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(71) Applicant (for all designated States except US): **DOW AGROSCIENCES LLC** [US/US]; 9330 Zionsville Road, Indianapolis, IN 46268-1054 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **YOUNG, David** [US/US]; 5263 Navajo Way, Carmel, IN 46033 (US). **SHABER, Steven** [US/US]; 10948 Perry Pear Drive, Zionsville, IN 46077 (US). **AVILA-ADAME, Cruz** [MX/US]; 14077 Honey Tree Drive, Carmel, IN 46032 (US). **BREAUX, Nneka** [US/US]; 1526 East Sturm Avenue, Indianapolis, IN 46201 (US). **RUIZ, James** [US/US]; 13448 Glen Oaks Court, Westfield, IN 46074 (US). **SIDDALL, Thomas** [US/US]; 1925 South 900 East, Zionsville, IN 46077 (US). **WEBSTER, Jeffery** [US/US]; 7581 W. Oakwood Court, New Palestine, IN 46163 (US).

(74) Agent: **ARNETT, Charles**; 9330 Zionsville Rd, Indianapolis, Indiana 46268 (US).

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(54) Title: FUNGICIDAL COMPOSITIONS INCLUDING HYDRAZONE DERIVATIVES AND COPPER

(57) Abstract: The present invention relates to the use of hydrazone compounds and copper for controlling the growth of fungi.



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**FUNGICIDAL COMPOSITIONS INCLUDING HYDRAZONE DERIVATIVES AND
COPPER**

Cross Reference to Related Applications

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 61/144,560, filed January 14, 2009, which is expressly incorporated by reference herein.

Field of the Invention

[0002] The present disclosure relates to hydrazone compounds, optionally with and without copper, and their use as fungicides. The compounds of the present disclosure may offer protection against ascomycetes, basidiomycetes, deuteromycetes and oomycetes.

Background

[0003] Copper is used to control the growth of organisms, especially microorganisms, in a variety of applications such as those described in the “Handbook of copper compounds and applications” edited by H. W. Richardson and published by Marcel Dekker, Inc. New York (1997), which is expressly incorporated by reference herein. These applications may include its use in agriculture to control a wide range of fungal and bacterial diseases of plants. Copper products may also be used as aquatic biocides in fresh or marine environments. Copper products may be used in antifouling applications and to control unwanted organisms in ponds and lakes based on the toxicity of copper towards algae, fungi, macrophytes and mollusks. Copper-based materials may also be used as wood preservatives and on other materials to inhibit fungal and bacterial growth. Other uses also include killing plant roots in sewer systems.

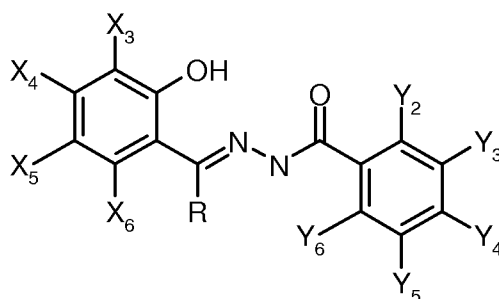
[0004] Ecological risk assessment studies have shown that copper products, which normally are applied at high use rates, may be toxic to birds, mammals, fish and other aquatic species (“Reregistration Eligibility Decision (RED) for Coppers”, EPA 738-R-06-020, July 2006, which is expressly incorporated by reference herein). Thus, while copper is a highly useful agent for controlling the growth of undesirable organisms in different environments, it is desirable to minimize the amount of copper applied.

[0005] Fungicides are compounds, of natural or synthetic origin, which act to protect and/or cure plants against damage caused by agriculturally relevant fungi. Generally, no

single fungicide is useful in all situations. Consequently, research is ongoing to produce fungicides that may have better performance, are easier to use, and cost less.

Summary of the Invention

[0006] One embodiment of the present disclosure may include compounds of Formula I:



Formula 1

wherein R is H, C1-C4 alkyl, C3-C6 cycloalkyl, C1-C4 haloalkyl, or C3-C6 halocycloalkyl,;

R1 is H, C1-C4 alkyl, C3-C6 cycloalkyl, C1-C4 haloalkyl, C3-C6 halocycloalkyl, substituted aryl, substituted heteroaryl, unsubstituted aryl, or unsubstituted heteroaryl;

X3, X4, X5, and X6 are independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 alkylthio, C1-C4 haloalkyl, C1-C4 haloalkoxy, C2-C4 haloalkenyl, C2-C4 haloalkynyl, C1-C4 haloalkylthio, -SO₂R1, SONR1R1, -CR1=NOR1, -CONR1R1, NR1COOR1, -COOR1, substituted aryl, substituted heteroaryl, unsubstituted aryl, and unsubstituted heteroaryl; and

Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 alkylthio, C1-C4 haloalkyl, C1-C4 haloalkoxy, C2-C4 haloalkenyl, C2-C4 haloalkynyl, C1-C4 haloalkylthio, -SO₂R1, SONR1R1, -R1=NOR1, -CONR1R1,

NR1COOR1, -COOR1, substituted aryl, substituted heteroaryl, unsubstituted aryl, unsubstituted heteroaryl, and phenoxy;

with the proviso that X3 and X4, X4 and X5, X5 and X6, Y2 and Y3, or Y3 and Y4 may form a 5 or 6 membered fused ring which may contain up to two heteroatoms selected from the group consisting of O, N, and S; and at least one X3, X4, X5, and X6 is C1-C4 haloalkyl.

[0007] Another embodiment of the present disclosure may include a fungicidal composition for the control or prevention of fungal attack comprising the compounds described below and a phytolegically acceptable carrier material.

[0008] Yet another embodiment of the present disclosure may include a method for the control or prevention of fungal attack on a plant, the method including the steps of applying a fungicidally effective amount of one or more of the compounds described below to at least one of the fungus, the plant, an area adjacent to the plant, and the seed adapted to produce the plant.

[0009] The term "alkyl" refers to a branched, unbranched, or cyclic carbon chain, including methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tertiary butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

[0010] The term "cycloalkyl" refers to a monocyclic or polycyclic, saturated substituent consisting of carbon and hydrogen.

[0011] The term "alkenyl" refers to a branched, unbranched or cyclic carbon chain containing one or more double bonds including ethenyl, propenyl, butenyl, isopropenyl, isobutenyl, cyclohexenyl, and the like.

[0012] The term "alkynyl" refers to a branched or unbranched carbon chain containing one or more triple bonds including propynyl, butynyl and the like.

[0013] As used throughout this specification, the term 'R' refers to the group consisting of C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C6 cycloalkyl, C1-C4 haloalkyl, C2-C4 haloalkenyl, C2-C4 haloalkynyl, or C3-C6 halocycloalkyl, unless stated otherwise.

[0014] The term "alkoxy" refers to an -OR substituent.

[0015] The term "alkylthio" refers to an -S-R substituent.

- [0016] The term “haloalkylthio” refers to an alkylthio, which is substituted with Cl, F, I, or Br or any combination thereof.
- [0017] The term “cyano” refers to a $-C\equiv N$ substituent.
- [0018] The term “hydroxyl” refers to an $-OH$ substituent.
- [0019] The term “haloalkoxy” refers to an $-OR-X$ substituent, wherein X is Cl, F, Br, or I, or any combination thereof.
- [0020] The term “haloalkyl” refers to an alkyl, which is substituted with Cl, F, I, or Br or any combination thereof.
- [0021] The term “halocycloalkyl” refers to a monocyclic or polycyclic, saturated substituent consisting of carbon and hydrogen, which is substituted with Cl, F, I, or Br or any combination thereof.
- [0022] The term “haloalkenyl” refers to an alkenyl, which is substituted with Cl, F, I, or Br or any combination thereof.
- [0023] The term “haloalkynyl” refers to an alkynyl which is substituted with Cl, F, I, or Br or any combination thereof.
- [0024] The term “halogen” or “halo” refers to one or more halogen atoms, defined as F, Cl, Br, and I.
- [0025] The term “nitro” refers to a $-NO_2$ substituent.
- [0026] The term “aryl” refers to a cyclic, aromatic substituent consisting of hydrogen and carbon.
- [0027] The term “heteroaryl” refers to a cyclic substituent that may be fully unsaturated, where the cyclic structure contains at least one carbon and at least one heteroatom, where said heteroatom is nitrogen, sulfur, or oxygen.
- [0028] Throughout the disclosure, reference to the compounds of Formula I is read as also including optical isomers and salts of Formula I, and hydrates thereof. Specifically, when Formula I contains a branched chain alkyl group, it is understood that such compounds include optical isomers and racemates thereof. Exemplary salts include: hydrochloride, hydrobromide, hydroiodide, and the like.
- [0029] Certain compounds disclosed in this document can exist as one or more isomers. The various isomers include stereoisomers, geometric isomers, diastereomers, and enantiomers. Thus, the compounds disclosed in this invention include geometric isomers, racemic mixtures, individual stereoisomers, and optically active mixtures. It will be appreciated by those skilled in the art that one isomer may be more active than the others.

The structures disclosed in the present disclosure are drawn in only one geometric form for clarity, but are intended to represent all geometric forms of the molecule.

[0030] It is also understood by those skilled in the art that additional substitution is allowable, unless otherwise noted, as long as the rules of chemical bonding and strain energy are satisfied and the product still exhibits fungicidal activity.

[0031] Another embodiment of the present disclosure is a use of a compound of Formula I, for protection of a plant against attack by a phytopathogenic organism or the treatment of a plant infested by a phytopathogenic organism, comprising the application of a compound of Formula I, or a composition comprising the compound to soil, a plant, a part of a plant, foliage, and/or seeds.

[0032] Additionally, another embodiment of the present disclosure is a composition useful for protecting a plant against attack by a phytopathogenic organism and/or treatment of a plant infested by a phytopathogenic organism comprising a compound of Formula I and a phytologically acceptable carrier material.

[0033] Additional features and advantages of the present invention will become apparent to those skilled in the art upon consideration of the following detailed description of the illustrative embodiments exemplifying the best mode of carrying out the invention as presently perceived.

Detailed Description of the Disclosure

[0034] The compounds of the present disclosure may be applied by any of a variety of known techniques, either as the compounds or as formulations comprising the compounds. For example, the compounds may be applied to the roots, seeds or foliage of plants for the control of various fungi, without damaging the commercial value of the plants. The materials may be applied in the form of any of the generally used formulation types, for example, as solutions, dusts, wettable powders, flowable concentrates, or emulsifiable concentrates.

[0035] The embodiments of the invention described herein are not intended to be exhaustive or to limit the invention to the precise forms disclosed. Rather, the embodiments selected for description have been chosen to enable one skilled in the art to practice the invention. Although the disclosure is described as a synergistic combination of copper, copper-based fungicides, or other copper-containing materials and a hydrazone or hydrazone derivative it should be understood that the concepts presented herein may be used in various applications and should not be limited.

[0036] The compounds of the present invention have fungitoxic activity against phytopathogenic fungi, against fungal pathogens of mammals, including humans, and against wood decay causing fungi. The compounds of the present invention may have broad spectrum fungitoxic activity, particularly against phytopathogenic fungi. They are active against fungi of a number of classes including Deuteromycetes (Fungi Imperfecti), Basidiomycetes, Oomycetes and Ascomycetes. More particularly, the method of this invention provides for activity against organisms including, but not limited to, *Phytophthora* species, *Plasmopara viticola*, *Pseudoperonospora cubensis*, *Pythium* species, *Pyricularia oryzae*, *Colletotrichum* species, *Helminthosporium* species, *Alternaria* species, *Septoria nodorum*, *Septoria tritici*, *Leptosphaeria nodorum*, *Ustilago maydis*, *Erysiphe graminis*, *Puccinia* species, *Sclerotinia* species, *Sphaerotheca fuliginea*, *Cercospora* species, *Rhizoctonia* species, *Uncinula necator* and *Podosphaera leucotricha*.

[0037] The method of the present invention also provides for activity against fungal pathogens of mammals (including humans) including, but not limited to, *Candida* species such as *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, and *C. tropicalis*, *Aspergillus* species such as *Aspergillus fumigatus*, *Fusarium* species, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Microsporum* species, and *Tricophyton* species. The method of the present invention also provides for activity against fungi which cause wood decay such as *Gleophyllum trabeur*, *Phialophora mutabilis*, *Poria palcenta* and *Trametes versicolor*.

[0038] Preferably, the compounds of the present disclosure are applied in the form of a formulation, comprising one or more of the compounds of Formula I with a phytolegically acceptable carrier. Concentrated formulations may be dispersed in water, or other liquids, for application, or formulations may be dust-like or granular, which may then be applied without further treatment. The formulations can be prepared according to procedures that are conventional in the agricultural chemical art.

[0039] The present disclosure contemplates all vehicles by which one or more of the compounds may be formulated for delivery and use as a fungicide. Typically, formulations are applied as aqueous suspensions or emulsions. Such suspensions or emulsions may be produced from water-soluble, water suspendible, or emulsifiable formulations which are solids, usually known as wettable powders; or liquids, usually known as emulsifiable concentrates, aqueous suspensions, or suspension concentrates. As will be readily appreciated, any material to which these compounds may be added may be used, provided it

yields the desired utility without significant interference with the activity of these compounds as antifungal agents.

[0040] Wettable powders, which may be compacted to form water dispersible granules, comprise an intimate mixture of one or more of the compounds of Formula I, an inert carrier and surfactants. The concentration of the compound in the wettable powder may be from about 10 percent to about 90 percent by weight based on the total weight of the wettable powder, more preferably about 25 weight percent to about 75 weight percent. In the preparation of wettable powder formulations, the compounds may be compounded with any finely divided solid, such as prophyllite, talc, chalk, gypsum, Fuller's earth, bentonite, attapulgit, starch, casein, gluten, montmorillonite clays, diatomaceous earths, purified silicates or the like. In such operations, the finely divided carrier and surfactants are typically blended with the compound(s) and milled.

[0041] Emulsifiable concentrates of the compounds of Formula I may comprise a convenient concentration, such as from about 10 weight percent to about 50 weight percent of the compound, in a suitable liquid, based on the total weight of the concentrate. The compounds may be dissolved in an inert carrier, which is either a water-miscible solvent or a mixture of water-immiscible organic solvents, and emulsifiers. The concentrates may be diluted with water and oil to form spray mixtures in the form of oil-in-water emulsions. Useful organic solvents include aromatics, especially the high-boiling naphthalenic and olefinic portions of petroleum such as heavy aromatic naphtha. Other organic solvents may also be used, for example, terpenic solvents, including rosin derivatives, aliphatic ketones, such as cyclohexanone, and complex alcohols, such as 2-ethoxyethanol.

[0042] Emulsifiers which may be advantageously employed herein may be readily determined by those skilled in the art and include various nonionic, anionic, cationic and amphoteric emulsifiers, or a blend of two or more emulsifiers. Examples of nonionic emulsifiers useful in preparing the emulsifiable concentrates include the polyalkylene glycol ethers and condensation products of alkyl and aryl phenols, aliphatic alcohols, aliphatic amines or fatty acids with ethylene oxide, propylene oxides such as the ethoxylated alkyl phenols and carboxylic esters solubilized with the polyol or polyoxyalkylene. Cationic emulsifiers include quaternary ammonium compounds and fatty amine salts. Anionic emulsifiers include the oil-soluble salts (e.g., calcium) of alkylaryl sulphonic acids, oil-soluble salts or sulfated polyglycol ethers and appropriate salts of phosphated polyglycol ether.

[0043] Representative organic liquids which may be employed in preparing the emulsifiable concentrates of the compounds of the present invention are the aromatic liquids such as xylene, propyl benzene fractions; or mixed naphthalene fractions, mineral oils, substituted aromatic organic liquids such as dioctyl phthalate; kerosene; dialkyl amides of various fatty acids, particularly the dimethyl amides of fatty glycols and glycol derivatives such as the *n*-butyl ether, ethyl ether or methyl ether of diethylene glycol, and the methyl ether of triethylene glycol and the like. Mixtures of two or more organic liquids may also be employed in the preparation of the emulsifiable concentrate. Organic liquids include xylene, and propyl benzene fractions, with xylene being most preferred in some cases. Surface-active dispersing agents are typically employed in liquid formulations and in an amount of from 0.1 to 20 percent by weight based on the combined weight of the dispersing agent with one or more of the compounds. The formulations can also contain other compatible additives, for example, plant growth regulators and other biologically active compounds used in agriculture.

[0044] Aqueous suspensions comprise suspensions of one or more water-insoluble compounds of Formula I, dispersed in an aqueous vehicle at a concentration in the range from about 5 to about 50 weight percent, based on the total weight of the aqueous suspension. Suspensions are prepared by finely grinding one or more of the compounds, and vigorously mixing the ground material into a vehicle comprised of water and surfactants chosen from the same types discussed above. Other components, such as inorganic salts and synthetic or natural gums, may also be added to increase the density and viscosity of the aqueous vehicle. It is often most effective to grind and mix at the same time by preparing the aqueous mixture and homogenizing it in an implement such as a sand mill, ball mill, or piston-type homogenizer.

[0045] Aqueous emulsions comprise emulsions of one or more water-insoluble pesticidally active ingredients emulsified in an aqueous vehicle at a concentration typically in the range from about 5 to about 50 weight percent, based on the total weight of the aqueous emulsion. If the pesticidally active ingredient is a solid it must be dissolved in a suitable water-immiscible solvent prior to the preparation of the aqueous emulsion. Emulsions are prepared by emulsifying the liquid pesticidally active ingredient or water-immiscible solution thereof into an aqueous medium typically with inclusion of surfactants that aid in the formation and stabilization of the emulsion as described above. This is often accomplished with the aid of vigorous mixing provided by high shear mixers or homogenizers.

[0046] The compounds of Formula I can also be applied as granular formulations, which are particularly useful for applications to the soil. Granular formulations generally contain from about 0.5 to about 10 weight percent, based on the total weight of the granular formulation of the compound(s), dispersed in an inert carrier which consists entirely or in large part of coarsely divided inert material such as attapulgite, bentonite, diatomite, clay or a similar inexpensive substance. Such formulations are usually prepared by dissolving the compounds in a suitable solvent and applying it to a granular carrier which has been preformed to the appropriate particle size, in the range of from about 0.5 to about 3 mm. A suitable solvent is a solvent in which the compound is substantially or completely soluble. Such formulations may also be prepared by making a dough or paste of the carrier and the compound and solvent, and crushing and drying to obtain the desired granular particle.

[0047] Dusts containing the compounds of Formula I may be prepared by intimately mixing one or more of the compounds in powdered form with a suitable dusty agricultural carrier, such as, for example, kaolin clay, ground volcanic rock, and the like. Dusts can suitably contain from about 1 to about 10 weight percent of the compounds, based on the total weight of the dust.

[0048] The formulations may additionally contain adjuvant surfactants to enhance deposition, wetting and penetration of the compounds onto the target crop and organism. These adjuvant surfactants may optionally be employed as a component of the formulation or as a tank mix. The amount of adjuvant surfactant will typically vary from 0.01 to 1.0 percent by volume, based on a spray-volume of water, preferably 0.05 to 0.5 volume percent. Suitable adjuvant surfactants include, but are not limited to ethoxylated nonyl phenols, ethoxylated synthetic or natural alcohols, salts of the esters or sulphosuccinic acids, ethoxylated organosilicones, ethoxylated fatty amines and blends of surfactants with mineral or vegetable oils. The formulations may also include oil-in-water emulsions such as those disclosed in U.S. Patent Application Serial No. 11/495,228, the disclosure of which is expressly incorporated by reference herein.

[0049] The formulations may optionally include combinations that contain other pesticidal compounds. Such additional pesticidal compounds may be fungicides, insecticides, herbicides, nematocides, miticides, arthropodocides, bactericides or combinations thereof that are compatible with the compounds of the present invention in the medium selected for application, and not antagonistic to the activity of the present compounds. Accordingly, in such embodiments, the other pesticidal compound is employed

as a supplemental toxicant for the same or for a different pesticidal use. The compounds of Formula I and the pesticidal compound in the combination can generally be present in a weight ratio of from 1:100 to 100:1.

[0050] For pharmaceutical use, the compounds described herein may be taken up in pharmaceutically acceptable carriers, such as, for example, solutions, suspensions, tablets, capsules, ointments, elixirs and injectable compositions. Pharmaceutical preparations may contain from 0.1% to 99% by weight of active ingredient. Preparations which are in single dose form, "unit dosage form", preferably contain from 20% to 90% active ingredient, and preparations which are not in single dose form preferably contain from 5% to 20% active ingredient. As used herein, the term "active ingredient" refers to compounds described herein, salts thereof, and mixtures of compounds described herein with other pharmaceutically active compounds. Dosage unit forms such as, for example, tablets or capsules, typically contain from about 0.05 to about 1.0 g of active ingredient.

[0051] Suitable means of administering the pharmaceutical preparations include oral, rectal, topical (including dermal, buccal and sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) and by nasogastric tube. It will be understood by those skilled in the art that the preferred route of administration will depend upon the condition being treated and may vary with factors such as the condition of the recipient.

[0052] The compounds of the present disclosure may also be combined with other fungicides to form fungicidal mixtures and synergistic mixtures thereof. The fungicidal compounds of the present disclosure are often applied in conjunction with one or more other fungicides to control a wider variety of undesirable diseases. When used in conjunction with other fungicide(s), the presently claimed compounds may be formulated with the other fungicide(s), tank mixed with the other fungicide(s) or applied sequentially with the other fungicide(s). Such other fungicides may include 2-(thiocyanatomethylthio)-benzothiazole, 2-phenylphenol, 8-hydroxyquinoline sulfate, ametocetradin, amisulbrom, antimycin, *Ampelomyces quisqualis*, azaconazole, azoxystrobin, *Bacillus subtilis*, benalaxyl, benomyl, benthiavalicarb-isopropyl, benzylaminobenzene-sulfonate (BABS) salt, bicarbonates, biphenyl, bismethiazol, bitertanol, bixafen, blasticidin-S, borax, Bordeaux mixture, boscalid, bromuconazole, bupirimate, calcium polysulfide, captafol, captan, carbendazim, carboxin, carpropamid, carvone, chloroneb, chlorothalonil, chlozolate, *Coniothyrium minitans*, copper hydroxide, copper octanoate, copper oxychloride, copper sulfate, copper sulfate

(tribasic), cuprous oxide, cyazofamid, cyflufenamid, cymoxanil, cyproconazole, cyprodinil, dazomet, debacarb, diammonium ethylenebis-(dithiocarbamate), dichlofluanid, dichlorophen, diclocymet, diclomezine, dichloran, diethofencarb, difenoconazole, difenzoquat ion, diflumetorim, dimethomorph, dimoxystrobin, diniconazole, diniconazole-M, dinobuton, dinocap, diphenylamine, dithianon, dodemorph, dodemorph acetate, dodine, dodine free base, edifenphos, enestrobin, epoxiconazole, ethaboxam, ethoxyquin, etridiazole, famoxadone, fenamidone, fenarimol, fenbuconazole, fenfuram, fenhexamid, fenoxanil, fenpiclonil, fenpropidin, fenpropimorph, fentin, fentin acetate, fentin hydroxide, ferbam, ferimzone, fluazinam, fludioxonil, flumorph, fluopicolide, fluopyram, fluoroimide, fluoxastrobin, fluquinconazole, flusilazole, flusulfamide, flutianil, flutolanil, flutriafol, fluxapyroxad, folpet, formaldehyde, fosetyl, fosetyl-aluminium, fuberidazole, furalaxyl, furametpyr, guazatine, guazatine acetates, GY-81, hexachlorobenzene, hexaconazole, hymexazol, imazalil, imazalil sulfate, imibenconazole, iminoctadine, iminoctadine triacetate, iminoctadine tris(albesilate), ipconazole, iprobenfos, iprodione, iprovalicarb, isoprothiolane, isopyrazam, isotianil, kasugamycin, kasugamycin hydrochloride hydrate, kresoxim-methyl, mancopper, mancozeb, mandipropamid, maneb, mepanipyrim, mepronil, mercuric chloride, mercuric oxide, mercurous chloride, metalaxyl, mefenoxam, metalaxyl-M, metam, metam-ammonium, metam-potassium, metam-sodium, metconazole, methasulfocarb, methyl iodide, methyl isothiocyanate, metiram, metominostrobin, metrafenone, mildiomicin, myclobutanil, nabam, nitrothal-isopropyl, nuarimol, octhilinone, ofurace, oleic acid (fatty acids), orysastrobin, oxadixyl, oxine-copper, oxpoconazole fumarate, oxycarboxin, pefurazoate, penconazole, pencycuron, penflufen, pentachlorophenol, pentachlorophenyl laurate, pen thiopyrad, phenylmercury acetate, phosphonic acid, phthalide, picoxystrobin, polyoxin B, polyoxins, polyoxorim, potassium bicarbonate, potassium hydroxyquinoline sulfate, probenazole, prochloraz, procymidone, propamocarb, propamocarb hydrochloride, propiconazole, propineb, proquinazid, prothioconazole, pyraclostrobin, pyrametostrobin, pyraoxystrobin, pyrazophos, pyribencarb, pyributicarb, pyrifenox, pyrimethanil, pyroquilon, quinoclamine, quinoxifen, quintozone, *Reynoutria sachalinensis* extract, sedaxane, silthiofam, simeconazole, sodium 2-phenylphenoxide, sodium bicarbonate, sodium pentachlorophenoxide, spiroxamine, sulfur, SYP-Z071, SYP-Z048, tar oils, tebuconazole, tebufloquin, tecnazene, tetraconazole, thiabendazole, thifluzamide, thiophanate-methyl, thiram, tiadinil, tolclofos-methyl, tolylfluanid, triadimefon, triadimenol, triazoxide, tricyclazole, tridemorph, trifloxystrobin, triflumizole, triforine, triticonazole, validamycin,

valifenalate, valiphenal, vinclozolin, zineb, ziram, zoxamide, *Candida oleophila*, *Fusarium oxysporum*, *Gliocladium* spp., *Phlebiopsis gigantea*, *Streptomyces griseoviridis*, *Trichoderma* spp., (RS)-N-(3,5-dichlorophenyl)-2-(methoxymethyl)-succinimide, 1,2-dichloropropane, 1,3-dichloro-1,1,3,3-tetrafluoroacetone hydrate, 1-chloro-2,4-dinitronaphthalene, 1-chloro-2-nitropropane, 2-(2-heptadecyl-2-imidazolin-1-yl)ethanol, 2,3-dihydro-5-phenyl-1,4-dithi-ine 1,1,4,4-tetraoxide, 2-methoxyethylmercury acetate, 2-methoxyethylmercury chloride, 2-methoxyethylmercury silicate, 3-(4-chlorophenyl)-5-methylrhodanine, 4-(2-nitroprop-1-enyl)phenyl thiocyanateme, ampropylfos, anilazine, azithiram, barium polysulfide, Bayer 32394, benodanil, benquinox, bentazon, benzamacril; benzamacril-isobutyl, benzamorf, binapacryl, bis(methylmercury) sulfate, bis(tributyltin) oxide, buthiobate, cadmium calcium copper zinc chromate sulfate, carbamorph, CECA, chlombenthiazole, chloraniformethan, chlorfenazole, chlorquinox, climbazole, cyclafuramid, cypendazole, cyprofuram, decafentin, dichlone, dichlozoline, diclobutrazol, dimethirimol, dinocron, dinosulfon, dinoterbon, dipyrithione, ditalimfos, dodicin, drazoxolon, EBP, ESBP, etaconazole, etem, ethirim, fenaminosulf, fenapanil, fenitropan, 5-fluorocytosine and profungicides thereof, fluotrimazole, furcarbanil, furconazole, furconazole-cis, furmecyclox, furophanate, glyodine, griseofulvin, halacrinat, Hercules 3944, hexylthiofos, ICIA0858, isopamphos, isovaldione, mebenil, mecarbinid, metazoxolon, methfuroxam, methylmercury dicyandiamide, metsulfovax, milneb, mucochloric anhydride, myclozolin, N-3,5-dichlorophenyl-succinimide, N-3-nitrophenylitaconimide, natamycin, N-ethylmercurio-4-toluenesulfonanilide, nickel bis(dimethyldithiocarbamate), OCH, phenylmercury dimethyldithiocarbamate, phenylmercury nitrate, phosdiphen, picolinamide UK-2A and derivatives thereof, prothiocarb; prothiocarb hydrochloride, pyracarbolid, pyridinitril, pyroxychlor, pyroxyfur, quinacetol; quinacetol sulfate, quinazamid, quinconazole, rabenzazole, salicylanilide, SSF-109, sultropen, tecoram, thiadifluor, thicyofen, thiochlorfenphim, thiophanate, thioquinox, tioxyimid, triamipfos, triarimol, triazbutil, trichlamide, urbacid, XRD-563, and zarilamide, IK-1140, and any combinations thereof.

[0053] The compounds of the present invention can also be combined with other antifungal compounds used to control infections in mammals to form fungicidal mixtures and synergistic mixtures thereof. The fungicidal compounds of the present invention can be applied in conjunction with one or more other antifungal compounds or their pharmaceutically acceptable salts to control a wider variety of undesirable diseases. When used in conjunction with other antifungal compounds, the presently claimed compounds can

be formulated with the other antifungal compound(s), coadministered with the other antifungal compound(s) or applied sequentially with the other antifungal compound(s). Typical antifungal compounds include, but are not limited to compounds selected from the group consisting of an azole such as fluconazole, voriconazole, itraconazole, ketoconazole, and miconazole, a polyene such as amphotericin B, nystatin or liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil, a purine nucleotide inhibitor such as 5-fluorocytosine, a polyoxin such as nikkomycin, and pneumocandin or echinocandin derivatives such as caspofungin and micofungin.

[0054] Additionally, the compounds of the present invention may be combined with other pesticides, including insecticides, nematocides, miticides, arthropodicides, bactericides or combinations thereof that are compatible with the compounds of the present invention in the medium selected for application, and not antagonistic to the activity of the present compounds to form pesticidal mixtures and synergistic mixtures thereof. The fungicidal compounds of the present disclosure may be applied in conjunction with one or more other pesticides to control a wider variety of undesirable pests. When used in conjunction with other pesticides, the presently claimed compounds may be formulated with the other pesticide(s), tank mixed with the other pesticide(s) or applied sequentially with the other pesticide(s). Typical insecticides include, but are not limited to: *antibiotic insecticides* such as allosamidin and thuringiensin; *macrocyclic lactone insecticides* such as spinosad and spinetoram; *avermectin insecticides* such as abamectin, doramectin, emamectin, eprinomectin, ivermectin and selamectin; *milbemycin insecticides* such as lepipmectin, milbemectin, milbemycin oxime and moxidectin; *arsenical insecticides* such as calcium arsenate, copper acetoarsenite, copper arsenate, lead arsenate, potassium arsenite and sodium arsenite; *botanical insecticides* such as anabasine, azadirachtin, *d*-limonene, nicotine, pyrethrins, cinerins, cinerin I, cinerin II, jasmolin I, jasmolin II, pyrethrin I, pyrethrin II, quassia, rotenone, ryania and sabadilla; *carbamate insecticides* such as bendiocarb and carbaryl; *benzofuranyl methylcarbamate insecticides* such as benfuracarb, carbofuran, carbosulfan, decarbofuran and furathiocarb; *dimethylcarbamate insecticides* dimitan, dimetilan, hyquincarb and pirimicarb; *oxime carbamate insecticides* such as alanycarb, aldicarb, aldoxycarb, butocarboxim, butoxycarboxim, methomyl, nitrilacarb, oxamyl, tazimcarb, thiocarboxime, thiodicarb and thiofanox; *phenyl methylcarbamate insecticides* such as allyxycarb, aminocarb, bufencarb, butacarb, carbanolate, cloethocarb, dicresyl, dioxacarb, EMPC, ethiofencarb, fenethacarb, fenobucarb, isoprocarb, methiocarb, metolcarb,

mexacarbate, promacyl, promecarb, propoxur, trimethacarb, XMC and xylylcarb; *dessicant insecticides* such as boric acid, diatomaceous earth and silica gel; *diamide insecticides* such as chlorantraniliprole, cyantraniliprole and flubendiamide; *dinitrophenol insecticides* such as dinex, dinoprop, dinosam and DNOC; *fluorine insecticides* such as barium hexafluorosilicate, cryolite, sodium fluoride, sodium hexafluorosilicate and sulfluramid; *formamidine insecticides* such as amitraz, chlordimeform, formetanate and formparanate; *fumigant insecticides* such as acrylonitrile, carbon disulfide, carbon tetrachloride, chloroform, chloropicrin, para-dichlorobenzene, 1,2-dichloropropane, ethyl formate, ethylene dibromide, ethylene dichloride, ethylene oxide, hydrogen cyanide, iodomethane, methyl bromide, methylchloroform, methylene chloride, naphthalene, phosphine, sulfuryl fluoride and tetrachloroethane; *inorganic insecticides* such as borax, calcium polysulfide, copper oleate, mercurous chloride, potassium thiocyanate and sodium thiocyanate; *chitin synthesis inhibitors* such as bistrifluron, buprofezin, chlorfluazuron, cyromazine, diflubenzuron, flucycloxuron, flufenoxuron, hexaflumuron, lufenuron, novaluron, noviflumuron, penfluron, teflubenzuron and triflumuron; *juvenile hormone mimics* such as epofenonane, fenoxycarb, hydroprene, kinoprene, methoprene, pyriproxyfen and triprene; *juvenile hormones* such as juvenile hormone I, juvenile hormone II and juvenile hormone III; *moulting hormone agonists* such as chromafenozide, halofenozide, methoxyfenozide and tebufenozide; *moulting hormones* such as α -ecdysone and ecdysterone; *moulting inhibitors* such as diofenolan; *precocenes* such as precocene I, precocene II and precocene III; *unclassified insect growth regulators* such as dicyclanil; *neriestoxin analogue insecticides* such as bensultap, cartap, thiocyclam and thiosultap; *nicotinoid insecticides* such as flonicamid; *nitroguanidine insecticides* such as clothianidin, dinotefuran, imidacloprid and thiamethoxam; *nitromethylene insecticides* such as nitenpyram and nithiazine; *pyridylmethyl-amine insecticides* such as acetamiprid, imidacloprid, nitenpyram and thiacloprid; *organochlorine insecticides* such as bromo-DDT, camphechlor, DDT, pp'-DDT, ethyl-DDD, HCH, gamma-HCH, lindane, methoxychlor, pentachlorophenol and TDE; *cyclodiene insecticides* such as aldrin, bromocyclen, chlorbicyclen, chlordane, chlordecone, dieldrin, dilor, endosulfan, alpha-endosulfan, endrin, HEOD, heptachlor, HHDN, isobenzan, isodrin, kelevan and mirex; *organophosphate insecticides* such as bromfenvinfos, chlorfenvinfos, crotoxyphos, dichlorvos, dicrotophos, dimethylvinphos, fospirate, heptenophos, methocrotophos, mevinphos, monocrotophos, naled, naftalofos, phosphamidon, propaphos, TEPP and tetrachlorvinphos; *organothiophosphate insecticides* such as dioxabenzofos, fosmethilan and

phenthoate; *aliphatic organothiophosphate insecticides* such as acethion, amiton, cadusafos, chlorethoxyfos, chlormephos, demephion, demephion-O, demephion-S, demeton, demeton-O, demeton-S, demeton-methyl, demeton-O-methyl, demeton-S-methyl, demeton-S-methylsulphon, disulfoton, ethion, ethoprophos, IPSP, isothioate, malathion, methacrifos, oxydemeton-methyl, oxydeprofos, oxydisulfoton, phorate, sulfotep, terbufos and thiometon; *aliphatic amide organothiophosphate insecticides* such as amidithion, cyanthoate, dimethoate, ethoate-methyl, formothion, mecarbam, omethoate, prothoate, sophamide and vamidothion; *oxime organothiophosphate insecticides* such as chlorphoxim, phoxim and phoxim-methyl; *heterocyclic organothiophosphate insecticides* such as azamethiphos, coumaphos, coumithoate, dioxathion, endothion, menazon, morphothion, phosalone, pyraclofos, pyridaphenthion and quinothion; *benzothiopyran organothiophosphate insecticides* such as dithicrofos and thicrofos; *benzotriazine organothiophosphate insecticides* such as azinphos-ethyl and azinphos-methyl; *isoindole organothiophosphate insecticides* such as dialifos and phosmet; *isoxazole organothiophosphate insecticides* such as isoxathion and zolaprofos; *pyrazolopyrimidine organothiophosphate insecticides* such as chlorprazophos and pyrazophos; *pyridine organothiophosphate insecticides* such as chlorpyrifos and chlorpyrifos-methyl; *pyrimidine organothiophosphate insecticides* such as butathiofos, diazinon, etrimfos, lirimfos, pirimiphos-ethyl, pirimiphos-methyl, primidophos, pyrimite and tebupirimfos; *quinoxaline organothiophosphate insecticides* such as quinalphos and quinalphos-methyl; *thiadiazole organothiophosphate insecticides* such as athidathion, lythidathion, methidathion and prothidathion; *triazole organothiophosphate insecticides* such as isazofos and triazophos; *phenyl organothiophosphate insecticides* such as azothoate, bromophos, bromophos-ethyl, carbophenothion, chlorthiophos, cyanophos, cythioate, dicapthon, dichlofenthion, etaphos, famphur, fenchlorphos, fenitrothion, fensulfothion, fenthion, fenthion-ethyl, heterophos, jodfenphos, mesulfenfos, parathion, parathion-methyl, phenkapton, phosnichlor, profenofos, prothiofos, sulprofos, temephos, trichlormetaphos-3 and trifenofos; *phosphonate insecticides* such as butonate and trichlorfon; *phosphonothioate insecticides* such as mecarphon; *phenyl ethylphosphonothioate insecticides* such as fonofos and trichloronat; *phenyl phenylphosphonothioate insecticides* such as cyanofenphos, EPN and leptophos; *phosphoramidate insecticides* such as crufomate, fenamiphos, fosthietan, mephosfolan, phosfolan and pirimetaphos; *phosphoramidothioate insecticides* such as acephate, isocarbophos, isofenphos, isofenphos-methyl, methamidophos and propetamphos; *phosphorodiamide insecticides* such as dimefox, mazidox, mipafox and schradan; *oxadiazine*

insecticides such as indoxacarb; *oxadiazoline insecticides* such as metoxadiazone; *phthalimide insecticides* such as dialifos, phosmet and tetramethrin; *pyrazole insecticides* such as tebufenpyrad, tolefenpyrad; *phenylpyrazole insecticides* such as acetoprole, ethiprole, fipronil, pyrafluprole, pyriprole and vanilprole; *pyrethroid ester insecticides* such as acrinathrin, allethrin, bioallethrin, barthrin, bifenthrin, bioethanomethrin, cyclothrin, cycloprothrin, cyfluthrin, beta-cyfluthrin, cyhalothrin, gamma-cyhalothrin, lambda-cyhalothrin, cypermethrin, alpha-cypermethrin, beta-cypermethrin, theta-cypermethrin, zeta-cypermethrin, cyphenothrin, deltamethrin, dimefluthrin, dimethrin, empenthrin, fenfluthrin, fenpirithrin, fenpropathrin, fenvalerate, esfenvalerate, flucythrinate, fluvalinate, tau-fluvalinate, furethrin, imiprothrin, meperfluthrin, metofluthrin, permethrin, biopermethrin, transpermethrin, phenothrin, prallethrin, profluthrin, pyresmethrin, resmethrin, bioresmethrin, cismethrin, tefluthrin, terallethrin, tetramethrin, tetramethylfluthrin, tralomethrin and transfluthrin; *pyrethroid ether insecticides* such as etofenprox, flufenprox, halfenprox, protrifenbute and silafluofen; *pyrimidinamine insecticides* such as flufenerim and pyrimidifen; *pyrrole insecticides* such as chlorfenapyr; *tetramic acid insecticides* such as spirotetramat; *tetronic acid insecticides* such as spiromesifen; *thiourea insecticides* such as diafenthiuron; *urea insecticides* such as flucofuron and sulcofuron; and *unclassified insecticides* such as closantel, copper naphthenate, crotamiton, EXD, fenazaflor, fenoxacrim, hydramethylnon, isoprothiolane, malonoben, metaflumizone, nifluridide, plifenate, pyridaben, pyridalyl, pyrifluquinazon, rafoxanide, sulfoxaflor, triarathene and triazamate, and any combinations thereof.

[0055] Additionally, the compounds of the present invention may be combined with herbicides that are compatible with the compounds of the present invention in the medium selected for application, and not antagonistic to the activity of the present compounds to form pesticidal mixtures and synergistic mixtures thereof. The fungicidal compounds of the present disclosure may be applied in conjunction with one or more herbicides to control a wide variety of undesirable plants. When used in conjunction with herbicides, the presently claimed compounds may be formulated with the herbicide(s), tank mixed with the herbicide(s) or applied sequentially with the herbicide(s). Typical herbicides include, but are not limited to: *amide herbicides* such as allidochlor, beflubutamid, benzadox, benzipram, bromobutide, cafenstrole, CDEA, cyprazole, dimethenamid, dimethenamid-P, diphenamid, epronaz, etnipromid, fentrazamide, flupoxam, fomesafen, halosafen, isocarbamid, isoxaben, napropamide, naptalam, pethoxamid, propyzamide, quinonamid and tebutam; *anilide*

herbicides such as chloranocryl, cisanilide, clomeprop, cypromid, diflufenican, etobenzanid, fenasulam, flufenacet, flufenican, mefenacet, mefluidide, metamifop, monalide, naproanilide, pentanochlor, picolinafen and propanil; *arylalanine herbicides* such as benzoylprop, flamprop and flamprop-M; *chloroacetanilide herbicides* such as acetochlor, alachlor, butachlor, butenachlor, delachlor, diethatyl, dimethachlor, metazachlor, metolachlor, S-metolachlor, pretilachlor, propachlor, propisochlor, prynachlor, terbuchlor, thenylchlor and xylachlor; *sulfonanilide herbicides* such as benzo-fluor, perfluidone, pyrimisulfan and profluzol; *sulfonamide herbicides* such as asulam, carbasulam, fenasulam and oryzalin; *thioamide herbicides* such as chlorthiamid; *antibiotic herbicides* such as bilanafos; *benzoic acid herbicides* such as chloramben, dicamba, 2,3,6-TBA and tricamba; *pyrimidinyloxybenzoic acid herbicides* such as bispyribac and pyriminobac; *pyrimidinylthiobenzoic acid herbicides* such as pyri-thiobac; *phthalic acid herbicides* such as chlorthal; *picolinic acid herbicides* such as aminopyralid, clopyralid and picloram; *quinolinecarboxylic acid herbicides* such as quinclorac and quinmerac; *arsenical herbicides* such as cacodylic acid, CMA, DSMA, hexaflurate, MAA, MAMA, MSMA, potassium arsenite and sodium arsenite; *benzoylcyclohexanedione herbicides* such as mesotrione, sulcotrione, tefuryltrione and tembotrione; *benzofuranyl alkylsulfonate herbicides* such as benfuresate and ethofumesate; *benzothiazole herbicides* such as benzazolin; *carbamate herbicides* such as asulam, carboxazole chlorprocarb, dichlormate, fenasulam, karbutilate and terbucarb; *carbanilate herbicides* such as barban, BCPC, carbasulam, carbetamide, CEPC, chlorbufam, chlorpropham, CPPC, desmedipham, phenisopham, phenmedipham, phenmedipham-ethyl, propham and swep; *cyclohexene oxime herbicides* such as alloxydim, butroxydim, clethodim, cloproxydim, cycloxydim, profoxydim, sethoxydim, tepraloxym and tralkoxydim; *cyclopropylisoxazole herbicides* such as isoxachlortole and isoxaflutole; *dicarboximide herbicides* such as cinidon-ethyl, flumezin, flumiclorac, flumioxazin and flumipropyn; *dinitroaniline herbicides* such as benfluralin, butralin, dinitramine, ethalfluralin, fluchloralin, isopropalin, methalpropalin, nitratin, oryzalin, pendimethalin, prodiamine, profluralin and trifluralin; *dinitrophenol herbicides* such as dinofenat, dinoprop, dinosam, dinoseb, dinoterb, DNOC, etinofen and medinoterb; *diphenyl ether herbicides* such as ethoxyfen; *nitrophenyl ether herbicides* such as acifluorfen, aclonifen, bifenox, chlormethoxyfen, chlornitrofen, etnipro-mid, fluorodifen, fluoroglycofen, fluoronitrofen, fomesafen, furyloxyfen, halosafen, lactofen, nitrofen, nitrofluorfen and oxyfluorfen; *dithiocarbamate herbicides* such as dazomet and metam; *halogenated aliphatic herbicides*

such as alorac, chloropon, dalapon, flupropanate, hexachloroacetone, iodomethane, methyl bromide, monochloroacetic acid, SMA and TCA; *imidazolinone herbicides* such as imazamethabenz, imazamox, imazapic, imazapyr, imazaquin and imazethapyr; *inorganic herbicides* such as ammonium sulfamate, borax, calcium chlorate, copper sulfate, ferrous sulfate, potassium azide, potassium cyanate, sodium azide, sodium chlorate and sulfuric acid; *nitrile herbicides* such as bromobonil, bromoxynil, chloroxynil, dichlobenil, iodobonil, ioxynil and pyraclonil; *organophosphorus herbicides* such as amiprofos-methyl, anilofos, bensulide, bilanafos, butamifos, 2,4-DEP, DMPA, EBEP, fosamine, glufosinate, glufosinate-P, glyphosate and piperophos; *phenoxy herbicides* such as bromofenoxim, clomeprop, 2,4-DEB, 2,4-DEP, difenopenten, disul, erbon, etnipromid, fenteracol and trifopstime; *oxadiazoline herbicides* such as methazole, oxadiargyl, oxadiazon; *oxazole herbicides* such as fenoxasulfone; *phenoxyacetic herbicides* such as 4-CPA, 2,4-D, 3,4-DA, MCPA, MCPA-thioethyl and 2,4,5-T; *phenoxybutyric herbicides* such as 4-CPB, 2,4-DB, 3,4-DB, MCPB and 2,4,5-TB; *phenoxypropionic herbicides* such as cloprop, 4-CPP, dichlorprop, dichlorprop-P, 3,4-DP, fenoprop, mecoprop and mecoprop-P; *aryloxyphenoxypropionic herbicides* such as chlorazifop, clodinafop, clofop, cyhalofop, diclofop, fenoxaprop, fenoxaprop-P, fenthiafop, fluazifop, fluazifop-P, haloxyfop, haloxyfop-P, isoxapyrifop, metamifop, propaquizafop, quizalofop, quizalofop-P and trifop; *phenylenediamine herbicides* such as dinitramine and prodiamine; *pyrazole herbicides* such as pyroxasulfone; *benzoylpyrazole herbicides* such as benzofenap, pyrasulfotole, pyrazolynate, pyrazoxyfen, and topramezone; *phenylpyrazole herbicides* such as fluazolate, nipyraclufen, pioxaden and pyraflufen; *pyridazine herbicides* such as credazine, pyridafol and pyridate; *pyridazinone herbicides* such as brompyrazon, chloridazon, dimidazon, flufenpyr, metflurazon, norflurazon, oxapyrazon and pydanon; *pyridine herbicides* such as aminopyralid, cliodinate, clopyralid, dithiopyr, fluroxypyr, haloxydine, picloram, picolinafen, pyriclor, thiazopyr and triclopyr; *pyrimidinediamine herbicides* such as iprymidam and tioclorim; *quaternary ammonium herbicides* such as cyperquat, diethamquat, difenzoquat, diquat, morfamquat and paraquat; *thiocarbamate herbicides* such as butylate, cycloate, di-allate, EPTC, esprocarb, ethiolate, isopolinate, methiobencarb, molinate, orbencarb, pebulate, prosulfocarb, pyributicarb, sulfallate, thiobencarb, tiocarbamil, tri-allate and vernolate; *thiocarbonate herbicides* such as dimexano, EXD and propan; *thiourea herbicides* such as methiuron; *triazine herbicides* such as dipropetryn, indaziflam, triaziflam and trihydroxytriazine; *chlorotriazine herbicides* such as atrazine, chlorazine, cyanazine, cyprazine, eglazine, ipazine, mesoprazine, procyazine,

proglinazine, propazine, sebuthylazine, simazine, terbuthylazine and trietazine; *methoxytriazine herbicides* such as atraton, methometon, prometon, secbumeton, simeton and terbumeton; *methylthiotriazine herbicides* such as ametryn, aziprotryne, cyanatryn, desmetryn, dimethametryn, methoprotryne, prometryn, simetryn and terbutryn; *triazinone herbicides* such as ametridione, amibuzin, hexazinone, isomethiozin, metamitron and metribuzin; *triazole herbicides* such as amitrole, cafenstrole, epronaz and flupoxam; *triazolone herbicides* such as amicarbazone, bencarbazone, carfentrazone, flucarbazone, ipfencarbazone, propoxycarbazone, sulfentrazone and thiencarbazone-methyl; *triazolopyrimidine herbicides* such as cloransulam, diclosulam, florasulam, flumetsulam, metosulam, penoxsulam and pyroxsulam; *uracil herbicides* such as benzfendizone, bromacil, butafenacil, flupropacil, isocil, lenacil, saflufenacil and terbacil; *urea herbicides* such as benzthiazuron, cumyluron, cycluron, dichloralurea, diflufenzopyr, isonoruron, isouron, methabenzthiazuron, monisouron and noruron; *phenylurea herbicides* such as anisuron, buturon, chlorbromuron, chloreturon, chlorotoluron, chloroxuron, daimuron, difenoxuron, dimefuron, diuron, fenuron, fluometuron, fluothiuron, isoproturon, linuron, methiuron, methylglyphosate, metobenzuron, metobromuron, metoxuron, monolinuron, monuron, neburon, parafluron, phenobenzuron, siduron, tetrafluron and thidiazuron; *pyrimidinylsulfonyleurea herbicides* such as amidosulfuron, azimsulfuron, bensulfuron, chlorimuron, cyclosulfamuron, ethoxysulfuron, flazasulfuron, flucetosulfuron, flupyralsulfuron, foramsulfuron, halosulfuron, imazosulfuron, mesosulfuron, metazosulfuron, nicosulfuron, orthosulfamuron, oxasulfuron, primisulfuron, propyrisulfuron, pyrazosulfuron, rimsulfuron, sulfometuron, sulfosulfuron and trifloxysulfuron; *triazinylsulfonyleurea herbicides* such as chlorsulfuron, cinosulfuron, ethametsulfuron, iodosulfuron, metsulfuron, prosulfuron, thifensulfuron, triasulfuron, tribenuron, triflurosulfuron and tritosulfuron; *thiadiazolyleurea herbicides* such as buthiuron, ethidimuron, tebuthiuron, thiazafluron and thidiazuron; and *unclassified herbicides* such as acrolein, allyl alcohol, aminocyclopyrachlor, azafenidin, bentazone, benzobicyclon, bicyclopypyrone, buthidazole, calcium cyanamide, cambendichlor, chlorfenac, chlorfenprop, chlorflurazole, chlorflurenol, cinmethylin, clomazone, CPMF, cresol, cyanamide, ortho-dichlorobenzene, dimepiperate, endothal, fluoromidone, fluridone, flurochloridone, flurtamone, fluthiacet, indanofan, methyl isothiocyanate, OCH, oxaziclomefone, pentachlorophenol, pentoxazone, phenylmercury acetate, prosulfalin, pyribenzoxim, pyriftalid, quinochloramine, rhodethanil, sulglycapin, thidiazimin, tridiphane, trimeturon, tripropindan and tritac.

[0056] The compounds have broad ranges of efficacy as fungicides. The exact amount of the hydrazones and copper-containing materials to be applied is dependent not only on the specific active materials being applied and relative amounts of hydrazone and copper in the mixtures, but also on the particular action desired, the fungal species to be controlled, and the stage of growth thereof, as well as the part of the plant or other product to be contacted with the compound. Thus, all the compounds, and formulations containing the same, may not be equally effective at similar concentrations or against the same fungal species.

[0057] Another embodiment of the present disclosure is a method for the control or prevention of fungal attack. This method comprises applying to the soil, plant, roots, foliage, seed or locus of the fungus, or to a locus in which the infestation is to be prevented (for example applying to cereal or grape plants), a fungicidally effective amount of one or more of the compounds of Formula I. The compounds are suitable for treatment of various plants at fungicidal levels, while exhibiting low phytotoxicity. The compounds may be useful both in a protectant and/or an eradicant fashion.

[0058] The compounds have been found to have significant fungicidal effect particularly for agricultural use. Many of the compounds are particularly effective for use with agricultural crops and horticultural plants.

[0059] It will be understood by those in the art that the efficacy of the compound for the foregoing fungi establishes the general utility of the compounds as fungicides.

[0060] The compounds are effective in use with plants in a disease-inhibiting and phytologically acceptable amount. The term "disease-inhibiting and phytologically acceptable amount" refers to an amount of a compound that kills or inhibits the plant disease for which control is desired, but is not significantly toxic to the plant. This amount will generally be from about 0.1 to about 1000 ppm (parts per million), with 1 to 500 ppm being preferred. The exact amount of a compound required varies with the fungal disease to be controlled, the type of formulation employed, the method of application, the particular plant species, climate conditions, and the like. A suitable application rate is typically in the range from about 0.10 to about 4 pounds/acre (about 0.01 to 0.45 grams per square meter, g/m²).

[0061] For foliar control of fungal infections on plants, the amount of copper used in mixture with hydrazone may range from 0.001 to 5 kg/ha, and preferably from 0.05 to 1 kg/ha. The amount of hydrazone used in mixture with copper may range from 0.001 to 5 kg/ha, and preferably from 0.05 to 1 kg/ha. The molar ratio of copper to hydrazone may

range from 0.1:1 to 10,000:1, preferably from 0.5:1 to 1000:1 and more preferably from 1:1 to 20:1.

[0062] It should be understood that the preferred amount of a copper material to be mixed with hydrazone in a given application may be influenced by availability of copper from other sources such as copper present in the soil or irrigation water, copper present on the foliage from natural sources, copper applied for fungal or bacterial disease control, copper applied as a fertilizer component, copper present in the water used in preparing fungicide solutions for application such as in spray application, copper present in formulations used in preparing spray solutions or dusts for application, or any other suitable copper source.

[0063] For fungal control the hydrazone may be applied before or after the application of copper such that the mixture is generated in the location where fungal control is desired. Additionally, multiple applications of copper or the hydrazone may be applied.

[0064] As a seed protectant, the amount of toxicant coated on the seed is usually at a dosage rate of about 10 to about 250 grams (g) and preferably from about 20 to about 60 g per 50 kilograms of seed. As a soil fungicide, the chemical can be incorporated in the soil or applied to the surface usually at a rate of 0.5 to about 20 kg and preferably about 1 to about 5 kg per hectare.

[0065] The compounds of the present invention may have broad spectrum fungitoxic activity, particularly against phytopathogenic fungi. They are active against fungi of a number of classes including Deuteromycetes (Fungi Imperfecti), Basidiomycetes, Oomycetes and Ascomycetes. More particularly, the method of this invention provides for activity against organisms including, but not limited to, *Phytophthora* species, *Plasmopara viticola*, *Pseudoperonospora cubensis*, *Pythium* species, *Pyricularia oryzae*, *Colletotrichum* species, *Helminthosporium* species, *Alternaria* species, *Septoria nodorum*, *Septoria tritici*, *Leptosphaeria nodorum*, *Ustilago maydis*, *Erysiphe graminis*, *Puccinia* species, *Sclerotinia* species, *Sphaerotheca fuliginea*, *Cercospora* species, *Rhizoctonia* species, *Uncinula necator* and *Podosphaera leucotricha*.

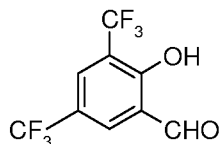
[0066] Any range or desired value given herein may be extended or altered without losing the effects sought, as is apparent to the skilled person for an understanding of the teachings herein.

[0067] The compounds of Formula I may be made using well-known chemical procedures. Intermediates not specifically mentioned in this disclosure are either commercially available, may be made by routes disclosed in the chemical literature, or may

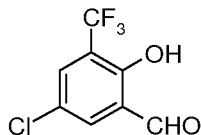
be readily synthesized from commercial starting materials utilizing standard procedures. Methods for preparation of salicylaldehyde benzoylhydrazones and 2-hydroxyphenylketone benzoylhydrazones from salicylaldehydes or 2-hydroxyphenyl ketones and a benzoic hydrazide are well known in the literature. In addition the preparation of metal complexes of these materials is also well known (see for example *Journal of Inorganic Biochemistry* **1999**, 77, 125-133 and *Inorganica Chimica Acta* **2007**, 360, 1753-1761, which are expressly incorporated by reference herein). Methods of preparation of precursor hydrazides are also well known. Hydrazides can be prepared, for example, from carboxylic acids such as in Maxwell et al., *J. Med. Chem.* **1984**, 27, 1565-1570, and from carboxylic esters such as in Dydio et al., *J. Org. Chem.* **2009**, 74, 1525-1530, both of which are expressly incorporated by reference herein. Thus, the synthesis of any benzoylhydrazone of the present invention and its metal complex(es) is fully described where the starting aldehyde or ketone, and the starting benzoic hydrazide, acid, or ester are described. The hydrazones disclosed may also be in the form of pesticidally acceptable salts and hydrates. Example 11 below provides a typical method for the preparation of such benzoylhydrazones. Example 15 below provides a general method for the preparation of their metal complexes.

[0068] The following examples are presented to illustrate the various aspects of the compounds of the present disclosure and should not be construed as limitations to the claims.

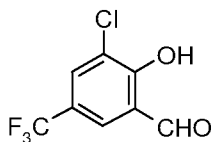
Example 1. Preparation of 2-hydroxy-3,5-bis-trifluoromethylbenzaldehyde



[0069] 3,5-Bis(trifluoromethyl)anisaldehyde (prepared as in Sui and Macielag, *Synth. Commun.* **1997**, 27, 3581-3590, which is expressly incorporated by reference herein; 2.0 grams (g), 7.7 millimoles (mmol)) was dissolved in dry dichloromethane (CH_2Cl_2 ; 15 milliliters (mL), cooled to -78°C and treated in portions with boron tribromide (BBr_3 , 1 M solution in CH_2Cl_2 ; 8.0 mL, 8.0 mmol). The mixture was stirred and allowed to warm to 25°C . After 20 hours (h), the mixture was cooled to -40°C , carefully treated with water (H_2O ; 10 mL) and warmed to room temperature. The separated organic phase was washed with H_2O (10 mL), saturated (satd) sodium chloride (NaCl) solution (5 mL), dried over sodium sulfate (Na_2SO_4) and evaporated. The residue was purified by silica gel chromatography with a 0 to 20% gradient of ethyl acetate (EtOAc) in hexane to give the aldehyde (1.4 g, 70%) as an oil: ^1H NMR (400 MHz, CDCl_3) δ 12.05 (s, 1H), 10.02 (s, 1H), 8.07 (s, 2 H);. EIMS m/z 258.

Example 2. Preparation 5-chloro-2-hydroxy-3-trifluoromethylbenzaldehyde

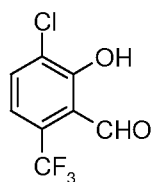
[0070] 5-Chloro-2-fluorobenzotrifluoride (1.5 grams (g), 7.5 millimoles (mmol)) was dissolved in dry tetrahydrofuran (THF; 10 milliliters (mL)), treated with tetramethylethylenediamine (TMEDA; 1.6 mL, 1.2 g, 11 mmol), cooled to -78 °C and treated in portions with *n*-butyl lithium (*n*-BuLi, 2.5 M in hexanes; 3.9 mL, 9.8 mmol). After stirring at -78 °C for 90 minutes (min), the mixture was treated with *N,N*-dimethylformamide (DMF; 770 microliters (μL), 730 milligrams (mg), 10 mmol) and stirred for a further 30 min. The cooling bath was removed and mixture warmed to 25 °C over 30 min. The reaction was quenched by the addition of satd ammonium chloride (NH₄Cl) solution and then diluted with diethyl ether (Et₂O; 30 mL). The separated organic phase was washed with satd NaCl solution (10 mL), dried (Na₂SO₄) and evaporated. The residue was dissolved in dry methanol (CH₃OH; 10 mL) and treated with 30% sodium methoxide solution in CH₃OH (14 g). The mixture was stirred at 25 °C for 20 h, diluted with H₂O (50 mL) and extracted with Et₂O (2 x 40 mL). The combined organic phases were washed with satd NaCl solution (20 mL), dried (Na₂SO₄) and evaporated. The residue was purified by silica gel chromatography using a 0 to 10% EtOAc gradient in hexane to give the benzaldehyde (1.1 g). This material (1.0 g, 4.2mmol) was dissolved in dry CH₂Cl₂ (10 mL), cooled to -78 °C and treated with BBr₃ (1 M solution in CH₂Cl₂; 5 mL, 5 mmol). The mixture was allowed to warm to 25 °C and stirred for 22 h. After cooling to -45 °C, the mixture was treated with H₂O (5 mL), warmed to 25 °C and extracted with EtOAc (2 x 15 mL). The combined extracts were washed with satd NaCl solution (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by silica gel chromatography using a 0 to 10% EtOAc gradient in hexane to give the aldehyde (950 mg): ¹H NMR (400 MHz, CDCl₃) δ 11.61 (s, 1H), 9.91 (s, 1H), 7.77 (dd, *J* = 18.5, 2.6 Hz, 2H); EIMS *m/z* 224.

Example 3. Preparation of 3-chloro-2-hydroxy-5-trifluoromethylbenzaldehyde

[0071] 3-Chloro-2-fluoro-5-trifluoromethylbenzaldehyde (5.0 g, 22 mmol) was dissolved in dry CH₃OH (50 mL), treated with 25% sodium methoxide solution (30 mL) and

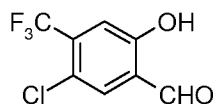
heated to reflux for 2 h. After cooling, the volatiles were removed by evaporation, and the residue was taken up in H₂O (20 mL) plus Et₂O (80 mL). The aqueous phase was extracted with Et₂O (50 mL), and the combined organic phases were washed with satd NaCl solution (15 mL), dried (Na₂SO₄) and evaporated. The residue was dissolved in dry CH₂Cl₂ (50 mL), cooled to -78 °C and treated with BBr₃ (1 M solution in CH₂Cl₂; 25 mL, 25 mmol). After warming to 25 °C, the mixture was stirred for 21 h, cooled to -40 °C and quenched by addition of H₂O (30 mL). After warming, the aqueous phase was extracted with CH₂Cl₂ (30 mL) and the combined organic phases were washed with satd NaCl solution (30 mL), dried (Na₂SO₄) and evaporated. The residue was purified by silica gel chromatography with 0-20% EtOAc gradient in hexane to give the aldehyde (2.7 g): ¹H NMR (400 MHz, CDCl₃) δ 11.81 (s, 1H), 9.96 (s, 1H), 7.87 (d, *J* = 2.1 Hz, 1H), 7.84–7.77 (m, 1H); EIMS *m/z* 224.

Example 4. Preparation of 3-chloro-2-hydroxy-6-trifluoromethylbenzaldehyde



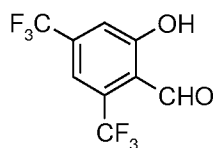
[0072] 4-Chloro-3-fluoro-6-trifluoromethylbenzaldehyde (1.0 g, 4.4 mmol) was dissolved in dry CH₃OH (10 mL), treated with 30% sodium methoxide in CH₃OH (7.9 g, 44 mmol) and heated at reflux for 1 h. After cooling, the mixture was diluted with H₂O (15 mL) and extracted with Et₂O (2 x 30 mL). The combined ether extracts were washed with satd NaCl solution (10 mL), dried (Na₂SO₄), and evaporated. The residue was purified by silica gel chromatography with 0-10% EtOAc/hexane to give the anisole intermediate (1.0 g). This material was dissolved in dry CH₂Cl₂ (15 mL), cooled to -78 °C, treated with BBr₃ (1 M in CH₂Cl₂; 5.0 mL, 5 mmol), allowed to warm to 25 °C and stirred for 20 h. The reaction was cooled in ice and quenched by addition of H₂O (10 mL). The separated organic phase was washed with satd NaCl solution (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by silica gel chromatography with 0-10% EtOAc/hexane to give the aldehyde (980 mg): ¹H NMR (400 MHz, CDCl₃) δ 12.78 (s, 1H), 10.28 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H); EIMS *m/z* 224.

Example 5. Preparation of 5-chloro-2-hydroxy-4-trifluoromethylbenzaldehyde

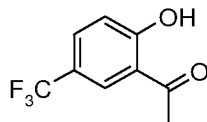


[0073] 2-Chloro-5-hydroxybenzotrifluoride (5.0 g, 25 mmol) was dissolved in acetic acid (50 mL) and treated with bromine (4.8 g, 30 mmol). The mixture was stirred at 25 °C for 6 h and poured into H₂O (200 mL) with stirring. The precipitated phenol was collected by filtration and washed well with H₂O. The solid was taken up in EtOAc (150 mL), washed with satd NaCl solution (50 mL), dried (Na₂SO₄) and evaporated to give the product (6.0 g, circa 90% pure). This material (2.0 g, 7.3 mmol) was dissolved in dry THF (65 mL), cooled to -78 °C and treated dropwise with *n*-BuLi (2.5 M in hexanes; 6.4 mL, 16 mmol). The mixture was stirred for 90 min at -78 °C and treated with DMF (1.4 mL, 1.3 g, 18 mmol). After stirring at -78 °C for 30 min, the mixture was warmed to 25 °C, quenched with satd NH₄Cl solution (10 mL) and worked up with H₂O (30 mL) and Et₂O (75 mL). The organic phase was washed with satd NaCl solution (20 mL), dried (Na₂SO₄) and evaporated. The residue was purified by reverse-phase high-performance liquid chromatography (RP-HPLC) to give the product (300 mg, circa 70% purity), which was used without further purification: EIMS *m/z* 224.

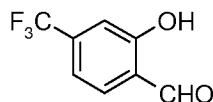
Example 6. Preparation of 2-hydroxy-4,6-bis-trifluoromethyl-benzaldehyde



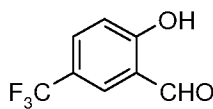
[0074] 3,5-Bis(trifluoromethyl)anisole (5.0 g 21 mmol) and TMEDA (4.0 mL, 3.0 g, 26 mmol) were dissolved in dry Et₂O (60 mL), cooled to -10 °C and treated in portions with *n*-BuLi (2.5 M in hexanes; 10 mL, 25 mmol) warmed to 25 °C and stirred for 90 min. The mixture was cooled to -78 °C, treated dropwise with DMF (2.3 mL, 2.2 g, 30 mmol), stirred for 30 min, warmed to 25 °C and stirred for 30 min. The reaction was quenched by addition of H₂O (50 mL) and extracted with Et₂O (2 x 75 mL). The combined organic fractions were washed with satd NaCl solution (30 mL), dried (Na₂SO₄) and evaporated. The residue was purified by silica gel chromatography to give the anisaldehyde derivative (3.3 g). This material (3.0 g, 11 mmol) was dissolved in CH₂Cl₂ (75 mL), cooled to -78 °C and treated with BBr₃ (1 M solution in CH₂Cl₂; 12 mL, 12 mmol). The mixture was stirred for 30 min at -78 °C, warmed to 25 °C and stirred for 90 min. H₂O (100 mL) was added and stirring was continued for 30 min. The separated organic phase was washed with satd NaCl solution, dried (Na₂SO₄) and evaporated. The residue was purified by silica gel chromatography with 0-20% EtOAc/hexane to give the purified aldehyde (2.0 g): ¹H NMR (400 MHz, CDCl₃) δ 12.27 (s, 1H), 10.34 (s, 1H), 7.51 (s, 1H); EIMS *m/z* 258.

Example 7. Preparation of 1-(2-hydroxy-5-trifluoromethylphenyl)-ethanone

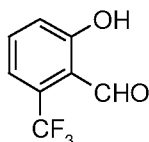
[0075] 1-(2-Hydroxy-5-trifluoromethylphenyl)-ethanone was prepared from commercially available starting materials as described in EP 129812, which is expressly incorporated by reference herein.

Example 8. Preparation of 2-hydroxy-4-trifluoromethylbenzaldehyde

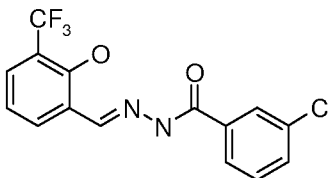
[0076] 2-Hydroxy-4-trifluoromethylbenzaldehyde was prepared from commercially available starting materials as described in Faeh et al., U.S. Pat. Appl. Publ. 2007185113 A1, which is expressly incorporated by reference herein.

Example 9. Preparation of 2-hydroxy-5-trifluoromethylbenzaldehyde

[0077] 2-Hydroxy-5-trifluoromethylbenzaldehyde was prepared from commercially available starting materials as described in Bonnert et al., PCT Int. Appl. WO 2006056752 A1, which is expressly incorporated by reference herein.

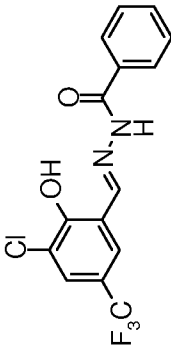
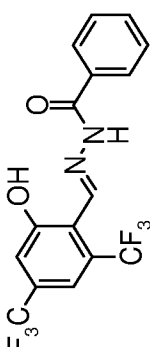
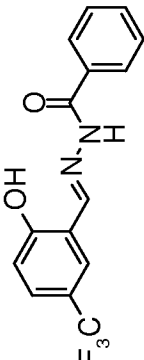
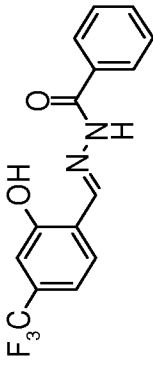
Example 10. Preparation of 2-hydroxy-6-trifluoromethylbenzaldehyde

[0078] 2-Hydroxy-6-trifluoromethylbenzaldehyde was prepared from commercially available starting materials as described in Stokker et al., *J. Med. Chem.* **1980**, 23, 1414-1427, which is expressly incorporated by reference herein.

Example 11. Preparation of 3-chloro-benzoic acid [1-(2-hydroxy-3-trifluoromethyl-phenyl)-methylidene]-hydrazide

[0079] 2-Hydroxy-3-(trifluoromethyl)benzaldehyde (100 mg, 0.53 mmol) and 3-chlorobenzhydrazide (90 mg, 53 mmol) were shaken together and heated to 60 °C in absolute ethanol (EtOH; 3 mL) for 24 h. After cooling to room temperature, H₂O (~ 0.5 mL) was added and the resulting solid was filtered, washed with H₂O and Et₂O and dried in a vacuum oven at 50 °C for several hours to give the desired product (145 mg, 80%) as a white solid: mp 185-187 °C; ¹H NMR (300 MHz, solvent) δ 12.91 (s, 1H), 12.56 (s, 1H), 8.65 (s, 1H), 8.04–7.98 (m, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.1 Hz, 1H), 7.76–7.71 (m, 1H), 7.68 (d, *J* = 7.3 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H); ESIMS *m/z* 343 ([M+H]⁺), 341 ([M-H]⁻).

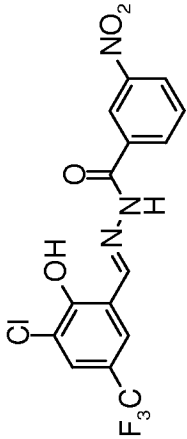
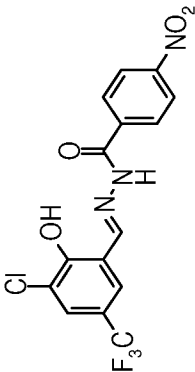
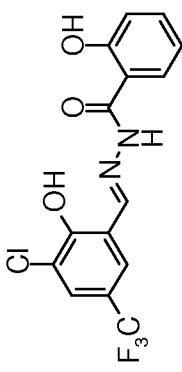
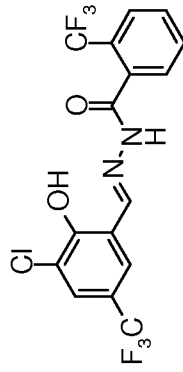
Table 1.

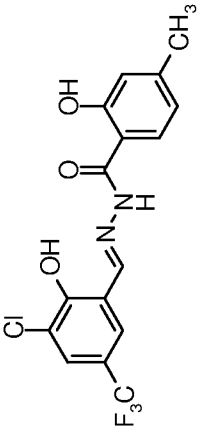
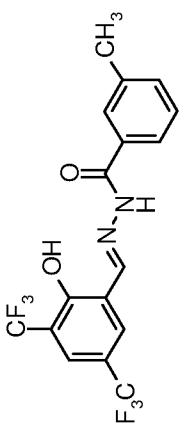
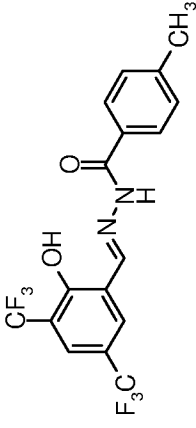
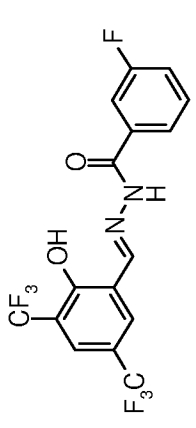
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
1		216–222	343	341	13.24 (s, 1H), 12.64 (s, 1H), 8.69 (s, 1H), 8.04–7.88 (m, 4H), 7.62 (dt, <i>J</i> = 31.2, 7.3 Hz, 3H)
2		144–193	377	375	13.34 (s, 1H), 12.74 (s, 1H), 8.97 (s, 1H), 7.99 (d, <i>J</i> = 7.3 Hz, 2H), 7.72–7.65 (m, 2H), 7.60 (t, <i>J</i> = 7.5 Hz, 3H)
3		214–217	309	307	12.25 (s, 1H), 11.84 (s, 1H), 8.73 (s, 1H), 8.01 (s, 1H), 7.95 (d, <i>J</i> = 7.9 Hz, 2H), 7.59 (dt, <i>J</i> = 30.0, 7.5 Hz, 4H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H)
4		215–217	309	307	12.24 (s, 1H), 11.56 (s, 1H), 8.73 (s, 1H), 7.95 (d, <i>J</i> = 7.3 Hz, 2H), 7.87 (d, <i>J</i> = 8.0 Hz, 1H), 7.67–7.60 (m, 1H), 7.60–7.52 (m, 2H), 7.29–7.20 (m, 2H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
5		232–234	377	375	13.92 (s, 1H), 12.78 (s, 1H), 8.72 (s, 1H), 8.35 (s, 1H), 7.98 (d, <i>J</i> = 7.4 Hz, 2H), 7.94 (s, 1H), 7.70–7.64 (m, 1H), 7.62–7.56 (m, 2H)
6		170–173	309	307	13.03 (s, 1H), 12.49 (s, 1H), 8.65 (s, 1H), 7.97 (d, <i>J</i> = 7.3 Hz, 2H), 7.80 (d, <i>J</i> = 7.5 Hz, 1H), 7.71–7.62 (m, 2H), 7.61–7.53 (m, 2H), 7.11 (t, <i>J</i> = 7.7 Hz, 1H)
7		228–230	309	307	12.93 (s, 1H), 12.56 (s, 1H), 8.96 (s, 1H), 8.01–7.94 (m, 2H), 7.70–7.62 (m, 1H), 7.62–7.55 (m, 2H), 7.52 (t, <i>J</i> = 8.0 Hz, 1H), 7.36 (d, <i>J</i> = 7.5 Hz, 1H), 7.31 (d, <i>J</i> = 8.4 Hz, 1H)
8		242–243	343	341	12.33 (s, 1H), 11.64 (s, 1H), 8.69 (s, 1H), 7.96 (d, <i>J</i> = 6.2 Hz, 3H), 7.64 (t, <i>J</i> = 7.2 Hz, 1H), 7.56 (t, <i>J</i> = 7.5 Hz, 2H), 7.36 (s, 1H)

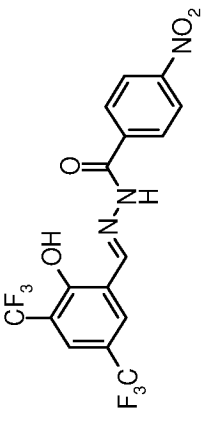
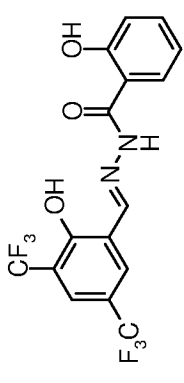
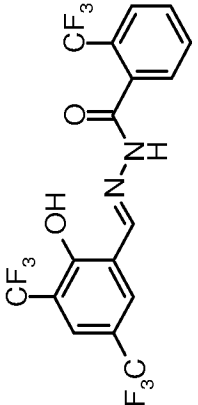
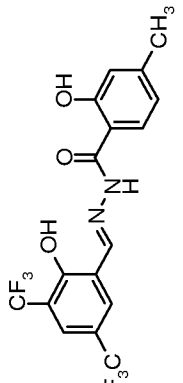
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
9		216–218	343	341	13.84 (s, 1H), 12.70 (s, 1H), 8.95 (d, <i>J</i> = 1.2 Hz, 1H), 8.03–7.95 (m, 2H), 7.76–7.64 (m, 2H), 7.60 (t, <i>J</i> = 7.5 Hz, 2H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H)
10		225–226	343	341	13.15 (s, 1H), 12.64 (s, 1H), 8.61 (s, 1H), 8.04–7.90 (m, 3H), 7.75–7.52 (m, 4H)
11		204–206	357	355	13.74–12.87 (m, 1H), 12.60 (s, 1H), 8.68 (s, 1H), 8.00 (s, 1H), 7.90 (d, <i>J</i> = 1.7 Hz, 1H), 7.82–7.72 (m, 2H), 7.46 (d, <i>J</i> = 5.0 Hz, 2H), 2.41 (s, 3H)
12		269–271	357	355	13.15 (s, 1H), 12.69 (s, 1H), 8.69 (s, 1H), 8.03 (s, 1H), 7.91 (d, <i>J</i> = 1.8 Hz, 1H), 7.80 (dd, <i>J</i> = 19.3, 8.7 Hz, 2H), 7.64 (d, <i>J</i> = 5.8 Hz, 1H), 7.52 (d, <i>J</i> = 1.9 Hz, 1H), 2.40 (s, 3H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
13		210–212	361	359	13.15 (s, 1H), 12.69 (s, 1H), 8.69 (s, 1H), 8.03 (s, 1H), 7.91 (d, <i>J</i> = 1.8 Hz, 1H), 7.80 (dd, <i>J</i> = 19.3, 8.7 Hz, 2H), 7.64 (d, <i>J</i> = 5.8 Hz, 1H), 7.52 (d, <i>J</i> = 1.9 Hz, 1H)
14		200–202	361	359	13.4 (s, 1H), 12.66 (s, 1H), 8.68 (s, 1H), 8.11–7.98 (m, 2H), 7.90 (d, <i>J</i> = 2.1 Hz, 1H), 7.43 (t, <i>J</i> = 8.8 Hz, 2H), 7.35–7.24 (m, 1H)
15		210–212	377	375	13.1 (s, 1H), 12.71 (s, 1H), 8.68 (s, 1H), 8.02 (d, <i>J</i> = 7.2 Hz, 2H), 7.93 (d, <i>J</i> = 10.3 Hz, 2H), 7.72 (s, 1H), 7.63 (d, <i>J</i> = 7.8 Hz, 1H)
16		208–210	377		13.25 (s, 1H), 12.70 (s, 1H), 8.68 (s, 1H), 8.07–7.95 (m, 3H), 7.90 (d, <i>J</i> = 1.7 Hz, 1H), 7.66 (d, <i>J</i> = 8.5 Hz, 2H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
17		237–238	388	386	12.95 (s, 2H), 8.80 (t, <i>J</i> = 1.8 Hz, 1H), 8.72 (s, 1H), 8.48 (dd, <i>J</i> = 8.2, 1.4 Hz, 1H), 8.40 (d, <i>J</i> = 7.9 Hz, 1H), 8.03 (d, <i>J</i> = 1.7 Hz, 1H), 7.88 (dd, <i>J</i> = 13.6, 5.3 Hz, 2H)
18		253–255	388	386	12.96 (s, 2H), 8.71 (s, 1H), 8.41 (d, <i>J</i> = 8.7 Hz, 2H), 8.20 (d, <i>J</i> = 8.7 Hz, 2H), 8.04 (s, 1H), 7.91 (d, <i>J</i> = 1.9 Hz, 1H)
19		258–260	359	357	13.11 (s, 1H), 12.35 (s, 1H), 11.45 (s, 1H), 8.73 (s, 1H), 7.98 (d, <i>J</i> = 1.7 Hz, 1H), 7.95–7.83 (m, 2H), 7.54–7.40 (m, 1H), 7.00 (dd, <i>J</i> = 14.0, 7.4 Hz, 2H)
20		169–171	411	409	12.84 (s, 1H), 12.73 (s, 1H), 8.56 (s, 1H), 8.03 (s, 1H), 7.94–7.56 (m, 5H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
21		255–257	373	371	13.09 (s, 1H), 12.37 (s, 1H), 11.63 (s, 1H), 8.72 (s, 1H), 7.97 (d, <i>J</i> = 1.7 Hz, 1H), 7.90 (d, <i>J</i> = 1.8 Hz, 1H), 7.81 (d, <i>J</i> = 8.5 Hz, 1H), 6.81 (d, <i>J</i> = 8.5 Hz, 3H), 2.32 (d, <i>J</i> = 6.7 Hz, 3H)
22		210–213	391	389	13.92 (s, 1H), 12.73 (s, 1H), 8.71 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.81–7.74 (m, 2H), 7.50–7.43 (m, 2H), 2.42 (s, 3H)
23		274–277	391	389	13.94 (s, 1H), 12.70 (s, 1H), 8.71 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H), 7.89 (d, <i>J</i> = 8.1 Hz, 2H), 7.39 (d, <i>J</i> = 8.0 Hz, 2H), 2.40 (s, 3H)
24		240–242	395	393	13.81 (s, 1H), 12.83 (s, 1H), 8.72 (s, 1H), 8.37 (s, 1H), 7.95 (s, 1H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.78 (d, <i>J</i> = 9.6 Hz, 1H), 7.69–7.61 (m, 1H), 7.53 (td, <i>J</i> = 8.4, 2.1 Hz, 1H)

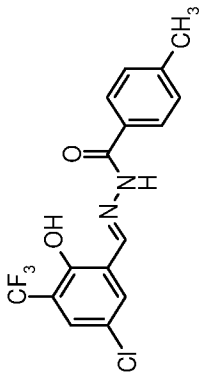
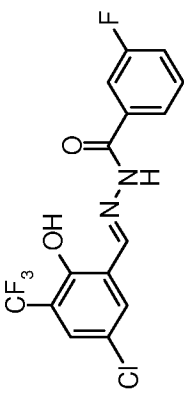
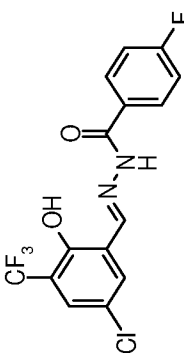
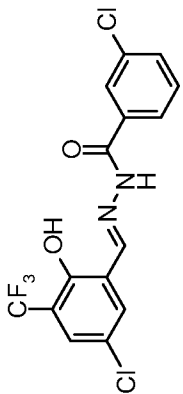
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
25		226–228	395	393	13.87 (s, 1H), 12.79 (s, 1H), 8.71 (s, 1H), 8.36 (s, 1H), 8.06 (dd, <i>J</i> = 8.7, 5.5 Hz, 2H), 7.94 (s, 1H), 7.47–7.39 (m, 2H)
26		230–233	411	409	13.80 (s, 1H), 12.85 (s, 1H), 8.71 (s, 1H), 8.37 (s, 1H), 8.04–8.00 (m, 1H), 7.97–7.91 (m, 2H), 7.74 (d, <i>J</i> = 9.1 Hz, 1H), 7.66–7.59 (m, 1H)
27		233–236	411	409	13.85 (s, 1H), 12.84 (s, 1H), 8.71 (s, 1H), 8.36 (s, 1H), 8.00 (d, <i>J</i> = 8.5 Hz, 2H), 7.94 (s, 1H), 7.67 (d, <i>J</i> = 8.5 Hz, 2H)
28		256–258		420	13.76 (s, 1H), 13.08 (s, 1H), 8.80 (t, <i>J</i> = 1.8 Hz, 1H), 8.75 (s, 1H), 8.50 (dd, <i>J</i> = 8.2, 1.4 Hz, 1H), 8.41 (d, <i>J</i> = 7.9 Hz, 1H), 8.37 (s, 1H), 7.96 (s, 1H), 7.89 (t, <i>J</i> = 8.0 Hz, 1H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
29		244–247		420	13.75 (s, 1H), 13.07 (s, 1H), 8.75 (s, 1H), 8.42 (d, <i>J</i> = 8.8 Hz, 2H), 8.39 (s, 1H), 8.21 (d, <i>J</i> = 8.8 Hz, 2H), 7.96 (s, 1H)
30		231–235	393	391	13.79 (s, 1H), 12.50 (s, 1H), 11.47 (s, 1H), 8.77 (s, 1H), 8.30 (s, 1H), 7.95 (s, 1H), 7.87 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.52–7.44 (m, 1H), 7.05–6.96 (m, 2H)
31		210–214	445	443	13.59, 12.89, 12.70, 11.12 (4s, 2H), 8.60, 8.38 (2s, 1H), 8.36, 8.15 (2s, 1H), 7.97–7.63 (m, 5H); Note: rotational isomers
32		251–254	407	405	13.80 (s, 1H), 12.48 (s, 1H), 11.60 (s, 1H), 8.76 (s, 1H), 8.30 (s, 1H), 7.94 (s, 1H), 7.81 (d, <i>J</i> = 8.5 Hz, 1H), 6.87–6.78 (m, 2H), 2.32 (s, 3H)

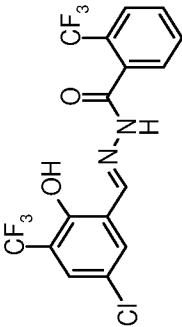
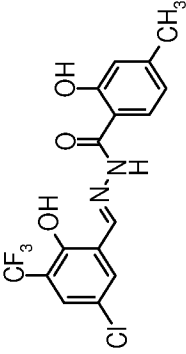
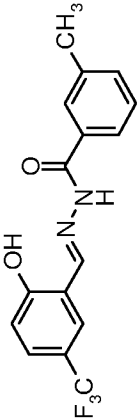
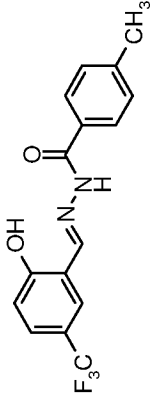
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
33		188–190	323	321	(300 MHz, DMSO- <i>d</i> ₆) 13.03 (s, 1H), 12.44 (s, 1H), 8.64 (s, 1H), 7.82–7.72 (m, 3H), 7.67 (d, <i>J</i> = 7.3 Hz, 1H), 7.46 (d, <i>J</i> = 5.0 Hz, 2H), 7.11 (t, <i>J</i> = 7.8 Hz, 1H), 2.41 (s, 3H)
34		239–241	323	321	(300 MHz, DMSO- <i>d</i> ₆) 13.05 (s, 1H), 12.41 (s, 1H), 8.64 (s, 1H), 7.88 (d, <i>J</i> = 8.2 Hz, 2H), 7.79 (d, <i>J</i> = 7.5 Hz, 1H), 7.66 (d, <i>J</i> = 7.7 Hz, 1H), 7.38 (d, <i>J</i> = 7.9 Hz, 2H), 7.10 (t, <i>J</i> = 7.8 Hz, 1H), 2.40 (s, 3H)
35		176–180	327	325	(300 MHz, DMSO- <i>d</i> ₆) 12.92 (s, 1H), 12.54 (s, 1H), 8.65 (s, 1H), 7.86–7.73 (m, 3H), 7.72–7.59 (m, 2H), 7.51 (td, <i>J</i> = 8.5, 2.2 Hz, 1H), 7.12 (t, <i>J</i> = 7.7 Hz, 1H)
36		187–188	327		(300 MHz, DMSO- <i>d</i> ₆) 12.96 (s, 1H), 12.52 (s, 1H), 8.64 (s, 1H), 8.10–8.00 (m, 2H), 7.80 (d, <i>J</i> = 7.2 Hz, 1H), 7.67 (d, <i>J</i> = 7.6 Hz, 1H), 7.43 (t, <i>J</i> = 8.8 Hz, 2H), 7.11 (t, <i>J</i> = 7.7 Hz, 1H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
37		185–187	343	341	(300 MHz, DMSO- <i>d</i> ₆) 12.91 (s, 1H), 12.56 (s, 1H), 8.65 (s, 1H), 8.04–7.98 (m, 1H), 7.93 (d, <i>J</i> = 7.9 Hz, 1H), 7.82 (d, <i>J</i> = 7.1 Hz, 1H), 7.76–7.71 (m, 1H), 7.68 (d, <i>J</i> = 7.3 Hz, 1H), 7.62 (t, <i>J</i> = 7.9 Hz, 1H), 7.12 (t, <i>J</i> = 7.8 Hz, 1H)
38		215–216	343	341	12.96 (s, 1H), 12.55 (s, 1H), 8.64 (s, 1H), 7.99 (d, <i>J</i> = 8.6 Hz, 2H), 7.81 (d, <i>J</i> = 7.5 Hz, 1H), 7.71–7.63 (m, 3H), 7.11 (t, <i>J</i> = 7.7 Hz, 1H)
39		215–217	354	352	12.84 (s, 2H), 8.83–8.77 (m, 1H), 8.68 (s, 1H), 8.49 (d, <i>J</i> = 8.2 Hz, 1H), 8.41 (d, <i>J</i> = 7.9 Hz, 1H), 7.89 (t, <i>J</i> = 8.0 Hz, 1H), 7.82 (d, <i>J</i> = 7.7 Hz, 1H), 7.69 (d, <i>J</i> = 7.0 Hz, 1H), 7.12 (t, <i>J</i> = 7.7 Hz, 1H)
40		253–255		352	12.86 (s, 2H), 8.67 (s, 1H), 8.42 (d, <i>J</i> = 8.8 Hz, 2H), 8.20 (d, <i>J</i> = 8.8 Hz, 2H), 7.83 (d, <i>J</i> = 7.1 Hz, 1H), 7.69 (d, <i>J</i> = 7.3 Hz, 1H), 7.13 (t, <i>J</i> = 7.7 Hz, 1H)

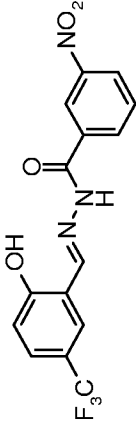
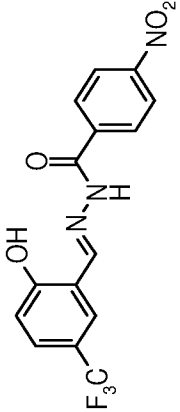
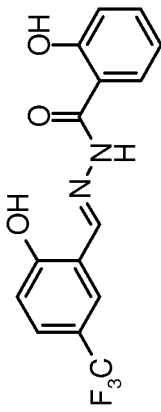
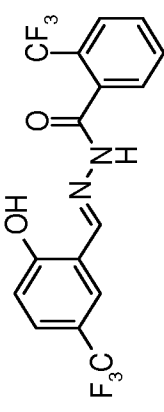
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
41		230–234	325	323	12.95 (s, 1H), 12.28 (s, 1H), 11.56 (s, 1H), 8.71 (s, 1H), 7.88 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.79 (d, <i>J</i> = 7.6 Hz, 1H), 7.68 (d, <i>J</i> = 7.1 Hz, 1H), 7.52–7.44 (m, 1H), 7.12 (t, <i>J</i> = 7.8 Hz, 1H), 7.05–6.96 (m, 2H)
42		248–253	339	337	12.95 (s, 1H), 12.26 (s, 1H), 11.67 (s, 1H), 8.70 (s, 1H), 7.80 (t, <i>J</i> = 9.1 Hz, 2H), 7.67 (d, <i>J</i> = 7.4 Hz, 1H), 7.11 (t, <i>J</i> = 7.8 Hz, 1H), 6.83 (d, <i>J</i> = 7.4 Hz, 2H), 2.31 (s, 3H)
43		169–171	377	375	12.78, 12.63, 12.47, 10.39 (4s, 2H), 8.50, 8.29 (2s, 1H), 7.92–7.54 (m, 6H), 7.11, 7.04 (2t, <i>J</i> = 7.7 Hz, 1H); Note: rotational isomers
44		199–201	357	355	13.21 (s, 1H), 12.61 (s, 1H), 8.60 (s, 1H), 7.99 (d, <i>J</i> = 2.4 Hz, 1H), 7.82–7.72 (m, 2H), 7.69 (d, <i>J</i> = 2.4 Hz, 1H), 7.51–7.40 (m, 2H), 2.41 (s, 3H)

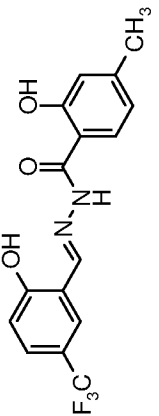
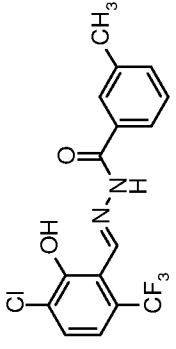
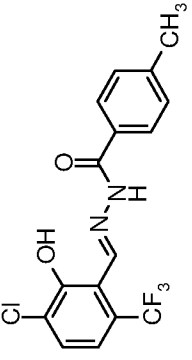
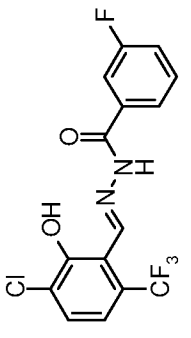
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
45		276–278	357	355	13.23 (s, 1H), 12.59 (s, 1H), 8.60 (s, 1H), 7.99 (d, <i>J</i> = 2.4 Hz, 1H), 7.88 (d, <i>J</i> = 8.1 Hz, 2H), 7.70 (d, <i>J</i> = 2.5 Hz, 1H), 7.38 (d, <i>J</i> = 8.0 Hz, 2H), 2.40 (s, 3H)
46		219–221	361	359	13.09 (s, 1H), 12.72 (s, 1H), 8.61 (s, 1H), 8.03 (d, <i>J</i> = 2.5 Hz, 1H), 7.82 (d, <i>J</i> = 7.8 Hz, 1H), 7.79–7.74 (m, 1H), 7.72 (d, <i>J</i> = 2.4 Hz, 1H), 7.64 (td, <i>J</i> = 8.0, 5.9 Hz, 1H), 7.52 (td, <i>J</i> = 8.4, 2.2 Hz, 1H)
47		227–228	361	359	13.16 (s, 1H), 12.68 (s, 1H), 8.60 (s, 1H), 8.26–7.87 (m, 3H), 7.71 (d, <i>J</i> = 2.4 Hz, 1H), 7.43 (t, <i>J</i> = 8.8 Hz, 2H)
48		228–229	377	375	13.08 (s, 1H), 12.74 (s, 1H), 8.60 (s, 1H), 8.05–7.97 (m, 2H), 7.93 (d, <i>J</i> = 7.8 Hz, 1H), 7.72 (t, <i>J</i> = 5.3 Hz, 2H), 7.62 (t, <i>J</i> = 7.9 Hz, 1H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
49		232–234	377	375	13.13 (s, 1H), 12.72 (s, 1H), 8.60 (s, 1H), 8.00 (dd, <i>J</i> = 10.9, 5.5 Hz, 3H), 7.71 (d, <i>J</i> = 2.4 Hz, 1H), 7.66 (d, <i>J</i> = 8.6 Hz, 2H)
50		235–237	388	386	13.00 (s, 1H), 8.83–8.74 (m, 1H), 8.63 (s, 1H), 8.56–8.44 (m, 1H), 8.40 (d, <i>J</i> = 7.9 Hz, 1H), 8.03 (d, <i>J</i> = 2.5 Hz, 1H), 7.88 (t, <i>J</i> = 8.0 Hz, 1H), 7.72 (d, <i>J</i> = 2.5 Hz, 1H)
51		245–247	388	386	12.99 (d, <i>J</i> = 25.6 Hz, 2H), 8.63 (s, 1H), 8.41 (d, <i>J</i> = 8.8 Hz, 2H), 8.20 (d, <i>J</i> = 8.8 Hz, 2H), 8.04 (d, <i>J</i> = 2.5 Hz, 1H), 7.73 (d, <i>J</i> = 2.5 Hz, 1H)
52		258–260	359	357	13.10 (s, 1H), 12.43 (s, 1H), 11.51 (s, 1H), 8.66 (s, 1H), 7.97 (d, <i>J</i> = 2.5 Hz, 1H), 7.87 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.71 (d, <i>J</i> = 2.5 Hz, 1H), 7.55–7.39 (m, 1H), 7.06–6.91 (m, 2H)

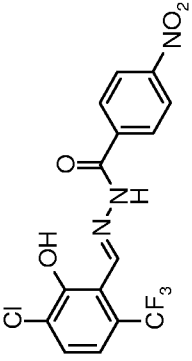
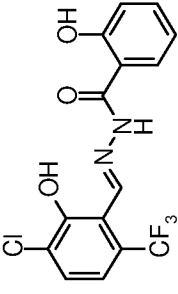
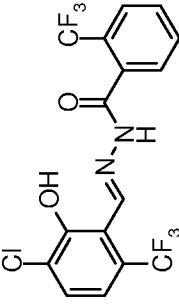
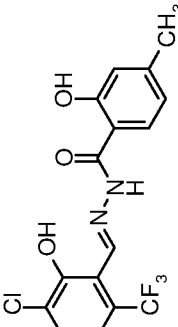
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
53		203–204	411	409	12.92 (s, 1H), 12.79 (s, 1H), 8.48 (s, 1H), 8.01 (d, <i>J</i> = 2.5 Hz, 1H), 7.95–7.55 (m, 5H)
54		252–254	373	371	13.10 (s, 1H), 12.37 (s, 1H), 11.63 (s, 1H), 8.65 (s, 1H), 7.96 (d, <i>J</i> = 2.4 Hz, 1H), 7.80 (d, <i>J</i> = 8.4 Hz, 1H), 7.71 (d, <i>J</i> = 2.4 Hz, 1H), 6.82 (d, <i>J</i> = 7.6 Hz, 2H), 2.30 (d, <i>J</i> = 8.7 Hz, 3H)
55		192–194	323	321	12.21 (s, 1H), 11.82 (s, 1H), 8.72 (s, 1H), 8.00 (s, 1H), 7.75 (dd, <i>J</i> = 9.3, 4.5 Hz, 2H), 7.64 (dd, <i>J</i> = 8.7, 1.8 Hz, 1H), 7.44 (d, <i>J</i> = 4.7 Hz, 2H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H), 2.40 (s, 3H)
56		245–249	323	321	12.19 (s, 1H), 11.88 (s, 1H), 8.72 (s, 1H), 8.00 (s, 1H), 7.86 (d, <i>J</i> = 8.1 Hz, 2H), 7.63 (dd, <i>J</i> = 8.6, 1.9 Hz, 1H), 7.36 (d, <i>J</i> = 8.0 Hz, 2H), 7.12 (d, <i>J</i> = 8.5 Hz, 1H), 2.39 (s, 3H)

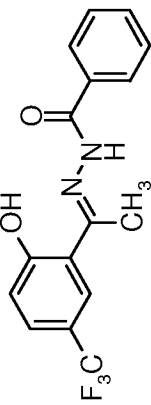
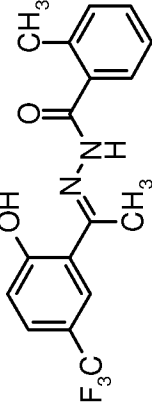
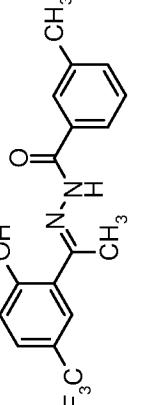
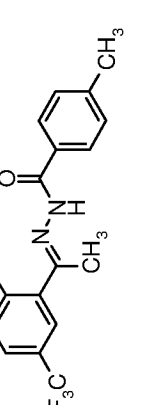
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
57		188–196	327	325	12.28 (s, 1H), 11.75 (s, 1H), 8.73 (s, 1H), 8.03 (d, <i>J</i> = 1.3 Hz, 1H), 7.78 (dd, <i>J</i> = 18.8, 9.0 Hz, 2H), 7.68–7.57 (m, 2H), 7.49 (td, <i>J</i> = 8.7, 2.3 Hz, 1H), 7.12 (d, <i>J</i> = 8.5 Hz, 1H)
58		229–231	327	325	12.26 (s, 1H), 11.80 (s, 1H), 8.72 (s, 1H), 8.10–7.96 (m, 3H), 7.64 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 7.40 (t, <i>J</i> = 8.8 Hz, 2H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H)
59		187–197	343	341	12.30 (s, 1H), 11.73 (s, 1H), 8.73 (s, 1H), 8.06–7.94 (m, 2H), 7.91 (dd, <i>J</i> = 7.8, 1.2 Hz, 1H), 7.74–7.54 (m, 3H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H)
60		252–254	343	341	12.30 (s, 1H), 11.77 (s, 1H), 8.72 (s, 1H), 8.06–7.90 (m, 3H), 7.64 (d, <i>J</i> = 8.5 Hz, 3H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H)

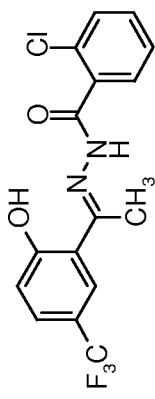
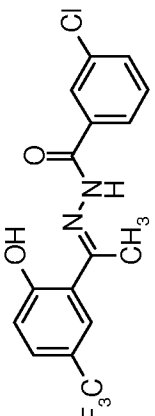
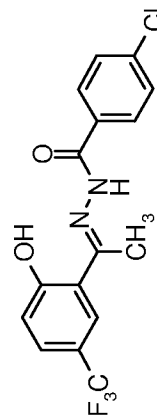
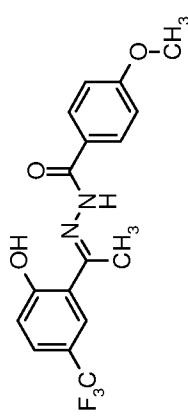
Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
61		218–220	354	352	12.51 (s, 1H), 11.74 (s, 1H), 8.80 (dd, <i>J</i> = 6.6, 4.8 Hz, 2H), 8.51–8.35 (m, 2H), 8.05 (d, <i>J</i> = 1.8 Hz, 1H), 7.87 (t, <i>J</i> = 8.0 Hz, 1H), 7.65 (dd, <i>J</i> = 8.7, 2.2 Hz, 1H), 7.13 (d, <i>J</i> = 8.6 Hz, 1H)
62		259–265	354	352	12.47 (s, 1H), 11.71 (s, 1H), 8.76 (s, 1H), 8.44–8.36 (m, 2H), 8.23–8.15 (m, 2H), 8.05 (d, <i>J</i> = 2.0 Hz, 1H), 7.65 (dd, <i>J</i> = 8.7, 2.2 Hz, 1H), 7.13 (d, <i>J</i> = 8.6 Hz, 1H)
63		277–281	325	323	12.15 (s, 1H), 11.78 (s, 2H), 8.75 (s, 1H), 8.01 (d, <i>J</i> = 1.8 Hz, 1H), 7.89 (dd, <i>J</i> = 7.8, 1.2 Hz, 1H), 7.65 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 7.50–7.42 (m, 1H), 7.13 (d, <i>J</i> = 8.6 Hz, 1H), 7.03–6.94 (m, 2H)
64		174–176	377	375	12.30 (s, 1H), 11.55 (s, 1H), 8.57 (s, 1H), 8.03 (d, <i>J</i> = 2.1 Hz, 1H), 7.91–7.47 (m, 5H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
65		264–271	339	337	12.12 (s, 1H), 11.89 (s, 1H), 11.78 (s, 1H), 8.75 (s, 1H), 8.00 (s, 1H), 7.83 (d, <i>J</i> = 8.5 Hz, 1H), 7.65 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H), 6.80 (d, <i>J</i> = 7.0 Hz, 2H), 2.31 (s, 3H)
66		219–221	357	355	13.85 (s, 1H), 12.65 (s, 1H), 8.94 (s, 1H), 7.79 (dd, <i>J</i> = 9.2, 3.4 Hz, 2H), 7.72 (d, <i>J</i> = 8.3 Hz, 1H), 7.47 (dd, <i>J</i> = 8.8, 4.1 Hz, 2H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H), 2.42 (s, 3H)
67		216–218	357	355	13.86 (s, 1H), 12.62 (s, 1H), 8.93 (s, 1H), 7.90 (d, <i>J</i> = 8.1 Hz, 2H), 7.71 (d, <i>J</i> = 8.3 Hz, 1H), 7.37 (dd, <i>J</i> = 14.8, 8.2 Hz, 3H), 2.40 (s, 3H)
68		227–229	361	359	13.79 (s, 1H), 12.69 (s, 1H), 8.92 (s, 1H), 8.11–8.00 (m, 2H), 7.72 (d, <i>J</i> = 8.3 Hz, 1H), 7.44 (dd, <i>J</i> = 12.2, 5.4 Hz, 2H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
69		231–233	361	359	13.73 (s, 1H), 12.73 (s, 1H), 8.93 (s, 1H), 7.87–7.60 (m, 4H), 7.53 (td, <i>J</i> = 8.3, 2.3 Hz, 1H), 7.37 (d, <i>J</i> = 8.4 Hz, 1H)
70		242–245	377	375	13.73 (s, 1H), 12.74 (s, 1H), 8.92 (s, 1H), 8.02 (t, <i>J</i> = 1.7 Hz, 1H), 7.94 (d, <i>J</i> = 7.8 Hz, 1H), 7.78–7.67 (m, 2H), 7.63 (t, <i>J</i> = 7.9 Hz, 1H), 7.37 (d, <i>J</i> = 8.4 Hz, 1H)
71		236–238	377	375	13.76 (s, 1H), 12.73 (s, 1H), 8.92 (s, 1H), 8.00 (d, <i>J</i> = 8.6 Hz, 2H), 7.72 (d, <i>J</i> = 8.3 Hz, 1H), 7.67 (d, <i>J</i> = 8.6 Hz, 2H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H)
72		277–279	388	386	13.71 (s, 1H), 12.96 (s, 1H), 8.94 (s, 1H), 8.80 (t, <i>J</i> = 1.8 Hz, 1H), 8.49 (dd, <i>J</i> = 8.2, 1.5 Hz, 1H), 8.41 (d, <i>J</i> = 7.8 Hz, 1H), 7.89 (t, <i>J</i> = 8.0 Hz, 1H), 7.73 (d, <i>J</i> = 8.3 Hz, 1H), 7.37 (d, <i>J</i> = 8.4 Hz, 1H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
73		305–307	388	386	13.73 (s, 1H), 12.91 (s, 1H), 8.94 (s, 1H), 8.43 (d, <i>J</i> = 8.8 Hz, 2H), 8.22 (d, <i>J</i> = 8.9 Hz, 2H), 7.74 (d, <i>J</i> = 8.3 Hz, 1H), 7.37 (d, <i>J</i> = 8.4 Hz, 1H)
74		278–280	358	356	13.82 (s, 1H), 12.57 (s, 1H), 11.28 (s, 1H), 8.98 (d, <i>J</i> = 1.3 Hz, 1H), 7.84 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.73 (d, <i>J</i> = 8.3 Hz, 1H), 7.53–7.45 (m, 1H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H), 7.01 (dd, <i>J</i> = 13.2, 7.7 Hz, 2H)
75		203–205	358	356	13.55 (s, 1H), 12.83 (s, 1H), 8.77 (s, 1H), 7.93 (d, <i>J</i> = 7.6 Hz, 1H), 7.88–7.70 (m, 4H), 7.38 (d, <i>J</i> = 8.4 Hz, 1H)
76		258–260	373	371	13.81 (s, 1H), 12.61 (s, 1H), 11.54 (s, 1H), 8.97 (s, 1H), 7.74 (dd, <i>J</i> = 18.2, 8.4 Hz, 2H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H), 6.83 (d, <i>J</i> = 5.9 Hz, 2H), 2.31 (d, <i>J</i> = 7.9 Hz, 3H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
77		226–229	323	321	14.07 (s, 1H), 11.53 (s, 1H), 8.02–7.87 (m, 3H), 7.69–7.59 (m, 2H), 7.58–7.50 (m, 2H), 7.11 (d, <i>J</i> = 8.5 Hz, 1H), 2.56 (s, 3H)
78		200–203	337	335	14.06 (s, 1H), 11.61 (s, 1H), 7.89 (s, 1H), 7.65 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 7.53 (d, <i>J</i> = 7.6 Hz, 1H), 7.44 (t, <i>J</i> = 6.9 Hz, 1H), 7.37–7.28 (m, 2H), 7.11 (d, <i>J</i> = 8.6 Hz, 1H), 2.48 (s, 3H), 2.41 (s, 3H)
79		235–238	337	335	14.08 (s, 1H), 11.48 (s, 1H), 7.92 (s, 1H), 7.80–7.72 (m, 2H), 7.65 (d, <i>J</i> = 7.0 Hz, 1H), 7.48–7.43 (m, 2H), 7.11 (d, <i>J</i> = 8.6 Hz, 1H), 2.56 (s, 3H), 2.41 (s, 3H)
80		225–229	337	335	14.09 (s, 1H), 11.44 (s, 1H), 7.91 (s, 1H), 7.87 (d, <i>J</i> = 7.9 Hz, 2H), 7.64 (dd, <i>J</i> = 8.6, 1.8 Hz, 1H), 7.36 (d, <i>J</i> = 8.1 Hz, 2H), 7.10 (d, <i>J</i> = 8.6 Hz, 1H), 2.55 (s, 3H), 2.40 (s, 3H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
81		189–191	357	355	13.86 (s, 1H), 11.82 (s, 1H), 7.90 (s, 1H), 7.69–7.45 (m, 5H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H), 2.48 (s, 3H)
82		241–245	357	355	13.96 (s, 1H), 11.61 (s, 1H), 8.02 (s, 1H), 7.94–7.89 (m, 2H), 7.71 (d, <i>J</i> = 8.8 Hz, 1H), 7.68–7.63 (m, 1H), 7.59 (t, <i>J</i> = 7.9 Hz, 1H), 7.11 (d, <i>J</i> = 8.6 Hz, 1H), 2.57 (s, 3H)
83		263–265	357	355	14.00 (s, 1H), 11.58 (s, 1H), 7.99 (d, <i>J</i> = 8.5 Hz, 2H), 7.92 (s, 1H), 7.68–7.61 (m, 3H), 7.11 (d, <i>J</i> = 8.7 Hz, 1H), 2.56 (s, 3H)
84		228–231	353	351	14.12 (s, 1H), 11.36 (s, 1H), 7.96 (d, <i>J</i> = 8.7 Hz, 2H), 7.90 (s, 1H), 7.64 (dd, <i>J</i> = 8.7, 1.9 Hz, 1H), 7.12–7.06 (m, 3H), 3.85 (s, 3H), 2.55 (s, 3H)

Compound Number	Structure	mp (°C)	ESIMS (+)	ESIMS (-)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ unless otherwise stated), δ
85		256–259	402	400	13.99 (s, 1H), 11.58 (s, 1H), 7.94–7.89 (m, 3H), 7.78 (d, <i>J</i> = 8.4 Hz, 2H), 7.66 (d, <i>J</i> = 8.8 Hz, 1H), 7.11 (d, <i>J</i> = 8.5 Hz, 1H), 2.56 (s, 3H)
86		228–234	391	389	13.95 (s, 1H), 11.73 (s, 1H), 8.15 (d, <i>J</i> = 8.1 Hz, 2H), 7.97–7.91 (m, 3H), 7.69–7.64 (m, 1H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H), 2.57 (s, 3H)
87		192–200	402	400	13.87, 11.81, 11.70, 11.28 (4s, 2H), 7.91–7.39 (m, 6H), 7.21, 6.87 (2d, <i>J</i> = 8.6 Hz, 1H), 2.48, 2.42 (2s, 3H); Note: rotational isomers
88		277–297	361 (+ Na)		13.84 (s, 1H), 11.71 (s, 2H), 7.98 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.93 (s, 1H), 7.68–7.63 (m, 1H), 7.50–7.43 (m, 1H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H), 7.08–6.98 (m, 2H), 2.49 (s, 3H)

[0080] As exemplified below, hydrazones of the present invention, or their metal complexes, in a mixture with copper or in a mixture with inorganic or organic mono- or divalent copper salts or chelates (hereinafter referred to as “copper products”) increase the biological potency of copper products, enabling comparable or improved efficacy at lower copper use rates. While not intending to be all-inclusive, copper products which may be mixed with the compounds of the present invention to provide enhanced potency may include the following: copper oxychloride, copper octanoate, copper ammonium carbonate, copper arsenate, copper oxysulfate, copper formate, copper propionate, copper oxyacetate, copper citrate, copper chloride, copper diammonium chloride, copper nitrate, copper carbonate, copper phosphate, copper pyrophosphate, copper disodium EDTA, copper diammonium EDTA, copper oxalate, copper tartrate, copper gluconate, copper glycinate, copper glutamate, copper aspartate, copper adipate, copper palmitate, copper stearate, copper caprylate, copper decanoate, copper undecylenate, copper neodecanoate, copper linoleate, copper oleate, copper borate, copper methanesulfonate, copper sulfamate, copper acetate, copper hydroxide, copper oxide, copper oxychloride-sulfate, copper sulfate, basic copper sulfate, copper-oxine, copper 3-phenylsalicylate, copper chloride hydroxide, copper dimethyldithiocarbamate, ammonium copper sulfate, copper magnesium sulfate, copper naphthenate, copper ethanolamine, chromated copper arsenate, ammoniacal copper arsenate, ammoniacal copper zinc arsenate, ammoniacal copper borate, Bordeaux mixture, copper zinc chromate, cufraneb, cupric hydrazinium sulfate, cuprobam, nano-copper materials, and copper didecyldimethylammonium chloride and where appropriate the hydrates of such compounds.

[0081] Salicylaldehyde benzoylhydrazones such as those of the current invention are known in the literature as chelators of metal cations (*Inorganica Chimica Acta* **1982**, 67, L25-L27, which is expressly incorporated by reference herein), including copper. Antimicrobial activity has been reported for *o*-hydroxybenzaldehyde-*N*-salicyloylhydrazone and its copper, nickel and cobalt complexes towards *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger* and *A. flavus* (*Proceedings of the National Academy of Sciences, India* **1991**, Section A Part IV, Vol. LXI, pp. 447-452, which is expressly incorporated by reference herein). However, data in this report showed that the copper complex of *o*-hydroxybenzaldehyde-*N*-salicyloylhydrazone had a similar level of antimicrobial activity to that of *o*-hydroxybenzaldehyde-*N*-

salicyloylhydrazone alone and the nickel and cobalt complexes, and provided no indication that salicylaldehyde benzoylhydrazones might show any synergistic antimicrobial effect in combination with copper.

Example 12. Effect of copper on fungitoxicity of hydrazones towards *Leptosphaeria nodorum*

[0082] *In vitro* fungitoxicity assays against *Leptosphaeria nodorum* (LEPTNO) were conducted using the liquid growth medium described by Coursen and Sisler (*American Journal of Botany* **1960**, 47, 541-549) except that copper micronutrient, normally included as CuSO₄, was omitted. The medium, termed “copper-minus”, was prepared by dissolving 10 g glucose, 1.5 g K₂HPO₄, 2 g KH₂PO₄ and 1 g (NH₄)₂SO₄ in 1 liter of deionized water and treating the solution with 0.5 g Chelex 100 resin (Bio-Rad Analytical grade, 50-100 mesh, sodium form, cat# 142-2822) by stirring at room temperature for 1 h. MgSO₄•7H₂O (0.5 g) was added, and stirring was continued for a further hour. Trace elements (minus CuSO₄), and vitamins described by Coursen and Sisler were added from concentrated stock solutions and the entire medium was sterilized by filtration. Medium containing copper was prepared by adding CuCl₂•2H₂O to the copper-minus medium at 20 µM. Test compounds were dissolved in dimethylsulfoxide (DMSO) then dilutions in copper-minus and copper-plus growth media were prepared as 100 µL aliquots in flat-bottomed 96-well microtiter plates.

[0083] LEPTNO was grown on potato dextrose agar in 9 cm diameter petri dishes for 7 days. Sterile deionized water (20 mL) was added to a culture plate and spores suspended by scraping the surface gently with a sterile plastic loop. The resulting suspension was filtered through a double layer of sterile cheesecloth. Filtered spore suspension (5 mL) was centrifuged in a bench centrifuge at 2000 rpm for 2 min. The resulting spore pellet was resuspended in 10 mL sterile deionized water (which had been treated with Chelex 100 resin using 0.5 g resin per liter of water by stirring at room temperature for 1 h), and recentrifuged. The spores were resuspended in copper-minus medium, and the suspension adjusted to 2 x 10⁵ spores per mL. Microtiter plates were inoculated with 100 µL of this spore suspension and the plates incubated at 25 °C for 72 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader. Growth inhibition was determined by comparing growth in the presence of test compound with growth in control wells lacking test compound.

[0084] Results for growth inhibition by test compounds in copper-plus medium (“% Inhn. Plus Copper Observed”) were compared with predicted values (“% Inhn. Plus Copper Predicted”) that were calculated using the formula set forth by S.R. Colby in *Weeds* **1967**, 15, 20-22 based on results obtained for the same compounds in copper-minus medium (“% Inhn. Minus Copper Observed”) and the inhibition attributed to copper chloride alone, as determined by comparing growth in copper-minus and copper-plus media without any test compound across experiments. Data are presented in Table 2. Results illustrate that hydrazones and copper produce a synergistic fungitoxic effect towards LEPTNO.

Example 13. Efficacy of hydrazones in mixture with copper against tomato blight
(*Phytophthora infestans*)

[0085] Hydrazone compounds at 50 ppm in combination with 50 μM $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ were evaluated as prophylactic treatments applied 24 h before inoculation. Efficacy was determined based on percentage of disease control against tomato late blight (TLB), causal agent *Phytophthora infestans*. Treatments were arranged in a completely randomized design with 3 repetitions each. A pot with one tomato plant was considered as an experimental unit. Hydrazones were dissolved in acetone and re-suspended in water containing 0.01% Triton® X-100, 0.1% Atlox 4913 and 50 μM $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ to a final concentration of 10% acetone. All treatments were applied to run off 24 h before inoculation using a spin-table sprayer. Inoculation with an aqueous suspension of *P. infestans* sporangia was performed using a Delta painting sprayer. Percentage of disease control was determined 7 days after inoculation. Data are presented in Table 2, and illustrate the efficacy of hydrazones in mixture with copper for control of tomato late blight.

Table 2

Compound Number	Concn. ($\mu\text{g/mL}$)	LEPTNO %Inhn. Minus Copper Observed	LEPTNO % Inhn. Plus Copper Observed	LEPTNO % Inhn. Plus Copper Predicted	TLB % Control
1	0.05	0.0	98.4	7.1	79.7
2	0.05	5.5	97.8	12.2	71.2
3	0.05	1.9	97.5	8.9	86.4
4	0.05	1.7	94.2	8.7	72.9
5	0.05	5.8	98.0	12.5	89.8
6	0.05	8.3	97.7	14.8	84.7

Compound Number	Concn. (µg/mL)	LEPTNO %Inhn. Minus Copper Observed	LEPTNO % Inhn. Plus Copper Observed	LEPTNO % Inhn. Plus Copper Predicted	TLB % Control
7	0.05	0.0	96.4	7.1	69.5
8	0.05	3.1	97.3	10.0	71.2
9	0.05	18.1	96.6	23.9	78.0
10	0.05	17.1	96.4	23.0	100.0
11	0.05	11.7	96.6	18.0	100.0
12	0.05	20.9	97.9	26.5	95.0
13	0.05	16.1	98.1	22.1	100.0
14	0.05	2.3	96.3	9.2	98.0
15	0.05	0.0	95.7	7.1	100.0
16	0.05	6.9	95.6	13.5	93.0
17	0.05	1.2	95.7	8.3	98.0
18	0.05	0.0	95.1	7.1	99.0
19	0.05	14.0	93.5	20.1	99.0
20	0.05	5.3	92.9	12.1	99.0
21	0.05	22.8	97.8	28.2	100.0
22	0.05	2.0	93.9	8.9	89.0
23	0.05	16.2	93.2	22.1	85.0
24	0.05	10.9	97.8	17.2	98.0
25	0.05	10.2	96.8	16.6	95.0
26	0.05	16.6	97.8	22.5	98.0
27	0.05	22.4	98.0	27.9	97.0
28	0.05	9.0	98.1	15.5	96.0
29	0.05	1.5	95.4	8.5	100.0
30	0.05	18.0	96.2	23.8	95.0
31	0.05	1.2	88.9	8.2	63.0
32	0.05	9.1	98.3	15.6	86.0
33	0.05	2.8	95.4	9.7	97.0
34	0.05	31.5	91.8	36.4	100.0
35	0.05	18.8	97.9	24.6	97.0
36	0.05	30.0	96.7	34.9	96.0
37	0.05	13.8	98.4	19.9	97.0
38	0.05	16.3	98.3	22.2	100.0
39	0.05	17.4	96.9	23.3	97.0
40	0.05	11.3	94.9	17.6	97.0
41	0.05	7.7	96.1	14.3	100.0
42	0.05	8.8	98.4	15.3	100.0
43	0.05	0.0	94.8	7.1	81.0
44	0.05	13.6	96.5	19.8	98.0
45	0.05	29.9	97.6	34.9	100.0

Compound Number	Concn. (µg/mL)	LEPTNO %Inhn. Minus Copper Observed	LEPTNO % Inhn. Plus Copper Observed	LEPTNO % Inhn. Plus Copper Predicted	TLB % Control
46	0.05	26.3	98.4	31.6	97.0
47	0.05	26.7	98.2	31.9	100.0
48	0.05	36.1	98.3	40.6	100.0
49	0.05	31.8	98.6	36.6	100.0
50	0.05	19.3	98.5	25.0	96.0
51	0.05	20.3	95.7	25.9	100.0
52	0.05	28.6	95.8	33.6	100.0
53	0.05	5.4	94.6	12.1	100.0
54	0.05	41.1	98.4	45.3	100.0
55	0.05	4.7	97.2	11.5	100.0
56	0.05	14.6	98.2	20.7	94.0
57	0.05	9.2	97.0	15.6	100.0
58	0.05	0.0	94.2	7.1	98.0
59	0.05	0.0	100.0	7.1	96.0
60	0.05	2.9	100.0	9.8	98.0
61	0.05	0.0	100.0	7.1	96.0
62	0.05	0.0	100.0	7.1	98.0
63	0.05	14.6	100.0	20.7	83.0
64	0.05	0.0	100.0	7.1	91.0
65	0.05	13.2	100.0	19.4	90.0
66	0.05	20.0	96.6	25.7	100.0
67	0.05	27.1	97.5	32.3	100.0
68	0.05	7.2	98.5	13.8	92.0
69	0.05	1.1	93.5	8.1	100.0
70	0.05	4.6	100.0	11.4	100.0
71	0.05	12.9	100.0	19.1	100.0
72	0.05	5.6	100.0	12.3	100.0
73	0.05	12.4	100.0	18.6	100.0
74	0.05	16.7	100.0	22.6	100.0
75	0.05	0.0	100.0	7.1	100.0
76	0.05	6.7	100.0	13.3	100.0
77	0.05	7.6	97.6	14.2	78.0
78	0.05	8.7	97.7	15.2	73.0
79	0.05	15.3	97.7	21.3	46.0
80	0.05	9.8	96.2	16.2	59.0
81	0.05	0.0	97.3	7.1	80.0
82	0.05	4.9	91.4	11.7	56.0
83	0.05	6.2	97.0	12.9	34.0
84	0.05	5.1	95.7	11.9	61.0

Compound Number	Concn. (µg/mL)	LEPTNO %Inhn. Minus Copper Observed	LEPTNO % Inhn. Plus Copper Observed	LEPTNO % Inhn. Plus Copper Predicted	TLB % Control
85	0.05	10.1	97.7	16.5	56.0
86	0.05	21.1	93.4	26.7	24.0
87	0.05	12.2	96.2	18.5	90.0
88	0.05	12.4	96.5	18.6	44.0
CuCl ₂ , 10 µM			7.1 ± 6.0		

Example 14. Effect of copper on fungitoxicity of hydrazones towards *Phytophthora capsici*

[0086] *In vitro* fungitoxicity assays against *Phytophthora capsici* were conducted using the asparagine-sucrose (AS) medium described in *Canadian Journal of Microbiology* **1961**, 7, 15-25, except that copper micronutrient, normally included as CuSO₄, was omitted. The medium, termed “copper-minus AS”, was prepared by dissolving 2 g asparagine, 0.43 g KH₂PO₄, 0.3 g K₂HPO₄, 0.4 mL of a 0.5 mg/mL thiamine-HCl solution and 15 g sucrose in 1 liter of deionized water and treating the solution with 0.5 g Chelex 100 resin (Bio-Rad Analytical grade, 50-100 mesh, sodium form, cat# 142-2822) by stirring at room temperature for 1 h. The pH was adjusted to 6.4, then MgSO₄•7H₂O (100 µg/mL), FeSO₄•7H₂O (1 µg/mL), CaCl₂ (50 µg/mL), ZnSO₄•7H₂O (1 µg/mL), NaMoO₄•2H₂O (0.2 µg/mL) and MnCl₂•4H₂O (0.2 µg/mL) were added and the entire medium was sterilized by filtration. “Copper-plus AS” medium was prepared by adding CuCl₂•2H₂O to the copper-minus AS medium at 100 µM. Test compounds were dissolved in DMSO then dilutions in copper-minus AS and copper-plus AS media were prepared as 100 µL aliquots in flat-bottomed 96-well microtiter plates.

[0087] *Phytophthora capsici* was grown on petri plates, 9 cm in diameter, containing 15 mL V-8 agar, pH 7.0, containing 200 mL V-8 juice, 4 g CaCO₃, and 20 g agar per liter. Plates were inoculated with 7-mm plugs from a 1-week old culture, incubated at 25 °C in the dark for 3 days, and then placed under fluorescent lights for 4 days to induce sporulation. Zoospore release from sporangia was induced by adding 15 mL of sterile deionized water (which had been treated with Chelex 100 resin using 0.5 g resin per liter of water by stirring at room temperature for 1 h) to each plate, and incubating for 10 min at 25 °C followed by 20 min at 4 °C. The plates were returned to 25 °C for 10 min and the aqueous suspension of released zoospores was recovered.

The zoospore suspension was adjusted to 5×10^4 spores/mL by dilution into Chelex 100-treated water. Microtiter plates were inoculated with 100 μ L of spore suspension and incubated at 25 °C for 48 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader. Growth inhibition was determined by comparing growth in the presence of test compound with growth in control wells lacking test compound.

[0088] Results for growth inhibition by test compounds in copper-plus AS medium (“% Inhn. Plus Copper Observed”) were compared with predicted values (“% Inhn. Plus Copper Predicted”) that were calculated using the formula set forth by S.R. Colby in Weeds (1967), 15, 20-22 based on results obtained for the same compounds in copper-minus AS medium (“% Inhn. Minus Copper Observed”) and the inhibition attributed to copper chloride alone, as determined by comparing growth in copper-minus AS and copper-plus AS media without any test compound across experiments. Data are presented in Table 3. Results illustrate that hydrazones and copper produce a synergistic fungitoxic effect towards *Phytophthora capsici*.

Table 3.

Compound Number	Concentration (μ g/mL)	%Inhn Minus copper Observed	%Inhn Plus copper Observed	%Inhn Plus copper Predicted
1	0.050	0.0	91.2	4.5
3	0.050	0.0	88.2	4.5
10	0.050	2.9	81.4	7.3
27	0.050	4.7	42.1	9.0
41	0.050	0.0	87.9	4.5
52	0.050	0.0	71.1	4.5
63	0.050	2.4	91.2	6.8
74	0.050	0.0	30.8	4.5
CuCl ₂ , 50 uM		4.5 $\pm$ 7.9		

Example 15. Effect of copper on fungitoxicity of hydrazones towards *Ustilago maydis*

[0089] *In vitro* fungitoxicity assays against *Ustilago maydis* were conducted using the copper-minus medium described in Example 12. Medium containing copper was prepared by adding CuCl₂•2H₂O to the copper-minus medium at 20 μ M. Test compounds were dissolved in dimethylsulfoxide (DMSO) at 200 μ g/mL and 1 μ L aliquots were added to two wells of flat-bottomed 96-well microtiter plates. Copper-minus medium (100 μ L) was added to one of the

wells and copper-plus medium to the second well. Control wells, included for each medium, received 1 μ L DMSO and 100 μ L of medium.

[0090] *Ustilago maydis* was grown in 50 mL potato dextrose broth with shaking at 25 °C for 24 h. A 10 mL aliquot of the culture was centrifuged at 2000 rpm for 2 min, resuspended in 10 mL of sterile Chelex 100-treated water, and centrifuged again. The spores were resuspended in copper-minus medium, and the suspension adjusted to a concentration of 1×10^5 spores per mL. Microtiter plate wells containing test compound of DMSO (control) as described above were inoculated with 100 μ L of this spore suspension and the plates incubated at 25 °C for 48 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader. Growth inhibition was determined by comparing growth in the presence of test compound with growth in control wells lacking test compound.

[0091] Results for growth inhibition by test compounds at 1 μ g/mL in copper-plus medium (“% Inhn. Plus Copper Observed”) were compared with predicted results (“% Inhn. Plus Copper Predicted”) that were calculated using the formula set forth by S.R. Colby in *Weeds* **1967**, 15, 20-22 based on results obtained for the same compounds in copper-minus medium (“% Inhn. Minus Copper Observed”) and the inhibition attributed to copper chloride alone, as determined by comparing growth in copper-minus and copper-plus media without any test compound. Data are presented in Table 4. Results illustrate that hydrazones and copper produce a synergistic fungitoxic effect towards *Ustilago maydis*.

Table 4.

Compound Number	%Inhn. Minus copper Observed	%Inhn. Plus copper Observed	%Inhn. Plus copper Predicted
1	0.0	92.2	11.9
3	1.7	83.5	13.4
10	0.0	95.2	11.9
19	16.2	41.8	26.2
27	22.0	97.8	31.3
41	27.1	97.7	35.8
52	13.6	96.6	23.9
63	10.2	35.3	20.9
74	0.0	96.0	11.9
CuCl ₂ , 10 μ M		11.9	

Example 16. Effect of copper on fungitoxicity of hydrazones towards *Septoria tritici*

[0092] *In vitro* fungitoxicity assays against *Septoria tritici* were conducted using the copper-minus medium described in Example 12. Medium containing copper was prepared by adding $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ to the copper-minus medium at 2 μM . Test compounds were dissolved in dimethylsulfoxide (DMSO) at 10 $\mu\text{g}/\text{mL}$ and 1 μL aliquots were added to two wells of flat-bottomed 96-well microtiter plates. Copper-minus medium (100 μL) was added to one of the wells and copper-plus medium to the second well. Control wells, included for each medium, received 1 μL DMSO and 100 μL of medium.

[0093] *Septoria tritici* isolate USA-184 was grown on potato dextrose agar at 18 °C under black lights for 3 days. A loopful of spores was transferred from the culture to a 15 mL tube containing 5 mL of sterile Chelex-treated water. The spores were centrifuged at 2000 rpm for 2 min, resuspended in 10 mL water, and centrifuged again. The spores were resuspended in copper-minus medium, and the suspension adjusted to a concentration of 1×10^5 spores per mL. Microtiter plate wells containing test compound of DMSO (control) as described above were inoculated with 100 μL of this spore suspension and the plates incubated at 25 °C for 90 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader. Growth inhibition was determined by comparing growth in the presence of test compound with growth in control wells lacking test compound.

[0094] Results for growth inhibition by test compounds at 0.05 $\mu\text{g}/\text{mL}$ in copper-plus medium (“% Inhn. Plus Copper Observed”) were compared with predicted results (“% Inhn. Plus Copper Predicted”) that were calculated using the formula set forth by S.R. Colby in *Weeds* **1967**, 15, 20-22 based on results obtained for the same compounds in copper-minus medium (“% Inhn. Minus Copper Observed”) and the inhibition attributed to copper chloride alone, as determined by comparing growth in copper-minus and copper-plus media without any test compound. In this experiment, copper chloride alone (1 μM) had no effect on growth. Data are presented in Table 5. Results illustrate that hydrazones and copper produce a synergistic fungitoxic effect towards *Septoria tritici*.

Table 5.

Compound Number	%Inhibition Minus copper Observed	%Inhibition Plus copper Observed	%Inhibition Plus copper Predicted
1	16.2	93.5	16.2
3	3.6	88.0	3.6
10	9.5	92.1	9.5
19	14.9	55.1	14.9
27	46.8	97.1	46.8
41	44.4	97.1	44.4
52	57.5	97.0	57.5
63	5.8	92.0	5.8
74	27.5	92.4	27.5
CuCl ₂ , 1 μ M		0	

Example 15. Comparative efficacy of isolated copper-hydrazone complexes and parent hydrazones towards *Leptosphaeria nodorum*

[0095] Hydrazones and their isolated copper complexes were compared with respect to their *in vitro* fungitoxicity towards LEPTNO. Copper complexes of hydrazones were prepared by precipitation from ethanol with CuCl₂•2H₂O, at a 1:1 molar ratio, as described in general by Ainscough, Brodie, Dobbs, Ranford, and Waters (*Inorganica Chimica Acta* **1998**, 267, 27-38, which is expressly incorporated by reference herein).

[0096] A general synthesis of 1:1 metal-hydrazone complexes is as follows. The starting salicylaldehyde benzoylhydrazone or 2-hydroxyphenylketone benzoylhydrazone is dissolved (or suspended) in EtOH (generally 0.1 mmol hydrazone per mL solvent) and agitated at a temperature ranging from room temperature to 80 °C for 30 min. To this solution (or suspension) is added 1 equivalent of the metal salt (generally as a 1 M solution in EtOH). The mixture is agitated for a period ranging from 1 to 24 h at a temperature ranging from room temperature to 80 °C. The metal-hydrazone complex generally precipitates during the reaction or upon cooling and is isolated by filtration, washed with EtOH and finally washed with Et₂O. In the instances where the complex does not precipitate, the solvent is removed and the resulting solid metal-hydrazone complex is washed with Et₂O. Properties of particular copper complexes of hydrazones are provided in Table 6 below.

Table 6.

Complex Number	Compound Number	Metal Salt	Ratio Hydrazone:Metal Salt	Description	mp (°C)
89	3	CuCl ₂ •2H ₂ O	1:1	olive green solid	286-289
90	10	CuCl ₂ •2H ₂ O	1:1	olive green solid	280-286
91	27	CuCl ₂ •2H ₂ O	1:1	olive green solid	279-281
92	38	CuCl ₂ •2H ₂ O	1:1	olive green solid	295-305
93	49	CuCl ₂ •2H ₂ O	1:1	olive green solid	279-281
94	60	CuCl ₂ •2H ₂ O	1:1	olive green solid	259-281
95	71	CuCl ₂ •2H ₂ O	1:1	olive green solid	270-274

[0097] *In vitro* fungitoxicity assays were conducted using the copper-minus medium described in Example 12. Test compounds were dissolved in dimethylsulfoxide (DMSO) then dilutions in copper-minus medium were prepared as 100 µL aliquots in flat-bottomed 96-well microtiter plates. Microtiter plates were inoculated with 100 µL of spore suspension at a concentration of 2×10^5 spores per mL, prepared as in Example 12. The plates were incubated at 25 °C for 72 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader. Growth inhibition was determined by comparing growth in the presence of test compound with growth in control wells lacking test compound.

[0098] Results for growth inhibition by hydrazones and corresponding isolated copper complexes (each at 0.1 µg/mL) are shown in Table 7. The results illustrate that isolated copper complexes of hydrazones are much more fungitoxic than the corresponding hydrazones.

Table 7.

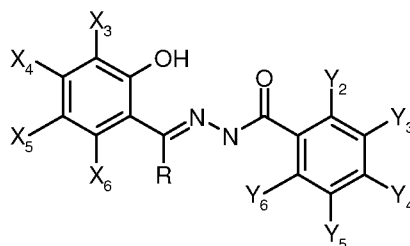
Complex Number	Compound Number	Metal Salt	Ratio*	Hydrazone % Inhibition	Complex % Inhibition
89	3	CuCl ₂ •2H ₂ O	1:1	0.6	91.9

Complex Number	Compound Number	Metal Salt	Ratio*	Hydrazone % Inhibition	Complex % Inhibition
90	10	CuCl ₂ •2H ₂ O	1:1	22.1	94.6
91	27	CuCl ₂ •2H ₂ O	1:1	39.9	97.9
92	38	CuCl ₂ •2H ₂ O	1:1	23.9	91.8
93	49	CuCl ₂ •2H ₂ O	1:1	43.9	97.1
94	60	CuCl ₂ •2H ₂ O	1:1	23.8	95.8
95	71	CuCl ₂ •2H ₂ O	1:1	19.3	96.7

*Molar ratio of hydrazone:metal used to prepare complexes.

CLAIMS:

1. A compound of Formula 1



Formula 1

wherein R is H, C1-C4 alkyl, C3-C6 cycloalkyl, C1-C4 haloalkyl, or C3-C6 halocycloalkyl,;

R1 is H, C1-C4 alkyl, C3-C6 cycloalkyl, C1-C4 haloalkyl, C3-C6 halocycloalkyl, substituted aryl, substituted heteroaryl, unsubstituted aryl, or unsubstituted heteroaryl;

X3, X4, X5, and X6 are independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 alkylthio, C1-C4 haloalkyl, C1-C4 haloalkoxy, C2-C4 haloalkenyl, C2-C4 haloalkynyl, C1-C4 haloalkylthio, -SO₂R1, SONR1R1, -CR1=NOR1, -CONR1R1, NR1COOR1, -COOR1, substituted aryl, substituted heteroaryl, unsubstituted aryl, and unsubstituted heteroaryl; and

Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 alkylthio, C1-C4 haloalkyl, C1-C4 haloalkoxy, C2-C4 haloalkenyl, C2-C4 haloalkynyl, C1-C4 haloalkylthio, -SO₂R1, SONR1R1, -R1=NOR1, -CONR1R1, NR1COOR1, -COOR1, substituted aryl, substituted heteroaryl, unsubstituted aryl, unsubstituted heteroaryl, and phenoxy;

with the proviso that

X3 and X4, X4 and X5, X5 and X6, Y2 and Y3, or Y3 and Y4 may form a 5 or 6 membered fused ring which may contain up to two heteroatoms selected from the group consisting of O, N, and S; and

at least one X3, X4, X5, and X6 is C1-C4 haloalkyl.

2. The compound of claim 1, wherein

R is H, C1-C4 alkyl, C3-C6 cycloalkyl, C1-C4 haloalkyl, or C3-C6 halocycloalkyl;

R1 is H, C1-C4 alkyl, C3-C6 cycloalkyl, C1-C4 haloalkyl, C3-C6 halocycloalkyl, substituted aryl, or unsubstituted aryl;

X3, X4, X5, and X6 are independently selected from the group consisting of halogen, nitro, cyano, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C2-C4 alkenyl, and C1-C4 alkylthio; and

Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylthio, C1-C4 haloalkyl, C1-C4 haloalkoxy, C1-C4 haloalkylthio - NR1R1, unsubstituted aryl, substituted aryl, and phenoxy;

with the proviso that

X3 and X4, X5 and X6, or Y3 and Y4 may form a 5 or 6 membered fused ring which may contain up to two heteroatoms selected from the group consisting of O and N.

3. The compound of claim 2, wherein

R is H or CH₃;

X3, X4, X5, and X6 are independently selected from the group consisting of halogen, nitro, cyano, C1-C4 alkyl, C1-C4 fluoroalkyl, and C1-C4 alkoxy; and

Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, and C1-C4 haloalkoxy;

with the proviso that

at least one of X3, X4, X5, and X6 is C1-C4 fluoroalkyl; and

Y3 and Y4 may form a 5 or 6 membered fused ring which may contain up to two heteroatoms selected from the group consisting of O and N.

4. The compound of claim 3, wherein

X3, X4, X5, and X6 are independently selected from the group consisting of halogen, nitro, cyano, trifluoromethyl, methyl, and methoxy; and

Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of H, halogen, nitro, hydroxyl, trifluoromethyl, methyl, and methoxy;

with the proviso that

at least one of X3, X4, X5, and X6 is trifluoromethyl; and

Y3 and Y4 may form a 5 or 6 membered fused ring which may contain up to two heteroatoms selected from the group consisting of O and N.

5. The compound of claim 4, wherein

X3, X4, X5, and X6 are independently selected from the group consisting of halogen and trifluoromethyl.

6. A synergistic mixture including a compound of claim 1 and copper.
7. Use of the synergistic mixture of claim 6 for controlling the growth of fungal pathogens of plants.
8. Use of the synergistic mixture of claim 6 for controlling the growth of fungal of mammals.
9. Use of the synergistic mixture of claim 6 for controlling the growth of fungi on inert substrates selected from the group consisting essentially of wood, metal, and plastic.
10. Use of the synergistic mixture of claim 6 for controlling the growth of fungi belonging to at least one of Ascomycete, Basidiomycete, Oomycete, and Deuteromycete classes of fungi.
11. The mixture of synergistic claim 6 wherein the fungi is selected from the group consisting of *Phytophthora* species, *Plasmopara viticola*, *Pseudoperonospora cubensis*, *Pythium* species, *Pyricularia oryzae*, *Colletotrichum* species, *Helminthosporium* species, *Alternaria* species, *Septoria nodorum*, *Leptosphaeria nodorum*, *Ustilago maydis*, *Erysiphe graminis*, *Puccinia* species, *Sclerotinia* species, *Sphaerotheca fuliginea*, *Cercospora* species, *Rhizoctonia* species, *Uncinula necator* and *Podosphaera leucotricha*.
12. The synergistic mixture of claim 6, wherein a growth inhibiting amount of a compound of Formula 1 in mixture with copper is provided as a mixture in which the total molar ratio of copper to the compound of claim 1 exceeds 1:1.

13. The synergistic mixture of claim 1, wherein a growth inhibiting amount of a compound of Formula 1 is provided as an isolated hydrazone-copper complex in which the molar ratio of the copper to the compound of claim 1 is one of 1:1 and 1:2.

14. The synergistic mixture of claim 1, wherein the compound of Formula 1 to be combined with copper is complexed with a metal.

15. The synergistic mixture of claim 14, wherein the metal complexed with the compound of Formula 1 is selected from the group consisting essentially of Cu^+ , Cu^{2+} , Fe^{2+} , Fe^{3+} , Zn^{2+} , and Mn^{2+} .

16. The synergistic mixture of claim 1, wherein the copper is provided as at least one of the group consisting of copper oxychloride, copper octanoate, copper ammonium carbonate, copper arsenate, copper oxysulfate, copper formate, copper propionate, copper oxyacetate, copper citrate, copper chloride, copper diammonium chloride, copper nitrate, copper carbonate, copper phosphate, copper pyrophosphate, copper disodium EDTA, copper diammonium EDTA, copper oxalate, copper tartrate, copper gluconate, copper glycinate, copper glutamate, copper aspartate, copper adipate, copper palmitate, copper stearate, copper caprylate, copper decanoate, copper undecylenate, copper neodecanoate, copper linoleate, copper oleate, copper borate, copper methanesulfonate, copper sulfamate, copper acetate, copper hydroxide, copper oxide, copper oxychloride-sulfate, copper sulfate, basic copper sulfate, copper-oxine, copper 3-phenylsalicylate, copper chloride hydroxide, copper dimethyldithiocarbamate, ammonium copper sulfate, copper magnesium sulfate, coppernaphthenate, copper ethanolamine, chromated copper arsenate, ammoniacal copper arsenate, ammoniacal copper zinc arsenate, ammoniacal copper borate, Bordeaux mixture, copper zinc chromate, cufraneb, cupric hydrazinium sulfate, cuprobam, nano-copper materials, and copper didecyldimethylammonium chloride.