Supporting Information

Discovery of AMG 853, A CRTH2 and DP Dual Antagonist

Jiwen Liu, An-Rong Li, Yingcai Wang, Mike G. Johnson, Yongli Su, Wang Shen, Xuemei Wang, Sarah Lively, Matthew Brown, SuJen Lai, Felix Gonzalez Lopez De Turiso, Qingge Xu, Bettina Van Lengerich, Mike Schmitt, Zice Fu, Ying Sun, Shanna Lawlis, Lisa Seitz, Jay Danao, Jill Wait, Qiuping Ye, Hua Lucy Tang, Mark Grillo, Tassie L. Collins, Timothy J. Sullivan and Julio C. Medina*

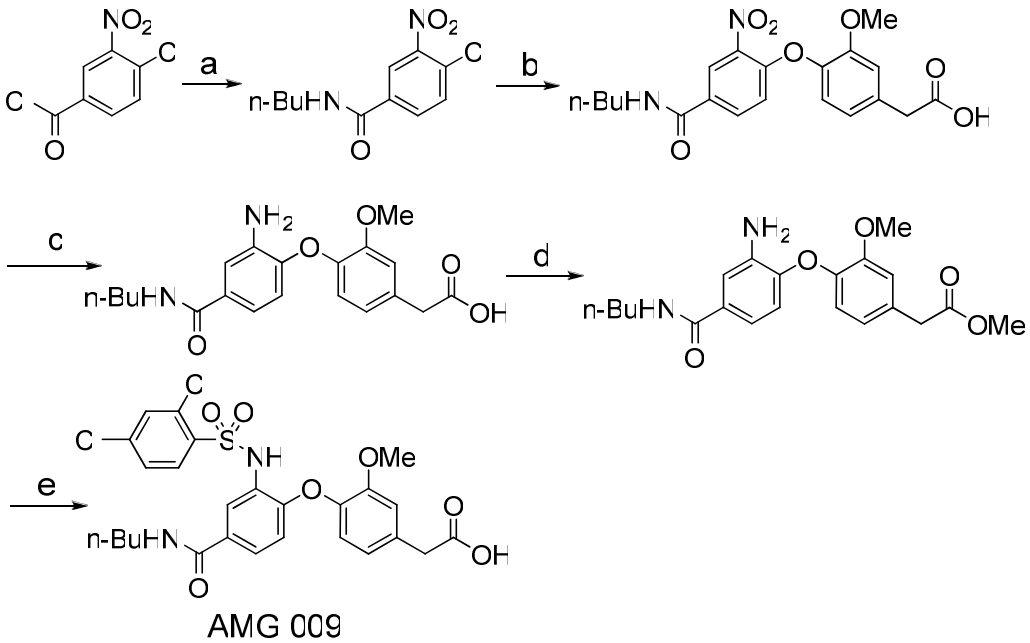
Amgen Inc., 1120 Veterans Blvd., South San Francisco, CA 94080.

*To whom correspondence should be addressed. Phone: 1-650-244-2425. E-mail: medinaj@amgen.com

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Dry organic solvents (DriSolv) were purchased from EMD Chemicals and packaged under nitrogen in Sure Seal bottles. Reactions were monitered using thin-layer chromatography on 250 μm plates or using Agilent 1100 series LCMS with UV detection at 254 nm and a low resonance electrospray mode (ESI). Purification of title compounds was accomplished by flash column chromatography using silica gel 60 (particle size 0.04-0.063 mm, 230-400 mesh) or medium pressure liquid chromatography on a CombiFlash Companion (Teledyne Isco) with RediSep normal phase silica gel. ^{1}H NMR spectra were recorded on a Bruker spectrometer (400 or 500 MHz) at ambient temperature. Chemical shifts are reported in ppm relative to $CDCl_3$ or DMSO and coupling constants (J) are reported in hertz (Hz). Purity of final compounds was ≥95% based on analytical HPLC and NMR analysis.

The synthetic procedure of AMG 009 is provided below. All other compounds (**1-23**, AMG 853) were prepared in the same way as AMG 009. Alternative synthesis of AMG 853 can be found in US2009/0275659A1.



N-butyl-4-chloro-3-nitrobenzamide Step a: To a solution of 4-chloro-3-nitrobenzoyl chloride (440g, 2mol), in THF (1L) at 0°C, was added slowly a mixture of n-butylamine (198mL, 2mol) and

triethylamine (279mL, 2mol) over 4 hours. During addition the temperature of the reaction mixture was kept below 5°C. After addition, the mixture was stirred at 0°C for 12 hours. The reaction mixture was treated with EtOAc (1L) and water (1L). The aqueous layer was separated, and the organic layer was washed with brine (2N HCl was added to adjust PH to 2) twice and water once. The organic layer was then treated with hexane (2.5L). After stirring, the solid generated was collected by filtration to give 400g of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (t, J = 5.1, 1H), 8.51 (d, J = 2.1, 1H), 8.15 (dd, J = 8.4, 2.1, 1H), 7.91 (d, J = 8.4, 1H), 3.26-3.32 (m, 2H), 1.49-1.57 (m, 2H), 1.30-1.38 (m, 2H), 0.92 (t, J = 7.3, 3H). MS (ESI) $[M+H]^+$: 257.

2-(4-(4-(Butylcarbamoyl)-2-nitrophenoxy)-3-methoxyphenyl)acetic acid Step b: To a mixture of N-butyl-4-chloro-3-nitrobenzamide (339g, 1.32mol) and homovanilic acid (244g, 1.34mol) in DMSO (1L), was added cesium carbonate (947g, 2.9mol). The mixture was then heated to 65°C. After 1 hour of heating, 100g of cesium carbonate and 200mL of DMSO were added. Two hours later, another 100g of cesium carbonate and 200mL of DMSO were added. Heating and stirring were continued for 6 more hours. After cooling, EtOAc (3L) and water (2L) were added, and the mixture was acidified with concentrated HCl to PH2. During the acidification, the temperature was kept below 30°C. The aqueous was separated, and the organic layer was heated to 50°C and washed with brine (2N HCl was added to adjust PH to 2) twice and water once. The organic layer was cooled to 0°C, and the crystal formed was collected and washed with 50% EtOAc/hexane. The mother liquor was concentrated, and the residue was recrystalized in hot EtOAc to give a second batch of the product. Yield 480g. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.64 (t, J = 5.6, 1H), 8.50 (d, J = 2.2, 1H), 8.04 (dd, J = 8.8, 2.2, 1H), 7.19 (d, J = 8.1, 1H), 7.16 (d, J = 1.9, 1H), 6.96 (dd, J = 8.2, 1.9, 1H), 6.86 (d, J = 8.8, 1H), 3.73 (s, 3H), 3.65 (s, 2H), 3.24-3.30 (m, 2H), 1.50-1.54 (m, 2H), 1.30-1.37 (m, 2H), 0.91 (t, J = 7.3, 3H). MS (ESI) $[M+H]^+$: 403.

2-(4-(2-Amino-4-(butylcarbamoyl)phenoxy)-3-methoxyphenyl)acetic acid Step c: Pd/C (15g, 10% wet) was added to 2-(4-(4-(butylcarbamoyl)-2-nitrophenoxy)-3-methoxyphenyl)acetic acid (402g, 1mol) in 1N NaOH (1L, 1mol) and water (0.2L). Air was removed and the mixture was shacked under hydrogen (40psi) for 3 hours at r.t.. The catalyst was removed by filtration through celite, and the celite was washed with water (1L). While stirred vigorously, the filtrate was neutralized by slow addition of 2N HCl (0.5L). The fine powder generated was collected by filtration, washed and dried to give 365g of the desired product.

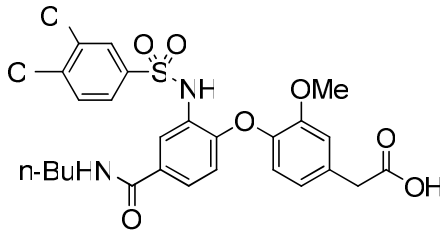
Alternative method: To a solution of 2-(4-(4-(butylcarbamoyl)-2-nitrophenoxy)-3-methoxyphenyl)acetic acid (1.06 g, 2.64 mmol, 1.0 equiv.) in 20 mL of EtOAc was added $SnCl_2$•$2H_2O$ (1.91 g, 8.4 mmol, 3.2 equiv.). The mixture was heated to 60°C for 4 h. After cooling to room temperature, the mixture was poured into 50 mL of water. Saturated $NaHCO_3$ was added to adjust the pH value of the mixture to 5. The mixture was filtered through Celite to remove solid precipitates. The filtrate was extracted with EtOAc. The EtOAc extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give 0.64 g of a light tan solid. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.40 (s, 1H), 8.13 (t, J = 5.6, 1H), 7.24 (d, J = 2.1, 1H), 7.07 (d, J = 1.7, 1H), 6.93 (dd, J = 8.3, 2.1, 1H), 6.87 (d, J = 8.1, 1H), 6.84 (dd, J = 8.1, 1.7, 1H), 6.43 (d, J = 8.3, 1H), 5.10 (s, 2H), 3.77 (s, 3H), 3.58 (s, 2H), 3.18-3.24 (m, 2H), 1.46-1.50 (m, 2H), 1.29-1.35 (m, 2H), 0.90 (t, J = 7.3, 3H). MS (ESI) $[M+H]^+$: 373.

Methyl 2-(4-(4-(butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl) acetate Step d: Concentrated sulfuric acid (22.4mL) was added dropwise to a stirred solution of 2-(4-(2-amino-4-(butylcarbamoyl)phenoxy)-3-methoxyphenyl)acetic acid (150g) in methanol (800mL) at r.t.. The mixture was then heated to 60°C for 5 hours. Most of the methanol was removed under vacuum, and the residue was taken by EtOAc (800mL) and neutralized by saturated sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted with EtOAc (400mL). The combined organic layers were dried with $MgSO_4$ and concentrated to give the desired product. Yield: quantitative. ^{1}H NMR (400 MHz, DMSO- d_6) δ 8.14 (t, J = 5.6, 1H), 7.24 (d, J = 2.1, 1H), 7.08 (d, J = 1.6, 1H),

6.93 (dd, *J* = 8.3, 2.1, 1H), 6.87 (d, *J* = 8.1, 1H), 6.84 (dd, *J* = 8.1, 1.6, 1H), 6.45 (d, *J* = 8.3, 1H), 5.05 (s, 2H), 3.77 (s, 3H), 3.70 (s, 2H), 3.65 (s, 3H), 3.18-3.24 (m, 2H), 1.46-1.50 (m, 2H), 1.29-1.35 (m, 2H), 0.90 (t, *J* = 7.3, 3H). MS (ESI) $[M+H]^+$: 387.

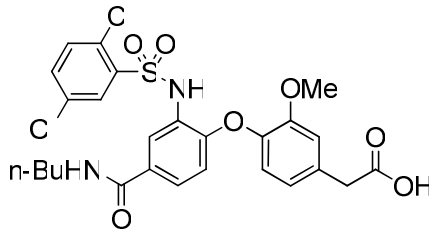
2-(4-(4-(Butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (AMG 009) Step e: 2,4-Dichlorophenyl sulfonyl chloride (112g, 455mmol) was added to a mixture of methyl 2-(4-(4-(butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl) acetate (135g, 350mmol) and 2,6-lutidine (57mL, 490mmol) in THF (500mL) at r.t.. The mixture was then heated and stirred at 60°C for 12h. After cooling to r.t., water (300mL) and 10N NaOH (180mL) were added. The mixture was stirred at r.t. for 2 hours, acidified to PH2 with concentrated HCl, and extracted with EtOAc (1L). The organic layer was washed with brine (2N HCl was added to adjust PH to 2) three times, dried with $MgSO_4$, and concentrated. The crude product was treated with DCM (300mL), stirred, and collected by filtration. Then the crude product was recrystalized in hot EtOH(95%) (400mL) to give 120g desired product. The mother liquor was concentrated, and the residue was recrystalized again in hot EtOH to give additional 30g of the product. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.37 (s, 1H); 10.19 (s, 1H); 8.38 (t, *J* = 5.5 Hz, 1H); 7.87 (d, *J* = 2.0 Hz, 1H); 7.84 (d, *J* = 8.5 Hz, 1H); 7.74 (d, *J* = 1.9 Hz, 1H); 7.58 (dd, *J* = 8.6, 2.1 Hz, 1H); 7.49 (dd, *J* = 8.6, 2.1 Hz, 1H); 7.04 (d, *J* = 1.6 Hz, 1H); 6.81 (dd, *J* = 8.2, 1.5 Hz, 1H); 6.55 (d, *J* = 8.1 Hz, 1H); 6.41 (d, *J* = 8.6 Hz, 1H); 3.62 (s, 3H); 3.59 (s, 2H); 3.23 (q, *J* = 6.4 Hz, 2H); 1.49 (tt, *J* = 7.3, 7.3 Hz, 2H); 1.31 (tq, *J* = 7.3, 7.3 Hz, 2H); 0.90 (t, *J* = 7.3, 3H). MS (ESI) $[M+H]^+$: 581. Anal. Calcd. for $C_{26}H_{26}Cl_2N_2O_7S$: C, 53.71; H, 4.51; N, 4.82. Found: C, 55.46; H, 4.49; N, 4.75.

2-(4-(4-(butylcarbamoyl)-2-(3,4-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (1)



^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3(bs, 1H), 10.3(bs, 1H), 8.38(t, *J* = 5.7 Hz, 1H), 7.95(d, *J* = 2 Hz, 1H), 7.88(d, *J* = 2.1 Hz, 1H), 7.80(d, *J* = 8.4 Hz, 1H), 7.69(dd, *J* = 8.4, 2.2 Hz, 1H), 7.58(dd, *J* = 8.6, 2.2 Hz, 1H), 7.05(d, *J* = 1.8 Hz, 1H), 6.83(dd, *J* = 8.2, 2 Hz, 1H), 6.50(d, *J* = 8 Hz, 1H), 6.41(d, *J* = 8.7 Hz, 1H), 3.62(s, 3H), 3.59(s, 2H), 3.23(q, *J* = 7.0 Hz, 2H), 1.49(m, 2H), 1.31(m, 2H), 0.91(t, J = 7.4 Hz, 3H). MS (ESI) $[M+H]^+$: 581.

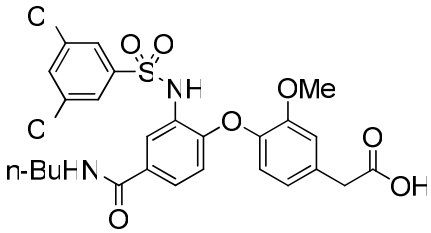
2-(4-(4-(butylcarbamoyl)-2-(2,5-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (2)



^{1}H NMR (400 MHz, DMSO-d_6) δ 12.4(bs, 1H), 10.3(bs, 1H), 8.38(t, *J* = 5.7 Hz, 1H), 7.86(d, *J* = 2.2 Hz, 1H), 7.82(d, *J* = 2.4 Hz, 1H), 7.60(m, 3H), 7.03(d, *J* = 2 Hz, 1H), 6.82(dd, *J* = 8.2, 2 Hz, 1H),

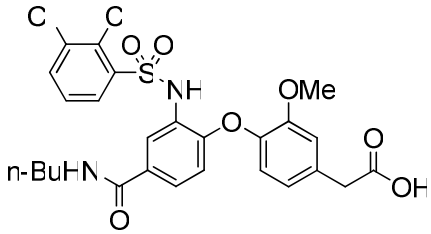
6.61(d, *J* = 8 Hz, 1H), 6.44(d, *J* = 8.6 Hz, 1H), 3.61(s, 3H), 3.58(s, 2H), 3.23(q, *J* = 7.0 Hz, 2H), 1.49(m, 2H), 1.31(m, 2H), 0.91(t, *J* = 7.4 Hz, 3H). MS (ESI) $[M+H]^+$: 581.

2-(4-(4-(butylcarbamoyl)-2-(3,5-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (3)



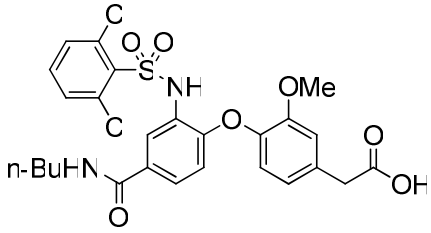
^{1}H NMR (400 MHz, DMSO- d_6) δ 12.4(bs, 1H), 10.4(bs, 1H), 8.39(t, J = 5.7 Hz, 1H), 7.90(d, J = 2 Hz, 1H), 7.87(d, J = 2.1 Hz, 1H), 7.73(d, J = 2 Hz, 2H), 7.60(dd, J = 8.6, 2.1 Hz, 1H), 7.06(d, J = 1.7 Hz, 1H), 6.84(dd, J = 8.2, 2 Hz, 1H), 6.57(d, J = 8.1 Hz, 1H), 6.44(d, J = 8.6 Hz, 1H), 3.61(s, 3H), 3.58(s, 2H), 3.23(q, J = 7.0 Hz, 2H), 1.49(m, 2H), 1.31(m, 2H), 0.91(t, J = 7.4 Hz, 3H). MS (ESI) $[M+H]^+$: 581.

2-(4-(4-(butylcarbamoyl)-2-(2,3-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (4)



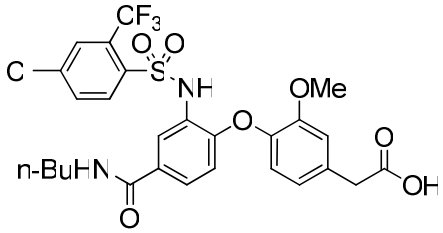
^{1}H NMR (400 MHz, DMSO- d_6) δ 12.4(bs, 1H), 10.3(bs, 1H), 8.38(t, J = 5.7 Hz, 1H), 7.85(m, 3H), 7.58(dd, J = 8.6, 2.1 Hz, 1H), 7.41(t, J = 8 Hz, 1H), 7.03(d, J = 1.8 Hz, 1H), 6.80(dd, J = 8, 2 Hz, 1H), 6.50(d, J = 8 Hz, 1H), 6.40(d, J = 8.6 Hz, 1H), 3.61(s, 3H), 3.58(s, 2H), 3.23(q, J = 7.0 Hz, 2H), 1.49(m, 2H), 1.31(m, 2H), 0.91(t, J = 7.4 Hz, 3H). MS (ESI) $[M+H]^+$: 581.

2-(4-(4-(butylcarbamoyl)-2-(2,6-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (5)



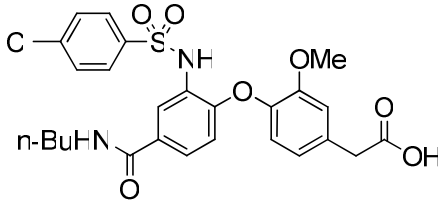
^{1}H NMR (400 MHz, DMSO- d_6) δ 12.4(bs, 1H), 10.2(bs, 1H), 8.37(t, J = 5.7 Hz, 1H), 7.88(d, J = 2.2 Hz, 1H), 7.59(dd, J = 8.8, 2.4 Hz, 1H), 7.52(m, 2H), 7.45(dd, J = 9.3, 6.9 Hz, 1H), 7.00(d, J = 1.7 Hz, 1H), 6.80(dd, J = 8.0, 1.7 Hz, 1H), 6.56(d, J = 8 Hz, 1H), 6.43(d, J = 8.6 Hz, 1H), 3.61(s, 3H), 3.58(s, 2H), 3.23(q, J = 7.0 Hz, 2H), 1.49(m, 2H), 1.31(m, 2H), 0.91(t, J = 7.4 Hz, 3H). MS (ESI) $[M+H]^+$: 581.

2-(4-(4-(butylcarbamoyl)-2-(4-chloro-2-(trifluoromethyl)phenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (6)



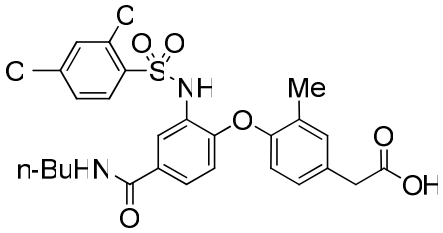
^{1}H NMR (400 MHz, DMSO- d_6) δ 12.4(bs, 1H), 10.4(bs, 1H), 8.39(t, J = 5.7 Hz, 1H), 8.06(d, J = 8 Hz, 1H), 7.99(s, 1H), 7.88(d, J = 2.1 Hz, 1H), 7.79(d, J = 8.2 Hz, 1H), 7.60(d, J = 8.8 Hz, 1H), 7.00(d, J = 2 Hz, 1H), 6.77(dd, J = 8.2, 2 Hz, 1H), 6.45(d, J = 8 Hz, 1H), 6.40(d, J = 8.6 Hz, 1H), 3.61(s, 3H), 3.58(s, 2H), 3.23(q, J = 7.0 Hz, 2H), 1.49(m, 2H), 1.31(m, 2H), 0.91(t, J = 7.4 Hz, 3H). MS (ESI) $[M+H]^+$: 615.

2-(4-(4-(butylcarbamoyl)-2-(4-chlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (7)



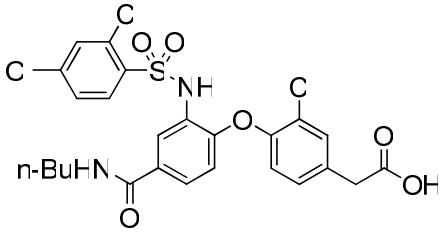
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 4.0Hz, 1H), 7.71 (dd, J = 8.0, 4.0Hz, 2H), 7.55 (dd, J = 8.0, 4.0Hz, 1H), 7.36-7.40 (m, 3H), 6.91 (d, J = 4.)Hz, 1H), 6.83 (dd, J = 8, 4.0Hz, 1H), 6.58 (dd, J = 8.0, 4.0Hz, 2H), 6.18 (br dd, J=8.0, 4.0Hz, 1H), 3.71 (s, 3H), 3.68 (s, 2H), 3.47 (m, 2H), 1.64 (m, 2H), 1.44 (m, 2H), 1.0 (dd, J = 8, 8Hz, 3H). MS (ESI) $[M+H]^+$: 547.

2-(4-(4-(butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-methylphenyl)acetic acid (8)



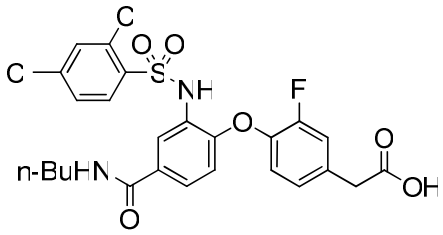
^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3(bs, 1H), 10.3(bs, 1H), 8.41(t, J = 5.7 Hz, 1H), 7.90(d, J = 2.1 Hz, 1H), 7.83(d, J = 8.6 Hz, 1H), 7.69(d, J = 2.1 Hz, 1H), 7.63(dd, J = 8.6, 2.1 Hz, 1H), 7.49(dd, J = 8.6, 2.1 Hz, 1H), 7.17(d, J = 1.7 Hz, 1H), 7.02(dd, J = 8.2, 1.8 Hz, 1H), 6.48(d, J = 8.6 Hz, 1H), 6.37(d, J = 8.2 Hz, 1H), 3.54(s, 2H), 3.23(q, J = 7.0 Hz, 2H), 1.96(s, 3H), 1.49(m, 2H), 1.33(m, 2H), 0.91(t, J = 7.4 Hz, 3H). MS (ESI) $[M+H]^+$: 565.

2-(4-(4-(butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-chlorophenyl)acetic acid (9)



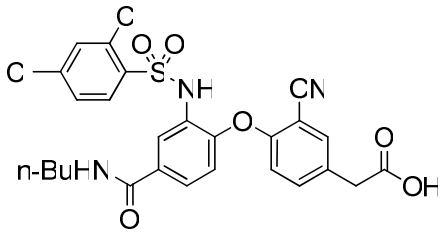
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1 H), 10.38 (s, 1 H), 8.44 (t, *J*=5.97 Hz, 1 H), 7.90 (d, *J*=1.96 Hz, 1 H), 7.80 (d, *J*=8.41 Hz, 1 H), 7.70 (d, *J*=1.96 Hz, 1 H), 7.64 (d, *J*=8.41 Hz, 1 H), 7.36 - 7.49 (m, 2 H), 7.16 (dd, *J*=8.41, 1.96 Hz, 1 H), 6.64 (d, *J*=8.41 Hz, 1 H), 6.57 (d, *J*=8.61 Hz, 1 H), 3.61 (s, 2 H), 3.59(s, 2H), 3.23 (q, *J*=6.78 Hz, 2 H), 1.40 - 1.57 (m, 2 H), 1.22 - 1.40 (m, 2 H), 0.90 (t, *J*=7.34 Hz, 3 H). MS (ESI) $[M+H]^+$: 585.

2-(4-(4-(butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-fluorophenyl)acetic acid (10)



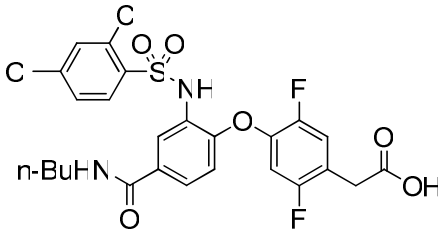
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (1 H, d, *J*=8.4 Hz), 7.91 (1 H, d, *J*=2.2 Hz), 7.69 (1 H, s), 7.51 (1 H, dd, *J*=8.6, 2.2 Hz), 7.39 (1 H, d, *J*=2.2 Hz), 7.32 (1 H, dd, *J*=8.5, 2.1 Hz), 7.17 (1 H, dd, *J*=11.1, 2.1 Hz), 7.03 (1 H, d, *J*=8.2 Hz), 6.77 (1 H, t, *J*=8.3 Hz), 6.65 (1 H, d, *J*=8.6 Hz), 6.07 (1 H, t, *J*=5.5 Hz), 3.68 (2 H, s), 3.39 - 3.49 (2 H, m), 1.55 - 1.67 (2 H, m), 1.42 (2 H, dq, *J*=15.0, 7.4 Hz), 0.98 (3 H, t, *J*=7.3 Hz). MS (ESI) $[M+H]^+$: 569.

2-(4-(4-(butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-cyanophenyl)acetic acid (11)



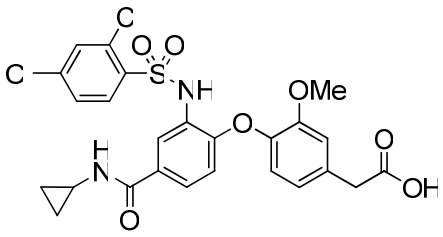
^{1}H NMR (400 MHz, Me-d_3-OD) δ 7.98 (d, J = 2.2 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.56 (m, 2H), 7.23 (m, 3H), 6.83 (d, J = 8.5 Hz, 1H), 6.28 (d, J = 8.5 Hz, 1H), 3.58 (s, 2H), 3.28 (t, J = 7.1 Hz, 2H), 1.51 (m, 2H), 1.31 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H) ppm. MS (ESI) $[M+H]^+$: 576.

2-(4-(4-(butylcarbamoyl)-2-(3,4-dichlorophenylsulfonamido)phenoxy)-2,5-difluorophenyl)acetic acid (12)



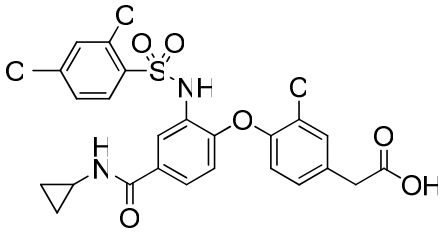
^{1}H NMR (400 MHz, Me-d_3-OD) δ 8.05 (d, *J* = 2.08Hz, 1H); 7.89 (d, *J* =8.53Hz, 1H); 7.61 (dd, *J* = 2.08, 8.60Hz, 1H); 7.48 (d, *J* = 1.93Hz, 1H); 7.37 (dd, *J* = 1.93, 8.53Hz, 1H); 7.24 (dd, *J* = 6.78, 10.81Hz, 1H); 6.80 (d, *J* = 8.60Hz, 1H); 6.46 (dd, *J* = 6.78, 10.81Hz, 1H); 3.68 (s, 2H); 3.37 (t, *J* = 7.1Hz, 2H); 1.58-1.65 (m, 2H); 1.38-1.47 (m, 2H); 0.99 (t, *J* = 14.6 Hz, 3H). MS (ESI) $[M+H]^+$: 587.

2-(4-(4-(cyclopropylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-methoxyphenyl)acetic acid (13)



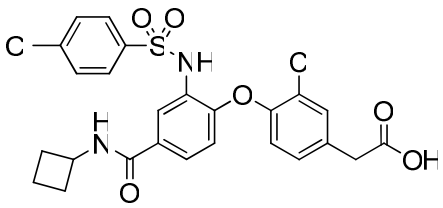
^{1}H NMR (400 MHz, acetone-d_6) δ 8.8 (br s, 1H), 8.02 (dd, J = 2.12, 1.71Hz, 1H), 7.94 (dd, H = 8.2, 1.80Hz, 1H), 7.29 (br s, 1H), 7.61 (dd, J = 3.89, 2.05Hz, 1H), 7.53(dd, J=8.60, 2.15Hz, 1H), 7.49 (ddd, J=8.52, 2.07, 1.86Hz, 1H), 7.09 (d, J=1.87Hz, 1H), 6.88 (dd, J=8.12, 1.94Hz, 1H), 6.74 (dd, J=8.10, 1.69Hz, 1H), 6.47 (dd, J=8.6, 1.72Hz, 1H), 3.67 (s, 3H), 3.65 (s,2H), 2.04 (m, 1H), 0.71 (m, 2H), 0.58 (m, 2H). MS (ESI) $[M+H]^+$: 565.

2-(4-(4-(cyclopropylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-chlorophenyl)acetic acid (14)



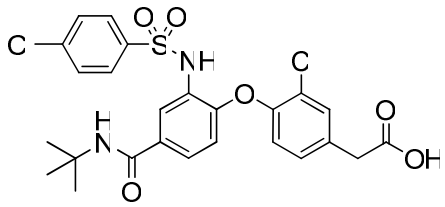
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1 H, d, *J*=8.5 Hz), 7.91 (1 H, s), 7.70 (1 H, s), 7.45 - 7.49 (1 H, m), 7.44 (1 H, s), 7.39 (1 H, d, *J*=1.8 Hz), 7.34 (1 H, dd, *J*=8.4, 2.0 Hz), 7.16 (1 H, d, *J*=10.4 Hz), 6.69 (1 H, d, *J*=8.2 Hz), 6.57 (1 H, d, *J*=8.2 Hz), 6.36 (1 H, br. s.), 3.70 (2 H, s), 2.90 (1 H, br. s.), 0.91 (2 H, d, *J*=5.8 Hz), 0.67 (2 H, br. s.). MS (ESI) $[M+H]^+$: 569.

2-(3-chloro-4-(2-(4-chlorophenylsulfonamido)-4-(cyclobutylcarbamoyl)phenoxy)phenyl)acetic acid (15)



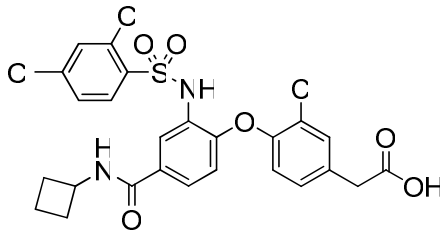
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (1 H, d, *J*=2.0 Hz), 7.69 (2 H, d, *J*=8.6 Hz), 7.55 (1 H, dd, *J*=8.6, 2.0 Hz), 7.38 (1 H, d, *J*=2.0 Hz), 7.36 (2 H, d, *J*=8.6 Hz), 7.22 (1 H, s), 7.13 (1 H, dd, *J*=8.3, 1.7 Hz), 6.54 (2 H, t, *J*=8.3 Hz), 6.41 (1 H, d, *J*=7.3 Hz), 4.57 (1 H, dt, *J*=16.0, 8.1 Hz), 3.66 (2 H, s), 2.38 - 2.50 (2 H, m), 1.95 - 2.08 (2 H, m), 1.76 - 1.87 (2 H, m). MS (ESI) $[M+H]^+$: 549.

2-(4-(4-(tert-butylcarbamoyl)-2-(4-chlorophenylsulfonamido)phenoxy)-3-chlorophenyl)acetic acid (16)



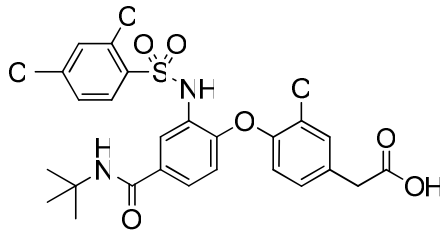
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (1 H, d, *J*=2.1 Hz), 7.70 (2 H, d, *J*=8.5 Hz), 7.50 (1 H, dd, *J*=8.5, 2.1 Hz), 7.37 - 7.41 (2 H, m), 7.36 (1 H, s), 7.16 (1 H, s), 7.12 (1 H, dd, *J*=8.4, 2.0 Hz), 6.54 (2 H, dd, *J*=8.5, 2.1 Hz), 5.98 (1 H, s), 3.66 (2 H, s), 1.50 (9 H, s). MS (ESI) $[M+H]^+$: 551.

2-(3-chloro-4-(2-(2,4-dichlorophenylsulfonamido)-4-(cyclobutylcarbamoyl)phenoxy)phenyl)acetic acid (17)



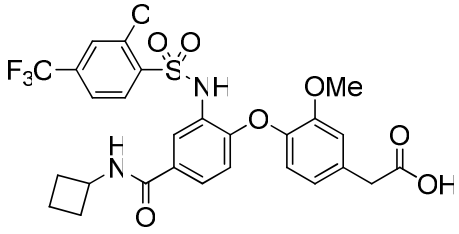
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1 H, d, *J*=8.3 Hz), 7.94 (1 H, d, *J*=2.2 Hz), 7.68 (1 H, s), 7.49 (1 H, dd, *J*=8.4, 2.1 Hz), 7.44 (1 H, d, *J*=2.0 Hz), 7.38 (1 H, d, *J*=2.0 Hz), 7.30 - 7.35 (1 H, m), 7.14 (1 H, dd, *J*=8.4, 2.1 Hz), 6.66 (1 H, d, *J*=8.3 Hz), 6.57 (1 H, d, *J*=8.6 Hz), 6.20 (1 H, d, *J*=7.6 Hz), 4.51 - 4.62 (1 H, m), 3.68 (2 H, s), 2.42 - 2.50 (2 H, m), 1.96 - 2.02 (2 H, m), 1.77 - 1.85 (2 H, m). MS (ESI) $[M+H]^+$: 583.

2-(4-(4-(tert-butylcarbamoyl)-2-(2,4-dichlorophenylsulfonamido)phenoxy)-3-chlorophenyl)acetic acid (18)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1 H, d, *J*=8.5 Hz), 7.86 - 7.91 (1 H, m), 7.71 (1 H, s), 7.40 - 7.46 (2 H, m), 7.38 (1 H, d, *J*=1.8 Hz), 7.32 (1 H, dd, *J*=8.5, 1.8 Hz), 7.10 - 7.17 (1 H, m), 6.65 (1 H, d, *J*=8.2 Hz), 6.56 (1 H, d, *J*=8.5 Hz), 6.01 (1 H, br. s.), 3.68 (2 H, s), 1.48 (9 H, s). MS (ESI) $[M+H]^+$: 585.

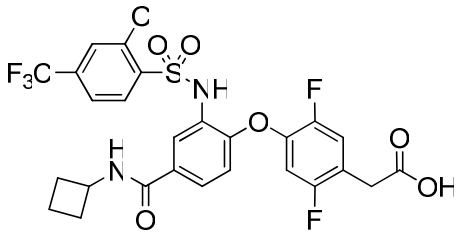
2-(4-(2-(2-chloro-4-(trifluoromethyl)phenylsulfonamido)-4-(cyclobutylcarbamoyl)phenoxy)-3-methoxyphenyl)acetic acid (19)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (1 H, d, *J*=8.2 Hz), 7.91 (1 H, d, *J*=2.2 Hz), 7.84 (1 H, s), 7.66 (1 H, s), 7.61 (1 H, d, *J*=8.2 Hz), 7.46 (1 H, dd, *J*=8.6, 2.2 Hz), 6.91 (1 H, d, *J*=2.0 Hz), 6.82 (1 H, dd, *J*=8.1,

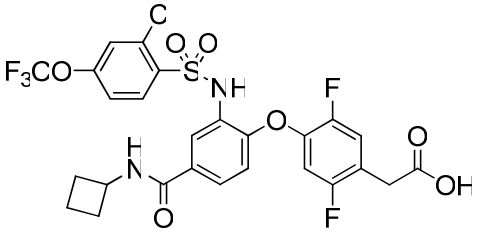
1.9 Hz), 6.68 (1 H, d, *J*=8.0 Hz), 6.56 (1 H, d, *J*=8.6 Hz), 6.15 (1 H, d, *J*=8.4 Hz), 4.47 - 4.63 (1 H, m), 3.68 (2 H, s), 3.66 (3 H, s), 2.38 - 2.51 (2 H, m), 1.95 - 2.02 (2 H, m), 1.76 - 1.84 (2 H, m). HRMS (m/z): Calcd. for $C_{27}H_{25}ClF_3N_2O_7S$ $[M+H]^+$: 613.1018; Found: 613.1023.

2-(4-(2-(2-chloro-4-(trifluoromethyl)phenylsulfonamido)-4-(cyclobutylcarbamoyl)phenoxy)-2,5-difluorophenyl)acetic acid (20)



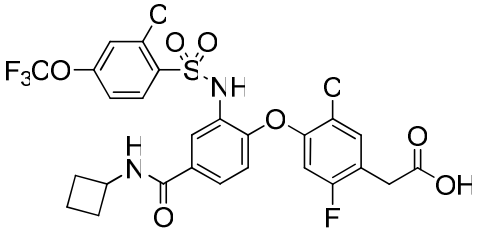
^{1}H NMR (400 MHz, Me-d_3-OD) δ 8.10 (d, *J* = 8.2Hz, 1H); 8.06 (s, 1H); 7.77 (s, 1H); 7.61-7.67 (m, 2H), 7.19 (dd, *J* = 10.70, 6.72Hz, 1H); 6.75 (d, *J* = 8.20Hz, 1H); 6.50 (dd, *J* = 10.70, 6.72Hz, 1H); 4.49 (m, 1H); 3.65 (s, 2H); 2.35-2.36 (m, 2H); 2.09-2.14 (m, 2H); 1.76-1.81 (m, 2H). HRMS (m/z): Calcd. for $C_{26}H_{21}ClF_5N_2O_6S$ $[M+H]^+$: 619.0724; Found: 619.0738.

2-(4-(2-(2-chloro-4-(trifluoromethoxy)phenylsulfonamido)-4-(cyclobutylcarbamoyl)phenoxy)-2,5-difluorophenyl)acetic acid (21)



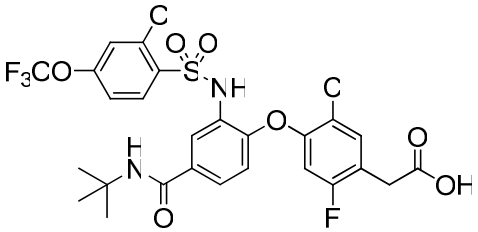
^{1}H NMR (400 MHz, Me-d_3-OD) δ 8.06 (d, *J* = 2.12Hz, 1H); 8.02 (d, *J* =8.80Hz, 1H); 7.62 (dd, *J* = 2.12, 8.80Hz, 1H); 7.41 (d, *J* = 1.45Hz, 1H); 7.20-7.27 (m, 2H); 6.75 (d, *J* = 8.6Hz, 1H); 6.56 (dd, *J* = 7.10, 9.52Hz, 1H); 4.45-4.51 (m, 1H); 3.67 (s, 2H); 2.34-2.36 (m, 2H); 2.04-2.16 (m, 2H); 1.74-1.82 (m, 2H). HRMS (m/z): Calcd. for $C_{26}H_{21}ClF_5N_2O_7S$ $[M+H]^+$: 635.0673; Found: 635.0684.

2-(5-chloro-4-(2-(2-chloro-4-(trifluoromethoxy)phenylsulfonamido)-4-(cyclobutylcarbamoyl)phenoxy)-2-fluorophenyl)acetic acid (22)



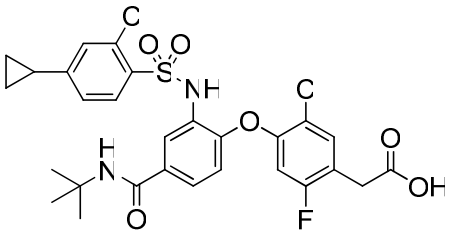
^{1}H NMR (400 MHz, Me-d_3-OD) δ 8.08 (d, *J* = 2.08Hz, 1H); 8.03 (d, *J* =8.80Hz, 1H); 7.61 (dd, *J* = 2.08, 8.60Hz, 1H); 7.47 (d, *J* = 7.46Hz, 1H); 7.42 (s, 1H); 7.29 (d, *J* = 8.80Hz, 1H); 6.67 (d, *J* = 8.60Hz, 1H); 6.49 (d, *J* = 10.76Hz, 1H); 4.45-4.53 (m, 1H); 3.67 (s, 2H); 2.34-2.39 (m, 2H); 2.07-2.17 (m, 2H); 1.74-1.82 (m, 2H). HRMS (m/z): Calcd. for $C_{26}H_{21}Cl_2F_4N_2O_7S$ $[M+H]^+$: 651.0377; Found: 651.0389.

2-(4-(4-(tert-butylcarbamoyl)-2-(2-chloro-4-(trifluoromethoxy)phenylsulfonamido)phenoxy)-5-chloro-2-fluorophenyl)acetic acid (23)



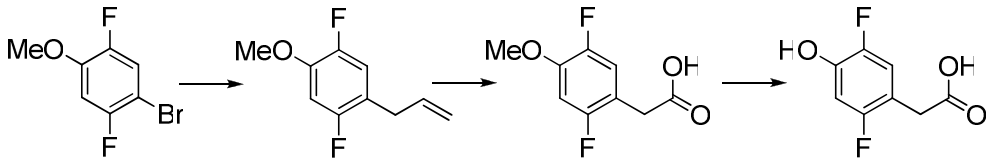
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J=8.8 Hz, 1H); 7.93 (d, J=2.2 Hz, 1H); 7.73 (s, 1H); 7.49 (dd, J=1.9, 8.6 Hz, 1H); 7.38 (d, J=7.3 Hz, 1H); 7.22 (s, 1H); 7.17 (d, J=8.6 Hz, 1H); 6.62 (d, J=8.6 Hz, 1H); 6.38 (d, J=9.5 Hz, 1H); 5.94 (s, 1H); 3.67 (s, 2H); 1.47 (s, 9H) ppm. HRMS (m/z): Calcd. for $C_{26}H_{23}Cl_2F_4N_2O_7S$ $[M+H]^+$: 653.0534; Found: 653.0537.

2-(4-(4-(tert-butylcarbamoyl)-2-(2-chloro-4-cyclopropylphenylsulfonamido)phenoxy)-5-chloro-2-fluorophenyl)acetic acid (AMG 853)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H); 7.87 (d, J = 6.5 Hz, 1H); 7.62 (s, 1H); 7.52 (dd, J = 8.5, 2.1 Hz, 1H); 7.39 (d, J = 7.4 Hz, 1H); 7.01 (s, 1H); 6.96 (d, J = 8.2 Hz, 1H); 6.63 (d, J = 8.5 Hz, 1H); 6.27 (d, J = 9.6 Hz, 1H); 5.88 (s, 1H); 3.69 (s, 2H); 1.87-1.81 (m, 1H); 1.47 (s, 9H); 1.11-1.07 (m, 2H); 0.75-0.71 (m, 2H). HRMS (m/z): Calcd. for $C_{28}H_{27}Cl_2FN_2O_6S$ $[M+H]^+$: 609.1024; Found: 609.1037. Anal. Calcd. for $C_{28}H_{27}Cl_2FN_2O_6S$: C, 55.18; H, 4.47; N, 4.60; Found: C, 55.23; H, 4.46; N, 4.50.

Synthesis of 2-(2,5-difluoro-4-hydroxyphenyl)acetic acid

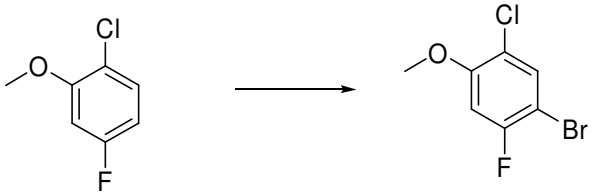


1-Allyl-2,5-difluoro-4-methoxybenzene. Under Argon atmosphere, the mixture of 1-bromo-2,5-difluoro-4-methoxybenzene (5g, 22.4mmol) and allyltributyltin (8.91g, 27mmol) in the presence of $Pd(PPh_3)_4$ (2.59g, 2.24mmol) in anhydrous DMF (100ml) was stirred at 110°C for 4 hours. The solution was diluted with ethyl acetate and then filtered. The filtrate was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 100% hexane eluent) to give the desired compound (4.0g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 13.7 Hz, 1H); 7.19 (d, *J* = 7.8 Hz, 1H); 5.87-5.97 (m, 1H); 5.07-5.12 (m, 2H); 3.91 (s, 3H); 3.33 (d, *J* = 6.45 Hz, 2H).

2-(2,5-Difluoro-4-methoxyphenyl)acetic acid. To a solution of 1-allyl-2,5-difluoro-4-methoxybenzene (4.0g, 22mmol) in a mixed solvent (CCl_4:CH_3CN:H_2O = 1:1:1.5, 350ml), $NaIO_4$ (23.25g, 22mmol) and $RuCl_3.H_2O$ (0.68g, 3.3mmol) were added in one portion. The reaction mixture was stirred at room temperature for 1 hour and then poured into water. The aqueous layer was extracted with DCM (3x), the combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired compound (2.7g, 56%). MS (ESI) $[M-H]^-$: 201.

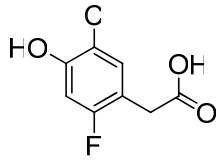
2-(2,5-Difluoro-4-hydroxyphenyl)acetic acid. Under N_2, to a solution of 2-(2,5-difluoro-4-methoxyphenyl)acetic acid (2.7g, 13.4mmol) in DCM (60ml) at -78°C, was added a solution of BBr_3 in dichloromethane (1M, 38mmol) dropwise over 1 hour. The reaction mixture was stirred at room temperature for 5 hours and then poured into ice water. The aqueous layer was extracted with ethyl acetate (3x), the combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 2-(2,5-difluoro-4-hydroxyphenyl)acetic acid (2.5g, 97%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.14 (dd, J = 11.0, 7.2 Hz 1H); 6.74 (dd, J = 11.0, 7.2 Hz, 1H); 3.49 (s, 2H). MS (ESI) $[M+H]^+$: 189.

2-(5-chloro-2-fluoro-4-hydroxyphenyl)acetic acid was synthesized in the same way as 2-(2,5-difluoro-4-hydroxyphenyl)acetic acid from 1-bromo-5-chloro-2-fluoro-4-methoxybenzene, which was prepared as shown below.



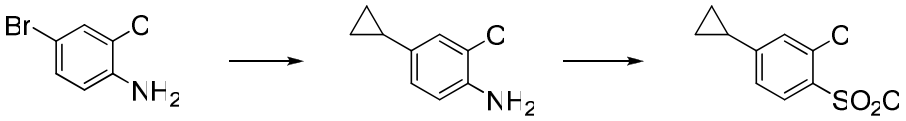
1-Bromo-5-chloro-2-fluoro-4-methoxybenzene. 1-Chloro-4-fluoro-2-methoxybenzene (15 g, 93 mmol) was dissolved in anhydrous chloroform (300 mL) and heated to 65 °C. A solution of bromine (9.95 mL, 187 mmol) in anhydrous chloroform (30 mL) was added dropwise. After 2 hours, the reaction was cooled to room temperature, treated with $Na_2S_2O_3$ (600 mL, saturated aqueous solution) and extracted with DCM (3X). The layers were separated and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow product was purified by flash chromatography (silica gel, 100% hexane eluent) to give the desired compound (20g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 7.1Hz, 1H); 6.66 (d, J = 9.8Hz, 1H); 3.81 (s, 3H). MS (ESI) $[M+H]^+$: 241.

2-(5-Chloro-2-fluoro-4-hydroxyphenyl)acetic acid.



^{1}H NMR (500 MHz, DMSO-d_6) δ 12.41 (bs, 1H); 10.54 (bs, 1H); 7.32 (d, J = 8.1Hz, 1H); 6.74 (d, J = 11.0, 1H); 3.50 (s, 2H). MS (ESI) $[M-H]^-$: 203.

Synthesis of 2-chloro-4-cyclopropylbenzene-1-sulfonyl chloride



2-Chloro-4-cyclopropylbenzenamine. To a 5L jacketed reactor equipped with a mechanical stirrer and a reflux condenser under nitrogen was added 4-bromo-2-chloroaniline (103 g, 499 mmol), cyclopropylboronic acid (58 g, 673 mmol),and potassium phosphate (376 g, 1771 mmol) in 2.5L toluene. The reaction flask was evacuated and back filled with nitrogen before adding tricyclohexylphosphine (14 g, 51 mmol) followed by water (100mL). The reaction was again evacuated and back-filled with nitrogen 3 times before adding palladium(II) acetate (5.8 g, 26 mmol). The flask

was evacuated and back-filled with nitrogen one more time and heated to 94°C using a heating mantle. Upon heating, the gummy precipitate turned into a dark brown solution. After 2.5 hours, the reaction was checked by HPLC to find that no starting materials remained. The reaction was cooled to room temperature and then transferred to a separation funnel to be extracted with water (2x 500mL) and then brine (500mL). The organics were stirred over $MgSO_4$ for 10 minutes and then filtered and the filtrate concentrated under *in vacuo* to afford an orange oil as the crude material (80g). The crude material was then purified by flash chromatography (Silica; 1-10% EtOAc in Hexanes) as a gradient. The final purified product (67.7g, 81% yield) was collected as an orange oil which crystallized overnight**.** MS (ESI) $[M+H]^+$: 168.

2-Chloro-4-cyclopropylbenzene-1-sulfonyl chloride. To a 5L jacketed reaction vessel equipped with an overhead stirrer, nitrogen inlet, and a temperature probe was dissolved 2-chloro-4-cyclopropylbenzenamine (66.0 g, 394 mmol) in 1.6 L acetonitrile. To this stirring solution was added concentrated hydrochloric acid (632 ml). [Note: the jacketed reactor was set to 15°C for the HCl addition] Upon addition of HCl, the reaction exothermed slightly (from 18°C to 22°C). The reaction was then cooled to -2-0°C before adding sodium nitrite (15 ml, 472 mmol) as a solution in water (80.0 ml) via dropping funnel over 20 minutes. This resulting orange mixture was then stirred under cooled conditions (0-5°C) for an additional hour before adding 750 mL chilled acetic acid. Then sulfur dioxide (141g) was bubbled into the reaction mixture by lecture bottle through a gas dispersion tube over a period of 20 minutes. Then, a mixture of copper (II) chloride (27 g, 201 mmol) and copper(I) chloride (0.1 ml, 5 mmol) was added all at once to the reaction. The resulting green reaction mixture was equilibrated to room temperature and stirred overnight. The reaction mixture was filtered to remove solids. The filtrate was then concentrated *in vacuo* until a precipitate developed. The mixture was then diluted with ethyl acetate (1L) and extracted with water (2 X 500mL) and brine (1 X 500mL). The organic layer was stirred over magnesium sulfate, filtered and the filtrate concentrated to a dark orange oily solid. The crude material was purified by column chromatography (Silica; 0-5% EtOAc in Hexanes). The final product (86 g, 87% yield) was obtained as a light yellow (oily textured) solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J=8.4 Hz, 1H); 7.29 (d, J=1.7 Hz, 1H); 7.13 (dd, J=2.0, 8.6 Hz, 1H); 1.99 (m, 1H); 1.21 (m, 2H); 0.87 (m, 2H).