

Discovery of sulfonylated aminosalicylates as dual MCL-1/BCL-xL inhibitors

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Chemistry

General Procedures

All reactions were performed in oven-dried glassware under an inert (N_2) atmosphere, unless otherwise stated. Anhydrous solvents were used as supplied without further purification. 1H and ^{13}C NMR spectra were recorded on a Varian 400 MHz NMR spectrometer at 25 °C. Chemical shifts are reported in parts per million (ppm) and are referenced to residual non-deuterated solvent peak ($CHCl_3$: δH 7.26, δC 77.2; DMSO: δH 2.50, δC 39.5). Mass spectra were recorded on a Bruker AmaZon X mass spectrometer using atmospheric pressure chemical ionization (APCI). All final molecules were confirmed to be >95% pure by HPLC prior to biological testing using a Waters 1525 analytical/preparative HPLC equipped with a Atlantis T3 C18 reversed phase column according to the following gradients: 25% solvent (A) to 100% solvent (B) over 22 min at 1 ml min^{-1} , where solvent (A) is H_2O with 0.1% TFA and solvent (B) is CH_3CN-H_2O , 9:1 with 0.1% TFA; data are represented as retention time (t_R) followed by % purities in parentheses.

General procedure A: Methyl esterification. The acid (1 eq) was suspended in MeOH (0.5 M), cooled to 0 °C, and H_2SO_4 (7 eq) was added drop wise. The reaction was slowly warmed up to room temperature and then refluxed overnight. TLC indicated the reaction was complete. The volatiles were evaporated and the residue was poured into ice. The pH was adjusted to 7 using 1M NaOH solution. The precipitate was filtered and washed with water, then dried in the vacuum oven overnight to yield the methyl ester as a white solid.

General procedure B: O-Benzoylation. The phenol (1 eq) was dissolved in anhydrous DMF (0.1 M), cooled to 0 °C, followed by addition of K^tOBu (1.1 eq). Benzyl bromide (1.1 eq) was then added and the reaction was stirred at room temperature overnight. TLC indicated the reaction was complete, which was then partitioned between EtOAc and H_2O . The organic layer was collected, washed repeatedly with H_2O (4x), then dried over Na_2SO_4 , filtered, concentrated and purified by flash column chromatography over silica gel using an eluent of Hex/EtOAc 1:1 to yield the product.

General procedure C: Reductive amination. The aniline (1 eq) was dissolved in dichloroethane (0.1 M), then the corresponding aldehyde/ketone (1.3 eq) and acetic acid (1.2 eq) were added. Next, $NaBH(OAc)_3$ (2.5 eq) was added batchwise into the reaction and stirred at room temperature overnight. TLC indicated the reaction was complete. Saturated $NaHCO_3$ (aq) was poured into the reaction mixture and bubbled for 30 min. The mixture was then collected and partitioned between water and DCM (3x). The combined organic layers were dried over Na_2SO_4 , filtered, concentrated and purified by flash column chromatography over silica gel using an eluent of Hex/EtOAc 4:1 to afford the product.

General procedure D: Sulfonamide synthesis. The aniline (1 eq) was dissolved in anhydrous $CHCl_3$ (0.1 M), followed by the addition of the desired sulfonyl chloride (1.5 eq), DIPEA (3 eq) and DMAP (0.1 eq).

The reaction was heated at 65 °C overnight under N₂ atmosphere. TLC indicated the reaction was complete. The volatiles were evaporated and the residual was reconstituted in EtOAc and washed with 1M HCl. The organic layer was collected and dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography over silica gel using an eluent of Hex/EtOAc 4:1 to give the product.

General procedure E: Nucleophilic aromatic substitution (S_NAr). The fluorobenzene (1 eq) was dissolved in anhydrous DMSO (0.1 M), followed by adding corresponding phenol (5 eq), and K₂CO₃ (5 eq). The reaction was heated at 100 °C overnight. TLC indicated the reaction was complete, which was then partitioned between EtOAc (and H₂O). The organic layer was collected, washed repeatedly with H₂O (4x), then dried over Na₂SO₄, filtered, concentrated and then reconstituted with Et₂O. The Et₂O solution was washed with 1M NaOH (4x), then dried over Na₂SO₄, filtered, concentrated and then purified by flash column chromatography over silica gel using an eluent of Hex/EtOAc 4:1 to furnish the product..

General procedure F: Ester hydrolysis. The ester (1 eq) was dissolved in a mixed solvent of THF/MeOH/H₂O 3:1:1 (0.1 M). LiOH·H₂O (4 eq) was added to the reaction, which was stirred at room temperature overnight, or until TLC indicated the reaction was complete. The volatiles were evaporated and the residue was partitioned between EtOAc and 1M HCl. The organic layer was collected, dried over Na₂SO₄, filtered, and concentrated to yield the product.

General procedure G: Debonylation. The benzylation phenol (1 eq) was dissolved in a solvent mixture of toluene/TFA 2:1 (0.1 M), and stirred at room temperature overnight. TLC indicated the reaction was complete. The volatiles were evaporated and the residue was purified by preparative TLC using an eluent of DCM/MeOH/AcOH 92:7:1 to deliver the product.

Methyl 4-nitrobenzoate (8): 4-Nitrobenzoic acid (7) was esterified on a scale of 18 mmol according to general procedure A to yield the product as a beige solid (3.2g, 98%) [Yoshida, M., et al., *Org. Biomol. Chem.* 2009, 7, 4062-406].

Methyl 4-aminobenzoate (9): Methyl 4-aminobenzoate (8; 3g, 16.7 mmol, 1 eq) was dissolved in EtOAc (0.1 M), followed by addition of stannous chloride dehydrate (19g, 83 mmol, 5 eq) portion wise, and the reaction mixture was stirred at room temperature overnight. TLC indicated the reaction was completed. Saturated NaHCO₃ (aq) was added to reaction to quench the reaction, and mixture was partitioned between EtOAc and H₂O, then washed with H₂O twice more. The organic layer dried over Na₂SO₄, filtered, and concentrated to yield the product as a beige solid (2.1g, 85%): ¹H NMR (CDCl₃, 400MHz) δ 7.85 (2H, d, *J* = 8.4 Hz, Ar), 6.64 (2H, d, *J* = 8.8 Hz, Ar), 4.06 (2H, s, NH₂), 3.85 (3H, s, CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 150.8, 131.6, 119.7, 113.8, 51.6;

Methyl 4-(isobutylamino)benzoate (10): Methyl 4-aminobenzoate (9) was reductive aminated according to general procedure C on a scale of 3.4 mmol to give the product as a light brown solid (600mg, 86%): ¹H

NMR (CDCl₃, 400MHz) δ 7.85 (2H, d, J = 6.8 Hz, Ar), 6.54 (2H, d, J = 8.0 Hz, Ar), 4.29 (1H, s, NH), 3.85 (3H, s, CH₃), 2.98 (2H, d, J = 6.4 Hz, CH₂), 1.93-1.86 (1H, m, CH), 0.99 (6H, d, J = 6.0 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 167.3, 152.1, 131.5, 117.9, 111.4, 51.5, 51.1, 28.0, 20.4.

Methyl 4-(N-isobutylphenylsulfonamido)benzoate (11a): Methyl 4-(isobutylamino)benzoate (**10**) was coupled to benzenesulfonyl chloride according to general procedure D on a scale of 0.74 mmol to yield the product as a light brown solid (231 mg, 90%): ¹H NMR (CDCl₃, 400MHz) δ 7.97 (2H, d, J = 7.6 Hz, Ar), 7.60-7.52 (3H, m, Ar), 7.45 (2H, t, J = 7.2 Hz, Ar), 7.14 (2H, d, J = 8.8 Hz, Ar), 3.92 (3H, s, CH₃), 3.34 (2H, d, J = 7.2 Hz, CH₂), 1.58-1.53 (1H, m, CH), 0.90 (6H, d, J = 6.8 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 166.3, 143.6, 137.7, 132.8, 130.3, 129.2, 128.9, 128.1, 127.5, 57.4, 52.3, 26.9, 19.8.

Methyl 4-(N-isobutyl-naphthalene-2-sulfonamido)benzoate (11b): methyl 4-(isobutylamino)benzoate was coupled to 2-naphthalenesulfonyl chloride according to general procedure D on a scale of 0.66 mmol to yield the product as a light brown solid (209 mg, 80%): ¹H NMR (CDCl₃, 400MHz) δ 8.13 (1H, s, Ar), 7.95 (2H, d, J = 8.4 Hz, Ar), 7.89-7.85 (3H, m, Ar), 7.64-7.56 (2H, m, Ar), 7.47-7.45 (1H, m, Ar), 7.14 (2H, d, J = 8.8 Hz, Ar), 3.89 (3H, s, CH₃), 3.38 (2H, d, J = 7.6 Hz, Ar), 1.59-1.52 (1H, m, CH), 0.89 (6H, d, J = 6.8 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 166.3, 143.7, 134.9, 134.8, 131.9, 130.3, 129.3, 129.2, 129.0, 128.8, 128.7, 128.2, 127.9, 127.5, 122.8, 57.5, 52.3, 26.9, 19.8.

Methyl 4-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (11c): Methyl 4-(isobutylamino)benzoate (**10**) was coupled to biphenyl-4-sulfonyl chloride according to general procedure D on a scale of 0.71 mmol to give the product as a light brown solid (276mg, 92%): ¹H NMR (CDCl₃, 400MHz) δ 7.97 (2H, d, J = 7.6 Hz, Ar), 7.63 (2H, d, J = 7.6 Hz, Ar), 7.59-7.56 (4H, m, Ar), 7.48-7.44 (2H, m, Ar), 7.42-7.38 (1H, m, Ar), 7.18 (2H, d, J = 7.2 Hz, Ar), 3.90 (3H, s, CH₃), 3.37 (2H, d, J = 7.6 Hz, CH₂), 1.59-1.55 (1H, m, CH), 0.90 (6H, d, J = 7.6 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 166.3, 145.6, 143.7, 139.1, 136.3, 130.3, 129.2, 129.1, 128.5, 128.1, 128.0, 127.4, 127.3, 57.4, 52.3, 26.9, 19.8.

Methyl 4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (11d): Methyl 4-(isobutylamino)benzoate (**10**) was coupled to 4-fluoro-benzenesulfonyl chloride according to general procedure D on a scale of 2.46 mmol to yield the product as a light brown solid (718 mg, 80%): ¹H NMR (CDCl₃, 400MHz) δ 7.99 (2H, d, J = 7.6 Hz, Ar), 7.55-7.52 (2H, m, Ar), 7.16-7.10 (4H, m, Ar), 3.92 (3H, s, CH₃), 3.34 (2H, d, J = 6.8 Hz, CH₂), 1.59-1.55 (1H, m, CH), 0.90 (6H, d, J = 6.8 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 143.4, 130.4, 130.2, 130.1, 129.3, 128.1, 116.2, 116.0, 57.4, 52.3, 26.9, 19.8.

Methyl 4-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoate (11e): Methyl 4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**11d**) was reacted with 3,5-dimethyl-4-chloro-phenol according to general procedure E on a scale of 0.42 mmol to yield the product as a light brown solid (181 mg, 86%): ¹H NMR (CDCl₃, 400MHz) δ 7.98 (2H, d, J = 7.6 Hz, Ar), 7.46 (2H, d, J = 8.8 Hz, Ar), 7.18 (2H, d, J = 8.0 Hz, Ar), 6.93 (2H, d, J = 8.0 Hz, Ar), 6.79 (2H, s, Ar), 3.91 (3H, s, CH₃), 3.34 (2H, d, J =

7.2 Hz, Ar), 2.37 (6H, s, 2*CH₃), 1.61-1.55 (1H, m, CH), 0.90 (6H, d, *J* = 6.0 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 166.3, 161.6, 152.6, 143.7, 138.3, 131.5, 130.7, 130.3, 129.7, 129.1, 128.1, 120.1, 117.1, 57.3, 52.3, 26.9, 20.9, 20.4, 19.8.

4-(N-Isobutylphenylsulfonamido)benzoic acid (6a): Methyl 4-(N-isobutylphenylsulfonamido)benzoate (**11a**) was hydrolyzed according to general procedure F on a scale of 0.57 mmol to furnish the product as a white solid (186mg, 98%): ¹H NMR (400 MHz, d₆-DMSO) δ 13.06 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.56-7.48 (m, 4H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.35 (d, *J* = 8 Hz, 2H), 1.43-1.36 (m, 1H), 0.80 (d, *J* = 6 Hz, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 167.1, 143.3, 137.7, 133.7, 130.5, 130.1, 129.8, 128.4, 127.6, 56.9, 26.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 333.1, Found: 334.0 (M+H)⁺; t_R = 9.9 min (100%).

4-(N-Isobutylnaphthalene-2-sulfonamido)benzoic acid (6b): Methyl 4-(N-isobutylnaphthalene-2-sulfonamido)benzoate (**11b**) was hydrolyzed according to general procedure F on a scale of 0.5 mmol to deliver the product as a white solid (182 mg, 95%): ¹H NMR (400 MHz, d₆-DMSO) δ 13.05 (s, 1H), 8.26 (s, 1H), 8.12 (d, *J* = 8 Hz, 1H), 8.07-8.01 (m, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.71-7.61 (m, 2H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 3.42 (d, *J* = 6.8 Hz, 2H), 1.43-1.38 (m, 1H), 0.81 (d, *J* = 7.2 Hz, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 167.1, 143.4, 135.0, 134.8, 132.1, 130.5, 130.1, 129.8, 129.7, 129.5, 128.9, 128.5, 128.3, 128.1, 122.9, 57.1, 26.9, 20.0; MS (APCI+) *m/z* Calcd (M⁺): 383.1, Found: 384.0 (M+H)⁺; t_R = 11.8 min (100%).

4-(N-Isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoic acid (6c): Methyl 4-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (**11c**) was hydrolyzed according to general procedure F on a scale of 0.5 mmol to give the product as a white solid (202 mg, 99%): ¹H NMR (400 MHz, d₆-DMSO) δ 13.07 (s, 1H), 7.90-7.84 (m, 4H), 7.71 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.49-7.39 (m, 3H), 7.25 (d, *J* = 8 Hz, 2H), 3.39 (d, *J* = 8 Hz, 2H), 1.45-1.39 (m, 1H), 0.81 (d, *J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 167.1, 144.9, 143.3, 138.6, 136.5, 130.5, 130.2, 129.6, 129.1, 128.4, 128.3, 127.8, 127.5, 56.9, 26.9, 20.0; MS (APCI+) *m/z* Calcd (M⁺): 409.1, Found: 410.0 (M+H)⁺; t_R = 13.1 min (100%).

4-(4-Fluoro-N-isobutylphenylsulfonamido)benzoic acid (6d): Methyl 4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**11d**) was hydrolyzed according to general procedure F on a scale of 0.33 mmol to yield the product as a beige solid (105 mg, 91%): ¹H NMR (400 MHz, d₆-DMSO) δ 13.05 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.57-7.54 (m, 2H), 7.39 (t, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.8, 2H), 3.33 (t, *J* = 7.8 Hz, 2H), 1.41-1.37 (m, 1H), 0.80 (d, *J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 167.1, 143.2, 130.8, 130.7, 130.5, 130.3, 128.5, 117.1, 116.9, 56.9, 26.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 351.1, Found: 352.0 (M+H)⁺; t_R = 10.3 min (100%).

4-(4-(4-Chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoic acid (6e): Methyl 4-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoate (**11e**) was hydrolyzed according

to general procedure F on a scale of 0.3 mmol to give the product as a white solid (131 mg, 90%): ¹H NMR (400 MHz, d₆-DMSO) δ 13.02 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 9.2 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.99 (s, 2H), 3.33 (t, *J* = 5.8 Hz, 2H), 2.30 (s, 6H), 1.42-1.38 (m, 1H), 0.80 (d, *J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 167.1, 161.3, 153.0, 143.4, 138.3, 131.6, 130.5, 130.2 (2), 130.1, 128.5, 120.7, 117.9, 56.9, 26.9, 20.7, 20.0; MS (APCI+) *m/z* Calcd (M⁺): 487.1, found: 488.0 (M+H)⁺; *t_R* = 19.1 min (100%).

Methyl 4-amino-2-hydroxybenzoate (13): 4-Amino-2-hydroxybenzoic acid (**12**) was esterified according to general procedure A on a scale of 26 mmol to give the product as a brown solid (4.1 g, 95%): ¹H NMR (CDCl₃, 400MHz) δ 10.92 (1 H, s, OH), 7.59 (1 H, d, *J* = 7.6 Hz, Ar), 6.13 (1 H, d, *J* = 7.6 Hz, Ar), 6.11 (1 H, s, Ar), 3.85 (3 H, s, OCH₃); ¹³C NMR (CDCl₃, 100MHz) δ 170.5, 163.5, 153.3, 131.6, 106.8, 103.0, 100.7, 51.7; MS (APCI+) *m/z* Calcd (M⁺): 167.1, Found: 168.4 (M+H)⁺.

Methyl 4-amino-2-(benzyloxy)benzoate (14a): Methyl 4-amino-2-hydroxybenzoate (**13**) was *O*-benzylated according to general procedure B on a scale of 12 mmol to give the product as a beige solid (2.1 g, 70%): ¹H NMR (CDCl₃, 400MHz) δ 7.78 (1 H, d, *J* = 8.8 Hz, Ar), 7.55-7.46 (2 H, m, Ar), 7.37 (2 H, t, *J* = 7.2 Hz, Ar), 7.30 (1 H, t, *J* = 7.2 Hz, Ar), 6.35-6.24 (2 H, m, Ar), 5.12 (2 H, s, CH₂), 4.02 (2 H, br s, NH₂), 3.83 (3 H, s, OCH₃); ¹³C NMR (CDCl₃, 100MHz) δ 161.6, 155.9, 147.1, 132.1, 129.6, 123.8, 122.9, 121.9, 102.1, 94.7, 65.6, 46.7.

Benzyl 4-amino-2-(benzyloxy)benzoate (14b): 4-Aminosalicylic acid (**12**; 5 g, 32.6 mmol, 1 eq) was dissolved in DMF (0.1 M), and cooled to 0 °C. KO^tBu (8 g, 72 mmol, 2.2 eq) was added batch wise, followed by benzyl bromide (8.4 mL, 72 mmol, 2.2 eq), and the reaction was stirred at room temperature overnight. TLC indicated the reaction was complete. The reaction was partitioned between EtOAc and H₂O 3 times, organic layer was collected, combined, and washed with H₂O 3 times, dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography over silica gel using an eluent of Hexane/EtOAc 4:1 to give the product as a light brown solid (13g, 56%): ¹H NMR (DMSO-d₆, 400MHz) δ 7.47 (1H, d, *J* = 8.8 Hz, Ar), 7.36 (2H, d, *J* = 6.8 Hz, Ar), 7.27-7.16 (8H, m, Ar), 6.20 (1H, s, Ar), 6.06 (1H, d, *J* = 8.8 Hz, Ar), 5.86 (2H, s, NH₂), 5.08 (2H, s, O-CH₂), 4.95 (2H, s, N-CH₂); ¹³C NMR (DMSO-d₆, 100MHz) δ 165.3, 160.8, 155.2, 137.5, 134.6, 134.2, 129.1, 128.8, 128.7, 128.2, 128.1, 127.9, 127.4, 106.3, 105.9, 98.0, 96.7, 69.5, 65.2; MS (APCI+) *m/z* Calcd (M⁺): 333.1; Found: 334.1 (M+H)⁺.

Methyl 2-(benzyloxy)-4-(isobutylamino)benzoate (15a): Methyl 4-amino-2-(benzyloxy)benzoate (**14a**) was reductively aminated with isobutylaldehyde according to general procedure C on a scale of 3.6 mmol to give the product as a pale solid (970 mg, 86%): ¹H NMR (CDCl₃, 400MHz) δ 7.79 (1 H, d, *J* = 8.8 Hz, Ar), 7.53 (2 H, d, *J* = 7.6 Hz, Ar), 7.39 (2 H, t, *J* = 7.6 Hz, Ar), 7.30 (1 H, t, *J* = 7.6 Hz, Ar), 6.17 (1 H, d, *J* = 8.8 Hz, Ar), 6.12 (2 H, s, Ar), 5.16 (2 H, s, CH₂), 3.84 (3 H, s, OCH₃), 2.93 (2 H, d, *J* = 7.2 Hz, CH₂iPr), 1.90-1.80 (1 H, m, CH₂CH), 0.97 (6 H, d, *J* = 7.2 Hz, 2 x CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.4, 160.9,

153.3, 137.1, 134.2, 128.5, 127.6, 126.7, 107.9, 104.7, 97.0, 70.4, 51.4, 51.1, 28.0, 20.4; MS (APCI+) m/z Calcd (M^+): 313.1, Found: 314.2 ($M+H$)⁺.

Benzyl 2-(benzyloxy)-4-(cyclopentylamino)benzoate (15b): Benzyl 4-amino-2-(benzyloxy)benzoate (**14b**) underwent reductive amination with cyclopentanone according to general procedure C on a scale of 1.86 mmol to afford the product as a light brown solid (479 mg, 64%): ¹H NMR (DMSO-*d*₆, 400MHz) δ 7.62 (1H, d, J = 8.8 Hz, Ar) 7.48 (2H, d, J = 7.2 Hz, Ar), 7.39-7.28 (7H, m, Ar), 6.50 (1H, d, J = 6.4 Hz, Ar), 6.26 (1H, s, Ar), 6.20 (1H, d, J = 8.8 Hz, Ar), 5.21 (2H, s, O-CH₂), 5.11 (2H, s, O-CH₂), 3.77-3.73 (1H, m, CH), 1.93-1.39 (8H, m, Cp); ¹³C NMR (DMSO-*d*₆, 100MHz) δ 165.3, 160.8, 154.2, 137.6, 137.5, 133.9, 128.8, 128.7, 128.1, 128.0, 127.9, 127.4, 105.6, 105.0, 96.7, 72.2, 69.6, 65.2, 53.7, 32.8, 24.1, 23.0; MS (APCI+) m/z Calcd (M^+): 401.2; Found: 402.1 ($M+H$)⁺.

Methyl 2-(benzyloxy)-4-(N-isobutylphenylsulfonamido)benzoate (16aa): Methyl 2-(benzyloxy)-4-(isobutylamino)benzoate (**15a**) was coupled to benzenesulfonyl chloride according to general procedure D on a scale of 0.96 mmol to yield the product as a clear oil (153 mg, 35%); ¹H NMR (CDCl₃, 400MHz) δ 7.72 (1 H, d, J = 8.0 Hz, Ar), 7.61-7.52 (3 H, m, Ar), 7.48-7.41 (4 H, m, Ar), 7.37 (2 H, t, J = 8.0 Hz, Ar), 7.31 (1 H, d, J = 7.2 Hz, Ar), 6.83 (1 H, s, Ar), 6.56 (1 H, d, J = 7.2 Hz, Ar), 5.09 (2 H, s, CH₂), 3.90 (3 H, s, OCH₃), 3.27 (2 H, d, J = 8.0 Hz, CH₂iPr), 1.56-1.43 (1 H, m, CH₂CH), 0.84 (6 H, d, J = 8.0 Hz, 2 x CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.1, 158.2, 143.9, 137.7, 136.2, 132.7, 132.0, 128.8, 128.5, 127.9, 127.6, 126.8, 119.8, 119.2, 114.9, 70.6, 57.5, 52.1, 26.8, 19.8; MS (APCI+) m/z Calcd (M^+): 453.1, Found: 454.0 ($M+H$)⁺

Methyl 2-(benzyloxy)-4-(N-isobutyl-naphthalene-2-sulfonamido)benzoate (16ab): Methyl 2-(benzyloxy)-4-(isobutylamino)benzoate (**15a**) was coupled to 2-naphthalene sulfonyl chloride according to general procedure D on a scale of 0.96 mmol to give the product as a white foam (146 mg, 30%); ¹H NMR (CDCl₃, 400MHz) δ 8.16 (1 H, s, Ar), 7.96-7.86 (3 H, m, Ar), 7.75-7.58 (3 H, m, Ar), 7.50 (1 H, d, J = 8.8 Hz, Ar), 7.39-7.24 (5 H, m, Ar), 6.82 (1 H, s, Ar), 6.59 (1 H, d, J = 8.4 Hz, Ar), 5.00 (2 H, s, CH₂), 3.90 (3 H, s, OCH₃), 3.31 (2 H, d, J = 8.0 Hz, CH₂iPr), 1.56-1.45 (1 H, m, CH₂CH), 0.86 (6 H, d, J = 8.0 Hz, 2 x CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.1, 158.3, 144.0, 136.2, 134.8, 132.0, 129.3, 129.0, 128.9, 128.8, 128.5, 127.9, 127.8, 127.6, 126.8, 122.9, 119.8, 119.4, 114.9, 70.6, 57.6, 52.2, 26.8, 19.8; MS (APCI+) m/z Calcd (M^+): 503.1, Found: 504.1 ($M+H$)⁺.

Methyl 2-(benzyloxy)-4-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (16ac): Methyl 2-(benzyloxy)-4-(isobutylamino)benzoate (**15a**) was coupled to 4-biphenylsulfonyl chloride according to general procedure D on a scale of 0.96 mmol to give the product as a clear oil (63 mg, 13%); ¹H NMR (CDCl₃, 400MHz) δ 7.74 (1 H, d, J = 7.6 Hz, Ar), 7.68-7.56 (6 H, m, Ar), 7.48 (2 H, t, J = 7.2 Hz, Ar), 7.45-7.38 (3 H, m, Ar), 7.35 (2 H, t, J = 8.0 Hz, Ar), 7.31-7.25 (1 H, m, Ar), 6.87 (1 H, s, Ar), 6.62 (1 H, d, J = 8.0 Hz, Ar), 5.10 (2 H, s, CH₂), 3.90 (3 H, s, OCH₃), 3.30 (2 H, d, J = 7.2 Hz, CH₂iPr), 1.57-1.46 (1

H, m, CH₂CH), 0.86 (6 H, d, $J = 8.0$ Hz, 2 x CH₃); ¹³C NMR (CDCl₃, 100MHz) 158.2, 145.6, 144.0, 139.1, 136.2, 132.0, 129.1, 128.5, 128.1, 127.8, 127.4, 127.3, 126.8, 119.2, 114.9, 70.6, 57.5, 52.2, 26.8, 19.8; MS (APCI+) m/z Calcd (M⁺): 529.2, Found: 530.1 (M+H⁺).

Methyl 2-(benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (16ad): Methyl 2-(benzyloxy)-4-(isobutylamino)benzoate (**15a**) was coupled to 4-fluorobenzene sulfonyl chloride according to general procedure D on a scale of 1.5 mmol to give the product as a brown solid (586 mg, 83%): ¹H NMR (DMSO-d₆, 400MHz) δ 7.66-7.60 (3H, m, Ar), 7.43-7.37 (6H, m, Ar), 7.32-7.31 (1H, m, Ar), 6.88 (1H, s, Ar), 6.79 (1H, d, $J = 8.8$ Hz, Ar), 5.09 (2H, s, CH₂), 3.79 (3H, s, CH₃), 1.39-1.35 (1H, m, CH), 0.80 (6H, d, $J = 6.4$ Hz, 2*CH₃); ¹³C NMR (DMSO-d₆, 100MHz) δ 165.9, 157.8, 143.8, 136.9, 131.6, 130.8, 130.7, 128.8, 128.1, 127.4, 120.6, 120.2, 117.1, 116.8, 114.4, 70.3, 57.1, 52.4, 26.9, 20.0; MS (APCI+) m/z Calcd (M⁺): 471.1; Found: 472.0 (M+H)⁺.

Methyl 2-(benzyloxy)-4-(4-bromo-N-isobutylphenylsulfonamido)benzoate (16ae): Methyl 2-(benzyloxy)-4-(isobutylamino)benzoate (**15a**) was coupled to 4-bromobenzene sulfonyl chloride according to general procedure D on a scale of 0.32 mmol to give the product as a light brown solid (119 mg, 70%): ¹H NMR (CDCl₃, 400MHz) δ 7.47 (1H, d, $J = 8.0$ Hz, Ar), 7.32 (2H, d, $J = 7.6$ Hz, Ar), 7.18-7.13 (2H, m, Ar), 7.12-7.11 (4H, m, Ar), 7.06 (1H, t, $J = 7.2$ Hz, Ar), 7.00 (1H, s, Ar), 6.59 (1H, s, Ar), 7.29 (1H, d, $J = 9.2$ Hz, Ar), 4.87 (2H, s, O-CH₂), 3.65 (3H, s, O-CH₃), 2.99 (2H, d, $J = 8.0$ Hz, N-CH₂), 1.28-1.21 (1H, m, CH), 0.59 (6H, d, $J = 6.0$ Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.0, 160.8, 158.3, 143.5, 136.7, 136.1, 132.1, 129.0, 128.6, 127.9, 126.8, 120.0, 118.9, 114.9, 70.7, 57.5, 52.2, 26.8, 19.8.

Methyl 2-(benzyloxy)-4-(N-isobutyl-4-methylphenylsulfonamido)benzoate (16af): Methyl 2-(benzyloxy)-4-(isobutylamino)benzoate (**15a**) was coupled to *p*-toluenesulfonyl chloride according to general procedure D on a scale of 0.96 mmol to yield the product as a clear oil (153 mg, 34%): ¹H NMR (CDCl₃, 400MHz) δ 7.72 (1 H, d, $J = 8.8$ Hz, Ar), 7.47-7.34 (6 H, m, Ar), 7.31 (1 H, d, $J = 7.2$ Hz, Ar), 7.28-7.20 (2 H, m, Ar), 6.86 (1 H, s, Ar), 6.56 (1 H, d, $J = 8.4$ Hz, Ar), 5.10 (2 H, s, CH₂), 3.90 (3 H, s, OCH₃), 3.25 (2 H, d, $J = 8.0$ Hz, CH₂iPr), 2.42 (3 H, s, ArCH₃), 1.55-1.44 (1 H, m, CH₂CH), 0.84 (6 H, d, $J = 8.0$ Hz, 2 x CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.2, 158.2, 144.1, 143.6, 136.2, 132.0, 129.4, 128.5, 127.8, 127.6, 126.8, 119.6, 119.1, 114.9, 70.6, 57.3, 52.2, 26.8, 21.6, 19.8; MS (APCI+) m/z Calcd: 467.1, Found: 468.1 (M+H⁺).

Methyl 2-(benzyloxy)-4-(N-isobutyl-4-phenoxyphenylsulfonamido)benzoate (16ag): Methyl 2-(benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**15a**) was coupled to phenol according to general procedure E on a scale of 0.21 mmol to yield the product as a white solid (100 mg, 87%): ¹H NMR (CDCl₃, 400MHz) δ 7.73 (1H, d, $J = 8.0$ Hz, Ar), 7.49-7.44 (4H, m, Ar), 7.42-7.36 (4H, m, Ar), 7.30 (1H, t, $J = 8.0$ Hz, Ar), 7.22 (1H, t, $J = 8.0$ Hz, Ar), 7.05 (2H, d, $J = 8.0$ Hz, Ar), 6.96 (2H, d, $J = 8.8$ Hz, Ar), 6.88 (1H, s, Ar), 6.61 (1H, d, $J = 7.6$ Hz, Ar), 5.12 (2H, s, O-CH₂), 3.90 (3H, s, CH₃), 3.27 (2H, d, $J = 7.2$

Hz, N-CH₂), 1.54-1.47 (1H, m, CH), 0.85 (6H, d, $J = 6.8$ Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.1, 161.7, 158.3, 154.9, 144.1, 136.2, 131.9, 131.4, 130.2, 129.8, 128.6, 127.9, 126.9, 125.0, 120.3, 119.8, 119.1, 117.2, 114.9, 70.7, 57.4, 52.1, 26.9, 19.8; MS (APCI+) m/z Calcd (M⁺): 545.2; Found: 546.1 (M+H)⁺.

Methyl 2-(benzyloxy)-4-(N-isobutyl-4-(*p*-tolxyloxy)phenylsulfonamido)benzoate (16ah): Methyl 2-(benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**15a**) was coupled to *p*-cresol according to general procedure E on a scale of 0.32 mmol to yield the product as a white solid (125 mg, 70%): ¹H NMR (CDCl₃, 400MHz) δ 7.60 (1H, d, $J = 8.8$ Hz, Ar), 7.33-7.25 (4H, m, Ar), 7.23 (2H, t, $J = 7.6$ Hz, Ar), 7.16 (1H, t, $J = 6.8$ Hz, Ar), 7.04 (2H, d, $J = 8.0$ Hz, Ar), 6.79 (4H, d, $J = 8.0$ Hz, Ar), 6.73 (1H, s, Ar), 6.48 (1H, d, $J = 8.8$ Hz, Ar), 4.97 (2H, s, O-CH₂), 3.76 (3H, s, O-CH₃), 3.13 (2H, d, $J = 7.2$ Hz, N-CH₂), 2.22 (3H, s, Ph-CH₃), 1.40-1.33 (1H, m, CH), 0.71 (6H, d, $J = 6.8$ Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.1, 162.1, 158.3, 152.5, 144.2, 136.2, 134.8, 132.0, 131.0, 130.7, 129.7, 128.6, 127.9, 126.9, 120.3, 119.7, 119.2, 116.8, 114.9, 70.7, 57.4, 52.1, 26.8, 20.8, 19.8; MS (APCI+) m/z Calcd (M⁺): 559.2; Found: 560.1 (M+H)⁺.

Methyl 2-(benzyloxy)-4-(4-(3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoate (16ai): methyl 2-(benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**16ad**) was coupled to 3,5-dimethyl phenol according to general procedure E on a scale of 0.21 mmol to yield the product as an ivory solid (102 mg, 85%): ¹H NMR (CDCl₃, 400MHz) δ 7.74 (1H, d, $J = 8.4$ Hz, Ar), 7.46 (4H, t, $J = 8.4$ Hz, Ar), 7.38 (2H, t, $J = 6.8$ Hz, Ar), 7.31 (1H, d, $J = 8.0$ Hz, Ar), 6.95 (2H, d, $J = 8.8$ Hz, Ar), 6.86 (2H, d, $J = 7.2$ Hz, Ar), 6.67-6.62 (3H, m, Ar), 5.12 (2H, s, O-CH₂), 3.90 (3H, s, O-CH₃), 3.28 (2H, d, $J = 7.6$ Hz, N-CH₂), 2.31 (6H, s, 2*Ph-CH₃), 1.53-1.47 (1H, m, CH), 0.85 (6H, d, $J = 6.8$ Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.1, 161.9, 158.3, 154.8, 144.2, 140.1, 136.2, 132.0, 131.0, 129.7, 128.6, 127.8, 126.8, 126.7, 119.7, 119.2, 117.9, 117.1, 114.9, 113.1, 70.7, 57.4, 52.1, 26.8, 21.3, 19.8; MS (APCI+) m/z Calcd (M⁺): 573.2; Found: 574.1 (M+H)⁺.

Methyl 2-(benzyloxy)-4-(4-(2,4-dichlorophenoxy)-N-isobutylphenylsulfonamido)benzoate (16aj): methyl 2-(benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**16ad**) was coupled to 2,4-dichlorophenol according to general procedure E on a scale of 0.21 mmol to yield the product as a light yellow solid (76 mg, 59%): ¹H NMR (CDCl₃, 400MHz) δ 7.70 (1H, d, $J = 8.8$ Hz, Ar), 7.48-7.41 (4H, m, Ar), 7.36 (3H, t, $J = 7.2$ Hz, Ar), 7.28- 7.16 (2H, m, Ar), 7.01 (1H, d, $J = 8.8$ Hz, Ar), 6.88 (2H, d, $J = 8.8$ Hz, Ar), 6.82 (1H, s, Ar), 6.57 (1H, d, $J = 8.0$ Hz, Ar), 5.08 (2H, s, O-CH₂), 3.88 (3H, s, O-CH₃), 3.24 (2H, d, $J = 7.2$ Hz, N-CH₂), 1.51-1.44 (1H, m, CH), 0.82 (6H, d, $J = 6.8$ Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 158.7, 144.5, 136.7, 132.5, 131.3, 130.7, 130.3, 129.0, 128.4, 127.3, 123.8, 119.7, 118.2, 116.9, 115.3, 92.7, 71.2, 57.9, 52.6, 30.2, 27.3, 20.3; MS (APCI+) m/z Calcd (M⁺): 613.1; Found: 614.0 (M+H)⁺.

Methyl 2-(benzyloxy)-4-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido) benzoate (16ak): Methyl 2-(benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**16ad**) was reacted

with 4-chloro-3,5-dimethylphenol according to general procedure E on a scale of 1.26 mmol to yield the product as a yellow oil (527 mg, 69%): ^1H NMR (CDCl_3 , 400MHz) δ 7.74 (1 H d, $J = 7.6$ Hz, Ar), 7.68-7.56 (6 H, m, Ar), 6.94 (2 H, t, $J = 8.8$ Hz, Ar), 6.89 (1 H, s, Ar), 6.79 (2 H, s, Ar), 6.58 (2 H, s, Ar), 5.12 (2 H, s, CH_2), 3.91 (3 H, s, OCH_3), 3.28 (2 H, d, $J = 6.8$ Hz, CH_2iPr), 2.31 (6 H, s, 2 x ArCH_3), 1.57-1.46 (1 H, m, CH_2CH), 0.85 (6 H, d, $J = 8.0$ Hz, 2 x CH_3); ^{13}C NMR (CDCl_3 , 100MHz) δ 161.63, 158.3, 153.4, 152.5, 144.1, 138.3, 137.3, 136.2, 132.1, 131.4, 129.8, 128.6, 127.9, 126.9, 120.1, 19.7, 119.0, 117.1, 115.2, 115.0, 70.7, 57.4, 52.2, 26.8, 20.9, 20.8, 19.8.

Benzyl 2-(benzyloxy)-4-(N-cyclopentyl-naphthalene-2-sulfonamido)benzoate (16ba): Benzyl 2-(benzyloxy)-4-(cyclopentylamino)benzoate (**15b**) was coupled to 2-naphthalene-1-sulfonyl chloride according to general procedure D on a scale of 0.45 mmol to yield the product as a light brown solid (178 mg, 67%): ^1H NMR (DMSO-d_6 , 400MHz) δ 8.45 (1H, s, Ar), 8.24-8.17 (2H, m, Ar), 8.11 (1H, d, $J = 8.0$ Hz, Ar), 7.81 (1H, d, $J = 8.8$ Hz, Ar), 7.75 (1H, t, $J = 6.8$ Hz, Ar), 7.71-7.67 (2H, m, Ar), 7.39-7.33 (5H, m, Ar), 7.26-7.24 (3H, m, Ar), 7.14 (2H, s, Ar), 6.72 (1H, d, $J = 8.0$ Hz, Ar), 6.61 (1H, s, Ar), 5.29 (2H, s, O- CH_2), 4.93 (2H, s, O- CH_2), 4.51-4.47 (1H, m, CH), 1.68-1.08 (8H, m, Cp).

Benzyl 2-(benzyloxy)-4-(N-cyclopentyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (16bb): Benzyl 2-(benzyloxy)-4-(cyclopentylamino)benzoate (**15b**) was coupled to biphenyl-4-sulfonyl chloride according to general procedure D on a scale of 0.33 mmol to yield the product as a light brown solid (110 mg, 54%): ^1H NMR (DMSO-d_6 , 400MHz) δ 7.90 (2H, d, $J = 8.8$ Hz, Ar), 7.79 (2H, d, $J = 8.4$ Hz, Ar), 7.74 (2H, d, $J = 6.8$ Hz, Ar), 7.67 (1H, d, $J = 8.0$ Hz, Ar), 7.51-7.23 (13H, m, Ar), 6.69 (1H, d, $J = 8.8$ Hz, Ar), 6.64 (1H, s, Ar), 5.27 (2H, s, O- CH_2), 5.02 (2H, s, O- CH_2), 4.42-4.37 (1H, m, CH), 1.67-1.05 (8H, m, Cp).

Methyl 2-(benzyloxy)-4-(cyclopentylamino)benzoate (16bc'): Methyl 4-amino-2-(benzyloxy)benzoate (**14a**) was reductively aminated with cyclopentanone according to general procedure C on a scale of 0.8 mmol to give the product as a white solid (245 mg, 94%): ^1H NMR (DMSO-d_6 , 400MHz) δ 7.55-7.48 (3H, m, Ar), 7.36 (2H, t, $J = 6.8$ Hz, Ar), 7.27 (1H, t, $J = 6.8$ Hz, Ar), 6.43 (1H, d, $J = 6.4$ Hz, Ar), 6.20 (1H, s, Ar), 6.14 (1H, d, $J = 8.8$ Hz, Ar), 5.08 (2H, s, O- CH_2), 3.73-3.70 (1H, m, CH), 3.65 (3H, s, O- CH_3), 1.90-1.35 (8H, m, Cp); ^{13}C NMR (DMSO-d_6 , 100MHz) δ 165.8, 160.7, 154.0, 137.8, 133.7, 128.7, 127.8, 127.2, 105.7, 104.9, 96.9, 69.6, 53.7, 51.2, 32.8, 24.1; MS (APCI+) m/z Calcd (M^+): 325.2; Found: 326.1 ($\text{M}+\text{H}$) $^+$.

Methyl 2-(benzyloxy)-4-(N-cyclopentyl-4-fluorophenylsulfonamido)benzoate (16bc): Methyl 2-(benzyloxy)-4-(cyclopentylamino)benzoate (**16bc'**) was coupled to 4-fluorobenzenesulfonyl chloride according to general procedure D on a scale of 0.75 mmol to yield the product as a beige solid (200 mg, 55%): ^1H NMR (DMSO-d_6 , 400MHz) δ 7.84-7.80 (2H, m, Ar), 7.66 (1H, d, $J = 8.0$ Hz, Ar), 7.47 (2H, t, $J = 8.8$ Hz, Ar), 7.37 (4H, d, $J = 4.0$ Hz, Ar), 7.32-7.29 (1H, m, Ar), 6.69-6.65 (2H, m, Ar), 5.12 (2H, s, O- CH_2), 4.41-4.37 (1H, m, CH), 3.82 (3H, s, O- CH_3), 1.69-1.03 (8H, m, Cp); ^{13}C NMR (DMSO-d_6 , 100MHz)

δ 157.4, 140.8, 136.9, 131.4, 130.9, 130.8, 128.9, 128.1, 127.2, 124.1, 121.3, 117.9, 117.1, 116.9, 70.2, 60.9, 52.6, 30.4, 22.5; MS (APCI+) m/z Calcd (M^+): 483.1; Found: 484.0 ($M+H$)⁺.

Methyl 2-(benzyloxy)-4-(4-(4-chloro-3,5-dimethylphenoxy)-N-cyclopentylphenylsulfonamido)benzoate (16bd): Methyl 2-(benzyloxy)-4-(N-cyclopentyl-4-fluorophenylsulfonamido)benzoate (**16bc**) was coupled to 4-chloro-3,5-dimethylphenol according to general procedure E on a scale of 0.41 mmol to give the product as an ivory solid (200 mg, 78%): ¹H NMR (CDCl₃, 400MHz) δ 7.71 (1H, d, J = 8.8 Hz, Ar), 7.61 (2H, d, J = 8.8 Hz, Ar), 7.39-7.24 (5H, m, Ar), 6.95 (2H, d, J = 9.2 Hz, Ar), 6.78 (2H, s, Ar), 6.66 (1H, s, Ar), 6.60 (1H, d, J = 7.2 Hz, Ar), 5.07 (2H, s, O-CH₂), 4.46-4.41 (1H, m, CH), 3.88 (3H, s, O-CH₃), 2.34 (6H, s, 2*Ph-CH₃), 1.73-1.11 (8H, m, Cp); ¹³C NMR (CDCl₃, 100MHz) δ 166.1, 161.4, 157.9, 152.6, 141.0, 138.3, 136.2, 134.0, 131.7, 130.7, 129.8, 127.9, 126.7, 123.8, 120.9, 120.1, 118.3, 117.2, 70.6, 60.9, 52.2, 30.4, 22.4, 20.8; MS (APCI+) m/z Calcd (M^+): 619.1; Found: 620.1 ($M+H$)⁺.

2-Hydroxy-4-(N-isobutylphenylsulfonamido)benzoic acid (17aa): Methyl 2-(benzyloxy)-4-(N-isobutylphenylsulfonamido)benzoate (**16aa**) was hydrolyzed according to general procedure F on a scale of 0.34 mmol, and the product was dissolved in MeOH followed by the addition of 10% Pd/C (10 wt%). H₂ gas was next bubbled through the reaction, which was stirred at room temperature for 3 h under a balloon of H₂. TLC indicated the reaction was complete. The reaction mixture was filtered through Celite, and washed with MeOH. The filtrate was evaporated to give the product as a pink solid (43 mg, 36%): ¹H NMR (400 MHz, CDCl₃) δ 10.40 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.64-7.54 (m, 3H), 7.48 (t, J = 8.0 Hz, 2H), 6.80 (dd, J = 8.8, 1.6 Hz, 1H), 6.69 (s, 1H), 3.34 (d, J = 6.8 Hz, 2H), 1.69-1.58 (m, 1H), 0.91 (d, J = 6.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 162.4, 147.2, 137.7, 132.9, 131.3, 129.0, 127.5, 119.7, 116.3, 110.2, 57.1, 26.9, 19.8; MS (APCI+) m/z Calcd (M^+): 349.1, Found: 350.0 ($M+H$)⁺; t_R = 10.3 min (100%).

2-Hydroxy-4-(N-isobutyl-naphthalene-2-sulfonamido)benzoic acid (17ab): Methyl 2-(benzyloxy)-4-(N-isobutyl-naphthalene-2-sulfonamido)benzoate (**16ab**) was hydrolyzed according to general procedure F on a scale of 0.29 mmol, and the product was dissolved in MeOH followed by the addition of 10% Pd/C (10 wt%). H₂ gas was next bubbled through the reaction, which was stirred at room temperature for 3 h under a balloon of H₂. TLC indicated the reaction was complete. The reaction mixture was filtered through Celite, and washed with MeOH. The filtrate was evaporated to give the product as a pink solid (95mg, 82%): ¹H NMR (400 MHz, CDCl₃) δ 10.40 (s, 1H), 8.24 (s, 1H), 7.95-7.89 (m, 3H), 7.86 (d, J = 8.8 Hz, 1H), 7.70-7.58 (m, 2H), 6.81 (d, J = 8.8 Hz, 1H), 6.75 (s, 1H), 3.39 (d, J = 6.4 Hz, 2H), 1.69-1.58 (m, 1H), 0.92 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 162.4, 147.2, 134.9, 132.0, 131.4, 129.3, 129.2, 129.0, 128.9, 127.9, 127.6, 122.7, 119.6, 116.5, 110.2, 57.2, 26.9, 19.9; MS (APCI+) m/z Calcd (M^+): 399.1, Found: 400.0 ($M+H$)⁺; t_R = 12.5 min (96.1%).

2-Hydroxy-4-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoic acid (17ac): Methyl 2-(benzyloxy)-4-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (**16ac**) was hydrolyzed according to general procedure F on a scale of 0.12 mmol, and the product was dissolved in MeOH followed by the addition of 10% Pd/C (10 wt%). H₂ gas was next bubbled through the reaction, which was stirred at room temperature for 3 h under a balloon of H₂. TLC indicated the reaction was complete. The reaction mixture was filtered through Celite, and washed with MeOH. The filtrate was evaporated to give the product as a pink solid (23mg, 45%): ¹H NMR (400 MHz, CDCl₃) δ 10.44 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.70-7.60 (m, 6H), 7.50-7.41 (m, 3H), 6.84 (d, J = 8.8 Hz, 1H), 6.75 (s, 1H), 3.37 (d, J = 7.2 Hz, 2H), 1.70-1.62 (m, 1H), 0.93 (d, J = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 170.3, 161.6, 152.6, 140.0, 138.2, 134.9, 131.4, 130.1, 129.8, 129.5, 129.3, 129.2, 120.1, 117.2, 57.7, 26.9, 20.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 425.1, Found: 426.0 (M+H⁺); t_R = 13.9 min (100%).

2-(Benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoic acid (17ad'): Methyl 2-(benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**16ad**) was hydrolyzed according to general procedure F on a scale of 0.32 mmol to yield the product as a brown solid (124 mg, 85%): ¹H NMR (CDCl₃, 400MHz) δ 8.06 (1H, d, J = 8.8 Hz, Ar), 7.54-7.50 (2H, m, Ar), 7.43-7.41 (5H, m, Ar), 7.17-7.11 (3H, m, Ar), 6.57 (1H, d, J = 8.8 Hz, Ar), 5.29 (2H, s, O-CH₂), 3.30 (2H, d, J = 8.0 Hz, N-CH₂), 1.56-1.53 (1H, m, CH), 0.87 (6H, d, J = 7.2 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 164.8, 157.4, 145.2, 134.1, 133.9, 130.2, 130.1, 130.0, 129.2, 129.1, 128.0, 119.4, 117.2, 116.4, 116.2, 114.9, 72.4, 57.2, 26.9, 19.8; MS (APCI+) *m/z* Calcd (M⁺): 457.1; Found: 458.0 (M+H)⁺.

4-(4-Fluoro-N-isobutylphenylsulfonamido)-2-hydroxybenzoic acid (17ad): 2-(Benzyloxy)-4-(4-fluoro-N-isobutylphenylsulfonamido)benzoic acid (**17ad'**) was debenzylated according to general procedure G on a scale of 0.22 mmol to yield the product as a beige solid (69 mg, 86%): ¹H NMR (400 MHz, d₆-DMSO) δ 7.68 (s, 1H), 7.60-7.58 (m, 2H), 7.38 (t, J = 8.4 Hz, 2H), 6.61 (br s, 2H), 3.32 (d, J = 6.8 Hz, 2H), 1.45-1.42 (m, 1H), 0.80 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 166.2, 163.7, 144.7, 134.2, 130.7, 130.6, 118.5, 117.0 (2), 116.8, 116.4, 56.9, 26.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 367.1; Found: 368.0 (M+H)⁺; t_R = 10.9 min (100%).

2-(Benzyloxy)-4-(4-bromo-N-isobutylphenylsulfonamido)benzoic acid (17ae'): Methyl 2-(benzyloxy)-4-(4-bromo-N-isobutylphenylsulfonamido)benzoate (**16ae**) was hydrolyzed according to general procedure F on a scale of 0.27 mmol to give the product as a light brown solid (128 mg, 92%): ¹H NMR (CDCl₃, 400MHz) δ 8.05 (1H, d, J = 8.4 Hz, Ar), 7.57 (2H, d, J = 8.8 Hz, Ar), 7.42-7.40 (4H, br s, Ar), 7.34 (2H, d, J = 8.0 Hz, Ar), 7.24 (1H, s, Ar), 7.14 (1H, s, Ar), 6.56 (1H, d, J = 8.8 Hz, Ar), 5.27 (2H, s, O-CH₂), 3.27 (2H, d, J = 8.0 Hz, N-CH₂), 1.56-1.49 (1H, m, CH), 0.85 (6H, d, J = 6.4 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 164.5, 157.3, 145.1, 136.4, 134.2, 133.8, 132.3, 129.3, 129.1, 128.8, 128.1, 119.4, 117.3, 114.9, 72.5, 57.2, 26.9, 19.8.

4-(4-Bromo-N-isobutylphenylsulfonamido)-2-hydroxybenzoic acid (17ae): 2-(Benzyloxy)-4-(4-bromo-N-isobutylphenylsulfonamido)benzoic acid (**17ae'**) was debenzylated according to general procedure G on a scale of 0.22 mmol to yield the product as a beige solid (84 mg, 90%): ¹H NMR (400 MHz, d₆-DMSO) δ 7.76 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.44 (d, J = 8.0 Hz, 2H), 6.59 (br s, 2H), 3.31 (d, J = 6.8 Hz, 2H), 1.45-1.42 (m, 1H), 0.80 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 144.2, 137.1, 132.8 (2), 129.6 (2), 127.6, 118.2 (2), 116.4 (2), 56.9, 26.8, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 429.0; Found: 429.9 (M+H)⁺; t_R = 12.1 min (100%).

2-Hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)benzoic acid (17af): Methyl 2-(benzyloxy)-4-(N-isobutyl-4-methylphenylsulfonamido)benzoate (**16af**) was hydrolyzed according to general procedure F on a scale of 0.32 mmol, and the product was dissolved in MeOH followed by 10% Pd/C (10 wt%) and H₂ gas was bubbled through the reaction and stirred at room temperature for 3 hrs. TLC indicated the reaction was complete. The reaction mixture was filtered through celite, and washed with MeOH. The filtrate was collected and combined, evaporated to give the product as a pink solid (86mg, 74%): ¹H NMR (400 MHz, CDCl₃) δ 10.41 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.82 (dd, J = 8.8, 1.6 Hz, 1H), 6.70 (d, J = 1.6 Hz, 1H), 3.32 (d, J = 7.2 Hz, 2H), 1.66-1.59 (m, 1H), 0.91 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 162.4, 147.3, 143.8, 134.8, 131.3, 129.6, 127.5, 119.8, 116.2, 110.1, 57.0, 26.8, 21.6, 19.9. MS (APCI+) *m/z* Calcd (M⁺): 363.1, Found: 364.1 (M+H)⁺; t_R = 11.4 min (100%).

2-(Benzyloxy)-4-(N-isobutyl-4-phenoxyphenylsulfonamido)benzoic acid (17ag'): Methyl 2-(benzyloxy)-4-(N-isobutyl-4-phenoxyphenylsulfonamido)benzoate (**16ag**) was hydrolyzed according to general procedure F on a scale of 0.18 mmol to afford the product as a an ivory solid (82 mg, 86%): ¹H NMR (CDCl₃, 400MHz) δ 8.05 (1H, d, J = 8.4 Hz, Ar), 7.45-7.37 (8H, m, Ar), 7.23-7.18 (3H, m, Ar), 7.04 (2H, d, J = 7.6 Hz, Ar), 6.94 (2H, d, J = 8.4 Hz, Ar), 6.60 (1H, d, J = 8.0 Hz, Ar), 5.27 (2H, d, O-CH₂), 3.30 (2H, d, J = 7.2 Hz, N-CH₂), 1.57-1.51 (1H, m, CH), 0.86 (6H, d, J = 7.2 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 164.5, 161.9, 157.3, 145.6, 134.0, 130.9, 130.2, 129.6, 129.3, 129.2, 128.1, 125.1, 120.4, 119.5, 117.2, 116.9, 115.0, 72.5, 57.1, 26.9, 19.8, 14.2; MS (APCI+) *m/z* Calcd (M⁺): 531.1; Found: 532.1 (M+H)⁺.

2-Hydroxy-4-(N-isobutyl-4-phenoxyphenylsulfonamido)benzoic acid (17ag): 2-(Benzyloxy)-4-(N-isobutyl-4-phenoxyphenylsulfonamido)benzoic acid (**17ag'**) was debenzylated according to general procedure G on a scale of 0.15 mmol to afford the product as a beige solid (52 mg, 80%): ¹H NMR (400 MHz, d₆-DMSO) δ 8.15 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.91 (t, J = 7.4 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.08 (s, 2H), 3.78 (d, J = 6.8 Hz, 2H), 1.93-1.90 (m, 1H), 1.27 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 172.2, 162.4, 161.8, 155.6, 145.3, 132.3, 131.3,

130.6, 125.8, 120.9, 118.8, 118.4, 116.8, 114.6, 57.3, 27.3, 23.7, 20.5; MS (APCI+) m/z Calcd (M^+): 441.1; Found: 442.0 ($M+H$)⁺; t_R = 13.8 min (100%).

2-(Benzyloxy)-4-(N-isobutyl-4-(*p*-tolylloxy)phenylsulfonamido)benzoic acid (17ah'): Methyl 2-(benzyloxy)-4-(N-isobutyl-4-(*p*-tolylloxy)phenylsulfonamido)benzoate (**16ah**) was hydrolyzed according to general procedure F on a scale of 0.18 mmol to afford the product as an ivory solid (97 mg, 99%); ¹H NMR (CDCl₃, 400MHz) δ 8.04 (1H, d, J = 8.4 Hz, Ar), 7.41-7.38 (7H, m, Ar), 7.19-7.17 (3H, m, Ar), 6.93-6.91 (4H, m, Ar), 6.60 (1H, d, J = 8.8 Hz, Ar), 5.26 (2H, s, O-CH₂), 3.29 (2H, d, J = 7.2 Hz, N-CH₂), 2.34 (3H, s, O-CH₃), 1.57-1.50 (1H, m, CH), 0.85 (6H, d, J = 6.4 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 164.8, 162.4, 157.3, 152.4, 145.6, 134.9, 133.9, 130.7, 130.6, 129.6, 129.2, 129.1, 128.1, 120.3, 119.6, 117.0, 116.9, 114.9, 72.4, 57.1, 26.9, 20.8, 19.8; MS (APCI+) m/z Calcd (M^+): 545.2; Found: 546.1 ($M+H$)⁺.

2-Hydroxy-4-(N-isobutyl-4-(*p*-tolylloxy)phenylsulfonamido)benzoic acid (17ah): 2-(Benzyloxy)-4-(N-isobutyl-4-(*p*-tolylloxy)phenylsulfonamido)benzoic acid (**17ah'**) was debenzylated according to general procedure G on a scale of 0.18 mmol to afford the product as a beige solid (65 mg, 80%); ¹H NMR (400 MHz, d₆-DMSO) δ 7.69 (d, J = 6.8 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 7.05-6.90 (m, 4H), 6.63 (s, 2H), 3.30 (d, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.45-1.42 (m, 1H), 0.80 (d, J = 6.0 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 171.7, 161.8, 152.7, 145.2, 134.8, 131.5, 131.2, 131.1, 130.2, 120.9, 120.6, 118.6, 117.6, 116.4, 113.6, 56.8, 26.9, 20.8, 20.0; MS (APCI+) m/z Calcd (M^+): 455.1; Found: 456.0 ($M+H$)⁺; t_R = 15.1 min (96.7%).

2-(Benzyloxy)-4-(4-(3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoic acid (17ai'): Methyl 2-(benzyloxy)-4-(4-(3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoate (**16ai**) was hydrolyzed according to general procedure F on a scale of 0.17 mmol to afford the product as a light yellow solid (97 mg, 99%); ¹H NMR (CDCl₃, 400MHz) δ 8.05 (1H, d, J = 8.4 Hz, Ar), 7.43-7.39 (7H, m, Ar), 7.18 (1H, s, Ar), 6.93 (2H, d, J = 8.8 Hz, Ar), 6.84 (1H, s, Ar), 6.65-6.59 (3H, m, Ar), 5.27 (2H, s, O-CH₂), 3.29 (2H, d, J = 8.0 Hz, Ar), 2.29 (6H, s, 2*Ph-CH₃), 1.57-1.50 (1H, m, CH), 0.86 (6H, d, J = 6.4 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 164.6, 162.2, 157.3, 145.6, 140.2, 133.9, 129.6, 129.3, 129.1, 128.1, 126.8, 119.6, 117.9, 117.1, 115.0, 72.5, 60.4, 57.1, 26.9, 21.2, 21.0, 19.8, 14.2; MS (APCI+) m/z Calcd (M^+): 559.2; Found: 560.1 ($M+H$)⁺.

4-(4-(3,5-Dimethylphenoxy)-N-isobutylphenylsulfonamido)-2-hydroxybenzoic acid (17ai): 2-(benzyloxy)-4-(4-(3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoic acid (**17ai'**) was debenzylated according to general procedure G on a scale of 0.17 mmol to afford the product as a beige solid (66 mg, 83%); ¹H NMR (400 MHz, d₆-DMSO) δ 7.66 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 6.70 (s, 2H), 6.60-6.56 (m, 2H), 3.30 (d, J = 7.2 Hz, 2H), 2.24 (s, 6H), 1.46-1.41 (m, 1H), 0.80 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 161.5, 155.1, 144.7, 140.3 (2), 131.7,

130.9, 130.1 (2), 126.9 (2), 118.2, 118.0, 117.9, 116.3, 56.9, 26.9, 21.2, 20.0; MS (APCI+) m/z Calcd (M^+): 469.2; Found: 470.0 ($M+H$)⁺; t_R = 17.1 min (100%).

2-(Benzyloxy)-4-(4-(2,4-dichlorophenoxy)-N-isobutylphenylsulfonamido)benzoic acid (17aj'): Methyl 2-(benzyloxy)-4-(4-(2,4-dichlorophenoxy)-N-isobutylphenylsulfonamido)benzoate (16aj) was hydrolyzed according to general procedure F on a scale of 0.12 mmol to afford the product as an ivory solid (71 mg, 99%): ¹H NMR (CDCl₃, 400MHz) δ 8.30 (1H, d, J = 8.0 Hz, Ar), 7.74-7.62 (8H, m, Ar), 7.54-7.44 (2H, m, Ar), 7.30 (1H, d, J = 8.4 Hz, Ar), 7.16 (2H, d, J = 8.8 Hz, Ar), 6.86 (1H, d, J = 8.0 Hz, Ar), 6.52 (2H, s, O-CH₂), 3.56 (2H, d, J = 7.2 Hz, N-CH₂), 1.83-1.76 (1H, m, CH), 1.12 (6H, d, J = 6.4 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 165.1, 160.9, 157.6, 149.3, 145.7, 134.2, 131.9, 131.6, 131.2, 130.4, 130.1, 129.4, 128.9, 128.3, 128.1, 123.7, 119.9, 117.9, 117.4, 116.7, 115.1, 92.4, 72.6, 57.4, 29.9, 27.2, 20.1; MS (APCI+) m/z Calcd (M^+): 599.1; Found: 600.0 ($M+H$)⁺.

4-(4-(2,4-Dichlorophenoxy)-N-isobutylphenylsulfonamido)-2-hydroxybenzoic acid (17aj): 2-(benzyloxy)-4-(4-(2,4-dichlorophenoxy)-N-isobutylphenylsulfonamido)benzoic acid (17aj') was debenzylated according to general procedure G on a scale of 0.12 mmol to afford the product as a beige solid (39 mg, 64%): ¹H NMR (400 MHz, d₆-DMSO) δ 7.81 (s, 1H), 7.67 (s, 1H), 7.54-7.47 (m, 3H), 7.31 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 6.56 (s, 2H), 3.30 (d, J = 7.2 Hz, 2H), 1.48-1.41 (m, 1H), 0.80 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 160.4, 149.5, 144.5, 132.5, 130.9 (2), 130.6, 130.3 (2), 129.7 (2), 127.1, 124.5, 118.1, 117.4 (2), 116.3, 57.0, 26.9, 20.0; MS (APCI+) m/z Calcd (M^+): 509.1; Found: 509.9 ($M+H$)⁺; t_R = 17.0 min (100%).

4-(4-(4-Chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)-2-hydroxybenzoic acid (6e-OH): Methyl 2-(benzyloxy)-4-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoate (16ak) was hydrolyzed according to general procedure F on a scale of 0.15 mmol, and the product was dissolved in MeOH followed by 10% Pd/C (10 wt%) and H₂ gas was bubbled through the reaction and stirred at room temperature for 3 hrs. TLC indicated the reaction was complete. The reaction mixture was filtered through celite, and washed with MeOH. The filtrate was collected and combined, evaporated to give the product as a pink solid (75 mg, 99%): ¹H NMR (400 MHz, CDCl₃) δ 10.60 (s, 1H), 7.61 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.02-6.91 (m, 3H), 6.80 (s, 2H), 3.28 (d, J = 7.2 Hz, 2H), 2.37 (s, 6H), 1.65-1.53 (m, 1H), 0.92 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 172.9, 161.5, 161.5, 152.7, 138.3, 137.0, 131.5, 130.9, 130.8, 130.7, 129.9, 120.0, 118.5, 117.3, 111.7, 58.0, 26.8, 20.9, 19.9; MS (APCI+) m/z Calcd (M^+): 503.1, Found: 504.0 ($M+H$)⁺; t_R = 19.9 min (100%).

2-(Benzyloxy)-4-(N-cyclopentyl-naphthalene-2-sulfonamido)benzoic acid (17ba'): Benzyl 2-(benzyloxy)-4-(N-cyclopentyl-naphthalene-2-sulfonamido)benzoate (16ba) was hydrolyzed according to general procedure F on a scale of 0.3 mmol to yield the product as a light brown solid (103 mg, 83%): ¹H NMR (DMSO-d₆, 400MHz) δ 8.45 (1H, s, Ar), 8.24-8.18 (2H, m, Ar), 8.12 (1H, d, J = 8.4 Hz, Ar), 7.82-

7.68 (3H, m, Ar), 7.57 (1H, d, $J = 7.6$ Hz, Ar), 7.31- 7.14 (4H, m, Ar), 6.66 (1H, d, $J = 8.0$ Hz, Ar), 6.49 (1H, s, Ar), 4.91 (2H, s, O-CH₂), 4.53-4.45 (1H, m, CH), 1.65-1.04 (8H, m, Cp); MS (APCI+) m/z Calcd (M⁺): 501.1; Found: 502.1 (M+H)⁺.

4-(N-Cyclopentyl-naphthalene-2-sulfonamido)-2-hydroxybenzoic acid (17ba): 2-(Benzyloxy)-4-(N-cyclopentyl-naphthalene-2-sulfonamido)benzoic acid (**17ba'**) was debenzylated according to general procedure G on a scale of 0.25 mmol to yield the product as a beige solid (75 mg, 73%): ¹H NMR (400 MHz, d₆-DMSO) δ 8.42 (s, 1H), 8.18 (t, $J = 9.8$ Hz, 2H), 8.09 (d, $J = 7.6$ Hz, 1H), 7.79-7.66 (m, 4H), 6.53 (s, 2H), 4.54-4.49 (m, 1H), 1.80 (s, 2H), 1.41-1.27 (m, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 141.8, 137.5, 134.8, 132.2, 130.9, 129.9, 129.8 (2), 129.4, 128.8, 128.3, 128.1, 123.1, 122.2, 120.4, 61.0, 30.6, 22.6; MS (APCI+) m/z Calcd (M⁺): 411.1; Found: 412.0 (M+H)⁺; $t_R = 12.6$ min (100%).

2-(Benzyloxy)-4-(N-cyclopentyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoic acid (17bb'): Benzyl 2-(benzyloxy)-4-(N-cyclopentyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (**16bb**) was hydrolyzed according to general procedure F on a scale of 0.18 mmol to yield the product as a light brown solid (32 mg, 39%): ¹H NMR (DMSO-d₆, 400MHz) δ 7.95 (2H, d, $J = 7.6$ Hz, Ar), 7.83-7.78 (4H, m, Ar), 7.61 (1H, d, $J = 7.6$ Hz, Ar), 7.53 (2H, t, $J = 7.2$ Hz, Ar), 7.46 (1H, t, $J = 7.2$ Hz, Ar), 7.30-7.26 (5H, m, Ar), 6.69 (1H, d, $J = 7.6$ Hz, Ar), 6.57 (1H, s, Ar), 5.05 (2H, s, O-CH₂), 4.45-4.41 (1H, m, CH), 1.68-1.08 (8H, m, Cp); MS (APCI+) m/z Calcd (M⁺): 527.1; Found: 528.1 (M+H)⁺.

4-(N-Cyclopentyl-[1,1'-biphenyl]-4-ylsulfonamido)-2-hydroxybenzoic acid (17bb): 2-(benzyloxy)-4-(N-cyclopentyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoic acid (**17bb'**) was debenzylated according to general procedure G on a scale of 0.07 mmol to yield the product as an ivory solid (18 mg, 60%): ¹H NMR (400 MHz, d₆-DMSO) δ 7.89 (d, $J = 7.2$ Hz, 2H), 7.79-7.74 (m, 5H), 7.51- 7.42 (m, 3H), 6.48 (s, 2H), 4.44-4.41 (m, 1H), 1.77 (s, 2H), 1.38-1.20 (m, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 144.2, 141.1, 138.8, 138.2, 129.2 (2), 128.6, 127.9 (2), 127.4 (2), 127.1 (2), 121.4, 119.8, 60.5, 30.1, 22.1; MS (APCI+) m/z Calcd (M⁺): 437.1; Found: 438.0 (M+H)⁺; $t_R = 14.2$ min (100%).

2-(Benzyloxy)-4-(4-(4-chloro-3,5-dimethylphenoxy)-N-cyclopentylphenylsulfonamido)benzoic acid (17bd'): Methyl 2-(benzyloxy)-4-(4-(4-chloro-3,5-dimethylphenoxy)-N-cyclopentylphenylsulfonamido)benzoate (**16bd**) was hydrolyzed according to general procedure F on a scale of 0.32 mmol to give the product as a light brown solid (191 mg, 99%): ¹H NMR (CDCl₃, 400MHz) δ 8.09 (1H, d, $J = 8.0$ Hz, Ar), 7.63 (2H, d, $J = 8.8$ Hz, Ar), 7.42-7.38 (5H, m, Ar), 6.99-6.97 (3H, m, Ar), 6.81 (2H, s, Ar), 6.66 (1H, d, $J = 8.4$ Hz, Ar), 5.26 (2H, s, O-CH₂), 4.47-4.43 (1H, m, CH), 3.37 (6H, s, 2*Ph-CH₃), 1.86-1.19 (8H, m, Cp); ¹³C NMR (CDCl₃, 100MHz) δ 164.6, 161.7, 157.1, 152.5, 142.8, 138.3, 133.9, 133.8, 133.5, 131.6, 129.8, 129.8, 129.2, 129.1, 127.9, 124.8, 120.2, 118.2, 118.0, 117.2, 72.4, 61.2, 30.6, 22.4, 20.9; MS (APCI+) m/z Calcd (M⁺): 605.1; Found: 606.0 (M+H)⁺.

4-(4-(4-Chloro-3,5-dimethylphenoxy)-N-cyclopentylphenylsulfonamido)-2-hydroxybenzoic acid (17bd): 2-(Benzyloxy)-4-(4-(4-chloro-3,5-dimethylphenoxy)-N-cyclopentylphenylsulfonamido)benzoic acid (**17bd'**) was debenzylated according to general procedure G on a scale of 0.3 mmol to give the product as a beige solid (137 mg, 89%): ¹H NMR (400 MHz, d₆-DMSO) δ 7.73-7.67 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.06 (s, 2H), 6.40-6.34 (m, 2H), 4.42-4.38 (m, 1H), 2.35 (s, 6H), 1.76 (s, 2H), 1.40-1.24 (m, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 161.0, 153.1, 140.5, 138.3 (2), 134.6, 130.2 (2), 130.0, 120.9, 120.7 (2), 119.8, 117.9 (2), 60.8, 30.5, 22.6, 20.7; MS (APCI+) *m/z* Calcd (M⁺): 515.1; Found: 516.0 (M+H)⁺; t_R = 20.8 min (97.9%).

Benzyl 4-(benzylamino)-2-(benzyloxy)benzoate (15c): Benzyl 4-amino-2-(benzyloxy)benzoate (**14b**) was reductively aminated with benzaldehyde according to general procedure C on a scale of 1.5 mmol to afford the product as a light brown solid (425 mg, 67%): ¹H NMR (DMSO-d₆, 400MHz) δ 7.60 (1H, d, *J* = 8.8 Hz, Ar), 7.43 (2H, d, *J* = 6.8 Hz, Ar), 7.37-7.24 (12H, m, Ar), 7.09 (1H, t, *J* = 5.6 Hz, Ar), 6.35 (1H, s, Ar), 6.24 (1H, d, *J* = 8.0 Hz, Ar), 5.19 (2H, s, O-CH₂), 5.05 (2H, s, O-CH₂), 4.34 (2H, d, *J* = 6.4 Hz, N-CH₂); ¹³C NMR (DMSO-d₆, 100MHz) δ 165.3, 160.7, 154.4, 139.8, 137.4, 133.9, 128.8, 128.7, 128.6, 128.1, 127.9, 127.7, 127.5, 127.3, 106.3, 105.0, 96.9, 69.6, 65.2, 46.3; MS (APCI+) *m/z* Calcd (M⁺): 423.1; Found: 424.1 (M+H)⁺.

Benzyl 4-(N-benzyl-naphthalene-2-sulfonamido)-2-(benzyloxy)benzoate (16ca): Benzyl 4-(benzylamino)-2-(benzyloxy)benzoate (**15c**) was coupled to 2-naphthyl sulfonyl chloride according to general procedure D on a scale of 0.35 mmol to yield the product as a light yellow solid (96 mg, 45%): ¹H NMR (CDCl₃, 400MHz) δ 7.99 (1H, s, Ar), 7.67 (3H, d, *J* = 7.6 Hz, Ar), 7.44-7.32 (4H, m, Ar), 7.08-6.98 (10H, m, Ar), 6.94-6.92 (3H, m, Ar), 6.88-6.86 (2H, m, Ar), 6.47 (1H, s, Ar), 6.30 (1H, d, *J* = 8.4 Hz, Ar), 5.02 (2H, s, O-CH₂), 4.60 (2H, s, O-CH₂), 4.48 (2H, s, N-CH₂); ¹³C NMR (CDCl₃, 100MHz) δ 165.3, 158.1, 143.3, 135.8, 135.6, 135.0, 134.7, 131.9, 131.8, 128.1, 128.9, 128.8, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 126.8, 122.6, 119.4, 114.5, 70.4, 66.6, 54.2; MS (APCI+) *m/z* Calcd (M⁺): 613.2; Found: 614.1 (M+H)⁺.

Benzyl 4-(N-benzyl-[1,1'-biphenyl]-4-ylsulfonamido)-2-(benzyloxy)benzoate (16cb): Benzyl 4-(benzylamino)-2-(benzyloxy)benzoate (**15c**) was coupled to biphenyl-4-sulfonyl chloride according to general procedure D on a scale of 0.35 mmol to yield the product as a white solid (155 mg, 68%): ¹H NMR (CDCl₃, 400MHz) δ 7.68-7.65 (5H, m, Ar), 7.60 (2H, d, *J* = 7.2 Hz, Ar), 7.47 (2H, t, *J* = 7.2 Hz, Ar), 7.43-7.41 (1H, m, Ar), 7.33-7.28 (9H, m, Ar), 7.24 (1H, s, Ar), 7.18-7.11 (5H, m, Ar), 6.76 (1H, s, Ar), 6.58 (1H, d, *J* = 6.8 Hz, Ar), 5.27 (2H, s, O-CH₂), 4.94 (2H, s, O-CH₂), 4.71 (2H, s, N-CH₂); ¹³C NMR (CDCl₃, 100MHz) δ 165.5, 158.3, 145.8, 143.5, 139.0, 136.6, 136.1, 135.8, 135.2, 132.2, 129.1, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.5, 127.3, 127.1, 123.1, 119.6, 119.4, 114.8, 70.7, 66.8, 51.3; MS (APCI+) *m/z* Calcd (M⁺): 639.2; Found: 640.1 (M+H)⁺.

Benzyl 4-(N-benzyl-4-fluorophenylsulfonamido)-2-(benzyloxy)benzoate (16cc): Benzyl 4-(benzylamino)-2-(benzyloxy)benzoate (**15c**) was coupled to 4-fluorobenzene sulfonyl chloride according to general procedure D on a scale of 0.3 mmol to yield the product as a light beige solid (169 mg, 97%): ¹H NMR (CDCl₃, 400MHz) δ 8.00-7.92 (3H, m, Ar), 7.62-7.63 (10H, m, Ar), 7.51-7.44 (7H, m, Ar), 7.09 (1H, s, Ar), 6.85 (1H, d, *J* = 7.6 Hz, Ar), 5.61 (2H, s, O-CH₂), 5.30 (2H, s, O-CH₂), 5.01 (2H, s, N-CH₂); ¹³C NMR (CDCl₃, 100MHz) δ 166.8, 165.7, 164.2, 158.6, 143.6, 136.3, 136.1, 135.3, 134.5, 132.5, 130.6, 130.5, 128.8, 128.7, 128.6, 128.5, 128.2, 127.4, 120.1, 119.5, 116.7, 116.5, 115.1, 70.9, 67.2, 54.5; MS (APCI+) *m/z* Calcd (M⁺): 581.1; Found: 582.0 (M+H)⁺.

Benzyl 4-(N-benzyl-4-(4-chloro-3,5-dimethylphenoxy)phenylsulfonamido)-2-(benzyloxy)benzoate (16cd): Benzyl 4-(N-benzyl-4-fluorophenylsulfonamido)-2-(benzyloxy)benzoate (**16cc**) was coupled to 4-chloro-3,5-dimethylphenol according to general procedure E on a scale of 0.29 mmol to give the product as a beige solid (100 mg, 48%): ¹H NMR (CDCl₃, 400MHz) δ 8.00 (1H, d, *J* = 8.0 Hz, Ar), 7.90 (2H, d, *J* = 8.4 Hz, Ar), 7.67-7.63 (10H, m, Ar), 7.51-7.47 (5H, m, Ar), 7.30 (2H, d, *J* = 8.8 Hz, Ar), 7.13 (3H, s, Ar), 6.91 (1H, d, *J* = 8.4 Hz, Ar), 5.61 (2H, s, O-CH₂), 5.30 (2H, s, O-CH₂), 5.03 (2H, s, N-CH₂), 2.69 (6H, s, 2*Ph-CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 165.8, 162.1, 158.6, 152.8, 143.9, 138.7, 136.4, 136.1, 135.6, 132.5, 132.0, 131.2, 130.1, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 127.4, 120.5, 119.8, 119.5, 117.6, 115.1, 71.0, 67.2, 54.5, 21.2; MS (APCI+) *m/z* Calcd (M⁺): 717.2; Found: 718.1 (M+H)⁺.

4-(N-Benzyl-naphthalene-2-sulfonamido)-2-(benzyloxy)benzoic acid (17ca^o): Benzyl 4-(N-benzyl-naphthalene-2-sulfonamido)-2-(benzyloxy)benzoate was hydrolyzed according to general procedure F on a scale of 0.16 mmol to yield the product as an ivory solid (82 mg, 99%): ¹H NMR (CDCl₃, 400MHz) δ 8.23 (1H, s, Ar), 7.94-7.90 (4H, m, Ar), 7.69-7.60 (2H, m, Ar), 7.55 (1H, d, *J* = 8.0 Hz, Ar), 7.37-7.34 (4H, m, Ar), 7.30-7.29 (2H, m, Ar), 7.19-7.14 (4H, m, Ar), 6.99 (1H, s, Ar), 6.61 (1H, d, *J* = 8.4 Hz, Ar), 5.06 (2H, s, O-CH₂), 4.76 (2H, s, N-CH₂); ¹³C NMR (CDCl₃, 100MHz) δ 164.4, 157.2, 144.9, 134.9, 134.8, 133.9, 132.0, 129.4, 129.3, 129.2, 129.1, 129.0, 128.6, 128.4, 127.9, 127.8, 126.9, 122.5, 120.2, 119.1, 114.8, 72.5, 54.2; MS (APCI+) *m/z* Calcd (M⁺): 523.1; Found: 524.0 (M+H)⁺.

4-(N-Benzyl-naphthalene-2-sulfonamido)-2-hydroxybenzoic acid (17ca): 4-(N-Benzyl-naphthalene-2-sulfonamido)-2-(benzyloxy)benzoic acid (**17ca^o**) was debenzylated according to general procedure G on a scale of 0.15 mmol to give the product as an ivory solid (56 mg, 87%): ¹H NMR (400 MHz, d₆-DMSO) δ 8.47 (s, 1H), 8.21-8.15 (m, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.77-7.61 (m, 4H), 7.32-7.25 (m, 4H), 7.21 (d, *J* = 5.2 Hz, 1H), 6.72 (s, 2H), 4.93 (s, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 171.6, 161.6, 144.8, 136.5, 135.3, 134.9, 132.2, 130.9, 129.9, 129.6, 129.1, 128.8, 128.3, 128.2, 127.9, 122.9, 118.4, 116.1, 113.2, 53.3.; MS (APCI+) *m/z* Calcd (M⁺): 433.1; Found: 434.0 (M+H)⁺; t_R = 11.7 min (95.2%).

4-(N-Benzyl-[1,1'-biphenyl]-4-ylsulfonamido)-2-(benzyloxy)benzoic acid (17cb^o): Benzyl 4-(N-benzyl-[1,1'-biphenyl]-4-ylsulfonamido)-2-(benzyloxy)benzoate (**16cb**) was hydrolyzed according to general

procedure F on a scale of 0.24 mmol to yield the product as an ivory solid (120 mg, 92%): ¹H NMR (CDCl₃, 400MHz) δ 7.98 (1H, d, *J* = 8.8 Hz, Ar), 7.73-7.65 (4H, m, Ar), 7.60 (2H, d, *J* = 8.0 Hz, Ar), 7.50-7.33 (8H, m, Ar), 7.27-7.16 (5H, m, Ar), 7.05 (1H, s, Ar), 6.67 (1H, d, *J* = 8.4 Hz, Ar), 5.13 (2H, s, O-CH₂), 4.76 (2H, s, N-CH₂); ¹³C NMR (CDCl₃, 100MHz) δ 164.4, 157.2, 146.2, 144.9, 138.9, 136.3, 134.9, 133.9, 133.8, 129.3, 129.1, 128.7, 128.6, 128.4, 128.1, 127.9, 127.7, 127.3, 119.9, 117.0, 114.9, 72.5, 53.9; MS (APCI+) *m/z* Calcd (M⁺): 549.1; Found: 550.1 (M+H)⁺.

4-(N-Benzyl-[1,1'-biphenyl]-4-ylsulfonamido)-2-hydroxybenzoic acid (17cb): 4-(N-benzyl-[1,1'-biphenyl]-4-ylsulfonamido)-2-(benzyloxy)benzoic acid (**17cb'**) was debenzylated according to general procedure G on a scale of 0.22 mmol to give the product as an ivory solid (69 mg, 69%): ¹H NMR (400 MHz, d₆-DMSO) δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.75-7.72 (m, 4H), 7.59 (d, *J* = 6.4 Hz, 1H), 7.51-7.42 (m, 3H), 7.27-7.16 (m, 5H), 6.66 (s, 2H), 4.85 (s, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 145.1, 144.4, 138.6, 136.9, 136.5, 130.8, 129.6, 129.2, 128.8, 128.4 (2), 128.3 (2), 127.9 (2), 127.5 (2), 118.1, 116.0, 53.2; MS (APCI+) *m/z* Calcd (M⁺): 459.1; Found: 460.0 (M+H)⁺; t_R = 13.3 min (95.2%).

4-(N-Benzyl-4-(4-chloro-3,5-dimethylphenoxy)phenylsulfonamido)-2-(benzyloxy)benzoic acid (17cd'): Benzyl 4-(N-benzyl-4-(4-chloro-3,5-dimethylphenoxy)phenylsulfonamido)-2-(benzyloxy)benzoate (**16cd**) was hydrolyzed according to general procedure F on a scale of 0.24 mmol to afford the product as a beige solid (100mg, 67%): ¹H NMR (CDCl₃, 400MHz) δ 7.6 (1H, d, *J* = 8.4 Hz, Ar), 7.54 (2H, d, *J* = 8.4 Hz, Ar), 7.39-7.32 (6H, m, Ar), 7.29-7.16 (5H, m, Ar), 7.04 (1H, s, Ar), 6.97 (2H, d, *J* = 9.6 Hz, Ar), 6.80 (1H, s, Ar), 6.64 (1H, d, *J* = 8.8 Hz, Ar), 5.13 (2H, s, O-CH₂), 4.73 (2H, s, N-CH₂), 2.36 (6H, s, 2*Ph-CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 164.7, 162.1, 157.3, 152.3, 144.9, 138.4, 135.0, 133.8, 131.3, 129.8, 129.2, 129.1, 128.6, 128.3, 128.0, 127.9, 127.6, 126.9, 120.2, 119.7, 117.2, 116.9, 114.9, 72.4, 65.3, 53.9, 20.9; MS (APCI+) *m/z* Calcd (M⁺): 627.1; Found: 628.0 (M+H)⁺.

4-(N-Benzyl-4-(4-chloro-3,5-dimethylphenoxy)phenylsulfonamido)-2-hydroxybenzoic acid (17cd): 4-(N-Benzyl-4-(4-chloro-3,5-dimethylphenoxy)phenylsulfonamido)-2-(benzyloxy)benzoic acid (**17cd'**) was debenzylated according to general procedure G on a scale of 0.16 mmol to yield the product as a beige solid (68 mg, 79%): ¹H NMR (400 MHz, d₆-DMSO) δ 7.65-7.57 (m, 3H), 7.27-7.09 (m, 7H), 7.00 (s, 2H), 6.64-6.62 (m, 2H), 4.79 (s, 2H), 2.31 (s, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 161.8, 161.5, 153.0, 144.6, 138.4, 136.5, 132.0, 130.9, 130.3, 130.2, 128.8, 128.3, 127.9, 120.7 (2), 118.3, 118.1, 116.0, 53.2, 20.8; MS (APCI+) *m/z* Calcd (M⁺): 537.1; Found: 538.0 (M+H)⁺; t_R = 19.1 min (100%).

2-(Benzyloxy)-4-(4-phenoxyphenylsulfonamido)benzoic acid (17da'): Methyl 4-amino-2-(benzyloxy)benzoate (**14a**) was coupled to 4-phenoxybenzene-1-sulfonyl chloride according to general procedure D on a scale of 0.58 mmol to yield crude product, which was immediately hydrolyzed according to general procedure F to give the product as a beige solid (54 mg, 20%): ¹H NMR (CDCl₃, 400MHz) δ 7.79 (1H, d, *J* = 8.8 Hz, Ar), 7.53 (2H, d, *J* = 8.4 Hz, Ar), 7.35-7.28 (6H, m, Ar), 7.24 (1H, d, *J* = 8.0 Hz,

Ar), 7.13 (1H, t, $J = 7.2$ Hz, Ar), 6.98-6.92 (3H, m, Ar), 6.80 (2H, d, $J = 8.4$ Hz, Ar), 6.57 (1H, d, $J = 8.4$ Hz, Ar), 5.14 (2H, s, O-CH₂); ¹³C NMR (CDCl₃, 100MHz) δ 168.7, 166.3, 161.9, 158.6, 154.6, 143.6, 134.8, 134.3, 132.4, 130.1, 129.1, 128.8, 128.6, 127.4, 125.1, 120.4, 117.2, 111.7, 103.1, 71.4.

2-Hydroxy-4-(4-phenoxyphenylsulfonamido)benzoic acid (17da): 2-(Benzyloxy)-4-(4-phenoxyphenylsulfonamido)benzoic acid (**17da'**) was debenzylated according to general procedure G on a scale of 0.11 mmol to yield the product as a white solid (20 mg, 47%): ¹H NMR (400 MHz, d₆-DMSO) δ 10.65 (s, 1H), 7.70 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.13 (t, $J = 7.4$ Hz, 1H), 7.01-6.95 (m, 4H), 6.52 (m, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 196.6, 162.6, 161.6, 154.8, 144.5, 133.4, 131.9, 130.9 (2), 129.7, 125.6, 120.8, 117.9, 109.5, 105.4; MS (APCI+) m/z Calcd (M⁺): 385.1; Found: 342.0 (M-COOH+H)⁺; $t_R = 8.9$ min (100%).

Methyl 3-aminobenzoate (19a): 3-Aminobenzoic acid (**18a**) was esterified according to general procedure A, and ¹H NMR data were consistent with previously reported data.

Methyl 5-amino-2-hydroxybenzoate (19b): 5-Aminosalicylic acid (**18b**) was esterified according to general procedure A on a scale of 33 mmol to give the title product as a pink solid (3.7 g, 68%): ¹H NMR (DMSO-d₆, 400MHz) δ 9.77 (1H, s, OH), 7.01 (1H, s, Ar), 6.82 (1H, d, $J = 6.8$ Hz, Ar), 6.71 (1H, d, $J = 9.6$ Hz, Ar), 4.82 (2H, s, NH₂), 3.86 (3H, s, O-CH₃); ¹³C NMR (DMSO-d₆, 100MHz) δ 169.8, 151.6, 141.2, 123.1, 117.6, 112.8, 112.1, 52.3.

Methyl 3-(isobutylamino)benzoate (20a): Methyl 3-aminobenzoate was reductive aminated by isobutyl aldehyde according to general procedure C on a scale of 18.3 mmol to give the product as a yellow oil (2.8 g, 73%): ¹H NMR (CDCl₃, 400MHz) δ 7.35 (1 H, d, $J = 7.6$ Hz, Ar), 7.26 (1 H, s, Ar), 7.21 (1 H, t, $J = 7.6$ Hz, Ar), 6.78 (1 H, d, $J = 7.6$ Hz, Ar), H, Ar), 3.89 (3 H, s, OCH₃), 2.97 (2 H, d, $J = 6.8$ Hz, CH₂iPr), 1.93-1.84 (1 H, m, CH₂CH), 0.99 (6 H, d, $J = 6.8$ Hz, 2 x CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 167.6, 148.4, 131.0, 129.1, 118.2, 117.1, 113.2, 52.1, 51.7, 28.0, 20.5.

Methyl 2-hydroxy-5-(isobutylamino)benzoate (20b): Methyl 5-amino-2-hydroxybenzoate (**19b**) underwent reductive amination with isobutyraldehyde according to general procedure C on a scale of 2.99 mmol to give the title product as a brown oil (421 mg, 63%): ¹H NMR (DMSO-d₆, 400MHz) δ 9.78 (1H, s, OH), 7.01 (1H, s, Ar), 6.89-6.87 (2H, m, Ar), 6.76 (1H, d, $J = 8.8$ Hz, Ar), 5.37 (1H, t, $J = 5.0$ Hz, NH), 3.86(3H, s, O-CH₃), 2.74 (2H, t, $J = 6.2$ Hz, CH₂), 1.80 (1H, m, CH), 0.92 (6H, d, $J = 6.4$ Hz, 2*CH₃); MS (APCI+) m/z Calcd (M⁺): 223.1; Found: 224.3 (M+H)⁺.

Methyl 3-(N-isobutylphenylsulfonamido)benzoate (21aa): Methyl 3-(isobutylamino)benzoate (**20a**) was coupled to benzenesulfonyl chloride according to general procedure D on a scale of 3.0 mmol to yield the product as a clear oil (310 mg, 30%): ¹H NMR (CDCl₃, 400MHz) δ 7.97 (1 H, d, $J = 7.2$ Hz, Ar), 7.64 (1 H, s, Ar), 7.63-7.51 (3 H, m, Ar), 7.49-7.42 (2 H, m, Ar), 7.40 (1 H, d, $J = 7.6$ Hz, Ar), 7.33 (1 H, d, $J = 8.0$ Hz, Ar), 3.89 (3 H, s, OCH₃), 3.34 (2 H, d, $J = 7.6$ Hz, CH₂iPr), 1.60-1.51 (1 H, m, CH₂CH), 0.92 (6 H,

d, $J = 7.6$ Hz, 2 x CH_3); ^{13}C NMR (CDCl_3 , 100MHz) δ 166.1, 139.7, 137.8, 133.5, 132.8, 131.1, 129.1, 128.8, 127.6, 57.7, 52.3, 26.8, 19.8; MS (APCI+) m/z Calcd (M^+): 347.1, Found: 348.1 ($\text{M}+\text{H}^+$);

Methyl 3-(N-isobutyl-naphthalene-2-sulfonamido)benzoate (21ab): Methyl 3-(isobutylamino)benzoate (**20a**) was coupled to 2-naphthlenesulfonyl chloride according to general procedure D on a scale of 3.0 mmol to yield the product as a clear oil (373mg, 31%): ^1H NMR (CDCl_3 , 400MHz) δ 8.15 (1 H, s, Ar), 7.98 (1 H, d, $J = 7.6$ Hz, Ar), 7.95-7.86 (3 H, m, Ar), 7.69 (1 H, s, Ar), 7.68-7.56 (3 H, m, Ar), 7.51 (1 H, dd, $J = 8.8, 1.6$ Hz, Ar), 7.39 (1 H, t, $J = 8.0$ Hz, Ar), 7.32 (1 H, d, $J = 8.0$ Hz, Ar), 3.83 (3 H, s, OCH_3), 3.39 (2 H, d, $J = 6.8$ Hz, CH_2iPr), 1.60-1.51 (1 H, m, CH_2CH), 0.92 (6 H, d, $J = 6.8$ Hz, 2 x CH_3); ^{13}C NMR (CDCl_3 , 100MHz) δ 166.1, 139.8, 134.9, 134.8, 133.4, 132.0, 131.2, 129.3, 129.2, 129.1, 128.9, 128.8, 127.9, 127.5, 122.9, 57.8, 52.3, 26.9, 19.9; MS (APCI+) m/z Calcd (M^+): 397.1, Found: 398.0 ($\text{M}+\text{H}^+$);

Methyl 3-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (21ac): Methyl 3-(isobutylamino)benzoate (**20a**) was coupled to biphenyl-4-sulfonyl chloride according to general procedure D on a scale of 3.0 mmol to yield the product as a white solid (304mg, 24%): ^1H NMR (CDCl_3 , 400MHz) δ 7.99 (1 H, d, $J = 7.6$ Hz, Ar), 7.71 (1 H, s, Ar), 7.69-7.57 (6 H, m, Ar), 7.49 (2 H, t, $J = 7.2$ Hz, Ar), 7.45-7.36 (3 H, m, Ar), 3.88 (3 H, s, OCH_3), 3.38 (2 H, d, $J = 6.8$ Hz, CH_2iPr), 1.62-1.54 (1 H, m, CH_2CH), 0.93 (6 H, d, $J = 6.8$ Hz, 2 x CH_3); ^{13}C NMR (CDCl_3 , 100MHz) δ 166.2, 145.6, 139.8, 139.2, 136.4, 133.5, 131.2, 129.2, 129.1, 129.0, 128.9, 128.5, 128.1, 127.4, 127.3, 57.7, 52.3, 26.9, 19.9; MS (APCI+) m/z Calcd (M^+): 423.1, Found: 424.1 ($\text{M}+\text{H}^+$).

Methyl 3-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (21ad): Methyl 3-(isobutylamino)benzoate (**20a**) was coupled to 4-fluorobenzenesulfonyl chloride according to general procedure D on a scale of 3.0 mmol to yield the product as a clear oil (377mg, 34%): ^1H NMR (CDCl_3 , 400MHz) δ 7.98 (1 H, d, $J = 7.6$ Hz, Ar), 7.64 (1 H, s, Ar), 7.55 (2 H, dd, $J = 8.4, 4.4$ Hz, Ar), 7.42 (1 H, t, $J = 7.6$ Hz, Ar), 7.34 (1 H, d, $J = 7.6$ Hz, Ar), 7.14 (2 H, t, $J = 7.6$ Hz, Ar), 3.90 (3 H, s, OCH_3), 3.34 (2 H, d, $J = 7.2$ Hz, CH_2iPr), 1.60-1.52 (1 H, m, CH_2CH), 0.91 (6 H, d, $J = 7.2$ Hz, 2 x CH_3); ^{13}C NMR (CDCl_3 , 100MHz) δ 139.6, 133.9, 133.5, 131.2, 130.3, 130.2, 129.2, 129.0, 128.9, 116.2, 116.0, 57.7, 52.4, 26.8, 19.8; MS (APCI+) m/z Calcd (M^+): 365.1, Found: 366.0 ($\text{M}+\text{H}^+$).

Methyl 3-(N-isobutyl-4-methylphenylsulfonamido)benzoate (21ae): Methyl 3-(isobutylamino)benzoate (**20a**) was coupled to 4-methylbenzene-1-sulfonyl chloride according to general procedure D on a scale of 3.0 mmol to yield the product as a clear oil (314 mg, 29%): ^1H NMR (CDCl_3 , 400MHz) δ 7.96 (1 H, d, $J = 8.0$ Hz, Ar), 7.67 (1 H, s, Ar), 7.45-7.36 (3 H, m, Ar), 7.33 (1 H, d, $J = 8.8$ Hz, Ar), 7.24 (2 H, d, $J = 7.6$ Hz, Ar), 3.90 (3 H, s, OCH_3), 3.34 (2 H, d, $J = 7.6$ Hz, CH_2iPr), 2.42 (3 H, s, ArCH_3), 1.60-1.50 (1 H, m, CH_2CH), 0.90 (6 H, d, $J = 7.6$ Hz, 2 x CH_3); ^{13}C NMR (CDCl_3 , 100MHz) δ 166.2, 143.5, 139.9, 134.9, 133.5, 131.1, 129.5, 129.1, 129.0, 128.8, 127.6, 57.6, 52.3, 26.8, 21.5, 19.9; MS (APCI+) m/z Calcd (M^+): 361.1, Found: 362.1 ($\text{M}+\text{H}^+$).

Methyl 3-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoate (21af): Methyl 3-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**21ad**) was reacted with 3,5-dimethyl-4-chlorophenol according to general procedure E on a scale of 0.68 mmol to yield the product as a cream solid (200 mg, 60%): ¹H NMR (CDCl₃, 400MHz) δ 7.97 (1 H, d, *J* = 7.2 Hz, Ar), 7.66 (1 H, s, Ar), 7.47 (2 H, d, *J* = 8.4 Hz, Ar), 7.44-7.36 (2 H, m, Ar), 6.95 (2 H, d, *J* = 8.4 Hz, Ar), 6.82 (2 H, s, Ar), 3.91 (3 H, s, OCH₃), 3.34 (2 H, d, *J* = 6.8 Hz, CH₂iPr), 2.38 (6 H, s, 2 x ArCH₃) 1.60-1.50 (1 H, m, CH₂CH), 0.91 (6 H, d, *J* = 6.8 Hz, 2 x CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 166.2, 161.5, 152.7, 139.8, 138.2, 133.7, 131.4, 131.1, 129.8, 129.1, 128.9, 128.8, 120.1, 117.2, 57.6, 52.3, 26.8, 20.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 501.1, Found: 502.0 (M+H⁺).

Methyl 2-hydroxy-5-(N-isobutylphenylsulfonamido)benzoate (21ba): Methyl 2-hydroxy-5-(isobutylamino)benzoate (**20b**) was coupled to benzenesulfonyl chloride according to general procedure D on a scale of 0.23 mmol to yield the product as a brown solid (86 mg, 98 %): ¹H NMR (DMSO-d₆, 400MHz) δ 10.56 (1H, s, OH), 7.70 (1H, t, *J* = 7.0 Hz, Ar), 7.61-7.53 (4H, m, Ar), 7.41 (1H, s, Ar), 7.10 (1H, d, *J* = 8.4 Hz, Ar), 6.94 (1H, d, *J* = 9.6 Hz, Ar), 3.85 (3H, s, O-CH₃), 3.28 (2H, d, *J* = 6.8 Hz, CH₂), 1.44 (1H, m, CH), 0.85 (1H, d, *J* = 6.4 Hz, 2*CH₃); ¹³C NMR (DMSO-d₆, 100MHz) δ 168.4, 159.4, 137.7, 135.4, 130.7, 130.4, 129.7, 127.6, 118.6, 114.0, 57.6, 55.3, 26.8, 20.0.

Methyl 2-hydroxy-5-(N-isobutyl-naphthalene-2-sulfonamido)benzoate (21bb): Methyl 2-hydroxy-5-(isobutylamino)benzoate (**20b**) was coupled to 2-naphthalenesulfonyl chloride according to general procedure D on a scale of 0.45 mmol to yield the product as a clear solid (164 mg, 88 %): ¹H NMR (CDCl₃, 400MHz) δ 10.82 (1H, s, OH), 8.13 (1H, s, Ar), 7.89-7.86 (3H, br s, H), 7.62-7.55 (4H, br s, Ar), 7.03 (1H, d, *J* = 7.8 Hz, Ar), 6.85 (1H, d, *J* = 7.8 Hz, Ar), 3.79 (3H, s, O-CH₃), 3.32 (2H, d, *J* = 5.6 Hz, CH₂), 1.57 (1H, m, CH), 0.93 (6H, d, *J* = 4.0 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 169.7, 160.9, 135.6 134.9, 134.7, 132.0, 130.6, 130.5, 129.1, 129.0, 128.9, 128.7, 127.8, 127.4, 122.9, 118.2, 112.5, 58.1, 52.4, 26.7, 19.8; MS (APCI+) *m/z* Calcd (M⁺): 413.1; Found: 414.0 (M+H)⁺.

Methyl 2-hydroxy-5-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (21bc): Methyl 2-hydroxy-5-(isobutylamino)benzoate (**20b**) was coupled to biphenyl-4-sulfonyl chloride according to general procedure D on a scale of 0.45 mmol to yield the product as a clear solid (125 mg, 63 %): ¹H NMR (CDCl₃, 400MHz) δ 10.84 (1H, s, OH), 7.68-7.60 (7H, m, Ar), 7.47-7.45 (3H, m, Ar), 7.08 (1H, d, *J* = 7.6 Hz, Ar), 6.89 (1H, d, *J* = 8.4 Hz, Ar), 3.87 (3H, s, O-CH₃), 3.32 (2H, d, *J* = 7.2 Hz, CH₂), 1.60-1.57 (1H, m, CH), 0.93 (6H, d, *J* = 6.4 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 169.8, 160.9, 145.4, 139.1, 136.5, 135.5, 130.6, 130.5, 129.0, 128.5, 128.1, 127.3, 127.2, 118.2, 112.5, 58.0, 52.5, 26.8, 19.8; MS (APCI+) *m/z* Calcd (M⁺): 439.2; Found: 440.0 (M+H)⁺.

Methyl 5-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)-2-hydroxybenzoate (21bd): Methyl 2-hydroxy-5-(isobutylamino)benzoate (**20b**) was coupled to 4-fluorobenzene sulfonyl

chloride according to general procedure D on a scale of 0.45 mmol to yield the product as white crystals, which was *O*-benzylated according to general procedure B to yield a white solid. Then the compound was coupled to 4-chloro-3,5-dimethylphenol according to general procedure E to afford a pink semi-solid. Then, it was debenzylated according to general procedure G to give the product as a pale yellow solid (65 mg, 30%); ¹H NMR (CDCl₃, 400MHz) δ 10.82 (1H, s, Ar), 7.63 (1H, s, Ar), 7.50 (2H, d, *J* = 8.4 Hz, Ar), 7.04 (1H, d, *J* = 8.8 Hz, Ar), 6.96 (2H, d, *J* = 8.4 Hz, Ar), 6.89 (1H, d, *J* = 8.8 Hz, Ar), 6.80 (2H, s, Ar), 3.94 (3H, s, O-CH₃), 3.26 (2H, d, *J* = 7.2 Hz, CH₂), 2.37 (6H, s, 2*Ph-CH₃), 1.62-1.52 (1H, m, CH), 0.92 (6H, d, *J* = 6.4 Hz, 2*CH₃); ¹³C NMR (CDCl₃, 100MHz) δ 169.9, 161.5, 161.0, 152.8, 138.3, 135.4, 131.8, 130.8, 130.6, 129.9, 120.1, 118.3, 117.3, 112.7, 58.0, 52.6, 29.8, 26.8, 21.0, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 517.1; Found: 518.0 (M+H)⁺.

3-(N-Isobutylphenylsulfonamido)benzoic acid (22aa): Methyl 3-(N-isobutylphenylsulfonamido)benzoate (**21aa**) was hydrolyzed according to general procedure F on a scale of 0.28 mmol to give the product as a white solid (91 mg, 97%): ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 7.2 Hz, 1H), 7.68 (s, 1H), 7.63-7.52 (m, 3H), 7.50-7.38 (m, 4H), 3.35 (d, *J* = 7.2 Hz, 2H), 1.60-1.52 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 139.9, 137.7, 134.6, 132.8, 130.2, 129.5, 129.3, 128.9 (2), 127.6, 57.7, 26.9, 19.8; MS (APCI+) *m/z* Calcd (M⁺): 333.1, Found: 334.0 (M+H⁺); *t_R* = 9.1 min (100%).

3-(N-Isobutylnaphthalene-2-sulfonamido)benzoic acid (22ab): Methyl 3-(N-isobutylnaphthalene-2-sulfonamido)benzoate (**21ab**) was hydrolyzed according to general procedure F on a scale of 0.25 mmol to give the product as a white solid (77mg, 80%): ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 7.95-7.87 (m, 3H), 7.56 (s, 1H), 7.69-7.56 (m, 2H), 7.50 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.47-7.38 (m, 2H), 3.40 (d, *J* = 7.2 Hz, 2H), 1.63-1.51 (m, 1H), 0.93 (d, *J* = 6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 184.2, 170.5, 140.0, 134.9, 134.8, 134.4, 132.0, 130.2, 129.8, 129.3, 128.8, 127.9, 127.5, 123.0, 122.8, 57.8, 26.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 383.1, Found: 384.0 (M+H⁺); *t_R* = 11.4 min (100%).

3-(N-Isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoic acid (22ac): Methyl 3-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (**21ac**) was hydrolyzed according to general procedure F on a scale of 0.23 mmol to give the product as a white solid (59mg, 62%): ¹H NMR (400 MHz, CDCl₃) δ 8.07-8.02 (m, 1H), 7.73 (s, 1H), 7.70-7.65 (m, 2H), 7.64-7.57 (m, 4H), 7.50-7.38 (m, 5H), 3.39 (d, *J* = 7.2 Hz, 2H), 1.63-1.52 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 170.4, 145.7, 140.0, 139.2, 136.3, 134.6, 130.2, 129.6, 129.5, 129.3, 129.0, 128.5, 128.1, 127.5, 127.3, 57.7, 26.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 409.1, Found: 410.0 (M+H⁺); *t_R* = 13.1 min (100%).

3-(4-Fluoro-N-isobutylphenylsulfonamido)benzoic acid (22ad): Methyl 3-(4-fluoro-N-isobutylphenylsulfonamido)benzoate (**21ad**) was hydrolyzed according to general procedure F on a scale of 0.28 mmol to give the product as a white solid (58mg, 60%): ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* =

7.2 Hz, 1H), 7.69 (s, 1H), 7.59-7.55 (m, 2H), 7.51-7.40 (m, 2H), 7.15 (t, $J = 8.6$ Hz, 2H), 3.35 (d, $J = 7.2$ Hz, 2H), 1.63-1.52 (m, 1H), 0.92 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 139.7, 134.6, 130.3, 130.2 (2), 129.6, 129.4, 129.3, 116.3, 116.1, 57.7, 26.9, 19.8; MS (APCI+) m/z Calcd (M^+): 351.0, Found: 352.0 ($\text{M}+\text{H}^+$); $t_{\text{R}} = 10.3$ min (100%).

3-(N-Isobutyl-4-methylphenylsulfonamido)benzoic acid (22ae): Methyl 3-(N-isobutyl-4-methylphenylsulfonamido)benzoate (**21ae**) was hydrolyzed according to general procedure F on a scale of 0.28 mmol to give the product as a white solid (55mg, 56%): ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 7.2$ Hz, 1H), 7.71 (s, 1H), 7.49-7.40 (m, 4H), 7.28-7.22 (m, 2H), 3.33 (d, $J = 6.8$ Hz, 2H), 2.43 (s, 3H), 1.60-1.51 (m, 1H), 0.91 (d, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 143.6, 140.1, 134.8, 134.6, 130.1, 129.5 (2), 129.4, 129.2, 127.6, 57.6, 26.8, 21.5, 19.9; MS (APCI+) m/z Calcd (M^+): 347.1, Found: 348.1 ($\text{M}+\text{H}^+$); $t_{\text{R}} = 10.6$ min (100%).

3-(4-(4-Chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoic acid (22af): Methyl 3-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)benzoate (**21af**) was hydrolyzed according to general procedure F on a scale of 0.68 mmol to give the product as a white solid (248mg, 75%): ^1H NMR (400 MHz, CDCl_3) δ 8.06-8.00 (m, 1H), 7.68 (s, 1H), 7.51-7.44 (m, 4H), 6.96 (d, $J = 8.8$ Hz, 2H), 6.81 (s, 2H), 3.35 (d, $J = 7.2$ Hz, 2H), 2.63 (s, 6H) 1.63-1.52 (m, 1H), 0.92 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.6, 161.6, 152.6, 140.1, 138.3, 134.9, 131.4, 130.1, 129.8 (2), 129.5, 129.3, 129.2, 120.1, 117.3, 57.7, 26.9, 20.9, 19.9; MS (APCI+) m/z Calcd (M^+): 487.1, Found: 488.0 ($\text{M}+\text{H}^+$); $t_{\text{R}} = 19.1$ min (100%).

2-Hydroxy-5-(N-isobutylphenylsulfonamido)benzoic acid (22ba): Methyl 2-hydroxy-5-(N-isobutylphenylsulfonamido)benzoate (**21ba**) was hydrolyzed according to general procedure F on a scale of 0.19 mmol to give the product as a brown solid (30 mg, 45%): ^1H NMR (400 MHz, CDCl_3) δ 10.51 (s, 1H), 8.82 (br s, 1H), 7.61-7.58 (m, 4H), 7.49 (t, $J = 7.8$ Hz, 2H), 7.17 (dd, $J = 9.2$ Hz, 2.4 Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 3.29 (d, $J = 6.8$ Hz, 2H), 1.63-1.52 (m, 1H), 0.93 (d, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.3, 161.5, 137.7, 137.1, 132.8, 130.9, 130.8, 128.9, 127.6, 118.6, 111.6, 58.0, 26.8, 19.8; MS (APCI+) m/z Calcd (M^+): 349.0; Found: 350.0 ($\text{M}+\text{H}^+$); $t_{\text{R}} = 10.5$ min (100%).

2-Hydroxy-5-(N-isobutylnaphthalene-2-sulfonamido)benzoic acid (22bb): Methyl 2-hydroxy-5-(N-isobutylnaphthalene-2-sulfonamido)benzoate (**21bb**) was hydrolyzed according to general procedure F on a scale of 0.34 mmol to give the product as a white solid (121 mg, 89%): ^1H NMR (400 MHz, CDCl_3) δ 10.53 (s, 1H), 8.19 (s, 1H), 7.94-7.90 (m, 3H), 7.67-7.55 (m, 4H), 7.14 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 6.90 (d, $J = 8.8$ Hz, 1H), 3.34 (d, $J = 7.2$ Hz, 2H), 1.64-1.54 (m, 1H), 0.94 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.2, 161.5, 136.9, 134.8, 131.2, 130.7, 129.2, 129.1, 129.0, 128.8, 127.9, 127.5, 122.8, 118.5, 111.6, 58.1, 26.7, 19.8; MS (APCI+) m/z Calcd (M^+): 399.1; Found: 400.0 ($\text{M}+\text{H}^+$); $t_{\text{R}} = 12.3$ min (100%).

2-Hydroxy-5-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoic acid (22bc): Methyl 2-hydroxy-5-(N-isobutyl-[1,1'-biphenyl]-4-ylsulfonamido)benzoate (**21bc**) was hydrolyzed according to general procedure F on a scale of 0.23 mmol to give the product as a white solid (98 mg, 98%): ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 8.4 Hz, 2H), 7.64-7.56 (m, 5H), 7.48 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.14 (dd, J = 9.2 Hz, 2.4 Hz 1H), 6.90 (d, J = 8.8 Hz, 1H), 3.31 (d, J = 7.6 Hz, 2H), 1.65-1.54 (m, 1H), 0.94 (d, J = 6.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 161.2, 145.5, 139.1, 136.2, 135.8, 130.8, 130.1, 128.9, 128.4, 128.1, 127.3, 127.2, 117.9, 112.9, 58.1, 26.7, 19.8; MS (APCI+) *m/z* Calcd (M⁺): 425.1; Found: 426.0 (M+H)⁺; *t_R* = 13.5 min (100%).

5-(4-(4-Chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)-2-hydroxybenzoic acid (6e-OH-5): Methyl 5-(4-(4-chloro-3,5-dimethylphenoxy)-N-isobutylphenylsulfonamido)-2-hydroxybenzoate (**21bd**) was hydrolyzed according to general procedure F on a scale of 0.08 mmol to give the product as a cream solid (40 mg, 98%): ¹H NMR (400 MHz, CDCl₃) δ 10.60 (s, 1H), 7.61 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.02-6.91 (m, 3H), 6.80 (s, 2H), 3.28 (d, J = 7.2 Hz, 2H), 2.37 (s, 6H), 1.65-1.53 (m, 1H), 0.92 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 172.9, 161.5, 161.5, 152.7, 138.3, 137.0, 131.5, 130.9, 130.8, 130.7, 129.9, 120.0, 118.5, 117.3, 111.7, 58.0, 26.8, 20.9, 19.9; MS (APCI+) *m/z* Calcd (M⁺): 503.1; Found: 504.0 (M+H)⁺; *t_R* = 19.8 min (100%).

Biology

Protein Production

A His6-MBP tagged recombinant human Mcl-1 residues 172 to 327 was produced in *E. coli* in either LB or minimal media supplemented with ¹⁵NH₄Cl to produce unlabeled or ¹⁵N-labeled Mcl-1. The tagged protein was initially purified from the crude cell lysate by IMAC chromatography (GE Healthcare Life Sciences), and after dialysis to remove the imidazole the affinity tag was cleaved using PreScission Protease (GE Healthcare Life Sciences). A Sephacryl S-200 size exclusion column was used as a final purification step before the protein was concentrated with a 10,000 MWCO centrifugal filter concentrator (Millipore). The protein purity was shown to be >98% by Coomassie Brilliant Blue (Bio-Rad) stained SDS-PAGE gel and the final concentration was determined using the Bradford protein assay (Bio-Rad) with BSA standards (Pierce).

Peptide

A 6-aminohexanoic acid linker was conjugated to the N-terminus of the Bak BH3 peptide (GQVGRQLAIIGDDINR), capped with fluorescein (on the amino group of the linker), and the peptide

was amidated on the C-terminus to give FITC-Ahx-GQVGRQLAIIGDDINR-CONH₂, hereafter referred to as “FITC-Bak” (synthesized by Neo BioScience in >95% purity).

Fluorescence polarization experiments

Fluorescence polarization experiments were conducted using a BMG PHERAstar FS multimode microplate reader equipped with two PMTs for simultaneous measurements of the perpendicular and parallel fluorescence emission. The assays were performed in black polypropylene 384-well microplate (Costar) with a final volume of 20 μ L. The affinity (K_d) of the FITC-Bak peptide was determined by titrating Mcl-1¹⁷²⁻³²⁷ into 10 nM FITC-Bak peptide in 20 mM HEPES, pH 6.8, 50 mM NaCl, 3 mM DTT, 0.01% Triton X-100 and 5% DMSO at room temperature while monitoring the perpendicular and parallel fluorescence emission with a 485 nm excitation and 520 nm emission filters. The fluorescence polarization competition assay (FPCA) was performed using 100 nM Mcl-1¹⁷²⁻³²⁷ (or 15 nM Bcl-x_L²⁻²¹² (R&D Systems)) in the same buffer (thus, 10 nM FITC-Bak) with varying concentrations of either unlabeled peptide or 2,6-disubstituted nicotinate. Regression analysis was carried out using Origin (OriginLab, Northampton, MA) to fit the data to the Hill equation to determine the IC₅₀, which delivered K_d s for the FITC-Bak peptide to Mcl-1 of 33.8 ± 0.50 nM and to Bcl-x_L of 6.67 ± 0.05 nM. For the fluorescence polarization competition titrations, an equation derived by Nikolovska-Coleska *et al.*¹ was used to calculate the K_i from the IC₅₀ data. All experiments were run in three biological replicates, each in triplicate.

Nuclear Magnetic Resonance Spectroscopy: 2D HSQC

2D HSQC (heteronuclear single quantum coherence) NMR spectra were collected at 25 °C with a Bruker AVANCE 800 NMR spectrometer (800.27 MHz for protons) equipped with pulsed-field gradients, four frequency channels, and triple resonance, z-axis gradient cryogenic probes. A one-second relaxation delay was used, and quadrature detection in the indirect dimensions was obtained with states-TPPI phase cycling; initial delays in the indirect dimensions were set to give zero- and first-order phase corrections of 90° and -180°, respectively.^{2,3} Data were processed using the processing program nmrPipe on Linux workstations.⁴ All proton chemical shifts are reported with respect to the H₂O or HDO signal, taken to be 4.658 ppm relative to external TSP (0.0 ppm) at 37°C. The ¹⁵N chemical shifts were indirectly referenced using the zero-point frequency at 37 °C of 0.10132905 for ¹H-¹⁵N, as previously described.^{5,6}

Uniformly ¹⁵N-labeled Mcl-1 was used to collect two-dimensional ¹H-¹⁵N-fast HSQC spectra of Mcl-1 with and without compound to detect changes in the backbone ¹⁵N and ¹H resonances of Mcl-1 due to the direct interaction with compound **6e-OH**, which itself was initially dissolved in 100% *d*₆-DMSO.⁷ The

NMR samples contained 61.9 μM ^{15}N -labeled Mcl-1, 20 mM HEPES, pH 6.8, 36.4 mM NaCl, 0.20 mM NaN_3 , 2.2 mM DTT, 4.2% DMSO, 20% D_2O . Concentrated **6e-OH** was added in excess to a final protein:ligand ratio of 1:2 (i.e. 123.8 μM). NMR datasets were acquired with 200 indirect points and 32 scans at 299K on a Bruker Avance 800 MHz spectrometer equipped with a z-gradient cryogenic probe.

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