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Synthesis and Activity of Novel Fungicide 2-(3-Chlorophenylcarbamoyl)phenyl Acetate

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In the present study, 2-(3-chlorophenylcarbamoyl)phenyl acetate was synthesized by the ammonolysis of 2-(chlorocarbonyl)phenyl acetate. Its structure was confirmed by IR and ^{1}H NMR. Its antifungal activity against *Sclerotinia sclerotiorum* and *Helminthosprium maydis* has been determined in the laboratory. The results showed that it had good antifungal activity against the two different pathogenic fungi of plants. Its median effective concentrations (EC_{50}) reached 2 and 3.80 mg L^{-1}, respectively.

Keywords: Antifungal activity, 2-(3-Chlorophenylcarbamoyl)phenyl acetate.

INTRODUCTION

Sclerotinia sclerotiorum is a harmful disease of cole[1]. For a long period, benzimidazole fungicides have been mostly used to prevent it. In recent years, however, it has developed resistance to the fungicides[2-5]. Moreover, its scope of resistance continues to develop and has already included many new fungicides[6-8].

Likewise, *Helminthosprium maydis* is a pathogenic fungus of plants that has serious harm to vegetables and flowers. Over the past decades, synthetic fungicides including carbendazim have been used to prevent it. Nevertheless, the development of its resistance to all the fungicides has reduced the efficacy of fungicidal treatment[9-14].

It is well-known that since aspirin (acetylsalicylic acid) was first marketed in 1899, it has been widely used for the treatment of pains, fever and colds[15-23]. Thus, 2-(3-chlorophenylcarbamoyl)phenyl acetate was synthesized on the basis of it. In the meantime, its antifungal activity has been evaluated in the laboratory to find novel fungicides with high efficacy and low toxicity.

EXPERIMENTAL

Sclerotinia sclerotiorum and *Helminthosprium maydis* were obtained from the Chinese Academy of Agricultural Sciences. They were preserved at 4 °C. All chemicals and solvents were purchased from commercial sources unless specified otherwise. IR spectra were recorded on a Thermofisher Nicolet-6700 spectrophotometer. ^{1}H NMR spectra were taken on a Varian Unity Inova-400 instrument using deuteron-chloroform as the solvent.

Synthesis of target compound: The target compound was synthesized according to the reaction shown in Fig. 1. 3-chloroaniline (0.02 mol) and pyridine (0.02 mol) were dissolved in CH_2Cl_2 (15 mL). The mixture was stirred and heated to 35-45 °C. 2-(chlorocarbonyl)phenyl acetate (0.02 mol) with CH_2Cl_2 (15 mL) was slowly added to the above mixture under stirring until the reaction was complete. The precipitate was filtered and washed with distilled water. The pure compound was obtained by re-crystallization in anhydrous ethanol.

Synthesized compound ($C_{15}H_{12}O_3NCl$): White crystals; yield: 27 %; m.p. 126-127 °C; IR (KBr, ν_{max}, cm^{-1}): 3296, 3261, 3187, 3115, 3077, 1770, 1743, 1676, 1666, 1593, 1537, 1484, 1450, 1368, 1316, 1203, 1162, 1135, 784, 775, 751, 696, 583; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.31 (s, 3H), 7.12 (t, J = 8.0 Hz, 2H), 7.23-7.27 (m, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.76 (t, J = 8.0 Hz, 1H), 8.18 (s, 1H).

Assay of antifungal activity: Antifungal activity of the synthesized compound against *Sclerotinia sclerotiorum* and *Helminthosprium maydis* was determined using the plate growth rate method[24].

The synthesized compound and carbendazim (purity 90 %) were dissolved in dimethyl sulfoxide (DMSO), respectively. The two solutions were diluted into five different concentrations with distilled water, respectively. They were added to the sterile culture medium (PDA) at 45 °C, mixed to homogeneity and transferred to sterile petri dishes to solidify. A mycelium agar disc (5 mm in diameter) of the target fungi was placed in the center of PDA plates. They were incubated

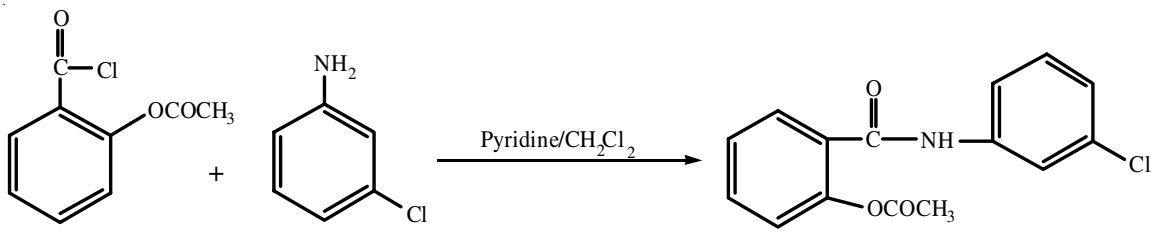

Fig. 1. Synthetic method of 2-(3-chlorophenylcarbamoyl)phenyl acetate

at 28 °C in the dark until the target fungi used as controls covered the surface of these plates. Control groups were treated with the corresponding solutions without the synthesized compound or carbendazim. The experiment for each concentration was replicated three times. The diameter of the fungi in the cultures was measured and the inhibition of growth was calculated according to the formula of Abbott. EC_{50} values were calculated with the Statistics Package for the Social Sciences (SPSS) based on probit analysis.

RESULTS AND DISCUSSION

Antifungal activity against *Sclerotinia sclerotiorum*: Compared with the efficient fungicide carbendazim, the synthesized compound was submitted to laboratory bioassay. The results are presented in Table-1. It had good antifungal activity against *Sclerotinia sclerotiorum*. Its EC_{50} value was 2 mg L^{-1}. The results of regressive and correlative analyses indicated that the correlation was significant between concentration and efficacy. Its correlative coefficient was 0.9842. Chi-square test demonstrated that the results were reliable (χ^2 = 4.074, $\delta f = 3$, $p > 0.05$).

Antifungal activity against *Helminthosprium maydis*: As shown in Table-2, using the efficient fungicide carbendazim as the comparative standard, the synthesized compound was subjected to laboratory bioassay. Its EC_{50} value reached 3.80 mg L^{-1}. The results of regressive and correlative analyses revealed that the correlation was significant between concentration and efficacy. The correlative coefficient was 0.9640. As for the results of *Helminthosprium maydis*, chi-square test also showed that the results were reliable (χ^2 = 0.549, $\delta f = 3$, $p > 0.05$).

The target compound [2-(3-chlorophenylcarbamoyl)phenyl acetate] has been successfully synthesized by means of the ammonolysis of 2-(chlorocarbonyl)phenyl acetate and then its structure has been confirmed with the aid of IR and ^{1}H NMR.

Results of laboratory bioassay have clearly shown that though the antifungal activity of 2-(3-chlorophenylcarbamoyl)-phenyl acetate against *Sclerotinia sclerotiorum* was inferior to carbendazim, its antifungal activity against *Helminthosprium maydis* was superior to carbendazim. Thus, the structural modification of aspirin was very successful. In addition, the structure of the obtained compound is simple and its chemical synthesis is easy. Therefore, on the basis of it, more derivatives may be further synthesized so as to survey quantitative structure-activity relationships and find novel fungicides with high efficacy and low toxicity as well as safety to non-target

TABLE-1
ANTIFUNGAL ACTIVITY OF 2-(3-CHLOROPHENYLCARBAMOYL)PHENYL ACETATE AGAINST *Sclerotinia sclerotiorum*

	2-(3-Chlorophenylcarbamoyl)phenyl acetate					Carbendazim				
Concentration (mg L^{-1})	12.5	6.25	3.13	1.56	0.78	50	25	12.5	6.3	3.1
Inhibition of growth* (%)	92.8	76.2	56.3	41.4	30.9	94.1	85.5	74.9	61.1	49.5
Regressive equation (Y = aX + b)	Y = 1.5421 X + 4.5362					Y = 1.2683 X + 4.3132				
EC_{50} (mg L^{-1})	2.0					3.5				
(95 % CL)	(1.63 – 2.39)					(2.4 – 4.6)				
Correlative coefficient r	0.9842					0.9614				
χ^2	4.074					0.605				

*Based on the mean of triplicates

TABLE-2
ANTIFUNGAL ACTIVITY OF 2-(3-CHLOROPHENYLCARBAMOYL) PHENYL ACETATE AGAINST *Helminthosprium maydis*

	2-(3-Chlorophenylcarbamoyl)phenyl acetate					Carbendazim				
Concentration (mg L^{-1})	100	50	25	12.5	6.3	100	50	25	12.5	6.3
Inhibition of growth* (%)	90.1	81.0	74.8	67.8	57.6	87.5	70.8	57.5	14.5	35.5
Regressive equation (Y = aX + b)	Y = 0.8483 X + 4.5084					Y = 1.2373 X + 3.5189				
EC_{50} (mg L^{-1})	3.8					15.7				
(95 % CL)	(1.4 – 6.4)					(12.1 – 19.6)				
Correlative coefficient r	0.9640					0.9808				
χ^2	0.549					2.862				

*Based on the mean of triplicates

organisms. On the other hand, the compound is also promising in the agricultural chemistry field because it possessed good antifungal activity against the two different pathogenic fungi of plants.

However, in order to realize the industrialization of the compound as a fungicide, more research work needs doing. Its antifungal spectrum needs to be determined. Its mode of action and its safety to humans and non-target organisms also need to be further investigated.

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