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

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



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**SYNERGISTIC 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 invention relates to the use of hydrazones in combination with copper, copper-based fungicides or other copper-containing materials as synergistic fungicidal mixtures.

Background

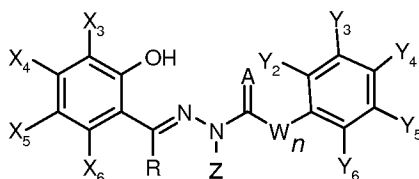
**[0003]** Copper is used to control the growth of organisms, especially microorganisms, in a variety of applications such as those described in the “Handbook of copper compounds and applications” edited by H. W. Richardson and published by Marcel Dekker, Inc. New York (1997), which is expressly incorporated 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.

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Summary of the Invention

**[0005]** One exemplary embodiment of the present disclosure includes a synergistic mixture for controlling the growth of fungi, the synergistic mixture including copper and a hydrazone compound of Formula I:



Formula I

wherein A is oxygen or sulfur;

Z is H or C1-C4 alkyl;

W is -CHR1-;

*n* is 0, 1, or 2;

R is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 haloalkyl, C2-C6 haloalkenyl, C2-C6 haloalkynyl, or C3-C6 halocycloalkyl;

R1 is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 haloalkyl, C2-C6 haloalkenyl, C2-C6 haloalkynyl, C3-C6 halocycloalkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl;

X3, X4, X5, and X6 are each 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, -SO<sub>2</sub>R1, SONR1R1, -CR1=NOR1, -CONR1R1, NR1COOR1, -COOR1, substituted aryl, substituted heteroaryl, unsubstituted aryl, and unsubstituted heteroaryl; and

Y2, Y3, Y4, Y5, and Y6 are each independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C2-C4 alkenyl, C2-C4

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alkynyl, C1-C4 alkylthio, C1-C4 haloalkyl, C1-C4 haloalkoxy, C2-C4 haloalkenyl, C2-C4 haloalkynyl, C1-C4 haloalkylthio, -SO<sub>2</sub>R<sub>1</sub>, SONR<sub>1</sub>R<sub>1</sub>, -R<sub>1</sub>=NOR<sub>1</sub>, -CONR<sub>1</sub>R<sub>1</sub>, NR<sub>1</sub>COOR<sub>1</sub>, -COOR<sub>1</sub>, NR<sub>1</sub>R<sub>1</sub>, substituted aryl, substituted heteroaryl, unsubstituted aryl, unsubstituted heteroaryl, and phenoxy;

with the proviso that X<sub>3</sub> and X<sub>4</sub>, X<sub>4</sub> and X<sub>5</sub>, X<sub>5</sub> and X<sub>6</sub>, Y<sub>2</sub> and Y<sub>3</sub>, or Y<sub>3</sub> and Y<sub>4</sub> 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.

**[0006]** 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.

**[0007]** The term "cycloalkyl" refers to a monocyclic or polycyclic, saturated substituent consisting of carbon and hydrogen.

**[0008]** 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.

**[0009]** The term "alkynyl" refers to a branched or unbranched carbon chain containing one or more triple bonds including propynyl, butynyl and the like.

**[0010]** As used throughout this specification, the term 'R' refers to the group consisting of C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 haloalkyl, C2-C6 haloalkenyl, C2-C6 haloalkynyl, or C3-C6 halocycloalkyl, unless stated otherwise.

**[0011]** The term "alkoxy" refers to an -OR substituent.

**[0012]** The term "alkylthio" refers to an -S-R substituent.

**[0013]** The term "haloalkylthio" refers to an alkylthio, which is substituted with Cl, F, I, or Br or any combination thereof.

**[0014]** The term "cyano" refers to a -C≡N substituent.

**[0015]** The term "hydroxyl" refers to an -OH substituent.

**[0016]** The term "haloalkoxy" refers to an -OR-X substituent, wherein X is Cl, F, Br, or I, or any combination thereof.

**[0017]** The term "haloalkyl" refers to an alkyl, which is substituted with Cl, F, I, or Br or any combination thereof.

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**[0018]** 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.

**[0019]** The term “haloalkenyl” refers to an alkenyl, which is substituted with Cl, F, I, or Br or any combination thereof.

**[0020]** The term “haloalkynyl” refers to an alkynyl which is substituted with Cl, F, I, or Br or any combination thereof.

**[0021]** The term “halogen” or “halo” refers to one or more halogen atoms, defined as F, Cl, Br, and I.

**[0022]** The term “aryl” refers to a cyclic, aromatic substituent consisting of hydrogen and carbon.

**[0023]** 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.

**[0024]** The term “phenoxy” refers to an -O substituted with a six-membered fully unsaturated ring consisting of hydrogen and carbon.

**[0025]** The term “nitro” refers to a -NO<sub>2</sub> substituent.

**[0026]** 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.

**[0027]** 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

**[0028]** 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

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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.

**[0029]** The mixtures of the present invention have fungitoxic activity against phytopathogenic fungi, against fungal pathogens of mammals, including humans, and against wood decay causing fungi. The mixtures 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*, *Leptosphaeria nodorum*, *Ustilago maydis*, *Erysiphe graminis*, *Puccinia* species, *Sclerotinia* species, *Sphaerotheca fuliginea*, *Cercospora* species, *Rhizoctonia* species, *Uncinula necator*, *Septoria tritici*, and *Podosphaera leucotricha*.

**[0030]** 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*, *Microsporium* 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*.

**[0031]** The present invention contemplates all vehicles by which the composition of the present invention can be formulated for delivery and use as a pesticide composition, including solutions, suspensions, emulsions, wettable powders and water dispersible granules, emulsifiable concentrates, granules, dusts, baits, and the like. Typically, formulations are applied following dilution of the concentrated formulation with water as aqueous solutions, suspensions or emulsions, or combinations thereof. Such solutions, suspensions or emulsions are produced from water-soluble, water-suspended or water-suspendable, water-emulsified or water-emulsifiable formulations or combinations thereof which are solids, including and usually known as wettable powders or water dispersible

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granules; or liquids including and usually known as emulsifiable concentrates, aqueous suspensions or suspension concentrates, and aqueous emulsions or emulsions in water, or mixtures thereof such as suspension-emulsions. As will be readily appreciated, any material to which this composition can be added may be used, provided they yield the desired utility without significant interference with the desired activity of the pesticidally active ingredients as pesticidal agents and improved residual lifetime or decreased effective concentration is achieved.

**[0032]** Wettable powders, which may be compacted to form water dispersible granules, comprise an intimate mixture of one or more of the pesticidally active ingredients, an inert carrier and surfactants. The concentration of the pesticidally active ingredient in the wettable powder is usually 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 pesticidally active ingredients can be compounded with any finely divided solid, such as prophyllite, talc, chalk, gypsum, Fuller's earth, bentonite, attapulgite, 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.

**[0033]** Emulsifiable concentrates of the pesticidally active ingredient comprise a convenient concentration, such as from about 10 weight percent to about 50 weight percent of the pesticidally active ingredient, in a suitable liquid, based on the total weight of the concentrate. The pesticidally active ingredients are 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, such as, for example, terpenic solvents, including rosin derivatives, aliphatic ketones, such as cyclohexanone, and complex alcohols, such as 2-ethoxyethanol.

**[0034]** Emulsifiers which can be advantageously employed herein can 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

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phenols and carboxylic esters esterified 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 sulfonic acids, oil-soluble salts of sulfated polyglycol ethers and appropriate salts of phosphated polyglycol ether.

**[0035]** Representative organic liquids which can be employed in preparing emulsifiable concentrates 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 dim-ethyl amides; and glycol ethers 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. Surface-active emulsifying 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 emulsifying agents. The formulations can also contain other compatible additives, for example, plant growth regulators and other biologically active compounds used in agriculture.

**[0036]** Aqueous suspensions comprise suspensions of one or more water-insoluble pesticidally active ingredients 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 pesticidally active ingredients, 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.

**[0037]** 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.

**[0038]** The compositions of the present invention can also be granular formulations, which are particularly useful for applications to the soil. Granular formulations usually contain from about 0.5 to about 10 weight percent, based on the total weight of the granular formulation of the pesticidally active ingredient(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 pesticidally active ingredients 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.

**[0039]** Dusts can be prepared by intimately mixing one or more of the pesticidally active ingredients 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.

**[0040]** The formulations may additionally contain adjuvant surfactants to enhance deposition, wetting and penetration of the pesticidally active ingredients onto the target site such as a crop or 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 of sulfosuccinic acids, ethoxylated organosilicones, ethoxylated fatty amines and blends of surfactants with mineral or vegetable oils.

**[0041]** The formulations may optionally include combinations that contain other pesticidal compounds. Such additional pesticidal compounds may be fungicides, insecticides, nematocides, miticides, arthropodocides, bactericides or combinations thereof that are compatible with the mixtures of the present invention in the medium selected for application, and not antagonistic to the activity of the present mixtures. Accordingly, in such embodiments, the other pesticidal compound is employed as a supplemental toxicant for the

same or for a different pesticidal use. The mixtures of the present invention, and the pesticidal compound in the combination can generally be present in a weight ratio of from 1:100 to 100:1.

**[0042]** For pharmaceutical use, the mixtures 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 mixtures described herein, salts thereof, hydrates, and mixtures 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.

**[0043]** The mixtures of the present invention can also be combined with other agricultural fungicides to form fungicidal mixtures and synergistic mixtures thereof. The fungicidal mixtures of the present invention 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 mixtures can 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 include amisulbrom 2-(thiocyanatomethylthio)-benzothiazole, 2-phenylphenol, 8-hydroxyquinoline sulfate, antimycin, Ampelomyces, quisqualis, azaconazole, azoxystrobin, *Bacillus subtilis*, benalaxyl, benomyl, benthiavalicarb-isopropyl, benzylaminobenzene-sulfonate (BABS) salt, bicarbonates, biphenyl, bismethiazol, bitertanol, bixafen, blasticidin-S, borax, , boscalid, bromuconazole, bupirimate, BYF 1047, calcium polysulfide, captafol, captan, carbendazim, carboxin, carpropamid, carvone, chloroneb, chlorothalonil, chlozolate, *Coniothyrium minitans*, cyazofamid, cyflufenamid, cymoxanil, cyproconazole, cyprodinil, coumarin, 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, fenciclonil,

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fenpropidin, fenpropimorph, fentin, fentin acetate, fentin hydroxide, ferbam, ferimzone, fluazinam, fludioxonil, flumorph, fluopicolide, fluopyram, fluoroimide, fluoxastrobin, fluquinconazole, flusilazole, flusulfamide, flutolanil, flutriafol, 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, meptyldinocap, 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, mildiomyacin, myclobutanil, nabam, nitrothal-isopropyl, nuarimol, octhilinone, ofurace, oleic acid (fatty acids), orysastrobin, oxadixyl, oxine-copper, oxpoconazole fumarate, oxycarboxin, pefurazoate, penconazole, pencycuron, pentachlorophenol, pentachlorophenyl laurate, penthiopyrad, phenylmercury acetate, phosphonic acid, phthalide, picoxystrobin, polyoxin B, polyoxins, polyoxorim, potassium bicarbonate, potassium hydroxyquinoline sulfate, probenazole, prochloraz, procymidone, propamocarb, propamocarb hydrochloride, propiconazole, propineb, pro-quinazid, prothioconazole, pyraclostrobin, pyrazophos, pyribencarb, pyributicarb, pyrifenox, pyrimethanil, pyroquilon, quinoclamine, quinoxifen, quintozone, *Reynoutria sachalinensis* extract, silthiofam, simeconazole, sodium 2-phenylphenoxide, sodium bicarbonate, sodium pentachlorophenoxide, spiroxamine, sulfur, SYP-Z071, SYP-048, SYP-Z048, tar oils, tebuconazole, tecnazene, tetraconazole, thiabendazole, thifluzamide, thiophanate-methyl, thiram, tiadinil, tolclofos-methyl, tolylfluanid, triadimefon, triadimenol, triazolopyrimidine, triazoxide, tricyclazole, tridemorph, trifloxystrobin, triflumizole, triforine, triticonazole, validamycin, vinclozolin, zineb, ziram, zoxamide, *Candida oleophila*, *Fusarium cocysporum*, *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-dithiane 1,1,4,4-tetraoxide, 2-methoxyethylmercury acetate, 2-methoxyethylmercury chloride, 2-methoxyethylmercury silicate, 3-(4-chloro-phenyl)-5-methylrhodanine, 4 - (2 -nitroprop-1-enyl) phenyl thiocyanateme, ampropylfos, anilazine, azithiram, barium polysulfide, Bayer 32394, benodanil,

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benquinox, bentaluron, benzamacril; benzamacril-isobutyl, benzamorf, binapacryl, bis (methylmercury) sulfate, bis (tributyltin) oxide, buthiobate, cadmium calcium copper zinc chromate sulfate, carbamorph, CECA, chlobenthiazole, chloraniformethan, chlorfenazole, chlorquinox, climbazole, cyclafuramid, cypendazole, cyprofuram, decafentin, dichlone, dichlozo-line, diclobutrazol, dimethirimol, dinocton, 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, isovalledione, mebenil, mecarbinzid, metazoxolon, methfuroxam, methylmercury dicyandiamide, metsulfovax, milneb, mucochloric anhydride, myclozolin, N-3,5-dichlorophenyl-succinimide, N-3-nitrophenyl-itaconimide, natamycin, N-ethylmercurio-4-toluenesulfonanilide, nickel bis(dimethyldithio-carbamate), OCH, phenylmercury dimethyldithiocarbamate, phenylmercury nitrate, phos-diphen, picolinamide UK-2A and derivatives thereof, prothiocarb; prothiocarb hydrochloride, pyracar-bolid, pyridinitril, pyroxychlor, pyroxyfur, quinacetol; quinacetol sulfate, quinazamid, quinconazole, rabenzazole, salicylanilide, SSF-109, sultropen, tecoram, thiadifluor, thi-cyofen, thiochlorfenphim, thiophanate, thioquinox, tioxymid, triamiphos, triarimol, triazbutil, trichlamide, urbacid, XRD-563, and zarilamide, IK-1140, propargyl amides and any combinations thereof.

**[0044]** The mixtures 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 mixtures 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 mixtures 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.

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**[0045]** Additionally, the mixtures of the present invention can be combined with other pesticides, including insecticides, nematocides, miticides, arthropodicides, bactericides or combinations thereof that are compatible with the mixtures of the present invention in the medium selected for application, and not antagonistic to the activity of the present mixtures to form pesticidal mixtures and synergistic mixtures thereof. The fungicidal mixtures of the present invention are often 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 mixtures can 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; avermectin insecticides such as abamectin, doramectin, emamectin, eprinomectin, ivermectin and selamectin; milbemycin insecticides such as lepmectin, 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 anabasin, 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, butoxy-carboxim, methomyl, nitrilcarb, 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, mexacarb, promacyl, promecarb, propoxur, trimethacarb, XMC and xylylcarb; 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,

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calcium polysulfide, copper oleate, mercurous chloride, potassium thiocyanate and sodium thiocyanate; chitin synthesis inhibitors such as bistrifluoron, 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 .alpha.-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; nereistoxin 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, 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

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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, pyrimitate 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, methamidophos and propetamphos; phosphorodiamide insecticides such as dimefox, mazidox, mipafox and schradan; oxadiazine insecticides such as indoxacarb; phthalimide insecticides such as dialifos, phosmet and tetramethrin; pyrazole insecticides such as acetoprole, cyenopyrafen, ethiprole, fipronil, pyrafluprole, pyriprole, tebufenpyrad, tolfenpyrad and vanilprole; pyrethroid ester insecticides such as acrinathrin, allethrin, bioallethrin, barthrin, bifenthrin, bioethanomethrin, cyclethrin, 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, metofluthrin, permethrin, biopermethrin, transpermethrin, phenothrin, prallethrin, profluthrin, pyresmethrin, resmethrin, bioresmethrin, cismethrin,

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tefluthrin, terallethrin, tetramethrin, tralomethrin and transfluthrin; pyrethroid ether insecticides such as etofenprox, flufenprox, halfenprox, protrifenbute and silafluofen; pyrimidinamine insecticides such as flufennerim and pyrimidifen; pyrrole insecticides such as chlorfenapyr; tetrone acid insecticides such as spiromesifen; thiourea insecticides such as diafenthiuron; urea insecticides such as flucofuron and sulcofuron; and unclassified insecticides such as closantel, crotamiton, EXD, fenazaflor, fenoxacrim, flubendiamide, hydramethylnon, isoprothiolane, malonoben, metaflumizone, metoxadiazon, nifluridide, pyridaben, pyridalyl, rafoxanide, triarathene, triazamate, meptyldinocap, pyribencarb and any combinations thereof.

**[0046]** The mixtures have broad ranges of efficacy as fungicides. The exact amounts of hydrazones and copper-containing materials to be applied is dependent not only on the specific materials being applied and relative amounts of hydrazone and copper in the mixtures, but also on the, 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 mixture. Thus, all the mixtures, and formulations containing the same, may not be equally effective at similar concentrations or against the same fungal species.

**[0047]** The mixtures 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 mixture that kills or inhibits the plant disease for which control is desired, but is not significantly toxic to the plant. The exact amount of a mixture 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. The dilution and rate of application will depend upon the type of equipment employed, the method and frequency of application desired and diseases to be controlled. 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.

**[0048]** 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

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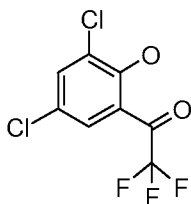
applied as a fertilizer component, copper present in the water used in preparing fungicide solutions for application such as in spray application, copper present in formulations used in preparing spray solutions or dusts for application, or any other suitable copper source.

**[0049]** 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.

**[0050]** 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.

**[0051]** 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, which is 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, 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. Examples 23, 24, and 25 below provide typical methods for the preparation of such benzoylhydrazones. Example 31 below provides a general method for the preparation of their metal complexes.

**Example 1. Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)-2,2,2-trifluoroethanone**

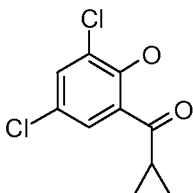


**[0052]** 2,4-Dichloro-6-iodophenol (2.0 grams (g), 6.9 millimoles (mmol)) was dissolved in dry tetrahydrofuran (THF; 20 milliliters (mL)), cooled to -30 to -40 °C, treated in

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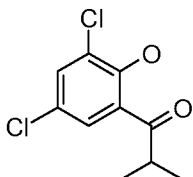
portions with isopropyl magnesium chloride-lithium chloride complex (1.3 M in THF; 7.3 mmol) and stirred for 45 minutes (min) as the temperature was allowed to rise to 0 °C. The mixture was cooled to -30 °C, treated with 8 mL (10 mmol) of the Grignard reagent and stirred for 30 min at -30 °C. Ethyl trifluoroacetate (2.4 mL, 2.8 g, 20 mmol) was added, and the mixture was stirred for 15 min at -30 °C, warmed to 25 °C and stirred for 2 hours (h). The reaction was quenched by addition of saturated (satd) ammonium chloride (NH<sub>4</sub>Cl; 10mL), diluted with ethyl acetate (EtOAc; 50 mL) and washed with 1 M hydrochloric acid (HCl; 20 mL), satd sodium chloride (NaCl; 10 mL), dried over sodium sulfate (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by silica gel chromatography with 0-20% EtOAc/hexane to give the purified ketone (1.2 g): mp 50–52 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 2.4 Hz, 1H), 5.92 (s, 1H); EIMS *m/z* 258.

**Example 2. Preparation of cyclopropyl-(3,5-dichloro-2-hydroxyphenyl)-methanone**



**[0053]** *N*-(3,5-Dichloro-2-hydroxybenzoyl)benzotriazole (prepared according to Katritzky et al., *Synthesis* **2007**, 20, 3141-3146, which is expressly incorporated by reference herein; 2.0 g, 6.5 mmol) was stirred in dry THF (25 mL), cooled to -30 °C, treated in portions with cyclopropylmagnesium bromide (0.5 M in THF; 28 mL, 14 mmol) and stirred at -30 °C for 30 min. The cooling bath was removed and the mixture was allowed to warm to 25 °C and stir for 3 h. The reaction was quenched by addition of 10 mL satd NH<sub>4</sub>Cl, and shaken with EtOAc (50 mL) plus 20% citric acid solution (30 mL). The organic phase was washed with satd NaCl (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by silica gel chromatography with 0-20% EtOAc/hexane to give the purified ketone (450 mg): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 13.03 (s, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.57 (d, *J* = 2.5 Hz, 1H), 2.70–2.54 (m, 1H), 1.41–1.32 (m, 2H), 1.24–1.15 (m, 2H); EIMS *m/z* 230.

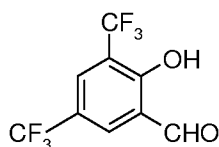
**Example 3. Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)-2-methylpropan-1-one**



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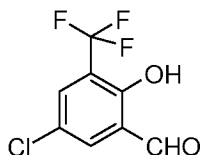
**[0054]** Methyl-3,5-dichlorosalicylate (prepared according to Ahmed et al., *Medicinal Chemistry* **2008**, 4, 298-308, which is expressly incorporated by reference herein; 2.0 g, 9.0 mmol) was dissolved in dry THF (30 mL), cooled to -40 °C and treated in portions with isopropyl magnesium chloride, 2.0 M in THF; 10 mL, 20 mmol). The mixture was stirred at -20 to -40 °C for 45 min, warmed to 25 °C and stirred for 4 h. The excess reagent was quenched by addition of satd NH<sub>4</sub>Cl (10 mL). The mixture was diluted with EtOAc (50 mL) and the pH was adjusted to ~1 by addition of 1 M HCl. The organic phase was washed with satd NaCl solution (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by reverse-phase high-performance liquid chromatography (RP-HPLC) with 70% acetonitrile to give the purified ketone (1.1 g): mp: 102–104 °C <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 2.5 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 3.54 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 6H); EIMS *m/z* 232.

**Example 4. Preparation of 2-hydroxy-3,5-bis-trifluoromethylbenzaldehyde**



**[0055]** 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 g, 7.7 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL), cooled to -78 °C and treated in portions with BBr<sub>3</sub> (1 M solution in CH<sub>2</sub>Cl<sub>2</sub>; 8.0 mL, 8.0 mmol). The mixture was stirred and allowed to warm to 25 °C. After 20 h, the mixture was cooled to -40 °C, carefully treated with H<sub>2</sub>O (10 mL) and warmed to room temperature. The separated organic phase was washed with H<sub>2</sub>O (10 mL), satd NaCl solution (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by silica gel chromatography with a 0 to 20% gradient of EtOAc in hexane to give the purified aldehyde (1.4 g, 70%) as an oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.05 (s, 1H), 10.02 (s, 1H), 8.07 (s, 2 H). EIMS *m/z* 258.

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

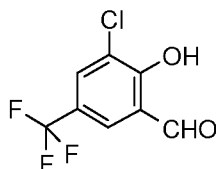


**[0056]** 5-Chloro-2-fluorobenzotrifluoride (1.5 g, 7.5 mmol) was dissolved in dry THF (10 mL), treated with tetramethylethylenediamine (TMEDA; 1.6 mL, 11 mmol), cooled

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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 min, the mixture was treated with *N,N*-dimethylformamide (DMF; 770  $\mu$ L, 730 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 addition of satd NH<sub>4</sub>Cl solution then diluted with Et<sub>2</sub>O (30 mL). The separated organic phase was washed with satd NaCl (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was dissolved in dry methanol (CH<sub>3</sub>OH; 10 mL) and treated with 30% sodium methoxide solution in CH<sub>3</sub>OH (14 g). The mixture was stirred at 25 °C for 20 h, diluted with H<sub>2</sub>O (50 mL) and extracted with Et<sub>2</sub>O (2 x 40 mL). The combined organic phases were washed with satd NaCl solution (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) 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, 4.2 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL), cooled to -78 °C and treated with BBr<sub>3</sub> (1 M solution in CH<sub>2</sub>Cl<sub>2</sub>; 5 mL, 5 mmol). The mixture was allowed to warm to 25 °C and stir for 22 h. After cooling to -45 °C, the mixture was treated with H<sub>2</sub>O (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 (Na<sub>2</sub>SO<sub>4</sub>) 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): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  11.61 (s, 1H), 9.91 (s, 1H), 7.77 (dd, *J* = 18.5, 2.6 Hz, 2H); EIMS *m/z* 224.

**Example 6. Preparation of 3-chloro-2-hydroxy-5-trifluoromethylbenzaldehyde**

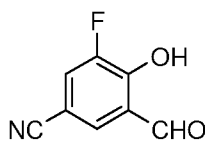


**[0057]** 3-Chloro-2-fluoro-5-trifluoromethylbenzaldehyde (5.0 g, 22 mmol) was dissolved in dry CH<sub>3</sub>OH (50 mL), treated with 25% sodium methoxide solution (30 mL) and heated to reflux for 2 h. After cooling the volatiles were removed by evaporation and the residue was taken up in H<sub>2</sub>O (20 mL) plus Et<sub>2</sub>O (80 mL). The aqueous phase was extracted with Et<sub>2</sub>O (50 mL), and the combined organic phases were washed with satd NaCl solution (15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL), cooled to -78 °C and treated with BBr<sub>3</sub> (1 M solution in CH<sub>2</sub>Cl<sub>2</sub>; 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 H<sub>2</sub>O (30 mL). After warming the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (30

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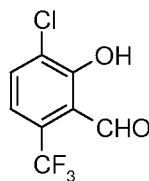
mL), and the combined org. phases were washed with satd NaCl solution (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was purified by silica gel chromatography with 0-20% EtOAc gradient in hexane to give the purified aldehyde (2.7 g):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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 7. Preparation of 3-fluoro-5-formyl-4-hydroxybenzonitrile**



**[0058]** 4-Cyano-2-fluorophenol (5.0 g, 38 mmol) was dissolved in acetic acid (50 mL) and treated dropwise with stirring with bromine (6.4 g, 40 mmol). After 2 h at 25 °C,  $\text{H}_2\text{O}$  (100 mL) was added. The precipitated product was collected by filtration, washed well with  $\text{H}_2\text{O}$  and then taken up in EtOAc (150 mL). The solution was washed with  $\text{H}_2\text{O}$  (50 mL), satd NaCl solution (50dmL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was crystallized from aqueous ethanol (EtOH) to give the bromophenol (4.1 g). This material (3.4 g, 16 mmol) was dissolved in dry THF (100 mL), cooled to -78 °C and treated dropwise with *n*-BuLi (2.5 M in hexanes; 16 mL, 39 mmol) over 15 min. After stirring for 90 min at -78 °C, DMF (3.5 mL, 3.3 g, 45 mmol) was added and stirring was continued for 30 min at -78 °C and then warmed to 25 °C over 2 h. Satd  $\text{NH}_4\text{Cl}$  solution (25 mL) and  $\text{Et}_2\text{O}$  (100 mL) were added, and the pH was adjusted to 2 with 1 M HCl. The separated organic phase was washed with satd NaCl solution, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was purified on silica gel chromatography with 10-50% EtOAc/hexane to give the aldehyde (2.1 g):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.48 (s, 1H), 9.96 (d,  $J = 1.7$  Hz, 1H), 7.78 (t,  $J = 1.5$  Hz, 2H), 7.61 (dd,  $J = 9.8, 1.9$  Hz, 2H); EIMS  $m/z$  165.

**Example 8. Preparation of 3-chloro-2-hydroxy-6-trifluoromethylbenzaldehyde**

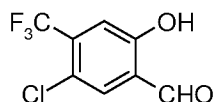


**[0059]** 4-Chloro-3-fluoro-6-trifluoromethylbenzaldehyde (1.0 g, 4.4 mmol) was dissolved in dry  $\text{CH}_3\text{OH}$  (10 mL), treated with 30% sodium methoxide solution in  $\text{CH}_3\text{OH}$  (7.9 g, 44 mmol) and heated at reflux for 1 h. After cooling the mixture was diluted with  $\text{H}_2\text{O}$  (15 mL) and extracted with  $\text{Et}_2\text{O}$  (30 mL). The combined organic extracts were washed with satd NaCl solution (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residue was purified by

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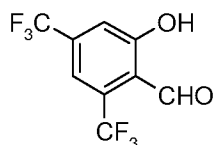
silica gel chromatography with 0-10% EtOAc/hexane to give the anisole intermediate (1.0 g). This material was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL), cooled to -78 °C, treated with BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>; 5.0 mL, 5 mmol), allowed to warm to 25 °C and stir for 20 h. The reaction was cooled in ice and quenched by addition of H<sub>2</sub>O (10 mL). The separated organic phase was washed with satd NaCl solution (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by silica gel chromatography with 0-10% EtOAc/hexane to give the aldehyde (980 mg): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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 9. Preparation of 5-chloro-2-hydroxy-4-trifluoromethylbenzaldehyde**



**[0060]** 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 H<sub>2</sub>O (200mL) with stirring. The precipitated phenol was collected by filtration and washed well with H<sub>2</sub>O. The solid was taken up in EtOAc (150 mL), washed with satd NaCl solution (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give 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 NH<sub>4</sub>Cl solution (10 mL) and worked up with H<sub>2</sub>O (30 mL) and Et<sub>2</sub>O (75 mL). The organic phase was washed with satd NaCl (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by RP-HPLC to give the product (300 mg, ~70% purity), which was used without further purification: EIMS *m/z* 224.

**Example 10. Preparation of 2-hydroxy-4,6-bis-trifluoromethyl-benzaldehyde**

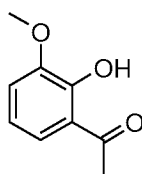


**[0061]** 3,5-Bis(trifluoromethyl)anisole (5.0 g 21 mmol) and TMEDA (4.0 mL, 3.0 g, 26 mmol) were dissolved in dry Et<sub>2</sub>O (60 mL), cooled to -10 °C and treated in portions with *n*-BuLi (2.5 M in hexanes; 10 mL, 25 mmol). The mixture was warmed to 25 °C and stirred for 90 min. The mixture was cooled to -78 °C, treated dropwise with DMF (2.3 mL, 2.2 g, 30

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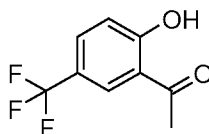
mmol), stirred for 30 min, warmed to 25 °C and stirred for 30 min. The reaction was quenched by addition of H<sub>2</sub>O (50 mL) and extracted with Et<sub>2</sub>O (2 x 75 mL). The combined organic fractions were washed with satd NaCl solution (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. 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 CH<sub>2</sub>Cl<sub>2</sub> (75 mL), cooled to -78 °C and treated with BBr<sub>3</sub> (1 M solution in CH<sub>2</sub>Cl<sub>2</sub>; 12 mL, 12 mmol). The mixture was stirred for 30 min at -78 °C, warmed to 25 °C and stirred for 90 min. H<sub>2</sub>O (100 mL) was added and stirring was continued for 30 min. The separated organic phase was washed with satd NaCl solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by silica gel chromatography with 0-20% EtOAc/hexane to give the purified aldehyde (2.0 g): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.27 (s, 1H), 10.34 (s, 1H), 7.51 (s, 1H); EIMS *m/z* 258.

**Example 11. Preparation of 1-(2-hydroxy-3-methoxyphenyl)-ethanone**



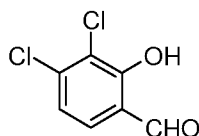
**[0062]** 1-(2-Hydroxy-3-methoxyphenyl)-ethanone was prepared from commercially available starting materials as described in US 038048, which is expressly incorporated by reference herein.

**Example 12. Preparation of 1-(2-hydroxy-5-trifluoromethylphenyl)-ethanone**



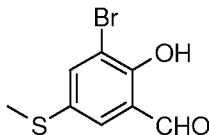
**[0063]** 1-(2-Hydroxy-5-trifluoromethylphenyl)-ethanone was prepared from commercially available starting materials as described in EP 129812, which is expressly incorporated by reference herein.

**Example 13. Preparation of 3,4-dichloro-2-hydroxybenzaldehyde**

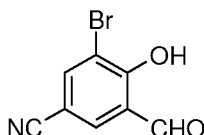


**[0064]** 3,4-Dichloro-2-hydroxybenzaldehyde was prepared from commercially available starting materials as described in Gu et al., *J. Med. Chem.* **2000**, 43, 4868-4876, which is expressly incorporated by reference herein.

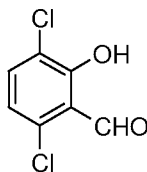
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**Example 14. Preparation of 3-bromo-2-hydroxy-5-methylsulfanyl-benzaldehyde**

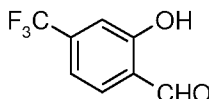
**[0065]** 3-Bromo-2-hydroxy-5-methylsulfanyl-benzaldehyde was prepared from commercially available starting materials as described in Guiles et al., PCT Int. Appl. WO 2008039641 A2, which is expressly incorporated by reference herein.

**Example 15. Preparation of 3-bromo-5-formyl-4-hydroxybenzonitrile**

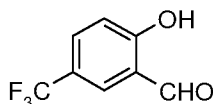
**[0066]** 3-Bromo-5-formyl-4-hydroxybenzonitrile was prepared from commercially available starting materials as described in Sakaitani et al., PCT Int. Appl. WO 2004037816 A1, which is expressly incorporated by reference herein.

**Example 16. Preparation of 3,6-dichloro-2-hydroxybenzaldehyde**

**[0067]** 3,6-Dichloro-2-hydroxybenzaldehyde was prepared from commercially available starting materials as described in Rafferty et al., PCT Int. Appl. WO 2008121602 A1, which is expressly incorporated by reference herein.

**Example 17. Preparation of 2-hydroxy-4-trifluoromethylbenzaldehyde**

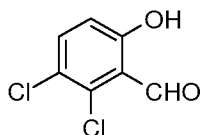
**[0068]** 2-Hydroxy-4-trifluoromethylbenzaldehyde was prepared from commercially available starting materials as described in Faeh et al., U.S. Pat. Appl. Publ. 2007185113 A1, which is expressly incorporated by reference herein.

**Example 18. Preparation of 2-hydroxy-5-trifluoromethylbenzaldehyde**

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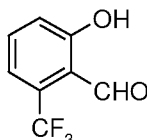
[0069] 2-Hydroxy-5-trifluoromethylbenzaldehyde was prepared from commercially available starting materials as described in Bonnert et al., PCT Int. Appl. WO 2006056752 A1, which is expressly incorporated by reference herein.

**Example 19. Preparation of 2,3-dichloro-6-hydroxybenzaldehyde**



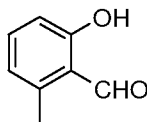
2,3-Dichloro-6-hydroxybenzaldehyde was prepared from commercially available starting materials as described in Stokker et al., *J. Med. Chem.* **1980**, 23, 1414-1427, which is expressly incorporated by reference herein.

**Example 20. Preparation of 2-hydroxy-6-trifluoromethylbenzaldehyde**



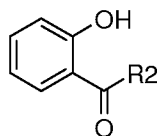
[0070] 2-Hydroxy-6-trifluoromethylbenzaldehyde was prepared from commercially available starting materials as described in Stokker et al., *J. Med. Chem.* **1980**, 23, 1414-1427, which is expressly incorporated by reference herein.

**Example 21. Preparation of 2-hydroxy-6-methylbenzaldehyde**



[0071] 2-Hydroxy-6-methylbenzaldehyde was prepared from commercially available starting materials as described in Hofsløkken and Skattebøl, *Acta Chemica Scandinavica* **1999**, 53, 258-262, which is expressly incorporated by reference herein.

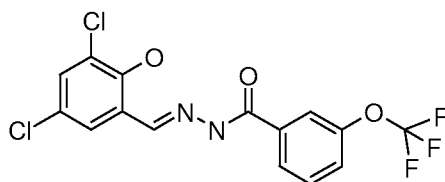
**Example 22. General preparation of ketone compounds**



[0072] Ketone compounds, wherein R2 is either *i*-propyl or *t*-butyl, were prepared from commercially available starting materials as described in Miller, J. A., *J. Org. Chem.* **1987**, 52, 322-323, which is expressly incorporated by reference herein.

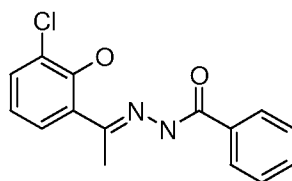
**Example 23. Preparation of 3-trifluoromethoxy-benzoic acid [1-(3,5-dichloro-2-hydroxy-phenyl)-methylidene]-hydrazide**

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**[0073]** A suspension of 3,5-dichloro-2-hydroxy-benzaldehyde (0.200, 1.05 mmol) and 3-trifluoromethoxy-benzoic acid hydrazide (0.243 g, 1.05 mmol) in ethanol (3.3 mL) was heated to 60 °C for 18 hours. The reaction mixture was cooled to room temperature to precipitate the product. The solid was collected via suction filtration and rinsed with ethanol to furnish 3-trifluoromethoxy-benzoic acid [1-(3,5-dichloro-2-hydroxy-phenyl)-methylidene]-hydrazide as an off-white solid (0.412 g, 99%); mp 180-182 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 12.39 (s, 1H), 8.60 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.91 (s, 1H), 7.76 – 7.63 (m, 4H); ESIMS *m/z* 393 ([M+H]<sup>+</sup>), 391 ([M-H]<sup>-</sup>).

**Example 24. Preparation of benzoic acid [1-(3-chloro-2-hydroxyphenyl)-ethylidene]-hydrazide**



**[0074]** A suspension of 1-(3-chloro-2-hydroxyphenyl)-ethanone (0.100g, 0.586 mmol), benzoic acid hydrazide (0.080 g, 0.586 mmol), and glacial acetic acid (0.180mL) in ethanol (1.8 mL) was heated to 60 °C for 18 hours. The reaction mixture was cooled to room temperature to precipitate the product. The solid was collected via suction filtration and rinsed with ethanol to furnish benzoic acid [1-(3-chloro-2-hydroxy-phenyl)-ethylidene]-hydrazide as a yellow solid (0.100 g, 59%); mp 202-203 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ 14.36 (s, 1H), 11.50 (s, 1H), 7.96 (d, *J* = 7.3 Hz, 2H), 7.68 – 7.61 (m, 2H), 7.56 (t, *J* = 6.7 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 8.0 Hz, 1H), 2.52 (s, 3H); ESIMS *m/z* 289 ([M+H]<sup>+</sup>), 287 ([M-H]<sup>-</sup>).

**Example 25. General method for the preparation of benzoic hydrazones of alkyl-*o*-hydroxyphenyl ketones**

**[0075]** The alkyl-*o*-hydroxyphenyl ketone (0.5mmol) and benzoic hydrazide (0.75mmol) were combined in *n*-propanol (5 mL) and acetic acid (4-5 drops) and heated to reflux for 20-24h. Upon cooling the mixture was diluted with water (2-5 mL) in portions to induce precipitation. The solids were collected by filtration, washed with water and dried

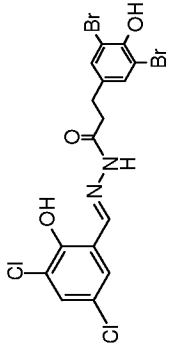
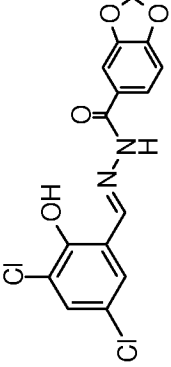
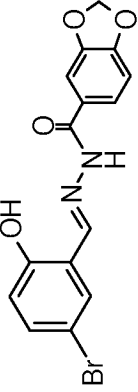
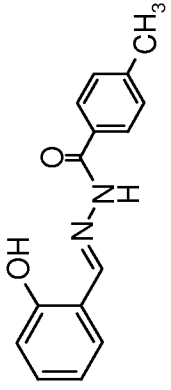
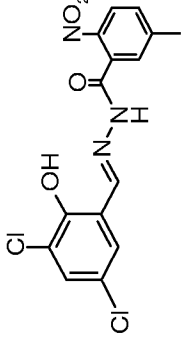
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under vacuum at 80°C. After analysis by HPLC-MS most of the hydrazones were found to be sufficiently pure for testing. The less pure materials were purified by RP-HPLC using acetonitrile-water mixtures on a 10mm X 250mm YMC-AQ column.

Table 1.

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), δ |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------|
| <b>1</b>        |           |         | 257       | 255       |                                                                                      |
| <b>2</b>        |           |         | 275       | 273       |                                                                                      |
| <b>3</b>        |           |         | 270       | 268       |                                                                                      |
| <b>4</b>        |           |         | 291       | 289       |                                                                                      |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$ |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------|
| 5               |    |         | 511       | 509       |                                                                                               |
| 6               |    |         | 353       | 351       |                                                                                               |
| 7               |    |         | 387 (+Na) | 363       |                                                                                               |
| 8               |   |         | 255       | 253       |                                                                                               |
| 9               |  |         | 368       | 366       |                                                                                               |

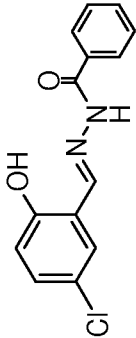
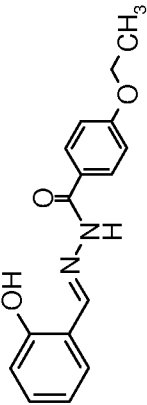
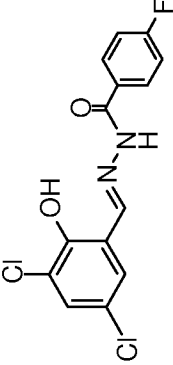
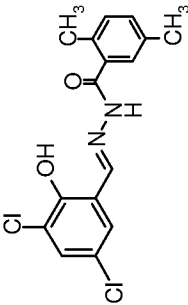
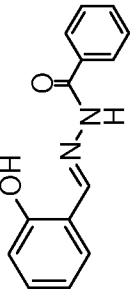
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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                            |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>10</b>       |           | 224–227 |           | 318       | 12.46 (s, 1H), 11.15 (s, 1H), 8.79 (d, <i>J</i> = 1.7 Hz, 1H), 8.68 (s, 1H), 8.51–8.35 (m, 2H), 7.86 (t, <i>J</i> = 8.0 Hz, 1H), 7.71 (d, <i>J</i> = 2.7 Hz, 1H), 7.34 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 6.97 (d, <i>J</i> = 8.8 Hz, 1H) |
| <b>11</b>       |           |         | 323       | 321       |                                                                                                                                                                                                                                          |
| <b>12</b>       |           | 259–262 | 320       | 318       | 12.43 (s, 1H), 11.15 (s, 1H), 8.67 (s, 1H), 8.39 (d, <i>J</i> = 8.8 Hz, 2H), 8.18 (d, <i>J</i> = 8.7 Hz, 2H), 7.71 (d, <i>J</i> = 2.7 Hz, 1H), 7.34 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 6.97 (d, <i>J</i> = 8.8 Hz, 1H)                    |
| <b>13</b>       |           |         | 381       | 379       |                                                                                                                                                                                                                                          |
| <b>14</b>       |           |         | 311       | 309       |                                                                                                                                                                                                                                          |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                            |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15              |           | 197–198 | 259       | 257       | 12.27 (s, 1H), 11.64 (s, 1H), 8.67 (s, 1H), 8.02–7.89 (m, 2H), 7.68–7.52 (m, 3H), 7.40 (d, <i>J</i> = 7.8 Hz, 1H), 7.35–7.24 (m, 1H), 6.99–6.88 (m, 1H)                  |
| 16              |           |         | 309       | 307       |                                                                                                                                                                          |
| 17              |           | 209–213 | 356       | 354       | 14.30 (s, 1H), 11.43 (s, 1H), 7.61 (dd, <i>J</i> = 10.3, 2.5 Hz, 2H), 7.37 (dd, <i>J</i> = 7.7, 4.8 Hz, 2H), 7.16 (t, <i>J</i> = 8.9 Hz, 2H), 3.74 (s, 2H), 2.44 (s, 3H) |
| 18              |           |         | 299       | 297       |                                                                                                                                                                          |
| 19              |           |         | 433 (+Na) | 410       |                                                                                                                                                                          |

65480 US

| Compound Number | Structure                                                                             | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                  |
|-----------------|---------------------------------------------------------------------------------------|-------------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------|
| 20              |    |             | 275       | 273       |                                                                                                                                                |
| 21              |    |             | 285       | 283       |                                                                                                                                                |
| 22              |    |             | 327       | 325       |                                                                                                                                                |
| 23              |   | 169–<br>172 | 337       | 335       | 12.46 (s, 1H), 12.37 (s, 1H), 8.45 (s, 1H), 7.64 (dd, <i>J</i> = 7.5, 2.5 Hz, 2H), 7.34 (s, 1H), 7.28–7.20 (m, 2H), 2.35 (s, 3H), 2.33 (s, 3H) |
| 24              |  |             | 241       | 239       |                                                                                                                                                |

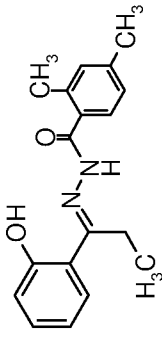
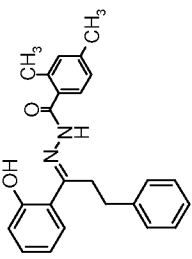
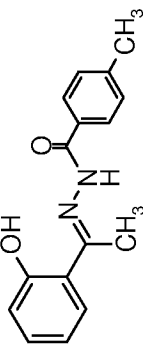
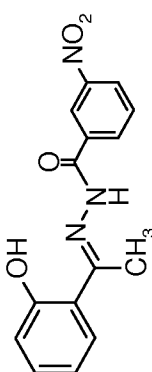
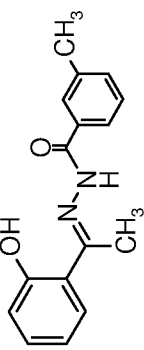
65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+)    | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                     |
|-----------------|-----------|-------------|--------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25              |           |             |              | 271       |                                                                                                                                                                   |
| 26              |           |             | 381          | 379       |                                                                                                                                                                   |
| 27              |           | 246–<br>247 | 337          | 335       | 12.51 (s, 1H), 12.34 (s, 1H), 8.45 (s, 1H), 7.64 (dd, <i>J</i> = 9.5, 2.5 Hz, 2H), 7.43 (d, <i>J</i> = 7.6 Hz, 1H), 7.18–7.10 (m, 2H), 2.38 (s, 3H), 2.33 (s, 3H) |
| 28              |           |             | 447<br>(+Na) | 423       |                                                                                                                                                                   |
| 29              |           |             | 283          | 281       |                                                                                                                                                                   |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                                       |
|-----------------|-----------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30              |           | 159–160 | 297       | 295       | 13.48 (s, 1H), 11.43 (s, 1H), 7.62 (d, <i>J</i> = 7.8 Hz, 1H), 7.38 (d, <i>J</i> = 7.6 Hz, 1H), 7.30 (t, <i>J</i> = 7.2 Hz, 1H), 7.17–7.09 (m, 2H), 6.94–6.86 (m, 2H), 2.94 (q, <i>J</i> = 7.5 Hz, 2H), 2.37 (s, 3H), 2.32 (s, 3H), 1.11 (t, <i>J</i> = 7.5 Hz, 3H) |
| 31              |           | 143–145 | 373       | 371       | 13.43 (s, 1H), 11.42 (s, 1H), 7.65 (d, <i>J</i> = 7.7 Hz, 1H), 7.33–7.26 (m, 6H), 7.25–7.17 (m, 1H), 7.16–7.09 (m, 2H), 6.96–6.89 (m, 2H), 3.31–3.22 (m, 2H), 2.88–2.79 (m, 2H), 2.35 (s, 3H), 2.33 (s, 3H)                                                         |
| 32              |           | 192–194 | 427       | 425       | 12.70 (s, 1H), 12.41 (s, 1H), 8.41 (s, 1H), 7.84 (d, <i>J</i> = 2.3 Hz, 1H), 7.79 (d, <i>J</i> = 2.3 Hz, 1H), 7.34 (s, 1H), 7.28–7.19 (m, 2H), 2.35 (s, 3H), 2.33 (s, 3H)                                                                                           |
| 33              |           | 188–190 | 283       | 281       | 13.37 (s, 1H), 11.38 (s, 1H), 7.62 (dd, <i>J</i> = 7.8, 1.3 Hz, 1H), 7.35–7.27 (m, 2H), 7.26–7.15 (m, 2H), 6.94–6.86 (m, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H)                                                                                              |

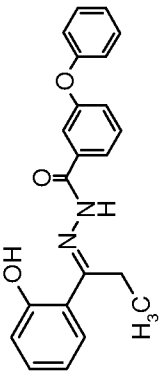
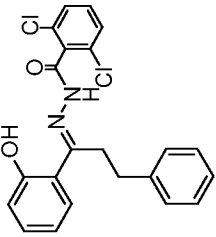
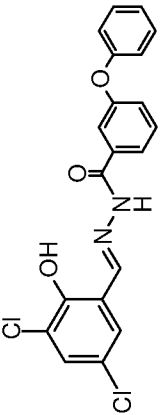
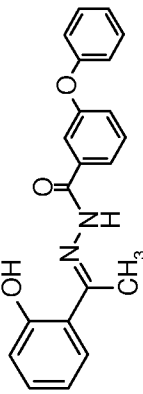
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                        |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>34</b>       |    | 175–176 | 297       | 295       | 13.47 (s, 1H), 11.50 (s, 1H), 7.66–7.59 (m, 1H), 7.33–7.27 (m, 2H), 7.26–7.16 (m, 2H), 6.95–6.87 (m, 2H), 2.94 (q, <i>J</i> = 7.5 Hz, 2H), 2.33 (s, 6H), 1.11 (t, <i>J</i> = 7.5 Hz, 3H)                             |
| <b>35</b>       |    | 162–166 | 373       | 371       | 13.41 (s, 1H), 11.46 (s, 1H), 7.66 (d, <i>J</i> = 7.9 Hz, 1H), 7.30 (d, <i>J</i> = 4.4 Hz, 5H), 7.25–7.20 (m, 3H), 7.16 (s, 1H), 6.96–6.89 (m, 2H), 3.32–3.24 (m, 2H), 2.87–2.80 (m, 2H), 2.33 (s, 3H), 2.32 (s, 3H) |
| <b>36</b>       |    |         | 269       | 267       |                                                                                                                                                                                                                      |
| <b>37</b>       |  |         | 300       | 298       |                                                                                                                                                                                                                      |
| <b>38</b>       |  |         | 269       | 267       |                                                                                                                                                                                                                      |

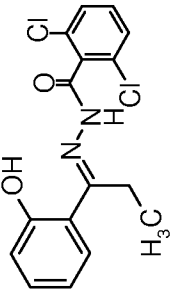
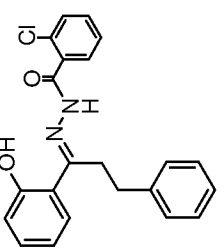
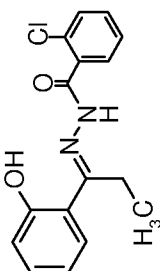
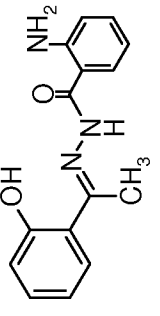
65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                                                                         |
|-----------------|-----------|-------------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>39</b>       |           |             | 283       | 281       |                                                                                                                                                                                                                                                     |
| <b>40</b>       |           |             | 297       | 295       |                                                                                                                                                                                                                                                     |
| <b>41</b>       |           | 261–<br>263 |           | 349       | 12.58 (s, 1H), 12.46 (s, 1H), 8.57 (s, 1H), 7.90 (d, <i>J</i> = 8.2 Hz, 2H), 7.68 (d, <i>J</i> = 2.5 Hz, 1H), 7.63 (d, <i>J</i> = 2.5 Hz, 1H), 7.44 (d, <i>J</i> = 8.2 Hz, 2H), 2.98 (hept, <i>J</i> = 6.7 Hz, 1H), 1.24 (d, <i>J</i> = 6.9 Hz, 6H) |
| <b>42</b>       |           | 270–<br>272 | 441       | 439       | 12.80 (s, 1H), 12.49 (s, 1H), 8.53 (s, 1H), 7.90 (d, <i>J</i> = 8.2 Hz, 2H), 7.83 (dd, <i>J</i> = 7.0, 2.2 Hz, 2H), 7.44 (d, <i>J</i> = 8.2 Hz, 2H), 3.04–2.92 (m, 1H), 1.24 (d, <i>J</i> = 6.9 Hz, 6H)                                             |
| <b>43</b>       |           | 250–<br>252 | 377       | 375       | 12.77, 12.67, 11.99, and 10.28 (4s, 2H), 8.45 and 8.31 (2s, 1H), 7.75–7.30 (m, 5H); Note: rotational isomers                                                                                                                                        |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>44</b>       |    | 148–163 | 361       | 359       | 13.37 (s, 1H), 11.41 (s, 1H), 7.68 (d, <i>J</i> = 7.6 Hz, 1H), 7.64 (d, <i>J</i> = 7.8 Hz, 1H), 7.56 (t, <i>J</i> = 7.9 Hz, 1H), 7.51 (s, 1H), 7.48–7.41 (m, 2H), 7.30 (t, <i>J</i> = 7.4 Hz, 1H), 7.25 (dd, <i>J</i> = 8.1, 1.9 Hz, 1H), 7.21 (t, <i>J</i> = 7.4 Hz, 1H), 7.10 (d, <i>J</i> = 7.8 Hz, 2H), 6.95–6.87 (m, 2H), 3.02 (q, <i>J</i> = 7.4 Hz, 2H), 1.13 (t, <i>J</i> = 7.5 Hz, 3H) |
| <b>45</b>       |    | 204–208 | 413       | 411       | 13.08, 12.07, 12.00, 10.65 (4s, 2H), 7.70–7.40 (m, 4H), 7.38–7.14 (m, 6H), 7.00–6.65 (m, 2H), 3.29–3.18 (m, 2H), 2.80 (dd, <i>J</i> = 11.0, 5.3 Hz, 2H); Note: rotational isomers                                                                                                                                                                                                               |
| <b>46</b>       |    | 170–171 | 401       | 399       | 12.54 (s, 1H), 12.47 (s, 1H), 8.57 (s, 1H), 7.75 (d, <i>J</i> = 7.9 Hz, 1H), 7.68 (d, <i>J</i> = 2.5 Hz, 1H), 7.64 (d, <i>J</i> = 2.5 Hz, 1H), 7.61–7.55 (m, 2H), 7.49–7.41 (m, 2H), 7.28 (dd, <i>J</i> = 7.9, 2.2 Hz, 1H), 7.21 (t, <i>J</i> = 7.4 Hz, 1H), 7.12–7.06 (m, 2H)                                                                                                                  |
| <b>47</b>       |  | 178–180 | 347       | 345       | 13.31 (s, 1H), 11.37 (s, 1H), 7.73 (d, <i>J</i> = 7.7 Hz, 1H), 7.67–7.62 (m, 1H), 7.60–7.53 (m, 2H), 7.48–7.41 (m, 2H), 7.34–7.28 (m, 1H), 7.25 (dd, <i>J</i> = 7.9, 2.1 Hz, 1H), 7.20 (t, <i>J</i> = 7.4 Hz, 1H), 7.11–7.07 (m, 2H), 6.94–6.87 (m, 2H), 2.48 (s, 3H)                                                                                                                           |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                      |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 48              |    | 181–184 | 337       | 335       | 13.16, 11.95, 11.87, 10.73 (4s, 2H), 7.68–7.17 (m, 5H), 6.97–6.66 (m, 2H), 2.97–2.85 (m, 2H), 1.16–1.04 (m, 3H); Note: rotational isomers                                                          |
| 49              |    | 173–177 | 379       | 377       | 13.24 (s, 1H), 11.74 (s, 1H), 7.66 (d, <i>J</i> = 7.8 Hz, 1H), 7.62–7.54 (m, 3H), 7.51–7.47 (m, 1H), 7.35–7.28 (m, 5H), 7.24–7.19 (m, 1H), 6.97–6.89 (m, 2H), 3.30–3.22 (m, 2H), 2.87–2.79 (m, 2H) |
| 50              |    |         | 303       | 301       |                                                                                                                                                                                                    |
| 51              |  |         | 270       | 268       |                                                                                                                                                                                                    |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                              |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 52              |           |         |           |           |                                                                                                                                                                                     |
| 53              |           |         | 285       | 283       |                                                                                                                                                                                     |
| 54              |           |         | 289       | 287       |                                                                                                                                                                                     |
| 55              |           |         | 333 (+Na) | 309       |                                                                                                                                                                                     |
| 56              |           | 106–111 | 377       | 375       | 12.62 (s, 1H), 12.17 (s, 1H), 8.45 (s, 1H), 7.92–7.88 (m, 1H), 7.83 (d, <i>J</i> = 7.0 Hz, 1H), 7.80–7.75 (m, 2H), 7.70 (d, <i>J</i> = 2.5 Hz, 1H), 7.66 (d, <i>J</i> = 2.5 Hz, 1H) |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                 |
|-----------------|-----------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 57              |           | 220–222 | 403       | 401       | 14.32 (s, 1H), 11.91 (s, 1H), 7.76 (dd, <i>J</i> = 7.8, 1.1 Hz, 1H), 7.67 (d, <i>J</i> = 2.5 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 1H), 7.61 (dd, <i>J</i> = 7.4, 1.8 Hz, 1H), 7.55–7.45 (m, 2H), 2.45 (s, 3H) |
| 58              |           | 208–210 | 323       | 321       | 13.18, 11.64, 11.59 (3s, 2H), 7.91–7.46 (m, 5H), 7.36–7.14 (m, 1H), 6.95–6.60 (m, 2H), 2.40, 2.38 (2s, 3H);<br>Note: rotational isomers                                                                       |
| 59              |           |         | 363 (+Na) | 339       |                                                                                                                                                                                                               |
| 60              |           |         | 345 (+Na) | 321       |                                                                                                                                                                                                               |
| 61              |           |         | 308       | 307       |                                                                                                                                                                                                               |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 62              |           |         | 273       | 271       |                                                                                        |
| 63              |           |         | 334       |           |                                                                                        |
| 64              |           |         | 333       | 331       |                                                                                        |
| 65              |           |         | 289       |           |                                                                                        |
| 66              |           |         | 269       | 267       |                                                                                        |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| <b>67</b>       |           |         | 357       | 355       |                                                                                        |
| <b>68</b>       |           |         | 343       | 341       |                                                                                        |
| <b>69</b>       |           |         |           | 323       |                                                                                        |
| <b>70</b>       |           |         | 343       | 341       |                                                                                        |
| <b>71</b>       |           |         | 389       | 387       |                                                                                        |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 72              |           |         | 323       |           |                                                                                                                                                                                                                                              |
| 73              |           | 202–209 | 339       | 337       | 12.67 (s, 1H), 12.35 (s, 1H), 12.31 (s, 1H), 8.65 (s, 1H), 7.80 (d, <i>J</i> = 7.8 Hz, 1H), 7.72 (d, <i>J</i> = 2.5 Hz, 1H), 7.66 (d, <i>J</i> = 2.5 Hz, 1H), 7.41 (d, <i>J</i> = 7.2 Hz, 1H), 6.91 (t, <i>J</i> = 7.7 Hz, 1H), 2.20 (s, 3H) |
| 74              |           |         | 407 (+Na) | 383       |                                                                                                                                                                                                                                              |
| 75              |           |         | 340       |           |                                                                                                                                                                                                                                              |

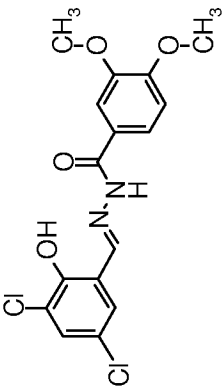
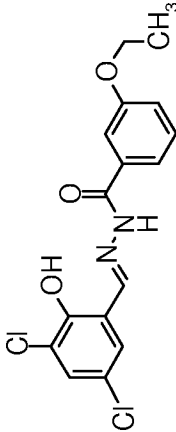
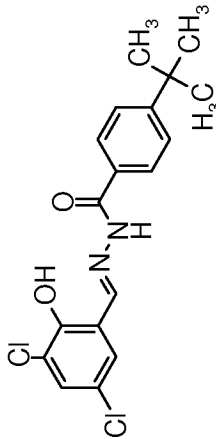
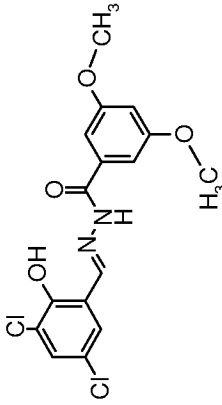
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$ |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------|
| 76              |           |         |           | 352       |                                                                                               |
| 77              |           |         | 323       | 321       |                                                                                               |
| 78              |           |         | 377       |           |                                                                                               |
| 79              |           | 248–249 | 377       | 375       | 12.57 (s, 1H), 12.29 (s, 1H), 8.57 (s, 1H), 8.00–7.90 (m, 3H), 7.75–7.61 (m, 2H)              |
| 80              |           |         |           | 385       |                                                                                               |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                         |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>81</b>       |           | 238–240 | 377       | 375       | 12.71 (s, 1H), 12.37 (s, 1H), 8.61 (s, 1H), 8.16 (d, <i>J</i> = 8.1 Hz, 2H), 7.96 (d, <i>J</i> = 8.2 Hz, 2H), 7.68 (dd, <i>J</i> = 27.3, 2.5 Hz, 2H)                           |
| <b>82</b>       |           |         | 339       | 337       |                                                                                                                                                                                |
| <b>83</b>       |           | 189–191 | 377       |           | 12.62 (s, 1H), 12.11 (s, 1H), 8.45 (s, 1H), 7.82 (t, <i>J</i> = 1.4 Hz, 1H), 7.71 (d, <i>J</i> = 2.6 Hz, 1H), 7.66 (d, <i>J</i> = 2.5 Hz, 1H), 7.65 (d, <i>J</i> = 1.4 Hz, 2H) |
| <b>84</b>       |           |         | 408 (+Na) | 387       |                                                                                                                                                                                |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 85              |    |         | 369       | 367       |                                                                                                                                                                                                                          |
| 86              |    | 207–209 | 353       | 351       | 12.52 (s, 1H), 12.47 (s, 1H), 8.58 (s, 1H), 7.68 (d, J = 2.5 Hz, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.55–7.50 (m, 1H), 7.50–7.43 (m, 2H), 7.19 (dd, J = 7.8, 1.9 Hz, 1H), 4.11 (q, J = 6.9 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H) |
| 87              |   |         | 364       | 363       |                                                                                                                                                                                                                          |
| 88              |  |         | 369       | 367       |                                                                                                                                                                                                                          |

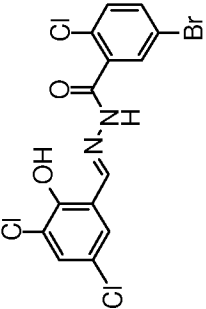
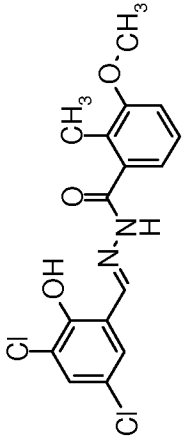
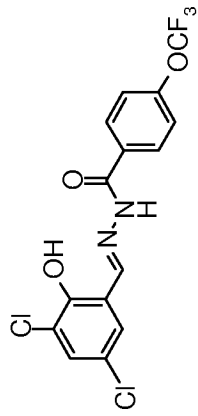
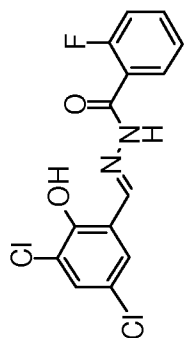
65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                     |
|-----------------|-----------|-------------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------|
| 89              |           |             |           | 325       |                                                                                                                   |
| 90              |           |             |           | 399       |                                                                                                                   |
| 91              |           |             | 324       | 322       |                                                                                                                   |
| 92              |           | 215–<br>217 | 359       |           | 12.70 (s, 1H), 12.60 (s, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 8.13–8.07 (m, 2H), 8.06–8.00 (m, 2H), 7.73–7.62 (m, 4H) |

65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                           |
|-----------------|-----------|-------------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 93              |           |             |           | 343       |                                                                                                                                                                                                                                                  |
| 94              |           |             |           | 337       |                                                                                                                                                                                                                                                  |
| 95              |           |             |           | 321       |                                                                                                                                                                                                                                                  |
| 96              |           |             |           | 353       |                                                                                                                                                                                                                                                  |
| 97              |           | 279–<br>281 | 353       | 351       | 12.64 (s, 1H), 12.40 (s, 1H), 8.55 (s, 1H), 7.94 (d, <i>J</i> = 8.7 Hz, 2H), 7.67 (d, <i>J</i> = 2.5 Hz, 1H), 7.62 (d, <i>J</i> = 2.5 Hz, 1H), 7.08 (d, <i>J</i> = 8.9 Hz, 2H), 4.13 (q, <i>J</i> = 7.0 Hz, 2H), 1.36 (t, <i>J</i> = 7.0 Hz, 3H) |

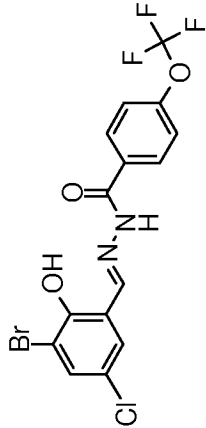
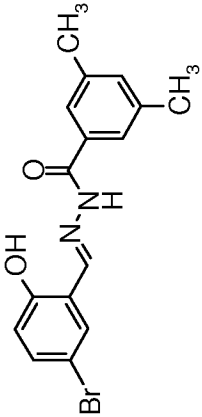
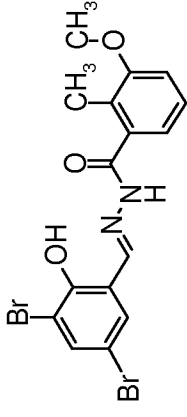
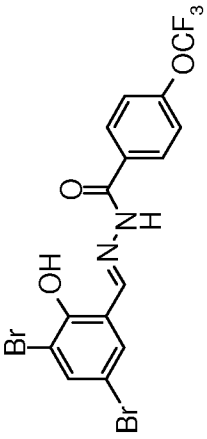
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                             |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>98</b>       |    | 191–192 |           | 421       | 12.62, 12.57, 12.1, 10.35 (4s, 2H), 8.45, 8.28 (2s, 1H), 8.5–7.4 (m, 5H); Note: rotational isomers                                                 |
| <b>99</b>       |    | 192–194 | 353       | 351       | 12.40 (s, 2H), 8.44 (s, 1H), 7.64 (dd, <i>J</i> = 7.6, 2.5 Hz, 2H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 7.19–7.03 (m, 2H), 3.84 (s, 3H), 2.20 (s, 3H) |
| <b>100</b>      |    | 220–229 | 393       | 391       | 12.61 (s, 1H), 12.44 (s, 1H), 8.58 (s, 1H), 8.09 (d, <i>J</i> = 8.8 Hz, 2H), 7.75–7.49 (m, 4H)                                                     |
| <b>101</b>      |  |         | 327       | 325       |                                                                                                                                                    |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                          |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 102             |           | 207–209 | 339       | 337       | 12.56 (s, 1H), 12.44 (s, 1H), 8.56 (s, 1H), 7.65 (dd, <i>J</i> = 14.1, 2.5 Hz, 2H), 7.57 (s, 2H), 7.27 (s, 1H), 2.36 (s, 6H)                                                                                           |
| 103             |           |         |           | 350       |                                                                                                                                                                                                                        |
| 104             |           |         | 343       |           |                                                                                                                                                                                                                        |
| 105             |           | 199–201 | 365       | 363       | 12.06 (s, 1H), 11.18 (s, 1H), 8.46 (s, 1H), 7.78 (d, <i>J</i> = 2.4 Hz, 1H), 7.47–7.37 (m, 1H), 7.34–7.21 (m, 1H), 7.07 (dd, <i>J</i> = 27.1, 7.9 Hz, 2H), 6.90 (d, <i>J</i> = 7.6 Hz, 1H), 3.83 (s, 3H), 2.19 (s, 3H) |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                      |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 106             |    | 210–220 | 439       | 437       | 12.64 (s, 2H), 8.55 (s, 1H), 8.09 (d, <i>J</i> = 8.8 Hz, 1H), 7.79–7.69 (m, 1H), 7.58 (d, <i>J</i> = 8.2 Hz, 1H)                                                   |
| 107             |    | 191–195 |           | 345       |                                                                                                                                                                    |
| 108             |   | 188–189 | 443       |           | 12.65 (s, 1H), 12.43 (s, 1H), 8.40 (s, 1H), 7.81 (dd, <i>J</i> = 19.3, 2.3 Hz, 2H), 7.31 (t, <i>J</i> = 7.9 Hz, 1H), 7.19–7.02 (m, 2H), 3.84 (s, 3H), 2.14 (s, 3H) |
| 109             |  | 224–230 | 483       | 481       | 12.66 (s, 2H), 8.54 (s, 1H), 8.09 (d, <i>J</i> = 8.8 Hz, 2H), 7.83 (d, <i>J</i> = 16.3 Hz, 2H), 7.58 (d, <i>J</i> = 8.1 Hz, 2H)                                    |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$  |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------|
| 110             |           | 209–211 | 427       |           |                                                                                                |
| 111             |           | 237–239 | 449       | 447       | 12.81 (s, 1H), 12.74 (s, 1H), 8.60 (m, 2H), 8.19–7.97 (m, 4H), 7.85 (s, 2H), 7.72–7.54 (m, 2H) |
| 112             |           |         |           | 430       |                                                                                                |
| 113             |           |         |           | 475       |                                                                                                |

65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|-------------|-----------|-----------|----------------------------------------------------------------------------------------|
| 114             |           |             |           | 427       |                                                                                        |
| 115             |           |             | 413       | 411       |                                                                                        |
| 116             |           |             |           | 415       |                                                                                        |
| 117             |           | 267–<br>269 |           | 465       | 12.76–12.63 (m, 1H), 12.59–12.46 (m, 1H), 8.62–8.46 (m, 1H), 8.05–7.77 (m, 5H)         |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 118             |           |         |           | 476       |                                                                                        |
| 119             |           |         |           | 415       |                                                                                        |
| 120             |           |         |           | 431       |                                                                                        |
| 121             |           |         | 421 (+Na) | 397       |                                                                                        |
| 122             |           |         |           | 430       |                                                                                        |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 123             |           |         | 359       | 357       |                                                                                        |
| 124             |           |         | 413       | 411       |                                                                                        |
| 125             |           |         | 324       | 322       |                                                                                        |
| 126             |           |         | 342       | 340       |                                                                                        |
| 127             |           |         | 300       | 298       |                                                                                        |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 128             |           |         | 269       | 267       |                                                                                                                                                                                              |
| 129             |           | 207–212 | 406       | 404       | 14.24 (s, 1H), 11.50 (s, 1H), 7.71 (d, <i>J</i> = 8.2 Hz, 2H), 7.62 (dd, <i>J</i> = 11.3, 2.5 Hz, 2H), 7.57 (d, <i>J</i> = 8.1 Hz, 2H), 3.88 (s, 2H), 2.45 (s, 3H)                           |
| 130             |           |         | 269       | 267       |                                                                                                                                                                                              |
| 131             |           |         | 283       | 281       |                                                                                                                                                                                              |
| 132             |           | 187–189 | 397       | 395       | 12.63 (s, 1H), 12.43 (s, 1H), 8.41 (s, 1H), 7.75 (d, <i>J</i> = 2.5 Hz, 1H), 7.68 (d, <i>J</i> = 2.5 Hz, 1H), 7.31 (t, <i>J</i> = 7.9 Hz, 1H), 7.18–7.04 (m, 2H), 3.84 (s, 3H), 2.20 (s, 3H) |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                            |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 133             |           | 122–128 |           | 317       | 12.06 (s, 1H), 11.17 (s, 1H), 8.46 (s, 1H), 7.65 (d, <i>J</i> = 2.7 Hz, 1H), 7.30 (ddd, <i>J</i> = 14.5, 7.7, 2.8 Hz, 2H), 7.11 (d, <i>J</i> = 8.1 Hz, 1H), 7.04 (d, <i>J</i> = 7.4 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 3.83 (s, 3H), 2.19 (s, 3H) |
| 134             |           | 196–199 | 303       |           | 12.11 (s, 1H), 11.30 (s, 1H), 8.62 (s, 1H), 7.66 (d, <i>J</i> = 2.6 Hz, 1H), 7.56 (s, 2H), 7.32 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 7.25 (s, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 2.34 (s, 6H)                                                            |
| 135             |           | 245–246 | 357       | 355       | 14.38 (s, 1H), 11.68 (s, 1H), 8.02 (s, 1H), 7.91 (d, <i>J</i> = 7.7 Hz, 1H), 7.72 (d, <i>J</i> = 9.1 Hz, 1H), 7.70 (d, <i>J</i> = 2.5 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 1H), 7.60 (t, <i>J</i> = 7.9 Hz, 1H), 2.53 (s, 3H)                            |
| 136             |           | 260–262 |           | 355       | 14.41 (s, 1H), 11.65 (s, 1H), 7.99 (d, <i>J</i> = 8.5 Hz, 2H), 7.68 (d, <i>J</i> = 2.5 Hz, 1H), 7.66–7.60 (m, 3H), 2.68–2.32 (m, 3H)                                                                                                                     |

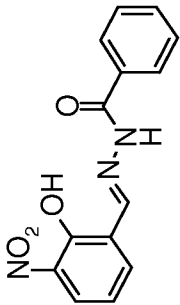
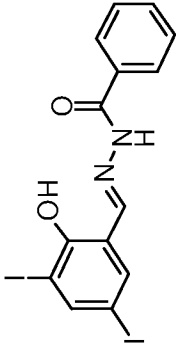
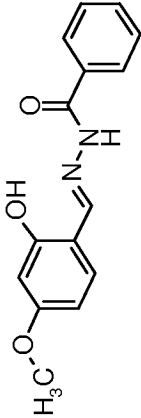
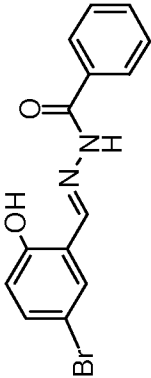
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                                     |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 137             |           | 226–230 | 337       |           | 14.50 (s, 1H), 11.70 (s, 1H), 7.65 (dd, <i>J</i> = 11.7, 2.4 Hz, 2H), 7.53 (d, <i>J</i> = 7.5 Hz, 1H), 7.45 (t, <i>J</i> = 7.0 Hz, 1H), 7.39 – 7.29 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H).                        |
| 138             |           | 247–253 | 403       | 401       | 14.38 (s, 1H), 11.68 (s, 1H), 8.14 (s, 1H), 7.95 (d, <i>J</i> = 7.9 Hz, 1H), 7.87–7.83 (m, 1H), 7.70 (d, <i>J</i> = 2.5 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 1H), 7.53 (t, <i>J</i> = 7.9 Hz, 1H), 2.53 (s, 3H) |
| 139             |           |         | 401       | 399       |                                                                                                                                                                                                                 |
| 140             |           | 199–204 | 338       | 336       | 14.27 (s, 1H), 11.44 (s, 1H), 7.61 (dd, <i>J</i> = 10.6, 2.5 Hz, 2H), 7.36–7.32 (m, 4H), 7.30–7.23 (m, 1H), 3.75 (s, 2H), 2.44 (s, 3H)                                                                          |

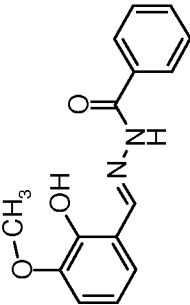
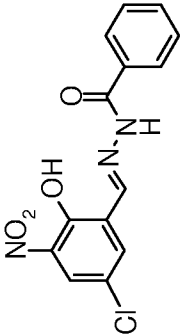
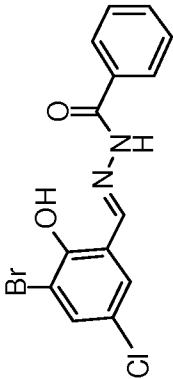
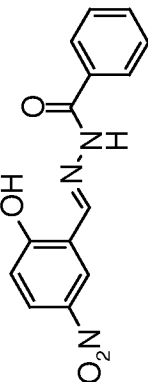
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                      |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 141             |           | 307–310 | 353       |           | 14.33 (s, 1H), 11.41 (s, 1H), 7.82–7.78 (m, 1H), 7.70 (d, <i>J</i> = 2.5 Hz, 1H), 7.64 (d, <i>J</i> = 2.4 Hz, 1H), 7.62–7.56 (m, 1H), 7.25 (d, <i>J</i> = 8.2 Hz, 1H), 7.13 (t, <i>J</i> = 7.7 Hz, 1H), 3.96 (s, 3H), 2.45 (s, 3H) |
| 142             |           | 250–253 | 368       | 366       | 14.25 (s, 1H), 11.98 (s, 1H), 8.26–8.20 (m, 1H), 7.94–7.88 (m, 1H), 7.85–7.78 (m, 2H), 7.67 (q, <i>J</i> = 2.5 Hz, 2H), 2.42 (s, 3H)                                                                                               |
| 143             |           |         | 281       |           |                                                                                                                                                                                                                                    |
| 144             |           |         | 365       | 363       |                                                                                                                                                                                                                                    |

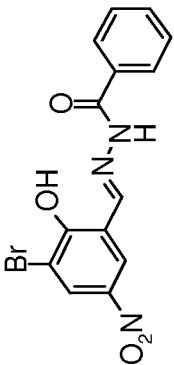
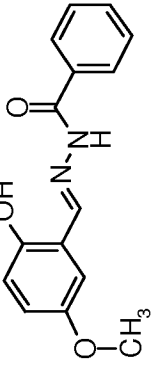
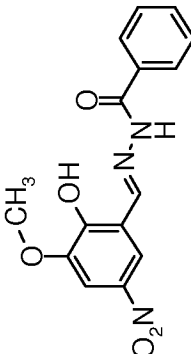
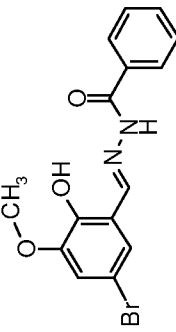
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+)    | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|---------------------------------------------------------------------------------------|---------|--------------|-----------|----------------------------------------------------------------------------------------|
| 145             |    |         | 286          | 284       |                                                                                        |
| 146             |    |         | 515<br>(+Na) | 491       |                                                                                        |
| 147             |    |         | 271          | 269       |                                                                                        |
| 148             |  |         |              | 317       |                                                                                        |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 149             |    |         | 271       | 269       |                                                                                        |
| 150             |    |         | 320       | 318       |                                                                                        |
| 151             |    |         | 374(+Na)  | 351       |                                                                                        |
| 152             |  |         |           | 284       |                                                                                        |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 153             |    |         |           | 362       |                                                                                        |
| 154             |    |         | 271       | 269       |                                                                                        |
| 155             |    |         | 316       | 314       |                                                                                        |
| 156             |  |         | 349       | 347       |                                                                                        |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 157             |           |         | 289       | 287       |                                                                                        |
| 158             |           |         | 335       | 333       |                                                                                        |
| 159             |           |         | 411 (+Na) |           |                                                                                        |
| 160             |           |         | 399       | 397       |                                                                                        |

65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                 |
|-----------------|-----------|-------------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| 161             |           |             |           | 387       |                                                                                                                                               |
| 162             |           |             | 367       |           |                                                                                                                                               |
| 163             |           |             | 456(+Na)  |           |                                                                                                                                               |
| 164             |           | 250–<br>251 | 423       | 419       | 12.75 (s, 1H), 12.60 (s, 1H), 8.57 (s, 1H), 8.16 (d, <i>J</i> = 8.1 Hz, 2H), 7.96 (d, <i>J</i> = 8.3 Hz, 2H), 7.76 (q, <i>J</i> = 2.5 Hz, 2H) |

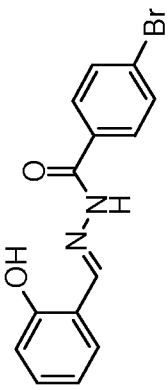
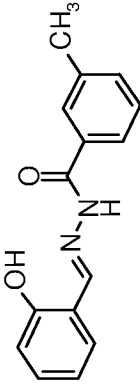
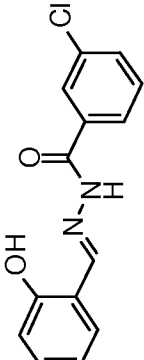
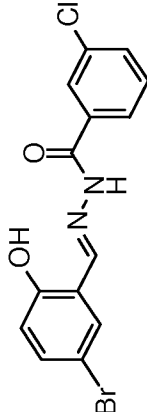
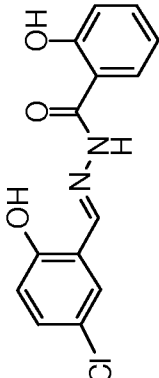
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                        |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>165</b>      |           | 218–221 | 385       | 383       | 12.58 (s, 1H), 12.35 (s, 1H), 8.61 (s, 1H), 7.85–7.77 (m, 1H), 7.75 (dd, <i>J</i> = 6.9, 2.5 Hz, 2H), 7.41 (d, <i>J</i> = 7.2 Hz, 1H), 6.91 (t, <i>J</i> = 7.7 Hz, 1H), 2.20 (s, 3H) |
| <b>166</b>      |           | 166–168 | 385       | 381       | 12.72 (s, 1H), 12.52 (s, 1H), 8.55 (s, 1H), 7.73 (dd, <i>J</i> = 14.6, 2.5 Hz, 2H), 7.59–7.43 (m, 3H), 7.27–7.12 (m, 1H), 3.85 (s, 3H)                                               |
| <b>167</b>      |           | 203–205 |           | 269       | 12.04 (s, 1H), 11.31 (s, 1H), 8.64 (s, 1H), 7.62–7.49 (m, 3H), 7.36–7.27 (m, 1H), 7.24 (s, 1H), 6.93 (t, <i>J</i> = 8.5 Hz, 2H), 2.36 (s, 6H)                                        |
| <b>168</b>      |           | 223–226 | 382       | 380       | 12.76 (s, 1H), 12.47 (s, 1H), 8.53 (s, 1H), 7.73 (dd, <i>J</i> = 18.0, 2.5 Hz, 2H), 7.57 (s, 2H), 7.28 (s, 1H), 2.36 (s, 6H)                                                         |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 169             |           |         | 373       | 371       |                                                                                        |
| 170             |           |         | 354       |           |                                                                                        |
| 171             |           |         | 354       |           |                                                                                        |
| 172             |           |         |           | 307       |                                                                                        |

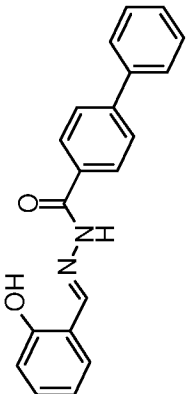
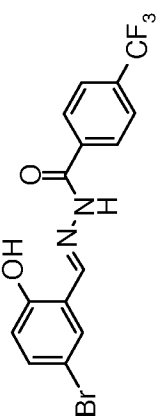
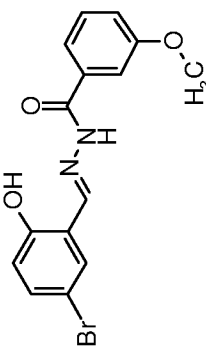
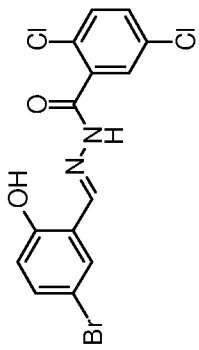
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 173             |    |         | 318       | 317       |                                                                                        |
| 174             |    |         | 255       | 253       |                                                                                        |
| 175             |    |         | 275       | 273       |                                                                                        |
| 176             |   |         | 375 (+Na) | 351       |                                                                                        |
| 177             |  |         |           |           |                                                                                        |

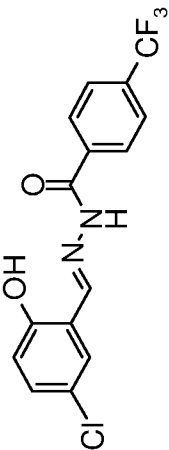
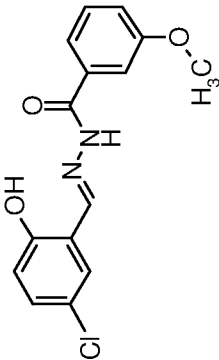
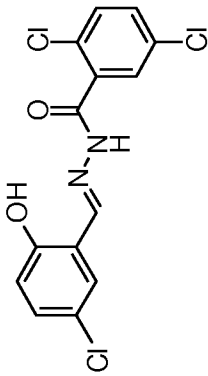
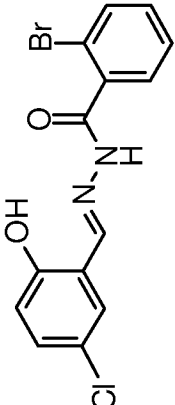
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+)    | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|-----------|---------|--------------|-----------|----------------------------------------------------------------------------------------|
| 178             |           |         | 331<br>(+Na) |           |                                                                                        |
| 179             |           |         | 332          |           |                                                                                        |
| 180             |           |         |              | 287       |                                                                                        |
| 181             |           |         | 354          |           |                                                                                        |
| 182             |           |         | 319          | 317       |                                                                                        |

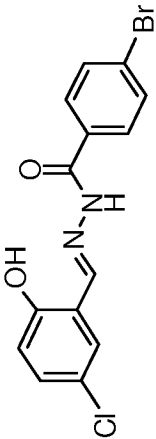
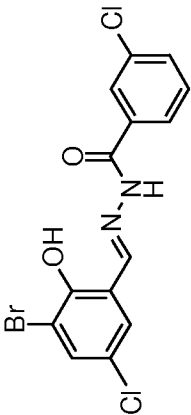
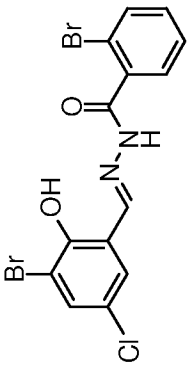
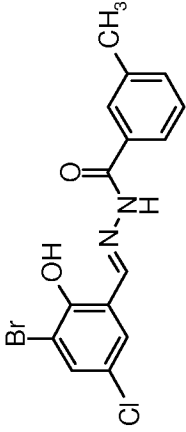
65480 US

| Compound Number | Structure                                                                             | mp (°C)     | ESIMS (+)    | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                      |
|-----------------|---------------------------------------------------------------------------------------|-------------|--------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 183             |    |             | 339<br>(+Na) | 315       |                                                                                                                                                                                             |
| 184             |    | 219–<br>222 | 388          | 386       | 12.36 (s, 1H), 11.19 (s, 1H), 8.65 (s, 1H), 8.04 (dd, <i>J</i> = 80.4, 8.3 Hz, 4H), 7.83 (d, <i>J</i> = 2.5 Hz, 1H), 7.45 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 6.92 (d, <i>J</i> = 8.8 Hz, 1H) |
| 185             |    |             | 349          | 347       |                                                                                                                                                                                             |
| 186             |  | 196–<br>202 | 389          | 387       | 12.25 (s, 1H), 10.99 (s, 1H), 7.82 (d, <i>J</i> = 2.5 Hz, 1H), 7.80 – 7.76 (m, 1H), 7.66 – 7.57 (m, 3H), 7.45 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 7.37 – 7.31 (m, 1H)                         |

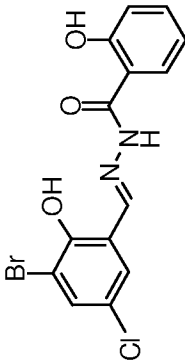
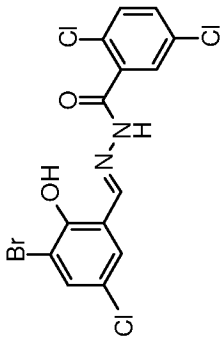
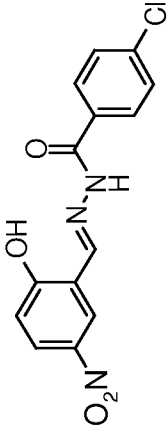
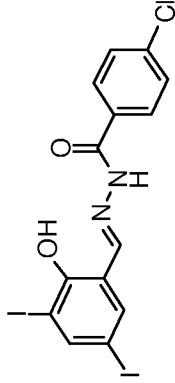
65480 US

| Compound Number | Structure                                                                             | mp (°C)      | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                |
|-----------------|---------------------------------------------------------------------------------------|--------------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 187             |    | 213--<br>218 | 343       | 341       | 12.36 (s, 1H), 11.18 (s, 1H), 8.66 (s, 1H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.94 (d, <i>J</i> = 8.3 Hz, 2H), 7.71 (d, <i>J</i> = 2.6 Hz, 1H), 7.34 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 6.97 (d, <i>J</i> = 8.8 Hz, 1H) |
| 188             |    |              | 305       | 303       |                                                                                                                                                                                                                       |
| 189             |   | 185--<br>188 | 344       | 342       | 12.25 (s, 1H), 10.98 (s, 1H), 8.47 (s, 1H), 7.81-7.67 (m, 1H), 7.66-7.57 (m, 2H), 7.34 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 7.23 (dt, <i>J</i> = 3.5, 2.3 Hz, 1H), 6.91 (dd, <i>J</i> = 42.1, 8.6 Hz, 1H)                |
| 190             |  |              | 353       | 351       |                                                                                                                                                                                                                       |

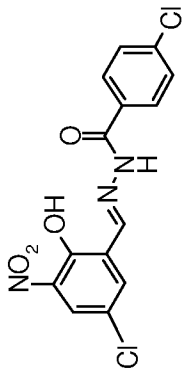
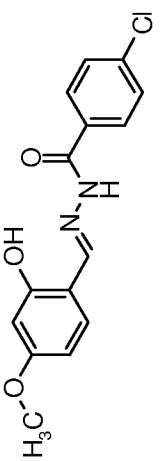
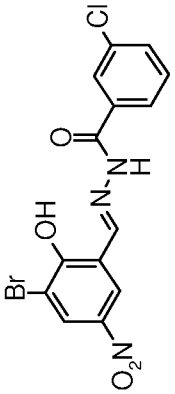
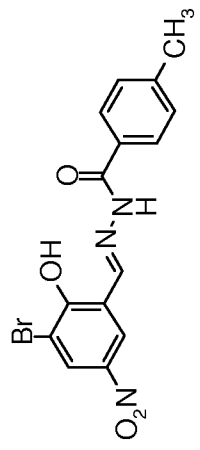
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$ |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------|
| 191             |    |         |           | 351       |                                                                                               |
| 192             |    |         |           | 385       |                                                                                               |
| 193             |    |         | 432       | 431       |                                                                                               |
| 194             |  |         | 369       | 367       |                                                                                               |

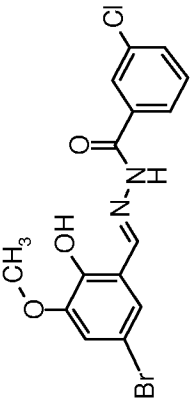
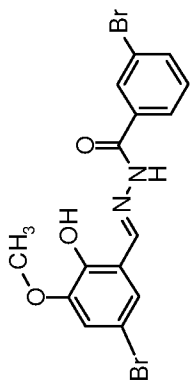
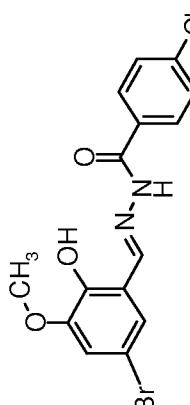
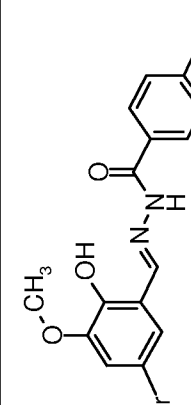
65480 US

| Compound Number | Structure                                                                             | mp (°C)      | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                        |
|-----------------|---------------------------------------------------------------------------------------|--------------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| 195             |    |              |           | 367       |                                                                                                                                                      |
| 196             |    | 169--<br>173 | 423       | 421       | 12.67 (s, 1H), 12.32 (s, 1H), 8.42 (s, 1H), 7.82 (t, <i>J</i> = 1.3 Hz, 1H), 7.77 (dd, <i>J</i> = 12.0, 2.5 Hz, 2H), 7.65 (d, <i>J</i> = 1.3 Hz, 2H) |
| 197             |    |              | 321       | 319       |                                                                                                                                                      |
| 198             |  |              |           | 525       |                                                                                                                                                      |

65480 US

| Compound Number | Structure                                                                            | mp (°C)      | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                           |
|-----------------|--------------------------------------------------------------------------------------|--------------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 199             |   |              | 354       | 352       |                                                                                                                                                                                                                                                         |
| 200             |   |              | 305       | 303       |                                                                                                                                                                                                                                                         |
| 201             |   | 276--<br>280 | 399       | 397       | 13.87 (s, 1H), 12.82 (s, 1H), 8.71 (s, 1H), 8.65 (d, <i>J</i> = 2.7 Hz, 1H), 8.48 (d, <i>J</i> = 2.7 Hz, 1H), 8.02 (t, <i>J</i> = 1.8 Hz, 1H), 7.94 (d, <i>J</i> = 7.8 Hz, 1H), 7.73 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 7.62 (t, <i>J</i> = 7.9 Hz, 1H). |
| 202             |  |              | 379       |           |                                                                                                                                                                                                                                                         |

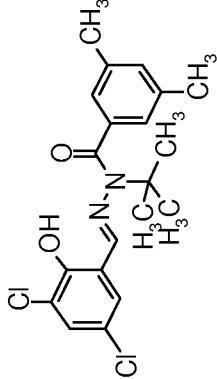
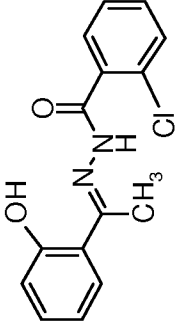
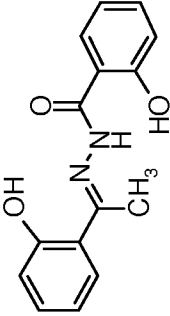
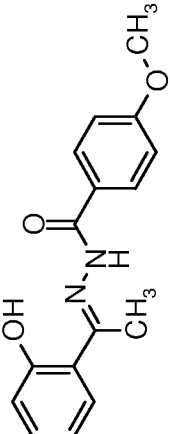
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------|
| 203             |    |         | 385       | 383       |                                                                                        |
| 204             |    |         | 429       | 427       |                                                                                        |
| 205             |    |         | 383       | 381       |                                                                                        |
| 206             |  |         | 363       | 361       |                                                                                        |

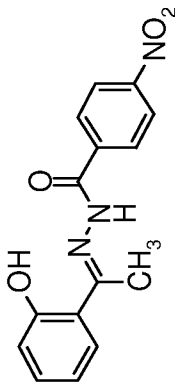
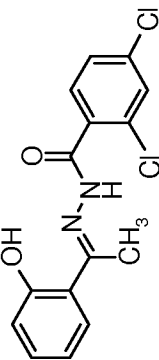
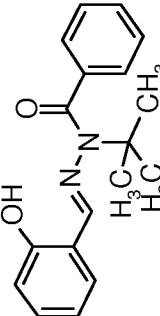
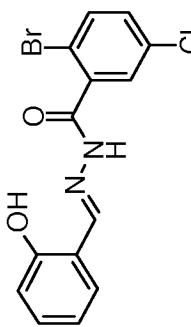
65480 US

| Compound Number | Structure | mp (°C)      | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                        |
|-----------------|-----------|--------------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 207             |           |              | 305       | 303       |                                                                                                                                                                      |
| 208             |           | 283--<br>300 | 393       | 391       | 14.01 (s, 1H), 12.65 (s, 1H), 8.69 (s, 1H), 8.60 (d, <i>J</i> = 2.7 Hz, 1H), 8.47 (d, <i>J</i> = 2.6 Hz, 1H), 7.59 (s, 2H), 7.29 (s, 1H), 2.37 (s, 6H)               |
| 209             |           | 189--<br>193 | 378       | 376       | 12.07 (s, 1H), 10.90 (s, 1H), 8.61 (s, 1H), 7.55 (s, 2H), 7.40 (d, <i>J</i> = 2.2 Hz, 1H), 7.24 (s, 1H), 7.17 (d, <i>J</i> = 2.2 Hz, 1H), 3.85 (s, 3H), 2.35 (s, 6H) |
| 210             |           |              | 369       | 367       |                                                                                                                                                                      |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                         |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| 211             |    | 220–227 | 393       | 391       | 11.76 (s, 1H), 8.19 (s, 1H), 7.65 (d, <i>J</i> = 2.5 Hz, 1H), 7.39 (d, <i>J</i> = 2.6 Hz, 1H), 7.04 (s, 2H), 6.94 (s, 1H), 2.18 (s, 6H), 1.53 (s, 9H) |
| 212             |    |         | 289       | 287       |                                                                                                                                                       |
| 213             |    |         | 271       | 269       |                                                                                                                                                       |
| 214             |  |         | 285       | 283       |                                                                                                                                                       |

65480 US

| Compound Number | Structure                                                                            | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------|-------------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 215             |   |             | 300       | 298       |                                                                                                                                                                                                   |
| 216             |   |             | 323       | 321       |                                                                                                                                                                                                   |
| 217             |   | 91-104      | 297       | 295       | 10.78 (s, 1H), 8.18 (s, 1H), 7.42 – 7.37 (m, 2H), 7.34 (dd, J = 7.7, 1.7 Hz, 1H), 7.32 – 7.24 (m, 4H), 6.80 (td, J = 8.3, 4.4 Hz, 2H), 1.53 (s, 9H)                                               |
| 218             |  | 222–<br>225 | 354       | 352       | 12.17 (s, 1H), 10.94 (s, 6H), 7.78 – 7.71 (m, 15H), 7.62 – 7.57 (m, 9H), 7.53 (dd, J = 8.6, 2.6 Hz, 6H), 7.27 (dddd, J = 27.4, 15.4, 7.9, 1.7 Hz, 14H), 6.96 – 6.89 (m, 12H), 6.83 – 6.76 (m, 7H) |

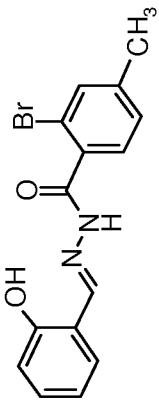
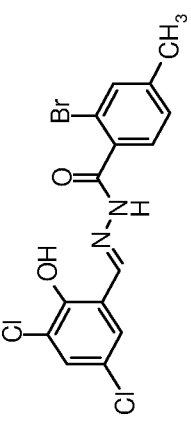
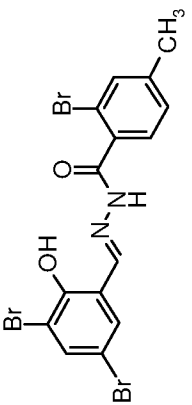
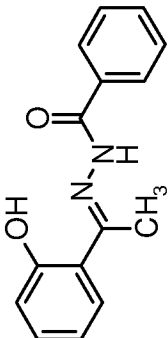
65480 US

| Compound Number | Structure | mp (°C)      | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                         |
|-----------------|-----------|--------------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 219             |           | 228--<br>231 | 423       | 421       | 12.60 (s, 1H), 12.10 (s, 1H), 7.80 – 7.75 (m, 2H), 7.69 (dd, J = 19.8, 2.6 Hz, 2H), 7.57 (dd, J = 2.5, 1.2 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H)                                                                                          |
| 220             |           | 215--<br>218 | 512       | 510       | 12.65 (s, 1H), 12.35 (s, 1H), 7.87 (q, J = 2.4 Hz, 2H), 7.82–7.75 (m, 3H), 7.64 (dd, J = 17.0, 2.4 Hz, 1H), 7.55 (ddd, J = 8.5, 6.0, 2.6 Hz, 1H)                                                                                      |
| 221             |           | 202--<br>205 | 446       | 444       | 12.14 (s, 1H), 10.95 (s, 1H), 8.48 (s, 1H), 7.93 (d, J = 2.1 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.59 (dd, J = 7.7, 1.5 Hz, 1H), 7.50 (dd, J = 12.0, 8.4 Hz, 1H), 7.35 – 7.18 (m, 1H), 6.96 – 6.89 (m, 1H), 6.80 (dd, J = 12.3, 5.2 Hz, 1H) |
| 222             |           | 201--<br>219 | 514       | 512       | 12.57 (s, 1H), 12.12 (s, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.81 (ddd, J = 11.4, 10.0, 2.2 Hz, 2H), 7.71 (d, J = 2.6 Hz, 1H), 7.66 (d, J = 2.5 Hz, 1H), 7.53 (dd, J = 8.4, 2.2 Hz, 1H)                                                    |

65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                            |
|-----------------|-----------|-------------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 223             |           | 215–<br>216 | 603       | 601       | 12.62 (s, 1H), 12.36 (s, 1H), 8.40 (s, 1H), 7.97 (d, <i>J</i> = 2.1 Hz, 1H), 7.86 (dd, <i>J</i> = 7.4, 2.3 Hz, 2H), 7.82–7.76 (m, 2H), 7.53 (d, <i>J</i> = 8.4 Hz, 1H)                                                   |
| 224             |           | 222–<br>226 | 401       | 399       | 12.15 (s, 1H), 10.94 (s, 1H), 8.49 (s, 1H), 7.97 (d, <i>J</i> = 2.1 Hz, 1H), 7.88 (dd, <i>J</i> = 8.4, 2.2 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.59 (dd, <i>J</i> = 7.7, 1.6 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.84 – 6.76 (m, 1H) |
| 225             |           | 198–<br>201 | 470       |           | 8.44 (s, 1H), 8.01 (d, <i>J</i> = 2.1 Hz, 1H), 7.89 (td, <i>J</i> = 8.7, 2.1 Hz, 2H), 7.68 (dd, <i>J</i> = 16.4, 2.5 Hz, 2H), 7.43–7.36 (m, 2H)                                                                          |
| 226             |           | 205–<br>212 | 559       |           | 12.64 (s, 1H), 12.36 (s, 1H), 8.40 (s, 1H), 8.01 (d, <i>J</i> = 2.1 Hz, 1H), 7.93–7.83 (m, 3H), 7.40 (t, <i>J</i> = 5.0 Hz, 1H)                                                                                          |

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| Compound Number | Structure                                                                            | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 227             |   | 86–122  | 334       | 332       | 12.04 (d, <i>J</i> = 17.6 Hz, 1H), 11.05 (s, 1H), 7.62–7.52 (m, 2H), 7.46 (d, <i>J</i> = 7.7 Hz, 1H), 7.34–7.26 (m, 2H), 6.96–6.88 (m, 2H), 6.80 (t, <i>J</i> = 6.0 Hz, 1H), 2.36 (s, 3H)                      |
| 228             |   | 240–242 | 403       | 401       | 12.49 (s, 1H), 12.25 (s, 1H), 8.44 (s, 1H), 7.67 (dd, <i>J</i> = 13.6, 2.5 Hz, 2H), 7.60 (d, <i>J</i> = 4.1 Hz, 1H), 7.56–7.43 (m, 1H), 7.33 (dd, <i>J</i> = 6.3, 2.2 Hz, 1H), 2.37 (d, <i>J</i> = 2.8 Hz, 3H) |
| 229             |   | 258–261 | 491       | 489       | 12.53 (s, 1H), 12.48 (s, 1H), 8.40 (s, 1H), 7.84 (dd, <i>J</i> = 11.5, 2.4 Hz, 2H), 7.60 (s, 1H), 7.49 (d, <i>J</i> = 7.7 Hz, 1H), 7.34 (q, <i>J</i> = 7.8 Hz, 1H), 2.37 (d, <i>J</i> = 3.5 Hz, 3H)            |
| 230             |  | 185–187 | 255       | 253       | (300 MHz, CDCl <sub>3</sub> ) 12.73 (s, 1H), 9.00 (s, 1H), 7.90–7.82 (m, 2H), 7.64–7.57 (m, 1H), 7.55–7.47 (m, 3H), 7.35–7.28 (m, 1H), 7.09–7.00 (m, 1H), 6.94–6.87 (m, 1H), 2.42 (s, 3H)                      |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                              |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 231             |           | 188–189 | 275       | 273       | 12.47 (s, 1H), 12.40 (s, 1H), 8.63 (s, 1H), 8.07–7.91 (m, 2H), 7.70–7.61 (m, 1H), 7.58 (t, <i>J</i> = 7.4 Hz, 2H), 7.50 (d, <i>J</i> = 7.9 Hz, 2H), 6.98 (t, <i>J</i> = 7.8 Hz, 1H) |
| 232             |           | 186–188 | 255       |           | 12.24 (s, 1H), 11.96 (s, 1H), 8.59 (s, 1H), 8.08–7.89 (m, 2H), 7.71–7.43 (m, 3H), 7.26 (dd, <i>J</i> = 24.4, 7.4 Hz, 2H), 6.86 (t, <i>J</i> = 7.5 Hz, 1H), 2.23 (s, 3H)             |
| 233             |           | 218–219 | 275       | 273       | 12.16 (s, 1H), 11.60 (s, 1H), 8.65 (s, 1H), 7.95 (d, <i>J</i> = 7.2 Hz, 2H), 7.59 (dt, <i>J</i> = 14.8, 7.7 Hz, 4H), 7.10–6.83 (m, 2H)                                              |
| 234             |           | 179–182 | 255       | 253       | 12.08 (s, 1H), 11.32 (s, 1H), 8.61 (s, 1H), 8.08–7.81 (m, 2H), 7.70–7.47 (m, 3H), 7.42 (d, <i>J</i> = 7.8 Hz, 1H), 6.89–6.68 (m, 2H), 2.29 (s, 3H)                                  |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 235             |           | 192–193 | 255       | 253       | 12.11 (s, 1H), 11.06 (s, 1H), 8.61 (s, 1H), 8.01–7.84 (m, 2H), 7.59 (dt, <i>J</i> = 27.8, 7.2 Hz, 3H), 7.36 (d, <i>J</i> = 1.4 Hz, 1H), 7.12 (dd, <i>J</i> = 8.3, 1.8 Hz, 1H), 6.85 (d, <i>J</i> = 8.3 Hz, 1H), 2.26 (s, 3H) |
| 236             |           | 247–248 | 275       | 273       | 12.53 (s, 1H), 12.48 (s, 1H), 9.06 (s, 1H), 8.08–7.90 (m, 2H), 7.62 (dt, <i>J</i> = 28.8, 7.2 Hz, 3H), 7.34 (t, <i>J</i> = 8.2 Hz, 1H), 7.06 (dd, <i>J</i> = 7.9, 0.7 Hz, 1H), 6.97 (d, <i>J</i> = 8.3 Hz, 1H)               |
| 237             |           | 215–216 | 271       | 269       | 12.26 (s, 1H), 12.21 (s, 1H), 8.98 (s, 1H), 8.03–7.90 (m, 2H), 7.66–7.49 (m, 3H), 7.28 (t, <i>J</i> = 8.3 Hz, 1H), 6.57 (dd, <i>J</i> = 8.3, 3.6 Hz, 2H), 3.86 (s, 3H)                                                       |
| 238             |           | 249–252 | 289       | 287       | 12.88 (s, 1H), 12.46 (s, 1H), 8.61 (s, 1H), 8.04–7.89 (m, 2H), 7.60 (ddd, <i>J</i> = 12.6, 11.5, 6.4 Hz, 4H), 7.23 (d, <i>J</i> = 8.4 Hz, 1H)                                                                                |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                      |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| 239             |           | 206–208 | 289       | 287       | 12.18 (s, 1H), 11.29 (s, 1H), 8.59 (s, 1H), 7.95 (dd, <i>J</i> = 11.2, 4.0 Hz, 2H), 7.69–7.47 (m, 4H), 6.94 (s, 1H), 2.30 (s, 3H)                  |
| 240             |           | 238–241 | 309       | 307       | 12.25 (s, 1H), 11.61 (s, 1H), 8.62 (s, 1H), 8.08–7.71 (m, 2H), 7.68–7.29 (m, 4H), 7.19 (s, 1H)                                                     |
| 241             |           | 273–274 | 309       | 307       | 12.76 (s, 1H), 12.55 (s, 1H), 9.06 (s, 1H), 8.09–7.90 (m, 2H), 7.62 (ddd, <i>J</i> = 22.7, 11.1, 7.0 Hz, 4H), 7.00 (d, <i>J</i> = 9.0 Hz, 1H)      |
| 242             |           | 273–274 | 309       | 307       | 12.92 (s, 1H), 12.52 (s, 1H), 8.98 (s, 1H), 8.09–7.88 (m, 2H), 7.73–7.52 (m, 3H), 7.22 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 (d, <i>J</i> = 2.0 Hz, 1H) |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                               |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 243             |           | 187–189 | 349       | 347       | 12.77 (s, 1H), 12.50 (s, 1H), 9.00 (s, 1H), 8.11–7.87 (m, 2H), 7.65 (t, <i>J</i> = 7.3 Hz, 1H), 7.58 (t, <i>J</i> = 7.4 Hz, 2H), 7.16 (d, <i>J</i> = 8.7 Hz, 1H), 6.99 (d, <i>J</i> = 8.7 Hz, 1H), 3.82 (s, 3H)             |
| 244             |           | 206–207 | 277       | 275       | 12.45 (d, <i>J</i> = 10.6 Hz, 1H), 12.42 (s, 1H), 8.77 (s, 1H), 7.97 (d, <i>J</i> = 7.5 Hz, 2H), 7.66 (t, <i>J</i> = 7.3 Hz, 1H), 7.58 (t, <i>J</i> = 7.5 Hz, 2H), 7.44–7.23 (m, 1H), 6.81 (td, <i>J</i> = 9.5, 3.4 Hz, 1H) |
| 245             |           | 216–218 | 259       | 257       | 12.35 (s, 1H), 12.10 (s, 1H), 8.82 (s, 1H), 8.04–7.89 (m, 2H), 7.76–7.61 (m, 1H), 7.58 (t, <i>J</i> = 7.4 Hz, 2H), 7.36 (dd, <i>J</i> = 15.2, 8.3 Hz, 1H), 6.91–6.70 (m, 2H)                                                |
| 246             |           | 212–213 | 255       | 253       | 12.19 (s, 2H), 8.92 (s, 1H), 8.03–7.90 (m, 2H), 7.69–7.60 (m, 1H), 7.57 (t, <i>J</i> = 7.3 Hz, 2H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 6.78 (dd, <i>J</i> = 14.2, 7.8 Hz, 2H), 2.43 (s, 3H)                                   |

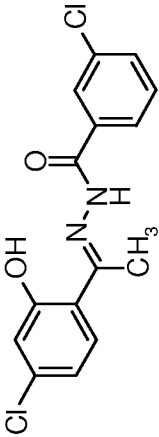
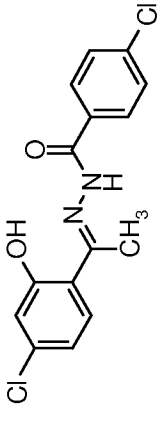
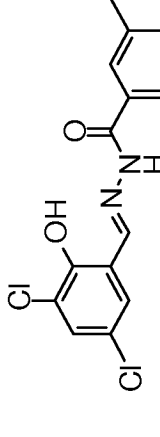
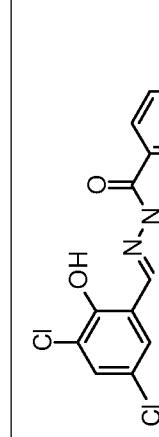
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                   |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 247             |           | 204–205 | 309       | 307       | 13.45 (s, 1H), 12.61 (s, 1H), 9.02 (s, 1H), 7.99 (d, <i>J</i> = 7.3 Hz, 2H), 7.66 (t, <i>J</i> = 7.3 Hz, 1H), 7.59 (t, <i>J</i> = 7.5 Hz, 2H), 7.53 (d, <i>J</i> = 8.6 Hz, 1H), 7.09 (d, <i>J</i> = 8.6 Hz, 1H) |
| 248             |           | 234–237 | 354       | 352       | 12.72 (s, 1H), 12.45 (s, 1H), 8.80 (t, <i>J</i> = 1.9 Hz, 1H), 8.62 (s, 1H), 8.51 – 8.37 (m, 2H), 7.88 (t, <i>J</i> = 8.0 Hz, 1H), 7.69 (dd, <i>J</i> = 24.9, 2.5 Hz, 2H)                                       |
| 249             |           | 165–169 |           | 375       | 12.70 (s, 1H), 12.38 (s, 1H), 8.60 (s, 1H), 8.32–8.23 (m, 2H), 8.02 (d, <i>J</i> = 7.8 Hz, 1H), 7.83 (t, <i>J</i> = 7.8 Hz, 1H), 7.68 (dd, <i>J</i> = 24.6, 2.5 Hz, 2H)                                         |
| 250             |           | 180–182 | 393       | 391       | 12.63 (s, 1H), 12.39 (s, 1H), 8.60 (s, 1H), 8.01 (d, <i>J</i> = 7.6 Hz, 1H), 7.91 (s, 1H), 7.76–7.63 (m, 4H)                                                                                                    |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                              |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 251             |           | 236–237 | 289       | 287       | 13.78 (s, 1H), 11.43 (s, 1H), 7.94 (d, <i>J</i> = 7.3 Hz, 2H), 7.70–7.51 (m, 2H), 7.03–6.92 (m, 4H), 2.49 (s, 3H)                                                                                        |
| 252             |           | 214–215 | 303       | 301       | 13.77 (s, 1H), 11.51 (s, 1H), 7.64 (d, <i>J</i> = 8.5 Hz, 1H), 7.51 (d, <i>J</i> = 7.5 Hz, 1H), 7.43 (dd, <i>J</i> = 10.7, 4.3 Hz, 1H), 7.36–7.29 (m, 2H), 7.01–6.92 (m, 2H), 2.41 (s, 3H), 2.40 (s, 3H) |
| 253             |           | 210–211 | 303       | 301       | 13.79 (s, 1H), 11.38 (s, 1H), 7.78–7.70 (m, 2H), 7.66 (d, <i>J</i> = 8.5 Hz, 1H), 7.48–7.40 (m, 2H), 7.01–6.93 (m, 2H), 2.48 (s, 3H), 2.41 (s, 3H)                                                       |
| 254             |           | 254–256 | 303       | 301       | 13.80 (s, 1H), 11.33 (s, 1H), 7.86 (d, <i>J</i> = 8.0 Hz, 2H), 7.66 (d, <i>J</i> = 8.5 Hz, 1H), 7.36 (d, <i>J</i> = 8.0 Hz, 2H), 7.02–6.91 (m, 2H), 2.48 (s, 3H), 2.40 (s, 3H)                           |
| 255             |           | 183–184 | 323       | 321       | 13.60 (s, 1H), 11.72 (s, 1H), 7.67–7.45 (m, 5H), 7.02–6.94 (m, 2H), 2.41 (s, 3H)                                                                                                                         |

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| Compound Number | Structure                                                                            | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                          |
|-----------------|--------------------------------------------------------------------------------------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 256             |   | 222–223 | 323       | 321       | 13.69 (s, 1H), 11.52 (s, 1H), 8.02–7.97 (m, 1H), 7.90 (d, <i>J</i> = 7.8 Hz, 1H), 7.73–7.65 (m, 2H), 7.59 (t, <i>J</i> = 7.9 Hz, 1H), 7.02–6.94 (m, 2H), 2.49 (s, 3H)                                                  |
| 257             |   | 246–247 | 323       | 321       | 13.72 (s, 1H), 11.48 (s, 1H), 7.97 (d, <i>J</i> = 8.4 Hz, 2H), 7.66 (d, <i>J</i> = 8.6 Hz, 1H), 7.63 (d, <i>J</i> = 8.5 Hz, 2H), 7.02–6.93 (m, 2H), 2.49 (s, 3H)                                                       |
| 258             |   | 277–280 |           | 337       | 12.42 (s, 2H), 11.47 (s, 1H), 8.61 (s, 1H), 7.66 (d, <i>J</i> = 13.7 Hz, 3H), 7.28 (dd, <i>J</i> = 8.4, 1.9 Hz, 1H), 6.91 (d, <i>J</i> = 8.4 Hz, 1H), 2.28 (s, 3H)                                                     |
| 259             |  | 245–252 |           | 336       | 12.81 (s, 1H), 12.16 (s, 1H), 8.51 (s, 1H), 7.77 (d, <i>J</i> = 8.7 Hz, 2H), 7.61 (dd, <i>J</i> = 13.2, 2.5 Hz, 2H), 6.61 (d, <i>J</i> = 8.7 Hz, 2H), 6.50 (q, <i>J</i> = 4.8 Hz, 1H), 2.75 (d, <i>J</i> = 4.9 Hz, 3H) |

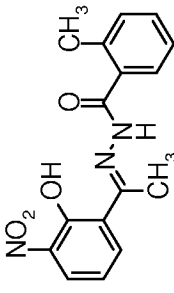
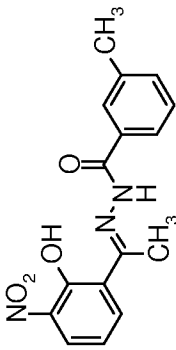
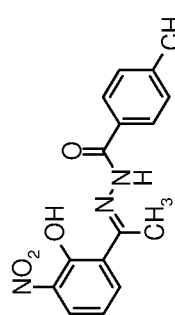
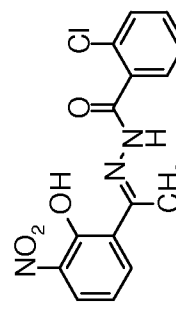
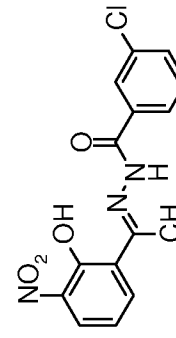
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                                                       |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 260             |           | 286–289 | 337       | 335       | 12.58 (s, 1H), 12.48 (s, 1H), 8.57 (s, 1H), 7.90 (d, <i>J</i> = 8.1 Hz, 2H), 7.68 (d, <i>J</i> = 2.4 Hz, 1H), 7.63 (d, <i>J</i> = 2.5 Hz, 1H), 7.41 (d, <i>J</i> = 8.1 Hz, 2H), 2.70 (q, <i>J</i> = 7.6 Hz, 2H), 1.22 (t, <i>J</i> = 7.6 Hz, 3H)                             |
| 261             |           | 150–152 | 285       | 283       | 12.85 (s, 1H), 11.33 (s, 1H), 7.94 (d, <i>J</i> = 7.3 Hz, 2H), 7.63 (t, <i>J</i> = 7.3 Hz, 1H), 7.55 (t, <i>J</i> = 7.4 Hz, 2H), 7.13 (d, <i>J</i> = 2.9 Hz, 1H), 6.95 (dd, <i>J</i> = 8.9, 2.8 Hz, 1H), 6.85 (d, <i>J</i> = 8.9 Hz, 1H), 3.75 (s, 3H), 2.49 (s, 3H)         |
| 262             |           | 146–155 | 299       | 297       | 12.81 (s, 1H), 11.40 (s, 1H), 7.51 (d, <i>J</i> = 7.5 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.33 (dd, <i>J</i> = 7.5, 3.9 Hz, 2H), 7.11 (d, <i>J</i> = 2.9 Hz, 1H), 6.94 (dd, <i>J</i> = 8.9, 2.9 Hz, 1H), 6.85 (d, <i>J</i> = 8.9 Hz, 1H), 3.75 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H) |
| 263             |           | 131–141 | 299       | 297       | 12.84 (s, 1H), 11.29 (s, 1H), 7.78–7.70 (m, 2H), 7.43 (d, <i>J</i> = 5.2 Hz, 2H), 7.13 (d, <i>J</i> = 2.9 Hz, 1H), 6.94 (dd, <i>J</i> = 8.9, 2.9 Hz, 1H), 6.85 (d, <i>J</i> = 8.8 Hz, 1H), 3.75 (s, 3H), 2.48 (s, 3H), 2.41 (s, 3H)                                          |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), δ                                                                                                                                                                                               |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 264             |           | 159–162 | 299       | 297       | 12.86 (s, 1H), 11.24 (s, 1H), 7.86 (d, <i>J</i> = 8.0 Hz, 2H), 7.35 (d, <i>J</i> = 8.1 Hz, 2H), 7.13 (d, <i>J</i> = 2.9 Hz, 1H), 6.94 (dd, <i>J</i> = 8.9, 2.9 Hz, 1H), 6.84 (d, <i>J</i> = 8.9 Hz, 1H), 3.75 (s, 3H), 2.48 (s, 3H), 2.40 (s, 3H)                                  |
| 265             |           | 170–184 | 319       | 317       | 12.67 (s, 1H), 11.61 (s, 1H), 7.65–7.44 (m, 5H), 7.11 (d, <i>J</i> = 3.0 Hz, 1H), 7.01–6.92 (m, 1H), 3.75 (s, 3H), 2.41 (s, 3H)                                                                                                                                                    |
| 266             |           | 190–201 | 319       | 317       | 12.75 (s, 1H), 11.43 (s, 1H), 8.00 (s, 1H), 7.90 (d, <i>J</i> = 7.7 Hz, 1H), 7.70 (d, <i>J</i> = 8.1 Hz, 1H), 7.58 (t, <i>J</i> = 7.9 Hz, 1H), 7.14 (d, <i>J</i> = 2.9 Hz, 1H), 6.95 (dd, <i>J</i> = 8.9, 2.9 Hz, 1H), 6.86 (d, <i>J</i> = 8.9 Hz, 1H), 3.75 (s, 3H), 2.50 (s, 3H) |
| 267             |           | 193–196 | 319       | 317       | 12.79 (s, 1H), 11.39 (s, 1H), 7.97 (d, <i>J</i> = 8.5 Hz, 2H), 7.63 (d, <i>J</i> = 8.5 Hz, 2H), 7.14 (d, <i>J</i> = 2.9 Hz, 1H), 6.95 (dd, <i>J</i> = 8.9, 2.9 Hz, 1H), 6.85 (d, <i>J</i> = 8.9 Hz, 1H), 3.75 (s, 3H), 2.49 (s, 3H)                                                |
| 268             |           | 215–224 | 300       | 298       | 15.25 (s, 1H), 11.65 (s, 1H), 8.02–7.91 (m, 4H), 7.66 (t, <i>J</i> = 7.3 Hz, 1H), 7.57 (t, <i>J</i> = 7.6 Hz, 2H), 7.07 (t, <i>J</i> = 8.0 Hz, 1H), 2.56 (s, 3H)                                                                                                                   |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                                                                |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 269             |    | 193–196 | 314       | 312       | 15.27 (s, 1H), 11.76 (s, 1H), 7.95 (dd, <i>J</i> = 13.4, 7.5 Hz, 2H), 7.54 (d, <i>J</i> = 7.5 Hz, 1H), 7.45 (t, <i>J</i> = 7.4 Hz, 1H), 7.35 (dd, <i>J</i> = 7.5, 4.3 Hz, 2H), 7.06 (t, <i>J</i> = 8.0 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H) |
| 270             |    | 235–239 | 314       | 312       | 15.25 (d, <i>J</i> = 8.4 Hz, 1H), 11.60 (s, 1H), 7.96 (ddd, <i>J</i> = 21.0, 8.0, 1.4 Hz, 2H), 7.76 (d, <i>J</i> = 11.3 Hz, 2H), 7.46 (d, <i>J</i> = 6.3 Hz, 2H), 7.06 (t, <i>J</i> = 8.0 Hz, 1H), 2.56 (s, 3H), 2.42 (s, 3H)              |
| 271             |    | 242–249 | 314       | 312       | 15.28 (s, 1H), 11.55 (s, 1H), 7.96 (ddd, <i>J</i> = 20.2, 8.0, 1.4 Hz, 2H), 7.88 (d, <i>J</i> = 8.0 Hz, 2H), 7.37 (d, <i>J</i> = 8.1 Hz, 2H), 7.06 (t, <i>J</i> = 8.0 Hz, 1H), 2.56 (s, 3H), 2.41 (s, 3H)                                  |
| 272             |   | 196–205 | 334       | 332       | 15.04 (s, 1H), 11.97 (s, 1H), 8.00–7.92 (m, 2H), 7.68–7.53 (m, 3H), 7.49 (td, <i>J</i> = 7.3, 1.3 Hz, 1H), 7.07 (t, <i>J</i> = 8.0 Hz, 1H), 2.48 (s, 3H)                                                                                   |
| 273             |  | 251–286 | 334       | 332       | 15.13 (s, 1H), 11.73 (s, 1H), 8.04–7.89 (m, 4H), 7.73 (d, <i>J</i> = 7.9 Hz, 1H), 7.60 (t, <i>J</i> = 7.9 Hz, 1H), 7.07 (t, <i>J</i> = 8.0 Hz, 1H), 2.57 (s, 3H)                                                                           |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                          |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 274             |           | 241–251 | 334       | 332       | 15.17 (s, 1H), 11.70 (s, 1H), 7.99 (d, <i>J</i> = 8.5 Hz, 3H), 7.94 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 7.65 (d, <i>J</i> = 8.5 Hz, 2H), 7.06 (t, <i>J</i> = 8.0 Hz, 1H), 2.56 (s, 3H) |
| 275             |           | 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)                                                                                |
| 276             |           | 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)                                                      |
| 277             |           | 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)                   |
| 278             |           | 221–223 | 337       | 335       | 14.48 (s, 1H), 11.54 (s, 1H), 7.79–7.72 (m, 2H), 7.68 (d, <i>J</i> = 2.5 Hz, 1H), 7.64 (d, <i>J</i> = 2.4 Hz, 1H), 7.47–7.42 (m, 2H), 2.52 (s, 3H), 2.41 (s, 3H)                     |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                          |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 279             |           | 262–264 | 337       | 335       |                                                                                                                                                                                                                 |
| 280             |           | 211–213 | 285       | 283       |                                                                                                                                                                                                                 |
| 281             |           | 170–172 | 299       | 297       | 13.65 (s, 1H), 11.29 (s, 1H), 7.53 (d, <i>J</i> = 8.7 Hz, 1H), 7.50 (d, <i>J</i> = 7.6 Hz, 1H), 7.42 (t, <i>J</i> = 6.9 Hz, 1H), 7.34–7.28 (m, 2H), 6.51–6.44 (m, 2H), 3.78 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H) |
| 282             |           | 184–185 | 299       | 297       | 13.68 (s, 1H), 11.19 (s, 1H), 7.77–7.68 (m, 2H), 7.56 (d, <i>J</i> = 8.7 Hz, 1H), 7.46–7.40 (m, 2H), 6.51–6.44 (m, 2H), 3.78 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H)                                                |

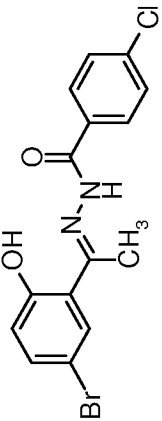
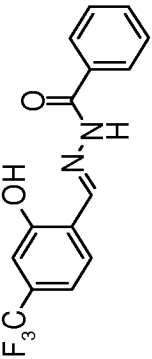
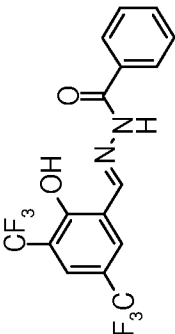
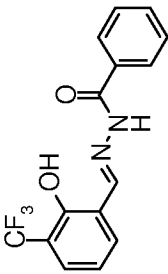
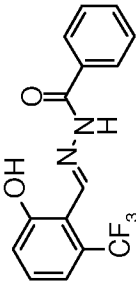
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                                 |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 283             |           | 206–207 | 299       | 297       | 13.69 (s, 1H), 11.14 (s, 1H), 7.84 (d, <i>J</i> = 8.0 Hz, 2H), 7.55 (d, <i>J</i> = 8.7 Hz, 1H), 7.35 (d, <i>J</i> = 8.1 Hz, 2H), 6.52–6.44 (m, 2H), 3.78 (s, 3H), 2.44 (s, 3H), 2.39 (s, 3H)                                                           |
| 284             |           | 174–175 | 319       | 317       |                                                                                                                                                                                                                                                        |
| 285             |           | 212–214 | 319       | 317       |                                                                                                                                                                                                                                                        |
| 286             |           | 227–229 | 319       | 317       |                                                                                                                                                                                                                                                        |
| 287             |           | 204–208 | 334       | 332       | 13.49 (s, 1H), 11.45 (s, 1H), 7.94 (d, <i>J</i> = 7.4 Hz, 2H), 7.76 (d, <i>J</i> = 2.3 Hz, 1H), 7.64 (t, <i>J</i> = 7.3 Hz, 1H), 7.55 (t, <i>J</i> = 7.5 Hz, 2H), 7.45 (dd, <i>J</i> = 8.7, 2.3 Hz, 1H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 2.49 (s, 3H) |

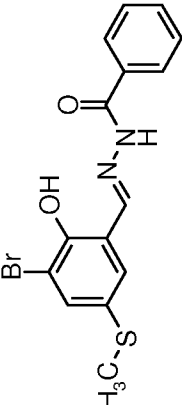
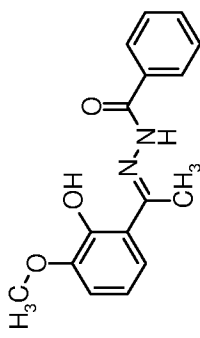
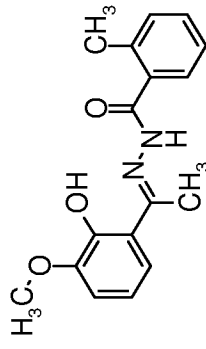
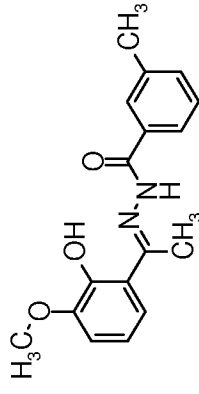
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                                               |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 288             |           | 201–203 | 348       | 346       | 13.49 (s, 1H), 11.53 (s, 1H), 7.74 (d, <i>J</i> = 2.4 Hz, 1H), 7.51 (d, <i>J</i> = 7.4 Hz, 1H), 7.47–7.41 (m, 2H), 7.33 (dd, <i>J</i> = 7.4, 4.5 Hz, 2H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H)                                                |
| 289             |           | 227–233 | 348       | 346       | 13.50 (s, 1H), 11.40 (s, 1H), 7.75 (t, <i>J</i> = 5.9 Hz, 3H), 7.49–7.41 (m, 3H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H)                                                                                                                        |
| 290             |           | 245–248 | 348       | 346       | 13.51 (s, 1H), 11.36 (s, 1H), 7.86 (d, <i>J</i> = 7.9 Hz, 2H), 7.75 (d, <i>J</i> = 2.3 Hz, 1H), 7.45 (dd, <i>J</i> = 8.7, 2.3 Hz, 1H), 7.36 (d, <i>J</i> = 8.1 Hz, 2H), 6.89 (d, <i>J</i> = 8.7 Hz, 1H), 2.48 (s, 3H), 2.40 (s, 3H)                                  |
| 291             |           | 198–201 | 368       | 366       | 13.31 (s, 1H), 11.73 (s, 1H), 7.74 (d, <i>J</i> = 2.3 Hz, 1H), 7.61–7.54 (m, 2H), 7.47 (dd, <i>J</i> = 13.1, 4.7 Hz, 3H), 6.91 (d, <i>J</i> = 8.7 Hz, 1H), 2.41 (s, 3H)                                                                                              |
| 292             |           | 235–240 | 368       | 366       | 13.40 (s, 1H), 11.54 (s, 1H), 8.00 (s, 1H), 7.90 (d, <i>J</i> = 7.7 Hz, 1H), 7.77 (d, <i>J</i> = 2.4 Hz, 1H), 7.71 (d, <i>J</i> = 9.0 Hz, 1H), 7.59 (t, <i>J</i> = 7.9 Hz, 1H), 7.46 (dd, <i>J</i> = 8.7, 2.3 Hz, 1H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 2.50 (s, 3H) |

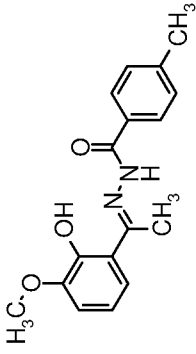
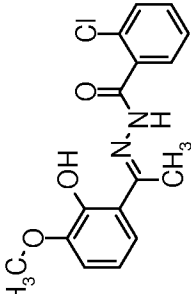
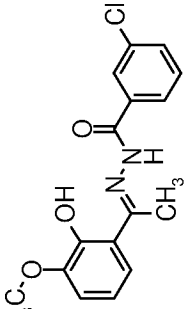
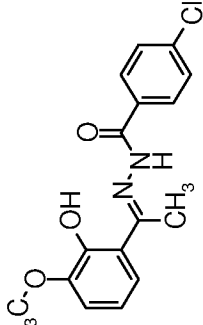
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 293             |    | 264–268 |           | 366       | 13.43 (s, 1H), 11.50 (s, 1H), 7.98 (d, <i>J</i> = 8.4 Hz, 2H), 7.76 (d, <i>J</i> = 2.3 Hz, 1H), 7.63 (d, <i>J</i> = 8.5 Hz, 2H), 7.46 (dd, <i>J</i> = 8.7, 2.3 Hz, 1H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 2.49 (s, 3H) |
| 294             |    | 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)                                                 |
| 295             |    | 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)                                                                         |
| 296             |   | 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)                                   |
| 297             |  | 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)                |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                    |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 298             |    | 207–209 | 365       | 363       | 12.54 (s, 1H), 12.50 (s, 1H), 8.55 (s, 1H), 7.99–7.92 (m, 2H), 7.68–7.61 (m, 1H), 7.61–7.50 (m, 4H), 2.50 (s, 3H)                                                                                                                                |
| 299             |    | 146–148 | 285       | 283       | 13.50 (s, 1H), 11.34 (s, 1H), 7.94 (d, <i>J</i> = 7.4 Hz, 2H), 7.66–7.60 (m, 1H), 7.59–7.52 (m, 2H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.04 (d, <i>J</i> = 7.9 Hz, 1H), 6.83 (t, <i>J</i> = 8.0 Hz, 1H), 3.79 (s, 3H), 2.48 (s, 3H)               |
| 300             |    | 208–209 | 299       | 297       | 13.50 (s, 1H), 11.40 (s, 1H), 7.52 (d, <i>J</i> = 7.4 Hz, 1H), 7.43 (t, <i>J</i> = 7.5 Hz, 1H), 7.36–7.27 (m, 2H), 7.22 (d, <i>J</i> = 8.1 Hz, 1H), 7.04 (d, <i>J</i> = 7.9 Hz, 1H), 6.83 (t, <i>J</i> = 8.1 Hz, 1H), 3.79 (s, 3H), 2.41 (s, 6H) |
| 301             |  | 121–123 | 299       | 297       | 13.51 (s, 1H), 11.28 (s, 1H), 7.79–7.68 (m, <i>J</i> = 9.6 Hz, 2H), 7.46–7.40 (m, 2H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.04 (d, <i>J</i> = 7.9 Hz, 1H), 6.83 (t, <i>J</i> = 8.0 Hz, 1H), 3.79 (s, 3H), 2.48 (s, 3H), 2.41 (s, 3H)               |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                                                |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 302             |    | 146–148 | 299       | 297       | 13.53 (s, 1H), 11.24 (s, 1H), 7.86 (d, <i>J</i> = 7.9 Hz, 2H), 7.36 (d, <i>J</i> = 8.0 Hz, 2H), 7.24 (d, <i>J</i> = 7.6 Hz, 1H), 7.03 (d, <i>J</i> = 7.8 Hz, 1H), 6.83 (t, <i>J</i> = 8.1 Hz, 1H), 3.80 (s, 3H), 2.47 (s, 3H), 2.40 (s, 3H)                                  |
| 303             |    | 233–234 | 319       | 317       | 13.34 (s, 1H), 11.61 (s, 1H), 7.64 (dd, <i>J</i> = 7.5, 1.5 Hz, 1H), 7.61–7.51 (m, 2H), 7.50–7.44 (m, 1H), 7.25–7.20 (m, 1H), 7.05 (d, <i>J</i> = 7.8 Hz, 1H), 6.83 (t, <i>J</i> = 8.1 Hz, 1H), 3.80 (s, 3H), 2.40 (s, 3H)                                                   |
| 304             |    | 146–148 | 319       | 317       | 13.42 (s, 1H), 11.43 (s, 1H), 8.00 (s, 1H), 7.90 (d, <i>J</i> = 7.7 Hz, 1H), 7.70 (d, <i>J</i> = 8.6 Hz, 1H), 7.59 (t, <i>J</i> = 7.9 Hz, 1H), 7.25 (d, <i>J</i> = 7.5 Hz, 1H), 7.05 (d, <i>J</i> = 7.9 Hz, 1H), 6.84 (t, <i>J</i> = 8.1 Hz, 1H), 3.79 (s, 3H), 2.49 (s, 3H) |
| 305             |  | 168–170 | 319       | 317       | 13.44 (s, 1H), 11.39 (s, 1H), 7.98 (d, <i>J</i> = 8.4 Hz, 2H), 7.63 (d, <i>J</i> = 8.4 Hz, 2H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.04 (d, <i>J</i> = 7.8 Hz, 1H), 6.83 (t, <i>J</i> = 8.1 Hz, 1H), 3.79 (s, 3H), 2.48 (s, 3H)                                                |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                              |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 306             |           | 290–291 | 344       |           | 13.66 (s, 1H), 12.68 (s, 1H), 8.59 (s, 1H), 8.19 (dd, <i>J</i> = 8.5, 1.8 Hz, 2H), 7.97 (d, <i>J</i> = 7.3 Hz, 2H), 7.66 (t, <i>J</i> = 7.3 Hz, 1H), 7.58 (t, <i>J</i> = 7.5 Hz, 2H)                       |
| 307             |           | 262–263 | 384       | 382       | 12.70 (s, 1H), 12.48 (s, 1H), 8.67 (s, 1H), 8.07–7.80 (m, 4H), 7.65 (t, <i>J</i> = 7.3 Hz, 1H), 7.57 (t, <i>J</i> = 7.5 Hz, 2H)                                                                            |
| 308             |           | 262–269 | 339       | 337       | 12.44 (s, 1H), 12.31 (s, 1H), 11.71 (s, 1H), 8.62 (s, 1H), 7.81 (d, <i>J</i> = 8.3 Hz, 1H), 7.65 (dd, <i>J</i> = 6.5, 2.4 Hz, 2H), 6.81 (d, <i>J</i> = 7.5 Hz, 2H), 2.31 (s, 3H)                           |
| 309             |           | 252–271 | 334       | 332       | 12.66 (s, 1H), 12.33 (s, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 8.25 (d, <i>J</i> = 8.0 Hz, 1H), 8.11 (d, <i>J</i> = 7.7 Hz, 1H), 7.79 (t, <i>J</i> = 7.8 Hz, 1H), 7.72 (s, 1H), 7.63 (d, <i>J</i> = 2.5 Hz, 1H) |

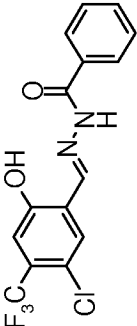
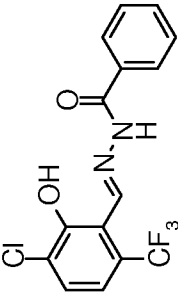
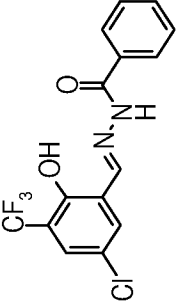
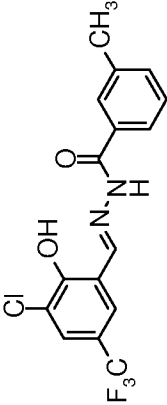
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                            |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>310</b>      |           | 234–270 |           | 332       | 12.82 (s, 1H), 12.37 (s, 1H), 8.11 – 8.02 (m, 4H), 7.76 (dd, J = 15.4, 2.6 Hz, 3H)                                                                                                                       |
| <b>311</b>      |           | 197–199 | 269       | 267       | 13.11 (s, 1H), 11.31 (s, 1H), 7.94 (d, J = 7.4 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.44 (s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 2.48 (s, 3H), 2.28 (s, 3H) |
| <b>312</b>      |           | 154–156 | 283       | 281       | 13.11 (s, 1H), 11.37 (s, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 5.6 Hz, 2H), 7.32 (dd, J = 7.4, 4.2 Hz, 2H), 7.11 (dd, J = 8.3, 1.6 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 2.40 (s, 6H), 2.27 (s, 3H)   |
| <b>313</b>      |           | 182–184 | 283       | 281       | 13.12 (s, 1H), 11.26 (s, 1H), 7.74 (d, J = 9.7 Hz, 2H), 7.43 (d, J = 5.2 Hz, 3H), 7.12 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 2.47 (s, 3H), 2.41 (s, 3H), 2.27 (s, 3H)                           |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                                   |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>314</b>      |           | 206–208 | 283       | 281       | 13.13 (s, 1H), 11.22 (s, 1H), 7.85 (d, <i>J</i> = 7.9 Hz, 2H), 7.44 (s, 1H), 7.35 (d, <i>J</i> = 8.0 Hz, 2H), 7.11 (d, <i>J</i> = 8.2 Hz, 1H), 6.81 (d, <i>J</i> = 8.3 Hz, 1H), 2.47 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H)                                        |
| <b>315</b>      |           | 154–158 | 303       | 301       | 12.95 (s, 1H), 11.59 (s, 1H), 7.65 – 7.57 (m, 2H), 7.46 (ddd, <i>J</i> = 12.5, 9.1, 1.4 Hz, 3H), 7.12 (dd, <i>J</i> = 8.3, 1.8 Hz, 1H), 6.82 (d, <i>J</i> = 8.3 Hz, 1H), 2.40 (s, 3H), 2.27 (s, 3H)                                                             |
| <b>316</b>      |           | 231–241 | 303       | 301       | 13.02 (s, 1H), 11.41 (s, 1H), 8.00 (s, 1H), 7.90 (d, <i>J</i> = 7.7 Hz, 1H), 7.70 (d, <i>J</i> = 8.9 Hz, 1H), 7.58 (t, <i>J</i> = 7.9 Hz, 1H), 7.45 (s, 1H), 7.13 (dd, <i>J</i> = 8.3, 1.5 Hz, 1H), 6.82 (d, <i>J</i> = 8.3 Hz, 1H), 2.49 (s, 3H), 2.28 (s, 3H) |
| <b>317</b>      |           | 203–210 | 303       | 301       | 13.05 (s, 1H), 11.37 (s, 1H), 7.97 (d, <i>J</i> = 8.5 Hz, 2H), 7.63 (d, <i>J</i> = 8.5 Hz, 2H), 7.45 (s, 1H), 7.12 (d, <i>J</i> = 8.2 Hz, 1H), 6.81 (d, <i>J</i> = 8.3 Hz, 1H), 2.48 (s, 3H), 2.27 (s, 3H)                                                      |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 318             |    | 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)           |
| 319             |    | 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) |
| 320             |    | 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)                                                                                      |
| 321             |  | 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)     |

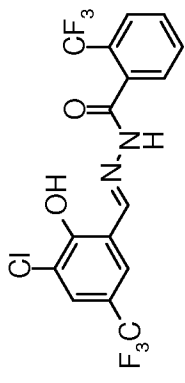
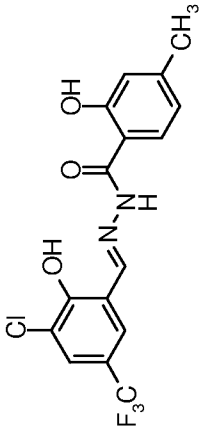
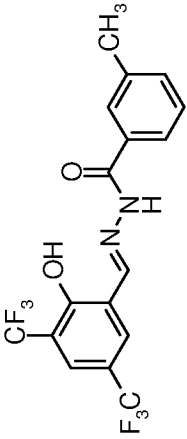
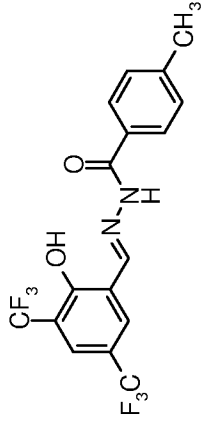
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                     |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 322             |           | 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) |
| 323             |           | 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)               |
| 324             |           | 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)                                                                 |
| 325             |           | 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)                                                       |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                 |
|-----------------|-----------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 326             |           | 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)                                                                               |
| 327             |           | 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) |
| 328             |           | 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)                                                                  |
| 329             |           | 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)                                      |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                  |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 330             |    | 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)                                                                                                                                                    |
| 331             |    | 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) |
| 332             |    | 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)                                                                                                     |
| 333             |  | 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)                                                                         |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                      |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 334             |           | 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) |
| 335             |           | 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)                                                                   |
| 336             |           | 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)                                                 |
| 337             |           | 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)                                                           |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                    |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 338             |           | 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) |
| 339             |           | 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)                                                                         |
| 340             |           | 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)                                               |
| 341             |           | 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                                                                                       |

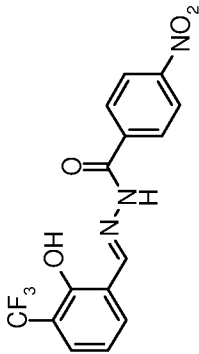
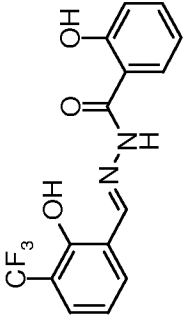
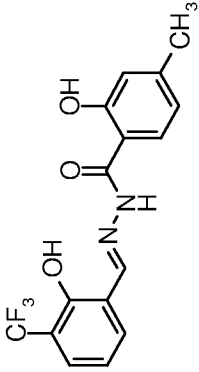
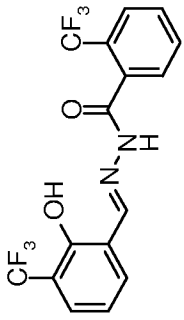
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), δ                                                                                                                                                                                  |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 342             |           | 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)                                                                                                               |
| 343             |           | 188–190 | 323       | 321       | (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) 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)                                                |
| 344             |           | 239–241 | 323       | 321       | (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) 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) |
| 345             |           | 176–180 | 327       | 325       | (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) 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)                                                                      |

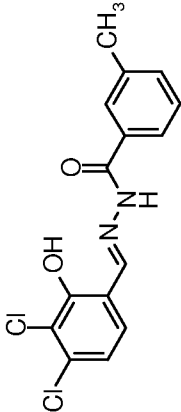
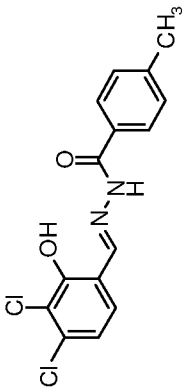
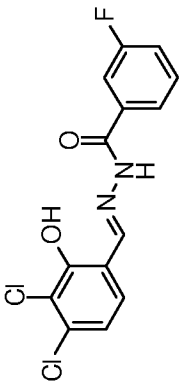
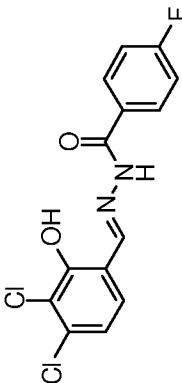
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                                                                                                                   |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 346             |           | 187–188 | 327       |           | (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) 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)                                                     |
| 347             |           | 185–187 | 343       | 341       | (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) 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) |
| 348             |           | 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)                                                                                                                              |
| 349             |           | 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)                                          |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                    |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 350             |    | 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)                                          |
| 351             |    | 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) |
| 352             |   | 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)                               |
| 353             |  | 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                                                                                             |

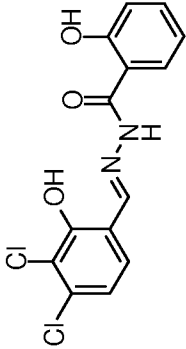
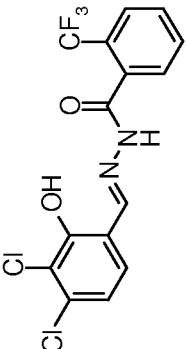
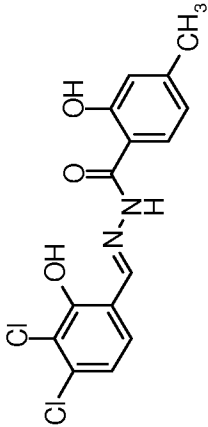
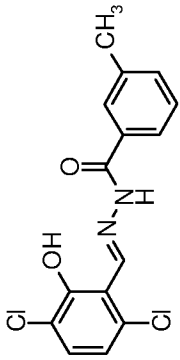
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 354             |    | 212–214 | 323       | 321       | 12.89 (s, 1H), 12.41 (s, 1H), 8.60 (s, 1H), 7.79–7.70 (m, 2H), 7.54 (d, <i>J</i> = 8.5 Hz, 1H), 7.45 (d, <i>J</i> = 4.4 Hz, 2H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H), 2.41 (s, 3H)                                             |
| 355             |    | 254–256 | 323       | 321       | 12.92 (s, 1H), 12.39 (s, 1H), 8.60 (s, 1H), 7.87 (d, <i>J</i> = 8.1 Hz, 2H), 7.54 (d, <i>J</i> = 8.4 Hz, 1H), 7.38 (d, <i>J</i> = 8.1 Hz, 2H), 7.23 (d, <i>J</i> = 8.4 Hz, 1H), 2.40 (s, 3H)                               |
| 356             |    | 215–218 | 327       | 325       | 12.75 (s, 1H), 12.50 (s, 1H), 8.61 (s, 1H), 7.81 (d, <i>J</i> = 7.8 Hz, 1H), 7.79–7.73 (m, 1H), 7.67–7.59 (m, 1H), 7.58 (d, <i>J</i> = 8.5 Hz, 1H), 7.51 (td, <i>J</i> = 8.4, 2.4 Hz, 1H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H) |
| 357             |  | 244–246 |           | 325       | 12.83 (s, 1H), 12.47 (s, 1H), 8.60 (s, 1H), 8.04 (dd, <i>J</i> = 8.7, 5.5 Hz, 2H), 7.56 (d, <i>J</i> = 8.5 Hz, 1H), 7.42 (t, <i>J</i> = 8.8 Hz, 2H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H)                                       |

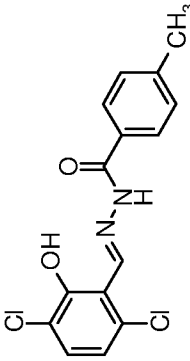
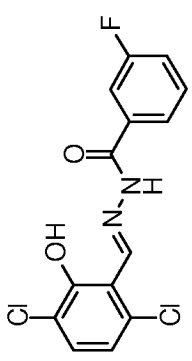
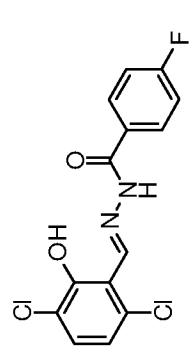
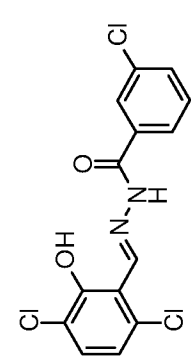
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                      |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 358             |           | 219–222 | 343       | 341       | 12.73 (s, 1H), 12.52 (s, 1H), 8.60 (s, 1H), 8.00 (t, <i>J</i> = 1.8 Hz, 1H), 7.92 (d, <i>J</i> = 7.8 Hz, 1H), 7.74–7.69 (m, 1H), 7.61 (t, <i>J</i> = 7.9 Hz, 1H), 7.57 (d, <i>J</i> = 8.5 Hz, 1H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H) |
| 359             |           | 260–262 | 343       | 341       | 12.79 (s, 1H), 12.51 (s, 1H), 8.60 (s, 1H), 7.98 (d, <i>J</i> = 8.5 Hz, 2H), 7.66 (d, <i>J</i> = 8.5 Hz, 2H), 7.57 (d, <i>J</i> = 8.5 Hz, 1H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H)                                                     |
| 360             |           | 269–271 |           | 352       | 12.70 (s, 2H), 8.79 (s, 1H), 8.65 (s, 1H), 8.50–8.46 (m, 1H), 8.42–8.37 (m, 1H), 7.88 (t, <i>J</i> = 8.0 Hz, 1H), 7.59 (d, <i>J</i> = 8.5 Hz, 1H), 7.25 (d, <i>J</i> = 8.4 Hz, 1H)                                                 |
| 361             |           | 237–243 |           | 352       | 12.69 (s, 2H), 8.63 (s, 1H), 8.40 (d, <i>J</i> = 8.7 Hz, 2H), 8.19 (d, <i>J</i> = 8.7 Hz, 2H), 7.59 (d, <i>J</i> = 8.4 Hz, 1H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H)                                                                    |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                            |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 362             |    | 280–282 | 325       | 323       | 12.78 (s, 1H), 12.26 (s, 1H), 11.57 (s, 1H), 8.66 (s, 1H), 7.87 (dd, <i>J</i> = 7.9, 1.4 Hz, 1H), 7.54 (d, <i>J</i> = 8.5 Hz, 1H), 7.50–7.44 (m, 1H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H), 7.03–6.96 (m, 2H) |
| 363             |    | 209–213 | 377       | 375       | 12.56, 12.52, 12.41, 10.48 (4s, 2H), 8.47, 8.26 (2s, 1H), 7.92–7.59 (m, 4H), 7.57, 7.31 (2d, <i>J</i> = 8.5 Hz, 1H), 7.57, 7.31 (2d, <i>J</i> = 8.5 Hz, 1H); Note: rotational isomers                    |
| 364             |   | 271–278 | 339       | 337       | 12.79 (s, 1H), 12.24 (s, 1H), 11.69 (s, 1H), 8.66 (s, 1H), 7.80 (d, <i>J</i> = 8.6 Hz, 1H), 7.54 (d, <i>J</i> = 8.5 Hz, 1H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H), 6.84–6.79 (m, 2H), 2.31 (s, 3H)            |
| 365             |  | 214–216 | 323       |           | 13.46 (s, 1H), 12.57 (s, 1H), 9.01 (s, 1H), 7.82–7.75 (m, 2H), 7.53 (d, <i>J</i> = 8.6 Hz, 1H), 7.49–7.45 (m, 2H), 7.10 (d, <i>J</i> = 8.6 Hz, 1H), 2.42 (s, 3H)                                         |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                      |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 366             |    | 267–269 | 323       | 321       | 13.48 (s, 1H), 12.54 (s, 1H), 9.01 (s, 1H), 7.89 (d, <i>J</i> = 8.1 Hz, 2H), 7.52 (d, <i>J</i> = 8.6 Hz, 1H), 7.39 (d, <i>J</i> = 8.0 Hz, 2H), 7.09 (d, <i>J</i> = 8.6 Hz, 1H), 2.40 (s, 3H)                                       |
| 367             |    | 203–209 | 327       | 325       | 13.35 (s, 1H), 12.65 (s, 1H), 9.01 (s, 1H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.81–7.76 (m, 1H), 7.69–7.61 (m, 1H), 7.56–7.48 (m, 2H), 7.11 (d, <i>J</i> = 8.6 Hz, 1H)                                                              |
| 368             |    | 264–267 | 327       | 325       | 13.41 (s, 1H), 12.62 (s, 1H), 9.00 (s, 1H), 8.10–8.01 (m, 2H), 7.53 (d, <i>J</i> = 8.6 Hz, 1H), 7.44 (t, <i>J</i> = 8.8 Hz, 2H), 7.10 (d, <i>J</i> = 8.6 Hz, 1H)                                                                   |
| 369             |  | 232–234 | 343       | 341       | 13.34 (s, 1H), 12.67 (s, 1H), 9.00 (s, 1H), 8.04–8.00 (m, 1H), 7.94 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (d, <i>J</i> = 9.0 Hz, 1H), 7.63 (t, <i>J</i> = 7.9 Hz, 1H), 7.54 (d, <i>J</i> = 8.6 Hz, 1H), 7.10 (d, <i>J</i> = 8.6 Hz, 1H) |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                            |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 370             |           | 271–273 | 343       |           | 13.38 (s, 1H), 12.66 (s, 1H), 9.00 (s, 1H), 8.00 (d, <i>J</i> = 8.5 Hz, 2H), 7.67 (d, <i>J</i> = 8.5 Hz, 2H), 7.53 (d, <i>J</i> = 8.6 Hz, 1H), 7.10 (d, <i>J</i> = 8.6 Hz, 1H)                                                           |
| 371             |           | 273–277 | 354       | 352       | 13.33 (s, 1H), 12.91 (s, 1H), 9.03 (s, 1H), 8.84–8.81 (m, 1H), 8.50 (dd, <i>J</i> = 8.2, 1.4 Hz, 1H), 8.42 (d, <i>J</i> = 7.8 Hz, 1H), 7.90 (t, <i>J</i> = 8.0 Hz, 1H), 7.55 (d, <i>J</i> = 8.6 Hz, 1H), 7.12 (d, <i>J</i> = 8.6 Hz, 1H) |
| 372             |           | 260–262 | 325       | 323       | 13.43 (s, 1H), 12.46 (s, 1H), 11.48 (s, 1H), 9.06 (s, 1H), 7.86 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.54 (d, <i>J</i> = 8.6 Hz, 1H), 7.52–7.45 (m, 1H), 7.10 (d, <i>J</i> = 8.6 Hz, 1H), 7.05–6.96 (m, 2H)                                 |
| 373             |           | 221–222 | 377       | 375       | 13.18, 12.73, 12.58, 10.82 (4s, 2H), 8.85, 8.65 (2s, 1H), 7.95–7.62 (m, 4H), 7.56, 7.44 (2d, <i>J</i> = 8.6 Hz, 1H), 7.11, 7.05 (2d, <i>J</i> = 8.6 Hz, 1H); Note: rotational isomers                                                    |

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| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                 |
|-----------------|-----------|-------------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 374             |           | 248–254     | 339       | 337       | 13.42 (s, 1H), 12.44 (s, 1H), 11.61 (s, 1H), 9.05 (s, 1H), 7.79 (d, <i>J</i> = 8.5 Hz, 1H), 7.53 (d, <i>J</i> = 8.6 Hz, 1H), 7.09 (t, <i>J</i> = 7.6 Hz, 1H), 6.85–6.81 (m, 2H), 2.32 (s, 3H) |
| 375             |           | 250–300 dec | 354       | 352       | 13.31 (s, 1H), 12.87 (s, 1H), 9.03 (s, 1H), 8.45–8.39 (m, 2H), 8.24–8.18 (m, 2H), 7.55 (d, <i>J</i> = 8.6 Hz, 1H), 7.11 (d, <i>J</i> = 8.6 Hz, 1H)                                            |
| 376             |           | 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)                              |
| 377             |           | 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)  |

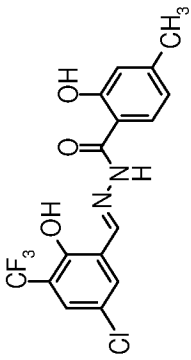
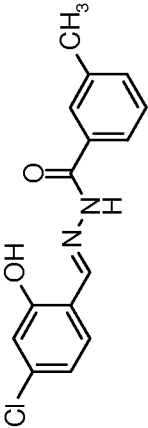
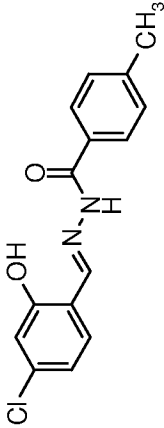
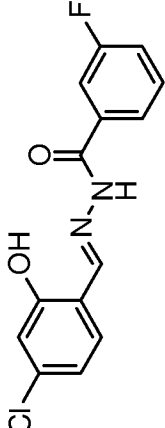
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                         |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 378             |           | 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) |
| 379             |           | 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)                                                                                                                |
| 380             |           | 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)                                                                               |
| 381             |           | 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)                                                                                           |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                            |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 382             |           | 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)    |
| 383             |           | 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)                      |
| 384             |           | 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) |
| 385             |           | 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)                                                                                                           |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                  |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 386             |    | 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) |
| 387             |    | 201–203 | 289       | 287       | 12.10 (s, 1H), 11.58 (s, 1H), 8.63 (s, 1H), 7.78–7.69 (m, 2H), 7.62 (d, <i>J</i> = 8.1 Hz, 1H), 7.43 (d, <i>J</i> = 4.7 Hz, 2H), 7.03–6.95 (m, 2H), 2.40 (s, 3H)                                                               |
| 388             |    | 258–260 | 289       | 287       | 12.09 (s, 1H), 11.62 (s, 1H), 8.63 (s, 1H), 7.85 (d, <i>J</i> = 8.1 Hz, 2H), 7.62 (d, <i>J</i> = 8.2 Hz, 1H), 7.35 (d, <i>J</i> = 8.0 Hz, 2H), 7.04–6.94 (m, 2H), 2.39 (s, 3H)                                                 |
| 389             |  | 218–222 | 293       | 291       |                                                                                                                                                                                                                                |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                              |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 390             |           | 226–228 | 293       | 291       | 12.16 (s, 1H), 11.54 (s, 1H), 8.63 (s, 1H), 8.06–7.98 (m, 2H), 7.64 (d, <i>J</i> = 8.1 Hz, 1H), 7.44–7.35 (m, 2H), 7.03–6.95 (m, 2H)                                                                                       |
| 391             |           | 212–214 |           | 307       | 12.20 (s, 1H), 11.45 (s, 1H), 8.64 (s, 1H), 8.01–7.96 (m, 1H), 7.90 (d, <i>J</i> = 7.8 Hz, 1H), 7.73–7.63 (m, 2H), 7.63–7.55 (m, 1H), 7.02–6.95 (m, 2H)                                                                    |
| 392             |           | 257–260 | 309       | 307       | 12.20 (s, 1H), 11.50 (s, 1H), 8.64 (s, 1H), 7.96 (d, <i>J</i> = 8.5 Hz, 2H), 7.67–7.60 (m, 3H), 7.03–6.94 (m, 2H)                                                                                                          |
| 393             |           | 233–238 | 320       | 318       | 12.41 (s, 1H), 11.42 (s, 1H), 8.81–8.77 (m, 1H), 8.69 (s, 1H), 8.46 (dd, <i>J</i> = 8.1, 1.8 Hz, 1H), 8.39 (d, <i>J</i> = 7.8 Hz, 1H), 7.86 (t, <i>J</i> = 8.0 Hz, 1H), 7.69 (d, <i>J</i> = 8.1 Hz, 1H), 7.04–6.96 (m, 2H) |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                   |
|-----------------|-----------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 394             |           | 278–281 | 320       | 318       | 12.40 (s, 1H), 11.41 (s, 1H), 8.68 (s, 1H), 8.39 (d, <i>J</i> = 8.8 Hz, 2H), 8.18 (d, <i>J</i> = 8.8 Hz, 2H), 7.68 (d, <i>J</i> = 8.0 Hz, 1H), 7.03–6.96 (m, 2H)                |
| 395             |           | 210–213 | 291       | 289       |                                                                                                                                                                                 |
| 396             |           | 197–200 | 343       | 341       | 12.20, 12.13, 11.27, 10.30 (4s, 2H), 8.47, 8.26 (2s, 1H), 7.90–7.16 (m, 5H), 7.01–6.80 (m, 2H); Note: rotational isomers                                                        |
| 397             |           | 283–287 | 305       | 303       | 12.02 (s, 1H), 11.90 (s, 1H), 11.51 (s, 1H), 8.67 (s, 1H), 7.81 (d, <i>J</i> = 8.5 Hz, 1H), 7.63 (d, <i>J</i> = 8.1 Hz, 1H), 7.04–6.95 (m, 2H), 6.83–6.76 (m, 2H), 2.31 (s, 3H) |

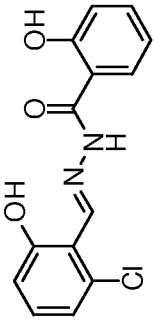
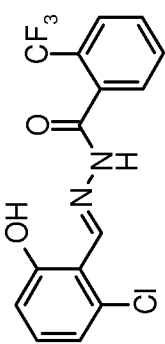
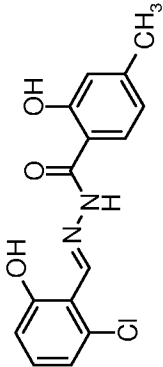
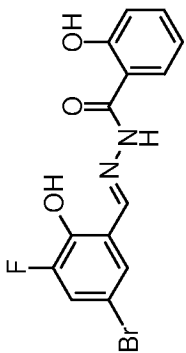
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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                               |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 398             |           | 245–248 | 289       | 287       | 12.57 (s, 1H), 12.43 (s, 1H), 9.05 (s, 1H), 7.83–7.73 (m, 2H), 7.46 (d, <i>J</i> = 4.8 Hz, 2H), 7.34 (t, <i>J</i> = 8.2 Hz, 1H), 7.06 (dd, <i>J</i> = 7.9, 0.8 Hz, 1H), 6.96 (d, <i>J</i> = 8.3 Hz, 1H), 2.41 (s, 3H)                                       |
| 399             |           | 250–252 | 289       | 287       | 12.59 (s, 1H), 12.40 (s, 1H), 9.04 (s, 1H), 7.88 (d, <i>J</i> = 8.1 Hz, 2H), 7.38 (d, <i>J</i> = 8.0 Hz, 2H), 7.33 (t, <i>J</i> = 8.2 Hz, 1H), 7.06 (d, <i>J</i> = 8.0 Hz, 1H), 6.96 (d, <i>J</i> = 8.3 Hz, 1H), 2.40 (s, 3H)                               |
| 400             |           | 257–259 | 293       | 291       | 12.52 (s, 1H), 12.48 (s, 1H), 9.04 (s, 1H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.80–7.75 (m, 1H), 7.68–7.60 (m, 1H), 7.52 (td, <i>J</i> = 8.5, 2.4 Hz, 1H), 7.35 (t, <i>J</i> = 8.2 Hz, 1H), 7.07 (d, <i>J</i> = 7.9 Hz, 1H), 6.97 (d, <i>J</i> = 8.3 Hz, 1H) |
| 401             |           | 266–268 | 293       | 291       | 12.53 (s, 1H), 12.48 (s, 1H), 9.03 (s, 1H), 8.09–8.00 (m, 2H), 7.47–7.39 (m, 2H), 7.34 (t, <i>J</i> = 8.2 Hz, 1H), 7.06 (d, <i>J</i> = 7.8 Hz, 1H), 6.96 (d, <i>J</i> = 8.3 Hz, 1H)                                                                         |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                                             |
|-----------------|-----------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 402             |           | 250–253 | 309       | 307       | 12.54 (s, 1H), 12.47 (s, 1H), 9.04 (s, 1H), 8.05–7.98 (m, 1H), 7.96–7.90 (m, 1H), 7.76–7.69 (m, 1H), 7.62 (t, <i>J</i> = 7.9 Hz, 1H), 7.35 (t, <i>J</i> = 8.2 Hz, 1H), 7.07 (dd, <i>J</i> = 8.0, 1.0 Hz, 1H), 6.97 (d, <i>J</i> = 8.0 Hz, 1H)                             |
| 403             |           | 273–277 | 309       | 307       | 12.53 (s, 1H), 12.51 (s, 1H), 9.04 (s, 1H), 8.03–7.95 (m, 2H), 7.71–7.63 (m, 2H), 7.34 (t, <i>J</i> = 8.2 Hz, 1H), 7.07 (dd, <i>J</i> = 7.9, 0.9 Hz, 1H), 6.96 (d, <i>J</i> = 8.2 Hz, 1H)                                                                                 |
| 404             |           | 269–270 | 320       | 318       | 12.77 (s, 1H), 12.48 (s, 1H), 9.07 (s, 1H), 8.82 (t, <i>J</i> = 1.9 Hz, 1H), 8.52–8.45 (m, 1H), 8.41 (d, <i>J</i> = 7.9 Hz, 1H), 7.89 (t, <i>J</i> = 8.0 Hz, 1H), 7.36 (t, <i>J</i> = 8.2 Hz, 1H), 7.08 (dd, <i>J</i> = 7.9, 0.8 Hz, 1H), 6.98 (d, <i>J</i> = 8.2 Hz, 1H) |
| 405             |           | >300    | 320       | 318       | 12.73 (s, 1H), 12.44 (s, 1H), 9.06 (s, 1H), 8.46–8.38 (m, 2H), 8.25–8.16 (m, 2H), 7.36 (t, <i>J</i> = 8.2 Hz, 1H), 7.08 (dd, <i>J</i> = 8.0, 0.9 Hz, 1H), 6.97 (d, <i>J</i> = 8.1 Hz, 1H)                                                                                 |

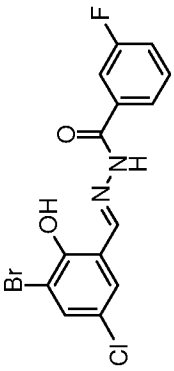
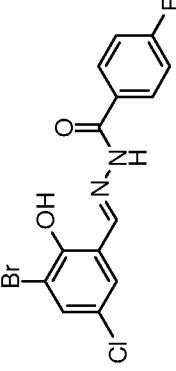
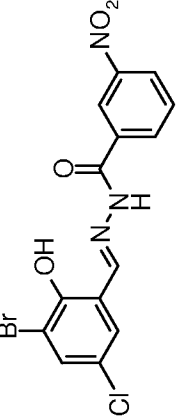
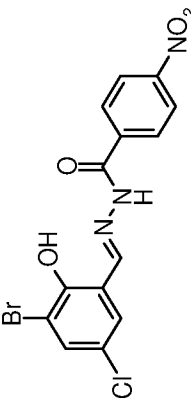
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                    |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 406             |    | 277–280 | 291       | 289       | 12.52 (s, 1H), 12.37 (s, 1H), 11.55 (s, 1H), 9.07 (s, 1H), 7.86 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.52–7.43 (m, 1H), 7.35 (t, <i>J</i> = 8.2 Hz, 1H), 7.07 (dd, <i>J</i> = 7.9, 0.9 Hz, 1H), 7.03–6.95 (m, 3H)   |
| 407             |    | 222–226 | 343       | 341       | 12.57, 12.45, 12.30, 10.21 (4s, 2H), 8.88, 8.64 (2s, 1H), 7.92–6.70 (m, 7H); Note: rotational isomers                                                                                                            |
| 408             |    | 273–276 | 305       | 303       | 12.51 (s, 1H), 12.35 (s, 1H), 11.70 (s, 1H), 9.07 (s, 1H), 7.82–7.75 (m, 1H), 7.34 (t, <i>J</i> = 8.2 Hz, 1H), 7.09–7.03 (m, 1H), 6.96 (d, <i>J</i> = 8.3 Hz, 1H), 6.82 (d, <i>J</i> = 4.2 Hz, 2H), 2.32 (s, 3H) |
| 409             |  | 297–299 | 337       | 335       | 12.20 (s, 1H), 11.63 (s, 2H), 8.66 (s, 1H), 7.88 (dd, <i>J</i> = 7.9, 1.4 Hz, 1H), 7.66 (d, <i>J</i> = 1.3 Hz, 1H), 7.61 (dd, <i>J</i> = 10.4, 2.3 Hz, 1H), 7.53–7.38 (m, 1H), 7.07–6.88 (m, 2H)                 |

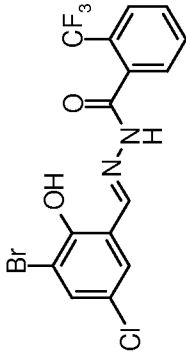
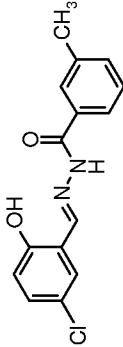
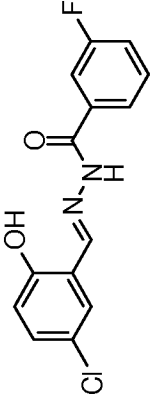
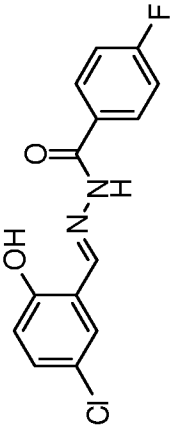
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                    |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>410</b>      |           | 211–212 | 337       | 335       | 12.36 (s, 1H), 11.72 (s, 1H), 8.63 (s, 1H), 7.96 (d, <i>J</i> = 7.3 Hz, 2H), 7.72–7.48 (m, 5H)                                                                                   |
| <b>411</b>      |           | 228–229 | 351       | 349       | 12.30 (s, 1H), 11.76 (s, 1H), 8.62 (s, 1H), 7.87 (d, <i>J</i> = 8.0 Hz, 2H), 7.67 (s, 1H), 7.59 (dd, <i>J</i> = 10.5, 2.1 Hz, 1H), 7.36 (d, <i>J</i> = 8.0 Hz, 2H), 2.39 (s, 3H) |
| <b>412</b>      |           | 240–241 | 405       | 403       | 12.51 (s, 1H), 11.58 (s, 1H), 8.66 (s, 1H), 8.15 (d, <i>J</i> = 8.1 Hz, 2H), 7.95 (d, <i>J</i> = 8.3 Hz, 2H), 7.73–7.67 (m, 1H), 7.61 (dd, <i>J</i> = 10.4, 2.3 Hz, 1H)          |
| <b>413</b>      |           | 279–282 | 368       |           | 12.78 (s, 1H), 12.49 (s, 1H), 8.54 (s, 1H), 7.88 (d, <i>J</i> = 8.1 Hz, 2H), 7.73 (dd, <i>J</i> = 13.1, 2.5 Hz, 2H), 7.37 (d, <i>J</i> = 8.1 Hz, 2H), 2.40 (s, 3H)               |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                     |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>414</b>      |    | 209–215 | 372       | 370       | 12.69 (s, 1H), 12.58 (s, 1H), 8.54 (s, 1H), 8.04 (dd, J = 8.7, 5.5 Hz, 2H), 7.74 (dd, J = 7.7, 2.5 Hz, 2H), 7.42 (t, J = 8.8 Hz, 2H)              |
| <b>415</b>      |    | 200–211 | 372       | 370       | 12.62 (s, 2H), 8.55 (s, 1H), 7.86–7.71 (m, 4H), 7.67–7.47 (m, 2H)                                                                                 |
| <b>416</b>      |    | 167–226 | 399       | 397       | 12.85 (s, 1H), 12.55 (s, 1H), 8.80 (t, J = 1.8 Hz, 1H), 8.59 (s, 1H), 8.52–8.37 (m, 2H), 7.88 (t, J = 8.0 Hz, 1H), 7.76 (dd, J = 6.4, 2.5 Hz, 2H) |
| <b>417</b>      |  | 237–250 | 399       | 397       | 12.68 (s, 2H), 8.58 (s, 1H), 8.41 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H), 7.77 (q, J = 2.5 Hz, 2H)                                         |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                        |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>418</b>      |    | 266–274 | 422       | 420       | 12.66 (s, 1H), 8.42 (s, 1H), 7.94–7.71 (m, 7H)                                                                                                                                                                                                       |
| <b>419</b>      |    | 188–196 | 289       | 287       | 12.16 (s, 1H), 11.30 (s, 1H), 8.62 (s, 1H), 7.80–7.59 (m, 3H), 7.43 (d, <i>J</i> = 4.6 Hz, 2H), 7.33 (dd, <i>J</i> = 8.7, 2.6 Hz, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 2.40 (s, 3H)                                                                 |
| <b>420</b>      |    | 205–224 | 372       |           | 12.23 (s, 1H), 11.21 (s, 1H), 8.64 (s, 1H), 7.83–7.72 (m, 2H), 7.70 (d, <i>J</i> = 2.7 Hz, 1H), 7.61 (td, <i>J</i> = 8.0, 5.9 Hz, 1H), 7.48 (td, <i>J</i> = 8.4, 2.1 Hz, 1H), 7.33 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 6.97 (d, <i>J</i> = 8.8 Hz, 1H) |
| <b>421</b>      |  | 234–243 | 372       |           | 12.21 (s, 1H), 11.26 (s, 1H), 8.62 (s, 1H), 8.03 (dd, <i>J</i> = 8.4, 5.6 Hz, 2H), 7.69 (d, <i>J</i> = 2.5 Hz, 1H), 7.45–7.27 (m, 3H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H)                                                                               |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), δ                                                                                                                        |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>422</b>      |           | 154–164 | 343       | 341       | 12.25 (s, 1H), 11.01 (s, 1H), 8.47 (s, 1H), 7.91–7.65 (m, 7H)                                                                                                                                               |
| <b>423</b>      |           | 166–169 | 289       | 287       | (400 MHz, CDCl <sub>3</sub> ) 8.59 (d, <i>J</i> = 12.0 Hz, 1H), 7.76 (d, <i>J</i> = 10.0 Hz, 2H), 7.47 (dd, <i>J</i> = 15.6, 6.2 Hz, 4H), 6.97 (t, <i>J</i> = 7.8 Hz, 1H), 2.39 (d, <i>J</i> = 12.0 Hz, 3H) |
| <b>424</b>      |           | 230–232 | 289       | 287       | (400 MHz, CDCl <sub>3</sub> ) 8.60 (s, 1H), 7.87 (d, <i>J</i> = 8.1 Hz, 2H), 7.49 (d, <i>J</i> = 7.9 Hz, 2H), 7.37 (d, <i>J</i> = 8.1 Hz, 2H), 6.97 (t, <i>J</i> = 7.8 Hz, 1H), 2.40 (s, 3H)                |
| <b>425</b>      |           | 178–184 | 293       | 291       | (400 MHz, CDCl <sub>3</sub> ) 8.62 (s, 1H), 7.86–7.72 (m, 2H), 7.63 (dd, <i>J</i> = 13.8, 8.0 Hz, 1H), 7.51 (dd, <i>J</i> = 7.1, 5.5 Hz, 3H), 6.98 (t, <i>J</i> = 7.8 Hz, 1H)                               |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                                   |
|-----------------|-----------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 426             |           | 194–198 | 293       | 291       | (400 MHz, CDCl <sub>3</sub> ) 8.60 (s, 1H), 8.08–7.99 (m, 2H), 7.54–7.46 (m, 2H), 7.42 (t, <i>J</i> = 8.8 Hz, 2H), 6.98 (t, <i>J</i> = 7.8 Hz, 1H)                                                            |
| 427             |           | 174–178 | 309       | 307       | (400 MHz, CDCl <sub>3</sub> ) 8.61 (s, 1H), 8.00 (t, <i>J</i> = 1.7 Hz, 1H), 7.95–7.68 (m, 2H), 7.61 (t, <i>J</i> = 7.9 Hz, 1H), 7.55–7.47 (m, 2H), 6.98 (t, <i>J</i> = 7.8 Hz, 1H)                           |
| 428             |           | 217–219 | 309       | 307       | (400 MHz, CDCl <sub>3</sub> ) 8.61 (s, 1H), 7.98 (d, <i>J</i> = 8.6 Hz, 2H), 7.66 (d, <i>J</i> = 8.6 Hz, 2H), 7.50 (ddd, <i>J</i> = 7.9, 4.5, 1.4 Hz, 2H), 6.98 (t, <i>J</i> = 7.8 Hz, 1H)                    |
| 429             |           | 236–239 | 320       | 318       | (400 MHz, CDCl <sub>3</sub> ) 8.80 (t, <i>J</i> = 1.9 Hz, 1H), 8.66 (s, 1H), 8.52–8.36 (m, 2H), 7.88 (t, <i>J</i> = 8.0 Hz, 1H), 7.53 (ddd, <i>J</i> = 9.7, 7.9, 1.5 Hz, 2H), 6.99 (t, <i>J</i> = 7.8 Hz, 1H) |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                        |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 430             |           | 284–287 | 320       | 318       | (400 MHz, CDCl <sub>3</sub> ) 8.64 (s, 1H), 8.41 (d, <i>J</i> = 8.5 Hz, 2H), 8.19 (d, <i>J</i> = 8.6 Hz, 2H), 7.56–7.47 (m, 2H), 6.98 (t, <i>J</i> = 7.8 Hz, 1H)                                   |
| 431             |           | 266–268 | 291       | 289       | (400 MHz, CDCl <sub>3</sub> ) 8.66 (s, 1H), 7.87 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.54–7.42 (m, 3H), 6.98 (dddd, <i>J</i> = 7.8, 5.6, 3.9 Hz, 3H)                                                 |
| 432             |           | 118–121 | 343       | 341       | (400 MHz, CDCl <sub>3</sub> ) 8.36 (d, <i>J</i> = 82.5 Hz, 1H), 7.95–7.24 (m, 6H), 6.92 (dt, <i>J</i> = 42.3, 7.9 Hz, 1H)                                                                          |
| 433             |           | 258–266 | 305       | 303       | (400 MHz, CDCl <sub>3</sub> ) 8.66 (s, 1H), 7.80 (d, <i>J</i> = 8.6 Hz, 1H), 7.49 (dd, <i>J</i> = 7.9, 2.1 Hz, 2H), 6.98 (t, <i>J</i> = 7.8 Hz, 1H), 6.81 (d, <i>J</i> = 7.3 Hz, 2H), 2.31 (s, 3H) |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                          |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 434             |           | 262–268 | 384       | 382       | (400 MHz, CDCl <sub>3</sub> ) 8.58 (s, 1H), 7.80 (d, <i>J</i> = 8.1 Hz, 1H), 7.72 (dd, <i>J</i> = 27.0, 2.4 Hz, 2H), 6.81 (d, <i>J</i> = 7.7 Hz, 2H), 2.31 (s, 3H)                                                     |
| 435             |           | 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) |
| 436             |           | 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)       |
| 437             |           | 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)         |

65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                    |
|-----------------|-----------|-------------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 438             |           | 229–<br>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)                                                           |
| 439             |           | 187–<br>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)                                                                         |
| 440             |           | 252–<br>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)                                                                                                  |
| 441             |           | 218–<br>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) |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                    |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 442             |           | 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)                                        |
| 443             |           | 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) |
| 444             |           | 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)                                                                                                  |
| 445             |           | 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)  |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                          |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 446             |           | 282–286 | 305       | 303       | 12.03 (s, 2H), 11.24 (s, 1H), 8.65 (s, 1H), 7.82 (d, <i>J</i> = 8.6 Hz, 1H), 7.67 (d, <i>J</i> = 2.6 Hz, 1H), 7.33 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 6.80 (d, <i>J</i> = 7.3 Hz, 2H), 2.31 (d, <i>J</i> = 6.5 Hz, 3H) |
| 447             |           | 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)                                               |
| 448             |           | 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)                                                                                     |
| 449             |           | 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)                                                                                |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                          |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 450             |           | 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)                                                                                                                  |
| 451             |           | 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)                                                      |
| 452             |           | 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)                                                                         |
| 453             |           | 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) |

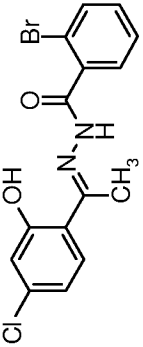
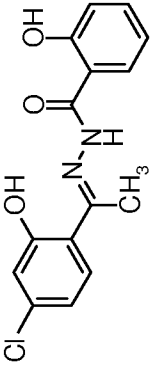
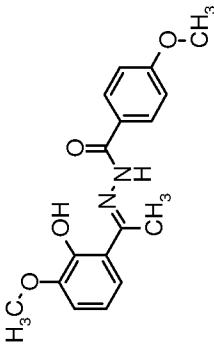
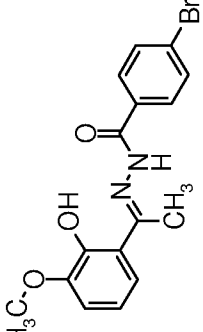
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                    |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 454             |           | 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)                                                                   |
| 455             |           | 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) |
| 456             |           | 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)                                                                                                                  |
| 457             |           | 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)                                             |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                  |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 458             |           | 218–221 | 333       | 331       | 13.31 (s, 1H), 11.41 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 2H), 7.77 (d, <i>J</i> = 8.5 Hz, 2H), 7.67–7.62 (m, 1H), 7.35–7.28 (m, 1H), 6.94–6.87 (m, 2H), 2.49 (s, 3H)          |
| 459             |           | 262–263 | 319       | 317       | 13.84 (s, 1H), 11.26 (s, 1H), 7.94 (d, <i>J</i> = 8.7 Hz, 2H), 7.65 (d, <i>J</i> = 8.5 Hz, 1H), 7.08 (d, <i>J</i> = 8.8 Hz, 2H), 7.00–6.92 (m, 2H), 3.85 (s, 3H), 2.48 (s, 3H) |
| 460             |           | 258–259 | 367       | 365       | 13.72 (s, 1H), 11.48 (s, 1H), 7.89 (d, <i>J</i> = 8.5 Hz, 2H), 7.77 (d, <i>J</i> = 8.5 Hz, 2H), 7.67 (d, <i>J</i> = 8.5 Hz, 1H), 7.01–6.94 (m, 2H), 2.48 (s, 3H)               |
| 461             |           | 244–245 | 357       | 355       | 13.69 (s, 1H), 11.63 (s, 1H), 8.13 (d, <i>J</i> = 8.1 Hz, 2H), 7.94 (d, <i>J</i> = 8.3 Hz, 2H), 7.68 (d, <i>J</i> = 8.5 Hz, 1H), 7.03–6.94 (m, 2H), 2.50 (s, 3H)               |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 462             |    | 187–188 | 367       |           | 13.61, 11.71, 11.04 (3s, 2H), 7.76–7.40 (m, 5H), 7.00, 6.76 (2d, <i>J</i> = 2.2 Hz, 1H), 6.97, 6.88 (2dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 2.41, 2.37 (2s, 3H); Note: rotational isomers                                                        |
| 463             |    | 311–312 | 305       |           | 13.59 (s, 1H), 11.64 (s, 2H), 7.97 (dd, <i>J</i> = 7.9, 1.7 Hz, 1H), 7.68 (d, <i>J</i> = 8.6 Hz, 1H), 7.49–7.42 (m, 1H), 7.07–6.95 (m, 4H), 2.43 (s, 3H)                                                                                    |
| 464             |   | 140–141 | 315       | 313       | 13.55 (s, 1H), 11.17 (s, 1H), 7.94 (d, <i>J</i> = 8.6 Hz, 2H), 7.23 (d, <i>J</i> = 7.5 Hz, 1H), 7.08 (d, <i>J</i> = 8.8 Hz, 2H), 7.03 (d, <i>J</i> = 7.8 Hz, 1H), 6.83 (t, <i>J</i> = 8.0 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.47 (s, 3H) |
| 465             |  | 176–177 |           | 362       | 13.44 (s, 1H), 11.40 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 2H), 7.77 (d, <i>J</i> = 8.4 Hz, 2H), 7.24 (d, <i>J</i> = 7.7 Hz, 1H), 7.04 (d, <i>J</i> = 7.9 Hz, 1H), 6.83 (t, <i>J</i> = 8.1 Hz, 1H), 3.79 (s, 3H), 2.48 (s, 3H)               |

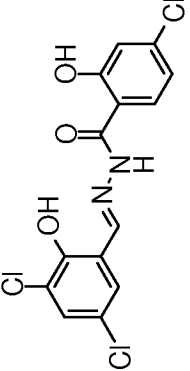
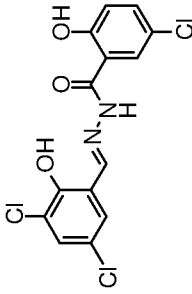
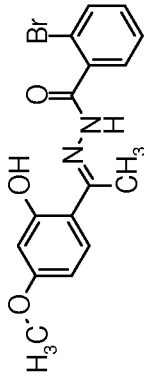
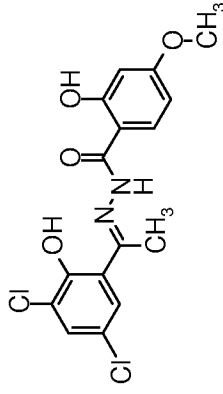
65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> unless otherwise stated), $\delta$                                                                                                                                                               |
|-----------------|-----------|-------------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 466             |           | 175–<br>176 | 353       | 351       | 13.40 (s, 1H), 11.54 (s, 1H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.93 (d, <i>J</i> = 8.3 Hz, 2H), 7.25 (d, <i>J</i> = 8.1 Hz, 1H), 7.05 (d, <i>J</i> = 7.8 Hz, 1H), 6.84 (t, <i>J</i> = 8.1 Hz, 1H), 3.80 (s, 3H), 2.49 (s, 3H)                             |
| 467             |           | 245–<br>247 | 363       | 361       | 13.32, 11.61, 11.55, 10.72 (4s, 2H), 7.76–7.40 (m, 4H), 7.72, 7.10 (2dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 7.05, 6.92 (2d, <i>J</i> = 7.5 Hz, 1H), 6.84, 6.76 (2t, <i>J</i> = 8.1 Hz, 1H), 3.80, 3.66 (2s, 3H), 2.41, 2.37 (2s, 3H). Note: rotational isomers. |
| 468             |           | 255–<br>257 | 301       | 299       | 13.29 (s, 1H), 11.75 (s, 1H), 11.58 (s, 1H), 7.99 (dd, <i>J</i> = 7.8, 1.4 Hz, 1H), 7.50–7.42 (m, 1H), 7.26 (d, <i>J</i> = 8.1 Hz, 1H), 7.02 (dd, <i>J</i> = 17.9, 7.7 Hz, 3H), 6.84 (t, <i>J</i> = 8.1 Hz, 1H), 3.80 (s, 3H), 2.43 (s, 3H)               |
| 469             |           | 226–<br>227 | 353       | 351       | 14.53 (s, 1H), 11.43 (s, 1H), 7.96 (d, <i>J</i> = 8.8 Hz, 2H), 7.68 (d, <i>J</i> = 2.5 Hz, 1H), 7.63 (d, <i>J</i> = 2.5 Hz, 1H), 7.09 (d, <i>J</i> = 8.8 Hz, 2H), 3.85 (s, 3H), 2.52 (s, 3H)                                                              |

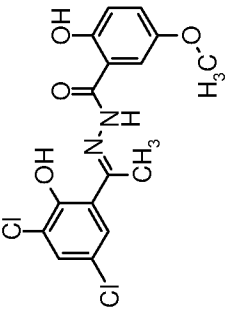
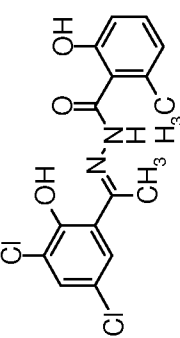
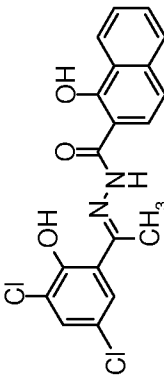
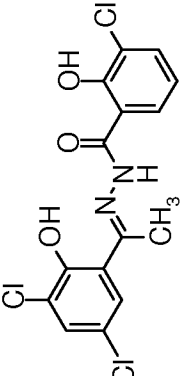
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                   |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 470             |           | 237–238 |           | 389       | 14.37 (s, 1H), 11.80 (s, 1H), 8.15 (d, <i>J</i> = 8.1 Hz, 2H), 7.94 (d, <i>J</i> = 8.3 Hz, 2H), 7.70 (d, <i>J</i> = 2.4 Hz, 1H), 7.66 (d, <i>J</i> = 2.3 Hz, 1H), 2.54 (s, 3H)                           |
| 471             |           | 306–308 | 339       | 337       |                                                                                                                                                                                                          |
| 472             |           | 251–252 |           | 352       | 13.59 (s, 1H), 11.45 (s, 1H), 8.12 (d, <i>J</i> = 8.1 Hz, 2H), 7.93 (d, <i>J</i> = 8.2 Hz, 2H), 7.57 (d, <i>J</i> = 8.7 Hz, 1H), 6.49 (dt, <i>J</i> = 5.8, 2.5 Hz, 2H), 3.78 (s, 3H), 2.46 (s, 3H)       |
| 473             |           | 276–278 | 301       | 299       | 13.49 (s, 1H), 11.75 (s, 1H), 11.49 (s, 1H), 7.97 (dd, <i>J</i> = 7.9, 1.7 Hz, 1H), 7.58 (d, <i>J</i> = 8.6 Hz, 1H), 7.48–7.41 (m, 1H), 7.06–6.96 (m, 2H), 6.53–6.45 (m, 2H), 3.78 (s, 3H), 2.40 (s, 3H) |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                      |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 474             |    | 276–279 | 359       | 357       | 12.45 (s, 2H), 11.90 (s, 1H), 8.60 (s, 1H), 7.86 (d, <i>J</i> = 8.5 Hz, 1H), 7.68–7.62 (m, 2H), 7.08–7.02 (m, 2H)                                                                                                                                  |
| 475             |    | 287–92  | 359       | 357       |                                                                                                                                                                                                                                                    |
| 476             |    | 205–206 | 363       | 363       | 13.50, 11.50, 11.05 (3s, 2H), 7.75–7.38 (m, 5H), 6.51–6.22 (m, 2H), 3.78, 3.68 (2s, 3H), 2.37, 2.34 (2s, 3H);<br>Note: rotational isomers                                                                                                          |
| 477             |  | 310–312 | 369       | 367       | 14.32 (s, 1H), 11.99 (s, 1H), 11.54 (s, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.70 (d, <i>J</i> = 2.5 Hz, 1H), 7.63 (d, <i>J</i> = 2.5 Hz, 1H), 6.62 (dd, <i>J</i> = 8.9, 2.4 Hz, 1H), 6.55 (d, <i>J</i> = 2.4 Hz, 1H), 3.80 (s, 3H), 2.45 (s, 3H) |

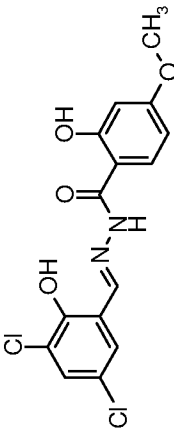
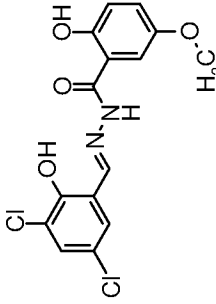
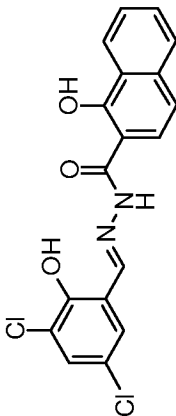
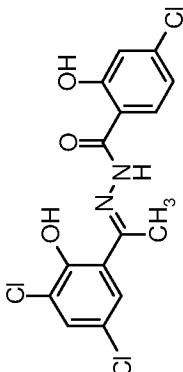
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 478             |    | 327–331 |           | 367       | 14.28 (s, 1H), 11.76 (s, 1H), 11.39 (s, 1H), 7.71 (d, <i>J</i> = 2.5 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 1H), 7.48 (d, <i>J</i> = 3.2 Hz, 1H), 7.10 (dd, <i>J</i> = 8.9, 3.2 Hz, 1H), 7.00 (d, <i>J</i> = 8.9 Hz, 1H), 3.76 (s, 3H), 2.45 (s, 3H)                   |
| 479             |    | 245     | 352       |           | 14.55, 11.80, 11.69, 11.46, 9.82, 9.72 (6s, 3H), 7.64–7.50 (m, 2H), 7.16 (t, <i>J</i> = 7.9 Hz, 1H), 6.77–6.71 (m, 2H), 2.40, 2.38 (2s, 3H), 2.22, 2.14 (2s, 3H); Note: rotational isomers                                                                           |
| 480             |    | 264–246 |           | 387       | 14.34 (s, 1H), 13.31 (s, 1H), 11.83 (s, 1H), 8.34 (d, <i>J</i> = 8.3 Hz, 1H), 8.05 (d, <i>J</i> = 8.8 Hz, 1H), 7.94 (d, <i>J</i> = 8.1 Hz, 1H), 7.73 (d, <i>J</i> = 2.5 Hz, 1H), 7.72–7.65 (m, 2H), 7.64–7.58 (m, 1H), 7.50 (d, <i>J</i> = 8.9 Hz, 1H), 2.59 (s, 3H) |
| 481             |  | 260–262 | 373       | 371       | 14.28 (s, 1H), 11.96 (s, 2H), 7.93–7.88 (m, 1H), 7.72 (d, <i>J</i> = 2.4 Hz, 1H), 7.70–7.64 (m, 2H), 7.02 (t, <i>J</i> = 7.9 Hz, 1H), 2.52 (s, 3H)                                                                                                                   |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                              |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>482</b>      |           | 226–227 | 315       | 313       | 13.72 (s, 1H), 11.07 (s, 1H), 7.93 (d, <i>J</i> = 8.7 Hz, 2H), 7.55 (d, <i>J</i> = 8.7 Hz, 1H), 7.07 (d, <i>J</i> = 8.8 Hz, 2H), 6.51–6.44 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.44 (s, 3H)                                        |
| <b>483</b>      |           | 239–241 | 363       | 361       | 13.70 (s, 1H), 11.30 (s, 1H), 7.88 (d, <i>J</i> = 8.5 Hz, 2H), 7.75 (d, <i>J</i> = 8.5 Hz, 2H), 7.55 (d, <i>J</i> = 8.8 Hz, 1H), 6.51–6.42 (m, 2H), 3.77 (s, 3H), 2.44 (s, 3H)                                                      |
| <b>484</b>      |           | 258–259 | 369       | 367       | 14.46 (s, 1H), 11.58 (s, 2H), 7.69 (d, <i>J</i> = 2.5 Hz, 1H), 7.63 (d, <i>J</i> = 2.4 Hz, 1H), 7.53 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.21 (d, <i>J</i> = 7.0 Hz, 1H), 6.95 (t, <i>J</i> = 8.0 Hz, 1H), 3.86 (s, 3H), 2.45 (s, 3H) |
| <b>485</b>      |           | 217–219 | 339       | 337       | 12.48, 12.31, 12.12, 10.62, 9.85, 9.72 (6s, 3H), 8.37, 8.17 (2s, 1H), 7.64–7.46 (m, 2H), 7.16 (t, <i>J</i> = 7.9 Hz, 1H), 6.78–6.70 (m, 2H), 2.21, 2.14 (2s, 3H); Note: rotational isomers                                          |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 486             |    | 267–269 | 355       | 353       | 12.46 (s, 1H), 12.30 (s, 1H), 12.17 (s, 1H), 8.60 (s, 1H), 7.89 (d, <i>J</i> = 8.9 Hz, 1H), 7.66 (d, <i>J</i> = 2.5 Hz, 1H), 7.64 (d, <i>J</i> = 2.5 Hz, 1H), 6.59 (dd, <i>J</i> = 8.9, 2.4 Hz, 1H), 6.53 (d, <i>J</i> = 2.4 Hz, 1H), 3.81 (s, 3H)                                                    |
| 487             |    | 250–252 | 355       | 353       | 12.41 (s, 1H), 12.29 (s, 1H), 11.13 (s, 1H), 8.63 (s, 1H), 7.69–7.61 (m, 2H), 7.41 (d, <i>J</i> = 3.1 Hz, 1H), 7.11 (dd, <i>J</i> = 9.0, 3.1 Hz, 1H), 6.95 (d, <i>J</i> = 9.0 Hz, 1H), 3.76 (s, 3H)                                                                                                   |
| 488             |    | 276–278 | 375       | 373       | 13.74 (s, 1H), 12.79 (s, 1H), 12.41 (s, 1H), 8.70 (s, 1H), 8.32 (d, <i>J</i> = 8.2 Hz, 1H), 7.98 (d, <i>J</i> = 8.9 Hz, 1H), 7.93 (d, <i>J</i> = 8.1 Hz, 1H), 7.75 (d, <i>J</i> = 2.5 Hz, 1H), 7.73–7.68 (m, 1H), 7.67 (d, <i>J</i> = 2.5 Hz, 1H), 7.63–7.58 (m, 1H), 7.49 (d, <i>J</i> = 8.9 Hz, 1H) |
| 489             |  | 314–317 | 375       | 373       | 14.26 (s, 1H), 12.18 (s, 1H), 11.66 (s, 1H), 7.95 (d, <i>J</i> = 9.0 Hz, 1H), 7.71 (d, <i>J</i> = 2.5 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 1H), 7.10–7.04 (m, 2H), 2.45 (s, 3H)                                                                                                                       |

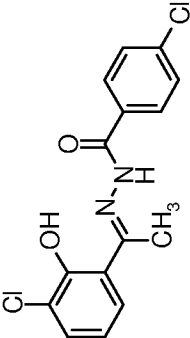
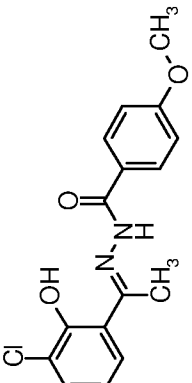
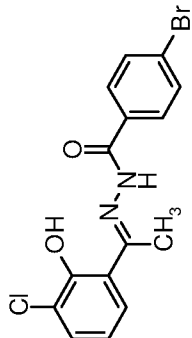
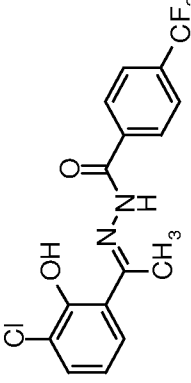
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                               |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 490             |           | 322–325 | 374       |           | 14.28 (s, 1H), 12.07–11.66 (m, 2H), 7.90 (d, <i>J</i> = 2.8 Hz, 1H), 7.71 (d, <i>J</i> = 2.5 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 1H), 7.51 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.06 (d, <i>J</i> = 8.8 Hz, 1H), 2.46 (s, 3H) |
| 491             |           | 320–323 | 353       |           | 14.31 (s, 1H), 11.69 (s, 2H), 7.89 (d, <i>J</i> = 7.8 Hz, 1H), 7.71 (d, <i>J</i> = 2.5 Hz, 1H), 7.64 (d, <i>J</i> = 2.4 Hz, 1H), 6.88–6.79 (m, 2H), 2.45 (s, 3H), 2.31 (s, 3H)                                              |
| 492             |           | 202–203 | 289       | 287       | 14.36 (s, 1H), 11.50 (s, 1H), 7.96 (d, <i>J</i> = 7.3 Hz, 2H), 7.68–7.61 (m, 2H), 7.56 (t, <i>J</i> = 6.7 Hz, 2H), 7.49 (d, <i>J</i> = 7.8 Hz, 1H), 6.92 (t, <i>J</i> = 8.0 Hz, 1H), 2.52 (s, 3H)                           |
| 493             |           | 193–198 | 303       | 301       | 14.37 (s, 1H), 11.59 (s, 1H), 7.63 (dd, <i>J</i> = 8.0, 1.3 Hz, 1H), 7.55–7.41 (m, 3H), 7.34 (dd, <i>J</i> = 7.5, 4.3 Hz, 2H), 6.92 (t, <i>J</i> = 8.0 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H)                                  |

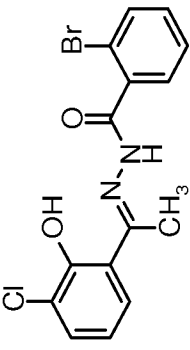
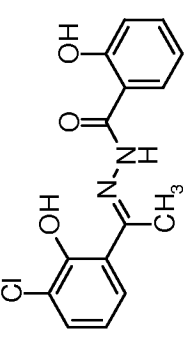
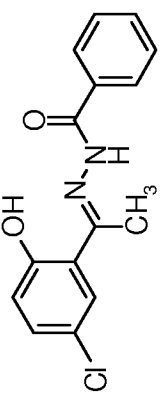
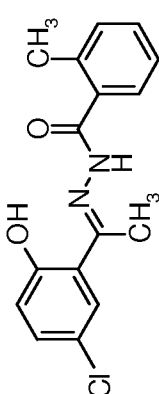
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                             |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 494             |           | 164–178 | 303       | 301       | 14.36 (s, 1H), 11.45 (s, 1H), 7.76 (d, <i>J</i> = 9.6 Hz, 2H), 7.65 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 7.48 (dt, <i>J</i> = 15.0, 3.6 Hz, 3H), 6.92 (t, <i>J</i> = 8.0 Hz, 1H), 2.52 (s, 3H), 2.42 (s, 3H)                                 |
| 495             |           | 195–200 | 303       | 301       | 14.38 (s, 1H), 11.40 (s, 1H), 7.87 (d, <i>J</i> = 8.0 Hz, 2H), 7.64 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.49 (dd, <i>J</i> = 7.9, 1.3 Hz, 1H), 7.37 (d, <i>J</i> = 8.0 Hz, 2H), 6.92 (t, <i>J</i> = 8.0 Hz, 1H), 2.51 (s, 3H), 2.40 (s, 3H) |
| 496             |           | 189–193 | 323       | 321       | 14.19 (s, 1H), 11.81 (s, 1H), 7.68–7.53 (m, 4H), 7.52–7.47 (m, 2H), 6.93 (t, <i>J</i> = 8.0 Hz, 1H), 2.44 (s, 3H)                                                                                                                         |
| 497             |           | 197–219 | 323       | 321       | 14.26 (s, 1H), 11.59 (s, 1H), 8.01 (s, 1H), 7.91 (d, <i>J</i> = 7.8 Hz, 1H), 7.75–7.55 (m, 3H), 7.50 (dd, <i>J</i> = 7.9, 1.1 Hz, 1H), 6.93 (t, <i>J</i> = 8.0 Hz, 1H), 2.53 (s, 3H)                                                      |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 498             |    | 208–209 | 323       | 321       | 14.29 (s, 1H), 11.55 (s, 1H), 7.99 (d, <i>J</i> = 8.5 Hz, 2H), 7.65 (ddd, <i>J</i> = 4.9, 3.8, 1.7 Hz, 3H), 7.50 (dd, <i>J</i> = 7.9, 1.2 Hz, 1H), 6.93 (t, <i>J</i> = 8.0 Hz, 1H), 2.52 (s, 3H)                                          |
| 499             |    | 203–204 | 319       | 317       | 14.40 (s, 1H), 11.33 (s, 1H), 7.96 (d, <i>J</i> = 8.7 Hz, 2H), 7.64 (dd, <i>J</i> = 8.0, 1.3 Hz, 1H), 7.48 (dd, <i>J</i> = 7.9, 1.2 Hz, 1H), 7.09 (d, <i>J</i> = 8.8 Hz, 2H), 6.92 (t, <i>J</i> = 8.0 Hz, 1H), 3.85 (s, 3H), 2.51 (s, 3H) |
| 500             |    | 226–232 | 368       | 366       | 14.29 (s, 1H), 11.55 (s, 1H), 7.91 (d, <i>J</i> = 8.4 Hz, 2H), 7.78 (d, <i>J</i> = 8.5 Hz, 2H), 7.65 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 7.49 (dd, <i>J</i> = 7.9, 1.1 Hz, 1H), 6.92 (t, <i>J</i> = 8.0 Hz, 1H), 2.52 (s, 3H)               |
| 501             |  | 250–256 | 357       | 355       | 14.26 (s, 1H), 11.70 (s, 1H), 8.15 (d, <i>J</i> = 8.1 Hz, 2H), 7.94 (d, <i>J</i> = 8.3 Hz, 2H), 7.66 (dd, <i>J</i> = 8.1, 1.3 Hz, 1H), 7.51 (dd, <i>J</i> = 7.9, 1.1 Hz, 1H), 6.93 (t, <i>J</i> = 8.0 Hz, 1H), 2.53 (s, 3H)               |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 502             |    | 178–183 | 368       | 366       | 14.20 (s, 1H), 11.80 (s, 1H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 7.66–7.59 (m, 2H), 7.53–7.46 (m, 3H), 6.93 (t, <i>J</i> = 8.0 Hz, 1H), 2.44 (s, 3H)                                                                                        |
| 503             |    | 283–287 | 305       | 303       | 14.17 (s, 1H), 11.68 (s, 2H), 7.99 (dd, <i>J</i> = 7.9, 1.7 Hz, 1H), 7.67 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 7.48 (ddd, <i>J</i> = 14.2, 7.4, 1.5 Hz, 2H), 7.09–6.99 (m, 2H), 6.93 (t, <i>J</i> = 8.0 Hz, 1H), 2.46 (s, 3H)                |
| 504             |    | 207–208 | 289       | 287       | 13.46 (s, 1H), 11.45 (s, 1H), 7.95 (d, <i>J</i> = 7.3 Hz, 2H), 7.64 (dd, <i>J</i> = 13.0, 4.9 Hz, 2H), 7.55 (t, <i>J</i> = 7.5 Hz, 2H), 7.34 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 2.50 (s, 3H)              |
| 505             |  | 192–193 | 303       | 301       | 13.46 (s, 1H), 11.53 (s, 1H), 7.64 (d, <i>J</i> = 2.6 Hz, 1H), 7.52 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 (td, <i>J</i> = 7.6, 1.2 Hz, 1H), 7.33 (dt, <i>J</i> = 7.3, 2.4 Hz, 3H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H) |

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| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                              |
|-----------------|-----------|-------------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 506             |           | 222–<br>228 | 303       | 301       | 13.47 (s, 1H), 11.40 (s, 1H), 7.75 (d, <i>J</i> = 10.4 Hz, 2H), 7.66 (d, <i>J</i> = 2.5 Hz, 1H), 7.44 (d, <i>J</i> = 5.9 Hz, 2H), 7.34 (dd, <i>J</i> = 8.7, 2.5 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H)       |
| 507             |           | 221–<br>228 | 303       |           | 13.48 (s, 1H), 11.35 (s, 1H), 7.86 (d, <i>J</i> = 7.9 Hz, 2H), 7.65 (d, <i>J</i> = 2.5 Hz, 1H), 7.34 (dd, <i>J</i> = 13.8, 5.2 Hz, 3H), 6.94 (d, <i>J</i> = 8.8 Hz, 1H), 2.49 (s, 3H), 2.40 (s, 3H)                                        |
| 508             |           | 210–<br>217 | 323       | 321       | 13.28 (s, 1H), 11.73 (s, 1H), 7.56 (dddd, <i>J</i> = 30.0, 21.9, 7.6, 1.5 Hz, 5H), 7.35 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 2.42 (s, 3H)                                                                    |
| 509             |           | 244–<br>249 | 323       | 321       | 13.37 (s, 1H), 11.53 (s, 1H), 8.01 (s, 1H), 7.90 (d, <i>J</i> = 7.7 Hz, 1H), 7.69 (dd, <i>J</i> = 16.9, 5.2 Hz, 2H), 7.59 (t, <i>J</i> = 7.9 Hz, 1H), 7.35 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 2.50 (s, 3H) |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                       |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 510             |           | 248–252 | 323       | 321       | 13.40 (s, 1H), 11.50 (s, 1H), 7.98 (d, <i>J</i> = 8.5 Hz, 2H), 7.65 (dd, <i>J</i> = 11.0, 5.5 Hz, 3H), 7.35 (dd, <i>J</i> = 8.7, 2.5 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 2.49 (s, 3H)                                         |
| 511             |           | 203–228 | 319       | 317       | 13.51 (s, 1H), 11.28 (s, 1H), 7.95 (d, <i>J</i> = 8.7 Hz, 2H), 7.65 (d, <i>J</i> = 2.6 Hz, 1H), 7.33 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 7.09 (t, <i>J</i> = 5.8 Hz, 2H), 6.94 (d, <i>J</i> = 8.8 Hz, 1H), 3.85 (s, 3H), 2.49 (s, 3H) |
| 512             |           | 269–271 | 368       | 366       | 13.39 (s, 1H), 11.50 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 2H), 7.77 (d, <i>J</i> = 8.5 Hz, 2H), 7.66 (d, <i>J</i> = 2.5 Hz, 1H), 7.35 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 2.49 (s, 3H)               |
| 513             |           | 271–273 | 357       | 355       | 13.35 (s, 1H), 11.65 (s, 1H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.94 (d, <i>J</i> = 8.3 Hz, 2H), 7.67 (d, <i>J</i> = 2.5 Hz, 1H), 7.36 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 2.51 (s, 3H)               |

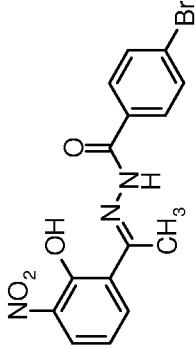
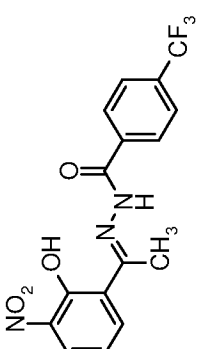
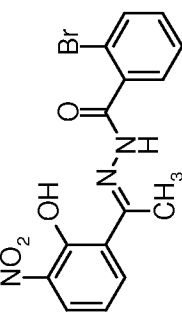
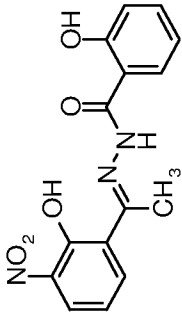
65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                       |
|-----------------|-----------|-------------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 514             |           | 222–<br>225 | 368       | 366       | 13.29 (s, 1H), 11.73 (s, 1H), 7.75 (dd, <i>J</i> = 7.8, 1.1 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.49 (ddd, <i>J</i> = 9.5, 7.5, 1.5 Hz, 2H), 7.35 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 2.42 (s, 3H)         |
| 515             |           | 298–<br>318 | 305       | 303       | 13.25 (s, 1H), 11.67 (d, <i>J</i> = 54.4 Hz, 2H), 7.98 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.67 (d, <i>J</i> = 2.5 Hz, 1H), 7.50–7.42 (m, 1H), 7.34 (dd, <i>J</i> = 8.7, 2.5 Hz, 1H), 7.08–6.93 (m, 3H), 2.43 (s, 3H)                 |
| 516             |           | 202–<br>252 | 364       | 362       | 13.56 (s, 1H), 11.28 (s, 1H), 7.95 (d, <i>J</i> = 8.7 Hz, 2H), 7.75 (d, <i>J</i> = 2.4 Hz, 1H), 7.44 (dd, <i>J</i> = 8.7, 2.4 Hz, 1H), 7.08 (d, <i>J</i> = 8.8 Hz, 2H), 6.89 (d, <i>J</i> = 8.7 Hz, 1H), 3.85 (s, 3H), 2.48 (s, 3H) |
| 517             |           | 270–<br>275 | 413       | 411       | 13.44 (s, 1H), 11.50 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 2H), 7.81 – 7.72 (m, 4H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 2.49 (s, 3H)                                                                                                   |

65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                         |
|-----------------|-----------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 518             |           | 272–280 | 402       | 400       | 13.38 (s, 1H), 11.65 (s, 1H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.93 (d, <i>J</i> = 8.3 Hz, 2H), 7.78 (d, <i>J</i> = 2.4 Hz, 1H), 7.47 (dd, <i>J</i> = 8.7, 2.3 Hz, 1H), 6.91 (d, <i>J</i> = 8.8 Hz, 1H), 2.50 (s, 3H) |
| 519             |           | 216–218 | 413       | 411       | 13.31 (s, 1H), 11.73 (s, 1H), 7.75 (dd, <i>J</i> = 6.2, 1.7 Hz, 2H), 7.62–7.58 (m, 1H), 7.50–7.43 (m, 3H), 6.91 (d, <i>J</i> = 8.8 Hz, 1H), 2.41 (s, 3H)                                                              |
| 520             |           | 281–303 | 350       | 348       | 13.27 (s, 1H), 11.67 (d, <i>J</i> = 51.7 Hz, 2H), 7.98 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.78 (d, <i>J</i> = 2.4 Hz, 1H), 7.50–7.43 (m, 2H), 7.07–6.98 (m, 2H), 6.91 (d, <i>J</i> = 8.7 Hz, 1H), 2.43 (s, 3H)         |
| 521             |           | 204–212 | 330       | 328       | 15.32 (s, 1H), 11.48 (s, 1H), 8.01–7.90 (m, 4H), 7.13–7.01 (m, 3H), 3.86 (s, 3H), 2.56 (s, 3H)                                                                                                                        |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 522             |    | 244–252 | 379       |           | 15.16 (s, 1H), 11.70 (s, 1H), 8.02–7.87 (m, 4H), 7.79 (d, <i>J</i> = 8.5 Hz, 2H), 7.06 (t, <i>J</i> = 8.0 Hz, 1H), 2.56 (s, 3H)                                                                                                               |
| 523             |    | 267–278 | 368       | 366       | 15.11 (s, 1H), 11.85 (s, 1H), 8.15 (d, <i>J</i> = 8.1 Hz, 2H), 8.00 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 3H), 7.08 (t, <i>J</i> = 8.0 Hz, 1H), 2.57 (s, 3H)                                                          |
| 524             |    | 186–188 | 379       | 377       | 15.06 (s, 1H), 11.97 (s, 1H), 7.95 (dd, <i>J</i> = 8.3, 1.2 Hz, 2H), 7.76 (dd, <i>J</i> = 7.8, 1.1 Hz, 1H), 7.62 (dd, <i>J</i> = 7.4, 1.8 Hz, 1H), 7.53 (ddd, <i>J</i> = 7.4, 6.8, 1.5 Hz, 2H), 7.07 (t, <i>J</i> = 8.0 Hz, 1H), 2.49 (s, 3H) |
| 525             |  | 274–283 |           | 314       | 15.02 (s, 1H), 11.73 (s, 1H), 11.69 (s, 1H), 8.05–7.89 (m, 3H), 7.51–7.43 (m, 1H), 7.11–6.98 (m, 3H), 2.50 (s, 3H)                                                                                                                            |

65480 US

| Compound Number | Structure | mp (°C)  | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                      |
|-----------------|-----------|----------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 526             |           | 76.9–187 | 315       | 313       | 13.80 (s, 1H), 7.92 (d, <i>J</i> = 7.3 Hz, 1H), 7.64 – 7.42 (m, 2H), 6.15 (dd, <i>J</i> = 9.6, 7.4 Hz, 1H), 6.10 (dd, <i>J</i> = 12.6, 2.3 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.77 (s, 1H), 3.74 (d, <i>J</i> = 1.3 Hz, 1H), 2.55 (s, 3H) |
| 527             |           | 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)                                                                                                        |
| 528             |           | 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)         |
| 529             |           | 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)                                                              |

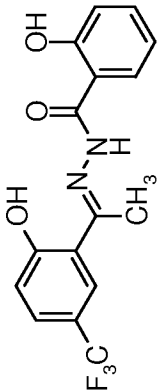
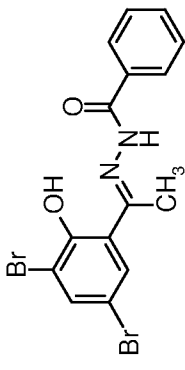
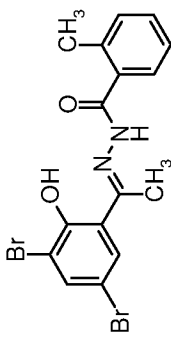
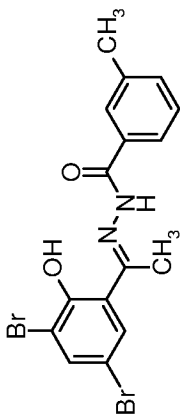
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                    |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 530             |           | 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) |
| 531             |           | 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)                                                                                                     |
| 532             |           | 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)                |
| 533             |           | 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)                                                                    |

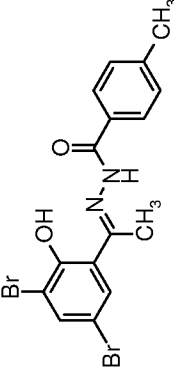
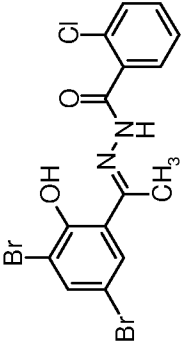
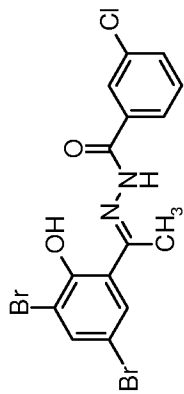
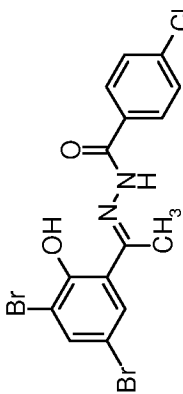
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                     |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 534             |           | 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) |
| 535             |           | 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)  |
| 536             |           | 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)                |
| 537             |           | 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                     |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+)  | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                            |
|-----------------|---------------------------------------------------------------------------------------|---------|------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 538             |    | 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)         |
| 539             |    | 242–245 | 414        |           |                                                                                                                                                                                                   |
| 540             |    | 221–222 |            | 425       | 14.64 (s, 1H), 11.71 (s, 1H), 7.84 (d, <i>J</i> = 2.2 Hz, 1H), 7.79 (d, <i>J</i> = 2.3 Hz, 1H), 7.53 (d, <i>J</i> = 7.5 Hz, 1H), 7.49–7.41 (m, 1H), 7.37–7.29 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H) |
| 541             |  | 236–238 | 427        | 425       | 14.62 (s, 1H), 11.55 (s, 1H), 7.84 (d, <i>J</i> = 2.3 Hz, 1H), 7.81 (d, <i>J</i> = 2.3 Hz, 1H), 7.78–7.72 (m, 2H), 7.48–7.41 (m, 2H), 2.52 (s, 3H), 2.41 (s, 3H)                                  |

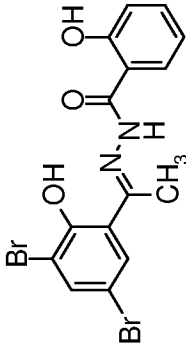
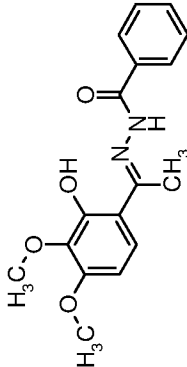
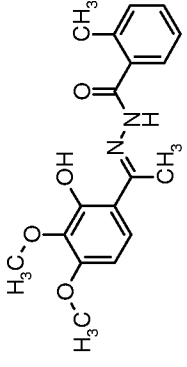
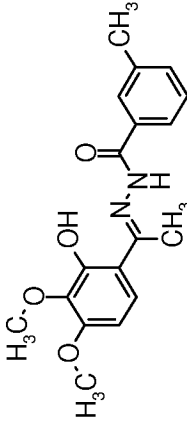
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 542             |    | 258–259 | 425       |           | 14.64 (s, 1H), 11.50 (s, 1H), 7.87 (d, <i>J</i> = 8.0 Hz, 2H), 7.84 (d, <i>J</i> = 2.3 Hz, 1H), 7.81 (d, <i>J</i> = 2.3 Hz, 1H), 7.37 (d, <i>J</i> = 8.0 Hz, 2H), 2.51 (s, 3H), 2.40 (s, 3H)                    |
| 543             |    | 207–209 | 447       | 445       | 14.46 (s, 1H), 11.92 (s, 1H), 7.86 (d, <i>J</i> = 2.3 Hz, 1H), 7.80 (d, <i>J</i> = 2.3 Hz, 1H), 7.66–7.53 (m, 3H), 7.51–7.46 (m, 1H), 2.44 (s, 3H)                                                              |
| 544             |    | 255–256 | 447       |           | 14.52 (s, 1H), 11.69 (s, 1H), 8.02 (s, 1H), 7.91 (d, <i>J</i> = 7.7 Hz, 1H), 7.85 (d, <i>J</i> = 2.2 Hz, 1H), 7.82 (d, <i>J</i> = 2.3 Hz, 1H), 7.74–7.70 (m, 1H), 7.60 (t, <i>J</i> = 7.9 Hz, 1H), 2.53 (s, 3H) |
| 545             |  | 255–258 |           | 445       | 14.55 (s, 1H), 11.65 (s, 1H), 7.99 (d, <i>J</i> = 8.5 Hz, 2H), 7.85 (d, <i>J</i> = 2.2 Hz, 1H), 7.82 (d, <i>J</i> = 2.3 Hz, 1H), 7.67–7.61 (m, 2H), 2.52 (s, 3H)                                                |

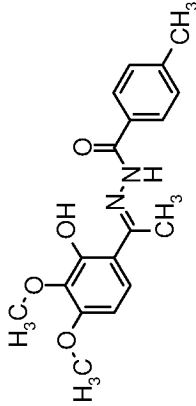
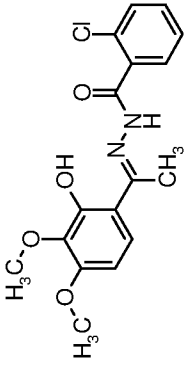
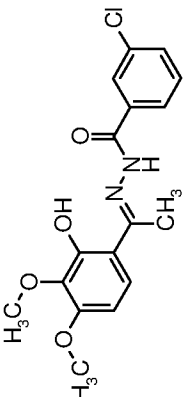
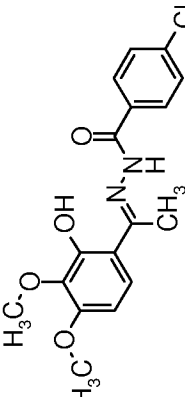
65480 US

| Compound Number | Structure | mp (°C)     | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                                                            |
|-----------------|-----------|-------------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 546             |           | 247–<br>248 |           | 441       | 14.66 (s, 1H), 11.43 (s, 1H), 7.96 (d, <i>J</i> = 8.8 Hz, 2H), 7.83 (d, <i>J</i> = 2.3 Hz, 1H), 7.80 (d, <i>J</i> = 2.4 Hz, 1H), 7.12–7.06 (m, 2H), 3.85 (s, 3H), 2.51 (s, 3H)                                                                                           |
| 547             |           | 264–<br>266 | 493       | 491       | 14.55 (s, 1H), 11.65 (s, 1H), 7.91 (d, <i>J</i> = 8.5 Hz, 2H), 7.85 (d, <i>J</i> = 2.2 Hz, 1H), 7.82 (d, <i>J</i> = 2.3 Hz, 1H), 7.80–7.76 (m, 2H), 2.52 (s, 3H)                                                                                                         |
| 548             |           | 255–<br>257 | 481       |           | 14.51 (s, 1H), 11.80 (s, 1H), 8.15 (d, <i>J</i> = 8.1 Hz, 2H), 7.94 (d, <i>J</i> = 8.3 Hz, 2H), 7.86 (d, <i>J</i> = 2.2 Hz, 1H), 7.83 (d, <i>J</i> = 2.3 Hz, 1H), 2.53 (s, 3H)                                                                                           |
| 549             |           | 214–<br>216 | 491       | 489       | 14.46 (s, 1H), 11.91 (s, 1H), 7.86 (d, <i>J</i> = 2.3 Hz, 1H), 7.80 (d, <i>J</i> = 2.3 Hz, 1H), 7.76 (dd, <i>J</i> = 7.8, 1.2 Hz, 1H), 7.61 (dd, <i>J</i> = 7.4, 1.8 Hz, 1H), 7.53 (td, <i>J</i> = 7.4, 1.3 Hz, 1H), 7.47 (td, <i>J</i> = 7.6, 1.9 Hz, 1H), 2.44 (s, 3H) |

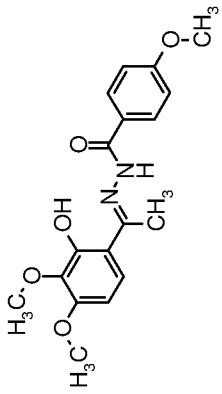
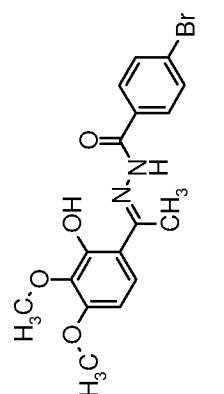
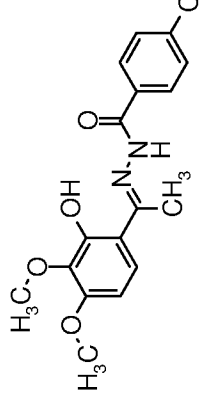
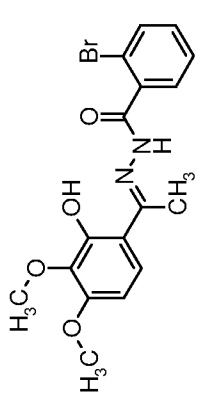
65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 550             |    | 305–306 |           | 427       | 14.43 (s, 1H), 11.71 (s, 2H), 7.97 (dd, <i>J</i> = 7.9, 1.7 Hz, 1H), 7.86–7.82 (m, 2H), 7.50–7.43 (m, 1H), 7.08–6.98 (m, 2H), 2.45 (s, 3H)                                                                        |
| 551             |    | 154–155 | 315       | 313       | 13.71 (s, 1H), 11.27 (s, 1H), 7.93 (d, <i>J</i> = 7.2 Hz, 2H), 7.65–7.59 (m, 1H), 7.58–7.51 (m, 2H), 7.38 (d, <i>J</i> = 9.0 Hz, 1H), 6.60 (d, <i>J</i> = 9.0 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.45 (s, 3H)   |
| 552             |   | 150–152 | 329       | 327       | 13.71 (s, 1H), 11.34 (s, 1H), 7.50 (d, <i>J</i> = 7.6 Hz, 1H), 7.46–7.39 (m, 1H), 7.32 (dt, <i>J</i> = 11.7, 8.4 Hz, 3H), 6.60 (d, <i>J</i> = 9.0 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H) |
| 553             |  | 158–162 | 329       | 327       | 13.70 (s, 1H), 11.22 (s, 1H), 7.77–7.68 (m, 2H), 7.46–7.41 (m, 2H), 7.37 (d, <i>J</i> = 9.0 Hz, 1H), 6.61 (d, <i>J</i> = 9.1 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H)                      |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 554             |    | 245–249 | 329       | 327       | 13.71 (s, 1H), 11.18 (s, 1H), 7.85 (d, <i>J</i> = 8.0 Hz, 2H), 7.41–7.31 (m, 3H), 6.60 (d, <i>J</i> = 9.1 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H)                                                                        |
| 555             |    | 77–86   | 349       | 347       | 13.54, 11.55, 10.92 (3s, 2H), 7.63–7.44 (m, 4H), 7.36, 7.25 (2d, <i>J</i> = 9.1 Hz, 1H), 6.61, 6.53 (2d, <i>J</i> = 9.1 Hz, 1H), 3.82, 3.75, 3.71, 3.50 (4s, 6H), 2.38, 2.35 (2s, 3H); Note: rotational isomers                                  |
| 556             |    | 194–201 | 349       | 347       | 13.60 (s, 1H), 11.37 (s, 1H), 8.00–7.97 (m, 1H), 7.89 (d, <i>J</i> = 7.8 Hz, 1H), 7.72–7.67 (m, 1H), 7.58 (t, <i>J</i> = 7.9 Hz, 1H), 7.39 (d, <i>J</i> = 9.0 Hz, 1H), 6.61 (d, <i>J</i> = 9.1 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.46 (s, 3H) |
| 557             |  | 230–235 | 349       | 347       | 13.63 (s, 1H), 11.33 (s, 1H), 7.96 (d, <i>J</i> = 8.5 Hz, 2H), 7.63 (d, <i>J</i> = 8.5 Hz, 2H), 7.38 (d, <i>J</i> = 9.0 Hz, 1H), 6.61 (d, <i>J</i> = 9.1 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.45 (s, 3H)                                       |

65480 US

| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                            |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 558             |    | 230–232 | 345       | 343       | 13.73 (s, 1H), 11.11 (s, 1H), 7.93 (d, <i>J</i> = 8.7 Hz, 2H), 7.36 (d, <i>J</i> = 9.0 Hz, 1H), 7.08 (d, <i>J</i> = 8.9 Hz, 2H), 6.60 (d, <i>J</i> = 9.1 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 2.44 (s, 3H) |
| 559             |    | 241–245 | 393       | 391       | 13.62 (s, 1H), 11.33 (s, 1H), 7.89 (d, <i>J</i> = 8.5 Hz, 2H), 7.77 (d, <i>J</i> = 8.5 Hz, 2H), 7.38 (d, <i>J</i> = 9.0 Hz, 1H), 6.61 (d, <i>J</i> = 9.1 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.45 (s, 3H)               |
| 560             |   | 229–233 | 383       | 381       | 13.60 (s, 1H), 11.48 (s, 1H), 8.12 (d, <i>J</i> = 8.1 Hz, 2H), 7.93 (d, <i>J</i> = 8.3 Hz, 2H), 7.39 (d, <i>J</i> = 9.0 Hz, 1H), 6.62 (d, <i>J</i> = 9.1 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.46 (s, 3H)               |
| 561             |  | 195–200 | 393       | 391       | 13.54, 11.55, 10.90 (3s, 2H), 7.76–7.42 (m, 4H), 7.36, 7.25 (2d, <i>J</i> = 9.1 Hz, 1H), 6.61, 6.53 (2d, <i>J</i> = 9.1 Hz, 1H), 3.82, 3.75, 3.71, 3.50 (4s, 6H), 2.38, 2.34 (2s, 3H); Note: rotational isomers          |

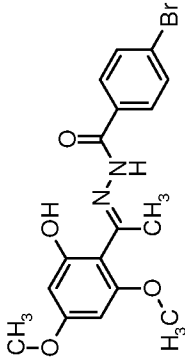
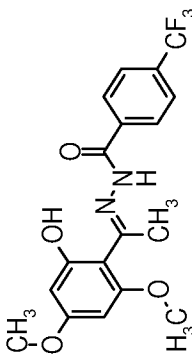
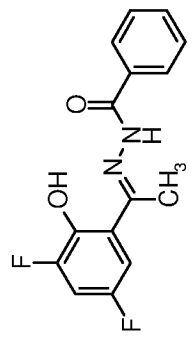
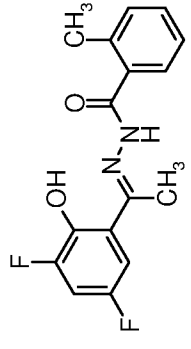
65480 US

| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                            |
|-----------------|-----------|---------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 562             |           | 279–297 | 331       | 329       | 13.51 (s, 1H), 11.74 (s, 1H), 11.51 (s, 1H), 7.98 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.49–7.42 (m, 1H), 7.40 (d, <i>J</i> = 9.0 Hz, 1H), 7.07–6.97 (m, 2H), 6.62 (d, <i>J</i> = 9.0 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.40 (s, 3H)     |
| 563             |           | 287–292 | 375       | 373       | (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) 12.48 (s, 1H), 11.17 (s, 1H), 8.63 (s, 1H), 8.44 (s, 1H), 7.94 (d, <i>J</i> = 8.2 Hz, 1H), 7.78 (d, <i>J</i> = 8.3 Hz, 1H), 7.71–7.64 (m, 2H), 7.58–7.49 (m, 1H), 7.42–7.32 (m, 2H)              |
| 564             |           | 312–315 |           | 387       | 14.42 (s, 1H), 12.04–11.57 (m, 2H), 8.60 (s, 1H), 8.00 (d, <i>J</i> = 8.0 Hz, 1H), 7.79 (d, <i>J</i> = 8.2 Hz, 1H), 7.73 (d, <i>J</i> = 2.5 Hz, 1H), 7.66 (d, <i>J</i> = 2.5 Hz, 1H), 7.56–7.51 (m, 1H), 7.41–7.35 (m, 2H), 2.50 (s, 3H) |
| 565             |           | 278–279 |           | 351       | 14.33 (s, 1H), 11.75 (s, 2H), 7.86 (d, <i>J</i> = 7.9 Hz, 1H), 7.72 (d, <i>J</i> = 2.5 Hz, 1H), 7.66 (d, <i>J</i> = 2.4 Hz, 1H), 7.41 (d, <i>J</i> = 7.2 Hz, 1H), 6.92 (t, <i>J</i> = 7.7 Hz, 1H), 2.54 (s, 3H), 2.23 (s, 3H)            |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                     |
|-----------------|-----------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 566             |           | 177–184 | 329       | 327       | 12.89 (s, 1H), 11.04 (s, 1H), 7.83 (d, <i>J</i> = 7.9 Hz, 2H), 7.34 (d, <i>J</i> = 7.9 Hz, 2H), 6.12 (d, <i>J</i> = 5.0 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H)           |
| 567             |           | 206–215 | 349       | 347       | 10.05 (s, 1H), 9.70 (s, 1H), 7.59 (dd, <i>J</i> = 8.9, 2.1 Hz, 2H), 7.47 (d, <i>J</i> = 5.7 Hz, 2H), 6.17 (d, <i>J</i> = 2.0 Hz, 1H), 6.14 (d, <i>J</i> = 2.1 Hz, 1H), 3.74 (s, 6H), 2.15 (s, 2H) |
| 568             |           | 136–140 | 349       | 347       | 12.80 (s, 1H), 11.19 (s, 1H), 7.95 (d, <i>J</i> = 8.4 Hz, 2H), 7.61 (d, <i>J</i> = 8.3 Hz, 2H), 6.14–6.09 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.38 (s, 3H)                                       |
| 569             |           | 143–146 | 345       | 343       | 12.91 (s, 1H), 10.98 (s, 1H), 7.92 (d, <i>J</i> = 8.7 Hz, 2H), 7.07 (d, <i>J</i> = 8.7 Hz, 2H), 6.12 (dd, <i>J</i> = 7.6, 2.3 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 2.37 (s, 3H)     |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                   |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 570             |    | 134–159 | 394       | 392       | 12.78 (s, 1H), 11.19 (s, 1H), 7.87 (d, <i>J</i> = 8.4 Hz, 2H), 7.75 (d, <i>J</i> = 8.4 Hz, 2H), 6.12 (dd, <i>J</i> = 7.8, 2.2 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.37 (s, 3H) |
| 571             |    | 131–133 | 383       | 381       | 12.70 (s, 1H), 11.33 (s, 1H), 8.11 (d, <i>J</i> = 8.1 Hz, 2H), 7.92 (d, <i>J</i> = 8.3 Hz, 2H), 6.13 (dd, <i>J</i> = 7.1, 2.3 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.38 (s, 3H) |
| 572             |    | 222–225 | 291       | 289       | 13.55 (s, 1H), 11.54 (s, 1H), 7.95 (d, <i>J</i> = 7.4 Hz, 2H), 7.65 (t, <i>J</i> = 7.3 Hz, 1H), 7.56 (t, <i>J</i> = 7.5 Hz, 2H), 7.43–7.34 (m, 2H), 2.50 (s, 3H)                |
| 573             |  | 186–188 | 305       | 303       | 13.56 (s, 1H), 11.63 (s, 1H), 7.53 (d, <i>J</i> = 7.6 Hz, 1H), 7.45 (t, <i>J</i> = 8.0 Hz, 1H), 7.40–7.29 (m, 4H), 2.42 (s, 3H), 2.40 (s, 3H)                                   |

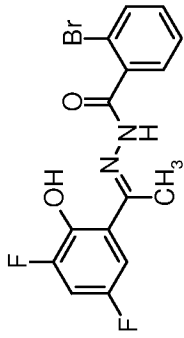
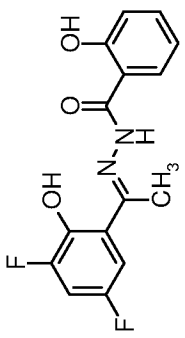
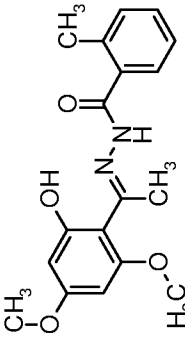
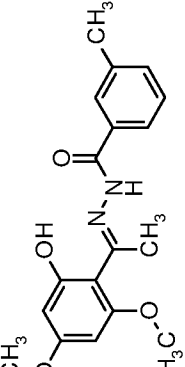
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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                                                             |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 574             |           | 215–216 | 305       | 303       | 13.56 (s, 1H), 11.49 (s, 1H), 7.75 (d, <i>J</i> = 11.6 Hz, 2H), 7.45 (d, <i>J</i> = 6.2 Hz, 2H), 7.39 (td, <i>J</i> = 8.9, 2.8 Hz, 2H), 2.49 (s, 3H), 2.41 (s, 3H)                                 |
| 575             |           | 220–22  | 305       | 303       | 13.57 (s, 1H), 11.44 (s, 1H), 7.87 (d, <i>J</i> = 7.9 Hz, 2H), 7.38 (dd, <i>J</i> = 13.4, 6.6 Hz, 4H), 2.49 (s, 3H), 2.40 (s, 3H)                                                                  |
| 576             |           | 205–209 | 325       | 323       | 13.38 (s, 1H), 11.83 (s, 1H), 7.60 (dddd, <i>J</i> = 15.2, 9.7, 7.7, 1.6 Hz, 3H), 7.48 (td, <i>J</i> = 7.3, 1.4 Hz, 1H), 7.44–7.34 (m, 2H), 2.42 (s, 3H)                                           |
| 577             |           | 279–282 | 325       | 323       | 13.45 (s, 1H), 11.62 (s, 1H), 8.02 (s, 1H), 7.91 (d, <i>J</i> = 7.7 Hz, 1H), 7.72 (d, <i>J</i> = 8.1 Hz, 1H), 7.60 (t, <i>J</i> = 7.9 Hz, 1H), 7.41 (dd, <i>J</i> = 9.5, 7.1 Hz, 2H), 2.50 (s, 3H) |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), δ                                                                            |
|-----------------|-----------|---------|-----------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 578             |           | 276–280 | 325       | 323       | 13.48 (s, 1H), 11.59 (s, 1H), 7.98 (d, <i>J</i> = 8.5 Hz, 2H), 7.64 (d, <i>J</i> = 8.5 Hz, 2H), 7.43–7.36 (m, 2H), 2.50 (s, 3H)                                   |
| 579             |           | 243–247 | 321       | 319       | 13.59 (s, 1H), 11.36 (s, 1H), 7.96 (d, <i>J</i> = 8.7 Hz, 2H), 7.37 (dd, <i>J</i> = 9.4, 3.2 Hz, 2H), 7.09 (d, <i>J</i> = 8.9 Hz, 2H), 3.85 (s, 3H), 2.49 (s, 3H) |
| 580             |           | 268–270 | 370       | 368       | 13.48 (s, 1H), 11.59 (s, 1H), 7.91 (d, <i>J</i> = 8.4 Hz, 2H), 7.78 (d, <i>J</i> = 8.5 Hz, 2H), 7.44–7.36 (m, 2H), 2.49 (s, 3H)                                   |
| 581             |           | 287–291 | 359       | 357       | 13.44 (s, 1H), 11.73 (s, 1H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.94 (d, <i>J</i> = 8.3 Hz, 2H), 7.41 (dd, <i>J</i> = 9.5, 7.5 Hz, 2H), 2.51 (s, 3H)               |

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| Compound Number | Structure                                                                             | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 582             |    | 190–195 | 370       | 368       | 13.38 (s, 1H), 11.84 (s, 1H), 7.75 (dd, <i>J</i> = 7.8, 1.0 Hz, 1H), 7.62 (d, <i>J</i> = 1.8 Hz, 1H), 7.60 (d, <i>J</i> = 1.8 Hz, 1H), 7.55–7.48 (m, 2H), 7.37 (dd, <i>J</i> = 8.4, 2.2 Hz, 1H), 2.42 (s, 3H) |
| 583             |    | 308–323 | 307       | 305       | 13.37 (s, 1H), 11.70 (s, 2H), 7.98 (dd, <i>J</i> = 7.9, 1.7 Hz, 1H), 7.44 (ddd, <i>J</i> = 28.3, 14.3, 6.0 Hz, 3H), 7.07–6.98 (m, 2H), 2.43 (s, 3H)                                                           |
| 584             |    | 269–274 | 329       | 327       | 9.96 (s, 1H), 9.24 (s, 1H), 7.35–7.27 (m, 2H), 7.19 (t, <i>J</i> = 3.6 Hz, 2H), 6.08 (d, <i>J</i> = 10.7 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 2.26 (s, 3H), 2.12 (s, 3H)                                      |
| 585             |  | 207–209 | 329       | 327       | 12.87 (s, 1H), 11.09 (s, 1H), 7.72 (d, <i>J</i> = 9.4 Hz, 2H), 7.42 (d, <i>J</i> = 4.6 Hz, 2H), 6.12 (dd, <i>J</i> = 7.8, 2.1 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H)                 |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                        |
|-----------------|-----------|---------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 586             |           | 182–199 | 331       | 329       | 13.80 (s, 1H), 12.50 (s, 1H), 11.54 (s, 1H), 7.96 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.47–7.35 (m, 1H), 7.08–6.91 (m, 2H), 6.14 (d, <i>J</i> = 2.3 Hz, 1H), 6.08 (d, <i>J</i> = 2.4 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.35 (s, 3H) |
| 587             |           | 195–96  | 377       | 375       | 11.38 (s, 1H), 10.47 (s, 1H), 7.71 (dd, <i>J</i> = 15.3, 4.9 Hz, 3H), 7.58 (d, <i>J</i> = 7.4 Hz, 1H), 7.49 (t, <i>J</i> = 7.5 Hz, 2H), 7.35 (d, <i>J</i> = 2.3 Hz, 1H)                                                              |
| 588             |           | gum     | 351       | 349       | 12.49 (s, 1H), 9.88 (s, 1H), 7.96 (d, <i>J</i> = 2.2 Hz, 1H), 7.86 (d, <i>J</i> = 2.2 Hz, 1H), 7.62–7.31 (m, 4H), 7.13 (s, 1H), 3.78–3.65 (m, 1H), 1.07 (d, <i>J</i> = 9.5 Hz, 6H)                                                   |
| 589             |           | 218–219 | 349       | 347       | 13.96 (s, 1H), 11.71 (s, 1H), 7.95 (d, <i>J</i> = 7.1 Hz, 2H), 7.88 (s, 1H), 7.62 (dt, <i>J</i> = 23.1, 7.2 Hz, 4H), 2.08–1.91 (m, 1H), 1.28 (d, <i>J</i> = 7.4 Hz, 2H), 0.79 (d, <i>J</i> = 4.4 Hz, 2H)                             |

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| Compound Number | Structure | mp (°C) | ESIMS (+) | ESIMS (-) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> , unless otherwise stated), $\delta$                                                                                                                                          |
|-----------------|-----------|---------|-----------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 590             |           | 214–215 | 337       | 335       | 14.55 (s, 1H), 11.67 (s, 1H), 7.91 (d, <i>J</i> = 7.4 Hz, 2H), 7.75–7.61 (m, 3H), 7.57 (t, <i>J</i> = 7.5 Hz, 2H), 3.06 (q, <i>J</i> = 7.4 Hz, 2H), 1.14 (t, <i>J</i> = 7.5 Hz, 3H)                                                    |
| 591             |           | 208–210 | 309       | 307       | 10.75 (s, 1H), 10.47 (s, 1H), 7.73–7.63 (m, 2H), 7.62–7.53 (m, 1H), 7.47 (dd, <i>J</i> = 10.4, 4.6 Hz, 2H), 7.43–7.35 (m, 1H), 7.25 (d, <i>J</i> = 7.6 Hz, 1H), 7.03 (d, <i>J</i> = 8.3 Hz, 1H), 6.96 (td, <i>J</i> = 7.6, 0.9 Hz, 1H) |
| 592             |           | 241–243 | 297       | 295       | 9.90 (s, 1H), 8.78 (s, 1H), 7.57–7.24 (m, 6H), 7.11–6.87 (m, 3H), 1.18 (s, 9H)                                                                                                                                                         |

**[0076]** As exemplified below, hydrazones of the present invention, or their metal complexes, 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.

**[0077]** 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 26. Effect of copper on fungitoxicity of hydrazones towards *Leptosphaeria nodorum*.**

**[0078]** *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 CuSO<sub>4</sub>, was omitted. The medium, termed “copper-minus”, was prepared by dissolving 10 g glucose, 1.5 g K<sub>2</sub>HPO<sub>4</sub>, 2 g KH<sub>2</sub>PO<sub>4</sub> and 1 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> 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. MgSO<sub>4</sub>•7H<sub>2</sub>O (0.5 g) was added, and stirring continued for a further hour. Trace elements (minus CuSO<sub>4</sub>), 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 CuCl<sub>2</sub>•2H<sub>2</sub>O 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.

**[0079]** 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 10<sup>5</sup> 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.

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**[0080]** 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 3. Results illustrate that hydrazones and copper produce a synergistic fungitoxic effect towards LEPTNO.

**Example 27. Efficacy of hydrazones in mixture with copper against tomato blight (*Phytophthora infestans*)**

**[0081]** Hydrazone compounds at 50 ppm in combination with 50  $\mu\text{M}$   $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  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  $\mu\text{M}$   $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  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 |
|-----------------|-----------------------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| <b>1</b>        | 0.05                        | 0.7                                 | 96.2                                | 7.8                                  | 64.0          |
| <b>2</b>        | 0.05                        | 0.0                                 | 95.1                                | 7.1                                  | 61.4          |
| <b>3</b>        | 0.05                        | 2.3                                 | 93.0                                | 9.3                                  | 47.0          |
| <b>4</b>        | 0.05                        | 4.4                                 | 94.5                                | 11.2                                 | 67.8          |
| <b>5</b>        | 0.05                        | 4.8                                 | 56.1                                | 11.6                                 | 22.0          |
| <b>6</b>        | 0.05                        | 3.9                                 | 96.4                                | 10.7                                 | 88.1          |

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| 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           | 2.6                                 | 97.2                                | 9.5                                  | 54.6          |
| 8               | 0.05           | 0.0                                 | 92.6                                | 7.1                                  | 59.6          |
| 9               | 0.05           | 0.0                                 | 93.6                                | 7.1                                  | 67.3          |
| 10              | 0.05           | 6.9                                 | 97.2                                | 13.5                                 | 96.0          |
| 11              | 0.05           | 0.3                                 | 97.2                                | 7.4                                  | 42.1          |
| 12              | 0.05           | 0.5                                 | 97.4                                | 7.6                                  | 94.0          |
| 13              | 0.05           | 0.0                                 | 96.2                                | 7.1                                  | 33.3          |
| 14              | 0.156          | 2.9                                 | 59.1                                | 9.8                                  | 7.5           |
| 15              | 0.05           | 4.4                                 | 96.6                                | 11.1                                 | 58.5          |
| 16              | 0.05           | 0.0                                 | 97.1                                | 7.1                                  | 94.0          |
| 17              | 0.05           | 9.4                                 | 95.9                                | 15.9                                 | 69.0          |
| 18              | 0.05           | 0.0                                 | 96.9                                | 7.1                                  | 38.6          |
| 19              | 0.05           | 2.9                                 | 88.8                                | 9.8                                  | 25.0          |
| 20              | 0.05           | 2.8                                 | 96.5                                | 9.7                                  | 96.5          |
| 21              | 0.05           | 0.1                                 | 94.1                                | 7.2                                  | 65.5          |
| 22              | 0.05           | 16.0                                | 97.6                                | 22.0                                 | 93.2          |
| 23              | 0.05           | 2.3                                 | 95.4                                | 9.2                                  | 53.3          |
| 24              | 0.05           | 7.6                                 | 92.8                                | 14.1                                 | 8.9           |
| 25              | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 35.1          |
| 26              | 0.05           | 2.1                                 | 98.4                                | 9.1                                  | 12.3          |
| 27              | 0.05           | 16.5                                | 97.9                                | 22.4                                 | 43.3          |
| 28              | 0.05           | 7.0                                 | 96.8                                | 13.6                                 | 62.7          |
| 29              | 0.05           | 0.0                                 | 98.0                                | 7.1                                  | 50.8          |
| 30              | 0.05           | 0.0                                 | 97.0                                | 7.1                                  | 40.7          |
| 31              | 0.05           | 2.2                                 | 89.0                                | 9.2                                  | 33.3          |
| 32              | 0.05           | 0.0                                 | 94.4                                | 7.1                                  | 74.6          |
| 33              | 0.05           | 0.0                                 | 93.1                                | 7.1                                  | 50.9          |
| 34              | 0.05           | 0.0                                 | 97.8                                | 7.1                                  | 68.4          |
| 35              | 0.05           | 3.8                                 | 96.5                                | 10.6                                 | 0.0           |
| 36              | 0.05           | 5.9                                 | 98.4                                | 12.6                                 | 33.9          |
| 37              | 0.05           | 3.3                                 | 97.0                                | 10.2                                 | 33.0          |
| 38              | 0.05           | 2.4                                 | 98.3                                | 9.4                                  | 17.0          |
| 39              | 0.05           | 1.3                                 | 97.9                                | 8.3                                  | 18.6          |
| 40              | 0.05           | 0.0                                 | 94.8                                | 7.1                                  | 64.9          |
| 41              | 0.05           | 0.0                                 | 97.2                                | 7.1                                  | 87.0          |
| 42              | 0.05           | 9.2                                 | 93.2                                | 15.6                                 | 60.0          |
| 43              | 0.156          | 14.2                                | 75.4                                | 20.3                                 | 68.8          |
| 44              | 0.05           | 0.3                                 | 93.0                                | 7.3                                  | 0.7           |
| 45              | 0.05           | 0.0                                 | 96.2                                | 7.1                                  | 49.0          |

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| 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           | 20.5                                | 95.9                                | 26.1                                 | 72.7          |
| 47              | 0.05           | 0.0                                 | 97.1                                | 7.1                                  | 33.0          |
| 48              | 0.05           | 0.3                                 | 94.6                                | 7.4                                  | 40.0          |
| 49              | 0.05           | 14.6                                | 97.1                                | 20.7                                 | 0.7           |
| 50              | 0.05           | 3.5                                 | 97.4                                | 10.4                                 | 43.5          |
| 51              | 0.05           | 0.0                                 | 97.6                                | 7.1                                  | 4.8           |
| 52              | 0.2            | 12.3                                | 96.4                                | 18.5                                 | NT            |
| 53              | 0.05           | 0.0                                 | 96.8                                | 7.1                                  | 62.0          |
| 54              | 0.05           | 0.0                                 | 95.7                                | 7.1                                  | 17.0          |
| 55              | 0.05           | 0.0                                 | 95.5                                | 7.1                                  | 43.9          |
| 56              | 0.05           | 2.1                                 | 96.3                                | 9.1                                  | 81.3          |
| 57              | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 89.5          |
| 58              | 0.05           | 0.0                                 | 95.0                                | 7.1                                  | 49.0          |
| 59              | 0.05           | 12.8                                | 97.5                                | 19.0                                 | 79.7          |
| 60              | 0.05           | 7.3                                 | 97.5                                | 13.9                                 | 85.0          |
| 61              | 0.05           | 3.8                                 | 93.6                                | 10.6                                 | 60.0          |
| 62              | 0.05           | 0.0                                 | 96.3                                | 7.1                                  | 56.1          |
| 63              | 0.05           | 0.0                                 | 96.7                                | 7.1                                  | 40.4          |
| 64              | 0.05           | 0.0                                 | 97.8                                | 7.1                                  | 43.0          |
| 65              | 0.05           | 0.0                                 | 98.3                                | 7.1                                  | 10.0          |
| 66              | 0.05           | 0.1                                 | 97.4                                | 7.2                                  | 51.0          |
| 67              | 0.05           | 2.6                                 | 91.8                                | 9.5                                  | 75.0          |
| 68              | 0.05           | 15.8                                | 97.0                                | 21.8                                 | 75.9          |
| 69              | 0.05           | 19.3                                | 96.9                                | 25.1                                 | 90.8          |
| 70              | 0.05           | 19.6                                | 98.2                                | 25.3                                 | 93.1          |
| 71              | 0.05           | 2.6                                 | 91.2                                | 9.5                                  | 78.0          |
| 72              | 0.05           | 14.1                                | 91.3                                | 20.2                                 | 81.3          |
| 73              | 0.05           | 8.6                                 | 98.0                                | 15.1                                 | 87.3          |
| 74              | 0.05           | 3.0                                 | 95.7                                | 9.8                                  | 63.6          |
| 75              | 0.05           | 0.0                                 | 98.4                                | 7.1                                  | 15.8          |
| 76              | 0.05           | 0.0                                 | 97.0                                | 7.1                                  | 89.8          |
| 77              | 0.05           | 7.6                                 | 96.1                                | 14.1                                 | 55.5          |
| 78              | 0.05           | 7.9                                 | 96.3                                | 14.4                                 | 70.9          |
| 79              | 0.05           | 12.2                                | 97.1                                | 18.4                                 | 84.4          |
| 80              | 0.05           | 0.0                                 | 98.4                                | 7.1                                  | 91.5          |
| 81              | 0.05           | 2.4                                 | 96.1                                | 9.3                                  | 97.0          |
| 82              | 0.05           | 8.4                                 | 97.4                                | 14.9                                 | 60.6          |
| 83              | 0.05           | 5.9                                 | 98.0                                | 12.5                                 | 60.6          |
| 84              | 0.05           | 5.6                                 | 95.5                                | 12.3                                 | 83.6          |

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| 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           | 5.3                                 | 90.0                                | 12.0                                 | 51.5          |
| 86              | 0.05           | 0.3                                 | 97.6                                | 7.4                                  | 80.7          |
| 87              | 0.05           | 8.1                                 | 98.6                                | 14.7                                 | 69.5          |
| 88              | 0.05           | 10.7                                | 96.7                                | 17.0                                 | 4.8           |
| 89              | 0.05           | 17.5                                | 95.9                                | 23.3                                 | 85.8          |
| 90              | 0.05           | 9.5                                 | 96.4                                | 15.9                                 | 54.6          |
| 91              | 0.05           | 0.0                                 | 79.3                                | 7.1                                  | 18.0          |
| 92              | 0.05           | 1.9                                 | 98.2                                | 8.8                                  | 71.9          |
| 93              | 0.05           | 6.0                                 | 95.2                                | 12.7                                 | 77.2          |
| 94              | 0.05           | 0.0                                 | 92.9                                | 7.1                                  | 37.0          |
| 95              | 0.05           | 14.1                                | 94.0                                | 20.2                                 | 81.2          |
| 96              | 0.05           | 1.2                                 | 93.6                                | 8.2                                  | 78.2          |
| 97              | 0.05           | 18.2                                | 98.3                                | 24.0                                 | 76.3          |
| 98              | 0.05           | 16.8                                | 98.1                                | 22.7                                 | 79.7          |
| 99              | 0.05           | 8.9                                 | 94.5                                | 15.4                                 | 50.3          |
| 100             | 0.05           | 8.2                                 | 97.0                                | 14.7                                 | 74.2          |
| 101             | 0.05           | 7.8                                 | 97.3                                | 14.3                                 | 85.3          |
| 102             | 0.05           | 0.0                                 | 93.4                                | 7.1                                  | 74.0          |
| 103             | 0.05           | 17.9                                | 98.1                                | 23.8                                 | 63.2          |
| 104             | 0.05           | 27.7                                | 98.2                                | 32.8                                 | 70.2          |
| 105             | 0.05           | 5.8                                 | 95.2                                | 12.5                                 | 74.6          |
| 106             | 0.05           | 0.0                                 | 94.6                                | 7.1                                  | 88.7          |
| 107             | 0.05           | 0.0                                 | 97.2                                | 7.1                                  | 74.6          |
| 108             | 0.05           | 21.3                                | 97.6                                | 26.9                                 | 50.9          |
| 109             | 0.05           | 27.8                                | 98.3                                | 32.9                                 | 89.1          |
| 110             | 0.05           | 19.9                                | 98.2                                | 25.6                                 | 76.4          |
| 111             | 0.05           | 16.8                                | 97.4                                | 22.7                                 | 63.6          |
| 112             | 0.05           | 8.1                                 | 97.8                                | 14.6                                 | 78.2          |
| 113             | 0.05           | 17.0                                | 98.0                                | 22.9                                 | 94.7          |
| 114             | 0.05           | 0.0                                 | 36.9                                | 7.1                                  | 7.5           |
| 115             | 0.05           | 6.1                                 | 97.4                                | 12.7                                 | 78.2          |
| 116             | 0.05           | 8.4                                 | 98.2                                | 14.9                                 | 88.8          |
| 117             | 0.05           | 28.8                                | 98.5                                | 33.9                                 | 89.5          |
| 118             | 0.05           | 10.6                                | 98.3                                | 16.9                                 | 85.3          |
| 119             | 0.05           | 2.2                                 | 95.7                                | 9.1                                  | 91.9          |
| 120             | 0.05           | 19.9                                | 98.2                                | 25.6                                 | 92.6          |
| 121             | 0.05           | 0.0                                 | 98.3                                | 7.1                                  | 88.1          |
| 122             | 0.05           | 13.5                                | 98.7                                | 19.6                                 | 92.7          |
| 123             | 0.05           | 7.5                                 | 95.5                                | 14.1                                 | 71.0          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 124             | 0.05           | 0.0                                 | 88.2                                | 7.1                                  | 23.0          |
| 125             | 0.05           | 2.4                                 | 94.4                                | 9.3                                  | 87.0          |
| 126             | 0.05           | 13.2                                | 92.4                                | 19.4                                 | 73.0          |
| 127             | 0.05           | 0.0                                 | 97.1                                | 7.1                                  | 40.0          |
| 128             | 0.05           | 10.8                                | 88.6                                | 17.1                                 | 38.0          |
| 129             | 0.05           | 5.5                                 | 97.8                                | 12.2                                 | 49.0          |
| 130             | 0.05           | 1.2                                 | 98.6                                | 8.2                                  | 50.8          |
| 131             | 0.05           | 0.0                                 | 96.8                                | 7.1                                  | 62.0          |
| 132             | 0.05           | 9.1                                 | 97.7                                | 15.5                                 | 65.5          |
| 133             | 0.05           | 8.8                                 | 98.5                                | 15.3                                 | 71.9          |
| 134             | 0.05           | 4.2                                 | 95.3                                | 11.0                                 | 57.0          |
| 135             | 0.05           | 0.2                                 | 98.6                                | 7.3                                  | 96.0          |
| 136             | 0.05           | 9.7                                 | 98.6                                | 16.2                                 | 95.0          |
| 137             | 0.05           | 4.5                                 | 98.5                                | 11.3                                 | 74.0          |
| 138             | 0.05           | 4.0                                 | 98.1                                | 10.8                                 | 91.0          |
| 139             | 0.05           | 1.7                                 | 97.1                                | 8.6                                  | 93.0          |
| 140             | 0.05           | 6.7                                 | 96.7                                | 13.3                                 | 81.0          |
| 141             | 0.05           | 1.5                                 | 96.2                                | 8.5                                  | 52.0          |
| 142             | 0.05           | 1.1                                 | 98.2                                | 8.1                                  | 79.0          |
| 143             | 0.05           | 2.1                                 | 98.2                                | 9.0                                  | 64.4          |
| 144             | 0.05           | 0.0                                 | 98.5                                | 7.1                                  | 87.0          |
| 145             | 0.05           | 2.4                                 | 97.2                                | 9.3                                  | 55.9          |
| 146             | 0.05           | 0.0                                 | 96.2                                | 7.1                                  | 71.2          |
| 147             | 0.05           | 0.0                                 | 95.6                                | 7.1                                  | 13.5          |
| 148             | 0.05           | 15.4                                | 97.9                                | 21.5                                 | 72.9          |
| 149             | 0.05           | 0.0                                 | 97.1                                | 7.1                                  | 22.1          |
| 150             | 0.05           | 10.0                                | 97.5                                | 16.4                                 | 87.5          |
| 151             | 0.05           | 11.8                                | 97.6                                | 18.1                                 | 83.0          |
| 152             | 0.05           | 0.0                                 | 89.1                                | 7.1                                  | 26.0          |
| 153             | 0.05           | 0.0                                 | 97.0                                | 7.1                                  | 34.6          |
| 154             | 0.05           | 3.4                                 | 70.7                                | 10.3                                 | 36.6          |
| 155             | 0.05           | 1.9                                 | 78.3                                | 8.9                                  | 32.0          |
| 156             | 0.05           | 7.4                                 | 94.8                                | 14.0                                 | 51.5          |
| 157             | 0.05           | 7.8                                 | 96.9                                | 14.3                                 | 61.8          |
| 158             | 0.05           | 6.2                                 | 96.9                                | 12.9                                 | 84.7          |
| 159             | 0.05           | 11.4                                | 98.5                                | 17.7                                 | 91.9          |
| 160             | 0.05           | 3.4                                 | 96.1                                | 10.2                                 | 65.5          |
| 161             | 0.05           | 7.0                                 | 97.7                                | 13.6                                 | 58.2          |
| 162             | 0.05           | 0.0                                 | 96.9                                | 7.1                                  | 94.0          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 163             | 0.05           | 5.9                                 | 98.0                                | 12.6                                 | 87.7          |
| 164             | 0.05           | 10.8                                | 98.6                                | 17.1                                 | 96.5          |
| 165             | 0.05           | 14.9                                | 98.4                                | 21.0                                 | 88.4          |
| 166             | 0.05           | 2.6                                 | 97.9                                | 9.5                                  | 71.9          |
| 167             | 0.05           | 0.0                                 | 95.8                                | 7.1                                  | 67.3          |
| 168             | 0.05           | 13.3                                | 97.7                                | 19.5                                 | 59.6          |
| 169             | 0.05           | 2.7                                 | 98.1                                | 9.6                                  | 78.9          |
| 170             | 0.05           | 0.0                                 | 94.5                                | 7.1                                  | 65.5          |
| 171             | 0.05           | 4.0                                 | 98.3                                | 10.8                                 | 15.8          |
| 172             | 0.05           | 13.2                                | 97.9                                | 19.4                                 | 27.1          |
| 173             | 0.05           | 8.3                                 | 97.7                                | 14.8                                 | 12.2          |
| 174             | 0.05           | 0.0                                 | 97.0                                | 7.1                                  | 72.7          |
| 175             | 0.05           | 4.9                                 | 97.9                                | 11.6                                 | 80.0          |
| 176             | 0.05           | 8.8                                 | 98.2                                | 15.2                                 | 61.4          |
| 177             | 0.05           | 12.5                                | 95.2                                | 18.7                                 | 91.0          |
| 178             | 0.05           | 8.5                                 | 98.3                                | 15.0                                 | 59.3          |
| 179             | 0.05           | 18.7                                | 98.0                                | 24.4                                 | 35.1          |
| 180             | 0.05           | 10.8                                | 95.1                                | 17.1                                 | 43.9          |
| 181             | 0.05           | 16.0                                | 97.6                                | 22.0                                 | 90.5          |
| 182             | 0.05           | 0.0                                 | 97.6                                | 7.1                                  | 74.6          |
| 183             | 0.05           | 0.0                                 | 96.7                                | 7.1                                  | 66.7          |
| 184             | 0.05           | 7.1                                 | 97.0                                | 13.7                                 | 70.9          |
| 185             | 0.05           | 0.0                                 | 95.2                                | 7.1                                  | 54.6          |
| 186             | 0.05           | 0.0                                 | 97.6                                | 7.1                                  | 61.8          |
| 187             | 0.05           | 20.7                                | 97.5                                | 26.3                                 | 92.7          |
| 188             | 0.05           | 7.9                                 | 96.5                                | 14.5                                 | 74.6          |
| 189             | 0.05           | 19.2                                | 95.9                                | 24.9                                 | 72.7          |
| 190             | 0.05           | 5.6                                 | 95.7                                | 12.3                                 | 70.9          |
| 191             | 0.05           | 15.4                                | 98.1                                | 21.4                                 | 29.8          |
| 192             | 0.05           | 7.8                                 | 94.7                                | 14.3                                 | 84.2          |
| 193             | 0.05           | 0.0                                 | 95.1                                | 7.1                                  | 80.0          |
| 194             | 0.05           | 16.1                                | 96.9                                | 22.0                                 | 80.4          |
| 195             | 0.05           | 19.2                                | 97.9                                | 24.9                                 | 89.5          |
| 196             | 0.05           | 4.4                                 | 97.7                                | 11.2                                 | 94.5          |
| 197             | 0.05           | 0.0                                 | 97.1                                | 7.1                                  | 43.7          |
| 198             | 0.05           | 11.8                                | 97.7                                | 18.1                                 | 75.4          |
| 199             | 0.05           | 4.0                                 | 98.0                                | 10.8                                 | 56.1          |
| 200             | 0.05           | 0.0                                 | 95.0                                | 7.1                                  | 78.9          |
| 201             | 0.05           | 4.0                                 | 96.0                                | 10.8                                 | 50.9          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 202             | 0.05           | 2.0                                 | 96.6                                | 9.0                                  | 49.1          |
| 203             | 0.05           | 6.9                                 | 95.7                                | 13.5                                 | 56.4          |
| 204             | 0.05           | 7.3                                 | 95.5                                | 13.8                                 | 77.2          |
| 205             | 0.05           | 15.4                                | 97.2                                | 21.5                                 | 78.9          |
| 206             | 0.05           | 16.4                                | 98.4                                | 22.3                                 | 80.7          |
| 207             | 0.05           | 0.0                                 | 95.3                                | 7.1                                  | 52.7          |
| 208             | 0.05           | 5.4                                 | 97.0                                | 12.1                                 | 32.8          |
| 209             | 0.05           | 17.6                                | 95.9                                | 23.4                                 | 67.3          |
| 210             | 0.05           | 1.9                                 | 94.1                                | 8.9                                  | 37.0          |
| 211             | 0.05           | 7.0                                 | 97.1                                | 13.6                                 | 16.0          |
| 212             | 0.05           | 0.0                                 | 95.2                                | 7.1                                  | 14.0          |
| 213             | 0.05           | 3.7                                 | 98.8                                | 10.6                                 | 56.1          |
| 214             | 0.05           | 7.0                                 | 98.0                                | 13.6                                 | 60.0          |
| 215             | 0.05           | 0.5                                 | 98.6                                | 7.5                                  | 37.0          |
| 216             | 0.05           | 6.3                                 | 98.4                                | 12.9                                 | 57.9          |
| 217             | 0.05           | 0.0                                 | 92.7                                | 7.1                                  | 0.0           |
| 218             | 0.05           | 0.0                                 | 92.5                                | 7.1                                  | 70.9          |
| 219             | 0.05           | 34.5                                | 97.9                                | 39.2                                 | 68.4          |
| 220             | 0.05           | 0.0                                 | 95.3                                | 7.1                                  | 89.1          |
| 221             | 0.05           | 0.0                                 | 92.4                                | 7.1                                  | 66.0          |
| 222             | 0.05           | 0.0                                 | 94.5                                | 7.1                                  | 67.3          |
| 223             | 0.05           | 26.9                                | 97.2                                | 32.1                                 | 54.0          |
| 224             | 0.05           | 0.0                                 | 91.0                                | 7.1                                  | 67.3          |
| 225             | 0.05           | 0.0                                 | 96.6                                | 7.1                                  | 78.2          |
| 226             | 0.05           | 0.0                                 | 94.5                                | 7.1                                  | 71.0          |
| 227             | 0.05           | 5.0                                 | 95.0                                | 11.7                                 | 52.7          |
| 228             | 0.05           | 2.6                                 | 97.0                                | 9.6                                  | 68.4          |
| 229             | 0.05           | 6.0                                 | 98.0                                | 12.7                                 | 70.9          |
| 230             | 0.05           | 9.0                                 | 98.3                                | 15.5                                 | 65.0          |
| 231             | 0.05           | 0.0                                 | 98.5                                | 7.1                                  | 81.3          |
| 232             | 0.05           | 2.3                                 | 97.5                                | 9.3                                  | 57.6          |
| 233             | 0.05           | 5.6                                 | 98.1                                | 12.3                                 | 88.1          |
| 234             | 0.05           | 0.0                                 | 94.3                                | 7.1                                  | 72.9          |
| 235             | 0.05           | 0.0                                 | 96.3                                | 7.1                                  | 80.0          |
| 236             | 0.05           | 3.5                                 | 97.0                                | 10.4                                 | 88.1          |
| 237             | 0.05           | 0.0                                 | 91.8                                | 7.1                                  | 45.0          |
| 238             | 0.05           | 0.5                                 | 97.6                                | 7.5                                  | 92.5          |
| 239             | 0.05           | 0.1                                 | 97.8                                | 7.2                                  | 66.1          |
| 240             | 0.05           | 0.0                                 | 98.1                                | 7.1                                  | 74.6          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 241             | 0.05           | 0.5                                 | 97.0                                | 7.5                                  | 62.7          |
| 242             | 0.05           | 6.9                                 | 98.0                                | 13.5                                 | 78.0          |
| 243             | 0.05           | 5.3                                 | 96.7                                | 12.1                                 | 86.4          |
| 244             | 0.05           | 0.0                                 | 96.1                                | 7.1                                  | 62.7          |
| 245             | 0.05           | 0.0                                 | 96.7                                | 7.1                                  | 52.7          |
| 246             | 0.05           | 0.0                                 | 95.3                                | 7.1                                  | 50.9          |
| 247             | 0.05           | 10.1                                | 94.0                                | 16.5                                 | 84.7          |
| 248             | 0.05           | 12.4                                | 96.3                                | 18.7                                 | 98.0          |
| 249             | 0.05           | 27.8                                | 95.8                                | 32.9                                 | 100.0         |
| 250             | 0.05           | 8.7                                 | 98.1                                | 15.2                                 | 97.0          |
| 251             | 0.05           | 3.5                                 | 98.1                                | 10.3                                 | 33.0          |
| 252             | 0.05           | 7.8                                 | 98.4                                | 14.4                                 | 28.0          |
| 253             | 0.05           | 4.9                                 | 98.0                                | 11.6                                 | 14.0          |
| 254             | 0.05           | 8.3                                 | 98.1                                | 14.8                                 | 0.0           |
| 255             | 0.05           | 3.6                                 | 98.2                                | 10.4                                 | 28.0          |
| 256             | 0.05           | 3.0                                 | 98.7                                | 9.8                                  | 18.0          |
| 257             | 0.05           | 6.0                                 | 94.4                                | 12.6                                 | 21.0          |
| 258             | 0.05           | 34.1                                | 97.4                                | 38.8                                 | 87.0          |
| 259             | 0.05           | 9.9                                 | 97.9                                | 16.3                                 | 32.0          |
| 260             | 0.05           | 11.2                                | 97.1                                | 17.5                                 | 81.0          |
| 261             | 0.05           | 2.7                                 | 97.9                                | 9.6                                  | 10.0          |
| 262             | 0.05           | 3.1                                 | 94.0                                | 9.9                                  | 4.6           |
| 263             | 0.05           | 4.1                                 | 97.9                                | 10.9                                 | 14.0          |
| 264             | 0.05           | 6.0                                 | 98.4                                | 12.7                                 | 21.0          |
| 265             | 0.05           | 0.0                                 | 98.1                                | 7.1                                  | 15.0          |
| 266             | 0.05           | 4.5                                 | 95.4                                | 11.3                                 | 28.0          |
| 267             | 0.05           | 5.7                                 | 98.3                                | 12.4                                 | 33.0          |
| 268             | 0.05           | 1.2                                 | 98.7                                | 8.2                                  | 31.0          |
| 269             | 0.05           | 0.0                                 | 98.8                                | 7.1                                  | 21.0          |
| 270             | 0.05           | 6.9                                 | 98.6                                | 13.5                                 | 61.0          |
| 271             | 0.05           | 6.9                                 | 98.9                                | 13.5                                 | 61.0          |
| 272             | 0.05           | 2.0                                 | 98.1                                | 8.9                                  | 37.0          |
| 273             | 0.05           | 0.4                                 | 97.7                                | 7.5                                  | 44.0          |
| 274             | 0.05           | 0.0                                 | 96.3                                | 7.1                                  | 89.0          |
| 275             | 0.05           | 0.0                                 | 98.4                                | 7.1                                  | 79.7          |
| 276             | 0.05           | 5.5                                 | 97.8                                | 12.2                                 | 71.2          |
| 277             | 0.05           | 1.9                                 | 97.5                                | 8.9                                  | 86.4          |
| 278             | 0.05           | 1.7                                 | 97.7                                | 8.7                                  | 90.0          |
| 279             | 0.05           | 5.1                                 | 98.6                                | 11.8                                 | 96.0          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 280             | 0.05           | 2.2                                 | 98.2                                | 9.1                                  | 88.0          |
| 281             | 0.05           | 1.4                                 | 98.4                                | 8.4                                  | 67.0          |
| 282             | 0.05           | 0.0                                 | 94.7                                | 7.1                                  | 52.0          |
| 283             | 0.05           | 0.0                                 | 95.9                                | 7.1                                  | 67.0          |
| 284             | 0.05           | 0.0                                 | 97.1                                | 7.1                                  | 74.0          |
| 285             | 0.05           | 3.4                                 | 97.5                                | 10.3                                 | 51.0          |
| 286             | 0.05           | 2.3                                 | 98.4                                | 9.2                                  | 75.0          |
| 287             | 0.05           | 0.0                                 | 98.3                                | 7.1                                  | 65.0          |
| 288             | 0.05           | 1.8                                 | 98.2                                | 8.8                                  | 26.0          |
| 289             | 0.05           | 0.0                                 | 97.6                                | 7.1                                  | 45.0          |
| 290             | 0.05           | 0.4                                 | 95.5                                | 7.5                                  | 21.0          |
| 291             | 0.05           | 2.2                                 | 95.4                                | 9.2                                  | 67.0          |
| 292             | 0.05           | 5.0                                 | 97.6                                | 11.7                                 | 21.0          |
| 293             | 0.05           | 7.9                                 | 95.7                                | 14.4                                 | 19.0          |
| 294             | 0.05           | 1.7                                 | 94.2                                | 8.7                                  | 72.9          |
| 295             | 0.05           | 5.8                                 | 98.0                                | 12.5                                 | 89.8          |
| 296             | 0.05           | 8.3                                 | 97.7                                | 14.8                                 | 84.7          |
| 297             | 0.05           | 0.0                                 | 96.4                                | 7.1                                  | 69.5          |
| 298             | 0.05           | 0.7                                 | 95.0                                | 7.8                                  | 74.6          |
| 299             | 0.05           | 0.0                                 | 97.9                                | 7.1                                  | 74.0          |
| 300             | 0.05           | 0.0                                 | 97.2                                | 7.1                                  | 70.0          |
| 301             | 0.05           | 0.0                                 | 97.9                                | 7.1                                  | 82.0          |
| 302             | 0.05           | 0.0                                 | 96.4                                | 7.1                                  | 82.0          |
| 303             | 0.05           | 0.0                                 | 98.0                                | 7.1                                  | 45.0          |
| 304             | 0.05           | 0.0                                 | 97.9                                | 7.1                                  | 77.0          |
| 305             | 0.05           | 0.5                                 | 98.3                                | 7.5                                  | 61.0          |
| 306             | 0.05           | 0.0                                 | 95.2                                | 7.1                                  | 35.0          |
| 307             | 0.05           | 0.0                                 | 91.3                                | 7.1                                  | 25.0          |
| 308             | 0.05           | 37.2                                | 97.7                                | 41.6                                 | 96.0          |
| 309             | 0.05           | 5.5                                 | 97.4                                | 12.2                                 | 74.0          |
| 310             | 0.05           | 2.4                                 | 96.6                                | 9.3                                  | 64.0          |
| 311             | 0.05           | 3.3                                 | 98.3                                | 10.2                                 | 37.0          |
| 312             | 0.05           | 3.8                                 | 97.8                                | 10.6                                 | 1.4           |
| 313             | 0.05           | 8.5                                 | 98.5                                | 15.0                                 | 28.0          |
| 314             | 0.05           | 0.0                                 | 97.7                                | 7.1                                  | 8.8           |
| 315             | 0.05           | 2.7                                 | 95.8                                | 9.6                                  | 18.0          |
| 316             | 0.05           | 4.5                                 | 97.1                                | 11.3                                 | 14.0          |
| 317             | 0.05           | 16.3                                | 97.9                                | 22.3                                 | 24.0          |
| 318             | 0.05           | 3.1                                 | 97.3                                | 10.0                                 | 71.2          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 319             | 0.05           | 18.1                                | 96.6                                | 23.9                                 | 78.0          |
| 320             | 0.05           | 17.1                                | 96.4                                | 23.0                                 | 100.0         |
| 321             | 0.05           | 11.7                                | 96.6                                | 18.0                                 | 100.0         |
| 322             | 0.05           | 20.9                                | 97.9                                | 26.5                                 | 95.0          |
| 323             | 0.05           | 16.1                                | 98.1                                | 22.1                                 | 100.0         |
| 324             | 0.05           | 2.3                                 | 96.3                                | 9.2                                  | 98.0          |
| 325             | 0.05           | 0.0                                 | 95.7                                | 7.1                                  | 100.0         |
| 326             | 0.05           | 6.9                                 | 95.6                                | 13.5                                 | 93.0          |
| 327             | 0.05           | 1.2                                 | 95.7                                | 8.3                                  | 98.0          |
| 328             | 0.05           | 0.0                                 | 95.1                                | 7.1                                  | 99.0          |
| 329             | 0.05           | 14.0                                | 93.5                                | 20.1                                 | 99.0          |
| 330             | 0.05           | 5.3                                 | 92.9                                | 12.1                                 | 99.0          |
| 331             | 0.05           | 22.8                                | 97.8                                | 28.2                                 | 100.0         |
| 332             | 0.05           | 2.0                                 | 93.9                                | 8.9                                  | 89.0          |
| 333             | 0.05           | 16.2                                | 93.2                                | 22.1                                 | 85.0          |
| 334             | 0.05           | 10.9                                | 97.8                                | 17.2                                 | 98.0          |
| 335             | 0.05           | 10.2                                | 96.8                                | 16.6                                 | 95.0          |
| 336             | 0.05           | 16.6                                | 97.8                                | 22.5                                 | 98.0          |
| 337             | 0.05           | 22.4                                | 98.0                                | 27.9                                 | 97.0          |
| 338             | 0.05           | 9.0                                 | 98.1                                | 15.5                                 | 96.0          |
| 339             | 0.05           | 1.5                                 | 95.4                                | 8.5                                  | 100.0         |
| 340             | 0.05           | 18.0                                | 96.2                                | 23.8                                 | 95.0          |
| 341             | 0.05           | 1.2                                 | 88.9                                | 8.2                                  | 63.0          |
| 342             | 0.05           | 9.1                                 | 98.3                                | 15.6                                 | 86.0          |
| 343             | 0.05           | 2.8                                 | 95.4                                | 9.7                                  | 97.0          |
| 344             | 0.05           | 31.5                                | 91.8                                | 36.4                                 | 100.0         |
| 345             | 0.05           | 18.8                                | 97.9                                | 24.6                                 | 97.0          |
| 346             | 0.05           | 30.0                                | 96.7                                | 34.9                                 | 96.0          |
| 347             | 0.05           | 13.8                                | 98.4                                | 19.9                                 | 97.0          |
| 348             | 0.05           | 16.3                                | 98.3                                | 22.2                                 | 100.0         |
| 349             | 0.05           | 17.4                                | 96.9                                | 23.3                                 | 97.0          |
| 350             | 0.05           | 11.3                                | 94.9                                | 17.6                                 | 97.0          |
| 351             | 0.05           | 7.7                                 | 96.1                                | 14.3                                 | 100.0         |
| 352             | 0.05           | 8.8                                 | 98.4                                | 15.3                                 | 100.0         |
| 353             | 0.05           | 0.0                                 | 94.8                                | 7.1                                  | 81.0          |
| 354             | 0.05           | 18.4                                | 95.4                                | 24.2                                 | 98.0          |
| 355             | 0.05           | 19.6                                | 89.8                                | 25.3                                 | 87.0          |
| 356             | 0.05           | 18.6                                | 98.0                                | 24.4                                 | 93.0          |
| 357             | 0.05           | 56.7                                | 97.4                                | 59.7                                 | 93.0          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 358             | 0.05           | 12.7                                | 98.3                                | 18.9                                 | 100.0         |
| 359             | 0.05           | 41.4                                | 97.3                                | 45.6                                 | 92.0          |
| 360             | 0.05           | 17.6                                | 96.9                                | 23.4                                 | 97.0          |
| 361             | 0.05           | 3.3                                 | 96.4                                | 10.2                                 | 97.0          |
| 362             | 0.05           | 11.1                                | 97.2                                | 17.4                                 | 97.0          |
| 363             | 0.05           | 4.3                                 | 94.7                                | 11.1                                 | 92.0          |
| 364             | 0.05           | 8.4                                 | 95.8                                | 14.9                                 | 97.0          |
| 365             | 0.05           | 13.8                                | 95.6                                | 19.9                                 | 95.0          |
| 366             | 0.05           | 14.2                                | 96.6                                | 20.3                                 | 100.0         |
| 367             | 0.05           | 13.1                                | 97.9                                | 19.2                                 | 95.0          |
| 368             | 0.05           | 0.0                                 | 96.9                                | 7.1                                  | 98.0          |
| 369             | 0.05           | 7.0                                 | 95.5                                | 13.6                                 | 98.0          |
| 370             | 0.05           | 3.5                                 | 97.5                                | 10.4                                 | 91.0          |
| 371             | 0.05           | 12.6                                | 96.1                                | 18.8                                 | 98.0          |
| 372             | 0.05           | 15.1                                | 97.4                                | 21.1                                 | 98.0          |
| 373             | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 90.0          |
| 374             | 0.05           | 11.1                                | 98.2                                | 17.4                                 | 98.0          |
| 375             | 0.05           | 7.2                                 | 98.2                                | 13.7                                 | 90.0          |
| 376             | 0.05           | 13.6                                | 96.5                                | 19.8                                 | 98.0          |
| 377             | 0.05           | 29.9                                | 97.6                                | 34.9                                 | 100.0         |
| 378             | 0.05           | 26.3                                | 98.4                                | 31.6                                 | 97.0          |
| 379             | 0.05           | 26.7                                | 98.2                                | 31.9                                 | 100.0         |
| 380             | 0.05           | 36.1                                | 98.3                                | 40.6                                 | 100.0         |
| 381             | 0.05           | 31.8                                | 98.6                                | 36.6                                 | 100.0         |
| 382             | 0.05           | 19.3                                | 98.5                                | 25.0                                 | 96.0          |
| 383             | 0.05           | 20.3                                | 95.7                                | 25.9                                 | 100.0         |
| 384             | 0.05           | 28.6                                | 95.8                                | 33.6                                 | 100.0         |
| 385             | 0.05           | 5.4                                 | 94.6                                | 12.1                                 | 100.0         |
| 386             | 0.05           | 41.1                                | 98.4                                | 45.3                                 | 100.0         |
| 387             | 0.05           | 13.5                                | 96.9                                | 19.6                                 | 87.0          |
| 388             | 0.05           | 17.2                                | 98.1                                | 23.1                                 | 61.0          |
| 389             | 0.05           | 7.7                                 | 97.6                                | 14.2                                 | 95.0          |
| 390             | 0.05           | 4.2                                 | 97.5                                | 11.0                                 | 95.0          |
| 391             | 0.05           | 6.0                                 | 96.9                                | 12.7                                 | 92.0          |
| 392             | 0.05           | 15.8                                | 97.9                                | 21.8                                 | 46.0          |
| 393             | 0.05           | 4.3                                 | 96.1                                | 11.1                                 | 73.0          |
| 394             | 0.05           | 8.0                                 | 95.9                                | 14.6                                 | 71.0          |
| 395             | 0.05           | 8.2                                 | 93.9                                | 14.8                                 | 76.0          |
| 396             | 0.05           | 0.0                                 | 95.5                                | 7.1                                  | 49.0          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 397             |                | NT                                  | NT                                  | NT                                   | 6.7           |
| 398             | 0.05           | 5.4                                 | 94.7                                | 12.1                                 | 98.0          |
| 399             | 0.05           | 5.8                                 | 97.1                                | 12.5                                 | 88.0          |
| 400             | 0.05           | 0.5                                 | 97.9                                | 7.6                                  | 96.0          |
| 401             | 0.05           | 0.0                                 | 94.8                                | 7.1                                  | 98.0          |
| 402             | 0.05           | 0.0                                 | 95.2                                | 7.1                                  | 100.0         |
| 403             | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 97.0          |
| 404             | 0.05           | 0.0                                 | 94.9                                | 7.1                                  | 97.0          |
| 405             | 0.05           | 2.8                                 | 96.2                                | 9.7                                  | 98.0          |
| 406             | 0.05           | 6.7                                 | 96.1                                | 13.3                                 | 98.0          |
| 407             | 0.05           | 0.0                                 | 92.0                                | 7.1                                  | 70.0          |
| 408             | 0.05           | 8.4                                 | 79.7                                | 14.9                                 | 94.0          |
| 409             | 0.05           | 7.9                                 | 96.3                                | 14.4                                 | 98.0          |
| 410             | 0.05           | 1.9                                 | 97.6                                | 8.9                                  | 95.0          |
| 411             | 0.05           | 8.2                                 | 97.9                                | 14.7                                 | 85.0          |
| 412             | 0.05           | 7.7                                 | 97.8                                | 14.3                                 | 100.0         |
| 413             | 0.05           | 18.9                                | 97.9                                | 24.7                                 | 94.0          |
| 414             | 0.05           | 14.6                                | 97.9                                | 20.7                                 | 90.0          |
| 415             | 0.05           | 2.9                                 | 96.1                                | 9.8                                  | 100.0         |
| 416             | 0.05           | 4.3                                 | 97.5                                | 11.1                                 | 93.0          |
| 417             | 0.05           | 10.7                                | 98.2                                | 17.0                                 | 100.0         |
| 418             | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 93.0          |
| 419             | 0.05           | 3.2                                 | 94.9                                | 10.1                                 | 90.0          |
| 420             | 0.05           | 11.4                                | 97.5                                | 17.7                                 | 100.0         |
| 421             | 0.05           | 8.2                                 | 96.6                                | 14.7                                 | 94.0          |
| 422             | 0.05           | 0.0                                 | 95.5                                | 7.1                                  | 90.0          |
| 423             | 0.05           | 0.8                                 | 98.0                                | 7.9                                  | 98.0          |
| 424             | 0.05           | 22.3                                | 97.0                                | 27.8                                 | 100.0         |
| 425             | 0.05           | 17.5                                | 97.6                                | 23.4                                 | 95.0          |
| 426             | 0.05           | 34.8                                | 97.3                                | 39.5                                 | 98.0          |
| 427             | 0.05           | 26.1                                | 97.9                                | 31.3                                 | 98.0          |
| 428             | 0.05           | 44.1                                | 98.4                                | 48.1                                 | 97.0          |
| 429             | 0.05           | 10.4                                | 97.4                                | 16.8                                 | 94.0          |
| 430             | 0.05           | 16.6                                | 98.2                                | 22.5                                 | 100.0         |
| 431             | 0.05           | 8.5                                 | 95.1                                | 15.0                                 | 91.0          |
| 432             | 0.05           | 0.0                                 | 95.9                                | 7.1                                  | 72.0          |
| 433             | 0.05           | 10.8                                | 97.8                                | 17.2                                 | 100.0         |
| 434             | 0.05           | 25.6                                | 97.4                                | 30.9                                 | 100.0         |
| 435             | 0.05           | 4.7                                 | 97.2                                | 11.5                                 | 100.0         |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 436             | 0.05           | 14.6                                | 98.2                                | 20.7                                 | 94.0          |
| 437             | 0.05           | 9.2                                 | 97.0                                | 15.6                                 | 100.0         |
| 438             | 0.05           | 0.0                                 | 94.2                                | 7.1                                  | 98.0          |
| 439             | 0.05           | 0.0                                 | 100.0                               | 7.1                                  | 96.0          |
| 440             | 0.05           | 2.9                                 | 100.0                               | 9.8                                  | 98.0          |
| 441             | 0.05           | 0.0                                 | 100.0                               | 7.1                                  | 96.0          |
| 442             | 0.05           | 0.0                                 | 100.0                               | 7.1                                  | 98.0          |
| 443             | 0.05           | 14.6                                | 100.0                               | 20.7                                 | 83.0          |
| 444             | 0.05           | 0.0                                 | 100.0                               | 7.1                                  | 91.0          |
| 445             | 0.05           | 13.2                                | 100.0                               | 19.4                                 | 90.0          |
| 446             | 0.05           | 23.5                                | 95.4                                | 29.0                                 | 57.0          |
| 447             | 0.05           | 20.0                                | 96.6                                | 25.7                                 | 100.0         |
| 448             | 0.05           | 27.1                                | 97.5                                | 32.3                                 | 100.0         |
| 449             | 0.05           | 7.2                                 | 98.5                                | 13.8                                 | 92.0          |
| 450             | 0.05           | 1.1                                 | 93.5                                | 8.1                                  | 100.0         |
| 451             | 0.05           | 4.6                                 | 100.0                               | 11.4                                 | 100.0         |
| 452             | 0.05           | 12.9                                | 100.0                               | 19.1                                 | 100.0         |
| 453             | 0.05           | 5.6                                 | 100.0                               | 12.3                                 | 100.0         |
| 454             | 0.05           | 12.4                                | 100.0                               | 18.6                                 | 100.0         |
| 455             | 0.05           | 16.7                                | 100.0                               | 22.6                                 | 100.0         |
| 456             | 0.05           | 0.0                                 | 100.0                               | 7.1                                  | 100.0         |
| 457             | 0.05           | 6.7                                 | 100.0                               | 13.3                                 | 100.0         |
| 458             | 0.05           | 3.7                                 | 96.6                                | 10.6                                 | 46.0          |
| 459             | 0.05           | 7.3                                 | 96.9                                | 13.8                                 | 20.0          |
| 460             | 0.05           | 0.0                                 | 97.6                                | 7.1                                  | 39.0          |
| 461             | 0.05           | 3.4                                 | 96.7                                | 10.3                                 | 54.0          |
| 462             | 0.05           | 0.0                                 | 95.0                                | 7.1                                  | 86.0          |
| 463             | 0.05           | 5.1                                 | 96.3                                | 11.9                                 | 61.0          |
| 464             | 0.05           | 6.7                                 | 94.8                                | 13.4                                 | 93.0          |
| 465             | 0.05           | 1.7                                 | 96.5                                | 8.6                                  | 93.0          |
| 466             | 0.05           | 2.7                                 | 97.9                                | 9.6                                  | 69.0          |
| 467             | 0.05           | 0.0                                 | 95.7                                | 7.1                                  | 80.0          |
| 468             | 0.05           | 6.2                                 | 98.1                                | 12.8                                 | 92.0          |
| 469             | 0.05           | 1.0                                 | 97.8                                | 8.1                                  | 95.0          |
| 470             | 0.05           | 4.0                                 | 98.0                                | 10.8                                 | 93.0          |
| 471             | 0.05           | 7.9                                 | 97.8                                | 14.4                                 | 83.0          |
| 472             | 0.05           | 0.0                                 | 97.7                                | 7.1                                  | 49.0          |
| 473             | 0.05           | 0.0                                 | 97.5                                | 7.1                                  | 78.0          |
| 474             | 0.05           | 39.2                                | 97.6                                | 43.5                                 | 100.0         |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 475             | 0.05           | 33.8                                | 97.1                                | 38.5                                 | 100.0         |
| 476             | 0.05           | 0.0                                 | 93.9                                | 7.1                                  | 69.0          |
| 477             | 0.05           | 6.2                                 | 83.4                                | 12.8                                 | 93.0          |
| 478             | 0.05           | 0.7                                 | 94.7                                | 7.7                                  | 65.0          |
| 479             | 0.05           | 0.0                                 | 97.5                                | 7.1                                  | 97.0          |
| 480             | 0.05           | 9.5                                 | 95.3                                | 15.9                                 | 4.7           |
| 481             | 0.05           | 10.3                                | 97.8                                | 16.7                                 | 76.0          |
| 482             | 0.05           | 0.0                                 | 96.4                                | 7.1                                  | 66.0          |
| 483             | 0.05           | 0.0                                 | 97.9                                | 7.1                                  | 63.0          |
| 484             | 0.05           | 12.6                                | 93.2                                | 18.8                                 | 88.0          |
| 485             | 0.05           | 8.0                                 | 96.7                                | 14.5                                 | 95.0          |
| 486             | 0.05           | 12.8                                | 96.6                                | 19.0                                 | 95.0          |
| 487             | 0.05           | 11.2                                | 93.9                                | 17.5                                 | 100.0         |
| 488             | 0.05           | 20.1                                | 92.6                                | 25.7                                 | 72.0          |
| 489             | 0.05           | 15.8                                | 97.8                                | 21.8                                 | 85.0          |
| 490             | 0.05           | 31.5                                | 97.0                                | 36.4                                 | 55.0          |
| 491             | 0.05           | 25.0                                | 97.5                                | 30.3                                 | 75.0          |
| 492             | 0.05           | 0.0                                 | 98.1                                | 7.1                                  | 93.0          |
| 493             | 0.05           | 0.0                                 | 97.8                                | 7.1                                  | 95.0          |
| 494             | 0.05           | 0.0                                 | 97.7                                | 7.1                                  | 96.0          |
| 495             | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 91.0          |
| 496             | 0.05           | 0.7                                 | 97.8                                | 7.8                                  | 94.0          |
| 497             | 0.05           | 0.0                                 | 98.1                                | 7.1                                  | 75.0          |
| 498             | 0.05           | 0.0                                 | 97.5                                | 7.1                                  | 85.0          |
| 499             | 0.05           | 0.0                                 | 97.4                                | 7.1                                  | 85.0          |
| 500             | 0.05           | 9.2                                 | 93.2                                | 15.6                                 | 80.0          |
| 501             | 0.05           | 0.5                                 | 98.0                                | 7.6                                  | 89.0          |
| 502             | 0.05           | 4.2                                 | 97.2                                | 11.0                                 | 85.0          |
| 503             | 0.05           | 5.2                                 | 97.0                                | 11.9                                 | 66.0          |
| 504             | 0.05           | 1.3                                 | 97.6                                | 8.3                                  | 94.0          |
| 505             | 0.05           | 7.1                                 | 97.3                                | 13.7                                 | 46.0          |
| 506             | 0.05           | 2.7                                 | 97.5                                | 9.6                                  | 44.0          |
| 507             | 0.05           | 7.6                                 | 97.0                                | 14.1                                 | 66.0          |
| 508             | 0.05           | 9.4                                 | 97.1                                | 15.9                                 | 92.0          |
| 509             | 0.05           | 0.0                                 | 96.2                                | 7.1                                  | 85.0          |
| 510             | 0.05           | 6.2                                 | 95.5                                | 12.8                                 | 56.0          |
| 511             | 0.05           | 0.0                                 | 97.8                                | 7.1                                  | 73.0          |
| 512             | 0.05           | 7.4                                 | 97.8                                | 13.9                                 | 59.0          |
| 513             | 0.05           | 14.0                                | 98.0                                | 20.1                                 | 53.0          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 514             | 0.05           | 0.0                                 | 97.7                                | 7.1                                  | 75.0          |
| 515             | 0.05           | 0.0                                 | 97.6                                | 7.1                                  | 47.0          |
| 516             | 0.05           | 0.0                                 | 97.9                                | 7.1                                  | 59.0          |
| 517             | 0.05           | 0.0                                 | 96.7                                | 7.1                                  | 56.0          |
| 518             | 0.05           | 24.2                                | 97.4                                | 29.6                                 | 58.0          |
| 519             | 0.05           | 9.1                                 | 95.7                                | 15.6                                 | 88.0          |
| 520             | 0.05           | 14.9                                | 96.7                                | 20.9                                 | 49.0          |
| 521             | 0.05           | 5.0                                 | 95.9                                | 11.8                                 | 83.0          |
| 522             | 0.05           | 9.4                                 | 97.3                                | 15.9                                 | 95.0          |
| 523             | 0.05           | 7.0                                 | 97.7                                | 13.6                                 | 92.0          |
| 524             | 0.05           | 9.3                                 | 95.8                                | 15.7                                 | 39.0          |
| 525             | 0.05           | 5.4                                 | 97.4                                | 12.1                                 | 78.0          |
| 526             | 0.05           | 1.8                                 | 16.2                                | 8.7                                  | 41.0          |
| 527             | 0.05           | 7.6                                 | 97.6                                | 14.2                                 | 78.0          |
| 528             | 0.05           | 8.7                                 | 97.7                                | 15.2                                 | 73.0          |
| 529             | 0.05           | 15.3                                | 97.7                                | 21.3                                 | 46.0          |
| 530             | 0.05           | 9.8                                 | 96.2                                | 16.2                                 | 59.0          |
| 531             | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 80.0          |
| 532             | 0.05           | 4.9                                 | 91.4                                | 11.7                                 | 56.0          |
| 533             | 0.05           | 6.2                                 | 97.0                                | 12.9                                 | 34.0          |
| 534             | 0.05           | 5.1                                 | 95.7                                | 11.9                                 | 61.0          |
| 535             | 0.05           | 10.1                                | 97.7                                | 16.5                                 | 56.0          |
| 536             | 0.05           | 21.1                                | 93.4                                | 26.7                                 | 24.0          |
| 537             | 0.05           | 12.2                                | 96.2                                | 18.5                                 | 90.0          |
| 538             | 0.05           | 12.4                                | 96.5                                | 18.6                                 | 44.0          |
| 539             | 0.05           | 1.6                                 | 98.0                                | 8.6                                  | 100.0         |
| 540             | 0.05           | 0.0                                 | 97.5                                | 7.1                                  | 95.0          |
| 541             | 0.05           | 0.0                                 | 97.5                                | 7.1                                  | 93.0          |
| 542             | 0.05           | 0.0                                 | 95.8                                | 7.1                                  | 100.0         |
| 543             | 0.05           | 1.3                                 | 93.9                                | 8.3                                  | 100.0         |
| 544             | 0.05           | 6.9                                 | 97.6                                | 13.5                                 | 97.0          |
| 545             | 0.05           | 19.6                                | 97.9                                | 25.3                                 | 95.0          |
| 546             | 0.05           | 7.6                                 | 97.7                                | 14.2                                 | 100.0         |
| 547             | 0.05           | 10.8                                | 97.7                                | 17.1                                 | 88.0          |
| 548             | 0.05           | 6.7                                 | 97.5                                | 13.3                                 | 98.0          |
| 549             | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 94.0          |
| 550             | 0.05           | 4.6                                 | 97.2                                | 11.4                                 | 63.0          |
| 551             | 0.05           | 1.7                                 | 96.0                                | 8.7                                  | 90.0          |
| 552             | 0.05           | 0.0                                 | 94.2                                | 7.1                                  | 71.0          |

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| Compound Number | Concn. (µg/mL) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|-----------------|----------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| 553             | 0.05           | 0.0                                 | 93.2                                | 7.1                                  | 88.0          |
| 554             | 0.05           | 0.0                                 | 97.3                                | 7.1                                  | 100.0         |
| 555             | 0.05           | 3.7                                 | 92.5                                | 10.5                                 | 46.0          |
| 556             | 0.05           | 7.7                                 | 95.9                                | 14.2                                 | 75.0          |
| 557             | 0.05           | 13.0                                | 95.7                                | 19.2                                 | 90.0          |
| 558             | 0.05           | 3.8                                 | 95.7                                | 10.6                                 | 80.0          |
| 559             | 0.05           | 10.0                                | 97.3                                | 16.4                                 | 93.0          |
| 560             | 0.05           | 1.3                                 | 90.7                                | 8.3                                  | 65.0          |
| 561             | 0.05           | 0.0                                 | 92.2                                | 7.1                                  | 60.0          |
| 562             | 0.05           | 1.4                                 | 97.3                                | 8.4                                  | 91.0          |
| 563             | 0.05           | 20.6                                | 96.9                                | 26.2                                 | 70.0          |
| 564             | 0.05           | 17.4                                | 94.2                                | 23.3                                 | 1.3           |
| 565             | 0.05           | 12.2                                | 97.4                                | 18.4                                 | 98.0          |
| 566             | 0.05           | 6.8                                 | 95.9                                | 13.4                                 | 70.0          |
| 567             | 0.05           | 2.5                                 | 42.3                                | 9.5                                  | 14.0          |
| 568             | 0.05           | 8.0                                 | 94.3                                | 14.6                                 | 61.0          |
| 569             | 0.05           | 6.1                                 | 15.8                                | 12.7                                 | 70.0          |
| 570             | 0.05           | 3.2                                 | 97.2                                | 10.1                                 | 39.0          |
| 571             | 0.05           | 0.0                                 | 84.7                                | 7.1                                  | 31.0          |
| 572             | 0.05           | 2.5                                 | 97.4                                | 9.5                                  | 94.0          |
| 573             | 0.05           | 2.4                                 | 98.4                                | 9.3                                  | 93.0          |
| 574             | 0.05           | 2.8                                 | 98.3                                | 9.7                                  | 93.0          |
| 575             | 0.05           | 0.0                                 | 98.1                                | 7.1                                  | 100.0         |
| 576             | 0.05           | 0.7                                 | 97.9                                | 7.7                                  | 90.0          |
| 577             | 0.05           | 1.9                                 | 97.9                                | 8.8                                  | 100.0         |
| 578             | 0.05           | 7.2                                 | 98.0                                | 13.8                                 | 100.0         |
| 579             | 0.05           | 0.0                                 | 97.6                                | 7.1                                  | 97.0          |
| 580             | 0.05           | 3.1                                 | 98.1                                | 10.0                                 | 97.0          |
| 581             | 0.05           | 13.6                                | 98.2                                | 19.7                                 | 93.0          |
| 582             | 0.05           | 12.2                                | 97.8                                | 18.4                                 | 94.0          |
| 583             | 0.05           | 13.2                                | 98.0                                | 19.4                                 | 100.0         |
| 584             | 0.05           | 3.0                                 | 11.8                                | 9.9                                  | 7.6           |
| 585             | 0.05           | 6.3                                 | 86.3                                | 13.0                                 | 62.0          |
| 586             | 0.05           | 0.0                                 | 87.3                                | 7.1                                  | 31.0          |
| 587             | 0.05           | 6.2                                 | 96.6                                | 12.8                                 | 2.4           |
| 588             | 0.05           | 7.6                                 | 96.3                                | 14.2                                 | 5.6           |
| 589             | 0.05           | 8.7                                 | 97.9                                | 15.2                                 | 61.0          |
| 590             | 0.05           | 10.0                                | 98.6                                | 16.4                                 | 88.0          |
| 591             | 0.05           | 0.0                                 | 9.9                                 | 7.1                                  | 11.0          |

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| Compound Number                    | Concn. ( $\mu\text{g/mL}$ ) | LEPTNO %Inhn. Minus Copper Observed | LEPTNO % Inhn. Plus Copper Observed | LEPTNO % Inhn. Plus Copper Predicted | TLB % Control |
|------------------------------------|-----------------------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------|
| <b>592</b>                         | 0.05                        | 0.0                                 | 25.4                                | 7.1                                  | 1.4           |
| CuCl <sub>2</sub> 10 $\mu\text{M}$ |                             |                                     | 7.1 $\pm$ 6.0                       |                                      |               |

NT = not tested

**Example 28. Effect of copper on fungitoxicity of hydrazones towards *Phytophthora capsici***

**[0082]** *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 CuSO<sub>4</sub>, was omitted. The medium, termed “copper-minus AS”, was prepared by dissolving 2 g asparagine, 0.43 g KH<sub>2</sub>PO<sub>4</sub>, 0.3 g K<sub>2</sub>HPO<sub>4</sub>, 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 MgSO<sub>4</sub>·7H<sub>2</sub>O (100  $\mu\text{g/mL}$ ), FeSO<sub>4</sub>·7H<sub>2</sub>O (1  $\mu\text{g/mL}$ ), CaCl<sub>2</sub> (50  $\mu\text{g/mL}$ ), ZnSO<sub>4</sub>·7H<sub>2</sub>O (1  $\mu\text{g/mL}$ ), NaMoO<sub>4</sub>·2H<sub>2</sub>O (0.2  $\mu\text{g/mL}$ ) and MnCl<sub>2</sub>·4H<sub>2</sub>O (0.2  $\mu\text{g/mL}$ ) were added and the entire medium was sterilized by filtration. “Copper-plus AS” medium was prepared by adding CuCl<sub>2</sub>·2H<sub>2</sub>O to the copper-minus AS medium at 100  $\mu\text{M}$ . Test compounds were dissolved in DMSO then dilutions in copper-minus AS and copper-plus AS media were prepared as 100  $\mu\text{L}$  aliquots in flat-bottomed 96-well microtiter plates.

**[0083]** *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 CaCO<sub>3</sub>, 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  $5 \times 10^4$  spores/mL by dilution into Chelex 100-treated water. Microtiter plates were inoculated with 100  $\mu\text{L}$  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.

**[0084]** 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 (µg/mL) | %Inhn Minus copper Observed | %Inhn Plus copper Observed | %Inhn Plus copper Predicted |
|-----------------|-----------------------|-----------------------------|----------------------------|-----------------------------|
| <b>1</b>        | 0.039                 | 9.7                         | 87.2                       | 13.8                        |
| <b>3</b>        | 0.039                 | 0.0                         | 88.5                       | 4.5                         |
| <b>5</b>        | 0.039                 | 18.6                        | 93.9                       | 22.3                        |
| <b>6</b>        | 0.039                 | 28.8                        | 95.8                       | 32.0                        |
| <b>14</b>       | 0.039                 | 0.0                         | 87.2                       | 4.5                         |
| <b>15</b>       | 0.039                 | 80.4                        | 91.8                       | 81.2                        |
| <b>16</b>       | 0.050                 | 0.0                         | 91.9                       | 4.5                         |
| <b>20</b>       | 0.050                 | 2.1                         | 90.4                       | 6.5                         |
| <b>21</b>       | 0.039                 | 0.0                         | 90.0                       | 4.5                         |
| <b>23</b>       | 0.039                 | 10.8                        | 93.8                       | 14.8                        |
| <b>24</b>       | 0.039                 | 10.2                        | 92.4                       | 14.2                        |
| <b>28</b>       | 0.039                 | 11.4                        | 93.8                       | 15.4                        |
| <b>43</b>       | 0.039                 | 54.2                        | 90.3                       | 56.2                        |
| <b>52</b>       | 0.039                 | 40.6                        | 91.2                       | 43.3                        |
| <b>56</b>       | 0.039                 | 57.5                        | 94.1                       | 59.4                        |
| <b>60</b>       | 0.050                 | 4.1                         | 76.4                       | 8.4                         |
| <b>61</b>       | 0.039                 | 17.6                        | 95.6                       | 21.3                        |
| <b>69</b>       | 0.050                 | 0.0                         | 87.6                       | 4.5                         |
| <b>74</b>       | 5                     | 17.2                        | 89.4                       | 20.9                        |
| <b>83</b>       | 0.039                 | 27.9                        | 96.2                       | 31.1                        |

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| Compound Number | Concentration<br>( $\mu\text{g/mL}$ ) | %Inhn<br>Minus<br>copper<br>Observed | %Inhn<br>Plus copper<br>Observed | %Inhn<br>Plus copper<br>Predicted |
|-----------------|---------------------------------------|--------------------------------------|----------------------------------|-----------------------------------|
| <b>84</b>       | 0.039                                 | 47.5                                 | 95.0                             | 49.8                              |
| <b>91</b>       | 0.039                                 | 52.1                                 | 93.2                             | 54.3                              |
| <b>96</b>       | 0.039                                 | 55.2                                 | 91.9                             | 57.2                              |
| <b>99</b>       | 0.039                                 | 23.6                                 | 94.0                             | 27.1                              |
| <b>100</b>      | 0.039                                 | 10.0                                 | 88.8                             | 14.0                              |
| <b>101</b>      | 0.039                                 | 70.0                                 | 88.2                             | 71.4                              |
| <b>102</b>      | 0.039                                 | 15.7                                 | 93.6                             | 19.4                              |
| <b>119</b>      | 0.039                                 | 37.9                                 | 95.1                             | 40.7                              |
| <b>121</b>      | 0.050                                 | 0.0                                  | 90.4                             | 4.5                               |
| <b>123</b>      | 0.039                                 | 16.3                                 | 94.8                             | 20.0                              |
| <b>124</b>      | 0.039                                 | 25.0                                 | 89.7                             | 28.3                              |
| <b>125</b>      | 0.039                                 | 66.6                                 | 89.4                             | 68.1                              |
| <b>129</b>      | 0.039                                 | 10.6                                 | 96.3                             | 14.6                              |
| <b>131</b>      | 0.039                                 | 5.6                                  | 93.7                             | 9.9                               |
| <b>140</b>      | 0.050                                 | 0.0                                  | 91.4                             | 4.5                               |
| <b>143</b>      | 0.039                                 | 6.0                                  | 94.5                             | 10.3                              |
| <b>146</b>      | 0.039                                 | 11.8                                 | 91.4                             | 15.8                              |
| <b>162</b>      | 0.050                                 | 5.2                                  | 91.6                             | 9.5                               |
| <b>177</b>      | 0.050                                 | 0.0                                  | 92.4                             | 4.5                               |
| <b>182</b>      | 0.039                                 | 25.9                                 | 90.9                             | 29.2                              |
| <b>183</b>      | 0.039                                 | 0.0                                  | 88.9                             | 4.5                               |
| <b>204</b>      | 0.050                                 | 6.0                                  | 81.9                             | 10.2                              |
| <b>207</b>      | 0.039                                 | 0.0                                  | 88.9                             | 4.5                               |
| <b>210</b>      | 0.039                                 | 36.6                                 | 92.7                             | 39.4                              |
| <b>218</b>      | 0.050                                 | 10.7                                 | 93.3                             | 14.7                              |
| <b>219</b>      | 0.050                                 | 15.3                                 | 90.6                             | 19.1                              |
| <b>220</b>      | 0.050                                 | 13.4                                 | 85.5                             | 17.3                              |
| <b>221</b>      | 0.050                                 | 12.0                                 | 92.2                             | 15.9                              |
| <b>222</b>      | 0.050                                 | 11.3                                 | 76.8                             | 15.3                              |
| <b>223</b>      | 0.050                                 | 2.5                                  | 51.3                             | 6.9                               |
| <b>224</b>      | 0.050                                 | 6.2                                  | 93.3                             | 10.4                              |
| <b>225</b>      | 0.050                                 | 11.4                                 | 82.8                             | 15.4                              |
| <b>226</b>      | 0.050                                 | 2.3                                  | 62.1                             | 6.7                               |
| <b>227</b>      | 0.050                                 | 1.7                                  | 93.4                             | 6.2                               |
| <b>228</b>      | 0.050                                 | 10.0                                 | 86.9                             | 14.0                              |

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| Compound Number           | Concentration (µg/mL) | %Inhn Minus copper Observed | %Inhn Plus copper Observed | %Inhn Plus copper Predicted |
|---------------------------|-----------------------|-----------------------------|----------------------------|-----------------------------|
| <b>229</b>                | 0.050                 | 1.6                         | 89.1                       | 6.0                         |
| <b>230</b>                | 0.050                 | 5.8                         | 93.6                       | 10.1                        |
| <b>275</b>                | 0.050                 | 0.0                         | 91.2                       | 4.5                         |
| <b>277</b>                | 0.050                 | 0.0                         | 88.2                       | 4.5                         |
| <b>320</b>                | 0.050                 | 2.9                         | 81.4                       | 7.3                         |
| <b>337</b>                | 0.050                 | 4.7                         | 42.1                       | 9.0                         |
| <b>351</b>                | 0.050                 | 0.0                         | 87.9                       | 4.5                         |
| <b>364</b>                | 0.050                 | 0.0                         | 23.2                       | 4.5                         |
| <b>369</b>                | 0.050                 | 0.0                         | 44.5                       | 4.5                         |
| <b>384</b>                | 0.050                 | 0.0                         | 71.1                       | 4.5                         |
| <b>405</b>                | 0.050                 | 0.6                         | 85.9                       | 5.1                         |
| <b>427</b>                | 0.050                 | 9.1                         | 88.6                       | 13.2                        |
| <b>443</b>                | 0.050                 | 2.4                         | 91.2                       | 6.8                         |
| <b>455</b>                | 0.050                 | 0.0                         | 30.8                       | 4.5                         |
| <b>578</b>                | 0.050                 | 2.8                         | 90.4                       | 7.2                         |
| CuCl <sub>2</sub> , 50 µM |                       | 4.5 ± 7.9                   |                            |                             |

**Example 29. Effect of copper on fungitoxicity of hydrazones towards *Ustilago maydis***

**[0085]** *In vitro* fungitoxicity assays against *Ustilago maydis* were conducted using the copper-minus medium described in Example 26. Medium containing copper was prepared by adding CuCl<sub>2</sub>•2H<sub>2</sub>O to the copper-minus medium at 20 µM. Test compounds were dissolved in dimethylsulfoxide (DMSO) at 200 µg/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.

**[0086]** *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 x 10<sup>5</sup> 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 48 h

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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.

**[0087]** Results for growth inhibition by test compounds at 1 µg/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 |
|-----------------|------------------------------|-----------------------------|------------------------------|
| <b>16</b>       | 0.0                          | 80.0                        | 11.9                         |
| <b>20</b>       | 1.2                          | 91.0                        | 12.9                         |
| <b>60</b>       | 0.0                          | 93.5                        | 11.9                         |
| <b>69</b>       | 0.0                          | 96.2                        | 11.9                         |
| <b>121</b>      | 0.0                          | 96.9                        | 11.9                         |
| <b>140</b>      | 0.0                          | 95.7                        | 11.9                         |
| <b>162</b>      | 8.8                          | 96.4                        | 19.7                         |
| <b>177</b>      | 0.0                          | 33.3                        | 11.9                         |
| <b>204</b>      | 0.0                          | 77.0                        | 11.9                         |
| <b>230</b>      | 11.9                         | 94.4                        | 22.4                         |
| <b>275</b>      | 0.0                          | 92.2                        | 11.9                         |
| <b>277</b>      | 1.7                          | 83.5                        | 13.4                         |
| <b>320</b>      | 0.0                          | 95.2                        | 11.9                         |
| <b>329</b>      | 16.2                         | 41.8                        | 26.2                         |
| <b>337</b>      | 22.0                         | 97.8                        | 31.3                         |
| <b>351</b>      | 27.1                         | 97.7                        | 35.8                         |
| <b>364</b>      | 65.5                         | 92.9                        | 69.6                         |
| <b>369</b>      | 3.1                          | 93.6                        | 14.7                         |
| <b>384</b>      | 13.6                         | 96.6                        | 23.9                         |
| <b>405</b>      | 9.6                          | 90.0                        | 20.4                         |

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| Compound Number                | %Inhn. Minus copper Observed | %Inhn. Plus copper Observed | %Inhn. Plus copper Predicted |
|--------------------------------|------------------------------|-----------------------------|------------------------------|
| <b>427</b>                     | 34.3                         | 89.3                        | 42.1                         |
| <b>443</b>                     | 10.2                         | 35.3                        | 20.9                         |
| <b>455</b>                     | 0.0                          | 96.0                        | 11.9                         |
| <b>578</b>                     | 47.4                         | 93.8                        | 53.6                         |
| CuCl <sub>2</sub> , 10 $\mu$ M |                              | 11.9                        |                              |

**Example 30. Effect of copper on fungitoxicity of hydrazones towards *Septoria tritici***

**[0088]** *In vitro* fungitoxicity assays against *Septoria tritici* were conducted using the copper-minus medium described in Example 26. Medium containing copper was prepared by adding CuCl<sub>2</sub>•2H<sub>2</sub>O to the copper-minus medium at 2  $\mu$ M. Test compounds were dissolved in dimethylsulfoxide (DMSO) at 10  $\mu$ g/mL and 1  $\mu$ L aliquots were added to two wells of flat-bottomed 96-well microtiter plates. Copper-minus medium (100  $\mu$ L) was added to one of the wells and copper-plus medium to the second well. Control wells, included for each medium, received 1  $\mu$ L DMSO and 100  $\mu$ L of medium.

**[0089]** *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  $1 \times 10^5$  spores per mL. Microtiter plate wells containing test compound of DMSO (control) as described above were inoculated with 100  $\mu$ L 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.

**[0090]** Results for growth inhibition by test compounds at 0.05  $\mu$ 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

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determined by comparing growth in copper-minus and copper-plus media without any test compound. In this experiment, copper chloride alone (1  $\mu$ M) 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 |
|-------------------------------|-----------------------------------|----------------------------------|-----------------------------------|
| <b>16</b>                     | 35.8                              | 93.6                             | 35.8                              |
| <b>20</b>                     | 0.0                               | 95.3                             | 0.0                               |
| <b>60</b>                     | 20.6                              | 94.8                             | 20.6                              |
| <b>69</b>                     | 0.0                               | 96.7                             | 0.0                               |
| <b>121</b>                    | 9.7                               | 96.5                             | 9.7                               |
| <b>140</b>                    | 0.0                               | 96.6                             | 0.0                               |
| <b>162</b>                    | 36.3                              | 97.1                             | 36.3                              |
| <b>177</b>                    | 0.2                               | 95.2                             | 0.2                               |
| <b>204</b>                    | 0.0                               | 84.4                             | 0.0                               |
| <b>230</b>                    | 43.6                              | 96.7                             | 43.6                              |
| <b>275</b>                    | 16.2                              | 93.5                             | 16.2                              |
| <b>277</b>                    | 3.6                               | 88.0                             | 3.6                               |
| <b>320</b>                    | 9.5                               | 92.1                             | 9.5                               |
| <b>329</b>                    | 14.9                              | 55.1                             | 14.9                              |
| <b>337</b>                    | 46.8                              | 97.1                             | 46.8                              |
| <b>351</b>                    | 44.4                              | 97.1                             | 44.4                              |
| <b>364</b>                    | 22.4                              | 93.7                             | 22.4                              |
| <b>369</b>                    | 9.3                               | 93.2                             | 9.3                               |
| <b>384</b>                    | 57.5                              | 97.0                             | 57.5                              |
| <b>405</b>                    | 18.8                              | 89.9                             | 18.8                              |
| <b>427</b>                    | 43.8                              | 96.7                             | 43.8                              |
| <b>443</b>                    | 5.8                               | 92.0                             | 5.8                               |
| <b>455</b>                    | 27.5                              | 92.4                             | 27.5                              |
| <b>578</b>                    | 26.7                              | 90.7                             | 26.7                              |
| CuCl <sub>2</sub> , 1 $\mu$ M |                                   | 0                                |                                   |

**Example 31. Comparative efficacy of isolated metal-hydrazone complexes and parent hydrazones towards *Leptosphaeria nodorum***

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**[0091]** Hydrazones and their isolated metal complexes were compared with respect to their *in vitro* fungitoxicity towards LEPTNO. Metal complexes of hydrazones were prepared by precipitation from ethanol with various metal salts, at 1:1, 2:1 or 3:1 molar ratios, 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).

**[0092]** 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 Et<sub>2</sub>O. In the instances where the complex does not precipitate, the solvent is removed and the resulting solid metal-hydrazone complex is washed with Et<sub>2</sub>O. Properties of particular metal complexes of hydrazones are provided in Table 6 below.

Table 6.

| Complex Number | Compound Number | Metal Salt                                             | Ratio Hydrazone:Metal Salt | Description       | mp (°C) |
|----------------|-----------------|--------------------------------------------------------|----------------------------|-------------------|---------|
| <b>593</b>     | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 1:1                        | brown black solid | 199–202 |
| <b>594</b>     | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 2:1                        | dark green solid  | 258–260 |
| <b>595</b>     | 78              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 3:1                        | dark green solid  | 258–261 |
| <b>596</b>     | 16              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1                        | dark green solid  |         |
| <b>597</b>     | 16              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 2:1                        | tan solid         | 310–312 |
| <b>598</b>     | 16              | CuSO <sub>4</sub> •5H <sub>2</sub> O                   | 1:1                        | dark green solid  | 307–308 |
| <b>599</b>     | 16              | CuSO <sub>4</sub> •5H <sub>2</sub> O                   | 2:1                        | dark green solid  | 310–312 |

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| Complex Number | Compound Number | Metal Salt                                             | Ratio<br>Hydrazone:Metal<br>Salt | Description                  | mp (°C) |
|----------------|-----------------|--------------------------------------------------------|----------------------------------|------------------------------|---------|
| <b>600</b>     | 16              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | light green<br>olive solid   | 311–312 |
| <b>601</b>     | 16              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 2:1                              | light green<br>solid         | 288–290 |
| <b>602</b>     | 69              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | olive-<br>brown<br>solid     | 250–255 |
| <b>603</b>     | 84              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | olive green<br>solid         | 278–280 |
| <b>604</b>     | 83              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | olive<br>brown<br>solid      | 282–285 |
| <b>605</b>     | 77              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | olive green<br>solid         | 273–274 |
| <b>606</b>     | 96              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | olive green<br>solid         | 258–260 |
| <b>607</b>     | 70              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | olive<br>brown<br>glass      | 278–279 |
| <b>608</b>     | 43              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | green black<br>solid         | 310–312 |
| <b>609</b>     | 76              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | brown<br>solid               | 272–273 |
| <b>610</b>     | 100             | $\text{Cu}(\text{OCOCH}_3)_2 \cdot \text{H}_2\text{O}$ | 1:1                              | brown<br>black solid         | 315–317 |
| <b>611</b>     | 16              | $\text{MnCl}_2$                                        | 2:1                              | mustard-<br>colored<br>solid | 250     |
| <b>612</b>     | 16              | $\text{ZnCl}_2$                                        | 2:1                              | yellow-<br>green solid       | 250     |
| <b>613</b>     | 299             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | dark green<br>solid          | 160–163 |
| <b>614</b>     | 300             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | dark green<br>solid          | 129–132 |
| <b>615</b>     | 301             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$              | 1:1                              | dark brown<br>solid          | 73–78   |

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| Complex Number | Compound Number | Metal Salt                                | Ratio<br>Hydrazone:Metal<br>Salt | Description       | mp (°C) |
|----------------|-----------------|-------------------------------------------|----------------------------------|-------------------|---------|
| <b>616</b>     | 302             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | dark green solid  | 167–170 |
| <b>617</b>     | 303             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | dark green solid  | 137–139 |
| <b>618</b>     | 304             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | dark green solid  | 177–225 |
| <b>619</b>     | 305             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | dark brown solid  | 201–211 |
| <b>620</b>     | 16              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 293–302 |
| <b>621</b>     | 151             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 283–294 |
| <b>622</b>     | 238             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 299–308 |
| <b>623</b>     | 231             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 260–275 |
| <b>624</b>     | 233             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 286–290 |
| <b>625</b>     | 20              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 286–288 |
| <b>626</b>     | 236             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 259–263 |
| <b>627</b>     | 277             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 286–289 |
| <b>628</b>     | 320             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 280–286 |
| <b>629</b>     | 68              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 226–228 |
| <b>630</b>     | 159             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 224–235 |
| <b>631</b>     | 359             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 240–254 |
| <b>632</b>     | 370             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 257–267 |

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| Complex Number | Compound Number | Metal Salt                                | Ratio<br>Hydrazone:Metal<br>Salt | Description       | mp (°C) |
|----------------|-----------------|-------------------------------------------|----------------------------------|-------------------|---------|
| <b>633</b>     | 428             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 212–270 |
| <b>634</b>     | 392             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 262–293 |
| <b>635</b>     | 348             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 295–305 |
| <b>636</b>     | 440             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 259–281 |
| <b>637</b>     | 337             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 279–281 |
| <b>638</b>     | 381             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 279–281 |
| <b>639</b>     | 452             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 270–274 |
| <b>640</b>     | 69              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 298–299 |
| <b>641</b>     | 151             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 287–289 |
| <b>642</b>     | 172             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 311–313 |
| <b>643</b>     | 403             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 296–297 |
| <b>644</b>     | 60              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 215–219 |
| <b>645</b>     | 137             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 207–211 |
| <b>646</b>     | 278             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 242–246 |
| <b>647</b>     | 279             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 236–239 |
| <b>648</b>     | 67              | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 176–87  |
| <b>649</b>     | 135             | $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ | 1:1                              | olive green solid | 245–248 |

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| Complex Number | Compound Number | Metal Salt                                             | Ratio<br>Hydrazone:Metal<br>Salt | Description       | mp (°C) |
|----------------|-----------------|--------------------------------------------------------|----------------------------------|-------------------|---------|
| <b>650</b>     | 136             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1                              | olive green solid | 242–247 |
| <b>651</b>     | 411             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1                              | olive green solid | 292–295 |
| <b>652</b>     | 412             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1                              | olive green solid | 309–310 |
| <b>653</b>     | 68              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1                              | brown-black solid | >350    |

**[0093]** *In vitro* fungitoxicity assays were conducted using the copper-minus medium described in Example 26. 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  $2 \times 10^5$  spores per mL, prepared as in Example 26. 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.

**[0094]** Results for growth inhibition by hydrazones and corresponding isolated metal complexes (each at 0.1 µg/mL) are shown in Table 7. The results illustrate that isolated Cu complexes of hydrazones are much more fungitoxic than the corresponding hydrazones and also are much more active than isolated Fe, Mn and Zn complexes of hydrazones.

Table 7.

| Complex Number | Compound Number | Metal Salt                                             | Ratio* | Hydrazone<br>% Inhibition | Complex<br>% Inhibition |
|----------------|-----------------|--------------------------------------------------------|--------|---------------------------|-------------------------|
| <b>593</b>     | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 1:1    | 10.6                      | 7.1                     |
| <b>594</b>     | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 2:1    | 10.6                      | 4.9                     |
| <b>595</b>     | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 3:1    | 10.6                      | 3.1                     |
| <b>596</b>     | 16              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 19.9                      | 98.4                    |
| <b>597</b>     | 16              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 2:1    | 19.9                      | 94.6                    |
| <b>599</b>     | 16              | CuSO <sub>4</sub> •5H <sub>2</sub> O                   | 2:1    | 19.9                      | 97.3                    |
| <b>600</b>     | 16              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 19.9                      | 95.3                    |

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| Complex Number | Compound Number | Metal Salt                                             | Ratio* | Hydrazone % Inhibition | Complex % Inhibition |
|----------------|-----------------|--------------------------------------------------------|--------|------------------------|----------------------|
| 601            | 16              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 2:1    | 19.9                   | 97.0                 |
| 602            | 69              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 32.4                   | 94.9                 |
| 603            | 84              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 6.7                    | 95.6                 |
| 604            | 83              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 27.9                   | 95.1                 |
| 605            | 77              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 10.6                   | 97.2                 |
| 606            | 96              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 10.7                   | 90.3                 |
| 607            | 70              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 29.4                   | 48.3                 |
| 608            | 43              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 3.6                    | 21.2                 |
| 609            | 76              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 92.8                   | 95.5                 |
| 610            | 100             | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 24.7                   | 96.7                 |
| 611            | 16              | MnCl <sub>2</sub> •4H <sub>2</sub> O                   | 2:1    | 19.9                   | 31.3                 |
| 612            | 16              | ZnCl <sub>2</sub>                                      | 2:1    | 19.9                   | 21.4                 |
| 613            | 299             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 18.6                   | 96.3                 |
| 614            | 300             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 2.5                    | 66.9                 |
| 615            | 301             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 3.5                    | 87.3                 |
| 616            | 302             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 22.9                   | 95.5                 |
| 617            | 303             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 10.6                   | 88.0                 |
| 618            | 304             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 13.3                   | 94.1                 |
| 619            | 305             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 27.1                   | 96.3                 |
| 621            | 151             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 30.9                   | 97.4                 |
| 622            | 238             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 20.0                   | 97.5                 |
| 623            | 231             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 10.7                   | 98.0                 |
| 624            | 233             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 8.4                    | 96.8                 |
| 625            | 20              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 14.7                   | 96.9                 |
| 626            | 236             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 4.7                    | 94.9                 |
| 627            | 277             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0.6                    | 91.9                 |
| 628            | 320             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 22.1                   | 94.6                 |
| 629            | 68              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 7.1                    | 97.8                 |
| 630            | 159             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 27.4                   | 97.8                 |
| 631            | 359             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 24.1                   | 98.0                 |
| 632            | 370             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 23.1                   | 97.5                 |
| 633            | 428             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 29.9                   | 97.3                 |
| 634            | 392             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 22.8                   | 75.8                 |
| 635            | 348             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 23.9                   | 91.8                 |
| 636            | 440             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 23.8                   | 95.8                 |
| 637            | 337             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 39.9                   | 97.9                 |

| Complex Number | Compound Number | Metal Salt                                             | Ratio* | Hydrazone % Inhibition | Complex % Inhibition |
|----------------|-----------------|--------------------------------------------------------|--------|------------------------|----------------------|
| <b>638</b>     | 381             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 43.9                   | 97.1                 |
| <b>639</b>     | 452             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 19.3                   | 96.7                 |
| <b>641</b>     | 195             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 21.7                   | 95.2                 |
| <b>642</b>     | 172             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 28.7                   | 97.2                 |
| <b>643</b>     | 403             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 12.1                   | 93.9                 |
| <b>644</b>     | 60              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 23.3                   | 98.0                 |
| <b>645</b>     | 137             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 27.2                   | 97.7                 |
| <b>646</b>     | 278             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 16.2                   | 97.5                 |
| <b>647</b>     | 279             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 19.9                   | 96.9                 |
| <b>648</b>     | 67              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 4.2                    | 95.9                 |
| <b>649</b>     | 135             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 20.6                   | 96.0                 |
| <b>650</b>     | 136             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 34.7                   | 98.3                 |
| <b>651</b>     | 411             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 32.1                   | 97.5                 |
| <b>652</b>     | 412             | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 40.4                   | 97.0                 |
| <b>653</b>     | 68              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 7.1                    | 96.9                 |

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

**Example 32. Comparative efficacy of isolated Cu-hydrazone complexes and parent hydrazones against glume blotch of wheat (*Leptosphaeria nodorum*)**

**[0095]** Hydrazones and their copper complexes were compared with respect to their ability to control glume blotch of wheat. Compound formulation was accomplished by dissolving technical materials in acetone and adding 9 volumes de-ionized water containing 0.01% Triton® X-100.

**[0096]** Wheat (cultivar Yuma) was grown in a soilless peat-based potting mixture ("Metromix") until the seedlings were 10 – 20 cm tall. These plants were then sprayed to run-off with the test compound at a rate of 200 ppm. After 24 h, the test plants were inoculated by spraying with an aqueous suspension of LEPTNO spores and kept in a dew chamber overnight. The plants were then transferred to the greenhouse until disease developed in the untreated control plants. Results, shown in Table 8, show that copper complexes of hydrazones have higher fungicidal activity towards glume blotch than the corresponding hydrazones without copper.

Table 8.

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| Complex Number | Compound Number | Metal Salt                                             | Ratio* | Hydrazone % Control | Complex % Control |
|----------------|-----------------|--------------------------------------------------------|--------|---------------------|-------------------|
| <b>600</b>     | 16              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 41                  | 93                |
| <b>602</b>     | 69              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 25                  | 83                |
| <b>603</b>     | 84              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 37                  | 92                |
| <b>604</b>     | 83              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 38                  | 75                |
| <b>605</b>     | 77              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0                   | 75                |
| <b>606</b>     | 96              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0                   | 91                |
| <b>607</b>     | 70              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0                   | 91                |
| <b>608</b>     | 43              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0                   | 84                |
| <b>609</b>     | 76              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0                   | 97                |
| <b>610</b>     | 100             | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 0                   | 94                |

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

**Example 33. Effect of copper on fungitoxicity of metal-hydrazone complexes towards *Leptosphaeria nodorum***

**[0097]** *In vitro* fungitoxicity assays against LEPTNO were conducted using the copper-minus medium described in Example 26. Medium containing copper was prepared by adding CuCl<sub>2</sub>•2H<sub>2</sub>O to the copper minus medium at 20 μM. Test compounds were dissolved in dimethylsulfoxide (DMSO) then dilutions in copper-minus and copper-plus media 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 x 10<sup>5</sup> spores per mL, prepared as in Example 26. 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. 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 9. Results show that fungitoxicity of metal complexes of hydrazones towards LEPTNO is synergistically enhanced in the presence of added copper.

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Furthermore, the fungitoxicity of copper complexes of hydrazones is synergistically enhanced in the presence of added copper.

Table 9.

| Complex Number            | Compound Number | Metal salt                                             | Ratio* | Concn. (µg/mL) | %Inhn. Minus copper Observed | %Inhn. Plus copper Observed | %Inhn. Plus copper Predicted |
|---------------------------|-----------------|--------------------------------------------------------|--------|----------------|------------------------------|-----------------------------|------------------------------|
| <b>593</b>                | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 1:1    | 0.05           | 31.3                         | 93.7                        | 33.6                         |
| <b>594</b>                | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 2:1    | 0.05           | 0.8                          | 92.7                        | 4.1                          |
| <b>595</b>                | 77              | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 3:1    | 0.05           | 9.8                          | 93.3                        | 12.8                         |
| <b>596</b>                | 16              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 0.0125         | 4.5                          | 56.7                        | 7.7                          |
| <b>596</b>                | 16              | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 0.0125         | 6.4                          | 85.4                        | 9.5                          |
| <b>598</b>                | 16              | CuSO <sub>4</sub> •5H <sub>2</sub> O                   | 1:1    | 0.10           | 57.3                         | 91.2                        | 58.7                         |
| <b>599</b>                | 16              | CuSO <sub>4</sub> •5H <sub>2</sub> O                   | 2:1    | 0.0125         | 28.6                         | 55.2                        | 31.0                         |
| <b>600</b>                | 16              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0.0125         | 29.6                         | 84.3                        | 31.9                         |
| <b>601</b>                | 16              | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 2:1    | 0.0125         | 27.2                         | 68.9                        | 29.6                         |
| <b>611</b>                | 16              | MnCl <sub>2</sub> •4H <sub>2</sub> O                   | 2:1    | 0.05           | 36.6                         | 96.1                        | 38.8                         |
| <b>612</b>                | 16              | ZnCl <sub>2</sub>                                      | 2:1    | 0.05           | 36.3                         | 67.5                        | 38.5                         |
| CuCl <sub>2</sub> , 10 µM |                 |                                                        |        |                | 3.3                          |                             |                              |

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

#### Example 34. Effect of copper on fungitoxicity of metal-hydrazone complexes towards

##### *Phytophthora capsici*

**[0098]** *In vitro* fungitoxicity assays against *Phytophthora capsici* were conducted using the copper-minus AS medium described in Example 28. Medium containing copper was prepared by adding CuCl<sub>2</sub>•2H<sub>2</sub>O to the copper-minus AS medium at 100 µM. Test compounds were dissolved in dimethylsulfoxide (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. Microtiter plates were inoculated with 100 µL of zoospore suspension at a concentration of 5 x 10<sup>4</sup> spores per mL, prepared as in Example 28. The plates were incubated at 25 °C for 48 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader.

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Growth inhibition was determined by comparing growth in the presence of test compound with growth in control wells lacking test compound.

**[0099]** 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 and copper-plus media without any test compound across experiments. Data are presented in Table 10. Results show that fungitoxicity of metal complexes of hydrazones towards *Phytophthora capsici* is synergistically enhanced in the presence of added copper. Furthermore, the fungitoxicity of copper complexes of hydrazones is synergistically enhanced in the presence of added copper.

Table 10.

| Complex Number            | Compound Number | Metal salt                                             | Ratio* | Concn. (μg/mL) | %Inhn. Minus copper Observed | %Inhn. Plus copper Observed | %Inhn. Plus copper Predicted |
|---------------------------|-----------------|--------------------------------------------------------|--------|----------------|------------------------------|-----------------------------|------------------------------|
| <b>593</b>                | <b>77</b>       | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 1:1    | 0.025          | 7.0                          | 93.7                        | 11.3                         |
| <b>594</b>                | <b>77</b>       | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 2:1    | 0.025          | 0.0                          | 93.6                        | 4.6                          |
| <b>595</b>                | <b>77</b>       | FeCl <sub>3</sub> •6H <sub>2</sub> O                   | 3:1    | 0.025          | 0.0                          | 93.7                        | 4.6                          |
| <b>596</b>                | <b>16</b>       | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 0.0125         | 0.9                          | 95.4                        | 5.5                          |
| <b>596</b>                | <b>16</b>       | Cu(OCOCH <sub>3</sub> ) <sub>2</sub> •H <sub>2</sub> O | 1:1    | 0.025          | 10.1                         | 95.8                        | 14.3                         |
| <b>598</b>                | <b>16</b>       | CuSO <sub>4</sub> •5H <sub>2</sub> O                   | 1:1    | 0.025          | 0.0                          | 94.8                        | 4.6                          |
| <b>599</b>                | <b>16</b>       | CuSO <sub>4</sub> •5H <sub>2</sub> O                   | 2:1    | 0.025          | 8.4                          | 96.1                        | 12.6                         |
| <b>601</b>                | <b>16</b>       | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 2:1    | 0.025          | 4.1                          | 94.0                        | 8.5                          |
| <b>602</b>                | <b>16</b>       | CuCl <sub>2</sub> •2H <sub>2</sub> O                   | 1:1    | 0.025          | 12.7                         | 94.4                        | 16.7                         |
| <b>611</b>                | <b>16</b>       | MnCl <sub>2</sub> •4H <sub>2</sub> O                   | 2:1    | 0.025          | 9.3                          | 95.1                        | 13.5                         |
| <b>612</b>                | <b>16</b>       | ZnCl <sub>2</sub>                                      | 2:1    | 0.025          | 5.2                          | 90.2                        | 9.6                          |
| CuCl <sub>2</sub> , 50 μM |                 |                                                        |        | 0.025          | 4.6                          |                             |                              |

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

**Example 35. Fungitoxicity of copper-hydrazone mixtures containing different ratios of components towards *Leptosphaeria nodorum***

**[00100]** *In vitro* fungitoxicity assays against LEPTNO were conducted using the copper-minus medium described in Example 26. Mixtures containing hydrazone compound **16** at 200 nM and CuCl<sub>2</sub> at 0.2 μM (1:1 molar ratio), 0.8 μM (1:4 ratio), 12.5 μM (1:62.5 ratio) and 200 μM (1:1000 ratio) were prepared in copper-minus medium. Two-fold dilution series of these mixtures were then prepared in 100 μL aliquots of copper-minus medium in flat-bottomed 96-well microtiter plates. A suspension of LEPTNO spores in copper-minus medium at 2 x 10<sup>5</sup> spores per mL was prepared as in Example 26. Microtiter plates were inoculated with 100 μL of the spore suspension and the plates were incubated at 25 °C for 72 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader.

**[00101]** Growth inhibition was determined by comparing growth in the presence of copper-hydrazone mixture with growth in control wells lacking the copper-hydrazone mixture. EC50 values were calculated from dose-response curves, and are expressed as the amounts of hydrazone or copper in each test mixture at the rates providing 50% inhibition of growth as compared to a control lacking the copper-hydrazone mixture. Data are presented in Table 11. The results show that copper-hydrazone mixtures representing a wide range of molar ratios of copper:hydrazone are substantially more efficacious against LEPTNO than either hydrazone or copper alone.

Table 11.

| Hydrazone:Cu ratio                  | Amounts of hydrazone and CuCl <sub>2</sub><br>at EC50 values |                                |
|-------------------------------------|--------------------------------------------------------------|--------------------------------|
|                                     | Hydrazone<br>EC50 (nM)                                       | CuCl <sub>2</sub><br>EC50 (μM) |
| Hydrazone without CuCl <sub>2</sub> | >3200                                                        |                                |
| 1 to 1                              | 72.2                                                         | 0.072                          |
| 1 to 4                              | 43.0                                                         | 0.172                          |
| 1 to 62.5                           | 28.4                                                         | 1.77                           |
| 1 to 1000                           | 14.0                                                         | 14.0                           |
| CuCl <sub>2</sub> without hydrazone |                                                              | 117.9                          |

**Example 36. Fungitoxicity of copper-hydrazone mixtures containing different ratios of components towards *Phytophthora capsici***

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**[00102]** *In vitro* fungitoxicity assays against *Phytophthora capsici* were conducted using the copper-minus AS medium described in Example 28. Mixtures containing hydrazone compound **16** at 200 nM and CuCl<sub>2</sub>•2H<sub>2</sub>O at 0.2 μM (1:1 molar ratio), 0.8 μM (1:4 ratio), 3.2 μM (1:16 ratio), 12.5 μM (1:62.5 ratio), 50 μM (1:200 ratio) and 200 μM (1:1000 ratio) were prepared in copper-minus AS medium. Two-fold dilution series of these mixtures were then prepared in 100 μL aliquots of copper-minus AS medium in flat-bottomed 96-well microtiter plates. A suspension of *P. capsici* zoospores in Chelex-treated water at 5 x 10<sup>4</sup> spores per mL was prepared as in Example 28. Microtiter plates were inoculated with 100 μL of the spore suspension and incubated at 25 °C for 48 h before assessing fungal growth by measuring light scattering in a NepheloStar plate reader.

**[00103]** Growth inhibition was determined by comparing growth in the presence of copper-hydrazone mixture with growth in control wells lacking the copper-hydrazone mixture. EC50 values were calculated from dose-response curves, and are expressed as the amounts of hydrazone or copper in each test mixture at the rates providing 50% inhibition of growth as compared to a control lacking the copper-hydrazone mixture. Data are presented in Table 12. The results show that copper-hydrazone mixtures representing a wide range of molar ratios of copper:hydrazone are substantially more efficacious against *Phytophthora capsici* than either hydrazone or copper alone.

Table 12.

| Hydrazone:Cu ratio                  | Amounts of hydrazone and CuCl <sub>2</sub><br>at EC50 values |                                |
|-------------------------------------|--------------------------------------------------------------|--------------------------------|
|                                     | Hydrazone<br>EC50 (nM)                                       | CuCl <sub>2</sub><br>EC50 (μM) |
| Hydrazone without CuCl <sub>2</sub> | 143.2                                                        |                                |
| 1 to 1                              | 71.1                                                         | 0.071                          |
| 1 to 4                              | 47.1                                                         | 0.189                          |
| 1 to 16                             | 27.5                                                         | 0.441                          |
| 1 to 62.5                           | 16.6                                                         | 1.04                           |
| 1 to 250                            | 7.6                                                          | 1.90                           |
| 1 to 1000                           | 4.6                                                          | 4.56                           |
| CuCl <sub>2</sub> without hydrazone |                                                              | 720.0                          |

**Example 37. Synergistic effect between hydrazone compound 16 and various copper materials against tomato late blight (*Phytophthora infestans*), tomato early blight (*Alternaria solani*), and cucumber anthracnose (*Colletotrichum lagenarium*)**

**[00104]** Hydrazone compound **16** was tested alone or in combination with  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ , Kocide® 2000 (copper hydroxide), or CUREX 3 (tribasic copper sulfate). All materials and mixtures were evaluated as prophylactic treatments applied 24 h before inoculation. Efficacy was determined based on percentage of disease control against tomato late blight (*Phytophthora infestans*), tomato early blight (*Alternaria solani*), and anthracnose on cucumbers (*Colletotrichum lagenarium*). Treatments were arranged as a factorial experiment in a completely randomized design. Hydrazone and copper were regarded as factors with hydrazone at 10, 50, 200, and 400  $\mu\text{M}$ , and copper materials at 10, 50, 200, 400, and 800  $\mu\text{M}$  with respect to their copper content. All treatments were performed in triplicate. Plant varieties used were Outdoor Girl and Bush Pickle, for tomato and cucumber, respectively. Treatments were prepared in 0.01 % Triton® X-100 and applied to run-off 24 h before inoculation using a spin-table sprayer. Inoculation was performed with aqueous spore suspensions using a Delta painting sprayer. Percentage of disease control was determined 7 days after inoculation.

**[00105]** Results (Tables 13-24) for disease control by hydrazone-copper mixtures were compared with predicted values (shown in brackets) which were calculated using the Colby formula based on disease control by the hydrazone alone and copper material alone. The data show that hydrazone-copper mixtures provided greater disease control than predicted based on control delivered by the individual components of the mixtures.

Table 13. Synergistic fungicidal effect between hydrazone Compound **16** and  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  against tomato late blight (*Phytophthora infestans*)

| CuCl <sub>2</sub> (μM) | % Control of Tomato Late Blight |             |             |             |              |
|------------------------|---------------------------------|-------------|-------------|-------------|--------------|
|                        | Hydrazone (μM)                  |             |             |             |              |
|                        | 0                               | 10          | 50          | 200         | 400          |
| 0                      | 0.0                             | 1.5         | 11.3        | 21.4        | 25.7         |
| 10                     | 1.7                             | 33.5 (3.1)  | 41.9 (12.8) | 67.8 (22.7) | 64.4 (26.9)  |
| 50                     | 8.5                             | 39.7 (9.9)  | 63.0 (18.8) | 96.6 (28.1) | 91.7 (32.0)  |
| 200                    | 38.2                            | 69.0 (39.2) | 91.5 (45.2) | 95.8 (51.5) | 91.7 (54.1)  |
| 400                    | 56.0                            | 75.7 (56.6) | 91.7 (60.9) | 90.8 (65.4) | 99.8 (67.3)  |
| 800                    | 70.2                            | 94.2 (70.7) | 98.3 (73.6) | 96.7 (76.6) | 100.0 (77.9) |

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Table 14. Synergistic fungicidal effect between hydrazone Compound **16** and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  against tomato late blight (*Phytophthora infestans*)

|                                   | % Control of Tomato Late Blight |             |             |             |             |
|-----------------------------------|---------------------------------|-------------|-------------|-------------|-------------|
|                                   | Hydrazone ( $\mu\text{M}$ )     |             |             |             |             |
| $\text{CuSO}_4$ ( $\mu\text{M}$ ) | 0                               | 10          | 50          | 200         | 400         |
| 0                                 | 0                               | 1.5         | 11.3        | 21.4        | 25.7        |
| 10                                | 1.7                             | 26.3 (3.1)  | 56.8 (12.8) | 78.0 (22.7) | 41.5 (26.9) |
| 50                                | 4.8                             | 28.1 (6.2)  | 67.7 (15.5) | 81.3 (25.1) | 54.5 (29.2) |
| 200                               | 49.7                            | 56.0 (50.4) | 72.9 (55.4) | 93.2 (60.4) | 87.2 (62.6) |
| 400                               | 76.0                            | 77.3 (76.4) | 78.0 (78.8) | 95.8 (81.2) | 96.6 (82.2) |
| 800                               | 82.9                            | 72.2 (83.1) | 91.6 (84.8) | 97.5 (86.5) | 98.3 (87.3) |

Table 15. Synergistic fungicidal effect between hydrazone Compound **16** and Kocide® 2000 against tomato late blight (*Phytophthora infestans*)

|                           | % Control of Tomato Late Blight |             |             |             |             |
|---------------------------|---------------------------------|-------------|-------------|-------------|-------------|
|                           | Hydrazone ( $\mu\text{M}$ )     |             |             |             |             |
| Kocide® ( $\mu\text{M}$ ) | 0                               | 10          | 50          | 200         | 400         |
| 0                         | 0                               | 1.5         | 11.3        | 21.4        | 25.7        |
| 10                        | 5.8                             | 26.8 (7.2)  | 41.2 (16.4) | 53.4 (26.0) | 65.3 (30.0) |
| 50                        | 6.8                             | 43.1 (8.2)  | 46.4 (17.3) | 77.3 (26.7) | 79.6 (30.8) |
| 200                       | 30.4                            | 51.6 (31.4) | 65.8 (38.3) | 94.8 (45.3) | 93.2 (48.3) |
| 400                       | 63.1                            | 64.9 (63.7) | 78.3 (67.3) | 89.9 (71.0) | 94.9 (72.6) |
| 800                       | 67.4                            | 80.8 (67.9) | 95.6 (71.1) | 100 (74.4)  | 100 (75.8)  |

Table 16. Synergistic fungicidal effect between hydrazone Compound **16** and CUREX 3 against tomato late blight (*Phytophthora infestans*)

|                           | % Control of Tomato Late Blight |             |             |             |             |
|---------------------------|---------------------------------|-------------|-------------|-------------|-------------|
|                           | Hydrazone ( $\mu\text{M}$ )     |             |             |             |             |
| CUREX 3 ( $\mu\text{M}$ ) | 0                               | 10          | 50          | 200         | 400         |
| 0                         | 0                               | 1.5         | 11.3        | 21.4        | 25.7        |
| 10                        | 0.0                             | 42.4 (1.5)  | 72.9 (11.3) | 77.9 (21.4) | 61.7 (25.7) |
| 50                        | 0.0                             | 61.0 (1.5)  | 88.0 (11.3) | 88.0 (21.4) | 85.5 (25.7) |
| 200                       | 26.2                            | 63.6 (27.3) | 88.9 (34.5) | 100.0(42.0) | 93.5 (45.1) |
| 400                       | 41.2                            | 77.3 (42.0) | 96.7 (47.8) | 96.7 (53.8) | 98.3 (56.3) |
| 800                       | 60.8                            | 89.8 (61.4) | 97.4 (65.3) | 99.5 (69.2) | 99.1 (70.9) |

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Table 17. Synergistic fungicidal effect between hydrazone Compound **16** and  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  against tomato early blight (*Alternaria solani*)

|                                   | % Control of Tomato Early Blight |             |             |             |             |
|-----------------------------------|----------------------------------|-------------|-------------|-------------|-------------|
|                                   | Hydrazone ( $\mu\text{M}$ )      |             |             |             |             |
| $\text{CuCl}_2$ ( $\mu\text{M}$ ) | 0                                | 10          | 50          | 200         | 400         |
| 0                                 | 0.0                              | 3.9         | 8.0         | 28.4        | 32.4        |
| 10                                | 0.0                              | 38.4 (3.9)  | 39.8 (8.0)  | 46.1 (28.4) | 59.2 (32.4) |
| 50                                | 0.0                              | 44.5 (3.9)  | 56.0 (8.0)  | 69.9 (28.4) | 86.3 (32.4) |
| 200                               | 50.4                             | 62.1 (52.4) | 73.2 (54.5) | 82.0 (64.5) | 94.7 (66.5) |
| 400                               | 72.5                             | 80.3 (73.6) | 79.7 (74.7) | 94.2 (80.3) | 98.1 (81.4) |
| 800                               | 83.3                             | 86.0 (83.9) | 89.6 (84.6) | 98.8 (88.0) | 98.3 (88.7) |

Table 18. Synergistic fungicidal effect between hydrazone Compound **16** and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  against tomato early blight (*Alternaria solani*)

|                                   | % Control of Tomato Early Blight |             |             |             |             |
|-----------------------------------|----------------------------------|-------------|-------------|-------------|-------------|
|                                   | Hydrazone ( $\mu\text{M}$ )      |             |             |             |             |
| $\text{CuSO}_4$ ( $\mu\text{M}$ ) | 0                                | 10          | 50          | 200         | 400         |
| 0                                 | 0                                | 3.9         | 8.0         | 28.4        | 32.4        |
| 10                                | 0.0                              | 48.7 (3.9)  | 53.8 (8.0)  | 55.6 (28.4) | 54.7 (32.4) |
| 50                                | 7.1                              | 53.0 (10.7) | 70.5 (14.5) | 74.6 (33.5) | 80.9 (37.2) |
| 200                               | 54.4                             | 66.0 (56.2) | 83.0 (58.1) | 89.7 (67.4) | 89.4 (69.2) |
| 400                               | 64.1                             | 82.1 (65.5) | 89.5 (67.0) | 93.3 (74.3) | 96.8 (75.7) |
| 800                               | 71.6                             | 83.5 (72.7) | 93.0 (73.9) | 96.0 (79.7) | 97.7 (80.8) |

Table 19. Synergistic fungicidal effect between hydrazone Compound **16** and Kocide® 2000 against tomato early blight (*Alternaria solani*)

|                           | % Control of Tomato Early Blight |             |             |             |             |
|---------------------------|----------------------------------|-------------|-------------|-------------|-------------|
|                           | Hydrazone ( $\mu\text{M}$ )      |             |             |             |             |
| Kocide® ( $\mu\text{M}$ ) | 0                                | 10          | 50          | 200         | 400         |
| 0                         | 0                                | 3.9         | 8           | 28.4        | 32.4        |
| 10                        | 1.1                              | 35.6 (5.0)  | 52.4 (9.0)  | 29.8 (29.2) | 27.2 (33.1) |
| 50                        | 3.9                              | 55.4 (7.6)  | 77.6 (11.6) | 69.8 (31.2) | 75.3 (35.0) |
| 200                       | 36                               | 66.1 (38.5) | 92.4 (41.1) | 84.8 (54.2) | 81.4 (56.7) |
| 400                       | 52.7                             | 74.7 (54.5) | 92.2 (56.5) | 92.4 (66.1) | 90.6 (68.0) |
| 800                       | 62.9                             | 83.4 (64.3) | 93.6 (65.9) | 93.4 (73.4) | 95.1 (74.9) |

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Table 20. Synergistic fungicidal effect between hydrazone Compound **16** and CUREX 3 against tomato early blight (*Alternaria solani*)

|                           | % Control of Tomato Early Blight |             |             |             |             |
|---------------------------|----------------------------------|-------------|-------------|-------------|-------------|
|                           | Hydrazone ( $\mu\text{M}$ )      |             |             |             |             |
| CUREX 3 ( $\mu\text{M}$ ) | 0                                | 10          | 50          | 200         | 400         |
| 0                         | 0                                | 3.9         | 8.0         | 28.4        | 32.4        |
| 10                        | 0.0                              | 39.6 (3.9)  | 29.2 (8.0)  | 46.0 (28.4) | 44.2 (32.4) |
| 50                        | 4.9                              | 48.5 (8.6)  | 64.4 (12.5) | 74.8(31.9)  | 65.1 (35.7) |
| 200                       | 36.6                             | 54.7 (39.1) | 74.7 (41.7) | 85.1 (54.6) | 82.3 (57.2) |
| 400                       | 49.1                             | 65.6 (51.1) | 80.0 (53.2) | 94.9 (63.6) | 93.4 (65.6) |
| 800                       | 40.2                             | 63.6 (42.5) | 88.0 (45.0) | 96.6 (57.2) | 94.9 (59.6) |

Table 21. Synergistic fungicidal effect between hydrazone Compound **16** and  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  against cucumber anthracnose (*Colletotrichum lagenarium*).

|                                   | % Control of Cucumber Anthracnose |             |             |             |             |
|-----------------------------------|-----------------------------------|-------------|-------------|-------------|-------------|
|                                   | Hydrazone ( $\mu\text{M}$ )       |             |             |             |             |
| $\text{CuCl}_2$ ( $\mu\text{M}$ ) | 0                                 | 10          | 50          | 200         | 400         |
| 0                                 | 0                                 | 10.0        | 33.8        | 63.8        | 70.8        |
| 10                                | 9.6                               | 46.9 (18.6) | 72.5 (40.1) | 82.8 (67.3) | 83.6 (73.6) |
| 50                                | 1.4                               | 47.8 (11.3) | 81.0 (34.8) | 86.2 (64.3) | 89.0 (71.2) |
| 200                               | 37.2                              | 73.0 (43.5) | 85.3 (58.4) | 95.4 (77.3) | 98.9 (81.7) |
| 400                               | 76.2                              | 87.2 (78.6) | 94.9 (84.2) | 98.8 (91.4) | 99.6 (93.0) |
| 800                               | 90.0                              | 91.0 (91.0) | 97.5 (93.4) | 97.8 (96.4) | 98.6 (97.1) |

Table 22. Synergistic fungicidal effect between hydrazone Compound **16** and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  against cucumber anthracnose (*Colletotrichum lagenarium*).

|                                   | % Control of Cucumber Anthracnose |             |             |             |             |
|-----------------------------------|-----------------------------------|-------------|-------------|-------------|-------------|
|                                   | Hydrazone ( $\mu\text{M}$ )       |             |             |             |             |
| $\text{CuSO}_4$ ( $\mu\text{M}$ ) | 0                                 | 10          | 50          | 200         | 400         |
| 0                                 | 0                                 | 10.0        | 33.8        | 63.8        | 70.8        |
| 10                                | 1.4                               | 55.8 (11.2) | 67.5 (34.7) | 94.5 (64.3) | 90.7 (71.2) |
| 50                                | 0.0                               | 58.9 (10.0) | 78.3 (33.8) | 92.0 (63.8) | 98.7 (70.8) |
| 200                               | 61.3                              | 70.6 (65.2) | 89.8 (74.4) | 97.5 (86.0) | 99.6 (88.7) |
| 400                               | 75.7                              | 92.0 (78.1) | 95.2 (83.9) | 98.4 (91.2) | 99.7 (92.9) |
| 800                               | 87.1                              | 96.2 (88.4) | 95.6 (91.5) | 96.5 (95.3) | 99.6 (96.2) |

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Table 23. Synergistic fungicidal effect between hydrazone Compound **16** and Kocide® 2000 against cucumber anthracnose (*Colletotrichum lagenarium*)

|              | % Control of Cucumber Anthracnose |             |             |             |             |
|--------------|-----------------------------------|-------------|-------------|-------------|-------------|
|              | Hydrazone (μM)                    |             |             |             |             |
| Kocide® (μM) | 0                                 | 10          | 50          | 200         | 400         |
| 0            | 0                                 | 10          | 33.8        | 63.8        | 70.8        |
| 10           | 15.9                              | 40.4 (24.3) | 56.5 (44.3) | 83.7 (69.6) | 72.2 (75.4) |
| 50           | 15                                | 64.9(23.5)  | 83.7 (43.7) | 93.9 (69.2) | 97 (75.2)   |
| 200          | 28.9                              | 80 (36.0)   | 95.3 (52.9) | 97.2 (74.3) | 97.5 (79.2) |
| 400          | 68.8                              | 79.9 (71.9) | 89.5 (79.3) | 99.4 (88.7) | 98.5 (90.9) |
| 800          | 67.5                              | 90.3 (70.8) | 95.9 (78.5) | 99.2 (88.2) | 99.3 (90.5) |

Table 24. Synergistic fungicidal effect between hydrazone Compound **16** and CUREX 3 against cucumber anthracnose (*Colletotrichum lagenarium*)

|              | % Control of Cucumber Anthracnose |             |             |             |             |
|--------------|-----------------------------------|-------------|-------------|-------------|-------------|
|              | Hydrazone (μM)                    |             |             |             |             |
| CUREX 3 (μM) | 0                                 | 10          | 50          | 200         | 400         |
| 0            | 0                                 | 10.0        | 33.8        | 63.8        | 70.8        |
| 10           | 7.8                               | 42.1 (17.0) | 78.0 (39.0) | 84.4(66.6)  | 93.0 (73.1) |
| 50           | 10.9                              | 51.9 (19.8) | 91.4 (41.0) | 92.8 (67.7) | 95.8 (74.0) |
| 200          | 23.0                              | 58.6 (30.7) | 93.5 (49.0) | 99.1 (72.1) | 99.2 (77.5) |
| 400          | 38.7                              | 71.1 (44.8) | 92.9 (59.4) | 99.4 (77.8) | 98.3 (82.1) |
| 800          | 31.5                              | 55.2 (38.4) | 84.0 (54.7) | 96.2 (75.2) | 95.0 (80.0) |

**Example 38. Control of grape downy mildew (*Plasmopara viticola*) and tomato late blight (*Phytophthora infestans*) by Compound **16**, its copper complex, and copper chloride**

**[00106]** Test compounds were hydrazone Compound **16**, the complex of Compound **16** with copper (“hydrazone-copper”) prepared by precipitation with  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  using a 1:1 molar ratio, and  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  alone. Hydrazone and hydrazone-copper were formulated in 10% acetone /0.1% Trycol 5941 in de-ionized water.  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  was formulated with 0.1% Trycol 5941 in de-ionized water. Grape and tomato plants were sprayed with 160 μM suspensions of the formulated test compounds at a spray volume of 0.8 mL per plant. After 24 h, the undersides of the grape leaves were inoculated with an aqueous suspension of *Plasmopara viticola* sporangia and tomato plants were inoculated with an aqueous suspension of *Phytophthora infestans* sporangia. Plants were kept in high humidity overnight, then transferred to a greenhouse (grapes) or growth room (tomatoes) until disease developed on untreated control plants.

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**[00107]** Results for disease control by hydrazone-copper were compared with predicted results calculated using the Colby formula based on disease control by the hydrazone alone and CuCl<sub>2</sub> alone. Results, shown in Table 25, show that hydrazone-copper provided greater disease control than predicted based on control observed for hydrazone and CuCl<sub>2</sub> alone.

Table 25.

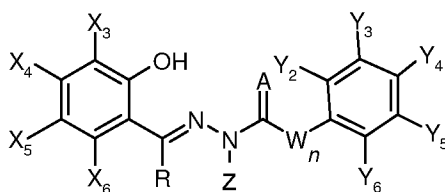
| Disease      | Treatment                   | $\mu$ M | % Control Observed | % Control Predicted |
|--------------|-----------------------------|---------|--------------------|---------------------|
| Downy mildew | Hydrazone <b>16</b>         | 160     | 29                 |                     |
|              | Hydrazone-copper <b>600</b> | 160     | 78                 | 30                  |
|              | CuCl <sub>2</sub>           | 160     | 1                  |                     |
| Late blight  | Hydrazone <b>16</b>         | 160     | 49                 |                     |
|              | Hydrazone-copper <b>600</b> | 160     | 100                | 84                  |
|              | CuCl <sub>2</sub>           | 160     | 69                 |                     |

**[00108]** While this disclosure has been described as having exemplary compounds, the present disclosure can be further modified within the spirit and scope of this disclosure. For example, all of the disclosed components of the preferred and alternative embodiments are interchangeable providing disclosure herein of many systems having combinations of all the preferred and alternative embodiment components. This application is therefore intended to cover any variations, uses, or adaptations of the disclosure using its general principles. Further, this application is intended to cover such departures from the present disclosure as come within known or customary practice in the art to which this disclosure pertains and which fall within the limits of the appended claims.

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## CLAIMS:

1. A synergistic mixture for controlling the growth of fungi, the synergistic mixture including copper and a hydrazone compound of Formula 1:



Formula 1

wherein A is oxygen or sulfur;

Z is H or C1-C4 alkyl;

W is -CHR1-;

*n* is 0, 1, or 2;

R is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 haloalkyl, C2-C6 haloalkenyl, C2-C6 haloalkynyl, or C3-C6 halocycloalkyl;

R1 is H, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 haloalkyl, C2-C6 haloalkenyl, C2-C6 haloalkynyl, C3-C6 halocycloalkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl;

X3, X4, X5, and X6 are each 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, -SO<sub>2</sub>R1, -SONR1R1, -CR1=NOR1, -CONR1R1, NR1COOR1, -COOR1, substituted aryl, substituted heteroaryl, unsubstituted aryl, and unsubstituted heteroaryl; and

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Y2, Y3, Y4, Y5, and Y6 are each 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, -SO<sub>2</sub>R1, SONR1R1, -R1=NOR1, -CONR1R1, NR1COOR1, -COOR1, NR1R1, 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.

2. Use of the synergistic mixture of claim 1 for controlling the growth of fungal pathogens of plants.
3. Use of the synergistic mixture of claim 1 for controlling the growth of fungal of mammals.
4. Use of the synergistic mixture of claim 1 for controlling the growth of fungi on inert substrates selected from the group consisting essentially of wood, metal, and plastic.
5. Use of the synergistic mixture of claim 1 for controlling the growth of fungi belonging to at least one of Ascomycete, Basidiomycete, Oomycete, and Deuteromycete classes of fungi.
6. The synergistic mixture of claim 1 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*.
7. The synergistic mixture of claim 1, wherein a growth inhibiting amount of the hydrazone compound of Formula I in mixture with copper is provided as a mixture in which the total molar ratio of copper to the hydrazone compound of Formula 1 exceeds 1:1.

8. The synergistic mixture of claim 1, wherein a growth inhibiting amount of the hydrazone compound of Formula I is provided as an isolated hydrazone-copper complex in which the molar ratio of the copper to the hydrazone compound of Formula 1 is one of 1:1 and 1:2.
9. The synergistic mixture of claim 1, wherein the hydrazone compound of Formula 1 to be combined with copper is complexed with a metal.
10. The synergistic mixture of claim 8, wherein the metal complexed with the hydrazone compound of Formula 1 is selected from the group consisting essentially of  $\text{Cu}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Zn}^{2+}$ , and  $\text{Mn}^{2+}$ .
11. 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, 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.
12. The synergistic mixture of claim 1, wherein

W is -CHR- or -CH(R)O-;

$n$  is 0 or 1;

A is O or S;

R is H, C1-C6 alkyl, C1-C6 fluoroalkyl, C2-C6 alkenyl, C2-C6 alkynyl, or C3-C6 cycloalkyl;

R1 is H, C1-C6 alkyl, C1-C6 fluoroalkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, substituted aryl, or unsubstituted aryl;

Z is H or  $-\text{C}(\text{CH}_3)_3$ ;

X3, X4, X5, and X6 are each independently selected from the group consisting of H, 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 each independently selected from the group consisting of H, halogen, nitro, hydroxyl, cyano, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy C1-C4 alkylthio,  $-\text{NR}_1\text{R}_1$ , substituted aryl, unsubstituted 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.

13. The synergistic mixture of claim 12, wherein

W is  $-\text{CH}_2-$ ;

$n$  is 0 or 1;

A is O or S;

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

Z is H;

X3, X4, X5, and X6 are each independently selected from the group consisting of H, halogen, nitro, C1-C2 alkyl, C1-C2 haloalkyl, and C1-C2 alkoxy; and

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

with the proviso that 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.

14. The synergistic mixture of claim 13, wherein

$n$  is 0;

A is O;

R is H, C1-C4 alkyl, or cyclopropyl;

Z is H;

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

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

with the proviso that Y3 and Y4 may form a 5 or 6 membered fused ring which may contain up to two oxygen atoms.

15. The synergistic mixture of claim 1, wherein a ratio of the hydrazone to the copper is from 1:0.1 to 1:10,000.

16. An agriculturally active composition including the synergistic mixture of claim 1 and at least one of a herbicide, an insecticide, a bacteriocide, a nematocide, a miticide, a biocide, a termiticide, a rodenticide, a molluscide, a arthropodicide, a fertilizer, a growth regulator, and a pheromone.