Antifungal Activities of Some Indole Derivatives

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Nine indole derivatives were evaluated *in vitro* against *Fusarium graminearum*, *Alternaria alternata*, *Helminthosporium sorokinianum*, *Pyricularia oryzae*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Fusarium oxysporum* f. sp. *cucumarinum*, and *Alternaria brassicae*. Most of the compounds were found to possess antifungal activities. Especially compounds **2**, **5**, **8**, and **9** exhibited broad-spectrum antifungal activities against the above-mentioned seven phytopathogenic fungi, and showed more potent activities than hymexazole, a commercial agricultural fungicide.

Key words: Indole, Antifungal Activity, Phytopathogenic Fungi

Introduction

Recently, indole subunits have gained widespread interest due to their key role in medically important formations, such as those exhibiting a promising potential in the treatment of hyperlipidemia and atherosclerosis (Al-Qirim *et al*., 2009), displaying antimicrobial and antiviral activity (Olgen *et al*., 2009), and showing potent and selective ligation for the human serotonin 5-HT_6 receptor (Tsai *et al*., 2000; Russell *et al*., 2001; Pullagurla *et al*., 2005). However, to the best of our knowledge, little attention has been paid to the antifungal activities of simple indole derivatives against phytopathogenic fungi, and only Dekker *et al*. (1975) reported that some simple indole derivatives were found to possess antifungal activities against *Botrytis allii*, *Cladosporium cucumerinum*, *Penicillium italicum*, and *Aspergillus niger*. Meanwhile, many crops are easily infected by phytopathogenic fungi which are hard to control. Therefore, the development of bioactive compounds for controlling those agricultural diseases is highly desirable. As a consequence and in continuation of our program aimed at the discovery and development of bioactive molecules (Xu *et al*., 2007, 2009; Xu and Xiao, 2009), here we report the antifungal activities of nine simple indole derivatives against seven phytopathogenic fungi.

Experimental

Nine indole derivatives, **1**–**9** were used as purchased from commercial sources, and their purity exceeded 98%. Subsequently, compounds **1**–**9** were screened *in vitro* for their antifungal activities against the phytopathogenic fungi by the poisoned food technique (Xu *et al*., 2007). Seven phytopathogenic fungi, namely *Fusarium graminearum*, *Alternaria alternata*, *Helminthosporium sorokinianum*, *Pyricularia oryzae*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Fusarium oxysporum* f. sp. *cucumarinum*, and *Alternaria brassicae*, were used for the biological assays. Potato dextrose agar (PDA) medium was prepared in flasks and sterilized. Compounds **1**–**9** were dissolved in acetone before mixing with PDA, and the final concentration of the test compounds in the medium was fixed at 100 or 50 μg/mL. The medium was then poured into sterilized Petri dishes. All types of fungi were incubated in PDA at (28 ± 1) °C for 5 d to get new mycelium for the antifungal assays. Then mycelium disks of approx. 5 mm diameter cut from the culture medium were picked up with a sterilized inoculation needle and inoculated in each centre of each PDA Petri dish. The inoculated Petri dishes were incubated at (28 ± 1) °C for 4 d. Acetone without any compound mixed with PDA served as control, while hymexazole (Binzhou De'dong Chemical Engineering Co., Ltd., Shandong province, China), a commercial agricultural fungicide, severed as positive

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control. For each treatment, three replicates were conducted. The radial growth of the fungal colonies was measured, and the data were statistically analyzed. The inhibitory effects of the test compounds on these fungi *in vitro* were calculated by the formula

$$\text{inhibition rate } (\%) = (C - T) \cdot 100/C,$$

where C represents the diameter of fungal growth on untreated PDA, and T represents the diameter of fungal growth on treated PDA.

Results and Discussion

As outlined in Table I, eight compounds, **2**–**9** (Fig. 1), at 100 μg/mL were found to possess more potent antifungal activities against the seven phytopathogenic fungi than hymexazole, a commercial agricultural fungicide. Especially the inhibition rates of compounds **2**, **5**, **8**, and **9** against the tested phytopathogenic fungi exceeded 80%, while the corresponding inhibition rates of hymexazole were less than 76%. Interestingly, even at 50 μg/mL compounds **2**, **5**, **8**, and **9** still showed potent antifungal activities, for example the inhibition rates of **5** against *Fusarium graminearum*, *Alternaria alternata*, *Helminthosporium sorokinianum*, *Pyricularia oryzae*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Fusarium oxysporum* f. sp. *cucumarinum*, and *Alternaria brassicae* were 46.6%, 76.8%, 91.5%, 88.2%, 89.6%, 75.6%, and 79.8%, respectively.

Some structure-activity relationships of these simple indole derivatives could be drawn as follows:

(1) The influence of substituents at the indolyl ring on the antifungal activities was very obvious. For example, at 100 μg/mL, the inhibition rates of indole (**1**) against *Fusarium graminearum*, *Alternaria alternata*, *Helminthosporium sorokinianum*, *Pyricularia oryzae*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Fusarium oxysporum* f. sp. *cucumarinum*, and *Alternaria brassicae* were only 26.7%, 31.0%, 39.3%, 41.2%, 46.1%, 40.3%, and 34.9%, respectively. However, when the methyl, cyano, or nitro group was introduced at the indolyl ring, the inhibition rates of the corresponding compounds increased considerably.

(2) The position of the substituents at the indolyl ring was also essential for the activity. For example, at 100 μg/mL, when the methyl group was introduced at the 4- or 2,3-position of indole and the nitro group was introduced at the 5-position of indole, compounds **2**, **8**, and **5** exhibited more potent activities than others.

(3) Especially when the nitro group was introduced at the 5-position of indole to give **5**, the inhibition rates against the seven phytopathogenic fungi were nearly 100%.

In conclusion, nine indole derivatives were evaluated *in vitro* against *Fusarium graminearum*, *Alternaria alternata*, *Helminthosporium sorokinianum*, *Pyricularia oryzae*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Fusarium oxysporum* f. sp. *cucumarinum*, and *Alternaria brassicae*. Many compounds were found to possess antifungal activities at 100 μg/mL. Especially compounds **2**, **5**, **8**, and **9** exhibited broad-spectrum antifungal activities against the above-mentioned seven phytopathogenic fungi, and showed more potent activities than hymexazole, a commercial agricultural fungicide.

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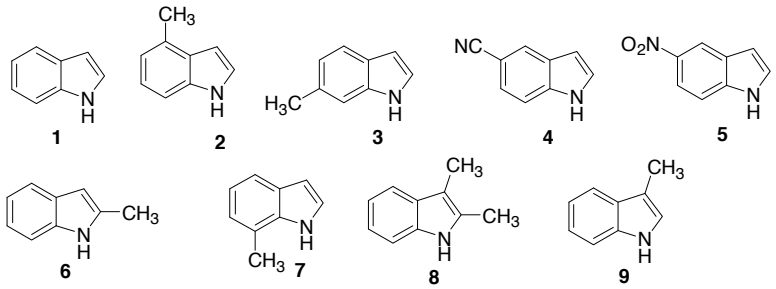

Fig. 1. Chemical structures of the indole derivatives **1**–**9**.

Table I. Antifungal activity (inhibition rate in %)[a] of indole derivatives **1**–**9** against phytopathogenic fungi *in vitro*.

Compound	Concentration [μg/mL]	*Fusarium graminearum*	*Alternaria alternata*	*Helminthosporium sorokinianum*	*Pyricularia oryzae*	*Fusarium oxysporum* f. sp. *vasinfectum*	*Fusarium oxysporum* f. sp. *cucumarinum*	*Alternaria brassicae*
1	100	26.7 (± 1.5)	31.0 (± 1.3)	39.3 (± 1.3)	41.2 (± 2.5)	46.1 (± 1.3)	40.3 (± 2.6)	34.9 (± 1.4)
2	100	85.5 (± 0.8)	97.8 (± 0)	91.1 (± 0)	94.6 (± 1.4)	91.9 (± 1.3)	96.6 (± 1.5)	98.1 (± 0)
	50	54.1 (± 0.7)	54.7 (± 0.6)	74.4 (± 0)	70.0 (± 0.7)	64.2 (± 0.6)	66.1 (± 0.8)	66.4 (± 1.1)
3	100	54.2 (± 1.5)	79.8 (± 2.2)	86.0 (± 1.3)	83.4 (± 2.4)	79.7 (± 1.3)	81.8 (± 2.6)	74.8 (± 1.1)
4	100	51.2 (± 0.8)	85.8 (± 1.3)	66.7 (± 0)	85.1 (± 0.7)	75.3 (± 0.6)	92.2 (± 0)	87.7 (± 1.0)
5	100	99.5 (± 0.9)	100 (± 0)	100 (± 0)	100 (± 0)	100 (± 0)	100 (± 0)	100 (± 0)
	50	46.6 (± 0.4)	76.8 (± 1.1)	91.5 (± 0)	88.2 (± 0.7)	89.6 (± 0)	75.6 (± 0.8)	79.8 (± 0.5)
6	100	52.7 (± 1.5)	64.7 (± 1.3)	67.3 (± 1.3)	65.2 (± 1.4)	73.8 (± 0)	69.1 (± 1.5)	60.2 (± 1.9)
7	100	51.6 (± 0.9)	87.6 (± 1.1)	81.6 (± 1.3)	91.2 (± 1.4)	86.2 (± 1.3)	91.7 (± 2.7)	96.2 (± 0)
	50	18.6 (± 0.7)	55.3 (± 0.6)	42.5 (± 0.6)	48.2 (± 0.7)	25.6 (± 1.6)	71.6 (± 0.8)	50.0 (± 0)
8	100	81.2 (± 0.9)	86.5 (± 2.3)	97.8 (± 0)	93.6 (± 1.4)	76.0 (± 0)	94.0 (± 1.5)	98.7 (± 0)
	50	39.6 (± 0.7)	75.0 (± 1.3)	75.1 (±0.6)	72.1 (± 0.7)	65.0 (± 0.6)	71.6 (± 0.8)	54.0 (± 0.5)
9	100	100 (± 0)	99.3 (± 1.3)	97.8 (± 0)	97.6 (± 0)	76.0 (± 0)	97.4 (± 0)	100 (± 0)
	50	38.6 (± 0.4)	58.4 (± 0.6)	76.7 (± 0)	73.4 (± 1.7)	57.7 (± 0.6)	78.8 (± 0.8)	51.5 (± 0.5)
Hy[b]	100	66.7 (± 0.4)	67.0 (± 0.7)	63.3 (± 0.6)	75.8 (± 1.8)	72.7 (± 1.1)	73.5 (± 2.0)	57.1 (± 1.0)
	50	57.4 (± 0)	56.9 (± 0)	38.3 (± 0.6)	62.5 (± 1.1)	57.7 (± 0.6)	72.2 (± 0)	43.4 (± 0.9)
Acetone[c]	/	0	0	0	0	0	0	0

[a] Values are means of three experiments, standard deviations are given in parentheses. [b] Hymexazole as a reference compound. [c] Control.

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