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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. Specifically, bicyclic heteroaryl derivatives containing a imidazole, thiazole or oxazole fused to a pyridinone, pyrimidinone or pyrimidindione are provided. These compounds have therapeutic utility toward treating an ACC enzyme mediated disorder such as obesity in a subject, upon administration in an effective amount to said subject.

ACC INHIBITORS AND USES THEREOF

BACKGROUND OF THE INVENTION

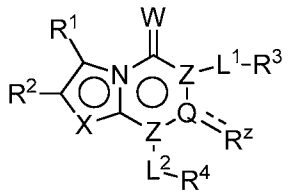
[0001] Obesity is a health crisis of epic proportions. The health burden of obesity, measured by quality-adjusted life-years lost per adult, has surpassed that of smoking to become the most serious, preventable cause of death. In the US, about 34% of adults have obesity, up from 31% in 1999 and about 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.

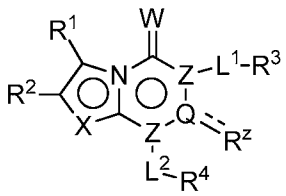
[0005] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of the production or oxidation of fatty acids. Such diseases, disorders, or conditions include those described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

Q is C or N; wherein if Q is N, then R^z is absent;

X is –O-, -S-, or –NR-;

each Z is independently C or N; provided that both Z are not 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; 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; and

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.

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.

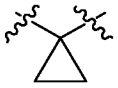
[0012] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl),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

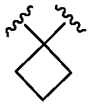
[0013] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

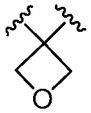
[0014] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[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; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O(CH_2)_{0-4}R^{o}$, $-O-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}CH(OR°)_2$; $-(CH_2)_{0-4}SR°$; $-(CH_2)_{0-4}Ph$, 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; $-N_3$; $-(CH_2)_{0-4}N(R°)_2$; $-(CH_2)_{0-4}N(R°)C(O)R°$; $-N(R°)C(S)R°$; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $-(CH_2)_{0-4}N(R°)C(O)OR°$; $-N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $-(CH_2)_{0-4}C(O)R°$; $-C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}C(O)SR°$; $-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR-$, SC(S)SR°; $-(CH_2)_{0-4}SC(O)R°$; $-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; $-C(S)SR°$; –SC(S)SR°, $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $-OP(O)(OR°)_2$; $SiR°_3$; $-(C_{1-4}$ straight or branched alkylene)O–$N(R°)_2$; or $-(C_{1-4}$ straight or branched alkylene)C(O)O–$N(R°)_2$, 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, $-R^{\bullet}$, -(halo$R^{\bullet}$), -OH, $-OR^{\bullet}$, -(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.

[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.

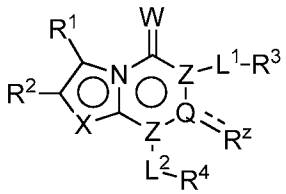
[0035] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^{+}(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include

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;

Q is C or N; wherein if Q is N, then R^z is absent;

X is –O-, -S-, or –NR-;

each Z is independently C or N; provided that both Z are not 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; 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; and

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, Q is C or N. In some embodiments Q is C. In some embodiments Q is N.

[0041] As defined generally above, X is –O-, -S-, or –NR-. In certain embodiments, X is –O-. In certain embodiments, X is –S-. In some embodiments, X is –NR-. In certain embodiments, X is –NH-.

[0042] As defined generally above, each Z is independently C or N, provided that both Z are not simultaneously N. In some embodiments one Z group is C while the other is N. In some embodiments, both Z groups are C.

[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, 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. 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] 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.

[0046] 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;

[0047] 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, $-SO_2R$, $-B(OH)_2$, 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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)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.

[0057] 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.

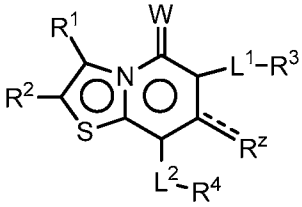
[0058] As described generally above, R^6 is -R, $-C(O)N(R)_2$, or -C(O)R. In certain embodiments R^6 is –R. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is isopropyl. In certain embodiments R^6 is tetrahydropyranyl. In certain embodiments R^6 is tetrahydrofuranyl. In certain embodiments, R^6 is tetrahydro-*2H*-thiopyran-1,1-dioxide. In certain embodiments, R^6 is 4-hydroxycyclohexyl.

[0059] 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.

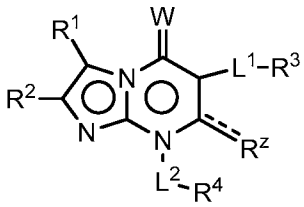
[0060] As defined generally above, n is 0-5. In certain embodiments, n is 0. In some embodiments, n is 1-2. In some embodiments, n is 1. In some embodiments, n is 5.

[0061] 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.

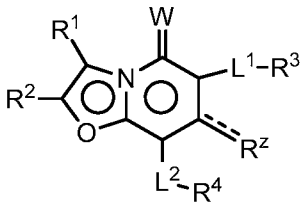
[0062] In some embodiments, the present invention provides a compound of formula **I** selected from formulas **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f, I-g**, and **I-h**:



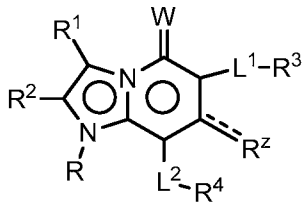
I-a



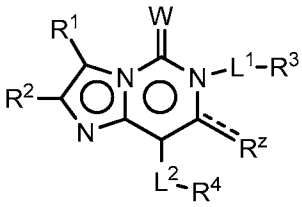
I-b



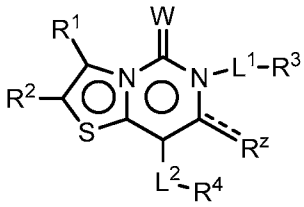
I-c



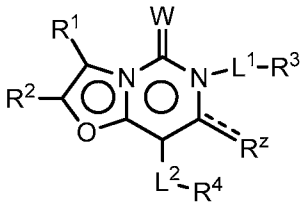
I-d



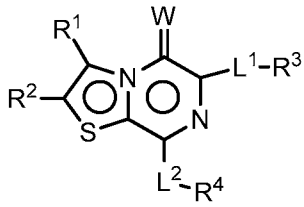
I-e



I-f



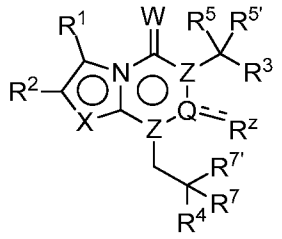
I-g



I-h

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.

[0063] In certain embodiments, the present invention provides a compound of formula **II**:

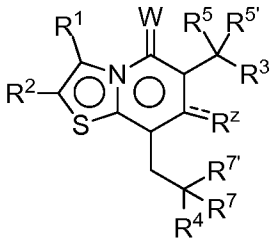


II

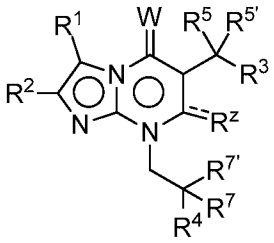
or a pharmaceutically acceptable salt thereof, wherein:

each of W, Q, X, 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;

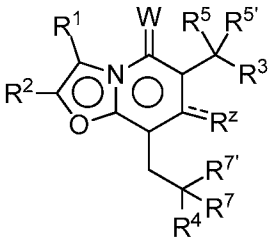
[0064] In certain embodiments, the present invention provides a compound of formula **II** selected from formulas **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, **II-f**, **II-g**, and **II-h**:



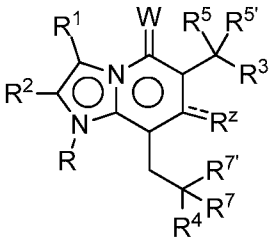
II-a



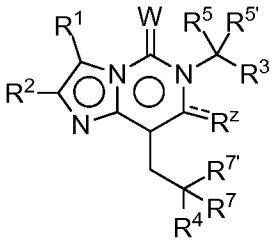
II-b



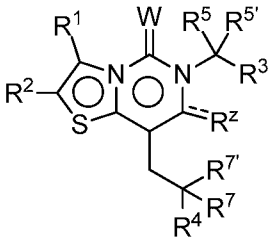
II-c



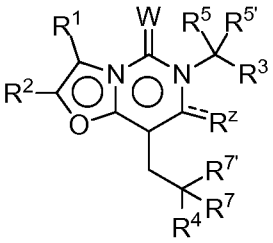
II-d



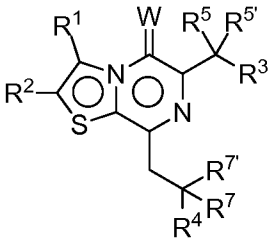
II-e



II-f



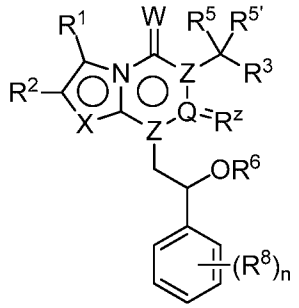
II-g



I-h

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.

[0065] In certain embodiments, the present invention provides a compound of formula **III**:

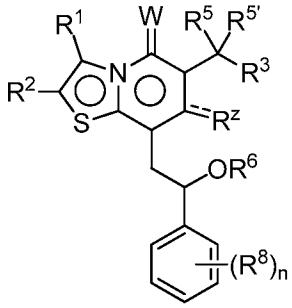


III

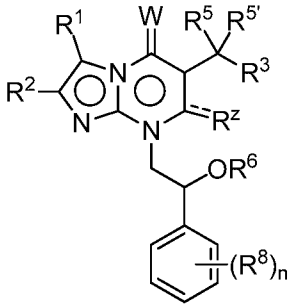
or a pharmaceutically acceptable salt thereof, wherein:

each of W, Q, X, 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.

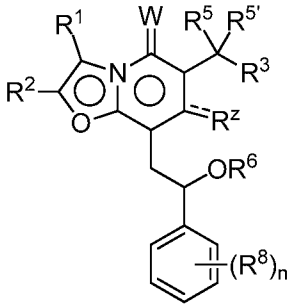
[0066] In certain embodiments, the present invention provides a compound of formula **III** selected from formulas **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, **III-f**, **III-g**, and **III-h**:



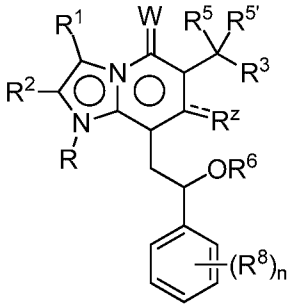
III-a



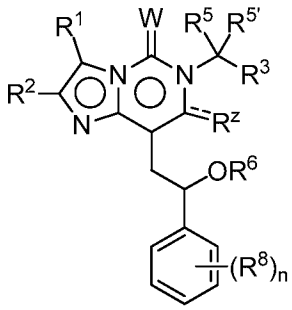
III-b



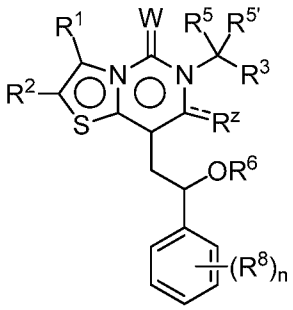
III-c



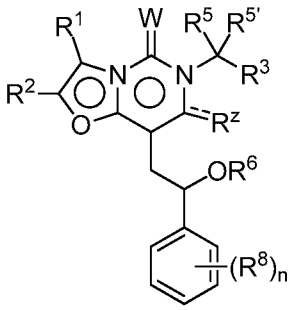
III-d



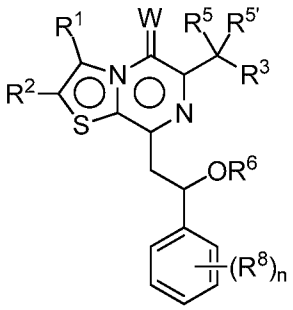
III-e



III-f



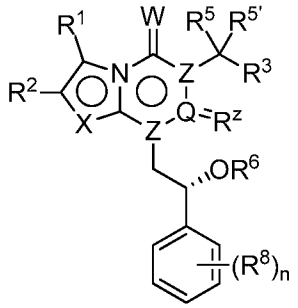
III-g



III-h

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.

[0067] In certain embodiments, the present invention provides a compound of formula **IV**:



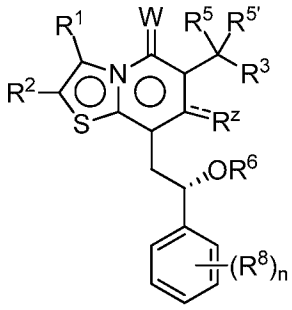
IV

or a pharmaceutically acceptable salt thereof, wherein:

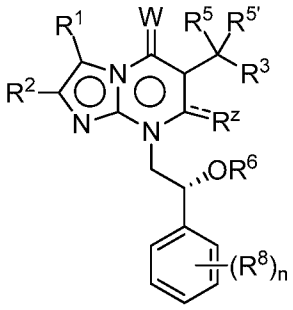
each of W, Q, X, Z, R, R^1, R^2, R^3, R^5, $R^{5'}$, R^6, R^8, n, and R^z is as described in embodiments for formulas **I**, **II**, and **III**, *supra*, or described in embodiments herein, both singly and in combination.

[0068] In some embodiments, the present invention provides a compound of formula **IV**, wherein R^2 is selected from bromine, Hy or –C(O)OR. In some embodiments, the present invention provides a compound of formula **IV**, wherein R^2 is Hy. n some embodiments, the present invention provides a compound of formula **IV**, wherein R^2 is –C(O)OR.

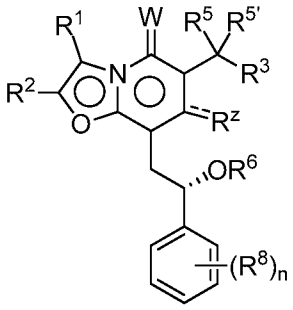
[0069] In certain embodiments, the present invention provides a compound of formula **IV** selected from formulas **IV-a**, **IV-b**, **IV-c**, **IV-d**, **IV-e**, **IV-f**, **IV-g**, and **IV-h**:



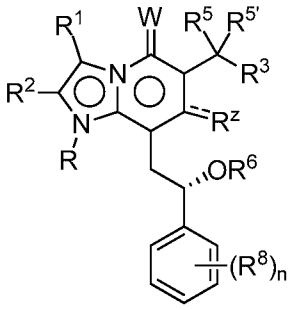
IV-a



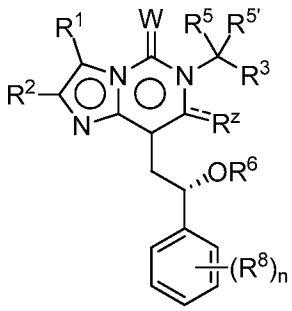
IV-b



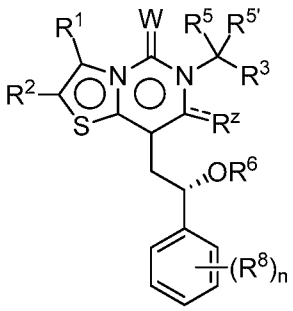
IV-c



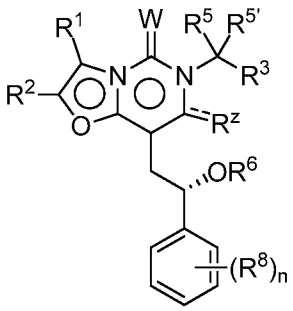
IV-d



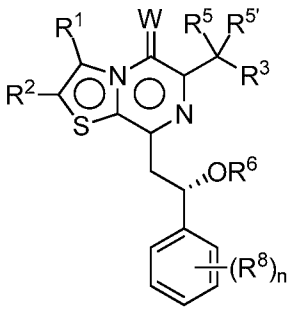
IV-e



IV-f



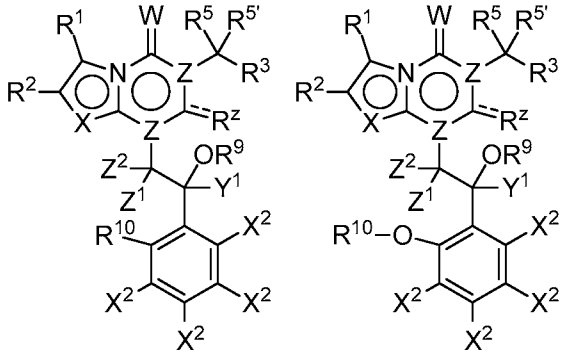
IV-g



IV-h

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**:



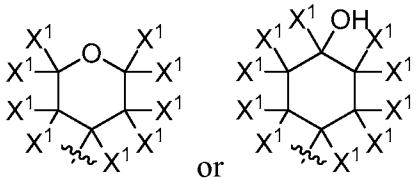
V-i **V-ii**,

or a pharmaceutically acceptable salt thereof, wherein W, Q, X, Z, R^2, R^3, R^5, $R^{5'}$, 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:

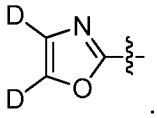


or ; wherein each X^1 is independently H or D;

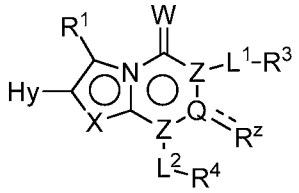
each instance of X^2, Y^1, Z^1, and Z^2 is independently H or D; and

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  .

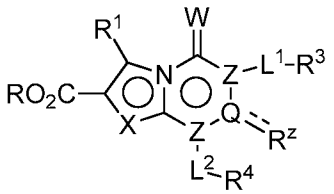
[0073] In certain embodiments, the present invention provides a compound of formula **I**, wherein R^2 is Hy, thereby forming a compound of formula **VI**:



VI

or a pharmaceutically acceptable salt thereof, wherein each of W, Q, X, 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.

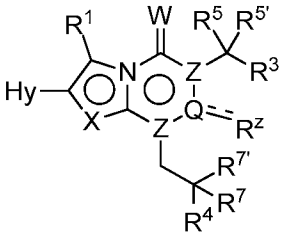
[0074] In certain embodiments, the present invention provides a compound of formula **I**, wherein R^2 is –C(O)OR, thereby forming a compound of formula **VII**:



VII

or a pharmaceutically acceptable salt thereof, wherein each of W, Q, X, 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.

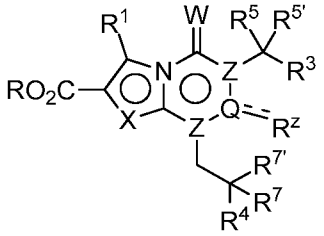
[0075] In certain embodiments, the present invention provides a compound of formula **II**, wherein R^2 is Hy, thereby forming a compound of formula **VIII**:



VIII

or a pharmaceutically acceptable salt thereof, wherein each of W, Q, X, 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.

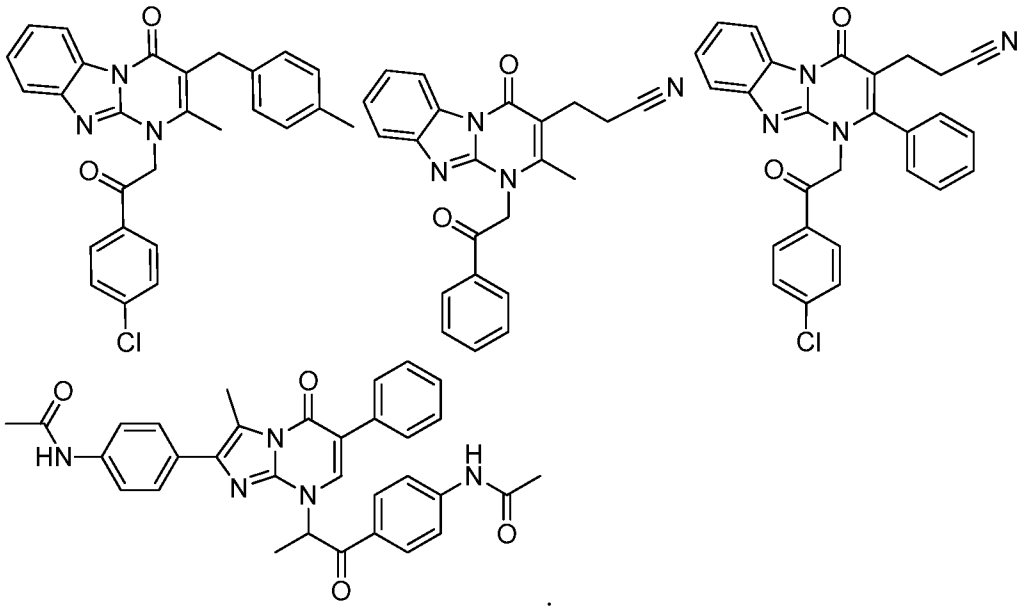
[0076] In certain embodiments, the present invention provides a compound of formula **II**, wherein R^2 is –C(O)OR, thereby forming a compound of formula **IX**:



IX

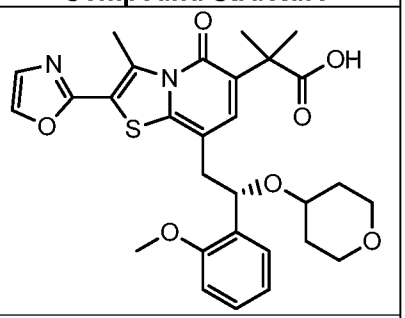
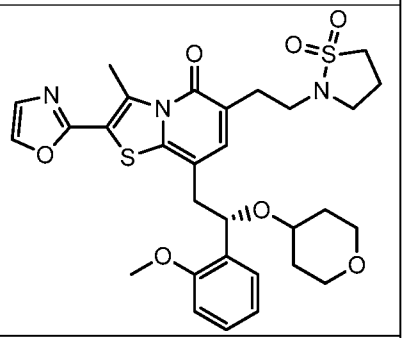
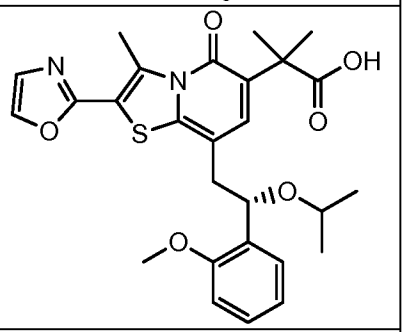
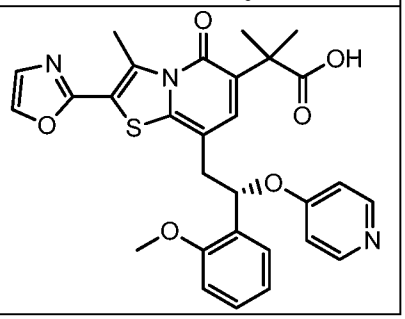
or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, R^3, R^4, R^5, $R^{5'}$, R^7, and $R^{7'}$ is defined above and described in embodiments herein, both singly and in combination.

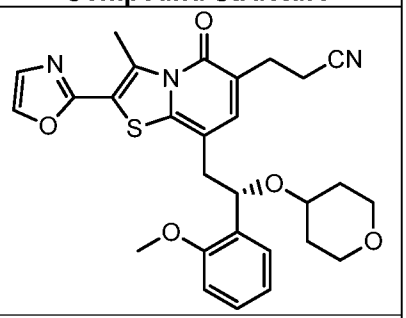
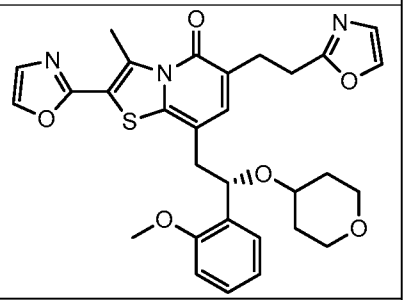
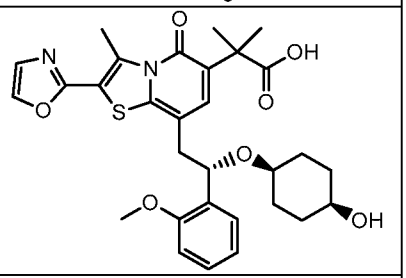
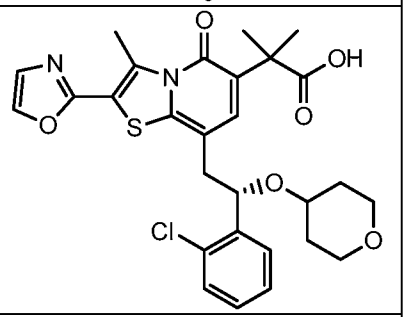
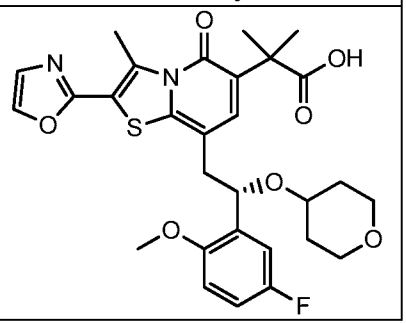
[0077] In some embodiments, compounds of the present invention are not selected from the following formulas:

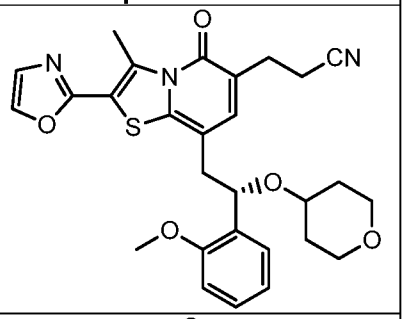
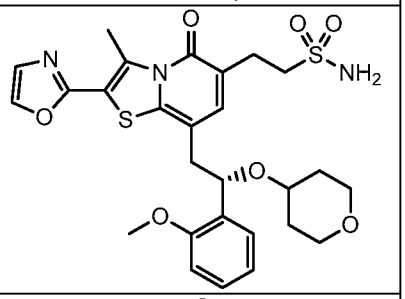
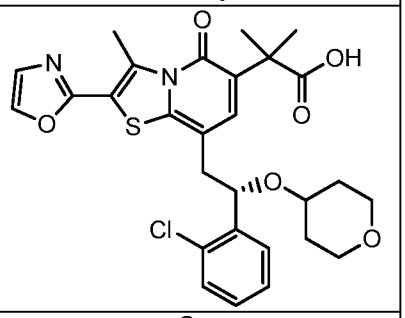
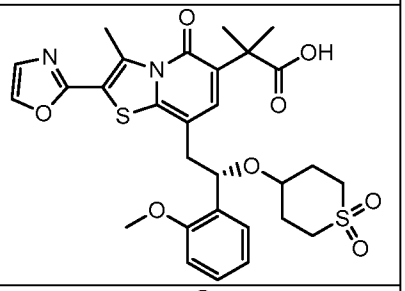
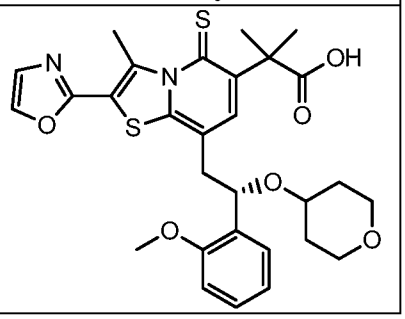


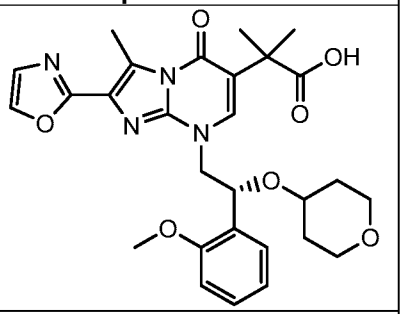
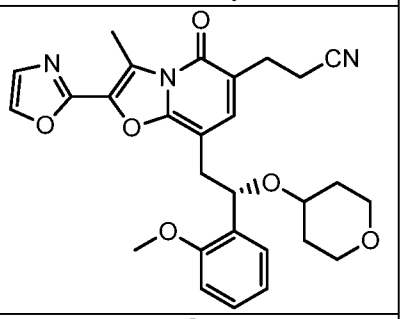
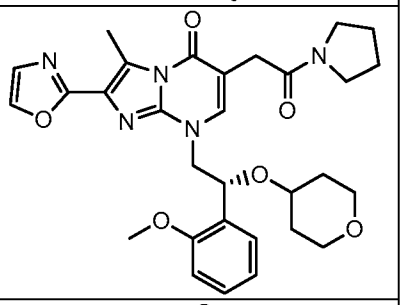
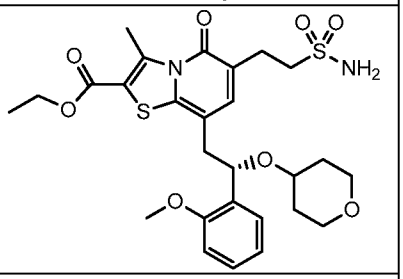
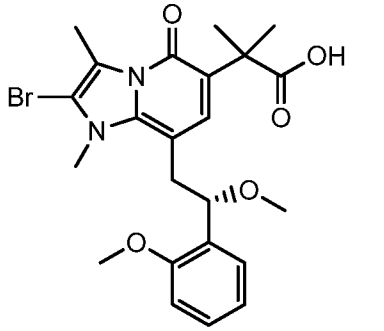
[0078] Exemplary compounds of formula **I** are set forth in Table 1, below:

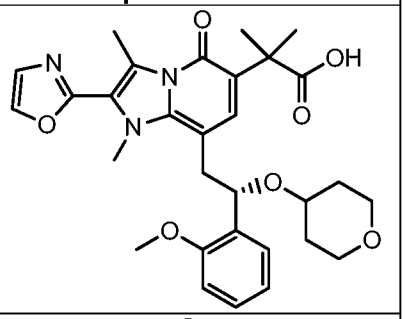
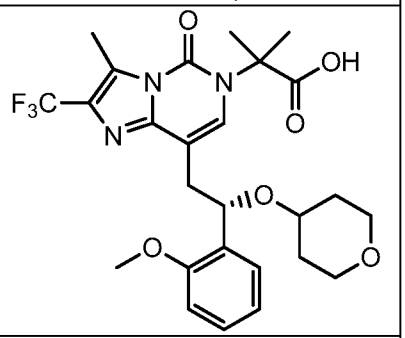
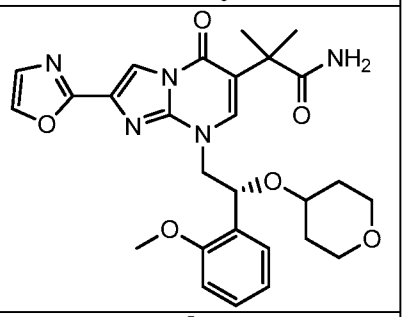
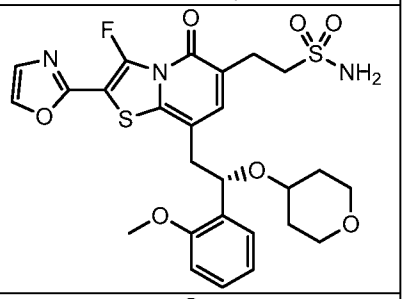
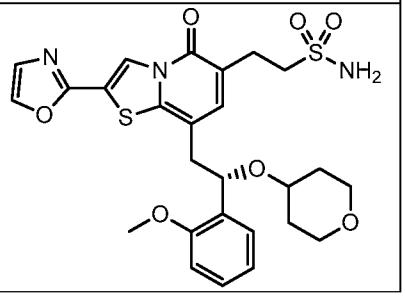
Table 1. Exemplary Compounds of Formula I

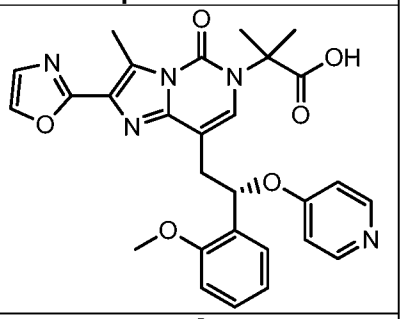
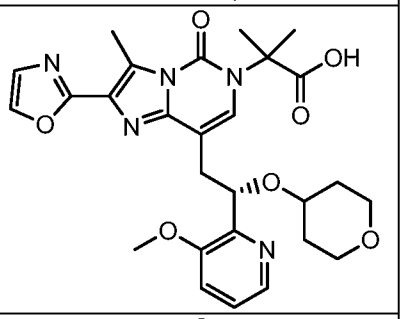
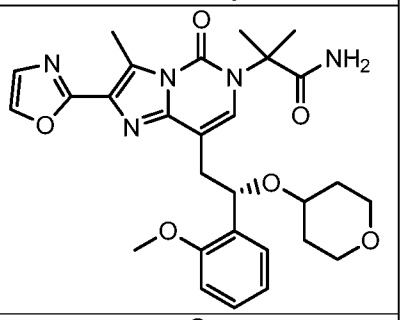
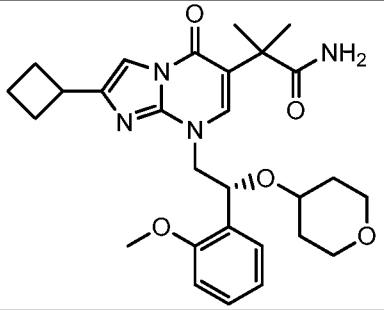
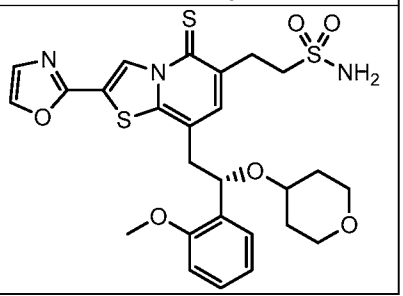
Cmpd #	Compound Structure
I-1	
I-2	
I-3	
I-4	

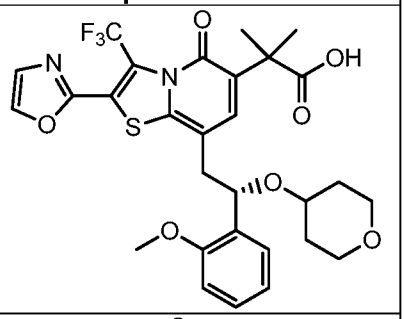
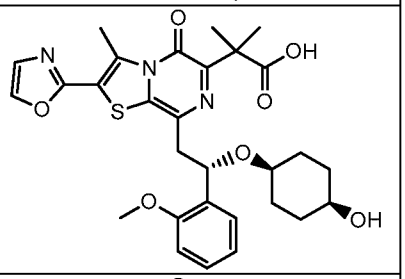
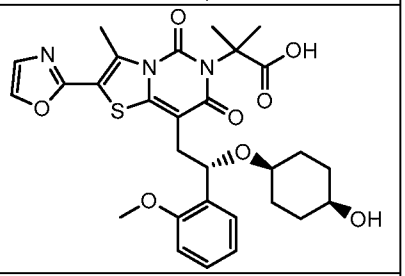
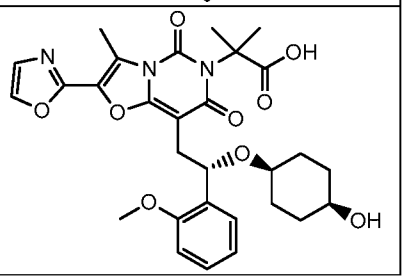
Cmpd #	Compound Structure
I-5	
I-6	
I-7	
I-8	
I-9	

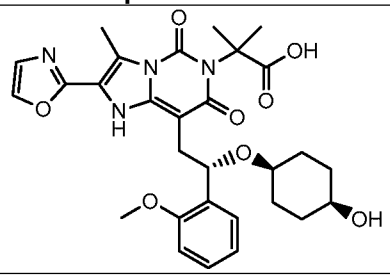
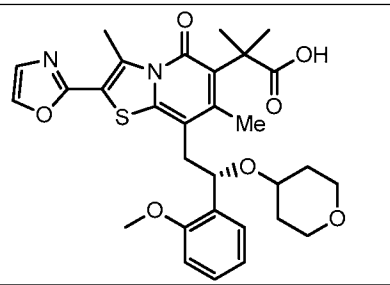
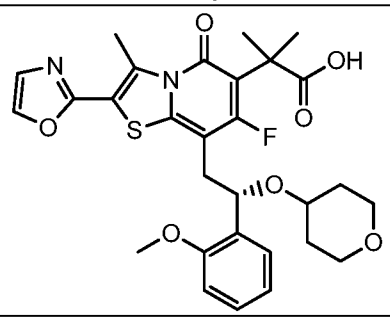
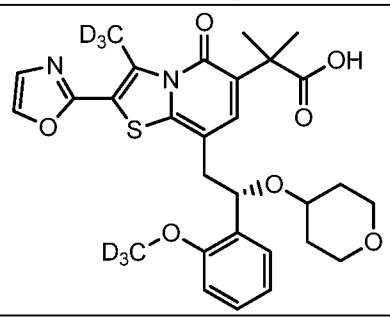
Cmpd #	Compound Structure
I-10	
I-11	
I-12	
I-13	
I-14	

Cmpd #	Compound Structure
I-15	
I-16	
I-17	
I-18	
I-19	

Cmpd #	Compound Structure
I-20	
I-21	
I-22	
I-23	
I-24	

Cmpd #	Compound Structure
I-25	
I-26	
I-27	
I-28	
I-29	

Cmpd #	Compound Structure
I-30	
I-31	
I-32	
I-33	

Cmpd #	Compound Structure
I-34	
I-35	
I-36	
I-37	

[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.

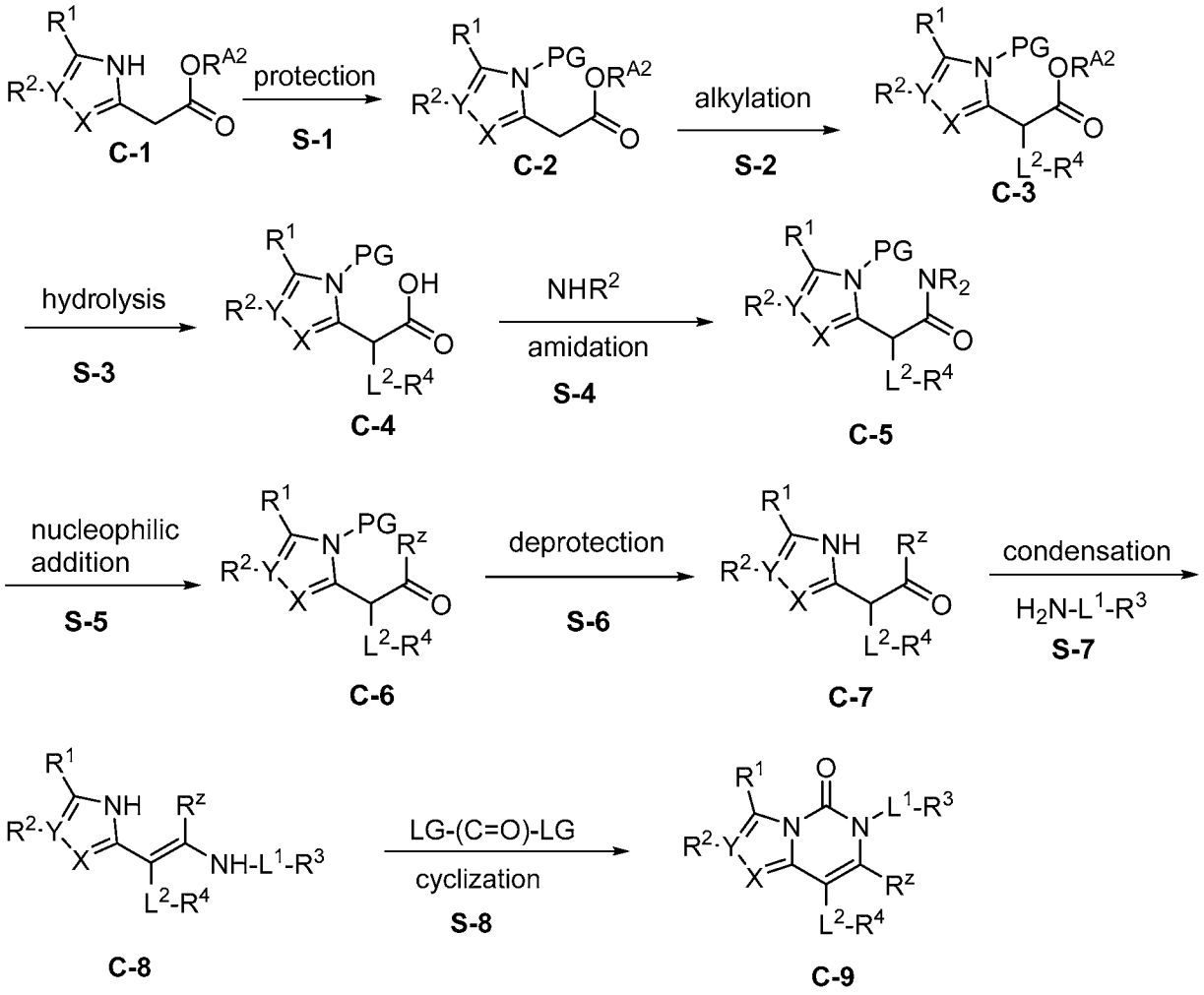
EXEMPLIFICATION

[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:

Example 1

Scheme I



[00261] In Scheme I above, LG is a leaving group, PG is a protecting group, and each of, R^1, R^2, R^3, R^4, R^z, R^{A2}, L^1, L^2, X and Y is as defined above and below and in classes and subclasses as described herein.

[00262] Suitable leaving groups, LG, include but are not limited to alkoxys, halogens and sulfonates. In certain embodiments, LG is a halogen. In certain embodiments, LG is alkoxy. In certain embodiments, LG is chlorine.

[00263] Suitable protecting groups, PG, include but are not limited to hydrogenolytically labile groups, photolabile groups and hydrolytically labile groups. In some embodiments, PG is an optionally substituted group selected from a benzyl group, a benzhydryl group, a trityl group or a carbamate group.

[00264] In one aspect, the present invention provides methods for preparing compounds of formula **C-9** according to the steps depicted in Scheme III, above. In some embodiments, at step

S-1, a heterocycle of formula **C-1** is protected to form a heterocycle of formula **C-2**. In some embodiments the protecting group is benzyl. In some embodiments the protection step if performed in the presence of a base. In some embodiments, the base is potassium carbonate. In some embodiments step **S-1** is performed in a solvent. In some embodiments the solvent is DMF. In some embodiments the solvent is acetone.

[00265] In some embodiments, step **S-2** comprises treating a compound of formula **C-2** with a base and an alkylating agent to form a compound of formula **C-3**. In some embodiments the base is lithium diisopropylamide (LDA). In some embodiments the alkylating agent is an alkyl halide. In some embodiments step **S-2** is performed in a solvent. In some embodiments the solvent is tetrahydrofuran (THF).

[00266] In some embodiments step **S-3** comprises treating a compound of formula **C-3** with an aqueous base to form a carboxylic acid of formula **C-4**. In some embodiments the base is lithium hydroxide. In some embodiments step **S-3** is performed in a solvent. In some embodiments the solvent is a mixture of THF and water.

[00267] In some embodiments step **S-4** comprises treating a compound of formula **C-4** with a coupling reagent and an amine to form a compound of formula **C-5**. In some embodiments the amine is N,O-dimethylhydroxylamine. 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 hydroxybenzotriazole (HOBT). In some embodiments the solvent is DMF.

[00268] In some embodiments step **S-5** comprises treating a compound of formula **C-5** with a nucleophile to form a compound of formula **C-6**. In some embodiments the nucleophile is lithium aluminum hydride. In some embodiments the nucleophile is an organometallic reagent. In some embodiments the solvent is THF. In some embodiments the solvent is diethyl ether. In some embodiments the solvent is DCM.

[00269] In some embodiments step **S-6** comprises treating a compound of formula **C-6** with a reagent or combination of reagents for the removal of PG to form a compound of formula **C-7**. In some embodiments the reagents are hydrogen gas and palladium. In some embodiments the solvent is ethyl acetate.

[00270] In some embodiments step **S-7** comprises condensing a compound of formula **C-7** with an amine to form a compound of formula **C-8**. In some embodiments step **S-7** is performed

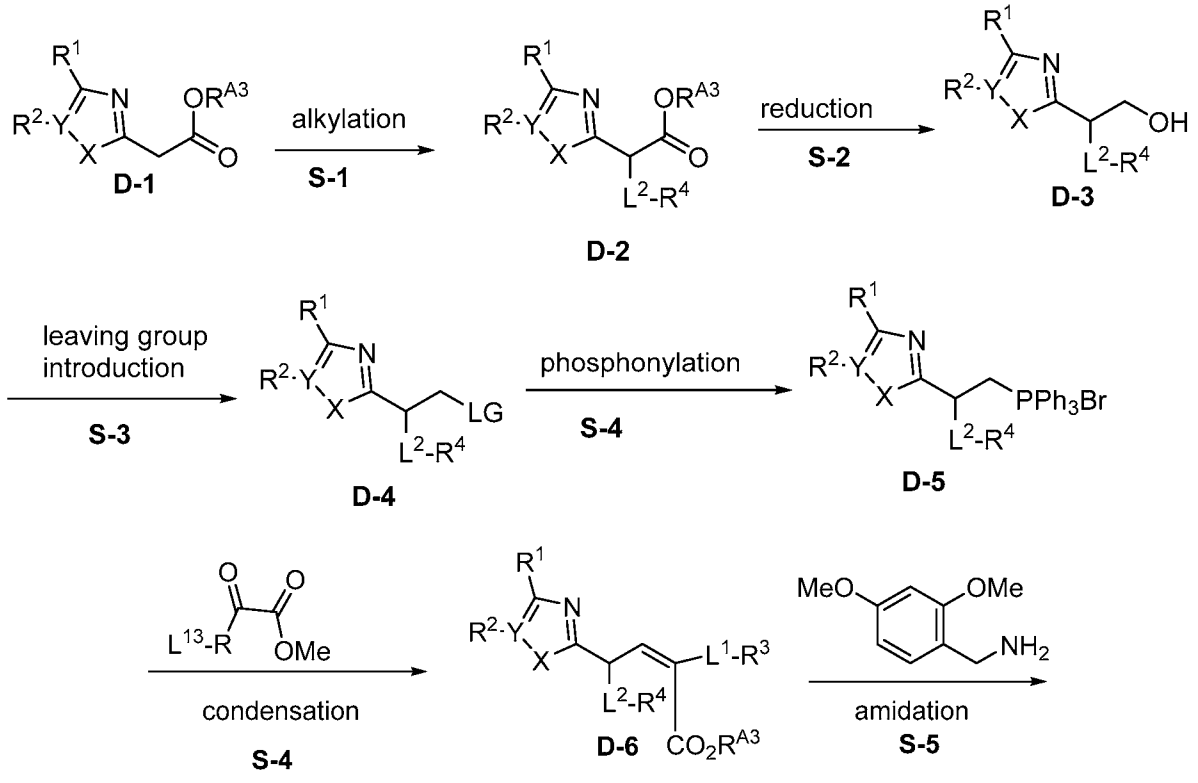
in the presence of a desiccating agent. In some embodiments the desiccating agent is magnesium sulfate. In some embodiments the desiccating agent is molecular sieves. In some embodiments **S-7** is performed in a solvent. In some embodiments the solvent is DCM.

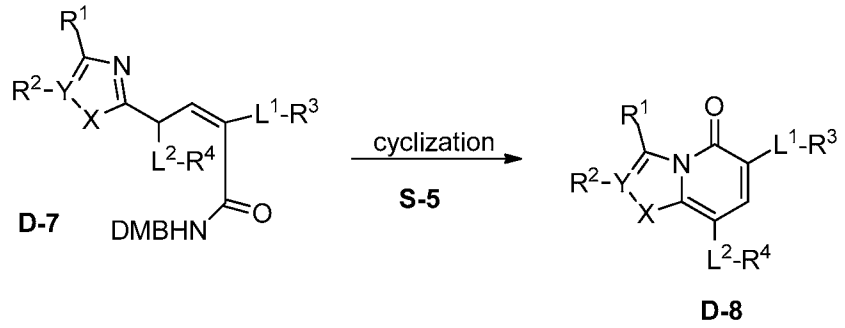
[00271] In some embodiments step **S-8** comprises treating a compound of formula **C-8** with a carbonylating reagent to form a compound of formula **C-9**. In some embodiments the carbonylating reagent is phosgene. In some embodiments the carbonylating reagent is 1,1'-carbonyldiimidazole (CDI) (see for example D. P. Arama et al. Tetrahedron Letters 2013, 54, 1364, the entirety of which is incorporated herein by reference). In some embodiments the solvent is acetonitrile. In some embodiments the solvent is methylene chloride.

[00272] In certain embodiments, compounds of the present invention are generally prepared according to Scheme IIset forth below:

Example 2

Scheme II





[00273] In Scheme II above, each of LG, R^1, R^2, R^3, R^4, R^z, R^{A4}, L^1, L^2, X and Y is as defined above and below and in classes and subclasses as described herein.

[00274] In one aspect, the present invention provides methods for preparing compounds of formula **D-8** according to the steps depicted in Scheme II, above. In some embodiments, step **S-1** comprises treating a compound of formula **D-1** with a base and an alkylating agent to form a compound of formula **D-2**. In some embodiments the base is lithium diisopropylamide (LDA). In some embodiments the alkylating agent is an alkyl halide. In some embodiments step **S-1** is performed in a solvent. In some embodiments the solvent is tetrahydrofuran (THF).

[00275] In some embodiments, step **S-2** comprises treating a compound of formula **D-2** with a reducing agent to form a compound of formula **D-3**. In some embodiments the reducing agent is lithium aluminum hydride. In some embodiments the reducing agent is DIBAL-H. In some embodiments the solvent is THF. In some embodiments the solvent is diethyl ether. In some embodiments the solvent is toluene.

[00276] In some embodiments, step **S-3** comprises contacting the compound of formula **D-3** with a reagent to convert the hydroxyl group into a leaving group LG. In some embodiments LG is a halogen. In some embodiments LG is bromine. In some embodiments the reagents used to convert the hydroxyl group into LG are triphenylphosphine and carbon tetrabromide. In some embodiments step **S-3** is performed in a solvent. In some embodiments the solvent is DCM.

[00277] In some embodiments, step **S-4** comprises treating a compound of formula **D-4** with triphenylphosphine to form a compound of formula **D-5**. In some embodiments the solvent is toluene.

[00278] In some embodiments, step **S-4** comprises treating a compound of formula **D-5** with a ketoester and a base to form a compound of formula **D-6**. In some embodiments the base is *n*-BuLi. In some embodiments the base is potassium *tert*-butoxide. In some embodiments the solvent is THF.

[00279] In some embodiments step **S-5** comprises treating a compound of formula **D-6** with an amine and a Lewis acid to form a compound of formula **D-7**. In some embodiments the amine is (2,4-dimethoxyphenyl)methanamine. In some embodiments the Lewis acid is trimethylaluminum.

[00280] In some embodiments step **S-6** comprises treating a compound of formula **D-7** with an acid to form a compound of formula **D-8**. In some embodiments the acid is hydrogen chloride. In some embodiments the solvent is diethyl ether. For an application of these conditions see J. Fetter et al. J. Chem. Res. Synopses 1995, 11, 444, the entirety of which is incorporated herein by reference.

[00281] Additional compounds of formula **I** were prepared in a manner substantially similar to that described above.

[00282] 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.

[00283] 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 3

In Vitro Acetyl-CoA Carboxylase (ACC) Inhibition Assay

[00284] 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).

[00285] 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.

[00286] 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.

Example 4

Thermal Shift Assay

[00287] 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.

[00288] 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 5

[^{14}C] Acetate Incorporation Assay

[00289] 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).

[00290] 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.

[00291] 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 6

[00292] 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.

[00293] 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).

[00294] 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.

[00295] 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 7

[00296] 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.

[00297] 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.

[00298] 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 8

[00299] 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.

[00300] 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.

[00301] 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 9

[00302] 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.

[00303] 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.

[00304] 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 10

[00305] 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.

[00306] 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.

[00307] 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.

[00308] 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 11

[00309] Compounds of the present invention are also assayed in high fat diet induced obesity (DIO) studies. A representative protocol for the assay follows.

[00310] 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.

[00311] 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.

[00312] 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.

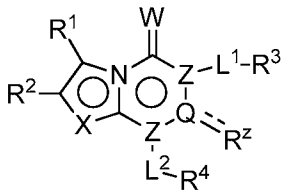
[00313] The anti-obesity, insulin sensitizing, hyperinsulinemia-reversing, and hepatic steatosis-reversing potential of compounds of the present invention are assayed by administering compounds of the invention once daily by oral gavage in 0.5% methylcellulose in saline at doses of 0, 3, 10, and 30 mg/kg 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.

[00314] 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;

Q is C or N; wherein if Q is N, then R^z is absent;

X is –O-, -S-, or –NR-;

each Z is independently C or N; provided that both Z are not 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; 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; and

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;

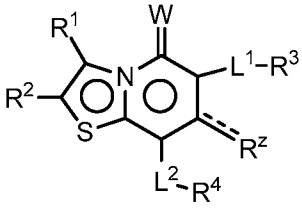
R^6 is -R, -C(O)N(R_2), or -C(O)R;

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

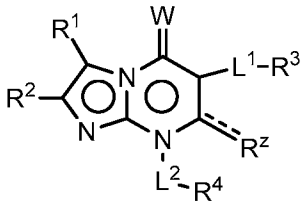
R^z is selected from hydrogen, halogen, methyl, -CN, =O, and =S; and

n is 0-5.

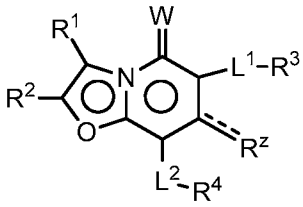
2. The compound according to claim 1 wherein the compound is selected from the group consisting of formulas **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f, I-g**, and **I-h**:



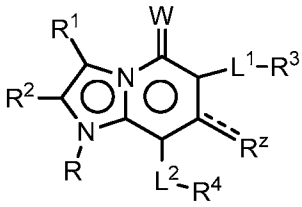
I-a



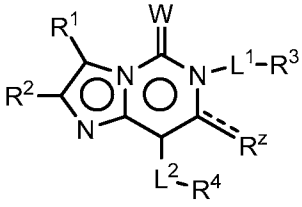
I-b



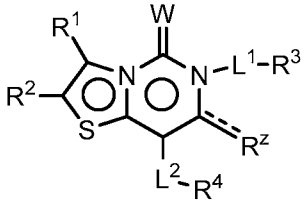
I-c



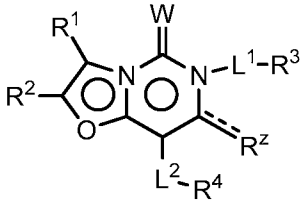
I-d



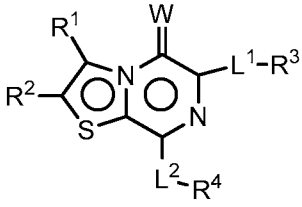
I-e



I-f



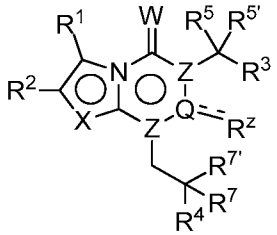
I-g



I-h

or a pharmaceutically acceptable salt thereof.

3. The compound according to 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 14/37363

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/517; A61K 31/4375 (2014.01)
USPC - 514/266.3; 514/300
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)
IPC(8): A61K 31/517; A61K 31/4375 (2014.01)
USPC: 514/266.3; 514/300

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/258.1; 514/266.31; 514/312; 546/121
CPC: C07D 239/96; C07D 471/04

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, PubWEST
bicyclic pyridone, pyrimidindione, dioxo, imidazo[1,2-a]pyridinone, thiazolo[3,2-a]pyridin-5-one, oxazolo[3,2-a]pyridin-5-one, ACC, acetyl-CoA carboxylase, inhibitor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0139607 A1 (ALMQUIST et al.) 12 June 2008 (12.06.2008) para [0028], [0029], [0031], [0231]	1-14
Y	US 2012/0142714 A1 (YASUMA et al.) 07 June 2012 (07.06.2012) para [0048]-[0049]; pg 140, Ex.No.83; para [0686]	1-14
Y	US 2012/0010247 A1 (KAMATA et al.) 12 January 2012 (12 01.2012) para [0044], [02227]-[2230], [2683]	3
Y	US 2011/0244059 A1 (JIN) 06 October 2011 (06.10.2011) para [0013]-[0014]	10-11
Y	US 2010/0113473 A1 (PLAYER et al.) 06 May 2010 (06.05.2010) para [0033], [0040]	13
Y	US 2012/0144525 A1 (GALLIE et al.) 07 June 2012 (07.06.2012) abstract; para [0020]-[0021]	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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2014 (11.08.2014)	16 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

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

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代理人 沈锦华

(51)Int.Cl.
A61K 31/517(2006.01)
A61K 31/4375(2006.01)

权利要求书3页 说明书67页

(54)发明名称

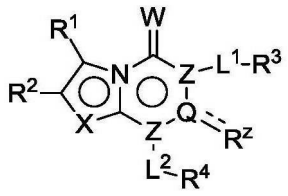
ACC 抑制剂和其用途

(57)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。具体来说，提供含有与吡啶酮、嘧啶酮或嘧啶二酮稠合的咪唑、噻唑或噁唑的双环杂芳基衍生物。这些化合物在以有效量投与个体后具有治疗所述个体的如肥胖症的 ACC 酶介导的病症的治疗效用。

CN 105358154 A

1.一种化合物,其具有式Ⅰ:



Ⅰ

或其医药学上可接受的盐,其中:

W为氧或硫;

Q为C或N;其中如果Q为N,那么R^z不存在;

X为-O-、-S-或-NR-;

每个Z独立地为C或N;其限制条件为两个Z不均为N;

R^1为氢或C_{1-4}脂肪族基团,任选地经一或多个卤素、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2RN(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-C(O)OR$、$-S(O)R$或$-SO_2R$取代;

R^2为卤素、-R、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-S(O)R$、$-SO_2R$、$-B(OR)_2$或Hy,其中Hy选自具有1到2个独立地选自氮、氧或硫的杂原子的4到8元饱和或部分不饱和单环杂环、具有1到4个独立地选自氮、氧或硫的杂原子的5到6元单环杂芳环、或具有1到5个独立地选自氮、氧或硫的杂原子的8到10元双环杂芳环;或

R^1和R^2连在一起以形成任选经取代的4到7元部分不饱和碳环基稠环、或杂环基稠环、苯并稠环或5到6元杂芳基稠环;

每个R独立地为氢、氘或选自以下各者的任选经取代的基团:C_{1-6}脂肪族基团、3到8元饱和或部分不饱和单环碳环、苯基、8到10元双环芳香族碳环;具有1到2个独立地选自氮、氧或硫的杂原子的4到8元饱和或部分不饱和单环杂环、具有1到4个独立地选自氮、氧或硫的杂原子的5到6元单环杂芳环、或具有1到5个独立地选自氮、氧或硫的杂原子的8到10元双环杂芳环;

L^1为共价键或任选地经R^5和$R^{5'}$取代的1到6元直链或支链二价烃链;

L^2为共价键或任选地经R^7和$R^{7'}$取代的1到6元直链或支链二价烃链;

R^3为卤素、-CN、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)RN(R)_2$、$-C(O)N(R)S(O)_2R$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-S(O)R$、$-SO_2R$、$-B(OR)_2$、或选自苯基或具有1到4个独立地选自氮、氧或硫的杂原子的5到6元杂芳基的任选经取代的环;

R^4为氢或选自以下各者的环:3到8元单环饱和或部分不饱和碳环、具有1到2个独立地选自氮、氧或硫的杂原子的4到8元单环饱和或部分不饱和杂环、苯基、8到10元双环芳基环、具有1到4个独立地选自氮、氧或硫的杂原子的5到6元单环杂芳基环、或具有1到4个独立地选自氮、氧或硫的杂原子的8到10元双环杂芳基环;其中所述环任选地经R^8的n个实例取代;

R^5和$R^{5'}$中的每一者独立地为-R、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)$

$N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-S(O)R$ 或 $-SO_2R$；或 R^5 和 $R^{5'}$ 连在一起以形成环丙烯基、环丁烯基或氧杂环丁烷基；且

R^7 和 $R^{7'}$ 中的每一者独立地为 -R、$-OR^6$、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-S(O)R$、$-SO_2R$、$-B(OR)_2$；或 R^7 和 $R^{7'}$ 连在一起以形成 3 到 8 元饱和或部分不饱和单环碳环、或具有 1 到 2 个独立地选自氮、氧或硫的杂原子的 4 到 8 元饱和或部分不饱和单环杂环；

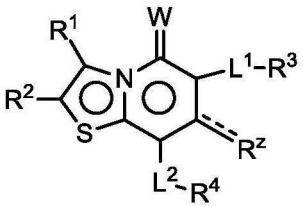
R^6 为 -R、$-C(O)N(R)_2$ 或 $-C(O)R$；

每个 R^8 独立地选自卤素、-R、-OR、-SR、$-N(R)_2$ 或氘；

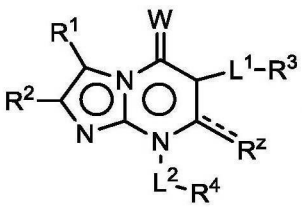
R^z 是选自氢、卤素、甲基、-CN、=O 和 =S；且

n 为 0 到 5。

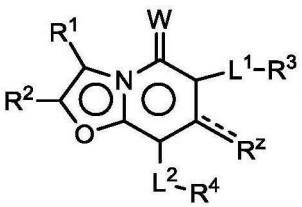
2. 根据权利要求 1 所述的化合物，其中所述化合物选自由以下各者组成的群组：式 I-a、I-b、I-c、I-d、I-e、I-f、I-g 和 I-h：



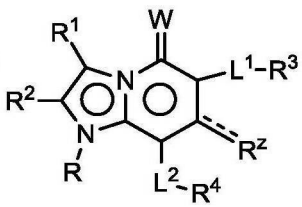
I-a



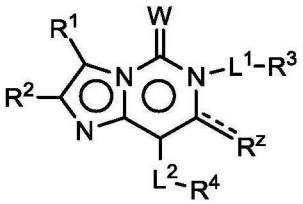
I-b



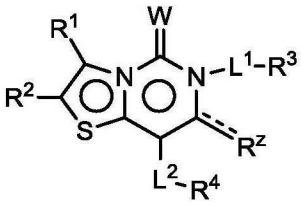
I-c



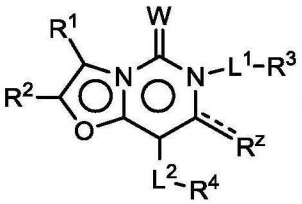
I-d



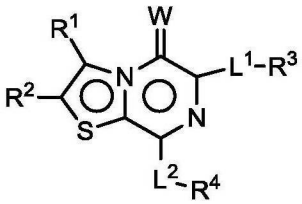
I-e



I-f



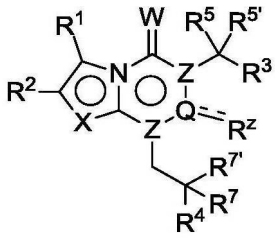
I-g



I-h

或其医药学上可接受的盐。

3. 根据权利要求 1 所述的化合物，其具有式 II：



II

或其医药学上可接受的盐。

4. 一种组合物，其包含根据权利要求 1 所述的化合物和医药学上可接受的载剂、佐剂或媒剂。

5. 一种抑制有需要的患者的 ACC 的方法，其包含向所述患者投与根据权利要求 4 所述的组合物。

6. 一种抑制生物样品中的 ACC 的方法，其包含使所述生物样品与根据权利要求 1 所述

的化合物接触。

7. 一种治疗有需要的患者的代谢病症的方法，其包含向所述患者投与根据权利要求 4 所述的组合物。

8. 根据权利要求 7 所述的方法，其中所述代谢病症为肥胖症。

9. 根据权利要求 7 所述的方法，其中所述代谢病症为血脂异常或高脂质血症。

10. 根据权利要求 8 所述的方法，其中所述肥胖症为普拉德－威利综合症、巴比二氏综合症、科恩综合症或 MOMO 综合症的症状。

11. 根据权利要求 8 所述的方法，其中所述肥胖症为投与另一种药物的副作用，所述另一种药物包括（但不限于）胰岛素、磺脲、噻唑烷二酮、抗精神病药、抗抑郁剂、类固醇、抗惊厥剂（包括苯妥英和丙戊酸盐）、苯噻啶或激素避孕药。

12. 一种治疗有需要的患者的癌症或其它增生性病症的方法，其包含向所述患者投与根据权利要求 4 所述的组合物。

13. 一种治疗有需要的患者的真菌、寄生虫或细菌感染的方法，其包含向所述患者投与根据权利要求 4 所述的组合物。

14. 一种抑制植物的 ACC 的方法，其包含使所述植物与根据权利要求 1 所述的化合物接触。

ACC 抑制剂和其用途

背景技术

[0001] 肥胖症是巨大比例的健康危机。肥胖症的健康负荷（利用每个成人质量调节的寿命年数损失来测量）已超越吸烟的健康负荷，从而变成最严重的、可预防的死亡原因。在美国，约 34％的成人患有肥胖症，1999 年达 31％，且在 1960 年到 1980 年约 15％。肥胖症增加所有年龄以及所有人种和民族人群中男性和女性两者的所有病因的死亡率。肥胖症还产生社会耻辱和歧视，这会显著降低生活质量。由肥胖症引起的慢性疾病使美国经济每年在体重相关的医学账单方面花费超过 1500 亿美元。此外，约一半的肥胖人群和 25％的普通人群具有代谢综合症，一种与腹部肥胖症、高血压、血浆甘油三酯增加、HDL 胆固醇降低和胰岛素抵抗相关的病况，其增加 2 型糖尿病 (T2DM)、中风和冠心病的风险。[哈伍德 (Harwood), 治疗目标专家意见 (Expert Opin.Ther.Targets)9:267,2005]。

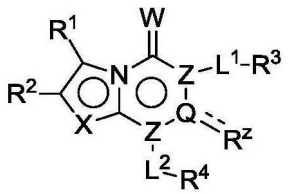
[0002] 饮食和运动甚至当与当前药物疗法结合使用时也并不提供长期健康益处所需的可持续的体重减轻。目前，在美国仅批准了几种抗肥胖症药物，脂肪吸收抑制剂奥利司他 (orlistat，Xenical®)、5-HT_{2C}拮抗剂氯卡色林 (lorcaserin，Belviq®) 和组合疗法苯丁胺 / 托吡酯 (phentermine/topiramate，Qsymia®)。令人遗憾的是，较差功效和无吸引力的胃肠道副作用限制了奥利司他的使用。手术可为有效的，但限于身体质量指数 (BMI) 极高的患者，且手术的低通量将此模态的影响限制为每年约 20 万患者。大部分处于临床开发中的肥胖症药物被设计成用于经 CNS 的中枢作用来减少热量摄取（例如减食欲剂和饱腹感剂）。然而，FDA 已采取对抗 CNS 活性剂的反对立场，归因于其不太大的功效和观察到的 / 潜在的副作用特征。

[0003] 持续和渐增的肥胖症问题以及当前用于其治疗的安全且有效的药物的缺乏突显了对治疗此病况和其潜在病因的新药物的势不可挡的需求。

发明内容

[0004] 现已发现，本发明化合物和其医药学上可接受的组合物作为乙酰基 -CoA 羧化酶 (ACC) 的抑制剂有效。所述化合物具有通式 I：

[0005]



I

[0006] 或其医药学上可接受的盐，其中每个变量如本文中所定义和描述。

[0007] 本发明的化合物和其医药学上可接受的组合物适用于治疗与脂肪酸制造或氧化的调节相关的多种疾病、病症或病况。所述疾病、病症或病况包括本文所述的那些疾病、病症或病况。

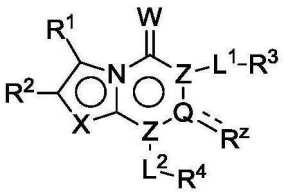
[0008] 由本发明提供的化合物还适用于 ACC 酶在生物和病理现象中的研究；在脂肪生成组织中存在的胞内信号转导路径的研究；以及体外或体内新 ACC 抑制剂或其它脂肪酸层面调节剂的比较性评估。

具体实施方式

[0009] 1. 本发明化合物的一般描述：

[0010] 在某些实施例中，本发明提供 ACC 的抑制剂。在一些实施例中，所述化合物包括式 I 的化合物：

[0011]



I

[0012] 或其医药学上可接受的盐，其中：

[0013] W 为氧或硫；

[0014] Q 为 C 或 N；其中如果 Q 为 N，那么 R^z不存在；

[0015] X 为 -O-、-S- 或 -NR-；

[0016] 每个 Z 独立地为 C 或 N；其限制条件为两个 Z 不均为 N；

[0017] R^1为氢或 C_{1-4}脂肪族基团，任选地经一或多个卤素、-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 或 $-SO_2R$ 取代；

[0018] R^2为卤素、-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、$-SO_2R$、$-B(OR)_2$或 Hy，其中 Hy 选自具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环、或具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环；或

[0019] R^1和 R^2连在一起以形成任选经取代的 4-7 元部分不饱和碳环基稠环、或杂环基稠环、苯并稠环或 5-6 元杂芳基稠环；

[0020] 每个 R 独立地为氢、氘或选自以下各者的任选经取代的基团：C_{1-6}脂肪族基团、3-8 元饱和或部分不饱和单环碳环、苯基、8-10 元双环芳香族碳环；具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环、或具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环；

[0021] L^1为共价键或任选地经 R^5和 $R^{5'}$取代的 1-6 元直链或支链二价烃链；

[0022] L^2为共价键或任选地经 R^7和 $R^{7'}$取代的 1-6 元直链或支链二价烃链；

[0023] R^3为 卤 素、-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、$-SO_2R$、$-B(OR)_2$、或选自苯基或具有 1-4 个独立地选自氮、氧或硫的杂

原子的 5-6 元杂芳基的任选经取代的环；

[0024] R^4为氢或选自以下各者的环：3-8 元单环饱和或部分不饱和碳环、具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元单环饱和或部分不饱和杂环、苯基、8-10 元双环芳基环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳基环、或具有 1-4 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳基环；其中所述环任选地经 R^8的 n 个实例取代；

[0025] R^5和 $R^{5'}$中的每一者独立地为 -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 或 $-SO_2R$；或 R^5和 $R^{5'}$连在一起以形成环丙烯基、环丁烯基或氧杂环丁烷基；且

[0026] R^7和 $R^{7'}$中的每一者独立地为 -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、$-SO_2R$、$-B(OR)_2$；或 R^7和 $R^{7'}$连在一起以形成 3-8 元饱和或部分不饱和单环碳环、或具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环；

[0027] R^6为 -R、$-C(O)N(R)_2$或 -C(O)R；

[0028] 每个 R^8独立地选自卤素、-R、-OR、-SR、$-N(R)_2$或氘；

[0029] R^z是选自氢、卤素、甲基、-CN、＝ O 和＝ S；且

[0030] n 为 0-5。

[0031] 2. 化合物和定义：

[0032] 本发明化合物包括在上文中一般描述，且通过本文所公开的类别、子类和种类进一步说明的那些化合物。如本文中所用，除非另外指明，否则以下定义应适用。出于本发明的目的，化学元素是根据元素周期表，CAS版本，化学与物理手册 (Handbook of Chemistry and Physics)，第 75 版来鉴别。另外，有机化学的一般原理描述于“有机化学 (Organic Chemistry)”，托马斯索雷尔 (Thomas Sorrell)，大学科学书籍 (University Science Books)，索萨利托 (Sausalito)：1999 和“马奇高等有机化学 (March's Advanced Organic Chemistry)”，第 5 版，编辑：史密斯 M.B.(Smith,M.B.) 和马奇 J.(March,J.)，约翰·威利父子公司 (John Wiley&Sons)，纽约 (New York)：2001 中，这些文献的全部内容特此以引用的方式并入。

[0033] 如本文中所用，术语“脂肪族”或“脂肪族基团”意指完全饱和或含有一或多个不饱和单元的直链（即，非支链）或支链的经取代或未经取代的烃链，或完全饱和或含有一或多个不饱和单元、但不是芳香族的单环烃或双环烃（在本文中也被称作“碳环”、“环脂族”或“环烷基”），其与分子剩余部分具有单一连接点。除非另外规定，否则脂肪族基团含有 1-6 个脂肪族碳原子。在一些实施例中，脂肪族基团含有 1-5 个脂肪族碳原子。在其它实施例中，脂肪族基团含有 1-4 个脂肪族碳原子。在其它实施例中，脂肪族基团含有 1-3 个脂肪族碳原子，并且在其它实施例中，脂肪族基团含有 1-2 个脂肪族碳原子。在一些实施例中，“环脂族”（或“碳环”或“环烷基”）是指完全饱和或含有一或多个不饱和单元、但不是芳香族的单环 C_3-C_6烃，其与分子剩余部分具有单一连接点。适合的脂肪族基团包括（但不限于）直链或支链、经取代或未经取代的烷基、烯基、炔基和其混合物，如（环烷基）烷基、（环烯基）烷基或（环烷基）烯基。

[0034] 术语“低碳烷基”是指 C_{1-4}直链或支链烷基。示例性低碳烷基为甲基、乙基、丙基、异丙基、丁基、异丁基和叔丁基。

[0035] 术语“低碳卤烷基”是指经一或多个卤素原子取代的 C_{1-4}直链或支链烷基。

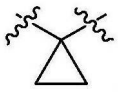
[0036] 术语“杂原子”意指氧、硫、氮、磷或硅中的一或多者（包括氮、硫、磷或硅的任何氧化形式；任何碱性氮的季铵化形式；或杂环的可取代氮，例如 N（如 3,4- 二氢 -2H- 吡咯基中）、NH（如吡咯烷基中）或 NR^+（如 N 经取代吡咯烷基中））。

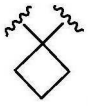
[0037] 如本文中所用，术语“不饱和”意指具有一或多个不饱和单元的部分。

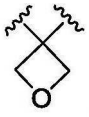
[0038] 如本文中所用，术语“二价 C_{1-8}（或 C_{1-6}）饱和或不饱和、直链或支链烃链”是指如本文中所定义的直链或支链的二价亚烷基、亚烯基和亚炔基链。

[0039] 术语“亚烷基”是指二价烷基。“亚烷基链”是聚亚甲基，即，$-(CH_2)_n-$，其中 n 是正整数，优选是 1 到 6、1 到 4、1 到 3、1 到 2 或 2 到 3。经取代亚烷基链为聚亚甲基，其中一或多个亚甲基氢原子由取代基置换。适合的取代基包括下文关于经取代的脂肪族基团所描述的取代基。

[0040] 术语“亚烯基”是指二价烯基。经取代亚烯基链为含有至少一个双键的聚亚甲基，其中一或多个氢原子经取代基置换。适合的取代基包括下文关于经取代的脂肪族基团所描述的取代基。

[0041] 如本文中所用，术语“环丙烯基”是指以下结构的二价环丙基：  。

[0042] 如本文中所用，术语“环丁烯基”是指以下结构的二价环丁基：  。

[0043] 如本文所用，术语“氧杂环丁烷基”是以下结构的二价氧杂环丁烷基：  。

[0044] 术语“卤素”意指 F、Cl、Br 或 I。

[0045] 如在“芳烷基”、“芳烷氧基”或“芳氧基烷基”中单独或作为较大部分的一部分使用的术语“芳基”是指具有总共五到十四个环成员的单环或双环系统，其中系统中的至少一个环是芳香族并且其中系统中的每个环含有 3 到 7 个环成员。术语“芳基”可以与术语“芳基环”互换使用。

[0046] 如在“芳烷基”、“芳烷氧基”或“芳氧基烷基”中单独或作为较大部分的一部分使用的术语“芳基”是指具有总共五到 10 个环成员的单环和双环系统，其中系统中的至少一个环是芳香族并且其中系统中的每个环含有三到七个环成员。术语“芳基”可以与术语“芳基环”互换使用。在本发明的某些实施例中，“芳基”是指芳环系统，其包括（但不限于）苯基、联苯基、萘基、蒽基等，其可以具有一或多个取代基。如本文中所用，在术语“芳基”范围内还包括芳环稠合到一或多个非芳香族环的基团，如茚满基、邻苯二甲酰亚胺基、萘酰亚胺基、啡啶基或四氢萘基等。

[0047] 单独或作为例如“杂芳烷基”或“杂芳烷氧基”的较大部分的一部分使用的术语“杂芳基”和“杂芳 -”是指具有 5 到 10 个环原子、优选地 5、6 或 9 个环原子；在环阵列中共用 6、10 或 14 个 π 电子；并且除碳原子以外具有一到五个杂原子的基团。术语“杂原子”是指氮、

氧或硫，并且包括氮或硫的任何氧化形式；和碱性氮的任何季铵化形式。杂芳基包括（但不限于）噻吩基、呋喃基、吡咯基、咪唑基、吡唑基、三唑基、四唑基、噁唑基、异噁唑基、噁二唑基、噻唑基、异噻唑基、噻二唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、吲哚嗪基、嘌呤基、萘啶基和蝶啶基。如本文中所用，术语“杂芳基”和“杂芳 -”还包括杂芳环稠合到一或多个芳基、环脂族基或杂环基环的基团，其中自由基或连接点在杂芳环上。非限制性实例包括吲哚基、异吲哚基、苯并噻吩基、苯并呋喃基、二苯并呋喃基、吲唑基、苯并咪唑基、苯并噻唑基、喹啉基、异喹啉基、噌啉基、酞嗪基、喹唑啉基、喹喔啉基、4H- 喹嗪基、咔唑基、吖啶基、啡嗪基、啡噻嗪基、啡噁嗪基、四氢喹啉基、四氢异喹啉基和吡啶并 [2,3-b]-1,4- 噁嗪 -3(4H)- 酮。杂芳基可以是单环或双环。术语“杂芳基 (heteroaryl)”可以与术语“杂芳基环 (heteroaryl ring)”、“杂芳基 (heteroaryl group)”或“杂芳族基 (heteroaromatic)”互换使用，所述术语中的任一者包括任选地经取代的环。术语“杂芳烷基”是指经杂芳基取代的烷基，其中烷基和杂芳基部分独立地任选被取代。

[0048] 如本文中所用，术语“杂环 (heterocycle)”、“杂环基 (heterocyclyl)”、“杂环基 (heterocyclic radical)”和“杂环 (heterocyclic ring)”可互换使用并且是指稳定 5 到 7 元单环或 7-10 元双环杂环部分，其是饱和或部分不饱和的，并且除碳原子以外具有一或多个、优选地一到四个如上文所定义的杂原子。当关于杂环的环原子使用时，术语“氮”包括经取代的氮。作为一个实例，在具有 0-3 个选自氧、硫或氮的杂原子的饱和或部分不饱和环中，氮可以是 N（如 3,4- 二氢 -2H- 吡咯基中）、NH（如吡咯烷基中）或 $^{+}$NR（如 N 经取代吡咯烷基中）。

[0049] 杂环可以在任何杂原子或碳原子处连接到其侧基，从而产生稳定结构，并且任何环原子可以任选地经取代。所述饱和或部分不饱和杂环基的实例包括（但不限于）四氢呋喃基、四氢噻吩基吡咯烷基、哌啶基、吡咯啉基、四氢喹啉基、四氢异喹啉基、十氢喹啉基、噁唑烷基、哌嗪基、二氧杂环己烷基、二氧戊环基、二氮呼基、噁氮呼基、噻环氮己三烯基、吗啉基和奎宁环基。本文中术语“杂环 (heterocycle)”、“杂环基 (heterocyclyl)”、“杂环基环 (heterocyclyl ring)”、“杂环基 (heterocyclic group)”、“杂环部分 (heterocyclic moiety)”和“杂环基 (heterocyclic radical)”可互换使用，且包括其中杂环基环稠合到一或多个芳基、杂芳基或环脂族环的基团，如吲哚啉基、3H- 吲哚基、色满基、啡啶基或四氢喹啉基，其中自由基或连接点在杂环基环上。杂环基可以是单环或双环。术语“杂环基烷基”是指经杂环基取代的烷基，其中烷基和杂环基部分独立地任选经取代。

[0050] 如本文中所用，术语“部分不饱和”是指包括至少一个双键或三键的环部分。术语“部分不饱和”打算涵盖具有多个不饱和位点的环，但并不打算包括如本文所定义的芳基或杂芳基部分。

[0051] 如本文中所述，本发明的化合物可以含有“任选地被取代的”部分。一般来说，术语“经取代的”无论前面有还是没有术语“任选地”，都意指指定部分的一或多个氢经适合的取代基置换。除非另外指示，否则“任选经取代”基团可以在基团的每个可取代位置处具有适合的取代基，并且当任何既定结构中的一个以上位置可以经一个以上选自规定基团的取代基取代时，在每一位置处取代基可以是相同或不同的。本发明所预想的取代基的组合优选地是形成稳定或化学可行的化合物的组合。如本文中所用，术语“稳定”是指化合物在经历允许其产生、检测和在某些实施例中其回收、纯化和用于本文中所公开的一或多种目的

的条件时实质上不发生改变。

[0052] “任选经取代”基团的可取代碳原子上的适合的单价取代基独立地为卤素；$-(CH_2)_{0-4}R^{\circ}$；$-(CH_2)_{0-4}OR^{\circ}$；$-O(CH_2)_{0-4}R^{\circ}$，$-O-(CH_2)_{0-4}C(O)OR^{\circ}$；$-(CH_2)_{0-4}CH(OR^{\circ})_2$；$-(CH_2)_{0-4}SR^{\circ}$；$-(CH_2)_{0-4}Ph$，其可经 R° 取代；$-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$，其可经 R° 取代；-CH = CHPh，其可经 R° 取代；$-(CH_2)_{0-4}O(CH_2)_{0-1}-$ 吡啶基，其可经 R° 取代；$-NO_2$；-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)$SR^{\circ}$；$-(CH_2)_{0-4}SC(O)R^{\circ}$；$-(CH_2)_{0-4}C(O)NR^{\circ}_2$；$-C(S)NR^{\circ}_2$；$-C(S)SR^{\circ}$；$-SC(S)SR^{\circ}$，$-(CH_2)_{0-4}OC(O)NR^{\circ}_2$；$-C(O)N(OR^{\circ})R^{\circ}$；$-C(O)C(O)R^{\circ}$；$-C(O)CH_2C(O)R^{\circ}$；$-C(NOR^{\circ})R^{\circ}$；$-(CH_2)_{0-4}SSR^{\circ}$；$-(CH_2)_{0-4}S(O)_2R^{\circ}$；$-(CH_2)_{0-4}S(O)_2OR^{\circ}$；$-(CH_2)_{0-4}OS(O)_2R^{\circ}$；$-S(O)_2NR^{\circ}_2$；$-(CH_2)_{0-4}S(O)R^{\circ}$；$-N(R^{\circ})S(O)_2NR^{\circ}_2$；$-N(R^{\circ})S(O)_2R^{\circ}$；$-N(OR^{\circ})R^{\circ}$；$-C(NH)NR^{\circ}_2$；$-P(O)_2R^{\circ}$；$-P(O)R^{\circ}_2$；$-OP(O)R^{\circ}_2$；$-OP(O)(OR^{\circ})_2$；$SiR^{\circ}_3$；$-(C_{1-4}$直链或支链亚烷基$)O-N(R^{\circ})_2$；或 $-(C_{1-4}$直链或支链亚烷基$)C(O)O-N(R^{\circ})_2$，其中每个 R° 可如下所定义地经取代且独立地为氢、C_{1-6}脂肪族基团、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$、$-CH_2-$(5-6 元杂芳环）或具有 0-4 个独立地选自氮、氧或硫的杂原子的 5-6 元饱和、部分不饱和或芳环，或不管以上定义，两个独立出现的 R° 与其中间原子连在一起形成具有 0-4 个独立地选自氮、氧或硫的杂原子的 3 至 12 元饱和、部分不饱和或芳基单环或双环，其可如下所定义地经取代。

[0053] R°（或由与其中间原子连在一起的两个独立出现的 R° 形成的环）上的适合的单价取代基独立地为卤素、$-(CH_2)_{0-2}R^{\bullet}$、-（卤基 $R^{\bullet}$）、$-(CH_2)_{0-2}OH$、$-(CH_2)_{0-2}OR^{\bullet}$、$-(CH_2)_{0-2}CH(OR^{\bullet})_2$；-O（卤基 $R^{\bullet}$）、-CN、$-N_3$、$-(CH_2)_{0-2}C(O)R^{\bullet}$、$-(CH_2)_{0-2}C(O)OH$、$-(CH_2)_{0-2}C(O)OR^{\bullet}$、$-(CH_2)_{0-2}SR^{\bullet}$、$-(CH_2)_{0-2}SH$、$-(CH_2)_{0-2}NH_2$、$-(CH_2)_{0-2}NHR^{\bullet}$、$-(CH_2)_{0-2}NR^{\bullet}_2$、$-NO_2$、$-SiR^{\bullet}_3$、$-OSiR^{\bullet}_3$、$-C(O)SR^{\bullet}$、$-(C_{1-4}$直链或支链亚烷基$)C(O)OR^{\bullet}$ 或 $-SSR^{\bullet}$，其中每个 $R^{\bullet}$ 未经取代或当前面有“卤基”时，仅经一或多个卤素取代，且独立地选自 C_{1-4}脂肪族基团、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$ 或具有 0-4 个独立地选自氮、氧或硫的杂原子的 5-6 元饱和、部分不饱和或芳基环。R° 的饱和碳原子上的适合的二价取代基包括 = O 和 = S。

[0054] “任选经取代”基团的饱和碳原子的适合的二价取代基包括以下：= O、= S、$=NNR^*_2$、$=NNHC(O)R^*$、$=NNHC(O)OR^*$、$=NNHS(O)_2R^*$、$=NR^*$、$=NOR^*$、$-O(C(R^*_2))_{2-3}O-$ 或 $-S(C(R^*_2))_{2-3}S-$，其中每个独立出现的 R^* 选自氢、可如下所定义地经取代的 C_{1-6}脂肪族基团或具有 0-4 个独立地选自氮、氧或硫的杂原子的未经取代 5-6 元饱和、部分不饱和或芳基环。结合到“任选经取代”基团的邻接可取代碳的适合的二价取代基包括：$-O(CR^*_2)_{2-3}O-$，其中每个独立出现的 R^* 选自氢、可如下所定义地经取代的 C_{1-6}脂肪族基团或具有 0-4 个独立地选自氮、氧或硫的杂原子的未经取代 5-6 元饱和、部分不饱和或芳基环。

[0055] R^* 的脂肪族基团的适合的取代基包括卤素、$-R^{\bullet}$、-（卤基 $R^{\bullet}$）、-OH、$-OR^{\bullet}$、-O（卤基 $R^{\bullet}$）、-CN、-C(O)OH、$-C(O)OR^{\bullet}$、$-NH_2$、$-NHR^{\bullet}$、$-NR^{\bullet}_2$ 或 $-NO_2$，其中每个 $R^{\bullet}$ 未经取代或当前面有“卤基”时，仅经一或多个卤素取代，且独立地为 C_{1-4}脂肪族基团、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$ 或具有 0-4 个独立地选自氮、氧或硫的杂原子的 5-6 元饱和、部分不饱和或芳基环。

[0056] “任选经取代”基团的可取代氮上的适合的取代基包括 $-R^{\dagger}$、$-NR^{\dagger}_2$、$-C(O)R^{\dagger}$、

$-C(O)OR^{\dagger}$、$-C(O)O(O)R^{\dagger}$、$-C(O)CH_2C(O)R^{\dagger}$、$-S(O)_2R^{\dagger}$、$-S(O)_2N\,R^{\dagger}{}_2$、$-C(S)NR^{\dagger}{}_2$、$-C(NH)NR^{\dagger}{}_2$或$-N(R^{\dagger})S(O)_2R^{\dagger}$;其中每个$R^{\dagger}$独立地为氢、可如下文所定义地经取代的$C_{1-6}$脂肪族基团、未经取代的 -OPh、或具有 0-4 个独立地选自氮、氧或硫的杂原子的未经取代 5-6 元饱和、部分不饱和或芳基环;或不管以上定义,两个独立出现的$R^{\dagger}$与其中间原子连在一起形成具有 0-4 个独立地选自氮、氧或硫的杂原子的未经取代 3-12 元饱和、部分不饱和或芳基单环或双环。

[0057] $R^{\dagger}$的脂肪族基团的适合的取代基独立地为卤素、$-R^{\bullet}$、-(卤基$R^{\bullet}$)、-OH、$-OR^{\bullet}$、-O(卤基$R^{\bullet}$)、-CN、-C(O)OH、$-C(O)OR^{\bullet}$、$-NH_2$、$-NHR^{\bullet}$、$-NR^{\bullet}{}_2$或$-NO_2$,其中每个$R^{\bullet}$未经取代或当前面有“卤基”时,仅经一或多个卤素取代,且独立地为C_{1-4}脂肪族基团、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$或具有 0-4 个独立地选自氮、氧或硫的杂原子的 5-6 元饱和、部分不饱和或芳基环。

[0058] 如本文中所用,术语“医药学上可接受的盐”是指在合理医学判断范围内适用于与人类和低等动物的组织接触而无不当毒性、刺激、过敏反应等,并且与合理利益 / 风险比相称的那些盐。医药学上可接受的盐在本领域中众所周知。举例来说,S.M. 贝尔奇 (S.M.Berge) 等人在以引用的方式并入本文中的药物科学杂志 (J.Pharmaceutical Sciences),1977,66,1-19 中详细描述了医药学上可接受的盐。本发明化合物的医药学上可接受的盐包括那些从适合的无机酸和有机酸和无机碱和有机碱衍生的盐。医药学上可接受的无毒酸加成盐的实例为与无机酸形成的氨基盐,所述无机酸为如盐酸、氢溴酸、磷酸、硫酸和高氯酸;或与有机酸形成的氨基盐,所述有机酸为如乙酸、乙二酸、顺丁烯二酸、酒石酸、柠檬酸、丁二酸或丙二酸,或通过使用所属领域中所用的其它方法(如离子交换)形成的氨基盐。其它医药学上可接受的盐包括己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷丙酸盐、二葡糖酸盐、十二烷基硫酸盐、乙烷磺酸盐、甲酸盐、反丁烯二酸盐、葡庚糖酸盐、甘油磷酸盐、葡糖酸盐、半硫酸盐、庚酸盐、己酸盐、氢碘酸盐、2- 羟基 - 乙烷磺酸盐、乳糖酸盐、乳酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、顺丁烯二酸盐、丙二酸盐、甲烷磺酸盐、2- 萘磺酸盐、烟碱酸盐、硝酸盐、油酸盐、草酸盐、棕榈酸盐、双羟萘酸盐、果胶酸盐、过硫酸盐、3- 苯基丙酸盐、磷酸盐、特戊酸盐、丙酸盐、硬脂酸盐、丁二酸盐、硫酸盐、酒石酸盐、硫氰酸盐、对甲苯磺酸盐、十一烷酸盐、戊酸盐等。

[0059] 衍生自适当碱的盐包括碱金属盐、碱土金属盐、铵盐和$N^{+}(C_{1-4}$烷基$)_4$盐。代表性碱金属或碱土金属盐包括钠盐、锂盐、钾盐、钙盐、镁盐等。其它医药学上可接受的盐包括(适当时)使用平衡离子形成的无毒铵、季铵和胺阳离子,所述平衡离子为如卤离子、氢氧根、羧酸根、硫酸根、磷酸根、硝酸根、低碳烷基磺酸根和芳基磺酸根。

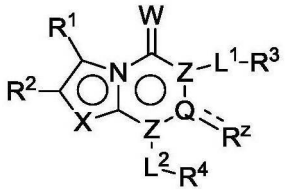
[0060] 除非另外说明,否则本文所描绘的结构也意图包括所述结构的所有异构(例如,对映异构、非对映异构和几何异构(或构象异构))形式,例如每个不对称中心的 R 和 S 构型,Z 和 E 双键异构体以及 Z 和 E 构象异构体。因此,本发明化合物的单一立体化学异构体以及对映异构、非对映异构以及几何异构(或构象异构)混合物都在本发明的范围内。除非另有说明,否则本发明化合物的所有互变异构形式都在本发明的范围内。另外,除非另有说明,否则本文所描绘的结构还意图包括不同之处仅在于存在一或多个同位素富集原子的

化合物。举例来说，包括由氘或氚置换氢或由 ^{13}C 或 ^{14}C 富集的碳置换碳的具有本发明结构的化合物在本发明的范围内。所述化合物适用作（例如）分析工具，用作生物分析中的探针，或用作根据本发明的治疗剂。

[0061] 3. 示例性实施例的描述：

[0062] 在某些实施例中，本发明提供 ACC 的抑制剂。在一些实施例中，所述化合物包括式 I 的化合物：

[0063]



I

[0064] 或其医药学上可接受的盐，其中：

[0065] W 为氧或硫；

[0066] Q 为 C 或 N；其中如果 Q 为 N，那么 R^z 不存在；

[0067] X 为 -O-、-S- 或 -NR-；

[0068] 每个 Z 独立地为 C 或 N；其限制条件为两个 Z 不均为 N；

[0069] R^1 为氢或 C_{1-4} 脂肪族基团，任选地经一或多个卤素、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2RN(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-C(O)OR$、$-S(O)R$ 或 $-SO_2R$ 取代；

[0070] R^2 为卤素、-R、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-S(O)R$、$-SO_2R$、$-B(OR)_2$ 或 Hy，其中 Hy 选自具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环、或具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环；或

[0071] R^1 和 R^2 连在一起以形成任选经取代的 4-7 元部分不饱和碳环基稠环、或杂环基稠环、苯并稠环或 5-6 元杂芳基稠环；

[0072] 每个 R 独立地为氢、氘或选自以下各者的任选经取代的基团：C_{1-6} 脂肪族基团、3-8 元饱和或部分不饱和单环碳环、苯基、8-10 元双环芳香族碳环；具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环、或具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环；

[0073] L^1 为共价键或任选地经 R^5 和 $R^{5'}$ 取代的 1-6 元直链或支链二价烃链；

[0074] L^2 为共价键或任选地经 R^7 和 $R^{7'}$ 取代的 1-6 元直链或支链二价烃链；

[0075] R^3 为 卤 素、-CN、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)RN(R)_2$、$-C(O)N(R)S(O)_2R$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、$-C(O)R$、$-C(O)OR$、$-OC(O)R$、$-S(O)R$、$-SO_2R$、$-B(OR)_2$、或选自苯基或具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元杂芳基的任选经取代的环；

[0076] R^4 为氢或选自以下各者的环：3-8 元单环饱和或部分不饱和碳环、具有 1-2 个独

立地选自氮、氧或硫的杂原子的 4-8 元单环饱和或部分不饱和杂环、苯基、8-10 元双环芳基环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳基环、或具有 1-4 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳基环；其中所述环任选地经 R^8 的 n 个实例取代；

[0077] R^5 和 $R^{5'}$ 中的每一者独立地为 -R、-OR、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、-C(O)R、-C(O)OR、-OC(O)R、-S(O)R 或 $-SO_2R$；或 R^5 和 $R^{5'}$ 连在一起以形成环丙烯基、环丁烯基或氧杂环丁烷基；且

[0078] R^7 和 $R^{7'}$ 中的每一者独立地为 -R、$-OR^6$、-SR、$-N(R)_2$、$-N(R)C(O)R$、$-C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)N(R)_2$、$-N(R)C(O)OR$、$-OC(O)N(R)_2$、$-N(R)SO_2R$、$-SO_2N(R)_2$、-C(O)R、-C(O)OR、-OC(O)R、-S(O)R、$-SO_2R$、$-B(OR)_2$；或 R^7 和 $R^{7'}$ 连在一起以形成 3-8 元饱和或部分不饱和单环碳环、或具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环；

[0079] R^6 为 -R、$-C(O)N(R)_2$ 或 -C(O)R；

[0080] 每个 R^8 独立地选自卤素、-R、-OR、-SR、$-N(R)_2$ 或氘；

[0081] R^z 是选自氢、卤素、甲基、-CN、＝O 和＝S；且

[0082] n 为 0-5。

[0083] 在某些实施例中，如果 L^2 为共价键，那么 R^4 不为氢。在某些实施例中，当 R^2 为未经取代的烷基时，基团 $-L^2-R^4$ 不为烷基。在某些实施例中，连在一起的基团 $-L^1-R^3$ 不为未经取代的烷基。在某些实施例中，当连在一起的 $-L^1-R^3$ 为未经取代的烷基时，R^1 不为基团 $-CH_2C(O)N(R)V$，其中 V 为芳基或杂芳基环。

[0084] 如在上文中一般定义，W 为氧或硫。在一些实施例中，W 为氧。在一些实施例中，W 为硫。

[0085] 如在上文中一般定义，Q 为 C 或 N。在一些实施例中，Q 为 C。在一些实施例中，Q 为 N。

[0086] 如在上文中一般定义，X 为 -O-、-S- 或 -NR-。在某些实施例中，X 为 -O-。在某些实施例中，X 为 -S-。在一些实施例中，X 为 -NR-。在某些实施例中，X 为 -NH-。

[0087] 如在上文中一般定义，每个 Z 独立地为 C 或 N，其条件是两个 Z 不同时为 N。在一些实施例中，一个 Z 基团为 C，而另一个为 N。在一些实施例中，两个 Z 基团均为 C。

[0088] 如在上文中一般定义，R^1 是氢或 C_{1-4} 脂肪族基团，任选地经一或多个卤素、-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 或 $-SO_2R$ 取代。在某些实施例中，R^1 为氢。在一些实施例中，R^1 为 C_{1-4} 脂肪族基团。在一些实施例中，R^1 为甲基。在一些实施例中，R^1 为三氟甲基。

[0089] 如在上文中一般定义，R^2 为卤素、-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、$-SO_2R$、$-B(OR)_2$ 或 Hy，其中 Hy 选自具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环、或具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环。在某些实施例中，R^2 为卤素。在某些实施例中，R^2 为甲基。在某些实施例中，R^2 为三氟甲

基。在某些实施例中，R^2为氟。在某些实施例中，R^2为氯。在某些实施例中，R^2为溴。在某些实施例中，R^2为碘。在某些实施例中，R^2为 -C(O)OR 或 -C(O)N(R)$_2$。在一些实施例中，R^2为 Hy。在一些实施例中，R^2为 3-8 元饱和或部分不饱和单环碳环。在一些实施例中，R^2为环丁基。

[0090] 如在上文中一般定义，Hy 选自具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环、或具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环。在一些实施例中，Hy 为具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环。在一些实施例中，Hy 为具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环。在一些实施例中，Hy 为具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环。在一些实施例中，Hy 为噁唑基。在一些实施例中，Hy 为噻唑基。在一些实施例中，Hy 为三唑基。

[0091] 在一些实施例中，R^1和 R^2连在一起以形成任选经取代的 4-7 元部分不饱和碳环。在一些实施例中，R^1和 R^2连在一起以形成任选经取代的 4-7 元部分不饱和碳环基稠环、或杂环基稠环、苯并稠环或 5-6 元杂芳基稠环；

[0092] 如在上文中一般定义，R^3为卤素、-CN、-OR、-SR、-N(R)$_2$、-N(R)C(O)R、-C(O)N(R)$_2$、-C(O)N(R)S(O)$_2$R、-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(OH)$_2$、或选自苯基和具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元杂环基或杂芳基的任选经取代的环。在某些实施例中，R^3为 -CN、-OR、-C(O)OR、-C(O)N(R)$_2$、-SO_2R、或选自苯基和具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元杂环基或杂芳基的任选经取代的环。在一些实施例中，R^3为 -OR。在一些实施例中，R^3为 -C(O)OR。在一些实施例中，R^3为苯基或四唑基。在一些实施例中，R^3为异噻唑烷 -1,1- 二氧化物。在一些实施例中，R^3为吡咯烷基羰基。

[0093] 如在上文中一般定义，每个 R 独立地为氢或选自以下各者的任选经取代的基团：C_{1-6}脂肪族基团、3-8 元饱和或部分不饱和单环碳环、苯基、8-10 元双环芳香族碳环；具有 1-2 个独立地选自氮、氧或硫的杂原子的 4-8 元饱和或部分不饱和单环杂环、具有 1-4 个独立地选自氮、氧或硫的杂原子的 5-6 元单环杂芳环、或具有 1-5 个独立地选自氮、氧或硫的杂原子的 8-10 元双环杂芳环。

[0094] 在某些实施例中，每个 R 独立地为氢或选自 C_{1-6}脂肪族基团、3-8 元不饱和或部分不饱和单环碳环的任选经取代的基团。在一些实施例中，每个 R 独立地为氢或任选经取代的 C_{1-6}脂肪族基团。

[0095] 如在上文中一般定义，L^1为共价键或任选地经 R^5和 $R^{5'}$取代的 1-6 元直链或支链二价烃链、或环丙烯基、环丁烯基或氧杂环丁烷基。在某些实施例中，L^1为任选地经 R^5和 $R^{5'}$取代的 C_{1-3}直链或支链二价烃链。在一些实施例中，L^1为直链或支链二价 C_2烃链。在一些实施例中，L^1为直链或支链二价 C_3烃链。在某些实施例中，L^1为经 R^5和 $R^{5'}$取代的 C_1二价烃链。在一些实施例中，L^1为环丙烯基、环丁烯基或氧杂环丁烷基。

[0096] 如在上文中一般定义，在一些实施例中，L^2为共价键或任选地经 R^7和 $R^{7'}$取代的 1-6 元直链或支链二价烃链。任选经取代的 C_{1-3}直链或支链烃链。在一些实施例中，L^2为任选经取代的 C_2直链烃链。在一些实施例中，L^2为任选经取代的 C_3直链或支链烃链。

[0097] 如在上文中一般定义，R^4为氢或选自以下各者的环：3-8元单环饱和或部分不饱和碳环、具有1-2个独立地选自氮、氧或硫的杂原子的4-8元单环饱和或部分不饱和杂环、苯基、8-10元双环芳基环、具有1-4个独立地选自氮、氧或硫的杂原子的5-6元单环杂芳基环、或具有1-4个独立地选自氮、氧或硫的杂原子的8-10元双环杂芳基环；其中所述环任选地经R^8的n个实例取代。

[0098] 在某些实施例中，R^4为氢。在一些实施例中，R^4为5-6元单环饱和或部分不饱和环；其中所述环任选地经R^8的n个实例取代。在一些实施例中，R^4为具有1-2个独立地选自氮、氧或硫的杂原子的5-6元单环饱和或部分不饱和杂环；其中所述环任选地经R^8的n个实例取代。在一些实施例中，R^4为苯基；其中所述环任选地经R^8的n个实例取代。在一些实施例中，R^4为10元双环芳基环；其中所述环任选地经R^8的n个实例取代。在一些实施例中，R^4为具有1-4个独立地选自氮、氧或硫的杂原子的5-6元单环杂芳基环；其中所述环任选地经R^8的n个实例取代。在一些实施例中，R^4为具有1-4个独立地选自氮、氧或硫的杂原子的8-10元双环杂芳基环；其中所述环任选地经R^8的n个实例取代。

[0099] 如在上文中一般定义，R^5和$R^{5'}$中的每一者独立地为-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或$-SO_2R$；或R^5和$R^{5'}$连在一起以形成环丙烯基、环丁烯基或氧杂环丁烷基。

[0100] 在一些实施例中，R^5和$R^{5'}$中的每一者为-R，其中-R不为氢。在一些实施例中，R^5和$R^{5'}$中的每一者为甲基。在一些实施例中，R^5和$R^{5'}$连在一起以形成环丙烯基、环丁烯基或氧杂环丁烷基。在一些实施例中，R^5和$R^{5'}$连在一起以形成环丁烯基。

[0101] 如在上文中一般定义，R^7和$R^{7'}$中的每一者独立地为氢、-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、$-SO_2R$或$-B(OR)_2$；或R^7和$R^{7'}$连在一起以形成3-8元饱和或部分不饱和单环碳环、或具有1-2个独立地选自氮、氧或硫的杂原子的4-8元饱和或部分不饱和单环杂环。

[0102] 在某些实施例中，R^7和$R^{7'}$中的一者为氢，且另一者为$-OR^6$。在一些实施例中，R^7和$R^{7'}$中的一者为氢，且另一者为异丙氧基。在一些实施例中，R^7和$R^{7'}$连在一起以形成3-6元饱和或部分不饱和单环碳环。在一些实施例中，R^7和$R^{7'}$连在一起以形成具有1-2个独立地选自氮、氧或硫的杂原子的4-6元饱和或部分不饱和单环杂环。在一些实施例中，R^7和$R^{7'}$中的一者为氢，且另一者为$-OR^6$。

[0103] 如在上文中一般所述，R^6为-R、$-C(O)N(R)_2$或-C(O)R。在某些实施例中，R^6为-R。在某些实施例中，R^6为氢。在某些实施例中，R^6为异丙基。在某些实施例中，R^6为四氢吡喃基。在某些实施例中，R^6为四氢呋喃基。在某些实施例中，R^6为四氢-2H-硫代吡喃-1,1-二氧化物。在某些实施例中，R^6为4-羟基环己基。

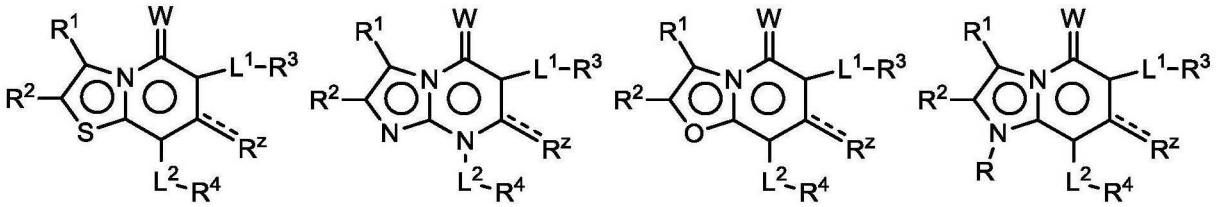
[0104] 如在上文中一般定义，每个R^8独立地选自卤素、-R、-OR、-SR、$-N(R)_2$或氘。在某些实施例中，每个R^8独立地选自卤素、-R和-OR。在某些实施例中，每个R^8为卤素。在某些实施例中，R^8为-OR。在某些实施例中，R^8为甲氧基。

[0105] 如在上文中一般定义，n为0-5。在某些实施例中，n为0。在一些实施例中，n为1-2。在一些实施例中，n为1。在一些实施例中，n为5。

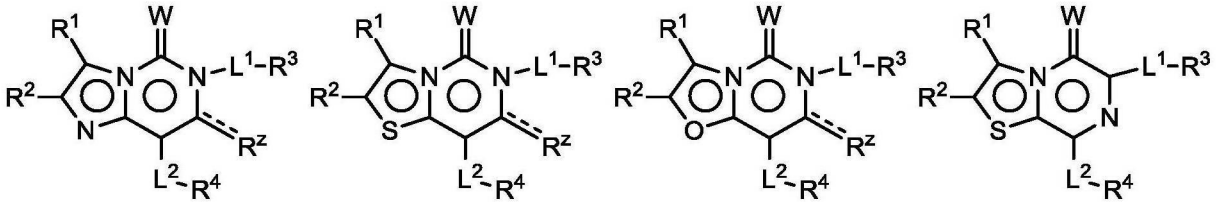
[0106] 如在上文中一般定义，R^z是选自氢、卤素、甲基、-CN、＝O和＝S。在一些实施例中，R^z为氢。在一些实施例中，R^z是选自卤素、甲基、-CN、＝O和＝S。所属领域的技术人员将了解，当R^z为＝O或＝S时，将所述原子连接于环上的环外键形式上为双键，但由于所述基团在其所连接的环的芳香性方面的互变异构，其也可表示为-OH或-SH。

[0107] 在一些实施例中，本发明提供式I化合物，其选自式I-a、I-b、I-c、I-d、I-e、I-f、I-g和I-h：

[0108]



I-a I-b I-c I-d

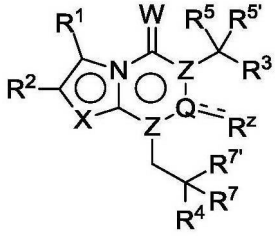


I-e I-f I-g I-h

[0109] 或其医药学上可接受的盐；其中单独和呈组合形式的W、R^1、R^2、R^3、R^4、R^z、L^1和L^2中的每一者均如关于上文式I的实施例中所述，或描述在本文中的实施例中。

[0110] 在某些实施例中，本发明提供式II化合物：

[0111]



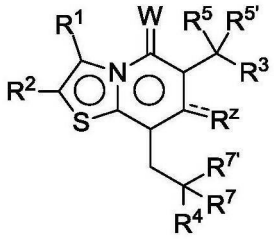
II

[0112] 或其医药学上可接受的盐，其中：

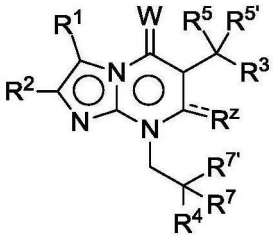
[0113] 单独和呈组合形式的W、Q、X、Z、R^1、R^2、R^3、R^4、R^5、$R^{5'}$、R^7、$R^{7'}$和R^z中的每一者均如关于上文式I的实施例中所述，或描述在本文中的实施例中。

[0114] 在某些实施例中，本发明提供式II化合物，其选自式II-a、II-b、II-c、II-d、II-e、II-f、II-g和II-h：

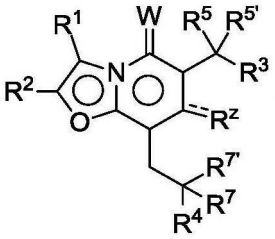
[0115]



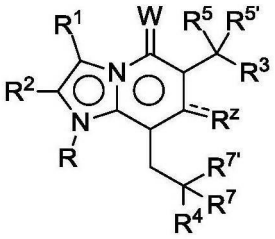
II-a



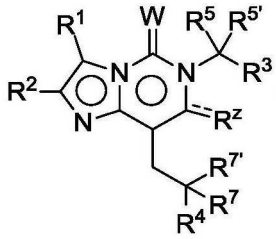
II-b



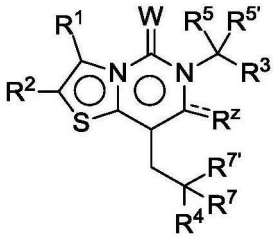
II-c



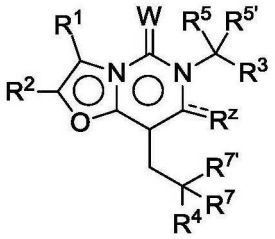
II-d



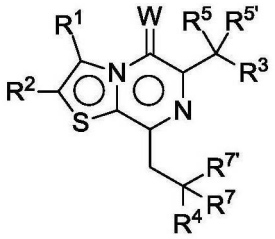
II-e



II-f



II-g

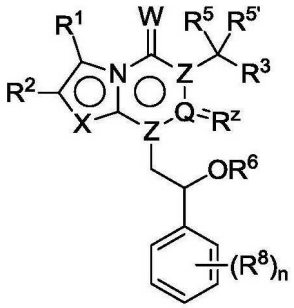


I-h

[0116] 或其医药学上可接受的盐;其中单独和呈组合形式的每个变量均如关于上文式II的实施例中所述,或描述在本文中的实施例中。

[0117] 在某些实施例中,本发明提供式III化合物:

[0118]



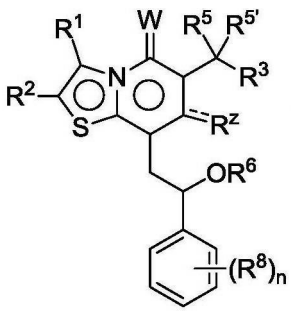
III

[0119] 或其医药学上可接受的盐,其中:

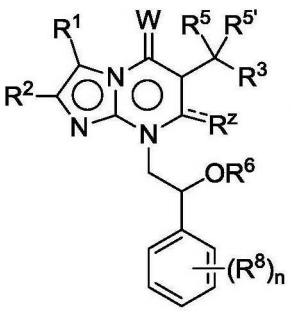
[0120] 单独和呈组合形式的W、Q、X、Z、R、R^1、R^2、R^3、R^5、$R^{5'}$、R^6、R^8、R^z和n中的每一者均如关于上文式I和II的实施例中所述,或描述在本文中的实施例中。

[0121] 在某些实施例中,本发明提供式III化合物,其选自式III-a、III-b、III-c、III-d、III-e、III-f、III-g和III-h:

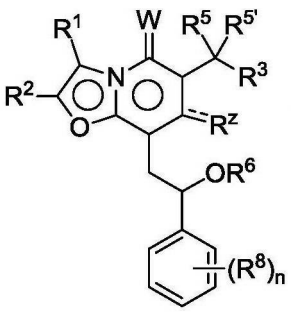
[0122]



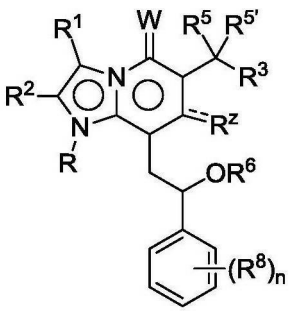
III-a



III-b

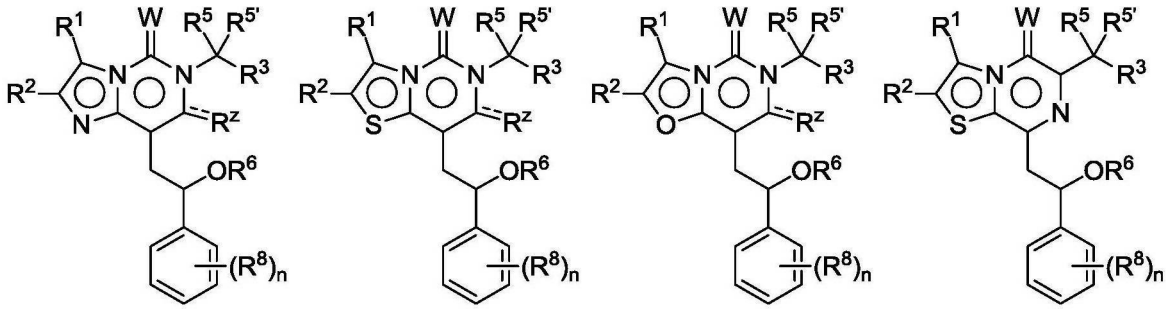


III-c



III-d

[0123]

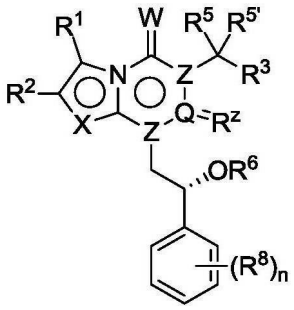


III-e III-f III-g III-h

[0124] 或其医药学上可接受的盐；其中单独和呈组合形式的每个变量均如关于上文式 III 的实施例中所述，或描述在本文中的实施例中。

[0125] 在某些实施例中，本发明提供式 IV 化合物：

[0126]



IV

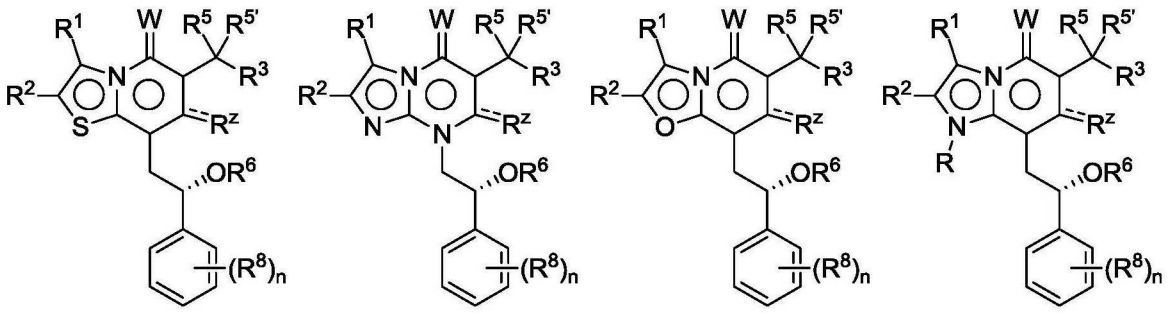
[0127] 或其医药学上可接受的盐，其中：

[0128] 单独和呈组合形式的 W、Q、X、Z、R、R^1、R^2、R^3、R^5、$R^{5'}$、R^6、R^8、n 和 R^z中的每一者均如关于上文式 I、II 和 III 的实施例中所述，或描述在本文中的实施例中。

[0129] 在一些实施例中，本发明提供式 IV 化合物，其中 R^2是选自溴、Hy 或 -C(O)OR。在一些实施例中，本发明提供式 IV 化合物，其中 R^2为 Hy。在一些实施例中，本发明提供式 IV 化合物，其中 R^2为 -C(O)OR。

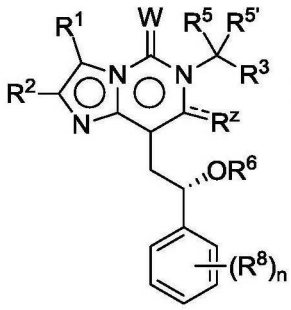
[0130] 在某些实施例中，本发明提供式 IV 化合物，其选自式 IV-a、IV-b、IV-c、IV-d、IV-e、IV-f、IV-g 和 IV-h：

[0131]

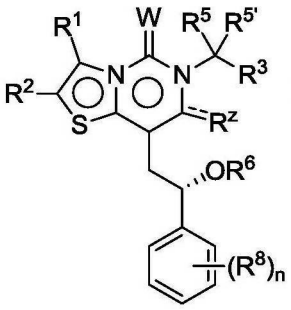


IV-a IV-b IV-c IV-d

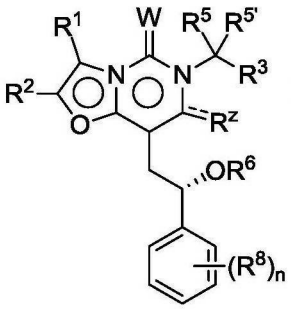
[0132]



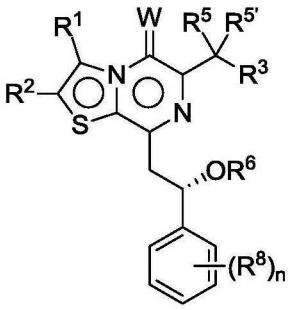
IV-e



IV-f



IV-g

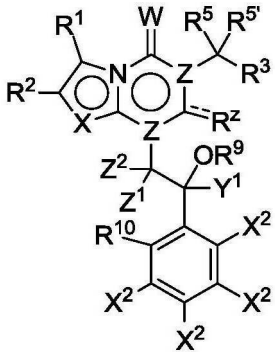


IV-h

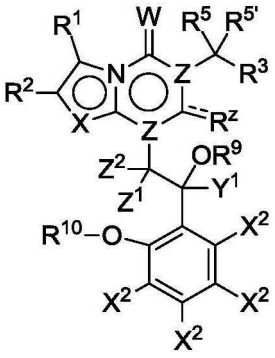
[0133] 或其医药学上可接受的盐；其中单独和呈组合形式的每个变量均如关于上文式III的实施例中所述，或描述在本文中的实施例中。

[0134] 在某些实施例中，本发明提供式V-i或V-ii化合物：

[0135]



V-i



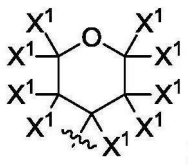
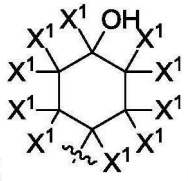
V-ii，

[0136] 或其医药学上可接受的盐，其中W、Q、X、Z、R^2、R^3、R^5、$R^{5'}$如上文关于式I的实施例中所述；且

[0137] R^1为H、D、CH_3或CD_3；

[0138] R^5和$R^{5'}$中的每一者独立地为CH_3或CD_3

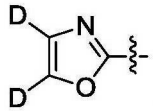
[0139] R^9为$CH(CH_3)_2$、$CH(CD_3)_2$、$CD(CH_3)_2$、$CD(CD_3)_2$或具有下式的基团：

[0140]  或  ；其中每个X^1独立地为H或D；

[0141] X^2、Y^1、Z^1和Z^2在每次出现时独立地为H或D；且

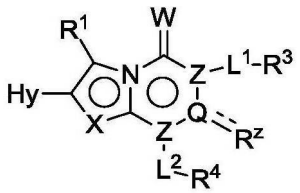
[0142] R^{10}为CH_3、CD_3、CH_2CH_3、$CH(CH_3)_2$、$CH_2CH(CH_3)_2$、CF_2H、CH_2CD_3、CD_2CH_3或CD_2CD_3。

[0143] 在一些实施例中，式V-i或V-ii化合物含有至少一个氘原子。在一些实施例中，式V-i或V-ii化合物含有至少两个氘原子。在一些实施例中，式V-i或V-ii化合物含有至少三个氘原子。

[0144] 在一些实施例中，本发明提供式V-i或V-ii化合物，其中R^2选自溴、$-C(O)OCD_2CD_3$、$-C(O)OCD_2CH_3$、$-C(O)OCH_2CD_3$和  。

[0145] 在某些实施例中，本发明提供式 I 化合物，其中 R^2 为 Hy，由此形成式 VI 化合物：

[0146]

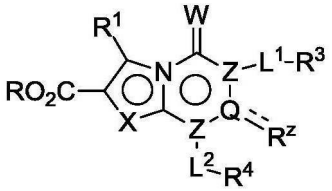


VI

[0147] 或其医药学上可接受的盐，其中单独和呈组合形式的 W、Q、X、Z、L^1、L^2、R^1、R^3、R^4 和 Hy 中的每一者在上文定义和描述在本文中的实施例中。

[0148] 在某些实施例中，本发明提供式 I 化合物，其中 R^2 为 -C(O)OR，由此形成式 VII 化合物：

[0149]

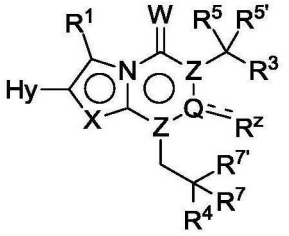


VII

[0150] 或其医药学上可接受的盐，其中单独和呈组合形式的 W、Q、X、Z、L^1、L^2、R、R^1、R^3 和 R^4 中的每一者在上文定义和描述在本文中的实施例中。

[0151] 在某些实施例中，本发明提供式 II 化合物，其中 R^2 为 Hy，由此形成式 VIII 化合物：

[0152]

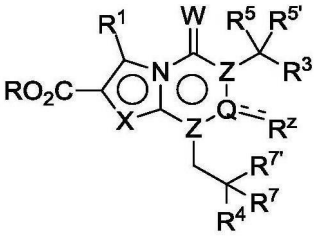


VIII

[0153] 或其医药学上可接受的盐，其中单独和呈组合形式的 W、Q、X、Z、R^1、R^3、R^4、R^5、$R^{5'}$、R^7、$R^{7'}$ 和 Hy 中的每一者在上文定义和描述在本文中的实施例中。

[0154] 在某些实施例中，本发明提供式 II 化合物，其中 R^2 为 -C(O)OR，由此形成式 IX 化合物：

[0155]

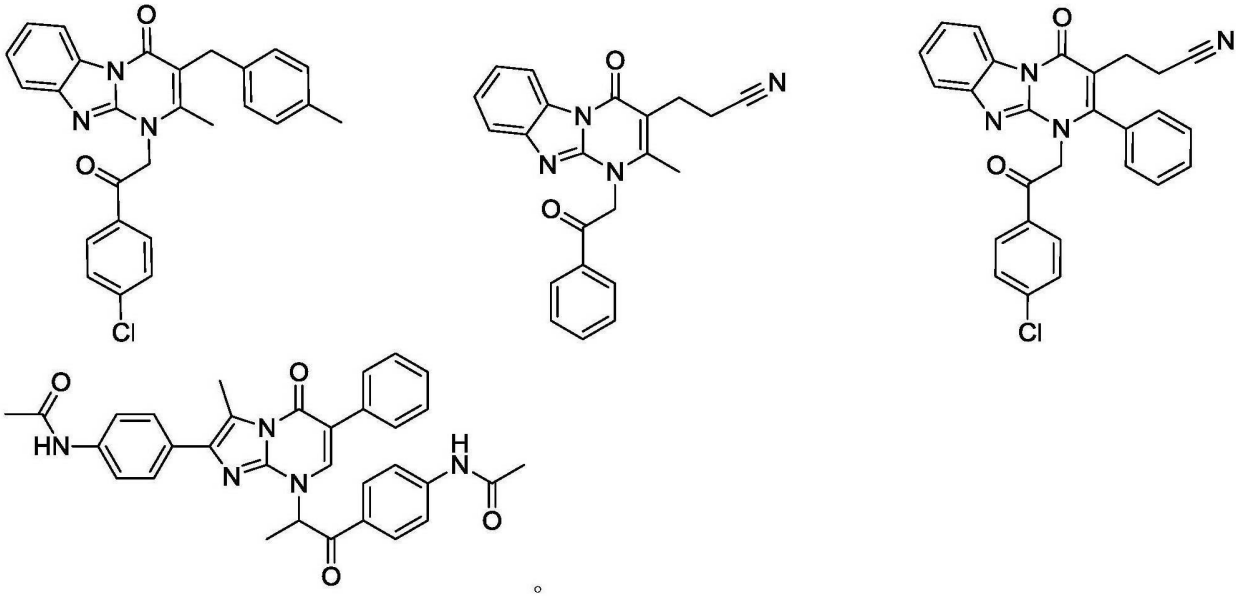


IX

[0156] 或其医药学上可接受的盐，其中单独和呈组合形式的 R、R^1、R^3、R^4、R^5、$R^{5'}$、R^7和 $R^{7'}$ 中的每一者在上文定义和描述在本文中的实施例中。

[0157] 在一些实施例中，本发明化合物不选自下式：

[0158]

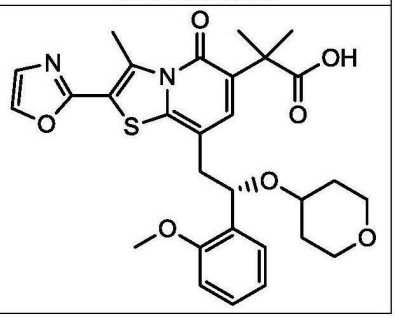


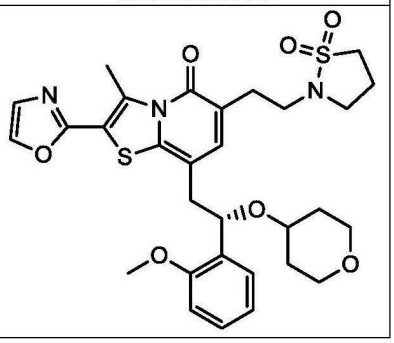
。

[0159] 示例性式 I 化合物列举在下表 1 中：

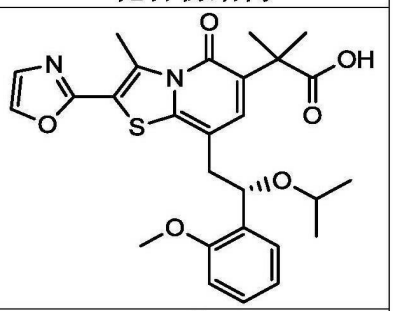
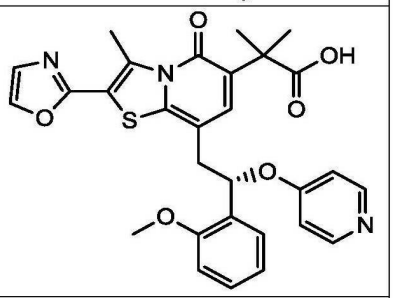
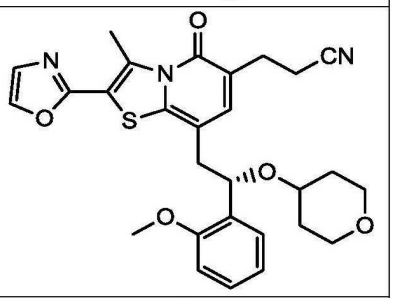
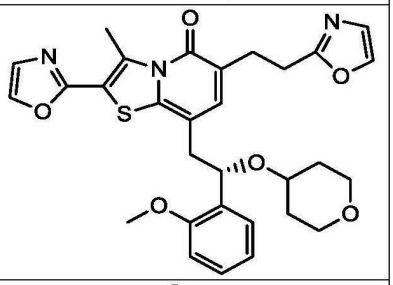
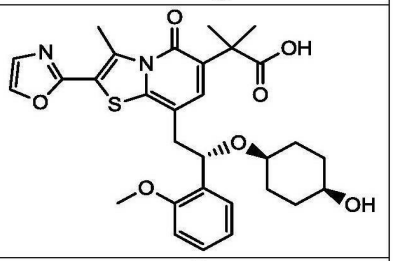
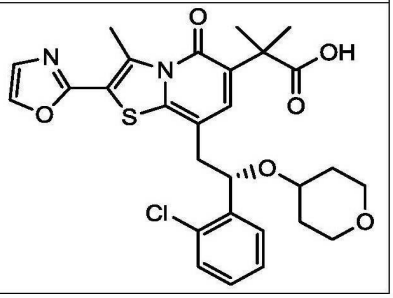
[0160] 表 1. 示例性式 I 化合物

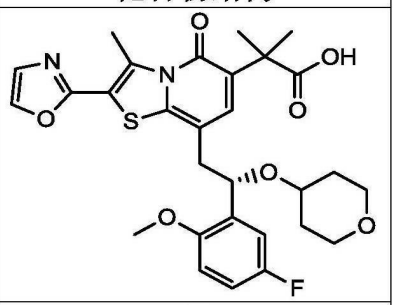
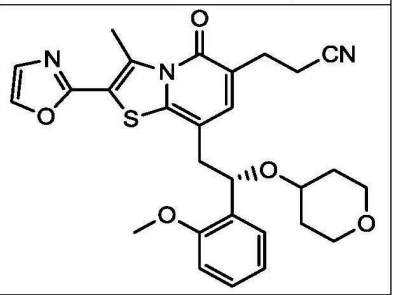
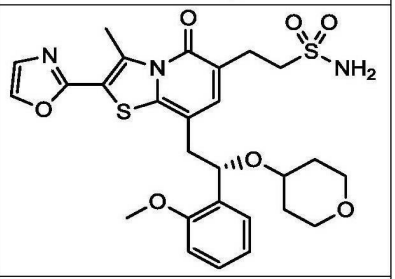
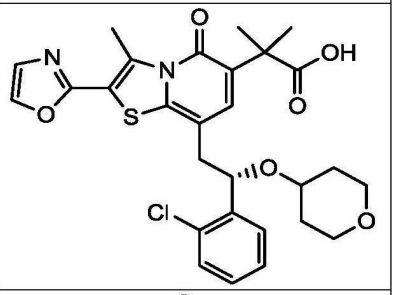
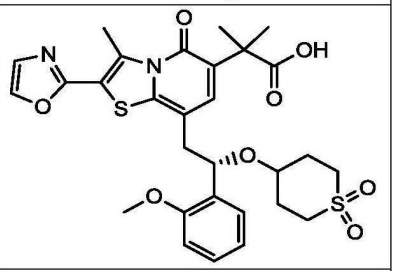
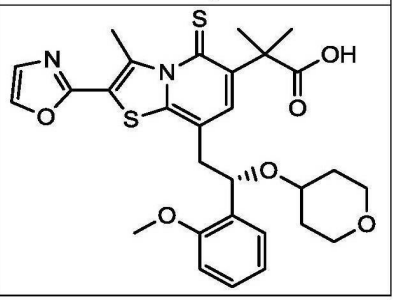
[0161]

化合物编号	化合物结构
I-1	

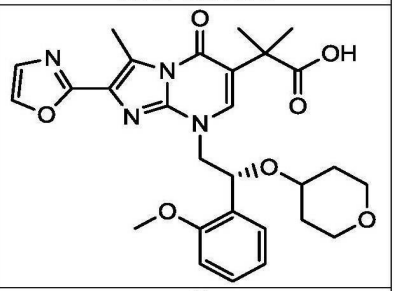
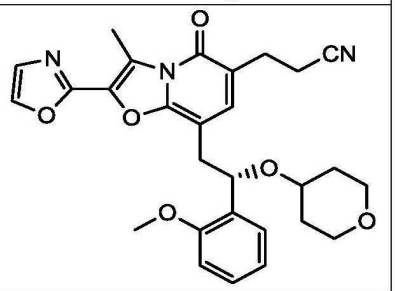
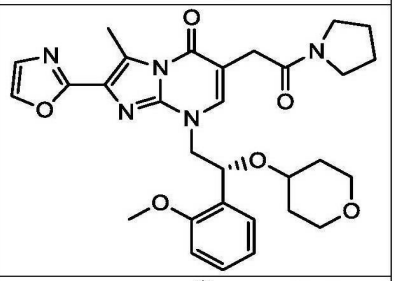
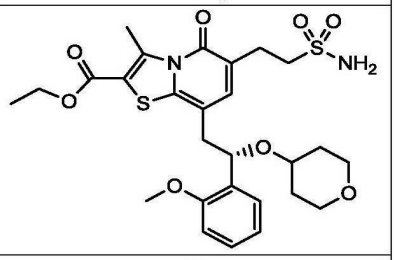
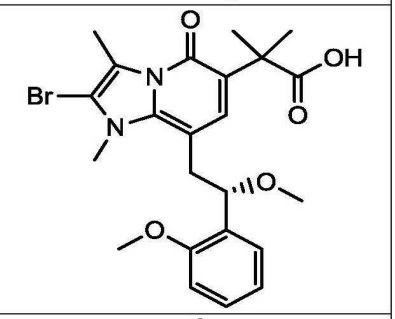
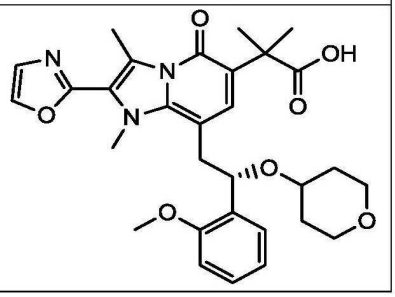
化合物编号	化合物结构
I-2	

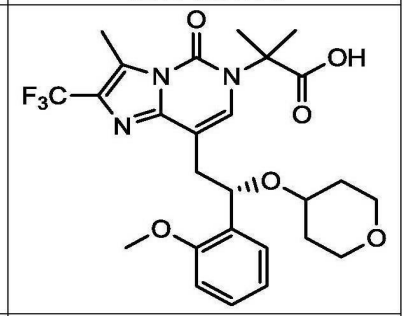
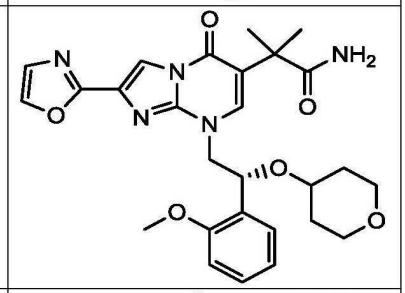
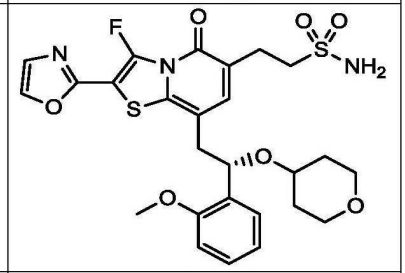
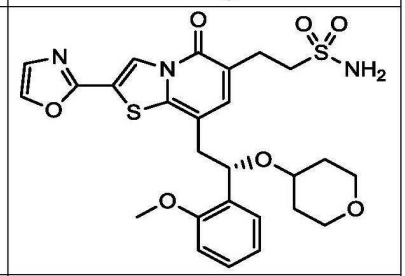
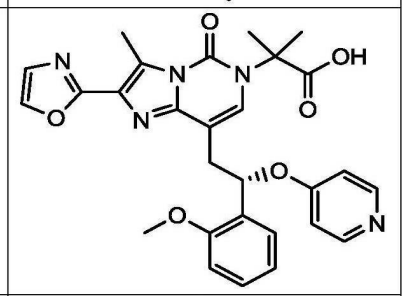
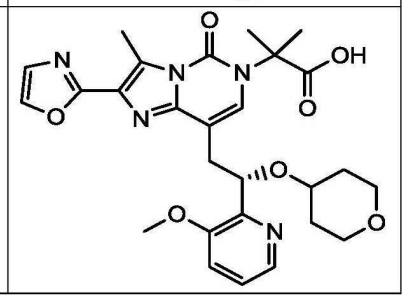
[0162]

化合物编号	化合物结构
I-3	
I-4	
I-5	
I-6	
I-7	
I-8	

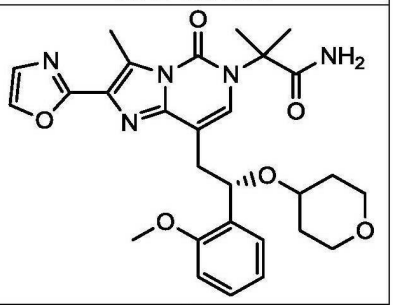
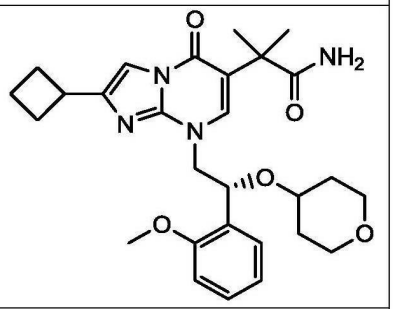
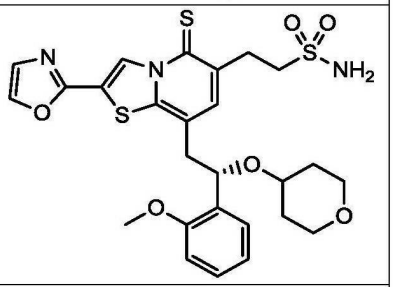
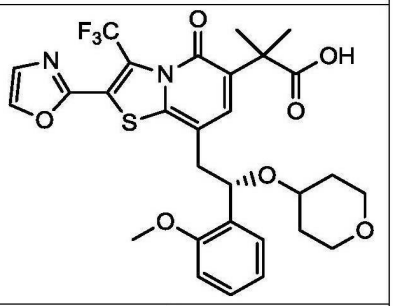
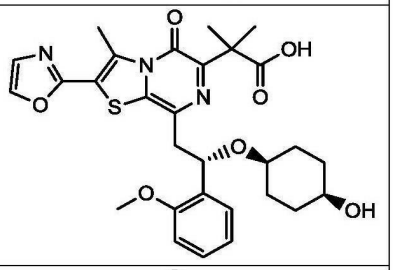
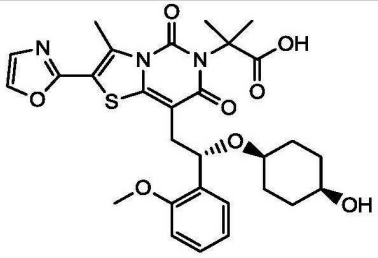
化合物编号	化合物结构
I-9	
I-10	
I-11	
I-12	
I-13	
I-14	

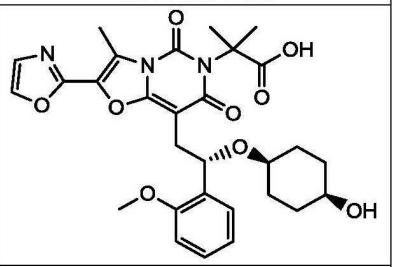
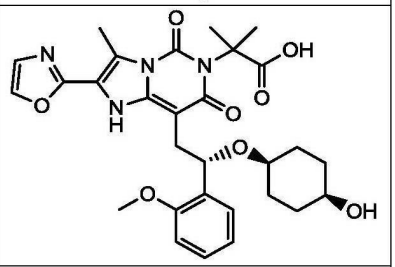
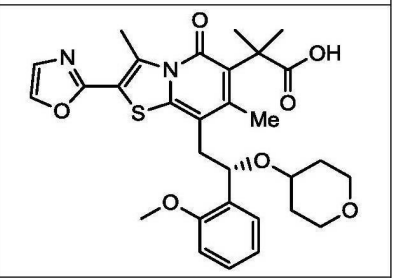
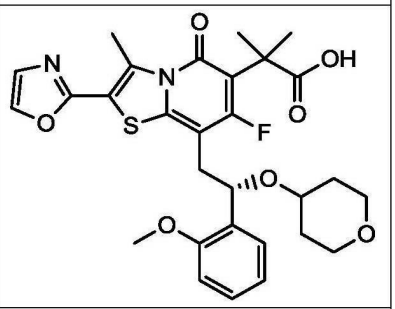
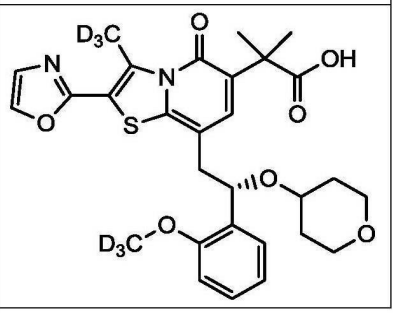
[0163]

化合物编号	化合物结构
I-15	
I-16	
I-17	
I-18	
I-19	
I-20	

化合物编号	化合物结构
I-21	
I-22	
I-23	
I-24	
I-25	
I-26	

[0164]

化合物编号	化合物结构
I-27	
I-28	
I-29	
I-30	
I-31	
I-32	

化合物编号	化合物结构
I-33	
I-34	
I-35	
I-36	
I-37	

[0165] 在某些实施例中，本发明提供选自上表 1 中所描绘的化合物的任何化合物或其医药学上可接受的盐。

[0166] 4. 用途、调配和投药和医药学上可接受的组合物

[0167] 根据另一实施例，本发明提供一种组合物，其包含本发明化合物或其医药学上可接受的盐、酯或酯的盐和医药学上可接受的载剂、佐剂或媒剂。本发明组合物中的化合物的量使得有效可测量地抑制生物样品或患者中的ACC。在某些实施例中，本发明组合物中的化合物的量使得有效可测量地抑制生物样品或患者中的ACC。在某些实施例中，调配本发明组合物用于向需要所述组合物的患者投药。在一些实施例中，本发明的组合物经调配用于向患者经口投药。

[0168] 如本文中所用，术语“患者”意指动物，优选地是哺乳动物，并且最优选地是人类。

[0169] 术语“医药学上可接受的载剂、佐剂或媒剂”是指不会破坏一起调配的化合物的药理学活性的无毒载剂、佐剂或媒剂。可以在本发明的组合物中使用的医药学上可接受的载剂、佐剂或媒剂包括（但不限于）离子交换剂、氧化铝、硬脂酸铝、卵磷脂、血清蛋白（如人血清白蛋白）、缓冲物质（如磷酸盐）、甘氨酸、山梨酸、山梨酸钾、饱和植物脂肪酸的偏甘油酯混合物、水、盐或电解质（如硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠、锌盐）、胶态二氧化硅、三硅酸镁、聚乙烯吡咯烷酮、基于纤维素的物质、聚乙二醇、羧甲基纤维素钠、聚丙烯酸酯、蜡、聚乙烯－聚氧丙烯－嵌段聚合物、聚乙二醇和羊毛脂。

[0170] “医药学上可接受的衍生物”意指在向接受者投与后能够直接或间接提供本发明化合物或其抑制活性的代谢物或残余物的本发明化合物的任何无毒盐、酯、酯的盐或其它衍生物。

[0171] 如本文中所用，术语“其抑制活性代谢物或残余物”意指其代谢物或残余物也是ACC抑制剂。

[0172] 本发明的组合物可以经口、肠胃外、通过吸入喷雾、局部、经直肠、经鼻、经颊、经阴道或经由植入式贮器投与。如本文所用，术语“肠胃外”包括皮下、静脉内、肌肉内、关节内、滑膜内、胸骨内、鞘内、肝内、病灶内和颅内注射或输注技术。优选地，组合物为经口、腹膜内或静脉内投与。本发明组合物的无菌可注射形式可以是水性或油性悬浮液。这些悬浮液可以根据所属领域中已知的技术使用适合的分散剂或湿润剂和悬浮剂来调配。无菌可注射制剂还可以是于无毒肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液或悬浮液，例如呈于1,3-丁二醇中的溶液形式。可采用的可接受的媒剂和溶剂是水、林格氏溶液(Ringer's solution)和等张氯化钠溶液。此外，通常使用无菌不挥发性油作为溶剂或悬浮介质。

[0173] 出于此目的，可以采用任何温和不挥发性油，包括合成的单酸甘油酯或二酸甘油酯。如油酸的脂肪酸和其甘油酯衍生物如同天然医药学上可接受的油（如橄榄油或蓖麻油，尤其呈其聚氧乙基化形式）般适用于制备可注射剂。这些油溶液或悬浮液还可以含有长链醇稀释剂或分散剂，如羧甲基纤维素或常用于调配医药学上可接受的剂型（包括乳液和悬浮液）的类似分散剂。出于调配的目的，还可以使用其它常用表面活性剂（如Tweens、Spans）和其它常用于制造医药学上可接受的固体、液体或其它剂型的乳化剂或生物可用性增强剂。

[0174] 本发明的医药学上可接受的组合物可以按任何经口可接受剂型经口投与，所述剂型包括（但不限于）胶囊、片剂、水性悬浮液或溶液。在用于经口使用的片剂的情况下，常用载剂包括乳糖和玉米淀粉。还通常添加如硬脂酸镁的润滑剂。对于以胶囊形式经口投药，适用的稀释剂包括乳糖和干燥的玉米淀粉。当为了经口用途需要水性悬浮液时，将活性成

分与乳化剂和悬浮剂组合。必要时，也可以添加某些甜味剂、调味剂或着色剂。

[0175] 或者，本发明的医药学上可接受的组合物可以按用于经直肠投药的栓剂形式投与。这些栓剂可以通过将药剂与适合的非刺激性赋形剂混合来制备，所述赋形剂在室温下为固体但在直肠温度下为液体且因此将在直肠中熔化以释放药物。此类物质包括可可脂、蜂蜡和聚乙二醇。

[0176] 本发明的医药学上可接受的组合物也可以局部投与，尤其当治疗目标包括通过局部施用容易达到的区域或器官（包括眼睛、皮肤或下部肠道的疾病）时。容易制备适合的局部调配物用于这些区域或器官中的每一者。

[0177] 下部肠道的局部施用可以直肠栓剂调配物（参见上文）形式或以适合的灌肠调配物形式实现。也可使用局部经皮贴片。

[0178] 对于局部施用来说，所提供的医药学上可接受的组合物可以按含有活性组分悬浮或溶解在一或多种载剂中的适合的软膏形式调配。用于本发明化合物的局部投药的载剂包括（但不限于）矿物油、液体矿脂、白矿脂、丙二醇、聚氧乙烯、聚氧丙烯化合物、乳化蜡以及水。或者，所提供的医药学上可接受的组合物可以含有活性组分悬浮或溶解在一或多种医药学上可接受的载剂中的适合的洗剂或乳膏形式调配。适合的载剂包括（但不限于）矿物油、脱水山梨糖醇单硬脂酸酯、聚山梨醇酯 60、十六酯蜡、十六醇十八醇、2- 辛基十二醇、苯甲醇和水。

[0179] 对于眼科使用，所提供的医药学上可接受的组合物可在有或无防腐剂（如氯苯甲烷铵）存在下，调配成在 pH 值经调整的等张无菌盐水中的微粉化悬浮液或优选调配成在 pH 值经调整的等张无菌盐水中的溶液。或者，对于眼科使用，医药学上可接受的组合物可调配于如矿脂的软膏中。

[0180] 本发明的医药学上可接受的组合物还可以通过鼻气雾剂或吸入投与。所述组合物根据药物调配领域中众所周知的技术制备，并且可以采用苯甲醇或其它适合的防腐剂、增强生物可用性的吸收促进剂、碳氟化合物和 / 或其它常规增溶剂或分散剂，以在盐水中的溶液形式制备。

[0181] 最优选地，调配本发明的医药学上可接受的组合物以用于经口投与。所述调配物可以在存在或不存在食品的情况下投与。在一些实施例中，本发明的医药学上可接受的组合物在不存在食品的情况下投与。在其它实施例中，本发明的医药学上可接受的组合物在存在食品的情况下投与。

[0182] 可以与载剂物质组合以产生呈单一剂型的组合物的本发明化合物的量将取决于所治疗的主体、特定投药模式而变化。优选地，应该调配所提供的组合物以使得可以向接受这些组合物的患者投与剂量介于 0.01-100 毫克 / 千克体重 / 天之间的抑制剂。

[0183] 还应了解，针对任何特定患者的特定剂量和治疗方案将取决于多种因素，包括所用特定化合物的活性、年龄、体重、整体健康状况、性别、饮食、投药时间、排泄率、药物组合以及治疗医师的判断和所治疗特定疾病的严重程度。组合物中本发明化合物的量也将取决于组合物中的特定化合物。

[0184] 化合物和医药学上可接受的组合物的使用

[0185] 乙酰基 -CoA 羧化酶 (ACC) 催化乙酰基 -CoA 的 ATP 依赖性羧化以形成丙二酰基 -CoA。此反应（其以两个半反应进行，即生物素羧化酶 (BC) 反应和羧基转移酶 (CT)

反应）为脂肪酸（FA）生物合成中的第一个关键步骤，且为所述路径的限速反应。丙二酰基-CoA(ACC催化的反应的产物）除了其作为FA生物合成中的底物的作用之外，还在经由异位抑制肉碱棕榈酰基转移酶I(CPT-I，催化线粒体FA氧化中的第一个关键步骤的酶）控制线粒体FA摄取中起到重要监管作用。因此，丙二酰基-CoA对于控制FA制造和回应于动物中的饮食变化和改变的营养需求（例如在运动期间）的利用来说为关键的代谢信号，且因此在控制肝脏和骨骼肌中碳水化合物与脂肪利用之间转变中起到关键作用［哈伍德，2005］。

[0186] 在哺乳动物中，ACC以两种组织特异性同工酶形式存在，即存在于脂肪生成组织（肝脏、脂肪）中的ACC1和存在于氧化组织（肝脏、心脏、骨骼肌）中的ACC2。ACC1和ACC2由独立基因编码，展示不同细胞分布，且除了在ACC2的N端处将ACC2引导到线粒体膜的延伸部分，共有75％总体氨基酸序列一致性。缺乏此靶向序列的ACC1定位于细胞质。在合成脂肪酸能力有限的心脏和骨骼肌中，利用ACC2形成的丙二酰基-CoA用于调节FA氧化。在肝脏中，经由ACC1作用形成于细胞质中的丙二酰基-CoA用于FA合成和延伸，引起甘油三酯形成和VLDL制造，而在线粒体表面处利用ACC2形成的丙二酰基-CoA起到调节FA氧化的作用［唐（Tong）和哈伍德，细胞生物化学杂志（J.Cellular Biochem.）99:1476,2006］。丙二酰基-CoA的此区室化由合成接近性［阿布－艾勒加（Abu-Elheiga）等人，美国国家科学院院刊（PNAS(USA)）102:12011,2005］和丙二酰基-CoA脱羧酶的快速作用［郑（Cheng）等人，药物化学杂志（J.Med.Chem.）49:1517,2006］的组合产生。

[0187] ACC1和ACC2的酶活性的同时抑制提供抑制脂肪生成组织（例如肝脏和脂肪）中的从头FA制造同时刺激氧化组织（例如肝脏和骨骼肌）中的FA氧化的能力，且因此提供以一致的方式有利地影响与肥胖症、糖尿病、胰岛素抵抗和代谢综合症相关的众多心血管风险因素的有吸引力的模态。

[0188] 若干条证据强有力地支持这一观念：直接抑制作为治疗肥胖症、糖尿病、胰岛素抵抗和代谢综合症的重要治疗目标的ACC活性。

[0189] 阿布－艾勒加等人［美国国家科学院院刊100:10207-10212,2003］证实了ACC2基因敲除小鼠展现出骨骼肌和心肌丙二酰基-CoA减少、肌肉FA氧化增加、肝脏脂肪减少、总体脂减少、骨骼肌解偶联蛋白-3(UCP3)升高（其指示能量消耗增加）、体重降低、血浆游离FA减少、血浆葡萄糖减少以及组织肝糖减少，且受到保护免于饮食诱发的糖尿病和肥胖症。

[0190] 萨维治（Savage）等人［临床研究杂志（J.Clin.Invest.）116:817,2006］使用ACC1和ACC2反义寡核苷酸展示了经分离大鼠肝细胞和喂饲高脂肪饮食的大鼠中的FA氧化的刺激、和肝脏甘油三酯降低、胰岛素敏感性改善、肝脏葡萄糖制造减少、以及喂饲高脂肪的大鼠中的UCP1mRNA增加。与当ACC1或ACC2表达单独受抑制时相比，当ACC1和ACC2两者表达受抑制时，这些作用较大。

[0191] 哈伍德等人［生物化学杂志（J.Biol.Chem.）278:37099,2003］展示了同等抑制从大鼠、小鼠、猴和人类中分离的ACC1和ACC2(IC_{50}＝约60nM)而不抑制丙酮酸羧化酶或丙酰-CoA羧化酶的同工酶非选择性ACC抑制剂CP-640186在不影响胆固醇合成的情况下减少Hep-G2细胞中的FA合成、甘油三酯合成和分泌，且在不影响apoA1分泌的情况下减少apoB分泌。CP-640186还刺激C2C12细胞和大鼠肌肉切片中的FA氧化且增加Hep-G2细胞

中的 CPT-I 活性。在实验动物中，CP-640186 急剧减少在喂饲和禁食两种状态下的脂肪生成组织和氧化组织两者中的丙二酰基 -CoA 浓度，减少肝脏和脂肪组织 FA 合成，且增加全身 FA 氧化。在用 CP-640186 处理三周的喂饲蔗糖的大鼠中，CP-640186 时间依赖性地且剂量依赖性地减少肝脏、肌肉和脂肪甘油三酯，降低体重（归因于选择性脂肪减少且不减少瘦体质），减少瘦素水平，减轻由高蔗糖饮食产生的高胰岛素血症而不改变血浆葡萄糖水平，且改善胰岛素敏感性。

[0192] 萨哈 (Saha) 等人 [糖尿病 (Diabetes)55:A288,2006] 展示了 CP-640186 在投与化合物的 30 分钟内对胰岛素抵抗大鼠肌肉组织的胰岛素敏感性的刺激，且富勒 (Furler) 等人 [糖尿病 55:A333,2006] 的研究使用双重示踪剂分析展示出用 CP-640186 急性 (46 分钟）处理大鼠会刺激 FA 清除率且不减小葡萄糖清除率。

[0193] ACC 在脂肪酸合成中是限速酶，且其产物丙二酰基 CoA 充当脂肪酸氧化的重要调节剂。因此，ACC 抑制剂既减少从头脂质合成又促进现有脂肪的氧化。对脂质代谢的这一双重作用提高 ACC 抑制剂与其它机制相比将实质上更有效地减少过量脂肪的可能性。此外，ACC 抑制剂将影响胰岛素敏感性、血浆和组织甘油三酯以及空腹血浆葡萄糖，因此全身和组织特异性脂肪质量减少且不需要多重用药。

[0194] ACC 抑制剂仅需要在外周隔室中接近肝脏和肌肉。避开 CNS 将解决与靶向 CNS 受体的晚期肥胖症程序相关的许多副作用。还预期 ACC 抑制剂会具有优于现有代谢疾病药剂的安全性特征。举例来说，ACC 抑制剂将不大可能促成如在胰岛素模拟物、胰岛素促分泌物和胰岛素降解抑制剂下通常可见的危及生命的低血糖。此外，由于 ACC 抑制剂将减少全身脂肪质量，故其将优于会增加全身脂肪质量作为其作用机制一部分的格列酮 (glitazone)。

[0195] 引起显著体重减轻且改进其它代谢终点的外周起作用的药剂正好符合美国 FDA 批准新肥胖症药剂的要求。然而，如果对肥胖症的批准在 5-7 年内持续具挑战性，那么 ACC 抑制剂可被批准用于家族性联合高脂质血症和非酒精性脂肪性肝炎 (NASH)。目前尚无市售的 ACC 抑制剂，因此同工酶非选择性 ACC 抑制剂将代表用于治疗肥胖症和代谢综合症的首创新药疗法。

[0196] 可在体外或体内分析在本发明中用作 ACC 的抑制剂或者肥胖症或代谢综合症治疗的化合物的活性。可使用肥胖症或代谢综合症的动物模型（例如啮齿动物或灵长类动物模型）进行本发明化合物功效的体内评估。可使用例如从表达 ACC 的组织中分离的细胞系执行基于细胞的分析。另外，可执行基于生物化学或机制的分析，例如使用经纯化蛋白的转录分析、RNA 印迹 (Northern blot)、RT-PCR 等。体外分析包括测定经本发明化合物处理的细胞的细胞形态、蛋白质表达、和 / 或细胞毒性、酶抑制活性、和 / 或后续功能后果的分析。替代性体外分析定量抑制剂结合于细胞内的蛋白或核酸分子的能力。抑制剂结合可通过在结合之前放射性标记所述抑制剂、分离抑制剂 / 目标分子复合物以及测定所结合的放射性标记的量来测量。或者，抑制剂结合可以通过执行竞争实验来测定，其中将新抑制剂与结合到已知放射性配体的经纯化蛋白或核酸一起孵育。用于分析在本发明中用作 ACC 抑制剂的化合物的详细条件阐述于以下实例中。上述分析为示例性的且并不打算限制本发明的范围。熟练的从业者可了解，可对常规分析进行修改以开发会获得相同结果的等效分析。

[0197] 如本文中所用，术语“治疗 (treatment)”、“治疗 (treat)”和“治疗 (treating)”是指逆转、减轻如本文中所述的疾病或病症或其一或多种症状，延迟其发作，或抑制其进展。

在一些实施例中，治疗可在已出现一或多种症状后投与。在其它实施例中，治疗可在不存在症状下投与。举例来说，可以在症状发作之前向易感个体（例如根据症状病史和/或根据遗传学或其它易感性因素）投与治疗。还可以在症状已消退之后继续进行治疗，例如以预防或延迟其复发。

[0198] 根据本发明方法的化合物和组合物可使用有效治疗代谢病症或病况、癌症、细菌感染、真菌感染、寄生虫感染（例如疟疾）、自身免疫病症、神经退化性或神经病症、精神分裂症、骨相关病症、肝病或心肌病症或者减轻其严重度的任何量和任何投药途径投与。

[0199] 在一些实施例中，根据本发明方法的化合物和组合物可使用有效治疗与ACC相关的疾病或减轻其严重度的任何量和任何投药途径投与（唐等人“乙酰基-辅酶A羧化酶：关键的新陈代谢酶和对于药物发现来说有吸引力的目标(Acetyl-coenzyme A carboxylase:crucial metabolic enzyme and attractive target for drug discovery)”细胞和分子生命科学(Cell and Molecular Life Sciences)(2005)62,1784-1803)。

[0200] 在一些实施例中，根据本发明方法的化合物和组合物可使用有效治疗代谢病症、疾病或病况或减轻其严重度的任何量和任何投药途径投与。在一些实施例中，代谢病症为肥胖症；代谢综合症；糖尿病或糖尿病相关的病症，包括1型糖尿病（胰岛素依赖性糖尿病，IDDM）和2型糖尿病（非胰岛素依赖性糖尿病，NIDDM）；葡萄糖耐受性异常；胰岛素抵抗；高血糖症；糖尿病并发症，包括（但不限于）动脉粥样硬化、冠心病、中风、外周血管疾病、肾病变、高血压、神经病变和肾病变；肥胖症并存病，包括（但不限于）代谢综合症、血脂异常、III型血脂异常、高血压、胰岛素抵抗、糖尿病（包括1型和2型糖尿病）、冠状动脉疾病和心脏衰竭。在一些实施例中，代谢病症、疾病或病况为非酒精性脂肪肝病或肝脏胰岛素抵抗。

[0201] 在一些实施例中，本发明提供一种治疗本文中描述的代谢病症、疾病或病况的方法，其包含投与本发明化合物以及一或多种医药剂。可以与本发明化合物组合使用的适合的医药剂包括抗肥胖症药剂（包括食欲抑制剂）、抗糖尿病药剂、抗高血糖药剂、降脂剂和抗高血压药剂。

[0202] 可与本发明化合物结合使用的适合的降脂剂包括（但不限于）胆酸螯合剂、HMG-CoA还原酶抑制剂、HMG-CoA合成酶抑制剂、胆固醇吸收抑制剂、酰基辅酶A-胆固醇酰基转移酶(ACAT)抑制剂、CETP抑制剂、角鲨烯合成酶抑制剂、PPAR-α激动剂、FXR受体调节剂、LXR受体调节剂、脂蛋白合成抑制剂、肾素-血管紧张素系统抑制剂、PPAR-δ部分激动剂、胆酸再吸收抑制剂、PPAR-γ激动剂、甘油三酯合成抑制剂、微粒体甘油三酯转运抑制剂、转录调节剂、角鲨烯环氧酶抑制剂、低密度脂蛋白受体诱导剂、血小板凝集抑制剂、5-LO或FLAP抑制剂、烟碱酸和烟碱酸结合的铬。

[0203] 可与本发明化合物结合使用的适合的抗高血压药剂包括（但不限于）利尿剂、β-肾上腺素阻断剂、钙离子通道阻断剂、血管收缩素转化酶(ACE)抑制剂、中性内肽酶抑制剂、内皮素拮抗剂、血管扩张剂、血管紧张素II受体拮抗剂、α/β肾上腺素阻断剂、α1阻断剂、α2激动剂、醛固酮抑制剂、盐皮质激素受体抑制剂、肾素抑制剂和血管生成素2结合剂。

[0204] 可与本发明化合物结合使用的适合的抗糖尿病药剂包括（但不限于）其它乙酰基-CoA羧化酶(ACC)抑制剂、DGAT-1抑制剂、AZD7687、LCQ908、DGAT-2抑制剂、

单酰基甘油O-酰基转移酶抑制剂、PDE-10抑制剂、AMPK活化剂、磺酰脲(例如乙酰苯磺酰环己脲(acetohexamide)、氯磺丙脲(chlorpropamide)、氢磺丙脲(diabinese)、格列本脲(glibenclamide)、格列吡嗪(glipizide)、格列苯脲(glyburide)、格列美脲(blimipiride)、格列齐特(gliclazide)、格列太特(glipentide)、格列喹酮(gliquidone)、格列索脲(glisolamide)、甲磺吖庚脲(tolazamide)、甲苯磺丁脲(tolbutamide))、美格替耐(meglitinides)、α-淀粉酶抑制剂(例如淀粉酶抑肽(tendamistat)、萃他丁(treastatin)、AL-3688)、α-葡糖苷水解酶抑制剂(例如阿卡波糖(acarbose))、α-葡糖苷酶抑制剂(例如脂解素(adiposine)、卡格列波糖(camiglibose)、乙格列酯(emiglitate)、米格列醇(miglitol)、伏格列波糖(voglibose)、普拉米星-Q(pradimicin-Q)、萨保菌素(sarbostatin))、PPAR-γ激动剂(例如巴拉列酮(balaglitazone)、环格列酮(ciglitazone)、达格列酮(darglitazone)、恩格列酮(englitazone)、伊萨列酮(isaglitazone)、吡格列酮(pioglitazone)、罗格列酮(rosiglitazone)、曲格列酮(troglitazone))、PPAR-α/γ激动剂(例如CLX-0940、GW-1536、GW-1929、GW-2433、KRP-297、L-796449、LR-90、MK-0767、SB-219994)、双胍(例如二甲双胍(metformin)、丁双胍(buformin))、GLP-1调节剂(肠促胰岛素类似物(exendin)-3、肠促胰岛素类似物-4)、利拉鲁肽(liraglutide)、阿必鲁肽(albiglutide)、艾塞那肽(exenatide,Byetta)、他司鲁肽(taspoglutide)、利司那肽(lixisenatide)、度拉糖肽(dulaglutide)、司美鲁肽(semaglutide)、N,N-9924、TTP-054、PTP-1B抑制剂(特罗杜明(trodusquemine)、西替欧醛萃取物(hyrtiosal extract))、SIRT-1抑制剂(例如白藜芦醇(resveratrol)、GSK2245840、GSK184072)、DPP-IV抑制剂(例如西他列汀(sitagliptin)、维格列汀(vildagliptin)、阿格列汀(alogliptin)、多格列汀(dutogliptin)、利拉利汀(linagliptin)、沙格列汀(saxagliptin))、胰岛素促分泌物、脂肪酸氧化抑制剂、A2拮抗剂、JNK抑制剂、葡糖激酶活化剂(例如TTP-399、TTP-355、TTP-547、AZD1656、ARRY403、MK-0599、TAK-329、AZD5658、GKM-001)、胰岛素、胰岛素模拟物、肝糖磷酸化酶抑制剂(例如GSK1362885)、VPAC2受体激动剂、SGLT2抑制剂(达格列净(dapagliflozin)、卡格列净(canagliflozin)、BI-10733、托格列净(tofogliflozin)、ASP-1941、THR1474、TS-071、ISIS388626、LX4211)、升糖素受体调节剂、GPR119调节剂(例如MBX-2982、GSK1292263、APD597、PSN821)、FGF21衍生物、TGR5(GPBAR1)受体激动剂(例如INT777)、GPR40激动剂(例如TAK-875)、GPR120激动剂、烟酸受体(HM74A)活化剂、SGLT1抑制剂(例如GSK1614235)、肉碱棕榈酰基转移酶抑制剂、果糖1,6-二磷酸酶抑制剂、醛糖还原酶抑制剂、盐皮质激素受体抑制剂、TORC2抑制剂、CCR2抑制剂、CCR5抑制剂、PKC(例如PKC-α、PKC-β、PKC-γ)抑制剂、脂肪酸合成酶抑制剂、丝氨酸棕榈酰基转移酶抑制剂、GPR81调节剂、GPR39调节剂、GPR43调节剂、GPR41调节剂、GPR105调节剂、Kv1.3抑制剂、视黄醇结合蛋白4抑制剂、糖皮质激素受体调节剂、生长抑素受体(例如SSTR1、SSTR2、SSTR3、SSTR5)抑制剂、PDHK2抑制剂、PDHK4抑制剂、MAP4K4抑制剂、IL1-β调节剂和RXR-α调节剂。

[0205] 适合的抗肥胖症药剂包括(但不限于)11-β-羟基类固醇去氢酶1抑制剂、硬脂酰基-CoA去饱和酶(SCD-1)抑制剂、MCR-4激动剂、CCK-A激动剂、单胺再摄取抑制剂(例如西布曲明(sibutramine))、拟交感神经药药剂、β-3-肾上腺素受体激动剂、多巴

胺受体激动剂（例如溴麦角环肽(bromocriptine)）、黑色素细胞刺激激素和其类似物、5-HT_{2C}激动剂（例如氯卡色林(lorcaserin)/百维克(Belviq)）、黑色素浓集激素拮抗剂、瘦素、瘦素类似物、瘦素激动剂、甘丙胺素拮抗剂、脂肪酶抑制剂（例如四氢利普司他汀(tetrahydrolipstatin)/奥利司他）、厌食剂（例如铃蟾素(bombesin)激动剂）、NPY拮抗剂（例如韦利贝特(velneperit)、PYY_{3-36}（和其类似物）、BRS3调节剂、类鸦片受体混合拮抗剂、拟甲状腺素药剂、脱氢表雄酮、糖皮质激素激动剂或拮抗剂、食欲素拮抗剂、GLP-1激动剂、睫状神经营养因子（例如阿索开(Axokine)）、人类鼠灰色相关蛋白质(AGRP)抑制剂、H3拮抗剂或反向激动剂、神经介肽U激动剂、MTP/ApoB抑制剂（例如消化道选择性MTP抑制剂，如迪罗哌德(dirlotapide)、JTT130、优斯他派(Usistapide)、SLX4090)、MetAp2抑制剂（例如ZGN-433）；在升糖素、GIP和GLP1受体中的两者或两者以上处具有混合调节活性的药剂（例如MAR-701、ZP2929）；去甲肾上腺素再摄取抑制剂、类鸦片拮抗剂（例如纳曲酮(naltrexone)）、CB1受体拮抗剂或反向激动剂、胃内激素激动剂或拮抗剂、胃泌酸调节素和其类似物、单胺摄取抑制剂（例如泰索酚辛(tesofensine)）、和组合药剂（例如丁胺苯丙酮(buproprion)加唑尼沙胺(zonisamide)（恩派提克(Empatic)）、普兰林肽(pramlintide)加美曲普汀(metreleptin)、丁胺苯丙酮(buproprion)加纳曲酮（肯特拉伍(Contrave)）、苯丁胺加托吡酯(topiramate)（奎斯米亚(Qsymia)）。

[0206] 在一些实施例中，与本发明化合物组合使用的抗肥胖症药剂选自消化道选择性MTP抑制剂（例如迪罗哌德、米瑞他匹(mitratapide)、英普他派(implitapide)、R56918)、CCK-A激动剂、5-HT_{2C}激动剂（例如氯卡色林/百维克）、MCR4激动剂、脂肪酶抑制剂（例如赛利司他(Cetilistat)）、PYY_{3-36}（包括其类似物和聚乙二醇化类似物）、类鸦片拮抗剂（例如纳曲酮）、油酰基雌酮、奥尼匹肽(obinepitide)、普兰林肽、泰索酚辛、瘦素、溴麦角环肽、奥利司他、AOD-9604和西布曲明。

[0207] 在一些实施例中，根据本发明方法的化合物和组合物可使用有效治疗LKB1或Kras相关疾病或减轻其严重度的任何量和任何投药途径投与。在一些实施例中，LKB1或Kras相关疾病是选自肝细胞癌、LKB1突变体癌症、LKB1杂合性缺失(LOH)驱动的癌症、Kras突变体癌症、普-杰二氏综合症(Peutz-Jeghers syndrome，PJS)、考登氏病(Cowden's disease，CD)和结节性脑硬化(TS)（马科夫斯基(Makowski)等人“LKB1在肺癌发展中的作用(Role of LKB1in Lung Cancer Development)”英国癌症杂志(British Journal of Cancer)(2008)99,683-688)。在一些实施例中，LKB1或Kras相关疾病为Kras阳性/LKB1缺陷型肺肿瘤。

[0208] 在一些实施例中，根据本发明方法的化合物和组合物可使用有效治疗癌症或减轻其严重度或抑制癌细胞生长或诱导其凋亡的任何量和任何投药途径投与（王(Wang)等人“乙酰基-CoA羧化酶-α抑制剂TOFA诱导人类癌细胞凋亡(Acetyl-CoA Carboxylase-alpha Inhibitor TOFA Induces Human Cancer Cell Apoptosis)”生物化学与生物物理学研究通讯(Biochem Biophys Res Commun).(2009)385(3),302-306；沙热(Chajes)等人“乙酰基-CoA羧化酶α为乳癌细胞存活所必需的(Acetyl-CoA Carboxylase alpha Is Essential to Breast Cancer Cell Survival)”癌症研究(Cancer Res.)(2006)66,5287-5294；贝克尔斯(Beckers)等人“乙酰基-CoA羧化酶的化学抑制诱导癌细胞中的生长停滞和细胞毒性选择性(Chemical Inhibition of

Acetyl-CoA Carboxylase Induces Growth Arrest and Cytotoxicity Selectivity in Cancer Cells)”癌症研究(2007)8180-8187;布鲁塞尔曼斯(Brusselmans)等人“乙酰基-CoA-羧化酶-α基因的RNA干扰介导的沉默诱导前列腺癌细胞的生长抑制和细胞凋亡(RNA Interference-Mediated Silencing of the Acetyl-CoA-Carboxylase-alpha Gene Induces Growth Inhibition and Apoptosis of Prostate Cancer Cells)”癌症研究(2005)65,6719-6725;布鲁奈特(Brunet)等人“BRCA1和乙酰基-CoA羧化酶:乳癌的代谢综合症(BRCA1and Acetyl-CoA Carboxylase:The Metabolic Syndrom of Breast Cancer)”分子癌发生(Molecular Carcinogenesis)(2008)47,157-163;凯恩斯(Cairns)等人“癌细胞代谢的调节(Regulation of Cancer Cell Metabolism)”(2011)11,85-95;基亚拉东纳(Chiaradonna)等人“从癌症代谢到新生物标记物和药物目标(From Cancer Metabolism to New Biomarkers and Drug Targets)”生物技术进展(Biotechnology Advances)(2012)30,30-51)。

[0209] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗黑素瘤或减轻其严重度的任何量和任何投药途径投与。在一些实施例中,黑素瘤为携有活化MAPK路径的黑素瘤(派提(Petti)等人“AMPK活化剂抑制携有活化MAPK路径的人类黑素瘤的增殖(AMPK activators inhibit the proliferation of human melanomas bearing the activated MAPK pathway)”黑素瘤研究(Melanoma Research)(2012)22,341-350)。

[0210] 本发明化合物特别适用于三阴性乳癌,因为肿瘤抑制因子蛋白BRCA1结合ACC的非活性形式且使其稳定,由此上调从头脂质合成,引起癌细胞增殖(布鲁奈特等人“BRCA1和乙酰基-CoA羧化酶:乳癌代谢综合症代谢综合症(BRCA1and acetyl-CoA carboxylase:the metabolic syndrome of breast cancer)”分子癌发生(2008)47(2),157-163)。

[0211] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗脂肪肉瘤或减轻其严重度的任何量和任何投药途径投与。脂肪肉瘤已展示出依赖于从头长链脂肪酸合成以便生长,且沙罗酚A(soraphen A)对ACC的抑制会抑制脂肪生成以及肿瘤细胞生长(奥尔森(Olsen)等人“脂肪酸合成为人类脂肪肉瘤中的治疗目标(Fatty acid synthesis is a therapeutic target in human liposarcoma)”国际肿瘤学杂志(International J.of Oncology)(2010)36,1309-1314)。

[0212] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗肝病或减轻其严重度的任何量和任何投药途径投与。在一些实施例中,肝病是选自丙型肝炎、肝细胞癌、家族性联合高脂质血症和非酒精性脂肪性肝炎(NASH)、肝癌、胆管癌、血管肉瘤、血管内皮瘤和进行性家族性肝内胆汁郁积。

[0213] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗细菌感染或减轻其严重度或抑制细菌生长的任何量和任何投药途径投与。

[0214] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗真菌感染或减轻其严重度或抑制真菌细胞生长的任何量和任何投药途径投与(沈(Shen)等人“巨环聚酮天然产物沙罗酚A强力抑制真核乙酰基-辅酶A羧化酶的机制(A Mechanism for the Potent Inhibition of Eukaryotic Acetyl-Coenzyme A Carboxylase by Soraphen A,a Macrocyclic Polyketide Natural Product)”分子细胞(Molecular Cell)

(2004)16,881-891)。在一些实施例中,真菌感染出现在人类中。在一些实施例中,真菌感染为假丝酵母(Candida)感染。

[0215] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗细菌感染或减轻其严重度的任何量和任何投药途径投与(唐,L.等人细胞生物化学杂志(2006)99,1476-1488)。

[0216] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗病毒感染或减轻其严重度的任何量和任何投药途径投与(芒格(Munger)等人自然·生物技术(Nat. Biotechnol.)(2008)26,1179-1186)。在一些实施例中,病毒感染为丙型肝炎。

[0217] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗神经疾病或减轻其严重度的任何量和任何投药途径投与(亨德森(Henderson)等人神经病疗法(Neurotherapeutics)(2008)5,470-480;科斯坦蒂尼(Costantini)等人神经科学(Neurosci.)(2008)9增刊2:S16;巴拉南诺(Baranano)等人当前神经病学治疗观点(Curr.Treat.Opin.Neurol.)(2008)10,410-419)。

[0218] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗寄生虫感染或减轻其严重度或抑制寄生虫生长的任何量和任何投药途径投与(例如疟疾和弓虫:格尔尼茨基(Gornicki)等人"顶体脂肪酸生物合成作为顶覆门寄生虫中医学干预的目标(Apicoplast fatty acid biosynthesis as a target for medical intervention in apicomplexan parasites)"国际寄生虫学杂志(International Journal of Parasitology)(2003)33,885-896;楚特(Zuther)等人"靶向乙酰基-CoA羧化酶的芳氧基苯氧基丙酸酯除草剂抑制刚地弓形虫的生长(Growth of Toxoplasma gondii is inhibited by aryloxyphenoxypropionate herbicides targeting acetyl-CoA carboxylase)"美国国家科学院院刊(1999)96(23)13387-13392)。

[0219] 在一些实施例中,根据本发明方法的化合物和组合物可使用有效治疗心肌病症或减轻其严重度的任何量和任何投药途径投与。在一些实施例中,心肌病症为心脏肥大。在一些实施例中,心肌病症通过由经由ACC抑制增加脂肪酸氧化引起的心脏保护机制治疗或减轻其严重度(珂勒维茨(Kolwicz)等人"乙酰基CoA羧化酶2(ACC2)的心肌特异性缺失预防压力过载肥大期间的代谢重构(Cardiac-specific deletion of acetyl CoA carboxylase 2(ACC2)prevents metabolic remodeling during pressure-overload hypertrophy)"循环研究(Circ.Res.)(2012);DOI:10.1161/CIRCRESAHA.112.268128)。

[0220] 在某些实施例中,根据本发明方法的化合物和组合物可以用作除草剂。在一些实施例中,本发明提供一种抑制植物生长或存活力的方法,其包含用本发明化合物处理植物。在本发明的一些实施例中,本发明化合物可以用于通过抑制ACC来抑制植物的生长或存活力。在一些实施例中,本发明的方法包含使用本发明化合物以在植物中抑制脂肪酸制造或增加脂肪酸氧化。

[0221] 所需的精确量将在个体之间变化,取决于个体的物种、年龄以及整体状况、感染的严重程度、特定药剂、其投药模式等。优选地按单位剂型调配本发明化合物以实现易于投药和剂量均一性。如本文中所用的表述"单位剂型"是指适于待治疗患者的药剂的物理不连续单位。然而,应了解,本发明的化合物和组合物的每日总用量将由主治医师在合理医学判断范围内来决定。针对任何特定患者或有机体的特定有效剂量水平将取决于多种因素,包括

所治疗的病症和病症的严重程度；所用特定化合物的活性；所用特定组合物；患者的年龄、体重、一般健康状况、性别和饮食；所用特定化合物的投药时间、投药途径和排泄率；治疗持续时间；与所用特定化合物组合或同时使用的药物；和医学领域中熟知的类似因素。如本文所用，术语“患者”意指动物，优选地是哺乳动物，并且最优选地是人类。

[0222] 本发明的医药学上可接受的组合物可以取决于所治疗感染的严重程度而经口、经直肠、肠胃外、脑池内、阴道内、腹膜内、局部（如通过散剂、软膏或滴剂）、经颊、作为经口或鼻喷雾等向人类和其它动物投与。在某些实施例中，本发明化合物可以每日每千克个体体重约 0.01 毫克到约 50 毫克且优选地每千克个体体重约 1 毫克到约 25 毫克，每日一或多次经口或肠胃外投与，以获得所要治疗效果。

[0223] 用于经口投药的液体剂型包括（但不限于）医药学上可接受的乳液、微乳液、溶液、悬浮液、糖浆和酏剂。除活性化合物外，液体剂型还可含有所属领域中常用的惰性稀释剂，例如水或其它溶剂、增溶剂和乳化剂，诸如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苯甲醇、苯甲酸苯甲酯、丙二醇、1,3- 丁二醇、二甲基甲酰胺、油类（尤其是棉籽油、落花生油、玉米油、胚芽油、橄榄油、蓖麻油和芝麻油）、甘油、四氢糠醇、聚乙二醇和脱水山梨糖醇脂肪酸酯和其混合物。除惰性稀释剂外，口服组合物还可包括佐剂，如湿润剂、乳化剂和悬浮剂、甜味剂、调味剂和芳香剂。

[0224] 可根据已知技术使用适合的分散剂或湿润剂和悬浮剂来调配可注射制剂，例如无菌可注射水性或油性悬浮液。无菌可注射制剂也可以是在无毒肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液、悬浮液或乳液，例如呈在 1,3- 丁二醇中的溶液形式。可使用的可接受媒剂和溶剂包括水、林格氏溶液、U.S.P. 和等张氯化钠溶液。另外，常规地采用无菌不挥发性油作为溶剂或悬浮介质。出于这个目的，可以使用任何温和不挥发性油，包括合成单酸甘油酯或二酸甘油酯。此外，在可注射剂制备中使用脂肪酸，如油酸。

[0225] 可注射调配物可例如通过经由截留细菌的过滤器过滤和 / 或通过并入杀菌剂来杀菌，所述调配物呈在使用之前可溶解或分散于无菌水或其它无菌可注射介质中的无菌固体组合物形式。

[0226] 为了延长本发明化合物的作用，通常需要减慢从皮下或肌肉内注射吸收化合物。这可以使用具有弱水溶性的结晶或非晶形物质的液体悬浮液来实现。化合物的吸收速率则取决于其溶解速率，溶解速率又可以取决于晶体尺寸和结晶形式。或者，通过将化合物溶解或悬浮于油媒剂中来延迟肠胃外投与的化合物形式的吸收。通过形成化合物在可生物降解聚合物（如聚丙交酯 - 聚乙交酯）中的微胶囊基质来制造可注射积存形式。取决于化合物与聚合物的比率和所用特定聚合物的性质，可以控制化合物的释放速率。其它可生物降解聚合物的实例包括聚（原酸酯）和聚（酸酐）。还通过将化合物覆埋于与身体组织可相容的脂质体或微乳液中来制备积存可注射调配物。

[0227] 用于直肠或阴道投与的组合物优选是栓剂，其可通过混合本发明化合物与适合的无刺激性赋形剂或载剂（如可可脂、聚乙二醇）或栓剂蜡来制备，所述栓剂蜡在环境温度下是固体，但在体温下是液体，且因此在直肠或阴道腔中熔融并释放活性化合物。

[0228] 用于经口投药的固体剂型包括胶囊、片剂、丸剂、散剂和颗粒。在所述固体剂型中，将活性剂与如以下至少一种惰性的医药学上可接受的赋形剂或载剂混合：柠檬酸钠或磷酸二钙；和 / 或 a) 填充剂或增量剂，如淀粉、乳糖、蔗糖、葡萄糖、甘露糖醇和硅酸；b) 粘合剂，

如羧甲基纤维素、藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖和阿拉伯胶 ;c) 保湿剂,如甘油 ;d) 崩解剂,如琼脂 - 琼脂、碳酸钙、马铃薯或木薯淀粉、海藻酸、某些硅酸盐和碳酸钠 ;e) 溶解延迟剂,如石蜡 ;f) 吸收加速剂,如季铵化合物 ;g) 湿润剂,如鲸蜡醇和单硬脂酸甘油酯 ;h) 吸附剂,如高岭土和膨润土 ;和 i) 润滑剂,如滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、月桂基硫酸钠,和其混合物。在胶囊、片剂和丸剂的情况下,剂型也可包含缓冲剂。

[0229] 也可使用相似类型的固体组合物作为使用如乳糖 (lactose/milk sugar) 以及高分子量聚乙二醇等的赋形剂的软质和硬质填充明胶胶囊中的填充剂。片剂、糖衣药丸、胶囊、丸剂和颗粒的固体剂型可以用包衣和外壳 (如肠溶包衣和医药调配技术中众所周知的其它包衣) 来制备。它们可以任选地含有乳浊剂,并且也可以具有使其任选地以延迟方式仅或优先在肠道某一部分中释放活性成分的组成。可使用的包埋组合物的实例包括聚合物和蜡。也可使用相似类型的固体组合物作为使用如乳糖 (lactose/milk sugar) 以及高分子量聚乙二醇等的赋形剂的软质和硬质填充明胶胶囊中的填充剂。

[0230] 活性化合物还可以呈与一或多种如上文所示的赋形剂的微囊封形式。片剂、糖衣药丸、胶囊、丸剂以及颗粒的固体剂型可以用包衣和外壳 (如肠溶衣、释放控制包衣和药物调配技术中众所周知的其它包衣) 来制备。在此类固体剂型中,活性化合物可以与至少一种惰性稀释剂 (如蔗糖、乳糖或淀粉) 混合。正常实践时,此类剂型还可以包含除惰性稀释剂以外的其它物质,例如压片润滑剂和其它压片助剂,如硬脂酸镁和微晶纤维素。在胶囊、片剂和丸剂的情况下,所述剂型还可包含缓冲剂。其可任选含有遮光剂,且也可具有使其任选地以延迟方式仅在或优先在肠道某一部分释放活性成分的组成。可使用的包埋组合物的实例包括聚合物和蜡。

[0231] 用于局部或经皮投与本发明化合物的剂型包括软膏、糊剂、乳膏、洗剂、凝胶、散剂、溶液、喷雾剂、吸入剂或贴片。在无菌条件下将活性组分与医药学上可接受的载剂和任何所需防腐剂或缓冲剂按要求混合。还预期眼用调配物、滴耳剂和滴眼剂处于本发明的范围内。此外,本发明涵盖使用经皮贴片,其具有提供化合物向身体的控制传递的额外优点。所述剂型可通过将化合物溶解或分散于适当介质中来制备。也可使用吸收增强剂来增加化合物穿过皮肤的流量。速率可通过提供速率控制膜或将化合物分散于聚合物基质或凝胶中来控制。

[0232] 根据一个实施例,本发明涉及一种抑制生物样品中的 ACC 的方法,其包含以下步骤 :使所述生物样品与本发明化合物或包含所述化合物的组合物接触。

[0233] 在某些实施例中,本发明涉及一种调节生物样品中的脂肪酸水平的方法,其包含以下步骤 :使所述生物样品与本发明化合物或包含所述化合物的组合物接触。

[0234] 如本文中所用,术语“生物样品”包括 (但不限于) 细胞培养物或其提取物 ;由哺乳动物获得的活组织检查物质或其提取物 ;和血液、唾液、尿液、粪便、精液、眼泪或其它体液或其提取物。

[0235] 抑制生物样品中的酶适用于所属领域的技术人员已知的多种目的。所述目的的实例包括 (但不限于) 生物学分析、基因表达研究和生物目标鉴别。

[0236] 本发明的另一实施例涉及一种抑制患者的 ACC 的方法,其包含以下步骤 :向所述患者投与本发明化合物或包含所述化合物的组合物。

[0237] 根据另一实施例,本发明涉及一种在患者中抑制脂肪酸制造、刺激脂肪酸氧化或

两者皆有的方法，其包含以下步骤：向所述患者投与本发明化合物或包含所述化合物的组合物。根据某些实施例，本发明涉及一种在患者中抑制脂肪酸制造、刺激脂肪酸氧化或两者皆有使得减轻肥胖症或缓解代谢综合症的症状的方法，其包含以下步骤：向所述患者投与本发明化合物或包含所述化合物的组合物。在其它实施例中，本发明提供一种治疗有需要的患者的由 ACC 介导的病症的方法，其包含以下步骤：向所述患者投与根据本发明的化合物或其医药学上可接受的组合物。所述病症详细地描述在本文中。

[0238] 在一些实施例中，本发明的化合物和组合物可以用于治疗肥胖症或另一种代谢病症的方法。在某些实施例中，本发明的化合物和组合物可以用于治疗哺乳动物的肥胖症或其它代谢病症。在某些实施例中，哺乳动物为人类患者。在某些实施例中，本发明的化合物和组合物可以用于治疗人类患者的肥胖症或其它代谢病症。

[0239] 在一些实施例中，本发明提供一种治疗肥胖症或另一种代谢病症的方法，其包含向患有肥胖症或另一种代谢病症的患者投与本发明的化合物或组合物。在某些实施例中，治疗肥胖症或另一种代谢病症的方法包含向哺乳动物投与本发明的化合物和组合物。在某些实施例中，哺乳动物为人类。在一些实施例中，代谢病症为血脂异常、III 型血脂异常或高脂质血症。在一些实施例中，高脂质血症为高甘油三酯血症。在一些实施例中，肥胖症为普拉德－威利综合症 (Prader-Willi syndrome)、巴比二氏综合症 (Bardet-Biedl syndrome)、科恩综合症 (Cohen syndrome) 或 MOMO 综合症的症状。在一些实施例中，肥胖症为投与另一种药物的副作用，所述另一种药物包括（但不限于）胰岛素、磺脲、噻唑烷二酮、抗精神病药、抗抑郁剂、类固醇、抗惊厥剂（包括苯妥英 (phenytoin) 和丙戊酸盐）、苯噻啶 (pizotifen) 或激素避孕药。

[0240] 在某些实施例中，本发明提供一种治疗癌症或另一种增生性病症的方法，其包含向患有癌症或另一种增生性病症的患者投与本发明的化合物或组合物。在某些实施例中，治疗癌症或另一种增生性病症的方法包含向哺乳动物投与本发明的化合物和组合物。在某些实施例中，哺乳动物为人类。

[0241] 如本文所用，术语“抑制癌症”和“抑制癌细胞增殖”是指通过细胞毒性、营养物耗乏或诱导细胞凋亡来抑制个别地或与其它癌细胞聚集的癌细胞的生长、分裂、成熟或存活力和 / 或引起癌细胞死亡。

[0242] 含有增殖受到本文所述的化合物和组合物抑制且本文所述的方法适用于对抗的癌细胞的组织的实例包括（但不限于）乳房、前列腺、脑、血液、骨髓、肝脏、胰脏、皮肤、肾脏、结肠、卵巢、肺、睾丸、阴茎、甲状腺、副甲状腺、垂体、胸腺、视网膜、葡萄膜、结膜、脾、头、颈、气管、胆囊、直肠、唾液腺、肾上腺、咽喉、食道、淋巴结、汗腺、皮脂腺、肌肉、心脏和胃。

[0243] 在一些实施例中，利用本发明的化合物或组合物治疗的癌症为黑素瘤、脂肪肉瘤、肺癌、乳癌、前列腺癌、白血病、肾癌、食道癌、脑癌、淋巴瘤或结肠癌。在某些实施例中，癌症为原发性渗出性淋巴瘤 (PEL)。在某些优选实施例中，待利用本发明的化合物或组合物治疗的癌症为携有活化 MAPK 路径的癌症。在一些实施例中，携有活化 MAPK 路径的癌症为黑素瘤。在某些优选实施例中，利用本发明的化合物或组合物治疗的癌症为与 BRCA1 突变相关的癌症。在一个尤其优选的实施例中，利用本发明的化合物或组合物治疗的癌症为三阴性乳癌。在一些实施例中，肺癌为非小细胞肺癌 (NSCLC)。

[0244] 在某些实施例中，可利用本发明化合物治疗的疾病为神经病症。在一些实施

例中，所述神经病症为阿尔茨海默病 (Alzheimer's Disease)、帕金森病 (Parkinson's Disease)、癫痫症、局部缺血、年龄相关的记忆损伤、轻度认知障碍、弗里德希氏共济失调 (Friedreich's Ataxia)、GLUT1 缺陷型癫痫症、矮妖精貌综合症 (Leprechaunism)、拉布桑－门登霍尔综合症 (Rabson-Mendenhall Syndrome)、冠状动脉旁路移植痴呆、麻醉诱发的记忆丢失、肌肉萎缩性侧索硬化、神经胶质瘤亨廷顿病 (gliomaor Huntington's Disease)。

[0245] 在某些实施例中，可利用本发明化合物治疗的疾病为感染性疾病。在一些实施例中，感染性疾病为病毒感染。在一些实施例中，病毒感染为巨细胞病毒感染或流感感染。在一些实施例中，感染性疾病为真菌感染。在一些实施例中，感染性疾病为细菌感染。

[0246] 在一些实施例中，本发明化合物可用于治疗

[0247] 取决于待治疗的特定病况或疾病，通常投与以治疗所述病况的额外治疗剂可以与本发明的化合物和组合物组合投与。如本文所用，通常投与以治疗特定疾病或病状的额外治疗剂被称为“适于所治疗的疾病或病况”。

[0248] 在某些实施例中，所提供的化合物或其组合物与另一种 ACC 抑制剂或抗肥胖药剂组合投与。在一些实施例中，所提供的化合物或其组合物与一或多种其它治疗剂组合投与。所述治疗剂药剂包括（但不限于）如奥利司他（罗氏鲜 (Xenical))、CNS 刺激剂、奎斯米亚或百维克。

[0249] 在某些实施例中，所提供的化合物或其组合物与另一种抗癌药、细胞毒素或化学治疗剂组合投与有需要的患者。

[0250] 在某些实施例中，与本发明的化合物或组合物组合使用的抗癌药或化学治疗剂包括（但不限于）二甲双胍、苯乙双胍 (phenformin)、丁双胍、伊马替尼 (imatinib)、尼罗替尼 (nilotinib)、吉非替尼 (gefitinib)、舒尼替尼 (sunitinib)、卡非唑米 (carfilzomib)、盐孢菌素 A(salinosporamide A)、视黄酸、顺铂 (cisplatin)、卡铂 (carboplatin)、奥沙利铂 (oxaliplatin)、二氯甲二乙胺 (mechlorethamine)、环磷酰胺 (cyclophosphamide)、苯丁酸氮芥 (chlorambucil)、异环磷酰胺 (ifosfamide)、硫唑嘌呤 (azathioprine)、巯嘌呤 (mercaptopurine)、去氧氟尿苷 (doxifluridine)、氟尿嘧啶 (fluorouracil)、吉西他滨 (gemcitabine)、甲氨蝶呤 (methotrexate)、硫鸟嘌呤 (tioguanine)、长春新碱 (vincristine)、长春碱 (vinblastine)、长春瑞滨 (vinorelbine)、长春地辛 (vindesine)、鬼臼毒素 (podophyllotoxin)、依托泊苷 (etoposide)、替尼泊苷 (teniposide)、塔呋泊苷 (tafluposide)、太平洋紫杉醇 (paclitaxel)、多西他赛 (docetaxel)、伊立替康 (irinotecan)、拓扑替康 (topotecan)、安吖啶 (amsacrine)、放射菌素 (actinomycin)、多柔比星 (doxorubicin)、道诺霉素 (daunorubicin)、伐柔比星 (valrubicin)、艾达霉素 (idarubicin)、表柔比星 (epirubicin)、普卡霉素 (plicamycin)、丝裂霉素 (mitomycin)、米托蒽醌 (mitoxantrone)、美法仑 (melphalan)、白消安 (busulfan)、卡培他滨 (capecitabine)、培美曲塞 (pemetrexed)、埃博霉素 (epothilones)、13- 顺式－视黄酸、2-CdA、2- 氯去氧腺苷、5- 阿扎胞苷 (Azacitidine)、5- 氟尿嘧啶、5-FU、6- 巯嘌呤、6-MP、6-TG、6- 硫鸟嘌呤、阿布拉生 (Abraxane)、Accutane®、放射菌素 D(Actinomycin-D)、Adriamycin®、Adrucil®、Afinitor®、Agrylin®、Ala-Cort®、阿地白介素 (Aldesleukin)、阿仑单抗 (Alemtuzumab)、ALIMTA、阿利维甲酸 (Alitretinoin)、

Alkaban-AQ®、Alkeran®、全反式维甲酸、α 干扰素、六甲蜜胺(Altretamine)、氨甲蝶呤(Amethopterin)、氨磷汀(Amifostine)、氨鲁米特(Aminoglutethimide)、阿那格雷(Anagrelide)、Anandron®、阿那曲唑(Anastrozole)、阿糖胞苷(Arabinosylcytosine)、Ara-C、Aranesp®、Aredia®、Arimidex®、Aromasin®、Arranon®、三氧化二砷、Arzerra™、天冬酰胺酶、ATRA、Avastin®、阿扎胞苷(Azacitidine)、BCG、BCNU、苯达莫司汀(Bendamustine)、贝伐单抗(Bevacizumab)、贝瑟罗汀(Bexarotene)、BEXXAR®、比卡鲁胺(Bicalutamide)、BiCNU、Blenoxane®、博莱霉素(Bleomycin)、硼替佐米(Bortezomib)、白消安(Busulfan)、Busulfex®、C225、甲酰四氢叶酸钙(Calcium Leucovorin)、Campath®、Camptosar®、喜树碱(Camptothecin)-11、卡培他滨(Capecitabine)、Carac™、卡铂、卡莫司汀(Carmustine)、卡莫司汀晶片、Casodex®、CC-5013、CCI-779、CCNU、CDDP、CeeNU、Cerubidine®、西妥昔单抗(Cetuximab)、苯丁酸氮芥(Chlorambucil)、柠胶因子(Citrovorum Factor)、克拉屈滨(Cladribine)、可的松(Cortisone)、Cosmegen®、CPT-11、Cytadren®、Cytosar-U®、Cytoxan®、达卡巴嗪(Dacarbazine)、达克金(Dacogen)、放线菌素(Dactinomycin)、达贝泊汀 α(Darbepoetin Alfa)、达沙替尼(Dasatinib)、道诺霉素(Daunomycin)、道诺霉素盐酸盐、道诺霉素脂质体、DaunoXome®、地卡特隆(Decadron)、地西他滨(Decitabine)、Delta-Cortef®、Deltasone®、地尼白介素(Denileukin)、迪夫托斯(Diftitox)、DepoCyt™、地塞米松(Dexamethasone)、地塞米松乙酸酯、地塞米松磷酸钠、德克松(Dexasone)、右雷佐生(Dexrazoxane)、DHAD、DIC、迪欧戴克斯(Diodex)、多西他赛(Docetaxel)、Doxil®、多柔比星(Doxorubicin)、多柔比星脂质体、Droxia™、DTIC、DTIC-Dome®、Duralone®、Efudex®、Eligard™、Ellence™、Eloxatin™、Elspar®、Emcyt®、表柔比星(Epirubicin)、依伯汀 α(Epoetin Alfa)、爱必妥(Erbitux)、埃罗替尼(Erlotinib)、欧文菌属(Erwinia)L-天冬酰胺酶、雌莫司汀(Estramustine)、益护尔(Ethyol)、Etopophos®、依托泊苷(Etoposide)、磷酸依托泊苷、Eulexin®、依维莫司(Everolimus)、Evista®、依西美坦(Exemestane)、Fareston®、Faslodex®、Femara®、非格司亭(Filgrastim)、氟尿苷(Floxuridine)、Fludara®、氟达拉宾(Fludarabine)、Fluoroplex®、氟尿嘧啶(Fluorouracil)、氟尿嘧啶(乳膏)、氟羟甲睾酮(Fluoxymesterone)、氟他胺(Flutamide)、亚叶酸、FUDR®、氟维司群(Fulvestrant)、G-CSF、吉非替尼(Gefitinib)、吉西他滨(Gemcitabine)、吉妥单抗(Gemtuzumab)、奥唑米星(ozogamicin)、Gemzar Gleevec™、Gliadel®晶片、GM-CSF、戈舍瑞林(Goserelin)、粒细胞群落刺激因子、颗粒球巨噬细胞群落刺激因子、Halotestin®、Herceptin®、甲氟烯索(Hexadrol)、Hexalen®、六甲蜜胺(Hexamethylmelamine)、HMM、Hycamtin®、Hydrea®、Hydrocort Acetate®、氢化可的松(Hydrocortisone)、氢化可的松磷酸钠(Hydrocortisone Sodium Phosphate)、氢化可的松琥珀酸钠、氢化可的松磷酸酯、羟基脲(Hydroxyurea)、异贝莫单抗(Ibritumomab)、异贝莫单抗、泰泽坦(Tiuxetan)、Idamycin®、Idarubicin Ifex®、IFN-α、异环磷酰胺(Ifosfamide)、

IL-11、IL-2、甲磺酸伊马替尼 (Imatinib mesylate)、咪唑甲酰胺、干扰素 α、干扰素 α-2b(PEG 结合物)、白介素 -2、白介素 -11、Intron A® (干扰素 α-2b)、Iressa®、伊立替康 (Irinotecan)、异维甲酸 (Isotretinoin)、伊沙匹隆 (Ixabepilone)、Ixempra™、Kidrolase®、Lanacort®、拉帕替尼 (Lapatinib)、L- 天冬酰胺酶、LCR、来那度胺 (Lenalidomide)、来曲唑 (Letrozole)、甲酰四氢叶酸 (Leucovorin)、瘤可宁 (Leukeran)、Leukine™、亮丙立德 (Leuprolide)、新长春碱 (Leurocristine)、Leustatin™、脂质体 Ara-C、Liquid Pred®、洛莫司汀 (Lomustine)、L-PAM、L- 溶肉瘤素 (L-Sarcolysin)、Lupron®、Lupron Depot®、Matulane®、玛西德克斯 (Maxidex)、二氯甲二乙胺、二氯甲二乙胺盐酸盐、Medralone®、Medrol®、Megace®、甲地孕酮 (Megestrol)、乙酸甲地孕酮、美法仑 (Melphalan)、巯嘌呤 (Mercaptopurine)、美司钠 (Mesna)、Mesnex™、甲氨蝶呤 (Methotrexate)、甲氨蝶呤钠、甲基泼尼松龙 (Methylprednisolone)、Meticorten®、丝裂霉素 (Mitomycin)、丝裂霉素 -C、米托蒽醌 (Mitoxantrone)、M-Prednisol®、MTC、MTX、Mustargen®、氮芥 (Mustine)、Mutamycin®、Myleran®、Mylocel™、Mylotarg®、Navelbine®、奈拉滨 (Nelarabine)、Neosar®、Neulasta™、Neumega®、Neupogen®、Nexavar®、Nilandron®、尼罗替尼 (Nilotinib)、尼鲁米特 (Nilutamide)、Nipent®、氮芥 (Nitrogen Mustard)、Novaldex®、Novantrone®、奈普雷特 (Nplate)、奥曲肽 (Octreotide)、乙酸奥曲肽、奥法木单抗 (Ofatumumab)、Oncospar®、Oncovin®、Ontak®、Onxal™、奥普瑞白介素 (Oprelvekin)、Orapred®、Orasone®、奥沙利铂 (Oxaliplatin)、太平洋紫杉醇、结合蛋白质的太平洋紫杉醇、帕米膦酸盐 (Pamidronate)、帕尼单抗 (Panitumumab)、Panretin®、Paraplatin®、帕唑帕尼 (Pazopanib)、Pediapred®、PEG 干扰素、培门冬酶 (Pegaspargase)、乙二醇化非格司亭 (Pegfilgrastim)、PEG-INTRON™、PEG-L- 天冬酰胺酶、培美曲塞 (PEMETREXED)、喷司他汀 (Pentostatin)、苯丙氨酸氮芥、Platinol®、Platinol-AQ®、泼尼松龙 (Prednisolone)、强的松 (Prednisone)、Prelone®、丙卡巴肼 (Procarbazine)、PROCRIT®、Proleukin®、Prolifeprospan 20 与卡莫司汀插入物、Purinethol®、雷诺昔酚 (Raloxifene)、Revlimid®、Rheumatrex®、Rituxan®、利妥昔单抗 (Rituximab)、Roferon-A® (干扰素 α-2a)、罗米司亭 (Romiplostim)、Rubex®、红比霉素盐酸盐 (Rubidomycin hydrochloride)、Sandostatin®、Sandostatin LAR®、沙格司亭 (Sargramostim)、Solu-Cortef®、Solu-Medrol®、索拉非尼 (Sorafenib)、SPRYCEL™、STI-571、链脲霉素 (Streptozocin)、SU11248、舒尼替尼 (Sunitinib)、Sutent®、他莫昔芬 (Tamoxifen)、Tarceva®、Targretin®、Tasigna®、Taxol®、Taxotere®、Temodar®、替莫唑胺 (Temozolomide)、坦罗莫司 (Temsirolimus)、替尼泊苷 (Teniposide)、TESPA、沙立度胺 (Thalidomide)、Thalomid®、TheraCys®、硫鸟嘌呤 (Thioguanine)、硫鸟嘌呤 Tabloid®、硫代磷酰胺 (Thiophosphoamide)、Thioplex®、噻替派 (Thiotepa)、TICE®、Toposar®、拓扑替康 (Topotecan)、托瑞米芬 (Toremifene)、Torisel®、托西莫单抗 (Tositumomab)、曲

妥珠单抗 (Trastuzumab)、Treanda®、维甲酸 (Tretinoin)、Trexall™、Trisenox®、TSPA、TYKERB®、VCR、Vectibix™、 Velban®、 Velcade®、 VePesid®、 Vesanoid®、Viadur™、Vidaza®、长春碱 (Vinblastine)、硫酸长春碱、Vincasar Pfs®、长春新碱 (Vincristine)、长春瑞滨 (Vinorelbine)、酒石酸长春瑞滨、VLB、VM-26、伏立诺他 (Vorinostat)、维曲特 (Votrient)、VP-16、Vumon®、 Xeloda®、 Zanosar®、Zevalin™、Zinecard®、 Zoladex®、唑来膦酸 (Zoledronic acid)、佐林扎 (Zolinza)、Zometa®或以上各者中的任一者的组合。

[0251] 在某些实施例中,本发明化合物可与选自二甲双胍、苯乙双胍或丁双胍的双胍一起投与有需要的患者。在某些实施例中,被投与本发明化合物和双胍的组合的患者罹患癌症、肥胖症、肝病、糖尿病或上述中的两者或两者以上。

[0252] 在某些实施例中,2 种或 2 种以上治疗剂的组合可与本发明化合物一起投与。在某些实施例中,3 种或 3 种以上治疗剂的组合可与本发明化合物一起投与。

[0253] 本发明抑制剂也可与之组合的药剂的其它实例包括(但不限于):维生素和营养补充剂;癌症疫苗;用于嗜中性白血球减少症的疗法(例如 G-CSF、非格司亭 (filgrastim)、来格司亭 (lenograstim));用于血小板减少的疗法(例如血液输液、促红细胞生成素);PI3 激酶 (PI3K) 抑制剂;MEK 抑制剂;mTOR 抑制剂;CPT1 抑制剂;AMPK 活化剂;PCSK9 抑制剂;SREBP 位点 1 蛋白酶抑制剂;HMG CoA- 还原酶抑制剂;止吐药(例如 5-HT_3 受体拮抗剂、多巴胺拮抗剂、NK1 受体拮抗剂、组胺受体拮抗剂、大麻素 (cannabinoid)、苯并二氮呯或抗胆碱激导性剂);用于阿尔茨海默病的疗法,如 Aricept®和 Excelon®;用于帕金森氏病的疗法,如 L-DOPA/ 卡比多巴 (carbidopa)、恩他卡朋 (entacapone)、罗匹尼洛 (ropinrole)、普拉克索 (pramipexole)、溴麦角环肽 (bromocriptine)、培高利特 (pergolide)、三己芬迪 (trihexephendyl) 和金刚胺 (amantadine);用于治疗多发性硬化症 (MS) 的药剂,如 β 干扰素(例如 Avonex®和 Rebif®)、Copaxone®和米托蒽醌 (mitoxantrone);用于哮喘的疗法,如沙丁胺醇 (albuterol) 和 Singulair®;用于治疗精神分裂症的药剂,如再普乐 (zyprexa)、理斯必妥 (risperdal)、思瑞康 (seroquel) 和氟哌啶醇 (haloperidol);消炎剂,如皮质类固醇、TNF 阻断剂、IL-1RA、硫唑嘌呤、环磷酰胺和柳氮磺胺吡啶 (sulfasalazine);免疫调节剂和免疫抑制剂,如环孢素 (cyclosporin)、他克莫司 (tacrolimus)、雷帕霉素 (rapamycin)、霉酚酸吗啉乙酯 (mycophenolate mofetil)、干扰素、皮质类固醇、环磷酰胺、硫唑嘌呤和柳氮磺胺吡啶;神经营养因子,如乙酰胆碱酯酶抑制剂、MAO 抑制剂、干扰素、抗惊厥剂、离子通道阻断剂、利鲁唑 (riluzole) 和抗帕金森氏病剂;用于治疗心血管疾病的药剂,如 β- 阻断剂、ACE 抑制剂、利尿剂、硝酸盐、钙离子通道阻断剂和他汀类药 (statin)、贝特类药 (fibrate)、胆固醇吸收抑制剂、胆酸螯合剂和烟碱酸;用于治疗肝病的药剂,如皮质类固醇、消胆胺 (cholestyramine)、干扰素和抗病毒剂;用于治疗血液病症的药剂,如皮质类固醇、抗白血病药剂和生长因子;用于治疗免疫缺乏病症的药剂,如 γ 球蛋白;和抗糖尿病药剂,如双胍(二甲双胍、苯乙双胍、丁双胍)、噻唑烷二酮(罗格列酮、吡格列酮、曲格列酮)、磺酰脲(甲苯磺丁脲、乙酰苯磺酰环己脲、甲磺吖庚脲、氯磺丙脲、格列吡嗪、格列苯脲、格列美脲、格列齐特)、美格替耐(瑞格列奈

(repaglinide)、那格列奈(nateglinide))、α-葡糖苷酶抑制剂(米格列醇、阿卡波糖)、肠促胰岛素模拟物(艾塞那肽、利拉鲁肽、他司鲁肽)、胃抑制性肽类似物、DPP-4 抑制剂(维格列汀、西他列汀、沙格列汀、利拉利汀、阿格列汀)、淀粉素类似物(普兰林肽)以及胰岛素和胰岛素类似物。

[0254] 在某些实施例中,本发明化合物或其医药学上可接受的组合物与反义药剂、单克隆或多克隆抗体或 siRNA 治疗剂组合投与。

[0255] 那些额外的药剂可以与含有本发明化合物的组合物分开投与,作为多次给药方案的一部分。或者,那些药剂可以是单一剂型的一部分,在单一组合物中与本发明化合物一起混合。如果作为多次给药方案的一部分投与,那么两种活性剂可以同时、依次或彼此间隔一定时间段(通常彼此间隔在五小时以内)提供。

[0256] 如本文中所用,术语“组合(combination)”、“组合(combined)”和相关术语是指同时或依次投与根据本发明的治疗剂。举例来说,本发明化合物可以与另一治疗剂以独立单位剂型或共同呈单一单位剂型同时或依次投与。因此,本发明提供包含式 I 化合物、其它治疗剂和医药学上可接受的载剂、佐剂或媒剂的单一单位剂型。

[0257] 可以与载剂物质组合产生单一剂型的本发明化合物和其它治疗剂两者(在包含如上所述的其它治疗剂的那些组合物中)的量将取决于所治疗的宿主和特定投药模式而变化。优选地,应该调配本发明组合物,使得可以投与剂量介于每天每公斤体重 0.01-100mg 之间的本发明。

[0258] 在包含其它治疗剂的那些组合物中,所述其它治疗剂和本发明化合物可以协同地起作用。因此,这些组合物中其它治疗剂的量将低于仅使用所述治疗剂的单一疗法中所需的量。在这些组合物中,可以投与剂量介于每天每公斤体重 0.01-100μg 之间的其它治疗剂。

[0259] 存在于本发明组合物中的其它治疗剂的量将不大于通常在包含所述治疗剂作为唯一活性剂的组合物中所投与的量。优选地,本发明所公开的组合物中其它治疗剂的量将在通常存在于包含所述药剂作为唯一治疗活性剂的组合物中的量的约 50%到 100%范围内。

[0260] 本发明进一步涉及一种农业组合物,其包含至少一种如上文所定义的式 I 化合物或其农业上可接受的盐和液体或固体载剂。下文定义适合的载剂以及也可含于本发明的组合物中的助剂和其它活性化合物。

[0261] 适合的“农业上可接受的盐”包括(但不限于)阳离子和阴离子分别对式 I 化合物的杀真菌作用无不良影响的那些阳离子的盐或那些酸的酸加成盐。因此,适合的阳离子尤其为碱金属的离子,优选是钠和钾;碱土金属的离子,优选是钙、镁和钡;和过渡金属的离子,优选是锰、铜、锌和铁;以及铵离子,其必要时可携带一到四个 C_1-C_4- 烷基取代基和/或一个苯基或苯甲基取代基,优选是二异丙基铵、四甲基铵、四丁基铵、三甲基苯甲基铵。其它农业上可接受的盐包括鏻离子;硫鎓离子,优选是三(C_1-C_4- 烷基)硫鎓;和锍氧离子,优选是三(C_1-C_4- 烷基)锍氧。适用的酸加成盐的阴离子主要为氯离子、溴离子、氟离子、氢硫酸根、硫酸根、二氢磷酸根、磷酸氢根、磷酸根、硝酸根、碳酸氢根、碳酸根、六氟硅酸根、六氟磷酸根、苯甲酸根、以及 C_1-C_4- 烷酸的阴离子(优选是甲酸根、乙酸根、丙酸根和丁酸根)。所述农业上可接受的酸加成盐可通过使携有碱性可电离基团的式 I 化合物与对应阴离子的

酸（优选是盐酸、氢溴酸、硫酸、磷酸或硝酸）反应来形成。

[0262] 根据本发明的式 I 化合物和组合物分别适用作杀真菌剂。其特点为对广谱的植物病原性真菌具有显著有效性，所述真菌包括土传真菌，其尤其来源于以下纲：根肿菌纲 (Plasmodiophoromycetes)、卵菌纲 (Peronosporomycetes)（同义词：卵菌纲 (Oomycetes))、壶菌纲 (Chytridiomycetes)、接合菌纲 (Zygomycetes)、子囊菌纲 (Ascomycetes)、担子菌纲 (Basidiomycetes) 和半知菌纲 (Deuteromycetes)（同义词：半知菌纲 (Fungi imperfecti))。一些为系统地有效的且其可在作物保护中用作叶面杀真菌剂、拌种杀真菌剂和土壤杀真菌剂。此外，其适合于控制尤其存在于木材或植物根中的有害真菌。

[0263] 在一些实施例中，根据本发明的式 I 化合物和组合物在控制各种栽培植物和植物繁殖材料（如种子）和这些植物的作物材料上的植物病原性真菌方面尤其重要，所述栽培植物如谷物，例如小麦、黑麦、大麦、黑小麦、燕麦或稻米；甜菜，例如糖用甜菜或饲料甜菜；果实，如梨果、核果或软果，例如苹果、梨、李、桃、杏仁、樱桃、草莓、覆盆子、黑莓或醋栗；豆科植物，如扁豆、豌豆、苜蓿或大豆；含油植物，如油菜、芥菜、橄榄、向日葵、椰子、可可豆、蓖麻油植物、油棕、落花生或大豆；葫芦科植物，如南瓜、黄瓜或甜瓜；纤维植物，如棉花、亚麻、大麻或黄麻；柑橘果实，如柑橘、柠檬、葡萄柚或蜜橘；蔬菜，如菠菜、莴苣、芦笋、甘蓝、胡萝卜、洋葱、蕃茄、马铃薯、葫芦或红辣椒；月桂科植物，如鳄梨、肉桂或樟脑；能量和原料植物，如玉米、大豆、油菜、甘蔗或油棕；玉米；烟草；坚果；咖啡；茶；香蕉；藤本植物（餐桌葡萄和葡萄汁葡萄藤）；蛇麻子；草皮；天然橡胶植物或观赏植物和林业植物，如花卉、灌木、阔叶树或常青树，例如针叶树。

[0264] 在一些实施例中，式 I 化合物和其组合物分别用于控制田间作物上的众多真菌，所述田间作物如马铃薯、糖甜菜、烟草、小麦、黑麦、大麦、燕麦、稻米、玉米、棉花、大豆、油菜、豆荚、向日葵、咖啡或甘蔗；果实；藤本植物；观赏性植物；或蔬菜，如黄瓜、蕃茄、菜豆或南瓜。

[0265] 术语“植物繁殖材料”应理解为表示植物中可用于植物繁殖的所有有性部分（如种子）和无性植物材料（如插条和块茎（例如马铃薯））。此植物繁殖材料包括种子、根、果实、块茎、鳞茎、根茎、芽、新枝和植物的其它部分，包括欲在发芽之后或自土壤中出苗之后移植的秧苗和幼小植物。这些幼小植物也可在移植之前通过用浸没或浇注进行整体或部分处理来保护。

[0266] 在一些实施例中，用式 I 化合物和其组合物分别处理植物繁殖材料用于控制谷类（如小麦、黑麦、大麦和燕麦）、稻米、玉米、棉花和大豆上的众多真菌。

[0267] 术语“栽培植物”应被理解为包括已通过育种、诱变或遗传工程改造而修饰的植物，包括（但不限于）市场上或研发中的农业生物技术产品。经基因修饰的植物为遗传物质已通过使用重组 DNA 技术进行修饰的在天然情形下不能轻易通过交叉育种、突变或天然重组获得的植物。通常，已将一或多种基因整合到遗传修饰植物的遗传物质中，以便改良植物的某些特性。所述基因修饰还包括（但不限于）例如通过糖基化或聚合物添加（如异戊二烯基化、乙酰基化或法呢基化部分或 PEG 部分）进行的蛋白质、寡肽或多肽的靶向翻译后修饰。

[0268] 作为常规育种或遗传工程改造方法的结果，已促使通过育种、诱变或遗传工程

改造而修饰的植物耐受特定类别除草剂的施用，所述除草剂为如羟基苯基丙酮酸双加氧酶 (HPPD) 抑制剂；乙酰乳酸合成酶 (ALS) 抑制剂，如磺酰脲（参见例如 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) 或咪唑啉酮（参见例如 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)；烯醇丙酮酰莽草酸 -3- 磷酸酯合成酶 (EPSPS) 抑制剂，如草甘膦 (glyphosate)（参见例如 WO 92/00377)；谷氨酰胺合成酶 (GS) 抑制剂，如草铵膦 (glufosinate)（参见例如 EP-A 242 236、EP-A 242 246) 或苯腈除草剂（参见例如 US 5,559,024)。通过常规育种（诱变）方法已促使数种栽培植物耐受除草剂，例如 Clearfield® 夏季油菜（芥花 (Canola)，德国巴斯夫股份公司 (BASF SE,Germany)) 耐受咪唑啉酮，例如甲氧咪草烟 (imazamox)。已使用遗传工程改造方法促使如大豆、棉花、玉米、甜菜和油菜的栽培植物耐受如草甘膦和草铵膦的除草剂，其中的一些以商品名 RoundupReady®（耐草甘膦，美国孟山都 (Monsanto,U.S.A.)) 和 LibertyLink®（耐草铵膦，德国拜耳作物科学 (CropScience,Germany)) 可购得。

[0269] 此外，还涵盖通过使用重组 DNA 技术而能够合成以下各者的植物：一或多种杀昆虫蛋白质，尤其已知来自芽孢杆菌属细菌，具体来说来自苏云金芽孢杆菌 (Bacillus thuringiensis) 的蛋白质，如 δ- 内毒素，例如 CrylA(b)、CrylA(c)、CrylF、CrylF(a2)、CryllA(b)、CrylllA、CrylllB(bi) 和 Cry θ c；营养期杀昆虫蛋白质 (VIP)，例如 VIP1、VIP2、VIP3 或 VIP3A；细菌定殖线虫的杀昆虫蛋白质，例如光杆状菌属 (Photorhabdus spp.) 或致病杆菌属 (Xenor-habdus spp.)；由动物产生的毒素，如蝎毒素、蜘蛛毒素、黄蜂毒素或其它昆虫特异性神经毒素；由真菌产生的毒素，如链霉菌毒素、植物凝集素，如豌豆或大麦凝集素；凝血素 (agglutinin)；蛋白酶抑制剂，如胰蛋白酶抑制剂、丝氨酸蛋白酶抑制剂、块茎储藏蛋白 (patatin)、胱抑素 (cystatin) 或木瓜蛋白酶抑制剂；核糖体失活蛋白 (RIP)，如蓖麻毒素 (ricin)、玉米 RIP、相思豆毒素 (abrin)、丝瓜毒素 (luffin)、沙泊宁 (saporin) 或异株泻根毒蛋白 (bryodin)；类固醇代谢酶，如 3- 羟基类固醇氧化酶、蜕皮类固酸 -IDP- 糖基 - 转移酶、胆固醇氧化酶、蜕皮激素抑制剂或 HMG-CoA 还原酶；离子通道阻断剂，如钠或钙通道阻断剂；保幼激素酯酶；利尿剂激素受体（异株泻根毒蛋白受体）；芪合成酶、联苄合成酶、几丁质酶或葡聚糖酶。在本发明的上下文中，这些杀昆虫蛋白质或毒素也应明确地理解为前毒素、杂交蛋白质、截短或以其它方式修饰的蛋白质。杂交蛋白质的特征为蛋白质域的新组合（参见例如 WO 02/015701)。所述毒素或能够合成所述毒素的经基因修饰的植物的其它实例公开在例如 EP-A 374 753、WO 93/007278、WO 95/34656、EP-A 427 529、EP-A 451 878、WO 03/18810 和 WO 03/52073 中。产生所述经基因修饰植物的方法通常为所属领域的技术人员所已知并且描述于例如以上提及的出版物中。经基因修饰的植物中所含的这些杀昆虫蛋白质赋予产生这些蛋白质的植物对来自节肢动物的所有分类群的有害害虫，尤其对甲虫（鞘翅目）、双翅昆虫（双翅目）和蛾类（鳞翅目）和对线虫（线虫纲）的耐受性。能够合成一或多种杀昆虫蛋白质的经基因修饰的植物例如描述于上文所提及的出版物中，且其中一些可在市面上购得，如 YieldGard®（产生 CryiAb 毒素的玉米栽培品种）、YieldGard® Plus（产生 Cry1Ab 和 Cry3Bb1 毒素的玉米栽培品种）、Starlink®

(产生Cry9c毒素的玉米栽培品种)、Herculex® RW(产生Cry34Ab1、Cry35Ab1和酶(草胺膦-N-乙酰基转移酶[PAT])的玉米栽培品种);NuCOTN® 33B(产生Cry1Ac毒素的棉花栽培品种)、Bollgard® I(产生CryiAc毒素的棉花栽培品种)、Bollgard® II(产生CryiAc和Cry2Ab2毒素的棉花栽培品种);VIPCOT®(产生VIP-毒素的棉花栽培品种);NewLeaf®(产生Cry3A毒素的马铃薯栽培品种);来自法国先正达种子公司(Syngenta Seeds SAS,France)的Bt-Xtra®、NatureGard®、KnockOut®、BiteGard®、Protecta®、Bt 11(例如Agrisure® CB)和Bt176(产生CryiAb毒素和PAT酶的玉米栽培品种)、来自法国先正达种子公司的MIR604(产生Cry3A毒素的经修饰型式的玉米栽培品种,参看WO 03/018810)、来自比利时孟山都欧洲公司(Monsanto Europe S.A.,Belgium)的MON 863(产生Cry3Bb1毒素的玉米栽培品种)、来自比利时孟山都欧洲公司的IPC 531(产生CryiAc毒素的经修饰型式的棉花栽培品种)和来自比利时先锋海外公司(Pioneer Overseas Corporation,Belgium)的1507(产生Cry1F毒素和PAT酶的玉米栽培品种)。

[0270] 此外,还涵盖通过使用重组DNA技术而能够合成一或多种用于增加那些植物对细菌、病毒或真菌病原体的抗性或耐受性的蛋白质的植物。所述蛋白质的实例为所谓的"发病机制相关蛋白"(PR蛋白质,参见例如EP-A 392225)、植物疾病抗性基因(例如表达针对衍生自墨西哥野生型马铃薯球栗薯(Solanum bulbocastanum)的致病疫霉(Phytophthora infestans)起作用的抗性基因的马铃薯栽培品种)或T4-溶菌酶(例如能够合成这些具有增加的针对如梨火疫病菌(Erwinia amylvora)的细菌的抗性的蛋白质的马铃薯栽培品种)。产生所述经基因修饰植物的方法通常为所属领域的技术人员所已知并且描述于例如以上提及的出版物中。

[0271] 此外,还涵盖通过使用重组DNA技术而能够合成一或多种用于增加那些植物的产率(例如生物质产量、谷粒产量、淀粉含量、油含量或蛋白质含量);对干旱、盐度或其它限制生长的环境因素的耐受性;或对害虫和真菌性、细菌性或病毒性病原体的耐受性的蛋白质的植物。

[0272] 此外,还涵盖通过使用重组DNA技术而含有经改进量的物质含量或新物质含量确切地说用以改善人类或动物营养的植物,例如产生促进健康的长链ω-3脂肪酸或不饱和ω-9脂肪酸的含油作物(例如Nexera®油菜,加拿大陶氏农业科学(DOW Agro Sciences,Canada))。

[0273] 此外,还涵盖通过使用重组DNA技术而含有经改进量的内含物物质或新内含物物质确切地说用以改善原料产量的植物,例如产生增加量的支链淀粉的马铃薯(例如Amflora®马铃薯,德国巴斯夫股份公司)。

[0274] 式I化合物和其组合物分别尤其适用于控制以下植物疾病:

[0275] 观赏植物、蔬菜(例如白锈菌(A.candida)和向日葵(例如婆罗门参白锈菌(A.tragopogonis))上的白锈菌属(Albugo spp.);蔬菜、油菜(芸苔生链格孢菌(A.brassicola)或芸苔链格孢菌(A.brassicae))、糖用甜菜(极细链格孢菌(A.tenuis))、水果、稻米、大豆、马铃薯(例如立枯链格孢菌(A.solani)或赤星链格孢菌(A.alternata))、蕃茄(例如立枯链格孢菌或赤星链格孢菌)和小麦上的链

格孢菌属(Alternaria spp.)(链格孢菌属叶斑病);糖用甜菜和蔬菜上的丝囊霉属(Aphanomyces spp.);谷物和蔬菜上的壳二孢属(Ascochyta spp.),例如小麦上的小麦壳二孢(A.tritici)(炭疽病)和大麦上的大麦壳二孢(A.hordei);平脐蠕孢属(Bipolaris spp.)和内脐蠕孢属(Drechslera spp.)(有性型:旋孢腔菌属(Cochliobolus spp.)),例如玉米上的南方叶枯病(玉蜀黍内脐蠕孢(D.maydis))或北方叶枯病(玉米生平脐蠕孢(β.zeicola)),例如谷物上的斑点病(麦根腐平脐蠕孢(β.sorokiniana))和例如稻米和草皮上的稻平脐蠕孢(B.oryzae);谷物上(例如小麦或大麦上)的布氏白粉菌(Blumeria graminis(先前为Erysiphe))(白粉病);水果和浆果(例如草莓)、蔬菜(例如莴苣、胡萝卜、芹菜和甘蓝)、油菜、花卉、葡萄藤、林业植物和小麦上的灰葡萄孢菌(Botrytis cinerea)(有性型:富氏葡萄孢盘菌(Botryotinia fuckeliana):灰色霉病);莴苣上的莴苣露菌病(Bremia lactucae)(霜霉病);阔叶树和常青树上的长喙壳属(Ceratocystis spp.)(同义词Ophiostoma)(枯病或萎蔫病),例如榆树上的榆长喙壳(C.ulmi)(荷兰榆树病);玉米上(例如灰色叶斑病:玉蜀黍尾孢菌(C.zeaemaydis))、稻米、糖用甜菜(例如甜菜尾孢菌(C.beticola)、甘蔗、蔬菜、咖啡、大豆(例如大豆尾孢菌(C.sojina)或菊池尾孢菌(C.kikuchii))和稻米的尾孢菌属(Cercospora spp.)(尾孢菌叶斑病);蕃茄(例如黄枝孢菌(C.fulvum):叶霉病)和谷物上的枝孢菌属(Cladosporium spp.),例如小麦上的草芽枝孢菌(C.herbarum)(黑穗病);谷物上的紫色麦角菌(Claviceps purpurea)(麦角病);玉米(灰色旋孢腔菌(C.carbonum))、谷物(例如禾旋孢腔菌(C.sativus,无性型):麦根腐平脐蠕孢)和稻米(例如宫部旋孢腔菌(C.miyabeanus,无性型):稻长蠕孢(H.oryzae))上的旋孢腔菌属(无性型:(平脐蠕孢属的长蠕孢))(叶斑病);棉花(例如棉炭疽病菌(C.gossypii))、玉米(例如禾生炭疽病菌(C.graminicola):炭疽茎枯病)、软果、马铃薯(例如西瓜炭疽病菌(C.coccodes):黑斑病)、蚕豆(例如菜豆炭疽病菌(C.lindemuthianum))和大豆(例如大豆炭疽病菌(C.truncatum)或胶孢炭疽病菌(C.gloeosporioides))上的炭疽病菌属(Colletotrichum)(有性型:小丛壳(Glomerella)(炭疽病);伏革菌属(Corticium spp.),例如稻米上的笹木伏革菌(C.sasakii)(外皮枯萎病);大豆和观赏植物上的多主棒孢霉(Corynespora cassiicola)(叶斑病);锈斑病菌属(Cycloconium spp.),例如橄榄树上的橄榄锈斑病菌(C.oleaginum);果树、葡萄藤(例如鹅掌楸柱孢菌(C.liriodendri),有性型:鹅掌楸新丛赤壳菌(Neonectria liriodendri):乌脚病)和观赏植物上的柱孢菌属(Cylindrocarpon spp.)(例如果树溃疡病或幼葡萄藤衰弱病,有性型:丛赤壳属(Nectria spp.)或新丛赤壳属(Neonectria spp.);大豆上的白纹羽束丝菌(Dematophora necatrix(有性型:白纹病菌属(Rosellinia)))(根和茎枯病);北茎溃疡菌属(Diaporthe spp.),例如大豆上的大豆北茎溃疡病菌(D.phaseolorum)(猝倒病);玉米、谷物(如大麦(例如大麦网斑内脐蠕孢(D.teres),网斑病)和小麦(例如黄褐斑内脐蠕孢(D.tritici-repentis):黄褐斑病))、稻米和草皮上的内脐蠕孢属(同义词Helminthosporium,有性型:核腔菌属(Pyrenophora));由斑褐孔菌(Formitiporia punctata(同义词Phellinus))、海洋孔菌(F.mediterranea)、根霉格抱菌(Phaeomoniella chlamydospora)(以前为Phaeoacremonium chlamydosporum)、鸡腿蘑丝孢(Phaeoacremonium aleophilum)和/或葡萄座腔菌(Botryosphaeria obtusa)引起的葡萄藤上的埃斯卡病(Esca)(顶枯病、干枯病);梨果(E.pyri)和软果(覆盆子痂囊腔

菌 (E.veneta)：炭疽病）和葡萄藤（葡萄痂囊腔菌 (E.ampelina)：炭疽病）上的痂囊腔菌属 (Elsinoe spp.)；稻米上的稻叶黑粉菌 (Entyloma oryzae)（叶黑粉病）；小麦上的附球菌属 (Epicoccum spp.)（黑霉病）；糖用甜菜（甜菜白粉菌 (E.betae)）、蔬菜（例如豌豆白粉菌 (E.pisi)）（如黄瓜（例如二孢白粉菌 (E.cichoracearum)）、甘蓝、油菜（例如十字花科白粉菌 (E.cruciferarum)）上的白粉菌属 (Erysiphe spp.)（白粉病）；果树、葡萄藤和观赏树木上的侧弯孢菌 (Eutypa lata)（侧弯孢菌溃疡病或顶枯病，无性型：长额囊孢菌 (Cytosporina lata)，同义词 (Libertella blepharis)）；玉米（例如玉米大斑病菌 (E.turcicum)）上的突脐蠕孢属 (Exserohilum spp.)（同义词 Helminthosporium）；各种植物上的镰刀菌属 (Fusarium spp.)（有性型：赤霉 (Gibberella)）（枯萎病，根或茎枯病），如谷物（例如小麦或大麦）上的禾谷镰刀菌 (F.graminearum) 或黄色镰刀菌 (F.culmorum)（根枯病、疮痂病或头枯萎病）、蕃茄上的尖镰刀菌 (F.oxysporum)、大豆上的茄腐镰刀菌 (F.solani) 和玉米上的轮枝镰刀菌 (F.verticillioides)；谷物（例如小麦或大麦）和玉米上的禾顶囊壳 (Gaeumannomyces graminis)（全蚀病）；谷物（例如玉蜀黍赤霉 (G.zeae)）和稻米（例如藤仓赤霉 (G.fujikuroi)：恶苗病）上的赤霉属 (Gibberella spp.)；葡萄藤、梨果和其它植物上的围小丛壳菌 (Glomerella cingulata) 和棉花上的棉小丛壳菌 (G.gossypii)；稻米上的谷粒染色复合物；葡萄藤上的葡萄球座菌 (Guignardia bidwellii)（黑枯病）；蔷薇科植物和刺柏上的锈菌属 (Gymnosporangium spp.)，例如梨上的圆柏锈菌 (G.sabinae)（锈病）；玉米、谷物和稻米上的长蠕孢属 (Helminthosporium spp.)（同义词 Drechslera，有性型：旋孢腔菌属）；驼孢锈菌属 (Hemileia spp.)，例如咖啡上的咖啡鸵孢锈菌 (H.vastatrix)（咖啡叶锈病）；葡萄藤上的揭斑拟棒束孢 (Isariopsis clavispora)（同义词 Cladosporium vitis)；大豆和棉花上的菜豆壳球孢 (Macrophomina phaseolina)（同义词 phaseoli)）（根和茎枯病）；谷物（例如小麦或大麦）上的雪腐镰刀菌 (Microdochium nivale)（同义词 Fusarium)（粉色雪霉病）；大豆上的扩散叉丝壳 (Microsphaera diffusa)（白粉病）；链核盘菌属 (Monilinia spp.)，例如核果和其它蔷薇科植物上的核果链核盘菌 (M.laxa)、美澳型核果链核盘菌 (M.fructicola) 和果生链核盘菌 (M.fructigena)（花枝枯萎病，褐枯病）；谷物、香蕉、软果和落花生上的球腔菌属 (Mycosphaerella spp.)，如小麦上的禾生球腔菌 (M.graminicola)（无性型：小麦壳针孢 (Septoria tritici)，壳针孢叶斑病）或香蕉上的斐济球腔菌 (M.fijiensis)（黑斑病）；甘蓝（例如芸苔霜霉 (P.brassicae)）、油菜（例如寄生霜霉 (P.parasitica)）、洋葱（例如葱霜霉 (P.destructor)）、烟草（烟草霜霉 (P.tabacina)）和大豆（例如大豆霜霉 (P.manshurica)）上的霜霉属 (Peronospora spp.)（霜霉病）；大豆上的豆薯层锈菌 (Phakopsora pachyrhizi) 和山马蝗层锈菌 (P.meibomiae)（大豆锈病）；例如葡萄藤（例如维管束瓶霉菌 (P.tracheiphila) 和四孢瓶霉菌 (P.tetraspora)）和大豆（例如大豆蓬揭腐病菌 (P.gregata)：茎枯病）上的瓶霉菌属 (Phialophora spp.)；油菜和甘蓝上的黑胫茎点霉 (Phoma lingam)（根和茎枯病）以及糖用甜菜上的甜菜茎点霉 (P.betae)（根枯病、叶斑病和猝倒病）；向日葵、葡萄藤（例如葡萄黑腐病菌 (P.viticola)：茎和叶斑病）和大豆（例如茎枯病：菜豆疫霉病菌 (P.phaseoli)，有性型：大豆北茎溃疡病菌 (Diaporthe phaseolorum)）上的拟茎点霉属 (Phomopsis spp.)；玉米上的玉蜀黍褐斑病菌 (Physoderma maydis)（褐斑

病）;各种植物（如红辣椒和葫芦（例如辣椒疫霉(P.capsici)）、大豆（例如大豆疫霉(P.megasperma)，同义词P.sojae)）、马铃薯和蕃茄（例如致病疫霉(P.infestans)：晚疫病）和阔叶树（例如栎树猝死病菌(P.ramorum)：橡树猝死病）上的疫霉属(Phytophthora spp.）;甘蓝、油菜、萝卜和其它植物上的芸苔根肿菌(Plasmodiophora brassicae)（根肿病）;单轴霉属(Plasmopara spp.)，例如葡萄藤上的葡萄生单轴霉(P.viticola)（葡萄藤霜霉病）和向日葵上的霍尔斯单轴霉(P.halstediiou)；蔷薇科植物、蛇麻子、梨果和软果上的叉丝单囊壳属(Podosphaera spp.)（白粉病)，例如苹果上的苹果白粉病菌(P.leucotricha)；谷物（如大麦和小麦)（禾谷多粘菌(P.graminis)）和糖用甜菜（甜菜多粘菌(P.betae)）上的多粘菌属(Polymyxa spp.）以及由此传播的病毒性病害；谷物（例如小麦或大麦）上的铺毛拟小尾孢(Pseudocercosporella herpotrichoides)（眼斑病，有性型：塔普斯菌(Tapesia yallundae)）;各种植物上的假霜霉属(Pseudoperonospora)（霜霉病)，例如葫芦上的古巴假霜霉(P.cubensis)或蛇麻子上的葎草假霜(P.humili)；葡萄藤上的维管束假无柄盘菌(Pseudopezicula tracheiphila)（红火病(red fire disease或rotbrenner')，无性型：瓶霉属(Phialo-phora)）;各种植物上的柄锈菌属(Puccinia spp.)（锈病)，例如谷物（如小麦、大麦或黑麦）和芦笋（例如天门冬属柄锈病(P.asparagi)）上的小麦柄锈菌(P.triticina)（褐锈病或叶锈病)，条形柄锈病(P.striiformis)（条锈病或黄锈病)，大麦柄锈病(P.hordei)（萎缩锈病)，禾柄锈菌(P.graminis)（茎锈病或黑锈病）或小麦叶锈菌(P.recondita)（褐锈病或叶锈病）;小麦上的黄褐斑核腔菌(Pyrenophora tritici-repentis)（无性型：内脐蠕孢属)（黄褐斑病）或大麦上的大麦网斑核腔菌(P.teres)（网斑病）;梨孢属(Pyricularia spp.)，例如稻米上的稻梨孢菌(P.oryzae)（有性型：稻瘟病菌(Magnaporthe grisea)，稻热病）和草皮谷物上的稻瘟梨孢菌(P.grisea)；草皮、稻米、玉米、小麦、棉花、油菜、向日葵、大豆、糖用甜菜、蔬菜和各种其它植物上的腐霉属(Pythium spp.)（猝倒病)（例如终极腐霉(P.ultimum)或瓜果腐霉(P.aphanidermatum)）;柱隔孢属(Ramularia spp.)，例如大麦上的大麦柱隔孢(R.collo-cygni)（柱隔孢属叶斑病、生理叶斑病）和糖用甜菜上的甜菜柱隔孢(R.beticola)；棉花、稻米、马铃薯、草皮、玉米、油菜、马铃薯、糖用甜菜、蔬菜和各种其它植物上的丝核菌属(Rhizoctonia spp.)，例如大豆上的立枯丝核菌(R.solani)（根枯病和茎枯病）、稻米上的立枯丝核菌（外皮枯萎病）或小麦或大麦上的禾谷丝核菌(R.cerealis)（丝核菌春季枯萎病）；草莓、胡萝卜、甘蓝、葡萄藤和蕃茄上的葡枝根霉(Rhizopus stolonifer)（黑霉病、软枯病）；大麦、黑麦和黑小麦上的黑麦喙孢(Rhynchosporium secalis)（褐斑病）；稻米上的稻帚枝霉(Sarocladium oryzae)和渐狭帚枝霉(S.attenuatum)（外皮枯病）；蔬菜和田间作物（如油菜、向日葵（例如向日葵核盘菌(S.sclerotiorum)）和大豆（例如齐整核盘菌(S.rolfsii)或向日葵核盘菌））上的核盘菌属(Sclerotinia spp.)（茎枯病或白霉病）;各种植物上的壳针孢属(Septoria spp.)，例如大豆上的大豆壳针孢(S.glycines)（褐斑病）、小麦上的小麦壳针孢(S.tritici)（壳针孢叶斑病）和谷物上的颖枯壳针孢(S.nodorum)（同义词Stagonospora)（叶花斑枯病）；葡萄藤上的葡萄钩丝壳菌(Uncinula necator)（同义词Erysiphe)（白粉病，无性型：葡萄粉孢(Oidium tuckeri)）;玉米（例如玉米大斑病菌(S.turcicum)，同义词Helminthosporium turcicum)和草皮上的大斑病菌属(Setospaeria spp.)（叶枯萎

病）；玉米（例如丝轴黑粉菌（S.reiliana）：头黑穗病）、高粱和甘蔗上的轴黑粉菌属（Sphacelotheca spp.）（黑穗病）；葫芦上的单丝壳白粉菌（Sphaerotheca fuliginea）（白粉病）；马铃薯上的粉痴菌（Spongospora subterranea）（粉痂病）和由此传播的病毒性病害；谷物上的壳多孢属（Stagonospora spp.），例如小麦上的颖枯壳多孢（S.nodorum）（叶花斑枯病，有性型：颖枯球腔菌（Leptosphaeria nodorum［同义词Phaeosphaeria］））；马铃薯上的内生集壶菌（Synchytrium endobioticum）（马铃薯癌肿病）；外囊菌属（Taphrina spp.），例如桃上的畸形外囊菌（T.deformans）（缩叶病）和李上的李外囊菌（T.pruni）（李袋果病）；烟草、梨果、蔬菜、大豆和棉花上的根串珠霉属（Thielaviopsis spp.）（黑色根枯病），例如黑色根串珠霉（T.basicola）（同义词Chalara elegans）；谷物上的腥黑粉菌属（Tilletia spp.）（普通黑穗病（common bunt）或腥黑穗病（stinking smut）），如小麦上的小麦腥黑粉菌（T.tritici）（同义词T.caries，小麦黑穗病）和小麦矮腥黑穗菌（T.controversa）（萎缩黑穗病）；大麦或小麦上的肉孢核瑚菌（Typhula incarnata）（灰雪霉病）；条黑粉菌属（Urocystis spp.），例如黑麦上的隐条黑粉菌（U.occulta）（茎黑穗病）；蔬菜（如蚕豆（例如疣顶单胞锈菌（U.appendiculatus），同义词U.phaseoli）和糖用甜菜（例如甜菜单胞锈菌（U.betae））上的单孢锈菌属（Uromyces spp.）（锈病）；谷物（例如裸单胞锈菌（U.nuda）和燕麦散黑粉菌（U.avaenae））、玉米（例如玉蜀黍黑粉菌（U.maydis）：玉米黑穗病）和甘蔗上的黑粉菌属（Ustilago spp.）（散黑穗病）；苹果（例如苹果黑星病（V.inaequalis））和梨上的黑星菌属（Venturia spp.）（疮痂病）；和各种植物（如果树和观赏植物、葡萄藤、软果、蔬菜和田间作物）上的轮枝菌属（Verticillium spp.）（萎蔫病），例如草莓、油菜、马铃薯和蕃茄上的大丽轮枝菌（V.dahliae）。

[0276] 式Ⅰ化合物和其组合物分别也适用于在保护储藏产品或收获物时或在保护材料时控制有害真菌。术语“材料保护”应理解为表示保护工业材料和非生活材料，如粘着剂、胶、木材、纸和纸板、织物、皮革、油漆分散液、塑料、冷却润滑剂、纤维或织物，以防由有害微生物（如真菌和细菌）造成的侵袭和破坏。关于木材和其它材料的保护，应特别注意以下有害真菌：子囊菌纲，如长喙霉属（Ophiostoma spp.）、长喙壳属（Ceratocystis spp.）、出芽短梗霉菌（Aureobasidium pullulans）、核茎点霉属（Sclerophoma spp.）、毛壳菌属（Chaetomium spp.）、腐殖菌属（Humicola spp.）、石座菌属（Petriella spp.）、毛束霉属（Trichurus spp.）；担子菌纲，如粉孢革菌属（Coniophora spp.）、革盖菌属（Coriolus spp.）、粘褶菌属（Gloeophyllum spp.）、香菇属（Lentinus spp.）、侧耳属（Pleurotus spp.）、卧孔菌属（Poria spp.）、蠕龙介属（Serpula spp.）和干酪菌属（Tyromyces spp）；半知菌纲，如曲霉菌属（Aspergillus spp.）、枝孢菌属（Cladosporium spp.）、青霉菌属（Penicillium spp.）、木霉菌属（Trichorma spp.）、链格孢菌属（Alternaria spp.）、拟青霉菌属（Paecilomyces spp.）；和接合菌纲，如白霉菌属（Mucor spp.）；且另外在储藏产品和收获物的保护中，值得注意的是以下酵母菌：假丝酵母属（Candida spp.）和酿酒酵母（Saccharomyces cerevisae）。

[0277] 式Ⅰ化合物和其组合物分别可以用于改良植物的健康状况。本发明还涉及一种通过以下方式改良植物健康状况的方法：用有效量的式Ⅰ化合物或其组合物分别处理植物、其繁殖材料和/或植物正在生长或欲生长的地点。

[0278] 术语“植物健康”应理解为表示植物和/或其产品由若干指标单独或彼此组合所

确定的状况，所述指标如产量（例如增加的生物质和/或增加的有价值成分含量）、植物活力（例如改良的植物生长和/或较绿的叶子（“绿化效应”））、质量（例如改良的某些成分的含量或组成）和对非生物胁迫和/或生物胁迫的耐受性。以上经鉴别用于植物健康状况的指标可相互依赖或可由彼此产生。

[0279] 式I化合物可以生物活性可不同的不同晶体变体形式存在。所述晶体变体同样为本发明的主题。

[0280] 式I化合物按原样或以组合物形式使用，以通过用杀真菌有效量的活性物质处理真菌或植物、植物繁殖材料（如种子）、土壤、表面、材料或空间而免受真菌攻击。可在真菌感染植物、植物繁殖材料（如种子）、土壤、表面、材料或空间之前与之后进行施用。

[0281] 可预防性地在种植或移植之时或之前用式I化合物按原样或包含至少一种式I化合物的组合物处理植物繁殖材料。

[0282] 本发明还涉及包含溶剂或固体载剂和至少一种式I化合物的农用化学组合物以及控制有害真菌的用途。

[0283] 农用化学组合物包含杀真菌有效量的化合物I和/或II。术语“有效量”表示足以控制栽培植物上或在保护材料时的有害真菌且对经处理植物不产生实质性破坏的组合物或式I化合物的量。所述量可在广泛范围内变化且取决于各种因素，如欲控制的真菌种类、所处理的栽培植物或材料、气候条件和所用的特定式I化合物。

[0284] 式I化合物和其盐可转化成惯用类型的农用化学组合物，例如溶液、乳液、悬浮液、撒粉、粉剂、糊剂和颗粒。组合物类型取决于特定预定目的；在各种情况下，应确保本发明化合物的精细且均匀的分布。

[0285] 组合物类型的实例为悬浮液(SC、OD、FS)、可乳化浓缩物(EC)、乳液(EW、EO、ES)、糊剂、片剂、可湿性粉剂或撒粉(WP、SP、SS、WS、DP、DS)或颗粒(GR、FG、GG、MG)(其可具水溶性或可湿性)，以及用于处理如种子的植物繁殖材料的凝胶调配物(GF)。

[0286] 组合物类型（例如SC、OD、FS、EC、WG、SG、WP、SP、SS、WS、GF）通常在稀释后使用。如DP、DS、GR、FG、GG和MG的组合物类型通常未经稀释即使用。

[0287] 组合物以已知方式制备(参看US 3,060,084,EP-A 707445(关于液体浓缩物)，伯朗宁(Browning):“团聚作用(Agglomeration)”，化学工程(Chemical Engineering),1967年12月4日,147-48,佩里化学工程师手册(Perry's Chemical Engineer's Handbook),第4版，纽约麦格劳-希尔公司(McGraw-Hill,New York),1963,第8-57页和以下各页,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,克林曼(Klingman):作为科学的杂草控制(Weed Control as a Science)(纽约威利父子出版公司(J.Wiley&Sons,New York),1961),汉斯(Hance)等人：杂草控制手册(Weed Control Handbook)(第8版，牛津布莱克威尔科学出版社(Blackwell Scientific,Oxford),1989)和摩勒H.(Mollet,H.)和格鲁比曼A.(Grubemann,A.):调配技术(Formulation technology)(魏因海姆威利出版集团(Wiley VCH Verlag,Weinheim),2001)。

[0288] 农用化学组合物还可包含农用化学组合物中惯用的助剂。所用助剂分别取决于特定施用形式和活性物质。

[0289] 适合助剂的实例为溶剂、固体载剂、分散剂或乳化剂（如其它增溶剂、保护性胶

体、表面活性剂和粘着剂）、有机和无机增稠剂、杀细菌剂、抗冻剂、消泡剂、（适当时）着色剂和增粘剂或粘合剂（例如用于种子处理调配物）。适合的溶剂为水；有机溶剂，如中沸点到高沸点矿物油部分，如煤油或柴油；此外为煤焦油和植物或动物来源的油；脂肪族、环状和芳香族烃，例如甲苯、二甲苯、石蜡、四氢萘、烷基化萘或其衍生物；醇，如甲醇、乙醇、丙醇、丁醇和环己醇；二醇；酮，如环己酮；和 γ- 丁内酯；脂肪酸二甲基酰胺；脂肪酸和脂肪酸酯和强力极性溶剂，例如胺，如 N- 甲基吡咯烷酮。

[0290] 固体载剂为矿物土，如硅酸盐、二氧化硅凝胶、滑石、高岭土、石灰石、石灰、白垩、红玄武土、黄土、粘土、白云石、硅藻土、硫酸钙、硫酸镁、氧化镁；粉碎合成材料；肥料（如硫酸铵、磷酸铵、硝酸铵、脲）；和植物来源的产品（如谷物粗粉、树皮粗粉、木材粗粉和坚果壳粗粉）、纤维素粉末和其它固体载剂。

[0291] 适合的表面活性剂（佐剂、湿润剂、增粘剂、分散剂或乳化剂）为芳香族磺酸（如木质素磺酸（Borresperse® 型，挪威宝利葛公司 (Borregard, Norway)）、酚磺酸、萘磺酸（Morwet® 型，美国阿克苏诺贝尔公司 (Akzo Nobel, U.S.A.)）、二丁基萘磺酸（Nekal® 型，德国巴斯夫公司 (BASF, Germany)））的碱金属、碱土金属和铵盐，和脂肪酸、烷基磺酸盐、烷基芳基磺酸盐、烷基硫酸盐、月桂基醚硫酸盐、脂肪醇硫酸盐和硫酸化己酸盐、硫酸化庚酸盐和硫酸化十八烷酸盐、硫酸化脂肪醇二醇醚，此外为萘或萘磺酸与苯酚和甲醛的缩合物、聚氧乙烯辛基苯基醚、乙氧基化异辛基苯酚、辛基苯酚、壬基苯酚、烷基苯基聚乙二醇醚、三丁基苯基聚乙二醇醚、三硬脂酰基苯基聚乙二醇醚、烷基芳基聚醚醇、醇与脂肪醇 / 环氧乙烷缩合物、乙氧基化蓖麻油、聚氧乙烯烷基醚、乙氧基化聚氧丙烯、月桂醇聚乙二醇醚缩醛、山梨糖醇酯、木质素亚硫酸盐废液和蛋白质、变性蛋白质、多糖（例如甲基纤维素）、疏水改性的淀粉、聚乙烯醇（Mowiol® 型，瑞士科莱恩公司 (Clariant, Switzerland)）、聚羧酸酯（Sokolan® 型，德国巴斯夫公司）、聚烷氧基化物、聚乙烯胺（Lupasol® 型，德国巴斯夫公司）、聚乙烯吡咯烷酮和其共聚物。

[0292] 增稠剂（即赋予组合物改变的流动性，即在静态条件下具高粘度且在搅动期间具低粘度的化合物）的实例为多糖和有机与无机粘土，如黄原胶 (Xanthan gum)（Kelzan®，美国斯比凯克公司 (CP Kelco, U.S.A.)）、Rhodopol® 23（法国罗地亚公司 (Rhodia, France)）、Veegum® (RT. 美国范德比尔特 (Vanderbilt, U.S.A.)) 或 Attaclay®（美国新泽西州安格化工有限公司 (Engelhard Corp., NJ, USA)）。

[0293] 可添加杀细菌剂以保存组合物且使其稳定。适合的杀细菌剂的实例为基于双氯酚 (dichlorophene) 和苯甲醇半缩甲醛的杀细菌剂（来自 ICI 的 Proxel® 或来自索尔化学公司 (Thor Chemie) 的 Acticide® RS 和来自罗门哈斯公司 (Rohm&Haas) 的 Kathon® MK) 和异噻唑啉酮衍生物，如烷基异噻唑啉酮和苯并异噻唑啉酮（来自索尔化学公司的 Acticide® MBS)。

[0294] 适合的抗冻剂的实例为乙二醇、丙二醇、脲和丙三醇。

[0295] 消泡剂的实例为硅酮乳液（如 Silikon® SRE，德国瓦克公司 (Wacker, Germany) 或 Rhodorsil®，法国罗地亚公司）、长链醇、脂肪酸、脂肪酸盐、有机氟化合物和其混合物。

[0296] 适合的着色剂为低水溶性颜料和水溶性染料。所提及的实例和名称为罗丹明

B(rhodamin B)、C.I. 颜料红 112、C.I. 溶剂红 1、颜料蓝 15:4、颜料蓝 15:3、颜料蓝 15:2、颜料蓝 15:1、颜料蓝 80、颜料黄 1、颜料黄 13、颜料红 112、颜料红 48:2、颜料红 48:1、颜料红 57:1、颜料红 53:1、颜料橙 43、颜料橙 34、颜料橙 5、颜料绿 36、颜料绿 7、颜料白 6、颜料棕 25、碱性紫 10、碱性紫 49、酸性红 51、酸性红 52、酸性红 14、酸性蓝 9、酸性黄 23、碱性红 10、碱性红 108。

[0297] 增粘剂或粘合剂的实例为聚乙烯吡咯烷酮、聚乙酸乙烯酯、聚乙烯醇和纤维素醚(Tylose®,日本信越公司 (Shin-Etsu, Japan))。

[0298] 粉剂、撒布用材料和撒粉可通过混合或同时研磨式 I 化合物和(适当时)其它活性物质与至少一种固体载剂来制备。

[0299] 颗粒,例如经涂布颗粒、经浸渍颗粒和均质颗粒可通过使活性物质结合于固体载剂来制备。固体载剂的实例为矿物土,如二氧化硅凝胶、硅酸盐、滑石、高岭土、美国活性白土 (attaclay)、石灰石、石灰、白垩、红玄武土、黄土、粘土、白云石、硅藻土、硫酸钙、硫酸镁、氧化镁;粉碎合成材料;肥料(如硫酸铵、磷酸铵、硝酸铵、脲);和植物来源的产品(如谷物粗粉、树皮粗粉、木材粗粉和坚果壳粗粉)、纤维素粉末和其它固体载剂。

[0300] 组合物类型的实例包括(但不限于):1. 用于用水稀释的组合物类型,i) 水溶性浓缩物 (SL、LS):将 10 重量份的本发明式 I 化合物溶解于 90 重量份的水或水溶性溶剂中。作为一个替代方案,添加湿润剂或其它助剂。在用水稀释时活性物质溶解。以此方式,获得活性物质含量为 10 重量%的组合物。ii) 可分散浓缩物 (DC):将 20 重量份的本发明式 I 化合物溶解于 70 重量份的环己酮中,且添加 10 重量份的分散剂(例如聚乙烯吡咯烷酮)。用水稀释得到分散液。活性物质含量为 20 重量%。iii) 可乳化浓缩物 (EC):将 15 重量份的本发明式 I 化合物溶解于 75 重量份的二甲苯中,且添加十二烷基苯磺酸钙和乙氧基化蓖麻油(各者为 5 重量份)。用水稀释得到乳液。组合物的活性物质含量为 15 重量%。iv) 乳液 (EW、EO、ES):将 25 重量份的本发明式 I 化合物溶解于 35 重量份的二甲苯中,且添加十二烷基苯磺酸钙和乙氧基化蓖麻油(各者为 5 重量份)。此混合物借助于乳化机 (Ultraturrax) 引入到 30 重量份的水中且制成均质乳液。用水稀释得到乳液。组合物的活性物质含量为 25 重量%。v) 悬浮液 (SC、OD、FS):在搅动式球磨机中,将 20 重量份的本发明式 I 化合物粉碎,且添加 10 重量份的分散剂和湿润剂和 70 重量份的水或有机溶剂,得到精细活性物质悬浮液。用水稀释得到活性物质的稳定悬浮液。组合物中的活性物质含量为 20 重量%。vi) 水分散性颗粒的水溶性颗粒 (WG、SG),将 50 重量份的本发明式 I 化合物细磨,且添加 50 重量份的分散剂和湿润剂,且借助于工业级设备(例如挤出机、喷雾塔、流体化床)制备为水分散性或水溶性颗粒。用水稀释得到活性物质的稳定分散液或溶液。组合物的活性物质含量为 50 重量%。vii) 水分散性粉剂和水溶性粉剂 (WP、SP、SS、WS),将 75 重量份的本发明式 I 化合物在转子-定子研磨机中粉碎,且添加 25 重量份的分散剂、湿润剂和硅胶。用水稀释得到活性物质的稳定分散液或溶液。组合物的活性物质含量为 75 重量%。viii) 凝胶 (GF):在搅动式球磨机中,将 20 重量份的本发明式 I 化合物粉碎,且添加 10 重量份的分散剂、1 重量份的胶凝剂湿润剂和 70 重量份的水或有机溶剂,得到活性物质的精细悬浮液。用水稀释,得到活性物质的稳定悬浮液,借此获得具有 20% (w/w) 活性物质的组合物。

[0301] 2. 未经稀释即施用的组合物类型:ix) 可粉化粉剂 (DP、DS):将 5 重量份的本发

明式 I 化合物细磨，且与 95 重量份的细粉状高岭土均匀混合。此举得到活性物质含量为 5 重量％的可粉化组合物。x) 颗粒 (GR、FG、GG、MG) :将 0.5 重量份的本发明式 I 化合物细磨且与 99.5 重量份的载剂缔合。当前方法为挤出、喷雾干燥或流体化床。此举得到活性物质含量为 0.5 重量％的未经稀释即施用的颗粒。xi)ULV 溶液 (UL)，将 10 重量份的本发明式 I 化合物溶解于 90 重量份的有机溶剂 (例如二甲苯) 中。此举得到活性物质含量为 10 重量％的未经稀释即施用的组合物。

[0302] 农用化学组合物通常包含在 0.01 重量％与 95 重量％之间、优选在 0.1 重量％与 90 重量％之间、最优选在 0.5 重量％与 90 重量％之间的活性物质。活性物质以 90％到 100％、优选 95％到 100％ (根据 NMR 光谱) 的纯度使用。

[0303] 出于处理植物繁殖材料、尤其种子的目的，通常采用水溶性浓缩物 (LS)、可流动浓缩物 (FS)、用于干燥处理的粉剂 (DS)、用于浆料处理的水分散性粉剂 (WS)、水溶性粉剂 (SS)、乳液 (ES)、可乳化浓缩物 (EC) 和凝胶 (GF)。这些组合物可在稀释后或未经稀释即施用于植物繁殖材料，尤其种子。所讨论的组合物在两倍到十倍稀释之后在即用制剂中得到 0.01 重量％到 60 重量％、优选 0.1 重量％到 40 重量％的活性物质浓度。可在播种之前或期间进行施用。用于分别施用或处理农用化学化合物和组合物到植物繁殖材料、尤其种子上的方法为所属领域中已知的，且包括繁殖材料的敷裹、包覆、粒化、撒粉、浸泡和沟内施用方法。在一个优选实施例中，通过不会诱导萌芽的方法，例如通过拌种、粒化、包覆和除尘将化合物或其组合物分别施用到植物繁殖材料上。

[0304] 在一个优选实施例中，悬浮液型 (FS) 组合物用于种子处理。FS 组合物通常可包含 1-800g/l 活性物质、1-200g/l 表面活性剂、0 到 200g/l 抗冻剂、0 到 400g/l 粘合剂、0 到 200g/l 颜料和最多 1 升溶剂 (优选是水)。

[0305] 活性物质可以按原样或以其组合物形式使用，例如以可直接喷雾溶液、粉剂、悬浮液、分散液、乳液、分散液、糊剂、可粉化产品、用于撒布的材料或颗粒形式借助于喷雾、雾化、撒粉、撒布、刷拭、浸没或浇灌来使用。施用形式完全取决于预定目的 ;意欲确保在各种情况下本发明的活性物质尽可能的最精细地分布。水性施用形式可从乳液浓缩物、糊剂或可湿性粉剂 (可喷雾粉剂、油分散液) 通过添加水来制备。为了制备乳液、糊剂或油分散液，按原样或溶解于油或溶剂中的物质可在水中借助于湿润剂、增粘剂、分散剂或乳化剂均质化。或者，可制备由活性物质、湿润剂、增粘剂、分散剂或乳化剂以及 (适当时) 溶剂或油构成的浓缩物，且所述浓缩物适用于用水稀释。

[0306] 即用制剂中的活性物质浓度可在相对较宽范围内改变。一般来说，其为 0.0001 重量％到 10 重量％、优选为 0.001 重量％到 1 重量％的活性物质。

[0307] 活性物质也可成功地用于超低体积工艺 (ULV)，可施用包含超过 95 重量％活性物质的组合物，或甚至施用无添加剂的活性物质。

[0308] 当用于植物保护时，取决于所需效果的种类，活性物质的施用量为每公顷 0.001 到 2kg，优选是每公顷 0.005 到 2kg，更优选是每公顷 0.05 到 0.9kg，尤其是每公顷 0.1 到 0.75kg。

[0309] 在植物繁殖材料 (如种子) 例如通过撒粉、包覆或浸湿种子的处理中，通常需要活性物质的量为每 100 千克植物繁殖材料 (优选是种子)0.1 到 1000g、优选地 1 到 1000g、更优选地 1 到 100g 且最优选地 5 到 100g。

[0310] 当用于材料或储存产品的保护中时，活性物质的施用量取决于施用区域的种类和所要效果。在材料保护中惯常施用的量为例如每立方米所处理材料 0.001g 到 2kg、优选是 0.005g 到 1kg 活性物质。

[0311] 可向活性物质或包含其的组合物中添加各种类型的油、湿润剂、佐剂、除草剂、杀细菌剂、其它杀真菌剂和 / 或农药，适当时直到在即将使用前才添加（槽混）。这些试剂可以 1:100 到 100:1、优选 1:10 到 10:1 的重量比与本发明的组合物混合。

[0312] 可使用的佐剂尤其为有机改性型聚硅氧烷，如 Break Thru S 240®；烷氧基化醇，如 Atplus 245®、Atplus MBA1303®、PIurafac LF 300®和 LutensolON 30®；EO/PO 嵌段聚合物，例如 Pluronic RPE 2035®和 Genapol B®；乙氧基化醇，如 Lutensol XP 80®；以及磺基丁二酸二辛钠，如 Leophen RA®。

[0313] 本发明组合物以作为杀真菌剂的使用形式还可与其它活性物质一起，例如与除草剂、杀昆虫剂、生长调节剂、杀真菌剂一起或者与肥料一起以预混物形式存在，或适当时直到在即将使用前才混合（槽混）。

[0314] 将呈作为杀真菌剂的使用形式的式 I 化合物或包含其的组合物与其它杀真菌剂混合在许多情况下会扩大所获得活性的杀真菌范围或防止杀真菌剂抗性发展。此外，在许多情况下，获得协同效应。

[0315] 可与本发明化合物联合使用的活性物质的以下清单打算说明可能的组合，但并不限于此：

[0316] A) 嗜球果伞素类 (strobilurin)：亚托敏 (azoxystrobin)、醚菌胺 (dimoxystrobin)、烯肟菌酯 (enestroburin)、氟嘧菌酯 (fluoxastrobin)、克收欣 (kresoxim methyl)、苯氧菌胺 (meto-minostrobin)、肟醚菌胺 (orysastrobin)、啶氧菌酯 (picoxystrobin)、百克敏 (pyraclostrobin)、吡菌苯威 (pyribencarb)、三氟敏 (trifloxystrobin)、2-(2-(6-(3- 氯 -2- 甲基 - 苯氧基)-5- 氟 - 嘧啶 -4- 基氧基)- 苯基)-2- 甲氧基亚氨基 -N- 甲基 - 乙酰胺、3- 甲氧基 -2-(2-(N-(4- 甲氧基 - 苯基)- 环丙烷 - 羧亚胺酰基硫基甲基)- 苯基)- 丙烯酸甲酯、(2- 氯 -5-[1-(3- 甲基苯甲氧基亚氨基) 乙基] 苯甲基) 氨基甲酸甲酯和 2-(2-(3-(2,6- 二氯苯基)-1- 甲基 - 亚烯丙基胺氧基甲基)- 苯基)-2- 甲氧基亚氨基 -N- 甲基 - 乙酰胺；

[0317] B) 羧酰胺和羧酰苯胺类：本达乐 (benalaxyl)、右本达乐 (benalaxyl-M)、麦锈灵 (benodanil)、必杀吩 (bixafen)、白克列 (boscalid)、萎锈灵 (carboxin)、甲呋酰胺 (fenfuram)、环酰菌胺 (fenhexamid)、氟酰胺 (flutolanil)、福拉比 (furametpyr)、异吡瑞沙 (isopyrazam)、异噻菌胺 (isotianil)、克拉昔 (kiralaxyl)、灭普宁 (me-pronil)、灭达乐 (metalaxyl)、右灭达乐 (metalaxyl-M/mefenoxam)、呋酰胺 (ofurace)、欧杀斯 (oxadixyl)、萎锈散 (oxycarboxin)、吡噻菌胺 (penthiopyrad)、赛达森 (sedaxane)、叶枯酞 (tecloftalam)、噻氟菌胺 (thifluzamide)、噻酰菌胺 (tiadinil)、2- 氨基 -4- 甲基 - 噻唑 -5- 甲酰苯胺、2- 氯 -N-(1,1,3- 三甲基 - 茚满 -4- 基)- 烟碱酰胺、N-(3',4',5'- 三氟联苯 -2- 基)-3- 二氟甲基 -1- 甲基 -1H- 吡唑 -4- 甲酰胺、N-(4'- 三氟甲基硫代联苯 -2- 基)-3- 二氟甲基 -1- 甲基 -1H- 吡唑 -4- 甲酰胺、N-(2-(1,3- 二甲基 - 丁基)- 苯基)-1,3- 二甲基 -5- 氟 -1H- 吡唑 -4- 甲酰胺和 N-(2-(1,3,3- 三甲基 - 丁基)- 苯基)-1,3- 二甲基 -5- 氟 -1H- 吡唑 -4- 甲酰胺；羧吗啉类 (carboxylic morpholide)：达

灭芬 (dimethomorph)、氟吗啉 (flumorph)、丁吡吗啉 (pyrimorph) ;苯甲酸酰胺类 :氟酰菌胺 (flumetover)、氟吡菌胺 (fluopicolide)、氟吡胺 (fluopyram)、苯酰菌胺 (zoxamide)、N-(3- 乙基 -3,5,5- 三甲基 - 环己基)-3- 甲酰胺基 -2- 羟基 - 苯甲酰胺 ;其它甲酰胺类 :加普胺 (carpropamid)、双环维林 (dicyclomet)、双炔酰菌胺 (mandiproamid)、土霉素 (oxytetracyclin)、硅噻菌胺 (silthiofarm) 和 N-(6- 甲氧基 - 吡啶 -3- 基) 环丙烷甲酸酰胺 ;

[0318] C) 唑和三唑类 :阿扎康唑 (azaconazole)、比多农 (bitertanol)、溴克座 (bromuconazole)、环克座 (cyproconazole)、待克利 (difenoconazole)、达克利 (diniconazole)、右达克利 (diniconazole-M)、依普座 (epoxiconazole)、芬克座 (fenbuconazole)、氟喹唑 (fluquinconazole)、护硅得 (flusilazole)、护汰芬 (flutriafol)、菲克利 (hexaconazole)、易胺座 (imibenconazole)、种菌唑 (ipconazole)、灭特座 (metconazole)、迈克尼 (myclobutanil)、噁咪唑 (oxpoconazole)、巴克素 (paclobutrazole)、平克座 (penconazole)、普克利 (propiconazole)、丙硫菌唑 (prothioconazole)、硅氟唑 (simeconazole)、得克利 (tebuconazole)、四克利 (tetraconazole)、三泰芬 (triadimefon)、三泰隆 (triadimenol)、灭菌唑 (triticonazole)、烯效唑 (uniconazole)、1-(4- 氯 - 苯基)-2-([1,2,4] 三唑 -1- 基)- 环庚醇 ;咪唑类 :赛座灭 (cyazofamid)、依灭列 (imazalil)、披扶座 (pefurazoate)、扑克拉 (prochloraz)、赛福座 (triflumizol) ;苯并咪唑类 :苯菌灵 (benomyl)、贝芬替 (carbendazim)、麦穗灵 (fuberidazole)、噻苯达唑 (thiabendazole) ;- 其它 :噻唑菌胺 (ethaboxam)、依得利 (etridiazole)、杀纹宁 (hymexazole) 和 2-(4- 氯 - 苯基)-N-4-(3,4- 二甲氧基 - 苯基)- 异噁唑 -5- 基]-2- 丙 -2- 炔氧基 - 乙酰胺 ;

[0319] D) 杂环化合物吡啶类 :扶吉胺 (fluazinam)、啶斑肟 (pyrifenox)、3-[5-(4- 氯 - 苯基)-2,3- 二甲基 - 异噁唑烷 -3- 基]- 吡啶、3-[5-(4- 甲基 - 苯基)-2,3- 二甲基 - 异噁唑烷 -3- 基]- 吡啶、2,3,5,6- 四 - 氯 -4- 甲磺酰基 - 吡啶、3,4,5- 三氯吡啶 -2,6- 二 - 甲腈、N-(1-(5- 溴 -3- 氯 - 吡啶 -2- 基)- 乙基)-2,4- 二氯烟碱酰胺、N-[(5- 溴 -3- 氯 - 吡啶 -2- 基)- 甲基]-2,4- 二氯 - 烟碱酰胺 ;嘧啶类 :布瑞莫 (bupirimate)、嘧菌环胺 (cyprodinil)、二氟林 (diflumetorim)、芬瑞莫 (fenarimol)、嘧菌腙 (ferimzone)、嘧菌胺 (mepanipyrim)、氯啶 (nitrapyrin)、尼瑞莫 (nuarimol)、嘧霉胺 (pyrimethanil) ;哌嗪类 :嗪氨灵 (triforine) ;吡咯类 :拌种咯 (fenpiclonil)、咯菌腈 (fludioxonil) ;吗啉类 :阿迪吗啉 (aldimorph)、吗菌灵 (dodemorph)、吗菌灵乙酸酯 (dodemorph-acetate)、丁苯吗啉 (fenpropimorph)、克啉菌 (tridemorph) ;哌啶类 :苯锈啶 (fenpropidin) ;- 二甲酰亚胺类 :氟菌安 (fluoroimid)、依普同 (iprodione)、腐霉利 (procymidone)、农利灵 (vinclozolin) ;非芳香族 5 元杂环 :凡杀同 (famoxadone)、咪唑菌酮 (fenamidone)、氟噻菌净 (flutianil)、辛噻酮 (octhilinone)、噻菌灵 (probenazole)、5- 氨基 -2- 异丙基 -3- 氧代 -4- 邻位 - 甲苯基 -2,3- 二氢 - 吡唑 -1- 硫代甲酸 S- 烯丙酯 ;其它 :活化酯 -S- 甲基、吲唑磺菌胺 (amisulbrom)、敌菌灵 (anilazin)、杀稻瘟菌素 -S(blasticidin-S)、四氯丹 (captafol)、盖普丹 (captan)、螨离丹 (chinomethionat)、迈隆 (dazomet)、咪菌威 (debacarb)、哒菌酮 (diclomezine)、野燕枯 (difenzoquat)、野燕枯甲基硫酸酯 (difenzoquat-methylsulfate)、氰菌胺 (fenoxanil)、灭菌丹 (Folpet)、

欧索林酸 (oxolinic acid)、粉病灵 (piperalin)、丙氧喹啉 (proquinazid)、咯喹酮 (pyroquilon)、喹氧灵 (quinoxyfen)、咪唑嗪 (triazoxide)、三赛唑 (tricyclazole)、2- 丁氧基 -6- 碘基 -3- 丙基苯并吡喃 -4- 酮、5- 氯 -1-(4,6- 二甲氧基 - 嘧啶 -2- 基)-2- 甲基 -1H- 苯并咪唑、5- 氯 -7-(4- 甲基哌啶 -1- 基)-6-(2,4,6- 三氟苯基)-[1,2,4] 三唑并 [1,5-a] 嘧啶和 5- 乙基 -6- 辛基 -[1,2,4] 三唑并 [1,5-a] 嘧啶 -7- 基胺 ;

[0320] E) 氨基甲酸酯类硫代氨基甲酸酯和二硫代氨基甲酸酯 :福美铁 (ferbam)、代森锰锌 (mancozeb)、代森锰 (maneb)、威百亩 (metam)、磺菌威 (methasulphocarb)、代森联 (metiram)、甲基锌乃浦 (propineb)、福美双 (thiram)、代森锌 (zineb)、福美锌 (ziram) ;氨基甲酸酯类 :苯噻菌胺 (benthiavalicarb)、乙霉威 (diethofencarb)、丙森锌 (iprovalicarb)、霜霉威 (propamocarb)、盐酸霜霉威 (propamo-carb hydrochlorid)、霜霉灭 (valiphenal) 和 N-(1-(1-(4- 氰基 - 苯基) 乙烷磺酰基)- 丁 -2- 基) 氨基甲酸 -(4- 氟苯基) 酯 ;

[0321] F) 其它活性物质 - 胍类 :胍、多宁 (dodine)、无多宁碱 (dodine free base)、双胍盐 (guazatine)、双胍乙酸盐 (guazatine-acetate)、双胍辛胺 (iminoctadine)、双胍辛胺三乙酸酯 (iminoctadine-triacetate)、双胍三辛烷基苯磺酸盐 (iminoctadine-tris(albesilate)) ;抗生素类 :嘉赐霉素 (kasugamycin)、水合盐酸嘉赐霉素 (kasugamycin hydrochloride-hydrate)、链霉素 (streptomycin)、保粒霉素 (pol-yoxine)、有效霉毒 A(validamycin A) ;硝基苯基衍生物 :百螨克 (binapacryl)、消螨通 (dinobuton)、白粉克 (dinocap)、酞菌酯 (nitrthal-isopropyl)、四氯硝基苯 (tecnazen),有机金属化合物 :三苯锡盐 (fentin salt)、如三苯乙锡 (fentin-acetate)、三苯氯锡 (fentin chloride) 或三苯羟锡 (fentin hydroxide) ;含硫杂环基化合物 :腈硫醌 (dithianon)、稻瘟灵 (isoprothiolane) ;有机磷化合物 :护粒松 (edifenphos)、福赛得 (fosetyl)、福赛得铝 (fosetyl-aluminum)、丙基喜乐松 (iproben-fos)、亚磷酸和其盐、白粉松 (pyrazophos)、脱克松 (tolclofos-methyl) ;有机氯化合物 :四氯异苯腈 (chlorothalonil)、益发灵 (dichlofluanid)、二氯酚 (dichlorophen)、磺菌胺 (flusulfamide)、六氯苯 (hexachlorobenzene)、宾克隆 (pencycuron)、五氯酚和其盐、热必斯 (phthalide)、五氯硝基苯 (quintozene)、甲基多保净 (thiophanate-methyl)、甲基益发灵 (tolylfluanid)、N-(4- 氯 -2- 硝基 - 苯基)-N- 乙基 -4- 甲基 - 苯磺酰胺 ;无机活性物质 :波尔多混合物 (Bordeaux mixture)、乙酸铜、氢氧化铜、氧氯化铜、碱性硫酸铜、硫 ;联苯、溴硝丙二醇 (bronopol)、环氟菌胺 (cyflufenamid)、克绝 (cymoxanil)、二苯胺 (diphenylamin)、灭芬农 (metrafenone)、灭粉霉素 (mildiomycin)、快得宁 (oxin-copper)、调环酸钙 (prohexadione-calcium)、螺恶茂胺 (spiroxamine)、甲基益发灵、N-(环丙基甲氧基亚氨基 -(6- 二氟 - 甲氧基 -2,3- 二氟 - 苯基)- 甲基)-2- 苯基乙酰胺、N'-(4-(4- 氯 -3- 三氟甲基 - 苯氧基)-2,5- 二甲基 - 苯基)-N- 乙基 -N- 甲基甲脒、N'-(4-(4- 氟 -3- 三氟甲基 - 苯氧基)-2,5- 二甲基 - 苯基)-N- 乙基 -N- 甲基甲脒、N'-(2- 甲基 -5- 三氟甲基 -4-(3- 三甲基硅烷基 - 丙氧基)- 苯基)-N- 乙基 -N- 甲基甲脒、N'-(5- 二氟甲基 -2- 甲基 -4-(3- 三甲基硅烷基 - 丙氧基)- 苯基)-N- 乙基 -N- 甲基甲脒、2-{1-[2-(5- 甲基 -3- 三氟甲基 - 吡唑 -1- 基)- 乙酰基]- 哌啶 -4- 基 }- 噻唑 -4- 甲酸甲基 -(1,2,3,4- 四氢 - 萘 -1- 基)- 酰胺、2-{1-[2-(5- 甲基 -S- 三氟甲基 - 吡唑 -i-y0- 乙

酰基 ^- 哌啶 ^-ylJ- 噻唑 ^- 甲酸甲基 -(R)-1,2,3,4- 四氢 - 萘 -1- 基 - 酰胺、乙酸 6- 叔丁基 -8- 氟 -2,3- 二甲基 - 喹啉 -4- 基酯和甲氧基 - 乙酸 6- 叔丁基 -8- 氟 -2,3- 二甲基 - 喹啉 -4- 基酯。

[0322] G) 生长调节剂脱落酸 (abscisic acid)、先甲草胺 (amidochlor)、环丙嘧啶醇 (ancymidol)、6- 苯甲基氨基嘌呤、芸苔素内酯 (brassinolide)、比达宁 (butralin)、克美素 (chlormequat)(矮壮素 (chlormequat chloride))、氯化胆碱 (choline chloride)、环丙酸酰胺 (cyclanilide)、亚拉生长素 (daminozide)、调呋酸 (dikegulac)、获萎得 (dimethipin)、2,6- 二甲基嘌啶、益收生长素 (ethephon)、氟节胺 (flumetralin)、呋嘧醇 (flurprimidol)、氟噻乙草酯 (fluthiacet)、福芬素 (forchlorfenuron)、赤霉酸 (gibberellic acid)、依纳素 (inabenfide)、吲哚 -3- 乙酸、顺丁烯二酰肼、氟磺酰草胺 (mefluidide)、壮棉素 (mepiquat)(缩节胺 (mepiquat chloride))、萘乙酸、N-6- 苯甲基腺嘌呤、巴克素 (paclobutrazol)、调环酸 (prohexadione)(调环酸钙)、茉莉酸丙酯 (prohydrojasmon)、噻苯隆 (thidiazuron)、抑芽唑 (triapenthenol)、三硫代磷酸三丁酯 (tributyl phosphorotrithioate)、2,3,5- 三碘苯甲酸、抗倒酯 (trinexapac-ethyl) 和烯效唑 ;

[0323] H) 除草剂乙酰胺类 : 乙草胺 (acetochlor)、甲草胺 (alachlor)、去草胺 (butachlor)、二甲草胺 (dimethachlor)、噻吩草胺 (dimethenamid)、氟噻胺 (flufen-acet)、苯噻酰草胺 (mefenacet)、异丙甲草胺 (metolachlor)、吡草胺 (metazachlor)、萘丙酰草胺 (napropamide)、萘丙胺 (naproanilide)、烯草胺 (pethox-amid)、丙草胺 (pretilachlor)、毒草胺 (propachlor)、甲氧噻草胺 (thenylchlor) ; 氨基酸衍生物 : 双丙氨酰膦 (bilanafos)、草甘膦、草铵膦、草硫膦 (sulfosate) ; 芳氧基苯氧基丙酸酯类 : 炔草酸 (clodinafop)、丁基赛伏草 (cyhalofop-butyl)、噁唑禾草灵 (fenoxaprop)、吡氟禾草灵 (fluazifop)、合氯氟 (haloxyfop)、噁唑酰草胺 (metamifop)、普拔草 (propaquizafop)、快伏草 (quizalofop)、喹禾糠酯 (quizalofop-P-tefuryl) ; 联吡啶类 : 敌草快 (diquat)、百草枯 (paraquat) ;(硫代) 氨基甲酸酯类 : 黄草灵 (asulam)、苏达灭 (butylate)、草长灭 (carbetamide)、甜菜安 (desmedipham)、哌草丹 (dimepiperate)、扑草灭 (eptam, EPTC)、戊草丹 (esprocarb)、得草灭 (molinate)、坪草丹 (orbencarb)、甜菜宁 (phenmedipham)、苄草丹 (prosulfocarb)、稗草丹 (pyributicarb)、杀丹 (thiobencarb)、野麦畏 (triallate) ; 环己二酮类 : 丁苯草酮 (butroxydim)、烯草酮 (clethodim)、环杀草 (cycloxydim)、环苯草酮 (profoxydim)、稀禾定 (sethoxydim)、吡喃草酮 (tepraloxydim)、肟草酮 (tralkoxydim) ;- 二硝基苯胺类 : 氟草胺 (benfluralin)、乙丁烯氟灵 (ethalfluralin)、氨磺乐灵 (oryzalin)、二甲戊乐灵 (pendimethalin)、氨基丙氟灵 (prodiamine)、氟乐灵 (trifluralin) ; 二苯基醚类 : 三氟羧草醚 (acifluorfen)、苯草醚 (aclonifen)、治草醚 (bifenox)、禾草灵 (diclofop)、氯氟草醚 (ethoxyfen)、氟磺胺草醚 (fomesafen)、乳氟禾草灵 (lactofen)、乙氧氟草醚 (oxyfluorfen) ; 羟基苯甲腈类 : 溴草腈 (bomoxynil)、敌草腈 (dichlobenil)、碘苯腈 (ioxynil) ;- 咪唑啉酮类 : 咪草酸 (imazamethabenz)、甲氧咪草烟 (imazamox)、甲基咪草烟 (imazapic)、灭草烟 (imazapyr)、灭草喹 (imazaquin)、咪草烟 (imazethapyr) ; 苯氧基乙酸类 : 稗草胺 (clomeprop)、2,4- 二氯苯氧基乙酸 (2,4-D)、2,4-DB、滴丙酸 (dichlorprop)、

MCPA、MCPA-硫基乙基、MCPB、甲氯丙酸(Mecoprop);吡嗪类:氯草敏(chloridazon)、氟哒嗪草乙酯(flufenpyr-ethyl)、氟噻乙草酯(fluthiacet)、达草灭(norflurazon)、哒草特(pyridate);吡啶类:氯氨吡啶酸(aminopyralid)、二氯吡啶酸(clopyralid)、吡氟草胺(diflufenican)、氟硫草定(dithiopyr)、氟啶草酮(fluridone)、氟草定(fluroxypyr)、毕克烂(picloram)、氟吡草胺(picolinafen)、噻草啶(thiazopyr);磺酰脲类:酰嘧磺隆(amidosulfuron)、四唑嘧磺隆(azimsulfuron)、苄嘧磺隆(bensulfuron)、乙基氯嘧磺隆(chlorimuron-ethyl)、氯磺隆(chlorsulfuron)、醚磺隆(cinosulfuron)、环磺隆(cyclosulfamuron)、乙氧嘧磺隆(ethoxysulfuron)、嘧啶磺隆(flazasulfuron)、氟吡磺隆(flucetosulfuron)、氟啶嘧磺隆(flupyrsulfuron)、甲酰嘧磺隆(foramsulfuron)、氯吡嘧磺隆(halosulfuron)、唑吡嘧磺隆(imazosulfuron)、碘甲磺隆(iodosulfu-ron)、甲基二磺隆(mesosulfuron)、甲磺隆(metsulfuron-methyl)、烟嘧磺隆(nicosulfuron)、环氧嘧磺隆(oxasulfuron)、氟嘧磺隆(primisulfuron)、氟磺隆(prosulfuron)、吡嘧磺隆(pyrazosulfuron)、砜嘧磺隆(rimsulfuron)、甲嘧磺隆(sulfometuron)、磺酰磺隆(sulfosulfuron)、噻吩磺隆(thifensulfuron)、醚苯磺隆(triasulfuron)、苯磺隆(tribenuron)、三氟啶磺隆(trifloxysulfuron)、氟胺磺隆(triflusulfuron)、三氟甲磺隆(tritosulfuron)、1-((2-氯-6-丙基-咪唑并[1,2-b]哒嗪-3-基)磺酰基)-3-(4,6-二甲氧基-嘧啶-2-基)脲;三嗪类:莠灭净(ametryn)、莠去津(atrazine)、氰草津(cyanazine)、异戊乙净(dimethametryn)、乙嗪草酮(ethiozin)、六嗪酮(hexazinone)、苯嗪草酮(metamitron)、赛克津(metribuzin)、扑草净(prometryn)、西玛津(simazine)、特丁津(terbuthylazine)、去草净(terbutryn)、三嗪氟草胺(triaziflam);脲类:绿麦隆(chlorotoluron)、杀草隆(daimuron)、敌草隆(diuron)、伏草隆(fluometuron)、异丙隆(isoproturon)、利谷隆(linuron)、甲基苯噻隆(metha-benzthiazuron)、丁噻隆(tebuthiuron);其它乙酰乳酸合成酶抑制剂:双草醚钠(bispyribac-sodium)、氯酯磺草胺(cloransulam-methyl)、双氯磺草胺(diclosulam)、双氟磺草胺(florasulam)、氟酮磺隆(flucarbazone)、唑嘧磺草胺(flumetsulam)、磺草唑胺(metosulam)、唑嘧磺草胺(ortho-sulfamuron)、五氟磺草胺(penoxsulam)、丙苯磺隆(propoxycarbazone)、丙酯草醚(pyribambenz-propyl)、嘧啶肟草醚(pyribenzoxim)、环酯草醚(pyriftalid)、嘧草醚(pyriminobac-methyl)、嘧啶硫蕃(pyrimisulfan)、嘧硫草醚(pyrithiobac)、吡咯磺隆(pyroxasulfone)、嘧氧磺胺(pyroxsulam);其它:氨唑草酮(amicarbazone)、氨基三唑(aminotriazole)、莎稗磷(anilofos)、氟丁酰草胺(beflubutamid)、草除灵(benazolin)、酰苯草酮(bencar-bazone)、呋草黄(benfluresate)、吡草酮(benzofenap)、灭草松(bentazone)、苯并双环酮(benzobicyclon)、除草定(bromacil)、溴丁酰草胺(bromo-butide)、氟丙嘧草酯(butafenacil)、抑草磷(butamifos)、唑草胺(cafenstrole)、唑草酮(carfentrazone)、吲哚酮草酯(cinidon-ethlyl)、敌草索(chlor-thal)、环庚草醚(cinmethylin)、异噁草酮(clomazone)、苄草隆(cumyluron)、可普磺酰胺(cyprosulfamide)、麦草畏(dicamba)、野燕枯(difenzoquat)、二氟吡隆(diflufenzopyr)、稗内脐蠕孢菌(Drechslera monoceras)、草藻灭(endothal)、乙呋草黄(ethofumesate)、乙氧苯草胺(etobenzanid)、四唑酰草胺(fen-trazamide)、氟胺草酯(flumiclorac-pentyl)、丙炔氟草胺(flumioxazin)、氟胺草唑(flupoxam)、氟咯草酮

(flurochloridone)、呋草酮(flurtamone)、茚草酮(indanofan)、异噁草胺(isoxaben)、异噁唑草酮(isoxaflutole)、环草定(lenacil)、敌稗(propanil)、戊炔草胺(propyzamide)、二氯喹啉酸(quinclorac)、喹草酸(quinmerac)、甲基磺草酮(mesotrione)、甲基胂酸、萘草胺(naptalam)、丙炔噁草酮(oxadiargyl)、噁草酮(oxadiazon)、噁唑草酮(oxaziclomefone)、环戊噁草酮(pentoxazone)、唑啉草酯(pinoxaden)、双唑草腈(pyraclonil)、吡草醚(pyraflufen-ethyl)、吡磺夫特(pyrasulfo-tole)、苄草唑(pyrazoxyfen)、吡唑特(pyrazolynate)、灭藻醌(quinoclamine)、索氟纳西(saflufenacil)、磺草酮(sulcotrione)、甲磺草胺(sulfentra-zone)、特草定(terbacil)、特呋喃隆(tefuryltrione)、环磺酮(tembotrione)、噻酮磺隆(thiencarbazone)、苯吡唑草酮(topramezone)、4-羟基-3-[2-(2-甲氧基-乙氧基甲基)-6-三氟甲基-吡啶-3-羰基]-双环[3.2.1]辛-3-烯-2-酮、(3-[2-氯-4-氟-5-(3-甲基-2,6-二氧代-4-三氟甲基-3,6-二氢-2H-嘧啶-1-基)-苯氧基]-吡啶-2-基氧基)-乙酸乙酯、6-氨基-5-氯-2-环丙基-嘧啶-4-甲酸甲酯、6-氯-3-(2-环丙基-6-甲基-苯氧基)-哒嗪-4-醇、4-氨基-3-氯-6-(4-氯-苯基)-5-氟-吡啶-2-甲酸、4-氨基-3-氯-6-(4-氯-2-氟-3-甲氧基-苯基)-吡啶-2-甲酸甲酯和4-氨基-3-氯-6-(4-氯-3-二甲基氨基-2-氟-苯基)-吡啶-2-甲酸甲酯。

[0324] I)杀昆虫剂-有机(硫代)磷酸酯类:高灭磷(acephate)、甲基吡啶磷(azamethiphos)、谷硫磷(azinphos-methyl)、陶斯松(chlorpyrifos)、甲基陶斯松(chlorpyrifos-methyl)、克芬松(chlorfenvinphos)、二嗪磷(diazinon)、二氯松(dichlorvos)、百治磷(dicrotophos)、大灭松(dimethoate)、二硫松(disulfoton)、乙硫磷(ethion)、杀螟硫磷(fenitrothion)、倍硫磷(fenthion)、异噁唑磷(isoxathion)、马拉松(malathion)、达马松(methamido-phos)、杀扑磷(methidathion)、甲基巴拉松(methyl-parathion)、速灭磷(mevinphos)、久效磷(monocrotophos)、亚砜磷(oxydemeton-methyl)、巴拉奥克松(paraoxon)、巴拉松(parathion)、稻丰散(phenthoate)、伏杀磷(phosalone)、亚胺硫磷(phosmet)、磷胺(phosphamidon)、甲拌磷(phorate)、巴赛松(phoxim)、嘧啶磷(pirimiphos-methyl)、丙溴磷(profenofos)、丙硫磷(prothiofos)、杀普松(sulprophos)、乐本松(tetra-chlorvinphos)、特丁磷(terbufos)、三唑磷(triazophos)、三氯磷酸酯(trichlorfon);氨基甲酸酯类:棉灵威(alanycarb)、得灭克(aldicarb)、恶虫威(bendiocarb)、丙硫克百威(benfuracarb)、加保利(carbaryl)、加保扶(carbofuran)、丁基加保扶(carbosulfan)、苯氧威(fenoxycarb)、呋线威(furathiocarb)、灭虫威(methiocarb)、灭多虫(methomyl)、草氨酰(oxamyl)、抗蚜威(pirimicarb)、残杀威(propoxur)、硫敌克(thiodicarb)、唑蚜威(triazamate);拟除虫菊酯类:丙烯菊酯(allethrin)、联苯菊酯(bifenthrin)、赛扶宁(cyfluthrin)、赛洛宁(cyhalothrin)、苯氰菊酯(cyphenothrin)、赛灭宁(cypermethrin)、α-赛灭宁(alpha-cypermethrin)、β-赛灭宁(beta-cypermethrin)、ξ-赛灭宁(zeta-cypermethrin)、第灭宁(deltamethrin)、高氰戊菊酯(esfenvalerate)、依芬宁(etofenprox)、甲氰菊酯(fenpropathrin)、氰戊菊酯(fenvalerate)、炔咪菊酯(imiprothrin)、λ-赛洛宁(lambda-cyhalothrin)、苄氯菊酯(permethrin)、炔丙菊酯(prallethrin)、除虫菊酯(pyrethrin)I和II、苄呋菊脂(resmethrin)、氟硅菊

酯 (silafluofen)、τ- 氟胺氰菊酯 (tau-fluvalinate)、七氟菊酯 (tefluthrin)、胺菊酯 (tetramethrin)、四溴菊酯 (tralomethrin)、四氟苯菊酯 (transfluthrin)、丙氟菊酯 (profluthrin)、四氟甲醚菊酯 (dimefluthrin) ;昆虫生长调节剂 :a) 甲壳素合成抑制剂 : 苯甲酰基脲类 :克福隆 (chlorfluazuron)、赛灭净 (cyramazin)、除虫脲 (diflubenzuron)、氟环脲 (flucycloxuron)、氟芬隆 (flufenoxuron)、六伏隆 (hexaflumuron)、禄芬隆 (lufenuron)、诺伐隆 (novaluron)、氟苯脲 (teflubenzuron)、三福隆 (triflumuron) ;布芬净 (buprofezin)、苯虫醚 (diofenolan)、噻螨酮 (hexythiazox)、依杀螨 (etoxazole)、克芬螨 (clofentazine) ;b) 蜕皮激素拮抗剂 :氯虫酰肼 (halofenozide)、甲氧虫酰肼 (methoxyfenozide)、虫酰肼 (tebufenozide)、印楝素 (azadirachtin) ;c) 类幼年素 :百利普芬 (pyriproxyfen)、烯虫酯 (methoprene)、苯氧威 (fenoxycarb) ;d) 脂质生物合成抑制剂 :螺螨酯 (spirodiclofen)、螺甲螨酯 (spiromesifen)、螺虫乙酯 (spirotetramat) ; 烟碱受体激动剂 / 拮抗剂化合物 :可尼丁 (clothianidin)、呋虫胺 (dinotefuran)、益达胺 (imi-dacloprid)、噻虫嗪 (thiamethoxam)、烯啶虫胺 (nitenpyram)、啶虫脒 (acetamiprid)、噻虫啉 (thiacloprid)、1-(2- 氯 - 噻唑 -5- 基甲基)-2- 硝基亚氨基 -3,5- 二甲基 -[1,3,5] 三嗪烷 ;GABA 拮抗剂化合物 :硫丹 (endosulfan)、乙虫清 (ethiprole)、氟虫腈 (fipronil)、凡尼普罗 (vaniliprole)、氟虫腈 (pyrafluprole)、派瑞乐 (pyriprole)、5- 氨基 -1-(2,6- 二氯 -4- 甲基 - 苯基)-4- 胺亚磺酰基 -1H- 吡唑 -3- 硫代甲酸酰胺 ;巨环内酯杀昆虫剂 :阿巴汀 (abamectin)、因灭汀 (emamectin)、密灭汀 (milbemectin)、林皮没丁 (lepimectin)、赐诺杀 (spinosad)、斯平托兰 (spinetoram) ;线粒体电子传递抑制剂 (METI)I 杀螨剂 :芬杀螨 (fenazaquin)、毕达本 (pyrida-ben)、吡螨胺 (tebufenpyrad)、唑虫酰胺 (tolfenpyrad)、嘧虫胺 (flufenerim) ;METI II 和 III 化合物 : 亚醌螨 (acequinocyl)、福瑞姆 (fluacyprim)、爱美松 (hydramethylnon) ;去偶合剂 :克凡派 (chlorfenapyr) ;- 氧化磷酸化抑制剂 :锡螨丹 (cyhexatin)、丁醚脲 (diafenthiuron)、苯丁锡 (fenbutatin oxide)、克螨特 (propargite) ; 蜕皮瓦解化合物 : 赛灭净 (cryomazine) ;混合功能氧化酶抑制剂 :胡椒基丁醚 (piperonyl butoxide) ;钠通道阻断剂 :因得克 (indoxacarb)、氰氟虫腙 (metaflumizone) ;- 其它 :苯氯噻 (benclothiaz)、毕芬载 (bifenazate)、培丹 (cartap)、氟尼胺 (flonicamid)、啶虫丙醚 (pyridalyl)、吡蚜酮 (pymetrozine)、硫、杀虫环 (thiocyclam)、氟虫双酰胺 (flubendiamide)、氯虫苯甲酰胺 (chlorantraniliprole)、斯阿皮 (cyazypyr, HGW86)、腈吡螨酯 (cyenopyrafen)、吡氟硫磷 (flupyrazofos)、丁氟螨酯 (cyflumetofen)、磺胺螨酯 (amidoflumet)、新烟磷 (imicyafos)、双三氟虫脲 (bistrifluron) 和吡氟喹腙 (pyrifluquinazon)。

[0325] 此外,本发明涉及农用化学组合物,其包含以下的混合物 :至少一种式 I 化合物 (组分 1) ;和如上文所述的至少一种适用于植物保护的其它活性物质,例如选自群组 A) 到 I) 的活性物质 (组分 2),尤其一种其它杀真菌剂,例如一或多种来自群组 A) 到 F) 的杀真菌剂 ;和必要时一种适合的溶剂或固体载剂。由于那些混合物中有许多在相同施用量下对有害真菌展示出较高效率,故其备受关注。此外,以式 I 化合物与如上文所述的至少一种来自群组 A) 到 F) 的杀真菌剂的混合物对抗有害真菌相较于以个别式 I 化合物或来自群组 A) 到 F) 的个别杀真菌剂对抗那些真菌更有效。通过将式 I 化合物与至少一种来自群组 A) 到 I) 的活性物质一起施用,可获得协同效应,即获得超过个别效应的简单相加 (协同混合

物）。

[0326] 根据本发明，将式 I 化合物与至少一种其它活性物质一起施用应理解为表示杀真菌有效量的至少一种式 I 化合物和至少一种其它活性物质同时出现在作用场所（即待控制的有害真菌或其生境，如经感染的植物、植物繁殖材料（尤其种子）、表面、材料或土壤以及欲免受真菌攻击的植物、植物繁殖材料（尤其种子）、土壤、表面、材料或空间）。此可通过同时联合（例如以槽混物形式）或独立施用或依次施用式 I 化合物和至少一种其它活性物质而获得，在依次施用时选择个别施用之间的时间间隔以确保在施用其它活性物质时首先施用的活性物质仍以足够的量出现在作用场所。施用次序对于本发明的操作并不重要。

[0327] 在二元混合物中，即包含一种化合物 I（组分 1）和一种其它活性物质（组分 2）（例如一种来自群组 A）到 I）的活性物质）的本发明组合物中，组分 1 与组分 2 的重量比通常取决于所用活性物质的特性，其通常在 1:100 到 100:1 范围内，经常在 1:50 到 50:1 范围内，优选在 1:20 到 20:1 范围内，更优选地在 1:10 到 10:1 范围内，且尤其在 1:3 到 3:1 范围内。

[0328] 在三元混合物，即包含一种化合物 I（组分 1）和第一其它活性物质（组分 2）和第二其它活性物质（组分 3）（例如两种来自群组 A）到 I）的活性物质）的本发明组合物中，组分 1 与组分 2 的重量比取决于所用活性物质的特性，其优选在 1:50 到 50:1 范围内，且尤其在 1:10 到 10:1 范围内，且组分 1 与组分 3 的重量比优选在 1:50 到 50:1 范围内，且尤其在 1:10 到 10:1 范围内。

[0329] 组分可单独使用或已部分或完全彼此混合以制备本发明组合物。也可将所述组分包装且进一步作为如组成部分的试剂盒的组合型组合物使用。

[0330] 在本发明的一个实施例中，试剂盒可包括一或多种（包括所有）可以用于制备本发明农用化学组合物的组分。举例来说，试剂盒可包括一或多种杀真菌剂组分和 / 或佐剂组分和 / 或杀昆虫剂组分和 / 或生长调节剂组分和 / 或除草剂。组分中的一或多者可能已组合在一起或经预调配。在试剂盒中提供两种以上组分的那些实施例中，组分可能已经组合在一起并且按原样包装在如小瓶、瓶、罐、囊、袋或小罐的单一容器中。在其它实施例中，试剂盒的两种或两种以上组分可单独地包装，即，未经预调配。因此，试剂盒可包括一或多个单独的容器，如小瓶、罐、瓶、囊、袋或小罐，每个容器含有农用化学组合物的单独组分。在两种形式中，试剂盒的一种组分可与其它组分分开施用或一起施用，或作为本发明的组合型组合物的组分来制备本发明组合物。

[0331] 使用者通常用预配药装置、背负式喷雾器、喷雾槽或喷雾机施用本发明组合物。此处，农用化学组合物是用水和 / 或缓冲液制成所需施用浓度，适当时可添加其它助剂，且由此获得本发明的即用喷雾液或农用化学组合物。在一些实施例中，每公顷农业上适用的区域施用 50 到 500 升即用喷雾液。在一些实施例中，每公顷施用 100 到 400 升即用喷雾液。在一些实施例中，本发明提供一种用于温室施用的本发明的即用组合物的试剂盒。

[0332] 根据一个实施例，本发明组合物的个别组分，如试剂盒的部分或二元或三元混合物的部分可由使用者本人在喷雾槽中混合且适当时可添加其它助剂（槽混）。在另一实施例中，本发明组合物的个别组分或部分预混合组分，例如包含式 I 化合物和 / 或来自群组 A）到 I）的活性物质的组分可由使用者在喷雾槽中混合且适当时可添加其它助剂和添加剂（槽混）。

[0333] 在另一实施例中，本发明组合物的个别组分或部分预混合的组分，例如包含式 I 化合物和 / 或来自群组 A) 到 I) 的活性物质的组分可联合（例如在槽混之后）或相继施用。

[0334] 在一些实施例中，本发明提供一种混合物，其包含式 I 化合物（组分 1) 和至少一种选自群组 A) 的嗜球果伞素类且尤其选自亚托敏、醚菌胺、氟嘧菌酯、克收欣、肟醚菌胺、啶氧菌酯、百克敏和三氟敏的活性物质（组分 2)。

[0335] 在一些实施例中，本发明提供一种混合物，其包含式 I 化合物（组分 1) 和至少一种选自群组 B) 的羧酰胺类的活性物质（组分 2)。在一些实施例中，羧酰胺类选自由以下各者组成的群组 :必杀吩、白克列、赛达森、环酰菌胺、灭达乐、异吡瑞沙、右灭达乐、呋酰胺、达灭芬、氟吗啉、氟吡菌胺（吡考苯胺 (picobenzamid))、苯酰菌胺、加普胺、双炔酰菌胺和 N-(3',4',5'- 三氟联苯 -2- 基)-3- 二氟甲基 -1- 甲基 -1H- 吡唑 -4- 甲酰胺。

[0336] 在一些实施例中，本发明提供一种混合物，其包含式 I 化合物（组分 1) 和至少一种选自群组 C) 的唑类的活性物质（组分 2)。在一些实施例中，唑选自由以下各者组成的群组 :环克座、待克利、依普座、氟喹唑、护硅得、护汰芬、灭特座、迈克尼、平克座、普克利、丙硫菌唑、三泰芬、三泰隆、得克利、四克利、灭菌唑、扑克拉、赛座灭、苯菌灵、贝芬替和噻唑菌胺。

[0337] 在一些实施例中，本发明提供一种混合物，其包含式 I 化合物（组分 1) 和至少一种选自群组 D) 的杂环化合物的活性物质（组分 2)。在一些实施例中，群组 D) 的杂环化合物选自由以下各者组成的群组 :扶吉胺、嘧菌环胺、芬瑞莫、嘧菌胺、嘧霉胺、嗪氨灵、咯菌腈、吗菌灵、丁苯吗啉、克啉菌、苯锈啶、依普同、农利灵、凡杀同、咪唑菌酮、噻菌灵、丙氧喹啉、活化酯 -S- 甲基、四氯丹、灭菌丹、氰菌胺、喹氧灵和 5- 乙基 -6- 辛基 -[1,2,4] 三唑并 [1,5-a] 嘧啶 -7- 基胺。

[0338] 在一些实施例中，本发明提供一种混合物，其包含式 I 化合物（组分 1) 和至少一种选自群组 E) 的氨基甲酸酯类的活性物质（组分 2)。在一些实施例中，氨基甲酸酯类选自由以下各者组成的群组 :代森锰锌、代森联、甲基锌乃浦、福美双、丙森锌、苯噻菌胺和霜霉威。

[0339] 在一些实施例中，本发明提供一种混合物，其包含式 I 化合物（组分 1) 和至少一种选自在群组 F) 中给出的杀真菌剂的活性物质（组分 2)。在一些实施例中，群组 F) 的杀真菌剂选自由以下各者组成的群组 :腈硫醌、三苯锡盐（如三苯乙锡）、福赛得、福赛得铝、H3PO3 和其盐、四氯异苯腈、益发灵、甲基多保净、乙酸铜、氢氧化铜、氧氯化铜、硫酸铜、硫、克绝、灭芬农和螺恶茂胺。

[0340] 称为组分 2 的活性物质、其制备和其对抗有害真菌的活性为所属领域中已知的。在一些实施例中，这些物质为可商购的。由 IUPAC 命名法描述的化合物、其制备和其杀真菌活性也为所属领域中已知的（参看加拿大植物科学杂志 (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)。

[0341] 通过常用方式,例如通过针对式 I 化合物的组合物所给出的方式,可将活性物质的混合物制备成除活性成分以外还包含至少一种惰性成分的组合物。

[0342] 关于所述组合物的常用成分,提及针对含有式 I 化合物的组合物所给出的解释。

[0343] 本发明的活性物质的混合物如同式 I 化合物般适用作杀真菌剂。在一些实施例中,本发明的混合物和组合物适用于保护植物免于广谱植物病原性真菌。在一些实施例中,植物病原性真菌来自以下纲:子囊菌纲、担子菌、半知菌纲和卵菌纲(同义词:卵菌纲)。

[0344] 式 I 化合物和其医药学上可接受的盐也适用于治疗人类和动物的疾病,尤其作为抗霉菌剂用于治疗癌症和用于治疗病毒感染。术语“抗霉菌剂”不同于术语“杀真菌剂”,是指对抗动物病原性真菌或人类病原性真菌,即用于对抗动物、尤其哺乳动物(包括人类)和禽鸟中的真菌的药物。

[0345] 在一些实施例中,本发明提供一种药物,其包含至少一种式 I 化合物或其医药学上可接受的盐和医药学上可接受的载剂。

[0346] 在一些实施例中,本发明涉及式 I 化合物或其医药学上可接受的盐的用途,其用于制备抗霉菌药物;即,用于制备供治疗和/或预防人类病原性真菌和/或动物病原性真菌感染用的药物。

[0347] 范例

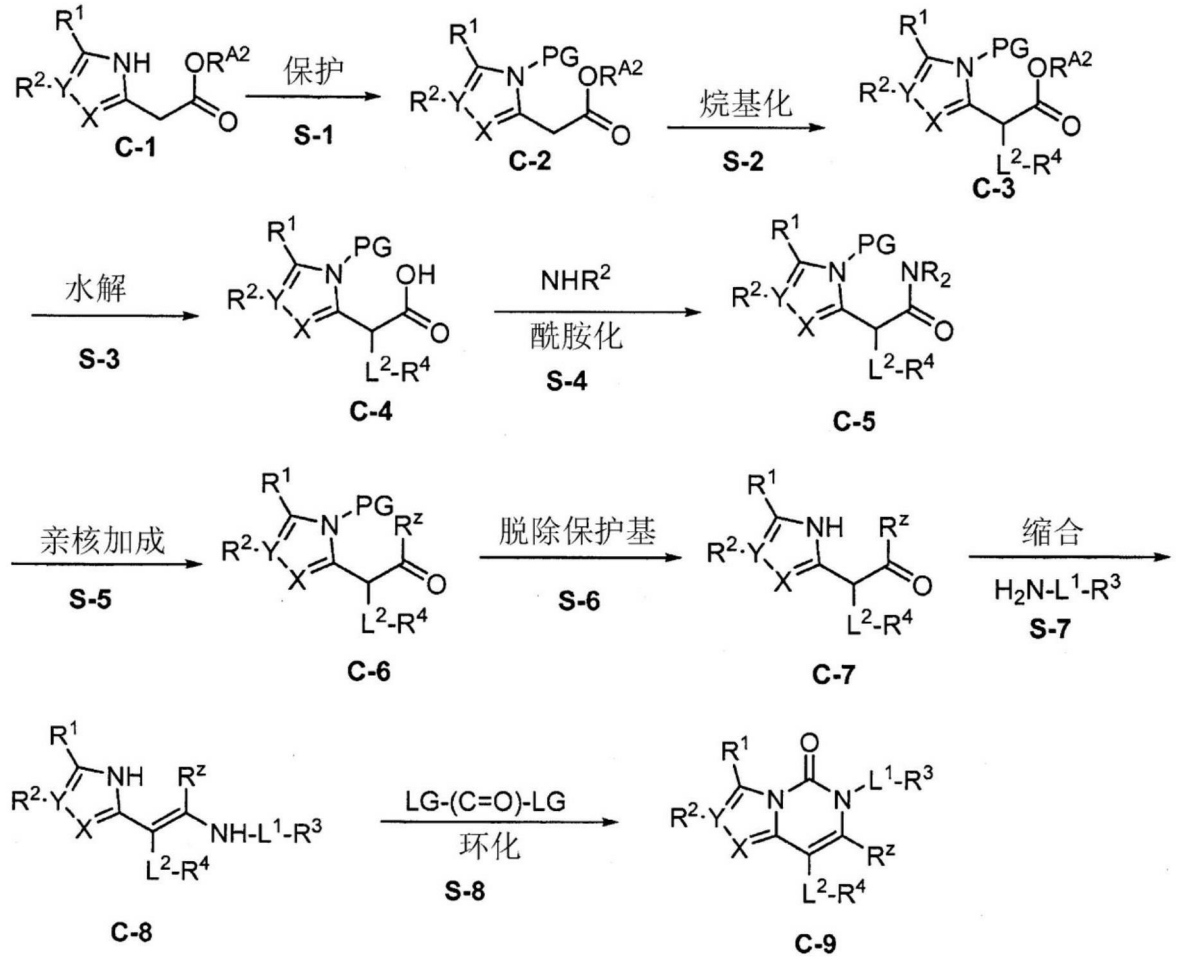
[0348] 如以下实例中所描绘,在某些示例性实施例中,化合物根据以下一般程序制备。应了解,虽然一般方法描绘了某些本发明化合物的合成,但以下一般方法和所属领域的技术人员已知的其它方法可以适用于如本文中所述的所有化合物和这些化合物中的每一者的子类和种类。

[0349] 在某些实施例中,本发明的化合物通常根据以下阐述的流程 I 制备:

[0350] 实例 1

[0351] 流程 I

[0352]



[0353] 在以上流程 I 中，LG 为离去基，PG 为保护基，且 R^1、R^2、R^3、R^4、R^z、R^{A2}、L^1、L^2、X 和 Y 中的每一者如在上文和下文中以及在如本文所述的类别和子类中所定义。

[0354] 适合的离去基 LG 包括（但不限于）烷氧基、卤素和磺酸酯。在某些实施例中，LG 为卤素。在某些实施例中，LG 为烷氧基。在某些实施例中，LG 为氯。

[0355] 适合的保护基 PG 包括（但不限于）氢解不稳定的基团、光不稳定基团和水解不稳定基团。在一些实施例中，PG 为选自苯甲基、二苯甲基、三苯甲基或氨基甲酸酯的任选经取代的基团。

[0356] 在一个方面中，本发明提供用于根据以上流程 III 中所描绘的步骤制备式 C-9 化合物的方法。在一些实施例中，在步骤 S-1 处，式 C-1 的杂环被保护以形成式 C-2 的杂环。在一些实施例中，保护基为苯甲基。在一些实施例中，保护步骤在碱存在下执行。在一些实施例中，碱为碳酸钾。在一些实施例中，步骤 S-1 在溶剂中执行。在一些实施例中，溶剂为 DMF。在一些实施例中，溶剂为丙酮。

[0357] 在一些实施例中，步骤 S-2 包含用碱和烷化剂处理式 C-2 化合物，以形成式 C-3 化合物。在一些实施例中，碱为二异丙基氨基锂 (LDA)。在一些实施例中，烷化剂为烷基卤化物。在一些实施例中，步骤 S-2 在溶剂中执行。在一些实施例中，溶剂为四氢呋喃 (THF)。

[0358] 在一些实施例中，步骤 S-3 包含用碱水溶液处理式 C-3 化合物，以形成式 C-4 的甲酸。在一些实施例中，碱为氢氧化锂。在一些实施例中，步骤 S-3 在溶剂中执行。在一些实施例中，溶剂为 THF 和水的混合物。

[0359] 在一些实施例中，步骤 S-4 包含用偶合试剂和胺处理式 C-4 化合物，以形成式 C-5

化合物。在一些实施例中，胺为N,O- 二甲基羟胺。在一些实施例中，偶合试剂为EDC。在一些实施例中，反应在EDC和添加剂两者下执行。在一些实施例中，添加剂为羟基苯并三唑(HOBT)。在一些实施例中，溶剂为DMF。

[0360] 在一些实施例中，步骤S-5包含用亲核试剂处理式C-5化合物，以形成式C-6化合物。在一些实施例中，亲核试剂为氢化锂铝。在一些实施例中，亲核试剂为有机金属试剂。在一些实施例中，溶剂为THF。在一些实施例中，溶剂为乙醚。在一些实施例中，溶剂为DCM。

[0361] 在一些实施例中，步骤S-6包含以用于移除PG的试剂或试剂的组合处理式C-6化合物，以形成式C-7化合物。在一些实施例中，试剂为氢气和钯。在一些实施例中，溶剂为乙酸乙酯。

[0362] 在一些实施例中，步骤S-7包含使式C-7化合物与胺缩合，以形成式C-8化合物。在一些实施例中，步骤S-7在干燥剂存在下执行。在一些实施例中，干燥剂为硫酸镁。在一些实施例中，干燥剂为分子筛。在一些实施例中，S-7在溶剂中执行。在一些实施例中，溶剂为DCM。

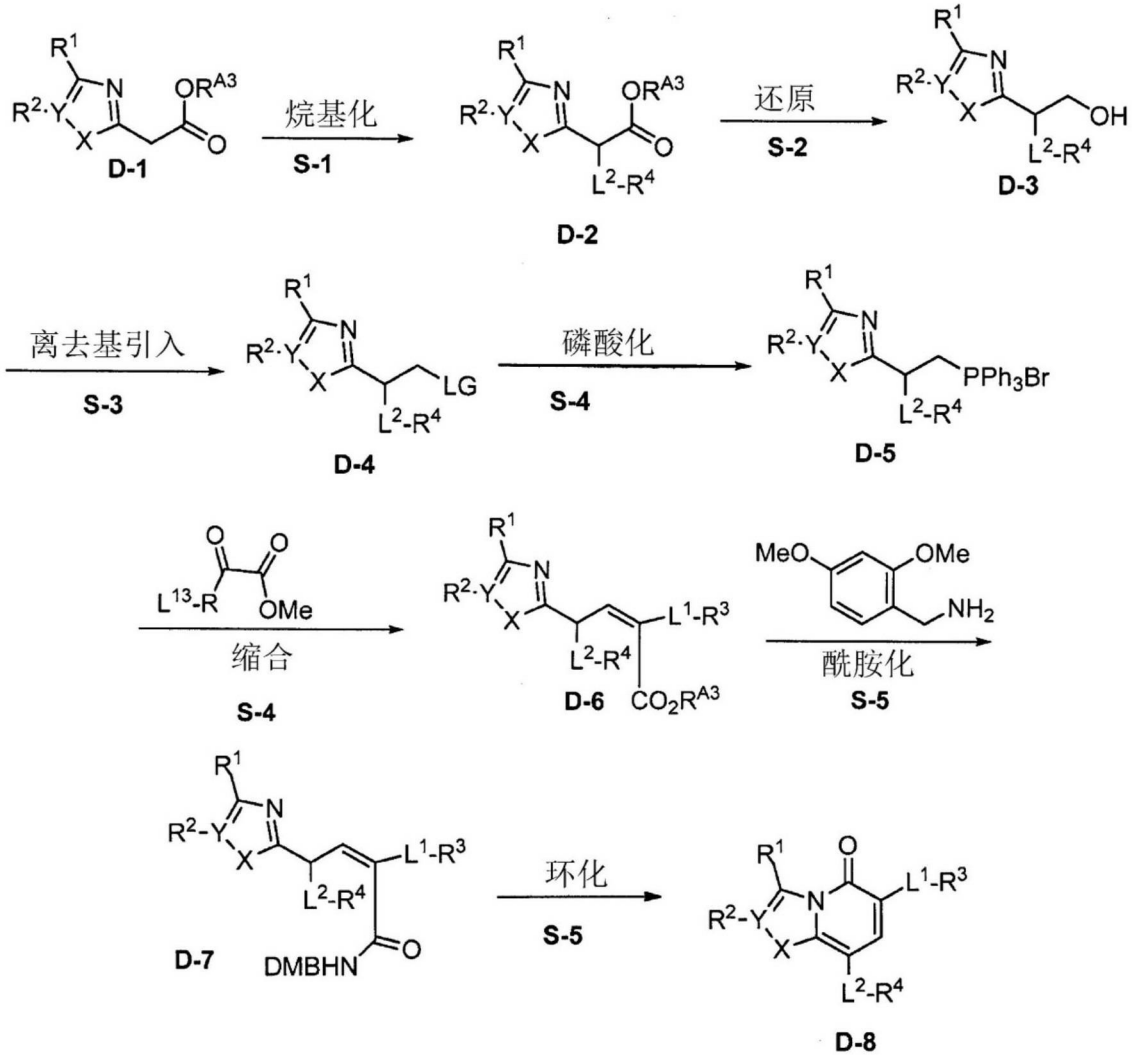
[0363] 在一些实施例中，步骤S-8包含用羰基化试剂处理式C-8化合物，以形成式C-9化合物。在一些实施例中，羰基化试剂为光气。在一些实施例中，羰基化试剂为1,1'-羰基二咪唑(CDI)(参见例如D.P.阿拉马(D.P.Arama)等人四面体通讯(Tetrahedron Letters)2013,54,1364，其全部内容以引用的方式并入本文中)。在一些实施例中，溶剂为乙腈。在一些实施例中，溶剂为二氯甲烷。

[0364] 在某些实施例中，本发明的化合物通常根据以下阐述的流程II制备：

[0365] 实例2

[0366] 流程II

[0367]



[0368] 在以上流程 II 中，LG、R^1、R^2、R^3、R^4、R^z、R^{A4}、L^1、L^2、X 和 Y 中的每一者如在上文和下文中以及在如本文所述的类别和子类中所定义。

[0369] 在一个方面中，本发明提供用于根据以上流程 II 中所描绘的步骤制备式 D-8 化合物的方法。在一些实施例中，步骤 S-1 包含用碱和烷化剂处理式 D-1 化合物以形成式 D-2 化合物。在一些实施例中，碱为二异丙基氨基锂 (LDA)。在一些实施例中，烷化剂为烷基卤化物。在一些实施例中，步骤 S-1 在溶剂中执行。在一些实施例中，溶剂为四氢呋喃 (THF)。

[0370] 在一些实施例中，步骤 S-2 包含用还原剂处理式 D-2 化合物，以形成式 D-3 化合物。在一些实施例中，还原剂为氢化锂铝。在一些实施例中，还原剂为 DIBAL-H。在一些实施例中，溶剂为 THF。在一些实施例中，溶剂为乙醚。在一些实施例中，溶剂为甲苯。

[0371] 在一些实施例中，步骤 S-3 包含使式 D-3 化合物与试剂接触以将羟基转化成离去基 LG。在一些实施例中，LG 为卤素。在一些实施例中，LG 为溴。在一些实施例中，用于将羟基转化成 LG 的试剂为三苯基膦和四溴化碳。在一些实施例中，步骤 S-3 在溶剂中执行。在一些实施例中，溶剂为 DCM。在一些实施例中，步骤 S-4 包含用三苯基膦处理式 D-4 化合物，以形成式 D-5 化合物。在一些实施例中，溶剂为甲苯。

[0372] 在一些实施例中，步骤 S-4 包含用酮酯和碱处理式 D-5 化合物，以形成式 D-6 化合物。在一些实施例中，碱为 n-BuLi。在一些实施例中，碱为叔丁醇钾。在一些实施例中，溶剂为 THF。

[0373] 在一些实施例中，步骤S-5包含用胺和路易斯酸(Lewis acid)处理式D-6化合物，以形成式D-7化合物。在一些实施例中，胺为(2,4-二甲氧基苯基)甲胺。在一些实施例中，路易斯酸为三甲基铝。

[0374] 在一些实施例中，步骤S-6包含用酸处理式D-7化合物，以形成式D-8化合物。在一些实施例中，酸为氯化氢。在一些实施例中，溶剂为乙醚。关于这些条件的应用，参见J. 弗艾特(J.Fetter)等人化学研究杂志概要(J.Chem.Res.Synopses)1995,11,444，其全部内容以引用的方式并入本文中。

[0375] 其它式I化合物以与上文描述的方式实质上类似的方式制备。

[0376] 在某些实施例中，本发明的化合物使用所属领域中已知的方法(包括哈伍德等人同工酶非选择性N经取代的联哌啶基羧酰胺乙酰基-CoA羧化酶抑制剂在经培养细胞和实验动物中降低组织丙二酰基-CoA浓度、抑制脂肪酸合成且增加脂肪酸氧化(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)，生物化学杂志，2003，第278卷，37099-37111中含有的方法)作为ACC抑制剂分析。在一些实施例中，所用分析选自体外ACC酶抑制分析、体外细胞培养物分析和动物中的体内功效分析。在一些实施例中，将本发明化合物的分析结果与针对ACC或相关酶的已知抑制剂获得的结果相比。在一些实施例中，用于比较的ACC抑制剂为CP-640186或沙罗酚A。

[0377] 本发明的化合物如由哈伍德等人，2003(其全部内容以引用的方式并入本文中)所述在体外ACC抑制分析中评估。

[0378] 实例3

[0379] 体外乙酰基-CoA羧化酶(ACC)抑制分析

[0380] 可以用于测定本发明化合物对ACC1或ACC2的抑制性作用的体外ACC抑制分析的示范性程序如下。使用来自普洛麦格(Promega)的ADP-Glo™激酶分析试剂盒。ADP-Glo™激酶分析是一种通过定量在酶反应期间产生的ADP的量来测量酶活性的发光ADP检测分析。分析在两个步骤中执行；首先，在酶反应之后，添加等体积的ADP-Glo™试剂以终止反应且耗乏剩余ATP。其次，添加激酶检测试剂，以将ADP同时转化成ATP且允许使用荧光素酶/荧光素反应测量新合成的ATP。发光可通过使用ATP到ADP转化曲线而与ADP浓度相关。详细程序如下。向384孔稀释板中添加50μL所测试的化合物(600μM于DMSO中)。化合物依次1:3稀释在DMSO中以实现每行11孔。0.5μL ACC2工作溶液添加到384孔白色Optiplate分析板中。将来自步骤2的每列中的0.5μL经稀释化合物溶液添加到分析板中，每行含有2份重复。对于最后2行，在一行中添加0.5μL阴性对照(DMSO)，且在另一行中添加0.5μL阳性对照(化合物I-97)。在室温下孵育板15分钟。向每孔中添加5μL底物工作溶液以启动反应。最终ACC2反应浓度由以下各者组成：5nM ACC2、20μM ATP、20μM乙酰基-CoA、12mM NaHCO3、0.01％Brij35、2mM DTT、5％DMSO，测试化合物浓度：30μM、10μM、3.33μM、1.11μM、0.37μM、0.123μM、0.0411μM、0.0137μM、0.00457μM、0.00152μM和0.00051μM。在室温下孵育板60分钟。添加10μL ADP glo试剂。在室温下孵育板40分钟。添加20μL激酶检测试剂。在室温下孵育板40分钟，接着在珀金埃尔

默 (Perkin Elmer)EnVision 2104 读板仪上读取呈相对光单位 (RLU) 形式的发光。

[0381] 将每个浓度以及阳性和阴性对照的数据平均化,且计算标准偏差。抑制百分比利用下式计算 :100×(平均阴性对照 - 化合物)/(平均阴性对照 - 平均阳性对照)。每个化合物的 IC50 通过将数据与以下非线性回归方程拟合来计算 :Y = 底部 +(顶部 - 底部)/(1+10^((LogIC50-X)* 希尔斜率 (HillSlope))),其中 X 为化合物浓度的对数,且 Y 为抑制百分比。

[0382] 在一些实施例中,化合物的 IC_{50}为 5-20μM。在一些实施例中,化合物的 IC_{50}≤ 5μM。在一些实施例中,化合物的 IC_{50}≤ 1μM。在一些实施例中,化合物的 IC_{50}≤ 0.1μM。在一些实施例中,化合物的 IC_{50}≤ 0.01μM。在一些实施例中,化合物的 IC_{50}≤ 0.001μM。

[0383] 实例 4

[0384] 热偏移分析

[0385] 本发明的化合物使用与由维达迪 (Vedadi) 等人“鉴别促进蛋白质稳定、蛋白质结晶和结构测定的配体的化学筛选方法 (Chemical screening methods to identify ligands that promote protein stability,protein crystallization,and structure determination)”. 美国国家科学院院刊 (PNAS)(2006) 第 103 卷 ,43,15835-15840(其全部内容以引用的方式并入本文中) 描述的那些方法实质上类似的方法在热偏移分析中加以评估。

[0386] 热偏移分析测试本发明化合物有效结合且引发蛋白质上构象变化得到其异位抑制机制的能力。

[0387] 实例 5

[0388] [^{14}C] 乙酸酯结合分析

[0389] 本发明的化合物在 [^{14}C] 乙酸酯结合分析中加以评估。测量同位素标记的乙酸酯结合到脂肪酸中的分析的示范性程序如下。将 HepG2 细胞维持在含有补充有 2mM l- 谷氨酰胺、青霉素 G(100 单位 /ml)、链霉素 100μg/ml 与 10% FBS 的 DMEM 的 T-75 烧瓶中,且在含湿气孵育箱中在 5% CO2 下在 37℃下孵育。每 2-3 天喂养细胞。在第 1 天,细胞以 1.2×105 个细胞 / 毫升 / 孔的密度用生长培养基接种于 24 孔板中。在第 3 天,用含有 10% FBS 的新鲜培养基替换培养基。在第 4 天,用含有测试化合物 (在 DMSO 中 ;最终 [DMSO] 为 0.5%) 的 0.5mL 新鲜培养基替换培养基,且在 37℃下孵育细胞 1 小时。向板的一个复本中添加 4μl[2-^{14}C] 乙酸酯 (56mCi/mmol ;1mCi/ml ;珀金埃尔默),且在 37℃、5% CO2 下孵育细胞 5 小时。向板的第二复本中添加 4μl 冷乙酸酯,且在 37℃、5% CO2 下孵育细胞 5 小时。此板用于蛋白质浓度测量。将培养基移出且置放于 15ml 离心机试管 (碧迪公司 (BD), Falcon/352096) 中。细胞用 1ml PBS 冲洗,接着抽吸,且重复冲洗和抽吸步骤。向每个孔中添加 0.5ml 0.1N NaOH,且在室温下静置以溶解细胞单层。剩余细胞悬浮液与培养基一起汇集。对于蛋白质测定板,移出一个等分试样以用于蛋白质测定 (25μl)。向含有培养基和细胞悬浮液的试管中添加 1.0ml EtOH 和 0.17ml 50% KOH。在 90℃下孵育细胞 1 小时,接着冷却到室温。每个试管添加 5ml 石油醚,剧烈振荡,在 1000rpm 下离心 5 分钟,且将 500μL 石油醚层转移到试管中以用于 Microbeta 读数,接着向每个试管中添加 2ml Aquasol-2,振荡试管,且用 Microbeta 液体闪烁计数器 (珀金埃尔默) 计数。

[0390] 丢弃剩余石油醚层，且保留脂肪酸萃取物的水相。水相用 1ml 浓 HCl 酸化，检查一或两个萃取物的 pH 以确保 pH 低于 1。每个试管添加 5ml 石油醚，剧烈振荡，在 1000rpm 下离心 5 分钟，且将 4ml 石油醚层转移到新玻璃管 (10×18mm) 中。每个试管添加 5ml 石油醚，剧烈振荡，在 1000rpm 下离心 5 分钟，且将 5ml 石油醚层转移到玻璃管中，且再次重复萃取。汇集石油醚萃取物，且蒸发到干燥过夜。在第 5 天，将来自石油醚部分的残余物再悬浮在作为载剂的含有 200μg 亚油酸的 120μL 氯仿 - 己烷 (1:1) 中。将 5μL 此物质点样到硅胶板上，且使用庚烷 - 乙醚 - 乙酸 (90:30:1) 作为洗脱剂使板显色。脂肪酸条带用碘蒸气观测，且将对应条带切出到闪烁小瓶中。向每个小瓶中添加 2ml Aquasol-2，且振荡小瓶，且在闪烁计数器上计数。

[0391] [^{14}C] 乙酸酯结合分析说明了本发明化合物抑制同位素标记的乙酸酯结合到脂肪酸中的能力。在一些实施例中，抑制在小于 100nM 的 IC_{50} 下出现。

[0392] 实例 6

[0393] 在抗真菌活性分析中评估本发明的化合物。测量各种假丝酵母属对抗真菌化合物的易感性的分析的示范性程序如下。将待测试的化合物 (包括氟康唑 (fluconazole) 和两性霉素 B(amphotericin B)) 溶解于 DMSO 中，获得浓度为 1mg/mL 的溶液。这些储备溶液使用 0.22μm 尼龙针筒过滤器无菌过滤，接着稀释在无菌水中以获得 128μg/mL 的最终浓度。

[0394] 所有种属均通过直接接种到新鲜制备的沙保罗氏右旋糖琼脂 (Sabouraud Dextrose agar，碧迪公司，Difco) 上而从冷冻储备液生长，且在环境空气中在 35℃下孵育过夜 24 小时。通过使用浸泡在无菌盐水中的无菌拭子从过夜培养物获取个别菌落来在 RPMI1640+MOPS(龙沙 (Lonza)，拜沃维泰克 (Biowhittaker)) 中制备直接悬浮液。悬浮液的浓度使用预先确定的标准曲线确定。接着，将这些悬浮液稀释到 5×10^3CFU/mL 以在按照 CLSI 指南 (M27-A3，第 28 卷第 14 期) 添加到微量滴定板中后获得 2.5×10^3CFU/mL 的最终浓度。

[0395] 培养液微量滴定 MIC 攻击板根据 CLSI 指南 (M27-A3，第 28 卷第 14 期) 制备。原始 CLSI 指南集中于在 48 小时孵育之后读取假丝酵母 MIC。由于在仅 24 小时之后读数提供清楚的患者护理的优点，故已为在 24 小时下所有药物确立 QC 限制。话虽如此，两性霉素 B 在 24 小时下无已知的解释断点，且当前氟康唑解释断点是基于 48 小时读数。在 48 小时下记录测试化合物的 MIC 断点，且对于沙罗酚对照，添加 24 小时时间点。所有 MIC 测定值均通过视觉上比较在抗生素攻击的孔中发现的生长与生长对照的生长来获得。将在稀释流程中发现的展示不生长 (或完全抑制) 的第一孔记录为 MIC。

[0396] 在一些实施例中，抗真菌活性分析说明本发明化合物具有在低 μg/mL 范围内的抗真菌活性 MIC。

[0397] 实例 7

[0398] 本发明化合物也在如由贝克尔斯等人“乙酰基 -CoA 羧化酶的化学抑制诱导癌细胞中的生长停滞和选择性细胞毒性”癌症研究 (2007)67,8180-8187 所述的癌细胞存活率分析中分析。测量在投与抑制剂化合物之后癌细胞存活百分比的分析的示范性程序如下。

[0399] 在 37℃下孵育以每 6cm 盘 4×10^5 个接种的 LNCaP(前列腺癌细胞系) 细胞，且第二天，其用递增浓度的抑制剂化合物处理且孵育。从第 0 天起使用台盼蓝染色 (trypan blue staining) 每天计数活细胞且计算死亡细胞百分比，持续 5 天。

[0400] 在一些实施例中，癌细胞存活率分析展示本发明化合物以 5μM 的浓度完全抑制细胞群体生长的能力。

[0401] 实例 8

[0402] 本发明的化合物也在如由哈伍德等人“同工酶非选择性 N 经取代的联哌啶基羧酰胺乙酰基 -CoA 羧化酶抑制剂在经培养细胞和实验动物中降低组织丙二酰基 -CoA 浓度、抑制脂肪酸合成且增加脂肪酸氧化”生物化学杂志 (2008)278,37099-37111 所述的体内脂肪酸合成研究中分析。测量结合到大鼠肝脏组织中的放射性 [C^{14}]- 乙酸酯的量的分析的示范性程序如下。

[0403] 随意给食物和水的动物用含有 0.5％甲基纤维素（媒剂）的水溶液或含有 0.5％甲基纤维素加测试化合物的水溶液以 1.0mL/200g 体重（大鼠）的体积经口处理。在化合物投与后一到四小时，动物接受 0.5mL[C^{14}]- 乙酸酯 (64μCi/mL ;56μCi/mL) 的腹膜内注射。在放射性标记的乙酸酯投与后一小时，通过 CO_2室息处死动物，且移出两片 0.75g 肝脏且在 70℃下在 1.5mL 2.5M NaOH 中皂化 120 分钟。在皂化之后，向每个样品中添加 2.5mL 无水乙醇，且将溶液混合并允许静置过夜。接着向每个样品中添加石油醚 (4.8mL)，且首先剧烈振荡混合物 2 分钟，且接着在 1000×g 下在台式 Sorvall 中离心 5 分钟。移出且丢弃含有不可皂化脂质的所得石油醚层。其余的水层通过添加 12M HCl 来酸化到 pH<2，且用 4.8mL 石油醚萃取两次。将汇集的有机部分转移到液体闪烁小瓶，在氮气下干燥，溶解于 7mL Aquasol 液体闪烁液中，且使用 Beckman 6500 液体闪烁计数器评估放射性。将记录结果为衰变数 / 分钟 (DPM)/ 毫克组织。

[0404] 在一些实施例中，体内脂肪酸合成研究展示出本发明化合物的 ED_{50}小于 0.3mg/kg 体重。

[0405] 实例 9

[0406] 本发明的化合物也在如由哈伍德等人“同工酶非选择性 N 经取代的联哌啶基羧酰胺乙酰基 -CoA 羧化酶抑制剂在经培养细胞和实验动物中降低组织丙二酰基 -CoA 浓度、抑制脂肪酸合成且增加脂肪酸氧化”生物化学杂志 (2008)278,37099-37111 所述的呼吸商测量分析中分析。测量大鼠的二氧化碳制造与耗氧量的比率的分析的示范性程序如下。

[0407] 雄性史泊格 - 多利大鼠 (Sprague-Dawley rat,350-400g) 在实验之前圈养在标准实验室条件下，饲喂普通食物、禁食或禁食且再饲喂高蔗糖膳食 2 天，将所述大鼠从其栖息笼移出，称重，且放入量热计的经密封腔室 (43″43″10cm) 中（每个腔室一只大鼠）。将腔室放入活动监视器中。在每次使用之前校准量热计，将空气流速调整到 1.6 升 / 分钟，且将系统静置和取样时间分别设定为 60 秒和 15 秒。在处理之前，每 10 分钟测量基线耗氧量、CO_2制造和可走动活动，持续最多 3 小时。在收集基线数据之后，打开腔室，且给予大鼠 0.5％甲基纤维素水溶液（媒剂对照）或含有测试化合物的 0.5％甲基纤维素水溶液的 1.0ml 经口团注，且接着使其返回到 Oxymax 腔室。每 30 分钟进行测量，在给药之后再持续 3-6 小时。饲喂媒剂对照用于评估通过媒剂投与和通过在实验过程期间 RQ 测量值的偏移（如果存在）产生的作用。过夜禁食的媒剂处理的对照用于测定最大潜在 RQ 减少。结果绘制为其随时间推移的绝对 RQ 值 (±SEM)。

[0408] 在一些实施例中，体内脂肪酸合成研究展示出本发明化合物将 RQ 降低到其基线值的约 80-90％，且展示出 RQ 的剂量依赖性降低。

[0409] 实例 10

[0410] 本发明的化合物也基于凡恩格兰德 (van Engeland) 等人“测量在培养物中附着细胞的细胞凋亡期间质膜不对称性损失的新颖分析 (A novel assay to measure loss of plasma membrane asymmetry during apoptosis of adherent cells in culture)”血细胞计数 (Cytometry)(1996)24(2),131-139 在碘化丙锭 (PI) 细胞死亡分析中分析。测量在施加药物之后完整有丝分裂细胞数量的分析的示范性程序如下。

[0411] 将肝细胞癌细胞 (如 HepG2 或 Hep3B) 以 1.106 个 /ml 的密度接种于 24 孔板的 0.5ml 培养基中,且孵育 3 小时以允许细胞附着的时间。在处理之后,细胞用实验化合物、1μM 多柔比星 (1、2) 或媒剂 (DMSO) 对照处理 120 小时。a) 首先将培养物上清液移到 2mL 聚丙烯试管中且置放在冰上 ;b) 用 0.5mL PBS 洗涤孔,将洗液体积转移到含有培养物上清液 (漂浮细胞) 的 2mL 试管中。将细胞保持在冰上。通过向孔中添加 200μL accutase 持续 5 分钟来收集。用 300μL 培养基灭活。上下吸取以混合,且将胰蛋白酶化的细胞从孔转移到具有漂浮细胞 (总体积 :1.5mL) 的 2mL 试管中。将细胞保持在冰上。在 4℃下旋转细胞 0.6rcf 持续 10 分钟。抽吸培养基。通过脉冲涡旋约 15 秒来再悬浮在 500μL 培养基中。将细胞保持在冰上。

[0412] 对于细胞计数 :在脉冲涡旋 15 秒之后,将 20μL 细胞添加到板中。将板保持在冰上。接着添加 20μL 台盼蓝,随即进行计数。用 TC10 伯乐 (biorad) 细胞计数器计数细胞。在 4℃下使细胞以 0.6rcf 旋转 10 分钟。小心地抽吸培养基。通过涡旋再悬浮在 500μL 1× 膜联蛋白结合缓冲剂中。将细胞悬浮液转移到 5mL FACS 试管中,接着添加 5μl 碘化丙锭。温和地混合细胞,且在室温下在黑暗中孵育 15 分钟。

[0413] 对于流式细胞分析,在每个时间点使用未染色 / 未处理的样品作为阴性对照,且在每个时间点使用多柔比星处理的样品作为阳性对照。使用 FACScan 流式细胞仪,且用 FlowJo 软件分析 FL2-A 直方图。

[0414] 实例 11

[0415] 还在高脂肪饮食诱发的肥胖症 (DIO) 研究中分析本发明化合物。分析的代表性方案如下。

[0416] 本发明化合物易适于作为抗肥胖症药剂、胰岛素敏化剂、高胰岛素血症逆转剂和肝性脂肪变性逆转剂供临床使用。所述活性通过在哺乳动物中相对于不含测试化合物的对照媒剂评估减少体重和体脂肪百分比,降低血浆胰岛素水平,减缓对口服葡萄糖激发作出反应的血浆胰岛素和葡萄糖水平的上升和 / 或加速其下降,且降低肝脏脂质含量的测试化合物的量来确定。在投与测试化合物之前和期间,向史泊格多利大鼠喂饲普通食物、高蔗糖饮食 (例如 AIN76A 啮齿动物饮食 ;研究饲料公司 (Research diets Inc.) 目录号 10001) 或高脂肪饮食 (例如研究饲料公司目录号 12451) 持续 3-8 周。

[0417] 通过使用基于所属领域的技术人员已知的标准程序的方法评估对脂质和碳水化合物代谢的多种参数的改变来展示本发明化合物的抗肥胖症、胰岛素敏化、高胰岛素血症逆转和肝性脂肪变性逆转潜力。举例来说,在随意喂饲普通食物、高脂肪饮食或高蔗糖饮食 3-8 周时段之后,通过使用每日一次 (Q.D.)、每日两次 (B.I.D) 或每日三次 (T.I.D.) 给药方案于水或盐水或含有 0.5% 甲基纤维素的水或盐水中经口管饲而投与测试化合物来处理继续接受饮食的动物持续 1-8 周。在研究期间的多个时间和在处死 (通过 CO_2 窒息) 时,

从未麻醉大鼠的尾静脉或从处死时动物的腔静脉收集血液到含有肝素或 EDTA 的试管中以便离心分离来制备血浆。使用所属领域的技术人员已知的方法测量与抗肥胖症、胰岛素敏化、高胰岛素血症逆转和肝性脂肪变性逆转作用相一致改变的所属领域的技术人员已知的脂质和碳水化合物代谢参数的血浆水平，所述参数包括（但不限于）胆固醇和甘油三酯、葡萄糖、胰岛素、瘦素、脂联素、酮体、游离脂肪酸和甘油。

[0418] 还可通过评估本发明化合物引起体重下降、体脂肪百分比（通过例如双能量 x 射线吸收测定 (DEXA) 分析测量）减少和血浆瘦素水平降低的潜力来展示本发明化合物的抗肥胖症潜力。还可通过使用所属领域的技术人员已知的提取和定量程序评估本发明化合物降低肝脏中的甘油三酯浓度的潜力来展示本发明化合物的抗肥胖症和肝性脂肪变性逆转潜力。还可通过使用所属领域的技术人员已知的程序评估本发明化合物减缓对口服葡萄糖激发作出反应的血浆胰岛素和葡萄糖水平的上升和 / 或加速其下降来展示本发明化合物的胰岛素敏化和高胰岛素血症逆转潜力。

[0419] 通过每日一次通过于含 0.5％甲基纤维素的盐水中以 0、3、10 和 30mg/kg 的剂量经口管饲将本发明化合物投与在起始给药之前已消耗高脂肪饮食 4 周且贯穿投与测试化合物的 2 周中继续消耗相同高脂肪饮食的史泊格多利大鼠，分析本发明化合物的抗肥胖症、胰岛素敏化、高胰岛素血症逆转和肝性脂肪变性逆转潜力。在一些实施例中，相对于不伴随食物消耗减少的媒剂处理的对照动物，本发明化合物引起总体重的剂量依赖性降低。体重降低的程度与在研究结束时测量的血浆药物水平成平行关系。本发明化合物减少已知作为全身脂肪质量的指标且因投与高脂肪饮食而增加的血浆瘦素水平。还评估接受标准普通食物饮食的动物的血浆瘦素水平（瘦型对照）以确定由本发明化合物引起的参数归一化的程度。本发明化合物使因高脂肪饮食而增加的血浆胰岛素水平降低到接近瘦型对照水平而不伴随有血浆葡萄糖水平降低，此指示在处理之后胰岛素敏感性的改进。因高脂肪饮食而升高的肝脏甘油三酯在投与本发明化合物之后以剂量依赖性方式降低，且在一些实施例中在所评估的最高剂量下归一化达到瘦型对照水平。在一些实施例中，用本发明化合物处理并不增加肝体重或肝功能标记物 ALT 和 AST。

[0420] 虽然我们已经描述多个本发明实施例，但显而易知，可以改变我们的基础实例以提供利用本发明的化合物和方法的其它实施例。因此，应了解，本发明范围应该由所附权利要求书而不是举例表示的特定实施例来界定。