

First Concise Total Synthesis of Biologically Interesting Natural Licoagrochalcone B and Its Unnatural Derivatives

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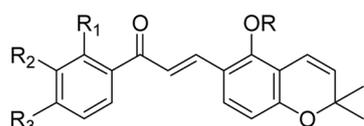
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Pyranochalcones are an abundant subclass of the flavonoid and are widely distributed in nature.¹ Members of the pyranochalcones have been associated with a wide variety of biological activities such as antimutagenic, antimicrobial, anti-ulcer, and antitumor activities and some plants are used in traditional medicines in China and Europe.² As part of an ongoing study into traditional medicine and pharmacological tests, the biologically interesting compound, licoagrochalcone B (**1**) with the pyranochalcone moiety was isolated from *Patrinia villosa*³ (*BaiJiangCao* in China) and *Glycyrrhiza glabra*⁴ (Figure 1). Licoagrochalcone B (**1**) shows potent anticancer activity against human cancer cell such as A549, BEL-7402, SGC-7901, MCF-7, HT-29, K562, and A 498.^{3a} *Patrinia* species are distributed mainly in Central to East Asia and northeast North America. The *ShenNongBenCaoJing*, a famous ancient Chinese medicinal literary, has documented their use as medicinal plants for more than 2000 years. Some of these plants are still used in traditional medicine as antiviral and antibacterial agents.³

Licorice, the root and stolon of *Glycyrrhiza* species, is also one of the oldest and important medicinal plants.⁴ It has been shown to have a variety of biological properties such as antimutagenic, anti-ulcer, antitumor, antioxidant, and antimicrobial activities.⁵ In addition, one of the fractions from the extract of licorice has been developed as an anti-ulcer drug (Aspalon) in Japan.⁴ This wide range of biological properties has stimulated interest in the synthesis of naturally occurring licoagrochalcone B (**1**) and its derivatives **2-7**.

Recently, we reported the synthesis of natural products of lonchocarpin (**12**) and its derivative **13** with the pyranochalcone moiety starting from 1,3-cyclohexanedione (**8**) utilizing ethylenediamine diacetate-catalyzed 2*H*-pyran formation as a key step (Scheme 1).⁶ However, although this lonchocarpin (**12**) and its derivative **13** contain pyranochalcone structure, they are different from licoagrochalcone B and its derivatives in the chalcone moiety. As an extension of our work to the synthesis of pyranochalcones, we report the first synthesis of a biologically interesting natural compound, licoagrochalcone B (**1**) along with its derivatives **2-7**.



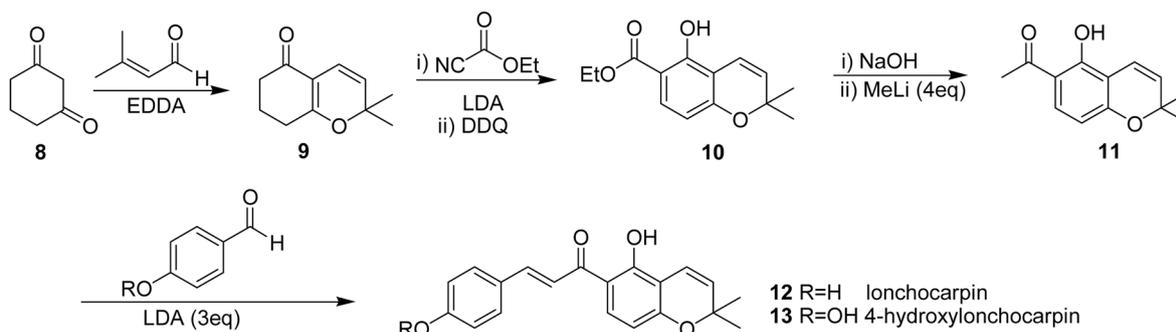
- 1** R=CH₃, R₁=R₂=H, R₃=OH licoagrochalcone B
2 R=R₁=R₂=R₃=H
3 R=H, R₁=OCH₃, R₂=R₃=H
4 R=R₁=H, R₂=OCH₃, R₃=H
5 R=R₁=R₂=H, R₃=OCH₃
6 R=R₁=R₂=H, R₃=CH₃
7 R=CH₃, R₁=R₂=R₃=H

Figure 1. Naturally occurring licoagrochalcone B (**1**) and unnatural its derivatives **2-7**.

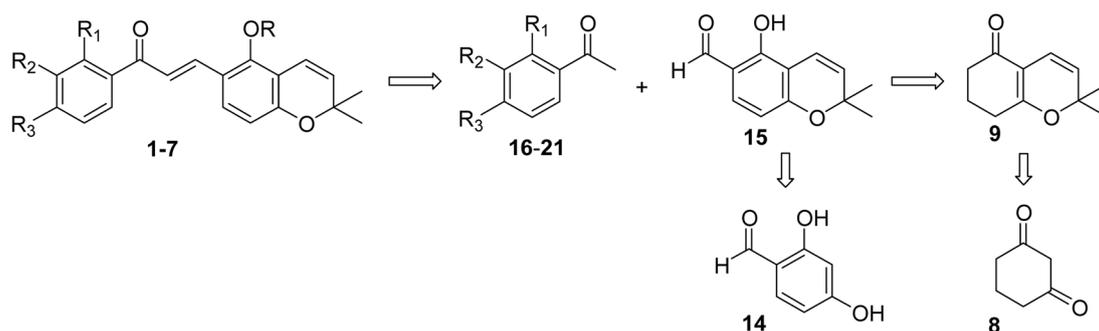
Results and Discussion

The retrosynthetic strategy of licoagrochalcone B (**1**) and its derivatives **2-7** is shown in Scheme 2. Licoagrochalcone B (**1**) and its derivatives **2-7** could be prepared from a base-catalyzed aldol reactions of acetophenones **16-21** to benzopyran **15**. The crucial intermediate **15** could be generated from the commercially available material **8** or **14** via ethylenediamine diacetate-catalyzed 2*H*-pyran or benzopyran formation reactions.

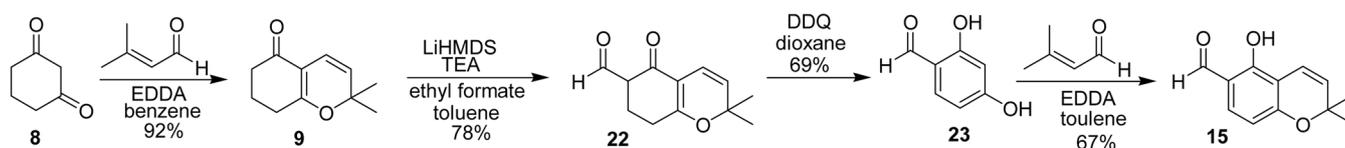
The benzopyran **15** was first achieved from 1,3-cyclohexanedione (**8**) in 50% overall yield (3 steps) using the



Scheme 1



Scheme 2. Retrosynthetic analysis of licoagrochalcone (**1**) and its derivatives **2-7**.



Scheme 3

methodology described previously, as shown in Scheme 3.⁷ A reaction of compound **8** with 3-methyl-2-butenal in the presence of 10 mol % of ethylenediamine diacetate in refluxing benzene for 3 h gave the adduct **9** in 92% yield. Treatment of compound **9** with ethyl formate in the presence of LiHMDS/TEA at $-78\text{ }^{\circ}\text{C}$ gave compound **22** in 78% yield.⁸ The oxidation of compound **22** with DDQ in refluxing dioxane afforded compound **15** in 69% yield. Recently, we also reported a new methodology for the preparation of a variety of benzopyrans by ethylenediamine diacetate-catalyzed reactions of substituted resorcinols or trihydroxybenzenes to α,β -unsaturated aldehydes.⁹ These reactions involve a formal [3+3]-cycloaddition through a 6π -electrocyclization. To develop more convenient and efficient method for the preparation of benzopyran **15**, a one-step reaction was next attempted starting from 2,4-dihydroxybenzaldehyde (**23**). The reaction of compound **23** with 3-methyl-2-butenal in the presence of 10 mol % of ethylenediamine diacetate in refluxing toluene for 10 h afforded the adduct **15** in 67% yield.

To complete the synthesis of licoagrochalcone B (**1**), an aldol reaction was next tried as shown in Scheme 4. Attempts to condense 4-hydroxyacetophenone or protected compound **16** to benzopyran **15** using KOH in ethanol were unsuccessful. After examining many procedures, a reaction of compound **16** with benzopyran **15** using NaH in DMSO at room temperature for 48 h provided compound **24** in 71% yield. The assignment of *E* stereochemistry of compound **24** was easily defined as (*E*) by observation of vicinal coupling constants ($J = 15.6\text{ Hz}$) of α,β -unsaturated carbonyl group. Methylation of compound **24** with methyl iodide under

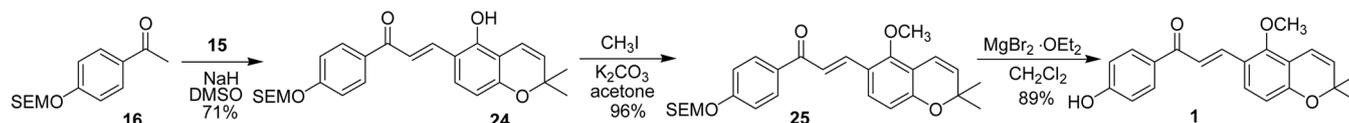
K_2CO_3 in acetone at room temperature for 10 h gave compound **25** (96%).¹⁰ Deprotection of 2-(trimethylsilyl)ethoxymethyl (SEM) group of compound **25** using TBAF gave product **1** in low yield (38%). Fortunately, reaction of **25** with $\text{MgBr}_2\cdot\text{OEt}_2$ in dichloromethane at room temperature for 3 h afforded licoagrochalcone B (**1**) in high yield (89%). The spectral data of compound **1** was in good agreement with that of the natural product reported in the literature.^{4a}

In order to extend the utility of this reaction, the synthesis of various analogues of compound **1** was also attempted through further aldol reactions as shown in Scheme 5. Reactions of compounds **17-21** with benzopyran **15** using NaH in DMSO at room temperature for 48 h gave products **2-6** in 83, 78, 82, 80, and 83% yield, respectively. Reaction of compound **2** with methyl iodide under K_2CO_3 in acetone at room temperature for 10 h gave compound **7** in 94% yield.¹⁰

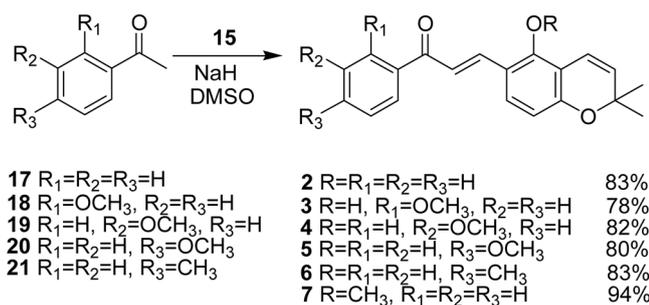
In conclusion, the synthesis of biologically interesting natural licoagrochalcone B (**1**) and its derivatives **2-7** was accomplished from commercially available 1,3-cyclohexanedione (**8**) or 2,4-dihydroxybenzaldehyde (**23**). The key strategy in the synthetic strategy involves the formation of 2H-pyran or benzopyran and an aldol reaction.

Experimental Section

2,2-Dimethyl-2,6,7,8-tetrahydrochromen-5-one (9). To a solution of 1,3-cyclohexanedione (**8**) (1.120 g, 10.0 mmol) and 3-methyl-2-butenal (1.680 g, 20.0 mmol) in benzene (50 mL) was added ethylenediamine diacetate (180 mg, 1 mmol) at room temperature. The reaction mixture was refluxed for



Scheme 4



Scheme 5

3 h and then cooled to room temperature. Water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by column chromatography on silica gel gave **9** (1.639 g, 92%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 6.38 (1H, d, *J* = 10.0 Hz), 5.21 (1H, d, *J* = 10.0 Hz), 2.39-2.34 (4H, m), 1.99-1.90 (2H, m), 1.37 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 195.3, 172.1, 123.2, 116.1, 110.9, 80.1, 36.8, 29.0, 28.5, 28.5, 21.0; IR (neat) 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905 cm⁻¹; HRMS *m/z* (M⁺) calcd for C₁₁H₁₄O₂: 178.0994. Found: 178.0996.

2,2-Dimethyl-5-oxo-5,6,7,8-tetrahydro-2H-chromene-6-carbaldehyde (22). To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (1.162 g, 7.2 mmol) in 30 mL of dry toluene was added a solution of *n*-BuLi (2.5 M, 2.6 mL) in hexane at -78 °C. After stirring at the same temperature for 30 min, compound **9** (0.570 g, 3.2 mmol) in toluene (2 mL) and TEA (3.290 g, 32.5 mmol) were added through a cannula. After 30 min, ethyl formate (0.474 g, 6.4 mmol) in toluene (1 mL) was added. The reaction mixture was stirred at the same temperature for 3 h, warmed to room temperature, quenched by addition of aqueous NH₄Cl solution. The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **22** as an oil (0.515 g, 78%): ¹H NMR (300 MHz, CDCl₃) δ 13.78 (1H, d, *J* = 11.0 Hz), 7.12 (1H, d, *J* = 11.0 Hz), 6.4 (1H, d, *J* = 10.0 Hz), 5.27 (1H, d, *J* = 10.0 Hz), 2.57-2.35 (4H, m), 1.40 (6H, s); IR (neat) 2978, 1637, 1586, 1433, 1358, 1273, 1225, 1208, 1134, 1088, 972, 899 cm⁻¹; HRMS *m/z* (M⁺) Calcd for C₁₂H₁₄O₃: 206.0943. Found: 206.0941.

5-Hydroxy-2,2-dimethyl-2H-chromene-6-carbaldehyde (15) from 22. A mixture of **22** (0.455 g, 2.2 mmol) and DDQ (0.749 g, 3.3 mmol) in dioxane (30 mL) was heated under reflux for 3 h. The resulting mixture was cooled in an ice bath and solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure and purified by flash column chromatography on silica gel to give **15** (0.310 g, 69%) as a solid: mp 45-47 °C; ¹H NMR (300 MHz, CDCl₃) δ 11.63 (1H, s), 9.64 (1H, s), 7.27 (1H, d, *J* = 8.5 Hz), 6.67 (1H, d, *J* = 10.1 Hz), 6.40 (1H, d, *J* = 8.5 Hz), 5.59 (1H, d, *J* = 10.0 Hz), 1.54 (3H, s), 1.44 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 194.9, 161.0, 159.1, 135.1, 129.0, 115.6, 115.5, 109.8, 109.2, 78.6, 29.8, 28.8; IR (KBr) 2974,

1657, 1580, 1489, 1433, 1375, 1335, 1300, 1256, 1217, 1181, 1111, 1088, 974, 937, 900, 845 cm⁻¹; HRMS *m/z* (M⁺) Calcd for C₁₂H₁₂O₃: 204.0786. Found: 204.0788.

5-Hydroxy-2,2-dimethyl-2H-chromene-6-carbaldehyde (15) from 23. To a solution of 2,4-dihydroxybenzaldehyde (**23**) (138 mg, 1.0 mmol) and 3-methyl-2-butenal (168 mg, 2.0 mmol) in toluene (20 mL) was added ethylenediamine diacetate (18 mg, 1 mmol) at room temperature. The reaction mixture was refluxed for 10 h and then cooled to room temperature. Yield 67% (137 mg).

(E)-3-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-1-[4-(2-trimethylsilylanyloxyethoxy)phenyl]propenone (24). To a solution of **16** (160 mg, 0.6 mmol) in DMSO (10 mL) was added sodium hydride (72 mg, 60% in oil, 1.8 mmol) and aldehyde **15** (143 mg, 0.7 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Addition of water (30 mL) and extraction with ethyl acetate (3 × 50 mL), washing with 2 N-HCl solution and brine, drying over MgSO₄ and removal of the solvent followed by flash column chromatography on silica gel gave **24** (193 mg, 71%) as a solid: mp 117-118 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.52 (1H, d, *J* = 15.6 Hz), 8.02 (2H, d, *J* = 8.8 Hz), 7.47 (1H, d, *J* = 15.6 Hz), 7.46 (1H, d, *J* = 8.6 Hz), 7.09 (2H, d, *J* = 8.8 Hz), 6.91 (1H, d, *J* = 10.0 Hz), 6.42 (1H, d, *J* = 8.6 Hz), 5.54 (1H, d, *J* = 10.0 Hz), 5.28 (2H, s), 3.72 (2H, t, *J* = 8.6 Hz), 1.43 (6H, s), 0.95 (2H, t, *J* = 8.6 Hz), -0.02 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ 190.4, 161.7, 157.2, 153.5, 141.6, 132.4, 131.2, 129.4, 128.2, 118.2, 117.0, 116.4, 116.2, 110.6, 110.2, 93.0, 77.7, 76.9, 30.1, 28.4, 18.5, -0.99; IR (KBr) 2926, 1638, 1601, 1510, 1464, 1233, 1173, 1092, 992, 837 cm⁻¹; HRMS *m/z* (M⁺) Calcd for C₂₆H₃₂O₅Si: 452.2019. Found: 452.2021.

(E)-3-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-1-[4-(2-trimethylsilylanyloxyethoxy)phenyl]propenone (25). Yield 96%. ¹H NMR (300 MHz, CDCl₃) δ 8.01 (2H, d, *J* = 8.8 Hz), 7.97 (1H, d, *J* = 15.6 Hz), 7.50 (1H, d, *J* = 15.6 Hz), 7.46 (1H, d, *J* = 8.6 Hz), 7.09 (2H, d, *J* = 8.8 Hz), 6.62 (1H, d, *J* = 10.0 Hz), 6.59 (1H, d, *J* = 8.6 Hz), 5.65 (1H, d, *J* = 10.0 Hz), 5.27 (2H, s), 3.77 (3H, s), 3.75 (2H, t, *J* = 8.6 Hz), 1.43 (6H, s), 0.94 (2H, t, *J* = 8.6 Hz), -0.02 (9H, s); IR (neat) 2955, 1658, 1603, 1476, 1424, 1250, 1169, 1115, 1094, 988, 837 cm⁻¹; EIMS *m/z* 466 (M⁺, 10), 436 (32), 435 (100), 393 (49), 378 (25), 377 (83), 218 (924), 73 (64); HRMS *m/z* (M⁺) Calcd for C₂₇H₃₄O₅Si: 466.2176. Found: 466.2174.

Licoagrochalcone B (1). To a solution of **25** (100 mg, 0.2 mmol) in CH₂Cl₂ (10 mL) was added MgBr₂·OEt₂ (207 mg, 0.8 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with saturated NaHCO₃ solution (30 mL) and dried over MgSO₄. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel to give **1** (64 mg, 89%) as a solid: mp 230-231 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.98 (2H, d, *J* = 8.8 Hz), 7.94 (1H, d, *J* = 15.6 Hz), 7.52 (2H, d, *J* = 15.6 Hz), 7.46 (1H, d, *J* = 8.6 Hz), 6.94 (2H, d, *J* = 8.8 Hz), 6.62 (1H, d, *J* = 10.0 Hz), 6.60 (1H, d, *J* = 8.6 Hz), 5.66 (1H, d, *J* = 10.0 Hz), 3.78 (3H, s), 1.44 (6H, s); ¹³C NMR (75

MHz, acetone- d_6) δ 188.2, 162.6, 157.1, 138.2, 131.8, 131.7, 131.6, 129.2, 121.9, 121.3, 117.2, 116.2, 116.1, 115.8, 113.8, 77.4, 63.2, 28.2; IR (KBr) 2924, 1601, 1462, 1373, 1262, 1074, 802, 741 cm^{-1} ; HRMS m/z (M^+) Calcd for $C_{21}H_{20}O_4$: 336.1362. Found: 336.1364.

(E)-3-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-1-phenylpropenone (2). To a solution of **17** (48 mg, 0.4 mmol) in DMSO (10 mL) was added sodium hydride (96 mg, 60% in oil, 2.4 mmol) and aldehyde **15** (102 mg, 0.5 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Addition of water (30 mL) and extraction with ethyl acetate (3×50 mL), washing with 2 N-HCL solution and brine, drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel gave **2** (102 mg, 83%) as a solid: mp 112-113 $^{\circ}C$; 1H NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, d, $J = 15.6$ Hz), 8.02-7.99 (2H, m), 7.59-7.42 (5H, m), 6.75 (1H, d, $J = 10.0$ Hz), 6.45 (1H, d, $J = 8.6$ Hz), 5.65 (1H, d, $J = 10.0$ Hz), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 157.3, 153.3, 141.9, 138.9, 133.2, 129.7, 128.9, 128.7, 118.8, 116.7, 116.1, 110.5, 110.4, 77.9, 28.4; IR (KBr) 3270, 2976, 1644, 1586, 1564, 1481, 1352, 1318, 1209, 1181, 1123, 1069, 1042, 1024, 995, 772 cm^{-1} ; EIMS m/z (M^+ , 25), 292 (21), 291 (100), 289 (18), 275 (23), 185 (10), 105 (88), 77 (31), 69 (12), 57 (16), 55 (14).

(E)-3-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-1-(2-methoxyphenyl)propenone (3). Yield 78%. mp 126-127 $^{\circ}C$; 1H NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, d, $J = 15.7$ Hz), 7.67-7.61 (2H, m), 7.44 (1H, t, $J = 8.6$ Hz), 7.35 (1H, d, $J = 15.7$ Hz), 7.32 (1H, d, $J = 8.6$ Hz), 7.03-6.95 (2H, m), 6.84 (1H, d, $J = 10.0$ Hz), 6.39 (1H, d, $J = 8.6$ Hz), 5.59 (1H, d, $J = 10.0$ Hz), 3.97 (3H, s), 1.44 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 158.2, 156.5, 152.8, 140.3, 132.9, 130.4, 129.4, 129.1, 128.7, 124.1, 120.6, 116.4, 115.8, 111.7, 110.1, 109.7, 76.4, 55.7, 27.9; IR (KBr) 2920, 1636, 1599, 1580, 1483, 1464, 1263, 1117, 1065, 1034, 810, 739 cm^{-1} ; EIMS m/z (M^+ , 27), 322 (11), 321 (52), 320 (14), 319 (14), 305 (38), 207 (12), 173 (11), 135 (100), 129 (15), 77 (12).

(E)-3-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-1-(3-methoxyphenyl)propenone (4). Yield 82%. mp 135-136 $^{\circ}C$; 1H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, d, $J = 15.6$ Hz), 7.88 (1H, s), 7.60-7.53 (2H, m), 7.47-7.32 (3H, m), 7.09 (1H, d, $J = 8.1$ Hz), 6.86 (1H, d, $J = 10.0$ Hz), 6.86 (1H, d, $J = 8.6$ Hz), 5.63 (1H, d, $J = 10.0$ Hz), 3.83 (3H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 160.2, 157.5, 153.6, 142.4, 140.3, 129.9, 129.5, 128.5, 121.6, 119.8, 118.5, 116.9, 116.2, 113.3, 110.6, 110.3, 77.4, 55.8, 28.4; IR (KBr) 2975, 1635, 1574, 1464, 1115, 901, 804, 737 cm^{-1} ; EIMS m/z (M^+ , 30), 322 (21), 321 (100), 319 (12), 305 (20), 185 (11), 135 (69), 107 (12).

(E)-3-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-1-(4-methoxyphenyl)propenone (5). Yield 80%. mp 144-145 $^{\circ}C$; 1H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, d, $J = 15.6$ Hz), 8.02 (2H, d, $J = 8.8$ Hz), 7.46 (1H, d, $J = 15.6$ Hz), 7.45 (1H, d, $J = 8.7$ Hz), 6.97-6.92 (3H, m), 6.42 (1H, d, $J = 8.7$ Hz),

5.62 (1H, d, $J = 10.0$ Hz), 3.86 (3H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3 + DMSO-d_6$) δ 190.2, 163.8, 157.1, 153.4, 141.2, 131.7, 131.3, 129.4, 128.4, 118.5, 117.0, 116.4, 114.2, 110.6, 110.2, 76.9, 55.9, 28.3; IR (KBr) 3175, 2973, 1634, 1605, 1582, 1553, 1350, 1258, 1235, 1207, 1165, 1030, 993, 829, 783, 721 cm^{-1} ; EIMS m/z (M^+ , 22), 322 (13), 321 (60), 320 (37), 319 (33), 306 (20), 305 (95), 173 (27), 135 (100), 129 (17), 83 (16), 73 (18), 71 (19), 69 (21), 57 (29), 55 (22).

(E)-3-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-1-(4-methylphenyl)propenone (6). Yield 83%. mp 141-142 $^{\circ}C$; 1H NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, d, $J = 15.6$ Hz), 7.92 (2H, d, $J = 8.8$ Hz), 7.46 (1H, d, $J = 15.6$ Hz), 7.42 (1H, d, $J = 8.6$ Hz), 7.26 (2H, d, $J = 8.8$ Hz), 6.82 (1H, d, $J = 10.0$ Hz), 6.43 (1H, d, $J = 8.6$ Hz), 5.64 (1H, d, $J = 10.0$ Hz), 2.41 (3H, s), 1.43 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3 + DMSO-d_6$) δ 190.7, 156.9, 153.7, 143.5, 141.1, 136.6, 129.6, 129.2, 129.1, 128.9, 119.4, 117.4, 116.8, 111.0, 110.0, 76.7, 28.3, 22.1; IR (KBr) 2973, 1634, 1610, 1283, 1115, 819, 737 cm^{-1} ; EIMS m/z (M^+ , 25), 306 (17), 305 (81), 303 (11), 289 (15), 185 (11), 129 (40), 119 (100), 112 (10), 91 (26), 73 (12), 71 (14), 70 (12), 69 (21), 57 (20), 55 (14).

(E)-3-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-1-phenylpropenone (7). Yield 94%. 1H NMR (300 MHz, $CDCl_3$) δ 8.02-7.97 (3H, m), 7.55-7.45 (5H, m), 6.62 (1H, d, $J = 8.6$ Hz), 6.59 (1H, d, $J = 10.0$ Hz), 5.66 (1H, d, $J = 10.0$ Hz), 3.78 (3H, s), 1.44 (6H, s); IR (neat) 2976, 1658, 1589, 1476, 1372, 1296, 1252, 1208, 1115, 1073, 988, 889, 818, 775 cm^{-1} ; EIMS m/z (M^+ , 10), 306 (21), 305 (100), 290 (21), 289 (99), 274 (10), 185 (44), 105 (15), 77 (15).

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