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Synthesis and Antifungal Activity of Aspirin Derivatives

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Using aspirin as a lead compound, a series of its derivatives (compounds **1-7**) were designed and synthesized. Their activity of anti-pathogenic fungi of plants has been evaluated in the laboratory. The results showed that these compounds had good antifungal activity against *Sclerotinia sclerotiorum*, *Helminthosprium maydis*, *Botrytis cinerea* and *Rhizoctonia solani*. Among them, the inhibition of growth for compounds **1** and **2** against *Helminthosprium maydis* reached 92.5 and 91.6 % at a concentration of 100 mg L^{-1}, respectively, which was superior to carbendazim.

Keywords: Aspirin derivatives, Antifungal activity.

INTRODUCTION

Sclerotinia sclerotiorum, *Helminthosprium maydis*, *Botrytis cinerea* and *Rhizoctonia solani* are harmful pathogenic fungi of crops or vegetables[1-4]. Over the past decades, synthetic fungicides including carbendazim have been used to prevent them. However, in recent years, they have developed resistance to the fungicides[5-9]. Moreover, their scope of resistance continues to expand and has already included many new fungicides[10-12]. Therefore, new fungicides are continually required.

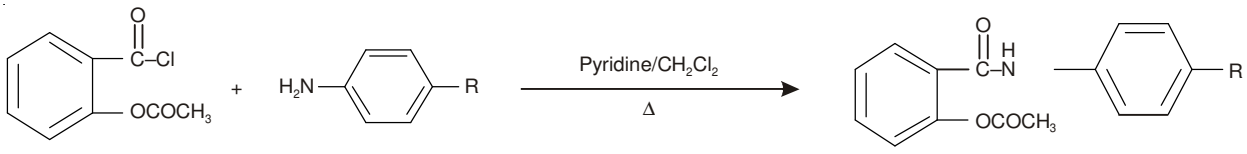
It is well-known that since aspirin (acetylsalicylic acid) was first marketed in 1899, it has been widely used for the treatment of pains, fever and colds[13-16]. Therefore, in the present study, aspirin derivatives were synthesized based on aspirin. In the meantime, their antifungal activity has been evaluated in the laboratory to find new fungicides with high efficacy and low toxicity.

EXPERIMENTAL

Sclerotinia sclerotiorum, *Helminthosprium maydis*, *Botrytis cinerea* and *Rhizoctonia solani* 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 compounds: The target compounds were synthesized in accordance with the reaction shown in Fig. 1. Aniline or its derivatives (0.01 mol) and pyridine (0.01 mol) were dissolved in CH_2Cl_2 (15 mL). The mixture was stirred and heated to 35-45 °C. 2-(Chlorocarbonyl)phenyl acetate (0.01 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 stilled water. The pure compounds were obtained by re-crystallization in anhydrous ethanol.

Compound 1 ($C_{15}H_{13}O_3N$): Light yellow powder; yield: 75 %; m.p. 152-153 °C; IR (KBr, ν_{max}, cm^{-1}): 3243, 3191, 3131, 3072, 3040, 1760, 1649, 1597, 1542, 1494, 1451, 1370, 1327, 1300, 1195, 1156, 1097, 758, 748, 709, 596; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H),



1: R=H; 2: R=Cl; 3: R=Br; 4: R= -NO_2; 5: R= -CH_3; 6: R= -OCH_3; 7: R= -$COCH_3$

Fig. 1. Synthetic method of target compounds **1-7**

7.60 (d, *J* = 8.0 Hz, 2H), 7.49-7.53 (m, 1H), 7.33-7.38 (m, 3H), 7.13-7.17 (m, 2H), 2.32 (s, 3H).

Compound 2 ($C_{15}H_{12}O_3NCl$): White needle crystal; yield: 40 %; m.p. 133-134 °C; IR (KBr, ν_{max}, cm^{-1}): 3487, 3285, 3190, 3111, 3048, 1755, 1656, 1608, 1595, 1533, 1493, 1447, 1396, 1317, 1207, 1172, 830, 751, 701, 589; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.49-7.55 (m, 3H), 7.30-7.36 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 2.31 (s, 3H).

Compound 3 ($C_{15}H_{12}O_3NBr$): Light yellow needle crystal; yield: 82 %; m.p. 138-139 °C; IR (KBr, ν_{max}, cm^{-1}): 3485, 3281, 3183, 3105, 3042, 1755, 1656, 1597, 1607, 1587, 1526, 1490, 1446, 1391, 1317, 1208, 1173, 826, 750, 700, 589; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.15 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.42-7.52 (m, 5H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 2.30 (s, 3H).

Compound 4 ($C_{15}H_{12}O_5N_2$): Golden yellow crystal; yield: 54 %; m.p. 90-91 °C; IR (KBr, ν_{max}, cm^{-1}): 3315, 3123, 3068, 3030, 1775, 1675, 1604, 1585, 1501, 1451, 1370, 1298, 1176, 1146, 1121, 812, 744, 693, 592; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.10 (s, 1H), 8.91 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.21-7.26 (m, 2H), 2.36 (s, 3H).

Compound 5 ($C_{16}H_{15}O_3N$): Light yellow crystal; yield: 85 %; m.p. 139-140 °C; (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 6 ($C_{16}H_{15}O_4N$): Light purple solid; yield: 77 %; m.p. 119-120 °C; 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).

Compound 7 ($C_{17}H_{15}O_4N$): Orange yellow crystal; yield: 35 %; m.p. 160-161 °C; (KBr, ν_{max}, cm^{-1}): 3502, 3330, 3184, 3104, 3000, 1772, 1682, 1601, 1586, 1522, 1447, 1366, 1314, 1218, 1196, 1180, 820, 759, 698, 595; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.37 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.82-7.85 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.51-7.56 (m, 1H), 7.34-7.38 (m, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 2.58 (s, 3H), 2.33 (s, 3H).

Assay of antifungal activity: The antifungal activity of the synthesized compounds against *Sclerotinia sclerotiorum*, *Helminthosprium maydis*, *Botrytis cinerea* and *Rhizoctonia solani* were determined using the plate growth rate method[17].

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

RESULTS AND DISCUSSION

All the synthesized derivatives of aspirin were screened for their activity against *Sclerotinia sclerotiorum*, *Helminthosprium maydis*, *Botrytis cinerea* and *Rhizoctonia solani*. The results are presented in Table-1. Most of them were active against the four different pathogenic fungi at a concentration of 100 mg L^{-1}. The inhibition rate of compounds **1** and **2** against *Helminthosprium maydis* reached 92.5 and 91.6 %, respectively, which was higher than carbendazim. The inhibition rate of compound **3** against *Botrytis cinerea* reached 90.6 %, which was close to carbendazim.

A series of derivatives of aspirin have been successfully synthesized and tested for their antifungal activity against *Sclerotinia sclerotiorum, Helminthosprium maydis*, *Botrytis cinerea* and *Rhizoctonia solani*. The preliminary results suggested that the design and synthesis of these compounds may be conducive to the antifungal activity of derivatives of aspirin. They are also promising and beneficial to further studies in developing new and more effective fungicides in the agricultural chemistry field. However, there is more work

TABLE-1
ANTIFUNGAL ACTIVITY OF COMPOUNDS **1-7** AGAINST *Sclerotinia sclerotiorum*, *Helminthosprium maydis*, B*otrytis cinerea* AND *Rhizoctonia solani* AT 100 mg L^{-1}

Compound	R	Inhibition of growth (%)*			
		Sclerotinia sclerotiorum	*Helminthosprium maydis*	*Botrytis cinerea*	*Rhizoctonia solani*
1	H	87.5	92.5	72.0	88.7
2	4-Cl	93.7	91.6	88.8	63.8
3	4-Br	87.7	72.7	90.6	61.3
4	4-NO_2	50.6	67.8	66.4	67.7
5	4-CH_3	91.1	78.5	68.2	48.9
6	4-OCH_3	91.1	70.4	60.8	46.2
7	4-$COCH_3$	71.7	79.4	77.2	37.1
Carbendazim	–	100	87.5	91.3	100

*Based on the mean of triplicates

to be done. A number of derivatives of aspirin should be further synthesized for screening and surveying quantitative structure-activity relationships so as to find novel fungicides with high effect and low toxicity. Meanwhile, the mode of action of compounds **1** and **2** and their safety to humans and non-target organisms also need to be investigated.

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