Supporting Information: Synthesis and Evaluation of Antiproliferative Microtubule-Destabilising Combretastatin A-4 Piperazine Conjugates. *Organic & Biomolecular Chemistry 2019.*

Supporting Information

Synthesis and Evaluation of Antiproliferative Microtubule-Destabilising Combretastatin A-4 Piperazine Conjugates

Niamh M. O'Boyle,[1,2†] Gloria Ana,[1†] Patrick M. Kelly,[1] Seema M. Nathwani,[2] Sara Noorani,[1] Darren Fayne,[2] Sandra Bright,[2] Brendan Twamley,[3] Daniela M. Zisterer,[2] and Mary J. Meegan[1]

[1]School of Pharmacy and Pharmaceutical Sciences, Trinity Biomedical Sciences Institute, Trinity College Dublin, 152−160 Pearse Street, Dublin 2 D02 R590, Ireland

[2]School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, 152−160 Pearse Street, Dublin 2 D02 R590, Ireland

[3]School of Chemistry, Trinity College Dublin, Dublin 2, Ireland

Contents

Experimental Procedure for Stability Study of Compounds 4l and 4n

Analytical high-performance liquid chromatography (HPLC) stability studies were performed using a Symmetry® column (C18, 5 µm, 4.6 × 150 mm), a Waters 2487 Dual Wavelength Absorbance detector, a Waters 1525 binary HPLC pump and a Waters 717 plus Autosampler (Waters Corporation, Milford, MA, USA). Samples were detected at wavelength of 254 nm. All samples were analysed using acetonitrile (60%): water (40%) as the mobile phase over 10 min and a flow rate of 1 mL/min. Stock solutions were prepared by dissolving 5 mg of either compound **4l** and **4n** in 10 mL of mobile phase. Phosphate buffers at the desired pH values (4, 7.4 and 9) were prepared in accordance with the British Pharmacopoeia monographs 2015. Stock solution (30 µL) was diluted with buffer of the appropriate pH (1 mL), shaken and injected immediately. Samples were withdrawn and analysed at time intervals of every 30 min for the first 3 hours and then every hour to 24 h.

Experimental Characterisation for Acrylic Acids 3b – 3g

(*E*)-3-(3-Fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acrylic acid (3b)[1] was synthesised from 3-fluoro-4-methoxybenzaldehyde and 3,4,5-trimethoxyphenylacetic acid by general methods IA and IB as fine yellow solid (IA: 0.47 g, 43%; IB: 0.71 g, 65%). MP: 203-205 °C. IR: ν_{max} (KBr) cm^{-1}: 3448, 2998, 2942, 2626, 1667, 1616, 1516, 1506, 1414, 1278, 1257, 1129, 1024, 1003, 924, 818, 772; ^{1}H NMR (DMSO-d_6) δ 12.65 (br s, 1H), 7.67 (s, 1H), 7.09 (t, 1H, *J* =9 Hz), 7.00 (d, 1H, *J* =7 Hz), 6.83 (dd, 1H, *J* =2 Hz), 6.47 (s, 2H), 3.81 (s, 3H), 3.72 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 56.4, 60.6, 65.4, 106.9, 113.9, 117.3, 117.5, 127.8, 128.3, 132.3, 132.4, 148.3, 153.8, 168.7; HRMS (EI): Found 363.1144 $(M+H)^+$, $C_{19}H_{20}O_6F$ requires 363.1166.

(*E*)-3-(3-Hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acrylic acid (3c)[2] was synthesised from 3-hydroxy-4-methoxybenzaldehyde and 3,4,5-trimethoxyphenylacetic acid by general methods IA and IB as a fine yellow solid (IA: 0.55 g, 51%; 0.69 g, IB: 64%). MP: 237-239 °C. IR: ν_{max} (KBr) cm^{-1}: 3423 (w), 2939, 1671, 1585, 1509, 1455, 1411, 1268, 1239, 1126; ^{1}H NMR (DMSO-d_6) δ 12.45 (br s, 1H), 8.98 (br s, 1H), 7.57(s, 1H), 6.81 (d, 1H, *J* = 8.5 Hz), 6.60 (d, 1H, *J* = 8.5 Hz), 6.53 (s, 1H), 6.44 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 55.4, 55.9, 60.1, 106.6, 111.5, 117.2, 122.9, 127.0, 130.3, 132.2, 136.9, 139.1, 145.8, 148.9, 153.1, 168.61; HRMS (EI): Found 383.1103 $(M+Na)^+$, $C_{19}H_{20}O_7Na$ requires 383.1107.

***(E)*-3-(4-Methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl)acrylic acid (3d)** was synthesised from 3,4,5-trimethoxyphenylacetic acid and 4-methoxy-3-nitro-benzaldehyde by general method IB as a yellow solid (0.42 g, 36%). MP: 224 – 226 °C. IR: V_{max} (KBr) cm^{-1}: 3318-2994, 1661; ^{1}H NMR (DMSO-d_6) δ 3.65 (s, 6H) 3.67 (s, 3H) 3.85 (s, 3H) 6.45 (s, 2H) 7.22 (s, 1H) 7.38 (dd, *J* =9.12, 2.49 Hz, 1H) 7.51 (d, *J* =2.07 Hz, 1H) 7.68 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 56.1, 56.9, 60.1, 106.5, 114.3, 126.5, 119.0, 126.5, 126.8, 131.3, 136.1, 137.4, 138.7, 152.3, 153.4, 167.9; HRMS (EI): Identified 412.1024 $(M + Na)^+$, $C_{19}H_{19}NO_8Na$, requires 412.0997.

(*E*)-3-(3-Methoxy-4-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)acrylic acid (3e) was synthesised from 4-hydroxy-3-methoxybenzaldehyde and 3,4,5-trimethoxyphenylacetic acid by general method IB as fine yellow needles (0.89 g, 83%); MP: 237-239 °C. IR: ν_{max} (KBr) cm^{-1}: 3423 (br), 2939, 1671, 1585, 1509, 1455, 1411, 1268, 1239, 1126; ^{1}H NMR (DMSO-d_6) δ 12.45 (br s, 1H), 8.98 (br s, 1H), 7.57(s, 1H),

[1] Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGrown, A. T., *J. Org. Chem.* **2001,** *66*, 8135.
[2] Cushman, M.; Nagarathnam, D.; Gopal, D.; He, H.; Lin, C. M.; Hamel, E., *J. Med. Chem.* **1992,** *35*, 2293-96.

6.81 (d, *J* = 7 Hz, 1H), 6.60 (d, *J* = 7 Hz, 1H), 6.53 (s, 1H), 6.44 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 168.6, 153.1, 148.9, 145.8, 139.1, 136.9, 132.2, 130.3, 127.0, 122.9, 117.2, 111.5, 106.7, 60.1, 55.9, 55.5; HRMS (EI): Found 383.1103 $(M+Na)^+$, $C_{19}H_{20}O_7Na$ requires 383.1107.

(*E*)-2-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid (3f)[3] was synthesised from 2-(4-methoxyphenyl)acetic acid and 3,4,5-trimethoxybenzaldehyde by general method IB as pale yellow crystals (0.63 g, 61%). MP: 206-208 °C. IR: ν_{max} (KBr) cm^{-1}: 2967, 2939, 2838, 1676, 1612, 1577, 1500, 1274, 1271, 1119, 1002, 917, 843, 790, 746; ^{1}H NMR ($CDCl_3$) δ 3.56 - 3.61 (m, 6H) 3.81 - 3.85 (m, 6H) 6.38 (s, 2H) 6.94 - 6.99 (m, 2H) 7.19 - 7.24 (m, 2H) 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.7, 60.9, 108.3, 114.3, 127.7, 129.6, 130.2, 131.2, 139.2, 142.2, 152.6, 159.4, 172.9; HRMS (EI): Found 343.1176 (M-H) $C_{19}H_{20}O_6$ requires 343.1181.

(*E*)-2-(3-Hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid (3g) was synthesised from 3-hydroxy-4-methoxyphenylacetic acid and 3-benzyloxy-4-methoxybenzaldehyde by general method IB as a pale yellow solid (0.17 g, 16%). MP: 204-207 °C. IR: ν_{max} (ATR) cm^{-1}: 3395, 2939, 2838, 1681, 1603, 1578, 1504, 1459, 1418, 1333, 1266, 1182, 1119, 1015, 997, 909, 838, 759, 744, 659, 638. ^{1}H NMR (DMSO-d_6) δ 3.50 (s, 6H), 3.62 (s, 3H), 3.77 (s, 3H), 6.47 (s, 2H), 6.58 - 6.59 (m, 1H), 6.60 (d, *J* =2.1 Hz, 1H), 6.96 (d, *J* =8.3 Hz, 1H), 7.61 (s, 1H), 9.03 (br s, 1H), 12.50 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.3, 55.8, 60.0, 108.0, 112.8, 116.7, 120.2, 129.0, 129.8, 132.2, 138.1, 138.6, 146.8, 147.2, 152.2, 168.5; HRMS (EI): Found 383.1110 $(M+Na)^+$; $C_{19}H_{20}NaO_7$ requires 383.1107.

Experimental Characterisation for Piperazine Conjugates 4b – 4l, 4n, 4o, 4r – 4v, 4y and 4z

(*E*)-3-(3-Fluoro-4-methoxyphenyl)-1-piperazin-1-yl-2-(3,4,5-trimethoxyphenyl)propenone (4b) was prepared from **3b** and piperazine by general method II. The crude product was purified *via* flash chromatography on silica gel (eluent, ethyl acetate: DCM 1:2) to afford the product as a white solid. (0.19 g, 32%); MP: 79-80 °C. IR: ν_{max} (KBr) cm^{-1}: 3058, 2836, 2934, 1598, 1580, 1439, 1412, 1276, 1236, 1126, 1006, 1150, 902, 931, 972; ^{1}H NMR (DMSO-d_6) δ 6.92 (s, 1H), 6.91 (s, 1H), 6.80 (t, *J* = 6.5 Hz, 1H), 6.58 (s, 1H), 6.53 (s, 2H), 3.87 (s, 6H), 3.73 (s, 6H), 3.71 (br s, 4H), 2.89 (br s, 4H); ^{13}C NMR (DMSO-d_6) δ 169.5, 153.1, 152.5, 150.0, 147.1, 137.7, 135.5, 129.8, 128.6, 127.2, 125.6, 125.6, 116.3, 116.2, 112.2, 105.3, 60.5, 55.7, 55.6; HRMS (EI): Found 431.1995 $(M+H)^+$, $C_{23}H_{28}FN_2O_5$ requires 431.1982.

***tert*-Butyl-(*E*)-4-(3-(4-methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl)piperazine-1-carboxylate (4c)** was prepared from **3d** and Boc-piperazine by general method III. The crude product

[3] Nguyen-Hai, N.; Ahn, B.-Z., Combretastatin-Chalcone Hybrids: Synthesis and Cytotoxicity. *Medicinal Chemistry* **2007,** *3* (4), 373-377.

was purified by column chromatography (eluent: ethyl acetate: hexane, 6:4) and used without further purification (0.68 g, 88%). IR: ν_{max} (ATR) cm^{-1}: 3410, 2944, 1616, 1579, 1528, 1436, 1412, 1240, 1122, 1088, 1001, 908, 775. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H) 3.25 (br s, 2H) 3.44 (br s, 4H) 3.63 (br s, 2H) 3.71 (s, 6H) 3.86 (s, 3H) 3.91 (s, 3H) 6.51 (s, 2H) 6.58 (s, 1H) 6.88 (d, *J* =9.1 Hz, 1H) 7.27 (d, *J* =2.1 Hz, 1H) 7.68 (d, *J* =2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.1, 154.4, 153.8, 152.3, 139.2, 138.6, 138.0, 134.9, 129.7, 127.6, 126.6, 113.1, 105.7, 80.4, 61.0, 56.6, 56.3, 28.3; HRMS (EI)**:** Found 580.2280 $(M+Na)^+$ $C_{28}H_{35}N_3O_9$ requires 580.2271.

(*E*)-3-(4-Methoxy-3-nitrophenyl)-1-(piperazin-1-yl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4d) was prepared from **4c** by general method IV as an yellow oil (0.16 g, 35%). IR: ν_{max} (ATR) cm^{-1}: 3413, 2945, 1617, 1579, 1527, 1507, 1413, 1356, 1276, 1243, 1156, 1121, 836, 820, 775, 683; ^{1}H NMR (DMSO-d_6) δ 2.58 (br s, 2H), 2.64 (dd, *J* =3.7, 2.1 Hz, 2H), 3.42 - 3.47 (m, 4H), 3.63 (s, 6H), 3.66 (s, 3H), 3.86 (s, 3H), 6.53 (s, 2H), 6.59 (s, 1H), 7.23 (d, *J* =9.1 Hz, 1H), 7.38 (dd, *J* =9.1, 2.1 Hz, 1H), 7.65 (d, *J* =2.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 43.4, 54.9, 55.9, 56.8, 60.1, 105.61, 114.01, 125.4, 127.6, 130.5, 134.9, 137.3, 137.6, 138.7, 151.3, 153.2, 168.2; HRMS (EI): Found 458.1938 $(M+H)^+$; $C_{23}H_{27}N_3O_7$ requires 458.1927.

(*E*)-1-(4-Acetylpiperazin-1-yl)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)propenone (4e) was prepared from **3a** and 1-acetyl-piperazine by general method II. The material was purified *via* flash chromatography over silica gel (eluent, ethyl acetate: DCM, 1:1) to afford the product as a brown resin (0.075 g, 12%). IR: ν_{max} (KBr) cm^{-1}: 3088, 2764, 2543, 1543, 9873, 974, 789, 876, 769. ^{1}H NMR (DMSO-d_6) δ 7.10 (s, 1H), 7.08 (s, 1H), 6.73 (s, 1H), 6.65 (s, 1H), 6.52 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.69 (s, 6H), 3.57 (br s, 8H), 2.08 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.1, 168.7, 159.0, 153.0, 137.4, 134.0, 130.5, 130.3, 130.1, 126.8, 113.1, 105.3, 60.5, 55., 54.77,7 45.5, 40.8, 20.9; HRMS (EI): Found 477.2005 $(M+Na)^+$, $C_{25}H_{30}N_2NaO_6$ requires 477.2002.

(*E*)-1-(4-Acetylpiperazin-1-yl)-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) propenone (4f) was prepared from **3c** and 1-acetylpiperazine by general method II. The material was purified *via* flash chromatography on silica gel (eluent ethyl acetate: DCM 1:2) to afford the product as a white solid (0.097 g, 15%); MP: 124-126 °C. IR: ν_{max} (KBr) cm^{-1}: 3243, 2645, 2345, 2534, 1534, 1534, 1635, 1436, 1325, 1298, 1154, 1098, 987, 983, 876, 854. ^{1}H NMR (DMSO-d_6) δ 6.75 (s, 1H), 6.63 (s, 2H), 6.56 (s, 1H), 6.51 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.66 (s, 6H), 3.52-3.42 (m, 8H), 2.04 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.2, 168.8, 152.9, 146.5, 144.9, 137.4, 134.1, 130.2, 130.1, 127.4, 121.4, 115.2, 109.9, 105.3, 60.4, 55.3, 53.3, 45.5, 40.7, 20.7; HRMS (EI):. Found 493.1933 $(M+Na)^+$, $C_{25}H_{30}N_2NaO_7$ requires 493.1951.

(*E*)-1-(4-Acetylpiperazin-1-yl)-3-(3-fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)propenone (4g) was prepared from **3b** and 1-acetylpiperazine by general method II. The material was purified *via* flash chromatography on silica gel to afford the product as a white solid (0.15 g, 23%); MP: 121-125°C. IR: ν_{max} (KBr) cm^{-1}: 2843, 3452, 2456, 2334, 1987, 1894, 1745, 1876, 1745, 1454, 1004, 957, 876, 764, 734, 908, 648. ^{1}H NMR (DMSO-d_6) δ 6.93 (s, 1H), 6.90 (s, 1H), 6.81 (m, 1H), 6.62 (s, 1H), 6.54 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.71 (s, 6H), 3.61-3.48 (m, 8H), 2.11 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.7, 168.7, 153.1, 147.0, 137.7, 135.5, 129.7, 127.4, 127.3, 125.6, 116.4, 116.2, 112.2, 105.3, 60.5, 55.7, 55.6, 20.9; HRMS (EI):. Found 495.1910 $(M+Na)^+$, $C_{25}H_{29}N_2FNaO_6$ requires 495.1907.

(*E*)-1-(4-Acetylpiperazin-1-yl)-3-(4-methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4h) was prepared from **3d** and 1-acetylpiperazine by general method III. The crude material was purified using flash column chromatography (eluent, DCM: Ethyl-Acetate, 1:1) to yield a brown resin which was used without further purification (0.007 g, 1%); IR: ν_{max} (KBr) cm^{-1}: 3388, 2969, 2845, 1736, 1614, 1579, 1528, 1453, 1412, 1280, 1237, 1169, 1122, 1005. ^{1}H NMR ($CDCl_3$) δ 1.12 (br s, 3H), 3.30 (br s, 3H), 3.38 (br s, 4H), 3.65 (s, 6H), 3.80 (s, 3H), 3.85 (s, 3H), 6.49 (s, 2H), 6.65 (s, 1H), 6.82 (d, *J* =8.7 Hz, 2H), 6.98 (d, *J* =9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 55.7, 55.9, 56.2, 60.8, 80.4, 106.1, 125.6, 128.4, 129.9, 130.3, 133.1, 138.1, 138.9, 151.8, 153.5, 168.5, 169.9.

(*E*)-3-(4-Methoxyphenyl)-1-[4-((*E*)-3-phenylallyl)-piperazin-1-yl]-2-(3,4,5-trimethoxyphenyl) propenone (4i) was prepared from **3a** and *trans*-1-cinnamylpiperazine by general method II. The material was purified *via* flash chromatography on silica gel (eluent, ethyl acetate: DCM 1:2) to afford the product as a brown resin (0.116 g, 16%); IR: ν_{max} (KBr) cm^{-1}: 2934, 2744, 2211, 1568, 1464, 1644, 1159, 1063, 1032, 955, 944, 932, 902, 863, 841, 832, 799; ^{1}H NMR (DMSO-d_6) δ 7.33 (m, 2H), 7.31 (t, 2H), 7.27 (m, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 6.5 Hz, 2H), 6.52 (s, 1H), 6.56 (s, 2H) 6.54 (d, *J* = 6.5 Hz, 1H), 6.24 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.71 (s, 6H), 3.79-3.61 (m, 4H), 3.17 (d, 2H), 2.53-2.37 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 169.8, 158.9, 152.9, 137.3, 134.3, 130.4, 129.8, 128.2, 127.5, 127.0, 126.0, 113.1, 105.4, 60.5, 60.2, 55.6, 54.8, 53.3, 52.2; HRMS (EI): Found 529.2684 $(M+H)^+$, $C_{32}H_{37}N_2O_5$ requires 529.2702.

(*E*)-3-(3-Fluoro-4-methoxyphenyl)-1-[4-((E)-3-phenylallyl)-piperazin-1-yl]-2-(3,4,5-trimethoxyphenyl)propenone (4j) was prepared from **3b** and *trans*-1-cinnamylpiperazine by general method II. The material was purified by flash chromatography on silica gel (eluent, ethyl acetate: DCM 1:2) to afford the product as a brown solid (0.143 g, 19%); MP: 126-129 °C. IR: ν_{max} (KBr) cm^{-1}: 3094, 2847, 1934, 1544, 1532, 1477, 1302, 1127, 1102, 1163, 1183, 944, 945, 857, 756, 621; ^{1}H NMR (DMSO-d_6) δ 7.37 (m, 2H), 7.32 (t, 2H), 7.26 (m, 1H), 6.93 (d, *J* = 7 Hz, 1H), 6.90 (s, 1H), 6.80 (s, 1H), 6.58 (s,

1H), 6.54 (s, 2H), 6.55-6.52 (m, 1H), 6.62-6.22 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.72 (s, 6H), 3.81-3.60 (m, 4H), 3.20 (d, *J* = 5 Hz, 2H), 2.56-2.38 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 169.4, 153.0, 152.4, 146.9, 146.4, 137.6, 135.9, 129.9, 128.3, 128.1, 127.6, 127.3, 125.9, 125.5, 116.4, 116.2, 112.2, 105.3, 60.5, 60.3, 55.7, 53.3, 52.4; HRMS (EI): Found 546.2544 $(M+H)^+$, $C_{32}H_{35}FN_2O_5$ requires 546.2530**.**

***(E)*-1-(4-Cinnamylpiperazin-1-yl)-3-(4-methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4k)** was synthesised from **3d** and *trans*-1-cinnamylpiperazine by general method II. The crude product was purified using flash chromatography over silica gel (eluent, DCM:EtOAc, 1:1, followed by 5% methanol in DCM:EtOAc, 1:1) to afford a dull yellow oil (0.30 g, 38%). ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.34 (d, *J* = 7.3 Hz, 2H), 7.31 – 7.25 (m, 5H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.62 (s, 1H), 6.55 (d, *J* = 9.1 Hz, 2H), 6.50 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.69 (s, 6H), 3.51 (s, 4H), 2.57-2.77 (br, 2H); ^{13}C NMR ($CDCl_3$) δ 169.4, 153.7, 152.3, 139.7, 139.2, 138.4, 137.6, 136.0, 135.1, 129.8, 128.6, 128.2, 127.6, 127.5, 126.5, 120.5, 113.1, 106.1, 105.7, 61.0, 60.3, 56.6, 56.2. (NCH_2).

(*E*)-3-(4-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-2-(3,4,5-trimethoxyphenyl)propenone (4l) was prepared from **3a** and 1-phenylpiperazine by general method II. The material was purified *via* flash chromatography on silica gel (eluent, ethyl acetate: DCM, 1:1) to afford the product as a brown solid (0.195 g, 29%); MP: 126-129 °C. IR: ν_{max} (KBr) cm^{-1}: 2833, 2432, 1704, 1873, 1789, 1647, 1528, 1384, 1267, 1301, 1145, 1038, 1022, 984, 604; ^{1}H NMR (DMSO-d_6) δ 7.34 (s, 2H), 7.22 (s, 2H), 7.04 (s, 2H), 6.93 (s, 2H), 6.83 (s, 1H), 6.63 (s, 1H), 6.50 (s, 2H), 3.90 (s, 6H), 3.87-3.82 (br s, 4H), 3.75 (s, 6H), 3.25-3.12 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 169.5, 153.1, 137.8, 129.8, 129.2, 127.5, 125.6, 116.4, 116.2, 112.2, 105.3, 60.6, 55.8, 33.4, 25.1; HRMS (EI): Found 511.2204 $(M+Na)^+$, $C_{29}H_{32}N_2NaO_5$ requires 511.2209.

(*E*)-3-(3-Fluoro-4-methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-2-(3,4,5-trimethoxyphenyl) propenone (4n) was prepared from **3b** and 1-phenylpiperazine by general method II. The material was purified by flash chromatography over silica gel (eluent, ethyl acetate: DCM 1:2) to afford the product as a brown resin (0.216 g, 31%), MP 112-115 °C; IR: ν_{max} (KBr) cm^{-1}: 2994, 2746, 2245, 1633, 1535, 1366, 1098, 1970, 1095, 948, 985, 901, 833, 823, 743, 618, 532; ^{1}H NMR (DMSO-d_6) δ 7.35 (s, 2H), 7.07 (s, 2H), 6.93 (s, 3H), 6.83 (s, 1H), 6.65 (s, 1H), 6.52 (s, 2H), 3.89 (s, 6H), 3.89-3.80 (m, 4H), 3.75 (s, 6H), 3.24-3.11 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 169.5, 153.1, 137.8, 129.8, 129.2, 127.5, 125.6, 116.4, 116.2, 112.2, 105.3, 60.6, 55.8, 33.4, 25.1; HRMS (EI):. Found 529.2109 $(M+Na)^+$, $C_{29}H_{31}FN_2NaO_5$ requires 529.2115.

(*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-2-(3,4,5-trimethoxyphenyl)propenone (4o) was prepared from **3e** and phenylpiperazine by general method II.

The material was purified by flash chromatography over silica gel (eluent, ethyl acetate: DCM 1:2) to afford the product as a brown solid (0.215 g, 31%), MP 79-98 °C; IR: ν_{max} (KBr) cm^{-1}: 3003, 2740, 2345, 2232, 2045, 1747, 1522, 1642, 1587, 1548, 1427, 1254, 1234, 1087, 839, 756, 665; ^{1}H NMR (DMSO-d_6) δ 7.29 (s, 2H), 7.07 (s, 1H), 6.91 (s, 3H), 6.74 (s, 2H), 6.65 (s, 1H), 6.51 (s, 2H), 3.90 (s, 12H), 3.89-3.80 (m, 4H), 3.24-3.11 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 168.7, 153.0, 146.1, 145.6, 137.8, 133.3, 128.9, 127.3, 127.2, 123.3, 123.3, 105.5, 102.5, 60.5, 55.7, 55.4, 40.5, 33.4; HRMS (EI): Found 527.2161 $(M+Na)^+$, $C_{29}H_{32}N_2NaO_6$ requires 527.2158.

(*E*)-1-(4-Benzylpiperazin-1-yl)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4r) was prepared from **3a** and benzylpiperazine by general method III. The crude product was purified by flash column chromatography (eluent, ethyl acetate: DCM, 1:1), as a pale yellow solid (0.035 g, 5%). IR: ν_{max} (KBr) cm^{-1} 2999, 2919, 2835, 2849, 2765, 1628, 1578, 1507, 1411, 1430, 1175, 1029, 999, 887, 825, 699, 671, 554; ^{1}H NMR ($CDCl_3$) δ 2.25 (d, *J* =7.88 Hz, 2H), 2.44 (br s, 2H), 3.48 (s, 2H), 3.52 (br s, 2H), 3.66 (s, 6H), 3.74 (s, 3H), 3.83 (s, 3H), 6.50 (s, 2H), 6.59 (s, 1H), 6.68 - 6.72 (m, 2H), 7.07 (d, *J* =8.71 Hz, 2H), 7.22 - 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 54.2, 55.0, 59.9, 61.8, 104.9, 112.5, 126.3, 126.6, 127.3, 128.1, 128.7, 129.8, 130.0, 134.1, 136.7, 152.3, 158.2, 169.2; HRMS (EI): Found 503.2541 $(M+H)^+$, $C_{30}H_{34}N_2O_5$ requires 503.2540.

(*E*)-1-(4-Benzylpiperazin-1-yl)-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4s) was prepared from **3c** and benzylpiperazine by general method III. The crude product was purified by flash column chromatography (eluent, ethyl acetate: DCM, 1:1) to afford a brown oil (0.20 g, 28%); IR: ν_{max} (KBr) cm^{-1}: 3388, 2962, 2936, 1723, 1653, 1577, 1411, 1259, 1236, 1118, 1006, 802, 770; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.31 (ddd, *J* = 8.9, 6.7, 1.9 Hz, 2H), 6.65 (s, 1H), 6.54 (dd, *J* = 13.3, 5.5 Hz, 3H), 6.46 (s, 12H), 6.14 (t, *J* = 6.7 Hz, 2H), 3.85 (s, 3H), 3.83 (d, *J* = 2.8 Hz, 3H), 3.81 (s, 2H), 3.53 (s, 6H), 2.83 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 175.2, 153.5, 145.1, 139.5, 138.2, 130.9, 129.1, 128.7, 127.8, 120.7, 115.4, 110.2, 106.0, 63.7, 60.9, 56.2, 56.1, 55.8, 51.5; HRMS (EI): Found 519.2507 $(M+H)^+$; $C_{30}H_{34}N_2O_6$ requires 519.2495.

***(E)-1*-(4-Benzylpiperazin-1-yl)-3-(3-fluoro-4-methoxy-phenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4t)** was synthesised from **3b** and 1-benzylpiperazine using general method II. The crude product was purified using flash column chromatography over silica gel (eluent, ethyl acetate: DCM 1:2) to afford a yellow oil (0.16 g, 22%). ^{1}H NMR ($CDCl_3$) δ 7.35 (d, *J* = 7.6 Hz, 3H,), 7.29 (d, *J* = 12.0 Hz, 2H), 6.94 – 6.88 (m, 2H), 6.80 (t, *J* = 8.7 Hz, 1H), 6.57 (s, 1H), 6.53 (s, 2H), 3.88 (d, *J* = 10.9 Hz, 6H), 3.72 (s, 6H), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 169.8, 153.5, 150.9, 147.4, 138.1, 136.4, 130.4, 129.3, 129.2,

128.7, 128.4, 128.2, 128.2, 125.9, 116.7, 112.7, 105.9, 62.7, 61.0, 56.2, 52.6; ^{19}F-NMR (376 MHz, $CDCl_3$) δ -135.38; LRMS (ESI): Found 521.3399 $(M+H)^+$; $C_{30}H_{34}FN_2O_5$ requires 521.2446.

(*E*)-1-(4-Benzylpiperazin-1-yl)-3-(4-methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4u) was prepared from **3d** and benzylpiperazine by general method III. The crude product was purified via flash column chromatography (eluent ethyl acetate: DCM 1:1) to afford a yellow resin (0.23 g, 31%); IR: ν_{max} (KBr) cm^{-1}: 2938, 2829, 1615, 1578, 1528, 1452, 1350, 1279, 1264, 1236, 1122, 999, 813, 734, 699, 667, 614. ^{1}H NMR ($CDCl_3$) δ 2.24 (br s, 2H), 2.43 (br s, 2H), 3.47 (br s, 2H), 3.66 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 6.46 (s, 2H), 6.53 (s, 1H), 6.84 (d, *J* =9.1 Hz, 1H), 7.22 (s, 2H), 7.24 (d, *J* =2.1 Hz, 2H), 7.26 (s, 3H), 7.64 (d, *J* =2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 169.2, 153.6, 152.2, 139.2, 138.4, 135.8, 134.9, 129.8, 129.2, 128.3, 127.0, 126.5, 113.0, 109.4, 105.7, 62.6, 61.0, 56.5, 56.2; HRMS (EI): Found 548.2375 $(M-H)^+$ $C_{30}H_{33}N_3O_7$ requires 548.2397.

(*E*)-3-(3-Amino-4-methoxyphenyl)-1-(4-benzylpiperazin-1-yl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4v): was prepared from **4u** by general method V and was obtained as a yellow oil (0.063 g, 32%); IR: ν_{max} (KBr) cm^{-1}: 3426, 3355, 3304, 3301, 2938, 2834, 1662, 1580, 1505, 1411, 1233, 1122, 998, 910, 726, 699; ^{1}H NMR ($CDCl_3$) δ 7.29 (d, *J* = 5.8 Hz, 5H), 6.60 (d, *J* = 2.3 Hz, 1H), 6.58 (s, 1H), 6.53 (s, 2H), 6.51 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.68 (s, 6H), 3.49 (s, 2H), 2.37 (d, *J* = 48.6 Hz, 8H); ^{13}C NMR ($CDCl_3$) δ 170.4, 153.2, 147.1, 137.7, 135.6, 134.6, 131.1, 130.2, 129.1, 128.3, 127.3, 120.4, 115.5, 109.8, 106.0, 62.7, 60.9, 56.1, 56.0, 55.7, 55.4; HRMS (EI): Found 518.2650 $(M+H)^+$; $C_{30}H_{36}N_3O_5$ requires 518.2649.

***tert*-Butyl-(*E*)-4-(3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl)-1,4-diazepane-1-carboxylate (4y)** was prepared from **3c** and BOC-homopiperazine by general method III. The crude product was purified by column chromatography (eluent, dichloromethane: ethyl acetate, 1:1) as a yellow solid and used without further purification (0.33 g, 44%); ^{1}H NMR ($CDCl_3$) δ 7.09 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.58 (s, 1H), 6.55 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.68 (s, 6H), 3.59 – 3.20 (m, 8H), 1.99 – 1.83 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.5, 159.2, 155.0, 153.3, 137.9, 130.8, 129.3, 127.5, 113.5, 105.9, 79.7, 60.9, 56.1, 55.2, 48.0, 46.8, 45.0, 28.7, 28.4; HRMS (EI): Found 527.1686 $(M+H)^+$, $C_{29}H_{38}N_2O_7$ requires 527.2757.

(*E*)-1-(1,4-Diazepan-1-yl)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4z) was prepared from **4y** by general method IV as a clear oil (0.168 g, 38%); IR: ν_{max} (KBr) cm^{-1}: 3430, 2993, 2939, 2835, 1604, 1577, 1506, 1452, 1414, 1122, 1022, 1008, 920, 904, 845, 832, 799; ^{1}H NMR ($CDCl_3$) δ 7.09 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.63 (s, 1H), 6.55 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.68 (s, 6H), 3.61 (s, 2H), 3.11 (s, 2H), 2.91 (d, *J* = 4.1 Hz, 3H), 2.77 (s, 2H), 1.87 (d, *J* = 4.9 Hz, 2H); ^{13}C

NMR ($CDCl_3$) δ 171.6, 159.3, 153.4, 137.9, 130.9, 129.8, 127.5, 126.7, 113.5, 105.9, 60.9, 56.1, 55.2, 47.6, 45.8, 28.6.; LRMS (EI): Found 427.24 $(M+H)^+$; $C_{24}H_{31}N_2O_5$ requires 427.22**.**

Experimental Characterisation for Piperazine Conjugates 5a – 5f

***tert*-Butyl (*E*)-4-(2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl)piperazine-1-carboxylate (5a)** was prepared from **3f** and BOC-piperazine by general method III. The crude product was purified *via* flash column chromatography (eluet, ethylacetate:DCM, 1:1) as a yellow oil (0.29 g, 41%). ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 3.20 (br s, 2H), 3.37 (br s, 2H), 3.48 (br s, 2H), 3.59 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 6.36 (s, 2H), 6.56 (s, 1H), 6.83 (d, *J* =8.7 Hz, 2H), 7.24 - 7.28 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 28.3, 55.3, 55.8, 60.9, 80.3, 106.6, 114.2, 127.6, 129.7, 130.2, 130.6, 136.2, 137.7, 152.7, 154.5, 159.3, 170.5. HRMS (EI): Found 513.2618 $(M+H)^+$ $C_{28}H_{36}N_2O_7$ requires 513.2602.

(*E*)-2-(4-Methoxyphenyl)-1-(piperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (5b) was prepared from **5a** by general method IV as a brown oil (0.29 g, 70%). IR: ν_{max} (KBr) cm^{-1}: 3368, 2935, 2835, 2470, 2248, 1692, 1614, 1598, 1579, 1504, 1459, 1234, 1122, 1003, 905, 798, 760, 694. ^{1}H NMR ($CDCl_3$) δ 2.79 (br s, 4H), 3.26 (br s, 4H), 3.61 (s, 6H), 3.79 (s, 3H), 3.81 (s, 3H), 6.38 (s, 2H), 6.57 (s, 1H), 6.83 - 6.88 (m, 2H), 7.24 - 7.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.4, 55.3, 55.7, 60.8, 106.6, 114.1, 127.7, 129.3, 130.2, 130.7, 136.3, 137.6, 152.7, 159.4, 170.4; HRMS (EI): Found 413.2090 $(M+H)^+$ $C_{23}H_{28}N_2O_5$ requires 413.2077.

(*E*)-2-(4-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (5c) was prepared from **3f** and benzylpiperazine by general method III. The product **6d** was obtained as white crystals (0.296 g, 44%) by flash column chromatography (eluent, ethyl acetate: DCM, 1:1); IR: ν_{max} (KBr) cm^{-1}: 3013, 2969,2993, 2843, 2819, 1614, 1604, 1597, 1453, 1244, 1126, 996, 834, 766. ^{1}H NMR ($CDCl_3$) δ 2.97 (br s, 2H), 3.13 (br s, 2H), 3.60 (s, 6H), 3.70 (br s, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 6.38 (s, 2H), 6.59 (s, 1H), 6.81 - 6.90 (m, 5H), 7.23 (s, 1H), 7.27 (br s, 1H), 7.28 (d, *J* =8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.8, 60.9, 106.6, 114.2, 116.6, 120.5, 127.8, 129.2, 129.6, 130.3, 136.3, 137.7, 150.9, 152.7, 159.4, 170.4; HRMS (EI): Found 489.2412 $(M+H)^+$ $C_{29}H_{32}N_2O_5$ requires 489.22390.

(*E*)-2-(3-Hydroxy-4-methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (5d) was prepared from **3g** and phenylpiperazine by general method III. The crude product was purified *via* flash column chromatography (eluent: ethyl acetate/DCM 1:1) as a yellow oil (0.153 g, 22%). IR: ν_{max} (ATR) cm^{-1}: 3115, 2937, 2840, 1619, 1583, 1528, 1503, 1461, 1332, 1275, 1263, 1235, 1120, 1014, 1087, 1065, 905, 818, 760, 730, 661; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.25 (s, 1H), 6.94 (d, *J*

= 2.1 Hz, 1H), 6.90 (s, 1H), 6.88 (s, 2H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 1H), 6.40 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.62 (s, 6H), 3.07 (d, *J* = 52.1 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 170.2, 152.7, 146.4, 146.0, 145.7, 141.9, 139.2, 130.5, 129.2, 128.7, 128.6, 121.5, 121.0, 116.1, 115.0, 110.8, 106.7, 60.8, 55.8, 55.6, 49.5; HRMS (EI): found 505.2360 $(M+H)^+$; $C_{29}H_{33}N_2O_6$ requires 505.2339.

***tert*-Butyl-(*E*)-4-(2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl)-1,4-diazepane-1-carboxylate (5e)** was prepared from **3f** and BOC-homopiperazine by general method III. The crude product was purified *via* flash column chromatography (eluent, ethyl acetate,DCM 1:1) as an off white solid (0.48 g, 66%). MP: 96-100 °C. **IR:** ν_{max} (ATR) cm^{-1}: 2944, 1677, 1611, 1578, 1526, 1504, 1412, 1350, 1237, 1115, 1009, 922, 877, 851, 827, 763, 554. ^{1}H NMR ($CDCl_3$) δ 1.41 - 1.49 (m, 9 H), 1.92 (br s, 2H), 3.24 - 3.34 (m, 2H), 3.47 - 3.60 (m, 4H), 3.62 (s, 6H), 3.80 (s, 3H), 3.82 (s, 3H), 6.36 - 6.43 (m, 2H), 6.55 (br s, 1H), 6.85 (d, *J* =8.3 Hz, 2H), 7.31 (d, *J* =7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 171.5, 159.4, 152.7, 137.6, 130.77, 130.2, 128.9, 124.8, 114.1, 106.6, 79.7, 60.8, 55.8, 55.2, 49.9, 47.9, 46.7, 44.9, 28.4, 26.5; HRMS (EI): Found 549.2559 $(M+Na)^+$; $C_{29}H_{38}N_2NaO_7$ requires 549.2557.

(*E*)-1-(1,4-Diazepan-1-yl)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (5f) was prepared from **5e** by general method IV as a yellow oil (0.269 g, 63%). **IR:** ν_{max} (ATR) cm^{-1}: 3413, 2937, 2836, 1603, 1579, 1506, 1417, 1328, 1371, 1288, 1240, 1174, 1120, 1002, 836, 771, 728; ^{1}H NMR ($CDCl_3$) δ 1.56 (br s, 1H), 1.82 (br s, 1H), 2.62 (br s, 2H), 2.75 (br s, 1H), 2.80 (br s, 1H), 3.48 - 3.54 (m, 2H), 3.56 (s, 6H), 3.64 (t, *J* =5.4 Hz, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 6.33 (s, 2H), 6.52 (s, 1H), 6.79 (d, *J* =8.7 Hz, 2H), 7.21 - 7.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 44.7, 47.7, 55.2, 55.7, 60.7, 106.4, 114.0, 127.5, 128.5, 130.1, 130.7, 137.0, 137.2, 152.6, 159.2, 171.4; HRMS (EI): Found 427.2217 $(M+H)^+$: $C_{24}H_{31}N_2O_5$ requires 427.2234.

Experimental Characterisation for Piperidine Conjugate 6a

(*E*)-3-(4-Methoxyphenyl)-1-(piperidin-1-yl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (6a) was prepared from 3a by general method III. The crude product was purified *via* flash column chromatography (eluent: DCM-ethyl acetate, 1:1). (0.126 g, 38%, yellow oil.). IR: ν_{max} (ATR) cm^{-1}: 2996, 2935, 2854, 2838, 1619, 1577, 1604, 1506, 1410, 1234, 1025, 1004, 996, 827, 852, 802, 716, 704. ^{1}H NMR ($CDCl_3$) δ 1.40 (br s, 2H), 1.64 (br s, 4H), 3.53 (br s, 2H), 3.56 - 3.68 (m, 2H), 3.71 (s, 6H), 3.77 (s, 3H), 3.87 (s, 3H), 6.57 (s, 2H), 6.59 (s, 1H), 6.71 - 6.77 (m, 2 H), 7.11 (m, *J* =8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 24.6 (3xCH_2), 55.2, 56.1, 60.9, 105.9, 113.5, 127.9, 128.8, 130.8, 131.25, 135.7, 137.7, 153.3, 159.2, 170.2. HRMS (EI): Found 412.2121 $(M+H)^+$; $C_{24}H_{30}NO_5$ requires 412.2124.

Experimental Characterisation for Piperazine Dimer 7

(2*E*,2'*E*)-1,1'-(Piperazine-1,4-diyl)bis(3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one) (7) was prepared from **3a** by general method III. The crude product was purified *via* flash column chromatography (eluent: DCM/ethyl acetate 1:1) to afford a pale yellow solid (0.397 g, 39%); IR: ν_{max} (ATR) cm^{-1}: 3002, 2833, 1607, 1576, 1509, 1459, 1428, 1293, 1239, 1177, 1121, 1032, 996, 920, 862, 823, 800, 726, 554; ^{1}H NMR ($CDCl_3$) δ 7.07 (d, *J* = 8.7 Hz, 4H), 6.71 (d, *J* = 8.8 Hz, 4H), 6.61 (s, 2H), 6.50 (s, 4H), 3.84 (s, 6H), 3.75 (s, 6H), 3.68 (s, 12H), 3.62 – 3.39 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 170.6, 159.5, 153.5, 137.9, 134.4, 130.9, 130.5, 127.3, 113.6, 105.9, 60.9, 56.7, 55.2; HRMS (EI): Found 739.3235 $(M+H)^+$; $C_{42}H_{47}N_2O_{10}$ requires 739.3231.

Figure S1. NMR data for compound 4m.

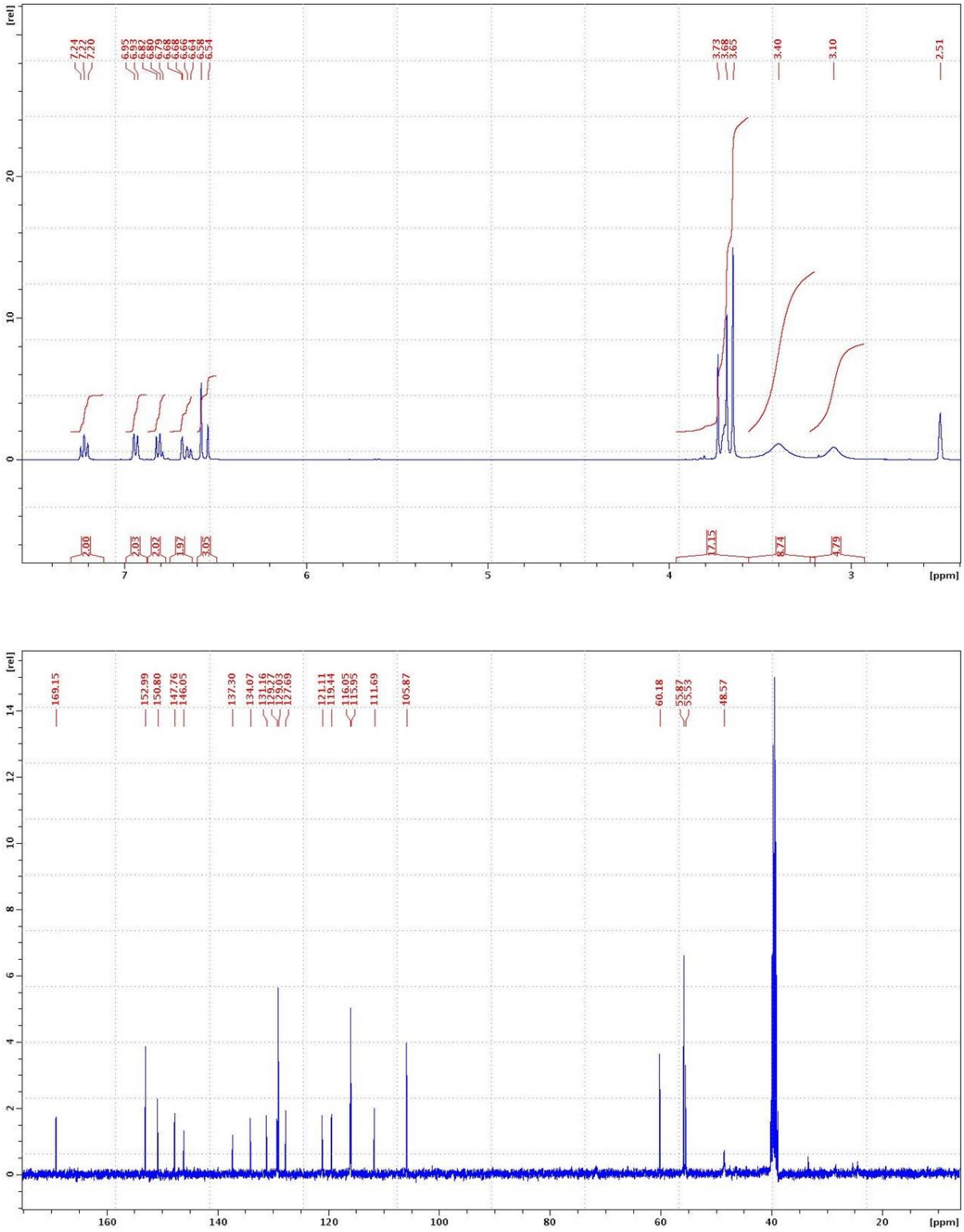
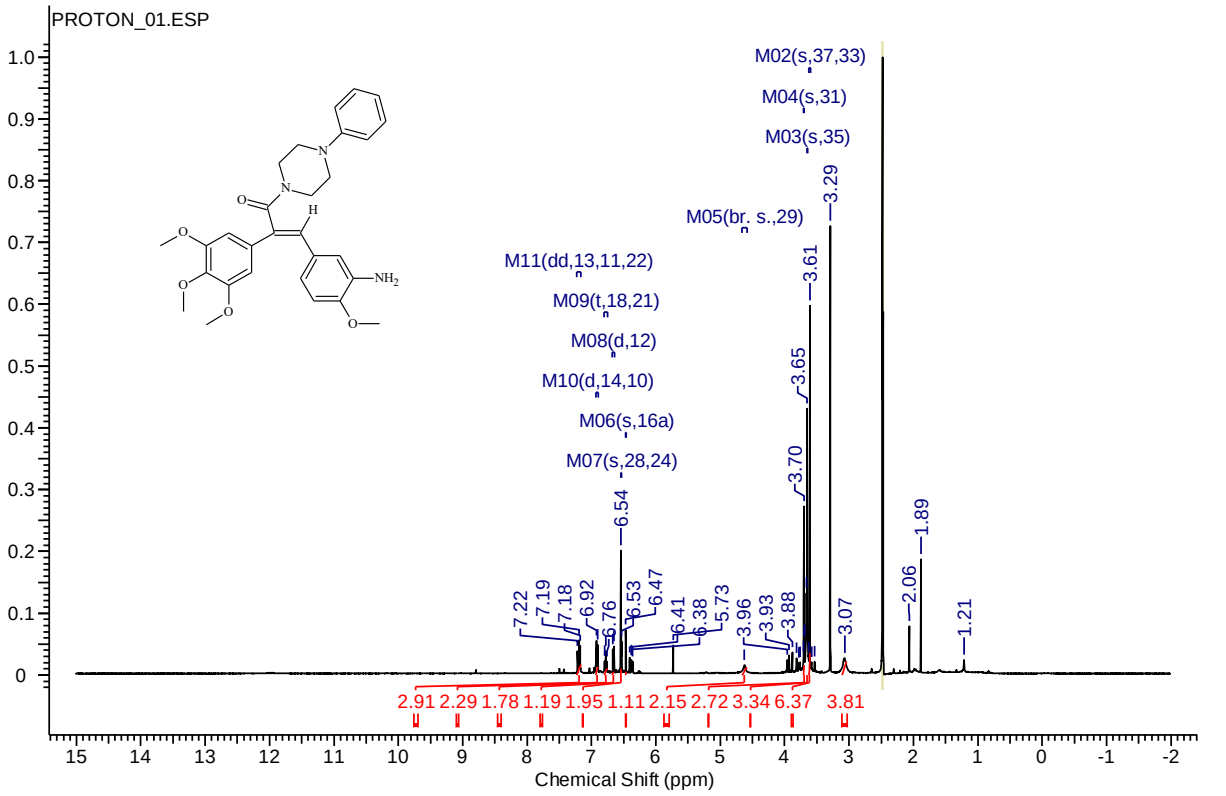


Figure S2. NMR data for compound 4q.

(*E*)-3-(3-Amino-4-methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**4q**)



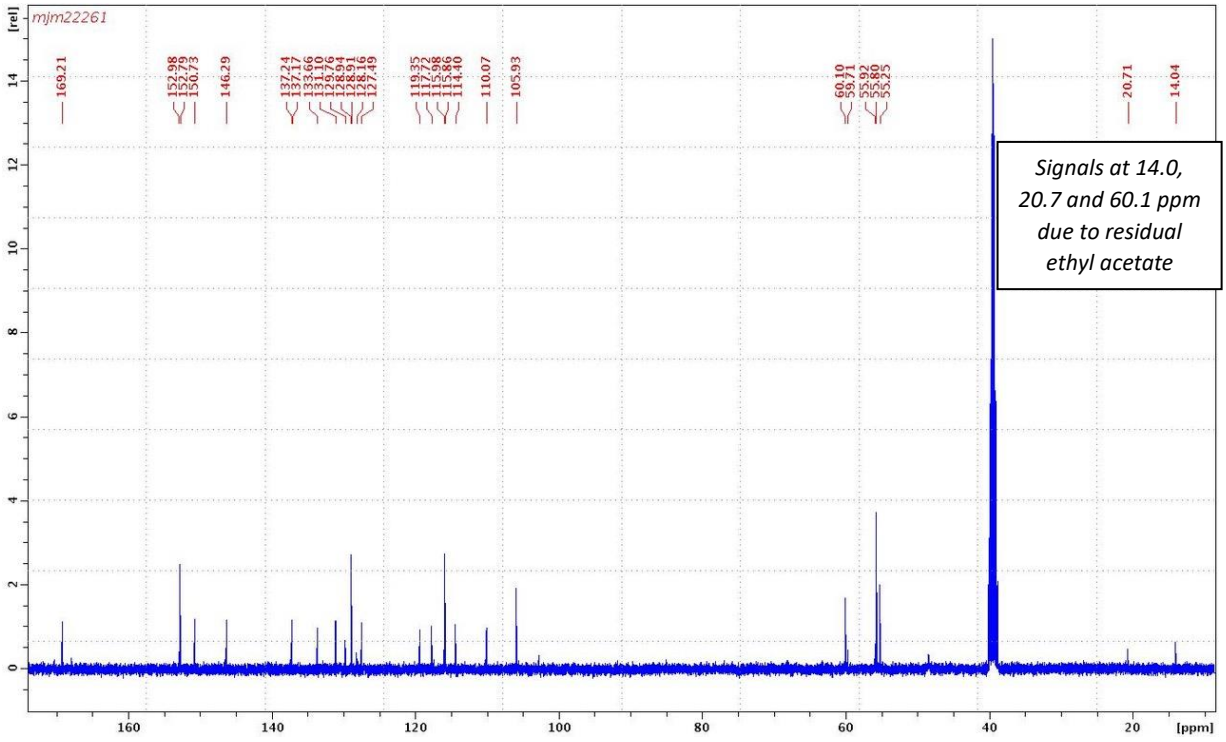
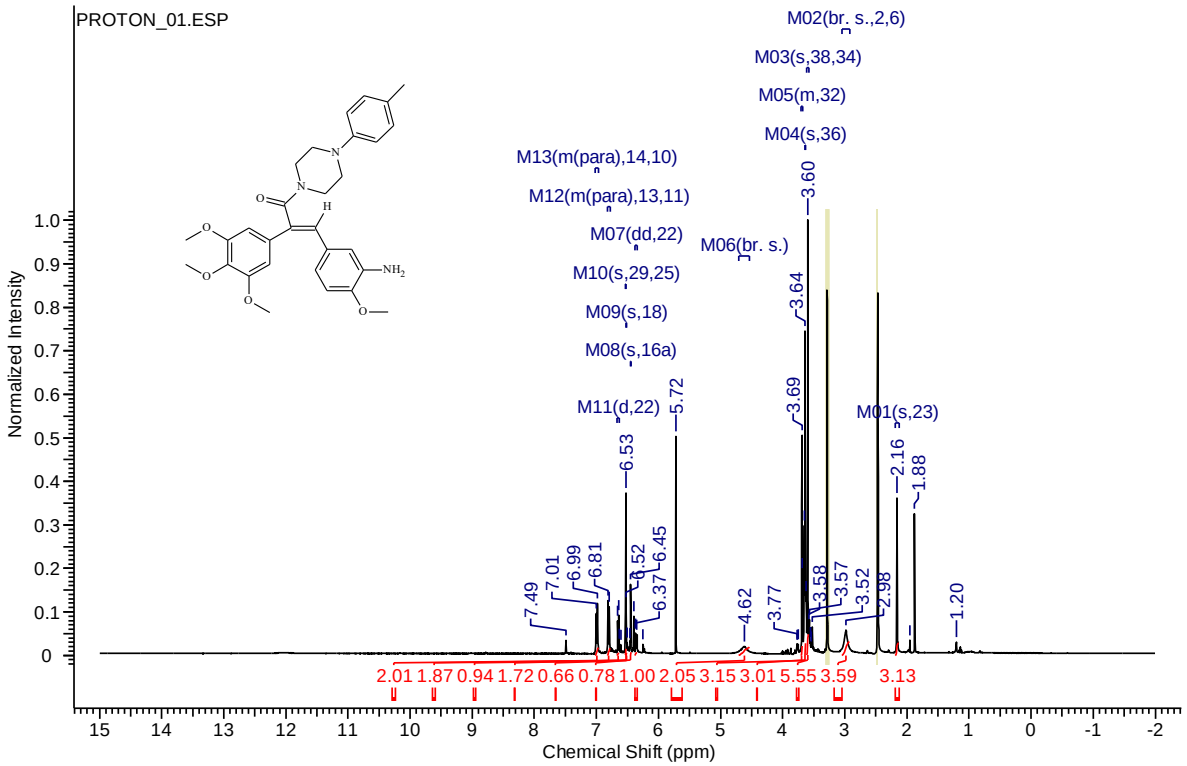


Figure S3. NMR data for compound 4x

(*E*)-3-(3-Amino-4-methoxyphenyl)-1-(4-(*p*-tolyl)piperazin-1-yl)-2-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **(4x)**



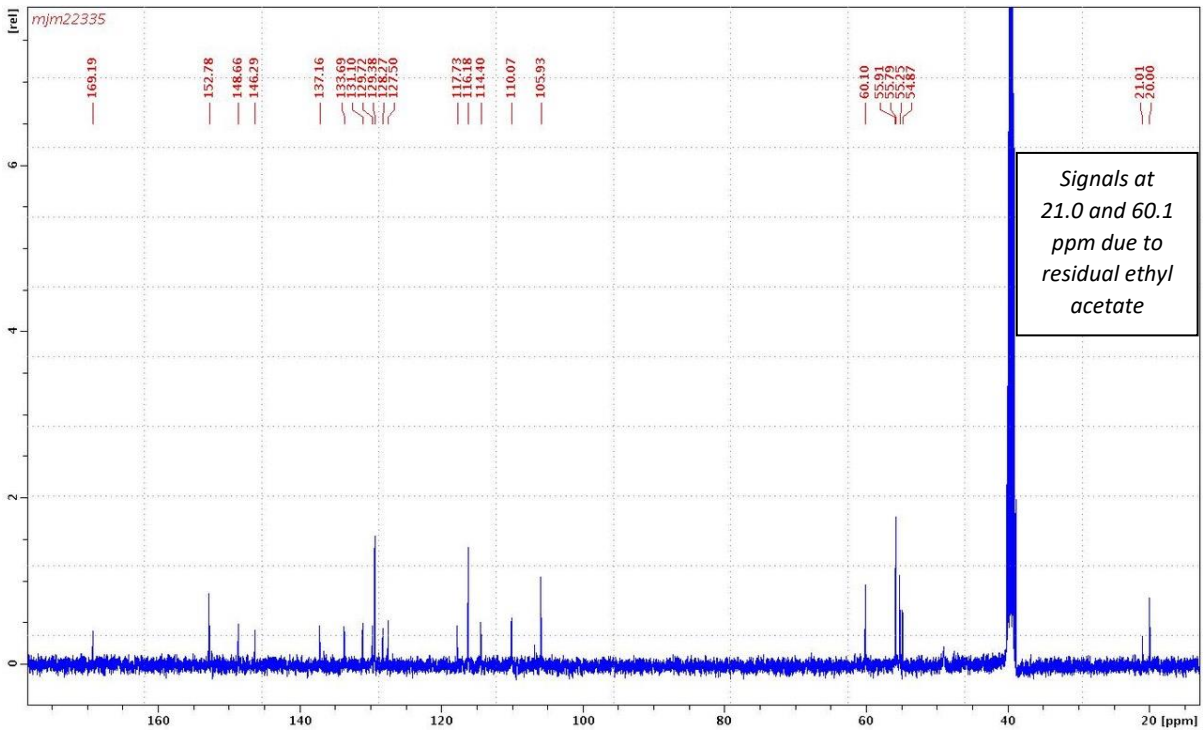
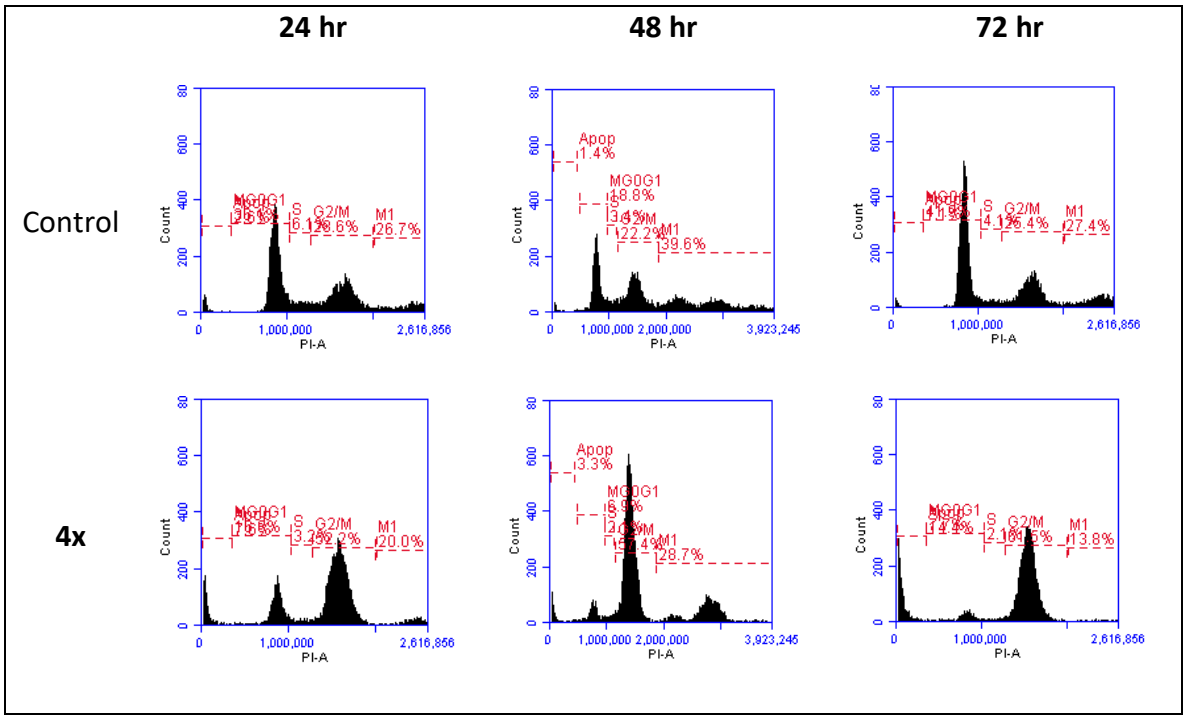


Figure S4. Representative Data from FACS Analysis of Vehicle-Treated and 4x-Treated MCF-7 Cells

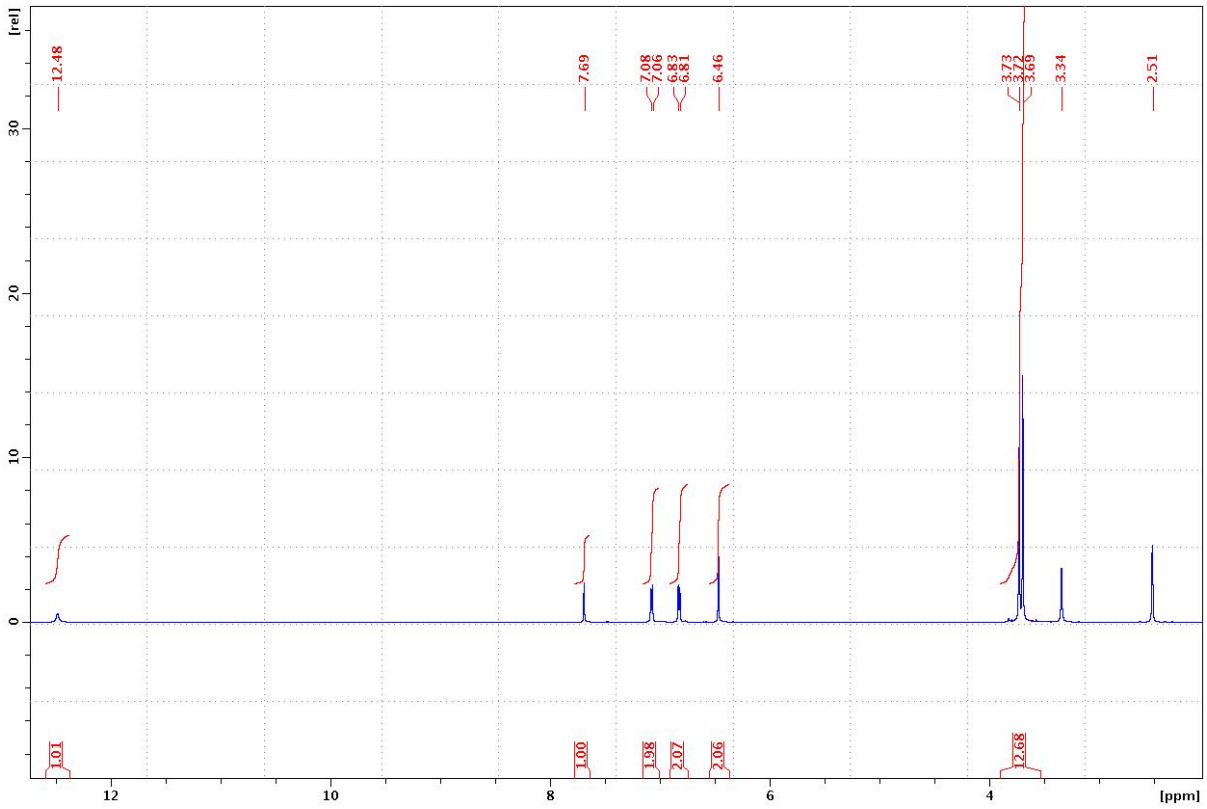


Effects of 4x on the cell cycle distribution of MCF-7 cells. MCF-7 cells were treated with either vehicle control (ethanol) or compound **4x** (1 µM) for 24, 48 hr or 72 hr. Cells were then fixed, stained with PI, and analysed by flow cytometry with CellQuest software.

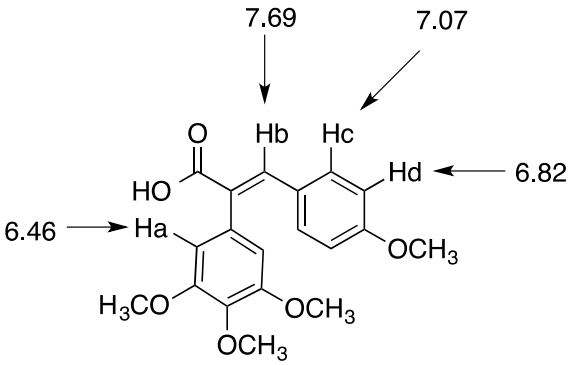
Figure S5. NMR NOE experimental data for acrylic acid 3a

^{1}H NMR (DMSO-d_6) δ 12.48 (br s, 1H), 7.69 (s, 1H), 7.07 (d, 2H, *J* =9 Hz), 6.82 (d, 2H, *J* =9 Hz), 6.46 (s, 2H), 3.72 (s, 6H), 3.69 (s, 6H)

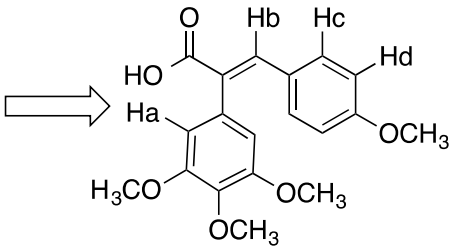
^{1}H NMR spectrum of compound **3a**:

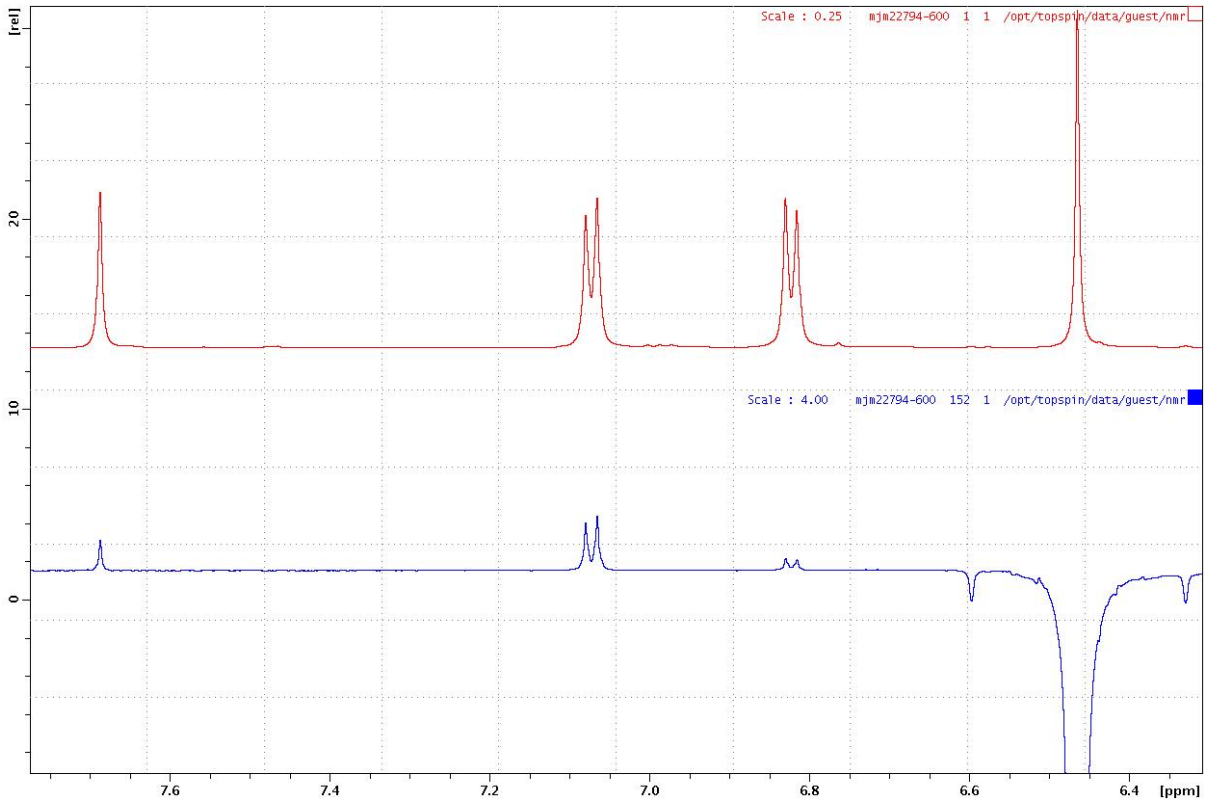


Protons irradiated in nOe experiments:

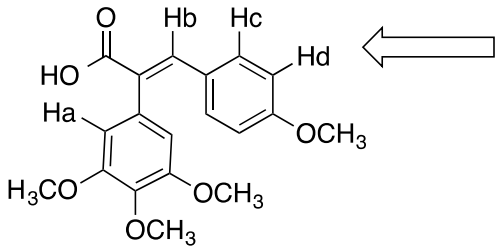


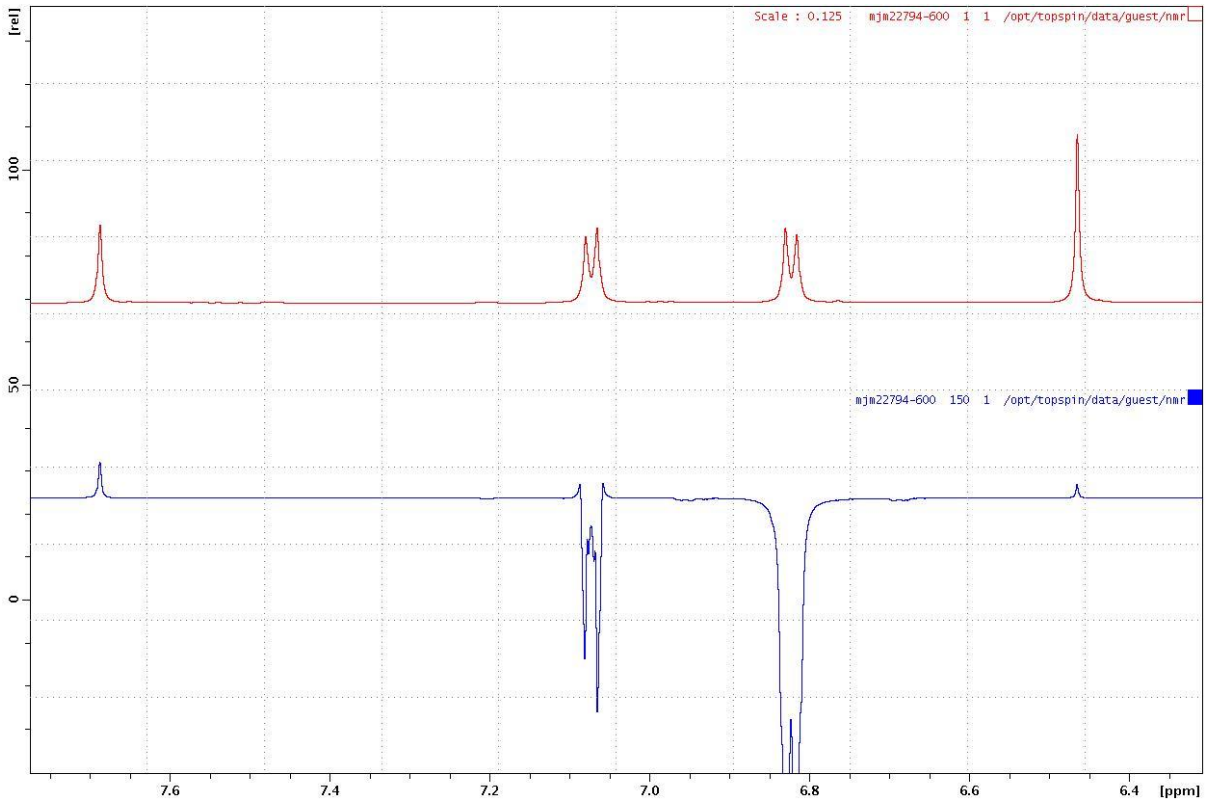
nOe experiment 1: Irradiation of Ha at 6.45 ppm; some enhancement of Hc and Hb, little effect on Hd



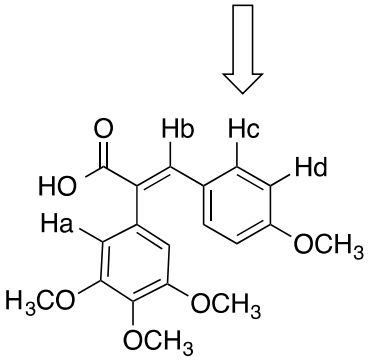


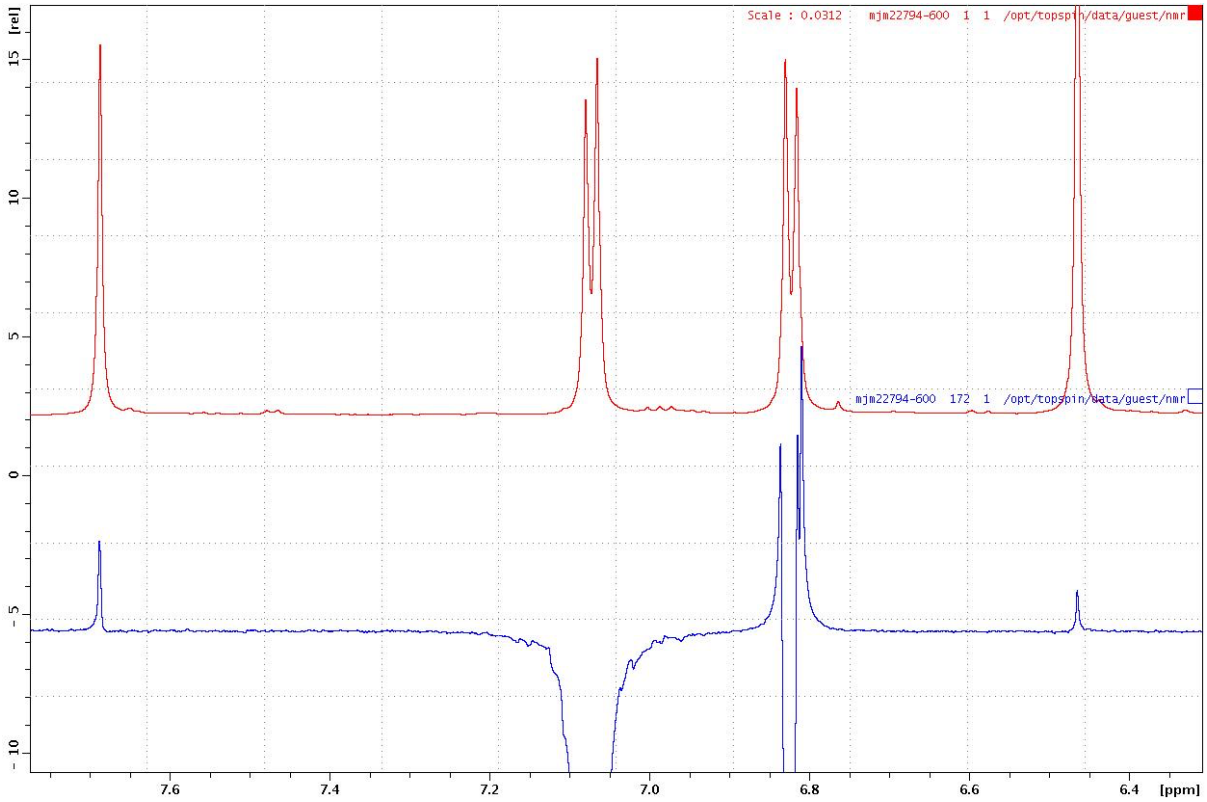
nOe experiment 2: Irradiation of Hd at 6.8 ppm; slight effect on Ha and Hb



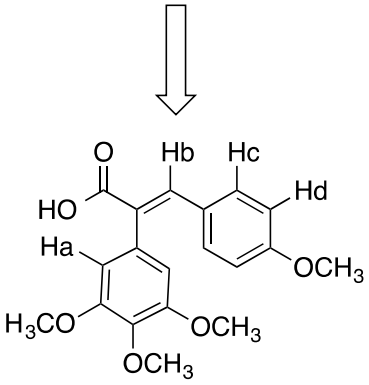


nOe experiment 3: Irradiation of Hc at 7.08 ppm; enhancement of Ha and Hb





nOe experiment 4: Irradiation of Hb at 7.7 ppm; enhancement of Hc, no effect on Ha or Hd



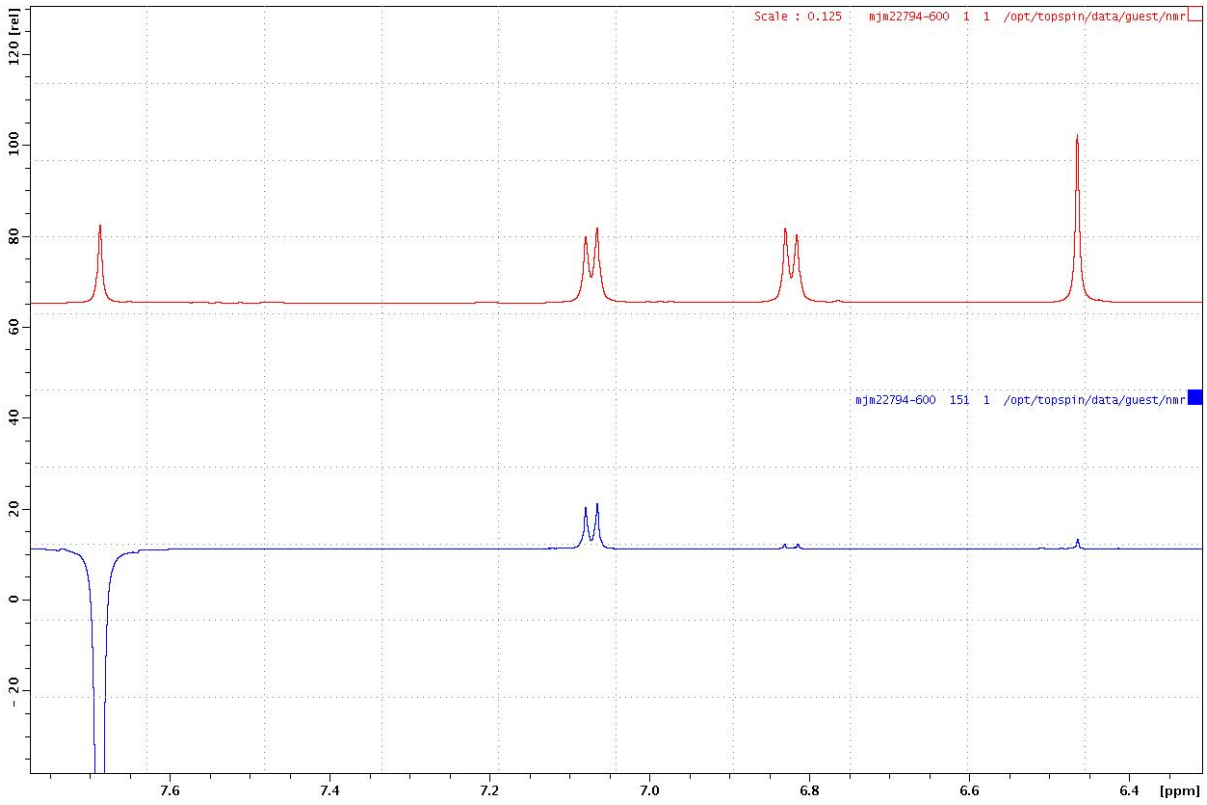


Table S1. Effect of reaction time on the isolated yields of 3a (microwave enhanced synthesis)[a]

Time (min)	Yield (mg)	Yield %
1	50	4.7
5	200	19
10	320	30
30	378	36
60	467	44
90	440	41
120	420	39
180	0	0

[a]Temperature for all reactions was 100 °C. The yield for the conventional reflux (reflux temperature, 240 min) was 40%.

Table S2. Effect of reaction temperature on the isolated yields of 3a (microwave enhanced synthesis)[a]

Temp (˚C)	Yield (mg)	Yield %
100	378	36
110	454	43
120	460	43
130	285	27
140	0	0
150	0	0
200	0	0

[a]Time for all reactions was 30 min. The yield for the conventional reflux (reflux temperature, 240 min) was 40%.

Table S3. Antiproliferative evaluation of compound 4m against the NCI-60 cell line panel

Leukemia		***Non-Small Cell Lung Cancer***		***Colon Cancer***		***CNS Cancer***	
Cell line	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**
CCRF-CEM	3.55E-7	A549/ATCC	7.64E-7	COLO 205	3.89E-6	SF-268	5.43E-7
HL-60(TB)	2.39E-7	EKVX	6.31E-7	HCC-2998	4.99E-7	SF-295	8.08E-7
K-562	2.96E-7	HOP-62	5.50E-7	HCT-116	3.70E-7	SF-539	2.05E-7
MOLT-4	3.68E-7	HOP-92	2.20E-5	HCT-15	3.41E-7	SNB-19	4.81E-7
RPMI-8226	3.74E-7	NCI-H226	6.09E-5	HT29	5.00E-6	SNB-75	2.93E-7
SR	3.81E-7	NCI-H23	9.38E-7	KM12	4.14E-7	U251	4.45E-7
Melanoma		NCI-H322M	7.65E-7	SW-620	4.69E-7	***Prostate Cancer***	
Cell line	**GI_{50} (M)**	NCI-H460	3.74E-7	***Renal Cancer***		**Cell line**	**GI_{50} (M)**
LOX IMVI	3.98E-7	NCI-H522	1.28E-7	**Cell line**	**GI_{50} (M)**	PC-3	5.80E-7
MALME-3M	2.47E-5	***Ovarian Cancer***		786-0	4.10E-6	DU-145	4.51E-7
M14	3.15E-7	**Cell line**	**GI_{50} (M)**	A498	2.11E-7	***Breast Cancer***	
MDA-MB-435	1.50E-7	IGROV1	5.19E-7	ACHN	4.57E-7	**Cell line**	**GI_{50} (M)**
SK-MEL-2	3.87E-7	OVCAR-3	3.22E-7	CAKI-1	nt	MCF7	3.07E-7
SK-MEL-28	6.71E-7	OVCAR-4	2.70E-6	RXF 393	nt	MDA-MB-231/ATCC	3.78E-7
SK-MEL-5	3.61E-7	OVCAR-5	6.78E-7	SN12C	5.63E-7	HS 578T	7.12E-7
UACC-257	3.07E-5	OVCAR-8	4.19E-7	TK-10	2.34E-5	BT-549	3.91E-7
UACC-62	3.32E-7	NCI/ADR-RES	6.76E-7	UO-31	1.00E-6	T-47D	5.13E-5
		SK-OV-3	5.86E-7			MDA-MB-468	5.75E-7

Table S4. Antiproliferative evaluation of compound 4q against the NCI-60 cell line panel

Leukemia		***Non-Small Cell Lung Cancer***		***Colon Cancer***		***CNS Cancer***	
Cell line	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**
CCRF-CEM	3.01E-7	A549/ATCC	6.80E-7	COLO 205	3.62E-7	SF-268	7.11E-7
HL-60(TB)	2.41E-7	EKVX	5.61E-7	HCC-2998	5.56E-7	SF-295	3.42E-7
K-562	3.16E-7	HOP-62	4.29E-7	HCT-116	3.56E-7	SF-539	2.23E-7
MOLT-4	5.24E-7	HOP-92	3.53E-6	HCT-15	3.88E-7	SNB-19	4.44E-7
RPMI-8226	5.24E-7	NCI-H226	3.20E-6	HT29	3.66E-7	SNB-75	2.20E-7
SR	4.09E-7	NCI-H23	2.18E-6	KM12	4.23E-7	U251	3.61E-7
Melanoma		NCI-H322M	5.76E-7	SW-620	4.01E-7	***Prostate Cancer***	
Cell line	**GI_{50} (M)**	NCI-H460	3.64E-7	***Renal Cancer***		**Cell line**	**GI_{50} (M)**
LOX IMVI	6.96E-7	NCI-H522	2.42E-7	**Cell line**	**GI_{50} (M)**	PC-3	4.14E-7
MALME-3M	1.22E-5	***Ovarian Cancer***		786-0	7.66E-7	DU-145	5.31E-7
M14	2.54E-7	**Cell line**	**GI_{50} (M)**	A498	1.42E-7	***Breast Cancer***	
MDA-MB-435	1.38E-7	IGROV1	6.97E-7	ACHN	6.12E-7	**Cell line**	**GI_{50} (M)**
SK-MEL-2	7.25E-7	OVCAR-3	3.66E-7	CAKI-1	nt	MCF7	3.26E-7
SK-MEL-28	1.47E-6	OVCAR-4	3.05E-6	RXF 393	2.72E-7	MDA-MB-231/ATCC	4.11E-7
SK-MEL-5	3.86E-7	OVCAR-5	5.69E-7	SN12C	6.43E-7	HS 578T	3.57E-7
UACC-257	3.65E-6	OVCAR-8	3.75E-7	TK-10	7.21E-5	BT-549	5.30E-7
UACC-62	2.72E-7	NCI/ADR-RES	6.23E-7	UO-31	8.11E-7	T-47D	nt
		SK-OV-3	4.72E-7			MDA-MB-468	2.51E-7

Table S5. Antiproliferative evaluation of compound 4x against the NCI-60 cell line panel

Leukemia		***Non-Small Cell Lung Cancer***		***Colon Cancer***		***CNS Cancer***	
Cell line	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**
CCRF-CEM	4.27E-7	A549/ATCC	4.55E-7	COLO 205	2.89E-7	SF-268	4.39E-7
HL-60(TB)	2.36E-7	EKVX	5.93E-7	HCC-2998	4.03E-7	SF-295	3.17E-7
K-562	2.34E-7	HOP-62	4.53E-7	HCT-116	1.93E-7	SF-539	1.80E-7
MOLT-4	4.73E-7	HOP-92	4.40E-7	HCT-15	3.52E-7	SNB-19	4.26E-7
RPMI-8226	3.31E-7	NCI-H226	3.52E-7	HT29	3.08E-7	SNB-75	1.44E-6
SR	2.88E-7	NCI-H23	4.39E-7	KM12	3.14E-7	U251	3.94E-7
Melanoma		NCI-H322M	6.14E-7	SW-620	4.57E-7	***Prostate Cancer***	
Cell line	**GI_{50} (M)**	NCI-H460	3.63E-7	***Renal Cancer***		**Cell line**	**GI_{50} (M)**
LOX IMVI	2.11E-7	NCI-H522	9.60E-8	**Cell line**	**GI_{50} (M)**	PC-3	4.32E-7
MALME-3M	6.15E-7	***Ovarian Cancer***		786-0	2.98E-7	DU-145	3.08E-7
M14	2.33E-7	**Cell line**	**GI_{50} (M)**	A498	1.46E-7	***Breast Cancer***	
MDA-MB-435	1.41E-7	IGROV1	2.99E-7	ACHN	1.80E-7	**Cell line**	**GI_{50} (M)**
SK-MEL-2	6.40E-7	OVCAR-3	2.80E-7	CAKI-1	9.35E-7	MCF7	2.20E-7
SK-MEL-28	5.40E-7	OVCAR-4	1.05E-5	RXF 393	3.52E-7	MDA-MB-231/ATCC	3.78E-7
SK-MEL-5	2.68E-7	OVCAR-5	8.47E-7	SN12C	4.50E-7	HS 578T	3.80E-7
UACC-257	> 1.00E-4	OVCAR-8	4.81E-7	TK-10	6.55E-7	BT-549	1.80E-7
UACC-62	2.46E-7	NCI/ADR-RES	2.92E-7	UO-31	7.01E-7	T-47D	nt
		SK-OV-3	2.88E-7			MDA-MB-468	2.55E-7

Table S6. Antiproliferative evaluation of compound 6a against the NCI-60 cell line panel

Leukemia		***Non-Small Cell Lung Cancer***		***Colon Cancer***		***CNS Cancer***	
Cell line	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**	**Cell line**	**GI_{50} (M)**
CCRF-CEM	1.17E-6	A549/ATCC	1.50E-6	COLO 205	6.64E-7	SF-268	1.79E-6
HL-60(TB)	4.41E-7	EKVX	3.40E-6	HCC-2998	2.82E-6	SF-295	4.22E-7
K-562	4.52E-7	HOP-62	9.11E-7	HCT-116	3.79E-7	SF-539	4.98E-7
MOLT-4	2.06E-6	HOP-92	1.24E-5	HCT-15	5.79E-7	SNB-19	9.46E-7
RPMI-8226	4.13E-6	NCI-H226	3.40E-6	HT29	4.12E-7	SNB-75	4.83E-7
SR	5.93E-7	NCI-H23	3.88E-6	KM12	4.82E-7	U251	1.48E-6
Melanoma		NCI-H322M	2.80E-6	SW-620	5.06E-7	***Prostate Cancer***	
Cell line	**GI_{50} (M)**	NCI-H460	4.97E-7	***Renal Cancer***		**Cell line**	**GI_{50} (M)**
LOX IMVI	1.04E-6	NCI-H522	1.70E-6	**Cell line**	**GI_{50} (M)**	PC-3	5.27E-7
MALME-3M	nt	***Ovarian Cancer***		786-0	4.04E-7	DU-145	1.50E-6
M14	4.78E-7	**Cell line**	**GI_{50} (M)**	A498	6.82E-7	***Breast Cancer***	
MDA-MB-435	2.57E-7	IGROV1	6.99E-7	ACHN	7.13E-7	**Cell line**	**GI_{50} (M)**
SK-MEL-2	9.67E-7	OVCAR-3	3.25E-7	CAKI-1	4.92E-7	MCF7	4.54E-7
SK-MEL-28	8.89E-6	OVCAR-4	1.80E-5	RXF 393	1.91E-6	MDA-MB-231/ATCC	4.54E-6
SK-MEL-5	7.53E-7	OVCAR-5	5.26E-6	SN12C	4.52E-6	HS 578T	9.66E-7
UACC-257	> 1.00E-4	OVCAR-8	6.12E-6	TK-10	> 1.00E-4	BT-549	4.17E-7
UACC-62	4.40E-7	NCI/ADR-RES	1.15E-6	UO-31	4.76E-6	T-47D	nt
		SK-OV-3	9.39E-7			MDA-MB-468	4.98E-7

Table S7: Standard COMPARE analysis of compound 4m[a]

Rank	**Compound**	***r***
	Based on GI_{50} mean graph	
1	Methotrexate	0.464
2	Paclitaxel (Taxol)	0.458
3	Vincristine sulfate	0.445
4	Maytansine	0.44
5	Tiazofurin	0.434
	Based on TGI mean graph	
1	Vinblastine sulphate	0.73
2	Maytansine	0.696
3	Paclitaxel (Taxol)	0.674
4	Rhizoxin	0.673
5	Vincristine sulfate	0.669
Rank	**Compound**	***r***
	Based on LC_{50} mean graph	
1	Thioguanine	0.951
2	Morpholino-ADR	0.842
3	Vinblastine sulfate	0.811
4	Mitramycin	0.811
5	Bispyridocarbazolium DMS	0.80

[a]The target set was the standard agent database and the target set endpoints were selected to be equal to the seed end points. Standard COMPARE analysis was performed. Correlation values (r) are Pearson correlation coefficients. [National Cancer Institute biological testing branch; National Cancer Institute; Bethesda, MD; **2019.** https://dtp.Nci.Nih.Gov/branches/btb/hfa.Html (accessed 10th January 2019)].