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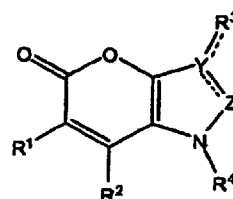
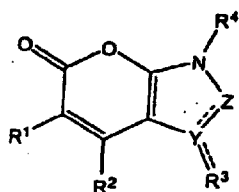
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(54) Title: BICYCLIC PYRANONE DERIVATIVES AS NICOTINIC ACID RECEPTOR AGONISTS



(57) Abstract: The present invention relates to Bicyclic Pyranone Derivatives, their compositions and uses 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. Formula (I). Y is -C- when an optional and additional bond is present and Y is -CH- when an optional and additional bond is not present; Z is -O-, -NH- or -N(alkyl)- when the optional and additional bond between Y and Z is absent, and Z is -N- when the optional and additional bond between Y and Z is present; R¹ is H1 halo or -CN; R² is alkyl, alkenyl or -(alkylene)cydoalkyl; t is 0 or 1; R³ is O when the optional and additional bond between Y and R³ is present, and R³ is alkyl, haloalkyl, -C(O)OR⁵, -alkylene-O-alkyl or -O-alkyl when the optional and additional bond between Y and R³ is absent; R⁴ is H, alkyl or aryl, wherein an aryl group can be unsubstituted or optionally substituted.

BICYCLIC PYRANONE DERIVATIVES AS NICOTINIC ACID RECEPTOR AGONISTS

FIELD OF THE INVENTION

The present invention relates to Bicyclic Pyranone Derivatives, compositions
5 comprising a Bicyclic Pyranone Derivative and methods for using the Bicyclic
Pyranone Derivatives 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 complicaton, obesity, an obesity-related disorder or non-alcoholic fatty liver
10 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
15 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
20 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.

25 The use of heterocyclic compounds as nicotinic acid receptor agonists is known
in the art and such compounds are disclosed, for example, in M. Ridi, *Gazzetta Chim.
Ital.* (1950) vol. 80, p. 121 and M. Ridi, *Gazzetta Chim. Ital.* (1952) vol. 82, p. 23,
which disclose syntheses of barbituric acid derivatives useful as nicotinic acid
receptor (NAR) agonists. FR 2563223 discloses nucleoside analogs. T. Paterson et
30 al., *J. Chem. Soc., Perkins Trans. I* (1972), vol. 8, pp. 1041-1050 discloses the
synthesis of 8-substituted pyrido[2,3-d]pyrimidines. S. Rao, *Indian J. Chem.* (1974),

12(10), pp. 1028-1030 discloses the synthesis of pyrano[2,3-d]pyrimidines. M. Skof, *Heterocycles*, (1999), 51(5), pp. 1051-1058 discloses one step transformations of (S)-1-benzoyl-3-[(E)-dimethylaminomethylidene]-5-methoxycarbonyl-pyrrolidin-2-one into quinoliziny- and 2H-2-pyranonyl-substituted alanine derivatives. R. Toplak, *J. Heterocyclic Chem.* (1999), 36(1), pp. 225-235 discloses the synthesis of pyran-2-ones.

International Publication No. WO 04/110368 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.

International Publication No. WO 04/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic 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.

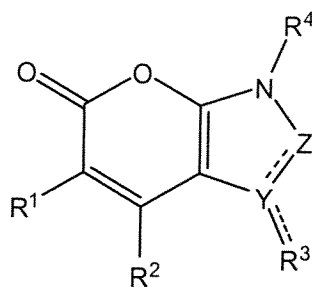
International Publication No. WO 05/077950 describes xanthine derivatives which are agonists of the nicotinic acid receptor HM74A.

Despite the medicinal chemistry efforts directed to discovering NAR receptor modulators, there 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 of Formula (I):

3



(I)

and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein each dotted line represents an optional and additional bond, and wherein:

5 Y is -C- when an optional and additional bond is present and Y is -CH- when an optional and additional bond is not present;

Z is -O- , -NH- or -N(alkyl)- when the optional and additional bond between Y and Z is absent, and Z is -N- when the optional and additional bond between Y and Z is present;

10 R^1 is H, halo or -CN ;

R^2 is alkyl, alkenyl or $\text{-(alkylene)}_t\text{-cycloalkyl}$;

R^3 is O when the optional and additional bond between Y and R^3 is present, and R^3 is alkyl, haloalkyl, -C(O)OR^5 , -alkylene-O-alkyl or -O-alkyl when the optional and additional bond between Y and R^3 is absent;

15 R^4 is H, alkyl or aryl, wherein an aryl group can be unsubstituted or optionally substituted with up to 4 groups, which can be the same or different, and are selected from alkyl, halo, haloalkyl, -CN , -NO_2 , -C(O)OR^5 , $\text{-C(O)N(R}^5)_2$ or $\text{-N(R}^5)_2$;

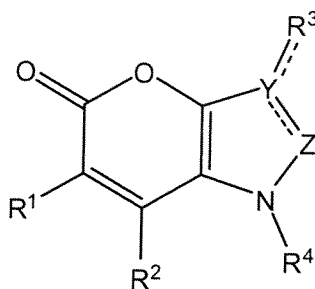
each occurrence of R^5 is independently H, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; and

20 t is 0 or 1,

such that only one optional and additional bond may be present.

In another aspect, the present invention provides Compounds of Formula (II):

4



(II)

and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein each dotted line represents an optional and additional bond, and wherein:

5 Y is -C- when an optional and additional bond is present and Y is -CH- when an optional and additional bond is not present;

Z is -O- , -NH- or -N(alkyl)- when the optional and additional bond between Y and Z is absent, and Z is -N- when the optional and additional bond between Y and Z is present;

10 R^1 is H, halo or -CN ;

R^2 is alkyl, alkenyl or $\text{-(alkylene)}_t\text{-cycloalkyl}$;

R^3 is O when the optional and additional bond between Y and R^3 is present, and R^3 is alkyl, haloalkyl, -C(O)OR^5 , -alkylene-O-alkyl or -O-alkyl when the optional and additional bond between Y and R^3 is absent;

15 R^4 is H, alkyl or aryl, wherein an aryl group can be unsubstituted or optionally substituted with up to 4 groups, which can be the same or different, and are selected from alkyl, halo, haloalkyl, -CN , -NO_2 , -C(O)OR^5 , $\text{-C(O)N(R}^5)_2$ or $\text{-N(R}^5)_2$;

each occurrence of R^5 is independently H, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; and

20 t is 0 or 1,

such that only one optional and additional bond may be present.

The Compounds of Formulas (I) and (II) (the "Bicyclic Pyranone Derivatives") are useful for treating or preventing a metabolic disorder, dyslipidemia, a
25 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 Bicyclic Pyranone Derivatives.

5 In a further aspect, the invention provides compositions comprising an effective amount of one or more Bicyclic Pyranone Derivatives and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

10 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.

20 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.

25 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.

30 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

5 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;

10 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 Bicyclic
15 Pyranone Derivative 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 Bicyclic Pyranone Derivative is present, or in the combination therapies of the present invention, an effective amount can refer to each individual agent or to
20 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 "alkyl," 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
25 atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In another embodiment, an alkyl group contains from about 1 to about 6 carbon atoms. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or
30 more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, -CN, -OH, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –

C(O)O-alkyl. In one embodiment, an alkyl group is unsubstituted. In another embodiment, an alkyl group is linear. In another embodiment, an alkyl 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 "alkynyl," 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 alkynyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butyne and 3-methylbutynyl. An alkynyl 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 alkynyl 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 alkylene groups include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH(CH₃)CH₂CH₂- and -CH₂CH(CH₃)CH₂-. In one embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear.

"Aryl" means an aromatic monocyclic or polycyclic 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.

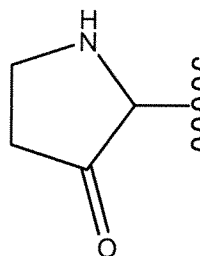
The term "cycloalkyl," as used herein, refers to a non-aromatic mono- or polycyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 3 to about 7 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 5 to about 7 ring atoms. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of polycyclic 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 polycyclic 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, thienyl, pyrimidinyl, pyridonyl (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-

thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinoliny, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, 5 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.

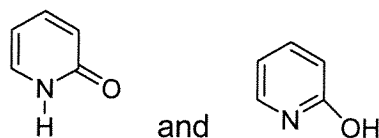
10 The term "heterocycloalkyl," as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 10 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S or N and the remainder of the ring atoms are carbon atoms. A heterocycloalkyl group can be joined via a ring carbon or ring nitrogen atom. In one embodiment, a heterocycloalkyl group has from 15 about 5 to about 10 ring atoms. In another embodiment, a heterocycloalkyl 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 heterocycloalkyl ring may exist protected such as, for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part of this invention. A heterocycloalkyl 20 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 heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, oxetanyl, thiomorpholinyl, 25 thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is pyrrolidonyl:

10



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

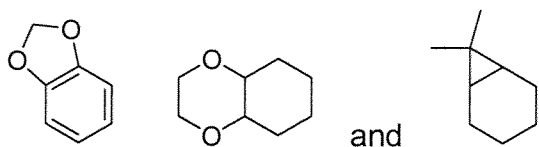
5 It should also be noted that tautomeric forms such as, for example, the moieties:



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)O-alkyl, -C(O)O-aryl, -C(O)O-alkylene-aryl, -S(O)-alkyl, -S(O)₂-alkyl, -S(O)-aryl, -S(O)₂-aryl, -S(O)-heteroaryl, -S(O)₂-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -S-alkylene-aryl, -S-alkylene-heteroaryl, cycloalkyl, heterocycloalkyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH₂, -C(=NH)-NH₂, -C(=NH)-NH(alkyl), Y₁Y₂N-, Y₁Y₂N-alkyl-, Y₁Y₂NC(O)- and Y₁Y₂NSO₂-, wherein Y₁ and Y₂ can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, 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:

11



"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,
5 wherein one or more of the alkyl 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 alkyl group as defined
10 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
15 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
20 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
25 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
30 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 , 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 Bicyclic Pyranone Derivative 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 Bicyclic Pyranone Derivative 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, (C₁–C₈)alkyl, (C₂–C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxy-carbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxy-carbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxy-carbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxy-carbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxy-carbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁–C₂)alkylamino(C₂–C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁–C₂)alkyl, N,N-di (C₁–C₂)alkylcarbamoyl-(C₁–C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂–C₃)alkyl, and the like.

Similarly, if a Bicyclic Pyranone Derivative 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, (C₁–C₆)alkanoyloxymethyl, 1-((C₁–C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁–C₆)alkanoyloxy)ethyl, (C₁–C₆)alkoxy-carbonyloxymethyl, N-(C₁–C₆)alkoxy-carbonylaminomethyl, succinoyl, (C₁–C₆)alkanoyl, α-amino(C₁–C₄)alkyl, α-amino(C₁–C₄)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁–C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a Bicyclic Pyranone Derivative 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 (C₁–C₁₀)alkyl, (C₃–C₇) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl, —C(OH)C(O)OY¹ wherein Y¹ is H, (C₁–C₆)alkyl or benzyl, —C(OY²)Y³ wherein Y² is (C₁–C₄) alkyl and Y³ is (C₁–C₆)alkyl, -C(O)O-(C₁–C₆)alkyl, amino(C₁–C₄)alkyl or mono-N—or di-N,N-(C₁–C₆)alkylaminoalkyl, —C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N—or di-N,N-(C₁–C₆)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 ethanولات, methanولات, and the like. A "hydrate" is a solvate wherein the solvent molecule is H₂O.

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 PharmSciTech*, 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 Bicyclic Pyranone Derivatives can form salts which are also within the scope of this invention. Reference to a Bicyclic Pyranone Derivative 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 Bicyclic Pyranone Derivative 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 Bicyclic Pyranone

Derivative 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, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

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 hydroxyl 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, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonate (for example, methanesulfonate); (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 C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di (C₆₋₂₄)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 Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivative 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 ^2H , ^3H , ^{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 ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) 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., ^2H) 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. In one embodiment, a Compound of Formula (I) or (II) has one or more of its hydrogen atoms replaced with a deuterium atom.

Isotopically labelled Compounds of Formulas (I) and (II) can generally be prepared using synthetic chemical procedures analogous to those disclosed herein for making the Compounds of Formulas (I) and (II), by substituting an appropriate

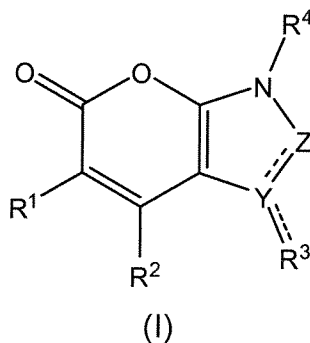
isotopically labelled starting material or reagent for a non-isotopically labelled starting material or reagent.

Polymorphic forms of the Bicyclic Pyranone Derivatives, and of the salts, solvates, hydrates, esters and prodrugs of the Bicyclic Pyranone Derivatives, are intended to be included in the present invention.

The following abbreviations are used herein and have the following meanings: n-Bu is n-butyl, 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, PPh₃ is triphenylphosphine and TFAA is trifluoroacetic acid.

The Compounds of Formula (I)

The present invention provides compounds having the formula (I):



and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein a dotted line represents an optional and additional bond and Y, Z, R¹, R², R³ and R⁴ are defined above for the Compounds of Formula (I).

In one embodiment, R¹ is H.

In one embodiment, R² is alkyl.

In another embodiment, R² is alkenyl.

In another embodiment, R² is -alkylene-cycloalkyl.

In one embodiment, R² is -C₁-C₆ alkyl, -(CH₂)₃CH=CH₂ or -(CH₂)₃-cyclopropyl.

In another embodiment, R² is ethyl, n-butyl, -(CH₂)₃CH=CH₂ or -(CH₂)₃-cyclopropyl.

In another embodiment, R² is ethyl.

In still another embodiment, R^2 is n-butyl.

In another embodiment, R^2 is $-(CH_2)_3CH=CH_2$.

In yet another embodiment, R^2 is $-(CH_2)_3$ -cyclopropyl.

In one embodiment, the optional and additional bond between Y and R^3 is
5 absent.

In another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is haloalkyl.

In still another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is -O-alkyl.

10 In another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is -alkylene-O-alkyl.

In another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is $-C(O)OR^5$.

15 In a further embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is alkyl.

In one embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is methyl, -O-ethyl, $-CH_2-O-CH_3$, $-C(O)OH$, $-C(O)O$ -ethyl, $-CHF_2$ or $-CF_3$.

20 In another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is methyl.

In another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is -O-ethyl.

In still another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is $-CH_2-O-CH_3$.

25 In another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is $-C(O)OH$ or $-C(O)O$ -ethyl.

In yet another embodiment, the optional and additional bond between Y and R^3 is absent and R^3 is $-CHF_2$ or $-CF_3$.

In one embodiment, R^4 is H.

30 In another embodiment, R^4 is alkyl.

In another embodiment, R^4 is aryl.

In one embodiment, R^4 is H, phenyl or 4-nitrophenyl.

In another embodiment, R^4 is phenyl.

In still another embodiment, R^4 is 4-nitrophenyl.

In one embodiment, the optional and additional bond between Y and R^3 is present and R^3 is O.

5 In one embodiment, the optional and additional bond between Y and Z is absent.

In another embodiment, the optional and additional bond between Y and Z is absent and Z is $-NH-$.

10 In one embodiment, the optional and additional bond between Y and Z is present.

In another embodiment, the optional and additional bond between Y and Z is present and Z is $-N-$.

In another embodiment, the optional and additional bond between Y and Z is present and Y is C.

15 In another embodiment, the optional and additional bond between Y and Z is present, Y is C, and Z is $-N-$.

In another embodiment, the optional and additional bond between Y and Z is absent; the optional and additional bond between Y and R^3 is present; R^3 is O; and Z is $-NH-$.

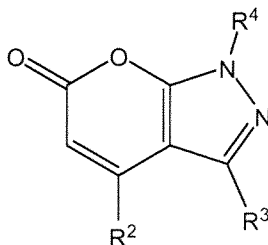
20 In one embodiment, R^1 and R^4 are each H.

In another embodiment, R^1 and R^4 are each H; the optional and additional bond between Y and Z is present; the optional and additional bond between Y and R^3 is absent; and Z is $-N-$.

25 In one embodiment, for the Compounds of Formula (I), Y, Z, R^1 , R^2 , R^3 and R^4 are selected independently of each other.

In another embodiment, the Compounds of Formula (I) are in purified form.

In one embodiment, the Compounds of Formula (I) have the formula (Ia):



(Ia)

wherein R^2 and R^3 are defined above for the Compounds of Formula (I) and R^4 is H or optionally-substituted phenyl.

In one embodiment, for the Compound of Formula (Ia), R^2 is alkyl.

5 In another embodiment, for the Compound of Formula (Ia), R^2 is alkenyl.

In another embodiment, for the Compound of Formula (Ia), R^2 is cycloalkyl.

In one embodiment, for the Compound of Formula (Ia), R^2 is $-C_1-C_6$ alkyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

10 In another embodiment, for the Compound of Formula (Ia), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

In another embodiment, for the Compound of Formula (Ia), R^2 is ethyl.

In still another embodiment, for the Compound of Formula (Ia), R^2 is n-butyl.

In another embodiment, for the Compound of Formula (Ia), R^2 is $-(CH_2)_3CH=CH_2$.

15 In yet another embodiment, for the Compound of Formula (Ia), R^2 is $-(CH_2)_3$ -cyclopropyl.

In one embodiment, for the Compound of Formula (Ia), R^3 is haloalkyl.

In another embodiment, for the Compound of Formula (Ia), R^3 is $-O$ -alkyl.

20 In another embodiment, for the Compound of Formula (Ia), R^3 is $-alkylene-O$ -alkyl.

In still another embodiment, for the Compound of Formula (Ia), R^3 is $-C(O)OR^5$.

In another embodiment, for the Compound of Formula (Ia), R^3 is alkyl.

25 In yet another embodiment, for the Compound of Formula (Ia), R^3 is methyl, $-O$ -ethyl, $-CH_2-O-CH_3$, $-C(O)OH$, $-C(O)O$ -ethyl, $-CHF_2$ or $-CF_3$.

In another embodiment, for the Compound of Formula (Ia), R^3 is methyl.

In a further embodiment, for the Compound of Formula (Ia), R^3 is $-O$ -ethyl.

In another embodiment, for the Compound of Formula (Ia), R^3 is $-CH_2-O-CH_3$.

30 In another embodiment, for the Compound of Formula (Ia), R^3 is $-C(O)OH$ or $-C(O)O$ -ethyl.

In still another embodiment, for the Compound of Formula (Ia), R^3 is $-CHF_2$ or $-CF_3$.

In one embodiment, for the Compound of Formula (Ia), R^4 is H, phenyl or 4-nitrophenyl.

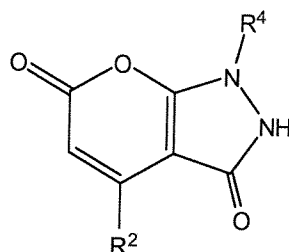
In another embodiment, for the Compound of Formula (Ia), R^4 is H.

In another embodiment, for the Compound of Formula (Ia), R^4 is phenyl.

5 In still another embodiment, for the Compound of Formula (Ia), R^4 is 4-nitrophenyl.

In one embodiment, for the Compound of Formula (Ia), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl and R^3 is methyl, $-O$ -ethyl, $-CH_2-O-CH_3$, $-C(O)OH$, $-C(O)O$ -ethyl, $-CHF_2$ or $-CF_3$.

10 In one embodiment, the Compounds of Formula (I) have the formula (Ib):



(Ib)

wherein R^2 is defined above for the Compounds of Formula (I) and R^4 is H or optionally-substituted phenyl.

15

In one embodiment, for the Compound of Formula (Ib), R^2 is alkyl.

In another embodiment, for the Compound of Formula (Ib), R^2 is alkenyl.

In another embodiment, for the Compound of Formula (Ib), R^2 is cycloalkyl.

20 In one embodiment, for the Compound of Formula (Ib), R^2 is $-C_1-C_6$ alkyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

In another embodiment, for the Compound of Formula (Ib), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

In another embodiment, for the Compound of Formula (Ib), R^2 is ethyl.

In still another embodiment, for the Compound of Formula (Ib), R^2 is n-butyl.

25 In another embodiment, for the Compound of Formula (Ib), R^2 is $-(CH_2)_3CH=CH_2$.

In yet another embodiment, for the Compound of Formula (Ib), R^2 is $-(CH_2)_3$ -cyclopropyl.

In one embodiment, for the Compound of Formula (Ib), R^4 is H, phenyl or 4-nitrophenyl.

In another embodiment, for the Compound of Formula (Ib), R^4 is H.

In another embodiment, for the Compound of Formula (Ib), R^4 is phenyl.

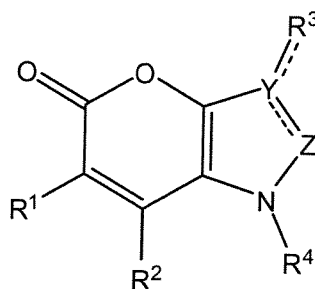
5 In still another embodiment, for the Compound of Formula (Ib), R^4 is 4-nitrophenyl.

In one embodiment, for the Compound of Formula (Ib), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl and R^4 is H, phenyl or 4-nitrophenyl.

10

The Compounds of Formula (II)

The present invention provides compounds having the formula (II):



(II)

15 and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein a dotted line represents an optional and additional bond and Y, Z, R^1 , R^2 , R^3 and R^4 are defined above for the Compounds of Formula (II).

In one embodiment, R^1 is H.

In one embodiment, R^2 is alkyl.

In another embodiment, R^2 is alkenyl.

20 In another embodiment, R^2 is cycloalkyl.

In one embodiment, R^2 is $-C_1$ - C_6 alkyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

In another embodiment, R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

In another embodiment, R^2 is ethyl.

25 In still another embodiment, R^2 is n-butyl.

In another embodiment, R^2 is $-(CH_2)_3CH=CH_2$.

In yet another embodiment, R^2 is $-(CH_2)_3$ -cyclopropyl.

In one embodiment, the optional and additional bond between Y and R³ is absent.

In another embodiment, the optional and additional bond between Y and R³ is absent and R³ is haloalkyl.

5 In still another embodiment, the optional and additional bond between Y and R³ is absent and R³ is -O-alkyl.

In another embodiment, the optional and additional bond between Y and R³ is absent and R³ is -alkylene-O-alkyl.

10 In another embodiment, the optional and additional bond between Y and R³ is absent and R³ is -C(O)OR⁵.

In a further embodiment, the optional and additional bond between Y and R³ is absent and R³ is alkyl.

15 In one embodiment, the optional and additional bond between Y and R³ is absent and R³ is methyl, -O-ethyl, -CH₂-O-CH₃, -C(O)OH, -C(O)O-ethyl, -CHF₂ or -CF₃.

In another embodiment, the optional and additional bond between Y and R³ is absent and R³ is methyl.

In another embodiment, the optional and additional bond between Y and R³ is absent and R³ is -O-ethyl.

20 In still another embodiment, the optional and additional bond between Y and R³ is absent and R³ is -CH₂-O-CH₃.

In another embodiment, the optional and additional bond between Y and R³ is absent and R³ is -C(O)OH or -C(O)O-ethyl.

25 In yet another embodiment, the optional and additional bond between Y and R³ is absent and R³ is -CHF₂ or -CF₃.

In one embodiment, R⁴ is H.

In another embodiment, R⁴ is alkyl.

In another embodiment, R⁴ is aryl.

In one embodiment, R⁴ is H, phenyl or 4-nitrophenyl.

30 In another embodiment, R⁴ is phenyl.

In another embodiment, R⁴ is 4-nitrophenyl.

In one embodiment, the optional and additional bond between Y and R³ is present and R³ is O.

In one embodiment, the optional and additional bond between Y and Z is absent.

5 In another embodiment, the optional and additional bond between Y and Z is absent and Z is –NH–.

In one embodiment, the optional and additional bond between Y and Z is present.

10 In another embodiment, the optional and additional bond between Y and Z is present and Z is –N–.

In another embodiment, the optional and additional bond between Y and Z is absent; the optional and additional bond between Y and R³ is present; R³ is O; and Z is –NH–.

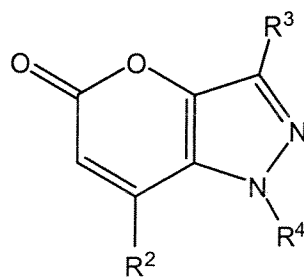
In one embodiment, R¹ and R⁴ are each H.

15 In another embodiment, R¹ and R⁴ are each H; the optional and additional bond between Y and Z is present; the optional and additional bond between Y and R³ is absent; and Z is –N–.

In one embodiment, for the Compounds of Formula (II), Y, Z, R¹, R², R³ and R⁴ are selected independently of each other.

20 In another embodiment, the Compounds of Formula (II) are in purified form.

In one embodiment, the Compounds of Formula (II) have the formula (IIa):



(IIa)

25 wherein R² and R³ are defined above for the Compounds of Formula (II) and R⁴ is H or optionally-substituted phenyl.

In one embodiment, for the Compound of Formula (IIa), R² is alkyl.

In another embodiment, for the Compound of Formula (IIa), R² is alkenyl.

In another embodiment, for the Compound of Formula (IIa), R² is cycloalkyl.

In one embodiment, for the Compound of Formula (IIa), R^2 is $-C_1-C_6$ alkyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

In another embodiment, for the Compound of Formula (IIa), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

5 In another embodiment, for the Compound of Formula (IIa), R^2 is ethyl.

In still another embodiment, for the Compound of Formula (IIa), R^2 is n-butyl.

In another embodiment, for the Compound of Formula (IIa), R^2 is $-(CH_2)_3CH=CH_2$.

10 In yet another embodiment, for the Compound of Formula (IIa), R^2 is $-(CH_2)_3$ -cyclopropyl.

In one embodiment, for the Compound of Formula (IIa), R^3 is haloalkyl.

In another embodiment, for the Compound of Formula (IIa), R^3 is $-O$ -alkyl.

In another embodiment, for the Compound of Formula (IIa), R^3 is $-alkylene-O$ -alkyl.

15 In still another embodiment, for the Compound of Formula (IIa), R^3 is $-C(O)OR^5$.

In another embodiment, for the Compound of Formula (IIa), R^3 is alkyl.

In yet another embodiment, for the Compound of Formula (IIa), R^3 is methyl, $-O$ -ethyl, $-CH_2-O-CH_3$, $-C(O)OH$, $-C(O)O$ -ethyl, $-CHF_2$ or $-CF_3$.

20 In another embodiment, for the Compound of Formula (IIa), R^3 is methyl.

In a further embodiment, for the Compound of Formula (IIa), R^3 is $-O$ -ethyl.

In another embodiment, for the Compound of Formula (IIa), R^3 is $-CH_2-O-CH_3$.

In another embodiment, for the Compound of Formula (IIa), R^3 is $-C(O)OH$ or $-C(O)O$ -ethyl.

25 In still another embodiment, for the Compound of Formula (IIa), R^3 is $-CHF_2$ or $-CF_3$.

In one embodiment, for the Compound of Formula (IIa), R^4 is H, phenyl or 4-nitrophenyl.

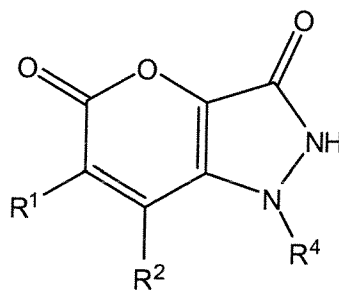
In another embodiment, for the Compound of Formula (IIa), R^4 is H.

30 In another embodiment, for the Compound of Formula (IIa), R^4 is phenyl.

In still another embodiment, for the Compound of Formula (IIa), R^4 is 4-nitrophenyl.

In another embodiment, for the Compound of Formula (IIa), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl; R^3 is methyl, $-O$ -ethyl, $-CH_2-O-CH_3$, $-C(O)OH$, $-C(O)O$ -ethyl, $-CHF_2$ or $-CF_3$; R^4 is H, phenyl or 4-nitrophenyl.

5 In one embodiment, the Compounds of Formula (II) have the formula (IIb):



(IIb)

wherein R^2 is defined above for the Compounds of Formula (II) and R^4 is H or optionally-substituted phenyl.

10 In one embodiment, for the Compound of Formula (IIb), R^2 is alkyl.

In another embodiment, for the Compound of Formula (IIb), R^2 is alkenyl.

In another embodiment, for the Compound of Formula (IIb), R^2 is cycloalkyl.

In one embodiment, for the Compound of Formula (IIb), R^2 is $-C_1-C_6$ alkyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

15 In another embodiment, for the Compound of Formula (IIb), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

In another embodiment, for the Compound of Formula (IIb), R^2 is ethyl.

In still another embodiment, for the Compound of Formula (IIb), R^2 is n-butyl.

20 In another embodiment, for the Compound of Formula (IIb), R^2 is $-(CH_2)_3CH=CH_2$.

In yet another embodiment, for the Compound of Formula (IIb), R^2 is $-(CH_2)_3$ -cyclopropyl.

In one embodiment, for the Compound of Formula (IIb), R^4 is H, phenyl or 4-nitrophenyl.

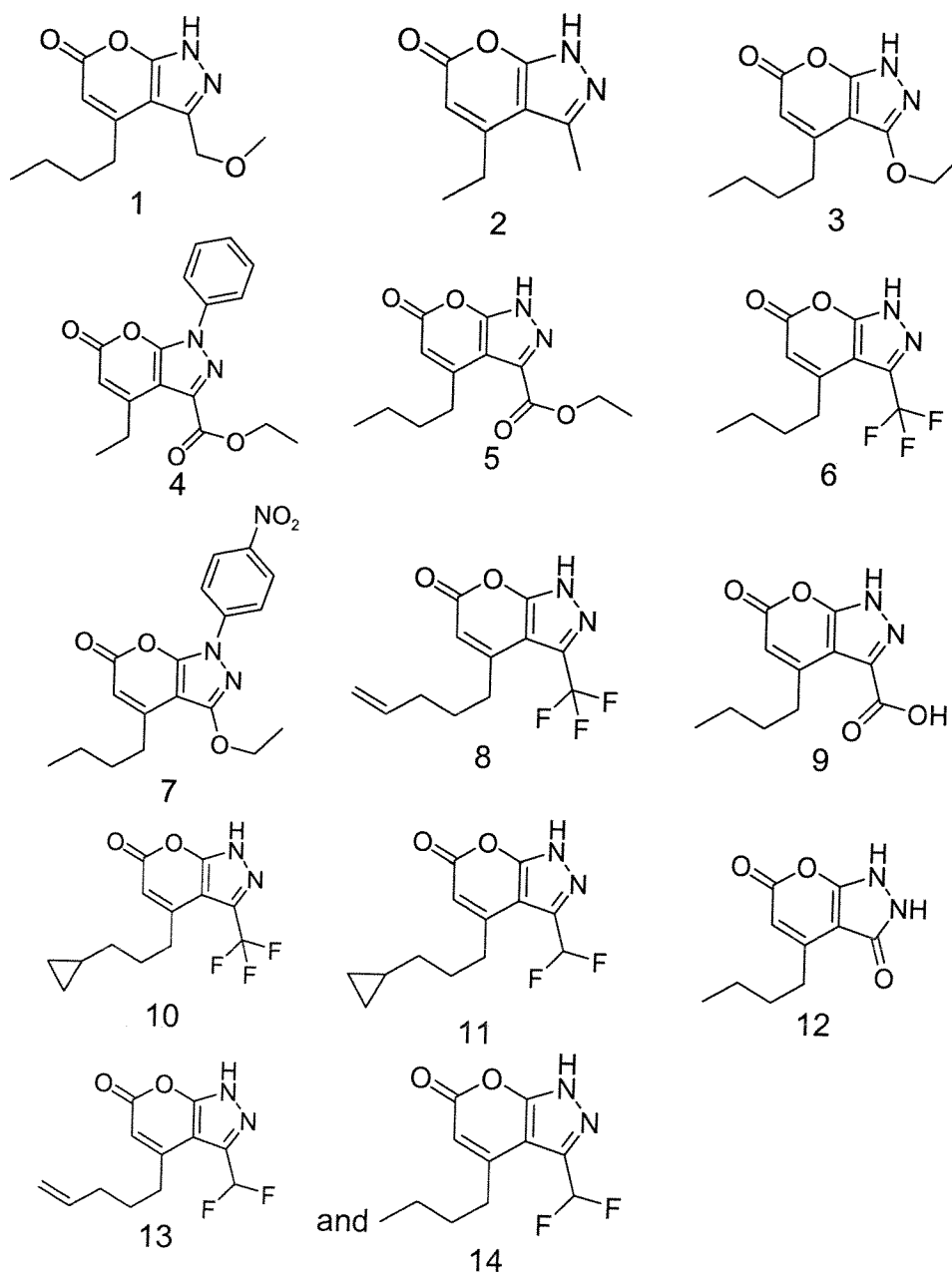
25 In another embodiment, for the Compound of Formula (IIb), R^4 is H.

In another embodiment, for the Compound of Formula (IIb), R^4 is phenyl.

In still another embodiment, for the Compound of Formula (IIb), R^4 is 4-nitrophenyl.

In one embodiment, for the Compound of Formula (IIb), R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl and R^4 is H, phenyl or 4-nitrophenyl.

Non-limiting examples of the Bicyclic Pyranone Derivatives of the present
5 invention include compounds 1-14 as set forth below:



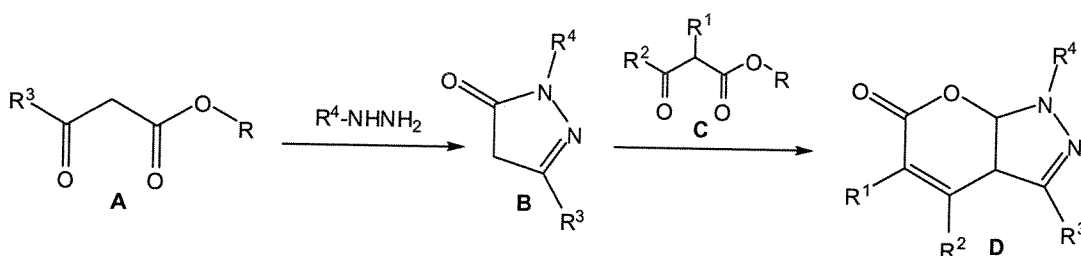
and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof.

Methods for Making the Bicyclic Pyranone Derivatives

Methods useful for making the Bicyclic Pyranone Derivatives are set forth below in Scheme 1 and in the Examples below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

5 Scheme 1 illustrates a method for making the bicyclic pyranone derivatives of the present invention.

Scheme 1



10 wherein R is H or $-\text{C}(\text{O})\text{O-alkyl}$, and R^1 , R^2 , R^3 and R^4 are defined above for the Compounds of Formula (I).

A Compound of Formula **A** can be reacted with a hydrazine Compound of Formula $\text{R}^4\text{-NHNH}_2$ to provide the cyclic intermediates of formula **B**. A Compound of Formula **B** can then be reacted with a Compound of Formula **C** to provide the bicyclic
15 Compounds of Formula **D**, which correspond to the Compounds of Formula (I) wherein the optional bond is present between variables Y and Z.

The starting materials and reagents depicted in Scheme 1 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
20 the art of organic synthesis.

One skilled in the art will recognize that the synthesis of compounds of Formula (I) or (II) 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
25 Compounds of Formula (I) or (II) 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

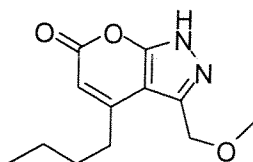
The following examples exemplify illustrative examples of compounds of the present invention and are not to be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

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: Altech platinum C18, 3 μ m, 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 Analtech Silica gel GF plates. Chiral HPLC was performed using a Varian PrepStar system equipped with a Chiralpak OD column (Chiral Technologies).

Example 1

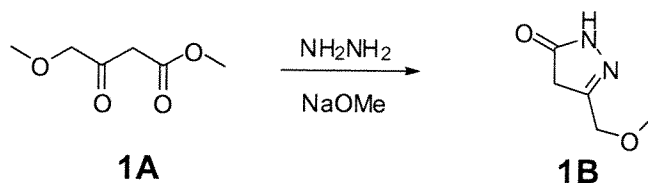
Preparation of Compound 1



1

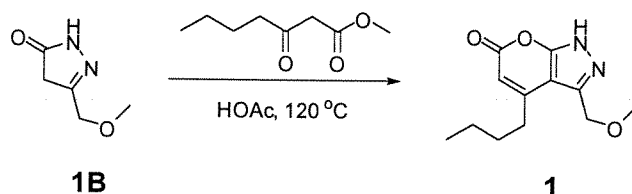
Step A – Synthesis of Compound 1B

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To a solution of ketoester **1A** (2.92 g, 20 mmol) and anhydrous hydrazine (640 mg, 20 mmol) in MeOH (100 mL) was added NaOMe (25% solution in MeOH, 1 drop) and the resulting reaction was allowed to stir at room temperature for 1 hour. The reaction mixture was then concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (0-5% MeOH/CH₂Cl₂) to provide compound **1B**.

Step B – Synthesis of Compound 1



To a solution of compound **1B** (250 mg, 1.95 mmol) in acetic acid (2.5 mL) was added methyl-3-oxo-pentanoate (926 mg, 5.85 mmol) and the resulting reaction was heated to 120 °C and allowed to stir at this temperature for about 15 hours. The reaction mixture was allowed to cool to room temperature, then concentrated *in vacuo*. The resulting residue was diluted with DMF (2 mL) and the resulting solution was purified using Reverse Phase HPLC (Gilson system) with C18 Axia column (Phenomenex, 100 X 21 X 20 mm) eluted with 10-100% MeCN/H₂O containing 0.5% TFA at 25 mL/min to provide compound **1**. MS [M+1]⁺ 237.1.

Example 2

Nicotinic Acid Receptor Assay

The nicotinic acid receptor 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

nicotinic acid receptor (NAR) are harvested enzymatically, washed 1X in phosphate buffered saline (PBS) and resuspended in PBS containing 0.5 mM IBMX at 3×10^6 cells/mL. 10 μ L of cell suspension is added to each well of a 384-well plate, each well containing 10 μ L of test compound. Test compounds are diluted with PBS containing
5 6 μ M 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 μ L/well) as per the manufacturer's protocol. Plates are then incubated from 45 minutes to overnight. Prior to reading, 10 μ L 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
10 concentration using a standard curve run on each plate. Compound EC₅₀ values can then determined from concentration gradients of test compounds.

Uses of the Bicyclic Pyranone Derivatives

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

Methods For Treating or Preventing Pain

20 The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

25 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
30 headache, pain caused by arthritis, 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 Bicyclic Pyranone Derivatives are useful for treating or preventing diabetes
5 in a patient. Accordingly, in one embodiment, the present invention provides a
method for treating diabetes in a patient, comprising administering to the patient an
effective amount of one or more Bicyclic Pyranone Derivatives.

Examples of diabetes treatable or preventable using the Bicyclic Pyranone
Derivatives include, but are not limited to, type I diabetes (insulin-dependent diabetes
10 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
15 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, lipatrophic
diabetes, diabetes induced by β -cell toxins, and diabetes induced by drug therapy
(such as diabetes induced by antipsychotic agents).

20 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 Bicyclic Pyranone Derivatives are useful for treating or preventing a
25 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 Bicyclic
Pyranone Derivatives.

Examples of diabetic complications treatable or preventable using the present
30 methods include, but are not limited to, diabetic cataract, glaucoma, retinopathy,
aneuropathy (such as diabetic neuropathy, polyneuropathy, mononeuropathy,
autonomic neuropathy, microalbuminuria 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 diabetorumobesity), 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 Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

Methods For Treating or Preventing Impaired Fasting Glucose

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

Methods For Treating or Preventing Obesity

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

Methods For Treating or Preventing a Hematological Disorder

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

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 thrombotic disorder, a platelet disorder or a clotting disorder.

Methods For Treating or Preventing a Neurological Disorder

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

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 Bicyclic Pyranone Derivatives 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,
5 comprising administering to the patient an effective amount of one or more Bicyclic Pyranone Derivatives.

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,
10 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.

15 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

20 The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

25 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 mediastal disorder, a pleural disorder, pneumonia or sarcoidosis.

Methods For Treating or Preventing a Gastroenterological Disorder

30 The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

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 For Treating or Preventing Inflammation

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

Methods For Treating or Preventing Non-Alcoholic Fatty Liver Disease

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

Methods For Treating or Preventing Dyslipidemia

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

Methods For Treating or Preventing a Metabolic Disorder

The Bicyclic Pyranone Derivatives can also be useful for treating a metabolic disorder. 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 Bicyclic Pyranone Derivatives, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof.

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.

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 Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives.

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-small 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 promyelocytic 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, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma. The Bicyclic

5 Pyranone Derivatives 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.

10 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 Bicyclic Pyranone Derivatives can be useful in the
15 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 Bicyclic Pyranone Derivatives can be useful in
20 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
25 Bicyclic Pyranone Derivatives, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof and at least one additional therapeutic agent that is not a Bicyclic Pyranone Derivative, wherein the amounts administered are together effective to treat or prevent a Condition.

Non-limiting examples of additional therapeutic agents useful in the present
30 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 transporter 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, β 3 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, α -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 thiazolidinedione 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 Ingelheim), 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 α -glucokinase activators, such as acarbose, adipose, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, salbostatin, CDK-711, MDL-25,637, MDL-73,945, and MOR 14.

5 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, gliamilide, gliclazide, glibenclamide and tolazamide.

10 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).

15 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.

20 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, Liraglutinide, CJC-1131 (ConjuChem, Exanatide-LAR (Amylin), BIM-51077 (Ipsen/LaRoche), ZP-10 (Zealand Pharmaceuticals), and compounds 25 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 formulations of insulin, including long acting and short acting forms of insulin.

30 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 anti-obesity agent, including, but not limited to those set forth below herein.

5 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, amlodipine, and mybefradil), ACE inhibitors (for example captopril, lisinopril, enalapril, spirapril, ceranopril, zefenopril, fosinopril, 10 cilazopril, and quinapril), AT-1 receptor antagonists (for example losartan, irbesartan, and valsartan), 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 15 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 20 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; 25 camiglibose; certain polyamines as disclosed in International Publication No. 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 International Publication No. 30 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
5 treating a Condition include an appetite suppressant; a 5-HT_{2C} 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.

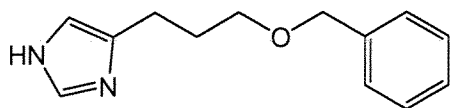
Non-limiting examples of appetite suppressant agents useful in the present
10 methods for treating or preventing a Condition include cannabinoid receptor 1 (CB₁) antagonists or inverse agonists (*e.g.*, rimonabant); Neuropeptide Y (NPY1, NPY2, NPY4 and NPY5) antagonists; metabotropic glutamate subtype 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);
15 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-methoxynaltrexone, naloxone and
20 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.

25 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 (β 3) agonists; diacylglycerol acyltransferase inhibitors (DGAT1 and DGAT2); fatty acid synthase (FAS) inhibitors (*e.g.*, Cerulenin); phosphodiesterase (PDE) inhibitors (*e.g.*, theophylline,
30 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., oleoyl-estrone); glucocorticoid antagonists; 11-beta hydroxy steroid dehydrogenase type 1 (11 β HSD-1) inhibitors; melanocortin-3 receptor (Mc3r) agonists; and stearyl-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 diethylumbelliferyl phosphate); fatty acid transporter inhibitors; dicarboxylate transporter inhibitors; glucose transporter inhibitors; and phosphate transporter inhibitors.

Non-limiting examples of H₃ antagonists/inverse agonists useful in combination with the Bicyclic Pyranone Derivatives include thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, and GT2394 (Gliatech), those described in International Publication No. WO 02/15905 (herein incorporated by reference); O-[3-(1H-imidazol-4-yl)propanol]carbamates described in Kiec-Kononowicz, K. *et al.*, *Pharmazie*, 55:349-55 (2000) (herein incorporated by reference), piperidine-containing histamine H₃-receptor antagonists described in Lazewska, D. *et al.*, *Pharmazie*, 56:927-32 (2001) (herein incorporated by reference), benzophenone derivatives and related compounds described in Sasse, A. *et al.*, *Arch. Pharm.(Weinheim)* 334:45-52 (2001)(herein incorporated by reference), substituted N-phenylcarbamates described in Reidemeister, S. *et al.*, *Pharmazie*, 55:83-6 (2000)(herein incorporated by reference), and proxifan derivatives described in Sasse, A. *et al.*, *J. Med. Chem.* 43:3335-43 (2000)(each of the preceding references is herein incorporated by reference), and the following compound:



Non-limiting examples of cholesterol biosynthesis inhibitors useful in the present methods for treating or preventing a Condition include HMG-CoA reductase inhibitors, squalene synthase inhibitors, squalene 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 squalene synthesis inhibitors useful in the present methods for treating or preventing a Condition include, but are not limited to, squalene synthetase inhibitors, such as squalastatin 1; and squalene epoxidase inhibitors, such as NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)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), colestesvelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin 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 poliglusam, 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, benzothiepine such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-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, niceritol, 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 11/771538, 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 stanols 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 International Publication No. WO 02/066464, 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), pitavastatin (such as NK-104 of Negma Kowa of Japan).

A non-limiting example of a HMG-CoA synthetase inhibitor useful in combination with the Bicyclic Pyranone Derivatives 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 ([2,4,6-tris(1-methylethyl)phenyl]acetyl)sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, lecimibide (DuP-128) and CL-277082 (N-(2,4-difluorophenyl)-N-[[4-(2,2-dimethylpropyl)phenyl]methyl]-N-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 International Publication No. WO 00/38721 and 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 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.*, "Wiedendiol-A and-B, Cholesteryl Ester Transfer Protein Inhibitors From The Marine Sponge Xestospongia Wiedenmayeri", *Bioorg. Med. Chem. Lett*, 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 Kuo *et al. J. Am. Chem. Soc.*, 117, 10629-34 (1995), 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 International Publication Nos. 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 International Publication Nos. WO 00/017164, WO 00/017166, WO 00/140190, WO 00/213797, and WO 05/033082 (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 (see International Publication Nos. WO 00/213797, WO 04/056358, WO 04/056359, and WO 05/011634).

A non-limiting example of a fish oil containing Omega 3 fatty acids useful in combination with the Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives is the sitostanol ester
5 used in BENECOL[®] margarine.

A non-limiting example of an anti-oxidant useful in combination with the Bicyclic Pyranone Derivatives includes probucol.

Non-limiting examples of NE (norepinephrine) transport inhibitors useful in combination with the Bicyclic Pyranone Derivatives include GW 320659, despiramine,
10 talsupram, and nomifensine.

Non-limiting examples of CB₁ antagonists/inverse agonists useful in combination with the Bicyclic Pyranone Derivatives include rimonabant, SR-147778 (Sanofi Aventis), and the compounds described in US Patent Nos. 5,532,237, 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,624,941 and 6,028,084;
15 International Publication Nos. WO 96/33159, WO 98/33765, WO 98/43636, WO 98/43635, WO 01/09120, WO 98/31227, WO 98/41519, WO 98/37061, WO 00/10967, WO 00/10968, WO 97/29079, WO 99/02499, WO 01/58869, WO 02/076949; and European Patent Application No. EP-658546 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of ghrelin antagonists useful in combination with the Bicyclic Pyranone Derivatives include those described in International Publication Nos. 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
25 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)
30 agonists/antagonists useful in combination with the Bicyclic Pyranone Derivatives include those described in International Publication Nos. WO 01/82925, WO 01/87834, WO 02/06245, WO 02/04433, WO 02/51809, and Japanese Patent

Application No. 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 Bicyclic Pyranone Derivatives include those described in US Patent No. 6,001,836; International Publication Nos. 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 NPY2 agonists useful in combination with the Bicyclic Pyranone Derivatives include PYY3-36 as described in Batterham, *et al.*, *Nature*, 418:650-654 (2003), NPY3-36, and other Y2 agonists such as N acetyl [Leu(28,31)] NPY 24-36 (White-Smith and Potter, *Neuropeptides* 33:526-33 (1999)), TASP-V (Malis *et al.*, *Br. J. Pharmacol.* 126:989-96 (1999)), cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY (Cabrele and Beck-Sickinger *J-Pept-Sci.* 6:97-122 (2000)) (each of the preceding references is herein incorporated by reference).

Non-limiting examples of NPY4 agonists useful in combination with the Bicyclic Pyranone Derivatives 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 NPY5 antagonists useful in combination with the Bicyclic Pyranone Derivatives include those described in US Patent Nos. 6,140,354, 6,191,160, 6,258,837, 6,313,298, 6,337,332, 6,329,395, 6,340,683, 6,326,375, 6,335,345; European Patent Application Nos. EP-01010691 and EP-01044970; International Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/27063, WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 02/48152, WO 02/49648, WO 01/14376, WO 04/110375 and WO 05/000217; and Norman *et al.*, *J. Med. Chem.* 43:4288-4312 (2000) (each of the preceding references is herein incorporated by reference); and 152,804, GW-569180A, GW-594884A, GW-587081X, GW-548118X; FR226928, FR

240662, FR252384; 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104.

Non-limiting examples of mGluR5 (Metabotropic glutamate subtype 5 receptor) antagonists useful in combination with the Bicyclic Pyranone Derivatives 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.*, *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 2002;303(3):1044-51 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of leptins, leptin derivatives, and leptin agonists/modulators useful in combination with the Bicyclic Pyranone Derivatives 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 Patent Nos. 5,552,524, 5,552,523, 5,552,522 and 5,521,283; and International Publication Nos. 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 Bicyclic Pyranone Derivatives include nalmefene (RevexTM), 3-methoxynaltrexone, naloxone, and naltrexone, as well as opioid antagonists described in International Publication No. WO 00/21509 (herein incorporated by reference).

Non-limiting examples of orexin receptor antagonists useful in combination with the Bicyclic Pyranone Derivatives include SB-334867-A, as well as those described in International Publication Nos. 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 Bicyclic Pyranone Derivatives include GI-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 Bicyclic Pyranone Derivatives include axokine (Regeneron) and those described in International Publication Nos. WO 94/09134, WO 98/22128, and WO 99/43813 (each of which is herein incorporated by reference).

5 Non-limiting examples of 5HT_{2c} agonists useful in combination with the Bicyclic Pyranone Derivatives include BVT933, DPCA37215, WAY161503, and R-1065, as well as those described in US Patent No. 3,914,250, and International Publication Nos. 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
10 reference).

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

Non-limiting examples of monoamine reuptake inhibitors useful in combination with the Bicyclic Pyranone Derivatives include sibutramine (MeridiaTM/ReductilTM), as well as those described in International Publication Nos. WO 01/27068 and WO 01/62341; US Patent Nos. 4,746,680, 4,806,570 and 5,436,272; and US Patent
20 Publication No. 2002/0006964 (each of which is herein incorporated by reference).

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

25 Non-limiting examples of α -amylase inhibitors useful in combination with the Bicyclic Pyranone Derivatives include tendamistat, trestatin, and AI-3688.

Non-limiting examples of α -glucokinase activators useful in combination with the Bicyclic Pyranone Derivatives include acarbose, adipose, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, salbostatin, CDK-711, MDL-25,637, MDL-73,945,
30 and MOR 14.

Non-limiting examples of fatty acid oxidation inhibitors useful in combination with the Bicyclic Pyranone Derivatives include clomoxir and etomoxir.

Non-limiting examples of A2 antagonists useful in combination with the Bicyclic Pyranone Derivatives include midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan.

Non-limiting examples of glycogen phosphorylase inhibitors useful in
5 combination with the Bicyclic Pyranone Derivatives 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.

10 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;
15 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
20 oxyphenbutazone; a coxib, such as celecoxib, etoricoxib, lumiracoxib 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
25 diphenylpropylamine derivative, a benzomorphan derivative, an oripavine derivative and a morphinane derivative. Additional illustrative examples of opiates include morphine, diamorphine, heroin, buprenorphine, dipipanone, pethidine, dextromoramide, alfentanil, fentanyl, remifentanyl, methadone, codeine, dihydrocodeine, tramadol, pentazocine, vicodin, oxycodone, hydrocodone, percocet,
30 percodan, norco, dilaudid, darvocet or lorcet.

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

The Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivative. 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 an Bicyclic Pyranone Derivative, 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 Bicyclic Pyranone Derivative, 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 epothilones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil); anti-metabolites (such as methotrexate); alkylating agents (such as temozolomide (TEMODARTM from Schering-Plough Corporation, Kenilworth, New Jersey), cyclophosphamide); Farnesyl protein transferase inhibitors (such as, SARASARTM(4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-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 gemcitabine.

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 Idec), sunitinib (Sutent® from Pfizer), dasatinib (or BMS-354825 from Bristol-Myers Squibb), tezacitabine (from Aventis Pharma), Sml1, 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-aminopyridine-2-carboxaldehyde thiosemicarbazone), MDL-101,731 ((E)-2'-deoxy-2'-(fluoromethylene)cytidine) 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, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ from Sanofi-Synthelabo Pharmaceuticals, France), Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17β-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Oxaliplatin, Aroplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane,

Mitoxantrone, Levamisole, Navelbene, Anastrozole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, Herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Profimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane,

5 Fulvestrant, Ifosfomide, Rituximab, C225 and Campath.

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
10 agents in inducing apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Bicyclic Pyranone Derivatives 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; Bicyclic Pyranone Derivatives may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For
15 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
20 a patient, comprising administering to the patient an amount of at least one Bicyclic Pyranone Derivative, or a pharmaceutically acceptable salt, solvate, ester, prodrug or stereoisomer thereof, and one or more other anticancer treatment modalities, wherein the amounts of the Bicyclic Pyranone Derivative(s)/ other treatment modality result in the desired therapeutic effect. In one embodiment, the at least one Bicyclic Pyranone
25 Derivative and the one or more other treatment modalities act synergistically. In one embodiment, the at least one Bicyclic Pyranone Derivative 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.

30 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 Bicyclic Pyranone Derivative, an antidiabetic agent and/or an antiobesity agent.

5 In another embodiment, the present combination therapies for treating or preventing diabetes comprise administering a Bicyclic Pyranone Derivative and an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing diabetes comprise administering a Bicyclic Pyranone Derivative and an anti-obesity agent.

10 In one embodiment, the present combination therapies for treating or preventing obesity comprise administering a Bicyclic Pyranone Derivative, an antidiabetic agent and/or an antiobesity agent.

In another embodiment, the present combination therapies for treating or preventing obesity comprise administering a Bicyclic Pyranone Derivative and an
15 antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing obesity comprise administering a Bicyclic Pyranone Derivative and an anti-obesity agent.

In one embodiment, the additional therapeutic agent is a cholesterol
20 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
25 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
30 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 Bicyclic Pyranone Derivative, an antidiabetic agent and/or an antiobesity agent.

5 In another embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering a Bicyclic Pyranone Derivative and an antidiabetic agent.

In another embodiment, the present combination therapies for treating or preventing metabolic syndrome comprise administering a Bicyclic Pyranone Derivative and an anti-obesity agent.

10 In one embodiment, the present combination therapies for treating or preventing a cardiovascular disease comprise administering one or more Bicyclic Pyranone Derivatives, and an additional agent useful for treating or preventing a cardiovascular disease.

15 In addition, the Bicyclic Pyranone Derivatives 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).

20 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).

25 In one embodiment, the one or more Bicyclic Pyranone Derivatives are administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

30 In another embodiment, the one or more Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivatives and the additional therapeutic agent(s) act synergistically and are administered in doses
5 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 Bicyclic Pyranone Derivatives and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another
10 embodiment, this composition is suitable for intravenous administration.

The one or more Bicyclic Pyranone Derivatives 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
15 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 Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivative. In another embodiment, the additional therapeutic agent is an agent useful for reducing any potential side effect of a Bicyclic Pyranone Derivative. Such potential side effects include, but are not limited to, nausea,
25 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
30 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 Bicyclic Pyranone Derivative(s) and the other agent(s) for treating or preventing diseases or conditions listed above can be administered simultaneously or sequentially. This is 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 Bicyclic Pyranone Derivatives 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 still 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 Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, PA.

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 Bicyclic Pyranone Derivatives 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 Bicyclic Pyranone Derivative is administered orally.

In another embodiment, a Bicyclic Pyranone Derivative is administered intravenously.

In another embodiment, a Bicyclic Pyranone Derivative is administered intranasally.

In still another embodiment, a Bicyclic Pyranone Derivative is administered topically.

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.

5 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.

10 The amount and frequency of administration of the Bicyclic Pyranone Derivatives 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
15 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 Bicyclic Pyranone Derivatives and an additional therapeutic agent, the two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical
20 composition comprising one or more Bicyclic Pyranone Derivatives 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
25 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.

30 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 Bicyclic Pyranone Derivatives, 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 Bicyclic Pyranone Derivatives, 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.

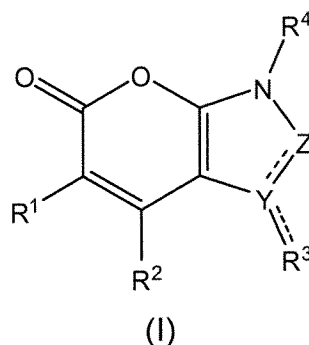
When the components of a combination therapy regimen are to be administered in more than one composition, they can be provided in a kit comprising a single package containing one or more containers, wherein one container contains one or more Bicyclic Pyranone Derivatives in a pharmaceutically acceptable 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 having the formula:



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein each dotted line represents an optional and additional bond, and wherein:

Y is -C- when an optional and additional bond is present and Y is -CH- when an optional and additional bond is not present;

Z is -O- , -NH- or -N(alkyl)- when the optional and additional bond between Y and Z is absent, and Z is -N- when the optional and additional bond between Y and Z is present;

R^1 is H, halo or -CN ;

R^2 is alkyl, alkenyl or $\text{-(alkylene)}_t\text{-cycloalkyl}$;

R^3 is O when the optional and additional bond between Y and R^3 is present, and R^3 is alkyl, haloalkyl, -C(O)OR^5 , -alkylene-O-alkyl or -O-alkyl when the optional and additional bond between Y and R^3 is absent;

R^4 is H, alkyl or aryl, wherein an aryl group can be unsubstituted or optionally substituted with up to 4 groups, which can be the same or different, and are selected from alkyl, halo, haloalkyl, -CN , -NO_2 , -C(O)OR^5 , $\text{-C(O)N(R}^5)_2$ or $\text{-N(R}^5)_2$;

each occurrence of R^5 is independently H, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; and

t is 0 or 1,

such that only one optional and additional bond may be present.

2. The compound of claim 1, wherein R^1 is H.

3. The compound of claim 1, wherein R^2 is alkyl, alkenyl or $\text{-alkylene-cycloalkyl}$.

4. The compound of claim 1, wherein R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

5 5. The compound of claim 1, wherein the optional and additional bond between Y and R^3 is absent.

6. The compound of claim 5, wherein R^3 is methyl, -O-ethyl, $-CH_2-O-CH_3$, $-C(O)OH$, $-C(O)O$ -ethyl, $-CHF_2$ or $-CF_3$.

10

7. The compound of claim 1, wherein R^4 is H, alkyl or aryl.

8. The compound of claim 7, wherein R^4 is phenyl or 4-nitrophenyl.

15 9. The compound of claim 1, wherein the optional and additional bond between Y and R^3 is present and R^3 is O.

10. The compound of claim 1, wherein the optional and additional bond between Y and Z is present.

20

11. The compound of claim 10, wherein Y is C and Z is N.

12. The compound of claim 2, wherein R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

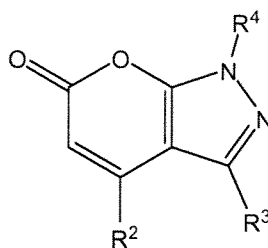
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13. The compound of claim 12, wherein R^3 is methyl, -O-ethyl, $-CH_2-O-CH_3$, $-C(O)OH$, $-C(O)O$ -ethyl, $-CHF_2$ or $-CF_3$.

14. The compound of claim 1, having the formula:

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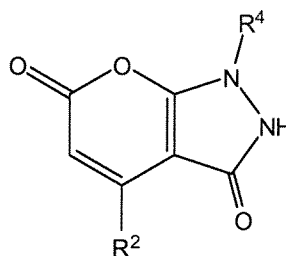
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(Ia)

wherein R^4 is H or optionally-substituted phenyl.

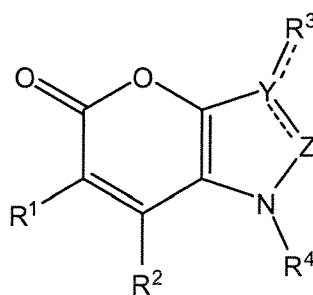
- 5 15. The compound of claim 1, having the formula:



(Ib)

wherein R^4 is H or optionally-substituted phenyl.

- 10 16. A compound having the formula:



(II)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein each dotted line represents an optional and additional bond, and wherein:

- 15 Y is $-C-$ when an optional and additional bond is present and Y is $-CH-$ when an optional and additional bond is not present;

Z is $-O-$, $-NH-$ or $-N(alkyl)-$ when the optional and additional bond between Y and Z is absent, and Z is $-N-$ when the optional and additional bond between Y and Z is present;

- 20 R^1 is H, halo or $-CN$;

R^2 is alkyl, alkenyl or $-(\text{alkylene})_t\text{-cycloalkyl}$;

R^3 is O when the optional and additional bond between Y and R^3 is present, and R^3 is alkyl, haloalkyl, $-\text{C}(\text{O})\text{OR}^5$, $-\text{alkylene-O-alkyl}$ or $-\text{O-alkyl}$ when the optional and additional bond between Y and R^3 is absent;

5 R^4 is H, alkyl or aryl, wherein an aryl group can be unsubstituted or optionally substituted with up to 4 groups, which can be the same or different, and are selected from alkyl, halo, haloalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{C}(\text{O})\text{N}(\text{R}^5)_2$ or $-\text{N}(\text{R}^5)_2$;

each occurrence of R^5 is independently H, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; and

10 t is 0 or 1,

such that only one optional and additional bond may be present.

17. The compound of claim 16, wherein R^1 is H.

15 18. The compound of claim 16, wherein R^2 is alkyl, alkenyl or $-\text{alkylene-cycloalkyl}$.

19. The compound of claim 18, wherein R^2 is ethyl, n-butyl, $-(\text{CH}_2)_3\text{CH=CH}_2$ or $-(\text{CH}_2)_3\text{-cyclopropyl}$.

20 20. The compound of claim 16, wherein the optional and additional bond between Y and R^3 is absent.

21. The compound of claim 20, wherein R^3 is methyl, $-\text{O-ethyl}$, $-\text{CH}_2\text{-O-CH}_3$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O-ethyl}$, $-\text{CHF}_2$ or $-\text{CF}_3$.

25

22. The compound of claim 16, wherein R^4 is H, alkyl or aryl.

23. The compound of claim 22, wherein R^4 is phenyl or 4-nitrophenyl.

30 24. The compound of claim 16, wherein the optional and additional bond between Y and R^3 is present and R^3 is O.

25. The compound of claim 16, wherein the optional and additional bond between Y and Z is present.

26. The compound of claim 25, wherein Y is C and Z is N.

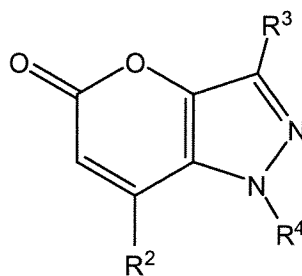
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27. The compound of claim 27, wherein R^2 is ethyl, n-butyl, $-(CH_2)_3CH=CH_2$ or $-(CH_2)_3$ -cyclopropyl.

28. The compound of claim 27, wherein R^3 is methyl, -O-ethyl, $-CH_2-O-CH_3$, -C(O)OH, -C(O)O-ethyl, $-CHF_2$ or $-CF_3$.

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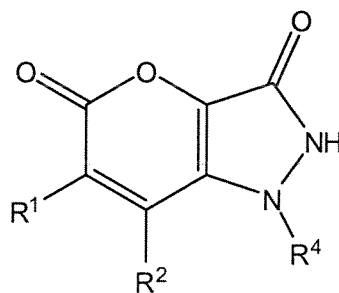
29. The compound of claim 16, having the formula:



(IIa)

15 wherein R^4 is H or optionally-substituted phenyl.

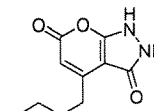
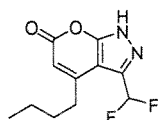
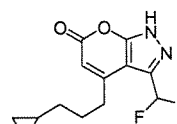
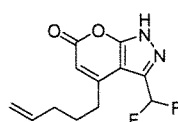
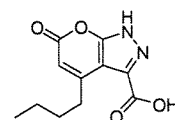
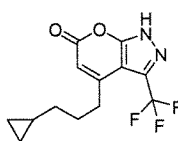
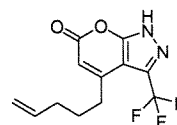
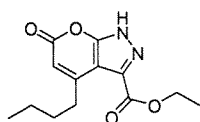
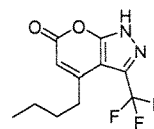
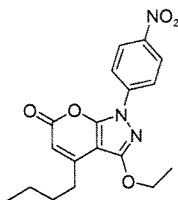
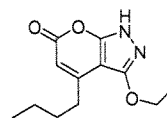
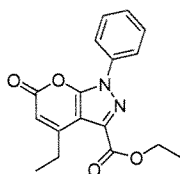
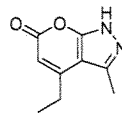
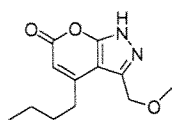
30. The compound of claim 16, having the formula:



(IIb)

20 wherein R^4 is H or optionally-substituted phenyl.

31. A compound having the structure:



or

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

32. A composition comprising an effective amount of one or more compounds of
 5 claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and a
 pharmaceutically acceptable carrier.

33. The composition of claim 32, 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.

34. The composition of claim 33, wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

35. The composition of claim 34, wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

36. The composition of claim 35, wherein the HMG-CoA reductase inhibitor is simvastatin.

37. The composition of claim 33, further comprising a cholesteryl ester transfer protein inhibitor.

38. The composition of claim 33, further comprising Vytorin[®], ezetimibe, aspirin, ibuprofen or acetaminophen or a combination thereof.

39. A composition comprising an effective amount of one or more compounds of claim 16 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and a pharmaceutically acceptable carrier.

40. The composition of claim 39, 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.

41. The composition of claim 40, wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

42. The composition of claim 41, wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

43. The composition of claim 42, wherein the HMG-CoA reductase inhibitor is simvastatin.

44. The composition of claim 40, further comprising a cholesteryl ester transfer protein inhibitor.

45. The composition of claim 40, further comprising Vytorin[®], ezetimibe, aspirin, ibuprofen or acetaminophen or a combination thereof.

46. 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.

47. The method of claim 46, wherein the treating is for diabetes.

48. The method of claim 47, wherein the diabetes is type 2 diabetes.

5 49. The method of claim 46, wherein the treating is for obesity.

50. The method of claim 46, wherein the treating is for dyslipidemia.

51. The method of claim 50, wherein the treating is for hypercholesterolemia.

10

52. The method of claim 46, 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
15 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.

20

53. The method of claim 50, further comprising administering to the patient an HMG-CoA reductase inhibitor.

54. The method of claim 53, wherein the HMG-CoA reductase inhibitor is selected
25 from lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

55. The method of claim 54, wherein the HMG-CoA reductase inhibitor is simvastatin.

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56. The method of claim 50, further comprising administering to the patient a cholesteryl ester transfer protein inhibitor.

57. The method of claim 50, further comprising administering to the patient Vytorin[®], ezetimibe, aspirin, ibuprofen or acetaminophen or a combination thereof.

58. A method for treating a metabolic disorder, dyslipidemia, a cardiovascular
5 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 16, or a pharmaceutically acceptable salt, solvate, ester
10 or prodrug thereof.

59. The method of claim 58, wherein the treating is for diabetes.

60. The method of claim 59, wherein the diabetes is type 2 diabetes.
15

61. The method of claim 58, wherein the treating is for obesity.

62. The method of claim 58, wherein the treating is for dyslipidemia.

20 63. The method of claim 62, wherein the treating is for hypercholesterolemia.

64. The method of claim 58, 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,
25 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)
30 inhibitor and a low-density lipoprotein (LDL) activator.

65. The method of claim 62, further comprising administering to the patient an HMG-CoA reductase inhibitor.

66. The method of claim 65, wherein the HMG-CoA reductase inhibitor is selected
5 from lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

67. The method of claim 66, wherein the HMG-CoA reductase inhibitor is simvastatin.

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68. The method of claim 62, further comprising administering to the patient a cholesteryl ester transfer protein inhibitor.

69. The method of claim 62, further comprising administering to the patient
15 Vytorin[®], ezetimibe, aspirin, ibuprofen or acetaminophen or a combination thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/068022

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D491/052 A61K31/4162 A61P3/00 A61P9/00 A61P29/00
A61P7/00 A61P11/00 A61P25/00 A61P1/00 A61P35/00

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)
C07D

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 practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHENG-CHU KUO ET AL: "Studies on heterocyclic compounds. 6. Synthesis and analgesic and antiinflammatory activities of 3,4-dimethylpyrano[2,3-c]pyrazol-6-one derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no. 4, 1984, pages 539-544, XP002572940 Scheme I; Tables I, III	1-3, 5-7, 10, 11, 14, 32, 46
X	MISBAHUL AIN KHAN ET AL: "Pyranopyrazoles. II(1). Synthesis and reactions of 1H,6H-pyrano[2,3-c]pyrazol-6-ones" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 19, no. 5, 1982, pages 1077-1085, XP002572941 Schemes 1, 2; Table 1	1-3, 5-8, 10, 11, 14
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document 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.

"&" document member of the same patent family

Date of the actual completion of the international search

12 March 2010

Date of mailing of the international search report

19/04/2010

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Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/068022

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. GENO SAMARITONI ET AL: "Synthesis and chemistry of N-arylated pyrano[2,3-c]pyrazoles". JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 44, no. 6, 2007, pages 1389-1393, XP002572942 Abstract, compounds [1]; Scheme 1, compounds 1a,c,e -----	1-3,5-7, 10,11,14
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1891, XP002572943 Database accession no. 262659 (BRN) abstract & ALFRED KLAUBER MONATSHFTE FÜR CHEMIE, vol. 12, 1891, pages 211-220, -----	1-3,5-7, 10,11,14
X	CARL BÜLOW: "Über die Kondensationsprodukte des 2,4-Dichlorphenyl-hydrazins mit Aldehyden, 1.2-, 1.3- und 1.4-Diketonen und 1.3-Ketocarbonsäure-estern, und ihr Verhalten gegen Chlor" CHEMISCHE BERICHTE, vol. 51, no. 1, 1918, pages 399-417, XP002572944 page 415, paragraph 2 -----	1-3,5-7, 10,11,14
X	A. MAQUESTIAU ET AL: "Etude de la réactivité du 3-amino-2-buténoate d'éthyle vis-à-vis d'azoline-5-ones" BULLETIN DES SOCIETES CHIMIQUES BELGES, vol. 93, no. 12, 1984, pages 1073-1081, XP009130683 compounds 20-24 -----	1-3,5-8, 10,11,14
X	MOHAMMAD M. MOJTAHEDI ET AL: "Facile synthesis of pyrano[2,3-c]pyrazol-6-one derivatives under microwave irradiation in solvent-free conditions" SYNTHETIC COMMUNICATIONS, vol. 36, no. 1, 2006, pages 51-57, XP009130687 compounds 3a,f, 5a-c ----- -/--	1-3,5-8, 10,11,14

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/068022

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUSSEIN F. ZOHDI ET AL: "Reactions with 5-trifluoromethyl-2,4-dihydropyrazol-3-one derivatives: a new route for the synthesis of fluorinated polyfunctionally substituted pyrazole and pyrano[2,3-c]pyrazole derivatives" JOURNAL OF CHEMICAL RESEARCH, MINIPRINT, vol. 12, 1992, pages 3015-3025, XP009130666 compound 7a	1-3,5-8, 10,11,14
X	TAISEI UEDA ET AL: "Synthesis of pyrazolone derivatives. XXXIX. Synthesis and analgesic activity of pyrano[2,3-c]pyrazoles" CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 29, no. 12, 1981, pages 3522-3528, XP002572945 compounds VIIa-c	1-3,5-8, 10,11,14
X	A. MAQUESTIAU ET AL: "Etude comparative de la réactivité de l'acétoacétate d'éthyle et du 3-aminocrotonate d'éthyle vis-à-vis de composés pyrazoloniques" BULLETIN DES SOCIETES CHIMIQUES BELGES, vol. 92, no. 5, 1983, pages 451-458, XP009130681 compounds 3,8	1-3, 5-11,14, 15
A	WO 2006/124490 A2 (SCHERING CORP [US]; PALANI ANANDAN [US]; SU JING [US]; XIAO DONG [US];) 23 November 2006 (2006-11-23) the whole document	1-69

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/068022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006124490	A2	23-11-2006	
		AR 053728 A1	16-05-2007
		AU 2006247695 A1	23-11-2006
		CA 2608405 A1	23-11-2006
		EP 1885726 A2	13-02-2008
		JP 2008540652 T	20-11-2008
		KR 20080016567 A	21-02-2008
