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Efficient synthesis and biological evaluation of 4-arylcoumarin derivatives

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Abstract

Two bioactive natural 4-arylcoumarins, 5,7,4′-trimethoxy-4-phenylcoumarin (**1a**), 5,7-dimethoxy-4-phenylcoumarin (**1b**) and five closely related derivatives **1c–g** were synthesized. *In vitro* evaluation with a catechol subunit for antioxidant and antimicrobial activity, these compounds using standard methods showed that compounds **1d**, **1f** displayed promise radical scavenging activity and **1f** was found to be the most active one against *Bacillus dysenteriae*.

Keywords: 4-Arylcoumarin; Synthesis; Antimicrobial; Antioxidant

4-Arylcoumarins (neoflavones) represent a minor class of natural compounds with C6–C3–C6 skeleton and a characteristic 4-aryl group. These compounds have commonly been classified as the family members of flavonoids. There are at least 131 4-arylcoumarins were isolated from 58 plants belonging to the families *Clusiaceae*, *Fabaceae*, *Rubiaceae*, *Thelypteridaceae*, *Passifloraceae*, *Asteraceae* and *Rutaceae* [1]. 5,7,4′-Trimethoxy-4-phenylcoumarin **1a** and 5,7-dimethoxy-4-phenylcoumarin **1b** isolated as the major active ingredients from the culture filtrate of *Streptomyces aureofaciens* CMUAc130 are proved to be the most outstanding compounds possessing antifungal [2], anti-inflammatory [3,4], antiallergenic [5], antitumor activities [6], and closely related with antiprotozoal [7] and antimalarial properties [8].

The scarcity in nature and the capability for extensive chemical modification of 4-arylcoumarins make this class of compounds exceedingly attractive in organic synthesis. The synthetic methods represented by 5,7,4′-trimethoxy-4-phenylcoumarin (**1a**) and 5,7-dimethoxy-4-phenylcoumarin (**1b**) are mainly involved Pechmann reaction, Perkin reaction, Ponndorf reaction, Houben–Hoesch reaction and Wittig reaction [9–16]. However, most of the reported methods suffered from one or more drawbacks such as harsh reaction conditions, long reaction times, low yields, use of toxic reagents and inconvenient workup procedures. Therefore, facile synthetic procedure for the preparation of 4-arylcoumarin and derivatives is highly desirable. In continuation of our ongoing program to develop arylcoumarin analogues with medical interest, we herein report a phenylpropiolic acid based condensation with corresponding

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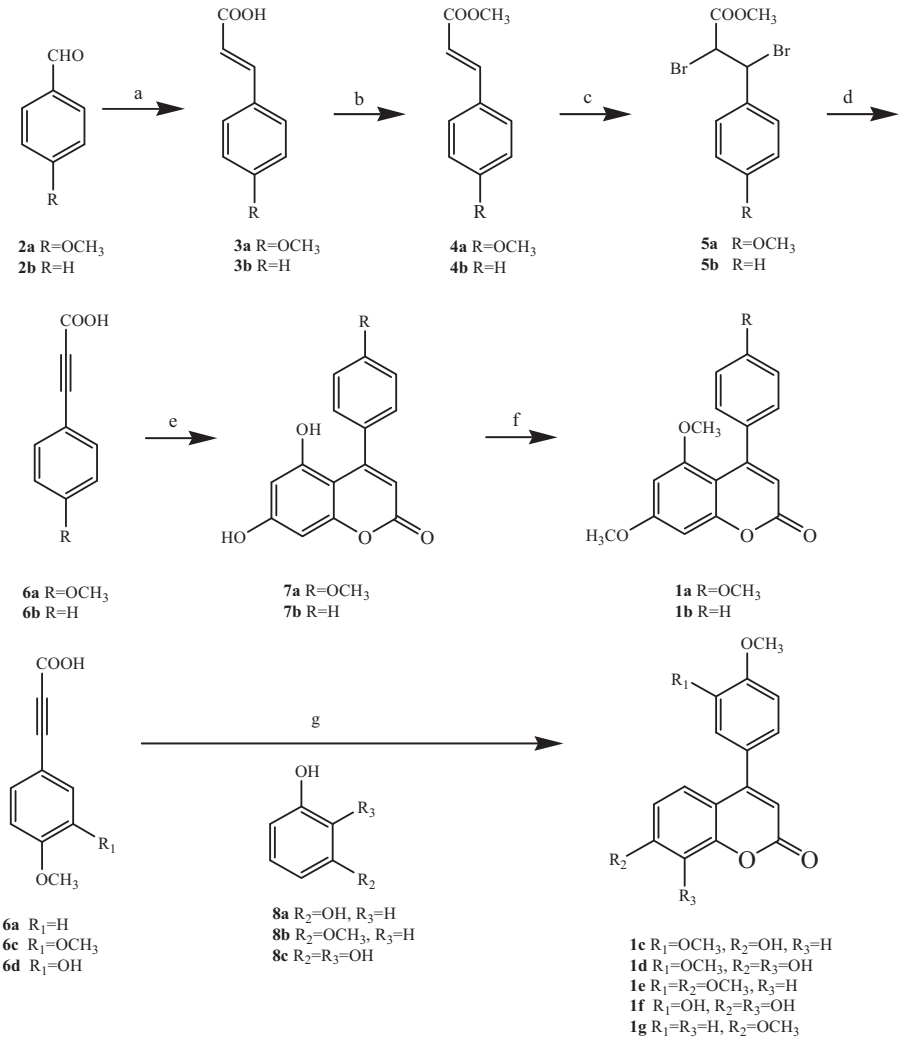

Scheme 1. Reagents and conditions: (a) malonic acid, pyridine and piperidine 90 °C, 4 h 88.2% **3a** and 83.0% **3b**; (b) MeOH, $SOCl_2$, reflux, 4 h, 97.8% **4a** and 96.0% **4b**; (c) Br_2, CH_2Cl_2, 0 °C, 20 min, 91.3% for **5a** and 92.9% for **5b**; (d) KOH, EtOH, reflux, 6 h, 74.6% for **6a** and 75.9% for **6b**; (e) phloroglucinol, CF_3COOH, r.t., 4 h. for **7a**, 91.1%; 60 °C, 12 h for **7b**, 89.1%; (f) $(CH_3)_2SO_4$, K_2CO_3, $(Me)_2CO$, reflux, 4 h, 72.7% for **1a** and 70.5% for **1b**; (g) CF_3COOH, r.t., 4–8 h, 56.4% for **1c**, 58.0% for **1d**, 53.8% for **1e**, 53.7% for **1f**, 60.1% for **1 g**.

polyphenols which lead to 5,7,4′-trimethoxy-4-phenylcoumarin (**1a**) and 5,7-dimethoxy-4-phenyl-coumarin (**1b**) as well as their analogues **1c**–**1g** under mild conditions with satisfactory yields.

As shown in Scheme 1, starting from the readily available benzaldehydes **2a**, **2b**, the cinnamic acids **3a**, **3b** can be obtained through condensation reaction with malonic acid in the presence of pyridine and piperidine. Esterification of **3a**, **3b** with methanol in the presence of $SOCl_2$ gave methyl cinnamates **4a**, **4b** which were readily brominated to give the dibromides **5a**, **5b** in high yields. Treatment of the dibromides **5a**, **5b** with KOH in ethanol at 80 °C afforded the key intermediate phenylpropiolic acid **6a**, **6b**. Then, a straightforward tandem reaction between **6a**, **6b** and phloroglucinol in the presence of CF_3COOH at room temperature was conducted, giving hydroxylated 4-arylcoumarins **7a**, **7b** in approximately 90% yield. It is worth mentioning that, unlike the published procedure which utilized the arylpropiolic acid chlorides or ethyl esters for coupling with phloroglucinol [13–16], our protocol showed improvements both in simplicity and production yield. Finally, through methylation with dimethyl sulfate, the target molecules **1a**, **1b** were obtained in 38.9% and 35.3% overall yield, respectively. Crude product of **1a**, **1b** can be purified either by column chromatography on silica gel or by washing with water, dried and crystallized from ethyl

Table 1
In vitro antimicrobial activity and DPPH radical scavenging activity (EC_{50}, μmol/L)[a] for compounds **1c–1g**.

Compound	EC_{50} (μmol/L) for DPPH radical scavenging[b]	MIC (μg/mL)[b]			
		S. aureus	*E. coli*	*B. dysenteriae*	*C. albicans*
1c	–[c]	–[d]	–[d]	–[d]	–[d]
1d	3.06 ± 0.25	117	–[d]	29.3	78
1e	–[c]	–[d]	–[d]	–[d]	–[d]
1f	2.85 ± 0.38	156	156	4.9	58.5
1g	–[c]	–[d]	–[d]	–[d]	–[d]
Amoxicillin		<1.95	23	29	<1.95
Gentamicin		<1.95	<1.95	<1.95	2.9
Ascorbic acid	4.42 ± 0.33				
BHT[e]	142.4 ± 0.8				

[a] The negative control DMSO showed no activity.
[b] Average of three experiments.
[c] Totally inactive (EC_{50} > 1250 μmol/mL).
[d] Totally inactive (MIC > 1250 μg/mL).
[e] BHT (2,6-di-*tert*-butyl-4-methylphenol).

acetate and petroleum ether for two or three times. The ^{1}H NMR, ^{13}C NMR, EI-MS data of the synthetic compounds **1a** and **1b** were identical with those of reported [20].

Based on the above-mentioned results, the scope of this protocol was further explored by reactions between methoxy or hydroxy substituted phenylpropiolic acid **6a**, **6c**, **6d** and corresponding polyphenols **8a–8c**. As shown in Scheme 1, all of the tested combinations successfully provided 4-arylcoumarins **1c–1g** with 53–60% isolated yields in presence of trifluoroacetic acid at room temperature. However, the attempt to produce these 4-arylcoumarins by means of another catalyst $POCl_3/BF_3$-Et_2O resulted low yields of desired compounds. The newly synthesized compounds were characterized by ^{1}H NMR, IR and MS analyses [21] and were screened for antioxidant and antimicrobial activity.

The radical scavenging activity of the synthesized compounds (**1c–1g**) was evaluated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay [17], the results are summarized in Table 1. The compound **1d** and **1f** which bear a catechol moiety (7,8-dihydroxy group) showed strong scavenging activities against DPPH radical (ED_{50} = 3.06 μmol/L, 2.85 μmol/L, respectively), whereas compounds **1c**, **1e**, **1g** without such group were totally inactive in the same experiments. These results were in good agreement with recent reports on the hydroxylated isoflavone derivatives [18].

The synthesized compounds (**1c–1g**) were also evaluated for their *in vitro* activity against four microorganisms, including *Staphylococcus aureus* (*ATCC2592*) (Gram-positive), *Escherichia coli* (*ATCC25922*) (Gram-negative), *Bacillus dysenteriae* (Bacillaceae) and *Candida albicans* (*ATCC2002*) (fungus) according to published techniques [19]. Minimum inhibitory concentration (MIC) is defined as the concentration of the compound required to exert complete inhibition of bacterial growth. Compounds **1d** and **1f** exhibited relatively high activity against *B. dysenteriae* (MIC = 29.3, 4.9 μg/mL, respectively) and displayed weak to moderate inhibitory activity against *S. aureus* and *C. albicans* (MIC = 58.5–156 μg/mL) (Table 1). The results also demonstrated that the catechol moiety in 4-arylcoumarins played an essential role in antimicrobial activity.

In conclusion, an efficient and straightforward portocol for the synthesis of 4-arylcoumarins **1a**, **1b** and their closely related derivatives **1c–1g** was described. Compounds **1d**, **1f** with a catechol moiety exhibited remarkable *in vitro* antioxidant and antimicrobial activity, suggesting that the catechol moiety may be a beneficial scaffold for therapeutic purpose.

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[20] **1a**: mp 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (s, 3H, 5-OCH_3), 3.83 (2 × s, 6H, 7-OCH_3, 4′-OCH_3), 5.97 (s, 1H, 3-H), 6.22 (d, 1H, J = 2.4 Hz, 6-H), 6.49(d, 1H, J = 2.5 Hz, 8-H), 6.87 (dd, 2H, J = 6.8 Hz and 2.0 Hz, 3′-H, 5′-H), 7.20 (dd, 2H, J = 6.8 Hz and 2.0 Hz, 2′-H, 6′-H), IR(KBr): 1712, 1624, 1591, 1510, 1460, 1356, 1244, 1228, 1203, 1157, 1107 cm^{-1}; EI-MS: *m/z*: 312 [M]$^+$, 284 [M-CO]$^+$, 269 [M-CO-Me]$^+$, 226, 211, 167, 149. **1b**: mp 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40(s, 3H, 5-OCH_3), 3.85(s, 3H, 7-OCH_3), 5.99(s, 1H, 3-H), 6.21(d, 1H, J = 2.0 Hz, 6-H), 6.51(d, 1H, J = 2.0 Hz, 8-H), 7.23–7.25 (m, 2H, 3′-H, 5′-H), 7.34–7.36 (m, 3H, 2′-H, 4′-H, 6′-H), IR(KBr): 1716, 1612, 1460, 1352, 1227, 1205, 1159, 1111 cm^{-1}; EI-MS: *m/z*: 282 [M]$^+$, 254 [M-CO]$^+$, 239[M-CO-Me]$^+$, 211, 196, 168, 152, 139.
[21] 1c: mp 233–234 °C; ^{1}H NMR (400 MHz, CD_3COCD_3):δ 3.90 and 3.94(s, 6H, 3H and 3H, 2× OCH_3), 6.20(s, 1H, 3-H), 6.74(s, 1H, J = 2.4 Hz and 8.0 Hz, 6′-H), 6.91(s, 1H, J = 2.4 Hz, 2′-H), 6.97(d, 1H, J = 8.0 Hz, 5′-H), 6.98(d, 1H, J = 2.0 Hz, 8-H), 7.02(dd, 1H, J = 2 Hz and 8.8 Hz, 6-H), 7.45(d, 1H, J = 8.8 Hz, 5-H); IR(KBr): 3194(OH), 1695(CO), 1624, 1599, 1518, 1263 and 1140 cm^{-1}; EI-MS m/z (%) 298[M]$^+$, 283[M−CH_3]$^+$, 270, 255, 227, 199, 184, 113. 1d: mp 271–272 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 3.87 and 3.88(s, 6H, 3H and 3H, 2× OCH_3), 6.07(s, 1H, 3-H), 6.83 and 7.00 (2 × d, 2H, J = 8.8 Hz, 5-H and 6-H) 7.06(dd, 1H, J = 2.0 Hz and 8.4 Hz, 5′-H), 7.10(d, 1H, J = 2.0 Hz, 2′-H), 7.11(d, 1H, J = 8.4 Hz, 6′-H); IR(KBr): 2987, 1726(CO), 1618, 1518, 1379, 1255, 1147 and 814 cm^{-1}; EI-MS m/z (%) 314[M]$^+$, 286[M−CO]$^+$, 271[M−CO–CH_3]$^+$, 161, 133, 115, 103. 1e: mp 148–149 °C; ^{1}H NMR (400 MHz, CD_3COCD_3):δ 3.88, 3.89 and 3.93(s, 9H, 3H, 3H and 3H, 3× OCH_3), 6.14(s, 1H, 3-H), 6.90(dd, 1H, J = 8.4, 2.0 Hz, 6′-H), 6.94(d, H, J = 2.0 Hz, 2′-H), 7.08(dd, 1H, J = 8.8, 2.4 Hz, 6-H), 7.12(d, H, J = 2.4 Hz, 8-H), 7.12(d, H, J = 8.4 Hz, 5′-H), 7.55(d, H, 8.8 Hz, 5-H); IR(KBr): 3411(OH), 1695(CO), 1606, 1518, 1448, 1173 and 1140 cm^{-1}; EI-MS m/z (%) 312[M]$^+$, 297[M−CH_3]$^+$, 284[M−CO–CH_3]$^+$, 269, 213, 183, 139. 1f: mp 176–177 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 3.91(s, 3H, OCH_3), 6.03(s, 1H, 3-H), 6.83(d, 1H, J = 8.8 Hz, 6-H), 6.95–6.99(m, 3H, 5-H, 2′-H and 6′-H), 7.10(d, 1H, J = 8.0 Hz, 5′-H); IR(KBr): 3371(OH), 1695(CO), 1653, 1599, 1448, 1240, 1178 and 1130 cm^{-1}; EI-MS m/z (%) 300[M]$^+$, 272[M−CO]$^+$, 257[M−CO–CH_3]$^+$, 229, 115. 1g: mp 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86(s, 6H, 2× OCH_3), 6.18(s, 1H, 3-H), 6.78(dd, 1H, J = 8.8 Hz and 2.4 Hz, 6-H), 6.87(d, 1H, J = 2.4 Hz, 8-H), 7.01(dd, 2H, J = 8.4 Hz and 2 Hz, 3′-H, 5′-H) and 7.37(dd, 2H, J = 8.4 Hz and 2 Hz, 2′-H, 6′-H), 7.43(d, 1H, J = 8.8 Hz, 5-H); IR(KBr): 3440, 3064, 2993, 1738(CO), 1612, 1510, 1375, 1250, and 825 cm^{-1}; EI-MS m/z (%) 282[M]$^+$, 254[M−CO]$^+$, 239[M−CO–CH_3]$^+$, 211, 196, 168, 152, 140, 127.