67 mg, 0.31 mmol), carboxylic acid (1.26 mmol), diisopropylethylamine (1.55 mmol) were mixed in DMF (2 mL). HATU was added. The resulting mixture was heated at 50°C overnight. The solution was cooled to room temperature and the volatile was removed. Methanol (2 mL) and water (2 mL) were added. The precipitation was collected as the desired product.

PREPARATIVE EXAMPLE 74
The starting material (500 mg, 2.16 mmol) was dissolved in AC2O (2 mL) and HOAc (2 mL). The mixture was cooled with ice bath and fuming HN0₃ (0.15 mL) was added. The resulting mixture was stirred at room temperature for 1 h. The volatile was removed. The residue was taken up with methanol, and filtered. The filtrate was concentrated and purified over silica gel column, eluted with MeOH:DCM (1:40), to give 74A (371 mg, 25%), 74 (220 mg, 25%).

PREPARATIVE EXAMPLE 89

Compound 74 (150 mg, 0.54 mmol) was taken up in THF (10 mL), 10% palladium on carbon (150 mg) as added. The mixture was heated at 50°C under 1 atm of H₂ for 4 h. The mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated and purified by preparatory TLC, eluted with MeOH:DCM (1:10) to give the desired product 89 (77 mg, 58%).

PREPARATIVE EXAMPLE 133

Compound 83 (20 mg, 0.07 mmol) was taken up in HOAc (1 mL) and cooled with ice bath. NBS (11 mg, 0.06 mmol) was added. The resulting mixture was stirred at room temperature overnight. The volatile was removed, and the residue was taken up in water and EtOAc. The organic layer was dried (MgSO₄) and concentrated. The residue was purified by preparatory TLC, eluted with MeOH:DCM (1:10) to give compound 133A (15 mg, 50%) and compound 133 (14 mg, 46%).

PREPARATIVE EXAMPLE 177
Compound 73 (1.03 g, 4.73 mmol) was taken up in DMF (5 mL) and THF (5 mL) and NaN(TMS)_2 (1.0 M in THF, 10 mL, 10 mmol) was added. The resulting solution was heated to reflux for 1 h. The mixture was cooled to room temperature and B0C2O (1.25 g, 5.73 mmol) was added. The resulting mixture was heated at 70°C overnight. The mixture was cooled to room temperature, water and DCM was added. The mixture was filtered, and the filtrate was transferred to a separatory funnel and the DCM layer was separated. The combined DCM layer was dried (MgSO_4) and concentrated. The residue was purified by preparatory TLC, eluted with MeOH:DCM (1:15) to give 177 (0.45 g, 22%) and 177A (0.56 g, 37%).

PREPARATIVE EXAMPLE 141

Starting material was taken up in DMF (4 mL) and THF (1 mL), cooled with ice-bath, NaH (97% oil dispersion, 35 mg, 1.38 mmol) was added. The resulting mixture was stirred at room temperature for 20 min. To the slurry, Tf_NPh (144 mg, 0.56 mmol) was added. The resulting slurry was stirred at room temperature overnight. The mixture was poured into satd. NaHCO_3(aq.), and extracted with DCM. The organic layers were combined, dried (MgSO_4), filtered and concentrated. The residue was purified with prep-TLC, eluted with MeOH:DCM (1:10), to give 141 (112 mg, 63%).

PREPARATIVE EXAMPLE 176

Compound 141 (92 mg, 0.26 mmol), Pd(PPh_3)2Cl_2 (36 mg, 0.05 mmol) were mixed in Et_3N (1 mL), DMF (1 mL) and methanol (1 mL). The mixture was place under a CO balloon and heated at 85°C overnight. The reaction mixture was cooled to room temperature, filtered. The filtrate was concentrated. The residue was purified by preparatory TLC, eluted with MeOH:DCM (1:10) to give 176A (15 mg, 22%).
Compound 176A (27 mg, 0.10 mmol) was taken up with water (0.5 mL), THF (1 mL) and MeOH (0.5 mL). The resulting mixture was heated at 50°C, until it turned homogenous. The mixture was cooled to room temperature, LiOH (42 mg, 1.0 mmol) was added, and stirred at room temperature overnight. HCl (1N, aq.) was added until the mixture is acidic. The volatile was removed, EtOAc and water was added. The mixture was filtered, and the solid was collected to give compound 176 (17 mg, 70%).

PREPARATIVE EXAMPLE 178

Compound 141 (150 mg, 0.43 mmol) was dissolved in DMF (2 mL). Zn(CN)2 (100 mg, 0.85 mmol), Pd(PPh3)4 (20 mg, 0.017 mmol) was added. The resulting mixture was degassed by heated under nitrogen at 120°C overnight. The reaction mixture was cooled to room temperature. Solvent was removed. The residue was taken up with methanol, and filtered. The filtrate was concentrated, and the resulting solid was washed by water and EtOAc to give compound 178 (50 mg, 51%).

PREPARATIVE EXAMPLE 182

Compound 178 (44 mg, 0.19 mmol) was dissolved in DMF (3 mL), and NaN3 (101 mg, 1.55 mmol) was added. The reaction mixture was heated in a sealed tube at 150°C overnight. The mixture was cooled to room temperature and solvent was removed. The residue was purified by silica gel column, eluted with HOAc-EtOAc-Hexanes(1:10:10) to give compound 182 (13 mg, 25%).

PREPARATIVE EXAMPLE 118
Step A:

Compounds 118a (1.0 g) and 118b (1.0 mL were heated at 150 °C overnight. The mixture was cooled and purified with silica gel column eluted with EtOAc-Hexanes to give compound 118c.

Step B:

Compound 118c (0.88 g) in concentrate H₂SO₄ (6.0 mL) was stirred at 0 °C for 1 hour and then at room temperature for overnight. The reaction was worked with EtOAc and ice water. Organic phase was washed with water, brine, dried (MgSO₄). Solvent was removed under reduced pressure and the residue was purified with silica gel column eluted with EtOAc-Hexanes to give compound 118.

PREPARATIVE EXAMPLE 122

The mixture of compound 118 (50 mg) and NaOH (0.566 mL, 1.0 N) in MeOH/THF (v/v = 0.5/1.0) and was stirred at room temperature for over night. The reaction mixture was acidified with 2N HCl and extracted with EtOAc. Organic phase was washed with water, brine, dried (MgSO₄). Solvent was removed under reduced pressure and the residue was purified with PTLC eluted with EtOAc-Hexanes to give compound 122.

Compounds 123, 124, 148, 149, 158-163 were prepared using the similar procedure as that of 118 and 122 starting with the corresponding amino ester and ketoester.
PREPARATIVE EXAMPLE 142, 143

The mixture of compound 69 (0.47g, 2 mmol) in acetic acid (1.8 mL, ) and fuming HNO₃ (0.9 mL, 90%) was heated to 100 °C for 1h. The reaction mixture was neutralized with iced NaHCO₃ solution, extracted with dichloromethane. The organic solution was concentrated and separated using silica gel flash column chromatography eluting with dichloromethane to give compounds 142 (0.15g) and 143 (0.1 g).

PREPARATIVE EXAMPLE 144

The mixture of the compound 69 (0.6g, 2.53 mmol) in DMF (5 mL) and NIS (1.1g, 5.06 mmol) was heated to 50 °C for over night. The reaction mixture was separated using silica gel flash column chromatography eluting with methanol/dichloromethane (v/v = 1/99) to give compound 144 (0.012g).

PREPARATIVE EXAMPLE 150

The mixture of the compound 69 (0.6g, 2.53 mmol) in DMF (10 mL) and NBS (0.9g, 5.06 mmol) was heated to 60 °C for over night. The reaction mixture was poured into hot water (20 mL). The precipitate was isolated to give compound 150 (0.65g, 81%).

PREPARATIVE EXAMPLE 153

The mixture of compound 143 (0.095g, 0.34 mmol) in AcOH (1 mL) and Zinc (0.22g, 3.4 mmol) was stirred at room temperature for over night. The reaction mixture was filtered from solid, concentrated and separated using silica gel flash column
chromatography eluting with methanol/dichloromethane (v/v = 4/96) to give compound 153 (0.055g, 65%).

PREPARATIVE EXAMPLE 154

The mixture of compound 69 (0.12g, 0.5 mmol) in DMF (5 mL), 1-iodobutane (0.14g, 0.75 mmol), and Cs2CO3 (0.33g, 1 mmol) was stirred at room temperature for over night. The reaction mixture was poured to sat’d NH4Cl (10 mL) and extracted with ethyl acetate. The organic solution was concentrated and separated using silica gel flash column chromatography eluting with methanol/dichloromethane (v/v = 1/99) to give compound 154 (0.12g, 80%).

PREPARATIVE EXAMPLE 157

The mixture of compound 154 (0.1 g, 0.34 mmol) in MeOH/H2O (5 mL, v/v = 3/1) and NaOH (0.034g, 0.85 mmol) was stirred at room temperature for over night. The reaction mixture was acidified with 2N HCl. The precipitate was isolated to give compound 157 (0.080g, 89%).

PREPARATIVE EXAMPLE 181

The mixture of compound 69 (0.5g, 2.1 mmol) in DMF (10 mL) and ammonium hydroxide(20 mL) was stirred at room temperature for 24 hours. The reaction mixture was concentrated and separated using silica gel flash column chromatography eluting with methanol/dichloromethane (v/v = 7/93) to give compound 181 (0.19g, 40%).

PREPARATIVE EXAMPLE 94
3,5-dihydroxyaniline (500 mg, 3.1 mmol) and 8-Fluoro-3-oxo-octanoic acid methyl ester (707 mg, 1.2 eq) were combined and heated to 150°C for 1h. Compound purified on Gilson HPLC then prep TLC plate developed in 5% MeOH/DCM with 1% HOAc.

PREPARATIVE EXAMPLE 6-8

Step a:
To a suspension of 8a (0.21 g, 0.87mmol) in 5ml of dry THF was added n-BuLi (1.6M in hexane, 1.25ml, 2.0mmol) dropwise under N₂ at 0°C. After stirring at 0°C for 2h, the mixture was cooled to -78°C by dry ice-acetone bath. DMF (0.15ml, 2.0mmol) was added to the mixture. After stirring at -78°C for 30 mins, the cooling bath was removed. The mixture was slowly warmed up to r.t. and stirred at r.t. for 1h. 1N HCl was added to quench the reaction, and then the mixture was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered. The filtrate was concentrated and purified by flash column to give 0.035g of 6, yield: 15%. 0.02g of the isomer (7) of 8a was recovered during the purification.

Step b:
NaClO₂ (0.039g, 0.44mmol) in 2ml of H₂O was added dropwise to the suspension of 6 (0.034g, 0.12mmol) and NH₂SO₃H (0.042g, 0.44mmol) in 6ml of 1, 4-dioxane. After stirring at r.t. under N₂ for 1h, the mixture was extracted with CH₂Cl₂ and 1N HCl, washed with H₂O and brine, dried over Na₂SO₄, filtered. The filtrate was concentrated and washed with 3ml of ether to give 0.032g of 8 as a white solid. Yield: 89%.

The same synthetic procedures for the following compounds: 14-18, 23, 25-27, 35-37.

PREPARATIVE EXAMPLE 48
Step c:

To a solution of 48a (0.18g, 0.73mmol) in 10ml of EtOH was added HONH₂·HCl (0.51 g, 7.34mmol) and NaOAc (0.30g, 3.67mmol). After stirring at r.t. under N₂ for 24h, the mixture was extracted with CH₂Cl₂ and saturated NH₄Cl (aq.), washed with H₂O and brine, dried over Na₂SO₄, filtered. The filtrate was concentrated and purified by flash column to give 0.11g of 48 yield: 58%.

PREPARATIVE EXAMPLE 50-51

Step d:

To a solution of 51a (0.08g, 0.35mmol) in 10ml of toluene was added HONH₂·HCl (0.03g, 0.38mmol), MgSO₄ (0.17g, 1.40mmol) and p-MePhSO₃H·H₂O (0.01 g, 0.07mmol). After refluxing at 110°C under N₂ for 24h, the solvent was removed, the mixture was extracted with CH₂Cl₂ and 0.5N HCl, washed with H₂O and brine, dried over Na₂SO₄, filtered. The filtrate was concentrated and purified by flash column and prep-TLC to give 0.03g of 51, yield: 38%, and 0.005g of 50, yield: 6%.

The same procedure was used for making 64.

PREPARATIVE EXAMPLE 68

Step e:
To a solution of 68a (0.028g, 0.12mmol) in 3ml of 1,4-dioxane/H₂O (2:1) was added NaN₃ (0.024g, 0.36mmol) and ZnBr₂ (0.033g, 0.15mmol). The mixture was heated at 120 °C in a sealed tube for 48h, and then extracted with CH₂Cl₂ and 0.5N HCl, washed with H₂O and brine, dried over Na₂SO₄, filtered. The filtrate was concentrated and purified by reversal phase HPLC to give 0.012g of 68, yield: 36%.

PREPARATIVE EXAMPLE 86-87

Step f:

To a solution of 86a (1.0g, 4.08mmol) in 6ml of DMF was added Mel (0.69g, 4.89mmol) and Cs₂CO₃ (2.66 g, 8.16mmol). After heating at 60°C under N₂ for 24h, the mixture was extracted with CH₂Cl₂ and 0.5N HCl, washed with H₂O (3x) and brine, dried over Na₂SO₄, filtered. The filtrate was concentrated and purified by flash column to give 0.18g of 86, yield: 16%, and 0.71g of 87, yield: 67%.

PREPARATIVE EXAMPLE 90

Step g:

To a suspension of 90a (0.03g, 0.10mmol) in 3ml of THF was added CDI (0.018g, 0.11mmol). After stirring at 40°C under N₂ for 1h, the mixture was cooled to r.t., NH₂SO₂CH₃ (0.016g, 0.17mmol) and DBU (0.026g, 0.17mmol) were added, and the mixture was stirred at r.t. for 24h. Then the mixture was extracted with CH₂Cl₂ and 0.5N HCl, washed with H₂O and brine, dried over Na₂SO₄, filtered. The filtrate was concentrated and purified by prep-TLC to give 0.03g of 90, yield: 81%.

Step h:

The same procedure as step a to give 97, yield: 30%; 98, yield: 3.7%; 99, yield: 3.9%; and 101, yield: 2%.

Step i:

The same procedure as step b to give 114, yield: 66%; 108, yield: 53%; 109, yield: 47%; 111, yield: 44%; 112, yield: 16%; and 110, yield: 63%.

PREPARATIVE EXAMPLE 116

Step j:

To a solution of 97 (0.03g, 0.11mmol) in 10ml of CH₂Cl₂ and C₂H₄Cl₂ (1:1) was added DAST (0.105g, 0.66mmol). After heating at 60°C under N₂ for 72h, the mixture was extracted with CH₂Cl₂ and saturated NaHCO₃ (aq.), dried over Na₂SO₄, filtered.
The filtrate was concentrated and purified by reversal phase HPLC to give 0.0015g of 116, yield: 5%.

PREPARATIVE EXAMPLE 126

Step k:

The mixture of 126a (1.18g, 10.81mmol) and 126b (2.0g, 10.81mmol) was heated at 150°C for 4h, cooled to r.t, dissolved in CH₂Cl₂, and then purified by flash column to give 1.4g of 126, yield: 53%.

PREPARATIVE EXAMPLE 170, 179

Step 1:

To a solution of 170a (10.0g, 77.4mmol) in 150ml of EtOH and H₂O (2:1) was added HONH₂·HCl (6.5g, 92.9mmol) and K₂CO₃ (12.8g, 92.9mmol). After heating at 70°C under N₂ for 24h, additional HONH₂·HCl (6.5g, 92.9mmol) and K₂CO₃ (12.8g, 92.9mmol) were added. After heating at 90°C under N₂ for 24h, EtOH was removed, the mixture was extracted with CH₂Cl₂ (3x), dried over Na₂SO₄, filtered. The filtrate
was concentrated to give 9.5g of 170b. The aqueous layer was concentrated to remove H2O, and the solid was suspended in CH2Cl2 filtered. The filtrate was concentrated to give additional 2.5g of 170b, total yield: 94%.

Step nr.

To a suspension of picolinic acid (4.74g, 38.39mmol) in 20ml of dry DMF was added CDI (6.60g, 40.70mmol). After stirring at r.t. under N2 for 2h, 170b in 5ml of dry DMF (6.60g, 40.70mmol) was added, and the mixture was stirred at 100°C for 24h. The mixture was cooled to r.t., extracted with EtOAc and saturated NH4Cl (aq.), washed with H2O (3x) and brine, dried over Na2SO4, filtered. The filtrate was concentrated to give 7.4g of 170c, yield: 77%.

Step n:

2.5g of 170c was dissolved in 2ml of TFA. After stirring at r.t. under N2 for 24h, the solvent was removed; the product was extracted with CH2Cl2 and saturated NaHCO3 (aq.), dried over Na2SO4, filtered. The filtrate was concentrated to give 1.8g of 170d, yield: 88%.

Step o:

To a solution of 170d (0.91g, 4.48mmol) in 20ml of t-BuOH was added NaH2P04·H2O (1.24g, 8.96mmol) in 2ml of H2O, 2-methyl-1-butene (3.32ml, 31.36mmol), and NaCl02 (1.42g, 15.68mmol) in 3ml of H2O. After stirring at r.t. under N2 for 24h, the mixture was extracted with CH2Cl2 (5x) and saturated NH4Cl (aq.), dried over Na2SO4, filtered. The filtrate was concentrated to give 0.95g of 170e, yield: 95%.

Stop p:

To a solution of 170e (0.90g, 4.11mmol) in 15ml of THF and 2ml of DMF was added CDI (0.80g, 4.93mmol). After stirring at r.t. under N2 for 1h, MgCl2 (0.39g, 4.11mmol) and potassium monomethyl maionate (0.96g, 6.17mmol) were added. The mixture was stirred at r.t. for 24h, then extracted with EtOAc (2x) and saturated NH4Cl.
(aq.), washed with H$_2$O (2x) and brine, dried over Na$_2$SO$_4$, filtered. The filtrate was concentrated to give 1.0g of 170f, yield: 95%.

Step q:

The suspension of 170f (0.10g, 0.37mmol) and methyl 3-aminothiophene-4-carboxylate (0.06g, 0.37mmol) in 0.5ml of AcOH was heated at 120°C for 24h. The mixture was cooled to r.t., dissolved in 4ml of DMF, and purified by reversal phase HPLC followed by washing with 5ml of ether to give 0.035g of 170, yield 25%.

Step r:

To a solution of 170 (0.028g, 0.073mmol) in 5ml of MeOH and H$_2$O (1:1) was added LiOH·H$_2$O (0.006g, 0.146mmol). After heating at 60°C under N$_2$ for 24h, 2 drops of AcOH was added to the solution. The solvent was removed, the solid was dissolved in CH$_2$Cl$_2$/MeOH (9:1), dried over Na$_2$SO$_4$, filtered. The filtrate was concentrated to give 0.026g of 179, yield 96%.

**PREPARATION OF COMPOUND 183**

![183]

A suspension of compound 22 (300 mg, 1.37 mmol) and NIS (1.07 g, 4.8 mmol, 3.5 equiv) in 3.0 mL acetic acid was stirred at room temperature for 16 h. After the reaction was complete, 10 mL of water was added. The precipitate was filtered, triturated with water and ether to afford the desired product 183 as beige solid.

**PREPARATION OF COMPOUND 184**

![184]

A mixture of compound 183 (25 mg, 0.073 mmol), KCN (36 mg, 0.55 mmol, 7.5 equiv), and 18-crown-6 (145 mg, 0.55 mmol, 7.5 equiv) in 3 mL CH$_3$CN was heated to reflux. After 8 h, 5 mL H$_2$O was added and the mixture was extracted with EtOAc (2 x 10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. The crude mixture was purified using a Gilson to yield the desired product 184 as a clear film.
Nicotinic Acid Receptor Assay

The compounds described in Table 1 are all HM74 agonists except the three which are also HM74A agonists.

The HM74 agonist activity of the inventive compounds can be determined by following the inhibition of forskolin-stimulated cAMP accumulation in cells using the MesoScale Discovery cAMP detection kit following the manufacturer's protocol. Briefly, Chinese Hamster Ovary (CHO) cells expressing recombinant human HM74 are harvested enzymatically, washed 1X in phosphate buffered saline (PBS) and resuspended in PBS containing 0.5 mM IBMX at 3x10⁶ cells/mL. Ten µL of cell suspension is added to each well of a 384-well plate, each well containing 10 µL of test compound. Test compounds are diluted with PBS containing 6 µM of forskolin. Plates are incubated for 30 minutes at room temperature after the addition of cells. Lysis buffer containing cAMP-Tag is then added to each well (10 µL/well) as per the manufacturer's protocol. Plates are then incubated from 45 minutes to overnight. Prior to reading, 10 µL of read buffer is added to each well, and the plate is read in a Sector 6000 plate imager. The signal can be converted to cAMP concentration using a standard curve run on each plate. Compound EC₅₀ values can then be determined from concentration gradients of test compounds. The thus obtained EC₅₀ values for several of the compounds of List 1 are shown in Table 1. In Table 1, the following abbreviations apply for the EC₅₀ numbers:

*A: <1000 nM; B: 1000 nM to 10000 nM; C: >10000 nM.

<table>
<thead>
<tr>
<th>Compound #</th>
<th>MOLSTRUCTURE</th>
<th>HM74 EC₅₀</th>
<th>camp nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="MOLSTRUCTURE" /></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="MOLSTRUCTURE" /></td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
Uses of the compounds of List 1

The compounds of List 1 are useful in human and veterinary medicine for treating or preventing a Condition in a patient. In accordance with the invention, the compounds of List 1 can be administered to a patient in need of treatment or prevention of a Condition.

Methods For Treating or Preventing Pain

The compounds of List 1 are useful for treating or preventing pain in a patient. Accordingly, in one embodiment, the present invention provides a method for treating or preventing pain in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Illustrative examples of pain treatable or preventable using the present methods, include, but are not limited to acute pain, chronic pain, neuropathic pain, nociceptive pain, cutaneous pain, somatic pain, visceral pain, phantom limb pain, cancer pain (including breakthrough pain), pain caused by drug therapy (such as cancer chemotherapy), headache (including migraine, tension headache, cluster headache, pain caused by arthrits, pain caused by injury, toothache, or pain caused by a medical procedure (such as surgery, physical therapy or radiation therapy).

In one embodiment, the pain is neuropathic pain.
In another embodiment, the pain is cancer pain.
In another embodiment, the pain is headache.

Methods For Treating or Preventing Diabetes

The compounds of List 1 are useful for treating or preventing diabetes in a patient. Accordingly, in one embodiment, the present invention provides a method for
treat diabetes in a patient, comprising administering to the patient an effective amount of one or more compounds of **List 1**.

Examples of diabetes treatable or preventable using the compounds of **List 1** include, but are not limited to, type I diabetes (insulin-dependent diabetes mellitus), type II diabetes (non-insulin dependent diabetes mellitus), gestational diabetes, autoimmune diabetes, insulinopathies, idiopathic type I diabetes (Type 1b), latent autoimmune diabetes in adults, early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, diabetes due to pancreatic disease, diabetes associated with other endocrine diseases (such as Cushing's Syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism or somatostatinoma), type A insulin resistance syndrome, type B insulin resistance syndrome, Hpatrophic diabetes, diabetes induced by β-cell toxins, and diabetes induced by drug therapy (such as diabetes induced by antipsychotic agents).

In one embodiment, the diabetes is type I diabetes.

In another embodiment, the diabetes is type II diabetes.

**Methods For Treating or Preventing a Diabetic Complication**

The compounds of **List 1** are useful for treating or preventing a diabetic complication in a patient. Accordingly, in one embodiment, the present invention provides a method for treating a diabetic complication in a patient, comprising administering to the patient an effective amount of one or more compounds of **List 1**.

Examples of diabetic complications treatable or preventable using the present methods include, but are not limited to, diabetic cataract, glaucoma, retinopathy, aneuropathy (such as diabetic neuropathy, polyneuropathy, mononeuropathy, autonomic neuropathy, microaluminuria and progressive diabetic neuropathy), nephropathy, gangrene of the feet, immune-complex vasculitis, systemic lupus erythematosus (SLE), atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabeticorumobesity), hyperlipidemia, hypertension, syndrome of insulin resistance, coronary artery disease, a fungal infection, a bacterial infection, and cardiomyopathy.
Methods For Treating or Preventing Impaired Glucose Tolerance
The compounds of List 1 are useful for treating or preventing impaired glucose tolerance in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating impaired glucose tolerance in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Methods For Treating or Preventing Impaired Fasting Glucose
The compounds of List 1 are useful for treating or preventing impaired fasting glucose in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating impaired fasting glucose in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Methods For Treating or Preventing Obesity
The compounds of List 1 are useful for treating or preventing obesity or an obesity-related disorder in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating obesity or an obesity-related disorder in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Methods For Treating or Preventing a Hematological Disorder
The compounds of List 1 are useful for treating or preventing a hematological disorder in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating a hematological disorder in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Examples of hematological disorders treatable or preventable using the present methods include, but are not limited to, an anemia caused by hemolysis, an anemia caused by deficient erythropoiesis, a coagulation disorder, an eosinophilic disorder, hemostasis, a histiocytic syndrome, neutropenia, lymphocytopenia, thrombocytopenia, a thrombic disorder, a platelet disorder or a clotting disorder.

Methods For Treating or Preventing a Neurological Disorder
The compounds of List 1 are useful for treating or preventing a neurological disorder in a patient.
Accordingly, in one embodiment, the present invention provides a method for treating a neurological disorder in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Examples of neurological disorders treatable or preventable using the present methods include, but are not limited to, meningitis, a movement disorder (such as Parkinson's disease or Huntington's disease), delirium, dementia, a demyelinating disorder (such as multiple sclerosis or amyotrophic lateral sclerosis), aphasia, a peripheral nervous system disorder, a seizure disorder, a sleep disorder, a spinal cord disorder or stroke.
Methods For Treating or Preventing a Cardiovascular Disease

The compounds of List 1 are useful for treating or preventing a cardiovascular disease in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating a cardiovascular disease in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Illustrative examples of cardiovascular diseases treatable or preventable using the present methods, include, but are not limited to atherosclerosis, congestive heart failure, cardiac arrhythmia, myocardial infarction, atrial fibrillation, atrial flutter, circulatory shock, left ventricular hypertrophy, ventricular tachycardia, supraventricular tachycardia, coronary artery disease, angina, infective endocarditis, non-infective endocarditis, cardiomyopathy, peripheral artery disease, Reynaud's phenomenon, deep venous thrombosis, aortic stenosis, mitral stenosis, pulmonic stenosis and tricuspid stenosis.

In one embodiment, the cardiovascular disease is atherosclerosis.

In another embodiment, the cardiovascular disease is congestive heart failure.

In another embodiment, the cardiovascular disease is coronary artery disease.

Methods For Treating or Preventing a Respiratory Disorder

The compounds of List 1 are useful for treating or preventing a respiratory disorder in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating a respiratory disorder in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Examples of respiratory disorders treatable or preventable using the present methods include, but are not limited to, asthma, bronchiectasis, chronic obstructive pulmonary disease, an interstitial lung disease, a mediastinal disorder, a pleural disorder, pneumonia or sarcoidosis.

Methods For Treating or Preventing a Gastroenterological Disorder

The compounds of List 1 are useful for treating or preventing a gastroenterological disorder in a patient.
Accordingly, in one embodiment, the present invention provides a method for treating a gastroenterological disorder in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Examples of gastroenterological disorders treatable or preventable using the present methods include, but are not limited to, an anorectal disorder, diarrhea, irritable bowel syndrome, dyspepsia, gastroesophageal reflux disease, diverticulitis, gastritis, peptic ulcer disease, gastroenteritis, inflammatory bowel disease, a malabsorption syndrome or pancreatitis.

Methods ForTreating or Preventing Inflammation

The compounds of List 1 are useful for treating or preventing inflammation in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating inflammation in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Methods For Treating or Preventing Non-Alcoholic Fatty Liver Disease

The compounds of List 1 are useful for treating or preventing non-alcoholic fatty liver disease in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating non-alcoholic fatty liver disease in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Methods For Treating or Preventing Dyslipidemia

The compounds of List 1 are useful for treating or preventing dyslipidemia in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating dyslipidemia in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Methods For Treating or Preventing a Metabolic Disorder

The compounds of List 1 can also be useful for treating a metabolic disorder. Examples of metabolic disorders treatable include, but are not limited to, metabolic syndrome (also known as "Syndrome X"), impaired glucose tolerance, impaired fasting glucose, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, low HDL levels, hypertension, phenylketonuria, post-prandial lipidemia, a glycogen-storage
disease, Gaucher's Disease, Tay-Sachs Disease, Niemann-Pick Disease, ketosis and acidosis.

Accordingly, in one embodiment, the invention provides methods for treating a metabolic disorder in a patient, wherein the method comprises administering to the patient an effective amount of one or more compounds of List 1, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

In one embodiment, the metabolic disorder is hypercholesterolemia.
In another embodiment, the metabolic disorder is hyperlipidemia.
In another embodiment, the metabolic disorder is hypertriglyceridemia.
In still another embodiment, the metabolic disorder is metabolic syndrome.
In a further embodiment, the metabolic disorder is low HDL levels.

Methods For Treating or Preventing Cancer

The compounds of List 1 are useful for treating or preventing cancer in a patient.

Accordingly, in one embodiment, the present invention provides a method for treating cancer in a patient, comprising administering to the patient an effective amount of one or more compounds of List 1.

Non-limiting examples of cancers treatable or preventable using the present methods include the following cancers and metastases thereof: bladder cancer, breast cancer, colorectal cancer, kidney cancer, liver cancer, non-smal cell lung cancer, small cell lung cancer, non-small cell lung cancer, head and neck cancer, esophageal cancer, gall bladder cancer, ovarian cancer, pancreatic cancer, stomach cancer, cervical cancer, thyroid cancer, prostate cancer, skin cancer; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma, and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocyte leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including brain tumors (such as an astrocytoma, a neuroblastoma, a glioma or a schwannoma); and other tumors, including melanoma,
seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma. The compounds of List 1 are useful for treating primary tumors, metastatic tumors and tumors of unknown origin.

In one embodiment, the cancer treated is lung cancer.

In another embodiment, the cancer treated is breast cancer.

In another embodiment, the cancer treated is colorectal cancer.

In still another embodiment, the cancer treated is prostate cancer.

In another embodiment, the cancer treated is a leukemia.

In yet another embodiment, the cancer treated is a lymphoma.

In a further embodiment, the cancer treated is a metastatic tumor.

In one embodiment, the compounds of List 1 can be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

In another embodiment, the compounds of List 1 can be useful in inhibiting tumor angiogenesis and metastasis.

**Combination Therapy**

In one embodiment, the present invention provides methods for treating a Condition in a patient, the method comprising administering to the patient one or more compounds of List 1, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof and at least one additional therapeutic agent that is not a compound of List 1, wherein the amounts administered are together effective to treat or prevent a Condition.

Non-limiting examples of additional therapeutic agents useful in the present methods for treating or preventing a Condition include an anti-obesity agent, an antidiabetic agent, an agent useful for treating metabolic syndrome, an agent useful for treating a cardiovascular disease, an agent useful for treating hypercholesterolemia, an agent useful for treating dyslipidemia, a cholesterol biosynthesis inhibitor, a cholesterol absorption inhibitor, a bile acid sequestrant, a
probucol derivatives, an IBAT inhibitor, a nicotinic acid derivative, a nicotinic acid receptor (NAR) agonist, an ACAT inhibitors, a cholesteryl ester transfer protein (CETP) inhibitor, a low-density lipoprotein (LDL) activator, or any combination of two or more of these additional therapeutic agents.

Further non-limiting examples of additional therapeutic agents useful in the present methods for treating or preventing a condition include hydroxy-substituted azetidinone compounds, substituted β-lactam compounds, α-amylase inhibitors, α-glucoside hydrolase inhibitors, fatty acid oxidation inhibitors, A2 antagonists, c-jun amino-terminal kinase inhibitors, glycogen phosphorylase inhibitors, VPAC2 receptor agonists, glucokinase activators, nicotinic acid receptor antagonists, bile acid sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol O-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, anti-oxidants, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis inhibitors, renin angiotensin inhibitors, microsomal triglyceride transport protein inhibitors, bile acid reabsorption inhibitors, triglyceride synthesis inhibitors, squalene epoxidase inhibitors, low density lipoprotein receptor inducers or activators, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists, 5HT transport inhibitors, NE transporter inhibitors, ghrelin antagonists, H3 antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, leptin agonists/modulators, leptin derivatives, opioid antagonists, orexin receptor antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF agonists/modulators, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists, UCP-1 activators, UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors anti-hypertensive agents, anti-dyslipidemic agents, DP receptor antagonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists,
melanocyte-stimulating hormone receptor analogs, leptons, galanin receptor antagonists, bombesin agonists, thyromimetic agents, dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists, noradrenergic anorectic agents, hormone sensitive lipase antagonists, MSH-receptor analogs, δ-glucosidase inhibitors, apo A1 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), fatty acid transporter protein inhibitors (FATP), an antihypertensive agent.

Examples of antidiabetic agents useful in the present methods for treating or preventing a Condition include, but are not limited to: a sulfonylurea, an insulin sensitizer, a glucosidase inhibitor, an insulin secretagogue, a hepatic glucose output lowering agent, an anti-obesity agent, an antihypertensive agent, a meglitinide, an agent that slows or blocks the breakdown of starches and sugars in vivo, a histamine H3 receptor antagonist, an antihypertensive agent, a sodium glucose uptake transporter 2 (SGLT-2) inhibitor, a peptide that increases insulin production, and insulin or any insulin-containing composition.

In one embodiment, the antidiabetic agent is an insulin sensitizer.

Non-limiting examples of insulin sensitizers include PPAR activators, such as the glitazone and thiazoldinedione class of agents, which include rosiglitazone, rosiglitazone maleate (AVANDIA™ from GlaxoSmithKline), pioglitazone, pioglitazone hydrochloride (ACTOS™, from Takeda) ciglitazone and MCC-555 (Mitsubishi Chemical Co.), troglitazone and englitazone; biguanides, such as phenformin, metformin, metformin hydrochloride (such as GLUCOPHAGE® from Bristol-Myers Squibb), metformin hydrochloride with glyburide (such as GLUCOVANCE™ from Bristol-Myers Squibb) and buformin; DPP-IV inhibitors, such as sitagliptin, saxagliptin (Januvia™, Merck), denagliptin, vildagliptin (Galvus™, Novartis), alogliptin, alogliptin benzoate, ABT-279 and ABT-341 (Abbott), ALS-2-0426 (Alantos), ARI-2243 (Arisaph), BI-A and Bi-B (Boehringer Ingeheim), SYR-322 (Takeda), MP-513 (Mitsubishi), DP-893 (Pfizer), RO-0730699 (Roche) or a combination of sitagliptin/metformin HCl (Janumet™, Merck); PTP-1B inhibitors, such as A-401,674, KR 61639, OC-060062, OC-83839, OC-297962, MC52445, and MC52453; and □-glucokinase activators, such as acarbose, adipose, camiglibose, emiglitate, miglitol,
voglibose, pradimicin-Q, salbostatin, CDK-71 1, MDL-25,637, MDL-73,945, and MOR 14.

In one embodiment, the antidiabetic agent is a DPP-IV inhibitor. In another embodiment, the antidiabetic agent is a sulfonylurea. Non-limiting examples of sulfonylureas include glipizide, tolbutamide, glyburide, glimepiride, chlorpropamide, acetohexamide, glialimide, gliclazide, glibenclamide and tolazamide. In one embodiment, the antidiabetic agent is a SGLT-2 inhibitor. Non-limiting examples of SGLT-2 inhibitors useful in the present methods include dapagliflozin and sergliflozin, AVE2268 (Sanofi-Aventis) and T-1095 (Tanabe Seiyaku). In another embodiment, the antidiabetic agent is a hepatic glucose output lowering agent. Non-limiting examples of hepatic glucose output lowering agents include Glucophage and Glucophage XR. In one embodiment, the antidiabetic agent is an insulin secretagogue. Non-limiting examples of insulin secretagogues include GLP-1, GLP-1 mimetics, exendin, GIP, secretin, glipizide, chlorpropamide, nateglinide, meglitinide, glibenclamide, repaglinide and glimepiride. Non-limiting examples of GLP-1 mimetics useful in the present methods include Byetta-Exanatide, Liraglutide, CJC-1131 (ConjuChem, Exanatide-LAR (Amylin), BIM-51077 (Ipsen/LaRoche), ZP-10 (Zealand Pharmaceuticals), and compounds disclosed in International Publication No. WO 00/07617. In another embodiment, the antidiabetic agent is insulin or an insulin-containing preparation. The term "insulin" as used herein, includes all formuatlions of insulin, including long acting and short acting forms of insulin. Non-limiting examples of orally administrable insulin and insulin containing compositions include AL-401 from Autoimmune, and the compositions disclosed in U.S. Patent Nos. 4,579,730; 4,849,405; 4,963,526; 5,642,868; 5,763,396; 5,824,638; 5,843,866; 6,153,632; 6,191,105; and International Publication No. WO 85/05029, each of which is incorporated herein by reference.
In one embodiment, the antidiabetic agent is an anti-obesity agent, including, but not limited to those set forth below herein.

In another embodiment, the antidiabetic agent is an antihypertensive agent.

Non-limiting examples of antihypertensive agents useful in the present methods for treating diabetes include β-blockers and calcium channel blockers (for example diltiazem, verapamil, nifedipine, amiodipine, and mybefradil), ACE inhibitors (for example captopril, lisinopril, enalapril, spirapril, ceranopril, zefenopril, fosinopril, cilazopril, and quinapril), AT-1 receptor antagonists (for example losartan, irbesartan, and vaisartan), renin inhibitors and endothelin receptor antagonists (for example sitaxsentan).

In another embodiment, the antidiabetic agent is a meglitinide.

Non-limiting examples of meglitinides useful in the present methods for treating diabetes include repaglinide and nateglinide.

In still another embodiment, the antidiabetic agent is an agent that slows or blocks the breakdown of starches and sugars in vivo.

Non-limiting examples of antidiabetic agents that slow or block the breakdown of starches and sugars in vivo and are suitable for use in the compositions and methods of the present invention include alpha-glucosidase inhibitors and certain peptides for increasing insulin production. Alpha-glucosidase inhibitors help the body to lower blood sugar by delaying the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. Non-limiting examples of suitable alpha-glucosidase inhibitors include acarbose; miglitol; camiglibose; certain polyamines as disclosed in WO 01/47528 (incorporated herein by reference); voglibose. Non-limiting examples of suitable peptides for increasing insulin production including amlintide (CAS Reg. No. 122384-88-7 from Amylin; pramlintide, exendin, certain compounds having Glucagon-like peptide-1 (GLP-1) agonistic activity as disclosed in WO 00/07617 (incorporated herein by reference).

Non-limiting examples of orally administrable insulin and insulin containing compositions include AL-401 from Autoimmune, and the compositions disclosed in U.S. Patent Nos. 4,579,730; 4,849,405; 4,963,526; 5,642,868; 5,763,396; 5,824,638; 5,843,866; 6,153,632; 6,191,105; and International Publication No. WO 85/05029, each of which is incorporated herein by reference.
Non-limiting examples of anti-obesity agents useful in the present methods for treating a Condition include an appetite suppressant; a 5-HT2C agonist, such as lorcaserin; an AMP kinase activator; a histamine H₃ receptor antagonist or inverse agonist; a metabolic rate enhancer; or a nutrient absorption inhibitor.

Non-limiting examples of appetite suppressant agents useful in the present methods for treating or preventing a Condition include cannabinoid receptor 1 (CB₁) antagonists or inverse agonists (e.g., rimonabant); Neuropeptide Y (NPY1, NPY2, NPY4 and NPY5) antagonists; metabotropic glutamate subtype 5 receptor (mGlur5) antagonists (e.g., 2-methyl-6-(phenylethynyl)-pyridine and 3[(2-methyl-1,4-thiazol-4-yl)ethynyl]pyridine); melanin-concentrating hormone receptor (MCH1R and MCH2R) antagonists; melanocortin receptor agonists (e.g., Melanotan-II and Mc4r agonists); serotonin uptake inhibitors (e.g., dexfenfluramine and fluoxetine); serotonin (5HT) transport inhibitors (e.g., paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertaline and imipramine); norepinephrine (NE) transporter inhibitors (e.g., desipramine, talsupram and nomifensine); ghrelin antagonists; leptin, adiponectin, or derivatives thereof; opioid antagonists (e.g., nalmefene, 3-methoxy naltrexone, naloxone and nalterxone); orexin antagonists; bombesin receptor subtype 3 (BRS3) agonists; Cholecystokinin-A (CCK-A) agonists; ciliary neurotrophic factor (CNTF) or derivatives thereof (e.g., butabindide and axokine); monoamine reuptake inhibitors (e.g., sibutramine); glucagon-like peptide 1 (GLP-1) agonists; topiramate; and phytopharm compound 57.

Non-limiting examples of metabolic rate enhancers useful in the present methods for treating or preventing a Condition include acetyl-CoA carboxylase-2 (ACC2) inhibitors; beta adrenergic receptor 3 (β3) agonists; diacylglycerol acyltransferase inhibitors (DGAT1 and DGAT2); fatty acid synthase (FAS) inhibitors (e.g., Cerulenin); phosphodiesterase (PDE) inhibitors (e.g., theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram and cilomilast); thyroid hormone β agonists; uncoupling protein activators (UCP-1,2 or 3) (e.g., phytanic acid, 4-[(E)-2-(5,6,7,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid and retinoic acid); acyl-estrogens (e.g., oleoyi-estrone); glucocorticoid antagonists; 11-beta hydroxy steroid dehydrogenase type 1 (11β HSD-1) inhibitors;
melanocortin-3 receptor (Mc3r) agonists; and stearoyl-CoA desaturase-1 (SCD-1) compounds.

Non-limiting examples of nutrient absorption inhibitors useful in the present methods for treating or preventing a Condition include lipase inhibitors (e.g., orlistat, lipstatin, tetrahydrolipstatin, teasaponin and diethyllumbrelliferyl phosphate); fatty acid transporter inhibitors; dicarboxylate transporter inhibitors; glucose transporter inhibitors; and phosphate transporter inhibitors.


Non-limiting examples of cholesterol biosynthesis inhibitors useful in the present methods for treating or preventing a Condition include HMG-CoA reductase inhibitors, squaiene synthase inhibitors, squaiene epoxidase inhibitors, and mixtures thereof.

Non-limiting examples of cholesterol absorption inhibitors useful in the present methods for treating or preventing a Condition include ezetimibe. In one embodiment, the cholesterol absorption inhibitor is ezetimibe.

Non-limiting examples of squaiene synthesis inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, squaiene
synthetase inhibitors, such as squalestatin 1; and squalene epoxidase inhibitors, such as NB-598 ((EJ-N-ethyl-N -fe.e-dimethyl^hepten^-yntyJ-S-p^-bithiophen-S-yi)methoxy|benzene-methanamine hydrochloride).

Non-limiting examples of bile acid sequestrants useful in the present methods for treating or preventing a Condition include, but are not limited to, cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesveiaam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydridrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and poiglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

Probucol derivatives useful in the present methods for treating or preventing a Condition include, but are not limited to, AGI-1067 and others disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250.

IBAT inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, benzothiepines such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-l-benzothiepine 1,1-dioxide structure such as are disclosed in international Publication No. WO 00/38727.

Nicotinic acid derivatives useful in the present methods for treating or preventing a Condition include, but are not limited to, those having a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available. Other examples of nicotinic acid derivatives useful in the present methods include nicotinic acid, niceritroil, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide). An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release tablets) which are available from Kos Pharmaceuticals, Inc. (Cranbury, NJ). Further nicotinic
acid derivatives useful in the present methods for treating or preventing a Condition include, but are not limited to, the compounds disclosed in U.S. Patent Publication Nos. 2006/0264489 and 2007/0066630, and U.S. Patent Application No 11/771 538, each of which is incorporated herein by reference.

LDL-receptor activators useful in the present methods for treating or preventing a Condition include, but are not limited to, include HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity. See M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12.

Natural water-soluble fibers useful in the present methods for treating or preventing a Condition include, but are not limited to, psyllium, guar, oat and pectin.

Fatty acid esters of plant stands useful in the present methods for treating or preventing a Condition include, but are not limited to, the sitostanol ester used in BENECOL® margarine.

Non-limiting examples of hydroxy-substituted azetidinone compounds and substituted β-lactam compounds useful in the present methods for treating or preventing a Condition include those disclosed in U.S. Patents Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787, 5,756,470, U.S. Patent Application Nos. 2002/0137690 and 2002/0137689 and PCT Patent Application No. WO 2002/06464, each of which is incorporated herein by reference in their entirety. A preferred azetidinone compound is ezetimibe (for example, ZETIA® which is available from Schering-Plough Corporation).

Non-limiting examples of HMG-CoA reductase inhibitors useful in the present methods for treating or preventing a Condition include lovastatin (for example MEVACOR® which is available from Merck & Co.), simvastatin (for example ZOCOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), atorvastatin, fluvastatin, cerivastatin, Ci-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin calcium (CRESTOR® from AstraZeneca Pharmaceuticals), pravastatin (such as NK-104 of Negma Kowa of Japan).
A non-limiting example of a HMG-CoA synthetase inhibitor useful in combination with the compounds of List 1 is, for example, L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid).

Non-limiting examples of AcylCoA:Cholesterol O-acyltransferase ("ACAT") inhibitors useful in the present methods for treating or preventing a Condition include avasimibe (P,4,6-tris(1-methylethyl)phenylacetyl)sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, icemibide (DuP-128) and CL-277082 (4-(2,4-difluorophenyl)-4-[4-(2,2-dimethylpropyl)phenyl]methyl)-4-heptylurea), and the compounds described in P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul; 60(1); 55-93, which is incorporated by reference herein.

Non-limiting examples of cholesteryl ester transfer protein ("CETP") inhibitors useful in the present methods for treating or preventing a Condition include those disclosed in PCT Patent Application No. WO 00/38721, U.S. Patent Nos. 6,147,090, 6,958,346, 6,924,313, 6,906,082, 6,861,561, 6,803,388, 6,794,396, 6,787,570, 6,753,346, 6,723,752, 6,723,753, 6,710,089, 6,699,898, 6,696,472, 6,696,435, 6,683,113, 5,519,001, 5,512,548, 6,410,022, 6,426,365, 6,448,295, 6,387,929, 6,683,099, 6,677,382, 6,677,380, 6,677,379, 6,677,375, 6,677,353, 6,677,341, 6,605,624, 6,586,433, 6,451,830, 6,451,823, 6,462,092, 6,458,849, 6,458,803, 6,455,519, 6,583,183, 6,562,976, 6,555,113, 6,544,974, 6,521,607, 6,489,366, 6,482,862, 6,479,552, 6,476,075, 6,476,057, and 6,897,317, each of which are incorporated herein by reference; compounds described in Yan Xia et al., "Substituted 1,3,5-Triazines As Cholesterol Ester Transfer Protein Inhibitors", Bioorganic & Medicinal Chemistry Letters, vol. 6, No. 7, 1996, pp. 919-922, herein incorporated by reference; natural products described in S. Coval et al., "Wiedeniol-A and-B, Cholesteryl Ester Transfer Protein Inhibitors From The Marine Sponge Xestospongia Wiedenmayeri", Bioorganic & Medicinal Chemistry Letter, vol. 5, No. 6, pp. 605-610, 1995, herein incorporated by reference; the compounds described in Barrett et al. J. Am. Chem. Soc, 188, 7863-63 (1996), herein incorporated by reference; the compounds described in Pietzonka et al. Bioorg. Med. Chem. Lett, 6, 1951-54 (1996), herein incorporated by reference; the compounds
described in Lee et al. *J. Antibiotics*, 49, 693-96 (1996), herein incorporated by reference; the compounds described by Busch et al. *Lipids*, 25, 216-220, (1990), herein incorporated by reference; the compounds described in Morton and Zilversmit *J. Lipid Res.*, 35, 836-47 (1982), herein incorporated by reference; the compounds described in Connolly et al. *Biochem. Biophys. Res. Comm.*, 223, 42-47 (1996), herein incorporated by reference; the compounds described in Bisgaier et al. *Lipids*, 29, 811-8 (1994), herein incorporated by reference; the compounds described in EP 818448, herein incorporated by reference; the compounds described in JP 10287662, herein incorporated by reference; the compounds described in PCT applications WO 98/35937, WO 9914174, WO 9839299, and WO 9914215, each of which is herein incorporated by reference; the compounds of EP applications EP 796846, EP 801060, 818448, and 818197, each of which is herein incorporated by reference; probucol or derivatives thereof, such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250, herein incorporated by reference; low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity, described in M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12, herein incorporated by reference; 4-carboxyamino-2-substituted-1,2,3,4-tetrahydroquinolines, e.g., those described in WO 00/017164, WO 00/017166, WO 00/140190, WO 00/213797, and WO 2005/033082 (each of which is herein incorporated by reference). These 4-carboxyamino-2-substituted-1,2,3,4-tetrahydroquinolines can be combined with HMG-CoA reductase inhibitors such as atorvastatin (WO 00/213797, WO 2004/056358, WO 2004/056359, and WO2005/0 11634).

A non-limiting example of a fish oil containing Omega 3 fatty acids useful in combination with the compounds of List 1 is 3-PUFA.

Non-limiting examples of natural water soluble fibers useful in the present methods for treating or preventing a Condition include psyllium, guar, oat and pectin.

A non-limiting example of a plant stanol and/or fatty acid ester of plant stanols useful in combination with the compounds of List 1 is the sitostanol ester used in BENECOL® margarine.
A non-limiting example of an anti-oxidant useful in combination with the compounds of List 1 includes probucol.

Non-limiting examples of NE (norepinephrine) transport inhibitors useful in combination with the compounds of List 1 include GW 320659, despiramine, ta!supram, and nomifensine.


Non-limiting examples of ghrelin antagonists useful in combination with the compounds of List 1 include those described in WO 01/87335 and WO 02/08250 (each of the preceding references is herein incorporated by reference). Ghrelin antagonists are also known as GHS (growth hormone secretagogue receptor) antagonists. The pharmaceutical combinations and methods of the present invention therefore comprehend the use GHS antagonists in place of ghrelin antagonists (in combination with the nicotinic acid receptor agonists of the present invention).

Non-limiting examples of MCH1R (melanin-concentrating hormone 1 receptor) antagonists and MCH2R (melanin-concentrating hormone 2 receptor) agonists/antagonists useful in combination with the compounds of List 1 include those described in WO 01/82925, WO 01/87834, WO 02/06245, WO 02/04433, WO 02/51809, and JP 13226269 (each of the preceding references is herein incorporated by reference), and T-226296 (Takeda).

Non-limiting examples of NPY1 antagonists useful in combination with the compounds of List 1 include those described in US 6,001,836, WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528 (each of the preceding references is herein incorporated by reference); and BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, and GI-264879A.

Non-limiting examples of NPY4 agonists useful in combination with the compounds of List 1 include pancreatic peptide (PP) as described in Batterham et al., J. Clin. Endocrinol. Metab. 88:3989-3992 (2003), and other Y4 agonists such as 1229U91 (Raposinho et al., Neuroendocrinology. 71:2-7(2000) (both references are herein incorporated by reference).


Non-limiting examples of mGluR5 (Metabotropic glutamate subtype 5 receptor) antagonists useful in combination with the compounds of List 1 include 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine) (MTEP) and those compounds described in Anderson J. et al., J, Eur J Pharmacol. Jul. 18, 2003;473(1):35-40; Cosford N. et al., Bioorg Med Chem Lett. Feb. 10, 2003;13(3):351-4; and Anderson J. et al., J Pharmacol Exp Ther. December
Non-limiting examples of leptins, leptin derivatives, and leptin agonists/modulators useful in combination with the compounds of List 1 include recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen). Leptin derivatives (e.g., truncated forms of leptin) useful in the present invention include those described in US 5,552,524, US 5,552,523, US 5,552,522, US 5,521,283, WO 96/23513, WO 96/23514, WO 96/23515, WO 96/23516, WO 96/23517, WO 96/23518, WO 96/23519, and WO 96/23520 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of opioid antagonists useful in combination with the compounds of List 1 include nalmefene (Revex™), 3-methoxynaltrexone, naloxone, and naltrexone, as well as opioid antagonists described in WO 00/21509 (herein incorporated by reference).

Non-limiting examples of orexin receptor antagonists useful in combination with the compounds of List 1 include SB-334867-A, as well as those described in WO 01/96302, WO 01/68609, WO 02/51232, and WO 02/51838 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of CNTF (specific ciliary neurotrophic factors) useful in combination with the compounds of List 1 include G1-181771 (Glaxo-SmithKline); SR146131 (Sanofi Aventis); butabindide; PD170.292, PD 149164 (Pfizer).

Non-limiting examples of CNTF derivatives and CNTF agonists/modulators useful in combination with the compounds of List 1 include axokine (Regeneron) and those described in WO 94/09134, WO 98/22128, and WO 99/43813 (each of which is herein incorporated by reference).

Non-limiting examples of 5HT2c agonists useful in combination with the compounds of List 1 include BVT933, DPCA37215, WAY161503, and R-1065, as well as those described in US 3,914,250, WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457 (each of which is herein incorporated by reference).

Non-limiting examples of Mc4r agonists useful in combination with the compounds of List 1 include CHIR86036 (Chiron); ME-10142, and ME-10145
(Melacure), as well as those described in WO 01/991752, WO 01/74844, WO
02/12166, WO 02/11715, and WO 02/12178 (each of which is herein incorporated by
reference).

Non-limiting examples of monoamine reuptake inhibitors useful in combination
with the compounds of List 1 include sibutramine (Meridia™/Reductil™), as well as
those described in WO 01/27068, WO 01/62341, US 4,746,680, US 4,806,570, US
5,436,272, and US 2002/0006964 (each of which is herein incorporated by reference).

Non-limiting examples of serotonin reuptake inhibitors useful in combination
with the compounds of List 1 include dexfenfluramine, fluoxetine, and those described
in US 6,365,633, WO 01/27060, and WO 01/162341 (each of which is herein
incorporated by reference).

Non-limiting examples of a-amylase inhibitors useful in combination with the
compounds of List 1 include tendamistat, trestatin, and AI-3688.

Non-limiting examples of Oligokinase activators useful in combination with
the compounds of List 1 include acarbose, adipose, camiglibose, emiglitate, miglitol,
voglibose, pradimicin-Q, salbostatin, CDK-711, MDL-25,637, MDL-73,945, and MOR
14.

Non-limiting examples of fatty acid oxidation inhibitors useful in combination
with the compounds of List 1 include clomoxir and etomoxir.

Non-limiting examples of A2 antagonists useful in combination with the
compounds of List 1 include midaglizole, isaglidole, deriglidole, idazoxan, earoxan,
and fluparoxan.

Non-limiting examples of glycogen phosphorylase inhibitors useful in
combination with the compounds of List 1 include CP-368,296, CP-316,819, and
BAYR3401.

Non-limiting examples of additional analgesic agents useful in the present
methods for treating or preventing pain include acetaminophen, an NSAID, an opiate
or a tricyclic antidepressant.

In one embodiment, the other analgesic agent is acetaminophen or an NSAID.
In another embodiment, the other analgesic agent is an opiate.
In another embodiment, the other analgesic agent is a tricyclic antidepressant.
Non-limiting examples of NSAIDS useful in the present methods for treating or preventing pain include a salicylate, such as aspirin, amoxiprin, benorilate or diflunisal; an arylalkanoic acid, such as diclofenac, etodolac, indometacin, ketorolac, nabumetone, sulindac or tolmetin; a 2-arylpropionic acid (a "profen"), such as ibuprofen, carprofen, fenoprofen, flurbiprofen, loxoprofen, naproxen, tiaprofenic acid or suprofen; a fenamic acid, such as mefenamic acid or meclofenamic acid; a pyrazolidine derivative, such as phenylbutazone, azapropazone, metamizole or oxyphenbutazone; a coxib, such as celecoxib, etoricoxib, iumiracoxib or parecoxib; an oxicam, such as piroxicam, lornoxicam, meloxicam or tenoxicam; or a sulfonanilide, such as nimesulide.

Non-limiting examples of opiates useful in the present methods for treating or preventing pain include an anilidopiperidine, a phenylpiperidine, a diphenylpropylamine derivative, a benzomorphane derivative, an oripavine derivative and a morphinane derivative. Additional illustrative examples of opiates include morphine, diamorphine, heroin, buprenorphine, dipipanone, pethidine, dextromoramide, alfentanil, fentanyl, remifentanil, methadone, codeine, dihydrocodeine, tramadol, pentazocine, vicodin, oxycodone, hydrocodone, percocet, percodan, norco, dilaudid, darvocet or lorcet.

Non-limiting examples of tricyclic antidepressants useful in the present methods for treating or preventing pain include amitryptiline, carbamazepine, gabapentin or pregabailin.

The compounds of List 1 may also be useful in combination (administered together or sequentially in any order) with one or more separate anticancer treatments such as radiation therapy, and/or at least one anticancer agent different from the compound of List 1. The compounds of the present invention can be present in the same dosage unit as the anticancer agent or in separate dosage units.

Another aspect of the present invention is a method of treating one or more diseases associated with a cyclin dependent kinase, comprising administering to a patient in need of such treatment an amount of a first compound, which is a compound of List 1, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof; and an amount of at least one second compound, the second compound being an anticancer agent different from the compound of List 1, wherein
the amounts of the first compound and the second compound result in a therapeutic effect.

Non-limiting examples of additional anticancer agents suitable for use in the present methods for treating cancer include cytostatic agents, cytotoxic agents (such as for example, but not limited to, DNA interactive agents (such as cisplatin or doxorubicin)); taxanes (e.g. taxotere, taxol); topoisomerase II inhibitors (such as etoposide or teniposide); topoisomerase I inhibitors (such as irinotecan (or CPT-11), camptostar, or topotecan); tubulin interacting agents (such as paclitaxel, docetaxel or the epothiiones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil); anti-metabolites (such as methotrexate); alkylating agents (such as temozolomide (TEMODAR™ from Schering-Plough Corporation, Kenilworth, New Jersey), cyclophosphamide); Farnesyl protein transferase inhibitors (such as, SARASAR™(4-[2-[4-[(1R)-3,0-dibromo-8-chloro-6,1-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-1-yl]-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide, or SCH 66336 from Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra® or R115777 from Janssen Pharmaceuticals), L778.123 (a farnesyl protein transferase inhibitor from Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (a farnesyl protein transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); signal transduction inhibitors (such as, Iressa (from Astra Zeneca Pharmaceuticals, England), Tarceva (EGFR kinase inhibitors), antibodies to EGFR (e.g., C225), GLEEVEC™ (C-abl kinase inhibitor from Novartis Pharmaceuticals, East Hanover, New Jersey); interferons such as, for example, intron (from Schering-Plough Corporation), Peg-Intron (from Schering-Plough Corporation); hormonal therapy combinations; aromatase combinations; ara-C, adriamycin, Cytoxan, and gemicitabine.

Other useful additional anticancer agents include but are not limited to Uracil mustard, Chloromethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, ara-C, adriamycin, Cytoxan, Clofarabine (Clolar® from Genzyme Oncology, Cambridge, Massachusetts), cladribine (Leustat® from Janssen-Cilag Ltd.), aphidicolon, rituxan (from Genentech/Biogen Iidee), sunitinib (Sutent® from Pfizer), dasatinib (or BMS-354825 from Bristol-Myers Squibb), tezacitabine (from Aventis Pharma), SmI1, fludarabine (from Trigan Oncology Associates), pentostatin (from BC
Cancer Agency), triapine (from Vion Pharmaceuticals), didox (from Bioseeker Group), trimidox (from ALS Therapy Development Foundation), amidox, 3-AP (3-aminoypyridine-2-carboxaldehyde thiosemicarbazone), MDL-101,731 ((E)-2'-deoxy-2'-(fluoromethylenec)ytidine) and gemcitabine.

Other useful additional anticancer agents include but are not limited to Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fluorouracil, Pentostatin, Vinblastine, Vincristine, Vindesine, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fluorouracil, Pentostatin, Vinblastine, Vincristine, Vindesine, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fluorouracil, Pentostatin, Vinblastine, Vincristine, Vindesine, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fluorouracil, Pentostatin, Vinblastine, Vincristine, Vindesine, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fluorouracil, Pentostatin, Vinblastine, Vincristine, Vindesine, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fluorouracil, Pentostatin, Vinblastine, Vincristine, Vindesine.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the additional anticancer agent(s) or treatment within its dosage range. For example, the CDC2 inhibitor olomucine has been found to act synergistically with known cytotoxic agents in inducing apoptosis (J. Cell Sci., 1995) 108, 2897. The compounds of List 1 may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; the compounds of List 1 may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the
sequence of administration with anticancer agents. *Cancer Research*, (1997) 57, 3375. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

Accordingly, in an aspect, this invention includes methods for treating cancer in a patient, comprising administering to the patient an amount of at least one compound of **List 1**, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and one or more other anticancer treatment modalities, wherein the amounts of the compounds of **List 1**/other treatment modality result in the desired therapeutic effect. In one embodiment, the at least one compound of **List 1** and the one or more other treatment modalities act synergistically. In one embodiment, the at least one compound of **List 1** and the one or more other treatment modalities act additively.

In one embodiment, the other treatment modality is surgery.
In another embodiment, the other treatment modality is radiation therapy.
In another embodiment, the other treatment modality is biological therapy, such as hormonal therapy or anticancer vaccine therapy.

In one embodiment, the present combination therapies for treating or preventing diabetes comprise administering a compound of **List 1**, an antidiabetic agent and/or an antiobesity agent.

In another embodiment, the present combination therapies for treating or preventing diabetes comprise administering a compound of **List 1** and an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing diabetes comprise administering a compound of **List 1** and an anti-obesity agent.

In one embodiment, the present combination therapies for treating or preventing obesity comprise administering a compound of **List 1**, an antidiabetic agent and/or an antiobesity agent.

In another embodiment, the present combination therapies for treating or preventing obesity comprise administering a compound of **List 1** and an antidiabetic agent.
In another embodiment, the present combination therapies for treating or preventing obesity comprise administering a compound of List 1 and an anti-obesity agent.

In one embodiment, the additional therapeutic agent is a cholesterol biosynthesis inhibitor. In another embodiment, the cholesterol biosynthesis inhibitor is a squalene synthetase inhibitor. In another embodiment, the cholesterol biosynthesis inhibitor is a squalene epoxidase inhibitor. In still another embodiment, the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor. In another embodiment, the HMG-CoA reductase inhibitor is a statin. In yet another embodiment, the statin is lovastatin, pravastatin, simvastatin or atorvastatin.

In one embodiment, the additional therapeutic agent comprises a cholesterol absorption inhibitor and a cholesterol biosynthesis inhibitor. In another embodiment, the additional therapeutic agent comprises a cholesterol absorption inhibitor and a statin. In another embodiment, the additional therapeutic agent comprises ezetimibe and a statin. In another embodiment, the additional therapeutic agent comprises ezetimibe and simvastatin.

In one embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering a compound of List 1, an antidiabetic agent and/or an anti-obesity agent.

In another embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering a compound of List 1 and an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering a compound of List 1 and an anti-obesity agent.

In one embodiment, the present combination therapies for treating or preventing a cardiovascular disease comprise administering one or more compounds of List 1, and an additional agent useful for treating or preventing a cardiovascular disease.

In addition, the compounds of List 1 can also be used in combination with another therapeutic agent with comprises two or more active ingredients. A non-
limiting example of such an additional therapeutic agents is VYTORIN® (a combination of simvastatin and ezetimibe).

When administering a combination therapy to a patient in need of such administration, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts).

In one embodiment, the one or more compounds of List 1 are administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or vice versa.

In another embodiment, the one or more compounds of List 1 and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating or preventing a Condition.

In another embodiment, the one or more compounds of List 1 and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating or preventing a Condition.

In still another embodiment, the one or more compounds of List 1 and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating or preventing a Condition.

In one embodiment, the one or more compounds of List 1 and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration.

The one or more compounds of List 1 and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration
of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

In one embodiment, the administration of one or more compounds of List 1 and the additional therapeutic agent(s) may inhibit the resistance of a Condition to these agents.

In one embodiment, when the patient is treated for diabetes or a diabetic complication, the additional therapeutic agent is an antidiabetic agent which is not a compound of List 1. In another embodiment, the additional therapeutic agent is an agent useful for reducing any potential side effect of a compound of List 1. Such potential side effects include, but are not limited to, nausea, vomiting, headache, fever, lethargy, muscle aches, diarrhea, general pain, and pain at an injection site.

In one embodiment, the additional therapeutic agent is used at its known therapeutically effective dose. In another embodiment, the additional therapeutic agent is used at its normally prescribed dosage. In another embodiment, the additional therapeutic agent is used at less than its normally prescribed dosage or its known therapeutically effective dose.

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of a Condition can be determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the compound(s) of List 1 and the other agent(s) for treating or preventing diseases or conditions listed above can be administered simultaneously or sequentially. This particularly useful when the components of the combination are given on different dosing schedules, e.g., one component is administered once daily and another every six hours, or when the preferred pharmaceutical compositions are different, e.g. one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the one or more compounds of List 1 and the additional therapeutic agent(s) can, when administered as combination therapy, range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one
embodiment, the dosage is from about 0.2 to about 100 mg/day, administered in a
single dose or in 2-4 divided doses. In another embodiment, the dosage is from about
1 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In
another embodiment, the dosage is from about 1 to about 200 mg/day, administered
in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is
from about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided
doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day,
administered in a single dose or in 2-4 divided doses. In a further embodiment, the
dosage is from about 1 to about 20 mg/day, administered in a single dose or in 2-4
divided doses.

Compositions and Administration

For preparing pharmaceutical compositions from the compounds described by
this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.
Solid form preparations include powders, tablets, dispersible granules, capsules,
cachets and suppositories. The powders and tablets may be comprised of from about
5 to about 95 percent active ingredient. Suitable solid carriers are known in the art,
e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets,
powders, cachets and capsules can be used as solid dosage forms suitable for oral
administration. Examples of pharmaceutically acceptable carriers and methods of
manufacture for various compositions may be found in A. Gennaro (ed.), Remington's

Liquid form preparations include solutions, suspensions and emulsions. As an
example may be mentioned water or water-propylene glycol solutions for parenteral
injection or addition of sweeteners and opacifiers for oral solutions, suspensions and
emulsions. Liquid form preparations may also include solutions for intranasal
administration.

Aerosol preparations suitable for inhalation may include solutions and solids in
powder form, which may be in combination with a pharmaceutically acceptable carrier,
such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted,
shortly before use, to liquid form preparations for either oral or parenteral
administration. Such liquid forms include solutions, suspensions and emulsions.
The compounds of List 1 may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

In one embodiment, a compound of List 1 is administered orally. In another embodiment, a compound of List 1 is administered intravenously. In still another embodiment, a compound of List 1 is administered intranasally. In one embodiment, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 150 mg, preferably from about 1 mg to about 75 mg, more preferably from about 1 mg to about 50 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of List 1 and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 75 mg/day, in two to four divided doses.

When the invention comprises a combination of one or more compounds of List 1 and an additional therapeutic agent, the two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising one or more compounds of List 1 and an additional therapeutic agent in a
pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the additional therapeutic agent can be determined from published material, and may range from about 1 to about 1000 mg per dose. In one embodiment, when used in combination, the dosage levels of the individual components are lower than the recommended individual dosages because of the advantageous effect of the combination.

In one embodiment, the components of a combination therapy regime are to be administered simultaneously, they can be administered in a single composition with a pharmaceutically acceptable carrier.

In another embodiment, when the components of a combination therapy regime are to be administered separately or sequentially, they can be administered in separate compositions, each containing a pharmaceutically acceptable carrier.

The components of the combination therapy can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc.

**Kits**

In one aspect, the present invention provides a kit comprising an effective amount of one or more compounds of **List 1**, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and a pharmaceutically acceptable carrier.

In another aspect the present invention provides a kit comprising an amount of one or more compounds of **List 1**, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and an amount of at least one additional therapeutic agent listed above, wherein the combined amounts are effective for treating or preventing a Condition in a patient.

When the components of a combination therapy regimen are to be administered in more than one composition, they can be provided in a kit comprising a single package containing one or more containers, wherein one container contains one or more compounds of **List 1** in a pharmaceutically acceptable carrier, and a second, separate container comprises an additional therapeutic agent in a
pharmaceutically acceptable carrier, with the active components of each composition being present in amounts such that the combination is therapeutically effective.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.
What is claimed is:

1. A compound selected from the compounds of the following formulas:
2. A composition comprising an effective amount of one or more compounds of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

3. The composition of claim 2, further comprising one or more additional therapeutic agents selected from an anti-obesity agent, an antidiabetic agent, an agent useful for treating metabolic syndrome, an agent useful for treating a cardiovascular disease, an agent useful for treating hypercholesterolemia, an agent useful for treating dyslipidemia, a cholesterol biosynthesis inhibitor, a cholesterol
absorption inhibitor, a bile acid sequestrant, a probucol derivatives, an IBAT inhibitor, a nicotinic acid derivative, a nicotinic acid receptor (NAR) agonist, an ACAT inhibitors, a cholesteryl ester transfer protein (CETP) inhibitor and a low-density lipoprotein (LDL) activator.

4. The composition of claim 3, wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

5. The composition of claim 4, wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

6. The composition of claim 5, wherein the HMG-CoA reductase inhibitor is simvastatin.

7. The composition of claim 3, further comprising a cholesteryl ester transfer protein inhibitor.

8. The composition of claim 3, further comprising Vytorin®, ezetimibe, aspirin, ibuprofen or acetaminophen or a combination thereof.

9. A method for treating a metabolic disorder, dyslipidemia, a cardiovascular disease, a neurological disorder, a hematological disease, cancer, inflammation, a respiratory disease, a gastroenterological disease, diabetes, a diabetic complication, obesity, an obesity-related disorder or non-alcoholic fatty liver disease in a patient, wherein the method comprises administering to the patient an effective amount of one or more compounds of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

10. The method of claim 9, wherein the treating is for diabetes.

11. The method of claim 10, wherein the diabetes is type 2 diabetes.

12. The method of claim 9, wherein the treating is for obesity.

13. The method of claim 9, wherein the treating is for dyslipidemia.

14. The method of claim 9, wherein the treating is for hypercholesterolemia.

15. The method of claim 9, further comprising administering to the patient an effective amount of one or more additional therapeutic agents selected from an anti-obesity agent, an antidiabetic agent, an agent useful for treating metabolic syndrome, an agent useful for treating a cardiovascular disease, an agent useful for treating hypercholesterolemia, an agent useful for treating dyslipidemia, a cholesterol
biosynthesis inhibitor, a cholesterol absorption inhibitor, a bile acid sequestrant, a probucol derivative, an IBAT inhibitor, a nicotinic acid derivative, a nicotinic acid receptor (NAR) agonist, an ACAT inhibitors, a cholesteryl ester transfer protein (CETP) inhibitor and a low-density lipoprotein (LDL) activator.
## A. CLASSIFICATION OF SUBJECT MATTER

**USPC**: 514/235.2  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
USPC: 514/235.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Patentscope, SureChem

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Y</strong></td>
<td>US 5,942,522 A (ALFONSO et al.) 24 August 1999 (24.08.1999) col 2, ln 26 to col 4, ln 58</td>
<td>1-15</td>
</tr>
<tr>
<td><strong>Y</strong></td>
<td>US 4,442,106 A (TRIJZELLAAR et al.) 10 April 1984 (10.04.1984) col 1, ln 26-68; col 16, ln 52-55; col 16, ln 66 to col 17, ln 4; claim 20</td>
<td>1-15</td>
</tr>
<tr>
<td><strong>Y</strong></td>
<td>US 2006/0270722 A1 (THORNBERRY et al.) 30 November 2006 (30.11.2006) para [0017], [0020], [0100]-[0101], [0114]-[0115], [0118], [0120]</td>
<td>7-8, 10-12</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

- **A**: document defining the general state of the art which is not considered to be of particular relevance
- **E**: earlier application or patent but published on or after the international filing date
- **L**: document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O**: document referring to an oral disclosure, use, exhibition or other means
- **P**: document published prior to the international filing date but later than the priority date claimed
- **T**: later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X**: document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y**: document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **Z**: document member of the same patent family

Date of the actual completion of the international search: 03 January 2011 (03.01.2011)

Date of mailing of the international search report: 11 JAN 2011

Name and mailing address of the ISA/US  
Lee W. Young  
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-927-3281  
Authorized officer: Lee W. Young

Form PCT/ISA/210 (second sheet) (July 2009)