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ISOLATION, SYNTHESIS, AND ANTIFUNGAL ACTIVITY OF KOJIC ACID AND ITS DERIVATIVES

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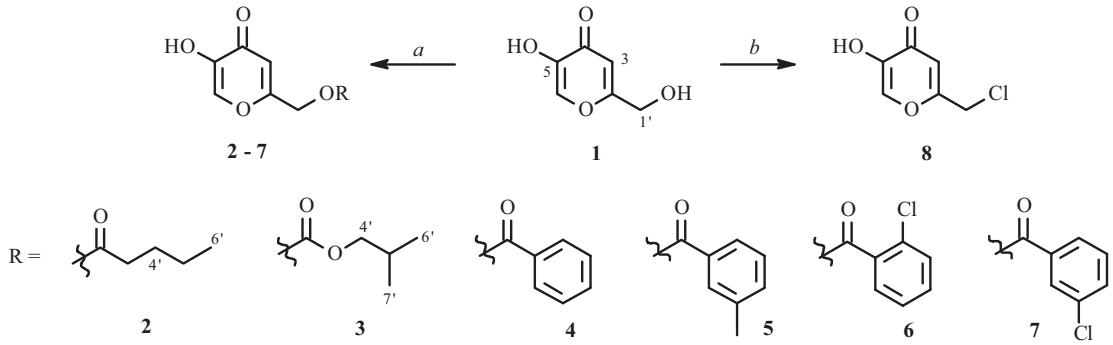
Microorganisms produce a vast number of secondary metabolites with useful biological activities for both the medicine and agricultural industries, including antibiotics, immunosuppressive and antitumor agents, as well as herbicides, insecticides, and antiparasitic agents [1–3]. In the process of screening of new antibiotics from microbial products, an endophytic fungus F52 was isolated from *Vigna unguiculata*, and it was identified as *Aspergillus flavus* F52 according to morphological characteristics and ITS region of rDNA.

In the present paper, 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (kojic acid) was isolated from the fermentation broth of *Aspergillus flavus* F52 by extracted with ethyl acetate and recrystallized with ethanol. Furthermore, seven derivatives of kojic acid, including five new compounds (**2**, **3**, **5**, **6**, and **7**), were synthesized by acylation with corresponding acyl chlorides (Scheme 1). Their structures were confirmed by ^{1}H NMR and elemental analysis. Antifungal activity tests indicated that the derivatives exhibited obvious inhibitory activities against the mycelial growth of *Glomerella cingulata* and *Botrytis cinerea* (Table 1).



a. RCOCl; *b*. $SOCl_2$

Scheme 1

5-Hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (1). White crystals, mp 151.2–152.3°C (ref. 151.5–152.3°C [4]). IR spectrum (KBr, ν, cm^{-1}): 3200 (OH), 2927 (CH), 1700 (C=O), 1625 (C=C), 1600, 1482 (CH), 1077 (CO). Mass spectrum (HR-ESI-MS), *m/z* 143.0342 $[M + H]^+$ (calcd for $C_6H_7O_4$, 143.0344). ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 4.41 (2H, s, CH_2O), 6.50 (1H, s, H-3), 7.94 (1H, s, H-6). ^{13}C NMR (100 MHz, CD_3OD, δ, ppm): 59.8 (C-1′), 109.4 (C-3), 139.6 (C-6), 145.9 (C-5), 169.0 (C-2), 175.5 (C-4).

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl Pentanoate (2). White wax. $C_{11}H_{14}O_5$. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.93 (3H, t, J = 7.5, 6′-CH_3), 1.34–1.39 (2H, m, 5′-CH_2), 1.63–1.67 (2H, m, 4′-CH_2), 2.41 (2H, t, J = 7.5, 3′-CH_2), 4.94 (2H, s, CH_2O), 6.51 (1H, s, H-3), 7.86 (1H, s, H-6).

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl Isobutyl Carbonate (3). White wax. $C_{11}H_{14}O_6$. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.96 (6H, d, J = 7.5, 6′, 7′-CH_3), 1.97–2.04 (1H, m, H-5′), 3.98 (2H, d, J = 6.5, 4′-CH_2), 4.97 (2H, s, CH_2O), 6.54 (1H, s, H-3), 7.86 (1H, s, H-6).

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TABLE 1. Antifungal Activity of Target Compounds against *G. cingulata* and *B. cinerea*

Compound	Inhibition ratio, %		Compound	Inhibition ratio, %	
	G. cingulata	*B. cinerea*		*G. cingulata*	*B. cinerea*
1	11.2	–	**5**	44.8	50.0
2	55.2	63.3	**6**	62.07	50.0
3	55.2	50.0	**7**	48.3	56.7
4	44.8	56.7	**8**	23.5	35.7
Azoxystrobin	86.2	46.7			

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl Benzoate (4). White crystals, $C_{13}H_{10}O_5$, mp 173.2–174.9°C (ref. 174–175°C [5]). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 5.22 (2H, s, CH_2O), 6.67 (1H, s, H-3), 7.48–7.52 (2H, m, Ar-H), 7.62–7.64 (1H, m, Ar-H), 8.01 (1H, s, H-6), 8.08 (2H, d, J = 7.0, Ar-H).

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 3-Methylbenzoate (5). White crystals, $C_{14}H_{12}O_5$, mp 99.7–101.2°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.42 (3H, s, Ar-CH_3), 5.17 (2H, s, CH_2O), 6.61 (1H, s, H-3), 7.36–7.44 (2H, m, Ar-H), 7.86 (2H, d, J = 8.0, Ar-H), 7.87 (1H, s, H-6).

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 2-Chlorobenzoate (6). White crystals, $C_{13}H_9ClO_5$, mp 142.3–144.1°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 5.19 (2H, s, CH_2O), 6.64 (1H, s, H-3), 7.34–7.38 (1H, m, Ar-H), 7.46–7.51 (2H, m, Ar-H), 7.89 (1H, s, H-6), 7.91 (1H, d, J = 8.0, Ar-H).

(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 3-Chlorobenzoate (7). White crystals, $C_{13}H_9ClO_5$, mp 145.3–147.1°C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 5.19 (2H, s, CH_2O), 6.60 (1H, s, H-3), 7.38–7.42 (1H, m, Ar-H), 7.49–7.52 (2H, m, Ar-H), 7.89 (1H, s, H-6), 7.92–7.97 (1H, m, Ar-H).

2-(Chloromethyl)-5-hydroxy-4*H*-pyran-4-one (8). Yellow crystals, mp 165.3–168.1°C [6–9].

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