Supplementary Material:

Development of new *N*-Arylbenzamides as STAT3 Dimerization Inhibitors

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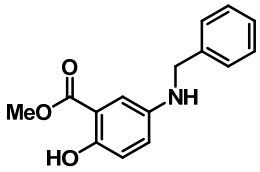
Contents **Page**

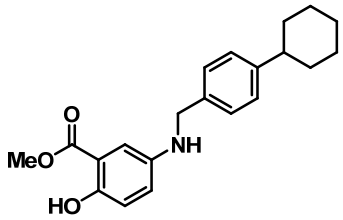
Chemistry

General. All reagents were purchased from commercial suppliers and used without further purification. Proton NMR spectra were recorded on an Agilent-Varian Mercury 400 MHz spectrometer with $CDCl_3$, CD_3OD or DMSO-d_6 as the solvent. Carbon (^{13}C) NMR spectra are recorded at 100 MHz. All coupling constants are measured in Hertz (Hz) and the chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) relative to TMS (δ 0), which was used as the internal standard. High resolution mass spectroscopy was carried out on an Agilent 6210 LC/MS (ESI-TOF). Low resolution mass spectroscopy (LRMS) was performed on an Agilent single quad G1956A (Chemistry Department, University of South Florida). Microwave reactions were performed in CEM Discover model 908005 and Biotage Initiator 8 synthesis systems. All final compounds were purified to ≥95% purity as determined HPLC analysis using a JASCO HPLC system equipped with a PU-2089 Plus quaternary gradient pump and a UV-2075 Plus UV-VIS detector, using an Alltech Kromasil C-18 column (150 × 4.6 mm, 5 μm) and Agilent Eclipse XDB-C18 (150 × 4.6 mm, 5 μm). Melting points were recorded on an Optimelt automated melting point system (Stanford Research Systems). Thin layer chromatography was performed using silica gel 60 F254 plates (Fisher), with observation under UV when necessary. Anhydrous solvents (acetonitrile, dimethylformamide, ethanol, isopropanol, methanol and tetrahydrofuran) were used as purchased from Aldrich. Burdick and Jackson HPLC grade solvents (methanol, acetonitrile and water) were purchased from VWR for HPLC and high resolution mass analysis. HPLC grade TFA was purchased from Fisher.

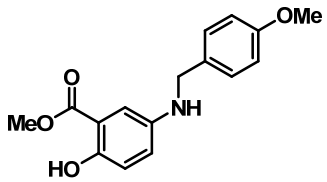
Synthesis of benzylaminosalicylates 19



Methyl 5-(benzylamino)-2-hydroxybenzoate (19a). To a stirred solution of methyl 5-aminosalicylate (**17**) (0.200 g, 1.196 mmol) in MeOH (10 ml) over 4Å molecular sieves was added benzaldehyde (0.121 mL, 1.196 mmol) followed by AcOH (0.106 mL). The solution was heated at 40 ºC and then allowed to stir at room temperature for 1 h. The solution was cooled to 5-10 ºC and $NaCNBH_3$ (0.097 g, 1.554 mmol) was slowly added in portions. The resulted mixture was stirred for 2 h at room temperature before being quenched by the addition of water. The solvents were evaporated and the crude mixture was taken up in CH_2Cl_2, washed with water, brine, dried (Na_2SO_4) and evaporated. Chromatography gave the ester **19a** (0.268 g, 1.042 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.38–7.26 (m, 5H), 7.08 (t, *J* = 1.7 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 2H), 4.27 (s, 2H), 3.91 (s, 3H). HRMS (ESI+ve) *m/z* 258.1127 $[M+H]^+$ (calcd for $C_{15}H_{16}NO_3$ 258.1125).

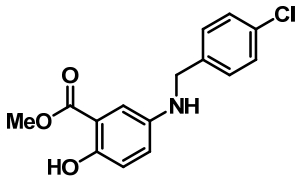


Methyl 5-(4-cyclohexylbenzylamino)-2-hydroxybenzoate (19b). This was obtained as a yellow oil (0.246 g, 0.78 mmol, 35%) from methyl 5-aminosalicylate (**17**) (0.411 g, 2.465 mmol) and 4-cyclohexylbenzaldehyde (0.464 g, 2.465 mmol) in the same manner as described for **19a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 2H), 4.23 (s, 2H), 2.52-2.45 (m, *J* 1H), 1.9–1.68 (m, 5H), 1.50–1.14 (m, 5H). HRMS (ESI+ve) *m/z* 340.1911 $[M+H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ 340.1907).

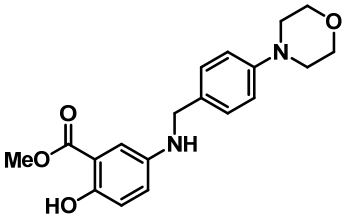


Methyl 2-hydroxy-5-(4-methoxybenzylamino)benzoate (19c). This was obtained as a solid from methyl 5-aminosalicylate (**17**) (1.00 g, 5.98 mmol) and 4-methoxybenzaldehyde (0.726 mL, 5.98 mmol) in the same manner as described for **19a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (s, 1H), 7.59 (d, *J* = 9.3 Hz, 1H), 7.25 (d, *J* =

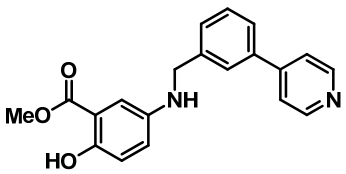
8.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.15–6.08 (m, 2H), 4.43 (t, *J* = 4.5 Hz, 1H), 4.28 (d, *J* = 5.3 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H). HRMS (ESI+ve) *m/z* 310.1048 $[M+Na]^+$ (calcd for $C_{16}H_{17}NNaO_4$ 310.1050).



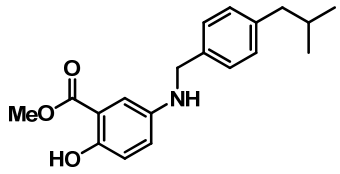
Methyl 5-(4-chlorobenzylamino)-2-hydroxybenzoate (19d). This was obtained as a solid from methyl 5-aminosalicylate (**17**) (1.00 g, 5.98 mmol) and 4-chlorobenzaldehyde (0.840 g, 5.98 mmol) in the same manner as described for **19a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.11 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 4.53 (s, 1H), 4.34 (d, *J* = 5.0 Hz, 2H), 3.87 (s, 3H). HRMS (ESI+ve) *m/z* 292.0727 $[M+H]^+$ (calcd for $C_{15}H_{15}NClO_3$ 292.0735).



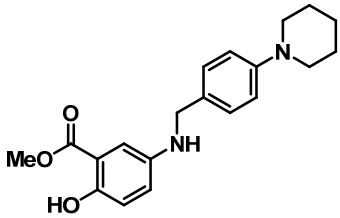
Methyl 2-hydroxy-5-(4-morpholinobenzylamino)benzoate (19e). This was obtained as a solid (0.960 g, 80%) from methyl 5-aminosalicylate (**17**) and 4-morpholinobenzaldehyde in the same manner as described for **19a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.08 (t, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 2H), 4.18 (s, 2H), 3.92 (s, 3H), 3.88–3.84 (m, 4H), 3.19–3.09 (m, 4H). HRMS (ESI+ve) *m/z* 365.1471 $[M+Na]^+$ (calcd for $C_{19}H_{22}N_2NaO_4$ 365.1472).



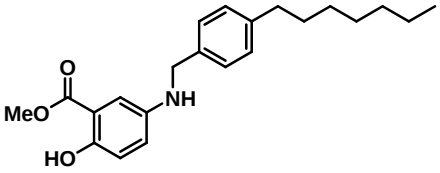
Methyl 2-hydroxy-5-(3-(pyridin-4-yl)benzylamino)benzoate (19f). This was obtained as a solid from methyl 5-aminosalicylate (**17**) (0.500 g, 2.99 mmol) and 3-(pyridin-4-yl)benzaldehyde (0.547 g, 2.99 mmol) in the same manner as described for **19a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.65 (d, *J* = 6.1 Hz, 1H), 7.65 (s, 1H), 7.56 (dt, *J* = 7.0, 1.9 Hz, 1H), 7.50 (d, *J* = 6.2 Hz, 1H), 7.47–7.43 (m, 2H), 7.12–7.09 (m, 1H), 6.88–6.83 (m, 2H), 4.37 (s, 2H), 3.91 (s, 3H). HRMS (ESI+ve) *m/z* 335.1397 $[M+H]^+$ (calcd for $C_{20}H_{19}N_2O_3$ 335.1390).



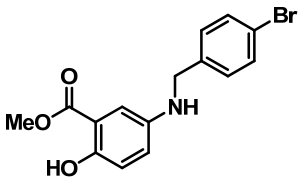
Methyl 2-hydroxy-5-(4-isobutylbenzylamino)benzoate (19g). This was obtained as an oil (40-45%) from methyl 5-aminosalicylate (**17**) (0.903 g, 5.41 mmol) and 4-isobutylbenzaldehyde (0.877 g, 5.41 mmol) in the same manner as described for **19a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 2H), 4.24 (s, 2H), 3.92 (s, 4H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.92–1.83 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H).



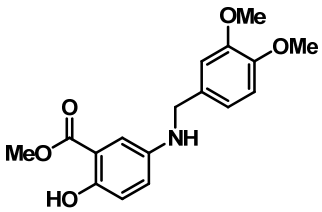
Methyl 2-hydroxy-5-(4-(piperidin-1-yl)benzylamino)benzoate (19h). This was obtained as a solid (0.800 g, 80%) from methyl 5-aminosalicylate (**17**) (0.500 g, 2.99 mmol) and 4-(piperidin-1-yl)benzaldehyde (0.566 g, 2.99 mmol) in the same manner as described for **19a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.08 (t, *J* = 1.7 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 1.7 Hz, 2H), 4.16 (s, 2H), 3.92 (s, 3H), 3.28–2.96 (m, 4H), 1.75–1.44 (m, 6H). HRMS (ESI+ve) *m/z* 341.1865 $[M+H]^+$ (calcd for $C_{20}H_{25}N_2O_3$ 341.1860).



Methyl 5-(4-heptylbenzylamino)-2-hydroxybenzoate (19i). This was obtained as an oil (1.04 g, 96%) from methyl 5-aminosalicylate (**17**) (0.500 g, 2.99 mmol) and 4-heptylbenzaldehyde (0.611 g, 2.99 mmol) in the same manner as described for **19a** and was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.28–7.26 (m, 3H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.10–7.09 (m, 1H), 6.85–6.84 (m, 2H), 4.23 (s, 2H), 3.92 (s, 3H), 2.72–2.49 (m, 3H), 1.61–1.60 (m, 3H), 1.42–1.25 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H).

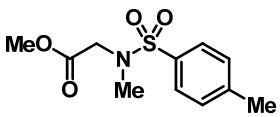


Methyl 5-(4-bromobenzylamino)-2-hydroxybenzoate (19j). This was obtained as a yellow solid (1.9 g, 60%) from methyl 5-aminosalicylate (**17**)(0.903 g, 5.41 mmol) and 4-cyclohexylbenzaldehyde (1.9 g, 5.41 mmol) in the same manner as described for **19a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 2.3 Hz, 1H), 6.86–6.82 (m, 2H), 4.24 (s, 2H), 3.91 (s, 3H).



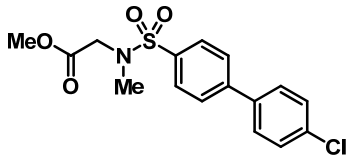
Methyl 5-(3,4-dimethoxybenzylamino)-2-hydroxybenzoate (19k). A solution of 3,4-dimethoxybenzaldehyde (0.546 g, 3.28 mmol), methyl 4-aminosalicylic acid (**17**)(0.551 g, 3.29 mmol) and Et_3N (0.5 ml) in anhydrous methanol (12 mL), was heated under reflux overnight. The solvent was then removed under reduced pressure. The obtained solid was then suspended in methanol (12 mL) and $NaBH_4$ (0.239 g, 6.26 mmol) was added portion-wise. The reaction mixture was then stirred at room temperature overnight. The solvent was removed under reduced pressure, water (10 mL) was added and the mixture extracted with EtOAc (2 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to provide a brown solid. The obtained crude material was slurried with Et_2O (10 mL), filtered and dried under vacuum to yield compound **19k** as an orange solid (0.483 g, 1.52 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.24 (d, *J* = 3.0 Hz, 1H), 7.08 (s, 1H), 6.89–6.81 (m, 6H), 4.19 (s, 2H), 3.91 (s, 3H), 3.86 (s, 6H). LCMS (ESI+ve) *m/z* $[M+Na]^+$ found 340.1

Synthesis of acids 20

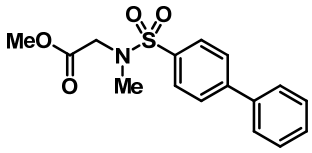


Methyl 2-(*N*,4-dimethylphenylsulfonamido)acetate (24a).[1] To a stirred solution of *N*-methylglycine methyl ester (**23**) (0.500 g, 3.58 mmol) in acetonitrile (15 mL) was added DIPEA (1.87 mL, 10.75 mmol) and *para*-toluenesulfonyl chloride (0.819 g, 4.3 mmol) was added in portions at 0 ºC. After the addition was complete, the ice bath was removed and the reaction was stirred at room temperature overnight. The solvents were

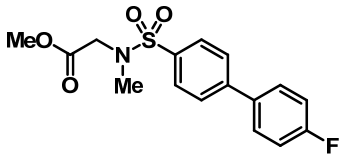
evaporated and the crude mixture was taken up in CH_2Cl_2 and washed with 0.1 N HCl, Sat. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The product **24a** (0.791 g, 86%) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 2H), 3.66 (s, 3H), 2.87 (s, 3H), 2.42 (s, 3H).



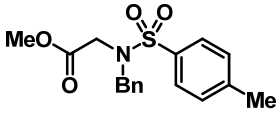
Methyl 2-(*N*,4-dimethylphenylsulfonamido)acetate (24b). This was obtained as an oil from *N*-methylglycine methyl ester (**23**) (1.5 g, 10.75 mmol) and 4-chlorobiphenylsulfonyl chloride (3.269 g, 12.9 mmol) in the same manner as described for **24a**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (d, *J* = 8.6 Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 4.04 (s, 2H), 3.64 (s, 3H), 2.90 (s, 3H).



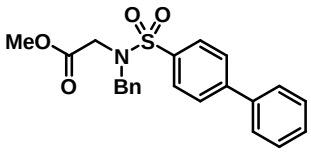
Methyl 2-(*N*-methylbiphenyl-4-ylsulfonamido)acetate (24c). This was obtained as an oil from *N*-methylglycine methyl ester (**23**) (1.5 g, 10.75 mmol) and 4-phenylbenzenesulfonyl chloride (3.705 g, 12.9 mmol) in the same manner as described for **24a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 1.5 Hz, 2H), 7.50–7.45 (m, 2H), 7.43–7.38 (m, 1H), 4.02 (s, 2H), 3.66 (s, 3H), 2.93 (s, 3H).



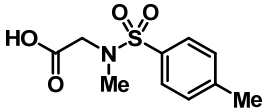
Methyl 2-(4'-fluoro-*N*-methylbiphenyl-4-ylsulfonamido)acetate (24d). This was obtained as a viscous oil (2.2 g) from *N*-methylglycine methyl ester (**23**) (1.9 g, 7.16 mmol) and 4-phenylbenzenesulfonyl chloride (2.33 g, 8.6 mmol) in the same manner as described for **24a.**



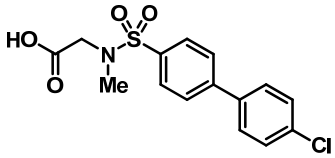
Methyl 2-(*N*-benzyl-4-methylphenylsulfonamido)acetate (24e).[2] This was obtained as a viscous oil from *N*-benzylglycine methyl ester (**22**) (1.0 g, 5.58 mmol) and tosyl chloride (1.27 g, 6.70 mmol) in the same manner as described for **24a.**



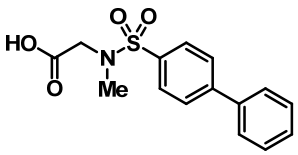
Methyl 2-(*N*-benzylbiphenyl-4-ylsulfonamido)acetate (24f). This was obtained as a viscous oil from *N*-benzylglycine methyl ester (**22**) (1.59 g, 8.37 mmol) and 4-phenyl-benzenesulfonyl chloride (2.53 g, 10.05 mmol) in the same manner as described for **24a.**



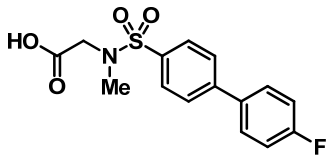
2-(*N*,4-Dimethylphenylsulfonamido)acetic acid (20a).[3] Lithium hydroxide (0.146 g, 6.10 mmol) was added to a solution of **24a** (0.705 g, 3.05 mmol) in MeOH-THF-H_2O (10 mL, 3:1:1) and was stirred overnight at room temperature. The organic solvent was then removed under reduced pressure. The resulting solution was acidified with HCl (aq. 1 M) and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to afford **20a** (97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.98 (s, 2H), 2.87 (s, 3H), 2.43 (s, 3H).



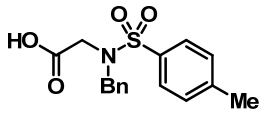
2-(4'-Chloro-*N*-methylbiphenyl-4-ylsulfonamido)acetic acid (20b). This was obtained as a solid from **24b** (2.4 g, 7.16 mmol) in the same manner as described for **20a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 4.04 (s, 2H), 2.93 (s, 3H). HRMS (ESI+ve) *m/z* 340.0408 $[M+H]^+$ (calcd for $C_{15}H_{16}ClNO_4S$ 340.0405).



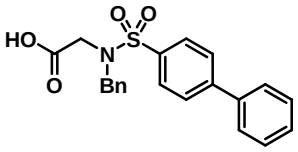
2-(*N*-Methylbiphenyl-4-ylsulfonamido)acetic acid (20c). This was obtained as a solid (70%) **24c** (0.551 g, 1.72 mmol) in the same manner as described for **20a.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.33–7.25 (m, 3H), 7.23–7.18 (m, 2H), 4.47 (s, 3H), 2.44 (s, 3H). HRMS (ESI+ve) *m/z* 306.0808 $[M+H]^+$ (calcd for $C_{15}H_{16}NO_4S$ 306.0795).



2-(4'-Fluoro-*N*-methylbiphenyl-4-ylsulfonamido)acetic acid (20d). This was obtained as a solid (0.500 g, 85%) from **24d** (0.500 g, 1.41 mmol) in the same manner as described for **20a.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.71 (dd, *J* = 8.9, 5.2 Hz, 2H), 7.22 (t, *J* = 8.8 Hz, 2H), 3.97 (s, 2H), 2.89 (s, 3H). HRMS (ESI+ve) *m/z* 324.0708 $[M+H]^+$ (calcd for $C_{15}H_{15}NFO_4S$ 324.0700).

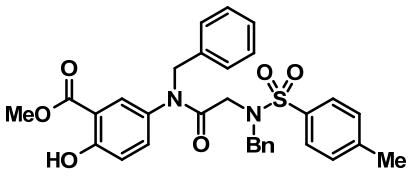


2-(*N*-Benzyl-4-methylphenylsulfonamido)acetic acid (20e).[2] This was obtained (1.119 g, 62%) from **24e** (1.896 g, 5.58 mmol) in the same manner as described for **20a.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.31–7.25 (m, 3H), 7.23–7.19 (m, 2H), 4.47 (s, 2H), 3.85 (s, 2H), 2.44 (s, 3H).

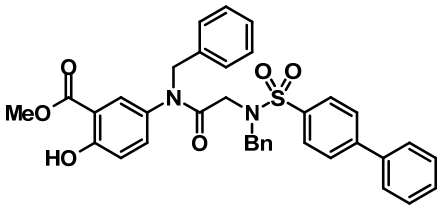


2-(*N*-Benzylbiphenyl-4-ylsulfonamido)acetic acid (20f). This was obtained as solid (0.500 g, 85%) from **24f** (0.500 g, 1.41 mmol) in the same manner as described for **20a.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.71–7.66 (m, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.33–7.20 (m, 6H), 4.53 (s, 3H), 3.90 (s, 2H).

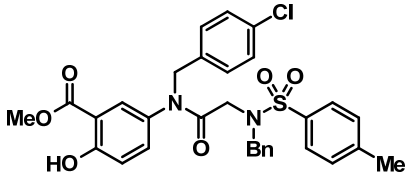
Synthesis of methyl esters 21



Methyl 5-(*N*-benzyl-2-(*N*-benzyl-4-methylphenylsulfonamido)acetamido)-2-hydroxybenzoate (**21a**). To a solution of an amine **19a** (0.100 g, 0.388 mmol) in CH_2Cl_2 (2 ml) was added the acid **20e** (0.130 g, 0.408 mmol) and coupling reagent Ph_3PCl_2 (0.010 g, 0.932 mmol) under argon atmosphere. The resultant mixture was heated at 80 ºC in a microwave reactor (Biotage) for 1 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The organic fractions are dried (Na_2SO_4) and evaporated *in vacuo*. The crude mixture was purified by column chromatography to afford the ester **21a** (0.100 g, 0.179 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.29–7.21 (m, 7H), 7.21–7.15 (m, 2H), 7.08–7.00 (m, 2H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.68 (s, 2H), 4.53 (s, 2H), 3.90 (s, 3H), 3.63 (s, 2H), 2.45 (s, 3H). HRMS (ESI+ve) *m/z* 559.1871 $[M+H]^+$ (calcd for $C_{31}H_{31}N_2O_6S$ 559.1897.

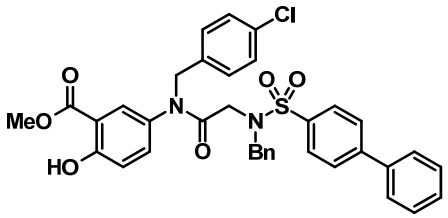


Methyl 5-(*N*-benzyl-2-(*N*-benzylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoate (**21b**). This was obtained as a solid (0.108 g, 75%) from acid **20f** (0.093 g, 0.244 mmol) and amine **19a** (0.060 g, 0.233 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.00 (d, *J* = 10.4 Hz, 1H), 7.73 (d, *J* = 10.3 Hz, 1H), 7.65–7.62 (m, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.44–7.39 (m, 1H), 7.30–7.16 (m, 9H), 7.07–7.04 (m, 2H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.69 (s, 2H), 4.58 (s, 2H), 3.91 (s, 3H), 3.68 (s, 2H). HRMS (ESI+ve) *m/z* 621.2022 $[M+H]^+$ (calcd for $C_{36}H_{33}N_2O_6S$ 621.2054).

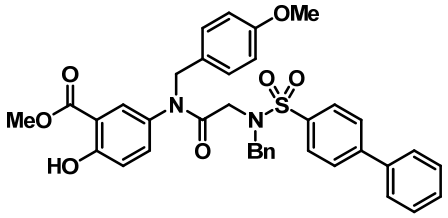


Methyl 5-(2-(*N*-benzyl-4-methylphenylsulfonamido)-*N*-(4-chlorobenzyl)acetamido)-2-hydroxybenzoate (21c). This was obtained as a solid (0.170 g, 70%) from acid **20c** (0.153 g, 0.482 mmol) and amine **19d** (0.120

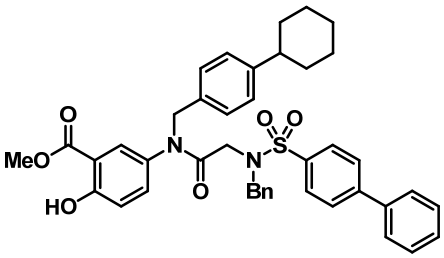
g, 0.411 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.26–7.22 (m, 6H), 7.18–7.13 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 1H), 6.56 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.64 (s, 2H), 3.92 (s, 2H), 3.63 (s, 3H), 2.45 (s, 3H). HRMS (ESI+ve) *m/z* 593.1482 $[M+H]^+$ (calcd for $C_{31}H_{30}ClN_2O_6S$ 593.1508).



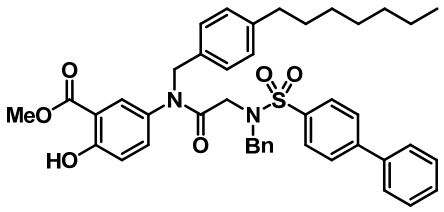
Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(4-chlorobenzyl)acetamido)-2-hydroxybenzoate (21d). This was obtained as a solid (0.114 g, 75%) from acid **20f** (0.093 g, 0.244 mmol) and amine **19d** (0.068 g, 0.233 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.54–7.47 (m, 1H), 7.44–7.38 (m, 1H), 7.25–7.20 (m, 4H), 7.02–7.16 (m, 4H), 7.00 (d, *J* = 8.4 Hz, 1H). 6.78 (d, *J* = 8.8 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.65 (s, 2H), 4.57 (s, 2H), 3.92 (s, 3H), 3.67 (s, 2H). HRMS (ESI+ve) *m/z* 655.1634 $[M+H]^+$ (calcd for $C_{36}H_{32}ClN_2O_6S$ 655.1664).



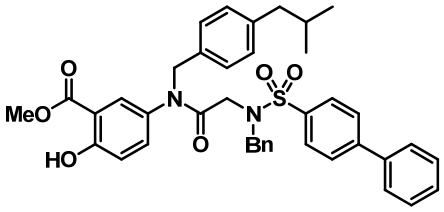
Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(4-methoxybenzyl)acetamido)-2-hydroxybenzoate (21e). This was obtained as a solid (0.111 g, 89%) from acid **20f** (0.084 g, 0.219 mmol) and amine **19c** (0.060 g, 0.209 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.51–7.45 (m, 1H), 7.44–7.37 (m, 1H), 7.29–7.14 (m, 7H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.77–6.70 (m, 3H), 6.53 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.63 (s, 2H), 4.59 (s, 2H), 3.74 (s, 3H), 3.66 (s, 2H). HRMS (ESI+ve) *m/z* 651.2126 $[M+H]^+$ (calcd for $C_{37}H_{35}N_2O_7S$ 651.2159 found.



Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(4-cyclohexylbenzyl)acetamido)-2-hydroxybenzoate (21f). This was obtained as a solid (0.146 g, 71%) from acid **20f** (0.118 g, 0.309 mmol) and amine **19b** (0.100 g, 0.294 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.01 (d, *J* = 10.3 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 7.0 Hz, 2H), 7.53–7.46 (m, 2H), 7.45–7.38 (m, 1H), 7.24–7.20 (m, 7H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.65 (s, 2H), 4.61 (s, 2H), 3.91 (s, 3H), 3.67 (s, 2H), 2.49–2.35 (m, 1H), 1.78 (m, 6H), 1.44–1.14 (m, 4H).

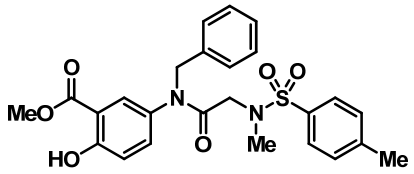


Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(4-heptylbenzyl)acetamido)-2-hydroxybenzoate (**21g**). This was obtained as a solid (0.160 g, 79%) from acid **20f** (0.112 g, 0.295 mmol) and amine **19i** (0.100 g, 0.282 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.29–7.13 (m, 6H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.66 (s, 2H), 3.92 (s, 2H), 3.68 (s, 3H), 2.66–2.35 (m, 2H), 1.66–1.46 (m, 1H), 1.35–1.17 (m, 9H), 0.88 (t, *J* = 6.9 Hz, 3H). HRMS (ESI+ve) *m/z* 719.3146 $[M+H]^+$ (calcd for $C_{43}H_{47}N_2O_6S$ 719.3149).

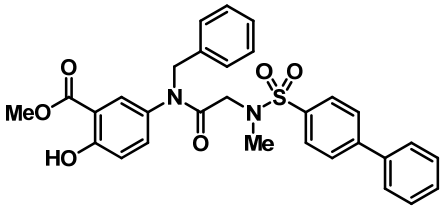


Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(4-isobutylbenzyl)acetamido)-2-hydroxybenzoate (21h). This was obtained as a solid (0.120 g, 70%) from acid **20f** (0.102 g, 0.344 mmol) and amine **19g** (0.100 g, 0.319 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.3 Hz,

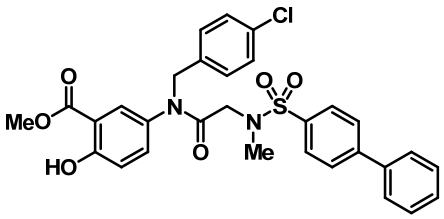
1H), 7.27–7.17 (m, 7H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.57 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.66 (s, 2H), 4.60 (s, 2H), 3.89 (s, 3H), 3.67 (s, 2H), 2.41 (d, *J* = 7.2 Hz, 2H), 1.89–1.68 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 5H). HRMS (ESI+ve) *m/z* $[M+H]^+$ 677.2686 (calcd for $C_{40}H_{41}N_2O_6S$ 677.2680).



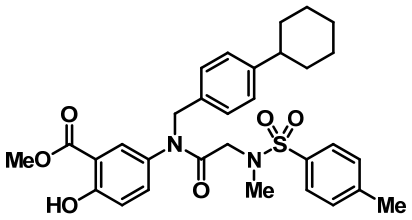
Methyl 5-(*N*-benzyl-2-(*N*,4-dimethylphenylsulfonamido)acetamido)-2-hydroxybenzoate (21i). This was obtained as a solid from acid **20f** (0.083 g, 0.342 mmol) and amine **19a** (0.084 g, 0.326 mmol) in the same manner as described for **21a** and used immediately in the next step.



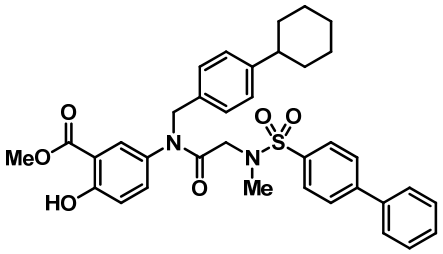
Methyl 5-(*N*-benzyl-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoate (21j). This was obtained as a solid (50-55%) from acid **20c** (0.250 g, 0.818 mmol) and amine **19a** (0.200 g, 0.778 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 8.3, 1.2 Hz, 3H), 7.51 (d, *J* = 2.6 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 2.3 Hz, 0H), 7.28–7.23 (m, 4H), 7.12 (d, *J* = 2.6 Hz, 1H), 7.00 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.79 (s, 2H), 3.94 (s, 3H), 3.78 (s, 2H), 2.93 (s, 3H).



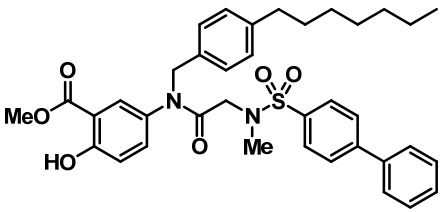
Methyl 5-(*N*-(4-chlorobenzyl)-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoate (21k). This was obtained as a solid from acid **20c** and amine **19d** in the same manner as described for **21a** and used immediately in the next step.



Methyl 5-(*N*-(4-cyclohexylbenzyl)-2-(*N*,4-dimethylphenylsulfonamido)acetamido)-2-hydroxybenzoate (21l). This was obtained as a solid (40-45%) from acid **20a** (0.075 g, 0.309 mmol) and amine **19b** (0.100 g, 0.294 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.05–6.97 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.73 (s, 2H), 3.93 (s, 3H), 3.70 (s, 2H), 2.86 (s, 3H), 2.47 (s, 3H), 2.48–2.41 (m, 1H), 1.79–1.65 (m, 6H), 1.46–1.15 (m, 4H).

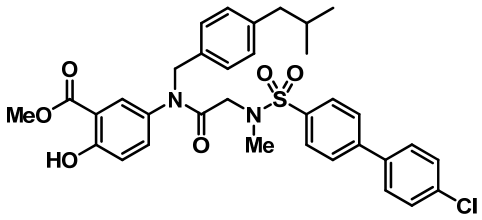


Methyl 5-(*N*-(4-cyclohexylbenzyl)-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxy-benzoate (21m). This was obtained as a solid (0.060 g, 0.096 mmol, 45%) from acid **20c** (0.076 g, 0.248 mmol) and **19b** (0.080 g, 0.236 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.63–7.59 (m, 3H), 7.50–7.45 (m, 2H), 7.44–7.40 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.03–6.98 (m, 3H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.73 (s, 2H), 3.93 (s, 3H), 2.93 (s, 3H), 2.44–2.42 (m, 1H), 1.82–1.73 (m, 6H), 1.42–1.14 (m, 2H). HRMS (ESI+ve) *m/z* 637.2529 $[M+H]^+$ (calcd for $C_{36}H_{39}N_2O_6S$ 627.2523).

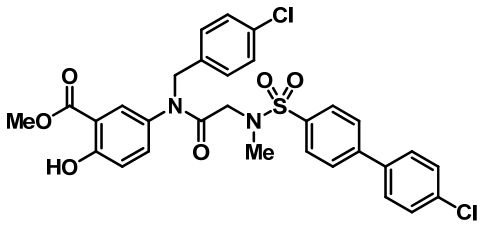


5-(*N*-(4-Heptylbenzyl)-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoic acid (21n). This was obtained as a solid (0.088 g, 50%) from acid **20c** (0.090 g, 0.294 mmol) and amine **19i** (0.100 g, 0.282 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 6.7 Hz, 1H), 7.63–7.59 (m, 2H), 7.52–7.45 (m, 2H), 7.44–7.39 (m, 1H), 7.10–6.97 (m,

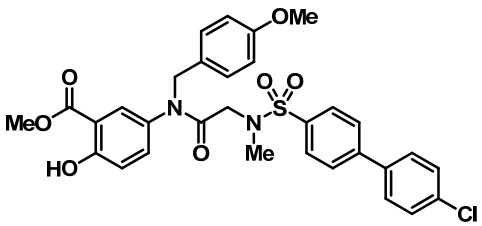
5H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.75 (s, 2H), 3.93 (s, 3H), 3.76 (s, 2H), 2.93 (s, 3H), 2.63–2.42 (m, 2H), 1.60–1.46 (m, 1H), 1.37–1.18 (m, 9H), 1.03–0.71 (m, 3H).



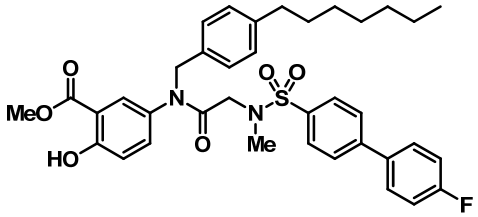
Methyl 5-(2-(4'-chloro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-isobutylbenzyl)acetamido)-2-hydroxybenzoate (21o). This was obtained as a solid (0.141g, 87%) from acid **20b** (0.091 g, 0.268 mmol) and amine **19g** (0.080 g, 0.255 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 7.87 (d, *J* = 1.5 Hz, 1H), 7.65 (d, *J* = 1.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.47–7.42 (m, 3H), 7.02–7.98 (m, 4H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.75 (s, 2H), 3.92 (s, 3H), 3.78 (s, 2H), 2.93 (s, 3H), 2.42 (d, *J* = 7.2 Hz, 2H), 1.76–1.86 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 6H). HRMS (ESI+ve) *m/z* 635.1982 $[M+H]^+$ (calcd for $C_{34}H_{36}ClN_2O_6S$ 635.1977).



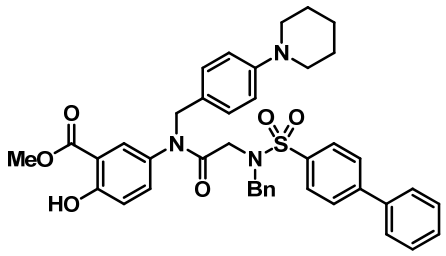
Methyl 5-(2-(4'-chloro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-chlorobenzyl)acetamido)-2-hydroxybenzoate (21p). This was obtained as a solid (0.085 g, 60%) from acid **20b** (0.083 g, 0.244 mmol) and amine **19d** (0.068 g, 0.233 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 6.7 Hz, 1H), 7.03–6.90 (m, 2H), 4.74 (s, 2H), 3.94 (s, 3H), 3.76 (s, 2H), 2.89 (s, 3H).



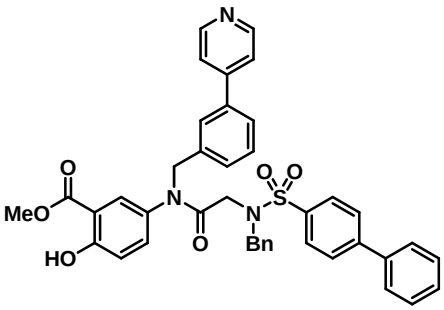
Methyl 5-(2-(4'-chloro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-methoxybenzyl)acetamido)-2-hydroxybenzoate (21q). This was obtained as a solid (0.100 g, 73%) from acid **20b** (0.075 g, 0.219 mmol) and amine **19c** (0.060 g, 0.209 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H)., 6.98–6.87 (m, 2H), 6.75 (d, *J* = 8.6 Hz, 1H), 4.71 (s, 2H), 3.94 (s, 3H), 3.76 (s, 5H), 2.90 (s, 3H). HRMS (ESI+ve) m/z 609.1448 $[M+H]^+$ (calcd for $C_{31}H_{30}ClN_2O_7S$ 609.1457).



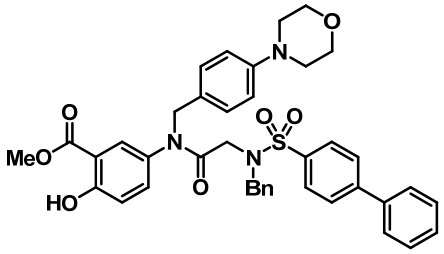
Methyl 5-(2-(4'-fluoro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-heptylbenzyl)acetamido)-2-hydroxybenzoate (21r). This was obtained as a solid from acid **20d** (0.095 g, 0.295 mmol) and amine **19i** (0.100 g, 0.282 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.58 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 7.03–6.90 (m, 4H), 4.75 (s, 2H), 3.94 (s, 3H), 3.78 (s, 2H), 2.92 (s, 3H), 2.64–2.46 (m, 2H), 1.56 (s, 1H), 1.42–1.17 (m, 9H), 0.99–0.77 (m, 3H).



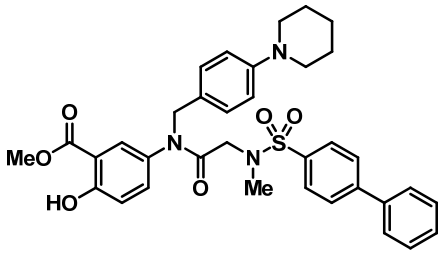
Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(4-(piperidin-1-yl)benzyl)acetamido)-2-hydroxybenzoate (21s). This was obtained as a solid (0.113 g, 55%) from acid **20f** (0.117 g, 0.308 mmol) and amine **19h** (0.100 g, 0.294 mmol) in the same manner as described for **21a** and was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.68–7.65 (m, 3H), 7.53–7.46 (m, 2H), 7.30–7.20 (m, 6H), 6.90–6.87 (m, 2H), 6.74 (dd, *J* = 8.7, 1.7 Hz, 2H), 6.55 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.63 (s, 2H), 3.94 (s, 2H), 3.92 (s, 3H), 3.66 (s, 2H), 3.21–2.84 (m, 4H), 1.77–1.42 (m, 6H). HRMS (ESI+ve) *m/z* 704.2788 $[M+H]^+$ (calcd for $C_{41}H_{42}N_3O_6S$ 704.2789).



Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(3-(pyridin-4-yl)benzyl)acetamido)-2-hydroxybenzoate (21t). This was obtained as a solid (0.085 g, 50%) from acid **20f** (0.119 g, 0.313 mmol) and amine **19f** (0.100 g, 0.299 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.63 (s, 2H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.73–7.60 (m, 8H), 7.59–7.33 (m, 16H), 7.29–7.12 (m, 7H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.65 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.79 (s, 2H), 4.56 (s, 2H), 3.90 (s, 2H), 3.71 (s, 3H). HRMS (ESI+ve) *m/z* 698.2330 $[M+H]^+$ (calcd for $C_{41}H_{36}N_3O_6S$ 698.2319).

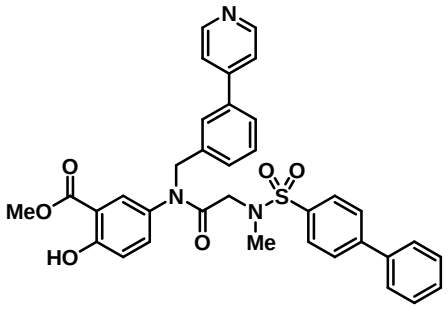


Methyl 5-(2-(*N*-benzylbiphenyl-4-ylsulfonamido)-*N*-(4-morpholinobenzyl)acetamido)-2-hydroxybenzoate (21u). This was obtained as a solid (0.100 g, 60%) from acid **20f** (0.117 g, 0.308) and amine **19e** (0.100 g, 0.294 mmol) in the same manner as described for **21a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.69–7.62 (m, 3H), 7.53–7.48 (m, 2H), 7.45–7.39 (m, 1H), 7.34–7.20 (m, 7H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.77 (s, 1H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.57 (dd, *J* = 8.9, 2.7 Hz, 1H), 4.64 (s, 3H), 3.93 (s, 4H), 3.87–3.81 (m, 7H), 3.66 (s, 2H), 3.12–3.02 (m, 7H).



Methyl 2-hydroxy-5-(2-(*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-(piperidin-1-yl)benzyl)acetamido)-benzoate (21v). This was obtained as a solid (0.080 g, 45%) from acid **20c** (0.094g g, 0.308 mmol) and amine **19h** (0.100 g, 0.294 mmol) in the same manner as described for **21a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s,

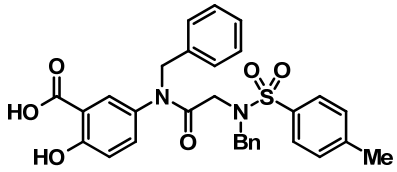
1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.63–7.58 (m, 2H), 7.51–7.44 (m, 3H), 7.41–7.40 (m, , 1H), 6.99–6.89 (m, 5H), 6.76 (d, *J* = 8.7 Hz, 2H), 4.67 (s, 2H), 3.95 (s, 3H), 3.74 (s, 2H), 3.13–3.01 (m, 4H), 2.93 (s, 3H), 1.67–1.65 (m, 4H), 1.59–1.48 (m, 1H); HRMS (ESI+ve) *m/z* 628.2475 $[M+H]^+$ (calcd for $C_{35}H_{36}N_3O_6S$ 628.2476).



Methyl 2-hydroxy-5-(2-(*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(3-(pyridin-4-yl)benzyl)acetamido)-benzoate (21w). This was obtained as a solid (0.050 g, 27%) from acid **20c** (0.096 g, 0.313 mmol) and amine **19f** (0.100 g, 0.299 mmol) in the same manner as described for **21a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.67–8.57 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.66–7.65 (m, 3H), 7.61–7.51 (m, 5H), 7.51–7.32 (m, 8H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 4.88 (s, 2H), 3.92 (s, 3H), 3.78 (s, 2H), 2.98 (s, 3H).

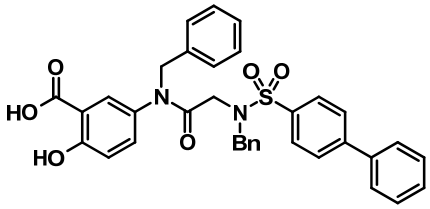
Synthesis of carboxylic acids 11

General protocol: Methyl ester **21** (0.1 mmol) was dissolved in THF (2 ml) and 2M NaOH (excess) was added. The resulting biphasic mixture was refluxed overnight and then acidified to pH 2 with 4N HCl. The precipitated solids were collected by filtration and dried to afford the desired acids in 70-80% yields.

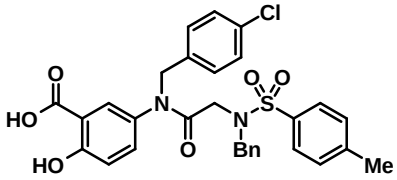


5-(*N*-Benzyl-2-(*N*-benzyl-4-methylphenylsulfonamido)acetamido)-2-hydroxybenzoic acid (11a). A mixture of **21a** (0.107 g, 0.107 mmol) in THF (2 mL) and sodium hydroxide (aq. 1 M, 2 mL) was refluxed overnight. The solvent was then removed under reduced pressure. The resulting solid was slurried in HCl (aq. 4 M), filtered, washed with HCl and dried under vacuum to afford **11a** as a solid (0.046 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.26–7.16 (m, 7H), 7.16–7.14 (m, 2H), 7.06–7.04 (m, 2H), 6.70 (m, 1H), 6.58–6.57 (m, 1H), 4.63 (s, 2H), 4.42 (s, 2H), 2.55 (s, 2H), 2.38(s, 3H); HRMS (ESI–ve)

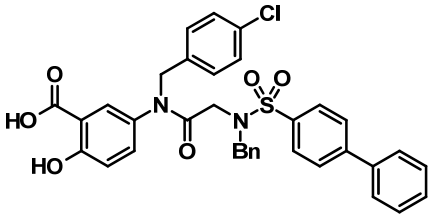
m/z 543.1596 [M–H]$^-$ (calcd for $C_{30}H_{27}N_2O_6S$ 543.1595); LC-MS (ESI–ve) 543.16; HPLC purity 100% [t_R = 9.3 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].



5-(*N*-Benzyl-2-(*N*-benzylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoic acid (11b). This was obtained as a solid (0.054 g, 92%) from **21b** (0.060 g, 0.097 mmol) in the same manner as described for **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (q, *J* = 8 Hz, 4H), 7.75 (d, *J* = 8 Hz, 2H), 7.51 (t, *J* = 8 Hz, 2H), 7.46–7.44 (m, 1H), 7.33–7.18 (m, 9H), 7.05 (d, *J* = 8 Hz, 2H), 6.72–6.50 (m, 2H), 4.63 (s, 2H), 4.49 (s, 2H), 3.65 (s, 1H); HRMS (ESI–ve) *m/z* 605.1755 [M–H]$^-$ (calcd for $C_{35}H_{29}N_2O_6S$ 605.1752); LC-MS (ESI–ve) 605.18; HPLC purity 100% [t_R = 17.8 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].

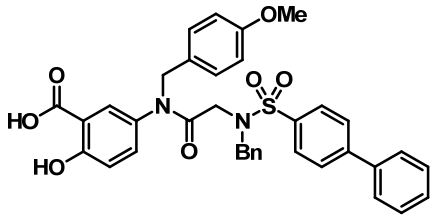


5-(2-(*N*-Benzyl-4-methylphenylsulfonamido)-*N*-(4-chlorobenzyl)acetamido)-2-hydroxybenzoic acid (11c). This was obtained as a solid (0.050 g, mmol, 86%) from **21c** (0.060 g, 0.101 mmol) in the same manner as described for **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.36–7.25 (m, 8H), 7.16–7.14 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.68–6.67 (m, 1H), 6.58–6.56 (m, 1H), 4.61 (s, 2H), 4.42 (s, 2H), 3.58 (s, 2H), 3.35 (s, 3H); HRMS (ESI–ve) *m/z* 577.1210 [M–H]$^-$ (calcd for $C_{30}H_{26}ClN_2O_6S$ 577.1206); LC-MS (ESI–ve) 577.11; HPLC purity 100% [t_R = 8.9 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].

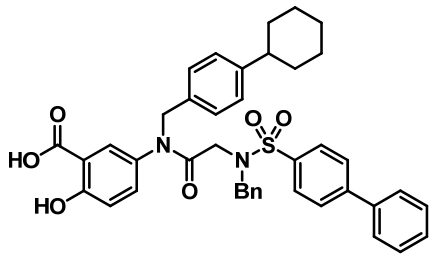


5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(4-chlorobenzyl)acetamido)-2-hydroxybenzoic acid (11d). This was obtained as a solid (0.052 g, mmol, 88%) from **21d** (0.060 g, 0.092 mmol) in the same manner as described for **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (q, *J* = 8 Hz, 4H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8 Hz, 2H), 7.36–7.45 (m, 1H), 7.30–7.26 (m, 6H), 7.21–7.19 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.71–6.69 (m,

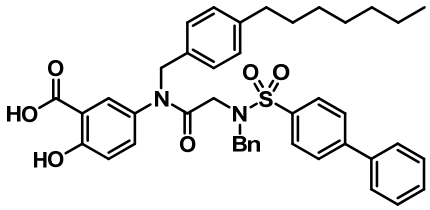
1H), 6.57–6.55 (m, 1H), 4.61 (s, 2H), 4.49 (s, 2H), 3.65 (s, 2H); HRMS (ESI–ve) *m/z* 639.1364 $[M–H]^-$ (calcd for $C_{35}H_{28}ClN_2O_6S$ 639.1362); LC-MS (ESI–ve) 639.13; HPLC purity 99% [t_R = 9.9 min, flow 1 ml/min, (MeCN:H_2O, 70:30)].



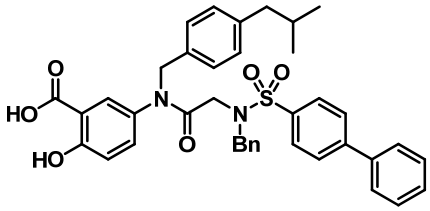
5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(4-methoxybenzyl)acetamido)-2-hydroxybenzoic acid (11e). This was obtained as a solid (0.054 g, 92%) from **21e** (0.060 g, 0.092 mmol) in the same manner as described for **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (broad s, 1H), 7.79–7.76 (m, 2H), 7.55–7.52 (m, 2H), 7.46–7.44 (m, 1H), 7.28–7.25 (m, 4H), 7.21–7.18 (m, 2H), 6.93 (d, *J* = 8 Hz, 2H), 6.74 (d, *J* = 8 Hz, 2H), 6.59–6.56 (m, 1H), 6.52–6.49 (m, 1H), 4.54 (s, 2H), 4.51 (s, 2H), 3.65 (s, 3H), 3.60 (s, 2H); HRMS (ESI–ve) *m/z* 635.1857 $[M–H]^-$ (calcd for $C_{36}H_{31}N_2O_7S$ 635.1857); LC-MS (ESI–ve) 635.138; HPLC purity 98% [t_R = 16.5 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].



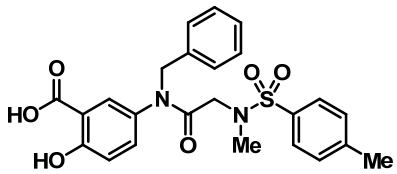
5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(4-cyclohexylbenzyl)acetamido)-2-hydroxybenzoic acid (11f). This was obtained as a solid (69%) from **21f** (0.100 g) in the same manner as described for **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93–7.89 (m, 4H), 7.79–7.76 (m, 2H), 7.53–7.44 (m, 3H), 7.32–7.18 (m, 4H), 7.0 (d, *J* = 8 Hz, 2 H), 6.90 (d, *J* = 8 Hz, 2H), 6.85–6.82 (m, 1H), 6.66–6.65 (m, 1H), 4.57 (s, 2H), 4.53 (s, 2H), 3.65 (s, 3H), 2.36 (m, 1H), 1.72–1.68 (m, 6H), 1.29–1.25 (m, 4H); HRMS (ESI–ve) *m/z* 635.2526 $[M–H]^-$ (calcd for $C_{41}H_{39}N_2O_6S$ 687.2534); LC-MS (ESI) 687.26; HPLC purity 99% [t_R = 7.3 min, flow 1 ml/min, (MeCN:H_2O, 80:20)].



5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(4-heptylbenzyl)acetamido)-2-hydroxybenzoic acid (11g). This was obtained as a solid (0.058 g) from **21g** in the same manner as described for **11a.** ^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.92–7.87 (m, 4H), 7.79–7.76 (m, 2H), 7.52–7.41 (m, 3H), 7.24–7.08 (m, 5H), 6.99 (d, *J* = 8 HZ, 2H), 6.91 (d, *J* = 8 Hz, 2H), 6.76–6.73 (m, 1H), 6.62–6.59 (m, 1H), 4.58 (s, 2H), 4.51 (s, 2H), 3.64 (s, 2H), 2.47–2.44 (m, 2H), 1.52–1.46 (m, 2H), 1.25–1.21 (m, 8H), 0.82 (t, *J* = 8 Hz, 3H); HRMS (ESI+ve) *m/z* 705.2986 $[M+H]^+$ (calcd for $C_{42}H_{45}N_2O_6S$ 705.2993) and 727.2808 $[M+Na]^+$ (calcd for $C_{42}H_{44}N_2O_6SNa$ 727.2812); LC-MS (ESI+ve) 705.32; HPLC purity 98% [t_R = 8.0 min, flow 1 ml/min, (MeCN:H_2O, 90:10)].

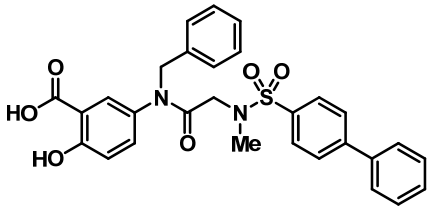


5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(4-isobutylbenzyl)acetamido)-2-hydroxybenzoic acid (11h). This was obtained as a solid (0.050 g) from **21h** in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92–7.87 (m, 4H), 7.79–7.76 (m, 2H), 7.53–7.41 (m, 3H), 7.28–7.17 (m, 6H), 6.95 (dd, *J* = 8, 24 Hz, 4H), 6.63–6.59 (m, 1H), 6.51–6.48 (m, 1H), 4.57 (s, 1H), 4.52 (s, 1H), 3.62 (s, 1H), 2.33 (d, *J* = 4 Hz, 2H), 1.71-1.68 (m, 1H), 0.80 (d, *J* = 6.8 Hz, 6H); HRMS (ESI+ve) *m/z* 663.2521 $[M+H]^+$ (calcd for $C_{39}H_{39}N_2O_6S$ 663.2523) and 685.2326 $[M+Na]^+$ (calcd for $C_{39}H_{38}N_2O_6SNa$ 685.2343); LC-MS (ESI) 663.27; HPLC purity 98% [t_R = 7.9 min, flow 1 ml/min, (MeCN:H_2O, 80:20)].

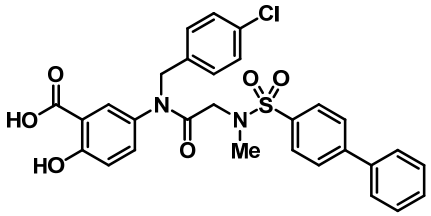


5-(*N*-Benzyl-2-(*N*,4-dimethylphenylsulfonamido)acetamido)-2-hydroxybenzoic acid (11i). This was obtained as a solid (0.030g, 78%) from **21i** (0.040 g, 0.083 mmol) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54–7.52 (m, 3H), 7.36–7.24 (m, 6H), 7.15–7.13 (m, 2H), 6.98–6.96 (m, 2H), 4.76 (s, 2H), 3.70 (s, 2H), 2.78 (s, 3H), 2.37 (s, 3H); HRMS (ESI–ve) *m/z* 467.1291 $[M–H]^-$ (calcd for

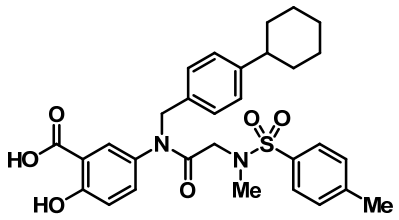
$C_{24}H_{23}N_2O_6S$ 467.1282); LC-MS (ESI–ve) 469.15; HPLC purity 99% [t_R = 11.0 min, flow 1 ml/min, (MeCN:H_2O, 50:50)].



5-(*N*-Benzyl-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoic acid (11j). This was obtained as a solid (0.034 g, 0.064 mmol, 87%) from **21j** (0.040 g, 0.074 mmol) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84–7.71 (m, 6H), 7.51–7.42 (m, 4H), 7.32–7.22 (m, 4H), 7.15–7.14 (m, 2H), 6.98–6.97 (m, 1H), 4.76 (s, 2H), 3.79 (s, 2H), 2.86 (s, 3H); HRMS (ESI–ve) *m/z* 529.1451 $[M–H]^-$ (calcd for $C_{29}H_{25}N_2O_6S$ 529.1439); LC-MS (ESI+ve) 531.17; HPLC purity 96% [t_R = 8.0 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].

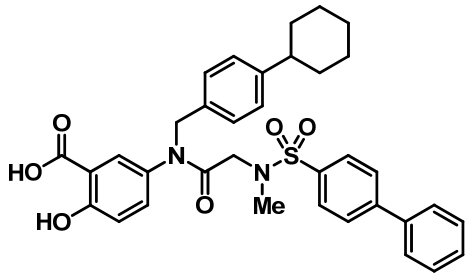


5-(*N*-(4-Chlorobenzyl)-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoic acid (11k). This was obtained as a solid from **21k** (0.060 g, 0.104 mmol) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, *J* = 8 Hz, 2H), 7.73–7.70 (m, 4H), 7.51–7.42 (m, 3H), 7.30–7.08 (m, 2H), 7.15 (d, *J* = 8 Hz, 2H), 7.09–7.08 (m, 1H), 6.78 (d, *J* = 8 Hz, 2H), 4.70 (s, 1H), 3.75 (s, 2H), 2.84 (s, 3H); HRMS (ESI+ve) *m/z* 565.1178 $[M+H]^+$ (calcd for $C_{29}H_{26}ClN_2O_6S$ 565.1195) and 587.1000 $[M+Na]^+$ (calcd for $C_{29}H_{25}ClN_2O_6SNa$ 587.1014); HPLC purity 95% [t_R = 7.0 min, flow 1 ml/min, (MeCN:H_2O, 65:35)].

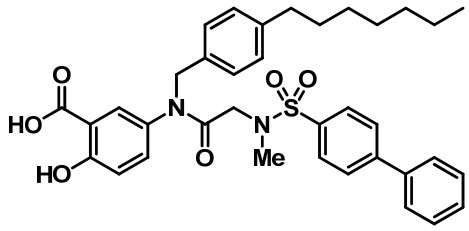


5-(*N*-(4-Cyclohexylbenzyl)-2-(*N*,4-dimethylphenylsulfonamido)acetamido)-2-hydroxybenzoic acid (11l). This was obtained as a solid (80%) from **21l** (0.030 g, 0.053 mmol) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 4 Hz, 1H), 7.33 (d, *J* = 8 Hz, 2H), 7.24

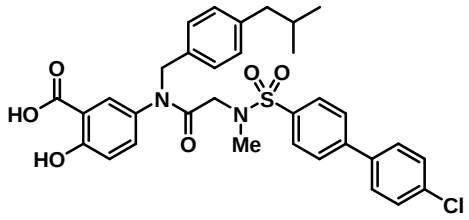
(dd, J = 4, 8 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 2H), 6.91 (d, J = 8 Hz, 1H), 4.68 (s, 2H), 3.66 (s, 2H), 2.75 (s, 3H), 2.46–2.42 (m, 1H), 2.35 (s, 3H), 1.77–1.73 (m, 5H), 1.33–121 (m, 5H); HRMS (ESI–ve) *m/z* 549.2072 $[M–H]^-$ (calcd for $C_{30}H_{33}N_2O_6S$ 549.2065); LC-MS (ESI–ve) 549.21; HPLC purity 98% [t_R = 8.8 min, flow 1 ml/min, (MeCN:H_2O, 70:30)].



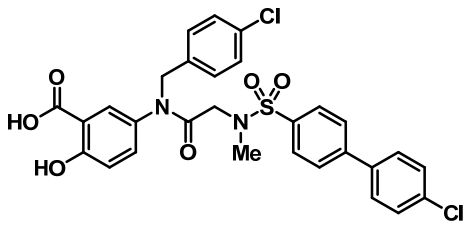
5-(*N*-(4-Cyclohexylbenzyl)-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoic acid (11m). This was obtained as a solid from **21m** (0.045 g, 0.0719 mmol) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 8 Hz, 2H), 7.76–7.74 (m, 4 H), 7.53–7.44 (m, 4H), 7.25 (dd, J = 4, 8 Hz, 1H), 7.07 (d, J = 8 Hz, 2H), 6,97 (d, J = 8 Hz, 2H), 6.93 (d, J = 8 Hz, 1H), 4.68 (s, 2H), 3.77 (s, 2H), 2.87 (s, 3H), 2.45–2.40 (m, 1H), 1.74–1.69 (m, 5H), 1.31–1.50 (m, 5H); HRMS (ESI–ve) *m/z* 611.2226 $[M–H]^-$ (calcd for $C_{35}H_{35}N_2O_6S$ 611.2221); LC-MS (ESI) 611.23; HPLC purity 93% [t_R = 14.7 min, flow 1 ml/min, (MeCN:H_2O, 70:30)].



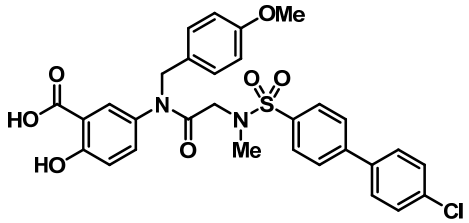
5-(*N*-(4-Heptylbenzyl)-2-(*N*-methylbiphenyl-4-ylsulfonamido)acetamido)-2-hydroxybenzoic acid (11n). This was obtained as a solid from **21n** (0.050 g) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 8 Hz, 2H), 7.70 (m, 4H), 7.51–7.42 (m, 4H), 7.12–6.98 (m, 5H), 6.81 (d, J = 8 Hz, 1H), 4.67 (s, 2H), 3.75 (s, 2H), 2.85 (s, 3H), 2.40 (broad s, 2H), 1.52–1.47 (m, 2H), 1.25–1.21 (m, 8H), 0.82 (t, J = 8 Hz, 3H); HRMS (ESI+ve) *m/z* 629.2669 $[M+H]^+$ (calcd for $C_{36}H_{41}N_2O_6S$ 629.2680) and 651.2490 $[M+Na]^+$ (calcd for $C_{36}H_{40}N_2O_6S$ 651.2499); LC-MS (ESI) 629.28; HPLC purity 96% [t_R = 10.7 min, flow 1 ml/min, (MeCN:H_2O, 80:20)].



5-(2-(4'-Chloro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-isobutylbenzyl)acetamido)-2-hydroxybenzoic acid (11o). This was obtained as a solid (0.040 g) from **21o** (0.050 g, 0.079 mmol) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.84 (d, *J* = 8 Hz, 2H), 7.78–7.75 (m, 4H), 7.55 (d, *J* = 8 Hz, 2H), 7.41 (d, *J* = 4 Hz, 1H), 7.05 (dd, *J* = 4, 8 Hz, 1H), 7.01–6.97 (m, 4H), 6.76 (d, *J* = 8 Hz, 1H), 4.65 (s, 2H), 3.74 (s, 2H), 2.86 (s, 3H), 2.34 (d, *J* = 8 Hz, 2H), 1.77–1.72 (m, 1H), 0.79 (s, 3H), 0.78 (s, 3H); HRMS (ESI+ve) *m/z* 621.1808 $[M+H]^+$ (calcd for $C_{33}H_{34}ClN_2O_6S$ 621.1821) and 643.1684 $[M+Na]^+$ (calcd for $C_{33}H_{33}ClN_2O_6SNa$ 643.1640); LC-MS (ESI+ve) 621.02; HPLC purity 99% [t_R = 6.0 min, flow 1 ml/min, (MeCN:H_2O, 80:20)].

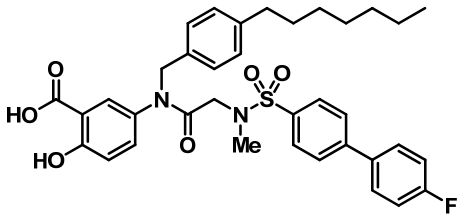


5-(2-(4'-Chloro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-chlorobenzyl)acetamido)-2-hydroxybenzoic acid (11p). This was obtained as a solid (0.043 g, 73%) from **21p** (0.060 g, 0.98 mmol) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.77–7.74 (m, 4H), 7.55 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 4H, 1H), 7.30 (d, *J* = 8 Hz, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.03 (dd, *J* = 8, 4 Hz, 1H), 6.74 (d, *J* = 8 Hz, 1H), 4.69 (s, 2H), 3.74 (s, 2H), 2.84 (s, 3H); HRMS (ESI–ve) *m/z* 597.0662 $[M-H]^-$ (calcd for $C_{29}H_{23}ClN_2O_6S$ 597.0659); LC-MS (ESI–ve) 597.07; HPLC purity 95% [t_R = 17.3 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].

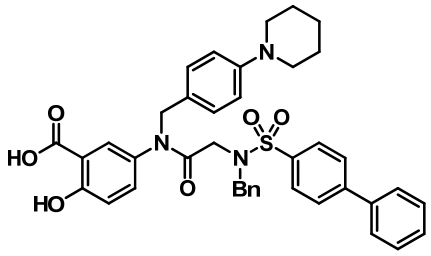


5-(2-(4'-Chloro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-methoxybenzyl)acetamido)-2-hydroxybenzoic acid (11q). This was obtained as a solid (0.035 g, 60%) from **21q** (0.060 g, 0.099 mmol) in the same manner as

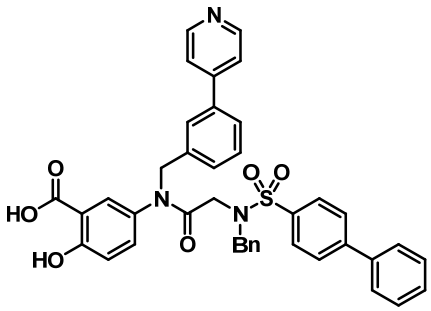
described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 8 Hz, 2H), 7.78–7.74 (m, 4H), 7.55 (d, *J* = 8 Hz, 2H), 7.43 (d, *J* = 4 Hz, 1H), 7.07–7.00 (m, 4H), 6.78 (d, *J* = 8 Hz, 2H), 4.63 (s, 2H), 3.72 (s, 2H), 3.67 (s, 3H), 2.84 (s, 3H); HRMS (ESI–ve) *m/z* 593.1154 $[M–H]^-$ (calcd for $C_{30}H_{26}ClN_2O_6S$ 593.1155); LC-MS (ESI–ve) 593.11; HPLC purity 96% [t_R = 11.3 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].



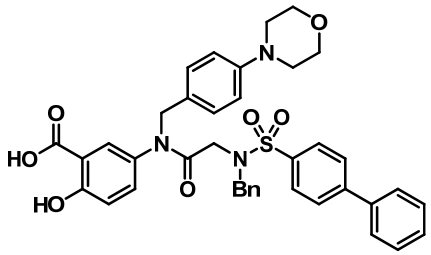
5-(2-(4'-Fluoro-*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-heptylbenzyl)acetamido)-2-hydroxybenzoic acid (11r). This was obtained as a solid from **21r** (0.080 g) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83–7.71 (m, 6H), 7.45 (d, *J* = 4 Hz, 1H), 7.36–7.33 (m, 2H), 7.04–6.97 (m, 5H), 6.75 (d, *J* = 8 Hz, 1H), 4.66 (s, 2H), 3.74 (s, 2H), 2.85 (s, 3H), 1.52–1.45 (m, 2H), 1.26–1.22 (m, 10H), 0.83 (t, *J* = 7.2 Hz, 3H); HRMS (ESI–ve) *m/z* 645.2433 $[M–H]^-$ (calcd for $C_{36}H_{38}FN_2O_6S$ 645.2440); LC-MS (ESI–ve) 645.23; HPLC purity 95% [t_R = 7.3 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].



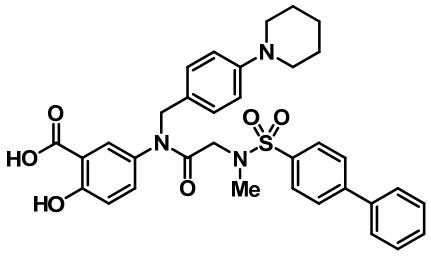
5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(4-(piperidin-1-yl)benzyl)acetamido)-2-hydroxybenzoic acid (11s). This was obtained as a solid (0.050 g) from **21s** in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91–7.86 (m, 4H), 7.77–7.75 (m, 2H), 7.53–7.49 (m, 2H), 7.47–7.42 (m, 1H), 7.32–7.26 (m, 4H), 7.21–7.15 (m, 2H), 6.95–6.91 (m, 1H), 6.81–6.78 (m, 3H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.52 (s, 2H), 4.51 (s, 2H), 3.63 (s, 2H), 3.01–2.98 (m, 4H), 1.72–1.34 (m, 6H); HRMS (ESI+ve) *m/z* 690.2638 $[M+H]^+$ (calcd for $C_{40}H_{40}N_3O_6S$ 690.2632); HPLC purity 72% [t_R = 2.8 min, flow 1 ml/min, (MeCN:H_2O, 65:35)].



5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(3-(pyridin-4-yl)benzyl)acetamido)-2-hydroxybenzoic acid (11t). This was obtained as a solid (0.050 g) from **21t** in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, *J* = 6.3 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.83–7.77 (m, 4H), 7.73–7.68 (m, 4H), 7.64–7.41 (m, 15H), 7.27–7.17 (m, 6H), 7.12 (d, *J* = 2.7 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 4.78 (s, 2H), 4.46 (s, 2H), 3.65 (s, 2H); HRMS (ESI+ve) *m/z* 684.2163 $[M+H]^+$ (calcd for $C_{40}H_{34}N_3O_6S$ 684.2163); HPLC purity 96% [t_R = 4.0 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].

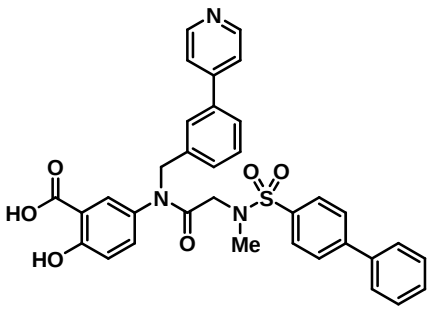


5-(2-(*N*-Benzylbiphenyl-4-ylsulfonamido)-*N*-(4-morpholinobenzyl)acetamido)-2-hydroxybenzoic acid (11u). This was obtained as a solid (0.056 g) from **21u** in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91–7.86 (s, 4H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 2.7 Hz, 1H), 7.29–7.23 (m, 3H), 7.21–7.17 (m, 2H), 6.95 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 4H), 6.71 (d, *J* = 8.7 Hz, 2H), 4.53 (s, 4H), 3.68–3.65 (m, 2H), 3.64 (s, 2H), 2.97–2.90 (m, 4H). HRMS (ESI–ve) *m/z* 690.2278 $[M-H]^-$ (calcd for $C_{39}H_{36}N_3O_7S$ 690.2279); HPLC purity 92% [t_R = 7.9 min, flow 1 ml/min, (MeCN:H_2O, 50:50)].



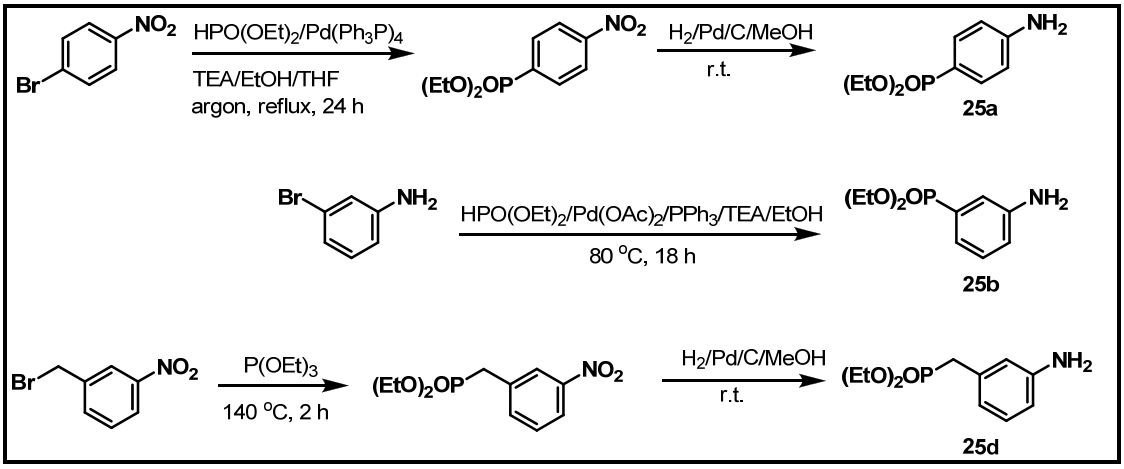
2-Hydroxy-5-(2-(*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(4-(piperidin-1-yl)benzyl)acetamido)benzoic acid (11v). This was obtained as a solid from **21v** (0.050 g) in the same manner as described for **11a.** ^{1}H NMR (400

MHz, DMSO-d_6) δ 7.84 (m, 3H), 7.75–7.67 (m, 4H), 7.56–7.40 (m, 4H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.06–6.94 (m, 4H), 4.65 (s, 2H), 3.75 (s, 2H), 3.14 (s, 4H), 2.85 (s, 3H), 1.64–1.52 (m, 6H); HRMS (ESI+ve) *m/z* 614.2305 $[M+H]^+$ (calcd for $C_{34}H_{36}N_3O_6S$ 614.2319); HPLC purity 98% [t_R = 13.5 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].

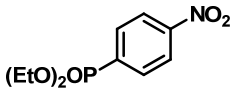


2-Hydroxy-5-(2-(*N*-methylbiphenyl-4-ylsulfonamido)-*N*-(3-(pyridin-4-yl)benzyl)acetamido)benzoic acid (11w). This was obtained as a solid from **21w** (0.050 g) in the same manner as described for **11a.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, *J* = 6.2 Hz, 2H), 7.83–7.78 (m, 1H), 7.76–7.67 (m, 8H), 7.64–7.57 (m, 3H), 7.53–7.41 (m, 5H), 7.37 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 4.86 (s, 2H), 3.81 (s, 3H), 2.83 (s, 4H); HRMS (ESI+ve) *m/z* 608.1832 $[M+H]^+$ (calcd for $C_{34}H_{30}N_3O_6S$ 608.1850); HPLC purity 95% [t_R = 11.9 min, flow 1 ml/min, (MeCN:H_2O, 60:40)].

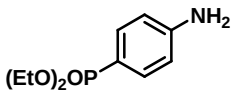
Synthesis of diethyl phosphonylanilines 25



Scheme S1. Synthesis of the phosphonate-containing anilines **25a**, **25b** and **25d.**

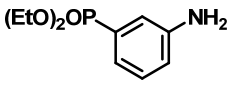


Diethyl 4-nitrophenylphosphonate.[4] 1-bromo-4-nitrobenzene (2.02 g, 10 mmol) was suspended in EtOH (10 ml) and THF (5 ml) was added to afford a homogeneous solution. The solution was degassed, a vacuum applied to the flask, which was then filled with argon. This process was repeated 3 times. The catalyst $Pd(Ph_3P)_4$ (0.578 g, 0.5 mmol) was added under argon atmosphere and the mixture was again degassed, a vacuum applied to the flask which was then refilled with argon. Triethylamine (2.8 ml, 20 mmol) and diethyl phosphite (1.93 ml, 15 mmol) were added via syringe. The resulting solution was refluxed for 24 h under argon and cooled to room temperature. The insoluble material was filtered and the filtrate concentrated to provide the crude product which was dissolved in EtOAc (50 ml) and filtered**.** The residue was washed with EtOAc (2 × 25 ml). The combined filtrates were concentrated and the crude product was purified via flash chromatography (50 silica gel, DCM/CH_3OH gradient) affording diethyl 4-nitrophenylphosphonate (3.44 g, containing *ca.* 14% diethyl phosphite in weight) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33–8.28 (m, 2H), 8.04–7.97 (m, 2H), 4.25–4.07 (m, 4H), 1.34 (t, J = 7.1 Hz, 6H); LC-MS (ESI+) *m/z* 204.01 $[M+H-2\times C_2H_4]^+$; HRMS (ESI+ve) *m/z* 260.0679 $[M+H]^+$ (calcd for $C_{10}H_{15}NO_5P$ 260.0682).

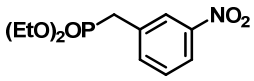


Diethyl 4-aminophenylphosphonate (25a).[4] Diethyl 4-nitrophenylphosphonate (1.700 g, containing *ca.* 14% diethyl phosphite) was dissolved in methanol (20 ml) and was stirred in the presence of Pd (10% on carbon,

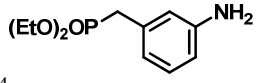
0.100g) under H_2 (balloon) at room temperature for 14 h. The Pd/C was filtered through a pad of celite. The filtrate was concentrated to dryness affording the title compound **25a** (1.200 g, 80%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.54 (m, 2H), 6.76–6.70 (m, 2H), 4.16–3.96 (m, 4H), 3.81 (br s, 2H), 1.30 (2t, *J* = 7.5Hz, 6H); LC-MS (ESI+) *m/z* 174.04 $[M+H-2\times C_2H_4]^+$; HRMS (ESI+) *m/z* 230.0936 $[M+H]^+$ (calcd for $C_{10}H_{17}NO_3P$ 230.0941).



Diethyl 3-aminophenylphosphonate (25b).[5] Anhydrous EtOH (10 mL), 3-bromoaniline (3.16 g, 18.36 mmol), diethyl phosphite (3.11 g, 22.53 mmol), and anhydrous Et_3N (3.9 mL) were added under Argon at room temperature to a round-bottom flask previously charged with $Pd(OAc)_2$ (0.245 g, 1.09 mmol) and PPh_3 (0.764 g, 2.91 mmol). The reaction mixture was stirred at 80 ºC (oil bath temperature) for 18 h. The solvent was removed under reduced pressure to provide a yellow oil. Flash chromatography (SiO_2) afforded **25b**[5] as a yellow oil (1.54 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.21 (m, 1H), 7.18–7.09 (m, 2H), 6.86–6.82 (m, 1H), 4.30–3.99 (m, 4H), 1.40–0.97 (m, 6H); LC-MS (ESI+ve) *m/z* found 230.2 $[M+H]^+$.

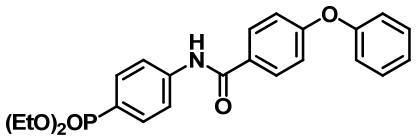


Diethyl 3-nitrobenzylphosphonate.[4] 3-Nitrobenzyl bromide (1.080 g, 5.00 mmol) was mixed with triethyl phosphite (1.04 ml, 6.00 mmol). The mixture was heated to 140 °C in an oil bath for 2 h and cooled to room temperature. The excess of triethyl phosphite and the byproduct ethyl bromide were evaporated *in vacuo* to provide diethyl 3-nitrobenzylphosphonate as a yellow oil (1.460 g, 100%) which did not require further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.14 (m, 1H), 8.14–8.10 (m, 1H), 7.69–7.62 (m, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 4.09–4.02 (m, 4H), 3.23 (d, *J* = 21.8 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H). LC-MS (ESI+) *m/z* 218.02 $[M+H-2\times C_2H_4]^+$; HRMS (ESI+ve) *m/z* 274.0843 $[M+H]^+$ (calcd for $C_{11}H_{17}NO_5P$ 274.0839).

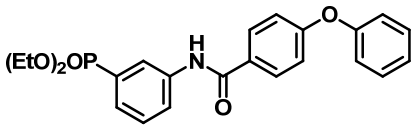


Diethyl 3-aminobenzylphosphonate (25d).[4] Diethyl 3-nitrobenzylphosphonate (1.366 g, 5.00 mmol) was dissolved in THF (5 ml). The solution was hydrogenated with Pd/C (10%, 0.100 g) catalyst under H_2 atmosphere at room temperature overnight. The catalyst was filtered off through a pad of celite and washed with THF (2 × 5 ml). The filtrate was concentrated to dryness affording the aniline **25c** (1.300 g, 100%) as yellow oil which was used without further purification.

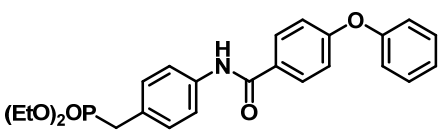
Synthesis of diethyl phosphonates 26



Diethyl 4-(4-phenoxybenzamido)phenylphosphonate (26a). This compound was synthesized according to the procedure used to prepare **26c** using 4-phenoxybenzoic acid (0.214 g, 1 mmol), **25a** (0.229 g, 1 mmol), EDC (0.211 g, 1.1 mmol) and DMAP (0.012g, 0.1 mmol) in DCM (5 ml). The reaction mixture was concentrated and the residue suspended in EtOAc (50 ml) and washed with HCl (1 N, 3 × 10 ml), water (2 × 10 ml) and brine (10 ml). The organic phase was dried over Na_2SO_4 and concentrated to give the crude product. Flash chromatography (SiO_2, DCM/CH_3OH gradient) afforded the title compound **26a** (0.180 g, 42%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.89–7.85 (m, 2H), 7.85–7.74 (m, 4H), 7.43–7.37 (m, 2H), 7.23–7.18 (m, 1H), 7.10–7.03 (m, 4H), 4.20–4.01 (m, 4H), 1.34–1.30 (m, 6H). LC-MS (ESI+) *m/z* 426.15 $[M+H]^+$; HRMS (ESI+ve) *m/z* 426.1458 $[M+H]^+$ (calcd for $C_{23}H_{25}NO_5P$ 426.1465).

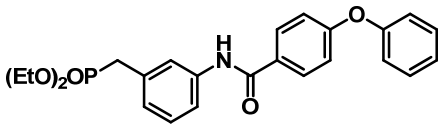


Diethyl 3-(4-phenoxybenzamido)phenylphosphonate (26b): Anhydrous DCM (2 mL) was added at 0 ºC under Argon to a round-bottom flask previously charged with **25b** (0.504 g, 2.20 mmol), 4-phenoxybenzoic acid (0.364 g, 1.69 mmol), DMAP (0.035 g, 0.286 mmol), EDC hydrochloride (0.399 g, 2.08 mmol). The reaction mixture was first allowed to warm up to room temperature without removing the ice-bath and then stirred at room temperature overnight. HCl (aq., 1M, 20 mL) was added, the organic layer extracted with DCM (2 × 20 mL), separated, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Chromatography (SiO_2) afforded **26b** as a yellow solid (0.643 g, 1.51 mmol, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.84–8.71 (m, 1H), 8.29 (s, 1H), 8.03–7.88 (m, 3H), 7.52–7.45 (m, 2H), 7.44–7.36 (m, 2H), 7.23–7.17 (m, 1H), 7.08–7.06 (m, 4H), 4.07–3.99 (m, 4H), 1.40–1.13 (m, 6H); HRMS (ESI+ve) *m/z* 426.1458 $[M+H]^+$ (calcd for $C_{23}H_{25}NO_5P$ 426.1465).



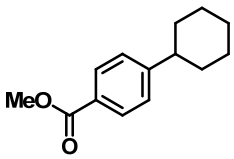
Diethyl 4-(4-phenoxybenzamido)benzylphosphonate (26c). 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.211 g, 1.1 mmol) and DMAP (0.012 g, 0.1 mmol) were added sequentially to a cooled mixture

(0 °C) of 4-phenoxybenzoic acid (0.243 g, 1 mmol) and diethyl 4-aminobenzylphosphonate (Acros Organic)(0.214 g, 1 mmol) in DCM (5 ml). The mixture was stirred at room temperature for 16 h and concentrated. The residue was slurried in HCl (1 N, 20 ml) and sonicated. The solid was isolated by filtration, washed with water (3 × 10 ml) and dried under vacuum to afford the title compound **26c** (0.423 g, 96%) as a white solid. m.p. 144-146 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.89–7.84 (m, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.42–7.37 (m, 2H), 7.31–7.26 (m, 2H), 7.22–7.17 (m, 1H), 7.09–7.02 (m, 4H), 4.06–3.94 (m, 4H), 3.13 (d, *J* = 21.4 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.38. LC-MS (ESI+) *m/z* 440.17 $[M+H]^+$; HRMS (ESI+ve) *m/z* 440.1625 $[M+H]^+$ (calcd for $C_{24}H_{27}NO_5P$ 440.1621).

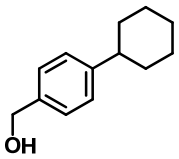


Diethyl 3-(4-phenoxybenzamido)benzylphosphonate (26d). This compound was synthesized according to the procedure used to prepare **26c** using 4-phenoxybenzoic acid (0.0.428 g, 2 mmol), **25d** (0.600 g, 2.5 mmol), EDC (0.383 g, 2 mmol) and DMAP (0.024 g, 0.2 mmol) in DCM (5 ml). The workup and purification procedure was the same as that used to make **26a** affording the title compound **26d** (0.860 g, 98%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.88–7.83 (m, 2H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.44–7.36 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.22–7.16 (m, 1H), 7.10–7.02 (m, 5H), 4.08–3.97 (m, 4H), 3.16 (d, *J* = 21.6 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 6H); LC-MS (ESI+) *m/z* 440.20 $[M+H]^+$; HRMS (ESI+ve) *m/z* 440.1628 $[M+H]^+$ (calcd for $C_{24}H_{27}NO_5P$ 440.1621).

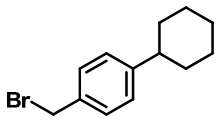
Benzyl bromide 27



Methyl 4-cyclohexylbenzoate. 4-Cyclohexylbenzoic acid (3.94 g, 18.28 mmol) in MeOH (35 mL) was refluxed under Argon for 40 h in presence of H_2SO_4 (conc., 0.40 mL). The reaction mixture was concentrated and $NaHCO_3$ (aq., sat., 100 ml) added to the residue. The mixture was extracted with EtOAc (2 × 100 mL). The organic phase was dried over Na_2SO_4 and concentrated to give methyl 4-cyclohexylbenzoate (4.014 g, 96%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 2H), 2.66–2.39 (m, 1H), 1.92–1.72 (m, 5H), 1.52–1.18 (m, 5H).

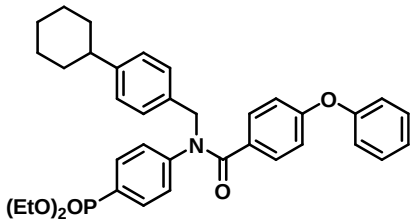


(4-Cyclohexylphenyl)methanol. Methyl 4-cyclohexylbenzoate (3.934 g, 18.04 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (1.693 g, 44.55 mmol) in anhydrous THF (15 mL) under Argon at 0 ºC. The reaction mixture was first allowed to warm up to room temperature and then stirred at room temperature for 16 h. The reaction mixture was then cooled to 0 ºC and sodium sulfate decahydrate (20 g) was added portionwise, followed by the addition of Et_2O (160 mL). The formed solid was filtered, washed with Et_2O (3 × 30 mL). The organic extracts were combined, washed with water (2 × 100 mL), separated, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to provide (4-cyclohexylphenyl)methanol (2.908 g, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 4.64 (s, 2H), 2.53-2.49 (m, 1H), 1.90–1.70 (m, 5H), 1.50–0.99 (m, 5H).



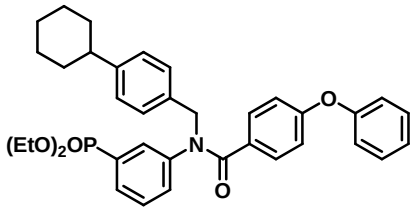
1-(Bromomethyl)-4-cyclohexylbenzene (17).[6] Supported triphenylphosphine PS-Ph_3P (1 g, 2 mmol) was added to (4-cyclohexylphenyl)methanol (0.190 g, 1 mmol) in DCM (10 ml). After 30 min, CBr_4 (0.332 g, 1 mmol) was added. The mixture was shaken at room temperature for 16 h and filtered. The resin was washed with DCM and the combined filtrates were concentrated to dryness affording the title compound **17**[6] (0.260 g, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 4.49 (s, 2H), 2.54–2.43 (m, 1H), 1.91–1.70 (m, 5H), 1.46–1.15 (m, 5H).

Synthesis of diethyl phosphonates 28

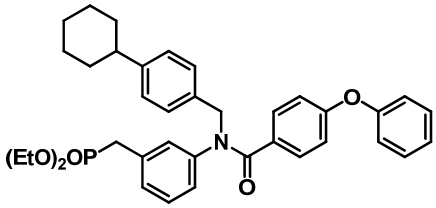


Diethyl 4-(*N*-(4-cyclohexylbenzyl)-4-phenoxybenzamido)phenylphosphonate (28a). This compound was prepared, according to the procedure used to make **28d**, from **26a** (0.115 g, 0.27 mmol), NaH (0.011 g, 0.27 mmol), **27** (0.076 g, 0.3 mmol) affording the title compound **28a** (0.041 g, 25%) as a colorless oil and the starting **26a** (0.041 g, 36%) was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 12.9, 8.1 Hz, 2H),

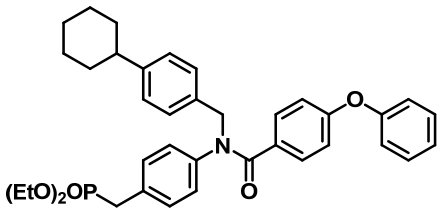
7.37–7.29 (m, 4H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.16–7.10 (m, 3H), 7.04 (dd, *J* = 8.1, 3.5 Hz, 2H), 6.99–6.94 (m, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.11 (s, 2H), 4.16–3.98 (m, 4H), 2.53–2.40 (m, 1H), 1.90–1.70 (m, 5H), 1.45–1.30 (m, 5H), 1.27 (t, *J* = 7.1 Hz, 6H); LC-MS (ESI+ve) *m/z* 598.27 $[M+H]^+$; HRMS (ESI+ve) *m/z* 598.2711 $[M+H]^+$ (calcd for $C_{36}H_{41}NO_5P$ 598.2717).



Diethyl 3-(*N*-(4-cyclohexylbenzyl)-4-phenoxybenzamido)phenylphosphonate (28b). Compound **26b** (0.256 g, 0.602 mmol) was added to a suspension of NaH (0.029 g, 0.727 mmol, 60% dispersion in mineral oil) in anhydrous THF (0.6 mL) under Argon at 0 ºC. The reaction mixture was stirred at 0 ºC under Argon for 1 h, followed by the addition of a solution of **27** (0.175 g, 0.694 mmol) in anhydrous THF (0.6 mL). After stirring at room temperature overnight, the reaction mixture was quenched with aq. HCl (1 M, 5 mL) and extracted with DCM (2 × 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Chromatography (SiO_2) afforded **28b** as a yellow oil (0.124 g, 0.207 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.58 (dd, *J* = 12.8, 7.5 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.34–7.28 (m, 4H), 7.22–7.18 (m, 3H), 7.14–7.06 (m, 3H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 5.10 (s, 2H), 3.97–3.89 (m, 2H), 3.85–3.78 (m, 2H), 2.47–2.47 (m, 1H), 1.82–1.61 (m, 5H), 1.41–1.31 (m, 4H) 1.25–1.18 (m, 7H); HRMS (ESI+ve) *m/z* 598.2721 $[M+H]^+$ (calcd for $C_{36}H_{41}NO_5P$ 598.2717).

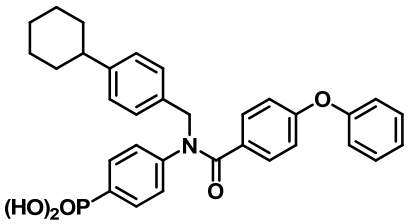


Diethyl 3-(N-(4-cyclohexylbenzyl)-4-phenoxybenzamido)benzylphosphonate (28c). This compound was prepared, according to the procedure used to make **28d**, from **26c** (0.439 g, 1 mmol), NaH (0.04 g, 1 mmol), **17** (0.253 g, 1 mmol) affording the title compound **28c** (0.441 g, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 4H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.14–7.03 (m, 5H), 7.01 (s, 1H), 6.96–6.90 (m, 2H), 6.79–6.69 (m, 3H), 5.07 (s, 2H), 3.99–3.80 (m, 4H), 3.01 (d, *J* = 21.7 Hz, 2H), 2.48–2.42 (m, 1H), 1.83–1.71 (m, 5H), 1.45–1.22 (m, 5H); LC-MS (ESI+) *m/z* 612.29 $[M+H]^+$; HRMS (ESI+ve) *m/z* 612.2872 $[M+H]^+$ (calcd for $C_{37}H_{43}NO_5P$ 612.2873).

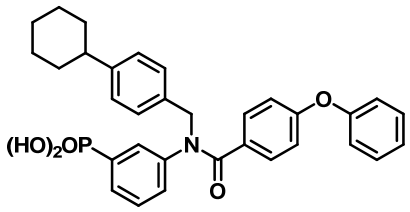


Diethyl 4-(*N*-(4-cyclohexylbenzyl)-4-phenoxybenzamido)benzylphosphonate (28d). Sodium hydride (60% in mineral oil, 0.012 g, 0.3 mmol) was suspended in THF (3 ml) and the mixture cooled to 0 °C. The phosphonate **26c** (0.132 g, 0.3 mmol) was added and the mixture stirred at 0 °C for 1 h. The alkyl bromide **17** (0.091 g, 0.36 mmol) was then added and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (30 ml) and washed with water (2 × 10 ml) and brine (10 ml). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified via flash chromatography (SiO_2, DCM/CH_3OH gradient) affording the title compound **28d** (0.126 g, 69%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 4H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.14–7.07 (m, 5H), 6.96–6.92 (m, 2H), 6.88 (d, *J* = 7.9 Hz, 2H), 6.74–6.69 (m, 2H), 5.06 (s, 2H), 3.99–3.80 (m, 4H), 3.04 (d, *J* = 21.7 Hz, 2H), 2.50–2.39 (m, 1H), 1.88–1.69 (m, 5H), 1.44–1.19 (m, 5H), 1.16 (t, *J* = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.90; LC-MS (ESI+) *m/z* 612.29 $[M+H]^+$; HRMS (ESI+ve) *m/z* 612.2855 $[M+H]^+$ (calcd for $C_{37}H_{43}NO_5P$ 612.2873).

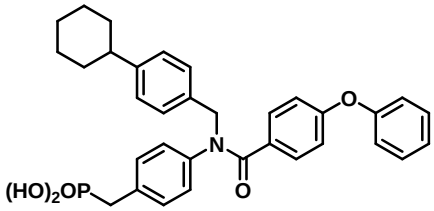
Synthesis of phosphonic acids 12



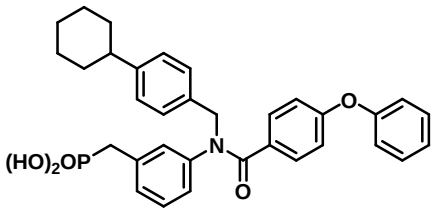
4-(*N*-(4-Cyclohexylbenzyl)-4-phenoxybenzamido)phenylphosphonic acid (12a). This compound was prepared, according to the procedure used to make **12c**, from **28a** (0.030 g, 0.05 mmol) and bromotrimethylsilane (0.1 ml, 0.5 mmol) in DCM (3 ml) affording the phosphonic acid **12a** (0.015 mg, 56%) as a white solid. m.p. 182.7 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (dd, *J* = 12.8, 8.3 Hz, 2H), 7.40–7.30 (m, 4H), 7.20–7.11 (m, 7H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.14 (s, 2H), 2.51–2.40 (m, 1H), 1.90–1.70 (m, 5H), 1.49–1.20 (m, 5H); LC-MS (ESI-) *m/z* 540.20 $[M–H]^–$; HRMS (ESI–ve) *m/z* 540.1935 $[M–H]^–$ (calcd for $C_{32}H_{31}NO_5P$ 540.1945); HPLC purity 100% {t_R = 2.7 min, flow 1 ml/min, [MeOH:(0.1% DEA in H_2O), 50:50]}.



3-(*N*-(4-cyclohexylbenzyl)-4-phenoxybenzamido)phenylphosphonic acid (12b). This was prepared from the amide **28b** (0.119 g, 0.199 mmol) in a similar manner as described for **29b**. The obtained crude material was slurried with hexane/EtOAc (9/1, 1 ml), filtered, washed with hexane (1 mL), dried under vacuum to afford **12b** as an off-white solid (0.059 g, 0.108 mmol, 55%). m.p 92.3-94.9 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.59–7.44 (m, 2H), 7.38–7.25 (m, 5H), 7.21–7.09 (m, 6H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.11 (s, 2H), 2.47–2.42 (m, 1H), 1.81–1.71 (m, 5H), 1.41–1.23 (m, 5H); HRMS (ESI+ve) *m/z* 542.2084 $[M+H]^+$ (calcd for $C_{32}H_{33}NO_5P$ 542.2091); HPLC purity 71% {t_R = 4.8 min, flow 1 ml/min, [MeOH:(0.1% TFA in H_2O), 70:30]}.

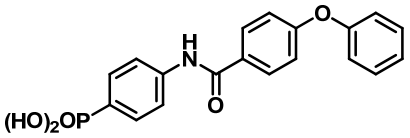


4-(*N*-(4-Cyclohexylbenzyl)-4-phenoxybenzamido)benzylphosphonic acid (12c). TMSBr (0.216 ml, 1.63 mmol) was added to a solution of **28c** (0.100 g, 0.163 mmol) in DCM (3 ml) at 0 °C. The mixture was stirred at room temperature for 4 h and concentrated. The residue was stirred with 90% CH_3OH/H_2O (10 ml) at room temperature for 1 h and concentrated. The crude product was slurried in acetone (2 ml) and filtered. The solid was washed with acetone (2 × 1 ml) and dried affording the title compound **12c** (0.046 g, 51%) as an off-white solid. m.p. 188 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.40–7.27 (m, 4H), 7.23–7.08 (m, 7H), 6.96 (t, *J* = 8.6 Hz, 4H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.08 (s, 2H), 3.03 (d, *J* = 21.7 Hz, 2H), 2.54–2.40 (m, 1H), 1.92–1.70 (m, 5H), 1.51–1.21 (m, 5H); ^{31}P NMR (162 MHz, CD_3OD) δ 24.54; LC-MS (ESI+ve) *m/z* 556.22 $[M+H]^+$; HRMS (ESI+ve) *m/z* 556.2250 $[M+H]^+$ (calcd for $C_{33}H_{35}NO_5P$ 556.2247); HPLC purity 100% {t_R = 4.2 min, flow 1 ml/min, [MeOH:(0.1% DEA in H_2O), 50:50]}.

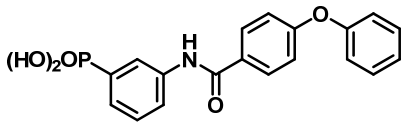


3-(*N*-(4-Cyclohexylbenzyl)-4-phenoxybenzamido)benzylphosphonic acid (12d). This compound was prepared, according to the procedure used to make **12c**, from **28d** (0.109 g, 0.18 mmol) and bromotrimethylsilane (0.24 ml, 1.78 mmol) in DCM (5 ml). Flash chromatography (SiO_2, DCM/CH_3OH gradient) afforded the title compound **12d** (0.080 g, 81%) as a brown solid. m.p. 97 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.36–7.30 (m, 4H), 7.20 (d, *J* = 8.1 Hz, 3H), 7.15–7.11 (m, 4H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 7.4 Hz, 1H), 5.08 (s, 2H), 3.04 (d, *J* = 21.7 Hz, 2H), 2.49-2.42 (m, 1H), 1.92–1.70 (m, 5H), 1.48–1.23 (m, 5H). LC-MS (ESI–ve) *m/z* 554.21 $[M–H]^-$ HRMS (ESI–ve) *m/z* 554.2088 $[M–H]^-$ (calcd for $C_{33}H_{33}NO_5P$ 554.2102); HPLC purity 100% {t_R = 6.9 min, flow 1 ml/min, [MeOH:(0.1% DEA in H_2O), 50:50]}.

Synthesis of phosphonic acids 29

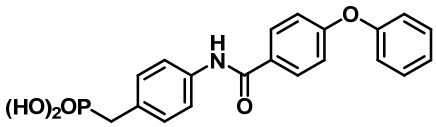


4-(4-Phenoxybenzamido)phenylphosphonic acid (29a). This compound was prepared, according to the procedure used to make **12c**, from **26a** (0.058 g, 0.136 mmol) affording the title compound **29a** (0.038 g, 76%) as an off-white solid. m.p. 212.1 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.99–7.92 (m, 2H), 7.88–7.74 (m, 4H), 7.46–7.39 (m, 2H), 7.25–7.18 (m, 1H), 7.11–7.03 (m, 4H); LC-MS (ESI+ve) *m/z* 370.08 $[M+H]^+$; HRMS (ESI+ve) *m/z* 370.0829 $[M+H]^+$ (calcd for $C_{19}H_{17}NO_5P$ 370.0839); HPLC purity 100% {t_R = 8.9 min, flow 1 ml/min, [MeOH:(0.1% DEA in H_2O), 10:90]}.



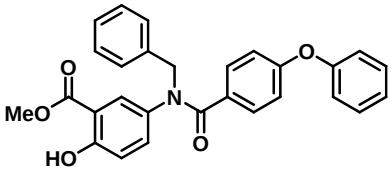
3-(4-Phenoxybenzamido)phenylphosphonic acid (29b). Bromotrimethylsilane (0.464 g, 3.03 mmol) was added dropwise under argon to a solution of **26b** (0.137 g, 0.322 mmol) in anhydrous DCM (0.5 mL). After stirring at room temperature overnight, the solvent and excess of TMS-Br were removed under reduced pressure. A mixture of MeOH/water (9/1, 2 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure to provide an orange oil. Water (10 mL) was added and the solid that precipitated was filtered, washed with water (5 mL) and dried under vacuum to afford pure **29b** as an off-white solid (0.096 g, 81%). m.p. 103.2-104.6 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 14.1 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 2H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.59–7.57 (m, 1H), 7.52–7.46 (m, 1H),

7.42 (t, J = 7.9 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H); HRMS (ESI+ve) *m/z* 370.0831 $[M+H]^+$ (calcd for $C_{19}H_{17}NO_5P$ 370.0839); HPLC purity 100% {t_R = 4.4 min, flow 1 ml/min, [MeOH:(0.1% TFA in H_2O), 80:20]}.

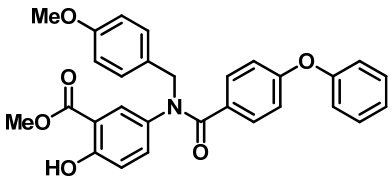


4-(4-Phenoxybenzamido)benzylphosphonic acid (29c). This compound was prepared according to the procedure used to make **12c** from **26c** (0.088 g, 0.2 mmol) and TMSBr (0.264 ml, 2.0 mmol). The crude product was slurried in DCM (20 ml) and filtered affording the title compound **29c** (0.077 g, 100%) as a white solid. m.p. >250 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.96–7.91 (m, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.45–7.39 (m, 2H), 7.31 (dd, J = 8.6, 2.5 Hz, 2H), 7.23–7.18 (m, 1H), 7.11–7.02 (m, 4H), 3.11 (d, J = 21.5 Hz, 2H); ^{31}P NMR (162 MHz, CD_3OD) δ 25.23; LC-MS (ESI+) *m/z* 384.11 $[M+H]^+$; HRMS (ESI+ve) *m/z* 384.0991 $[M+H]^+$ (calcd for $C_{20}H_{19}NO_5P$ 384.0995); HPLC purity 100% {t_R = 4.2 min, flow 1 ml/min, [MeOH:(0.1% DEA in H_2O), 20:80]}.

Synthesis of methyl esters 30

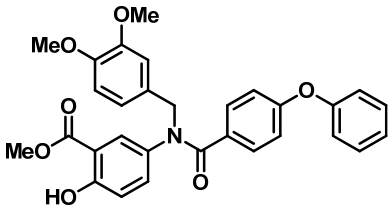


Methyl 5-(*N*-benzyl-4-phenoxybenzamido)-2-hydroxybenzoate (30a). This was prepared as a yellow oil (0.301 g, 0.664 mmol, 83%) from **19a** (0.205 g, 0.797 mmol) and 4-phenoxybenzoyl chloride (0.200 g, 0.862 mmol) in the same manner as described for **30g.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.34–7.26 (m, 9H), 7.14–7.07 (m, 1H), 6.95–6.92 (m, 2H), 6.89 (dd, J = 2.2, 9.1 Hz, 1H), 6.78–6.72 (m, 3H), 5.07 (s, 2H), 3.89 (s, 3H). HRMS (ESI+ve) *m/z* 454.1656 $[M+H]^+$ (calcd for $C_{28}H_{24}NO_5$ 454.1649).

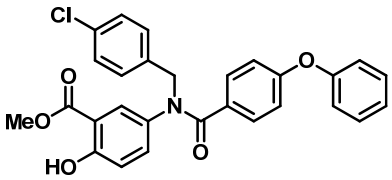


Methyl 2-hydroxy-5-(*N*-(4-methoxybenzyl)-4-phenoxybenzamido)benzoate (30b). This was prepared as a yellow oil (0.267 g, 0.552 mmol, 93%) from **19c** (0.170 g, 0.592 mmol) and 4-phenoxybenzoyl chloride (0.044

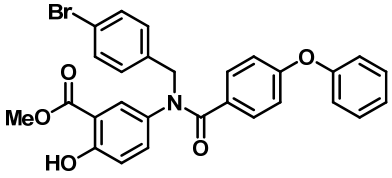
g, 0.655 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 7.34–7.27 (m, 4H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.15–7.08 (m, 1H), 6.96–6.90 (m, 2H), 6.86 (dd, *J* = 1.9, 8.8 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.75 (t, *J* = 8.8 Hz, 3H), 5.00 (s, 2H), 3.90 (s, 1H), 3.78 (s, 3H). HRMS (ESI+ve) *m/z* 484.1743 $[M+H]^+$ (calcd for $C_{29}H_{26}NO_6$ 484.1755).



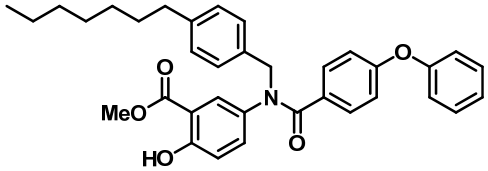
Methyl 2-hydroxy-5-(*N*-(4-methoxybenzyl)-4-phenoxybenzamido)benzoate (30c). A solution of 4-phenoxybenzoyl chloride (0.098 g, 0.422 mmol) in anhydrous THF (0.4 mL) was added to a mixture of **19k** (0.113 g, 0.356 mmol), and $NaHCO_3$ (0.066 g, 0.785 mmol) in anhydrous THF (0.3 mL) at room temperature under argon overnight. The reaction mixture was quenched by the addition of $NaHCO_3$ (aq, sat, 5 mL) and extracted with EtOAc (5 mL). The organic layer was then washed HCl (aq., 1 M, 5 mL), separated, dried (Na_2SO_4) and the solvent removed under reduced pressure. Chromatography afforded **30c** as a yellow oil (0.100 g, 0.194 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 7.42 (s, 1H), 7.34–7.26 (m, 3H), 7.14–7.09 (m, 1H), 6.97–6.84 (m, 4H), 6.80 – 6.71 (m, 5H), 4.99 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H). HRMS (ESI+ve) *m/z* 514.1863 $[M+H]^+$ (calcd for $C_{30}H_{28}NO_7$ 514.1860).



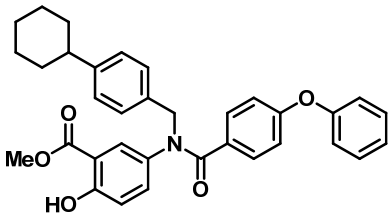
Methyl 5-(*N*-(4-chlorobenzyl)-4-phenoxybenzamido)-2-hydroxybenzoate (30d). This was prepared as a yellow oil (0.251 g, 0.515 mmol, 86%) from **19d** (0.174 g, 0.597 mmol) and 4-phenoxybenzoyl chloride (0.152 g, 0.655 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.42 (d, *J* = 2.6 Hz, 1H), 7.36–7.18 (m, 8H), 7.15–7.08 (m, 1H), 6.94–6.92 (m, 2H), 6.89 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.78–6.75 (m, 3H), 5.02 (s, 2H), 3.90 (s, 3H). HRMS (ESI+ve) *m/z* 488.1261 $[M+H]^+$ (calcd for $C_{28}H_{23}ClNO_5$ 488.1259).



Methyl 5-(*N*-(4-bromobenzyl)-4-phenoxybenzamido)-2-hydroxybenzoate (30e). This was prepared as a yellow oil (0.326 g, 0.612 mmol, 74%) from **19j** (0.279 g, 0.830 mmol) and 4-phenoxybenzoyl chloride (0.222 g, 0.956 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.43–7.39 (m, 3H), 7.35–7.27 (m, 4H), 7.18–7.08 (m, 3H), 6.95–6.92 (s, 2H), 6.89 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.7–6.75 (m, 3H), 5.01 (s, 2H), 3.90 (s, 3H); HRMS (ESI+ve) *m/z* 532.0674 $[M+H]^+$ (calcd for $C_{28}H_{23}BrNO_5$ 532.0754).

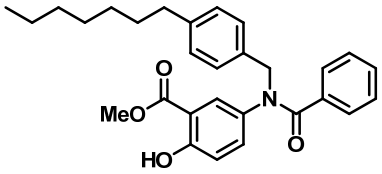


Methyl 5-(*N*-(4-heptylbenzyl)-4-phenoxybenzamido)-2-hydroxybenzoate (30f). To amine **19i** (0.100 g, 0.282 mmol) in CH_2Cl_2 (2 ml) was added 4-phenoxybenzoic acid (0.062 g, 0.294 mmol) and Ph_3PCl_2 (0.225 g, 0.677 mmol) under argon atmosphere. The mixture was heated at 80 ºC in a microwave reactor (Biotage) for 1 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The organic fractions were dried (Na_2SO_4) and evaporated *in vacuo*. The crude mixture was purified by column chromatography to afford the amide **30f** (0.130 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.44 (d, *J* = 2.3 Hz, 1H), 7.36–7.25 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.13–7.07 (m, 3H), 6.97–6.86 (m, 3H), 6.67–6.72 (m, 3H), 5.03 (s, 2H), 3.89 (s, 3H), 2.63–2.39 (m, 2H), 1.60-1.59 (m, 2H), 1.34–1.20 (m, 8H), 0.96–0.75 (m, 3H).

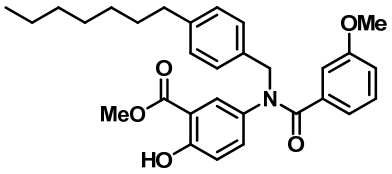


Methyl 5-(*N*-(4-cyclohexylbenzyl)-4-phenoxybenzamido)-2-hydroxybenzoate (30g). 4-Phenoxybenzoyl chloride (0.106 g, 0.456 mmol) was added to a mixture of **19b** (0.130 g, 0.383 mmol) and $NaHCO_3$ (0.106 g, 1.26 mmol) in anhydrous THF (1.5 mL) at room temperature under Argon. After stirring at room temperature overnight, the reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL). The organic layer was then washed with water (20 mL), HCl (aq., 1M, 20 mL), separated, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Chromatography (SiO_2) afforded **30g** as a yellow oil (0.201 g, 0.375 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.43 (d, *J* = 2.9 Hz, 1H), 7.36–7.27 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.16–7.08 (m, 4H), 7.04–6.99 (m, 1H), 6.94 (d, *J* = 9.6 Hz, 2H), 6.75 (t, *J* = 8.9 Hz,

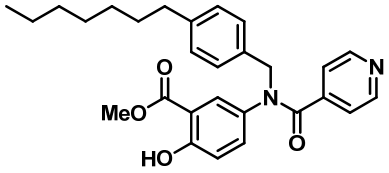
2H), 5.02 (s, 2H), 3.88 (s, 3H), 2.50–2.40 (m, 1H), 1.87–1.68 (m, 5H), 1.14–1.35 (m, 4H), 1.27–2.21 (m, 1H); HRMS (ESI+ve) *m/z* 536.2415 $[M+H]^+$ (calcd for $C_{34}H_{34}NO_5$ 536.2431).



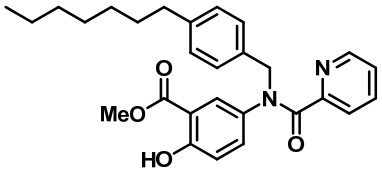
Methyl 5-(*N*-(4-heptylbenzyl)benzamido)-2-hydroxybenzoate (30h). This was prepared as a yellow oil (0.052 g, 0.119 mmol, 42%) from **19i** (0.097 g, 0.284 mmol) and 4-phenoxybenzoyl chloride (0.044 g, 0.293 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.42 (s, 1H), 7.31–7.28 (m, 2H), 7.25–7.16 (m, 5H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 5.00 (s, 2H), 3.88 (s, 3H), 2.56 (t, *J* = 7.5 Hz, 2H), 1.31–1.25 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); HRMS (ESI+ve) *m/z* 460.2503 $[M+H]^+$ (calcd for $C_{29}H_{34}NO_4$ 460.2482).



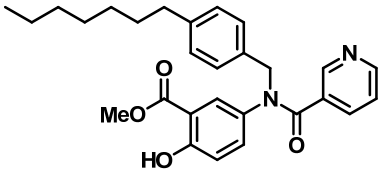
Methyl 5-(*N*-(4-heptylbenzyl)-3-methoxybenzamido)-2-hydroxybenzoate (30i). This was prepared as a yellow oil (0.062 g, 0.130 mmol, 38%) from **19i** (0.118 g, 0.345 mmol) and 3-methoxybenzoylchloride (0.064 g, 0.378 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.42 (s, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.11–7.03 (m, 3H), 6.96–6.68 (m, 5H), 5.02 (s, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.31–1.25 (m, 10H), 0.87 (t, *J* = 7.1 Hz, 3H); HRMS (ESI+ve) *m/z* 490.2580 $[M+H]^+$ (calcd for $C_{30}H_{36}NO_5$ 490.2588).



Methyl 5-(*N*-(4-heptylbenzyl)isonicotinamido)-2-hydroxybenzoate (30j). This was prepared as a yellow oil (0.083 g, 0.180 mmol, 53%) from **19i** (0.115 g, 0.337 mmol) and isonicotinoyl chloride hydrochloride (0.072 g, 0.404 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.47 (s, 2H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.18–7.13 (m, 4H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.87 (dd, *J* = 8.7, 2.3 Hz, 1H),6.74 (d, *J* = 8.9 Hz, 1H), 5.01 (s, 2H), 3.88 (s, 3H), 2.55 (t, *J* = 7.0 Hz, 2H), 1.35–1.18 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H); HRMS (ESI+ve) *m/z* 461.2419 $[M+H]^+$ (calcd for $C_{28}H_{33}N_2O_4$ 461.2435).

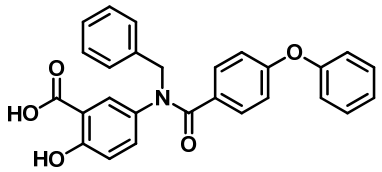


Methyl 5-(*N*-(4-heptylbenzyl)picolinamido)-2-hydroxybenzoate (30k). This was prepared as a yellow oil (0.037 g, 0.080 mmol, 30%) from **19i** (0.065 g, 0.269 mmol) and picolinoyl chloride hydrochloride (0.057 g, 0.320 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.32 (s, 1H), 7.63–7.54 (m, 1H), 7.48–7.38 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.12–7.07 (m, 4H), 6.91 (dd, *J* = 9.3, 1.9 Hz, 1H), 6.66 (d, *J* = 8.9 Hz, 1H), 5.05 (s, 2H), 3.85 (s, 3H), 2.56 (t, *J* = 7.8 Hz, 2H), 1.28–1.24 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H); HRMS (ESI+ve) *m/z* 461.2434 $[M+H]^+$ (calcd for $C_{28}H_{33}N_2O_4$ 461.2435).

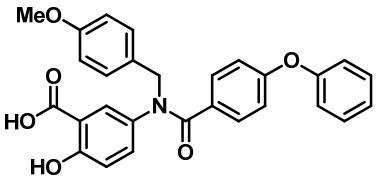


Methyl 5-(*N*-(4-heptylbenzyl)nicotinamido)-2-hydroxybenzoate (30l). This was prepared as a yellow oil (0.060 g, 0.130 mmol, 40%) from **19i** (0.110 g, 0.322 mmol) and nicotinoyl chloride (0.057 g, 0.403 mmol) in the same manner as described for **30g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.53 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.41 (s, 1H), 7.15–7.08 (m, 5H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 5.02 (s, 2H), 3.87 (s, 3H), 2.55 (t, *J* = 7.9 Hz, 2H), 1.27–1.24 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); HRMS (ESI+ve) *m/z* 461.2431 $[M+H]^+$ (calcd for $C_{28}H_{33}N_2O_4$ 461.2435).

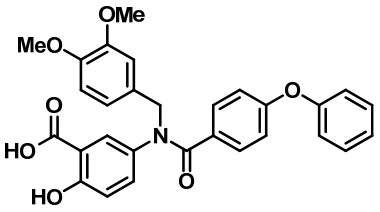
Synthesis of carboxylic acids 13



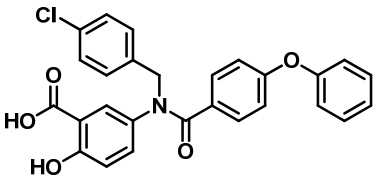
5-(*N*-Benzyl-4-phenoxybenzamido)-2-hydroxybenzoic acid (13a). This was prepared as a white solid (0.155 g, 0.353 mmol, 92%) from **30a** (0.174 g, 0.384 mmol) in the same manner as described for **13g**. m.p.> 191 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (d, *J* = 2.2 Hz, 1H), 7.37–7.19 (m, 9H), 7.15–7.08 (m, 1H), 6.98 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 1H), 5.09 (s, 2H); HRMS (ESI−ve) *m/z* 438.1349 $[M–H]^-$ (calcd for $C_{27}H_{20}NO_5$ 438.1347); HPLC purity 97% {t_R = 4.0 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70:30]}.



2-Hydroxy-5-(*N*-(4-methoxybenzyl)-4-phenoxybenzamido)benzoic acid (13b). This was prepared from **30b** (0.097 g, 0.200 mmol) in the same manner as described for **13g**. The crude product was slurried with methanol (1 mL), filtered and dried under vacuum to afford pure **13b** as a white solid (0.035 g, 0.074 mmol, 37%). m.p. 187-189 ºC; ^{1}H NMR (400 MHz, CD_3OD) δ 7.42–7.25 (m, 5H), 7.18 (d, J = 8.3 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.06 (dd, J = 8.8, 2.7 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 6.86–6.81 (m, 2H), 6.79–6.73 (m, 3H), 5.02 (s, 2H), 3.75 (s, 3H); HRMS (ESI−ve) *m/z* 468.1451 $[M–H]^-$ (calcd for $C_{28}H_{22}NO_6$ 468.1453); HPLC purity 97% {t_R = 2.7 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70:30]}.

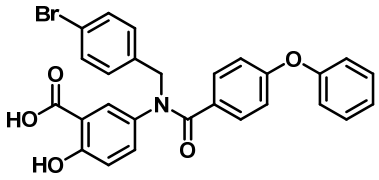


2-Hydroxy-5-(*N*-(3,4-dimethoxybenzyl)-4-phenoxybenzamido)benzoic acid (13c). A mixture of **30c** (0.081 g, 0.157 mmol) in THF (1 mL) and sodium hydroxide (aq. 1 M, 1 mL) was heated at 70 ºC in a sealed tube overnight. The solvent was then removed under reduced pressure. Hydrochloric acid (aq. 1 M, 2 mL) was added to the mixture which was then extracted with EtOAc (2 × 5 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to provide **13c** as a white solid (0.053 g, 0.106 mmol, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.37–7.26 (m, 4H), 7.16–7.05 (m, 1H), 6.96–6.87 (m, 3H), 6.86–6.70 (m, 5H), 6.58 (d, J = 8.6 Hz, 1H), 5.01 (s, 2H), 3.78 (s, 3H), 3.75 (s, 3H); HRMS (ESI+ve) *m/z* 500.1683 $[M+H]^+$ (calcd for $C_{29}H_{26}NO_7$ 500.1704); HPLC purity 97% {t_R = 8.5 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 50:50]}.

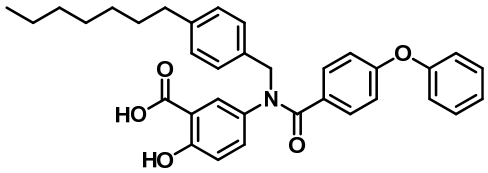


5-(*N*-(4-Chlorobenzyl)-4-phenoxybenzamido)-2-hydroxybenzoic acid (13d). This was prepared as a white solid (0.060 g, 0.126 mmol, 73%) from **30d** (0.084 g, 0.172 mmol) in the same manner as described for **13g**. m.p. >150 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, J = 2.4 Hz, 1H), 7.35–7.26 (m, 8H), 7.14– 7.07 (m, 2H), 6.92 (d, J = 8.3 Hz, 2H), 6.80–6.75 (m, 3H), 5.08 (s, 2H); HRMS (ESI−ve) *m/z* 472.0955 $[M–H]^-$

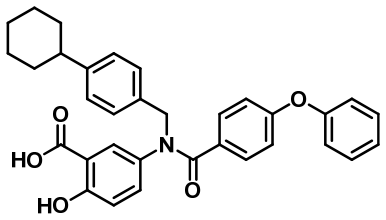
(calcd for $C_{27}H_{19}ClNO_5$ 472.0957). HPLC purity 95% {t_R = 3.3 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70:30]}.



5-(*N*-(4-Bromobenzyl)-4-phenoxybenzamido)-2-hydroxybenzoic acid (13e). This was prepared as a white solid (0.105 g, 0.202 mmol, 87%) from **30e** (0.125 g, 0.234 mmol) in the same manner as described for **13g**. m.p. >198 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.46–7.43 (m, 3H), 7.35–7.33 (m, 4H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.14–7.10 (m, 1H), 7.01 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 1H), 5.06 (s, 2H); HRMS (ESI−ve) *m/z* 516.0455 $[M–H]^-$ (calcd for $C_{27}H_{19}BrNO_5$ 516.0452); HPLC purity 95% {t_R = 3.4 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70:30]}.

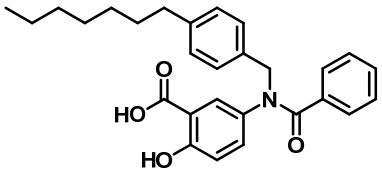


5-(*N*-(4-heptylbenzyl)-4-phenoxybenzamido)-2-hydroxybenzoic acid (13f). This was prepared from **30f** (0.050 g, 0.090 mmol) in the same manner as described for **13g**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40–7.33 (m, 2H), 7.30–7.28 (m, 3H), 7.15–7.11 (m, 3H), 7.09–7.05 (m, 3H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 1H), 4.97 (s, 2H), 1.61–1.42 (m, 2H), 1.22 (d, *J* = 8.2 Hz, 10H), 0.9–0.70 (m, 3H); HRMS (ESI−ve) *m/z* 538.2595 $[M+H]^+$ (calcd for $C_{34}H_{36}NO_5$ 538.2588); HPLC purity 100% {t_R = 10.5 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 80:20]}.

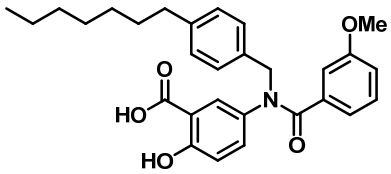


5-(*N*-(4-Cyclohexylbenzyl)-4-phenoxybenzamido)-2-hydroxybenzoic acid (13g). A mixture of **30g** (0.160 g, 0.299 mmol) in THF (1 mL) and sodium hydroxide (aq. 1 M, 1 mL) was heated at 70 ºC in a sealed tube for 7 h. The solvent was then removed under reduced pressure. The resulting solid was slurried in HCl (aq. 1 M, 10 mL), filtered, washed with HCl (aq. 1 M, 5 mL), water (10 mL) and dried under vacuum to afford **13g** as a white solid (0.139 g, 0.261 mmol, 90%). m.p.> 208ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 1.7

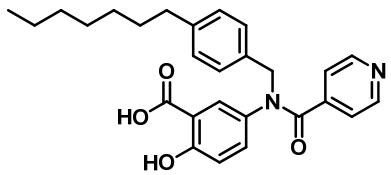
Hz, 1H), 7.37–7.26 (m, 4H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.13–7.09 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 3H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 1H), 5.04 (s, 2H), 2.49–2.44 (m, 1H), 1.88–1.17 (m, 5H), 1.43–1.38 (m, 4H), 1.32–1.21 (m, 1H); HRMS (ESI−ve) *m/z* 520.2130 $[M–H]^-$ (calcd for $C_{33}H_{30}NO_5$ 520.2129); HPLC purity 98% {t_R = 6.3 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 80/20]}.



5-(*N*-(4-Heptylbenzyl)benzamido)-2-hydroxybenzoic acid (13h). The ester **30h** (0.045 g, 0.101 mmol) in THF (1 mL) and NaOH (aq. 1 M, 1 mL) were heated at 70 ºC overnight in a sealed tube. The solvent was then removed under reduced pressure. The resulting solid was slurried in HCl (aq. 1M, 2 mL), filtered, water (3 mL) and dried under vacuum to afford pure **13h** as a white solid (0.039 g, 0.090 mmol, 89%). m.p. 142.8-143.6 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (s, 1H), 7.35–7.13 (m, 7H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 6.67 (d, *J* = 8.8 Hz, 1H), 5.06 (s, 2H), 2.55 (t, *J* = 6.4 Hz, 2H), 1.70–1.51 (m, 2H), 1.40–1.14 (m, 8H), 0.88 (t, *J* = 7.1 Hz, 3H); HRMS (ESI−ve) *m/z* 444.2187 $[M–H]^-$ (calcd for $C_{28}H_{30}NO_4$ 444.2180); HPLC purity 97% {t_R = 15.5 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70:30]}.

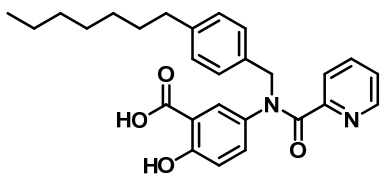


5-(*N*-(4-Heptylbenzyl)-3-methoxybenzamido)-2-hydroxybenzoic acid (13i). This was prepared as a white solid (0.046 g, 0.099 mmol, 81%) from **30i** (0.058 g, 0.122 mmol) in the same manner as described for **13h**. m.p. >81 ºC (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (s, 1H), 7.14–7.04 (m, 8H), 6.83–6.80 (m, 4H), 5.03 (s, 2H), 3.66 (s, 3H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.59–1.53 (m, 2H), 1.29–1.26 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); HRMS (ESI−ve) *m/z* 474.2277 $[M–H]^-$ (calcd for $C_{29}H_{32}NO_5$ 474.2286); HPLC purity 99% {t_R = 11.7 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70:30]}.

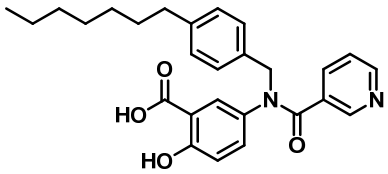


5-(*N*-(4-Heptylbenzyl)isonicotinamido)-2-hydroxybenzoic acid (13j). This was prepared from **30j** (0.079 g, 0.182 mmol) in the same manner as described for **13h**. The solvent was then removed under reduced pressure.

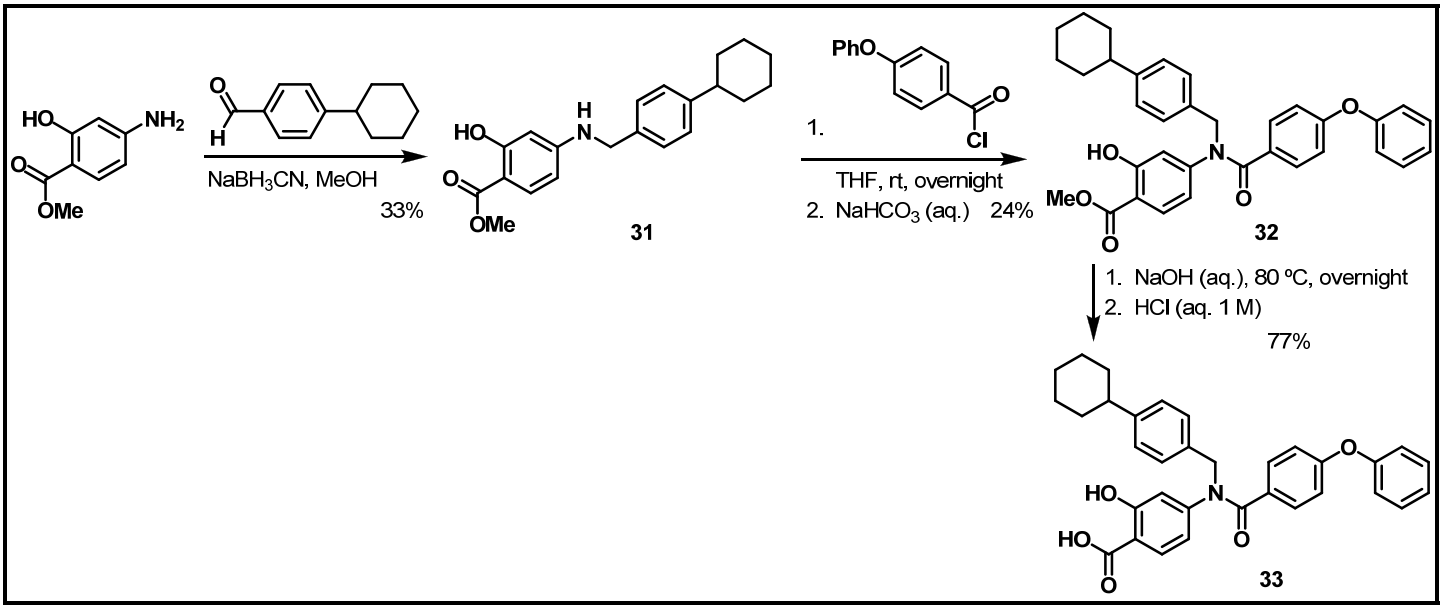
The obtained solid was slurried in citric acid (aq. sat., 10 mL), filtered, water (2 × 5 mL) and dried under vacuum to afford **13j** as a yellow solid (0.067 g, 0.154 mmol, 85%). m.p. 157.3-158.9 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 2H), 7.41 (d, *J* = 2.7 Hz, 1H), 7.32 (d, *J* = 5.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.06 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 5.05 (s, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.59–1.55 (m, 2H), 1.35–1.18 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H); HRMS (ESI−ve) *m/z* 445.2134 $[M–H]^-$ (calcd for $C_{27}H_{29}N_2O_5$ 445.2133); HPLC purity 98% {t_R = 4.2 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70/30]}.



5-(*N*-(4-Heptylbenzyl)picolinamido)-2-hydroxybenzoic acid (13k): This was obtained as a yellow solid (0.027 g, 0.062 mmol, 87%) from **30k** (0.045 g, 0.101 mmol) in the same manner as described for **13j**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.42–7.38 (m, 2H), 7.26 (s, 1H), 7.21 (d, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 9.3 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 5.07 (s, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.51–1.53 (m, 2H), 1.30–1.26 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H); HRMS (ESI−ve) *m/z* 445.2133 $[M–H]^-$ (calcd for $C_{27}H_{29}N_2O_5$ 445.2133); HPLC purity 99% {t_R = 8.7 min, flow 1 ml/min, [(CH_3CN:(0.1% TFA in H_2O), 70:30]}.

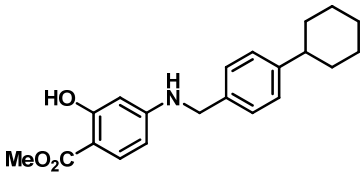


5-(*N*-(4-Heptylbenzyl)nicotinamido)-2-hydroxybenzoic acid (13l): This was obtained as a yellow solid (0.027 g, 0.062 mmol, 37%) from **30l** (0.050 g, 0.111 mmol) in the same manner as described for **13j**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1H), 7.76 (d, *J* = 9.7 Hz, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 5.07 (s, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.64–1.52 (m, 2H), 1.34–1.23 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); HRMS (ESI−ve) *m/z* 445.2132 $[M–H]^-$ (calcd for $C_{27}H_{29}N_2O_5$ 445.2133); HPLC purity 97% {t_R = 5.3 min, flow 1 ml/min, [CH_3CN:(0.1% TFA in H_2O), 70:30]}.

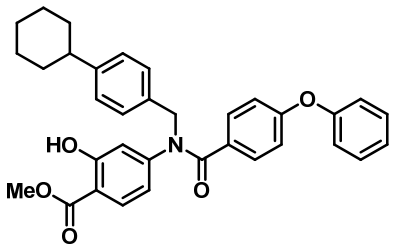


Scheme S2. Synthesis of the benzamide **33** derived from methyl 4-amino-2-hydroxybenzoate.

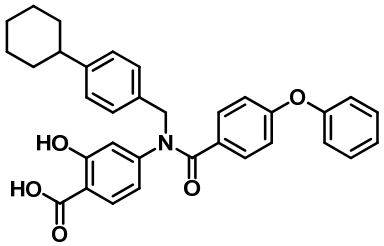
Synthesis of carboxylic acid 33



Methyl 4-(4-cyclohexylbenzylamino)-2-hydroxybenzoate (31). To a solution of methyl 4-amino-2-hydroxybenzoate (0.283 g, 1.69 mmol) and 4-cyclohexylbenzaldehyde (0.318 g; 1.68 mmol) in AcOH (1 M in 1,2-dichloroethane, 1.68 mL) was added $NaBH(OAc)_3$ (0.508 g; 2.39 mmol) in one portion and the reaction mixture was stirred at room temperature for 48 h. Water (10 mL) was added and the mixture neutralized using $NaHCO_3$ (sat. aq., 10 mL). The organic layer was extracted with DCM (2 × 10 mL), dried and evaporated. Chromatography afforded the ester **31** (0.191 g, 33%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (s, 1H), 7.59 (d, *J* = 9.3 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.14–6.08 (m, 1H), 4.47 (t, *J* = 5.4 Hz, 1H), 4.30 (d, *J* = 5.3 Hz, 2H), 3.87 (s, 3H), 2.55–2.43 (m, 1H), 1.90–1.68 (m, 5H), 1.49–1.17 (m, 6H); HRMS (ESI+ve) *m/z* 340.1902 $[M+H]^+$ (calcd for $C_{21}H_{26}NO_3$ 340.1907).



Methyl 4-(*N*-(4-cyclohexylbenzyl)-4-phenoxybenzamido)-2-hydroxybenzoate (32). This was prepared from **31** (0.093 g, 0.274 mmol) and 4-phenoxybenzoyl chloride (0.083 g, 0.357 mmol) in the same manner as described for **30c**. Chromatography afforded pure **32** as a colorless oil (0.035 g, 0.065 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.35–7.31 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.14–7.11 (m, 3H), 7.00–6.93 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 2.1 Hz, 1H), 6.42 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.09 (s, 2H), 3.90 (s, 3H), 2.63–2.35 (m, 1H), 1.89–1.65 (m, 5H), 1.48–1.08 (m, 6H); HRMS (ESI+ve) *m/z* 558.2277 $(M+Na)^+$ (calcd for $C_{34}H_{34}NO_5$ 558.2251).



4-(*N*-(4-Cyclohexylbenzyl)-4-phenoxybenzamido)-2-hydroxybenzoate (33). This was prepared from **32** (0.033 g, 0.061 mmol) in the same manner as described for **13c** as a white solid oil (0.025 g, 0.047 mmol, 77%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (d, *J* = 8.4 Hz, 1H), 7.42–7.32 (m, 4H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.17–7.08 (m, 3H), 6.99–6.89 (m, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 5.10 (s, 2H), 2.63–2.35 (m, 1H), 2.011.75 (m, 5H), 1.49–1.09 (m, 6H); HRMS (ESI+ve) *m/z* 522.2264 $[M+H]^+$ (calcd for $C_{33}H_{32}NO_5$ 522.2275); HPLC purity 97% {t_R = 6.51 min, flow 1 ml/min, [(MeCN:(0.1% TFA in H_2O), 80:20]}.

Fluorescence Polarization Assay

The fluorescence polarization (FP) assay was performed as described in detail elsewhere.[7] The assay measures differences in the fluorescence signal between free and STAT3 SH2 domain-bound fluorescently labeled phosphopeptide as described by Schust and Berg.[8, 9] FP assay buffer (16.5 µL of 50 mM NaCl, 10 mM Hepes, pH 7.5, 1 mM EDTA, 0.01% Triton-X100, 2 mM dithiothreitol) was added to each well of a 96-well half-area black plates (Corning, Tewksbury, MA, USA). Test compounds (3 µL in 5% DMSO) and STAT3 protein [purchased from SignalChem (Richmond, BC, Canada)](7.5 µL diluted by FP assay buffer from the commercial stock) were added to the well. The plate was incubated at room temperature on a shaker for 60 min. Fluorescent peptide 5-FAM-G(pTyr)LPQTV-$CONH_2$ purchased from Genscript (Piscataway, NJ, USA) (3 µL, to provide a reaction concentration of 10 nM) was added to the well and then incubated on a shaker at room temperature for 30 min. The fluorescence polarization signal was then measured using a 2104 EnVision® Multilabel Reader (Perkin Elmer, Waltham, Massachusetts, USA) in FITC FP Dual module with excitation

filter of FITC FP 480 and emission filter of FITC FP P-pol535 and S-pol535. For mP binding group (STAT3 only control), 19.5 µL FP assay buffer was added initially; and 27 µL FP assay buffer for mP free group (fluorescent peptide 5-FAM-G(pTyr)LPQTV-$CONH_2$). For all the wells, the final volume is 30 µL. The inhibition was calculated according to the equation Inhibition (%) = [1-($mP_{compound}$ – mP_{free})/($mP_{binding}$ – mP_{free})] × 100. Polarization values were calculated according to the equation mP = 1000 ×(S - G×P)/(S + G×P) where S is the value from the S channel, P the value from the P channel and G the G-factor). GraphPad was employed to determine the IC_{50} using nonlinear curve fitting (see Figure S1 for the IC_{50} of **13g**).

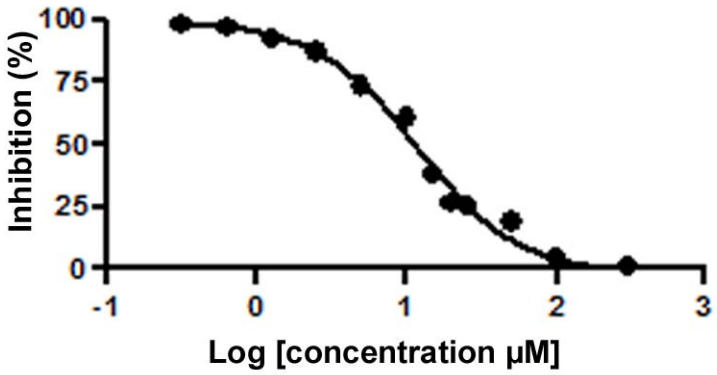


Figure S1: Dose-response of **13g** (IC_{50} 12 µM).

Molecular modeling

GLIDE (Schrödinger, Inc.) was used to the phosphonic acid **12d** and salicylic acids **13f** and **13g** to the ApY*LK model of the binding site of the STAT3 SH2 domain based on the X-ray crystal structure of the STAT3 dimer bound to DNA.[10] The docking methods are described in detail elsewhere.[7] PyMol (Schrodinger, Inc.) was used to produce the Figures 2, S2 and S3.

Effects of selected compounds upon pSTAT3 levels in MDA-MB-468 human breast cancer cells

The Western blot experiments were performed as described by us previously.[7] MDA-MB-468 cells were treated with the compounds (DMSO at 1%) for 4 hours. Cells were then lysed with RIPA buffer [Tris-HCl (pH 7.4, 20 mM), ethylenediaminetetraacetic acid (5 mM), sodium pyrophosphate ($Na_4P_2O_7$) (10 mM), sodium fluoride (100 mM), 2 mM sodium orthovanadate, 1% Tergitol®-type NP-40 (1%), phenylmethylsulfonyl fluoride (1 mM) and aprotinin (10 mg/ml)]. The cell lysates were denatured by boiling with 5 × SDS-PAGE sample buffers for 5 minutes and run on SDS-PAGE gel. The proteins were then transferred to membranes that were blocked with 5% non-fat milk in TBST (Tris Buffer Saline with 0.1% Tween-20) buffer for 30 minutes at room temperature, and incubated with primary antibodies (pY705STAT3, STAT3 and β-actin) at 4 °C overnight at dilution of 1:1000 in 3% BSA, followed by washing and incubation with secondary antibody at

dilution of 1:1000 in 5% non-milk TBST buffer for 1 hour at room temperature. The membranes were then washed with 1X PBS (Phosphate Buffered Saline) buffer for 10 minutes for 3 times and developed with ECL (enhanced chemiluminescence) kit (PerkinElmer, Waltham, MA, USA).

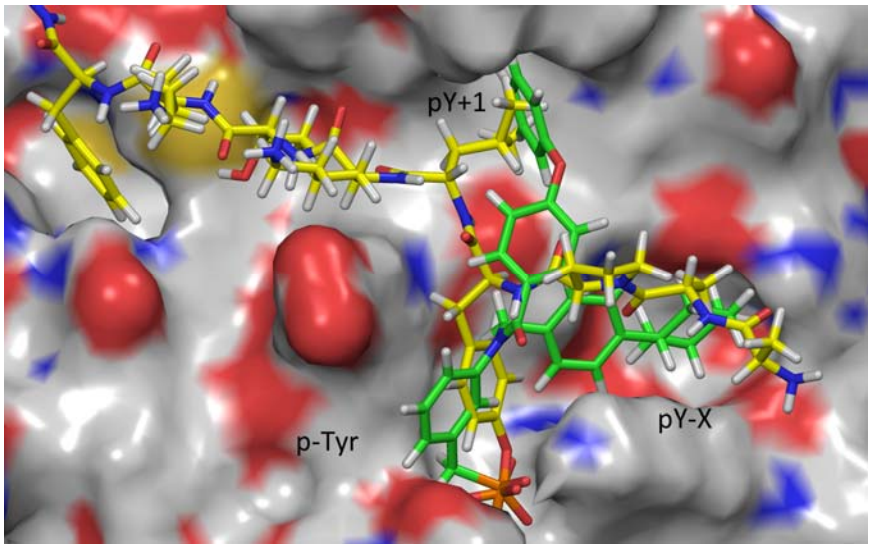


Figure S2. Overlay of phosphonic acid **12d** and STAT3 peptide in the STAT3 SH2 domain**.** a: surface rendering of **12d** (carbon atoms shown in green) docked to the STAT3 p-Tyr binding site (carbon and hydrogen atoms shown gray; oxygen atoms shown red and nitrogen atoms shown blue) overlaid with the STAT3 peptide (X-ray).

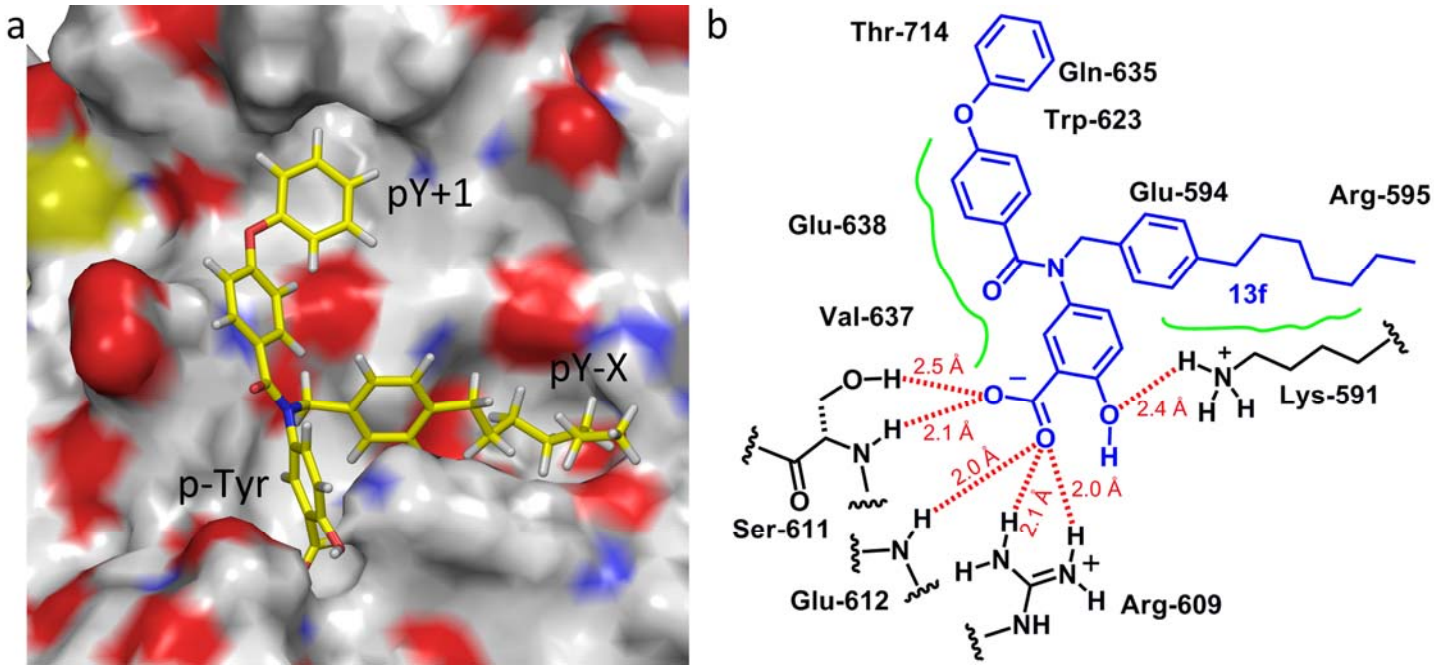


Figure S3. Salicylic acid **13f** docked to the STAT3 SH2 domain. a: surface rendering of **13f** docked to the STAT3 p-Tyr binding site (carbon and hydrogen atoms shown gray; oxygen atoms shown red and nitrogen atoms shown blue. b: Schematic binding mode of **13f** (blue) to the STAT3 SH2 domain showing the hydrogen bonds (red) and hydrophobic interactions (green).

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