Intramolecular cross dehydrogenative coupling of 4-substituted coumarins: rapid and efficient access to coumestans and indole[3,2-c]coumarins

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1. General

NMR spectra were recorded on a Mercury 300 spectrometer (300 MHz for $^1$H), and Varian spectrometer (125 MHz or 150 MHz for $^{13}$C). Chemical shifts are reported in $\delta$ ppm referenced to an internal SiMe$_4$ standard for $^1$H NMR and chloroform-$d$ ($\delta$ 77.16), DMSO-$d_6$ ($\delta$ 39.52) for $^{13}$C NMR. HRMS were recorded on a Q-TOF mass spectrometer with ESI resource or Magnetic Sector for EI. Melting point determinations were performed by the open capillary method.

2. General procedure for the synthesis of 4-aryloxy coumarin $[1-3]$

**Step 1**: A solution of substituted o-hydroxy acetophenone (9 mmol, 1 equiv) in toluene (15 mL) was added dropwise to a dry round-bottom flask containing sodium hydride (60% w/w suspension, 27 mmol, 3 equiv) in toluene (10 mL) at 0 °C. The mixture was stirred at the same temperature for 15 min followed by the dropwise addition of diethylcarbonate (13.5 mmol, 1.5 equiv) in toluene (10 mL). Then, the reaction mixture was heated at 120 °C and monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature. The solvents were removed under reduced pressure and resulting mixture residue was quenched at ice bath temperature by slow addition of water (20 mL) and acidified with 2 N HCl. The solid precipitate was filtered, washed with water, and dried under vacuum to afford the crude product (substituted 4-hydroxy coumarin)$[1]$ which was directly used in the next step.

**Step 2**: to a round bottom flask equipped with a magnetic stir bar and a reflux condenser was added the substituted 4-hydroxy coumarin (2.0 mmol) and toluene (8 mL). The reaction mixture was heated at 120 °C for 10 min and then Bu$_4$NBr (3.0 equiv) was added in two portions over 5 min. The reaction mixture was stirred vigorously for 10 min until the starting material completely dissolved. P$_2$O$_5$ (4.8 mmol) was then added in two portions over 10 min and the reaction was heated for 3-5 h until reaction completion. The reaction mixture was cooled to 23 °C and quenched with a saturated aqueous NaHCO$_3$ solution. Then the reaction mixture was extracted with toluene (3 × 10 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give substituted 4-bromo coumarin.$[2]$

**Step 3**: a solution of substituted 4-bromo coumarin (1.5 mmol), substituted phenol (1.5 mmol) and K$_2$CO$_3$ (3.0 mmol) in acetonitrile (3 mL) was stirred at 90 °C for 1-2 h. The reaction was allowed
to cool to ambient temperature. After quenching the reaction by addition of water (2 ml), white precipitates formed immediately. Filtration of the mixture afforded the precipitates as crude product which was then purified by column chromatography on silica gel (typically using DCM/PE as the eluent) to yield product 1.[3]


A mixture of substituted 4-hydroxycoumarin (2.0 mmol) and the corresponding amine (2.4-3 mmol) was placed in a 10 mL high pressure glass tube and placed into the microwave reactor for 10-30 min, the reaction mixture was allowed to cool to ambient temperature. Ice-cold acetone (10 mL) was added and the separated crystals were filtered off to give chromatographically (TLC) pure product 3.

4. General procedure for coumestans 2 and indole[3,2-c]coumarins 4

Coumarin substrate 1 or 3 (0.2 mmol), Pd(OAc)₂ (10 mol%), AgOAc (2 equiv) and CsOAc (2 equiv) were combined in PivOH (1.0 mL). Then the reaction mixture was heated to 100 ºC for 5-38 h as monitored by TLC (CH₂Cl₂/PE=1/1 as the mobile phase for substrate 1; CH₂Cl₂/MeOH=100/1 as the mobile phase for substrate 3). The reaction mixture was then diluted with CH₂Cl₂ and excess NaHCO₃ (aq.) was added to neutralize PivOH. After stirring the mixture for 10 min, the residue was washed with aqueous NaHCO₃. The isolated organic layer was dried over Na₂SO₄. After removal of solvent, the residue was purified by silica gel column chromatography (using CH₂Cl₂/PE as the eluent to get product 2; CH₂Cl₂/MeOH as the eluent for product 4) to give desired product 2 or 4.

In the work-up procedure for indole[3,2-c]coumarin 4, the drying up step of the organic layer over Na₂SO₄ is omitted due to the relatively poor solubility of 4. Compounds 2a[3], 2g[5], 2h[5], 2s[5], 4a[6] and 4e[7] are known compounds.

5. Characterization data of products 2 and 4

6H-benzofuro[3,2-c]chromen-6-one (2a).
White solid, 40.6 mg, 86%. mp 181-182 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.17-8.14 (m, 1H), 8.05 (dd, $J_1 = 7.8$, 0.9 Hz, 1H), 7.70-7.65 (m, 1H), 7.61 (dd, $J_2 = 7.2$, 1.2 Hz, 1H), 7.54-7.40 (m, 4H).

10-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2b).

White solid, 43.4 mg, 85%. mp 238-240 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.10 (d, $J_1 = 7.9$ Hz, 1H), 7.92 (d, $J_2 = 7.6$ Hz, 1H), 7.68-7.63 (m, 1H), 7.53 (d, $J_2 = 8.5$ Hz, 1H), 7.47-7.38 (m, 2H), 7.27-7.21 (m, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 160.7, 157.9, 153.9, 148.0 (d, $J_{CF} = 250.5$ Hz), 142.5 (d, $J_{CF} = 12.0$ Hz), 132.6, 126.9, 126.3 (d, $J_{CF} = 6.0$ Hz), 125.0, 122.2, 117.7, 117.6 (d, $J_{CF} = 3.0$ Hz), 113.5 (d, $J_{CF} = 13.5$ Hz), 112.4, 106.2. HRMS (EI): calcd for C$_{15}$H$_7$FO$_3$: 254.0379; found: 254.0374.

10-methyl-6H-benzofuro[3,2-c]chromen-6-one (2c).

White solid, 42.1 mg, 84%. mp 174-176 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.03 (d, $J_1 = 7.8$ Hz, 1H), 7.92 (d, $J_2 = 7.6$ Hz, 1H), 7.53 (d, $J_2 = 8.4$ Hz, 1H), 7.42-7.30 (m, $J = 20.0$, 7.6 Hz, 2H), 7.26-7.24 (m, 1H), 2.62 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 159.7, 158.3, 154.6, 153.7, 131.9, 127.9, 125.3, 124.7, 123.0, 122.2, 121.9, 119.3, 117.5, 112.8, 106.2, 15.1. HRMS (EI): calcd for C$_{16}$H$_{10}$O$_3$: 250.0630; found: 250.0633.

8,10-difluoro-6H-benzofuro[3,2-c]chromen-6-one (2d).

White solid, 45.2 mg, 83%. mp 234-236 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.08 (d, $J_1 = 7.7$ Hz, 1H), 7.71-7.63 (m, 2H), 7.53 (d, $J_2 = 8.4$ Hz, 1H), 7.46 (dd, $J_1 = 7.8$, 7.5 Hz, 1H), 7.04 (ddd, $J_2 = 10.2$, 9.3, 2.4 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.8, 160.2 (dd, $J_{CF} = 244.4$, 8.8 Hz), 157.5, 154.1, 146.3 (dd, $J_{CF} = 252.9$, 13.5 Hz), 139.1 (dd, $J_{CF} = 11.8$, 2.1 Hz), 133.0, 126.9 (dd, $J_{CF} = 12.9$, 3.3 Hz), 125.2, 122.3, 117.8, 112.3, 106.2 (t, $J_{CF} = 3.6$ Hz), 103.8 (dd, $J_{CF} = 26.0$, 4.4 Hz), 102.9 (dd, $J_{CF} = 29.5$, 19.7 Hz). HRMS (EI): calcd for C$_{15}$H$_6$F$_2$O$_3$: 272.0285; found: 272.0283.

8,10-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2e).

White solid, 45.2 mg, 86%. mp 228-230 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.06 (d, $J_1 = 7.8$ Hz, 1H), 7.76 (s, 1H), 7.61 (dd, $J_1 = 8.1$, 7.8 Hz, 1H), 7.50 (d, $J_2 = 8.3$ Hz, 1H), 7.42 (dd, $J_2 = 7.8$, 7.2 Hz, 1H), 7.10 (s, 1H), 2.60 (s, 3H), 2.47 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.8, 158.5, 153.6, 153.2, 135.3, 131.7, 129.3, 124.6, 123.1, 121.9, 121.6, 119.2, 117.6, 113.0, 106.1, 21.4, 15.1. HRMS (EI): calcd for C$_{17}$H$_{12}$O$_3$: 264.0786; found: 264.0787.

7,9-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2f).
Light yellow solid, 52.6 mg, 99%. mp 199-200 °C. 1H NMR (300 MHz, CDCl₃) δ 7.97 (d, J = 7.8 Hz, 1H), 7.56 (dd, J = 8.4, 7.2 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 7.8, 7.2 Hz, 1H), 7.23 (s, 1H), 6.99 (s, 1H), 2.92 (s, 3H), 2.45 (s, 3H). 13C NMR (125 MHz, CDCl₃) δ 159.6, 158.1, 156.2, 153.5, 137.6, 133.7, 131.6, 128.3, 124.5, 121.8, 120.3, 117.1, 112.7, 109.4, 106.6, 21.7, 21.2.


9-methyl-6H-benzofuro[3,2-c]chromen-6-one (2g).

Light yellow solid, 36.7 mg, 73%. mp 200-202 °C. 1H NMR (300 MHz, CDCl₃) δ 7.95 (dd, J = 7.7, 3.3 Hz, 2H), 7.56 (dd, J = 7.8, 7.5 Hz, 1H), 7.45-7.34 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 2.51 (s, 3H).

9-methoxy-6H-benzofuro[3,2-c]chromen-6-one (2h).

White solid, 45.8 mg, 86%. mp 215-217 °C. 1H NMR (300 MHz, CDCl₃) δ 7.97-7.94 (m, 2H), 7.58-7.53 (m, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.38 (dd, J = 7.5, 7.5 Hz, 1H), 7.16 (d, J = 1.3 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 3.90 (s, 3H).

9-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2i).

White solid, 33.1 mg, 65%. mp 248-250 °C. 1H NMR (300 MHz, CDCl₃) δ 8.06 (dd, J = 8.5, 5.4 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.61 (dd, J = 7.8, 7.5 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.44-7.38 (m, 2H), 7.25-7.18 (m, 1H). 13C NMR (150 MHz, CDCl₃) δ 162.1 (d, J_{CF} = 246.0 Hz), 160.7 (d, J_{CF} = 3.0 Hz), 158.0, 155.7 (d, J_{CF} = 13.5 Hz), 153.6, 132.1, 124.9, 122.6 (d, J_{CF} = 10.5 Hz), 121.9, 119.9, 117.7, 113.7 (d, J_{CF} = 24.0 Hz), 112.6, 105.8, 100.2 (d, J_{CF} = 27.0 Hz). HRMS (EI): calcd for C₁₅H₇FO₃: 254.0379; found: 254.0382.

7-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2j).

Light yellow solid, 16.0 mg, 31%. mp 218-220 °C. 1H NMR (300 MHz, CDCl₃) δ 8.02 (d, J = 7.8 Hz, 1H), 7.65 (dd, J = 7.5, 7.5 Hz, 1H), 7.52-7.36 (m, 4H), 7.16 (dd, J = 7.5, 7.5 Hz, 1H). 13C NMR (150 MHz, CDCl₃) δ 160.3, 156.4 (d, J_{CF} = 255.0 Hz), 157.1 (d, J_{CF} = 9.0 Hz), 156.8, 154.1, 132.6, 127.9 (d, J_{CF} = 7.5 Hz), 124.9, 122.2, 117.6, 112.7 (d, J_{CF} = 21.0 Hz), 112.2, 112.0 (d, J_{CF} = 19.5 Hz), 108.1 (d, J_{CF} = 4.5 Hz), 104.8 (d, J_{CF} = 4.5 Hz). HRMS (EI): calcd for C₁₅H₇FO₃: 254.0379; found: 254.0382.

8-(trifluoromethyl)-6H-benzofuro[3,2-c]chromen-6-one (2k).

White solid, 49.6 mg, 82%. mp 152-154 °C. 1H NMR (300 MHz, CDCl₃) δ 8.42 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.78-7.72 (m, 2H), 7.67 (dd, J = 8.4, 7.2 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 7.8, 7.5 Hz, 1H). 13C NMR (150 MHz, CDCl₃) δ 161.5, 157.6, 156.8, 154.0, 132.9, 128.2 (q, J_{CF}
= 32.5 Hz), 125.1, 124.1 (q, JCF = 3.0 Hz), 123.9, 123.3, 122.2, 119.7 (q, JCF = 4.5 Hz), 117.8, 112.4, 112.2, 105.7. HRMS (EI): calcd for C16H7F3O3: 304.0347; found: 304.0346.

8-methyl-6H-benzofuro[3,2-c]chromen-6-one (2l).

Light yellow solid, 41.7 mg, 83%. mp 201-203 °C. 1H NMR (300 MHz, CDCl3) δ 8.03 (dd, J = 7.8, 0.9 Hz, 1H), 7.95 (s, 1H), 7.63-7.50 (m, 3H), 7.42 (ddd, J = 7.7, 7.4, 0.9 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 2.52 (s, 3H).

13C NMR (125 MHz, CDCl3) δ 160.2, 158.3, 154.1, 153.7, 135.3, 131.9, 128.0, 124.7, 123.5, 121.9, 121.8, 112.4, 112.2, 105.7. HRMS (EI): calcd for C16H10O3: 250.0630; found: 250.0626.


Light yellow solid, 52.8 mg, 92%. mp 213-215 °C. 1H NMR (300 MHz, CDCl3) δ 8.35 (d, J = 8.2 Hz, 1H), 8.10 (ddd, J = 9.0, 9.0 Hz, 2H), 7.94 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 7.64 (ddd, J = 8.1, 7.5 Hz, 1H), 7.58-7.47 (m, 3H), 7.42 (dd, J = 7.8, 7.2 Hz, 1H). 13C NMR (125 MHz, CDCl3) δ 158.9, 158.4, 153.4, 151.5, 132.6, 131.5, 128.7, 127.2, 126.5, 126.0, 124.8, 121.7, 120.8, 120.0, 119.6, 119.0, 117.6, 112.9, 107.0. HRMS (EI): calcd for C19H10O3: 286.0630; found: 286.0623.

1,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2n).

White solid, 43.1 mg, 82%. mp 258-260 °C. 1H NMR (300 MHz, CDCl3) δ 8.14 (dd, J = 5.4, 3.4 Hz, 1H), 7.64 (dd, J = 6.2, 2.8 Hz, 1H), 7.44 (dd, J = 5.9, 3.2 Hz, 2H), 7.12 (s, 1H), 6.98 (s, 1H), 2.86 (s, 3H), 2.42 (s, 3H). 13C NMR (125 MHz, CDCl3) δ 161.5, 158.5, 155.4, 154.7, 142.6, 135.0, 128.1, 126.4, 125.2, 123.3, 121.8, 115.5, 111.7, 109.6, 105.2, 21.8, 21.3. HRMS (EI): calcd for C17H12O3: 264.0786; found: 264.0783.

1,3,7,9-tetramethyl-6H-benzofuro[3,2-c]chromen-6-one (2o).

White solid, 42.7 mg, 86%. mp 192-194 °C. 1H NMR (300 MHz, CDCl3) δ 7.23 (s, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 6.92 (s, 1H), 2.93 (s, 3H), 2.82 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 161.0, 158.2, 155.9, 154.4, 141.9, 136.9, 134.7, 133.4, 128.2, 127.9, 119.8, 115.0, 109.4, 109.2, 105.8, 21.7, 21.6, 21.4, 21.3. HRMS (EI): calcd for C19H16O3: 292.1099; found: 292.1095.

2-methyl-6H-benzofuro[3,2-c]chromen-6-one (2p).

White solid, 47.2 mg, 94%. mp 171-172 °C. 1H NMR (300 MHz, CDCl3) δ 8.16-8.13 (m, 1H), 7.83 (s, 1H), 7.68-7.65 (m, 1H), 7.51-7.44 (m, 2H), 7.41 (s, 2H), 2.50 (s, 3H). 13C NMR (125 MHz, CDCl3) δ 160.1, 158.4, 155.6, 152.0, 134.7, 133.1, 126.8, 125.3, 123.7, 121.9, 121.6, 117.3, 112.4, 111.8, 105.9, 21.1. HRMS (EI): calcd for C16H10O3: 250.0630; found: 250.0626.

2-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2q).
White solid, 43.4 mg, 85%. mp 211-213 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.15 (d, $J$ = 7.2 Hz, 1H), 7.71-7.67 (m, 2H), 7.54-7.45 (m, 3H), 7.32 (dd, $J$ = 8.6, 8.4, 2.4 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.1 (d, $J_{CF}$ = 245.0 Hz), 159.2 (d, $J_{CF}$ = 2.5 Hz), 157.8, 155.6, 149.9, 127.4, 125.6, 123.3, 122.2, 119.5 (d, $J_{CF}$ = 36.3 Hz), 119.4 (d, $J_{CF}$ = 2.5 Hz), 113.5 (d, $J_{CF}$ = 8.8 Hz), 112.0, 107.8 (d, $J_{CF}$ = 25.0 Hz), 106.7. HRMS (EI): calcd for C$_{13}$H$_7$FO$_3$: 254.0379; found: 254.0384.

2,4-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2r).

White solid, 48.0 mg, 91%. mp 249-250 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.14-8.11 (m, 1H), 7.64-7.61 (m, 2H), 7.48-7.41 (m, 2H), 7.21 (s, 1H), 2.48 (s, 3H), 2.42 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 160.6, 158.4, 155.6, 150.4, 134.6, 134.1, 126.8, 126.6, 125.2, 123.8, 121.9, 119.2, 112.1, 111.7, 105.6, 21.0, 16.1. HRMS (EI): calcd for C$_{17}$H$_{12}$O$_3$: 264.0786; found: 264.0782.

3-methoxy-6H-benzofuro[3,2-c]chromen-6-one (2s).

White solid, 44.7 mg, 85%. mp 199-200 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.08 (dd, $J$ = 5.7, 3.1 Hz, 1H), 7.89 (d, $J$ = 9.3 Hz, 1H), 7.42 (dd, $J$ = 5.9, 3.1 Hz, 2H), 6.97-6.95 (m, 2H), 3.90 (s, 3H).

3-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2t).

White solid, 44.2 mg, 87%. mp 231-232 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.12-8.10 (m, 1H), 8.02 (dd, $J$ = 8.3, 6.2 Hz, 1H), 7.67-7.44 (m, 2H), 7.24-7.14 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.8 (d, $J_{CF}$ = 252.5 Hz), 159.7, 157.8, 155.6, 155.0 (d, $J_{CF}$ = 13.8 Hz), 127.0, 125.5, 123.7 (d, $J_{CF}$ = 10.0 Hz), 123.4, 121.9, 113.1 (d, $J_{CF}$ = 22.5 Hz), 111.9, 109.5 (d, $J_{CF}$ = 2.5 Hz), 105.4 (d, $J_{CF}$ = 26.3 Hz), 105.0 (d, $J_{CF}$ = 2.5 Hz). HRMS (EI): calcd for C$_{15}$H$_7$FO$_3$: 254.0379; found: 254.0372.

chromeno[4,3-b]indol-6(11H)-one (4a).

Light yellow solid, 43.1 mg, 92%. mp >300 °C. $^1$H NMR (300 MHz, DMSO) $\delta$ 13.02 (s, 1H), 8.21 (d, $J$ = 7.6 Hz, 1H), 8.05 (d, $J$ = 7.8 Hz, 1H), 7.67 (d, $J$ = 8.4 Hz, 1H), 7.62 (d, $J$ = 8.1 Hz, 1H ), 7.55-7.31 (m, 4H).

10-methoxychromeno[4,3-b]indol-6(11H)-one (4b).

Light yellow solid, 41.1 mg, 78%. mp 285-287 °C. $^1$H NMR (300 MHz, DMSO) $\delta$ 13.11 (s, 1H), 8.48 (d, $J$ = 7.6 Hz, 1H), 7.64-7.50 (m, 3H), 7.44 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.27 (dd, $J$ = 8.1, 7.8 Hz, 1H), 7.01 (d, $J$ = 7.9 Hz, 1H), 4.04 (s, 3H). $^{13}$C NMR (125 MHz, DMSO) $\delta$ 158.0, 152.6, 146.4, 141.3, 130.7, 127.8, 125.7, 124.3, 123.2, 117.1, 113.4, 112.6, 105.5, 100.6, 55.5. HRMS (ESI): m/z [M-H]$^-$ calcd for C$_{16}$H$_{11}$NO$_3$: 264.0666; found: 264.0663.
7,9-dimethylchromeno[4,3-b]indol-6(11H)-one (4c).

Yellow solid, 45.9 mg, 86%. mp >300 °C. ¹H NMR (300 MHz, DMSO) δ 12.82 (s, 1H), 8.19 (d, J = 7.8 Hz, 1H), 7.62-7.41 (m, 3H), 7.23 (s, 1H), 6.89 (s, 1H), 2.90 (s, 3H), 2.42 (s, 3H). ¹³C NMR (125 MHz, DMSO) δ 157.7, 152.4, 141.6, 138.7, 134.5, 131.3, 130.4, 125.8, 124.0, 122.4, 121.5, 116.7, 113.0, 109.6, 100.6, 21.6, 21.1. HRMS (ESI): m/z [M-H]⁻ calcd for C₁₇H₁₃NO₂: 262.0874; found: 262.0868.

8-fluorochromeno[4,3-b]indol-6(11H)-one (4d).

Light yellow solid, 32.0 mg, 63%. mp >300 °C. ¹H NMR (300 MHz, DMSO) δ 13.13 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 7.71-7.62 (m, 1H), 7.55-7.46 (m, 2H), 7.28 (dd, J = 9.3, 9.2, 3.0 Hz, 1H). ¹³C NMR (125 MHz, DMSO) δ 158.5 (d, J₇CF = 235.0 Hz), 157.7, 152.8, 143.1, 154.5, 142.6, 137.6, 131.1, 125.0 (d, J₇CF = 11.3 Hz), 124.4, 122.8, 117.3, 113.8 (d, J₇CF = 10.0 Hz), 113.0, 112.8 (d, J₇CF = 25.0 Hz), 105.2 (d, J₇CF = 25.0 Hz), 100.1 (d, J₇CF = 3.8 Hz). HRMS (ESI): m/z [M-H]⁻ calcd for C₁₅H₈FNO₂: 252.0466; found: 252.0459.

3-methoxychromeno[4,3-b]indol-6(11H)-one (4e).

Light yellow solid, 45.9 mg, 87%. mp >300 °C. ¹H NMR (300 MHz, DMSO) δ 12.83 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.40-7.28 (m, 2H), 7.11-7.07 (m, 2H), 3.88 (s, 3H). ¹³C NMR (125 MHz, DMSO) δ 161.6, 158.0, 154.5, 142.6, 137.6, 124.5, 124.3, 123.7, 122.2, 119.9, 112.24, 112.20, 106.2, 101.6, 98.1, 55.8.


To a round bottom flask equipped with a magnetic stir bar and a reflux condenser was added the 4-hydroxy-7-methoxy-2H-chromen-2-one (2.0 mmol) and toluene (8 mL). The reaction mixture was heated at 120 °C for 10 min and then Bu₄NBr (3.0 equiv) was added in 2 portions over 5 min. The reaction mixture was stirred vigorously for 10 min until the starting material completely dissolved. P₂O₅ (4.8 mmol) was then added in 2 portions over 10 min and the reaction was heated for 1.5 h. The reaction mixture was cooled to 23 °C and quenched with a saturated aqueous NaHCO₃ solution. The reaction mixture was treated with toluene (3 x 10 mL). The organic layer was then dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give 4-bromo-7-methoxy-2H-chromen-2-one as a light yellow solid (65%). ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.81 (s, 1H), 6.68 (s, 1H), 3.90 (s, 3H).
A solution of 4-bromo-7-methoxy-2H-chromen-2-one (1.5 mmol), 3-methoxyphenol (1.5 mmol) and K$_2$CO$_3$ (3.0 mmol) in acetonitrile (3 mL) was stirred at 90 °C for 1 h. The reaction was allowed to cool to ambient temperature. After quenching the reaction by addition of water (2 ml), white precipitates formed immediately. Filtration of the mixture afforded the precipitates as crude product which was then purified by column chromatography on silica gel to yield product 1u as a white solid (97%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.90 (d, $J$ = 8.8 Hz, 1H), 7.36 (dd, $J$ = 8.1, 8.1 Hz, 1H), 6.93-6.85 (m, 3H), 6.77-6.70 (m, 2H), 5.33 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H).

2u$^{[5]}$ was synthesized from 1u following the general procedure for coumestans as a white solid (94%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.94 (d, $J$ = 8.5 Hz, 1H), 7.85 (d, $J$ = 9.3 Hz, 1H), 7.15 (s, 1H), 7.03 (d, $J$ = 8.5 Hz, 1H), 6.97-6.95 (m, 2H), 3.90 (s, 6H).

3,9-dimethoxy-6H-benzofuro[3,2-c]chromen-6-one (2u) (59.2 mg, 0.2 mmol) was dissolved in 2 mL of dry CH$_2$Cl$_2$, and the solution was cooled to 0 °C. A solution of BBr$_3$ in CH$_2$Cl$_2$ (1.0 M, 0.6 mL) was added via syringe. The reaction mixture was allowed to attain room temperature overnight. The reaction mixture was monitored by TLC using (DCM/MeOH = 20/1) as the mobile phase. Then hydrolyzed by ice water and filtered to give coumestrol. Light yellow solid, 96%, mp >300 °C. $^1$H NMR (300 MHz, DMSO) δ 10.70 (s, 1H), 10.03 (s, 1H), 7.86 (d, $J$ = 8.3 Hz, 1H), 7.17 (s, 1H), 6.95-6.91 (m, 3H).

7. Synthesis of flemichapparin C$^{[2b]}$ and 5$^{[9]}$

A solution of 4-bromo-7-methoxy-2H-chromen-2-one (1.5 mmol), benzo[d][1,3]dioxol-5-ol (1.5 mmol) and K$_2$CO$_3$ (3.0 mmol) in acetonitrile (3 mL) was stirred at reflux for 1 h. The reaction was allowed to cool to ambient temperature. After quenching the reaction by addition of water (2 ml),
white precipitates formed immediately. Filtration of the mixture afforded the precipitates as crude product which was then purified by column chromatography on silica gel to yield product 1v as a white solid (91%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.87 (d, J = 8.8 \text{ Hz}, 1\text{H}), 6.92-6.83 (m, 3\text{H}), 6.65-6.60 (m, 2\text{H}), 6.05 (s, 2\text{H}), 5.32 (s, 1\text{H}), 3.90 (s, 3\text{H}).\)

Flemichapparin C was synthesized from 1v following the general procedure for coumestans. White solid, 92%, mp 270-272 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.84 (d, J = 9.4 \text{ Hz}, 1\text{H}), 7.46 (s, 1\text{H}), 7.11 (s, 1\text{H}), 6.98-6.95 (m, 2\text{H}), 6.07 (s, 2\text{H}), 3.91 (s, 3\text{H}).\)

Compound 5 was synthesized following the procedure of synthesizing coumestrol from 2u. Light yellow solid, 96%. \(^1\)H NMR (300 MHz, DMSO) \(\delta 10.64 (s, 1\text{H}), 9.49 (s, 1\text{H}), 9.41 (s, 1\text{H}), 7.83 (d, J = 8.3 \text{ Hz}, 1\text{H}), 7.24 (s, 1\text{H}), 7.18 (s, 1\text{H}), 6.93-6.90 (m, 2\text{H}).\)

8. H/D exchange experimental study

4-(3,5-dimethylphenoxy)-5,7-dimethyl-2\(^H\)-chromen-2-one (1o) (0.1 mmol), Pd(OAc)\(_2\) (10 mol%), AgOAc (2 equiv) and CsOAc (2 equiv) were combined in PivOH (0.5 mL). Subsequently, D\(_2\)O (2 mmol, 20 equiv) was added and the reaction mixture was heated to 100 °C for specified time (1.5 h or 4.5 h). Then the reaction mixture was diluted with CH\(_2\)Cl\(_2\) and the excess NaHCO\(_3\) (aq.) was added to neutralize PivOH. After stirring the mixture for 10 min, the residue was washed with...
aqueous NaHCO₃ and the isolated organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using CH₂Cl₂/PE as the eluent to give product 2o. The starting material 1o was recovered and subjected to ¹H NMR analysis.

(a) Without D₂O

(b) 1.5 h

(c) 4.5 h
9. Copies of $^1$H NMR and $^{13}$C NMR spectra

$6H$-benzofuro[3,2-c]chromen-6-one (2a)
10-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2b)
10-methyl-6H-benzo[3,2-c]chromen-6-one (2c)
8,10-difluoro-6H-benzofuro[3,2-c]chromen-6-one (2d)

8,10-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2e)
7,9-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2f)
9-methyl-6H-benzofuro[3,2-c]chromen-6-one (2g)
9-methoxy-6H-benzofuro[3,2-c]chromen-6-one (2h)

9-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2i)
7-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2j)
8-(trifluoromethyl)-6H-benzofuro[3,2-c]chromen-6-one (2k)
8-methyl-6H-benzofuro[3,2-c]chromen-6-one (2l)
6H-naphtho[2',1':4,5]furo[3,2-c]chromen-6-one (2m)
1,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2n)
1,3,7,9-tetramethyl-6H-benzofuro[3,2-c]chromen-6-one (2o)
2-methyl-6H-benzofuro[3,2-c]chromen-6-one(2p)
2-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2q)
2,4-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (2r)
3-methoxy-6H-benzofuro[3,2-c]chromen-6-one (2s)
3-fluoro-6H-benzofuro[3,2-c]chromen-6-one (2t)
3,9-dimethoxy-6H-benzofuro[3,2-c]chromen-6-one (2u)

![Chemical Structure]

10-methoxychromeno[4,3-b]indol-6(11H)-one (4b) (in DMSO-d)

![Chemical Structure]
7,9-dimethylchromeno[4,3-b]indol-6(11H)-one (4c) (in DMSO-d$_6$)
8-fluorochromeno[4,3-b]indol-6(11H)-one (4d) (in DMSO-d)
3-methoxychromeno[4,3-b]indol-6(11H)-one (4e) (in DMSO-\textit{d})
3-methoxy-6H-[1,3]dioxolo[4',5':5,6]benzofuro[3,2-c]chromen-6-one (flemichapparin C)
3,9-dihydroxy-6H-benzofuro[3,2-c]chromen-6-one (coumestrol) (in DMSO-d)

3,8,9-trihydroxy-6H-benzofuro[3,2-c]chromen-6-one (5) (in DMSO-d)
Ref:


