Supporting Information

3-Substituted-*N*-(4-Hydroxynaphthalen-1-yl)arylsulfonamides as a Novel Class of Selective Mcl-1 Inhibitors: Structure-Based Design, Synthesis, SAR and Biological Evaluation

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Protein purification

His-tagged proteins containing Mcl-1 (residues 171–327), Bcl-2 (residues 1-202 with inserted Bcl-xL sequence from residues 35 to 50), Bcl-x_L (residues 1-209 lacking its C-terminal transmembrane domain with a deletion of the flexible loop region 45 – 85), Bcl-w (residues 1-155), A1/Bfl-1 (residues 1-151), were expressed from the pHis-TEV vector (a modified pET vector) in *E. coli* BL21 (DE3) cells. Cells were grown at 37 ºC in 2×YT containing antibiotics to an OD_{600} density of 0.6. Protein expression was induced by 0.4 mM IPTG at 37 ºC for 4 hours. Cells were lysed in 50 mM Tris pH 8.0 buffer containing 500 mM NaCl, 0.1% bME and 40 µl of Leupectin/Aprotin. All protein were purified from the soluble fraction using Ni-NTA resin (QIAGEN), following the manufacturer's instructions. Mcl-1

was further purified on a Source Q15 column (Amersham Biosciences) in 25 mM Tris pH 8.0 buffer, with NaCl gradient. Bcl-2 and Bcl-x_L were purified on a Superdex75 column (Amersham Biosciences) in 25 mM Tris pH 8.0 buffers containing 150 mM NaCl and 2 mM DTT and at -80 ºC in presence of 25% Glycerol.

Determination of the K_d values of fluorescent probes to anti-apoptotic proteins

Fluorescein tagged BID BH3 (Bcl-2 Homology 3) peptide was used as a fluorescent probe in the FP-based binding assays. Two fluorescent labeled BID BH3 peptide probes were used: i) fluorescein tagged BID peptide (Flu-BID), labeled with fluorescein on the N-terminus of the BH3 peptide (79-99); ii) Bid BH3 peptide (80-99) labeled with 5-FAM, named as FAM-BID (Abgent). Their K_d values were determined to all members of the Bcl-2 family proteins with a fixed concentration of the tracer (2 nM of Flu-BID and FAM-BID) and different concentrations of the tested proteins, in a final volume of 125 µl in the assay buffer (100 mM potassium phosphate, pH 7.5, 100 µg/ml bovine γ-globulin, 0.02% sodium azide, Invitrogen, Life Technologies, supplemented with 0.01% Triton X-100 and 4% DMSO). Plates were mixed and incubated at room temperature for 2 hours and the polarization values in millipolarization units (mP) were measured at an excitation wavelength of 485 nm and an emission wavelength of 530 nm. Equilibrium dissociation constants (K_d) were calculated by fitting the sigmoidal dose-dependent FP increases as a function of protein concentrations using Graphpad Prism 6.0 software. Based upon analysis of the dynamic ranges for the signals and their K_d values, Flu-BID was selected as the tracer in the Mcl-1 and Bcl-2 competitive binding assays, while FAM-BID was selected as the tracer for the rest of the proteins, A1/Bfl-1, Bcl-w and Bcl-xL. The K_d value of Flu-BID to Mcl-1 was 34 ± 3.5 nM, and to Bcl-2 was 20 ± 0.86 nM and the K_d values of FAM-BID to A1/Bfl-1 was 0.83 ± 0.06 nM, to Bcl-w was 5.5 ± 1.6 nM, and to Bcl-xL was 10 ± 4.0 nM respectively, in our saturation experiments.

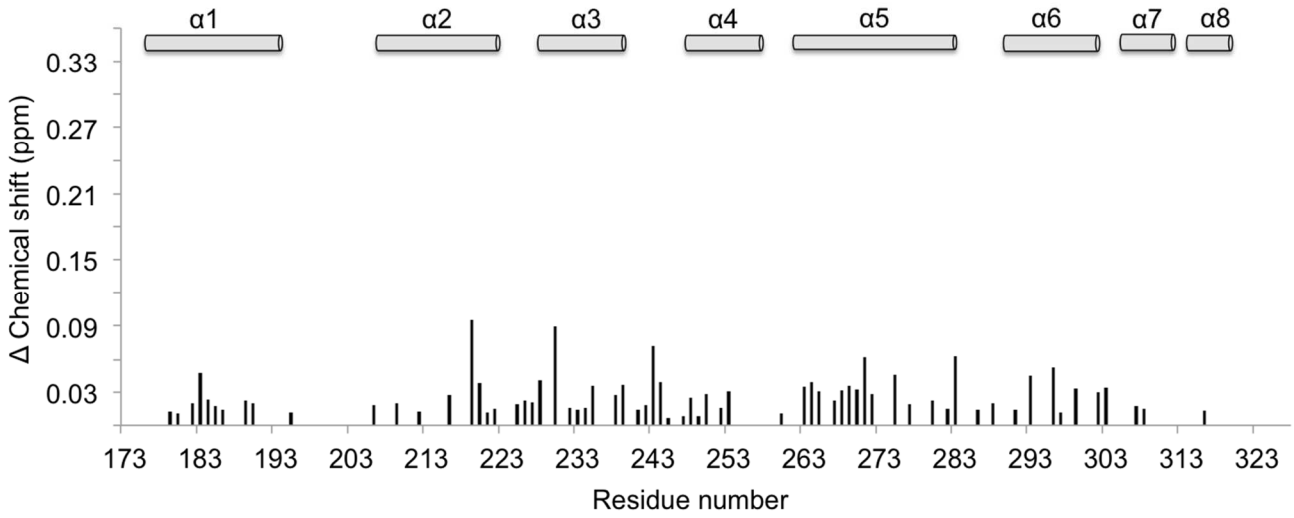


Figure S1. Plot of chemical shift changes of Mcl-1 residues upon addition of **2** (Mcl-1:**2** ratio of 1 to 2).

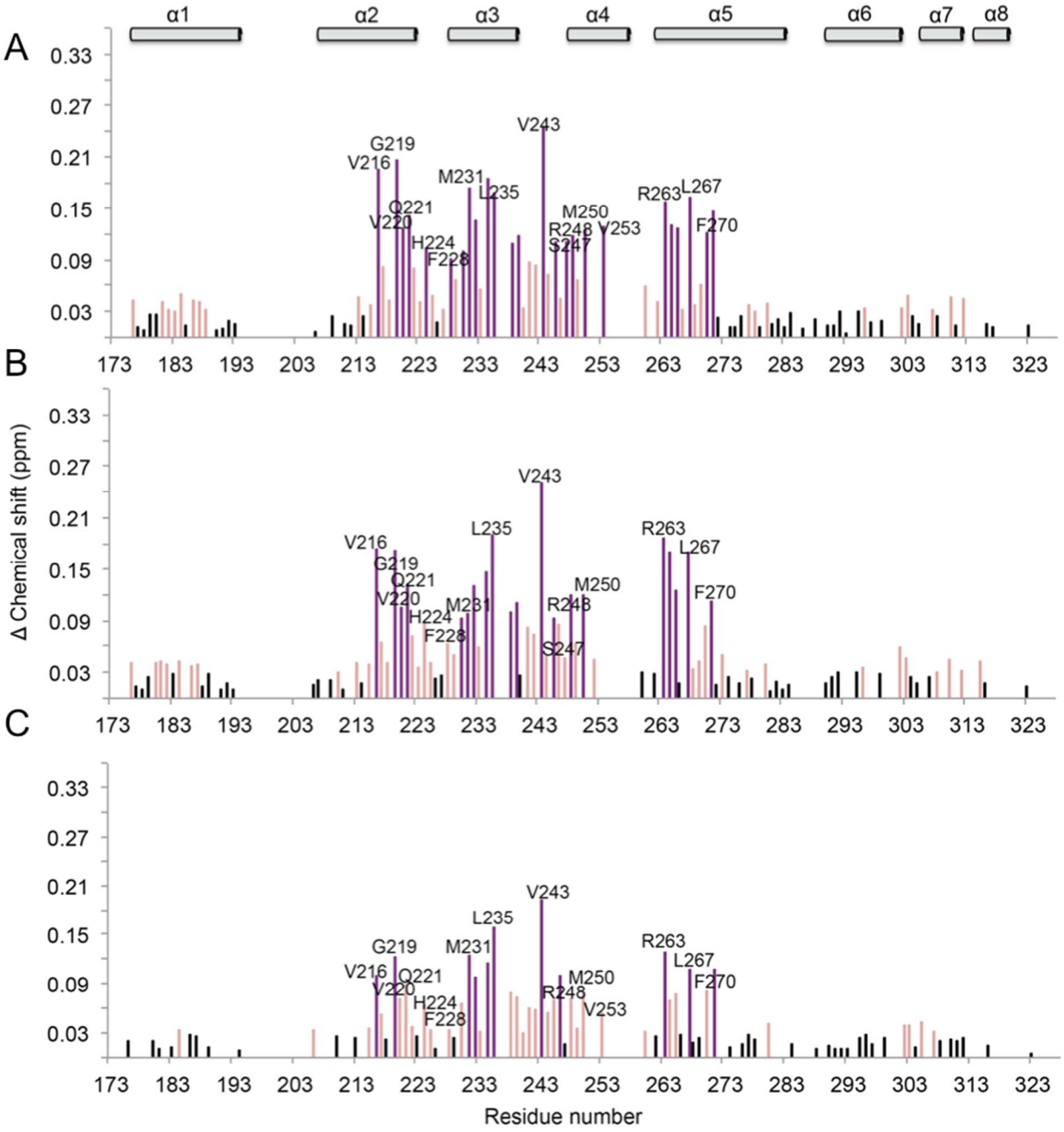


Figure S2. Plots of chemical shift changes of Mcl-1 residues upon addition of (A) **10** (Mcl-1:**10** ratio of 1 to 2) (B) **12** (Mcl-1:**12** ratio of 1 to 2) (C) **13** (Mcl-1:**13** ratio of 1 to 2).

Significant shift (> 0.09 ppm) is represented with purple, moderate shift (≥ 0.03 ppm and ≤ 0.09 ppm) represented with pink.

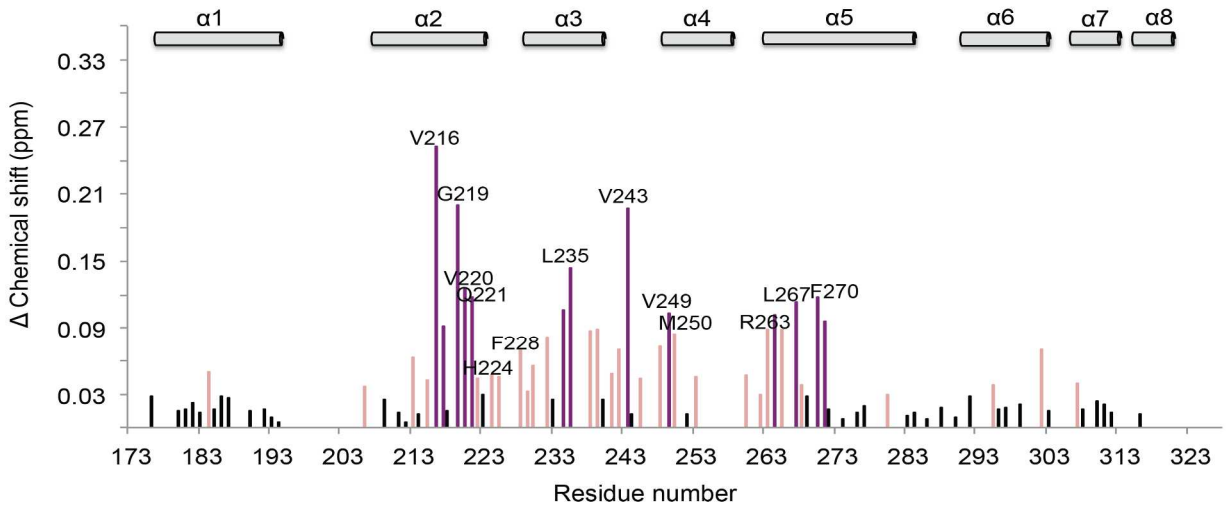


Figure S3. Plot of chemical shift changes of Mcl-1 residues upon addition of **19** (Mcl-1:**19** ratio of 1 to 2).
Significant shift (> 0.09 ppm) is represented with purple, moderate shift (≥ 0.03 ppm and ≤ 0.09 ppm) represented with pink.

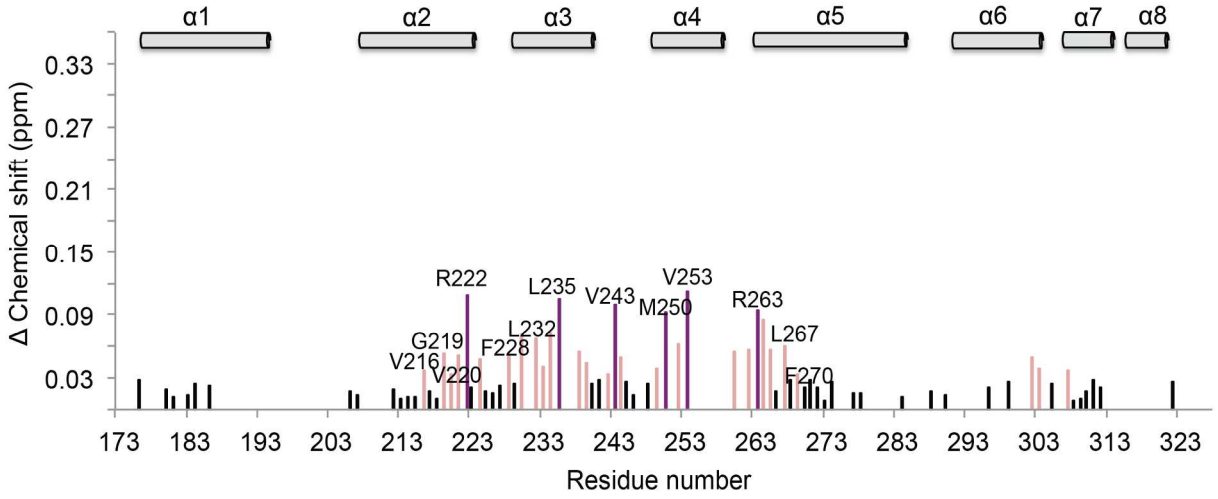


Figure S4. Plot of chemical shift changes of Mcl-1 residues upon addition of **25** (Mcl-1:**25** ratio of 1 to 2).
Significant shift (> 0.09 ppm) is represented with purple, moderate shift (≥ 0.03 ppm and ≤ 0.09 ppm) represented with pink.

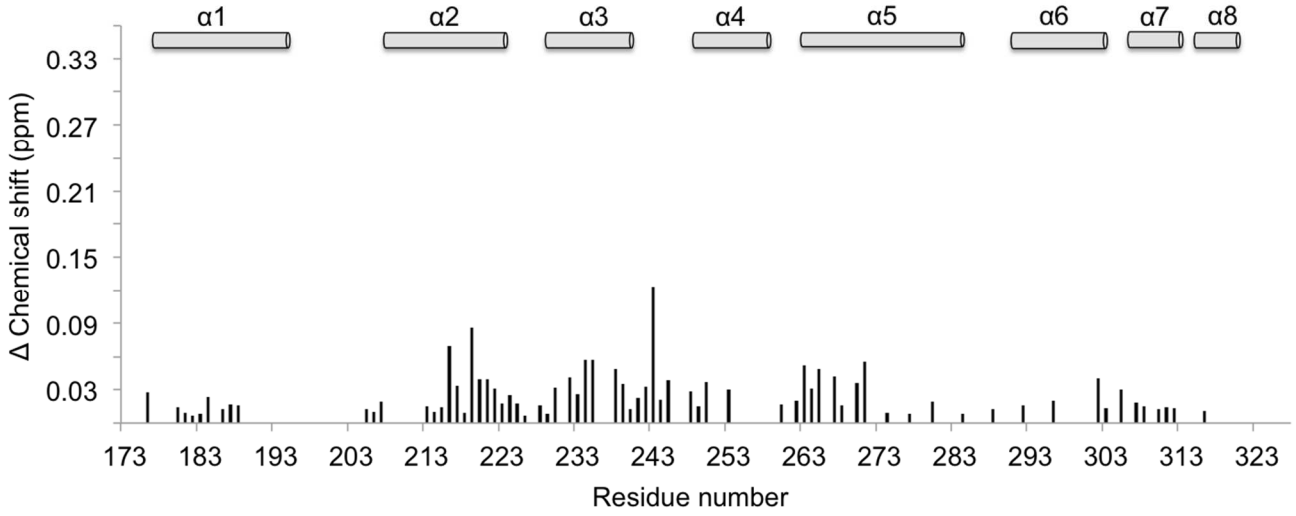


Figure S5. Plot of chemical shift changes of Mcl-1 residues upon addition of **41** (Mcl-1:**41** ratio of 1 to 2).

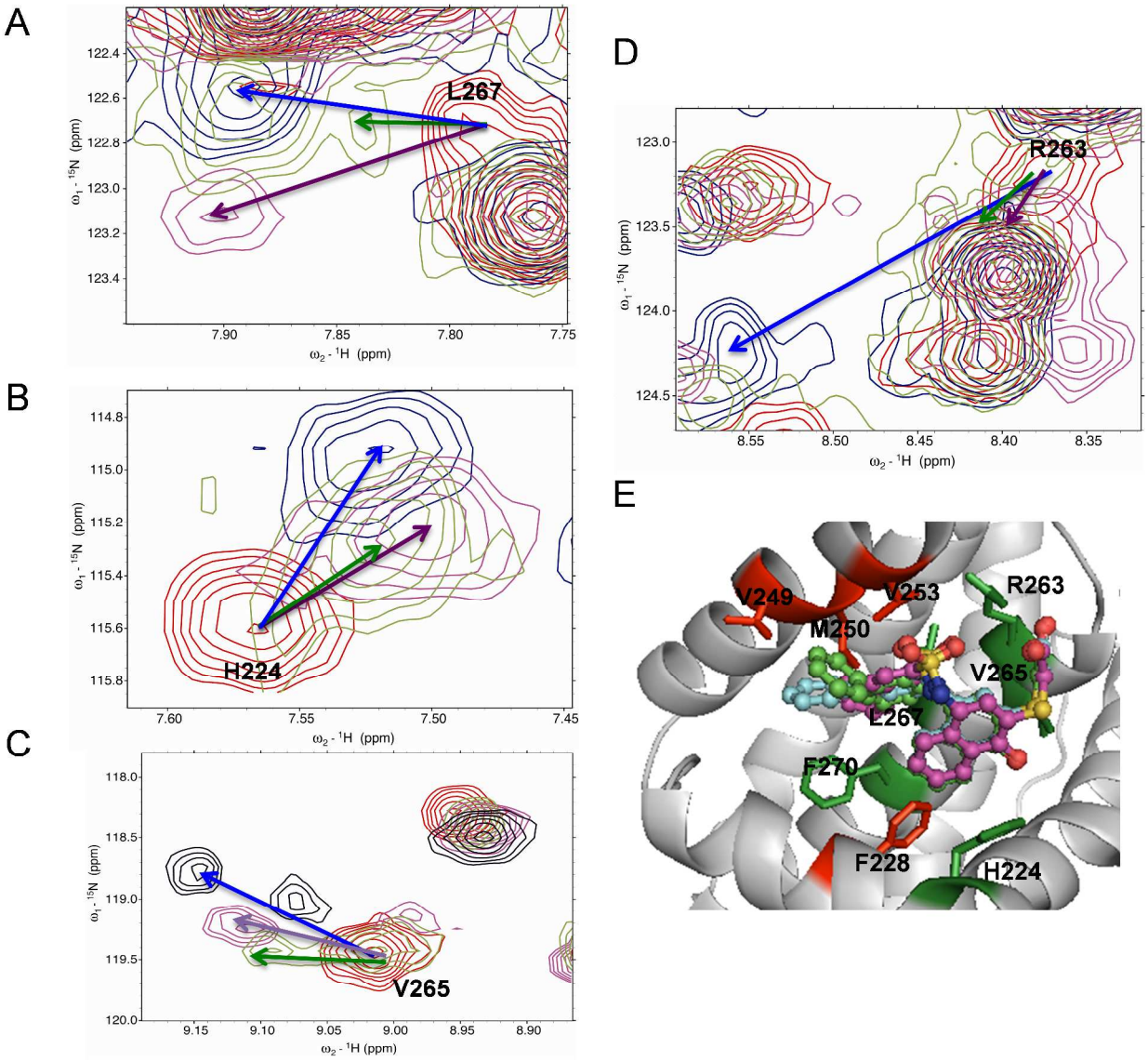


Figure S6. Overlaid ^{15}N-^{1}H HSQC spectra of Mcl-1 (red), and in the presence of **16** (Mcl-1:**16** ratio of 1:2) (purple), **17** (Mcl-1:**17** ratio of 1:2) (blue), **18** (Mcl-1:**18** ratio of 1:2) (green) for (A) Leu 267 (B) His 224 (C) Val 265 and (D) Arg 253. Arrows show the direction of chemical shift changes upon binding of compounds. (E) Overlay of putative binding modes of **16** (purple), **17** (blue), **18** (green) to Mcl-1 (PDB ID: 2NLA) highlighting in red Val 249, Met 250, and Val 253 on helix 4, Phe 228 on helix 3 of Mcl-1.

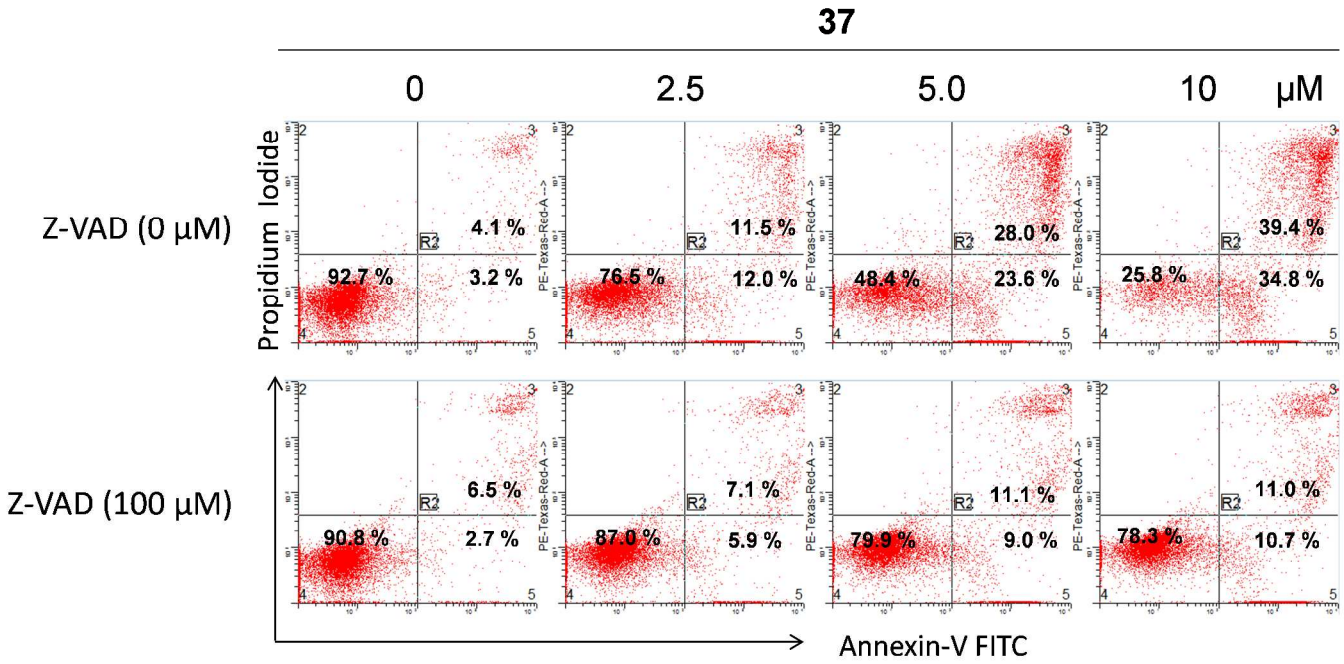
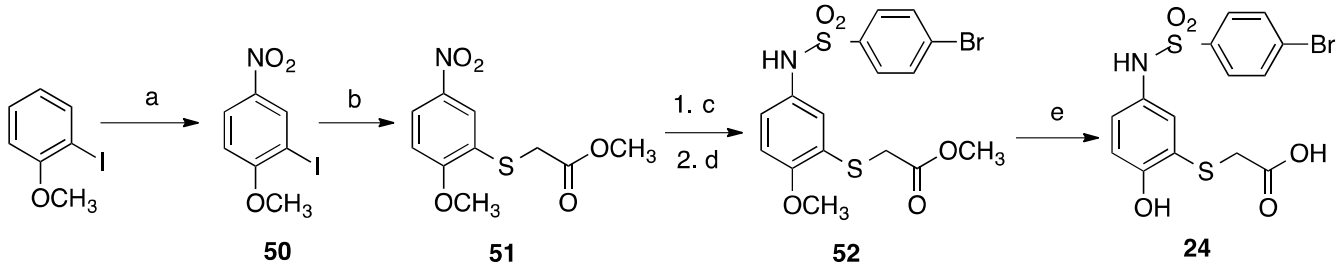


Figure S7. Induction of apoptosis by compound 37 in the HL-60 cell line with or without Z-VAD-FMK. Cells were treated for 20 h using indicated concentrations and apoptosis was assessed using Annexin-V and Propidium Iodide (PI) double staining and analyzed by flow cytometry. Early apoptotic cells were defined as Annexin-V positive/PI-negative, and late apoptotic cells as Annexin-V/PI-double positive.

Chemistry Materials and Methods.

All reactions were performed under anhydrous conditions. Reagents were used as supplied without further purification. Reactions were monitored by TLC using precoated silica gel 60 F254 plates. Silica gel chromatography was performed with silica gel (220–240 mesh) obtained from Silicycle. Purities of final compounds were assessed by analytical reverse-phase HPLC performed with one of the two methods. Method A: Agilent 1100 series with an Agilent Zorbax Eclipse Plus C18 (4.6 x 75 mm, 3.5µm particle size) column with the gradient 10% ACN/water (1 min), 10−90% ACN/water (6min), and 90% ACN/water (2 min) flow = 1 mL/min . Method B: Shimadzu system with a Restek Ultra C18 (4.6 x 150 mm, 5µm particle size) column with the gradient 50% ACN/water (5 min), 50−70% ACN/water (2min), and 70%-90% ACN/water (8 min) flow = 1 mL/min. Semi-preparative reverse-phase HPLC was performed on a Shimadzu system with a Restek Ultra C18 (21.2 x 150 mm, 5µm particle size) column. All NMR spectra were obtained in DMSO-d_6 or $CDCl_3$ and results were recorded at 400 MHz or 500 MHz on a Varian 400 or 500 instrument. Mass spectra were recorded on a Micromass LCT time-of-flight instrument utilizing electrospray ionization operating in positive-ion (ESI+) or negative-ion (ESI) modes where indicated. High resolution mass spectrometry (HRMS) analysis was performed on an Agilent Q-TOF system. All final compounds were purified to > 95% purity.

Scheme S1.[a] Synthesis of **24**



[a]Reagents and conditions: (a) HNO_3, AcOH, 0 °C to 50 °C, 1 h; (b) $HS(CH_2)_nCOOCH_3$, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, LiI, $ZnCl_2$, THF, 60 °C, 6 h; (c) Fe, AcOH, 70 °C, 1 h; (d) 4-bromobenzene sulfonyl chloride, pyridine, CH_2Cl_2, rt, overnight; (e) BBr_3, CH_2Cl_2, 0 °C to rt, 1 h.

2-Iodo-1-methoxy-4-nitrobenzene (50).[1] To a stirred solution of iodoanisole (1 mL, 7.7 mmol) in AcOH (2 mL) was added fuming nitric acid (0.8 mL, 17 mmol) dropwise at 0°C. The mixture was allowed to warm up to room temperature and then heated up to 50°C and stirred for 1h under nitrogen when the color of the mixture became dark red/orange. Solid precipitate formed on cooling which was collected by filtration. Solid was washed with a 4:1 mixture of EtOH:H_2O (10 mL) and dried on high vacuum to give **50** (1.2g, 56%) as a light orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.24 (d, *J* = 8.88 Hz, 1H), 6.85 (d, *J* = 8.88 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.01, 141.88, 135.10, 125.69, 109.56, 85.13, 57.13; ESI MS: m/z 279.8 $(M+H)^+$.

Methyl 2-((2-methoxy-5-nitrophenyl)thio)acetate (51). To a solution of Cs_2CO_3 (541 mg, 1.66 mmol) in dry THF (3 mL) under nitrogen was added methylthioglycolate (101 μL, 1.07 mmol). The mixture was stirred at room temperature for 10 min. At this time, a solution of $ZnCl_2$ (114 mg, 0.83 mmol) in dry THF (1 mL) was added and the mixture was stirred at room temperature for an additional 10 min. Meanwhile, in a separate flask $Pd(OAc)_2$ (16 mg, 0.07 mmol) and xantphos (34 mg, 0.06 mmol) were premixed in dry THF (2 mL) under nitrogen and stirred at room temperature for about 20 min. To the solution of thiol, Cs_2CO_3, and $ZnCl_2$ was added **50** (299 mg, 1.07 mmol), LiI (74 mg, 0.55 mmol) and premixed solution of the catalyst and ligand. The mixture was stirred at 60°C under nitrogen for 6.5 h. The reaction mixture was filtered to remove Cs_2CO_3 and silica was added to the mixture and the solvent was removed under reduced pressure. The adsorbed crude residue was purified by column chromatography (hexane/EtOAc 85:15) on silica gel to give **51** (178 mg, 63%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 2.70 Hz, 1H), 8.12 (dd, *J* = 2.70, 9.0 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 3.98 (s, 3H), 3.72 (s, 3H), 3.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.36, 161.83, 141.62, 125.41, 124.74, 124.07, 109.73, 56.65, 52.71, 33.99; ESI MS: m/z 279.9 $(M+Na)^+$.

Methyl 2-((5-(4-bromophenylsulfonamido)-2-methoxyphenyl)thio)acetate (52). To a suspension of iron powder (374 mg, 6.7 mmol) in glacial acetic acid (5 mL) was added **51** (171 mg, 0.66 mmol). The mixture was stirred at 70°C under nitrogen for 1 h when the mixture turned milky. The mixture was

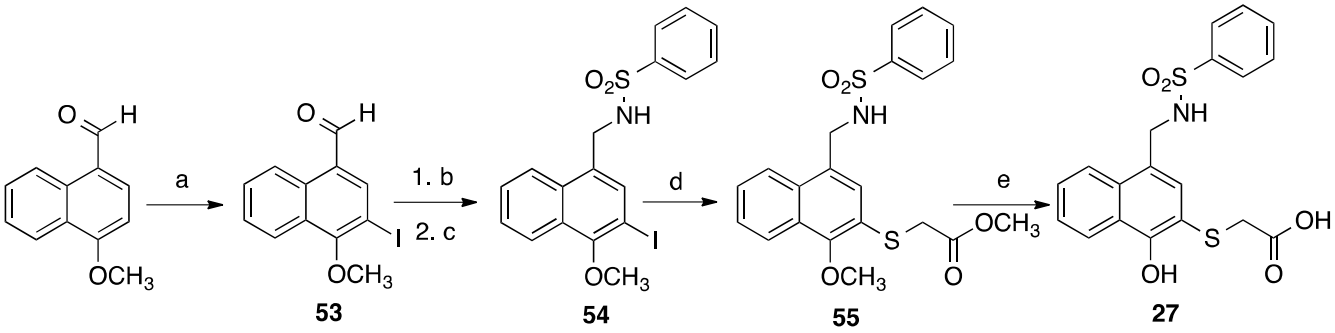
then diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL x 2) and brine (15 mL). Organic layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude as a purple oil. The crude was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 2.60 Hz, 1H), 6.64 (d, *J* = 8.58 Hz, 1H), 6.50 (dd, *J* = 2.60, 8.58 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.30, 150.99, 140.41, 123.27, 118.30, 115.00, 112.25, 56.34, 52.38, 34.91; ESI MS: m/z 228.0 $(M+H)^+$, 249.9 $(M+Na)^+$.

A solution of the crude amine dissolved in dry CH_2Cl_2 (4mL) was added to 4-bromobenzenesulfonyl chloride (184mg, 0.70 mmol). Addition of pyridine (0.11 mL, 1.36 mmol) was followed and the mixture was stirred at room temperature under nitrogen for 30 min when TLC did not show any starting material. The mixture was diluted with EtOAc (10 mL) and washed with H_2O (10 mL x 3) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Crude was triturated with cold CH_2Cl_2 to give **52** (122 mg, 41% over two steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.51 (m, 4H), 7.03 (d, *J* = 2.50 Hz, 1H), 6.89 (dd, *J* = 2.50, 8.70 Hz, 1H), 6.70 (d, *J* = 8.70 Hz, 1H), 6.58 (s, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.83, 156.05, 137.82, 132.26, 128.80, 128.72, 127.98, 126.06, 124.19, 123.85, 110.90, 56.04, 52.59, 34.33; ESI MS: m/z 445.9, 447.9 $(M+H)^+$, 467.8, 469.8 $(M+Na)^+$.

2-((5-(4-Bromophenylsulfonamido)-2-hydroxyphenyl)thio)acetic acid (24). To a stirred solution of **52** (82 mg, 0.18 mmol) suspended in dry CH_2Cl_2 (2.5 mL) was added BBr_3 (1 M in CH_2Cl_2, 0.55 mL, 0.55 mmol) dropwise at 0 ^{o}C under nitrogen. The mixture was allowed to warm up to room temperature. After 30 min stir, the starting material was entirely consumed and the product formed as determined by TLC and MS (ESI^-). The mixture was slowly added to a stirred solution of saturated aqueous NH_4Cl (20 mL) at 0^{o}C. The solution was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude was purified using a C_{18} reverse phase semi-preparative HPLC column with solvent

A (0.1% of TFA in water) and solvent B (0.1% of TFA in CH_3CN) as eluents to give **24** (22 mg**,** 29%) as a white solid. HPLC (Method B, t_R = 7.93 min), purity 97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 9.89 (s, 2H), 7.75 (d, *J* = 7.98 Hz, 2H), 7.58 (d, *J* = 7.98 Hz, 2H), 6.93 (s, 1H), 6.69-6.66 (m, 2H), 3.58 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.87, 153.27, 139.08, 132.62, 129.15, 126.97, 124.00, 122.38, 122.13, 115.50, 109.99, 34.26; ESI HRMS: m/z 415.9273 $(M-H)^-$.

Scheme S2.[a] Synthesis of **27**



[a]Reagents and conditions: (a) NIS, TFA, reflux, 8 h; (b) Benzenesulfonamide, Et_3N, $TiCl_4$, CH_2Cl_2, 0 °C to rt, 3 h; (c) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), 0 °C to rt, 45 min; (d) $HS(CH_2)_nCOOCH_3$, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, LiI, $ZnCl_2$, THF, 60 °C, 10 h; (e) BBr_3, CH_2Cl_2, 0 °C to rt, 1 h

3-Iodo-4-methoxy-1-naphthaldehyde (53). A mixture of commercially available 1-methoxy-4-naphthaldehyde (504 mg, 2.7 mmol), N-iodosuccinimide (704 mg, 3.1 mmol) in TFA (10 mL) was heated to reflux and stirred for 8 h under nitrogen. The reaction mixture was diluted with EtOAc (20 mL), washed with saturated aqueous $Na_2S_2O_3$ solution (20 mL), saturated aqueous $NaHCO_3$ (20 mL x 2), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and silica was added to filtrate and the solvent was removed under reduced pressure. The adsorbed crude residue was purified by flash column chromatography (hexane/EtOAc 96:4) on silica gel to give **53** (648 mg, 77%) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 9.22 (d, *J* = 8.48 Hz, 1H), 8.26 (s, 1H), 8.18 (d, *J* = 8.48 Hz, 1H), 7.71 (t, *J* = 7.63 Hz, 1H), 7.62 (t, *J* = 7.63 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.28, 162.11, 146.45, 131.97, 129.69, 129.44, 128.64, 127.75, 125.41, 122.73, 85.22, 62.06; ESI MS: m/z 313.0 $(M+H)^+$.

***N*-((3-Iodo-4-methoxynaphthalen-1-yl)methyl)benzenesulfonamide (54).** Synthesized using a reported procedure with modification.[2] To a solution of **53** (318 mg, 1 mmol) in dry CH_2Cl_2 (3.5 mL), benzenesulfonamide (209 mg, 1.3 mmol) and triethylamine (0.43 mL, 3.1 mmol) were successive added. After 5 min stir at room temperature, the reaction mixture was cooled down to 0 ^oC, and $TiCl_4$ (0.14 mL, 1.3 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was continued to stir at 0 ^oC for 10 min before warming up to room temperature. The reaction progress was monitoring by TLC. After 3h, the mixture was quenched saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and solvent was removed under reduced pressure. The crude product was used for the next step without further purification.

The previous crude product was dissolved in a mixture of MeOH (3mL) and CH_2Cl_2 (3mL). After cooling to 0°C, $NaBH_4$ (39mg, 1 mmol) was added in small portions, then brought to room temperature and stirred for 45 min. The mixture was quenched with H_2O, extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 85:15) on silica gel to give **54** (279 mg, 60% over two steps) as a yellow oil which solidified. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.61-7.56 (m, 2H), 7.55-7.47 (m, 5H), 4.48 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.92, 139.49, 136.02, 132.85, 132.29, 129.22, 129.13, 128.40, 127.47, 127.11, 126.88, 123.90, 122.97, 85.83, 61.65, 44.62; ESI MS: m/z 476.0 $(M+Na)^+$.

Methyl 2-((1-methoxy-4-(phenylsulfonamidomethyl)naphthalen-2-yl)thio)acetate (55). To a solution of Cs_2CO_3 (160 g, 0.49 mmol) in dry THF (2 mL) under nitrogen was added methylthioglycolate (31 μL, 0.33 mmol, 95% purity grade). The mixture was stirred at room temperature for 10 min. At this time, a solution of $ZnCl_2$ (29 mg, 0.21 mmol) in dry THF (1 mL) was added and the mixture was stirred at room temperature for an additional 10 min. Meanwhile, in a

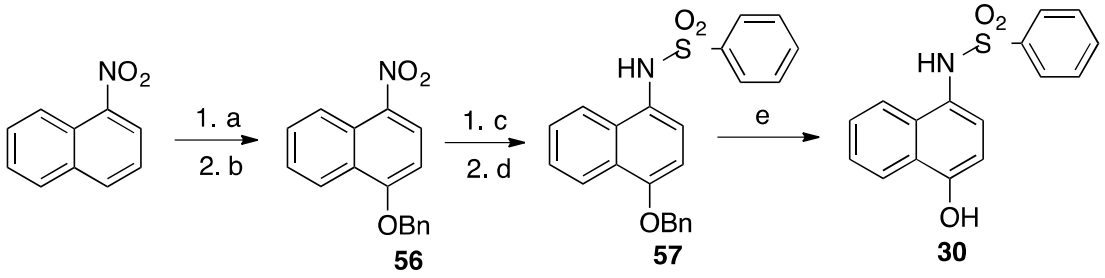
separate flask $Pd(OAc)_2$ (4 mg, 0.02 mmol) and xantphos (10 mg, 0.02 mmol) were premixed in dry THF (1 mL) under nitrogen and stirred at room temperature for about 20 min. To the solution of thiol, Cs_2CO_3, and $ZnCl_2$ was added **54** (151 mg, 0.33 mmol), LiI (20 mg, 0.15 mmol) and premixed solution of the catalyst and ligand successively. The mixture was stirred at 60°C under nitrogen for 10 h. The reaction mixture was filtered to remove Cs_2CO_3 and silica was added to the mixture and the solvent was removed under reduced pressure. The adsorbed crude residue was purified by column chromatography (hexane/EtOAc 7:3) on silica gel to give **55** (76 mg, 53%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.18 Hz, 1H), 7.83 (t, *J* = 7.87 Hz, 3H), 7.55-7.48 (m, 2H), 7.48 -7.39 (m, 4H), 7.27 (s, 1H), 4.45 (d, *J* = 5.95 Hz, 2H), 3.91 (s, 3H), 3.65 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.14, 155.33, 139.57, 132.66, 131.63, 129.02, 128.44, 128.17, 127.06, 127.02, 126.62, 123.71, 122.53, 122.48, 61.34, 52.59, 45.00, 35.20; ESI MS: m/z 454.1 $(M+Na)^+$.

2-((1-Hydroxy-4-(phenylsulfonamidomethyl)naphthalen-2-yl)thio)acetic acid (27). To a stirred solution of **55** (76 mg, 0.18 mmol) suspended in dry CH_2Cl_2 (2 mL) was added BBr_3 (1 M in CH_2Cl_2, 0.54 mL, 0.54 mmol) dropwise at 0°C under nitrogen. The mixture was allowed to warm up to room temperature. After 1hr stir, the starting material was entirely consumed and the product formed as determined by TLC and MS (ESI^-). The mixture was slowly added to a stirred solution of saturated aqueous NH_4Cl (20 mL) at 0°C. The solution was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude was purified using a C_{18} reverse phase semipreparative HPLC column with solvent A (0.1% of TFA in water) and solvent B (0.1% of TFA in CH_3CN) as eluents to give **27** (12.5 mg**,** 18%) as a white/tan solid. HPLC (Method A, t_R = 6.47 min), purity 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 9.64 (s, 1H), 8.16 (d, *J* = 7.82 Hz, 1H), 8.04 (t, *J* = 5.47 Hz, 1H), 7.92 (d, *J* = 7.82 Hz, 1H), 7.79 (d, *J* = 7.22 Hz, 2H), 7.63-7.57 (m, 1H), 7.57-7.47 (m, 4H), 7.32 (s, 1H), 4.24 (d, *J* = 5.75 Hz, 2H), 3.61 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.84, 153.54, 140.78, 132.75, 132.24, 132.00, 129.53, 127.37, 126.93, 125.87, 125.44, 124.59, 124.13, 123.24, 112.76, 44.59,

37.47; ESI HRMS: m/z 402.0475 $(M-H)^-$.

Scheme S3.[a] Synthesis of **30**

[a]Reagents and conditions: (a) cumene hydroperoxide, KOH, DMSO/H_2O (3:1), 0 ^oC to rt, 2 h; (b) benzyl bromide, NaH, DMF/THF (2:1), 0 ^oC to rt, 2-3 h; (c) Fe, AcOH, 70 ^oC, 1 h; (d) benzenesulfonyl chloride, pyridine, CH_2Cl_2, rt, overnight; (e) Pd/C, H_2 30 psi, MeOH, rt, overnight.



1-(benzyloxy)-4-nitronaphthalene (56).[3] A stirred solution of 1-nitronaphthalene (1.4 g, 8 mmole) in DMSO (30 mL) was cooled down to 0^oC. KOH (1.8 g, 32 mmole) dissolved in H_2O (10 mL) was added dropwise. Color of the solution changed from yellow to dark green. Addition of cumene hydroperoxide (technical grade, 1.5mL, 8 mmole) dissolved in DMSO (4mL) via syringe was followed at 0^oC to provide a dark brown solution which was stirred for 2 h at room temperature. Saturated aqueous $Na_2S_2O_3$ solution (10mL) was added and the mixture was stirred for another 15 min at room temperature. The mixture was diluted with H_2O (10 mL) and washed with EtOAc (30 mL x 2). Aqueous phase was acidified with 1N HCl and extracted with EtOAc (30 mL x 3). The organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to provide a black oil which was purified by flash column chromatography (hexane/EtOAc 3:2) on silica gel to give 4-nitronaphthalen-1-ol (1.03g, 67%) as a yellow/brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.64 (d, J = 8.78 Hz, 1H), 8.38 (d, J = 9.34 Hz, 1H), 8.30 (d, J = 8.16 Hz, 1H), 7.77 (t, J = 7.62 Hz, 1H), 7.61 (t, J = 7.62 Hz, 1H), 6.95 (d, J = 8.16 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.80, 137.07, 130.79, 128.95, 127.23, 126.57, 124.70, 123.54, 123.26, 107.19; ESI MS: m/z 190.0 $(M+H)^+$.

To a stirred solution of 4-nitronaphthalen-1-ol (505 mg, 2.7 mmol) in dry DMF (3 mL) was added NaH (60 wt% dispersion in oil, 193 mg, 4.8 mmol) suspended in dry DMF (3 mL) at 0°C. Benzyl bromide (0.46 mL, 3.9 mmol) in dry THF (3 mL) was added next at 0°C. The mixture was warmed up to room temperature and stirred under nitrogen for 2-3 h. Mixture was diluted with EtOAc (10 mL), washed with H_2O (10 mL x 4) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by column chromatography on silica to give **56** (465 mg, 64%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 9.40 Hz, 1H), 8.43 (d, *J* = 7.70 Hz, 1H), 8.36 (d, *J* = 7.70 Hz, 1H), 7.73 (t, *J* = 7.70 Hz, 1H), 7.58 (t, *J* = 7.70 Hz, 1H), 7.53-7.47 (m, 2H), 7.46-7.35 (m, 3H), 6.88 (d, *J* = 9.40 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.50, 139.36, 135.54, 130.06, 128.81, 128.50, 127.46, 127.01, 126.92, 126.60, 125.76, 123.47, 122.88, 103.15, 70.91; ESI MS: m/z 280.0 $(M+H)^+$, 302.0 $(M+Na)^+$.

***N*-(4-(benzyloxy)naphthalen-1-yl)benzenesulfonamide (57).** To a suspension of iron powder (601 mg, 10.7 mmol) in glacial acetic acid (6 mL) was added **56** (301 mg, 1.08 mmol). The mixture was stirred at 70 °C under nitrogen for 1.5 h when the mixture turned milky. The mixture was then diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL x 2) and brine (15 mL). Organic layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude as a purple oil. The crude was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.35 (m, 1H), 7.87-7.80 (m, 1H), 7.55-7.49 (m, 4H), 7.42 (t, *J* = 7.36 Hz, 2H), 7.39-7.31 (m, 3H), 6.78-6.69 (m, 2H), 5.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.64, 137.56, 134.70, 128.53, 127.81, 127.38, 126.40, 125.83, 125.46, 125.39, 122.79, 120.98, 110.41, 106.12, 70.56; ESI MS: m/z 250.0 $(M+H)^+$.

A solution of the crude amine dissolved in dry CH_2Cl_2 (5mL) was added to benzenesulfonyl chloride (218mg, 1.2 mmol). Addition of pyridine (0.18 mL, 2.2 mmol) was followed and the mixture was stirred at room temperature under nitrogen overnight. The mixture was diluted with EtOAc (10 mL) and washed with H_2O (10 mL x 3) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered

and the solvent was removed under reduced pressure. Crude was purified by flash column chromatography on silica gel to give **57** (236 mg, 55% over two steps) as a brown oil which solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.94 Hz, 1H), 7.75-7.66 (m, 3H), 7.49 (t, *J* = 6.20 Hz, 3H), 7.46-7.39 (m, 4H), 7.38-7.32 (m, 3H), 7.20 (d, *J* = 8.22 Hz, 1H), 6.75 (d, *J* = 8.22 Hz, 1H), 6.60 (s, 1H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.17, 139.41, 136.59, 132.70, 131.08, 128.83, 128.60, 128.07, 127.38, 127.30, 127.14, 126.13, 125.68, 125.61, 123.75, 122.58, 121.75, 104.42, 70.24; ESI MS: m/z 389.9 $(M+H)^+$, 411.9 $(M+Na)^+$.

***N*-(4-hydroxynaphthalen-1-yl)benzenesulfonamide (30).** A stirred solution of **57** (200 mg, 0.51 mmol) in MeOH (15 mL) was hydrogenated in the presence of 10% Pd/C (163 mg) at room temperature and under 30 psi of H_2 for 6 h. The suspension was filtered through a pad of celite. The filtrate diluted with EtOAc (20 mL) was washed with saturated aqueous NH_4Cl (20 mL x 2). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude was purified using a C_{18} reverse phase semipreparative HPLC column with solvent A (0.1% of TFA in water) and solvent B (0.1% of TFA in CH_3CN) as eluents to give **30** (32 mg**,** 21%) as a white solid. HPLC (Method B, t_R = 4.42 min), purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, *J* = 7.83 Hz, 1H), 7.86 (d, *J* = 7.83 Hz, 1H), 7.63 (d, *J* = 7.58 Hz, 2H), 7.60-7.53 (m, 1H), 7.48 (t, *J* = 7.37 Hz, 2H), 7.38 (p, *J* = 6.69 Hz, 2H), 6.85 (d, *J* = 7.98 Hz, 1H), 6.71 (d, *J* = 7.98 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.24, 139.13, 131.28, 130.38, 127.80, 125.58, 124.92, 124.39, 123.71, 123.55, 122.05, 122.01, 120.89, 106.09; ESI HRMS: m/z 298.0547 $(M-H)^-$.

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