Linker variation and structure-activity relationship analyses of carboxylic acid-based small molecule STAT3 inhibitors

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Select analogs disrupt the DNA-binding activities of both STAT3 and STAT5, but not that of STAT1 *in vitro*. In order to determine the specificity of select new analogs active against STAT3 activity, we investigated the effects on STAT1 and STAT5 DNA-binding activity *in vitro,* as previously reported [1-3]. EMSA analysis shows interestingly that many of the new analogs, including **1a-c, 1f**, **2a,** and **4g**, which potently inhibited STAT3 DNA-binding activity also disrupted STAT5 DNA-binding activity, but only weakly affected STAT1 activity (Supplementary Fig. S1). **2v** had only a relatively weak effect on STAT5 and none on STAT1 DNA-binding activity (Supplementary Fig. S1, **2v**). The inhibition of STAT5 DNA-binding activity by **1a** and **1e** was concentration-dependent (Supplementary Fig. S1B, **1a**, **1e**, IC_{50} 7.9 and 4.9 μM, respectively), while any non-specific effect on STAT1 DNA-binding activity was only observed at 30 μM (Supplementary Fig. S1B, 10 vs 30 μM). Interestingly, we noted that **1e**, which is the (*S*)-enantiomer of the Ala analog **1a**, showed a relatively stronger inhibitory effect on STAT5 DNA binding activity, with IC_{50} of 4.9 μM, as well as inhibition on STAT1 activity to a moderate extent, compared to its (*R*)-antipode, **1a** (Supplementary Fig. S1B). This interesting selectivity finding suggests further support for exploration of analogs with the *R*-configuration. Moreover and consistent with the (*R*)-configuration, compound **4b**, the tetrahydropyran (THP) analog of **1a**, showed minimum effect on STAT5 DNA binding activity at the lowest concentration that inhibits STAT3 DNA-binding activity *in vitro* (Supplementary Fig. S1A, top band **4b** vs. **1a**). Other analogs evaluated, including **1h, 4h, 1d, 1g, 2b, 1i**, and **1l**, inhibited both STAT1 and STAT5 DNA-binding activity (Supplementary Fig. S1). The results suggest that these other compounds contain multi-functional modifications that might promote non-specific inhibitory effects against STAT1, STAT3 and STAT5. These latter observations further enhance the importance of the STAT3 specificity found in the new optimized derivatives.

We next evaluated the ability of select analogs to inhibit constitutive STAT3 tyrosine phosphorylation in the human breast cancer, MDA-MB-231 and MDA-MB-468 cells, and the metastatic melanoma, C8161, 1205LU, and UACC903 cells. Immunoblotting analysis shows the treatment with the compounds, **2j**, **2p**, **2k**, and **2q** for 1 h all strongly inhibited persistent pY705STAT3 levels in MDA-MB-231 cells (Supplementary Fig. S2B(i)). Furthermore, 1 h treatment with **2v** strongly inhibited constitutive pY705STAT3 levels in both MDA-MB-231 and MDA-MB-468 lines (Supplementary Fig. S2B(ii) and (iii)), while 1 h treatment with 5 μM **1a**, **5d**, and **5e** inhibited pY705STAT3 levels in MDA-MB-231 (Supplementary Fig. S2B(iii)). Constitutive STAT3 Tyr705 phosphorylation in the three metastatic melanoma cells, C8161, 1205LU, and UACC903, is also strongly inhibited by treatment with **1a** at 10 or 20 μM for 1 and 3 h (Supplementary Fig. S2C). By contrast, immunoblotting analysis shows that 24 h treatment of MDA-MB-231 cells with 5 μM **2k** or **2q** had little effect on pJak2, pSrc, pERK1/2 (Supplementary Fig. S3), suggesting that at concentrations that inhibit STAT3 Tyr705 phosphorylation and STAT3 DNA-binding activity, these compounds have little effect on other signaling proteins.

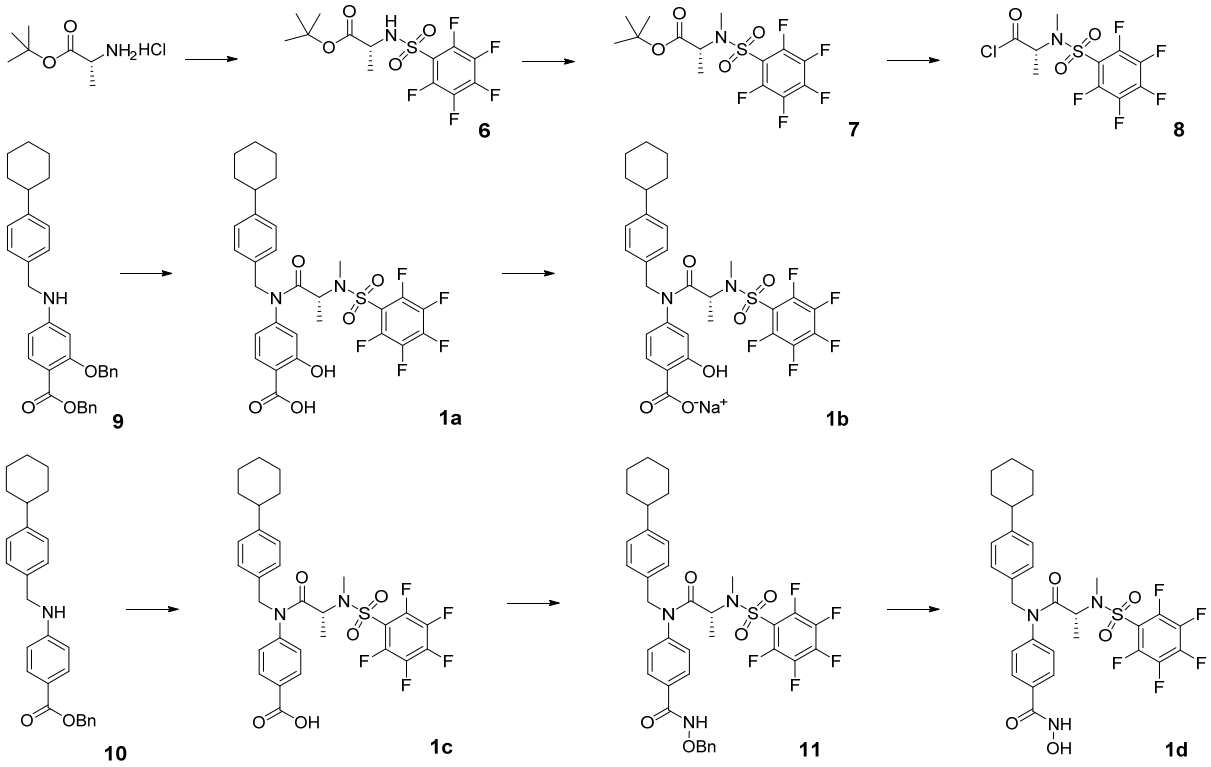
Novel active analogs decreased the growth, colony formation, and migration of human cancer cells harboring persistently-active STAT3. Specifically, analog, **2v**, suppressed the human breast cancer cell lines, MDA-MB-231 cell growth in a dose-dependent manner, as measured by trypan blue exclusion-phase contrast microscopy, with an IC_{50} of 3.9 μM (Supplementary Fig. S4A). Treatment with analog, **1e** also only weakly inhibited the viability of the STAT3 null mouse embryonic fibroblasts (MEF/STAT3-/-) (Supplementary Fig. S4B).

EXPERIMENTAL SECTION

General Methods for Chemistry. All reagents and solvents were purchased from commercial sources and used without further purification. All moisture sensitive reactions were performed under a static atmosphere of nitrogen or argon in oven dried glassware. Tetrahydrofuran (THF), dichloromethane (DCM), diethyl ether (Et_2O), toluene, dimethylformamide (DMF) used in the reactions were dried by being passed through a SPS system. Other anhydrous solvents were purchased from commercial sources. Thin layer chromatography (TLC) was performed on glass plates, 250 – 1000 □m. Flash column chromatography was performed on silica gel, 200-400 mesh. ^{1}H NMR spectra were obtained as $CDCl_3$, CD_3OD, or $(CD_3)_2SO$, solutions using an Agilent 300MHz NMR spectrometer with a Agilent DD2 console, and chemical shifts were expressed in δ (ppm) using residual solvent ($CDCl_3$, 7.26 ppm; CD_3OD, 3.31 ppm; and $(CD_3)_2SO$, 2.50 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br-s (broadened singlet), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when reported, are reported in hertz (Hz). All compounds were analyzed by LC/MS (liquid chromatography/mass spectrometry) using an Agilent Triple Quad 640 LC/MS. Ionization was generally achieved via electron spray (ESI) unless otherwise indicated. The LC fraction detection consisted of a variable wavelength detector and all tested compounds had purity greater than 95%. High resolution mass spectral (HRMS) data was obtained for all tested compounds using either and Agilent 6200 LC/MSD TOF or an Agilent 6545 Q-TOF LC/MS and reported exact masses were calculated based on an algorithm using MS (ESI) m/z for $[M + H]^+$ and $[M + Na]^+$ adducts and were within 5 ppm of the expected target mass. Chiral molecules were analyzed by chiral HPLC using Chiralpak AD-H or OD-H columns (4.6 mm x 250 mm, UV detection at 254 or 261nm), eluents used were hexane and *i*-PrOH.

Analogs from Table 1.

The preparation of the 4-(*N*-benzyl-(*N*-methylpentafluorophenylsulfonamido)acylamino)benzoic acids is illustrated in Scheme 1 with the preparation of the alanine-based benzoic acid derivatives **1a-1d**. Sulfonamide **7** was prepared from D-alanine *t*-butyl ester using pentafluorobenzenesulfonyl chloride to provide intermediate sulfonamide **6**, which was readily *N*-methylated in good overall yield. Deprotection of the t-butyl ester using TFA provided the acid, which was cleanly converted to the acid chloride **8** using oxalyl chloride and catalytic DMF. Acylation of aniline **9**[14] with acid chloride **8** could be effected using the standard conditions using DMAP or through the metallated anilide by pre-treating the aniline with methylmagnesium bromide or trimethylaluminum before introduction of the acid chloride. The best yield was obtained using the latter method providing amide **10** in 83% yield. Both *O*-benzyl-protecting groups could be cleanly removed by catalytic hydrogenolysis to afford the salicylate **1b** that could be converted to the corresponding sodium salt **1b** using sub-stoichiometric quantities of sodium bicarbonate. Benzoic acid analog **1c** was prepared starting from aniline **10**[14] using the standard DMAP coupling procedure. Further elaboration to the corresponding benzohydroxamic acid **1d** was accomplished by coupling the corresponding acid chloride with *O*-benzylhydroxylamine followed by catalytic hydrogenolysis of the benzyl protecting group. In parallel, the corresponding enantiomeric analogs **1e-g** were prepared starting from L-alanine *t*-butyl ester. Other amino acid-based benzoic acid derivatives, such as **1h - 1x,** were prepared analogously starting from the appropriate orthogonally-protected amino acid starting material. In each case, before the final hydrogenolysis step, normal-phase chiral HPLC was used to determine the enantiomeric purity.



Scheme 1.

***t*-Butyl ((pentafluorophenyl)sulfonyl)-D-alaninate (6)**. To a solution of D-alanine *tert*-butyl ester hydrochloride (5g, 27.5 mmol) and DIPEA (11 mL, 63.3 mmol) in 100 mL of anhydrous DCM at 0 °C was added pentafluorobenzenesulfonyl chloride (4.5 mL, 30.25 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured onto water and extracted with DCM (3X). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (15% EtOAc/hexanes) to afford **6** as a cream colored solid (8.21 g, 80% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.70 (d, *J* = 8.4 Hz, 1H), 4.18 (p, *J* = 7.2 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.40 (s, 9H).

***tert*-Butyl *N*-methyl-*N*-((pentafluorophenyl)sulfonyl)-D-alaninate (7).** To a stirred solution of **6** (8.21 g, 21.9 mmol) in 130 mL of anhydrous DMF was added K_2CO_3 (3.63 g, 26.3 mmol) and the resultant mixture was stirred for 10 min before dropwise addition methyl iodide (1.77 mL, 28.5 mmol). The

reaction mixture was stirred for 1h, then poured onto ice water (500 mL) and extracted with ether (3 X 250mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0-8% EtOAc/hexanes stepwise gradient) to afford **7** as a white solid (8.16 g, 96% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.80 (q, *J* = 7.3 Hz, 1H), 2.99 (s, 3H), 1.50 (d, *J* = 7.3 Hz, 3H), 1.40 (s, 9H).

***N*-Methyl-*N*-((pentafluorophenyl)sulfonyl)-D-alaninoyl chloride (8).** To a stirred solution of combined batches of **7** (11.4 g, 29.3 mmol) in 100 mL of DCM was added TFA (100 mL) and the resultant mixture was stirred at room temperature overnight. The resultant mixture was concentrated under reduced pressure, re-dissolved in toluene and concentrated *in vacuo* to give a cream-colored solid (9.6 g, 98% yield). The solid was triturated with a cold solution of 10% ether in hexanes (25 mL), washed twice and dried to provide *N*-methyl-*N*-((pentafluorophenyl)sulfonyl)-D-alanine as a white solid (8.1 g). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.97 (q, *J* = 7.3 Hz, 1H), 3.00 (s, 3H), 1.57 (d, *J* = 7.3 Hz, 3H).

To a stirred solution of *N*-methyl-*N*-((pentafluorophenyl)sulfonyl)-D-alanine (4.44 g, 13.33 mmol) in 100 mL of DCM under nitrogen was added DMF (3 drops) followed by oxalyl chloride (1.72 mL, 20 mmol) and the resultant mixture was stirred at room temperature for 2.5 h. The solution was concentrated under reduced pressure to give a cream colored solid that was triturated with hexanes and dried on the pump to afford pure **8** (4.46 g, 95% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.25 – 5.09 (m, 1H), 3.02 (s, 3H), 1.69 (d, *J* = 7.4 Hz, 3H).

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propan-amido)-2-hydroxybenzoic acid (1a). To a stirred solution of benzyl 4-((4-cyclohexylbenzyl)amino)benzoate (**9**)[14] (303 mg, 0.6 mmol) in THF (7 mL) under nitrogen at 0 °C was added a solution of trimethylaluminum (0.75 mL of 2M in toluene, 1.5 mmol) and the mixture was

warmed to room temperature over 15 min. To the resulting solution was added a solution of **8** (263 mg, 0.75 mmol) in THF (7 mL). The reaction mixture was stirred at reflux temperature for 3 h, poured onto 10% $KHSO_4$/ Na_2SO_4 buffer and ice and then extracted 3 times with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (0-5-10% EtOAc/(8:1 hexanes: DCM mixture)) as a stepwise gradient to afford benzyl (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzoate (407 mg, 83% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.28 (m, 10H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.67 (s, 1H), 5.36 (s, 2H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.90 (d and overlapping m, *J* = 12.1 Hz, 2H), 4.77 (d, *J* = 14.3 Hz, 1H), 4.63 (d, *J* = 14.3 Hz, 1H), 3.17 (s, 3H), 2.48 (s, 1H), 2.00 – 1.67 (m, 6H), 1.52 – 1.19 (m, 4H), 1.12 (d, *J* = 7.2 Hz, 3H). HRMS (ESI) m/z 821.2681 $[M + H]^+$. HRMS (ESI+) calculated for $C_{44}H_{41}F_5N_2O_6S$: 820.2605, found 820.2611.

To a stirred solution of benzyl (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzoate (375 mg, 0.46 mmol) in methanol (10 mL) and THF (10 mL) was added 10% Pd/C (32 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere until the reaction was complete as determined by LCMS (2 h). The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated to provide **1a** (298 mg, 100% yield) as a pale pink foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 2H), 6.64 (s and overlapping d, *J* = 8.2 Hz, 2H), 4.91 (d, *J* = 14.9 Hz, 1H), 4.80 (q, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 15.0 Hz, 1H), 3.06 (s, 3H), 2.47 (d, *J* = 11.5 Hz, 1H), 2.02 – 1.58 (m, 6H), 1.54 – 1.26 (m, 4H), 1.20 (d, *J* = 7.1 Hz, 3H). LCMS: 99% purity, HRMS (ESI) m/z 641.1743 $[M + H]^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_6S$: 640.1666, found 640.1686.

Sodium (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoate (1b). To a solution of **1a** (298 mg, 0.46 mmol) in 12 mL of 1:1:1 THF:MeOH:H_2O was added sodium bicarbonate (34.5 mg, 0.41 mmol) and the resultant mixture was stirred at room temperature for 5 h and then concentrated *in vacuo* to give a foam. Trituration with 1:1 ether: hexanes provided **1b** as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) 7.60 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.9 Hz, 2H), 6.98 (d, J = 7.9 Hz, 2H), 6.35 (s and overlapping d, J = 8.0 Hz, 2H), 4.87 (d and overlapping m, J = 14.7 Hz, 2H), 4.50 (d, J = 14.7 Hz, 1H), 3.08 (s, 3H), 2.43-2.36 (m overlapping DMSO peak), 1.89 – 1.60 (m, 6H), 1.49 – 1.27 (m, 4H), 1.20 (d, J = 7.1 Hz, 3H). LCMS: > 99% purity, HRMS (ESI) m/z 641.1745 $[M + H]^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_6S$: 640.1666, found 640.1671.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)-benzoic acid (1c). To a solution of benzyl 4-((4-cyclohexylbenzyl)amino)benzoate[14] (450 mg, 1.12 mmol) and **8** (590 mg, 1.68 mmol) in DCM (15 mL) under nitrogen was added DMAP (164 mg, 1.34 mmol) and the resultant solution was stirred at room temperature overnight. The reaction mixture was poured onto water and extracted with DCM (3X). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the resulting residue purified by flash chromatography (10-25% EtOAc/hexanes) to afford benzyl (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)-benzoate (350 mg, 44% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.11 (d, J = 8.5 Hz, 2H), 7.53 – 7.33 (m, 5H), 7.19 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 5.39 (s, 2H), 4.93 – 4.61 (m, 3H), 3.18 (s, 3H), 2.54 – 2.40 (m, 1H), 1.93 – 1.69 (m, 5H), 1.48 – 1.26 (m, 5H), 1.24 (d, J = 7.5 Hz, 3H). HRMS (ESI) m/z 715.2250. $[M + H]^+$. HRMS (ESI+) calculated for $C_{37}H_{35}F_5N_2O_5S$: 714.2187, found 714.2187.

To a stirred solution of benzyl (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzoate (330 mg, 0.43 mmol) in methanol (10 mL) and THF (10 mL) was added 10% Pd/C (50 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere overnight. The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated to provide **1c** (286 mg, 100% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 2H), 4.96 – 4.69 (m, 3H), 3.19 (s, 3H), 2.60 – 2.37 (m, 1H), 1.95 – 1.67 (m, 6H), 1.51 – 1.29 (m, 4H), 1.25 (d, *J* = 7.2 Hz, 3H). LCMS: > 99% purity, MS (APCI) m/z 625[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_5S$: 624.1717, found 624.1718.

(*R*)-*N*-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)benzamide (11). To a stirred solution of **1c** (211 mg, 0.34 mmol) in DCM (10 mL) was added 1 drop of DMF followed by oxalyl chloride (0.035 mL, 0.41 mmol). The resulting reaction solution was stirred at room temperature under nitrogen for 2 h and then concentrated under reduced pressure to afforded (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)benzoyl chloride, which was used as is. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.30 (doublet overlapping with $CHCl_3$), 7.13 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 4.93 – 4.73 (m, 3H), 3.17 (s, 3H), 2.60 – 2.44 (m, 1H), 2.04 – 1.66 (m, 6H), 1.54 – 1.31 (m, 4H), 1.25 (d, *J* = 7.2 Hz, 3H).

To a stirred solution of (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)propanamido)benzoyl chloride (0.34 mmol) in THF (5 mL) under nitrogen at 0 °C was added a solution of *O*-benzylhydroxylamine hydrochloride (76 mg, 0.473 mmol) and TEA (0.12 mL, 0.879 mmol) in DMF (4 mL). The resultant reaction mixture was stirred at room temperature for 1.5 h and then quenched with 10 % potassium bisulfate, poured onto water and extracted with ether (2 X). The

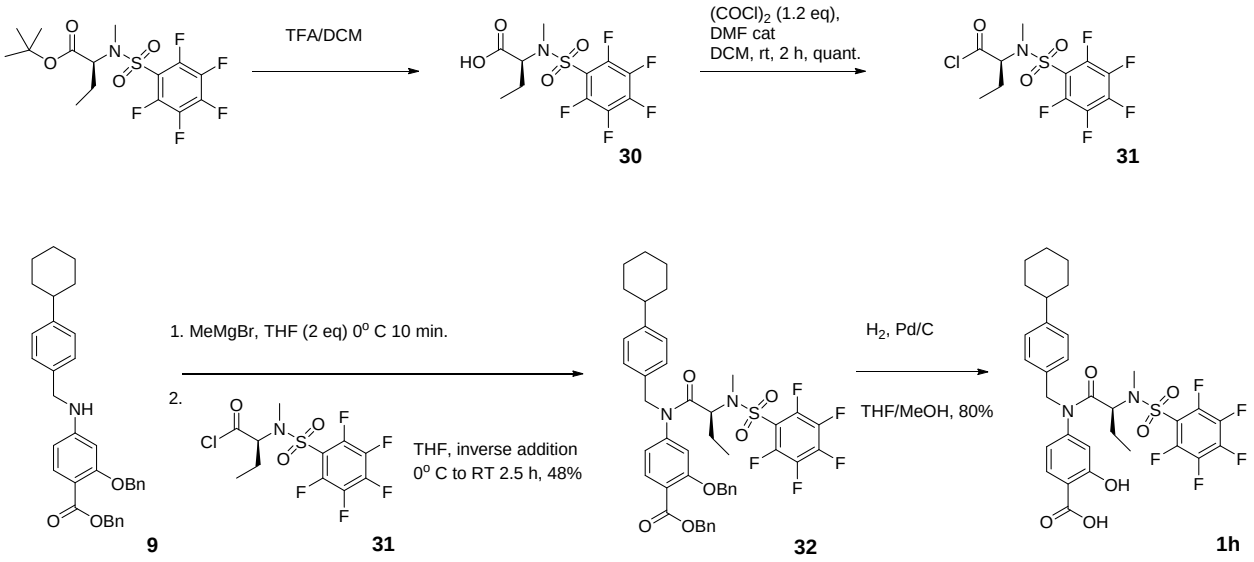
combined organic extracts were washed with water, then washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (40% EtOAc/ hexanes) to provide **11** (159 mg, 64% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.33 (m, 5H), 7.21 – 7.14 (m, 2H), 7.14 – 7.06 (m, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 5.06 (s, 2H), 4.88 – 4.64 (m, 3H), 3.18 (s, 3H), 2.55 – 2.41 (m, 1H), 1.94 – 1.69 (m, 6H), 1.50 – 1.32 (m, 4H), 1.22 (d, *J* = 7.2 Hz, 3H).

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propan-amido)-*N*-hydroxybenzamide (1d). To a stirred solution of **11** in methanol (8 mL) and THF (8 mL) was added 10% Pd/C (40 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 1 h. The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated and the resulting residue was purified by flash chromatography (3% MeOH in DCM eluent) to provide **1d** (109 mg, 81% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.96 – 4.69 (m, 3H), 3.19 (s, 3H), 2.60 – 2.37 (m, 1H), 1.95 – 1.67 (m, 6H), 1.51 – 1.29 (m, 4H), 1.25 (d, *J* = 7.2 Hz, 3H). LCMS: > 99% purity, MS (ESI) m/z 640[M + H]$^+$. HRMS (APCI+) calculated for $C_{30}H_{30}F_5N_3O_5S$: 639.1826, found 639.1804.

(*S*)-4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propan-amido)-2-hydroxybenzoic acid (1e). Product **1e** was prepared as described for **1a** except starting with L-alanine *tert*-butyl ester hydrochloride instead of D-alanine *tert*-butyl ester hydrochloride. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 – 7.80(m, 1H), 7.15 – 6.45 (m, 6H), 5.1 – 4.4 (m, *2*H), 3.55 (br. s, 1H), 3.02 (s, 3H), 2.35 (br. s, 1H), 1.85– 1.58 (m, 6H), 1.45 – 1.26 (m, 4H), 1.16 (d, *J* = 7.1 Hz, 3H). LCMS: 99% purity, MS (ESI) m/z 641[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_6S$: 640.1666, found 640.1643.

(*S*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propan-amido)benzoic acid (1f). Product **1f** was prepared as described for **1c** except starting with L-alanine *tert*-butyl ester hydrochloride instead of D-alanine *tert*-butyl ester hydrochloride. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 4.93 – 4.70 (m, 3H), 3.19 (s, 3H), 2.60 – 2.37 (m, 1H), 1.99 – 1.68 (m, 6H), 1.54 – 1.32 (m, 4H), 1.26 (d, *J* = 7.2 Hz, 3H). LCMS: > 99% purity, MS (ESI) m/z 625.1795[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_5S$: 624.1717, found 624.1723.

(*S*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propan-amido)-*N*-hydroxybenzamide (1g). Product **1g** was prepared as described for **1d** except starting with L-alanine *tert*-butyl ester hydrochloride instead of D-alanine *tert*-butyl ester hydrochloride. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 – 7.65 (m, 2H), 7.27 – 7.16 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 7.7 Hz, 2H), 4.91 – 4.65 (m, 3H), 3.17 (s, 3H), 2.48 (s, 1H), 1.98 – 1.62 (m, 5H), 1.55 – 1.26 (m, 5H), 1.23 (d, *J* = 6.7 Hz, 3H). LCMS: > 99% purity, HRMS (ESI) m/z 640.1897[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{30}F_5N_3O_5S$: 639.1826, found 639.1823.



Scheme 2.

(*S*)-2-((2,3,4,5,6-Pentafluoro-*N*-methylphenyl)sulfonamido)butanoic acid (30).

The starting ester, *tert*-butyl (S)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)butanoate, was prepared as described for **7** except starting with L-2-aminobutyric acid *tert*-butyl ester hydrochloride instead of D-alanine *tert*-butyl ester hydrochloride. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.55 (dd, *J* = 11.0, 4.8 Hz, 1H), 2.97 (s, 3H), 2.05 (dqd, *J* = 14.8, 7.5, 4.8 Hz, 1H), 1.70 (ddq, *J* = 14.5, 11.0, 7.2 Hz, 1H), 1.39 (s, 9H), 1.05 (t, *J* = 7.4 Hz, 3H). To a stirred solution of *tert*-butyl (S)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)butanoate (782 mg, 1.94 mmol) in DCM (10 mL) was added TFA (10 mL) and the resulting reaction solution was stirred overnight at room temperature and then concentrated *in vacuo* to provide **30** (718 mg, 100%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.61 (br. s, 1H), 4.71 (dd, *J* = 11.0, 4.8 Hz, 1H), 2.95 (s, 3H), 2.10 (dtd, *J* = 14.5, 7.4, 4.8 Hz, 1H), 1.77 (ddq, *J* = 14.5, 11.0, 7.4 Hz, 1H), 1.06 (t, *J* = 7.4 Hz, 3H).

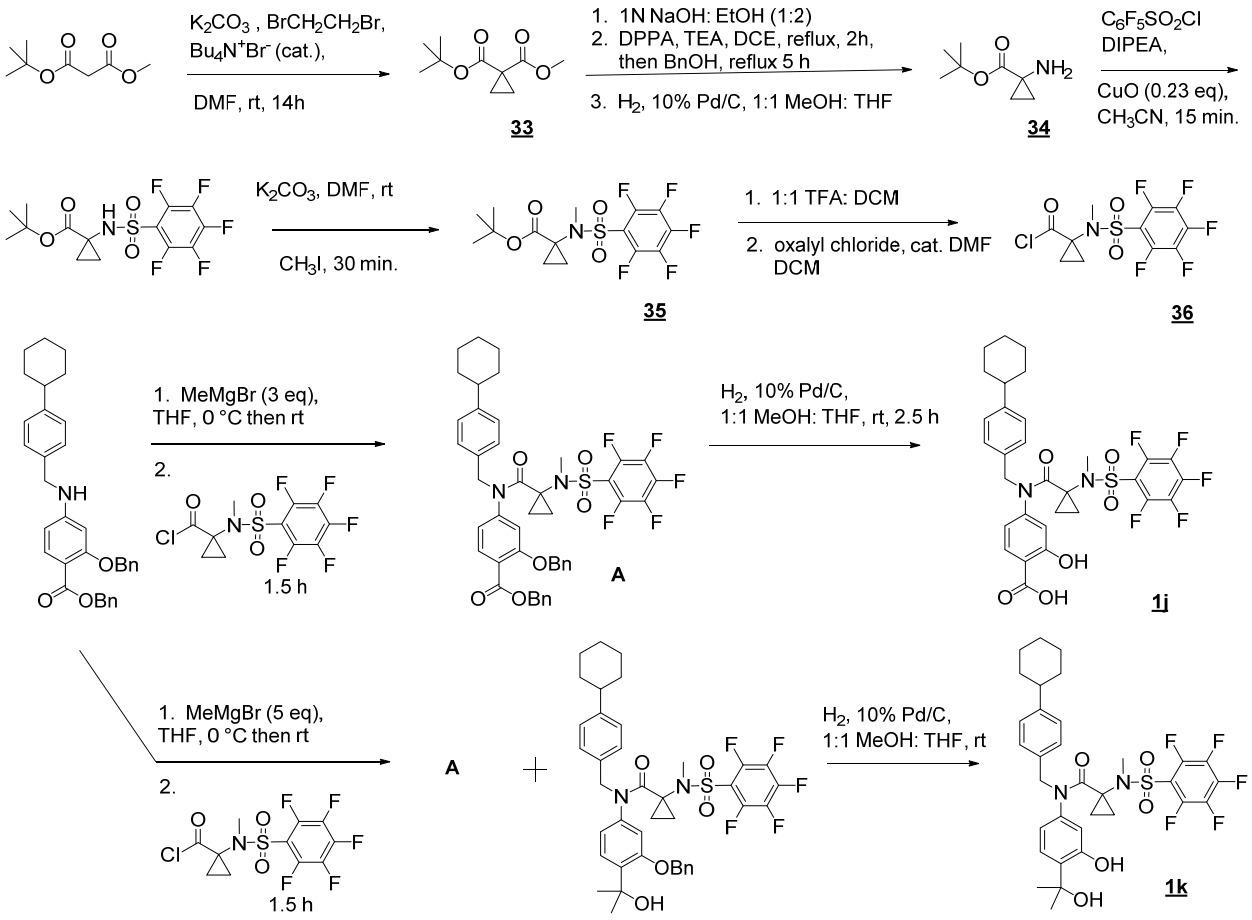
Benzyl (*S*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)butanamido)benzoate (32). To a stirred solution of **30** (76 mg, 0.22 mmol) in 2 mL of DCM under nitrogen was added DMF (2 drops) followed by oxalyl chloride (0.024 mL, 0.28 mmol) and the resultant mixture was stirred at room temperature for 2.5 h. The solution was concentrated under reduced pressure to provide acid chloride **31** that was used as is. To a stirred solution of **9** (88 mg, 0.175 mmol) in THF (2 mL) under nitrogen at 0 °C was added methylmagnesium bromide (0.25 mL of 1.4 M in 1:3 THF:toluene, 0.35 mmol, 2 equiv). Stirring was continued at 0 – 5 °C for 10 min. The resultant solution was added dropwise to a stirred solution of freshly prepared **31** (0.21 mmol) in THF (2 mL) under nitrogen at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and stirred at this temperature for 2.5 h, quenched with saturated ammonium chloride, poured onto water and extracted with EtOAc (3 X). The combined organic extracts were dried over anhydrous sodium sulfate,

concentrated under reduced pressure and resulting residue purified by flash chromatography (20% EtOAc/ hexane eluent) to afford **32** (88 mg, 48% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.29 (m, 10H), 7.11 (d, *J* = 7.9, 2H), 6.95 (d, *J* = 7.9, 2H), 6.70 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.71 – 6.62 (m, 1H), 5.36 (s, 2H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.89 (d, *J* = 12.1 Hz, 1H), 4.81 – 4.59 (m, 3H), 3.14 (s, 3H), 2.48 (br. s, 1H), 1.99 – 1.13 (m, 12H), 0.63 (t, *J* = 7.2 Hz, 3H). For $C_{45}H_{43}F_5N_2O_6S$, exact mass: 834.3. LRMS (ESI) m/z 857.2 $[M + Na]^+$.

(*S*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)butanamido)-2-hydroxybenzoic acid (1h). To a stirred solution of **32** (88 mg, 0.105 mmol) in methanol (8 mL) and THF (8 mL) was added 10% Pd/C (20 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere overnight. The reaction mixture was filtered through Celite® and washed with methanol (2X). The combined filtrate and washes were concentrated, purified by flash chromatography (3-7% MeOH/DCM gradient) to provide **1h** (54 mg, 79% yield) as an off-white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.77 (s, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 5.02 – 4.60 (m, 3H), 3.15 (s, 3H), 2.48 (br. s, 1H), 2.02 – 1.55 (m, 7H), 1.51 – 1.15 (m, 5H), 0.74 (t, *J* = 7.2 Hz, 3H). LCMS: 99% purity, MS (ESI) m/z 655.2$[M + H]^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_6S$: 654.1823, found 654.1829.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)butanamido)-2-hydroxybenzoic acid (1i). Product **1i** was prepared as described for **1h** except starting with D-2-aminobutyric acid *tert*-butyl ester hydrochloride instead of L-2-aminobutyric acid *tert*-butyl ester hydrochloride. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.78 (s, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.02 – 4.60 (m, 3H), 3.15 (s, 3H), 2.48 (br. s, 1H), 2.02 – 1.55 (m, 7H), 1.51 – 1.15 (m, 5H), 0.74 (t, *J* = 7.2 Hz, 3H). LCMS: > 99% purity, MS

(ESI) m/z 655.2[M + H]$^+$, m/z 677.2[M + Na]$^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_6S$: 654.1823, found 654.1811.



Scheme 3.

1-(*tert*-Butyl) 1-methyl cyclopropane-1,1-dicarboxylate (33). *tert*-Butyl methyl malonate (3.9 mL, 23 mmol), potassium carbonate (7.9 g, 57.5 mmol) and dibromoethane (2.57 mL, 29.9 mmol) were combined in DMF (75 mL) and the resulting reaction mixture was stirred at room temperature overnight. The mixture was poured onto water (500 mL) and extracted with ether (3 X). The combined ethereal layers were washed with water, then washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (0-5% EtOAc/ hexane) provided **33** (2.35 g, 51%

yield). Combined with another batch to afford the desired product (4.28 g). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.75 (s, 3H), 1.47 (s, 9H), 1.38 (s, 4H).

***tert*-Butyl 1-aminocyclopropane-1-carboxylate (34)**. To a stirred solution of **33** (4.28 g, 21.4 mmol) in ethanol (30 mL) was added 1N aqueous sodium hydroxide (30 mL, 30 mmol) and the resulting reaction mixture was stirred overnight. The crude reaction mixture was diluted with water and washed with ether (1 X). The aqueous phase was acidified with aqueous 1N HCl and the resulting mixture was extracted with DCM (3 X). The combined DCM extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide 1-(*tert*-butoxycarbonyl)cyclopropane-1-carboxylic acid (3.7 g, 93%) as a colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 1.84 – 1.76 (m, 2H), 1.70 – 1.63 (m, 2H), 1.49 (s, 9H). To a stirred solution of 1-(*tert*-butoxycarbonyl)cyclopropane-1-carboxylic acid (3.7 g, 19.8 mmol) in DCM (40 mL) was added under nitrogen TEA (2.75 mL, 19.8 mmol) followed by diphenylphosphoryl azide (4.27 mL, 19.8 mmol). The resultant reaction solution was warmed at reflux temperature for 2 h and removed from the oil bath. Benzyl alcohol (3.1 mL, 29.8 mmol) was added and the resulting reaction solution was warmed at reflux temperature for 5 h. The reaction mixture was allowed to cool to room temperature, poured onto 10% aqueous citric acid and extracted with DCM (2 X). The combined organic extracts were washed with 5% sodium bicarbonate, dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography (10 – 20% stepwise gradient) afforded intermediate product, *tert*-butyl 1-(((benzyloxy)carbonyl)amino)cyclopropane-1-carboxylate (4 g, 67% yield). To a stirred solution of *tert*-butyl 1-(((benzyloxy)carbonyl)amino)cyclopropane-1-carboxylate (2.4 g, 8.2 mmol) in methanol (40 mL) and THF (40 mL) was added 10% Pd/C (150 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere (6 h). The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated and the resultant residue purified by flash chromatography (2 -5% MeOH in DCM gradient) to provide **34**

(0.86 g, 67% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 1.96 (br. s, 2H), 1.44 (s, 9H), 1.25 – 1.17 (m, 2H), 0.97 – 0.89 (m, 2H).

***tert*-Butyl 1-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)cyclopropane-1-carboxylate (35)**. To a stirred solution of **34** (505 mg, 3.2 mmol) in dry acetonitrile (18 mL) was added copper (II) oxide (60 mg, 0.74 mmol) and DIPEA (0.612 mL, 3.52 mmol). To this vigorously stirred mixture was added pentafluorobenzenesulfonyl chloride (0.52 mL, 3.52 mmol). The reaction was exothermic and complete within 15 min. The mixture was poured onto water and extracted with EtOAc (3 X). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (10 -20% EtOAc/hexanes) provided intermediate, *tert*-butyl 1-((perfluorophenyl)sulfonamido)cyclopropane-1-carboxylate (867 mg, 50% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 1.61 – 1.45 (m, 4H), 1.32 (s, 9H). To a stirred solution of *tert*-butyl 1-((perfluorophenyl)sulfonamido)cyclopropane-1-carboxylate (863 mg, 2.23 mmol) in DMF (20 mL) was added potassium carbonate (370 mg, 2.68 mmol) and following stirring at room temperature for 10 min by addition of methyl iodide (0.17 mL, 2.68 mmol). The resultant reaction mixture was stirred at room temperature for 30 min, then poured onto water and extracted with ether (3 X). The combined ethereal layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography (7 % EtOAc/hexanes eluent provided **35** (871 mg, 97% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.15 (s, 3H), 1.87 (br. s, 4H), 1.37 (s, 9H).

1-((2,3,4,5,6-Pentafluoro-*N*-methylphenyl)sulfonamido)cyclopropane-1-carbonyl chloride (36). To a stirred solution of **35** (868 mg, 2.16 mmol) in DCM (20 mL) was added TFA (20 mL) and the resultant reaction solution was stirred at room temperature overnight. Concentration *in vacuo* afforded 1-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)cyclopropane-1-carboxylic acid (750 mg, 99% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.15 (s, 3H), 1.98 (br. s, 2H), 1.59 (br. s,

1H), 1.41 – 1.10 (m, 1H). To a stirred solution of 1-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)cyclopropane-1-carboxylic acid (376 mg, 1.09 mmol) in DCM (20 mL) under nitrogen was added DMF (2 drops) followed by oxalyl chloride (0.13 mL, 1.5 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h and then concentrated *in vacuo* to afford **36** (373 mg, 100 % yield) as an off-white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.16 (s, 3H), 2.30 (br. s, 2H), 1.91 (br. s, 1H), 1.45 (br. s, 1H).

4-(*N*-(4-Cyclohexylbenzyl)-1-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)cyclopropane-1-carboxamido)-2-hydroxybenzoic acid (1j). To a stirred solution of **9** (253 mg, 0.5 mmol) in THF (8 mL) under nitrogen at 0 °C was added methylmagnesium bromide (1.07 mL of 1.4 M in 1:3 THF:toluene, 1.5 mmol, 3 equiv). Stirring was continued at 0 – 5 °C for 5 min and then room temperature for 5 min. The resultant solution was added dropwise to a stirred solution of **36** (254 mg, 0.7 mmol) in THF (8 mL) under nitrogen. The resulting reaction mixture was stirred at room temperature for 1.5 h, quenched with saturated ammonium chloride, poured onto water and extracted with EtOAc (3 X). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and resulting residue purified by flash chromatography (15-25% EtOAc/ hexane) to afford benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)cyclopropane-1-carboxamido)benzoate (205 mg, 49% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.55 – 7.21 (m, 10H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.72 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 5.36 (s, 2H), 5.00 (s, 2H), 4.79 (s, 2H), 2.47 (s, 2H), 2.11 (s, 3H), 1.92 – 1.69 (m, 6H), 1.48 – 1.18 (m, 8H). HRMS (ESI) m/z 855.2504 $[M + Na]^+$. HRMS (ESI+) calculated for $C_{45}H_{41}F_5N_2O_6S$: 832.2605, found 832.2611.

To a stirred solution of benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)cyclopropane-1-carboxamido)benzoate (193 mg, 0.23 mmol) in methanol (3 mL) and THF (3 mL) was added 10% Pd/C (30 mg) and the resulting suspension was stirred at room

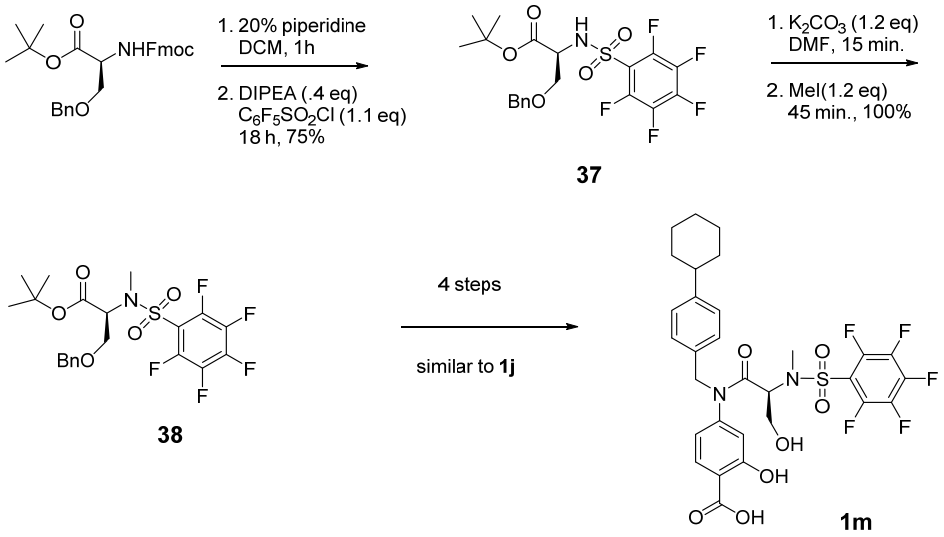
temperature under a hydrogen atmosphere for 2.5 h. The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated, purified by flash chromatography (5-7% MeOH/DCM gradient) to provide **1j** (107 mg, 71% yield) as a tan solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 4H), 6.87 – 6.60 (m, 2H), 4.86 (s, 2H), 2.44 (s, 1H), 2.30 (s, 3H), 2.00 – 1.08 (m, 10H), 0.89 (q, *J* = 7.5, 6.8 Hz, 4H).

LCMS: 99% purity, MS (ESI) m/z 653.1[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{29}F_5N_2O_6S$: 652.1666, found 652.1681.

N-(4-cyclohexylbenzyl)-N-(3-hydroxy-4-(2-hydroxypropan-2-yl)phenyl)-1-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)cyclopropane-1-carboxamide (1k). To a stirred solution of **9** (253 mg, 0.5 mmol) in THF (8 mL) under nitrogen at 0 °C was added methylmagnesium bromide (1.8 mL of 1.4 M in 1:3 THF:toluene, 2.5 mmol, 5 equiv). Stirring was continued at 0 – 5 °C for 10 min. The resultant solution was added dropwise to a stirred solution of **36** (254 mg, 0.7 mmol) in THF (8 mL) under nitrogen. The resulting reaction mixture was stirred at room temperature for 40 min, quenched with saturated ammonium chloride, poured onto water and extracted with EtOAc (3 X). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and resulting residue purified by flash chromatography (25% EtOAc/ hexane) to afford impure benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)cyclopropane-1-carboxamido)benzoate (115 mg) and major side product, *N*-(3-(benzyloxy)-4-(2-hydroxypropan-2-yl)phenyl)-N-(4-cyclohexylbenzyl)-1-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-cyclopropane-1-carboxamide (127 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.37 (m, 5H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.17 – 7.03 (m, 4H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.66 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.99 (s, 2H), 4.79 (s, 2H), 3.96 (s, 1H), 2.48 (s, 1H), 2.13 (s, 3H), 1.92 – 1.68 (m, 7H), 1.62 (s, 6H), 1.51 – 1.14 (m, 5H), 0.74 (s, 2H). HRMS (ESI) m/z 779.2551 [M + Na]$^+$. HRMS (ESI+) calculated for $C_{40}H_{41}F_5N_2O_5S$: 756.2656, found 756.2662.

To a stirred solution of *N*-(3-(benzyloxy)-4-(2-hydroxypropan-2-yl)phenyl)-N-(4-cyclohexylbenzyl)-1-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-cyclopropane-1-carboxamide (121 mg, 0.16 mmol) in methanol (3 mL) and THF (3 mL) was added 10% Pd/C (40 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 2.5 h. The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated, purified by flash chromatography (25-35% EtOAc/hexane) to provide **1k** (76 mg, 71% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.11 (s, 1H), 7.15 – 7.03 (m, 5H), 6.66 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 4.78 (s, 2H), 2.50 – 2.41 (m, 1H), 2.34 (s, 3H), 1.98 – 1.71 (m, 6H), 1.69 (s, 6H), 1.53 – 1.31 (m, 6H), 0.92 (d, *J* = 2.6 Hz, 2H). LCMS: > 99% purity, MS (ESI) m/z 667.2[M + H]$^+$. HRMS (ESI+) calculated for $C_{33}H_{35}F_5N_2O_5S$: 666.2187, found 666.2167.

4-(*N*-(4-cyclohexylbenzyl)-2-methyl-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoic acid (1l). Product **1l** was prepared as described for **1j** except starting with *tert*-butyl 2-amino-2-methylpropanoate instead of *tert*-butyl 1-aminocyclopropane-1-carboxylate (**34**) and using 2.2 equiv of methylmagnesium bromide instead of 3 equiv in the coupling step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.52 (br. s, 1H), 7.96 – 7.80 (m, 1H), 7.15 – 7.03 (m, 4H), 6.83 – 6.72 (m, 2H), 4.86 (s, 2H), 2.82 (s, 3H), 2.48 (br. s, 1H), 2.02 – 1.66 (m, 6H), 1.49 (s, 6H), 1.45 – 1.30 (m, 4H). LCMS: > 99% purity, MS (ESI) m/z 655.2[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_6S$: 654.1823, found 654.1839.



Scheme 4.

***tert*-Butyl *O*-benzyl-*N*-((perfluorophenyl)sulfonyl)-L-serinate (37)**. *tert*-Butyl *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*O*-benzyl-L-serinate was prepared as previously described (Foley, David et al., Organic & Biomolecular Chemistry, 7(18), 3652-3656; 2009) from commercially-available Fmoc-*O*-benzyl-L-serine. To a stirred solution of *tert*-Butyl *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*O*-benzyl-L-serinate (885 mg, 1.87 mmol) in DCM (10 mL) was added 3.9 mL of tris(2-aminoethyl)amine and the resultant mixture was stirred for 4 h at room temperature under nitrogen, then diluted with phosphate buffer (pH = 5-6) and extracted with DCM (2 X). The combined organic extracts were washed with phosphate buffer (1 X), saturated $KHCO_3$ (1 X), dried over sodium sulfate and concentrated under reduced pressure. The resulting crude product, *tert*-butyl *O*-benzyl-L-serinate (500 mg), was used as for the next step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.22 (m, 5H), 4.70 – 4.41 (m, 2H), 3.80 – 3.62 (m, 2H), 3.54 (dd, *J* = 5.1, 3.9 Hz, 1H), 1.71 (br. s, 2H), 1.47 (s, 9H). To a stirred solution of *tert*-butyl *O*-benzyl-L-serinate (500 mg, 1.87 mmol) in DCM (10 mL) under nitrogen at 0 °C was added DIPEA (0.43 mL, 2.43 mmol) followed by pentafluorobenzenesulfonyl chloride (0.31 mL, 2.06 mmol) and the resulting mixture was allowed to warm to room temperature and stirred at this temperature for 5 h. The reaction mixture was poured onto water and extracted with DCM (3 X). The combined extracts were

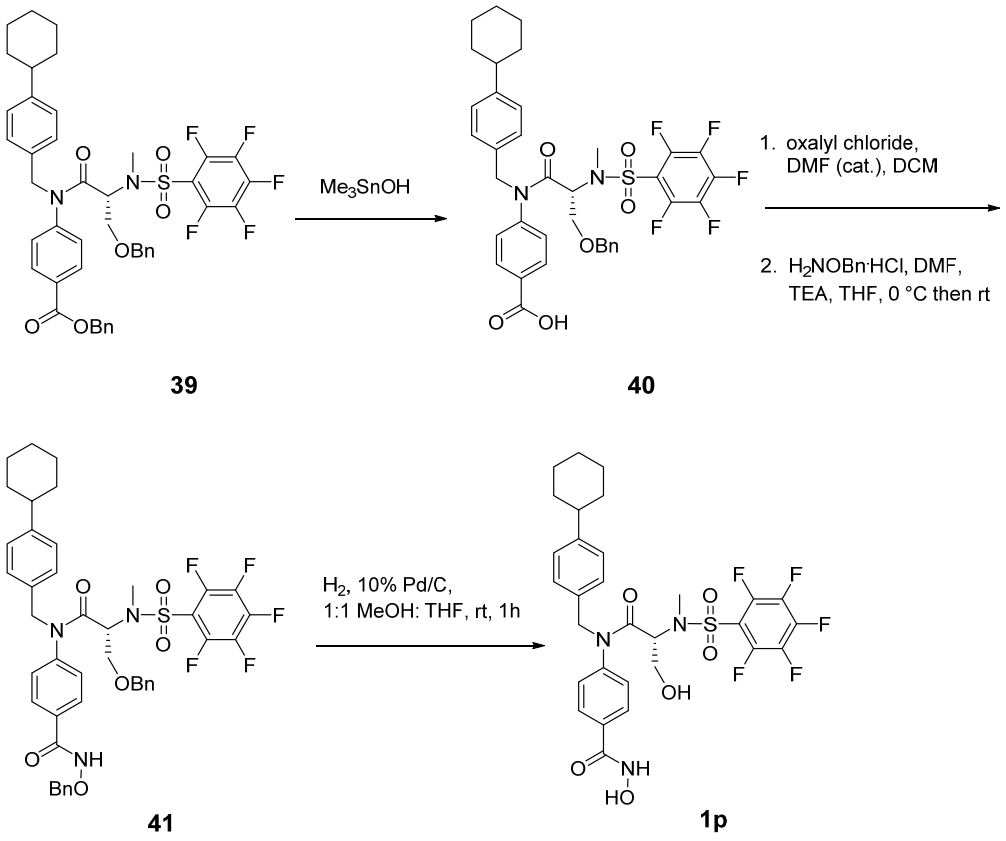
dried over anhydrous sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (10% EtOAc/hexane) to provide **37** (672 mg, 75% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.31 (m, 3H), 7.27 – 7.20 (m, 2H), 5.96 (d, *J* = 9.1 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.39 – 4.28 (m, 1H), 3.87 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.72 (dd, *J* = 9.4, 3.5 Hz, 1H), 1.39 (s, 9H). HRMS (ESI+) m/z 504.0871[M + Na]$^+$. HRMS (ESI+) calculated for $C_{20}H_{20}F_5NO_5S$: 481.0982, found 481.0979.

***tert*-Butyl *O*-benzyl-*N*-methyl-*N*-((perfluorophenyl)sulfonyl)-L-serinate (38)**. To a stirred solution of **37** (660 mg, 1.37 mmol) in DMF (12 mL) under nitrogen was added potassium carbonate (227 mg, 1.65 mmol) and the resulting mixture was stirred at room temperature for 1 h, poured onto water and extracted with ether (3 X). The combined ether extracts were washed with water and then saturated sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (8% EtOAc/hexane) afforded 38 (650 mg, 96% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38 – 7.31 (m, 3H), 7.27 – 7.19 (m, 2H), 4.92 (dd, *J* = 7.0, 4.3 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 3.97 – 3.78 (m, 2H), 3.12 (s, 3H), 1.43 (s, 9H).

(*S*)-4-(*N*-(4-cyclohexylbenzyl)-3-hydroxy-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoic acid (1m). Product **1m** was prepared as described for **1j** except replacing intermediate **38** for intermediate **36** in the synthesis. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.97 (br-s, 1H) ,7.88 (d, *J* = 8.4 Hz, 1H), 7.18 – 6.97 (m, 4H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 5.11 – 4.85 (m, 2H), 4.70 (d, *J* = 14.4 Hz, 1H), 3.99 – 3.67 (m, 2H), 3.25 (s, 3H), 2.59 – 2.39 (m, 1H), 1.97 – 1.64 (m, 5H), 1.53 – 1.15 (m, 5H). LCMS: 97% purity, MS (ESI) m/z 657[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_7S$: 656.1616, found 656.1628.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-3-hydroxy-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoic acid (1n). Product **1n** was prepared as described for **1m** except starting from Fmoc-*O*-benzyl-D-serine instead of Fmoc-*O*-benzyl-L-serine. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 – 7.83 (m, 1H), 7.19 – 6.98 (m, 4H), 6.74 (d, *J* = 1.7 Hz, 1H), 6.71 – 6.60 (m, 1H), 5.07 – 4.83 (m, 2H), 4.71 (d, *J* = 14.4 Hz, 1H), 4.02 – 3.60 (m, 2H), 3.25 (s, 3H), 2.60 – 2.40 (m, 1H), 2.02 – 1.66 (m, 5H), 1.56 – 1.16 (m, 5H). LCMS: 98% purity, MS (ESI) m/z 657[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_7S$: 656.1616, found 656.1629.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-3-hydroxy-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)benzoic acid (1o). Product **1o** was prepared as described for **1c** except replacing intermediate **38** for intermediate **7** in the synthesis. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 5.02 – 4.67 (m, 3H), 3.80 (d, *J* = 6.7 Hz, 2H), 3.25 (s, 3H), 2.48 (br. s, 1H), 2.01 – 1.58 (m, 4H), 1.55 – 1.05 (m, 6H). LCMS: > 99% purity, MS (ESI) m/z 641.2[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_6S$: 640.1666, found 640.1671, M-H = 639.1597.



Scheme 5.

Benzyl (*R*)-4-(3-(benzyloxy)-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)propanamido)benzoate (39). To a stirred solution of **38** (836 mg, 1.69 mmol) in DCM (12 mL) under nitrogen was added TFA (12 mL) and the resulting solution was stirred at room temperature overnight. The crude reaction mixture was concentrated *in vacuo* to give *O*-benzyl-*N*-methyl-*N*-((pentafluorophenyl)sulfonyl)-L-serine (763 mg, 100% yield) as a cream colored solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.31 (m, 3H), 7.23 – 7.13 (m, 2H), 5.02 (dd, *J* = 6.9, 3.6 Hz, 1H), 4.44 (q, *J* = 11.2 Hz, 2H), 4.07 – 3.79 (m, 2H), 3.09 (s, 3H). To a stirred solution of *O*-benzyl-*N*-methyl-*N*-((pentafluorophenyl)sulfonyl)-L-serine (440 mg, 1 mmol) in DCM (18 mL) under nitrogen was added DMF (2 drops) followed by oxalyl chloride (0.12 mL, 1.4 mmol) and the resulting reaction solution was stirred at room temperature before concentration under reduced pressure. The residue was dissolved in

toluene and concentrated *in vacuo* to afford *O*-benzyl-*N*-methyl-*N*-((pentafluorophenyl)sulfonyl)-L-serinoyl chloride which was used as is. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.31 (m, 3H), 7.23 – 7.14 (m, 2H), 5.26 (dd, *J* = 7.4, 3.4 Hz, 1H), 4.54 – 4.39 (m, 2H), 4.15 – 3.92 (m, 2H), 3.11 (s, 3H).

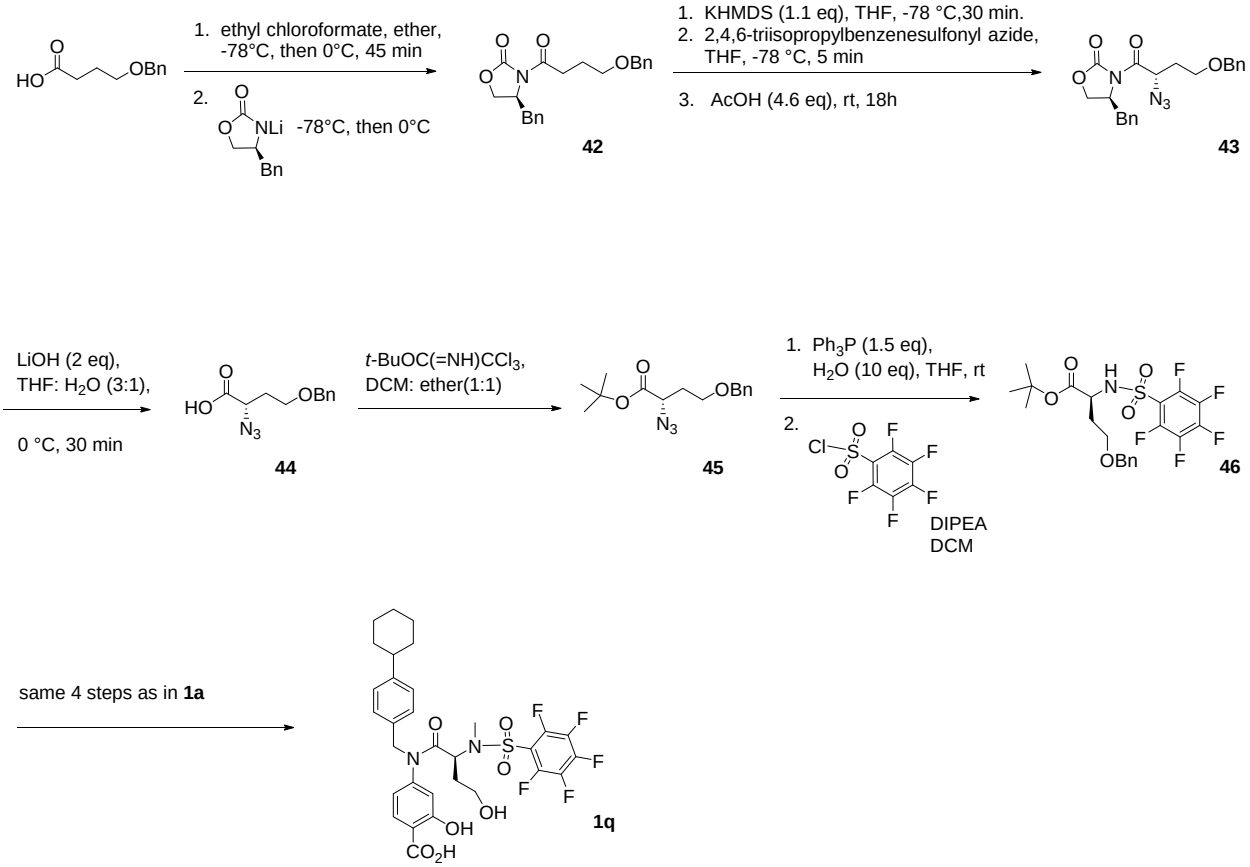
To a solution of the above, *O*-benzyl-*N*-methyl-*N*-((pentafluorophenyl)sulfonyl)-L-serinoyl chloride (1 mmol) and aniline **10** (332 mg, 0.83 mmol) in DCM (15 mL) was added DMAP (122 mg, 1 mmol) and the resulting reaction solution was stirred under nitrogen overnight. The crude reaction mixture was then poured onto water and extracted with DCM (3X). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (20-30% EtOAc/ hexanes) afforded **39** (152 mg, 22% yield). The product was combined with an earlier batch to provide 225 mg. HRMS (ESI+) m/z 821.2669[M + H]$^+$. HRMS (ESI+) calculated for $C_{44}H_{41}F_5N_2O_6S$: 820.2605, found 820.2603.

(*R*)-4-(3-(Benzyloxy)-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfon-amido)propanamido)benzoic acid (40). To a stirred solution of **39** (222mg, 0.27 mmol) in DCE (25 mL) under nitrogen was added trimethyltin hydroxide (390 mg, 2.16 mmol) and the resulting mixture was stirred at 85 °C for 24 h. The crude reaction was acidified with 10% aqueous HCl, poured onto water and extracted with EtOAc (3X). The combined organic extracts were washed with saturated sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (1-6% EtOAc/hexanes eluent) afforded recovered **39** (32 mg) and then continued elution with 5% methanol in DCM provided product **40** (153 mg, 63% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.47 – 6.95 (m overlapping $CHCl_3$), 5.01 – 4.75 (m, 3H), 4.35 – 4.08 (m, 2H), 3.65 (t, *J* = 10.1 Hz, 1H), 3.56 – 3.42 (m, 1H), 3.27 (s, 3H), 2.48 (br. s, 1H), 1.96 – 1.67 (m, 6H), 1.51 – 1.26 (m, 4H). LCMS: > 99% purity, HRMS (ESI+) m/z 731.2212[M + H]$^+$. HRMS (ESI+) calculated for $C_{37}H_{35}F_5N_2O_6S$: 730.2136, found 730.2140.

(*R*)-*N*-(Benzyloxy)-4-(3-(benzyloxy)-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methyl-phenyl)sulfonamido)propanamido)benzamide (41). To a stirred solution of **40** (153 mg, 0.21 mmol) in DCM (11 mL) was added 1 drop of DMF followed by oxalyl chloride (0.039 mL, 0.46 mmol). The resulting reaction solution was stirred at room temperature under nitrogen for 2 h and then concentrated under reduced pressure to afforded (*R*)-4-(3-(benzyloxy)-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)propanamido)benzoyl chloride, which was used as is. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 8.3 Hz, 2H), 7.47 – 6.98 (m overlapping $CHCl_3$), 5.01 – 4.72 (m, 3H), 4.37 – 4.04 (m, 2H), 3.65 (t, *J* = 10.0 Hz, 1H), 3.56 – 3.43 (m, 1H), 3.25 (s, 3H), 2.48 (br. s, 1H), 2.07 – 1.56 (m, 6H), 1.52 – 1.20 (m, 4H).

To a stirred solution of (*R*)-4-(3-(benzyloxy)-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)propanamido)benzoyl chloride (0.21 mmol) in THF (5 mL) under nitrogen at 0 °C was added a solution of *O*-benzylhydroxylamine hydrochloride (67 mg, 0.42 mmol) and TEA (0.088 mL, 0.63 mmol) in DMF (5 mL). The resultant reaction mixture was stirred at room temperature for 40 min and then quenched with 10 % potassium bisulfate, poured onto water and extracted with ether (3X). The combined organic extracts were washed with water, then washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (30% EtOAc/ hexanes) to provide **41** (125 mg, 71% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.55 – 7.20 (m overlapping $CHCl_3$), 7.15 – 6.96 (m, 7H), 5.07 (s, 2H), 4.79 (s and overlapping m, 3H), 4.34 – 4.06 (m, 2H), 3.63 (t, *J* = 10.0 Hz, 1H), 3.48 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.26 (s, 3H), 2.48 (br. s, 1H), 1.97 – 1.72 (m, 6H), 1.48 – 1.26 (m, 4H). HRMS (ESI+) m/z 836.2789$[M + H]^+$. HRMS (ESI+) calculated for $C_{44}H_{42}F_5N_3O_6S$: 835.2714, found 835.2720.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-3-hydroxy-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-*N*-hydroxybenzamide (1p). To a stirred solution of **41** (120 mg, 0.14 mmol) in methanol (5 mL) and THF (5 mL) was added 10% Pd/C (15 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 7 h. The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated and the resulting residue was purified by trituration with ether: hexane to provide **1p** (50 mg, 55% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.77 – 7.64 (m, 2H), 7.21 – 7.14 (m, 2H), 7.14 – 6.95 (m, 4H), 4.98 – 4.60 (m, 3H), 3.85 – 3.63 (m, 2H), 3.20 (s, 3H), 2.47 (br. s, 1H), 2.02 – 1.62 (m, 5H), 1.55 – 1.19 (m, 5H). LCMS: 97% purity, HRMS (ESI) m/z 656.1847[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{30}F_5N_3O_6S$: 655.1775, found 655.1775.



Scheme 6.

(*S*)-4-Benzyl-3-(4-(benzyloxy)butanoyl)oxazolidin-2-one (42). To a stirred solution of 4-benzyloxybutyric acid (2.05 mL, 11.6 mmol) in dry ether (115 mL) under nitrogen was added TEA (1.62 mL, 11.6 mmol) and the resulting solution was cooled to -78 °C. Ethyl chloroformate (1.10 mL, 11.6 mmol) was added dropwise to the solution and the resulting thick white suspension was stirred at 0 °C for 45 min and then cooled to -78 °C. In the meantime in a separate flask, to a solution of (S)-4-benzyloxazolidin-2-one (2.06 g, 11.6 mmol) in dry THF under nitrogen at -78 °C was added a solution of n-butyllithium (5.8 mL of 2M in hexanes, 11.6 mmol) and the resulting solution was stirred at -78 °C for 45 min before being added dropwise via cannula to the mixed anhydride of 4-benzyloxybutyric acid, prepared above at -78 °C. The resulting reaction was stirred for 1h at -78 °C, then quenched with saturated ammonium chloride, warmed to room temperature, poured onto water and extracted with EtOAc (3X). The combined organic extracts were washed with saturated sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography afforded **42** (2.00g, 53 % yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.14 (m, 10H), 4.63 (tdd, *J* = 7.2, 5.4, 3.5 Hz, 1H), 4.53 (s, 2H), 4.25 – 3.99 (m, 2H), 3.60 (t, *J* = 6.2 Hz, 2H), 3.29 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.72 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.17 – 1.92 (m, 2H).

(*S*)-3-((*S*)-2-Azido-4-(benzyloxy)butanoyl)-4-benzyloxazolidin-2-one (43). A mixture of **42** (1.907 g, 5.4 mmol) in dry THF (18 mL) was added at -78 °C under nitrogen to a solution of KHDMS (5.9 mL of 1.0 M solution in THF, 5.94 mmol) in dry THF (18 mL) at -78 °C by cannula. After stirring at -78°C for 30 min, a -78°C solution of 2,4,6-triisopropylbenzenesulfonyl azide (2.0 g, 6.48 mmol) in THF (13 mL) was added to the mixture by cannula. After five minutes of stirring, glacial acetic acid (1.4 mL, 24.84 mmol) was added. The solution was stirred at room temperature for 20 hours. The resulting solution was then diluted with EtOAc, poured onto saturated aqueous sodium bicarbonate and water and extracted with EtOAc (3X). The combined organic layers were washed with brine, dried over sodium sulfate and

evaporated under reduced pressure. The crude residue was taken up in DCM and filtered through Celite® and washed with DCM (2X). Concentration under reduced pressure and purification by flash column chromatography (hexane: DCM: EtOAc (80:12:8) eluent) gave **43** (0.92 g, 43% yield) as a clear oil. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.40 – 7.13 (m, 10H), 5.28 (t, *J* = 6.4 Hz, 1H), 4.46 (d, *J* = 2.3 Hz, 2H), 4.33 (ddt, *J* = 9.5, 8.0, 3.2 Hz, 1H), 4.01 (dd, *J* = 9.0, 2.9 Hz, 1H), 3.80 – 3.64 (m, 3H), 3.27 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.42 – 2.11 (m, 2H).

(*S*)-2-Azido-4-(benzyloxy)butanoic acid (44). To a mixture of compound **43** (0.889 g, 2.3 mmol) in 3:1 THF/H_2O mix (24mL/8mL) was added lithium hydroxide (0.108 g, 4.5 mmol) at 0 °C under argon. After stirring for 30 minutes, saturated aqueous sodium bicarbonate was added to solution and the THF was removed by evaporation under reduced pressure. The resulting mixture was extracted with DCM (3X) and the organic layers were collected and discarded. The aqueous phase was acidified with HCl (1N) to pH 2 and extracted with DCM (3X). The combined extracts from the second organic layer was collected, dried over sodium sulfate, and evaporated under reduced pressure to afford **44** (515 mg, 95 % yield).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.44 – 7.25 (m, 5H), 4.55 (d, *J* = 1.3 Hz, 2H), 4.22 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.66 (t, *J* = 5.6 Hz, 2H), 2.31 – 1.94 (m, 2H).

***tert*-Butyl (S)-2-azido-4-(benzyloxy)butanoate (45)**. To a stirred solution of **44** (506 mg, 2.15 mmol) in dry ether (10 mL) and dry DCM (10 mL) under nitrogen was added *tert*-butyl-2,2,2-trichloroacetimidate (1.16 mL, 6.46 mmol) and the resulting reaction mixture was stirred at room temperature for 5 days. Additional *tert*-butyl-2,2,2-trichloroacetimidate (0.6 mL, 3.22 mmol) was added and the reaction mixture was stirred at room temperature for 2 days. The reaction was poured onto saturated bicarbonate and water (1:1) and extracted with DCM (3X). The combined organic extract was dried over sodium sulfate, concentrated under reduced pressure and the resulting residue was purified by flash chromatography (hexanes eluent for one column volume and then 20% EtOAc/ hexanes eluent) to give **45** (440 mg, 70 %

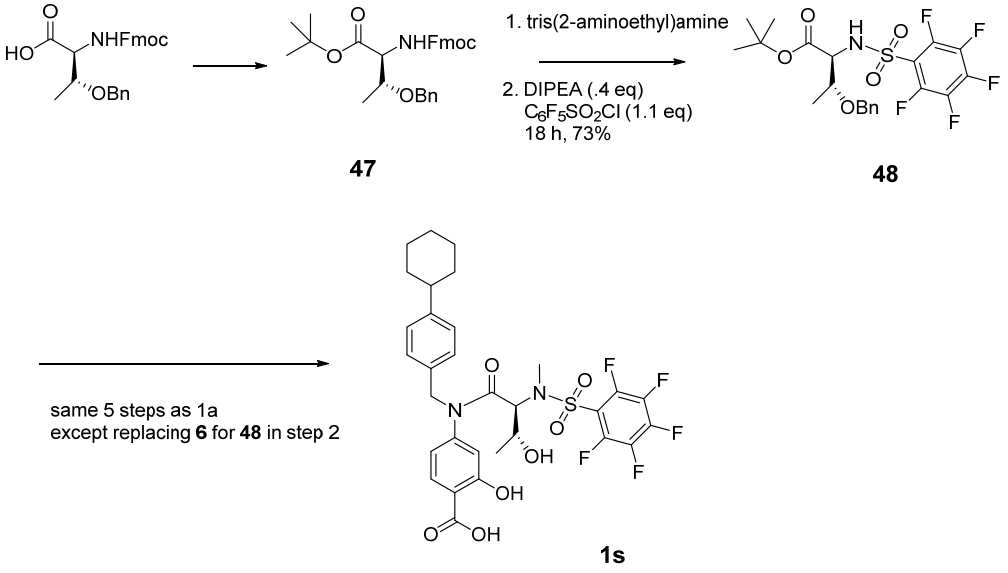
yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 – 7.30 (m, 5H), 4.54 (s, 2H), 4.06 – 3.94 (m, 1H), 3.66 – 3.55 (m, 2H), 2.26 – 2.09 (m, 1H), 1.93 (ddtd, *J* = 14.2, 9.1, 5.1, 0.8 Hz, 1H), 1.50 (s, 9H).

***tert*-Butyl *O*-benzyl-*N*-((perfluorophenyl)sulfonyl)-L-homoserinate (46)**. To a stirred solution of **45** (436 mg, 1.5 mmol) in THF (12 mL) under nitrogen was added triphenylphosphine (589 mg, 2.25 mmol) followed by water (0.270 mL, 15 mmol) and the resulting mixture was stirred at room temperature for 48 h, then poured onto 1:1 water: saturated sodium chloride and extracted with EtOAc (3X). The combined organic extracts were washed with saturated sodium chloride, dried over sodium sulfate and concentrated *in vacuo* to give crude *tert*-butyl *O*-benzyl-L-homoserinate. To a stirred solution of the crude *tert*-butyl *O*-benzyl-L-homoserinate (approx.1.5 mmol) in DCM (15 mL) at 0 °C under nitrogen was added pyridine (0.253 mL, 3.15 mmol) followed by pentafluorobenzenesulfonyl chloride (0.45 mL, 3.0 mmol) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was poured onto water and extracted with DCM (3X). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (10-20% EtOAc/ hexanes eluent) to provide **46** (260 mg, 35% yield over the 2 steps). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 5H), 6.30 (d, *J* = 8.9 Hz, 1H), 4.52 (d, *J* = 14.1 Hz, 1H), 4.48 (d, *J* = 14.1 Hz, 1H), 4.35 (ddd, *J* = 8.9, 6.5, 4.2 Hz, 1H), 3.71 – 3.45 (m, 2H), 2.30 – 2.12 (m, 1H), 2.04 (dddd, *J* = 14.8, 6.5, 5.0, 3.9 Hz, 1H), 1.35 (s, 9H).

(*S*)-4-(*N*-(4-Cyclohexylbenzyl)-4-hydroxy-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)-butanamido)-2-hydroxybenzoic acid (1q). Product **1q** was prepared using the sequence described for **1a** except starting with aminoester **46** instead of *tert*-butyl ((pentafluorophenyl)sulfonyl)-D-alaninate (**6**) in the second step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.97 (br. s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 2.1 Hz, 1H), 6.62 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.28 (dd, *J* = 11.3, 3.7 Hz, 1H), 5.05 (d, *J* = 14.5 Hz, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 3.91 – 3.41 (m, 3H), 3.20

(s, 3H), 2.58 – 2.40 (m, 1H), 2.13 – 1.64 (m, 7H), 1.53 – 1.17 (m, 5H). LCMS: 97% purity, HRMS (ESI) m/z 693.1651 $[M + Na]^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_7S$: 670.1772, found 670.1756.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-4-hydroxy-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)-butanamido)-2-hydroxybenzoic acid (1r). Product **1r** was prepared using the sequence described for **1q** except substituting (*R*)-4-benzyloxazolidin-2-one for (*S*)-4-benzyloxazolidin-2-one) in the first step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 8.3, 2.0 Hz, 1H), 5.28 (dd, *J* = 11.2, 3.7 Hz, 1H), 5.05 (d, *J* = 14.4 Hz, 1H), 4.54 (d, *J* = 14.4 Hz, 1H), 3.86 – 3.43 (m, 3H), 3.20 (s, 3H), 2.72 – 2.28 (m, 1H), 2.10 – 1.59 (m, 7H), 1.54 – 1.05 (m, 5H). LCMS: 98% purity, HRMS (ESI) m/z 671. 1846 $[M + H]^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_7S$: 670.1772, found 670.1769.



Scheme 7.

***tert*-Butyl *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*O*-benzyl-L-threoninate (47)**. To a stirred solution of commercially-available Fmoc-*O*-benzyl-L-threonine (1.5 g, 3.48 mmol) in dry ether (3 mL) and dry DCM (3 mL) under nitrogen was added *tert*-butyl-2,2,2-trichloroacetimidate (1.9 mL, 10.4 mmol) and the resulting reaction mixture was stirred at room temperature for 7 days. The suspension was filtered and rinsed once with a small volume of 1:1 ether: DCM and the combined filtrate and washes were applied directly to the flash column packed with silica in 80:20 hexanes DCM. The column was eluted with 80:20 hexanes: DCM eluent, then 80:20:7 hexanes: DCM: EtOAc eluent to afford 47 (1.63 g, 96% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.86 – 7.74 (m, 2H), 7.65 (dd, *J* = 7.5, 3.6 Hz, 2H), 7.47 – 7.27 (m, 9H), 5.56 (d, *J* = 9.7 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.55 – 4.13 (m, 7H), 1.48 (s, 9H), 1.29 (d, *J* = 11.5 Hz, 2H). HRMS (ESI) m/z 510.2250[M + Na]$^+$. HRMS (ESI+) calculated for $C_{30}H_{33}NO_5$: 487.2359, found 487.2358.

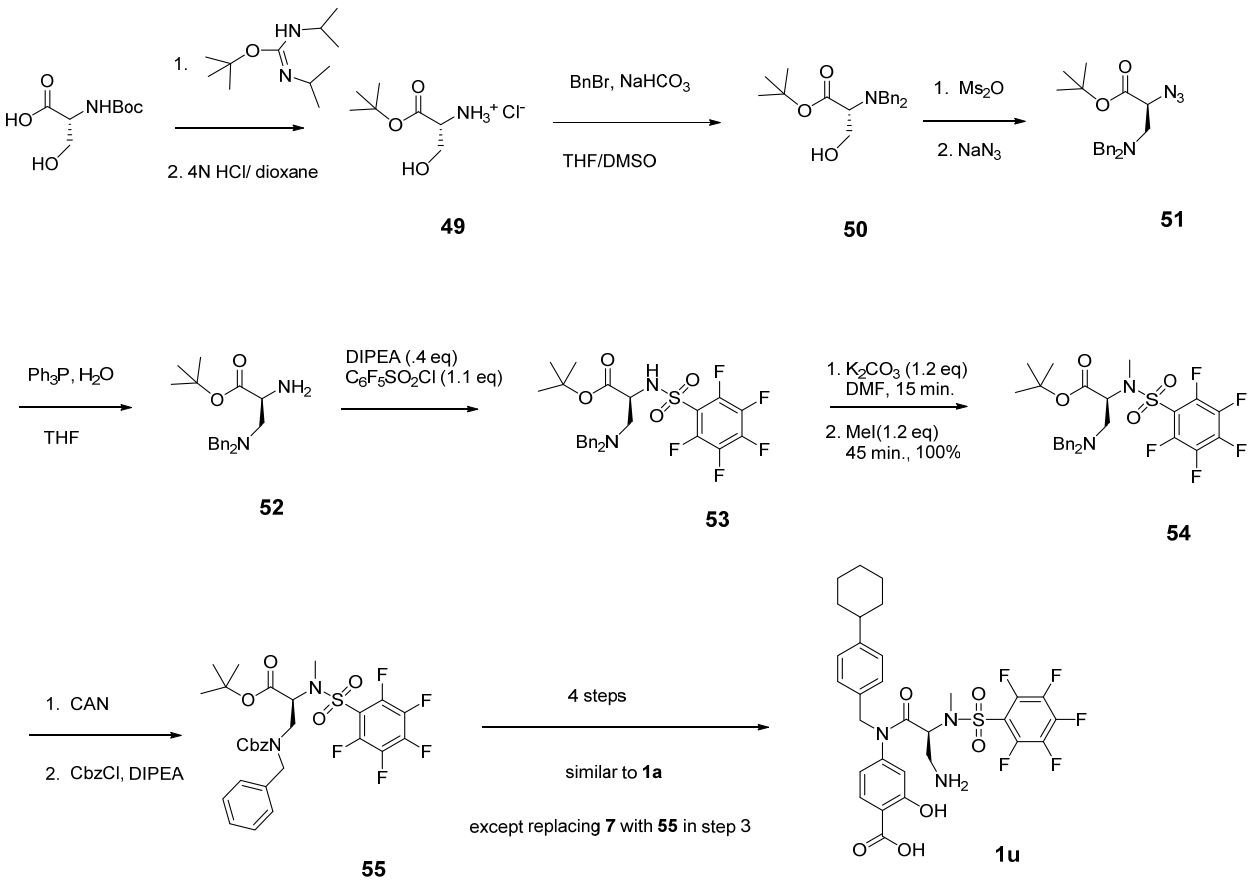
***tert*-Butyl *O*-benzyl-*N*-((pentafluorophenyl)sulfonyl)-L-threoninate (48)**. To a stirred solution of **47** (1.6 g, 3.28 mmol) in DCM (25 mL) was added 3.0 mL of tris(2-aminoethyl)amine and the resultant mixture was stirred overnight under nitrogen at room temperature. The crude reaction mixture was diluted with phosphate buffer (pH = 5-6), adjusted to pH = 7 with 5% aqueous HCl and extracted with DCM (2 X). The combined organic extracts were washed with phosphate buffer (1 X), saturated $NaHCO_3$ (1 X), dried over sodium sulfate and concentrated under reduced pressure. The resulting crude product, *tert*-butyl *O*-benzyl-L-threoninate was used as for the next step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 5H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 3.97 (qd, *J* = 6.3, 3.7 Hz, 1H), 3.30 (d, *J* = 3.7 Hz, 1H), 1.61 (br. s, 2H), 1.48 (s, 9H), 1.32 (d, *J* = 6.3 Hz, 3H).

To a stirred solution of *tert*-butyl *O*-benzyl-L-threoninate (approx. 3.28 mmol) in DCM (28 mL) under nitrogen at 0 °C was added DIPEA (0.80 mL, 4.59 mmol) followed by pentafluorobenzenesulfonyl chloride (0.58 mL, 3.94 mmol) and the resulting mixture was allowed to warm to room temperature and stirred at this temperature for overnight. The reaction mixture was poured onto water and extracted with

DCM (3X). The combined extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (0- 15% EtOAc/hexane) to provide **48** (1.26 g, 78% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.29 (m, 3H), 7.27 – 7.21 (m, 2H), 5.81 (d, *J* = 10.1 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.20 – 4.06 (m, 2H), 1.38 (d, *J* = 6.2 Hz, 3H), 1.35 (s, 9H).

4-((2S,3R)-N-(4-cyclohexylbenzyl)-3-hydroxy-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfon-amido)butanamido)-2-hydroxybenzoic acid (1s). Product **1s** was prepared using the sequence described for **1a** except starting with aminoester **48** instead of *tert*-butyl ((pentafluorophenyl)sulfonyl)-D-alaninate (**6**) in the second step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.66 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.23 – 6.92 (m, 4H), 6.84 – 6.52 (m, 2H), 4.98 – 4.76 (m, 2H), 4.75 – 4.57 (m, 1H), 4.30 – 4.08 (m, 1H), 3.25 (s, 3H), 3.23 – 3.01 (m, 1H), 2.48 (s, 1H), 2.03 – 1.55 (m, 5H), 1.54 – 1.00 (m, 8H). LCMS: > 99% purity, MS (ESI) m/z 671.1[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_7S$: 670.1772, found 670.1778, M+H = 671.1851.

4-((2R,3S)-N-(4-cyclohexylbenzyl)-3-hydroxy-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfon-amido)butanamido)-2-hydroxybenzoic acid (1t). Product **1t** was prepared using the sequence described for **1s** except replacing Fmoc-*O*-benzyl-L-threonine with Fmoc-*O*-benzyl-D-threonine in the first step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.66 (s, 1H), 7.99 – 7.79 (m, 1H), 7.23 – 6.92 (m, 4H), 6.84 – 6.52 (m, 2H), 5.06 – 4.74 (m, 2H), 4.73 – 4.53 (m, 1H), 4.29 – 4.02 (m, 1H), 3.25 (s, 3H), 2.48 (s, 1H), 2.03 – 1.55 (m, 5H), 1.51 – 0.93 (m, 8H). LCMS: 97% purity, MS (ESI) m/z 671.1[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_7S$: 670.1772, found 670.1758.



Scheme 8.

***tert*-Butyl D-serinate hydrochloride (49).** A solution of Boc-D-serine (2g, 9.75 mmol) in dry DCM (20 mL) was treated with 2-*tert*-butyl-1,3-diisopropylisourea (3.5 mL, 15.5 mmol) under nitrogen and the reaction was stirred at reflux overnight. The reaction was not complete. A additional portion of 2-*tert*-butyl-1,3-diisopropylisourea (3.5 mL, 15.5 mmol) was added and the reaction was stirred at reflux for 36 h. The reaction was cooled to room temperature, and the resulting suspension diluted with 40% ether/hexane, filtered and the solid washed with 40% ether/hexane. The combined filtrate and washes were concentrated under reduced pressure and the resulting residue purified by flash chromatography (0-30% EtOAc in hexanes gradient to provide *tert*-butyl (*tert*-butoxycarbonyl)-D-serinate (1.69 g, 66% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.43 (br. s, 1H), 4.27 (br. s, 1H), 3.91 (dd, *J* = 6.1, 3.9 Hz, 2H), 2.41 (br. s, 1H), 1.50 (s, 9H), 1.47 (s, 9H). To a stirred solution 4N HCl in anhydrous dioxane (70

mL) at 0 °C under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)-D-serinate (1.5 g, 5.75 mmol) in one portion. The resulting reaction mixture was stirred at 0 -20 °C for 2h and then concentrated *in vacuo* to afford **49** (1.17 g, 100% yield) as a white solid which was used as is.

***tert*-Butyl dibenzyl-D-serinate (50)**. To a stirred solution of **49** (1.16 g, 5.7 mmol) in dry THF (28 mL) and dry DMSO (7 mL) was added sodium bicarbonate (2.4g, 28.5 mmol) and benzyl bromide (2.0 mL, 17.1 mmol) and the resulting mixture was heated at reflux for 18 h under argon. The suspension was added to EtOAc and water and extracted with EtOAc (3X). The combined organic extract was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (0-20% EtOAc/hexanes eluent) gave **50** (1.42 g, 73% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.25 (m, 10H), 3.95 (d, *J* = 13.4 Hz, 2H), 3.72 (d and overlapping m, *J* = 13.4 Hz, 3H), 3.46 (t, *J* = 7.6 Hz, 1H), 2.55 (t, *J* = 5.7 Hz, 1H), 1.59 (s, 9H).

***tert*-Butyl (*S*)-2-azido-3-(dibenzylamino)propanoate (51)**. Following the procedure of Couturier et al. (Organic Letters (2006), 8(10), 2183-2186), to a stirred solution of **50** (1.41g, 4.13 mmol) in dry acetonitrile (28 mL) under nitrogen was added TEA (0.8 mL, 5.7 mmol) followed by methanesulphonic anhydride (0.93 g, 5.37 mmol) and the resulting reaction solution was stirred at room temperature until complete by tlc (2 h). To this reaction mixture was added sodium azide (0.81g, 12.39 mmol) followed by dry DMF (7 mL) and the resulting mixture was warmed at 60 -70 °C for 4 h, then cooled in an ice bath. The reaction mixture was poured onto water and ether and extracted with ether (3X). The combined ethereal layers were washed with saturated sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography (0-15% EtOAc/hexanes gradient) provided **51** (1.32 g, 87% yield) as a colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 10H), 3.81 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.70 (q, *J* = 13.6 Hz, 4H), 3.07 – 2.82 (m, 2H), 1.48 (s, 9H).

***tert*-Butyl (*S*)-2-amino-3-(dibenzylamino)propanoate (52)**. To a stirred solution of **51** (1.3 g, 3.55 mmol) in dry THF (24 mL) under nitrogen was added triphenylphosphine (1.4 g, 5.32 mmol) followed by water (0.64 mL, 35.5 mmol) and the resulting mixture was stirred at room temperature for 4 h, then poured onto water and EtOAc and extracted with EtOAc (3X). The combined organic extracts were washed with saturated sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography (30-60% EtOAc/ hexanes gradient) provided **52** (0.989 g, 82% yield) as a colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.22 (m, 10H), 3.72 (d, *J* = 13.5 Hz, 2H), 3.56 (d and overlapping m, *J* = 13.5 Hz, 3H), 2.80 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.57 (dd, *J* = 12.7, 8.4 Hz, 1H), 1.47 (s, 9H).

***tert*-Butyl (*S*)-3-(dibenzylamino)-2-((pentafluorophenyl)sulfonamido)propanoate (53)**. To a stirred solution of **52** (0.98 g, 2.88 mmol) in dry DCM (17 mL) under nitrogen at 0 °C was added DIPEA (0.65 mL, 3.74 mmol) followed by pentafluorobenzenesulfonyl chloride (0.47 mL, 3.17 mmol) and the resulting solution was allowed to warm to room temperature and stirred at this temperature for 18 h. The crude reaction mixture was poured onto water and extracted with DCM (3X). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by chromatography (8-15% EtOAc/hexanes gradient) to give **53** (1.34 g, 82 % yield) as a film. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.59 – 7.12 (m, 10H), 5.71 (br. s, 1H), 4.23 (t, *J* = 5.9 Hz, 1H), 3.74 – 3.52 (m, 4H), 2.88 (qd, *J* = 13.5, 5.9 Hz, 2H), 1.36 (s, 9H).

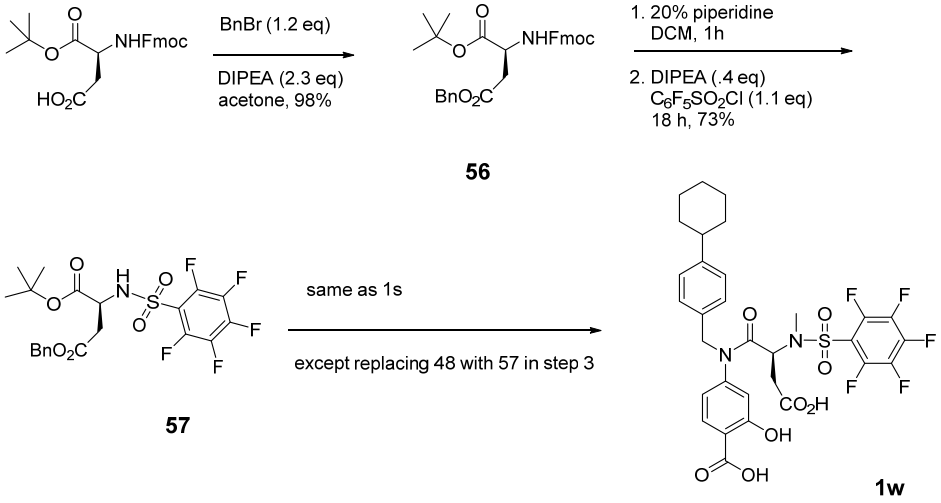
***tert*-Butyl (*S*)-3-(dibenzylamino)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanoate (54)**. To a stirred solution of **53** (1.28 g, 2.24 mmol) in dry DMF (18 mL) under nitrogen was added potassium carbonate (0.43 g, 3.14 mmol) and the resulting suspension was stirred at room temperature for 5 min before addition of methyl iodide (0.2 mL, 3.14 mmol). After continuing the stirring for an additional 50 min, the reaction mixture was poured onto water and extracted with ether (3X). The

combined organic layers were washed with saturated sodium chloride, dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (0-10% EtOAc/ hexanes gradient) to afford **54** (1.15 g, 88% yield) as a foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.23 (m, 10H), 5.03 (t, *J* = 7.4 Hz, 1H), 3.99 (d, *J* = 13.3 Hz, 2H), 3.38 (d, *J* = 13.3 Hz, 2H), 2.84 (d, *J* = 7.4 Hz, 2H), 2.59 (s, 3H), 1.36 (s, 9H).

***tert*-Butyl (*S*)-3-(benzyl((benzyloxy)carbonyl)amino)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)propanoate (55)**. To a stirred solution of **54** (1.13 g, 1.93 mmol) in acetonitrile (25 mL) and water (5 mL) under nitrogen was added ceric ammonium nitrate (2.65 g, 4.8 mmol) in one portion and the resulting orange mixture was stirred at room temperature for 2h. The crude reaction mixture was poured onto water/ saturated sodium bicarbonate (1:1) and extracted into EtOAc (2X) and DCM (1X). The combined organic extracts were washed with saturated sodium chloride, dried over sodium sulfate and concentrated *in vacuo* to afford *tert*-butyl (*S*)-3-(benzylamino)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanoate (1.09 g) which was used as is. To *tert*-butyl (*S*)-3-(benzylamino)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanoate (1.09 g, 1.9 mmol) in dry THF (18 mL) under nitrogen was added DIPEA (0.4 mL, 2.3 mmol) followed by benzyl chloroformate (0.33 mL, 2.3 mmol) and the resulting solution was stirred at room temperature for 24 h. The crude reaction mixture was poured onto water and extracted with DCM (3X). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (18% EtOAc/hexanes eluent) to provide **55** (1.16 g, 95% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) Rotomer 1: Rotomer 2 (1.8: 1 ratio) δ 7.48 – 7.30 (m, 9H), 7.27 – 7.18 (m, 1H), 5.34 – 5.14 (m, 2H), 5.09 – 4.96 (m, 1H), 4.85 (rotomer 1: d, *J* = 16.1 Hz, 1H), 4.75 (rotomer 2: d, *J* = 15.5 Hz, 1H), 4.54 (rotomer 2: d, *J* = 15.5 Hz, 1H), 4.41 (rotomer 1: d, *J* = 16.1 Hz, 1H), 3.93 (dd, *J* = 14.8, 10.8 Hz, 1H), 3.64 – 3.43 (m, 2H), 3.03 (rotomer 1: s, 3H), 2.84 (rotomer 2: s, 3H), 1.35 (rotomer 1: s, 9H), 1.29 (rotomer 2: s, 9H).

(*S*)-4-(3-Amino-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoic acid (1u). Product **1u** was prepared as described for **1a** except replacing **7** with **55** in step 3. ^{1}H NMR (300 MHz, DMSO-*d*6) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.50 – 6.26 (m, 2H), 5.16 – 5.02 (m, 1H), 4.91 (d, *J* = 14.7 Hz, 1H), 4.46 (d, *J* = 14.7 Hz, 1H), 3.09 (s, 3H), 2.43 (t, *J* = 6.1 Hz, 1H), 1.87 – 1.61 (m, 6H), 1.52 – 1.06 (m, 6H). LCMS: 97% purity, MS (ESI+) m/z 656.1848[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{30}F_5N_3O_6S$: 655.1775, found 655.1776.

(*R*)-4-(3-Amino-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoic acid (1v). Product **1v** was prepared as described for **1u** except replacing **49** with commercially available ***tert*-Butyl L-serinate hydrochloride** in step 2. ^{1}H NMR (300 MHz, DMSO-*d*6) δ 8.06 (br. s, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.50 – 6.26 (m, 2H), 5.16 – 5.02 (m, 1H), 4.91 (d, *J* = 14.7 Hz, 1H), 4.46 (d, *J* = 14.7 Hz, 1H), 3.49 – 3.19 (H_2O and overlapping m), 3.09 (s and overlapping m, 4H), 2.43 (t, *J* = 6.1 Hz, 1H), 1.87 – 1.61 (m, 5H), 1.52 – 1.06 (m, 5H). LCMS: 94% purity, HRMS (ESI+) m/z 656.1849[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{30}F_5N_3O_6S$: 655.1775, found 655.1777.



Scheme 9.

4-Benzyl 1-(*tert*-butyl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (56). To a stirred solution of *N*-Fmoc-L-aspartic acid *tert*-butyl ester (1.02 g, 2.48 mmol) in acetone (12 mL) under nitrogen at 0 °C was added DIPEA (0.52 mL, 2.98 mmol) followed by benzyl bromide (0.35 mL, 2.98 mmol). The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The resultant mixture was concentrated under reduced pressure, dissolved in EtOAc/ water, poured onto saturated sodium bicarbonate and extracted with EtOAc (3X). The combined organic extracts were washed with saturated sodium chloride, dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (0-20% EtOAc/ hexanes gradient) to provide **56** (1.23 g, 98% yield) as a colorless film. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.47 – 7.25 (m, 9H), 5.79 (d, *J* = 8.2 Hz, 1H), 5.16 (q, *J* = 12.2 Hz, 2H), 4.55 (dd, *J* = 8.2, 4.5 Hz, 1H), 4.48 – 4.29 (m, 2H), 4.24 (t, *J* = 7.1 Hz, 1H), 3.14 – 2.79 (m, 2H), 1.44 (s, 9H).

4-Benzyl 1-(*tert*-butyl) ((pentafluorophenyl)sulfonyl)-L-aspartate (57). To a stirred solution of **56** (1.2 g, 2.4 mmol) in dry DCM (15 mL) under nitrogen at 0 °C was added piperidine (3.75 mL) and the reaction mixture was stirred for 1 h at 0 °C and concentrated under reduced pressure. Toluene was added and the mixture was concentrated *in vacuo* to afford crude 4-benzyl 1-(*tert*-butyl) L-aspartate, which was used as is. To a stirred solution of crude 4-benzyl 1-(*tert*-butyl) L-aspartate (2.4 mmol) and DIPEA (0.17 mL, 0.96 mmol) in DCM (18 mL) under nitrogen at 0 °C was added pentafluorobenzenesulfonyl chloride (0.39 mL, 2.64 mmol). The reaction was allowed to warm to room temperature and stirred at this temperature overnight. The crude reaction mixture was poured onto 5% aq. HCl and extracted with DCM (3X). The combined extracts were washed with water, then brine and dried over sodium sulfate and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography (75:15:5 to 75:15:10 hexanes: DCM: EtOAc eluent) provided **57** (0.89 g, 73% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 – 7.30 (m, 5H), 5.14 (q, *J* = 12.1 Hz, 2H), 4.38 (dt, *J* = 8.9, 4.4 Hz, 1H), 3.19

– 2.82 (m, 2H), 1.33 (s, 9H). HRMS (ESI+) m/z 532.0821[M + Na]$^+$. HRMS (ESI+) calculated for $C_{21}H_{20}F_5NO_6S$: 509.0931, found 509.0930.

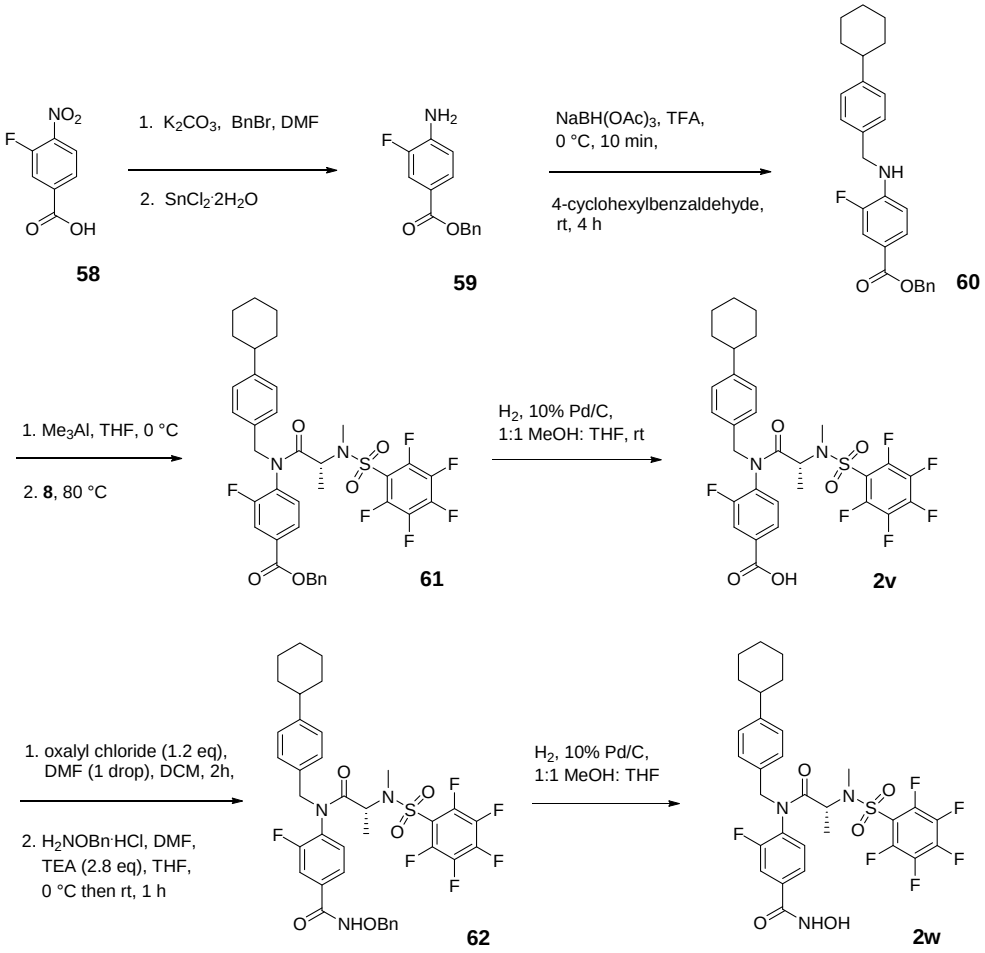
(*S*)-4-(3-carboxy-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoic acid (1w). Product **1w** was prepared using the sequence described for **1s** except replacing **48** with **57** in the third step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.83 – 6.69 (m, 2H), 5.43 – 5.31 (m, 1H), 4.99 (d, *J* = 14.4 Hz, 1H), 4.69 (d, *J* = 14.4 Hz, 1H), 3.13 (s, 3H), 2.94 – 2.60 (m, 2H), 2.57 – 2.39 (m, 1H), 2.06 – 1.60 (m, 5H), 1.55 – 1.13 (m, 5H). LCMS: 98% purity, HRMS (ESI) m/z 683.1497 [M - H]$^-$. HRMS (ESI$^-$) calculated for $C_{31}H_{29}F_5N_2O_8S$: 684.1565, found 684.1568.

(*R*)-4-(3-carboxy-*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-2-hydroxybenzoic acid (1x). Product **1x** was prepared using the sequence described for **1w** except starting with *N*-Fmoc-D-aspartic acid *tert*-butyl ester instead of *N*-Fmoc-L-aspartic acid *tert*-butyl ester in the first step. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.83 – 6.69 (m, 2H), 5.43 – 5.31 (m, 1H), 4.99 (d, *J* = 14.4 Hz, 1H), 4.69 (d, *J* = 14.4 Hz, 1H), 3.13 (s, 3H), 2.94 – 2.60 (m, 2H), 2.57 – 2.39 (m, 1H), 2.06 – 1.60 (m, 5H), 1.55 – 1.13 (m, 5H). LCMS: 97% purity, HRMS (ESI) m/z 707.1468 [M+Na$^+$] . HRMS (ESI+) calculated for $C_{31}H_{29}F_5N_2O_8S$: 684.1565, found 684.1576.

Analogs from Table 2

Analogs **2a-y** were prepared from the corresponding anilines by acylation with either *N*-methyl-*N*-((pentafluorophenyl)sulfonyl)glycinoyl chloride[14] or with acid chloride **8**. An example of variation of the benzoic acid portion of the molecule (Table 2) is illustrated in Scheme 10 with the preparation of analogs **2v** and **2w**. Starting with protection of 3-fluoro-4-nitrobenzoic acid as the benzyl ester using benzyl

bromide and potassium carbonate, followed by reduction of the nitro group with stannous chloride, aniline **59** was prepared in 88% overall yield. Reductive alkylation with 4- cyclohexylbenzaldehyde using sodium cyanoborohydride in TFA (Hadd, Michael J.; Hocker, Michael D.; Holladay, Mark W.; Liu, Gang; Rowbottom, Martin W.; Xu, Shimin PCT Int. Appl. (2013), WO 2013056070) provided the desired secondary aniline **60** that was acylated through the corresponding aluminum anilide with acid chloride **8** to give the benzyl-protected intermediate **61**. Catalytic hydrogenolysis afforded benzoic acid **2v,** which was further elaborated to the benzohydroxamic acid **2w** using the method described above for **1d.** Some representative examples are shown below:



Scheme 10.

Benzyl 4-amino-3-fluorobenzoate (59). To a stirred solution of 3-fluoro-4-nitrobenzoic acid (**58**, 4.05 g, 21.9 mmol) in DMF (109 mL) was added potassium carbonate (3.32 g, 24.1 mmol). Stirring was continued at room temperature for 10 min before addition of benzyl bromide (2.51 mL, 20.8 mmol). The resulting reaction mixture was stirred at room temperature for 3.75 h, then poured onto cold water and extracted with EtOAc (2 X). The combined organic extracts were washed with water (3 X), then saturated sodium chloride, dried over sodium sulfate and concentrated *in vacuo* to afford benzyl 3-fluoro-4-nitrobenzoate (6.19 g) as a yellow oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.12 (dd, *J* = 8.8, 7.0 Hz, 1H), 8.04 – 8.00 (m, 1H), 8.00 – 7.96 (m, 1H), 7.54 – 7.37 (m, 5H), 5.43 (s, 2H). To a stirred solution of crude 3-fluoro-4-nitrobenzoate (6.19 g, 22 mmol) in EtOAc (238 mL) under nitrogen was added $SnCl_2 \cdot 2H_2O$ (25.4 g, 112.6 mmol). The resulting reaction mixture was stirred over night at 80 °C, cooled, then poured onto cold water. The pH was adjusted to pH = 8 using aq. 10% sodium bicarbonate and the resulting mixture was stirred at room temperature for 45 min and then extracted with EtOAc (3 X). The combined organic extracts were washed with water and then brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (2:8 EtOAc/hexanes) provided **59** (4.83 g, 90% yield) as a pale yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.75 – 7.72 (m, 1H), 7.72 – 7.68 (m, 1H), 7.48 – 7.32 (m, 5H), 6.77 (t, *J* = 8.6 Hz, 1H), 5.33 (s, 2H).

Benzyl 4-((4-cyclohexylbenzyl)amino)-3-fluorobenzoate (60). To a solution of **59** (356 mg, 1.45 mmol) in TFA (3.3 mL) under nitrogen at 0 °C was added sodium triacetoxyborohydride (617 mg, 2.91 mmol) portion wise. The mixture was stirred at 0 °C for 10 min. before addition of 4-cyclohexylbenzaldehyde (290 mg, 1.54 mmol). The resulting reaction mixture was stirred at room temperature for 4 h, poured onto cold water and extracted with EtOAc (2 X). The combined organic extracts were washed with water (3 X), then with 10% aq. sodium bicarbonate (2 X), dried over sodium sulfate and concentrated under reduced pressure. The pH after the last wash was 7-8. Purification by flash chromatography (12: 88 hexane/EtOAc) provided **60** (446 mg, 74% yield) as a white solid. ^{1}H

NMR (300 MHz, Chloroform-*d*) δ 7.77 (ddd, *J* = 8.5, 1.9, 0.8 Hz, 1H), 7.70 (dd, *J* = 12.3, 1.9 Hz, 1H), 7.50 – 7.34 (m, 5H), 7.32 – 7.16 (m, 4H), 6.68 (t, *J* = 8.5 Hz, 1H), 5.33 (s, 2H), 4.40 (s, 2H), 2.64 – 2.36 (m, 1H), 2.03 – 1.68 (m, 5H), 1.59 – 1.15 (m, 5H).

Benzyl (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido) propanamido)-3-fluorobenzoate (61). To a stirred solution of **60** (596 mg, 1.42 mmol) in THF (11 mL) under nitrogen at 0 °C was added a solution of trimethylaluminum (1.78 mL of 2M in toluene, 3.57 mmol) and the mixture was warmed to room temperature and stirred at this temperature for 15 min. To the resulting solution was added a solution of **8** (652 mg, 1.85 mmol) in THF (7.7 mL). The reaction mixture was stirred at 80 °C for 4.5 h, poured onto 10% $KHSO_4$/ Na_2SO_4 buffer and ice and then extracted with EtOAc (2 X). The combined organic layers were washed with water and then saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (10 -14% EtOAc/hexane) provided **61** (497 mg, 48% yield) as a colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 12.0, 9.8 Hz, 2H), 7.51 – 7.33 (m, 5H), 7.20 – 6.87 (m, 5H), 5.38 (s, 2H), 5.32 (d, *J* = 14.3 Hz, 1H), 4.75 (q, *J* = 7.1 Hz, 1H), 4.20 (d, *J* = 14.3 Hz, 1H), 3.16 (s, 3H), 2.46 (s, 1H), 1.93 – 1.69 (m, 6H), 1.47 – 1.30 (m, 4H), 1.23 (d, *J* = 7.1 Hz, 3H).

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-3-fluorobenzoic acid (2v). To a stirred solution of **61** (487 mg, 0.665 mmol) in methanol (8 mL) and THF (8 mL) was added 10% Pd/C (60.3 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 6.5 h. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated to afford **2v** (443 mg, 100% yield). A portion of **2v** (100 mg) was purified by prep. TLC (1:1 hexane: EtOAc with 0.1% AcOH) and the resulting oil was recrystallized from 1:1 ether hexanes to give pure **2v**. ^{1}H NMR (300 MHz,

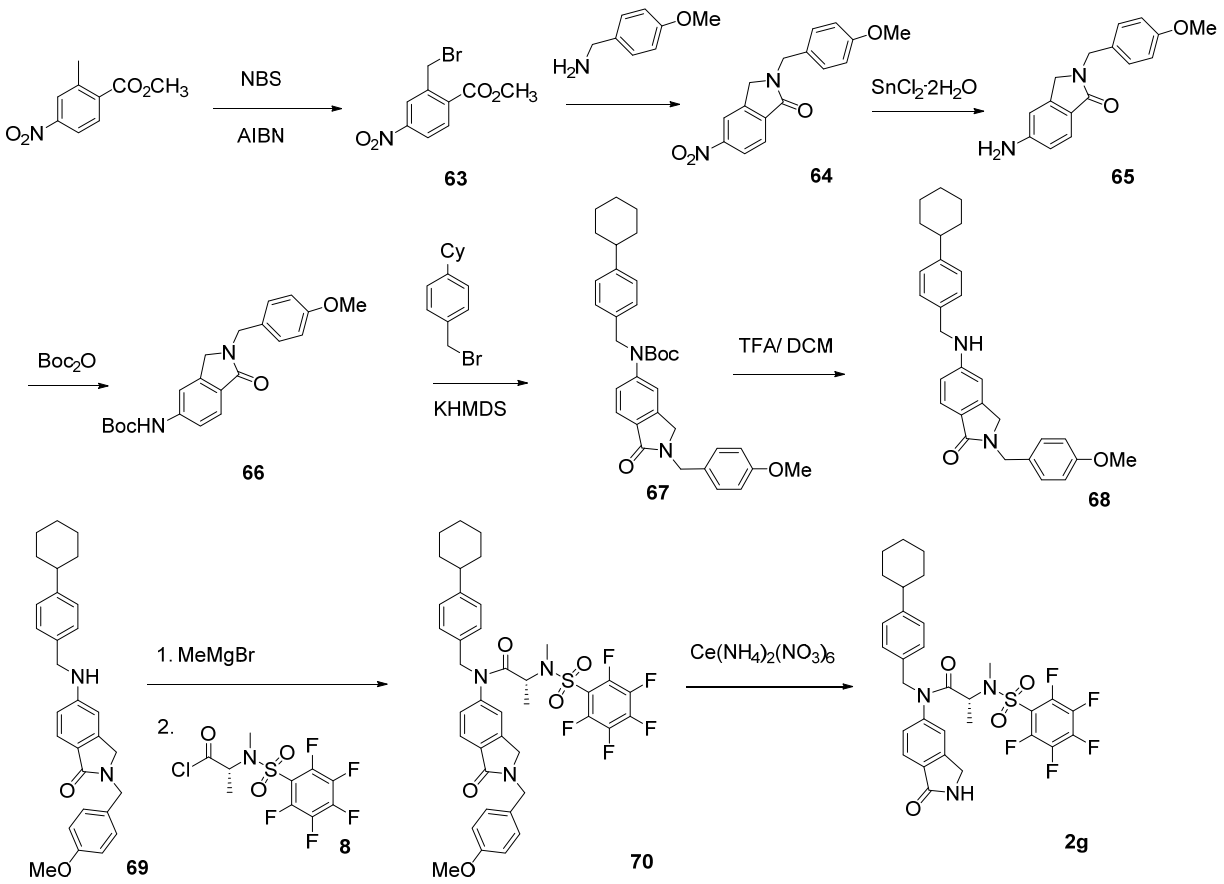
Chloroform-*d*) δ 7.88 (m, 2H), 7.32 – 6.82 (m, 5H), 5.27 (m, 1H), 4.75 (m, 1H), 4.23 (m, 1H), 3.13 (s, 3H), 2.40 (s, 1H), 1.95 – 1.62 (m, 5H), 1.54 – 1.01 (m, 8H).

LCMS: > 99% purity, MS (ESI) m/z 643[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{28}F_6N_2O_5S$: 642.1623, found 642.1613.

(*R*)-*N*-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)propanamido)-3-fluorobenzamide (62). To a stirred solution of **2v** (111 mg, 0.17 mmol) in DCM (3.1 mL) was added oxalyl chloride (0.018 mL, 0.208 mmol) and DMF (1 drop). The resulting reaction solution was stirred at room temperature under nitrogen for 2 h and then concentrated under reduced pressure. The resulting residue was re-dissolved in DCE (3 mL) and concentrated *in vacuo* to afford (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)prop-anamido)-3-fluorobenzoyl chloride, which was used as is.

To a solution of *O*-benzylhydroxylamine hydrochloride (38.6 mg, 0.242 mmol) in DMF (3.1 mL) was added TEA (0.068 mL, 0.49 mmol). The mixture was stirred for 15 min, then added to a solution of (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfon-amido)propanamido)-3-fluorobenzoyl chloride (0.173 mmol) in THF (3.1 mL) at 0 °C under nitrogen. The resultant reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with 10 % potassium bisulfate, poured onto water and extracted with EtOAc (2 X). The combined organic extracts were washed with water, then washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (25% EtOAc/ hexanes) to provide **62** (40.4 mg, 31% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 10.3 Hz, 1H), 7.51 – 7.37 (m, 5H), 7.14 – 6.89 (m, 6H), 5.30 (d, *J* = 13.8 Hz, 1H), 5.06 (br. s, 1H), 4.79 – 4.60 (m, 1H), 4.20 (d, *J* = 13.8 Hz, 1H), 3.16 (s, 3H), 2.53 – 2.39 (m, 1H), 1.93 – 1.69 (m, 6H), 1.47 – 1.33 (m, 4H), 1.23 (d, *J* = 7.1 Hz, 3H).

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-3-fluoro-*N*-hydroxybenzamide (2w). To a stirred solution of **62** (36.2 mg, 0.0484 mmol) in methanol (1.6 mL) and THF (1.6 mL) was added 10% Pd/C (4.2 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 2.5 h. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated under reduced pressure and residue purified by prep. TLC (65:35 hexane/ acetone eluent) to provide **2w** (17 mg, 53% yield) as a foam. ^{1}H NMR (300 MHz, Chloroform-*d*) mixture of rotomers δ 7.89 – 7.40 (m, 1H), 7.24 – 6.81 (m, 7H), 5.30 and 5.18 (2 d (5:2 ratio), *J* = 14.2 Hz, 1H), 4.86 – 4.56 (m, 1H), 4.38 and 4.24 (2 d (2:5 ratio), *J* = 14.2 Hz, 1H), 3.14 and 3.08 (2 s (5:2), 3H), 2.54 – 2.39 (m, 2H), 1.95 – 1.59 (m, 6H), 1.49 – 1.28 (m, 4H), 1.24 (d, *J* = 7.1 Hz, 3H). LCMS: > 99% purity, MS (ESI) m/z 658[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_6N_3O_5S$: 657.1732, found 657.1716.



Scheme 11.

Methyl 2-(bromomethyl)-4-nitrobenzoate (63). To a solution of 2-methyl-4-nitrobenzoic acid methyl ester (2.0 g, 10.36 mmol) in carbon tetrachloride (80 mL) and 1,1'azobis(cyclohexanecarbonitrile) (0.63 g, 2.56 mmol) was added N-bromosuccinimide (2.18 g, 12.25 mmol) and the resulting solution was heated at reflux for 5h and allowed to sit at room temperature overnight. The reaction mixture was concentrated under reduced pressure and to the resulting residue was added DCM. The solid was filtered off and washed several times with DCM. The combined filtrate and washes were loaded onto a silica column and eluted with 10% EtOAc/hexane to provide slightly impure **63** (1.82 g, 65% yield) which was carried on as is to the next step.

2-(4-Methoxybenzyl)-5-nitroisoindolin-1-one (64). To **63** (1.82 g, 6.68 mmol) in methanol (20 mL) was added 4-methoxybenzylamine (0.87 mL, 6.68 mmol) and TEA (2.8 mL, 20 mmol) and the resulting mixture was warmed at reflux for 48 h. The reaction mixture was allowed to cool, poured onto aqueous 10% HCl and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Chromatography (30% EtOAc/ hexanes eluent and then 0.5% methanol in DCM eluent) followed by trituration with small volume of 20% EtOAc/hexanes afforded pure **64** (989 mg, 47% yield) as a yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.38 (dd, *J* = 8.3, 2.1 Hz, 1H), 8.30 – 8.23 (m, 1H), 8.09 – 7.98 (m, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.79 (s, 2H), 4.38 (s, 2H), 3.82 (s, 3H).

5-Amino-2-(4-methoxybenzyl)isoindolin-1-one (65). To a stirred solution of crude **64** (925 mg, 3.1 mmol) in EtOAc (60 mL) under nitrogen was added $SnCl_2{\cdot}2H_2O$ (3.5 g, 15.5 mmol). The resulting reaction mixture was stirred for 5h at 80 °C, cooled, and then poured onto cold water. The pH was adjusted to pH = 8 using aqueous 10% sodium bicarbonate and the resulting mixture was stirred at room

temperature for 1h and then extracted with EtOAc (2X) and DCM (1X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield **65** (850 mg, 100% yield) as a yellow powder. HRMS (ESI+) m/z 269.1280$[M + H]^+$. HRMS (ESI+) calculated for $C_{16}H_{16}N_2O_2$: 268.1212, found 268.1208.

***tert*-Butyl (2-(4-methoxybenzyl)-1-oxoisoindolin-5-yl)carbamate (66).** To a suspension of **65** (400 mg, 1.5 mmol) in ethanol (20 mL) was added di-*tert*-butyl dicarbonate (981 mg, 4.5 mmol) and the resulting slurry was warmed at 70 °C overnight. The mixture was concentrated under reduced pressure and purified by flash chromatography to provide **66** (495 mg, 90% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.74 (br. s, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 7.18 (dd, *J* = 8.2 Hz, *J* = 1.7 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.77 (s, 1H), 4.73 (s, 2H), 4.21 (s, 2H), 3.80 (s, 3H), 1.53 (s, 9H).

***tert*-Butyl (4-cyclohexylbenzyl)(2-(4-methoxybenzyl)-1-oxoisoindolin-5-yl)carbamate (67).** To a stirred solution of **66** (486 mg, 1.32 mmol) in DMF (8 mL) at 0 °C under nitrogen was added KHMDS (1.58 mL of 1M in THF, 1.58 mmol). After stirring at 0 °C for 10 min, a solution of 1-(bromomethyl)-4-cyclohexylbenzene (514 mg, 1.98 mmol) was added. The reaction was allowed to warm to room temperature and stirring was continued at this temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride, poured onto water and extracted with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (20-50% EtOAc/hexanes gradient) provided **67** (550 mg, 77% yield). HRMS (ESI+) m/z 541.3038$[M + H]^+$. HRMS (ESI+) calculated for $C_{34}H_{40}N_2O_4$: 540.2988, found 540.2967.

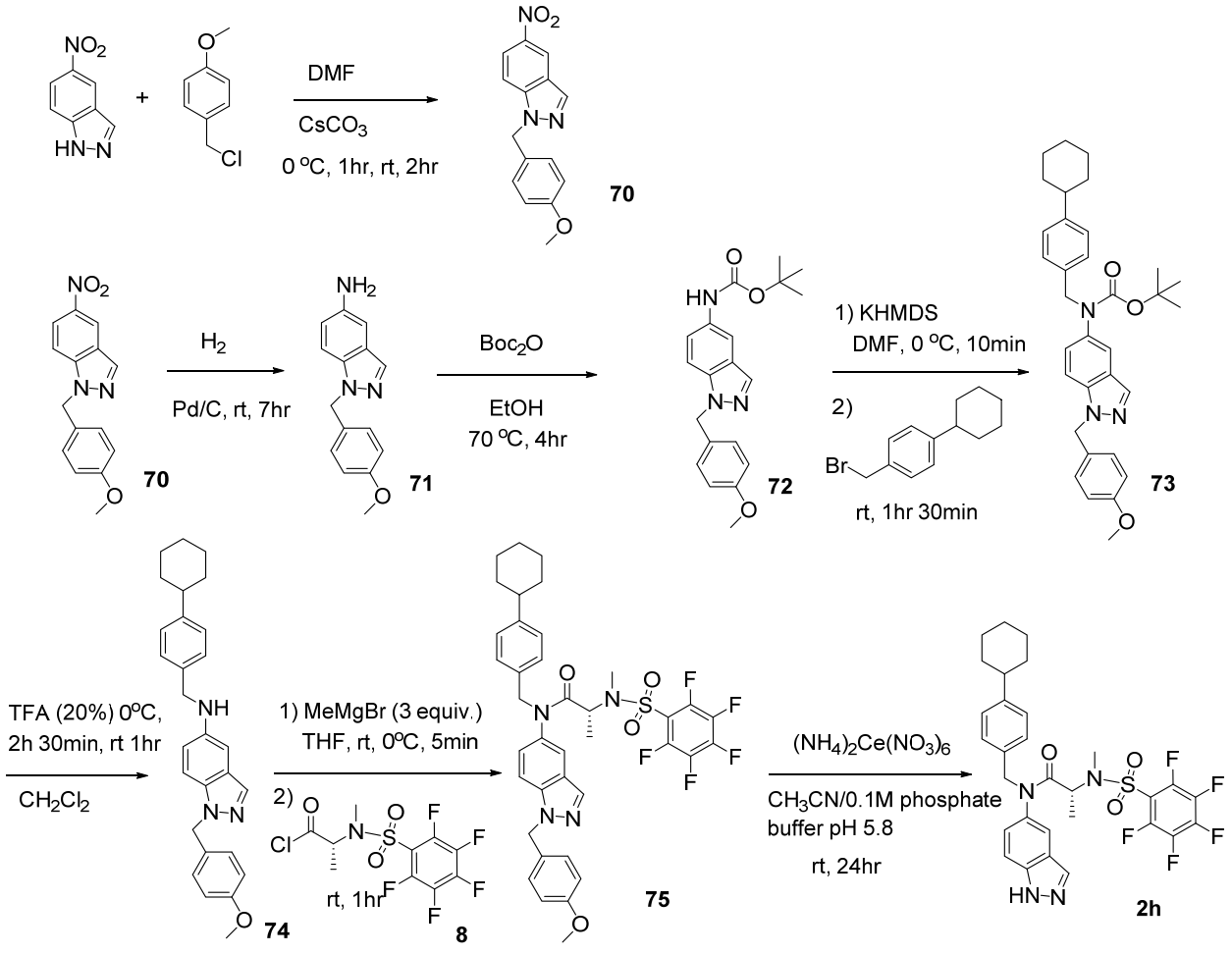
5-((4-Cyclohexylbenzyl)amino)-2-(4-methoxybenzyl)-isoindolin-1-one (68). To a stirred solution of **67** (265 mg, 0.49 mmol) in DCM (10 mL) at 0 °C under nitrogen was added TFA (2 mL). The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 5h. The mixture was poured onto ice

water, made basic by addition of saturated aqueous sodium bicarbonate and extracted with DCM (3X). The combined organic extracts were washed with dilute aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide **68** (206 mg, 96 % yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.2 Hz, 1H), 7.27 – 7.18 (m, 4H), 6.91 – 6.80 (m, 2H), 6.73 – 6.63 (dd, *J* = 8.2 Hz, *J* = 2.1 Hz, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 4.69 (s, 2H), 4.41 (t, *J* = 5.5 Hz, 1H), 4.33 (d, *J* = 4.5 Hz, 2H), 3.80 (s, 3H), 2.62 – 2.39 (m, 1H), 2.01 – 1.70 (m, 5H), 1.52 – 1.15 (m, 5H). HRMS (ESI+) m/z 441.2534[M + H]$^+$. HRMS (ESI+) calculated for $C_{29}H_{32}N_2O_2$: 440.2464, found 440.2464.

(*R*)-*N*-(4-Cyclohexylbenzyl)-*N*-(2-(4-methoxybenzyl)-1-oxoisoindolin-5-yl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)propanamide (69). To a stirred solution of **68** (110 mg, 0.25 mmol) in THF (5 mL) under nitrogen at room temperature was added methylmagnesium bromide (0.53 mL of 1.4 M in 1:3 THF:toluene, 0.75 mmol, 3 equiv). Stirring was continued at room temperature for 5 min. The resultant solution was added dropwise to a stirred solution of **8** (132 mg, 0.375 mmol) in THF (5 mL) under nitrogen at room temperature. The resulting reaction mixture was stirred at room temperature for 2 h, quenched with saturated aqueous ammonium chloride, poured onto water and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1% methanol in DCM eluent) to afford **69** (144 mg, 75% yield). For $C_{39}H_{38}F_5N_3O_5S$, exact mass: 755.2. LRMS (ESI) m/z 756.2[M + H]$^+$.

(*R*)-*N*-(4-Cyclohexylbenzyl)-*N*-(1-oxoisoindolin-5-yl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamide (2g). To a stirred solution of **69** (66 mg, 0.087 mmol) in acetonitrile (2 mL) and water (1 mL) was added ceric ammonium nitrate (143 mg, 0.261 mmol) and the resulting mixture was allowed to stir at room temperature overnight. An additional 50 mg of ceric

ammonium nitrate was added and the reaction was stirred at room temperature for an additional 30 min. The reaction mixture was poured onto water and extracted with EtOAc (3X) and DCM (1X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (50 -100% EtOAc/hexanes gradient) provided **2g** (40 mg, 72% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.76 (s, 1H), 5.05 – 4.62 (m, 3H), 4.45 (s, 2H), 3.18 (s, 3H), 2.66 – 2.31 (m, 1H), 1.98 – 1.70 (m, 5H), 1.53 – 1.05 (m, 8H). HRMS (ESI+) m/z 636.1936[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{30}F_5N_3O_4S$: 635.1877, found 635.1865.



Scheme 12.

1-(4-Methoxybenzyl)-5-nitro-*1H*-indazole (70). To a stirred solution of 5-nitro-*1H*-indazole (2.93 g, 18 mmol) in DMF (18 mL) under nitrogen was added cesium carbonate (6.5 g, 19.9 mmol). The solution was cooled to 0 °C. *p*-Methoxybenzyl chloride (2.7 mL, 19.9 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for 1 h and at room temperature for an additional 2 h. The reaction was quenched with saturated aqueous ammonium chloride and added to a mixture of ether and water. The aqueous phase was acidified with aqueous HCl. The precipitated solid was filtered off and washed with a small portion of DCM and dried. The filtrate and washes were added to a separatory funnel and the organic layer separated off. The aqueous phase was extracted with ether (2X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue and the solid from the filtration were combined and purified by flash chromatography (4:3:3 hexanes:DCM: EtOAc eluent) to provide **70** (1.6 g, 31% yield) as a yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 2.1 Hz, 1H), 8.27 – 8.19 (m, 2H), 7.41 (d, *J* = 9.3 Hz, 1H), 7.20 (d, *J* = 9.3 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.59 (s, 2H), 3.79 (s, 3H).

1-(4-Methoxybenzyl)-*1H*-indazol-5-amine (71). To a stirred solution of **70** (1.6 g, 5.6 mmol) in methanol (20 mL) and EtOAc (40 mL) under nitrogen was added 10% Pd/C (159 mg) and the suspension was placed under a hydrogen atmosphere and stirred at room temperature for 7 h. The reaction mixture was filtered through Celite® and washed with methanol (2X). The combined filtrate and washes were concentrated to provide **71** (1.39g, 96% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.22 – 7.09 (m, 3H), 6.97 – 6.91 (m, 1H), 6.88 – 6.75 (m, 3H), 5.48 (s, 2H), 3.78 (s, 3H), 3.60 (br. s, 2H).

***tert*-Butyl (1-(4-methoxybenzyl)-*1H*-indazol-5-yl)carbamate (72).** To a suspension of **71** (1.39 g, 5.5 mmol) in ethanol (73 mL) was added di-*tert*-butyl dicarbonate (3.6 g, 16.5 mmol) and the resulting slurry was warmed at 70 °C 4h. The mixture was concentrated under reduced pressure and purified by

trituration with 10% EtOAc/ hexanes to provide **72** (1.78 g, 92% yield) as a tan solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 0.8 Hz, 1H), 7.83 (s, 1H), 7.26 – 7.19 (m, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.51 (s, 1H), 5.52 (s, 2H), 3.78 (s, 3H), 1.54 (s, 9H).

***tert*-Butyl (4-cyclohexylbenzyl)(1-(4-methoxybenzyl)-*1H*-indazol-5-yl)carbamate (73).** To a stirred solution of **72** (488 mg, 1.38 mmol) in DMF (10 mL) at 0 °C under nitrogen was added KHMDS (2.1 mL of 1M in THF, 2.1 mmol). After stirring at 0 °C for 10 min, a solution of 1-(bromomethyl)-4-cyclohexylbenzene (689 mg, 2.65 mmol) was added. The reaction was allowed to warm to room temperature and stirring was continued at this temperature for 1.5 h. The reaction mixture was poured onto water and extracted with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (0-20% EtOAc/hexanes gradient) provided **73** (647 mg, 87% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.94 (t, *J* = 0.6 Hz, 1H), 7.44 (s, 1H), 7.21 – 7.08 (m, 8H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.50 (s, 2H), 4.81 (s, 2H), 3.78 (s, 3H), 2.59 – 2.40 (m, 1H), 1.99 – 1.68 (m, 5H), 1.52 – 1.34 (m and overlapping s, 14H).

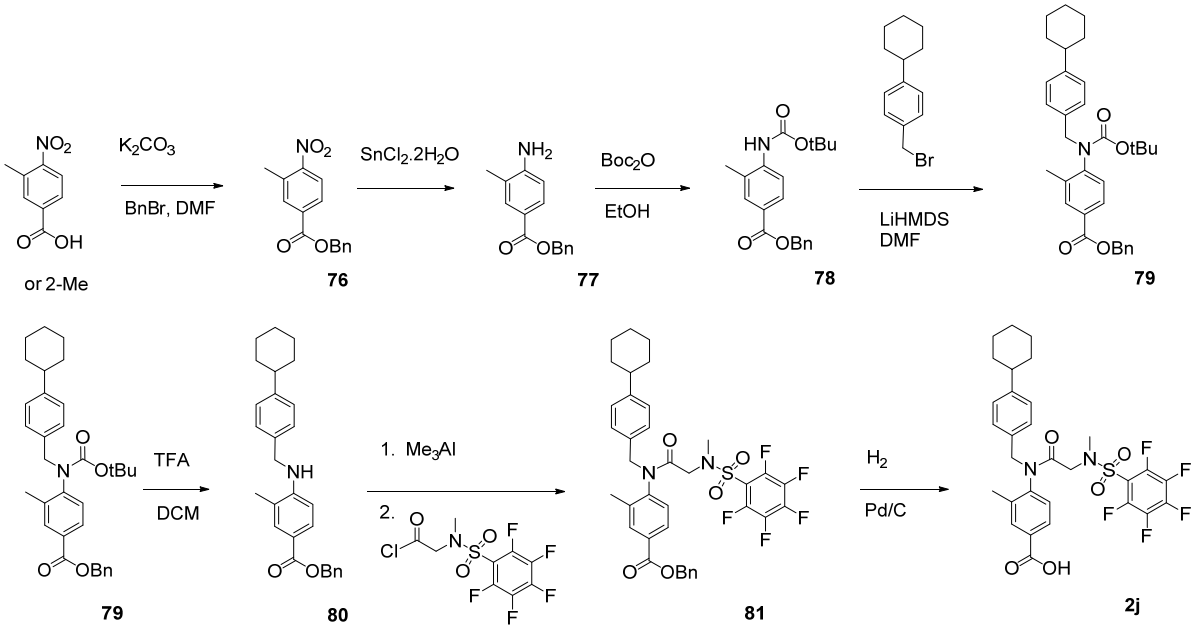
***N*-(4-Cyclohexylbenzyl)-1-(4-methoxybenzyl)-*1H*-indazol-5-amine (74).** To a stirred solution of **73** (643 mg, 1.2 mmol) in DCM (25 mL) at 0 °C under nitrogen was added TFA (5 mL). The reaction mixture was stirred at 0 °C for 2.25 h and then at room temperature for 1h. The mixture was poured onto ice water, made basic by addition of saturated aqueous sodium bicarbonate and extracted with DCM (3X). The combined organic extracts were washed with dilute aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide **74** (576 mg, 89 % yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 0.7 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.24 – 7.12 (m, 5H), 6.88 – 6.76 (m, 4H), 5.48 (s, 2H), 4.31 (s, 2H), 3.78 (s, 3H), 2.67 – 2.39 (m, 1H), 2.11 – 1.67 (m, 5H), 1.52 – 1.08 (m, 5H).

(*R*)-*N*-(4-Cyclohexylbenzyl)-*N*-(1-(4-methoxybenzyl)-*1H*-indazol-5-yl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamide (75). To a stirred solution of **74** (170 mg, 0.40 mmol) in THF (8 mL) under nitrogen at room temperature was added methylmagnesium bromide (0.86 mL of 1.4 M in 1:3 THF: toluene, 1.2 mmol, 3 equiv). Stirring was continued at room temperature for 5 min. The resultant solution was added dropwise to a stirred solution of **8** (211 mg, 0.60 mmol) in THF (8 mL) under nitrogen at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous ammonium chloride, poured onto water and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20-40% EtOAc/hexanes gradient) to afford **75** (257 mg, 87% yield). HRMS (ESI+) m/z 741.2524$[M + H]^+$. HRMS (ESI+) calculated for $C_{38}H_{37}F_5N_4O_4S$: 740.2456, found 740.2453.

(*R*)-*N*-(4-Cyclohexylbenzyl)-*N*-(1H-indazol-5-yl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamide (2h). To a stirred solution of **75** (206 mg, 0.279 mmol) in acetonitrile (12 mL) and 0.1 M phosphate buffer at pH=5.9 (6 mL) was added ceric ammonium nitrate (458 mg, 0.836 mmol) and the resulting mixture was allowed to stir at room temperature for 1 h. An additional 305 mg of ceric ammonium nitrate was added and the reaction was stirred at room temperature overnight. The reaction mixture was poured onto water and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (20-40% EtOAc/hexanes gradient) provided (*R*)-*N*-(4-cyclohexylbenzyl)-*N*-(1H-indazol-5-yl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamide (27 mg, 15% yield) as a yellow foam. ^{1}H NMR (300 MHz, Chloroform-d) δ 10.23 (br. s, 1H), 8.09 (s, 1H), 7.6 – 7.35 (m, 2H), 7.25 – 7.05 (m, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz,

2H), 4.80 (m, 3H), 3.21 (s, 3H), 2.54-2.41 (m, 1H), 1.92-1.14 (m, 13H). HRMS (ESI+) m/z 621.1928[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_4O_3S$: 620.1881, found 620.1859.

(*R*)-*N*-(4-cyclohexylbenzyl)-N-(*1H*-indazol-6-yl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamide (2i). Preparation by a similar procedure to **2h**, except substituting 6-nitro-*1H*-indazole for 5-nitro-*1H*-indazole in step 1 afforded (*R*)-*N*-(4-cyclohexylbenzyl)-N-(1H-indazol-6-yl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)propanamide as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.29 (br-s, 1H), 8.13 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.17 – 6.87 (m, 6H), 5.13 – 4.57 (m, 3H), 3.20 (s, 3H), 2.61 – 2.38 (m, 1H), 2.03 – 1.69 (m, 6H), 1.29 – 1.14 (m, 4H), 1.24 (d, *J* = 7.3 Hz, 3H). MS (ESI) m/z 621.2[M + H]$^+$. HRMS (ESI+) m/z 621.1936[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{30}F_5N_3O_6S$: 620.1881, found 620.1864.



Scheme 13.

Benzyl 3-methyl-4-nitrobenzoate (76). To a solution of 3-methyl-4-nitrobenzoic acid (1.0 g, 5.52 mmol) in DMF (25 mL) under nitrogen was added potassium carbonate (0.836 g, 6.08 mmol). After 10 min benzyl bromide (0.63 mL, 5.24 mmol) was added and the resultant solution was stirred at room temperature for 3.5 h. The mixture was poured onto cold water and extracted with EtOAc (2X). The combined organic extract was washed with water (2X), and then washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide crude product, **76** (1.64 g) as a yellow oil, which was used as is.

Benzyl 4-amino-3-methylbenzoate (77). To a stirred solution of **76** (1.64 g) in EtOAc (60 mL) under nitrogen was added $SnCl_2 \cdot H_2O$ (6.82 g) and the mixture was stirred at 80° C overnight. After cooling to room temperature, the mixture was poured onto cold water, the pH was adjusted to pH = 8 by addition of 10% aqueous sodium bicarbonate and mixture was extracted with EtOAc (2X). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide **77** (1.36 g, 100% yield over the 2 steps) as an oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.86 – 7.76 (m, 2H), 7.52 – 7.32 (m, 5H), 6.65 (d, *J* = 9.0 Hz, 1H), 5.34 (s, 2H), 4.02 (br. s, 2H), 2.20 (s, 3H).

Benzyl 4-((*tert*-butoxycarbonyl)amino)-3-methylbenzoate (78). To a stirred solution of **77** (419 mg, 1.74 mmol) in ethanol (4 mL) under nitrogen was added di-*tert*-butyl dicarbonate (1 mL, 4.35 mmol). The reaction mixture was heated at 50 °C for 3 days and then concentrated under reduced pressure. Hexanes was added and the resultant solid was filtered off and washed with hexanes to provide **78** (483 mg, 82% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.6 Hz, 1H), 7.94 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.88 (d, *J* = 2.1 Hz, 1H), 7.53 – 7.33 (m, 5H), 6.48 (s, 1H), 5.36 (s, 2H), 2.29 (s, 3H), 1.56 (s, 9H).

Benzyl 4-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-3-methylbenzoate (79). To a stirred solution of **78** (462 mg, 1.35 mmol) in DMF (4.6 mL) at 0 °C under nitrogen was added LiHMDS (1.63 mL of 1M in THF, 1.63 mmol). After stirring at 0 °C for 10 min, a solution of 1-(bromomethyl)-4-cyclohexylbenzene (514 mg, 1.98 mmol) was added in DMF (2.5 mL). The reaction was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride, poured onto water and extracted with EtOAc (2X). The combined organic extracts were washed with water and then brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (5-7.5% EtOAc/hexanes gradient) provided **79** (628.5 mg, 91% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.33 (m, 5H), 7.10 (s, 4H), 6.99 – 6.85 (m, 1H), 5.36 (s, 2H), 4.82 (d, *J* = 14.7 Hz, 1H), 4.53 (d, *J* = 14.7 Hz, 1H), 2.58 – 2.39 (m, 1H), 2.04 (s, 3H), 1.93 – 1.69 (m, 5H), 1.52 – 1.07 (m, 5H).

Benzyl 4-((4-cyclohexylbenzyl)amino)-3-methylbenzoate (80). To a stirred solution of **79** (621.7 mg, 1.21 mmol) under nitrogen in DCM (7.7 mL) was added TFA (2.5 mL) and the resultant mixture was stirred at room temperature for 1h. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in EtOAc, poured onto aqueous sodium bicarbonate and extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide **80** (534 mg) as a pale yellow oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.52 – 7.33 (m, 5H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 5.33 (s, 2H), 4.40 (s, 2H), 4.30 (br. s, 1H), 2.63 – 2.43 (m, 1H), 2.19 (s, 3H), 1.97 – 1.70 (m, 6H), 1.53 – 1.31 (m, 4H).

Benzyl 4-(N-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)-3-methylbenzoate (81). To a stirred solution of **80** (220.2 mg, 0.53 mmol) in THF (4.3 mL) under nitrogen at 0 °C was added trimethylaluminum (0.664 mL of 2M in

toluene, 1.33 mmol) and the resulting mixture was allowed to warm to room temperature and stirred at this temperature for 15 min before addition of *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride (101 mg, 0.3 mmol) in THF (3 mL). The resulting mixture was heated at reflux for 3 h. After cooling to 5 °C the resultant mixture was poured onto cold 10% aqueous potassium bisulfate/ sodium sulfate buffer and extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/ hexanes then 20% EtOAc/ hexanes eluent) provided **81** (187 mg, 49% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 1.6 Hz, 1H), 7.87 (dd, *J* = 8.2 Hz, *J* = 1.6 Hz, 1H), 7.53 – 7.36 (m, 5H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.39 (s, 2H), 5.00 (d, *J* = 13.9 Hz, 1H), 4.31 (d, *J* = 13.9 Hz, 1H), 3.93 – 3.64 (m, 2H), 3.10 (s, 3H), 2.62 – 2.37 (m, 1H), 2.10 (s, 3H), 1.96 – 1.69 (m, 6H), 1.49 – 1.33 (m, 4H).

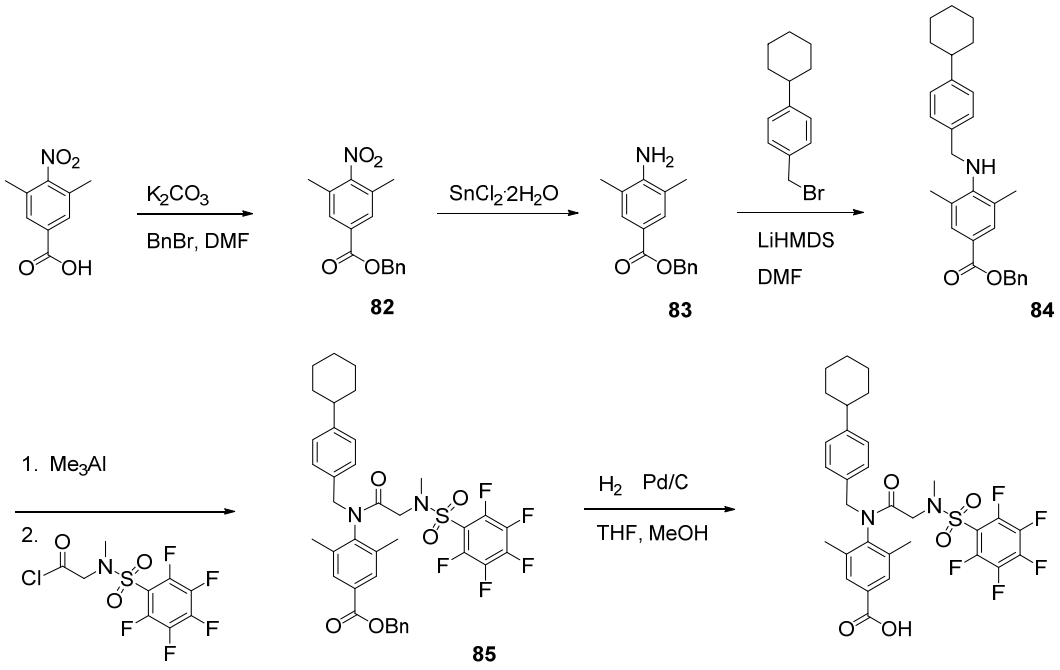
4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)acetamido)-3-methylbenzoic acid (2j). To a stirred solution of **81** (178 mg, 0.249 mmol) in methanol (3.6 mL) and THF (3.6 mL) was added 10% Pd/C (22.6 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 5 h. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated under reduced pressure and residue triturated with ether to provide **2j** (80.4 mg, 52% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, *J* = 2.0 Hz, 1H), 7.74 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.26 – 6.69 (m, 5H), 4.93 (d, *J* = 14.4 Hz, 1H), 4.35 (d, *J* = 14.4 Hz, 1H), 3.90 (d, *J* = 17.8 Hz, 1H), 3.69 (d, *J* = 17.8 Hz, 1H), 2.99 (s, 3H), 2.08 (s, 3H), 2.58 – 2.36 (m, 1H), 1.84 – 1.62 (m, 5H), 1.49 – 1.11 (m, 5H). HRMS (ESI) m/z 625.1742[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_5S$: 624.1717, found 624.1706.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)-3-methylbenzoic acid (2k). Preparation by a similar

procedure to 2j, except substituting *N*-methyl-*N*-((perfluorophenyl)sulfonyl)-*D*-alaninoyl chloride for *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride in step 6 afforded **2k**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 – 7.80 (m, 1H), 7.78 – 7.57 (m, 1H), 7.25 – 6.73 (m, 5H), 5.20 (d, *J* = 14.4 Hz, 1H), 5.03 (d, *J* = 14.4 Hz, 1H), 4.57 – 4.19 (m, 1H), 3.02 (m, 3H), 2.57 – 2.34 (m, 1H), 2.23 - 2.10 (m, 3H), 1.85 – 1.55 (m, 5H), 1.44 – 1.14 (m, 5H), 1.14 – 0.89 (m, 3H). HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_5S$: 638.1874, found 638.1905.

4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)acetamido)-2-methylbenzoic acid (2l). Preparation by a similar procedure to **2v**, except substituting except substituting 2-methyl-4-nitrobenzoic acid for 3-fluoro-4-nitrobenzoic acid in step 1 and substituting *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride for *N*-methyl-*N*-((perfluorophenyl)sulfonyl)-*D*-alaninoyl chloride in step 4 afforded **2l**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 7.07 – 6.78 (m, 4H), 4.74 (s, 2H), 3.99 (s, 2H), 3.11 (s, 3H), 2.82 – 2.30 (m, 4H), 2.09 - 1.59 (m, 5H), 1.59 – 1.04 (m, 5H). HRMS (ESI+) m/z 625.1791[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}F_5N_2O_5S$: 624.1717, found 624.1715.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)-2-methylbenzoic acid (2m). Preparation by a similar procedure to **2v**, except substituting 2-methyl-4-nitrobenzoic acid for 3-fluoro-4-nitrobenzoic acid in step 1 afforded **2m**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.08 – 6.92 (m, 4H), 5.00 – 4.65 (m, 3H), 3.19 (s, 3H), 2.64 (s, 3H), 2.58 – 2.37 (m, 1H), 1.97 – 1.63 (m, 5H), 1.54 – 1.11 (m, 5H), 1.26 (d, *J* = 7.2 Hz, 3H). HRMS (ESI+) m/z 639.1980[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_5S$: 638.1874, found 638.1890.



Scheme 14.

Benzyl 3,5-dimethyl-4-nitrobenzoate (82). To a solution of 3,5-dimethyl-4-nitrobenzoic acid (500 mg, 2.56 mmol) in DMF (12.5 mL) under nitrogen was added potassium carbonate (0.388 g, 2.82 mmol). After 10 min benzyl bromide (0.29 mL, 2.43 mmol) was added and the resultant solution was stirred at room temperature for 3.5 h. The mixture was poured onto cold water and extracted with EtOAc (2X). The combined organic extract was washed with water (2X), and then washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide crude product, **82** (679 mg, 93% yield) as an oil, which was used as is. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.86 (s, 2H), 7.56 – 7.33 (m, 5H), 5.39 (s, 2H), 2.36 (s, 6H).

Benzyl 4-amino-3,5-dimethylbenzoate (83). To a stirred solution of **82** (679 mg, 2.38 mmol) in EtOAc (25.2 mL) under nitrogen was added $SnCl_2 \cdot H_2O$ (2.68 g) and the mixture was stirred at 80° C overnight. After cooling to room temperature, the mixture was poured onto cold water, the pH was adjusted to pH = 8 by addition of 10% aqueous sodium bicarbonate and mixture was extracted with EtOAc (2X). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated

under reduced pressure to provide **83** (579 mg, 88% yield over the 2 steps). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.72 (s, 2H), 7.53 – 7.31 (m, 5H), 5.34 (s, 2H), 2.25 (s, 6H).

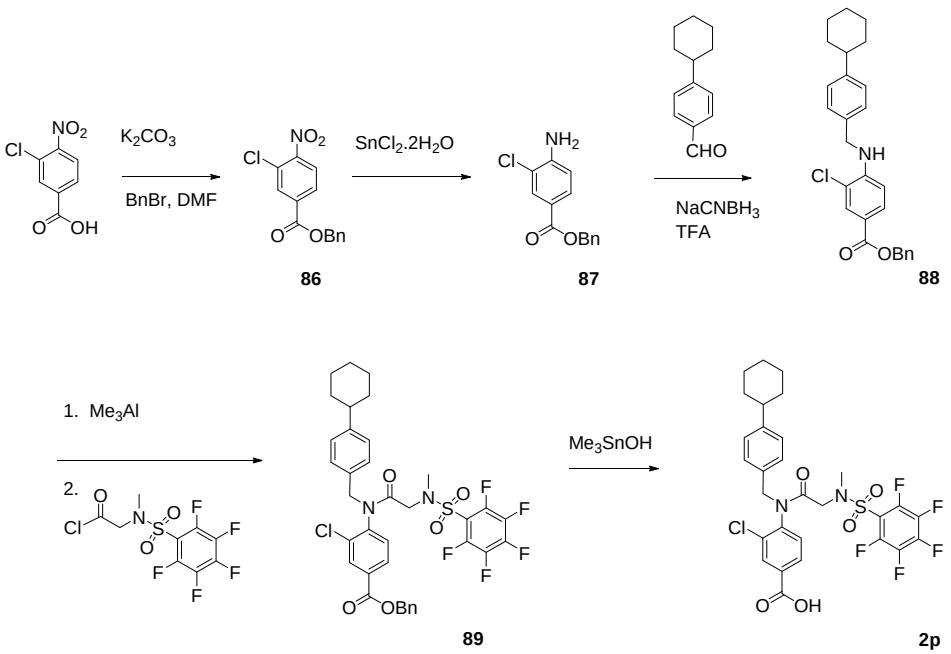
Benzyl 4-((4-cyclohexylbenzyl)amino)-3,5-dimethylbenzoate (84). To a stirred solution of **83** (110.8 mg, 0.434 mmol) in THF (3 mL) was added at 0 °C under nitrogen, a solution of LiHMDS (0.52 mL of 1M in THF, 0.52 mmol) and the resulting solution was stirred at 0 °C for 15 min before addition of 1-(bromomethyl)-4-cyclohexylbenzene (109.9 mg, 0.434 mmol) in THF (2 mL). The reaction mixture was allowed to warm to room temperature and stirred at this temperature overnight. The reaction mixture was poured onto saturated aqueous ammonium chloride and extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (5-10% EtOAc/hexanes eluent) provided **84** (108 mg, 58% yield) as a colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.72 (s, 2H), 7.51 – 7.33 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.35 (s, 2H), 4.34 (s, 2H), 2.59 – 2.42 (m, 1H), 2.32 (s, 6H), 2.00 – 1.65 (m, 6H), 1.49 – 1.25 (m, 4H).

Benzyl 4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)acetamido)-3,5-dimethylbenzoate (85). To a stirred solution of **84** (94.7 mg, 0.22 mmol) in THF (1.8 mL) under nitrogen at 0 °C was added trimethylaluminum (0.28 mL of 2M in toluene, 0.55 mmol) and the resulting mixture was allowed to warm to room temperature and stirred at this temperature for 15 min before addition of *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride (93.5 mg, 0.28 mmol) in THF (1.2 mL). The resulting mixture was heated at reflux for 3 h. After cooling to 5 °C the resultant mixture was poured onto cold 10% aqueous potassium bisulfate/ sodium sulfate buffer and extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/ hexanes then 20% EtOAc/ hexanes eluent) provided **85** (71.3 mg, 44%

yield) as a foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 (s, 2H), 7.53 – 7.35 (m, 5H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.38 (s, 2H), 4.60 (s, 2H), 3.67 (s, 2H), 3.08 (s, 3H), 1.90 (s, 6H), 1.87 – 1.69 (m, 6H), 1.48 – 1.31 (m, 4H).

4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)acetamido)-3,5-dimethylbenzoic acid (2n). To a stirred solution of **85** (65.8 mg, 0.090 mmol) in methanol (1.3 mL) and THF (1.3 mL) was added 10% Pd/C (8.2 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 5 h. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated under reduced pressure and residue purified by preparative TLC (40%EtOAc/hexanes with 0.1%acetic acid) to provide **2n** (41.6 mg, 72% yield) as a white solid. HRMS (ESI) m/z 639.1945 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (s, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 2H), 4.58 (s, 2H), 3.67 (s, 2H), 3.00 (s, H), 2.51 (m, 1H), 1.87 (s, 6H), 1.94 – 1.58 (m, 5H), 1.47 – 1.10 (m, 5H). HRMS (ESI+) calculated for $C_{31}H_{31}F_5N_2O_5S$: 638.1874, found 638.1868.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)-3,5-dimethylbenzoic acid (2o). Preparation by a similar procedure to **2n**, except substituting except substituting *N*-methyl-*N*-((perfluorophenyl)sulfonyl)-*D*-alaninoyl chloride for *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride in step 4 provided **2o**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67 (m, 2H), 7.10 (d, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 2H), 4.75 (d, *J* = 13.7 Hz, 1H), 4.52 (d, *J* = 13.7 Hz, 1H), 4.28 (m, 1H), 2.99 (s, 3H), 2.51 (m, 1H), 2.02 – 1.77 (m, 6H), 1.87 – 1.55 (m, 5H), 1.51 – 1.09 (m, 5H), 1.00 (d, *J* = 6.9 Hz, 3H). HRMS (ESI+) m/z 653.2095$[M + H]^+$. HRMS (ESI+) calculated for $C_{32}H_{33}F_5N_2O_5S$: 652.2030, found 652.2021.



Scheme 15.

Benzyl 3-chloro-4-nitrobenzoate (86). To a solution of 3-chloro-4-nitrobenzoic acid (1.0 g, 4.96 mmol) in DMF (25 mL) under nitrogen was added potassium carbonate (0.75 g, 5.46 mmol). After 10 min benzyl bromide (0.57 mL, 4.71 mmol) was added and the resultant solution was stirred at room temperature for 3.5 h. The mixture was poured onto cold water and extracted with EtOAc (2X). The combined organic extract was washed with water (2X), and then washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide crude product, **86** (1.49 g) as a yellow oil, which was used as is. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 1.7 Hz, 1H), 8.10 (dd, *J* = 8.4 Hz, *J* = 1.7 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.34 (m, 5H), 5.42 (s, 2H).

Benzyl 4-amino-3-chlorobenzoate (87). To a stirred solution of **86** (1.485 g) in EtOAc (60 mL) under nitrogen was added $SnCl_2 \cdot H_2O$ (28.4 mmol) and the mixture was stirred at 80° C overnight. After cooling to room temperature, the mixture was poured onto cold water, the pH was adjusted to pH = 8 by addition of 10% aqueous sodium bicarbonate and mixture was extracted with EtOAc (2X). The combined organic

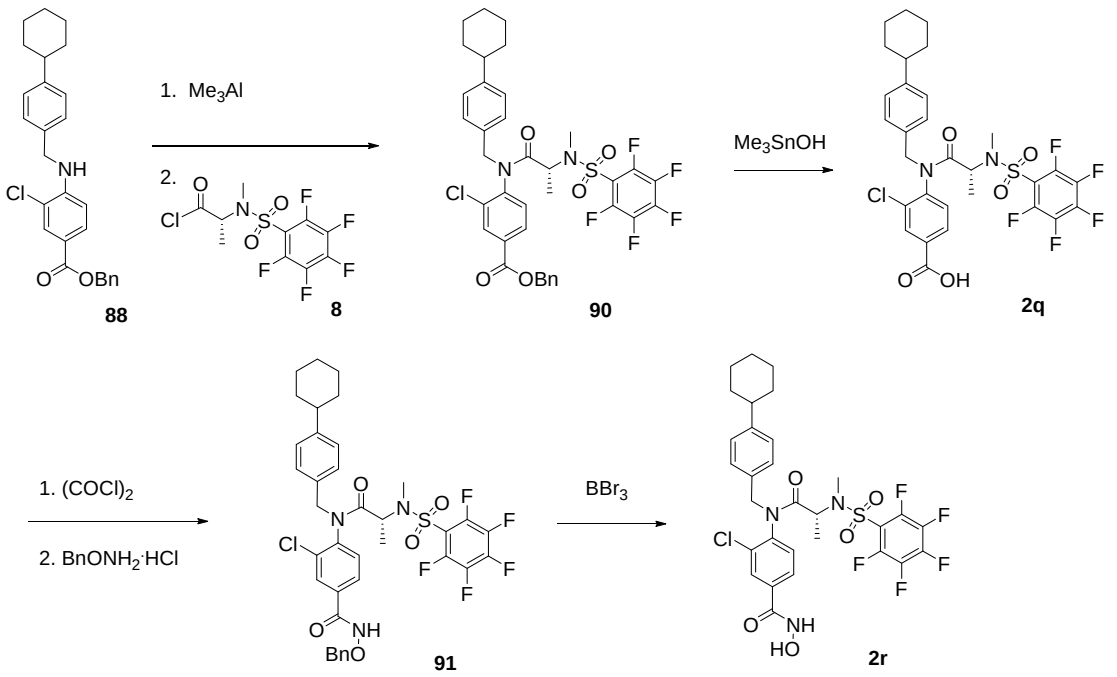
phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (10-20% EtOAc/hexanes eluent) provided **87** (1.12 g, 86% yield over the 2 steps) as a white solid.

Benzyl 4-((4-cyclohexylbenzyl)amino)-3-chlorobenzoate (88). To a solution of **87** (310 mg, 1.18 mmol) in TFA (2.7 mL) under nitrogen at 0 °C was added sodium triacetoxyborohydride (503 mg, 2.37 mmol) portion wise. The mixture was stirred at 0 °C for 10 min before addition of 4-cyclohexylbenzaldehyde (237 mg, 1.26 mmol). The resulting reaction mixture was stirred at room temperature for 4 h, poured onto cold water and extracted with EtOAc (2X). The combined organic extracts were washed with water (3X), then with 10% aqueous sodium bicarbonate (2X), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (3% EtOAc/ hexanes eluent) provided **88** (370 mg, 72% yield). The reaction was repeated using 424 mg of starting benzyl 4-amino-3-chlorobenzoate to provide additional **88** (462 mg, 66% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.01 (d, 2.0 Hz, 1H), 7.86 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.50 – 7.32 (m, 5H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 1H), 5.33 (s, 2H), 5.16 (t, *J* = 5.5 Hz, 1H), 4.43 (d, *J* = 5.5 Hz, 2H), 2.61 – 2.42 (m, 1H), 1.99 – 1.70 (m, 6H), 1.52 – 1.32 (m, 4H).

Benzyl 3-chloro-4-(N-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)benzoate (89). To a stirred solution of **88** (103.7 mg, 0.24 mmol) in THF (4 mL) under nitrogen at 0 °C was added trimethylaluminum (0.30 mL of 2M in toluene, 0.6 mmol) and the resulting mixture was allowed to warm to room temperature and stirred at this temperature for 15 min before addition of *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride (101 mg, 0.3 mmol) in THF (2 mL). The resulting mixture was heated at reflux overnight. After cooling to 5 °C the resultant mixture was poured onto cold 10% aqueous potassium bisulfate/ sodium sulfate buffer and extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over

anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/ hexanes then 20% EtOAc/ hexanes eluent) provided **89** (35 mg, 20% yield). HRMS (ESI) m/z 735.1686 $[M + H]^+$. HRMS (ESI+) calculated for $C_{36}H_{32}ClF_5N_2O_5S$: 734.1641, found 734.1625.

3-Chloro-4-(N-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)-sulfonamido)acetamido)benzoic acid (2p). To a stirred solution of **89** (34.5 mg, 0.047 mmol) in DCE (3.5 mL) under nitrogen was added trimethyltin hydroxide (84.8 mg, 0.47 mmol) and the resulting mixture was heated at 85 °C overnight. The mixture was concentrated under reduced pressure and the residue was taken up in EtOAc. The organic solution was washed with 10% aqueous potassium bisulfate/ sodium sulfate buffer, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (run up with 40% EtOAc/ hexane with 0.1-0.2% HOAc) and the product band eluted off the silica with 20% methanol in DCM to provide a white solid. Trituration with ether provided pure **2p** (8 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J = 1.9 Hz, 1H), 7.86 (dd, J = 8.2, 1.9 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.16 – 7.08 (m, 3H), 7.03 (d, J = 8.2 Hz, 2H), 5.09 (d, J = 14.6 Hz, 1H), 4.25 (d, J = 14.6 Hz, 1H), 4.06 – 3.88 (m, 1H), 3.79 (d, J = 17.6 Hz, 1H), 2.97 (s, 3H), 2.50 (p, J = 1.9 Hz, 16H), 1.75 (s, 6H), 1.35 (t, J = 9.9 Hz, 4H). HRMS (ESI) m/z 645.1248 $[M + H]^+$. HRMS (ESI+) calculated for $C_{29}H_{26}ClF_5N_2O_5S$: 644.1171, found 644.1170.



Scheme 16.

Benzyl (*R*)-3-chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzoate (90). To a stirred solution of **88** (509 mg, 1.17 mmol) in THF (9 mL) under nitrogen at 0 °C was added trimethylaluminum (1.47 mL of 2M in toluene, 2.94 mmol) and the resulting mixture was allowed to warm to room temperature and stirred at this temperature for 15 min before addition of **8** (516 mg, 1.47 mmol) in THF (6.3 mL). The resulting mixture was heated at reflux for 4.5 h. After cooling to 5 °C the resultant mixture was poured onto cold 10% aqueous potassium bisulfate/ sodium sulfate buffer and extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/ hexanes eluent) provided **90** (170.4 mg, 19% yield) as a colorless oil.

(*R*)-3-Chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzoic acid (2q). To a stirred solution of **90** (34.3 mg, 0.047 mmol) in DCE (2.5 mL) under nitrogen was added trimethyltin hydroxide (84.8 mg, 0.47 mmol)

and the resulting mixture was heated at 85 °C overnight. The mixture was concentrated under reduced pressure and the residue was taken up in EtOAc. The organic solution was washed with 10% aqueous potassium bisulfate/ sodium sulfate buffer, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (run up with 40% EtOAc/ hexane with 0.1-0.2% HOAc) and the product band eluted off the silica with 20% methanol in DCM to provide 23 mg of an oil. Hexanes was added and mixture re-concentrated to provide pure **2q** (20 mg) as a foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (m, 2H), 7.21 – 6.79 (m, 5H), 5.28 (m, 1H), 4.51 (m, 1H), 4.17 (m, 1H), 3.12 – 2.72 (m, 3H), 2.49 (s, 5H), 1.87 – 1.47 (m, 5H), 1.47 – 0.80 (m, 8H). HRMS (ESI) m/z 659.1455[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{28}ClF_5N_2O_5S$: 658.1328, found 658.1348.

(*R*)-*N*-(Benzyloxy)-3-chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzamide (91). To a stirred solution of (*R*)-3-chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzoic acid (85 mg, 0.129 mmol) in DCM (2.3 mL) was added 1 drop of DMF followed by oxalyl chloride (0.013 mL, 0.15 mmol). The resulting reaction solution was stirred at room temperature under nitrogen for 2 h and then concentrated under reduced pressure to afforded (*R*)-3-chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)propanamido)benzoyl chloride, which was used as is.

To a stirred solution of (*R*)-3-chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)-sulfonamido)propanamido)benzoyl chloride (0.129mmol) in THF (2.3 mL) under nitrogen at 0 °C was added a solution of *O*-benzylhydroxylamine hydrochloride (28.8 mg, 0.18 mmol) and TEA (0.05 mL, 0.365 mmol) in DMF (2.3 mL). The resultant reaction mixture was stirred at room temperature for 1.5 h and then quenched with 10 % aqueous potassium bisulfate, poured onto water and extracted with ether (2X). The combined organic extracts were washed with water, then washed with brine, dried over

anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc/ hexanes) to provide **91** (49 mg, 50% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.55 – 7.33 (m, 6H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.04 – 6.88 (m, 3H), 5.49 (d, *J* = 14.3 Hz, 1H), 5.04 (s, 2H), 4.74 – 4.49 (m, 1H), 4.06 (d, *J* = 14.3 Hz, 1H), 3.13 (s, 3H), 2.58 – 2.39 (m, 1H), 1.95 – 1.68 (m, 6H), 1.49 – 1.26 (m, 4H), 1.22 (d, *J* = 7.1 Hz, 3H).

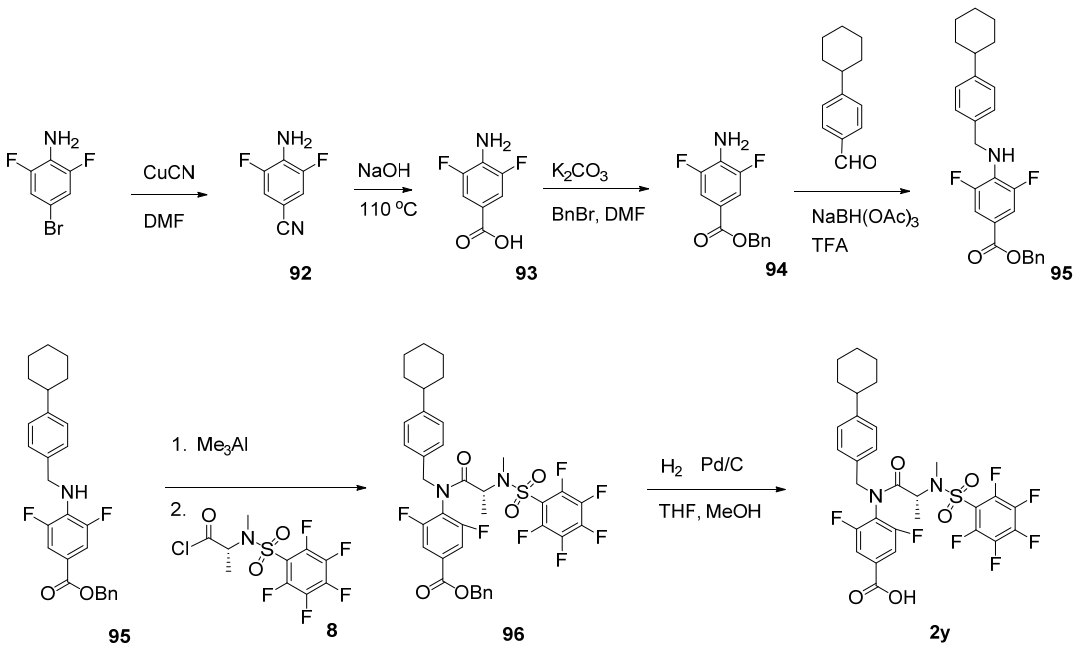
(*R*)-3-Chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)-*N*-hydroxybenzamide (2r). To a stirred solution of **91** (45.8mg, 0.06 mmol) in DCM (1.5 mL) under nitrogen at -15 °C was added boron tribromide (0.014 mL). The mixture was allowed to reach 0 °C and was stirred at this temperature for 3 h. Ice and saturated aqueous sodium bicarbonate were added and the resulting mixture was extracted with EtOAc (1X). The organic extract was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by preparative TLC (50% EtOAc/ hexanes eluent) provided **2r** (17 mg, 42% yield) as a foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.54 (s, 1H), 7.17 – 6.71 (m, 5H), 5.50 (dd, *J* = 25.3, 14.2 Hz, 1H), 6.08 (d, *J* = 7.1 Hz, 1H), 5.73 – 5.33 (m, 2H), 4.55 (s, 2H), 4.45 (s, 1H), 3.91 (s, 1H), 3.51 (d, *J* = 1.5 Hz, 1H), 3.40 – 3.08 (m, 6H), 2.98 – 2.45 (m, 12H). HRMS (ESI) m/z 674.1532[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{29}ClF_5N_3O_5S$: 673.1437, found 673.1460.

2-Chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)acetamido)benzoic acid (2s). Preparation by a similar procedure to compound **2p**, except substituting 2-chloro-4-nitrobenzoic acid for 3-chloro-4-nitrobenzoic acid in step 1 afforded **2s**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 – 6.53 (m, 7H), 5.03 – 4.41 (m, 2H), 4.01 (s, 2H), 3.10 (s, 3H), 2.70 – 2.25 (m, 1H), 2.15 – 1.56 (m, 5H), 1.56 – 1.01 (m, 5H). For $C_{29}H_{26}ClF_5N_2O_5S$, exact mass: 644.1. LRMS (ESI) m/z 645.1[M + H]$^+$.

(*R*)-2-Chloro-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)benzoic acid (2t). Preparation by a similar procedure to compound **2p**, except substituting except substituting 2-chloro-4-nitrobenzoic acid for 3-chloro-4-nitrobenzoic acid in step 1 and substituting *N*-methyl-*N*-((perfluorophenyl)sulfonyl)-*D*-alaninoyl chloride for *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride in step 4 afforded **2t**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.06 (br, 1H), 7.41 – 6.79 (m, 7H), 4.99 – 4.56 (m, 3H), 3.16 (s, 3H), 2.59 – 2.33 (m, 1H), 2.02 – 1.61 (m, 5H), 1.59 – 1.01 (m, 8H). HRMS (ESI+) m/z 659.1408[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{28}ClF_5N_2O_5S$: 658.1328, found 658.1337.

4-(N-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)-3-fluorobenzoic acid (2u). Preparation by a similar procedure to compound **2v**, except substituting *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride for *N*-methyl-*N*-((perfluorophenyl)sulfonyl)-*D*-alaninoyl chloride in step 3 afforded **2u**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.11 – 7.68 (m, 2H), 7.42 – 6.69 (m, 5H), 5.12 (d, *J* = 14.6 Hz, 1H), 4.39 (d, *J* = 14.6 Hz, 1H), 4.15 (d, *J* = 17.9 Hz, 1H), 3.83 (d, *J* = 17.9 Hz, 1H), 3.13 (s, 3H), 2.65 – 2.31 (m, 1H), 2.10 – 1.59 (m, 5H), 1.57 – 1.03 (m, 5H). For $C_{29}H_{26}F_6N_2O_5S$, exact mass: 628.16. MS (ESI+) m/z 629.10[M + H]$^+$.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamido)-2-fluorobenzoic acid (2x). Preparation by a similar procedure to compound **2v**, except substituting 2-fluoro-4-nitrobenzoic acid for 3-fluoro-4-nitrobenzoic acid in step 1 afforded **2x**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 6.48 (m, 7H), 5.10 – 4.43 (m, 3H), 3.11 (s, 3H), 2.63 – 2.33 (m, 1H), 2.11 – 1.58 (m, 5H), 1.57 – 0.68 (m, 8H). For $C_{30}H_{28}F_6N_2O_5S$, exact mass: 642.1. MS (ESI+) m/z 643.1[M + H]$^+$.



Scheme 17.

4-Amino-3,5-difluorobenzonitrile (92). To 4-bromo-2,6-difluoroaniline (1.0 g, 4.81 mmol) and copper (I) cyanide (1.28 g, 14.3 mmol) was added DMF (10 mL) under nitrogen and the resulting mixture was heated at 160 °C for 18 h. After 18 h, the mixture was cooled, poured onto a 12% aqueous ammonia solution and extracted with EtOAc (2X). The combined organic extract was washed with water. The organic phase was combined with a little water and was filtered through Celite to remove suspended solids. The organic phase was then separated from the water, then washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (12% EtOAc/ hexanes eluent) provided **92** as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 – 7.14 (m, 2H), 4.29 (br. s, 2H).

4-Amino-3,5-difluorobenzoic acid (93). Compound **92** (354.3 mg, 2.3 mmol) was suspended in 1M aqueous sodium hydroxide (12 mL) and the resulting suspension was heated at 110 °C for 16 h. After cooling, the mixture was washed with ether. The aqueous phase was acidified to pH = 2 with 10% $KHSO_4/Na_2SO_4$ buffer and extracted with EtOAc (2X). The combined EtOAc extracts were washed with

water, and then brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide **93** (335 mg, 84% yield) as a yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.66 – 7.58 (m, 2H).

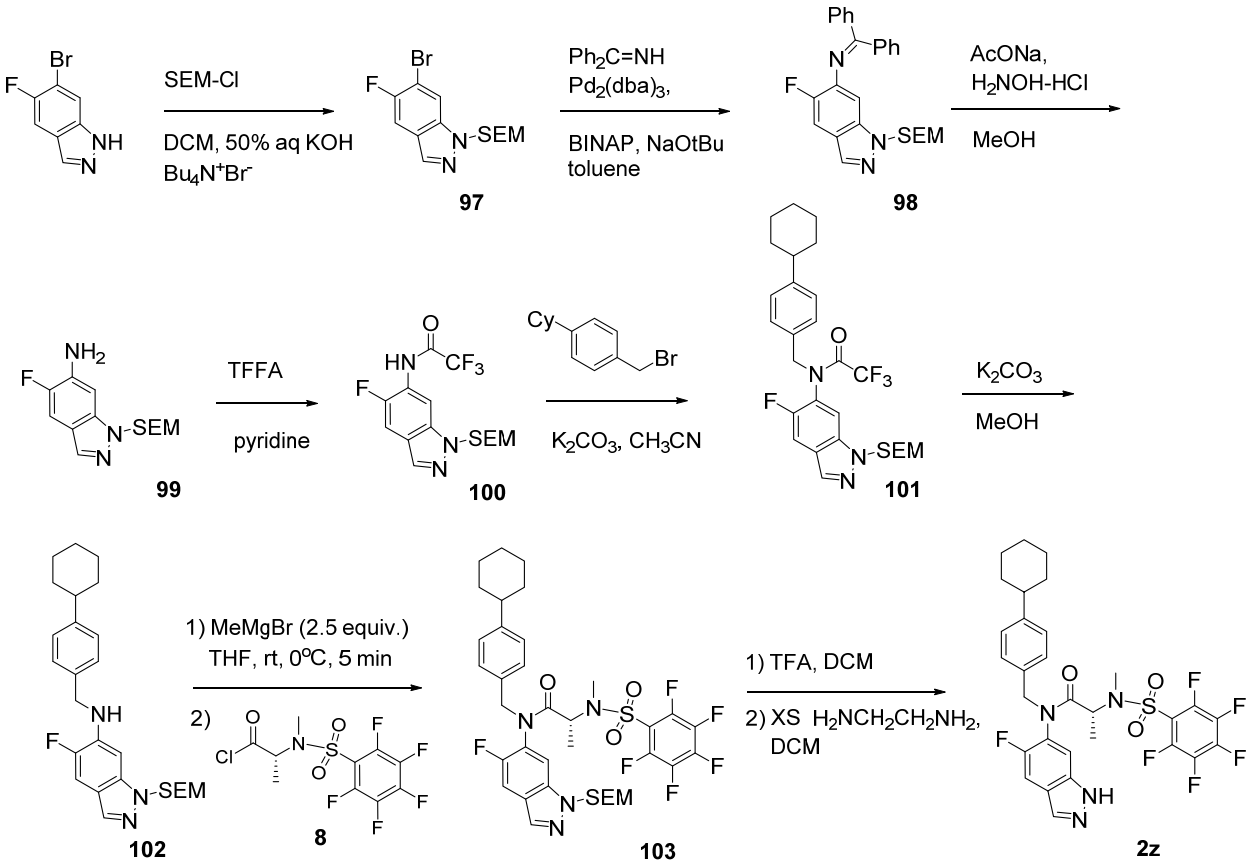
Benzyl 4-amino-3,5-difluorobenzoate (94). To a stirred solution of **93** (332.2 mg, 1.92 mmol) in DMF (9.7mL) was added potassium carbonate (0.29 g, 2.11 mmol) under nitrogen. Stirring continued at room temperature for 10 min before addition of benzyl bromide (0.22 mL, 1.82 mmol). The resulting reaction mixture was stirred at room temperature for 3 h, then poured onto cold water and extracted with EtOAc (2 X). The combined organic extracts were washed with water (2X), then brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford **94** (423 mg, 84% yield) as a pink solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.62 – 7.55 (m, 2H), 7.49 – 7.32 (m, 5H), 5.34 (s, 2H), 4.16 (br. s, 2H).

Benzyl 4-((4-cyclohexylbenzyl)amino)-3,5-difluorobenzoate (95). To a solution of **94** (199 mg, 0.756 mmol) in TFA (1.72 mL) under nitrogen at 0 °C was added sodium triacetoxyborohydride (321 mg, 1.51 mmol) portion wise. The mixture was stirred at 0 °C for 10 min. before addition of 4-cyclohexylbenzaldehyde (151 mg, 0.803 mmol). The resulting reaction mixture was stirred at room temperature for 4 h, poured onto cold water and extracted with EtOAc (2X). The combined organic extracts were washed with water (3X), then with 10% aqueous sodium bicarbonate (2X), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (3-6% EtOAc/hexanes) provided **95** (251 mg, 92% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.59 – 7.50 (m, 2H), 7.48 – 7.31 (m, 5H), 7.27 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 5.33 (s, 2H), 4.59 (s, 2H), 2.65 – 2.41 (m, 1H), 2.00 – 1.59 (m, 6H), 1.54 – 1.12 (m, 6H).

Benzyl (*R*)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)-propanamido)-3,5-difluorobenzoate (96). To a stirred solution of **95** (245 mg, 0.682 mmol) in THF (5.25 mL) under nitrogen at 0 °C was added a solution of trimethylaluminum (0.854 mL of 2M in toluene,

1.71 mmol) and the mixture was warmed to room temperature and stirred at this temperature for 15 min. To the resulting solution was added a solution of **8** (311.9 mg, 0.885 mmol) in THF (3.7 mL). The reaction mixture was stirred at 80 °C for 5 h, cooled and then poured onto 10% $KHSO_4$/ Na_2SO_4 buffer and ice and then extracted with EtOAc (2X). The combined organic layers were washed with water and then brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (4-6% EtOAc/hexane) provided **96** (125 mg, 24% yield). HRMS (ESI+) m/z 751.2072$[M + H]^+$. HRMS (ESI+) calculated for $C_{37}H_{33}F_7N_2O_5S$: 750.1998, found 750.2003.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-propanamido)-3,5-difluorobenzoic acid (2y). To a stirred solution of **96** (119 mg, 0.159 mmol) in methanol (2 mL) and THF (2 mL) was added 10% Pd/C (14.4 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 5 h. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated and the resulting residue was purified by preparative TLC (1:1 hexane: EtOAc with 1% AcOH) to provide **2y** as a light green foam (92.5 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89- 7.31 (br, 1H). 7.30 – 7.03 (m, 4H), 7.03 – 6.92 (m, 2H), 4.79 (d, J = 14.4 Hz, 1H), 4.63 (d, J = 14.4 Hz, 1H), 4.54 – 4.40 (m, 1H), 2.95 (s, 3H), 2.68 – 2.51 (m, 1H), 1.94 – 1.57 (m, 5H), 1.56 – 1.16 (m, 5H), 1.12 (d, J = 6.5 Hz, 3H). HRMS (ESI+) m/z 661.1610$[M + H]^+$. HRMS (ESI+) calculated for $C_{30}H_{27}F_7N_2O_5S$: 660.1529, found 658.1534.



Scheme 18.

6-Bromo-5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (97). To a suspension of 6-bromo-5-fluoro-*1H*-indazole (1.0 g, 4.65 mmol) and Bu_4N^+Br (15 mg, 0.046 mmol) in DCM (40 mL) under a nitrogen atmosphere at 0° C was added 50% KOH in water (20 mL). To the rapidly stirred biphasic mixture was added SEMCl (0.91 mL, 5.11 mmol) by dropwise addition. The reaction mixture was allowed to stir at 0 °C for 1 h and then at room temperature for 1.5 h. The reaction mixture was poured onto water/ DCM and extracted with DCM (2X). The combined DCM extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (5-10% EtOAc in hexane eluent) to provide **97** (1.02 g, 100% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 (s, 1H), 7.85 (d, *J* = 5.4 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 5.71 (s, 2H), 3.63 – 3.45 (m, 2H), 1.02 – 0.80 (m, 2H), -0.04 (s, 9H).

***N*-(5-Fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-indazol-6-yl)-1,1-diphenylmethanimine (98).** A dry 2-neck flask was evacuated and backflushed with argon (3X). Sodium t-butoxide (313 mg, 3.27 mmol), (+/-)BINAP (54 mg, 0.0877 mmol), and $Pd_2(dba)_3$ (26 mg, 0.0292 mmol) were added to the flask. A solution of **97** (810 mg, 2.34 mmol) in toluene (15 mL) was then added to the flask followed by benzophenone imine (0.47 mL, 2.81 mmol). The reaction mixture was stirred at 80 °C for 2 hours and then allowed to cool to room temperature. The reaction mixture was poured onto water and EtOAc and extracted with EtOAc (3X). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The reaction was 98% complete by LCMS. The crude product was combined with a previous small scale reaction to provide intermediate, **98** (approx. 2.93 mmol), which was used as is for the next reaction. For $C_{26}H_{28}FN_3OSi$, exact mass: 445.2. LRMS (ESI+) m/z 446.3$[M + H]^+$.

5-Fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-indazol-6-amine (99). To a solution intermediate, **98**, (approx. 2.93 mmol) in methanol (29 mL) under a nitrogen atmosphere was added potassium acetate (682 mg, 7 mmol) and hydroxylamine hydrochloride (363 mg, 5.2 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The reaction was not complete. Additional potassium acetate (682 mg, 7 mmol) and hydroxylamine hydrochloride (363 mg, 5.2 mmol) were added. The reaction mixture was stirred for an additional 45 min at room temperature. The reaction mixture was poured onto 1% aqueous KOH and DCM and extracted with DCM (3X). The combined organic extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography provided 538 mg of **99** in 66% overall yield for the 2 steps. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.29 (d, *J*= 10.7 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 5.63 (s, 2H), 4.03 (br. s, 2H), 3.61 – 3.43 (m, 2H), 1.00 – 0.79 (m, 2H), -0.05 (s, 9H).

2,2,2-Trifluoro-*N*-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-indazol-6-yl)acetamide (100). To a stirred solution of **99** (530 mg, 1.88 mmol) in DCM (10 mL) under nitrogen at 0 °C was added pyridine (0.18 mL, 2.25 mmol) followed by TFFA (0.29 mL, 2.07 mmol). The reaction mixture was

allowed to warm to room temperature and stirred at this temperature for 1.5 h. The reaction mixture was diluted with DCM, poured onto 10% aqueous $KHSO_4/Na_2SO_4$ buffer and extracted with DCM (3X). The organic extracts were washed with saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide **100** (820 mg, 100% yield) as a orange solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.43 – 7.09 (m, 4H), 6.85 (d, *J* = 7.2 Hz, 1H), 5.63 (s, 2H), 4.03 (s, 5H), 3.61 – 3.43 (m, 2H), 1.00 – 0.79 (m, 2H), -0.05 (s, 9H).

***N*-(4-Cyclohexylbenzyl)-2,2,2-trifluoro-*N*-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-indazol-6-yl)acetamide (101).** To a stirred solution of **100** (820 mg, 2.1 mmol) and 1-(bromomethyl)-4-cyclohexylbenzene (637 mg, 2.52 mmol) in acetonitrile (22 mL) was added potassium carbonate (434 mg, 3.15 mmol). The resulting reaction mixture under nitrogen was stirred at 60 °C for 2.5 h. After cooling to room temperature the reaction mixture was poured onto water and extracted with EtOAc (3X). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0-10% EtOAc/ hexanes eluent) to provide **101** (1.1 g, 95% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 7.20 – 6.96 (m, 5H), 5.67 – 5.45 (m, 3H), 4.29 (d, *J* = 14.1 Hz, 1H), 3.52 – 3.36 (m, 2H), 2.48 (m, 1H), 2.00 – 1.67 (m, 5H), 1.52 – 1.17 (m, 5H), 0.82 (dd, *J* = 9.3, 7.2 Hz, 2H), -0.06 (s, 9H).

***N*-(4-Cyclohexylbenzyl)-5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-indazol-6-amine (102).** To **101** (1.03 g, 1.87 mmol) in THF (18 mL) and MeOH (18 mL) under nitrogen was added potassium carbonate (460 mg, 3.36 mmol). Stirring was continued for 7 h before the reaction mixture was poured onto cold saturated aqueous ammonium chloride and water and extracted with EtOAc (3X). The combined organic extracts were washed with water and then with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide **102** (861 mg, 100 % yield). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.82 (s, 1H), 7.41 – 7.19 (m, 5H), 6.68 (d, J = 6.9 Hz, 2H), 5.63 (s, 2H), 4.55 (br. s, 1H), 4.43 – 4.35 (m, 2H), 3.59 – 3.50 (m, 2H), 2.62 – 2.44 (m, 1H), 2.00 – 1.72 (m, 5H), 1.54 – 1.32 (m, 5H),

0.93 – 0.85 (m, 2H), -0.04 (s, 9H). HRMS (ESI+) m/z 454.2669 $[M + H]^+$. HRMS (ESI+) calculated for $C_{26}H_{36}FN_3OSi$: 453.2612, found 453.2597.

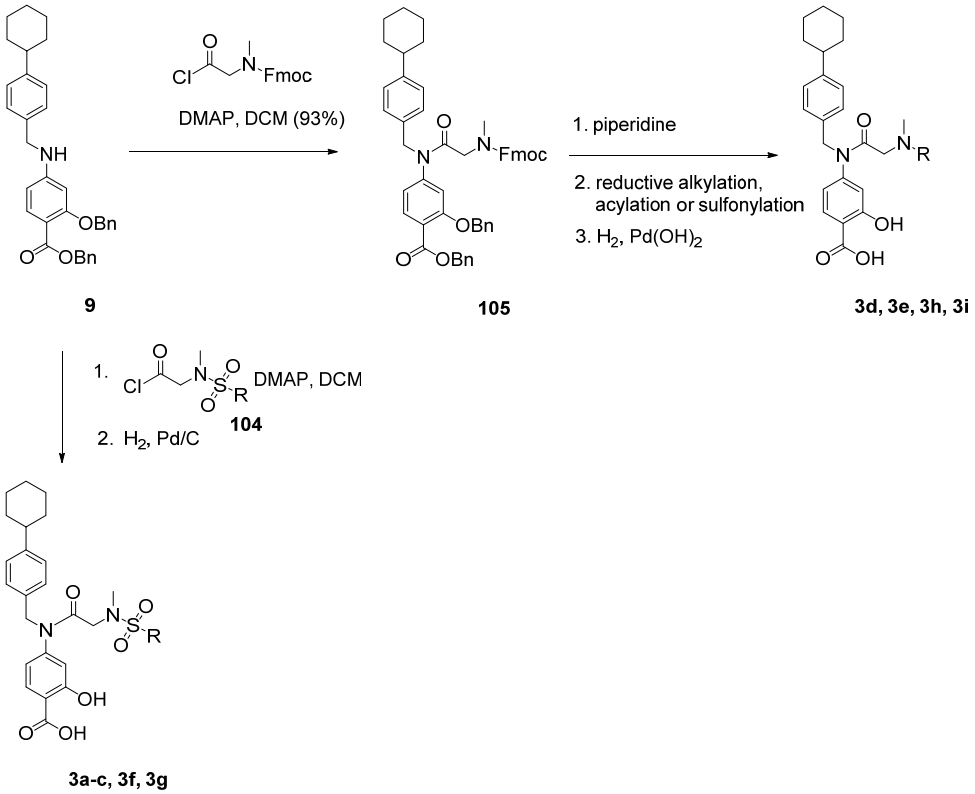
(*R*)-*N*-(4-Cyclohexylbenzyl)-*N*-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)propanamide (**103**). To a solution of **102** (275 mg, 0.606 mmol) in DCM (12 mL) under nitrogen was added acid chloride **8** (298 mg, 0.848 mmol) and DMAP (88 mg, 0.727 mmol). The mixture was allowed to stir for 19 h at room temperature. Additional acid chloride **8** (295 mg, 0.848 mmol) and DMAP (88 mg, 0.727 mmol) were added. The reaction mixture was allowed to stir for 2 d. Methanol (10 drops) was added and the mixture was stirred for 5 min. The mixture was poured onto water and extracted three times with DCM. The combined DCM layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography. The column was eluted with 85:15 hexane: ethyl acetate to give **103** (257 mg at 94% purity, 56% yield). ^{1}NMR showed a 3:1 mixture of rotomers: Major rotomer: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 0.9 Hz, 1H), 7.52 (d, *J* = 9.6 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 3H), 7.00 (d, *J* = 7.9 Hz, 3H), 5.68 (d, *J* = 11.2 Hz, 1H), 5.56 (d, *J* = 11.2 Hz, 1H), 5.33 (d, *J* = 14.3 Hz, 1H), 4.86 (q, *J* = 7.2 Hz, 1H), 4.26 (d, *J* = 14.3 Hz, 1H), 3.59 – 3.39 (m, 3H), 3.17 (s, 2H), 2.59 – 2.39 (m, 2H), 1.94 – 1.70 (m, 8H), 1.44 – 1.32 (m, 6H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.98 – 0.75 (m, 2H), -0.05 (s, 9H). HRMS (ESI+) m/z 791.2486 $[M + Na]^+$. HRMS (ESI+) calculated for $C_{36}H_{42}F_6N_4O_3SSi$: 768.2600, found 768.2596.

(*R*)-*N*-(4-cyclohexylbenzyl)-*N*-(5-fluoro-1H-indazol-6-yl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)propanamide (2z). To a stirred solution of **103** (257 mg, 0.23 mmol) in DCM (4 mL) under a nitrogen atmosphere was added TFA (2 mL) and the resulting solution was allowed to stir at room temperature for 3h. The reaction mixture was concentrated under reduced pressure. The crude reaction mixture was taken up in DCM (4 mL) and treated with ethylene diamine (9-10 drops). The reaction mixture was allowed to stir at room temperature overnight. The mixture was poured onto water and extracted with DCM (3X). The combined organic layer was dried over anhydrous sodium sulfate,

and concentrated under reduced pressure. The crude product was purified by flash chromatography. (75:25:5 hexane: DCM: EtOAc eluent, followed by 70:20:10 hexane: DCM: EtOAc eluent and then 50:20:20 hexane: DCM: EtOAc eluent). A second purification by flash chromatography (20% acetone in hexanes eluent) and isolation of the center cut provided **2z** (38 mg, 96% purity). ^{1}H NMR (300 MHz, Chloroform-*d*) 6:1 ratio of rotomers. Major rotomer: δ 10.43 (s, 1H), 8.10 (d, *J* = 1.1 Hz, 1H), 7.56 (d, *J* = 9.6 Hz, 1H), 7.21 (d, *J* = 6.1 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 5.45 (d, *J* = 14.3 Hz, 1H), 4.84 (q, *J* = 7.2 Hz, 1H), 4.14 (d, *J* = 14.3 Hz, 1H), 3.18 (s, 2H), 2.56 – 2.35 (m, 1H), 1.98 – 1.68 (m, 6H), 1.50 – 1.27 (m, 4H), 1.24 (d, *J* = 7.2 Hz, 3H). HRMS (ESI+) m/z 639.1854 $[M + H]^{+}$. HRMS (ESI+) calculated for $C_{30}H_{28}F_6N_4O_3S$: 638.1786, found 638.1781.

Analogs from Table 3

The synthesis of analogs with variation of the pentafluorophenylsulfonyl group (Table 3, **3a** – **3i**) was performed either by sulfonylation of sarcosine *t*-butyl ester, conversion to the acid chloride **104** and elaboration to the final product, or by preparation of the protected intermediate **105** starting from Fmoc-sarcosine followed by functionalization and subsequent deprotection (Scheme 19).



Scheme 19.

Benzyl 4-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-*N*-(4-cyclohexylbenzyl)acetamido)-2-(benzyloxy)benzoate (105). To a stirred solution of Fmoc-sarcosine monohydrate (329 mg, 1 mmol) in DCM (10 mL) was added DMF (0.030 mL) followed by oxalyl chloride (0.12 mL, 1.4 mmol). The resulting reaction mixture was stirred at room temperature for 90 min before concentration *in vacuo* to afford the acid chloride that was used as is. The crude acid chloride (1.0 mmol) and aniline **9** (330 mg, 0.65 mmol) were combined in DCM (10 mL) and placed under nitrogen. DMAP (95 mg, 0.78 mmol) was added and the resulting reaction mixture was stirred at room temperature for 20 h. Methanol (2-3 drops) was added to consume any remaining acid chloride. The mixture was poured onto water and extracted with DCM (3 X). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (20-30% EtOAc/hexane) to provide **105** (482 mg, 93% yield) as a white foam. ^{1}H NMR

(300 MHz, Chloroform-*d*) δ 7.88 – 7.71 (m, 3H), 7.67 – 7.59 (rotomer 1, m, 2H), 7.55 – 7.48 (rotomer 2, m, 2H), 7.46 – 7.17 (m, 14H), 7.16 – 7.01 (m, 4H), 6.76 (rotomer 1, dd, *J* = 8.2, 1.8 Hz, 1H), 6.60 (rotomer 1, s, 1H), 6.53 (rotomer 2, d, *J* = 8.2 Hz, 1H), 6.40 (rotomer 2, s, 1H), 5.37 (rotomer 2, s, 2H), 5.35 (rotomer 1, s, 2H), 4.96 (rotomer 1, s, 2H), 4.83 (rotomer 1, s, 2H), 4.80 (rotomer 2, s, 2H), 4.77 (rotomer 2, s, 2H), 4.46 – 4.34 (m, 2H), 4.33 – 4.25 (rotomer 1, m, 1H), 4.20 (rotomer 2, t, *J* = 6.8 Hz, 1H), 3.74 (rotomer 1, s, 2H), 3.62 (rotomer 2, s, 2H), 3.04 (rotomer 1, s, 3H), 2.97 (rotomer 2, s, 3H), 2.53 – 2.38 (m, 1H), 1.90 – 1.59 (m, 6H), 1.48 – 1.15 (m, 4H). LCMS: > 99% purity, HRMS (ESI+) m/z 799.3743 $[M + H]^+$. HRMS (ESI+) calculated for $C_{52}H_{50}N_2O_6$: 798.3669, found 798.3671.

4-(*N*-(4-Cyclohexylbenzyl)-2-((2,4,6-trifluoro-*N*-methylphenyl)sulfonamido)acetamido)-2-hydroxybenzoic acid (3d). To a stirred solution of **105** (445 mg, 0.56 mmol) in DCM (6 mL) under a nitrogen atmosphere at 0 °C was added piperidine (1.5 mL). The reaction mixture was stirred for 30 min and then concentrated *in vacuo*. Toluene was added and the resulting solution was concentrated *in vacuo* to provide benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-(methylamino)acetamido)benzoate. For $C_{37}H_{40}N_2O_4$, exact mass: 576.3. LRMS (ESI) m/z 577.3$[M + H]^+$.

To a stirred solution of benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-(methylamino)acetamido)benzoate (0.30 mmole) in DCM (5 mL) under a nitrogen atmosphere was added DIPEA (0.89 mL, 0.51 mmol) and the reaction mixture was cooled to 0 °C. To the mixture was added 2,4,6-trifluorobenzenesulfonyl chloride (0.063 mL, 0.45 mmol) and the resulting mixture was stirred at room temperature for 2 h. Methanol (2 drops) was added and the mixture was poured onto water and extracted with DCM (3X). The combined organic extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (12-30% EtOAc in hexane) provided protected intermediate, benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,4,6-trifluoro-*N*-methylphenyl)sulfonamido)acetamido)benzoate, (191 mg, 83% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.31 (m, 10H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J*

= 8.1 Hz, 2H), 6.79 – 6.65 (m, 3H), 6.51 (d, *J* = 1.8 Hz, 1H), 5.36 (s, 2H), 4.97 (s, 2H), 4.70 (s, 2H), 3.86 (s, 2H), 3.06 (s, 3H), 2.58 – 2.39 (m, 1H), 1.98 – 1.68 (m, 5H), 1.51 – 1.15 (m, 5H). MS (ESI) m/z 577.3$[M + H]^+$.

To a stirred solution of benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-((2,4,6-trifluoro-*N*-methylphenyl)sulfonamido)acetamido)benzoate, (168 mg, 0.22 mmol) in EtOAc (5 mL) and methanol (5 mL) was added 20% $Pd(OH)_2/C$ (16 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 80 min. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated *in vacuo* and foamed with ether to provide **3d** (132 mg, 100% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.81 – 6.67 (m, 3H), 6.66 – 6.53 (m, 1H), 4.77 (s, 2H), 4.06 (s, 2H), 3.10 (s, 3H), 2.58 – 2.40 (m, 1H), 1.98 – 1.64 (m, 5H), 1.52 – 1.20 (m, 5H).
HRMS (ESI) m/z 591.1778 $[M + H]^+$. Calculated for $C_{29}H_{29}F_3N_2O_6S$: 590.1698, found 590.1706.

4-(*N*-(4-Cyclohexylbenzyl)-2-((2,3,5-trifluoro-*N*-methylphenyl)sulfonamido)acetamido)-2-hydroxybenzoic acid (3e). Preparation by a similar procedure to compound **3d**, except substituting 2,3,5-trifluorobenzenesulfonyl chloride for 2,4,6-trifluorobenzenesulfonyl chloride afforded **3e**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.33 (m, 1H), 7.23 – 7.16 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.77 – 6.67 (m, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 4.79 (s, 2H), 4.03 (s, 2H), 3.07 (s, 3H), 2.58 – 2.38 (m, 1H), 1.99 – 1.66 (m, 5H), 1.53 – 1.13 (m, 5H). HRMS (ESI) m/z 591.1783 $[M + H]^+$. Calculated for $C_{29}H_{29}F_3N_2O_6S$: 590.1698, found 590.1709.

4-(*N*-(4-Cyclohexylbenzyl)-2-(2,3,4,5,6-pentafluoro-*N*-methylbenzamido)acetamido)-2-hydroxybenzoic acid (3h). Preparation by a similar procedure to compound **3d**, except substituting 2,3,4,5,6-pentafluorobenzoyl chloride for 2,4,6-trifluorobenzenesulfonyl chloride afforded **3h**. ^{1}H NMR (300 MHz, Chloroform-*d*) 5:1 mixture of rotomers. Major rotomer: δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.19 –

7.10 (m, 4H), 6.80 (d, *J* = 1.9 Hz, 1H), 6.76 – 6.65 (m, 1H), 4.92 (s, 2H), 4.17 (s, 2H), 3.85 – 3.64 (m, 1H), 3.08 (s, 3H), 2.58 – 2.36 (m, 1H), 2.02 – 1.63 (m, 6H), 1.54 – 1.12 (m, 4H). HRMS (ESI) m/z 591.1894 $[M + H]^+$. Calculated for $C_{30}H_{27}F_5N_2O_5$: 590.1840, found 590.1821.

4-(*N*-(4-Cyclohexylbenzyl)-2-(methyl((perfluorophenyl)methyl)amino)acetamido)-2-hydroxybenzoic acid (3i). To a stirred solution of benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-(methylamino)acetamido)benzoate (181mg, 0.31 mmol) in DCE (4mL) under nitrogen was added 2,3,4,5,6-pentafluorobenzaldehyde (93 mg, 0.47 mmol) in DCE (1 mL) followed by sodium triacetoxyborohydride (86 mg, 0.40 mmol). The resulting reaction mixture was stirred at room temperature overnight. The crude reaction mixture was poured onto 10% aqueous sodium bicarbonate and extracted with DCM (3X). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (25% EtOAc/hexanes eluent) to provide benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-(methyl((perfluorophenyl)methyl)amino)acetamido)benzoate (141 mg, 60% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.30 (m, 10H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.45 (s, 1H), 5.36 (s, 2H), 4.90 (s, 2H), 4.82 (s, 2H), 3.85 (s, 2H), 2.93 (s, 2H), 2.59 – 2.36 (m, 1H), 2.24 (s, 3H), 1.96 – 1.68 (m, 5H), 1.52 – 1.04 (m, 5H). For $C_{44}H_{41}F_5N_2O_4$, exact mass: 756.3. LRMS (ESI) m/z 757.2[M + H]+.

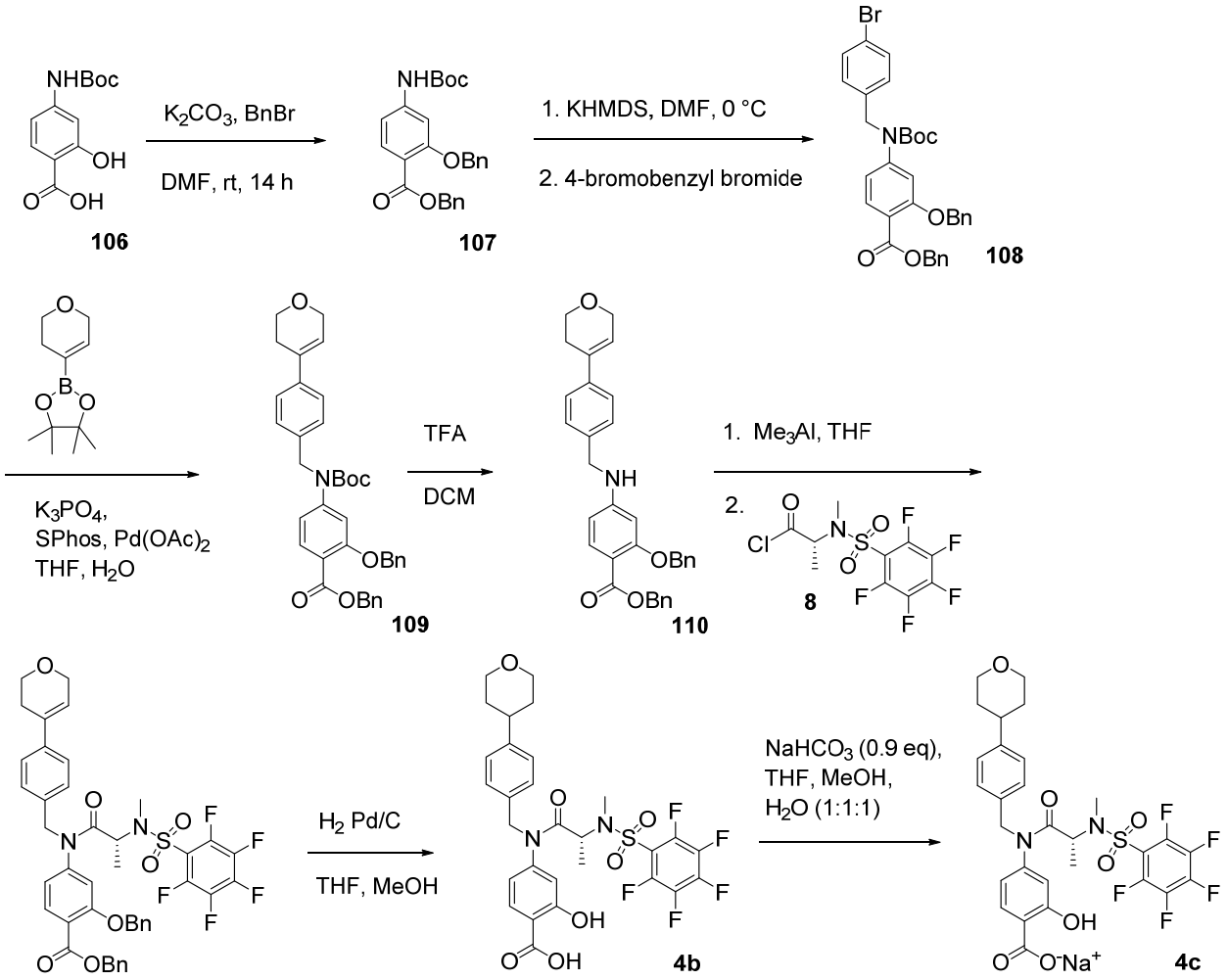
To a stirred solution of benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-(methyl((perfluorophenyl)methyl)amino)acetamido)benzoate (132 mg, 0.17 mmol) in methanol (4mL) and THF (4 mL) was added 20% $Pd(OH)_2$ on carbon (20 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 50 min. The reaction mixture was filtered through Celite® and washed with methanol (2X). The combined filtrate and washes were concentrated *in vacuo* to provide **3i** (111 mg, 100% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.3 Hz, 1H), 7.18 – 7.08 (m, 4H), 6.63 (s, 1H), 6.50 (d, *J* = 8.3 Hz, 1H), 4.87 (s, 2H), 4.17 (s, 2H), 3.35 (s, 2H), 2.60 (s, 3H),

2.53 – 2.38 (m, 1H), 2.13 – 1.58 (m, 5H), 1.53 – 1.12 (m, 5H). HRMS (ESI) m/z 577.2128[M + H]+. Calculated for $C_{30}H_{29}F_5N_2O_4$: 576.2047, found 576.2055.

Analogs from Table 4

Scheme 20 demonstrates preparation of analogs with variation of the cyclohexylbenzyl group (Table 4) as represented by the synthesis of tetrahydropyranylbenzyl analogs **4b** and **4c**. Deprotonation of anilide **107** with KHMDS and alkylation with 4-bromobenzylbromide gave intermediate arylbromide **108**. Suzuki-Miyaura cross coupling reaction of **107** with 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester to obtain the dihydropyanyl intermediate followed by thermal removal of the *t*-butoxycarbonyl protecting group using hexafluoroisopropanol [4] afforded the desired aniline **110**. Coupling with acid chloride **8** using trimethylaluminum and subsequent hydrogenolysis of the salicylate protecting groups yielded the tetrahydropyran (THP) analog **4b**, which was subsequently converted to the sodium salt, **4c**.

Below are selected examples:



Scheme 20.

Benzyl 2-(benzyloxy)-4-((*tert*-butoxycarbonyl)amino)benzoate (107). To a stirred solution of 4-((*tert*-butoxycarbonyl)amino)-2-hydroxybenzoic acid (**106**, 4.68 g, 18.48 mmol) in DMF (90 mL) under nitrogen was added potassium carbonate (6g, 43 mmol) followed by benzyl bromide (4.95 mL, 41.7 mmol). The resultant mixture was stirred at room temperature overnight, then poured onto water and extracted with ether (3 X). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (0-8% EtOAc/ hexanes gradient) provided **107** (7.34 g, 92% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.5

Hz, 1H), 7.57 – 7.29 (m, 11H), 6.75 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.66 (br. s, 1H), 5.34 (s, 2H), 5.19 (s, 2H), 1.55 (s, 9H).

Benzyl 2-(benzyloxy)-4-((4-bromobenzyl)(*tert*-butoxycarbonyl)amino)benzoate (108). To a stirred solution of **107** (3.97 g, 9.17 mmol) in DMF (45 mL) at 0 °C under nitrogen was added KHMDS (11 mL of 1M in THF, 11 mmol). After stirring at 0 °C for 10 min., a solution of 4-bromobenzyl bromide (3.2g, 12.8 mmol) in DMF (5 mL) was added. The reaction was allowed to warm to room temperature and stirring was continued at this temperature overnight. The reaction mixture was quenched with saturated ammonium chloride, poured onto water and extracted with ether (3 X). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (8-26% gradient of what solvents?) provided **108** (4.63g, 84% yield) as a cream colored solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.30 (m, 12H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.85 – 6.76 (m, 2H), 5.35 (s, 2H), 5.07 (s, 2H), 4.75 (s, 2H), 1.43 (s, 9H). HRMS (ESI) m/z 624.1356, 626.1342[M + Na]+. Calculated for $C_{33}H_{32}BrNO_5$: 601.1464, found 601.1464.

Benzyl 2-(benzyloxy)-4-((tert-butoxycarbonyl)(4-(3,6-dihydro-2H-pyran-4-yl)benzyl)amino)benzoate (109). In a dry flask under nitrogen was added **108** (363 mg, 0.6 mmol), $Pd(OAc)_2$ (8.8 mg, 0.039 mmol), SPhos (32.1 mg, 0.078 mmol), 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (126.6 mg, 0.6 mmol), potassium phosphate (255.6 mg, 1.20 mmol) and water (2 drops). The flask was back-flushed with nitrogen, THF (7.7 mL) was added and the flask was heated at 40 °C for 14 h. The crude reaction mixture was diluted with EtOAc, filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated under reduced pressure and the resulting residue purified by flash chromatography (10 – 20% EtOAc/hexanes) to afford **109** (120 mg, 30% yield). Product was combined with a previous batch to give 162 mg. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.29 (m, 12H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 1.9 Hz, 1H), 6.82 (dd, *J* =

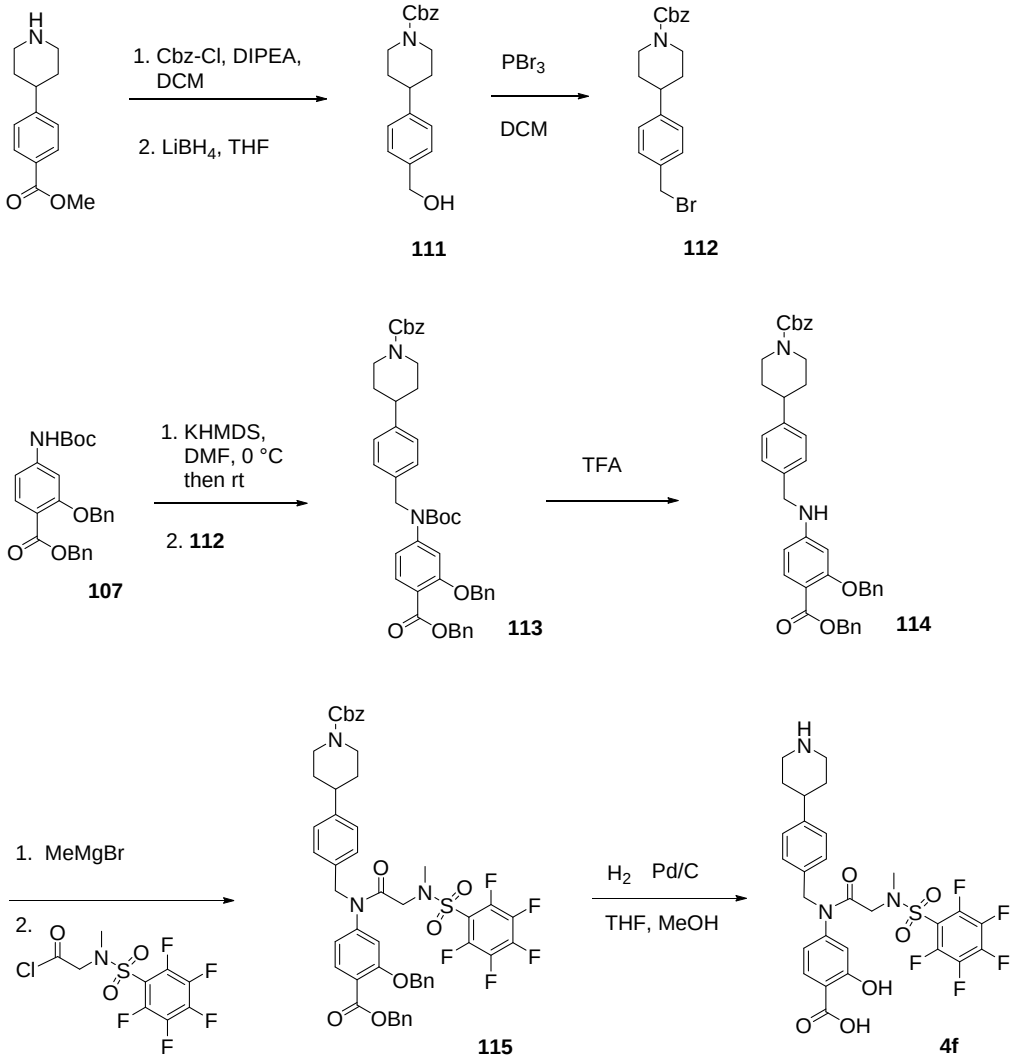
8.4, 1.9 Hz, 1H), 6.14 (s, 1H), 5.34 (s, 2H), 5.04 (s, 2H), 4.81 (s, 2H), 4.34 (dd, *J* = 5.5 Hz, *J* = 2.8 Hz, 2H), 3.95 (t, *J* = 5.6 Hz, 2H), 2.53 (t, *J* = 5.6 Hz, 2H), 1.44 (s, 9H). For $C_{38}H_{39}NO_6$, exact mass: 605. LRMS (ESI^+): 628 $[M + Na]^+$.

Benzyl 2-(benzyloxy)-4-((4-(3,6-dihydro-2H-pyran-4-yl)benzyl)amino)benzoate (110). A solution of **109** (150 mg, 0.248 mmol) in HFIP (4 mL) in a sealed tube under nitrogen was heated at 120 °C for 15 h. The mixture was concentrated to dryness, taken up in DCM and concentrated to dryness (2 X) and then purified by flash chromatography (20-25% EtOAc/hexane) to provide **110** (92 mg, 73% yield) as an off-white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.6 Hz, 1H), 7.49 – 7.29 (m, 14H), 6.23 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 6.15 (br. s, 1H), 5.32 (s, 2H), 5.10 (s, 2H), 4.35 (d, *J* = 2.5 Hz, 2H), 3.96 (t, *J* = 5.3 Hz, 2H), 2.54 (dq, *J* = 5.3, 2.9 Hz, 2H).

(*R*)-2-Hydroxy-4-(2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-*N*-(4-(tetrahydro-2H-pyran-4-yl)benzyl)propanamido)benzoic acid (4b). Final product **4b** was prepared as described for **1a** except using aniline **110** in place of aniline **8**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.80 – 6.65 (m, 2H), 4.94 (d, *J* = 15.0 Hz, 1H), 4.86 – 4.74 (m, 1H), 4.65 (d, *J* = 15.0 Hz, 1H), 4.07 – 3.84 (m, 2H), 3.51 – 3.30 (m overlapping water peak), 3.06 (s, 3H), 2.79 – 2.65 (m, 1H), 1.78 – 1.36 (m, 4H), 1.21 (d, *J* = 7.0 Hz, 3H). LCMS: 97% purity, HRMS (ESI) m/z 643.1563$[M + H]^+$. HRMS (ESI+) calculated for $C_{29}H_{27}F_5N_2O_7S$: 642.1459, found 642.1467.

Sodium (*R*)-2-hydroxy-4-(2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-*N*-(4-(tetrahydro-2H-pyran-4-yl)benzyl)propanamido)benzoate (4c). To a solution of **4b** (68 mg, 0.106 mmol) in 3 mL of 1:1:1 THF:MeOH:H_2O was added sodium bicarbonate (8 mg, 0.095 mmol) and the resultant mixture was stirred at room temperature for 4 h and then concentrated *in vacuo*. Trituration with ether provided **4c** (65 mg) as a cream colored solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.15 (d,

J = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.43 – 6.28 (m, 2H), 4.89 – 4.79 (d, *J* = 14.8 Hz, and overlapping m, 2H), 4.52 (d, *J* = 14.8 Hz, 1H), 3.93 (dd, *J* = 10.6, 3.5 Hz, 2H), 3.50 – 3.35 (m, overlapping water), 3.09 (s, 3H), 1.78 – 1.53 (m, 4H), 1.21 (d, *J* = 7.2 Hz, 3H). LCMS: 99% purity, HRMS (ESI) m/z 643.1580[M + H]$^+$. HRMS (ESI+) calculated for $C_{29}H_{27}F_5N_2O_7S$: 642.1459, found 642.1480.



Scheme 21.

Benzyl 4-(4-(hydroxymethyl)phenyl)piperidine-1-carboxylate (111). To a stirred solution of methyl 4-(piperidin-4-yl)benzoate (500 mg, 2.3 mmol) in DCM (25 mL) under a nitrogen atmosphere at 0 °C was added DIPEA (0.48 mL, 2.76 mmol) followed by benzyl chloroformate (0.36 mL, 2.5 mmol). The

reaction mixture was allowed to warm to room temperature and stirred at this temperature overnight. The reaction mixture was poured onto 1N aqueous HCl and extracted with DCM (3X). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting residue was dissolved in THF (16 mL) and placed under nitrogen. Solid lithium borohydride (100 mg, 4.6 mmol) was added. The reaction mixture was stirred at room temperature for 2h and then at 65 °C for 20 h. Ice was added and then 1N aqueous HCl was added dropwise until pH = 2. The mixture was stirred at room temperature for 1 h. The mixture was adjusted to pH = 8 with saturated aqueous sodium bicarbonate and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (20-40% EtOAc in hexane eluent) provided **111** (651 mg, 87% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 – 7.29 (m, 7H), 7.23 – 7.15 (m, 2H), 5.16 (s, 2H), 4.67 (d, *J* = 5.8 Hz, 2H), 4.47 – 4.17 (m, 2H), 3.03 – 2.77 (m, 2H), 2.76 – 2.54 (m, 1H), 1.84 (d, *J* = 12.9 Hz, 2H), 1.74 – 1.52 (m, 2H).

Benzyl 4-(4-(bromomethyl)phenyl)piperidine-1-carboxylate (112). To a stirred solution of **111** (428 mg, 1.32 mmol) in DCM (5 mL) under nitrogen at 0 °C was added PBr_3 (0.05 mL, 0.53 mmol) and the resulting mixture was stirred at this temperature for 45 min. The reaction mixture was poured onto ice-water and was extracted with DCM (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (10-25% EtOAc in hexane eluent) provided **112** (293 mg, 57% yield). This material was combined with a previous batch to provide a total of 453 mg. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 – 7.31 (m, 7H), 7.23 – 7.15 (m, 2H), 5.18 (s, 2H), 4.50 (s, 2H), 4.45 – 4.22 (m, 2H), 2.90 (t, *J* = 13.0 Hz, 2H), 2.69 (tt, *J* = 12.2, 3.6 Hz, 1H), 1.85 (d, *J* = 13.1 Hz, 2H), 1.76 – 1.51 (m, 2H).

Benzyl 4-(4-(((3-(benzyloxy)-4-((benzyloxy)carbonyl)phenyl)(tert-butoxycarbonyl)amino)methyl)-phenyl)piperidine-1-carboxylate (113). To a stirred solution of **107** (353 mg, 0.81 mmol) in DMF (8 mL) at 0 °C under nitrogen was added KHMDS (1.0 mL of 1M in THF, 1.0 mmol). After stirring at 0 °C for 10 min., a solution of **112** (442 mg, 1.1 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirring was continued at this temperature overnight. The reaction mixture was quenched with saturated ammonium chloride, poured onto water and extracted with ether (3 X). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (20-30% gradient) provided **113** (465 mg, 78% yield) as a colorless foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.44 – 7.30 (m, 15H), 7.15 – 7.09 (m, 4H), 6.89 – 6.85 (m, 1H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.33 (s, 2H), 5.17 (s, 2H), 5.03 (s, 2H), 4.79 (s, 2H), 4.52 – 4.22 (m, 2H), 2.89 (t, *J* = 12.8 Hz, 2H), 2.76 – 2.54 (m, 1H), 1.83 (d, *J* = 13.1 Hz, 2H), 1.75 – 1.58 (m, 2H), 1.43 (s, 9H).

Benzyl 4-(4-(((3-(benzyloxy)-4-((benzyloxy)carbonyl)phenyl)amino)methyl)phenyl)piperidine-1-carboxylate (114). To a solution of **113** (461 mg, 0.62 mmol) in DCM (15 mL) under nitrogen at 0 °C was added TFA (3 mL) and the mixture was stirred for 1 h. The mixture was poured onto saturated aqueous sodium bicarbonate. A few drops of aqueous sodium hydroxide were also added to adjust pH to 8-9. The mixture was extracted with DCM (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (10-30% gradient) provided **114** (223 mg, 56% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.6 Hz, 1H), 7.49 – 7.28 (m, 17H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.22 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 5.32 (s, 2H), 5.18 (s, 2H), 5.09 (s, 2H), 4.49 – 4.21 (m, 3H), 2.90 (t, *J* = 12.8 Hz, 2H), 2.69 (ddd, *J* = 12.2, 8.6, 3.7 Hz, 1H), 1.85 (d, *J* = 13.0 Hz, 2H), 1.76 – 1.59 (m, 2H). HRMS (ESI) m/z 641.3009[M + H]$^+$. HRMS (ESI+) calculated for $C_{41}H_{40}N_2O_5$: 640.2937, found 640.2938.

Benzyl 4-(4-((*N*-(3-(benzyloxy)-4-((benzyloxy)carbonyl)phenyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)acetamido)methyl)phenyl)piperidine-1-carboxylate (115). To a stirred solution of aniline, **114** (115 mg, 0.18 mmol) in THF (4 mL) under nitrogen at 0 °C was added methylmagnesium bromide (0.39 mL of 1.4 M in 1:3 THF:toluene, 0.54 mmol). Stirring was continued at 0 – 5 °C for 5 min. The resultant solution was added dropwise to a stirred solution of *N*-methyl-*N*-((perfluorophenyl)sulfonyl)glycinoyl chloride (109 mg, 0.32 mmol) in THF (4 mL) under nitrogen at room temperature. The resulting reaction mixture was allowed to stir at this temperature overnight, quenched with aqueous saturated ammonium chloride, poured onto water and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure and resulting residue purified by flash chromatography (25:10:1 hexane: DCM: EtOAc eluent and then 25:10:3 hexane: DCM: EtOAc) to afford **115** (105 mg, 62% yield). HRMS (ESI) m/z 964.2671[M + Na]$^+$. HRMS (ESI+) calculated for $C_{50}H_{44}F_5N_3O_8S$: 941.2769, found 941.2775.

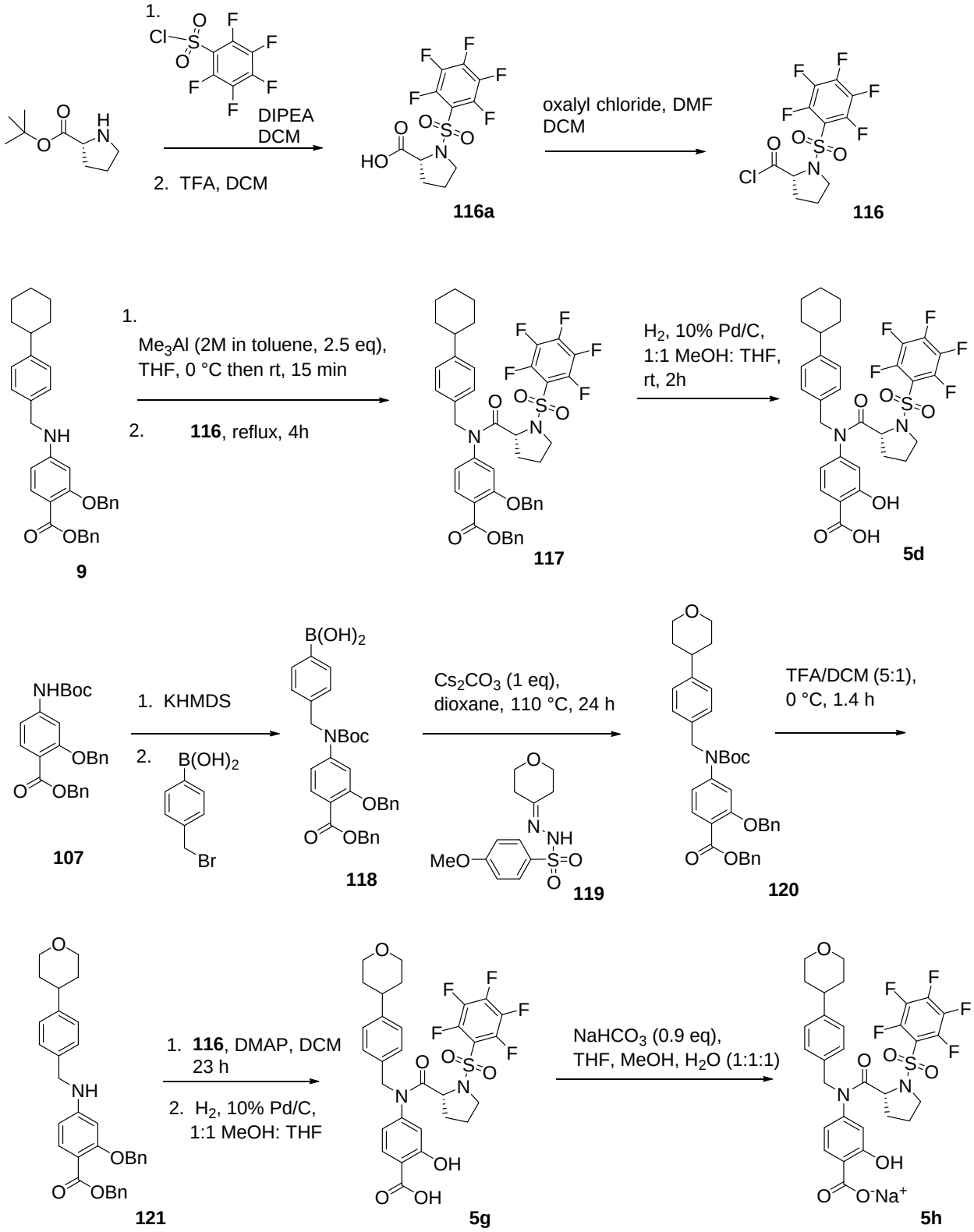
2-Hydroxy-4-(2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfonamido)-*N*-(4-(piperidin-4-yl)benzyl)acetamido)benzoic acid (4f). To a stirred solution of **115** (100 mg, 0.106 mmol) in methanol (5 mL) and THF (5 mL) was added 10% Pd/C (20 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere overnight. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated and the resulting residue was triturated with ether/hexane to provide **4f** as a white solid (49 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (br s, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.39 (d, *J* = 2.0 Hz, 1H), 6.35 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.70 (s, 2H), 4.08 (s, 2H), 3.11 – 2.65 (m and overlapping s, 5H), 2.06 – 1.54 (m, 4H). HRMS (ESI+) m/z 628.1533 [M + H]$^+$. HRMS (ESI+) calculated for $C_{28}H_{26}F_5N_3O_6S$: 627.1462, found 627.1462.

(*R*)-4-(N-(4-(4,4-difluorocyclohexyl)benzyl)-2-((2,3,4,5,6-pentafluoro-*N*-methylphenyl)sulfon-amido)propanamido)-2-hydroxybenzoic acid (4g). Preparation by a similar procedure to example **4b**, except substituting 4,4-difluorocyclohex-1-enylboronic acid pinacol ester for 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester in step 3 afforded **4g**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 6.42 – 6.28 (m, 2H), 4.98 – 4.74 (m, 2H), 4.51 (d, J = 14.9 Hz, 1H), 3.08 (s, 3H), 2.76 – 2.58 (m, 1H), 2.16 – 1.95 (m, 3H), 1.95 – 1.76 (m, 3H), 1.72 – 1.51 (m, 2H), 1.27 -1.11 (m, 3H). For $C_{30}H_{27}F_7N_2O_6S$, exact mass: 676.2. LRMS (ESI) m/z 677.1$[M + H]^+$.

Analogs from Table 5

The synthesis of proline analog **5d** (Scheme 22) was similar to that described for the alanine analog. The starting D-proline acid chloride **116** was prepared from D-proline t-butyl ester in 3 steps in 93% overall yield as a stable white solid. After pre-treatment of aniline **9** with trimethylaluminum, coupling with acid chloride **116** and final hydrogenolysis of the resultant intermediate **117**, the desired product **5d** was obtained in 48% overall yield. THP analog **5g** was prepared using a modified route (Scheme 4). Deprotonation of anilide **107** with KHMDS and alkylation with (4-(bromomethyl)phenyl)boronic acid gave intermediate boronic acid **118** in 54% yield.

The boronic acid **118** was coupled to the sulfonylhydrazide **119** in the presence of cesium carbonate in dioxane at 110 °C following Allwood's procedure [5] providing the protected aniline **120** in 66% yield. Treatment with TFA gave the aniline **121** which was converted to product **5g** in 89% yield by acylation with acid chloride **116** in the presence of DMAP, followed by catalytic hydrogenolysis of the purified intermediate. Treatment of **5g** with a sub-stoichiometric amount of sodium bicarbonate afforded the sodium salt, **5h**.


1.
2. TFA, DCM
DIPEA
DCM
oxalyl chloride, DMF
DCM
116a
116
1.
Me3Al (2M in toluene, 2.5 eq),
THF, 0 °C then rt, 15 min
2. 116, reflux, 4h
9
117
H2, 10% Pd/C,
1:1 MeOH: THF,
rt, 2h
5d
1. KHMDS
2.
107
118
Cs2CO3 (1 eq),
dioxane, 110 °C, 24 h
119
TFA/DCM (5:1),
0 °C, 1.4 h
120
1. 116, DMAP, DCM
23 h
2. H2, 10% Pd/C,
1:1 MeOH: THF
121
5g
NaHCO3 (0.9 eq),
THF, MeOH, H2O (1:1:1)
5h

Scheme 22.

((Pentafluorophenyl)sulfonyl)-D-proline (116a). To as stirred solution of *tert*-butyl D-prolinate (1.5 g, 8.7 mol) and DIPEA (2.1 mL, 12.2 mmol) in DCM (100 mL) under nitrogen at 0 °C was added pentafluorobenzenesulfonyl chloride (1.55 mL, 10.4 mmol). The reaction mixture was allowed to warm to room temperature, stirred overnight, then poured onto water and extracted with DCM (3 X). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the resulting residue purified by flash chromatography (2% EtOAc and 2% DCM in hexanes) to afford *tert*-butyl ((perfluorophenyl)sulfonyl)-D-prolinate (3.65 g). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.51 (dd, *J* = 8.5, 3.2 Hz, 1H), 3.78 – 3.56 (m, 2H), 2.42 – 2.19 (m, 1H), 2.14 – 1.87 (m, 3H), 1.43 (s, 9H).

To a stirred solution of *tert*-butyl ((pentafluorophenyl)sulfonyl)-D-prolinate (3.64 g, 9 mmol) in DCM (40 mL) was added TFA (40 mL) and the resulting reaction was stirred at room temperature for overnight before concentration *in vacuo*. The residue was triturated with 10% ether in hexanes and washed with this mixture (2X) to give **116a** (2.96 g, 98% yield) as a white powder. LCMS: > 98% purity, MS (ESI) m/z 368[M + Na]$^+$. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.64 (dd, *J* = 8.7, 3.6 Hz, 1H), 3.67 (q, *J* = 7.0, 6.5 Hz, 2H), 2.38 (dq, *J* = 12.7, 8.7 Hz, 1H), 2.28 – 1.98 (m, 3H).

((Pentafluorophenyl)sulfonyl)-D-prolinoyl chloride (116). To a stirred solution of **116a** (2.89 g, 8.38 mmol) in DCM (70 mL) was added DMF (2 drops) followed by oxalyl chloride (1.08 mL, 12.6 mmol) under nitrogen. The resultant reaction mixture was stirred for 1.7 h and then concentrated *in vacuo*. A small volume of EtOAc was added and the suspension was concentrated again to afford a white solid. The solid was triturated with a small volume of cold 5% ether in hexanes and washed with cold 5% ether in hexanes to provide **24** (2.91g, 96% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.94 (dd, *J* = 8.8, 3.8 Hz, 1H), 3.71 (ddd, *J* = 7.3, 6.5, 0.7 Hz, 2H), 2.58 – 2.28 (m, 2H), 2.19 – 2.00 (m, 2H).

Benzyl (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)benzoate (117). To a stirred solution of aniline **9**[14] (314 mg, 0.62 mmol) in THF (10 mL) under nitrogen at 0 °C was added trimethylaluminum (0.93 mL of a 2M solution in toluene, 1.86 mmol) and the resultant reaction solution was allowed to stir at room temperature for 10 min. To the reaction mixture was added a solution of **116** (316 mg, 0.87 mmol) in THF (6 mL). The resultant reaction mixture was warmed at reflux with stirring for 4 h, cooled to room temperature, poured onto 10% potassium bisulfate/ sodium sulfate buffer and extracted with EtOAc (3 X). The combined organic layers were washed with saturated sodium bicarbonate, then with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 -20% EtOAc/ hexanes) to provide **117** (250 mg, 48% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.48 – 7.29 (m, 10H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.60 (s, 1H), 5.36 (s, 2H), 5.11 (d, *J* = 14.3 Hz, 1H), 4.95 – 4.74 (m, 2H), 4.53 (d, *J* = 14.3 Hz, 1H), 4.45 (t, *J* = 6.7 Hz, 1H), 3.83 – 3.55 (m, 2H), 2.57 – 2.38 (m, 1H), 2.17 – 1.64 (m, 9H), 1.52 – 1.11 (m, 5H). LCMS: 98% purity, HRMS (ESI) m/z 833.2683[M + H]$^+$. HRMS (ESI+) calculated for $C_{45}H_{41}F_5N_2O_6S$: 832.2605, found 832.2612.

(*R*)-4-(*N*-(4-cyclohexylbenzyl)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)-2-hydroxybenzoic acid (5d). To a stirred solution of **117** (218 mg, 0.26 mmol) in methanol (9 mL) and THF (9 mL) was added 10% Pd/C (30 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere 2.5 h. The reaction mixture was filtered through Celite® and washed with methanol (2 X). The combined filtrate and washes were concentrated, then taken up in ether and concentrated again to provide **5d** (194 mg, 100% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.72 (br. s, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.84 (d, *J* = 14.4 Hz, 1H), 4.69 (d, *J* = 14.4

Hz, 1H), 4.63 – 4.53 (m, 1H), 3.86 – 3.60 (m, 3H), 2.62 – 2.40 (m, 1H), 2.21 – 1.60 (m, 10H), 1.56 – 1.11 (m, 4H).

LCMS: 98% purity, MS (ESI) m/z 653[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{29}F_5N_2O_6S$: 652.1666, found 652.1677.

(4-(((3-(Benzyloxy)-4-((benzyloxy)carbonyl)phenyl)(*tert*-butoxycarbonyl)amino)methyl)phenyl)-boronic acid (118). To a stirred solution of **107**[14] (4.1 g, 9.5 mmol) in 40 mL DMF at 0° C under nitrogen was added KHDMS (23 mL of 1M in THF, 23 mmol, 2.4 equiv.). Stirring was continued for 10 min. After 10 min, a solution of 4-bromomethylphenylboronic acid (2.9 g, 13.3 mmol, 1.4 equiv) in 20 mL DMF was added. The flask was rinsed with an additional 4 mL of DMF and that was added to reaction mixture. The reaction was allowed to warm to room temperature and stirring continued at room temperature overnight. The reaction mixture was poured onto dilute aqueous HCl and extracted with ether (3X). The combined ether layers were washed with brine, dried over sodium sulfate and evaporated under reduced pressure. Purification by flash column chromatography on silica with EtOAc/hexane (25-40%) eluent gave **118** (3.02 g, 54% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) rotomers (1:1) δ 8.18 (d, *J* = 7.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 5.8 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.26 (m, 11H), 7.21 (d, *J* = 7.9 Hz, 1H), 6.96 – 6.77 (m, 2H), 5.33 (s, 2H), 5.06 (s, *J* = 1H), 4.90 (s, 1H), 4.84(s, 1H), 1.50 – 1.38 (m, 9H). For $C_{33}H_{34}BNO_7$, exact mass: 567. LRMS (ESI): $[M+Na]^+$ = 590, $[2M+Na]^+$ = 1157.

Benzyl 2-(benzyloxy)-4-((*tert*-butoxycarbonyl)(4-(tetrahydro-*2H*-pyran-4-yl)benzyl)amino)benzoate (120)

A stirred solution of **118** (0.5 g, 1.75 mmol, 1 equiv), **119**[37] (1.5 g, 2.6 mmol, 1.5 equiv), and Cs_2CO_3 (0.86 g, 2.6 mmol, 1.5 equiv) in 1,4-dioxane (13 mL) was degassed and backfilled with argon. The flask was heated to 110°C for 23 h. The reaction mixture was poured onto aqueous sodium bicarbonate and

extracted with DCM (3 X). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. Purification by flash column chromatography with EtOAc/hexane (10-15%) eluent provided **120** (0.58 g, 55% yield) as a white solid. The reaction was performed twice and the yield ranged from 55-66%.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.06 (m, 4H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.34 (s, 2H), 5.03 (s, 2H), 4.80 (s, 2H), 4.08 (dd, *J* = 10.4, 3.7 Hz, 2H), 3.53 (td, *J* = 11.3, 3.3 Hz, 2H), 2.75 (tt, *J* = 10.8, 4.9 Hz, 1H), 1.92 – 1.66 (m, 4H), 1.44 (s, 9H). HRMS (ESI) m/z 630.2826[M + Na]$^+$. HRMS (ESI+) calculated for $C_{38}H_{41}NO_6$: 607.2934, found 607.2936.

Benzyl 2-(benzyloxy)-4-((4-(tetrahydro-*2H*-pyran-4-yl)benzyl)amino)benzoate (121). To a stirred solution of **28** (0.57 g, 0.95 mmol) in DCM (12 mL) under nitrogen at 0°C was added TFA (2.4 mL). Stirring was continued at 0° C for 1.4 hours. The reaction mixture was poured onto cold aqueous saturated $NaHCO_3$ and extracted with DCM (3 X). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. Purification by flash column chromatography with hexane/DCM/EtOAc (7:2:1) eluent yielded **121** (0.44 g, 66% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.6 Hz, 1H), 7.52 – 7.14 (m, 14H), 6.23 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 5.32 (s,2H), 5.10 (s, 2H), 4.46 (t, *J* = 5.4 Hz, 1H), 4.33 (d, *J* = 5.4 Hz, 2H), 4.11 (dt, *J* = 10.5, 3.3 Hz, 2H), 3.55 (td, *J* = 11.3, 3.3 Hz, 2H), 2.78 (tt, *J* = 10.5, 4.9 Hz, 1H), 1.97 – 1.69 (m, 4H). HRMS (ESI) m/z 508.2476[M + H]$^+$. HRMS (ESI+) calculated for $C_{33}H_{33}NO_4$: 507.2410, found 507.2406.

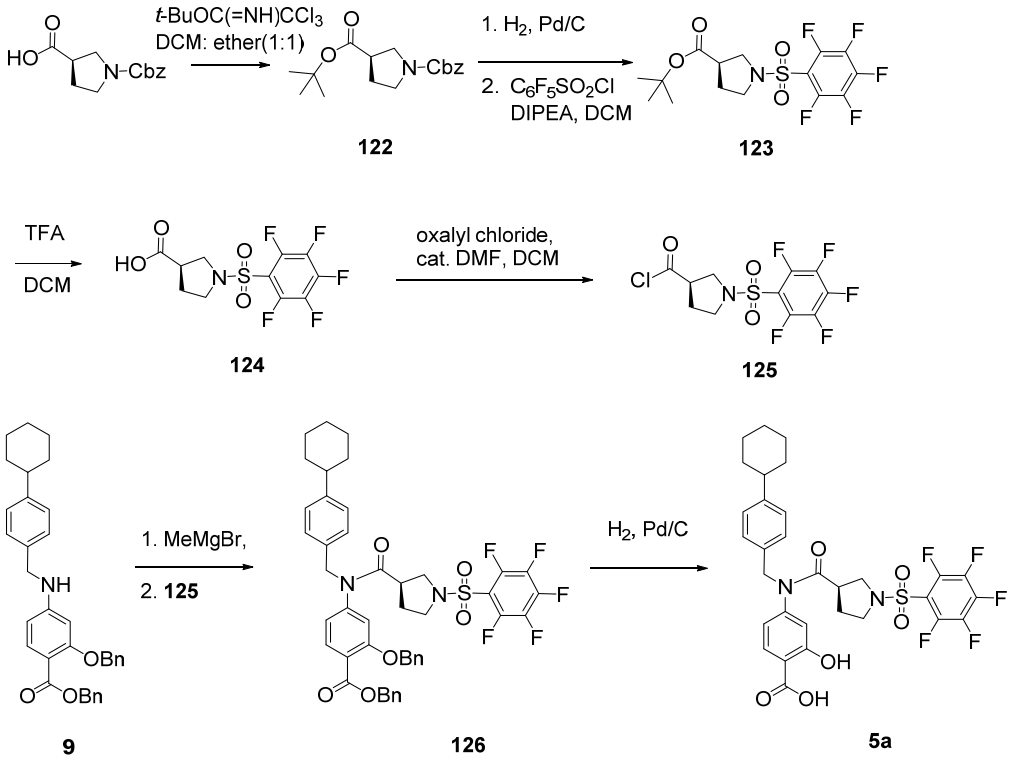
(*R*)-2-(Benzyloxy)-4-(1-((pentafluorophenyl)sulfonyl)-*N*-(4-(tetrahydro-*2H*-pyran-4-yl)benzyl)pyrrolidine-2-carboxamido)benzoate (5g). To a stirred solution of **121** (0.20 g, 0.39 mmol) and **116** (0.214 g, 0.59 mmol) in dry DCM (8 mL) under nitrogen was added DMAP (0.06 g, 0.47 mmol).

Stirring was continued for 23 h. Methanol (2-3 drops) was added to consume any excess acid chloride. The mixture was poured onto water and extracted with DCM (3 X). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. Purification by flash column chromatography (25% EtOAc/hexane eluent and then eluting with a mix of 25% EtOAc/(4:1 hexane:DCM mixture) afforded benzyl (*R*)-2-(benzyloxy)-4-(1-((pentafluorophenyl)sulfonyl)-*N*-(4-(tetrahydro-*2H*-pyran-4-yl)benzyl)pyrrolidine-2-carboxamido)benzoate (289 mg, 89% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.47 – 7.30 (m, 10H), 7.17 – 6.95 (m, 4H), 6.71 (d, *J* = 8.7 Hz, 2H), 5.37 (s, 2H), 5.23 – 4.86 (m, 2H), 4.86 – 4.57 (m, 2H), 4.48 (t, *J* = 6.5 Hz, 1H), 4.07 (dd, *J* = 10.7, 3.9 Hz, 2H), 3.69 (dd, *J* = 28.4, 7.8 Hz, 2H), 3.53 (td, *J* = 11.3, 3.2 Hz, 2H), 2.73 (td, *J* = 10.9, 5.0 Hz, 1H), 2.17 – 1.64 (m, 8H). HRMS (ESI) m/z 835.2484$[M + H]^+$. HRMS (ESI+) calculated for $C_{44}H_{39}F_5N_2O_7S$: 834.2398, found 834.2411.

To a stirred solution of benzyl (*R*)-2-(benzyloxy)-4-(1-((pentafluorophenyl)sulfonyl)-*N*-(4-(tetrahydro-*2H*-pyran-4-yl)benzyl)pyrrolidine-2-carboxamido)benzoate (266 mg, 0.32 mmol) in THF (6 mL) and methanol (6 mL) under nitrogen was added 10% $Pd(OH)_2$ (0.025 g). The solution was placed under a hydrogen balloon and stirred for an hour. The solution was filtered through Celite®, washed with methanol and evaporated under reduced pressure to afford **5g** (214 mg, 100% yield) as a white foam.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.89 (br s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.23 – 6.95 (m, 4H), 6.82 – 6.63 (m, 2H), 4.79 (s, 2H), 4.66 – 4.50 (m, 1H), 4.29 – 4.04 (m, 2H), 3.92 – 3.45 (m, 4H), 2.76 (tt, *J* = 10.6, 5.3 Hz, 1H), 2.23 – 1.62 (m, 8H). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 (d, *J* = 8.3 Hz, 1H), 7.26 – 6.97 (m, 4H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 4.62 (d, *J* = 15.2 Hz, 1H), 4.41 (s, 1H), 4.03 – 3.84 (m, 2H), 3.79 – 2.91 (m and overlapping water peak), 2.72 (tt, *J* = 10.2, 5.1 Hz, 1H), 2.10 – 1.50 (m, 8H). LCMS: > 99% purity, MS (ESI) m/z 655.2$[M + H]^+$. HRMS (ESI+) calculated for $C_{30}H_{27}F_5N_2O_7S$: 654.1459, found 654.1456.

Sodium (*R*)-2-hydroxy-4-(1-((pentafluorophenyl)sulfonyl)-*N*-(4-(tetrahydro-*2H*-pyran-4-yl)benzyl)pyrrolidine-2-carboxamido)benzoate (5h). To **5g** (134 mg, 0.20 mmol) in 9 mL 1:1:1 THF:methanol:water was added sodium bicarbonate (15.5 mg, 0.18 mmol). The reaction was stirred at room temperature for 5 h, then concentrated under reduced pressure. Ethanol was added and the resulting solution was concentrated *in vacuo* to yield **5h** (128 mg) as a salmon colored solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62 (d, J = 8.0 Hz, 1H), 7.21 – 6.97 (m, 4H), 6.51 – 6.30 (m, 2H), 4.85 (d, J = 14.9 Hz, 1H), 4.57 (d, J = 14.9 Hz, 1H), 4.48 (dd, J = 7.3, 4.1 Hz, 1H), 3.92 (dd, J = 10.1, 3.6 Hz, 2H), 3.71 – 2.86 (m and overlapping water peak), 2.72 (tt, J = 10.0, 4.8 Hz, 1H), 2.07 – 1.30 (m, 8H). LCMS: > 99% purity, HRMS (ESI) m/z 655.1537[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{27}F_5N_2O_7S$: 654.1459, found 654.1463.



Scheme 23.

1-Benzyl 3-(*tert*-butyl) (*R*)-pyrrolidine-1,3-dicarboxylate (122). To a stirred solution of commercially-available (*R*)-1-((benzyloxy)carbonyl)pyrrolidine-3-carboxylic acid (500 mg, 2 mmol) in 1:1 ether: DCM (4 mL) was added *tert*-butyl-2,2,2-trichloroacetimidate (0.716 mL, 4 mmol) and the resulting reaction for 36 h. Additional *tert*-butyl-2,2,2-trichloroacetimidate (0.4 mL, 2.2 mmol) was added and the mixture was stirred for 3 d. The resulting suspension was filtered and washed several times with 1:1 ether:DCM. The combined filtrate and washes were concentrated under reduced pressure, taken up in DCM with a drop of methanol, mixed with a small amount of silica and concentrated. The resulting silica mixture was dry-loaded onto a flash column and eluted with 14:5:1 hexane: DCM: EtOAc solvent mix to provide **122** (516 mg, 84% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.29 (m, 5H), 5.15 (s, 2H), 3.84 – 3.21 (m, 4H), 3.17 – 2.78 (m, 1H), 2.20 – 2.02 (m, 2H), 1.45 (s, 9H).

***tert*-Butyl (*R*)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-3-carboxylate (123).** To a stirred solution of **122** (510 mg, 1.6 mmol) in THF (5 mL) and methanol (10 mL) was added 10% Pd/C (30 mg) and the resulting mixture was placed under a hydrogen atmosphere and stirred for 2h. The reaction was then flushed with nitrogen, filtered through Celite® and washed with methanol (2X). The combined filtrate and washes were concentrated under reduced pressure to provide *tert*-butyl (*R*)-pyrrolidine-3-carboxylate (310 mg) as a colorless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.19 – 2.74 (m and overlapping br. s, 7H), 2.16 – 1.81 (m, 2H), 1.45 (s, 9H).

To a stirred solution of *tert*-butyl (*R*)-pyrrolidine-3-carboxylate (1.6 mmol) in dry DCM (8 mL) under nitrogen at 0 °C was added DIPEA (0.4 mL, 2.24 mmol) followed by pentafluorobenzenesulfonyl chloride (0.28 mL, 1.9 mmol). The reaction was allowed to warm to room temperature, stirred at this temperature overnight, then poured onto water and extracted with DCM (3X). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (0-18% EtOAc/ hexanes eluent) to provide **123** (474 mg, 74% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.74 – 3.61 (m, 2H), 3.60 – 3.44 (m, 2H), 3.04 (p, *J* = 6.7

Hz, 1H), 2.20 (q, *J* = 6.9 Hz, 2H), 1.43 (s, 9H). HRMS (ESI) m/z 424.0613[M + Na]$^+$. HRMS (ESI+) calculated for $C_{15}H_{16}F_5NO_4S$: 401.0720, found 401.0721.

(*R*)-1-((Pentafluorophenyl)sulfonyl)pyrrolidine-3-carboxylic acid (124). To a stirred solution of **123** (465 mg, 1.16 mmol) in DCM (8 mL) under nitrogen was added TFA (8 mL) and the resulting reaction solution was stirred at room temperature overnight. Concentration *in vacuo* afforded **124** (405 mg, 100% yield) as a white solid. For $C_{11}H_8F_5NO_4S$, exact mass: 345.0. LRMS (ESI) m/z 368.0 [M + Na]$^+$.

(*R*)-1-((Pentafluorophenyl)sulfonyl)pyrrolidine-3-carbonyl chloride (125). To a stirred solution of **124** (398 mg, 1.15mmol) in 16 mL of DCM under nitrogen was added DMF (2 drops) followed by oxalyl chloride (0.138 mL, 1.6 mmol) and the resultant mixture was stirred at room temperature for 3 h. The solution was concentrated *in vacuo* to provide acid chloride, **125** that was used as is.

Benzyl (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-3-carboxamido)benzoate (126). To a stirred solution of **9** (157 mg, 0.31 mmol) in THF (5 mL) under nitrogen at 0 °C was added methylmagnesium bromide (0.66 mL of 1.4 M in 1:3 THF:toluene, 0.93 mmol, 3 equiv). Stirring was continued at room temperature for 5 min. The resultant solution was added dropwise to a stirred solution of **125** (173 mg, 0.47 mmol) in THF (5 mL) under nitrogen at room temperature. The resulting reaction mixture was stirred at room temperature for 2 h, quenched with saturated aqueous ammonium chloride, poured onto water and extracted with EtOAc (3X). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and resulting residue purified by flash chromatography (30% DCM/ hexane, then 5% EtOAc in (30%DCM/hexanes mixture) eluent) to afford **126** (64 mg, 25% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.23 (m, 10H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.59 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.30 (d, *J* = 1.8 Hz, 1H), 5.36 (s, 2H), 4.97 (d, *J* = 12.5 Hz, 1H), 4.86 (d, *J*

= 12.5 Hz, 1H), 4.75 (d, *J* = 14.1 Hz, 1H), 4.62 (d, *J* = 14.1 Hz, 1H), 3.64 – 3.19 (m, 4H), 2.73 (p, *J* = 7.2 Hz, 1H), 2.58 – 2.38 (m, 1H), 2.02 – 1.59 (m, 8H), 1.49 – 1.08 (m, 4H). HRMS (ESI) m/z 833.2680 $[M + H]^+$. HRMS (ESI+) calculated for $C_{31}H_{29}F_5N_2O_6S$: 832.2605, found 832.2610.

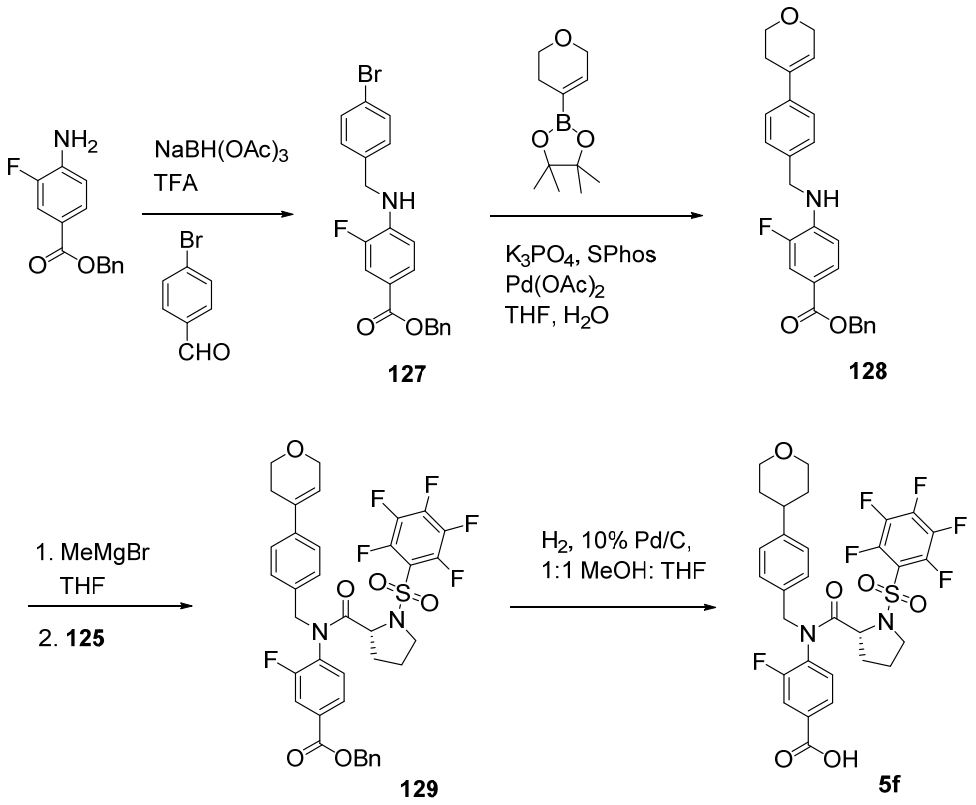
(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-3-carboxamido)-2-hydroxybenzoic acid (5a). To a stirred solution of **126** (60 mg, 0.072 mmol) in methanol (2.5 mL) and THF (2.5 mL) was added 10% Pd/C (25 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 6 h. The reaction mixture was filtered through Celite® and washed with methanol (2X). The combined filtrate and washes were concentrated, foamed with EtOAc/hexanes to provide **5a** (55 mg, 100% yield) as an off-white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.67 (s, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 4.80 (s, 2H), 3.84 – 3.52 (m, 3H), 3.46 (td, *J* = 10.0, 8.7, 5.0 Hz, 1H), 3.14 – 2.92 (m, 1H), 2.59 – 2.40 (m, 1H), 2.20 (dq, *J* = 14.3, 7.4 Hz, 1H), 2.10 – 1.93 (m, 1H), 1.92 – 1.62 (m, 5H), 1.53 – 1.14 (m, 5H). HRMS (ESI) m/z 653.1741 $[M + H]^+$. HRMS (ESI+) calculated for $C_{31}H_{29}F_5N_2O_6S$: 652.1666, found 652.1670.

(*S*)-4-(*N*-(4-Cyclohexylbenzyl)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-3-carboxamido)-2-hydroxybenzoic acid (5b). Preparation by a similar procedure to **5a**, except substituting (*S*)-1-((benzyloxy)carbonyl)pyrrolidine-3-carboxylic acid for (*R*)-1-((benzyloxy)carbonyl)pyrrolidine-3-carboxylic acid in step 1 afforded **5b** as an off-white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.66 (s, 1H), 6.59 – 6.46 (m, 1H), 4.78 (s, 2H), 3.67 – 3.50 (m, 3H), 3.45 (t, *J* = 7.7 Hz, 1H), 3.14 – 2.92 (m, 1H), 2.59 – 2.36 (m, 1H), 2.19 (dq, *J* = 14.2, 7.3 Hz, 1H), 2.01 (dt, *J* = 12.9, 6.6 Hz, 1H), 1.91 – 1.63 (m, 5H), 1.54 – 1.14 (m, 5H).

HRMS (ESI) m/z 653.1742 $[M + H]^+$. HRMS (ESI+) calculated for $C_{31}H_{29}F_5N_2O_6S$: 652.1666, found 652.1671.

(*S*)-4-(*N*-(4-Cyclohexylbenzyl)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)-2-hydroxybenzoic acid (5c). Preparation by a similar procedure to **5d**, except substituting *tert*-butyl L-prolinate for *tert*-butyl D-prolinate in step 1 afforded **5c** as a peach-colored foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.75 (d, *J* = 1.9 Hz, 1H), 6.71 (dd, *J* = 8.3, 1.9 Hz, 1H), 4.85 (d, *J* = 14.4 Hz, 1H), 4.71 (d, *J* = 14.4 Hz, 1H), 4.62 – 4.48 (m, 1H), 3.85 – 3.58 (m, 2H), 2.58 – 2.37 (m, 1H), 2.20 – 1.56 (m, 9H), 1.52 – 1.10 (m, 5H). HRMS (ESI) m/z 653.1761 $[M + H]^+$. HRMS (ESI+) calculated for $C_{31}H_{29}F_5N_2O_6S$: 652.1666, found 652.1688.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)-3-fluorobenzoic acid (5e). Preparation by a similar procedure to **2v**, except substituting ((perfluorophenyl)sulfonyl)-D-prolinoyl chloride for *N*-methyl-*N*-((perfluorophenyl)sulfonyl)-*D*-alaninoyl chloride in step 4 afforded **5e**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.0 – 7.72 (m, 2H), 7.33 – 7.15 (m, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.8 Hz, 2H), 5.16 (d, *J* = 18.0 Hz, 1H), 4.54 – 4.21 (m, 2H), 3.89 – 3.59 (m, 2H), 2.57 – 2.36 (m, 1H), 2.22 – 1.63 (m, 9H), 1.53 – 1.13 (m, 5H). HRMS (ESI+) m/z 655.1692$[M + H]^+$. HRMS (ESI+) calculated for $C_{31}H_{28}F_6N_2O_5S$: 654.1623, found 654.1620.



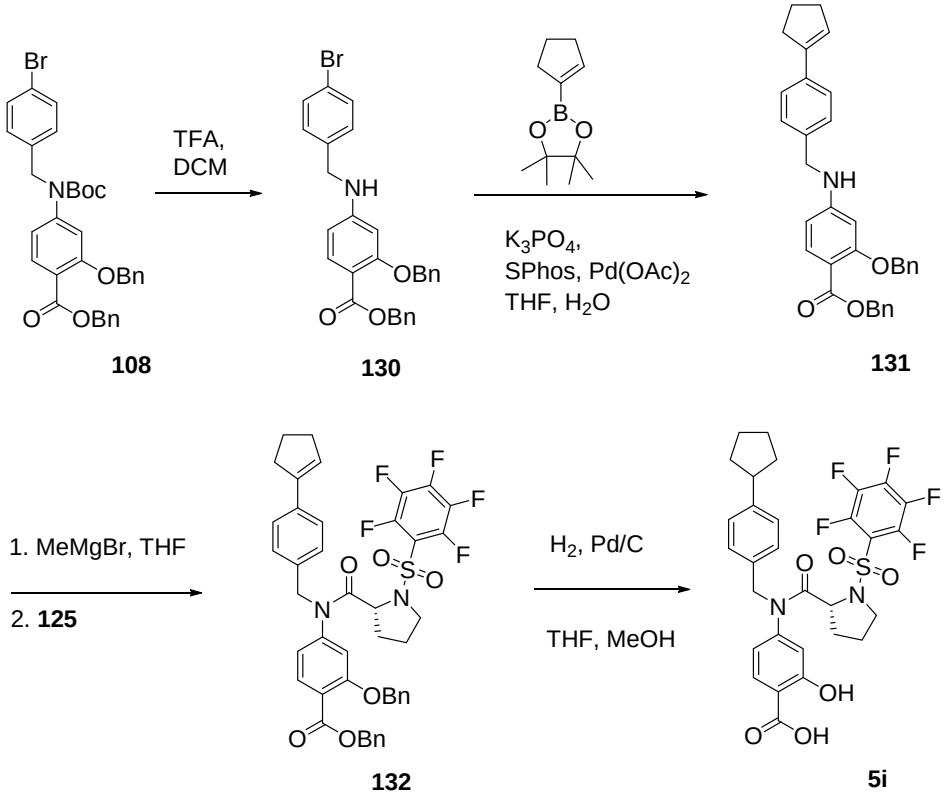
Scheme 24.

Benzyl 4-((4-bromobenzyl)amino)-3-fluorobenzoate (127). To a solution of benzyl 4-amino-3-fluorobenzoate (318 mg, 1.30 mmol) in TFA (3.0 mL) under nitrogen at 0 °C was added sodium triacetoxyborohydride (551 mg, 2.60 mmol) portion wise. The mixture was stirred at 0 °C for 10 min before addition of 4-bromobenzaldehyde (255 mg, 1.38 mmol). The resulting reaction mixture was stirred at room temperature for 4.5 h, poured onto cold water and extracted with EtOAc (1X). The organic extracts were washed with water, then with 10% aqueous sodium bicarbonate, then with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The pH after the last wash was 7-8. Purification by flash chromatography (8-10% EtOAc/hexanes) provided **127** (382 mg, 71% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 – 7.66 (m, 2H), 7.55 – 7.31 (m, 7H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.63 (t, *J* = 8.4 Hz, 1H), 5.32 (s, 2H), 4.41 (s, 2H).

Benzyl 4-((4-(3,6-dihydro-2H-pyran-4-yl)benzyl)amino)-3-fluorobenzoate (128). In a dry flask under nitrogen was added **127** (265 mg, 0.64 mmol), $Pd(OAc)_2$ (7.2 mg, 0.0320 mmol), SPhos (26.3 mg, 0.064 mmol), 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (201.6 mg, 0.96 mmol), potassium phosphate tribasic (271.6 mg, 1.28 mmol) and water (22.8 mg, 1.27 mmol). The flask was back-flushed with nitrogen, THF (8.2 mL) was added and the flask was heated at 40 °C for 16 h. The crude reaction mixture was poured onto water and extracted with EtOAc (1X). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10 – 15% EtOAc/hexanes) to provide **128** (219 mg, 82% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 – 7.64 (m, 2H), 7.51 – 7.29 (m, 9H), 6.69 (t, *J* = 8.3 Hz, 1H), 6.19 – 6.07 (m, 1H), 5.32 (s, 2H), 4.44 (s, 2H), 4.34 (q, *J* = 2.8 Hz, 2H), 3.95 (t, *J* = 5.5 Hz, 2H), 2.62 – 2.44 (m, 2H).

Benzyl (*R*)-4-(*N*-(4-(3,6-dihydro-*2H*-pyran-4-yl)benzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)-3-fluorobenzoate (129). To a stirred solution of **128 (**147.4 mg, 0.353 mmol) in THF (3 mL) at 0 °C under nitrogen was added a solution of methylmagnesium bromide (0.63 mL of 1.4M in THF, 0.883 mmol) and the mixture was stirred a 0 °C for 10 min before addition of **125** (192.6 mg, 0.53 mmol). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 14.5 h. To the reaction mixture was added a cold solution of saturated aqueous ammonium chloride followed by water and the resultant mixture was extracted with EtOAc (2X). The comb ined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (20-25% EtOAc/ hexanes eluent) followed by re-purification by preparative TLC (25% EtOAc/hexanes eluent) provided **129** (102.5 mg, 39% yield) as an oil. For $C_{37}H_{30}F_6N_2O_6S$, exact mass: 744.2. LRMS (ESI): 745.2 $[M + H]^+$.

(*R*)-3-Fluoro-4-(1-((perfluorophenyl)sulfonyl)-*N*-(4-(tetrahydro-*2H*-pyran-4-yl)benzyl)pyrrolidine-2-carboxamido)benzoic acid (5f). To a stirred solution of **129** (100 mg, 0.134 mmol) in methanol (1.6 mL) and THF (1.6mL) was added 10% Pd/C (12 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 22 h. The reaction mixture was filtered through Celite® and washed with DCM/ methanol (2 X). The combined filtrate and washes were concentrated and the resulting residue purified by preparative TLC (1:1 hexanes : EtOAc with 0.1% acetic acid) to provide **5f** (18 mg, 20% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 – 7.65 (m, 2H), 7.32 – 7.19 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 5.20 (d, *J* = 14.4 Hz, 1H), 4.52 – 4.40 (m, 1H), 4.34 (d, *J* = 14.4 Hz, 1H), 4.22 – 3.97 (m, 2H), 3.85 – 3.61 (m, 2H), 3.61 – 3.42 (m 2H), 2.87 – 2.61 (m, 1H), 2.33 – 1.46 (m, 8H). HRMS (ESI): 657.1492. $[M + H]^+$. HRMS (ESI+) calculated for $C_{30}H_{26}F_6N_2O_6S$: 656.1416, found 656.1421.



Scheme 25.

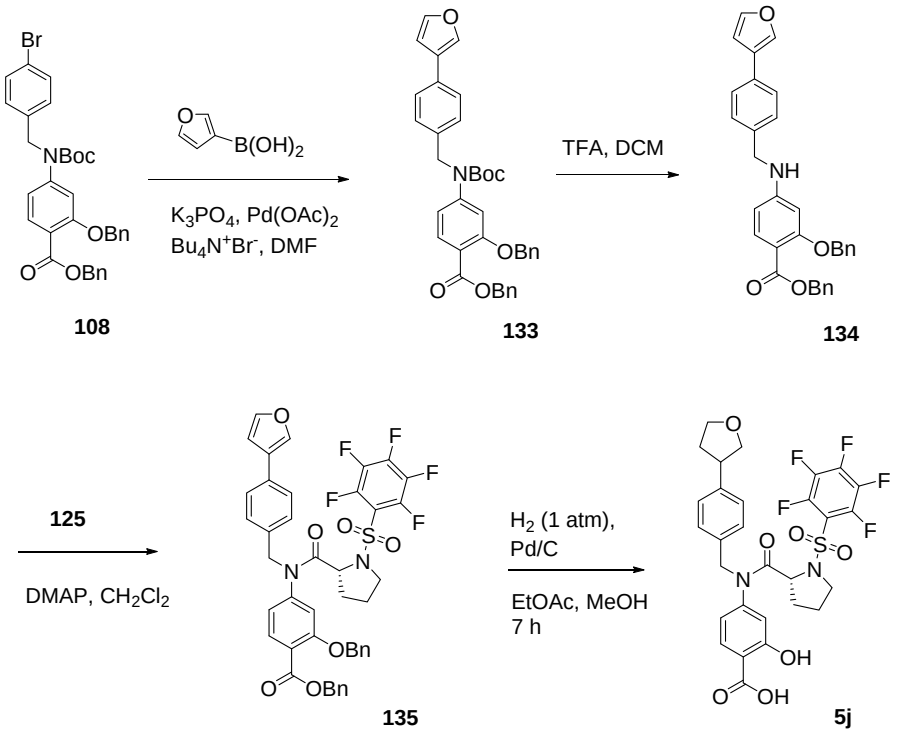
Benzyl 2-(benzyloxy)-4-((4-bromobenzyl)amino)benzoate (130). To a stirred solution of **108** (421 mg, 0.7 mmol) in DCM (7.8 mL) under nitrogen at 0 °C was added TFA (1.56 mL) and the resultant solution was stirred at 0 °C for 2 h. The mixture was poured onto cold 10% aqueous sodium bicarbonate and after bubbling had ceased was extracted with DCM (1X). The DCM extract was dried over anhydrous sodium sulfate, concentrated under reduced pressure and resulting residue purified by flash chromatography (15-30% EtOAc/ hexanes eluent) to afford **130** (190 mg, 54% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.6, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.30 (m, 10H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.21 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.14 (d, *J* = 2.2 Hz, 1H), 5.32 (s, 2H), 5.09 (s, 2H), 4.49 (br. s, 1H), 4.32 (s, 2H).

Benzyl 2-(benzyloxy)-4-((4-(cyclopent-1-en-1-yl)benzyl)amino)benzoate (131). In a dry flask under nitrogen was added **130** (187.1 mg, 0.37 mmol), $Pd(OAc)_2$ (4.18 mg, 0.0186 mmol), SPhos (15.3 mg, 0.037 mmol), 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (117.2 mg, 0.558 mmol), potassium phosphate tribasic (157.9 mg, 0.744 mmol) and water (13.3 mg, 0.744 mmol). The flask was back-flushed with nitrogen, THF (4.8 mL) was added and the flask was heated at 40 °C for 24 h. The crude reaction mixture was poured onto water and extracted with EtOAc (1X). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15% EtOAc/hexanes) followed by recrystallization from EtOAc/ ether and re-purification of the mother liquors by preparative TLC to provide **131** (124.3 mg, 68% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.6 Hz, 1H), 7.53 – 7.23 (m, 14H), 6.30 – 6.12 (m, 3H), 5.32 (s, 2H), 5.10 (s, 2H), 4.45 (s, 1H), 4.33 (d, *J* = 4.2 Hz, 2H), 2.82 – 2.63 (m, 2H), 2.54 (d, *J* = 8.3 Hz, 2H), 2.04 (p, *J* = 7.6 Hz, 2H).

Benzyl (*R*)-2-(benzyloxy)-4-(*N*-(4-(cyclopent-1-en-1-yl)benzyl)-1-((perfluorophenyl)sulfonyl)-pyrrolidine-2-carboxamido)benzoate (132). To a stirred solution of **131** (60.5 mg, 0.124 mmol) in THF (1 mL) at 0 °C under nitrogen was added a solution of methylmagnesium bromide (0.22 mL of 1.4M in

THF, 0.309 mmol) and the mixture was stirred a 0 °C for 10 min before addition of **125** (67.4 mg, 0.185 mmol). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 7.5 h. To the reaction mixture was added a cold solution of saturated aqueous ammonium chloride followed by water and the resultant mixture was extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (15-20% EtOAc/ hexanes eluent) provided **132** (93.8 mg, 93% yield as a colorless oil. For $C_{44}H_{37}F_5N_2O_6S$, exact mass: 816.23. LRMS (ESI) m/z 817.10 $[M + H]^+$.

(*R*)-4-(*N*-(4-Cyclopentylbenzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)-2-hydroxybenzoic acid (5i). To a stirred solution of **132** (90.7 mg, 0.111 mmol) in methanol (1.4 mL) and THF (1.4 mL) was added 10% Pd/C (10 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere overnight. The reaction mixture was filtered through Celite® and washed with EtOAc (2 X). The combined filtrate and washes were concentrated, purified by preparative TLC (50% EtOAc/hexane with 0.1% HOAc) to provide **5i** (12.8 mg, 18% yield) as a foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.23 – 7.50 (br, 1H), 7.34 – 6.85 (m, 4H), 6.85 – 6.52 (m, 2H), 5.10 – 4.44 (m, 3H), 3.88 – 3.47 (m, 3H), 3.04 – 2.79 (m, 1H), 2.29 – 1.38 (m, 12H). HRMS (ESI) m/z 639.1584[M + H]$^+$. HRMS (ESI+) calculated for $C_{30}H_{27}F_5N_2O_6S$: 638.1510, found 638.1516.



Scheme 26.

Benzyl 2-(benzyloxy)-4-((*tert*-butoxycarbonyl)(4-(furan-3-yl)benzyl)amino)benzoate (133). A mixture of **108** (904 mg, 1.5 mmol), furan-3-boronic acid (252 mg, 2.25 mmol, 1.5 equiv), potassium phosphate tribasic (1.6 g, 6 mmol, 4 equiv), and tetrabutylammonium bromide (60 mg) in DMF (20 mL) was degassed and backfilled with argon. Palladium (II) acetate (27 mg, 0.12 mmol, 0.08 equiv) was added and the reaction mixture was stirred at 80°C for 48 h. The reaction mixture was poured onto water and extracted with ether (3X). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. LCMS showed a mixture of product, starting material, mono-de-benzylated starting material and mono-de-benzylated product. This crude mixture was resubmitted to a benzylation reaction.

To a stirred solution of the crude mixture containing approx. 0.7 mmol of de-benzylated product (0.714 mg, 0.7 mmol) and potassium carbonate (116.1 mg, 0.84 mmol, 1.2 equiv) in DMF (5 mL) under nitrogen was added benzyl bromide (0.9 mL, 0.77 mmol, 1.1 equiv). The reaction was stirred at room temperature

overnight, then poured onto water and extracted with ether (3X). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure.

The procedure was repeated on the same scale except using 30 mg of tetrabutylammonium bromide and heating at 90°C for 24 h. The combined crude reaction mixtures were purified by flash chromatography (8% acetone/hexanes eluent) to provide recovered **108** (635 mg) and **133** (579 mg, 27% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.50 (t, *J* = 1.7 Hz, 1H), 7.46 – 7.28 (m, 12H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.92 – 6.80 (m, 2H), 6.71 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.34 (s, 2H), 5.06 (s, 2H), 4.82 (s, 2H), 1.45 (d, *J* = 1.1 Hz, 9H).

Benzyl 2-(benzyloxy)-4-((4-(furan-3-yl)benzyl)amino)benzoate (134). To a stirred solution of **133** (575 mg, 0.97 mmol) in DCM under nitrogen at 0°C was added dropwise TFA (2.4 mL). Stirring was continued for 1 h at room temperature. The solution was poured onto saturated sodium bicarbonate (aqueous phase kept at pH = 8-9) and extracted with DCM (3X). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (13:1:2 hexane/ethyl acetate/DCM eluent) to yield **134** (247 mg, 52% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.6 Hz, 1H), 7.75 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.56 – 7.23 (m, 12H), 6.71 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.24 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.19 (d, *J* = 2.2 Hz, 1H), 5.32 (s, 2H), 5.10 (s, 2H), 4.36 (s, 2H). HRMS (ESI) m/z 490.2010$[M + H]^+$. HRMS (ESI+) calculated for $C_{32}H_{27}NO_4$: 489.1940, found 489.1939.

Benzyl (*R*)-2-(benzyloxy)-4-(*N*-(4-(furan-3-yl)benzyl)-1-((pentafluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)benzoate (135). To a stirred solution of **134** (152 mg, 0.31 mmol) in dry DCM (8 mL) under nitrogen was added **125** (171 mg, 0.47 mmol, 1.5 equiv) and DMAP (45 mg, 0.37 mmol, 1.2 equiv) and the reaction mixture was stirred at room temperature overnight. The solution was poured onto water and extracted with DCM (3X). The combined organic layers were dried over sodium sulfate. A few

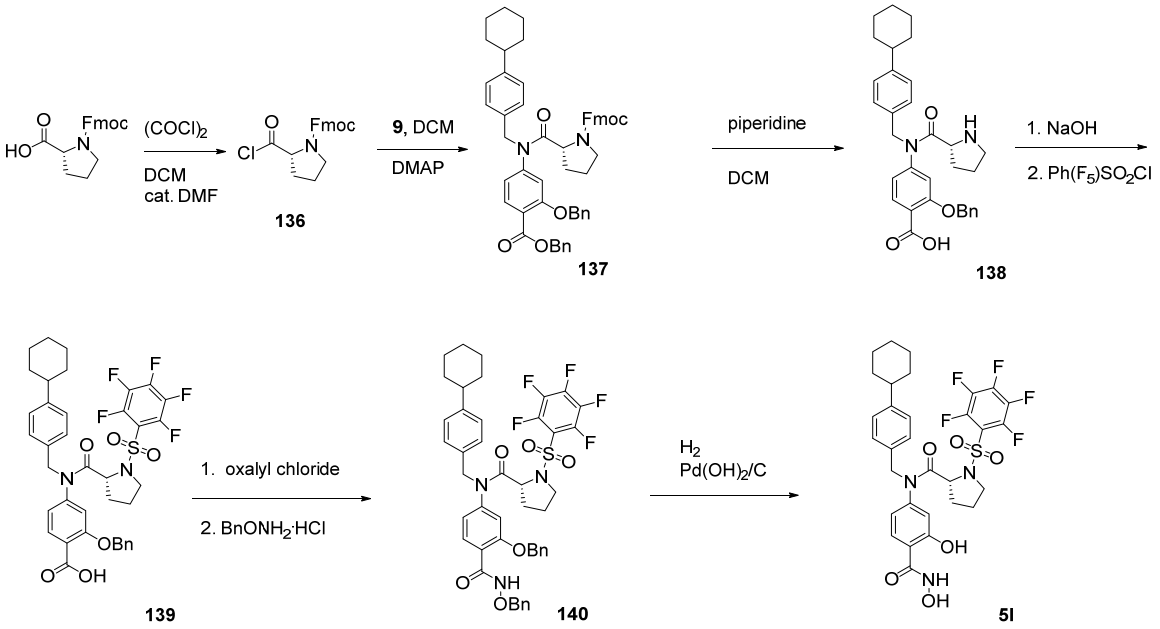
drops of methanol were added and then the resulting mixture was concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc/hexane to 31% EtOAc/hexane gradient) provided **135** (181 mg, 71% yield) as a white foam. HRMS (ESI) m/z 817.2011[M + H]$^+$. HRMS (ESI+) calculated for $C_{43}H_{33}F_5N_2O_7S$: 816.1929, found 816.1929.

2-Hydroxy-4-((2*R*)-1-((pentafluorophenyl)sulfonyl)-*N*-(4-(tetrahydrofuran-3-yl)benzyl)pyrrolidine-2-carboxamido)benzoic acid (5j). To a stirred solution of **135** (155 mg, 0.19 mmol) in methanol (6 mL) and EtOAc (6 mL) under nitrogen was added 20% $Pd(OH)_2$ on C (15 mg). The reaction mixture was stirred under a hydrogen atmosphere for 7 h, then filtered through Celite® and washed with EtOAc (2X). The combined filtrate and washes were concentrated *in vacuo* to yield 2-hydroxy-4-((2R)-1-((pentafluorophenyl)sulfonyl)-N-(4-(tetrahydrofuran-3-yl)benzyl)pyrrolidine-2-carboxamido)benzoic acid (114.6 mg, 94% yield) as a pale pink white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.88 (br-s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.78 – 6.62 (m, 2H), 4.93 – 4.68 (m, 2H), 4.59 (t, *J* = 6.1 Hz, 1H), 4.26 – 4.04 (m, 2H), 4.02 – 3.87 (m, 1H), 3.84 – 3.56 (m, 3H), 3.41 (p, *J* = 7.9 Hz, 1H), 2.39 (dtd, *J* = 12.3, 7.5, 4.5 Hz, 1H), 2.22 – 1.69 (m, 5H). HRMS (ESI+) m/z 641.1386 [M + H]$^+$. HRMS (ESI+) calculated for $C_{29}H_{25}F_5N_2O_7S$: 640.1303, found 640.1320.

(*R*)-2-Chloro-4-(*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)-pyrrolidine-2-carboxamido)benzoic acid (5k). To a stirred solution of benzyl 2-chloro-4-((4-cyclohexylbenzyl)amino)benzoate (164 mg, 0.378 mmol) in THF (3 mL) at 0 °C under nitrogen was added a solution of methylmagnesium bromide (0.67 mL of 1.4M in THF, 0.945 mmol) and the mixture was stirred a 0 °C for 10 min before addition of ((perfluorophenyl)sulfonyl)-D-prolinoyl chloride (206 mg, 0.567 mmol). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 7.5 h. To the reaction mixture was added a cold solution of saturated aqueous ammonium chloride followed by water and the resultant mixture was extracted with EtOAc (2X). The combined

organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/ hexanes eluent) provided benzyl (*R*)-2-chloro-4-(*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)benzoate (238 mg, 83% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.51 – 7.35 (m, 5H), 7.17 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 2H), 5.40 (s, 2H), 4.84 (d, *J* = 14.3 Hz, 1H), 4.66 (d, *J* = 14.3 Hz, 1H), 4.43 (t, *J* = 6.1 Hz, 1H), 3.85 – 3.59 (m, 2H), 2.58 – 2.40 (m, 1H), 2.00 – 1.65 (m, 8H), 1.48 – 1.32 (m, 6H).

To a stirred solution of benzyl (*R*)-2-chloro-4-(*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)benzoate (227.7 mg, 0.299 mmol) in DCE (8 mL) under nitrogen was added trimethyltin hydroxide (540 mg, 2.99 mmol) and the resulting mixture was heated at 85 °C for 6.5 h. The mixture was concentrated under reduced pressure and the residue was taken up in EtOAc. The organic solution was washed with 10% aqueous potassium bisulfate/ sodium sulfate buffer, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (run up with 50% EtOAc/ hexane with 0.1% HOAc) to provide pure **5k**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 1H), 7.18 – 7.07 (m, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 4.87 (d, *J* = 14.3 Hz, 1H), 4.70 (d, *J* = 14.3 Hz, 1H), 4.57 – 4.36 (m, 1H), 3.86 – 3.59 (m, 2H), 2.60 – 2.40 (m, 1H), 2.21 – 1.63 (m, 9H), 1.54 – 1.13 (m, 5H). HRMS (ESI) m/z 671.1404[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{28}ClF_5N_2O_5S$: 670.1328, found 670.1332.



Scheme 27.

(9*H*-Fluoren-9-yl)methyl (*R*)-2-((3-(benzyloxy)-4-((benzyloxy)carbonyl)phenyl)(4-cyclohexylbenzyl)carbamoyl)pyrrolidine-1-carboxylate (136). To a stirred solution of (((9H-fluoren-9-yl)methoxy)carbonyl)-D-proline (0.97 g, 2.88 mmol) in DCM (30 mL) under nitrogen was added oxalyl chloride (0.45 mL, 5.18 mmol) and DMF (2 drops). The resulting reaction solution was stirred at room temperature under nitrogen for 1.5 h and then concentrated *in vacuo* to provide **136** as a yellow foam which was used as is.

(9*H*-Fluoren-9-yl)methyl (*R*)-2-((3-(benzyloxy)-4-((benzyloxy)carbonyl)phenyl)(4-cyclohexylbenzyl)carbamoyl)pyrrolidine-1-carboxylate (137). To a stirred solution of the freshly generated acid chloride, **136**, (2.88 mmol) and aniline **9** (1.1 g, 2.19 mmol) in DCM (30 mL) under nitrogen was added DMAP (0.32 g, 2.63 mmol) and the resulting reaction was stirred at room temperature overnight. The reaction mixture was then poured onto water and extracted with DCM (3X). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (25% EtOAc/ hexanes eluent) to afford **137** (1.62 g, 90% yield). For $C_{54}H_{52}N_2O_6$, exact mass: 824.38. LRMS (ESI) m/z 825.30 $[M + H]^+$.

Benzyl (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)pyrrolidine-2-carboxamido)benzoate (138). To a stirred solution of **137** (390 mg, 0.47 mmol) in DCM (15 mL) under nitrogen at 0 °C was added piperidine (15 mL) and the resulting mixture was stirred at 0 °C for 2h. The reaction was complete by LCMS. Concentration *in vacuo* provided crude **138** that was used as is. For $C_{39}H_{42}N_2O_4$, exact mass: 602.31. LRMS (ESI) m/z 603.30 $[M + H]^+$.

(*R*)-2-(Benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)benzoic acid (139). To the crude product **138** (0.47 mmol) in methanol (9 mL) and THF (36 mL) was added 6N aqueous sodium hydroxide (9 mL) and the resulting mixture was stirred at room temperature overnight. The reaction was complete by LCMS. MS (ESI) m/z 513.30 $[M + H]^+$. The reaction mixture was concentrated to 15 mL, poured onto EtOAc/ water and the pH was adjusted to 5 with 10% aqueous HCl and the resulting mixture extracted with EtOAc (4X). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)pyrrolidine-2-carboxamido)benzoic acid which was used as is. To a solution of crude (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)pyrrolidine-2-carboxamido)benzoic acid (0.47 mmol) in DCM (10 mL) at 0 °C under nitrogen was added DIPEA (0.2 mL, 1.175 mmol) followed by pentafluorobenzenesulfonyl chloride (0.14 mL, 0.94mmol). The resulting reaction mixture was allowed to warm to room temperature and stirred at this temperature overnight. The crude reaction mixture was poured onto water and extracted with DCM (3X). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated under reduced pressure and the resulting residue purified by flash chromatography (10 – 30% EtOAc/hexanes gradient) to provide **139** (137 mg, 39% yield over the 2 steps). For $C_{38}H_{35}F_5N_2O_6S$, exact mass: 742.21. LRMS (ESI) m/z 743.20 $[M + H]^+$.

(*R*)-*N*-(3-(Benzyloxy)-4-((benzyloxy)carbamoyl)phenyl)-*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamide (140). To a stirred solution of **139** (137 mg,

0.18 mmol) in DCM (10 mL) under nitrogen was added oxalyl chloride (0.022 mL, 0.26 mmol) and DMF (small drop). The resulting reaction solution was stirred at room temperature under nitrogen for 2 h and then concentrated *in vacuo* to provide (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)benzoyl chloride which was used as is.

To a solution of *O*-benzylhydroxylamine hydrochloride (40 mg, 0.25 mmol) in DMF (2 mL) was added TEA (0.065 mL, 0.47 mmol). The mixture was stirred for 15 min, then added to a solution of the crude acid chloride, (*R*)-2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)-pyrrolidine-2-carboxamido)benzoyl chloride (0.18 mmol), in THF (5 mL) at 0 °C under nitrogen. The resultant reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction was quenched with 10% aqueous potassium bisulfate, poured onto water and extracted with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (25-35% EtOAc/ hexanes) to provide **140** (73 mg, 48% yield). For $C_{45}H_{42}F_5N_3O_6S$, exact mass: 847.27. LRMS (ESI) m/z 848.30 $[M + H]^+$.

(*R*)-*N*-(4-Cyclohexylbenzyl)-*N*-(3-hydroxy-4-(hydroxycarbamoyl)phenyl)-1-((perfluorophenyl)sulfonyl)pyrrolidine-2-carboxamide (5l). To a stirred solution of **140** (73 mg, 0.086 mmol) in methanol (2 mL) and THF (2 mL) was added 20% $Pd(OH)_2/C$ (5 mg) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere for 4 h. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined filtrate and washes were concentrated under reduced pressure and residue purified by flash chromatography (30% EtOAc/hexanes eluent) to provide **5l** (18 mg, 31% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.61 – 7.37 (m, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.83 – 6.48 (m, 2H), 4.81 (d, *J* = 14.3 Hz, 1H), 4.64 (d, *J* = 14.3 Hz, 1H), 4.56 – 4.38 (m, 1H), 3.84 – 3.57 (m, 2H), 2.58 – 2.31 (m, 1H), 2.25 – 1.56 (m, 10H), 1.54 –

1.07 (m, 4H). HRMS (ESI) m/z 668.1828[M + H]$^+$. HRMS (ESI+) calculated for $C_{31}H_{30}F_5N_3O_6S$: 667.1775, found 667.1768.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-1-((2,4,6-trifluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)-2-hydroxybenzoic acid (5m). Preparation by a similar procedure to compound **3d**, except substituting **137** for **105** afforded **5m** (98 mg, 100% yield) as a white foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.84 – 6.59 (m, 4H), 4.78 (q, *J* = 14.4 Hz, 2H), 4.65 – 4.44 (m, 1H), 3.84 – 3.56 (m, 2H), 2.66 – 2.38 (m, 1H), 2.24 – 1.60 (m, 9H), 1.56 – 1.09 (m, 5H). HRMS (ESI) m/z 617.1923[M + H]+. HRMS (ESI+) calculated for $C_{31}H_{31}F_3N_2O_6S$: 616.1855, found 616.1850.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-1-((2,3,5-trifluorophenyl)sulfonyl)pyrrolidine-2-carboxamido)-2-hydroxybenzoic acid (5n). Preparation by a similar procedure to compound **3e**, except substituting **137** for **105** afforded **5n** (127 mg, 100% yield) as a pink foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.32 (m, 1H), 7.20 – 6.98 (m, 5H), 6.77 (s, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 5.01 – 4.66 (m, 2H), 4.62 – 4.37 (m, 1H), 3.85 – 3.45 (m, 2H), 2.66 – 2.35 (m, 1H), 2.17 (dt, *J* = 12.3, 6.4 Hz, 1H), 2.09 – 1.93 (m, 2H), 1.93 – 1.61 (m, 7H), 1.55 – 1.07 (m, 4H). HRMS (ESI) m/z 617.1918[M + H]+. HRMS (ESI+) calculated for $C_{31}H_{31}F_3N_2O_6S$: 616.1855, found 616.1843.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-1-(perfluorobenzoyl)pyrrolidine-2-carboxamido)-2-hydroxybenzoic acid (5o). Preparation by a similar procedure to compound **3h**, except substituting **137** for **105** afforded **5o** (127 mg, 100% yield) as a pink foam. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.78 (br-s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.21 – 7.02 (m, 4H), 6.88 (d, *J* = 8.4Hz, 1H), 6.80 (s, 1H), 5.03 (d, *J* = 14.7 Hz, 1H), 4.81 (d, *J* = 14.7 Hz, 1H), 4.75 – 4.59 (m, 1H), 3.81 – 3.58 (m, 1H), 3.52 – 3.25 (m, 1H), 2.62 – 2.39 (m,

1H), 2.36 – 1.58 (m, 6H), 1.54 – 1.06 (m, 7H). HRMS (ESI) m/z 617.2071[M + H]+. HRMS (ESI+) calculated for $C_{32}H_{29}F_5N_2O_5$: 616.1977, found 616.1999.

(*R*)-4-(*N*-(4-Cyclohexylbenzyl)-1-((perfluorophenyl)methyl)pyrrolidine-2-carboxamido)-2-hydroxybenzoic acid (5p). Preparation by a similar procedure to compound **3i**, except substituting **138** for benzyl (R)-2-(benzyloxy)-4-(N-(4-cyclohexylbenzyl)pyrrolidine-2-carboxamido)benzoate afforded **5p**. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.92 – 7.72 (m, 1H), 7.18 – 7.03 (m, 4H), 6.61 (d, *J* = 1.8 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 5.03 – 4.68 (m, 2H), 4.18 (q, *J* = 13.7 Hz, 2H), 4.01 – 3.64 (m, 1H), 3.61 – 3.45 (m, 1H), 3.43 – 3.23 (m, 1H), 2.81 – 2.58 (m, 1H), 2.57 – 2.37 (m, 1H), 2.19 – 1.60 (m, 9H), 1.56 – 1.09 (m, 4 H). HRMS (ESI) m/z 603.2285[M + H]+. HRMS (ESI+) calculated for $C_{32}H_{31}F_5N_2O_4$: 602.2204, found 616.2212.

Cell lines and reagents. Normal mouse fibroblast (NIH3T3), and the human breast cancer MDA-MB-231, MDA-MB-468, and MCF-7 cell lines have been reported previously [2,3]. The STAT3 knockout mouse embryonic fibroblasts line (MEF/STAT3-/-) was generous gift from Dr. Valerie Poli (University of Turin) and have been previously reported [3]. Cells were grown in Dulbecco's modified Eagle's medium (DMEM) containing 10% heat-inactivated fetal bovine serum (for human cells) or bovine calf serum (for mouse cells). Human metastatic melanoma C8161, 1205LU, and C81-61 cell lines, an early stage melanoma from the same patient as the late stage C8161 cells, have been previously reported [6] and were maintained in RPMI with 10% FBS. The immortalized normal human melanocytes AR7119 (hTERT/CDKR24C/p53DD) line was maintained in Medium 254 supplemented with human growth factors (GIBCO) [6]. Antibodies against STAT3, pSTAT3, Src, pSrc Jak, pJak, Erk^{MAPK}, and pErk^{MAPK} were purchased from Cell Signaling Technology, Inc. (Danvers, MA). Tubulin was purchased from (Santa Cruz Biotechnology, Inc., Dallas, Texas).

Nuclear extract preparation, gel shift assays, and densitometric analysis. Nuclear extract preparations and DNA-binding activity/electrophoretic mobility shift assay (EMSA) were carried out as previously described [1-3,7]. The ^{33}P-labeled oligonucleotide probes used were hSIE (high affinity sis-inducible element from the c-fos gene, m67 variant, 5'-AGCTTCATTTCCCGTAAATCCCTA) that binds Stat1 and STAT3 and MGFe (mammary gland factor element from the bovine β-casein gene promoter, 5'-AGATTTCTAGGAATTCAA) for Stat1 and Stat5 binding. Except where indicated, nuclear extracts were pre-incubated with compound for 30 min at room temperature prior to incubation with the radiolabeled probe for 30 min at 30°C before subjecting to EMSA analysis. Where appropriate, bands corresponding to STAT:DNA complexes were scanned and quantified for each concentration of compound using ImageJ and plotted as percent of control (DMSO) against concentration of compound, from which the IC_{50} values were derived, or the percent inhibition was derived.

Immunoblotting analysis. Whole cell lysate preparation and immunoblotting analysis were performed as previously reported [1,2]. All antibodies tested were purchased from Cell Signaling Technology.

Cell proliferation, viability assay, and trypan blue exclusion/phase-contrast microscopy. Cells in 6-well or 96-well plates were treated with or without compounds for the indicated concentrations and time, and subjected to CyQuant cell viability assay (Invitrogen/ThermoFisher Scientific) [2,3], or harvested and the viable cells were counted by trypan blue exclusion with phase-contrast microscopy [2,3,8]. For MTT assay, each cell line was cultured in 96-well plate at 2 x 10^3 cells per well with the following conditions: no treatment, vehicle (DMSO), and compound at 10 or 20 μM. Viable cells were measured at 72 h by adding 0.1 volumes of 5 mg/ml Thiazolyl Blue Tetrazolium Bromide (Sigma, St. Louis, MO) in 1 x PBS were added to each well, incubated for 4 h at 37 ^{0}C, and equal volume of 10 % sodium dodecyl sulfate/0.1 NHCL was added to each well and incubated overnight at 37 ^{0}C. A 96-well plate reader (Infinite 200

Tecan USA, Durham, NC) was used to measure absorbance at 550 nM with a reference wavelength of 750 nM.

Clonogenic survival assays. Colony survival assay was performed as previously reported [2,3]. Briefly, cells were seeded as single-cell cultures in 6-cm dishes (350 cells per dish), treated once the next day with compounds at the indicated concentrations and allowed to culture until large colonies were visible. Colonies were stained with crystal violet for 4 h, counted and photographed.

Scratch assay for cell migration. Studies were performed as previously reported [3]. Briefly, wounds were made in 95-100% confluent cultures of cells in six-well plates using pipette tips. Subsequently, cells were treated with or without compounds at the designated concentrations and allowed to migrate into the denuded area over 33 h. The migration of cells was visualized at a 10X magnification using an Axiovert 300 Inverted Fluorescence Microscope (Zeiss, Göttingen Germany), with pictures taken using a mounted Canon Powershot A640 digital camera (Canon USA, Lake Success, NY).

Supplementary Figures

Supplementary Figure Legends

Figure S1. Effects of compounds on STAT3 DNA-binding activation and tyrosine phosphorylation in tumor cells. (A) Nuclear extracts of equal total protein prepared from the human breast cancer cells untreated (DMSO, Con, 0), or treated with 5 or 10 μM of the indicated analogs for 1, 3, 10, or 24 h were incubated with the hSIE probe that binds STAT3 and subjected to EMSA analysis for STAT3 DNA-binding activity, and (B, C) Immunoblotting analysis of whole-cell lysates of equal total protein prepared from (B) breast cancer lines untreated (DMSO, Con) or treated with 5 or 10 μM of the indicated compounds for 1 or 24 h, or (C) melanoma cells untreated (DMSO, 0) or treated with 10 or 20 μM of **1a**

for 1-3 h and probing for pY705STAT3, STAT3 or tubulin. Positions of STAT3:DNA complexes or proteins in gel are shown; control (0 or Con) lane represents whole-cell lysates or nuclear extracts prepared from 0.05% DMSO-treated cells. Data are representative of 2-3 independent determinations.

Figure S2. Effects of agents on STAT3-independent signal transduction events. Immunoblots of pY705STAT3, STAT3, pJak2, Jak2, pSrc, Src, pERK1/2^{MAPK}, and ERK1/2^{MAPK} from whole-cell lysates prepared from MDA-MB-231 cells treated with 5 μM of the indicated compounds for 24 h. Positions of proteins in gel are labeled; control lane (Con) represents whole-cell lysate prepared from 0.05% DMSO-treated cells. Data are representative of 2 independent determinations.

Figure S3. **Effects of select compounds on STAT1 and STAT5 DNA-binding activity.** EMSA analysis of STAT1 and STAT5 DNA-binding activity in nuclear extracts of equal total protein prepared from EGF-stimulated fibroblasts containing activated STAT1 and STAT5 pre-incubated with (A) 10 or 30 μM or (B) 0-30 μM of the indicated compounds for 30 min at room temperature prior to incubation with the radiolabeled MGFe probe that binds both STAT1 and STAT5. Positions of STAT:DNA complexes in gel are labeled; control lanes (0 or Con) represent nuclear extracts pre-treated with 0.05% DMSO. Bands corresponding STAT:DNA complexes were scanned and quantified, from which the percent of inhibition was calculated relative to the DMSO control (100%), or plotted for each concentration of compound from which IC_{50} values were derived. Data are representative of 2-3 independent determinations.

Figure S4. **Effects of compounds on cell viability and colony formation.** (A) Human breast cancer MDA-MB-231 cells harboring aberrantly-active STAT3 growing in 6-well plates were treated once with **2v** (0-5 μM) for 72 h and subjected to viable cell counting using trypan blue exclusion/phase-contrast microscopy, or (B) STAT3-null mouse embryonic fibroblasts (MEF/STAT3-/-) growing in 96-well plates were treated once with 0-20 μM of **1e** for 72 h and subjected to CyQuant cell proliferation assay for

viable cells and plotted as the number of viable cells or % cell viability against concentration; and (C) Human breast cancer, MDA-MB-231 cells in culture were wounded and treated once with 0-3 μM of the indicated compounds and allowed to culture until large colonies were visible, which were stained with crystal violet, and imaged. Control (0, DMSO) represents 0.05% DMSO-treated cells. Values, mean ± S.D. of 2-3 independent determinations. Data are representative of 2-3 independent determinations. *p<0.01, **p<0.005.

References

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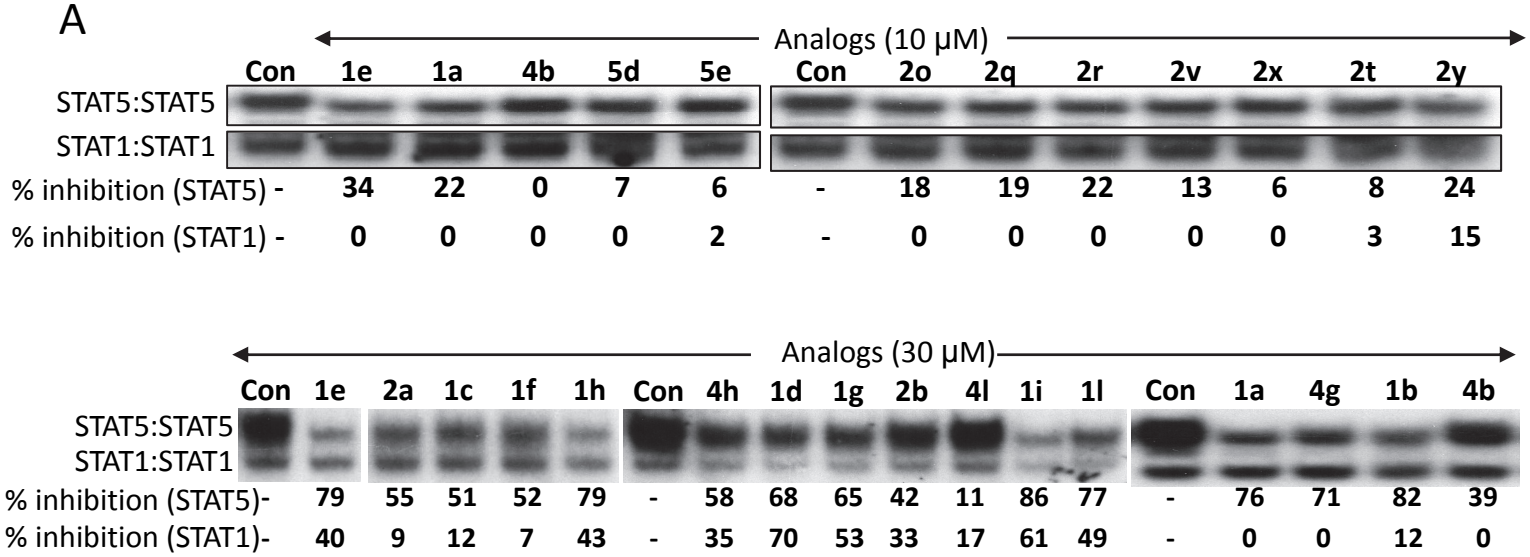
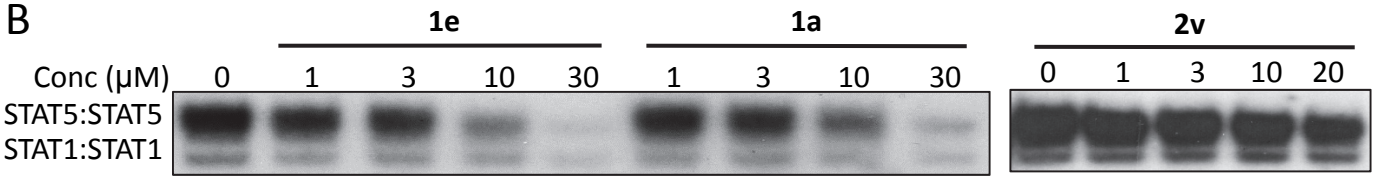
Fig. S1

A



B



IC_{50} (STAT5, μM) **4.9** **7.9** **>20**

IC_{50} (STAT1, μM) **>10** **>10** **>20**

Fig. S2

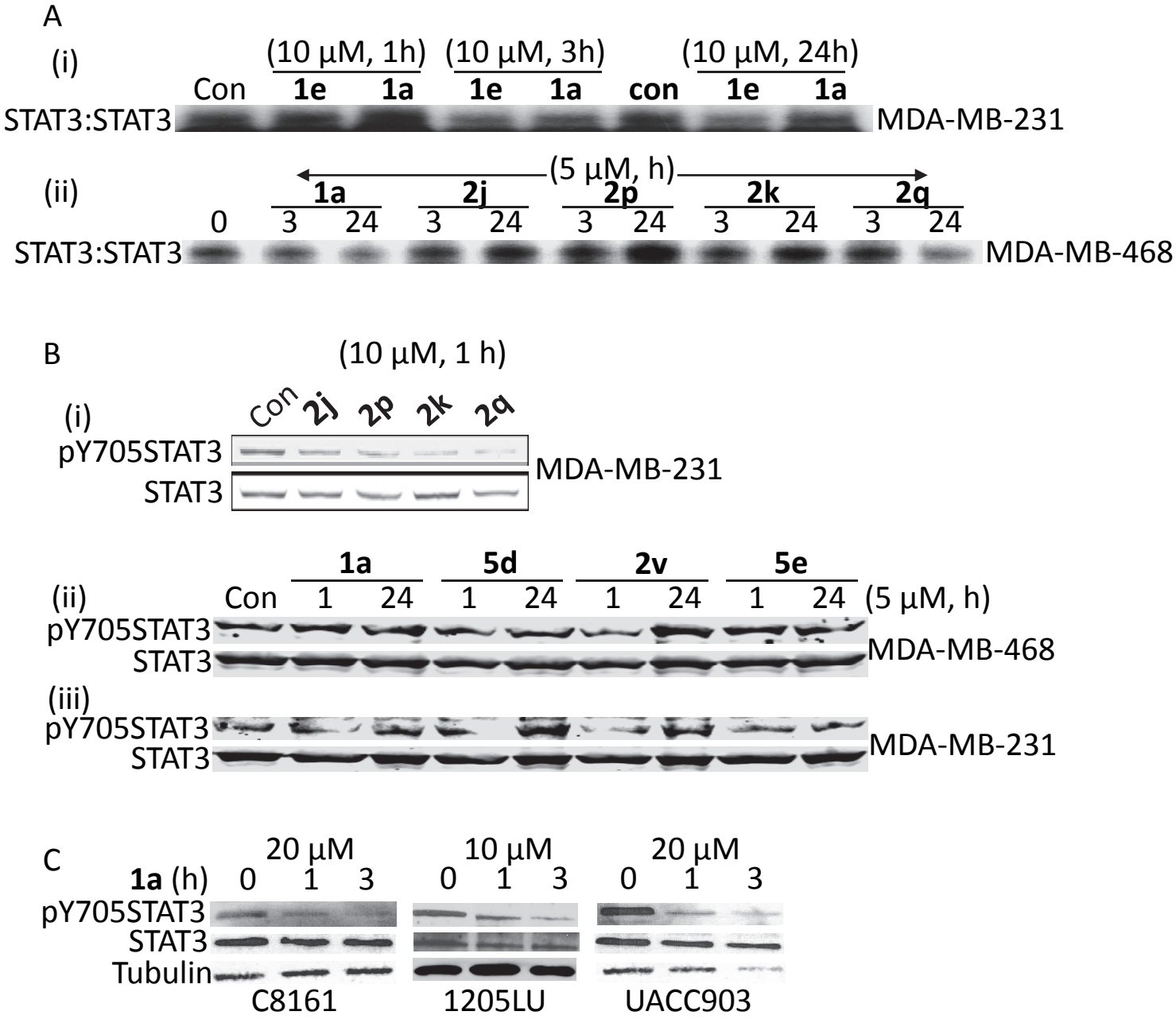

A
(i)
(10 μM, 1h)
(10 μM, 3h)
(10 μM, 24h)
Con
1e
1a
1e
1a
con
1e
1a
STAT3:STAT3
MDA-MB-231
(ii)
(5 μM, h)
1a
2j
2p
2k
2q
0
3
24
3
24
3
24
3
24
3
24
STAT3:STAT3
MDA-MB-468
B
(10 μM, 1 h)
(i)
Con
2j
2p
2k
2q
pY705STAT3
STAT3
MDA-MB-231
1a
5d
2v
5e
(ii)
Con
1
24
1
24
1
24
1
24
(5 μM, h)
pY705STAT3
STAT3
MDA-MB-468
(iii)
pY705STAT3
STAT3
MDA-MB-231
C
20 μM
10 μM
20 μM
1a (h)
0
1
3
0
1
3
0
1
3
pY705STAT3
STAT3
Tubulin
C8161
1205LU
UACC903

Fig. S3

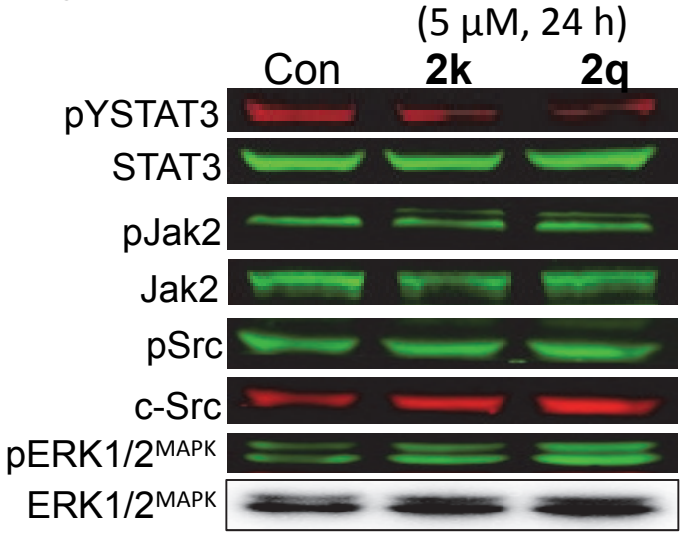
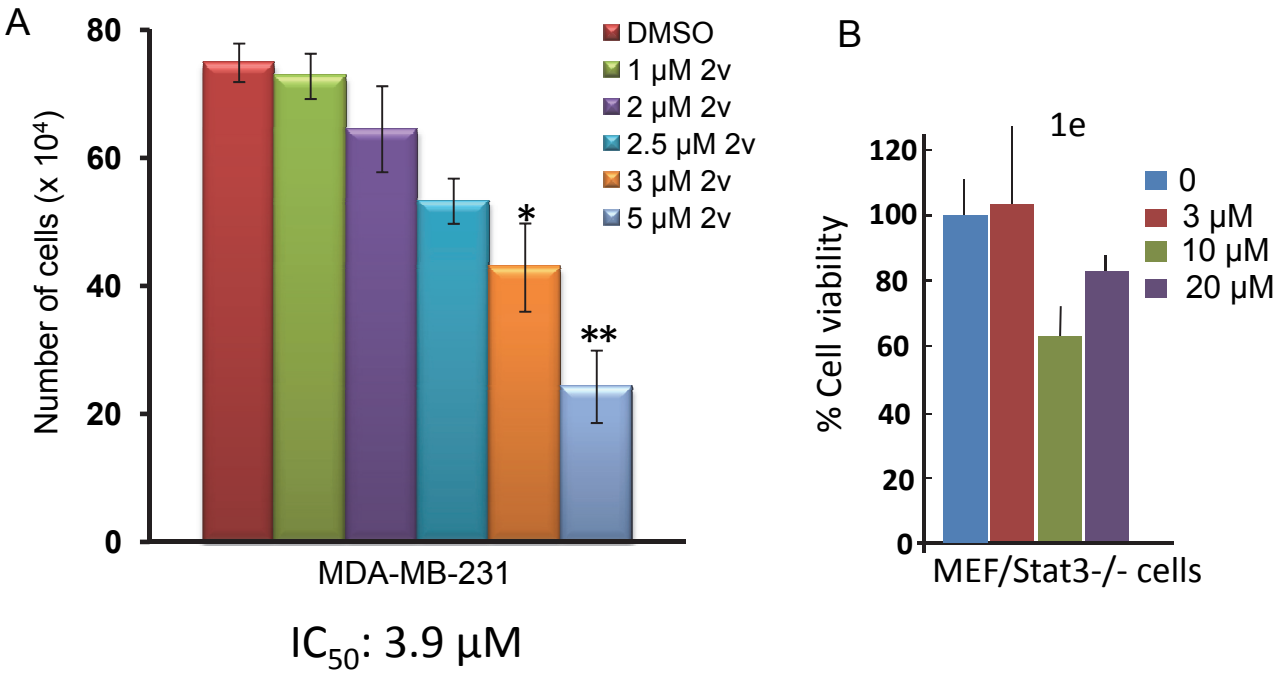

(5 μM, 24 h)
Con
2k
2q
pYSTAT3
STAT3
pJak2
Jak2
pSrc
c-Src
pERK1/2MAPK
ERK1/2MAPK

Fig. S4


A
80
60
40
20
0
Number of cells (x 10⁴)
DMSO
1 μM 2v
2 μM 2v
2.5 μM 2v
3 μM 2v
5 μM 2v
*
**
MDA-MB-231
IC50: 3.9 μM
B
1e
120
100
80
60
40
20
0
% Cell viability
0
3 μM
10 μM
20 μM
MEF/Stat3-/- cells

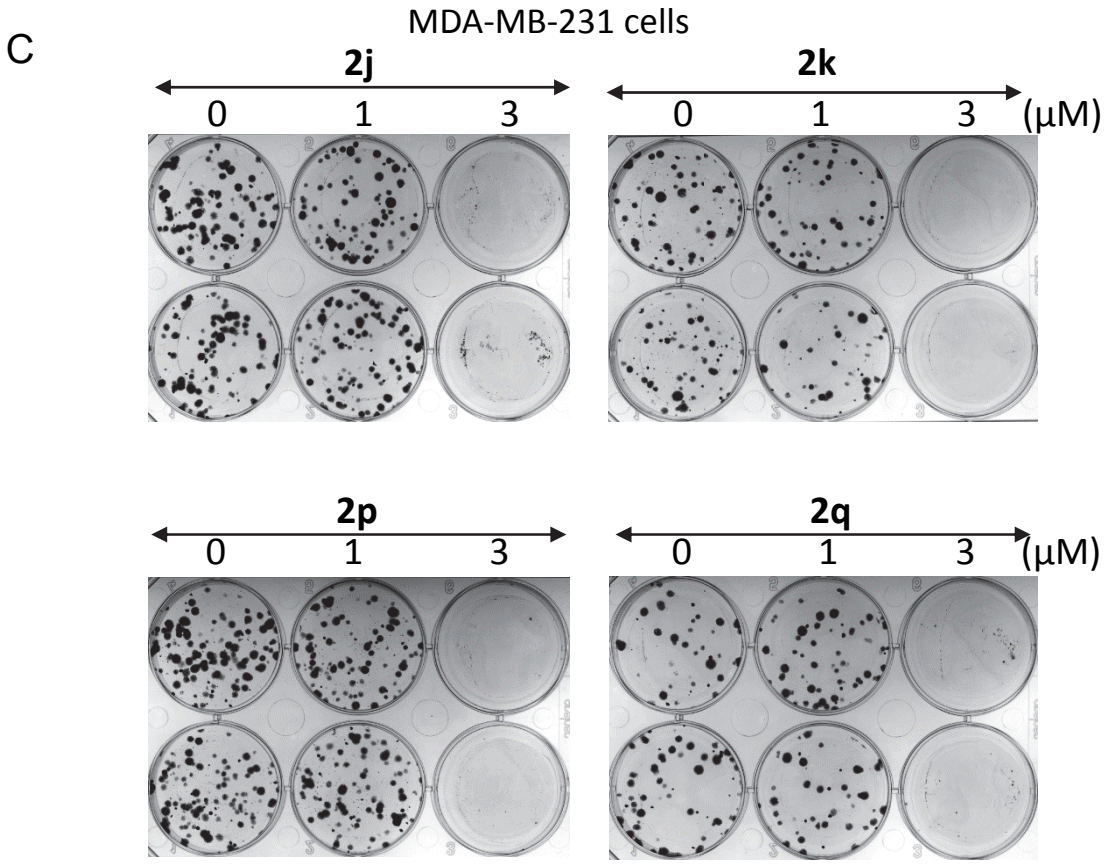
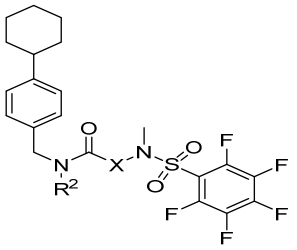
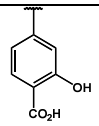
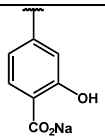
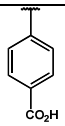
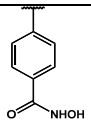
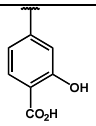
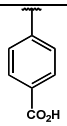
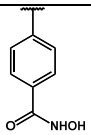
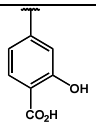
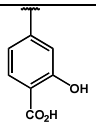
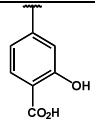
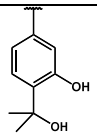
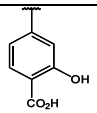
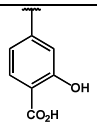
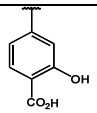
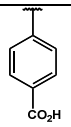
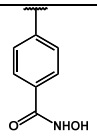
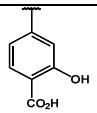
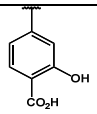
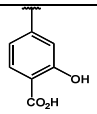
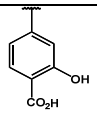
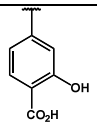
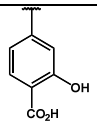
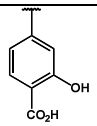

C
MDA-MB-231 cells
2j
0
1
3
2k
0
1
3
(μM)
2p
0
1
3
2q
0
1
3
(μM)

Table S1. SAR variation of the linker region



Entry	Compound	R^2	X	IC_{50} (μM)[#]
1	**1a**		(R)-CHMe	3.0±0.9
2	**1b**		(R)-CHMe	6.4±2.0
3	**1c**		(R)-CHMe	9.3±5.0
4	**1d**		(R)-CHMe	5.3±1.8
5	**1e**		(S) -CHMe	5.0±0.2
6	**1f**		(S)-CHMe	10.0±2.6
7	**1g**		(S)-CHMe	6.8±3.7
8	**1h**		(S)-CHEt	10.0±4.7
9	**1i**		(R)-CHEt	6.9±3.2
10	**1j**			12.8±4.3

11	**1k**			22.4±1.4
12	**1l**		$C(Me)_2$	8.5±1.3
13	**1m**		(S)-$CH(CH_2OH)$	12.9±4.5
14	**1n**		(R)-$CH(CH_2OH)$	7.4±4.4
15	**1o**		(R)-$CH(CH_2OH)$	> 30
16	**1p**		(R)-$CH(CH_2OH)$	23.1±1.7
17	**1q**		(S)-$CH(CH_2CH_2OH)$	20.0±2.4
18	**1r**		(R)-$CH(CH_2CH_2OH)$	14.2±3.4
19	**1s**		(S)-CH[(R)-CHMeOH]	17.6±2.2
20	**1t**		(R)-CH[(S)-CHMeOH]	19.6±1.4
21	**1u**		(S)-$CH(CH_2NH_2)$	11.6±2.2
22	**1v**		(R)-$CH(CH_2NH_2)$	27.4±4.2
23	**1w**		(S)-$CH(CH_2CO_2H)$	> 30

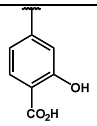
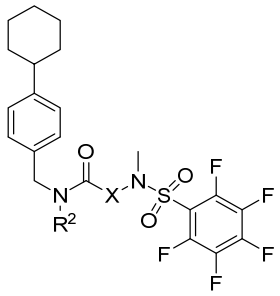
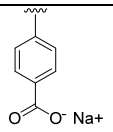
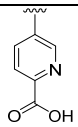
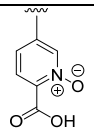
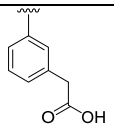
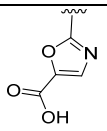
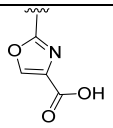
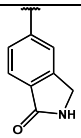
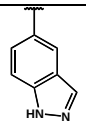
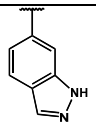
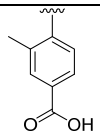
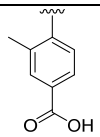
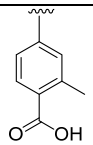
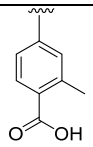
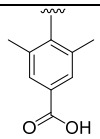
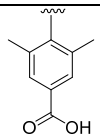
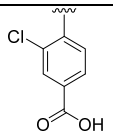
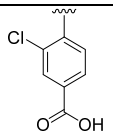
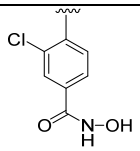
24	**1x**		(R)-CH(CH_2CO_2H)	30.0±11.2

Table S2. SAR variation at Benzoic acid binding region



Entry	Compound	R^2	X	IC_{50} (μM)[#]
1	**2a**		CH_2	8.1±0.3
2	**2b**		CH_2	13.6±3.3
3	**2c**		CH_2	>30
4	**2d**		CH_2	33.0±0.7
5	**2e**		CH_2	>30
6	**2f**		CH_2	17.3±4.8
7	**2g**		(R)-CHMe	10.8±3.4

8	**2h**		(R)-CHMe	> 30
9	**2i**		(R)-CHMe	18.3±6.9
10	**2j**		CH_2	13.1±3.0
11	**2k**		(R)-CHMe	5.7±1.4
12	**2l**		CH_2	13.0±3.3
13	**2m**		(R)-CHMe	6.6±0.8
14	**2n**		CH_2	10.6±1.5
15	**2o**		(R)-CHMe	4.3±0.7
16	**2p**		CH_2	8.6±1.5
17	**2q**		(R)-CHMe	4.1±0.6
18	**2r**		(R)-CHMe	3.5±0.6

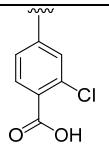
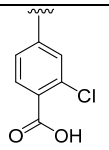
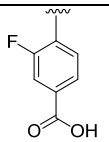
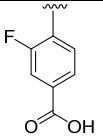
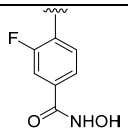
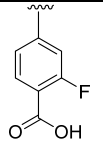
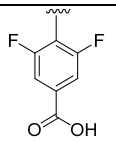
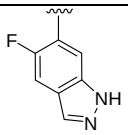
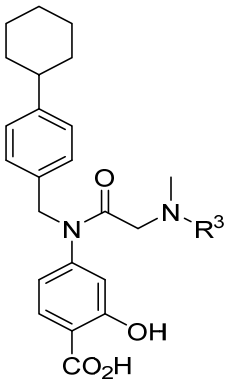
19	**2s**		CH_2	14.4±5.3
20	**2t**		(R)-CHMe	3.6±0.3
21	**2u**		CH_2	33.8±3.6
22	**2v**		(R)-CHMe	1.8±0.94
23	**2w**		(R)-CHMe	3.4±1.7
24	**2x**		(R)-CHMe	4.6±0.5
25	**2y**		(R)-CHMe	4.1±0.3
26	**2z**		(R)-CHMe	11.0

Table S3. SAR variation at Sulfonamide Region



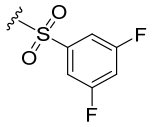
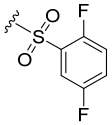
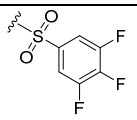
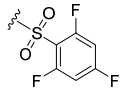
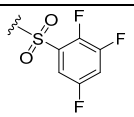
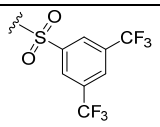
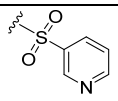
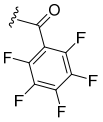
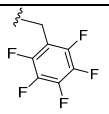
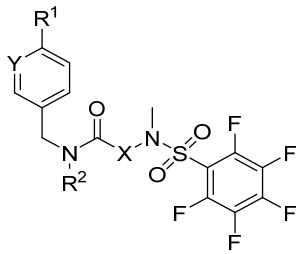
Entry	Compound	R^3	IC_{50} (μM)[#]
1	**3a**		>30
2	**3b**		>30
3	**3c**		>30
4	**3d**		>30
5	**3e**		>30
6	**3f**		36.0±5.4
7	**3g**		>30
8	**3h**		>30
9	**3i**		>30

Table S4. SAR variation of the Benzyl Region



Entry	Compound	R^1	R^2	X	Y	IC_{50} (μM)

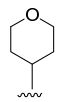
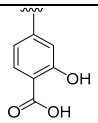
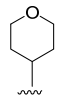
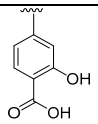
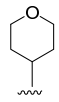
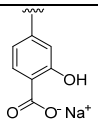
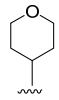
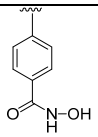
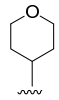
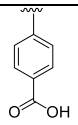
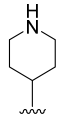
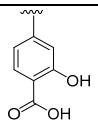
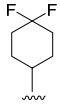
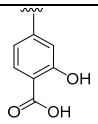
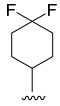
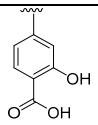
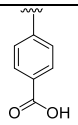
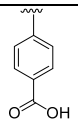
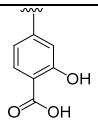
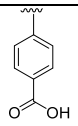
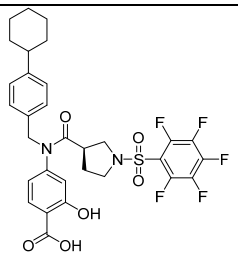
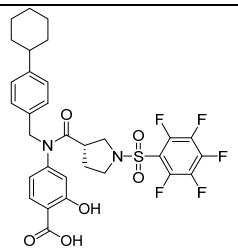
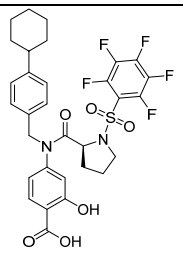
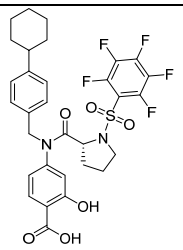
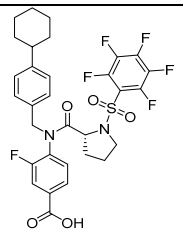
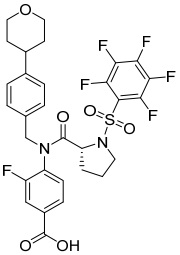
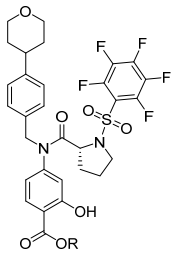
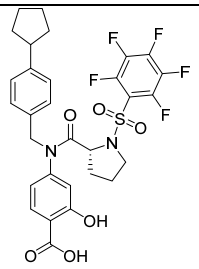
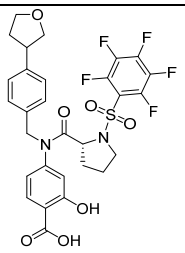
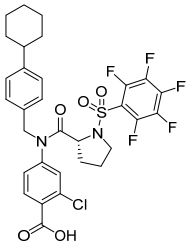
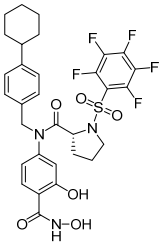
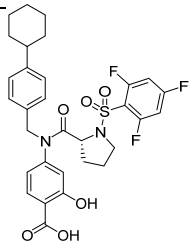
1	**4a**			CH_2	CH	11.4±4.4
2	**4b**			(R)-CHMe	CH	5.0±0.8
3	**4c**			(R)-CHMe	CH	11.6±0.6
4	**4d**			CH_2	CH	19.0±3.4
5	**4e**			CH_2	CH	>30
6	**4f**			CH_2	CH	30.1±3.8
7	**4g**			(R)-CHMe	CH	8.3±0.3
8	**4h**			CH_2	CH	16.6±6.4
9	**4i**			CH_2	CH	10.9±3.3
10	**4j**			CH_2	CH	15.6±8.4
11	**4k**			CH_2	N	19.4±5.4
12	**4l**			CH_2	CH	36.4±3.4

Table S5. SAR modifications using pyrrolidines, including proline-based variations

Entry	Compound	Structure	IC_{50} (μM)[#]
1	**5a**		6.5±2.5
2	**5b**		6.9±1.9
3	**5c**		7.2±3.4
4	**5d**		**2.4±0.2**
5	**5e**		5.3±0.4
6	**5f**		7.4±2.5

7	**5g** (R = H)		5.4
8	**5h** (R = Na)		7.0
9	**5i**		3.6±0.3
10	**5j**		4.5±1.0
11	**5k**		3.8±0.8
12	**5l**		5.5±1.4
13	**5m**		>30

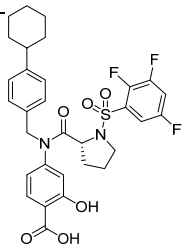
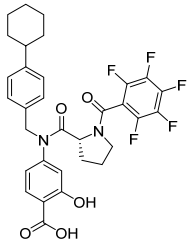
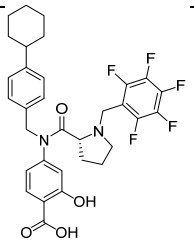
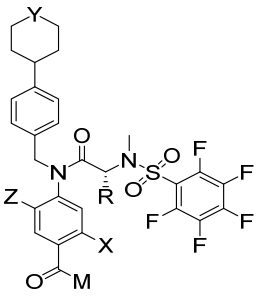
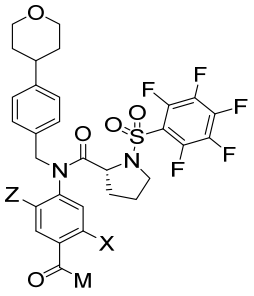
14	**5n**		>30
15	**5o**		>30
16	**5p**		>30

Table S6. Initial analyses of solubility, metabolic stability, and cell membrane permeability of lead STAT3 inhibitors and their analogs.



	M	R	X	Y	Z
SH4-54	OH	H	H	CH_2	H
SH5-07	NHOH	H	H	CH_2	H
1b	ONa	Me	OH	CH_2	H
2w	NHOH	Me	H	CH_2	F
4c	ONa	Me	OH	O	H
BP-1-102	**OH**	**H**	**OH**	**CH_2**	**H**



	M	X	Z
5f	OH	H	F
5h	ONa	OH	H

Compound	Solubility (µg/mL)		Metabolic Stability Half-Life (min)		Caco-2 Cells Permeability (Papp 10^{-6} cm/s)/ Recovery (%)	
	PBS	SIF	MLM	HLM	A to B	B to A
SH4-54	7.6	14	26	37	0/7	0/29
SH5-07	0.3	74	17	19	0/2	0/8
1b	127	127	5	4	0/6	0/2
2w	4.7	72				
4c	132	129	4	5	0/31	0.7/40
5f			26	54	0.1/8	0.1/67
5h	123	117	18	15	0.2/34	0.2/60

Abbreviations: PBS, Phosphate Buffer Saline (pH 7.4); SIF, Simulated Intestinal Fluid; MLM, Mouse Liver Microsomes; HLM, Human Liver Microsomes; A, Apical; B, Basolateral