

ANTIFUNGAL COMPOUNDS AND USE THEREOF

FIELD OF THE INVENTION

5 This invention relates to compounds for use in preventing and treating phytopathogenic fungal infection in plants. More particularly, this invention relates to a non-cytotoxic compounds for use in preventing and treating phytopathogenic fungal infection in plants, a process for producing the same, and an antifungal composition comprising the compound.

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BACKGROUND OF THE INVENTION

Synthetic pesticides are widely used for controlling plant diseases. There are more than 150 listed synthetic pesticides that are possible carcinogens. Many of them are
15 still in use now. The synthetic pesticides have longer half life than natural pesticides. However, synthetic pesticides are often cytotoxic. While attempts have been made to eliminate the cytotoxicity of synthetic pesticides or develop non-toxic pesticides, these attempts have failed to provide a completely effective, non-toxic pesticide. In particular, most of the existing pesticides are non-biodegradable, causing the pesticides to
20 continuously build up in the soil, subsequently, in the food chain. This long-term build up would often result in prolonged human health and environmental hazard.

As a result, many have turned to using natural pesticides. However, many of the existing natural pesticides are also known to be cytotoxic.

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US 2009/0028796 A1 discloses a pesticidal composition comprising indole derivatives that are especially active against phytopathogenic fungi. One of the derivatives disclosed in this publication includes brassilexin. Although this publication does not discuss the cytotoxicity of brassilexin, there are other reports which suggest that
30 brassilexin demonstrated cytotoxicity against human cancer cell cultures as it gave strong growth inhibition on human cancer cell cultures. See for example, *Tempete C. et. al.*, "Growth inhibitions on Human Cancer Cell Cultures with the Indole Sulphur-Containing Phytoalexins and Their Analogues", *Z. Naturforsch* 1991; 46:706-707.

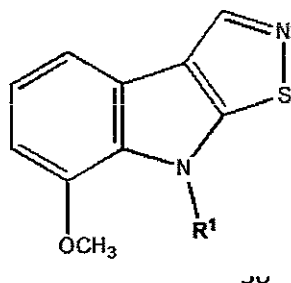
Little success has been attained in deriving a natural pesticide that is non-cytotoxic and effective. With the increase in use and demand for natural pesticides, there is an increasing need to look for a new source of natural pesticide to meet the demand.

- 5 Therefore, there is a need to provide compounds that seek to address at least one of the above problems, or at least to provide an alternative.

SUMMARY OF THE INVENTION

- 10 The above and other problems are solved and an advance in the art is made by compounds for use in preventing and treating phytopathogenic fungal infection in plants in accordance with this invention. A first advantage of the compounds in accordance with this invention is that the compounds do not exhibit any cytotoxic activity towards plants and mammals. A second advantage of the compounds in
15 accordance with this invention is that the compounds have potent antifungal activity against diseases derived from certain pathogens. A third advantage in accordance with this invention is that the composition comprising the compound of the invention is capable of providing a long-term prevention and treatment of phytopathogenic fungal infection in plants without harming the plants, crops, trees or mammals
20 coming in contact with the composition comprising the compound of the invention.

In accordance with an embodiment of this invention, a compound represented by the structure of formula (I) is provided:



wherein R¹ is alkyl, alkenyl, cycloalkyl or a methyl group, for use in preventing and treating phytopathogenic fungal infection in plants, wherein the compound does not exhibit any cytotoxic activity towards plants and mammals. The compound is isolated

from plant *Azima sarmentosa* Benth, a species of scrubs belonging to the Salvadoraceae family.

5 In accordance with another embodiment of this invention, methods for preventing and treating pathogenic fungal infection are provided. In one embodiment, the method comprises applying an effective amount of the compound in accordance with this invention to agricultural plants. In another embodiment, the method comprises applying an effective amount of the compound in accordance with this invention to agricultural product or in the course of producing the agricultural product.

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In accordance with yet another embodiment of this invention, a method of isolating and purifying the compound in accordance with the invention is provided. The method comprises the steps of: collecting and grounding dried roots of *Azima sarmentosa* Benth; preparing a crude extract from the grounded dried roots of *Azima sarmentosa* Benth; dissolving the crude extract in a mixture of methanol and water to obtain an aqueous methanol solution; extracting the aqueous methanol solution with hexane to remove non-polar soluble components from the aqueous methanol solution; partitioning the aqueous methanol solution with dichloromethane to obtain a dichloromethane fraction; evaporating the dichloromethane to obtain a dichloromethane extract; mixing
15 the dichloromethane extract with celite and subjecting the mixture to silica gel using a first solvent, followed by a second solvent to obtain several fractions; and isolating and purifying the fractions by column chromatography.

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In accordance with some embodiments of this invention, the steps for preparing the crude extract comprises extracting the grounded dried roots of *Azima sarmentosa* Benth with methanol by percolation.
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In accordance with some embodiments of this invention, the first solvent is a mixture of hexane and ethyl acetate. The second solvent is a mixture of dichloromethane and
30 methanol.

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In accordance with a further embodiment of this invention, an antifungal composition for agricultural applications comprising the compound of the present invention and a carrier is provided.

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In accordance with a further embodiment of this invention, an agricultural product comprising the compound of the present invention is provided.

5 In accordance with yet a further embodiment of this invention, a pesticide comprising the compound of the present invention is provided.

BRIEF DESCRIPTION OF THE DRAWINGS

10 The above and other features and advantages of the present invention will more clearly understood from the following detailed description taken in conjunction with the accompanying drawings:

Figure 1 is an NMR spectrum corresponding to a compound of formula (I).

15 Figure 2 shows a potato dextrose agar plate used in the experiments of the invention.

Figure 3 is a graph showing the inhibition effects of UTM_75B and UTM_85C on HepG2 cell line at a concentration of up to 500 µg/ml.

20 Figure 4 is a graph showing the inhibition effects of UTM_75B and UTM_85C on A549 cell line at a concentration of up to 500 µg/ml.

DETAILED DESCRIPTION OF THE INVENTION

25 Definitions

The following words and terms have the meanings given below, unless indicated otherwise. These are intended as general definitions and should in no way limit the scope of the present invention to those terms alone, but are put forth for better
30 understanding of the following description.

The term "agricultural product" as used herein refers to any preparation containing a compound of formula (I) which is capable of delivering the compound of formula (I) to the agricultural system being treated. The agricultural product can include, but is not

limited to, agricultural pesticides, fungicides, fertilizers, powders, sprays, pellets or other agricultural products.

5 The term "effective amount" as used herein refers to an amount of compound or composition according to the invention which is sufficient to prevent or treat the pathogenic fungal infection in plants, and which does not entail any appreciable symptom of cytotoxicity towards plants and mammals. The amount can vary within a wide range depending on the types of pathogenic fungal infection to be treated, the type of crop, the climatic conditions and the other compounds included in the
10 composition according to the invention. This amount can be determined by systematic field trials, which are within the capabilities of a person skilled in the art.

The term "alkyl" as used herein refers to straight or branched chain saturated aliphatic groups typically having from 1 to 20 carbon atoms. For example, the term "alkyl"
15 includes, but is not limited to, methyl, ethyl, propyl, isopropyl, 1-butyl, 2-butyl, isobutyl, tert-butyl, amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, and the like.

20 The term "alkenyl" as used herein refers to an unsaturated aliphatic hydrocarbon, including straight-chain, branched-chain and cyclic alkenyl groups having 1 to 6 carbons, with at least one double bond. For example, the term "alkenyl" includes, but is not limited to, vinyl, 1-propenyl, 2-propenyl, isopropenyl, 2-methyl-1-propenyl, 3-methyl-1-propenyl, 2-methyl-2-propenyl, 3-methyl-2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl
25 group, 3-methyl-2-butenyl and the like.

The term "cycloalkyl" as used herein refers to cyclic saturated aliphatic groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. For example, the term "cycloalkyl" includes, but is not limited to, cyclopropyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl, 2-methylcyclopentyl, 3-methylcyclopentyl,
30 cyclohexyl, cyclooctyl and the like.

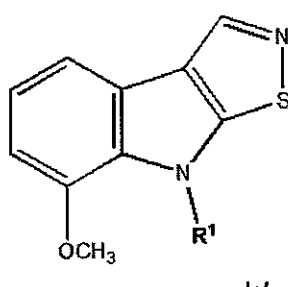
The term "cycloalkenyl" as used herein refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation.

For example, the term "cycloalkenyl" includes, but is not limited to, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

Compounds of the Invention

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The present invention relates to compounds for use in preventing and treating phytopathogenic fungal infection. In particular, the compounds are represented by a compound having the structure of formula (I):



wherein R¹ is alkyl, alkenyl, cycloalkyl or cycloalkenyl .

In a preferred embodiment, R¹ is methyl.

20 The compounds of the present invention do not exhibit any cytotoxic activity towards plants and mammals. Hence, the compounds are capable of providing a long-term prevention and treatment of phytopathogenic fungal infection in plants without harming the plants, crops, trees and mammals coming in contact with the compounds or the composition containing the compound.

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The compounds of the present invention exhibit anti-phytopathogenic activities against several pathogens. In a preferred embodiment of the invention, the pathogen is a fungus. Examples of some of the pathogenic fungi include, but are not limited to, *Colletotrichum gloeosporioides*, *Pestalotiopsis* sp., *Curvularia* sp. and *Rhizoctonia* sp.

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The compounds are useful as active ingredients of antifungal composition for the prevention and treatment of pathogenic fungal infections derived from fungi sensitive to the compounds of the present invention. The types of pathogenic fungal infections that can be prevented or treated using the compounds of the invention include, but are not limited to, anthracnose, leaf necrosis, leaf spot and bud rot disease, leaf/petiole/rachis

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(whole plant) blight, fruit rot, scab diseases, canker and twig dieback, black scurf, root rot, constriction of the stem and fungal diebacks.

In addition, the compounds of the present invention are also useful as active ingredients of composition for agricultural applications. The compounds can be converted into the customary formulations, for example, solutions, emulsions, suspensions, dispersions, powders, pastes, granules and powders, for use as agricultural products. The agricultural products may include, but are not limited to, agricultural pesticides, fungicides, fertilizers, powders, sprays, pellets and other agricultural products. In a preferred embodiment of the invention, the agricultural product is a pesticide. Suitable pesticide comprising the compound of the present invention may be prepared according to methods which are known to those of ordinary skill in the art. The pesticide may comprise the active compound disclosed herein and may include a conventional carrier or excipient.

The inhibition of pathogen in plants or crops is performed by, for example, administration of the compound of formula (I); a composition containing the compound of formula (I); or an agricultural product containing the compound of formula (I), to plants or crops that have been infected with the pathogen.

The compound of formula (I) is preferably incorporated in the composition or the agricultural product in accordance with the invention in an amount of about 10 mg/L to 500 mg/L.

The composition or the agricultural product comprising the compound of formula (I) may be used alone or in combination with or as a mixture thereof with other chemicals, such as insecticides, herbicides, bactericides, and growth-regulating substances of plants, or fertilizer or soil conditioners.

In an embodiment of the invention, the composition and the agricultural product comprising the compound of formula (I) are not cytotoxic.

The compound of formula (I) is a brassilexin analogue isolated from plant *Azima sarmentosa* Benth. *Azima sarmentosa* Benth is a species of scrubs belonging to the Salvadoraceae family. This species is widely distributed in South East Asia and is well

adapted to the arid environment. The method for preparing the compound of formula (I) from plant *Azima sarmentosa* Benth is described herein below.

Method for preparing the compound of formula (I)

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In one embodiment of the invention, the method comprises the steps of grounding dried roots of *Azima sarmentosa* Benth and extracting the grounded dried roots with methanol by percolation. The methanol extract is then concentrated and mixed with methanol and water mixture. This is followed by extracting the methanol extract with
10 hexane to obtain a hexane extract and an aqueous methanol solution. The aqueous methanol solution is partitioned with dichloromethane to obtain a dichloromethane fraction. The dichloromethane is then evaporated to obtain a dichloromethane extract. The extract obtained thereto is mixed with celite and the mixture is subjected to silica gel using hexane:ethyl acetate, followed by dichloromethane:methanol as a solvent
15 system providing, for example, seventeen fractions, fractions A to Q. All fractions were tested with antifungal assays against pathogenic fungal strains: *Colletotrichum gloesporoides*, *Pestalotiopsis* sp., *Curvularia* sp. and *Rhizoctonia* sp. Among all the fractions tested, two of the fractions, for example, fraction D and fraction E, demonstrated antifungal activities (see Table 1).

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In one embodiment, for example, fraction D is purified by using high-performance liquid chromatography (HPLC) to yield a pure compound of the present invention. The HPLC used in the method is preferably prepared by using RP C18 column and 0.1% of formic acid (A) and acetonitrile (ACN) (B) as a mobile phase.

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The following examples are provided to further illustrate and describe particular specific embodiments of the present invention, and are in no way to be construed to limit the invention to the specific procedures, conditions or compositions described therein.

30 **EXAMPLE**

About 500 g of dried roots of *Azima sarmentosa* Benth were ground and extracted with methanol (3 x 2L) for 24 hour by percolation. The methanol extracts were concentrated, mixed with methanol and water in a ratio of 9:1 to obtain an aqueous methanol solution.
35 The aqueous methanol solution was subsequently extracted with hexane (3 x 250 ml)

to remove non-polar soluble (hydrophobic) components from the aqueous methanol solution. The aqueous methanol solution (250 ml) was further partitioned with dichloromethane (3 x 250 ml). The dichloromethane fraction was evaporated, affording 20 g of a dichloromethane extract. The dichloromethane extract (20 g) was mixed with
 5 celite (20 g) and subjected to silica gel column chromatography (500 g) using a solvent containing hexane and ethyl acetate in a ratio of 7:3 and another solvent containing dichloromethane and methanol in a ratio of 7:3 to provide seventeen fractions (A-Q). Fractions D and E were purified by HPLC. The HPLC was prepared using RPC18 column and 0.1% of formic acid (A) and acetonitrile (ACN) (B) as a mobile phase, to
 10 yield about 18 mg of pure 1-methyl-7-methoxybrassilexin (UTM_75B) and about 20 mg of pure 1-methylbrassilexin (UTM_85C) respectively.

Determination of Fungicidal Activity

15 Four fungal species were tested in the experiments.

Colletotrichum gloeosporioides, *Pestalotiopsis* sp. and *Curvularia* sp. which are known as plant pathogens, were provided by Agri-Food & Veterinary Authority of Singapore.

20 *Aspergillus penicillioides*, which is an air borne environmental fungi growing on ceiling boards, was provided by National Environment Agency.

Preparation of agar plates

25 25 ml of sterilized liquid potato dextrose agar was pipetted into Petri dishes, for example, having a diameter of 86 mm. The agar was allowed to solidify. One well is punctured through the agar with a sterile straw 24 mm from the edge of the plate as shown in Figure 1.

30 Preparation of extracts and inoculation of test fungi

Azima sarmentosa Benth extracts, UTM_75B and UTM_85C of 2 mg each were dissolved in 50 µl of 50% of dimethyl sulfoxide (DMSO) respectively. The individual test fungi were inoculated 38 mm from the well (as shown in Figure 1) in each plate. 50
 35 µl of the UTM_75B and 50 µl of the UTM_85C were each added into the well in the

respective plate. A control, which was 50% DMSO, was used in this test. The plates were incubated at 24°C and measurements of growth/retardation of the fungus colony were recorded.

5 Method for measurement

Two values, R1 and R2 of the fungal growth were recorded. R1 represents growth of test fungi towards the well filled with 50% DMSO in mm, and R2 represents growth of test fungi towards the well filled with the extracts in mm. Rate of retardation was also
10 calculated, using the formula: $[(R1 - R2) / R1] \times 100\%$

Cytotoxicity assay

The cytotoxicity assay was conducted with HepG2 (human liver carcinoma) and A549
15 (human lung adenocarcinoma epithelial) cell lines. The assay used an indicator dye resazurin to measure the metabolic capacity of the cells.

The assay procedure included adding 100 µl at 10^5 /ml of HepG2 or A549 cells into a 96-well plate. The cells were incubated at 37°C overnight. On the second day, 10 µl of
20 the test sample was added to each well and the sample/cells mixture was then incubated for 24 hours at 37°C. On the third day, 20 µl of 0.2 mg/ml resazurin was added to each well and the sample/cells mixture was again incubated at 37°C for 4 hours. Results were obtained by reading the plate at an excitation wavelength of 535 nm and an emission wavelength of 590 nm using Tecan Infinite 200 microplate reader.

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Calculation for cytotoxicity assay

The percentage of inhibition is calculated as follows:

30 $\% \text{ inhibition} = (1 - ((\text{Sample}_{\text{readout}} - \text{Blank}_{\text{readout}}) / (\text{negative control}_{\text{readout}} - \text{blank}_{\text{readout}}))) \times 100$

IC₅₀: The concentration that shows 50% inhibition of the growth of mammalian cells.

Results:

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Table 1: Results of retardation rate against plant fungal pathogens and air borne nuisance fungi.

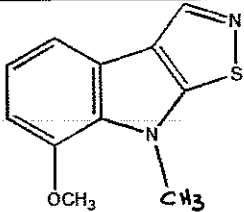
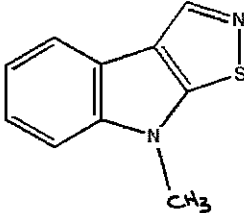
Sample ID	Best retardation rate against panel of test fungi (%)			
	<i>Colletotrichum gloeosporioides</i>	<i>Pestalotiopsis sp.</i>	<i>Curvularia sp.</i>	<i>Aspergillus penicillioides</i>
UTM_75B	36.4	18.4	27.0	none
UTM_85C	None	25.0	27.0	12.5

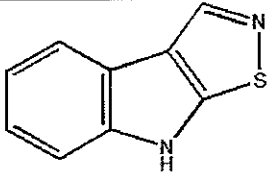
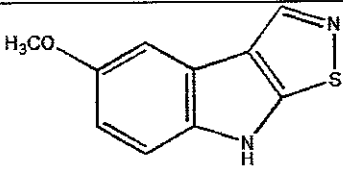
- 5 From Table 1, we can see that UTM_75B extract shows retardation against *Colletotrichum gloeosporioides*, *Pestalotiopsis sp* and *Curvularia sp.* at a rate of 36.4%, 18.4 % and 27.0% respectively between days five and six. The UTM_75B extract is also able to retain a retardation rate of above 10% against *Colletotrichum gloeosporioides* for eight days.

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UTM_85C extract shows retardation against *Pestalotiopsis sp.*, *Curvularia sp.* and the growth of air borne fungal, *Aspergillus penicillioides* at a rate of 25.0%, 27.0% and 12.5% respectively between days five and six.

- 15 Table 2: Cytotoxicity Results of Brassilexin Analogues with Human Cancer Cell Lines

Sample ID	Chemical name	Structure	Cytotoxicity assay IC ₅₀ or equivalent value (M)		
			HepG2	A549	KB cell
UTM_75B	1-methyl-7-methoxybrassilexin		$>2.3 \times 10^{-3}$	$>2.3 \times 10^{-3}$	-
UTM_85C	1-methylbrassilexin		1.9×10^{-3}	1.1×10^{-3}	-

-	*Brassilexin		-	-	4.6×10^{-5}
-	5-methoxybrassilexin		-	-	4.9×10^{-5}

The data in Table 2 shows that UTM_75B is not cytotoxic to HepG2 and A549 cell lines at a concentration of up to 2.3×10^{-3} M. However, UTM_85C is cytotoxic against A459 and HepG2 cell lines with IC_{50} of 1.9×10^{-3} M and 1.1×10^{-3} M respectively.

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Brassilexin is the most cytotoxic compound, as it was able to inhibit mammalian cell culture at LD_{50} (lethal dose 50%, which is equivalent to IC_{50} in *in vitro* assay) of 8 μ g/ml (or 4.6×10^{-5} M) (see Tempete C, at el., "Growth inhibitions on human cancer cell cultures with the indole sulphur-containing phytoalexins and their analogues", Z Naturforsch 1991; 46:706-707).

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In our study, the data showed that with a methyl group attached to N-1 (as in the case of 1-methylbrassilexin), the cytotoxicity was reduced to 1.9×10^{-3} M in HepG2 cell line and 1.1×10^{-3} M in A549 cell line. When a methoxyl group is attached to C7 position (as in the case of UTM_75B), the cytotoxic effects on mammalian cell lines reduced dramatically, with no cytotoxicity at all in HepG2 and A549 cell lines, at a concentration of up to 2.3×10^{-3} M (see Table 2, and Figures 3 and 4).

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In Figure 3, we can see that UTM_75B inhibits 0% of HepG2 cell growth at a concentration of up to 500 μ g/ml. In Figure 4, we can see that UTM_75B does not demonstrate any inhibition effects on A549 cell line or having negative inhibition, which indicates that UTM_75B promotes growth of A549 cell at a concentration of up to 500 μ g/ml. UTM_85C, on the other hand, inhibits about 100% of both HepG2 and A549 cells growth at a concentration of 500 μ g/ml.

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The above example shows that the compound UTM_75B, i.e. 1-methyl-7-methoxybrassicalexin, possesses antifungal effects against several plant pathogens, which shows no mammalian cytotoxicity effects at a concentration of up to 2.3×10^{-3} M (or 500 µg/ml or 500 mg/L) as compared to brassilexin and some of its analogues, such as 1-methylbrasselexin and 5-methoxybrassicalexin.

Brassinin analogues have been reported to exhibit antifungal activities. However, they also display cytotoxicity against human leukemia cell line, Jurkat cells (see M. Pilátová, et al., "Cruciferous phytoalexins: antiproliferative effects in T-Jurkat leukemic cells", Leukemia Res. 2005; 29:415-421).

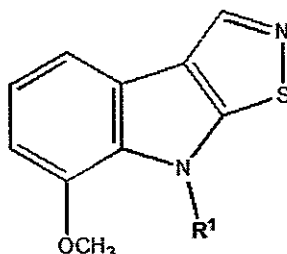
The above results thus show that compounds with a methoxyl group attached to C7 position of the compound of formula (I) are safer choice as antifungal pesticides as the compounds are capable of exhibiting anti-phytopathogenic activities against several pathogens, with no cytotoxic effect at a concentration of up to 2.3×10^{-3} M (or 500 mg/L). The extracts of *Azima sarmentosa* Benth with a methoxyl group attached to C7 position of the compound of formula (I) at a concentration of up to 500 mg/L can be developed into natural pesticides or agricultural products for preventing and treating plant pathogenic fungal infections.

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The above is a description of the subject matter the inventor regards as the invention. It is foreseeable that those skilled in the art can and will design alternative methods and compounds that include this invention based on the above disclosure.

CLAIMS:

1. A compound represented by the structure of formula (I):



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wherein R¹ is selected from the group consisting of alkyl, alkenyl, cycloalkyl or cycloalkenyl, for use in preventing and treating pathogenic fungal infection in plants, wherein the compound does not exhibit any cytotoxic activity towards plants and mammals.

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2. The compound according to claim 1, wherein the compound is isolated from plant *Azima sarmentosa* Benth.

3. The compound according to claim 1, wherein R¹ is methyl.

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4. The compound according to claim 1, wherein the compound is used as an active ingredient in agricultural product selected from the group consisting of agricultural pesticide, fungicide, fertilizer, powder, spray, pellet and other agricultural products.

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5. The compound according to claim 4, wherein the compound is used as an active ingredient in the agricultural pesticide.

6. The compound according to claim 1 or 4, wherein the compound is used in an amount of 10 mg/L to 500 mg/L.

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7. A method for preventing and treating pathogenic fungal infection, comprising applying an effective amount of the compound according to any one of claims 1 to 6 to agricultural plants.

8. A method for preventing and treating pathogenic fungal infection, comprising applying an effective amount of the compound according to any one of claims 1 to 6 to agricultural product or in the course of producing the agricultural product.

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9. A method for isolating and purifying a compound according to claim 1, the method comprising:

collecting and grounding dried roots of *Azima sarmentosa* Benth;

preparing a crude extract from the grounded dried roots of *Azima sarmentosa*

10 Benth;

dissolving the crude extract in a mixture of methanol and water to obtain an aqueous methanol solution;

extracting the aqueous methanol solution with hexane to remove non-polar soluble components from the aqueous methanol solution;

15 partitioning the aqueous methanol solution with dichloromethane to obtain a dichloromethane fraction;

evaporating the dichloromethane to obtain a dichloromethane extract;

mixing the dichloromethane extract with celite and subjecting the mixture to silica gel using a first solvent, followed by a second solvent to obtain several fractions;

20 and

isolating and purifying the fractions by column chromatography.

10. The method according to claim 9, wherein the steps for preparation of the crude extract comprises:

25 extracting the grounded dried roots of *Azima sarmentosa* Benth with methanol by percolation.

11. The method according to claim 9, wherein the first solvent is a mixture of hexane and ethyl acetate.

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12. The method according to claim 9, wherein the second solvent is a mixture of dichloromethane and methanol.

35 13. An antifungal composition for agricultural applications comprising the compound according to any one of claims 1 to 3 and a carrier.

14. An agricultural product comprising a compound as claimed in any one of claims 1 to 3.

5 15. The agricultural product of claim 14, wherein the agricultural product is selected from the group consisting of agricultural pesticide, fungicide, fertilizer, powder, spray, pellet and other agricultural products.

10 16. The agricultural product of claim 15, wherein the agricultural product is not cytotoxic.

17. A pesticide comprising a compound as claimed in any one of claims 1 to 3.

18. The pesticide according to claim 17, wherein the pesticide is not cytotoxic.