Development of Hsp90 C-terminal inhibitors with noviomimetics that manifest anti-proliferative activities

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Supporting Information

Materials and methods

PC3 cells were maintained in RPMI-1640 media, MDA-MB-231 cells were maintained in DMEM media and SKBr3 cells were maintained in McCoy's media and grown in a humidified atmosphere (37°C, 5% CO_2). The cells were grown to confluence, seeded (2000 cells/well (PC3, MDA-MB-231 and SKBr3) in a 96-well plate, and placed in the incubator for 24 h. Compounds or vehicle at varying concentrations in DMSO (0.5% DMSO final concentration) were administered and then incubated for 72 hours. At 72 h, the % of viable cells was determined using the MTS/PES cell proliferation kit (Promega) according to the manufacturer's instructions. Results were calculated based on the assumption that the number of living cells was proportional to the absorbance at 490 nm, and results are presented as means ± SD deviation from two independent experiments. Inhibition graphs are based on mean values obtained from each concentration relative to control values, and half-maximal inhibitory concentrations (IC_{50}) were calculated using GraphPad Prism software.

Western Blot

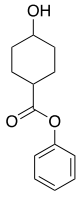
SKBr3 cells were seeded at 700,000 cells/well in 6-well plates (VWR, 10861-696). Once cells had reached ~80% confluency, the media was aspirated and replaced with 2 mL of media containing compound or vehicle (1% DMSO) and incubated for a 24 hour treatment time. After 24 hours, cells were washed with ice cold PBS and then lysed with cell lysis buffer (130 mM NaCl, 1% Triton S24 X-100, 1 mM EDTA, 0.1% SDS, 10 mM Tris-Cl pH 8.0 in water + freshly added 1 mM Protease Cocktail 2, 1 mM Protease Cocktail 3, 1 mM Phosphatase inhibitor, and 1 mM PMSF). Cell lysates were obtained by centrifugation at 10, 000 rpm for 10 min at 4 °C. Protein concentrations were determined using the Pierce BCA assay kit following the manufacturer's instructions. Then, 20 ug of each normalized protein lysate was electrophoresed on 10% SDS-polyacrylamide gels and transferred onto PVDF membranes. Membranes were washed in Tris-buffered saline containing Tween (TBST: 10 mM Tris-HCl, 150 mM NaCl, pH 7.2, and 0.1% Tween 20), incubated in blocking buffer (7% non-fat milk in H2O), and then incubated with primary antibodies at 4°C overnight. After washing with TBST, membranes were incubated in their

respective secondary antibodies for 1 hour at room temperature. The blots were developed using Clarity Max Western ECL Blotting Substrates (Bio-Rad). The following primary antibodies were obtained from Cell Signaling Technology (Danvers, MA): Akt (9272), β-Actin (8H10D10), HER2/ErbB2 (29D8) and CDK6 (D9G3E).The following primary antibodies were obtained from Enzo Life Sciences (Farmingdale, NY): Hsp70/Hsp72 (C92F3A-5), and Hsp90 (AC88). All primary antibodies were used at 1:1000 dilutions, and all secondary antibodies at 1:2000 dilutions unless otherwise stated. Horseradish peroxidase-conjugated secondary goat anti-mouse IgG, goat anti-mouse Ig, goat anti- rat IgG, and goat anti-rabbit IgG antibodies were purchased from Southern Biotech (Birmingham, AL).

Synthesis and characterization of final compounds

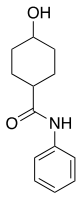
Chemistry General: ^{1}H NMR, and ^{13}C NMR spectra were performed and the data were recorded on either Bruker Ascend 400 MHz and/or 500 MHz NMR spectrometers. Spectra were obtained in solutions of $CDCl_3$, DMSO-d6 and chemical shifts were referenced to residual $CHCl_3$ and DMSO, unless stated otherwise. The chemical shifts (δ) are reported in ppm downfield from internal triethylsilane (TMS, δ0.00) and coupling constant values (J) are in Hz. ^{1}H NMR data are reported as follows: range of chemical shift (multiplicity [singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), doublet of triplets (dt), triplet of doublets (td), doublet of doublet of triplets (ddt), quartet (q), quintet (quint), multiplet (m)], coupling constant [Hz], integration). ^{13}C NMR data are reported as chemical shift in ppm. General NMR data were obtained at 25°C (298.15 K). Variable temperature NMR experiments were obtained at variable temperature.

Experimental procedures:

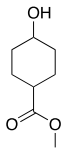


phenyl 4-hydroxycyclohexane-1-carboxylate (8a): To a stirred solution of 4-hydroxycyclohexane-1-carboxylic acid (100 mg, 1 Eq, 694 µmol) in DCM (3 mL) was added phenol (65.3 mg, 1 Eq, 694 µmol) and DMAP (25.4 mg, 0.3 Eq, 208 µmol) and the solution was cooled in an ice bath at 0°C. EDC (160 mg, 1.2 Eq, 832 µmol) was added to the reaction, and the solution was warmed to room temperature and stirred overnight. The reaction was quenched with water, washed with and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 11%) to afford **8a** (80% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.42 – 7.33 (m, 2H), 7.27 – 7.18 (m, 1H), 7.09 – 7.01 (m, 2H), 3.67 (tt, J = 10.5, 4.2 Hz, 1H), 2.51 (tt, J = 11.9, 3.7 Hz, 1H), 2.24 – 2.15 (m, 2H), 2.15 – 2.02 (m, 2H), 1.71 – 1.58 (m, 2H),

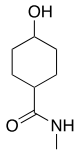
1.37 (tdd, *J* = 12.8, 10.6, 3.6 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 174.17, 150.84, 129.54, 125.90, 121.60, 69.85, 42.39, 34.50, 27.20; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{13}H_{16}O_3$ 220.27, found 220.71.



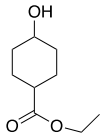
4-hydroxy-N-phenylcyclohexane-1-carboxamide (8b): To a stirred solution of 4-hydroxycyclohexane-1-carboxylic acid (200 mg, 1 Eq, 1.39 mmol) in DCM was added aniline (129 mg, 126 µL, 1 Eq, 1.39 mmol) and DMAP (50.8 mg, 0.3 Eq, 416 µmol) were dissolved (6.0 mL and the solution was cooled in an ice bath at 0°C. EDC (319 mg, 1.2 Eq, 1.66 mmol) was added to the reaction, and the solution was warmed to room temperature and stirred overnight. The reaction was quenched with water, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 12-90%) to afford **8b** (70% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.45 (t, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 16.1 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 3.53 (tt, *J* = 11.2, 4.5 Hz, 1H), 2.15 (tt, *J* = 11.9, 3.6 Hz, 1H), 1.98 (dq, *J* = 16.2, 7.4, 5.6 Hz, 2H), 1.92 – 1.82 (m, 2H), 1.63 – 1.49 (m, 2H), 1.22 (tdd, *J* = 13.3, 8.8, 3.6 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 175.34, 138.21, 128.63, 123.90, 119.90, 69.20, 44.77, 34.05, 27.69; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{13}H_{17}NO_2$ 219.28, found 219.62.



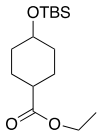
methyl 4-hydroxycyclohexane-1-carboxylate (9a): To a stirred solution of 4-hydroxycyclohexane-1-carboxylic acid (200 mg, 1 Eq, 1.39 mmol) in MeOH (8 mL) was added sulfuric acid (204 mg, 111 µL, 2.08 mmol) at RT. The reaction mixture was subsequently stirred at 80°C for 10h. Upon completion, the residue was quenched with a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (2 X 20 mL), washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford **9a** (88% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 3.65 (s, 3H), 3.58 (tt, *J* = 10.6, 4.0 Hz, 1H), 2.24 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.06 – 1.93 (m, 4H), 1.79 (s, 1H), 1.48 (tdd, *J* = 13.1, 11.7, 3.8 Hz, 2H), 1.34 – 1.19 (m, 2H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_8H_{14}O_3$ 158.20, found 158.62.



4-hydroxy-*N*-methylcyclohexane-1-carboxamide (9b): To a stirred solution of 4-hydroxycyclohexane-1-carboxylic acid (300 mg, 1 Eq, 2.08 mmol) in DCM (3.0 mL) in a pressure flask was added methanamine (64.6 mg, 1.04 mL, 2 molar, 2.08 mmol), and DMAP (76.3 mg, 0.3 Eq, 624 µmol) and the solution was cooled in an ice bath at 0°C. EDC (479 mg, 1.2 Eq, 2.50 mmol) was added to the reaction, and the solution was warmed to room temperature and stirred overnight. The reaction was quenched with water, extracted with EtOAc (2 X 30 mL), washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 10%) to afford **9b** (53% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 3.65 (s, 3H), 3.60 (tt, *J* = 10.6, 4.0 Hz, 1H), 2.24 (ddt, *J* = 15.5, 11.9, 3.7 Hz, 1H), 2.05 – 1.94 (m, 4H), 1.66 (q, *J* = 6.5 Hz, 1H), 1.56 – 1.42 (m, 2H), 1.34 – 1.21 (m, 2H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_8H_{15}NO_2$ 157.21, found 157.78.

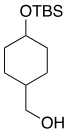


ethyl 4-hydroxycyclohexane-1-carboxylate (10): To a solution of ethyl 4-hydroxycyclohexane-1-carboxylic acid (4g, 0.03 mol) in ethanol (50.2 mL) was added concentrated sulfuric acid (4g, 2 mL, 0.04 mol) and stirred at room temperature (RT) for 15 mins before stirring at 80°C overnight. The reaction was cooled to RT and quenched with saturated solution of sodium bicarbonate. The mixture was extracted with ethyl acetate (2 x 100 mL), the organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure to afford **10** (90% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 4.04 (qd, *J* = 7.1, 2.0 Hz, 2H), 3.51 (tt, *J* = 10.7, 4.0 Hz, 1H), 2.16 (tt, *J* = 11.9, 3.5 Hz, 1H), 1.99 – 1.87 (m, 4H), 1.41 (tdd, *J* = 13.2, 11.8, 3.8 Hz, 2H), 1.26 – 1.14 (m, 5H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_9H_{16}O_3$ 172.22, found 172.90.

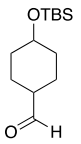


ethyl 4-((tert-butyldimethylsilyl)oxy)cyclohexane-1-carboxylate (11): To a solution of ethyl 4-hydroxycyclohexane-1-carboxylate (2.8g, 0.016 mol) in DMF (50 mL) was added TBS-Cl (4.9g, 2 mL, 0.033 mol) and triethylamine (2.8g, 0.016 mol) stirred at RT. After stirring for 2h, the reaction mixture was quenched with ice water (100 mL), acidified and extracted with ethyl acetate (2 x 150 mL). The organic phase was washed with brine (100 mL) dried with Na_2SO_4 and the solvent was removed under reduced

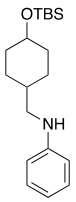
pressure to afford **11** (88% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.10 (qd, *J* = 7.1, 4.2 Hz, 2H), 3.55 (tt, *J* = 10.1, 4.2 Hz, 1H), 2.20 (tt, *J* = 11.6, 3.7 Hz, 1H), 1.95 (dtd, *J* = 13.1, 3.9, 1.9 Hz, 2H), 1.88 (dd, *J* = 13.1, 3.9 Hz, 2H), 1.53 – 1.38 (m, 2H), 1.37 – 1.19 (m, 5H), 0.86 (s, 9H), 0.08 (s, 6H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{15}H_{30}O_3Si$ 286.49, found 286.76.



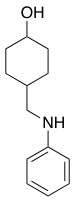
(4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methanol (12): To a solution of ethyl 4-((tert-butyldimethylsilyl)oxy)cyclohexane-1-carboxylate (480 mg, 1 Eq, 1.68 mmol) in ether (7 mL) was added dropwise a solution of lithium aluminum hydride (LAH) (127 mg, 1.68 mL, 2 molar, 2 Eq, 3.35 mmol) at 0°C. The resulting mixture was stirred at rt for 2 h. After cooling to 0-5°C, the reaction mixture was successively treated with water. The aqueous phase was extracted with EtOAc (3 X 50 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, eluted with Hexane:EtOAc 20%) to provide **12** (84% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.53 (tt, *J* = 10.7, 4.4 Hz, 1H), 3.44 (d, *J* = 6.3 Hz, 2H), 1.93 – 1.86 (m, 2H), 1.84 – 1.75 (m, 2H), 1.43 (dddd, *J* = 14.8, 8.3, 6.4, 3.0 Hz, 1H), 1.37 – 1.29 (m, 2H), 1.05 – 0.93 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{13}H_{28}O_2Si$ 244.45, found 244.68.



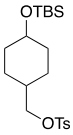
4-((tert-butyldimethylsilyl)oxy)cyclohexane-1-carbaldehyde (13): To a solution of (4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methanol (1.2 g, 1 Eq, 4.9 mmol) in DCM (24 mL) was added DMP (2.3 g, 1.1 Eq, 5.4 mmol) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was quenched with a saturated aq. $NaHCO_3$. After the phases were separated, the aqueous layer was extracted with DCM (3 X 100 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. . The residue was purified by flash chromatography (silica gel, eluted with Hexane:EtOAc 5%) to provide **13** (80% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.63 (s, 1H), 3.56 (ddq, *J* = 8.0, 5.9, 4.0 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.04 – 1.93 (m, 2H), 1.93 – 1.83 (m, 2H), 1.41 – 1.27 (m, 4H), 0.87 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 182.03, 70.17, 41.79, 34.43, 26.74, 25.68, 18.00; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{13}H_{26}O_2Si$ 242.43, found 242.68.



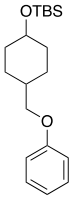
N-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methyl)aniline (14): To a stirred solution of Pd/C (219 mg, 1 Eq, 2.06 mmol), ammonium formate (1.30 g, 10 Eq, 20.6 mmol) in water (2 mL) was added isopropanol (9 mL) and stirred at RT for 1 minute to activate Pd/C. Aniline (192 mg, 188 µL, 1 Eq, 2.06 mmol) and 4-((tert-butyldimethylsilyl)oxy)cyclohexane-1-carbaldehyde (500 mg, 1 Eq, 2.06 mmol) were added and the reaction mixture was stirred at RT for 1 h. After completion of the reaction, Pd/C catalyst was filtered off on celite and the solvent was removed by rotary evaporation. The reaction mixture was diluted with DCM (250 mL) and washed with brine (150 mL). The organic phase was collected, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, eluted with Hexane:EtOAc 8%) to afford **14** (75.9 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (t, *J* = 7.9 Hz, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 3.83 – 3.65 (m, 1H), 3.60 – 3.48 (m, 1H), 2.95 (d, *J* = 6.6 Hz, 2H), 1.88 (t, *J* = 14.0 Hz, 4H), 1.58 – 1.48 (m, 1H), 1.36 – 1.25 (m, 2H), 1.03 (q, *J* = 14.1, 13.3 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.12 (m, 2H), 6.68 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.64 – 6.55 (m, 2H), 3.54 (tt, *J* = 10.7, 4.1 Hz, 1H), 3.18 (d, *J* = 5.4 Hz, 1H), 2.95 (d, *J* = 6.6 Hz, 2H), 1.94 – 1.81 (m, 4H), 1.52 (ddd, *J* = 11.6, 5.7, 2.7 Hz, 1H), 1.38 – 1.19 (m, 2H), 1.03 (tdd, *J* = 14.4, 13.2, 12.1, 3.8 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.79, 129.71, 117.64, 113.19, 72.17, 50.55, 37.20, 35.88, 29.88, 26.38, 18.71; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{19}H_{33}NOSi$ 319.56, found 319.92.



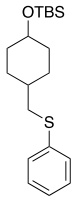
4-((phenylamino)methyl)cyclohexan-1-ol (15): To N-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methyl)aniline (250 mg, 1 Eq, 782 µmol) was added a solution mixture of 6 N HCl−THF−MeOH (1:2:2) (3 mL). The reaction was allowed to react for 1h and then concentrated to dryness under vacuum to leave an oily crude residue which was purified by flash chromatography (silica gel, eluted with Hexane:EtOAc 33%) to afford **15** (88.4% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.08 (m, 2H), 6.69 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.63 – 6.53 (m, 2H), 3.59 (tt, *J* = 10.8, 4.3 Hz, 1H), 2.97 (d, *J* = 6.7 Hz, 2H), 2.04 – 1.95 (m, 2H), 1.96 – 1.82 (m, 2H), 1.56 (dddd, *J* = 14.9, 11.7, 6.8, 3.2 Hz, 1H), 1.28 – 1.21 (m, 2H), 1.13 – 0.98 (m, 2H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{13}H_{19}NO$ 205.30, found 205.54.



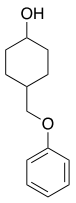
(4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methyl 4-methylbenzenesulfonate (16): To a stirred solution of (4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methanol (324 mg, 1 Eq, 1.33 mmol) in DCM (7 mL) cooled to 0°C was gradually added Ts-Cl (379 mg, 1.5 Eq, 1.99 mmol) and DMAP (162 mg, 1 Eq, 1.33 mmol) portionwise along with dropwise addition of DIPEA (377 mg, 508 µL, 2.2 Eq, 2.92 mmol). The resulting solution was stirred at RT for 24 hours. The solvent was evaporated and the residue was diluted with EtOAc and added a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with EtOAC(2 X 20 mL), washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 15%) to afford **16** (68% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.74 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.81 (d, *J* = 6.3 Hz, 2H), 3.47 (tt, *J* = 10.6, 4.3 Hz, 1H), 2.45 (s, 3H), 1.89 – 1.78 (m, 2H), 1.71 (dt, *J* = 13.2, 3.2 Hz, 2H), 1.57 (dtt, *J* = 9.4, 6.4, 2.6 Hz, 1H), 1.24 (tdd, *J* = 13.3, 10.5, 3.6 Hz, 2H), 1.04 – 0.89 (m, 2H), 0.86 (s, 9H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{20}H_{34}O_4SSi$ 398.63, found 398.94.



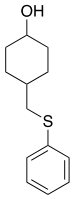
tert-butyldimethyl((4-(phenoxymethyl)cyclohexyl)oxy)silane (17a): To a stirred solution of (4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methyl 4-methylbenzenesulfonate (800 mg, 1 Eq, 2.01 mmol) in DMF (10 mL) was added phenol (227 mg, 2.41 mmol), potassium phosphate, tribasic (852 mg, 4.01 mmol) and heated at 75°C for 2 h. The reaction mixture was cooled and filtered. The filtrate was poured into H_2O (200 mL) and stirred for 30 min. The resulting solution was then extracted with toluene (3×50 mL), washed with saturated aqueous K_2CO_3 solution and H_2O (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Distillation of the residual oil afforded **17a** (73.5% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 3H), 6.95 – 6.86 (m, 3H), 3.75 (d, *J* = 6.3 Hz, 2H), 3.56 (tt, *J* = 10.5, 3.9 Hz, 1H), 1.95 – 1.86 (m, 4H), 1.79 – 1.67 (m, 1H), 1.35 (dt, *J* = 13.6, 11.4 Hz, 2H), 1.17 – 1.02 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.32, 129.55, 120.62, 114.58, 72.86, 71.83, 36.97, 35.45, 28.23, 26.08, 18.41; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{19}H_{32}O_2Si$ 320.55, found 320.96.



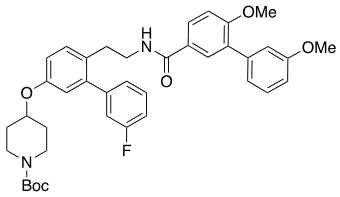
tert-butyldimethyl((4-(thiophenoxymethyl)cyclohexyl)oxy)silane (17b): To a stirred solution of (4-((tert-butyldimethylsilyl)oxy)cyclohexyl)methyl 4-methylbenzenesulfonate (500 mg, 1.25 mmol) in DMF (8 mL) was added benzenethiol (166 mg, 155 µL, 1.51 mmol), potassium phosphate, tribasic (532 mg, 208 µL, 2.51 mmol) and heated at 75°C for 2 h. The reaction mixture was cooled and filtered. The filtrate was poured into H_2O (200 mL) and stirred for 30 min. The resulting solution was then extracted with toluene (3×50 mL), washed with saturated aqueous K_2CO_3 solution and H_2O (160 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Distillation of the residual oil afforded **17b** (68% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.27 (m, 3H), 7.25 – 7.20 (m, 1H), 7.18 – 7.12 (m, 1H), 3.52 (tt, *J* = 10.4, 4.2 Hz, 1H), 2.80 (d, *J* = 6.8 Hz, 2H), 1.88 (dt, *J* = 21.2, 8.6 Hz, 4H), 1.49 (ddt, *J* = 11.1, 6.9, 3.4 Hz, 1H), 1.34 – 1.21 (m, 3H), 1.10 – 0.97 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{19}H_{32}OSSi$ 336.61, found 336.92.



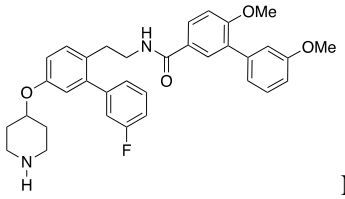
4-(phenoxymethyl)cyclohexan-1-ol (18a): To a stirred solution of tert-butyldimethyl((4-(phenoxymethyl)cyclohexyl)oxy)silane (73.8 mg, 1 Eq, 230 µmol) in THF (0.8 mL) cooled in an ice bath at 0°C was gradually added acetic acid (16.6 mg, 15.8 µL, 1.2 Eq, 276 µmol) and TBAF (72.2 mg, 276 µL, 1.0 molar, 1.2 Eq, 276 µmol) stirred at 0°C for 30 mins. Upon completion of reaction, THF was removed under reduced pressure, and ethyl acetate (2mL) was added. The organic layer was washed with water, then with aqueous $NaHCO_3$, dried with Na_2SO_4, and concentrated under reduced pressure to afford **18a** (95% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (dd, *J* = 7.0, 1.7 Hz, 2H), 6.98 – 6.84 (m, 3H), 3.76 (d, *J* = 6.3 Hz, 2H), 3.62 (tt, *J* = 10.9, 4.3 Hz, 1H), 2.04 – 1.87 (m, 4H), 1.76 (dddq, *J* = 15.5, 9.9, 6.5, 3.2 Hz, 1H), 1.39 – 1.27 (m, 2H), 1.20 – 1.08 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.92, 129.25, 120.36, 114.25, 72.36, 70.84, 36.63, 34.76, 27.73; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{13}H_{18}O_2$ 206.29, found 206.68.



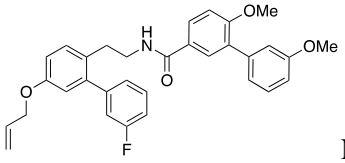
4-((phenylthio)methyl)cyclohexan-1-ol (18b): To a stirred solution of tert-butyldimethyl((4-((phenylthio)methyl)cyclohexyl)oxy)silane (82 mg, 1 Eq, 0.24 mmol) in THF (0.8 mL) and MeOH (0.8 mL) cooled in an ice bath at 0°C was gradually added HCl (8.9 mg, 6.0 µL, 1 Eq, 0.24 mmol) and stirred for 1h then concentrated under reduced pressure to afford an oily crude residue. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 15%) to afford **18b** (89% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.26 (m, 4H), 7.19 (ddt, *J* = 8.6, 6.4, 1.6 Hz, 1H), 3.59 (tt, *J* = 10.8, 4.1 Hz, 1H), 2.84 (d, *J* = 6.8 Hz, 2H), 2.09 – 1.94 (m, 4H), 1.60 – 1.52 (m, 1H), 1.27 (dtd, *J* = 13.0, 11.3, 10.6, 3.8 Hz, 2H), 1.10 (tdd, *J* = 13.0, 11.6, 3.6 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.04, 128.69, 128.60, 125.51, 70.61, 40.09, 36.48, 34.99, 30.53; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{13}H_{18}OS$ 222.35, found 222.78.



tert-butyl4-((6-(2-(3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamido)ethyl)-3'-fluoro-[1,1'-biphenyl]-3-yl)oxy)piperidine-1-carboxylate (27): To a mixture of tert-butyl 4-(tosyloxy)piperidine-1-carboxylate (407 mg, 1.2 Eq, 1.15 mmol) in DMF was added Cs2CO3 (622 mg, 2 Eq, 1.91 mmol) and N-(2-(3'-fluoro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (450 mg, 1 Eq, 954 µmol) and heated at 80°C ovenight. The residue was then cooled and filtered. The filtrate was poured into H_2O (200 mL) and the resulting mixture was stirred for 15 mins. It was then extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 32%) to afford **27** (81% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.55 (dd, *J* = 18.1, 2.4 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.25 – 7.18 (m, 1H), 7.13 – 6.93 (m, 6H), 6.93 – 6.80 (m, 2H), 6.74 (dd, *J* = 12.3, 2.7 Hz, 1H), 5.92 (q, *J* = 8.1, 6.9 Hz, 1H), 4.45 (tt, *J* = 7.1, 3.5 Hz, 1H), 3.86 – 3.83 (m, 6H), 3.68 (ddd, *J* = 12.0, 7.4, 3.8 Hz, 2H), 3.52 – 3.40 (m, 2H), 3.33 (ddd, *J* = 13.4, 7.6, 3.8 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 1.90 (td, *J* = 8.4, 7.7, 3.5 Hz, 2H), 1.74 (dtd, *J* = 12.3, 7.2, 3.8 Hz, 2H), 1.46 (s, 9H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{39}H_{43}FN_2O_6$ 654.66, found 655.27.

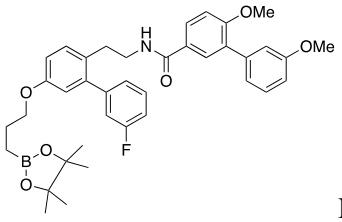


N-(2-(3'-fluoro-5-(piperidin-4-yloxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (27): To a solution of tert-butyl 4-((6-(2-(3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamido)ethyl)-3'-fluoro-[1,1'-biphenyl]-3-yl)oxy)piperidine-1-carboxylate (10 mg, 1 Eq, 15 μmol) in DCM was added TFA (1.7 mg, 1.2 μL, 1 Eq, 15 μmol) and stirred at RT for 5h. The reaction mixture was evaporated under reduced pressure to afford **27** (90% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.33 (q, *J* = 7.9 Hz, 2H), 7.24 (s, 1H), 7.10 – 6.94 (m, 6H), 6.89 (td, *J* = 8.4, 2.7 Hz, 2H), 6.76 (d, *J* = 2.7 Hz, 1H), 5.91 (t, *J* = 5.7 Hz, 1H), 4.38 (tt, *J* = 7.8, 3.7 Hz, 1H), 3.84 (d, *J* = 2.7 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 2H), 3.16 (dt, *J* = 11.7, 4.3 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.81 – 2.72 (m, 2H), 2.07 – 1.98 (m, 2H), 1.72 (qd, *J* = 11.3, 9.9, 5.3 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.60, 159.10, 158.74, 155.41, 141.99, 138.79, 130.88, 130.19, 129.76, 129.68, 129.15, 128.89, 128.34, 127.83, 126.68, 124.70, 121.78, 117.42, 116.05, 115.84, 115.42, 115.11, 114.08, 112.65, 110.62, 72.31, 55.59, 55.14, 43.09, 40.77, 31.79, 31.33; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{34}H_{35}FN_2O_4$ 554.66, found 555.27.

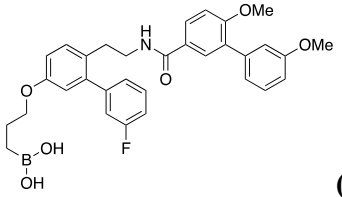


N-(2-(5-(allyloxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (30): To a stirred solution of 3-bromoprop-1-ene (61.6 mg, 44.0 μL, 1.2 Eq, 509 μmol) in DMF was added Cs_2CO_3 (276 mg, 2 Eq, 848 μmol) and N-(2-(3'-fluoro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (200 mg, 1 Eq, 424 μmol) and heated at 80^{o}C for 4h. The residue was then cooled and filtered. The filtrate was poured into H_2O (200 mL) and the resulting mixture was stirred for 15 mins. It was then extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 24%) to afford **30** (92% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 8.6, 2.4 Hz, 2H), 7.59 (d, *J* = 2.4 Hz, 2H), 7.34 (dd, *J* = 9.1, 6.8 Hz, 4H), 7.29 – 7.23 (m, 3H), 7.09 (d, *J* = 1.5 Hz, 2H), 7.09 – 7.00 (m, 9H), 6.97 (d, *J* = 8.6 Hz, 3H), 6.91 (dt, *J* = 8.7, 2.1 Hz, 4H), 6.78 (d, *J* = 2.7 Hz, 2H), 6.11 – 6.03 (m, 2H), 6.01 (dd, *J* = 5.5, 2.3 Hz, 2H), 5.42 (dq, *J* = 17.2, 1.6 Hz, 2H), 5.29 – 5.27 (m, 1H), 4.53 (dt, *J* = 5.3, 1.6

Hz, 4H), 3.85 (d, *J* = 3.1 Hz, 12H), 3.47 (q, *J* = 6.7 Hz, 4H), 2.86 (t, *J* = 7.3 Hz, 4H); HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{32}H_{30}FNO_4$ 511.59, found 511.89.

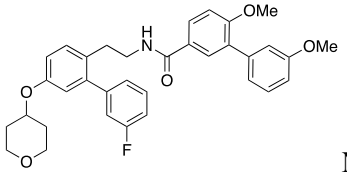


N-(2-(3'-fluoro-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (31): In a pressure flask purged with Argon was added acetoxysilver (1.11 mg, 0.1 Eq, 6.67 µmol), N-(2-(5-(allyloxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (34.1 mg, 1 Eq, 66.7 µmol) and Toluene (0.6 mL). Then 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.8 mg, 14.5 µL, 1.5 Eq, 100 µmol) was added drop wise by syringe over one minute under Ar. The resulting mixture was stirred at 120°C for 12 h. After cooling to RT, the reaction mixture was diluted with 5 mL of DCM and filtered through a plug of celite, followed by washing with 10–20 mL of DCM. The combined residue was concentrated under reduced pressure, The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 20%) to afford **31** (26% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.09 – 6.95 (m, 6H), 6.89 (td, *J* = 8.7, 2.7 Hz, 2H), 6.75 (d, *J* = 2.7 Hz, 1H), 5.90 (t, *J* = 5.7 Hz, 1H), 3.93 (t, *J* = 6.7 Hz, 2H), 3.84 (d, *J* = 2.7 Hz, 6H), 3.46 (q, *J* = 6.7 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 1.88 (p, *J* = 7.2 Hz, 2H), 1.23 (s, 12H), 0.94 – 0.88 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) 166.93, 159.41, 159.04, 157.70, 139.11, 131.04, 130.51, 130.02, 129.93, 129.53, 129.20, 128.10, 128.02, 127.02, 125.04, 125.02, 122.11, 116.38, 116.24, 116.17, 115.38, 114.49, 114.30, 114.09, 113.00, 110.92, 83.26, 69.85, 55.90, 55.45, 41.11, 32.06, 24.96, 23.89; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{38}H_{43}BFNO_6$ 639.57, found 640.324.



(3-((6-(2-(3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamido)ethyl)-3'-fluoro-[1,1'-biphenyl]-3-yl)oxy)propyl)boronic acid (32): To a stirred solution of N-(2-(5-(allyloxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (135 mg, 1 Eq, 264 µmol) in THF (1.32 mL) was added Borane tetrahydrofuran complex solution (45.4 mg, 528 µL, 1 molar, 2 Eq, 528 µmol) dropwise at 0 °C. The mixture was stirred for 2 h at room temperature and H_2O (2.0 mL) was slowly

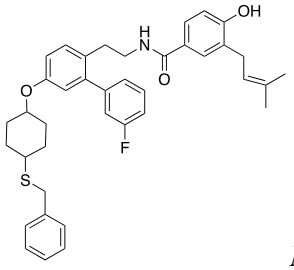
added. After stirring for additional 12 h at RT, the reaction mixture was diluted with ethyl acetate (50 mL), and washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The combined residue was concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with DCM:MeOH 1%) to afford **32** (20% yield). ^{1}H NMR (400 MHz, MeOH-*d*) 8.31 (t, *J* = 6.0 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.36 (q, *J* = 7.5 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 7.03 (dd, *J* = 5.8, 4.0 Hz, 4H), 6.86 (td, *J* = 8.8, 2.6 Hz, 2H), 6.69 (d, *J* = 2.7 Hz, 1H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.39 – 3.34 (m, 2H), 2.80 (t, *J* = 7.3 Hz, 2H), 1.81 (p, *J* = 6.9 Hz, 2H), 0.87 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, Methanol-*d*) 160.48, 160.22, 158.53, 143.11, 140.25, 132.00, 131.37, 130.77, 130.61, 129.65, 129.34, 129.02, 127.54, 125.99, 122.72, 116.69, 116.62, 116.04, 114.74, 114.59, 113.31, 111.75, 79.31, 78.98, 78.65, 70.44, 55.94, 55.41, 41.94, 32.66, 24.59; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{32}H_{33}BFNO_6$ 557.43, found 558.246.



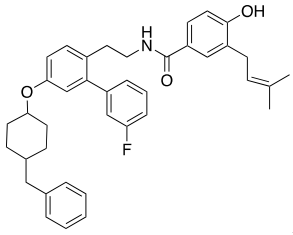
N-(2-(3'-fluoro-5-((tetrahydro-2H-pyran-4-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (34): A mixture of N-(2-(3'-fluoro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (19 mg, 1 Eq, 40 μmol), tetrahydro-2H-pyran-4-yl 4-methylbenzenesulfonate (21 mg, 2 Eq, 81 μmol), cesium carbonate (20 mg, 1.5 Eq, 60 μmol), and DMF (0.20 mL)was heated at 80°C with stirring for ovenight. The filtrate was poured into H2O (2 mL) and extracted with EA (3×5 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na2SO4, and concentrated. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 25%) to afford a white solid **34** (78% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.24 (s, 1H), 7.11 – 6.94 (m, 6H), 6.94 – 6.84 (m, 2H), 6.75 (d, *J* = 2.7 Hz, 1H), 5.96 (d, *J* = 6.6 Hz, 1H), 5.91 (t, *J* = 5.8 Hz, 1H), 5.24 (d, *J* = 16.9 Hz, 2H), 4.37 (s, 1H), 3.85 (d, *J* = 2.4 Hz, 6H), 3.47 (q, *J* = 6.8 Hz, 2H), 3.11 (s, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.79 (s, 2H), 2.64 – 2.20 (m, 2H), 2.09 (s, 2H), 1.90 (s, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.25, 159.73, 159.37, 155.99, 142.63, 139.41, 131.52, 130.80, 130.39, 130.31, 129.77, 129.52, 129.03, 128.49, 127.28, 125.32, 122.41, 118.06, 116.68, 116.47, 116.07, 115.75, 114.71, 114.51, 113.25, 111.24, 72.03, 65.53, 56.22, 55.76, 41.40, 32.42, 32.23; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{34}H_{34}FNO_5$ 555.65, found 556.249.

General procedure for the synthesis of compounds (22-25):

To a solution of N-(2-(3'-fluoro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide **23** (0.36 mmol) in anhydrous THF (5 mL) at 0°C was added diisopropyl azodicarboxylate (0.46 mmol), a requisite cyclohexanol derivative (0.4 mmol) and triphenylphosphine (0.46 mmol) and stirred at RT for 18 h. The resulting mixture was quenched with ice cold water (50 mL), extracted with ethyl acetate (3 x 50 mL), washed with saturated brine solution (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (Silica gel, eluted with Hexane:EtOAc 45%) to afford the product which was further purified by prep HPLC to give the pure compounds **22-25** (10- 40% yield).

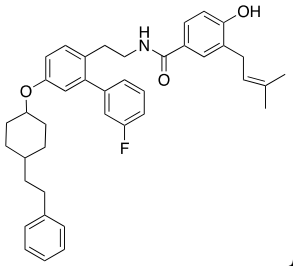


***N*-(2-(5-((4-(benzylthio)cyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-4-hydroxy-3-(3-methylbut-2-en-1-yl)benzamide (22a):** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (d, *J* = 2.2 Hz, 1H), 7.36 (dq, *J* = 8.0, 2.5 Hz, 2H), 7.34 – 7.28 (m, 4H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.06 (dd, *J* = 8.5, 3.0 Hz, 2H), 6.99 (ddd, *J* = 11.2, 8.4, 6.4 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.84 (t, *J* = 5.4 Hz, 1H), 5.28 (ddd, *J* = 8.8, 4.9, 1.6 Hz, 1H), 4.21 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.75 (s, 2H), 3.45 (q, *J* = 6.7 Hz, 2H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.83 (t, *J* = 7.1 Hz, 2H), 2.61 (d, *J* = 3.8 Hz, 1H), 2.18 – 2.12 (m, 2H), 2.09 (dd, *J* = 9.5, 4.2 Hz, 2H), 1.77 (t, *J* = 1.6 Hz, 6H), 1.46 (q, *J* = 10.6 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.22, 157.43, 156.10, 143.72, 138.69, 135.77, 131.12, 130.59, 130.04, 129.95, 129.42, 128.86, 128.67, 128.50, 127.10, 127.02, 126.42, 121.20, 117.70, 115.72, 115.66, 41.66, 41.01, 35.21, 32.09, 31.05, 30.61, 29.97, 25.98, 18.10; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{39}H_{42}FNO_3S$ 623.83, found 624.29.

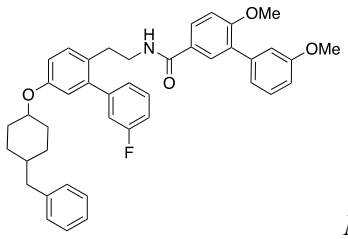


***N*-(2-(5-((4-benzylcyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-4-hydroxy-3-(3-methylbut-2-en-1-yl)benzamide (22b):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 2.3 Hz, 1H), 7.36 (ddt, *J* = 9.5, 7.9, 3.7 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.21 – 7.13 (m, 3H), 7.10 – 6.99 (m, 3H), 6.89 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.78 (dd, *J* = 5.5, 2.8 Hz, 2H), 5.84 (t, *J*

= 5.7 Hz, 1H), 5.53 (s, 1H), 5.33 – 5.24 (m, 1H), 4.50 (s, 1H), 3.45 (q, *J* = 6.8 Hz, 2H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.55 (d, *J* = 7.1 Hz, 2H), 2.01 (d, *J* = 11.2 Hz, 2H), 1.78 (t, *J* = 1.6 Hz, 6H), 1.61 (s, 1H), 1.54 – 1.42 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.91, 159.42, 156.24, 141.26, 139.12, 131.08, 130.51, 130.02, 129.50, 129.28, 129.21, 128.27, 128.13, 128.05, 125.84, 125.06, 125.03, 122.11, 117.92, 116.40, 116.19, 115.69, 115.40, 114.30, 114.09, 112.99, 110.92, 72.20, 55.91, 55.45, 43.38, 41.09, 38.91, 32.08, 29.44, 27.16, 22.07; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{39}H_{42}FNO_3$ 591.77, found 592.32.

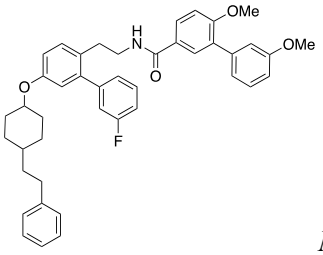


***N*-(2-(3'-fluoro-5-((4-phenethylcyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-4-hydroxy-3-(3-methylbut-2-en-1-yl)benzamide (22c):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 2.3 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 3H), 7.10 – 7.05 (m, 1H), 7.02 (ddd, *J* = 10.1, 5.7, 2.3 Hz, 2H), 6.89 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.81 – 6.75 (m, 2H), 5.86 (t, *J* = 5.8 Hz, 1H), 5.76 (s, 1H), 5.29 (td, *J* = 6.6, 6.0, 3.8 Hz, 1H), 4.51 (t, *J* = 3.4 Hz, 1H), 3.46 (q, *J* = 6.7 Hz, 2H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.68 – 2.59 (m, 2H), 2.02 (dd, *J* = 13.8, 8.0 Hz, 2H), 1.77 (s, 6H), 1.55 – 1.35 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.80, 156.56, 143.41, 135.94, 131.37, 130.31, 129.68, 128.81, 128.75, 128.75, 128.36, 127.41, 127.31, 126.74, 126.05, 125.40, 125.37, 121.58, 118.18, 116.72, 116.51, 116.07, 115.96, 72.69, 41.35, 38.83, 36.51, 33.72, 32.38, 30.21, 29.75, 27.63, 26.29, 18.41; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{40}H_{44}FNO_3$ 605.79, found 606.34.

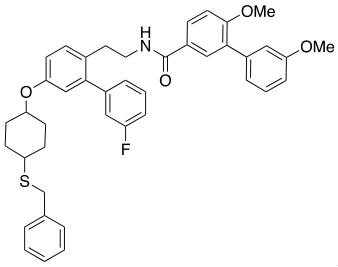


***N*-(2-(5-((4-benzylcyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25a):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.12 (m, 10H), 7.11 – 6.94 (m, 6H), 6.90 (ddd, *J* = 8.3, 5.3, 2.7 Hz, 2H), 6.77 (d, *J* = 2.7 Hz, 1H), 5.90 (t, *J* = 5.7 Hz, 1H), 5.02 – 4.88 (m, 1H), 4.52 – 4.47 (m, 1H), 3.84 (d, *J* = 3.3 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.55 (d, *J* = 7.1 Hz, 2H),

2.05 – 1.96 (m, 2H), 1.54 – 1.37 (m, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.91, 159.42, 156.24, 141.26, 139.12, 131.08, 130.51, 130.02, 129.50, 129.28, 129.21, 128.27, 128.13, 128.05, 125.84, 125.06, 125.03, 122.11, 117.92, 116.40, 116.19, 115.69, 115.40, 114.30, 114.09, 112.99, 110.92, 72.20, 55.91, 55.45, 43.38, 41.09, 38.91, 32.08, 29.44, 27.16, 22.07; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{42}FNO_4$ 643.80, found 644.32.

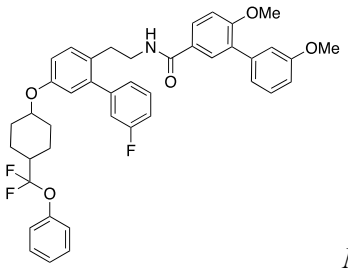


***N*-(2-(3'-fluoro-5-((4-phenethylcyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25b):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.26 (m, 4H), 7.23 (s, 1H), 7.18 (d, *J* = 7.3 Hz, 3H), 7.03 (ddt, *J* = 25.1, 14.5, 8.1 Hz, 6H), 6.90 (ddd, *J* = 8.5, 5.7, 2.7 Hz, 2H), 6.77 (d, *J* = 2.7 Hz, 1H), 5.90 (t, *J* = 5.6 Hz, 1H), 4.50 (d, *J* = 4.2 Hz, 1H), 3.85 (d, *J* = 3.2 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.68 – 2.59 (m, 2H), 2.00 (d, *J* = 12.0 Hz, 2H), 1.60 (q, *J* = 4.4, 2.8 Hz, 3H), 1.55 – 1.38 (m, 5H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.23, 159.74, 159.36, 156.58, 139.44, 131.39, 130.83, 129.82, 129.53, 128.81, 128.75, 128.45, 128.33, 126.05, 125.38, 122.43, 118.21, 116.04, 115.72, 113.31, 111.25, 72.66, 56.23, 55.77, 41.41, 38.84, 36.52, 33.72, 32.40, 29.75, 27.63; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{43}H_{44}FNO_4$ 657.83, found 658.33.

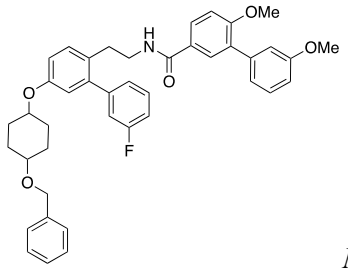


***N*-(2-(5-((4-(benzylthio)cyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25c):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.39 – 7.27 (m, 6H), 7.26 – 7.21 (m, 2H), 7.11 – 6.94 (m, 6H), 6.90 (dd, *J* = 8.1, 2.6 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.72 (d, *J* = 2.7 Hz, 1H), 5.89 (t, *J* = 5.7 Hz, 1H), 4.20 (dq, *J* = 9.2, 4.3, 3.8 Hz, 1H), 3.84 (d, *J* = 3.0 Hz, 6H), 3.75 (s, 2H), 3.46 (q, *J* = 6.7 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.60 (dt, *J* = 10.2, 5.9 Hz, 1H), 2.19 – 2.05 (m, 4H), 1.54 – 1.36 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.80, 156.56, 143.41, 135.94, 131.37, 130.31, 129.68, 128.81, 128.75, 128.75, 128.36, 127.41, 127.31, 126.74, 126.05, 125.40, 125.37, 121.58, 118.18, 116.72, 116.51,

116.07, 115.96, 72.69, 41.35, 38.83, 36.51, 33.72, 32.38, 30.21, 29.75, 27.63, 26.29, 18.41; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.22, 159.74, 159.37, 156.42, 142.55, 139.42, 139.01, 131.44, 130.38, 130.29, 129.79, 129.53, 129.18, 128.99, 128.77, 128.46, 127.41, 127.33, 125.34, 125.31, 122.42, 118.04, 116.69, 116.48, 116.01, 115.74, 114.68, 113.30, 111.25, 75.37, 56.23, 55.78, 41.98, 41.39, 35.52, 32.41, 31.35, 30.92; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{42}FNO_4S$ 675.86, found 676.29.

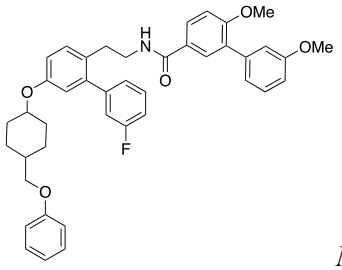


***N*-(2-(5-((4-(difluoro(phenoxy)methyl)cyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25d):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.57 (d, *J* = 2.3 Hz, 1H), 7.37 – 7.27 (m, 5H), 7.18 (dd, *J* = 11.6, 7.7 Hz, 3H), 7.11 – 6.95 (m, 6H), 6.91 (ddd, *J* = 8.8, 6.6, 2.6 Hz, 2H), 6.80 (d, *J* = 2.7 Hz, 1H), 5.90 (t, *J* = 5.7 Hz, 1H), 4.60 – 4.53 (m, 1H), 3.84 (d, *J* = 3.3 Hz, 6H), 3.47 (q, *J* = 6.8 Hz, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.18 (d, *J* = 14.5 Hz, 3H), 1.95 – 1.82 (m, 4H), 1.60 (d, *J* = 2.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 170.4, 163.7, 161.7, 156.0, 150.6, 143.8, 142.3, 131.1, 130.1, 129.4(3), 128.87, 127.85, 127.81, 126.69, 125.4, 125.2, 122.0, 117.9, 116.4, 116.2, 115.8, 114.4, 114.2, 113.99, 112.88, 110.81, 70.8, 55.79, 55.33, 40.9, 32.0, 28.8(2), 20.1; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{40}F_3NO_5$ 695.78, found 696.29.

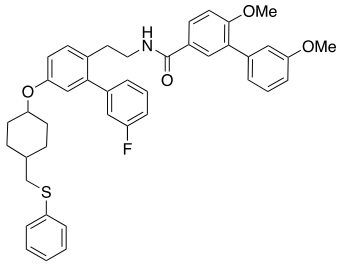


***N*-(2-(5-((4-(benzyloxy)cyclohexyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25e):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dt, *J* = 8.6, 2.1 Hz, 1H), 7.58 (t, *J* = 2.6 Hz, 1H), 7.39 – 7.26 (m, 7H), 7.23 (s, 1H), 7.10 – 6.95 (m, 7H), 6.88 (qd, *J* = 5.8, 3.0 Hz, 2H), 6.75 (dd, *J* = 6.8, 2.7 Hz, 1H), 5.91 (d, *J* = 7.0 Hz, 1H), 4.55 (s, 2H), 4.35 (td, *J* = 6.0, 4.9, 2.2 Hz, 1H), 3.84 (d, *J* = 3.3 Hz, 6H), 3.56 – 3.42 (m, 3H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.13 – 1.85 (m, 4H), 1.73 – 1.64 (m, 2H), 1.53 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.60, 159.08, 158.96, 158.71, 155.82, 130.78, 130.16, 129.69, 129.22, 129.17, 128.87, 127.85, 127.81, 126.69, 124.69, 121.77, 120.30, 117.58, 116.06, 115.85, 115.38, 115.09, 114.31, 113.98, 113.77, 112.64,

110.59, 72.49, 71.68, 55.57, 55.12, 40.77, 36.52, 31.75, 28.77, 23.79; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{42}FNO_5$ 659.80, found 660.31.

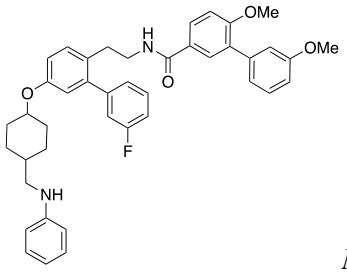


***N*-(2-(3'-fluoro-5-((4-(phenoxymethyl)cyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25f):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.24 (s, 1H), 7.10 – 6.93 (m, 7H), 6.92 – 6.88 (m, 4H), 6.78 (d, *J* = 2.7 Hz, 1H), 5.95 (t, *J* = 5.7 Hz, 1H), 4.56 (dd, *J* = 4.2, 2.3 Hz, 1H), 3.84 (d, *J* = 2.7 Hz, 6H), 3.82 (d, *J* = 6.6 Hz, 2H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.07 (dd, *J* = 11.1, 3.7 Hz, 2H), 1.92 (ddq, *J* = 10.1, 6.8, 3.5 Hz, 1H), 1.72 (dt, *J* = 11.9, 3.5 Hz, 2H), 1.58 (ddd, *J* = 18.1, 11.7, 3.1 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.61, 159.09, 158.72, 141.87, 138.78, 130.79, 130.19, 129.72, 129.63, 129.19, 128.89, 128.20, 128.17, 127.93, 127.82, 127.79, 127.29, 127.21, 126.70, 124.69, 121.78, 117.45, 117.42, 116.06, 115.85, 115.49, 115.33, 115.08, 114.00, 113.79, 112.67, 110.61, 75.21, 74.30, 72.68, 69.56, 55.58, 55.13, 40.77, 31.76, 28.20, 28.11, 27.29, 27.16; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{42}FNO_5$ 659.80, found 660.31.

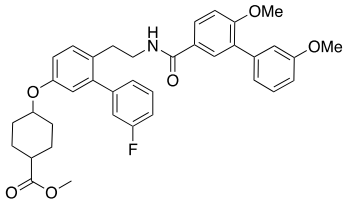


***N*-(2-(3'-fluoro-5-((4-((phenylthio)methyl)cyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25g):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.33 – 7.16 (m, 7H), 7.15 – 7.06 (m, 1H), 7.03 (t, *J* = 1.3 Hz, 1H), 7.03 – 6.94 (m, 4H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.89 – 6.79 (m, 2H), 6.71 (d, *J* = 2.7 Hz, 1H), 5.89 (t, *J* = 5.7 Hz, 1H), 4.45 (dq, *J* = 4.3, 2.1 Hz, 1H), 3.79 (d, *J* = 3.1 Hz, 6H), 3.42 (q, *J* = 6.7 Hz, 2H), 2.86 – 2.75 (m, 4H), 2.02 – 1.91 (m, 2H), 1.72 – 1.60 (m, 2H), 1.59 (s, 1H), 1.56 – 1.38 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.23, 159.71, 159.34, 156.40, 139.41, 137.75, 131.40, 130.79, 130.32, 130.24, 129.80, 129.50, 129.29, 129.17, 128.49, 128.44, 127.32, 126.04, 125.35, 125.32, 122.41, 118.18, 116.69, 116.48, 115.98, 115.72, 114.61, 114.40, 113.27, 111.22, 72.13, 56.20, 55.75, 41.40,

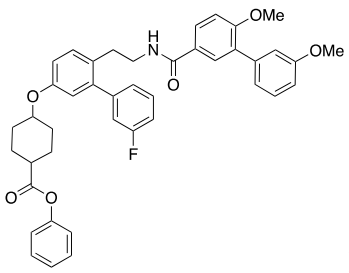
40.64, 36.97, 32.38, 29.59, 27.22; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{42}FNO_4S$ 675.78, found 676.29.



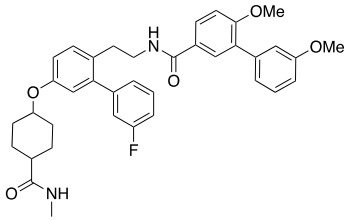
***N*-(2-(3'-fluoro-5-((4-((phenylamino)methyl)cyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25h):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.24 (s, 1H), 7.22 – 7.12 (m, 2H), 7.11 – 6.94 (m, 6H), 6.94 – 6.85 (m, 2H), 6.77 (d, *J* = 2.7 Hz, 1H), 6.68 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.65 – 6.56 (m, 2H), 5.91 (t, *J* = 5.8 Hz, 1H), 4.54 (q, *J* = 3.5, 3.0 Hz, 1H), 3.84 (d, *J* = 3.0 Hz, 6H), 3.75 (s, 1H), 3.47 (q, *J* = 6.7 Hz, 2H), 3.06 – 2.99 (m, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.08 – 2.01 (m, 2H), 1.70 (dq, *J* = 6.7, 3.3 Hz, 1H), 1.67 – 1.61 (m, 2H), 1.57 – 1.43 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.24, 159.74, 159.37, 156.46, 148.90, 131.43, 130.82, 130.35, 130.26, 129.80, 129.71, 129.53, 128.49, 128.46, 127.35, 125.37, 122.43, 118.21, 117.45, 116.50, 116.01, 115.74, 114.64, 114.43, 113.30, 113.09, 111.25, 72.36, 56.23, 55.77, 50.33, 41.42, 36.95, 32.41, 29.57, 25.70; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{43}FN_2O_4$ 658.81, found 659.33.



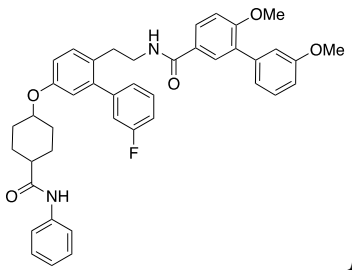
Methyl 4-((6-(2-(3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamido)ethyl)-3'-fluoro-[1,1'-biphenyl]-3-yl)oxy)cyclohexane-1-carboxylate (25i): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (ddd, *J* = 8.6, 6.1, 2.3 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.21 (d, *J* = 14.5 Hz, 1H), 7.10 – 6.95 (m, 6H), 6.89 (td, *J* = 8.6, 2.7 Hz, 2H), 6.76 (d, *J* = 2.7 Hz, 1H), 5.89 (d, *J* = 6.0 Hz, 1H), 4.53 – 4.43 (m, 1H), 3.85 (d, *J* = 3.0 Hz, 6H), 3.68 (s, 3H), 3.52 – 3.39 (m, 2H), 2.85 (td, *J* = 7.1, 2.7 Hz, 2H), 2.47 – 2.36 (m, 1H), 2.06 – 1.90 (m, 4H), 1.73 (dt, *J* = 13.7, 4.3 Hz, 2H), 1.63 (td, *J* = 12.2, 10.1, 5.4 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 175.92, 166.90, 159.42, 159.05, 155.97, 139.12, 131.12, 130.52, 130.04, 129.95, 129.51, 129.20, 128.34, 128.11, 127.04, 125.01, 122.11, 117.84, 116.38, 116.17, 115.75, 115.41, 114.33, 114.13, 112.99, 110.93, 71.63, 55.91, 55.45, 51.78, 41.93, 41.08, 32.09, 29.04; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{37}H_{38}FNO_6$ 611.71, found 612.27.



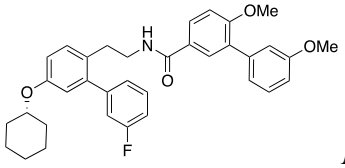
Phenyl 4-((6-(2-(3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamido)ethyl)-3'-fluoro-[1,1'-biphenyl]-3-yl)oxy)cyclohexane-1-carboxylate (25j): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.36 (ddd, *J* = 17.4, 8.3, 6.5 Hz, 4H), 7.26 – 7.20 (m, 2H), 7.07 (ddd, *J* = 7.4, 2.2, 1.1 Hz, 3H), 7.06 – 6.98 (m, 4H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.79 (d, *J* = 2.7 Hz, 1H), 5.92 (t, *J* = 5.7 Hz, 1H), 4.52 (dq, *J* = 7.4, 3.7, 3.3 Hz, 1H), 3.84 (d, *J* = 3.1 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.67 (tt, *J* = 10.2, 3.8 Hz, 1H), 2.19 – 2.02 (m, 4H), 1.91 (dt, *J* = 13.3, 4.2 Hz, 2H), 1.77 – 1.65 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.94, 166.91, 159.42, 159.04, 155.94, 139.11, 131.16, 130.51, 129.97, 129.54, 129.50, 129.20, 128.41, 128.12, 127.02, 125.87, 125.04, 125.01, 122.10, 121.68, 117.83, 116.39, 116.18, 115.76, 115.41, 114.14, 112.98, 110.93, 71.58, 55.91, 55.45, 42.05, 41.08, 32.10, 29.03; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{42}H_{40}FNO_6$ 673.78, found 674.29.



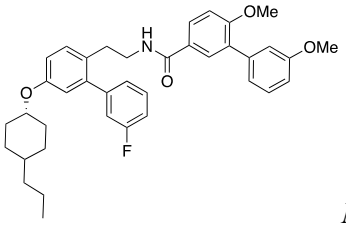
***N*-(2-(3'-fluoro-5-((4-(methylcarbamoyl)cyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25k):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.64 (m, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.24 (d, *J* = 9.2 Hz, 1H), 7.09 – 6.95 (m, 6H), 6.89 (td, *J* = 8.3, 2.4 Hz, 2H), 6.76 (d, *J* = 2.7 Hz, 1H), 5.90 (t, *J* = 5.6 Hz, 1H), 4.46 (q, *J* = 3.9 Hz, 1H), 3.85 (d, *J* = 3.0 Hz, 6H), 3.68 (s, 3H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.41 (tt, *J* = 10.2, 3.8 Hz, 1H), 2.05 – 1.90 (m, 4H), 1.74 (dq, *J* = 13.2, 4.9, 4.5 Hz, 2H), 1.67 – 1.58 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.24, 167.23, 159.74, 159.37, 156.29, 139.43, 131.44, 130.84, 130.36, 130.27, 129.83, 129.52, 128.65, 128.43, 127.35, 125.36, 125.33, 122.42, 118.15, 116.70, 116.49, 116.07, 115.72, 114.65, 114.44, 113.31, 111.25, 71.95, 56.23, 55.77, 52.10, 42.24, 41.40, 32.41, 29.36; HRMS (ESI) m/z $[M+Na]^+$: calculated for $C_{37}H_{39}FN_2O_5$ 610.73, found 611.19.



***N*-(2-(3'-fluoro-5-((4-(phenylcarbamoyl)cyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25l):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.52 (t, *J* = 8.1 Hz, 2H), 7.37 – 7.28 (m, 4H), 7.25 (s, 1H), 7.13 – 6.96 (m, 7H), 6.91 (dt, *J* = 8.0, 2.7 Hz, 2H), 6.79 (d, *J* = 2.7 Hz, 1H), 5.90 (t, *J* = 5.7 Hz, 1H), 4.56 (s, 1H), 3.84 (d, *J* = 3.8 Hz, 6H), 3.46 (dq, *J* = 13.1, 6.8 Hz, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.33 (d, *J* = 11.1 Hz, 1H), 2.21 – 2.12 (m, 2H), 2.01 (d, *J* = 18.1 Hz, 2H), 1.90 – 1.68 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.60, 166.93, 159.44, 159.04, 155.94, 139.13, 131.17, 130.51, 129.53, 129.22, 129.16, 128.11, 127.02, 125.87, 125.04, 125.01, 122.12, 119.92, 117.86, 116.39, 116.19, 115.81, 115.43, 113.00, 112.98, 110.96, 70.85, 55.92, 55.47, 42.05, 41.08, 32.11, 29.14; HRMS (ESI) m/z $[M+Na]^+$: calculated for $C_{42}H_{41}FN_2O_5Na$ 672.8, found 695.29.



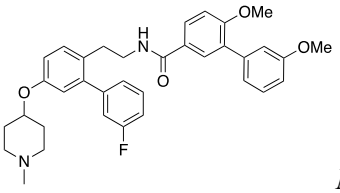
***N*-(2-(5-(cyclohexyloxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25m):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.58 (d, *J* = 2.3 Hz, 1H), 7.32 (qd, *J* = 7.9, 5.3 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.09 – 6.95 (m, 6H), 6.89 (ddd, *J* = 11.3, 8.4, 2.7 Hz, 2H), 6.75 (d, *J* = 2.7 Hz, 1H), 5.91 (t, *J* = 5.8 Hz, 1H), 4.22 (tt, *J* = 8.8, 3.9 Hz, 1H), 3.85 (d, *J* = 2.5 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 1.97 (dd, *J* = 13.0, 5.1 Hz, 2H), 1.79 (dq, *J* = 9.6, 5.7, 4.7 Hz, 2H), 1.60-1.54 (m, 2H), 1.42 – 1.28 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.91, 159.41, 159.04, 156.32, 142.16, 139.11, 131.07, 130.51, 130.02, 129.93, 129.51, 129.20, 128.12, 128.08, 127.03, 125.04, 122.10, 117.69, 116.39, 116.18, 115.73, 115.39, 114.29, 114.08, 113.01, 110.92, 75.55, 55.91, 55.45, 41.09, 32.08, 31.95; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{35}H_{36}FNO_4$ 553.67, found 554.27.



***N*-(2-(3'-fluoro-5-((4-propylcyclohexyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (25n):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.32 (dt, *J* = 11.7, 7.6 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.11 – 7.06 (m, 2H), 7.06 – 6.99 (m, 3H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.89 (td, *J* = 8.4, 7.9, 2.5 Hz, 2H), 6.76 (d, *J* = 2.7 Hz, 1H), 5.92 (t, *J* = 5.7 Hz, 1H), 4.49 (t, *J* = 3.7 Hz, 1H), 3.85 (d, *J* = 2.5 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.02 – 1.93 (m, 2H), 1.59 – 1.52 (m, 2H), 1.51 (d, *J* = 3.6 Hz, 2H), 1.45 – 1.28 (m, 5H), 1.23 (dt, *J* = 12.3, 6.0 Hz, 2H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.22, 159.73, 159.34, 156.62, 142.46, 139.43, 131.36, 130.31, 130.23, 129.82, 129.52, 128.44, 128.26, 127.36, 125.37, 125.34, 122.42, 118.21, 116.71, 116.50, 116.03, 115.70, 114.58, 114.37, 113.31, 111.23, 72.82, 56.22, 55.76, 41.40, 39.25, 36.65, 32.39, 29.82, 27.73, 20.47, 14.84; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{38}H_{42}FNO_4$ 595.76, found 596.317.

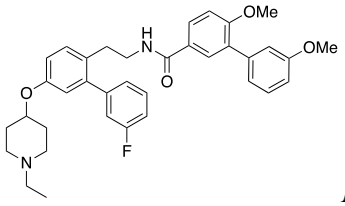
General procedure for the synthesis of compounds (28):

N-(2-(3'-fluoro-5-(piperidin-4-yloxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (7.4 mg, 1 Eq, 13 µmol), alkyl halide (1.4 mg, 1.2 µL, 0.8 Eq, 11 µmol), were dissolved in DMF (0.05 mL). DIPEA (1.7 mg, 2.3 µL, 1 Eq, 13 µmol) was added to the reaction after half an hour and the mixture was stirred at RT overnight. The reaction was quenched with water, washed with and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with MeOH:DCM 10%) to afford **28** (55-80% yield).

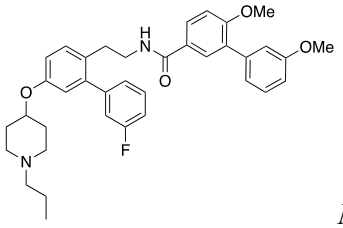


***N*-(2-(3'-fluoro-5-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (28a):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.11 – 6.96 (m, 6H), 6.91 (td, *J* = 8.6, 2.7 Hz, 2H), 6.78 (d, *J* = 2.6 Hz, 1H), 6.04 (t, *J* = 5.7 Hz, 1H), 4.35 (dp, *J* = 7.3, 3.7 Hz, 1H), 3.86 (d, *J* = 2.8 Hz, 6H), 3.49 (q, *J* = 6.7 Hz, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.78 – 2.68 (m, 2H), 2.38 (m, 2H), 2.35 (s, 3H), 2.04 (ddt, *J* = 11.5, 6.9, 3.9 Hz, 2H), 1.88 (dtd, *J* = 11.9, 7.7, 3.5 Hz, 2H); ^{13}C NMR (101

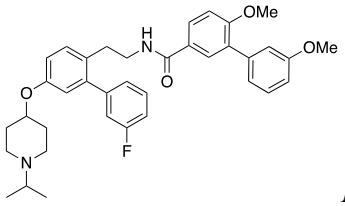
MHz, Chloroform-*d*) δ 167.23, 159.69, 159.32, 156.16, 139.39, 131.44, 130.76, 130.34, 130.25, 129.78, 129.48, 128.84, 128.44, 127.28, 125.31, 125.28, 122.38, 118.06, 116.65, 116.44, 115.96, 115.70, 114.64, 114.43, 113.24, 111.21, 56.18, 55.73, 46.48, 41.38, 32.38; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{35}H_{37}FN_2O_4$ 568.69, found 569.28.



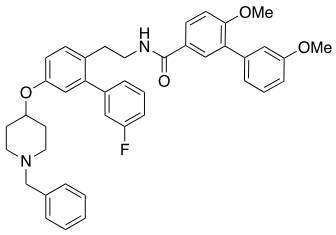
***N*-(2-(5-((1-ethylpiperidin-4-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (28b):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.10 – 7.05 (m, 2H), 7.05 – 6.96 (m, 4H), 6.92 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.74 (d, *J* = 2.8 Hz, 1H), 5.91 (t, *J* = 5.8 Hz, 1H), 4.71 (s, 1H), 3.85 (d, *J* = 1.0 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 3H), 3.13 (q, *J* = 7.3 Hz, 3H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.73 (t, *J* = 14.9 Hz, 1H), 2.21 (d, *J* = 15.0 Hz, 1H), 1.55 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.15, 142.77, 139.10, 131.60, 130.24, 130.17, 129.99, 129.36, 129.26, 128.23, 126.89, 124.92, 124.90, 122.10, 117.81, 116.30, 116.13, 115.60, 115.16, 114.66, 114.49, 112.87, 111.03, 77.36, 55.95, 55.56, 41.01, 32.20, 29.85, 9.27; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{36}H_{39}FN_2O_4$ 582.72, found 583.30.



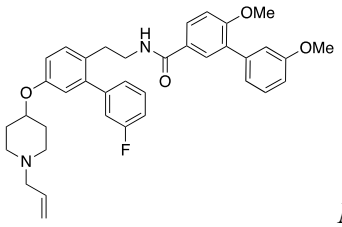
***N*-(2-(3'-fluoro-5-((1-propylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (28c):** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.34 (td, *J* = 8.0, 6.3 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.09 – 7.02 (m, 4H), 7.01 – 6.95 (m, 2H), 6.92 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 5.91 (t, *J* = 5.8 Hz, 1H), 4.55 (s, 1H), 3.85 (d, *J* = 1.8 Hz, 6H), 3.47 (q, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 9.5 Hz, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.72 (s, 2H), 2.45 (s, 2H), 2.10 – 2.03 (m, 2H), 1.87 – 1.78 (m, 2H), 1.33 – 1.27 (m, 2H), 1.00 – 0.95 (m, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.38, 155.39, 143.63, 142.82, 139.36, 131.67, 130.42, 130.35, 129.66, 129.49, 128.45, 125.21, 125.19, 122.36, 118.06, 116.58, 116.41, 115.79, 115.65, 114.79, 114.62, 113.17, 111.25, 60.10, 56.19, 55.77, 41.29, 32.42, 30.36, 30.10, 11.92; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{37}H_{41}FN_2O_4$ 596.74, found 597.31.



***N*-(2-(3'-fluoro-5-((1-isopropylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (28d):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.09 – 7.01 (m, 4H), 6.98 (dd, *J* = 9.0, 3.4 Hz, 2H), 6.91 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.96 (t, *J* = 5.8 Hz, 1H), 4.67 (t, *J* = 2.9 Hz, 1H), 3.84 (d, *J* = 1.5 Hz, 6H), 3.47 (q, *J* = 6.7 Hz, 2H), 3.41 (td, *J* = 6.6, 2.5 Hz, 1H), 3.27 – 3.09 (m, 4H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.79 – 2.67 (m, 2H), 2.15 (d, *J* = 14.7 Hz, 2H), 1.44 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.24, 159.75, 155.05, 139.38, 131.82, 130.52, 130.44, 130.07, 129.69, 129.54, 128.54, 127.19, 125.24, 122.39, 118.20, 116.63, 116.41, 115.86, 115.41, 114.94, 114.73, 113.15, 111.28, 67.51, 58.46, 56.24, 55.81, 43.75, 41.34, 32.47, 27.11, 17.18; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{37}H_{41}FN_2O_4$ 596.74, found 597.31.



***N*-(2-(5-((1-benzylpiperidin-4-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (28e):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 5H), 7.29 (s, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.09 – 7.02 (m, 4H), 7.02 – 6.95 (m, 2H), 6.88 (ddd, *J* = 11.6, 8.4, 2.7 Hz, 2H), 6.74 (d, *J* = 2.6 Hz, 1H), 5.89 (t, *J* = 5.8 Hz, 1H), 4.32 (t, *J* = 17.1 Hz, 1H), 3.84 (d, *J* = 3.2 Hz, 6H), 3.65 – 3.49 (m, 2H), 3.49 – 3.38 (m, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.75 (s, 2H), 2.39 – 2.17 (m, 2H), 1.90 (ddt, *J* = 46.1, 25.2, 13.2 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.58, 159.11, 158.74, 141.97, 138.79, 130.86, 130.19, 129.75, 129.66, 129.15, 128.90, 127.83, 126.69, 124.70, 124.67, 121.78, 117.46, 116.06, 115.85, 115.34, 115.12, 112.65, 110.62, 55.60, 55.15, 40.75, 31.78, 29.54; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{41}H_{41}FN_2O_4$ 644.79, found 645.31.



***N*-(2-(5-((1-allylpiperidin-4-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (28f):** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.24 (s, 1H), 7.11 – 6.94 (m, 6H), 6.94 – 6.84 (m, 2H), 6.75 (d, *J* = 2.7 Hz, 1H), 5.96 (d, *J* = 6.6 Hz, 1H), 5.91 (t, *J* = 5.8 Hz, 1H), 5.24 (d, *J* = 16.9 Hz, 2H), 4.37 (s, 1H), 3.85 (d, *J* = 2.4 Hz, 6H), 3.47 (q, *J* = 6.8 Hz, 2H), 3.11 (s, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.79 (s, 2H), 2.64 – 2.20 (m, 2H), 2.09 (s, 2H), 1.90 (s, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.59, 159.10, 158.74, 155.41, 142.01, 138.78, 130.89, 130.17, 129.76, 129.68, 129.14, 128.90, 128.37, 127.84, 126.66, 124.69, 124.66, 121.77, 117.45, 116.05, 115.84, 115.29, 115.12, 114.09, 113.88, 112.63, 110.62, 61.25, 55.59, 55.14, 40.75, 31.78; HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{37}H_{39}FN_2O_4$ 594.73, found 595.30.