

FUNGICIDAL ARYL AMIDINES

CROSS REFERENCE TO RELATED APPLICATIONS

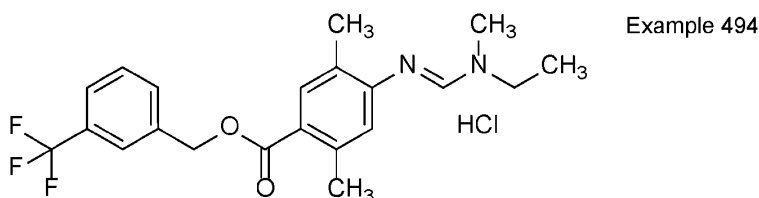
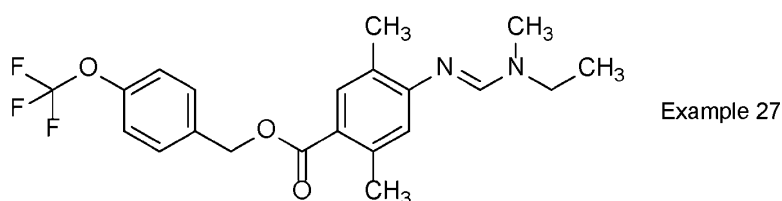
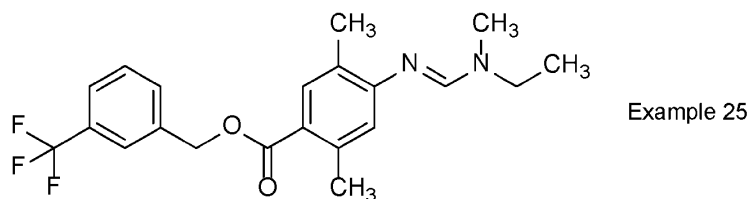
[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 63/501,465 filed May 11, 2023, the complete disclosure of which is expressly incorporated by reference herein.

BACKGROUND & SUMMARY

[0002] Fungicides are compounds of natural or synthetic origin, which act to protect and/or cure plants against damage caused by agriculturally relevant fungi. Generally, no single fungicide is useful in all situations. Consequently, research is ongoing to produce fungicides that may have better performance (e.g., better efficacy at lower use rates), are easier to use, and cost less.

[0003] The present disclosure relates to aryl amidines and their use as fungicides. The disclosure also relates to processes for the preparation of these compounds, to agricultural compositions comprising them, and to their use in the treatment and control of fungal diseases or disorders in agriculture.

[0004] PCT Application Publication No. WO 2020/237131 A1 (hereinafter “the ‘131 application”) describes a series of fungicidal compounds. Three particular compounds disclosed in the ‘131 application are 3-(trifluoromethyl)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Example 25), 4-(trifluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Example 27), and 3-(trifluoromethyl)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Example 494), the structures of which are shown below.



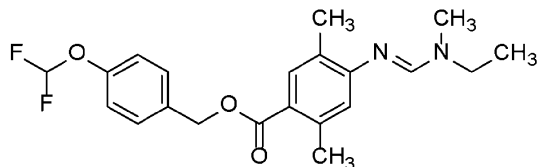
Examples 25, 27, and 494 of WO 2020/237131 A1

[0005] The compounds described in the '131 application have demonstrated activity against one or more agriculturally relevant fungi, such as Septoria leaf blotch of wheat caused by *Zymoseptoria tritici*, wheat brown rust caused by *Puccinia triticina*, Asian soybean rust caused by *Phakopsora pachyrhizi*, leaf blotch of barley caused by *Rhynchosporium secalis*, and spot blotch of barley caused by *Cochliobolus sativus*.

[0006] There still remains a need for antifungal compounds that demonstrate an improved fungicidal spectrum of activity and increased fungicidal activity at lower use rates, such as activity against Septoria leaf blotch of wheat caused by *Zymoseptoria tritici*, net blotch of barley caused by *Pyrenophora teres*, Ramularia leaf spot of barley caused by *Ramularia collo-cygni*, leaf blotch of barley caused by *Rhynchosporium secalis*, sugar beet leaf spot caused by *Cercospora beticola*, anthracnose of cucurbits caused by *Colletotrichum orbiculare*, blast of rice caused by *Magnaporthe oryzae*, and brown rust of barley caused by *Puccinia hordei*.

[0007] It is therefore an objective of the present disclosure to provide compounds that address one or more of the foregoing needs.

[0008] In one embodiment, the present disclosure provides a compound of Formula I:

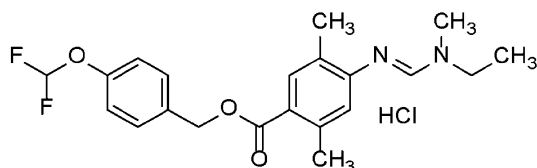


Formula I

or an acceptable salt, solvate, or hydrate thereof.

[0009] In another embodiment, the present disclosure provides a compound of Formula I, wherein the acceptable salts of Formula I include but are not limited to hydrochloride, hydrobromide, sulfate, phosphate, trifluoroacetate, formate, citrate, maleate, oxalate, tartrate, fumarate, benzenesulfonate, *p*-toluenesulfonate, succinate, methanesulfonate, L-malate, acetate, benzoate, or 4-hydroxybenzoate.

[0010] In another embodiment, the present disclosure provides a compound of Formula I, wherein the acceptable salt is the hydrochloride salt (Formula I-B):



Formula I-B

[0011] In another embodiment, the present disclosure provides an agricultural composition comprising a compound of Formula I as defined herein, or an acceptable salt, solvate, or hydrate thereof, and one or more phytolegically acceptable carrier material.

[0012] In another embodiment, the present disclosure provides a compound of Formula I as defined herein, or an acceptable salt, solvate, or hydrate thereof, or an agricultural composition as defined herein, for use in the treatment or prevention of fungal diseases or disorders in or on a plant.

[0013] Yet another embodiment of the present disclosure may include a method for the control or prevention of fungal attack on a plant, the method including the steps of applying a fungicidally effective amount of one of the compounds described above to at least one of the fungus, a seed, the plant, and an area adjacent to the plant.

[0014] Another embodiment of the present disclosure may include a method for the control or prevention of fungal attack on a plant, the method including the steps of applying a fungicidally effective amount of one of the compounds described above to a growth medium adapted to grow a plant or a seed.

[0015] Another embodiment of the present disclosure is a use of a compound of Formula I, as defined herein, or an acceptable salt, solvate, or hydrate thereof, for protection of a plant against attack by a phytopathogenic organism or the treatment of a plant infested by a phytopathogenic organism, comprising the application of a compound of Formula I, as defined herein, or an acceptable salt, solvate, or hydrate thereof, or a composition comprising the compound to soil, a plant, a part of a plant, foliage, and/or roots.

[0016] Additionally, another embodiment of the present disclosure is a composition useful for protecting a plant against attack by a phytopathogenic organism and/or treatment of a plant infested by a phytopathogenic organism comprising a compound of Formula I and a phytologically acceptable carrier material.

[0017] The present disclosure further provides a method of synthesizing a compound of Formula I, or an acceptable salt, solvate, or hydrate thereof, as defined herein.

[0018] In another embodiment, the present disclosure provides a compound of Formula I, or an acceptable salt, solvate, or hydrate thereof, obtainable by, or obtained by, or directly obtained by a method of synthesis as defined herein.

[0019] Like those in compounds in the '131 application, the present compounds have activity against one or more agriculturally relevant fungi, such as early blight of tomato caused by *Alternaria solani*, grey mold caused by *Botrytis cinerea*, cucumber powdery mildew caused by *Podosphaera xanthii*, Cercospora leaf blight caused by *Cercospora kikuchii*, target spot of soybean caused by *Corynespora cassiicola*, leaf spot of soybean caused by *Septoria glycines*, and wheat brown rust caused by *Puccinia triticina*.

[0020] The terms “ambient temperature” and “room temperature” refer to temperatures ranging from about 20 °C to about 24 °C.

[0021] The terms “phytologically acceptable carrier”, “phytologically acceptable carrier material”, “agriculturally acceptable carrier”, or “agriculturally acceptable carrier material” refer

to a carrier or an excipient that is useful in preparing an agricultural composition and is generally not phytotoxic to valuable crops.

[0022] The term “crystalline” refers to a solid state form where the molecules are arranged to form a crystal lattice comprising distinguishable unit cells. A certain crystalline form can be identified by the specific diffraction peaks when subjected to X-ray radiation.

[0023] Throughout the disclosure, in a solvate of Formula I or an acceptable salt thereof, the ratio of solvent molecules to the compound of Formula I or an acceptable salt thereof may be, but is not limited to, 1:2, 1:1, or 2:1.

[0024] Throughout the disclosure, in a hydrate of Formula I or an acceptable salt or solvate thereof, the ratio of water molecules to the compound of Formula I or an acceptable salt or solvate thereof may be, but is not limited to, 1:2 (hemi-hydrate), 1:1 (monohydrate), 2:1 (dihydrate).

[0025] Throughout the disclosure, reference to the compound of Formula I or compounds of Formula I is read as also including acceptable salts, solvates, or hydrates thereof, unless otherwise indicated herein or clearly contradicted by context.

[0026] Throughout the disclosure, reference to the compound of or compounds of Formula I is read as also including all regioisomers, structural isomers, geometrical isomers, rotational isomers, tautomers, and stereoisomers, for example diastereomers, enantiomers, and mixtures thereof.

[0027] The compounds of the disclosure may also contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage e.g., restriction resulting from the presence of a ring or a double bond. Accordingly, any *cis/trans* and *E/Z* isomers are expressly included in the present disclosure.

[0028] The compounds of the disclosure may also be present in multiple tautomeric forms. Where one or more tautomeric forms exist, the disclosure expressly includes all such tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented.

[0029] The compounds of the present disclosure may exist in an amorphous solid form or as an oil.

[0030] The compounds of the present disclosure may exist in one or more crystalline or polymorphic forms. All crystalline forms and polymorphs of the compounds of the disclosure are expressly included in the present disclosure.

[0031] In an embodiment, the present disclosure provides a crystalline form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I).

[0032] In another embodiment, the crystalline form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I) is an anhydrous and solvent-free crystalline polymorph form.

[0033] In another embodiment, the crystalline form is crystalline polymorph Form A (referred to herein as Form A) of Formula I.

[0034] In another embodiment, the present disclosure provides one or more crystalline forms of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B).

[0035] In another embodiment, the one or more crystalline forms are crystalline polymorph Forms 1, 2, and 3 (individually referred to herein as Form 1, Form 2, and Form 3, respectively) of Formula I-B.

[0036] In another embodiment, the crystalline polymorph Form 1 of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) is a hemi-hydrate crystalline polymorph form.

[0037] In another embodiment, the crystalline polymorph Form 2 and Form 3 of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) are anhydrous and solvent-free crystalline polymorph forms.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] FIG. 1 is a graph showing the combined biological efficacy in a greenhouse study against Septoria leaf blotch caused by *Zymoseptoria tritici*.

[0039] FIG. 2 is a graph showing the biological efficacy in a cross-trial analysis of replicated field trials in three geographic locations against Septoria leaf blotch caused by *Zymoseptoria tritici*.

[0040] FIG. 3 is a graph showing the biological efficacy in a cross-trial analysis of replicated field trials in three geographic locations against net blotch of barley caused by *Pyrenophora teres*.

[0041] FIG. 4 is a graph showing the biological efficacy in a cross-trial analysis of replicated field trials in three geographic locations against Ramularia leaf spot of barley caused by *Ramularia collo-cygni*.

[0042] FIG. 5 is a graph showing the biological efficacy in a cross-trial analysis of replicated field trials in three geographic locations against leaf blotch of barley caused by *Rhynchosporium secalis*.

[0043] FIG. 6 is a graph showing the biological efficacy in a cross-trial analysis of replicated field trials in three geographic locations against brown rust of barley caused by *Puccinia hordei*.

[0044] FIG. 7 shows a powder X-ray diffraction pattern of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I), Form A (solvent-free and anhydrous), as prepared in Example 12 of the present disclosure.

[0045] FIG. 8 shows a powder X-ray diffraction pattern of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B), Form 1 (hemi-hydrate), as prepared in Example 17 of the present disclosure.

[0046] FIG. 9 shows a powder X-ray diffraction pattern of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B), Form 2 (solvent-free and anhydrous), as prepared in Example 19 of the present disclosure.

[0047] FIG. 10 shows a powder X-ray diffraction pattern of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, solvent-free and anhydrous), Form 3, as prepared in Example 24 of the present disclosure.

DETAILED DESCRIPTION

[0048] The compounds of the present disclosure may be applied by any of a variety of known techniques, either as the compounds or as formulations comprising the compounds. For example, the compounds may be applied to the roots or foliage of plants for the control of various fungi, without damaging the commercial value of the plants. The materials may be

applied in the form of any of the generally used formulation types, for example, as solutions, dusts, wettable powders, flowable concentrates, or emulsifiable concentrates.

[0049] Preferably, the compounds of the present disclosure are applied in the form of a formulation, comprising one of the compounds of Formula I with a phytologically acceptable carrier. Concentrated formulations may be dispersed in water, or other liquids, for application, or formulations may be dust-like or granular, which may then be applied as is by the end user. The formulations can be prepared according to procedures that are conventional in the agricultural chemical art.

[0050] The present disclosure contemplates all vehicles by which one of the compounds may be formulated for delivery and used as a fungicide. Typically, formulations are applied as aqueous suspensions or emulsions. Such suspensions or emulsions may be produced from water-soluble, water-suspendible, or emulsifiable formulations which are solids, usually known as wettable powders; or liquids, usually known as emulsifiable concentrates, aqueous suspensions, or suspension concentrates. As will be readily appreciated, the compounds of the present disclosure may be added to any material, provided the material yields the desired utility without significant interference to the activity of these compounds as antifungal agents.

[0051] Wettable powders, which may be compacted to form water-dispersible granules, comprise an intimate mixture of one of the compounds of Formula I, an inert carrier, and optional additives such as surfactants. The concentration of the compound of Formula I in the wettable powder may be from about 10 percent to about 90 percent by weight based on the total weight of the wettable powder, more preferably about 25 weight percent to about 75 weight percent. In the preparation of wettable powder formulations, the compound of Formula I may be mixed with any finely divided solid carrier, such as prophyllite, talc, chalk, gypsum, Fuller's earth, bentonite, attapulgate, starch, casein, gluten, montmorillonite clays, diatomaceous earths, purified silicates or the like. In such operations, the finely divided carrier and other optional additives are typically blended with the compound of Formula I and milled.

[0052] Emulsifiable concentrates comprise an active ingredient, such as the compounds of Formula I, dissolved in an inert carrier, which is either a water-miscible solvent or a mixture of water-immiscible organic solvents, and emulsifiers. Emulsifiable concentrates may comprise a convenient concentration, such as from about 1 weight percent to about 50 weight percent of the

compound of Formula I, based on the total weight of the concentrate. The emulsifiable concentrates may be diluted with water to form spray mixtures in the form of oil-in-water emulsions. Other ingredients, including but not limited to surfactants, adjuvants, oils, antifoam agents, and stabilizers, may be added to the emulsifiable concentrate, or may be mixed with the emulsifiable concentrate during the dilution to form the spray mixture.

[0053] Emulsifiers which may be advantageously employed herein may be readily determined by those skilled in the art and include various nonionic, anionic, cationic and amphoteric emulsifiers, or a blend of two or more emulsifiers. Examples of nonionic emulsifiers useful in preparing the emulsifiable concentrates include the polyalkylene glycol ethers and condensation products of alkyl and aryl phenols, aliphatic alcohols, aliphatic amines or fatty acids with ethylene oxide, propylene oxides such as the ethoxylated alkyl phenols and carboxylic esters solubilized with the polyol or polyoxyalkylene. Cationic emulsifiers include quaternary ammonium compounds and fatty amine salts. Anionic emulsifiers include the oil-soluble salts (e.g., calcium) of alkylaryl sulfonic acids, oil-soluble salts or sulfated polyglycol ethers and appropriate salts of phosphated-polyglycol ether.

[0054] Representative organic liquids which may be employed in preparing the emulsifiable concentrates of the compounds of the present disclosure are the aromatic liquids such as xylene, propyl benzene fractions, or mixed naphthalene fractions; substituted aromatic organic liquids such as dioctyl phthalate; kerosene; dialkyl amides of various fatty acids, particularly the dimethyl amides of fatty glycols and glycol derivatives such as the *n*-butyl ether, ethyl ether or methyl ether of diethylene glycol or the methyl ether of triethylene glycol; petroleum fractions or hydrocarbons such as mineral oil, aromatic solvents, paraffinic oils, and the like; terpenic solvents, including rosin derivatives; aliphatic ketones, such as cyclohexanone; complex alcohols, such as 2-ethoxyethanol; vegetable oils such as soybean oil, rapeseed oil, olive oil, castor oil, sunflower seed oil, coconut oil, corn oil, cottonseed oil, linseed oil, palm oil, peanut oil, safflower oil, sesame oil, tung oil and the like; esters of the above vegetable oils; and the like. Mixtures of two or more organic liquids may also be employed in the preparation of the emulsifiable concentrate. Organic liquids include xylene, and propyl benzene fractions, with xylene being most preferred in some cases. Surface-active dispersing agents are typically employed in liquid formulations and in an amount of from 0.1 to 20 percent by weight based on

the combined weight of the dispersing agent with one of the compounds. The formulations can also contain other compatible additives, for example, plant growth regulators and other biologically active compounds used in agriculture.

[0055] Aqueous suspensions comprise finely divided solids or powders of a water-insoluble active ingredient, such as a compound of Formula I, dispersed in an aqueous carrier at a concentration in the range from about 1 to about 50 weight percent, based on the total weight of the aqueous suspension. Suspensions are prepared by finely grinding the compound, and vigorously mixing the ground material into a carrier comprising 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 carrier.

[0056] The compounds of Formula I can also be applied as granular formulations, which are particularly useful for applications to the soil. Granular formulations generally contain from about 0.5 to about 10 weight percent of the active ingredient, based on the total weight of the granular formulation, dispersed in an inert solid 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 may be prepared by dissolving the compounds in a suitable solvent and applying it to the solid carrier which has been preformed to the appropriate particle size, e.g., in the range of from about 0.5 to about 3 millimeters (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 with a solvent, and crushing and drying the dough or paste to obtain the desired granular particle. Such formulations may also be prepared by making a dough or paste of the carrier and the compound with a solvent, then extruding the dough or paste to form granules of the formulation.

[0057] Dusts containing the compounds of Formula I may be prepared by intimately mixing one of the compounds in powdered form with a suitable dusty agricultural carrier, such as, for example, kaolin clay, ground volcanic rock, and the like. Dusts can suitably contain from about 1 to about 10 weight percent of the compounds, based on the total weight of the dust.

[0058] The formulations may additionally contain adjuvant surfactants to enhance deposition, wetting, and penetration of the compounds onto the target crop and organism. These adjuvant surfactants may optionally be employed as a component of the formulation or as a tank

mix. The amount of adjuvant surfactant will typically vary from 0.01 to 1.0 percent by volume, based on a spray-volume of water, preferably 0.05 to 0.5 volume percent. Suitable adjuvant surfactants include, but are not limited to ethoxylated nonyl phenols, ethoxylated synthetic or natural alcohols, salts or the esters of sulfosuccinic acids, ethoxylated organosilicones, ethoxylated fatty amines, blends of surfactants with mineral or vegetable oils, crop oil concentrate (mineral oil (85%) + emulsifiers (15%)); nonylphenol ethoxylate; benzylcocoalkyldimethyl quaternary ammonium salt; blend of petroleum hydrocarbon, alkyl esters, organic acid, and anionic surfactant; C₉ – C₁₁ alkylpolyglycoside; phosphated alcohol ethoxylate; natural primary alcohol (C₁₂ – C₁₆) ethoxylate; di-*sec*-butylphenol EO-PO block copolymer; polysiloxane-methyl cap; nonylphenol ethoxylate + urea ammonium nitrate; emulsified methylated seed oil; tridecyl alcohol (synthetic) ethoxylate (8EO); tallow amine ethoxylate (15 EO); PEG(400) dioleate-99. The formulations may also include oil-in-water emulsions such as those disclosed in U.S. Patent Application Serial No. 11/495,228, the disclosure of which is expressly incorporated by reference herein.

[0059] Another embodiment of the present disclosure is a method for the control or prevention of fungal attack. This method comprises applying to the soil, plant, roots, foliage, or locus of the fungus, or to a locus in which the infestation is to be prevented (for example applying to cereal or grape plants), a fungicidally effective amount of one of the compounds of Formula I. The compounds are suitable for treatment of various plants at fungicidal levels, while exhibiting low phytotoxicity. The compounds may be useful both in a protectant and/or an eradicant fashion.

[0060] The compounds of Formula I have been found to have significant fungicidal effect particularly for agricultural use. Many of the compounds are particularly effective for use with agricultural crops and horticultural plants.

[0061] It will be understood by those skilled in the art that the efficacy of the compound for the foregoing fungi establishes the general utility of the compounds as fungicides. The compounds of Formula I have broad ranges of activity against fungal pathogens. Exemplary pathogens may include, but are not limited to, the causative agent of Septoria leaf blotch of wheat (*Zymoseptoria tritici*), spot blotch of barley (*Cochliobolus sativus*), wheat brown rust (*Puccinia triticina*), wheat stripe rust (*Puccinia striiformis*), blister smut of maize (*Ustilago*

maydis), powdery mildew of grapevine (*Uncinula necator*), leaf blotch of barley (*Rhynchosporium secalis*), blast of rice (*Magnaporthe oryzae*), Asian soybean rust (*Phakopsora pachyrhizi*), glume blotch of wheat (*Parastagonospora nodorum*), anthracnose of cucurbits (*Colletotrichum orbiculare*), brown rust of barley (*Puccinia hordei*), sugar beet leaf spot (*Cercospora beticola*), early blight of tomato (*Alternaria solani*), net blotch of barley (*Pyrenophora teres*), powdery mildew of wheat (*Blumeria graminis f. sp. tritici*), powdery mildew of barley (*Blumeria graminis f. sp. hordei*), powdery mildew of cucurbits (*Erysiphe cichoracearum*), powdery mildew of cucumber (*Podosphaera xanthii*), collar rot or damping-off of seedlings (*Rhizoctonia solani*), grey mold (*Botrytis cinerea*), Ramularia leaf spot (*Ramularia collo-cygni*), tan spot of wheat (*Pyrenophora tritici-repentis*), Northern leaf blight of maize (*Exserohilum turcicum*), Southern rust of maize (*Puccinia polysora*), white mold (*Sclerotinia sclerotiorum*), powdery mildew of soybean (*Erysiphe diffusa*), powdery mildew of apple (*Podosphaera leucotricha*), anthracnose of soybean (*Colletotrichum truncatum*), Cercospora leaf blight (*Cercospora kikuchii*), frogeye leaf spot (*Cercospora sojae*), target spot of soybean (*Corynespora cassicola*), and leaf spot of soybean (*Septoria glycines*). The exact amount of the active material to be applied is dependent not only on the specific active material being applied, but also on the particular action desired, the fungal species to be controlled, and the stage of growth thereof, as well as the part of the plant or other product to be contacted with the active material. Thus, all the compounds, and formulations containing the same, may not be equally effective at similar concentrations or against the same fungal species.

[0062] The compounds of Formula I are effective in use with plants in a disease-inhibiting and phytologically acceptable amount. The terms "disease-inhibiting amount" or "phytologically acceptable amount" refer to an amount of a compound that kills or inhibits the plant disease for which control is desired, but is not significantly toxic to the plant. This amount will generally be from about 0.1 to about 1000 ppm (parts per million), with 1 to 500 ppm being preferred. The exact concentration of compound required varies with the fungal disease to be controlled, the type of formulation employed, the method of application, the particular plant species, climate conditions, and the like. A suitable application rate is typically in the range from about 0.10 to about 4 pounds per acre (about 0.01 to 0.45 grams per square meter, g/m²).

[0063] Crystalline forms disclosed herein may be prepared using a number of different solvents and solvent mixtures from solvent classes such as alcohols, ketones, esters, ethers, hydrocarbons, polar aprotic solvents, and water. For example, crystalline Form A of Formula I may be prepared using ethyl acetate. For example, crystalline Form 1 of Formula I-B may be prepared using a number of different solvents, including but not limited to toluene, ethanol, isopropyl alcohol, dichloromethane, ethyl acetate, isopropyl acetate, methyl isobutyl ketone, methyl ethyl ketone, heptane, chloroform, acetonitrile, acetone, methyl *tert*-butyl ether, and mixtures thereof. For example, crystalline Form 2 of Formula I-B may be prepared using a number of different solvents, including but not limited to isopropyl alcohol, methyl isobutyl ketone, methyl ethyl ketone, heptane, 2-methyl tetrahydrofuran, methyl *tert*-butyl ether, and mixtures thereof. For example, crystalline Form 3 of Formula I-B may be prepared using a number of different solvents, including but not limited to ethyl acetate, tetrahydrofuran, methyl isobutyl ketone, acetone, methyl *tert*-butyl ether, and mixtures thereof.

[0064] A unique physical form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I), polymorph Form A, has been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of polymorph Form A is shown in FIG. 7, with corresponding tabulated data shown in Table A.

Table A

2theta (2 θ) (degrees)	d-spacing (Å)	Relative Peak Height (I _{rel})	Qualitative Intensity*
5.54	15.9286	510.86	s
5.57	15.8421	95.07	vw
11.05	7.9998	95.84	vw
12.35	7.1599	847.35	vs
14.17	6.2462	493.22	m
15.14	5.8487	112.46	w
15.17	5.8371	43.27	vw
16.13	5.4889	104.96	w
16.68	5.3109	238.66	m
17.56	5.0473	58.39	vw
18.28	4.8485	46.66	vw
18.77	4.7245	407.71	m
19.22	4.6139	63.25	vw
19.55	4.5361	36.2	vw

20.58	4.3116	68.05	vw
21.28	4.1722	461.23	m
21.61	4.1086	681.2	s
21.88	4.0581	460.79	m
23.31	3.8136	1000	vs
23.34	3.8087	123.96	w
23.70	3.7512	216.43	m
24.34	3.6547	207.47	m
25.49	3.4923	37.24	vw
25.91	3.4361	35.43	vw
26.76	3.3292	127.76	w
27.12	3.2855	698.62	s
28.18	3.1643	61.04	vw
28.87	3.0896	29.78	vw
31.02	2.8804	52.62	vw
31.30	2.8559	28.62	vw
33.02	2.7106	114.36	w
34.29	2.613	36.53	vw

* S = strong (>50% Relative intensity), M = medium (20-50% Relative intensity), W = weak (<20% Relative intensity); V = very

[0065] In some embodiments, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 5.5 ± 0.2 , 5.6 ± 0.2 , 11.1 ± 0.2 , 12.4 ± 0.2 , 14.2 ± 0.2 , 15.1 ± 0.2 , 15.2 ± 0.2 , 16.1 ± 0.2 , 16.7 ± 0.2 , 17.6 ± 0.2 , 18.3 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 20.6 ± 0.2 , 21.3 ± 0.2 , 21.6 ± 0.2 , 21.9 ± 0.2 , 23.3 ± 0.2 , 23.3 ± 0.2 , 23.7 ± 0.2 , 24.3 ± 0.2 , 25.5 ± 0.2 , 25.9 ± 0.2 , 26.8 ± 0.2 , 27.1 ± 0.2 , 28.2 ± 0.2 , 28.9 ± 0.2 , 31.0 ± 0.2 , 31.3 ± 0.2 , 33.0 ± 0.2 , and 34.3 ± 0.2 . In some embodiments, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 5.5 ± 0.1 , 5.6 ± 0.1 , 11.1 ± 0.1 , 12.4 ± 0.1 , 14.2 ± 0.1 , 15.1 ± 0.1 , 15.2 ± 0.1 , 16.1 ± 0.1 , 16.7 ± 0.1 , 17.6 ± 0.1 , 18.3 ± 0.1 , 18.8 ± 0.1 , 19.2 ± 0.1 , 19.6 ± 0.1 , 20.6 ± 0.1 , 21.3 ± 0.1 , 21.6 ± 0.1 , 21.9 ± 0.1 , 23.3 ± 0.1 , 23.3 ± 0.1 , 23.7 ± 0.1 , 24.3 ± 0.1 , 25.5 ± 0.1 , 25.9 ± 0.1 , 26.8 ± 0.1 , 27.1 ± 0.1 , 28.2 ± 0.1 , 28.9 ± 0.1 , 31.0 ± 0.1 , 31.3 ± 0.1 , 33.0 ± 0.1 , and 34.3 ± 0.1 . In some embodiments, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising a combination of two or more peaks at diffraction angles (2θ) as provided in the above embodiments. It will be appreciated that the

diffraction angles (2θ) provided in Table A are within the experimental error of the values provided above and also referred to in the present disclosure.

[0066] In a further embodiment, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 23.3 ± 0.2 . In a further embodiment, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.4 ± 0.2 and 23.3 ± 0.2 . In a further embodiment, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.4 ± 0.2 , 23.3 ± 0.2 , and 27.1 ± 0.2 . In a further embodiment, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.4 ± 0.2 , 21.6 ± 0.2 , 23.3 ± 0.2 , and 27.1 ± 0.2 . In a further embodiment, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 5.5 ± 0.2 , 12.4 ± 0.2 , 21.6 ± 0.2 , 23.3 ± 0.2 , and 27.1 ± 0.2 .

[0067] In a further embodiment, the crystalline polymorph Form A of Formula I has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) essentially the same as shown in FIG. 7.

[0068] A unique physical form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B), polymorph Form 1, has been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of polymorph Form 1 is shown in FIG. 8, with corresponding tabulated data shown in Table B.

Table B

2theta (2θ) (degrees)	d-spacing (Å)	Relative Peak Height (I_{rel})	Qualitative Intensity*
6.91	12.7903	191.88	w
9.42	9.384	59.4	vw
10.54	8.3892	335.38	m
12.08	7.3207	683.03	s
12.59	7.0228	139.62	w
13.77	6.4237	117.21	w
15.08	5.872	247.76	m
15.77	5.6144	61.99	wv
16.89	5.2447	132.5	w
18.01	4.9211	35.99	vw

18.71	4.7396	429.15	m
20.61	4.3054	68.54	vw
21.13	4.2017	45.63	vw
21.85	4.0637	274.81	m
23.03	3.8581	269.9	m
23.58	3.7702	1000	vs
24.76	3.5931	32.77	vw
25.33	3.5128	121.41	w
25.91	3.4361	323.91	m
26.70	3.3366	257.7	m
27.36	3.2569	185.21	w
28.93	3.0833	89.55	vw
29.69	3.0064	34.28	vw
30.27	2.9506	94.86	vw
30.78	2.9025	71.77	vw
31.60	2.8293	81	vw
33.78	2.6516	29.53	vw

* S = strong (>50% Relative intensity), M = medium (20-50% Relative intensity), W = weak (<20% Relative intensity); V = very

[0069] In some embodiments, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.2 , 9.4 ± 0.2 , 10.5 ± 0.2 , 12.1 ± 0.2 , 12.6 ± 0.2 , 13.8 ± 0.2 , 15.1 ± 0.2 , 15.8 ± 0.2 , 16.9 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 20.6 ± 0.2 , 21.1 ± 0.2 , 21.9 ± 0.2 , 23.0 ± 0.2 , 23.6 ± 0.2 , 24.8 ± 0.2 , 25.3 ± 0.2 , 25.9 ± 0.2 , 26.7 ± 0.2 , 27.4 ± 0.2 , 28.9 ± 0.2 , 29.7 ± 0.2 , 30.3 ± 0.2 , 30.8 ± 0.2 , 31.6 ± 0.2 , and 33.8 ± 0.2 . In some embodiments, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 9.4 ± 0.1 , 10.5 ± 0.1 , 12.1 ± 0.1 , 12.6 ± 0.1 , 13.8 ± 0.1 , 15.1 ± 0.1 , 15.8 ± 0.1 , 16.9 ± 0.1 , 18.0 ± 0.1 , 18.7 ± 0.1 , 20.6 ± 0.1 , 21.1 ± 0.1 , 21.9 ± 0.1 , 23.0 ± 0.1 , 23.6 ± 0.1 , 24.8 ± 0.1 , 25.3 ± 0.1 , 25.9 ± 0.1 , 26.7 ± 0.1 , 27.4 ± 0.1 , 28.9 ± 0.1 , 29.7 ± 0.1 , 30.3 ± 0.1 , 30.8 ± 0.1 , 31.6 ± 0.1 , and 33.8 ± 0.1 . In some embodiments, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising a combination of two or more peaks at diffraction angles (2θ) as provided in the above embodiments. It will be appreciated that the diffraction

angles (2θ) provided in Table B are within the experimental error of the values provided above and also referred to in the present disclosure.

[0070] In a further embodiment, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 23.6 ± 0.2 . In a further embodiment, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.1 ± 0.2 and 23.6 ± 0.2 . In a further embodiment, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.1 ± 0.2 , 18.7 ± 0.2 , and 23.6 ± 0.2 . In a further embodiment, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 10.5 ± 0.2 , 12.1 ± 0.2 , 18.7 ± 0.2 , and 23.6 ± 0.2 . In a further embodiment, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 10.5 ± 0.2 , 12.1 ± 0.2 , 18.7 ± 0.2 , 23.6 ± 0.2 , and 25.9 ± 0.2 .

[0071] In a further embodiment, the crystalline polymorph Form 1 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) essentially the same as shown in FIG. 8.

[0072] A unique physical form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B), polymorph Form 2, has been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of polymorph Form 2 is shown in FIG. 9, with corresponding tabulated data shown in Table C.

Table C

2theta (2θ) (degrees)	d-spacing (Å)	Relative Peak Height (I_{rel})	Qualitative Intensity*
4.88	18.1008	496.56	m
9.60	9.2069	1000	vs
12.23	7.2305	70.21	vw
12.84	6.8909	180.56	w
12.87	6.8748	32.38	vw
13.44	6.582	176.74	w
14.32	6.1805	150.32	w
14.86	5.9552	245.3	m
14.89	5.9432	49.78	vw
16.10	5.4991	345.88	m

17.01	5.2077	123.8	w
17.50	5.0647	128.13	w
18.13	4.8886	334.84	m
19.04	4.6575	73.25	vw
20.28	4.3753	287.25	m
20.92	4.2438	160.89	w
21.58	4.1143	642.8	s
21.61	4.1086	95.24	vw
22.55	3.9398	131.06	w
23.31	3.8136	123.27	w
23.82	3.7324	79.83	vw
24.52	3.628	453.78	m
25.09	3.5462	99.54	vw
25.94	3.4322	38.33	vw
27.00	3.2999	103.72	w
27.42	3.2499	44.29	vw
28.63	3.1152	87.17	vw
29.42	3.0337	124.28	w
29.69	3.0064	77.8	vw
30.42	2.9363	34.36	vw
31.60	2.8293	83	vw
33.72	2.6562	41.02	vw
38.41	2.3419	45.94	vw

* S = strong (>50% Relative intensity), M = medium (20-50% Relative intensity), W = weak (<20% Relative intensity); V = very

[0073] In some embodiments, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , 12.2 ± 0.2 , 12.8 ± 0.2 , 12.9 ± 0.2 , 13.4 ± 0.2 , 14.3 ± 0.2 , 14.9 ± 0.2 , 14.9 ± 0.2 , 16.1 ± 0.2 , 17.0 ± 0.2 , 17.5 ± 0.2 , 18.1 ± 0.2 , 19.0 ± 0.2 , 20.3 ± 0.2 , 20.9 ± 0.2 , 21.6 ± 0.2 , 21.6 ± 0.2 , 22.6 ± 0.2 , 23.3 ± 0.2 , 23.8 ± 0.2 , 24.5 ± 0.2 , 25.1 ± 0.2 , 25.9 ± 0.2 , 27.0 ± 0.2 , 27.4 ± 0.2 , 28.6 ± 0.2 , 29.4 ± 0.2 , 30.4 ± 0.2 , 31.6 ± 0.2 , 33.7 ± 0.2 , and 38.4 ± 0.2 . In some embodiments, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 4.9 ± 0.1 , 9.6 ± 0.1 , 12.2 ± 0.1 , 12.8 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 14.3 ± 0.1 , 14.9 ± 0.1 , 14.9 ± 0.1 , 16.1 ± 0.1 , 17.0 ± 0.1 , 17.5 ± 0.1 , 18.1 ± 0.1 , 19.0 ± 0.1 , 20.3 ± 0.1 , 20.9 ± 0.1 , 21.6 ± 0.1 , 21.6 ± 0.1 , 22.6 ± 0.1 , 23.3 ± 0.1 , $23.8 \pm$

0.1, 24.5 ± 0.1 , 25.1 ± 0.1 , 25.9 ± 0.1 , 27.0 ± 0.1 , 27.4 ± 0.1 , 28.6 ± 0.1 , 29.4 ± 0.1 , 30.4 ± 0.1 , 31.6 ± 0.1 , 33.7 ± 0.1 , and 38.4 ± 0.1 . In some embodiments, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising a combination of two or more peaks at diffraction angles (2θ) as provided in the above embodiments. It will be appreciated that the diffraction angles (2θ) provided in Table C are within the experimental error of the values provided above and also referred to in the present disclosure.

[0074] In a further embodiment, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 9.6 ± 0.2 . In a further embodiment, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.6 ± 0.2 and 21.6 ± 0.2 . In a further embodiment, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , and 21.6 ± 0.2 . In a further embodiment, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , 21.6 ± 0.2 , and 24.5 ± 0.2 . In a further embodiment, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , 16.1 ± 0.2 , 21.6 ± 0.2 , and 24.5 ± 0.2 .

[0075] In a further embodiment, the crystalline polymorph Form 2 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) essentially the same as shown in FIG. 9.

[0076] A unique physical form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B), polymorph Form 3, has been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of polymorph Form 3 is shown in FIG. 10, with corresponding tabulated data shown in Table D.

Table D

2theta (2θ) (degrees)	d-spacing (Å)	Relative Peak Height (I_{rel})	Qualitative Intensity*
4.67	18.922	694.44	s
4.70	18.8001	216.98	m
9.36	9.4445	1000	vs
12.84	6.8909	137.53	w

12.87	6.8748	31.82	vw
13.47	6.5673	90.13	vw
14.05	6.2997	94.5	vw
14.44	6.129	144.21	w
15.80	5.6038	19.81	vw
16.50	5.3689	186.48	w
17.22	5.1441	175.59	w
17.89	4.9542	24.35	vw
18.95	4.6796	369.6	m
20.25	4.3817	45.97	vw
21.10	4.2076	333.2	m
22.28	3.9873	99.36	vw
22.67	3.919	113.55	w
23.34	3.8087	87.07	vw
24.67	3.6061	352.35	m
25.12	3.5419	186.85	w
25.67	3.468	46.26	vw
26.85	3.3182	72.47	vw
27.36	3.2569	81.57	vw
28.03	3.1811	104.52	w
29.18	3.0583	46.73	vw
29.78	2.9975	47.66	vw
30.24	2.9535	28.86	vw
30.81	2.8997	40.57	vw
33.38	2.6819	24.32	vw
34.35	2.6085	20.26	vw
37.23	2.4134	32.87	vw
38.07	2.3616	34.64	vw
38.41	2.3419	21.54	vw

* S = strong (>50% Relative intensity), M = medium (20-50% Relative intensity), W = weak (<20% Relative intensity); V = very

[0077] In some embodiments, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 4.7 ± 0.2 , 4.7 ± 0.2 , 9.4 ± 0.2 , 12.8 ± 0.2 , 12.9 ± 0.2 , 13.5 ± 0.2 , 14.1 ± 0.2 , 14.4 ± 0.2 , 15.8 ± 0.2 , 16.5 ± 0.2 , 17.2 ± 0.2 , 17.9 ± 0.2 , 19.0 ± 0.2 , 20.3 ± 0.2 , 21.1 ± 0.2 , 22.3 ± 0.2 , 22.7 ± 0.2 , 23.3 ± 0.2 , 24.7 ± 0.2 , 25.1 ± 0.2 , 25.7 ± 0.2 , 26.9 ± 0.2 , 27.4 ± 0.2 , 28.0 ± 0.2 , 29.2 ± 0.2 , 29.8 ± 0.2 , $30.2 \pm$

0.2, 30.8 ± 0.2 , 33.4 ± 0.2 , 34.4 ± 0.2 , 37.2 ± 0.2 , 38.1 ± 0.2 , and 38.4 ± 0.2 . In some embodiments, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 4.7 ± 0.1 , 4.7 ± 0.1 , 9.4 ± 0.1 , 12.8 ± 0.1 , 12.9 ± 0.1 , 13.5 ± 0.1 , 14.1 ± 0.1 , 14.4 ± 0.1 , 15.8 ± 0.1 , 16.5 ± 0.1 , 17.2 ± 0.1 , 17.9 ± 0.1 , 19.0 ± 0.1 , 20.3 ± 0.1 , 21.1 ± 0.1 , 22.3 ± 0.1 , 22.7 ± 0.1 , 23.3 ± 0.1 , 24.7 ± 0.1 , 25.1 ± 0.1 , 25.7 ± 0.1 , 26.9 ± 0.1 , 27.4 ± 0.1 , 28.0 ± 0.1 , 29.2 ± 0.1 , 29.8 ± 0.1 , 30.2 ± 0.1 , 30.8 ± 0.1 , 33.4 ± 0.1 , 34.4 ± 0.1 , 37.2 ± 0.1 , 38.1 ± 0.1 , and 38.4 ± 0.1 . In some embodiments, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising a combination of two or more peaks at diffraction angles (2θ) as provided in the above embodiments. It will be appreciated that the diffraction angles (2θ) provided in Table D are within the experimental error of the values provided above and also referred to in the present disclosure.

[0078] In a further embodiment, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 9.4 ± 0.2 . In a further embodiment, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.7 ± 0.2 and 9.4 ± 0.2 . In a further embodiment, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.7 ± 0.2 , 9.4 ± 0.2 , and 19.0 ± 0.2 . In a further embodiment, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.7 ± 0.2 , 9.4 ± 0.2 , 19.0 ± 0.2 , and 24.7 ± 0.2 . In a further embodiment, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.7 ± 0.2 , 9.4 ± 0.2 , 19.0 ± 0.2 , 21.1 ± 0.2 , and 24.7 ± 0.2 .

[0079] In a further embodiment, the crystalline polymorph Form 3 of Formula I-B has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) essentially the same as shown in FIG. 10.

[0080] Any range or desired value given herein may be extended or altered without losing the effects sought, as is apparent to the skilled person for an understanding of the teachings herein.

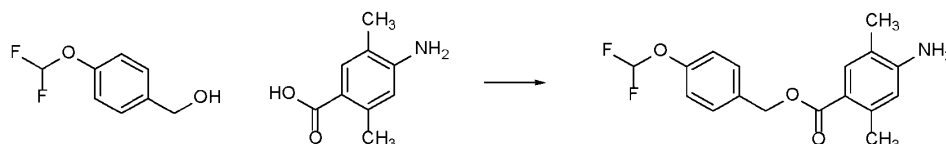
[0081] The compounds of Formula I may be made using well-known chemical procedures. Intermediates not specifically mentioned in this disclosure are either commercially available, may be made by routes disclosed in the chemical literature, or may be readily synthesized from commercial starting materials utilizing standard procedures.

[0082] The following examples further illustrate the compounds of Formula I within the disclosure but, of course, should not be construed as in any way limiting its scope.

[0083] Starting materials, reagents, and solvents that were obtained from commercial sources were used without further purification. Anhydrous solvents were purchased as Sure/Seal™ from Aldrich and were used as received. Melting points were obtained on an OptiMelt Automated Melting Point System from Stanford Research Systems and were uncorrected. Molecules were named according to the naming program within ChemDraw (version 22.2.0.3300). If such a program is unable to name a molecule, such molecule was named using conventional naming rules. ¹H NMR spectral data are in ppm (δ) and were recorded at 396, 400 and 500 MHz; ¹⁹F NMR spectral data are in ppm (δ) and were recorded at 376 or 471 MHz; and ³¹P NMR spectral data are in ppm (δ) and were recorded at 202 MHz, unless otherwise stated.

EXAMPLES AND METHODS

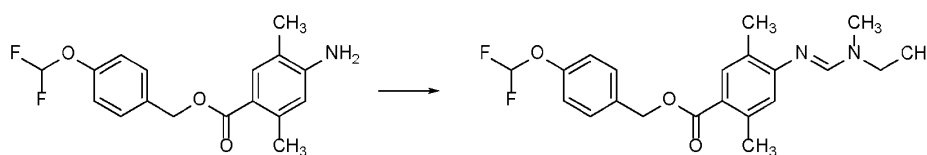
Example 1: Preparation of 4-(difluoromethoxy)benzyl 4-amino-2,5-dimethylbenzoate



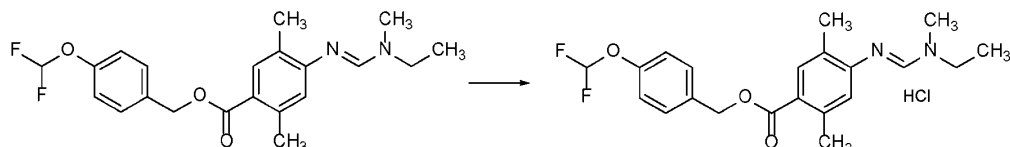
[0084] In a 20 milliliter (mL) vial, (4-(difluoromethoxy)phenyl)methanol (253 milligrams (mg), 1.45 millimoles (mmol)), 4-amino-2,5-dimethylbenzoic acid (200 mg, 1.21 mmol) and 4-dimethylaminopyridine (DMAP, 14.8 mg, 0.121 mmol) were dissolved in dichloromethane (DCM, 6.05 mL), and the mixture was cooled to 0 °C in an ice/water bath. After ~5 minutes, *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC, 279 mg, 1.45 mmol) was added in one portion, and the resulting pale yellow reaction mixture was stirred overnight, slowly warming to room temperature as the ice melted. After 18 hours, thin-layer chromatography (TLC) indicated consumption of starting material. The reaction mixture was concentrated to afford an oil. The resultant material was purified by flash column chromatography (silica gel

(SiO₂), 0→100% ethyl acetate in hexane) to afford the title compound (255 mg, 0.794 mmol, 66% yield) as a clear, colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.73 (s, 1H), 7.43 – 7.38 (m, 2H), 7.11 – 7.07 (m, 2H), 6.49 (t, *J* = 73.9 Hz, 1H), 6.42 (s, 1H), 5.24 (s, 2H), 3.94 (s, 2H), 2.50 (s, 3H), 2.08 (s, 3H); ¹⁹F NMR (471 MHz, CDCl₃) δ -80.68 (d, *J* = 73.8 Hz); ESIMS *m/z* 322 ([M+H]⁺).

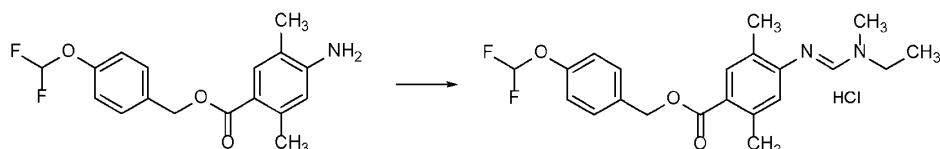
Example 2: Preparation of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate



[0085] In a 20 mL vial, 4-(difluoromethoxy)benzyl 4-amino-2,5-dimethylbenzoate (239 mg, 0.744 mmol) was dissolved in trimethyl orthoformate (2 mL) and then *p*-toluenesulfonic acid monohydrate (14.2 mg, 0.074 mmol) was added. The reaction mixture was heated to reflux (100 °C) and stirred for 3 hours. After 3 hours, TLC indicated near complete consumption of starting material. The reaction was quenched with saturated aqueous sodium bicarbonate (NaHCO₃, 10 mL), and the mixture was extracted with DCM (3 x 10 mL). The combined organic phases were passed through a phase separator and concentrated to a pale-yellow oil. The residue was dissolved in DCM (0.5 mL), and *N*-ethyl-*N*-methylamine (66.0 mg, 1.12 mmol) was added dropwise via syringe. The solution was heated to 40 °C and stirred for 3 hours. The reaction was quenched with water (10 mL), and the mixture was extracted with DCM (3 x 10 mL). The combined organic phases were passed through a phase separator and concentrated. The resultant material was purified by flash column chromatography (C18 reverse phase, 30→100% acetonitrile in water) to afford the title compound (230 mg, 0.589 mmol, 79% yield) as a clear, colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.78 (s, 1H), 7.51 – 7.46 (m, 1H), 7.46 – 7.42 (m, 2H), 7.14 – 7.08 (m, 2H), 6.57 (s, 1H), 6.50 (t, *J* = 73.9 Hz, 1H), 5.27 (s, 2H), 3.57 – 3.24 (m, 2H), 3.00 (s, 3H), 2.55 (s, 3H), 2.23 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ¹⁹F NMR (471 MHz, CDCl₃) δ -80.73 (d, *J* = 73.7 Hz); ESIMS *m/z* 391 ([M+H]⁺).

*Example 3: Preparation of 4-(difluoromethoxy)benzyl 4-**(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride*

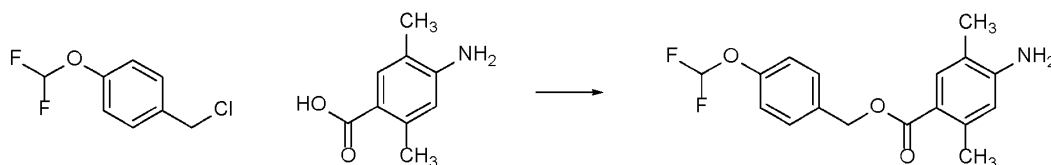
[0086] In a 25 mL vial, a solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (230 mg, 0.589 mmol) was prepared in DCM (2.95 mL). Hydrochloric acid (147 microliters (μL), 0.589 mmol, 4.0 M solution in dioxane) was added in one portion, and the resulting clear colorless solution was allowed to stir at ambient temperature for 4 hours. The volatiles were removed under reduced pressure to afford a colorless film. *Tert*-butyl methyl ether (5 mL) was added, and the resulting mixture was stirred vigorously. The title compound (133 mg, 0.341 mmol, 58% yield) was isolated via vacuum filtration as a white solid and as a mixture of isomers: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.18 – 10.79 (m, 1H), 8.54 – 8.27 (m, 1H), 7.79 (s, 1H), 7.55 (d, $J = 8.2$ Hz, 2H), 7.38 – 7.33 (m, 1H), 7.26 (t, $J = 74.1$ Hz, 1H), 7.22 (d, $J = 8.2$ Hz, 2H), 5.32 (s, 2H), 3.75 – 3.61 (m, 2H), 3.32 – 3.25 (m, 3H), 2.52 – 2.49 (m, 3H), 2.38 – 2.32 (m, 3H), 1.30 – 1.23 (m, 3H) (~2:1 ratio of *E*:*Z* isomers); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -82.14; mp 95–100 °C.

*Example 4: Preparation of 4-(difluoromethoxy)benzyl 4-**(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride*

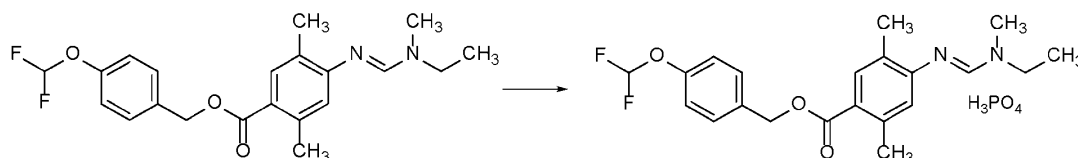
[0087] The title compound can also be prepared as follows. A 500 mL jacketed reactor was equipped with a nitrogen inlet, temperature probe, agitator and outlet attached to a scrubber. The reaction was charged with *N*-ethyl-*N*-methylformamide (8.83 g, 97.4 mmol, 96.0 wt %) and anhydrous DCM (130 mL). The jacket was set to 20 °C, and the mixture was stirred at 250 revolutions per minute (rpm). Oxalyl chloride (8.17 mL, 93.4 mmol) was added over 30 minutes. The mixture was stirred for an additional hour after complete addition. 4-

(Difluoromethoxy)benzyl 4-amino-2,5-dimethylbenzoate (25.0 g, 77.8 mmol) was added as a solution in DCM (64.8 mL) over 90 minutes. The mixture was stirred for an additional hour after complete addition. After 1 hour, the reaction was sampled and analyzed by HPLC, showing high conversion of starting material. The reaction mixture was collected from the reactor and diluted with DCM (100 mL). The mixture was concentrated to ~1/2 volume; heptane (100 mL) was added; and the mixture was concentrated to dryness. Thorough drying overnight under vacuum afforded the title compound (31.2 g, 73.1 mmol, 94% yield) as an off-white solid and as a mixture of isomers.

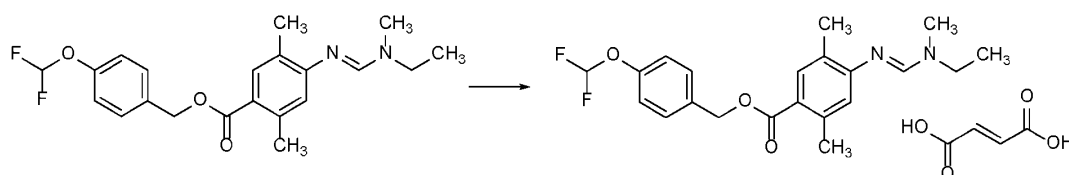
Example 5: Preparation of 4-(difluoromethoxy)benzyl 4-amino-2,5-dimethylbenzoate



[0088] A solution of 4-amino-2,5-dimethylbenzoic acid (0.750 g, 4.54 mmol) was prepared in anhydrous *N,N*-dimethylformamide (DMF, 5.00 mL) in a magnetically stirred 20 mL vial. Potassium carbonate (0.816 g, 5.90 mmol) was added in portions at ambient temperature. The mixture was stirred for ~10 minutes. 1-(Chloromethyl)-4-(difluoromethoxy)benzene (0.874 g, 4.54 mmol) was added dropwise over ~5 minutes, and the resulting amber mixture was stirred at ambient temperature overnight. Ultra performance liquid chromatography (UPLC) analysis indicated near complete consumption of starting material. The reaction mixture was poured into water (25 mL) and extracted with diethyl ether (4 x 5 mL). The combined organic extracts were washed with water (5 x 20 mL) and brine (20 mL), dried over sodium sulfate, filtered, and concentrated to afford the material as a burgundy oil. Purification by flash column chromatography (C18 reverse phase, 20→100% acetonitrile in water) afforded the title compound (1.05 g, 3.28 mmol, 72% yield) as an off-white solid.

*Example 6: Preparation of 4-(difluoromethoxy)benzyl 4-((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate**phosphate*

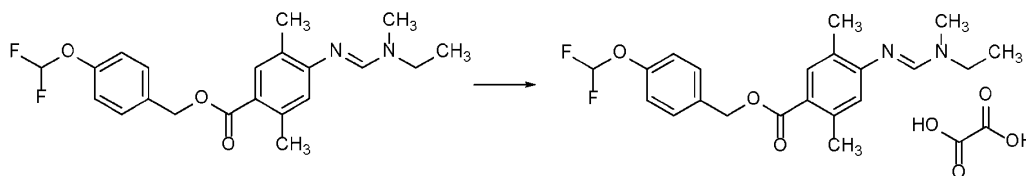
[0089] In a 40 mL vial equipped with a magnetic stir bar, a solution of 4-(difluoromethoxy)benzyl 4-((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (200 mg, 0.512 mmol) was prepared in dry acetonitrile (1 mL). In a separate 4 mL vial, phosphoric acid (55.2 mg, 0.563 mmol) was dissolved in dry acetonitrile (1 mL), and this solution was added dropwise via syringe to the solution of starting material. The resulting solution was stirred at ambient temperature for 15 minutes. The solvent was removed under reduced pressure, and a light-yellow solid was obtained. The solid was dried under high vacuum and was triturated with dry diethyl ether (2 mL). The solvent was decanted (x3) to afford the title compound (220 mg, 0.450 mmol, 88% yield) as a white solid and as a mixture of isomers: ^1H NMR (500 MHz, Acetone- d_6) δ 8.10 – 7.87 (m, 1H), 7.77 (s, 1H), 7.61 – 7.53 (m, 2H), 7.25 – 7.18 (m, 2H), 7.17 – 6.80 (m, 2H), 5.31 (s, 2H), 3.73 – 3.57 (m, 2H), 3.26 (d, J = 6.5 Hz, 3H), 2.51 (s, 3H), 2.29 (d, J = 11.5 Hz, 3H), 1.29 (q, J = 8.4 Hz, 3H); ^{19}F NMR (471 MHz, Acetone- d_6) δ -82.72; ^{31}P NMR (202 MHz, Acetone- d_6) δ 1.80.

*Example 7: Preparation of 4-(difluoromethoxy)benzyl 4-((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate**fumarate*

[0090] A solution of 4-(difluoromethoxy)benzyl 4-((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (200 mg, 0.512 mmol) was prepared in methanol (2 mL) in a 20 mL vial equipped with a magnetic stir bar. To this solution was added fumaric acid (59.5 mg, 0.512

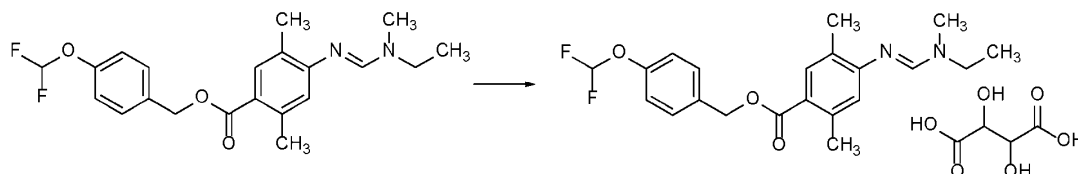
mmol), and the resulting solution was stirred at ambient temperature for 15 minutes. The solvent was removed under reduced pressure, and the resulting oil was dried under high vacuum to yield a foamy solid, which was triturated with dry diethyl ether (2 mL). The solvent was decanted (x3) to afford the title compound (132 mg, 0.261 mmol, 51% yield) as a white solid and as a mixture of isomers: ^1H NMR (500 MHz, CD_3OD) δ 8.16 – 7.90 (m, 1H), 7.81 (s, 1H), 7.54 – 7.46 (m, 2H), 7.20 – 7.12 (m, 2H), 7.05 (s, 1H), 6.99 – 6.64 (m, 3H), 5.31 (s, 2H), 3.60 (q, J = 7.2 Hz, 2H), 3.25 – 3.15 (m, 3H), 2.54 (s, 3H), 2.30 (s, 3H), 1.31 (dt, J = 13.1, 7.3 Hz, 3H), no COO(H); ^{19}F NMR (471 MHz, CD_3OD) δ -83.43.

Example 8: Preparation of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate oxalate



[0091] A solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (215 mg, 0.551 mmol) was prepared in DCM (2.75 mL) in a 5 mL vial equipped with a magnetic stir bar. To this clear, colorless solution was added oxalic acid (49.6 mg, 0.551 mmol), and the resulting solution was stirred at ambient temperature for 3 hours. The solvent was removed under a stream of nitrogen. Dry diethyl ether (2 mL) was added, and the vial was shaken to provide a white solid precipitate that was collected via vacuum filtration. The title compound (185 mg, 0.385 mmol, 70% yield) was isolated as a white solid and as a mixture of isomers: ^1H NMR (396 MHz, $\text{DMSO}-d_6$) δ 7.93 (d, J = 65.1 Hz, 1H), 7.70 (s, 1H), 7.62 – 7.39 (m, 2H), 7.35 – 7.02 (m, 3H), 6.90 (d, J = 24.7 Hz, 1H), 5.27 (s, 2H), 3.47 (dq, J = 13.9, 6.8 Hz, 2H), 3.06 (d, J = 22.6 Hz, 3H), 2.47 (s, 3H), 2.20 (m, 3H), 1.18 (q, J = 5.7 Hz, 3H), no COO(H); ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ -82.03 (d, J = 73.8 Hz); mp 102–106 °C.

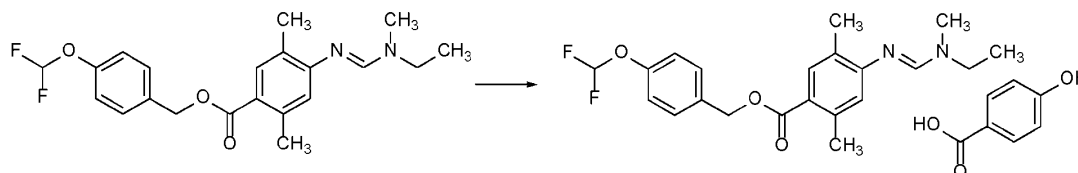
Example 9: Preparation of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate tartrate



[0092] A solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (200 mg, 0.512 mmol) was prepared in methanol (2 mL) in a 20 mL vial equipped with a magnetic stir bar. To this solution was added tartaric acid (77.0 mg, 0.512 mmol), and the resulting solution was stirred at ambient temperature for 15 minutes. The solvent was removed under reduced pressure, and the resulting oil was dried under high vacuum to yield a brown foamy solid, which was triturated with dry diethyl ether (2 mL). The solvent was decanted (x3) to afford the title compound (238 mg, 0.440 mmol, 86% yield) as a white solid and as a mixture of isomers: ^1H NMR (500 MHz, CD_3OD) δ 8.19 – 7.98 (m, 1H), 7.82 (s, 1H), 7.55 – 7.44 (m, 2H), 7.20 – 7.13 (m, 2H), 7.13 – 7.08 (m, 1H), 6.83 (t, $J = 74.1$ Hz, 1H), 5.32 (s, 2H), 4.42 (s, 2H), 3.63 (q, $J = 7.2$ Hz, 2H), 3.32 – 3.19 (m, 3H), 2.55 (s, 3H), 2.32 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H), no -O(H) or COO(H); ^{19}F NMR (471 MHz, CD_3OD) δ -83.44; mp 147 °C.

Example 10: Preparation of 4-(difluoromethoxy)benzyl 4-

(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate 4-hydroxybenzoate

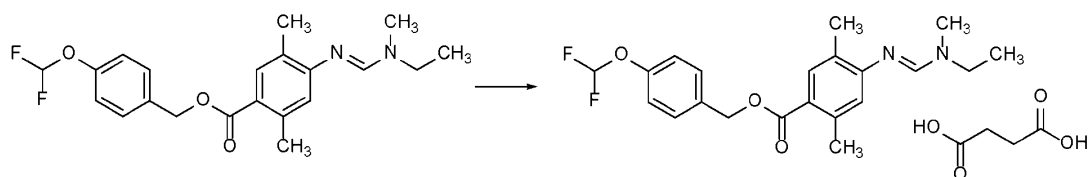


[0093] A solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (200 mg, 0.512 mmol) was prepared in methanol (2 mL) in a 20 mL vial equipped with a magnetic stir bar. To this solution was added 4-hydroxybenzoic acid (70.8 mg, 0.512 mmol), and the resulting solution was stirred at ambient temperature for 15 minutes. The solvent was removed under reduced pressure. The resulting brown oil was dried under high vacuum to yield a brown foamy solid which was triturated with dry diethyl ether (2 mL). The solvent was decanted (x3) to afford the title compound (235 mg, 0.445 mmol, 87% yield) as a light brown solid and as a mixture of isomers: ^1H NMR (500 MHz, CD_3OD) δ 7.90 – 7.83 (m,

2H), 7.74 (s, 2H), 7.53 – 7.44 (m, 2H), 7.19 – 7.12 (m, 2H), 7.02 – 6.62 (m, 4H), 5.28 (s, 2H), 3.56 – 3.37 (m, 2H), 3.05 (s, 3H), 2.51 (s, 3H), 2.22 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), no -O(H) or COO(H); ^{19}F NMR (471 MHz, CD_3OD) δ -83.34; mp 64 °C.

Example 11: Preparation of 4-(difluoromethoxy)benzyl 4-

(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate succinate



[0094] A solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (214 mg, 0.548 mmol) was prepared in a mixture of acetone (2.47 mL) and water (0.27 mL) in a 20 mL vial equipped with a magnetic stir bar. Succinic acid (64.7 mg, 0.548 mmol) was added, and the resulting clear colorless solution was stirred at ambient temperature for 2 hours. The volatiles were removed, and the residue was diluted sequentially with the following solvents and then evaporated – diethyl ether (~2 mL), DCM (~2 mL), and hexanes (~2 mL) – to provide a semi-solid foam material. The solid was isolated via suction filtration, washing with hexanes. The title compound (70 mg, 0.138 mmol, 25% yield) was isolated as a white foam and as a mixture of isomers: ^1H NMR (500 MHz, CD_3OD) δ 7.98 – 7.87 (m, 1H), 7.80 (s, 1H), 7.55 – 7.48 (m, 2H), 7.22 – 7.14 (m, 2H), 6.94 (s, 1H), 6.84 (t, $J = 74.1$ Hz, 1H), 5.31 (s, 2H), 3.63 – 3.47 (m, 2H), 3.22 – 3.00 (m, 3H), 2.56 (d, $J = 0.8$ Hz, 7H), 2.28 (d, $J = 5.8$ Hz, 3H), 1.31 (td, $J = 7.2, 3.8$ Hz, 3H), no COO(H); ^{19}F NMR (471 MHz, CD_3OD) δ -83.34.

Example 12: Crystallization of 4-(difluoromethoxy)benzyl 4-

(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I) as Form A – evaporative crystallization from ethyl acetate

[0095] 1 g of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I) as a colorless oil was dissolved in ethyl acetate. The solution was concentrated under vacuum with stirring at 35 °C for 5 hours. The oil crystallized to an off-white

solid upon cooling to room temperature. A sample was analyzed by powder X-ray diffraction (PXRD) according to Method 1 and assigned the designation Form A.

Example 13: Crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 1 – evaporative crystallization from isopropyl alcohol

[0096] A saturated solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) in isopropyl alcohol was prepared. The solution was evaporated to dryness at 50 °C without stirring before placing under vacuum at 50 °C to provide a crystalline solid. A sample was analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 1.

Example 14: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 1 – slow evaporative crystallization from acetone or combinations of dichloromethane, ethyl acetate and/or heptane

[0097] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 15 mg) was dissolved in acetone or a combination of dichloromethane, ethyl acetate and/or heptane in a vial. A needle was inserted through the septum of the cap to allow for slow evaporation at room temperature to provide crystalline solids. Samples were analyzed by powder X-ray diffraction (PXRD) according to Method 1 and assigned the designation Form 1.

Example 15: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 1 – solvent/antisolvent crystallization from ethanol/methyl tert-butyl ether, acetonitrile/isopropyl acetate, chloroform/heptane, or chloroform/methyl isobutyl ketone

[0098] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was fully dissolved in solvent (ethanol, acetonitrile, or chloroform) in a vial. An antisolvent (methyl *tert*-butyl ether, isopropyl acetate,

heptane, or methyl isobutyl ketone) was added dropwise until 4x the initial solvent volume was reached. Samples were stirred at room temperature overnight. If no precipitation occurred, solutions were then put in a -20 °C freezer. Once precipitation occurred, samples were filtered to provide crystalline solids. Samples were analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 1.

Example 16: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 1 – fast cooling crystallization from toluene/acetonitrile

[0099] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was dissolved in toluene–acetonitrile (70:30) at 50 °C, and the solution was quickly added to an ice bath without stirring. Stirring was started after 10 minutes. Once precipitation occurred, the sample was filtered to provide crystalline solid. A sample was analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 1.

Example 17: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 1 – slow cooling crystallization from methyl isobutyl ketone/acetone, ethanol/heptane, toluene/acetonitrile, ethyl acetate/heptane, or ethyl acetate/chloroform

[0100] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was added to 2 mL vials. Solvent mixtures (methyl isobutyl ketone/acetone, ethanol/heptane, toluene/acetonitrile, ethyl acetate/heptane, or ethyl acetate/chloroform) were added incrementally at 50 °C until fully dissolved. The solutions were cooled slowly to room temperature over ~12 hours. If solids did not precipitate after reaching room temperature, the solutions were cooled further to 0 °C or even further to -20°C by placing the vial(s) in a freezer overnight. Once precipitation occurred, the samples were filtered to provide crystalline solids. Samples were analyzed by powder X-ray diffraction (PXRD) according to Methods 1 and 2 and assigned the designation Form 1.

Example 18: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 1 – stagnant cooling crystallization from methyl ethyl ketone or mixtures of dichloromethane and heptane

[0101] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was dissolved in methyl ethyl ketone or a mixture of dichloromethane and heptane at 50 °C. The solutions were stored in the freezer. Once precipitation occurred, the samples were filtered to provide crystalline solids. Samples were analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 1.

Example 19: Crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 2 – evaporative crystallizations from 2-methyl tetrahydrofuran or methyl isobutyl ketone

[0102] A saturated solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) in 2-methyl tetrahydrofuran and an undersaturated solution of Formula I-B in methyl isobutyl ketone were prepared. The solutions were evaporated to dryness at 50 °C without stirring before placing under vacuum at 50 °C to provide crystalline solids. Samples were analyzed by powder X-ray diffraction (PXRD) according to Methods 1 and 2 and assigned the designation Form 2.

Example 20: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 2 – solvent/antisolvent crystallization from isopropyl alcohol/methyl tert-butyl ether

[0103] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was fully dissolved in isopropyl alcohol in a vial. An antisolvent (methyl *tert*-butyl ether) was added dropwise until 4x the initial solvent volume was reached. The sample was stirred at room temperature overnight. If no precipitation had occurred, the solution was put in a -20°C freezer. Once precipitation occurred, the sample

was filtered to provide crystalline solid. A sample was analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 2.

Example 21: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-

(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as

Form 2 – slow cooling crystallization from methyl isobutyl ketone or heptane/isopropyl alcohol

[0104] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was added to vials. Methyl isobutyl ketone or a mixture of heptane and isopropyl alcohol was added incrementally at 50 °C until the material fully dissolved. The solutions were cooled slowly to room temperature over ~12 hours. If solids did not precipitate after reaching room temperature, the solutions were cooled further to 0 °C or even further to -20 °C by placing in a freezer overnight. Once precipitation occurred, the samples were filtered to provide crystalline solids. Samples were analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 2.

Example 22: Crystallization of 4-(difluoromethoxy)benzyl 4-

(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as

Form 3 – evaporative crystallization from methyl isobutyl ketone

[0105] A saturated solution of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) in methyl isobutyl ketone was prepared. The solution was evaporated to dryness at 50 °C without stirring before placing under vacuum at 50 °C to provide a crystalline solid. A sample was analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 3.

Example 23: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-

(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as

Form 3 – fast cooling crystallization from methyl isobutyl ketone/acetone

[0106] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was dissolved in methyl isobutyl

ketone/acetone (70:30) at 50 °C, and the solution was quickly added to an ice bath without stirring. Stirring was started after 10 minutes. Once precipitation occurred, the sample was filtered to provide crystalline solid. A sample was analyzed by powder X-ray diffraction (PXRD) according to Method 2 and assigned the designation Form 3.

Example 24: Alternate crystallization of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) as Form 3 – slow cooling crystallization from ethyl acetate or tetrahydrofuran/methyl tert-butyl ether

[0107] 4-(Difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B, 25 mg) was added to vials. Ethyl acetate or a mixture of tetrahydrofuran and methyl *tert*-butyl ether was added incrementally at 50 °C until the material was fully dissolved. The solutions were cooled slowly to room temperature over ~12 hours. If solids did not precipitate after reaching room temperature, the solutions were cooled further to 0 °C or even further to -20 °C by placing in a freezer overnight. Once precipitation occurred, the samples were filtered to provide crystalline solids. Samples were analyzed by powder X-ray diffraction (PXRD) according to Methods 1 and 2 and assigned the designation Form 3.

Method 1: Powder X-ray Diffraction (PXRD) of crystalline polymorph Form A of Formula I and Forms 1-3 of Formula I-B

[0108] Samples were analyzed using a Bruker D2 Phaser using Cu K α radiation (30 kilovolts (kV), 10 milliamperes (mA)) and a θ - θ goniometer. The incident beam passed through a 0.2 millimeter (mm) divergence slit. A 1 mm air scatter screen was placed above the sample, and the beam stop was removed. The diffracted beam passed through a 3 mm air scatter slit, 2.5° Soller slits, and a 0.5 K β filter followed by a Lynxeye SSD160 Detector with a position sensitive detector (PSD) opening of 1.5°. Samples were measured under ambient conditions as flat plate specimens using powder as received. The samples were prepared on a polished, zero-background (510) silicon wafer by gently pressing onto the flat surface or packed into a cut cavity. The

sample was rotated in its own plane at 15 rpm. Data were collected from 3 to 40° 2 θ with a step size of 0.03° 2 θ and collection time of 0.5 seconds.

Method 2: Alternative Powder X-ray Diffraction (PXRD) of crystalline polymorph Forms 1-3 of Formula I-B

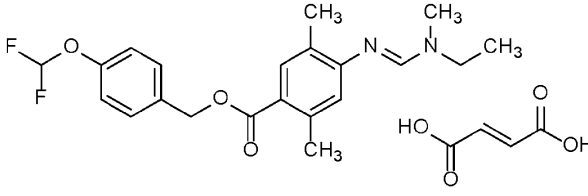
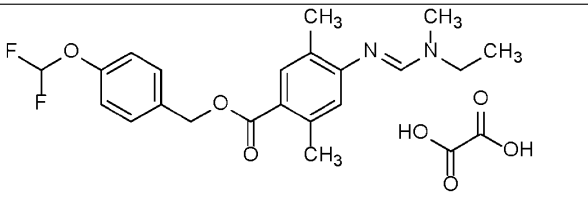
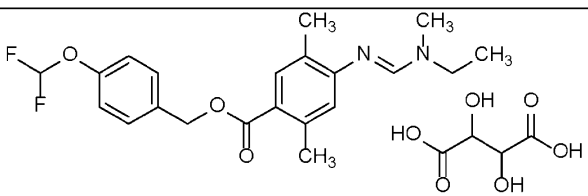
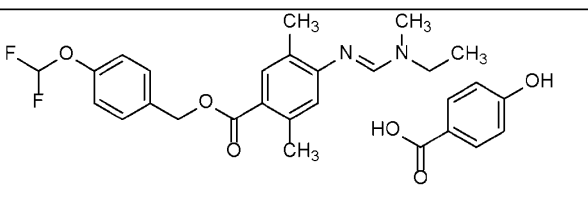
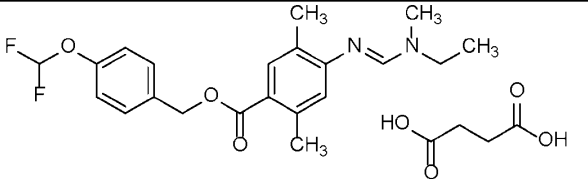
[0109] Samples were analyzed using a Bruker D8 Advance X-ray diffraction system equipped with LYNXEYE detector configured for reflection BraggBrentano geometry. The parameters for PXRD methods used are listed in Table F.

Table E: Parameters Used in PXRD Method 2

Parameter	Regular Scan	High Resolution Scan
X-ray wavelength	Cu K α 1, 1.540598 Å	Cu K α 1, 1.540598 Å
X-ray tube setting	40 kV, 40 mA	40 kV, 40 mA
Slit condition	0.6 mm div. + 2.5° soller	0.6 mm div. + 2.5° soller
Scan mode	Step	Step
Scan range (°2 θ)	4-30	4-40
Step size (°2 θ)	0.03	0.02
Dwell time (s/step)	0.23	0.9
Spin	Yes (0.5 Hz)	Yes (0.5 Hz)

Table F: Structures of compounds tested

Compound	Structure
Formula I	
Formula I-B Hydrochloride Salt of Formula I	
Comparator: Example 25 of WO 2020/237131 A1	
Comparator: Example 27 of WO 2020/237131 A1	
Comparator: Example 494 of WO 2020/237131 A1	
Phosphate Salt of Formula I	

Fumarate Salt of Formula I	
Oxalate Salt of Formula I	
Tartrate Salt of Formula I	
4-Hydroxybenzoate Salt of Formula I	
Succinate Salt of Formula I	

GENERAL BIOLOGICAL EXPERIMENTAL DETAILS AND EXAMPLES

Example A: Evaluation of Fungicidal Activity in Track Sprayer Applications: Septoria Leaf Blotch of Wheat (Zymoseptoria tritici; EPPO code SEPTTR)

[0110] Technical grade material of each tested compound was formulated as a 10% emulsifiable concentrate (EC) with one part active ingredient to nine parts of a mixture of water-

miscible and water-immiscible solvents and nonionic surfactants, each of which was then mixed with water (H₂O) containing 0.1% Break Thru S233 and 0.3% Plurafac LF1300. The details of the EC formulation are provided in Table 1. The fungicide solutions were applied onto wheat seedlings using an automated track sprayer at a volume of 200 liters per hectare (L/ha) at a pressure of 220 kilopascal (kPa) (32 pounds per square inch (psi)). All sprayed plants were allowed to air dry prior to further handling.

Table 1. Details of formulations used in this study.

Component	Role	Percentage (%)
Technical material of AI	Active	10%
Agnique CSO-25	Emulsifier	10%
Atlas G-5002L	Emulsifier	5%
TamiSolve NxG	Solvent	35%
<i>N,N</i> -dimethyl decanamide	Solvent	40%

[0111] Wheat plants (variety ‘Yuma’) were propagated in soil-less potting mix, with each pot having 7-10 plants, and used for testing when the first leaf was fully emerged. Test plants were inoculated with a spore suspension of *Zymoseptoria tritici* either 3 days prior to fungicide treatment (3-day curative; 3DC) or 1 day after fungicide treatment (1-day protectant; 1DP). After inoculation the plants were kept in 100% relative humidity for three days to permit spores to germinate and infect the leaf. The plants were then transferred to a greenhouse for disease to develop. When disease symptoms were fully expressed on the first leaves of untreated plants, infection levels were visually assessed on a scale of 0 to 100 percent disease severity. Percent disease control was calculated using the ratio of disease severity on treated plants relative to untreated plants. Data are shown in FIG. 1.

[0112] FIG. 1 shows the percent disease control at 3 days prior to fungicide treatment (3-day curative; 3DC) or 1 day after fungicide treatment (1-day protectant; 1DP) against test concentrations of Formula I (—◆—), Example 25 (—◆—), Example 27 (—▲—), Example 494 (—■—), and Formula I-B (—■—).

Example B: Evaluation of Fungicidal Activity in Microplot Field Trials: Septoria Leaf Blotch of Wheat (Zymoseptoria tritici; EPPO code SEPTTR)

[0113] Technical grade material of each tested compound was formulated as a 10% emulsifiable concentrate (EC) with one part active ingredient to nine parts of a mixture of water-miscible and water-immiscible solvents and nonionic surfactants, each of which was then mixed with water (H₂O) containing 0.1% Break Thru S233 and 0.3% Plurafac LF1300. The details of the EC formulation are provided in Table 1. The fungicide solutions were applied onto 1-meter by 2-meter plots of wheat plants using a backpack sprayer and a flat fan nozzle at a volume of 200 L/ha at a pressure of 220 kPa.

[0114] Wheat plants (varieties 'Lancer', 'Barrel', and 'Tobak') were established in microplots of 1-meter by 2-meters and materials applied at a curative application timing between growth stages 39 and 55 or at a protectant timing between growth stages 37 and 39 depending on geographic region. Four replicates were used in a random block design. Disease severity on a scale of 0 to 100 percent disease was visually assessed at multiple time points at approximately a 7-to-14-day interval to generate percent disease control based on the area under the disease progress curve. Trials were conducted at up to three geographical locations. Data are shown in FIG. 2.

[0115] FIG. 2 shows the percent disease control against test concentrations of Formula I (—◆—) and Example 25 (-◆-) in a cross-trial analysis of replicated field trials.

Example C: Evaluation of Fungicidal Activity in Microplot Field Trials: Net Blotch of Barley (Pyrenophora teres; EPPO code PYRNTE)

[0116] Technical grade material of each tested compound was formulated as a 10% emulsifiable concentrate (EC) with one part active ingredient to nine parts of a mixture of water-miscible and water-immiscible solvents and nonionic surfactants, each of which was then mixed with water (H₂O) containing 0.1% Break Thru S233 and 0.3% Plurafac LF1300. The details of the EC formulation are provided in Table 1. The fungicide solutions were applied onto 1-meter by 2-meter plots of barley plants using a backpack sprayer and a flat fan nozzle at a volume of 200 L/ha at a pressure of 240-250 kPa.

[0117] Barley plants (varieties ‘Snakebite’, ‘Planet’, and ‘LG Caspari’) were established in microplots of 1-meter by 2-meters and materials applied at a protectant application timing between growth stages 45 and 49 depending on geographic region. Four replicates were used in a random block design. Disease severity on a scale of 0 to 100 percent disease was visually assessed at multiple time points at approximately a 7-day interval to generate percent disease control based on the area under the disease progress curve. Trials were conducted at up to three geographical locations. Data are shown in FIG. 3.

[0118] FIG. 3 shows the percent disease control against test concentrations of Formula I (—◆—) and Example 25 (—■—) in a cross-trial analysis of replicated field trials.

Example D: Evaluation of Fungicidal Activity in Microplot Field Trials: Ramularia Leaf Spot of Barley (Ramularia collo-cygni; EPPO code RAMUCC)

[0119] Technical grade material of each tested compound was formulated as a 10% emulsifiable concentrate (EC) with one part active ingredient to nine parts of a mixture of water-miscible and water-immiscible solvents and nonionic surfactants, each of which was then mixed with water (H₂O) containing 0.1% Break Thru S233 and 0.3% Plurafac LF1300. The details of the EC formulation are provided in Table 1. The fungicide solutions were applied onto 1-meter by 2-meter plots of barley plants using a backpack sprayer and a flat fan nozzle at a volume of 200 L/ha at a pressure of 250-300 kPa.

[0120] Barley plants (varieties ‘Taverna’, ‘Lomerit’ and ‘LG Caspari’) were established in microplots of 1-meter by 2-meters and materials applied at a protectant application timing between growth stages 33 and 41 depending on geographic region. Four replicates were used in a random block design. Disease severity on a scale of 0 to 100 percent disease was visually assessed at multiple time points at approximately a 7-to-14-day interval to generate percent disease control based on the area under the disease progress curve. Trials were conducted at up to three geographical locations. Data are shown in FIG. 4.

[0121] FIG. 4 shows the percent disease control against test concentrations of Formula I (—◆—) and Example 25 (—■—) in a cross-trial analysis of replicated field trials.

Example E: Evaluation of Fungicidal Activity in Microplot Field Trials: Leaf Blotch of Barley (Rhynchosporium secalis; EPPO code RHYNSE)

[0122] Technical grade material of each tested compound was formulated as a 10% emulsifiable concentrate (EC) with one part active ingredient to nine parts of a mixture of water-miscible and water-immiscible solvents and nonionic surfactants, each of which was then mixed with water (H₂O) containing 0.1% Break Thru S233 and 0.3% Plurafac LF1300. The details of the EC formulation are provided in Table 1. The fungicide solutions were applied onto 1 by 2-meter plots of barley plants using a backpack sprayer and a flat fan nozzle at a volume of 200 L/ha at a pressure of 250-300 kPa.

[0123] Barley plants (varieties 'Snakebite' and 'Pixel') were established in microplots of 1-meter by 2-meters and materials applied at a protectant application timing between growth stages 33 and 41 depending on geographic region. Four replicates were used in a random block design. Disease severity on a scale of 0 to 100 percent disease was visually assessed at multiple time points at approximately a 7-to-14-day interval to generate percent disease control based on the area under the disease progress curve. Trials were conducted at up to three geographical locations. Data are shown in FIG. 5,

[0124] FIG. 5 shows the percent disease control against test concentrations of Formula I (—◆—) and Example 25 (-◆-) in a cross-trial analysis of replicated field trials.

Example F: Evaluation of Fungicidal Activity in Microplot Field Trials: Brown Rust of Barley (Puccinia hordei; EPPO code PUCCHD)

[0125] Technical grade material of each tested compound was formulated as a 10% emulsifiable concentrate (EC) with one part active ingredient to nine parts of a mixture of water-miscible and water-immiscible solvents and nonionic surfactants, each of which was then mixed with water (H₂O) containing 0.1% Break Thru S233 and 0.3% Plurafac LF1300. The details of the EC formulation are provided in Table 1. The fungicide solutions were applied onto 1-meter by 2-meter plots of barley plants using a backpack sprayer and a flat fan nozzle at a volume of 200 L/ha at a pressure of 200-300 kPa.

[0126] Barley plants (varieties 'Pixel' and 'Faro') were established in microplots of 1-meter by 2-meters and materials applied at a protectant application timing between growth stages 41

and 65 depending on geographic region. Four replicates were used in a random block design. Disease severity on a scale of 0 to 100 percent disease was visually assessed at multiple time points at approximately a 7-to-14-day interval to generate percent disease control based on the area under the disease progress curve. Trials were conducted at up to three geographical locations. Data are shown in FIG. 6.

[0127] FIG. 6 shows the percent disease control against test concentrations of Formula I (—◆—) and Example 25 (—◆—) in a cross-trial analysis of replicated field trials.

Example G: Evaluation of Fungicidal Activity: Sugar Beet Leaf Spot (Cercospora beticola; EPPO code CERCBE)

[0128] Technical grade material of each tested compound was dissolved in acetone, which was then mixed with nine volumes of water (H₂O) containing 110 ppm Triton X-100. The fungicide solutions were applied onto sugar beet seedlings using an automated booth sprayer to run-off. All sprayed plants were allowed to air dry prior to further handling.

[0129] Sugar beet plants (variety 'SV333') were propagated in soil-less potting mix, with each pot having 1 plant, and used for testing when the first leaf was fully emerged. Test plants were inoculated with a spore suspension of *Cercospora beticola* 1 day (1-day protectant; 1DP) after fungicide treatment. After inoculation, the plants were kept in a dark dew room with 100% relative humidity for two days to permit spores to germinate and infect the leaf. The plants were then transferred to a greenhouse for disease to develop. Disease assessment was conducted as described in Example A. Data are shown in Table 2.

Example H: Evaluation of Fungicidal Activity: Anthracnose of Cucurbits (Colletotrichum orbiculare; EPPO code COLLA)

[0130] Cucumber seedlings (variety 'Bush Pickle') were propagated in soil-less potting mix, with each pot having 1 plant, and used for testing when the first leaf was fully emerged. Test plants were inoculated with a spore suspension of *Colletotrichum orbiculare* one day after fungicide treatments (1-day protectant; 1DP). After inoculation, the plants were kept in 100% relative humidity for two days to permit spores to germinate and infect the leaf. The plants were then transferred to a greenhouse for disease to develop. Fungicide formulation and application

were made as described in Example G. Disease assessment was conducted as described in Example A. Data are shown in Table 2.

*Example I: Evaluation of Fungicidal Activity: Blast of Rice (*Magnaporthe oryzae*; EPPO code PYRIOR)*

[0131] Rice seedlings (variety ‘M202’) were propagated in soil-less potting mix, with each pot having 8 to 10 plants, and used for testing when the first leaf was fully emerged. Test plants were inoculated with a spore suspension of *Magnaporthe oryzae* one day after fungicide treatments (1-day protectant; 1DP). After inoculation the plants were kept in 100% relative humidity for two days to permit spores to germinate and infect the leaf. The plants were then transferred to a greenhouse for disease to develop. Fungicide formulation and application were made as described in Example G. Disease assessment was conducted as described in Example A. Data are shown in Table 2.

Table 2. Fungicidal activity as percent disease control in a 1-day protectant application at 200 and 50 ppm.

Percent (%) Disease Control 1-Day Protectant						
Cmpd. No.	CERCBE		COLLLA		PYRIOR	
	200 ppm	50 ppm	200 ppm	50 ppm	200 ppm	50 ppm
Example 25	53	0	80	2	37	5
Example 494	88	28	74	56	70	52
Example 27	85	68	91	11	74	0
Formula I	88	91	98	92	85	44
Formula I-B	72	63	95	55	94	29

*Example J: Evaluation of Fungicidal Activity: Asian Soybean Rust (*Phakopsora pachyrhizi*; EPPO code PHAKPA)*

[0132] Technical grade material of each tested compound was dissolved in acetone, each of which was then mixed with nine volumes of water (H₂O) containing 0.011% Tween 20. The

fungicide solutions were applied onto soybean seedlings using an automated booth sprayer to run-off. All sprayed plants were allowed to air dry prior to further handling.

[0133] Soybean plants (variety ‘Williams 82’) were propagated in soil-less potting mix, with each pot having 1 plant, and used for testing when the first leaf was fully emerged. Test plants were inoculated as described in Example A. After inoculation plants were kept in 100% relative humidity for 24 hours to permit spores to germinate and infect the leaf. The plants were transferred to a growth room for disease to develop. Fungicide application and disease assessment were made as described in Example A. Data are shown in Table 3.

Table 3. Fungicidal activity as percent disease control in 1-day protectant (1DP) and 3-day curative (3DC) applications at 200, 50, 12.5, and 3.125 ppm.

Percent (%) Disease Control PHAKPA								
Cmpd. No.	1DP				3DC			
	200 ppm	50 ppm	12.5 ppm	3.125 ppm	200 ppm	50 ppm	12.5 ppm	3.125 ppm
Example 25	100	100	100	76	99	98	96	71
Example 27	100	100	97	55	100	99	95	77
Example 494	100	100	100	98	100	99	99	88
Formula I	100	100	100	86	98	100	100	86
Formula I-B	100	100	99	81	100	100	96	63

Example K: Evaluation of Fungicidal Activity: Early Blight of Tomato (Alternaria solani; EPPO code ALTESO)

[0134] Tomato plants (variety ‘Brandywine’) were propagated in soil-less potting mix, with each pot having 1 plant, and used for testing when the first leaf was fully emerged. Test plants were inoculated with a spore suspension of *Alternaria solani* one day after fungicide treatments (1-day protectant; 1DP). After inoculation, the plants were kept in a dark dew room with 100% relative humidity for 2 days to permit spores to germinate and infect the leaf. The plants were then transferred to a greenhouse for disease to develop. Fungicide formulation and application

were made as described in Example G. Disease assessment was conducted as described in Example A. Data are shown in Table 4.

Table 4. Fungicidal activity as percent disease control in a 1-day protectant (1DP) application at 200 and 50 ppm.

Percent (%) Disease Control ALTESO		
Cmpd. No.	1DP	
	200 ppm	50 ppm
Example 25	98	79
Example 27	99	97
Example 494	97	78
Formula I	100	100
Formula I-B	100	99

Example L: Evaluation of Fungicidal Activity: Grey Mold (Botrytis cinerea; EPPO code BOTRCI)

[0135] Grape plants (variety ‘Pinot noir’) were propagated in soil-less potting mix, with each pot having 1 plant, and trimmed to the first fully emerged leaf. Test plants were inoculated with a spore suspension of *Botrytis cinerea* one day after fungicide treatments (1-day protectant; 1DP). After inoculation the plants were kept in a dark dew room with 100% relative humidity for 4 days to permit spores to germinate and infect the leaf. The plants were then transferred to a greenhouse for disease to develop. Fungicide formulation and application were made as described in Example G. Disease assessment was conducted as described in Example A. Data are shown in Table 5.

Table 5. Fungicidal activity as percent disease control in a 1-day protectant (1DP) application at 200 and 50 ppm.

Percent (%) Disease Control BOTRCI		
Cmpd. No.	1DP	
	200 ppm	50 ppm
Example 25	100	94
Example 27	99	100
Example 494	99	95
Formula I	100	100
Formula I-B	100	100

*Example M: Evaluation of Fungicidal Activity: Cucumber Powdery Mildew (*Podosphaera xanthii*; EPPO code PODOXA)*

[0136] Cucumber plants (variety ‘Straight eight’) were propagated in soil-less potting mix, with each pot having 1 plant, and used for testing when the first leaf was fully emerged. Test plants were inoculated with a spore suspension of *Podosphaera xanthii* one day after fungicide treatments (1-day protectant; 1DP). After inoculation the plants were then transferred to a greenhouse for disease to develop. Fungicide formulation and application were made as described in Example G. Disease assessment was conducted as described in Example A. Data are shown in Table 6.

Table 6. Fungicidal activity as percent disease control in a 1-day protectant (1DP) application at 200 and 50 ppm.

Percent (%) Disease Control PODOXA		
Cmpd. No.	1DP	
	200 ppm	50 ppm
Example 25	100	98
Example 27	99	100
Example 494	100	100
Formula I	100	98
Formula I-B	100	98

Example N: Evaluation of In vitro Fungicidal Activity: Cercospora kikuchii, EPPO code CERCKI; Corynespora cassiicola, EPPO code CORYCA; and Septoria glycines, EPPO code SEPTGL

[0137] Test compounds were serially diluted in dimethyl sulfoxide (DMSO), and 2 microliter (μL) aliquots were added to 96-well flat-bottomed microtiter plates (Falcon Products).

[0138] Fungal cultures of *Cercospora kikuchii*, *Corynespora cassiicola* and *Septoria glycines* were grown for 7-14 days on potato dextrose agar (BD DIFCO™ product 213400) or V-8 agar (V8 Juice 200.0 milliliters (mL), calcium carbonate (CaCO_3) 3.0 g, Sucrose 1 g, Agar 15.0 grams per liter (g/L) pH 7.2 ± 0.2 until sporulation. Spore suspensions were prepared in Difco YNB (6.7 g/L, yeast nitrogen base without amino acids; BD Diagnostic Systems) supplemented with 2 g of glucose and 3 g each of potassium dihydrogen phosphate and dipotassium hydrogen phosphate per liter (L). Total assay volume was 200 μL per well. Plates were held for 3-5 days at 22 °C, and growth inhibition was assessed using a NepheloStar nephelometer (BMG LABTECH). Percent growth inhibition was calculated by reference to control wells containing growth media and inoculum amended with 1% DMSO. Data are shown in Table 7.

Table 7. Percent (%) inhibition of *in vitro* fungal growth at 10, 2, 0.4, and 0.08 ppm

Percent (%) Inhibition CERCKI CORYCA SEPTGL												
Organism	CERCKI				CORYCA				SEPTGL			
Test Conc (ppm)	10	2	0.4	0.08	10	2	0.4	0.08	10	2	0.4	0.08
Example 25	70	60	50	20	90	90	60	0	90	100	70	0
Example 494	100	80	70	60	100	90	40	0	100	90	80	10
Example 27	70	50	50	50	100	90	80	40	100	100	100	90
Formula I	80	50	50	30	100	90	100	30	100	100	100	90
Formula I-B	70	60	50	40	90	90	100	40	100	100	100	100

Example O: Evaluation of Fungicidal Activity: Wheat Brown Rust (Puccinia triticina; Synonym: Puccinia recondita f. sp. tritici; Bayer code PuccRT):

[0139] Wheat plants (variety ‘Yuma’) were grown from seed in a greenhouse in soil-less potting mix until the first leaf was fully emerged, with 7-10 seedlings per pot. These plants were inoculated with an aqueous spore suspension of *Puccinia triticina* after fungicide treatments. After inoculation, the plants were kept in a dark dew room with 100% relative humidity overnight to permit spores to germinate and infect the leaf. The plants were then transferred to a greenhouse for disease to develop. Fungicide formulation and application were made as described in Example G. Disease assessment was conducted as described in Example A. Data are shown in Table 8.

Table 8. Fungicidal activity as percent disease control in a 1-day protectant (1DP) application at 200, 50, 12.5, and 3.125 ppm.

Percent (%) Disease Control PuccRT				
Compound	1DP			
	200 ppm	50 ppm	12.5 ppm	3.125 ppm
Example 25	100	100	100	100
Example 27	100	100	98	24
Example 494	97	98	93	86
Formula I	100	100	100	53
Formula I-B	100	100	100	53

Example P: Evaluation of In vitro Fungicidal Activity: Alternaria solani, EPPO code ALTESO; Botrytis cinerea, EPPO code BOTRCI; Colletotrichum orbiculare, EPPO code COLLLA; Corynespora cassiicola, EPPO code CORYCA; Magnaporthe oryzae, EPPO code PYRIOR; Zymoseptoria tritici, EPPO code SEPTTR; and Ustilago maydis, EPPO code USTIMA

[0140] Test compounds were diluted in dimethyl sulfoxide (DMSO), and 2 microliter (μL) aliquots were added to 96-well flat-bottomed microtiter plates (Falcon Products).

[0141] Spore suspensions were prepared in Difco YNB (6.7 g/L, yeast nitrogen base without amino acids; BD Diagnostic Systems) supplemented with 2 g of glucose and 3 g each of potassium dihydrogen phosphate and dipotassium hydrogen phosphate per liter (L). Total assay volume was 200 μL per well. Initial inoculum density was adjusted to 100,000 spores/mL for BOTRCI, CORYCA and SEPTTR, 250,000 spores/mL for COLLLA, 40,000 spores/mL for PYRIOR, 50,000 spores/mL for USTIMA and 10,000-20,000 spores/mL for ALTESO.

[0142] Immediately after addition of spore suspensions, initial cell density readings were determined using a NepheloStar nephelometer (BMG LABTECH Gmb, Ortenberg, Germany). After incubation in a New Brunswick Innova 44 incubator (Eppendorf, Inc., Enfield, CT) for 48 hours at 22 °C (ALTESO, BOTRCI, PYRIOR, and USTIMA), 72 hours at 22 °C (SEPTTR), 96 hours at 22 °C (CORYCA), or 96 h at 28 °C (COLLLA), the plates were read in the NepheloStar a second time to assess growth. Percentage growth inhibition was calculated by reference to control wells containing growth media and inoculum amended with 1% DMSO. Data are shown in Table 9.

Table 9. Percent (%) inhibition of *in vitro* fungal growth at 5 ppm

Percent inhibition of fungal growth <i>in vitro</i>								
Free base form	Salt form	ALTESO	BOTRCI	COLLA	CORYCA	PYRIOR	SEPTTR	USTIMA
Formula I	None (free base)	60	50	100	100	70	80	90
Formula I	Hydrochloride (Formula I-B)	70	100	100	100	80	90	90
Formula I	Phosphate	N/A	90	100	100	70	80	70
Formula I	Fumarate	40	90	100	100	80	80	70
Formula I	Oxalate	60	90	100	100	70	70	60
Formula I	Tartrate	60	90	100	100	50	80	50
Formula I	4-Hydroxybenzoate	40	80	100	100	40	70	10
Formula I	Succinate	50	80	100	100	50	80	60
Example 25	None (free base)	60	70	70	100	60	80	90
Example 25	Hydrochloride (Example 494 from WO 2020/237131 A1)	N/A	N/A	N/A	100	70	90	90

[0143] In light of the above, the compounds of the present disclosure may be described as embodiments in any of the following enumerated clauses. It will be understood that any of the embodiments described herein may be used in connection with any other embodiments described herein to the extent that the embodiments do not contradict one another.

1. A crystalline form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I).
2. The crystalline form of embodiment 1, wherein the crystalline form is a crystalline polymorph form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I).
3. The crystalline form of embodiment 1 or 2, wherein the crystalline form is an anhydrous and solvent-free crystalline polyform form.
4. A crystalline polymorph Form A of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate (Formula I) having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 23.3 ± 0.2 .
5. The crystalline polymorph form of embodiment 4, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.4 ± 0.2 and 23.3 ± 0.2 .

6. The crystalline polymorph form of embodiment 4 or 5, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 12.4 ± 0.2 , 23.3 ± 0.2 , and 27.1 ± 0.2 .
7. The crystalline polymorph form of any one of embodiments 4 to 6, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 12.4 ± 0.2 , 21.6 ± 0.2 , 23.3 ± 0.2 , and 27.1 ± 0.2 .
8. The crystalline polymorph form of any one of embodiments 4 to 7, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 5.5 ± 0.2 , 12.4 ± 0.2 , 21.6 ± 0.2 , 23.3 ± 0.2 , and 27.1 ± 0.2 .
9. The crystalline polymorph form of any one of embodiments 4 to 8, wherein the crystalline form has a powder X-ray diffraction pattern comprising one or more peaks essentially the same as shown in FIG. 7.
10. A crystalline form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B).
11. The crystalline form of embodiment 10, wherein the crystalline form is a crystalline polymorph form of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B).
12. The crystalline form of embodiment 10 or 11, wherein the crystalline form is a hemi-hydrate crystalline polymorph form.
13. A crystalline polymorph Form 1 of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 23.6 ± 0.2 .
14. The crystalline polymorph form of embodiment 13, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.1 ± 0.2 and 23.6 ± 0.2 .
15. The crystalline polymorph form of embodiment 13 or 14, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 12.1 ± 0.2 , 18.7 ± 0.2 , and 23.6 ± 0.2 .

16. The crystalline polymorph form of any one of embodiments 13 to 15, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 10.5 ± 0.2 , 12.1 ± 0.2 , 18.7 ± 0.2 , and 23.6 ± 0.2 .
17. The crystalline polymorph form of any one of embodiments 13 to 16, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 10.5 ± 0.2 , 12.1 ± 0.2 , 18.7 ± 0.2 , 23.6 ± 0.2 , and 25.9 ± 0.2 .
18. The crystalline polymorph form of any one of embodiments 13 to 17, wherein the crystalline form has a powder X-ray diffraction pattern comprising one or more peaks essentially the same as shown in FIG. 8.
19. The crystalline form of embodiment 10 or 11, wherein the crystalline form is an anhydrous and solvent-free crystalline polymorph form.
20. A crystalline polymorph Form 2 of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 9.6 ± 0.2 .
21. The crystalline polymorph form of embodiment 20, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.6 ± 0.2 and 21.6 ± 0.2 .
22. The crystalline polymorph form of embodiment 20 or 21, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , and 21.6 ± 0.2 .
23. The crystalline polymorph form of any one of embodiments 20 to 22, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , 21.6 ± 0.2 , and 24.5 ± 0.2 .
24. The crystalline polymorph form of any one of embodiments 20 to 23, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , 16.1 ± 0.2 , 21.6 ± 0.2 , and 24.5 ± 0.2 .
25. The crystalline polymorph form of any one of embodiments 20 to 24, wherein the crystalline form has a powder X-ray diffraction pattern comprising one or more peaks essentially the same as shown in FIG. 9.

26. A crystalline polymorph Form 3 of 4-(difluoromethoxy)benzyl 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B) having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 9.4 ± 0.2 .
27. The crystalline polymorph form of embodiment 26, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 4.7 ± 0.2 and 9.4 ± 0.2 .
28. The crystalline polymorph form of embodiment 26 or 27, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 4.7 ± 0.2 , 9.4 ± 0.2 , and 19.0 ± 0.2 .
29. The crystalline polymorph form of any one of embodiments 26 to 28, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 4.7 ± 0.2 , 9.4 ± 0.2 , 19.0 ± 0.2 , and 24.7 ± 0.2 .
30. The crystalline polymorph form of any one of embodiments 26 to 29, wherein the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angle (2θ) of 4.7 ± 0.2 , 9.4 ± 0.2 , 19.0 ± 0.2 , 21.1 ± 0.2 , and 24.7 ± 0.2 .
31. The crystalline polymorph form of any one of embodiments 26 to 30, wherein the crystalline form has a powder X-ray diffraction pattern comprising one or more peaks essentially the same as shown in FIG. 10.

[0144] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

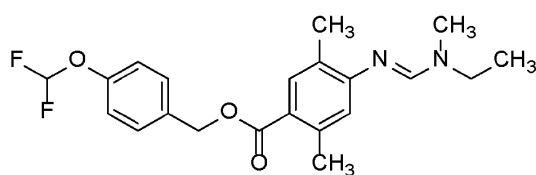
[0145] The use of the terms “a” and “an” and “the” and “at least one” and similar referents in the context of the present disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “at least one” followed by a list of one or more items (for example, “at least one of A and B”) is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including,

but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the present disclosure and does not pose a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of any embodiment herein.

CLAIMS

What is claimed is:

1. A compound of Formula I:



Formula I

or an acceptable salt, solvate, or hydrate thereof.

2. The compound according to claim 1, wherein the acceptable salt is selected from the group consisting of hydrochloride, phosphate, oxalate, tartrate, fumarate, succinate, and 4-hydroxybenzoate.
3. The compound according to claim 1 or claim 2, wherein the acceptable salt is hydrochloride.
4. The compound according to claim 3, wherein the compound is 4-((difluoromethoxy)methyl)-2,5-dimethylbenzoate 4-(((ethyl(methyl)amino)methylene)amino)-2,5-dimethylbenzoate hydrochloride (Formula I-B).
5. The compound according to any one of claims 1 to 4 for use in controlling a fungal pathogen.
6. The compound according to claim 5, wherein the fungal pathogen is one of *Zymoseptoria tritici*, *Cochliobolus sativus*, *Puccinia triticina*, *Puccinia striiformis*, *Ustilago maydis*, *Uncinula necator*, *Rhynchosporium secalis*, *Magnaporthe oryzae*, *Phakopsora pachyrhizi*, *Parastagonospora nodorum*, *Colletotrichum orbiculare*, *Puccinia hordei*, *Cercospora beticola*, *Alternaria solani*, *Pyrenophora teres*, *Blumeria graminis f. sp. tritici*, *Blumeria graminis f. sp. hordei*, *Erysiphe cichoracearum*,

Podosphaera xanthii, *Rhizoctonia solani*, *Botrytis cinerea*, *Ramularia collo-cygni*, *Pyrenophora tritici-repentis*, *Exserohilum turcicum*, *Puccinia polysora*, *Sclerotinia sclerotiorum*, *Erysiphe diffusa*, *Podosphaera leucotricha*, *Colletotrichum truncatum*, *Cercospora kikuchii*, *Cercospora sojina*, *Corynespora cassiicola*, and *Septoria glycines*.

7. The compound according to claim 6, wherein the fungal pathogen is one of *Zymoseptoria tritici*, *Pyrenophora teres*, *Ramularia collo-cygni*, *Rhynchosporium secalis*, *Puccinia hordei*, *Cercospora beticola*, *Colletotrichum orbiculare*, *Magnaporthe oryzae*, *Phakopsora pachyrhizi*, *Alternaria solani*, *Botrytis cinerea*, *Podosphaera xanthii*, *Cercospora kikuchii*, *Corynespora cassiicola*, *Septoria glycines*, *Ustilago maydis*, and *Puccinia triticina*.
8. The compound according to claim 5, wherein the compound treats one of the following diseases from the fungal pathogen: Septoria leaf blotch of wheat (*Zymoseptoria tritici*), spot blotch of barley (*Cochliobolus sativus*), wheat brown rust (*Puccinia triticina*), wheat stripe rust (*Puccinia striiformis*), blister smut of maize (*Ustilago maydis*), powdery mildew of grapevine (*Uncinula necator*), leaf blotch of barley (*Rhynchosporium secalis*), blast of rice (*Magnaporthe oryzae*), Asian soybean rust (*Phakopsora pachyrhizi*), glume blotch of wheat (*Parastagonospora nodorum*), anthracnose of cucurbits (*Colletotrichum orbiculare*), brown rust of barley (*Puccinia hordei*), sugar beet leaf spot (*Cercospora beticola*), early blight of tomato (*Alternaria solani*), net blotch of barley (*Pyrenophora teres*), powdery mildew of wheat (*Blumeria graminis f. sp. tritici*), powdery mildew of barley (*Blumeria graminis f. sp. hordei*), powdery mildew of cucurbits (*Erysiphe cichoracearum*), powdery mildew of cucumber (*Podosphaera xanthii*), collar rot or damping-off of seedlings (*Rhizoctonia solani*), grey mold (*Botrytis cinerea*), Ramularia leaf spot (*Ramularia collo-cygni*), tan spot of wheat (*Pyrenophora tritici-repentis*), Northern leaf blight of maize (*Exserohilum turcicum*), Southern rust of maize (*Puccinia polysora*), white mold (*Sclerotinia sclerotiorum*), powdery mildew of soybean (*Erysiphe diffusa*), powdery mildew of apple (*Podosphaera leucotricha*), anthracnose of soybean (*Colletotrichum truncatum*),

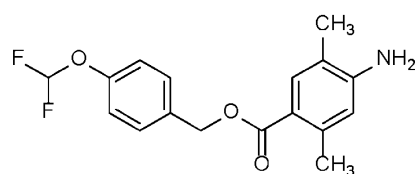
Cercospora leaf blight (*Cercospora kikuchii*), frog-eye leaf spot (*Cercospora sojina*), target spot of soybean (*Corynespora cassiicola*), and leaf spot of soybean (*Septoria glycines*).

9. The compound according to claim 8, wherein the compound treats one of the following diseases from the fungal pathogen: Septoria leaf blotch of wheat (*Zymoseptoria tritici*), net blotch of barley (*Pyrenophora teres*), Ramularia leaf spot (*Ramularia collo-cygni*), leaf blotch of barley (*Rhynchosporium secalis*), brown rust of barley (*Puccinia hordei*), sugar beet leaf spot (*Cercospora beticola*), anthracnose of cucurbits (*Colletotrichum orbiculare*), blast of rice (*Magnaporthe oryzae*), Asian soybean rust (*Phakopsora pachyrhizi*), early blight of tomato (*Alternaria solani*), grey mold (*Botrytis cinerea*), powdery mildew of cucumber (*Podosphaera xanthii*), *Cercospora* leaf blight (*Cercospora kikuchii*), target spot of soybean (*Corynespora cassiicola*), leaf spot of soybean (*Septoria glycines*), blister smut of maize (*Ustilago maydis*), and wheat brown rust (*Puccinia triticina*).
10. A composition for use in the control of a fungal pathogen, the composition comprising a phytologically acceptable amount of a compound of any one of claims 1 to 4 and a carrier.
11. The composition according to claim 10, wherein the fungal pathogen is one of *Zymoseptoria tritici*, *Cochliobolus sativus*, *Puccinia triticina*, *Puccinia striiformis*, *Ustilago maydis*, *Uncinula necator*, *Rhynchosporium secalis*, *Magnaporthe oryzae*, *Phakopsora pachyrhizi*, *Parastagonospora nodorum*, *Colletotrichum orbiculare*, *Puccinia hordei*, *Cercospora beticola*, *Alternaria solani*, *Pyrenophora teres*, *Blumeria graminis* f. sp. *tritici*, *Blumeria graminis* f. sp. *hordei*, *Erysiphe cichoracearum*, *Podosphaera xanthii*, *Rhizoctonia solani*, *Botrytis cinerea*, *Ramularia collo-cygni*, *Pyrenophora tritici-repentis*, *Exserohilum turcicum*, *Puccinia polysora*, *Sclerotinia sclerotiorum*, *Erysiphe diffusa*, *Podosphaera leucotricha*, *Colletotrichum truncatum*, *Cercospora kikuchii*, *Cercospora sojina*, *Corynespora cassiicola*, and *Septoria glycines*.

12. The composition according to claim 11, wherein the fungal pathogen is one of *Zymoseptoria tritici*, *Pyrenophora teres*, *Ramularia collo-cygni*, *Rhynchosporium secalis*, *Puccinia hordei*, *Cercospora beticola*, *Colletotrichum orbiculare*, *Magnaporthe oryzae*, *Phakopsora pachyrhizi*, *Alternaria solani*, *Botrytis cinerea*, *Podosphaera xanthii*, *Cercospora kikuchii*, *Corynespora cassiicola*, *Septoria glycines*, *Ustilago maydis*, and *Puccinia triticina*.
13. The composition according to claim 10, wherein the composition treats one of the following diseases from the fungal pathogen: Septoria leaf blotch of wheat (*Zymoseptoria tritici*), spot blotch of barley (*Cochliobolus sativus*), wheat brown rust (*Puccinia triticina*), wheat stripe rust (*Puccinia striiformis*), blister smut of maize (*Ustilago maydis*), powdery mildew of grapevine (*Uncinula necator*), leaf blotch of barley (*Rhynchosporium secalis*), blast of rice (*Magnaporthe oryzae*), Asian soybean rust (*Phakopsora pachyrhizi*), glume blotch of wheat (*Parastagonospora nodorum*), anthracnose of cucurbits (*Colletotrichum orbiculare*), brown rust of barley (*Puccinia hordei*), sugar beet leaf spot (*Cercospora beticola*), early blight of tomato (*Alternaria solani*), net blotch of barley (*Pyrenophora teres*), powdery mildew of wheat (*Blumeria graminis* f. sp. *tritici*), powdery mildew of barley (*Blumeria graminis* f. sp. *hordei*), powdery mildew of cucurbits (*Erysiphe cichoracearum*), powdery mildew of cucumber (*Podosphaera xanthii*), collar rot or damping-off of seedlings (*Rhizoctonia solani*), grey mold (*Botrytis cinerea*), Ramularia leaf spot (*Ramularia collo-cygni*), tan spot of wheat (*Pyrenophora tritici-repentis*), Northern leaf blight of maize (*Exserohilum turcicum*), Southern rust of maize (*Puccinia polysora*), white mold (*Sclerotinia sclerotiorum*), powdery mildew of soybean (*Erysiphe diffusa*), powdery mildew of apple (*Podosphaera leucotricha*), anthracnose of soybean (*Colletotrichum truncatum*), Cercospora leaf blight (*Cercospora kikuchii*), frog-eye leaf spot (*Cercospora soja*), target spot of soybean (*Corynespora cassiicola*), and leaf spot of soybean (*Septoria glycines*).
14. The composition according to claim 13, wherein the composition treats one of the following diseases from the fungal pathogen: Septoria leaf blotch of wheat

(*Zymoseptoria tritici*), net blotch of barley (*Pyrenophora teres*), Ramularia leaf spot (*Ramularia collo-cygni*), leaf blotch of barley (*Rhynchosporium secalis*), brown rust of barley (*Puccinia hordei*), sugar beet leaf spot (*Cercospora beticola*), anthracnose of cucurbits (*Colletotrichum orbiculare*), blast of rice (*Magnaporthe oryzae*), Asian soybean rust (*Phakopsora pachyrhizi*), early blight of tomato (*Alternaria solani*), grey mold (*Botrytis cinerea*), powdery mildew of cucumber (*Podosphaera xanthii*), Cercospora leaf blight (*Cercospora kikuchii*), target spot of soybean (*Corynespora cassiicola*), leaf spot of soybean (*Septoria glycines*), blister smut of maize (*Ustilago maydis*), and wheat brown rust (*Puccinia triticina*).

15. A seed treated with a phytologically acceptable amount of the compound according to any one of claims 1 to 4 or the composition according to claim 10.
16. A method of controlling fungal attack on a plant, the method comprising contacting an area adjacent to the plant, soil adapted to support growth of the plant, a root of the plant, foliage of the plant, and a growth medium adapted to grow a plant or a seed, with a phytologically acceptable amount of the compound according to any one of claims 1 to 4 or the composition according to claim 10.
17. A compound, 4-(difluoromethoxy)benzyl 4-amino-2,5-dimethylbenzoate



or acceptable salts, solvates, isotopes, or tautomers thereof.

18. A crystalline polymorph Form A of the compound of Formula I according to claim 1, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising at least two peaks at diffraction angles (2θ) of 5.5 ± 0.2 , 12.4 ± 0.2 , 21.6 ± 0.2 , 23.3 ± 0.2 , and 27.1 ± 0.2 .

19. A crystalline polymorph Form 1 of the compound according to claim 3 or claim 4, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising at least two peaks at diffraction angles (2θ) of 10.5 ± 0.2 , 12.1 ± 0.2 , 18.7 ± 0.2 , 23.6 ± 0.2 , and 25.9 ± 0.2 .
20. A crystalline polymorph Form 2 of the compound according to claim 3 or claim 4, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising at least two peaks at diffraction angles (2θ) of 4.9 ± 0.2 , 9.6 ± 0.2 , 16.1 ± 0.2 , 21.6 ± 0.2 , and 24.5 ± 0.2 .
21. A crystalline polymorph Form 3 of the compound according to claim 3 or claim 4, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising at least two peaks at diffraction angles (2θ) of 4.7 ± 0.2 , 9.4 ± 0.2 , 19.0 ± 0.2 , 21.1 ± 0.2 , and 24.7 ± 0.2 .