(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 April 2020 (16.04.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/074364 A1

(51) International Patent Classification:
C07D 405/06 (2006.01) *A01N 43/653* (2006.01)

(21) International Application Number:
PCT/EP2019/076838

(22) International Filing Date:
03 October 2019 (03.10.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1816444.2 09 October 2018 (09.10.2018) GB

(71) Applicant: **SYNGENTA CROP PROTECTION AG** [CH/CH]; Rosentalstrasse 67, 4058 Basel (CH).

(72) Inventors: **FORREST, James, Owen**; Syngenta Limited Syngenta, Jealott's Hill International Research Centre, Bracknell Berkshire RG42 6EY (GB). **GEORGE, Neil**; Syngenta Limited Syngenta, Jealott's Hill International Research Centre, Bracknell Berkshire RG42 6EY (GB).

(74) Agent: **SYNGENTA IP**; Rosentalstrasse 67, 4058 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: CO-CRYSTALS OF DIFENOCONAZOLE

(57) Abstract: The present invention relates to novel co-crystals of difenoconzaole and fumaric acid and their use in fungicidal compositions, in particular agrochemical compositions.

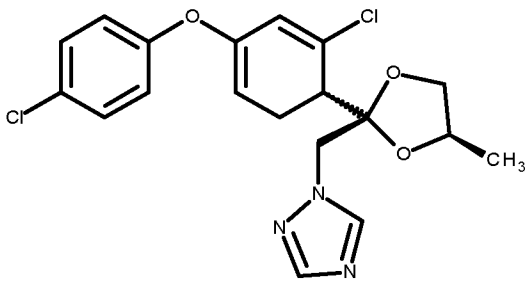
WO 2020/074364 A1

CO-CRYSTALS OF DIFENOCONAZOLE

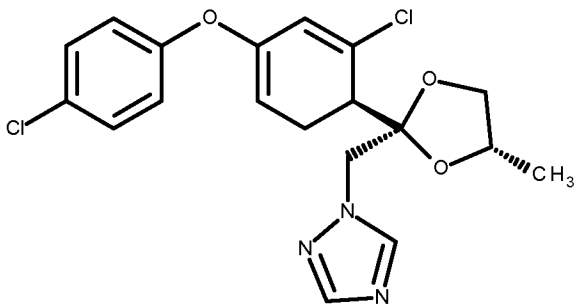
The present invention relates to novel co-crystals of difenoconzaole and their use in fungicidal compositions, in particular agrochemical compositions.

Difenconazole (1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl-methyl]-1H-1,2,4-triazole) is a broad spectrum fungicide which acts by inhibition of demethylation during ergosterol biosynthesis. It is available commercially and is described in "The Pesticide Manual" [The Pesticide Manual, Seventeenth Edition; Editor J. Turner; The British Crop Protection Council].

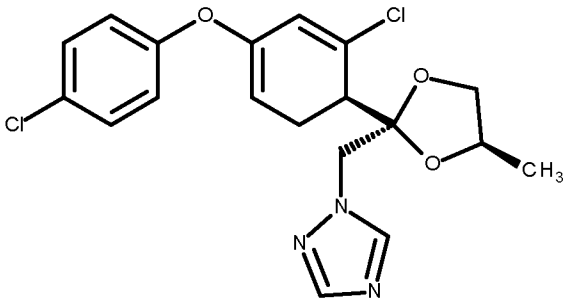
Four difenoconazole isomers are known:



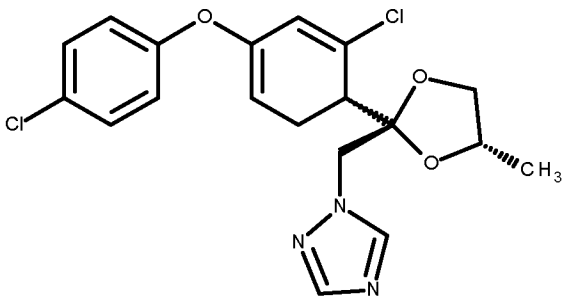
(Ia); 2S, 4R (cis)



(Ib); 2R, 4S (cis)



(Ic); 2R, 4R (trans)



(Id) 2S, 4S (trans)

During manufacture, difenoconazole is normally produced in a ratio of about 60:40 cis:trans, with a ratio of 1:1 between cis and trans racemates, i.e. 60:40 2S, 4R (Ia) and 2R, 4S (Ib) : 2R, 4R (Ic) and 2S, 4S (Id) and 1:1 of 2S, 4R (Ia): 2R, 4S (Ib) and 1:1 2R, 4R (Ic): 2S, 4S (Id). In typical manufacture, the resulting difenoconazole contains about 30% (Ia), about 30% (Ib), about 20% (Ic) and about 20% (Id). These are usually present as a 1:1:1:1 co-crystal of (Ia) : (Ib) : (Ic) : (Id), with the excess (Ia) and (Ib) being present as a 1:1 cis-racemate co-crystal.

Difenoconazole has a melting point around 79°C, but the onset of melting may occur at temperatures closer to 70°C. The melting point may be further depressed in the presence of other organic compounds and this may lead to difficulties in formulating difenoconazole.

A number of technologies are used to formulate difenoconazole. For example, it may be co-milled with other active ingredients and their co-formulants – this ensures a homogenous distribution of all components in the mixture as well as reducing capital overhead costs and providing greater speed and efficiency. Alternatively, granulation may be used. In both of these methods, mixing the components will depress the melting point of the difenoconazole – this can result in partial melting of the solids and a failure of the milling and/or granulation process.

Spray granulation may also be used to formulate difenoconazole. In this process, the active ingredient is mixed with other formulation components, wet milled to reduce the particle size and then spray-dried to create a porous 'raspberry-like' structure. Use of a material with a low melting point in spray granulation can lead to milling failures as detailed above and, in addition, the high temperatures that the granules experience during the spray drying process (70-90°C) can also lead to complete melting and clogging of the spray-drying equipment or partial melting leading to granules that do not redisperse on dilution in the spray tank.

Formulation of a co-crystal with a higher melting point that the original active ingredient can overcome all these problems and prevent formulation failures.

Accordingly, the present invention provides a co-crystal of difenoconazole with fumaric acid which has a higher melting point that difenoconazole alone.

The co-crystalline form of difenoconazole and the crystal forming compound may be characterised by a crystal morphology or by selected peaks of the powder X-ray diffraction pattern expressed in terms of 2 theta angles.

In one embodiment, the present invention provides a co-crystal of the cis racemate of difenoconazole (i.e. (Ia) and (Ib)) with fumaric acid.

In a further embodiment, the co-crystal form of difenoconazole cis racemate and fumaric acid is characterised by the unit cell parameters of its single crystal as shown in Table 1. The co-crystal was obtained using the method of Example 1a and crystallographic data was obtained at 100°K.

Table 1

Class	Monoclinic
Space Group	C 2/c
Cell Lengths (Å)	a = 47.98, b = 5.43, c = 22.02
Cell Angles (°)	$\alpha = 90$, $\beta = 130.75$, $\gamma = 90$
Unit Cell Volume (Å^3)	4346
Z	8

Thus, in this embodiment of the present invention, the co-crystal form of difenoconazole cis racemate and fumaric acid has the following lattice parameters: a=47.98 Å ± 2.40 Å, b=5.43 Å ± 0.30 Å, c=22.02 Å ± 1.10 Å, $\alpha = 90°$, $\beta = 130.75° \pm 6.54°$, $\gamma = 90°$ and volume = 4346Å^3 ± 220 Å^3.

In a further embodiment, the co-crystal form of difenoconazole cis racemate and fumaric acid is characterised by a powder X-ray diffraction pattern expressed in terms of 2θ angles or d spacings, wherein the powder X-ray diffraction pattern comprises at least three, at least 6, at least 9 or all 2θ angle values selected from the group comprising 4.9 ± 0.2, 9.8 ± 0.2, 10.7 ± 0.2, 11.2 ± 0.2, 14.4 ± 0.2, 18.6 ± 0.2, 20.5 ± 0.2, 20.9 ± 0.2, 23.2 ± 0.2, 23.9 ± 0.2 and 24.9 ± 0.2. These 2θ angle values are derived from a powder X-ray diffraction pattern of a difenoconazole cis racemate-fumaric acid co-crystal obtained using the method of Example 1a.

The values are generated using an average wavelength of 1.54060 with a 2θ step size of 0.0092°. Table 2 shows these 2θ angles and the corresponding d spacing values.

Table 2

2-θ	d spacing
4.9	17.8
9.8	9.0
10.7	8.3
11.2	7.9
14.4	6.2
18.6	4.8
20.5	4.3
20.9	4.2
23.2	3.8
23.9	3.7
24.9	3.6

In a further embodiment, the the co-crystal form of difenoconazole cis racemate and fumaric acid has a melting point of 134°C. This melting point is obtained using Differential Scanning Calorimetry (DSC), with a heating rate of 10°C/minute.

In another embodiment, the present invention provides a co-crystal of the trans racemate of difenoconazole (i.e. (Ic) and (Id)) with fumaric acid.

In a further embodiment, the co-crystal form of difenoconazole trans racemate and fumaric acid is characterised by the unit cell parameters of its single crystal as shown in Table 3. The co-crystal was obtained using the method of Example 1b and crystallographic data was obtained at 100°K.

Table 3

Class	Monoclinic
Space Group	Pn
Cell Lengths (Å)	a = 18.11, b = 5.60, c = 21.68
Cell Angles (°)	α = 90, β = 98.92, γ = 90
Unit Cell Volume ($Å^3$)	2173
Z	2/6

Thus, in this embodiment of the present invention, the co-crystal form of difenoconazole trans racemate and fumaric acid has the following lattice parameters: a=18.11 Å ± 0.01 Å, b=5.60 Å ± 0.01 Å, c=21.68 Å ± 0.01 Å, $\alpha = 90^{o}$, $\beta = 98.92^{o} \pm 4.95^{o}$, $\gamma = 90^{o}$ and volume = 2173Å^3 ± 110 Å^3.

In a further embodiment, the co-crystal form of difenoconazole trans racemate and fumaric acid is characterised by a powder X-ray diffraction pattern expressed in terms of 2θ angles or d spacings, wherein the powder X-ray diffraction pattern comprises at least three, at least 6, at least 9, at least 12 or all 2θ angle values selected from the group comprising 6.0 ± 0.2, 10.0 ± 0.2, 12.7 ± 0.2, 16.7 ± 0.2, 17.0 ± 0.2, 17.4 ± 0.2, 18.0 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, 20.0 ± 0.2, 20.4 ± 0.2, 21.0 ± 0.2, 22.8 ± 0.2, 23.0 ± 0.2 and 24.0 ± 0.2. These 2θ angle values are derived from a powder X-ray diffraction pattern of a difenoconazole trans racemate-fumaric acid co-crystal obtained using the method of Example 1b. The values are generated using an average wavelength of 1.54060 with a 2θ step size of 0.0092°. Table 3 shows these 2θ angles and the corresponding d spacing values.

Table 3

2-θ	d spacing
6.0	14.6
10.0	8.8
12.7	6.9
16.7	5.3
17.0	5.2
17.4	5.1
18.0	4.9
18.9	4.7
19.6	4.5
20.0	4.4
20.4	4.3
21.0	4.2
22.8	3.9
23.0	3.9
24.0	3.7

In a further embodiment, the the co-crystal form of difenoconazole trans racemate and fumaric acid has a melting point of 123°C. This melting point is obtained using Differential Scanning Calorimetry (DSC), with a heating rate of 10°C/minute.

The co-crystals of the present invention are formed by contacting the difenoconazole with the fumaric acid. This may be done by (i) grinding two solids together; (ii) melting one

or both components and allowing them to recrystallise; and (iiia) solubilising, or partially solubilising, the difenoconazole and adding the co-crystal forming compound or (iiib) solubilising, or partially solubilising, the co-crystal forming compound and adding the difenoconazole. It may also be possible to solubilise, or partially solubilise, the difenoconazole in the co-crystal forming compound and vice versa. Preferably, the co-crystals of the invention are formed by grinding two solids together. In particular, the difenoconazole and the fumaric acid may be mixed in a high sheer mixer and then milled. Crystallisation is then allowed to occur under suitable conditions. For example, crystallisation may require alteration of a property of the solutions, such as pH or temperature and may require concentration of solute, usually by removal of the solvent and typically by drying the solution. Solvent removal results in the concentration of difenoconazole increasing over time so as to facilitate crystallisation. In some cases, microwave irradiation or sonication (or both microwave irradiation and sonication) may be used to facilitate crystallisation. Once the solid phase comprising any crystals is formed, it may be tested as described herein.

Accordingly, the present invention provides a process for the production of a co-crystal of the invention comprising

(a) grinding, heating or contacting in solution the difenoconazole with the fumaric acid, under crystallisation conditions so as to form a solid phase;

(b) isolating co-crystals comprising the difenoconazole and fumaric acid.

As used herein 'co-crystal' means a crystalline material which comprises two or more unique components in a stoichiometric ratio each containing distinctive physical characteristics such as structure, melting point and heat of fusion. As used herein, a co-crystal is distinct from a crystalline salt as it consists of neutral components and not charged components as would be found in a salt. The co-crystal can be constructed through several modes of molecular recognition including hydrogen-bonding, Π (pi)-stacking, guest-host complexation and Van-Der-Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. Preferred co-crystals of the present invention are those where hydrogen bonding occurs between the fumaric acid and the difenoconazole. It is noted that multi-point contacts may be formed in the crystal. For example, two molecules of

difenoconazole may form contacts with different functional groups on the same fumaric acid molecule, or, indeed, there may be multi-point contacts between a single molecule of difenoconazole and a single fumaric acid molecule.

It is noted that hydrogen bonding can result in several different intermolecular assemblies and, as such, the co-crystals of the present invention may exist in one or more polymorphic forms. fumaric acid, but typically will be in the range of from 5:1 to 1:5Each polymorphic form may be defined by one or more solid state analytical techniques including single crystal X-ray diffraction, powder X-ray diffraction, DSC, Raman or infra-red spectroscopy.

Suitably, the molar ratio of difenoconazole to co-crystal forming compound in the co-crystal is in the range of from 5:1 to 1:5. More suitably, the molar ratio of difenoconazole to co-crystal forming compound in the co-crystal is in the range of from 3:1 to 1:3. Even more suitably, the molar ratio of difenoconazole to co-crystal forming compound is in the range of 2:1 to 1:1 and, in particular, may be 2:1.

Assaying the solid phase for the presence of co-crystals of the difenoconazole and fumaric acid may be carried out by conventional methods known in the art. For example, it is convenient and routine to use powder X-ray diffraction techniques to assess the presence of the co-crystals. This may be effected by comparing the spectra of difenoconazole, fumaric acid and putative co-crystals in order to establish whether or not true co-crystals have been formed. Other techniques used in an analogous fashion, include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and Raman or Infra-red spectroscopy, NMR, gas chromatography or HPLC. Single crystal X-ray diffraction is especially useful in identifying co-crystal structures.

The co-crystals of the invention may applied in unchanged form but are more preferably incorporated into fungicidal compositions (including agrochemical compositions) by conventional means. Accordingly, the invention also provides a fungicidal composition comprising a co-crystal of the invention as defined above and one or more carriers or diluents.

In particular, the present invention provides a composition comprising (i) the co-crystal of difenoconazole cis racemate and fumaric acid or (ii) the co-crsytal of difenoconazole trans racemate and fumaric acid or (iii) a mixture of the co-crystal of difenoconazole cis racemate and fumaric acid and the co-crsytal of difenoconazole trans racemate and fumaric acid.

Where a mixture of the co-crystals is used, preferably, the ratio of cis co-crystal to trans co-crystal in the composition is from 99:1 to 1:99, more preferably from 70:30 to 40:60 and, most preferably, from 60:40 to 50:50.

In one embodiment, the fungicidal composition is an agrochemical composition. The agrochemical compositions comprising the co-crystals of the present invention can be used for the control of plant pathogenic fungi on a number of plant species. Accordingly, the invention also provides a method of preventing or controlling fungal infection on plants or plant propagation material comprising treating the plant or plant propagation material, or locus thereof, with a fungicidally effective amount of an agricultural composition of the invention.

The term "fungicide" as used herein means a compound that controls, modifies, or prevents the growth of fungi. The term "fungicidally effective amount" means the quantity of such a compound or combination of such compounds that is capable of producing an effect on the growth of fungi. Controlling or modifying effects include all deviation from natural development, such as killing, retardation and the like, and prevention includes barrier or other defensive formation in or on a plant to prevent fungal infection.

The term "locus" as used herein means fields in or on which plants are growing, or where seeds of cultivated plants are sown, or where seed will be placed into the soil. It includes soil, seeds, and seedlings, as well as established vegetation.

The term "plants" refers to all physical parts of a plant, including seeds, seedlings, saplings, roots, tubers, stems, stalks, foliage, and fruits.

The term "plant propagation material" denotes all generative parts of a plant, for example seeds or vegetative parts of plants such as cuttings and tubers. It includes seeds in the strict sense, as well as roots, fruits, tubers, bulbs, rhizomes, and parts of plants.

Crops of useful plants in which the composition according to the invention can be used include perennial and annual crops, such as berry plants for example blackberries, blueberries, cranberries, raspberries and strawberries; cereals for example barley, maize (corn), millet, oats, rice, rye, sorghum triticale and wheat; fibre plants for example cotton, flax, hemp, jute and sisal; field crops for example sugar and fodder beet, coffee, hops, mustard, oilseed rape (canola), poppy, sugar cane, sunflower, tea and tobacco; fruit trees for example apple, apricot, avocado, banana, cherry, citrus, nectarine, peach, pear and plum;

grasses for example Bermuda grass, bluegrass, bentgrass, centipede grass, fescue, ryegrass, St. Augustine grass and Zoysia grass; herbs such as basil, borage, chives, coriander, lavender, lovage, mint, oregano, parsley, rosemary, sage and thyme; legumes for example beans, lentils, peas and soya beans; nuts for example almond, cashew, ground nut, hazelnut, peanut, pecan, pistachio and walnut; palms for example oil palm; ornamentals for example flowers, shrubs and trees; other trees, for example cacao, coconut, olive and rubber; vegetables for example asparagus, aubergine, broccoli, cabbage, carrot, cucumber, garlic, lettuce, marrow, melon, okra, onion, pepper, potato, pumpkin, rhubarb, spinach and tomato; and vines for example grapes.

Crops are to be understood as being those which are naturally occurring, obtained by conventional methods of breeding, or obtained by genetic engineering. They include crops which contain so-called output traits (e.g. improved storage stability, higher nutritional value and improved flavour).

Crops are to be understood as also including those crops which have been rendered tolerant to herbicides like bromoxynil or classes of herbicides such as ALS-, EPSPS-, GS-, HPPD- and PPO-inhibitors. An example of a crop that has been rendered tolerant to imidazolinones, e.g. imazamox, by conventional methods of breeding is Clearfield® summer canola. Examples of crops that have been rendered tolerant to herbicides by genetic engineering methods include e.g. glyphosate- and glufosinate-resistant maize varieties commercially available under the trade names RoundupReady®, Herculex I® and LibertyLink®.

Crops are also to be understood as being those which naturally are or have been rendered resistant to harmful insects. This includes plants transformed by the use of recombinant DNA techniques, for example, to be capable of synthesising one or more selectively acting toxins, such as are known, for example, from toxin-producing bacteria. Examples of toxins which can be expressed include δ-endotoxins, vegetative insecticidal proteins (Vip), insecticidal proteins of bacteria colonising nematodes, and toxins produced by scorpions, arachnids, wasps and fungi.

An example of a crop that has been modified to express the *Bacillus thuringiensis* toxin is the Bt maize KnockOut® (Syngenta Seeds). An example of a crop comprising more than one gene that codes for insecticidal resistance and thus expresses more than one toxin is

VipCot® (Syngenta Seeds). Crops or seed material thereof can also be resistant to multiple types of pests (so-called stacked transgenic events when created by genetic modification). For example, a plant can have the ability to express an insecticidal protein while at the same time being herbicide tolerant, for example Herculex I® (Dow AgroSciences, Pioneer Hi-Bred International).

In particular, the compositions according to the invention are particularly effective against powdery mildews; rusts; leafspot species; early blights and molds; especially against Septoria, Puccinia, Erysiphe, Pyrenophora and Tapesia in cereals; Phakopsora in soybeans; Hemileia in coffee; Phragmidium in roses; Alternaria in potatoes, tomatoes and cucurbits; Sclerotinia in turf, vegetables, sunflower and oil seed rape; black rot, red fire, powdery mildew, grey mold and dead arm disease in vine; Botrytis cinerea in fruits; Monilinia spp. in fruits and Penicillium spp. in fruits.

The compositions according to the invention are furthermore particularly effective against seedborne and soilborne diseases, such as Alternaria spp., Ascochyta spp., Botrytis cinerea, Cercospora spp., Claviceps purpurea, Cochliobolus sativus, Colletotrichum spp., Epicoccum spp., Fusarium graminearum, Fusarium moniliforme, Fusarium oxysporum, Fusarium proliferatum, Fusarium solani, Fusarium subglutinans, Gäumannomyces graminis , Helminthosporium spp., Microdochium nivale, Phoma spp., Pyrenophora graminea, Pyricularia oryzae, Rhizoctonia solani, Rhizoctonia cerealis, Sclerotinia spp., Septoria spp., Sphacelotheca reilliana, Tilletia spp., Typhula incarnata, Urocystis occulta, Ustilago spp. or Verticillium spp.; in particular against pathogens of cereals, such as wheat, barley, rye or oats; maize; rice; cotton; soybean; turf; sugarbeet; oil seed rape; potatoes; pulse crops, such as peas, lentils or chickpea; and sunflower.

The compositions according to the invention are furthermore particularly effective against post harvest diseasese such as Botrytis cinerea, Colletotrichum musae, Curvularia lunata, Fusarium semitecum, Geotrichum candidum, Monilinia fructicola, Monilinia fructigena, Monilinia laxa, Mucor piriformis, Penicilium italicum, Penicilium solitum, Penicillium digitatum or Penicillium expansum in particular against pathogens of fruits, such as pomefruits, for example apples and pears, stone fruits, for example peaches and plums, citrus, melons, papaya, kiwi, mango, berries, for example strawberries, avocados, pomegranates and bananas, and nuts.

The compositions according to the invention are particularly useful for controlling the following diseases on the following crops:

Alternaria species in fruit and vegetables; Ascochyta species in pulse crops; Botrytis cinerea in strawberries, tomatoes, sunflower, pulse crops, vegetables and grapes, such as Botrytis cinerea on grape; Cercospora arachidicola in peanuts; Cochliobolus sativus in cereals; Colletotrichum species in pulse crops; Erysiphe species in cereals; such as Erysiphe graminis on wheat and Erysiphe graminis on barley; Erysiphe cichoracearum and Sphaerotheca fuliginea in cucurbits; Fusarium species in cereals and maize; Gäumannomyces graminis in cereals and lawns; Helminthosporium species in maize, rice and potatoes; Hemileia vastatrix on coffee; Microdochium species in wheat and rye; Mycosphaerella fijiensis in banana; Phakopsora species in soybeans, such as Phakopsora pachyrizi in soybeans; Puccinia species in cereals, broadleaf crops and perennial plants; such as Puccinia recondita on wheat, Puccinia striiformis on wheat and Puccinia recondita on barley; Pseudocercosporella species in cereals, such as Pseudocercosporella herpotrichoides in wheat; Phragmidium mucronatum in roses; Podosphaera species in fruits; Pyrenophora species in barley, such as Pyrenophora teres on barley; Pyricularia oryzae in rice; Ramularia collo-cygni in barley; Rhizoctonia species in cotton, soybean, cereals, maize, potatoes, rice and lawns, such as Rhizoctonia solani on potato, rice, turf and cotton; Rhynchosporium secalis on barley, Rhynchosporium secalis on rye; Sclerotinia species in lawns, lettuce, vegetables and oil seed rape, such as Sclerotinia sclerotiorum on oilseed rape and Sclerotinia homeocarpa on turf; Septoria species in cereals, soybean and vegetables, such as Septoria tritici on wheat, Septoria nodorum on wheat and Septoria glycines on soybean; Sphacelotheca reilliana in maize; Tilletia species in cereals; Uncinula necator, Guignardia bidwellii and Phomopsis viticola in vines; Urocystis occulta in rye; Uromyces species in beans; Ustilago species in cereals and maize; Venturia species in fruits, such as Venturia inequalis on apple; Monilinia species on fruits; Penicillium species on citrus and apples.

The rate at which the agrochemical composition of the invention is applied will depend upon the particular type of fungus to be controlled, the degree of control required and the timing and method of application and can be readily determined by the person skilled in the art. In general, the compositions of the invention can be applied at an application rate of between 0.005 kilograms/hectare (kg/ha) and about 5.0kg/ha, based on the total amount of active fungicide in the composition. An application rate of between about 0.1kg/ha and about

1.5kg/ha is preferred, with an application rate of between about 0.3kg/ha and 0.8kg/ha being especially preferred.

As noted, the co-crystals according to the invention can be used as pesticidal agents in unmodified form, but they are generally incorporated in compositions in various ways using formulation adjuvants, such as carriers, solvents and surface-active substances. The formulations can be in various physical forms, e.g. in the form of dusting powders, gels, wettable powders, water-dispersible granules, water-dispersible tablets, effervescent pellets, emulsifiable concentrates, microemulsifiable concentrates, oil-in-water emulsions, oil-flowables, aqueous dispersions, oily dispersions, suspo-emulsions, capsule suspensions, emulsifiable granules, soluble liquids, water-soluble concentrates (with water or a water-miscible organic solvent as carrier), impregnated polymer films or in other forms known e.g. from the Manual on Development and Use of FAO and WHO Specifications for Pesticides, United Nations, First Edition, Second Revision (2010). Such formulations can either be used directly or diluted prior to use. The dilutions can be made, for example, with water, liquid fertilisers, micronutrients, biological organisms, oil or solvents.

The formulations can be prepared e.g. by mixing the co-crystals of the invention ('active ingredients') with the formulation adjuvants in order to obtain compositions in the form of finely divided solids, granules, solutions, dispersions or emulsions. The active ingredients can also be formulated with other adjuvants, such as finely divided solids, mineral oils, oils of vegetable or animal origin, modified oils of vegetable or animal origin, organic solvents, water, surface-active substances or combinations thereof.

The active ingredients can also be contained in very fine microcapsules. Microcapsules contain the active ingredients in a porous carrier. This enables the active ingredients to be released into the environment in controlled amounts (e.g. slow-release). Microcapsules usually have a diameter of from 0.1 to 500 microns. They contain active ingredients in an amount of about from 25 to 95 % by weight of the capsule weight. The active ingredients can be in the form of a monolithic solid, in the form of fine particles in solid or liquid dispersion or in the form of a suitable solution. The encapsulating membranes can comprise, for example, natural or synthetic rubbers, cellulose, styrene/butadiene copolymers, polyacrylonitrile, polyacrylate, polyesters, polyamides, polyureas, polyurethane or chemically modified polymers and starch xanthates or other polymers that are known to the person skilled in the art. Alternatively, very fine microcapsules can be formed in which

the active ingredient is contained in the form of finely divided particles in a solid matrix of base substance, but the microcapsules are not themselves encapsulated.

The formulation adjuvants that are suitable for the preparation of the compositions according to the invention are known *per se*. As liquid carriers there may be used: water, toluene, xylene, petroleum ether, vegetable oils, acetone, methyl ethyl ketone, cyclohexanone, acid anhydrides, acetonitrile, acetophenone, amyl acetate, 2-butanone, butylene carbonate, chlorobenzene, cyclohexane, cyclohexanol, alkyl esters of acetic acid, diacetone alcohol, 1,2-dichloropropane, diethanolamine, p-diethylbenzene, diethylene glycol, diethylene glycol abietate, diethylene glycol butyl ether, diethylene glycol ethyl ether, diethylene glycol methyl ether, *N,N*-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, dipropylene glycol, dipropylene glycol methyl ether, dipropylene glycol dibenzoate, diproxitol, alkylpyrrolidone, ethyl acetate, 2-ethylhexanol, ethylene carbonate, 1,1,1-trichloroethane, 2-heptanone, alpha-pinene, d-limonene, ethyl lactate, ethylene glycol, ethylene glycol butyl ether, ethylene glycol methyl ether, gamma-butyrolactone, glycerol, glycerol acetate, glycerol diacetate, glycerol triacetate, hexadecane, hexylene glycol, isoamyl acetate, isobornyl acetate, isooctane, isophorone, isopropylbenzene, isopropyl myristate, lactic acid, laurylamine, mesityl oxide, methoxypropanol, methyl isoamyl ketone, methyl isobutyl ketone, methyl laurate, methyl octanoate, methyl oleate, methylene chloride, m-xylene, *n*-hexane, *n*-octylamine, octadecanoic acid, octylamine acetate, oleic acid, oleylamine, o-xylene, phenol, polyethylene glycol, propionic acid, propyl lactate, propylene carbonate, propylene glycol, propylene glycol methyl ether, p-xylene, toluene, triethyl phosphate, triethylene glycol, xylenesulfonic acid, paraffin, mineral oil, trichloroethylene, perchloroethylene, ethyl acetate, amyl acetate, butyl acetate, propylene glycol methyl ether, diethylene glycol methyl ether, methanol, ethanol, isopropanol, and alcohols of higher molecular weight, such as amyl alcohol, tetrahydrofurfuryl alcohol, hexanol, octanol, ethylene glycol, propylene glycol, glycerol, *N*-methyl-2-pyrrolidone and the like.

Suitable solid carriers are, for example, talc, titanium dioxide, pyrophyllite clay, silica, attapulgite clay, kieselguhr, limestone, calcium carbonate, bentonite, calcium montmorillonite, cottonseed husks, wheat flour, soybean flour, pumice, wood flour, ground walnut shells, lignin and similar substances.

A large number of surface-active substances can advantageously be used in both solid and liquid formulations, especially in those formulations which can be diluted with a carrier

prior to use. Surface-active substances may be anionic, cationic, non-ionic or polymeric and they can be used as emulsifiers, wetting agents or suspending agents or for other purposes. Typical surface-active substances include, for example, salts of alkyl sulfates, such as diethanolammonium lauryl sulfate; salts of alkylarylsulfonates, such as calcium dodecyl-benzenesulfonate; alkylphenol/alkylene oxide addition products, such as nonylphenol ethoxylate; alcohol/alkylene oxide addition products, such as tridecylalcohol ethoxylate; soaps, such as sodium stearate; salts of alkylnaphthalenesulfonates, such as sodium dibutylnaphthalenesulfonate; dialkyl esters of sulfosuccinate salts, such as sodium di(2-ethylhexyl)sulfosuccinate; sorbitol esters, such as sorbitol oleate; quaternary amines, such as lauryltrimethylammonium chloride, polyethylene glycol esters of fatty acids, such as polyethylene glycol stearate; block copolymers of ethylene oxide and propylene oxide; and salts of mono- and di-alkylphosphate esters; and also further substances described e.g. in McCutcheon's Detergents and Emulsifiers Annual, MC Publishing Corp., Ridgewood New Jersey (1981).

Further adjuvants that can be used in pesticidal formulations include crystallisation inhibitors, viscosity modifiers, suspending agents, dyes, anti-oxidants, foaming agents, light absorbers, mixing auxiliaries, antifoams, complexing agents, neutralising or pH-modifying substances and buffers, corrosion inhibitors, fragrances, wetting agents, take-up enhancers, micronutrients, plasticisers, glidants, lubricants, dispersants, thickeners, antifreezes, microbicides, and liquid and solid fertilisers.

The compositions according to the invention can include an additive comprising an oil of vegetable or animal origin, a mineral oil, alkyl esters of such oils or mixtures of such oils and oil derivatives. The amount of oil additive in the composition according to the invention is generally from 0.01 to 10 %, based on the mixture to be applied. For example, the oil additive can be added to a spray tank in the desired concentration after a spray mixture has been prepared. Preferred oil additives comprise mineral oils or an oil of vegetable origin, for example rapeseed oil, olive oil or sunflower oil, emulsified vegetable oil, alkyl esters of oils of vegetable origin, for example the methyl derivatives, or an oil of animal origin, such as fish oil or beef tallow. Preferred oil additives comprise alkyl esters of C_8-C_{22} fatty acids, especially the methyl derivatives of C_{12}-C_{18} fatty acids, for example the methyl esters of lauric acid, palmitic acid and oleic acid (methyl laurate, methyl palmitate and methyl oleate, respectively). Many oil derivatives are known from the Compendium of Herbicide Adjuvants, 10th Edition, Southern Illinois University, 2010.

The inventive compositions generally comprise from 0.1 to 99 % by weight, especially from 0.1 to 95 % by weight, of compounds of the present invention and from 1 to 99.9 % by weight of a formulation adjuvant which preferably includes from 0 to 25 % by weight of a surface-active substance. Whereas commercial products may preferably be formulated as concentrates, the end user will normally employ dilute formulations.

The rates of application vary within wide limits and depend on the nature of the soil, the method of application, the crop plant, the pest to be controlled, the prevailing climatic conditions, and other factors governed by the method of application, the time of application and the target crop. As a general guideline compounds may be applied at a rate of from 1 to 2000 l/ha, especially from 10 to 1000 l/ha.

Preferred formulations can have the following compositions (weight %):

Emulsifiable concentrates:

active ingredient:	1 to 95 %, preferably 60 to 90 %
surface-active agent:	1 to 30 %, preferably 5 to 20 %
liquid carrier:	1 to 80 %, preferably 1 to 35 %

Dusts:

active ingredient:	0.1 to 10 %, preferably 0.1 to 5 %
solid carrier:	99.9 to 90 %, preferably 99.9 to 99 %

Suspension concentrates:

active ingredient:	5 to 75 %, preferably 10 to 50 %
water:	94 to 24 %, preferably 88 to 30 %
surface-active agent:	1 to 40 %, preferably 2 to 30 %

Wettable powders:

active ingredient:	0.5 to 90 %, preferably 1 to 80 %
surface-active agent:	0.5 to 20 %, preferably 1 to 15 %
solid carrier:	5 to 95 %, preferably 15 to 90 %

Granules:

active ingredient:	0.1 to 30 %, preferably 0.1 to 15 %

solid carrier: 99.5 to 70 %, preferably 97 to 85 %

The following Examples further illustrate, but do not limit, the invention.

Wettable powders	a)	b)	c)
active ingredient	25 %	50 %	75 %
sodium lignosulfonate	5 %	5 %	-
sodium lauryl sulfate	3 %	-	5 %
sodium diisobutylnaphthalenesulfonate	-	6 %	10 %
phenol polyethylene glycol ether	-	2 %	-
(7-8 mol of ethylene oxide)			
highly dispersed silicic acid	5 %	10 %	10 %
Kaolin	62 %	27 %	-

The combination is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording wettable powders that can be diluted with water to give suspensions of the desired concentration.

Powders for dry seed treatment	a)	b)	c)
active ingredient	25 %	50 %	75 %
light mineral oil	5 %	5 %	5 %
highly dispersed silicic acid	5 %	5 %	-
Kaolin	65 %	40 %	-
Talcum	-		20

The combination is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording powders that can be used directly for seed treatment.

Emulsifiable concentrate	
active ingredient	10 %
octylphenol polyethylene glycol ether	3 %
(4-5 mol of ethylene oxide)	
calcium dodecylbenzenesulfonate	3 %
castor oil polyglycol ether (35 mol of ethylene oxide)	4 %
Cyclohexanone	30 %
xylene mixture	50 %

Emulsions of any required dilution, which can be used in plant protection, can be obtained from this concentrate by dilution with water.

Dusts	a)	b)	c)
active ingredients	5 %	6 %	4 %
Talcum	95 %	-	-
Kaolin	-	94 %	-
mineral filler	-	-	96 %

Ready-for-use dusts are obtained by mixing the combination with the carrier and grinding the mixture in a suitable mill. Such powders can also be used for dry dressings for seed.

Extruder granules	
active ingredient	15 %
sodium lignosulfonate	2 %
carboxymethylcellulose	1 %
Kaolin	82 %

The combination is mixed and ground with the adjuvants, and the mixture is moistened with water. The mixture is extruded and then dried in a stream of air.

Coated granules	
active ingredient	8 %
polyethylene glycol (mol. wt. 200)	3 %
Kaolin	89 %

The finely ground combination is uniformly applied, in a mixer, to the kaolin moistened with polyethylene glycol. Non-dusty coated granules are obtained in this manner.

Suspension concentrate

active ingredient	40 %
propylene glycol	10 %
nonylphenol polyethylene glycol ether (15 mol of ethylene oxide)	6 %
Sodium lignosulfonate	10 %
carboxymethylcellulose	1 %
silicone oil (in the form of a 75 % emulsion in water)	1 %
Water	32 %

The finely ground combination is intimately mixed with the adjuvants, giving a suspension concentrate from which suspensions of any desired dilution can be obtained by dilution with water. Using such dilutions, living plants as well as plant propagation material can be treated and protected against infestation by microorganisms, by spraying, pouring or immersion.

Flowable concentrate for seed treatment

active ingredient	40 %
propylene glycol	5 %
copolymer butanol PO/EO	2 %
Tristyrenephenole with 10-20 moles EO	2 %
1,2-benzisothiazolin-3-one (in the form of a 20% solution in water)	0.5 %
monoazo-pigment calcium salt	5 %
Silicone oil (in the form of a 75 % emulsion in water)	0.2 %
Water	45.3 %

The finely ground combination is intimately mixed with the adjuvants, giving a suspension concentrate from which suspensions of any desired dilution can be obtained by dilution with water. Using such dilutions, living plants as well as plant propagation material can be treated and protected against infestation by microorganisms, by spraying, pouring or immersion.

Slow Release Capsule Suspension

28 parts of the active ingredients are mixed with 2 parts of an aromatic solvent and 7 parts of toluene diisocyanate/polymethylene-polyphenylisocyanate-mixture (8:1). This mixture is emulsified in a mixture of 1.2 parts of polyvinylalcohol, 0.05 parts of a defoamer and 51.6 parts of water until the desired particle size is achieved. To this emulsion a mixture of 2.8 parts 1,6-diaminohexane in 5.3 parts of water is added. The mixture is agitated until the polymerization reaction is completed. The obtained capsule suspension is stabilized by adding 0.25 parts of a thickener and 3 parts of a dispersing agent. The capsule suspension formulation contains 28% of the active ingredients. The medium capsule diameter is 8-15 microns. The resulting formulation is applied to seeds as an aqueous suspension in an apparatus suitable for that purpose.

Each of the above formulations can be prepared as a package containing the fungicides together with other ingredients of the formulation (diluents, emulsifiers,

surfactants, etc.). The formulations can also be prepared by a tank mix method, in which the ingredients are obtained separately and combined at the grower site.

These formulations can be applied to the areas where control is desired by conventional methods. Dust and liquid compositions, for example, can be applied by the use of power-dusters, broom and hand sprayers and spray dusters. The formulations can also be applied from airplanes as a dust or a spray or by rope wick applications. Both solid and liquid formulations may also be applied to the soil in the locus of the plant to be treated allowing the active ingredient to penetrate the plant through the roots. The formulations of the invention may also be used for dressing applications on plant propagation material to provide protection against fungus infections on the plant propagation material as well as against phytopathogenic fungi occurring in the soil. Suitably, the active ingredient may be applied to plant propagation material to be protected by impregnating the plant propagation material, in particular, seeds, either with a liquid formulation of the fungicide or coating it with a solid formulation. In special cases, other types of application are also possible, for example, the specific treatment of plant cuttings or twigs serving propagation.

Suitably, the agrochemical compositions and formulations of the present invention are applied prior to disease development. Rates and frequency of use of the formulations are those conventionally used in the art and will depend on the risk of infestation by the fungal pathogen.

Normally, in the management of a crop a grower would use one or more other agronomic chemicals in addition to the compositions and formulations of the present invention. Examples of agronomic chemicals include pesticides, such as acaricides, bactericides, fungicides, herbicides, insecticides, nematicides, as well as plant nutrients and plant fertilizers. In particular, the composition of the present invention may be used in combination at lease one further fungicides.

The co-crystals of the invention may be mixed with one or more of compounds selected from those in the following chemical or functional classes:- 1,2,4-thiadiazoles, 2,6-dinitroanilines, acylalanines, aliphatic nitrogenous compounds, amidines, aminopyrimidinols, anilides, anilino-pyrimidines, anthraquinones, antibiotics, aryl-phenylketones, benzamides, benzene-sulfonamides, benzimidazoles, benzothiazoles, benzothiodiazoles, benzothiophenes, benzoylpyridines, benzthiadiazoles, benzylcarbamates, butylamines, carbamates, carboxamides, carpropamids, chloronitriles, cinnamic acid amides, copper containing

compounds, cyanoacetamideoximes, cyanoacrylates, cyanoimidazoles, cyanomethylene-thiazolidines, dicarbonitriles, dicarboxamides, dicarboximides, dimethylsulphamates, dinitrophenol carbonates, dinitrophenysl, dinitrophenyl crotonates, diphenyl phosphates, dithiino compounds, dithiocarbamates, dithioethers, dithiolanes, ethyl-amino-thiazole carboxamides, ethyl-phosphonates, furan carboxamides, glucopyranosyls, glucopyranoxyls, glutaronitriles, guanidines, herbicides/plant growth regulatosr, hexopyranosyl antibiotics, hydroxy(2-amino)pyrimidines, hydroxyanilides, hydroxyisoxazoles, imidazoles, imidazolinones, insecticides/plant growth regulators, isobenzofuranones, isoxazolidinyl-pyridines, isoxazolines, maleimides, mandelic acid amides, mectin derivatives, morpholines, norpholines, n-phenyl carbamates, organotin compounds, oxathiin carboxamides, oxazoles, oxazolidine-diones, phenols, phenoxy quinolines, phenyl-acetamides, phenylamides, phenylbenzamides, phenyl-oxo-ethyl-thiophenes amides, phenylpyrroles, phenylureas, phosphorothiolates, phosphorus acids, phthalamic acids, phthalimides, picolinamides, piperazines, piperidines, plant extracts, polyoxins, propionamides, pthalimides, pyrazole-4-carboxamides, pyrazolinones, pyridazinones, pyridines, pyridine carboxamides, pyridinyl-ethyl benzamides, pyrimdinamines, pyrimidines, pyrimidine-amines, pyrimidione-hydrazone, pyrrolidines, pyrrolquinoliones, quinazolinones, quinolines, quinoline derivatives, quinoline-7-carboxylic acids, quinoxalines, spiroketalamines, strobilurins, sulfamoyl triazoles, sulphamides, tetrazolyloximes, thiadiazines, thiadiazole carboxamides, thiazole carboxanides, thiocyanates, thiophene carboxamides, toluamides, triazines, triazobenthiazoles, triazoles, triazole-thiones, triazolo-pyrimidylamine, valinamide carbamates, ammonium methyl phosphonates, arsenic-containing compounds, benyimidazolylcarbamates, carbonitriles, carboxanilides, carboximidamides, carboxylic phenylamides, diphenyl pyridines, furanilides, hydrazine carboxamides, imidazoline acetates, isophthalates, isoxazolones, mercury salts, organomercury compounds, organophosphates, oxazolidinediones, pentylsulfonyl benzenes, phenyl benzamides, phosphonothionates, phosphorothioates, pyridyl carboxamides, pyridyl furfuryl ethers, pyridyl methyl ethers, SDHIs, thiadiazinanethiones, thiazolidines.

Particularly preferred fungicidal combinations include the following where "I" designates the co-crsytals of the invention: I + etridiazole, I + fluazinam, I + benalaxyl, I + benalaxyl-M (kiralaxyl), I + furalaxyl, I + metalaxyl, I + metalaxyl-M (mefenoxam), I + dodicin, I + N'-(2,5-Dimethyl-4-phenoxy-phenyl)-N-ethyl-N-methyl-formamidine, I + N'-[4-(4,5-Dichloro-thiazol-2-yloxy)-2,5-dimethyl-phenyl]-N-ethyl-N-methyl-formamidine, I + N'-[4-[[3-[(4-chlorophenyl)methyl]-1,2,4-thiadiazol-5-yl]oxy]-2,5-dimethyl-phenyl]-N-ethyl-N-

methyl-formamidine, I + ethirimol, I + 3′-chloro-2-methoxy-N-[(3RS)-tetrahydro-2-oxofuran-3-yl]acet-2′,6′-xylidide (clozylacon), I + cyprodinil, I + mepanipyrim, I + pyrimethanil, I + dithianon, I + aureofungin, I + blasticidin-S, I + biphenyl, I + chloroneb, I + dicloran, I + hexachlorobenzene, I + quintozene, I + tecnazene, (TCNB), I + tolclofos-methyl, I + metrafenone, I + 2,6-dichloro-N-(4-trifluoromethylbenzyl)-benzamide, I + fluopicolide (flupicolide), I + tioxymid, I + flusulfamide, I + benomyl, I + carbendazim, I + carbendazim chlorhydrate, I + chlorfenazole, I + fuberidazole, I + thiabendazole, I + thiophanate-methyl, I + benthiavalicarb, I + chlobenthiazone, I + probenazole, I + acibenzolar, I + bethoxazin, I + pyriofenone (IKF-309), I + acibenzolar-S-methyl, I + pyribencarb (KIF-7767), I + butylamine, I + 3-iodo-2-propinyl n-butylcarbamate (IPBC), I + iodocarb (isopropanyl butylcarbamate), I + isopropanyl butylcarbamate (iodocarb), I + Picarbutrazox, I + polycarbamate, I + propamocarb, I + tolprocarb, I + 3-(difluoromethyl)-N-(7-fluoro-1,1,3,3-tetramethyl-indan-4-yl)-1-methyl-pyrazole-4-carboxamide I + diclocymet, I + N-[(5-chloro-2-isopropyl-phenyl)methyl]-N-cyclopropyl-3-(difluoromethyl)-5-fluoro-1-methyl-pyrazole-4-carboxamide I + N-cyclopropyl-3-(difluoromethyl)-5-fluoro-N-[(2-isopropylphenyl)methyl]-1-methyl-pyrazole-4-carboxamide I + carpropamid, I + chlorothalonil, I + flumorph, I + oxine-copper, I + cymoxanil, I + phenamacril, I + cyazofamid, I + flutianil, I + thicyofen, I + chlozolinate, I + iprodione, I + procymidone, I + vinclozolin, I + bupirimate, I + dinocton, I + dinopenton, I + dinobuton, I + dinocap, I + meptyldinocap, I + diphenylamine, I + phosdiphen, I + 2,6-dimethyl-[1,4]dithiino[2,3-c:5,6-c']dipyrrole-1,3,5,7(2H,6H)-tetraone, I + azithiram, I + etem, I + ferbam, I + mancozeb, I + maneb, I + metam, I + metiram (polyram), I + metiram-zinc, I + nabam, I + propineb, I + thiram, I + vapam (metam sodium), I + zineb, I + ziram, I + dithioether, I + isoprothiolane, I + ethaboxam, I + fosetyl, I + phosetyl-Al (fosetyl-al), I + methyl bromide, I + methyl iodide, I + methyl isothiocyanate, I + cyclafuramid, I + fenfuram, I + validamycin, I + streptomycin, I + (2RS)-2-bromo-2-(bromomethyl)glutaronitrile (bromothalonil), I + dodine, I + doguadine, I + guazatine, I + iminoctadine, I + iminoctadine triacetate, I + 2,4-D, I + 2,4-DB, I + kasugamycin, I + dimethirimol, I + fenhexamid, I + hymexazole, hydroxyisoxazole I + imazalil, I + imazalil sulphate, I + oxpoconazole, I + pefurazoate, I + prochloraz, I + triflumizole, I + fenamidone, I + Bordeaux mixture, I + calcium polysulfide, I + copper acetate, I + copper carbonate, I + copper hydroxide, I + copper naphthenate, I + copper oleate, I + copper oxychloride, I + copper oxyquinolate, I + copper silicate, I + copper sulphate, I + copper tallate, I + cuprous oxide, I + sulphur, I + carbaryl, I + phthalide (fthalide), I + dingjunezuo (Jun Si Qi), I +

oxathiapiprolin, I + fluoroimide, I + mandipropamid, I + KSF-1002, I + benzamorf, I + dimethomorph, I + fenpropimorph, I + tridemorph, I + dodemorph, I + diethofencarb, I + fentin acetate, I + fentin hydroxide, I + carboxin, I + oxycarboxin, I + drazoxolon, I + famoxadone, I + m-phenylphenol, I + p-phenylphenol, I + tribromophenol (TBP), I + 2-[2-[(7,8-difluoro-2-methyl-3-quinolyl)oxy]-6-fluoro-phenyl]propan-2-ol I + 2-[2-fluoro-6-[(8-fluoro-2-methyl-3-quinolyl)oxy]phenyl]propan-2-ol I + cyflufenamid, I + ofurace, I + oxadixyl, I + flutolanil, I + mepronil, I + isofetamid, I + fenpiclonil, I + fludioxonil, I + pencycuron, I + edifenphos, I + iprobenfos, I + pyrazophos, I + phosphorus acids, I + tecloftalam, I + captafol, I + captan, I + ditalimfos, I + CAS 517875-34-2 (DAS777), I + triforine, I + fenpropidin, I + piperalin, I + osthol, I + 1-methylcyclopropene, I + 4-CPA, I + chlormequat, I + clofencet, I + dichlorprop, I + dimethipin, I + endothal, I + ethephon, I + flumetralin, I + forchlorfenuron, I + gibberellic acid, I + gibberellins, I + hymexazol, I + maleic hydrazide, I + mepiquat, I + naphthalene acetamide, I + paclobutrazol, I + prohexadione, I + prohexadione-calcium, I + thidiazuron, I + tribufos (tributyl phosphorotrithioate), I + trinexapac, I + uniconazole, I + α-naphthalene acetic acid, I + polyoxin D (polyoxrim), I + BLAD, I + chitosan, I + fenoxanil, I + folpet, I + pydiflumetofen, I + benzovindiflupyr, I + bixafen, I + fluxapyroxad, I + furametpyr, I + isopyrazam, I + penflufen, I + penthiopyrad, I + sedaxane, I + fenpyrazamine, I + diclomezine, I + pyrifenox, I + boscalid, I + fluopyram, I + diflumetorim, I + fenarimol, I + 5-fluoro-2-(p-tolylmethoxy)pyrimidin-4-amine I + ferimzone, I + dimetachlone (dimethaclone), I + pyroquilon, I + proquinazid, I + ethoxyquin, I + quinoxyfen, I + 4,4,5-trifluoro-3,3-dimethyl-1-(3-quinolyl)isoquinoline I + 4,4-difluoro-3,3-dimethyl-1-(3-quinolyl)isoquinoline I + 5-fluoro-3,3,4,4-tetramethyl-1-(3-quinolyl)isoquinoline I + 9-fluoro-2,2-dimethyl-5-(3-quinolyl)-3H-1,4-benzoxazepine I + tebufloquin, I + oxolinic acid, I + chinomethionate (oxythioquinox, quinoxymethionate), I + spiroxamine, I + (E)-N-methyl-2- [2- (2, 5-dimethylphenoxymethyl) phenyl]-2-methoxy-iminoacetamide, (mandestrobin), I + azoxystrobin, I + coumoxystrobin, I + dimoxystrobin, I + enestroburin, enoxastrobin I + fenamistrobin, I + flufenoxystrobin, I + fluoxastrobin, I + kresoxim-methyl, I + mandestrobin, I + metaminostrobin, I + metominostrobin, I + orysastrobin, I + picoxystrobin, I + pyraclostrobin, I + pyrametostrobin, I + pyraoxystrobin, I + triclopyricarb , I + trifloxystrobin, I + amisulbrom, I + dichlofluanid, I + tolylfluanid, I + but-3-ynyl N-[6-[[(Z)-[(1-methyltetrazol-5-yl)-phenyl-methylene]amino]oxymethyl]-2-pyridyl]carbamate I + dazomet, I + isotianil, I + tiadinil, I + thifluzamide, I + benthiazole (TCMTB), I + silthiofam, I + zoxamide, I + anilazine, I + tricyclazole, I + (.+-.)-cis-1-(4-

chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)-cycloheptanol (huanjunzuo), I + 1-(5-bromo-2-pyridyl)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1,2,4-triazol-1-yl)propan-2-ol I + 2-(1-tert-butyl)-1-(2-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol (TCDP), I + azaconazole, I + bitertanol (biloxazol), I + bromuconazole, I + climbazole, I + cyproconazole, I + difenoconazole, I + dimetconazole, I + diniconazole, I + diniconazole-M, I + epoxiconazole, I + etaconazole, I + fenbuconazole, I + fluquinconazole, I + flusilazole, I + flutriafol, I + hexaconazole, I + imibenconazole, I + ipconazole, I + metconazole, I + myclobutanil, I + penconazole, I + propiconazole, I + prothioconazole, I + simeconazole, I + tebuconazole, I + tetraconazole, I + triadimefon, I + triadimenol, I + triazoxide, I + triticonazole, I + 2-[[(1R,5S)-5-[(4-fluorophenyl)methyl]-1-hydroxy-2,2-dimethyl-cyclopentyl]methyl]-4H-1,2,4-triazole-3-thione I + 2-[[3-(2-chlorophenyl)-2-(2,4-difluorophenyl)oxiran-2-yl]methyl]-4H-1,2,4-triazole-3-thione I + ametoctradin (imidium), I + iprovalicarb, I + valifenalate, I + 2-benzyl-4-chlorophenol (Chlorophene), I + allyl alcohol, I + azafenidin, I + benzalkonium chloride, I + chloropicrin, I + cresol, I + daracide, I + dichlorophen (dichlorophene), I + difenzoquat, I + dipyrithione, I + N-(2-p-chlorobenzoylethyl)-hexaminium chloride, I + NNF-0721, I + octhilinone, I + oxasulfuron, I + propamidine, I + propionic acid.

In particular, the following fungicidal mixing partners are preferred:

a strobilurin fungicide selected from the group consisting of azoxystrobin, dimoxystrobin, fluoxastrobin, kresoxim-methyl, metominostrobin, orysastrobin, picoxystrobin, pyraclostrobin and trifloxystrobin.

an azole fungicide selected from the group consisting of azaconazole, bromuconazole, cyproconazole, difenoconazole, diniconazole, diniconazole-M, epoxiconazole, fenbuconazole, fluquinconazole, flusilazole, flutriafol, hexaconazole, imazalil, imibenconazole, ipconazole, metconazole, myclobutanil, oxpoconazole, pefurazoate, penconazole, prochloraz, propiconazole, prothioconazole, simeconazole, tebuconazole, tetraconazole, triadimefon, triadimenol, triflumizole, triticonazole, diclobutrazol, etaconazole, furconazole, furconazole-cis and quinconazole.

a succinate dehydrogenase inhibitor (SDHI) selected from the group consisting of flutolanil, mepronil, isofetamid, fluopyram, carboxin, oxycarboxin, thifluzamide, benzovindiflupyr, bixafen, fluxapyroxad, furametpyr, isopyrazam, penflufen, penthiopyrad, pydiflumetofen, sedaxane, boscalid, isopyrazam, benodanil and fenfuram.

Whilst compositions comprising the co-crystals of the invention and another fungicide are explicitly disclosed above, the skilled man will appreciate that the invention extends to three-way, and further multiple combinations comprising the above two-way mixtures.

Thus, for example, the co-crystals of the invention may be combined with a strobilurin and an SDHI fungicide.

Pesticidal agents referred to herein using their common name are known, for example, from "The Pesticide Manual", 15th Ed., British Crop Protection Council 2009. For the avoidance of doubt, even if not explicitly stated above, the mixing partners of may also be in the form of any suitable agrochemically acceptable ester or salt, as mentioned e.g. in "The Pesticide Manual", 15th Ed., British Crop Protection Council 2009.

In a particular embodiment, the invention provides a composition comprising:

(a) a co-crystal of difenoconazole cis racemate and fumaric acid, a co-crystal of difenoconazole trans racemate and fumaric acid, or a mixture of the two;

(b) a strobilurin fungicide

(c) an SDHI fungicide.

Preferably, the strobilurin fungicide is selected from the group consisting of azoxystrobin, dimoxystrobin, fluoxastrobin, kresoxim-methyl, metominostrobin, orysastrobin, picoxystrobin, pyraclostrobin and trifloxystrobin. More preferably, the strobilurin is azoxystrobin.

Preferably, the SDHI fungicide is selected from the group consisting of flutolanil, mepronil, isofetamid, fluopyram, carboxin, oxycarboxin, thifluzamide, benzovindiflupyr, bixafen, fluxapyroxad, furametpyr, isopyrazam, penflufen, penthiopyrad, pydiflumetofen, sedaxane, boscalid, isopyrazam, benodanil and fenfuram. More preferably, the SDHI fungicide is benzovindiflupyr, isopyrazam, sedaxane or pydiflumetofen. Most preferably the SDHI fungicide is benzovindiflupyr.

Preferably, the formulation is a wettable granule.

The present invention will now be described by way of the following non-limiting examples and figures, wherein:

FIG. 1 shows the measured powder X-ray diffraction pattern of the co-crystal of the cis (racemate) of difenoconazole and fumaric acid.

FIG. 2 shows the predicted powder X-ray diffraction pattern of the co-crystal of the cis (racemate) of difenoconazole and fumaric acid.

FIG. 3 shows the measured powder X-ray diffraction pattern of the co-crystal of the trans (racemate) of difenoconazole and fumaric acid.

FIG. 4 shows the predicted powder X-ray diffraction pattern of the co-crystal of the cis (racemate) of difenoconazole and fumaric acid.

FIG. 5 shows a DSC trace of the co-crystal of the cis (racemate) of difenoconazole and fumaric acid.

FIG. 6 shows a DSC trace of the co-crystal of the trans (racemate) of difenoconazole and fumaric acid.

EXAMPLES

1. Preparation of Co-crystals

a. Preparation of a co-crystal of the cis (racemate) of difenoconazole and fumaric acid.

Difenoconazole (cis-racemate) (0.12g) was added to fumaric acid (0.02g) and 20μL of ethanol or acetonitrile. The resulting mixture was milled using the Retsch MM200 at 500rpm for 1 hour. The resulting crystals were filtered and dried.

b. Preparation of a co-crystal of the trans (racemate) of difenoconazole and fumaric acid.

Difenoconazole (trans-racemate) (0.14g) was added to fumaric acid (0.02g) and 20μL of ethanol. The resulting mixture was milled using the Retsch MM200 at 500rpm for 1 hour. The resulting crystals were filtered and dried.

2. Analysis of polymorphs

After preparation by the methods detailed above, the samples were subject to analysis by powder X-ray diffraction and/or single crystal X-ray diffraction and/or differential scanning calorimetry (DSC).

Powder X-ray diffraction analysis of solid material was carried out using the Bruker D8 powder diffractometer at room temperature and at relative humidities above 40%. Samples were mounted in Perspex sample holders and the samples flattened. The sample holder was rotated and X-rays were collected from 4° to 34° 2-theta, with a scan time of 25 to 30 minutes depending on the pattern intensity. Measured powder X-ray diffraction patterns for the co-crystals of the invention are shown in FIG. 1 (cis-racemate), and FIG. 3 (trans-racemate).

Single crystal intensity data was collected on an Oxford Xcalibar PX Ultra diffractometer using Cu Kα radiation (λ=1.5418 Å) with a graphite monochromator. The crystal was mounted in Paratone N oil at 100K for data collection. The data was solved using the CRYSTALS software package. Predicted X-ray diffraction patterns for the co-crystals of the invention are shown in FIG. 2 (cis-racemate) and FIG. 4 (trans-racemate).

DSC was carried out using a Mettler Toledo DSC1. A sample loading of around 5mg was used and this was heated from from 25°C to 300°C at a rate of 10°C/minute. The lid of the DSC crucible was pierced to allow the escape of any gas formed during the heating of the sample. The DSC analysis confirmed the presence of the co-crystals of the invention with a melting point of 134°C (cis-racemate) and 123°C (trans-racemate). A DSC trace of the co-crystals of the invention is shown in FIG. 5 (cis-racemate) and FIG. 6 (trans-racemate).

Although the invention has been described with reference to preferred embodiments and examples thereof, the scope of the present invention is not limited only to those described embodiments. As will be apparent to persons skilled in the art, modifications and adaptations to the above-described invention can be made without departing from the spirit and scope of the invention, which is defined and circumscribed by the appended claims. All publications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication were specifically and individually indicated to be so incorporated by reference.

CLAIMS

1. A co-crystal of the cis racemate of difenoconazole with fumaric acid.

2. The co-crystal of claim 1 which has the following lattice parameters: a=47.98 Å ± 2.40 Å, b=5.43 Å ± 0.30 Å, c=22.02 Å ± 1.10 Å, $\alpha = 90^{o}$, $\beta = 130.75^{o} \pm 6.54^{o}$, $\gamma = 90^{o}$ and volume = 4346Å^3 ± 220 Å^3.

3. The co-crystal of claim 1 which is characterised by a powder X-ray diffraction pattern expressed in terms of 2θ angles, wherein the powder X-ray diffraction pattern comprises at least three 2θ angle values selected from the group comprising 4.9 ± 0.2, 9.8 ± 0.2, 10.7 ± 0.2, 11.2 ± 0.2, 14.4 ± 0.2, 18.6 ± 0.2, 20.5 ± 0.2, 20.9 ± 0.2, 23.2 ± 0.2, 23.9 ± 0.2 and 24.9 ± 0.2.

4. The co-crystal of claim 1, which has a melting point of 134°C ± 2°C.

5. A co-crystal of the trans racemate of difenoconazole with fumaric acid.

6. The co-crystal of claim 5, which has the following lattice parameters: a=18.11 Å ± 0.01 Å, b=5.60 Å ± 0.01 Å, c=21.68 Å ± 0.01 Å, $\alpha = 90^{o}$, $\beta = 98.92^{o} \pm 4.95^{o}$, $\gamma = 90^{o}$ and volume = 2173Å^3 ± 110 Å^3.

7. The co-crystal of claim 5 which is characterised by a powder X-ray diffraction pattern expressed in terms of 2θ angles, wherein the powder X-ray diffraction pattern comprises at least three 2θ angle values selected from the group comprising 6.0 ± 0.2, 10.0 ± 0.2, 12.7 ± 0.2, 16.7 ± 0.2, 17.0 ± 0.2, 17.4 ± 0.2, 18.0 ± 0.2, 18.9 ± 0.2, 19.6 ± 0.2, 20.0 ± 0.2, 20.4 ± 0.2, 21.0 ± 0.2, 22.8 ± 0.2, 23.0 ± 0.2 and 24.0 ± 0.2.

8. The co-crystal of claim 5, which has a melting point of 123°C ± 2°C.

9. A process for the production of a co-crystal as claimed in any one of claim 1 to 8 comprising:

   (a) grinding, heating or contacting in solution the difenoconazole with the fumaric acid, under crystallisation conditions so as to form a solid phase;

   (b) isolating co-crystals comprising the difenoconazole and fumaric acid.

10. A fungicidal composition comprising a co-crystal of the invention as claimed in any one of claims 1 to 8 and one or more carriers or diluents.

11. The fungicidal composition of claim 10, which is an agrochemical composition.

12. The fungicidal composition as claimed in claim 10 or claim 11, which comprises (i) the co-crystal of difenoconazole cis racemate and fumaric acid or (ii) the co-crsytal of difenoconazole trans racemate and fumaric acid or (iii) a mixture of the co-crystal of difenoconazole cis racemate and fumaric acid and the co-crsytal of difenoconazole trans racemate and fumaric acid.

13. The fungicidal composition as claimed in any one of claims 10 to 12 which further comprises at least one additional fungicide.

14. The composition of claim 13, wherein the at least one additional fungicide is selected from a strobilurin fungicide, an azole fungicide or a succinate dehydrogenase inhibitor fungicide.

15. The composition of claim 14, wherein the strobilurin fungicide is selected from the group consisting of azoxystrobin, dimoxystrobin, fluoxastrobin, kresoxim-methyl, metominostrobin, orysastrobin, picoxystrobin, pyraclostrobin and trifloxystrobin.

16. The composition of claim 14, wherein the azole fungicide is selected from the group consisting of azaconazole, bromuconazole, cyproconazole, difenoconazole, diniconazole, diniconazole-M, epoxiconazole, fenbuconazole, fluquinconazole, flusilazole, flutriafol, hexaconazole, imazalil, imibenconazole, ipconazole, metconazole, myclobutanil, oxpoconazole, pefurazoate, penconazole, prochloraz, propiconazole, prothioconazole, simeconazole, tebuconazole, tetraconazole, triadimefon, triadimenol, triflumizole, triticonazole, diclobutrazol, etaconazole, furconazole, furconazole-cis and quinconazole.

17. The composition of claim 14, wherein the succinate dehydrogenase inhibitor fungicide is selected from the group consisting of flutolanil, mepronil, isofetamid, fluopyram, carboxin, oxycarboxin, thifluzamide, benzovindiflupyr, bixafen, fluxapyroxad, furametpyr, isopyrazam, penflufen, penthiopyrad, pydiflumetofen, sedaxane, boscalid, isopyrazam, benodanil and fenfuram.

18. The composition of claim 13, which comprises as additional fungicides, a strobilurin and a succinate dehydrogenase inhibitor fungicide.

19. The composition of any one of claims 12 to 18 which is a wettable granule.

20. A method of preventing or controlling fungal infection on plants or plant propagation material comprising treating the plant or plant propagation material, or locus thereof,

with a fungicidally effective amount of an agricultural composition as claimed in any one of claims 12 to 19.

FIG. 1

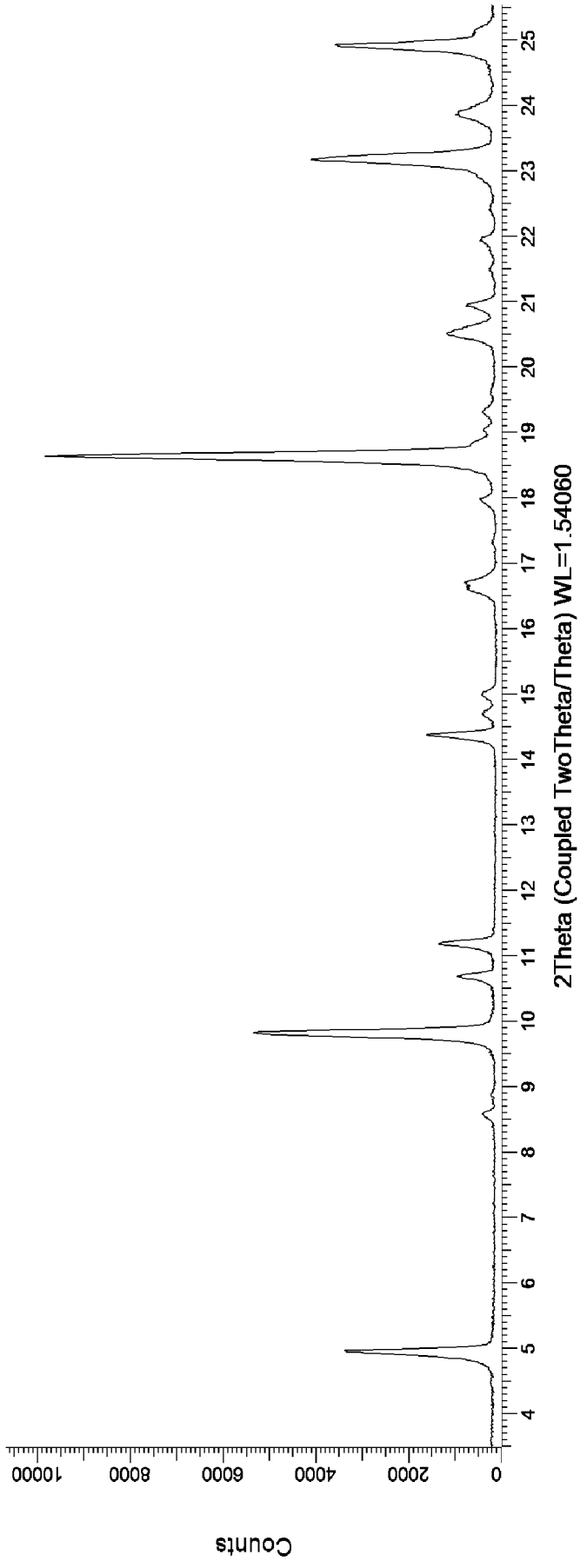

Counts
0
2000
4000
6000
8000
10000
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
2Theta (Coupled TwoTheta/Theta) WL=1.54060

FIG. 2

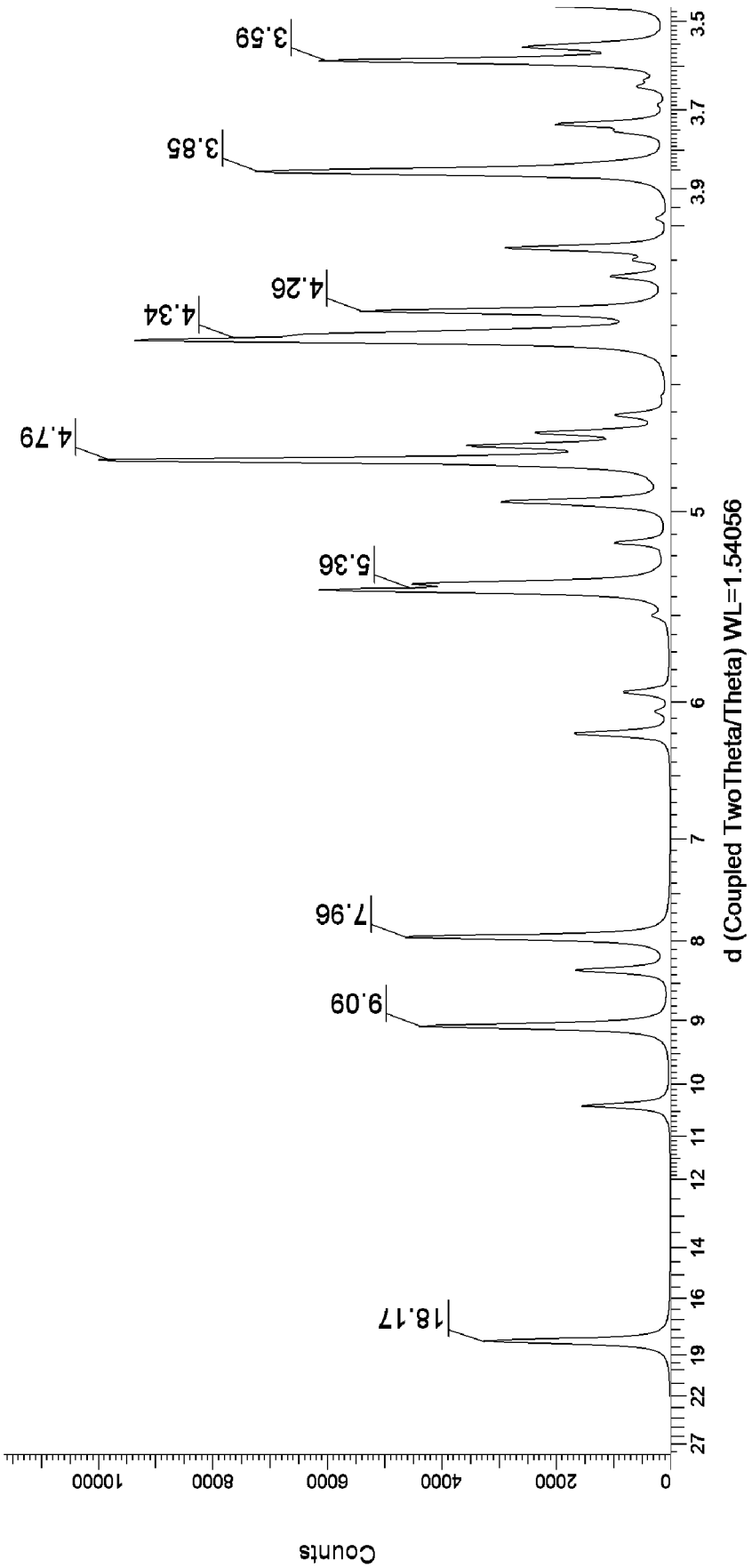

18.17
9.09
7.96
5.36
4.79
4.34
4.26
3.85
3.59
Counts
0
2000
4000
6000
8000
10000
27
22
19
16
14
12
11
10
9
8
7
6
5
3.9
3.7
3.5
d (Coupled TwoTheta/Theta) WL=1.54056

FIG. 3

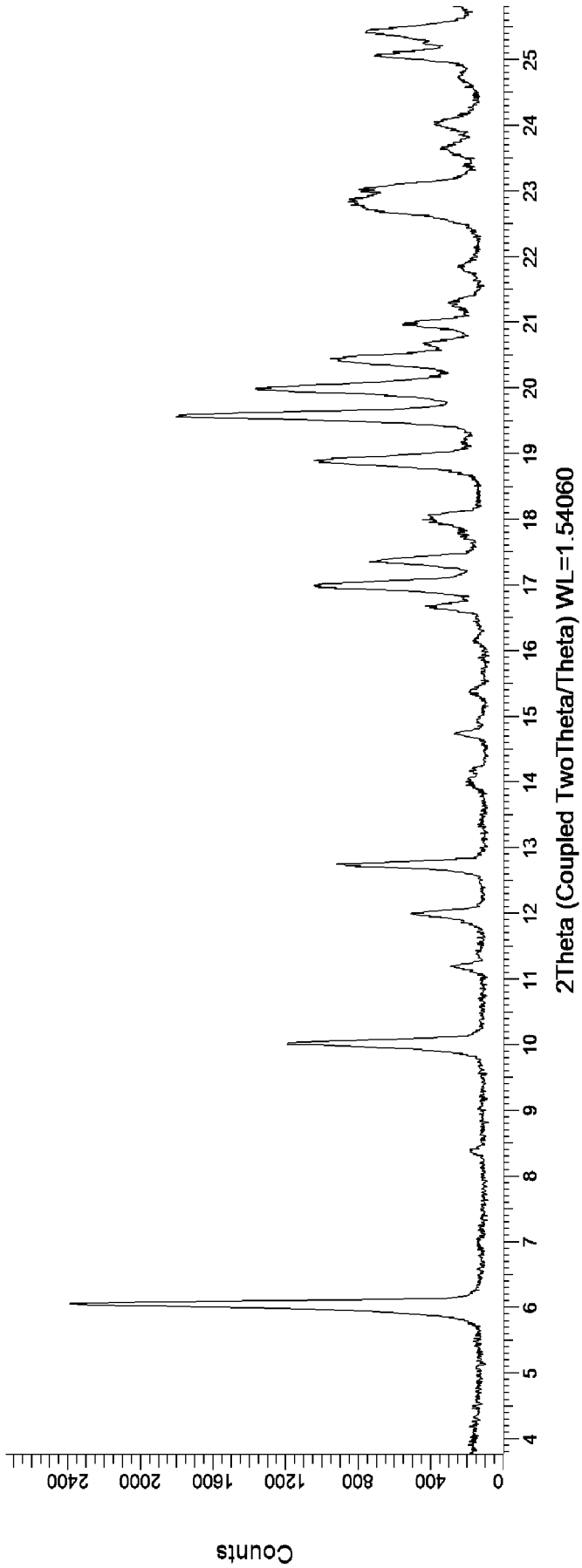

Counts
0
400
800
1200
1600
2000
2400
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
2Theta (Coupled TwoTheta/Theta) WL=1.54060

FIG. 4

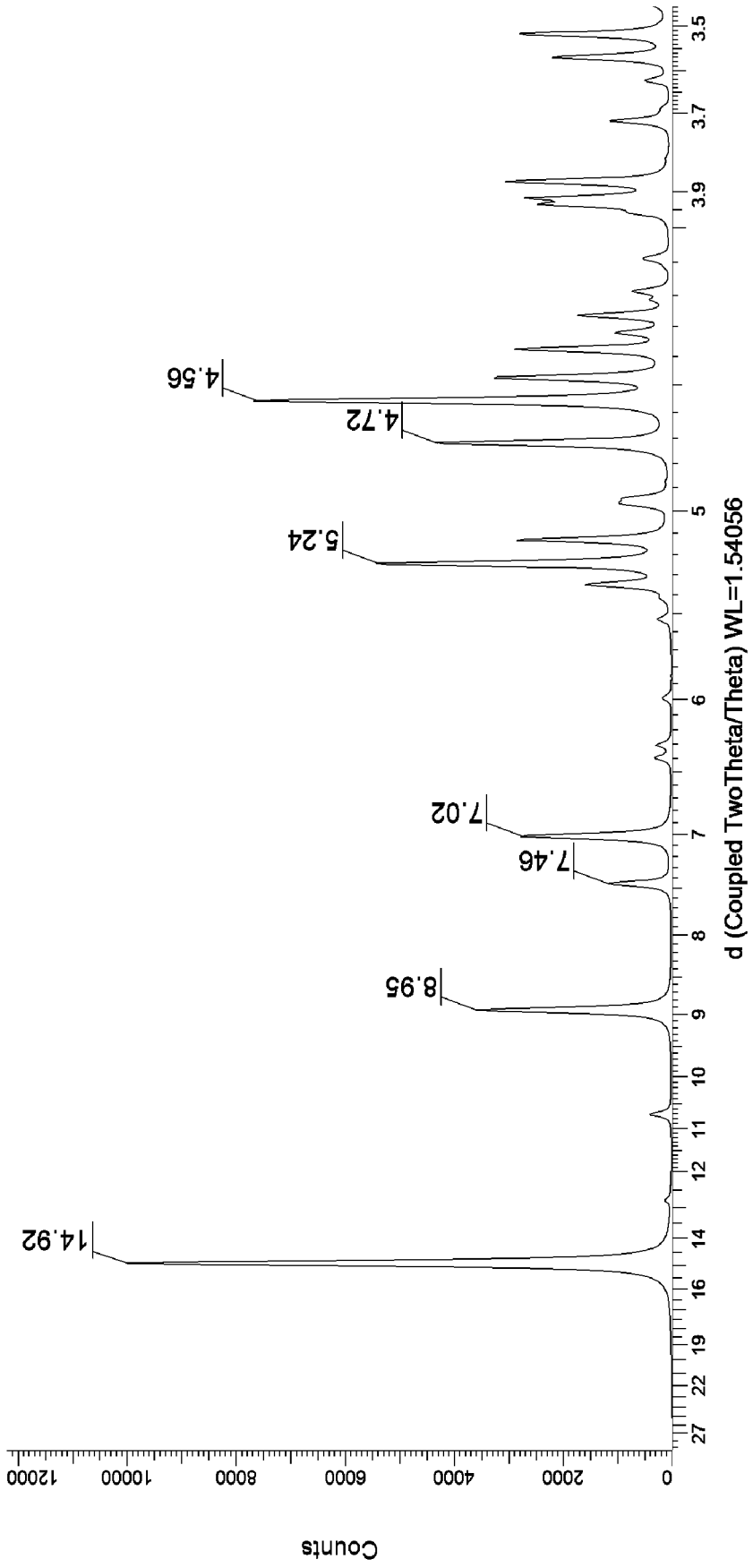

14.92
8.95
7.46
7.02
5.24
4.72
4.56
Counts
0
2000
4000
6000
8000
10000
12000
d (Coupled TwoTheta/Theta) WL=1.54056
27
22
19
16
14
12
11
10
9
8
7
6
5
3.9
3.7
3.5

FIG. 5

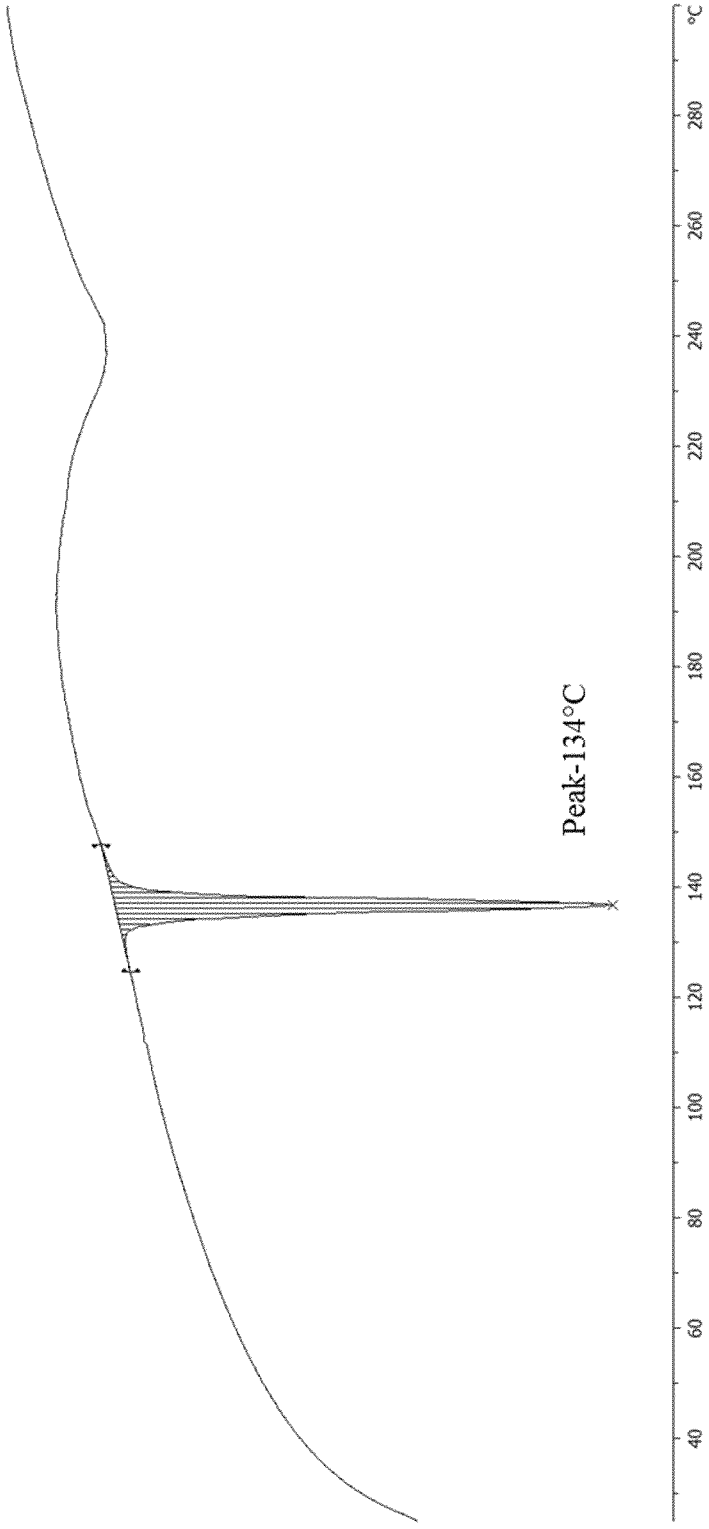
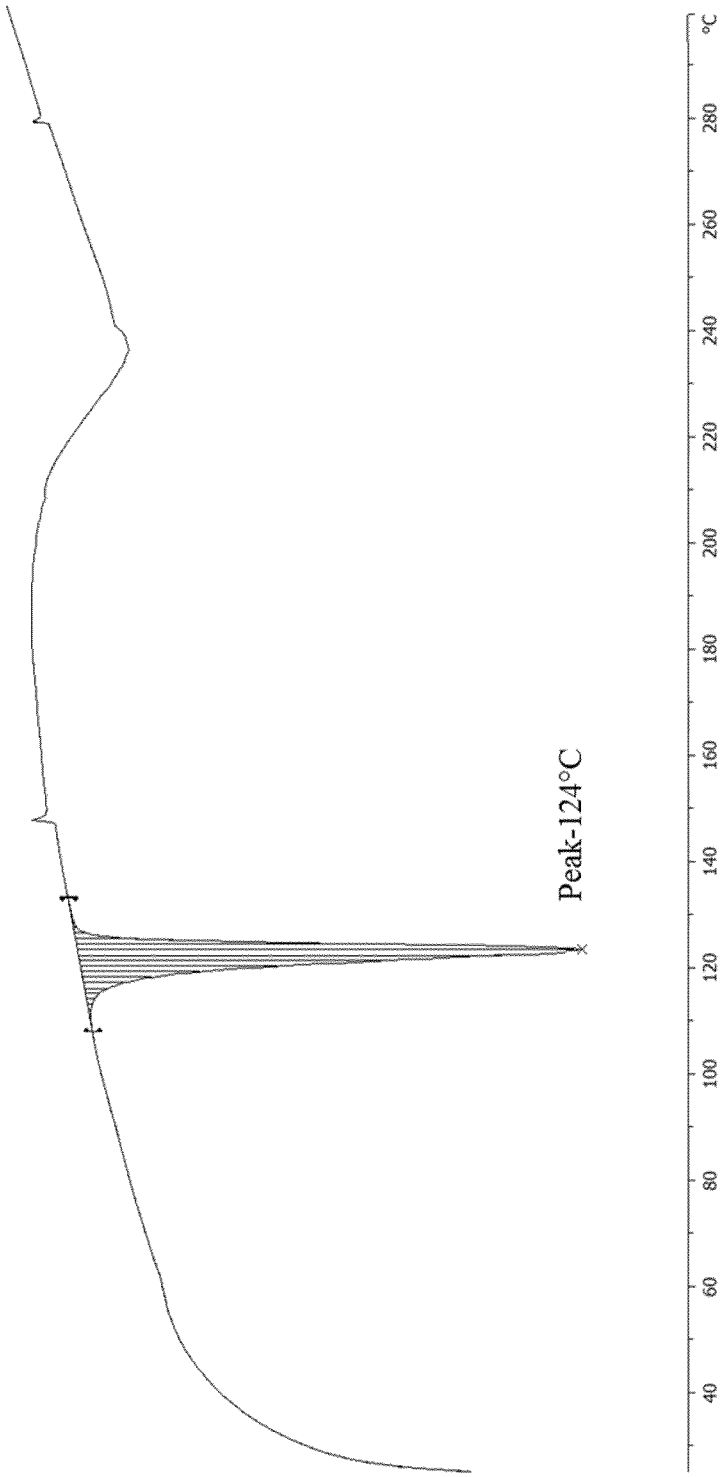


FIG. 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/076838

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/06 A01N43/653
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2015/366203 A1 (GODWIN JEREMY ROBERT [CH] ET AL) 24 December 2015 (2015-12-24) paragraphs [0004], [0007]	1-20
Y	"The Pesticide Manual, Twelfth Edition, Editor: C D S Tomlin", 2000, The British Crop Protection Council, XP002796028, ISBN: 1901396126 page 1,2,290, the whole document	1-20

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2019	10/12/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Bhupinder Singh Sekhon: "Co-crystals of agrochemical actives", International Journal of Agricultural Sciences, 1 May 2015 (2015-05-01), pages 471-475, XP055567453, India Retrieved from the Internet: URL:http://www.internationalscholarsjournals.org/download.php?id=904273700268786541.pdf&type=application/pdf&op=1 [retrieved on 2019-03-12] page 472	1-20
Y	FLAVIA A. MARTIN ET AL: "Ketoconazole Salt and Co-crystals with Enhanced Aqueous Solubility", CRYSTAL GROWTH & DESIGN., vol. 13, no. 10, 2 October 2013 (2013-10-02), pages 4295-4304, XP055645980, US ISSN: 1528-7483, DOI: 10.1021/cg400638g figure 7	1-20

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/076838

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015366203 A1	24-12-2015	AR 095138 A1	30-09-2015
		AU 2014211574 A1	23-07-2015
		BR 112015018180 A2	18-07-2017
		CA 2897526 A1	07-08-2014
		CN 104968202 A	07-10-2015
		EP 2950653 A1	09-12-2015
		ES 2718915 T3	05-07-2019
		JP 2016510334 A	07-04-2016
		RU 2015137600 A	10-03-2017
		UA 118257 C2	26-12-2018
		US 2015366203 A1	24-12-2015
		WO 2014118127 A1	07-08-2014