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(19)

(54) 4-OXO-3-QUINOLINE-CARBOXYLIC ACID DERIVATIVES USED FOR TREATING DISEASES IN PLANTS

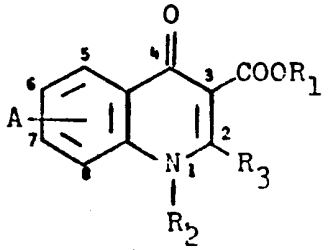
(71) We, SUMITOMO CHEMICAL COMPANY, LIMITED, a Japanese Company, of No. 15, Kitahama 5-chome, Higashi-ku, Osaka-shi, Osaka, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a method for preventing and eradicating plant disease caused by bacterial infection and, more particularly, it relates to a plant disease prevention and eradication method which comprises applying a composition containing, as an effective component, a 4(1H)-oxo-3-quinoline-carboxylic acid derivative.

Recently, many new organic synthetic fungicides have been discovered as plant-disease prevention agents and they have largely contributed to an increased production of foods. However, although they are effective for diseases caused by fungi, they are ineffective for bacterially-caused diseases. Except for a few antibiotics (e.g., streptomycin, novobiocin, and chloramphenicol) which have a narrow applicable range, chemical compositions exhibiting specific activities to bacterially-caused plant diseases have not yet been developed at present.

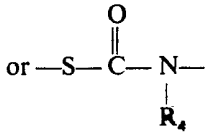
We have discovered that the compounds represented by the general formula (I) below have a strong systemic activity in plants and a surprisingly excellent effect in the prevention and the eradication of these bacterially-caused diseases of plants. Furthermore, it has also been found that the compounds of this invention do not adversely affect agricultural and horticultural crops.

Thus, according to the present invention, there is provided a method for preventing and eradicating plant diseases caused by bacterial infection which comprises applying to a plant or to seeds at least one 4(1H)-oxo-3-quinoline-carboxylic acid derivative represented by the general formula (I):



(I)

where A represents —OCH_2O—(attached to the 6 and 7 positions) or



(attached to the 6 and 5 positions), wherein R_4 represents a hydrogen atom or a (C_1—C_4)alkyl group; R_1 represents a hydrogen atom, a (C_1—C_4)alkyl group, an amino group, an ammonium group or an alkali metal atom; R_2 represents a (C_1—C_4)alkyl group, a halogenated (C_1—C_4)alkyl group, a (C_1—C_4)hydroxyalkyl group, a (C_2 or C_3)alkenyl group or a (C_1—C_4)alkoxy group; and R_3 represents a hydrogen atom or a (C_1—C_4)alkyl group. In the above, the alkali metal atom for R_1 is preferably a sodium or potassium atom, the halogenated (C_1—C_4)alkyl group for R_2 is preferably an ethyl group preferably substituted with a fluorine or chlorine atom and the alkenyl group for R_2 is preferably a vinyl group.

In preferred compounds, A represents said —OCH_2O— group, R_1 represents a hydrogen, sodium or potassium atom and R_2 represents one of said alkyl, halogenated alkyl or alkenyl groups, e.g. an ethyl, vinyl or monofluoroethyl group.

Some of the compounds used in this invention within the scope of the general formula (I) are already known as anti-bacterial agents in the medical field as disclosed in, for example, U.S. Patent 3,287,458, Japanese Patent Publication No. 26,638/74, and Japanese Patent Applications (OPI) Nos. 31,998/72, 89,396/75 and 43,798/76, which describe the utilization of them as chemotherapeutic agents for animal diseases caused by bacteria. However, none of these references teach or suggest that these compounds could be utilized as agricultural and horticultural eradicants for plant diseases caused by bacterial infection.

As the result of intensive investigations on utilization of various medicines having chemotherapeutic properties as agents for preventing and eradicating bacterially-caused diseases of agricultural and horticultural crops, it has been discovered that only the compounds represented by the general formula (I) have quite excellent effects as such eradicants. Practically speaking, as shown in the test results of Table 2 in Example 1 given hereinafter, nalidixic acid and sulfa drugs such as sulfamine which are widely used for curing urethral meatus infection and intestinal infection, as well as chlorhexidine which is used for the local prophylaxis of bacterial infections, were all observed to have no effect for preventing the occurrence of the soft rot disease of Chinese cabbage caused by *Erwinia aroideae,* while the compounds of this invention showed an excellent effect superior to the comparison drug, streptomycin-sulfate.

Furthermore, by performing simultaneously an anit-bacterial test in vitro and a disease-prevention test, a quite surprising result was obtained. It was found that Compounds Nos. 2, 8 and 11 in Example 2, which possess very weak antibacterial activity against *Erwinia carotovora,* were observed to be highly effective in preventing and eradicating soft rot disease of Chinese cabbage caused by this bacterium. This fact shows clearly that chemotherapeutical materials used as medicaments cannot always be utilized as compositions for controlling plant diseases.

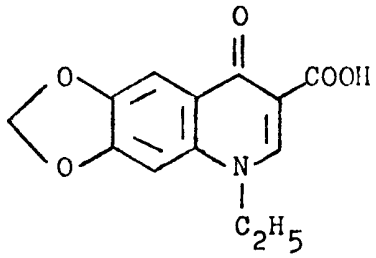
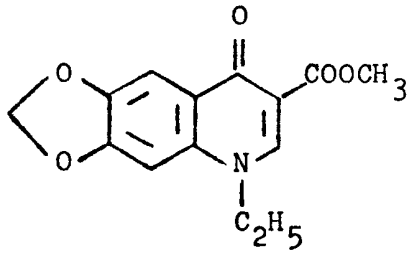
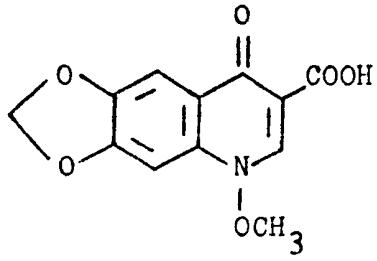
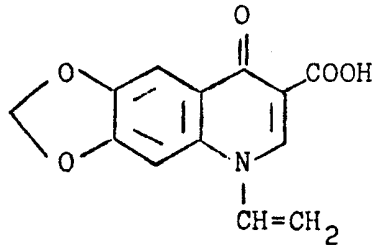
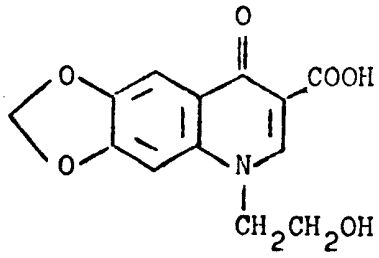
Moreover, as the result of further investigations of the properties of the compounds used in this invention, it has also been demonstrated that the compounds used in this invention have the property of readily being absorbed in a plant through the roots and translated into the aerial parts of the plant. This property contributes greatly to the anti-bacterial activity against bacteria that parasitize and propagate inside a plant. Accordingly, systemic action of antibacterial agents in a plant is essential for prevention and eradication of bacterial diseases. The reason that conventional antibacterial materials for medical use show almost no effect on plant disease control when they are practically applied to plants is due to lack of systemic activity in a plant. On the other hand, since the compounds of this invention have a high systemic activity in a plant, in addition to their antibacterial activity, the compounds exhibit quite high efficacy in preventing and eradicating bacterially caused plant diseases. These properties of the compounds have only now been discovered.

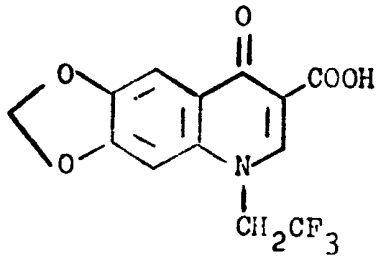
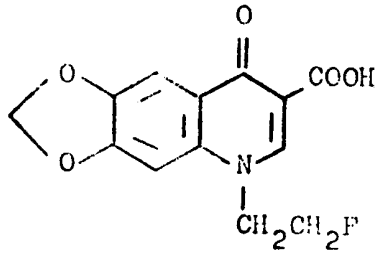
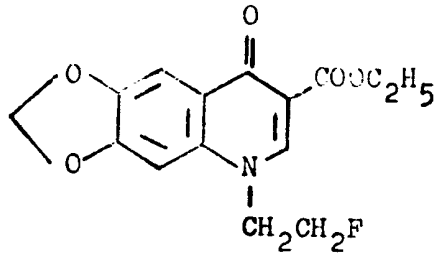
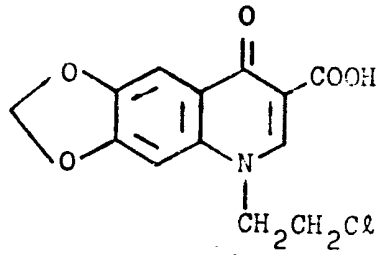
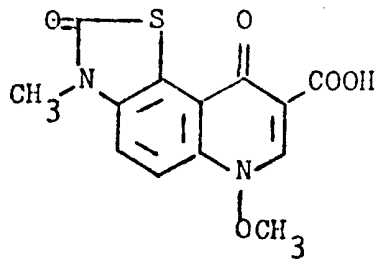
The compounds used in this invention can be prepared by the processes described in the above patent references and Japanese Patent Application (OPI) No. 31,999/72, which discloses a process which comprises reacting a 2-hydro-6-alkyl-6,9,dihydro-9-oxothiazolo [5,4-f]-quinoline-8-carboxylic acid with an alkylating agent.

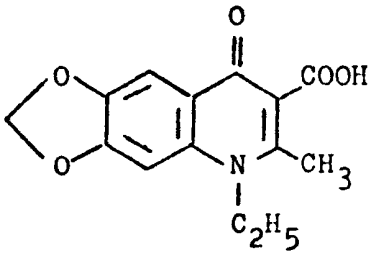
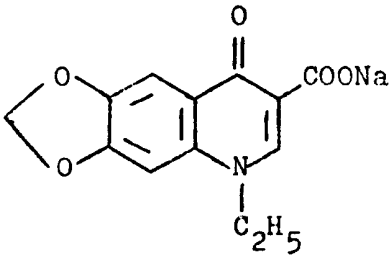
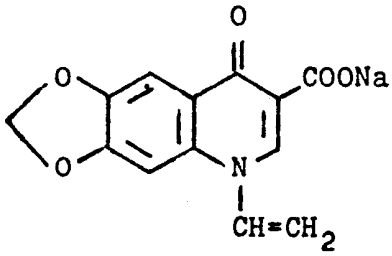
Some specific examples of the compounds which can be used in this invention are illustrated in Table 1 below but this invention is not to be construed as being limited to these compounds only.

TABLE 1

4(1H)-Oxo-3-quinolinecarboxylic Acid Derivatives

Compound No.	Chemical Formula	Physical Property
(1)		m.p. 310°C (decomposition)
(2)		m.p. 198-199°C
(3)		m.p. 260°C (decomposition)
(4)		m.p. 277-278°C
(5)		m.p. 303-305°C (decomposition)

Compound No.	Chemical Formula	Physical Property
(6)		m.p. 327-329°C
(7)*		m.p. 311-314°C
(8)*		m.p. 229-230°C
(9)*		m.p. 279-280°C (decomposition)
(10)		m.p. 312-315°C (decomposition)

Compound No.	Chemical Formula	Physical Property
(11)		m.p. 305°C (decomposition)
(12)		m.p. more than 300°C (decomposition)
(13)		m.p. more than 300°C (decomposition)

* Compounds (7), (8) and (9) are compounds undisclosed in the prior art.

Compounds (3) and (11) are described in J.Med Chem *20*, p.791 (1977); Compound (6) in Belgian Patent No. 832,343 and Compound (10) in U.S. Patent No. 3,954,775.

In the present invention, a method for eradicating plant disease caused by bacterial infection can be carried out by, for example, dusting, spraying or applying a compound of the formula (I) as described above to a plant, maingling it with soil around the plant roots or immersing a plant into a solution or suspension of a compound of the formula (I) so that a compound of the formula (I) comes in contact with the plant.

For this purpose, a compound of the formula (I) can be used alone, but usually it is used in the form of an appropriate agricultural preparation such as dusts, wettable powders, oilsprays, tablets, emulsifiable concentrates, granules, fine granules and aerosols.

These agricultural preparations can be prepared in a conventional manner by mixing a compound of the formula (I) with an appropriate solid or liquid carrier and appropriate adjuvants (e.g., surfactants, adherents, dispersants, stabilizers and) for improving the dispersibility and other properties of the compound (I) at use.

Examples of appropriate solid carriers which can be used are a fine powder or granules of a botanical carrier (e.g., flour, tobacco stalk powder, soybean powder, walnut shell powder, wood powder, saw dust, bran, bark powder, cellulose powder or vegetable extract residue); fibrous materials (e.g., paper, corrugated cardboard and old rags); synthesized plastic powders; clays (e.g., kaolin, bentonite and fuller's earth); talcs; other inorganic minerals (e.g., pyrophyllite, sericite, pumice, sulfur powder, and active carbon) and chemical fertilizers (e.g., ammonium sulfate, ammonium phosphate, ammonium nitrate, urea, ammonium and chloride).

Examples of appropriate liquid carriers which can be used are water, alcohols (e.g., methyl alcohol and ethyl alcohol); ketones (e.g., acetone and methyl ethyl ketone,); ethers (e.g., diethyl ether, dioxane, 2-methoxy ethanol and tetrahydrofuran); aromatic hydrocarbons (e.g., benzene, toluene, xylene and methyl naphthalene); aliphatic hydrocarbons (e.g., gasoline, kerosene and lamp oil); esters; nitriles; acidamides (e.g., dimethylformamide, and dimethylacetamide); and halogenated hydrocarbons (e.g., dichloroethane and carbon tetrachloride).

Examples of surfactants which can be used in the present invention are alkyl sulfuric ester alkyl sulfonates, alkylaryl sulfonate, polyethyleneglycol ethers and polyhydric alcohol esters. Examples of adherents and dispersants which can be used in the present invention may include casein, gelatin, starch powder, carboxymethyl cellulose, gum arabic, alginic acid, lignin, bentonite, molasses, polyvinyl alcohol, pine oil and agar. As a stabilizer, use can be made of members such as PAP (isopropyl acid phosphates mixture), TCP (tricresyl phosphate), tolu oil, epoxidized oil, various surfactants and various fatty acids and esters thereof.

Furthermore, if necessary, the compounds of this invention can be used as a mixture thereof with other agricultural chemicals such as fungicides, insecticides, miticides, nematocides, herbicides, plant growth regulators, and synergists, or fertilizers and, in this case all of the components present can be effectively used without reducing the effect of any component.

The particular dosase of the compound (I) used in the present invention will be decided taking into consideration various conditions such as the kind, stage or degree of the disease to be eradicated, the properties of the compound, and the growth circumstances of the plant.

Generally speaking, a compound of the formula (I) may be used at a concentration of 10 to 2,000 ppm. For example, in case of field application, 10 to 300 g per 10 are of a compound of the formula (I) may be used at this concentration.

Diseases of agricultural and horticultural crops to which the compounds used in this invention are effective are described below in more detail. That is, the compounds used in this invention exhibit excellent disease-prevention effects to many bacterially-caused diseases of various crops such as bacterial leaf blight of rice, the soft rot of various vegetables, black rot, bacterial wilt of egg plants, the bacterial canker of tomatoes, angular leaf spot disease of melons, the bacterial canker of tulips, the shot hole of peaches, the wild fire of tobacco, the bacterial canker of citrus fruits, the fire blight of apples and pears, and the black leg of potatoes. Also, as is clear from the results shown in the Examples described hereinafter, the compounds used in this invention exhibit excellent disease-prevention effects not only when dusted or sprayed onto stalks and leaves but also when treated as a soil drench, by root immersion or as a seed dressing.

The invention will further be explained more specifically by reference to the following formulation embodiments and Examples but the invention is not to be construed as being limited thereto. In addition, the numerical designations for the compounds used as the effective components in the formulation embodiments and the examples correspond to the numerical designations for the compounds shown hereinbefore in Table I

(a) Dust:

By crushing and mixing well 2 parts by weight of Compound (1) and 98 parts by weight of clay, a powder containing 2% of active ingredient was obtained.

(b) Wettable powder:

By crushing and mixing well 20 parts by weight of Compound (4), 75 parts by weight of diatomaceous earth, and 5 parts by weight of a wetting extender (an alkylbenzene-sulfonate), a wettable powder containing 20% of the active ingredient was obtained.

(c) Emulsifiable concentrate:

By mixing 10 parts by weight of Compound (9), 80 parts by weight of dimethyl sulfoxide, and 10 parts by weight of an emulsifying agent (a polyoxyethylene phenylphenol ether), an emulsifiable concentrate containing 10% of the active ingredient was obtained.

(d) Granules:

By crushing and mixing well 5 parts by weight of Compound (7), 3.5 parts by weight of clay, and 1.5 parts by weight of a binder (polyvinyl alcohol) and, after kneading with water, granulating the mixture followed by drying, granules containing 5% of the active ingredient were obtained.

The following Examples are given to illustrate the effects of the present

invention more specifically. Unless otherwise indicated, all parts, percents, ratios and the like are by weight.

Example 1.

Test for Disease-Prevention Effect on Soft Rot of Chinese Cabbage Caused by *E. aroideae*

Onto Chinese cabbage (*Brassica pekinesis* Rupr. cr.) grown in a flower pot of a diameter of 9 cm at two-leaf stage, the test sample in a dilute emulsion form was sprayed at a rate of 7 ml per flower pot. Three days thereafter, the leaves of the Chinese cabbage were injured and inoculated with a suspension of *E. aroideae*. Thereafter the flower pot was placed in a dark and moist chamber (90—100% RH) for 2 days at 28°C and then incidence of the disease was assessed in the following manner. That is, the severity of disease was calculated according to the following relationship by measuring the ratio of the diseased area of the leaves, classifying the severity into grades 0, 1, 2, . . ., 8 depending on the degree of the disease and recording the number of leaves n_0, n_1, n_2, . , n_5 corresponding to the each disease index:

Disease Index	*Ratio of Diseased Area*
0	No disease
1	Diseased area: less than 5%
2	Diseased area: 5 to less than 30%
4	Diseased area: 30 to less than 60%
8	Diseased area: 60% or more

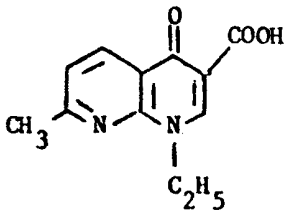
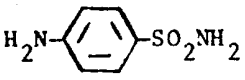
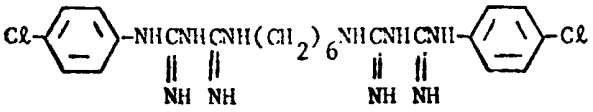
$$\text{Disease Severity (\%)} = \frac{0 \times n_0 + 1 \times n_1 + \ldots + 8 \times n_5}{8 \times n} \times 100$$

Two flower pots with two plants in each were used for each treatment. The results obtained are shown in Table 2 below.

TABLE 2

Test Results of Disease Prevention Effect on Soft Rot of Chinese Cabbage

Compound	Concentration of Active Ingredient (ppm)	Severity of Disease (%)
(1)	500	0
	100	0
(2)	500	0
	100	7
(3)	500	0
	100	9
(4)	500	0
	100	0
(5)	500	0
	100	14
(6)	500	0
	100	0
(7)	500	0
	100	0
(8)	500	0
	100	0
(9)	500	0
	100	0

Compound	Concentration of Active Ingredient (ppm)	Severity of Disease (%)
(10)	500	0
	100	12
(11)	500	0
	100	4
(12)	500	0
	100	0
(13)	500	0
	100	0
Nalidixic Acid * 	500	100
Sulfamine * 	500	100
Chlorohexidine * 	500	100
Streptomycin Sulfate	200	14
Control (no spraying)	—	100

* Reference compounds which have chemotherapeutic activity against bacterial disease in warm-blooded animals, having antibacterial activities.

Example 2.

Simultaneous Test for Antibacterial Activity against *E. carotovora* and Curative Effect on Soft Rot of Chinese Cabbage Caused by *E. carotovora*

The test compound was mixed with a bacteriological culture medium containing 1.5% agar at various concentrations and the mixture was poured in a Petri dish of a diameter of 8 cm followed by solidifying. 24 hour-culture in a bacteriological culture medium of *E. crotovora* from a stock culture was diluted 10 times with sterilized water and inoculated on the agar culture medium. After incubation for 3 days at 27°C, the growth of the bacterium was observed, whereby the minimum inhibitory concentration (MIC, μg-ml) of each compound was determined. Evaluation test of curative effect on soft rot of Chinese Cabbage caused by *E. carotovora* was carried out in a similar method to that of Example 1, except that samples were sprayed on a plant at a concentration of 500 ppm 16 hours after inoculation. The results obtained are shown in Table 3 below.

TABLE 3

Test for Antibacterial Activity to Erwinia carotovora

Compound	MIC (μg/ml)	Severity of Disease
(1)	1.56	0
(2)	>50	12
(3)	0.39	0
(4)	0.78	0
(6)	3.12	0
(7)	0.78	0
(8)	>50	8
(9)	1.56	0
(10)	0.049	0
(11)	>50	12
(12)	1.56	0
(13)	0.78	0
Nalidixic acid	6.25	100
Control (No spray)	—	100

Example 3.

Plant Systemic Activity

Chinese cabbage (Nozaki ≠2) at the two-leaf stage grown in a flower pot of a diameter of 9 cm was withdrawn from the soil with care not to injure the roots and the roots of the Chinese cabbage were immersed in a solution of the test compound at a concentration of 10 ppm. After 2 days, a suspension of Erwinia carotovora was inoculated by scratching the leaves. The incidence of disease was assessed in the same manner as described in Example 1. Five plants were used for each treatment. The results obtained are shown in Table 4 below.

TABLE 4

Plant Systemic Activity

Compound	Concentration of Active Ingredient	Severity of Disease
	(ppm)	(%)
(1)	10	0
(2)	10	0
(4)	10	0
(7)	10	0
(8)	10	0
(9)	10	0
(10)	10	25
(13)	10	0
Streptomycin Sulfate *	10	31
None	—	100

* Commercially-available comparison compound containing streptomycin as the active ingredient.

Example 4.

Test for Disease-Prevention Effect on Angular Leaf Spot of Cucumber

Onto a cucumber (*Cucumis sativus* L. Sagami Hanjiro Fushinari) at the two-leaf stage grown in a flower pot having a diameter of 9 cm the test sample in a water-soluble powder form was diluted with water and sprayed at a rate of 15 ml per pot. Four hours after the application of the sample, a suspension of *Pseudomonas lachrymans* was inoculated by spraying on the plant. Thereafter, the plant was placed in a moist chamber (90—100% RH) for 3 days at 25°C and then placed in a green house for 3—4 days. Incidence of disease was assessed in the following manner. That is, the severity of disease was calculated according to the following relationship by measuring the ratio of the diseased area of the leaves, classifying it into grades of 0, 0.5, 1, ... , 4, and recording the number of leaves n_0, n_1, n_2, ... , n_5 corresponding to ech index of the disease:

Disease Index	*Ratio of Diseased Area*
0	Healthy
0.5	1—3% disease spots
1	1—10% diseased spot areas
2	11—25% diseased spot areas
3	26—50% diseased spot areas
4	>50% diseased spot areas

Disease Severity =

$$\frac{0 \times n_0 + 0.5 \times n_1 + \ldots + 4 \times n_5}{4 \times n} \times 100$$

Five plants were used for each treatment. The results obtained are shown in Table 5 below.

TABLE 5

Test for Disease-Prevention Effect on Angular Leaf Spot of Cucumber

Compound	Concentration of Active Ingredient	Severity of Disease
	(ppm)	(%)
(1)	500	7.9
(2)	500	25
(4)	500	4.6
(7)	500	12
(8)	500	21
(9)	500	19
(13)	500	2.4
Streptomycin Sulfate*	200	28
Kocide**	830	46
None	–	80

* Commercially-available comparison compound.

** Commercially-available comparison composition containing copper hydroxide as the active ingredient.

Example 5.

Test for Disease-Prevention Effect on Bacterial Wilt of Tomato

Tomatoes (breed: Sekai Ichi) at the 4—5 leaf stage grown in a flower pot of a diameter of 9 cm were inoculated with a soil drench of a suspension of *Pseudomonas solanacearum* at a rate of 20 ml per pot. After one day, the test compound in an emulsion form diluted with water was applied to the soil in the flower pot at a rate of 15 ml per pot. Then, after an additional 10 days, the incidence of disease condition was assessed. Four flower pots with two plants each were used for treatment. The results obtained are shown in Table 6 below.

TABLE 6

Test for Disease-Prevention Effect on Bacterial Wilt of Tomato

Compound	Concentration of Active Ingredient	Ratio of Diseased Seedling
	(ppm)	(%)
(1)	500	10
(2)	500	36
(4)	500	6
(7)	500	18
(8)	500	24
(9)	500	14
(13)	500	4
Streptomycin Sulfate*	200	86
None	—	100
None**	—	0

* Commercially-available comparison compound.

** Neither treated nor inoculated.

Example 6.

Test for Disease-Prevention Effect on Bacterial Leaf Blight of Rice Plant

Onto a rice plant (breed: Kinki ≠33) at the 5-leaf stage grown in a flower pot of a diameter of 9 cm, the test sample in an emulsion form diluted with water was sprayed at a rate of 10 ml per pot. After 4 hours, a suspension of *Xanthomonas oryzae* was inoculated by scratching the central portion of the second leaf. The inoculated plant was placed in a moist chamber (90—100% RH) for one day and cultivated in a green house. Seven days after the inoculation, the incidence of disease was assessed using the bacterial-exudation method. That is, the bacteria exuded from the leaf sections cut at portions 1, 3 and 5 cm apart from the inoculated portion of the plant were observed using a microscope and then the severity of disease was calculated by the following relationship.

$$\text{Disease Severity} = \frac{\text{Mean Bacterial Infection Distance}}{10} \times 100$$

Five flower pots with 10 plants each were used for each treatment. The results obtained are shown in Table 7 below.

TABLE 7

Test for Disease-Prevention Effect on Bacterial Leaf Blight of Rice Plants

Compound	Concentration of Active Ingredient	Severity of Disease
	(ppm)	(%)
(1)	500	0
(2)	500	0
(4)	500	0
(7)	500	0
(8)	500	0
(9)	500	0
(13)	500	0
Chloromycetin*	200	1
Phenazine**	200	45

* Commercially-available comparison composition containing chloramphenicol as the active ingredient.

** Commercially-available comparison composition containing phenazine-5-oxide as the active ingredient.

Example 7.

Test for Controlling Angular Leaf Spot of Cucumber by Seed Treatment

Seeds of cucumber (*Cucumis sativus* L. cv. Sagami Hanjiro Fushinari), which were inoculated by immersing them in a suspension of *P. lachrymans* at a concentration of 10^8 to 10^9 cells/ml for 30 minutes and followed by drying in air, were soaked in an aqueous solution of the test sample in an emulsion form for 30 minutes. Ten seeds were sowed in a flower pot containing sterilized soil. They were grown in a green house for 2 weeks. The number of infected cucumber plants were recorded. Fifty seeds were used for each treatment.

TABLE 8

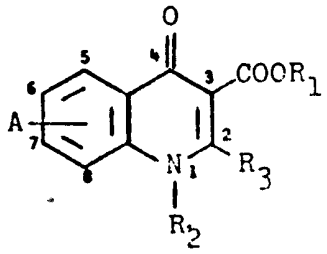
Test for Controlling Angular Leaf Spot of Cucumber by Seed Treatment

Compound	Concentration of Active Ingredient	Infected Plants
	(ppm)	(%)
(1)	500	0
(2)	500	0
(4)	500	0
(7)	500	0
(8)	500	0
(12)	500	0
(13)	500	0
Sodium Hypochlorite *	2,000	7.5
Streptomycin Sulfate *	200	26.5
Water	–	77.3

* Commercially-available comparison compound.

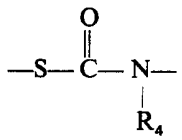
WHAT WE CLAIM IS:—

1. A method for eradicating or preventing plant disease caused by bacterial infection which comprises applying to a plant or to seeds, at least one 4(1H)-oxo-3-quinoline-carboxylic acid derivative represented by the general formula (I):



(I)

wherein A represents —OCH_2O—(attached at the 6- and 7-positions) or



(attached at the 5- and 6-positions), wherein R_4 represents a hydrogen atom or a (C_1—C_4)alkyl group; R_1 represents a hydrogen atom, a (C_1—C_4)alkyl group, an amino group, an ammonium group, or an alkali metal atom; R_2 represents a (C_1—C_4)alkyl group, a halogenated (C_1—C_4)alkyl group, a (C_1—C_4)hydroxyalkyl group, a (C_2 or C_3)alkenyl group, or a (C_1—C_4)alkoxy group; and R_3 represents a hydrogen atom or a (C_1—C_4)alkyl group.

2. A method according to Claim 1, wherein R_2 represents an ethyl group, a vinyl group, a monofluoroethyl group or a monochloroethyl group.

3. A method according to Claim 1, wherein A represents said —OCH_2O— group; R_1 represents a hydrogen atom, a sodium atom or a potassium atom; and R_2 represents said alkyl, halogenated alkyl or alkenyl group.

4. A method according to Claim 3, wherein R_2 represents an ethyl group, a vinyl group or a 2-fluorethyl group.

5. A method as claimed in Claim 1 and substantially as herein described.

6. A method according to Claim 1 substantially as herein described with reference to any one of the foregoing Examples.

7. Compounds Nos. (7), (8) and (9) herein defined.

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