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(54) Title: ACC INHIBITORS AND USES THEREOF

(57) Abstract: The present invention provides compounds useful as inhibitors of Acetyl CoA Carboxylase (ACC), compositions thereof, and methods of using the same.

ACC INHIBITORS AND USES THEREOF

BACKGROUND OF THE INVENTION

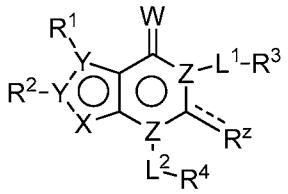
[0001] Obesity is a health crisis of epic proportions. The health burden of obesity, measured by quality-adjusted life-years lost per adult, has surpassed that of smoking to become the most serious, preventable cause of death. In the US, about 34% of adults have obesity, up from 31% in 1999 and about 15% in the years 1960 through 1980. Obesity increases the rate of mortality from all causes for both men and women at all ages and in all racial and ethnic groups. Obesity also leads to social stigmatization and discrimination, which decreases quality of life dramatically. The chronic diseases that result from obesity cost the US economy more than $150 billion in weight-related medical bills each year. Furthermore, about half of the obese population, and 25% of the general population, have metabolic syndrome, a condition associated with abdominal obesity, hypertension, increased plasma triglycerides, decreased HDL cholesterol, and insulin resistance, which increases the risk for type-2 diabetes (T2DM), stroke and coronary heart disease. [Harwood, *Expert Opin. Ther. Targets* 9: 267, 2005].

[0002] Diet and exercise, even when used in conjunction with the current pharmacotherapy, do not provide sustainable weight loss needed for long-term health benefit. Currently, only a few anti-obesity drugs are approved in the US, the fat absorption inhibitor orlistat (Xenical®), the 5-HT_{2C} antagonist lorcaserin (Belviq®), and the combination therapy phentermine/topiramate (Qsymia®). Unfortunately, poor efficacy and unappealing gastrointestinal side effects limit the use of orlistat. Surgery can be effective but is limited to patients with extremely high body-bass indices (BMI) and the low throughput of surgery limits the impact of this modality to about 200k patients per year. The majority of obesity drugs in clinical development are designed to reduce caloric intake through central action in the CNS (e.g., anorectics and satiety agents). However, the FDA has taken an unfavorable position against CNS-active agents, due to their modest efficacy and observed/potential side-effect profiles.

[0003] The continuing and increasing problem of obesity, and the current lack of safe and effective drugs for treating it, highlight the overwhelming need for new drugs to treat this condition and its underlying causes.

SUMMARY OF THE INVENTION

[0004] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of Acetyl-CoA carboxylase (ACC). Such compounds have the general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

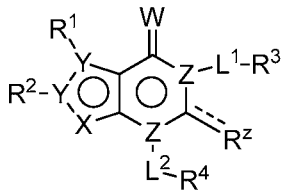
[0005] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of the production or oxidation of fatty acids. Such diseases, disorders, or conditions include those described herein.

[0006] Compounds provided by this invention are also useful for the study of ACC enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in lipogenic tissues; and the comparative evaluation of new ACC inhibitors or other regulators of fatty acid levels *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention:

[0007] In certain embodiments, the present invention provides inhibitors of ACC. In some embodiments, such compounds include those of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

W is oxygen or sulfur;

X is O, S, N or NR;

each Y is independently C, N, or O;

each Z is independently C or N;

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogens, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2RN(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R, -$B(OR)_2$, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^2 is not optionally substituted benzyl; or

R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen, deuterium, or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^5 and $R^{5'}$;

L^2 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^7 and $R^{7'}$;

R^3 is halogen, -CN, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)RN(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OR)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen or a ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein said ring is optionally substituted with n instances of R^8;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

each of R^7 and $R^{7'}$ is independently, -R, $-OR^6$, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, or $-B(OR)_2$; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^6 is -R, $-C(O)N(R)_2$, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, $-N(R)_2$ or deuterium;

R^z is selected from hydrogen, halogen, methyl, -CN, =O, and =S; and

n is 0-5.

2. Compounds and Definitions:

[0008] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical

elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0009] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0010] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0011] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

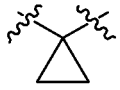
[0012] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

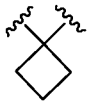
[0013] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

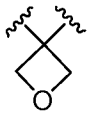
[0014] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0015] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0016] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0017] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure: .

[0018] As used herein, the term "cyclobutylenyl" refers to a bivalent cyclobutyl group of the following structure: .

[0019] As used herein, the term "oxetanyl" refers to a bivalent oxetanyl group of the following structure: .

[0020] The term "halogen" means F, Cl, Br, or I.

[0021] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring."

[0022] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic and bicyclic ring systems having a total of five to 10 ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0023] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0024] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0025] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono– or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0026] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0027] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a

specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0028] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0029] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^{\bullet}$, $-(haloR^{\bullet})$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; $-O(haloR^{\bullet})$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, $-C(O)SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^{\bullet}$, or $-SSR^{\bullet}$ wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0030] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0031] Suitable substituents on the aliphatic group of R^* include halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, -OH, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0032] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein

each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0033] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, –$R^{\bullet}$, -(halo$R^{\bullet}$), –OH, –$OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, –C(O)$OR^{\bullet}$, –NH_2, –$NHR^{\bullet}$, –$NR^{\bullet}_2$, or -NO_2, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, –CH_2Ph, –O$(CH_2)_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0034] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate,

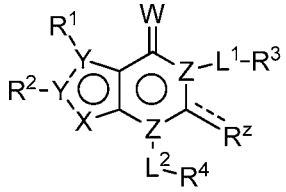
palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0035] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0036] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

3. Description of Exemplary Embodiments:

[0037] In certain embodiments, the present invention provides inhibitors of ACC. In some embodiments, such compounds include those of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

W is oxygen or sulfur;

X is O, S, N or NR;

each Y is independently C, N, or O;

each Z is independently C or N;

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogens, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2RN(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO_2R, -$B(OR)_2$, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^2 is not optionally substituted benzyl; or

R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen, deuterium, or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^5 and $R^{5'}$;

L^2 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^7 and $R^{7'}$;

R^3 is halogen, -CN, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)RN(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OR)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen or a ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein said ring is optionally substituted with n instances of R^8;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

each of R^7 and $R^{7'}$ is independently, -R, $-OR^6$, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OR)_2$; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^6 is -R, $-C(O)N(R)_2$, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, $-N(R)_2$ or deuterium;

R^z is selected from hydrogen, halogen, methyl, -CN, =O, and =S; and

n is 0-5.

[0038] In certain embodiments, if L^2 is a covalent bond, then R^4 is not hydrogen. In certain embodiments, the group $-L^2-R^4$ is not alkyl when R^2 is unsubstituted alkyl. In certain embodiments, the group $-L^1-R^3$ taken together is not unsubstituted alkyl. In certain

embodiments, R^1 is not the group $-CH_2C(O)N(R)V$, where V is an aryl or heteroaryl ring, when $-L^1-R^3$ taken together is unsubstituted alkyl.

[0039] As defined generally above, W is oxygen or sulfur. In some embodiments W is oxygen. In some embodiments W is sulfur.

[0040] As defined generally above, X is O, S, N, or NR. In certain embodiments, X is O. In certain embodiments, X is S. In some embodiments, X is N. In some embodiments, X is NR. In certain embodiments, X is NH.

[0041] As defined generally above, each Y is independently C, N, or O. In some embodiments one Y group is C while the other is N. In some embodiments, both Y groups are C. In some embodiments, both Y groups are N. In some embodiments, one Y group is C while the other is O. One of skill in the art will appreciate that when the Y group shown as connected to R^1 is O, R^1 is absent.

[0042] As defined generally above, each Z is independently C or N. In some embodiments one Z group is C while the other is N. In some embodiments, both Z groups are C. In some embodiments, both Z groups are N.

[0043] As defined generally above, R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogens, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$. In certain embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_{1-4} aliphatic. In some embodiments, R^1 is methyl. In some embodiments, R^1 is trifluoromethyl.

[0044] As defined generally above, R^2 is halogen, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OR)_2$, or Hy. In certain embodiments, R^2 is halogen. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 is trifluoromethyl. In certain embodiments, R^2 is fluorine. In certain embodiments, R^2 is chlorine. In certain embodiments, R^2 is bromine. In certain embodiments, R^2 is iodine. In certain embodiments, R^2 is -C(O)OR or $-C(O)N(R)_2$. In some embodiments, R^2 is Hy. In some embodiments, R^2 is a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, R^2 is cyclobutyl.

[0045] In some embodiments, R^2 is not chlorine or optionally substituted phenyl.

[0046] As defined generally above, Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is oxazolyl. In some embodiments, Hy is thiazolyl. In some embodiments, Hy is triazolyl.

[0047] In some embodiments, R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclic ring. In some embodiments, R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

[0048] As defined generally above, R^3 is halogen, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OR)_2$, or an optionally substituted ring selected from phenyl, and a 5-6 membered heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, R^3 is –CN, –OR, -C(O)OR, $-C(O)N(R)_2$, $-SO_2R$, or an optionally substituted ring selected from phenyl and a 5-6 membered heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^3 is –OR. In some embodiments, R^3 is –C(O)OR. In some embodiments, R^3 is phenyl or tetrazolyl. In some embodiments, R^3 is isothiazolidine-1,1-dioxide. In some embodiments, R^3 is pyrrolidinylcarbonyl.

[0049] As defined generally above, each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially

unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0050] In certain embodiments, each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-8 membered unsaturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[0051] As defined generally above, L^1 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^5 and $R^{5'}$, or a cyclopropylenyl, cyclobutylenyl, or oxetanyl group. In certain embodiments, L^1 is a C_{1-3} straight or branched bivalent hydrocarbon chain optionally substituted with R^5 and $R^{5'}$. In some embodiments, L^1 is a straight or branched bivalent C_2 hydrocarbon chain. In some embodiments L^1 is a straight or branched bivalent C_3 hydrocarbon chain. In certain embodiments, L^1 is a C_1 bivalent hydrocarbon chain substituted with R^5 and $R^{5'}$. In some embodiments, L^1 is a cyclopropylenyl, cyclobutylenyl, or oxetanyl group.

[0052] As defined generally above, In some embodiments, L^2 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^7 and $R^{7'}$. optionally substituted C_{1-3} straight or branched hydrocarbon chain. In some embodiments L^2 is an optionally substituted C_2 straight hydrocarbon chain. In some embodiments L^2 is an optionally substituted C_3 straight or branched hydrocarbon chain.

[0053] As defined generally above, R^4 is hydrogen or a ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein said ring is optionally substituted with n instances of R^8.

[0054] In certain embodiments, R^4 is hydrogen. In some embodiments, R^4 is a 5-6 membered monocyclic saturated or partially unsaturated ring; wherein said ring is optionally substituted with n instances of R^8. In some embodiments R^4 is a 5-6 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein said ring is optionally substituted with n instances of R^8. In some embodiments, R^4 is phenyl; wherein said ring is optionally substituted with n instances of R^8. In some embodiments R^4 is an 10 membered bicyclic aryl ring; wherein said ring is optionally substituted with n instances of R^8. In some embodiments, R^4 is an 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein said ring is optionally substituted with n instances of R^8. In some embodiments, R^4 is an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein said ring is optionally substituted with n instances of R^8.

[0055] As defined generally above, each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group.

[0056] In some embodiments, each of R^5 and $R^{5'}$ is –R, wherein –R is not hydrogen. In some embodiments, each of R^5 and $R^{5'}$ is methyl. In some embodiments, R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group. In some embodiments, R^5 and $R^{5'}$ are taken together to form a cyclobutylenyl group.

[0057] As defined generally above, each of R^7 and $R^{7'}$ is independently hydrogen, -R, -OR^6, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)O R, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO_2R, or -$B(OR)_2$; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0058] In certain embodiments, one of R^7 and $R^{7'}$ is hydrogen, and the other is –OR^6. In some embodiments one of R^7 and $R^{7'}$ is hydrogen, and the other is isopropoxy. In some embodiments R^7 and $R^{7'}$ are taken together to form a 3-6 membered saturated or partially

unsaturated monocyclic carbocyclic ring. In some embodiments R^7 and $R^{7'}$ are taken together to form a 4-6 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, one of R^7 and $R^{7'}$ is hydrogen and the other is $-OR^6$.

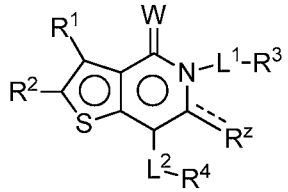
[0059] As described generally above, R^6 is -R, $-C(O)N(R)_2$, or -C(O)R. In certain embodiments R^6 is –R. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is isopropyl. In certain embodiments R^6 is tetrahydropyranyl. In certain embodiments R^6 is tetrahydrofuranyl. In certain embodiments, R^6 is tetrahydro-*2H*-thiopyran-1,1-dioxide. In certain embodiments, R^6 is 4-hydroxycyclohexyl.

[0060] As defined generally above, each R^8 is independently selected from halogen, -R, -OR, -SR, $-N(R)_2$ or deuterium. In certain embodiments, each R^8 is independently selected from halogen, -R, and -OR. In certain embodiments, each R^8 is halogen. In certain embodiments, R^8 is –OR. In certain embodiments, R^8 is methoxy.

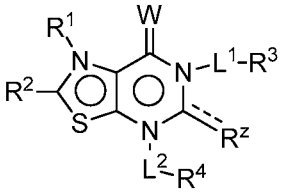
[0061] As defined generally above, n is 0-5. In certain embodiments, n is 0. In some embodiments, n is 1-2. In some embodiments, n is 1. In some embodiments, n is 5.

[0062] As defined generally above, R^z is selected from hydrogen, halogen, methyl, -CN, =O, and =S. In some embodiments R^z is hydrogen. In some embodiments R^z is selected from halogen, methyl, -CN, =O, and =S. One of skill in the art will appreciate that when R^z is =O or =S, the exocyclic bond connecting said atoms to the ring is formally a double bond, but owing to the tautomerism of said groups in the aromaticity of the ring to which they are attached, they may also be represented as –OH or –SH.

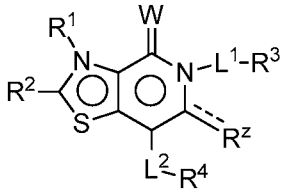
[0063] In some embodiments, the present invention provides a compound of formula **I** selected from formulas **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, and **I-i**:



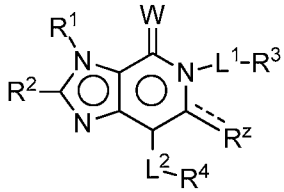
I-a



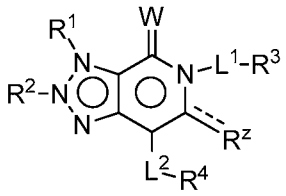
I-b



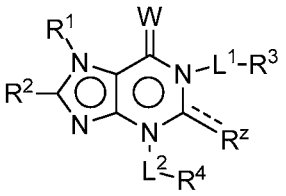
I-c



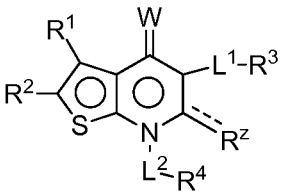
I-d



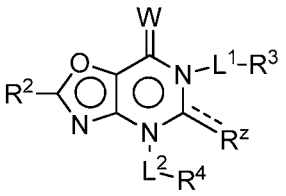
I-e



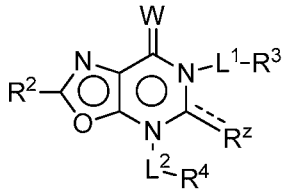
I-f



I-g



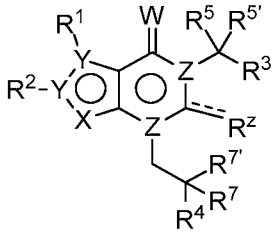
I-h



I-i

or a pharmaceutically acceptable salt thereof; wherein each of W, R^1, R^2, R^3, R^4, R^z, L^1, and L^2 is as described in embodiments for formula **I**, *supra*, or described in embodiments herein, both singly and in combination.

[0064] In certain embodiments, the present invention provides a compound of formula **II**:

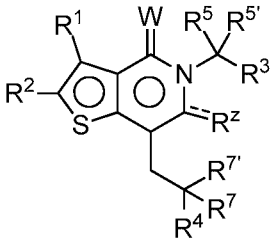


II

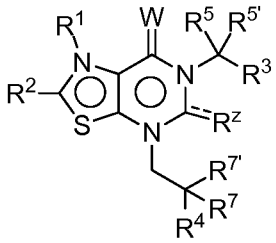
or a pharmaceutically acceptable salt thereof, wherein:

each of W, X, Y, Z, R^1, R^2, R^3, R^4, R^5, $R^{5'}$, R^7, $R^{7'}$ and R^z is as described in embodiments for formula **I**, *supra*, or described in embodiments herein, both singly and in combination.

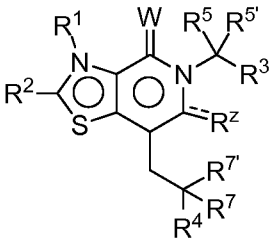
[0065] In certain embodiments, the present invention provides a compound of formula **II** selected from formulas **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, **II-f**, **II-g**, **II-h**, and **II-i**:



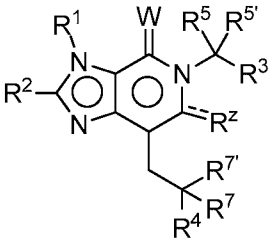
II-a



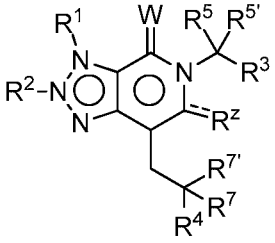
II-b



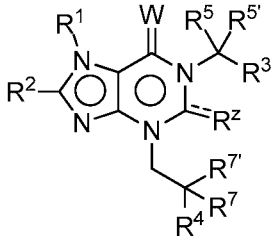
II-c



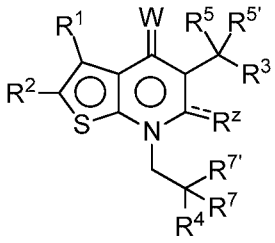
II-d



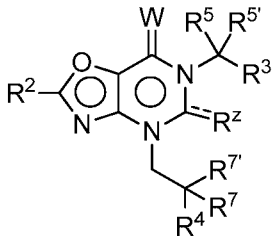
II-e



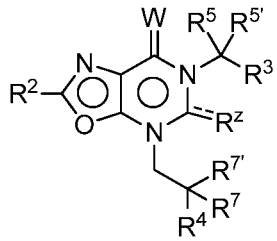
II-f



II-g



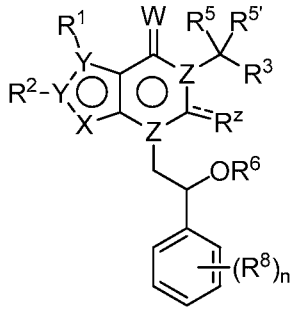
II-h



II-i

or a pharmaceutically acceptable salt thereof; wherein each variable is as described in embodiments for formula **II**, *supra*, or described in embodiments herein, both singly and in combination.

[0066] In certain embodiments, the present invention provides a compound of formula **III**:

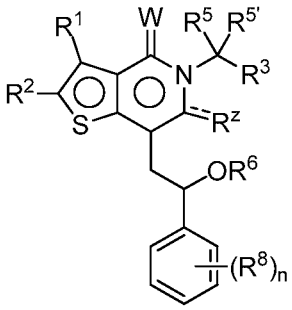


III

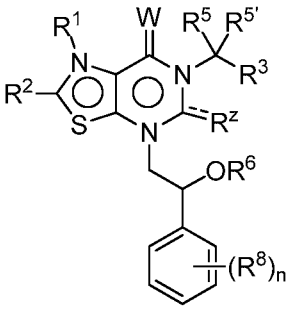
or a pharmaceutically acceptable salt thereof, wherein:

each of W, X, Y, Z, R, R^1, R^2, R^3, R^5, $R^{5'}$, R^6, R^8, R^z, and n is as described in embodiments for formulas **I** and **II**, *supra*, or described in embodiments herein, both singly and in combination.

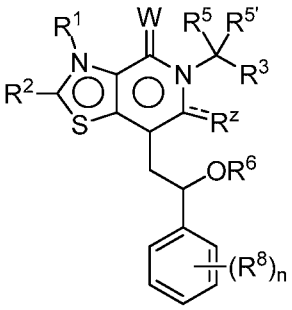
[0067] In certain embodiments, the present invention provides a compound of formula **III** selected from formulas **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, **III-f**, **III-g**, **III-h**, and **III-i**:



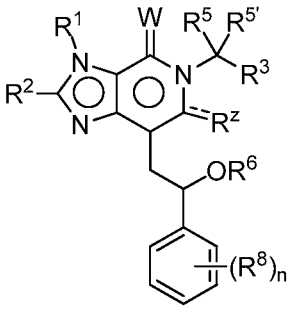
III-a



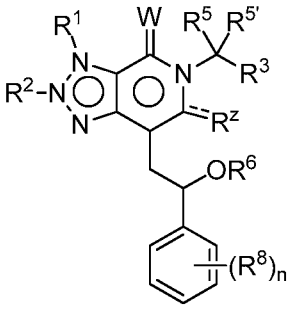
III-b



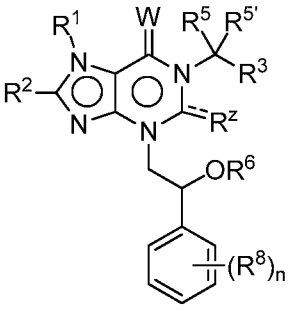
III-c



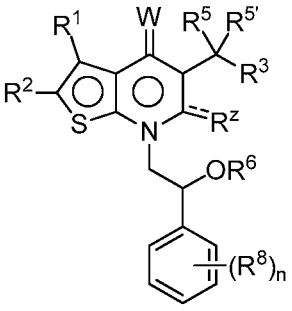
III-d



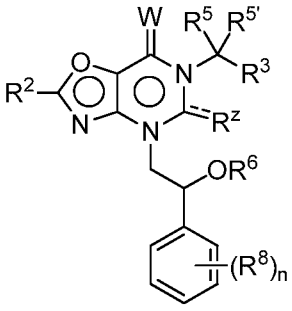
III-e



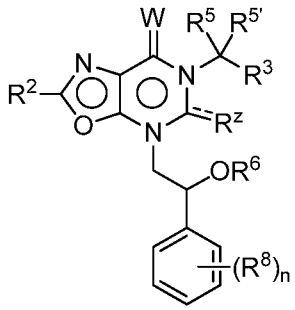
III-f



III-g



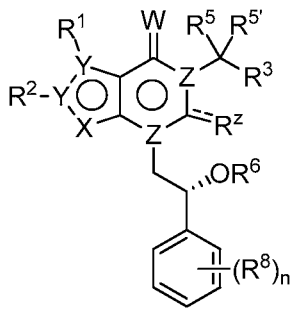
III-h



III-i

or a pharmaceutically acceptable salt thereof; wherein each variable is as described in embodiments for formula **III**, *supra*, or described in embodiments herein, both singly and in combination.

[0068] In certain embodiments, the present invention provides a compound of formula **IV**:

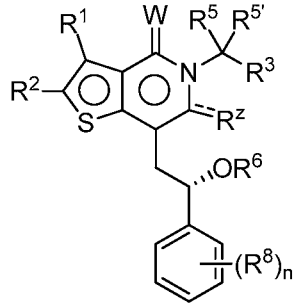


IV

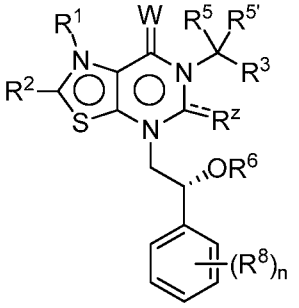
or a pharmaceutically acceptable salt thereof, wherein:

each of W, X, Y, Z, R, R^1, R^2, R^3, R^5, $R^{5'}$, R^6, R^8, n, and R^z is as described in embodiments for formulas **I**, **II**, and **III**, *supra*, or described in embodiments herein, both singly and in combination.

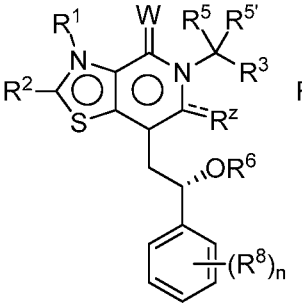
[0069] In certain embodiments, the present invention provides a compound of formula **IV** selected from formulas **IV-a**, **IV-b**, **IV-c**, **IV-d**, **IV-e**, **IV-f**, **IV-g**, **IV-h**, and **IV-i**:



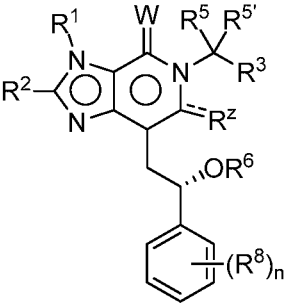
IV-a



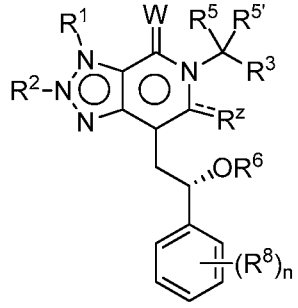
IV-b



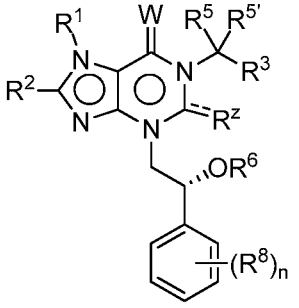
IV-c



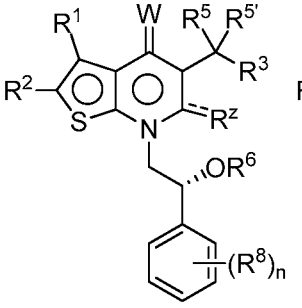
IV-d



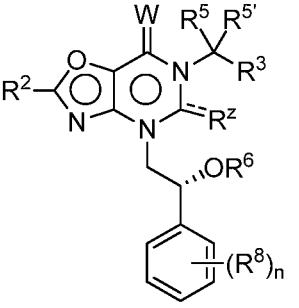
IV-e



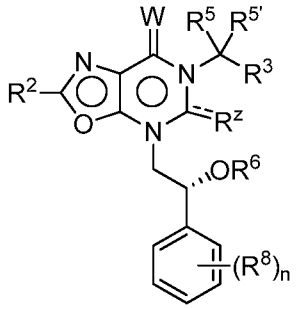
IV-f



IV-g



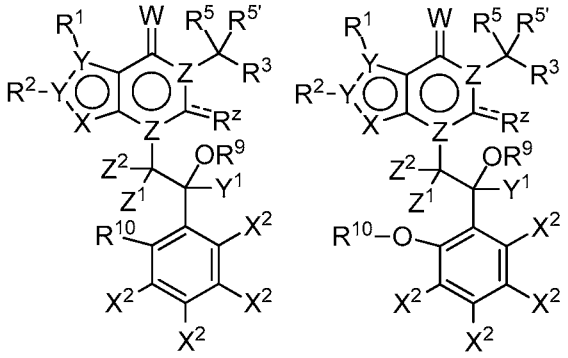
IV-h



IV-i

or a pharmaceutically acceptable salt thereof; wherein each variable is as described in embodiments for formula **III**, *supra*, or described in embodiments herein, both singly and in combination.

[0070] In certain embodiments, the present invention provides a compound of formula **V-i** or **V-ii**:



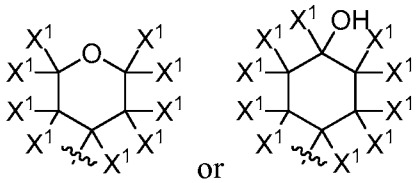
V-i **V-ii**,

or a pharmaceutically acceptable salt thereof, wherein Q, W, X, Y, Z, R^2, and R^3 are as described in embodiments for formula **I**, *supra*; and

R^1 is H, D, CH_3 or CD_3;

each of R^5 and $R^{5'}$ is independently CH_3 or CD_3

R^9 is $CH(CH_3)_2$, $CH(CD_3)_2$, $CD(CH_3)_2$, $CD(CD_3)_2$, or a group of formula:

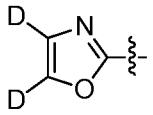


; wherein each X^1 is independently H or D;

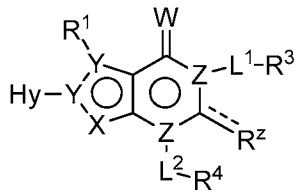
each instance of X^2, Y^1, Z^1, and Z^2 is independently H or D; and

R^{10} is CH_3, CD_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, CF_2H, CH_2CD_3, CD_2CH_3, or CD_2CD_3.

[0071] In some embodiments, the compound of formula **V-i** or **V-ii** contains at least one deuterium atom. In some embodiments, the compound of formula **V-i** or **V-ii** contains at least two deuterium atoms. In some embodiments, the compound of formula **V-i** or **V-ii** contains at least three deuterium atoms.

[0072] In some embodiments, the present invention provides a compound of formula **V-i** or **V-ii** wherein R^2 is selected from bromine, $-C(O)OCD_2CD_3$, $-C(O)OCD_2CH_3$, $-C(O)OCH_2CD_3$ and .

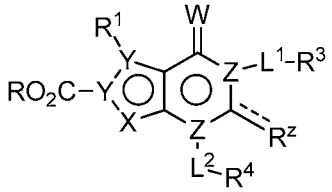
[0073] In certain embodiments, the present invention provides a compound of formula **I**, wherein R^2 is Hy, thereby forming a compound of formula **VI**:



VI

or a pharmaceutically acceptable salt thereof, wherein each of W, X, Y, Z, L^1, L^2, R^1, R^3, R^4, and Hy is defined above and described in embodiments herein, both singly and in combination.

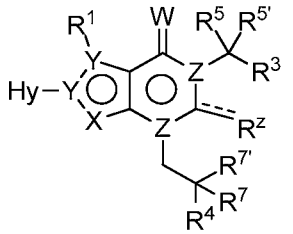
[0074] In certain embodiments, the present invention provides a compound of formula **I**, wherein R^2 is –C(O)OR, thereby forming a compound of formula **VII**:



VII

or a pharmaceutically acceptable salt thereof, wherein each of W, X, Y, Z, L^1, L^2, R, R^1, R^3, and R^4 is defined above and described in embodiments herein, both singly and in combination.

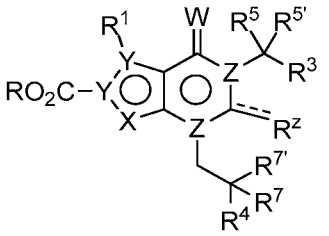
[0075] In certain embodiments, the present invention provides a compound of formula **II**, wherein R^2 is Hy, thereby forming a compound of formula **VIII**:



VIII

or a pharmaceutically acceptable salt thereof, wherein each of W, X, Y, Z, R^1, R^3, R^4, R^5, $R^{5'}$, R^7, $R^{7'}$, and Hy is defined above and described in embodiments herein, both singly and in combination.

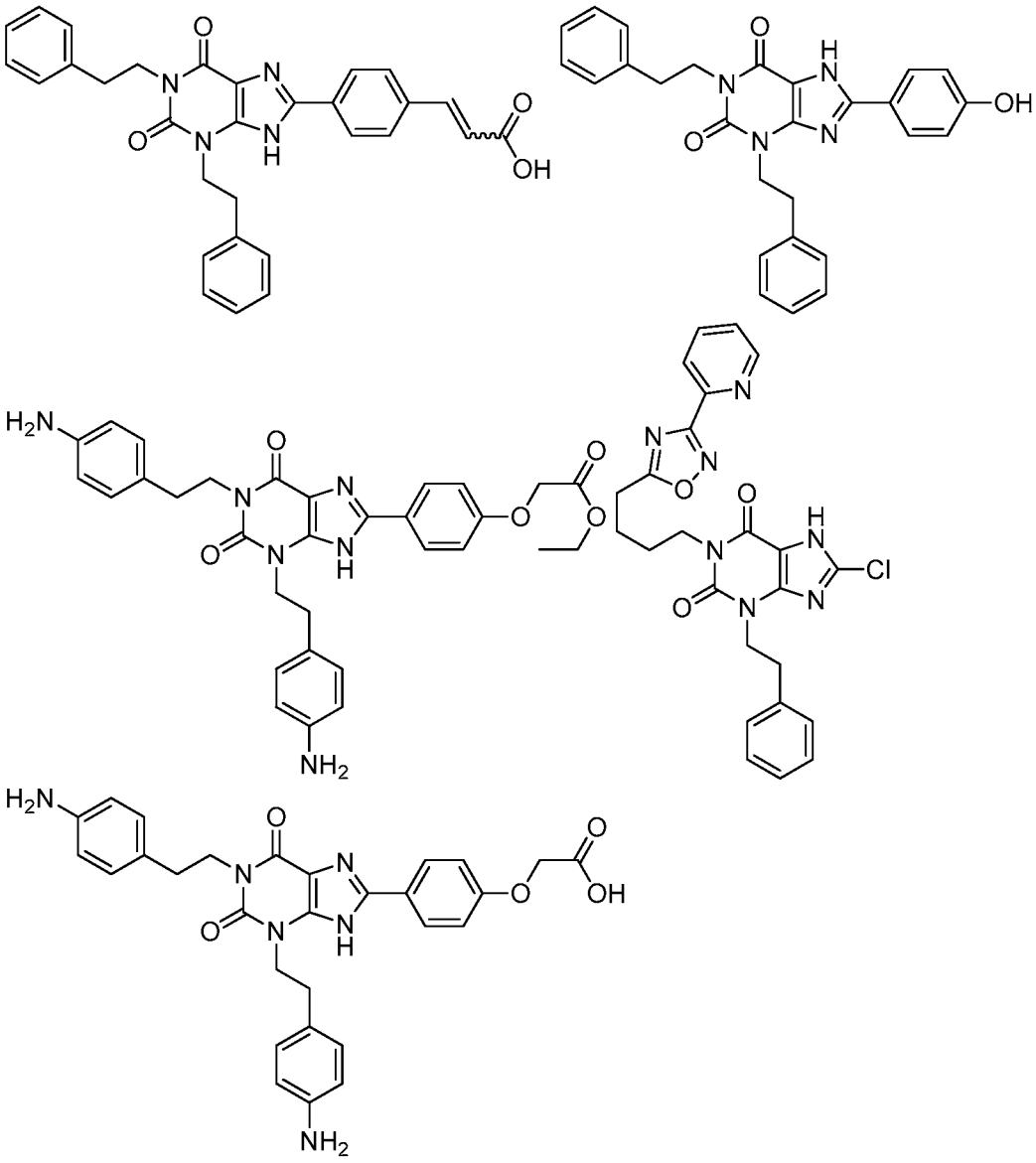
[0076] In certain embodiments, the present invention provides a compound of formula **II**, wherein R^2 is –C(O)OR, thereby forming a compound of formula **IX**:

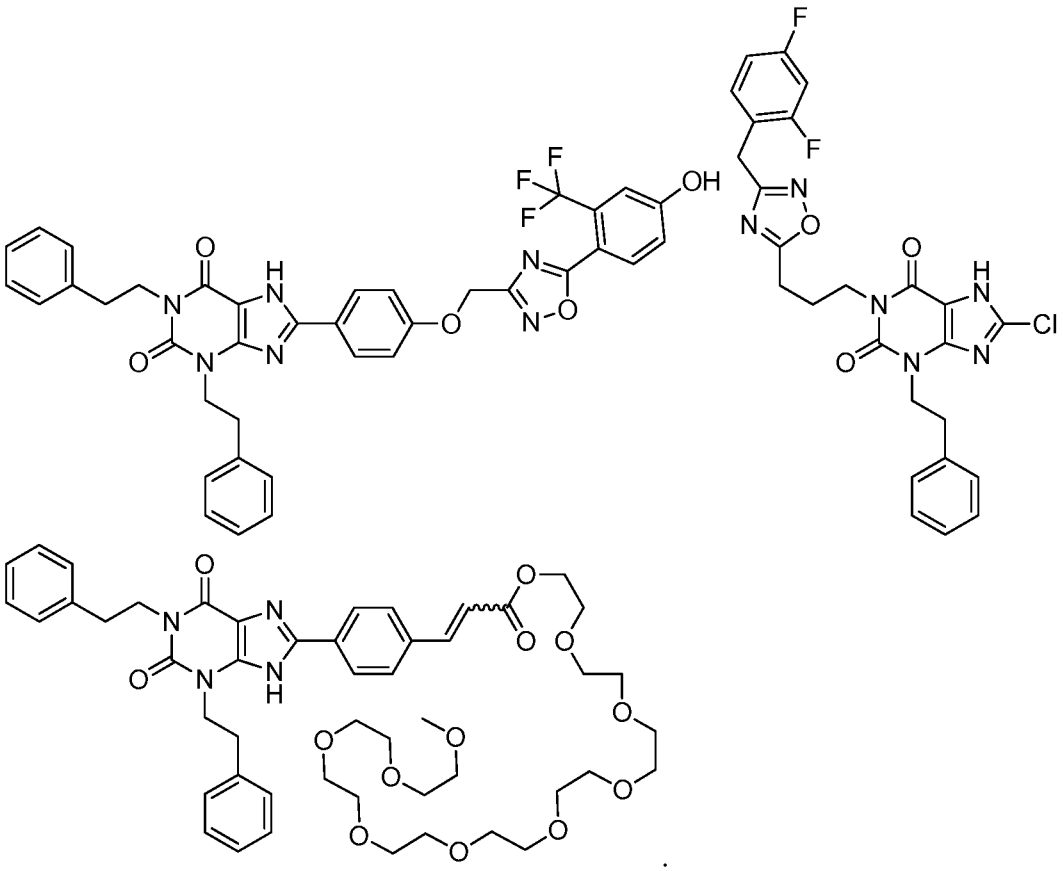


IX

or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, R^3, R^4, R^5, $R^{5'}$, R^7, and $R^{7'}$ is defined above and described in embodiments herein, both singly and in combination.

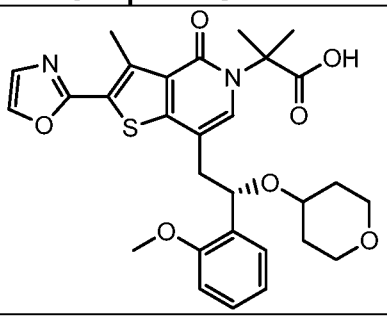
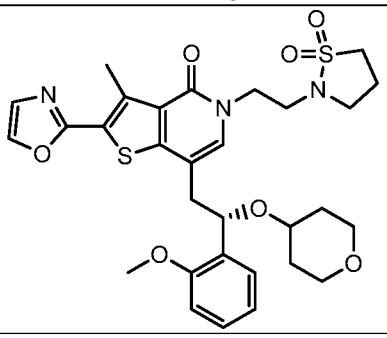
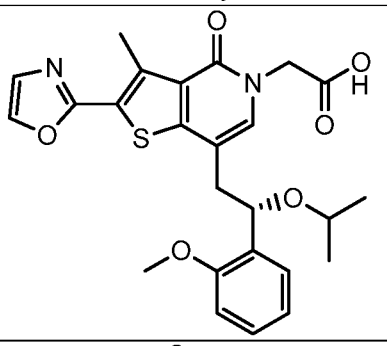
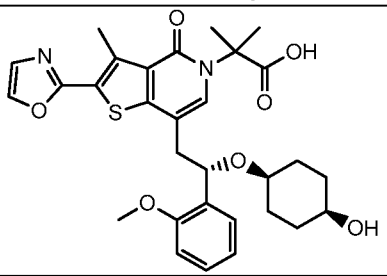
[0077] In some embodiments, compounds of the invention are not selected from the following formulas:

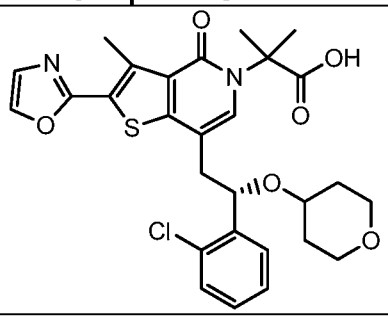
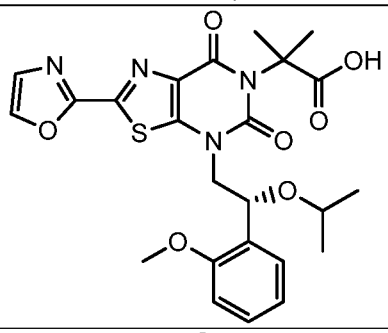
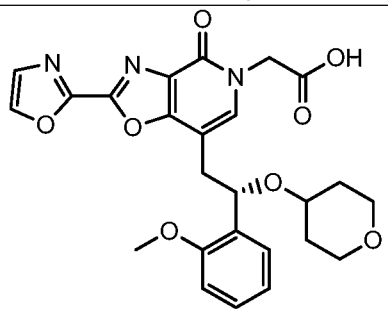
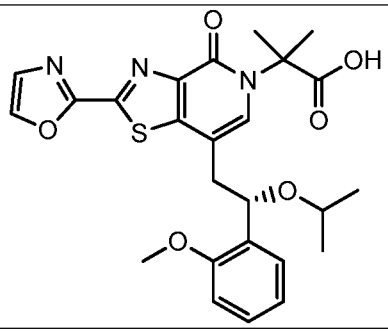


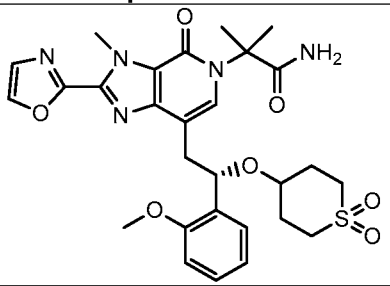
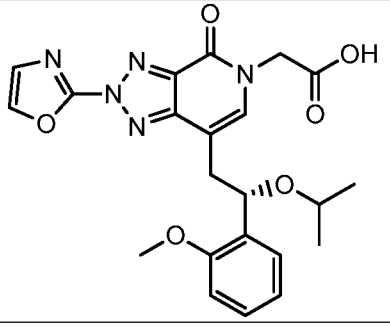
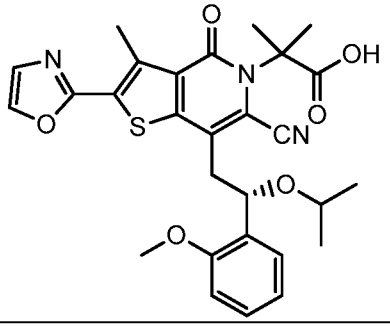
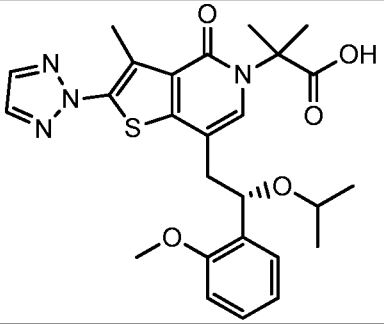
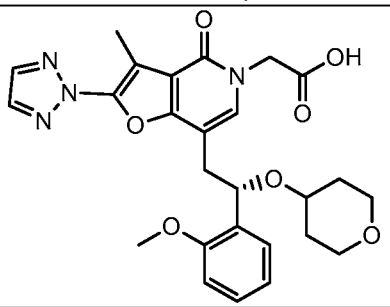


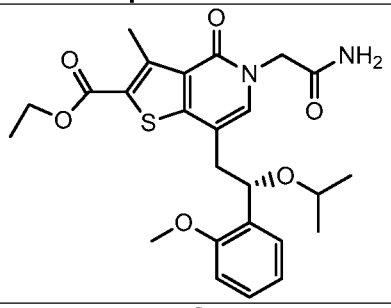
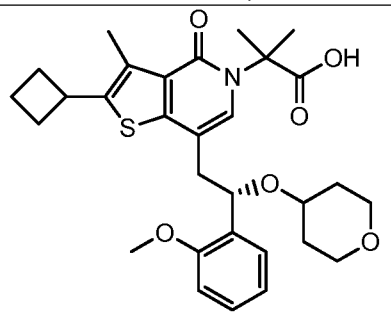
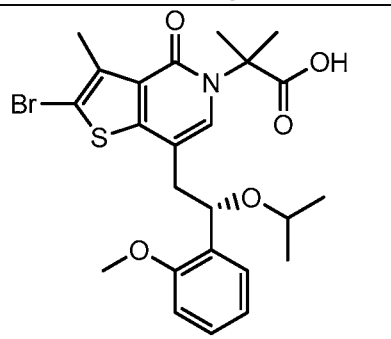
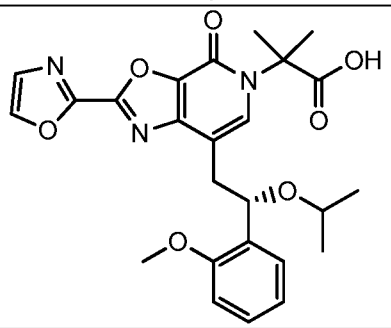
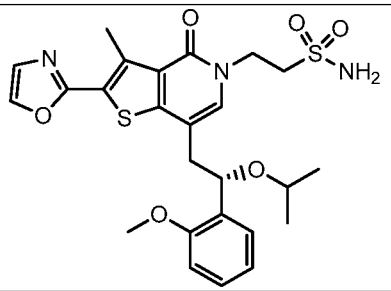
[0078] Exemplary compounds of formula **I** are set forth in Table 1, below:

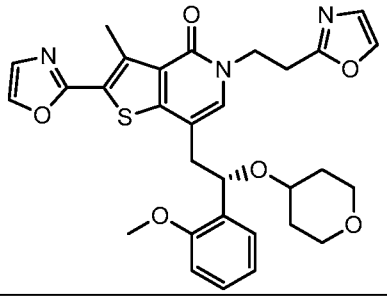
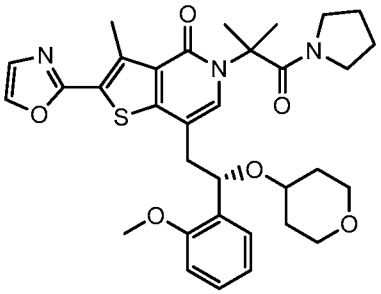
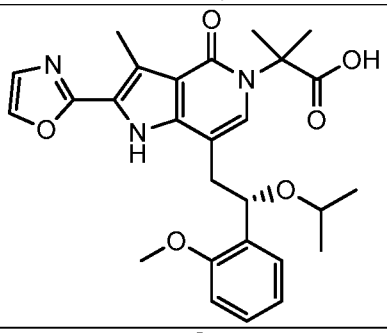
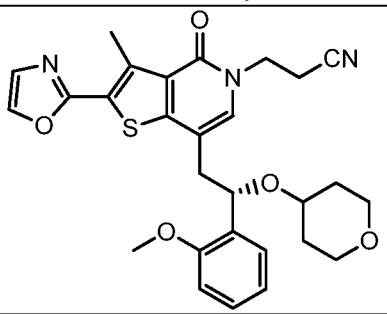
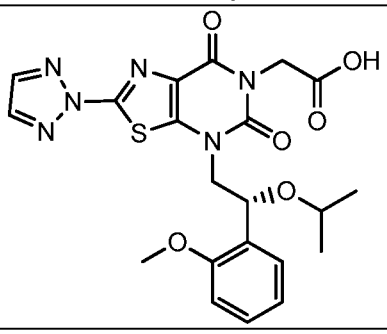
Table 1. Exemplary Compounds of Formula I

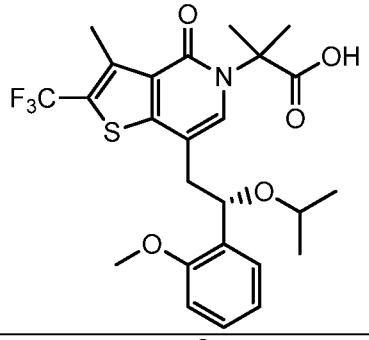
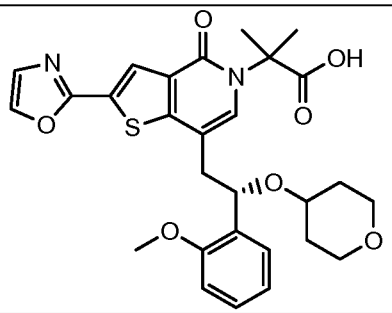
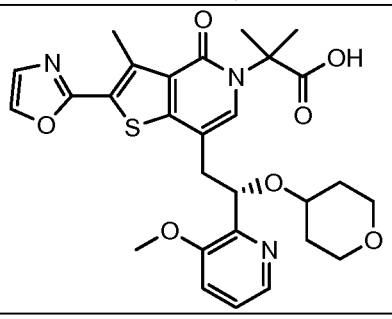
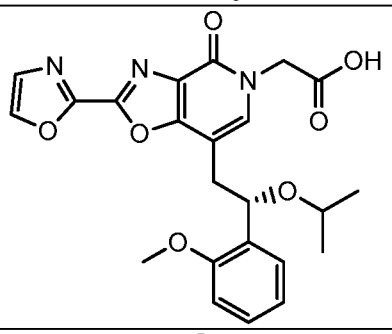
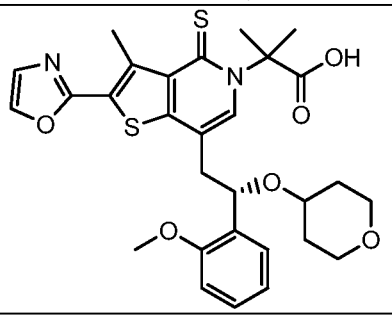
Cmpd #	Compound Structure
I-1	
I-2	
I-3	
I-4	

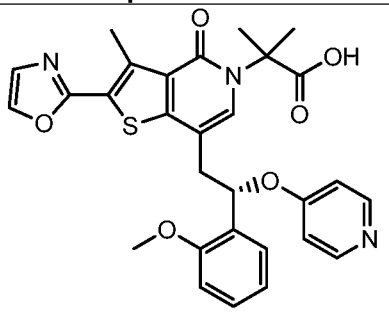
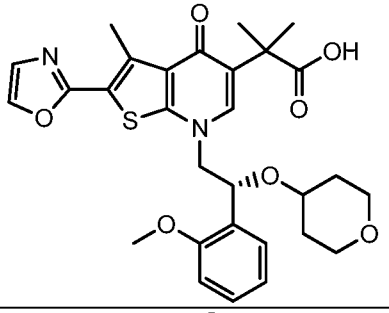
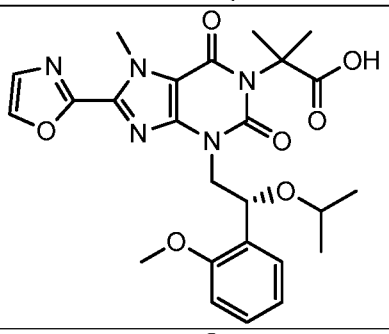
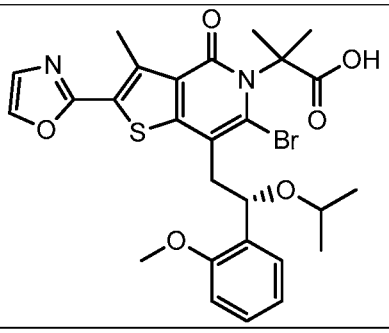
Cmpd #	Compound Structure
I-5	
I-6	
I-7	
I-8	

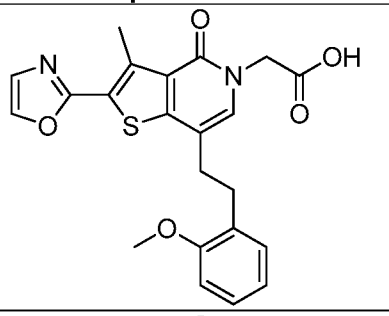
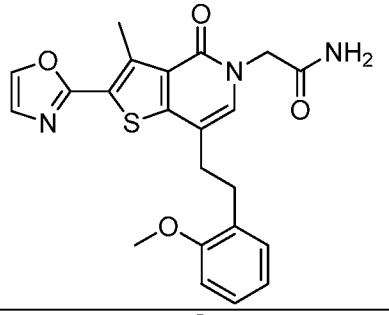
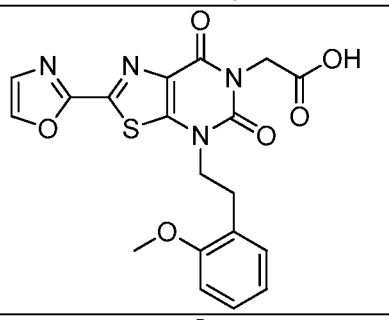
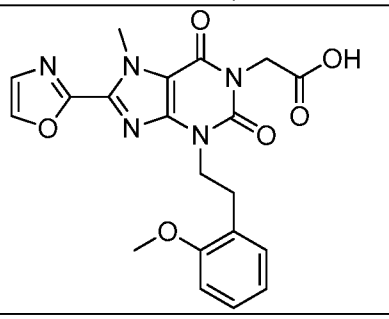
Cmpd #	Compound Structure
I-9	
I-10	
I-11	
I-12	
I-13	

Cmpd #	Compound Structure
I-14	
I-15	
I-16	
I-17	
I-18	

Cmpd #	Compound Structure
I-19	
I-20	
I-21	
I-22	
I-23	

Cmpd #	Compound Structure
I-24	
I-25	
I-26	
I-27	
I-28	

Cmpd #	Compound Structure
I-29	
I-30	
I-31	
I-32	

Cmpd #	Compound Structure
I-33	
I-34	
I-35	
I-36	

[0079] In certain embodiments, the present invention provides any compound selected from those depicted in Table 1, above, or a pharmaceutically acceptable salt thereof.

4. Uses, Formulation and Administration and Pharmaceutically acceptable compositions

[0080] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable salt, ester, or salt of ester thereof

and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably inhibit ACC, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably inhibit ACC, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[0081] The term "patient," as used herein, means an animal, preferably a mammal, and most preferably a human.

[0082] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0083] A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[0084] As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of ACC.

[0085] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally,

intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0086] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0087] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0088] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0089] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0090] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0091] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0092] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0093] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0094] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are

administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[0095] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0096] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[0097] Acetyl-CoA carboxylase (ACC) catalyzes the ATP-dependent carboxylation of acetyl-CoA to form malonyl-CoA. This reaction, which proceeds in two half-reactions, a biotin carboxylase (BC) reaction and a carboxyltransferase (CT) reaction, is the first committed step in fatty acid (FA) biosynthesis and is the rate-limiting reaction for the pathway. In addition to its role as a substrate in FA biosynthesis, malonyl-CoA, the product of the ACC-catalyzed reaction, also plays an important regulatory role in controlling mitochondrial FA uptake through allosteric inhibition of carnitine palmitoyltransferase I (CPT-I), the enzyme catalyzing the first committed step in mitochondrial FA oxidation. Malonyl-CoA, therefore, is a key metabolic signal for the control of FA production and utilization in response to dietary changes and altered nutritional requirements in animals, for example during exercise, and therefore plays a key role in controlling the switch between carbohydrate and fat utilization in liver and skeletal muscle [Harwood, 2005].

[0098] In mammals, ACC exists as two tissue-specific isozymes, ACC1 which is present in lipogenic tissues (liver, adipose) and ACC2, which is present in oxidative tissues (liver, heart, skeletal muscle). ACC1 and ACC2 are encoded by separate genes, display distinct cellular distributions, and share 75% overall amino acid sequence identity, except for an extension at the

N-terminus of ACC2 that direct ACC2 to the mitochondrial membrane. ACC1, which lacks this targeting sequence, is localized to the cytoplasm. In the heart and skeletal muscle, which have a limited capacity to synthesize fatty acids, the malonyl-CoA formed by ACC2 functions to regulate FA oxidation. In the liver, the malonyl-CoA formed in the cytoplasm through the actions of ACC1 is utilized for FA synthesis and elongation leading to triglyceride formation and VLDL production, whereas the malonyl-CoA formed at the mitochondrial surface by ACC2 acts to regulate FA oxidation [Tong and Harwood, *J. Cellular Biochem.* 99: 1476, 2006]. This compartmentalization of malonyl-CoA results from a combination of synthesis proximity [Abu-Elheiga *et al.,* PNAS (USA) 102: 12011, 2005] and the rapid action of malonyl-CoA decarboxylase [Cheng *et al., J. Med. Chem.* 49:1517, 2006].

[0099] Simultaneous inhibition of the enzymatic activities of ACC1 and ACC2 offers the ability to inhibit *de novo* FA production in lipogenic tissues (e.g. liver & adipose) while at the same time stimulating FA oxidation in oxidative tissues (e.g. liver & skeletal muscle) and therefore offers an attractive modality for favorably affecting, in a concerted manner, a multitude of cardiovascular risk factors associated with obesity, diabetes, insulin resistance, and the metabolic syndrome.

[00100] Several lines of evidence strongly support the concept of direct inhibition of ACC activity as an important therapeutic target for treating obesity, diabetes, insulin resistance, and the metabolic syndrome.

[00101] Abu-Elheiga *et al.* [*Proc. Natl. Acad. Sci.* USA 100:10207-10212, 2003] demonstrated that ACC2 knock-out mice exhibit reduced skeletal and cardiac muscle malonyl-CoA, increased muscle FA oxidation, reduced hepatic fat, reduced total body fat, elevated skeletal muscle uncoupling protein-3 (UCP3) which is indicative of increased energy expenditure, reduced body weight, reduced plasma free FAs, reduced plasma glucose, and reduced tissue glycogen, and are protected from diet-induced diabetes and obesity.

[00102] Savage *et al.* [*J. Clin. Invest.* 116: 817, 2006], using ACC1 and ACC2 antisense oligonucleotides, demonstrated stimulation of FA oxidation in isolated rat hepatocytes and in rats fed high-fat diets, and lowering of hepatic triglycerides, improvements in insulin sensitivity, reductions in hepatic glucose production, and increases in UCP1 mRNA in high fat-fed rats. These effects were greater when both ACC1 and ACC2 expression were suppressed than when either ACC1 or ACC2 expression alone was suppressed.

[00103] Harwood *et al.* [J. *Biol. Chem.* 278: 37099, 2003] demonstrated that the isozyme-nonselective ACC inhibitor, CP-640186, which equally inhibits ACC1 and ACC2 (IC_{50} = ~60 nM) isolated from rat, mouse, monkey and human without inhibiting either pyruvate carboxylase or propionyl-CoA carboxylase, reduced FA synthesis, triglyceride synthesis and secretion in Hep-G2 cells without affecting cholesterol synthesis, and reduced apoB secretion without affecting apoA1 secretion. CP-640186 also stimulated FA oxidation in C2C12 cells and in rat muscle slices and increased CPT-I activity in Hep-G2 cells. In experimental animals, CP-640186 acutely reduced malonyl-CoA concentration in both lipogenic and oxidative tissues in both the fed and fasted state, reduced liver and adipose tissue FA synthesis, and increased whole body FA oxidation. In sucrose-fed rats treated with CP-640186 for three weeks, CP-640186 time- and dose-dependently reduced liver, muscle and adipose triglycerides, reduced body weight due to selective fat reduction without reducing lean body mass, reduced leptin levels, reduced the hyperinsulinemia produced by the high sucrose diet without changing plasma glucose levels, and improved insulin sensitivity.

[00104] Saha *et al.* [*Diabetes* 55:A288, 2006] demonstrated stimulation of insulin sensitivity in insulin-resistant rat muscle tissue by CP-640186 within 30 min of compound administration, and studies by Furler *et al.* [*Diabetes* 55:A333, 2006] used dual tracer analysis to show that acute (46 min) treatment of rats with CP-640186 stimulated FA clearance without decreasing glucose clearance.

[00105] ACC is the rate-limiting enzyme in fatty acid synthesis and its product, malonyl CoA, serves as an important regulator of fatty acid oxidation. Hence, ACC inhibitors both reduce *de novo* lipid synthesis and promote the oxidation of existing fat. This dual effect on lipid metabolism raises the possibility that ACC inhibitors will be substantially more effective in reducing excess fat than other mechanisms. Furthermore, ACC inhibitors will impact insulin sensitivity, plasma and tissue triglycerides, and fasting plasma glucose as a consequence of whole-body and tissue-specific fat mass reduction without the need for poly-pharmacy.

[00106] ACC inhibitors need only access the liver and muscle in the peripheral compartment. Avoiding the CNS will address many of side effects associated with the late-stage obesity programs targeting CNS receptors. ACC inhibitors are also expected to have superior safety profiles to existing metabolic disease agents. For example, it is unlikely that an ACC inhibitor will precipitate life-threatening hypoglycemia as is often seen with insulin mimetics, insulin

secretagogues, and insulin degradation inhibitors. Also, since ACC inhibitors will reduce whole-body fat mass, they will be superior to the glitazones that increase whole-body fat mass as part of their mechanism of action.

[00107] A peripherally acting agent that causes significant weight loss and improves other metabolic endpoints fits well within the US FDA's requirements for approval of a new obesity agent. However, if an approval for obesity continues to be challenging in 5-7 years, ACC inhibitors could be approved for familial combined hyperlipidemia and non-alcoholic steatohepatitis (NASH). There are currently no marketed ACC inhibitors, so an isozyme-nonselective ACC inhibitor would represent first-in-class therapy for treating obesity and metabolic syndrome.

[00108] The activity of a compound utilized in this invention as an inhibitor of ACC or treatment for obesity or metabolic syndrome, may be assayed *in vitro* or *in vivo*. An in vivo assessment of the efficacy of the compounds of the invention may be made using an animal model of obesity or metabolic syndrome, e.g., a rodent or primate model. Cell-based assays may be performed using, e.g., a cell line isolated from a tissue that expresses ACC. Additionally, biochemical or mechanism-based assays, e.g., transcription assays using a purified protein, Northern blot, RT-PCR, etc., may be performed. *In vitro* assays include assays that determine cell morphology, protein expression, and/or the cytotoxicity, enzyme inhibitory activity, and/or the subsequent functional consequences of treatment of cells with compounds of the invention. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to protein or nucleic acid molecules within the cell. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/target molecule complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with purified proteins or nucleic acids bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of ACC are set forth in the Examples below. The aforementioned assays are exemplary and not intended to limit the scope of the invention. The skilled practitioner can appreciate that modifications can be made to conventional assays to develop equivalent assays that obtain the same result.

[00109] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or

more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00110] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a metabolic disorder or condition, cancer, a bacterial infection, a fungal infection, a parasitic infection (e.g. malaria), an autoimmune disorder, a neurodegenerative or neurological disorder, schizophrenia, a bone-related disorder, liver disease, or a cardiac disorder.

[00111] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a disease associated with ACC (Tong *et al.* "Acetyl-coenzyme A carboxylase: crucial metabolic enzyme and attractive target for drug discovery" Cell and Molecular Life Sciences (2005) 62, 1784-1803).

[00112] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a metabolic disorder, disease, or condition. In some embodiments, the metabolic disorder is obesity, metabolic syndrome, diabetes or diabetes-related disorders including Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM) and Type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM), impaired glucose tolerance, insulin resistance, hyperglycemia, diabetic complications, including, but not limited to atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, nephropathy, hypertension, neuropathy and nephropathy; obesity comorbidities including but not limited to metabolic syndrome, dyslipidemia, Type III dyslipidemia, hypertension, insulin resistance, diabetes (including Type 1 and Type 2 diabetes), coronary artery disease, and heart failure. In some embodiments, the metabolic disorder, disease or condition is non-alcoholic fatty liver disease or hepatic insulin resistance.

[00113] In some embodiments, the present invention provides a method of treating a metabolic disorder, disease, or condition described herein, comprising administering a compound

of the invention in conjunction with one or more pharmaceutical agents. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-obesity agents (including appetite suppressants), anti-diabetic agents, anti-hyperglycemic agents, lipid lowering agents, and anti-hypertensive agents.

[00114] Suitable lipid lowering agents that can be used in conjunction with compounds of the present invention include but are not limited to, bile acid sequestrants, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, cholesterol absorption inhibitors, acyl coenzyme A-cholesterol acyl transferase (ACAT) inhibitors, CETP inhibitors, squalene synthetase inhibitors, PPAR-alpha agonists, FXR receptor modulators, LXR receptor modulators, lipoprotein synthesis inhibitors, renin-angiotensin system inhibitors, PPAR-delta partial agonists, bile acid reabsorption inhibitors, PPAR-gamma agonists, triglyceride synthesis inhibitors, microsomal triglyceride transport inhibitors, transcription modulators, squalene epoxidase inhibitors, low density lipoprotein receptor inducers, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, niacin, and niacin-bound chromium.

[00115] Suitable anti-hypertensive agents that can be used in conjunction with compounds of the present invention include but are not limited to diuretics, beta-adrenergic blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, neutral endopeptidase inhibitors, endothelin antagonists, vasodilators, angiotensin II receptor antagonists, alpha/beta adrenergic blockers, alpha 1 blockers, alpha 2 agonists, aldosterone inhibitors, mineralocorticoid receptor inhibitors, renin inhibitors, and angiopoietin 2 binding agents.

[00116] Suitable anti-diabetic agents that can be used in conjunction with compounds of the present invention include but are not limited to other acetyl-CoA carboxylase (ACC) inhibitors, DGAT-1 inhibitors, AZD7687, LCQ908, DGAT-2 inhibitors, monoacylglycerol O-acyltransferase inhibitors, PDE-10 inhibitors, AMPK activators, sulfonylureas (e.g. acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, blimipiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, tolbutamide), meglitinides, alpha-amylase inhibitors (e.g. tendamistat, treastatin, AL-3688), alpha-glucoside hydrolase inhibitors (e.g. acarbose), alpha-glucosidase inhibitors (e.g. adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, sarbostatin), PPAR-gamma agonists (e.g. balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone, rosiglitazone, troglitazone), PPAR-alpha/gamma agonists (e.g. CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449,

LR-90, MK-0767, SB-219994), biguanides (e.g. metformin, buformin), GLP-1 modulators (exendin-3, exendin-4), liraglutide, albiglutide, exenatide (Byetta), taspoglutide, lixisenatide, dulaglutide, semaglutide, N,N-9924, TTP-054, PTP-1B inhibitors (trodusquemine, hyrtiosal extract), SIRT-1 inhibitors (e.g. resveratrol, GSK2245840, GSK184072), DPP-IV inhibitors (e.g. sitagliptin, vildagliptin, alogliptin, dutogliptin, linagliptin, saxagliptin), insulin secretagogues, fatty acid oxidation inhibitors, A2 antagonists, JNK inhibitors, glucokinase activators (e.g. TTP-399, TTP-355, TTP-547, AZD1656, ARRY403, MK-0599, TAK-329, AZD5658, GKM-001), insulin, insulin mimetics, glycogen phosphorylase inhibitors (e.g. GSK1362885), VPAC2 receptor agonists, SGLT2 inhibitors (dapagliflozin, canagliflozin, BI-10733, tofogliflozin, ASP-1941, THR1474, TS-071, ISIS388626, LX4211), glucagon receptor modulators, GPR119 modulators (e.g. MBX-2982, GSK1292263, APD597, PSN821), FGF21 derivatives, TGR5 (GPBAR1) receptor agonists (e.g. INT777), GPR40 agonists (e.g. TAK-875), GPR120 agonists, nicotinic acid receptor (HM74A) activators, SGLT1 inhibitors (e.g. GSK1614235), carnitine palmitoyl transferase enzyme inhibitors, fructose 1,6-diphosphatase inhibitors, aldose reductase inhibitors, mineralocorticoid receptor inhibitors, TORC2 inhibitors, CCR2 inhibitors, CCR5 inhibitors, PKC (e.g. PKC-alpha, PKC-beta, PKC-gamma) inhibitors, fatty acid synthetase inhibitors, serine palmitoyl transferase inhibitors, GPR81 modulators, GPR39 modulators, GPR43 modulators, GPR41 modulators, GPR105 modulators, Kv1.3 inhibitors, retinol binding protein 4 inhibitors, glucocorticoid receptor modulators, somatostatin receptor (e.g. SSTR1, SSTR2, SSTR3, SSTR5) inhibitors, PDHK2 inhibitors, PDHK4 inhibitors, MAP4K4 inhibitors, IL1-beta modulators, and RXR-alpha modulators.

[00117] Suitable anti-obesity agents include but are not limited to, 11-beta-hydroxysteroid dehydrogenase 1 inhibitors, stearoyl-CoA desaturase (SCD-1) inhibitors, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors (e.g. sibutramine), sympathomimetic agents, beta-3-adrenergic receptor agonists, dopamine receptor agonists (e.g. bromocriptine), melanocyte-stimulating hormone and analogs thereof, 5-HT_{2C} agonists (e.g. lorcaserin / Belviq), melanin concentrating hormone antagonists, leptin, leptin analogs, leptin agonists, galanin antagonists, lipase inhibitors (e.g. tetrahydrolipstatin / Orlistat), anorectic agents (e.g. bombesin agonists), NPY antagonists (e.g. velneperit), PYY_{3-36} (and analogs thereof), BRS3 modulators, opioid receptor mixed antagonists, thyromimetic agents, dehydroepiandrosterone, glucocorticoid agonists or antagonists, orexin antagonists, GLP-1 agonists, ciliary neurotrophic factors (e.g.

Axokine), human agouti-related protein (AGRP) inhibitors, H3 antagonists or inverse agonists, neuromedin U agonists, MTP/ApoB inhibitors (e.g. gut-selective MTP inhibitors such as dirlotapide, JTT130, Usistapide, SLX4090), MetAp2 inhibitors (e.g. ZGN-433), agents with mixed modulatory activity at two or more of glucagon, GIP, and GLP1 receptors (e.g. MAR-701, ZP2929), norepinephrine reuptake inhibitors, opioid antagonists (e.g. naltrexone), CB1 receptor antagonists or inverse agonists, ghrelin agonists or antagonists, oxyntomodulin and analogs thereof, monoamine uptake inhibitors (e.g. tesofensine), and combination agents (e.g. buproprion plus zonisamide (Empatic), pramlintide plus metreleptin, buproprion plus naltrexone (Contrave), phentermine plus topiramate (Qsymia).

[00118] In some embodiments, the anti-obesity agents used in combination with compounds of the invention are selected from gut-selective MTP inhibitors (e.g. dirlotapide, mitratapide, implitapide, R56918), CCK-A agonists, 5-HT_{2C} agonists (e.g. lorcaserin / Belviq), MCR4 agonists, lipase inhibitors (e.g. Cetilistat), PYY_{3-36} (including analogs and PEGylated analogs thereof), opioid antagonists (e.g. naltrexone), oleoyl estrone, obinepitide, pramlintide, tesofensine, leptin, bromocriptine, orlistat, AOD-9604, and sibutramine.

[00119] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a LKB1 or Kras associated disease. In some embodiments, the LKB1 or Kras associated disease is selected from hepatocellular carcinoma, LKB1 mutant cancers, LKB1 loss of heterozygosity (LOH) driven cancers, Kras mutant cancers, Peutz-Jeghers syndrome (PJS), Cowden's disease (CD), and tubeous sclerosis (TS) (Makowski *et al.* "Role of LKB1 in Lung Cancer Development" British Journal of Cancer (2008) 99, 683-688). In some embodiments, the LKB1 or Kras associated disease is a Kras positive/LKB1 deficient lung tumor.

[00120] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer, or inhibiting the growth of or inducing apoptosis in cancer cells (Wang *et al.* "Acetyl-CoA Carboxylase-alpha Inhibitor TOFA Induces Human Cancer Cell Apoptosis" Biochem Biophys Res Commun. (2009) 385(3), 302-306; Chajes *et al.* "Acetyl-CoA Carboxylase alpha Is Essential to Breast Cancer Cell Survival" Cancer Res. (2006) 66, 5287-5294; Beckers *et al.* "Chemical Inhibition of Acetyl-CoA

Carboxylase Induces Growth Arrest and Cytotoxicity Selectivity in Cancer Cells" Cancer Res. (2007) 8180-8187; Brusselmans *et al.* "RNA Interference-Mediated Silencing of the Acetyl-CoA-Carboxylase-alpha Gene Induces Growth Inhibition and Apoptosis of Prostate Cancer Cells" Cancer Res. (2005) 65, 6719-6725; Brunet *et al.* "BRCA1 and Acetyl-CoA Carboxylase: The Metabolic Syndrom of Breast Cancer" Molecular Carcinogenesis (2008) 47, 157-163; Cairns *et al.* "Regulation of Cancer Cell Metabolism" (2011) 11, 85-95; Chiaradonna *et al.* "From Cancer Metabolism to New Biomarkers and Drug Targets" Biotechnology Advances (2012) 30, 30-51).

[00121] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a melanoma. In some embodiments, the melanoma is one bearing an activated MAPK pathway (Petti *et al.* "AMPK activators inhibit the proliferation of human melanomas bearing the activated MAPK pathway" Melanoma Research (2012) 22, 341-350).

[00122] Compounds of the present invention find special utility in triple negative breast cancer, as the tumor suppressor protein BRCA1 binds and stabilizes the inactive form of ACC, thus upregulating de novo lipid synthesis, resulting in cancer cell proliferation Brunet et al. "BRCA1 and acetyl-CoA carboxylase: the metabolic syndrome of breast cancer" Mol. Carcinog. (2008) 47(2), 157-163.

[00123] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a liposarcoma. Liposarcomas have been shown to depend on *de* novo long-chain fatty acid synthesis for growth, and inhibition of ACC by soraphen A inhibited lipogenesis as well as tumor cell growth (Olsen *et al.* "Fatty acid synthesis is a therapeutic target in human liposarcoma" International J. of Oncology (2010) 36, 1309-1314).

[00124] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a liver disease. In some embodiments, the liver disease is selected from hepatitis C, hepatocellular carcinoma, familial combined hyperlipidemia

and non-alcoholic steatohepatitis (NASH), liver cancer, cholangiocarcinoma, angiosarcoma, hemangiosarcoma, and progressive familial intrahepatic cholestasis.

[00125] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a bacterial infection or inhibiting the growth of bacteria.

[00126] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a fungal infection or inhibiting the growth of fungal cells (Shen *et al.* "A Mechanism for the Potent Inhibition of Eukaryotic Acetyl-Coenzyme A Carboxylase by Soraphen A, a Macrocyclic Polyketide Natural Product" Molecular Cell (2004) 16, 881-891). In some embodiments, the fungal infection occurs in a human. In some embodiments, the fungal infection is a Candida infection.

[00127] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a bacterial infection (Tong, L. et al. J. Cell. Biochem. (2006) 99, 1476-1488).

[00128] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a viral infection (Munger et al. Nat. Biotechnol. (2008) 26, 1179-1186). In some embodiments, the viral infection is Hepatitis C.

[00129] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a neurological disease (Henderson et al. Neurotherapeutics (2008) 5, 470-480; Costantini et al. Neurosci. (2008) 9 Suppl. 2:S16; Baranano et al. Curr. Treat. Opin. Neurol. (2008) 10, 410-419).

[00130] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a parasitic infection or inhibiting the growth of parasites (e.g. malaria and toxoplasma: Gornicki *et al.* "Apicoplast fatty acid biosynthesis as a target for medical intervention in apicomplexan parasites" International Journal of Parasitology

(2003) 33, 885-896; Zuther *et al.* "Growth of *Toxoplasma gondii* is inhibited by aryloxyphenoxypropionate herbicides targeting acetyl-CoA carboxylase" PNAS (1999) 96 (23) 13387-13392).

[00131] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cardiac disorder. In some embodiments, the cardiac disorder is cardiac hypertrophy. In some embodiments the cardiac disorder is treated or its severity lessened by the cardioprotective mechanism resulting from increased fatty acid oxidation via ACC inhibition (Kolwicz *et al.* "Cardiac-specific deletion of acetyl CoA carboxylase 2 (ACC2) prevents metabolic remodeling during pressure-overload hypertrophy" Circ. Res. (2012); DOI: 10.1161/CIRCRESAHA.112.268128).

[00132] In certain embodiments, the compounds and compositions, according to the method of the present invention, may be used as herbicides. In some embodiments, the present invention provides a method to inhibit the growth or viability of plants comprising treating plants with compounds of the present invention. In some embodiments of the present invention, compounds of the present invention can be used to inhibit the growth or viability of plants by inhibiting ACC. In some embodiments, the method of the present invention comprises using compounds of the present invention to inhibit fatty acid production in or increase fatty acid oxidation in plants.

[00133] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental

with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00134] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00135] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00136] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00137] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid

compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00138] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00139] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00140] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium

lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00141] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00142] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00143] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches,

which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00144] According to one embodiment, the invention relates to a method of inhibiting ACC in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00145] In certain embodiments, the invention relates to a method of modulating fatty acid levels in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00146] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00147] Inhibition of enzymes in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to biological assays, gene expression studies, and biological target identification.

[00148] Another embodiment of the present invention relates to a method of inhibiting ACC in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00149] According to another embodiment, the invention relates to a method of inhibiting fatty acid production, stimulating fatty acid oxidation, or both, in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. According to certain embodiments, the invention relates to a method of inhibiting fatty acid production, stimulating fatty acid oxidation, or both in a patient, leading to decreasing obesity or alleviating symptoms of metabolic syndrome, comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by ACC, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00150] In some embodiments the compounds and compositions of the present invention may be used in a method of treating obesity or another metabolic disorder. In certain embodiments the compounds and compositions of the present invention may be used to treat obesity or other metabolic disorder in a mammal. In certain embodiments the mammal is a human patient. In certain embodiments the compounds and compositions of the present invention may be used to treat obesity or other metabolic disorder in a human patient.

[00151] In some embodiments the present invention provides a method of treating obesity or another metabolic disorder, comprising administering a compound or composition of the present invention to a patient with obesity or another metabolic disorder. In certain embodiments the method of treating obesity or another metabolic disorder comprises administering compounds and compositions of the present invention to a mammal. In certain embodiments the mammal is a human. In some embodiments the metabolic disorder is dyslipidemia, Type III dyslipidemia, or hyperlipidemia. In some embodiments the hyperlipidemia is hypertriglyceridemia. In some embodiments, the obesity is a symptom of Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome or MOMO syndrome. In some embodiments, the obesity is a side effect of the administration of another medication, including but not limited to insulin, sulfunylureas, thiazolidinediones, antipsychotics, antidepressants, steroids, anticonvulsants (including phenytoin and valproate), pizotifen, or hormonal contraceptives.

[00152] In certain embodiments, the present invention provides a method of treating cancer or another proliferative disorder, comprising administering a compound or composition of the present invention to a patient with cancer or another proliferative disorder. In certain embodiments, the method of treating cancer or another proliferative disorder comprises administering compounds and compositions of the present invention to a mammal. In certain embodiments, the mammal is a human.

[00153] As used herein, the terms "inhibition of cancer" and "inhibition of cancer cell proliferation" refer to the inhibition of the growth, division, maturation or viability of cancer cells, and/or causing the death of cancer cells, individually or in aggregate with other cancer cells, by cytotoxicity, nutrient depletion, or the induction of apoptosis.

[00154] Examples of tissues containing cancerous cells whose proliferation is inhibited by the compounds and compositions described herein and against which the methods described herein are useful include but are not limited to breast, prostate, brain, blood, bone marrow, liver,

pancreas, skin, kidney, colon, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, and stomach.

[00155] In some embodiments, the cancer treated by compounds or compositions of the invention is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer, brain cancer, lymphoma or colon cancer. In certain embodiments, the cancer is a primary effusion lymphoma (PEL). In certain preferred embodiments the cancer to be treated by compounds or compositions of the invention is one bearing an activated MAPK pathway. In some embodiments the cancer bearing an activated MAPK pathway is a melanoma. In certain preferred embodiments the cancer treated by compounds or compositions of the invention is one associated with BRCA1 mutation. In an especially preferred embodiment, the cancer treated by compounds or compositions of the invention is a triple negative breast cancer. In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC).

[00156] In certain embodiments, the disease which can be treated by compounds of the invention are neurological disorders. In some embodiments, the neurological disorder is Alzheimer's Disease, Parkinson's Disease, epilepsy, ischemia, Age Associated Memory Impairment, Mild Cognitive Impairment, Friedreich's Ataxia, GLUT1-deficient epilepsy, Leprechaunism, Rabson-Mendenhall Syndrome, Coronary Arterial Bypass Graft dementia, anaesthesia-induced memory loss, amyotrophic lateral sclerosis, gliomaor Huntington's Disease.

[00157] In certain embodiments, the disease which can be treated by compounds of the invention is an infectious disease. In some embodiments, the infectious disease is a viral infection. In some embodiments the viral infection is cytomegalovirus infection or influenza infection. In some embodiments, the infectious disease is a fungal infection. In some embodiments, the infectious disease is a bacterial infection.

[00158] In some embodiments, compounds of the present invention can be used in the treatment of

[00159] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional

therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00160] In certain embodiments, a provided compound, or composition thereof, is administered in combination with another inhibitor of ACC or antiobesity agent. In some embodiments, a provided compound, or composition thereof, is administered in combination with one or more other therapeutic agents. Such therapeutic agents agents include, but are not limited to agents such as orlistat (Xenical), CNS stimulants, Qsymia, or Belviq.

[00161] In certain embodiments, a provided compound, or a composition thereof, is administered in combination with another anti-cancer, cytotoxin, or chemotherapeutic agent, to a patient in need thereof.

[00162] In certain embodiments, the anti-cancer or chemotherapeutic agents used in combination with compounds or compositions of the invention include, but are not limited to metformin, phenformin, buformin, imatinib, nilotinib, gefitinib, sunitinib, carfilzomib, salinosporamide A, retinoic acid, cisplatin, carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide, azathioprine, mercaptopurine, doxifluridine, fluorouracil, gemcitabine, methotrexate, tioguanine, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, etoposide, teniposide, tafluposide, paclitaxel, docetaxel, irinotecan, topotecan, amsacrine, actinomycin, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, plicamycin, mitomycin, mitoxantrone, melphalan, busulfan, capecitabine, pemetrexed, epothilones, 13-cis-Retinoic Acid, 2-CdA, 2-Chlorodeoxyadenosine, 5-Azacitidine, 5-Fluorouracil, 5-FU, 6-Mercaptopurine, 6-MP, 6-TG, 6-Thioguanine, Abraxane, Accutane ®, Actinomycin-D, Adriamycin ®, Adrucil ®, Afinitor ®, Agrylin ®, Ala-Cort ®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ ®, Alkeran ®, All-transretinoic Acid, Alpha Interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron ®, Anastrozole, Arabinosylcytosine, Ara-C, Aranesp ®, Aredia ®, Arimidex ®, Aromasin ®, Arranon ®, Arsenic Trioxide, Arzerra™, Asparaginase, ATRA, Avastin ®, Azacitidine, BCG, BCNU, Bendamustine, Bevacizumab, Bexarotene, BEXXAR ®, Bicalutamide, BiCNU, Blenoxane ®, Bleomycin, Bortezomib, Busulfan, Busulfex ®, C225, Calcium Leucovorin, Campath ®, Camptosar ®, Camptothecin-11, Capecitabine, Carac ™, Carboplatin, Carmustine, Carmustine Wafer, Casodex ®, CC-5013, CCI-779, CCNU, CDDP, CeeNU, Cerubidine ®, Cetuximab, Chlorambucil, Citrovorum Factor, Cladribine, Cortisone, Cosmegen ®, CPT-11,

Cytadren ®, Cytosar-U ®, Cytoxan ®, Dacarbazine, Dacogen, Dactinomycin, Darbepoetin Alfa, Dasatinib, Daunomycin, Daunorubicin Hydrochloride, Daunorubicin Liposomal, DaunoXome ®, Decadron, Decitabine, Delta-Cortef ®, Deltasone ®, Denileukin, Diftitox, DepoCyt ™, Dexamethasone, Dexamethasone Acetate, Dexamethasone Sodium Phosphate, Dexasone, Dexrazoxane, DHAD, DIC, Diodex, Docetaxel, Doxil ®, Doxorubicin, Doxorubicin Liposomal, Droxia ™, DTIC, DTIC-Dome ®, Duralone ®, Efudex ®, Eligard ™, Ellence ™, Eloxatin ™, Elspar ®, Emcyt ®, Epirubicin, Epoetin Alfa, Erbitux, Erlotinib, Erwinia L-asparaginase, Estramustine, Ethyol, Etopophos ®, Etoposide, Etoposide Phosphate, Eulexin ®, Everolimus, Evista ®, Exemestane, Fareston ®, Faslodex ®, Femara ®, Filgrastim, Floxuridine, Fludara ®, Fludarabine, Fluoroplex ®, Fluorouracil, Fluorouracil (cream), Fluoxymesterone, Flutamide, Folinic Acid, FUDR ®, Fulvestrant, G-CSF, Gefitinib, Gemcitabine, Gemtuzumab, ozogamicin, ,Gemzar Gleevec ™, Gliadel ® Wafer, GM-CSF, Goserelin, Granulocyte - Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor, Halotestin ®, Herceptin ®, Hexadrol, Hexalen ®, Hexamethylmelamine, HMM, Hycamtin ®, Hydrea ®, Hydrocort Acetate ®, Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortone Phosphate, Hydroxyurea, Ibritumomab, Ibritumomab, Tiuxetan, Idamycin ®, Idarubicin Ifex ®, IFN-alpha, Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon alfa, Interferon Alfa-2b (PEG Conjugate), Interleukin-2, Interleukin-11, Intron A® (interferon alfa-2b), Iressa ®, Irinotecan, Isotretinoin, Ixabepilone, Ixempra ™, Kidrolase ®, Lanacort ®, Lapatinib, L-asparaginase, LCR, Lenalidomide, Letrozole, Leucovorin, Leukeran, Leukine ™, Leuprolide, Leurocristine, Leustatin ™, Liposomal Ara-C, Liquid Pred ®, Lomustine, L-PAM, L-Sarcolysin, Lupron ®, Lupron Depot ®, Matulane ®, Maxidex, Mechlorethamine, Mechlorethamine Hydrochloride, Medralone ®, Medrol ®, Megace ®, Megestrol, Megestrol Acetate, Melphalan, Mercaptopurine, Mesna, Mesnex ™, Methotrexate, Methotrexate Sodium, Methylprednisolone, Meticorten ®, Mitomycin, Mitomycin-C, Mitoxantrone, M-Prednisol ®, MTC, MTX, Mustargen ®, Mustine, Mutamycin ®, Myleran ®, Mylocel ™, Mylotarg ®, Navelbine ®, Nelarabine, Neosar ®, Neulasta ™, Neumega ®, Neupogen ®, Nexavar ®, Nilandron ®, Nilotinib, Nilutamide, Nipent ®, Nitrogen Mustard, Novaldex ®, Novantrone ®, Nplate, Octreotide, Octreotide acetate, Ofatumumab, Oncospar ®, Oncovin ®, Ontak ®, Onxal ™, Oprelvekin, Orapred ®, Orasone ®, Oxaliplatin, Paclitaxel, Paclitaxel Protein-bound, Pamidronate, Panitumumab, Panretin ®, Paraplatin ®, Pazopanib,

Pediapred ®, PEG Interferon, Pegaspargase, Pegfilgrastim, PEG-INTRON ™, PEG-L-asparaginase, PEMETREXED, Pentostatin, Phenylalanine Mustard, Platinol ®, Platinol-AQ ®, Prednisolone, Prednisone, Prelone ®, Procarbazine, PROCRIT ®, Proleukin ®, Prolifeprospan 20 with Carmustine Implant, Purinethol ®, Raloxifene, Revlimid ®, Rheumatrex ®, Rituxan ®, Rituximab, Roferon-A ® (Interferon Alfa-2a), Romiplostim, Rubex ®, Rubidomycin hydrochloride, Sandostatin ®, Sandostatin LAR ®, Sargramostim, Solu-Cortef ®, Solu-Medrol ®, Sorafenib, SPRYCEL ™, STI-571, Streptozocin, SU11248, Sunitinib, Sutent ®, Tamoxifen, Tarceva ®, Targretin ®, Tasigna ®, Taxol ®, Taxotere ®, Temodar ®, Temozolomide, Temsirolimus, Teniposide, TESPA, Thalidomide, Thalomid ®, TheraCys ®, Thioguanine, Thioguanine Tabloid ®, Thiophosphoamide, Thioplex ®, Thiotepa, TICE ®, Toposar ®, Topotecan, Toremifene, Torisel ®, Tositumomab, Trastuzumab, Treanda ®, Tretinoin, Trexall ™, Trisenox ®, TSPA, TYKERB ®, VCR, Vectibix ™, Velban ®, Velcade ®, VePesid ®, Vesanoid ®, Viadur ™, Vidaza ®, Vinblastine, Vinblastine Sulfate, Vincasar Pfs ®, Vincristine, Vinorelbine, Vinorelbine tartrate, VLB, VM-26, Vorinostat, Votrient, VP-16, Vumon ®, Xeloda ®, Zanosar ®, Zevalin ™, Zinecard ®, Zoladex ®, Zoledronic acid, Zolinza, Zometa ®, or combinations of any of the above.

[00163] In certain embodiments, compounds of the present invention may be administered together with a biguanide selected from metformin, phenformin, or buformin, to a patient in need thereof. In certain embodiments, the patient administered a combination of a compound of the invention and a biguanide is suffering from a cancer, obesity, a liver disease, diabetes or two or more of the above.

[00164] In certain embodiments, a combination of 2 or more therapeutic agents may be administered together with compounds of the invention. In certain embodiments, a combination of 3 or more therapeutic agents may be administered with compounds of the invention.

[00165] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: vitamins and nutritional supplements, cancer vaccines, treatments for neutropenia (e.g. G-CSF, filgrastim, lenograstim), treatments for thrombocytopenia (e.g. blood transfusion, erythropoietin), PI3 kinase (PI3K) inhibitors, MEK inhibitors, mTOR inhibitors, CPT1 inhibitors, AMPK activators, PCSK9 inhibitors, SREBP site 1 protease inhibitors, HMG CoA-reductase inhibitors, antiemetics (e.g. 5-HT_3 receptor antagonists, dopamine antagonists, NK1 receptor antagonists, histamine receptor antagonists, cannabinoids, benzodiazepines, or

anticholinergics), treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins, fibrates, cholesterol absorption inhibitors, bile acid sequestrants, and niacin; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating immunodeficiency disorders such as gamma globulin; and anti-diabetic agents such as biguanides (metformin, phenformin, buformin), thiazolidinediones (rosiglitazone, pioglitazone, troglitazone), sulfonylureas (tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide), meglitinides (repaglinide, nateglinide), alpha-glucosidase inhibitors (miglitol, acarbose), incretin mimetics (exenatide, liraglutide, taspoglutide), gastric inhibitory peptide analogs, DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin, alogliptin), amylin analogs (pramlintide), and insulin and insulin analogs.

[00166] In certain embodiments, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with antisense agents, a monoclonal or polyclonal antibody or an siRNA therapeutic.

[00167] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents

may be submitted simultaneously, sequentially or within a period of time from one another, normally within five hours from one another.

[00168] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of formula **I**, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00169] The amount of both, an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive can be administered.

[00170] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 - 100 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00171] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00172] The invention further refers to an agricultural composition comprising at least one compound of formula I as defined above or an agriculturally acceptable salt thereof and a liquid or solid carrier. Suitable carriers, as well as auxiliaries and further active compounds which may also be contained in the composition of the invention are defined below.

[00173] Suitable "agriculturally acceptable salts" include but are not limited to the salts of those cations or the acid addition salts of those acids whose cations and anions, respectively, have no adverse effect on the fungicidal action of the compounds of formula I. Thus, suitable cations are in particular the ions of the alkali metals, preferably sodium and potassium, of the alkaline earth metals, preferably calcium, magnesium and barium, and of the transition metals, preferably manganese, copper, zinc and iron, and also the ammonium ion which, if desired, may carry one to four C_1-C_4-alkyl substituents and/or one phenyl or benzyl substituent, preferably diisopropylammonium, tetramethylammonium, tetrabutylammonium, trimethylbenzylammonium. Additional agriculturally acceptable salts include phosphonium ions, sulfonium ions, preferably tri(C_1-C_4-alkyl)sulfonium and sulfoxonium ions, preferably tri(C_1-C_4-alkyl)sulfoxonium. Anions of useful acid addition salts are primarily chloride, bromide, fluoride, hydrogen- sulfate, sulfate, dihydrogenphosphate, hydrogenphosphate, phosphate, nitrate, bicarbonate, carbonate, hexafluorosilicate, hexafluorophosphate, benzoate, and also the anions of C_1-C_4-alkanoic acids, preferably formate, acetate, propionate and butyrate. Such agriculturally acceptable acid addition salts can be formed by reacting compounds of formula I bearing a basic ionizable group with an acid of the corresponding anion, preferably hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or nitric acid.

[00174] The compounds of formula I and the compositions according to the invention, respectively, are suitable as fungicides. They are distinguished by an outstanding effectiveness against a broad spectrum of phytopathogenic fungi, including soil-borne fungi, which derive especially from the classes of the Plasmodiophoromycetes, Peronosporomycetes (syn. Oomycetes), Chytridiomycetes, Zygomycetes, Ascomycetes, Basidiomycetes and Deuteromycetes (syn. Fungi imperfecti). Some are systemically effective and they can be used in crop protection as foliar fungicides, fungicides for seed dressing and soil fungicides. Moreover, they are suitable for controlling harmful fungi, which inter alia occur in wood or roots of plants.

[00175] In some embodiments, the compounds of formula I and the compositions according to the invention are particularly important in the control of phytopathogenic fungi on various cultivated plants, such as cereals, e.g. wheat, rye, barley, triticale, oats or rice; beet, e.g. sugar beet or fodder beet; fruits, such as pomes, stone fruits or soft fruits, e.g. apples, pears, plums, peaches, almonds, cherries, strawberries, raspberries, blackberries or gooseberries; leguminous plants, such as lentils, peas, alfalfa or soybeans; oil plants, such as rape, mustard, olives,

sunflowers, coconut, cocoa beans, castor oil plants, oil palms, ground nuts or soybeans; cucurbits, such as squashes, cucumber or melons; fiber plants, such as cotton, flax, hemp or jute; citrus fruit, such as oranges, lemons, grapefruits or mandarins; vegetables, such as spinach, lettuce, asparagus, cabbages, carrots, onions, tomatoes, potatoes, cucurbits or paprika; lauraceous plants, such as avocados, cinnamon or camphor; energy and raw material plants, such as corn, soybean, rape, sugar cane or oil palm; corn; tobacco; nuts; coffee; tea; bananas; vines (table grapes and grape juice grape vines); hop; turf; natural rubber plants or ornamental and forestry plants, such as flowers, shrubs, broad-leaved trees or evergreens, e.g. conifers; and on the plant propagation material, such as seeds, and the crop material of these plants.

[00176] In some embodiments, compounds of formula I and compositions thereof, respectively are used for controlling a multitude of fungi on field crops, such as potatoes sugar beets, tobacco, wheat, rye, barley, oats, rice, corn, cotton, soybeans, rape, legumes, sunflowers, coffee or sugar cane; fruits; vines; ornamentals; or vegetables, such as cucumbers, tomatoes, beans or squashes.

[00177] The term "plant propagation material" is to be understood to denote all the generative parts of the plant such as seeds and vegetative plant material such as cuttings and tubers (e.g. potatoes), which can be used for the multiplication of the plant. This includes seeds, roots, fruits, tubers, bulbs, rhizomes, shoots, sprouts and other parts of plants, including seedlings and young plants, which are to be transplanted after germination or after emergence from soil. These young plants may also be protected before transplantation by a total or partial treatment by immersion or pouring.

[00178] In some embodiments, treatment of plant propagation materials with compounds of formula I and compositions thereof, respectively, is used for controlling a multitude of fungi on cereals, such as wheat, rye, barley and oats; rice, corn, cotton and soybeans.

[00179] The term "cultivated plants" is to be understood as including plants which have been modified by breeding, mutagenesis or genetic engineering including but not limiting to agricultural biotech products on the market or in development. Genetically modified plants are plants, which genetic material has been so modified by the use of recombinant DNA techniques that under natural circumstances cannot readily be obtained by cross breeding, mutations or natural recombination. Typically, one or more genes have been integrated into the genetic material of a genetically modified plant in order to improve certain properties of the plant. Such

genetic modifications also include but are not limited to targeted post-translational modification of protein(s), oligo- or polypeptides e.g. by glycosylation or polymer additions such as prenylated, acetylated or farnesylated moieties or PEG moieties.

[00180] Plants that have been modified by breeding, mutagenesis or genetic engineering, e.g. have been rendered tolerant to applications of specific classes of herbicides, such as hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors; acetolactate synthase (ALS) inhibitors, such as sulfonyl ureas (see e.g. US 6,222,100, WO 01/82685, WO 00/26390, WO 97/41218, WO 98/02526, WO 98/02527, WO 04/106529, WO 05/20673, WO 03/14357, WO 03/13225, WO 03/14356, WO 04/16073) or imida- zolinones (see e.g. US 6,222,100, WO 01/82685, WO 00/026390, WO 97/41218, WO 98/002526, WO 98/02527, WO 04/106529, WO 05/20673, WO 03/014357, WO 03/13225, WO 03/14356, WO 04/16073); enolpyruvylshikimate-3-phosphate synthase (EPSPS) inhibitors, such as glyphosate (see e.g. WO 92/00377); glutamine synthetase (GS) inhibitors, such as glufosinate (see e.g. EP-A 242 236, EP-A 242 246) or oxynil herbicides (see e.g. US 5,559,024) as a result of conventional methods of breeding or genetic engineering. Several cultivated plants have been rendered tolerant to herbicides by conventional methods of breeding (mutagenesis), e.g. Clearfield® summer rape (Canola, BASF SE, Germany) being tolerant to imidazolinones, e.g. imazamox. Genetic engineering methods have been used to render cultivated plants, such as soybean, cotton, corn, beets and rape, tolerant to herbicides such as glyphosate and glufosinate, some of which are commercially available under the trade names RoundupReady® (glyphosate-tolerant, Monsanto, U.S.A.) and LibertyLink® (glufosinate-tolerant, Bayer CropScience, Germany).

[00181] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, are capable to synthesize one or more insecticidal proteins, especially those known from the bacterial genus Bacillus, particularly from Bacillus thuringiensis, such as δ-endotoxins, e.g. CrylA(b), CrylA(c), CrylF, CrylF(a2), CryllA(b), CrylllA, CrylllB(bi) or Cryθc; vegetative insecticidal proteins (VIP), e.g. VIP1 , VIP2, VIP3 or VIP3A; insecticidal proteins of bacteria colonizing nematodes, e.g. Photorhabdus spp. or Xenor-habdus spp.; toxins produced by animals, such as scorpion toxins, arachnid toxins, wasp toxins, or other insect-specific neurotoxins; toxins produced by fungi, such Streptomycetes toxins, plant lectins, such as pea or barley lectins; agglutinins; proteinase inhibitors, such as trypsin inhibitors, serine protease inhibitors, patatin, cystatin or pa- pain inhibitors; ribosome-inactivating proteins (RIP), such as

ricin, maize-RIP, abrin, luffin, saporin or bryodin; steroid metabolism enzymes, such as 3-hydroxysteroid oxidase, ecdysteroid-IDP-glycosyl-transferase, cholesterol oxidases, ecdysone inhibitors or HMG-CoA-reductase; ion channel blockers, such as blockers of sodium or calcium channels; juvenile hormone esterase; diuretic hormone receptors (helicokinin receptors); stilben synthase, bibenzyl synthase, chitinases or glucanases. In the context of the present invention these insecticidal proteins or toxins are to be understood expressly also as pre-toxins, hybrid proteins, truncated or otherwise modified proteins. Hybrid proteins are characterized by a new combination of protein domains, (see, e.g. WO 02/015701). Further examples of such toxins or genetically modified plants capable of synthesizing such toxins are disclosed, e.g., in EP-A 374 753, WO 93/007278, WO 95/34656, EP-A 427 529, EP-A 451 878, WO 03/18810 und WO 03/52073. The methods for producing such genetically modified plants are generally known to the person skilled in the art and are described, e.g., in the publications mentioned above. These insecticidal proteins contained in the genetically modified plants impart to the plants producing these proteins tolerance to harmful pests from all taxonomic groups of arthropods, especially to beetles (Coleoptera), two-winged insects (Diptera), and moths (Lepidoptera) and to nematodes (Nematoda). Genetically modified plants capable to synthesize one or more insecticidal proteins are, e.g., described in the publications mentioned above, and some of them are commercially available such as YieldGard® (corn cultivars producing the CryiAb toxin), YieldGard® Plus (corn cultivars producing Cry1 Ab and Cry3Bb1 toxins), Starlink® (corn cultivars producing the Cry9c toxin), Her- culex® RW (corn cultivars producing Cry34Ab1 , Cry35Ab1 and the enzyme Phosphi- nothricin-N-Acetyltransferase [PAT]); NuCOTN® 33B (cotton cultivars producing the Cry1 Ac toxin), Bollgard® I (cotton cultivars producing the CryiAc toxin), Bollgard® Il (cotton cultivars producing CryiAc and Cry2Ab2 toxins); VIPCOT® (cotton cultivars producing a VIP-toxin); NewLeaf® (potato cultivars producing the Cry3A toxin); Bt-Xtra®, NatureGard®, KnockOut®, BiteGard®, Protecta®, Bt 1 1 (e.g. Agrisure® CB) and Bt176 from Syngenta Seeds SAS, France, (corn cultivars producing the CryiAb toxin and PAT enyzme), MIR604 from Syngenta Seeds SAS, France (corn cultivars producing a modified version of the Cry3A toxin, c.f. WO 03/018810), MON 863 from Monsanto Europe S.A., Belgium (corn cultivars producing the Cry3Bb1 toxin), IPC 531 from Monsanto Europe S.A., Belgium (cotton cultivars producing a modified version of the CryiAc toxin) and 1507 from Pioneer Overseas Corporation, Belgium (corn cultivars producing the Cry1 F toxin and PAT enzyme).

[00182] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, are capable to synthesize one or more proteins to increase the resistance or tolerance of those plants to bacterial, viral or fungal pathogens. Examples of such proteins are the so-called "pathogenesis-related proteins" (PR proteins, see, e.g. EP-A 392225), plant disease resistance genes (e.g. potato cultivars, which express resistance genes acting against Phytophthora infestans derived from the Mexican wild potato Solanum bulbocastanum) or T4-lysozym (e.g. potato cultivars capable of synthesizing these proteins with increased resistance against bacteria such as Erwinia amylvora). The methods for producing such genetically modified plants are generally known to the person skilled in the art and are described, e.g., in the publications mentioned above.

[00183] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, are capable to synthesize one or more proteins to increase the productivity (e.g. biomass production, grain yield, starch content, oil content or protein content), tolerance to drought, salinity or other growth-limiting environmental factors or tolerance to pests and fungal, bacterial or viral pathogens of those plants.

[00184] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, contain a modified amount of substances of content or new substances of content, specifically to improve human or animal nutrition, e.g. oil crops that produce health- promoting long-chain omega-3 fatty acids or unsaturated omega-9 fatty acids (e.g. Nexera® rape, DOW Agro Sciences, Canada).

[00185] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, contain a modified amount of substances of content or new substances of content, specifically to improve raw material production, e.g. potatoes that produce increased amounts of amylopectin (e.g. Amflora® potato, BASF SE, Germany).

[00186] The compounds of formula I and compositions thereof, respectively, are particularly suitable for controlling the following plant diseases:

[00187] Albugo spp. (white rust) on ornamentals, vegetables (e.g. A. Candida) and sunflowers (e.g. A. tragopogonis); Altemaria spp. (Alternaria leaf spot) on vegetables, rape {A. brassicola or brassicae), sugar beets (A. tenuis), fruits, rice, soybeans, potatoes (e.g. A. solani or A. alternata), tomatoes (e.g. A. solani or A. alternata) and wheat; Aphanomyces spp. on sugar beets and vegetables; Ascochyta spp. on cereals and vegetables, e.g. A. tritici (anthracnose) on wheat and

A. hordei on barley; Bipolaris and Drechslera spp. (teleomorph: Cochliobolus spp.), e.g. Southern leaf blight (D. maydis) or Northern leaf blight (β. zeicola) on corn, e.g. spot blotch (β. sorokiniana) on cereals and e.g. B. oryzae on rice and turfs; Blumeria (formerly Erysiphe) graminis (powdery mildew) on cereals (e.g. on wheat or barley); Botrytis cinerea (teleomorph: Botryotinia fuckeliana: grey mold) on fruits and berries (e.g. strawberries), vegetables (e.g. lettuce, carrots, celery and cabbages), rape, flowers, vines, forestry plants and wheat; Bremia lactucae (downy mildew) on lettuce; Ceratocystis (syn. Ophiostoma) spp. (rot or wilt) on broad-leaved trees and evergreens, e.g. C. ulmi (Dutch elm disease) on elms; Cercospora spp. (Cercospora leaf spots) on corn (e.g. Gray leaf spot: C. zeaemaydis), rice, sugar beets (e.g. C. beticola), sugar cane, vegetables, coffee, soybeans (e.g. C. sojina or C. kikuchii) and rice; Cladosporium spp. on tomatoes (e.g. C. fulvum: leaf mold) and cereals, e.g. C. herbarum (black ear) on wheat; Claviceps purpurea (ergot) on cereals; Cochliobolus (anamorph: Helminthosporium of Bipolaris) spp. (leaf spots) on corn (C. carbonum), cereals (e.g. C. sativus, anamorph: B. sorokiniana) and rice (e.g. C. miyabeanus, anamorph: H. oryzae); Colletotrichum (teleomorph: Glomerella) spp. (an- thracnose) on cotton (e.g. C. gossypii), corn (e.g. C. graminicola: Anthracnose stalk rot), soft fruits, potatoes (e.g. C. coccodes: black dot), beans (e.g. C. lindemuthianum) and soybeans (e.g. C. truncatum or C. gloeosporioides); Corticium spp., e.g. C. sasakii (sheath blight) on rice; Corynespora cassiicola (leaf spots) on soybeans and ornamentals; Cycloconium spp., e.g. C. oleaginum on olive trees; Cylindrocarpon spp. (e.g. fruit tree canker or young vine decline, teleomorph: Nectria or Neonectria spp.) on fruit trees, vines (e.g. C. liriodendri, teleomorph: Neonectria liriodendri. Black Foot Disease) and ornamentals; Dematophora (teleomorph: Rosellinia) necatrix (root and stem rot) on soybeans; Diaporthe spp., e.g. D. phaseolorum (damping off) on soybeans; Drechslera (syn. Helminthosporium, teleomorph: Pyrenophora) spp. on corn, cereals, such as barley (e.g. D. teres, net blotch) and wheat (e.g. D. tritici-repentis: tan spot), rice and turf; Esca (dieback, apoplexy) on vines, caused by Formitiporia (syn. Phellinus) punctata, F. mediterranea, Phaeomoniella chlamydospora (earlier Phaeo- acremonium chlamydosporum), Phaeoacremonium aleophilum and/or Botryosphaeria obtusa; Elsinoe spp. on pome fruits (E. pyri), soft fruits (E. veneta: anthracnose) and vines (E ampelina: anthracnose); Entyloma oryzae (leaf smut) on rice; Epicoccum spp. (black mold) on wheat; Erysiphe spp. (powdery mildew) on sugar beets (E. betae), vegetables (e.g. E. pisi), such as cucurbits (e.g. E. cichoracearum), cabbages, rape (e.g. E. cruciferarum);

Eutypa lata (Eutypa canker or dieback, anamorph: Cytosporina lata, syn. Libertella blepharis) on fruit trees, vines and ornamental woods; Exserohilum (syn. Helminthosporium) spp. on corn (e.g. E. turcicum); Fusarium (teleomorph: Gibberella) spp. (wilt, root or stem rot) on various plants, such as F. graminearum or F. culmorum (root rot, scab or head blight) on cereals (e.g. wheat or barley), F. oxysporum on tomatoes, F. solani on soybeans and F. verticillioides on corn; Gaeumannomyces graminis (take-all) on cereals (e.g. wheat or barley) and corn; Gibberella spp. on cereals (e.g. G. zeae) and rice (e.g. G. fujikuroi: Bakanae disease); Glomerella cingulata on vines, pome fruits and other plants and G. gossypii on cotton; Grain- staining complex on rice; Guignardia bidwellii (black rot) on vines; Gymnosporangium spp. on rosaceous plants and junipers, e.g. G. sabinae (rust) on pears; Helminthosporium spp. (syn. Drechslera, teleomorph: Cochliobolus) on corn, cereals and rice; Hemileia spp., e.g. H. vastatrix (coffee leaf rust) on coffee; lsariopsis clavispora (syn. Cladosporium vitis) on vines; Macrophomina phaseolina (syn. phaseoli) (root and stem rot) on soybeans and cotton; Microdochium (syn. Fusarium) nivale (pink snow mold) on cereals (e.g. wheat or barley); Microsphaera diffusa (powdery mildew) on soybeans; Monilinia spp., e.g. M. laxa, M. fructicola and M. fructigena (bloom and twig blight, brown rot) on stone fruits and other rosaceous plants; Mycosphaerella spp. on cereals, bananas, soft fruits and ground nuts, such as e.g. M. graminicola (anamorph: Septoria tritici, Septoria blotch) on wheat or M. fijiensis (black Sigatoka disease) on bananas; Peronospora spp. (downy mildew) on cabbage (e.g. P. brassicae), rape (e.g. P. parasitica), onions (e.g. P. destructor), tobacco (P. tabacina) and soybeans (e.g. P. manshurica); Phakopsora pachyrhizi and P. meibomiae (soybean rust) on soybeans; Phialophora spp. e.g. on vines (e.g. P. tracheiphila and P. tetraspora) and soybeans (e.g. P. gregata: stem rot); Phoma lingam (root and stem rot) on rape and cabbage and P. betae (root rot, leaf spot and damping-off) on sugar beets; Phomopsis spp. on sunflowers, vines (e.g. P. viticola: can and leaf spot) and soybeans (e.g. stem rot: P. phaseoli, teleomorph: Diaporthe phaseolorum); Physoderma maydis (brown spots) on corn; Phytophthora spp. (wilt, root, leaf, fruit and stem root) on various plants, such as paprika and cucurbits (e.g. P. capsici), soybeans (e.g. P. megasperma, syn. P. sojae), potatoes and tomatoes (e.g. P. infestans: late blight) and broad-leaved trees (e.g. P. ramorum: sudden oak death); Plasmodiophora brassicae (club root) on cabbage, rape, radish and other plants; Plasmopara spp., e.g. P. viticola (grapevine downy mildew) on vines and P. halstediiou sunflowers; Podosphaera spp. (powdery mildew) on rosaceous plants, hop, pome and soft fruits, e.g. P. leucotricha on apples; Polymyxa

spp., e.g. on cereals, such as barley and wheat (P. graminis) and sugar beets (P. betae) and thereby transmitted viral diseases; Pseudocercosporella herpotrichoides (eyespot, teleomorph: Tapesia yallundae) on cereals, e.g. wheat or barley; Pseudoperonospora (downy mildew) on various plants, e.g. P. cubensis on cucurbits or P. humili on hop; Pseudopezicula tracheiphila (red fire disease or , rotbrenner' , anamorph: Phialo- phora) on vines; Puccinia spp. (rusts) on various plants, e.g. P. triticina (brown or leaf rust), P. striiformis (stripe or yellow rust), P. hordei (dwarf rust), P. graminis (stem or black rust) or P. recondita (brown or leaf rust) on cereals, such as e.g. wheat, barley or rye, and asparagus (e.g. P. asparagi); Pyrenophora (anamorph: Drechslera) tritici- repentis (tan spot) on wheat or P. feres (net blotch) on barley; Pyricularia spp., e.g. P. oryzae (teleomorph: Magnaporthe grisea, rice blast) on rice and P. grisea on turf and cereals; Pythium spp. (damping-off) on turf, rice, corn, wheat, cotton, rape, sunflowers, soybeans, sugar beets, vegetables and various other plants (e.g. P. ultimum or P. aphanidermatum); Ramularia spp., e.g. R. collo-cygni (Ramularia leaf spots, Physiological leaf spots) on barley and R. beticola on sugar beets; Rhizoctonia spp. on cotton, rice, potatoes, turf, corn, rape, potatoes, sugar beets, vegetables and various other plants, e.g. R. solani (root and stem rot) on soybeans, R. solani (sheath blight) on rice or R. cerealis (Rhizoctonia spring blight) on wheat or barley; Rhizopus stolonifer (black mold, soft rot) on strawberries, carrots, cabbage, vines and tomatoes; Rhynchosporium secalis (scald) on barley, rye and triticale; Sarocladium oryzae and S. attenuatum (sheath rot) on rice; Sclerotinia spp. (stem rot or white mold) on vegetables and field crops, such as rape, sunflowers (e.g. S. sclerotiorum) and soybeans (e.g. S. rolfsii or S. sclerotiorum); Septoria spp. on various plants, e.g. S. glycines (brown spot) on soybeans, S. tritici (Septoria blotch) on wheat and S. (syn. Stagonospora) nodorum (Stagonospora blotch) on cereals; Uncinula (syn. Erysiphe) necator (powdery mildew, anamorph: Oidium tuckeri) on vines; Setospaeria spp. (leaf blight) on corn (e.g. S. turcicum, syn. Helminthosporium turcicum) and turf; Sphacelotheca spp. (smut) on corn, (e.g. S. miliaria: head smut), sorghum und sugar cane; Sphaerotheca fuliginea (powdery mildew) on cucurbits; Spongospora subterranea (powdery scab) on potatoes and thereby transmitted viral diseases; Stagonospora spp. on cereals, e.g. S. nodorum (Stagonospora blotch, teleomorph: Leptosphaeria [syn. Phaeosphaeria] nodorum) on wheat; Synchytrium endobioticum on potatoes (potato wart disease); Taphrina spp., e.g. T. deformans (leaf curl disease) on peaches and T. pruni (plum pocket) on plums; Thielaviopsis spp. (black root rot) on tobacco, pome fruits, vegetables,

soybeans and cotton, e.g. T. basicola (syn. Chalara elegans); Tilletia spp. (common bunt or stinking smut) on cereals, such as e.g. T. tritici (syn. T. caries, wheat bunt) and T. controversa (dwarf bunt) on wheat; Typhula incamata (grey snow mold) on barley or wheat; Urocystis spp., e.g. U. occulta (stem smut) on rye; Uromyces spp. (rust) on vegetables, such as beans (e.g. U. appendiculatus, syn. U. phaseoli) and sugar beets (e.g. U. betae); Ustilago spp. (loose smut) on cereals (e.g. U. nuda and U. avaenae), corn (e.g. U. maydis: corn smut) and sugar cane; Venturia spp. (scab) on apples (e.g. V. inaequalis) and pears; and Verticillium spp. (wilt) on various plants, such as fruits and ornamentals, vines, soft fruits, vegetables and field crops, e.g. V. dahliae on strawberries, rape, potatoes and tomatoes.

[00188] The compounds of formula I and compositions thereof, respectively, are also suitable for controlling harmful fungi in the protection of stored products or harvest and in the protection of materials. The term "protection of materials" is to be understood to denote the protection of technical and non-living materials, such as adhesives, glues, wood, paper and paperboard, textiles, leather, paint dispersions, plastics, colling lubricants, fiber or fabrics, against the infestation and destruction by harmful microorganisms, such as fungi and bacteria. As to the protection of wood and other materials, the particular attention is paid to the following harmful fungi: Ascomycetes such as Ophiostoma spp., Ceratocystis spp., Aureobasidium pullulans, Sclerophoma spp., Chaetomium spp., Humicola spp., Petriella spp., Trichurus spp.; Basidiomycetes such as Coniophora spp., Coriolus spp., Gloeophyllum spp., Lentinus spp., Pleurotus spp., Poria spp., Serpula spp. and Tyromyces spp., Deuteromycetes such as Aspergillus spp., Cladosporium spp., Penicillium spp., Trichorma spp., Altemaria spp., Paecilomyces spp. and Zygomycetes such as Mucor spp., and in addition in the protection of stored products and harvest the following yeast fungi are worthy of note: Candida spp. and Saccharomyces cerevisae.

[00189] The compounds of formula I and compositions thereof, respectively, may be used for improving the health of a plant. The invention also relates to a method for improving plant health by treating a plant, its propagation material and/or the locus where the plant is growing or is to grow with an effective amount of compounds of formula I or compositions thereof, respectively.

[00190] The term "plant health" is to be understood to denote a condition of the plant and/or its products which is determined by several indicators alone or in combination with each other such as yield (e.g. increased biomass and/or increased content of valuable ingredients), plant vigor (e.g. improved plant growth and/or greener leaves ("greening effect")), quality (e.g.

improved content or composition of certain ingredients) and tolerance to abiotic and/or biotic stress. The above identified indicators for the health condition of a plant may be interdependent or may result from each other.

[00191] The compounds of formula I can be present in different crystal modifications whose biological activity may differ. They are likewise subject matter of the present invention.

[00192] The compounds of formula I are employed as such or in form of compositions by treating the fungi or the plants, plant propagation materials, such as seeds, soil, surfaces, materials or rooms to be protected from fungal attack with a fungicidally effective amount of the active substances. The application can be carried out both before and after the infection of the plants, plant propagation materials, such as seeds, soil, surfaces, materials or rooms by the fungi.

[00193] Plant propagation materials may be treated with compounds of formula I as such or a composition comprising at least one compound of formula I prophylactically either at or before planting or transplanting.

[00194] The invention also relates to agrochemical compositions comprising a solvent or solid carrier and at least one compound of formula I and to the use for controlling harmful fungi.

[00195] An agrochemical composition comprises a fungicidally effective amount of a compound I and/or II. The term "effective amount" denotes an amount of the composition or of the compound of formula I, which is sufficient for controlling harmful fungi on cultivated plants or in the protection of materials and which does not result in a substantial damage to the treated plants. Such an amount can vary in a broad range and is dependent on various factors, such as the fungal species to be controlled, the treated cultivated plant or material, the climatic conditions and the specific compound of formula I used.

[00196] The compounds of formula I and salts thereof can be converted into customary types of agrochemical compositions, e.g. solutions, emulsions, suspensions, dusts, powders, pastes and granules. The composition type depends on the particular intended purpose; in each case, it should ensure a fine and uniform distribution of the compound according to the invention.

[00197] Examples for composition types are suspensions (SC, OD, FS), emulsifiable concentrates (EC), emulsions (EW, EO, ES), pastes, pastilles, wettable powders or dusts (WP, SP, SS, WS, DP, DS) or granules (GR, FG, GG, MG), which can be water- soluble or wettable, as well as gel formulations for the treatment of plant propagation materials such as seeds (GF).

[00198] Usually the composition types (e.g. SC, OD, FS, EC, WG, SG, WP, SP, SS, WS, GF) are employed diluted. Composition types such as DP, DS, GR, FG, GG and MG are usually used undiluted.

[00199] The compositions are prepared in a known manner (cf. US 3,060,084, EP-A 707 445 (for liquid concentrates), Browning: "Agglomeration", Chemical Engineering, Dec. 4, 1967, 147-48, Perry's Chemical Engineer's Handbook, 4th Ed., McGraw-Hill, New York, 1963, pp. 8-57 et seq., WO 91/13546, US 4,172,714, US 4,144,050, US 3,920,442, US 5,180,587, US 5,232,701 , US 5,208,030, GB 2,095,558, US 3,299,566, Klingman: Weed Control as a Science (J. Wiley & Sons, New York, 1961), Hance et al.: Weed Control Handbook (8th Ed., Blackwell Scientific, Oxford, 1989) and Mollet, H. and Grubemann, A.: Formulation technology (Wiley VCH Verlag, Weinheim, 2001).

[00200] The agrochemical compositions may also comprise auxiliaries which are customary in agrochemical compositions. The auxiliaries used depend on the particular application form and active substance, respectively.

[00201] Examples for suitable auxiliaries are solvents, solid carriers, dispersants or emulsifiers (such as further solubilizers, protective colloids, surfactants and adhesion agents), organic and inorganic thickeners, bactericides, anti-freezing agents, anti-foaming agents, if appropriate colorants and tackifiers or binders (e.g. for seed treatment formulations). Suitable solvents are water, organic solvents such as mineral oil fractions of medium to high boiling point, such as kerosene or diesel oil, furthermore coal tar oils and oils of vegetable or animal origin, aliphatic, cyclic and aromatic hydrocarbons, e.g. toluene, xylene, paraffin, tetrahydronaphthalene, alkylated naphthalenes or their derivatives, alcohols such as methanol, ethanol, propanol, butanol and cyclohexanol, glycols, ketones such as cyclohexanone and gamma-butyrolactone, fatty acid dimethylamides, fatty acids and fatty acid esters and strongly polar solvents, e.g. amines such as N- methylpyrrolidone.

[00202] Solid carriers are mineral earths such as silicates, silica gels, talc, kaolins, limestone, lime, chalk, bole, loess, clays, dolomite, diatomaceous earth, calcium sulfate, magnesium sulfate, magnesium oxide, ground synthetic materials, fertilizers, such as, e.g., ammonium sulfate, ammonium phosphate, ammonium nitrate, ureas, and products of vegetable origin, such as cereal meal, tree bark meal, wood meal and nutshell meal, cellulose powders and other solid carriers.

[00203] Suitable surfactants (adjuvants, wetters, tackifiers, dispersants or emulsifiers) are alkali metal, alkaline earth metal and ammonium salts of aromatic sulfonic acids, such as ligninsoulfonic acid (Borresperse® types, Borregard, Norway) phenolsulfonic acid, naphthalenesulfonic acid (Morwet® types, Akzo Nobel, U.S.A.), dibutylnaphthalene- sulfonic acid (Nekal® types, BASF, Germany), and fatty acids, alkylsulfonates, alkyl- arylsulfonates, alkyl sulfates, laurylether sulfates, fatty alcohol sulfates, and sulfated hexa-, hepta- and octadecanolates, sulfated fatty alcohol glycol ethers, furthermore condensates of naphthalene or of naphthalenesulfonic acid with phenol and formaldehyde, polyoxy-ethylene octylphenyl ether, ethoxylated isooctylphenol, octylphenol, nonylphenol, alkylphenyl polyglycol ethers, tributylphenyl polyglycol ether, tristearyl- phenyl polyglycol ether, alkylaryl polyether alcohols, alcohol and fatty alcohol/ethylene oxide condensates, ethoxylated castor oil, polyoxyethylene alkyl ethers, ethoxylated polyoxypropylene, lauryl alcohol polyglycol ether acetal, sorbitol esters, lignin-sulfite waste liquors and proteins, denatured proteins, polysaccharides (e.g. methylcellulose), hydrophobically modified starches, polyvinyl alcohols (Mowiol® types, Clariant, Switzerland), polycarboxylates (Sokolan® types, BASF, Germany), polyalkoxylates, polyvinyl- amines (Lupasol® types, BASF, Germany), polyvinylpyrrolidone and the copolymers therof.

[00204] Examples for thickeners (i.e. compounds that impart a modified flowability to compositions, i.e. high viscosity under static conditions and low viscosity during agitation) are polysaccharides and organic and anorganic clays such as Xanthan gum (Kelzan®, CP Kelco, U.S.A.), Rhodopol® 23 (Rhodia, France), Veegum® (RT. Vanderbilt, U.S.A.) or Attaclay® (Engelhard Corp., NJ, USA).

[00205] Bactericides may be added for preservation and stabilization of the composition. Examples for suitable bactericides are those based on dichlorophene and benzylalcohol hemi formal (Proxel® from ICI or Acticide® RS from Thor Chemie and Kathon® MK from Rohm & Haas) and isothiazolinone derivatives such as alkylisothiazolinones and benzisothiazolinones (Acticide® MBS from Thor Chemie).

[00206] Examples for suitable anti-freezing agents are ethylene glycol, propylene glycol, urea and glycerin.

[00207] Examples for anti-foaming agents are silicone emulsions (such as e.g. Silikon® SRE, Wacker, Germany or Rhodorsil®, Rhodia, France), long chain alcohols, fatty acids, salts of fatty acids, fluoroorganic compounds and mixtures thereof.

[00208] Suitable colorants are pigments of low water solubility and water-soluble dyes. Examples to be mentioned und the designations rhodamin B, C. I. pigment red 112, C. I. solvent red 1 , pigment blue 15:4, pigment blue 15:3, pigment blue 15:2, pigment blue 15:1 , pigment blue 80, pigment yellow 1 , pigment yellow 13, pigment red 112, pigment red 48:2, pigment red 48:1 , pigment red 57:1 , pigment red 53:1 , pigment orange 43, pigment orange 34, pigment orange 5, pigment green 36, pigment green 7, pigment white 6, pigment brown 25, basic violet 10, basic violet 49, acid red 51 , acid red 52, acid red 14, acid blue 9, acid yellow 23, basic red 10, basic red 108.

[00209] Examples for tackifiers or binders are polyvinylpyrrolidons, polyvinylacetates, polyvinyl alcohols and cellulose ethers (Tylose®, Shin-Etsu, Japan).

[00210] Powders, materials for spreading and dusts can be prepared by mixing or concomitantly grinding the compounds of formula I and, if appropriate, further active substances, with at least one solid carrier.

[00211] Granules, e.g. coated granules, impregnated granules and homogeneous granules, can be prepared by binding the active substances to solid carriers. Examples of solid carriers are mineral earths such as silica gels, silicates, talc, kaolin, attaclay, limestone, lime, chalk, bole, loess, clay, dolomite, diatomaceous earth, calcium sulfate, magnesium sulfate, magnesium oxide, ground synthetic materials, fertilizers, such as, e.g., ammonium sulfate, ammonium phosphate, ammonium nitrate, ureas, and products of vegetable origin, such as cereal meal, tree bark meal, wood meal and nutshell meal, cellulose powders and other solid carriers.

[00212] Examples for composition types include, but are not limited to: 1. Composition types for dilution with water, i) Water-soluble concentrates (SL, LS): 10 parts by weight of a compound of formula I according to the invention are dissolved in 90 parts by weight of water or in a water-soluble solvent. As an alternative, wetting agents or other auxiliaries are added. The active substance dissolves upon dilution with water. In this way, a composition having a content of 10% by weight of active substance is obtained. ii) Dispersible concentrates (DC): 20 parts by weight of a compound of formula I according to the invention are dissolved in 70 parts by weight of cyclohexanone with addition of 10 parts by weight of a dispersant, e.g. polyvinylpyrrolidone.

Dilution with water gives a dispersion. The active substance content is 20% by weight. iii) Emulsifiable concentrates (EC): 15 parts by weight of a compound of formula I according to the invention are dissolved in 75 parts by weight of xylene with addition of calcium dodecylbenzenesulfonate and castor oil ethoxylate (in each case 5 parts by weight). Dilution with water gives an emulsion. The composition has an active substance content of 15% by weight. iv) Emulsions (EW, EO, ES): 25 parts by weight of a compound of formula I according to the invention are dissolved in 35 parts by weight of xylene with addition of calcium dodecylbenzenesulfonate and castor oil ethoxylate (in each case 5 parts by weight). This mixture is introduced into 30 parts by weight of water by means of an emulsifying machine (Ultraturrax) and made into a homogeneous emulsion. Dilution with water gives an emulsion. The composition has an active substance content of 25% by weight. v) Suspensions (SC, OD, FS): In an agitated ball mill, 20 parts by weight of a compound of formula I according to the invention are comminuted with addition of 10 parts by weight of dispersants and wetting agents and 70 parts by weight of water or an organic solvent to give a fine active sub- stance suspension. Dilution with water gives a stable suspension of the active substance. The active substance content in the composition is 20% by weight. vi) Water-dispersible granules and water-soluble granules (WG, SG) 50 parts by weight of a compound of formula I according to the invention are ground finely with addition of 50 parts by weight of dispersants and wetting agents and prepared as water-dispersible or water-soluble granules by means of technical appliances (e.g. extrusion, spray tower, fluidized bed). Dilution with water gives a stable dispersion or solution of the active substance. The composition has an active substance content of 50% by weight. vii) Water-dispersible powders and water-soluble powders (WP, SP, SS, WS) 75 parts by weight of a compound of formula I according to the invention are ground in a rotor-stator mill with addition of 25 parts by weight of dispersants, wetting agents and silica gel. Dilution with water gives a stable dispersion or solution of the active substance. The active substance content of the composition is 75% by weight. viii) Gel (GF): In an agitated ball mill, 20 parts by weight of a compound of formula I according to the invention are comminuted with addition of 10 parts by weight of dispersants, 1 part by weight of a gelling agent wetters and 70 parts by weight of water or of an organic solvent to give a fine suspension of the active substance. Dilution with water gives a stable suspension of the active substance, whereby a composition with 20% (w/w) of active substance is obtained.

[00213] 2. Composition types to be applied undiluted: ix) Dustable powders (DP, DS): 5 parts by weight of a compound of formula I according to the invention are ground finely and mixed intimately with 95 parts by weight of finely divided kaolin. This gives a dustable composition having an active substance content of 5% by weight. x) Granules (GR, FG, GG, MG): 0.5 parts by weight of a compound of formula I according to the invention is ground finely and associated with 99.5 parts by weight of carriers. Current methods are extrusion, spray-drying or the fluidized bed. This gives granules to be applied undiluted having an active substance content of 0.5% by weight. xi) ULV solutions (UL) 10 parts by weight of a compound of formula I according to the invention are dissolved in 90 parts by weight of an organic solvent, e.g. xylene. This gives a composition to be applied undiluted having an active substance content of 10% by weight.

[00214] The agrochemical compositions generally comprise between 0.01 and 95%, preferably between 0.1 and 90%, most preferably between 0.5 and 90%, by weight of active substance. The active substances are employed in a purity of from 90% to 100%, preferably from 95% to 100% (according to NMR spectrum).

[00215] Water-soluble concentrates (LS), flowable concentrates (FS), powders for dry treatment (DS), water-dispersible powders for slurry treatment (WS), water-soluble powders (SS), emulsions (ES) emulsifiable concentrates (EC) and gels (GF) are usually employed for the purposes of treatment of plant propagation materials, particularly seeds. These compositions can be applied to plant propagation materials, particularly seeds, diluted or undiluted. The compositions in question give, after two-to-tenfold dilution, active substance concentrations of from 0.01 to 60% by weight, preferably from 0.1 to 40% by weight, in the ready-to-use preparations. Application can be carried out before or during sowing. Methods for applying or treating agrochemical compounds and compositions thereof, respectively, on to plant propagation material, especially seeds, are known in the art, and include dressing, coating, pelleting, dusting, soaking and in- furrow application methods of the propagation material. In a preferred embodiment, the compounds or the compositions thereof, respectively, are applied on to the plant propagation material by a method such that germination is not induced, e.g. by seed dressing, pelleting, coating and dusting.

[00216] In a preferred embodiment, a suspension-type (FS) composition is used for seed treatment. Typcially, a FS composition may comprise 1-800 g/l of active substance, 1-200 g/l

Surfactant, 0 to 200 g/l antifreezing agent, 0 to 400 g/l of binder, 0 to 200 g/l of a pigment and up to 1 liter of a solvent, preferably water.

[00217] The active substances can be used as such or in the form of their compositions, e.g. in the form of directly sprayable solutions, powders, suspensions, dispersions, emulsions, dispersions, pastes, dustable products, materials for spreading, or granules, by means of spraying, atomizing, dusting, spreading, brushing, immersing or pouring. The application forms depend entirely on the intended purposes; it is intended to ensure in each case the finest possible distribution of the active substances according to the invention. Aqueous application forms can be prepared from emulsion concentrates, pastes or wettable powders (sprayable powders, oil dispersions) by adding water. To prepare emulsions, pastes or oil dispersions, the substances, as such or dissolved in an oil or solvent, can be homogenized in water by means of a wetter, tackifier, dispersant or emulsifier. Alternatively, it is possible to prepare concentrates composed of active substance, wetter, tackifier, dispersant or emulsifier and, if appropriate, solvent or oil, and such concentrates are suitable for dilution with water.

[00218] The active substance concentrations in the ready-to-use preparations can be varied within relatively wide ranges. In general, they are from 0.0001 to 10%, preferably from 0.001 to 1 % by weight of active substance.

[00219] The active substances may also be used successfully in the ultra-low-volume process (ULV), it being possible to apply compositions comprising over 95% by weight of active substance, or even to apply the active substance without additives.

[00220] When employed in plant protection, the amounts of active substances applied are, depending on the kind of effect desired, from 0.001 to 2 kg per ha, preferably from 0.005 to 2 kg per ha, more preferably from 0.05 to 0.9 kg per ha, in particular from 0.1 to 0.75 kg per ha.

[00221] In treatment of plant propagation materials such as seeds, e.g. by dusting, coating or drenching seed, amounts of active substance of from 0.1 to 1000 g, preferably from 1 to 1000 g, more preferably from 1 to 100 g and most preferably from 5 to 100 g, per 100 kilogram of plant propagation material (preferably seed) are generally required.

[00222] When used in the protection of materials or stored products, the amount of active substance applied depends on the kind of application area and on the desired effect. Amounts customarily applied in the protection of materials are, e.g., 0.001 g to 2 kg, preferably 0.005 g to 1 kg, of active substance per cubic meter of treated material.

[00223] Various types of oils, wetters, adjuvants, herbicides, bactericides, other fungicides and/or pesticides may be added to the active substances or the compositions comprising them, if appropriate not until immediately prior to use (tank mix). These agents can be admixed with the compositions according to the invention in a weight ratio of 1 :100 to 100:1 , preferably 1 :10 to 10:1.

[00224] Adjuvants which can be used are in particular organic modified polysiloxanes such as Break Thru S 240®; alcohol alkoxylates such as Atplus 245®, Atplus MBA 1303®, PIurafac LF 300® and Lutensol ON 30®; EO/PO block polymers, e.g. Pluronic RPE 2035® and Genapol B®; alcohol ethoxylates such as Lutensol XP 80®; and dioctyl sulfosuccinate sodium such as Leophen RA®.

[00225] The compositions according to the invention can, in the use form as fungicides, also be present together with other active substances, e.g. with herbicides, insecticides, growth regulators, fungicides or else with fertilizers, as pre-mix or, if appropriate, not until immediately prior to use (tank mix).

[00226] Mixing the compounds of formula I or the compositions comprising them in the use form as fungicides with other fungicides results in many cases in an expansion of the fungicidal spectrum of activity being obtained or in a prevention of fungicide resistance development. Furthermore, in many cases, synergistic effects are obtained.

[00227] The following list of active substances, in conjunction with which the compounds according to the invention can be used, is intended to illustrate the possible combinations but does not limit them:

[00228] A) strobilurins azoxystrobin, dimoxystrobin, enestroburin, fluoxastrobin, kresoxim-methyl, meto- minostrobin, orysastrobin, picoxystrobin, pyraclostrobin, pyribencarb, trifloxystrobin, 2-(2-(6-(3-chloro-2-methyl-phenoxy)-5-fluoro-pyrimidin-4-yloxy)-phenyl)-2-methoxyimino-N-methyl-acetamide, 3-methoxy-2-(2-(N-(4-methoxy-phenyl)- cyclopropane-carboximidoylsulfanylmethyl)-phenyl)-acrylic acid methyl ester, methyl (2-chloro-5-[1-(3-methylbenzyloxyimino)ethyl]benzyl)carbamate and 2-(2-(3-(2,6-dichlorophenyl)-1-methyl-allylideneaminooxymethyl)-phenyl)-2-methoxyimino-N-methyl-acetamide;

[00229] B) carboxamides and carboxanilides: benalaxyl, benalaxyl-M, benodanil, bixafen, boscalid, carboxin, fenfuram, fenhexamid, flutolanil, furametpyr, isopyrazam, isotianil, kiralaxyl, me- pronil, metalaxyl, metalaxyl-M (mefenoxam), ofurace, oxadixyl, oxycarboxin, pen-

thiopyrad, sedaxane, tecloftalam, thifluzamide, tiadinil, 2-amino-4-methyl- thiazole-5-carboxanilide, 2-chloro-N-(1,1,3-trimethyl-indan-4-yl)-nicotinamide, N- (3',4',5'-trifluorobiphenyl-2-yl)-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxamide, N-(4'-trifluoromethylthiobiphenyl-2-yl)-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxamide, N-(2-(1,3-dimethyl-butyl)-phenyl)-1 ,3-dimethyl-5-fluoro-1H-pyrazole-4-carboxamide and N-(2-(1,3,3-trimethyl-butyl)-phenyl)-1,3-dimethyl-5-fluoro-1H-pyrazole-4-carboxamide; carboxylic morpholides: dimethomorph, flumorph, pyrimorph; benzoic acid amides: flumetover, fluopicolide, fluopyram, zoxamide, N-(3-Ethyl-3,5,5-trimethyl-cyclohexyl)-3-formylamino-2-hydroxy-benzamide; other carboxamides: carpropamid, dicyclomet, mandiproamid, oxytetracyclin, silthiofarm and N-(6-methoxy-pyridin-3-yl) cyclopropanecarboxylic acid amide;

[00230] C) azoles and triazoles: azaconazole, bitertanol, bromuconazole, cyproconazole, difenoconazole, diniconazole, diniconazole-M, epoxiconazole, fenbuconazole, fluquinconazole, flusilazole, flutriafol, hexaconazole, imibenconazole, ipconazole, metconazole, myclobutanil, oxpoconazole, paclobutrazole, penconazole, propiconazole, prothioconazole, simeconazole, tebuconazole, tetraconazole, triadimefon, triadimenol, triticonazole, uniconazole, 1-(4-chloro-phenyl)-2-([1,2,4]triazol-1-yl)-cycloheptanol; imidazoles: cyazofamid, imazalil, pefurazoate, prochloraz, triflumizol; benzimidazoles: benomyl, carbendazim, fuberidazole, thiabendazole; - others: ethaboxam, etridiazole, hymexazole and 2-(4-chloro-phenyl)-N-[4-(3,4-dimethoxy-phenyl)-isoxazol-5-yl]-2-prop-2-ynyloxy-acetamide;

[00231] D) heterocyclic compounds pyridines: fluazinam, pyrifenox, 3-[5-(4-chloro-phenyl)-2,3-dimethyl-isoxazolidin- 3-yl]-pyridine, 3-[5-(4-methyl-phenyl)-2,3-dimethyl-isoxazolidin-3-yl]-pyridine, 2,3,5,6-tetra-chloro-4-methanesulfonyl-pyridine, 3,4,5-trichloropyridine-2,6-di-carbonitrile, N-(1-(5-bromo-3-chloro-pyridin-2-yl)-ethyl)-2,4-dichloronicotinamide, N-[(5-bromo-3-chloro-pyridin-2-yl)-methyl]-2,4-dichloro-nicotinamide; pyrimidines: bupirimate, cyprodinil, diflumetorim, fenarimol, ferimzone, mepanipyrim, nitrapyrin, nuarimol, pyrimethanil; piperazines: triforine; pyrroles: fenpiclonil, fludioxonil; morpholines: aldimorph, dodemorph, dodemorph-acetate, fenpropimorph, tridemorph; piperidines: fenpropidin; - dicarboximides: fluoroimid, iprodione, procymidone, vinclozolin; non-aromatic 5-membered heterocycles: famoxadone, fenamidone, flutianil, octhilinone, probenazole, 5-amino-2-isopropyl-3-oxo-4-ortho-tolyl-2,3-dihydro-pyrazole-1-carbothioic acid S-allyl ester; others: acibenzolar-S-methyl, amisulbrom, anilazin, blasticidin-S, captafol, captan, chinomethionat, dazomet,

debacarb, diclomezine, difenzoquat, difenzoquat- methylsulfate, fenoxanil, Folpet, oxolinic acid, piperalin, proquinazid, pyroquilon, quinoxyfen, triazoxide, tricyclazole, 2-butoxy-6-iodo-3-propylchromen-4-one, 5-chloro-1-(4,6-dimethoxy-pyrimidin-2-yl)-2-methyl-1H-benzimidazole, 5-chloro-7-(4-methylpiperidin-1-yl)-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine and 5-ethyl-6-octyl-[1,2,4]triazolo[1,5-a]pyrimidine-7-ylamine;

[00232] E) carbamates thio- and dithiocarbamates: ferbam, mancozeb, maneb, metam, methasulphocarb, metiram, propineb, thiram, zineb, ziram; carbamates: benthiavalicarb, diethofencarb, iprovalicarb, propamocarb, propamo- carb hydrochlorid, valiphenal and N-(1-(1-(4-cyano-phenyl)ethanesulfonyl)-but-2-yl) carbamic acid-(4-fluorophenyl) ester;

[00233] F) other active substances - guanidines: guanidine, dodine, dodine free base, guazatine, guazatine-acetate, iminoctadine, iminoctadine-triacetate, iminoctadine-tris(albesilate); antibiotics: kasugamycin, kasugamycin hydrochloride-hydrate, streptomycin, pol- yoxine, validamycin A; nitrophenyl derivates: binapacryl, dinobuton, dinocap, nitrthal-isopropyl, tecna-zen, organometal compounds: fentin salts, such as fentin-acetate, fentin chloride or fentin hydroxide; sulfur-containing heterocyclyl compounds: dithianon, isoprothiolane; organophosphorus compounds: edifenphos, fosetyl, fosetyl-aluminum, iproben-fos, phosphorous acid and its salts, pyrazophos, tolclofos-methyl; organochlorine compounds: chlorothalonil, dichlofluanid, dichlorophen, flusulfamide, hexachlorobenzene, pencycuron, pentachlorphenole and its salts, phthalide, quintozene, thiophanate-methyl, tolylfluanid, N-(4-chloro-2-nitro-phenyl)-N-ethyl-4-methyl-benzenesulfonamide; inorganic active substances: Bordeaux mixture, copper acetate, copper hydroxide, copper oxychloride, basic copper sulfate, sulfur; biphenyl, bronopol, cyflufenamid, cymoxanil, diphenylamin, metrafenone, mildiomycin, oxin-copper, prohexadione-calcium, spiroxamine, tolylfluanid, N-(cyclopropylmethoxyimino-(6-difluoro-methoxy-2,3-difluoro-phenyl)-methyl)-2-phenylacetamide, N'-(4-(4-chloro-3-trifluoromethyl-phenoxy)-2,5-dimethyl-phenyl)-N-ethyl-N-methylformamidine, N'-(4-(4-fluoro-3-trifluoromethyl-phenoxy)-2,5-dimethyl-phenyl)-N-ethyl-N-methyl formamidine, N'-(2-methyl-5-trifluoromethyl-4-(3-trimethylsilanyl-propoxy)-phenyl)-N-ethyl-N-methylformamidine, N'-(5-difluoromethyl-2-methyl-4-(3-trimethylsilanyl-propoxy)-phenyl)-N-ethyl-N-methylformamidine, 2-{1-[2-(5-methyl-3-trifluoromethyl-pyrazole-1-yl)-acetyl]-piperidin-4-yl}-thiazole-4-carboxylic acid methyl-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amide, 2-{1-[2-(5- methyl-S-trifluoromethyl-pyrazole-i-yO-acety^-piperidin^-ylJ-thiazole^-carboxylic acid methyl-(R)-1

,2,3,4-tetrahydro-naphthalen-1-yl-amide, acetic acid 6-tert-butyl- 8-fluoro-2,3-dimethyl-quinolin-4-yl ester and methoxy-acetic acid 6-tert-butyl-8- fluoro-2,3-dimethyl-quinolin-4-yl ester.

[00234] G) growth regulators abscisic acid, amidochlor, ancymidol, 6-benzylaminopurine, brassinolide, butralin, chlormequat (chlormequat chloride), choline chloride, cyclanilide, daminozide, dikegulac, dimethipin, 2,6-dimethylpuridine, ethephon, flumetralin, flurprimidol, fluthiacet, forchlorfenuron, gibberellic acid, inabenfide, indole-3-acetic acid , maleic hydrazide, mefluidide, mepiquat (mepiquat chloride), naphthaleneacetic acid, N-6-benzyladenine, paclobutrazol, prohexadione (prohexadione-calcium), prohydrojasmon, thidiazuron, triapenthenol, tributyl phosphorotrithioate, 2,3,5-tri-iodobenzoic acid , trinexapac-ethyl and uniconazole;

[00235] H) herbicides acetamides: acetochlor, alachlor, butachlor, dimethachlor, dimethenamid, flufen- acet, mefenacet, metolachlor, metazachlor, napropamide, naproanilide, pethox- amid, pretilachlor, propachlor, thenylchlor; amino acid derivatives: bilanafos, glyphosate, glufosinate, sulfosate; aryloxyphenoxypropionates: clodinafop, cyhalofop-butyl, fenoxaprop, fluazifop, haloxyfop, metamifop, propaquizafop, quizalofop, quizalofop-P-tefuryl; Bipyridyls: diquat, paraquat; (thio)carbamates: asulam, butylate, carbetamide, desmedipham, dimepiperate, eptam (EPTC), esprocarb, molinate, orbencarb, phenmedipham, prosulfocarb, pyributicarb, thiobencarb, triallate; cyclohexanediones: butroxydim, clethodim, cycloxydim, profoxydim, sethoxydim, tepraloxydim, tralkoxydim; - dinitroanilines: benfluralin, ethalfluralin, oryzalin, pendimethalin, prodiamine, trifluralin; diphenyl ethers: acifluorfen, aclonifen, bifenox, diclofop, ethoxyfen, fomesafen, lactofen, oxyfluorfen; hydroxybenzonitriles: bomoxynil, dichlobenil, ioxynil; - imidazolinones: imazamethabenz, imazamox, imazapic, imazapyr, imazaquin, imazethapyr; phenoxy acetic acids: clomeprop, 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4-DB, dichlorprop, MCPA, MCPA-thioethyl, MCPB, Mecoprop; pyrazines: chloridazon, flufenpyr-ethyl, fluthiacet, norflurazon, pyridate; pyridines: aminopyralid, clopyralid, diflufenican, dithiopyr, fluridone, fluroxypyr, picloram, picolinafen, thiazopyr; sulfonyl ureas: amidosulfuron, azimsulfuron, bensulfuron, chlorimuron-ethyl, chlorsulfuron, cinosulfuron, cyclosulfamuron, ethoxysulfuron, flazasulfuron, flucetosulfuron, flupyrsulfuron, foramsulfuron, halosulfuron, imazosulfuron, iodosulfu- ron, mesosulfuron, metsulfuron-methyl, nicosulfuron, oxasulfuron, primisulfuron, prosulfuron, pyrazosulfuron, rimsulfuron,

sulfometuron, sulfosulfuron, thifensulfuron, triasulfuron, tribenuron, trifloxysulfuron, triflusulfuron, tritosulfuron, 1-((2-chloro-6-propyl-imidazo[1,2-b]pyridazin-3-yl)sulfonyl)-3-(4,6-dimethoxy-pyrmidin-2-yl)urea; triazines: ametryn, atrazine, cyanazine, dimethametryn, ethiozin, hexazinone, metamitron, metribuzin, prometryn, simazine, terbuthylazine, terbutryn, triaziflam; ureas: chlorotoluron, daimuron, diuron, fluometuron, isoproturon, linuron, metha-benzthiazuron,tebuthiuron; other acetolactate synthase inhibitors: bispyribac-sodium, cloransulam-methyl, diclosulam, florasulam, flucarbazone, flumetsulam, metosulam, ortho-sulfamuron, penoxsulam, propoxycarbazone, pyribambenz-propyl, pyribenzoxim, pyriftalid, pyriminobac-methyl, pyrimisulfan, pyrithiobac, pyroxasulfone, pyroxsulam; others: amicarbazone, aminotriazole, anilofos, beflubutamid, benazolin, bencar- bazone,benfluresate, benzofenap, bentazone, benzobicyclon, bromacil, bromo- butide, butafenacil, butamifos, cafenstrole, carfentrazone, cinidon-ethlyl, chlor- thal, cinmethylin, clomazone, cumyluron, cyprosulfamide, dicamba, difenzoquat, diflufenzopyr, Drechslera monoceras, endothal, ethofumesate, etobenzanid, fen- trazamide, flumiclorac-pentyl, flumioxazin, flupoxam, flurochloridone, flurtamone, indanofan, isoxaben, isoxaflutole, lenacil, propanil, propyzamide, quinclorac, quinmerac, mesotrione, methyl arsonic acid, naptalam, oxadiargyl, oxadiazon, oxaziclomefone, pentoxazone, pinoxaden, pyraclonil, pyraflufen-ethyl, pyrasulfo- tole, pyrazoxyfen, pyrazolynate, quinoclamine, saflufenacil, sulcotrione, sulfentra- zone, terbacil, tefuryltrione, tembotrione, thiencarbazone, topramezone, 4- hydroxy-3-[2-(2-methoxy-ethoxymethyl)-6-trifluoromethyl-pyridine-3-carbonyl]- bicyclo[3.2.1]oct-3-en-2-one, (3-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4- trifluoromethyl-3,6-dihydro-2H-pyrimidin-1-yl)-phenoxy]-pyridin-2-yloxy)-acetic acid ethyl ester, 6-amino-5-chloro-2-cyclopropyl-pyrimidine-4-carboxylic acid methyl ester, 6-chloro-3-(2-cyclopropyl-6-methyl-phenoxy)-pyridazin-4-ol, 4-amino-3-chloro-6-(4-chloro-phenyl)-5-fluoro-pyridine-2-carboxylic acid, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-pyridine-2-carboxylic acid methyl ester, and 4-amino-3-chloro-6-(4-chloro-3-dimethylamino-2-fluoro-phenyl)- pyridine-2-carboxylic acid methyl ester.

[00236] I) insecticides - organo(thio)phosphates: acephate, azamethiphos, azinphos-methyl, chlorpyrifos, chlorpyrifos-methyl, chlorfenvinphos, diazinon, dichlorvos, dicrotophos, dimethoate, disulfoton, ethion, fenitrothion, fenthion, isoxathion, malathion, methamido- phos, methidathion, methyl-parathion, mevinphos, monocrotophos, oxydemeton- methyl, paraoxon, parathion, phenthoate, phosalone, phosmet, phosphamidon, phorate, phoxim, pirimiphos-methyl,

profenofos, prothiofos, sulprophos, tetra- chlorvinphos, terbufos, triazophos, trichlorfon; carbamates: alanycarb, aldicarb, bendiocarb, benfuracarb, carbaryl, carbofuran, carbosulfan, fenoxycarb, furathiocarb, methiocarb, methomyl, oxamyl, pirimicarb, propoxur, thiodicarb, triazamate; pyrethroids: allethrin, bifenthrin, cyfluthrin, cyhalothrin, cyphenothrin, cypermethrin, alpha-cypermethrin, beta-cypermethrin, zeta-cypermethrin, deltamethrin, esfenvalerate, etofenprox, fenpropathrin, fenvalerate, imiprothrin, lambda- cyhalothrin, permethrin, prallethrin, pyrethrin I and II, resmethrin, silafluofen, tau- fluvalinate, tefluthrin, tetramethrin, tralomethrin, transfluthrin, profluthrin, dimefluthrin; insect growth regulators: a) chitin synthesis inhibitors: benzoylureas: chlorfluazuron, cyramazin, diflubenzuron, flucycloxuron, flufenoxuron, hexaflumuron, lufenuron, novaluron, teflubenzuron, triflumuron; buprofezin, diofenolan, hexythiazox, etoxazole, clofentazine; b) ecdysone antagonists: halofenozide, methoxyfenozide, tebufenozide, azadirachtin; c) juvenoids: pyriproxyfen, methoprene, fenoxycarb; d) lipid biosynthesis inhibitors: spirodiclofen, spiromesifen, spirotetramat; nicotinic receptor agonists/antagonists compounds: clothianidin, dinotefuran, imi- dacloprid, thiamethoxam, nitenpyram, acetamiprid, thiacloprid, 1-(2-chloro- thiazol-5-ylmethyl)-2-nitrimino-3,5-dimethyl-[1,3,5]triazinane; GABA antagonist compounds: endosulfan, ethiprole, fipronil, vaniliprole, pyrafluprole, pyriprole, 5-amino-1 -(2,6-dichloro-4-methyl-phenyl)-4-sulfinamoyl-1H-pyrazole-3-carbothioic acid amide; macrocyclic lactone insecticides: abamectin, emamectin, milbemectin, lepimectin, spinosad, spinetoram; mitochondrial electron transport inhibitor (METI) I acaricides: fenazaquin, pyrida- ben, tebufenpyrad, tolfenpyrad, flufenerim; METI II and III compounds: acequinocyl, fluacyprim, hydramethylnon; Uncouplers: chlorfenapyr; - oxidative phosphorylation inhibitors: cyhexatin, diafenthiuron, fenbutatin oxide, propargite; moulting disruptor compounds: cryomazine; mixed function oxidase inhibitors: piperonyl butoxide; sodium channel blockers: indoxacarb, metaflumizone; - others: benclothiaz, bifenazate, cartap, flonicamid, pyridalyl, pymetrozine, sulfur, thiocyclam, flubendiamide, chlorantraniliprole, cyazypyr (HGW86), cyenopyrafen, flupyrazofos, cyflumetofen, amidoflumet, imicyafos, bistrifluron, and pyrifluquinazon.

[00237] The present invention furthermore relates to agrochemical compositions comprising a mixture of at least one compound of formula I (component 1) and at least one further active substance useful for plant protection, e.g. selected from the groups A) to I) (component 2), in particular one further fungicide, e.g. one or more fungicide from the groups A) to F), as

described above, and if desired one suitable solvent or solid carrier. Those mixtures are of particular interest, since many of them at the same application rate show higher efficiencies against harmful fungi. Furthermore, combating harmful fungi with a mixture of compounds of formula I and at least one fungicide from groups A) to F), as described above, is more efficient than combating those fungi with individual compounds of formula I or individual fungicides from groups A) to F). By applying compounds of formula I together with at least one active substance from groups A) to I) a synergistic effect can be obtained, i.e. more than simple addition of the individual effects is obtained (synergistic mixtures).

[00238] According to this invention, applying the compounds of formula I together with at least one further active substance is to be understood to denote that at least one compound of formula I and at least one further active substance occur simultaneously at the site of action (i.e. the harmful fungi to be controlled or their habitats such as infected plants, plant propagation materials, particularly seeds, surfaces, materials or the soil as well as plants, plant propagation materials, particularly seeds, soil, surfaces, materials or rooms to be protected from fungal attack) in a fungicidally effective amount. This can be obtained by applying the compounds of formula I and at least one further active substance simultaneously, either jointly (e.g. as tank-mix) or separately, or in succession, wherein the time interval between the individual applications is selected to ensure that the active substance applied first still occurs at the site of action in a sufficient amount at the time of application of the further active substance(s). The order of application is not essential for working of the present invention.

[00239] In binary mixtures, i.e. compositions according to the invention comprising one compound I (component 1) and one further active substance (component 2), e.g. one active substance from groups A) to I), the weight ratio of component 1 and component 2 generally depends from the properties of the active substances used, usually it is in the range of from 1 :100 to 100:1 , regularly in the range of from 1 :50 to 50:1 , preferably in the range of from 1 :20 to 20:1 , more preferably in the range of from 1 :10 to 10:1 and in particular in the range of from 1 :3 to 3:1.

[00240] In ternary mixtures, i.e. compositions according to the invention comprising one compound I (component 1) and a first further active substance (component 2) and a second further active substance (component 3), e.g. two active substances from groups A) to I), the weight ratio of component 1 and component 2 depends from the properties of the active

substances used, preferably it is in the range of from 1:50 to 50:1 and particularly in the range of from 1 :10 to 10:1 , and the weight ratio of component 1 and component 3 preferably is in the range of from 1:50 to 50:1 and particularly in the range of from 1:10 to 10:1.

[00241] The components can be used individually or already partially or completely mixed with one another to prepare the composition according to the invention. It is also possible for them to be packaged and used further as combination composition such as a kit of parts.

[00242] In one embodiment of the invention, the kits may include one or more, including all, components that may be used to prepare a subject agrochemical composition. E. g., kits may include one or more fungicide component(s) and/or an adjuvant component and/or an insecticide component and/or a growth regulator component and/or a herbicide. One or more of the components may already be combined together or pre-formulated. In those embodiments where more than two components are provided in a kit, the components may already be combined together and as such are packaged in a single container such as a vial, bottle, can, pouch, bag or canister. In other embodiments, two or more components of a kit may be packaged separately, i.e., not pre- formulated. As such, kits may include one or more separate containers such as vials, cans, bottles, pouches, bags or canisters, each container containing a separate component for an agrochemical composition. In both forms, a component of the kit may be applied separately from or together with the further components or as a component of a combination composition according to the invention for preparing the composition according to the invention.

[00243] The user applies the composition according to the invention usually from a predosage device, a knapsack sprayer, a spray tank or a spray plane. Here, the agrochemical composition is made up with water and/or buffer to the desired application concentration, it being possible, if appropriate, to add further auxiliaries, and the ready-to-use spray liquor or the agrochemical composition according to the invention is thus obtained. In some embodiments, 50 to 500 liters of the ready-to-use spray liquor are applied per hectare of agricultural useful area. In some embodiments 100 to 400 liters of the ready-to-use spray liquor are applied per hectare. In some embodiments, the invention provides a kit for greenhouse application of a ready-to-use composition of the invention.

[00244] According to one embodiment, individual components of the composition according to the invention such as parts of a kit or parts of a binary or ternary mixture may be mixed by the user himself in a spray tank and further auxiliaries may be added, if appropriate (tank mix). In a

further embodiment, either individual components of the composition according to the invention or partially premixed components, e.g. components comprising compounds of formula I and/or active substances from the groups A) to I), may be mixed by the user in a spray tank and further auxiliaries and additives may be added, if appropriate (tank mix).

[00245] In a further embodiment, either individual components of the composition according to the invention or partially premixed components, e.g. components comprising compounds of formula I and/or active substances from the groups A) to I), can be applied jointly (e.g. after tankmix) or consecutively.

[00246] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the strobilurines of group A) (component 2) and particularly selected from azoxystrobin, dimoxystrobin, fluoxastrobin, kresoxim-methyl, orysastrobin, picoxystrobin, pyraclostrobin and trifloxystrobin.

[00247] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the carboxamides of group B) (component 2). In some embodiments, the carboxamide is selected from the group consisting of bixafen, boscalid, sedaxane, fenhexamid, metalaxyl, isopyrazam, mefenoxam, ofurace, dimethomorph, flumorph, fluopicolid (picobenzamid), zoxamide, carpropamid, mandipropamid and N-(3',4',5'-trifluorobiphenyl-2-yl)-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxamide.

[00248] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the azoles of group C) (component 2). In some embodiments, the azole is selected from the group consisting of cyproconazole, difenoconazole, epoxicona- zole, fluquinconazole, flusilazole, flutriafol, metconazole, myclobutanil, penconazole, propiconazole, prothioconazole, triadimefon, triadimenol, tebuconazole, tetraconazole, triticonazole, prochloraz, cyazofamid, benomyl, carbendazim and ethaboxam.

[00249] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the heterocyclic compounds of group D) (component 2). In some embodiments, the heterocyclic compounds of group D) are selected from the group consisting of fluazinam, cyprodinil, fenarimol, mepanipyrim, pyrimethanil, triforine, fludioxonil, dodemorph, fenpropimorph, tridemorph,

fenpropidin, iprodione, vinclozolin, famoxadone, fenamidone, probenazole, proquina- zid, acibenzolar-S-methyl, captafol, folpet, fenoxanil, quinoxyfen and 5-ethyl-6-octyl-[1,2,4]triazolo[1,5-a]pyrimidine-7-ylamine.

[00250] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the carbamates of group E) (component 2). In some embodiments, the carbamates are selected from the group consisting of mancozeb, metiram, propineb, thiram, iprovalicarb, benthiavalicarb and propamocarb.

[00251] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the fungicides given in group F) (component 2). In some embodiments, the fungicides of group F) are selected from the group consisting of dithianon, fentin salts, such as fentin acetate, fosetyl, fosetyl-aluminium, H3PO3 and salts thereof, chlorthalonil, dichlofluanid, thiophanat-methyl, copper acetate, copper hydroxide, copper oxychloride, copper sulfate, sulfur, cymoxanil, metrafenone and spiroxamine.

[00252] The active substances referred to as component 2, their preparation and their activity against harmful fungi is known in the art. In some embodiments these substances are commercially available. The compounds described by IUPAC nomenclature, their preparation and their fungicidal activity are also known in the art (cf. Can. J. Plant Sci. 48(6), 587-94, 1968; EP-A 141 317; EP-A 152 031 ; EP-A 226 917; EP-A 243 970; EP-A 256 503; EP-A 428 941 ; EP-A 532 022; EP-A 1 028 125; EP-A 1 035 122; EP-A 1 201 648; EP-A 1 122 244, JP 2002316902; DE 19650197; DE 10021412; DE 102005009458; US 3,296,272; US 3,325,503; WO 98/46608; WO 99/14187; WO 99/24413; WO 99/27783; WO 00/29404; WO 00/46148; WO 00/65913; WO 01/54501 ; WO 01/56358; WO 02/22583; WO 02/40431 ; WO 03/10149; WO 03/1 1853; WO 03/14103; WO 03/16286; WO 03/53145; WO 03/61388; WO 03/66609; WO 03/74491 ; WO 04/49804; WO 04/83193; WO 05/120234; WO 05/123689; WO 05/123690; WO 05/63721 ; WO 05/87772; WO 05/87773; WO 06/15866; WO 06/87325; WO 06/87343; WO 07/82098; WO 07/90624).

[00253] The mixtures of active substances can be prepared as compositions comprising besides the active ingredients at least one inert ingredient by usual means, e.g. by the means given for the compositions of compounds of formula I.

[00254] Concerning usual ingredients of such compositions reference is made to the explanations given for the compositions containing compounds of formula I.

[00255] The mixtures of active substances according to the present invention are suitable as fungicides, as are the compounds of formula I. In some embodiments the mixtures and compositions of the present invention are useful for the protection of plants against a broad spectrum of phytopathogenic fungi. In some embodiments, the phytopathogenic fungi are from the classes of the Ascomycetes, Basidiomycetes, Deuteromycetes and Peronosporomycetes (syn. Oomycetes).

[00256] The compounds of formula I and pharmaceutically acceptable salts thereof are also suitable for treating diseases in men and animals, especially as antimycotics, for treating cancer and for treating virus infections. The term "antimycotic", as distinguished from the term "fungicide", refers to a medicament for combating zoopathogenic or humanpathogenic fungi, i.e. for combating fungi in animals, especially in mammals (including humans) and birds.

[00257] In some embodiments, the present invention provides a medicament comprising at least one compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

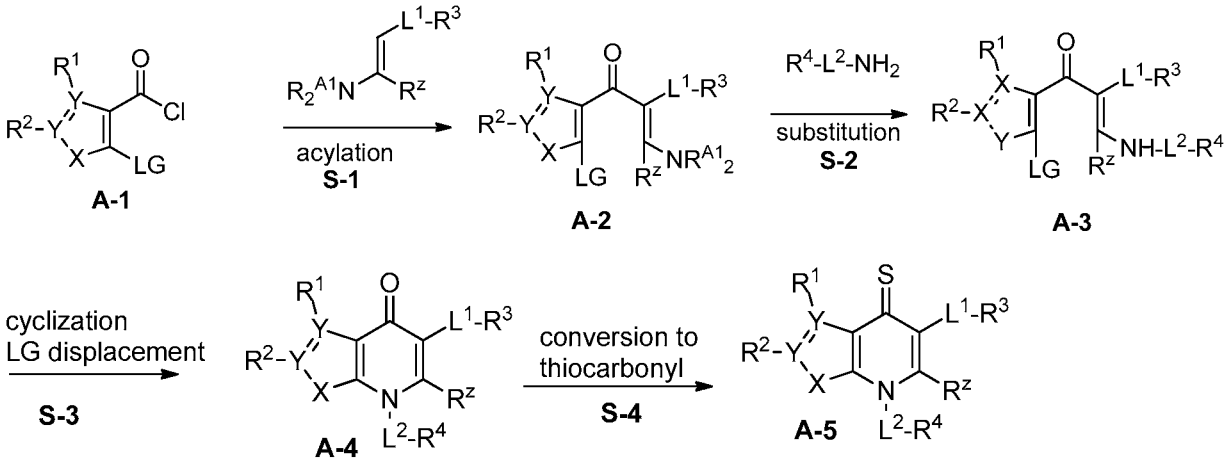
[00258] In some embodiments, the invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for preparing an antimycotic medicament; i.e. for preparing a medicament for the treatment and/or prophylaxis of infections with humanpathogenic and/or zoopathogenic fungi.

EXEMPLIFICATION

[00259] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[00260] In certain embodiments, compounds of the present invention are generally prepared according to Scheme I set forth below:

Scheme I



[00261] In Scheme I above, LG is a leaving group and each of R^1, R^2, R^3, R^4, R^z, R^{A1}, L^1, L^2, X and Y is as defined above and below and in classes and subclasses as described herein. Suitable leaving groups, LG, include but are not limited to hydroxyls, halogens and sulfonates. In certain embodiments, LG is a halogen. In certain embodiments, LG is hydroxyl. In certain embodiments, LG is chlorine.

[00262] In one aspect, the present invention provides methods for preparing compounds of formula **A-4** according to the steps depicted in Scheme I, above. In some embodiments, at step **S-1**, a heterocyclic acid chloride of formula **A-1** is reacted with an enamine to form an enamide of formula **A-2**. For example, 1-phenylmethyl-5-chloro-1,2,3-triazole-4-carbonyl chloride reacts with 1-(1-pyrrolidinyl)cyclopentene to afford 5-chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl)[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone under the conditions described in T.-M. Chan et al. J. Het. Chem. 1990, 27, 1135, the entirety of which is incorporated herein by reference. In certain embodiments, the acylation reaction is performed in the presence of a base and a solvent. In some embodiments the base is TEA (triethylamine). In some embodiments the solvent is DCM (dichloromethane). In some embodiments **A-1** is a triazole. In some embodiments **A-1** is a thiophene (see for example M. E. Schnute et al. WO 2004022566, the entirety of which is incorporated herein by reference). In some embodiments R^{A1} is a C_{5-6} cycloalkyl group.

[00263] In some embodiments, step **S-2** comprises treating a compound of formula **A-2** with an amine to form a compound of formula **A-3**. For example, 5-chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl)[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone reacts with aniline under the conditions described in T.-M. Chan et al. J. Het. Chem. 1990, 27, 1135, the entirety of which is

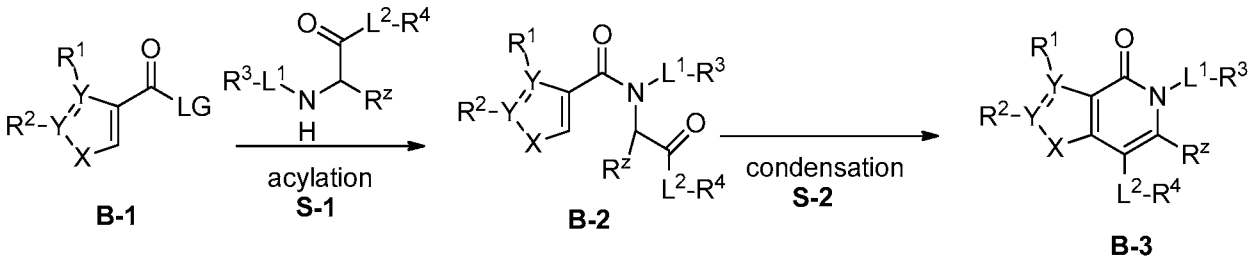
incorporated herein by reference. In some embodiments the amine is (R)-2-(2-methoxyphenyl)-2-((tetrahydro-2H-pyran-4-yl)oxy)ethanamine, prepared by resolution of commercially-available 2-(2-methoxyphenyl)-2-((tetrahydro-2H-pyran-4-yl)oxy)ethanamine. In some embodiments step **S-2** is performed with benzene as solvent. In some embodiments step **S-2** is performed in the presence of anhydrous *p*-toluenesulfonic acid. In some embodiments steps **S-1** and **S-2** are performed without an intermediate purification of compound **A-2**.

[00264] In some embodiments, step **S-3** comprises contacting the intermediate of formula **A-3** with potassium *tert*-butoxide to form a pyridone compound of formula **A-4** according to the method of T.-M. Chan et al. J. Het. Chem. 1990, 27, 1135. In some embodiments step **S-3** is performed with *tert*-butanol as solvent.

[00265] In some embodiments, step **S-4** comprises contacting the compound of formula **A-4** with a reagent to convert the carbonyl group into a thiocarbonyl group. In some embodiments the reagent used to convert the hydroxyl group into a carbonyl group is Lawesson's reagent. In some embodiments step **S-4** is performed in a solvent. In some embodiments the solvent is dioxane. In some embodiments the solvent is toluene.

[00266] In certain embodiments, compounds of the present invention are generally prepared according to Scheme II set forth below:

Scheme II



[00267] In Scheme II above, each of LG, R^1, R^2, R^3, R^4, R^z, L^1, L^2, X and Y is as defined above and below and in classes and subclasses as described herein.

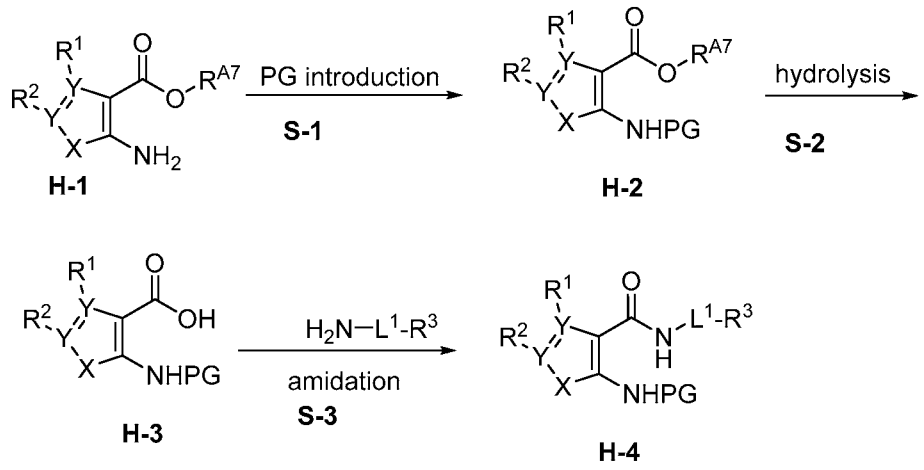
[00268] In one aspect, the present invention provides methods for preparing compounds of formula **B-3** according to the steps depicted in Scheme II, above. In some embodiments, at step **S-1**, a heterocyclic acid chloride of formula **B-1** (LG = Cl) is reacted with an aminoketone to effect an acylation reaction to form an amide of formula **B-2**. In certain embodiments, the acylation reaction is performed in the presence of an amine. In some embodiments the base is

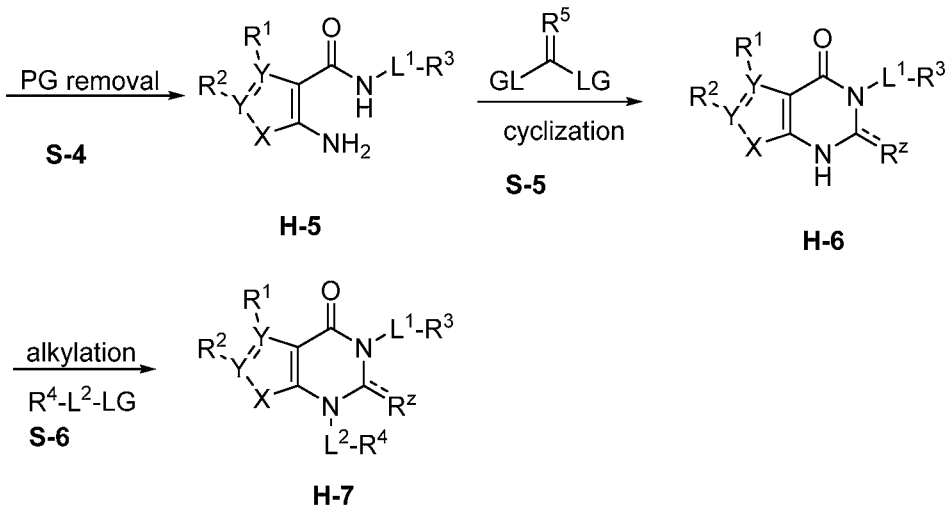
TEA. In some embodiments a heterocyclic acid of formula **B-1** (LG = OH) is reacted with an aminoketone in the presence of a coupling agent. In some embodiments the coupling reagent is (dimethylamino)-N,N-dimethyl(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methaniminium hexafluorophosphate (HATU). In some embodiments the coupling reagent is 3-(ethyliminomethyleneamino)-N,N-dimethylpropan-1-amine (EDC). In some embodiments the reaction is performed with both EDC and an additive. In some embodiments the additive is hydroxybenzotriazole (HOBT). In some embodiments the solvent is THF. In some embodiments the solvent is DMF.

[00269] In some embodiments, step **S-2** comprises contacting a compound of formula **B-2** with trifluoroacetic acid to form a compound of formula **B-3**, following the method described in R. Cincinelli et al. Synlett 2008, (9), 1309 (the entirety of which is incorporated herein by reference) for the synthesis of β-carbolin-1-ones. In some embodiments the solvent is acetonitrile. In some embodiments, step **S-2** comprises contacting a compound of formula **B-2** with sodium iodide and trimethylsilylchloride to form a compound of formula **B-3**, following the alternative method described in S. Cananzi et al. Bioorg. Med. Chem. 2011, 19, 4971 (the entirety of which is incorporated herein by reference) for the synthesis of β-carbolin-1-ones.

[00270] In certain embodiments, compounds of the present invention are generally prepared according to Scheme III set forth below.

Scheme III





[00271] In Scheme I above, each of PG, LG, R^1, R^2, R^3, R^4, R^{A7}, R^z, L^1, L^2, X and Y is as defined above and below and in classes and subclasses as described herein.

[00272] In one aspect, the present invention provides methods for preparing compounds of formula **H-7** according to the steps depicted in Scheme I, above. In some embodiments, step **S-1** comprises treating a heteroaryl amine of formula **H-1** with a reagent for the protection of the amine moiety to form compounds of formula **H-2**. In some embodiments the reagent is di-*tert*-butyl dicarbonate. In some embodiments a catalyst is added. In some embodiments the catalyst is DMAP. In some embodiments the solvent is acetonitrile.

[00273] In some embodiments step **S-2** comprises contacting a compound of formula **H-2** with a reagent to convert the ester group into a carboxylic acid, thereby forming a compound of formula **H-4**. In some embodiments the deesterification reagent is a base. In some embodiments the base is lithium hydroxide. In some embodiments the reagent is an acid. In some embodiments the reaction is performed in aqueous solvent. In some embodiments tetrahydrofuran is employed as a cosolvent.

[00274] In some embodiments, at step **S-3** a carboxylic acid of formula **H-3** is reacted with an amine to form an amide of formula **H-4**. In certain embodiments, the acylation reaction is performed in the presence of an amine. In some embodiments the base is TEA. In some embodiments the reaction is performed in the presence of a coupling agent. In some embodiments the coupling reagent HATU. In some embodiments the coupling reagent is EDC.

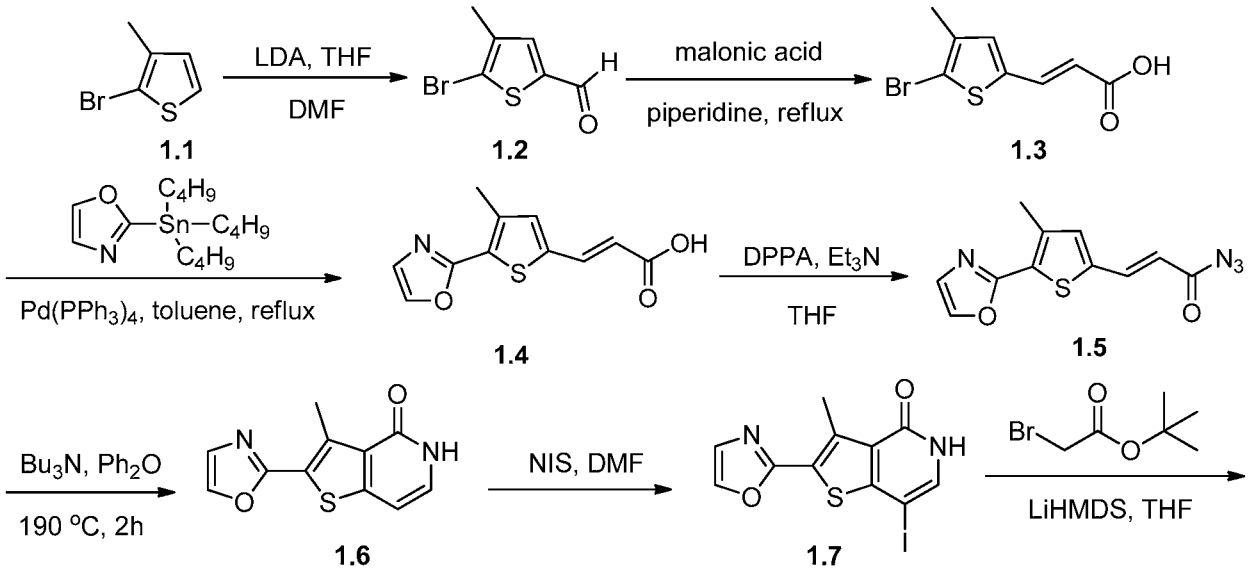
In some embodiments the reaction is performed with both EDC and an additive. In some embodiments the additive is HOBT. In some embodiments the solvent is DMF.

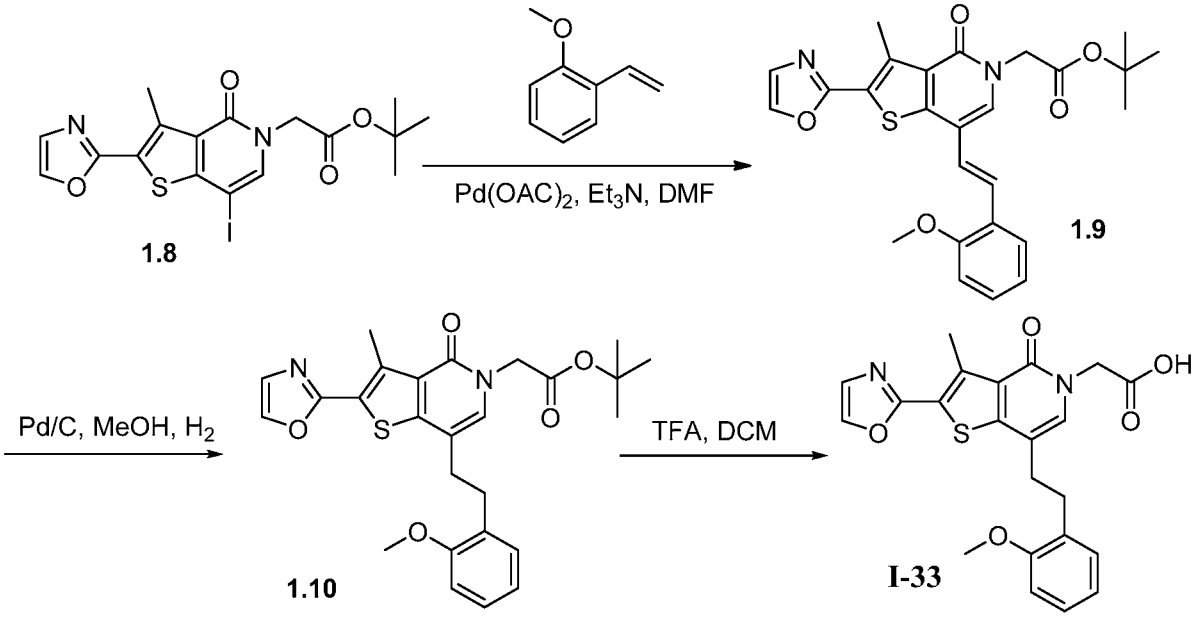
[00275] In some embodiments step **S-4** comprises treating a compound of formula **H-4** with a reagent for the removal of PG to form a compound of formula **H-5**. In some embodiments, as for example when PG is a *tert*-butoxycarbonyl group, the reagent is trifluoroacetic acid. In some embodiments when the reagent is trifluoroacetic acid the solvent is DCM.

[00276] In some embodiments step **S-5** comprises treating a compound of formula **H-5** with a carbonylation or thiocarbonylation reagent to form a compound of formula **H-7**. In some embodiments the carbonylating reagent is phosgene. In some embodiments the thiocarbonylating reagent is thiophosgene. In some embodiments the solvent is DCM. In some embodiments the solvent is toluene.

[00277] In some embodiments step **S-6** comprises treating a compound of formula **H-6** with a base and an alkylating agent to form a compound of formula **H-7**. In some embodiments the base is sodium hydride. In some embodiments the alkylating agent is an alkyl halide. In some embodiments the alkylating agent is an alkyl sulfonate. In some embodiments the solvent is THF.

[00278] Example 1. Synthesis of compound 2-(7-(2-methoxyphenethyl)-3-methyl-2-(oxazol-2-yl)-4-oxothieno[3,2-c]pyridin-5(4H)-yl)acetic acid, I-33.





[00279] **Synthesis of compound 1.2.** Into a 250-mL 3-necked round-bottom flask under nitrogen, was placed bis(propan-2-yl)amine (15.2 g, 150.21 mmol, 1.50 equiv) in THF (100 mL). The mixture was cooled to -40°C and butyllithium (60 mL, 1.50 equiv, 2.5 mol/L) was added slowly stirred for 30 mins. The mixture was stirred at -40 °C for 30 min. Then, the above solution was added to a solution of 2-bromo-3-methylthiophene, compound **1.1** (17.7 g, 99.96 mmol, 1.00 equiv) in THF (100 mL) at -78°C and stirred for 30 min. N,N-dimethylformamide (100 mL) was added at -78°C. Reaction was stirred for 1 hour at -78°C. The reaction was then quenched by the addition of 1 L of NH_4Cl (aq.). and extracted with 3x500 mL of ethyl acetate. Organic layers were combined and washed with 2x1000 mL of brine. Organic layer was dried over anhydrous magnesium sulfate and solvents were under vacuum. The crude product was purified by re-crystallization from hexane to furnish 18.2 g (89%) of 5-bromo-4-methylthiophene-2-carbaldehyde, compound **1.2** as a brown solid.

[00280] **Synthesis of compound 1.3.** Into a 500-mL 4-necked round-bottom flask, was placed a solution of compound **1.2** (10.2 g, 49.74 mmol, 1.00 equiv) in pyridine (150 mL), propanedioic acid (20.8 g, 199.88 mmol, 4.00 equiv), and piperidine (202 mg, 2.37 mmol, 0.05 equiv). Reaction was stirred overnight at 110 °C in an oil bath. Upon completion solvents were removed under a reduced pressure. The pH value of the solution was adjusted to 2 with hydrogen chloride (1 mol/L) and precipitate was collected by filtration to afford 12 g (98%) of compound **1.3** as a brown solid.

[00281] **Synthesis of compound 1.4.** Into a 1000-mL round-bottom flask, under nitrogen, was placed a solution of compound **1.3** (13 g, 52.61 mmol, 1.00 equiv) in toluene (300 mL), 2-(tributylstannyl)-1,3-oxazole (28.5 g, 79.58 mmol, 1.50 equiv), and tetrakis(triphenylphosphane) palladium (3.1 g, 2.68 mmol, 0.05 equiv). Reaction solution was stirred overnight at 110 °C in an oil bath. Upon completion of the reaction, solvents were removed under vacuum, and residue was dissolved in 200 mL of ethyl acetate. Organic layer was washed with 3x200 mL of saturated sodium bicarbonate solution. The pH value of the solution was adjusted to 2 with hydrogen chloride (1 mol/L) and the resulting solids were filtered to furnish 2.5 g (20%) of compound **1.4** as a yellow solid.

[00282] **Synthesis of compound 1.5.** A 50-mL round-bottom flask, was charged with THF (20 mL) solution of compound **1.5** (200 mg, 0.85 mmol, 1.00 equiv), [[azido(phenoxy)phosphoryl]oxy]benzene (280 mg, 1.02 mmol, 1.20 equiv), Et_3N (258 mg, 2.55 mmol, 3.00 equiv). Reaction was stirred overnight at room temperature. Upon completion reaction was quenched by the addition of 50 mL of water and extracted with 3x50 mL of ethyl acetate. Organic layers were combined and washed with 2x200 mL of brine and dried over anhydrous sodium sulfate. Solvents were removed under reduced pressure to yield 220 mg (crude) of compound **1.5** as a yellow solid.

[00283] **Synthesis of compound 1.6.** A 50-mL 3-necked round-bottom flask maintained under an inert atmosphere of nitrogen, was charged with compound **1.5** (3 g, 11.53 mmol, 1.00 equiv) in Ph_2O (20 mL) and tributylamine (2.13 mg, 0.01 mmol, 1.00 equiv). Reaction was stirred for 2 h at 190 °C. Upon completion solvents were removed under vacuum and product was precipitated by the addition of methanol. Isolated solids were washed with 100 mL of hexane and collected by filtration which resulted in 530 mg (20%) of compound **1.6** as a gray solid.

[00284] **Synthesis of compound 1.7.** A 100-mL round-bottom flask, was charged with a solution of compound **1.6** (530 mg, 2.28 mmol, 1.00 equiv) in DMF(50 mL), and 1-iodopyrrolidine-2,5-dione (616 mg, 2.74 mmol, 1.20 equiv). Reaction was stirred overnight at room temperature and subsequently quenched by the addition of 20 mL of water. The resulting solution was extracted with 3x20 mL of ethyl acetate. Organic layers were combined and washed with 3x50 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 650 mg (crude) of compound **1.7** as a gray solid.

[00285] **Synthesis of compound 1.8.** Into a 100-mL 3-necked round-bottom flask purged and maintained under an atmosphere of nitrogen, was placed a compound **1.7** (650 mg, 1.81 mmol, 1.00 equiv) as a solution in THF (60 mL). To the solution was added lithiobis(trimethylsilyl)amine (2.2 mL, 1.20 equiv, 1mol/L) dropwise with stirring at 0°C. After stirring for 30 min at 0°C, tert-butyl 2-bromoacetate (426 mg, 2.18 mmol, 1.20 equiv) was dropwise while maintaining 0°C . Reaction was stirred at room temperature overnight. The reaction was then quenched by the addition of 10 mL of saturated NH_4Cl solution. The resulting solution was extracted with 2x10 mL of ethyl acetate. Organic layers combined and washed with 3x50 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. Crude was purified using flash column chromatography to furnish 500 mg (58%) of compound **1.8** as a brown solid.

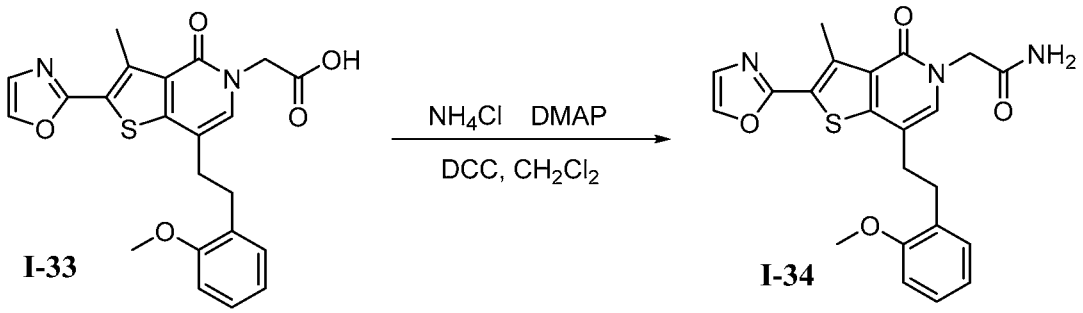
[00286] **Synthesis of compound 1.9.** A 25-mL round-bottom flask, was charged with a solution of compound 1.8 (500 mg, 1.06 mmol, 1.00 equiv) in DMF (5 mL), 1-ethenyl-2-methoxybenzene (170 mg, 1.27 mmol, 1.20 equiv), $Pd(OAc)_2$ (48 mg, 0.21 mmol, 0.20 equiv) and Et_3N (214 mg, 2.11 mmol, 2.00 equiv). Reaction was stirred overnight at 100 °C in an oil bath and then quenched by the addition of 10 mL of water. Resulting solution was extracted with 2x100 mL of ethyl acetate. Organic layers were combined and washed with 2x100 mL of brine, dried over sodium sulfate and concentrated under vacuum. The crude product was re-crystallized from n-hexane, and the solids were collected by filtration to provide 150 mg (30%) of compound **1.9** as a brown solid.

[00287] **Synthesis of compound 1.10.** A 25-mL round-bottom flask, was charged with a solution of compound **1.9** (70 mg, 1.00 equiv) in methanol (5 mL) and palladium on carbon (5 mg). Hydrogen gas was introduced. Reaction was stirred overnight at room temperature. Upon completion of reaction, suspension was filtered and solids washed by methanol (5 mL). Organic layers were combined and concentrated under vacuum to furnish 60 mg (crude) of compound 1.10 as a white solid.

[00288] **Synthesis of compound I-33.** Into a 10-mL round-bottom flask, was placed a solution of compound **1.10** (60 mg, 0.12 mmol, 1.00 equiv) in dichloromethane (2 mL), and trifluoroacetic acid (0.5 mL). Reaction was stirred overnight at room temperature. Upon completion of the reaction solvents were removed under reduced pressure. The crude product was purified by Prep-HPLC to furnish 28.5 mg (54%) of 2-(7-(2-methoxyphenethyl)-3-methyl-2-

(oxazol-2-yl)-4-oxothieno[3,2-c]pyridin-5(4H)-yl)acetic acid, **I-33** as a white solid. LCMS (ES, *m/z*): 425 $[M+H]^+$; ^1H NMR (400MHz,DMSO-d_6): δ2.72-2.80(m, 2H), 2.88-2.98(m, 5H), 3.83(s, 3H), 4.40(s, 2H), 6.86-6.90(t, 1H), 6.95-7.01(d, 1H), 7.15-7.25(m, 2H), 7.35-7.48(m, 2H), 8.26 (s, 1H).

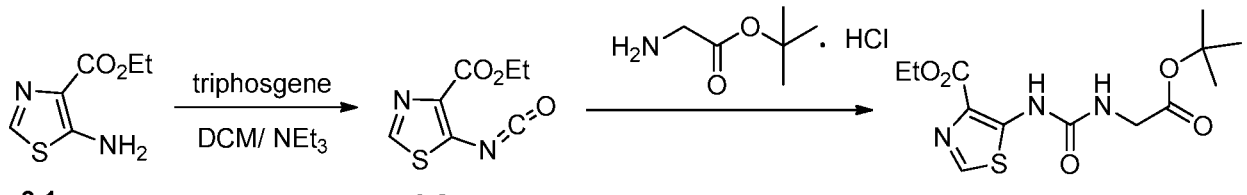
[00289] Example 2. Synthesis of compound 2-(7-(2-methoxyphenethyl)-3-methyl-2-(oxazol-2-yl)-4-oxothieno[3,2-c]pyridin-5(4H)-yl)acetamide, I-34.



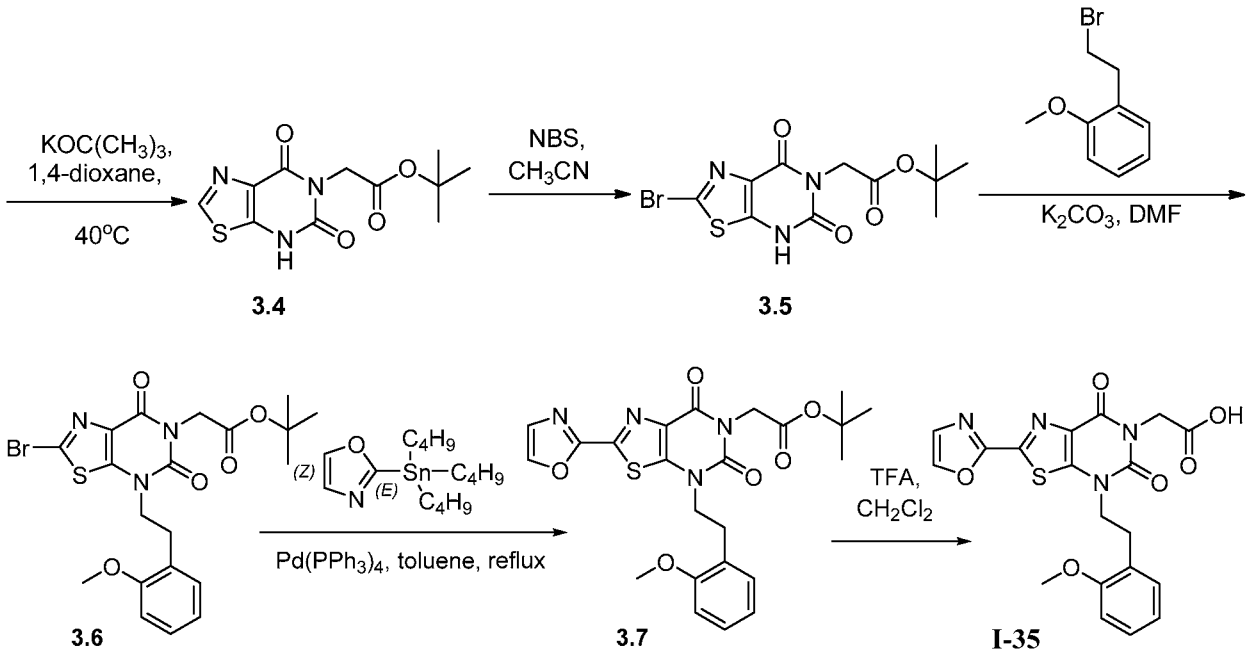
I-33 **I-34**

A 25-mL 3-necked round-bottom flask kept under nitrogen, was charged with compound **I-33** (40 mg, 0.08 mmol, 1.00 equiv), DCC (64 mg, 0.31 mmol, 3.73 equiv), CH_2Cl_2 (8 mL), NH_4Cl (24.8 mg, 0.46 mmol, 5.57 equiv) and 4-dimethylaminopyridine (38 mg, 0.31 mmol, 3.74 equiv). Reaction was stirred overnight at 50 °C. Upon completion, solvents were removed under reduced pressure. Crude was purified by preparative TLC and then by preparative HPLC to provide 1.9 mg (5%) of 2-(7-(2-methoxyphenethyl)-3-methyl-2-(oxazol-2-yl)-4-oxothieno[3,2-c]pyridin-5(4H)-yl)acet-amide, **I-34** as a white solid. LCMS (ES, *m/z*): 424 $[M+H]^+$; ^1H NMR (300MHz, DMSO-d_6): δ2.73-2.78(t,2H), 2.89-2.96(m,5H), 3.84(s,3H), 4.54 (s,2H), 6.88-6.91(t,1H), 6.97-7.00(dd,2H), 7.19-7.24(m, 3H), 7.44-7.47(dd,2H), 7.61(s,1H), 8.26(s,1H).

[00290] Example 3. Synthesis of 2-(4-(2-methoxyphenethyl)-2-(oxazol-2-yl)-5,7-dioxo-4,5-dihydrothiazolo[5,4-d]pyrimidin-6(7H)-yl)acetic acid I-35.



3.1 **3.2** **3.3**



[00291] **Synthesis of compound 3.2.** A 50-mL 3-necked round-bottom flask, was charged with compound **3.1** (200 mg, 1.16 mmol, 1.00 equiv), dichloromethane (10 mL) and triphosgene (115 mg, 0.39 mmol, 0.33 equiv). Triethylamine (352 mg, 3.48 mmol, 3.00 equiv) was the added dropwise while stirring at 0 °C. The resulting solution was stirred for 1 h at 0°C and used directly in the next step.

[00292] **Synthesis of compound 3.3.** Into a 50-mL 3-necked round-bottom flask, was placed solution of compound **3.2** and tert-butyl 2-aminoacetate hydrochloride (194 mg, 1.16 mmol, 1.00 equiv). Reaction was stirred for 2 h at room temperature. Upon completion reaction was then quenched by the addition of 10 mL of NH_4Cl(aq.) and extracted with 2x10 mL of dichloromethane. Organic layers were combined and concentrated under vacuum. The crude was purified using flash column chromatography to furnish 290 mg (76%) of compound **3.3** as a white solid.

[00293] **Synthesis of compound 3.4.** Into a 50-mL round-bottom flask, were placed compound **3.3** (290 mg, 0.88 mmol, 1.00 equiv), 1,4-dioxane (10 mL), $KOC(CH_3)_3$ (296 mg). Reaction was stirred for 4 h at 40°C in an oil bath. Upon completion reaction was quenched by the addition of 10 mL of NH_4Cl (aq.) and extracted with 2x10 mL of ethyl acetate. Organic layers combined and concentrated under vacuum. The crude was purified via flash column chromatography to furnish 100 mg (40%) of compound **3.4** as a white solid.

[00294] **Synthesis of compound 3.5**. Into a 50-mL round-bottom flask, was placed compound **3.4** (80 mg, 0.28 mmol, 1.00 equiv), CH_3CN (5 mL) and NBS (50 mg, 0.28 mmol, 0.99 equiv). Reaction was stirred for 3 h at room temperature. Upon completion of the reaction solvents were removed in vacuo and crude was purified via flash column chromatography to furnish 100 mg (98%) of compound **3.5** as a yellow solid.

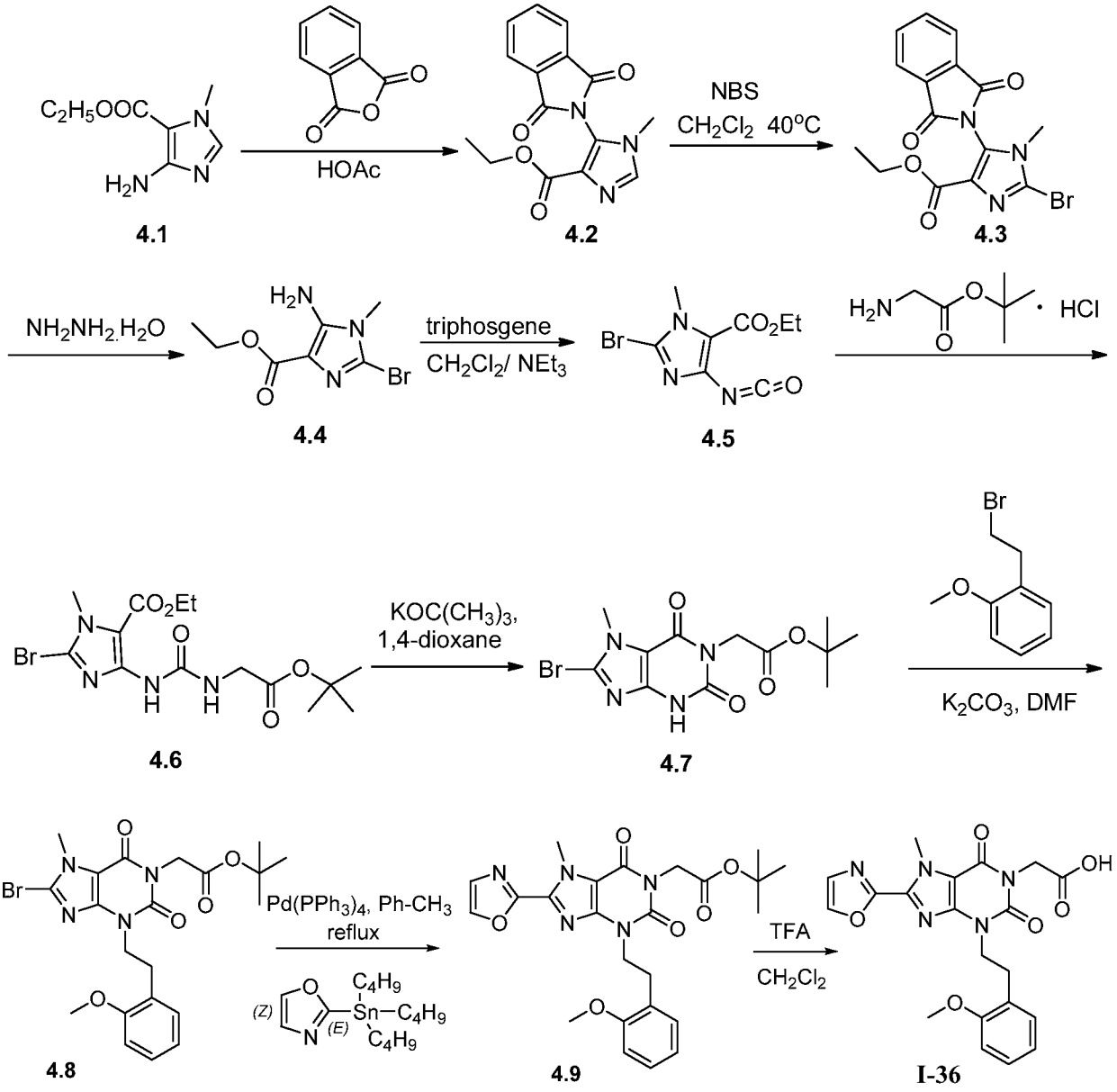
[00295] **Synthesis of compound 3.6.** A 25-mL round-bottom flask was charged with compound **3.5** (80 mg, 0.22 mmol, 1.00 equiv), potassium carbonate (91 mg, 0.66 mmol, 2.98 equiv), N, N-dimethylformamide (5 mL) and 1-(2-bromoethyl)-2-methoxy-benzene (71 mg, 0.33 mmol, 1.49 equiv). Reaction was stirred overnight at room temperature and then quenched by addition of 10 mL of water. The solids were collected by filtration and dried in an oven under reduced pressure to furnish 105 mg (96%) of compound **3.6** as a yellow solid.

[00296] **Synthesis of compound 3.7.** Into a 50-mL round-bottom flask, were placed compound **3.6** (105 mg, 0.21 mmol, 1.00 equiv), toluene (5 mL), $Pd(PPh_3)_4$ (10 mg, 0.01 mmol, 0.04 equiv) and 2-(tributylstannyl)-1,3-oxazole (113 mg, 0.32 mmol, 1.49 equiv). Reaction was stirred overnight at 110 ^{o}C in an oil bath. The resulting mixture was concentrated under vacuum and crude was purified using flash column chromatography to furnish 40 mg (39%) of compound **3.7** as a white solid.

[00297] **Synthesis of compound I-35.** A 25-mL round-bottom flask, was charged with compound **3.7** (40 mg, 0.08 mmol, 1.00 equiv), dichloromethane (5 mg, 0.06 mmol, 0.71 equiv) and trifluoroacetic acid (1 mL). Reaction was stirred overnight at room temperature. Upon completion solvent was removed under reduced pressure and crude was purified to furnish 30.4 mg (86%) of 2-(4-(2-methoxyphenethyl)-2-(oxazol-2-yl)-5,7-dioxo-4,5-dihydrothiazolo[5,4-d]pyrimidin-6(7H)-yl)acetic acid, **I-35** as a white solid.

LCMS: (ES, *m/z*): 429 $[M+H]^+$; ^{1}H NMR (300MHz, CD_3OD): δ3.12-3.18(m, 2H), δ3.85(s, 3H), δ4.24-4.28(t, 2H), δ4.77(s, 2H), δ6.81-6.91(m, 2H), δ7.15-7.21(m, 2H),δ7.39(s, 1H) ,δ8.13(s, 1H)

[00298] **Example 4. Synthesis of 2-(3-(2-methoxyphenethyl)-7-methyl-8-(oxazol-2-yl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)acetic acid, I-36.**



[00299] **Synthesis of compound 4.2.** A 50-mL round-bottom flask, was charged with compound **4.1** (1.4 g, 8.28 mmol, 1.00 equiv), 1,3-dihydro-2-benzofuran-1,3-dione (1.48 g, 9.99 mmol, 1.10 equiv) and acetic acid (10 mL). Reaction was stirred for 10 h at 110 °C. Upon reaction completion solvent was removed under vacuum and crude was purified by re-crystallization from ethyl ether to provide 2.4 g (97%) of compound **4.2** as a white solid.

[00300] **Synthesis of compound 4.3.** Into a 50-mL round-bottom flask, was placed compound **4.2** (2.9 g, 9.69 mmol, 1.00 equiv), dichloromethane (25 mL) and NBS (3.4 g, 19.1 mmol, 2.0

equiv.). The resulting solution was stirred for 20 h at room temperature. Upon completion of the reaction, solvent was removed under vacuum and crude purified by re-crystallization from ethylether which resulted in 3.5 g (96%) of compound **4.3** as a white solid.

[00301] **Synthesis of compound 4.4.** A 100-mL round-bottom flask was charged with compound **4.3** (3.5 g, 9.25 mmol, 1.00 equiv), ethanol (25 mL) and hydrazine hydrate (5.8 g, 115.86 mmol, and 12.13 equiv). Reaction was stirred for 2 h at 80 °C. The solids were filtered and solvent was removed under vacuum. Crude was purified using flash column chromatography to provide 2 g (87%) of compound **4.4** as a off-white solid.

[00302] **Synthesis of compound 4.5.** Into a 50-mL 3-necked round-bottom flask kept under nitrogen, was introduced a solution of compound **4.4** (500 mg, 2.02 mmol, 1.00 equiv) in dichloromethane (20 mL) followed by triphosgene (238 mg, 0.81 mmol, 0.40 equiv). This was followed by the addition of triethylamine (818 mg, 8.08 mmol, 4.01 equiv) dropwise with stirring at 0°C. Reaction was stirred for 1 h at 0°C. The mixture was concentrated under vacumm which provided 450 mg (crude) of compound **4.5** as yellow oil.

[00303] **Synthesis of compound 4.6.** A 50-mL 3-necked round-bottom flask, was charged with compound **4.5** (450 mg, 1.64 mmol, 1.00 equiv), 2-[(2-aminoacetyl)oxy]-2-methylpropyl hydrochloride (340 mg, 2.04 mmol, 1.00 equiv) and dichloromethane (20 mL). Reaction was stirred for 1 h at 0 °C. Upon completion the reaction was quenched with 10 mL of water and extracted with 2x10 mL of dichloromethane. Organic layers were combined and concentrated under vacuum to provide 640 mg (96%) of compound **4.6** as a off-white solid.

[00304] **Synthesis of compound 4.7.** Into a 25-mL round-bottom flask, were introduced compound **4.6** (600 mg, 1.48 mmol, 1.00 equiv), 1, 4-dioxane (5 mL) and (tert-butoxy)-potassium (166 mg, 1.48 mmol, 1.00 equiv). Reaction was stirred for 1 hour at room temperature and then quenched by the addition of 10 mL of water and extracted with 2x10 mL of dichloromethane. Organic layers were combined and concentrated under vacuum to provide 500 mg (94%) of compound **4.7** as a yellow solid.

[00305] **Synthesis of compound 4.8.** Into a 25-mL round-bottom flask, were introduced compound **4.7** (450 mg, 1.25 mmol, 1.00 equiv), 1-(2-bromoethyl)-2-methoxybenzene (400 mg, 1.86 mmol, 1.50 equiv), N,N-dimethylformamide (4 mL) and K_2CO_3 (260 mg, 1.87 mmol, 1.50 equiv). Reaction was stirred for 10 h at 80°C and then quenched by the addition of 5 mL of water. The resulting solution was extracted with 3x10 mL of ethyl acetate and the organic layers

combined and concentrated under vacuum. The crude was purified by re-crystallization from ethyl ether to provide 450 mg (73%) of compound **4.8** as an off-white solid.

[00306] **Synthesis of compound 4.9.** Into a 25-mL round-bottom flask under nitrogen, were introduced compound **4.8** (430 mg, 0.87 mmol, 1.00 equiv), 2-(tributylstannyl)-1,3-oxazole (470 mg, 1.31 mmol, 1.50 equiv), toluene (3 mL) and tetrakis(triphenyl-phosphane) palladium (200 mg, 0.17 mmol, 0.20 equiv). Reaction was stirred for 10 h at 110°C. The resulting mixture was concentrated under vacuum and crude purified using flash column chromatography to provide 150 mg (36%) of compound **4.9** as an off-white solid.

[00307] **Synthesis of compound I-36.** Into a 10-mL round-bottom flask, were placed compound **4.9** (60 mg, 0.12 mmol, 1.00 equiv), dichloromethane (2 mL) and trifluoroacetic acid (500 mg, 4.42 mmol, 35.50 equiv). The resulting solution was stirred for 2 h at room temperature. Upon completion of the reaction solvents were removed in vacuoo. Resulting crude product was purified by re-crystallization from ethyl ether to provide 35.8 mg (68%) of 2-(3-(2-methoxyphenethyl)-7-methyl-8-(oxazol-2-yl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)acetic acid, **I-36** as a white solid. LCMS (ES, *m/z*): 426 $[M+H]^+$ ^{1}HNMR(400MHz,DMSO-d_6): δ2.95-2.98(t,2H), δ3.78(s,3H), δ4.23-4.28(m,5H), δ4.44(s,2H), δ6.80-6.83(m,1H), δ6.89-6.91(m,1H), δ7.09-7.17(m,2H), δ7.60(s,1H), δ8.42(s,1H).

[00308] Additional compounds of formula **I** were prepared in a manner substantially similar to that described above.

[00309] In certain embodiments, compounds of the present invention are assayed as inhibitors of ACC using methods known in the art including those contained in Harwood et al. Isozyme-nonselective *N*-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals, J. Biol. Chem., 2003, vol. 278, 37099-37111. In some embodiments the assays used are selected from an *in vitro* ACC enzyme inhibition assays, *in vitro* cell culture assays, and *in vivo* efficacy assays in animals. In some embodiments, assay results for compounds of the present invention are compared to results obtained for known inhibitors of ACC or related enzymes. In some embodiments, the ACC inhibitor used for comparison is CP-640186 or soraphen A.

[00310] Compounds of the present invention are evaluated in an *in vitro* ACC inhibition assay as described by Harwood, et al, 2003, the entirety of which is incorporated herein by reference.

Example 5

In Vitro Acetyl-CoA Carboxylase (ACC) Inhibition Assay

[00311] An exemplary procedure for the *in vitro* ACC inhibition assay, which can be used to determine the inhibitory action of compounds of the invention toward either ACC1 or ACC2, follows. The ADP-Glo™ Kinase Assay kit from Promega is used. The ADP-Glo™ Kinase Assay is a luminescent ADP detection assay to measure enzymatic activity by quantifying the amount of ADP produced during an enzyme reaction. The assay is performed in two steps; first, after the enzyme reaction, an equal volume of ADP-Glo™ Reagent is added to terminate the reaction and deplete the remaining ATP. Second, the Kinase Detection Reagent is added to simultaneously convert ADP to ATP and allow the newly synthesized ATP to be measured using a luciferase/luciferin reaction. Luminescence can be correlated to ADP concentrations by using an ATP-to-ADP conversion curve. The detailed procedure is as follows. 50 μL of the compound being tested (600 uM in DMSO) is added to a 384-well dilution plate. The compound is diluted 1:3 in succession in DMSO for each row for 11 wells. .5 μL ACC2 working solution is added to 384-well white Optiplate assay plate. 0.5 μL diluted compound solution in each column from step 2 is added to the assay plate, each row containing 2 replicates. For the last 2 rows, add 0.5 μL negative control (DMSO) in one row and 0.5 μL positive control (compound I-97) in the other. The plates are incubated at room temperature for 15 minutes. 5 μL substrate working solution is added to each well to initiate reaction. Final ACC2 reaction concentrations consist of: 5 nM ACC2, 20 μM ATP, 20 μM acetyl-CoA, 12 mM NaHCO3, 0.01% Brij35, 2 mM DTT, 5% DMSO, test compound concentrations: 30 μM, 10 μM, 3.33 μM, 1.11 μM, 0.37 μM, 0.123 μM, 0.0411 μM, 0.0137 μM, 0.00457 μM, 0.00152 μM, and 0.00051 μM. Plates are incubated at room temperature for 60 minutes. 10 μL ADP glo reagent is added. Plates are incubated at room temperature for 40 minutes. 20 μL kinase detection reagent is added. Plates are incubated at room temperature for 40 minutes, then read on a Perkin Elmer EnVision 2104 plate reader for luminescence as Relative Light Units (RLU).

[00312] Data for each concentration, as well as the positive and negative controls are averaged, and the standard deviation calculated. Percent inhibition is calculated by the formula: 100 x (average negative control – compound) / (average negative control – average positive control). The IC50 for each compound is calculated by fitting the data with a non-linear

regression equation: Y=Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope)), where X is the log of compound concentration and Y is percent inhibition.

[00313] In some embodiments, compounds have an IC_{50} of 5-20 μM. In some embodiments, compounds have an $IC_{50} \leq 5$ μM. In some embodiments, compounds have an $IC_{50} \leq 1$ μM. In some embodiments, compounds have an $IC_{50} \leq 0.1$ μM. In some embodiments, compounds have an $IC_{50} \leq 0.01$ μM. In some embodiments, compounds have an $IC_{50} \leq 0.001$ μM.

[00314] The results of the *in vitro* ACC2 inhibition assay are set forth in **Table 2**. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an activity designated as "AA" provided an $IC_{50} \leq 1$ μM; compounds having an activity designated as "A" provided an $IC_{50} \leq 5$ μM; compounds having an activity designated as "B" provided an IC_{50} of 5-20 μM; compounds having an activity designated as "C" provided an IC_{50} of 20-50 μM; and compounds having an activity designated as "D" provided an $IC_{50} \geq 50$ μM.

Table 2. Results of *in vitro* ACC2 inhibition assay

Cpd	ACC2 IC_{50}
I-33	AA
I-34	AA
I-35	B
I-36	B

Example 6

Thermal Shift Assay

[00315] Compounds of the present invention are evaluated in a thermal shift assay using methods substantially similar to those described by Vedadi *et al.* "Chemical screening methods to identify ligands that promote protein stability, protein crystallization, and structure determination." PNAS (2006) vol. 103, 43, 15835-15840, the entirety of which is incorporated herein by reference.

[00316] The thermal shift assay tests the ability of compounds of the invention to bind effectively to and elicit a conformational change on the protein resulting in its allosteric inhibition mechanism.

Example 7

[^{14}C] Acetate Incorporation Assay

[00317] Compounds of the present invention are evaluated in a [^{14}C] Acetate Incorporation Assay. An exemplary procedure for the assay, which measures the incorporation of isotopically labeled acetate into fatty acids, follows. HepG2 cells are maintained in T-75 flasks containing DMEM supplemented with 2mM l-glutamine, penicillin G (100 units/ml), streptomycin 100µg/ml with 10% FBS and incubated in a humidified incubator with 5% CO2 at 37°C. Cells are fed every 2-3 days. On Day 1. cells are seeded in 24 well plates at a density of 1.2 X 105 cells/ml/well with the growth medium. On Day 3 the medium is replaced with fresh medium containing10% FBS. On Day 4 the medium is replaced with 0.5 ml of fresh medium containing test compound (in DMSO; final [DMSO] is 0.5 %) and the cells are incubated at 37°C for 1 hour. To one copy of plate, 4 ul of [2-^{14}C] acetate (56mCi/mmol; 1 mCi/ml; PerkinElmer) is added and the cells are incubated at 37°C, 5% CO2 for 5 hrs. To a second copy of plate, 4 ul of cold acetate are added and the cells are incubated at 37°C, 5% CO2 for 5 hrs. This plate is used for protein concentration measurement. Medium is removed and placed in a 15 ml centrifuge tube (BD, Falcon/352096). Cells are rinsed with 1ml PBS, then aspirated, and the rinse and aspiration steps are repeated. 0.5ml of 0.1N NaOH are added to each well and let sit at RT to dissolve cell monolayer. The remaining cell suspension is pooled with medium. For the protein determination plate, an aliquot is removed for protein determination (25 ul). 1.0 ml of EtOH and 0.17 ml 50% KOH are added to tubes containing medium and cell suspensions. Cells are incubated at 90°C for 1 hr, then cooled to room temperature. 5 ml petroleum ether is added per tube, shaken vigorously, centrifuged at 1000 rpm for 5 min, and 500 uL of the petroleum ether layer is transferred to tubes for Microbeta reading, then 2 ml Aquasol-2 ae added to each tube, the tubes are shaken and counted with a Microbeta Liquid Scintillation Counter (Perkin Elmer).

[00318] The remaining petroleum ether layer is discarded and the aqueous phase reserved for fatty acid extractions. The aqueous phase is acidified with 1 ml of concentrated HCl, checking pH of one or two extracts to make sure pH is below 1. 5 ml of petroleum ether is added per tube, shaken vigorously, centrifuged at 1000 rpm for 5 min, and 4 ml of the petroleum ether layer is transferred to a new glass tube (10*18 mm). 5 ml of petroleum ether is added per tube, shaken vigorously, centrifuged at 1000 rpm for 5 min, and 5 ml of the petroleum ether layer is transferred to the glass tube, and the extraction repeated again. The petroleum ether extracts are

pooled and evaporated to dryness overnight. On Day 5 the residue from the petroleum ether fractions is resuspended in 120 uL of chloroform-hexane (1:1) containing 200 ug of linoleic acid as a carrier. 5 uL of this is spotted onto silica gel sheets, and the plates developed using heptane-diethyl ether-acetic acid (90:30:1) as eluent. The fatty acid band is visualized with iodine vapor and the corresponding bands are cut out into scintillation vials. 2 ml of Aquasol-2 is added to each vial, and the vials are shaken and counted on a scintillation counter.

[00319] The [^{14}C] Acetate Incorporation Assay illustrates the ability of compounds of the invention to inhibit incorporation of isotopically labeled acetate into fatty acids. In some embodiments, the inhibition occurs with an IC_{50} of less than 100 nM.

Example 8

[00320] Compounds of the present invention are evaluated in an Anti-Fungal Activity Assay. An exemplary procedure for the assay, which measures the susceptibility of various Candida species to anti-fungal compounds, follows. Compounds to be tested (including fluconazole and amphotericin B) are dissolved in DMSO to obtain a solution having a concentration of 1 mg/mL. These stock solutions are sterile filtered using a 0.22 um nylon syringe filter, then diluted in sterile water to achieve a final concentration of 128 ug/mL.

[00321] All species are grown from frozen stock by directly plating on to freshly prepared Sabouraud Dextrose agar (BD, Difco) and incubated overnight in ambient air at 35°C for 24h. A direct suspension is prepared in RPMI 1640 + MOPS (Lonza, Biowhittaker) by taking individual colonies from the overnight cultures using sterile swabs soaked in sterile saline. The concentration of the suspension is determined using pre-determined standard curves. These suspensions are then diluted down to 5 x 10^3 CFU/mL to achieve a final concentration of 2.5 x 10^3 CFU/mL once added to the microtiter plate as per CLSI guidelines (M27-A3, Vol.28 No.14).

[00322] Broth microtiter MIC challenge plates are prepared following CLSI guidelines (M27-A3, Vol. 28 No. 14). The original CLSI guidelines focused on reading *Candida* MICs after 48h of incubation. As reading after only 24h offers a clear advantage of patient care, QC limits are being established for all drugs at 24h. That being said there are no known interpretive breakpoints for amphotericin B at 24h and the current fluconazole interpretive breakpoints are based on a 48h reading. The MIC breakpoints for the test compounds are recorded at 48h, and for the soraphen control the 24h time-point is added. All MIC determinations are achieved by

visually comparing the growth found in the antibiotic challenged wells to that of the growth control. The first well found in the dilution scheme that shows no growth (or complete inhibition) is recorded as the MIC.

[00323] In some embodiments, the Anti-Fungal Activity Assay illustrates that compounds of the invention have anti-fungal activity MICs in the low ug/mL range.

Example 9

[00324] Compounds of the invention are also assayed in a Cancer Cell Viability Assay as described by Beckers et al. "Chemical Inhibition of Acetyl-CoA Carboxylase Induces Growth Arrest and Cytotoxicity Selectively in Cancer Cells" Cancer Res. (2007) 67, 8180-8187. An exemplary procedure for the assay, which measures the percentage of cancer cells surviving following administration of inhibitor compounds, follows.

[00325] LNCaP (prostate cancer cell line) cells plated at 4 x 10^5 per 6 cm dish are incubated at 37°C, and the following day they are treated with increasing concentrations of inhibitor compounds and incubated. Viable cells and the percentage of dead cells are counted and calculated every day for 5 days from day 0, using trypan blue staining.

[00326] In some embodiments, the Cancer Cell Viability Assay shows the ability of compounds of the invention to completely inhibit cell population growth at a concentration of 5 uM.

Example 10

[00327] Compounds of the present invention are also assayed in an *In Vivo* Fatty Acid Synthesis Study as described by Harwood *et al.* "Isozyme-nonselective N-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals" Journal of Biological Chemistry (2008) 278, 37099-37111. An exemplary procedure for the assay, which measures the amount of radioactive [C^{14}]-acetate incorporated into rat liver tissue, follows.

[00328] Animals given food ad water *ad libitum* are treated orally at a volume of 1.0 mL/200g body weight (rat) with either an aqueous solution containing 0.5% methylcellulose (vehicle), or an aqueous solution containing 0.5% methylcellulose plus test compound. One to four hours after compound administration, animals receive an intraperitoneal injection of 0.5 mL of [C^{14}]-acetate (64 uCi/mL; 56 uCi/mL). One hour after radiolabeled acetate administration, animals are

sacrificed by CO_2 asphyxiation and two 0.75 g liver pieces are removed and saponified at 70 degrees C for 120 minutes in 1.5 mL of 2.5M NaOH. After saponification, 2.5 mL of absolute ethanol are added to each sample and the solutions are mixed and allowed to stand overnight. Petroleum ether (4.8 mL) is then added to each sample, and the mixtures are first shaken vigorously for 2 minutes and then centrifuged at 1000 x g in a benchtop Sorvall for 5 minutes. The resultant petroleum ether layers, which contain non-saponifiable lipids, are removed and discarded. The remaining aqueous layer is acidified to pH < 2 by the addition of 12M HCl and extracted two times with 4.8 mL of petroleum ether. The pooled organic fractions are transferred to liquid scintillation vials, dried under nitrogen, dissolved in 7 mL of Aquasol liquid scintillation fluid, and assessed for radioactivity using a Beckman 6500 liquid scintillation counter. Results are recorded as disintigrations per minute (DPM) per milligram of tissue.

[00329] In some embodiments, the *In Vivo* Fatty Acid Synthesis Study shows that the ED_{50} of compounds of the invention is less than 0.3 mg/Kg body weight.

Example 11

[00330] Compounds of the present invention are also assayed in a Respiratory Quotient Measurement Assay, as described by Harwood *et al.* "Isozyme-nonselective N-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals" Journal of Biological Chemistry (2008) 278, 37099-37111. An exemplary procedure for the assay, which measures the ratio of carbon dioxide production to oxygen consumption in rats, follows.

[00331] Male Sprague-Dawley rats (350–400 g) housed under standard laboratory conditions, either fed chow, fasted, or fasted and refed a diet high in sucrose for 2 days prior to experimentation are removed from their home cages, weighed, and placed into sealed chambers (43 " 43 " 10 cm) of the calorimeter (one rat per chamber). The chambers are placed in activity monitors. The calorimeter is calibrated before each use, air flow rate is adjusted to 1.6 liters/min, and the system settling and sampling times are set to 60 and 15 s, respectively. Base-line oxygen consumption, CO_2 production, and ambulatory activity are measured every 10 min for up to 3 h before treatment. After collecting base-line data, the chambers are opened and rats are given a 1.0-ml oral bolus of either an aqueous 0.5% methylcellulose solution (vehicle control) or an aqueous 0.5% methylcellulose solution containing test compound and then returned to the

Oxymax chambers. Measurements are made every 30 min for an additional 3–6 h after dose. Fed vehicle controls are used to assess effects produced by vehicle administration and by drift in the RQ measurement during the course of the experimentation (if any). Overnight-fasted, vehicle-treated controls are used to determine maximal potential RQ reduction. Results are plotted as their absolute RQ value (± SEM) over time.

[00332] In some embodiments, the *In Vivo* Fatty Acid Synthesis Study shows that compounds of the invention decrease RQ to approximately 80-90% of its baseline value, and show dose-dependent decreases in RQ.

Example 12

[00333] Compounds of the present invention are also assayed in a propidium iodide (PI) cell death assay, based on the procedure described by van Engeland *et al.* "A novel assay to measure loss of plasma membrane asymmetry during apoptosis of adherent cells in culture" Cytometry (1996) 24 (2), 131-139. An exemplary procedure for the assay, which measures the number of intact mitotic cells following drug application follows.

[00334] Hepatocellular carcinoma cells (such as HepG2 or Hep3B) are seeded in a 24-well plate at a density of 1.106/ml in 0.5 ml of culture medium, and incubated for 3 hours to allow time for cells to adhere. Cells are treated with experimental compounds, 1 uM doxorubicin (1,2) or vehicle (DMSO) control for 120 hours after treatment. a) First remove culture supernatant into 2mL polypropylene tube and place on ice; b) Wash wells with 0.5mL PBS, transferring the wash volume to the 2mL tube containing culture supernatant (floating cells). Keep cells on ice. Harvest by adding into the wells 200uL of accutase for 5 min. Inactivate with 300uL media. Pipette up and down to mix and transfer trypsinized cells from the well into the 2mL tube with the floating cells (total volume: 1.5mL). Keep cells on ice. Spin cells 0.6 rcf for 10 min at 4 degrees. Aspirate medium. Resuspend in 500uL of Media by vortexing in pulses for about 15s. Keep cells on ice.

[00335] For cell counting: add 20uL of cells to a plate after vortexing in pulses for 15s. Keep plate on ice. Then add 20uL trypan blue right before counting. Count cells with TC10 biorad cell counter. Spin cells 0.6 rcf for 10 min at 4 degrees. Aspirate the medium carefully. Resuspend in 500uL of annexin binding buffer 1X by vortexing. Transfer the cell suspension in a 5 ml FACS tube then add 5ul of Propidium Iodide. Gently mix the cells and incubate for 15 min at RT in the dark.

[00336] For the flow cytometric analysis, unstained/untreated samples are used at each time point as negative control, and doxorubicin treated samples are used at each time point as a positive control. A FACScan flow cytometer is used, and FL2-A histograms are analyzed with FlowJo software.

Example 13

[00337] Compounds of the present invention are also assayed in high fat diet induced obesity (DIO) studies. A representative protocol for the assay follows.

[00338] The compounds of the present invention are readily adapted to clinical use as anti-obesity agents, insulin sensitizing agents, hyperinsulinemia-reversing agents, and hepatic steatosis-reversing agents. Such activity is determined by assessing the amount of test compound that reduces body weight and percentage body fat, reduces plasma insulin levels, blunts the rise and/or accelerates the reduction in plasma insulin and glucose levels in response to an oral glucose challenge, and reduces hepatic lipid content relative to a control vehicle without test compound in mammals. Sprague Dawley rats are fed either chow, a diet high in sucrose (for example AIN76A rodent diet; Research diets Inc. Cat #10001) or a diet high in fat (for example Research diets Inc. Cat #12451), for from 3-8 weeks prior to and during test compound administration.

[00339] The anti-obesity, insulin sensitizing, hyperinsulinemia-reversing, and hepatic steatosis-reversing potential of compounds of the present invention are demonstrated by evaluating modifications to a variety of parameters of lipid and carbohydrate metabolism using methods based on standard procedures known to those skilled in the art. For example, after a 3-8 week period of ad libitum feeding of either a chow, high-fat, or high-sucrose diet, animals that continue to receive the diet are treated for 1-8 weeks with test compound administered either by oral gavage in water or saline or water or saline containing 0.5% methylcelulose using a Q.D., B.I.D, or T.I.D. dosing regimen. At various times during study and at sacrifice (by CO_2 asphyxiation), blood is collected either from the tail vein of an unanesthesized rat or from the vena cava of animals at sacrifice into heparin or EDTA containing tubes for centrifugal separation to prepare plasma. Plasma levels of parameters of lipid and carbohydrate metabolism known by those skilled in the art to be altered coincident with anti-obesity, insulin sensitizing, hyperinsulinemia-reversing, and hepatic steatosis-reversing actions, including but not limited to

cholesterol and triglycerides, glucose, insulin, leptin, adiponectin, ketone bodies, free fatty acids, and glycerol, are measured using methods known to those skilled in the art.

[00340] The anti-obesity potential of compounds of the present invention can also be demonstrated by evaluating their potential to produce a reduction in body weight, a reduction in percentage body fat (measured by for example dual-energy x-ray absorptiometry (DEXA) analysis), and a reduction in plasma leptin levels. The anti-obesity and hepatic steatosis-reversing potential of compounds of the present invention can also be demonstrated by evaluating their potential to reduce the concentration of triglycerides in the liver, using extraction and quantitation procedures known to those skilled in the art. The insulin sensitizing and hyperinsulinemia-reversing potential of compounds of the present invention can also be demonstrated by evaluating their potential to blunt the rise and/or accelerate the reduction in plasma insulin and glucose levels in response to an oral glucose challenge, using procedures known to those skilled in the art.

[00341] The anti-obesity, insulin sensitizing, hyperinsulinemia-reversing, and hepatic steatosis-reversing potential of compounds of the present invention are assayed by administering compounds of the invention once daily by oral gavage in 0.5% methylcellulose in saline at doses of 0, 3, 10, and 30 mg/kg to Sprague Dawley rats that have been consuming a high-fat diet for 4 weeks prior to initiation of dosing and continue to consume the same high-fat diet throughout the 2-weeks of test compound administration. In some embodiments compounds of the invention produce a dose-dependent reduction in total body weight relative to vehicle-treated control animals with no concomitant reduction in food consumption. The degree of body weight reduction paralleled plasma drug levels is measured at the end of the study. Plasma leptin levels, which are known to be an indicator of whole-body fat mass and which are increased by administration of the high-fat diet, are reduced by compounds of the invention. The plasma leptin levels for animals receiving the standard chow diet (lean controls) are also evaluated to determine the extent of parameter normalization produced by compounds of the invention. Plasma insulin levels, which are increased by a high-fat diet, are reduced to near lean control levels by compounds of the invention, with no concomitant reduction in plasma glucose levels, indicating an improvement in insulin sensitivity after treatment. Hepatic triglycerides, which are elevated by a high-fat diet, are reduced in a dose-dependent manner after administration of compounds of the invention, and in some embodiments are normalized to lean control levels by

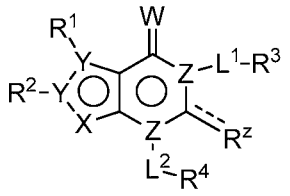
the highest dose evaluated. In some embodiments, treatment with compounds of the invention does not increase either liver weight or the markers of liver function, ALT and AST.

[00342] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

W is oxygen or sulfur;

X is O, S, N or NR;

each Y is independently C, N, or O;

each Z is independently C or N;

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogens, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2RN(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R, -$B(OR)_2$, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^2 is not optionally substituted benzyl; or

R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen, deuterium, or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic

ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^5 and $R^{5'}$;

L^2 is a covalent bond or a 1-6 membered straight or branched bivalent hydrocarbon chain optionally substituted with R^7 and $R^{7'}$;

R^3 is halogen, -CN, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)RN(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OR)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen or a ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein said ring is optionally substituted with n instances of R^8;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

each of R^7 and $R^{7'}$ is independently, -R, $-OR^6$, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, or $-B(OR)_2$; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered

saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

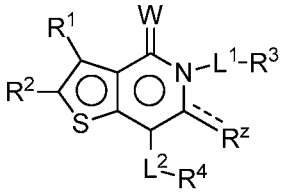
R^6 is -R, -C(O)N(R_2), or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, -N(R_2) or deuterium;

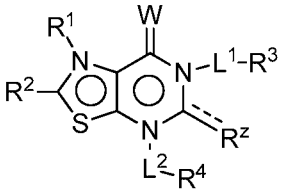
R^z is selected from hydrogen, halogen, methyl, -CN, =O, and =S; and

n is 0-5.

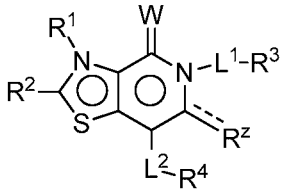
2. The compound of claim 1, wherein the compound is selected from formulas **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, and **I-i**:



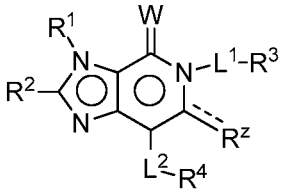
I-a



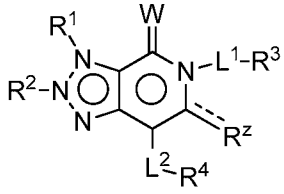
I-b



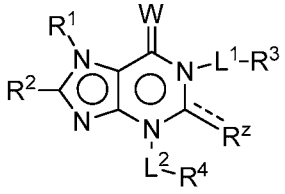
I-c



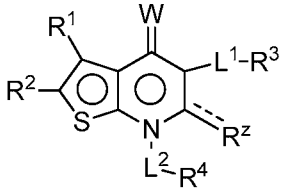
I-d



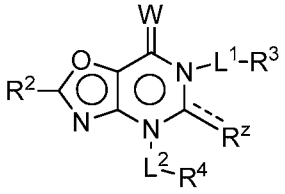
I-e



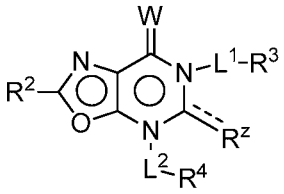
I-f



I-g



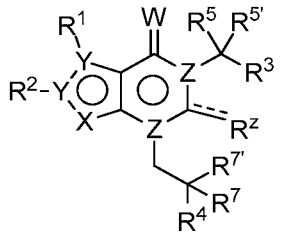
I-h



I-i

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 of formula **II**:



II

or a pharmaceutically acceptable salt thereof.

4. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

5. A method of inhibiting ACC in a patient in need thereof, comprising administering to said patient the composition according to claim 4.

6. A method of inhibiting ACC in a biological sample, comprising contacting the biological sample with the compound according to claim 1.

7. A method for treating a metabolic disorder in a patient in need thereof, comprising administering to said patient the composition according to claim 4.

8. The method according to claim 7, wherein the metabolic disorder is obesity.

9. The method according to claim 7, wherein the metabolic disorder is dyslipidemia or hyperlipidemia.

10. The method according to claim 8, wherein the obesity is a symptom of Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome or MOMO syndrome.

11. The method according to claim 8, wherein the obesity is a side effect of the administration of another medication, including but not limited to insulin, sulfunylureas,

thiazolidinediones, antipsychotics, antidepressants, steroids, anticonvulsants (including phenytoin and valproate), pizotifen, or hormonal contraceptives.

12. A method of treating a cancer or other proliferative disorder in a patient in need thereof, comprising administering to said patient the composition according to claim 4.

13. A method of treating a fungal, parasitic, or bacterial infection in a patient in need thereof, comprising administering to said patient the composition according to claim 4.

14. A method of inhibiting ACC in a plant, comprising contacting the plant with the compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/37360

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/497 (2014.01)
CPC - C07D 401/12; C07D 401/14; C07D 405/12
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 401/12; C 07D 401/14; C07D 405/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/252.11, 544/281, 514/252.16, 514/259.5

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
surechem, Thomson innovation (US Grant, AU Innov, CA App, US App, AU Grant, FR App, EP Grant, AU App, DE Util, EP App, GB App, DE Grant, WO App, CA Grant, DE App, JP App, KR Grant, KR App, Other, JP Util), Search terms: fused bicycl*, Acetyl-CoA carboxylase, dyslipidemia, hyperlipidemia, plant, indolinone

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y -- A	US 2010/0168158 A1 (Binch et al.) 01 July 2010 (01.07.2010) entire document especially para [0027]	1-2 --- 3-4, 7-9 and 12-13 --- 5-6, 10-11 and 14
Y -- A	US 2009/0137555 A1 (Wan et al.) 28 May 2009 (28.05.2009) entire document especially see para [0040]	3-4, 7-9 and 12-13 --- 5-6, 10-11 and 14
A	US 2011/0028487 A1 (Deadman et al.) 03 February 2011 (03.02.2011) entire document	1-14
A	US 6,146,867 A (Gengenbach et al.) 14 November 2000 (14.11.2000) entire document	1-14
A	US 2002/0112253 A1 (Wakil et al.) 15 August 2002 (15.08.2002) entire document	1-14

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

* 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 application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
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"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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2014 (27.08.2014)	11 SEP 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

摘要

本发明提供适用作乙酰基CoA羧化酶ACC抑制剂的化合物、其组合物和其使用方法 。