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Supporting Information

Synthesis and Biological Evaluation of Novobiocin Core Analogues as Hsp90 Inhibitors

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Supporting Information for Hsp90 paper

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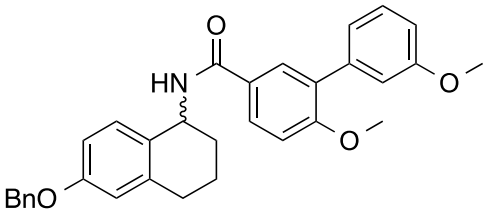
General

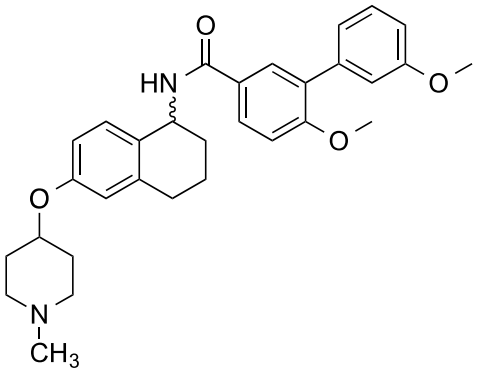
^{1}H NMR were recorded at 400 or 500 MHz (Bruker DRX- 400 Bruker with a H/C/P/F QNP gradient probe) spectrometer and ^{13}C NMR spectra were recorded at 125 MHz (Bruker DRX 500 with broadband, inverse triple resonance, and high resolution magic angle spinning HR-MA probe spectrometer); chemical shifts are reported in δ (ppm) relative to the internal reference $CDCl_3$ ($CDCl_3$, 7.26 ppm). FAB (HRMS) spectra were recorded with a LCT Premier (Waters Corp., Milford, MA) spectrometer and IR spectra were recorded on a Magna FT-IR spectrometer (Nicolet Instrument Corporation, Madison, WI). The purity of all compounds was determined to be >95% as determined by ^{1}H NMR and ^{13}C NMR spectra, unless otherwise noted. The most active 10 compounds were verified for >95% purity by HPLC analyses. 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:

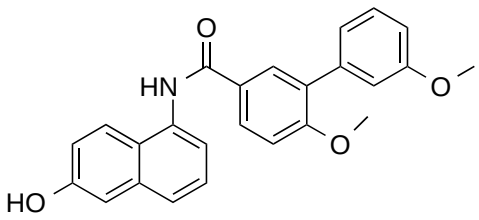


***N*-(6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (31a)** Ammonium acetate (1.094 g, 14.19 mmol) and sodium cyanoborohydride (0.892 g, 14.19 mmol) were added to a microwave vial (20 mL) containing a solution of 6-(benzyloxy)-3,4-dihydronaphthalen-1(2*H*)-one[1] (0.5 g, 2.84 mmol) in dry methanol (11.5 mL). The mixture was heated at 60 °C for 18 h. Upon cooling to rt, the solvent was removed under reduced pressure and the resulting residue diluted with water (10 mL), followed by the slow addition of concentrated hydrochloric acid (8 mL). The acidic solution was extracted with diethyl ether (2 x 10 mL) and the aqueous layer basified with 10 N sodium hydroxide (5 mL). The basic aqueous layer was extracted twice with ethyl acetate (2 x 10 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to yield the amine. Which was used in the next reaction without further purification. Diisopropylethylamine (0.16 mL, 0.908 mmol) was added dropwise to a mixture of amine (0.153 g, 0.605 mmol), carboxylic acid **A** (0.156 g, 0.605 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.174 g, 0.908 mmol) in anhydrous dichloromethane (6.1 mL) at 25 °C. The mixture was stirred at rt for 18h before it was quenched with water (5 mL). The mixture was extracted with dichloromethane (20 mL) and the organic layer washed with sat'd sodium chloride solution (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (3:1 hexanes/ethyl acetate), which provied a beige solid in 73% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J*=8.6, 2.4 Hz, 1H), 7.68 (d, *J*=2.4 Hz, 1H), 7.44–7.35 (m, 4H), 7.35–7.30 (m, 2H), 7.08 (ddd, *J*=7.6, 1.6, 1.1 Hz, 1H), 7.05 (dd, *J*=2.6, 1.5 Hz, 1H), 7.00 (d, *J*=8.6 Hz, 1H), 6.90 (ddd, *J*=8.2, 2.6, 0.9 Hz, 1H), 6.81 (dd, *J*=8.5, 2.7 Hz, 1H), 6.73 (d, *J*=2.6 Hz, 1H), 6.23 (d, *J*=8.2 Hz, 1H), 5.34 (dt, *J*=8.2, 5.7 Hz, 1H), 5.04 (s, 2H), 3.85 (s, 3H), 3.84 (s,

3H), 2.86–2.72 (m, 2H), 2.14–2.07 (m, 1H), 1.98–1.92 (m, 1H), 1.88–1.84 (m, 2H), 1.62 (s, br, 1H, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.22, 159.46, 159.19, 158.10, 139.40, 139.16, 137.18, 130.70, 130.41, 129.58, 129.41, 129.29, 128.80 (2C), 128.37, 128.17, 127.64 (2C), 127.14, 122.20, 115.51, 114.75, 113.72, 113.04, 111.03, 70.16, 56.01, 55.53, 47.63, 30.52, 29.86, 20.12. HRMS (ESI) calcd for $C_{32}H_{31}NO_4$ $(M+)^+$ 493.2253, found for 493.2227.

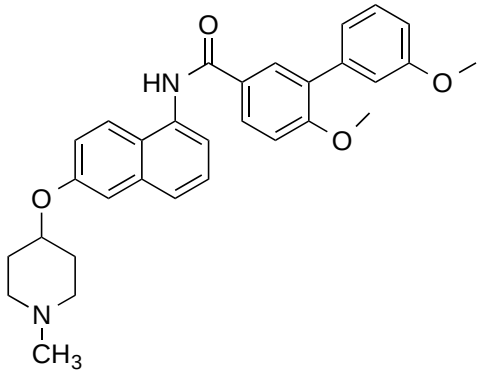


3',6-dimethoxy-*N*-(6-((1-methylpiperidin-4-yl)oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)-[1,1'-biphenyl]-3-carboxamide (6) 10% Palladium on carbon (0.1 equiv.) was added to a degassed solution of **31a** (0.0265 g, 0.0536 mmol) in ethanol (3 mL). The system was purged with argon and before the mixture 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 yield the phenol (**32a**) as a white solid. Phenol **32a** was used in the next reaction without further purification. Tributylphosphine (0.020 mL, 0.0805 mmol) and 1,-1'-azobis(N,N-dimethylformamide) (TMAD) (0.0139 g, 0.0805 mmol) were added to a solution of phenol **32a** (0.0216 g, 0.0537 mmol) and *N*-methyl-4-piperidinol (0.0093 g, 0. 0805 mmol) in benzene (1 mL) at 0 °C.[2] The resulting mixture was 70 °C and the stirred for 24 h. Upon cooling to rt, the mixture was diluted with ethyl acetate (20 mL), filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (10% methanol in dichloromethane), which provided a white solid in 32% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.24 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.08 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.05 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.90 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.74 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.66 (d, *J* = 2.6 Hz, 1H), 6.24 (d, *J* = 8.2 Hz, 1H), 5.38 – 5.30 (m, 1H), 4.30 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.78 (dt, *J* = 16.4, 6.4 Hz, 2H), 2.70 (d, *J* = 12.6 Hz, 2H), 2.31 (s, 3H), 2.14 – 2.07 (m, 1H), 2.04 – 1.89 (m, 3H), 1.90 – 1.82 (m, 3H) 1.62 (s, br, 1H, NH). . ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.21, 159.45, 159.17, 156.69, 139.40, 139.16, 130.67, 130.40, 129.54, 129.28, 129.22, 128.39, 127.13, 122.18, 116.08, 115.52, 114.67, 112.99, 111.02, 56.00, 55.52, 52.82, 47.62, 46.40 (2C), 38.52, 31.00, 30.51 (2C), 29.82, 20.12. HRMS (ESI) calcd for $C_{31}H_{37}N_2O_4$ $(M+H)^+$ 501.2753, found for 501.2791



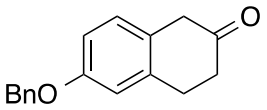
***N*-(6-hydroxynaphthalen-1-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (59)**
Tetrahydrofuran (3.25 mL) was added to a mixture of 5-amino-2-napthol (0.114 g, 0.715 mmol), carboxylic acid **A** (0.180 g, 0.650 mmol) and DMT-MM (0.198 g, 0.715 mmol).[3] The slurry was stirred for 3 d at rt. The reaction mixture was poured into water (10 mL) and extracted with diethyl ether (2 x 10 mL). The organic layer was washed with sat'd sodium carbonate (10 mL), water (10 mL), 1M hydrochloric acid (10 mL) and sat'd 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% ethyl acetate in hexanes then 1:1 hexanes/ethyl acetate) to provided a light purple solid in 54% yield: ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 – 8.07 (m, 1H), 8.04 (s, 1H), 7.85 (d, *J* = 9.1 Hz, 1H), 7.62 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.42 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.15 – 7.11 (m, 2H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.5, 1.1 Hz, 1H), 4.62 (s, 1H), 3.92 (s, 3H), 3.83 (s, 3H), 2.16 (s, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 169.47, 161.01, 160.83, 156.77, 140.49, 137.50, 134.74, 131.99, 131.48, 130.01, 127.71, 126.95, 126.59, 125.89, 125.69, 125.48, 123.05, 122.36, 119.66, 116.35, 113.73, 112.26, 110.32, 56.32, 55.70. HRMS (ESI) calcd for $C_{25}H_{21}NO_4Na$ $(M+Na)^+$ 422.1368, found for 422.1354

General Procedure A for Mitsunobu etherification:
Tributylphosphine (0.030 mL, 0.121 mmol) and 1,-1'-azobis(N,N-dimethylformamide) (TMAD) (0.021 g, 0.121 mmol) were added to a solution of phenol **59** (0.032 g, 0.081 mmol) and N-methyl-4-piperidinol (0.014 g, 0.121 mmol) in benzene (1.5 mL) at 0 °C. The resulting mixture was heated at 70 °C and the stirred for 24 h. Upon cooling to rt, the mixture was diluted with ethyl acetate (20 mL), filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (10% methanol in dichloromethane).

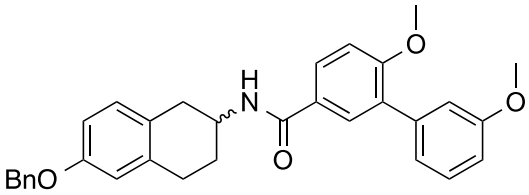


3',6-dimethoxy-*N*-(6-((1-methylpiperidin-4-yl)oxy)naphthalen-1-yl)-[1,1'-biphenyl]-3-carboxamide (7) was prepared following general procedure A for Mitsunobu etherification, which produced a white solid in 43% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.00 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.19 (q, *J* = 2.5 Hz, 2H), 7.18 – 7.14 (m, 2H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.93 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.55 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.82 (s, 2H), 2.49 (d, *J* = 18.6 Hz, 2H), 2.42 (s, 3H), 2.21 – 2.15 (m, 2H), 1.98 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.96, 159.65, 159.56, 155.38, 139.04, 135.73, 132.93, 131.04, 129.98, 129.40, 128.71, 127.22, 126.76, 125.18, 123.41, 123.18, 122.21, 120.12, 119.70, 115.55,

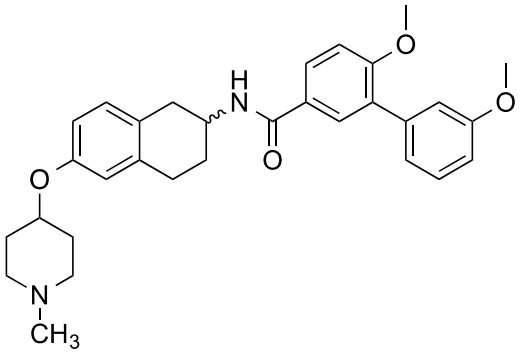
113.20, 111.31, 109.74, 56.11, 55.56, 53.65, 45.99 (2C), 36.34 (2C), 30.23. HRMS (ESI) calcd for $C_{31}H_{32}N_2O_4$ $(M+H)^+$ 497.2440, found for 497.2432



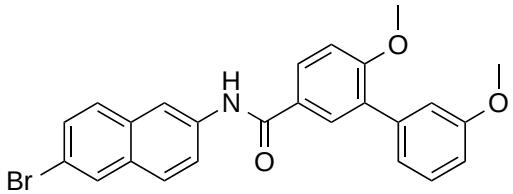
6-(benzyloxy)-3,4-dihydronaphthalen-2(1*H*)-one (58) Benzyl bromide (0.20 mL, 1.70 mmol) was added dropwise to a solution of 6-hydroxyl-3,4-dihydronaphtalen-2(1H)-one (0.250 g, 1.54 mmol), potassium iodide (0.026 g, 0.154 mmol) and cesium carbonate (0.602 g, 1.85 mmol) in anhydrousrous acetonitrile (12 mL). The mixture was heat to 50 °C and stirred for 16 h. Upon cooling, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (40 mL) and the organic solution was washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrousrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% ethyl acetate in hexanes), which produced the a light brown solid in 86% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.44 (m, 2H), 7.42–7.38 (m, 2H), 7.36–7.32 (m, 1H), 7.06–7.03 (m, 1H), 6.89 (d, *J*=2.6 Hz, 1H), 6.85 (dd, *J*=2.7, 8.2 Hz, 1H), 5.08 (s, 2H), 3.54 (s, 2H), 3.03 (t, *J* = 6.7 Hz, 2H), 2.55 (dd, *J* = 6.3, 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.17, 157.90, 138.15, 137.13, 129.34, 128.82 (2C), 128.20, 127.64 (2C), 125.69, 114.43, 113.41, 70.28, 44.49, 38.35, 28.83. HRMS (ESI) calcd for $C_{17}H_{16}O_2Na(M+Na)^+$ 501.2753, found for 501.2791



***N*-(6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide** (**31b**) was prepared following the same procedure for the synthesis of **31a**. This produced a white solid in 62% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.40 – 7.31 (m, 4H), 7.09 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.05 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.00 (dd, *J* = 8.5, 5.1 Hz, 2H), 6.91 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 6.06 (d, *J* = 7.8 Hz, 1H), 5.03 (s, 2H), 4.50 – 4.45 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.17 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.98 – 2.84 (m, 2H), 2.68 (dd, *J* = 15.9, 8.3 Hz, 1H), 2.16 (ddd, *J* = 8.3, 3.7, 1.9 Hz, 1H), 1.86 (dtd, *J* = 12.7, 9.1, 5.9 Hz, 1H), 1.71 (s,br, 1H, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.71, 159.47, 159.14, 157.39, 139.18, 137.33, 136.91, 130.65, 130.59, 129.57, 129.30, 128.78, 128.31, 128.12, 127.67, 127.26, 126.60, 122.20, 115.52, 114.64, 113.38, 113.03, 111.01, 70.21, 56.00, 55.53, 46.06, 35.31, 28.98, 27.78. HRMS (ESI) calcd for $C_{32}H_{32}NO_4$ $(M+H)^+$ 494.2331, found for 494.2342



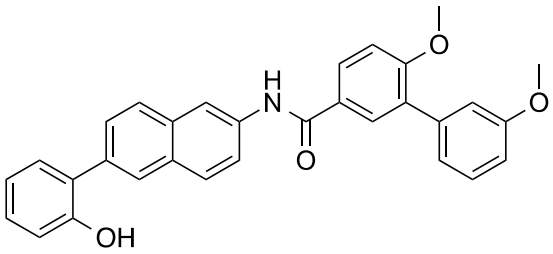
3',6-dimethoxy-*N*-(6-((1-methylpiperidin-4-yl)oxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-[1,1'-biphenyl]-3-carboxamide (**8**) was prepared following the same procedure for the synthesis of **31a**. This produced a white solid in 53% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J*=8.6, 2.4 Hz, 1H), 7.67 (d, *J*=2.4 Hz, 1H), 7.36–7.31 (m, 1H), 7.09 (ddd, *J*=7.6, 1.6, 1.0 Hz, 1H), 7.05 (dd, *J*=2.6, 1.5 Hz, 1H), 6.99 (dd, *J*=8.5, 2.8 Hz, 2H), 6.91 (ddd, *J*=8.3, 2.7, 1.0 Hz, 1H), 6.71 (dd, *J*=8.4, 2.7 Hz, 1H), 6.66 (d, *J*=2.6 Hz, 1H), 6.04 (d, *J*=7.8 Hz, 1H), 4.50–4.43 (m, 1H), 4.29 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.16 (dd, *J*=15.9, 5.2 Hz, 1H), 2.97–2.82 (m, 2H), 2.75–2.64 (m, 3H), 2.33 (s, 3H), 2.15 (dddd, *J*=12.3, 5.4, 4.2, 1.2 Hz, 1H), 2.03 (dt, *J*=10.6, 3.7 Hz, 2H), 1.89–1.82 (m, 4H), 1.73 (s,br, 1H, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.70, 159.48, 159.15, 155.85, 139.18, 136.96, 130.64, 130.62, 129.54, 129.31, 128.33, 127.27, 126.59, 122.20, 116.12, 115.53, 114.50, 113.03, 111.02, 56.00, 55.54, 52.71, 46.29, 46.06 (2C), 35.31 (2C), 30.85, 28.98 (2C), 27.76. HRMS (ESI) calcd for $C_{31}H_{37}N_2O_4$ $(M+H)^+$ 501.2753, found for 501.2700



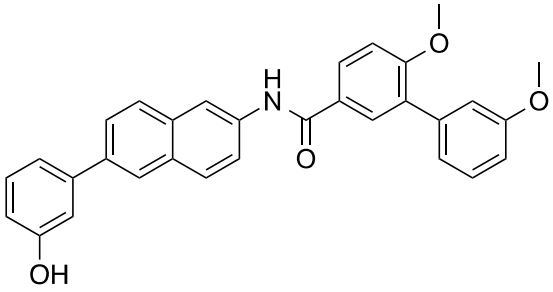
***N*-(6-bromonaphthalen-2-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (34)** A solution of 6-amino-2-bromonaphthalene (0.150 g, 0.675 mmol) in anhydrous dichloromethane (2 mL) was added to a solution of acid chloride C (0.280 g, 1.01 mmol) and triethylamine (0.56 mL, 4.052 mmol) in anhydrous dichloromethane (6.8 mL) at rt. After stirring for 16 h, the mixture was concentrated under reduced pressure. The resulting residue was purified via column chromatography (3:1 hexanes/ethyl acetate), which produced a light pink solid in 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.2 Hz, 1H), 7.97 – 7.94 (m, 2H), 7.92 (s, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.71 – 7.69 (m, 1H), 7.58 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.54 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.14 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.10 (s, 1H), 6.95 – 6.93 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 1.71 (s,br, 1H, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.44, 159.72, 159.57, 138.97, 136.12, 132.59, 131.85, 131.03, 130.14, 129.83, 129.71, 129.58, 129.42, 128.67, 128.15, 127.12, 122.18, 121.22, 119.03, 116.91, 115.56, 113.20, 111.38, 56.11, 55.57. HRMS (ESI) calcd for $C_{25}H_{21}BrNO_3$ $(M+H)^+$ 462.0705, found for 462.0724

General procedure for Suzuki coupling: A 4:1 solution of dimethylformamide/water (2.5 mL) was added to a microwave vial (5 mL) containing **34**, 2-hydroxyphenylboronic acid and

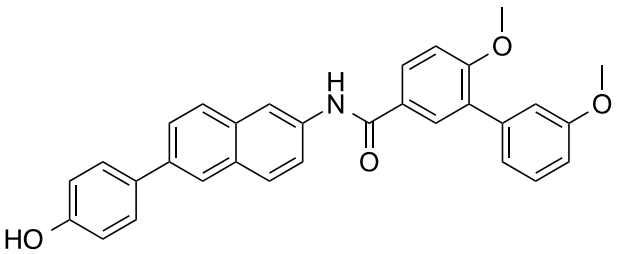
potassium carbonate under argon. The resulting mixture was degassed for 30 min. Then $Pd(dppf)Cl_2$ was added and the mixture was degassed for 10 min. Next, vial was placed in the microwave reactor and heated at 130 °C for 30 min. The mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL) and sat.'d sodium chloride solution (10 mL). The organic layer was dried over anhydrousrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (1:1 hexanes/ethyl acetate).



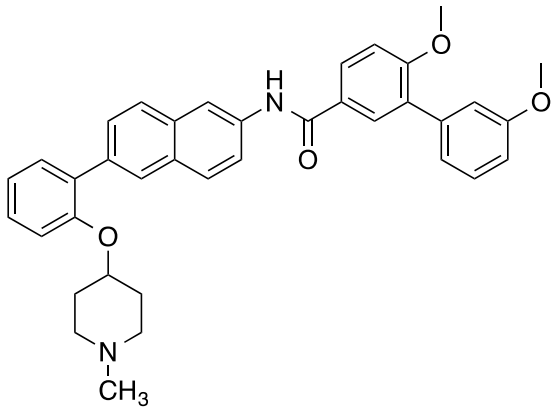
***N*-(6-(2-hydroxyphenyl)naphthalen-2-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (35a)** was prepared following the general procedure for Suzuki coupling. This produced a beige solid in 70% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 2.3 Hz, 1H), 8.00 – 7.94 (m, 3H), 7.91 (d, *J* = 1.7 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.63 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.58 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 7.15 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.12 – 7.09 (m, 2H), 7.06 – 6.99 (m, 2H), 6.94 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.32 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.43, 159.68, 159.57, 152.80, 139.00, 136.27, 133.82, 133.46, 131.01, 130.65, 130.54, 129.73, 129.42, 129.19, 129.14, 128.69, 128.20, 128.06, 127.76, 127.20, 122.20, 121.17, 120.93, 116.77, 116.11, 115.56, 113.19, 111.36, 108.48, 56.11, 55.57. HRMS (ESI) calcd for $C_{31}H_{26}NO_4$ $(M+H)^+$ 476.1862, found for 476.1885



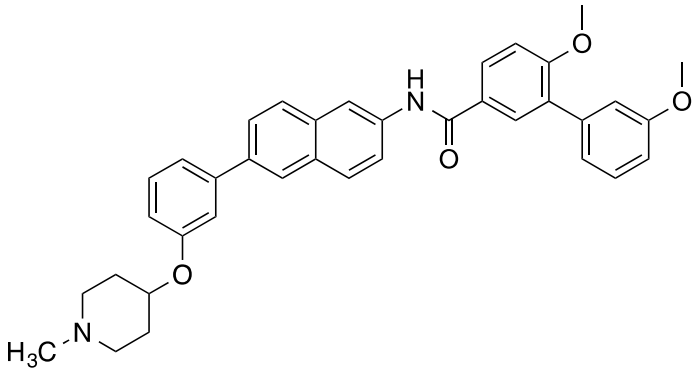
***N*-(6-(3-hydroxyphenyl)naphthalen-2-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (35b)** was prepared following the same procedure for the synthesis of **35a** This produced a beige solid in 62% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.1 Hz, 1H), 7.99 – 7.95 (m, 3H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 16.0, 8.7 Hz, 2H), 7.68 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.36 (dt, *J* = 15.7, 7.9 Hz, 2H), 7.28 (dd, *J* = 1.6, 1.0 Hz, 1H), 7.24 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.15 (ddd, *J* = 7.6, 1.6, 0.9 Hz, 1H), 7.12 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.94 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 6.86 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1H), 5.63 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.74, 159.70, 159.56, 156.46, 142.87, 138.98, 137.63, 135.72, 133.36, 131.09, 131.09, 131.01, 130.28, 129.73, 129.41, 128.73, 128.44, 127.15, 126.43, 125.67, 122.21, 120.68, 119.90, 116.90, 115.53, 114.55, 114.44, 113.24, 111.41, 56.10, 55.57. HRMS (ESI) calcd for $C_{31}H_{25}NO_4Na$ $(M+Na)^+$ 498.1760, found for 498.1715



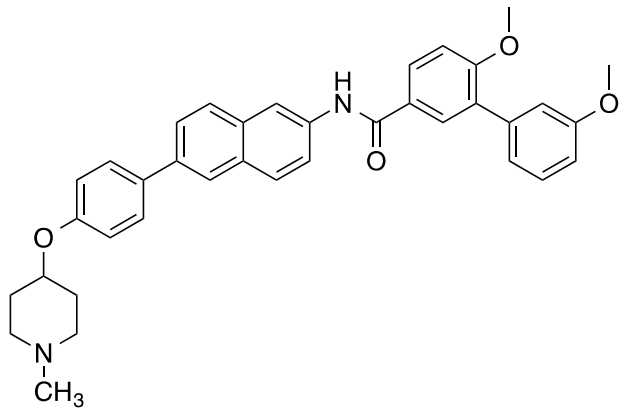
***N*-(6-(4-hydroxyphenyl)naphthalen-2-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (35c)** was prepared following the same procedure for the synthesis of **35a** This produced a beige solid in 63% yield: ^{1}H NMR (500 MHz, CD_3OD) δ 8.29 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 2H), 7.87 (dd, *J* = 19.2, 8.7 Hz, 2H), 7.76 – 7.71 (m, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.13 (dd, *J* = 7.4, 1.4 Hz, 2H), 6.94 – 6.88 (m, 3H), 6.61 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 168.54, 160.94, 160.85, 158.31, 151.24, 140.51, 139.07, 137.30, 133.94, 133.53, 132.65, 131.95, 131.34, 130.01, 129.92, 129.58, 129.22, 129.07, 128.28, 126.78, 125.22, 123.06, 122.54, 118.80, 116.77, 116.73, 116.40, 113.70, 112.22, 56.32, 55.71. HRMS (ESI) calcd for $C_{31}H_{25}NO_4Na$ $(M+Na)^+$ 498.1760, found for 498.1687



3',6-dimethoxy-*N*-(6-(2-((1-methylpiperidin-4-yl)oxy)phenyl)naphthalen-2-yl)-[1,1'-biphenyl]-3-carboxamide (10) was prepared following general procedure A for the Mitsunobu etherification. This produced a white solid in 53% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.99 – 7.96 (m, 2H), 7.93 (d, *J* = 1.7 Hz, 1H), 7.86 (dd, *J* = 7.7, 2.1 Hz, 2H), 7.70 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.36 – 7.33 (m, 1H), 7.16 – 7.14 (m, 1H), 7.11 (d, *J* = 2.3 Hz, 2H), 7.08 – 7.05 (m, 1H), 6.94 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 4.52 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.59 (m, 2H), 2.40 (m, 2H), 2.11 (s, 3H), 1.90 (m, 2H), 1.63 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.27, 159.49, 159.37, 159.16, 157.96, 142.89, 139.02, 138.79, 135.91, 133.40, 132.82, 131.19, 130.80, 130.45, 129.51, 129.23, 128.98, 128.88, 128.49, 128.07, 126.97, 125.73, 121.99, 120.45, 116.54, 115.91, 115.38, 112.96, 111.17, 55.90, 55.37, 53.66, 46.24 (2C), 36.34, 30.80, 29.93. HRMS (ESI) calcd for $C_{37}H_{37}N_2O_4$ $(M+H)^+$ 573.2753, found for 573.2699

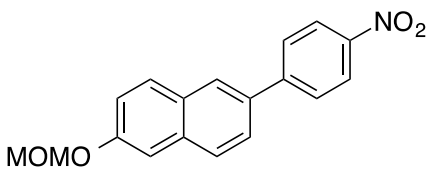


3',6-dimethoxy-*N*-(6-(3-((1-methylpiperidin-4-yl)oxy)phenyl)naphthalen-2-yl)-[1,1'-biphenyl]-3-carboxamide (12) was prepared following the general procedure A for the Mitsunobu etherification. This produced a white solid in 53% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.3 Hz, 1H), 7.99 – 7.96 (m, 3H), 7.91 – 7.85 (m, 3H), 7.73 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.38 (td, *J* = 7.9, 4.6 Hz, 2H), 7.31 (dd, *J* = 1.7, 1.0 Hz, 1H), 7.15 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.93 (tdd, *J* = 8.4, 2.6, 0.9 Hz, 2H), 6.39 (s, 1H), 4.46 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.78 (s, 2H), 2.38 – 2.36 (s, 3H), 2.11 (m, 2H), 1.95 (m, 2H), 1.67 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.41, 159.63, 159.56, 159.16, 157.96, 142.89, 139.02, 137.73, 135.91, 133.40, 131.04, 130.97, 130.13, 129.74, 129.41, 129.34, 128.67, 128.43, 127.30, 126.45, 125.73, 122.20, 120.70, 120.25, 116.74, 115.54, 114.89, 113.20, 111.34, 56.10, 55.56, 53.66, 46.24 (2C), 36.34, 30.80, 29.93. HRMS (ESI) calcd for $C_{37}H_{37}N_2O_4$ $(M+H)^+$ 573.2753, found for 573.2520

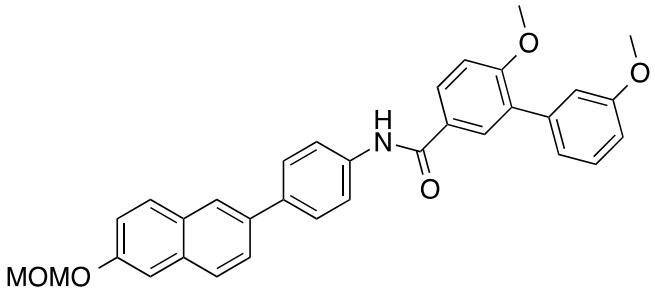


3',6-dimethoxy-*N*-(6-(4-((1-methylpiperidin-4-yl)oxy)phenyl)naphthalen-2-yl)-[1,1'-biphenyl]-3-carboxamide (14) was prepared following the general procedure A for the Mitsunobu etherification. This produced a white solid in 60% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.2 Hz, 1H), 8.00 (s, 1H), 7.97 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.94 – 7.93 (m, 1H), 7.88 – 7.84 (m, 2H), 7.71 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.61 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.16 – 7.13 (m, 1H), 7.11 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.94 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.39 (s, 1H), 4.43 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.80 (d, *J* = 10.3 Hz, 2H), 2.45 (m, 2H), 2.39 (s, 3H), 2.13 (s, 2H), 1.95 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.41, 159.59, 159.55, 159.15, 157.05, 139.02, 137.49, 135.64, 133.97, 132.97, 131.18, 130.94, 129.75, 129.39, 129.16, 128.66, 128.59 (2C), 128.39, 127.33, 126.27, 124.93, 122.20, 120.68, 116.80, 116.59, 115.52, 113.19,

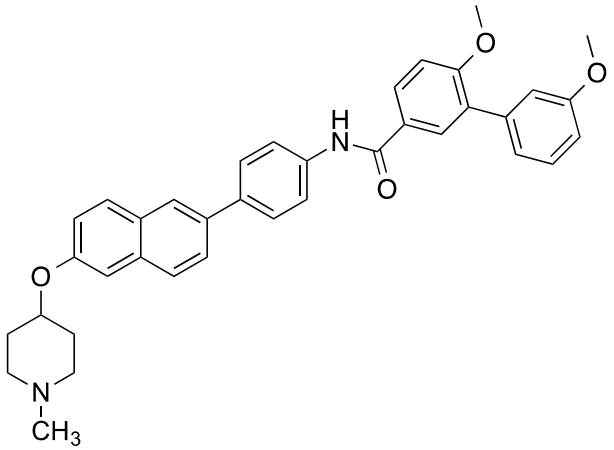
111.32, 56.08, 55.55, 52.51, 46.12 (2C), 36.33 (2C), 30.58. HRMS (ESI) calcd for $C_{37}H_{37}N_2O_4$ $(M+H)^+$ 573.2753, found for 573.2585



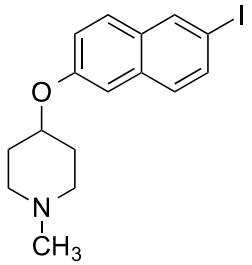
2-(methoxymethoxy)-6-(4-nitrophenyl)naphthalene (60) was prepared following the general procedure for the Suzuki coupling. This produced a white solid in 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 1.9 Hz, 1H), 7.88 – 7.84 (m, 4H), 7.72 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.29 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.33 (s, 2H), 3.55 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.09, 147.82, 147.07, 134.64, 134.36, 130.24, 129.64, 128.32, 127.96 (2C), 126.77, 125.58, 124.40 (2C), 120.17, 109.84, 94.68, 56.43. HRMS (ESI) calcd for $C_{18}H_{15}NO_4Na$ $(M+Na)^+$ 332.0899, found for 332.3339



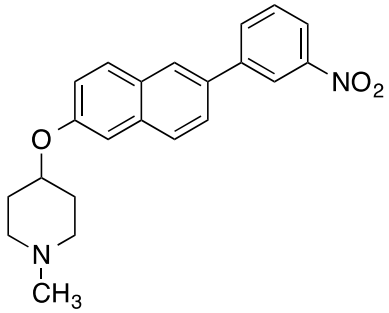
3',6-dimethoxy-*N*-(4-(6-(methoxymethoxy)naphthalen-2-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (61) 10% Palladium on carbon (0.1 equiv.) was added to a degassed solution of **60** (0.100 g, 0.323 mmol) in ethanol (3 mL). The system was purged with argon and before the mixture was stirred at room temperature for 18 hours under H_2 gas. The mixture was filtered through a pad of Celite® and concentrated under reduced pressure to yield the corresponding aniline as a white solid. A solution of aniline (0.060 g, 0.215 mmol) in anhydrous dichloromethane (1 mL) was added to a solution of acid chloride C (0.0892 g, 0.322 mmol) and triethylamine (0.18 mL, 1.29 mmol) in anhydrous dichloromethane (1 mL) at rt. After stirring for 16 h, the mixture was concentrated under reduced pressure. The resulting residue was purified via column chromatography (3:1 hexanes/ethyl acetate), which produced a white solid in 73% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.96 – 7.93 (m, 1H), 7.84 (d, *J* = 2.3 Hz, 2H), 7.83 – 7.79 (m, 2H), 7.77 – 7.74 (m, 2H), 7.74 – 7.70 (m, 3H), 7.42 (d, *J* = 2.5 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.14 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.10 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.94 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.32 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.54 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.29, 159.60, 159.56, 155.31, 153.71, 139.03, 137.47, 137.42, , 136.28, 133.88, 133.73, 130.97, 130.33, 129.93, 129.91, 128.64, 127.98, 127.13, 126.20, 126.01, 125.51, 122.20, 120.70, 119.63, 118.44, 115.54, 113.20, 111.32, 109.95, 94.76, 56.35, 56.09, 55.57. HRMS (ESI) calcd for $C_{33}H_{29}NO_5Na$ $(M+Na)^+$ 542.1943, found for 542.1945



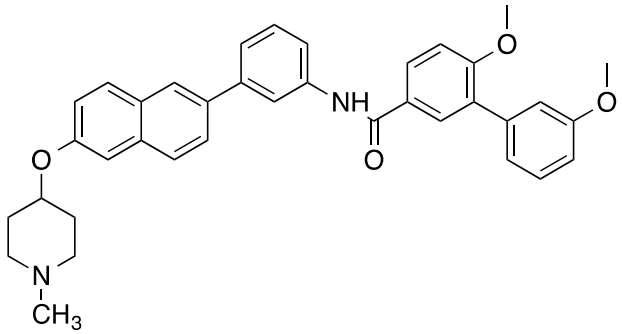
3',6-dimethoxy-*N*-(4-(6-((1-methylpiperidin-4-yl)oxy)naphthalen-2-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (62) 3M hydrochloric acid (0.40 mL, 1.207 mmol) was added to a solution of **61** (0.0627 g, 0.121 mmol) in methanol (2 mL) and the mixture was heated at reflux for 1 h. Upon cooling, the mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL) and sat'd sodium chloride solution (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting phenol was used in the Mitsunobu etherification (procedure A) without and further purification. This produced a beige solid in 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.94 (m, 2H), 7.89 – 7.85 (m, 3H), 7.76 (dd, *J* = 9.2, 6.8 Hz, 5H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.15 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 2H), 7.11 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.95 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 4.58 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.72 (m, 2H), 2.35 (s, 3H), 2.17 (d, *J* = 13.1 Hz, 2H), 2.03 (d, *J* = 20.3 Hz, 2H), 1.87 (s, 2H), 1.68 (s, 1H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.27, 159.55, 159.55, 155.31, 153.71, 139.03, 132.97, 131.18, 130.95, 130.94, 129.76, 129.39, 129.16, 128.63, 128.59 (2C), 128.39, 127.97, 127.33, 126.27, 124.93, 122.20, 120.65, 119.63, 118.44, 116.59, 115.52, 113.19, 111.29, 56.09, 55.56, 52.51, 46.33 (2C), 36.33 (2C), 30.58. HRMS (ESI) calcd for $C_{37}H_{37}N_2O_4$ $(M+H)^+$ 573.2753, found for 573.2595



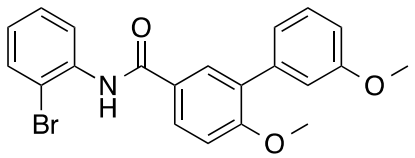
4-((6-iodonaphthalen-2-yl)oxy)-1-methylpiperidine (63) was prepared following general procedure A for the Mitsunobu etherification of 6-iodonaphthalen-2-ol. This produced a white solid in 90% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.6 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 4.46 (m, 1H), 2.72 (d, *J* = 9.2 Hz, 2H), 2.39 – 2.34 (m, 2H), 2.34 (s, 3H), 2.08 (ddt, *J* = 13.5, 7.5, 3.6 Hz, 2H), 1.92 (dtd, *J* = 11.4, 7.6, 3.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.91, 136.44, 134.92, 133.52, 130.79, 128.69, 128.50, 120.70, 108.65, 88.33, 52.81, 46.40 (2C), 36.34 (2C), 30.85. HRMS (ESI) calcd for $C_{16}H_{19}INO$ $(M+H)^+$ 368.0511, found for 368.0511



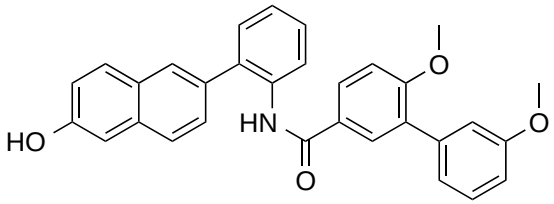
1-methyl-4-((6-(3-nitrophenyl)naphthalen-2-yl)oxy)piperidine (64) was prepared following the general procedure for the Suzuki coupling. This produced a white solid in 75% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (t, *J* = 2.0 Hz, 1H), 8.21 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.05 – 8.00 (m, 2H), 7.86 – 7.81 (m, 2H), 7.71 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.23 – 7.17 (m, 2H), 4.56 (s, 1H), 2.81 (m, 2H), 2.48 (m, 2H), 2.40 (s, 3H), 2.17 (d, *J* = 9.9 Hz, 2H), 1.99 (d, *J* = 12.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.08, 149.01, 143.06, 134.51, 133.98, 133.23, 130.27, 129.97, 129.22, 127.94, 126.32, 125.54, 122.13, 122.01, 120.74, 108.54, 52.54, 46.16 (2C), 30.48 (2C), 29.92. HRMS (ESI) calcd for $C_{22}H_{23}N_2O_3$ $(M+H)^+$ 363.1709, found for 363.1717



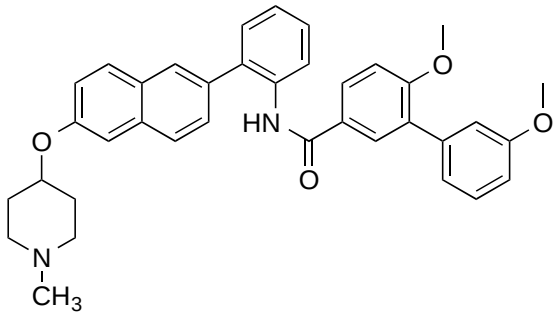
3',6-dimethoxy-*N*-(3-(6-((1-methylpiperidin-4-yl)oxy)naphthalen-2-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (65) was prepared following the same procedure for the synthesis of **61**. This produced a white solid in 53% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.02 – 8.01 (m, 1H), 7.96 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.88 (s, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.79 – 7.73 (m, 2H), 7.61 (dt, *J* = 7.0, 2.1 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 7.17 – 7.13 (m, 2H), 7.11 – 7.09 (m, 2H), 6.93 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.62 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.98 – 2.87 (m, 2H), 2.50 (s, 3H), 2.35 – 2.22 (m, 4H), 2.10 – 2.03 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.36, 159.62, 159.55, 155.31, 153.71, 142.28, 139.02, 138.81, 134.01, 132.97, 130.97, 130.32, 129.76, 129.72, 129.40, 128.65, 127.44, 127.27, 126.36, 125.93, 123.45, 122.20, 120.74, 119.11, 118.98, 115.54, 113.18, 111.33, 108.75, 56.09, 55.57, 52.51, 46.12 (2C), 36.33 (2C), 29.93. HRMS (ESI) calcd for $C_{37}H_{37}N_2O_4$ $(M+H)^+$ 573.2753, found for 573.2771



***N*-(2-bromophenyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (66)** was prepared following the same procedure for the synthesis of **34**. This produced a beige solid in 84% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.43 (s, 1H), 7.95 – 7.89 (m, 2H), 7.57 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.14 (ddd, *J* = 7.6, 1.6, 0.9 Hz, 1H), 7.11 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.09 (d, *J* = 8.6 Hz,1H), 7.01 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 6.93 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.98, 159.82, 159.52, 138.91, 136.15, 132.41, 131.15, 130.10, 129.38, 128.74, 128.34, 127.06, 125.26, 122.17, 121.90, 115.43, 113.88, 113.28, 111.29, 56.09, 55.52. HRMS (ESI) calcd for $C_{21}H_{18}BrNO_3Na$ $(M+Na)^+$ 434.0368, found for 434.0356

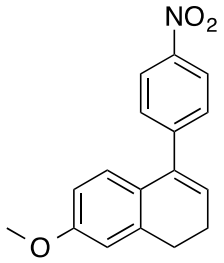


***N*-(2-(6-hydroxynaphthalen-2-yl)phenyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (67)** was prepared following the general procedure for the Suzuki coupling. This produced a white solid in 73% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.11 (s, 1H), 7.84 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.73 – 7.71 (m, 1H), 7.66 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.50 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.47 (t, *J* = 2.4 Hz, 1H), 7.46 – 7.43 (m, 1H), 7.38 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.22 (d, *J* = 3.2 Hz, 1H), 7.20 – 7.19 (m, 1H), 7.12 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.88 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.79 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 5.41 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.84, 159.40, 159.32, 154.32, 138.76, 135.48, 134.16, 133.23, 132.36, 130.74, 130.38, 130.08, 129.46, 129.28, 129.15, 128.79, 128.59, 128.43, 127.92, 127.70, 127.16, 124.47, 121.93, 121.19, 119.03, 115.22, 113.18, 111.26, 109.76, 55.98, 55.45. HRMS (ESI) calcd for $C_{31}H_{25}NO_4Na$ $(M+Na)^+$ 498.1681, found for 498.1701

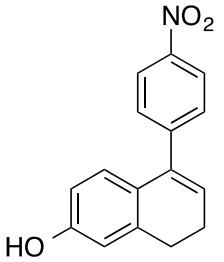


3',6-dimethoxy-*N*-(2-(6-((1-methylpiperidin-4-yl)oxy)naphthalen-2-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (68) was prepared following general procedure A for the Mitsunobu etherification of **67**. This produced a white solid in 67% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.77 – 7.71 (m, 1H), 7.67 – 7.62 (m, 2H), 7.53 – 7.49 (m, 2H), 7.45 (td, *J* = 7.8, 1.7 Hz, 1H), 7.37 (td, *J* = 6.6, 6.0, 3.3 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.21 – 7.16 (m, 2H), 6.98 (s,

1H), 6.94 – 6.79 (m, 4H), 4.59 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.75 (d, *J* = 43.7 Hz, 2H), 2.45 (s, 2H), 2.36 (s, 3H), 2.18 (m, 2H), 2.02 (d, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.02, 159.35, 159.33, 159.30, 138.80, 135.50, 135.37, 134.10, 133.40, 132.30, 130.89, 130.67, 129.86, 129.50, 128.78, 128.45, 128.39, 127.95, 127.90, 125.59, 124.55, 124.40, 121.93, 121.18, 120.73, 115.25, 113.24, 111.24, 108.65, 55.92, 55.45, 52.59, 46.24 (2C), 30.90 (2C), 29.92. HRMS (ESI) calcd for $C_{37}H_{37}N_2O_4$ $(M+H)^+$ 573.2753, found for 573.2682

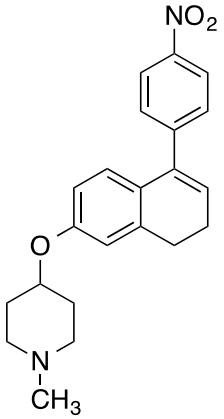


7-methoxy-4-(4-nitrophenyl)-1,2-dihydronaphthalene (39a) The general Suzuki coupling conditions were applied to coupling of vinyl triflate **37** and 4-nitrophenylboronic acid. This compound required the use of a vinyl triflate (**27**)[4] instead of an aryl halide. This produced a white solid in 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.07 (t, *J* = 4.7 Hz, 1H), 3.82 (s, 3H), 2.84 (t, *J* = 7.9 Hz, 2H), 2.43 (ddd, *J* = 9.1, 7.1, 4.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.19, 148.16, 147.12, 138.87, 138.30, 129.55, 127.85, 127.24, 126.49, 123.82, 114.27, 111.12, 55.52, 28.77, 23.73. HRMS (ESI) calcd for $C_{17}H_{15}NO_3Na$ $(M+Na)^+$ 304.0950, found for 304.2986

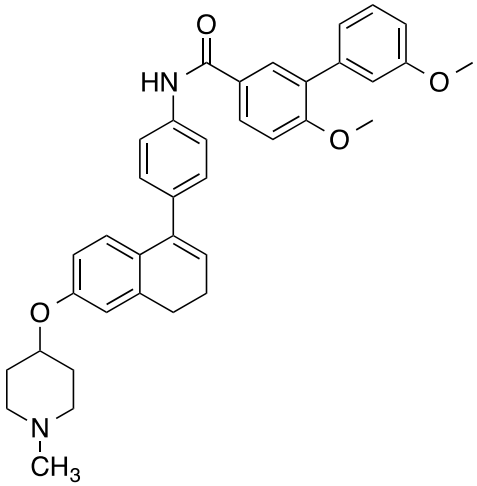


5-(4-nitrophenyl)-7,8-dihydronaphthalen-2-ol (40a) A solution of 1M solution of boron tribromide (3.82 mL, 3.82 mmol) in dichloromethane was added dropwise to a solution of **39a** (0.358 g, 1.27 mmol) in anhydrous dichloromethane, at -78 °C. The mixture was allowed to warm to rt and stirred to 14 h. The reaction was carefully quenched with sat'd aqueous ammonium chloride solution (5 mL). The mixture was extracted with dichloromethane (2 x 20) and 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), which produced a yellow oil in 70% yield: ^{1}H NMR (500 MHz, CD_3OD) δ 8.35 (dd, *J* = 8.8, 7.5 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.16 (dd, *J* = 5.5, 1.4 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.90 – 6.86 (m, 1H), 6.71 (d, *J* = 3.7 Hz, 1H), 2.95 (m, 1H), 2.89 (s, 2H), 2.88 (s, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 154.53, 148.16, 147.12, 136.77, 134.44, 133.59, 131.91, 131.42, 128.50, 127.32, 124.29, 116.64, 116.39, 101.39, 36.09, 30.16. HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3NH_4$ $(M+NH_4)^+$ 285.1239, found for 285.1687

General Procedure B for Mitsunobu etherification: Diisopropylazodicarboxylate (0.16 mL, 0.814 mmol) was added to a solution of **40a** (0.108 g, 0.405 mmol), N-methyl-4-piperidinol (0.056 g, 0.486 mmol) and triphenylphosphine (0.213 g, 0.814 mmol) in anhydrous THF (4 mL). The reaction mixture was then stirred at rt for 12 hours. Afterwards, the reaction mixture was concentrated under reduced pressure and the residue was purified via column chromatography (10% methanol in dichloromethane).

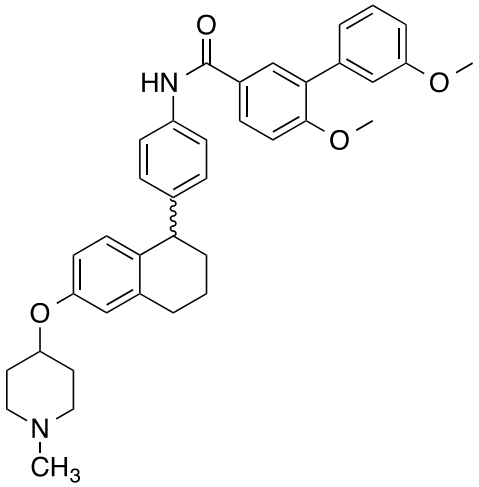


1-methyl-4-((5-(4-nitrophenyl)-7,8-dihydronaphthalen-2-yl)oxy)piperidine (41a) was prepared following procedure B for the Mitsunobu etherification of **40a**. This produced a beige solid was produced in 53% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (ddd, *J* = 7.9, 2.3, 1.4 Hz, 1H), 8.12 (td, *J* = 1.7, 0.8 Hz, 1H), 7.63-7.60 (m, 2H), 7.58 (dt, *J* = 7.6, 1.5 Hz, 1H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.55 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.41 (d, *J* = 8.6 Hz, 1H), 4.31 (s, 1H), 2.98 (dq, *J* = 12.6, 7.1 Hz, 4H), 2.70 (s, 2H), 2.33 (s, 3H), 2.03 (m, 2H), 1.88-1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.09, 148.55, 141.57, 136.51, 136.27, 136.24, 129.61, 128.31, 127.10, 125.23, 122.79, 121.98, 116.05, 113.31, 46.26, 35.15, 30.74, 29.91. HRMS (ESI) calcd for $C_{22}H_{23}N_2O_3$ $(M-H)^-$ 363.1709, found for 363.2239

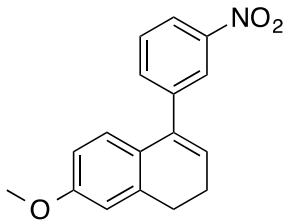


3',6-dimethoxy-*N*-(4-(6-((1-methylpiperidin-4-yl)oxy)-3,4-dihydronaphthalen-1-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (18) Hydrazine hydrate (0.01 mL, 0.233 mmol) was added dropwise to a microwave vial (5 mL) containing **41a** (0.425 g, 0.117 mmol) and iron (II) sulfate heptahydrate (0.0016 g, 0.00583) in a 1:1 solution of water/ethanol (2 mL).[5] This mixture was heated at 120 °C for 12 h. Upon cooling, the mixture was diluted with ethyl acetate (10 mL) and

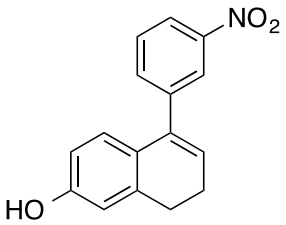
washed with water (5 mL) and sat'd sodium chloride solution (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting aniline **42a** was used in the next reaction without further purification. A solution of aniline (0.039 g, 0.117 mmol) in anhydrous dichloromethane (1 mL) was added to a solution of acid chloride C (0.0484 g, 0.117 mmol) and triethylamine (0.05 mL, 0.699 mmol) in anhydrous dichloromethane (1 mL) at rt. After stirring for 16 h, the mixture was concentrated under reduced pressure. The resulting residue was purified via column chromatography (3:1 hexanes/ethyl acetate), which produced a white solid in 34% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 9.3, 0.8 Hz, 1H), 7.97 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.93 (s, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.55 (dd, *J* = 9.3, 0.8 Hz, 1H), 7.40 – 7.35 (m, 4H), 7.16 – 7.14 (m, 1H), 7.12 – 7.09 (m, 3H), 6.94 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 4.51 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.92 – 2.87 (m, 4H), 2.80 (m, 2H), 2.36 (s, 3H), 2.27 (s, 2H), 2.22 (s, 2H), 2.07 – 1.99 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.39, 159.64, 159.56, 139.02, 137.44, 132.31, 132.14, 130.98, 129.75, 129.42, 128.68, 126.58, 122.19, 119.95, 115.60, 113.14, 111.34, 56.10, 55.57, 55.15, 46.27 (2C), 29.92 (2C), 29.27, 22.29, 22.17. HRMS (ESI) calcd for $C_{37}H_{38}N_2O_4$ $(M)^+$ 574.2832, found for 574.9377



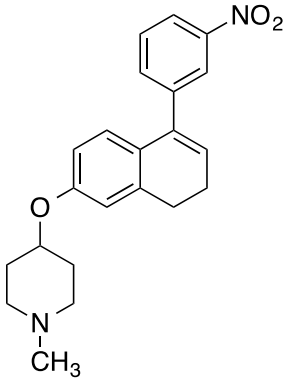
3',6-dimethoxy-*N*-(4-(6-((1-methylpiperidin-4-yl)oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (17) was prepared following the same procedure for the synthesis of **61**. The yielded a white solid in 32% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 1H), 7.85 – 7.79 (m, 1H), 7.75 – 7.71 (m, 1H), 7.68 – 7.63 (m, 1H), 7.56 – 7.50 (m, 1H), 7.40 – 7.31 (m, 2H), 7.16 – 7.03 (m, 4H), 7.01 (s, 1H), 6.93 (dddd, *J* = 8.3, 3.7, 2.6, 0.9 Hz, 1H), 6.79 – 6.72 (m, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.00 (t, *J* = 4.7 Hz, 1H), 4.42 (d, *J* = 28.8 Hz, 1H), 3.92 – 3.88 (s, 3H), 3.86 (s, 3H), 2.88 – 2.82 (m, 2H), 2.81 – 2.67 (m, 2H), 2.41 – 2.37 (m, 4H), 2.32 (s, 3H), 2.15 – 2.07 (m, 2H), 2.02 – 1.93 (m, 2H), 1.89 – 1.81 (m, 2H), 1.77 – 1.69 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.28, 159.55, 143.24, 139.02, 138.32, 137.45, 136.36, 134.79, 131.36, 130.95, 130.36, 129.74, 129.71, 128.59, 128.54, 127.42, 127.36, 126.47, 122.18, 120.43, 120.23, 115.91, 114.08, 113.22, 111.31, 56.07, 55.55, 52.23, 46.45, 44.66, 44.50, 33.66, 33.35, 30.29, 30.04, 28.69, 23.56. HRMS (ESI) calcd for $C_{37}H_{41}N_2O_4$ $(M+H)^+$ 577.3066, found for 577.3128



7-methoxy-4-(3-nitrophenyl)-1,2-dihydronaphthalene (39b) was prepared following the procedure used to synthesize **39a**. This produced a white solid in 83% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (t, *J* = 2.0 Hz, 1H), 8.18 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.68 (ddd, *J* = 7.6, 1.6, 1.1 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.05 (t, *J* = 4.7 Hz, 1H), 3.82 (s, 3H), 2.86 (t, *J* = 7.9 Hz, 2H), 2.44 (ddd, *J* = 9.1, 7.3, 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.16, 148.54, 142.96, 138.84, 137.94, 134.99, 129.31, 127.36, 127.31, 126.32, 123.77, 122.23, 114.31, 111.13, 55.51, 28.80, 23.68. HRMS (ESI) calcd for $C_{17}H_{15}NO_3Li$ $(M+Li)^+$ 288.1212, found for 288.1948

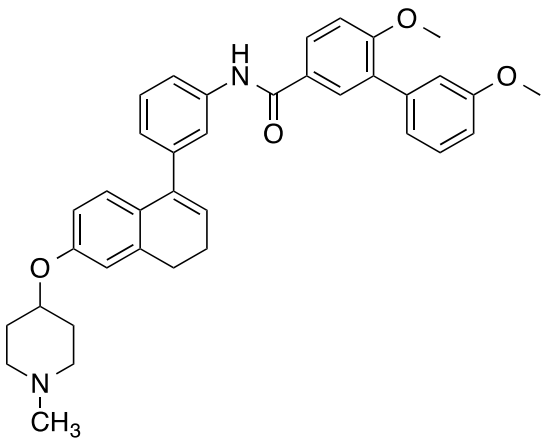


5-(3-nitrophenyl)-7,8-dihydronaphthalen-2-ol (40b) was prepared following the procedure used to synthesize **40a**. This produced a white solid in 75% yield: ^{1}H NMR (500 MHz, CD_3OD) δ 8.25 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1H), 8.04 (t, *J* = 1.9 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 2H), 7.58 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.67 – 6.64 (m, 1H), 6.44 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 2.97 (m, 2H), 2.95 – 2.91 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 157.05, 148.30, 141.66, 136.49, 136.09, 136.05, 129.40, 126.72, 126.63, 124.42, 122.04, 120.13, 114.52, 112.57, 34.71, 29.19. HRMS (ESI) calcd for $C_{16}H_{14}NO_3$ $(M+H)^+$ 268.0974, found for 268.0817

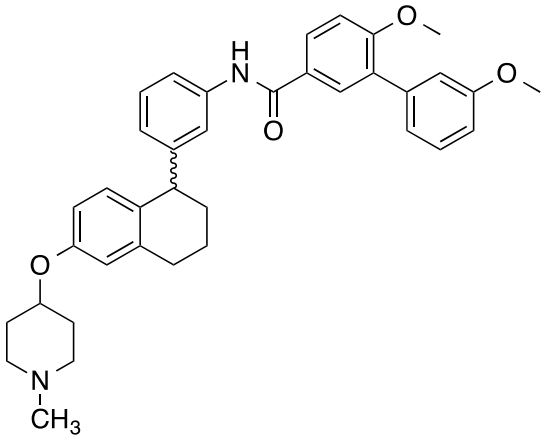


1-methyl-4-((5-(3-nitrophenyl)-7,8-dihydronaphthalen-2-yl)oxy)piperidine (41b) was prepared following procedure B for the Mitsunobu etherification. This produced a white solid in 45% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (ddd, *J* = 7.9, 2.3, 1.4 Hz, 1H), 8.12 (td, *J* = 1.7, 0.8 Hz, 1H), 7.63 - 7.60 (m, 2H), 7.58 (dt, *J* = 7.6, 1.5 Hz, 1H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.55 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.41 (d, *J* = 8.6 Hz, 1H), 4.31 (s, 1H), 2.98 (dq, *J* = 12.6, 7.1 Hz, 4H),

2.70 (s, 2H), 2.35 (m, 2H), 2.33 (s, 3H), 2.03 (m, 2H), 1.88-1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.09, 148.55, 141.57, 136.51, 136.27, 136.24, 129.61, 128.31, 127.10, 125.23, 122.79, 121.98, 116.05, 113.31, 52.60, 46.26 (2C), 35.15 (2C), 30.74, 29.91 (2C). HRMS (ESI) calcd for $C_{22}H_{23}N_2O_3$ $(M-H)^-$ 363.1709, found for 363.9677

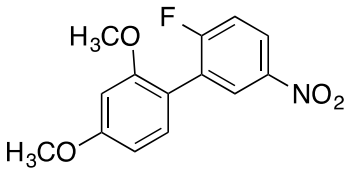


3',6-dimethoxy-*N*-(3-(6-((1-methylpiperidin-4-yl)oxy)-3,4-dihydronaphthalen-1-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (15) was prepared following the procedure used to synthesize **18**. This produced a white solid in 21% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 1.9 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.11 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.08 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.02 – 6.99 (m, 1H), 6.92 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.71 (d, *J* = 2.5 Hz, 1H), 6.60 – 6.52 (m, 2H), 4.27 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.99 – 2.92 (m, 4H), 2.67 (s, 2H), 2.36 – 2.31 (m, 2H), 2.29 (s, 3H), 2.01 – 1.92 (m, 2H), 1.81 (dtd, *J* = 11.8, 7.8, 3.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.21, 159.54, 159.52, 156.83, 140.90, 138.99, 138.37, 137.72, 136.27, 136.13, 130.92, 129.73, 129.40, 129.36, 129.04, 128.54, 127.57, 127.30, 125.98, 122.17, 121.28, 120.77, 119.39, 115.81, 115.45, 113.22, 111.28, 56.06, 55.54, 52.85, 46.44 (2C), 35.19 (2C), 31.06, 30.08 (2C). HRMS (ESI) calcd for $C_{37}H_{39}N_2O_4$ $(M+H)^+$ 575.2910, found for 575.2963

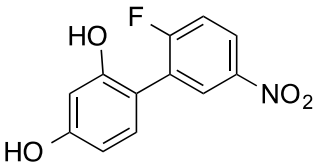


3',6-dimethoxy-*N*-(3-(6-((1-methylpiperidin-4-yl)oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-[1,1'-biphenyl]-3-carboxamide (16) was prepared following the same procedure for the synthesis of **61**. This produced a white solid in 35% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.71 (s, 1H), 7.61 (ddd, *J* = 8.0, 2.2, 1.0

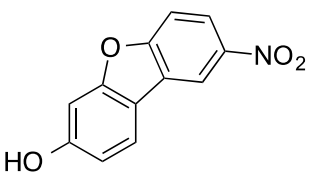
Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 2.0 Hz, 1H), 7.11 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.07 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.92 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.89 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.76 (dd, *J* = 8.6, 0.9 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.27 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.87 (td, *J* = 8.9, 8.3, 5.8 Hz, 2H), 2.78 (dd, *J* = 16.8, 6.0 Hz, 2H), 2.69 (s, 2H), 2.30 (s, 3H), 2.18 – 2.12 (m, 1H), 2.02 – 1.95 (m, 2H), 1.88 – 1.81 (m, 4H), 1.77 – 1.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.24, 159.52, 159.47, 155.67, 149.04, 139.04, 139.02, 138.18, 131.65, 131.39, 130.87, 129.69, 129.36, 129.14, 128.55, 127.40, 125.20, 122.18, 120.48, 118.13, 115.90, 115.47, 114.09, 113.18, 111.24, 56.05, 55.54, 52.96, 46.44 (2C), 45.16, 33.61 (2C), 31.16, 30.30 (2C), 21.21. HRMS (ESI) calcd for $C_{37}H_{41}N_2O_4$ $(M+H)^+$ 577.3066, found for 577.3004



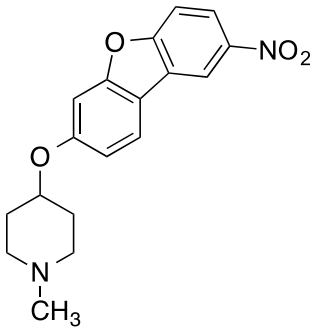
2'-fluoro-2,4-dimethoxy-5'-nitro-1,1'-biphenyl (46a) The general Suzuki coupling conditions were applied to coupling of 2-bromo-1-fluoro-4-nitrobenzene and 2,4-dimethoxybenzene boronic acid. This produced an orange solid in 48% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 2.9, 6.2 Hz, 1H), 8.20 (ddd, *J* = 2.9, 4.2, 9.0 Hz, 1H), 7.26 - 7.21 (m, 2H), 6.61 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.59 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.01, 162.95, 161.90, 158.01, 144.15, 131.82, 128.32, 124.53, 116.69, 115.27, 104.91, 99.05, 55.86, 55.71. HRMS (ESI) calcd for $C_{14}H_{12}FNO_4Na$ $(M+Na)^+$ 300.0648, found for 300.9039



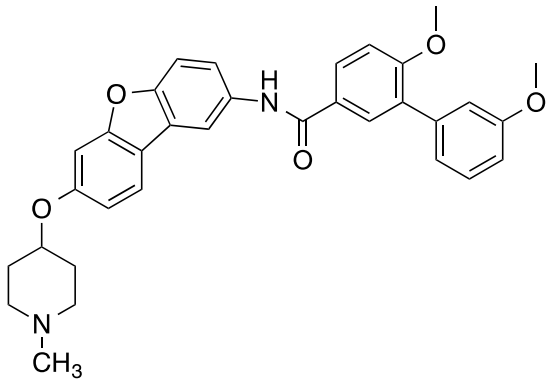
2'-fluoro-5'-nitro-[1,1'-biphenyl]-2,4-diol (47a)[6] Pyridine-HCl (8.85 g, 74.6 mmol) and **46a** (0.708 g, 2.55 mmol) were placed in microwave vial (20 mL) and heated in a microwave reactor at 220 °C for 10 min. The mixture was dissolved in sat'd ammonium chloride solution (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with a sat'd sodium chloride solution (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via column chromatography (1:1 hexanes/ethyl acetate), which produced a yellow solid in 45% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (td, *J* = 3.7, 1.4 Hz, 1H), 7.59 (ddd, *J* = 9.1, 4.7, 2.0 Hz, 1H), 6.66 (tdd, *J* = 9.0, 4.0, 2.3 Hz, 1H), 6.53 – 6.50 (m, 1H), 5.90 – 5.84 (m, 2H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.88, 162.82, 158.68, 155.55, 131.79, 128.17, 123.93, 116.56, 116.35, 112.33, 107.20, 102.74. HRMS (ESI) calcd for $C_{12}H_8FNO_4Na$ $(M+Na)^+$ 272.0335, found for 272.9459



8-nitrodibenzo[*b,d*]furan-3-ol (48a)[6] Acetonitrile was added to a mixture of cesium carbonate and 47a and the solution was heated at 150 °C for 30 min under microwave conditions. The mixture was diluted with ethyl acetate (15 mL) and washed with water and sat'd sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via column chromatography (40% ethyl acetate in hexanes), which produced a light brown solid in 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.4 Hz, 1H), 8.16 – 8.12 (m, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.44 (dd, *J* = 9.0, 1.1 Hz, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.34, 159.12, 158.89, 143.73, 125.60, 121.67, 115.77, 115.70, 114.97, 112.83, 111.39, 98.70. HRMS (ESI) calcd for $C_{12}H_7NO_4Na$ $(M+Na)^+$ 252.0273, found for 252.2408

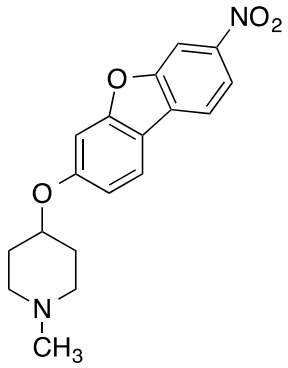


1-methyl-4-((8-nitrodibenzo[*b,d*]furan-3-yl)oxy)piperidine (49a) was prepared following procedure B for the Mitsunobu etherification. This produced a brown solid was produced in 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.3 Hz, 1H), 8.31 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.13 (d, *J* = 2.2 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.50 – 4.44 (m, 1H), 2.76 (d, *J* = 9.7 Hz, 2H), 2.42 (s, 2H), 2.37 (s, 3H), 2.12 (dd, *J* = 9.9, 5.6 Hz, 2H), 2.00 – 1.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.59, 159.14, 159.06, 144.14, 125.45, 121.98, 121.90, 116.30, 114.03, 111.77, 99.15, 55.11, 52.58, 46.24 (2C), 30.63, 29.20, 22.29. HRMS (ESI) calcd for $C_{18}H_{17}N_2O_4$ $(M-H)^-$ 325.1188, found for 325.1801

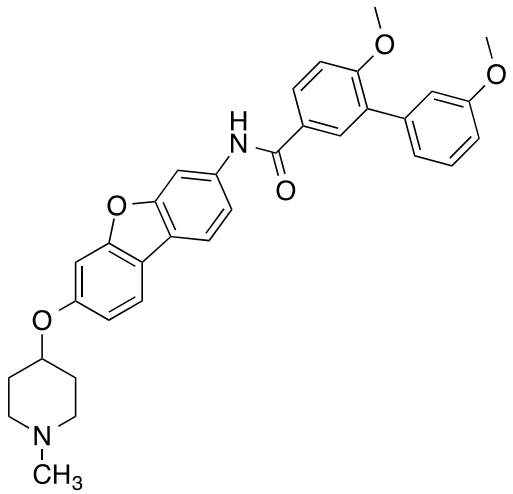


3',6-dimethoxy-*N*-(7-((1-methylpiperidin-4-yl)oxy)dibenzo[*b,d*]furan-2-yl)-[1,1'-biphenyl]-3-carboxamide (19) was prepared following the same procedure for the synthesis of **61**. This produced a light brown solid in 60% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.13 – 7.03 (m, 2H), 6.95 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.76 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 2H), 6.71 (dd, *J* = 8.4, 2.7 Hz, 2H), 6.63 (s, 1H), 4.44 (m, 1H), 3.70 (s, 3H), 3.62 (s, 3H), 2.36 (s, 3H), 2.15 – 2.00 (m, 2H), 1.93 (d, *J* = 10.3 Hz, 2H), 1.81 – 1.77 (m, 2H), 1.66 (q, *J* = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

170.23, 159.26, 158.46, 157.50, 154.67, 139.06, 132.25, 130.32, 129.57, 128.94, 128.20, 126.19, 125.48, 122.10, 121.57, 119.18, 117.11, 114.81, 113.21, 113.14, 112.06, 111.77, 110.37, 99.07, 62.80, 55.68, 55.24, 50.99, 46.24 (2C), 29.80 (2C), 24.41. HRMS (ESI) calcd for $C_{33}H_{32}N_2O_5Na$ $(M+Na)^+$ 559.2209, found for 559.3112

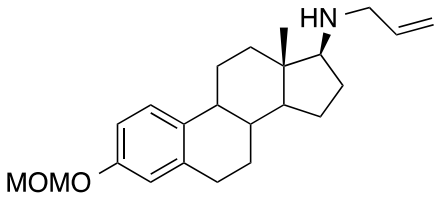


1-methyl-4-((7-nitrodibenzo[*b*,*d*]furan-3-yl)oxy)piperidine (49b) was prepared following procedure B for the Mitsunobu etherification of 7-nitrodibenzo[*b*,*d*]furan-3-ol.[6] This produced a brown solid was produced in 80% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.0 Hz, 1H), 8.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.50 (s, 1H), 2.79 (s, 2H), 2.45 (s, 2H), 2.39 (s, 3H), 2.14 (s, 2H), 1.97 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.19, 155.36, 145.82, 130.75, 122.62, 119.61, 119.03, 115.90, 114.32, 113.56, 107.88, 98.70, 52.50, 51.14 (2C), 46.14 (2C), 30.48. HRMS (ESI) calcd for $C_{18}H_{18}N_2O_4Li$ $(M+Li)^+$ 333.1427, found for 333.1556

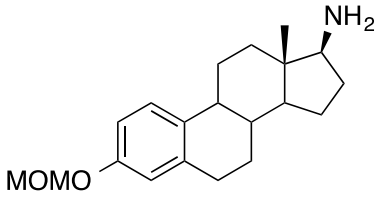


3',6-dimethoxy-*N*-(7-((1-methylpiperidin-4-yl)oxy)dibenzo[*b*,*d*]furan-3-yl)-[1,1'-biphenyl]-3-carboxamide (20) was prepared following the same procedure for the synthesis of **61**. This produced a light brown solid in 73% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 15.3, 8.3 Hz, 2H), 7.40 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.2 Hz, 2H), 6.77 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.60 (d, *J* = 1.1 Hz, 1H), 6.26 (m, 1H), 4.43 (m, 1H), 3.72 (d, *J* = 1.9 Hz, 3H), 3.60 (s, 3H), 2.75 (m, 2H), 2.28 (s, 3H), 2.07 (td, *J* = 12.9, 12.0, 5.2 Hz, 2H), 1.98 – 1.90 (m, 2H), 1.78 (ddd, *J* = 9.3, 5.0, 2.2 Hz, 2H), 1.69 – 1.64 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.15, 159.26, 158.35, 157.99, 157.65, 156.59, 142.00, 139.00, 132.21, 130.37, 129.64,

128.92, 128.10, 123.21, 123.16, 122.13, 121.23, 120.15, 116.98, 114.68, 113.35, 113.24, 111.11, 110.39, 99.07, 55.69, 55.21, 50.87, 46.29, 46.22, 30.77, 29.82, 24.48. HRMS (ESI) calcd for $C_{33}H_{33}N_2O_5$ $(M+H)^+$ 537.2389, found for 537.2388

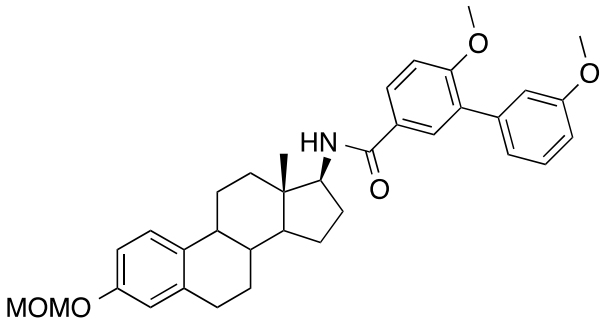


17'-Allylamino-3'-*O*-methoxymethyl-1,3,5(10)-estratriene (69)[7] Glacial acetic acid (0.29 mL, 5.09 mmol) was added to a solution of 3-*O*-methoxymethylestrone (0.400 g, 1.27 mmol), allylamine (0.38 mL, 5.09 mmol) and sodium triacetoxyborohydride (0.674 g, 3.18 mmol) in a 1:1 solution of tetrahydrofuran/1,2-dichloroethane (26 mL). The mixture was stirred for 36 h at rt. A sat'd sodium carbonate solution (26 mL) was added and the mixture was stirred for 10 min. The mixture was extracted with ethyl acetate (40 mL). The organic layer was washed with sat'd sodium carbonate solution (2 x 20 mL), water (10 x 20 mL) and sat'd sodium chloride solution (20 m). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure, which produced a white solid in 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.7, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 5.93 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.19 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.16 (s, 2H), 5.09 (dq, *J* = 10.2, 1.4 Hz, 1H), 3.48 (s, 3H), 3.33-3.30 (m, 1H), 2.88-2.84 (m, 2H), 2.67 (t, *J* = 8.5 Hz, 1H), 2.33-2.17 (m, 2H), 2.14-1.97 (m, 2H), 1.89 (ddt, *J* = 12.7, 5.7, 2.7 Hz, 1H), 1.75-1.69 (m, 1H), 1.56-1.23 (m, 8H), 0.76-0.75 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.18, 138.32, 137.72, 134.29, 126.54, 116.40, 115.71, 113.88, 94.65, 68.60, 56.10, 52.50, 51.66, 44.28, 43.25, 38.90, 38.27, 30.01, 29.92, 27.60, 26.64, 23.70, 12.05. HRMS (ESI) calcd for $C_{23}H_{34}NO_2$ $(M+H)^+$ 356.2590, found for 356.2599

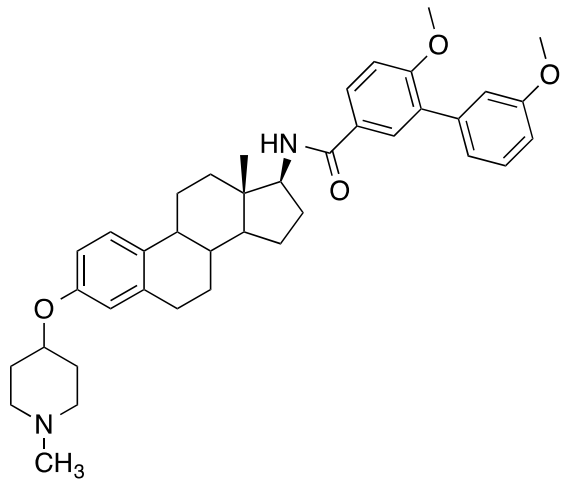


17'-amino-3'-*O*-methoxymethyl-1,3,5(10)-estratriene (70) [8] 1,3-Dimethylbarbituric acid (0.448 g, 2.87 mmol) and $Pd(PPh_3)_4$ (0.022 g, 0.0189 mmol) were added to a degassed solution of **69** (0.335 g, 0.943 mmol) in dichloromethane (10 mL). The mixture was heated at 35 °C for 4 h. Upon cooling, the mixture was concentrated and the residue was dissolved in diethyl ether (30 mL). The solution was washed with a sat'd sodium carbonate solution (4 x 20 mL), water (2 x 10 mL) and a sat'd 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 (40% ethyl acetate in hexanes), which produced a white solid in 80% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 5.15 (s, 2H), 3.48 (s, 3H), 2.90 – 2.82 (m, 2H), 2.79 (t, *J* = 8.8 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.25 – 2.16 (m, 1H), 2.15 – 2.04 (m, 1H), 1.95 – 1.85 (m, 2H), 1.77 – 1.68 (m, 1H), 1.54 – 1.46 (m, 1H), 1.48 – 1.17 (m, 5H), 0.71 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.20, 138.31, 134.20, 126.52, 116.41, 113.88, 94.64, 62.96,

56.09, 52.20, 44.22, 43.09, 39.16, 36.90, 31.16, 29.98, 27.60, 26.49, 23.56, 11.37. HRMS (ESI) calcd for $C_{20}H_{30}NO_2$ $(M+H)^+$ 316.2277, found for 316.2109

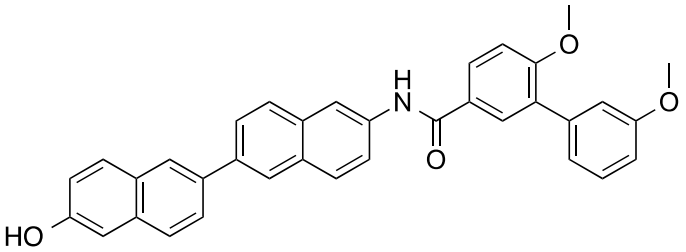


3',6-dimethoxy-*N*-((13*S*,17*S*)-3-(*O*-methoxymethyl)- ,3,5(10)-estratriene)-[1,1'-biphenyl]-3-carboxamide (71) was prepared following the same procedure for the synthesis of **34**. This produced a white solid in 90% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.22 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.11 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.08 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.92 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 5.94 (d, *J* = 8.9 Hz, 1H), 5.15 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.48 (s, 3H), 2.92 – 2.84 (m, 2H), 2.36 – 2.24 (m, 2H), 1.96 – 1.85 (m, 2H), 1.84 (s, 1H), 1.65 – 1.51 (m, 3H), 1.52 – 1.36 (m, 6H), 0.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.04, 159.50, 159.10, 155.25, 139.25, 138.22, 134.13, 130.68, 129.44, 129.32, 128.27, 127.49, 126.65, 122.21, 116.40, 115.56, 113.96, 113.03, 111.06, 94.69, 59.45, 56.13, 56.02, 55.55, 51.88, 44.11, 43.95, 39.16, 37.29, 30.00, 29.15, 27.55, 26.45, 23.63, 12.50. HRMS (ESI) calcd for $C_{35}H_{42}NO_5$ $(M+H)^+$ 556.3063, found for 556.3071

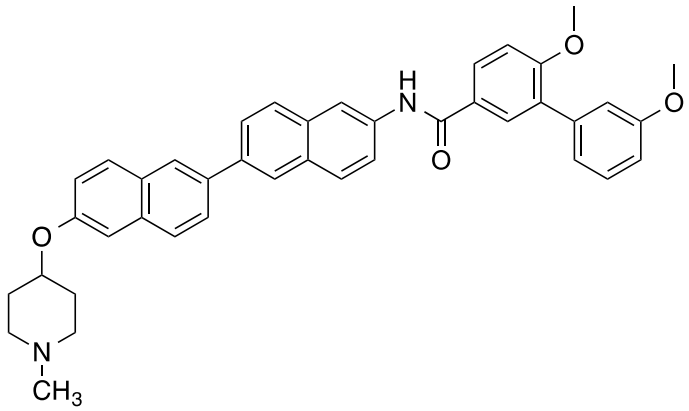


3',6-dimethoxy-*N*-((13*S*,17*S*)-3-((1-methylpiperidin-4-yl)oxy)- ,3,5(10)-estratriene)-[1,1'-biphenyl]-3-carboxamide (21) was prepared following the same procedure for the synthesis of **61**. This produced a white solid in 56% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.21 – 7.17 (m, 1H), 7.10 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.07 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.91 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.69 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 5.93 (d, *J* = 8.9 Hz, 1H), 4.36 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.87 – 2.81 (m, 4H), 2.43 (s, 3H), 2.32 – 2.23 (m, 1H), 2.15 (d, *J* = 22.4 Hz, 1H), 1.94 – 1.87 (m, 4H), 1.82 (q, *J* = 7.6, 5.4 Hz, 1H), 1.56 (td, *J* =

13.1, 3.7 Hz, 1H), 1.48 – 1.38 (m, 6H), 1.25 (s, 1H), 0.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.03, 159.50, 159.11, 155.10, 139.25, 138.31, 133.35, 130.67, 129.43, 129.32, 128.28, 127.48, 126.73, 122.21, 116.32, 115.57, 113.58, 113.01, 111.06, 59.44, 56.02, 55.55, 51.87, 45.78, 44.08 (2C), 43.97, 39.19, 37.29, 36.34, 30.02 (2C), 29.92, 29.13, 27.56, 26.46, 23.63, 12.50. HRMS (ESI) calcd for $C_{39}H_{49}N_2O_4$ $(M)^+$ 609.3692, found for 609.3637



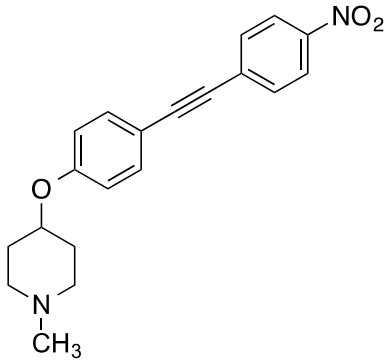
***N*-(6'-hydroxy-[2,2'-binaphthalen]-6-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (72)** was prepared following the general procedure for the Suzuki coupling. This produced a white solid in 75% yield: ^{1}H NMR (500 MHz, CD_3OD) δ 8.14 (d, *J* = 2.1 Hz, 1H), 7.97 (d, *J* = 1.5 Hz, 1H), 7.93 (d, *J* = 1.8 Hz, 1H), 7.84 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.73 – 7.70 (m, 2H), 7.66 – 7.62 (m, 2H), 7.60 – 7.54 (m, 2H), 7.16 – 7.11 (m, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.96 – 6.89 (m, 4H), 6.73 (ddd, *J* = 8.3, 2.4, 1.2 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 160.97, 140.52, 134.29 (2C), 132.65 (2C), 131.36, 130.91, 130.02 (2C), 129.94, 129.76 (2C), 129.26, 128.28 (2C), 127.95, 127.01, 126.71, 126.65, 126.12, 123.06 (2C), 122.63 (2C), 119.77, 118.77, 116.41 (2C), 113.71 (2C), 112.24, 109.74, 56.33, 55.72. HRMS (ESI) calcd for $C_{35}H_{27}NO_4Na$ $(M+Na)^+$ 548.1838, found for 548.1844



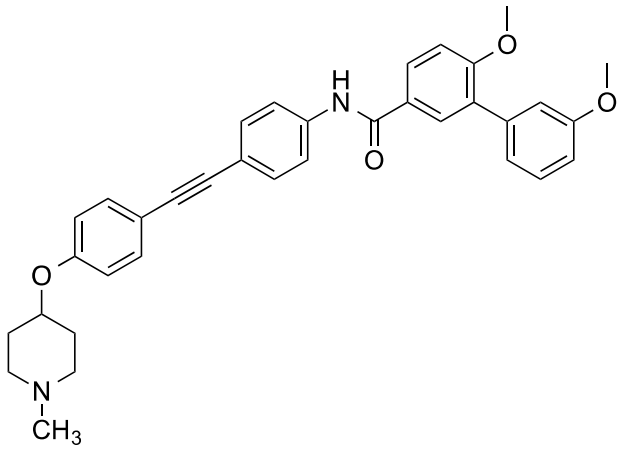
3',6-dimethoxy-*N*-(6'-((1-methylpiperidin-4-yl)oxy)-[2,2'-binaphthalen]-6-yl)-[1,1'-biphenyl]-3-carboxamide (22) was prepared following general procedure B for the Mitsunobu etherification of **72**. This produced a beige solid in 43% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 0H), 8.03 (s, 1H), 7.98 (s, 0H), 7.93 (dd, *J* = 8.6, 2.4 Hz, 0H), 7.88 – 7.83 (m, 1H), 7.82 (d, *J* = 2.4 Hz, 0H), 7.58 (dd, *J* = 8.8, 2.2 Hz, 0H), 7.31 (t, *J* = 7.9 Hz, 0H), 7.09 (ddd, *J* = 7.6, 1.6, 0.9 Hz, 0H), 7.07 – 7.02 (m, 1H), 6.87 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 0H), 4.92 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 1.55 (m, 2H), 1.41 – 1.26 (m, 2H), 1.18 (s, 2H),. ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.45, 159.56, 139.02, 134.29, 131.14, 130.97 (2C), 130.02 (2C), 129.78, 129.41 (2C), 129.34, 128.70, 128.28 (2C), 127.95, 127.01, 126.71, 126.12, 125.82, 123.06 (2C), 122.63 (2C),

122.21 (2C), 120.84, 116.80, 115.55, 113.19, 111.35 (2C), 56.10, 55.57, 52.37, 46.08 (2C), 29.93 (2C), 22.25. HRMS (ESI) calcd for $C_{41}H_{39}N_2O_4$ $(M+H)^+$ 623.2910, found for 623.2886

General Procedure for Sonogashira coupling: $Pd(PPh_3)_2Cl_2$ and copper (II) iodide was added to a degassed solution of 1-ethynyl-4-nitrobenzene and 4-(4-iodophenoxy)-1-methylpiperidine[9] in an anhydrous 4:1 mixture of tetrahydrofuran/triethylamine. The mixture was stirred for 16 h at rt. Afterwards, the mixture was concentrated under reduced pressure and purified via column chromatography (10% methanol in dichloromethane).

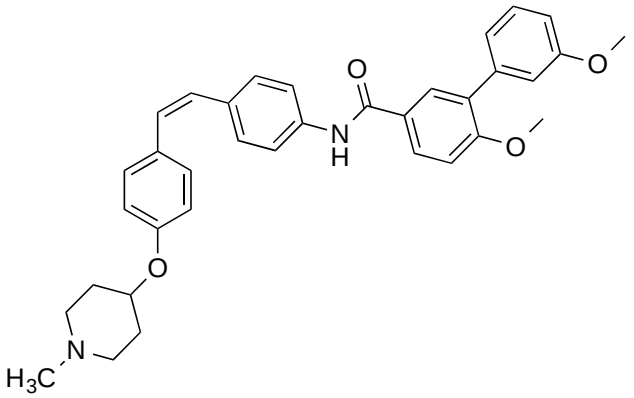


1-methyl-4-(4-((4-nitrophenyl)ethynyl)phenoxy)piperidine (55) was prepared following the general procedure for Sonogashira coupling. This produced a brown solid in 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J*=9.0 Hz, 2H), 7.63 (d, *J*=9.0 Hz, 2H), 7.51 (d, *J*=8.8 Hz, 2H), 6.91 (d, *J*=8.9 Hz, 2H), 4.64 (s, 1H), 3.06 (m, 4H), 2.65 (s, 3H), 2.49 (s, 2H), 2.16–2.10 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.50, 147.01, 133.92 (2C), 132.27 (2C), 130.64 (2C), 123.88 (2C), 116.00, 115.30, 94.74, 87.18, 50.92, 46.39 (2C), 44.84 (2C), 28.20. HRMS (ESI) calcd for $C_{20}H_{21}N_2O_3$ $(M+H)^+$ 337.1552, found for 337.1454

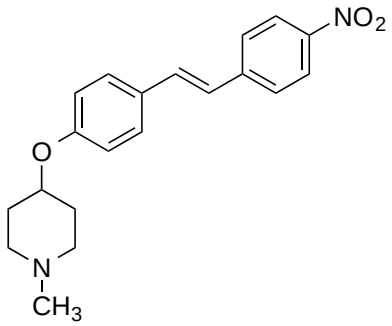


3',6-dimethoxy-*N*-(4-((4-((1-methylpiperidin-4-yl)oxy)phenyl)ethynyl)phenyl)-[1,1'-biphenyl]-3-carboxamide (23) was prepared following the procedure used to synthesize **18**. This produced a white solid in 51% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (ddd, *J* = 8.7, 5.5, 2.5 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.62 (dd, *J* = 9.2, 2.5 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.14 – 7.11 (m, 1H), 7.10 – 7.05 (m, 2H), 6.94 – 6.89 (m, 3H), 6.87 (d, *J* = 8.8 Hz, 1H), 4.41 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.75 (s, 2H), 2.37 (s, 3H), 2.08 (s, 2H), 1.90 (m, 2H), 1.66 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.21, 159.61, 159.54, 138.99, 137.72, 133.26, 132.51, 131.72, 131.28, 130.96 (2C), 130.45, 129.73, 129.40, 128.62, 128.25 (2C), 127.24, 124.09, 122.18, 119.86, 119.75, 116.07, 115.84, 115.51, 113.20, 111.31, 56.09, 55.56, 52.82, 46.15 (2C), 30.58 (2C), 29.93. HRMS (ESI) calcd for $C_{35}H_{35}N_2O_4$ $(M+H)^+$ 547.2597, found for 547.2797

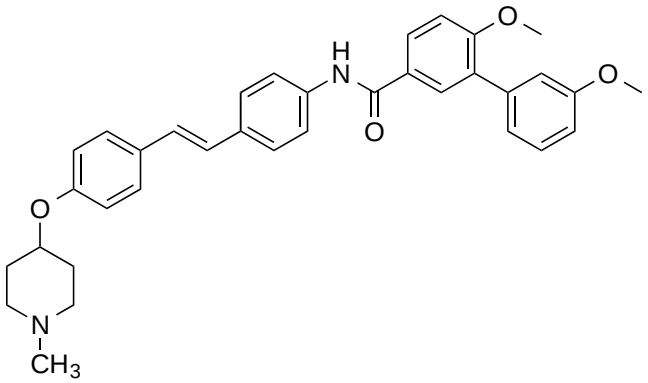


(*Z*)-3',6-dimethoxy-*N*-(4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-[1,1'-biphenyl]-3-carboxamide (24) Formic acid (0.01 mL) was added in a microwave vial (0.5-2 mL) containing a mixture of **23** (0.0278 g, 0.051)**,** nickel (II) bromide (0.0011 g, 0.0051) and zinc (0.0166 g, 0.254 mmol) in 1,4-dioxane (0.5 mL).[10] This mixture was heat to 120 °C and stirred for 16 h. Upon cool, the mixture was filtered through a plug of Celite®, rinsed with dichloromethane and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (7% methanol in dichloromethane), which produced a white solid in 32% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.76 (s, 1H), 7.53 – 7.50 (m, 2H), 7.36 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.13 – 7.11 (m, 1H), 7.09 – 7.07 (m, 2H), 6.93 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 3.1 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.40 (m, 2H), 3.24 (m, 2H), 2.80 (s, 3H), 2.65 (m, 3H), 2.23 (d, *J* = 14.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.25, 159.62, 159.55, 155.18, 138.97, 137.15, 133.56, 131.29, 130.95, 130.76, 129.77, 129.65, 129.41, 129.14, 128.59, 128.17, 127.24, 127.19, 124.09,122.15, 120.38, 119.95, 119.75, 116.07, 115.58, 113.12, 111.33, 56.09, 55.56, 52.82, 49.96, 44.13, 29.52 (2C), 26.98. HRMS (ESI) calcd for $C_{35}H_{37}N_2O_4$ $(M+H)^+$ 549.2753, found for 549.2566

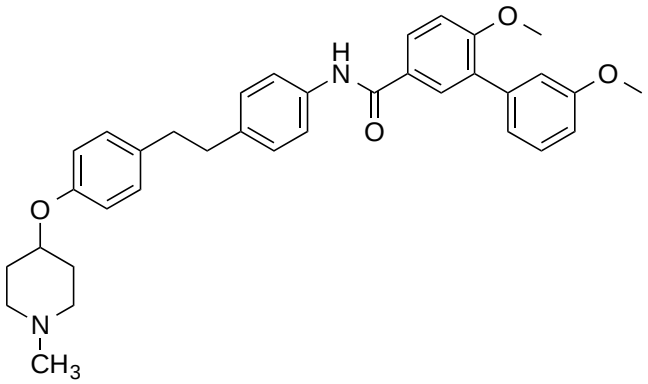


(*E*)-1-methyl-4-(4-(4-nitrostyryl)phenoxy)piperidine (73) was prepared following general procedure A for Mitsunobu etherification of 4-hydroxy-4'-nitrostibene. This produced a yellow solid in 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 16.3 Hz, 1H), 7.00 (d, *J* = 16.3 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.38 (s, 1H), 2.71 (m, 2H), 2.33 (s, 3H), 2.04 (d, *J* = 13.9 Hz, 2H), 1.87 (dtd, *J* =

12.3, 8.0, 3.2 Hz, 2H), 1.66 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.36, 146.60, 144.49, 133.08 (2C), 129.15, 128.67 (2C), 126.71 (2C), 124.38, 124.31, 116.44 (2C), 52.83, 46.42 (2C), 37.79, 37.28, 31.00 . HRMS (ESI) calcd for $C_{20}H_{23}N_2O_3$ $(M+H)^+$ 339.1709, found for 339.1819

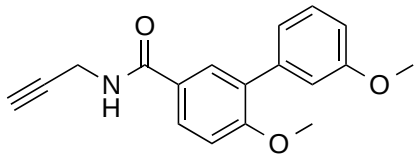


(*E*)-3',6-dimethoxy-*N*-(4-(4-((1-methylpiperidin-4-yl)oxy)styryl)phenyl)-[1,1'-biphenyl]-3-carboxamide (25) was prepare following the same procedure for the synthesis of **18**. This produced a white solid in 63% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93–7.89 (m, 1H), 7.81 (dd, *J*=3.9, 1.9 Hz, 2H), 7.64–7.62 (m, 1H), 7.53 (d, *J*=8.5 Hz, 1H), 7.49 (d, *J*=8.7 Hz, 1H), 7.43 (d, *J*=8.7 Hz, 1H), 7.36 (td, *J*=7.9, 1.9 Hz, 1H), 7.17–7.11 (m, 2H), 7.09 (dd, *J*=2.6, 1.7 Hz, 1H), 7.06 (dd, *J*=8.6, 3.8 Hz, 2H), 6.98 (d, *J*=18.8 Hz, 1H), 6.95 – 6.91 (m, 1H), 6.90 (d, *J*=8.7 Hz, 1H), 6.82 (d, *J*=8.6 Hz, 1H), 4.35 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.86 (h, *J*=3.4 Hz, 2H), 2.72 (s, 2H), 2.33 (s, 3H), 2.06–1.99 (m, 2H), 1.87 (qd, *J*=11.6, 9.1, 5.3 Hz, 2H), 1.71 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.15, 159.54, 157.24, 155.77, 139.01, 138.20, 137.35, 136.12, 134.06, 130.92, 130.49, 129.70, 129.64, 129.38, 129.28, 128.60, 127.86, 127.67, 127.11, 126.19, 122.18, 120.36, 116.43, 116.27, 115.50, 113.18, 111.28, 56.07, 55.55, 52.79, 46.37 (2C), 37.78, 37.27, 30.96. HRMS (ESI) calcd for $C_{35}H_{37}N_2O_4$ $(M+H)^+$ 549.2753, found for 549.2739

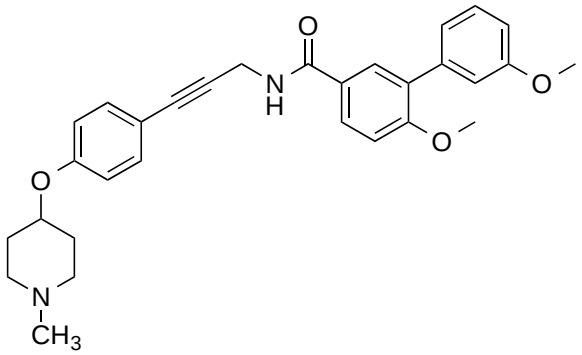


3',6-dimethoxy-*N*-(4-(4-((1-methylpiperidin-4-yl)oxy)phenethyl)phenyl)-[1,1'-biphenyl]-3-carboxamide (26) 10% Palladium on carbon (0.1 equiv.) was added to a degassed solution of **25** (0.030 g, 0.0973 mmol) in ethanol (5 mL). The system was purged with argon and before the mixture was stirred at room temperature for 18 hours under H_2 gas. The mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The resulting residue was purified via preparative TLC (8% methanol in dichloromethane), which produced a white solid in 32% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.72 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.14 –

7.11 (m, 1H), 7.10 – 7.05 (m, 4H), 6.93 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 2.90 – 2.83 (m, 4H), 2.75 (m, 2H), 2.35 (s, 3H), 2.08 – 2.03 (m, 2H), 1.87 (m, 2H), 1.63 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.21, 159.53, 159.47, 155.71, 139.05, 138.18, 137.35, 136.13, 134.30, 130.89, 129.67 (2C), 129.38, 129.29 (2C), 128.55, 127.86, 127.67, 127.43, 122.18, 120.33, 116.26 (2C), 115.50 (2C), 113.17, 111.26, 56.07, 55.55, 52.79, 46.19 (2C), 37.77, 37.26, 31.00. HRMS (ESI) calcd for $C_{35}H_{37}N_2O_4$ $(M+H)^+$ 551.2910, found for 551.2908

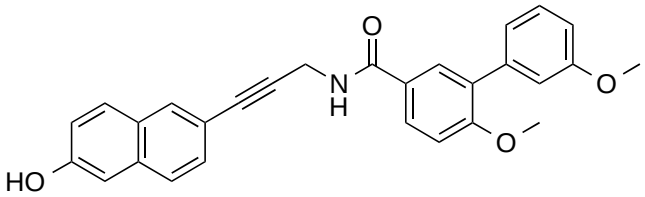


3',6-dimethoxy-*N*-(prop-2-yn-1-yl)-[1,1'-biphenyl]-3-carboxamide (74)
Diisopropylethylamine (0.30 mL, 1.74 mmol) was added dropwise to a mixture of propargyl amine (0.074 mL, 1.16 mmol), carboxylic acid **A** (0.300 g, 1.16 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.334 g, 1.74 mmol) in anhydrous dichloromethane (12 mL) at 25 °C. The mixture was stirred at rt for 18h before it was quenched with water (5 mL). The mixture was extracted with dichloromethane (2 x 15 mL) and the organic layer washed with sat'd sodium chloride solution (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (3:1 Hexanes/Ethyl Acetate), which produced the product as a white amorphous solid in 86% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.09 (ddd, *J* = 7.6, 1.7, 0.9 Hz, 1H), 7.08 – 7.03 (m, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.26 (m, 1H), 4.25 (dd, *J* = 5.2, 2.6 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.27 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.72, 159.48, 159.44, 139.04, 130.75, 129.77, 129.31, 128.48, 126.18, 122.16, 115.47, 113.10, 111.07, 79.83, 72.07, 56.00, 55.52, 29.98. HRMS (ESI) calcd for $C_{18}H_{17}NO_3Na(M+Na)^+$ 318.1106, found for 318.1205

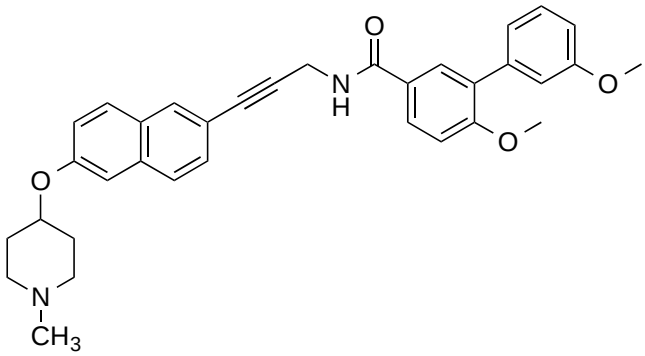


3',6-dimethoxy-*N*-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)prop-2-yn-1-yl)-[1,1'-biphenyl]-3-carboxamide (75) was prepared following the general procedure for Sonogashira coupling between **74** and 4-(4-iodophenoxy)-1-methylpiperidine.[9] This produced a white solid in 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.12 – 7.09 (m, 1H), 7.07 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.30 (m, 1H), 4.47 (d, *J* = 5.0 Hz, 2H), 4.33 (s., br., 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.89 (d, *J* = 11.5 Hz, 2H), 2.69 (m, 2H),

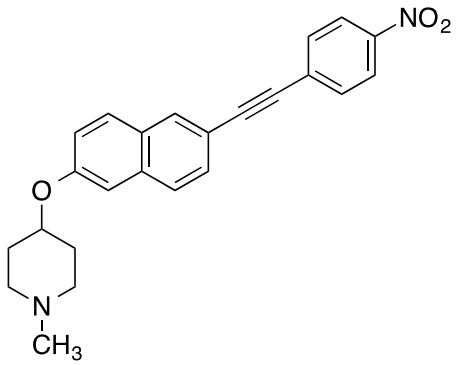
2.31 (s, 3H), 2.04 – 1.96 (m, 2H), 1.89 – 1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.65, 159.47, 159.37, 157.84, 139.09, 138.47, 133.47, 130.72, 129.76, 129.30, 128.48, 126.41 (2C), 122.18, 118.61, 115.99, 115.47, 114.71, 113.09, 111.06, 83.81, 83.56, 56.00, 55.52, 52.79, 46.40 (2C), 30.93 (2C), 22.29. HRMS (ESI) calcd for $C_{30}H_{33}N_2O_4$ $(M+H)^+$ 485.2440, found for 485.2207



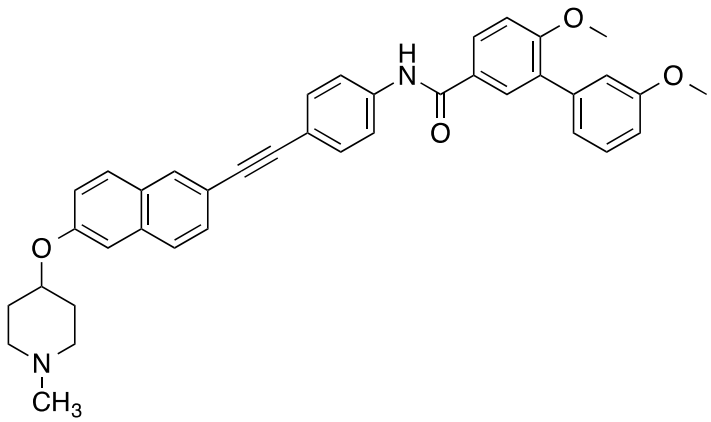
***N*-(3-(6-hydroxynaphthalen-2-yl)prop-2-yn-1-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (76)** was prepared following the general procedure for Sonogashira coupling between **74** and 6-iodonaphthalen-2-ol. This produced a white solid in 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.10 (m, 3H), 7.07 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.35 (m, 1H), 4.52 (d, *J* = 5.1 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.84, 159.49, 159.47, 154.57, 139.07, 134.40, 131.92, 130.79, 129.97, 129.80, 129.33, 129.26, 128.55, 128.45, 126.65, 126.30, 122.19, 118.74, 117.50, 115.50, 113.12, 111.12, 109.75, 84.56, 84.36, 56.02, 55.54, 31.01. HRMS (ESI) calcd for $C_{28}H_{23}NO_4Na(M+H)^+$ 460.1525, found for 460.1523



3',6-dimethoxy-*N*-(3-(6-((1-methylpiperidin-4-yl)oxy)naphthalen-2-yl)prop-2-yn-1-yl)-[1,1'-biphenyl]-3-carboxamide (28) was prepared following general procedure A for Mitsunobu etherification of **76**. This produced a white solid in 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.4 Hz, 1H), 7.86 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz,12H), 7.44 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.34 (dd, *J* = 8.8, 7.1 Hz, 1H), 7.15 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.12 – 7.09 (m, 2H), 7.07 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.91 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 2H), 6.29 (s, 1H), 4.53 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.78 (m, 2H), 2.39 (m, 4H), 2.13 (m, 2H), 1.97 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.71, 159.47, 159.41, 156.17, 139.09, 134.34, 131.76, 130.75, 129.80, 129.68, 129.31, 129.19, 128.52, 126.93, 126.37, 125.64, 122.19, 120.51, 117.61, 115.48, 113.11, 111.08, 108.62, 84.35, 70.92, 56.01, 55.53, 52.58, 46.26 (2C), 30.96, 30.95, 22.22, 22.17. HRMS (ESI) calcd for $C_{34}H_{35}N_2O_4$ $(M+H)^+$ 535.2597, found for 535.2611



1-methyl-4-((6-((4-nitrophenyl)ethynyl)naphthalen-2-yl)oxy)piperidine (77) was prepared following the general procedure for Sonogashira coupling between **63** and 1-ethynyl-4-nitrobenzene. This produced a yellow solid in 90% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.9 Hz, 1H), 8.14 (d, *J* = 1.6 Hz, 1H), 8.02 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.57 – 7.54 (m, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.19 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.15 (dd, *J* = 2.5, 1.1 Hz, 2H), 7.09 (d, *J* = 2.5 Hz, 1H), 4.60 (m, 1H), 2.94 – 2.85 (m, 2H), 2.69 (m, 2H), 2.48 (s, 3H), 2.29 (m, 2H), 2.08 – 2.02 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.27, 147.05, 136.48, 135.11, 133.45, 132.40, 130.90, 130.06, 129.06, 128.90, 127.24, 123.91, 120.55, 120.39, 117.35, 108.72, 95.67, 88.65, 87.73, 51.98, 45.66 (2C), 37.26, 29.62. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_3$ $(M-H)^-$ 385.1552, found for 385.9565



3',6-dimethoxy-*N*-(4-((6-((1-methylpiperidin-4-yl)oxy)naphthalen-2-yl)ethynyl)phenyl)-[1,1'-biphenyl]-3-carboxamide (29) was prepare following the same procedure for the synthesis of **18**. This produced a white solid in 62% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 1H), 7.83 – 7.74 (m, 3H), 7.69 – 7.66 (m, 1H), 7.58 – 7.46 (m, 3H), 7.38 – 7.33 (m, 1H), 7.28 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.14 – 7.04 (m, 4H), 6.94 – 6.90 (m, 1H), 6.71 – 6.58 (m, 1H), 4.56 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.00 (dd, *J* = 27.2, 9.1 Hz, 2H), 2.36 (s, 3H), 2.17 (m, 2H), 2.01 (m, 3H), 1.86 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.22, 159.54, 159.52, 139.04, 138.99, 138.95, 132.70, 129.93, 129.90, 129.76, 129.70, 129.39, 129.37, 129.27, 128.64, 128.55, 128.54, 127.96, 126.57, 122.17, 120.39, 119.90, 119.87, 119.75, 115.50, 113.18, 113.16, 111.30, 111.27, 111.24, 108.93, 56.06, 55.55, 52.33, 42.66 (2C), 38.06, 29.92, 22.24. HRMS (ESI) calcd for $C_{39}H_{37}N_2O_4$ $(M+H)^+$ 597.2753, found for 597.2725

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 PC3-MM2 cell lines were maintained in DMEM supplemented with 10% FBS, streptomycin, and penicillin at 37 °C, 5% CO_2. MDA-MB-468LN was grown in DMEM/F12 medium (Life Technologies, Carlsbad, CA) with 10% FBS (Sigma-Aldrich, St. Louis, MO) and 1% penicillin/Streptomycin (Life Technologies, Carlsbad, CA). 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. Each experiment was repeated a minimum of three times in triplicate.

Luciferase assay

Compound at varying concentrations in DMSO (1% DMSO final concentration) was added to wells of a white, round-bottom 96-well plate containing 50 μL of MEME media. Luciferase-expressing PC3-MM2 cells were grown to confluence, collected, and incubated for 8–12 min at 50 °C in pre-warmed MEME media until bioluminescence of luciferase was reduced to 1% of the initial counts. Cells were added (60,000 cells/50 μL) to wells (final concentration of 60,000 cells/100 μL), and the plate was returned to the incubator for 1 h. After 1 h, 100 μL of luciferase substrate reagent (75 mM tricine at pH7.8, 24 mM $MgSO_4$, 0.3 mM EDTA, 2 mM DTT, 0.313 D-luciferin, 0.64 mM coenzyme A, 0.66 mM ATP, 150 mM KCl, 10% Triton-X, 20% glycerol, and 3.5% DMSO) was added to wells, and the bioluminescence was immediately read (0.5 s integration time). Cells that were incubated in 1% DMSO were used as 100% bioluminescence (*i.e.*, DMSO = 100% refolding), and the relative refolding for each compound concentration was compared to that in 1% DMSO. The concentrations for each compound were in triplicate, and dose–response curves were generated using GraphPad Prism 5.0. Each experiment was repeated a minimum of three times in triplicate.

Western blot Analysis

PC3-MM2 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.

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