

Supporting Information

Synthesis of Butein Analogues and their Anti-proliferative Activity Against Gefitinib-resistant Non-small Cell Lung Cancer (NSCLC) through Hsp90 Inhibition

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General and analytical data of compounds (5b-k and 1b-k)

Compound 5b. $R_f = 0.28$ (1:9 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.8$ Hz, 1H), 7.69 (d, $J = 15.6$ Hz, 1H), 7.61 (d, $J = 16.0$ Hz, 1H), 7.56-7.54 (m, 2H), 7.34-7.31 (m, 3H), 6.53 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H), 6.47 (d, $J = 2.0$ Hz, 1H), 6.06-5.96 (m, 2H), 5.44-5.37 (m, 2H), 5.29-5.22 (m, 2H), 4.55-4.51 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 189.61, 162.78, 159.03, 141.09, 135.01, 132.55, 132.23, 132.02, 129.56, 128.43, 127.91, 126.95, 122.02, 117.71, 117.59, 106.06, 99.81, 68.89, 68.55.

Compound 1b. 39% yield. $R_f = 0.24$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 13.41 (s, 1H), 7.88 (d, $J = 15.6$ Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.66-7.63 (m, 2H), 7.57 (d, $J = 15.2$ Hz, 1H), 7.44-7.42 (m, 3H), 6.47 (d, $J = 2.4$ Hz, 1H), 6.45 (s, 1H).

Compound 5c. $R_f = 0.15$ (1:9 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 15.6$ Hz, 1H), 7.48-7.44 (m, 3H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.50 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H), 6.44 (d, $J = 2.0$ Hz, 1H), 6.03-5.93 (m, 2H), 5.42-5.34 (m, 2H), 5.26-5.20 (m, 2H), 4.53-4.48 (m, 4H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 189.89, 162.74, 161.01, 159.05, 141.32, 132.59, 132.47, 132.28, 129.78, 127.84, 124.90, 122.46, 117.85, 117.63, 114.08, 106.16, 100.01, 69.04, 68.72, 55.09.

Compound 1c. 67% yield. $R_f = 0.14$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, DMSO) δ 13.56 (s, 1H), 10.71 (s, 1H), 8.20 (d, $J = 8.8$ Hz, 1H), 7.89-7.76 (m, 4H), 7.03 (d, $J = 8.8$ Hz, 2H), 6.42 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 6.29 (d, $J = 2.0$ Hz, 1H), 3.83 (s, 3H).

Compound 5d. $R_f = 0.28$ (3:7 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, $J = 8.4$ Hz, 1H), 7.61 (d, $J = 15.6$ Hz, 1H), 7.46 (d, $J = 15.6$ Hz, 1H), 7.11-7.07 (m, 2H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.51 (dd, $J = 8.6$ Hz, 2.4 Hz, 1H), 6.45 (d, $J = 2.4$ Hz, 1H), 6.06-5.94 (m, 2H), 5.44-5.35 (m, 2H), 5.27-5.19 (m, 2H), 4.56-4.51 (m, 4H), 3.85 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 189.67, 162.57, 158.82, 150.52, 148.69, 141.52, 132.48, 132.23, 132.12, 127.97, 124.85, 122.73, 122.23, 117.74, 117.35, 110.63, 109.24, 105.94, 99.84, 68.86, 68.57, 55.53, 55.40.

Compound 1d. 45% yield. $R_f = 0.27$ (2:3 ethyl acetate: hexane). ^1H NMR (400 MHz, DMSO) δ 13.61 (s, 1H), 10.71

(s, 1H), 8.24 (d, $J = 9.2$ Hz, 1H), 7.87 (d, $J = 15.2$ Hz, 1H), 7.78 (d, $J = 15.2$ Hz, 1H), 7.57 (s, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.44 (d, $J = 8.8$ Hz, 1H), 6.30 (d, $J = 2.4$ Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H).

Compound 5e. $R_f = 0.18$ (1:9 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, $J = 8.4$ Hz, 1H), 7.60 (d, $J = 15.6$ Hz, 1H), 7.43 (d, $J = 15.6$ Hz, 1H), 7.08-7.02 (m, 2H), 6.78 (d, $J = 8.0$ Hz, 1H), 6.55 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 6.07-5.98 (m, 2H), 5.97 (s, 2H), 5.47-5.38 (m, 2H), 5.32-5.26 (m, 2H), 4.59-4.55 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 190.23, 163.08, 159.37, 149.48, 148.35, 141.70, 132.96, 132.69, 132.53, 129.98, 125.56, 124.92, 122.74, 118.29, 118.16, 108.62, 106.66, 106.43, 101.59, 100.39, 69.43, 69.08.

Compound 1e. 69% yield. $R_f = 0.26$ (1:3 ethyl acetate: hexane). ^1H NMR (400 MHz, Acetone-d₆) δ 13.56 (s, 1H), 9.51 (s, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.74 (s, 2H), 7.43 (d, $J = 1.2$ Hz, 1H), 7.23 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.44 (dd, $J = 8.8$ Hz, 1.2 Hz, 1H), 6.35 (d, $J = 1.2$ Hz, 1H), 6.04 (s, 2H).

Compound 5f. $R_f = 0.18$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.4$ Hz, 1H), 7.60 (d, $J = 15.6$ Hz, 1H), 7.52 (d, $J = 15.6$ Hz, 1H), 6.81 (s, 2H), 6.56 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H), 6.50 (d, $J = 2.0$ Hz, 1H), 6.09-6.00 (m, 2H), 5.48-5.39 (m, 2H), 5.32-5.23 (m, 2H), 4.61-4.57 (m, 4H), 3.87 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 189.83, 162.95, 159.13, 153.19, 141.69, 139.70, 132.83, 132.40, 132.34, 130.80, 126.43, 122.34, 118.04, 117.64, 106.24, 105.27, 100.13, 69.16, 68.85, 60.79, 55.92.

Compound 1f. 13% yield. $R_f = 0.30$ (2:3 ethyl acetate: hexane). ^1H NMR (400 MHz, DMSO) δ 8.25 (d, $J = 8.8$ Hz, 1H), 7.93 (d, $J = 15.2$ Hz, 1H), 7.77 (d, $J = 15.6$ Hz, 1H), 7.25 (s, 2H), 6.46 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 6.32 (s, 1H), 3.87 (s, 6H), 3.72 (s, 3H).

Compound 5g. $R_f = 0.10$ (1:9 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, $J = 16.0$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.48 (d, $J = 15.6$ Hz, 1H), 6.99 (s, 1H), 6.56 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H), 6.49 (d, $J = 2.0$ Hz, 1H), 6.08-5.99 (m, 2H), 5.45-5.39 (m, 2H), 5.32-5.22 (m, 2H), 4.60-4.56 (m, 4H), 3.92 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 190.04, 163.25, 159.35, 152.09, 150.23, 144.92, 137.72, 133.12, 132.61, 132.58, 129.04, 128.81, 122.59, 122.39, 118.28, 117.91, 106.51,

105.56, 100.36, 69.42, 69.09, 61.31, 61.14, 56.18.

Compound 1g. 42% yield. $R_f = 0.10$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, MeOD) δ 8.14 (d, $J = 15.6$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 7.68 (d, $J = 15.2$ Hz, 1H), 7.28 (s, 1H), 6.38 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 6.27 (d, $J = 2.4$ Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 191.54, 166.29, 165.35, 152.47, 149.94, 145.27, 138.93, 132.39, 128.30, 122.18, 122.05, 113.27, 107.92, 106.08, 102.43, 60.25, 60.20, 55.51.

Compound 5i. $R_f = 0.47$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.58 (d, $J = 15.6$ Hz, 1H), 8.31 (d, $J = 8.4$ Hz, 1H), 7.88-7.70 (m, 5H), 7.58-7.46 (m, 3H), 6.61-6.44 (m, 2H), 6.10-6.01 (m, 2H), 5.46-5.24 (m, 4H), 4.61-4.56 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 190.26, 163.25, 159.53, 138.42, 133.78, 133.09, 132.77, 132.63, 132.47, 131.87, 130.28, 129.86, 128.73, 126.75, 126.17, 125.50, 124.99, 123.70, 122.59, 118.21, 106.50, 100.38, 69.48, 69.03

Compound 1i. 58% yield. $R_f = 0.22$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, DMSO) δ 8.98 (d, $J = 15.2$ Hz, 1H), 8.55 (d, $J = 8.4$ Hz, 1H), 8.23-8.16 (m, 4H), 8.00 (d, $J = 15.2$ Hz, 1H), 7.89-7.79 (m, 3H), 6.74 (dd, $J = 9.0$ Hz, 2.4 Hz, 1H), 6.69 (d, $J = 2.4$ Hz, 1H).

Compound 5j. $R_f = 0.28$ (1:9 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.96-7.72 (m, 8H), 7.50-7.47 (m, 2H), 6.58 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H), 6.52 (d, $J = 2.0$ Hz, 1H), 6.09-6.02 (m, 2H), 5.50-5.42 (m, 2H), 5.34-5.27 (m, 2H), 4.60-4.55 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 189.70, 162.84, 159.12, 141.30, 133.77, 133.06, 132.68,

132.65, 132.27, 132.08, 129.81, 128.18, 127.42, 127.25, 126.70, 126.26, 123.56, 122.17, 117.83, 117.73, 106.11, 99.93, 69.00, 68.63.

Compound 1j. 24% yield. $R_f = 0.25$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, DMSO) δ 13.01 (s, 1H), 10.33 (s, 1H), 7.91 (s, 1H), 7.83 (d, $J = 9.2$ Hz, 1H), 7.71-7.65 (m, 2H), 7.56-7.50 (m, 4H), 7.17-7.13 (m, 2H), 6.01 (dd, $J = 9.0$ Hz, 2.0 Hz, 1H), 5.87 (d, $J = 2.0$ Hz, 1H).

Compound 5k. $R_f = 0.20$ (1:9 ethyl acetate: hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, $J = 15.6$ Hz, 1H), 8.31-8.26 (m, 2H), 7.82 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 15.6$ Hz, 1H), 7.59-7.55 (m, 1H), 7.52-7.48 (m, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.58 (dd, $J = 8.6$ Hz, 2.4 Hz, 1H), 6.51 (d, $J = 2.4$ Hz, 1H), 6.08-6.00 (m, 2H), 5.47-5.40 (m, 2H), 5.33-5.23 (m, 2H), 4.60-4.54 (m, 4H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 190.38, 162.95, 159.28, 157.20, 138.63, 132.84, 132.76, 132.60, 132.46, 127.25, 127.23, 125.98, 125.50, 125.38, 124.76, 123.21, 122.73, 122.55, 118.05, 117.94, 106.34, 103.78, 100.28, 69.33, 68.90, 55.55.

Compound 1k. 10% yield. $R_f = 0.13$ (1:4 ethyl acetate: hexane). ^1H NMR (400 MHz, Acetone- d_6) δ 13.65 (s, 1H), 8.71 (d, $J = 15.2$ Hz, 1H), 8.34-8.31 (m, 2H), 8.21-8.16 (m, 2H), 7.92 (d, $J = 15.2$ Hz, 1H), 7.72-7.68 (m, 1H), 7.61-7.57 (m, 1H), 7.08 (d, $J = 8.0$ Hz, 1H), 6.52 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 6.43 (d, $J = 2.4$ Hz, 1H), 4.11 (s, 3H). ^{13}C NMR (100 MHz, Acetone- d_6) δ 191.80, 166.82, 140.18, 132.87, 132.56, 127.68, 126.96, 125.56, 124.04, 122.88, 122.50, 120.42, 113.63, 107.96, 104.28, 102.92, 55.45.