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Note

Facile Synthesis of Fisetin and Its Analogues

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Flavonol-based compounds are known to exhibit antibacterial, antiviral, and antiallergic activities.

Fisetin (**1**), a flavanol, is presently studied as a therapeutic agent for various diseases, and it has been found to exhibit various therapeutic activities such as anticancer, neuroprotection, and antioxidant activities[1-3] (*Fig.* 1). It has been reported to be a potential therapeutic agent particularly in Alzheimer's disease by inhibiting the β-amyloid aggregation, which leads to nerve damage, and thus fisetin has been found to improve the memory by activating the signaling pathway of hippocampus.[4] In addition, it has been reported to increase the longevity, reduce age markers in tissues, and reduce age-related pathologies.[5]

Although fisetin is required in large amounts for fisetin-related studies, the amount of fisetin that can be extracted from natural sources is limited. The existing methods for the synthesis of fisetin require paeonol (**4**)[6] or quercetin[7] as the starting material. However, these methods are not suitable for the mass production of fisetin due to the expensive starting materials and requirement for compound separation at each step by column chromatography, which inevitably decreases the product yield. Thus, it is necessary to develop an efficient method for the synthesis of fisetin.

In this study, we developed a method that allowed the mass production of fisetin from resorcinol in four steps; each product was obtained exclusively by extraction and recrystallization, without the use of column chromatography in any of the steps (*Scheme* 1). First, 2,4-dihydroxy acetophenone (**3**) was synthesized from resorcinol (**2**) by Friedel-Craft acylation,[8,9] which was then methylated to give a mixture of paeonol (**4**) and a small amount (~10 mol%) of 2,4-dimethoxy acetophenone (**5**) for improved stability under a basic condition. However, compound **5** was removed during the work-up of the next reaction, and hence, no separation was required. The next reaction was conducted similar to that for the synthesis of 3-hydroxyflavone.[10] After the aldol-condensation of paeonol (**4**) and 3,4-dimethoxy benzaldehyde, a hydroxyl group was introduced at the C-3 position, and a one-step cyclization reaction was conducted according to the method reported by Algar-Flynn-Oyamada.[11]

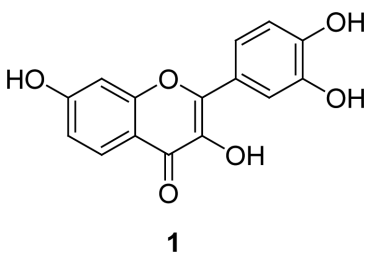

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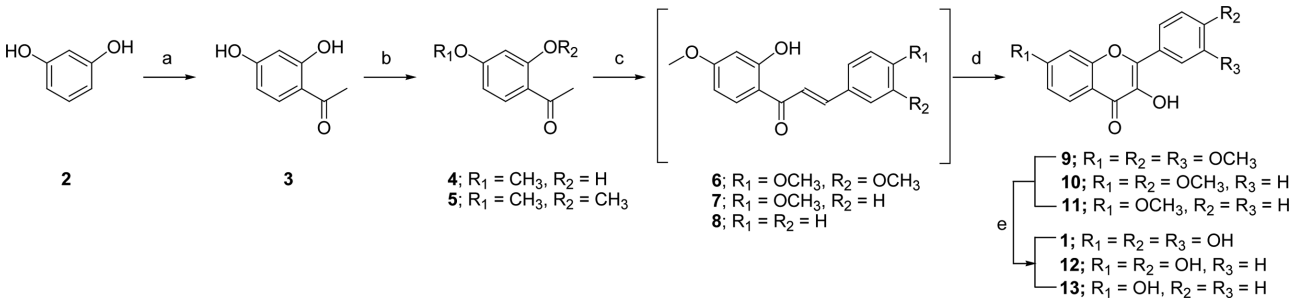
***Figure* 1.** Chemical structure of fisetin.

To proceed with this reaction, the intermediate chalcone-structured compound (**6**) was separated, and 0.5 N aqueous sodium hydroxide solution and 35% hydrogen peroxide solution were added; however, no product was obtained because of the poor solubility of compound **6** in 0.5 N aqueous sodium hydroxide solution. Although the reaction could be conducted under other condition (0.5 N NaOH and 35% H_2O_2 in ethanol), compound **9** was obtained in a low yield of 20%. In this study, compound **9** was synthesized by continuously adding 0.5 N aqueous sodium hydroxide solution and 35% hydrogen peroxide solution to the reaction mixture after the aldol condensation reaction. Finally, fisetin was synthesized by the demethylation of compound **9** using pyridine HCl.

Two additional fisetin analogues were synthesized using the method discussed above, under the same conditions (*Scheme* 1). A different type of benzaldehyde was used in the aldol condensation reaction. Consequently, 4'7-dihydroxyflavonol (**12**) and 7-hydroxyflavonol (**13**) were obtained.



***Scheme* 1.** Reagents and conditions: a) Ac_2O, BF_3Et_2O, E.A., 60 °C, 12 h, 95%; b) Me_2SO_4, K_2CO_3, Acetone, 60 °C, 7 h; c) substituted benzaldehyde, KOH, MeOH, 90 °C, 48 h; d) NaOH, H_2O_2, r.t. 24 h, 42%; e) pyridine HCl, 160 °C, 12 h, 97%.

Similar to fisetin, the two final products were synthesized only by recrystallization, without column chromatography.

Although fisetin has been synthesized previously, the synthetic methods are not suitable for mass production—expensive starting materials are required, and the reaction protocol is time consuming and tedious. In this study, fisetin was synthesized from resorcinol (**2**) in four steps. This synthetic method can be applied for the mass production of flavonol-structured compounds only by recrystallization, and no chromatographic separation was required. In this study, fisetin and its two analogues were synthesized from resorcinol with an overall yield of ~40% in four steps.

EXPERIMENTAL

Reagents and solvents were purchased from Aldrich, TCI, Alfa-aesar, Samchun, etc. and used without purification. Reactions were monitored by thin-layer chromatography on 0.25 mm Merck silica gel plates (60F254) by irradiating with 254-nm UV light. ^{1}H NMR spectra were using a JEOL superconducting magnet JMTC-400/54/JJ/YH (400 MHz). Chemical shifts were recorded in ppm, downfield from tetramethylsilane (TMS), and coupling constants (*J*) are given in Hertz.

Synthesis of 1-(2,4-dihydroxy-phenyl)-ethanone (**3**): Compound **2** (20.0 g, 181.7 mmol) and acetic anhydride (18.55 g, 181.7 mmol) were dissolved in ethyl acetate (80 mL). BF_3–Et_2O (51.6 g, 363.4 mmol) in ethyl acetate (20 mL) was added dropwise at room temperature, and the reaction mixture was stirred at 60 °C for 12 h. The resulting mixture was diluted with water (100 mL) and extracted with ethyl acetate (200 mL × 2). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (200 mL × 2). Water from the organic layer was removed with anhydrous $MgSO_4$, following which the organic layer was filtered. The filtrate was concentrated under reduced pressure to give an oily residue, which was recrystallized from hexane to afford compound **3** (26.3 g, 95%). ^{1}H-NMR (400 MHz, DMSO) δ : 2.47(3H, m), 6.20(1H, d, *J* = 2.32 Hz), 6.35(1H, dd, *J* = 8.8, 2.32 Hz), 7.73(1H, d, *J* = 8.8 Hz), 10.60(1H, s), 12.57(1H, s) ppm.

Synthesis of 1-(2-hydroxy-4-methoxy-phenyl)-ethanone (**4**): Potassium carbonate (17.0 g, 122.9 mmol) was added to a solution of compound **3** (18.7 g, 122.9 mmol) in acetone (100 mL). Dimethyl sulfate (17.1 g, 135.2 mmol) was added dropwise in the reaction vessel by separating three times for 1 h, and the mixture was stirred at 60 °C for 12 h. The resulting mixture was concentrated in vacuo. It was then diluted water (200 mL × 2) and extracted with ethyl acetate (200 mL). The organic layer was washed with brine (30 mL). Water from the organic layer was removed with anhydrous $MgSO_4$, following which the organic layer was filtered. The filtrate was concentrated under reduced pressure to give a mixture of compounds **4** and **5** (22.3 g). compound 4: ^{1}H-NMR(400 MHz, $CDCl_3$) δ : 2.54(3H, s), 3.82(3H, s), 6.44(2H, dd, *J* = 2.2, 1.9 Hz), 7.63(1H, d, *J* = 8.7 Hz), 12.74(1H, s) ppm.

Synthesis of 2-(3,4-dimethoxy-phenyl)-3-hydroxy-7-methoxy-chromen-4-one (**9**): A mixture of compounds **4** and **5** (22.3 g, 134.2 mmol) and 3,4-dimethoxy benzaldehyde (29.0 g, 174.4 mmol) were added to a solution of potassium hydroxide (113.0 g, 2013 mmol) in methanol (350 mL) and stirred at 90 °C for 48 h. The reaction mixture was cooled to room temperature, and sodium hydroxide (0.5 N, 580 mL) and hydrogen peroxide (35%, 43 mL) were added sequentially. The mixture was stirred at room temperature for 24 h and then neutralized with conc. HCl to pH 7. The resulting product was filtered to give solid **9** (17.0 g, 42% from compound **3**). ^{1}H-NMR(400 MHz, DMSO) δ: 3.82 (6H, d, *J* = 2.1 Hz), 3.89(3H, s), 7.02(1H, dd, *J* = 2.1, 2.0 Hz), 7.12(1H, d, *J* = 8.7 Hz), 7.27(1H, d, *J* = 1.9 Hz), 7.77

(1H, d, J = 1.4Hz), 7.84(1H, dd, J = 1.6, 1.6 Hz), 7.96(1H, d, J = 8.9 Hz), 9.28(1H, s) ppm.

Synthesis of 2-(3,4-dihydroxy-phenyl)-3,7-dihydroxy-chromen-4-one (**1**): Compound **9** (17.0 g, 51.78 mmol) and pyridine hydrochloride (35.0 g) were mixed and stirred at 160 °C for 12 h. To the solid mixture obtained, water (600 mL) was added and stirred at room temperature for 2 h. The resulting mixture was filtered to give solid **1** (14.4 g, 97%). ^{1}H-NMR(400 MHz, DMSO) δ : 6.87(3H, t, J = 7.1 Hz), 7.51 (1H, dd, J = 1.7, 1.68 Hz), 7.64(1H, s), 7.89(1H, d, J = 9.3 Hz), 8.98(1H, s), 9.21(1H, s), 9.44(1H, s), 10.68(1H, s) ppm; HRMS(ESI) calcd for $C_{15}H_{10}O_6$: 286.0477, Found:287.0544

Synthesis of 3-hydroxy-7-methoxy-2-(4-methoxy-phenyl)-chromen-4-one (**10**): A mixture of compounds **4** and **5** (3.0 g, 18.05 mmol) and 4-methoxybenzaldehyde (3.2 g, 23.47 mmol) were added to a solution of potassium hydroxide (15.2 g, 270.1 mmol) in methanol (70 mL) and it was stirred at 90 °C for 48 h. The reaction mixture was cooled to room temperature, and sodium hydroxide (0.5 N, 80 mL) and hydrogen peroxide (35%, 6 mL) were added sequentially. The mixture was stirred at room temperature for 24 h. The mixture was neutralized with conc. HCl until the pH reached to 7. The resulting mixture was filtered to give solid **10** (2.0 g, 40.4% from compound **3**). ^{1}H-NMR(400 MHz, DMSO) δ : 3.81(3H, s), 3.88(3H, s), 7.02(1H, dd, J = 2.2, 2.2 Hz), 7.10(2H, d, J = 9.0 Hz), 7.25(1H, d, J = 2.2 Hz), 7.96(1H, d, J = 8.9 Hz), 8.17(2H, d, J = 9.0 Hz), 9.30(1H, s) ppm.

Synthesis of 3-hydroxy-7-methoxy-2-phenyl-chromen-4-one (**11**): A mixture of compound **4** and **5** (3.0 g, 18.05 mmol) and benzaldehyde (3.8 g, 36.10 mmol) were added to a solution of potassium hydroxide (15.2 g, 270.1 mmol) in methanol (70 mL) and stirred at 90 °C for 48 h. The reaction mixture was cooled to room temperature, and sodium hydroxide (0.5 N, 80 mL) and hydrogen peroxide (35%, 6 mL) were added sequentially. The mixture was stirred at room temperature for 24 h. The mixture was neutralized with conc. HCl to pH 7. The resulting mixture was filtered to give solid **11** (1.85 g, 41.6% from compound **3**). ^{1}H-NMR (400 MHz, DMSO) δ : 3.88(3H, s), 7.03(1H, t, J = 2.2 Hz), 7.26(1H, d, J = 2.2 Hz), 7.47(1H, t, J = 7.2 Hz), 7.55(2H, t, J = 7.3 Hz), 7.98(1H, d, J = 8.9 Hz), 8.19(2H, d, J = 7.6 Hz), 9.48(1H, s) ppm.

Synthesis of 3,7-dihydroxy-2-(4-hydroxy-phenyl)-chromen-4-one (**12**): Compound **10** (1.0 g, 3.39 mmol) and pyridine hydrochloride (6.0 g) were mixed and stirred at 160 °C for 12 h. The solid mixture was obtained as water (50 mL) was added and stirred at room temperature for 2 h. The resulting mixture was filtered to give solid **12** (889 mg, 97%). ^{1}H-NMR(400 MHz, DMSO) δ : 6.85(1H, d, J = 2.0 Hz), 6.87(1H, s), 6.90(2H, t, J = 2.2 Hz), 7.89(1H, d, J = 8.6 Hz), 8.02(2H, d, J = 8.8 Hz), 9.04(1H, s), 9.99(1H, s), 10.71 (1H, s) ppm.

Synthesis of 3,7-dihydroxy-2-phenyl-chromen-4-one (**13**): Compound **11** (1.0 g, 3.39 mmol) and pyridine hydro chloride (6.0 g) were mixed and stirred at 160 °C for 12 h. The solid mixture was obtained as water (50 mL) was added and stirred at room temperature for 2 h. The resulting mixture was filtered to give solid **13** (836 mg, 97%). ^{1}H-NMR(400 MHz, DMSO) δ : 6.90(1H, t, J = 2.2 Hz), 6.92(1H, d, J = 2.0 Hz), 7.46(1H, m), 7.54(2H, m), 7.93(1H, d, J = 8.7 Hz), 8.13(1H, t, J = 1.4 Hz), 8.15(1H, t, J = 1.4 Hz), 9.33(1H, s), 10.78(1H, s) ppm.

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Conflicts of Interest. The authors declare no conflict of interest.

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