Antagonism of the Stat3-Stat3 Protein Dimer with Salicylic Acid-Based Small Molecules

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S.1 Chemical Methods

Anhydrous solvents methanol, DMSO, CH_2Cl_2, THF and DMF were purchased from Sigma Aldrich and used directly from Sure-Seal bottles. Molecular sieves were activated by heating to 300 °C under vacuum overnight. All reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware and were monitored for completeness by thin-layer chromatography (TLC) using silica gel (visualized by UV light, or developed by treatment with $KMnO_4$ stain or phosphomolybdic acid stain). ^1H and ^{13}C NMR spectra were recorded on Bruker 400 MHz and a Varian 500 MHz spectrometers in either $CDCl_3$, CD_3OD or d_6-DMSO. Chemical shifts (δ) are reported in parts per million after calibration to residual isotopic solvent. Coupling constants (*J*) are reported in Hz. Before biological testing, inhibitor purity was evaluated by reversed-phase HPLC (rpHPLC). Analysis by rpHPLC was performed using a Microsorb-MV 300 A C18 250 mm x 4.6 mm column run at 1 mL/min, and using gradient mixtures. The linear gradient consisted of a changing solvent composition of either (I) 100 % H_2O with 0.1 % TFA for two minutes to 100 % MeCN with 10 % H_2O and 0.1 % TFA (v/v) at 22 minutes and UV detection at 254nm or (II) 100 % H_2O with 0.1 % TFA for 2 mins to 100 % MeCN with

10 % H_2O and 0.1 % TFA (v/v) at 62 mins and UV detection at 214nm or (III) 100 % H_2O (0.01 M NH_4OAc) for 2 mins to 100 % MeOH at 22 mins and UV detection at 254nm or (IV) 100 % H_2O (0.01 M NH_4OAc) for 2 mins to 100 % MeOH at 62 minutes and UV detection at 254nm or (V) 100 % H_2O (0.01 M NH_4OAc) for 2 mins to 100 % MeOH at 25 minutes and UV detection at 254nm or (VI) 100 % H_2O (0.01 M NH_4OAc) for 2 mins to 100 % MeOH at 62 mins and UV detection at 254nm, each ending with 5 mins of 100% B. For reporting HPLC data, percentage purity is given in parentheses after the retention time for each condition. All biologically evaluated compounds are > 95 % chemical purity as measured by HPLC. The HPLC traces for all tested compounds are provided in supporting information.

S.2. Stat3 and Stat1 Fluorescent Polarization Assay

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Fluorescence polarization experiments were performed on an Infinite M1000 (Tecan, Crailsheim, Germany) using black 384-round bottom well plates (Corning), and buffer containing 50 mM NaCl, 10 mM Hepes, pH 7.5, 1 mM EDTA, and 2 mM dithiothreitol and a final concentration of 5 % DMSO. Stat1/Stat3 protein solutions (120 nM and 150 nM for Stat1 and Stat3, respectively) were treated with varying concentrations of inhibitor compounds (200 to 12.5 μM final concentrations). The fluorescent probe was added at a final concentration of 10 nM. Protein, inhibitor and probe were combined and incubated for 15 minutes prior to analysis. Polarized fluorescence was plotted against concentration and fitted using a standard dose response curve. K_i values were calculated using the following formula:

$$p(X) = \frac{p_1 \times IC_{50} + p_2 \times X}{IC_{50} + X}$$

where X was the concentration of inhibitor and p was the corresponding fluorescence at that concentration. The free parameter was half the maximal inhibitory concentration (IC_{50}) and the limiting values was the maximal measured fluorescence polarization (p_1) and the minimal fluorescence polarization (p_2). Origin curve fitting software utilizes the Levenberg-Marquardt algorithm and reduced chi-square criterion for convergence. The inhibitor dissociation constant, K_i, was calculated from the derived IC_{50} values, as per the following formula:

$$K_i = \frac{IC_{50}}{1 + \frac{[STAT3]}{K_d}}$$

where [STAT3] = 150nM and K_d= 100 nM.

S.2.1 Stat3 Fluorescence binding curves for salicylic-based inhibitors
Data are representative of 3 independent assays.

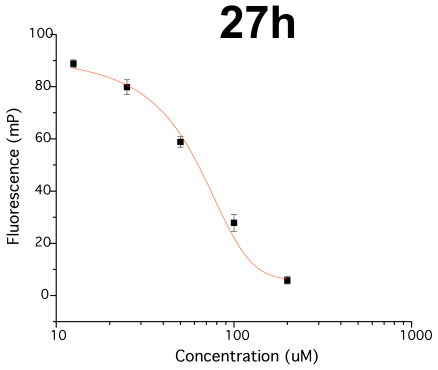


Figure 1. Competitive binding of **27h** measured by fluorescence polarization assay, with a calculated K_i = 15 ± 15 µM. Curve fitted using ORIGIN software.

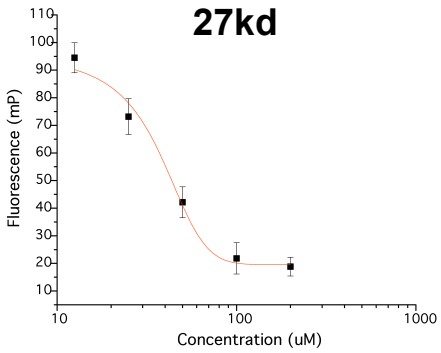


Figure 2. Competitive binding of **27kd** measured by fluorescence polarization assay, with a calculated K_i = 18.7 ± 1.4 μM. Curve fitted using ORIGIN software.

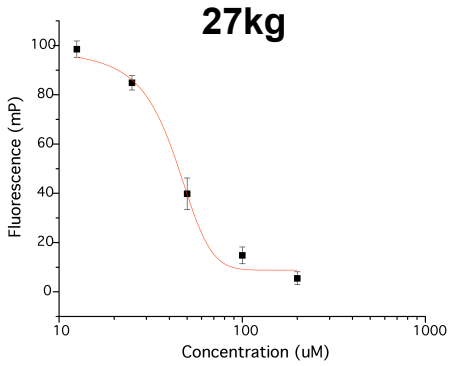


Figure 3. Competitive binding of **27kg** measured by fluorescence polarization assay, with a calculated K_i = 21.5 ± 2.2 μM. Curve fitted using ORIGIN software.

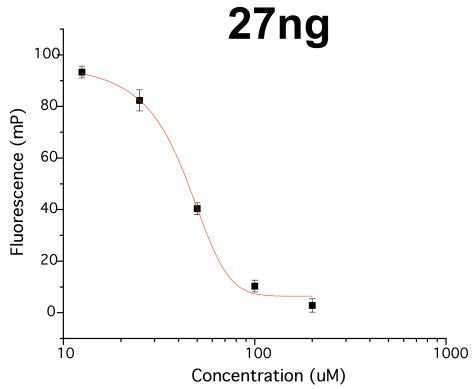


Figure 4. Competitive binding of **27ng** measured by fluorescence polarization assay, with a calculated K_i = 21.6 ± 0.9 μM. Curve fitted using ORIGIN software.

S.3 Apoptosis/immunoblotting analysis

Apoptosis of compound-treated cells was measured using the Annexin V-Flus Staining Kit (Boehringer Mannheim, Indianapolis, IN). Cell lines were plated at a cell density of 5 x 10^5 cells/mL in IMDM with 5% FCS in the presence of inhibitors / DMSO control at the indicated concentrations. Cells were harvested after 24 h, washed once in PBS and double stained with PI and FITC-conjugated Annexin V as per manufacturers

instructions. Samples were analzed on a FACSCalibur flow cytometer (BD Biosciences, San Jose, CA) using Flowjo software (Tree Star. Ashland, OR).

S.3.1 JJN3 cells

Human MM cell lines JJN3 were maintained in Iscoves modified Dulbecco medium (IMDM) supplemented with 5% fetal calf serum (FCS), JJN3 were treated overnight with 5 agents.

S.3.2 Immunoblotting

Cells were lysed in lysis buffer (50 mM Tris-HCL, 1 mM EDTA, 1% NP-40, 150 mM NaCl) for 30 minutes on ice, then freeze/thaw once at -80^{0}C and clarified by centrifugation at 12000*g* for 15 minutes. Proteins were separated by 6.5% to 15% sodium dodecyl–polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotted with the specified antibody. Protein bands were visualized using secondary antibodies coupled to horseradish peroxidase and the Chemiluminescence Reagent Plus (from Perkin Elmer Life Sciences) according to the manufacturer's instructions.

Anti cMyc is from Santa Cruz, anti surviving is from NOVUS Biologicals, Anti–Mcl-1, and anti–Bcl-x from BD Biosciences, (Mississauga, ON), anti-phospho STAT3 and STAT3, anti PARP are from Cell Signaling Technology, (Pickering, ON).

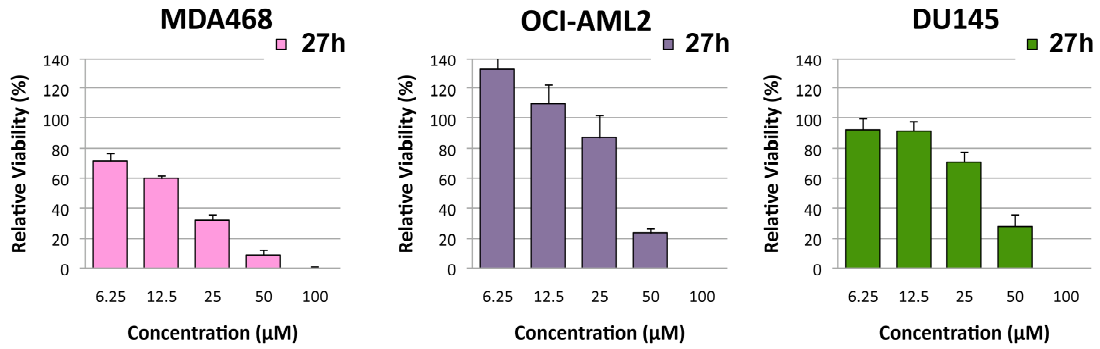
S.4. Whole Cell Viability Studies

To further test activity of these molecules, a whole-cell study involving cancer lines with known abherrant STAT3 expression was conducted. These human cell lines, including prostate cancer (DU145), OCI-AML2 and breast cancer (MDA468) were treated with the inhibitors and incubated for 72 hours. Disruption of cell viability was measured by MTS assay and EC_{50} values for the potential inhibitors was determined. Origin (Northampton, MA) was used to evaluate EC_{50} using the dose response curve defined as follows:

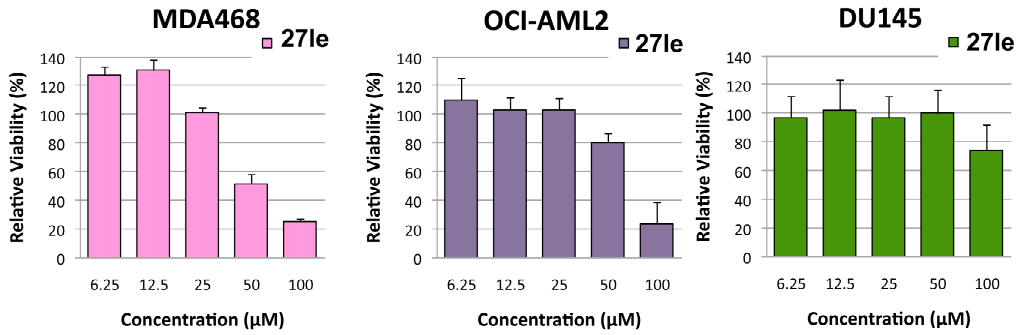
$$y = A1 + \frac{(A2 - A1)}{(1 + 10^{((logx_0 - x) \times p)})}$$

where y is the fraction of death, x is the log of drug concentration. A2 is the top asymptote, A1 is the bottom asymptote, $\log x_0$ is the center of the curve, and p is the hill slope. EC_{50} is determined by using this relationship: $EC_{50} = 10^{logx_o}$

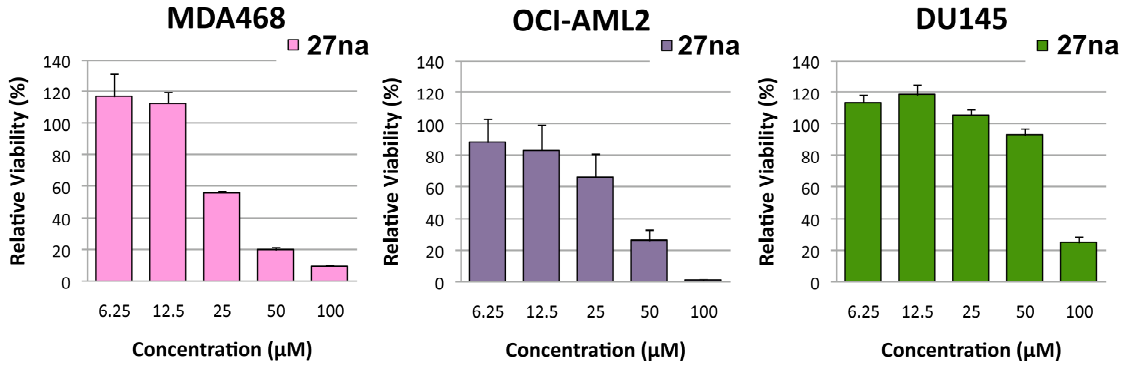
S.4.1 Tumor whole cell treatment with compound 27h



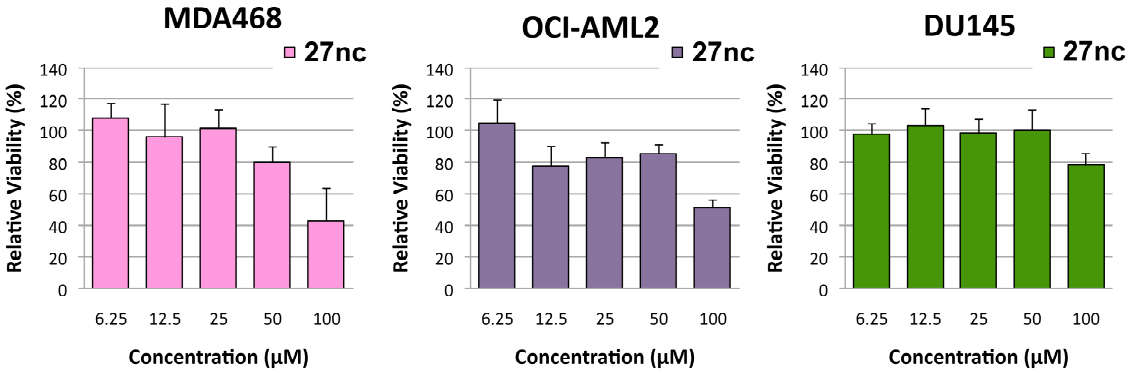
S.4.2 Tumor whole cell treatment with compound 27le



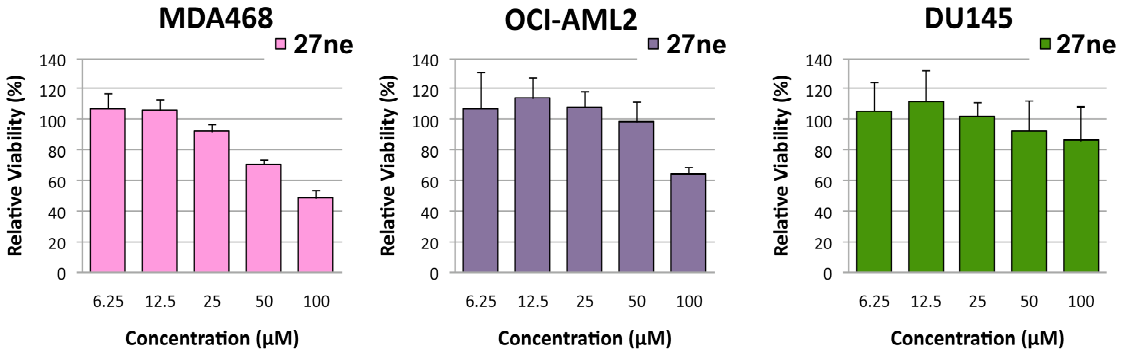
S.4.3 Tumor whole cell treatment with compound 27na



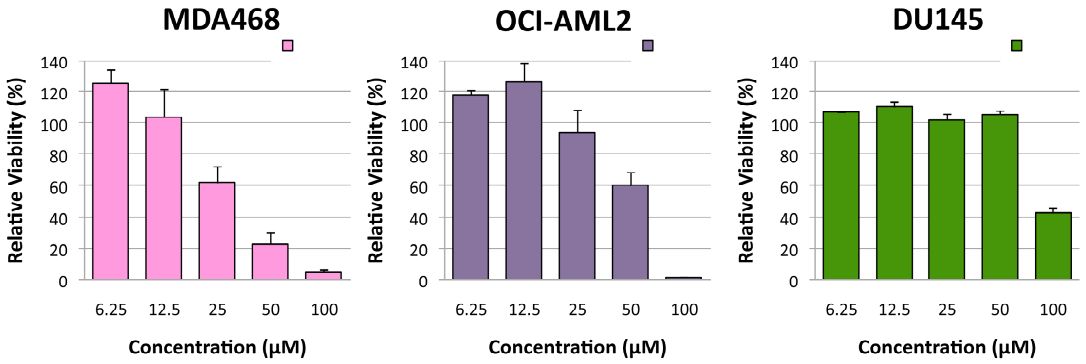
S.4.4 Tumor whole cell treatment with compound 27nc



S.4.5 Tumor whole cell treatment with compound 27ne



S.4.6 Tumor whole cell treatment with compound 27ng



S.5 General Reaction Procedures

General Procedure A (Reductive amination of amino salicyclic acid) – Reaction of R^1 aldehydes with benzyl protected 4-aminosalicyclic acid. To a solution of amine (1.0 equiv) and acetic acid (1.5 equiv) stirred in anhydrous MeOH (0.1 M) with 4 Å mol. sieves was added 1.0 equiv of aldehyde. The solution was then heated to 45 °C for 3 hr and then allowed to cool to rt. Next, $NaCNBH_3$ (1.3 equiv) was added portion-wise and

the reaction allowed to stir at rt overnight. When TLC indicated the reaction was complete, the reaction was diluted with CH_2Cl_2, filtered and concentrated *in vacuo*.

General Procedure B (PPh_3Cl_2 mediated Amide Coupling) – Reaction of secondary anilines with carboxylic acids. To a stirred solution of the secondary aniline (1.0 equiv) and carboxylic acid (1.0 equiv) in $CHCl_3$ (0.1 M) was added PPh_3Cl_2 (2.5 equiv). The reaction was then heated to 60 ^oC and stirred overnight. The reaction was allowed to cool and the solvents removed under reduced pressure. The concentrate was absorbed directly onto silica for column chromatography purification.

General Procedure C (Boc Protection). To a stirred solution of the appropriate secondary amine (1.0 equiv) and DIPEA (2.0 equiv) in $CHCl_3$ (0.1 M), was added Boc_2O (1.1 equiv) and left to stir overnight at rt. The reaction was then diluted with CH_2Cl_2, washed with H_2O, brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure.

General Procedure D (Nucleophilic aromatic substitution). The desired secondary amine (1.0 equiv) and arylfluoride substrate (1.5 equiv) were dissolved in anhydrous DMSO (0.1 M) followed by the addition of DIPEA (3.0 equiv). The reaction was heated to 120 °C and allowed to stir overnight. The reaction was quenched with H_2O and the aqueous layer extracted repeatedly into EtOAc. The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure.

General Procedure E (TFA deprotection with K_2CO_3 and MeOH). K_2CO_3 (3.0 equiv) was added to a stirred solution of TFA-protected compound (1 equiv) in MeOH (0.1 mol). The reaction was allowed to stir at room temperature for 1.5 hrs before quenching with saturated $NaHCO_3$ solution. The aqueous layer was then repeatedly extracted with EtOAc. The organic layers were then combined, washed with saturated $NaCO_3$ and dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure.

General Procedure F (HBTU mediated condensation reactions). The required carboxylic acid (1 equiv) was added in one portion to a solution of HBTU (1.1 equiv) and DIPEA (3.0 equiv) in DMF (0.1 M), and the resulting solution stirred at room temperature for 10 minutes. The required amine was then dissolved in a solution of DIPEA (2.0 equiv) in DMF (0.1 M) and added to the activated acid in one portion. The resulting solution was stirred for 4 hours, then diluted with EtOAc (0.1 M) and washed successively with equal volumes of: 2M HCl, saturated bicarbonate and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated.

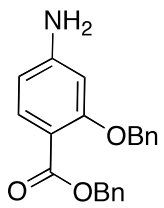
General Procedure G (Sulfonylation of secondary amines). To a stirred solution of amine (1.0 equiv) dissolved in CH_2Cl_2 (0.1 M) was added DIPEA (1.1 equiv) and the appropriate sulfonyl chloride (1.1 equiv). After 1 hr, the reaction was diluted with CH_2Cl_2, washed with water, followed by a brine wash and dried over Na_2SO_4. The organic layer was then concentrated under reduced pressure and purified by silica gel column chromatography to yield product.

General Procedure H (Suzuki Cross Coupling). A mixture of arylbromide (1.0 equiv), boronic acid (1.1 equiv), K_2CO_3 (2.5 equiv) and $Pd(PPh_3)_4$ (0.03 equiv) was suspended in DMF (0.1 M) in a sealed tube vessel and irradiated in a Biotage Initiator microwave reactor (17 mins, 170 °C). After cooling to rt, the reaction was diluted with water and repeatedly extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

General Procedure I (Hydrogenolysis of benzyl ether and benzyl ester) – Global deprotection of benzylated salicyclic acid. The benzyl protected salicyclic acid (1 equiv) was dissolved in a stirred solution of MeOH/THF (1:1) (0.1 M). The solution was degassed thoroughly before careful addition of 10 % Pd/C (10 mg/mmol). H_2 gas was bubbled through the solvent for 5 mins before the solution was put under an atmosphere of H_2 gas and stirred continuously for 3 hrs. The H_2 gas was evacuated and the reaction filtered (to remove the Pd catalyst) and concentrated under reduced pressure.

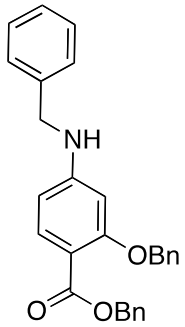
General Procedure J (TFA deprotection of benzyl ether). The benzyl protected compound (1 equiv) was dissolved in a 1:1 mixture of TFA:toluene (0.1 M) at rt for 5 minutes, then all solvents were evaporated under reduced pressure.

S.6 Intermediate characterization data



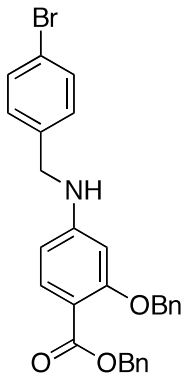
(17) Benzyl 4-amino-2-(benzyloxy)benzoate. To a stirred solution of 4-aminosalicyclic acid (3.00 g, 19.6 mmol) in DMF (0.1 M) at 0 ^oC, was added KO*t*Bu (2.42 g, 21.6 mmol).

After 15 mins, benzyl bromide (2.57 mL, 21.6 mmol) was added drop-wise. The suspension was allowed to stir at rt for a further 4 hrs before the reaction vessel was again cooled to 0 ^{o}C. A further 1.1 equivs of KtOBu (2.42 g, 21.6 mmol) were added prior to the drop-wise addition of benzyl bromide (2.57 mL, 21.6 mmol). The reaction was then stirred overnight before quenching with H_2O. The solution was then repeatedly extracted with ethyl acetate and the organics combined. The organics were then washed with H_2O and brine then concentrated, dried over Na_2SO_4 and concentrated *in vacuo* (3.40 g, 74 %): δ_H (400 MHz, d_6-DMSO) 5.07 (s, 2H, CH_2Ph), 5.21 (s, 2H, CH_2Ph), 5.99 (br s, 2H, NH_2), 6.18 (dd, J = 8.6 and 1.8 Hz, 1H, CH (Ph)), 6.32 (d, J = 1.7 Hz, 1H, CH (Ph)), 7.28 - 7.38 (8H, m, CH (Ph)), 7.47 (d, J = 7.2 Hz, 2H, CH (Ph)), 7.60 (d, J = 8.6 Hz, 1H, CH (Ph)); δ_C (100 MHz, d-$CDCl_3$) 65.8, 70.2, 99.1, 106.7, 109.0, 126.3, 126.8, 127.5, 127.7, 127.9, 128.1, 128.3, 128.4, 134.3, 136.6, 136.7, 152.2, 160.7, 165.7; LRMS (ES+) Calcd for [$C_{21}H_{19}NO_3$ + H] 334.14 found 334.17.

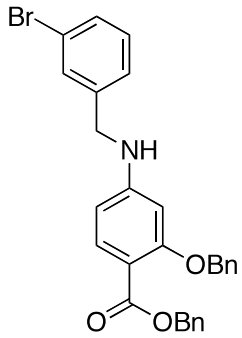


(18) Benzyl 4-(benzylamino)-2-(benzyloxy)benzoate. Primary aniline **17** was coupled to benzaldehyde on a 0.3 mmol scale *via* General Procedure A to furnish **18** (109 mg, 86%): δ_H (400 MHz, d-$CDCl_3$) 4.21 (s, 2H, NH_2CH_2Ph), 4.95 (s, 2H, CH_2Ph), 5.20 (s, 2H, CH_2Ph), 6.03 (d, J = 2.0 Hz, 1H, CH (Ph)), 6.09 (dd, J = 8.6 and 2.1 Hz, 1H, CH (Ph)), 7.15 - 7.34 (m, 15H, CH (Ph)), 7.73 (d, J = 8.6 Hz, 1H, CH (Ph)); δ_C (100 MHz, d-$CDCl_3$) 47.5, 66.7, 70.3, 97.2, 104.8, 108.3, 126.8, 127.2, 127.4, 127.5, 127.6, 127.9,

128.2, 128.3, 128.6, 134.2, 136.6, 136.7, 138.1, 152.8, 160.8, 165.6; LRMS (ES+) Calcd for [$C_{28}H_{25}NO_3$ + H] 424.19 found 424.22.

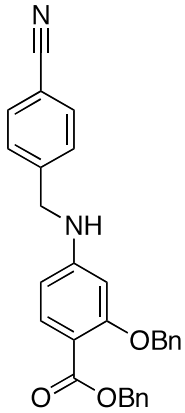


(19a) Benzyl 2-(benzyloxy)-4-(4-bromobenzylamino)benzoate. Primary aniline **17** was coupled to 4-bromobenzaldehyde on a 0.7 mmol scale *via* General Procedure A to furnish **19a** (274 mg, 78 %): δ_H (400 MHz, *d*-$CDCl_3$) 4.12 (s, 2H, CH_2, $NHCH_2Ph$), 4.50 (br s, 1H, NH), 4.92 (s, 2H, CH_2, CH_2Ph), 5.18 (s, 2H, CH_2, CH_2Ph), 5.98 (d, J = 1.8 Hz, 1H, CH (Ph)), 6.04 (dd, J = 8.6 and 1.8 Hz, 1H, CH (Ph)), 7.02 (d, J = 8.2 Hz, 2H, 2 CH (Ph)), 7.11 - 7.34 (m, 12H, 12 CH (Ph)), 7.70 (d, J = 8.6 Hz, 1H, CH (Ph)); δ_C (100 MHz, *d*-$CDCl_3$) 46.5, 65.4, 69.9, 97.0, 104.5, 108.2, 120.7, 126.4, 127.2, 127.4, 127.6, 128.0, 128.1, 128.4, 131.4, 133.9, 136.3, 137.0, 152.3, 160.4, 165.3; LRMS (ES+) Calcd for [$C_{28}H_{24}BrNO_3$ + H] 502.10, found 502.06.

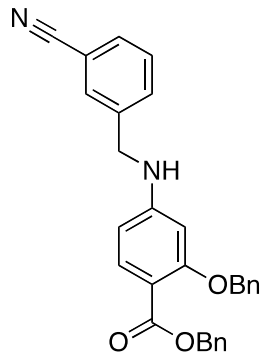


(19b) Benzyl 2-(benzyloxy)-4-(3-bromobenzylamino)benzoate. Primary aniline **17** was coupled to 3-bromobenzaldehyde on a 0.7 mmol scale *via* General Procedure A to furnish

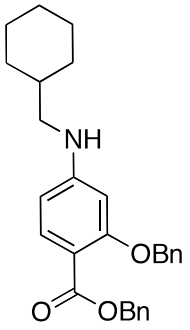
19b (267 mg, 89%): δ_H (400 MHz, *d*-$CDCl_3$) 4.27 (s, 2H, CH_2, $NHCH_2Ph$), 4.65 (br s, 1H, NH), 4.93 (s, 2H, CH_2, $NHCH_2Ph$), 5.19 (s, 2H, CH_2, $NHCH_2Ph$), 5.98 (d, *J* = 2.1 Hz, 1H, CH (Ph)), 6.04 (dd, *J* = 8.6 and 2.1 Hz, 1H, CH (Ph)), 7.16 - 7.30 (m, 12H, 12 CH (Ph)), 7.47 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.70 (d, *J* = 8.6 Hz, 1H, CH (Ph)); δ_C (100 MHz, *d*-$CDCl_3$) 46.9, 65.8, 70.3, 97.4, 104.9, 108.7, 122.7, 125.6, 126.8, 127.5, 127.7, 127.9, 128.3, 128.4, 130.1, 130.2, 130.5, 134.3, 136.7, 140.8, 152.5, 160.8, 165.6; LRMS (ES+) Calcd for [$C_{28}H_{24}BrNO_3$ + H] 502.10 found 502.00.



(19c) Benzyl 2-(benzyloxy)-4-(4-cyanobenzylamino)benzoate. Primary aniline **17** was coupled to 4-formylbenzonitrile on a 0.7 mmol scale *via* General Procedure A to furnish **19c** (211 mg, 79%): δ_H (400 MHz, *d*-$CDCl_3$) 4.27 (s, 2H, CH_2, $NHCH_2Ph$), 4.65 (br s, 1H, NH), 4.93 (s, 2H, CH_2, $NHCH_2Ph$), 5.19 (s, 2H, CH_2, $NHCH_2Ph$), 5.98 (d, *J* = 2.1 Hz, 1H, CH (Ph)), 6.04 (dd, *J* = 8.6 and 2.1 Hz, 1H, CH (Ph)), 7.16 - 7.30 (m, 12H, 12 CH (Ph)), 7.47 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.70 (d, *J* = 8.6 Hz, 1H, CH (Ph)); δ_C (100 MHz, *d*-$CDCl_3$) 46.6, 65.5, 70.0, 97.2, 104.5, 108.7, 110.7, 118.3, 126.4, 127.1, 127.3, 127.4, 127.6, 128.0, 128.1, 132.1, 134.0, 136.2, 143.7, 151.9, 160.4, 165.2; LRMS (ES+) Calcd for [$C_{29}H_{24}N_2O_4$ + H] 449.19 found 449.15.

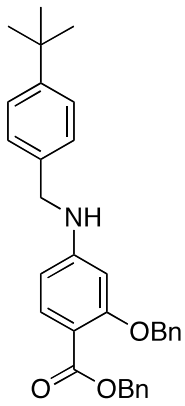


(19d) Benzyl 2-(benzyloxy)-4-(3-cyanobenzylamino)benzoate. Primary aniline **17** was coupled to 3-formylbenzonitrile on a 0.7 mmol scale *via* General Procedure A to furnish **19d** (251 mg, 94%): δ_H (400 MHz, *d*-$CDCl_3$) 4.19 (s, 2H, CH_2, $NHCH_2Ph$), 4.89 (s, 2H, CH_2, $NHCH_2Ph$), 5.17 (s, 2H, CH_2, $NHCH_2Ph$), 5.97 (d, J = 2.0 Hz, 1H, CH (Ph)), 6.02 (dd, J = 8.6 and 2.0 Hz, 1H, CH (Ph)), 7.13 - 7.42 (m, 14H, 14 CH (Ph)), 7.69 (d, J = 8.6 Hz, 1H, CH (Ph)); LRMS (ES+) Calcd for [$C_{29}H_{24}N_2O_4$ + H] 449.19 found 449.15.

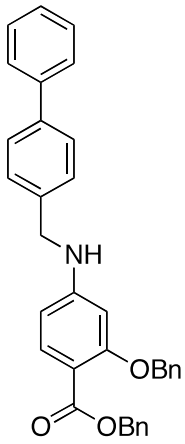


(19e) benzyl 2-(benzyloxy)-4-((cyclohexylmethyl)amino)benzoate. Primary aniline **17** was coupled to cyclohexanecarboxaldehyde on a 0.6 mmol scale *via* General Procedure A to furnish **19e** (184 mg, 72 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.15 - 1.30 (m, 5H, CH_2), 1.45 - 1.55 (m, 1H, CH), 1.65 - 1.81 (m, 5H, CH_2), 2.94 (d, J = 6.4 Hz, 2H, CH_2), 5.14 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 6.11 (d, J = 2.0 Hz, 1H, CH), 6.16 (d of d, J = 8.8 and 2.0 Hz, 1H, CH), 7.29 - 7.36 (m, 10H, CH), 7.41 (d, J = 8.0 Hz, 2H, CH), 7.48 (d, J = 8.0 Hz, 2H, CH), 7.85 (d, J = 8.8 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 25.7, 26.3, 31.0, 37.5,

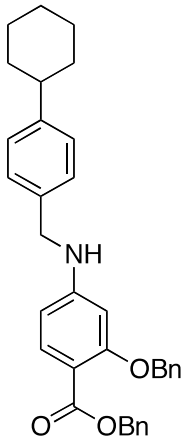
49.8, 65.6, 70.3, 96.8, 104.6, 107.5, 126.8, 127.5, 127.6, 127.9, 128.3, 128.4, 134.2, 136.8, 136.9, 153.4, 161.0, 165.7, 171.0; LRMS (ES+) Calcd for [$C_{28}H_{31}NO_3$ + H] 430.24 found 430.20.



(19f) Benzyl 2-(benzyloxy)-4-(4-*tert*-butylbenzylamino)benzoate. Primary aniline **17** was coupled to 4-*tert*-butylbenzaldehyde on a 0.7 mmol scale *via* General Procedure A to furnish **19f** (276 mg, 96%): δ_H (400 MHz, *d*-$CDCl_3$) 1.19 (s, 9H, 3 CH_3), 4.13 (s, 2H, $NHCH_2Ar$), 4.40 (br s, 1H, NH), 4.92 (s, 2H, CH_2Ph), 5.17 (s, 2H, CH_2Ph), 6.02 (d, *J* = 2.0 Hz, 1H, CH (Ph)), 6.06 (dd, *J* = 8.6 and 2.0 Hz, 1H, CH (Ph)), 7.08 - 7.32 (m, 14H, 14 CH), 7.71 (d, *J* = 8.6 Hz, 1H, CH (Ph)); δ_C (100 MHz, *d*-$CDCl_3$) 31.0, 34.2, 47.0, 65.5, 70.1, 96.9, 104.6, 107.9, 125.3, 126.7, 126.9, 127.3, 127.4, 127.7, 128.1, 128.2, 134.1, 134.9, 136.5, 136.6, 150.2, 152.8, 160.6, 165.5; LRMS (ES+) Calcd for [$C_{32}H_{33}NO_3$ + H] 480.25 found 480.21.

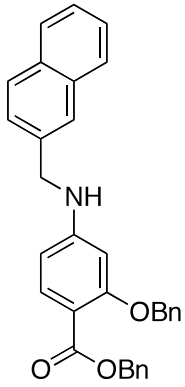


(19g) Benzyl 2-(benzyloxy)-4-(biphenyl-4-ylmethylamino)benzoate. Primary aniline **17** was coupled to biphenyl-4-carbaldehyde on a 0.7 mmol scale *via* General Procedure A to furnish **19g** (235 mg, 79%): δ_H (400 MHz, *d*-$CDCl_3$) 4.20 (s, 2H, NH_2CH_2), 4.48 (br s, 1H, NH), 4.94 (s, 2H, CH_2Ph), 5.18 (s, 2H, CH_2Ph), 6.03 (d, *J* = 1.8 Hz, 1H, CH (Ph)), 6.09 (dd, *J* = 8.6 and 1.8 Hz, 1H, CH (Ph)), 7.13 - 7.34 (m, 15H, CH (Ph)), 7.43 (d, *J* = 8.2 Hz, 2H, 2 CH (Ph)), 7.46 (d, *J* = 7.4 Hz, 2H, 2 CH (Ph)), 7.73 (d, *J* = 8.6 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 46.6, 65.2, 69.7, 96.7, 104.3, 107.7, 126.3, 126.4, 126.7, 126.8, 126.9, 127.1, 127.4, 127.7, 127.8, 128.1, 133.7, 136.1, 136.2, 136.7, 139.7, 139.9, 152.3, 160.3, 165.1; LRMS (ES+) Calcd for [$C_{34}H_{29}NO_3$ + H] 500.22 found 500.17.

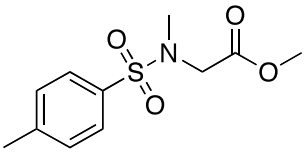


(19h) Benzyl 2-(benzyloxy)-4-(4-cyclohexylbenzylamino)benzoate. Primary aniline **17** was coupled to 4-cyclohexylbenzaldehyde on a 0.6 mmol scale *via* General Procedure A

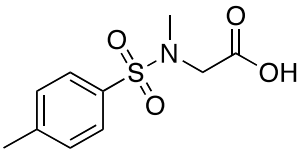
to furnish **19h** (250 mg, 83%): δ_H (400 MHz, *d*-$CDCl_3$) 1.25 - 1.48 (m, 6H, CH_2CH_2), 1.74 -1.95 (m, 4H, CH_2CH_2), 2.48 - 2.52 (m, 1H, CH), 4.28 (s, 2H, NH_2CH_2), 4.49 (br s, 1H, NH), 5.08 (s, 2H, CH_2Ph), 5.32 (s, 2H, CH_2Ph), 6.17 (d, *J* = 2.0 Hz, 1H, CH (Ph)), 6.21 (dd, *J* = 8.6 and 2.0 Hz, 1H, CH (Ph)), 7.19 - 7.27 (m, 4H, 4 CH (Ph)), 7.28 - 7.37 (m, 6H, 6 CH (Ph)), 7.40 - 7.49 (m, 4H, 4 CH (Ph)), 7.85 (d, *J* = 8.6 Hz, 1H, 1 CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 26.0, 26.7, 34.3, 44.1, 47.3, 65.7, 70.3, 97.1, 104.8, 108.2, 126.8, 127.0, 127.4, 127.5, 127.6, 127.9, 128.2, 128.3, 134.2, 135.4, 136.7, 136.8, 147.4, 152.9, 160.8, 165.8; LRMS (ES+) Calcd for [$C_{34}H_{35}NO_3$ + H] 506.27 found 506.22.



(19i) Benzyl 2-(benzyloxy)-4-(naphthalen-2-ylmethylamino)benzoate. Primary aniline **17** was coupled to 2-naphthaldehyde on a 0.6 mmol scale *via* General Procedure A to furnish **19i** (223 mg, 88 %): δ_H (400 MHz, *d*-$CDCl_3$) 4.35 (s, 2H, NH_2CH_2), 4.52 (br s, 1H, NH), 4.92 (s, 2H, CH_2Ph), 5.19 (s, 2H, CH_2Ph), 6.70 (d, *J* = 2.0 Hz, 1H, CH (Ph)), 6.12 (dd, *J* = 8.6 and 2.0 Hz, 1H, CH (Ph)), 7.11 - 7.22 (m, 6H, CH (Ph)), 7.25 - 7.30 (m, 4H, 4 CH (Ph)), 7.34 - 7.39 (m, 2H, 2 CH (Ph)), 7.61 - 7.75 (m, 5H, 5 CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 47.1, 65.2, 69.7, 96.7, 104.4, 107.9, 124.7, 125.2, 125.3, 125.7, 126.2, 126.9, 127.0, 127.1, 127.3, 127.7, 127.8, 127.9, 132.1, 132.7, 133.7, 135.1, 136.1, 152.3, 160.3, 165.1; LRMS (ES+) Calcd for [$C_{32}H_{27}NO_3$ + H] 474.21, found 474.16.

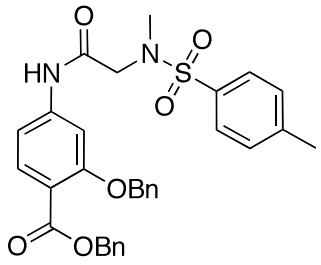


(22) methyl 2-(N,4-dimethylphenylsulfonamido)acetate. To a stirred solution of methyl 2-(4-methylphenylsulfonamido)acetate (3.10 g, 12.8 mmol) and Cs_2CO_3 (8.31 g, 25.5 mmol) in DMF (0.1 M) was added MeI (877 μL, 14.1 mmol). The reaction was allowed to stir overnight at rt. The reaction was then diluted with water and repeatedly extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish **22** (2.80 g, 85 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.42 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 7.31 (d, *J* = 8.4 Hz, 2H, CH), 7.69 (d, *J* = 8.4 Hz, 2H, CH); LRMS (ES+) Calcd for [$C_{11}H_{15}NO_4S$ + H] 258.08, found 258.06 [M+H].

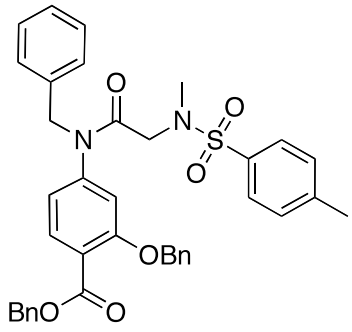


(23) 2-(*N*,4-dimethylphenylsulfonamido)acetic acid. Methyl ester **22** (2.60 g, 10.1 mmol) was dissolved in a 3:1:1 mixture of MeOH-THF-H_2O. $LiOH.H_2O$ (0.53 g, 12.6 mmol) was added at room temperature and the reaction allowed to stir for 3 hrs. All solvents were evaporated, apart from water. The remaining aqueous solvent was diluted further and thoroughly washed with ethyl acetate. The aqueous basic aqueous layer was then acidified to pH 2 with 1 M HCl and the product extracted with ethyl acetate. The organic layers were then combined and dried over Na_2SO_4, filtered and concentrated. (2.33 g, 95 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.43 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 7.32 (d, *J* = 8.0 Hz, 2H, CH), 7.69 (d, *J* = 8.0 Hz, 2H, CH); δ_C (100 MHz, *d*-

$CDCl_3$) 21.4, 35.7, 50.6, 127.3, 129.6, 134.8, 143.7, 173.5; LRMS (ES+) Calcd for [$C_{10}H_{13}NO_4S$ + H] 244.06, found 244.07 [M+H].

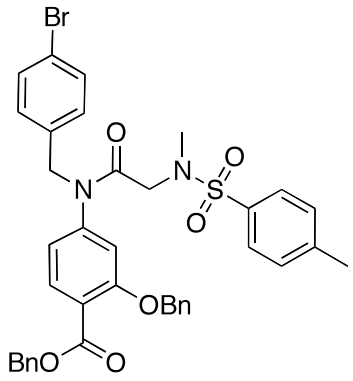


(24) benzyl 2-(benzyloxy)-4-(2-(N,4-dimethylphenylsulfonamido)-acetamido)benzoate. Primary aniline **17** was coupled to **23** on a 1.3 mmol scale *via* General Procedure B to furnish **24** (650 mg, 92 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.38 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 5.33 (s, 2H, CH_2), 7.10 (d, *J* = 8.4 Hz, 1H, CH), 7.25 - 7.34 (m, 8H, CH), 7.36 - 7.40 (m, 2H, CH), 7.43 (d, *J* = 7.2 Hz, 2H, CH), 7.64 (s, 1H, CH), 7.67 (d, *J* = 8.0 Hz, 2H, CH), 7.89 (d, *J* = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 37.1, 54.7, 66.4, 70.4, 104.6, 111.2, 115.6, 127.1, 127.5, 127.7, 127.9, 128.0, 128.3, 128.4, 130.0, 132.6, 133.0, 136.1, 136.2, 142.3, 144.5, 159.4, 165.5, 166.4; LRMS (ES+) Calcd for [$C_{31}H_{30}N_2O_6S$ + H] 559.19, found 559.19.

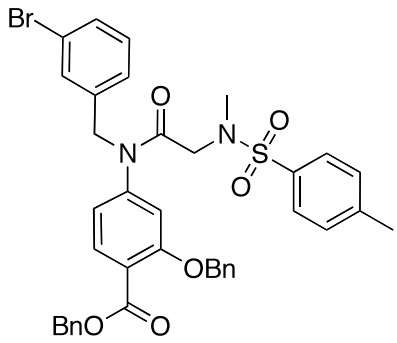


(25) benzyl 4-(N-benzyl-2-(N,4-dimethylphenylsulfonamido)acetamido)-2-(benzyloxy) benzoate. Secondary aniline **18** was coupled to **23** on a 0.18 mmol scale *via* General Procedure B to furnish **24** (76 mg, 70 %): LRMS (ES+) Calcd for [$C_{38}H_{36}N_2O_6S$

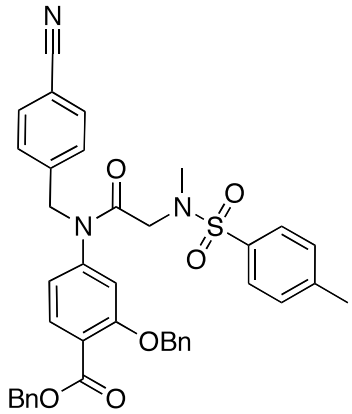
+ H] 649.24 found 649.16. As previously reported Fletcher, S., Page, B. D., Zhang, X., Singh, J., Turkson, J., **Gunning**, **P**. **T**. "Salicyclic acid derivatives as potent inhibitors of transcriptionally active Stat3 dimers." *ChemBioChem* **2009**, *10,* 1959-1964.



(26a) Benzyl 2-(benzyloxy)-4-(*N*-(4-bromobenzyl)-2-(*N*,4-dimethylphenylsulfon-amido)acetamido)benzoate. Secondary aniline **19a** was coupled to carboxylic acid **22** on a 0.2 mmol scale *via* General Procedure B to furnish **26a** (167 mg, 90%): δ_H (400 MHz, *d*-$CDCl_3$) 2.33 (s, 3H, CH_3Ar), 2.73 (s, 3H, CH_3Ar), 3.54 (s, 2H, CH_2CO), 4.64 (s, 2H, CH_2 Ar), 4.99 (s, 2H, CH_2Ar), 5.28 (s, 2H, CH_2Ar), 6.50 (br s, 1H, CH (Ar)), 6.55 (dd, *J* = 8.3 and 1.8 Hz, 1H, CH (Ar)), 6.88 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.16 - 7.34 (m, 14H, 14 CH (Ar)), 7.51 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.75 (d, *J* = 8.3 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 29.6, 36.0, 51.2, 52.4, 53.3, 66.9, 70.7, 113.9, 119.8, 120.9, 121.7, 126.9, 127.3, 127.9, 128.2, 128.5, 129.4, 130.5, 131.6, 133.1, 135.2, 135.5, 135.6, 135.7, 143.3, 144.7, 158.7, 165.2, 167.0; LRMS (ES+) Calcd for [$C_{38}H_{35}BrN_2O_6S$ + H] 727.15 found 726.83.

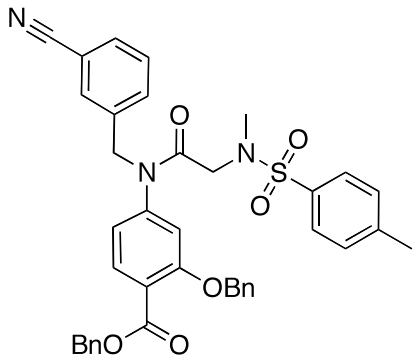


(26b) Benzyl 2-(benzyloxy)-4-(*N*-(3-bromobenzyl)-2-(*N*,4-dimethylphenyl-sulfonamido) acetamido) benzoate. Secondary aniline **19b** was coupled to carboxylic acid **23** on a 0.25 mmol scale *via* General Procedure B to furnish **26b** (149 mg, 82 %): LRMS (ES+) Calcd for [$C_{38}H_{35}BrN_2O_6S$ + H] 727.15 found 726.89. "Salicyclic acid derivatives as potent inhibitors of transcriptionally active Stat3 dimers." *ChemBioChem* **2009**, *10,* 1959-1964.

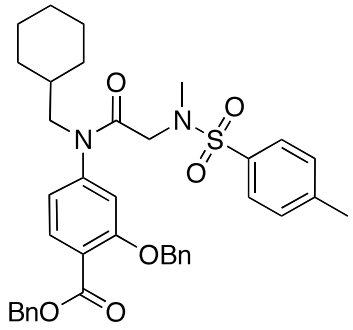


(26c) Benzyl 2-(benzyloxy)-4-(*N*-(4-cyanobenzyl)-2-(*N*,4-dimethylphenyl-sulfonamido) acetamido) benzoate. Secondary aniline **19c** was coupled to carboxylic acid **23** on a 0.2 mmol scale *via* General Procedure B to furnish **26c** (115 mg, 83 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.40 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.67 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 5.11 (s, 2H, CH_2), 5.36 (s, 2H, CH_2), 6.63 (d, *J* = 8.0 Hz, 1H, CH), 6.67 (s, 1H, CH), 7.20 (d, *J* = 8.4 Hz, 2H, CH), 7.24 (d, *J* = 8.4 Hz, 2H, CH) 7.29 - 7.36 (m 7H, CH), 7.38 - 7.42 (m, 2H, CH), 7.51 (d, *J* = 8.4 Hz, 2H, CH), 7.58 (d, *J* = 8.4 Hz, 2H, CH), 7.83

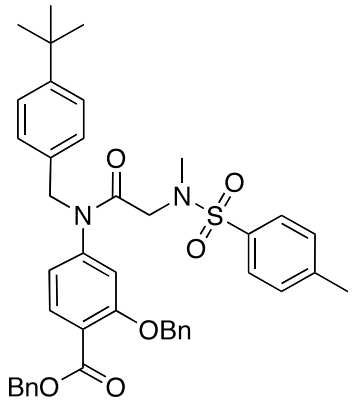
(d, J = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 36.1, 51.2, 52.8, 67.0, 70.6, 111.5, 113.7, 118.4, 119.6, 121.1, 126.8, 127.3, 128.0, 128.2, 128.5, 128.6, 129.2, 129.5, 132.2, 133.2, 135.0, 135.5, 135.6, 141.7, 143.4, 144.6, 158.8, 165.1, 167.3; LRMS (ES+) Calcd for [$C_{39}H_{35}N_3O_6S$ + Na] 696.21 found 696.17.



(26d) Benzyl 2-(benzyloxy)-4-(*N*-(3-cyanobenzyl)-2-(*N*,4-dimethylphenyl-sulfonamido)acetamido) benzoate. Secondary aniline **19d** was coupled to carboxylic acid **23** on a 0.30 mmol scale *via* General Procedure B to furnish **26d** (159 mg, 76 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.39 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.67 (s, 2H, CH_2), 4.82 (s, 2H, CH_2), 5.11 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.65 (d, J = 8.0 Hz, 1H, CH), 6.66 (s, 1H, CH), 7.27 (d, J = 8.0 Hz, 2H, CH), 7.29 - 7.44 (m 13H, CH), 7.52 - 7.56 (m, 1H, CH), 7.59 (d, J = 8.4 Hz, 2H, CH), 7.84 (d, J = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.6, 36.3, 51.5, 52.6, 67.2, 70.9, 112.8, 113.9, 118.6, 119.9, 121.4, 127.1, 127.5, 128.3, 128.4, 128.7, 128.8, 129.6, 129.7, 131.6, 132.3, 133.3, 133.5, 135.3, 135.8, 135.8, 138.2, 143.7, 144.7, 159.1, 165.3, 167.5; LRMS (ES+) Calcd for [$C_{39}H_{35}N_3O_6S$ + Na] 696.21 found 696 [M+H].

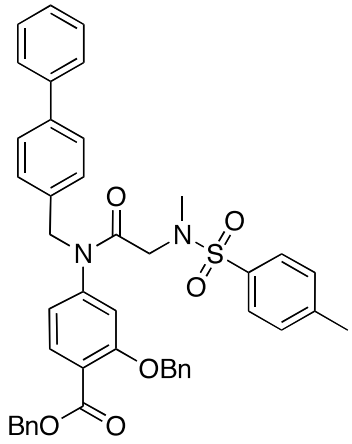


(26e) benzyl 2-(benzyloxy)-4-(N-(cyclohexylmethyl)-2-(N,4-dimethylphenyl-sulfonamido) acetamido)benzoate. Secondary aniline **19e** was coupled to carboxylic acid **23** on a 0.2 mmol scale *via* General Procedure B to furnish **26d** (92 mg, 68 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.04 - 1.17 (m, 3H, CH_2), 1.25 - 1.41 (m, 3H, CH_2 and CH), 1.50 - 1.71 (m, 5H, CH_2), 2.39 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.47 (d, *J* = 8.4 Hz, 2H, CH_2), 3.67 (s, 2H, CH_2), 5.22 (s, 2H, CH_2), 5.38 (s, 2H, CH_2), 6.79 - 6.84 (m, 2H, CH), 7.25 (d, *J* = 8.4 Hz, 2H, CH), 7.28 - 7.39 (m, 6H, CH), 7.40 - 7.47 (m, 4H, CH), 7.61 (d, *J* = 8.4 Hz, 2H, CH), 7.91 (d, *J* = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.5, 25.6, 26.2, 30.6, 35.9, 51.3, 55.4, 67.0, 70.8, 113.8, 119.8, 120.6, 127.0, 127.4, 128.0, 128.1, 128.2, 128.5, 128.6, 129.4, 133.1, 135.7, 135.9, 143.2, 145.9, 158.9, 165.4, 167.0; LRMS (ES+) Calcd for [$C_{38}H_{42}N_2O_6S$ + Na] 677.27 found 677.36.



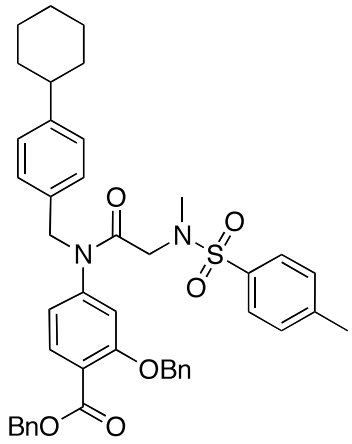
(26f) Benzyl 2-(benzyloxy)-4-(*N*-(4-*tert*-butylbenzyl)-2-(*N*,4-dimethylphenyl-sulfonamido)acetamido)benzoate. Secondary aniline **19f** was coupled to carboxylic

acid **23** on a 0.30 mmol scale *via* General Procedure B to furnish **26f** (146 mg, 76 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.27 (s, 9H, 3 CH_3), 2.38 (s, 3H, CH_3Ar), 2.73 (s, 3H, CH_3N), 3.57 (s, 2H, CH_2CO), 4.67 (s, 2H, CH_2Ar), 4.87 (s, 2H, CH_2Ar), 5.26 (s, 2H, CH_2Ar), 6.46 (s, 1H, CH (Ar)), 6.60 (d, *J* = 8.2 Hz, 1H, CH (Ar)), 6.95 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.14 - 7.33 (m, 14H, 14 CH (Ar)), 7.52 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.75 (d, *J* = 8.2 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.3, 31.1, 34.3, 35.7, 51.2, 52.5, 66.8, 70.5, 114.0, 119.8, 120.4, 125.2, 126.9, 127.3, 127.8, 128.0, 128.1, 128.3, 128.4, 129.3, 132.9, 133.4, 135.2, 135.5, 135.6, 143.1, 150.5, 158.5, 165.2, 166.6; LRMS (ES+) Calcd for [$C_{42}H_{44}N_2O_6S$ + H] 705.30 found 705.04.

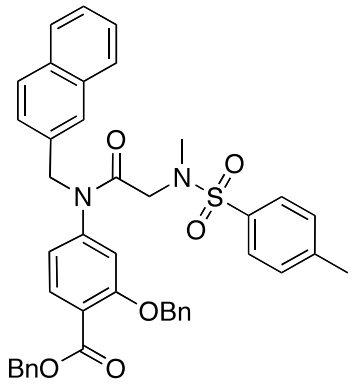


(26g) Benzyl 2-(benzyloxy)-4-(*N*-(biphenyl-4-ylmethyl)-2-(*N*,4-dimethylphenyl-sulfonamido)acetamido)benzoate. Secondary aniline **19g** was coupled to carboxylic acid **23** on a 0.2 mmol scale *via* General Procedure B to furnish **26g** (138 mg, 86 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.30 (s, 3H, CH_3Ar), 2.74 (s, 3H, CH_3N), 3.59 (s, 2H, CH_2CO), 4.74 (s, 2H, CH_2Ar), 4.92 (s, 2H, CH_2Ar), 5.26 (s, 2H, CH_2Ar), 6.53 (s, 1H, CH (Ar)), 6.60 (dd, *J* = 8.2 and 1.7 Hz, 1H, CH (Ar)), 7.08 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.14 - 7.37 (m, 14H, 14 CH (Ar)), 7.40 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.46 - 7.49 (m, 2H, 2 CH (Ar)), 7.52 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.75 (d, *J* = 8.2 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 35.9, 51.3, 52.7, 66.9, 70.6, 114.0, 119.9, 120.7, 126.9, 126.9,

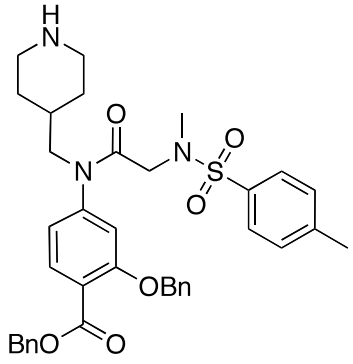
127.1, 127.4, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 129.2, 129.4, 133.1, 135.5, 135.6, 135.7, 140.3, 140.5, 143.3, 158.7, 165.3, 166.9; LRMS (ES+) Calcd for [$C_{44}H_{40}N_2O_6S$ + Na] 747.25 found 747.26.



(26h) Benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-(*N*,4-dimethylphenyl-sulfonamido) acetamido) benzoate. Secondary aniline **19h** was coupled to carboxylic acid **23** on a 0.2 mmol scale *via* General Procedure B to furnish **27h** (145 mg, 86 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.15 - 1.35 (m, 6H, CH_2), 1.61 - 1.80 (m, 4H, CH_2), 2.31 (s, 3H, CH_3Ar), 2.37 - 2.38 (m, 1H, CH), 2.73 (s, 3H, CH_3N), 3.57 (s, 2H, CH_2CO), 4.67 (s, 2H, CH_2Ar), 4.86 (s, 2H, CH_2Ar), 5.26 (s, 2H, CH_2Ar), 6.43 (s, 1H, CH (Ar)), 6.59 (dd, *J* = 8.2 and 1.5 Hz, 1H, CH (Ar)), 6.93 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.02 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.14 - 7.35 (m, 12H, 12 CH (Ar)), 7.52 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.75 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)); δ_C (400 MHz, *d*-$CDCl_3$) 21.4, 25.9, 26.6, 34.3, 35.8, 44.0, 51.2, 52.7, 66.8, 70.5, 114.1, 119.9, 120.5, 126.8, 126.9, 127.3, 127.8, 128.0, 128.1, 128.4, 128.5, 128.7, 129.3, 133.0, 133.8, 135.2, 135.6, 135.7, 143.1, 144.9, 147.6, 158.6, 165.2, 166.6; LRMS (ES+) Calcd for [$C_{44}H_{46}N_2O_6S$ + H] 731.32 found 731.28.

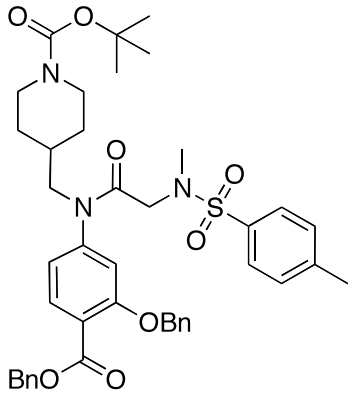


(26i) Benzyl 2-(benzyloxy)-4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-(naphthalen-2-ylmethyl) acetamido)benzoate. Secondary aniline **19i** was coupled to carboxylic acid **23** on a 0.2 mmol scale *via* General Procedure B to furnish **26i** (127 mg, 84 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.30 (s, 3H, CH_3Ar), 2.75 (s, 3H, CH_3N), 3.60 (s, 2H, CH_2CO), 4.82 (s, 2H, CH_2Ar), 4.87 (s, 2H, CH_2Ar), 5.25 (s, 2H, CH_2Ar), 6.47 (s, 1H, CH (Ar)), 6.58 (dd, *J* = 8.2 and 1.4 Hz, 1H, CH (Ar)), 7.12 - 7.32 (m, 13H, 13 CH (Ar)), 7.36 - 7.44 (m, 3H, 3 CH (Ar)), 7.53 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.63 - 7.75 (m, 4H, 4 CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.3, 35.9, 51.3, 53.1, 66.8, 70.5, 114.0, 119.9, 120.7, 126.0, 126.1, 126.4, 126.8, 127.3, 127.5, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 129.3, 132.6, 133.0, 133.9, 135.6, 143.2, 158.6, 165.2, 166.9; LRMS (ES+) Calcd for [$C_{42}H_{38}N_2O_6S$ + H] 699.25 found 699.23 [M+H].



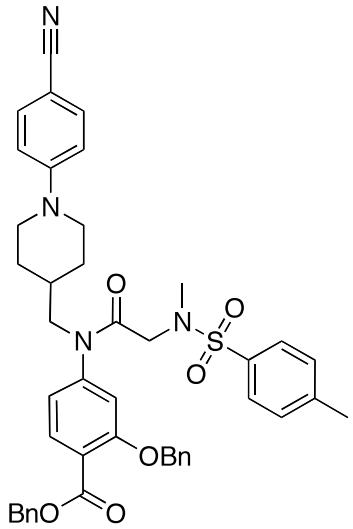
(26j) Benzyl 2-(benzyloxy)-4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-(piperidin-4-ylmethyl) acetamido) benzoate. Secondary aniline *tert*-butyl 4-(((3-(benzyloxy)-4-

((benzyloxy)carbonyl) phenyl)amino)methyl)piperidine-1-carboxylate was coupled to carboxylic acid **23** on a 2.8 mmol scale *via* General Procedure B to furnish **26j** (1.50 g, 67 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.40 - 1.86 (m, 4H, CH_2), 2.38 (s, 3H, CH_3Ar), 2.64 - 2.93 (m, 5H, CH and CH_2), 2.72 (s, 3H, NCH_3), 3.28 - 3.70 (m, 4H, CH_2), 5.24 (s, 2H, CH_2Bn), 5.38 (s, 2H, CH_2Bn), 6.85 (dd, *J* = 8.2 and 1.7 Hz, 1H, CH (Ar)), 6.89 (d, *J* = 1.7 Hz, 1H, CH (Ar)), 7.20 - 7.43 (m, 11H, 13 CH (Ar)), 7.58 (d, *J* = 8.2 Hz, 1H, 1 CH (Ar)), 7.90 (d, *J* = 8.2 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 27.4, 29.7, 33.2, 36.1, 44.1, 51.5, 54.3, 67.0, 70.7, 113.7, 119.5, 120.9, 127.0, 127.3, 127.4, 128.0, 128.2, 128.5, 128.6, 129.4, 129.5, 133.3, 135.0, 135.7, 135.9, 143.5, 145.5, 158.9, 165.3, 167.1, 167.6; LRMS (ES+) Calcd for [$C_{37}H_{41}N_3O_6S$ + H] 656.28 found 656.44.

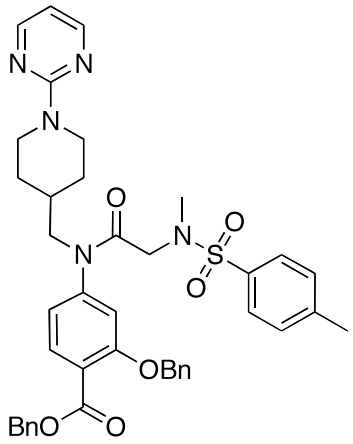


(28b) *tert*-butyl 4-((*N*-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(*N*,4-dimethylphenyl- sulfonamido) acetamido)methyl)piperidine-1-carboxylate. Compound **26j** was Boc protected with $(Boc)_2$ *via* General Procedure C on a 0.15 mmol scale to furnish **28b** (99 mg, 86 %): δ_H (400 MHz, *d*-$CDCl_3$) 0.80 - 1.02 (m, 3H, CH_2), 1.10 - 1.25 (m, 2H, CH_2), 1.36 (s, 9H, 3 CH_3), 2.31 (s, 3H, CH_3Ar), 2.45 - 2.55 (m, 2H, CH_2), 2.72 (s, 3H, NCH_3), 3.42 (s (br), 2H, CH_2), 3.58 (s, 2H, CH_2), 3.93 (br s, 2H, CH_2), 5.16 (s, 2H, CH_2Bn), 5.30 (s, 2H, CH_2Bn), 6.71 - 6.75 (m, 2H, 2 CH (Ar)), 7.15 - 7.38 (m, 12H, 12 CH (Ar)), 7.52 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.83 (d, *J* = 8.2 Hz, 1H, CH

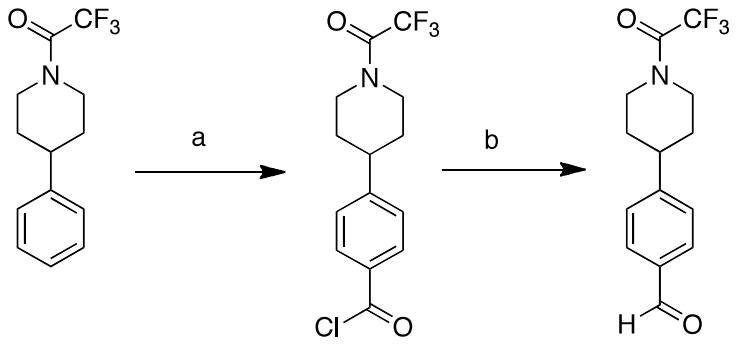
(Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 28.3, 29.6, 34.5, 36.0, 36.5, 51.3, 54.7, 66.9, 70.7, 79.3, 113.7, 119.5, 120.7, 126.9, 127.3, 128.0, 128.1, 128.5, 128.6, 129.4, 133.2, 135.6, 135.8, 143.3, 145.6. 154.5, 158.9, 165.2, 167.2.



(28c) benzyl 2-(benzyloxy)-4-(*N*-((1-(4-cyanophenyl)piperidin-4-yl)methyl)-2-(*N*,4-dimethylphenylsulfon amido)acetamido)benzoate. Nucleophilic aromatic substitution of **26ja** with 4-fluorobenzonitrile on a 0.2 mmol scale *via* General Procedure D furnished **28c** (87 mg, 76 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.20 - 1.31 (m, 3H, CH_2), 1.60 - 1.68 (m, 2H, CH_2), 2.38 (s, 3H, CH_3Ar), 2.72 (t, *J* = 12.0 Hz, 2H, CH_2), 2.78 (s, 3H, NCH_3), 3.55 (d, *J* = 6.8 Hz, 2H, CH_2CH), 3.66 (s, 2H, CH_2), 3.74 (d, *J* = 13.0 Hz, 2H, CH_2), 5.24 (s, 2H, CH_2Bn), 5.38 (s, 2H, CH_2Bn), 6.77 - 6.84 (m, 4H, 4 CH (Ar)), 7.21 - 7.47 (m, 14H, 14 CH (Ar)), 7.59 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.91 (d, *J* = 8.2 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 28.9, 34.3, 36.1, 47.1, 51.3, 54.5, 67.0, 70.7, 99.2, 113.7, 114.1, 119.5, 120.1, 120.8, 126.9, 127.3, 128.0, 128.2, 128.5, 128.6, 129.4, 133.2, 133.4, 135.6, 135.8, 143.3, 145.6, 152.9, 158.8, 165.2, 167.3.

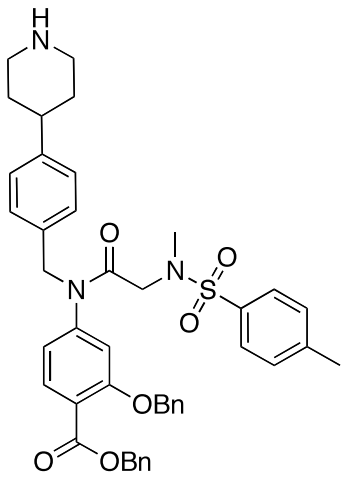


(28d) benzyl 2-(benzyloxy)-4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-((1-(pyrimidin-2-yl) piperidin-4-yl)methyl)acetamido)benzoate. Nucleophilic aromatic substitution of **26ja** with 2-chloropyrimidine on a 0.2 mmol scale *via* General Procedure D furnished **28jd** (108 mg, 96 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.15 - 1.40 (m, 2H, CH_2), 1.54 - 1.75 (m, 3H, CH_2 and CH), 2.38 (s, 3H, CH_3), 2.74 (t, *J* = 10.4 Hz, 2H, CH_2), 2.80 (s, 3H, CH_3), 3.52 (d, *J* = 7.2 Hz, 2H, CH_2), 3.68 (s, 2H, CH_2), 4.64 (d, *J* = 13.2 Hz, 2H, CH_2), 5.23 (s, 2H, CH_2), 5.37 (s, 2H, CH_2), 6.42 (t, *J* = 4.8 Hz, 1H, CH), 6.80 - 6.85 (m, 2H, CH), 7.23 - 7.37 (m, 8H, CH), 7.38 - 7.45 (m, 4H, CH), 7.60 (d, *J* = 8.0 Hz, 2H, CH), 7.91 (d, *J* = 8.8 Hz, 1H, CH), 8.27 (d, *J* = 4.8 Hz, 2H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 29.4, 34.8, 35.9, 36.5, 43.4, 51.3, 54.8, 66.9, 70.7, 109.3, 113.7, 119.5, 120.7, 126.9, 127.3, 128.0, 128.1, 128.4, 128.6, 129.4, 133.2, 135.2, 135.6, 135.8, 143.3, 145.7, 157.5, 158.9, 161.2, 165.2, 167.1.

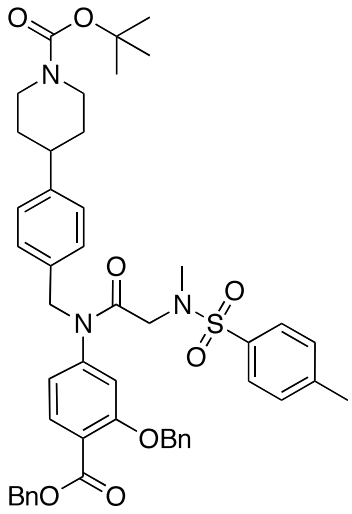


30 **31** **32**

(32) 4-(1-(2,2,2-trifluoroacetyl)piperidin-4-yl)benzaldehyde (2 step procedure): (a) To a flask containing $AlCl_3$ (534 mg, 4.0 mmol) under an N_2 atmosphere was added anhydrous CH_2Cl_2 (0.1 M), and the drop wise addition of oxalyl chloride (523 µL, 6.0 mmol) over a 20 min period at 15 °C. Next, a solution of **30** (2.0 mmol) in anhydrous CH_2Cl_2 (0.1 M) was added drop-wise to the initial solution over a 45 min period at 15 °C. When the reaction was complete as judged by TLC, ice was added to the solution in addition to $CaCl_2$ (1.70 g). The product was extract into CH_2Cl_2, washed with brine and dried over anhydrous Na_2SO_4 before concentrating under reduced pressure to yield crude **31**. **(b)** To a stirred solution of **31** (2.0 mmol) and DIPEA (697 µL, 4.0 mmol) in EtOAc (0.1 M) was added 10% Pd/C. The flask was then evacuated and filled with H_2 gas and allowed to stir for 30 mins. After which time the reaction contents were filtered and concentrated under reduced pressure to give crude product which was purified by silica gel column chromatography (hexanes:EtOAc, 2:1) to furnish **32** (320 mg, 59 % (yield over 2 steps)) δ_H (400 MHz, *d*-$CDCl_3$) 1.69 - 1.81 (m, 2H, CH_2), 1.98 - 2.06 (m, 2H, CH_2), 2.83 - 2.97 (m, 2H, CH_2), 3.27 (td, J = 12.8 and 2.4 Hz, 1H, CH), 4.13 - 4.21 (m, 1H, CH), 4.70 - 4.76 (m, 1H, CH_2), 7.37 (d, J = 8.4 Hz, 2H, CH), 7.85 (d, J = 8.4 Hz, 2H, CH), 9.99 (s, 1H, CHO); LRMS (ES+) Calcd for [$C_{14}H_{14}F_3NO_2$ + Na] 308.09 found 308.19 [M+Na].

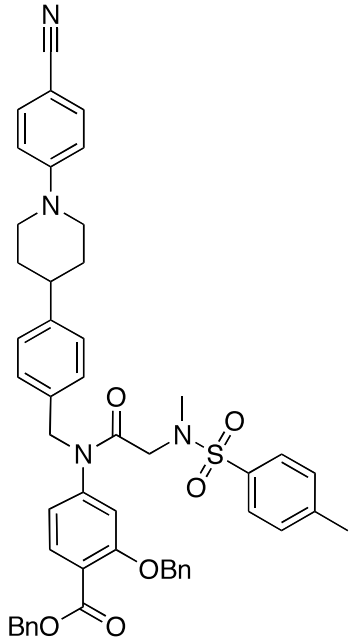


(33) benzyl 2-(benzyloxy)-4-(2-(N,4-dimethylphenylsulfonamido)-N-(4-(piperidin-4-yl)benzyl)acetamido)benzoate. Compound **26k** was TFA-deprotected on a 0.04 mmol scale *via* General Procedure E to furnish **33** (0.89 g, 81 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.68 - 1.82 (m, 2H, CH_2), 1.95 - 2.05 (m, 2H, CH_2) 2.41 (s, 3H, CH_3), 2.55 - 2.64 (m, 1H, CH), 2.69 - 2.78 (m, 2H, CH_2), 2.80 (s, 3H, CH_3), 3.17 - 3.21 (m, 2H, CH_2), 4.70 (s, 2H, CH_2), 4.75 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 6.53 (s, 1H, CH), 6.66 (d, *J* = 8.4 Hz, 1H, CH), 7.03 (d, *J* = 8.0 Hz, 2H, CH), 7.11 (d, *J* = 8.0 Hz, 2H, CH), 7.22 - 7.40 (m, 12H, CH), 7.60 (d, *J* = 8.4 Hz, 2H, CH), 7.80 (d, *J* = 8.4 Hz, 1H, CH); LRMS (ES+) Calcd for [$C_{43}H_{45}N_3O_6S$ + H] 732.31 found 732.40.



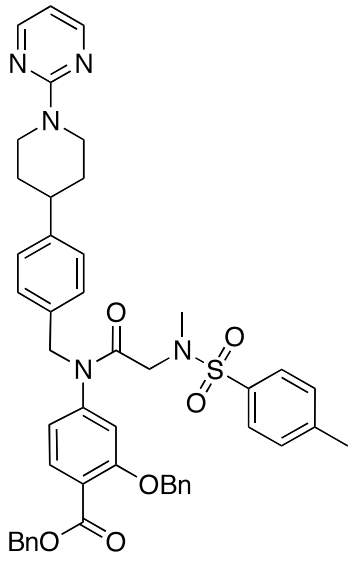
(34c) *tert*-butyl 4-(4-((N-(3-(benzyloxy)-4-((benzyloxy)carbonyl)phenyl)-2-(N,4-dimethyl-phenylsulfonamido)acetamido)methyl)phenyl)piperidine-1-carboxylate.

Compound **33** was Boc protected with $(Boc)_2$ *via* General Procedure C on a 0.10 mmol scale to furnish **34c** (83 mg, 99 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.47 (s, 9H, CH_3), 1.53 - 1.64 (m, 2H, CH_2), 1.72 - 1.80 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.54 - 2.64 (m, 2H, CH_2), 2.70 - 2.82 (m, 4H, CH_3 and CH), 3.64 (s, 2H, CH_2), 4.75 (s, 2H, CH_2), 4.97 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.56 (s, 1H, CH), 6.65 (dd, J = 8.0 and 1.6 Hz, 1H, CH), 7.03 (d, J = 8.0 Hz, 2H, CH), 7.09 (d, J = 8.0 Hz, 2H, CH), 7.24 (d, J = 8.0 Hz, 2H, CH), 7.28 - 7.40 (m, 10H, CH), 7.59 (d, J = 8.0 Hz, 2H, CH), 7.81 (d, J = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 28.3, 33.0, 35.9, 40.8, 42.2, 51.3, 52.7, 66.9, 70.6, 79.3, 114.0, 119.9, 120.6, 126.8, 127.0, 127.3, 127.9, 128.1, 128.2, 128.4, 128.5, 128.9, 129.4, 133.0, 134.5, 135.2, 135.6, 135.7, 143.2, 144.9, 145.3, 154.7, 158.6, 165.2, 166.7; LRMS (ES+) Calcd for [$C_{48}H_{53}N_3O_8S$ + Na] 854.35 found 854.62 [M+Na].



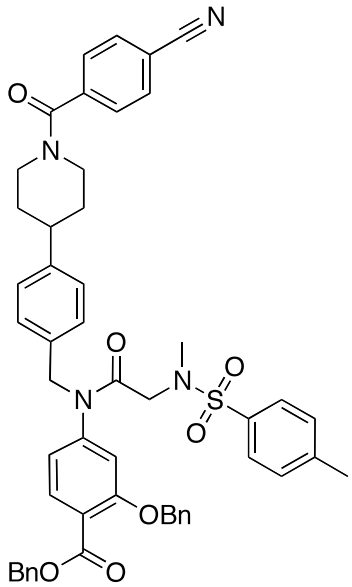
(34d) benzyl 2-(benzyloxy)-4-(N-(4-(1-(4-cyanophenyl)piperidin-4-yl)benzyl)-2-(N,4-dimethylphenylsulfonamido)acetamido)benzoate. Nucleophilic aromatic substitution

of **26ja** with 4-fluorobenzonitrile on a 0.1 mmol scale *via* General Procedure D furnished **34d** (87 mg, 95 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.68 - 1.80 (m, 2H, CH_2), 1.85 - 1.94 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.66 - 2.76 (m, 1H, CH), 2.80 (s, 3H, CH_3), 2.90 - 3.00 (m, 2H, CH_2), 3.65 (s, 2H, CH_2), 3.91 - 3.98 (m, 2H, CH_2), 4.77 (s, 2H, CH_2), 4.97 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.58 (s, 1H, CH), 6.66 (dd, *J* = 8.0 and 1.6 Hz, 1H, CH), 6.87 (d, *J* = 8.8 Hz, 2H, CH), 7.06 (d, *J* = 8.0 Hz, 2H, CH), 7.11 (d, *J* = 8.0 Hz, 2H, CH), 7.24 (d, *J* = 8.0 Hz, 2H, CH), 7.28 - 7.41 (m, 10H, CH), 7.48 (d, *J* = 8.8 Hz, 2H, CH), 7.59 (d, *J* = 8.4 Hz, 2H, CH), 7.82 (d, *J* = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 32.5, 35.9, 41.9, 48.1, 51.3, 52.7, 66.9, 70.6, 99.4, 114.0, 114.2, 120.0, 120.1, 150.6, 126.8, 127.0, 127.3, 128.1, 128.2, 128.4, 128.5, 129.0, 129.4, 133.0, 133.4, 134.6, 135.1, 135.6, 135.7, 143.3, 144.8, 144.9, 153.1, 158.6, 165.3, 166.8; LRMS (ES+) Calcd for [$C_{50}H_{48}N_4O_6S$ + Na] 855.32 found 855.34.



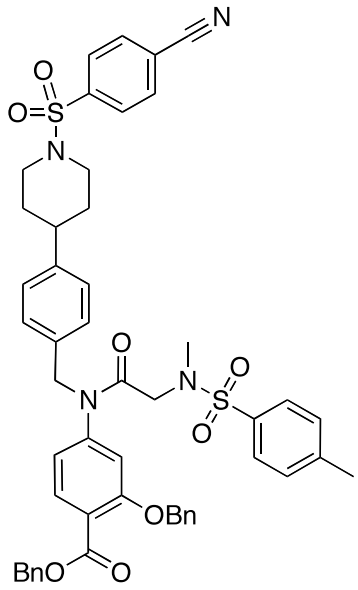
(34e) benzyl 2-(benzyloxy)-4-(2-(N,4-dimethylphenylsulfonamido)-N-(4-(1-(pyrimidin-2-yl)piperidin-4-yl)benzyl)acetamido)benzoate. Nucleophilic aromatic substitution of **33** with 2-chloropyrimidine on a 0.1 mmol scale *via* General Procedure D furnished **34e** (70 mg, 80 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.59 - 1.72 (m, 2H, CH_2), 1.83 -

1.94 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.71 - 2.83 (m, 4H, CH_3 and CH), 2.88 - 2.99 (m, 2H, CH_2), 3.65 (s, 2H, CH_2), 4.75 (s, 2H, CH_2), 4.86 - 4.94 (m, 2H, CH_2), 4.97 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.46 (t, *J* = 8.4 Hz, 1H, CH), 6.56 (s, 1H, CH), 6.65 (dd, *J* = 8.0 and 2.0 Hz, 1H, CH), 7.03 (d, *J* = 8.0 Hz, 2H, CH), 7.11 (d, *J* = 8.0 Hz, 2H, CH), 7.24 (d, *J* = 8.4 Hz, 2H, CH), 7.27 - 7.41 (m, 10H, CH), 7.59 (d, *J* = 8.4 Hz, 2H, CH), 7.82 (d, *J* = 8.4 Hz, 1H, CH), 8.30 (d, *J* = 8.8 Hz, 2H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 32.9, 35.8, 41.9, 48.1, 51.3, 52.7, 66.9, 70.6, 109.4, 113.9, 119.9, 120.6, 126.9, 127.0, 127.4, 127.9, 128.1, 128.2, 128.4, 128.5, 128.9, 129.4, 133.0, 134.4, 135.2, 135.6, 135.7, 143.2, 144.9, 145.5, 157.6, 158.6, 161.4, 165.2, 166.7; LRMS (ES+) Calcd for [$C_{47}H_{47}N_5O_6S$ + H] 810.33 found 810.44.



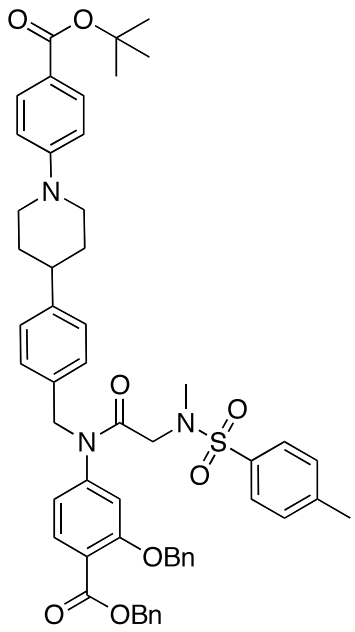
(34f) benzyl 2-(benzyloxy)-4-(N-(4-(1-(4-cyanobenzoyl)piperidin-4-yl)benzyl)-2-(N,4-dimethylphenylsulfonamido)acetamido)benzoate. Condensation of **33** with 4-cyanobenzoic acid on a 0.10 mmol scale *via* General Procedure F furnished **34f** (63 mg, 89 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.59 - 1.72 (m, 4H, CH_2), 1.83 - 1.94 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.79 - 3.21 (m, 8H, CH_3, CH and CH_2), 3.65 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 4.95 (s, 2H, CH_2), 4.97 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.60 (t, *J* = 8.4 Hz, 1H,

CH), 6.69 (dd, J = 8.0 and 1.6 Hz, 1H, CH), 7.03 - 7.12 (m, 4H, 4 CH (Ar)), 7.21 - 7.82 (m, 12H, 12 CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 29.5, 35.9, 42.0, 48.1, 51.3, 52.7, 66.9, 70.6, 113.3, 113.9, 119.9, 120.7, 126.7, 126.9, 127.3, 127.4, 127.9, 128.1 (2), 128.4, 128.5, 129.0, 129.4, 132.3, 132.9, 134.8, 135.0, 135.5, 135.6, 140.0, 143.3, 144.0, 144.8, 158.6, 165.2, 167.0, 168.3; LRMS (ES+) Calcd for [$C_{51}H_{48}N_4O_7S$ + H] 861.33 found 861.38.



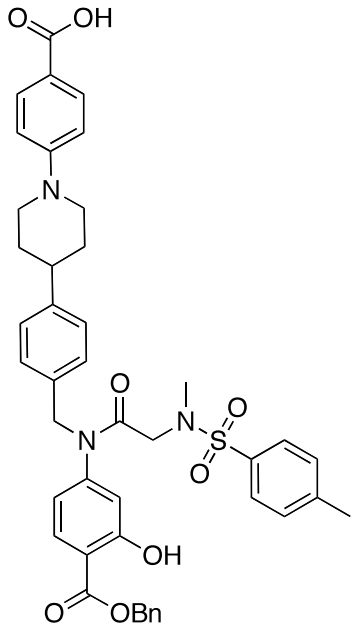
(34g) benzyl 2-(benzyloxy)-4-(N-(4-(1-((4-cyanophenyl)sulfonyl)piperidin-4-yl)benzyl)-2-(N,4-dimethylphenylsulfonamido)acetamido)benzoate. Sulfonylation of secondary amine **33** with 4-cyano-benzene-1-sulfonyl chloride on a 0.08 mmol scale *via* General Procedure F furnished **34g** (77 mgs, 99%): δ_H (400 MHz, *d*-$CDCl_3$) 1.72 - 1.91 (m, 4H, CH_2), 2.31 - 2.45 (m, 7H, CH_3 and 2 CH_2), 2.80 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 3.89 - 3.99 (m, 2H, CH_2), 4.74 (s, 2H, CH_2), 5.01 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.60 (t, J = 8.4 Hz, 1H, CH), 6.69 (dd, J = 8.0 and 1.6 Hz, 1H, CH), 6.99 - 7.09 (m, 4H, 4 CH (Ar)), 7.21 - 7.91 (m, 12H, 12 CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.3, 29.5, 32.3, 35.9, 40.8, 41.1, 46.5, 51.3, 52.6, 66.9, 70.6, 113.9, 116.3, 117.1 119.9, 120.6, 126.6, 126.9, 127.3, 127.9, 128.0, 128.1 (2), 128.4, 128.5, 129.0, 129.3, 132.7, 132.9, 134.9, 135.1,

135.5, 135.6, 140.7, 143.2, 143.8, 144.9, 158.6, 165.2, 166.8; LRMS (ES+) Calcd for [$C_{50}H_{48}N_4O_8S_2$ + Na] 919.28 found 919.40.



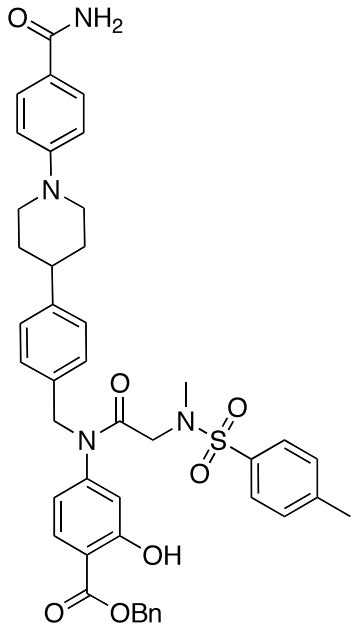
(34h) benzyl 2-(benzyloxy)-4-(*N*-(4-(1-(4-(*tert*-butoxycarbonyl)phenyl)piperidin-4-yl)benzyl)-2-(*N*,4-dimethylphenylsulfonamido)acetamido)benzoate. Nucleophilic aromatic substitution of **26ja** with *tert*-butyl 4-(chlorosulfonyl)benzoate on a 0.11 mmol scale *via* General Procedure D furnished **34h** (113 mg, 98%): δ_H (400 MHz, *d*-$CDCl_3$) 1.57 (s, 9H, $3CH_3$), 1.72 - 1.84 (m, 2H, CH_2), 1.86 - 1.96 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.64 - 2.75 (m, 1H, CH), 2.81 (s, 3H, CH_3), 2.91 (t, *J* = 10.4 Hz, 2H, CH_2), 3.66 (s, 2H, CH_2), 3.93 (d, *J* = 12.8 Hz, 2H, CH_2), 4.77 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.57 (s, 1H, CH), 6.67 (d, *J* = 8.0 Hz, 1H, CH), 6.88 (d, *J* = 8.8 Hz, 2H, CH), 7.06 (d, *J* = 8.0 Hz, 2H, CH), 7.12 (d, *J* = 8.0 Hz, 2H, CH), 7.24 (d, *J* = 7.6 Hz, 2H, CH), 7.29 - 7.39 (m, 10H, CH), 7.60 (d, *J* = 8.0 Hz, 2H, CH), 7.83 (d, *J* = 8.4 Hz, 1H, CH), 7.88 (d, *J* = 8.8 Hz, 2H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 28.2, 32.6, 35.9, 42.1, 48.7, 51.3, 52.7, 66.9, 70.6, 79.9, 113.8, 114.0, 119.8, 120.3, 121.2, 126.8, 127.0, 127.4, 128.0,

128.1, 128.2, 128.4, 128.5, 129.0, 129.4, 130.9, 133.0, 134.5, 135.3, 135.6, 135.7, 143.2, 144.8, 145.2, 153.8, 158.6, 165.3, 165.9, 166.8.

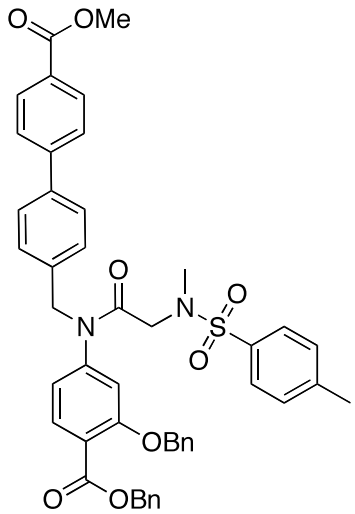


(35) 4-(4-(4-((*N*-(4-((benzyloxy)carbonyl)-3-hydroxyphenyl)-2-(*N*,4-dimethylphenylsulfon- amido)acetamido)methyl)phenyl)piperidin-1-yl)benzoic acid. *t*-Butyl ester **34h** (0.14 mmol) was dissolved in a 1:1 mixture of TFA:toluene (2.8 ml) and stirred at rt for 4 hrs. All solvents were subsequently evaporated, and the crude product passed through a short pad of silica gel (CH_2Cl_2) to furnish **35** (130 mg, 95%): δ_H (400 MHz, *d*-$CDCl_3$) 1.73 - 1.85 (m, 2H, CH_2), 1.90 - 1.98 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.68 - 2.78 (m, 1H, CH), 2.86 (s, 3H, CH_3), 2.98 (t, *J* = 12.0 Hz, 2H, CH_2), 3.82(s, 2H, CH_2), 4.02 (d, *J* = 12.8 Hz, 2H, CH_2), 4.80 (s, 2H, CH_2), 5.28 (s, 2H, CH_2), 5.39 (s, 2H, CH_2), 6.56 (dd, *J* = 8.4 and 1.6 Hz, 1H, CH), 6.67 (d, *J* = 1.6 Hz, 1H, CH), 6.91 (d, *J* = 8.8 Hz, 2H, CH), 7.08 (d, *J* = 8.0 Hz, 2H, CH), 7.12 (d, *J* = 8.0 Hz, 2H, CH), 7.26 (d, *J* = 7.6 Hz, 2H, CH), 7.34 - 7.48 (m, 5H, CH), 7.64 (d, *J* = 8.0 Hz, 2H, CH), 7.87 (d, *J* = 8.4 Hz, 1H, CH), 7.98 (d, *J* = 8.8 Hz, 2H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 32.5, 35.7, 42.0, 48.3, 51.4, 52.7, 53.3, 67.3, 112.2, 113.5, 116.8, 117.9, 119.0, 126.8, 127.4, 128.3,

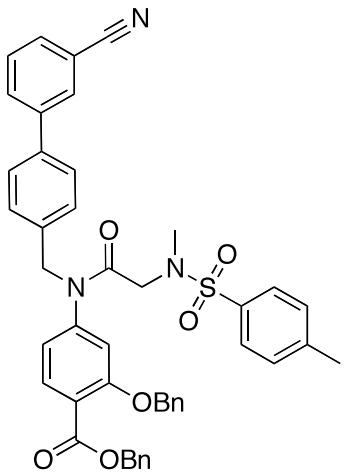
128.6 (br), 129.4, 131.4, 131.9, 134.4, 134.8, 135.2, 143.3, 144.9, 147.2, 154.4, 162.4, 166.7, 169.1, 171.9.



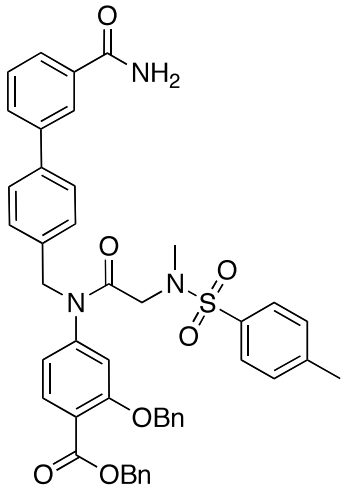
(36) 4-(N-(4-(1-(4-carbamoylphenyl)piperidin-4-yl)benzyl)-2-(N,4-dimethylphenyl-sulfonamido)acetamido)-2-hydroxybenzoate. Condensation of **35** with NH_4Cl on a 0.10 mmol scale *via* General Procedure F furnished **36** (58 mg, 98 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.70 - 1.96 (m, 4H, CH_2), 2.39 (s, 3H, CH_3), 2.63 - 2.73 (m, 1H, CH), 2.85 (s, 3H, CH_3), 2.86 - 2.9 (m, 2H, CH_2), 3.80 (s, 2H, CH_2), 3.92 - 3.97 (m, 2H, CH_2), 4.79 (s, 2H, CH_2), 5.38 (s, 2H, CH_2), 6.56 (dd, J = 8.4 and 2.0 Hz, 1H, CH), 6.67 (d, J = 2.0 Hz, 1H, CH), 6.91 (d, J = 8.4 Hz, 2H, CH), 7.03 - 7.14 (m, 4H, CH), 7.35 - 7.43 (m, 5H, CH), 7.63 (d, J = 8.4 Hz, 2H, CH), 7.73 (d, J = 7.6 Hz, 2H, CH), 7.86 (d, J = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 32.6, 35.7, 41.9, 48.7, 51.4, 52.7, 67.3, 112.2, 114.2, 116.8, 117.9, 118.9, 122.2, 126.8, 127.4, 128.3, 128.5, 128.6, 128.9, 129.4, 131.4, 134.4, 134.8, 135.2, 143.2, 145.0, 147.2, 153.6, 162.4, 166.6, 169.0; LRMS (ES+) Calcd for [$C_{43}H_{44}N_4O_7S$ + Na] 783.28 found 783.34.



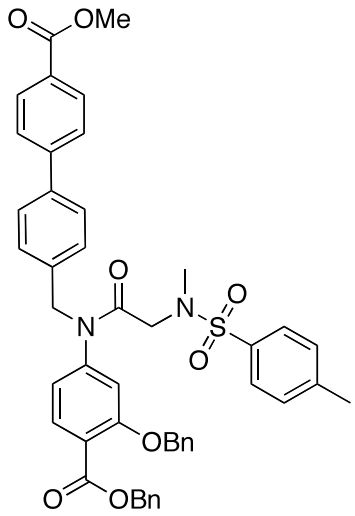
(37a) Methyl 4'-((*N*-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(*N*,4-dimethylphenyl-sulfonamido)acetamido)methyl)biphenyl-3-carboxylate. Aryl halide **26a** was coupled to 3-(methoxycarbonyl)phenylboronic acid to give **37a** on a 0.1 mmol scale *via* General Procedure H (65 mg, 62 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.40 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 3.94 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.62 (s, 1H, CH), 6.68 (dd, *J* = 8.0 and 1.6 Hz, 1H, CH), 7.19 (d, *J* = 8.0 Hz, 2H, CH), 7.30-7.42 (m, 10H, CH), 7.52 (d, *J* = 8.4 Hz, 2H, CH), 7.60-7.64 (m, 4H, CH), 7.78 (d, *J* = 7.6 Hz, 2H, CH), 7.84 (d, 1H, *J* = 8.0 Hz, CH), 8.02 (dt, *J* = 8.0 and 1.2 Hz, 1H, CH), 8.25 (t, *J* = 2.0 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.5, 36.0, 52.2, 52.8, 56.0, 67.5, 70.7, 117.2, 117.5, 120.1, 125.2, 127.0, 127.2, 127.4, 127.5, 128.0, 128.1, 128.1, 128.2, 128.2, 128.5, 128.6, 128.9, 129.5, 130.7, 131.3, 133.2, 135.7, 135.7, 136.1, 139.5, 141.2, 142.4, 158.8, 161.7, 166.9, 167.0, 168.4; LRMS (ES+) Calcd for [$C_{46}H_{42}N_2O_8S$ + H] 783.27 found 783.26.



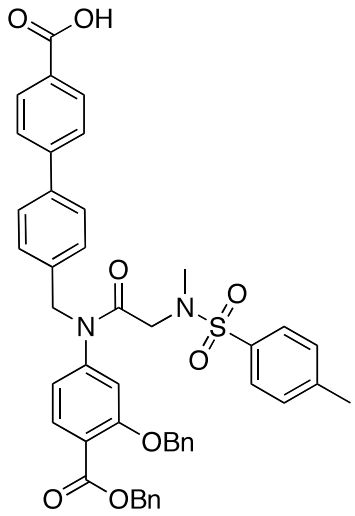
(37b) benzyl 2-(benzyloxy)-4-(*N*-((3'-cyanobiphenyl-4-yl)methyl)-2-(*N*,4-dimethylphenyl-sulfon-amido)acetamido)benzoate. Aryl halide **26a** was coupled to 3-cyanophenylboronic acid to give **37b** on a 0.1 mmol scale *via* General Procedure H (58 mg, 60 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.33 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.78 (s, 2H, CH_2), 4.97 (s, 2H, CH_2), 5.28 (s, 2H, CH_2), 6.60 - 6.62 (m, 2H, CH), 7.14-7.28 (m, 12H, CH), 7.25 - 7.28 (m, 2H, CH), 7.38 (d, J = 8.0 Hz, 2H, CH), 7.44 - 7.49 (m, 1H, CH), 7.54 - 7.57 (m, 3H, CH), 7.71 (dt, J = 7.6 and 1.2 Hz, 1H, CH), 7.76 (s, 1H, CH), 7.78 (s, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 36.0, 51.4, 52.7, 67.0, 70.7, 112.9, 114.0, 118.6, 120.0, 120.9, 127.0, 127.1, 127.4, 128.0, 128.2, 128.2, 128.5, 128.6, 128.7, 129.5, 129.5, 129.6, 130.5, 130.8, 131.2, 133.1, 135.6, 135.7, 136.8, 138.2, 141.7, 143.3, 158.8, 165.2, 167.1, 167.7; LRMS (ES+) Calcd for [$C_{45}H_{39}N_3O_6S$ + H] 750.26 found 750.26.



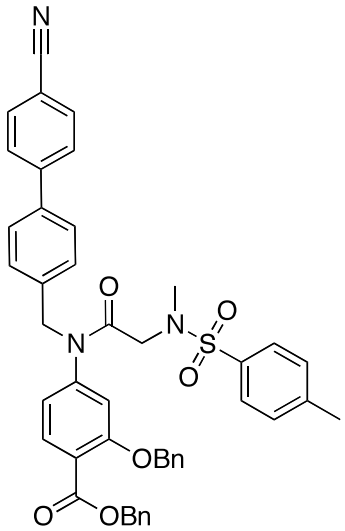
(37c) benzyl 2-(benzyloxy)-4-(*N*-((3'-carbamoylbiphenyl-4-yl)methyl)-2-(*N*,4-dimethyl phenylsulfonamido)acetamido)benzoate. Aryl halide **26a** was coupled to 3-carbamoylphenylboronic acid to give **37c** on a 0.1 mmol scale *via* General Procedure H (57 mg, 52 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.38 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 4.83 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 5.93 (s, 1H, NH_2), 6.33 (s, 2H, NH_2), 6.64 (s, 1H, CH), 6.67 (dd, J = 6.0 and 1.2 Hz, 1H, CH), 7.18 (d, J = 6.0 Hz, 2H, CH), 7.31 - 7.39 (m, 13H, CH), 7.50 (d, J = 6.0 Hz, 2H, CH), 7.60 (d, J = 6.3 Hz, 2H, CH), 7.70 (d, J = 5.7 Hz, 1H, CH), 7.77 (d, J = 5.7 Hz, 1H, CH), 7.83 (d, J = 6.0 Hz, 1H, CH), 8.03 (s, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.3, 35.9, 51.3, 52.7, 66.9, 70.6, 113.9, 119.2, 119.9, 126.0, 126.9, 127.0, 127.2, 127.3, 127.9, 128.1, 128.1, 128.4, 128.4, 128.7, 128.9, 129.2, 129.4, 130.3, 132.3, 133.0, 133.8, 135.1, 135.5, 135.6, 136.0, 139.4, 140.8, 143.3, 144.8, 158.7, 165.2, 167.0, 169.1; LRMS (ES+) Calcd for [$C_{45}H_{41}N_3O_7S$ + H] 768.27 found 768.27.



(37d) Methyl 4'-((*N*-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(*N*,4-dimethylphenyl-sulfonamido)acetamido)methyl)biphenyl-4-carboxylate. Aryl halide **26a** was coupled to 4-(methoxycarbonyl)phenylboronic acid to give **37d** on a 0.1 mmol scale *via* General Procedure H (53 mg, 52 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.39 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 3.93 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.64 (s, 1H, CH), 6.68 (dd, J = 8.4 and 1.2 Hz, 1H, CH), 7.19 (d, J = 8.0 Hz, 2H, CH), 7.23 - 7.34 (m, 8H, CH), 7.37 - 7.40 (m, 2H, CH), 7.50 - 7.54 (m, 3H, CH), 7.60 (d, J = 8.0 Hz, 2H, CH), 7.22 (d, J = 8.4 Hz, 2H, CH), 7.70 (dd, J = 5.6 and 3.2 Hz, 1H, CH), 7.83 (d, J = 8.0 Hz, 1H, CH) 8.09 (d, 2H, J = 8.4 Hz, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 36.0, 51.4, 52.1, 52.8, 67.0, 70.7, 114.1, 120.0, 120.9, 126.8, 126.9, 127.3, 127.4, 128.0, 128.2, 128.2, 128.5, 128.6, 128.7, 129.0, 129.4, 129.5, 130.1, 132.4, 133.1, 135.3, 135.7, 135.7, 136.5, 139.3, 143.3, 144.8, 144.9, 158.8, 166.8, 167.0, 167.7; LRMS (ES+) Calcd for [$C_{46}H_{42}N_2O_8S$ + H] 783.27 found 783.26.

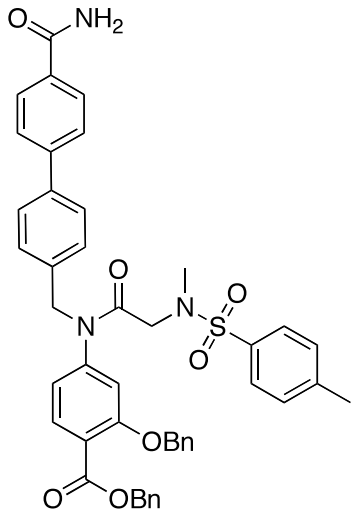


(37e) Methyl 4'-((*N*-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(*N*,4-dimethylphenyl sulfon-amido)acetamido)methyl)biphenyl-4-carboxylate. Aryl halide **26a** was coupled to 4-carboxyphenylboronic acid to give **37e** on a 0.1 mmol scale *via* General Procedure H. **37e** was not purified at this stage and was deprotected without purification.



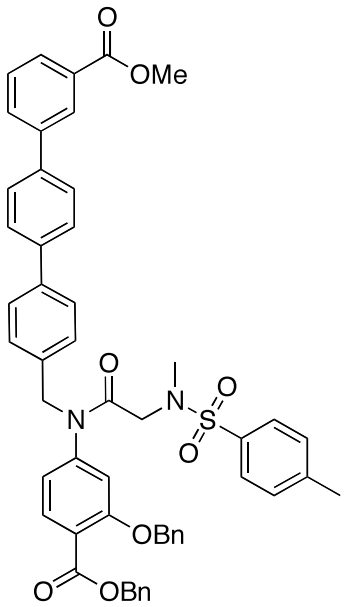
(37f) Benzyl 2-(benzyloxy)-4-(*N*-((4'-cyanobiphenyl-4-yl)methyl)-2-(*N*,4-dimethylphenyl-sulfon-amido)acetamido)benzoate. Aryl halide **26a** was coupled to 4-cyanophenylboronic acid to give **37f** on a 0.1 mmol scale *via* General Procedure H (73 mg, 71 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.39 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 4.85 (s, 2H, CH_2), 5.05 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.67 (s, 1H, CH), 6.69 (d, *J*

= 1.2 Hz, 1H, CH), 7.22 - 7.34 (m, 13H, CH), 7.38 - 7.40 (m, 2H, CH), 7.61 (d, *J* = 8.0 Hz, 2H, CH), 7.64 (d, *J* = 8.4 Hz, 2H, CH), 7.70 - 7.72 (m, 3H, CH), 7.84 (d, *J* = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 36.0, 51.4, 52.7, 67.0, 70.7, 111.0, 114.0, 118.7, 119.9, 120.8, 126.9, 127.3, 127.4, 127.5, 128.0, 128.2, 128.2, 128.5, 128.5, 128.7, 129.5, 130.8, 132.4, 132.5, 133.1, 135.6, 135.7, 137.1, 138.4, 143.3, 144.8, 158.8, 165.2, 167.1, 167.6; LRMS (ES+) Calcd for [$C_{45}H_{39}N_3O_6S$ + H] 750.26 found 750.26.

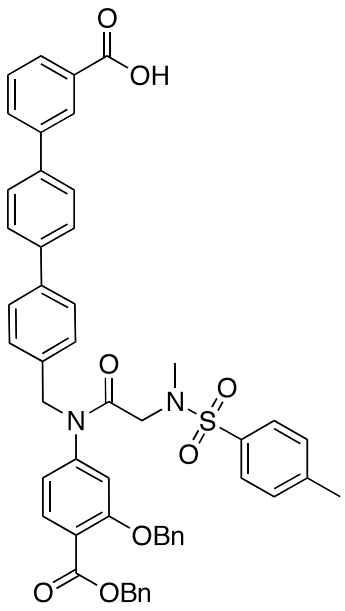


(37g) Benzyl 2-(benzyloxy)-4-(*N*-((4'-carbamoylbiphenyl-4-yl)methyl)-2-(*N*,4-dimethyl phenylsulfonamido)acetamido)benzoate. Aryl halide **26a** was coupled to 4-carbamoylphenylboronic acid to give **37g** on a 0.1 mmol scale *via* General Procedure E (62 mg, 49 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.38 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 4.39 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 5.91 (s, 1H, NH_2), 6.44 (s, 1H, NH), 6.65 (s, 1H, CH_2), 6.68 (d, 1H, CH), 7.19 (d, *J* = 6.0 Hz, 2H, CH), 7.24 - 7.35 (m, 4H, CH), 7.38 - 7.41 (m, 2H, CH), 7.44 - 7.50 (m, 6H, CH), 7.53 (d, *J* = 4.8 Hz, 1H, CH), 7.59 (s, 2H, CH), 7.61 (s, 2H, CH), 7.64 (d, *J* = 5.4 Hz, 2H, CH), 7.68 (d, *J* = 5.4 Hz, 2H, CH) , 7.83 (d, *J* = 6.3 Hz, 1H, CH), 7.89 (d, *J* = 6.0 Hz, 2H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.3, 35.9, 51.3, 52.7, 66.9, 70.6, 113.9, 119.9, 120.8, 126.8, 126.9, 127.1,

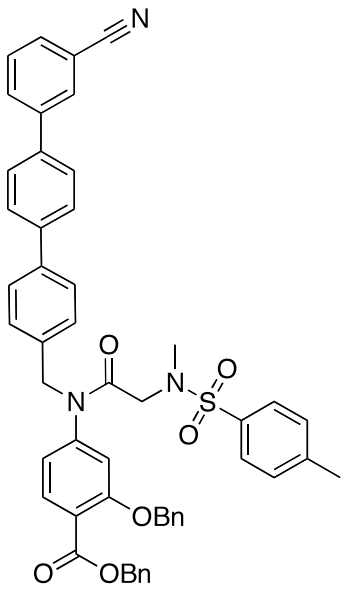
127.3, 127.9, 128.1, 128.1, 128.3, 128.4, 128.4, 129.4, 131.8, 131.8, 131.8, 131.9, 132.0, 132.8, 133.0, 135.1, 135.5, 135.6, 136.3, 139.1, 143.2, 143.8, 144.8, 158.7, 165.2, 167.0, 168.8; LRMS (ES+) Calcd for [$C_{45}H_{41}N_3O_7S$ + H] 768.27 found 768.27.



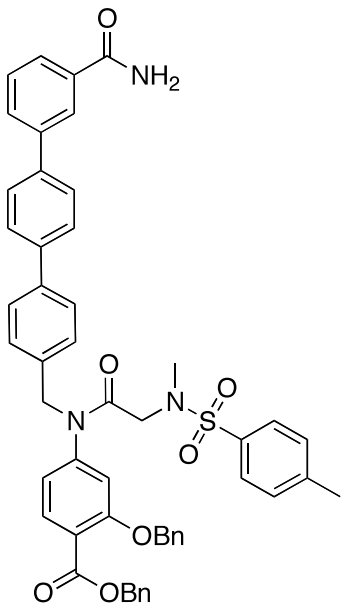
(38a) methyl 4'-((N-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(N,4-dimethylphenyl sulfonamido)acetamido)methyl)terphenyl-3-carboxylate. Aryl halide **26m** was coupled to 3-(methoxycarbonyl)phenylboronic acid on a 0.1 mmol scale *via* General Procedure H to yield **38a** (39 mg, 38 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.40 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 3.96 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.62 (s, 1H, CH), 6.70 (d, J = 8.0 Hz, 1H, CH) 7.19 (d, J = 8.0 Hz, 2H, CH), 7.26-7.34 (m, 10H, CH), 7.38-7.41 (m, 3H, CH), 7.54 (d, J = 8.0 Hz, 2H, CH), 7.62 (d, J = 8.4 Hz, 2H, CH), 7.68 (q, J = 8.0 Hz, 4H, CH), 7.84 (t, J = 8.0 Hz, 2H, CH), 8.03 (d, J = 8.0 Hz, 1H, CH), 8.32 (s, 1H, CH); LRMS (ES+) Calcd for [$C_{52}H_{46}N_2O_8S$ + H] 859.31 found 859.25.



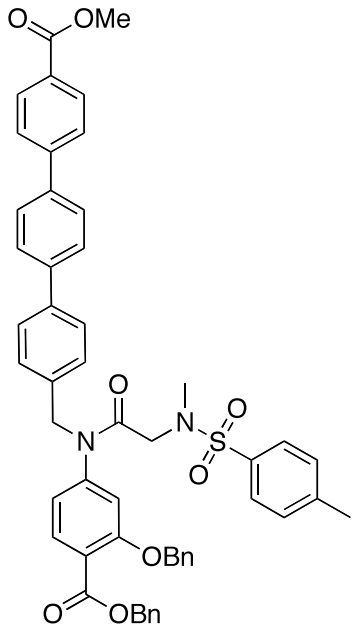
(38b) 4'-((N-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(N,4-dimethylphenylsulfon-amido)acetamido)methyl)terphenyl-3-carboxylic acid. Aryl halide **26m** was coupled to 3-carboxyphenylboronic acid on a 0.1 mmol scale *via* General Procedure H to yield **38b** (76 mg, 64 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.33 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 6.60 (s, 1H, CH), 6.66 (d, J = 8.4 Hz, 2H, CH), 7.15 (d, J = 8.0 Hz, 2H, CH), 7.13 - 7.28 (m, 12H, CH), 7.30 - 7.38 (m, 3H, CH), 7.50 (d, J = 7.2 Hz, 2H, CH), 7.47 - 7.63 (m, 6H, CH), 7.90 (d, J = 8.0 Hz, 2H, CH); LRMS (ES+) Calcd for [$C_{51}H_{44}N_2O_8S$ + H] 845.29 found 845.15.



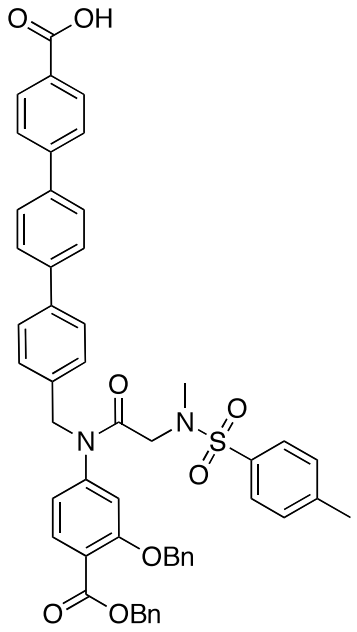
(38c) benzyl 2-(benzyloxy)-4-(N-((3'-Cyanoterphenyl-4-yl)methyl)-2-(N,4-dimethylphenyl sulfonamido)acetamido)benzoate. Aryl halide **26m** was coupled to 3-cyanophenylboronic acid on a 0.1 mmol scale *via* General Procedure H to yield **38c** (59 mg, 56 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.38 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 4.85 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.65 (s, 1H, CH), 6.70 (d, J = 8.0 Hz, 1H, CH), 7.20 (d, J = 8.0 Hz, 2H, CH), 7.23 (t, J = 8.4 Hz, 4H, CH), 7.30-7.34 (m, 6H, CH), 7.38-7.40 (m, 3H, CH), 7.50 (d, J = 8.4 Hz, 2H, CH), 7.60-7.63 (m, 5H, CH), 7.67 (d, J = 8.4 Hz, 2H, CH), 7.81 (d, J = 8.0 Hz, 2H, CH), 7.86 (s, 1H, CH). LRMS (ES+) Calcd for [$C_{51}H_{43}N_3O_6S$ + H] 848.28 found 848.45.



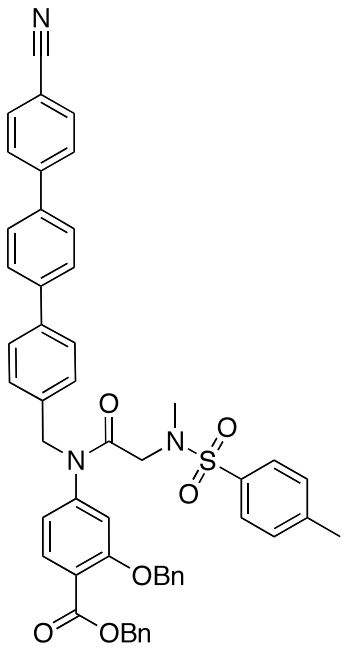
(38d) 4-(N-((3'-carbamoylbiphenyl-4-yl)methyl)-2-(N,4-dimethylphenylsulfonamido)acet-amido)-2-hydroxybenzoic acid. Aryl halide **26m** was coupled to 3-carbamoylphenylboronic acid on a 0.1 mmol scale *via* General Procedure E to give **38d** (38 mg, 32 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.39 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 4.84 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.63 (s, 1H, CH), 6.70 (d, *J* = 8.8 Hz, 1H, CH), 7.19 (d, *J* = 8.0 Hz, 2H, CH), 7.30 - 7.36 (m, 10H, CH), 7.38 - 7.41 (m, 3H, CH), 7.54 (d, *J* = 8.0 Hz, 2H, CH), 7.62 (d, *J* = 8.0 Hz, 2H, CH), 7.67 (q, *J* = 7.2 Hz, 4H, CH), 7.79 (t, 2H, *J* = 7.6 Hz, CH), 7.85 (d, *J* = 8.0 Hz, 1H, CH), 8.12 (s, 1H, CH). LRMS (ES+) Calcd for [$C_{51}H_{45}N_3O_7S$ + Na] 866.29 found 866.51.



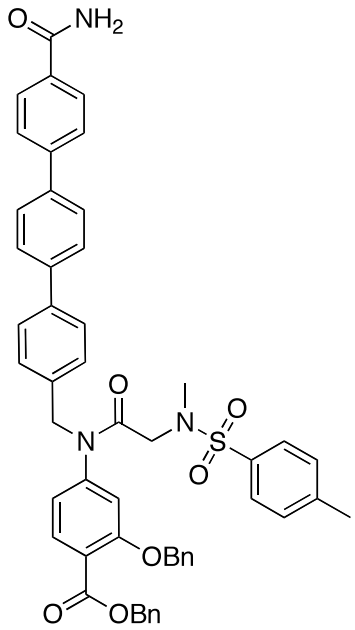
(38e) methyl 4'-((N-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(N,4-dimethyl phenylsulfonamido)acetamido)methyl)terphenyl-4-carboxylate. Aryl halide **26m** was coupled to 4-(methoxycarbonyl)phenylboronic acid to give **38e** on a 0.1 mmol scale *via* General Procedure H (59 mg, 47 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.38 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 3.93 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.64 (s, 1H, CH), 6.70 (dd, J = 8.4 and 1.6 Hz, 1H, CH), 7.20 (d, J = 8.0 Hz, 2H, CH), 7.24 - 7.28 (m, 6H, CH), 7.30 - 7.33 (m, 5H, CH), 7.36 - 7.41 (m, 3H, CH), 7.54 (d, J = 8.4 Hz, 2H, CH), 7.61 (d, J = 8.4 Hz, 2H, CH), 7.64 - 7.73 (m, 6H, CH), 7.85 (d, J = 8.4 Hz, 1H, CH). LRMS (ES+) Calcd for [$C_{52}H_{46}N_2O_8S$ + H] 881.29, found 881.39.



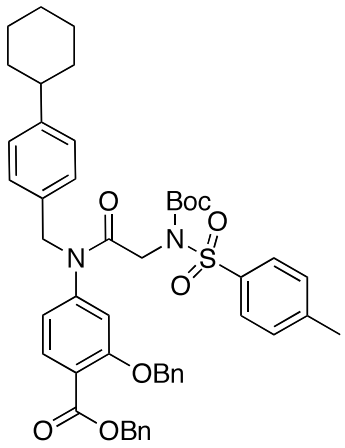
(38f) 4'-((N-(3-(benzyloxy)-4-(benzyloxycarbonyl)phenyl)-2-(N,4-dimethylphenyl-sulfonamido)acetamido)methyl)terphenyl-4-carboxylic acid. Aryl halide **26m** was coupled to 4-carboxyphenylboronic acid to give **38f** on a 0.1 mmol scale *via* General Procedure H (47 mg, 47 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.40 (s, 3H, CH_3), 2.84 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 4.86 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 5.36 (s, 2H, CH_2), 6.65 (s, 1H, CH), 6.71 (d, J = 8.4 Hz, 1H, CH), 7.21 (d, J = 8.0 Hz, 2H, CH), 7.27 - 7.43 (m, 12H, CH), 7.39 - 7.41 (m, 3H, CH), 7.55 (d, J = 8.4 Hz, 2H, CH), 7.63 (d, J = 8.0 Hz, 2H, CH), 7.67 - 7.75 (m, 4H, CH), 7.86 (d, J = 8.0 Hz, 1H, CH), 8.20 (d, J = 7.6 Hz, 1H, CH); LRMS (ES+) Calcd for [$C_{51}H_{44}N_2O_8S$ + H] 845.29 found 845.35.



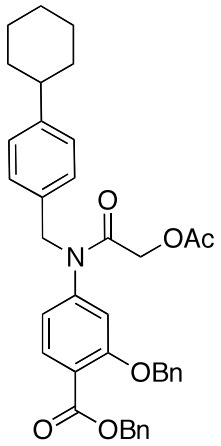
(38g) Benzyl 2-(benzyloxy)-4-(N-((4'-Cyanoterphenyl-4-yl)methyl)-2-(N,4-dimethylphenyl sulfonamido)acetamido)benzoate. Aryl halide **26m** was coupled to 4-cyanophenylboronic acid to give **38h** on a 0.1 mmol scale *via* General Procedure H (32 mg, 30 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.36 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 6.00 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 6.61 (s, 1H, CH), 6.66 (d, *J* = 8.4 Hz, 1H, CH), 7.17 (d, *J* = 8.4 Hz, 2H, CH), 7.23 (t, *J* = 8.0 Hz, 4H, CH), 7.30 - 7.33 (m, 5H, CH), 7.36 - 7.40 (m, 3H, CH), 7.70 (d, *J* = 8.0 Hz, 2H, CH), 7.58 (d, *J* = 8.0 Hz, 2H, CH), 7.66 - 7.73 (m, 8H, CH), 7.81 (d, *J* = 8.4 Hz, 1H, CH). LRMS (ES+) Calcd for [$C_{51}H_{44}N_3O_6S$ + H] 848.28 found 848.35.



(38h) benzyl 2-(benzyloxy)-4-(N-((4'-carbamoylterphenyl-4-yl)methyl)-2-(N,4-dimethyl phenylsulfonamido)acetamido)benzoate. Aryl halide **26m** was coupled to 4-carbamoylphenylboronic acid to give **38h** on a 0.1 mmol scale *via* General Procedure H (31 mg, 28 %): δ_H (400 MHz, *d*-$CDCl_3$) 2.40 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 4.58 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 5.36 (s, 2H, CH_2), 6.64 (s, 1H, CH), 6.70 (d, *J* = 7.6 Hz, 1H, CH), 7.21 (d, *J* = 8.0 Hz, CH), 7.24 - 7.29 (m, 5H, CH), 7.31 - 7.36 (m, 5H, CH), 7.38 - 7.42 (m, 2H, CH), 7.54 (d, *J* = 8.4 Hz, 2H, CH), 7.62 (d, *J* = 8.4 Hz, 2H, CH), 7.65 - 7.76 (m, 8H, CH), 7.85 (d, *J* = 8.0 Hz, 1H, CH). LRMS (ES+) Calcd for [$C_{51}H_{45}N_3O_7S$ + Na] 866.29 found 866.32.

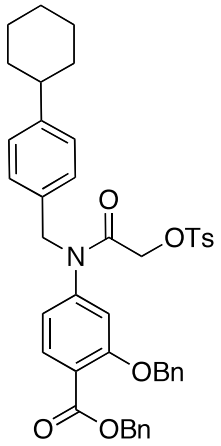


(42) benzyl 2-(benzyloxy)-4-(2-(*N*-(*tert*-butoxycarbonyl)-4-methylphenylsulfonamido)-*N*-(4-cyclohexylbenzyl)acetamido)benzoate. Compound **41** was Boc protected with $(Boc)_2$ *via* General Procedure C on a 0.10 mmol scale to furnish **42** (71 mgs, 89 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.30 (s, 9H, $3CH_3$), 1.31-1.43 (m, 5H, CH_2), 1.68-1.86 (m, 5H, CH_2), 2.42-2.52 (m, 4H, CH_3 and CH), 4.33 (s, 2H, CH_2), 4.85 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.66 (s, 1H, CH), 6.78 (d, J = 8.8 Hz, 1H, CH), 7.07-7.13 (m, 4H, CH), 7.29-7.40 (m, 12H, CH), 7.84 (d, J = 8.8 Hz, 1H, CH), 8.02 (d, J = 8.4 Hz, 2H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.5, 26.0, 26.7, 27.6, 34.3, 44.1, 47.2, 52.8, 66.9, 70.6, 84.4, 114.0, 120.1, 120.7, 126.8, 127.1, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 128.7 (br), 128.9, 133.0, 133.9, 135.5, 135.6, 136.8, 144.0, 145.0, 147.5, 150.5, 158.6, 165.3, 166.5.



(44) benzyl 4-(2-acetoxy-*N*-(4-cyclohexylbenzyl)acetamido)-2-(benzyloxy)benzoate. Primary aniline **19h** was coupled to 2-chloro-2-oxoethyl acetate on a 0.19 mmol scale *via* General Procedure B to furnish **44** (184 mg, 72 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.31 - 1.42 (m, 5H, CH_2), 1.68 - 1.84 (m, 5H, CH_2), 2.40 - 2.50 (m, 1H, CH), 4.28 (s, 2H, CH_2), 4.79

(s, 2H, CH_2), 4.91 (s, 2H, CH_2), 5.27 (s, 3H, CH_3) 5.32 (s, 2H, CH_2), 6.56 (s, 1H, CH), 6.71 (d, J = 8.4 Hz, 1H, CH), 7.05 (d, J = 8.0 Hz, 2H, CH), 7.10 (d, J = 8.0 Hz, 2H, CH), 7.28 - 7.39 (m, 10H, CH), 7.81 (d, J = 8.4 Hz, 1H, CH); LRMS Calcd for $C_{38}H_{39}NO_6$ + H = 606.29, found 606.56.



(45) benzyl 2-(benzyloxy)-4-(*N*-(4-cyclohexylbenzyl)-2-(tosyloxy)acetamido)-benzoate. To a stirred solution of **44** (54 mgs, 0.09 mmol) and DIPEA (25 μL, 1.44 mmol), was added TsCl (20 mgs, 0.10 mmol) and allowed to stir overnight at rt. The reaction was diluted with CH_2Cl_2, washed with 0.1 M HCl, water, brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using silica gel chromatography (hexanes:EtOAc, 1:1) to yield pure **45** (52 mg, 76 %): δ_H (400 MHz, *d*-$CDCl_3$) 1.30 - 1.41 (m, 5H, CH_2), 1.70 - 1.86 (m, 5H, CH_2), 2.39 (s, 3H, CH_3), 2.40 - 2.50 (m, 1H, CH), 4.33 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 4.89 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.46 (s, 1H, CH), 6.61 (d, J = 8.0 Hz, 1H, CH), 7.01 (d, J = 8.0 Hz, 2H, CH), 7.09 (d, J = 8.0 Hz, 2H, CH), 7.27-7.43 (m, 12H, CH), 7.73 (d, J = 8.0 Hz, 2H, CH), 7.79 (d, J = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.5, 25.9, 26.7, 34.3, 44.1, 52.8, 65.3, 66.9, 70.6, 113.8, 119.7, 120.9, 126.9, 127.0, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.9, 129.6, 132.6, 133.1, 133.3, 135.5, 135.6, 144.0, 144.9, 147.8, 158.6, 163.9, 165.2

Characterization of Final Compounds

(8) 2-Hydroxy-4-(2-(tosyloxy)acetamido)benzoic acid (S3I-201). δ_H (400 MHz, d_6-DMSO) 2.39 (s, 2H, CH_3Ar), 4.70 (s, 2H, $COCH_2$), 6.96 (dd, J = 8.6 and 2.0 Hz, 1H, CH (Ar)), 7.21 (d, J = 2.0 Hz, 1H, CH (Ar)), 7.47 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.71 (d, J = 8.6 Hz, 1H, CH (Ar)), 7.83 (d, J = 8.3 Hz, 2H, 2 CH (Ar)), 10.35 (s (br), 1H, OH); δ_C (100 MHz, d_6-DMSO) 21.0, 67.2, 106.2, 108.6, 110.1, 127.7, 130.1, 131.0, 131.9, 144.0, 145.2, 161.9, 163.7, 171.4; HRMS (ES+) calcd for [$C_{16}H_{16}NO_7S$ + H] 366.0660, found 366.0642; HPLC (I) t_R = 19.09 min (98.94 %), (II) t_R = 36.92 min (98.98 %).

(10) 4-(2-(*N*,4-Dimethylphenylsulfonamido)acetamido)-2-hydroxy-benzoic acid. δ_H (400 MHz, d_6-DMSO) 2.40 (s, 3H, CH_3Ar), 2.79 (s, 3H, CH_3N), 3.92 (s, 2H, CH_2CO), 7.00 (dd, J = 8.7 and 2.0 Hz, 1H, CH (Ar)), 7.27 (d, J = 2.0 Hz, 1H, CH (Ar)), 7.43 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.68 (d, J = 8.2 Hz, 2H, 2 CH (Ar)), 7.71 (d, J = 8.6 Hz, 1H, CH (Ar)), 10.20 (s (br), 1H, OH), 11.50 (s (br), 1H, OH); HRMS (ES+) calcd for [$C_{17}H_{19}N_2O_6S$ + H] 379.0963, found 379.0964; HPLC (I) t_R = 18.85 min (99.13 %), (II) t_R = 36.33 min (100 %).

(11) 4-(2-(N-(tert-butoxycarbonyl)-4-methylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, d_6-DMSO) 2.43 (s, 9H, CH_3), 4.58 (s, 2H, CH_2), 7.03 (d, J = 8.4 Hz, 1H, CH), 7.28 (s, 1H, CH), 7.47 (d, J = 8.0 Hz, 2H, CH), 7.73 (d, J = 8.4 Hz, 2H, CH), 7.94 (d, J = 8.4 Hz, 2H, CH), 10.48 (s, 1H, COOH); δ_C (100 MHz, d_6-DMSO) 23.5, 27.1, 47.5, 84.8, 106.6, 108.3, 110.3, 128.3, 128.5, 128.9, 131.1, 136.4,

144.5, 150.5, 162.4, 166.7, 171.6; HRMS (ES+) calcd for [$C_{21}H_{24}N_2O_8S$ + H] 465.1326, found 465.1307; HPLC (III) t_R = 15.57 min (68.82 %), (IV) t_R = 24.49 min (70.38 %).

(12) 4-(*N*-Benzyl-2-(tosyloxy)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.40 (s, 3H, CH_3Ar), 4.59 (s, 2H, CH_2O), 4.82 (s, 2H, CH_2Ar), 6.64 (dd, J = 8.2 and 1.6 Hz, 1H, CH (Ar)), 6.74 (d, J = 1.6 Hz, 1H, CH (Ar)), 7.13 (d, J = 7.0 Hz, 2H, 2 CH (Ar)), 7.20-7.30 (m, 3H, 3 CH (Ar)), 7.42 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.69 (d, J = 8.2 Hz, 2H (Ar)); δ_C (100 MHz, d_6-DMSO) 21.4, 52.0, 66.4, 111.8, 116.9, 118.0, 127.6, 127.9, 128.0, 128.3, 128.6, 130.3, 131.6, 132.2, 136.8, 145.5, 162.2, 164.2, 171.3; HRMS (ES+) calcd for [$C_{23}H_{22}NO_7S$ + H] 456.1125, found 456.1111; HPLC (I) t_R = 21.02 min (97.43 %), (II) t_R = 42.65 min (97.93%).

(13) 4-(*N*-Benzyl-2-(4-methylphenylsulfonamido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.37 (s, 3H, Ar-CH_3), 3.55 (d, J = 5.5 Hz, 2H, CH_2NH), 4.78 (s, 2H, CH_2Ar), 6.67 (dd, J = 8.2 and 2.0 Hz, 1H, CH (Ar)), 6.76 (d, J = 2.0 Hz, 1H (Ar)), 7.06 - 7.09 (m, 2H, 2 CH (Ar)), 7.19 - 7.28 (m, 3H, 3 CH (Ar)), 7.34 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.58 (d, J = 8.2 Hz, 2H, 2 CH (Ar)), 7.72 (d, J = 8.4 Hz, 1H, CH (Ar)), 7.88 (t, J = 5.9 Hz, 1H, NH), 11.40 (s (br), 1H, OH); HRMS (ES+) calcd for [$C_{23}H_{23}N_2O_6S$ + H] 455.1284, found 455.1271; HPLC (I) t_R = 19.74 min (97.32 %), (II) t_R = 39.35 min (99.31%).

(14) 4-(*N*-Benzyl-2-(*N*,4-dimethylphenylsulfonamido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.37 (s, 3H, CH_3Ar), 2.78 (s, 3H, CH_3N), 3.86 (s, 2H, CH_2CO), 4.84 (s, 2H, CH_2Ph), 6.77 (dd, J = 8.4 and 2.0 Hz, 1H, CH (Ar)), 6.86 (d, J =

2.0 Hz, 1H, CH (Ar)), 7.16 (d, *J* = 8.4 Hz, 2H, 2 CH (Ar)), 7.21 - 7.32 (m, 3H, 3 CH (Ar)), 7.36 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.53 (d, *J* = 8.4 Hz, 2H, 2 CH (Ar)), 7.75 (d, *J* = 8.4 Hz, 1H, CH (Ar)), 11.38 (s (br), 1H, OH); HRMS (ES+) calcd for [$C_{24}H_{24}N_2O_6S$ + H] 469.1431, found 469.1427; HPLC (I) t_R = 20.72 min (99.80 %), (II) t_R = 42.17 min (98.62 %).

(15) 4-(*N*-Benzyl-2-(*N*-(*tert*-butoxycarbonyl)-4-methylphenyl-sulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, $CDCl_3$) 1.31 (s, 9H, 3(CH_3)), 2.41 (s, 3H, CH_3Ar), 4.47 (s, 2H, $COCH_2$), 4.95 (s, 2H, CH_2Ar), 6.69 (d, *J* = 8.4 Hz, 1H, CH (Ar)), 6.81 (s, 1H, CH (Ar)), 7.20 - 7.32 (m, 7H, CH (Ar)), 7.87 (d, *J* = 8.4 Hz, 1H, CH (Ar)), 8.00 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 10.68 (s (br), 1H, OH); δ_C (100 MHz, $CDCl_3$) 21.6, 27.7, 47.4, 53.3, 84.8, 111.6, 117.2, 119.2, 127.7, 128.4, 128.5, 128.7, 129.0, 132.3, 136.2, 136.6, 144.2, 147.7, 150.6, 162.9, 166.8, 172.6; HRMS (ES+) calcd for [$C_{28}H_{31}N_2O_8S$ + H] 557.1615, found 577.1615; HPLC (I) t_R = 21.67 min (99.02%), (II) t_R = 46.05 min (98.14%).

(27a) 4-(*N*-(4-Bromobenzyl)-2-(*N*,4-dimethylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, $CDCl_3$) 2.37 (s, 3H, CH_3Ar), 2.81 (s, 3H, CH_3N), 3.75 (s, 2H, CH_2CO), 4.73 (s, 2H, CH_2Ph), 6.49 (d, *J* = 7.2 Hz, 1H, CH (Ar)), 6.61 (s, 1H, CH (Ar)), 6.99 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.22 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.35 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.58 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.83 (d, *J* = 7.6 Hz, 1H, CH (Ar)), 11.40 (s (br), 1H, OH); HRMS (ES+) calcd for [$C_{24}H_{24}Br$-N_2O_6S + H] 547.0545, found 547.0532; HPLC (I) t_R = 20.28 min (98.2 %), (II) t_R = 42.13 min (97.3 %).

(27b) 4-(*N*-(3-Bromobenzyl)-2-(*N*,4-dimethylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, $CDCl_3$) 2.40 (s, 3H, CH_3Ar), 2.86 (s, 3H, CH_3N), 3.86 (s, 2H, CH_2CO), 4.82 (s, 2H, CH_2Ph), 6.61 (d, *J* = 8.0 Hz, 1H, CH (Ar)), 6.72 (s, 1H, CH (Ar)), 7.08 (d, *J* = 7.7 Hz, 1H, CH (Ar)), 7.15 (t, *J* = 7.7 Hz, 1H, CH (Ar)), 7.27 - 7.36 (m, 3H, 3 CH (Ar)), 7.39 (d, *J* = 7.7 Hz, 1H, CH (Ar)), 7.65 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.91 (d, *J* = 8.2 Hz, 1H, CH (Ar)), 9.80 (s (br), 1H, OH), 10.68 (s (br), 1H, OH); δ_C (100 MHz, $CDCl_3$) 21.5, 35.9, 51.6, 52.6, 111.8, 116.9, 119.0, 122.6, 127.1, 127.5, 129.5, 130.1, 131.0, 131.4, 132.5, 135.0, 138.4, 143.5, 147.4, 163.0, 167.3, 172.6; HRMS (ES+) calcd for [$C_{24}H_{24}BrN_2O_6S$ + H] 547.0542, found 547.0532; HPLC (I) t_R = 20.08 min (98.1%), (II) t_R = 41.53 min (98.4%).

(27c) 4-(*N*-(4-Cyanobenzyl)-2-(*N*,4-dimethylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, $CDCl_3$) 2.40 (s, 3H, CH_3Ar), 2.84 (s, 3H, CH_3N), 3.82 (s, 2H, CH_2CO), 4.88 (s, 2H, CH_2Ph), 6.56 (dd, *J* = 8.2 and 1.6 Hz, 1H, CH (Ar)), 6.67 (d, *J* = 2.0 Hz, 1H, CH (Ar)), 7.26 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.29 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.57 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.62 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.88 (d, *J* = 8.2 Hz, 1H, CH (Ar)), 11.20 (s (br), 1H, OH); δ_C (100 MHz, $CDCl_3$) 21.5, 36.0, 51.5, 52.9, 111.6, 112.7, 116.5, 118.5, 118.6, 127.4, 129.1, 129.5, 132.4(2), 135.0, 141.7, 143.5, 146.6, 164.9, 165.7, 167.4; HRMS (ES+) calcd for [$C_{25}H_{24}N_3O_6S$ + H] 494.1391, found 494.1386; HPLC (I) t_R = 22.94 min (100%), (II) t_R = 47.70 min (96.6 %).

(27d) 4-(*N*-(3-Cyanobenzyl)-2-(*N*,4-dimethylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, $CDCl_3$) 2.39 (s, 3H, CH_3Ar), 2.85 (s, 3H, CH_3N), 3.84 (s, 2H, CH_2CO), 4.86 (s, 2H, CH_2Ph), 6.58 (d, *J* = 8.0 and 1.6 Hz, 1H, CH (Ar)),

6.68 (d, J = 2.0 Hz, 1H, CH (Ar)), 7.27 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.38 - 7.48 (m, 3H, 3 CH (Ar)), 7.56 (d, J = 7.3 Hz, 1H, CH (Ar)), 7.63 (d, J = 8.2 Hz, 2H, 2 CH (Ar)), 7.92 (d, J = 8.2 Hz, 1H, CH (Ar)), 11.02 (s (br), 1H, OH); δ_C (100 MHz, $CDCl_3$) 21.3, 35.9, 51.5, 52.5, 112.5, 112.8, 116.6, 118.3, 118.5, 127.4, 129.4, 129.5, 131.5, 132.0, 132.5, 133.0, 135.0, 137.9, 143.5, 146.5, 163.0, 167.5, 171.6; HRMS (ES+) calcd for [$C_{25}H_{24}N_3O_6S$ + H] 494.1384, found 494.1380; HPLC (I) t_R = 19.98 min (98.26 %), (II) t_R = 40.60 min (98.40 %).

(27e) 4-(N-(cyclohexylmethyl)-2-(N,4-dimethylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, d_6-DMSO) 1.02 - 1.11 (m, 3H, CH_2), 1.19 - 2.26 (m, 2H, CH_2), 1.53 – 1.64 (m, 6H, CH_2 and CH), 2.35 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.45 (d, J = 7.2 Hz, 2H, CH_2), 3.74 (s, 2H, CH_2), 5.73 (s, 2H, CH_20, 6.83 (d, J = 8.4 Hz, 1H, CH), 6.91 (s, 1H, CH), 7.33 (d, J = 8.0 Hz, 2H, CH), 7.52 (d, J = 8.4 Hz, 2H, CH), 7.82 (d, J = 8.4 Hz, 1H, CH); δ_C (100 MHz, d_6-DMSO) 20.9, 25.2, 25.9, 30.0, 35.6, 35.8, 50.9, 54.1, 112.6, 116.2, 118.7, 126.9, 129.6, 131.5, 135.1, 143.0, 147.4, 161.8, 166.3, 171.2; HRMS (ES+) calcd for [$C_{24}H_{30}N_2O_6S$ + H] 475.1897, found 475.1905; HPLC (III) t_R = 18.62 min (90.58 %), (IV) t_R = 40.70 min (90.17 %).

(27f) 4-(*N*-(4-*tert*-Butylbenzyl)-2-(*N*,4-dimethylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, $CDCl_3$) 1.29 (s, 9H, 3(CH_3)), 2.39 (s, 3H, CH_3Ar), 2.87 (s, 3H, CH_3N), 3.87 (s, 2H, $COCH_2$), 4.84 (s, 2H, CH_2Ar), 6.63 (d of d, J = 8.2 and 1.6 Hz, 1H, CH (Ar)), 6.72 (d, J = 2.0 Hz, 1H, CH (Ar)), 7.08 (d, J = 8.2 Hz, 2H, 2 CH (Ar)), 7.25-7.31 (m, 4H, 4 CH (Ar)), 7.65 (d, J = 8.4 Hz, 2H, 2 CH (Ar)), 7.89 (d, J = 8.4 Hz, 1H, CH (Ar)), 10.70 (s (br), 1H, OH); δ_C (100 MHz, $CDCl_3$) 21.5, 31.2, 34.5, 35.9,

51.6, 53.0, 111.6, 116.9, 119.1, 125.4, 127.5, 128.1, 129.5, 132.3, 133.0, 135.0, 143.5, 147.8, 150.7, 162.9, 167.2, 172.4; HRMS (ES+) calcd for [$C_{28}H_{33}N_2O_6S$ + H] 525.2033, found 525.2053; HPLC (I) t_R = 22.38 min (98.2 %), (II) t_R = 47.7 min (99.3%).

(27g) 4-(*N*-(Biphenyl-4-ylmethyl)-2-(*N*,4-dimethylphenylsulfon-amido)acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, d_6-DMSO) 2.36 (s, 3H, CH_3Ar), 2.80 (s, 3H, CH_3N), 3.83 (s, 2H, $COCH_2$), 4.82 (s, 2H, CH_2Ar), 6.52 (d, J = 8.0 Hz, 1H, CH (Ar)), 6.59 (s, 1H, CH (Ar)), 7.25 (d, J = 8.4 Hz, 2H, 2 CH (Ar)), 7.32 - 7.37 (m, 3H, 3 CH (Ar)), 7.44 (t, J = 7.3 Hz, 2H, 2 CH (Ar)), 7.55 (d, J = 8.3 Hz, 2H, 2 CH (Ar)), 7.59 (d, J = 8.3 Hz, 2H, 2 CH (Ar)), 7.60 - 7.68 (m, 3H, 3 CH (Ar)); δ_C (100 MHz, d_6-DMSO) 20.4, 35.3, 50.9, 52.2, 112.6, 116.0, 118.1, 126.3, 126.5, 126.7, 126.8, 128.3, 129.0, 131.6, 134.3, 134.8, 139.9, 140.0, 143.2, 146.0, 162.0, 166.9, 170.8; HRMS (ES+) calcd for [$C_{30}H_{29}N_2O_6S$ + H] 545.1729, found 545.1740; HPLC (I) t_R = 21.67 min (99.02 %), (II) t_R = 46.05 min (98.14%).

(27h) 4-(*N*-(4-Cyclohexylbenzyl)-2-(*N*,4-dimethylphenylsulfon-amido)acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, d_6-DMSO) 1.14 - 1.40 (m, 5H, CH_2), 1.64 - 1.81 (m, 5H, CH_2), 2.36 (s, 3H, CH_3Ar), 2.44 (s (br), 1H, CH), 2.77 (s, 3H, NCH_3), 3.86 (s, 2H, $COCH_2$), 4.79 (s, 2H, CH_2Ar), 6.79 (d, J = 8.6 Hz, 1H, CH (Ar)), 6.86 (s (br), 1H, CH (Ar)), 7.06 (d, J = 7.8 Hz, 2H, 2 CH (Ar)), 7.13 (d, J = 7.8 Hz, 2H, 2 CH (Ar)), 7.35 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.54 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.77 (d, J = 8.3 Hz, 1H, CH (Ar)), 11.30 (s (br), 1H, OH); δ_C (100 MHz, d_6-DMSO) 21.2, 25.1(2), 26.6, 34.2, 36.1, 42.3, 43.6, 51.2, 51.9, 112.7, 116.3, 118.9, 126.9, 127.2, 127.8, 129.9, 131.6, 134.5, 135.3, 143.4, 146.8, 147.3, 161.8, 167.0, 171.5; HRMS (ES+) calcd for [$C_{30}H_{35}N_2O_6S$ +

H] 551.2223, found 551.2210; HPLC (I) t_R = 24.35 min (98.11 %), (II) t_R = 52.80 min (98.16%).

(27i) 4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-(naphthalen-2-yl-methyl)acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, d_6-DMSO) 2.33 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 5.00 (s, 2H, CH_2), 6.79, (d, J = 8.4 Hz, 1H, CH), 6.90 (s, 1H, CH),7.32 -7.38 (m, 3H, CH), 7.45 - 7.52 (m, 2H, CH), 7.54 (d, J = 8.0 Hz, 2H, CH), 7.65 (s, 1H, CH), 7.73 (d, J = 8.0 Hz, 1H, CH), 7.80 - 7.85 (m, 1H, CH), 7.85 (d, J = 8.4 Hz, 2H, CH); δ_C (100 MHz, d_6-DMSO) 21.3, 36.2, 51.3, 52.3, 112.9, 116.5, 119.0, 126.2, 126.5, 126.6, 127.3, 127.8, 127.9, 128.4, 129.9, 131.7, 132.5, 133.1, 134.8, 135.4, 143.6, 147.2, 161.9, 167.2, 171.4; HRMS (ES+) calcd for [$C_{28}H_{27}N_2O_6S$ + H] 519.1584, found 519.1608; HPLC (I) t_R = 21.86 min (99.53 %), (II) t_R = 45.92 min (99.38 %).

(27ja) 4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-(piperidin-4-ylmethyl)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 1.20 - 1.37 (m, 2H, CH_2), 1.61 - 1.80 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.71 - 2.73 (m, 4H, CH_3 and CH), 2.77 (t, J = 12.0 Hz, 2H, CH_2), 3.24 (d, J = 10.4 Hz, 2H, CH_2), 3.48 (d, J = 6.8 Hz, 2H, CH_2), 3.71 (s, 2H, CH_2), 6.55 (d of d, J = 8.4 and 2.0 Hz, 1H, CH), 6.63 (d, J = 2.0 Hz, 1H, CH), 7.32 (d, J = 8.0 Hz, 2H, CH), 7.51 (d, J = 8.0 Hz, 2H, CH), 7.73 (d, J = 8.0 Hz, 1H, CH); δ_C (100 MHz, d-$CDCl_3$) 21.3, 26.4, 32.2, 39.2, 43.0, 48.9, 51.0, 53.1, 115.6, 115.8, 120.2, 127.2, 129.9, 131.4, 131.4, 135.6, 143.4, 143.9, 164.3, 167.0, 171.3; HRMS (ES+) calcd for [$C_{23}H_{29}N_3O_6S$ + H] 476.1849, found 476.1850; HPLC (I) t_R = 14.74 min (98.61 %), (II) t_R = 26.80 min (100 %).

(27jb) 4-(*N*-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-2-(*N*,4-dimethylphenyl-sulfon amido) acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*-$CDCl_3$) 1.44 (s, 9H, 3 CH_3), 1.58 - 1.78 (m, 2H, CH_2), 2.39 (s, 3H, CH_3Ar), 2.63 - 2.70 (m, 2H, CH_2), 2.82 (s, 4H, CH_3 and CH), 3.59 (s (br), 2H, CH_2), 3.81 (s, 2H, CH_2), 4.06 (s br, 2H, CH_2), 6.75 (d, *J* = 8.2 Hz, 1H, CH (Ar)), 6.81 (br s, 1H, CH (Ar)), 7.26 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.63 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.98 (d, *J* = 8.3 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 28.4, 29.6, 34.6, 35.9, 51.5, 54.8, 80.0, 112.2, 116.5, 118.5, 127.4, 129.5, 132.5, 135.1, 143.4, 147.8, 155.0, 163.0, 167.4, 171.9; HRMS (ES+) calcd for [$C_{28}H_{37}N_3O_8S$ + Na] 598.2193, found 598.2177; HPLC (I) t_R = 19.33 min (98.24 %), (II) t_R = 39.65 min (97.61 %).

(27jc) 4-(*N*-((1-(4-cyanophenyl)piperidin-4-yl)methyl)-2-(*N*,4-di-methylphenyl sulfonamido) acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*-$CDCl_3$) 1.25 - 1.41 (m, 2H, CH_2), 1.70 - 1.89 (m, 2H, CH_2), 2.39 (s, 3H, CH_3Ar), 2.80 - 2.90 (m, 6H, CH, CH_2 and CH_3), 3.65 (d, *J* = 6.7 Hz, 2H, CH_2CH), 3.59 - 3.91 (m, 4H, CH_2), 6.77 - 6.90 (m, 4H, 4 CH (Ar)), 7.27 (d, *J* = 8.6 Hz, 2H, 2 CH (Ar)), 7.45 (d, *J* = 8.6 Hz, 2H, 2 CH (Ar)), 7.63 (d, *J* = 8.6 Hz, 2H, 2 CH (Ar)), 8.00 (d, *J* = 8.2 Hz, 1H, CH (Ar)); δ_C (100 MHz, *d*-$CDCl_3$) 21.5, 28.9, 34.5, 36.0, 47.3, 51.7, 54.7, 99.3, 111.9, 114.3, 116.7, 118.7, 120.0, 127.4, 129.5, 132.6, 133.5, 134.9, 143.5, 148.0, 153.0, 163.1, 167.6, 172.2; HRMS (ES+) calcd for [$C_{30}H_{32}N_4O_6S$ + H] 577.2115, found 477.2093; HPLC (I) t_R = 20.91 min (98.25 %), (II) t_R = 43.52 min (98.91 %).

(27jd) 4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-((1-(pyrimidin-2-yl)piperidin-4-yl)methyl) acetamido)-2-hydroxybenzoic acid: δ_H (400 MHz, *d*$_6$-DMSO) 1.60 - 1.73

(m, 3H, CH_2), 2.34 (s, 3H, CH_3Ar), 2.46 - 2.48 (m, 2H, CH_2), 2.74 (s, 3H, CH_3N), 2.80 (t, *J* = 12.0 Hz, 1H, CH_2), 3.52 (d, *J* = 7.0 Hz, 2H, CH_2CH), 3.79 (s, 2H, CH_2), 4.57 (d, *J* = 13.0 Hz, 2H, CH_2), 6.57 (*t*, *J* = 4.7 Hz, 1H, CH (Ar)), 6.93 (dd, *J* = 8.4 and 2.0 Hz, 1H, CH (Ar)), 7.02 (d, *J* = 2.0 Hz, 1H, CH (Ar)), 7.35 (d, *J* = 8.4 Hz, 2H, 2 CH (Ar)), 7.55 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.86 (d, *J* = 8.4 Hz, 1H, CH (Ar)), 8.32 (d, *J* = 4.7 Hz, 2H, 2 CH (Ar)); δ_C (100 MHz, *d*$_6$-DMSO) 21.4, 29.6, 35.9, 44.1, 51.5, 53.3, 54.9, 109.3, 113.4, 116.3, 118.4, 127.4, 129.5, 132.5, 135.2, 143.4, 147.4, 157.6, 159.9, 163.0, 167.4, 172.3; HRMS (ES+) calcd for [$C_{27}H_{31}N_5O_6S$ + H] 554.2067, found 554.2058; HPLC (I) t_R = 23.04 min (100.00%), (II) t_R = 31.37 min (98.54 %).

(27ka) 4-(2-(N,4-dimethylphenylsulfonamido)-N-(4-(1-(2,2,2-tri-fluoroacetyl) piperidin-4-yl)benzyl)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*$_6$-DMSO) 1.61 - 1.75 (m, 2H, CH_2), 1.96 - 2.00 (m, 2H, CH_2) 2.40 (s, 3H, CH_3), 2.82-2.87 (m, 5H, CH_3 and CH_2), 3.25 (t, *J* = 12.4 Hz, 1H, CH_2), 3.84 (s, 2H, CH_2), 4.13 (d, *J* = 12.4 Hz, 1H, CH_2), 4.69 (d, *J* = 13.2 Hz, 1H, CH_2), 4.84 (s, 2H, CH_2), 6.61 (d, *J* = 8.4 Hz, 1H, CH), 6.69 (s, 1H, CH), 7.09 - 7.15 (m, 4H, CH), 7.27 (d, *J* = 7.2 Hz, 2H, CH), 7.64 (d, *J* = 8.4 Hz, 2H, CH), 7.89 (d, *J* = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 32.4, 33.4, 35.8, 41.8, 44.1, 46.2, 51.5, 52.8, 53.3, 115.0, 116.8, 118.9, 126.8, 127.4, 128.8, 129.4, 132.2, 134.6, 134.8, 143.4, 143.7, 147.3, 155.2, 155.6, 162.8, 167.1, 172.0; HRMS (ES+) calcd for [$C_{31}H_{32}N_3O_7S$ + H] 648.1985, found 648.1974; HPLC (I) t_R = 21.52 min (95.85 %), (II) t_R = 45.49 min (97.12 %).

(27kb) 4-(2-(N,4-dimethylphenylsulfonamido)-N-(4-(piperidin-4-yl)benzyl)aceta-mido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*$_6$-DMSO) 1.63 - 1.78 (m, 2H, CH_2), 1.86

- 2.40 (m, 2H, CH_2), 2.29 - 2.33 (m, 1H, CH), 2.34 (s, 3H, CH_3), 2.73 - 2.80 (m, 5H, CH_3 and CH_2), 2.90 - 3.02 (m, 2H, CH_2), 3.81 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 6.63 (d, J = 7.2 Hz, 1H, CH), 6.69 (s, 1H, CH), 7.12 (s (br), 4H, CH), 7.33 (d, J = 8.0 Hz, 2H, CH), 7.51 (d, J = 8.0 Hz, 2H, CH), 7.70 (d, J = 8.0 Hz, 1H, CH); HRMS (ES+) calcd for [$C_{29}H_{33}N_3O_6S$ + H] 552.2162, found 552.2149; HPLC (III) t_R = 17.99 min (71.92 %), (IV) t_R = 35.58 min (71.04 %).

(27kc) 4-(N-(4-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzyl)-2-(N,4-dimethyl phenylsulfon-amido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 1.38 - 1.39 (m, 2H, CH_2), 1.39 (s, 9H, CH_3), 1.69 (s, 2H, CH_2), 1.72 (s, 1H, CH_2), 2.36 (s (br), 2H, CH_2), 2.75 - 2.79 (m, 5H, CH_3 and CH_2), 4.05 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 6.79 (dd, J = 8.4 and 2.0 Hz, 1H, CH), 6.87 (d, J = 2.0 Hz, 1H, CH), 7.08 (d, J = 8.0 Hz, 2H, CH), 7.15 (d, J = 8.4 Hz, 2H, CH), 7.35 (d, J = 8.0 Hz, 2H, CH), 7.54 (d, J = 8.4 Hz, 2H, CH), 7.77 (d, J = 8.4 Hz, 1H, CH); δ_C (100 MHz, d-$CDCl_3$), 21.4, 28.3, 29.5, 29.8, 30.2, 32.9, 35.8, 42.1, 44.3, 51.4, 52.8, 79.9, 114.2, 116.6, 118.7, 126.8, 127.4, 128.6, 129.4, 132.1, 134.2, 135.1, 143.3, 145.0, 146.8, 155.0, 162.7, 166.9, 171.9; HRMS (ES+) calcd for [$C_{34}H_{41}N_3O_8S$ + H] 652.2687, found 652.2658; HPLC (I) t_R = 23.65 min (66.51 %), (II) t_R = 50.00 min (74.40 %).

(27kd) 4-(N-(4-(1-(4-cyanophenyl)piperidin-4-yl)benzyl)-2-(N,4-di-methylphenyl-sulfonamido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 1.56 - 1.68 (m, 2H, CH_2), 1.80 - 1.83 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.74 - 2.75 (m, 1H, CH), 2.52 - 2.53 (m, 2H, CH_2), 2.77 (s, 3H, CH_3), 2.88 - 2.98 (m, 2H, CH_2), 3.86 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 6.79 (dd, J = 8.0 and 2.0 Hz, 1H, CH), 6.87 (d, J = 2.0 Hz, 1H, CH), 7.03

(d, J = 7.2 Hz, 2H, CH), 7.09 (d, J = 8.0 Hz, 2H, CH), 7.17 (d, J = 8.0 Hz, 2H, CH), 7.35 (d, J = 8.0 Hz, 2H, CH), 7.53 - 7.56 (m, 4H, CH), 7.77 (d, J = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 29.5, 32.4, 35.8, 41.9, 48.2, 51.5, 52.9, 99.4, 114.3, 116.8, 118.9, 126.8, 127.4, 128.6, 129.4, 133.4, 134.3, 134.9, 143.4, 144.8, 147.4, 153.2, 162.8, 165.6, 171.8 ; LRMS (ES+) calcd for [$C_{36}H_{36}N_4O_6S$ + H] 653.24, found 653.46 [M+H]; HPLC (I) t_R = 23.32 min (99.22%), (II) t_R = 49.33 min (99.66 %).

(27ke) 4-(2-(N,4-dimethylphenylsulfonamido)-N-(4-(1-(pyrimidin-2-yl)piperidin-4-yl) benzyl)-acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*-$CDCl_3$) 1.65 - 1.67 (m, 2H, CH_2), 1.91 - 2.03 (m, 2H, CH_2), 2.30 - 2.32 (m, 1H, CH), 2.39 (s, 3H, CH_3), 2.76 - 2.79 (m, 2H, CH_2), 2.85 (s, 3H, CH_3), 2.97 - 3.05 (m, 2H, CH_2), 3.83 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 6.48 - 6.59 (m, 2H, CH), 6.68 (s, 1H, CH), 7.04 - 7.14 (m, 4H, CH), 7.28 (d, J = 7.2 Hz, 2H, CH), 7.65 (d, J = 7.2 Hz, 2H, CH), 7.85 (s, 1H, CH), 8.39 - 8.50 (m, 3H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.5, 32.7, 35.9, 41.9, 45.8, 51.8, 53.1, 109.0, 112.4, 116.8, 119.0, 122.8, 126.9, 127.6, 129.0, 129.5, 132.1, 134.8, 135.3, 137.6, 143.5, 144.0, 152.2, 157.0, 159.2, 161.5, 167.0, 171.5; HRMS (ES+) calcd for [$C_{33}H_{35}N_5O_6S$ + H] 630.2380, found 630.2379; HPLC (I) t_R = 18.68 min (100 %), (II) t_R = 37.21 min (95.91 %).

(27kf) 4-(N-(4-(1-(4-cyanobenzoyl)piperidin-4-yl)benzyl)-2-(N,4-di-methylphenyl sulfonamido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*-$CDCl_3$) 1.60 - 2.03 (m, 4H, CH_2), 2.39 (s, 3H, CH_3), 2.73 - 2.96 (m, 5H, CH_2 and CH_3), 3.11 - 3.25 (m, 1H, CH), 3.72 (d, J = 8.0 Hz, 2H, CH_2), 3.82 (s, 2H, CH_2), 4.82 (s, 2H, CH_2), 6.58 (d, J = 8.0 Hz, 1H, CH), 7.11 (s br, 4H, CH), 7.26 (d, J = 8.0 Hz, 2H, CH), 7.55 (d, J = 7.6 Hz, 2H,

CH), 7.64 (d, J = 8.0 Hz, 2H, CH), 7.73 (d, J = 8.4 Hz, 2H, CH), 7.85 (d, J = 7.6 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.4, 29.5, 32.5, 33.7, 35.8, 42.0, 43.0, 48.3, 51.5, 52.8, 113.5, 116.8, 117.9, 118.8, 126.7, 127.4, 127.5, 128.7, 129.4, 132.1, 132.4, 134.7, 135.0, 139.9, 143.4, 147.2, 162.7, 167.0, 168.6, 170.2; HRMS (ES+) calcd for [$C_{37}H_{36}N_4O_7S$ + H] 681.2377, found 681.2365; HPLC (I) t_R = 20.49 min (99.75 %), (II) t_R = 42.05 min (100 %).

(27kg) 4-(N-(4-(1-((4-cyanophenyl)sulfonyl)piperidin-4-yl)benzyl)-2-(N,4-dimethyl phenylsulfonamido)acetamido)-2-hydroxy-benzoic acid. δ_H (400 MHz, d_6-DMSO) 2.00 - 2.24 (m, 4H, CH_2), 2.66 - 2.78 (m, 6H, CH_3, CH and CH_2), 3.15 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 4.24 - 4.27 (m, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.88 (d, J = 8.0 Hz, 1H, CH), 6.97 (s, 1H, CH), 7.44 (d, J = 8.0 Hz, 2H, CH), 7.40 (d, J = 8.0 Hz, 2H, CH), 7.57 (d, J = 8.0 Hz, 2H, CH), 7.94 (d, J = 8.0 Hz, 2H, CH), 8.15 - 8.24 (m, 5H, CH); δ_C (100 MHz, d_6-DMSO) 21.4, 32.3, 35.8, 37.0, 41.2, 46.6, 51.5, 52.8, 116.3, 116.7, 116.8, 117.1, 118.7, 126.7, 127.4, 128.1, 128.7, 129.4, 132.2, 132.8, 134.7, 135.0, 140.7, 143.4, 143.8, 147.0, 162.7, 167.0, 170.6; HRMS (ES+) calcd for [$C_{36}H_{36}N_4O_8S$ + H] 717.2047, found 717.2036; HPLC (I) t_R = 22.01 min (94.07 %), (II) t_R = 46.38 min (100 %).

(27kh) 4-(*N*-(4-(1-(4-carboxyphenyl)piperidin-4-yl)benzyl)-2-(*N*,4-dimethylphenyl-sulfonamido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 1.58 - 1.73 (m, 2H, CH_2), 1.82 (d, J = 12.8 Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.69 - 2.79 (m, 4H, CH_3 and CH), 2.90 (t, J = 11.2 Hz, 2H, CH_2), 3.84 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 6.79 (d, J = 8.4 Hz, 1H, CH), 6.87 (s, 1H, CH), 6.99 (d, J = 8.8 Hz, 2H, CH), 7.09 (d, J = 8.0 Hz, 2H, CH), 7.18 (d, J = 8.0 Hz, 2H, CH), 7.35 (d, J = 8.0 Hz, 2H, CH), 7.54 (d, J = 8.0 Hz,

2H, CH), 7.76 (d, J = 8.8 Hz, 2H, CH), 7.78 (d, J = 8.4 Hz, 1H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.3, 32.5, 36.2, 41.4, 48.1, 48.9, 51.3, 52.0, 113.9, 116.5, 119.0, 119.3, 121.8, 127.0, 127.3, 128.0, 129.9, 131.3, 131.7, 135.0, 135.4, 143.5, 145.1, 147.5, 153.9, 161.9, 167.0, 167.6, 171.5; HRMS (ES+) calcd for [$C_{36}H_{37}N_3O_8S$ + H] 672.2374, found 672.2372; HPLC (III) t_R = 19.17 min (82.84 %), (IV) t_R = 39.60 min (90.47 %).

(27ki) 4-(N-(4-(1-(4-carbamoylphenyl)piperidin-4-yl)benzyl)-2-(N,4-dimethylphenyl sulfonamido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*$_6$-DMSO) 1.66 - 1.80 (m, 2H, CH_2), 1.82 - 1.91 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.58 - 2.68 (m, 1H, CH), 2.77 (s, 3H, CH_3), 2.86 (t, J = 12.0 Hz, 2H, CH_2), 3.72 (s, 2H, CH_2), 3.89 (d, J = 12.0 Hz, 2H, CH_2), 4.75 (s, 2H, CH_2), 6.49 (d, J = 7.2 Hz, 1H, CH), 6.58 (s, 1H, CH), 6.87 (d, J = 8.8 Hz, 2H, CH), 7.00 - 7.09 (m, 4H, CH), 7.20 (d, J = 8.0 Hz, 1H, CH), 7.54 (d, J = 8.0 Hz, 1H, CH), 7.67 (d, J = 8.4 Hz, 2H, CH), 7.80 (d, J = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*$_6$-DMSO) 21.2, 29.4, 32.5, 35.7, 41.9, 51.3, 52.7, 114.1, 116.4, 118.6, 121.6, 126.7, 127.2, 128.5, 128.9, 129.4, 132.0, 134.2, 134.9, 143.4, 144.9, 146.5, 150.2, 153.6, 162.4, 166.8, 169.2, 171.3; HRMS (ES+) calcd for [$C_{36}H_{38}N_4O_7S$ + H] 671.2533, found 671.2545; HPLC (III) t_R = 17.72 min (84.23 %), (IV) t_R = 24.81 min (74.07 %).

(27la) 4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-((3'-(methoxy-carbonyl)biphenyl-4-yl)methyl)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*-$CDCl_3$) 2.36 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 3.88 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 6.82 (dd, J = 8.4 and 2.0 Hz, 1H, CH), 6.92 (d, J = 2.0 Hz, 1H, CH), 7.29 (d, J = 8.0 Hz, 2H, CH), 7.36 (d, J = 8.0 Hz, 2H, CH), 7.56 (d, J = 8.0 Hz, 2H, CH), 7.69 (t, J = 8.0 Hz, 1H, CH), 7.64 (d, J = 8.0 Hz, 2H, CH), 7.78 (d, J = 8.4 Hz, 1H, CH), 7.93 (dd, J = 7.6 and 1.6

Hz, 2H, CH), 8.16 (t, J = 1.6 Hz, 1H, CH); δ_C (100 MHz, d-$CDCl_3$) 21.4, 35.9, 51.5, 52.1, 52.8, 116.6, 117.8, 118.7, 127.2, 127.5, 128.1, 128.3, 128.8, 129.1, 129.4, 130.5, 131.4, 132.2, 135.4, 136.0, 139.4, 140.8, 143.3, 146.7, 162.9, 163.0, 167.0, 171.8; HRMS (ES+) calcd for [$C_{32}H_{31}N_2O_8S$ + H] 603.1800, found 603.1795; HPLC (I) t_R = 23.65 min (100.0 %), (II) t_R = 48.73 min (100.0 %).

(27lb) 4-(*N*-((3'-cyanobiphenyl-4-yl)methyl)-2-(*N*,4-dimethylphenyl sulfonamido) acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d-$CDCl_3$) 2.37 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.91 (s, 2H, CH_2), 6.84 (dd, J = 8.4 and 1.6 Hz, 1H, CH), 6.93 (s, 1H, CH), 7.30 (d, J = 8.0 Hz, 2H, CH), 7.37 (d, J = 8.0 Hz, 2H, CH), 7.57 (d, J = 8.0 Hz, 2H, CH), 7.65 (t, J = 8.0 Hz, 1H, CH), 7.70 (d, J = 8.0 Hz, 2H, CH), 7.80 (t, J = 8.0 Hz, 2H, CH), 8.02 (d, J = 8.0 Hz, 1H, CH), 8.15 (s, 1H, CH); δ_C (100 MHz, d-$CDCl_3$) 20.8, 35.8, 50.8, 51.4, 112.0, 116.0, 118.4, 118.7, 120.0, 126.8, 126.9, 128.3, 128.5, 129.5, 130.0, 130.9, 131.2, 131.3, 135.0, 136.7, 137.1, 140.6, 143.0, 146.6, 161.6, 166.7, 171.0; HRMS (ES+) calcd for [$C_{31}H_{28}N_3O_6S$ + H] 570.1696, found 570.1693; HPLC (I) t_R = 22.84 min (98.3 %), (II) t_R = 47.61 min (98.43%).

(27lc) 4-(*N*-((3'-carbamoylbiphenyl-4-yl)methyl)-2-(*N*,4-dimethylphenylsulfon amido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.37 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.91 (s, 2H, CH_2), 6.84 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H, CH), 6.93 (d, J = 2Hz, 1H, CH), 7.29 (d, J = 8.0 Hz, 2H, CH), 7.37 (d, J = 8.4 Hz, 2H, CH), 7.42 (s, 1H, CH), 7.51 - 7.58 (m, 3H, CH), 7.77 (d, J = 8.0 Hz, 2H, CH), 7.78 - 7.85 (m, 3H, CH), 8.09 (s, 1H, CH), 8.14 (s, 1H, CH); δ_C (100 MHz, d-$CDCl_3$) 20.6, 35.6, 50.55, 51.3, 114.1, 115.5, 117.1, 125.2, 126.3, 126.32, 126.6, 128.1, 128.8, 128.9, 129.3,

130.9, 134.6, 134.8, 136.3, 138.1, 139.3, 142.8, 156.9, 162.1, 166.5, 167.4, 170.7; HRMS (ES+) calcd for [$C_{31}H_{30}N_3O_7S$ + H] 588.1794, found 588.1794; HPLC (I) t_R = 17.05 min (100 %), (II) t_R = 39.80 min (98.94 %).

(27ld) 4-(2-(*N*,4-dimethylphenylsulfonamido)-*N*-((4'-(methoxy-carbonyl)biphenyl-4-yl)methyl) acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*-$CDCl_3$) 2.40 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 3.94 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 6.64 (d, *J* = 7.6, 1H, CH), 6.74 (d, *J* = 1.2 Hz, 1H, CH), 7.25 - 7.28 (m, 3H, CH), 7.53 (d, *J* = 8.4 Hz, 2H, CH), 7.63 (d, *J* = 8.4 Hz, 2H, CH), 7.66 (d, *J* = 8.4 Hz, 2H, CH), 7.90 (d, *J* = 8.4 Hz, 1H, CH), 8.09 (d, *J* = 8.4 Hz, 2H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.5, 35.9, 51.6, 52.1, 52.9, 116.9, 117.0, 119.0 126.9, 127.4, 127.5, 128.9, 129.1, 129.5, 130.1, 132.4, 135.1, 136.3, 139.4, 143.5, 144.9, 147.5, 162.9, 167.0, 167.2, 171.2; HRMS (ES+) calcd for [$C_{32}H_{31}N_2O_8S$ + H] 603.1816, found 603.1795; HPLC (I) t_R = 23.76 min (99.37 %), (II) t_R = 48.78 min (100.0 %).

(27le) 4'-((*N*-(4-carboxy-3-hydroxyphenyl)-2-(*N*,4-dimethylphenyl sulfonamido) acetamido) methyl)-[1,1'-biphenyl]-4-carboxylic acid. δ_H (400 MHz, d_6-DMSO) 2.37 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.88 (s, 2H, CH_2), 4.89 (s, 2H, CH_2), 6.72 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H, CH), 6.81 (d, *J* = 1.6 Hz, 1H, CH), 7.30 (d, *J* = 8.4 Hz, 2H, CH), 7.37 (d, *J* = 8.0 Hz, 2H, CH), 7.56 (d, *J* = 8.4 Hz, 2H, CH), 7.68 (d, *J* = 8.4 Hz, 2H, CH), 7.75 (d, *J* = 8.4 Hz, 1H, CH), 7.79 (d, *J* = 8.4 Hz, 2H, CH), 8.00 (d, *J* = 8.4 Hz, 2H, CH); δ_C (100 MHz, d_6-DMSO) 20.8, 35.8, 50.8, 51.5, 115.8, 117.6, 118.1, 126.5, 126.8, 126.8, 128.3, 129.4, 129.5, 129.8, 131.1, 135.0, 137.1, 137.7, 143.0, 143.7, 145.8, 162.2, 166.6,

167.0; HRMS (ES+) calcd for [$C_{31}H_{29}N_2O_8S$ + H] 589.1628, found 589.1639; HPLC (I) t_R = 20.29 min (98.59 %), (II) t_R = 41.50 min (98.69%).

(27lf) 4-(*N*-((4'-cyanobiphenyl-4-yl)methyl)-2-(*N*,4-dimethylphenyl-sulfonamido) acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, *d*-$CDCl_3$) 2.36 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 4.91 (s, 2H, CH_2), 6.78 (dd, *J* = 8.4 and 1.6 Hz, 1H, CH), 6.89 (d, *J* = 2.0 Hz, 1H, CH), 7.30 (d, *J* = 8.0 Hz, 2H, CH), 7.37 (d, *J* = 8.0 Hz, 2H, CH), 7.57 (d, *J* = 8.0 Hz, 2H, CH), 7.70 (d, *J* = 8.0 Hz, 2H, CH), 7.78 (d, *J* = 8.0 Hz, 1H, CH), 7.86 - 7.92 (m, 4H, CH); δ_C (100 MHz, *d*-$CDCl_3$) 21.2, 36.2, 51.2, 51.8, 110.2, 118.6, 118.7, 119.1, 127.2, 127.3, 127.7, 128.8, 129.9, 131.6, 131.8, 132.0, 133.1, 135.4, 137.3, 138.0, 143.4, 144.4, 146.8, 162.1, 167.1, 167.2, 171.4; HRMS (ES+) calcd for [$C_{31}H_{28}N_3O_6S$ + H] 570.1696, found 570.1693; HPLC (I) t_R = 23.18 min (100.0 %), (II) t_R = 47.81 min (98.78%).

(27lg) 4-(*N*-((4'-carbamoylbiphenyl-4-yl)methyl)-2-(*N*,4-dimethyl phenylsulfon amido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.37 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 6.83 (dd, *J* = 8.4 Hz and 2.0 Hz, 1H, CH), 6.92 (d, *J* = 2Hz, 1H, CH), 7.28 (d, *J* = 7.6 Hz, 2H, CH), 7.37, d, *J* = 8.0 Hz, CH), 7.56 (d, *J* = 8.0 Hz, 2H, CH), 7.67 (d, *J* = 8.0 Hz, 2H, CH), 7.74 (d, *J* = 8.4 Hz, 2H, CH), 7.79 (d, *J* = 8.4 Hz, 1H, CH), 7.94 (d, *J* = 8.4 Hz, 2H, CH), 8.01 (s, 1H, OH); δ_C (100 MHz, d_6-DMSO) 21.2, 36.2, 51.1, 52.0, 116.0, 117.2, 120.4, 126.6, 127.1, 127.2, 128.4, 128.7, 129.9, 131.4, 133.3, 135.5, 137.3, 138.3, 142.5, 143.4, 163.0, 167.1, 167.8, 171.2, 172.3; HRMS (ES+) calcd for [$C_{31}H_{30}N_3O_7S$ + H] 588.1789, found 588.1798; HPLC (I) t_R = 19.49 min (91.83 %), (II) t_R = 40.09 min (98.42 %).

(27na) 4-(2-(N,4-dimethylphenylsulfonamido)-N-((3'-(methoxy carbonyl)terphenyl-4-yl)methyl)-acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.36 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 6.80 (d, 1H, J = 8.4 Hz, CH), 6.89 (s, 1H, CH), 7.29 (d, J = 8.4Hz, 2H, CH), 7.36 (d, J = 8.0 Hz, 2H, CH), 7.61 - 7.67 (m, 5H, CH), 7.76 - 7.79 (m, 4H, CH), 7.96 (d, J = 7.6 Hz, 1H, CH), 8.00 (d, J = 8.0 Hz, 1H, CH), 8.24 (s, 1H, CH), 8.32 (s, 1H, CH); δ_C (100 MHz, d_6-DMSO) 20.8, 35.8, 50.8, 51.5, 52.1, 115.9, 117.4, 118.1, 126.4, 126.8, 127.1, 127.2, 127.3, 127.8, 128.0, 128.3, 129.4, 129.5, 130.3, 131.2, 135.0, 136.3, 137.8, 138.1, 139.1, 139.9, 143.0, 146.3, 161.8, 166.0, 166.7, 171.0; HRMS (ES+) calcd for [$C_{37}H_{32}N_2O_8S$ + H] 679.2108, Found 679.2080; HPLC (I) t_R = 23.34 min (96.76 %), (II) t_R = 50.50 min (98.76 %).

(27nb) 4'-((N-(4-carboxy-3-hydroxyphenyl)-2-(N,4-dimethylphenyl sulfonamido) acetamido)methyl)terphenyl-3-carboxylic acid. δ_H (400 MHz, d_6-DMSO) 2.37 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 4.87 (s, 2H, CH_2), 6.68 (dd, J = 8.4 and 1.2 Hz, 1H, CH), 6.76 (d, J = 1.2 Hz, 1H, CH), 7.29 (d, J = 8.0 Hz, 2H, CH), 7.37 (d, J = 8.0 Hz, 2H, CH), 7.56 (d, J = 8.0 Hz, 2H, CH), 7.62 (t, J = 8.0 Hz, 2H, CH), 7.68 (d, J = 8.0 Hz, 1H, CH), 7.73 (d, J = 8.0 Hz, 1H, CH), 7.79 (s, 4H, CH), 7.94 (d, J = 8.0 Hz, 1H, CH) 7.98 (d, J = 8.0 Hz, 1H, CH), 8.23 (s, 1H, CH); δ_C (100 MHz, d_6-DMSO) 20.6, 35.8, 50.8, 51.5, 113.0, 116.0, 118.3, 126.4, 126.9, 127.0, 127.1, 127.2, 128.2, 128.3, 129.2, 129.5, 130.8, 131.3, 131.4, 135.0, 136.3, 138.0, 138.2, 138.9, 139.8, 143.0, 146.6, 161.7, 166.7, 167.1, 171.0; HRMS (ES+) calcd for [$C_{37}H_{32}N_2O_8S$ + H] 665.1952, Found 665.1957; HPLC (I) t_R = 21.07 min (96.72 %), (II) t_R = 44.44 min (97.21 %).

(27nc) 4-(N-((3'-Cyanoterphenyl-4-yl)methyl)-2-(N,4-dimethyl-phenylsulfonamido) acet-amido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.36 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 4.92 (s, 2H, CH_2), 6.85 (dd, J = 8.4 and 1.6 Hz, 1H, CH), 6.95 (d, J = 1.6 Hz, 1H, CH), 7.30 (d, J = 8.0 Hz, 2H, CH), 7.36 (d, J = 8.4 Hz, 2H, CH), 7.58 (d, J = 8.4 Hz, 2H, CH), 7.66 - 7.71 (m, 3H, CH), 7.78 - 7.86 (m, 6H, CH), 8.05 (d, J = 8.0 Hz, 1H, CH), 8.20 (s, 1H, CH); δ_C (100 MHz, d_6-DMSO) 20.8, 35.8, 50.9, 51.5, 112.0, 112.5, 116.0, 118.5, 118.7, 126.5, 126.9, 127.0, 127.3, 128.3, 129.5, 129.9, 130.0, 130.9, 131.2, 131.3, 135.0, 136.4, 136.8, 138.0, 139.4, 140.5, 143.0, 146.8, 161.6, 166.8, 171.1; HRMS (ES+) calcd for [$C_{37}H_{32}N_3O_6S$ + H] 646.2006, Found 646.1986; HPLC (I) t_R = 22.62 min (88.65 %), (II) t_R = 48.72 min (90.98 %).

(27nd) 4-(N-((3'-carbamoylterphenyl-4-yl)methyl)-2-(N,4-dimethylphenylsulfon amido)acet-amido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.36 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 4.91 (s, 2H, CH_2), 6.91 (dd, J = 7.6 and 1.2 Hz, 1H, CH), 6.90 (s, 1H, CH), 7.30 (d, J = 8.0 Hz, 2H, CH), 7.37 (d, J = 8.0 Hz, 2H, CH), 7.53 - 7.57 (m, 3H, CH), 7.68 (d, J = 8.4 Hz, 2H, CH), 7.73 (d, J = 7.6 Hz, 1H, CH), 7.75 - 7.88 (m, 6H, CH), 8.23 (s, 1H, CH); δ_C (100 MHz, d_6-DMSO) 20.8, 35.8, 50.8, 51.5, 113.3, 115.9, 118.2, 125.4, 126.4, 126.7, 126.9, 127.0, 127.2, 128.3, 128.8, 129.1, 129.3, 129.5, 131.2, 134.9, 135.0, 136.3, 138.2, 138.4, 139.4, 143.0, 146.4, 161.8, 166.7, 167.7, 171.0; HRMS (ES+) calcd for [$C_{37}H_{33}N_3O_7S$ + H] 663.2111, Found 665.2109; HPLC (I) t_R = 19.89 min (100 %), (II) t_R = 41.08 min (100 %).

(27ne) 4-(2-(N,4-dimethylphenylsulfonamido)-N-((4'-(methoxy-carbonyl)terphenyl-4-yl) methyl)-acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.38 (s,

3H, CH_3), 2.81 (s, 3H, CH_3), 3.88 (s, 5H, CH_2 and CH_3), 4.91 (s, 2H, CH_2), 6.80 (d, J = 8.4 Hz, 1H, CH), 6.89 (s, 1H, CH), 7.30 (d, J = 8.4 Hz, 2H, CH), 7.38 (d, J = 8.0 Hz, 2H, CH), 7.57 (d, J = 8.4 Hz, 2H, CH), 7.69 (d, J = 8.0 Hz, 2H, CH), 7.75 - 7.84 (m, 5H, CH), 7.90 (d, J = 8.8 Hz, 2H, CH), 8.03 (d, J = 8.8 Hz, 2H, CH) δ_C (100 MHz, d_6-DMSO) 20.8, 35.8, 50.8, 51.5, 52.0, 113.5, 115.9, 118.0, 126.4, 126.6, 126.8, 127.0, 127.2, 127.3, 128.3, 129.5, 129.7, 131.2, 135.0, 136.4, 137.5, 138.0, 139.4, 143.0, 143.9, 146.3, 161.8, 165.9, 166.7, 171.0; HRMS (ES+) calcd for [$C_{37}H_{32}N_2O_8S$ + H] 679.2108, Found 679.2081; HPLC (I) t_R = 23.54 min (100 %), (II) t_R = 51.01 min (100 %).

(27nf) 4'-((N-(4-carboxy-3-hydroxyphenyl)-2-(N,4-dimethylphenylsulfonamido)acet-amido)methyl)terphenyl-4-carboxylic acid. δ_H (400 MHz, d_6-DMSO) 2.37 (s, 2H, CH_3), 2.80 (s, 3H, CH_3), 3.88 (s, 2H, CH_2), 4.88 (s, 2H, CH_2), 6.72 (d, J = 6.8 Hz, 1H, CH), 6.81 (s, 1H, CH), 7.29 (d, J = 6.8 Hz, 2H, CH), 7.37 (d, J = 7.6 Hz, 2H, CH), 7.56 (d, J = 6.8 Hz, 2H, CH), 7.68 (d, J = 7.2 Hz, 2H, CH), 7.78 - 7.85 (m, 7H, CH), 8.03 (d, J = 7.2 Hz, 2H, CH); δ_C (100 MHz, d_6-DMSO) 20.8, 35.7, 51.5, 55.7, 107.4, 107.7, 117.4, 126.4, 126.5, 126.8, 127.1, 127.0, 127.3, 128.3, 129.5, 129.8, 131.1, 136.4, 137.0, 137.7, 138.0, 139.3, 143.0, 143.5, 158.0, 162.3, 166.7, 166.9, 171.4; HRMS (ES+) calcd for [$C_{37}H_{32}N_2O_8S$ + H] 665.1952, Found 665.1962; HPLC (I) t_R = 17.25 min (92.99 %), (II) t_R = 37.13 min (91.78 %).

(27ng) 4-(N-((4'-Cyanoterphenyl-4-yl)methyl)-2-(N,4-dimethyl phenylsulfonamido) acet-amido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.36 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 4.92 (s, 2H, CH_2), 6.85 (d, J = 8.4 Hz, 1H, CH), 6.95 (s, 1H, CH), 7.30 (d, J = 8.0 Hz, 2H, CH), 7.36 (d, J = 8.0 Hz, 2H, CH), 7.58 (d, J = 8.0 Hz,

2H, CH), 7.68 (d, J = 8.0 Hz, 2H, CH), 7.78 - 7.82 (m, 5H, CH), 7.93 - 7.95 (m, 4H, CH); δ_C (100 MHz, d_6-DMSO) 20.8, 35.8, 50.9, 51.5, 109.9, 112.5, 116.0, 118.5, 118.7, 126.5, 126.9, 127.1, 127.2, 127.5, 128.3, 129.5, 131.3, 132.7, 135.0, 136.5, 137.0, 138.0, 139.8, 143.0, 146.8, 161.5, 166.7, 171.1. HRMS (ES+) calcd for [$C_{37}H_{32}N_3O_6S$ + H] 646.2006, Found 646.1987; HPLC (I) t_R = 22.71 min (94.15 %), (II) t_R = 49.13 min (96.29 %).

(27nh) 4-(N-((4''-carbamoyl-[1,1':4',1''-terphenyl]-4-yl)methyl)-2-(N,4-dimethyl-phenylsulfonamido)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, d_6-DMSO) 2.35 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 4.88 (s, 2H, CH_2), 6.78 (d, J = 6.4 Hz, 1H, CH), 6.86 (s, 1H, CH), 7.29 (d, J = 8.4 Hz, 2H, CH), 7.37 (d, J = 8.0 Hz, 2H, CH), 7.55 - 7.69 (m, 6H, CH), 7.76 - 7.84 (m, 4H, CH), 7.95 - 8.04 (m, 3H, CH); δ_C (100 MHz, d_6-DMSO) 21.3, 30.7, 51.3, 52.0, 103.0, 116.2, 118.4, 126.2, 126.5, 127.0, 127.1, 127.3, 128.2, 128.4, 128.7, 128.8, 129.6, 131.4, 131.5, 132.0, 132.1, 132.2, 133.1, 133.2, 135.1, 136.4, 138.1, 138.3, 139.1, 142.1, 143.1, 146.8, 161.7, 166.8, 167.5, 171.1, 172.0; HRMS (ES+) calcd for [$C_{37}H_{33}N_3O_7S$ + H] 664.2111, Found 664.2141; HPLC (III) t_R = 19.22 min (76.63 %), (IV) t_R = 43.81 min (79.95 %).

(41) 4-(*N*-(4-Cyclohexylbenzyl)-2-(4-methylphenylsulfonamido) acetamido)-2-hydroxy benzoic acid. δ_H (400 MHz, d_6-DMSO) 1.06 - 1.40 (m, 5H, CH_2), 1.66 - 1.76 (m, 5H, CH_2), 2.37 (s, 3H, CH_3Ar), 2.43 (s (br), 1H, CH), 3.55 (d, J = 5.4 Hz, 2H, CH_2NH), 4.73 (s, 2H, CH_2Ar), 6.68 (dd, J = 8.4 and 2.0 Hz, 1H, CH (Ar)), 6.77 (d, J = 2.0 Hz, 1H, CH (Ar)), 6.99 (d, J = 8.2 Hz, 2H, 2 CH (Ar)), 7.10 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.34 (d, J = 7.8 Hz, 2H, 2 CH (Ar)), 7.57 - 7.59 (m, 2H, 2 CH (Ar)), 7.72 (d, J = 8.2 Hz, 1H, CH (Ar)), 7.86 (t, J = 5.8 Hz, 1H, NH), 11.40 (s (br), 1H, OH); HRMS (ES+)

calcd for [$C_{29}H_{32}N_2O_6S$ + H] 537.2059, found 537.2053; HPLC (I) t_R = 24.12 min (97.43 %), (II) t_R = 51.54 min (97.70%).

(43) 4-(2-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-*N*-(4-cyclohexyl-benzyl)acetamido)-2-hydroxybenzoic acid. δ_H (400 MHz, $CDCl_3$) 1.22-1.45 (m, 14H), 1.70–1.85 (m, 5H, CH_2), 2.42 (s, 3H, CH_3), 2.46 (s (br), 1H, CH), 4.46 (s, 2H, $COCH_2$), 4.91 (s, 2H, CH_2Ar), 6.70 (d, J = 8.0 Hz, 1H, CH (Ar)), 6.82 (s (br), 1H, CH (Ar)), 7.10–7.15 (m, 4H, 4 CH (Ar)), 7.30 (d, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.88 (d, J = 8.4 Hz, 1H, 1 CH (Ar)), 8.02 (d, J = 8.2 Hz, 2H, 2 CH (Ar)), 10.66 (s (br), 1H, OH); δ_C (100 MHz, $CDCl_3$) 21.6, 26.0, 26.8, 27.7, 34.3, 44.2, 47.5, 53.1, 84.7, 111.6, 117.2, 119.3, 126.9, 128.3, 128.8, 129.0, 132.3, 133.5, 136.6, 144.2, 147.5, 147.9, 150.5, 162.9, 166.7, 172.6; HRMS (ES+) calcd for [$C_{34}H_{41}N_2O_8S$ + H] 637.2547, found 637.2578; HPLC (I) t_R = 26.55 min (97.80 %), (II) t_R = 59.27 min (100%).

(46) 4-(*N*-(4-Cyclohexylbenzyl)-2-(tosyloxy)acetamido)-2-hydroxy-benzoic acid. δ_H (400 MHz, d_6-DMSO) 1.20 - 1.31 (m, 5H, CH_2), 1.70-1.75 (m, 5H, CH_2), 2.38 (s, 3H, CH_3Ar), 2.41 (s (br), 1H, CH), 4.56 (s, 2H, $COCH_2$), 4.75 (s, 2H, CH_2Ar), 6.66 (d, J = 8.4 Hz, 1H, CH (Ar)), 6.75 (s (br), 1H, CH (Ar)), 7.01 (d, J = 8.0 Hz, 2H, CH (Ar)), 7.09 (d, J = 8.0 Hz, 2H, CH (Ar)), 7.40 (d, J = 8.2 Hz, 2H, CH (Ar)), 7.65-7.68 (m, 3H, 3 CH (Ar)); δ_C (100 MHz, d_6-DMSO) 21.0, 25.4, 26.2, 33.8, 43.2, 51.5, 65.9, 111.6, 115.6, 117.3, 125.4, 126.5, 127.3, 127.9, 129.9, 131.1, 131.8, 133.8, 145.0, 146.4, 162.0, 163.7, 170.9; HRMS (ES+) calcd for [$C_{29}H_{32}NO_7S$ + H] 538.1912, found 538.1894; HPLC (I) t_R = 21.56 min (97.25 %), (II) t_R = 54.14 min (98.36 %).

(47) 4-(*N*-(4-cyclohexylbenzyl)-2-hydroxyacetamido)-2-hydroxy-benzoic acid. δ_H (400 MHz, d_6DMSO) 1.29 - 1.39 (m, 5H, CH_2), 1.62 - 1.77 (m, 5H, CH_2), 2.35 - 2.45 (m, 1H, CH), 3.89 9s, 2H, CH_2), 4.83 (s, 2H, CH_2), 6.77 (dd, J = 8.4 and 2.4 Hz, 1H, CH), 6.84 (d, J = 2.4 Hz, 1H, CH), 7.05-7.13 (m, 4H, CH), 7.71 (d, J = 8.4 Hz, 1H, CH); LRMS Calcd for [$C_{22}H_{25}NO_5$ + H] 384.45, found 384.32; HPLC (I) t_R= 18.94 mins (99.87 %), (II) t_R = 36.67 mins (99.98 %).