Supporting Information

"Synthesis and Evaluation of Non-covalent Naphthalene-Based KEAP1-NRF2 Inhibitors"

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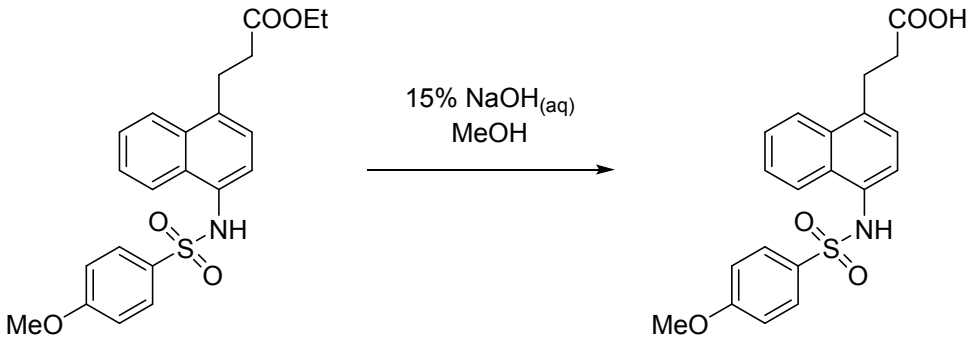
1. General Considerations

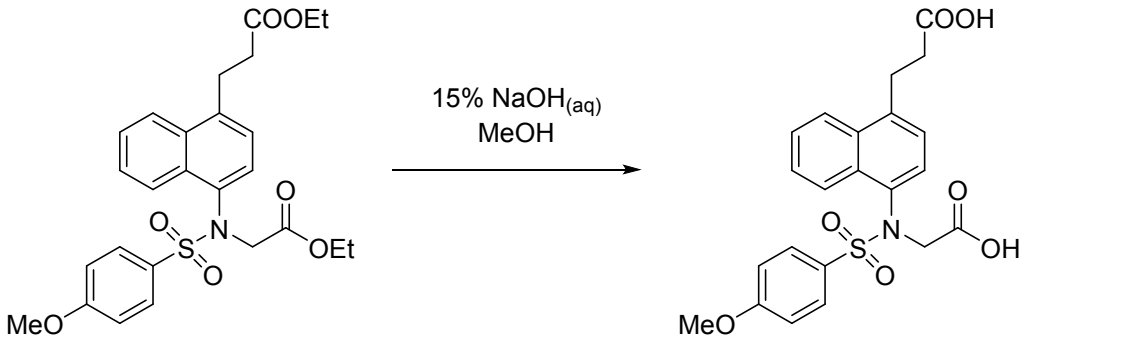
All starting materials and solvents were purchased from Sigma-Aldrich, Acros Organics, Fischer Scientific, ArkPharm, TCI America, or Matrix Scientific and used without further purification. Reactions were run without taking precautions to exclude air or moisture, unless otherwise noted. Known compounds **2** (1-nitro-4-methyl naphthalene), 1,4-bis(bromomethyl)naphthalene and 4-methoxy-*N*-(4-nitronaphthalen-1-yl)benzenesulfonamide were synthesized according to reported procedures, and the isolated products matched the literature spectra.[1-3] Compound identities were confirmed by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and high resolution mass spectrometry (HRMS). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz or Bruker 900 MHz spectrometer using the corresponding residual solvent peak ($CDCl_3$, ^{1}H δ = 7.26 and ^{13}C δ = 77.2; CD_3COCD_3, ^{1}H δ = 2.05 and ^{13}C δ = 29.2; CD_3OD, ^{1}H δ = 3.31 and ^{13}C = 49.2; CD_3CN, ^{1}H δ = 1.96 and ^{13}C δ = 118.3; DMSO-d_6, ^{1}H δ = 2.50 and ^{13}C δ = 39.5)) as an internal standard. HRMS spectra were recorded on a Shimadzu LCMS-IT-TOF, and the molecular weight of the compounds was within 0.05% of calculated values. Purity of each of the final, tested compounds was determined by HPLC on a Shimadzu LC-20AB (Solvent system: 0-2 minutes isocratic 30% MeCN/70% H_2O (+0.1 formic acid), 2-7 minutes gradient from 30% MeCN/70% H_2O to 95% MeCN/5% H_2O (+0.1% formic acid), 7-9 minutes 95% MeCN/5% H_2O (+0.1% formic acid); Column: Shimadzu C18, 50 µm, 50 × 4.6 mm) and was ≥90% (UV, 254 nm) unless otherwise noted. Flash chromatography was performed using silica gel (230–400 mesh). Reactions were monitored by thin-layer chromatography (TLC) on silica gel GHLF plates (250 µm, Macherey–Nagel, Inc., Bethlehem, PA). Optical rotations were determined on a Perkin-Elmer 241 Polarimeter at 589 nm. %ee was determined by chiral HPLC on a Shimadzu LC-20AT (Solvent system: isocratic 75% hexane/25% ethanol (+0.1% TFA); Column: Regis Technologies RegisPack, 5 µm, 25 cm × 4.6 mm)



3-(4-((4-methoxyphenyl)sulfonamido) naphthalen-1-yl)propanoic acid

2. 3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)propanoic acid (3)

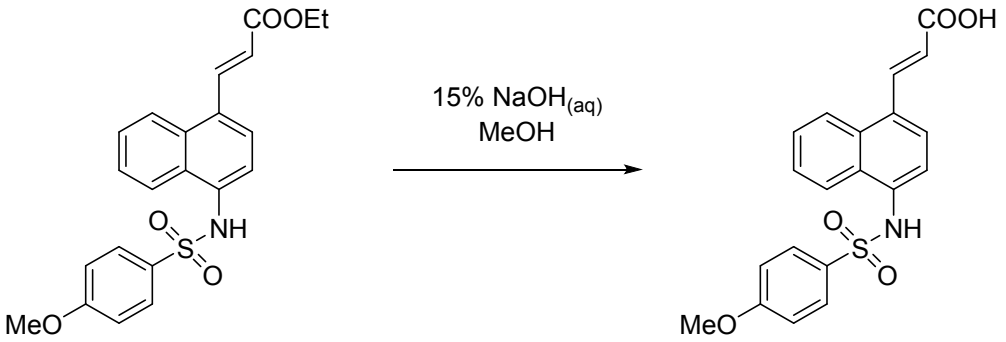
In a 20 mL screw-cap vial, ethyl 3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)propanoate (**8**, 50 mg, 1.21 mmol) was dissolved in MeOH (3 mL), and 15% $NaOH_{(aq)}$ (1 mL) was added. The reaction was stirred at room temperature for 4 hours. Upon completion methanol was removed under reduced pressure, and the residue was diluted with 10 mL water. The solution was acidified with 2 N $HCl_{(aq)}$ to pH 4. The resulting suspension was extracted with EtOAc (3 × 10 mL), and the combined organics were washed with brine (20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to afford 37 mg (79% yield) of (**3**) as an off-white solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ = 10.67 (br. s, 1 H), 8.78 (s, 1 H), 8.20 (d, *J* = 8.3 Hz, 1 H), 8.09 (d, *J* = 8.6 Hz, 1 H), 7.71 – 7.63 (m, 2 H), 7.58 – 7.50 (m, 1 H), 7.49 – 7.42 (m, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.00 – 6.93 (m, 2 H), 3.81 (s, 3 H), 3.36 (t, *J* = 7.8 Hz, 2 H), 2.77 – 2.68 (m, 2 H); ^{13}C NMR (101 MHz, CD_3COCD_3) δ = 174.1, 163.9, 137.0, 133.3, 133.1, 132.6, 131.3, 130.2, 127.2, 126.6, 126.4, 124.8, 124.7, 124.2, 114.9, 56.1, 35.1, 28.5. HRMS-ESI (+) (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{19}NO_5S$, 386.1062; found, 386.1046.



3-(4-((*N*-(carboxymethyl)-4-methoxyphenyl) sulfonamido)naphthalen-1-yl)propanoic acid

3. 3-(4-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)naphthalen-1-yl)propanoic acid (4)

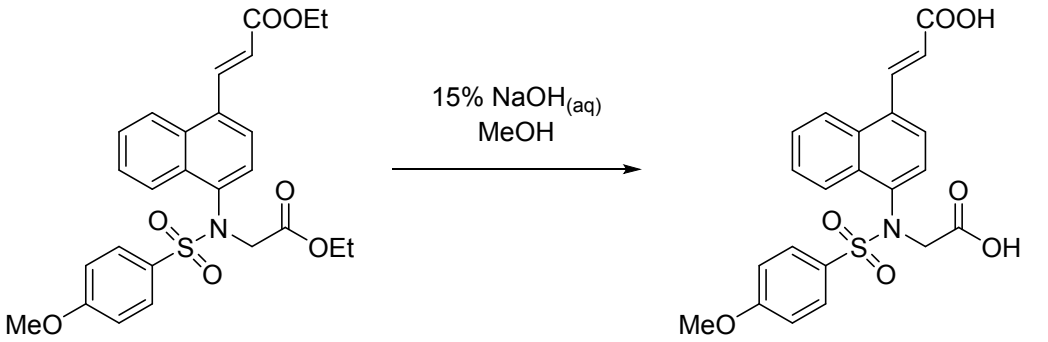
In a 20 mL screw-cap vial, ethyl 3-(4-((N-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)naphthalen-1-yl)propanoate (**24**, 114 mg, 0.23 mmol) was dissolved in MeOH (4 mL), and 15% $NaOH_{(aq)}$ (0.5 mL) was added. The reaction was stirred at room temperature for 4 hours. Upon completion methanol was removed under reduced pressure, and the residue was diluted with 10 mL water. The solution was acidified with 2 N $HCl_{(aq)}$ to pH 4. The resulting suspension was extracted with EtOAc (3 × 10 mL), and the combined organics were washed with brine (20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to afford 101 mg (99.8% yield) of (**4**) as an off-white solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ = 10.88 (br. s., 2 H), 8.28 (dd, *J* = 8.3, 0.7 Hz, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 7.69 – 7.64 (m, 2 H), 7.61 – 7.55 (m, 1 H), 7.55 – 7.49 (m, 1 H), 7.37 – 7.32 (m, 1 H), 7.25 (d, *J* = 7.6 Hz, 1 H), 7.10 – 6.99 (m, 2 H), 4.69 – 4.60 (m, 1 H), 4.43 (d, *J* = 17.8 Hz, 1 H), 3.89 (s, 3 H), 3.44 – 3.37 (m, 2 H), 2.80 – 2.72 (m, 2 H); ^{13}C NMR (101 MHz, CD_3COCD_3) δ = 174.0, 170.5, 164.2, 139.3, 136.7, 133.7, 133.4, 131.9, 131.1, 128.6, 127.4, 127.0, 126.2, 126.2, 124.6, 114.9, 56.2, 53.8, 35.0, 28.6; HRMS-ESI (+) (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{21}NO_7S$, 444.1117; found, 444.1127.



(*E*)-3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylic acid

4. (*E*)-3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylic acid (5)

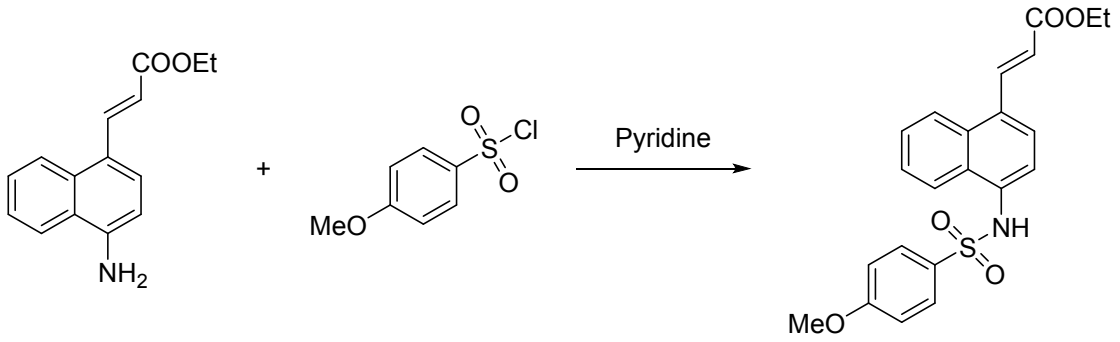
In a 20 mL screw-cap vial, ethyl (*E*)-3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylate (**7**, 50 mg, 0.12 mmol) was dissolved in MeOH (3 mL), and 15% $NaOH_{(aq)}$ (0.5 mL) was added. The reaction was stirred at room temperature for 4 hours. Upon completion, methanol was removed under reduced pressure, and the residue was diluted with 10 mL water. The solution was acidified with 2 N HCl(aq) to pH 4. The resulting suspension was extracted with EtOAc (3 × 10 mL), and the combined organics were washed with brine (20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to afford 37 mg (79% yield) of (**5**) as an off-white solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ = 8.44 (d, *J* = 15.9 Hz, 1 H), 8.23 (t, *J* = 8.6 Hz, 2 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 7.77 – 7.69 (m, 2 H), 7.62 (dt, *J* = 7.6, 1.1 Hz, 1 H), 7.57 – 7.49 (m, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.03 – 6.93 (m, 2 H), 6.57 (d, *J* = 15.7 Hz, 1 H), 3.82 (s, 3 H); ^{13}C NMR (101 MHz, CD_3COCD_3) δ = 167.9, 164.1, 141.4, 135.9, 133.1, 132.9, 130.9, 130.3, 130.1, 128.1, 127.2, 125.8, 124.5, 122.8, 122.3, 115.1, 101.0, 56.1; HRMS-ESI (+) (*m*/*z*): [M + H]+ calcd for $C_{20}H_{17}NO_5S$, 384.0906; found, 384.0900.



(*E*)-3-(4-((*N*-(carboxymethyl)-4-methoxyphenyl)sulfonamido) naphthalen-1-yl)acrylic acid

5. (*E*)-3-(4-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylic acid (6)

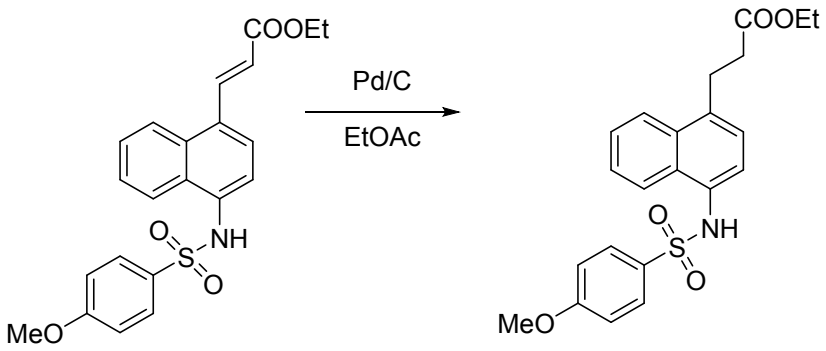
In a 20 mL screw-cap vial, ethyl (*E*)-3-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylate (**25**, 64 mg, 0.13 mmol) was dissolved in MeOH (3 mL) and 15% $NaOH_{(aq)}$ (0.5 mL) was added. The reaction was stirred at room temperature for 4 hours. Upon completion methanol was removed under reduced pressure, and the residue was diluted with 10 mL water. The solution was acidified with 2 N $HCl_{(aq)}$ to pH 4. The resulting suspension was extracted with EtOAc (3 × 10 mL), and the combined organics were washed with brine (20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to afford 55 mg (97% yield) of (**6**) as an off-white solid. ^{1}H NMR (400 MHz, CD_3COCD_3) δ = 8.48 (d, *J* = 15.9 Hz, 1 H), 8.33 (d, *J* = 8.6 Hz, 0 H), 8.24 (d, *J* = 8.1 Hz, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.72 – 7.63 (m, 3 H), 7.62 – 7.56 (m, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.11 – 7.05 (m, 2 H), 6.60 (d, *J* = 15.9 Hz, 1 H), 4.66 (d, *J* = 17.8 Hz, 1 H), 4.48 (d, *J* = 17.8 Hz, 1 H), 3.91 (s, 3 H); ^{13}C NMR (101 MHz, CD_3COCD_3) δ = 170.4, 167.5, 164.4, 141.6, 139.7, 133.6, 133.4, 133.4, 131.6, 131.1, 128.6, 128.2, 127.6, 126.3, 125.5, 124.3, 123.2, 115.1, 56.3, 53.8; HRMS-ESI (+) (*m*/*z*): [M + H]+ calcd for $C_{22}H_{19}NO_7S$, 442.0960; found, 442.0966.



Ethyl (*E*)-3-(4-((4-methoxyphenyl)sulfonamido) naphthalen-1-yl)acrylate

6. Ethyl (*E*)-3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylate (7)

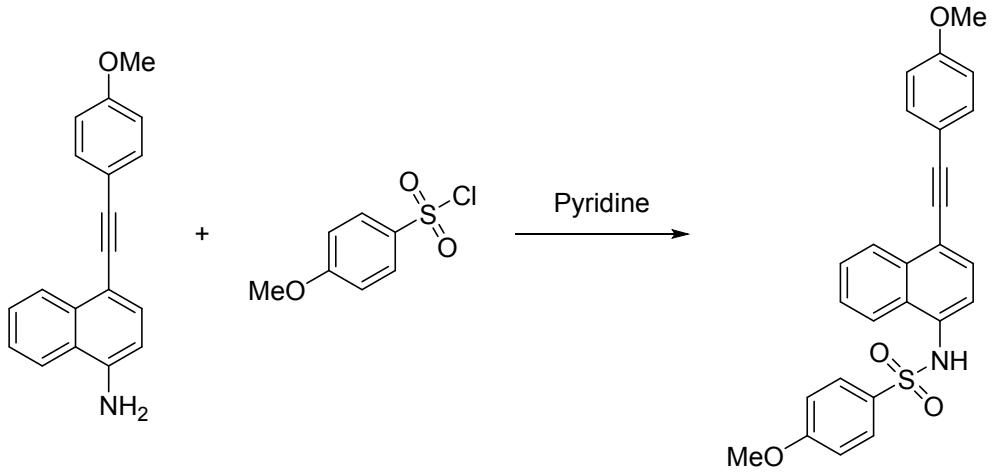
In a 10 mL round-bottom flask, ethyl (*E*)-3-(4-aminonaphthalen-1-yl)acrylate (**26,** 80 mg, 0.33 mmol) was dissolved in pyridine (1 mL), and 4-methoxybenzenesulfonyl chloride (83 mg,0.40 mmol) was added to the resulting solution. The reaction was stirred overnight. No starting material was present (LC-MS), and the reaction was quenched with 2 N HCl (10 mL). The mixture was extracted with EtOAc (2 × 20 mL), the combined organics were washed with 2N HCl (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated to yield 116 mg (85% yield) of (**7**) as a light brown solid. The product did not require further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.42 (d, *J* = 15.9 Hz, 1 H), 8.14 (d, *J* = 8.3 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.73 (d, *J* = 9.0 Hz, 2 H), 7.63 (d, *J* = 7.8 Hz, 1 H), 7.57 – 7.42 (m, 3 H), 7.40 (s, 1 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.46 (d, *J* = 15.9 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 3.81 – 3.76 (m, 3 H), 1.42 – 1.33 (m, 3 H).



Ethyl 3-(4-((4-methoxyphenyl)sulfonamido) naphthalen-1-yl)propanoate

7. Ethyl 3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)propanoate (8)

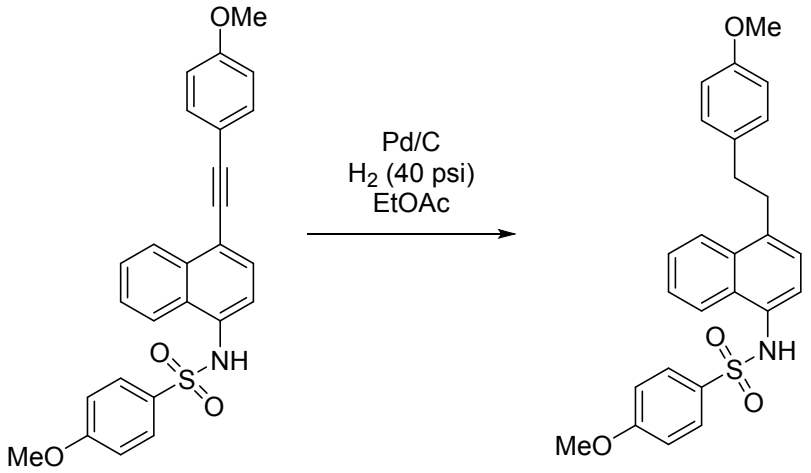
In a 500 mL Parr flask, (*E*)-3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylate (**7**) (114 g, 0.28 mmol) was placed and dissolved in EtOAc (3 mL). 10% Pd/C (18 mg) was added, and the flask was purged with argon. The flask was placed on a Parr shaker apparatus, purged with H_2, and shaken overnight under an atmosphere of H_2 (40 psi). The crude reaction mixture was filtered through a pad of celite, and the pad was washed with EtOAc. The solution was concentrated under reduced pressure to yield an off-white solid. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 30:70) to yield 114 mg (99.5% yield) of (**8**) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 – 7.97 (m, 1 H), 7.94 (td, *J* = 8.3, 0.9 Hz, 1 H), 7.71 – 7.65 (m, 2 H), 7.54 – 7.48 (m, 1 H), 7.47 – 7.41 (m, 1 H), 7.26 – 7.20 (m, 2 H), 6.98 (s, 1 H), 6.86 – 6.80 (m, 2 H), 4.15 (q, *J* = 7.3 Hz, 2 H), 3.80 (s, 3 H), 3.41 – 3.31 (m, 2 H), 2.75 - 2.67 (m, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H).



4-methoxy-*N*-(4-((4-methoxyphenyl)ethynyl) naphthalen-1-yl)benzenesulfonamide

8. 4-Methoxy-*N*-(4-((4-methoxyphenyl)ethynyl)naphthalen-1-yl)benzenesulfonamide (9)

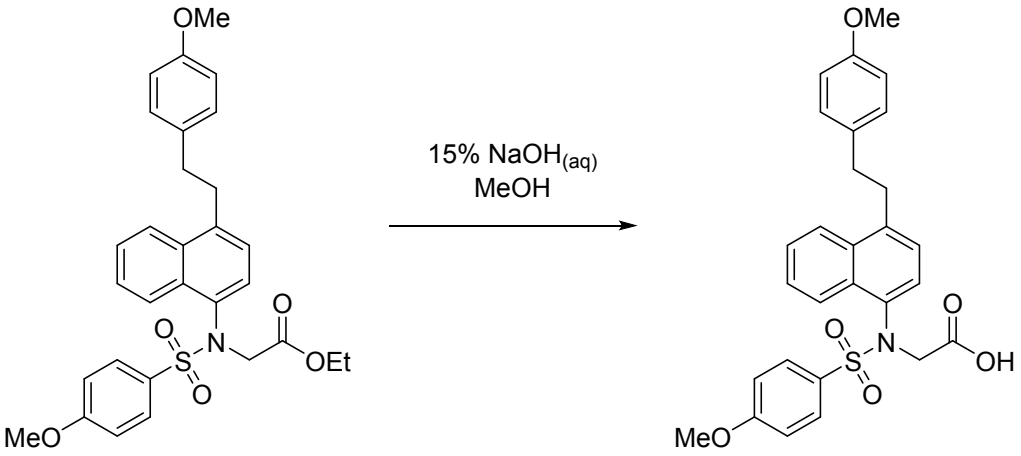
In a 4 mL screw-cap vial, 4-((4-methoxyphenyl)ethynyl)naphthalen-1-amine (**27,** 58 mg, 0.21 mmol) was dissolved in pyridine (0.75 mL), and 4-methoxybenzenesulfonyl chloride (49.6 mg, 0.24 mmol) was added to the resulting solution. The reaction was stirred overnight. No starting material was present by LC-MS, and the reaction was quenched with 2 N HCl (10 mL). The mixture was extracted with EtOAc (2 × 20 mL), and the combined organics were washed with 2N HCl (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated to yield 93 mg (99% yield) of (**9**) as a light-brown solid. The product did not require further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.45 – 8.39 (m, 1 H), 7.83 (d, *J* = 8.3 Hz, 1 H), 7.72 – 7.66 (m, 2 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.60 – 7.54 (m, 3 H), 7.52 – 7.46 (m, 1 H), 7.41 (d, *J* = 7.8 Hz, 1 H), 6.98 (s, 1 H), 6.95 – 6.90 (m, 2 H), 6.87 – 6.78 (m, 2 H), 3.86 (s, 3 H), 3.79 (s, 3 H).



4-methoxy-*N*-(4-(4-methoxyphenethyl) naphthalen-1-yl)benzenesulfonamide

9. 4-Methoxy-*N*-(4-(4-methoxyphenethyl)naphthalen-1-yl)benzenesulfonamide (10)

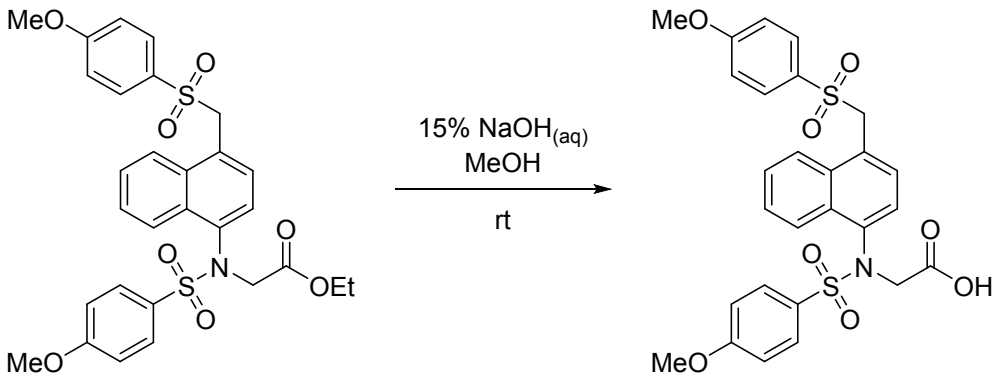
In a 500 mL Parr flask, 4-methoxy-*N*-(4-((4-methoxyphenyl)ethynyl)naphthalen-1-yl)benzenesulfonamide (**9**, 20 mg, 0.045 mmol) was placed and dissolved in EtOAc (3 mL). 10% Pd/C (4 mg) was added, and the flask was purged with argon. The flask was placed on a Parr shaker apparatus, purged with H_2, and shaken overnight under an atmosphere of H_2 (40 PSI). The crude reaction mixture was filtered through a pad of celite, and the pad was washed with EtOAc. The solution was concentrated under reduced pressure to yield 20 mg of an off-white solid. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 30:70) to yield 18 mg (89% yield) of (**10**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 – 8.02 (m, 1 H), 7.96 – 7.91 (m, 1 H), 7.70 – 7.64 (m, 2 H), 7.56 – 7.49 (m, 1 H), 7.49 – 7.43 (m, 1 H), 7.22 – 7.18 (m, 1 H), 7.16 – 7.11 (m, 1 H), 7.12 – 7.06 (m, 2 H), 6.88 – 6.80 (m, 4 H), 6.75 (s, 1 H), 3.81 (s, 3 H), 3.81 (s, 3 H), 3.34 – 3.24 (m, 2 H), 3.02 – 2.91 (m, 2 H).



***N*-(4-(4-methoxyphenethyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycine**

10. *N*-(4-(4-Methoxyphenethyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (11)

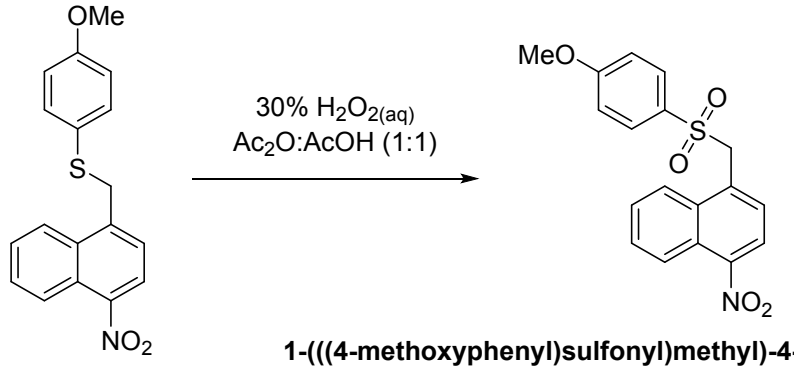
In a 20 mL screw-cap vial, ethyl *N*-(4-(4-methoxyphenethyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (**28**, 35 mg, 0.066 mmol) was dissolved in MeOH (3 mL), and 15% $NaOH_{(aq)}$ (0.5 mL) was added. The reaction was stirred at room temperature for 4 hours. Once the reaction was complete by TLC, methanol was removed under reduced pressure. The residual suspension was diluted with water (10 mL) and acidified with 2 N $HCl_{(aq)}$ to pH 2. The resulting suspension was extracted with EtOAc (3 × 10 mL), and the combined organics were washed with brine (20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to afford an off-white solid. The compound was purified by preparative HPLC (C18; MeCN/H_2O + 0.1% FA, 60:40 to 95:5) to yield 22 mg (66% yield) of (**11**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 – 8.03 (m, 2 H), 7.67 – 7.60 (m, 2 H), 7.60 – 7.47 (m, 2 H), 7.19 – 7.09 (m, 4 H), 6.95 – 6.80 (m, 4 H), 4.71 (d, *J* = 18.3 Hz, 1 H), 4.32 (d, *J* = 18.1 Hz, 1 H), 3.90 – 3.84 (m, 3 H), 3.84 – 3.76 (m, 3 H), 3.41 – 3.23 (m, 2 H), 2.99 (t, *J* = 8.1 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.1, 163.2, 157.9, 139.7, 134.5, 133.7, 132.9, 131.8, 130.4, 130.2, 129.3, 127.9, 126.5, 126.4, 125.4, 124.3, 124.1, 113.9, 113.8, 55.6, 55.3, 53.0, 35.8, 35.3; HRMS-ESI (+) (*m*/*z*): $[M + Na]^+$ calcd for $C_{28}H_{27}NO_6S$, 528.1457; found, 528.1444.



***N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)glycine**

11. *N*-((4-Methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)glycine (12)

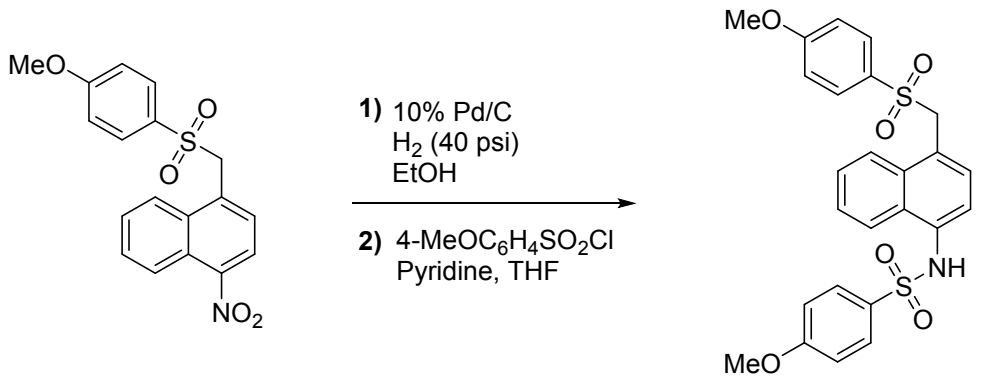
In a 20 mL screw-cap vial, ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)glycinate (**29**, 30 mg, 0.051 mmol) was dissolved in methanol (4 mL), and 15% $NaOH_{(aq)}$ (0.5 mL) was added. The reaction was stirred at room temperature for 4 hours. Upon completion the methanol was removed under reduced pressure, and the residual liquid was diluted with water (10 mL). The solution was adjusted to pH 4, and a white precipitate formed. The suspension was extracted with EtOAc (3 × 10 mL), washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over Na_2SO_4, and concentrated to yield 20 mg (70% yield) of (**12**) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.80 (br. s., 1 H), 8.23 – 8.16 (m, 1 H), 8.15 – 8.08 (m, 1 H), 7.63 – 7.55 (m, 4 H), 7.54 – 7.46 (m, 2 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 7.12 – 7.00 (m, 5 H), 5.12 (s, 2 H), 4.48 – 4.31 (m, 2 H), 3.84 (d, *J* = 9.3 Hz, 6 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.8, 163.3, 162.8, 137.2, 133.0, 132.0, 130.4, 130.1, 130.0, 129.9, 129.5, 126.6, 126.3, 126.2, 126.1, 125.1, 124.6, 114.3, 114.2, 58.1, 55.8, 55.7, 53.2; HRMS-ESI (+) (*m*/*z*): $[M + Na]^+$ calcd for $C_{27}H_{25}NO_8S_2$, 578.0919; found, 578.0923.



1-(((4-methoxyphenyl)sulfonyl)methyl)-4-nitronaphthalene

12. 1-(((4-Methoxyphenyl)sulfonyl)methyl)-4-nitronaphthalene (14)

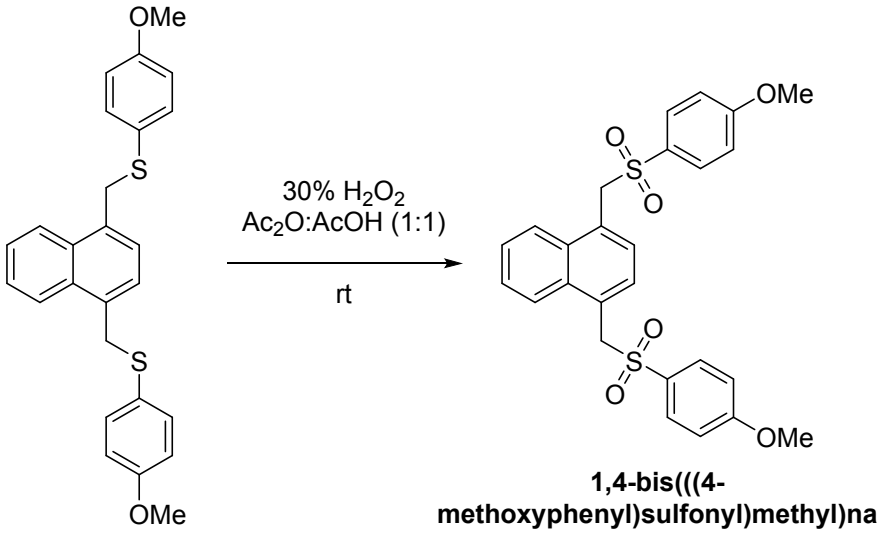
In a 3-neck round-bottom flask, a mixture of acetic anhydride (1 mL), acetic acid (1 mL) and 30% hydrogen peroxide in water (0.66 mL) was prepared, to which (4-methoxyphenyl)((4-nitronaphthalen-1-yl)methyl)sulfane (**30,** 150 mg, 0.46 mmol) was added. The mixture was stirred for 5 hours. Upon completion the reaction was diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_{3\,(aq)}$ (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated to yield a yellow solid. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 10:90) to afford 143 mg (87% yield) of (**14**) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (d, *J* = 8.3 Hz, 1 H), 8.04 (d, *J* = 7.8 Hz, 1 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.71 (ddd, *J* = 8.6, 7.0, 1.2 Hz, 1 H), 7.63 – 7.58 (m, 1 H), 7.58 – 7.53 (m, 2 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 6.90 – 6.84 (m, 2 H), 4.86 (s, 2 H), 3.85 (s, 3 H).



4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl) methyl)naphthalen-1-yl)benzenesulfonamide

13. 4-Methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)benzenesulfonamide (15)

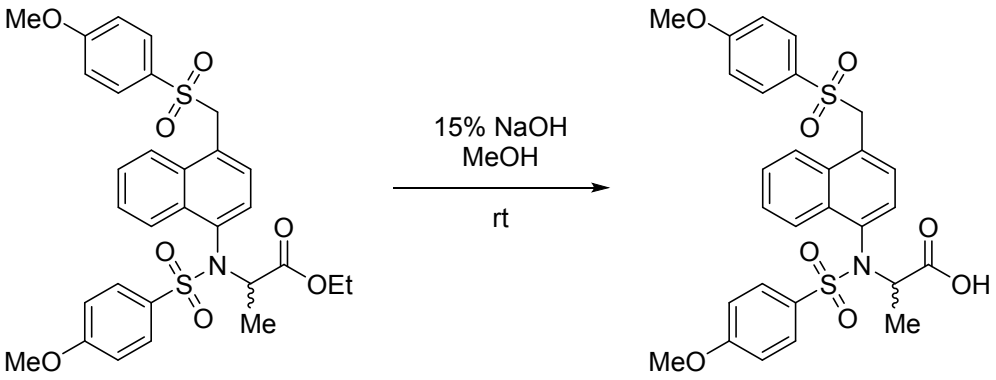
1-(((4-Methoxyphenyl)sulfonyl)methyl)-4-nitronaphthalene (**14,** 104 mg, 0.28 mmol) and 10% Pd/C (14 mg) were added to a Parr flask, which was sealed with a rubber septa and purged with argon. EtOAc (5 mL) was added under argon, and the flask was attached to a Parr shaker apparatus, purged with H_2 (40 psi), and shaken overnight. Upon completion, the flask was purged with argon, and the mixture was filtered through celite. The pad of celite was washed with EtOAc (10 mL), and the filtrate was concentrated to yield 92 mg (99% yield) of 4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-amine as an orange-brown solid. The crude 4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-amine (92 mg, 0.28 mmol) was placed in a single-neck round-bottom flask and dissolved in pyridine (1.6 mL) and THF (5 mL), and 4-methoxybenezenesulfonyl chloride (70.4 mg, 0.34 mmol) was added. The reaction was stirred overnight. Upon completion the reaction was quenched with 2M HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 2M HCl (2 × 15 mL), water (2 × 15 mL), and brine (2 × 15 mL); dried over Na_2SO_4; and concentrated to yield a brown oil. The crude product was purified by column chromatography (silica gel; EtOAc:Hexanes, 0:100 to 40:60) to afford 123 mg (88% yield) of (**15**) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 – 7.83 (m, 1 H), 7.84 – 7.78 (m, 1 H), 7.73 – 7.67 (m, 2 H), 7.47 – 7.42 (m, 2 H), 7.42 – 7.37 (m, 2 H), 7.30 (d, *J* = 7.8 Hz, 1 H), 7.16 (s, 1 H), 7.09 (d, *J* = 7.8 Hz, 1 H), 6.87 – 6.81 (m, 2 H), 6.80 – 6.74 (m, 2 H), 4.73 (s, 2 H), 3.81 (s, 3 H), 3.80 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.8, 163.1, 132.8, 132.8, 130.7, 130.6, 130.1, 129.5, 129.2, 128.5, 126.9, 126.5, 124.4, 123.6, 121.8, 120.9, 114.1, 114.0, 59.9, 55.6, 55.6; HRMS-ESI (+) (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{23}NO_6S_2$, 520.0864; found, 520.0872.



1,4-bis(((4-methoxyphenyl)sulfonyl)methyl)naphthalene

14. 1,4-bis(((4-methoxyphenyl)sulfonyl)methyl)naphthalene (16)

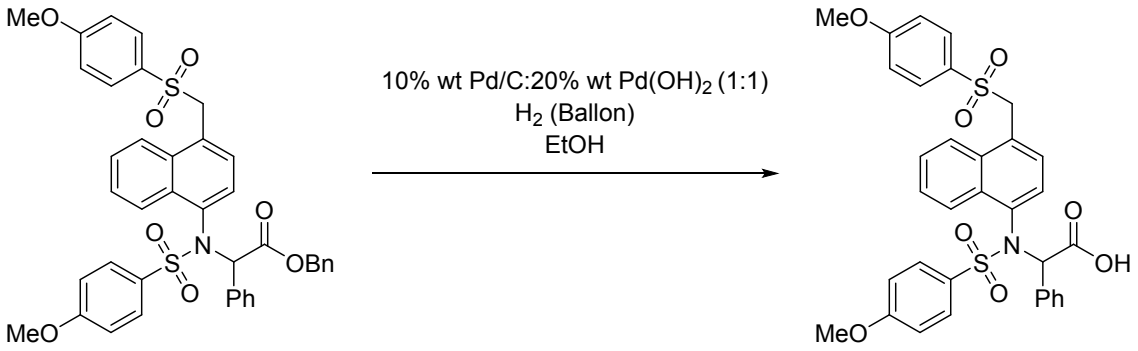
In a 4 mL screw-cap vial containing 1,4-bis(((4-methoxyphenyl)thio)methyl)naphthalene (**31**, 50.0 mg, 0.12 mmol), a 1:1 solution of acetic anhydride:acetic acid (140 µL) was added, followed by 30% H_2O_2 (120 µL). The resulting suspension was allowed to stir overnight. The reaction was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and washed. The layers were separated, and the organic layer was washed with sat. $NaHCO_3$ (10 mL) and water (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford 45 mg (78% yield) of **16** as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.82 (m, 2H), 7.68 – 7.47 (m, 4H), 7.45 – 7.37 (m, 2H), 7.11 (s, 2H), 6.97 – 6.81 (m, 4H), 4.79 (s, 4H), 3.83 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 132.3, 130.7, 129.6, 129.4, 126.5, 126.5, 124.4, 114.1, 60.1, 55.7; HRMS-ESI (+) (*m*/*z*): $[M + Na]^+$ calcd for $C_{26}H_{24}O_6S_2$, 519.0912; found, 519.0925.



***N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)alanine**

15. *N*-((4-Methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)alanine (19)

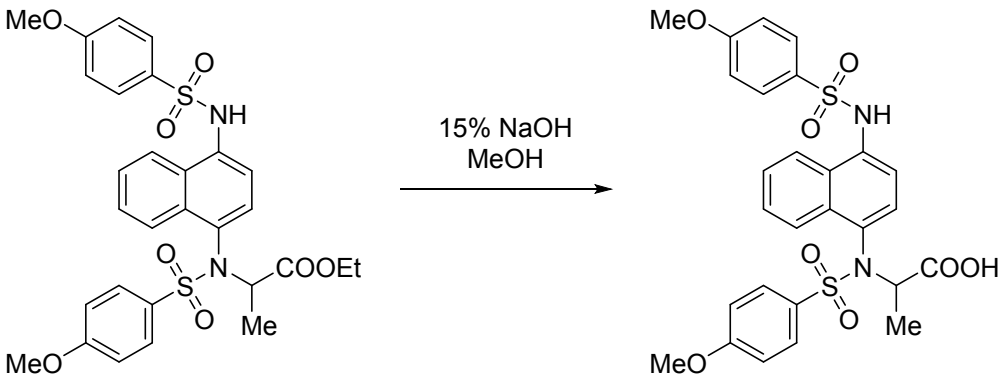
In a 20 mL screw-cap vial, ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)alaninate (**32**, 20 mg, 0.033 mmol) was dissolved in methanol (3 mL), and 15% $NaOH_{(aq)}$ (1 mL) was added. The reaction was stirred at room temperature for 4 hours. Upon completion the methanol was removed under reduced pressure, and the residual liquid was diluted with water (10 mL). The solution was adjusted to pH 4, and a white precipitate formed. The suspension was extracted with EtOAc (3 × 10 mL), washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over Na_2SO_4, and concentrated to yield an off-white solid. The crude product was purified by HPLC (C18; MeCN/H_2O 60%:40%, isocratic) to yield 15 mg (81% yield) of (**19**) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 – 8.08 (m, 1 H), 7.85 – 7.81 (m, 1 H), 7.64 – 7.51 (m, 3 H), 7.50 – 7.36 (m, 4 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 6.89 – 6.84 (m, 2 H), 6.81 – 6.73 (m, 2 H), 5.08 (q, *J* = 7.3 Hz, 1 H), 4.87 – 4.77 (m, 2 H), 3.89 – 3.70 (m, 6 H), 1.30 – 1.23 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.7, 163.9, 163.4, 163.2, 134.4, 134.1, 133.0, 130.8, 130.8, 130.4, 129.9, 129.9, 129.6, 129.2, 129.1, 129.0, 128.6, 127.1, 127.0, 127.0, 126.9, 126.7, 125.3, 125.0, 124.0, 123.7, 114.0, 113.7, 60.0, 58.2, 57.9, 55.6, 55.6, 16.8, 16.1; HRMS-ESI (+) (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{27}NO_8S_2$, 570.1256; found, 570.1260.



2-((4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)phenyl)sulfonamido)-2-phenylacetic acid

16. 2-((4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)phenyl)sulfonamido)-2-phenylacetic acid (20)

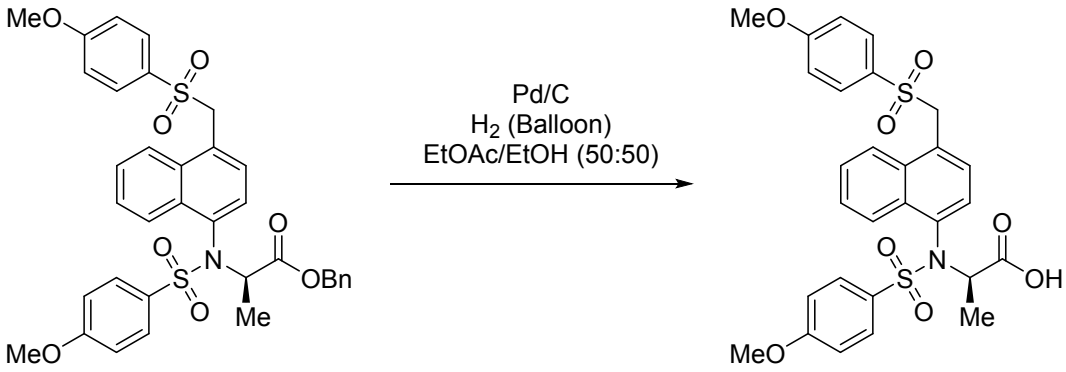
To a 4 mL screw-cap vial charged with benzyl 2-((4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)phenyl)sulfonamido)-2-phenylacetate (**33**, 20 mg, 0.028 mmol) was added 10% Pd/C (2 mg) and 20% $Pd(OH)_2$ (2 mg). The vial was purged with argon, and EtOH (0.5 mL) was added. The vial was purged with H_2 and stirred under a ballon of H_2 overnight. After 16 hours the reaction was diluted with EtOAc and filtered through a pad of celite. The pad was washed with EtOAc, and the filtrate was concentrated to a light-yellow oil. The crude compound was purified by preparative HPLC (C18; MeCN/H_2O + 0.1% FA, 60:40 to 95:5) to yield 12 mg (68% yield) of (**20**) as a white solid. A 61:49 mixture of atropisomers was observed; ^{1}H NMR data for the the major isomer are presented. ^{1}H NMR (400 MHz ,CD_3COCD_3) δ 7.86 (d, *J* = 8.3 Hz, 2 H), 7.71 – 7.59 (m, 3 H), 7.46 – 7.37 (m, 2 H), 7.35 – 7.28 (m, 1 H), 7.25 – 7.19 (m, 1 H), 7.16 – 6.97 (m, 9 H), 6.95 – 6.88 (m, 3 H), 6.27 (s, 1 H), 5.00 – 4.84 (m, 2 H), 3.92 (s, 3 H), 3.86 (s, 3 H); ^{13}C NMR (101 MHz, Acetone) δ 172.4, 172.0, 164.8, 164.7, 164.5, 164.2, 136.1, 135.9, 135.3, 134.9, 134.4, 134.2, 133.8, 133.6, 132.7, 131.8, 131.6, 131.3, 131.3, 130.8, 130.8, 130.6, 130.4, 130.2, 129.7, 129.5, 129.3, 129.0, 128.7, 128.5, 127.8, 127.5, 127.1, 126.7, 126.5, 126.2, 125.9, 124.9, 124.7, 115.0, 114.9, 114.7, 68.3, 67.1, 59.9, 59.7, 56.3, 56.2. HRMS-ESI (+) (*m*/*z*): $[M + Na]^+$ calcd for $C_{33}H_{29}NO_8S_2$, 654.1232; found, 654.1231.



***N*-(4-((4-methoxyphenyl)sulfonamido) naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)alanine**

17. *N*-(4-((4-Methoxyphenyl)sulfonamido)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)alanine (21)

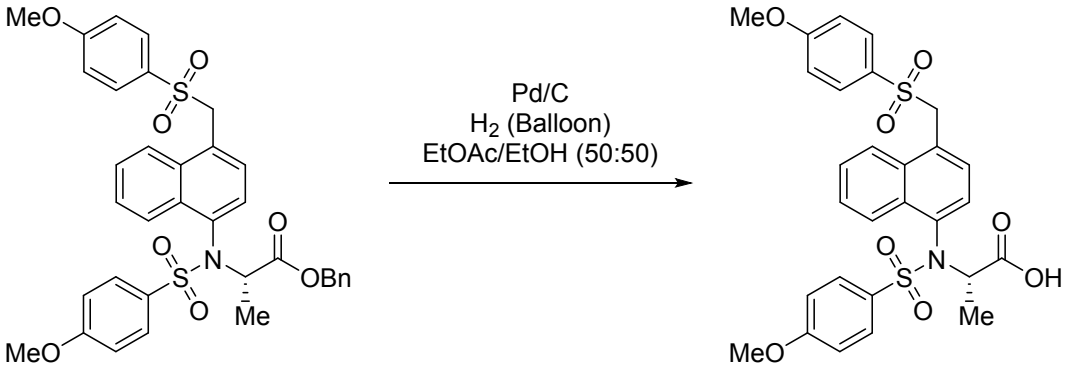
In a 20 mL screw cap vial, ethyl *N*-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)alaninate (**34,** 48 mg, 0.084 mmol) was dissolved in methanol (7 mL), and 15% $NaOH_{(aq)}$ (1 mL) was added. The reaction was stirred at room temperature for 4 hours. Upon completion, the methanol was removed under reduced pressure, and the residual liquid was diluted with water (10 mL). The solution was adjusted to pH 2, and a white precipitate formed. The suspension was extracted with EtOAc (3 × 10 mL), washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over Na_2SO_4, and concentrated to yield a brown solid. The crude product was purified by HPLC (C18; $MeCN/H_2O$ 35%:65% to 75%:25%) to yield 20 mg (43% yield) of (**21**) as an off-white solid. The compound was isolated as a 70:30 mixture of atropisomers; ^1H NMR data are given for the major atropisomer. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.12 – 8.04 (m, 1 H), 7.88 – 7.82 (m, 1 H), 7.77 – 7.66 (m, 2 H), 7.59 – 7.51 (m, 3 H), 7.47 – 7.42 (m, 2 H), 7.42 – 7.36 (m, 1 H), 7.35 – 7.31 (m, 1 H), 6.91 (d, *J* = 8.1 Hz, 1 H), 6.89 – 6.79 (m, 4 H), 5.12 – 5.03 (m, 1 H), 3.81 – 3.79 (m, 6 H), 1.30 – 1.20 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.5, 176.3, 163.4, 163.3, 163.3, 163.2, 134.8, 134.7, 133.1, 133.1, 131.4, 131.3, 130.7, 130.5, 130.5, 130.4, 130.3, 129.9, 129.5, 129.5, 129.3, 128.9, 128.5, 127.4, 127.2, 127.0, 125.4, 125.1, 121.4, 120.9, 120.3, 119.3, 114.2, 114.0, 113.6, 58.2, 57.9, 55.7, 55.6, 55.6, 16.8, 16.1; HRMS-ESI (+) (*m*/*z*): $[M - H]^-$ calcd for $C_{27}H_{26}N_2O_8S_2$, 569.1058; found, 569.1060.



***N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl) sulfonyl)methyl)naphthalen-1-yl)-*D*-alanine**

18. *N*-((4-Methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)-D-alanine (22)

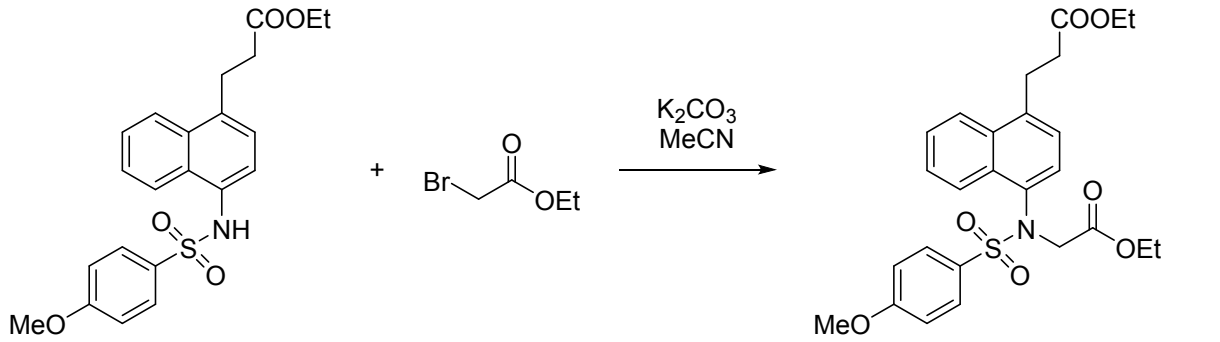
In a 4 mL screw-cap vial, benzyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)-D-alaninate (**35**, 19.9 mg, 0.03 mmol) and Pd/C (2 mg, 10% wt/wt) were placed. The vial was purged with argon followed by the addition of 50:50 EtOAc:EtOH (1 mL). The vial was then purged with H_2 and stirred under 1 atm H_2 (balloon) at 50 °C for 24 hours. The reaction was removed from heat and allowed to cool to room temperature. The reaction mixture was diluted with EtOAc and filtered through celite and concentrated to yield an off-white solid. The crude material was purified by HPLC (C18; MeCN/H_2O 60%:40%, isocratic) to yield 9.1 mg (53% yield) of (**22**) as an off-white solid. The compound was isolated as a 67:33 mixture of atropisomers. ^{1}H NMR (400 MHz ,$CDCl_3$) δ = 8.14 – 8.08 (m, 1 H), 7.85 – 7.80 (m, 1 H), 7.64 – 7.57 (m, 2 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.51 – 7.38 (m, 4 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 6.95 – 6.85 (m, 2 H), 6.81 – 6.73 (m, 2 H), 5.09 (q, *J* = 7.5 Hz, 1 H), 4.88 – 4.70 (m, 2 H), 3.86 – 3.82 (m, 3 H), 3.81 – 3.76 (m, 3 H), 1.27 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.3, 176.2, 163.9, 163.4, 163.2, 134.6, 134.4, 134.3, 134.2, 133.1, 133.0, 130.9, 130.8, 130.4, 129.9, 129.9, 129.6, 129.2, 129.1, 129.0, 128.6, 127.1, 127.0, 127.0, 126.9, 126.7, 125.3, 125.0, 124.0, 123.7, 114.0, 113.7, 60.1, 58.2, 57.9, 55.7, 55.6, 16.8, 16.1; $[\alpha]_D^{20}$ = +7.0; $CHCl_3$, 5.0 mg/mL. HRMS-ESI (+) (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{27}NO_8S_2$, 570.1256; found, 570.1246



***N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl) sulfonyl)methyl)naphthalen-1-yl)-*L*-alanine**

19. *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)-L-alanine (23)

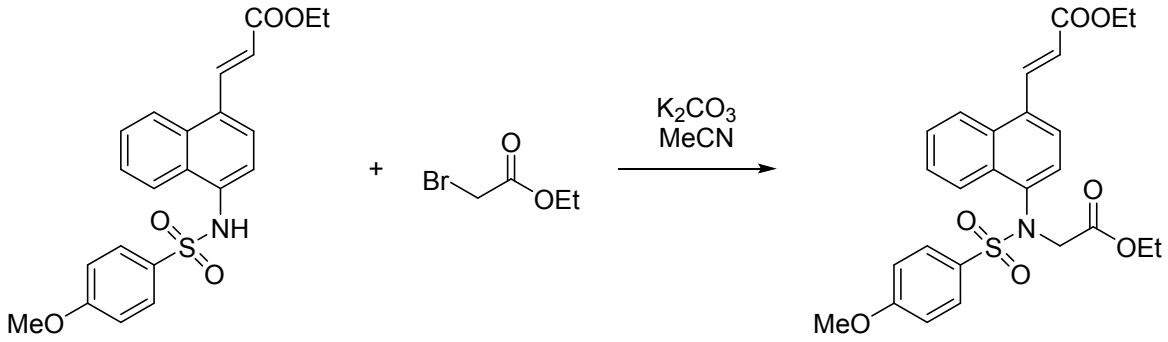
In a 4 mL screw-cap vial, benzyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)-L-alaninate (**36,** 13 mg, 0.02 mmol) and Pd/C (2 mg, 10% wt/wt) were placed. The vial was purged with argon followed by the addition of 50:50 EtOAc:EtOH (1 mL). The vial was then purged with H_2 and stirred under 1 atm H_2 (balloon) at 50 °C for 24 hours. The reaction was removed from heat and allowed to cool to room temperature. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated to yield an off-white solid. The crude material was purified by HPLC (C18; MeCN/H_2O 60%:40%, isocratic) to yield 9.1 mg (81% yield) of (**23**) as an off-white solid. The compound was isolated as a 67:33 mixture of atropisomers; ^{1}H NMR data are given for the major atropisomer. ^{1}H NMR (400 MHz ,$CDCl_3$) δ = 8.15 – 8.08 (m, 1 H), 7.87 – 7.75 (m, 1 H), 7.64 – 7.57 (m, 2 H), 7.55 (d, *J* = 7.8 Hz, 0 H), 7.51 – 7.37 (m, 4 H), 7.19 (dd, *J* = 7.7, 0.6 Hz, 1 H), 6.95 – 6.84 (m, 2 H), 6.81 – 6.74 (m, 2 H), 5.13 – 5.04 (m, 1 H), 4.88 – 4.68 (m, 2 H), 3.85 – 3.82 (m, 3 H), 3.81 – 3.76 (m, 3 H), 1.27 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz ,$CDCl_3$) δ = 176.9, 176.8, 163.9, 163.4, 163.2, 134.6, 134.4, 134.3, 134.1, 133.0, 133.0, 130.8, 130.8, 130.3, 129.9, 129.8, 129.6, 129.2, 129.1, 129.0, 128.6, 127.1, 127.0, 126.9, 126.7, 125.3, 125.0, 124.0, 123.7, 114.0, 113.7, 60.0, 58.2, 57.9, 55.6, 55.6, 16.8, 16.1; $[\alpha]_D^{20}$ = -10.0; $CHCl_3$, 10.0 mg/mL. HRMS-ESI (+) (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{27}NO_8S_2$, 570.1256; found, 570.1255



ethyl 3-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido) naphthalen-1-yl)propanoate

20. Ethyl 3-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)naphthalen-1-yl)propanoate (24)

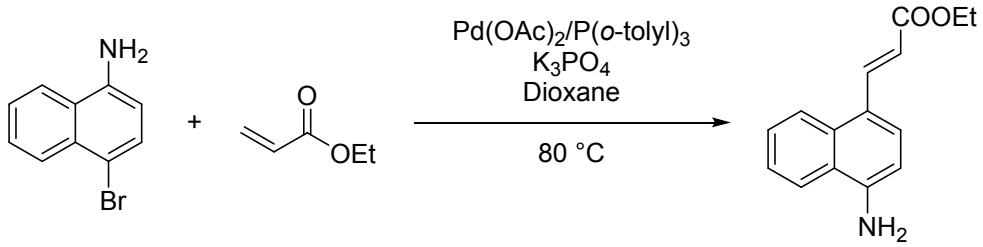
In a 4 mL screw-cap vial, ethyl 3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)propanoate (**8**, 114 mg, 0.28 mmol) and K_2CO_3 (57.2 mg, 0.41 mmol) were placed, and MeCN (2 mL) was added, followed by ethyl bromoacetate (46 μL, 0.42 mmol). The reaction was stirred overnight. Upon completion the reaction was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated under reduced pressure to a light-yellow oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 40:60) to yield 114 mg (83% yield) of (**24**) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 – 8.16 (m, 1 H), 8.05 – 8.00 (m, 1 H), 7.70 – 7.65 (m, 2 H), 7.58 – 7.50 (m, 2 H), 7.24 – 7.20 (m, 1 H), 7.19 – 7.14 (m, 1 H), 6.95 – 6.89 (m, 2 H), 4.67 (d, *J* = 17.9 Hz, 1 H), 4.29 (d, *J* = 17.6 Hz, 1 H), 4.19 – 4.04 (m, 4 H), 3.87 (s, 3 H), 3.45 – 3.35 (m, 2 H), 2.79 – 2.68 (m, 2 H), 1.30 – 1.21 (m, 3 H), 1.17 (t, *J* = 7.1 Hz, 3 H).



Ethyl (*E*)-3-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido) naphthalen-1-yl)acrylate

21. Ethyl (*E*)-3-(4-((N-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylate (25)

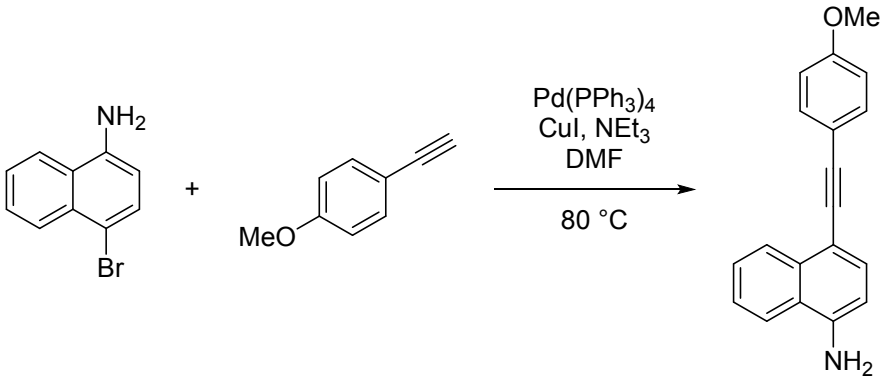
In a 4 mL screw-cap vial, ethyl (*E*)-3-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)acrylate (**7,** 70 mg, 0.17 mmol) and K_2CO_3 (28.2 mg, 0.2 mmol) were placed, and MeCN (1 mL) was added, followed by ethyl bromoacetate (28.3 μL, 0.26 mmol). The reaction was stirred overnight. Upon completion the reaction was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated under reduced pressure to a yellow oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 40:60) to yield 64 mg (76% yield) of (**25**) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 15.9 Hz, 1 H), 8.25 – 8.08 (m, 2 H), 7.73 – 7.64 (m, 2 H), 7.64 – 7.52 (m, 3 H), 7.33 – 7.21 (m, 1 H), 6.98 – 6.88 (m, 2 H), 6.49 (d, *J* = 15.6 Hz, 1 H), 4.67 (d, *J* = 17.6 Hz, 1 H), 4.37 – 4.28 (m, 3 H), 4.18 – 4.04 (m, 2 H), 3.88 (s, 3 H), 1.38 (t, *J* = 7.1 Hz, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H).



Ethyl (*E*)-3-(4-aminonaphthalen-1-yl)acrylate

22. Ethyl (*E*)-3-(4-aminonaphthalen-1-yl)acrylate (26)

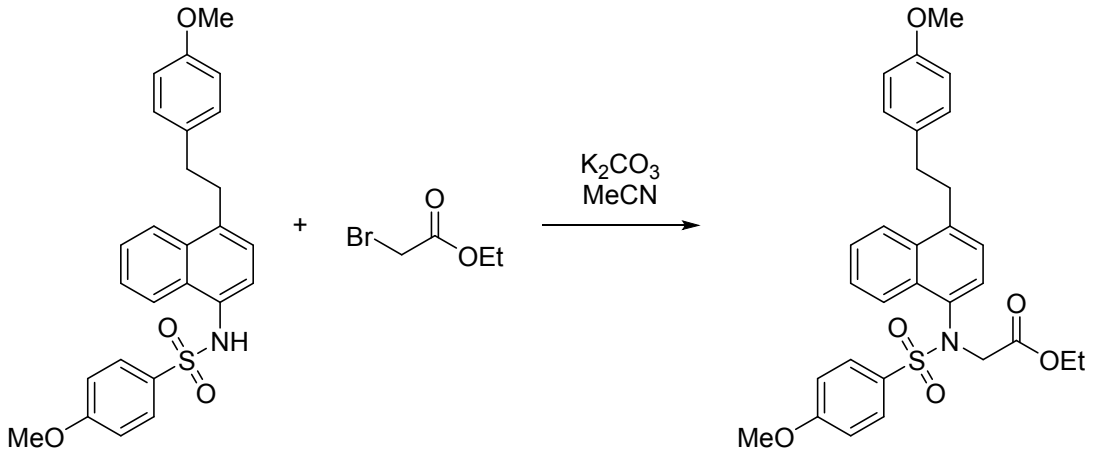
1-Amino-4-bromonaphthalene (**2**, 250 mg, 1.13 mmol), $Pd(OAc)_2$ (25.2 mg, 0.11 mmol), P(*o*-tolyl)$_3$ (34.3 mg, 0.11 mmol), and K_3PO_4 (525 mg, 2.47 mmol) were added to a flame-dried Schlenk tube. The tube was purged with argon, and ethyl acrylate (450 μL, 4.13 mmol) and dioxane (2.5 mL) were added under a positive pressure of argon. The tube was sealed and heated to 80 °C for 24 hours. Upon completion the reaction was diluted with water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (2 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield a brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/hexanes, 0/100 to 30/70) to yield 230 mg (85% yield) of (**26**) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (d, *J* = 15.7 Hz, 1 H), 8.24 (d, *J* = 8.3 Hz, 1 H), 7.86 – 7.80 (m, 1 H), 7.70 (d, *J* = 8.1 Hz, 1 H), 7.61 – 7.55 (m, 1 H), 7.54 – 7.48 (m, 1 H), 6.79 (d, *J* = 7.8 Hz, 1 H), 6.42 (d, *J* = 15.7 Hz, 1 H), 4.49 (br. s., 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H).



4-((4-methoxyphenyl)ethynyl)naphthalen-1-amine

23. 4-((4-Methoxyphenyl)ethynyl)naphthalen-1-amine (27)

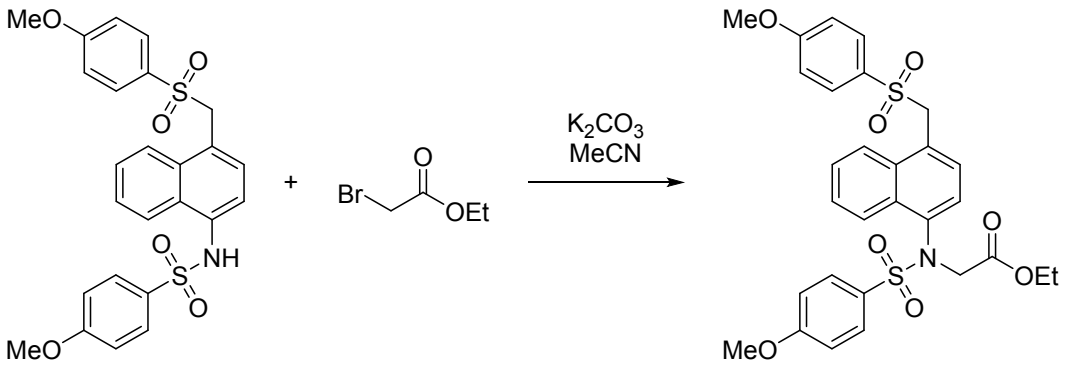
1-Amino-4-bromonaphthalene (**2**, 150 mg, 0.68 mmol), $Pd(PPh_3)_4$ (39 mg, 0.034 mmol), CuI (12.9 mg, 0.068 mmol), and 4-ethynyl anisole (116 mg, 0.88 mmol) were added to a flame-dried Schlenk tube. The tube was purged with argon, and trimethylamine (207 μL, 1.5 mmol) and dimthylformamide (1.5 mL) were added under a positive pressure of argon. The tube was sealed and heated to 80 °C for 18 hours. Upon completion the reaction was poured into H_2O/ice (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (2 × 50 mL), dried over Na_2SO_4 and concentrated under a reduced pressure to yield a brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/hexanes, 0/100 to 30/70) to yield 58 mg (31% yield) of (**27**) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.31 Hz, 1H), 7.82 (d, *J* = 8.56 Hz, 1H), 7.54 – 7.64 (m, 3H), 7.47 – 7.54 (m, 1H), 6.93 (d, *J* = 8.80 Hz, 1H), 6.75 (d, *J* = 7.82 Hz, 1H), 4.33 (br. s., 1H), 3.85 (s, 3H).



Ethyl *N*-(4-(4-methoxyphenethyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate

24. Ethyl *N*-(4-(4-methoxyphenethyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (28)

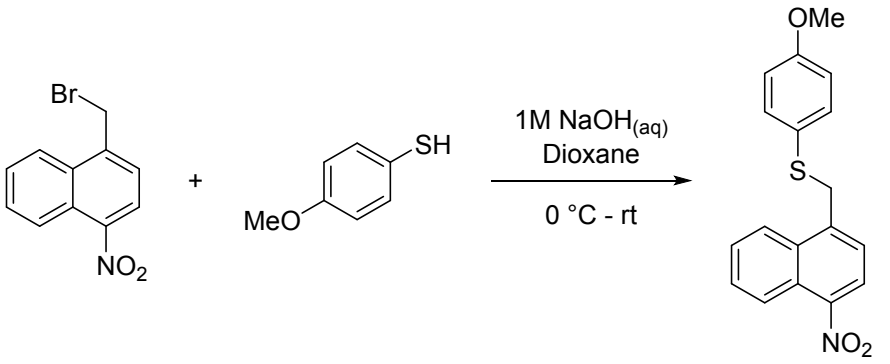
In a 4 mL screw-cap vial, 4-methoxy-*N*-(4-(4-methoxyphenethyl)naphthalen-1-yl)benzenesulfonamide (**10**, 30 mg, 0.067 mmol), potassium carbonate (11.1 mg, 0.08 mmol), and acetonitrile (0.5 mL) were added, followed by the addition of ethyl bromoacetate (9 μL, 0.08). The reaction was stirred at room temperature overnight. The reaction was diluted with ethyl acetate (2 mL) and filtered through a small pad of celite, washing with ethyl acetate. The filtrate was concentrated to an orange oil and purified by column chromatography (silica gel; ethyl acetate/hexanes, 0:100 to 40:60) to yield 35 mg (98% yield) of (**28**) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 – 8.19 (m, 1 H), 8.13 – 8.06 (m, 1 H), 7.71 – 7.63 (m, 2 H), 7.60 – 7.50 (m, 2 H), 7.17 – 7.06 (m, 4 H), 6.96 – 6.89 (m, 2 H), 6.89 – 6.83 (m, 2 H), 4.66 (d, *J* = 17.6 Hz, 1 H), 4.33 (d, *J* = 17.6 Hz, 1 H), 4.20 – 4.03 (m, 2 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.40 – 3.23 (m, 2 H), 3.06 – 2.90 (m, 2 H), 1.18 (t, *J* = 7.2 Hz, 3 H).



ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)glycinate

25. Ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)glycinate (29)

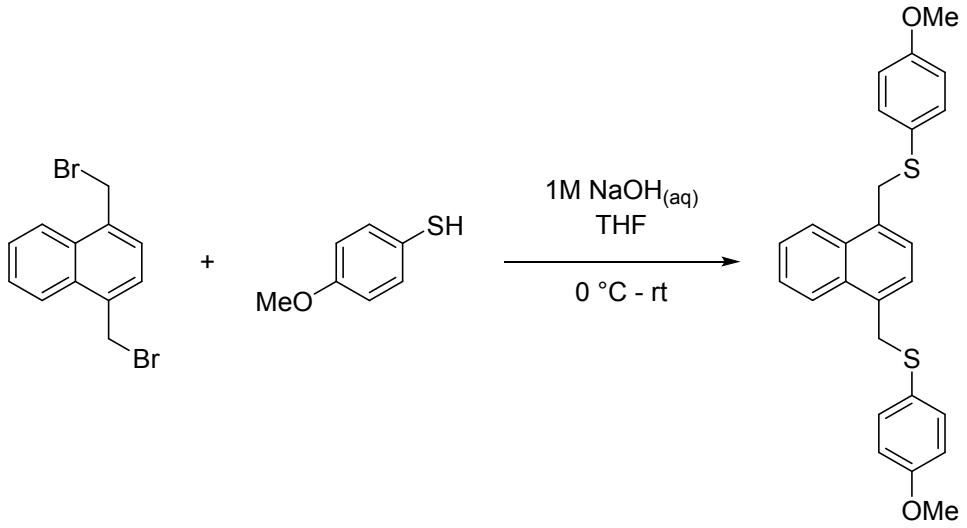
In a 4 mL screw-cap vial, 4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)benzenesulfonamide (**15,** 40 mg, 0.08 mmol) and K_2CO_3 (13.4 mg, 0.10 mmol) were suspended in acetonitrile, and ethyl bromoacetate (13.4 µL, 0.12 mmol) was added. The reaction was stirred overnight. Upon completion, the reaction was filtered through a short pad of celite, washed with EtOAc, and concentrated to yield a red-brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 30:70) to afford 39.6 mg (84% yield) of (**29**) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 – 8.16 (m, 1 H), 7.84 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.67 – 7.63 (m, 2 H), 7.52 – 7.43 (m, 4 H), 7.16 – 7.11 (m, 2 H), 6.96 – 6.92 (m, 2 H), 6.84 – 6.79 (m, 2 H), 4.77 (s, 2 H), 4.63 (d, *J* = 17.6 Hz, 1 H), 4.30 (d, *J* = 17.9 Hz, 1 H), 4.15 – 4.04 (m, 2 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H).



(4-methoxyphenyl)((4-nitronaphthalen-1-yl) methyl)sulfane

26. (4-Methoxyphenyl)((4-nitronaphthalen-1-yl)methyl)sulfane (30)

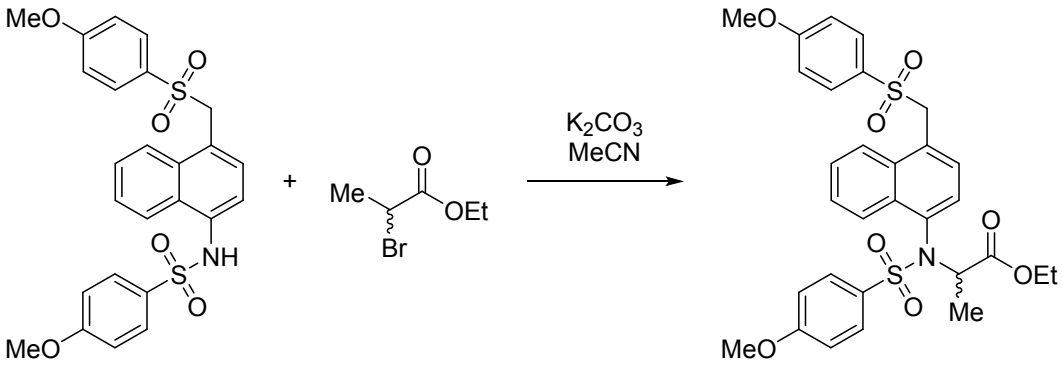
In a 3-neck round-bottom flask, 1M $NaOH_{(aq)}$ (2.5 mL) was cooled to 0 to 5 °C with an ice/water bath, and 4-methoxybenzenethiol (116 mg, 0.83 mmol) was added in one portion and stirred for 30 minutes. 1-(Bromomethyl)-4-nitronaphthalene (**37,** 213 mg, 0.80 mmol) was dissolved in dioxane (1.5 mL) and added dropwise to the stirred solution. After 5 hours the reaction was diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated to yield a yellow solid. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 20:80) to afford 183 mg (70% yield) of (**30**) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (d, *J* = 8.3 Hz, 1 H), 8.22 (s, 1 H), 8.00 (d, *J* = 7.8 Hz, 1 H), 7.75 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1 H), 7.71 – 7.66 (m, 1 H), 7.24 – 7.17 (m, 2 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 6.83 – 6.74 (m, 2 H), 4.43 (s, 2 H), 3.80 (s, 3 H).



1,4-bis(((4-methoxyphenyl)thio)methyl)naphthalene

27. 1,4-bis(((4-methoxyphenyl)thio)methyl)naphthalene (31)

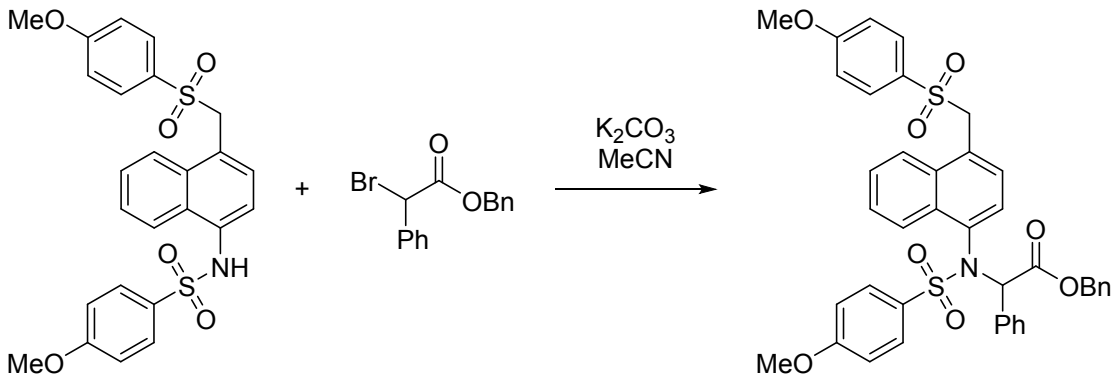
In a round-bottom flask 4-methoxybenzenethiol (236 mg, 1.68 mmol) was dissolved in 1 M NaOH (5 mL) at 0 °C, followed by the addition of a solution of 1,4-bis(bromomethyl)naphthalene (252 mg, 0.80 mmol) in THF (1.5 mL). The resulting mixture was allowed to stir for 30 minutes at 0 °C then the ice bath was removed and the reaction was stirred at room temperature for 3 hours. After 3.5 hours the reaction was diluted with EtOAc (10 mL), the layers were separated, and the organic layer was washed with sat. $NaHCO_3$ (10 mL) and water (10 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography (silica gel; DCM/Hexanes, 0:100 to 25:75) to afford 74.3 mg (21.5% yield) of (**31**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 2H), 7.62 – 7.56 (m, 2H), 7.26 – 7.21 (m, 4H), 6.96 (s, 2H), 6.83 – 6.77 (m, 4H), 4.40 (s, 4H), 3.84 – 3.74 (m, 6H).



ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)alaninate

28. Ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)alaninate (32)

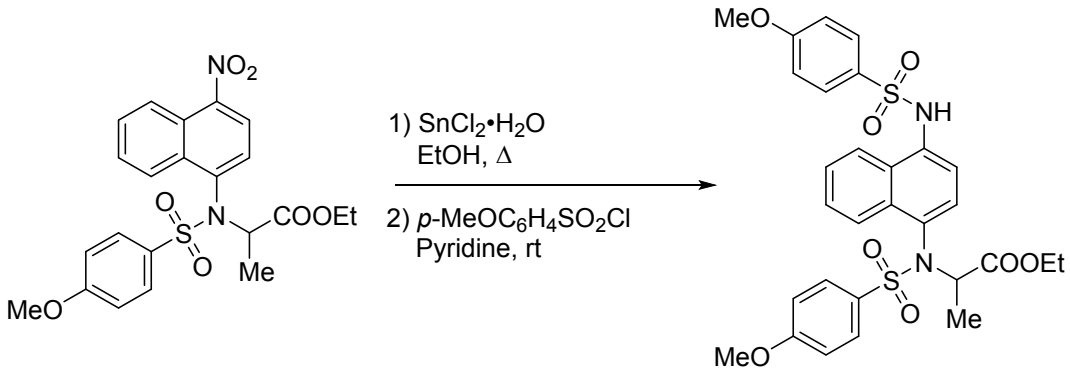
In a 4 mL screw-cap vial, 4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)benzenesulfonamide (**15**, 40 mg, 0.08 mmol) and K_2CO_3 (16.7 mg, 0.12 mmol) were suspended in acetonitrile (0.5 mL), and ethyl-2-bromopropionate (31.3 μL, 0.28 mmol) was added. The reaction was stirred for 48 h. Upon completion, the reaction was filtered through a short pad of celite, washed with EtOAc, and concentrated to yield a red-brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 30:70) to afford 28 mg (58% yield) of (**32**) as an off-white solid. The compound was isolated as a 70:30 mixture of atropisomers; NMR data are given for the major atropisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 – 8.17 (m, 1 H), 7.80 (d, *J* = 8.3 Hz, 1 H), 7.65 – 7.55 (m, 2 H), 7.51 – 7.35 (m, 5 H), 7.17 – 7.10 (m, 1 H), 6.95 – 6.85 (m, 2 H), 6.79 – 6.72 (m, 2 H), 5.07 (q, *J* = 7.3 Hz, 1 H), 4.87 – 4.71 (m, 2 H), 4.15 – 4.06 (m, 2 H), 3.79 – 3.74 (m, 3 H), 1.32 – 1.11 (m, 6 H).



benzyl 2-((4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)phenyl)sulfonamido)-2-phenylacetate

29. Benzyl 2-((4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)phenyl)sulfonamido)-2-phenylacetate (33)

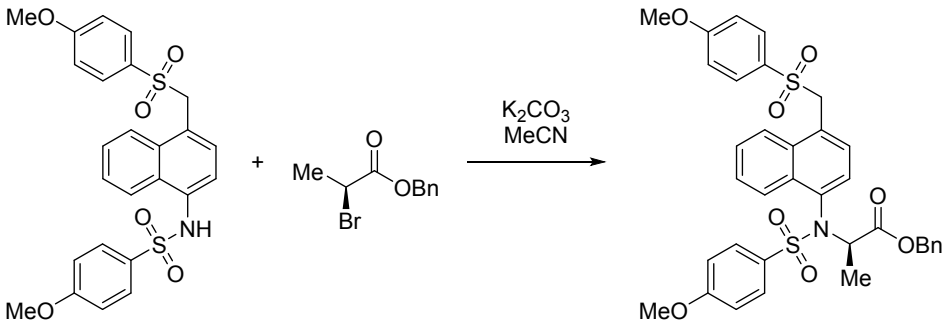
In a 4 mL screw-cap vial, 4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)benzenesulfonamide (**15**, 50 mg, 0.08 mmol) and K_2CO_3 (13.4 mg, 0.10 mmol) were suspended in acetonitrile, and benzyl 2-bromo-2-phenylacetate (**38**, 92 mg, 0.30 mmol) was added. The reaction was stirred overnight. Upon completion, the reaction was filtered through a short pad of celite, the pad was washed with EtOAc, and concentrated to yield a red-brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 30:70) to afford 53 mg (73% yield) of (**33**) as an off-white solid. A 61:49 mixture of atropisomers was observed; NMR data for the major isomer are presented. ^{1}H NMR (400MHz , $CDCl_3$) δ 7.72 – 7.63 (m, 1 H), 7.59 – 7.48 (m, 2 H), 7.43 – 7.28 (m, 6 H), 7.25 – 7.16 (m, 2 H), 7.14 – 7.05 (m, 2 H), 7.04 – 6.85 (m, 7 H), 6.85 – 6.79 (m, 2 H), 6.73 – 6.62 (m, 2 H), 6.29 (s, 1 H), 5.20 – 4.99 (m, 2 H), 4.79 – 4.55 (m, 2 H), 3.87 (s, 3 H), 3.77 (s, 1 H).



ethyl *N*-(4-((4-methoxyphenyl)sulfonamido) naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)alaninate

30. Ethyl *N*-(4-((4-methoxyphenyl)sulfonamido)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)alaninate (34)

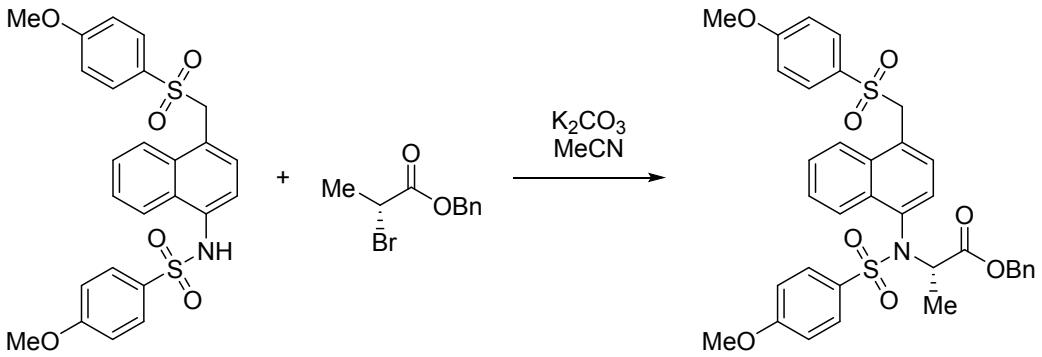
In a 15 mL round-bottom flask, ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-nitronaphthalen-1-yl)alaninate (**39,** 65 mg, 0.14 mmol) was dissolved in EtOH (2.8 mL, 200 proof), $SnCl_2•H_2O$ (236 mg, 1.05 mmol) was added, and the reaction was heated to reflux. After 1.5 hours TLC indicated that no starting material remained, and the reaction was removed from heat. The reaction was diluted with EtOAc (20 mL) and neutralized with sat. $NaHCO_{3(aq)}$. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (2 × 50 mL), brine (2 × 50 mL), dried over Na_2SO_4 and concentrated until about 10 mL of EtOAc remained. To the resulting solution, 3 mL of 2M HCl in EtOH was slowly added. The remaining solvent was removed and the sticky residue was triturated with Et_2O to afford 65 mg (99% yield) of a reddish precipitate. The precipitate was suspended in THF (3 mL), followed by the addition of pyridine (1.0 mL) and 4-methoxybenzesulfonyl chloride (35.4 mg, 0.17 mmol). The reaction was heated to reflux. After 30 hours the reaction was removed from heat and quenched with 2 M $HCl_{(aq)}$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with 2 M $HCl_{(aq)}$ (2 × 20 mL), H_2O (2 × 20 mL), brine (2 × 20 mL), dried over Na_2SO_4, and concentrated to yield a brown solid. The crude material was purified by column chromatography (silica gel; EtOAc/hexanes, 0:100 to 50:50) to afford 48 mg (60% yield) of (**34**) as a brown solid. The compound was isolated as a 70:30 mixture of atropisomers; NMR data are given for the major atropisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (d, *J* = 8.3 Hz, 1 H), 1.00 (d, *J* = 8.1 Hz, 1 H), 7.75 – 7.65 (m, 2 H), 7.61 – 7.52 (m, 2 H), 7.52 – 7.40 (m, 2 H), 7.39 – 7.29 (m, 1 H), 7.04 – 6.92 (m, 1 H), 6.92 – 6.79 (m, 4 H), 5.13 – 5.01 (m, 1 H), 4.18 – 4.06 (m, 2 H), 3.94 – 3.73 (m, 6 H), 1.29 – 1.14 (m, 6 H).



benzyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl) sulfonyl)methyl)naphthalen-1-yl)-*D*-alaninate

31. Benzyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)-D-alaninate (35)

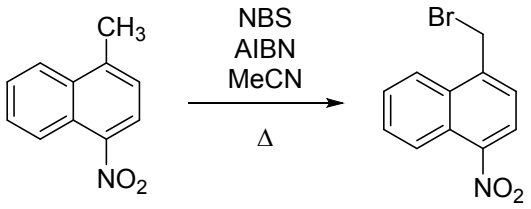
In a 4 mL screw-cap vial, 4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)benzenesulfonamide (**15**, 20 mg, 0.04 mmol) and K_2CO_3 (8.33 mg, 0.06 mmol) were suspended in acetonitrile (0.25 mL), and benzyl (*S*)-2-bromopropanoate (**40**, 41 mg, 0.16 mmol) was added. The reaction was stirred for 30 h. Upon completion, the reaction was filtered through a short pad of celite, washed with EtOAc, and concentrated to yield a red-brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 50:50) to afford 26 mg (98% yield) of **35** as an off-white solid. The compound was isolated as a 67:33 mixture of atropisomers; NMR data are given for the major atropisomer. ^{1}H NMR (400 MHz ,$CDCl_3$) δ = 8.22 – 8.17 (m, 1 H), 7.81 – 7.74 (m, 1 H), 7.62 – 7.56 (m, 1 H), 7.55 – 7.48 (m, 2 H), 7.47 – 7.34 (m, 7 H), 7.34 – 7.29 (m, 2 H), 7.04 (d, *J* = 7.8 Hz, 1 H), 6.89 – 6.84 (m, 1 H), 6.82 – 6.72 (m, 3 H), 5.18 – 5.02 (m, 3 H), 4.89 – 4.72 (m, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 1.27 – 1.22 (m, 3 H); $[\alpha]_D^{20}$ = +10.1; $CHCl_3$, 10.0 mg/mL.



benzyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl) sulfonyl)methyl)naphthalen-1-yl)-*L*-alaninate

32. Benzyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)-L-alaninate (36)

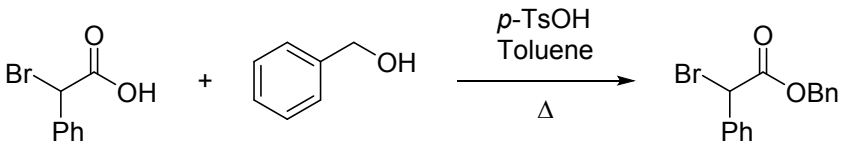
In a 4 mL screw-cap vial, 4-methoxy-*N*-(4-(((4-methoxyphenyl)sulfonyl)methyl)naphthalen-1-yl)benzenesulfonamide **(15,** 40 mg, 0.08 mmol) and K_2CO_3 (8.33 mg, 0.06 mmol) were suspended in acetonitrile (0.5 mL), and benzyl (*R*)-2-bromopropanoate (**41,** 81 mg, 0.32 mmol) was added. The reaction was stirred for 30 h. Upon completion, the reaction was filtered through a short pad of celite, washed with EtOAc, and concentrated to yield a red-brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 30:70) to afford 43.6 mg (82% yield) of **36** as an off-white solid. The compound was isolated as a 67:33 mixture of atropisomers; NMR data are given for the major atropisomer. ^{1}H NMR (400 MHz,$CDCl_3$) δ = 8.22 – 8.16 (m, 1 H), 7.83 – 7.73 (m, 1 H), 7.62 – 7.55 (m, 1 H), 7.55 – 7.48 (m, 2 H), 7.47 – 7.34 (m, 7 H), 7.34 – 7.29 (m, 2 H), 7.04 (d, *J* = 7.8 Hz, 1 H), 6.89 – 6.83 (m, 1 H), 6.82 – 6.71 (m, 3 H), 5.18 – 5.02 (m, 3 H), 4.90 – 4.69 (m, 2 H), 3.86 – 3.81 (m, 3 H), 3.77 (s, 3 H), 1.31 – 1.20 (m, 3 H); $[\alpha]_D^{20}$ = -11.0; $CHCl_3$, 10.0 mg/mL.



1-(bromomethyl)-4-nitronaphthalene

33. 1-(Bromomethyl)-4-nitronaphthalene (37)

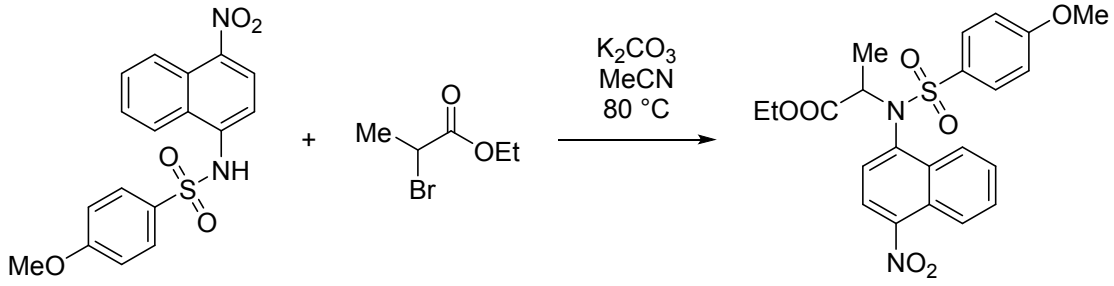
In a single-neck round-bottom flask, 1-methyl-4-nitronaphthalene (**13**) (200 mg, 1.05 mmol), *N*-bromosuccinimide (228 mg, 1.06 mmol), and azobisisobutyronitrile (AIBN, 17.5 mg, 0.11 mmol) were dissolved in acetonitrile (5 mL). The resulting solution was heated at reflux for 5 hours. After the reaction was complete, the acetonitrile was removed under reduced pressure, and the residue was dissolved in EtOAC. The organic layer was washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over sodium sulfate and concentrated to yield an orange solid. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 10:90) to afford 213 mg (75% yield) of **37** as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 – 8.51 (m, 1 H), 8.32 – 8.22 (m, 1 H), 8.11 (d, *J* = 7.8 Hz, 1 H), 7.82 – 7.73 (m, 2 H), 7.63 (d, *J* = 7.8 Hz, 2 H), 4.95 (s, 2 H).



benzyl 2-bromo-2-phenylacetate

34. Benzyl 2-bromo-2-phenylacetate (38)

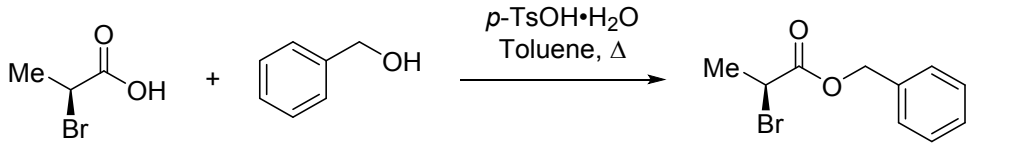
To a 50-mL round bottom flask containing α-bromophenylacetic acid (1.0 g, 4.65 mmol) was added toluene (20 mL), benzyl alcohol (1.508 g, 13.9 mmol), and *p*-toluenesulfonic acid monohydrate (88 mg, 0.46 mmol). The reaction was heated to reflux overnight. After 16 hours the reaction was cooled to room temperature and quenched with sat. $NaHCO_{3(aq)}$ (20 mL). The layers were separated, and the organic layer was washed with sat. $NaHCO_{3(aq)}$ (2 × 20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated to an oil. The compound was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 10:90) to afford 972 mg (68% yield) of **38**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 2H), 7.39 – 7.27 (m, 8H), 5.41 (s, 1H), 5.22 (s, 2H).



ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-nitronaphthalen-1-yl)alaninate

35. Ethyl *N*-((4-methoxyphenyl)sulfonyl)-*N*-(4-nitronaphthalen-1-yl)alaninate (39)

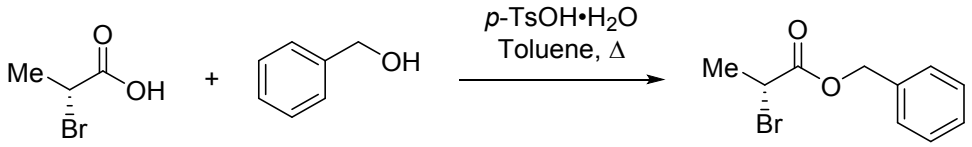
In a 5 mL round-bottom flask, 4-methoxy-*N*-(4-nitronaphthalen-1-yl)benzenesulfonamide (200 mg, 0.56 mmol),and K_2CO_3 (115 mg, 0.83 mmol), were suspended in acetonitrile (2.0 mL), and ethyl-2-bromopropionate (742 μL, 5.6 mmol) was added. The reaction was stirred for 24 h. Upon completion, the reaction was diluted with EtOAc (20 mL), washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over Na_2SO_4, and concentrated to a brown oil. The crude product was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 30:70) to afford 135 mg (58% yield) of **39** as a brown solid. The pure compound was isolated as a 70:30 mixture of atropisomers; NMR data are provided for the major atropisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 – 8.43 (m, 1 H), 8.39 – 8.34 (m, 1 H), 8.10 – 8.05 (m, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.77 – 7.70 (m, 1 H), 7.70 – 7.60 (m, 3 H), 6.97 – 6.88 (m, 2 H), 5.12 (q, *J* = 7.3 Hz, 1 H), 4.23 – 4.10 (m, 2 H), 3.88 (s, 3 H), 1.34 – 1.22 (m, 6 H).



benzyl (*S*)-2-bromopropanoate

36. Benzyl (*S*)-2-bromopropanoate (40)

(*S*)-2-Bromopropionic acid (1.0 g, 6.54 mmol) and benzyl alcohol (0.778 g, 7.20 mmol) were dissolved in benzene (2 mL), and *p*-toluenesulfonic acid monohydrate (28 mg, 0.014 mmol) was added. The reaction was heated at reflux overnight. After 18 hours the reaction was removed from heat and cooled to room temperature. The reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine (2 × 20 mL), dried over Na_2SO_4, and concentrated to a yellow oil. The crude material was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 5:95) to afford 1.413 g (89% yield) of **40** as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.31 (m, 5 H), 5.26 – 5.16 (m, *J* = 1.0 Hz, 2 H), 4.42 (q, *J* = 6.8 Hz, 1 H), 1.85 (d, *J* = 7.1 Hz, 3 H); $[\alpha]_D^{20}$ = -10.0; $CHCl_3$, 10.0 mg/mL.

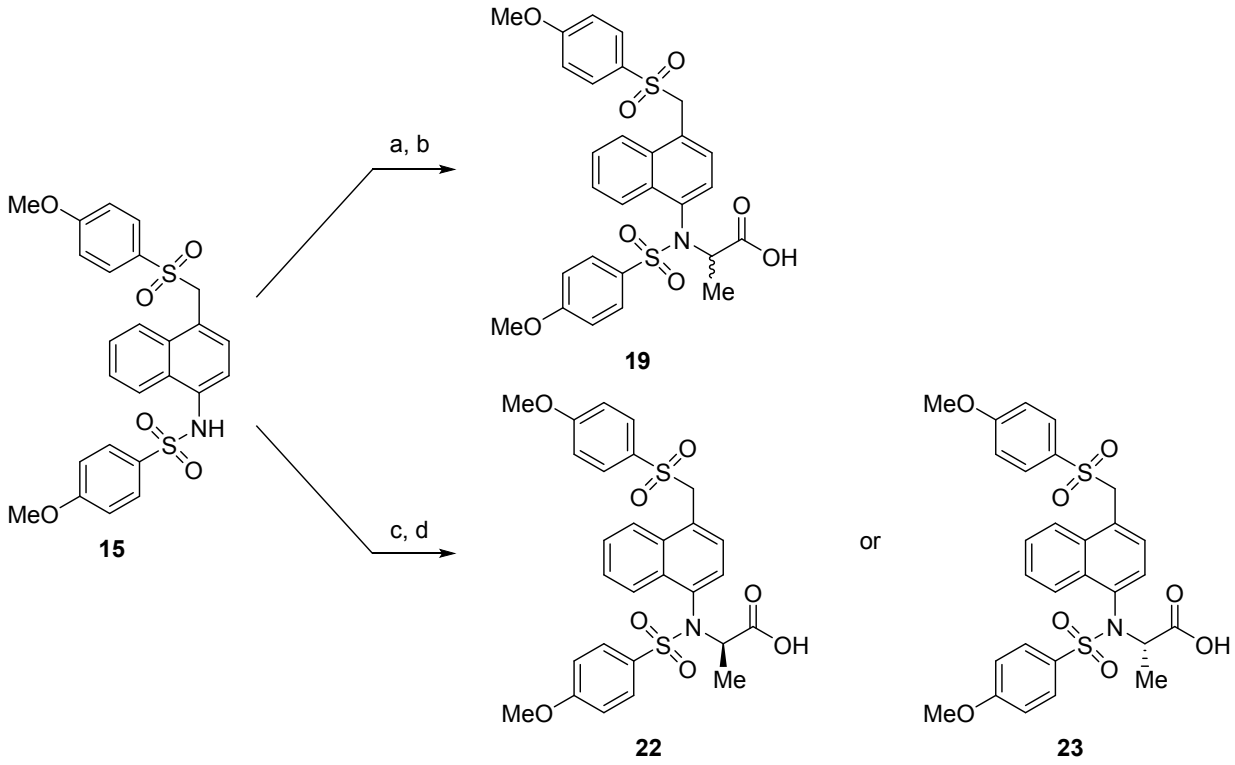


benzyl (*R*)-2-bromopropanoate

37. Benzyl (*R*)-2-bromopropanoate (41)

(*R*)-2-Bromopropionic acid (500 mg, 3.27 mmol) and benzyl alcohol (0.389 g, 3.60 mmol) were dissolved in benzene (1 mL), and *p*-toluenesulfonic acid monohydrate (17 mg, 0.09 mmol) was added. The reaction was heated at reflux overnight. After 18 hours the reaction was removed from heat and cooled to room temperature. The reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine (2 × 20 mL), dried over Na_2SO_4, and concentrated to a yellow oil. The crude material was purified by column chromatography (silica gel; EtOAc/Hexanes, 0:100 to 5:95) to afford 648 mg (82% yield) of **41** as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.32 (m, 5 H), 5.27 – 5.15 (m, *J* = 1.0 Hz, 2 H), 4.43 (q, *J* = 6.9 Hz, 1 H), 1.86 (d, *J* = 6.8 Hz, 3 H); $[\alpha]_D^{20}$ = +9.8; $CHCl_3$, 10.0 mg/mL.

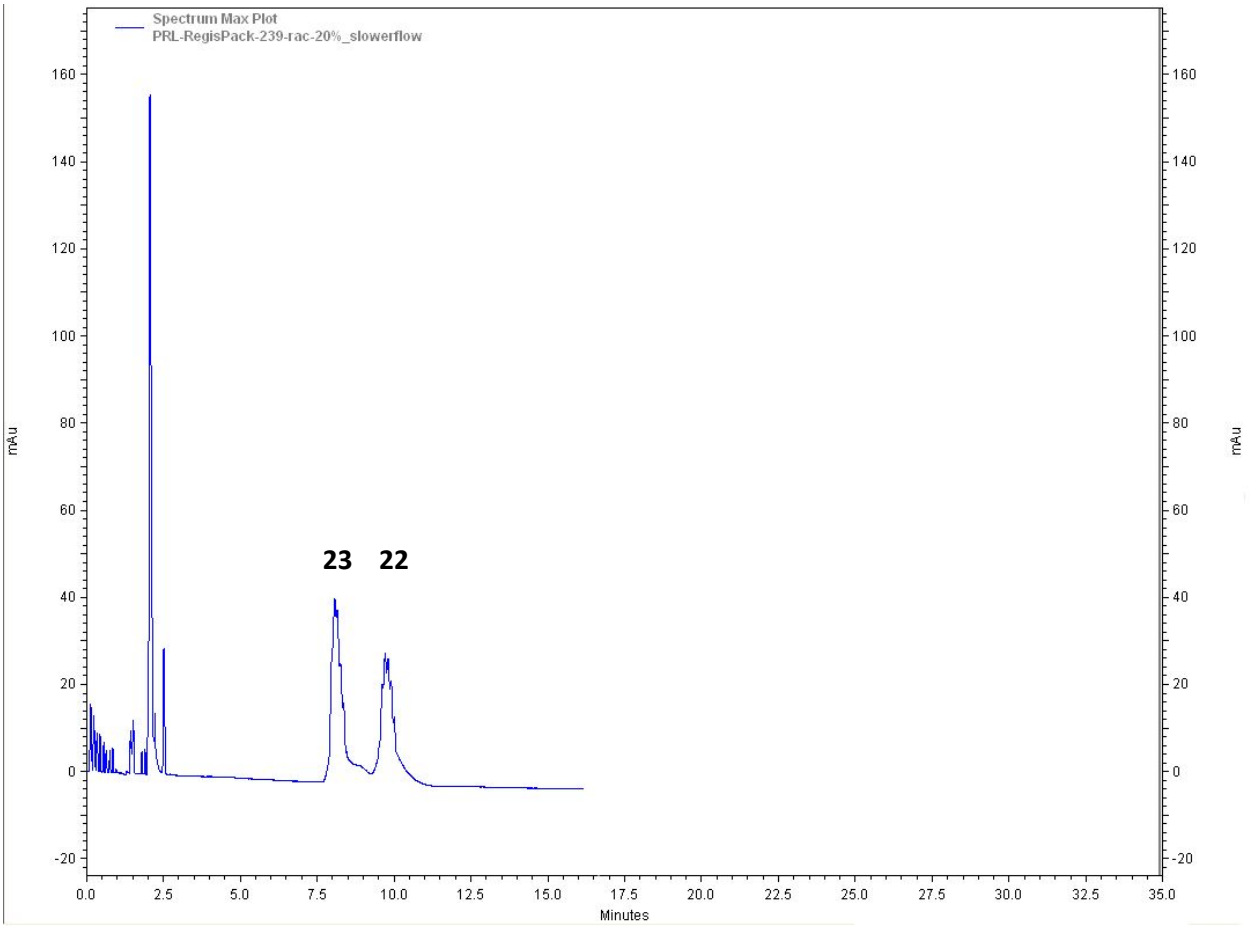
38. Synthesis of chiral analogs.



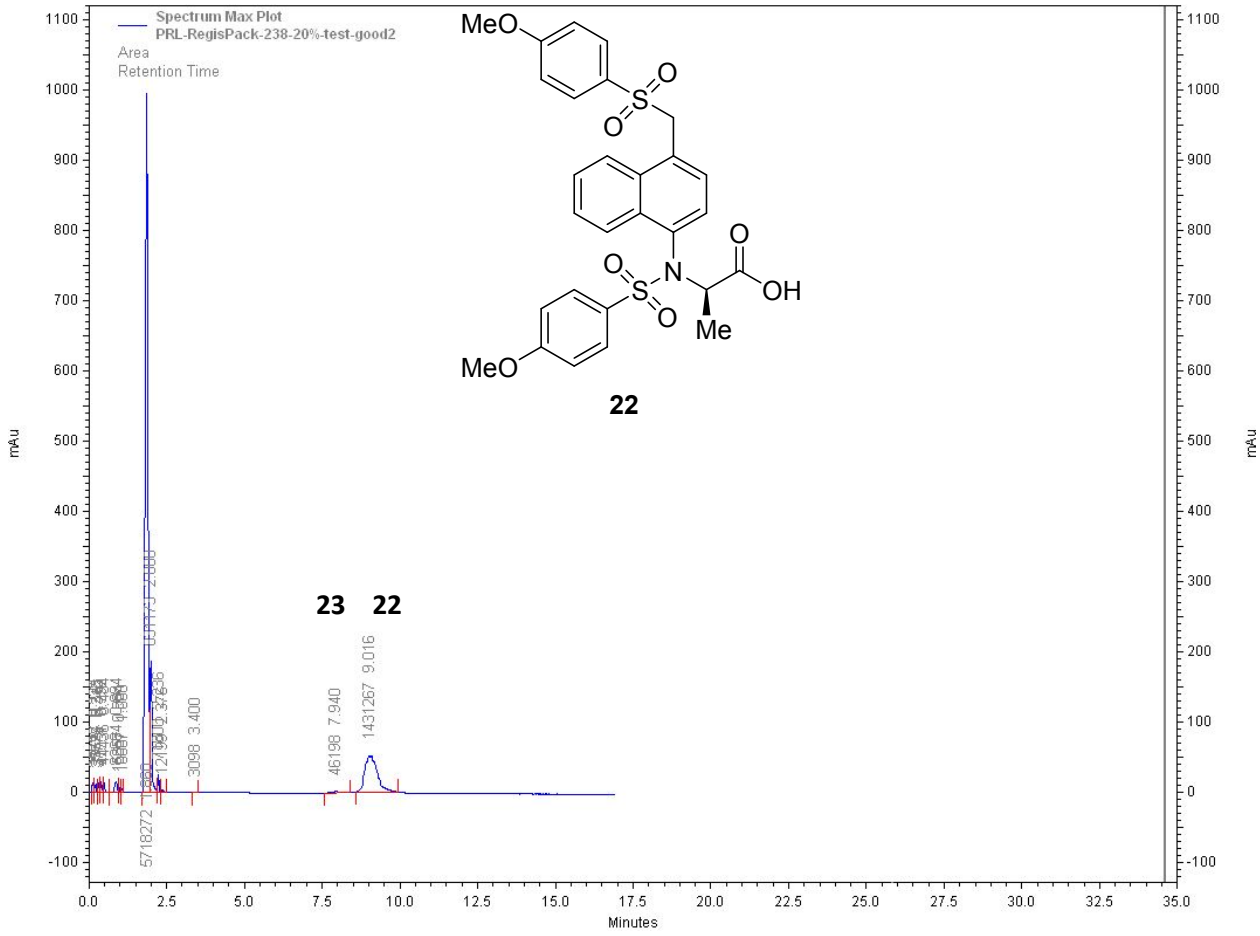
(a) Ethyl (*R*)-2-bromopropionate, K_2CO_3, MeCN, rt, 18 h; (b) 15% $NaOH_{(aq)}$, MeOH, rt, 5 h. (c) benzyl (*R*)-2-bromopropionate or benzyl (*S*)-2-bromopropionate, K_2CO_3, MeCN, rt, 18 h (d) 10% wt. Pd/C, H_2 (40 PSI), EtOAc/EtOH (1:1) 60 °C, 18 h

Analysis of chiral analogs.

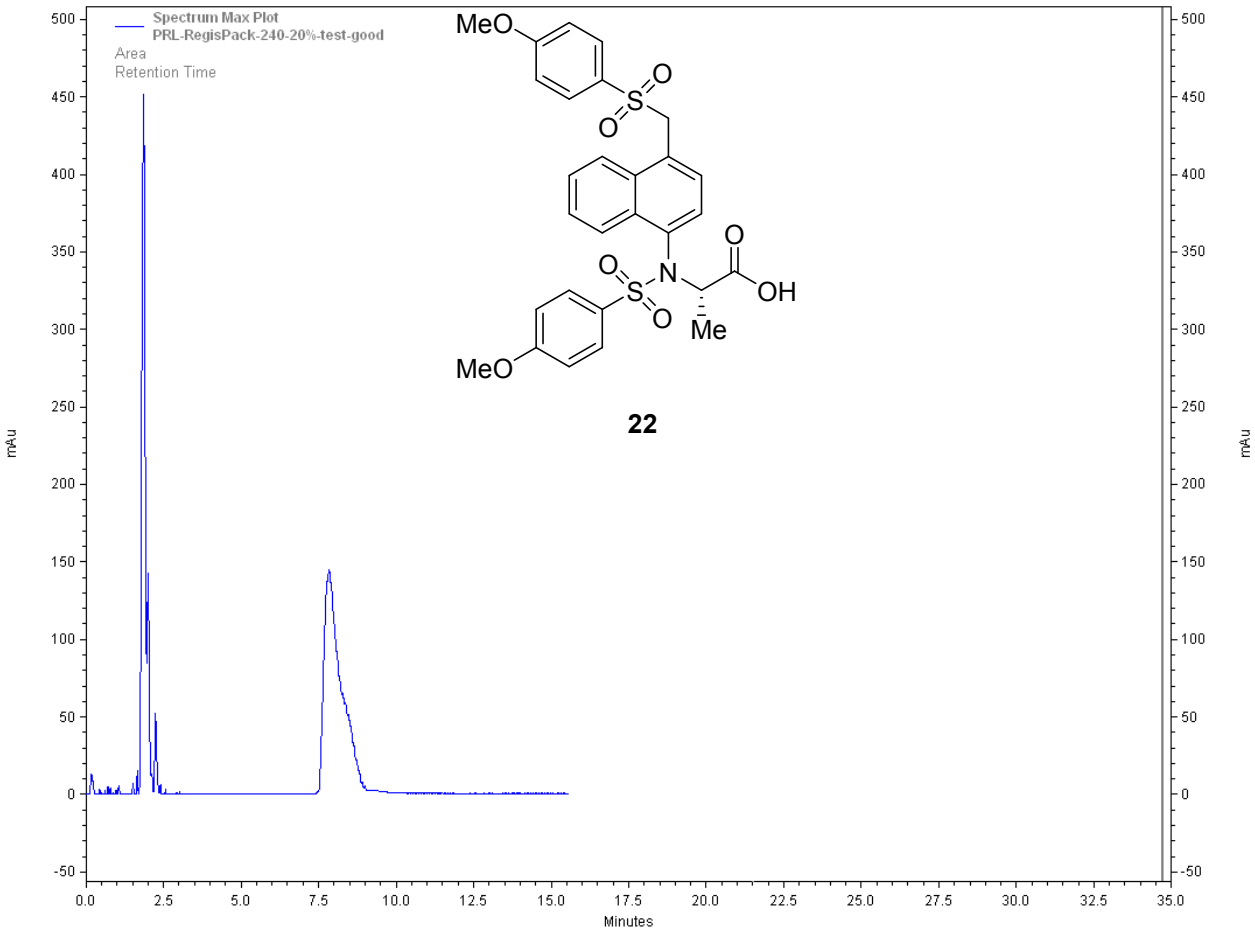
Racemate (Mixture of **22** and **23)**



Analysis of 22



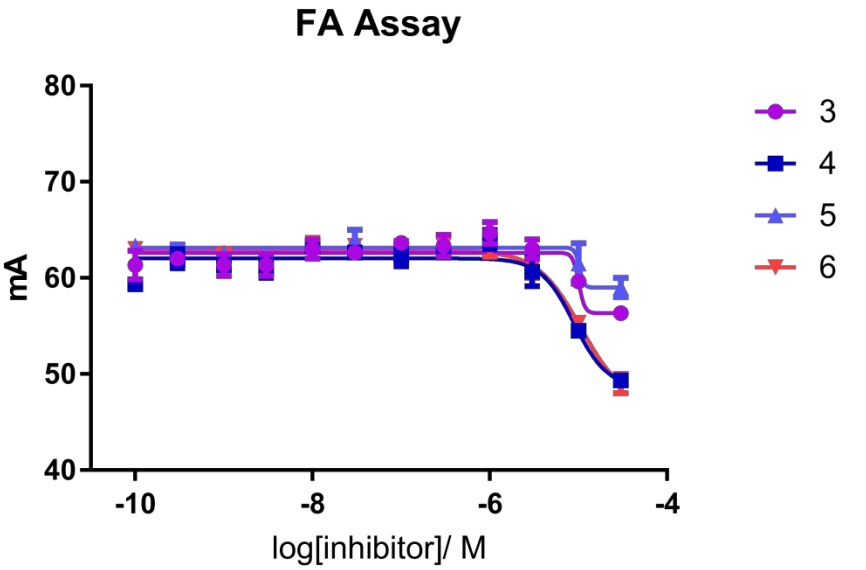
Analysis of 23

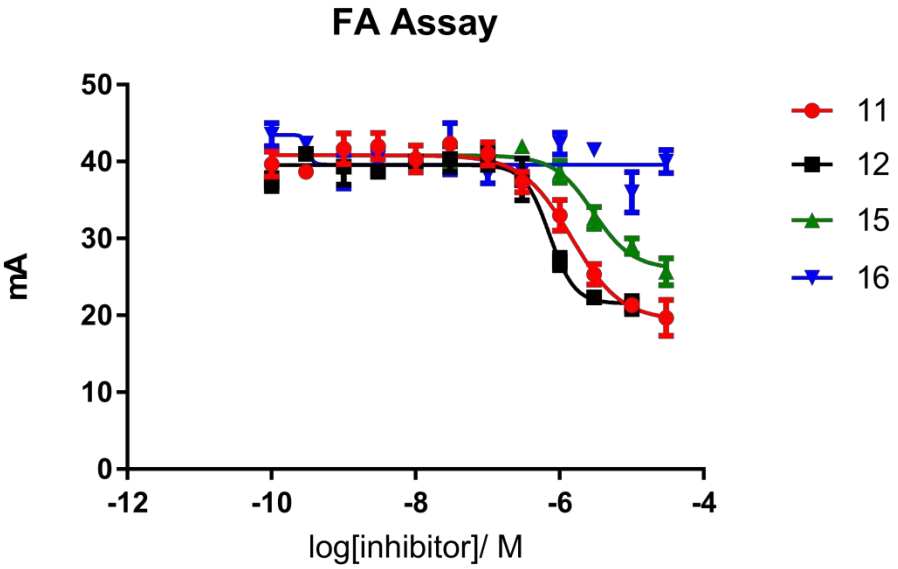


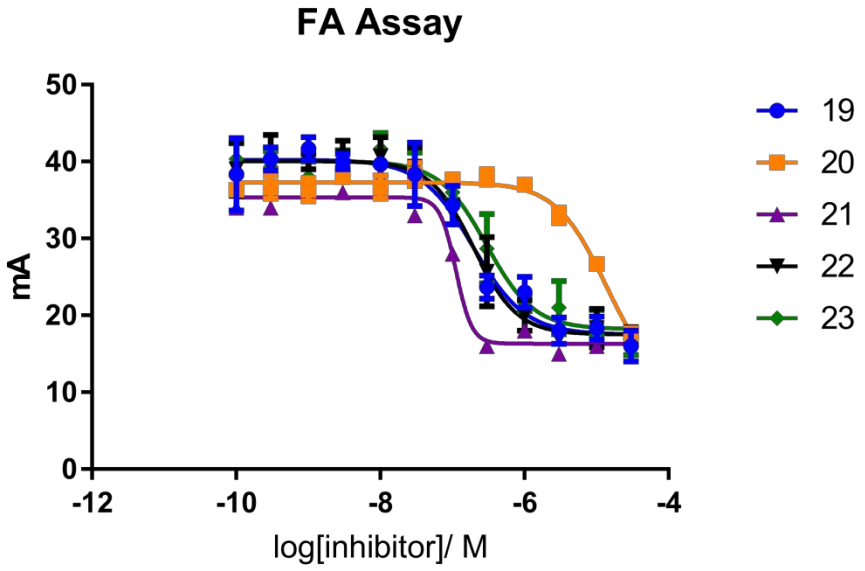
39. Biological Assay Information

Kelch Domain Expression and Purification. KEAP1 Kelch domain was expressed and purified as previously described.[4]

Fluorescence Anisotropy Assays. Fluorescence anisotropy assays were performed as previously described.[4] Briefly, small molecules' ability to inhibit the KEAP1-NRF2 interaction were assayed using the Kelch domain of KEAP1 and a fluorescein-labeled 9-mer peptide containing the ETGE motif of the Neh2 domain of NRF2.REF The experiments were performed in triplicate, and sigmoidal concentration-response curves were fitted to the data using GraphPad Prism 6.1 software.







40. Crystal Structure Information

Keap1 Kelch E540A/E542A purification and crystallization. Keap1 Kelch domain (aa 321-609) mutant (E540A/E542A)[5] was purified as previously described [6].

Crystals of Keap1 Kelch E540A/E542A complexed with **1c** were grown by hanging drop vapor diffusion at 12–16 °C. Prior to crystallization, 5-6 mg/mL Keap1 protein was incubated with 2-fold excess **1c** for 30 min on ice. Crystals of the complex were grown by mixing 2 µL of Keap1 E540A/E542A: **1c** with 0.4 µL of reservoir solution containing 3.5–3.8 M sodium formate, pH 7. Crystals grew overnight and were used to streak seed drops of Keap1 E540A/E542A:**1c** growing at lower saturation (1 µL Keap1 E540A/E542A:**1c** mixed with 0.3–0.5 µL of reservoir solution containing 3.1–3.6 M sodium formate, pH 7.0).

Data collection and structure refinement. The high concentration of sodium formate in the crystallization solution was sufficient to cryo-protect crystals, which were flash-cooled in liquid nitrogen. Data were collected on a MAR300 detector at 0.979 Å at the Life Sciences Collaborative Access Team beamline 21-ID-F at the Advanced Photon Source, Argonne National Laboratory. Data indexing, integration, and scaling were performed using HKL2000 [7], and phases were determined by molecular replacement using Molrep[8] and a Keap1 Kelch structure (PDB entry: 1U6D) as search model. Rigid body refinement followed by iterative rounds of restrained refinement and model building were performed with CCP4i[9] modules Refmac5[10] and Coot[11]. The coordinates and structure factors have been deposited with PDB accession code: 6V6Z.

Crystal Structure Parameters.

KEAP1 E540A/E542A compound **1c** (pdb 6V6Z)	Kelch with

Data Collection	
Space Group	P1
Cell Dimensions a,b,c (Å) α, β, γ (deg)	59.36 75.54 97.95 74.55 77.54 67.48
Resolution (Å)	50.0 (1.6)
Unique Observations	182432 (9249)
Completeness (%)	92.0 (94.3)
Redundancy	2.0 (2.0)
R_{merge}	0.057 (0.45)
I/σI	10.5 (1.6)
Source	LS-CAT ID-F
Collection date	6/22/2019
Wavelength	0.9787
Refinement	
Resolution (Å)	1.6
R_{work}/R_{free} (%)	18.6 (20.3)
Number of atoms (protein/other/solvent)	8807/359/1049
B-Factors ($Å^2$) (protein/other/water)	22.0/32.4/32.3
R.M.S.D. Bond (Å)	0.010
R.M.S.D. Angle (°)	1.54
Ramachandran favored (%)	97.26
Ramachandran allowed (%)	2.74
Rotamer outliers (%)	0.00
Molecules in ASU	4
Programs Used	
Processing	XDS
Scaling	XDS
Phasing	Molrep
Phasing Model	1U5D
Manual Build	Coot
Refinement	Refmac

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