Supporting Information for Hsp90 paper

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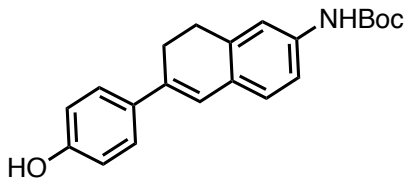
General

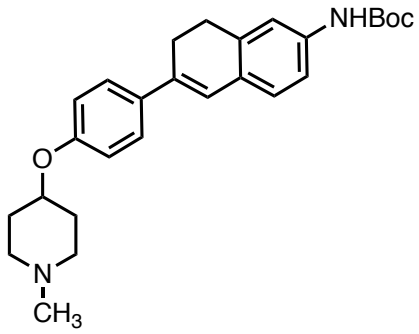
^{1}H NMR were recorded at 400 or 500 MHz (Bruker DRX- 400 Bruker with a H/C/P/F QNP gradient probe) spectrometer and ^{13}C NMR spectra were recorded at 125 MHz (Bruker DRX 500 with broadband, inverse triple resonance, and high resolution magic angle spinning HR-MA probe spectrometer); chemical shifts are reported in δ (ppm) relative to the internal reference for the solvent used. FAB (HRMS) spectra were recorded with a LCT Premier (Waters Corp., Milford, MA) spectrometer. The purity of all compounds was determined to be >95% as determined by ^{1}H NMR and ^{13}C NMR spectra, unless otherwise noted. TLC was performed on glass- backed silica gel plates (Uniplate) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure.

Synthesis:



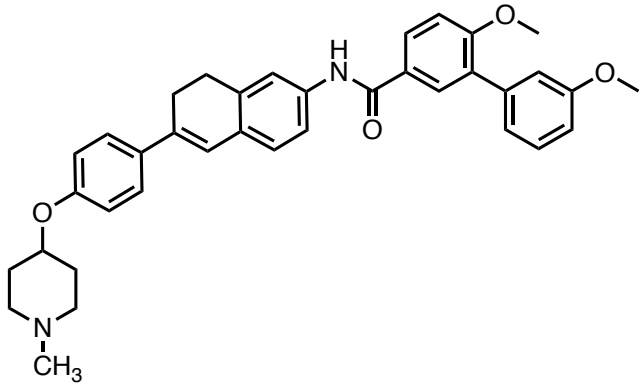
***tert*-butyl (6-(4-hydroxyphenyl)-7,8-dihydronaphthalen-2-yl)carbamate (9)** A 4:1 solution of dimethylformamide/water (14 mL) was added to a microwave vial containing **8**[1] (0.513 g, 1.30 mmol), 4-hydroxyphenylboronic acid (0.198 g, 1.43 mmol) and potassium carbonate (0.721 g, 5.26 mmol) under argon. The resulting mixture was degassed for 30 min. Then Pd(dppf)Cl_2 (0.024 g, 0.0326 mmol) was added and the mixture was degassed for 10 min. Next, the vial was placed in the microwave reactor and heated at 130 °C for 30 minutes. The mixture was diluted with ethyl acetate (20 mL) and washed with water (2 X 10 mL) and saturated sodium chloride solution (2 X 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography 1:1 hexanes/ethyl acetate. This produced a beige solid in 45% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.6 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.35 – 7.31 (m, 1H), 7.28 (dd, *J* = 8.5, 1.2 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 1H), 4.89 – 4.80 (m, 1H), 2.94 – 2.87 (m, 2H), 2.71 – 2.63 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 155.24, 155.03, 136.77, 133.81, 130.50, 129.92, 129.12, 128.69, 128.06, 127.91, 127.00, 126.55, 124.90, 123.99, 115.94, 115.49, 28.60, 28.58, 26.36. HRMS (ESI) calcd for $C_{21}H_{24}NO_3$ $(M+H)^+$ 338.1756, found for 338.2230

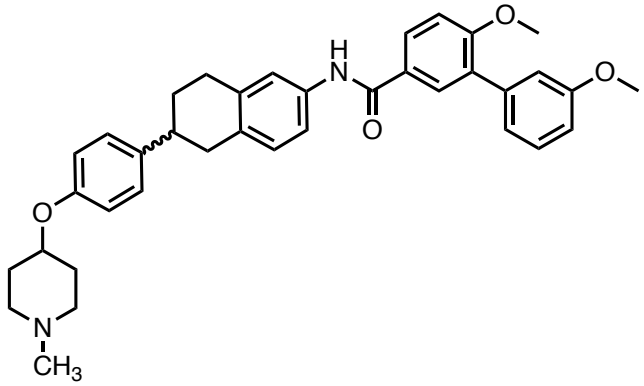


***tert*-butyl (6-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-7,8-dihydronaphthalen-2-yl)carbamate (11) General procedure for Mitsunobu etherification**
Tributylphosphine (0.12 mL, 0.47 mmol) and 1,-1'-azobis(N,N-dimethylformamide) (TMAD) (0.081 g, 0.47 mmol) were added to a solution of **9** (0.106 g, 0.313 mmol) and N-methyl-4-piperidinol (0.040 g, 0.345 mmol) in benzene (6 mL) at 0 °C. The resulting mixture was heated at 70 °C and the stirred for 20 h. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (20 mL) and filtered. The filtrate was washed with water (2 x 20 ml) and brine (20 ml) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (10% methanol in dichloromethane). This produced a beige solid in 25% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 (dd, *J* = 13.2, 8.6 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.09 – 7.00 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.72 (s, 1H), 6.49 (d, *J* = 12.1 Hz, 1H), 4.38 (s, 1H), 2.75 (m, 2H), 2.42 – 2.39 (m, 2H), 2.37 (s, 3H), 2.08 (m, 2H), 1.90 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.58, 136.76, 136.51, 135.68, 133.88, 130.25, 128.01, 126.79, 126.18, 125.31, 122.21, 117.49, 116.41, 115.98, 60.50, 56.96, 52.36, 45.96, 28.51, 28.37, 26.13. HRMS (ESI) calcd for $C_{27}H_{35}N_2O_3$ $(M+H)^+$ 435.2648, found for 435.2249

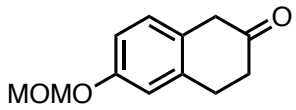
General Procedure for Amide Coupling:
The aniline (1 eq.) was added to a solution of acid chloride **12**[2] (1.5 eq.) and triethylamine (6 eq.) in anhydrous dichloromethane (0.1 M) at room temperature. After stirring for 16 h, the mixture was concentrated under reduced pressure. The resulting residue was purified via column chromatography.



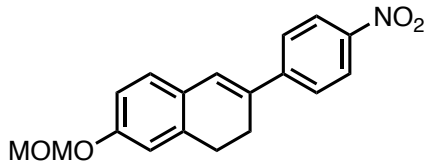
3',6-dimethoxy-*N*-(6-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-7,8-dihydronaphthalen-2-yl)-[1,1'-biphenyl]-3-carboxamide (3) Trifluoroacetic acid (1 mL) was carefully added to a solution of **11** (0.032 g, 0.075 mmol) in dichloromethane (1 mL) at room temperature. After stirring for 4 h, the mixture was concentrated under reduced pressure and the resulting aniline was used without further purification. The aniline was coupled with **12** following the general procedure for amide coupling. Column chromatography conditions: 10% methanol in dichloromethane. This produced a light brown solid in 39% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.73 (s, 1H), 7.56 (m, 1H), 7.49 (m, 2H), 7.40 – 7.33 (m, 2H), 7.16 – 7.06 (m, 3H), 6.94 (dd, *J* = 2.6, 1.0 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.76 (s, 2H), 4.36 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.96 (t, *J* = 8.1 Hz, 2H), 2.72 (t, *J* = 8.1 Hz, 2H), 2.54 (m, 2H), 2.35 (t, *J* = 7.6 Hz, 5H), 2.06 (d, *J* = 11.7 Hz, 2H), 1.91 – 1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.57, 139.10, 137.25, 136.63, 136.59, 135.75, 130.66, 130.10, 129.39, 129.26, 129.04, 128.12, 127.56, 126.28, 122.15, 122.01, 117.29, 116.14, 115.39, 115.31, 114.54, 113.16, 113.06, 112.85, 112.19, 110.96, 110.59, 55.96, 55.91, 55.50, 45.21, 44.67, 35.65, 29.93, 25.93. HRMS (ESI) calcd for $C_{37}H_{39}N_2O_4$ $(M+H)^+$ 575.2910, found for 575.2905



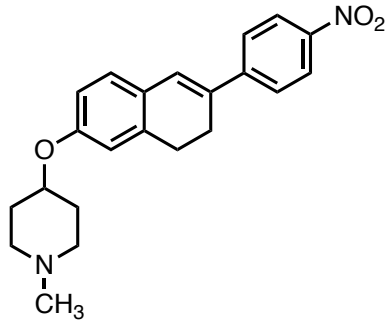
3',6-dimethoxy-*N*-(6-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-5,6,7,8-tetrahydronaphthalen-2-yl)-[1,1'-biphenyl]-3-carboxamide (13) 10% Palladium on carbon (0.1 equiv.) was added to a degassed solution of **3** (0.017 g, 0.030 mmol) in ethanol (3 mL). The system was purged with argon and before the mixture was stirred at rt for 18 hours under a H_2 atmosphere. The mixture was filtered through a pad of Celite® and concentrated under reduced pressure to produce **13** as a light brown solid in 58% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 7.73 (dd, *J* = 5.7, 3.3 Hz, 1H), 7.54 (dd, *J* = 5.7, 3.3 Hz, 1H), 7.50 (m, 2H), 7.49 – 7.46 (m, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.08 (dd, *J* = 1.6, 1.0 Hz, 1H), 7.07 – 7.05 (m, 3H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.89 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 2H), 4.09 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.30 (qd, *J* = 7.3, 5.4 Hz, 2H), 2.32 (m, 2H), 2.20 (m, 5H), 2.05 (m, 1H), 1.82 (s, 2H), 1.62 (s, 4H), 1.17 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.45, 158.55, 139.06, 137.60, 136.62, 136.37, 135.46, 131.14, 130.63, 130.12, 129.43, 129.25, 129.04, 128.11, 126.28, 122.43, 122.16, 117.58, 115.89, 115.39, 115.23, 113.36, 113.15, 110.92, 110.62, 72.02, 55.95, 55.50, 45.25, 44.78, 35.64, 27.93, 25.96, 19.39, 15.01. HRMS (ESI) calcd for $C_{37}H_{39}N_2O_4$ $(M+H)^+$ 577.3066, found for 577.3076



6-(methoxymethoxy)-3,4-dihydronaphthalen-2(1*H*)-one (15) A solution chloromethyl methyl ether (6 mmol/ml in dichloromethane) (4.42 mL, 26.5 mmol) was added to 6-hydroxy-2-tetralone (2 g, 8.85 mmol) in anhydrous dichloromethane (35 mL). Then diisopropylethylamine (4.78 mL, 27.4 mmol) was carefully added and the reaction was stirred for 18 hours at room temperature. Afterwards, the reaction was quenched with aqueous saturated ammonium chloride (10 mL) and extracted with dichloromethane. The organic layer was washed with a saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (10% ethyl acetate in hexanes). This produced a colorless oil in 60% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.04 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.90 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.17 (s, 2H), 3.53 (s, 2H), 3.49 (s, 3H), 3.03 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.08, 156.27, 138.17, 129.36, 126.73, 115.65, 115.09, 94.69, 56.22, 44.54, 38.30, 28.78. HRMS (ESI) calcd for $C_{12}H_{14}OLi$ $(M+Li)^+$ 213.1103, found for 213.1241

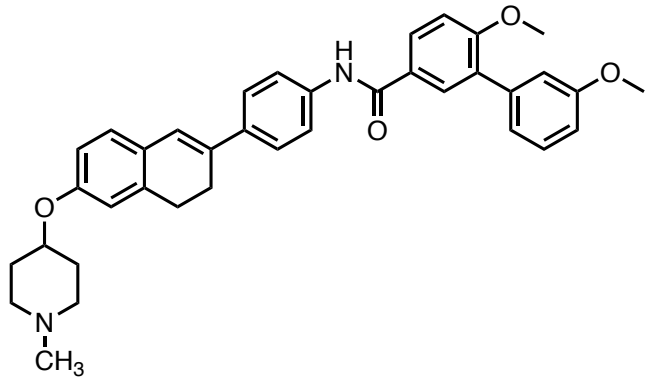


7-(methoxymethoxy)-3-(4-nitrophenyl)-1,2-dihydronaphthalene (16) was prepared following the same procedure for **9**. Column chromatography conditions: 3:1 hexanes/ethyl acetate. This produced an orange solid in 43% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 9.0 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.44 – 7.37 (m, 1H), 7.12 (d, *J* = 8.7 Hz, 10H), 6.98 (s, 1H), 6.89 (s, 1H), 5.20 (s, 2H), 3.50 (s, 3H), 2.97 (t, *J* = 8.3 Hz, 2H), 2.79 – 2.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.38, 147.98, 146.54, 137.14, 134.29, 129.93, 128.82, 127.88, 125.43, 124.10, 115.67, 114.45, 94.52, 56.31, 28.52, 26.06. HRMS (ESI) calcd for $C_{18}H_{18}NO_4$ $(M+H)^+$ 312.1236, found for 312.3650

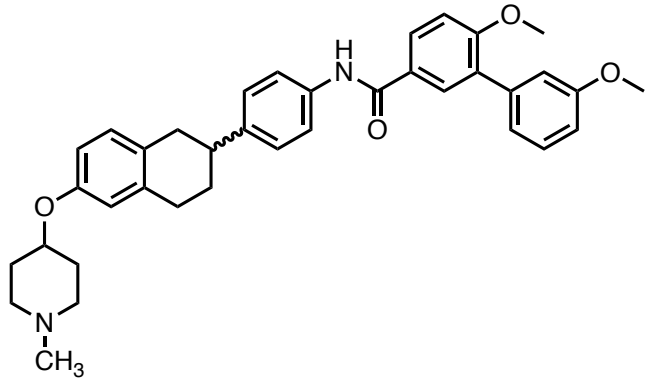


1-methyl-4-((6-(4-nitrophenyl)-7,8-dihydronaphthalen-2-yl)oxy)piperidine (17) 3M hydrochloric acid (1.60 mL, 4.82 mmol) was added to a solution of **16** (0.150 g, 0.482 mmol) in methanol (4.8 mL) and the mixture was heated at reflux for 1 h. Upon cooling, the mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL) and saturated sodium chloride solution (10 mL). The organic layer was dried over anhydrous

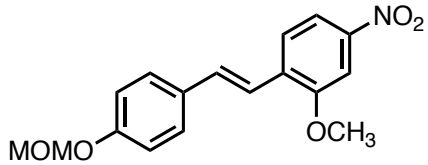
sodium sulfate, filtered and concentrated under reduced pressure. The resulting phenol was coupled with N-methyl-4-piperidinol via the general procedure for Mitsunobu etherification. This produced an orange solid in 23% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 0.7 Hz, 1H), 6.77 – 6.75 (m, 2H), 6.46 (s, 1H), 4.40 (m, 1H), 2.74 (ddd, *J* = 9.8, 7.0, 1.2 Hz, 4H), 2.40 (m, 2H), 2.38 (m, 5H), 2.10 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.19, 157.55, 148.00, 146.48, 137.27, 133.88, 128.90, 127.91, 127.40, 125.36, 124.10, 115.71, 113.80, 52.48, 46.12, 36.35, 28.57, 26.06. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_3$ $(M+H)^+$ 365.1865, found for 365.1902



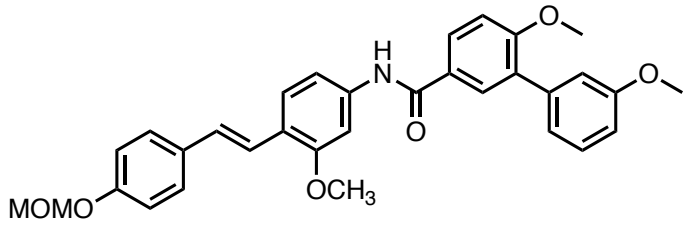
3',6-dimethoxy-*N*-(4-(6-((1-methylpiperidin-4-yl)oxy)-3,4-dihydronaphthalen-2-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (4) Iron, which was reduced with hydrogen, (0.050 g, 0.90 mmol) and ammonium chloride (0.048 g, 0.90 mmol) were added to a solution of nitro-containing compound (0.033 g, 0.090 mmol) in 1:1 ethanol/water (0.1 M). The reaction mixture was heated at reflux for 2 hours. Upon cooling, the mixture was filtered through a pad of Celite® and the filtrate was diluted with dichloromethane. The organic layer was washed with water (2 x 20 ml) and saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting aniline was used in the next reaction without further purification. The aniline was coupled with **12** following the general procedure for amide coupling. Column chromatography conditions: 10% methanol in dichloromethane. This produced a light brown solid in 50% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.13 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.06 (m, 3H), 6.93 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.80 (m, 1H), 6.75 – 6.70 (m, 2H), 4.42 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.92 (dd, *J* = 9.1, 7.0 Hz, 2H), 2.83 (m, 2H), 2.75 – 2.69 (m, 2H), 2.58 (m, 2H), 2.45 (s, 3H), 2.15 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.16, 159.54, 139.05, 139.02, 137.35, 137.22, 136.83, 135.75, 130.91, 129.71, 129.38, 128.62, 127.85, 127.63, 127.30, 125.74, 123.26, 122.19, 120.58, 120.17, 115.70, 115.52, 113.72, 113.16, 111.28, 56.07, 55.55, 52.16, 40.56, 37.13, 29.93, 28.82, 26.13. HRMS (ESI) calcd for $C_{37}H_{39}N_2O_4$ $(M+H)^+$ 575.2910, found for 575.2098



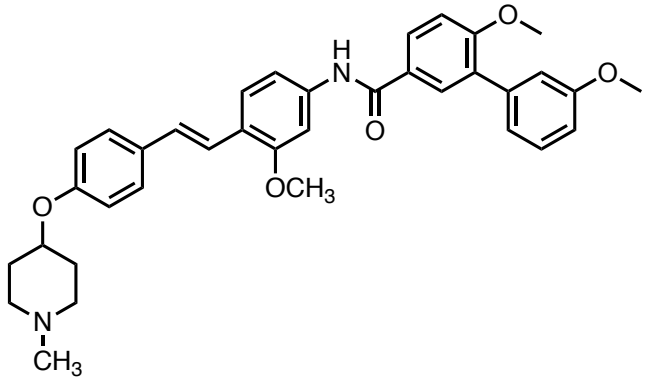
3',6-dimethoxy-*N*-(4-(6-((1-methylpiperidin-4-yl)oxy)-1,2,3,4-tetrahydronaphthalen-2-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (18) was prepared following the same procedure **13**. This produced a light brown solid in 32% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 7.91 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.75 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.39 – 7.33 (m, 1H), 7.13 (ddd, *J* = 7.6, 1.7, 1.0 Hz, 1H), 7.09 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.08 – 7.04 (m, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.93 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.74 – 6.70 (m, 1H), 6.69 (d, *J* = 5.4 Hz, 1H), 6.17 (m, 1H), 4.34 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.30 (qd, *J* = 7.3, 5.4 Hz, 2H), 2.32 (s, 2H), 2.20 (m, 5H), 2.07 – 2.01 (m, 1H), 1.82 (s, 2H), 1.62 (s, 4H), 1.17 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.45, 158.55, 139.06, 139.00, 137.35, 137.27, 136.53, 135.83, 131.14, 130.63, 130.12, 129.25, 128.11, 127.92, 127.69, 127.48, 125.98, 123.62, 122.16, 120.87, 115.53, 115.39, 113.15, 111.34, 110.92, 72.02, 55.95, 55.50, 45.25, 44.78, 35.64, 27.93, 25.96, 19.39, 15.01. HRMS (ESI) calcd for $C_{37}H_{41}N_2O_4$ $(M+H)^+$ 577.3066, found for 577.2725



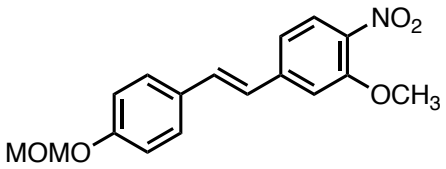
(*E*)-2-methoxy-1-(4-(methoxymethoxy)styryl)-4-nitrobenzene (20a) Triethanolamine (5 mL) was added to a mixture of styrene **19**[3] (0.449g, 2.73 mmol), 4-bromo-2-methoxy-1-nitrobenzene (0.763 g, 2.73 mmol) and $Pd(OAc)_2$ (0.006g, 0.273 mmol) under argon. The mixture was heated to 100 °C for 12 hours. Upon cooling, the mixture was dissolved in water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was washed with water (2 x 10 mL) and saturated sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via column chromatography (10% ethyl acetate in hexanes) and the product was isolated as a dark red solid in 39% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.47 (dd, *J* = 2.7, 0.5 Hz, 1H), 8.13 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.28 (dd, *J* = 16.5, 0.5 Hz, 1H), 7.18 (d, *J* = 16.5 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 9.1 Hz, 1H), 5.21 (s, 2H), 3.99 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.83, 131.41, 131.05, 130.10, 128.32, 127.85, 124.20, 121.66, 119.55, 116.64, 116.23, 110.57, 94.55, 56.44, 56.30. HRMS (ESI) calcd for $C_{17}H_{18}NO_5$ $(M+H)^+$ 316.1185, found for 316.0852



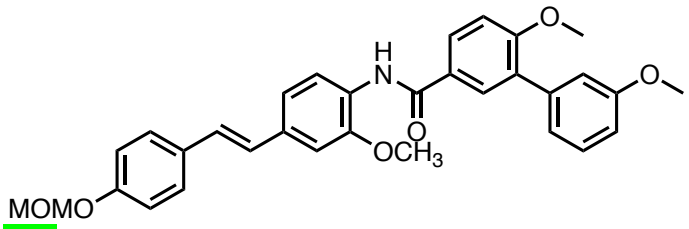
(*E*)-3',6-dimethoxy-*N*-(3-methoxy-4-(4-(methoxymethoxy)styryl)phenyl)-[1,1'-biphenyl]-3-carboxamide (22a) was prepared following the same procedure for **4**. This produced a red solid in 46% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.82 (dd, *J* = 3.6, 2.4 Hz, 1H), 7.76 (m, 1H), 7.51 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 1.6 Hz, 1H), 7.33 (d, *J* = 10.1 Hz, 1H), 7.13 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.11 – 7.09 (m, 1H), 7.08 – 7.04 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.95 – 6.91 (m, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 5.19 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.97, 139.09, 131.93, 131.49, 130.84, 129.65, 129.35, 129.31, 128.57, 128.02, 127.78, 127.37, 127.27, 122.20, 121.37, 120.82, 118.63, 116.54, 115.95, 115.51, 113.14, 112.65, 111.61, 111.26, 94.60, 60.63, 56.25, 56.10, 56.05, 55.55. HRMS (ESI) calcd for $C_{32}H_{32}NO_6$ $(M+H)^+$ 526.2230, found for 526.2238



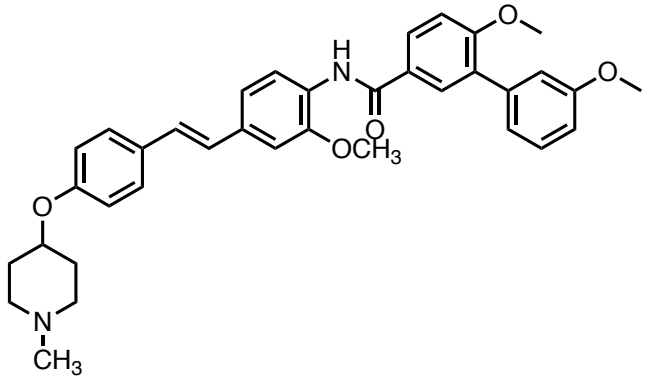
(*E*)-3',6-dimethoxy-*N*-(3-methoxy-4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-[1,1'-biphenyl]-3-carboxamide (23a) was prepared following the same procedure for **17**. This produced a orange solid in 43% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.88 (d, *J* = 2.7 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.73 (s, 1H), 7.49 – 7.44 (m, 3H), 7.38 – 7.35 (m, 1H), 7.34 (d, *J* = 13.2 Hz, 1H), 7.13 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.10 (dd, *J* = 4.0, 1.4 Hz, 1H), 7.08 – 7.05 (m, 1H), 6.93 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.89 (dd, *J* = 8.7, 5.7 Hz, 3H), 4.53 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 2.97 (m, 2H), 2.79 (m, 2H), 2.59 (s, 3H), 2.30 (m, 2H), 2.08 – 2.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.25, 159.54, 153.97, 139.08, 131.65, 131.50, 130.87, 129.63, 129.38, 129.15, 128.58, 128.25, 127.56, 127.34, 127.22, 122.20, 121.42, 120.82, 118.65, 116.23, 115.54, 113.14, 112.89, 111.62, 111.29, 56.10, 56.07, 55.56, 40.34, 36.73, 29.93, 22.01. HRMS (ESI) calcd for $C_{36}H_{39}N_2O_5$ $(M+H)^+$ 579.2859, found for 579.2601



(*E*)-2-methoxy-4-(4-(methoxymethoxy)styryl)-1-nitrobenzene (20b) was prepared following the same procedure for **20a**. This produced a red solid in 38% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.20 – 7.15 (m, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.99 – 6.93 (m, 2H), 5.21 (s, 2H), 4.02 (s, 2H), 3.50 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.51, 133.39, 132.66, 130.43, 128.52, 126.86, 125.02, 121.14, 118.00, 116.74, 113.84, 111.04, 94.50, 56.70, 56.35. HRMS (ESI) calcd for $C_{17}H_{18}NO_5$ $(M+H)^+$ 316.1185, found for 316.0688

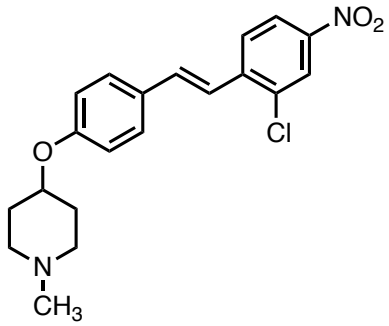


(*E*)-3',6-dimethoxy-*N*-(2-methoxy-4-(4-(methoxymethoxy)styryl)phenyl)-[1,1'-biphenyl]-3-carboxamide (22b) was prepared following the same procedure for **4**. This produced a red solid in 36% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.91 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.17 – 7.13 (m, 2H), 7.11 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.08 – 7.05 (m, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 10.2 Hz, 2H), 6.93 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 1H), 5.20 (s, 2H), 3.98 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.05, 148.53, 139.18, 133.54, 131.59, 130.96, 129.97, 129.93, 129.39, 129.37, 128.49, 128.47, 127.88, 127.80, 127.58, 127.40, 127.14, 122.29, 120.12, 120.00, 116.71, 115.53, 113.27, 111.26, 107.49, 94.69, 56.30, 56.13, 56.10, 55.58. HRMS (ESI) calcd for $C_{32}H_{31}NO_6Na$ $(M+Na)^+$ 548.2049, found for 548.1969

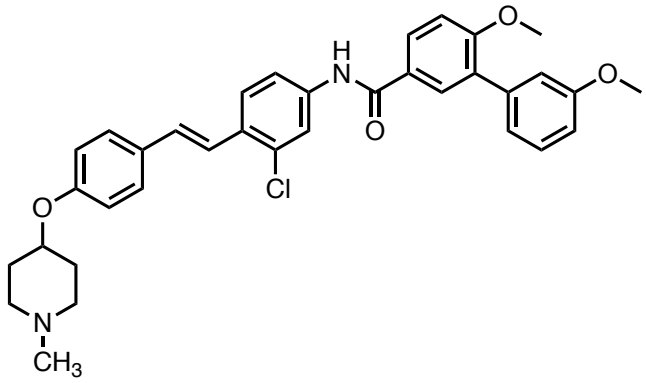


(*E*)-3',6-dimethoxy-*N*-(2-methoxy-4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-[1,1'-biphenyl]-3-carboxamide (23b) was prepared following the same procedure for **17**. This produced a orange solid in 56% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.08 (s, 1H), 7.92 – 7.80 (m, 1H), 7.52 – 7.46 (m, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.32 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.11 – 7.04 (m, 3H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.97 – 6.91 (m, 2H),

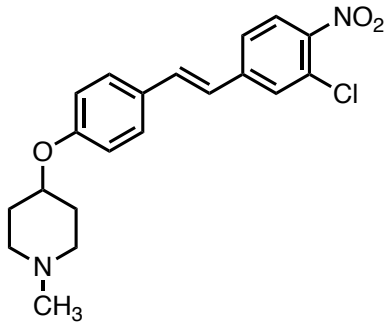
6.91 – 6.85 (m, 2H), 6.68 (d, *J* = 8.0 Hz, 1H), 4.53 (m, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 2.58 (m, 2H), 2.45 (m, 2H), 2.30 (s, 3H), 2.08 – 2.02 (m, 2H), 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.45, 158.61, 147.57, 138.97, 136.21, 131.00, 130.71, 130.04, 129.28, 128.88, 128.52, 128.11, 127.84, 127.60, 124.46, 122.14, 120.32, 116.32, 115.97, 115.87, 115.39, 114.97, 113.17, 111.02, 107.97, 55.98, 55.90, 55.51, 45.09, 44.47, 35.67, 25.86. HRMS (ESI) calcd for C36H39N2O5 $(M+H)^+$ 579.2859, found for 579.2968



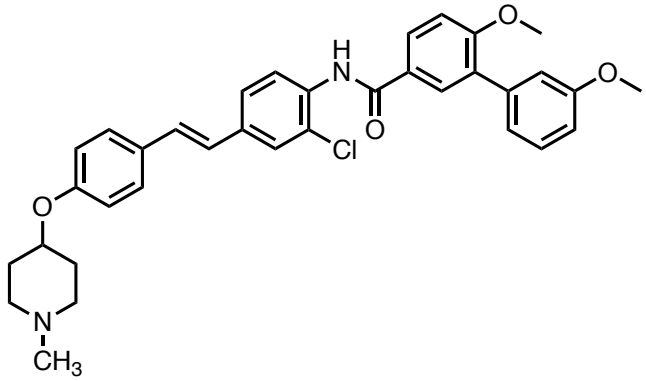
(*E*)-4-(4-(2-chloro-4-nitrostyryl)phenoxy)-1-methylpiperidine (51a) A 1M solution of sodium bis(trimethylsilyl) amide (0.82 mL, 0.847 mmol) was added to a solution of diethyl (2-chloro-4-nitrobenzyl)phosphonate (0.130 g, 0.424 mmol) in anhydrous tetrahydrofuran (2 mL) at 0 °C. After stirring for 30 minutes, a solution of 4-((1-methylpiperidin-4-yl)oxy)benzaldehyde in tetrahydrofuran (2.23 mL) was added to the mixture at 0 °C. The mixture was allowed to warm to room temperature while stirring for 16 hours. Afterwards, the reaction was quenched with water (4 mL) and diluted with ethyl acetate (20 mL). The organic layer was washed with water (2 x 20 mL) and saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via column chromatography (10% methanol in dichloromethane) and the product was isolated as a yellow solid in 45% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 (dd, *J* = 7.7, 2.3 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 16.2 Hz, 1H), 7.21 (d, *J* = 16.2 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 1H), 4.31 (m, 1H), 2.72 (m, 2H), 2.37 – 2.29 (m, 5H), 2.10 – 1.99 (m, 2H), 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.27, 130.66, 129.08, 127.40, 126.33, 125.53, 125.18, 122.17, 121.54, 116.44, 115.90, 113.80, 55.55, 46.12, 28.57, 26.06. HRMS (ESI) calcd for $C_{20}H_{22}ClN_2O_3$ $(M+H)^+$ 373.1319, found for 373.1129



(*E*)-*N*-(3-chloro-4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (37a) was prepared following the same procedure for **4**. This produced a light yellow solid in 56% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.73 (dd, *J* = 5.7, 3.3 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.50 – 7.47 (m, 1H), 7.45 – 7.42 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.99 (dd, *J* = 9.0, 6.4 Hz, 2H), 6.94 – 6.83 (m, 3H), 6.72 (dd, *J* = 11.4, 2.4 Hz, 1H), 4.44 (m, 1H), 3.85 (m, 3H), 3.83 (m, 3H), 2.46 (m, 2H), 2.36 (m, 2H), 2.23 (s, 3H), 1.97 (m, 2H), 1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.44, 156.65, 139.03, 132.28, 131.14, 130.64, 130.09, 129.25, 129.05, 128.11, 127.94, 127.30, 127.19, 126.02, 125.53, 122.15, 116.36, 115.89, 115.61, 115.38, 114.30, 113.15, 111.83, 110.94, 55.96, 55.91, 55.50, 45.22, 44.69, 35.65, 25.94. HRMS (ESI) calcd for $C_{35}H_{39}ClN_3O_4$ $(M+NH_4)^+$ 600.2629, found for 600.2490

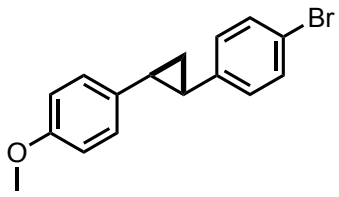


(*E*)-4-(4-(3-chloro-4-nitrostyryl)phenoxy)-1-methylpiperidine (51b) was prepared following the same procedure for **51a**. This produced a light yellow solid in 56% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.18 (d, *J* = 16.2 Hz, 1H), 7.13 (dd, *J* = 8.8, 0.7 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 1H), 4.40 (m, 1H), 2.74 (s, 2H), 2.41 (m, 2H) 2.36 (s, 3H), 2.09 – 2.02 (m, 2H), 1.91 – 1.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.74, 134.42, 133.81, 132.15, 130.51, 129.22, 128.79, 126.70, 124.83, 122.98, 116.42, 116.08, 52.58, 46.22, 30.67, 22.10. HRMS (ESI) calcd for $C_{20}H_{22}ClN_2O_3$ $(M+H)^+$ 373.1319, found for 373.1129

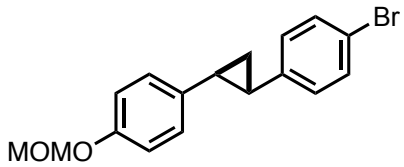


(*E*)-*N*-(2-chloro-4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (37b) was prepared following the same procedure for **4**. This produced a light yellow solid in 48% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.44 (m, 2H), 7.40 – 7.37 (m, 4H), 7.33 (q, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.0

Hz, 1H), 7.10 – 7.05 (m, 1H), 7.02 – 6.97 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 3H), 6.84 (d, *J* = 10.3 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 4.42 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.83 (m, 2H), 2.31 (m, 2H), 2.21 (s, 3H), 2.16 (m, 2H), 1.94 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.44, 142.26, 130.92, 130.36, 130.11, 129.47, 129.42, 129.36, 129.25, 128.11, 127.68, 127.30, 126.02, 125.89, 122.15, 122.11, 119.74, 116.39, 116.09, 115.87, 115.49, 115.38, 113.15, 111.12, 110.92, 55.95, 55.50, 45.25, 35.64, 29.92, 25.96. HRMS (ESI) calcd for $C_{35}H_{39}ClN_3O_4$ $(M+NH_4)^+$ 600.2629, found for 600.3028

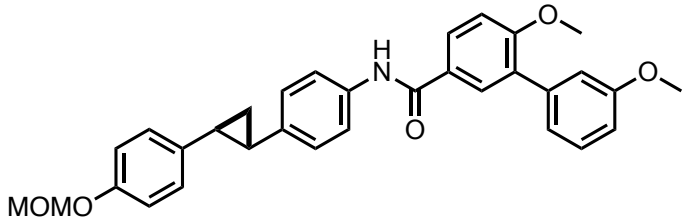


1-bromo-4-((1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropyl)benzene (25)[4] A solution of trifluoroacetic acid (0.11 mL, 0.138 mmol) in dichloromethane (1 mL) was added to a solution of diethyl zinc (1.38 mL, 0.138 mmol) in dichloromethane (1 mL) at 0°C. After stirring for 20 minutes, a solution of diiodomethane (0.11 mL, 0.138 mmol) in dichloromethane (1 mL) was added to the reaction mixture. After stirring for 20 minutes, a solution of (*E*)-1-bromo-4-(4-methoxystyryl)benzene[5] (0.200g, 0.692 mmol) in dichloromethane (1 mL) was slowly added to the mixture. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction was quenched with 0.1 M HCl (2 mL) and extracted with hexanes. (Note: The product is mostly soluble in hexanes, while the starting alkene is not soluble in hexanes. To ensure purity, no other organic solvents were used to extract the product.) The organic layer was washed with saturated sodium bicarbonate solution (20 mL), water (20 mL) and saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via column chromatography (2% diethyl ether in hexanes) and the product was isolated as a yellow solid in 52% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.09 (ddd, *J* = 8.8, 6.0, 4.5 Hz, 1H), 2.04 (ddd, *J* = 8.6, 5.8, 4.5 Hz, 1H), 1.40 (ddd, *J* = 8.7, 6.0, 5.3 Hz, 1H), 1.36 (dt, *J* = 8.8, 5.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.18, 142.03, 134.28, 131.59, 127.66, 127.12, 119.38, 114.13, 55.59, 27.76, 27.26, 18.10. HRMS (ESI) calcd for $C_{16}H_{15}BrONa$ $(M+Na)^+$ 325.0204, found for 325.1661

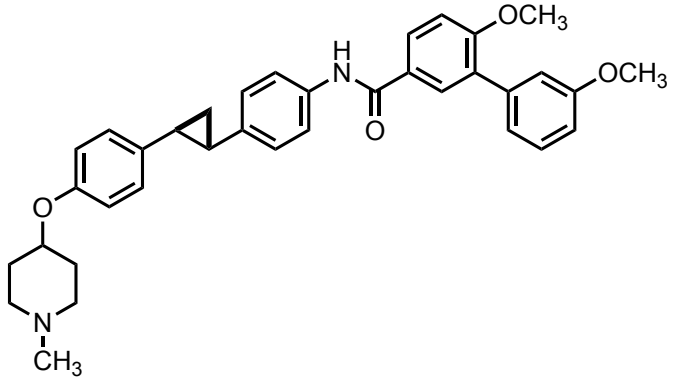


1-bromo-4-((1*S*,2*S*)-2-(4-(methoxymethoxy)phenyl)cyclopropyl)benzene (26) A solution of 1M solution of boron tribromide (5 mL, 4.97 mmol) in dichloromethane was added dropwise to a solution of **25** (0.753 g, 2.48 mmol) in anhydrous dichloromethane (25 mL) at 0 °C. The mixture was stirred for 1 hour and it was carefully quenched with saturated aqueous ammonium chloride solution (15 mL). The mixture was extracted with dichloromethane (2 x 20 mL) and the organic layer was dried over anhydrous sodium

sulfate, filtered and concentrated under reduced pressure. The phenol was used without further purification. **26** was prepared following the same procedure for **15**. This produced a white solid in 48% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.99 (t, *J* = 8.8 Hz, 4H), 5.16 (s, 2H), 3.48 (s, 3H), 2.09 (ddd, *J* = 8.8, 6.0, 4.5 Hz, 1H), 2.04 (ddd, *J* = 8.7, 5.9, 4.5 Hz, 1H), 1.43 – 1.34 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.72, 141.91, 135.63, 131.56, 127.64, 127.07, 119.39, 116.57, 94.79, 56.16, 27.75, 27.33, 18.13. HRMS (ESI) calcd for C17H17BrO2Na $(M+Na)^+$ 355.0310, found for 355.1791

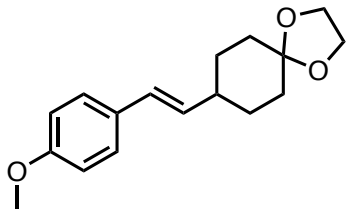


3',6-dimethoxy-*N*-(4-((1*S*,2*S*)-2-(4-(methoxymethoxy)phenyl)cyclopropyl)phenyl)-[1,1'-biphenyl]-3-carboxamide (28) *N*,*N*-Dimethylethylenediamine (0.015 mL, 0.014 mmol) was added to a mixture of **26** (0.048 g, 0.143 mmol), amide **27** (0.044 g, 0.171 mmol), copper (II) iodide (0.001 g, 0.0071 mmol) and potassium carbonate (0.040 g, 0.287 mmol) in anhydrous 1,4-Dioxane (0.7 mL). The mixture was heated to 100°C for 20 hours. Upon cooling, the reaction was filtered through a pad of Celite® and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure and purified via column chromatography (3:1 hexanes/ethyl acetate). This produced a white solid in 80% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.79 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.12 (d, *J* = 8.7 Hz, 3H), 7.07 (d, *J* = 8.8 Hz, 3H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.92 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 5.16 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.48 (s, 3H), 2.09 (dtd, *J* = 10.6, 6.4, 3.4 Hz, 2H), 1.39 (ddd, *J* = 8.0, 6.5, 1.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.03, 159.32, 159.26, 155.41, 138.85, 138.80, 135.87, 135.80, 130.65, 129.52, 129.16, 128.37, 127.19, 126.85, 126.31, 121.99, 120.34, 116.35, 115.30, 112.95, 111.03, 94.61, 55.96, 55.85, 55.34, 27.31, 27.29, 17.81. HRMS (ESI) calcd for C32H32NO5 $(M+H)^+$ 510.2280, found for 510.2283

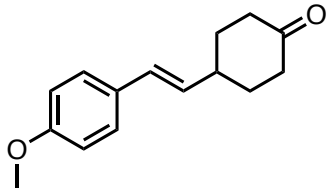


3',6-dimethoxy-*N*-(4-((1*S*,2*S*)-2-(4-((1-methylpiperidin-4-yl)oxy)phenyl)cyclopropyl)phenyl)-[1,1'-biphenyl]-3-carboxamide (6) was prepared following the same procedure for **17**. This produced a orange solid in 42% yield: ^{1}H

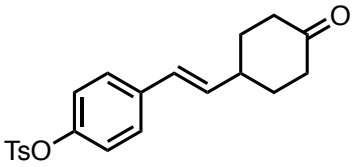
NMR (500 MHz, Chloroform-*d*) δ 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.75 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 3H), 7.08 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 2H), 6.92 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 4.34 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.79 (s, 2H), 2.48 (s, 2H), 2.40 (s, 3H), 2.15 – 2.02 (m, 4H), 1.91 (s, 2H), 1.38 (ddd, *J* = 8.1, 6.5, 2.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.12, 159.45, 159.40, 155.48, 138.97, 138.94, 135.92, 135.12, 130.80, 129.62, 129.30, 128.50, 127.30, 127.07, 126.44, 122.11, 120.45, 116.34, 115.43, 113.08, 111.18, 55.99, 55.48, 45.87, 32.08, 29.85, 27.41, 27.37, 17.93. HRMS (ESI) calcd for C36H39N2O4 $(M+H)^+$ 563.2910, found for 563.2911



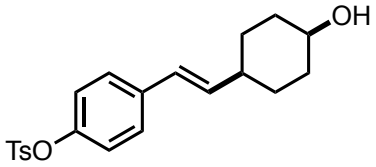
(***E***)**-8-(4-methoxystyryl)-1,4-dioxaspiro[4.5]decane (31)** was prepared following the same procedure for **51a**. This produced a white solid in 35% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.35 – 6.31 (m, 1H), 6.03 (dd, *J* = 15.9, 7.2 Hz, 1H), 3.96 (s, 4H), 3.80 (s, 3H), 2.20 – 2.13 (m, 1H), 1.83 – 1.78 (m, 4H), 1.65 – 1.48 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.88, 133.24, 130.78, 127.67, 127.24, 114.10, 108.86, 64.46, 55.50, 40.00, 34.49, 30.41. HRMS (ESI) calcd for $C_{17}H_{23}O_3$ $(M+H)^+$ 275.1647, found for 275.1772



(*E*)-4-(4-methoxystyryl)cyclohexan-1-one (32) 3M hydrochloric acid (14.6 mL, 43.7 mmol) was added to a solution of **31** (1.23 g, 4.37 mmol) in ethanol (14.6 mL) and the mixture was heated at reflux for 1 h. Upon cooling, the mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL) and saturated sodium chloride solution (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was isolated was a white solid in 98% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.08 (dd, *J* = 16.0, 6.9 Hz, 1H), 3.83 (s, 1H), 2.64 (dtdd, *J* = 10.8, 7.1, 3.5, 1.3 Hz, 1H), 2.51 – 2.40 (m, 4H), 2.20 – 2.14 (m, 2H), 1.79 – 1.69 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.80, 159.16, 131.11, 130.24, 128.77, 127.37, 114.19, 55.52, 40.83, 39.42, 32.90. HRMS (ESI) calcd for $C_{15}H_{18}O_2Na$ $(M+Na)^+$ 253.1205, found for 253.1255

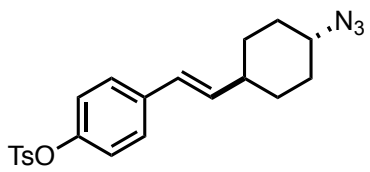


(*E*)-4-(2-(4-oxocyclohexyl)vinyl)phenyl 4-methylbenzenesulfonate (33) A solution of 1M solution of boron tribromide (15.3 mL, 15.3 mmol) in dichloromethane was added dropwise to a solution of **32** (1.18 g, 5.10 mmol) in anhydrous dichloromethane (50 mL) at 0 °C. The mixture was stirred for 1 hour and it was carefully quenched with saturated aqueous ammonium chloride solution (20 mL). The mixture was extracted with ethyl acetate (2 x 20 mL) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The phenol was used without further purification. A 10% aqueous solution of potassium carbonate (13.3 mL, 9.59 mmol) was added to a solution of phenol (1.10 g, 5.10 mmol) in tetrahydrofuran (10 mL). The resulting mixture was cooled to 0 °C and tosyl chloride (0.98 g, 5.15 mmol) in tetrahydrofuran (3.3 mL) was added to the solution. The mixture was allowed to warm to room temperature and stir for 2 hours. Then the reaction mixture was extracted with ethyl acetate (30 mL). The organic layer was washed with water (20 mL) and saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (3:1 hexanes/ethyl acetate). This produced the product as a white solid in 38% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.33 (dd, *J* = 16.1, 1.2 Hz, 1H), 6.07 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.56 (dqd, *J* = 7.3, 3.6, 1.2 Hz, 2H), 2.37 (s, 3H), 2.35 – 2.32 (m, 2H), 2.09 – 2.02 (m, 2H), 1.66 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.37, 148.81, 145.58, 136.47, 134.45, 132.53, 129.97, 128.74, 128.13, 127.30, 122.75, 40.74, 39.43, 32.66, 21.96. HRMS (ESI) calcd for $C_{21}H_{22}O_4SNa$ $(M+Na)^+$ 393.1137, found for 393.1229

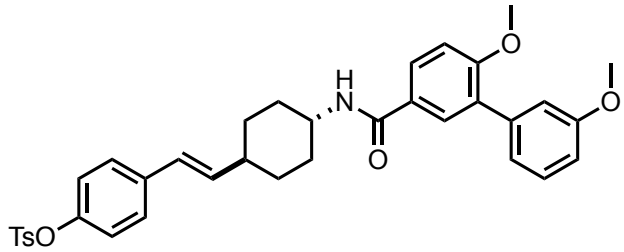


4-((*E*)-2-((1*s*,4*s*)-4-hydroxycyclohexyl)vinyl)phenyl 4-methylbenzenesulfonate (34) A 1M solution of L-Selectride (1.76 mL, 1.76 mmol) was added to a solution of **33** (0.503 g, 1.36 mmol) in anhydrous tetrahydrofuran (14 mL) at -78 °C. The reaction was allowed to warm to room temperature and stirred for 18 hours. Afterwards, the reaction was quenched with water (10 mL) and diluted with ethyl acetate. (20 mL). The organic layer was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (3:1 hexanes/ethyl acetate). This produced the syn-product as a white solid in 62% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.31 (dd, *J* = 16.0, 1.3 Hz, 1H), 6.16 (dd, *J* = 16.0, 6.9 Hz, 1H), 4.00 (m, 1H), 2.44 (s, 3H), 2.21 (m, 1H), 1.76 (m, 2H), 1.68 – 1.60 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.57, 145.52, 137.08, 136.88, 132.57, 129.96, 128.79, 127.18, 126.98, 122.66, 66.88,

39.76, 32.27, 27.06, 21.98. HRMS (ESI) calcd for $C_{21}H_{24}O_4SNa$ $(M+Na)^+$ 395.1293, found for 395.1260

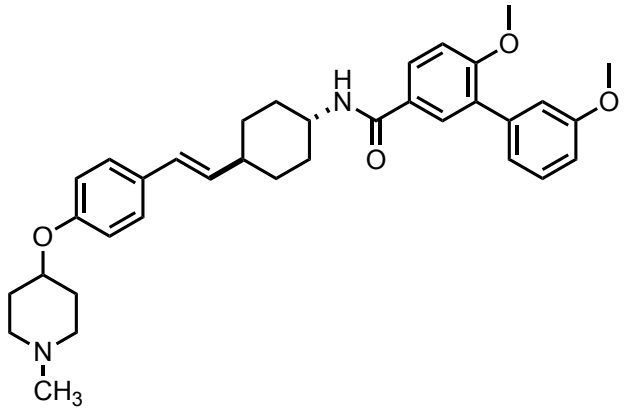


4-((*E*)-2-((1*r*,4*r*)-4-azidocyclohexyl)vinyl)phenyl 4-methylbenzenesulfonate (35) Methanesulfonyl chloride (0.055 mL, 0.706 mmol) and pyridine (0.071 mL, 0.882 mmol) was added to a solution of **34** (0.131 g, 0.353 mmol) in dichloromethane (3.53 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 18 hours. The mixture was diluted with dichloromethane (20 mL) and washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting mesylate was used without further purification. A solution of mesylate (0.159 g, 0.353 mmol) and tetrabutylammonium azide (0.201 g, 0.705 mmol) in anhydrous dimethylformamide (2 mL) was heated to 100 °C for 16 hours. Upon cooling, the mixture was diluted with ethyl acetate (15 mL) and washed with water and saturated sodium chloride solution (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (10% ethyl acetate in hexanes). This produced the anti-product as a white solid in 30% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.29 (m, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.30 (dd, *J* = 16.0, 1.2 Hz, 1H), 6.06 (dd, *J* = 16.0, 7.0 Hz, 1H), 3.26 (tt, *J* = 11.4, 4.1 Hz, 1H), 2.44 (s, 3H), 2.17 – 2.10 (m, 1H), 2.08 – 2.04 (m, 2H), 1.95 – 1.87 (m, 2H), 1.41 (tdd, *J* = 12.8, 11.4, 3.4 Hz, 2H), 1.31 – 1.21 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.65, 145.51, 136.74, 136.07, 132.56, 129.93, 128.74, 127.22, 127.19, 122.67, 59.97, 40.13, 31.49, 31.20, 21.95. HRMS (ESI) calcd for $C_{21}H_{27}N_4O_3S$ $(M+NH_4)^+$ 415.1804, found for 415.2423



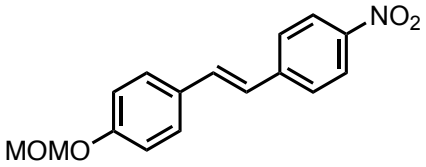
4-((*E*)-2-((1*r*,4*r*)-4-(3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamido)cyclohexyl)vinyl)phenyl 4-methylbenzenesulfonate (36) A solution of 35 (0.050 g, 0.126 mmol), zinc (0.016 g, 0.252 mmol) and ammonium formate (0.016 g, 0.252 mmol) in methanol (1.5 mL) was stirred for 16 hours at room temperature. The reaction mixture was then filtered through a pad of Celite® and diluted with ethyl acetate (10 mL). The organic layer was washed with water (20 mL) and saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting amine was used without further purification. Diisopylethylamine (0.028 mL, 0.166 mmol) was added to a solution of amine (0.041 g, 0.111 mmol), **21** (0.029 g, 0.111 mmol) and *N*-Ethyl-*N*′-(3-

dimethylaminopropyl)carbodiimide hydrochloride (0.032 g, 0.166 mmol) in anhydrous dichloromethane (2 mL). The reaction was stirred at room temperature for 18 hours. Afterwards, the reaction was diluted with ethyl acetate (20 mL) and washed with water (2 X 10 mL) and saturated sodium chloride solution (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (3:1 hexanes/ethyl acetate). This produced the product as a white solid in 33% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.32 – 7.29 (m, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.10 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.06 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.93 – 6.90 (m, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.34 – 6.28 (m, 1H), 6.10 (dd, *J* = 16.0, 7.0 Hz, 1H), 3.96 (ddt, *J* = 11.4, 7.4, 4.1 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.45 (s, 3H), 2.19 – 2.13 (m, 2H), 2.10 (td, *J* = 7.4, 3.6 Hz, 1H), 1.89 (d, *J* = 13.1 Hz, 2H), 1.39 (td, *J* = 12.5, 11.7, 3.1 Hz, 2H), 1.32 – 1.27 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.36, 159.50, 159.10, 148.61, 145.50, 139.26, 136.89, 136.66, 132.56, 130.60, 129.94, 129.42, 129.32, 128.77, 128.39, 127.37, 127.19, 126.96, 122.67, 122.20, 115.59, 112.97, 111.06, 56.01, 55.55, 48.79, 40.63, 33.13, 31.70, 21.96. HRMS (ESI) calcd for $C_{36}H_{37}NO_6SNa$ $(M+Na)^+$ 634.2197, found for 634.2109

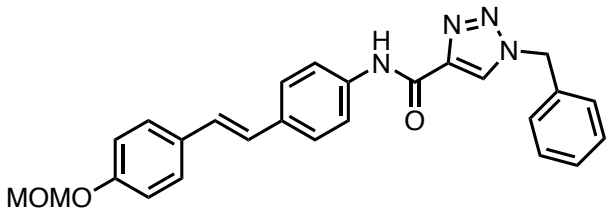


3',6-dimethoxy-*N*-((1*r*,4*r*)-4-((*E*)-4-((1-methylpiperidin-4-yl)oxy)styryl)cyclohexyl)-[1,1'-biphenyl]-3-carboxamide (7)) 3 M sodium hydroxide (0.50 mL) was added to a solution of **36** (0.010 g, 0.016 mmol) in ethanol (0.50 mL) and the mixture was heated at reflux for 1 h. Upon cooling, the mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL) and saturated sodium chloride solution (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting phenol was coupled with N-methyl-4-piperidinol via the general procedure for Mitsunobu etherification. This produced an orange solid in 17% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.04 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.00 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.85 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.25 (dd, *J* = 16.0, 1.1 Hz, 1H), 5.96 (dd, *J* = 15.9, 7.0 Hz, 1H), 4.34 (s, 1H), 3.90 (dtt, *J* = 11.5, 7.8, 3.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.77 (m, 2H), 2.53 (m, 2H), 2.39 (s, 3H), 2.13 – 2.02 (m, 4H), 1.91 – 1.78 (m, 3H), 1.37 – 1.26 (m, 3H), 1.22 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.49, 159.07, 156.30, 139.27, 136.89, 133.83, 131.21, 130.58, 129.43, 129.31, 128.42, 128.37, 127.43, 127.40, 122.21,

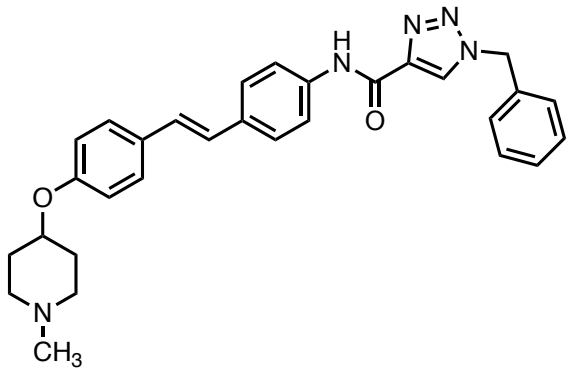
116.34, 115.57, 112.98, 111.05, 56.01, 55.55, 51.89, 48.86, 45.65, 40.65, 33.22, 31.90, 29.92, 29.59. HRMS (ESI) calcd for $C_{35}H_{43}N_2O_4$ $(M+H)^+$ 555.3223, found for 555.3204



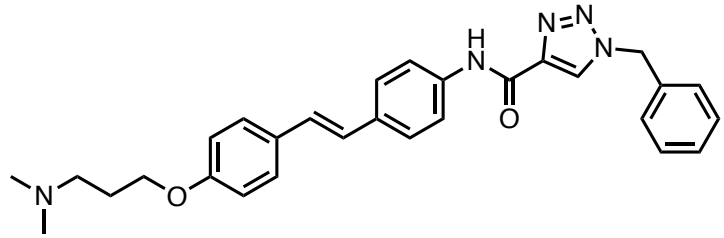
(*E*)-1-(methoxymethoxy)-4-(4-nitrostyryl)benzene (39) was prepared following the same procedure for **15**. This produced a white solid in 87% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.9 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 16.3 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 16.3 Hz, 1H), 5.21 (s, 2H), 3.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.04, 146.72, 144.39, 133.01, 130.28, 128.58, 126.80, 124.80, 124.37, 116.79, 94.54, 56.35. HRMS (ESI) calcd for $C_{16}H_{19}N_2O_4$ $(M+NH_4)^+$ 303.1345, found for 303.2112



(*E*)-1-benzyl-*N*-(4-(4-(methoxymethoxy)styryl)phenyl)-1*H*-1,2,3-triazole-4-carboxamide (52) Iron, which was reduced with hydrogen, (0.489 g, 8.76 mmol) and ammonium chloride (0.469 g, 8.76 mmol) were added to a solution of **39** (0.250 g, 0.876 mmol) in 1:1 ethanol/water (0.1 M). The reaction mixture was heated at reflux for 2 hours. Upon cooling, the mixture was filtered through a pad of Celite® and the filtrate was diluted with dichloromethane. The organic layer was washed with water (2 x 20 ml) and saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting aniline was used in the next reaction without further purification. Diisopylethylamine (0.10 mL, 0.588 mmol) was added to a solution of aniline (0.100 g, 0.392 mmol), 1-benzyl-1*H*-1,2,3-triazole-4-carboxylic acid (0.080 g, 0.392 mmol) and *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.113 g, 0.588 mmol) in anhydrous 4:1 dichloromethane/dimethylformamide (4 mL). The reaction was stirred at room temperature for 18 hours. Afterwards, the reaction was diluted with water (40 mL) and extracted with ethyl acetate. The organic layer washed with saturated sodium chloride (20 mL) and a yellow precipitate was formed. The organic layer was filtered and the precipitate was isolated as the product in 69% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.82 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.53 (t, *J* = 8.6 Hz, 3H), 7.44 – 7.33 (m, 5H), 7.10 (q, *J* = 16.4 Hz, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.70 (s, 2H), 5.20 (s, 2H), 3.38 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 153.51, 140.99, 140.87, 140.02, 135.63, 132.83, 128.84, 128.31, 128.00, 127.59, 127.52, 127.42, 126.82, 126.48, 126.21, 120.40, 116.34, 93.82, 55.59, 53.20. HRMS (ESI) calcd for $C_{24}H_{20}N_4O_2Na$ $(M+Na)^+$ 419.1484, found for 419.1458

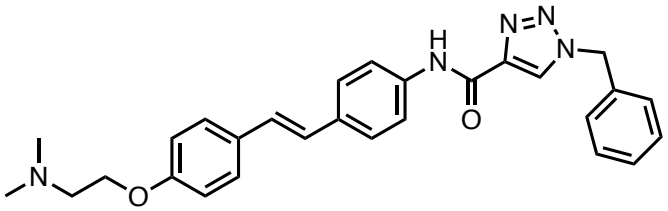


(*E*)-1-benzyl-*N*-(4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-1*H*-1,2,3-triazole-4-carboxamide (44) was prepared following the same procedure for **17**. This produced a white solid in 47% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.04 (s, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.44 – 7.38 (m, 5H), 7.34 – 7.30 (m, 2H), 7.01 (d, *J* = 16.3 Hz, 1H), 6.94 (d, *J* = 16.2 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.59 (s, 2H), 4.36 (m, 1H), 2.73 (m, 2H), 2.34 (s, 3H), 2.11 – 1.99 (m, 2H), 1.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.79, 143.97, 140.17, 137.94, 136.66, 134.24, 133.81, 133.78, 129.59, 129.46, 128.63, 128.54, 127.89, 127.76, 127.43, 127.15, 126.19, 125.86, 120.15, 116.43, 54.93, 46.32, 30.67, 29.93. HRMS (ESI) calcd for $C_{30}H_{32}N_5O_2$ $(M+H)^+$ 494.2556, found for 494.2556

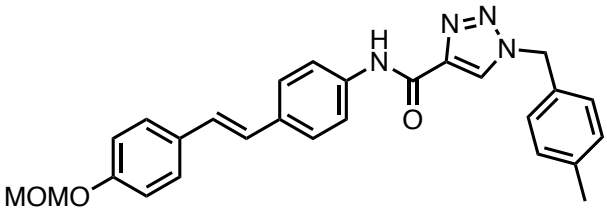


(*E*)-1-benzyl-*N*-(4-(4-(3-(dimethylamino)propoxy)styryl)phenyl)-1*H*-1,2,3-triazole-4-carboxamide (46) 3M hydrochloric acid (0.45 mL, 1.36 mmol) was added to a solution of **52** (0.60 g, 0.136 mmol) in ethanol (2 mL) and the mixture was heated at reflux for 1 h. Upon cooling, the mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL) and saturated sodium chloride solution (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was isolated as a light brown solid and used without further purification. A mixture of phenol (0.033 g, 0.083 mmol), 3-dimethylamino-1-propyl chloride HCl (0.013 g, 0.083 mmol), tetrabutylammonium iodide (0.001 g, 0.0017 mmol) and cesium carbonate (0.057 g, 0.175 mmol) in dimethylformamide (1 mL) was heated to 100 °C for 18 hours. Upon cooling, the reaction mixture was diluted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL) and saturated sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (10% methanol in dichloromethane) and the product was isolated was a white solid in 28% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.05 (s, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.45 – 7.37 (m, 5H), 7.34 – 7.29 (m, 2H), 7.01 (d, *J* = 16.3 Hz, 1H), 6.94 (d, *J* = 16.3 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.59 (s, 2H), 4.04 (t, *J* = 6.4 Hz, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 2.29 (s, 6H), 2.03 – 1.95 (m, 2H). ^{13}C NMR (126 MHz,

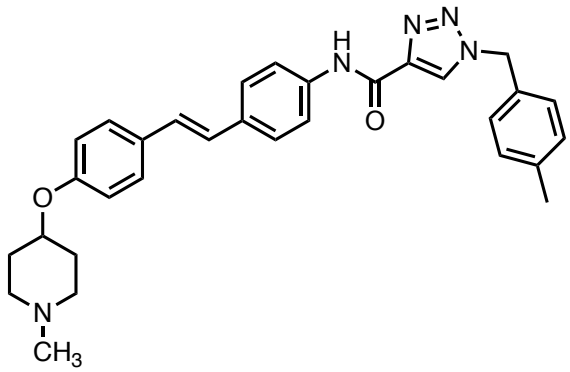
$CDCl_3$) δ 158.89, 157.80, 144.00, 136.64, 134.32, 133.81, 130.32, 129.65, 129.59, 129.45, 128.53, 127.94, 127.93, 127.89, 127.83, 127.13, 126.04, 125.87, 120.17, 114.93, 66.45, 56.59, 54.93, 45.62, 27.65. HRMS (ESI) calcd for $C_{29}H_{32}N_5O_2$ $(M+H)^+$ 482.2556, found for 482.2382



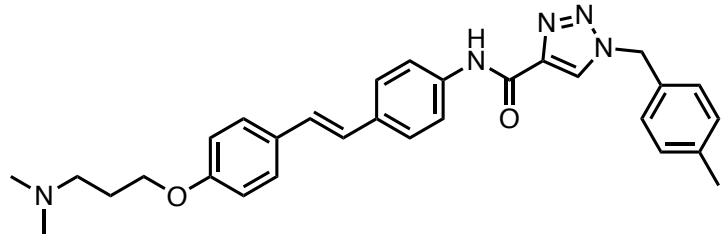
(*E*)-1-benzyl-*N*-(4-(4-(2-(dimethylamino)ethoxy)styryl)phenyl)-1*H*-1,2,3-triazole-4-carboxamide (48) was prepared following the same procedure for **37**. This produced a white solid in 32% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.04 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.45 – 7.39 (m, 5H), 7.31 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 19.3 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.59 (s, 2H), 4.11 (m, 2H), 3.43 – 3.33 (m, 2H), 2.38 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.14, 159.57, 157.02, 139.04, 137.45, 134.01, 131.58, 130.98, 129.71, 129.38, 128.59, 127.80, 127.63, 127.19, 126.64, 122.20, 120.37, 116.67, 115.54, 113.21, 111.33, 94.65, 56.26, 56.09, 55.57. HRMS (ESI) calcd for $C_{29}H_{32}N_5O_2$ $(M+H)^+$ 468.2400, found for 468.2392



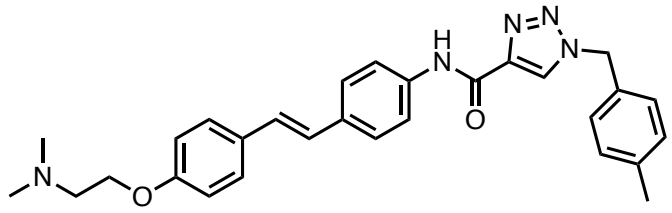
(*E*)-*N*-(4-(4-(methoxymethoxy)styryl)phenyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole-4-carboxamide (53) was prepared following the same procedure for **52**. This produced a orange solid in 55% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.78 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.53 (t, *J* = 8.3 Hz, 4H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 16.4 Hz, 1H), 7.07 (d, *J* = 16.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.64 (s, 2H), 5.20 (s, 2H), 3.38 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 158.16, 156.27, 143.00, 137.74, 137.68, 132.82, 132.61, 130.93, 129.36, 128.05, 127.52, 127.26, 126.81, 126.48, 126.21, 120.39, 116.34, 93.82, 55.59, 53.00, 20.70. HRMS (ESI) calcd for $C_{27}H_{26}N_4O_3Na$ $(M+Na)^+$ 477.1903, found for 477.1909



(*E*)-1-(4-methylbenzyl)-*N*-(4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-1*H*-1,2,3-triazole-4-carboxamide (45) was prepared following the same procedure for **17**. This produced a white solid in 34% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.02 (m, 1H), 7.69 (dd, *J* = 15.0, 8.6 Hz, 2H), 7.54 – 7.44 (m, 2H), 7.38 (dd, *J* = 17.0, 8.7 Hz, 1H), 7.21 (m, 4H), 7.10 (dd, *J* = 17.6, 8.7 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.55 (s, 2H), 4.72 (m, 1H), 3.34 (m, 2H), 3.16 (m, 2H), 2.80 (s, 3H), 2.65 (m, 2H), 2.37 (s, 3H), 2.21 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.79, 143.97, 140.21, 137.94, 136.59, 134.24, 133.74, 133.34, 129.83, 129.46, 128.63, 128.54, 127.89, 127.48, 127.15, 126.19, 125.58, 120.21, 116.43, 93.82, 54.61, 45.21, 32.08, 29.85, 22.23. HRMS (ESI) calcd for $C_{31}H_{34}N_5O_2$ $(M+H)^+$ 508.2713, found for 508.2656

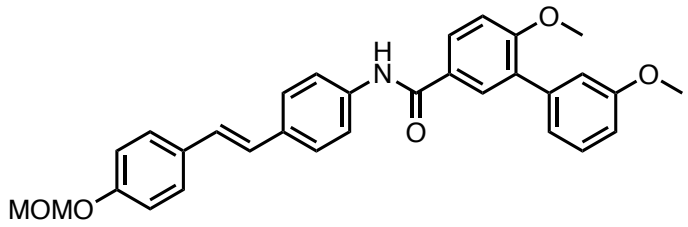


(*E*)-*N*-(4-(4-(3-(dimethylamino)propoxy)styryl)phenyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole-4-carboxamide (38) was prepared following the same procedure for **37**. This produced a white solid in 24% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.03 – 8.90 (m, 1H), 8.02 (s, 1H), 7.69 (dd, *J* = 16.5, 8.6 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.52 – 7.41 (m, 4H), 7.25 – 7.18 (m, 4H), 6.98 (d, *J* = 12.9 Hz, 1H), 6.91 – 6.84 (m, 1H), 5.54 (s, 2H), 4.12 (t, *J* = 5.5 Hz, 2H), 3.24 (m, 2H), 2.86 (s, 6H), 2.43 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.14, 159.57, 139.04, 137.45, 134.01, 130.26, 130.24, 129.71, 129.38, 128.59, 127.80, 127.21, 126.64, 122.20, 120.37, 116.67, 115.54, 113.21, 111.33, 94.65, 56.26, 56.09, 55.57, 27.38. HRMS (ESI) calcd for $C_{30}H_{34}N_5O_2$ $(M+H)^+$ 496.2713, found for 496.2611

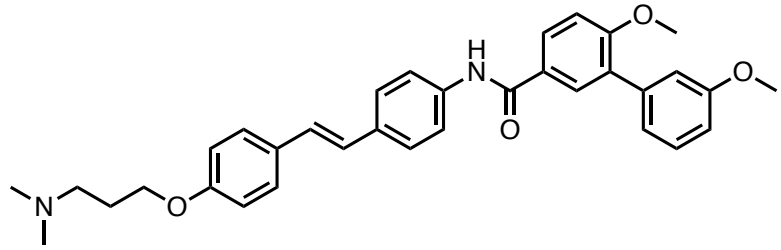


(*E*)-*N*-(4-(4-(2-(dimethylamino)ethoxy)styryl)phenyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole-4-carboxamide (49) was prepared following the same procedure for **37**. This

produced a white solid in 28% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.94 (s, 1H), 8.01 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.21 (s, 4H), 7.01 (d, *J* = 16.3 Hz, 1H), 6.97 – 6.88 (m, 3H), 5.54 (s, 2H), 4.09 (t, *J* = 5.8 Hz, 2H), 2.75 (t, *J* = 5.8 Hz, 2H), 2.37 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.50, 157.61, 143.68, 139.26, 136.46, 134.04, 130.53, 130.25, 130.01, 130.00, 128.36, 127.60, 127.59, 126.92, 125.93, 125.53, 119.93, 114.80, 66.03, 58.29, 54.52, 45.91, 21.19. HRMS (ESI) calcd for $C_{29}H_{32}N_5O_2$ $(M+H)^+$ 482.2556, found for 482.2554



(*E*)-3',6-dimethoxy-*N*-(4-(4-(methoxymethoxy)styryl)phenyl)-[1,1'-biphenyl]-3-carboxamide (54) was prepared following the same procedure for **52**. This produced a light brown solid in 55% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.79 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.13 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 15.8 Hz, 1H), 6.96 – 6.92 (m, 2H), 5.19 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.58, 159.57, 157.02, 139.04, 137.44, 134.01, 131.57, 129.71, 129.38, 128.59, 127.80, 127.77, 127.63, 127.34, 127.19, 126.64, 122.20, 120.37, 116.67, 115.54, 113.21, 111.33, 111.30, 94.65, 56.26, 56.08, 55.56. HRMS (ESI) calcd for $C_{31}H_{30}NO_5$ $(M+H)^+$ 496.2124, found for 496.2728



(*E*)-*N*-(4-(4-(3-(dimethylamino)propoxy)styryl)phenyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (50) was prepared following the same procedure for **37**. This produced a white solid in 42% yield: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.51 (s, 1H), 7.85 (ddd, *J* = 10.1, 8.6, 2.4 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.07 – 7.03 (m, 2H), 7.03 – 7.01 (m, 2H), 7.01 – 6.97 (m, 2H), 6.96 – 6.89 (m, 1H), 6.86 (dtd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 2H), 3.98 (t, *J* = 5.4 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.17 (m, 2H), 2.82 – 2.74 (m, 6H), 2.33 (td, *J* = 13.1, 10.7, 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.53, 156.51, 139.05, 137.92, 136.19, 134.70, 130.87, 129.84, 129.73, 129.38, 129.30, 128.56, 127.93, 127.39, 127.16, 122.19, 120.41, 120.33, 115.52, 114.75, 114.38, 113.15, 111.25, 56.26, 56.07, 55.56, 43.35, 37.69, 37.15, 24.81. HRMS (ESI) calcd for $C_{34}H_{37}N_2O_4$ $(M+H)^+$ 537.2753, found for 537.2723

Anti-proliferation assay

MCF-7 and SKBr3 cells were maintained in a Advanced DMEM/F12 (Gibco) supplemented with non-essential amino acids, 1% L-glutamine (2 mM), 1% penicillin/Streptomycin and 10% FBS. The HCT-116 cell lines were maintained in McCoy's 5a Medium supplemented with 10% FBS and 1% penicillin/Streptomycin. Cells were grown to confluence in a humidified atmosphere (37° C, 5% CO_2), seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach overnight. Compounds at varying concentrations in DMSO (1% DMSO final concentration) were added, and cells were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used at 100% proliferation, and values were adjusted accordingly. IC_{50} values were calculated from separate experiments performed in triplicate using GraphPad Prism.

Western blot Analysis

MCF-7 cells were cultured as described above and treated with various concentrations of drug, GDA in DMSO (0.1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in mammalian protein extraction reagent (MPER, Pierce) lysis buffer containing protease and phosphatase inhibitor cocktails (Roche) on ice for 1 h. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (2.5–20 μg) were electrophoresed under reducing conditions (8% polyacrylamide gel), transferred to a polyvinylidene fluoride membrane (PVDF), and immunoblotted with the corresponding specific antibodies. Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

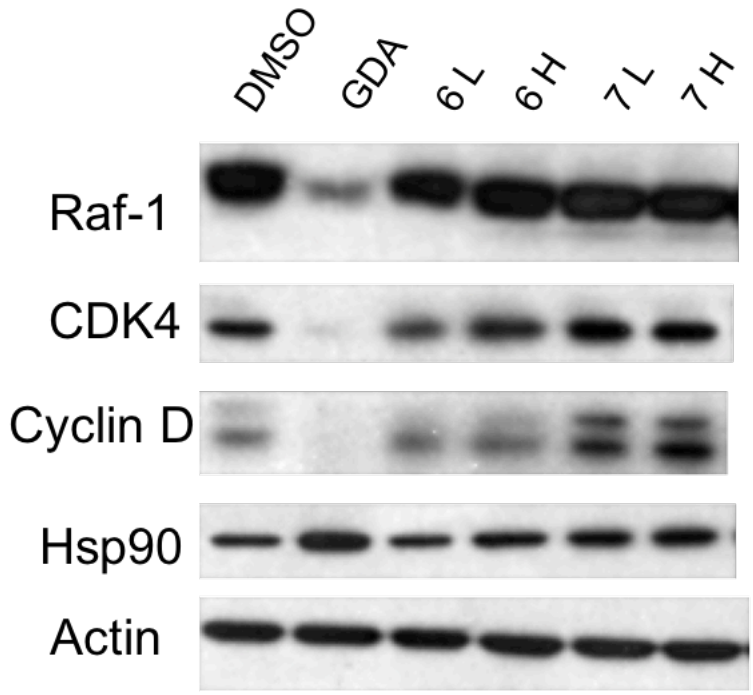
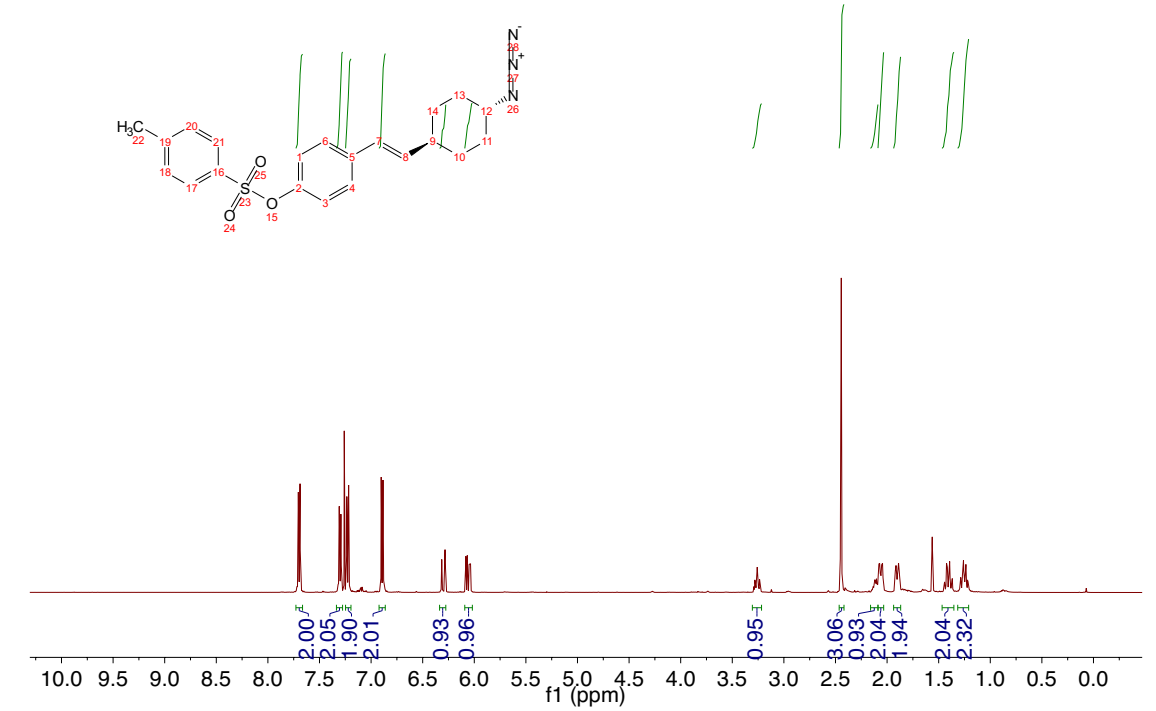
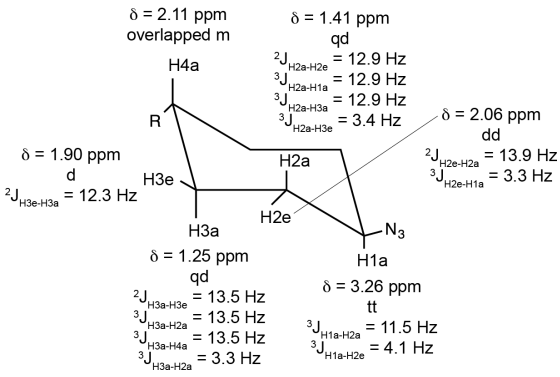
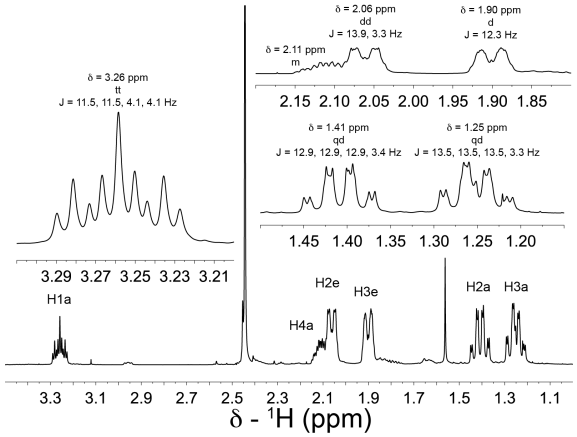


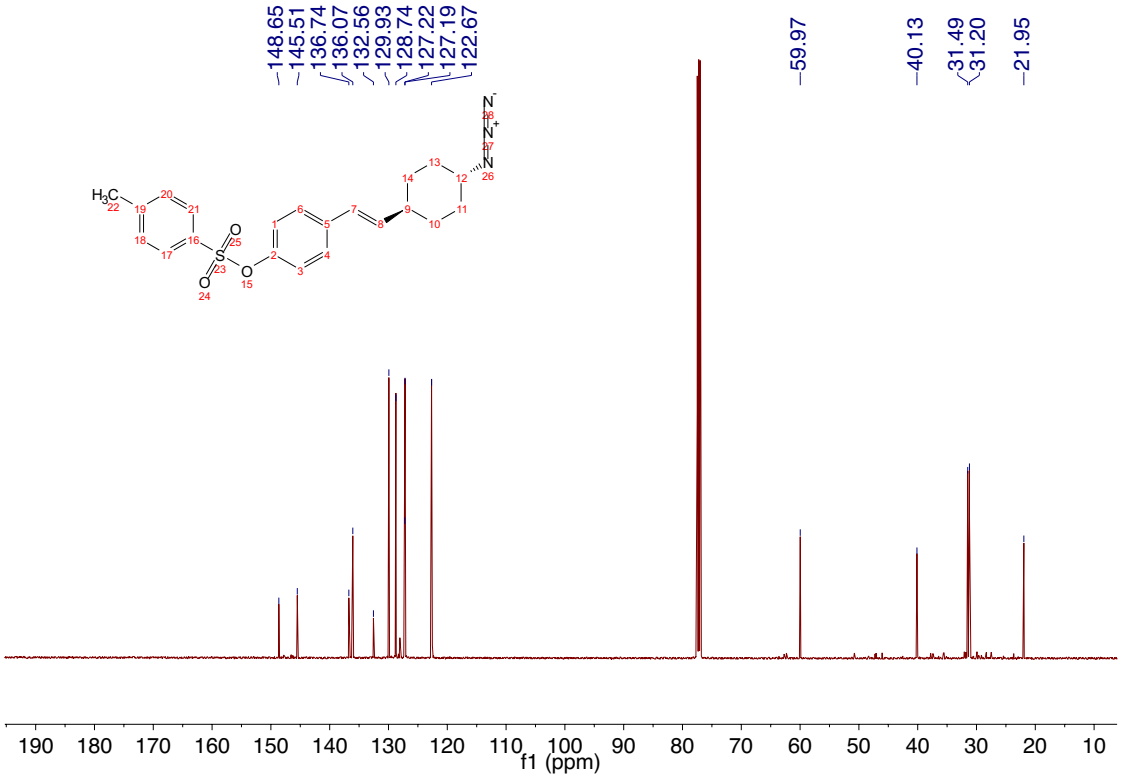
Figure 1S: Western blot analysis of Hsp90 client protein degradation in MCF-7 cells treated with **6** and **7**. Geldanamycin (GDA 500 nm) represents a positive control, while DMSO, represents the negative control. L represents a concentration ½ X IC_{50} value while H represents a concentration of 5 X IC_{50} value.

Select NMR Spectra





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31.20
21.95
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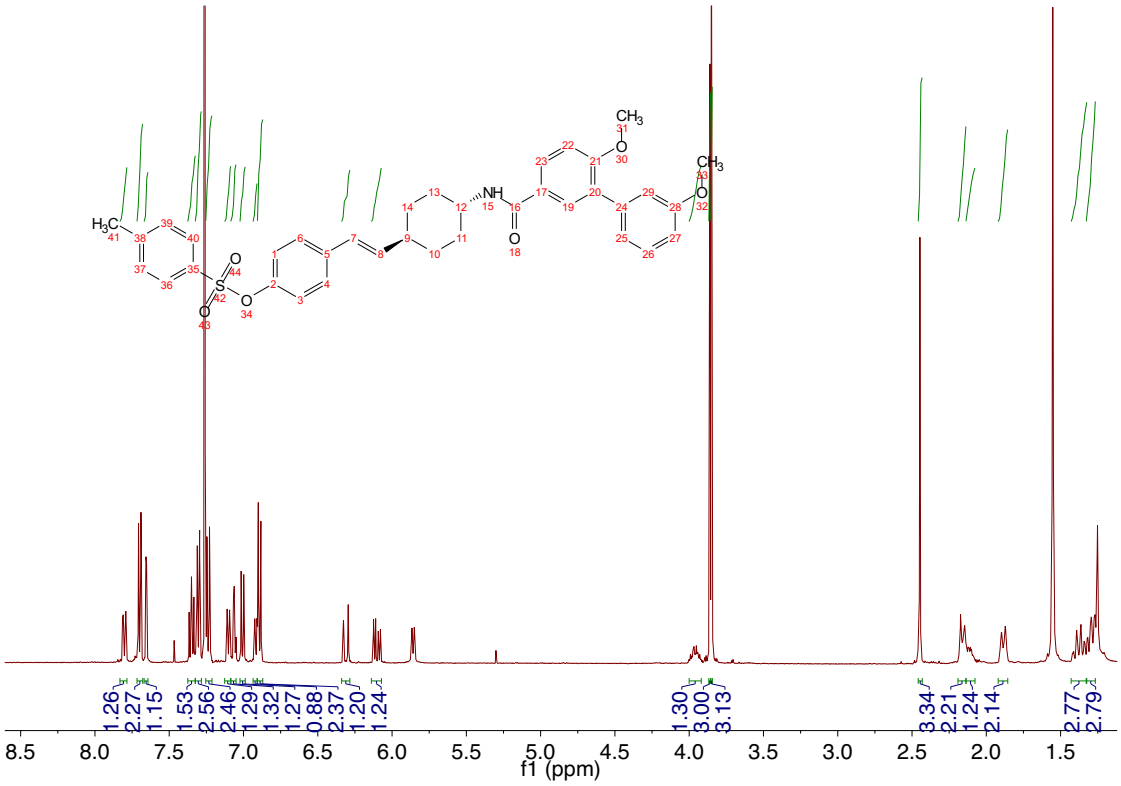
f1 (ppm)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2.27
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1.53
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2.46
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1.32
1.27
0.88
2.37
1.20
1.24
1.30
3.00
3.13
3.34
2.21
1.24
2.14
2.77
2.79
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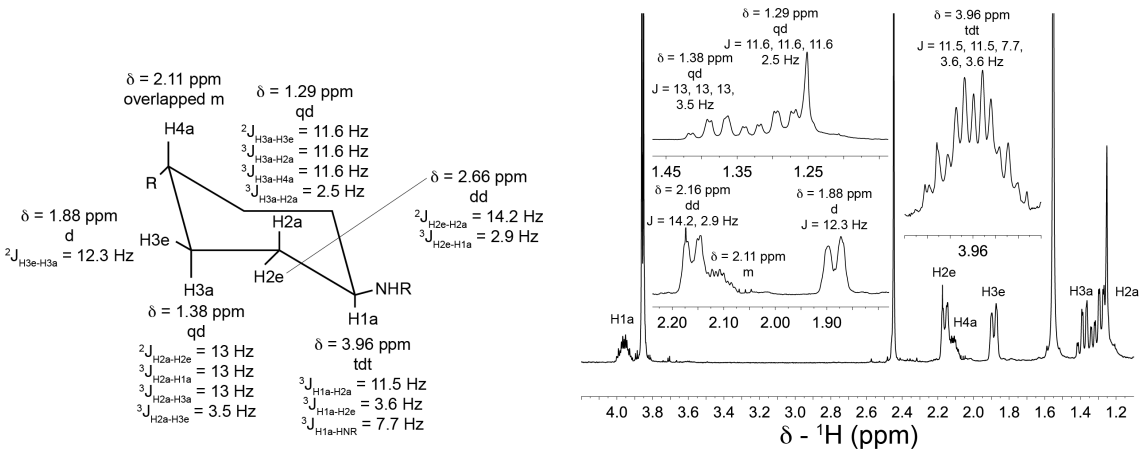
f1 (ppm)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overlapped m
δ = 1.29 ppm
qd
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$^3J_{H3a-H2a}$ = 11.6 Hz
$^3J_{H3a-H4a}$ = 11.6 Hz
$^3J_{H3a-H2a}$ = 2.5 Hz
δ = 2.66 ppm
dd
$^2J_{H2e-H2a}$ = 14.2 Hz
$^3J_{H2e-H1a}$ = 2.9 Hz
δ = 1.88 ppm
d
$^2J_{H3e-H3a}$ = 12.3 Hz
H4a
R
H3e
H2a
H3a
H2e
NHR
H1a
δ = 1.38 ppm
qd
$^2J_{H2a-H2e}$ = 13 Hz
$^3J_{H2a-H1a}$ = 13 Hz
$^3J_{H2a-H3a}$ = 13 Hz
$^3J_{H2a-H3e}$ = 3.5 Hz
δ = 3.96 ppm
tdt
$^3J_{H1a-H2a}$ = 11.5 Hz
$^3J_{H1a-H2e}$ = 3.6 Hz
$^3J_{H1a-HNR}$ = 7.7 Hz
δ = 1.29 ppm
qd
J = 11.6, 11.6, 11.6
2.5 Hz
δ = 1.38 ppm
qd
J = 13, 13, 13,
3.5 Hz
δ = 3.96 ppm
tdt
J = 11.5, 11.5, 7.7,
3.6, 3.6 Hz
1.45
1.35
1.25
δ = 2.16 ppm
dd
J = 14.2, 2.9 Hz
δ = 1.88 ppm
d
J = 12.3 Hz
δ = 2.11 ppm
m
3.96
H2e
H3e
H3a
H2a
H1a
H4a
2.20
2.10
2.00
1.90
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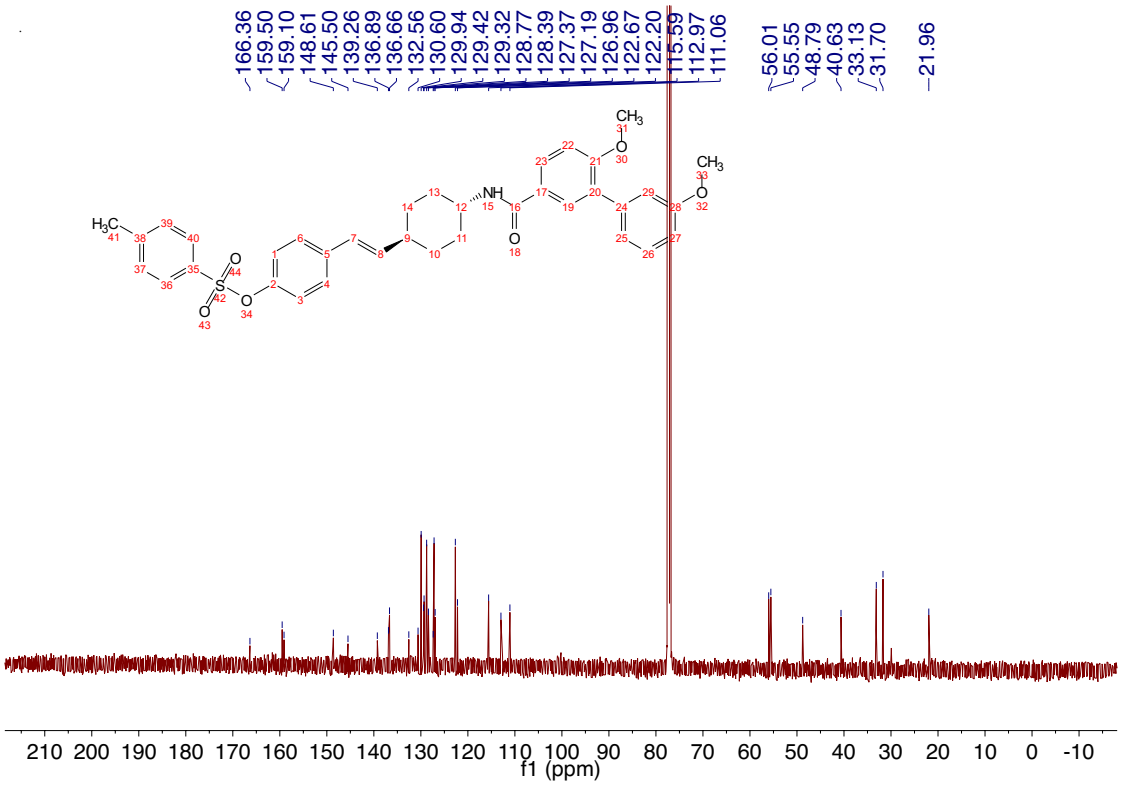
δ - ^{1}H (ppm)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128.77
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33.13
31.70
21.96
CH_3
CH_3
NH
H_3C
O
S
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Reference

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