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NOTE

Antifungal Activity of Aspirin Derivatives against *Sclerotinia sclerotiorum*

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Two aspirin derivatives [2-(4-methylphenylcarbamoyl)phenyl acetate and 2-(4-methoxyphenylcarbamoyl)phenyl acetate] were synthesized by the ammonolysis of 2-(chlorocarbonyl)phenyl acetate. Their structure was confirmed by IR and ^{1}H NMR. Their antifungal activity against *Sclerotinia sclerotiorum* has been determined in the laboratory. Results showed that they had good antifungal activity against *Sclerotinia sclerotiorum*. Their median effective concentrations (EC_{50}) were 19.1 and 23.4 mg L^{-1}, respectively.

Key Words: Antifungal activity, 2-(4-Methoxyphenylcarbamoyl)phenyl acetate, 2-(4-Methylphenylcarbamoyl)phenyl acetate.

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, it has developed resistance to the above-mentioned fungicides[2,3]. Moreover, its scope of resistance continues to expand and has already included many new fungicides[4,5]. Therefore, new fungicides are continually required.

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[6-10]. Therefore, in this study, on the basis of aspirin, 2-(4-methylphenylcarbamoyl)phenyl acetate and 2-(4-methoxyphenylcarbamoyl)phenyl acetate were synthesized. In the meantime, their antifungal activity has been evaluated in the laboratory so as to find new fungicides with high efficacy and low toxicity.

Sclerotinia sclerotiorum was obtained from the Chinese Academy of Agricultural Sciences. It was preserved at 4 ºC. 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 compounds: The target compounds were synthesized according to the route shown in Fig. 1. Aniline derivatives (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 ºC. 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

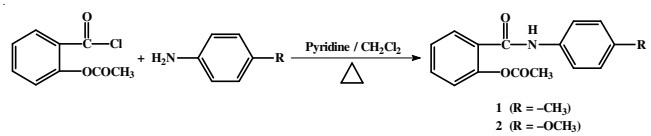

Fig. 1. Synthetic method of compounds **1** and **2**

precipitate was filtered and washed with distilled water. The pure compounds were obtained by re-crystallization in anhydrous ethanol.

Compound 1 ($C_{16}H_{15}O_3N$): Light yellow crystal; yield: 85.0 %; m.p. 139-140 ºC; IR (KBr, ν_{max}, cm^{-1}): 3494, 3280, 3193, 3122, 3060, 2921, 1756, 1654, 1606, 1533, 1513, 1446, 1382, 1220, 1206, 812, 762, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.98 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.47-7.53 (m, 3H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 3H), 2.34 (s, 3H), 2.32 (s, 3H).

Compound 2 ($C_{16}H_{15}O_4N$): Light purple solid; yield: 77.0 %; m.p. 119-120 ºC; IR (KBr, ν_{max}, cm^{-1}): 3341, 3246, 3123, 3044, 3009, 2937, 2839, 1760, 1643, 1608, 1599, 1513, 1445, 1371, 1301, 1219, 1198, 816, 759, 634; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.94 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.49-7.52 (m, 3H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 9.2 Hz, 2H), 3.81 (s, 3H), 2.33 (s, 3H).

Assay of antifungal activity: The antifungal activity of the synthesized compounds against *Sclerotinia sclerotiorum* was determined using the plate growth rate method[11].

The synthesized compounds and carbendazim (purity 90 %) were dissolved in dimethyl sulfoxide, respectively. These solutions

TABLE-1
ANTIFUNGAL ACTIVITY OF 2-(4-METHYLPHENYLCARBAMOYL)PHENYL ACETATE AGAINST *Sclerotinia sclerotiorum*

	2-(4-Methylphenylcarbamoyl)phenyl acetate					Carbendazim				
Concentration (mg L^{-1})	100	50	25	12.5	6.3	50	25	12.5	6.3	3.1
Inhibition of growth* (%)	91.1	70.5	54.1	41.5	22.5	94.1	85.5	74.9	61.1	49.5
Regressive equation (Y = aX + b)	Y = 1.5978X + 2.9531					Y = 1.2683X + 4.3132				
EC_{50} (mg L^{-1})	19.1					3.5				
(95 % CL)	(15.9-22.7)					(2.4-4.6)				
Correlative coefficient (r)	0.9682					0.9614				
χ^2	3.034					0.605				

*Based on the mean of triplicates.

TABLE-2
ANTIFUNGAL ACTIVITY OF 2-(4-METHOXYPHENYLCARBAMOYL)PHENYL ACETATE AGAINST *Sclerotinia sclerotiorum*

	2-(4-Methoxyphenylcarbamoyl)phenyl acetate					Carbendazim				
Concentration (mg L^{-1})	100	50	25	12.5	6.3	50	25	12.5	6.3	3.1
Inhibition of growth* (%)	91.1	75.3	45.2	32.3	13.8	94.1	85.5	74.9	61.1	49.5
Regressive equation (Y = aX + b)	Y = 1.9831X + 2.2842					Y = 1.2683X + 4.3132				
EC_{50} (mg L^{-1})	23.4					3.5				
(95 % CL)	(20.2-27.1)					(2.4-4.6)				
Correlative coefficient (r)	0.9549					0.9614				
χ^2	2.797					0.605				

*Based on the mean of triplicates.

were diluted into five different concentrations with distilled water, respectively. They were added to the sterile culture medium (PDA) at 45 ºC, 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 at 28 ºC 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 compounds 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.

Antifungal activity against *Sclerotinia sclerotiorum*: Compared with the efficient fungicide carbendazim, the synthesized compounds were submitted to laboratorial bioassay. The results are presented in Tables 1 and 2. Compound **1** had good antifungal activity against *Sclerotinia sclerotiorum*. Its EC_{50} value was 19.1 mg L^{-1}. The results of regressive and correlative analyses indicated that the correlation was significant between concentration and efficacy. Its correlative coefficient was 0.9682. Chi-square test demonstrated that the results were reliable ($\chi^2 = 3.034$, df = 3, $p > 0.05$).

Compound **2** had also good antifungal activity against *Sclerotinia sclerotiorum*. Its EC_{50} value was 23.4 mg L^{-1}. The results of regressive and correlative analyses revealed that the correlation was significant between concentration and efficacy. The correlative coefficient was 0.9549. As for the results of compound **1**, chi-square test also showed that the results were reliable ($\chi^2 = 2.797$, df = 3, $p > 0.05$).

Both compounds [2-(4-methylphenylcarbamoyl)phenyl acetate and 2-(4-methoxyphenylcarbamoyl)phenyl acetate] have been successfully synthesized by means of the ammonolysis of 2-(chlorocarbonyl)phenyl acetate and then their structure has been confirmed with the aid of IR and ^{1}H NMR.

The results of laboratory bioassay have clearly shown that they have good antifungal activity against *Sclerotinia sclerotiorum*. Therefore, the structural modification of aspirin was very successful. Thus, based on it, more derivatives can be further synthesized so as to survey quantitative structure-activity relationships and find new fungicides with high efficacy and low toxicity as well as safety to non-target organisms.

However, in order to realize the industrialization of the compounds as fungicides, more research work needs to be done.

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