Supporting Information

Synthesis of Flavokawain Analogues and their Anti-neoplastic Effects on Drug-resistant Cancer Cells Through Hsp90 Inhibition

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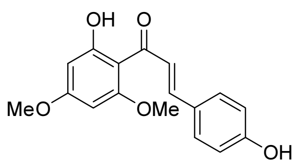
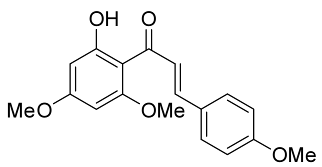
General Information of Synthesis

Unless otherwise noted, all reactions were performed under an argon atmosphere in oven-dried glassware. All purchased materials were used without further purification. Thin layer chromatography (TLC) was carried out using Merck silica gel 60 F_{254} plates. TLC plates were visualized using a combination of UV, *p*-anisaldehyde, ceric ammonium molybdate, ninhydrin, and potassium permanganate staining. NMR spectra were obtained on a Bruker 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), bd (broad doublet), dd (doublet of doublets), dt (doublet of triplets), or dq (doublet of quartets); the coupling constants are reported in hertz (Hz). Final products were purified by MPLC (Biotage Isolera One instrument) on a silica column (Biotage SNAP HP-Sil). On the basis of NMR and analytical HPLC data (Shimadzu prominence, VP-ODS C18 column), purity for all the tested compounds was found to be > 95%.



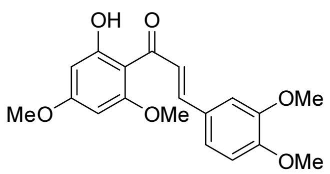
Compound **1b**

35% yield. R_f = 0.29 (3:7 ethyl acetate: hexane). ^{1}H NMR (400 MHz, Acetone) δ 7.91 (d, J = 15.2 Hz, 1H), 7.80 (d, J = 15.6 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.16 (d, J = 2.4 Hz, 1H), 6.12 (d, J = 2.0 Hz, 1H) 4.04 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 193.3, 166.6, 166.3, 162.9, 144.4, 131.7, 129.2, 124.8, 117.1, 107.3, 94.9, 92.1, 57.2, 56.07. ESI MS (m/e) = 301 $[M+1]^+$.



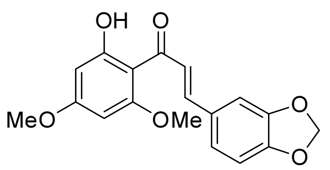
Compound **1c**

58% yield. R_f = 0.28 (2:8 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.41 (s, 1H), 7.79 (d, J = 1.2 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.10 (d, J = 2.0 Hz, 1H), 5.95 (d, J = 2.4 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 168.7, 166.3, 162.8, 161.7, 142.8, 130.4, 128.6, 125.4, 114.7, 106.6, 94.1, 91.5, 56.1, 55.9, 55.7. ESI MS (m/e) = 315 $[M+1]^+$.



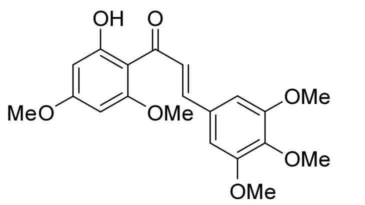
Compound **1d**

21% yield. R_f = 0.14 (2:8 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.41 (s, 1H), 7.80 (d, J = 15.6 Hz, 1H), 7.75 (d, J = 15.6 Hz, 1H), 7.21 (dd, J = 8.2 Hz, J = 2.0 Hz, 1H), 7.12 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.11 (d, J = 2.4 Hz, 1H), 5.96 (d, J = 2 .0 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 168.7, 166.4, 162.7, 151.4, 149.5, 143.0, 128.9, 125.8, 123.0, 111.5, 110.8, 106.7, 94.2, 91.6, 56.3, 56.2, 56.1, 55.9. ESI MS (m/e) = 345 $[M+1]^+$.



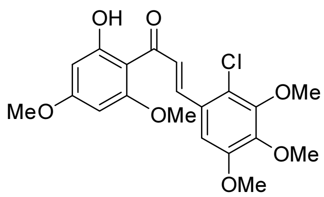
Compound **1e**

69% yield. R_f = 0.17 (1 : 9 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.39 (s, 1H), 7.73 (d, J = 2.8 Hz, 2H), 7.11-7.07 (m, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.09 (d, J = 2.4 Hz, 1H), 6.01 (s, 2H), 5.95 (d, J = 2.0 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 168.7, 166.4, 162.7, 149.9, 148.6, 142.7, 130.3, 125.8, 125.4, 108.9, 106.9, 106.6, 101.9, 94.1, 91.5, 56.2, 55.9. ESI MS (m/e) = 329 $[M+1]^+$.



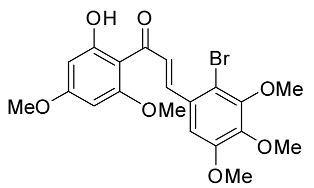
Compound **1f**

23.32% yield. R_f = 0.18 (2:8 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.32 (s, 1H), 7.80 (d, *J* = 15.6 Hz, 1H), 7.70 (d, *J* = 15.2 Hz, 1H), 6.84 (s, 2H), 6.11 (d, *J* = 2.4 Hz, 1H), 5.96 (d, *J* = 2.0 Hz, 1H), 3.91 (s, 6H), 3.91 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 168.8, 166.5, 162.7, 153.7, 142.8, 140.4, 131.5, 127.3, 106.6, 105.9, 94.2, 91.7, 61.4, 56.5, 56.2, 56.0. ESI MS (m/e) = 375 $[M+1]^+$.



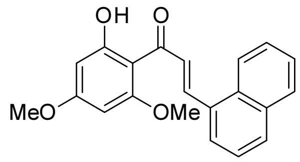
Compound **1g**

20% yield. R_f = 0.24 (2:8 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.25 (d, *J* = 0.4 Hz, 1H), 8.08 (d, *J* = 15.6 Hz, 1H), 7.77 (d, *J* = 15.6 Hz, 1H), 6.98 (s, 1H), 6.08 (d, *J* = 2.4 Hz, 1H), 5.92 (d, *J* = 2.0 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 168.8, 166.4, 162.7, 152.3, 150.5, 145.2, 138.4, 129.6, 129.5, 122.7, 106.5, 106.2, 94.1, 91.6, 61.6, 61.4, 56.4, 56.1, 55.9. ESI MS (m/e) = 409 $[M+1]^+$.



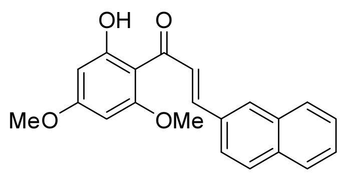
Compound **1h**

15% yield. R_f = 0.16 (2:8 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.24 (s, 1H), 8.08 (d, *J* = 15.2 Hz, 1H), 7.72 (d, *J* = 15.6 Hz, 1H), 7.01 (s, 1H), 6.09 (d, *J* = 2.4 Hz, 1H), 5.94 (d, *J* = 2.4 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 168.8, 166.7, 162.7, 153.0, 151.5, 145.0, 141.0, 131.4, 129.8, 113.7, 106.7, 106.6, 94.2, 91.6, 61.7, 61.3, 56.4, 56.1, 55.9. ESI MS (m/e) = 455 $[M+1]^+$.



Compound **1i**

32% yield. R_f = 0.27 (1:9 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.40 (s, 1H), 8.61 (d, *J* = 15.6 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 15.2 Hz, 1H), 7.90-7.87 (m, 2H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.60-7.49 (m, 3H), 6.13 (d, *J* = 2.0, 1H), 5.96 (d, *J* = 2.4 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 168.7, 166.6, 162.8, 139.3, 134.0, 133.2, 132.0, 130.6, 130.4, 129.0, 127.0, 126.4, 125.7, 125.4, 123.9, 106.6, 94.1, 91.5, 57.4, 56.1. ESI MS (m/e) = 335 $[M+1]^+$.



Compound **1j**

70% yield. R_f = 0.21 (1:9 ethyl acetate: hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.40 (s, 1H), 7.98 (t, *J* = 6.8 Hz, *J* = 5.2 Hz, 3H), 7.88-7.82 (m, 3H), 7.52-7.50 (m, 3H), 6.12 (d, *J* = 2.4 Hz, 1H), 5.97 (d, *J* = 2.4 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, Acetone) δ 193.4, 169.3, 167.7, 163.9, 143.2, 135.3, 134.6, 134.1, 131.4, 129.7, 129.6, 128.7, 128.2, 127.7, 124.8, 107.0, 94.8, 92.0, 56.7, 56.2. ESI MS (m/e) = 335 $[M+1]^+$.