Supporting Information

Discovery of AMG 369, a Thiazolo[5,4-b]pyridine Agonist of $S1P_1$ and $S1P_5$

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Table SI-1. Statistical analysis of $hS1P_1$ and $hS1P_3$ data

compound	hS1P1 RI (n)	hS1P1 RI EC50 (micromolar)	hS1P1 RI EC50 SD for n=2 or SE for n>2	hS1P1 RI %efficacy	hS1P1 RI %efficacy SD for n=2 or SE for n>2	hS1P3 Ca2+ (n)	hS1P3 Ca2+ EC50 (micromolar)	hS1P3 Ca2+ EC50 SD for n=2 or SE for n>2	hS1P3 Ca2+ %efficacy	hS1P3 Ca2+ %efficacy SD for n=2 or SE for n>2
3a	284	0.041	0.003	102	2	15	1.214	0.185	24	2
3b	8	0.144	0.014	106	10	2	10.050	0.756	63	43
3c	4	0.429	0.152	115	8	4	>25			
3d	10	0.138	0.037	125	13	8	2.887	0.194	36	3
4a	2	0.221	0.124	84	9	2	3.466	0.418	50	8
4b	4	1.602	0.254	75	1	2	>25			
4c	4	3.980	0.702	77	17	2	5.458	0.333	64	4
4d	4	0.199	0.063	92	9	2	0.478	0.097	94	4
5a	208	0.035	0.002	99	2	126	0.877	0.021	44	1
5b	38	0.038	0.004	87	3	44	0.996	0.045	45	2
5c	10	0.033	0.013	103	10	14	2.511	0.416	64	3
5d	14	0.002	0.0004	98	5	6	0.888	0.363	26	5
5e	2	0.119	0.051	124	33	2	1.307	0.043	68	1
5f	2	0.026	0.008	76	21	2	12% at 2.5 micromolar			
5g	2	0.033	0.011	108	17	2	0.836	0.013	41	1
6	6	0.038	0.005	93	5	10	4.668	0.815	56	3

For n=2, data was collected in duplicate from separate plates using the same cell culture on the same day. For n>2, data was collected in duplicate from separate plates using different cell cultures on different days.

QM Calculations of Fragments A-C and 2-(1-phenylcyclopropyl)pyridine

Gaussian 98, Revision A.5, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.

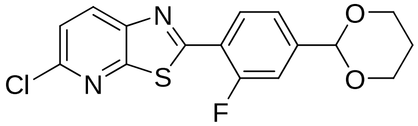
dihedral angle	5-(2-phenylpropan-2-yl)thiazolo[5,4-b]pyridine (A)	5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridine (B)	6-(1-phenylcyclopropyl)benzo[d]thiazole (C)	2-(1-phenylcyclopropyl)pyridine
0		0.00	2.834	1.434
10	1.001	0.15	2.922	1.539
20	1.104	1.21	3.534	1.798
30	0.644	1.25	3.815	2.167
40	1.331	0.85	3.905	2.374
50	0.412	0.81	3.945	2.451
60	0.518	0.76	3.9	2.302
70	0.688	0.76	3.862	2.302
80	1.147	0.77	3.697	2.183
90	1.662	0.70	3.608	2.096
100	1.143	0.67	3.565	2.027
110	0.322	0.54	3.337	1.981
120	0	0.47	3.135	1.772
130	0.105	0.40	2.784	1.494
140	0.088	0.55	2.482	1.122
150	0.425	0.61	2.094	0.624
160	1.782	0.51	1.72	0.291
170	1.137	0.33	1.211	0.225
180	1.557	0.20	0	0
190	1.137	0.331	1.211	0.225
200	1.782	0.51	1.72	0.291
210	0.425	0.611	2.094	0.624
220	0.088	0.55	2.482	1.122
230	0.105	0.395	2.784	1.494
240	0	0.466	3.135	1.772
250	0.322	0.537	3.337	1.981

260	1.143	0.671	3.565	2.027
270	1.662	0.697	3.608	2.096
280	1.147	0.767	3.697	2.183
290	0.688	0.759	3.862	2.302
300	0.518	0.758	3.9	2.302
310	0.412	0.811	3.945	2.451
320	1.331	0.854	3.905	2.374
330	0.644	1.252	3.815	2.167
340	1.104	1.208	3.534	1.798
350	1.001	0.152	2.922	1.539
360		0	2.834	1.434

Synthesis of 3a-d, 4a-d, 5a-g, 6

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. Silica gel chromatography was performed using medium pressure liquid chromatography (MPLC) on a CombiFlash® Companion® (Teledyne Isco) with RediSep® normal-phase silica gel (35 – 60 micron) columns and UV detection at 254 nm. Preparative reversed-phase HPLC was performed on a Gilson or Shimadzu, YMC-Pack Pro C18, 150 x 30 mm I.D. column, eluting with a binary solvent system A and B using a gradient elusion (A: H_2O with 0.1% TFA; B: CH_3CN with 0.1% TFA) with UV detection at 254 nm. All final compounds were purified to ≥95% purity as determined by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 254 nm (Method **A**: Zorbax SB-C8, 4.6 x 150 mm, 15 min; 1.5 mL/min flow rate; 0 to 100% 0.1% TFA in CH_3CN/0.1% TFA in H_2O; Method **B**: Phenomenex Synergi, 2 x 50 mm, 3 min, 1.0 mL/min flow rate, 5 to 95% 0.1% formic acid in CH_3CN /0.1% formic acid in H_2O). NMR spectra were determined with either a Bruker AV-400 (400 MHz) spectrometer or a Varian 400 MHz or a 300 MHz spectrometer at ambient temperature. Low-resolution mass spectral (MS) data were determined on an Agilent 1100 Series LCMS with UV detection at 254 nm and a low resonance electrospray mode (ESI). Chemical shifts are reported in ppm from the solvent resonance (DMSO-d_6 2.50 ppm or $CDCl_3$ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. High-resolution mass spectra (HRMS) were obtained on a high resonance electrospray time-of-flight mass spectrometer.

Synthesis of **5d**



Synthesis of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-chlorothiazolo[5,4-b]pyridine (**8**)

Step 1

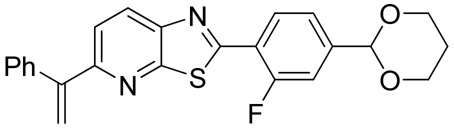
4-Bromo-3-fluorobenzaldehyde (100.0 g, 492.6 mmol) was added to toluene (1L). Propane-1,3-diol (42.72 mL, 591.1 mmol), and p-toluenesulfonic acid monohydrate (4.685 g, 24.63 mmol) were added to above and the reaction mixture was brought to reflux. The solvent (500 mL) was azeotroped off using a dean stark trap. The reaction mixture was cooled and extracted with sat. aqueous sodium bicarbonate (500 mL). The organics were dried over magnesium sulfate and concentrated in vacuo to give **7** (126 g, 98% yield) as a white solid: ^{1}H NMR (CHLOROFORM-d, 400 MHz): δ ppm 7.53 (dd, *J*=8.2, 7.0 Hz, 1 H), 7.25 - 7.30 (m, 1 H), 7.14 (dd, *J*=8.2, 1.8 Hz, 1 H), 5.44 (s, 1 H), 4.20 - 4.31 (m, 2 H), 3.97 (ddd, *J*=12.2, 12.2, 2.5 Hz, 2 H), 2.12 - 2.29 (m, 1 H), 1.39 - 1.51 (m, 1 H). MS (ESI) m/z: Calculated: 260.0; Observed: 260.9 (M^++1).

Step 2

A slurry of sodium carbonate (15.2 g, 144 mmol), 2,6-dichloropyridin-3-amine (9.00 g, 55.2 mmol), and thiophosgene (5.50 mL, 71.8 mmol) in 100 mL anhydrous DCM was allowed to stir in a sealed vessel for 2 days. The reaction mixture was filtered through a glass frit, rinsing with DCM. The filtrate was concentrated in vacuo to give 2,6-dichloro-3-isothiocyanatopyridine (12.0 g, quant.) as a peach-colored solid: ^{1}H NMR (DMSO-d_6, 400MHz): δ ppm 8.07 (d, *J*=8.0 Hz, 1 H), 7.68 (d, *J*=8.5 Hz, 1 H).

Step 3

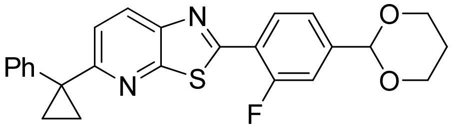
To a solution of 2-(4-bromo-3-fluorophenyl)-1,3-dioxane (7.65 g, 29.3 mmol) in 75 mL THF under argon at -78 °C was added 1-butyllithium 2.5M in hexanes (12.9 mL, 32.2 mmol) in portions over ~ 20 min. The reaction mixture was allowed to stir 20 min, and was yellow. A solution of 2,6-dichloro-3-isothiocyanatopyridine (6.01 g, 29.3 mmol) in 20 mL THF was added dropwise via cannula. The resulting dark brown solution was allowed to stir 15 min, then was quenched by addition of saturated aqueous NH_4Cl. The reaction mixture was partitioned between saturated aqueous NH_4Cl and Et_2O. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to give an orange solid. The solid was treated with sodium carbonate (4.66 g, 44.0 mmol) and approximately 15 mL DMF, and stirred under nitrogen at 90 °C. The reaction was heated overnight, and in the morning was a solid mass. The reaction was diluted with water, stirred rapidly for several hours, and filtered, rinsing with water and MeOH. The resulting solid was dried in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-chlorothiazolo[5,4-b]pyridine (**8**, 8.50 g, 83% yield): ^{1}H NMR (CHLOROFORM-d, 400 MHz): δ ppm 8.38 (dd, *J*=7.8 Hz, 1 H), 8.26 (d, *J*=8.5 Hz, 1 H), 7.37 - 7.51 (m, 3 H), 5.56 (s, 1 H), 4.32 (dd, *J*=10.8, 4.8 Hz, 2 H), 4.03 (ddd, *J*=12.2, 12.2, 2.3 Hz, 2 H), 2.13 - 2.36 (m, 1 H), 1.50 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 350.0; Observed: 350.9 (M^++1).



Synthesis of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylvinyl)thiazolo[5,4-b]pyridine (**9**)

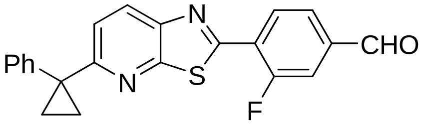
A mixture of bis(4-(di-tert-butylphosphino)-N,N-dimethylbenzenamine) palladium dichloride (0.252 g, 0.356 mmol), potassium carbonate (6.70 g, 48.5 mmol), 1-phenylvinylboronic acid (4.64 g, 31.4 mmol), and 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-chlorothiazolo[5,4-b]pyridine (5.00 g, 14.3 mmol) in 50 mL dioxane and 15 mL water was sealed and heated to 80 °C overnight. The reaction was cooled, diluted with DCM and water, and the aqueous layer was extracted with DCM. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to give a brown semi-solid. The solid was suspended in 100 mL EA, heated to 75 °C, and filtered, rinsing with a small volume of hot EA. The filtrate was allowed to stand overnight, resulting in crystals, and was placed in the freezer overnight. The crystals were collected by filtration, rinsing with a small volume of cold EA to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylvinyl)thiazolo[5,4-b]pyridine (**9**, 4.44 g, 74% yield) as light brown crystals: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.40 (dd, *J*=7.8, 7.8 Hz, 1 H), 8.25 (d, *J*=8.5 Hz, 1 H), 7.34 - 7.51 (m, 8 H), 6.17 (s, 1 H), 5.71 (s, 1

H), 5.57 (s, 1 H), 4.32 (dd, *J*=11.5, 4.5 Hz, 2 H), 3.97 - 4.08 (m, 2 H), 2.17 - 2.36 (m, 1 H), 1.50 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 418.1; Observed: 419.0 (M^++1).



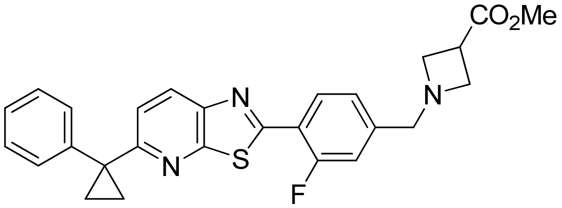
Synthesis of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclopropyl)-thiazolo[5,4-b]pyridine (**10**)

To a solution of potassium tert-butoxide (4.02 g, 35.8 mmol) in 100 mL DMSO under nitrogen was added trimethyl sulfoxonium iodide (7.89 g, 35.8 mmol) in 4 portions over about 20 minutes. 2-(4-(1,3-Dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylvinyl)-thiazolo[5,4-b]pyridine (10.0 g, 23.9 mmol) was suspended in 150 mL THF and filtered through a glass frit, rinsing with 25 mL THF. The filtrate was added to the reaction dropwise very slowly from an addition funnel over 1.5 – 2 h. The resulting orange reaction was allowed to stir 30 min, at which point the THF was removed in vacuo, resulting in a precipitate. Water and ice was added slowly with stirring (approximately 400 mL total). The solid was isolated by filtration rinsing with water and MeOH. The solid was dried in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridine (**10**, 7.70 g, 75% yield) as a light orange solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.35 (dd, *J*=7.8, 7.8 Hz, 1 H), 8.04 (d, *J*=8.5 Hz, 1 H), 7.29 - 7.51 (m, 7 H), 7.02 (d, *J*=8.5 Hz, 1 H), 5.56 (s, 1 H), 4.31 (dd, *J*=11.5, 5.0 Hz, 2 H), 4.03 (dd, 2 H), 2.16 - 2.36 (m, 1 H), 1.77 - 1.84 (m, 2 H), 1.50 (d, *J*=13.6 Hz, 1 H), 1.38 - 1.43 (m, 2 H). MS (ESI) m/z: Calculated: 432.1; Observed: 433.1 (M^++1).



Synthesis of 3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridine-2-yl)-benzaldehyde (**11**)

To a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclopropyl)-thiazolo[5,4-b]pyridine (22.3 g, 51.6 mmol) in 200 mL THF was added 200 mL 5N HCl. The reaction mixture became warm, was fitted with a water-cooled reflux condenser, and was heated to 65 °C in an oil bath under argon. After 3 h, the reaction was nearly homogeneous. The bath was turned off and the reaction allowed to stir overnight. In the morning a nice yellow precipitate was evident. The THF was removed in vacuo, and the resulting slurry was filtered, rinsing with water, and dried under nitrogen, then dried in vacuo overnight to give 3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridine-2-yl)benzaldehyde (**11**, 18.0 g, 93% yield) as a light orange solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.08 (s, 1 H), 8.59 (dd, *J*=7.3, 7.3 Hz, 1 H), 8.10 (d, *J*=8.5 Hz, 1 H), 7.84 (d, *J*=8.0 Hz, 1 H), 7.77 (d, *J*=10.5 Hz, 1 H), 7.30 - 7.55 (m, 5 H), 7.07 (d, *J*=8.5 Hz, 1 H), 1.78 - 1.95 (m, 2 H), 1.36 - 1.53 (m, 2 H). MS (ESI) m/z: Calculated: 374.1; Observed: 375.1 (M^++1).



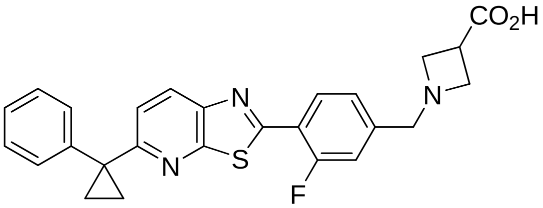
Synthesis of methyl 1-((3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (**12**)

Step 1

To a slurry of azetidine-3-carboxylic acid (20 g, 198 mmol) in 500 mL anhyd. MeOH under nitrogen at 0 °C was added slowly dropwise thionyl chloride (36 mL, 495 mmol) over 4 h. The resulting clear, light yellow solution was sealed and placed in a 0 °C freezer overnight. In the morning the reaction mixture was concentrated in vacuo, and the resulting oil was treated with 100 mL anhydrous benzene and concentrated in vacuo to give a solid. This was repeated anhydrous benzene. The resulting light yellow solid was dried in vacuo to give methyl azetidine-3-carboxylate hydrochloride (29.0 g, 97% yield). ^{1}H NMR (400 MHz, MeOH-*d*$_4$) δ ppm 4.21-4.30 (m, 4H), 3.78 (s, 3H), 3.71-3.78 (m, 1H).

Step 2

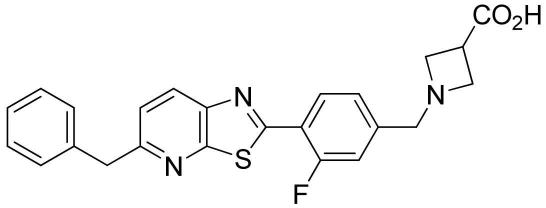
To a solution of 3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridin-2-yl)benzaldehyde (1.26 g, 3.37 mmol) in 15 mL DCM was added methyl azetidine-3-carboxylate hydrochloride (0.765 g, 5.05 mmol), acetic acid (0.777 mL, 13.5 mmol), and N,N-diisopropylethylamine (0.879 mL, 5.05 mmol), and 15 mL MeOH. The reaction was allowed to stir 30 min, at which time sodium cyanoborohydride (0.211 g, 3.37 mmol) was added. Bubbling was observed. After 1.5 h, the reaction was concentrated in vacuo, suspended in DCM, and the acid quenched with saturated aqueous $NaHCO_3$. The mixture was transferred to a separatory funnel with DCM and water. The layers were separated, and the aqueous layer was extracted 2 x DCM. The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by silica gel chromatography (0-100% EA/hexanes) gave methyl 1-((3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (**12**, 1.19 g, 75% yield) as a light yellow solid: ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 8.20 - 8.32 (m, 2 H), 7.29 - 7.48 (m, 7 H), 7.03 (d, *J*=8.5 Hz, 1 H), 3.66 (s, 2 H), 3.63 (s, 3 H), 3.43 - 3.52 (m, 2 H), 3.32 - 3.40 (m, 1 H), 3.23 - 3.29 (m, 2 H), 1.62 - 1.74 (m, 2 H), 1.30 - 1.46 (m, 2 H). MS (ESI) m/z: Calculated: 473.2; Observed: 474.1 (M^++1).



Synthesis of 1-((3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylic acid (**5d**)

Methyl 1-((3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (1.19 g, 2.51 mmol) was dissolved in 30 mL THF to give a yellow solution. Sodium hydroxide 1 M in water (5.03 mL, 5.03 mmol) was added rapidly dropwise to give a cloudy solution. After 2 h, the reaction was judged complete. The THF was removed in vacuo, and the resulting yellow solution was diluted with 10 mL water. 5 mL 1N HCl was added dropwise with rapid stirring, resulting in a very thick mixture, which was diluted with 10 mL 1M pH 6 sodium phosphate buffer and 10 mL water. The resulting thick cloudy mixture was stirred rapidly for 10 min, then filtered through a 0.45 micron filter, rinsing 3 x 20 mL water, then 3 x 10 mL EtOH. The material was dried under positive nitrogen and vacuum, then transferred to a flask and dried in vacuo to give 1-((3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylic acid (**5d**, 0.987 g, 86% yield) as an off-white powder: ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 174.5, 162.6, 159.7 (d, *J*=251.3 Hz), 159.0 (d, *J*=6.4 Hz), 157.4 (d, *J*=9.2 Hz), 145.1, 145.0, 142.7, 130.2, 129.9, 128.7, 128.7, 127.0, 124.9 (d, *J*=2.1 Hz), 120.6, 118.9 (d, *J*=10.6 Hz), 115.8 (d, *J*=21.9 Hz), 61.4, 56.6, 33.8, 31.7, 17.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.21 - 8.33 (m, 2 H), 7.28 - 7.49 (m, 7 H), 7.04 (d, *J*=8.5 Hz, 1 H), 3.65 (s, 2 H), 3.39 - 3.49 (m, 2 H), 3.18 - 3.37 (m, 3 H), 1.62 - 1.76 (m, 2 H), 1.32 - 1.45 (m, 2 H). HRMS (ESI) m/z: Calculated: 459.1492; Observed: 460.1417 (M^{+}+1).

Synthesis of **4d**



Step 1

A thick slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-chlorothiazolo[5,4-b]pyridine (2.50 g, 7.1 mmol) and bis(4-(di-tert-butylphosphino)-N,N-dimethyl-benzenamine) palladium dichloride (0.10 g, 0.14 mmol) in benzylzinc (II) bromide 0.5M in THF (21 mL, 11 mmol) was flushed with argon and sealed, and heated to 70 °C. All solids eventually dissolved over 1 h to give a dark brown solution. After 3 h, the reaction mixture was cooled and diluted with saturated aqueous NH_4Cl. Solid formed, and was taken up in EtOAc. The organic layer was washed saturated aqueous NH_4Cl, brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting solid was suspended in 50 mL MTBE and stirred for 30 min, then filtered, rinsing with a minimum amount of MTBE, and dried in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-benzylthiazolo[5,4-b]pyridine (2.5 g, 86% yield) as a gray solid: ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.42 (d, *J*=8.0 Hz, 1 H), 8.35 (dd, *J*=8.0 Hz, 1 H), 7.55 (d, *J*=8.5 Hz, 1 H), 7.42 - 7.51 (m, 2 H), 7.28 - 7.39 (m, 4 H), 7.18 - 7.25 (m, 1 H), 5.64 (s, 1 H), 4.27 (s, 2 H), 4.19 (dd, *J*=11.5, 5.0 Hz, 2 H), 3.98 (dd, *J*=12.0, 12.0 Hz, 2 H), 1.91 - 2.13 (m, 1 H), 1.49 (d, *J*=13.1 Hz, 1 H). MS (ESI) m/z: Calculated: 406.1; Observed: 407.1 (M^{+}+1).

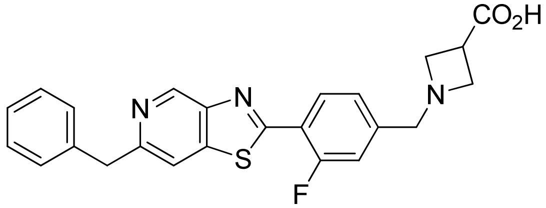
Step 2

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-benzylthiazolo[5,4-b]pyridine (0.133 g, 0.33 mmol) in 6 mL 1:1 THF/5N aqueous HCl was stirred rapidly in a sealed vial, and was heated to 70 °C for 5 h. The reaction was cooled, treated with ice, 10 N aqueous NaOH and DCM. The aqueous layer was extracted with DCM 2 times, and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting sticky orange solid was treated with 2 mL diethyl ether, sonicated, and filtered, rinsing with diethyl ether to give 4-(5-benzylthiazolo[5,4-b]pyridin-2-yl)-3-fluorobenzaldehyde (0.051 g, 45% yield) as a tan solid: ^{1}H NMR (DMSO-d$_6$, 400MHz): δ ppm 10.09 (s, 1 H), 8.57 (dd, *J*=7.5, 7.5 Hz, 1 H), 8.49 (d, *J*=8.5 Hz, 1 H), 7.95 - 8.05 (m, 2 H), 7.59 (d, *J*=8.0 Hz, 1 H), 7.27 - 7.39 (m, 4 H), 7.17 - 7.26 (m, 1 H), 4.29 (s, 2 H). MS (ESI) m/z: Calculated: 348.1; Observed: 349.0 (M$^+$+1).

Step 3

A slurry of 4-(5-benzylthiazolo[5,4-b]pyridin-2-yl)-3-fluorobenzaldehyde (0.051 g, 0.15 mmol), azetidine-3-carboxylic acid (0.030 g, 0.29 mmol), acetic acid (0.034 mL, 0.59 mmol) in 4 mL 1:1 DCM/MeOH was allowed to stir for 1 h. Sodium cyanoborohydride (0.0092 g, 0.15 mmol) was added and the mixture stirred overnight. The reaction was concentrated under a stream of nitrogen, dissolved in DMSO/1-2 drops TFA, purified by RPHPLC, 20-100% ACN/TFA in water/TFA. The product-containing fractions were concentrated and dried in vacuo to give 1-(4-(5-benzylthiazolo[5,4-b]pyridin-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid trifluoroacetic acid salt (0.039 g, 49% yield) as a white solid: ^{1}H NMR (DMSO-d$_6$, 400MHz): δ ppm 8.35 - 8.48 (m, 2 H), 7.63 (d, *J*=12.0 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.52 (d, *J*=8.0 Hz, 1 H), 7.27 - 7.37 (m, 4 H), 7.18 - 7.25 (m, 1 H), 4.45 (br. s., 2 H), 4.28 (s, 2 H), 4.20 (br. s., 4 H), 3.55 - 3.72 (m, 1 H). MS (ESI) m/z: Calculated: 433.1; Observed: 434.2 (M$^+$+1).

Synthesis of **4c**



Step 1

To a stirring slurry of 4,6-dichloropyridin-3-amine (2.00 g, 12 mmol) and sodium carbonate (3.4 g, 32 mmol) in 10 mL DCM was added thiophosgene (1.2 mL, 16 mmol). The orange mixture was sealed and allowed to stir at ambient temperature overnight. The reaction was determined complete by TLC, and was filtered, rinsing with DCM, and the filtrate concentrated in vacuo to give 2,4-dichloro-5-isothiocyanatopyridine (2.45 g, 97% yield) as an orange solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.28 (s, 1 H), 7.45 (s, 1 H).

Step 2

To a solution of 2-(4-bromo-3-fluorophenyl)-1,3-dioxane (3.12 g, 11.9 mmol) in 40 mL THF at -78 °C under argon was added butyllithium, 2.5 M solution in hexanes (5.26 mL, 13.1 mmol) slowly dropwise. The resulting solution was allowed to stir 1 h at -78 °C, at which point a solution at ambient temp of 2,4-dichloro-5-isothiocyanatopyridine (2.45 g, 11.9 mmol) in 10 mL THF was added slowly via cannula. The dark red reaction was allowed to stir 15 min, and was then removed from the bath and quenched by slow addition of saturated aqueous NH_4Cl. The reaction was diluted with 40 mL MTBE, and the organic layer washed 1 x water, 1 x brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting 5.10 g of an orange foam was treated with sodium carbonate (1.90 g, 17.9 mmol) and 10 mL DMF. The reaction was heated under nitrogen to 80 °C. A precipitate formed after ~ 30 min. An additional 5 mL DMF was added to give a stirrable slurry. After 30 min additional, the reaction was cooled slightly and treated with 100 mL water. After 10 min stirring, the mixture was filtered, rinsing 2 x water, 1 x MeOH. The solid was collected and dried in vacuo overnight to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-chlorothiazolo[4,5-c]pyridine (2.93 g, 69.9% yield) as a tan solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.17 (s, 1 H), 8.43 (dd, *J*=7.8, 7.8 Hz, 1 H) 7.92 (s, 1 H), 7.40 - 7.50 (m, 2 H), 5.57 (s, 1 H), 4.32 (dd, *J*=11.0, 5.0 Hz, 2 H), 3.95 - 4.09 (m, 2 H), 2.14 - 2.37 (m, 1 H), 1.51 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 350.0; Observed: 351.0 (M^++1).

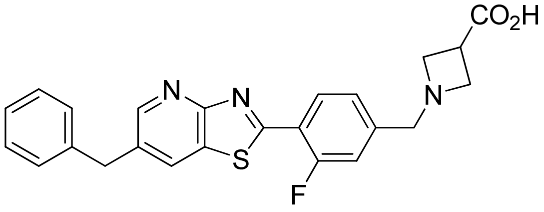
Step 3

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-chlorothiazolo[4,5-c]pyridine (0.500 g, 1.4 mmol) and benzylzinc (II) bromide 0.5 M in THF (5.7 mL, 2.9 mmol) was heated to 60 °C in a sealed tube overnight then bis(4-(di-tert-butylphosphino)-N,N-dimethyl-benzenamine) palladium dichloride (0.050 g, 0.071 mmol) was added. The reaction was heated at 60 °C for 1.5 h, at which point the reaction was cooled, additional benzylzinc (II) bromide 0.5 M in THF (5.7 mL, 2.9 mmol) was added, and the reaction was resealed and heated to 80 °C. Upon completion, the reaction was quenched with ice and saturated aqueous NH_4Cl and extracted 3 x DCM. The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting solid was suspended in MTBE, filtered, and the solid collected and dried in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-benzylthiazolo[4,5-c]pyridine (0.372 g, 64% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (s, 1 H), 8.38 (dd, *J*=8.0, 8.0 Hz, 1 H), 8.14 (s, 1 H), 7.42 - 7.55 (m, 2 H), 7.25 - 7.38 (m, 4 H), 7.15 - 7.24 (m, 1 H), 5.64 (s, 1 H), 4.24 (s, 2 H), 4.18 (dd, *J*=11.3, 4.8 Hz, 2 H), 3.92 - 4.05 (m, 2 H), 1.91 - 2.12 (m, 1 H), 1.48 (d, 1 H). MS (ESI) m/z: Calculated: 406.1; Observed: 407.0 (M^++1).

Step 4

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-benzylthiazolo[4,5-c]pyridine (0.209 g, 0.51 mmol) in 2 mL THF and 2 mL 5N aqueous HCl was heated to 70 °C for 2 h. The reaction was cooled and treated with ice and 10 N aqueous NaOH until basic. The mixture was extracted 3 x DCM, and the combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo to give 0.184 g of a brown solid. This material was combined with azetidine-3-carboxylic acid (0.16 g, 1.5 mmol), 1.5 mL DCM, acetic acid (0.15 g, 2.6 mmol), and 1.5 mL MeOH and stirred overnight. Sodium cyanoborohydride (0.032 g, 0.51 mmol) was added, and after 30 min the reaction was judged complete. The reaction was concentrated under a stream of nitrogen, dissolved in DMSO and TFA, filtered, and purified by RPHPLC, 10-100% ACN/TFA in water/TFA. Product-containing fractions were combined and concentrated in vacuo. The resulting glass was dissolved in MeOH, treated with water, frozen, and lyophilized to give 1-(4-(6-benzylthiazolo[4,5-c]pyridin-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid trifluoroacetic acid salt (0.032 g, 11% yield) as a white powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.32 (s, 1 H), 8.44 (dd, *J*=8.0, 8.0 Hz, 1 H), 8.17 (s, 1 H), 7.60 - 7.71 (m, 1 H), 7.54 (d, *J*=7.5 Hz, 1 H), 7.27 - 7.37 (m, 4 H), 7.21 (t, *J*=6.5 Hz, 1 H), 4.50 (br. s., 2 H), 4.26 (s, 2 H), 3.57 - 4.38 (m, 5 H). MS (ESI) m/z: Calculated: 433.1; Observed: 434.1 (M^++1).

Synthesis of **4b**



Step 1

A mixture of 3,5-dibromopyridin-2-amine (10.0 g, 39.7 mmol), SODIUM CARBONATE (12.6 g, 119 mmol), and THIOPHOSGENE (4.56 mL, 59.5 mmol) in 50 mL DCM was sealed and heated to 55 °C for 3 d. The reaction was allowed to stand for 7 d. The reaction was filtered through a frit and concentrated in vacuo to give 3,5-dibromo-2-isothiocyanatopyridine (11.6 g, 99% yield) as an orange solid: 1H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 8.64 (s, 1 H), 8.60 (s, 1 H).

Step 2

To a solution of 2-(4-bromo-3-fluorophenyl)-1,3-dioxane (3.00 g, 11 mmol) in 25 mL THF at -78 °C was added *n*-BuLi 2.5 M in hexanes (5.1 mL, 13 mmol) slowly dropwise. The reaction was allowed to stir 30 min, at which point 3,5-dibromo-2-isothiocyanatopyridine (16 mL, 11 mmol) was added as a solution in THF. The reaction became very dark, and after 15 min was quenched with saturated aqueous NH_4Cl. The reaction was diluted with Et_2O and water, and was washed 1 x brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The material was purified by silica gel chromatography, 120 g, 0-100% EA/hexanes. Product-containing fractions were combined and concentrated to give N-(3,5-dibromopyridin-2-yl)-4-(1,3-dioxan-2-yl)-2-fluorobenzothioamide (1.55 g, 28% yield) as an orange foam: ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 12.35 (s, 1 H), 8.71 (br. s., 1 H), 8.63 (s, 1 H), 7.64 (dd, *J*=7.3, 7.3 Hz, 1 H), 7.31 (d, *J*=8.0 Hz, 1 H), 7.24 (br. s., 1 H), 5.57 (s, 1 H), 4.16 (dd, *J*=11.3, 4.3 Hz, 2 H), 3.96 (dd, *J*=11.5, 11.5 Hz, 2 H), 1.94 - 2.10 (m, 1 H), 1.46 (d, *J*=13.1 Hz, 2 H). MS (ESI) m/z: Calculated: 475.9; Observed: 476.9 (M^++1).

Step 3

A slurry of N-(3,5-dibromopyridin-2-yl)-4-(1,3-dioxan-2-yl)-2-fluorobenzothioamide (1.55 g, 3.26 mmol) and SODIUM CARBONATE (0.690 g, 6.51 mmol) in 10 mL DMF under nitrogen was heated overnight at 90 °C. Upon complete conversion, the reaction was cooled and 100 mL water was added. Addition of 100 mL EA resulted in a biphasic mixture containing solid. The liquid was transferred to a separatory funnel, and the solid-containing suspension was sonicated in EA and filtered, rinsing with EA and Et_2O to give 0.540 g of a yellow solid. The filtrate was added to the separatory funnel and the layers separated. The organic layer was washed 1 x brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give an orange solid. The solid was suspended in diethyl ether, sonicated and filtered to give an additional 0.13 g as a brown solid. The aqueous layer was extracted 3 x DCM, and the combined organics dried over sodium sulfate, filtered and concentrated, to give additional material. The materials were combined to give a total of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-bromothiazolo[4,5-b]pyridine (0.96 g, 74% yield) as an orange solid: ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 9.01 (s, 1 H), 8.85 (s, 1 H), 8.43 (dd, *J*=7.8, 7.8 Hz, 1 H), 7.43 - 7.56 (m, 2 H), 5.65 (s, 1 H), 4.19 (dd, *J*=11.5, 5.0 Hz, 2 H), 3.99 (dd, *J*=11.3, 11.3 Hz, 2

H), 1.92 - 2.13 (m, 1 H), 1.49 (d, 1 H). MS (ESI) m/z: Calculated: 394.0; Observed: 395.0 (M^{+}+1).

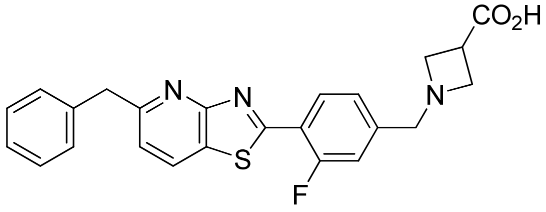
Step 4

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-bromothiazolo[4,5-b]pyridine (0.460 g, 1.2 mmol) and bis(4-(di-tert-butylphosphino)-N,N-dimethyl-benzenamine) palladium dichloride (0.041 g, 0.058 mmol) in benzylzinc(II) bromide 0.5 M in THF (4.7 mL, 2.3 mmol) was stirred under argon at ambient temp overnight. The reaction was partitioned between EtOAc and saturated aqueous NH_4Cl. The organic layer was washed 1 x brine, and the combined aqueous layers re-extracted with DCM. The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo. The orange residue was sonicated in 5 mL Et_2O, filtered, rinsing with Et_2O, to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-benzylthiazolo[4,5-b]pyridine (0.169 g, 36% yield) as a light orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1 H), 8.53 (s, 1 H), 8.40 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.42 - 7.53 (m, 2 H), 7.27 - 7.37 (m, 4 H), 7.17 - 7.26 (m, 1 H), 5.64 (s, 1 H), 4.11 - 4.25 (m, 4 H), 3.99 (dd, *J*=11.3, 11.3 Hz, 2 H), 1.88 - 2.15 (m, 1 H), 1.48 (d, *J*=15.6 Hz, 1 H). MS (ESI) m/z: Calculated: 406.1; Observed: 407.1 (M^{+}+1).

Step 5

A mixture of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-benzylthiazolo[4,5-b]pyridine (0.169 g, 0.416 mmol) in 2 mL THF and 2 mL 5 N HCl was heated to 70 °C in a sealed vial for 4 h. The reaction was cooled with ice and and quenched with 10 N NaOH until basic. Extracted 3 x DCM, and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography, 12 g, 0-100% EA/hexanes to give 0.10 g of an impure orange solid. This material was treated with azetidine-3-carboxylic acid (0.064 g, 0.63 mmol) and acetic acid (0.072 mL, 1.3 mmol) in 4 mL 1:1 DCM/MeOH, and the mixture was stirred 1 h. Sodium cyanoborohydride (0.020 g, 0.32 mmol) was added and the reaction stirred overnight. The reaction was concentrated under nitrogen and dissolved in 4 mL DMSO with TFA. The material was filtered then purified by RPHPLC, 10-100% ACN/TFA in H2O/TFA to give 1-(4-(6-benzylthiazolo[4,5-b]pyridin-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid trifluoroacetic acid salt (0.036 g, 21% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.16 (br. s., 1 H), 10.33 (s, 1 H), 8.73 (s, 1 H), 8.55 (s, 1 H), 8.47 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.64 (d, *J*=13.6 Hz, 1 H), 7.55 (d, *J*=7.5 Hz, 1 H), 7.28 - 7.39 (m, 4 H), 7.15 - 7.27 (m, 1 H), 4.49 (br. s., 2 H), 4.18 (s, 2 H), 4.13 - 4.38 (m, 4 H), 3.54 - 3.75 (m, 1 H). MS (ESI) m/z: Calculated: 433.1; Observed: 434.1 (M^{+}+1).

Synthesis of **3b**



Step 1

bis(di-tert-Butyl(phenyl)phosphine) palladium dichloride (0.40 g, 0.64 mmol), 6-bromopyridin-2-amine (4.40 g, 25 mmol), and potassium phosphate (16 g, 76 mmol) were treated with 9-benzyl-9-bora-bicyclo[3.3.1]nonane 0.5 M in THF (102 mL, 51 mmol) under argon. The yellow reaction was sealed and heated to 60 °C overnight. The reaction was cooled and filtered through Celite, rinsing with 200 mL Et_2O. The organic layer was extracted 3 x 2 N aq HCl. The combined HCl layers were washed 1 x Et_2O. The HCl layer was cooled with ice and neutralized with ~ 55 mL 10 N NaOH resulting in a biphasic mixture. The mixture was extracted 2 x DCM. The combined extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by silica gel chromatography gave 6-benzylpyridin-2-amine (3.75 g, 80% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.10 - 7.34 (m, 6 H), 6.32 (d, *J*=7.0 Hz, 1 H), 6.24 (d, *J*=8.0 Hz, 1 H), 5.82 (s, 2 H), 3.79 (s, 2 H). MS (ESI) m/z: Calculated: 184.1; Observed: 185.1 (M^++1).

Step 2

To a solution of 6-benzylpyridin-2-amine (3.75 g, 20.4 mmol) in 50 mL CCl_4 was added 1-bromopyrrolidine-2,5-dione (7.25 g, 40.7 mmol). The reaction was protected from light and stirred overnight. In the morning, a thick slurry was evident. The reaction was concentrated in vacuo, dissolved in DCM, and treated with 20 g silica gel and dried. The material was purified by silica gel chromatography, 120 g, 0-20% EtOAc/hexanes to give a red solid, which was suspended in hexanes and filtered, rinsing with hexanes, to give 6-benzyl-3,5-dibromopyridin-2-amine (5.03 g, 72.3% yield) as a slightly orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.93 (s, 1 H), 7.10 - 7.36 (m, 5 H), 6.45 (br. s., 2 H), 4.01 (s, 2 H). MS (ESI) m/z: Calculated: 341.9; Observed: 342.9 (M^++1).

Step 3

To a stirring suspension of sodium carbonate (5.6 g, 53 mmol) and 6-benzyl-3,5-dibromopyridin-2-amine (3.00 g, 8.8 mmol) in 50 mL DCM at ambient temperature was added thiophosgene (2.0 mL, 26 mmol). The reaction was allowed to stir under nitrogen overnight. The reaction was transferred to a 150 mL sealable vessel, and 1.0 equiv thiophosgene was added. The sealed reaction was allowed to stir for 2 days. The reaction was partitioned between water and DCM. The aqueous layer was extracted with DCM 2 times, and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The material was adsorbed onto 20 g silica gel and purified by silica gel chromatography, 80 g, 0-20% EA/hexanes to give 2-benzyl-3,5-dibromo-6-isothiocyanatopyridine (1.5 g, 45% yield) as an off-white solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.04 (s, 1 H), 7.29 - 7.35 (m, 4 H), 7.19 - 7.26 (m, 1 H), 4.23 (s, 2 H).

Step 4

A solution of 4-bromo-3-fluorobenzaldehyde (20.0 g, 99 mmol), ((1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid (0.5 g, 2 mmol), and triethoxymethane (49 mL, 296 mmol) was allowed to stir under nitrogen overnight. The reaction was judged complete by TLC (10% EA/H). The reaction was diluted with 200 mL Et_2O and washed 1 x 1N NaOH and 1 x brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Concentration in vacuo at 75 °C to remove triethoxymethane gave 1-bromo-4-(diethoxymethyl)-2-fluorobenzene (27.2 g, quant. yield) as a light yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.72 (dd, *J*=7.8, 7.8 Hz, 1 H), 7.32 (d, *J*=10.0 Hz, 1 H), 7.20 (d, *J*=8.0 Hz, 1 H), 5.50 (s, 1 H), 3.41 - 3.63 (m, 4 H), 1.15 (t, *J*=6.8 Hz, 6 H).

Step 5

To a -78 °C solution of 1-bromo-4-(diethoxymethyl)-2-fluorobenzene (1.54 g, 5.57 mmol) in 20 mL THF under argon was added *n*-butyllithium 2.5 M solution in hexanes (2.34 mL, 5.85 mmol) slowly dropwise over 5 min. The light yellow solution was allowed to stir 15 min, at which point a -78 °C solution of 2-benzyl-3,5-dibromo-6-isothiocyanatopyridine (1.07 g, 2.79 mmol) in 7 mL THF was added dropwise via cannula. After 10 min the dark red reaction was quenched by dropwise addition of saturated aqueous NH_4Cl. The reaction was warmed to ambient temperature, partitioned between Et_2O and water, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The material was adsorbed onto 12 g silica gel from Et_2O, dried, and purified by silica gel chromatography, 80 g, 0-30% EtOAc/hexanes to give N-(6-benzyl-3,5-dibromopyridin-2-yl)-4-(diethoxymethyl)-2-fluorobenzothioamide (0.600 g, 37.0% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.33 (s, 1 H), 8.58 (s, 1 H), 7.67 (br. s., 1 H), 7.00 - 7.46 (m, 6 H), 5.54 (s, 1 H), 4.25 (br. s., 2 H), 3.44 - 3.68 (m, 4 H), 1.17 (t, *J*=6.8 Hz, 6 H). MS (ESI) m/z: Calculated: 582.0; Observed: 582.8 (M^++1).

Step 6

A sealable tube was charged with cesium carbonate (0.504 g, 1.55 mmol), 1,10-phenanthroline (0.0743 g, 0.412 mmol), copper (I) iodide (0.0392 g, 0.206 mmol), and a solution of N-(6-benzyl-3,5-dibromopyridin-2-yl)-4-(diethoxymethyl)-2-fluorobenzothioamide (0.600 g, 1.03 mmol) in 10 mL dioxane was added. The reaction was sealed and heated overnight. The reaction was quenched carefully with 5N HCl with rapid stirring, to give a precipitate after about 10 min. The reaction was stirred rapidly 30 min total, cooled to 0 °C and basified with 10 N NaOH. The aqueous layer was extracted 3 x DCM, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting material was adsorbed onto 3 g silica gel and purified by ISCO, 40 g, 0-100% EtOAc/hexanes to give 4-(5-benzyl-6-bromothiazolo[4,5-b]pyridin-2-yl)-3-fluorobenzaldehyde (0.397 g, 90.2% yield) as a light yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.10 (s, 1 H), 9.04 (s, 1 H), 8.63 (dd, *J*=7.3,7.3 Hz, 1 H), 7.92 - 8.09 (m, 2 H), 7.31 (d, *J*=4.0 Hz, 4 H), 7.16 - 7.26 (m, 1 H), 4.45 (s, 2 H). MS (ESI) m/z: Calculated: 426.0; Observed: 426.9 (M^++1).

Step 7

To a solution of 4-(5-benzyl-6-bromothiazolo[4,5-b]pyridin-2-yl)-3-fluorobenzaldehyde (0.440 g, 1.03 mmol) and methyl azetidine-3-carboxylate hydrochloride (0.234 g, 1.54 mmol) and diisopropylethylamine (0.269 mL, 1.54 mmol) was added acetic acid (0.236 mL, 4.12 mmol). The reaction was allowed to stir 1 h at ambient temperature. Sodium cyanoborohydride (0.0647 g, 1.03 mmol) was added and bubbling was observed. The reaction was allowed to stir several hours. The reaction was concentrated in vacuo, then quenched with saturated aqueous sodium bicarbonate and DCM. The aqueous layer was extracted 3 x DCM. The organic layer was dried over sodium sulfate, filtered, and concentrated. The resulting material was purified by silica gel chromatography to give methyl 1-((4-(5-benzyl-6-bromothiazolo[4,5-b]pyridin-2-yl)-3-fluorophenyl)methyl)azetidine-3-carboxylate (0.437 g, 81% yield): MS (ESI) m/z: Calculated: 525.1; Observed: 525.9 (M^++1).

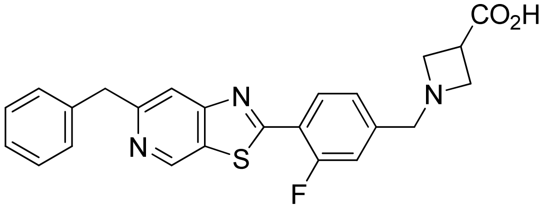
Step 8

A 10 mL rbf was charged with methyl 1-((4-(5-benzyl-6-bromothiazolo[4,5-b]pyridin-2-yl)-3-fluorophenyl)methyl)azetidine-3-carboxylate (0.100 g, 0.19 mmol) and 10% palladium on carbon, 50% water wet (0.20 g, 0.19 mmol), and was treated under nitrogen with 1.5 mL MeOH and triethylamine (0.13 mL, 0.95 mmol). The reaction was exposed to balloon pressure of hydrogen for 1 h with rapid stirring. The reaction was flushed with nitrogen and filtered through celite, rinsing with MeOH. The filtrate was concentrated and the solid purified by silica gel chromatography, 12 g, 30-100% EtOAc/hexanes to give methyl 1-((4-(5-benzylthiazolo[4,5-b]pyridin-2-yl)-3-fluorophenyl)methyl)azetidine-3-carboxylate (0.061 g, 72% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.56 (d, *J*=8.0 Hz, 1 H), 8.33 (dd, *J*=8.3, 8.3 Hz, 1 H), 7.16 - 7.49 (m, 8 H), 4.25 (s, 2 H), 3.67 (s, 2 H), 3.63 (s, 3 H), 3.44 - 3.53 (m, 2 H), 3.24 - 3.40 (m, 3 H). MS (ESI) m/z: Calculated: 447.1; Observed: 448.0 (M^++1).

Step 9

To a solution of methyl 1-((4-(5-benzylthiazolo[4,5-b]pyridin-2-yl)-3-fluorophenyl)methyl)azetidine-3-carboxylate (0.061 g, 0.14 mmol) in 2 mL THF was added a solution of lithium hydroxide hydrate (0.017 g, 0.41 mmol) in 2 mL water. The reaction was allowed to stir 1 h and was judged complete by LCMS. The THF was removed under a stream of nitrogen, and the base was neutralized by addition of 0.41 mL 1N HCl. 5 mL 1M pH 6 sodium phosphate buffer was added and the suspension sonicated for 15 min. The slurry was filtered, rinsing with water, and EtOH, and the solid dried in vacuo to give 1-((4-(5-benzylthiazolo[4,5-b]pyridin-2-yl)-3-fluorophenyl)methyl)azetidine-3-carboxylic acid (0.046 g, 78% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.39 (br. s., 1 H), 8.56 (d, *J*=8.0 Hz, 1 H), 8.33 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.14 - 7.51 (m, 8 H), 4.25 (s, 2 H), 3.67 (s, 2 H), 3.15 - 3.53 (m, 5 H). MS (ESI) m/z: Calculated: 433.1; Observed: 434.2 (M^++1).

Synthesis of **3c**



Step 1

A slurry of sodium carbonate (7.80 g, 73.6 mmol) and 2,5-dichloropyridin-4-amine (3.00 g, 18.40 mmol) in 20 mL DCM was treated with thiophosgene (2.82 mL, 36.8 mmol) was sealed and allowed to stir rapidly for 48 h. The cap was removed cautiously (some bubbling), and TLC showed complete conversion. The reaction was filtered through a glass frit, rinsing with DCM and the filtrate concentrated in vacuo to give an orange oil. This was filtered through a 3 cm pad of silica gel with 10% EA/hexanes and the filtrate was concentrated in vacuo to give 2,5-dichloro-4-isothiocyanatopyridine (3.43 g, 16.73 mmol, 91 % yield) as a red solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.40 (s, 1 H), 7.16 (s, 1 H).

Step 2

To a solution of 2-(4-bromo-3-fluorophenyl)-1,3-dioxane (4.37 g, 16.73 mmol) in 50 mL THF under argon at -78 °C was added *n*-butyllithium 2.5 M in hexanes (7.36 mL, 18.40 mmol) slowly dropwise via syringe. After 20 min, a solution of 2,5-dichloro-4-isothiocyanatopyridine (3.43 g, 16.73 mmol) in 15 mL THF was added slowly dropwise via addition funnel, over about 15 min. The resulting dark brown reaction was allowed to stir 15 min and was then quenched with saturated aqueous NH_4Cl, diluted with diethyl ether, and the organic layer was washed 1 x brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give an orange solid 6.76 g. The unpurified solid was treated with sodium carbonate (2.66 g, 25.09 mmol) and 20 mL DMF in a flask fitted with a water-cooled reflux condensor, and the slurry was heated to 120 °C under argon overnight. The reaction was cooled and diluted with ice, water and DCM. The aqueous layer was extracted 3 x DCM. The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo to a brown sludge, which was treated with 50 mL MeOH and was sonicated. The solid was collected by filtration, rinsing 3 x MeOH, and was dried in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-chlorothiazolo[5,4-c]pyridine (2.22 g, 6.33 mmol, 37.8 % yield) as a brown solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.02 (s, 1 H), 8.46 (dd, *J*=7.7, 7.7 Hz, 1 H), 8.01 (s, 1 H), 7.41 - 7.53 (m, 2 H), 5.57 (s, 1 H), 4.32 (dd, *J*=11.0, 4.3 Hz, 2 H), 4.03 (dd, *J*=11.9, 11.9 Hz, 2 H), 2.16 - 2.37 (m, 1 H), 1.51 (d, *J*=13.5 Hz, 1 H). MS (ESI) m/z: Calculated: 350.0; Observed: 351.0 (M^++1).

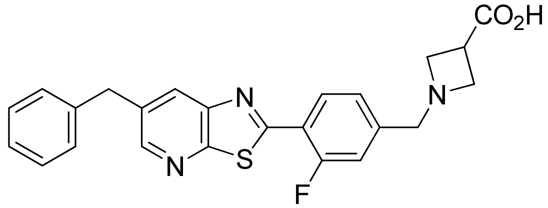
Step 3

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-chlorothiazolo[5,4-c]pyridine (0.200 g, 0.570 mmol) and bis(4-(di-tert-butylphosphino)-N,N-dimethyl-benzenamine) palladium dichloride (7.56 mg, 0.029 mmol) in benzylzinc (II) bromide 0.5 M in THF (2.281 mL, 1.140 mmol) was flushed with argon and sealed, heated to 70 °C. After 3 h, the reaction was cooled, and additional benzylzinc (II) bromide 0.5 M in THF (2.281 mL, 1.140 mmol) and bis(4-(di-tert-butylphosphino)-N,N-dimethyl-benzenamine) palladium dichloride (7.56 mg, 0.029 mmol) was added, the reaction was resealed and heated to 80 °C. After 4 h, the reaction was cooled and quenched with ice and saturated aqueous NH_4Cl, and the aqueous layer was extracted 3 x DCM. The combined organics were washed 1 x with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting oil was purified by silica gel chromatography, 12 g, 0-40% EA/hexanes to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-benzylthiazolo[5,4-c]pyridine (0.116 g, 0.285 mmol, 50 % yield) as a white solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.20 (s, 1 H), 8.42 (dd, *J*=8.2, 7.4 Hz, 1 H), 7.80 (s, 1 H), 7.40 - 7.49 (m, 2 H), 7.30 - 7.39 (m, 5 H), 5.56 (s, 1 H), 4.39 (br. s., 2 H), 4.25 - 4.35 (m, 2 H), 3.95 - 4.10 (m, 2 H), 2.15 - 2.34 (m, 1 H), 1.45 - 1.56 (m, 1 H). MS (ESI) m/z: Calculated: 406.1; Observed: 406.8 (M^++1).

Step 4

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-benzylthiazolo[5,4-c]pyridine (0.116 g, 0.285 mmol) in 3 mL 1:1 THF:5N aqueous HCl was sealed and heated to 70 °C for 2 h. The reaction was cooled, and quenched with ice and 10 N NaOH until basic. The reaction was partitioned between DCM and water, and the aqueous layer was extracted 3 x DCM. The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo to give 0.102 g of a yellow-orange soild. This material was treated with azetidine-3-carboxylic acid (0.087 g, 0.856 mmol), 1.5 mL DCM, acetic acid (0.082 mL, 1.427 mmol), 1.5 mL MeOH, and after 30 min, sodium cyanoborohydride (0.011 g, 0.285 mmol) was added. After 30 min, the reaction was concentrated, and dissolved in 2 mL DMSO + TFA. The solution was filtered and purified by RPHPLC, ACN/H2O/TFA to give 1-(4-(6-benzylthiazolo[5,4-c]pyridine-2-yl)-3-fluorobenzyl)azetidine-3-carboxylic acid trifluoroacetic acid salt (0.040 g, 0.092 mmol, 32.3 % yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.21 – 10.52 (br. s., 1 H), 9.39 (s, 1 H), 8.46 (dd, *J*=7.8, 7.8 Hz, 1 H), 7.98 (s, 1 H), 7.61 – 7.74 (m, 1 H), 7.55 (d, *J*=7.8 Hz, 1 H), 7.27 – 7.39 (m, 4 H), 7.17 – 7.24 (m, 1 H), 4.50 (br. s., 2 H), 4.13 – 4.40 (m, 6 H), 3.57 – 3.73 (m, 1 H). MS (ESI) m/z: Calculated: 433.1; Observed: 434.1 (M^++1).

Synthesis of **3d**



Step 1

To 5-bromo-2-chloropyridin-3-amine (2.20 g, 11 mmol) and bis(di-tert-butyl(phenyl)phosphine) palladium dichloride (0.16 g, 0.27 mmol) under argon in a 75 mL sealable vial was added benzylzinc (II) bromide 0.5M in THF (23 mL, 12 mmol). The reaction was sealed and allowed to stir at ambient temperature overnight. The reaction was adsorbed onto 10 g silica gel from DCM/THF. The material was purified by silica gel chromatography, 0-100% EtOAc/hexanes to give 5-benzyl-2-chloropyridin-3-amine (1.62 g, 70% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 (s, 1 H), 7.25 - 7.35 (m, 2 H), 7.16 - 7.24 (m, 3 H), 6.90 (s, 1 H), 5.48 (s, 2 H), 3.82 (s, 2 H). MS (ESI) m/z: Calculated: 218.1; Observed: 219.0 (M^++1).

Step 2

To a slurry of 5-benzyl-2-chloropyridin-3-amine (1.60 g, 7.32 mmol), sodium carbonate (1.55 g, 14.6 mmol) in 25 mL DCM was added thiophosgene (0.673 mL, 8.78 mmol). The mixture was allowed to stir for 4 h. The reaction was judged complete by TLC, and was diluted with water and DCM. The aqueous layer was extracted 1 x DCM, and the combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo to give 5-benzyl-2-chloro-3-isothiocyanatopyridine (1.20 g, 62.9% yield) as an orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (s, 1 H), 7.92 (s, 1 H), 7.07 - 7.44 (m, 5 H), 3.98 (s, 2 H).

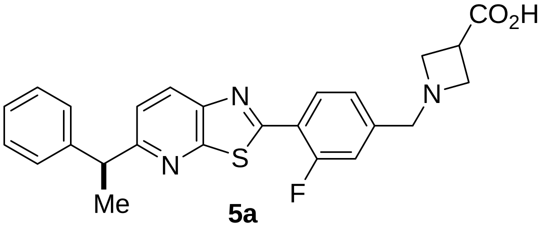
Step 3

To a solution of 1-bromo-4-(diethoxymethyl)-2-fluorobenzene (1.06 g, 3.84 mmol) in 15 mL THF under nitrogen at -78 °C was added 1-butyllithium 2.5M in hexanes (1.69 mL, 4.22 mmol) slowly dropwise. The resulting slightly pink solution was allowed to stir 15 min, at which point a room temperature solution of 5-benzyl-2-chloro-3-isothiocyanatopyridine (1.00 g, 3.84 mmol) in THF was added slowly dropwise via syringe. The reaction became dark brown. After 15 min, the reaction was quenched by dropwise addition of saturated aqueous NH_4Cl, and was warmed to ambient temperature. The reaction was partitioned between saturated aqueous NH_4Cl and DCM. The aqueous layer was extracted with DCM once, and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting orange oil was purified by silica gel chromatography, 80 g, 0-30% EtOAc/hexanes. Product-containing fractions were combined and concentrated to give 0.99 g of an orange oil which solidified on standing to an orange solid. The solid was suspended in 10 mL dioxane, sonicated, and filtered. The solid was collected and was treated with DCM and 1N NaOH. The aqueous layer was extracted 2 x DCM, combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo to give 0.313 g of an off-white solid. The filtrate from the previous filtration was treated with 2N HCl with rapid stirring for 10 min, partitioned between NaOH and DCM, and the organics dried over sodium sulfate, filtered, and concentrated to give 0.486 g solid. This was treated with 4 mL diethyl ether and sonicated. The slurry was filtered, rinsing with 1 mL Et$_2$O to give 0.360 g of a tan solid. Solids were combined to give a total of 4-(6-benzylthiazolo[5,4-b]pyridin-2-yl)-3-fluorobenzaldehyde (0.673 g, 50.4% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.10 (s, 1 H), 8.69 (s, 1 H), 8.56 (dd, *J*=7.5,7.5 Hz, 1 H), 8.42 (s, 1 H), 7.94 - 8.06 (m, 2 H), 7.28 - 7.41 (m, 4 H), 7.19 - 7.26 (m, 1 H), 4.20 (s, 2 H). MS (ESI) m/z: Calculated: 348.1; Observed: 349.0 (M^{+}+1).

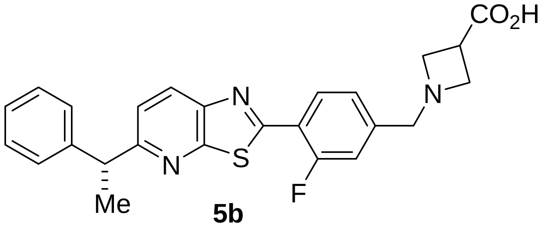
Step 4

A slurry of 4-(6-benzylthiazolo[5,4-b]pyridin-2-yl)-3-fluorobenzaldehyde (0.311 g, 0.89 mmol) and azetidine-3-carboxylic acid (0.18 g, 1.8 mmol) in 4 mL 1:1 DCM/MeOH was added acetic acid (0.10 mL, 1.8 mmol). The slurry was allowed to stir for 1 h, at which point sodium cyanoborohydride (0.056 g, 0.89 mmol) was added. The reaction was stirred overnight and the reaction was concentrated, and slurried in DCM. The solid was collected and further sonicated for 10 min in 4 mL pH 6 1.0 M phosphate buffer and filtered, rinsing with water and EtOH to give 1-((4-(6-benzylthiazolo[5,4-b]pyridin-2-yl)-3-fluorophenyl)methyl)azetidine-3-carboxylic acid (0.052 g, 13% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.31 (br. s., 1 H), 8.62 (s, 1 H), 8.35 (s, 1 H), 8.27 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.27 - 7.44 (m, 5 H), 7.22 (dd, *J*=6.8, 6.8 Hz, 1 H), 4.18 (s, 2 H), 3.66 (s, 2 H), 3.39 - 3.50 (m, 2 H), 3.14 - 3.30 (m, 3 H). MS (ESI) m/z: Calculated: 433.1; Observed: 434.1 (M^{+}+1).

Synthesis of **5a** and **5b**



5a



5b

Step 1

To a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-benzylthiazolo[5,4-b]pyridine (Synthesis of **4d**, Step 1, 1.00 g, 2.46 mmol) in 4 mL DMF was added lithium bis(trimethylsilyl)amide, 1.0m solution in tetrahydrofuran (2.95 mL, 2.95 mmol) slowly dropwise. The reaction became dark blue. After 5 min, METHYL IODIDE (0.461 mL, 7.38 mmol) was added, the blue color turned light brown. After 20 min, the reaction was quenched with water. The reaction was partitioned between water and EtOAc, and was washed 2 x water, 1 x brine, the organic layer was dried over sodium sulfate, filtered, and concentrated. The resulting solid was suspended in MeOH and filtered to give *rac*-2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylethyl)thiazolo[5,4-b]pyridine (0.685 g, 66.2% yield) as an orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.30 - 8.45 (m, 2 H), 7.54 (d, *J*=8.5 Hz, 1 H), 7.42 - 7.51 (m, 2 H), 7.26 - 7.39 (m, 4 H), 7.19 (dd, *J*=7.3, 7.3 Hz, 1 H), 5.63 (s, 1 H), 4.49 (q, *J*=7.2 Hz, 1 H), 4.18 (dd, *J*=10.5, 5.0 Hz, 2 H), 3.92 - 4.04 (m, 2 H), 1.91 - 2.14 (m, 1 H), 1.70 (d, *J*=7.5 Hz, 3 H), 1.48 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 420.1; Observed: 421.1 (M^{+}+1).

Step 2

To a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylethyl)thiazolo[5,4-b]pyridine (18.2 g, 43.3 mmol) in 100 mL THF was added 100 mL 5 N HCl. The mixture became warm and was fitted with a water-cooled reflux condensor and was heated to 70 °C. After 2 h, the reaction reached 90% conversion. The reaction was cooled, poured onto ice, and basified with 10 N NaOH. The aqueous layer was extracted 3 x DCM, and the combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo to give a dull yellow solid. This material was resubjected to the reaction conditions and after 2 h, ~1-2% of starting material remained. Work up by the same procedure to give a dull yellow solid. The material was suspended in ~ 50 mL MTBE and stirred rapidly until a fine suspension resulted. The solid was isolated by filtration, rinsing with 50 mL cold MTBE. The solid was dried in vacuo to give a light yellow solid (13.1 g). The filtrate was diluted with EA and washed 3 x water and 1 x brine, dried over sodium sulfate, filtered, and concentrated to give an orange solid, which was further purified by silica gel chromatography (40 g, 10-50% EA/hexanes gradient) to give an additional 0.75 g. Total of *rac*-3-fluoro-4-(5-(1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)benzaldehyde (13.9 g, 88.6% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.10 (s, 1 H), 8.56 (dd, *J*=7.5,7.5 Hz, 1 H), 8.45 (d, *J*=8.5 Hz, 1 H), 7.94 - 8.04 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.35 - 7.39 (m, 2 H), 7.31 (dd, *J*=7.8, 7.8 Hz, 2 H), 7.20 (dd, *J*=7.3, 7.3 Hz, 1 H), 4.51 (q, *J*=7.0 Hz, 1 H), 1.71 (d, *J*=7.0 Hz, 3 H). MS (ESI) m/z: Calculated: 362.1; Observed: 363.1 (M^{+}+1).

Step 3

To a slurry of 3-fluoro-4-(5-(1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)benzaldehyde (0.900 g, 2.5 mmol) and methyl azetidine-3-carboxylate hydrochloride (0.56 g, 3.7 mmol) in 8 mL anhydrous DCM under nitrogen was added N,N-diisopropylethylamine (0.65 mL, 3.7 mmol), acetic acid (0.57 mL, 9.9 mmol), and 8 mL anhydrous MeOH. The reaction was allowed to stir 1 h, at which point sodium cyanoborohydride (0.17 g, 2.7 mmol) was added in one portion. Bubbling was observed. After 1 h, the reaction was concentrated in vacuo. The reaction was partitioned between saturated aqueous sodium bicarbonate and DCM. The aqueous layer was extracted 3 x DCM, and the combined extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (40 g, 0-100% EA/DCM) to give to give *rac*-methyl 1-((3-fluoro-4-(5-(1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (1.07 g, 93% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (d, *J*=8.5 Hz, 1 H), 8.26 (dd, *J*=7.8, 7.8 Hz, 1 H), 7.53 (d, *J*=8.5 Hz, 1 H), 7.26 - 7.41 (m, 6 H), 7.15 - 7.22 (m, 1 H), 4.49 (q, *J*=7.0 Hz, 1 H), 3.66 (s, 2 H), 3.64 (s, 3 H), 3.47 (m, 2 H), 3.33 - 3.40 (m, 1 H), 3.26 (m, 2 H), 1.70 (d, *J*=7.0 Hz, 3 H). MS (ESI) m/z: Calculated: 461.1; Observed: 462.1 (M^{+}+1).

Step 4

Enantiomeric separation of *rac*-methyl 1-((3-fluoro-4-(5-(1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (1.07 g) was achieved by supercritical fluid chromatography: Berger Multigram II SFC; Column: Chiralcel OJ-H (250x21mm, 5um); Mobile Phase: A: Liquid CO_2 B: methanol with

0.2% DEA; Isocratic: 35%B; Flow Rate: 65mL/min; Column/Oven Temperature: 40 °C; Outlet Pressure: 100 bar; 1mL/injection. The first and second eluting peaks were collected separately and concentrated in vacuo to give peak 1: methyl 1-((3-fluoro-4-(5-((S)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.405 g) and peak 2: methyl 1-((3-fluoro-4-(5-((R)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.495 g). Both materials were judged >99.9% ee by analytical SFC: Column: Chiralcel OJ-H (150 x 4.6 mm, 5 micron); Mobile Phase: A: Liquid CO_2; B: methanol with 0.2% DEA; Isocratic: 35%B; Flow Rate: 4.0 mL/min; Column/Oven Temperature: 40 °C; Outlet Pressure: 100 bar.

Step 5: Synthesis of sodium 1-((3-fluoro-4-(5-((S)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (**5a**)

To a solution of methyl 1-((3-fluoro-4-(5-((S)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.405 g, 0.877 mmol) in 4 mL THF was added sodium hydroxide 1M in water (2.63 mL, 2.63 mmol) to give a cloudy mixture. A small amount of water was added until the reaction became a clear, light yellow solution. After 1 h, the reaction was judged complete by LCMS. The THF was removed in vacuo to give a solid. The reaction was treated with 2.63 mL 1N HCl and 4 mL pH 6 1 M phosphate buffer, and about 4 mL water. The resulting gel was filtered The solid was rinsed with EtOH and dried in vacuo to give 0.212 g solid. This was suspended in 2 mL water and 1 mL of 1N NaOH was added. The material went into solution, then gradually precipitated out. After 30 min stirring, the material was isolated by filtration, rinsed with water and diethyl ether, then dried in vacuo overnight, to give sodium 1-((3-fluoro-4-(5-((S)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.200 g, 48.5% yield) as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.37 (d, *J*=8.5 Hz, 1 H), 8.25 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.52 (d, *J*=8.5 Hz, 1 H), 7.25 - 7.41 (m, 6 H), 7.16 - 7.24 (m, 1 H), 4.48 (q, *J*=7.0 Hz, 1 H), 3.59 (s, 2 H), 3.27 - 3.35 (m, 2 H), 3.11 (m, 2 H), 2.71 - 2.85 (m, 1 H), 1.70 (d, *J*=7.0 Hz, 3 H). MS (ESI) m/z: Calculated: 447.1; Observed: 448.1 (M^++1).

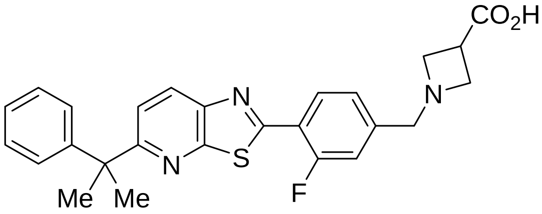
Step 6: Synthesis of sodium 1-((3-fluoro-4-(5-((R)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (**5b**)

To a solution of methyl 1-((3-fluoro-4-(5-((R)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.495 g, 1.07 mmol) in 4 mL THF was added sodium hydroxide 1M in water (3.22 mL, 3.22 mmol). The reaction was stirred for 1 h, then THF was removed in vacuo. The reaction was treated with 3.22 mL 1N HCl and dilute with 4 mL 1M pH 6 sodium phosphate buffer, and 4 mL water. 10 N NaOH was added until basic, then the resulting solid was isolated by filtration, rinsing 1 x water. The wet filter cake was dried in vacuo overnight to give sodium 1-((3-fluoro-4-(5-((R)-1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.369 g, 73.3% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.37 (d, *J*=8.6 Hz, 1 H), 8.24 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.52 (d, *J*=8.4 Hz, 1 H), 7.25 - 7.40 (m, 6 H), 7.14 - 7.23 (m, 1 H), 4.48 (q, *J*=7.2 Hz, 1 H), 3.59 (s, 2 H), 3.27 - 3.37 (m, 2 H), 3.11 (m, 2 H), 2.71 - 2.84 (m, 1 H), 1.70 (d, *J*=7.2 Hz, 3 H). MS (ESI) m/z: Calculated: 447.1; Observed: 448.0 (M^++1).

Step 7: Stereochemical assignment of **5a** and **5b**:

rac-2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylethyl)thiazolo[5,4-b]pyridine (0.685 g) was resolved into component enantiomers by chiral supercritical fluid chromatography (Berger Multigram II SFC; Column: Chiralcel OJ-H(250x21mm, 5um); Mobile Phase: A: Liquid CO_2 B: Methanol; Isocratic: 30%B; Flow Rate: 65mL/min; Column/Oven Temperature: 40 ^oC; Outlet Pressure: 100 bar; UV at 270nm), to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-((S)-1-phenylethyl)thiazolo[5,4-b]pyridine (Peak 1, 0.280 g) and 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-((R)-1-phenylethyl)thiazolo[5,4-b]pyridine (Peak 2, 0.292 g). Analytical SFC indicated an enantiomeric excess of >99.9% for each enantiomer (Column: Chiralcel OJ-H (150 x 4.6 mm, 5 micron); Mobile Phase: A: Liquid CO_2 B: Methanol; Isocratic: 25%B; Flow Rate: 4.0 mL/min; Column/Oven Temperature: 40 ^oC; Outlet Pressure: 100 bar). Single crystals of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-((S)-1-phenylethyl)thiazolo[5,4-b]pyridine (Peak 1) were grown by diffusion (EtOAc/hexanes). Single crystal x-ray analysis established the (S) stereochemistry. 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-((S)-1-phenylethyl)thiazolo[5,4-b]pyridine was converted to (S)-1-(3-fluoro-4-(5-(1-phenylethyl)thiazolo[5,4-b]pyridin-2-yl)benzyl)azetidine-3-carboxylic acid (**5a**), which established the identity **5a** and **5b**.

Synthesis of **5c**



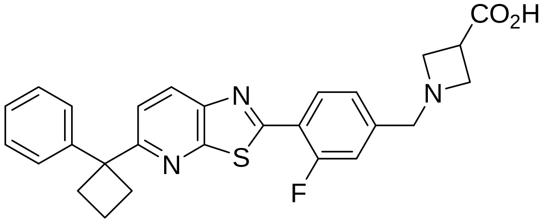
Step 1

Argon was bubbled through a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylethyl)thiazolo[5,4-b]pyridine (0.500 g, 1.19 mmol) in 5 mL DMF at ambient temperature. Sodium hexamethyldisilylazide, 1 M in THF (1.78 mL, 1.78 mmol) was added dropwise, and the resulting dark blue solution allowed to stir for 5 min. Iodomethane (0.297 mL, 4.76 mmol) was added rapidly dropwise, and the color faded to light yellow over several minutes. The reaction was quenched with saturated aqueous NH_4Cl and EA, and the organic layer was washed 1 x water, 1 x brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude reaction mixture was taken up in minimal DCM and purified by silica gel chromatography (40 g; 0-50-100% EA/hexanes). Product-containing fractions were combined and concentrated in vacuo to afford 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(2-phenylpropan-2-yl)thiazolo[5,4-b]pyridine (0.370 g, 71.6% yield) as a white solid: ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.36 (dd, *J*=8.0, 8.0 Hz, 1 H), 8.16 (d, *J*=8.5 Hz, 1 H), 7.38 - 7.48 (m, 2 H), 7.28 - 7.36 (m, 4 H), 7.14 - 7.25 (m, 2 H), 5.56 (s, 1 H), 4.31 (dd, *J*=11.0, 5.0 Hz, 2 H), 3.96 - 4.09 (m, 2 H), 2.16 - 2.38 (m, 1 H), 1.85 (s, 6 H), 1.50 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 434.1; Observed: 435.1 (M^++1).

Step 2

2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(2-phenylpropan-2-yl)thiazolo[5,4-b]pyridine (0.137 g, 0.32 mmol) was dissolved in 1 mL THF and 1 mL 5N HCl and heated to 80 °C for 1 h. The reaction was cooled and a precipitate formed. The reaction was treated with ice and 10 N NaOH, then extracted 3 x DCM. The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo to give 0.119 g yellow solid. This material was dissolved in 1 mL DCM and treated with azetidine-3-carboxylic acid (0.096 g, 0.95 mmol), acetic acid (0.091 mL, 1.6 mmol), and 1 mL MeOH. After 1 h, sodium cyanoborohydride (0.020 g, 0.32 mmol) was added. After 30 min, the reaction was concentrated under a stream of nitrogen, dissolved in DMSO+TFA and purified by RPHPLC (15-100% ACN/TFA in H_2O/TFA) and the product-containing fractions were combined and concentrated in vacuo to give 1-(3-fluoro-4-(5-(2-phenylpropan-2-yl)thiazolo[5,4-b]pyridin-2-yl)benzyl)azetidine-3-carboxylic acid trifluoroacetic acid salt (0.063 g, 35% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.14 (br. s., 1 H), 10.45 (br. s., 1 H), 8.33 - 8.46 (m, 2 H), 7.64 (d, *J*=12.0 Hz, 1 H), 7.53 (d, *J*=7.5 Hz, 1 H), 7.41 (d, *J*=8.5 Hz, 1 H), 7.24 - 7.34 (m, 4 H), 7.20 (dd, *J*=6.8, 6.8 Hz, 1 H), 4.47 (br. s., 2 H), 4.22 (br. s., 4 H), 3.55 - 3.71 (m, 1 H), 1.67 - 1.88 (m, 6 H). MS (ESI) m/z: Calculated: 461.2; Observed: 462.1 (M^++1).

Synthesis of **5e**



Step 1

To a solution of 1-bromo-2-fluoro-4-methylbenzene (10.0 g, 53 mmol) in 100 mL THF at -78 °C in a 500 mL 3-neck rbf with temperature monitor and addition funnel was added butyllithium 2.5 M in hexanes (23 mL, 58 mmol) slowly dropwise via addition funnel such that the temp did not exceed -72 °C. After 20 min, a solution of 2,6-dichloro-3-isothiocyanatopyridine (11 g, 53 mmol) in 35 mL THF was added slowly dropwise via addition funnel, and after 20 min, the reaction was quenched with saturated aqueous ammonium chloride, warmed to ambient temperature, and diluted with 100 mL MTBE. The organic layer was washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to an orange solid, 15.7 g. The solid was treated with sodium carbonate (11 g, 106 mmol), 100 mL DMF, and heated to 80 °C for 4 h under nitrogen. The resulting dark brown mixture was cooled slightly, and treated with ice and water until about 500 mL total volume. The mixture was stirred overnight, then the resulting precipitate was collected by filtration, washing with water, MeOH, and diethyl ether, dried in vacuo to give 5-chloro-2-(2-fluoro-4-methylphenyl)thiazolo[5,4-b]pyridine (8.5 g, 58% yield) as a tan solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.21 - 8.31 (m, 2 H), 7.46 (d, *J*=8.5 Hz, 1 H), 7.15 (d, *J*=8.0 Hz, 1 H), 7.08 (d, *J*=12.5 Hz, 1 H), 2.46 (s, 3 H). MS (ESI) m/z: calculated: 278.0; Observed: 279.0 (M^++1).

Step 2

5-chloro-2-(2-fluoro-4-methylphenyl)thiazolo[5,4-b]pyridine (8.00 g, 28.7 mmol), 1-phenylvinylboronic acid (9.34 g, 63.1 mmol), bis(4-(di-tert-butylphosphino)-N,N-dimethyl-benzenamine) palladium dichloride (0.508 g, 0.718 mmol), and potassium carbonate (13.9 g, 100 mmol) were combined in a 350 mL sealable reaction vessel. The reaction was flushed with argon, diluted with 100 mL dioxane and 30 mL water, sealed, and heated to 80 °C overnight. The reaction was cooled, and diluted with DCM and water. The resulting emulsion was filtered through celite, and the layers separated. The aqueous layer was extracted 3 x DCM, and the combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo to a thick oil. 100 mL Et_2O was added, and the slightly cloudy solution was cooled in the freezer, and the solid was isolated by filtration and dried in vacuo to give 2-(2-fluoro-4-methylphenyl)-5-(1-phenylvinyl)thiazolo[5,4-b]pyridine (7.60 g, 76.4% yield): ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.17 - 8.32 (m, 2 H), 7.34 - 7.46 (m, 6 H), 7.14 (d, *J*=8.0 Hz, 1 H), 7.08 (d, *J*=12.0 Hz, 1 H), 6.15 (s, 1 H), 5.69 (s, 1 H), 2.46 (s, 3 H). MS (ESI) m/z: calculated: 346.1; Observed: 347.1 (M^++1).

Step 3

A solution of N,N-dimethylacetamide (0.320 mL, 3.46 mmol) in 30 mL anhydrous 1,2-DCE in a 3-neck flask under argon fitted with addition funnel was cooled to -17 °C with ice/salt. Trifluoromethanesulfonic anhydride (0.679 mL, 4.04 mmol) was added over 2 min by syringe, and the reaction mixture became yellow and the temperature rose to -13 °C. After 5 min, a solution of 2,6-di-tert-butylpyridine (0.893 mL, 4.04 mmol) and 2-(2-fluoro-4-methylphenyl)-5-(1-phenylvinyl)thiazolo[5,4-b]pyridine (1.00 g, 2.89 mmol) in 15 mL DCE was added slowly dropwise via addition funnel over 10 min. The reaction was fitted with a water-cooled reflux condenser and placed in a 110 °C oil bath. After 1 h, the reaction mixture was allowed to cool to ambient temperature overnight. 45 mL water was added and the reaction mixture reheated to 110 °C. After 7 h, the reaction mixture was cooled, layers separated, and the aqueous layer was extracted with DCM. The combined organics were dried over sodium sulfate, filtered, and concentrated. The crude material was adsorbed onto 5 g silica gel and purify by silica gel chromatography, 0-100% EA/hexanes to give a yellow solid containing the desired product. This was further purified by trituration with diethyl ether to give 3-(2-(2-fluoro-4-methylphenyl)-thiazolo[5,4-b]pyridine-5-yl)-3-phenylcyclobutanone (0.241 g, 21.5% yield) as a light yellow solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.28 (dd, *J*=7.8, 7.8 Hz, 1 H), 8.20 (d, *J*=8.5 Hz, 1 H), 7.38 - 7.51 (m, 4 H), 7.32 (dd, *J*=6.8, 6.8 Hz, 1 H), 7.05 - 7.21 (m, 3 H), 4.11 - 4.25 (m, 2 H), 3.75 - 3.90 (m, 2 H), 2.46 (s, 3 H). MS (ESI) m/z: calculated: 388.1; Observed: 389.1 (M^++1).

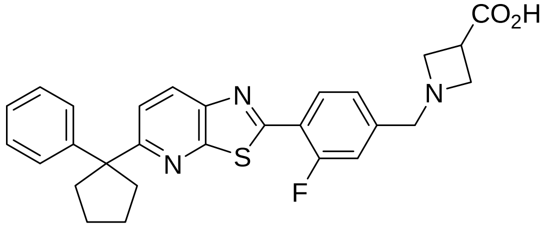
Step 4

To a thick slurry of p-methylbenzenesulfonylhydrazine (0.036 g, 0.19 mmol) and 3-(2-(2-fluoro-4-methylphenyl)thiazolo[5,4-b]pyridine-5-yl)-3-phenylcyclobutanone (0.050 g, 0.13 mmol) in 0.3 mL MeOH under nitrogen was added a pre-mixed suspension of sodium cyanoborohydride (0.016 g, 0.26 mmol) and zinc chloride, 0.5 M solution in THF (0.26 mL, 0.13 mmol) in 0.26 mL MeOH, via pipette. The reaction mixture was sealed and heated to 70 °C for 3 h. The reaction mixture was adsorbed onto 600 mg silica gel and dried. Purification by silica gel chromatography, 12 g, 0-50% EA/hexanes provided 2-(2-fluoro-4-methylphenyl)-5-(1-phenylcyclobutyl)-thiazolo[5,4-b]pyridine (0.012 g, 25% yield) as a light yellow oil that slowly solidified: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.14 - 8.26 (m, 2 H), 7.43 (d, *J*=7.5 Hz, 2 H), 7.29 - 7.36 (m, 3 H), 7.19 (dd, *J*=7.3, 7.3 Hz, 1 H), 7.12 (d, *J*=8.0 Hz, 1 H), 7.07 (d, *J*=12.0 Hz, 1 H), 3.03 - 3.19 (m, 2 H), 2.76 - 2.90 (m, 2 H), 2.44 (s, 3 H), 1.95 - 2.12 (m, 2 H). MS (ESI) m/z: calculated: 374.1; Observed: 375.1 (M^++1).

Step 5

A slurry of 2-(2-fluoro-4-methylphenyl)-5-(1-phenylcyclobutyl)thiazolo[5,4-b]pyridine (0.059 g, 0.16 mmol), AIBN (0.013 g, 0.079 mmol), and N-bromosuccinimide (0.034 g, 0.19 mmol) in 1 mL CCl_4 in a sealed tube was heated to 100 °C for 30 min. The reaction mixture became clear, then a precipitate formed. Allowed to stir 30 min longer, then cooled and allowed to stand overnight. The solvent was removed and the crude material treated with methyl azetidine-3-carboxylate hydrochloride (0.14 g, 0.95 mmol) and N,N-diisopropylethylamine (0.27 mL, 1.6 mmol), and 1 mL DMF. The solution was sealed and heated to 100 °C for 30 min. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EA, and the organic layer was washed with water, brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting material was dissolved in 2 mL THF and treated with NaOH 1.0 M (0.47 mL, 0.47 mmol). After 1 h, the reaction mixture was concentrated under nitrogen stream, and treated with 2 mL DMSO and TFA until a solution resulted. The solution was filtered and purified by RPHPLC, 10-100% TFA/ACN in TFA/H_2O to give 1-(3-fluoro-4-(5-(1-phenylcyclobutyl)thiazolo[5,4-b]pyridine-2-yl)benzyl)azetidine-3-carboxylic acid trifluoroacetic acid salt (0.023 g, 25% yield) as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.18 (br. s., 1 H), 10.66 (br. s., 1 H), 8.32 - 8.45 (m, 2 H), 7.59 - 7.71 (m, 1 H), 7.53 (dd, *J*=8.0, 4.0 Hz, 2 H), 7.41 (d, *J*=7.5 Hz, 2 H), 7.31 (dd, *J*=7.8, 7.8 Hz, 2 H), 7.17 (dd, *J*=7.3, 7.3 Hz, 1 H), 4.49 (s, 2 H), 4.14 - 4.33 (m, 4 H), 3.57 - 3.71 (m, 1 H), 2.93 - 3.05 (m, 2 H), 2.67 - 2.82 (m, 2 H), 1.82 - 1.99 (m, 2 H). MS (ESI) m/z: calculated: 473.2; Observed: 474.1 (M^++1).

Synthesis of **5f**



Step 1

To a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-benzylthiazolo[5,4-b]pyridine (2.28 g, 5.6 mmol) in 40 mL DMF under argon was added lithium bis(trimethylsilyl)amide, 1.0m solution in tetrahydrofuran (7.0 mL, 7.0 mmol). A very deep blue solution resulted. After 2 min, allyl iodide (0.77 mL, 8.4 mmol) was added via syringe and the reaction became brown. After 5 min, saturated aqueous NH_4Cl was added and the reaction partitioned between water and EA. The organic was washed with water, brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting material was sonicated in MTBE, filtered, and dried to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylbut-3-enyl)thiazolo[5,4-b]pyridine (1.66 g, 66% yield) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.39 (d, *J*=8.5 Hz, 1 H), 8.34 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.61 (d, *J*=8.5 Hz, 1 H), 7.38 - 7.51 (m, 4 H), 7.30 (m, 2 H), 7.13 - 7.22 (m, 1 H), 5.65 - 5.78 (m, 1 H), 5.64 (s, 1 H), 5.04 (d, *J*=17.6 Hz, 1 H), 4.91 (d, *J*=10.5 Hz, 1 H), 4.42 (dd, *J*=7.8, 7.8 Hz, 1 H), 4.18 (dd, *J*=11.5, 5.0 Hz, 2 H), 3.98 (dd, *J*=11.3, 11.3 Hz, 2 H), 3.01 - 3.16 (m, 1 H), 2.79 - 2.94 (m, 1 H), 1.93 - 2.15 (m, 1 H), 1.48 (d, *J*=12.5 Hz, 1 H). MS (ESI) m/z: Calculated: 446.2; Observed: 447.1 (M^++1).

Step 2

To a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylbut-3-enyl)-thiazolo[5,4-b]pyridine (1.17 g, 2.62 mmol) in 20 mL DMF under argon was added sodium bis(trimethylsilyl)amide, 1.0 M solution in tetrahydrofuran (3.28 mL, 3.28 mmol). The reaction mixture became deep blue/purple. After 2 min, allyl iodide (0.362 mL, 3.93 mmol) was added and the reaction became light orange after 1 min. After 5 min total, the reaction mixture was quenched with saturated aqueous NH_4Cl, EtOAc, and water. The organic layer was washed with water, brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography, ISCO, 80 g, 0-40% EA/hexanes to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(4-phenylhepta-1,6-dien-4-yl)thiazolo[5,4-b]pyridine (1.07 g, 83.9% yield) as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.29 - 8.42 (m, 2 H), 7.43 - 7.56 (m, 2 H), 7.26 - 7.39 (m, 3 H), 7.12 - 7.25 (m, 3 H), 5.64 (s, 1 H), 5.32 - 5.49 (m, 2 H), 4.89 - 5.08 (m, 4 H), 4.19 (dd, *J*=11.0, 5.0 Hz, 2 H), 3.92 - 4.05 (m, 2 H), 2.99 - 3.18 (m, 4 H), 1.92 - 2.14 (m, 1 H), 1.49 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 486.2; Observed: 487.1 (M^++1).

Step 3

To a solution of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(4-phenylhepta-1,6-dien-4-yl)thiazolo[5,4-b]pyridine (1.07 g, 2.20 mmol) in 44 mL DCM under argon was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (93.3 mg, 0.110 mmol). The reaction mixture became red-brown and was fitted with a water-cooled reflux condenser and heated to reflux. After 5 h, the reaction mixture was cooled, concentrated in vacuo, loaded onto an 80 g silica gel column, and purified with a gradient of 0-30% EA/hexanes to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclopent-3-enyl)thiazolo[5,4-b]pyridine (0.930 g, 92.2% yield) as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.29 - 8.40 (m, 2 H), 7.54 (d, *J*=9.0 Hz, 1 H), 7.42 - 7.50 (m, 2 H), 7.24 - 7.33 (m, 4 H), 7.12 - 7.21 (m, 1 H), 5.79 - 5.88 (m, 2 H), 5.63 (s, 1 H), 4.18 (dd, *J*=11.0, 5.0 Hz, 2 H), 3.92 - 4.04 (m, 2 H), 3.52 (d, *J*=14.6 Hz, 2 H), 3.02 (d, *J*=14.6 Hz, 2 H), 1.92 - 2.14 (m, 1 H), 1.48 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 458.2; Observed: 459.1 (M^++1).

Step 4

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclopent-3-enyl)-thiazolo[5,4-b]pyridine (0.550 g, 1.20 mmol) in 8 mL 1:1 THF/5N HCl was heated to 70 °C in a sealed vial. After 30 min, the reaction mixture was cooled, treated with ice, 10N NaOH until basic, and EA. The organic layer was washed with water, brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give a 0.48 g of a solid, which was treated with methyl azetidine-3-carboxylate hydrochloride (0.365 g, 2.41 mmol), 4 mL DCM, diisopropylethylamine (0.419 mL, 2.41 mmol), and acetic acid (0.278 mL, 4.81 mmol), followed by 4 mL MeOH. The resulting yellow solution was allowed to stir for 1 h, and sodium cyanoborohydride (0.0756 g, 1.20 mmol) was added in one portion. The resulting cloudy mixture was allowed to stir 2 h, and the reaction was concentrated in vacuo and partitioned between DCM and saturated aqueous $NaHCO_3$. The aqueous layer was extracted 3 x DCM, dried over sodium sulfate, filterd, and concentrated. The resulting oil was purified by silica gel chromatography, 40 g, 0-50-100% EA/hexanes to give methyl 1-((3-fluoro-4-(5-(1-phenylcyclopent-3-enyl)thiazolo[5,4-b]pyridin-2-

yl)phenyl)methyl)azetidine-3-carboxylate (0.419 g, 69.7% yield) as an oil which partially solidified to a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.35 (d, *J*=8.5 Hz, 1 H), 8.26 (dd, *J*=7.8, 7.8 Hz, 1 H), 7.53 (d, *J*=8.5 Hz, 1 H), 7.32 - 7.41 (m, 2 H), 7.23 - 7.31 (m, 4 H), 7.10 - 7.21 (m, 1 H), 5.83 (s, 2 H), 3.66 (s, 2 H), 3.64 (s, 3 H), 3.44 - 3.57 (m, 4 H), 3.23 - 3.40 (m, 3 H), 3.02 (d, *J*=15.1 Hz, 2 H). MS (ESI) m/z: Calculated: 499.0; Observed: 500.1 (M^++1).

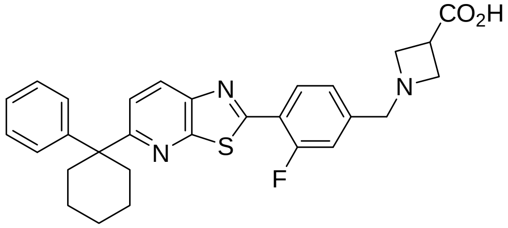
Step 5

To a mixture of methyl 1-((3-fluoro-4-(5-(1-phenylcyclopent-3-enyl)thiazolo[5,4-b]pyridine-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.333 g, 0.667 mmol) and 10% Pd/C, 50% water (0.355 g, 0.333 mmol) under nitrogen was added 5 mL MeOH and 5 mL THF. The resulting mixture was stirred rapidly under an H_2 balloon for 4 h. The reaction mixture was flushed with nitrogen, filtered, rinsing with DCM, and concentrated in vacuo. The resulting oil was purified by silica gel chromatography, 0-100% EA/hexanes, to give methyl 1-((3-fluoro-4-(5-(1-phenylcyclopentyl)thiazolo[5,4-b]pyridine-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.321 g, 96.0% yield) as a clear and colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (d, *J*=8.5 Hz, 1 H), 8.25 (dd, *J*=7.8, 7.8 Hz, 1 H), 7.53 (d, *J*=8.5 Hz, 1 H), 7.23 - 7.42 (m, 6 H), 7.12 - 7.20 (m, 1 H), 3.66 (s, 2 H), 3.64 (s, 3 H), 3.47 (dd, *J*=7.0, 7.0 Hz, 2 H), 3.32 - 3.40 (m, 1 H), 3.26 (dd, *J*=6.5, 6.5 Hz, 2 H), 2.69 - 2.82 (m, 2 H), 2.19 - 2.31 (m, 2 H), 1.52 - 1.75 (m, 4 H). MS (ESI) m/z: Calculated: 501.2; Observed: 502.1 (M^++1).

Step 6

To a solution of methyl 1-((3-fluoro-4-(5-(1-phenylcyclopentyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.321 g, 0.64 mmol) in 3 mL THF was added 1.7 mL water and sodium hydroxide 1.0 M in water (1.3 mL, 1.3 mmol). The reaction was stirred for 3 h. The cap was removed and THF allowed to evaporate off overnight. The resulting white solid was treated with 1.3 mL 1N HCl, water, and 4 mL 1M pH 6 sodium phosphate buffer. The material was stirred rapidly for 10 min, then filtered, rinsing with water, and EtOH. The filter paper and gummy material was treated with 1L MeOH and heated to 60 deg, then filtered. The filtrate was concentrated in vacuo to give 1-((3-fluoro-4-(5-(1-phenylcyclopentyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylic acid (0.233 g, 75% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.32 (d, *J*=8.5 Hz, 1 H), 8.24 (dd, *J*=7.8, 7.8 Hz, 1 H), 7.53 (d, *J*=8.5 Hz, 1 H), 7.23 - 7.43 (m, 6 H), 7.15 (dd, *J*=7.3, 7.3 Hz, 1 H), 3.65 (s, 2 H), 3.38 - 3.50 (m, 2 H), 3.19 - 3.29 (m, 3 H), 2.68 - 2.82 (m, 2 H), 2.25 (m, 2 H), 1.53 - 1.79 (m, 4 H). MS (ESI) m/z: Calculated: 487.2; Observed: 488.1 (M^++1).

Synthesis of **5g**



Step 1

Argon was bubbled through a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-benzylthiazolo[5,4-b]pyridine (1.00 g, 2.46 mmol) in 20 mL DMF for 5 min. To the rapidly stirring reaction mixture was added LiHMDS 1.0M in THF (2.71 mL, 2.71 mmol) rapidly dropwise. The resulting deep blue reaction mixture was stirred for 2 min, at which point 4-bromo-1-butene (0.499 mL, 4.92 mmol) was added rapidly via syringe. The color of the reaction slowly became purple over 5 min, then brown over about 10-15 min additional. After 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and MTBE. The organic layer was washed with water, brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylpent-4-enyl)thiazolo[5,4-b]pyridine (1.02 g, 90.0% yield) as an orange solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.36 (dd, *J*=7.8, 7.8 Hz, 1 H), 8.19 (d, *J*=8.5 Hz, 1 H), 7.36 - 7.47 (m, 4 H), 7.28 - 7.35 (m, 3 H), 7.16 - 7.25 (m, 1 H), 5.77 - 5.95 (m, 1 H), 5.56 (s, 1 H), 4.94 - 5.05 (m, 2 H), 4.31 (dd, *J*=11.3, 4.8 Hz, 2 H), 4.25 (t, *J*=7.8 Hz, 1 H) 4.03 (dd, *J*=11.0, 11.0 Hz, 2 H), 2.38 - 2.55 (m, 1 H), 2.17 - 2.35 (m, 2 H), 1.99 - 2.13 (m, 2 H), 1.50 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 460.2; Observed: 461.1 (M^++1).

Step 2

Argon was bubbled through a slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylpent-4-enyl)thiazolo[5,4-b]pyridine (1.02 g, 2.21 mmol) in 20 mL DMF for 5 min. The slurry was treated with sodium bis(trimethylsilyl)amide, 1.0M solution in tetrahydrofuran (2.66 mL, 2.66 mmol) rapidly via syringe, to give a dark blue solution. After 2 min, allyl iodide (0.306 mL, 3.32 mmol) was added via syringe, and the color gradually faded from blue to light brown. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and MTBE. The organic layer was washed with water, brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting oil was dissolved in DCM, adsorbed onto 7 g silica gel, dried, and purified by silica gel chromatography, 40 g, gradient, 0-50% EA/hexanes, to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(4-phenylocta-1,7-dien-4-yl)thiazolo[5,4-b]pyridine (0.580 g, 52.3% yield) as a light yellow foam: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.37 (dd, *J*=8.0, 8.0 Hz, 1 H), 8.17 (d, *J*=8.5 Hz, 1 H), 7.39 - 7.48 (m, 2 H), 7.27 - 7.34 (m, 4 H), 7.19 - 7.25 (m, 3 H), 7.16 (d, *J*=8.5 Hz, 1 H), 5.70 - 5.86 (m, 1 H), 5.57 (s, 1 H), 5.35 - 5.51 (m, 1 H), 4.84 - 5.10 (m, 4 H), 4.32 (dd, *J*=11.0, 4.5 Hz, 2 H), 4.03 (dd, *J*=11.3, 11.3 Hz, 2 H), 3.18 - 3.29 (m, 1 H), 3.02 - 3.14 (m, 1 H), 2.34 - 2.48 (m, 2 H), 2.17 - 2.32 (m, 1 H), 1.82 - 1.96 (m, 1 H), 1.64 - 1.80 (m, 1 H), 1.50 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 500.2; Observed: 501.1 (M^++1).

Step 3

To a solution of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(4-phenylocta-1,7-dien-4-yl)thiazolo[5,4-b]pyridine (0.580 g, 1.16 mmol) in 22 mL DCM under argon was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (0.0492 g, 0.0579 mmol). The flask was fitted with a water-cooled reflux condenser and heated to reflux. The reaction was checked after 4 h and judged complete. Silica gel (4 g) was added and the reaction mixture was dried, purified by silica gel chromatography, gradient, 0-100% EA/hexanes, to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclohex-3-enyl)thiazolo[5,4-b]pyridine (0.492 g, 89.9% yield) as a foam/oil which solidified to an off-white solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.35 (dd, *J*=7.8, 7.8 Hz, 1 H), 8.14 (d, *J*=8.5 Hz, 1 H), 7.36 - 7.47 (m, 2 H), 7.25 - 7.31 (m, 4 H), 7.15 - 7.25 (m, 2 H), 5.89 (d, *J*=9.5 Hz, 1 H), 5.65 (d, *J*=9.5 Hz, 1 H), 5.56 (s, 1 H), 4.31 (dd, *J*=11.0, 4.5 Hz, 2 H), 4.02 (dd, *J*=11.3, 11.3 Hz, 2 H), 2.87 - 2.99 (m, 1 H), 2.66 - 2.82 (m, 2 H), 2.46 - 2.56 (m, 1 H), 2.17 - 2.34 (m, 1 H), 1.74 - 2.01 (m, 2 H), 1.50 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 472.2; Observed: 473.2 (M^{+}+1).

Step 4

A mixture of 10% palladium on carbon, 50% water wet (0.33 g, 0.31 mmol) and 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclohex-3-enyl)thiazolo[5,4-b]pyridine (0.492 g, 1.0 mmol) under nitrogen was treated with 10 mL THF and exposed to 1 atm H_2 gas via balloon. The reaction mixture was allowed to stir 36 h, then was flushed with nitrogen, filtered, rinsing with DCM. The filtrate was concentrated in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclohexyl)thiazolo[5,4-b]pyridine (0.467 g, 95% yield) as a light yellow solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.34 (dd, *J*=7.8, 7.8 Hz, 1 H), 8.14 (d, *J*=8.5 Hz, 1 H), 7.34 - 7.48 (m, 4 H), 7.24 - 7.32 (m, 3 H), 7.16 (dd, *J*=7.3, 7.3 Hz, 1 H), 5.56 (s, 1 H) 4.31 (dd, *J*=11.5, 5.0 Hz, 2 H), 4.02 (dd, *J*=11.3, 11.3 Hz, 2 H), 2.63 - 2.77 (m, 2 H), 2.18 - 2.37 (m, 3 H), 1.42 - 1.72 (m, 7 H). MS (ESI) m/z: Calculated: 474.2; Observed: 475.1 (M^{+}+1).

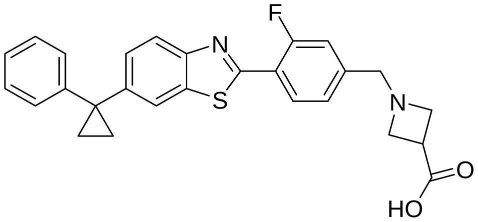
Step 5

A slurry of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylcyclohexyl)-thiazolo[5,4-b]pyridine (0.467 g, 0.984 mmol) in 5 mL 1:1 THF/5N HCl was sealed and heated to 80 °C. The resulting yellow solution was allowed to stir 3 h, was cooled, and then was treated with ice and 10N NaOH until basic. The reaction mixture was partitioned between EA and water, washed with water, brine, dried over sodium sulfate, filtered, concentrated in vacuo to give 0.36 g of material which was treated with methyl azetidine-3-carboxylate hydrochloride (0.388 g, 2.56 mmol), 2 mL DCM, acetic acid (0.244 mL, 4.26 mmol), N,N-diisopropylethylamine (0.445 mL, 2.56 mmol), and 2 mL MeOH. After 1 h, sodium cyanoborohydride (0.0536 g, 0.852 mmol) was added and the reaction was allowed to stir overnight. In the morning the reaciton was concentrated under a stream of nitrogen, acid was quenched with saturated aqueous $NaHCO_3$, and the mixture was partitioned between water and DCM. The aqueous layer was extracted 3 x DCM, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting oil was purified by silica gel chromatography, 40 g, 0-100% EA/hexanes to give methyl 1-((3-fluoro-4-(5-(1-phenylcyclohexyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.290 g, 66.0% yield) as an oil which slowly solidified to a white solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.27 (dd, *J*=8.0, 8.0 Hz, 1 H), 8.12 (d, *J*=8.5 Hz, 1 H), 7.35 - 7.44 (m, 2 H), 7.12 - 7.33 (m, 6 H), 3.74 (s, 3 H), 3.70 (br. s., 2 H), 3.61 (br. s., 2 H), 3.39 (br. s., 3 H), 2.62 - 2.73 (m, 2 H), 2.22 - 2.35 (m, 2 H), 1.41 - 1.70 (m, 6 H). MS (ESI) m/z: Calculated: 515.2; Observed: 516.1 (M^{+}+1).

Step 6

To a solution of methyl 1-((3-fluoro-4-(5-(1-phenylcyclohexyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.290 g, 0.562 mmol) in 3 mL THF was added sodium hydroxide 1.0 M in water (1.12 mL, 1.12 mmol). The slightly cloudy, light yellow mixture was allowed to stir overnight. In the morning the THF was removed under a stream of nitrogen, and the mixture diluted with water, and the base was quenched with 1.1 mL 1N HCl. The resulting mixture was treated with 2-3 mL 1M pH 6 sodium phosphate buffer, additional water, and allowed to stir rapidly overnight. The slurry was diluted with water and then filtered, rinsed with 2 x EtOH, and the wet solid was transferred to a vial and dried in vacuo to give 1-((3-fluoro-4-(5-(1-phenylcyclohexyl)thiazolo[5,4-b]pyridin-2-yl)phenyl)methyl)azetidine-3-carboxylic acid (0.219 g, 77.6% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 (d, *J*=8.5 Hz, 1 H), 8.25 (dd, *J*=8.0, 8.0 Hz, 1 H), 7.53 (d, *J*=8.5 Hz, 1 H), 7.24 - 7.43 (m, 6 H), 7.14 (dd, *J*=7.3, 7.3 Hz, 1 H), 3.66 (s, 2 H), 3.45 (s, 2 H), 3.18 - 3.29 (m, 3 H), 2.59 - 2.73 (m, 2 H), 2.16 - 2.30 (m, 2 H), 1.35 - 1.65 (m, 6 H). MS (ESI) m/z: Calculated: 501.2; Observed: 502.1 (M^++1).

Synthesis of **6**



Step 1

Thiophosgene (22 mL, 289 mmol) was added to a suspension of sodium carbonate (61.0 g, 579 mmol) and 4-bromo-2-fluoroaniline (50.0 g, 263 mmol) in $CHCl_3$ (1L). The reaction mixture was stirred overnight at ambient temperature, the inorganic salts were filtered off, and the filtrate was concentrated to give 4-bromo-2-fluoro-1-isothiocyanatobenzene (61.1 g, quant.) as a tan solid: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.33 (dd, *J*=9.0, 2.2 Hz, 1 H), 7.23 - 7.28 (m, 1 H), 7.05 (dd, *J*=8.2, 8.2 Hz, 1 H).

Step 2

n-Butyllithium 2.5 M in hexanes (22 mL, 55 mmol) was added to a solution of 2-(4-bromo-3-fluorophenyl)-1,3-dioxane (13 g, 50 mmol) in THF (200 mL) at -78 °C. The resulting light yellow solution was stirred for 15 min, then a solution of 4-bromo-2-fluoro-1-isothiocyanatobenzene (11500 mg, 50 mmol) in THF (10 mL) was added. The mixture was stirred for 30 min, quenched with NH_4Cl (saturated aqueous), and warmed to ambient temperature. The organic layer was separated and washed with brine, dried ($MgSO_4$), and concentrated to 1/4 volume, at which time solution became suspension. The solid was filtered off and dried to give a yellow solid, which was dissolved in DMF (150 mL) and then heated to 110 °C overnight in the presence of Na_2CO_3 (1 equiv, 26 mmol, 2.76 g), cooled to ambient temperature, and treated with water. The resulting suspension was filtered, washed with water, and dried to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-bromobenzo[d]thiazole (9.81 g, 50%) as a light yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.51 (d, *J*=2.0 Hz, 1 H), 8.38 (dd, *J*=7.9, 7.9 Hz, 1 H), 8.06 (d, *J*=8.8 Hz, 1 H), 7.74 (dd, *J*=8.7, 2.1 Hz, 1 H), 7.42 - 7.52 (m, 2 H), 5.64 (s, 1 H), 4.19 (dd, *J*=10.7, 5.0 Hz, 2 H), 3.99 (ddd, *J*=12.1, 12.1, 2.5 Hz, 2 H), 1.93 - 2.13 (m, 1 H) 1.49 (ddd, *J*=13.5, 1.3, 1.3 Hz, 1 H). MS (ESI) m/z: Calculated: 393.0 ; Observed: 394.0 (M^++1).

Step 3

A slurry of bis(4-(di-tert-butylphosphino)-N,N-dimethyl-benzenamine) palladium dichloride (0.114 g, 0.161 mmol), potassium carbonate (2.85 g, 20.6 mmol), 1-phenylvinylboronic acid (2.10 g, 14.2 mmol), 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-

bromobenzo[d]thiazole (2.54 g, 6.44 mmol) in 20 mL dioxane/4 mL water was flushed with argon and sealed, and heated at 90 °C overnight. In the morning the reaction mixture was cooled and judged complete by LCMS. The reaction mixture was partitioned between EA/H_2O and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to give a solid. The material was suspended in MeOH, and filtered. The resulting solid was dried in vacuo to give 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-(1-phenylvinyl)benzo[d]thiazole (1.87 g, 69.5% yield) as a dull yellow solid: ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 8.39 (dd, *J*=8.0, 8.0 Hz, 1 H), 8.15 (s, 1 H), 8.10 (d, *J*=8.5 Hz, 1 H), 7.32 - 7.54 (m, 8 H), 5.64 (s, 2 H), 5.60 (s, 1 H), 4.19 (dd, *J*=11.3, 4.8 Hz, 2 H), 3.99 (dd, *J*=12.0, 12.0 Hz, 2 H), 1.91 - 2.15 (m, 1 H), 1.49 (d, *J*=13.6 Hz, 1 H). MS (ESI) m/z: Calculated: 417.1 ; Observed: 418.0 (M^++1).

Step 4

In a reactor bottle (trimethylsilyl)diazomethane, 2.0 M in diethyl ether (2.4 mL, 4.8 mmol) was added to a mixture of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-(1-phenylvinyl)benzo[d]thiazole (0.650 g, 1.6 mmol), in anhydrous dioxane (15 mL). The reaction mixture was heated to 150 °C for 18 h. The crude reaction mixture was concentrated in vacuo and purified by silica gel chromatography to afford 1.3 g of material containing 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-(1-phenyl-2 (trimethyl-silyl)cyclopropyl)benzo[d]thiazole. This material was treated with neat tetrabutylammonium fluoride (25 mL, 25 mmol) in a reactor bottle. The reaction mixture was heated to 110 °C in an oil bath and allowed to stir for 2 h. The mixture was cooled and extracted with EtOAc and water, dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography afforded 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-(1-phenylcyclopropyl)benzo[d]thiazole (0.415 g, 60%): ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.39 (dd, *J*=7.9, 7.9 Hz, 1 H), 8.01 (d, *J*=8.5 Hz, 1 H), 7.79 (d, *J*=1.2 Hz, 1 H), 7.16 - 7.47 (m, 8 H), 5.55 (s, 1 H), 4.31 (dd, *J*=11.0, 4.8 Hz, 2 H), 3.95 - 4.09 (m, 2 H), 2.15 - 2.37 (m, 1 H), 1.49 (d, *J*=13.6 Hz, 1 H), 1.40 (s, 4 H). MS (ESI) m/z: Calculated: 431.1; Observed: 432.1(M^++1).

Step 5

A mixture of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-6-(1-phenylcyclopropyl)-benzo[d]thiazole (0.061g, 0.14 mmol) and 5N aqueous HCl (3.50 mL, 0.14 mmol) in THF (7.0 mL) was heated to 70 °C for 3 h. The reaction was cooled and concentrated in vacuo, placed in an ice bath, and basified with 5 N aqueous NaOH. The solid was collected by filtration, rinsed with water and MeOH, and was dried in vacuo to afford 3-fluoro-4-(6-(1-phenylcyclopropyl)benzo[d]thiazol-2-yl)benzaldehyde (0.050 g, 95%): ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 10.07 (d, *J*=1.8 Hz, 1 H), 8.62 - 8.78 (m, 1 H), 8.09 (d, *J*=8.6 Hz, 1 H), 7.80 - 7.89 (m, 2 H), 7.76 (dd, *J*=10.8, 1.0 Hz, 1 H), 7.46 (d, *J*=6.9 Hz, 1 H), 7.17 - 7.37 (m, 5 H), 1.42 (s, 4 H). MS (ESI) m/z: Calculated: 373.1 ; Observed: 374.0 (M^++1).

Step 6

A mixture of 3-fluoro-4-(6-(1-phenylcyclopropyl)benzo[d]thiazol-2-yl)benzaldehyde (0.050 g, 0.13 mmol), methyl azetidine-3-carboxylate hydrochloride (0.030 g, 0.20 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.035 mL, 0.20 mmol) in dichloromethane (2.0 mL, 0.13 mmol) and methanol (2.0 mL, 0.13 mmol) was stirred for 5 min. Acetic acid (0.031 mL, 0.54 mmol) was added, and the solution was allowed to stir for 60 min, at which time the reaction was treated with $NaCNBH_3$ (0.0042 g, 0.067

mmol). The solvent was removed in vacuo and the material adsorbed onto silica gel. Purification by silica gel chromatography, 12 g, 20-30 % EtOAc/hexanes, followed by 40% (3% TEA in EtOAc)/hexanes provided methyl 1-((3-fluoro-4-(6-(1-phenylcyclopropyl)benzo[d]thiazol-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.056 g, 89%): ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.32 (dd, *J*=7.9, 7.9 Hz, 1 H), 8.00 (d, *J*=8.5 Hz, 1 H), 7.79 (d, *J*=1.6 Hz, 1 H), 7.41 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.14 - 7.34 (m, 7 H), 3.73 (s, 3 H), 3.69 (s, 2 H), 3.54 - 3.64 (m, 2 H), 3.32 - 3.43 (m, 3 H), 1.40 (s, 4 H). MS (ESI) m/z: Calculated: 472.2; Observed: 473.1 (M^++1).

Step 7

To a solution of methyl 1-((3-fluoro-4-(6-(1-phenylcyclopropyl)benzo[d]thiazol-2-yl)phenyl)methyl)azetidine-3-carboxylate (0.0562 g, 0.12 mmol) in THF (2.00 mL) was added a solution of lithium hydroxide (0.014 g, 0.59 mmol) in 1.0 mL of water. Upon completion, the THF was removed in vacuo, the resulting aqueous solution was acidified to pH 1 with 1N HCl. The resulting solid was collected by filtration and rinsed with water and diethyl ether. The solid was dried in vacuo for 3 h at 50 °C to give 1-((3-fluoro-4-(6-(1-phenylcyclopropyl)benzo[d]thiazol-2-yl)phenyl)methyl)azetidine-3-carboxylic acid hydrochloride (0.041 g, 70%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.98 (br. s., 1 H), 8.35 (d, *J*=7.7, 7.7 Hz, 1 H), 8.09 (s, 1 H), 8.01 (d, *J*=8.4 Hz, 1 H), 7.55 (d, *J*=11.2 Hz, 1 H), 7.40 - 7.49 (m, 2 H), 7.24 - 7.35 (m, 4 H), 7.16 - 7.23 (m, 1 H), 4.16 (br. s., 2 H), 3.75 - 4.02 (m, 3 H), 3.48 (br. s., 2 H), 1.28 - 1.44 (m, 4 H). MS (ESI) m/z: Calculated: 458.2; Observed: 459.1 (M^++1).

hS1PR Cellular Assays

The hS1P1 receptor internalization assay was performed using a U2OS cell line expressing hS1P1-eGFP chimeric protein (Thermo Scientific, Søborg, Denmark). Upon compound treatment, the hS1P1 receptor was internalized into the cytoplasm, forming GFP-containing-endosomes. This event was detected using an ArrayScan automated microscope (Thermo Scientific Cellomics, Pittsburg, PA), and the degree of receptor internalization was quantitated by counting the number of GFP-containing endosomes per cell. hS1P1-eGFP expressing U2OS cells were starved in serum free media for two hours prior to compound treatment. Compounds were incubated with the starved cells at 37 °C for one hour. Compound-treated cells were subsequently fixed using 4% formaldehyde, and nuclei were stained using Hoechst dye (Invitrogen/Molecular Probes, Cat. #H3570). The cells were then imaged by ArrayScan, and the potency and efficacy of the compounds were determined by plotting the number of GFP-containing endosomes per cell against corresponding compound concentration.

The Ca^{2+}-mobilization assay was performed using CHO cell lines stably co-expressing $hS1P_3$ receptor and a chimeric $G_{q/i5}$ G-protein (50K cells/well). S1P (a known agonist, solubilized in 0.4% fatty acid free BSA) or compound treatment of these cells activated the PLC-β/IP3 pathway, triggering release of Ca^{2+} from intracellular storage (e.g., the ER). Cells were loaded with Ca^{2+} sensitive fluorescent dye (Calcium Indicator Dye, Cat. #51-9000177BK, BD Biosciences) and a fluorescence quencher (PBX Signal Enhancer, Cat. #51-9006254, BD Biosciences) with a ratio of dye:quencher:buffer of 1:100:1000 and 50 μL total volume, 60-90 minutes prior to compound treatment. Intracellular Ca^{2+} release resulted in Ca^{2+} binding to the dye and fluorescence (525 nm emission wavelength) of the dye upon excitation at 480 nm. The level of receptor activation was quantitated by measuring fluorescence intensity following compound treatment. In this assay, cells were starved in medium containing charcoal/dextran stripped serum for 16–20 hours. Compounds were added to cells loaded with Ca^{2+} sensitive dye and fluorescence quencher inside a FLIPR plate reader (Molecular Devices, Sunnyvale, CA), and the fluorescence signal was measured. CHO cells expressing only the chimeric $G_{q/i5}$ G-protein were employed as a negative control. The potency and efficacy of the compounds were determined by plotting fluorescence intensity against corresponding compound concentration.

Rat Lymphocyte Depletion Study

Female Lewis rats (150-175 grams, 6-8 wks) were received from Charles River Laboratories and allowed to acclimatize for at least one week before being placed on study. Rats (n = 5/group) were administered vehicle (20% captisol in water) or compound or **5d** at 0.01, 0.03, 0.1 mg/kg (20% captisol in water orally (po, 10 mL/kg) at time 0. 24 h postdose, animals were sacrificed by CO_2 inhalation. Using a 18G needle and 1 cc syringe, blood was collected by cardiac puncture. Approximately 500 μL of blood was placed in a microtainer tube containing EDTA (BD #365973), and the sample was mixed thoroughly. Differential cell counts were perfomed using an Advia 120 hematology system by Bayer.

Rat Experimental Autoimmune Encephalomyelitis Study

In a blinded study, 11-week old female Lewis rats (n = 15 per group) were immunized in the right footpad with 60 µg of guinea pig myelin basic protein (Bachem Americas, Torrance, CA. Catalog #H-6875) in CFA (Adjuvant Complete H37 Ra, Difco Laboratories, Detroit, MI. Catalog #F5506) containing 100 mg of dessicated *M. tuberculosis* H37 Ra (Difco Laboratories, Detroit, MI). Compound **5d** was administered to rats (PO at 20 µg/rat, approximating 0.1 mg/kg, formulated in 20% captisol in water, pH 2, CyDex Pharmaceuticals, Inc., Lenexa, KS) daily beginning on the day of immunization. Beginning on day 9, rats were scored daily for EAE on a scale ranging from 0 to 6 based on limb paralysis. On day 20, rats received a final EAE score, were euthanized via CO_2 inhalation, and blood was collected via cardiac puncture for complete blood count and pharmacokinetic drug analysis. Clinical scores are expressed as the mean ± standard error. The Wilcoxon Exact 2-sided Test of equivalence was used to asses mean clinical score for each time point for this study. Each treatment group was compared to the immunized plus vehicle group without an adjustment to the p-values for the multiple comparisons. Analyses were performed using SAS version 9.1 on a Windows NT Professional operating system. All comparisons use the 0.05 alpha level to determine significance. A p-value of ≤ 0.05 was considered significant.

Disease onset was defined as a score of 0.5 (see values below).

Clinical disease scoring was noted as follows:

0 : no sign
0.5 : distal limp tail
1 : limp tail
2 : mild paraparesis, ataxia
3 : moderate paraparesis
3.5: one hind leg paralysis
4.0 : complete hind leg paralysis
5 : complete hind leg paralysis and incontinence
5.5: tetraplegia
6 : moribund state or death

Rat Cardiovascular Safety Study

Female SD rats (300-350g) with surgically implanted abdominal aortic telemetry transponders (Data Sciences TA11PA-C40 Implant) were obtained from Charles River Laboratories. Blood pressure and heart rate readings from free-moving conscious rats were recorded continuously and expressed as average values at 10-min intervals for the first 6 hours then 1 hr intervals for the remaining 10 hours. Compound **5d** was administered as an oral bolus in a volume of 5 mg/ml in 20% Captisol.

Crystallographic data for intermediate to 5a

Experimental Section:

A colorless needle crystal of a single enantiomer of 2-(4-(1,3-dioxan-2-yl)-2-fluorophenyl)-5-(1-phenylethyl)thiazolo[5,4-b]pyridine with dimensions 0.40 x 0.14 x 0.14 mm was mounted on a Nylon loop using very small amount of paratone oil.

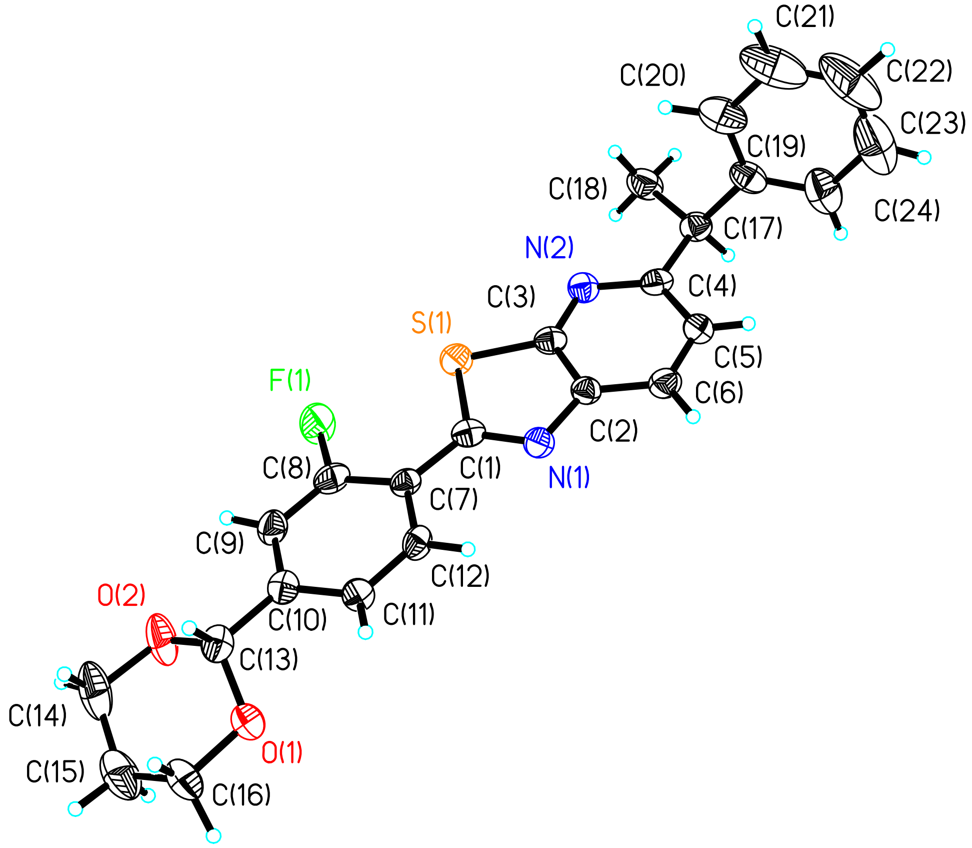
Data were collected using a Bruker CCD (charge coupled device) based diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at 173 K. Data were measured using omega and phi scans of 0.5° per frame for 30 s. The total number of images was based on results from the program COSMO[1] where redundancy was expected to be 4.0 and completeness to100% out to 0.83 Å. Cell parameters were retrieved using APEX II software[2] and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software[3] which corrects for Lp. Scaling and absorption corrections were applied using SADABS[4] multi-scan technique, supplied by George Sheldrick. The structures are solved by the direct method using the SHELXS-97[5] program and refined by least squares method on F^2, SHELXL- 97, [6] incorporated in SHELXTL-PC V 6.10.[7]

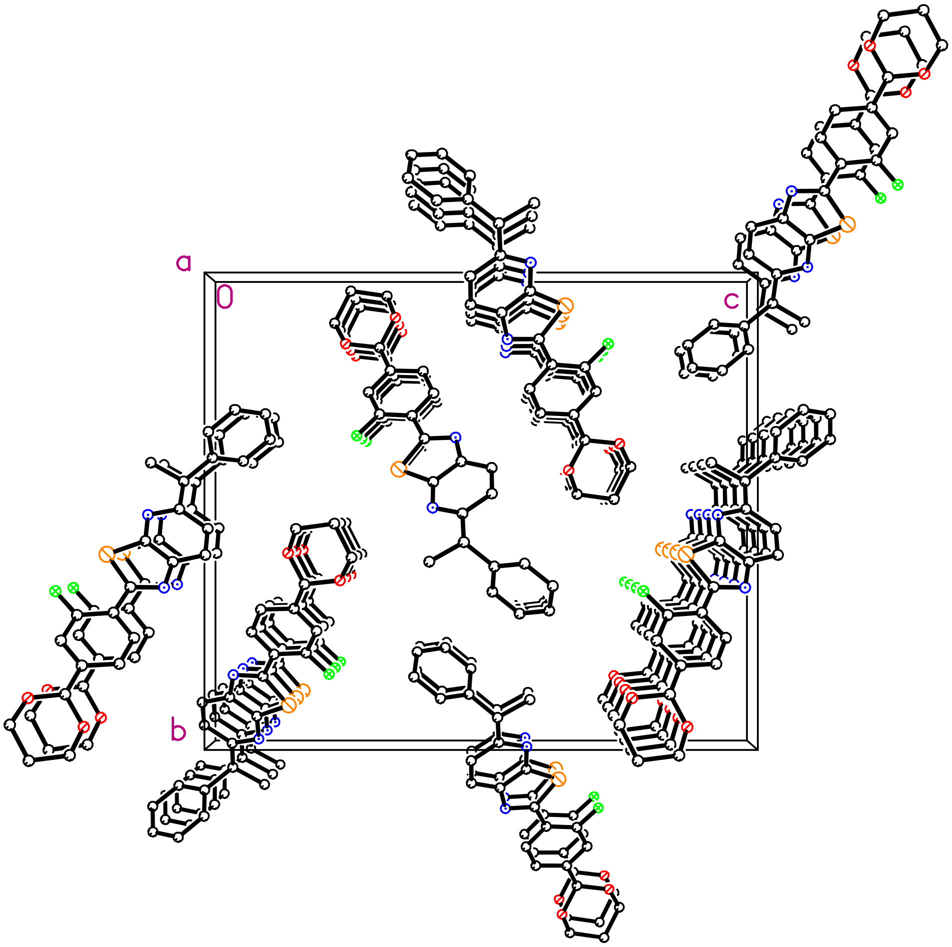
The structure was solved in the space group $P2_12_12_1$ (# 19). All non-hydrogen atoms are refined anisotropically. Hydrogen atoms were found by difference Fourier methods and refined isotropically The Flack[8] parameter is used to determine chirality of the crystal studied, the value should be near zero, a value of one is the other enantiomer and a value of 0.5 is racemic. The Flack parameter was refined to 0.07(8), confirming the absolute stereochemistry. The crystal used for the diffraction study showed no decomposition during data collection. All drawings are done at 50% ellipsoids.

References

1. COSMO V2.0, *Software for the CCD Detector Systems for Determining Data Collection Parameters.* Bruker Analytical X-ray Systems, Madison, WI (2006).
2. APEX2 V 1.2-0 Software *for the CCD Detector System*; Bruker Analytical X-ray Systems, Madison, WI (2006).
3. SAINT V 7.34 Software *for the Integration of CCD Detector System* Bruker Analytical X-ray Systems, Madison, WI (2001).
4. SADABS V2.10 *Program for absorption corrections using Bruker-AXS CCD based on the method of Robert Blessing*; Blessing, R.H. *Acta Cryst. A51,* 1995, 33-38.
5. Sheldrick, G. M. SHELXS-90, *Program for the Solution of Crystal Structure*, University of Göttingen, Germany, 1990.
6. Sheldrick, G. M. SHELXL-97, *Program for the Refinement of Crystal Structure,* University of Göttingen, Germany, 1997.
7. SHELXTL 6.1 (PC-Version), *Program library for Structure Solution and Molecular Graphics*; Bruker Analytical X-ray Systems, Madison, WI (2000).
8. Flack, H. D. *Acta Cryst. A39*, **1983**, 876--881

The following are 50% thermal ellipsoidal drawings of the molecule in the asymmetric cell with various amount of labeling.


C(21)
C(20)
C(22)
C(23)
C(19)
C(18)
C(17)
C(24)
N(2)
C(3)
C(4)
S(1)
C(5)
F(1)
C(6)
C(2)
C(8)
C(1)
N(1)
C(7)
C(9)
C(12)
O(2)
C(10)
C(11)
C(13)
C(14)
O(1)
C(15)
C(16)



This is a drawing of the packing along the a-axis.

Table 1. Crystal data and structure refinement for amg807AR_0m.

Identification code	amg807ar_0m	
Empirical formula	C24 H21 F N2 O2 S	
Formula weight	420.49	
Temperature	446(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 4.7269(3) Å	α= 90°.
	b = 19.2496(14) Å	β= 90°.
	c = 22.3038(16) Å	γ = 90°.
Volume	2029.4(2) Å^3	
Z	4	
Density (calculated)	1.376 Mg/m^3	
Absorption coefficient	0.193 mm^{-1}	
F(000)	880	
Crystal size	0.40 x 0.16 x 0.16 mm^3	
Theta range for data collection	2.11 to 19.54°.	
Index ranges	-4<=h<=4, -18<=k<=18, -20<=l<=20	
Reflections collected	11255	
Independent reflections	1776 [R(int) = 0.0475]	
Completeness to theta = 19.54°	99.7 %	
Absorption correction	None	
Max. and min. transmission	0.9698 and 0.9270	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1776 / 0 / 355	
Goodness-of-fit on F^2	1.075	
Final R indices [I>2sigma(I)]	R1 = 0.0220, wR2 = 0.0585	
R indices (all data)	R1 = 0.0227, wR2 = 0.0591	
Absolute structure parameter	0.07(8)	
Largest diff. peak and hole	0.125 and -0.140 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for amg807AR_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	790(2)	5862(1)	8539(1)	35(1)
F(1)	4216(4)	6577(1)	7759(1)	54(1)
O(1)	10121(4)	9143(1)	8416(1)	46(1)
O(2)	10301(4)	8583(1)	7497(1)	53(1)
N(1)	1528(4)	6523(1)	9542(1)	30(1)
N(2)	-3024(4)	5073(1)	9153(1)	31(1)
C(1)	2374(5)	6507(1)	8985(1)	28(1)
C(2)	-475(6)	6020(1)	9647(1)	27(1)
C(3)	-1156(5)	5598(1)	9155(1)	29(1)
C(4)	-4349(6)	4956(1)	9674(1)	31(1)
C(5)	-3830(7)	5358(1)	10186(1)	34(1)
C(6)	-1895(6)	5884(1)	10183(1)	34(1)
C(7)	4458(5)	6996(1)	8752(1)	26(1)
C(8)	5332(6)	7039(1)	8160(1)	35(1)
C(9)	7253(6)	7516(1)	7948(1)	35(1)
C(10)	8438(5)	7989(1)	8334(1)	29(1)
C(11)	7657(6)	7963(2)	8938(1)	29(1)
C(12)	5735(6)	7481(1)	9135(1)	30(1)
C(13)	10563(6)	8507(1)	8121(1)	33(1)
C(14)	12391(8)	9059(2)	7271(2)	62(1)
C(15)	12175(10)	9748(2)	7575(2)	61(1)
C(16)	12275(8)	9641(2)	8248(1)	55(1)
C(17)	-6569(6)	4382(1)	9701(1)	33(1)
C(18)	-6915(8)	3997(2)	9108(1)	44(1)
C(19)	-6032(6)	3895(1)	10225(1)	38(1)
C(20)	-3986(8)	3377(2)	10193(2)	60(1)
C(21)	-3582(12)	2932(2)	10669(3)	93(2)
C(22)	-5097(14)	3006(3)	11179(3)	99(2)
C(23)	-7062(13)	3512(3)	11230(2)	91(1)
C(24)	-7567(8)	3960(2)	10745(2)	60(1)

Table 3. Bond lengths [Å] and angles [°] for amg807AR_0m.

S(1)-C(3)	1.729(3)
S(1)-C(1)	1.758(2)
F(1)-C(8)	1.366(3)
O(1)-C(13)	1.406(3)
O(1)-C(16)	1.447(4)
O(2)-C(13)	1.406(3)
O(2)-C(14)	1.438(4)
N(1)-C(1)	1.305(3)
N(1)-C(2)	1.374(3)
N(2)-C(4)	1.341(3)
N(2)-C(3)	1.342(3)
C(1)-C(7)	1.458(3)
C(2)-C(6)	1.395(4)
C(2)-C(3)	1.403(3)
C(4)-C(5)	1.400(4)
C(4)-C(17)	1.524(4)
C(5)-C(6)	1.364(4)
C(5)-H(5)	0.89(3)
C(6)-H(6)	0.93(2)
C(7)-C(8)	1.387(3)
C(7)-C(12)	1.401(3)
C(8)-C(9)	1.376(4)
C(9)-C(10)	1.371(4)
C(9)-H(9)	0.92(3)
C(10)-C(11)	1.398(4)
C(10)-C(13)	1.492(4)
C(11)-C(12)	1.371(4)
C(11)-H(11)	0.86(2)
C(12)-H(12)	0.92(2)
C(13)-H(13)	1.02(3)
C(14)-C(15)	1.492(5)
C(14)-H(14A)	0.97(3)
C(14)-H(14B)	0.99(3)
C(15)-C(16)	1.516(5)

C(15)-H(15A)	0.99(4)
C(15)-H(15B)	0.98(4)
C(16)-H(16A)	1.07(3)
C(16)-H(16B)	1.05(3)
C(17)-C(19)	1.521(4)
C(17)-C(18)	1.526(4)
C(17)-H(17)	1.01(3)
C(18)-H(18A)	1.01(3)
C(18)-H(18B)	1.01(3)
C(18)-H(18C)	0.96(3)
C(19)-C(24)	1.373(4)
C(19)-C(20)	1.391(4)
C(20)-C(21)	1.377(5)
C(20)-H(20)	1.03(4)
C(21)-C(22)	1.352(7)
C(21)-H(21)	0.98(5)
C(22)-C(23)	1.350(7)
C(22)-H(22)	0.89(5)
C(23)-C(24)	1.406(6)
C(23)-H(23)	0.90(4)
C(24)-H(24)	0.95(3)
C(3)-S(1)-C(1)	89.11(13)
C(13)-O(1)-C(16)	110.6(2)
C(13)-O(2)-C(14)	110.6(2)
C(1)-N(1)-C(2)	110.94(19)
C(4)-N(2)-C(3)	115.5(2)
N(1)-C(1)-C(7)	122.1(2)
N(1)-C(1)-S(1)	115.11(19)
C(7)-C(1)-S(1)	122.80(19)
N(1)-C(2)-C(6)	127.6(2)
N(1)-C(2)-C(3)	115.6(2)
C(6)-C(2)-C(3)	116.8(2)
N(2)-C(3)-C(2)	126.1(2)
N(2)-C(3)-S(1)	124.62(18)
C(2)-C(3)-S(1)	109.25(19)

N(2)-C(4)-C(5)	122.2(2)
N(2)-C(4)-C(17)	118.5(2)
C(5)-C(4)-C(17)	119.3(2)
C(6)-C(5)-C(4)	121.6(3)
C(6)-C(5)-H(5)	118.4(16)
C(4)-C(5)-H(5)	120.1(16)
C(5)-C(6)-C(2)	117.8(3)
C(5)-C(6)-H(6)	122.2(14)
C(2)-C(6)-H(6)	120.0(14)
C(8)-C(7)-C(12)	114.4(2)
C(8)-C(7)-C(1)	125.4(2)
C(12)-C(7)-C(1)	120.3(2)
F(1)-C(8)-C(9)	117.7(2)
F(1)-C(8)-C(7)	118.0(2)
C(9)-C(8)-C(7)	124.3(2)
C(10)-C(9)-C(8)	119.8(3)
C(10)-C(9)-H(9)	124.1(17)
C(8)-C(9)-H(9)	116.1(16)
C(9)-C(10)-C(11)	118.2(3)
C(9)-C(10)-C(13)	121.2(2)
C(11)-C(10)-C(13)	120.5(3)
C(12)-C(11)-C(10)	120.6(3)
C(12)-C(11)-H(11)	121.1(14)
C(10)-C(11)-H(11)	118.2(14)
C(11)-C(12)-C(7)	122.7(3)
C(11)-C(12)-H(12)	119.5(13)
C(7)-C(12)-H(12)	117.7(13)
O(1)-C(13)-O(2)	111.0(2)
O(1)-C(13)-C(10)	109.5(2)
O(2)-C(13)-C(10)	109.0(2)
O(1)-C(13)-H(13)	109.2(13)
O(2)-C(13)-H(13)	108.4(13)
C(10)-C(13)-H(13)	109.7(13)
O(2)-C(14)-C(15)	111.1(3)
O(2)-C(14)-H(14A)	105.3(18)
C(15)-C(14)-H(14A)	115.2(16)

O(2)-C(14)-H(14B)	109.9(16)
C(15)-C(14)-H(14B)	108.8(15)
H(14A)-C(14)-H(14B)	106(2)
C(14)-C(15)-C(16)	109.1(3)
C(14)-C(15)-H(15A)	114(2)
C(16)-C(15)-H(15A)	103.3(19)
C(14)-C(15)-H(15B)	110.0(19)
C(16)-C(15)-H(15B)	104.6(18)
H(15A)-C(15)-H(15B)	115(2)
O(1)-C(16)-C(15)	108.9(3)
O(1)-C(16)-H(16A)	110.8(15)
C(15)-C(16)-H(16A)	106.6(15)
O(1)-C(16)-H(16B)	103.4(17)
C(15)-C(16)-H(16B)	109.8(16)
H(16A)-C(16)-H(16B)	117(2)
C(19)-C(17)-C(4)	111.2(2)
C(19)-C(17)-C(18)	112.6(2)
C(4)-C(17)-C(18)	113.1(2)
C(19)-C(17)-H(17)	104.7(13)
C(4)-C(17)-H(17)	106.7(12)
C(18)-C(17)-H(17)	107.8(13)
C(17)-C(18)-H(18A)	108.2(14)
C(17)-C(18)-H(18B)	107.3(14)
H(18A)-C(18)-H(18B)	110.4(18)
C(17)-C(18)-H(18C)	112.1(15)
H(18A)-C(18)-H(18C)	108(2)
H(18B)-C(18)-H(18C)	111(2)
C(24)-C(19)-C(20)	118.5(3)
C(24)-C(19)-C(17)	120.3(3)
C(20)-C(19)-C(17)	121.3(3)
C(21)-C(20)-C(19)	120.2(4)
C(21)-C(20)-H(20)	121(2)
C(19)-C(20)-H(20)	118(2)
C(22)-C(21)-C(20)	120.6(5)
C(22)-C(21)-H(21)	119(3)
C(20)-C(21)-H(21)	119(3)

C(23)-C(22)-C(21)	120.8(4)
C(23)-C(22)-H(22)	115(3)
C(21)-C(22)-H(22)	124(3)
C(22)-C(23)-C(24)	119.6(5)
C(22)-C(23)-H(23)	128(3)
C(24)-C(23)-H(23)	112(3)
C(19)-C(24)-C(23)	120.3(5)
C(19)-C(24)-H(24)	119.9(16)
C(23)-C(24)-H(24)	119.7(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for amg807AR_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	42(1)	34(1)	28(1)	-4(1)	-3(1)	-4(1)
F(1)	73(1)	58(1)	30(1)	-13(1)	6(1)	-21(1)
O(1)	59(1)	36(1)	42(1)	6(1)	15(1)	-4(1)
O(2)	51(1)	83(1)	25(1)	10(1)	3(1)	-23(1)
N(1)	37(1)	29(1)	24(2)	-1(1)	-2(1)	-2(1)
N(2)	35(1)	31(1)	28(1)	2(1)	-4(1)	1(1)
C(1)	30(2)	26(2)	29(2)	-1(1)	-8(1)	4(1)
C(2)	30(2)	24(1)	28(2)	2(1)	-1(2)	1(2)
C(3)	31(2)	26(1)	30(2)	-1(1)	-6(1)	2(2)
C(4)	35(2)	24(1)	34(2)	-2(1)	-2(2)	5(2)
C(5)	37(2)	29(2)	37(2)	3(2)	7(2)	1(2)
C(6)	41(2)	30(2)	30(2)	-4(2)	-1(2)	0(2)
C(7)	32(1)	25(1)	22(2)	-2(1)	-3(2)	3(1)
C(8)	43(2)	33(2)	28(2)	-10(2)	-7(2)	2(2)
C(9)	40(2)	39(2)	25(2)	-2(2)	4(2)	1(2)
C(10)	25(2)	34(2)	28(2)	4(1)	-3(1)	7(1)
C(11)	30(2)	33(2)	25(2)	-2(2)	-5(2)	-4(2)
C(12)	35(2)	37(2)	18(2)	-1(2)	-1(2)	3(2)
C(13)	33(2)	40(2)	26(2)	5(1)	-2(2)	6(2)
C(14)	53(2)	104(3)	30(2)	16(2)	2(2)	-24(3)
C(15)	56(2)	62(3)	64(3)	33(2)	4(2)	-3(2)
C(16)	68(2)	44(2)	53(2)	12(2)	17(2)	-12(2)
C(17)	31(2)	31(2)	37(2)	-3(1)	-1(1)	-2(2)
C(18)	54(2)	34(2)	44(2)	2(2)	-3(2)	-10(2)
C(19)	41(2)	33(2)	42(2)	5(1)	-9(2)	-10(2)
C(20)	62(2)	45(2)	71(3)	15(2)	-13(2)	3(2)
C(21)	100(4)	59(3)	120(5)	34(3)	-46(4)	-3(3)
C(22)	134(5)	88(3)	77(4)	48(3)	-55(4)	-42(4)
C(23)	101(4)	111(4)	61(3)	17(3)	2(3)	-47(4)
C(24)	67(2)	68(2)	45(2)	13(2)	0(2)	-8(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for amg807AR_0m.

	x	y	z	U(eq)
H(5)	-4740(60)	5267(12)	10525(12)	34(8)
H(6)	-1530(50)	6152(11)	10520(10)	23(7)
H(9)	7690(60)	7487(12)	7546(13)	43(8)
H(11)	8490(50)	8237(11)	9184(10)	11(7)
H(12)	5190(40)	7480(9)	9532(11)	14(6)
H(13)	12560(60)	8332(12)	8214(10)	36(7)
H(14A)	12110(60)	9067(13)	6841(14)	61(9)
H(14B)	14300(60)	8869(13)	7339(11)	44(8)
H(15A)	10360(80)	9987(17)	7512(14)	77(11)
H(15B)	13850(80)	10029(17)	7485(14)	82(11)
H(16A)	14340(70)	9446(14)	8350(12)	58(9)
H(16B)	11640(70)	10096(16)	8467(13)	79(10)
H(17)	-8420(50)	4614(11)	9797(10)	28(7)
H(18A)	-8560(60)	3663(14)	9149(10)	42(7)
H(18B)	-5100(60)	3733(13)	9032(11)	45(9)
H(18C)	-7330(60)	4308(14)	8780(13)	52(8)
H(20)	-2710(90)	3355(19)	9817(17)	110(14)
H(21)	-1920(110)	2630(20)	10670(20)	118(16)
H(22)	-4990(90)	2710(20)	11490(20)	118(17)
H(23)	-8260(90)	3590(20)	11538(19)	105(17)
H(24)	-8910(60)	4327(14)	10785(12)	49(9)

Table 6. Torsion angles [°] for amg807AR_0m.

C(2)-N(1)-C(1)-C(7)	178.8(2)
C(2)-N(1)-C(1)-S(1)	-0.5(2)
C(3)-S(1)-C(1)-N(1)	0.03(19)
C(3)-S(1)-C(1)-C(7)	-179.2(2)
C(1)-N(1)-C(2)-C(6)	-179.0(2)
C(1)-N(1)-C(2)-C(3)	0.9(3)
C(4)-N(2)-C(3)-C(2)	0.6(3)
C(4)-N(2)-C(3)-S(1)	-179.12(19)
N(1)-C(2)-C(3)-N(2)	179.4(2)
C(6)-C(2)-C(3)-N(2)	-0.7(3)
N(1)-C(2)-C(3)-S(1)	-0.8(3)
C(6)-C(2)-C(3)-S(1)	179.10(18)
C(1)-S(1)-C(3)-N(2)	-179.8(2)
C(1)-S(1)-C(3)-C(2)	0.43(18)
C(3)-N(2)-C(4)-C(5)	0.4(3)
C(3)-N(2)-C(4)-C(17)	178.1(2)
N(2)-C(4)-C(5)-C(6)	-1.4(4)
C(17)-C(4)-C(5)-C(6)	-179.1(2)
C(4)-C(5)-C(6)-C(2)	1.3(4)
N(1)-C(2)-C(6)-C(5)	179.6(2)
C(3)-C(2)-C(6)-C(5)	-0.3(3)
N(1)-C(1)-C(7)-C(8)	-175.9(2)
S(1)-C(1)-C(7)-C(8)	3.3(3)
N(1)-C(1)-C(7)-C(12)	3.4(3)
S(1)-C(1)-C(7)-C(12)	-177.38(19)
C(12)-C(7)-C(8)-F(1)	179.1(2)
C(1)-C(7)-C(8)-F(1)	-1.6(4)
C(12)-C(7)-C(8)-C(9)	-0.9(3)
C(1)-C(7)-C(8)-C(9)	178.4(2)
F(1)-C(8)-C(9)-C(10)	-179.8(2)
C(7)-C(8)-C(9)-C(10)	0.2(4)
C(8)-C(9)-C(10)-C(11)	0.6(4)
C(8)-C(9)-C(10)-C(13)	179.0(2)
C(9)-C(10)-C(11)-C(12)	-0.7(4)

C(13)-C(10)-C(11)-C(12)	-179.1(2)
C(10)-C(11)-C(12)-C(7)	-0.1(4)
C(8)-C(7)-C(12)-C(11)	0.9(3)
C(1)-C(7)-C(12)-C(11)	-178.5(2)
C(16)-O(1)-C(13)-O(2)	-63.5(3)
C(16)-O(1)-C(13)-C(10)	176.1(2)
C(14)-O(2)-C(13)-O(1)	61.6(3)
C(14)-O(2)-C(13)-C(10)	-177.8(3)
C(9)-C(10)-C(13)-O(1)	142.3(2)
C(11)-C(10)-C(13)-O(1)	-39.4(3)
C(9)-C(10)-C(13)-O(2)	20.6(3)
C(11)-C(10)-C(13)-O(2)	-161.0(2)
C(13)-O(2)-C(14)-C(15)	-56.9(4)
O(2)-C(14)-C(15)-C(16)	53.2(4)
C(13)-O(1)-C(16)-C(15)	59.2(3)
C(14)-C(15)-C(16)-O(1)	-53.8(4)
N(2)-C(4)-C(17)-C(19)	129.5(3)
C(5)-C(4)-C(17)-C(19)	-52.8(3)
N(2)-C(4)-C(17)-C(18)	1.6(3)
C(5)-C(4)-C(17)-C(18)	179.3(3)
C(4)-C(17)-C(19)-C(24)	100.6(3)
C(18)-C(17)-C(19)-C(24)	-131.3(3)
C(4)-C(17)-C(19)-C(20)	-79.2(3)
C(18)-C(17)-C(19)-C(20)	49.0(4)
C(24)-C(19)-C(20)-C(21)	1.7(5)
C(17)-C(19)-C(20)-C(21)	-178.6(3)
C(19)-C(20)-C(21)-C(22)	-2.2(6)
C(20)-C(21)-C(22)-C(23)	0.9(6)
C(21)-C(22)-C(23)-C(24)	0.9(6)
C(20)-C(19)-C(24)-C(23)	0.1(4)
C(17)-C(19)-C(24)-C(23)	-179.7(3)
C(22)-C(23)-C(24)-C(19)	-1.4(6)

Symmetry transformations used to generate equivalent atoms: