Discovery of AM-6226. A Potent and Orally Bioavailable GPR40 Full Agonist that Displays Efficacy in Non-Human Primates.

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Supplemental Material

Abbreviations of the solvents and reagents: $CDCl_3$, deuterochloroform; DMSO-d_6, hexadeuterodimethyl sulfoxide; AcOEt, ethyl acetate; MeOH, methanol; EtOH, ethanol; iPrOH, 2-propanol; DMF, N,N-dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; Et_2O, diethyl ether; DME, 1,2-dimethoxyethane; CH_3CN, acetonitrile; CH_2Cl_2, dichloromethane; $NaBH_4$, sodium borohydride; $LiAlH_4$, lithium aluminum hydride; NaOH, sodium hydroxide; LiOH, Lithium hydroxide; $Na_2S_2O_3$, sodium thiosulfate; NH_4Cl, ammonium chloride; $NaHCO_3$, sodium hydrogen carbonate; $MgSO_4$, magnesium sulfate; Na_2SO_4, sodium sulfate; K_2CO_3, potassium carbonate; Cs_2CO_3, cesium carbonate; K_3PO_4, potassium phosphate; TBAF, tetrabutylammonium fluoride; KI, potassium iodine; m-CPBA, m-chloroperbenzoic acid; Pd/C, palladium on carbon; $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0); n-BuLi, n-butyl lithium; PPh_3, triphenylphosphine; DEAD, diethyl azodicarboxylate; Et_3N, TEA, triethylamine; HCl, hydrochloric acid; AcOH, acetic acid; NCS, N-chlorosuccinimide; binap, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; PPTS, pyridinium p-toluenesulfonate; S-phos, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; DBU, 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine;

Aequorin assay: A cell-based aequorin assay may be employed to characterize the modulatory activity of compounds on the GPR40 signaling pathway. CHO cells are transfected in a 15 cm plate containing 14 million cells with 5 μg or 0.05 μg of GPR40 expression vector and 5 μg or 0.05 μg of Aequorin expression vector (Euroscreen) using Lipofectamine 2000 (Invitrogen). After 17–24 h post-transfection, cells are washed with phosphate buffered saline (PBS) and detached from the tissue culture dish with 2 mL of trypsin (0.25%(w/v)). Trypsinization is halted with 28 mL of Hanks Buffered Salt Solution containing 20 mM Hepes (H/HBSS) and 0.01% fatty acid-free bovine serum albumin (BSA) or 0.625% fatty acid-free human serum albumin (HSA). Coelantrazine is added to 1 ug/mL and the cells are incubated for 2 h at room temperature. Cells are gently mixed every 15 minutes. Compounds are dissolved in dimethyl sulfoxide for preparation of 10 mM stock solutions. Compounds are diluted in H/HBSS containing 0.01% BSA. Serial dilutions of the test compounds are prepared to determine dose response.

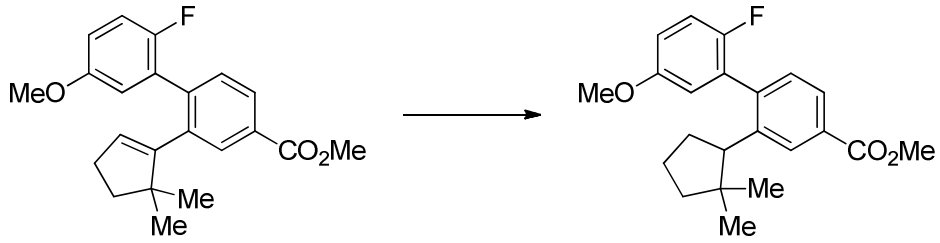
Aequorin luminescence measurements are made using an EG&G Berthold 96-well luminometer and the response is measured over a 20 second interval after cells and compounds were mixed. The area-under-curve from 2–20 seconds is plotted to determine dose reponse. The EC_{50} (effective concentration to reach 50% maximal response) is determined from the dose response plot. The mean realative standard error for this assay is 14%.

***In vivo* procedures: Cynomolgus monkey OGTT:** Cynomolgus monkey OGTTs were performed at the Yunnan National Laboratory Primate Center in Kunming, China. All procedures in monkeys were approved by the IACUC at the Yunnan National Laboratory Primate and comply with the governmental regulations of China. Animals were housed in individual cages in a controlled environment (18-26°C, 60-80% relative humidity, lights-on from 0600-1800 h) and fed a standard chow twice daily. Water was provided *ad libidum*. At least 10 days prior to the experiment, animals were acclimated to procedures used during an OGTT, including primate chair restraint, oral gavage and venipuncture.

Animals were fasted overnight prior to experiments. AM-6226 and sitagliptin were formulated in 1%HPMC, 10% HPbCD, 1% Tween-80 and were dosed by oral gavage in a volume of 10 mL/kg. Animals were tested in a cross-over study design and personnel performing the procedures were blinded to the treatments. Two hours following drug dose,

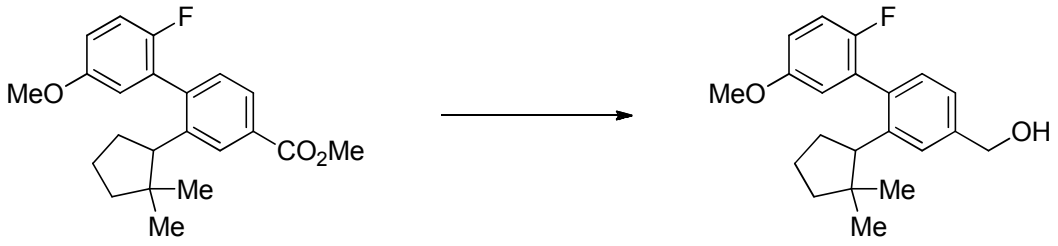
glucose was administered at 4 g/kg by oral gavage in a volume of 10 mL/kg. Plasma glucose was determined using the glucose oxidase method on a Hitachi 7020 Automatic Analyzer.

1. Experimental Section

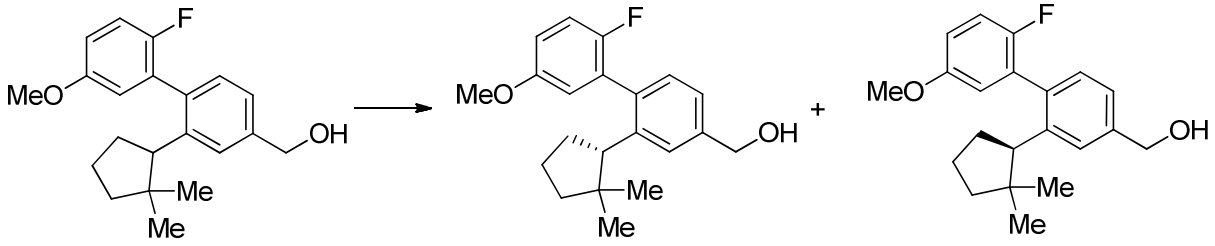


19 **25**

Synthesis of methyl 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-carboxylate 25. To a stirred solution of **19** (0.660 g, 1.86 mmol) in MeOH (20.0 mL) at 23 °C was added Pd/C (0.02 g, 0.19 mmol). Stirring continued under an atmosphere of hydrogen (0.0038 g, 1.86 mmol) for 16 h. The reaction mixture was then filtered and concentrated in *vacuo* to give **25** as a clear oil (0.600 g, 90 % yield). $C_{22}H_{25}FO_3$ Exact Mass 356.18, MS ESI (pos.) m/e: 357.2 $(M+H)^+$.

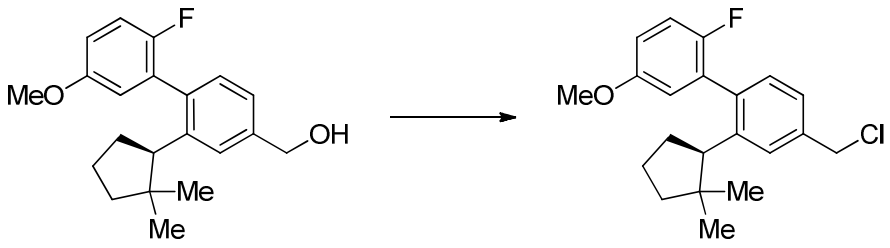


25 **26**



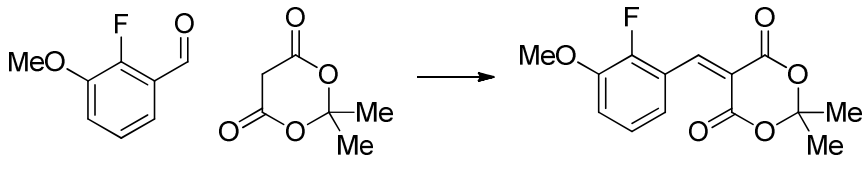
26 **27** **28**

Synthesis of (*S*)-(2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methanol (27) and (*R*)-(2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methanol (28). . To a stirred solution of **25** (0.500 g, 1.4 mmol) in THF (7.0 mL) at 0 °C was added LAH (1.4 mL, 1.4 mmol). After addition, the reaction was then stirred for 1.5 h. 1 N NaOH (aq) was then added to quench the reaction, and the mixture was then extracted with EtOAc. The organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting product was then purified on silica gel (0%-20% EtOAc/hexanes) to give **26** (0.44 g, 96% yield). Chiral separation of **26** was accomplished on Chiracel-OD (3%IPA in hexanes) to provide **27** and **28**. Analytical column (Chiracel-OD (2% IPA in hexanes, 45 min run) Peak 1-15.5 mins, Peak 2-38.0 mins). $C_{21}H_{25}FO_2$ Exact Mass 328.18, MS ESI (pos.) m/e: 311.2 $(M\text{-}HO)^+$.



28 **20**

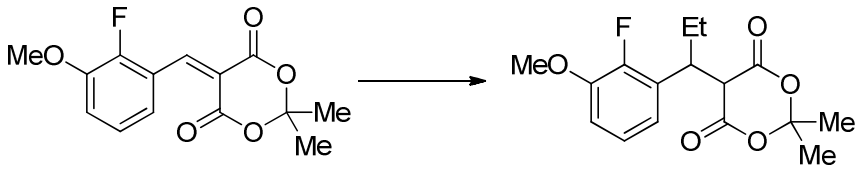
4-(Chloromethyl)-2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl 20. Thionyl chloride (1.5 mL, 20 mmol) was added to a stirred solution of **28** (3.28 g, 10.0 mmol) in dichloromethane (100 mL) and DMF (0.77 mL) at 0 °C. Stirring was continued at room temperature for 2 h. The reaction mixture was then concentrated in vacuo and purified on silica gel (0-10% EtOAc in hexanes) to give the desired product **20** (3.00 g, 87 % yield) as a clear oil.



21 **22**

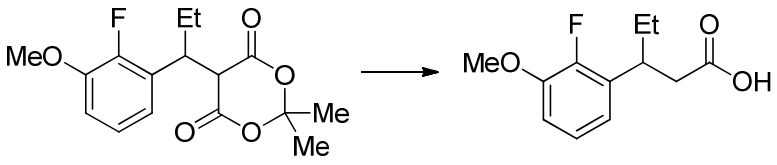
5-(2-Fluoro-3-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (21). A 500 mL round bottom flask was charged with 2-fluoro-3-methoxybenzaldehyde (available from Frontier Scientific, 28.6 g, 186 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (available from Aldrich, 34.8

g, 241 mmol) and water (350 mL). The heterogeneous mixture was stirred for 2 h at 90 °C, cooled to room temperature, and filtered. The crude solid was triturated with ether to afford **22** (30.6 g, 59% yield) as a crystalline white powder. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.43 - 7.38 (m, 1H), 7.19 - 7.10 (m, 2H), 3.92 (s, 3H), 1.83 (s, 6H).



22 **29**

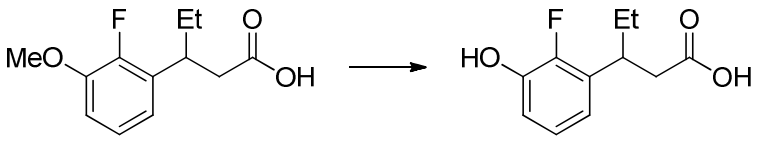
5-(1-(2-Fluoro-3-methoxyphenyl)propyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (29). A 500 mL round bottom flask was charged with **22** (5.00 g, 17.8 mmol) and THF (100 mL) and cooled to 0 °C under N_2. To the cold slurry was added ethylmagnesium bromide (3.0 M in ether, available from Aldrich, 11.9 mL, 35.7 mmol) dropwise over 15 minutes. The cooling bath was removed, and the mixture was stirred for 1 h at ambient temperature. The reaction was quenched with 1 N HCl and extracted with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated to afford **29** (5.17 g, 93 % yield) as a yellow oil. The crude product was used without further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.12 - 7.04 (m, 2H), 6.92 - 6.85 (m, 1H), 4.05 (td, *J*=4.1, 10.3 Hz, 1H), 3.91 - 3.87 (m, 3H), 3.79 (d, *J*=3.5 Hz, 1H), 2.25 - 2.12 (m, 1H), 1.91 - 1.78 (m, 1H), 1.71 (s, 3H), 1.60 (s, 3H), 0.93 (t, *J*=7.2 Hz, 3H).



29 **30**

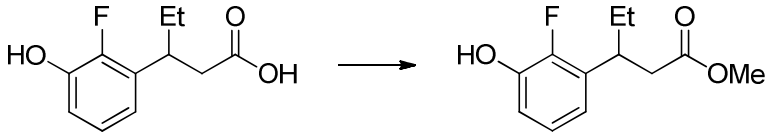
3-(2-Fluoro-3-methoxyphenyl)pentanoic acid (30). A 500 mL round bottom flask was charged with **29** (5.17 g, 16.7 mmol) and 10:1 DMF/water (80 mL). The resulting solution was stirred overnight at 90 °C, cooled to room temperature, and diluted with ether. The organics were washed with water and brine, dried ($MgSO_4$), and concentrated to afford **30** (3.44 g, 91 % yield) as a yellow oil. The crude product was used without further purification. ^{1}H NMR (400MHz,

$CDCl_3$) δ 7.01 (dt, *J*=1.6, 8.0 Hz, 1H), 6.84 (dt, *J*=1.6, 8.0 Hz, 1H), 6.75 (ddd, *J*=1.4, 6.2, 7.7 Hz, 1H), 3.91 - 3.86 (m, 3H), 3.36 (dtd, *J*=5.5, 7.4, 9.4 Hz, 1H), 2.73 - 2.68 (m, 2H), 1.82 - 1.60 (m, 2H), 0.82 (t, *J*=7.2 Hz, 3H). Acidic proton not observed.



30 **31**

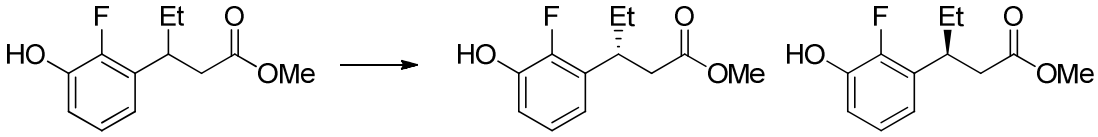
3-(2-Fluoro-3-hydroxyphenyl)pentanoic acid (31). A 500 mL round bottom flask was charged with **30** (26.0 g, 115 mmol), N-methylpyrrolidone (250 mL), sodium hydroxide (20.7 g, 518 mmol), and 1-dodecanethiol (available from Aldrich, 96.5 mL). The mixture was stirred for 5 h at 125 °C, cooled to room temperature, quenched with 1 N HCl, and diluted with EtOAc. The organics were washed with water and brine, dried ($MgSO_4$), and concentrated to give a biphasic mixture. The greasy top layer was diluted with hexanes and decanted. The polar bottom layer was purified by silica gel flash chromatography (20-50% EtOAc/hexanes) to afford **31** (21.5 g, 88% yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.00 - 6.94 (m, 1H), 6.87 (dt, *J*=1.8, 8.1 Hz, 1H), 6.71 (dt, *J*=1.6, 7.0 Hz, 1H), 5.12 (d, *J*=11.0 Hz, 1H), 3.40 - 3.26 (m, 1H), 2.78 - 2.63 (m, 2H), 1.82 - 1.70 (m, 1H), 1.70 - 1.59 (m, 1H), 0.83 (t, *J*=7.2 Hz, 3H). Acidic proton not observed.



31 **32**

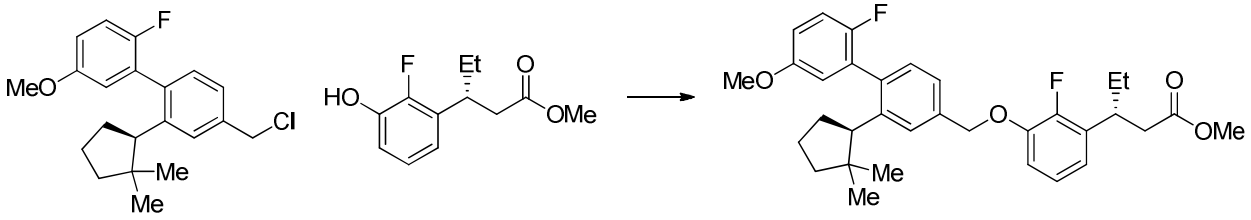
Methyl 3-(2-fluoro-3-hydroxyphenyl)pentanoate (32). A 500 mL round bottom flask was charged with **31** (21.5 g, 101 mmol), MeOH (300 mL), and sulfuric acid (1.08 mL, 20.3 mmol). The solution was stirred for 1 h at 80 °C, cooled to room temperature, and diluted with ether. The organics were washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (0-30% EtOAc/hexanes) to afford **32** (20.6 g, 90% yield) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.00 - 6.93 (m, 1H), 6.86 (dt, *J*=1.8, 8.1 Hz, 1H), 6.70 (dt, *J*=1.6, 7.2 Hz, 1H), 5.14 (d,

J=4.3 Hz, 1H), 3.61 (s, 3H), 3.40 - 3.28 (m, 1H), 2.74 - 2.60 (m, 2H), 1.79 - 1.60 (m, 2H), 0.82 (t, *J*=7.2 Hz, 3H).



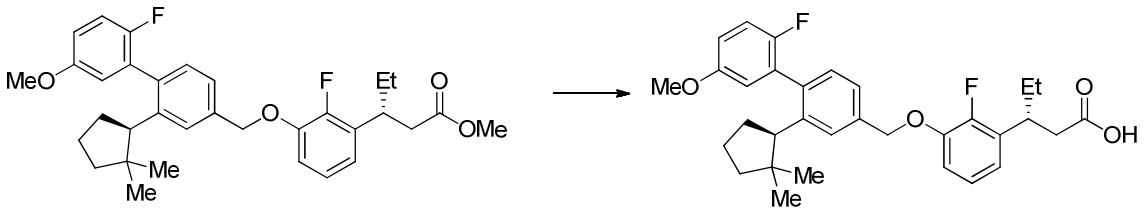
32 **24** **33**

(*R*)-Methyl 3-(2-fluoro-3-hydroxyphenyl)pentanoate (24) and (*S*)-Methyl 3-(2-fluoro-3-hydroxyphenyl)pentanoate (33). Racemic **32** (20 g) was resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexanes, detection at 220 nm) to afford (in order of elution) **24** (8 g, 80% yield, 99% e.e.) and **33** (8 g, 80% yield, 99% e.e.) as colorless oils.



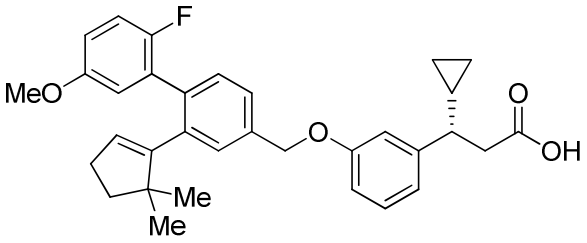
20 **24** **34**

(*R*)-methyl 3-(3-((2-((*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2-fluorophenyl)pentanoate (34). To a flask containing (*R*)-methyl 3-(2-fluoro-3-hydroxyphenyl)pentanoate (**24**, 430 mg, 1.90 mmol) and cesium carbonate (0.805 g, 2.47 mmol) in DMF (10 ml) was added **20** (0.725 g, 2.09 mmol) and stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and then purified by silic gel chromatography (0 to 20% EtOAc/ Hexanes) to provide **34** (1.02 g, 100% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.49 - 7.42 (m, 1H), 7.36 - 7.30 (m, 1H), 7.25 - 7.18 (m, 1H), 7.09 - 6.95 (m, 2H), 6.93 - 6.88 (m, 1H), 6.87 - 6.82 (m, 1H), 6.80 - 6.75 (m, 2H), 6.67 (dd, *J*=3.2, 5.9 Hz, 1H), 5.19 - 5.14 (m, 2H), 3.80 (s, 3H), 3.62 (s, 3H), 3.42 - 3.33 (m, 1H), 2.83 (ddd, *J*=2.2, 8.2, 10.4 Hz, 1H), 2.74 - 2.63 (m, 2H), 2.19 - 2.10 (m, 1H), 2.05 - 1.95 (m, 1H), 1.84 - 1.59 (m, 4H), 1.51 (dt, *J*=4.3, 8.4 Hz, 1H), 1.41 - 1.32 (m, 1H), 0.83 (t, *J*=7.3 Hz, 3H), 0.71 - 0.66 (m, 3H), 0.62 - 0.55 (m, 3H)



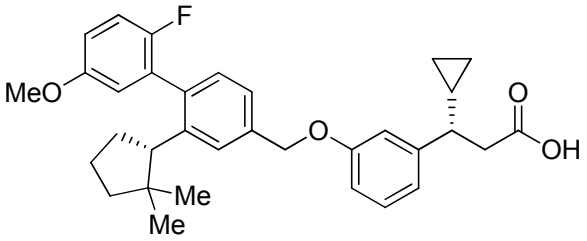
34 **14**

(*R*)-3-{3-[2-((*S*)-2,2-Dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-pentanoic acid (14). To a solution of 34 (1.10 g, 2.05 mmol) in THF/MeOH (2/1, 15 ml) was added 1.0N lithium hydroxide (5.0 ml). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organics were dried over Na2SO4 and concentrated in vacuo. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford 14 (1.02 g, 95 % yield). 1H NMR (380 K, 500 MHz, DMSO-d6) δ 0.60 (s, 3 H) 0.68 (s, 3 H) 0.74 (t, J=7.34 Hz, 3 H) 1.30 - 1.40 (m, 1 H) 1.46 - 1.58 (m, 2 H) 1.58 - 1.68 (m, 1 H) 1.74 - 1.84 (m, 2 H) 1.92 - 2.09 (m, 2 H) 2.17 - 2.31 (m, 2 H) 2.86 (br s, 1 H) 3.29 - 3.38 (m, 1 H) 3.40 - 3.46 (m, 1 H) 3.78 (s, 3 H) 5.20 (s, 2 H) 6.78 (br s, 1 H) 6.81 - 6.87 (m, 1 H) 6.93 - 7.02 (m, 1 H) 6.96 - 7.00 (m, 2 H) 7.11 - 7.20 (m, 1 H) 7.16 - 7.20 (m, 1 H) 7.33 (br d, J=7.65 Hz, 1 H) 7.48 (s, 1 H). 13C NMR (380 K, 126 MHz, DMSO-d6) δ 12.09 (s, 1 C) 22.39 (s, 1 C) 24.45 (s, 1 C) 28.27 (s, 1 C) 29.41 (br s, 1 C) 32.89 (br s, 1 C) 38.23 (s, 1 C) 42.31 (s, 1 C) 43.09 (br s, 1 C) 44.49 (s, 1 C) 51.27 (br s, 1 C) 56.44 (s, 1 C) 71.45 (s, 1 C) 113.71 (s, 1 C) 115.04 (br d, J=8.17 Hz, 1 C) 116.25 (dt, J=18.62, 8.86 Hz, 1 C) 117.18 - 118.70 (m, 1 C) 121.42 (d, J=4.54 Hz, 1 C) 123.77 (d, J=4.54 Hz, 1 C) 125.28 (br s, 1 C) 127.61 (br d, J=4.54 Hz, 1 C) 130.25 (br s, 1 C) 130.43 (s, 1 C) 135.26 (d, J=12.71 Hz, 1 C) 136.22 (br s, 1 C) 136.77 (s, 1 C) 141.79 (br s, 1 C) 146.79 (d, J=11.81 Hz, 1 C) 151.47 (d, J=242.51 Hz, 1 C) 155.92 (br s, 1 C) 175.33 (s, 1 C), C22 is missing, because of coupling to 19F and line broadening. 19F NMR (380 K, 471 MHz, DMSO-d6) δ -139.47 (br s, 1 F) -126.55 -124.30 (m, 1 F). [a]21 -14.9^{o} (c 0.52, CH_3OH). MS ESI (neg.) m/e: 521.2 (M-H). HRMS m/z calcd for $C_{32}H_{36}F_2O_4$ (M^+ + Na) 545.2479, found 545.2458.



2

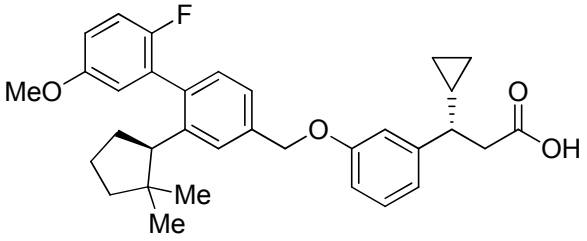
(3*S*)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1 H, dd, *J*=7.8, 1.8 Hz), 7.34 (1 H, d, *J*=7.8 Hz), 7.30 (1 H, m), 7.25 (1H, m), 6.93 - 7.02 (1 H, m), 6.84 - 6.91 (3 H, m), 6.78 - 6.81 (2 H, m), 5.53 (1 H, s), 5.10 (2 H, s), 3.76 (3 H, s), 2.73 - 2.86 (2 H, m), 2.33 - 2.42 (1 H, m), 2.25 (2 H, td, *J*=7.0, 2.4 Hz), 1.66 (2 H, t, *J*=7.0 Hz), 0.98 - 1.09 (1 H, m), 0.85 (6 H, m), 0.60 (1 H, tt, *J*=9.0, 4.5 Hz), 0.40 - 0.48 (1 H, m), 0.31 (1 H, dq, *J*=9.6, 4.8 Hz), 0.17 (1 H, dq, *J*=9.7, 5.0 Hz). Acidic proton not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.25, 157.95, 154.47, 152.55, 149.26, 148.84, 137.07, 136.52, 134.18, 130.54, 129.66, 129.56, 128.76, 128.66, 125.98, 120.22, 117.24, 115.80, 115.60, 114.38, 111.30, 68.57, 55.60, 47.71, 47.09, 45.30, 40.75, 29.39, 26.78, 17.99, 4.69, 3.98. ESI (neg.) m/e: 513.3 $(M-H)^+$. HRMS m/z calcd for $C_{33}H_{35}FO_4$ $(M^+ + H)$ 515.2597, found 515.2590. IR (cm^{-1}) 3406, 2954, 1582, 1485, 1406, 1207, 1038, 824, 776, 742, and 701.



4

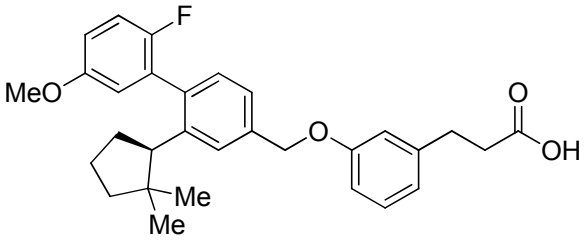
(3*S*)-3-Cyclopropyl-3-(3-(((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (4). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 - 7.40 (m, 1H), 7.37 - 7.30 (m, 1H), 7.27 - 7.18 (m, 2H), 7.10 - 6.97 (m, 1H), 6.91 - 6.82 (m, 4H), 6.78 -6.66 (m, 1H), 5.11 (s, 2H), 3.80 (s, 3H), 3.02 - 2.70 (m, 3H), 2.37 (td, *J*=7.4, 9.8 Hz, 1H), 2.21 - 2.09 (m, 1H), 2.05 - 1.94 (m, 1H), 1.87 - 1.73 (m, 1H), 1.73 - 1.58 (m, 1H), 1.56 - 1.47 (m, 1H), 1.42 - 1.32 (m, 1H), 1.09 - 0.95 (m, 1H), 0.74 - 0.66 (m, 3H), 0.64 - 0.54 (m, 4H), 0.50 - 0.38 (m, 1H), 0.30 (qd, *J*=4.9, 9.6 Hz, 1H), 0.21 - 0.12 (m, 1H). Acidic proton not observed.

MS ESI (neg.) m/e: 515.3 $(M-H)^+$. HRMS m/z calcd for $C_{33}H_{37}FO_4$ (M^+ + Na) 539.2574, found 539.2551.



5

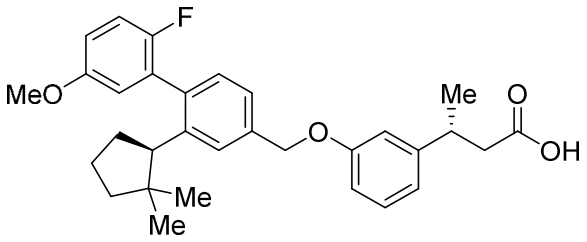
(3*R*)-3-Cyclopropyl-3-(3-(((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (5). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 - 7.40 (m, 1H), 7.36 - 7.29 (m, 1H), 7.27 - 7.18 (m, 2H), 7.09 - 6.97 (m, 1H), 6.91 - 6.81 (m, 4H), 6.78-6.68 (m, 1H), 5.10 (s, 2H), 3.80 (s, 3H), 3.01 - 2.73 (m, 3H), 2.41 - 2.31 (m, 1H), 2.21 - 2.09 (m, 1H), 2.08 - 1.94 (m, 1H), 1.86 - 1.73 (m, 1H), 1.73 - 1.58 (m, 1H), 1.52 (tdd, *J*=4.1, 8.3, 12.4 Hz, 1H), 1.42 - 1.30 (m, 1H), 1.03 (tt, *J*=4.9, 12.9 Hz, 1H), 0.73 - 0.66 (m, 3H), 0.63 - 0.54 (m, 4H), 0.49 - 0.38 (m, 1H), 0.30 (qd, *J*=4.8, 9.4 Hz, 1H), 0.17 (qd, *J*=4.9, 9.5 Hz, 1H). Acidic proton not observed. $C_{33}H_{37}FO_4$ Exact Mass 516.27, MS ESI (neg.) m/e: 515.2 $(M-H)^+$.



6

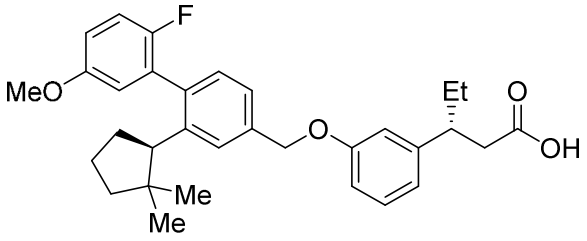
3-(3-(((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (6). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.48 - 7.40 (m, 1H), 7.33 (dt, *J*=1.6, 8.2 Hz, 1H), 7.26 - 7.19 (m, 2H), 7.10 - 6.98 (m, 1H), 6.9 - 6.67 (m, 5H), 5.14 - 5.07 (m, 2H), 3.80 (s, 3H), 2.96 (t, *J*=7.8 Hz, 2H), 2.84 (ddd, *J*=2.2, 8.2, 10.4 Hz, 1H), 2.74 - 2.64 (m, 2H), 2.22 - 2.10 (m, 1H), 2.09 - 1.96 (m, 1H), 1.79 (dtd, *J*=4.1, 8.4, 12.8 Hz, 1H), 1.73 - 1.59 (m, 1H), 1.53 (tdd, *J*=4.2, 8.3, 12.3 Hz, 1H), 1.42 - 1.32 (m, 1H), 0.73 - 0.67 (m, 3H), 0.65 -

0.55 (m, 3H). Acidic proton not observed. MS ESI (neg.) m/e: 475.3 $(M-H)^+$. HRMS m/z calcd for $C_{30}H_{33}FO_4$ (M^+ + Na) 499.2261, found 499.2244.



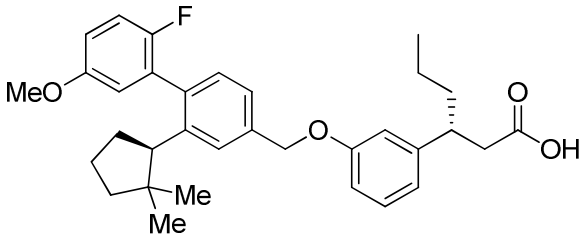
7

***(3R)*-3-(3-(((2-((1*R*)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (7)**. ^{1}H NMR (400 MHz, CD_3CN) δ 0.50 - 0.58 (m, 3 H) 0.63 - 0.72 (m, 3 H) 1.24 (dd, *J*=7.04, 1.57 Hz, 3 H) 1.47 - 1.57 (m, 1 H) 1.65 (ddd, *J*=12.52, 8.02, 4.89 Hz, 1 H) 1.73 - 1.87 (m, 1 H) 1.98 - 2.13 (m, 3 H) 2.48 - 2.63 (m, 2 H) 2.75 - 3.03 (m, 1 H) 3.10 - 3.23 (m, 1 H) 3.72 - 3.81 (m, 3 H) 5.11 - 5.17 (m, 2 H) 6.82 - 6.87 (m, 2 H) 6.82 - 6.87 (m, 1 H) 6.89 - 6.95 (m, 2 H) 7.03 - 7.15 (m, 1 H) 7.17 - 7.25 (m, 2 H) 7.28 - 7.37 (m, 1 H) 7.46 - 7.54 (m, 1 H), Acidic proton not observed. $C_{31}H_{35}FO_4$ Exact Mass 490.25, MS ESI (neg.) m/e: 489.2 $(M-H)^+$.



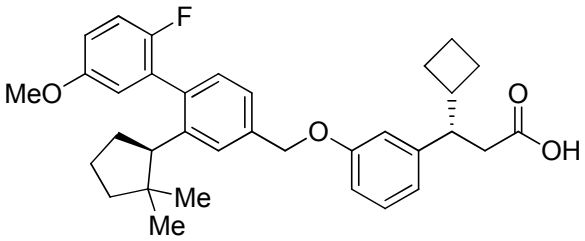
8

(*R*)-3-(3-((2-((*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)pentanoic acid (8). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.48 - 7.41 (m, 1H), 7.33 (dt, *J*=1.6, 8.6 Hz, 1H), 7.26 - 7.18 (m, 2H), 7.09 - 6.98 (m, 1H), 6.89 - 6.68 (m, 5H), 5.10 (s, 2H), 3.80 (s, 3H), 3.04 - 2.93 (m, 1H), 2.84 (ddd, *J*=2.2, 8.2, 10.4 Hz, 1H), 2.71 - 2.58 (m, 2H), 2.14 (ddd, *J*=3.9, 8.6, 12.9 Hz, 1H), 2.06 - 1.96 (m, 1H), 1.86 - 1.47 (m, 5H), 1.42 - 1.31 (m, 1H), 0.80 (t, *J*=7.4 Hz, 3H), 0.72 - 0.66 (m, 3H), 0.63 - 0.54 (m, 3H), Acidic proton not observed. $C_{32}H_{37}FO_4$ Exact Mass 504.27, MS ESI (neg.) m/e: 503.3 (M-H).



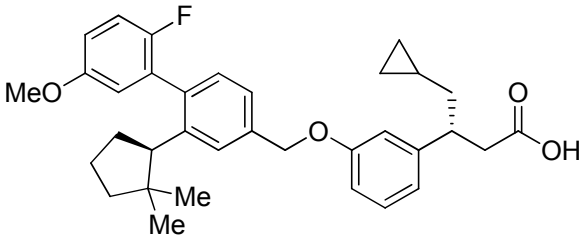
9

***(3R)*-3-(3-(((2(1*R*)-(2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (9)**. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 1H), 7.33 (dt, *J*=1.4, 8.5 Hz, 1H), 7.25 - 7.20 (m, 2H), 7.09 - 6.99 (m, 1H), 6.87 - 6.67 (m, 5H), 5.10 (s, 2H), 3.80 (s, 3H), 3.12 – 3.04 (m, 1H), 3.00 – 2.81 (m, 1H), 2.68 - 2.58 (m, 2H), 2.20 – 1.97 (m, 2H), 1.85 - 1.74 (m, 1H), 1.74 - 1.48 (m, 4H), 1.41 - 1.33 (m, 1H), 1.23 - 1.14 (m, 2H), 0.88 - 0.84 (m, 3H), 0.71 - 0.69 (m, 3H), 0.62 - 0.57 (m, 3H), Acidic proton not observed. $C_{33}H_{39}FO_4$ Exact Mass 518.28, MS ESI (neg.) m/e: 517.3 (M-H).



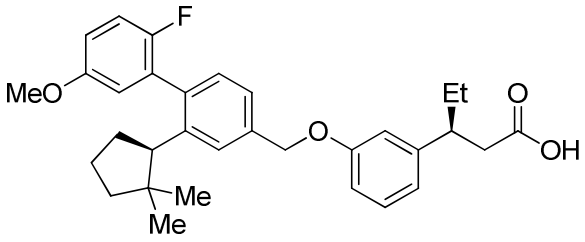
10

(*S*)-3-cyclobutyl-3-(3-((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)propanoic acid (10). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 - 7.39 (m, 1H), 7.32 (dt, *J*=1.6, 8.6 Hz, 1H), 7.26 - 7.17 (m, 2H), 7.09 - 6.98 (m, 1H), 6.88 - 6.82 (m, 2H), 6.82 - 6.75 (m, 2H), 6.68 (dd, *J*=3.1, 5.9 Hz, 1H), 5.09 (s, 2H), 3.80 (s, 3H), 3.06 - 2.94 (m, 1H), 2.84 (ddd, *J*=2.2, 8.2, 10.4 Hz, 1H), 2.67 - 2.58 (m, 1H), 2.54 - 2.43 (m, 2H), 2.21 - 1.95 (m, 3H), 1.86 - 1.46 (m, 8H), 1.42 - 1.32 (m, 1H), 0.75 - 0.67 (m, 3H), 0.65 - 0.54 (m, 3H), Acidic proton not observed. HRMS m/z calcd for $C_{34}H_{39}FO_4$ (M^+ + Na) 553.2730, found 553.2716.



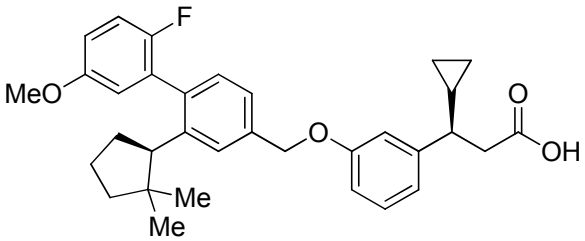
11

(3*R*)-4-Cyclopropyl-3-(3-(((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (11). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 - 7.40 (m, 1H), 7.36 - 7.29 (m, 1H), 7.26 - 7.18 (m, 2H), 7.09 - 6.97 (m, 1H), 6.89 - 6.82 (m, 4H), 6.78-6.68 (m, 1H), 5.11 (s, 2H), 3.80 (s, 3H), 3.27 - 3.16 (m, 1H), 3.01 - 2.81 (m, 1H), 2.79 - 2.70 (m, 1H), 2.70 - 2.60 (m, 1H), 2.21 - 2.09 (m, 1H), 2.05 - 1.95 (m, 1H), 1.85 - 1.59 (m, 3H), 1.57 - 1.46 (m, 1H), 1.43 - 1.30 (m, 2H), 0.73 - 0.65 (m, 3H), 0.64 - 0.47 (m, 4H), 0.45 - 0.28 (m, 2H), 0.10 - 0.01 (m, 1H), 0.01 - -0.07 (m, 1H). Acidic proton not observed. MS ESI (neg.) m/e: 529.3 $(M-H)^+$. HRMS m/z calcd for $C_{34}H_{39}FO_4$ (M^+ + Na) 553.2730, found 553.2703.



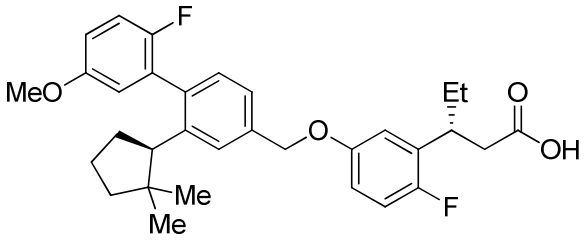
12

(3*S*)-3-(3-(((2-((1*R*)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (12). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 1H), 7.35 - 7.31 (m, 1H), 7.25 - 7.19 (m, 2H), 7.08 - 6.99 (m, 1H), 6.88 - 6.67 (m, 5H), 5.10 (s, 2H), 3.80 (s, 3H), 3.00 - 2.81 (m, 1H), 2.70 – 2.59 (dd, *J*=7.43, 4.7 Hz, 2H), 2.20 - 1.98 (m, 2H), 1.83 - 1.33 (m, 7H), 0.80 (t, *J*=7.24 Hz, 3H), 0.72 - 0.64 (m, 3H), 0.64 - 0.52 (m, 3H), Acidic proton not observed. MS ESI (neg.) m/e: 503.2 $(M-H)^+$. HRMS m/z calcd for $C_{32}H_{37}FO_4$ (M^+ + Na) 527.2574, found 527.2558.



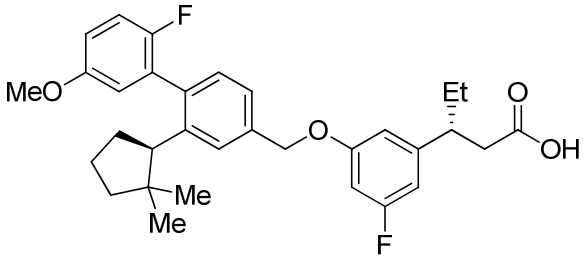
13

(3*R*)-3-cyclopropyl-3-(3-(((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (13). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 - 7.41 (m, 1H), 7.33 (t, *J*=8.2 Hz, 1H), 7.27 - 7.18 (m, 2H), 7.09 - 6.98 (m, 1H), 6.91 - 6.82 (m, 4H), 6.78 - 6.68 (m, 1H), 5.11 (s, 2H), 3.80 (s, 3H), 3.02 - 2.72 (m, 3H), 2.42 - 2.33 (m, 1H), 2.15 (ddt, *J*=4.1, 8.9, 13.1 Hz, 1H), 2.08 - 1.96 (m, 1H), 1.87 - 1.73 (m, 1H), 1.72 - 1.58 (m, 1H), 1.57 - 1.47 (m, 1H), 1.42 - 1.32 (m, 1H), 1.08 - 0.97 (m, 1H), 0.74 - 0.66 (m, 3H), 0.65 - 0.53 (m, 4H), 0.49 - 0.38 (m, 1H), 0.30 (qd, *J*=4.9, 9.6 Hz, 1H), 0.16 (qd, *J*=4.9, 9.5 Hz, 1H). Acidic proton not observed. MS ESI (neg.) m/e: 515.2 $(M-H)^+$. HRMS m/z calcd for $C_{33}H_{37}FO_4$ (M^+ + Na) 539.2574, found 539.2554.



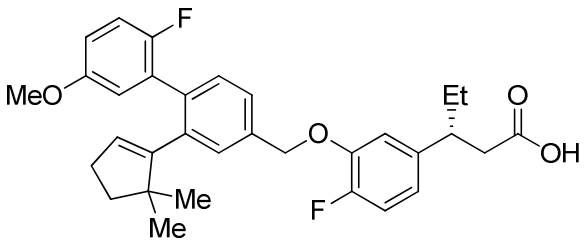
15

(3*R*)-3-(5-(((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (15). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44 - 7.40 (m, 1H), 7.33 - 7.29 (m, 1H), 7.25 - 7.19 (m, 1H), 7.08 - 6.92 (m, 2H), 6.86 – 6.66 (m, 4H), 5.06 (m, 2H), 3.80 (s, 3H), 3.33 – 3.26 (m, 1H), 3.00 – 2.81 (m, 1H), 2.70 - 2.68 (m, 2H), 2.20 - 2.11 (m, 1H), 2.06 - 1.96 (m, 1H), 1.83 - 1.60 (m, 4H), 1.55- 1.33 (m, 2H), 0.77 (t, *J*=7.2 Hz, 3H), 0.69 - 0.62 (m, 3H), 0.61 - 0.51 (m, 3H), Acidic proton not observed. HRMS m/z calcd for $C_{32}H_{36}F_2O_4$ (M^+ + Na) 545.2479, found 545.2453.



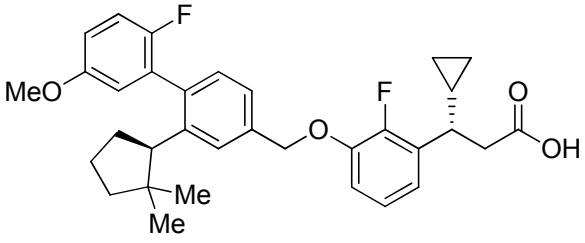
16

(3*R*)-3-(5-(((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid (16). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 - 7.38 (m, 1H), 7.31 (dt, *J*=1.4, 8.1 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.10 - 6.98 (m, 1H), 6.89 - 6.82 (m, 1H), 6.79 – 6.67 (m, 1H), 6.63 (s, 1H), 6.61 - 6.56 (m, 1H), 6.53 (d, *J*=9.4 Hz, 1H), 5.08 (s, 2H), 3.80 (s, 3H), 3.03 - 2.92 (m, 1H), 2.84 (ddd, *J*=2.2, 8.2, 10.4 Hz, 1H), 2.70 - 2.54 (m, 2H), 2.21 - 2.11 (m, 1H), 2.06 - 1.95 (m, 1H), 1.87 - 1.46 (m, 5H), 1.43 - 1.32 (m, 1H), 0.81 (t, *J*=7.4 Hz, 3H), 0.74 - 0.66 (m, 3H), 0.64 - 0.54 (m, 3H). Acidic proton not observed. HRMS m/z calcd for $C_{32}H_{36}F_2O_4$ (M^+ + Na) 545.2479, found 545.2454.



17

(3*R*)-3-(3-((2-((1*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-4-fluorophenyl)pentanoic acid (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (t, *J*=7.34 Hz, 3 H) 0.85 (m, 6 H) 1.53 (ddd, *J*=13.69, 9.39, 7.24 Hz, 1 H) 1.63 - 1.75 (m, 3 H) 2.25 (td, *J*=7.04, 2.35 Hz, 2 H) 2.50 - 2.68 (m, 2 H) 2.88 - 2.98 (m, 1 H) 3.76 (s, 3 H) 5.18 (s, 2 H) 5.50 - 5.54 (m, 1 H) 6.73 (ddd, *J*=8.31, 4.21, 2.15 Hz, 1 H) 6.77 - 6.87 (m, 3 H) 6.93 - 7.06 (m, 2 H) 7.30 - 7.35 (m, 2 H) 7.37 - 7.43 (m, 1 H). Acidic proton not observed. $C_{32}H_{34}F_2O_4$ Exact Mass 520.24, MS ESI (neg.) m/e: 519.2 (M-H).



18

(*S*)-3-cyclopropyl-3-(3-((2-((*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2-fluorophenyl)propanoic acid (18). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.49 - 7.42 (m, 1H), 7.37 - 7.29 (m, 1H), 7.25 - 7.18 (m, 1H), 7.09 - 6.96 (m, 2H), 6.96 - 6.89 (m, 1H), 6.88 - 6.82 (m, 2H), 6.78 - 6.67 (m, 1H), 5.17 (s, 2H), 3.80 (s, 3H), 2.97 - 2.80 (m, 3H),

2.68 (td, *J*=7.4, 9.8 Hz, 1H), 2.21 - 2.10 (m, 1H), 2.05 - 1.96 (m, 1H), 1.86 - 1.74 (m, 1H), 1.73 - 1.59 (m, 1H), 1.52 (tdd, *J*=4.0, 8.4, 12.3 Hz, 1H), 1.42 - 1.32 (m, 1H), 1.21 - 1.08 (m, 1H), 0.72 - 0.64 (m, 3H), 0.63 - 0.54 (m, 4H), 0.46 - 0.38 (m, 1H), 0.33 (qd, *J*=4.8, 9.4 Hz, 1H), 0.20 (qd, *J*=4.8, 9.6 Hz, 1H). Acidic proton not observed. Mass spectrum (pos.) m/z 557.2 $(M+Na)^+$, 552.3 $(M+H_2O)^+$, 535.3 $(M+H)^+$. HRMS m/z calcd for $C_{33}H_{36}F_2O_4$ (M^+ + Na) 557.2479, found 557.2456.