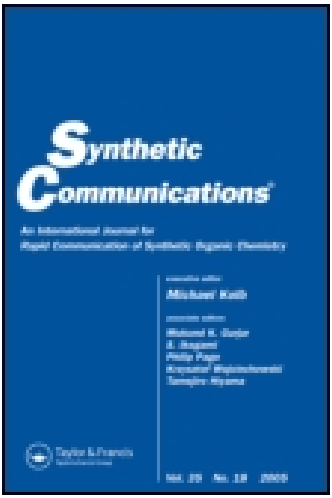

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SYNTHESIS OF 2-METHYLCHROMONE-8-ACETIC ACIDS AND 2-METHYLCHROMONE-8-CARBOXYLIC ACIDS

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SYNTHESIS OF 2-METHYLCHROMONE-8-ACETIC ACIDS AND 2-METHYL-CHROMONE-8-CARBOXYLIC ACIDS

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ABSTRACT

2-Hydroxy-3-allylacetophenones on Claisen condensation with EtOAc/Na gave intermediate diketone, followed by cyclization in AcOH/HCl gave 8-allyl/-1-propenylchromones, which on ozonolysis gave 8-acetaldehydes or 8-carboxaldehydes. The above aldehydes on oxidation with $KMnO_4$ furnished corresponding 8-acetic acids and 8-carboxylic acids.

8-Substituted flavones are reported to have several types of pharmacological activities. 3-Methylflavone-8-carboxylic acid derivatives have coronary vasodilatory activity. These are also used for relaxation of convulsion of smooth muscle of the lower urinary tract. The salt of 2-piperidinoethyl-3-methylflavone-8-carboxylate, named *flavoxate hydrochloride*, has been used as an excellent diuretic and effective remedial

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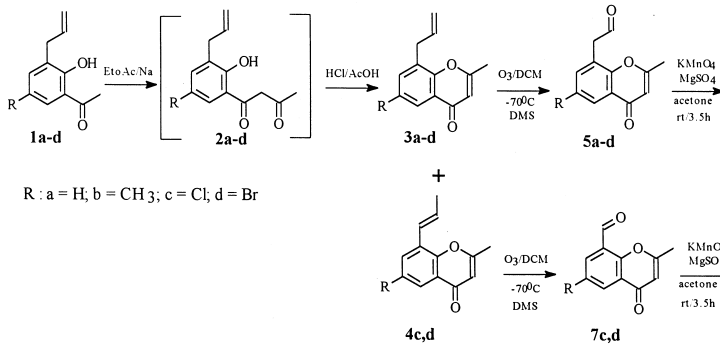
agent for treating Pollakiuria anosognosia.[1] Recently, flavone-8-acetic acid has been identified as a drug in the treatment of cancer named *mito flaxone*.[2] 8-Allyl-6-methoxy-2-styrylchromone is reported as an antitumor lead structure. It inhibits the growth of implanted colon-38 tumors in mice.[3] From our laboratory, Reddy et al.[4] reported the synthesis of some analogs of 8-allyl-2-styrylchromones. Recently, Kapoor et al.[5] reported the synthesis of chromone-8-ylalkanoic acids and assessed their in vitro antileishaminal activity on *Leishmania donovam* strain UR-6.

We now report a new and facile synthesis of 2-methylchromone-8-acetic/carboxylic acids. Claisen condensation of 2-hydroxy-3-allylacetophenone (**1a**)[6] with ethyl acetate in the presence of pulverized sodium gave diketone (**2a**), which was not isolated. On cyclization with HCl in AcOH medium and purification by chromatography, 2-methyl-8-allylchromone (**3a**) was obtained (70%) (Scheme). On ozonolysis[7,8] at $-70^{\circ}C$, **3a** yielded 2-methylchromone-8-acetaldehyde (**5a**, 66%). **5a** was oxidized with $KMnO_4$ under neutral conditions to give 2-methylchromone-8-acetic acid (**6a**, 48%).



Scheme.

Similarly, 5-methyl-3-allyl-2-hydroxyacetophenone (**1b**) via 4-(3-allyl-2-hydroxy-5-methylphenyl)-2,4-butadione (**2b**) 2,6-dimethyl-8-allylchromone (**3b**), on oxidation with ozone gave aldehyde (**5b**), which was further oxidized with $KMnO_4$ to 2,6-dimethylchromone-8-acetic acid (**6b**).

However, under similar Claisen condensation conditions, 5-chloro-3-allyl-2-hydroxy-acetophenone (**1c**)[4] gave an inseparable 1:1 mixture of 6-chloro-2-methyl-8-allyl-chromone and 6-chloro-2-methyl-8-(1-propenyl) chromone (**3c** and **4c**) (^{1}H NMR). The formation of this mixture is due to isomerization of the allylic double bond under strong basic conditions of the Claisen condensation. The mixture was ozonized at $-70^{\circ}C$ to yield two

compounds, which were separated by chromatography, 6-chloro-2-methylchromone-8-acetaldehyde (**5c**) and 6-chloro-2-methylchromone-8-carboxaldehyde (**7c**). Aldehyde (**5c**) was oxidized with $KMnO_4$ under neutral conditions to give the acid (**6c**), and aldehyde **7c** was oxidized with $KMnO_4$ under neutral conditions to give the acid **8c**.

Similarly 6-bromo-2-hydroxy-3-allylacetophenone **1d**, on Clasien condensation, gave an inseparable 1:1 mixture of 6-bromo-2-methyl-8-allylchromone (**3d**) and 6-bromo-2-methyl-8- (1-propenyl) chromone (**4d**).The mixture was ozonized at –70°C to yield two compounds, 6-bromo-2-methylchromone-8-acetaldehyde (**5d**) and 6-bromo-2-methylchromone-8-carboxaldehyde (**7d**). Aldehyde **5d** was oxidized with $KMnO_4$ under neutral conditions to give the acid **6d**, and aldehyde **7d** was oxidized with $KMnO_4$ under neutral conditions to give the acid **8d**.

EXPERIMENTAL

Melting points were taken in open capillary tubes in sulfuric acid bath and are uncorrected. FT-IR (KBr) spectra were obtained on a Perkin-Elmer 1605 spectrometer. ^1H NMR and ^{13}C NMR of all compounds were taken in $CDCl_3$ and **8c** and **8d** in DMSO-d_6 on Varian Gemini 200 and 50.3 MHz, with TMS as internal standard (chemical shifts in δ ppm). EI mass spectra were obtained on a modified Hitachi RMU-6L instrument. Ozonizer, model-T-816 (Welesbech product, Line Son JOSC, California) was used.

Synthesis of 2-Methylchromone-8-acetic Acid (6a)

Synthesis of 2-methyl-8-allylchromone (**3a**)

A mixture of 2-hydroxy-3-allylacetophenone (**1a**)[6] (8.0 g, 46 mmol) and ethyl acetate (200 mL) was refluxed in the presence of pulverized Na (3.0 g) for 3 h. Excess Na was decomposed with methanol (50 mL), the mixture concentrated under vacuum, and then poured onto crushed ice. The mixture was neutralized with dil AcOH (10%), the solid was filtered, washed with chilled water, and dried in air to yield diketone **2a** as a cream-yellow powder. The solution of crude **2a** in acetic acid (70 mL) and concentrated HCl (20 mL) was refluxed for 1.5 h, then poured into ice water. The mixture was filtered and purified by chromatography (silica gel, 200 g, 60–120 mesh) by elution with pet-ether + chloroform (8:2, v/v), 25 fractions each fraction 150 mL were collected. Fractions 5–23 concentrated and recrystallized from chloroform to give **3a** as light yellowish needles (7.0 g, 76%) m.p. 123°C.

IR 1648 (C = O) cm^{-1}, ^1H NMR δ 2.4 (s, 3H, CH_3) 3.6 (d, J = 7, 2H, H-1') 5.1 (m, 2H, H-3') 6.0 (m, 1H, H-2') 6.1 (s, 1H, H-3) 7.4 (t, 1H, H-6) 7.6 (dd, J = 8,2, 1H, H-7) 8.0 (dd, J = 8,2, 1H, H-5). Mass *m/z* at (M^+) 200. Analysis $C_{13}H_{12}O_2$, calc.; C, 77.98; H, 6.04. Found C, 77.96; H, 6.08%.

Synthesis of 2-methylchromone-8-acetaldehyde (**5a**)

Through a solution of 2-methyl-8-allylchromone (**3a**) (3.0 g, 15 mmol) in dry dichloromethane (100 mL) at −70°C, ozone gas was bubbled for 1.5 h. The reaction mixture was quenched with dimethylsulfide (DMS) (1.0 g, 16.2 mmol). Dichloromethane was distilled off. The mixture was poured into ice-cold water and extracted with chloroform. On concentration, a gummy mass was obtained, which was purified by chromatography (silica gel, 100 g, 60–120 mesh) elution with chloroform. Twenty fractions, each 100 mL, were collected. Fractions 4–17 concentrated and recrystallized from chloroform to give **5a** as light cream crystals (2.0 g, 66%), m.p. 137°C. IR 1729 (CHO) 1638 (C = O) cm^{-1}, ^1H NMR δ 2.40 (s, 3H, CH_3) 4.05 (s, 2H, H-1') 6.10 (s, 1H, H-3) 7.70 (t, 1H, H-6) 8.10 (dd, J = 8,2, 1H, H-7) 8.30 (dd, J = 8,2, 1H, H-5) 9.71 (s, CHO) ppm. Mass *m/z* at (M^+) 202. Analysis $C_{12}H_{10}O_3$, calc.; C, 71.26; H, 4.99. Found C, 71.29; H, 4.50%.

Synthesis of 2-methylchromone-8-acetic acid (**6a**)

The mixture of 2-methylchromone-8-acetaldehyde (**5a**) (1.5 g, 7.5 mmol), $MgSO_4$ (1.56 g, 13 mmol) and dry acetone (40 mL) and $KMnO_4$ (1.0 g, 7 mmol) was stirred for 3 h. Acetone was distilled off and the mixture was dissolved in water, filtered, the filtrate was washed with chloroform, and then acidified with dil HCl (10%) to pH 2.0. A colorless solid separated, which was filtered, and recrystallized from methanol to yield 2-methylchromone-8-acetic acid (**6a**), (0.75 g, 48%), m.p. 248°C. IR 3470 (OH) 1632 (C = O) cm^{-1}, UV (MeOH) 230 nm (log ε 4.47) 310 (3.82). ^1H NMR δ 2.4 (s, 3H, CH_3) 4.0 (s, 2H, H-1') 6.1 (s, 1H, H-3) 7.5 (t, 1H, H-6) 7.8 (dd, J = 8,2, 1H, H-7,) 8.6 (dd, J = 8,2, 1H, H-5) 11.5 (s, OH) ppm. Mass *m/z* at (M^+) 218. Analysis $C_{12}H_{10}O_4$, calc.; C, 66.04; H, 4.62. Found C, 66.04; H, 4.64%.

Synthesis of 2,6-Dimethylchromone-8-acetic Acid (6b)

2-Hydroxy-3-allyl-5-methylacetophenone (**1b**)

2-Hydroxy-3-allyl-5-methylacetophenone (**1b**) was prepared by following the procedure in ref (4) with 87% yield b.p. 157°C. ^{1}H NMR δ 2.5 (3H, s, CH_3) 2.6 (3H, s, $COCH_3$) 3.4 (2H, d, J = 7, H-1') 5.2 (2H, m, H-3') 5.9, (1H, m, H-2') 7.3 (1H, d, J = 2.5, H-4) 7.6 (1H, d, J = 2.5, H-6) 12.5 (1H, s, OH) ppm. Mass m/z at (M^+) 276. Analysis $C_{12}H_{14}O_2$, calc.; C, 75.78; H, 7.42. Found C, 75.76; H, 7.40%.

Synthesis of 2,6-dimethyl-8-allylchromone (**3b**)

A mixture of 2-hydroxy-3-allyl-5-methylacetophenone (**1b**) (8.0 g, 42 mmol) and ethyl acetate (200 mL) was refluxed in the presence of pulverized Na (3.0 g) for 3 h. Excess Na was decomposed with methanol (50 mL); the mixture was concentrated under vacuum and then poured onto crushed ice. The mixture was neutralized with dil AcOH (10%), the solid was filtered, washed with chilled water, and dried in air to yield diketone **2b** as a colorless powder. The solution of crude **2b** in acetic acid (70 mL) and conc HCl (20 mL) was refluxed for 1.5 h, then poured into ice water. The mixture was filtered and purified by chromatography (silica gel, 200 g, 60–120 mesh) by elution with pet-ether + chloroform (7:3, v/v). Thirty fractions, each fraction 100 mL, were collected. Fractions 7–24 concentrated and recrystallized from chloroform to give **3b** as brownish crystals (5.85 g, 65%) m.p. 98°C. IR 1646 (C = O) cm^{-1}, ^{1}H NMR δ 2.3 (s, 3H, CH_3) 2.4 (s, 3H, CH_3) 3.5 (d, J = 7, 2H, H-1') 5.1 (m, 2H, H-3') 5.9 (m, 1H, H-2') 6.1 (s, 1H, H-3) 7.2 (d, J = 2, 1H, H-7) 7.7 (dd, J = 8,2, 1H, H-5) ppm. Mass m/z at (M^+) 214. Analysis $C_{14}H_{14}O_2$, calc.; C, 78.47; H, 6.59. Found C, 78.49; H, 6.57%.

Synthesis of 2,6-dimethylchromone-8-acetaldehyde (**5b**)

Through a solution of 2-methyl-8-allylchromone (**3b**) (3.0 g, 14 mmol) in dry dichloromethane (100 mL) at −70°C, ozone gas was bubbled for 1.5 h. The reaction mixture was quenched with dimethylsulfide (DMS) (1.0 g, 16.2 mmol). Dichloromethane was distilled off. The mixture was poured into ice-cold water and extracted with chloroform. On concentration, a gummy mass was obtained, which was purified by chromatography (silica gel, 200 g, 60–120 mesh) elution with pet-ether + chloroform, (1:1, v/v). Twenty-three fractions, each 100 mL, were collected. Fractions 5–16

concentrated and recrystallized from chloroform to give **5b** as a colorless powder (1.8 g, 60%), m.p. 142°C. IR 1718 (CHO) 1635 (C = O) cm^{-1}, ^1H NMR δ 2.2 (s, 3H, CH_3) 2.4 (s, 3H, CH_3) 4.0 (s, 2H, H-1') 6.0 (s, 1H, H-3) 7.7 (d, J = 1.5, 1H, H-7) 8.3 (dd, J = 8,2, 1H, H-5) 9.7 (s, CHO) ppm. Mass *m/z* at (M^+) 216. Analysis $C_{13}H_{12}O_3$, calc.; C, 72.20; H, 5.60. Found C, 72.18; H, 5.64%.

Synthesis of 2,6-dimethylchromone-8-acetic acid (**6b**)

The mixture of 2,6-dimethylchromone-8-acetaldehyde (**5b**) (1.3 g, 6 mmol), $MgSO_4$ (1.44 g, 12 mmol), dry acetone (40 mL) and $KMnO_4$ (0.9 g, 5.8 mmol) was stirred for 3 h. Acetone was distilled off and the mixture was dissolved in water, filtered, the filtrate was washed with chloroform, and then acidified with dil HCl (10%) to pH 2.0. A solid separate, which was filtered recrystallized from methanol to yield 2,6-dimethylchromone-8-acetic acid (**6b**) as light cream crystals (0.62 g, 45%), m.p. 230°C. IR 3445 (OH) 1637 (C = O) cm^{-1}, UV (MeOH) 236 nm (loge 4.43) 313 (3.64). ^1H NMR δ 2.2 (s, 3H, CH_3) 2.4 (s, 3H, CH_3) 4.0 (s, 2H, H-1') 6.0 (s, 1H, H-3) 7.8 (d, J = 1.5, 1H, H-7) 8.3 (dd, J = 8,2, 1H, H-5) 11.6 (s, OH) ppm. Mass *m/z* at (M^+) 232. Analysis $C_{13}H_{12}O_4$, calc.; C, 67.22; H, 5.21. Found C, 67.24; H, 5.19%.

Synthesis of 6-Chloro-2-methylchromone-8-acetic Acid (6c) and 6-Chloro-2-methylchromone-8-carboxylic Acid (8c)

Synthesis of 6-chloro-2-methyl-8-allylchromone (**3c**) and 6-chloro-2-methyl-8-(1-propenyl)chromone (**4c**)

A mixture of 2-hydroxy-3-allyl-5-chloroacetophenone (**1c**)[4] (8.0 g, 38 mmol), ethyl acetate (200 mL), and Na (3.0 g) was refluxed for 3 h. Then excess Na was decomposed with methanol (50 mL), the mixture concentrated under vacuum and then poured onto crushed ice. The mixture was neutralized with dil AcOH (10%), the solid was filtered, washed with chilled water, and dried in air to yield diketone **2c** as a light orange powder. The solution of crude **2c** in acetic acid (70 mL) and conc HCl (20 mL) was refluxed for 1.5 h, then poured into ice water. The mixture was filtered and purified by crystallization from methanol to give as yellowish crystals (7.0 g, 79%) m.p. 116°C. IR 1647 (C = O) cm^{-1}, ^1H NMR indicated the product to be a 1:1 mixture of two compounds, 6-chloro-2-methyl-8-allylchromone (**3c**), δ 2.4 (s, 3H, CH_3) 3.6 (d, J = 7, 2H, H-1') 5.1 (m, 2H, H-3')

6.0 (m, 1H, H-2') 6.1 (s, 1H, H-3) 7.6 (d, J = 2, 1H, H-7) 8.0 (d, J = 2, 1H, H-5), 6-chloro-2-methyl-8-(1-propenyl)chromone (**4c**) δ 2.0 (m, 3H, H-3') 2.4 (s, 3H, CH_3) 6.1 (s, 1H, H-3) 6.4 (m, 1H, H-2') 6.8 (d, J = 16,1H, H-1') 7.4 (d, J = 2, 1H, H-7) 8.0 (d, J = 2, 1H, H-5) ppm. Mass *m/z* at (M^+) 234. Analysis $C_{13}H_{11}O_2Cl$, calc.; C, 66.65; H, 4.74. Found C, 66.62; H, 4.75%. The mixture could not be purified by chromatography.

Synthesis of 6-chloro-2-methylchromone-8-acetaldehyde (**5c**) and 6-chloro-2-methylchromone-8-carboxaldehyde (**7c**)

Through a solution of the mixture 6-chloro-2-methyl-8-allylchromone (**3c**) and 6-chloro-2-methyl-8-(1-propenyl)chromone (**4c**) (6.0 g, 67 mmol) in dry dichloromethane (150 mL) at -70°C, ozone gas was bubbled for 1.5 h. The reaction mixture was quenched with dimethylsulfide (DMS) (1.62 g, 26 mmol). Dichloromethane was distilled off. The mixture was poured into ice-cold water and extracted with chloroform. On concentration, a colorless gummy mass was obtained, which was purified by chromatography (silica gel, 150 g, 60–120 mesh) elution with pet-ether + chloroform, (1:1, v/v). Thirty-five fractions, each 150 mL, were collected. Fractions 5–16 concentrated and recrystallized from methanol to give aldehyde **5c** as colorless crystals (1.7 g, 56%), m.p.118°C. IR 1725 (CHO) 1645 (C = O) cm^{-1}, ^{1}H NMR δ 2.42 (s, 3H, CH_3) 3.95(s, 2H, H-1') 6.19 (s, 1H, H-3) 7.49(d, J = 2, 1H, H-7) 8.08 (d, J = 2, 1H, H-5) 9.89 (s, CHO) ppm. Mass *m/z* at (M^+) 236. Analysis $C_{12}H_9O_3Cl$, calc.; C, 61.04; H, 3.84. Found C, 61.01; H, 3.86%.

Fractions 20–32 concentrated and recrystallized from methanol to give **7c** as light cream crystals (1.0 g, 35%), m.p. 135°C. IR 1695 (CHO) 1652 (C = O) cm^{-1}, ^{1}H NMR δ 2.45 (s, 3H, CH_3) 6.24 (s, 1H, H-3) 8.13 (d, J = 2, 1H, H-7) 8.38 (d, J = 2, 1H, H-5) 10.6 (s, CHO) ppm. Mass *m/z* at (M^+) 222. Analysis $C_{11}H_7O_3Cl$, calc.; C, 59.39; H, 3.17. Found C, 59.39; H, 3.13%.

Synthesis of 6-chloro-2-methylchromone-8-acetic acid (**6c**)

The mixture of 6-chloro-2-methylchromone-8-acetaldehyde (**5c**) (1.0 g, 4.23 mmol), $MgSO_4$ (0.63 g, 3.3 mmol), and dry acetone (40 mL) and $KMnO_4$ (0.6 g, 3.68 mmol) was stirred for 3 h. Acetone was distilled off and the mixture was dissolved in water, filtered, the filtrate was washed with chloroform, and then acidified with dil HCl (10%) to pH 2.0. A solid separate, which was filtered, recrystallized from methanol to yield 6-chloro-2-methylchromone-8-acetic acid (**6c**) as colorless crystals (0.45 g, 42%),

m.p.213°C. IR 3437 (OH) 1628 (C=O) cm^{-1}, UV (MeOH) 236 nm (log ε 4.36) 323 (3.75). ^1H NMR δ 2.47 (s, 3H, CH_3) 3.98 (s, 2H, H-1') 6.22 (s, 1H, H-3) 8.08 (bs, 1H, H-7) 8.50 (bs, 1H, H-5) 11.65 (s, OH) ppm. Mass m/z at (M^+) 236. Analysis $C_{12}H_9O_4Cl$, calc.; C, 55.46; H, 2.96. Found C, 55.42; H, 2.94%.

Synthesis of 6-chloro-2-methylchromone-8-carboxylic acid (**8c**)

The mixture of 6-chloro-2-methylchromone-8-carboxyaldehyde (**7c**) (0.7 g, 3.15 mmol), $MgSO_4$ (0.6 g, 5 mmol), and dry acetone (40 mL) and $KMnO_4$ (0.56 g, 3.6 mmol) was stirred for 3 h. Acetone was distilled off and the mixture was dissolved in water, filtered, the filtrate was washed with chloroform, and then acidified with dil HCl (10%) to pH 2.0. A solid separate, which was filtered, recrystallized from methanol to yield 6-chloro-2-methylchromone-8-carboxylic acid (**8c)** as colorless crystals (0.28 g, 38%), m.p. 210°C. IR 3384 (OH) 1645 (C=O) cm^{-1}, ^1H NMR δ 2.48 (s, 3H, CH_3) 4.05 (s, OH) 6.22 (s, 1H, H-3) 8.13 (d, J=2, 1H, H-7) 8.25 (d, J=2, 1H, H-5) ppm. Mass m/z at (M^+) 222. Analysis $C_{11}H_2O_4Cl$, calc.; C, 55.37; H, 2.90. Found C, 55.39; H, 2.94%.

Synthesis of 6-Bromo-2-methylchromone-8-acetic Acid (6d) and 6-Bromo-2-methylchromone-8-carboxylic Acid (8d)

2-hydroxy-3-allyl-5-bromoacetophenone (**1d**)

2-Hydroxy-3-allyl-5-bromoacetophenone was prepared by following the procedure in ref. (4) with 90% yield, b.p. 157°C. ^1H NMR δ 2.52 (3H, s, $COCH_3$) 3.42 (2H, d, J=7, H-1') 5.18 (2H, m, H-3') 5.99 (1H, m, H-2') 7.44 (d, J=2.0, H-4) 7.68 (1H, d, J=2.0, H-6) 12.57 (1H, s, OH) ppm. Mass m/z at (M^+) 254. Analysis $C_{11}H_{11}O_2Br$, calc.; C, 51.79; H, 4.35. Found C, 51.81; H, 4.33%.

Synthesis of 6-bromo-2-methyl-8-allylchromone (**3d**) and 6-bromo-2-methyl-8-(1-propenyl)chromone (**4d**)

A mixture of 2-hydroxy-3-allyl-5-bromoacetophenone (**1d**) (10 g, 40 mmol), ethyl acetate (200 mL), and Na (3.0 g) was refluxed for 3 h. Then excess Na was decomposed with methanol (50 mL), the mixture was concentrated under vacuum, and then poured onto crushed ice. The mixture was neutralized with dil AcOH (10%), the solid was filtered, washed with chilled water, and dried in air to yield diketone **2d** as a brownish powder.

The solution of crude **2d** in acetic acid (70 mL) and conc HCl (22 mL) was refluxed for 1.5 h, then poured into ice water. The mixture was filtered and purified by crystallization from methanol to give an olive-gray powder (9.5 g, 87%) m.p. 110°C. IR 1649 (C = O) cm^{-1}. ^1H NMR indicated the product to be a 1:1 mixture of two compounds, 6-bromo-2-methyl-8-allyl-chromone (**3d**), δ 2.4 (s, 3H, CH_3) 3.6 (d, J = 7, 2H, H-1') 5.1 (m, 2H, H-3') 6.0 (m, 1H, H-2') 6.1 (s, 1H, H-3) 7.7 (d, J = 2, 1H, H-7) 8.15 (d, J = 2, 1H, H-5), 6-bromo-2-methyl-8-(1-propenyl) chromone (**4d**) δ 2.0 (m, 3H, H-3') 2.4 (s, 3H, CH_3) 6.1 (s, 1H, H-3) 6.4 (m, 1H, H-2') 6.7 (d, J = 16, 1H, H-1') 7.5 (d, J = 2, 1H, H-7) 8.1 (d, J = 2, 1H, H-5) ppm. Mass m/z at (M^+) 278. Analysis $C_{13}H_{11}O_2Br$, calc.; C, 56.12; H, 3.39. Found C, 56.14; H, 3.42%. The mixture could not be purified by chromatography.

Synthesis of 6-bromo-2-methylchromone-8-acetaldehyde (**5d**) and 6-bromo-2-methylchromone-8-carboxaldehyde (**7d**)

Through a solution of the mixture 6-bromo-2-methyl-8-allylchromone (**3d**) and 6-bromo-2-methyl-8-(1-propenyl)chromone (**4d**) (6.0 g, 22 mmol) in dry dichloro methane (150 mL) at −70°C, ozone gas was bubbled for 1.5 h. The reaction mixture was quenched with dimethylsulfide (DMS) (1.5 g, 24 mmol). Dichloromethane was distilled off. The mixture was poured into ice-cold water and extracted with chloroform. On concentration a colorless gummy mass was obtained, which was purified by chromatography (silica gel, 100 g, 60–120 mesh) elution with pet-ether + ethyl acetate, (1:1, v/v). Thirty fractions, each 150 mL, were collected. Fractions 4–17 concentrated and recrystallized from methanol to give aldehyde **5d** as colorless crystals (1.38 g, 46%), m.p. 129°C. IR 1721 (CHO) 1648 (C = O) cm^{-1}, ^1H NMR δ 2.4 (s, 3H, CH_3) 3.9(s, 2H, H-1') 6.1 (s, 1H, H-3) 7.6 (d, J = 2, 1H, H-7) 8.2 (d, J = 2, 1H, H-5) 9.8 (s, CHO) ppm. Mass m/z at (M^+) 280. Analysis $C_{12}H_9O_3Br$, calc.; C, 51.39; H, 3.26. Found C, 51.43; H, 3.24%.

Fractions 20–28 concentrated and recrystallized from methanol to give **7d** as colorless crystals (1.5 g, 52%), m.p. 147°C. IR 1699 (CHO) 1647 (C = O) cm^{-1}, ^1H NMR δ 2.4 (s, 3H, CH_3) 6.2 (s, 1H, H-3) 8.2 (d, J = 2, 1H, H-7) 8.5 (d, J = 2, 1H, H-5) 10.6 (s, CHO) ppm. Mass m/z at (M^+) 266. Analysis $C_{11}H_7O_3Br$, calc.; C, 49.47; H, 2.64. Found C, 49.51; H, 2.58%.

Synthesis of 6-bromo-2-methylchromone-8-acetic acid (**6d**)

The mixture of 6-bromo-2-methylchromone-8-acetaldehyde (**5d**) (1.0 g, 3.5 mmol), $MgSO_4$ (0.64 g, 5.35 mmol), and dry acetone (40 mL)

and $KMnO_4$ (0.6 g, 3.68 mmol) was stirred for 3 h. Acetone was distilled off and the mixture was dissolved in water, filtered, the filtrate was washed with chloroform, and then acidified with dil HCl (10%) to pH 2.0. A solid was filtered and recrystallized from methanol to yield 6-bromo-2-methylchromone-8-acetic acid (**6d)** as colorless crystals (0.55 g, 35%), m.p. 261°C. IR 3449 (OH) 1632 (C = O) cm^{-1}, UV (MeOH) 228 nm (log ε 4.42) 307 (3.71). ^1H NMR δ 2.4 (s, 3H, CH_3) 3.9 (s, 2H, H-1') 6.2 (s, 1H, H-3) 7.7 (bs, 1H, H-7) 8.4 (bs, 1H, H-5) 11.5 (s, OH) ppm. Mass *m/z* at (M^+) 296. Analysis $C_{12}H_9O_4Br$, calc.; C, 49.63; H, 2.65. Found C, 49.61; H, 2.64%.

Synthesis of 6-bromo-2-methylchromone-8-carboxylic Acid (**8d**)

The mixture of 6-bromo-2-methylchromone-8-carboxaldehyde (**7d)** (1.0 g, 3.75 mmol), $MgSO_4$ (0.71 g, 6 mmol), and dry acetone (40 mL) and $KMnO_4$ **(**0.67 g, 4.3 mmol) was stirred for 3 h. Acetone was distilled off and the mixture was dissolved in water, filtered, the filtrate was washed with chloroform, and then acidified with dil HCl (10%) to pH 2.0. A solid was filtered and recrystallized from methanol to yield 6-bromo-2-methylchromone-8-acetic acid (**8d)** as colorless crystals (0.44 g, 42%), m.p. 225°C. IR 3384 (OH) 1648 (C = O) cm^{-1}, ^1H NMR δ 2.4 (s, 3H, CH_3) 3.5 (s, OH) 6.2 (s, 1H, H-3) 8.2 (d, J = 2, 1H, H-7) 8.3 (d, J = 2, 1H, H-5) ppm. Mass *m/z* at (M^+) 282. Analysis $C_{11}H_7O_4Br$, calc.; C, 46.67; H, 2.49. Found C, 46.65; H, 2.47%.

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