Structure-Activity Relationship for Thiirane-Based Gelatinase Inhibitors

*Mijoon Lee, Masahiro Ikejiri, Dennis Klimpel, Marta Toth, Mana Espahbodi, Dusan Hesek, Christopher Forbes, Malika Kumarasiri, Bruce C. Noll, Mayland Chang and Shahriar Mobashery**

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556, USA

Supporting Information

Contents

Experimental Procedures ····· S2

Syntheses of compounds 1 to 43 ····· S3

Table S1. Spectral data of final compounds ····· S18

Figure S1. High-throughput screening of synthetic compounds with MMP-2 ····

····· S36

Table S2. Full slow-binding kinetic parameters for inhibition of MMP-2

by selected compounds ····· S43

Figure S2. The docked conformation of selected compounds ····· S44

References ····· S44

Experimental Procedures.

Enzyme Inhibition Kinetics. Human recombinant active MMP-2 and MMP-7 and catalytic domains of MMP-3 and MMP-14 were purchased from EMD Biosciences. The catalytic domains of human recombinant MMP-1 and MMP-9 were from Biomol. The fluorogenic substrate MOCAcPLGLA2pr(Dnp)AR-NH_2 and MOCAcRPKPVE (Nva)WRK(Dnp)-NH_2 were purchased from Peptides International and (Dnp)P(Cha)GC(Me)HAK(NMa)NH_2 was obtained from R&D Systems. Inhibitor stock solutions (10 mM) were prepared in DMSO. The methodology for enzyme inhibition and assays was the same as that reported previously.[1]

Screening of MMP-2 inhibitors on 96-well plates. Initial screenings of various synthetic compounds on MMP-2 activity were performed on 96-well plates with Varian Cary Eclipse fluorescence spectrophotometer. Substrate hydrolysis were monitored for 15 minutes in a buffer (50 mM HEPES, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$, 0.01% Brij-35 and 1% DMSO) contained 10 μM substrate, 2-5 nM enzyme and various concentrations (30 μM, 3 μM, or 300 nM) of compound. The enzyme was either preincubated with the inhibitor 2 hrs before assessment of activity, or no delaytime in activity measurements. The control reactions did not include inhibitor. Slopes of progress curves were plotted on bar graph as percentage of the value for the control runs (100%).

Metabolic Stability. Compounds (10 μM) were incubated with male rat liver S9 (1 mg protein/mL, BD Biosciences, Woburn, MA, USA) and nicotinamide adenine dinucleotide phosphare reduced (0.5 mM) in potassium phosphate buffer (50 mM, pH 7.4) at 37 °C for up to 60 min. Aliquots were taken at each of five or more time points, and the reaction was terminated by the addition of one and a half volumes of acetonitrile containing 10 μM of an internal standard. The reaction mixtures were centrifuged (13 min, 13,000 g) and aliquots of the supernatants of compounds **22a**, **26**, **32**, and **33a** were analyzed by Ultra Performance Liquid Chromatography (UPLC) with UV detection. The remaining compounds were analyzed by multiple reaction monitoring (MRM) mass spectrometry. All analyses were conducted in duplicate.

UPLC Chromatography. The UPLC system consisted of a Waters Acquity UltraPerformance LC Binary Solvent Manager, Sample Manager, and PDA eλ Detector (Waters Corporation, Milford, Massachusetts, USA). Samples were analyzed on a Waters Acquity UltraPerformance HSS C18 1.8 μm, 2.1 mm i.d. × 100 mm column (Waters Corporation, Milford, Massachusetts, USA). The mobile phase consisted of elution at 0.4 mL/min with a 12-min linear gradient from 80% A/20% B to 20% A/80% B, followed by a 3-min linear gradient back to 80% A/20% B (A = water with 5% acetonitrile, B = acetonitrile). Effluent was monitored by UV detection at 245 nm.

Mass Spectrometry. The mass spectrometry system consisted of a Waters Acquity UltraPerformance LC Binary Solvent Manager, Sample Manager, PDA Detector, and Triple Quadrupole (TQ) Detector (Waters Corporation, Milford, Massachusetts, USA), using MASSLYNX V4.1 software. The mass spectrometry system was operated in ESI positive mode with the following parameters for compound **36**: capillary voltage = 2.8 kV,

cone voltage = 30 V, extractor voltage = 3 V, RF lens voltage = 0.1 V, source temperature = 150 °C, desolvation temperature = 350 °C, desolvation gas flow rate (N_2) = 450 L/hr, and cone gas (Xe) flow rate = 0 L/hr. For the remaining compounds, the instrument was operated in ESI negative mode with the following parameters: capillary voltage = 2.8 kV, cone voltage = 35 V, extractor voltage = 3 V, RF lens voltage = 0.3 V, source temperature = 150 °C, desolvation temperature = 350 °C, desolvation gas flow rate (N_2) = 650 L/hr, and cone gas (Xe) flow rate = 50 L/hr. Samples were maintained at 4 °C in an autosampler tray and were analyzed on a Waters Acquity UltraPerformance BEH C18 1.7 μm, 2.1 × 50 mm column (Waters Corporation, Milford, Massachusetts, USA) at 40 °C. The mobile phase consisted of elution at 0.5 mL/min with a 5-min linear gradient from 40% C/60% D to 10% C/90% D (C = water with 5% acetonitrile and 0.1% formic acid, D = acetonitrile with 0.1 % formic acid). Effluent was monitored by MRM. The fragments were analyzed with a dwell time of 0.1s and a collision energy of 20 V. The transitions that were monitored for each compound were: 305 → 168 for **1**, 323 → 186 for **19a** and **19b**, 389 → 252 for **38a**, 321 → 184 for **30a**, 399 → 184 for **35a**, 322 → 185 for **36**, and 434 → 156 for the internal standard.

Half-life Determination. Peak area ratios relative to internal standard were measured. Half-lives of the compounds in rat liver S9 were calculated according to the first-order rate law. The standard deviations in the half-lives were calculated from the error in the linear regressions fit to the data averaged from the two replicates using the LINEST function in Microsoft Excel. The error was propagated appropriately.

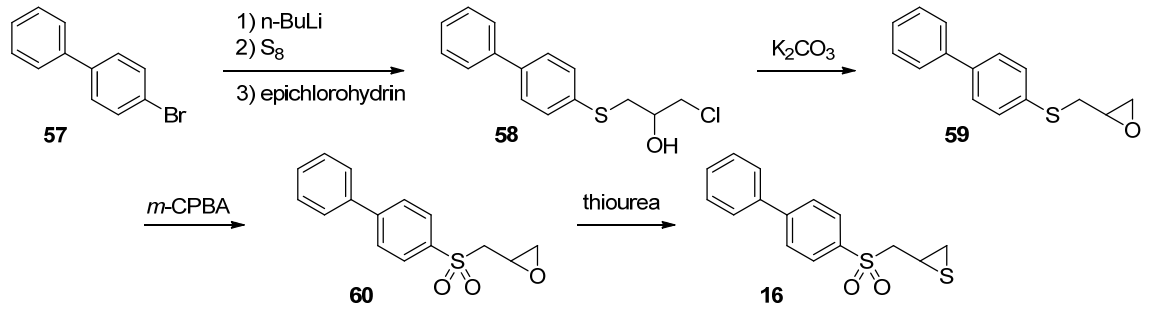
Identification of Metabolites. Compounds (50 μM, **19a**, **26**, **38a**, **30a**) were incubated with rat liver microsomes (0.5 mg, BD Biosciences, Woburn, MA, USA) at 37°C for 15 min in 50 mM potassium phosphate buffer at pH 7.4 and 0.5 mM NADPH. A second incubation of compound **30a** was carried out in the presence of uridine 5'-diphosphoglucuronic acid (3 mM). The incubations were terminated by addition of one volume of acetonitrile. The precipitated protein was centrifuged (10 min, 13,000 g) and the supernatant was analyzed by reversed-phase HPLC with tandem mass spectrometry.

Syntheses of compounds 1 to 43.

General Information. All reactions were performed under an atmosphere of nitrogen, unless noted otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-500 or Varian Unity*Plus* 300 spectrometer. Thin-layer chromatography was performed with Whatman reagents 0.25 mm silica gel 60-F plates. Flash chromatography was carried out with silica gel 60, 230-400 mesh (0.040-0.063 mm particle size) purchased from EM Science. High-resolution mass spectra were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame by FAB ionization, using a JEOL AX505HA mass spectrometer or ESI ionization, using Bruker micrOTOF/Q2 mass spectrometer.

A representative example of each route in Scheme 1 (in main manuscript) is given as Schemes S1-S6. The compounds, which were prepared not by a general scheme, are given in Schemes S7-S15.

Scheme S1. Synthesis of compound 16 via route A

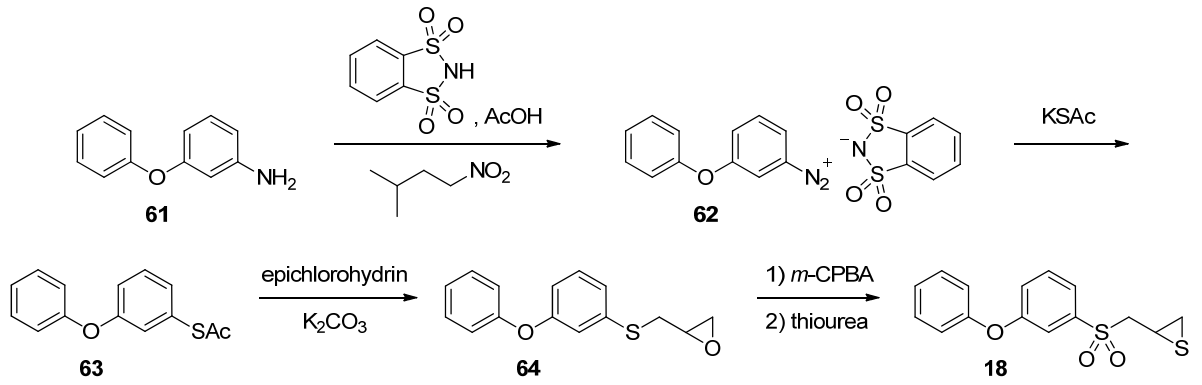


4-Biphenylsulfonylmethyloxirane (60). ***General procedure of route A.*** *n*-BuLi (10.7 mL, 2.5 M in hexane) was added to a solution of bromide **57** (6.25 g, 26.8 mmol) in anhydrous THF (120 mL) with vigorous stirring at -78 °C. After stirring for 30 min, sulfur (0.86 g, 26.8 mmol) was added to the reaction mixture. The mixture was stirred for 0.5 h, while temperature was raised to 0 °C. After cooled down to -78 °C, epichlorohydrin (2.2 mL, 28.1 mmol) was added dropwise to the reaction mixture. Stirring was continued for 1 h, while temperature was raised to room temperature. The reaction was quenched by the addition of a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate and the organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (4.86 g, 65%). Potassium carbonate (2.81 g, 20.4 mmol) was added to a solution of compound **58** (2.84 g, 10.2 mmol) in a 1:2 mixture of methanol and acetonitrile (100 mL) in ice-water bath with vigorous stirring. After 10 min, ice-water bath was removed and stirring was continued for 1 h at room temperature and was filtered through a small layer of silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography to afford the desired product (2.10 g, 85%). To a solution of compound **59** (1.88 g, 7.74 mmol) in CH_2Cl_2 (20 mL) was added *m*-chloroperoxybenzoic acid (*m*-CPBA, 3.47 g, 15.5 mmol, 77%) in ice-water bath. After 30 min, the suspension was filtered, and the filtrate was diluted with CH_2Cl_2 and washed with 10% aqueous sodium thiosulfate, followed by saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and was concentrated. The product was purified by silica gel chromatography to yield the title compound as an oil (1.61 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (dd, *J* = 4.8, 2.0 Hz, 1H), 2.84 (t, *J* = 4.0 Hz, 1H), 3.35 (m, 3H), 7.41 - 7.53 (m, 3H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.0, 46.1, 59.7, 124.7, 127.4, 127.6, 128.1, 128.1, 128.9, 128.9, 129.1, 129.3, 137.8, 139.1, 147.2; HRMS (ESI) calcd for $C_{15}H_{15}O_3S$ ($M+H^+$) 275.0736, found 275.0729.

4-Biphenylsulfonylmethylthirane (16). Thiourea (0.26 g, 3.4 mmol) was added to a solution of compound **60** (0.47 g, 1.7 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water, the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and the suspension was filtered.

Evaporation of solvent gave the crude product, which was purified by column chromatography (0.41 g, 84%). Spectral data is given in Table S1.

Scheme S2. Synthesis of compound 18 via route B



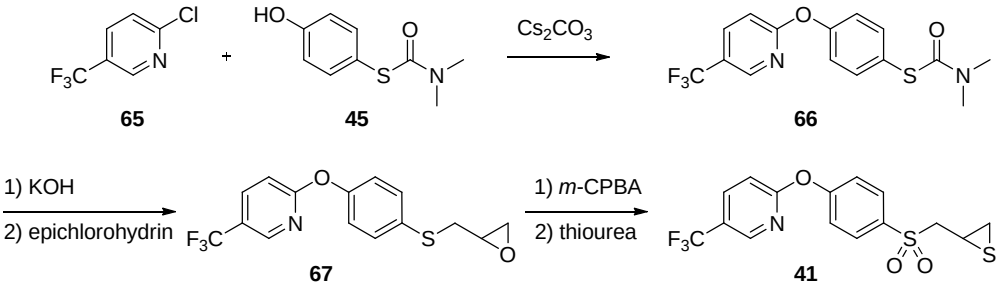
3-Phenoxyphenyl-2-thioacetate (63). ***General procedure of route B.*** Condition is adapted from the literature methods.[2, 3] A solution of *o*-benzenedisulfonimide (2.6 g, 12 mmol) in glacial acetic acid (40 mL) was slowly added, over a period of 10 min, to a solution of 3-phenoxyaniline (**61**, 1.85 g, 10 mmol) in acetic acid (20 mL) in an ice bath. Isoamylnitrite (1.5 mL, 11 mmol) was added dropwise to the reaction mixture over 10 min and the resulting mixture was stirred for 0.5 h at the same temperature. Addition of diethyl ether to the reaction mixture resulted in diazonium salt, **62**, as an orange powder, which was filtered, and washed with cold diethyl ether. Potassium thioacetate (0.98 g, 10 mmol) in acetonitrile (10 mL) was added to the crude diazonium salt (2.0 g) in anhydrous acetonitrile (10 mL) and the resulting suspension was stirred at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel to afford the desired product (0.97 g, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.09-7.22 (m, 6H), 7.38-7.44 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.3, 119.4, 119.8, 123.9, 124.4, 129.1, 130.4, 156.7, 157.9, 193.6; HRMS (FAB) calcd for $C_{14}H_{12}O_2S$ (M^+) 244.0558, found 244.0556.

2-(3-Phenoxyphenylsulfanylmethyl)oxirane (64). Compound **63** (0.61 g, 2.5 mmol) was stirred at room temperature for 0.5 h in the presence of K_2CO_3 (1.4 g, 10 mmol) in anhydrous acetonitrile (10 mL). Epibromohydrin (0.8 mL, 10 mmol) was added dropwise to the reaction mixture and the resulting solution was stirred at room temperature for additional 1 h. The reaction mixture was filtered, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel to afford the desired product (0.56 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (dd, 1H, J = 2.2, 4.7 Hz), 2.81 (t, 1H, J = 4.2 Hz), 2.98 (q, 1H, J = 7.8 Hz), 3.16-3.20 (m, 2H), 6.88 (dd, 1H, J = 2.5, 7.9 Hz), 7.04-7.09 (m, 3H), 7.16 (t, 2H, J = 7.4 Hz), 7.28 (t, 1H, J = 7.8 Hz), 7.38 (t, 2H, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3, 47.6, 51.0, 117.0, 119.3, 119.8, 123.8, 124.4, 130.0, 130.3, 137.4, 156.8, 157.9; HRMS (FAB) calcd for $C_{15}H_{14}O_2S$ (M^+) 258.0715, found 258.0713.

2-(3-Phenoxyphenylsulfonylmethyl)thiirane (18). Compound **18** was prepared by treatment of *m*-CPBA in CH_2Cl_2, followed by thiourea in MeOH. Spectral data is given in Table S1.

Synthesis of SB-3CT (1) via route C is reported in the literature by our laboratory.[4] Detailed experimental condition is given in reference 4.

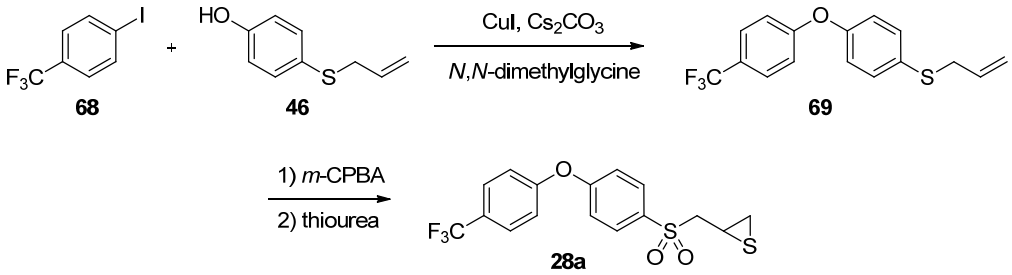
Scheme S3. Synthesis of compound 41 via direct aromatic substitution (ii) / Route D



Compouund 66. ***General procedure of direct aromatic substitution.*** To a stirred solution of **45** (2.0 g, 10 mmol) in DMF (30 ml) were added cesium carbonate (4.9 g, 15 mmol) and 2-chloro-5-trifluoromethylpyridine (1.8 g, 10 mmol) at room temperature, and the mixture was stirred for 18 h. After dilution with water, the mixture was extracted into CH_2Cl_2. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Tritulation of the crude product with ether gave **66** (3.1 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.11 (s, 3H), 7.04 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.1, 111.7, 122.2, 125.7, 137.0 (q, *J* = 3.3 Hz), 137.5, 145.6 (q, *J* = 4.1 Hz), 154.2, 165.6, 166.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -61.69 (s, 1F); HRMS (ESI) calcd for $C_{15}H_{14}F_3N_2O_2S$ ($M+H^+$) 343.0723, found 343.0746.

Compound 67. ***General procedure of route D.*** Compound **66** (3.8 g, 11 mmol) was added to methanolic KOH (6.3 g, 88 mmol) in MeOH (80 mL) and then refluxed for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in acetonitrile / MeOH (2:1, 60 mL) and neutralized by addition of acetic acid (5.0 mL, 88 mmol). The reaction mixture was treated with K_2CO_3 (5.9 g, 43 mmol) and stirring was continued for 0.5 h. Addition of epichlorohydrin (1.67 mL, 21.4 mmol) to the reaction mixture was followed and it was stirred at room temperature for 2 h and was filtered through a layer of silica gel. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography to give compound **67** (2.6 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (dd, *J* = 3.5, 2.5 Hz, 1H), 2.84 (t, *J* = 4.2 Hz, 1H), 3.01 (d, *J* = 5.6 Hz, 1H), 3.16 - 3.25 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.5, 47.6, 51.2, 111.7, 122.3, 132.2, 132.5, 137.0 (q, *J* = 3.3 Hz), 145.6 (q, *J* = 4.1 Hz), 152.4, 165.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -61.69 (s, 1F); HRMS (ESI) calcd for $C_{15}H_{13}F_3NO_2S$ (M^+) 328.0619, found 328.0614. Conversion from compound **67** to compound **41** was followed by the same method as described in Scheme S1. Spectral data is given in Table S1.

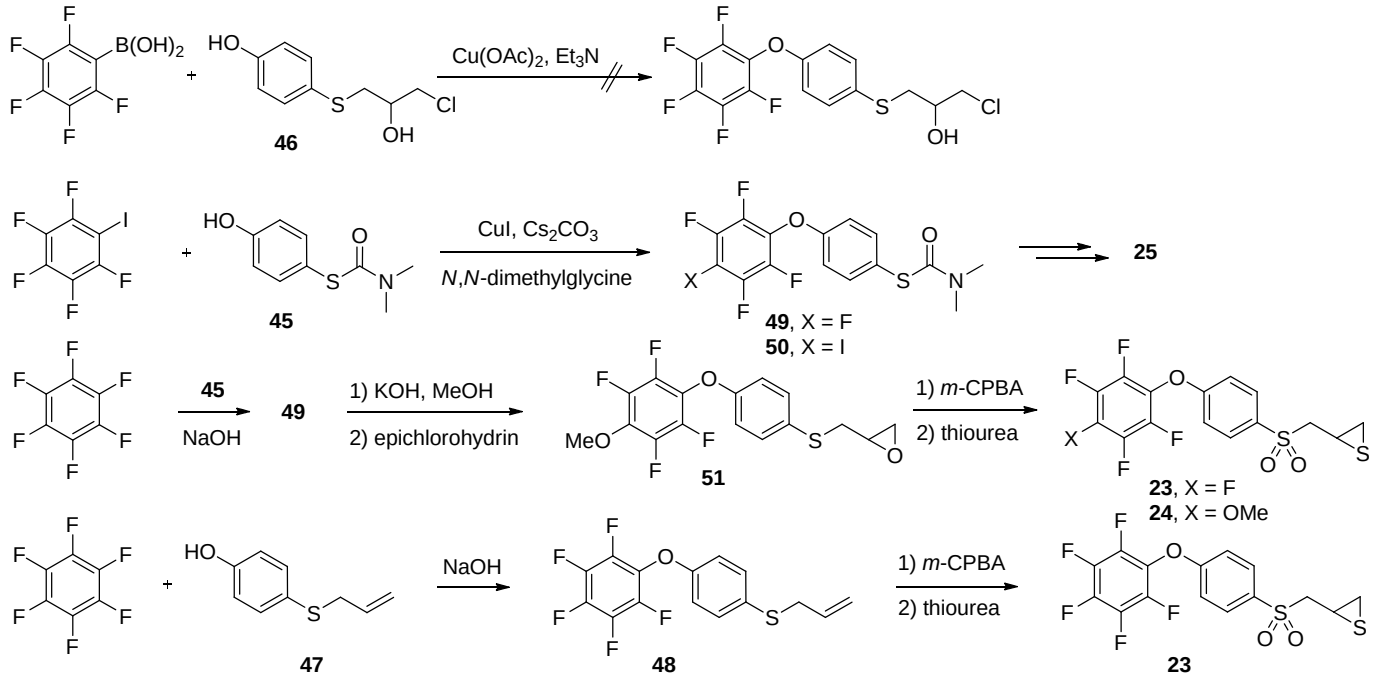
Scheme S4. Synthesis of compound 28a via Ullmann Condensation (i) / route E



4-(4-Trifluoromethylphenoxy)-1-allylthiobenzene (69). ***General procedure of Ullmann condensation.*** The procedure was adapted from that reported by Ma et al.[5] A mixture of 4-iodobenzotrifluoride (1.5 mL, 10 mmol), 4-allythiophenol (2.5 g, 15 mmol), Cs_2CO_3 (6.8 g, 21 mmol), *N*,*N*-dimethylglycine hydrochloride salt (0.44 g, 3.2 mmol), CuI (0.20 mg, 1.1 mmol) in degassed 1,4-dioxane (20 mL) was heated at 90 ºC for 22 h under a nitrogen atmosphere. After dilution with water, the mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resultant residue was purified by column chromatography to give compound **69** as a white solid (2.4 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (d, *J* = 7.4 Hz, 2H), 5.20 (d, *J* = 16.9 Hz, 1H), 5.37 (d, *J* = 10.2 Hz, 1H), 5.82 (m, 1H), 7.15 (dd, *J* = 13.5, 8.7 Hz, 4H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 61.1, 118.6, 120.0, 124.8, 125.0, 127.7, 127.7, 131.1, 133.2, 158.2, 161.2; 19F NMR (282 MHz, $CDCl_3$) δ -62.0 (s, 1F); HRMS (FAB) calcd for $C_{16}H_{13}F_3OS$ (M^+) 310.0639, found 310.0620.

2-(4-Trifluoromethylphenoxyphenylsulfanylmethyl)thiirane (28a). Compound **28a** was prepared by treatment of *m*-CPBA in CH_2Cl_2, followed by thiourea in MeOH. Spectral data is given in Table S1.

Scheme S5. Synthesis of compound 23 via aromatic substitution / route E



Synthesis of pentafluorinated compound (**23**) turned out to be challenging. The initial attempt to form the diphenyl ether using pentafluorophenyl boronic acid was not successful. When 1-iodo-pentafluorobenzene was subjected to Ullmann condensation, compound **50** formed as the main product, instead of the desired product **49**. Since hexafluorobenzene is highly activated and can undergo substitution reactions readily under basic condition, we attempted direct aromatic substitution using sodium hydroxide, resulting in the desired product **49**. The thiocarbamate in **49** was then hydrolyzed under basic condition and simultaneously alkylated with epichlorohydrin. ^{1}H NMR of the resulting product (originally expected to be **23**) showed a singlet at 3.6 ppm, which thought to be originated from methanol, which was used as a solvent. It turned out that 4-OMe substituted compound (**24**) had formed as a main product, instead of the pentafluoro derivative, which was confirmed by high-resolution mass spectrometry.

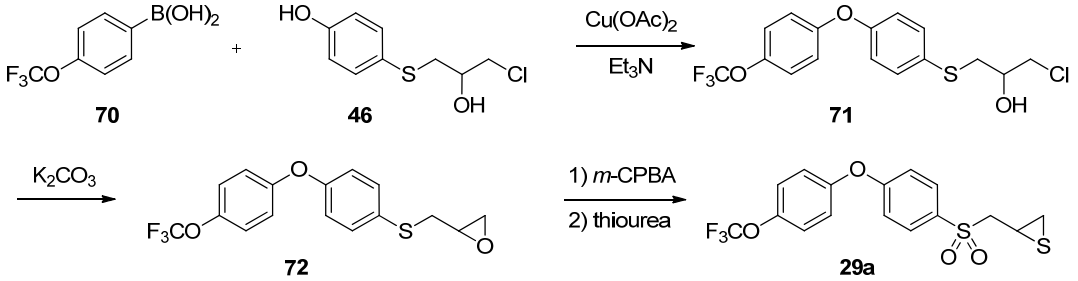
The fluorine at the *p*-position is highly activated and it was substituted by methanol (reaction solvent) under basic condition. High reactivity of the *p*-fluoride prompted us to seek an intermediate whose conversion to thiirane did not require basic reaction conditions. We decided to use allylthiophenol (**47**) instead of thiocarbamate (**45**), which obviated the use of basic reaction conditions. We encountered no difficulty in obtaining compound **48** through direct aromatic substitution, which was then smoothly converted to the sulfone that had the oxirane in place using *m*-CPBA. Our typical substitution of oxygen in oxirane for sulfur requires the use of methanol as a solvent, which concerned us due to the possibility of OMe substitution at the *para* position of the left-terminal ring. We set up several reactions using different solvents, including methanol, 2-propanol, and ethylene glycol.

The reaction did not take place when 2-propanol or ethylene glycol were used by themselves as solvents. But addition of a small quantity of methanol accelerated the reaction rate. During this reaction, OMe substituted thiirane was not formed as a by-product and only the desired product (**23**) was obtained.

4-(4-*penta*-Fluorophenoxy)-1-allylthiobenzene (48). NaOH (0.60 g, 15 mmol) was added to a mixture of pentafluorobenzene (1.2 mL, 10 mmol) and compound **47** (1.7 g, 10 mmol) in DMF (10 mL) in ice-water bath. The resulting mixture was stirred at the same temperature for 0.5 h and was filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product (2.9 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49 (d, *J* = 7.0 Hz, 2H), 5.05 (s, 1H), 5.08 (d, *J* = 8.2 Hz, 1H), 5.82 - 5.90 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -162.20 (dd, *J* = 22.0, 17.4 Hz, 1F), -159.98 (t, *J* = 21.5 Hz, 1F), -154.13 (d, *J* = 17.4 Hz, 1F); HRMS (ESI) calcd for $C_{15}H_{10}F_5OS$ (M^+) 333.0367, found 333.0344.

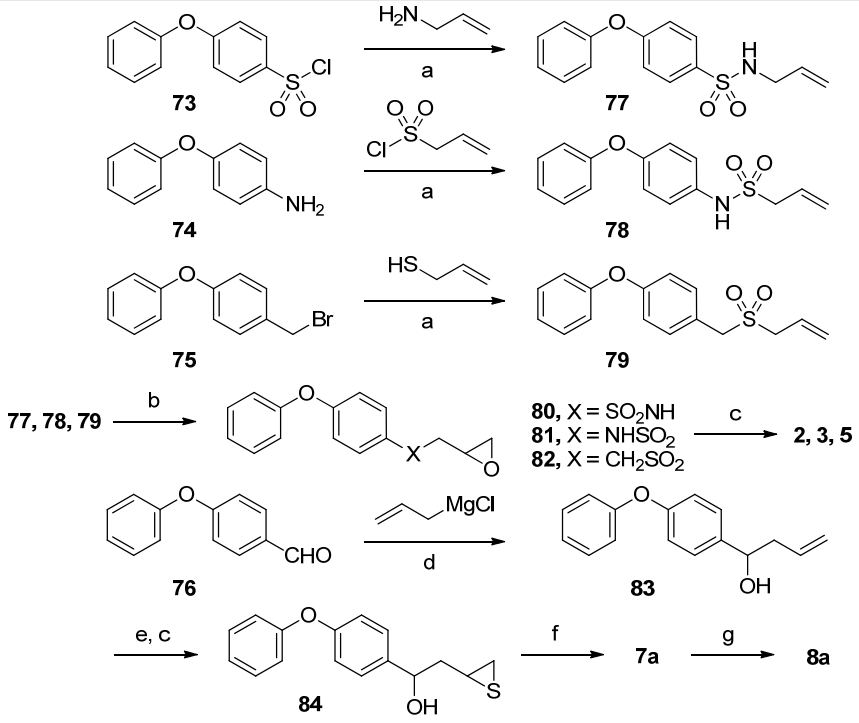
2-(4-*penta*-Fluorophenoxyphenylsulfanylmethyl)thiirane (23). Compound **23** was prepared by treatment of *m*-CPBA in CH_2Cl_2, followed by thiourea in 5% MeOH in CH_2Cl_2. Spectral data is given in Table S1.

Scheme S6. Synthesis of compound 29a via Cu-mediated Suzuki-type coupling



1-Chloro-3-[4-(trifluoromethoxyphenoxy)phenylsulfanyl]propan-2-ol (71). ***General procedure of Cu-mediated Suzuki type reaction.*** The procedure was adapted from that reported by Chan et al. and Evan et al.[6, 7] A mixture of compound **46** (0.85 g, 3.9 mmol), $Cu(OAc)_2$ (0.72 g, 4.0 mmol), trifluoromethoxyphenyl boronic acid (**70**, 1.6 g, 7.9 mmol), and powdered 4 Å molecular sieves was stirred in CH_2Cl_2 and triethylamine (1.10 mL, 7.9 mmol) was added. After stirring for 36 h at room temperature, the resulting slurry was filtered through a layer of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to give the desired product (0.68 g, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (d, *J* = 4.8 Hz, 1H), 3.04 (dd, *J* = 13.8, 7.0 Hz, 1H), 3.14 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.69 (m, *J* = 5.0, 5.0 Hz, 2H), 3.92 (m, *J* = 5.1, 1.5 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.7, 48.2, 69.7, 119.8, 120.1, 120.2, 122.9, 133.2, 133.4, 155.4, 156.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -58.3; HRMS (FAB) calcd for $C_{16}H_{14}ClF_3O_3S$ ($M+H^+$) 379.0383, found 379.0365. Conversion from compound **71** to compound **72, 29a** was followed by the same method as described in Scheme S1. Spectral data of **29a** is given in Table S1.

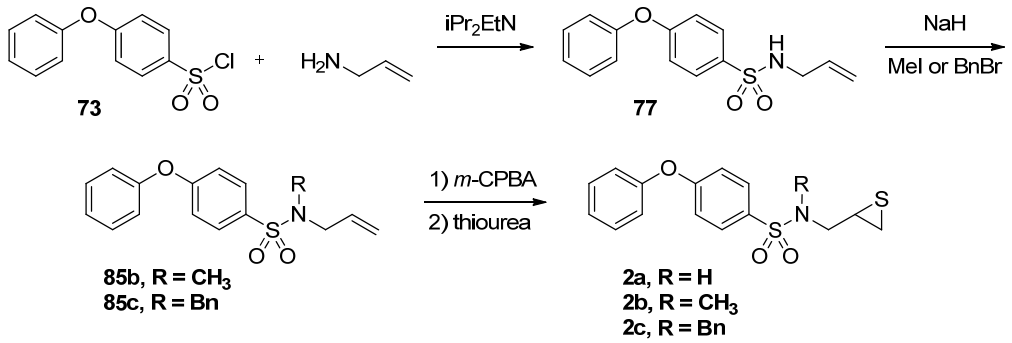
Scheme S7. Syntheses of SAR-1 derivatives [a]



[a] Reagents and conditions; (a) *i*Pr_2EtN; (b) *m*-CPBA; or NMO, OsO_4; DEAD, PPh_3, Et_3N; (c) thiourea; (d) *i*Pr_2EtN; (e) NBS, NaOH; (f) PCC; (g) $NH_2OH \cdot HCl$, NaOAc.

Syntheses of SAR-1 series are shown in Scheme 2. All these compounds were prepared by the reaction of phenoxyphenyl derivatives (**73-76**) and allyl containing reagents (amine, sulfonyl chloride, thiol, and magnisum chloride). Functional group transformations from allylsulfide to sulfonylmethyl expoxide, and to thiirane were successfully carried out by standard conditions outlined in Fig. 1 in the main manuscript. For the syntheses of ketone and oxime derivative (**7** and **8**), the double bond in compound **83** was converted to epoxide via hydrobromination. The oxidation of alcohol to ketone had to be performed after the formation of thiirane, as decomposition of ketone was observed under the epoxide-formation condition. Ketone **7a** was transformed to oxime **8a** in the presence of hydroxylamine hydrochloride and sodium acetate.

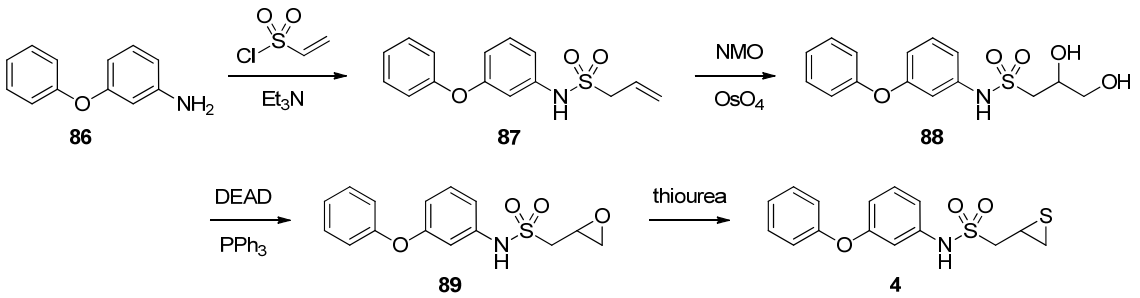
Scheme S8. Synthesis of compounds 2a – 2c



***N*-Allyl-(4-phenoxyphenyl)sulfonamides (77).** To a stirred solution of allylamine (0.29 mL, 3.9 mmol) and *i*Pr_2EtN (0.78 mL, 4.5 mmol) in CH_2Cl_2 (10 mL), is added the 4-phenoxybenzene sulfonyl chloride (1.0 g, 3.7 mmol)) dissolved in CH_2Cl_2 (10 mL) over a 1 minute period. After stirring at room temperature for 0.5 h, the resultant was diluted with CH_2Cl_2 and water and then layers were separated. The organic layer was washed with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the pure sulfonamide in nearly quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.0 Hz, 2H), 4.69 (t, *J* = 6.1 Hz, 1H), 5.10 - 5.22 (m, 2H), 5.75 (m, *J* = 16.8, 10.6, 5.8, 5.8 Hz, 1H), 7.05 (m, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.83 (m, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 45.9, 117.8, 117.9, 120.5, 125.1, 129.5, 130.4, 133.1, 133.6, 155.3, 161.8; HRMS (FAB) calcd for $C_{15}H_{16}NO_3S$ ($M+H^+$) 290.0851, found 290.0868.

***N*-Allyl-*N*-methyl-(4-phenoxyphenyl)sulfonamides (85b).** NaH (16 mg, 0.65 mmol, 60% in mineral oil) was added to a solution of iodomethane (81 μL, 1.3 mmol) and sulfonamide **77** (126 mg, 0.44 mmol) in DMF (5 mL) at room temperature. After stirring 18 h at room temperature, the resultant was diluted with ethyl acetate and water and then layers were separated. The organic layer was washed with 1 N HCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude compound was purified by column chromatography on silica gel (131 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (s, 3H), 3.65 (d, *J* = 6.2 Hz, 2H), 5.18 - 5.24 (m, 2H), 5.73 (m, *J* = 16.8, 10.4, 6.2, 6.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.4, 53.2, 117.7, 119.4, 120.5, 125.1, 129.8, 130.4, 131.2, 132.7, 155.2, 161.7; HRMS (FAB) calcd for $C_{16}H_{18}NO_3S$ ($M+H^+$) 304.1007, found 304.1025. Conversion from compounds **77, 85b,c** to compounds **2a,b,c** was followed by the same method as described in Scheme S1.

Scheme S9. Synthesis of compound 4



Compound 87. Compound **86** (2.4 g, 13 mmol) in THF (10 mL) was treated with triethylamine (2.2 mL, 16 mmol). Allylsulfonyl chloride (2.2 g, 16 mmol) in THF (5 mL) was slowly added dropwise to the above solution at ice-water temperature. The resulting mixture was stirred for 1 h, while the temperature was gradually warmed to room temperature. Additional triethylamine (2.2 mL, 16 mmol) was added to the reaction mixture and the resultant solution was stirred for 0.5 h. The reaction mixture was filtered through a small layer of silica gel and the volatile was evaporated. The residue was taken up in ethyl acetate and washed with water, 5% $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel to afford the desired product (2.8 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (d, *J* = 7.4 Hz, 2H), 5.32 (d, *J* = 17.3 Hz, 1H), 5.43 (d, *J* = 10.4 Hz, 1H), 5.88 (m, 1H), 6.78 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.97 (s, 1H), 6.99 - 7.07 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.48 (br.s., 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.7, 110.8, 114.8, 114.9, 119.3, 123.9, 125.0, 130.0, 130.7, 138.5, 156.5, 158.5; HRMS (FAB) calcd for $C_{15}H_{16}NO_3S$ ($M+H^+$) 290.0851, found 290.0870.

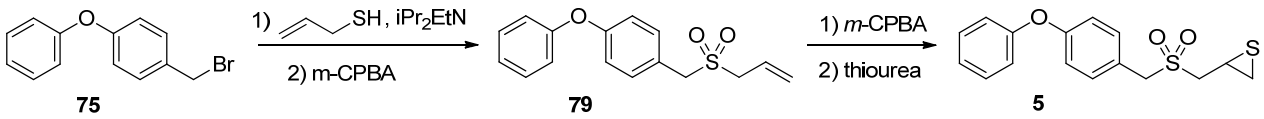
Compound 88. A mixture of compound **87** (0.95 g, 3.3 mmol) and *N*-methylmorpholine *N*-oxide (0.75 g, 6.3 mmol) in acetone-water (90 mL, 4:1) was treated with osmium tetraoxide (0.9 mL, 141 μmol, 4% aqueous solution) and the resultant solution was stirred at room temperature for 18 h under dark. Sodium sulfite (0.3 g) was added and the resulting mixture was stirred for an additional 1 h. After filtration through a small layer of silica gel, the filtrate was evaporated and the residue was purified by column chromatography on silica gel to give the title compound (0.91 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24 (dd, *J* = 14.8, 3.0 Hz, 1H), 3.33 (dd, *J* = 14.8, 8.9 Hz, 1H), 3.52 (dd, *J* = 11.9, 6.4 Hz, 1H), 3.63 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.32 (m, 1H), 6.71 (m, 1H), 6.98 - 7.01 (m, 4H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.20 (dd, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 8.4, 7.4 Hz, 2H); 13C NMR (126 MHz, $CDCl_3$) δ 53.4, 65.3, 67.7, 111.5, 114.9, 115.6, 119.3, 123.9, 129.9, 130.7, 138.3, 156.4, 158.3; HRMS (FAB) calcd for $C_{15}H_{18}NO_5S$ ($M+H^+$) 324.0906, found 324.0987.

Compound 89. Conversion of diol **88** to oxirane **89** was done by two methods. The first method is using Mitsunobu condition. The second is via the formation of tosylated intermediate. A mixture of compound **88** (171 mg, 530 μmol), triphenylphosphine (142 mg, 530 μmol), and diethylazodicarboxylate (90 μL, 530 μmol) was

refluxed for 4 h in anhydrous benzene (10 mL) and the volatile was evaporated. The residue was purified by column chromatography on silica gel to afford the title compound (104 mg, 64%).

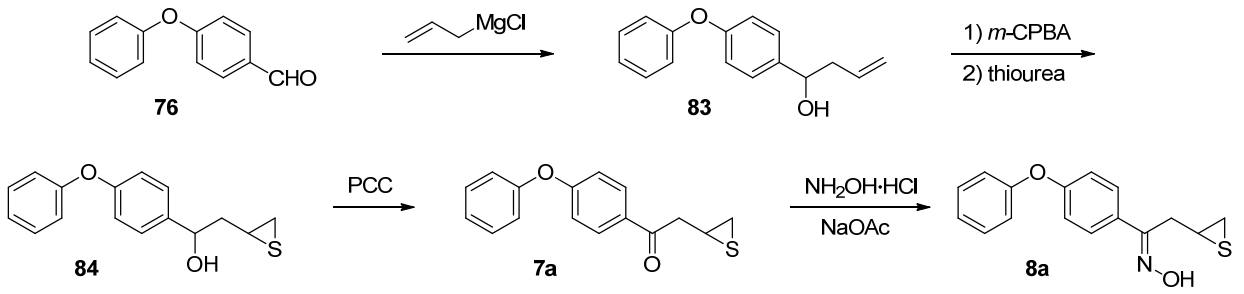
The second procedure involving formation of tosylated intermediate: A mixture of compound **88** (171 mg, 530 μmol) and tosyl chloride (111 mg, 583 μmol) in CH_2Cl_2 (2 mL) was treated with pyridine (138 μL, 1.75 mmol) in ice-water bath and the resulting mixture was stirred for 18 h at room temperature. The reaction mixture was washed with water several times and volatile was concentrated. The crude product was used for the next step without further purification. The crude tosylate was dissolved in anhydrous THF (2 mL) and cooled down in ice-water bath. To this reaction mixture, NaH (35 mg, 875 μmol, 60% in oil) was added and the resulting mixture was stirred for 10 min and filtered through a small layer of silica gel and washed with THF. The combined filtrate was evaporated under reduced pressure and the resulting crude product was purified by column chromatography to afford the desired product (121 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (dd, J = 4.7, 2.2 Hz, 1H), 2.93 (t, J = 4.2 Hz, 1H), 3.19 (dd, J = 15.3, 8.4 Hz, 1H), 3.39 - 3.49 (m, 2H), 6.83 (m, 1H), 7.00 (s, 1H), 7.02 - 7.10 (m, 2H), 7.14 - 7.21 (m, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.4, 46.6, 53.7, 111.5, 115.4, 115.7, 119.5, 124.0, 130.0, 130.7, 138.0, 156.5, 158.5; HRMS (FAB) calcd for $C_{15}H_{16}NO_4S$ ($M+H^+$) 306.0800, found 306.0789. Conversion from compound **89** to compound **4** was followed by the same method as described in Scheme S1.

Scheme S10. Synthesis of compound 5



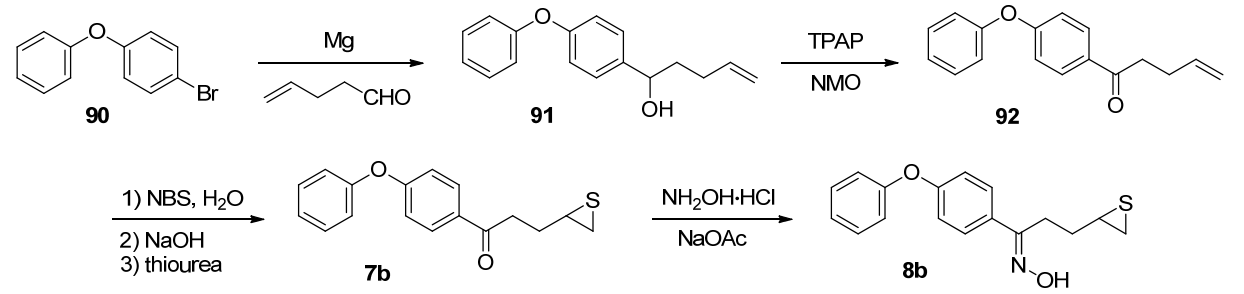
Compound 79. Allyl mercaptan (0.56 mL, 7.1 mmol) was added to a solution of bromide **75** (1.2 g, 4.7 mmol) and *i*Pr_2EtN (1.4 mL, 8.2 mmol) in CH_2Cl_2 (5 mL). After stirring at room temperature for 1 h, the resultant was diluted with CH_2Cl_2 and water and then layers were separated. The organic layer was washed with 1 N HCl and saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was redissolved in CH_2Cl_2 (30 mL) and *m*-CPBA (4.1 g, 23 mmol, 77%) was added in ice-water bath. After 30 min, the suspension was filtered, and the filtrate was diluted with CH_2Cl_2 and washed with 10% aqueous sodium thiosulfate, followed by saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and was concentrated. The product was purified by silica gel chromatography to yield the title compound (1.0 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (d, J = 7.2 Hz, 2H), 4.20 (s, 2H), 5.37 - 5.58 (m, 2H), 5.86 - 6.03 (m, 1H), 7.02 (t, J = 9.1 Hz, 3H), 7.16 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 8.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.1, 57.3, 118.8, 119.7, 121.9, 124.1, 125.0, 125.1, 130.0, 132.4, 156.4, 158.5; HRMS (FAB) calcd for $C_{16}H_{17}O_3S$ (M^+) 289.0898, found 289.0880. Conversion from compound **79** to compound **3** was followed by the same method as described in Scheme S1.

Scheme S11. Synthesis of compounds 7a and 8a



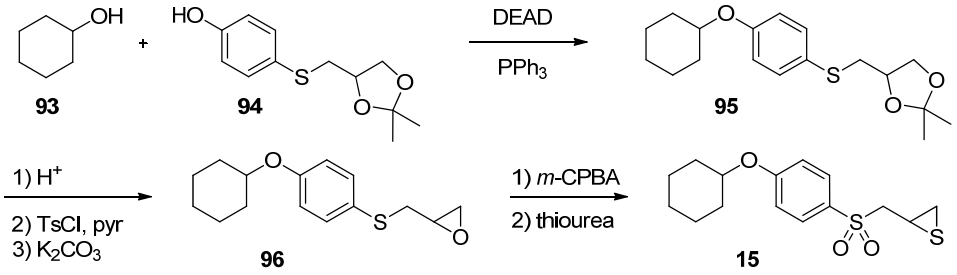
Compound 8a. Allylmagnesium chloride (28 mL, 1 M solution in diethyl ether) was added to a solution of 4-phenoxybenzaldehyde (5.0 g, 25 mmol) in diethyl ether (50 mL) in ice-water bath. After 1 h, reaction was quenched with saturated NH_4Cl and extracted with diethyl ether. Organic layer was washed with 5% HCl, water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude material was purified by silica gel column chromatography to give the titled compound (3.8 g, 62%). Conversion from compound **83** to compound **84** was followed by the same method as described in Scheme S1. A mixture of compound **84** (500 mg, 1.8 mmol) and PCC (790 mg, 3.7 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 2 h. After quenching with addition of *i*-propanol, the reaction mixture was diluted with diethyl ether and filtered. The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, and the volatile was evaporated. The resultant was purified by silica gel column chromatography to give the desired compound, **7a** (370 mg, 74%) as a pure red solid. A mixture of compound **7a** (340 mg, 1.3 mmol), $NH_2OH·HCl$ (263 mg, 3.8 mmol), and NaOAc (310 mg, 3.8 mmol) in 5:1 solution of EtOH:water (10 mL) was stirred at room temperature for 3.5 h . The resulting solution was diluted with ethyl acetate and water and layers were separated. Organic layer was washed with saturated $NaHCO_3$, water and brine. The crude product was purified by column chromatography to give the desired product. E/Z isomers were separable by column chromatography (140 mg (51%), less polar, 40 mg (11%), more polar isomer). Spectral data is given in Table S1.

Scheme S12. Synthesis of compounds 7b and 8b



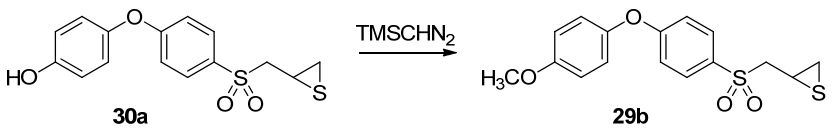
Compound 8b. Aldehyde (1.2 mL, 12 mmol) was added to a solution of 4-phenoxyphenylmagnesium bromide (3.3 g, 12 mmol) in anhydrous THF (20 mL) in ice-water bath. After 15 min, stirring was continued at room temperature for 1 h and reaction was quenched with saturated NH_4Cl solution. After extraction with ethyl acetate, the organic layer was washed with water and brine. The crude product was purified by column chromatography to give the desired product (2.4 g, 79%). A mixture of compound **91** (100 mg, 0.39 mmol), TPAP (14 mg, 0.039 mmol), and NMO (138 mg, 1.30 mmol) in CH_2Cl_2 (5 mL) was stirred for 5 min and concentrated to dryness. The crude product was purified by column chromatography to give the desired product (88 mg, 89%) as a white solid. A mixture of compound **92** (88 mg, 0.35 mmol) and NBS (68 mg, 0.39mmol) in 3:1 solution of THF:water (2 mL) was stirred at room temperature for 1 h. 2.5 N NaOH (280 μL) was added to the reaction mixture and stirred for 3 h. The reaction mixture was diluted with diethyl ether and washed with brine. The crude product was purified by column chromatography to give the desired product (75 mg, 81%) as a colorless oil. Conversion to compound **8b** was followed by the same method as described in Scheme S10. Spectral data is given in Table S1.

Scheme S13. Synthesis of compound 15



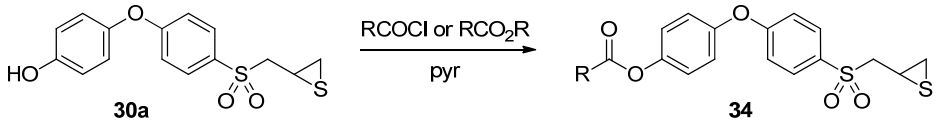
Compound 95. Diethylazodicarboxylate (3.0 mL, 19 mmol) was added to a mixture of compound **93** (1.9 g, 19 mmol), compound **94** (4.2 g, 17 mmol), and triphenylphosphine (5.1 g, 19 mmol) in THF (50 mL) in ice-water bath. The reaction mixture was stirred for 2 h, while temperature was gradually raised to room temperature. The volatile was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the title compound (3.1 g, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 - 1.67 (m, 6H), 1.33, 1.42 (2s, 6H), 1.69 - 1.84 (m, 2H), 1.89 - 2.05 (m, 2H), 2.84 (dd, *J* = 13.3, 8.3 Hz, 1H), 3.10 (dd, *J* = 13.4, 5.0 Hz, 1H), 3.70 (dd, *J* = 8.5, 6.1 Hz, 1H), 4.07 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.13 - 4.31 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.9, 25.7, 27.1, 31.9, 39.3, 69.0, 75.1, 75.7, 79.0, 116.8, 133.8, 135.9, 157.7; HRMS (FAB) calcd for $C_{18}H_{27}O_3S$ ($M+H^+$) 323.1681, found 323.1675. Compound **95** (0.87 g, 2.7 mmol) was dissolved in 80% AcOH (50 mL), and the resulting acidic solution was stirred at room temperature for 18 h. The volatiles were removed under reduced pressure and the crude compound was coevaporated with toluene. Conversion of resulting diol to compound **15** was followed by the same method as described in Scheme S9. Spectral data is given in Table S1.

Scheme S14. Synthesis of compound 29b



2-(4-Methoxyphenoxyphenylsulfanylmethyl)thiirane (29b). (Trimethylsilyl)diazomethane (0.90 mL, 2 M solution in diethylether) was added dropwise to a stirred solution of **30a** (0.20 g, 0.62 mmol) in CH_2Cl_2 / MeOH (5:1, 3.5 mL). After stirring at room temperature for 18 h, the reaction mixture was concentrated in vacuo and purified by column chromatography (0.11 g, 53%). Spectral data is given in Table S1.

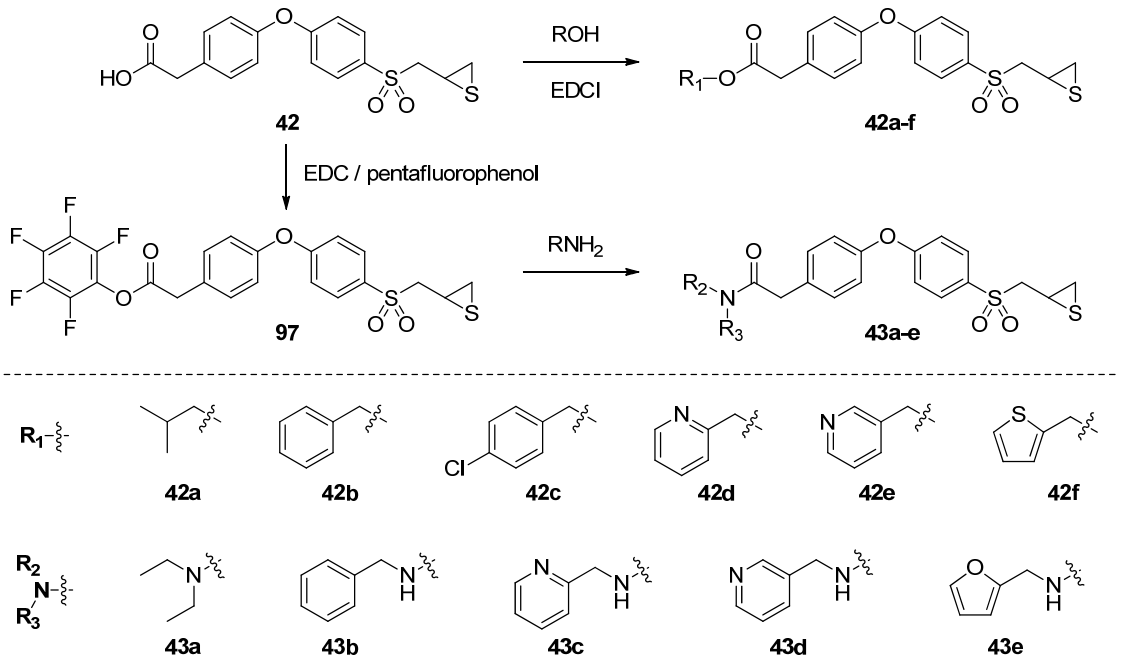
Scheme S15. Synthesis of compound 36



The ester derivatives of **30a** were prepared by acylation using a corresponding acyl chloride or anhydride in the presence of pyridine. Sulfonate derivatives of **30a** were also prepared by similar method using sulfonyl chloride and triethylamine.

Compound 34a. To a stirred solution of **30a** (0.20 g, 0.62 mmol) in CH_2Cl_2 (15 ml) were added pyridine (0.13 mL, 1.6 mmol) and acetic anhydride (75 μL, 0.78 mmol) at ice-water temperature, and the mixture was stirred at the same temperature for 1 h. Subsequent to the addition of saturated $NaHCO_3$, the mixture was extracted with ethyl acetate. The combined organic layer was washed with aqueous HCl, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography to give **34a** (0.15 g, 67%) as a white solid. Compounds **34b-34d** were prepared in the same manner as described for compound **36a** with the exception of corresponding acyl chloride was used instead of acetic anhydride. Spectral data is given in Table S1.

Scheme S16. Synthesis of compounds 42a-f and 43 a-e.



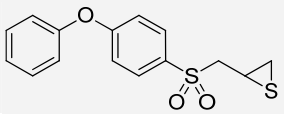
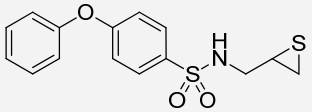
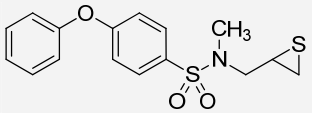
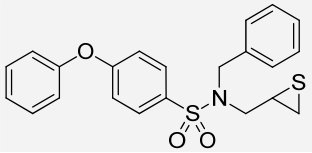
Compound 42a. To s stirred solution of **42**[8] (50 mg, 0.14 mmol), EDCI (53 mg, 0.28 mmol), DMAP (1.3 mg, 0.01 mmol) in CH_2Cl_2 (5 ml) was added *i*-butanol (0.013 mml, 10.43 mg, 0.14 mmol) and the mixture was stirred at room temperature for 2h. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% citric acid, saturated $NaHCO_3$, water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **42a** as a colorless oil (35 mg, 60%). Compounds **42b**-**42f** were prepared in the same manner as described for compound **42a** with the exception of corresponding alcohol was used instead of *i*-butanol. Spectral data is given in Table S1.

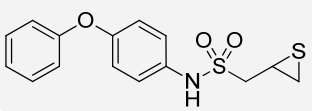
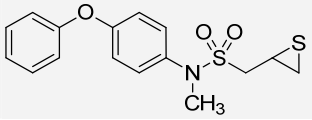
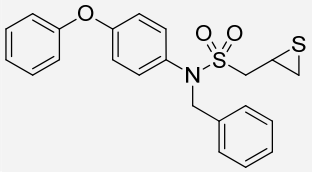
Compound 43a. To s stirred solution of **42** (521 mg, 1.43 mmol), EDCI (548 mg, 2.86 mmol), DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (30 ml) was added pentafluorophenol (PfP) (263 mg, 1.43 mmol) and the mixture was stirred for 18 h at room temperature. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% citric acid solution, saturated $NaHCO_3$ solution, water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude PfP-ester (636 mg). The crude material was used for the next step. To a stirred solution of **97** (54 mg, 0.10 mmol) in CH_2Cl_2 (5 ml) is added diethylamine (15 mg, 0.10 mmol) and the mixture is stirred for 18 h at room temperature. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% citric acid solution, saturated $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **43a** (23 mg, 55%) as a colorless oil. Compounds **43b**-**43e** were prepared in the same manner as described for

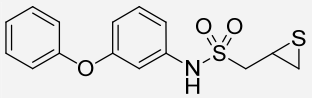
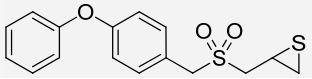
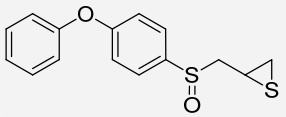
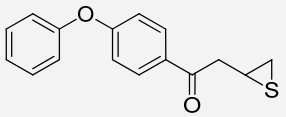
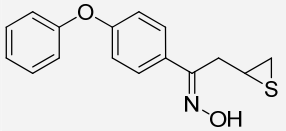
compound **43a** with the exception of corresponding amine was used instead of diethylamine. Spectral data is given in Table S1.

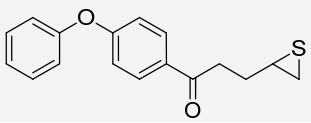
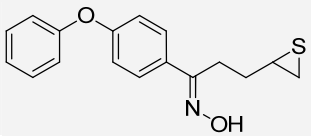
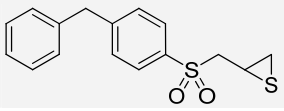
Table S1. Spectral data of the final compounds.

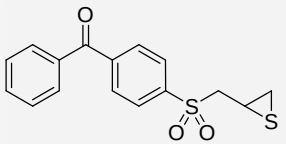
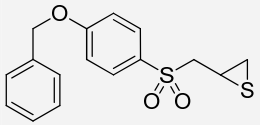
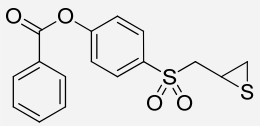
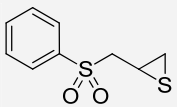
Spectral data of all final compounds are given in Table S1. The used preparation route of each compound is indicated. When the compound was prepared by literature method, the literature is given. The purity of final compounds was >95% determined by HPLC, otherwise it is noted.

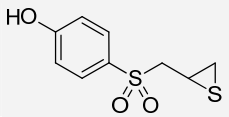
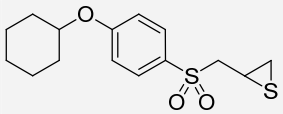
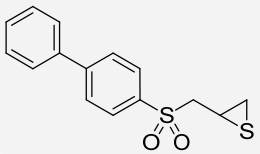
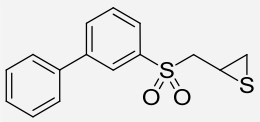
Compound No	
1	
Preparation Route	lit.[4, 9, 10]
2a	
Preparation Route	Scheme S7
Overall yield	48% from **73**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.25 (d, *J* = 5.2 Hz, 1H), 2.47 (d, *J* = 6.2 Hz, 1H), 3.02 - 3.16 (m, 2H), 3.37 (dt, *J* = 13.3, 5.6 Hz, 1H), 4.90 (t, *J* = 6.0 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.81 (d, *J* = 9.0 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 23.8, 33.5, 47.4, 117.9, 120.5, 125.2, 129.4, 130.4, 133.5, 155.2, 161.9
HRMS (FAB)	calcd for $C_{15}H_{16}NO_3S_2$ ($M+H^+$) 322.0572, found 322.0558
2b	
Preparation Route	Scheme S7
Overall yield	47% from **73**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.23 (m, 1H), 2.54 (dd, *J* = 6.2, 1.0 Hz, 1H), 2.89 (s, 3H), 3.02 (quin, *J* = 5.9 Hz, 1H), 3.21 - 3.29 (m, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.08 (d, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.1, 31.7, 35.9, 56.1, 117.8, 120.6, 125.2, 129.7, 130.4, 131.4, 155.2, 161.9
HRMS (FAB)	calcd for $C_{16}H_{18}NO_3S_2$ ($M+H^+$) 336.0728, found 336.0721
2c	
Preparation Route	Scheme S7
Overall yield	40% from **73**

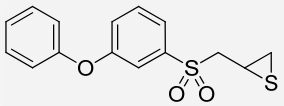
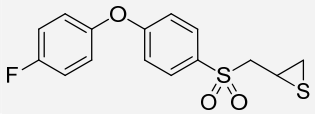
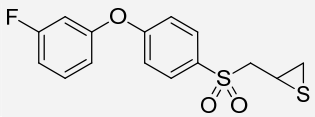
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.88 (d, *J* = 5.0 Hz, 1H), 2.24 (d, *J* = 5.8 Hz, 1H), 2.80 (m, 1H), 3.03 (dd, *J* = 14.9, 7.9 Hz, 1H), 3.52 (dd, *J* = 14.9, 4.7 Hz, 1H), 4.43 (m, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.19 - 7.37 (m, 6H), 7.44 (m, *J* = 7.6, 7.6 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 25.2, 32.0, 53.0, 54.1, 117.9, 120.5, 125.2, 128.3, 128.6, 128.9, 129.5, 130.4, 133.3, 136.3, 155.2, 161.9
HRMS (FAB)	calcd for $C_{22}H_{22}NO_3S_2$ ($M+H^+$) 412.1041, found 412.1035
3a	
Preparation Route	Scheme S8
Overall yield	28% from **74**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.35 (m, 1H), 2.66 (m, 1H), 3.17-3.27 (m, 2H), 3.50 (dd, *J* = 13.6, 5.0 Hz, 1H), 6.75 (s, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.8, 26.8, 57.5, 119.3, 119.8, 123.9, 124.0, 130.1, 131.1, 155.8, 156.9
HRMS (FAB)	calcd for $C_{15}H_{15}NO_3S_2$ (M^+) 321.0493, found 321.0483
3b	
Preparation Route	Scheme S8
Overall yield	24% from **74**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.41 (dd, *J* = 5.1, 1.5 Hz, 1H), 2.68 (d, *J* = 5.2 Hz, 1H), 3.02 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.20 (m, 1H), 3.37 (s, 3H), 3.54 (dd, *J* = 14.0, 5.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.32-7.43 (m, 4H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 25.3, 26.8, 39.2, 55.9, 119.1, 119.7, 124.2, 128.5, 130.1, 135.7, 156.5, 157.1
HRMS (FAB)	calcd for $C_{16}H_{18}NO_3S_2$ ($M+H^+$) 336.0728, found 336.0717
3c	
Preparation Route	Scheme S8
Overall yield	25% from **74**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.46 (dd, *J* = 5.2, 1.6 Hz, 1H), 2.73 (m, 1H), 3.15 (dd, *J* = 14.0, 7.8 Hz, 1H), 3.28 (m, 1H), 3.58 (dd, *J* = 13.9, 5.5 Hz, 1H), 4.79 (d, *J* = 14.6 Hz, 1H), 4.96 (d, *J* = 14.6 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 7.15 - 7.24 (m, 3H), 7.26 - 7.40 (m, 7H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 25.2, 27.0, 56.2, 57.7, 118.9, 119.9, 124.3, 128.2, 128.7, 128.9, 130.1, 131.0, 133.2, 136.3, 156.2, 157.6
HRMS (FAB)	calcd for $C_{22}H_{22}NO_3S_2$ ($M+H^+$) 412.1041, found 412.1031

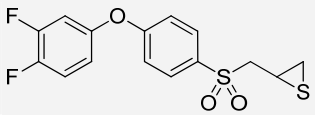
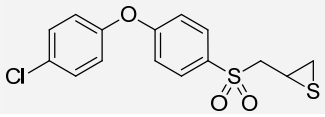
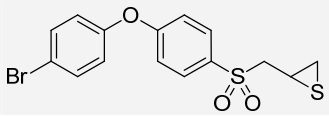
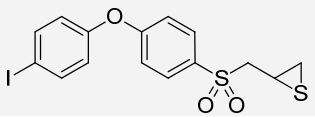
4	
Preparation Route	Scheme S8
Overall yield	24% from **61**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.32 (d, *J* = 5.4 Hz, 1H), 2.64 (d, *J* = 5.9 Hz, 1H), 3.19 (m, 1H), 3.26 (dd, *J* = 14.3, 7.4 Hz, 1H), 3.57 (dd, *J* = 14.1, 5.7 Hz, 1H), 6.77 - 6.83 (m, 2H), 6.91 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.28 - 7.32 (m, 1H), 7.39 (t, *J* = 7.7 Hz, 1H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.8, 26.7, 57.9, 110.5, 114.6, 115.1, 119.6, 124.2, 130.1, 131.0, 137.9, 156.4, 158.9.
HRMS (FAB)	calcd for $C_{15}H_{15}NO_3S_2$ (M^+) 321.0493, found 321.0499
5	
Preparation Route	Scheme S9
Overall yield	39% from **75**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.39 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.70 (d, *J* = 6.1 Hz, 1H), 3.04 (dd, *J* = 13.8, 6.9 Hz, 1H), 3.19 (dt, *J* = 12.1, 6.0 Hz, 1H), 3.33 (dd *J* = 14.1, 6.1 Hz, 1H), 4.30 (dd, *J* = 23.5, 14.1 Hz, 2H), 7.03 (t, *J* = 9.4 Hz, 4H), 7.17 (t, *J* = 7.5, Hz, 1H), 7.31 - 7.50 (m, 4H)
^{13}C NMR	(75 MHz, $CDCl_3$) δ 24.9, 26.1, 57.7, 59.3, 118.9, 119.9, 124.3, 125.1, 130.1, 132.5, 156.3, 158.8
HRMS (ESI)	calcd for $C_{16}H_{17}O_3S_2$ (M+Na) 343.0433, found 343.0431
6	
Preparation Route	Lit.[11]
7a	
Preparation Route	Scheme S10
Overall yield	31% from **76**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.3 (d, *J* = 5.4 Hz, 1H), 2.7 (d, *J* = 6.4 Hz, 1H), 3.2 (dd, *J* = 17.1, 6.8 Hz, 1H), 3.3 (quin, *J* = 6.1 Hz, 1H), 3.5 (dd, *J* = 17.0, 5.9 Hz, 1H), 7.0 (d, *J* = 8.8 Hz, 2H), 7.1 (d, *J* = 8.4 Hz, 2H), 7.2 (t, *J* = 7.4 Hz, 1H), 7.4 (t, *J* = 7.9 Hz, 2H), 7.9 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 25.4, 29.5, 45.5, 117.3, 120.2, 124.7, 130.0, 130.4, 130.9, 155.2, 162.3, 196.1
HRMS (FAB)	calcd for $C_{16}H_{15}O_2S$ ($M+H^+$) 271.0793, found 271.0796
7b	
Preparation Route	Scheme S10

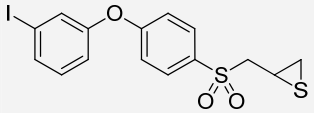
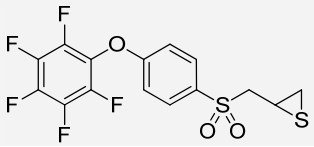
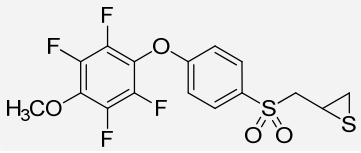
Overall yield	49% from **90**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.21 (dd, *J* = 5.6, 1.0 Hz, 1H), 2.52 (m, 1H), 2.78 - 2.92 (m, 2H), 3.02(m, 1H), 6.97 - 7.11 (m, 4H), 7.17 (t *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 8.27 (br.s, 1H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 25.6, 31.7, 42.3, 117.8, 119.7, 124.0, 126.9, 129.81, 129.89, 155.7, 156.1, 158.3
HRMS (FAB)	calcd for $C_{16}H_{16}NO_2S$ ($M+H^+$) 286.0902, found 286.0923
8a	
Preparation Route	Scheme S11
Overall yield	19% from **76**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 1.61 - 1.73 (m, 1H), 2.25 (dd, *J* = 5.4, 0.9 Hz, 1H), 2.46 - 2.52 (m, 1H), 2.56 (d, *J* = 6.0 Hz, 1H), 3.01 - 3.18 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 26.3, 30.7, 35.6, 37.6, 117.2, 120.1, 124.6, 130.0, 130.2, 131.3, 155.3, 162.0, 197.6
HRMS (FAB)	calcd for $C_{17}H_{17}O_2S$ ($M+H^+$) 285.0949, found 285.0959
8b	
Preparation Route	Scheme S11
Overall yield	29% from **90**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 1.64 - 1.76 (m, 1H), 2.13 - 2.24 (m, 2H), 2.50 (d, *J* = 6.0 Hz, 1H), 2.89 - 3.13 (m, 3H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 8.92 (br.s, 1H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 25.7, 25.9, 33.1, 35.5, 118.3, 119.5, 123.8, 127.7, 129.85, 129.93, 156.4, 157.9, 158.6
HRMS (FAB)	calcd for $C_{17}H_{18}NO_2S_2$ ($M+H^+$) 300.1058, found 300.1057
9	
Preparation Route	Scheme S2
Overall yield	28% from 4-benzylaniline
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.16 (dd, *J* = 5.2, 1.8 Hz, 1H), 2.54 (dd, *J* = 6.2, 1.6 Hz, 1H), 3.06 (m, 1H), 3.17 (dd, *J* = 14.3, 8.1 Hz, 1H), 3.56 (dd, *J* = 14.2, 5.4 Hz, 1H), 4.11 (s, 2H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 41.9, 62.6, 126.8, 128.7, 128.9, 129.1, 130.0, 136.4, 139.4, 148.4
HRMS (FAB)	calcd for $C_{16}H_{17}O_2S_2$ ($M+H^+$) 305.0670, found 305.0641

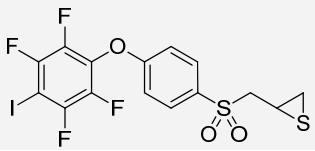
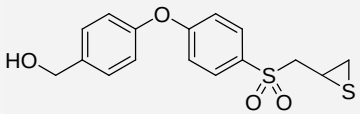
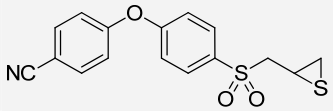
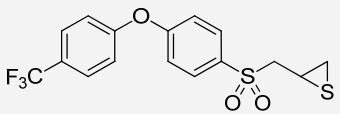
10	
Preparation Route	Scheme S2
Overall yield	26% from 4-aminobenzophenone
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.19 (dd, *J* = 5.1, 1.7 Hz, 1H), 2.57 (dd, *J* = 6.2, 1.8 Hz, 1H), 3.11 (m, 1H), 3.31 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.57 (dd, *J* = 14.4, 6.0 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 8.08 (d, *J* = 8.2 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.0, 62.6, 128.7, 128.9, 130.3, 130.7, 133.7, 136.5, 141.8, 142.9, 195.3.
HRMS (FAB)	calcd for $C_{16}H_{15}O_3S_2$ ($M+H^+$) 319.0463, found 319.0445
11	
Preparation Route	Scheme S4
Overall yield	41% from **47**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.12 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.50 (d, *J* = 5.2 Hz, 1H), 3.05 (m, 1H), 3.15 (dd, *J* = 14.2, 8.0 Hz, 1H), 3.51 (dd, *J* = 14.2, 5.4 Hz, 1H), 5.14 (s, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.33 - 7.47 (m, 5H), 7.85 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.3, 62.7, 70.5, 115.6, 127.6, 128.6, 128.9, 130.3, 130.7, 135.7, 163.3
HRMS (FAB)	calcd for $C_{16}H_{17}O_3S_2$ ($M+H^+$) 321.0619, found 321.0621
12	
Preparation Route	Scheme S4 and S14
Overall yield	23% from **47**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 5.0, 1.6 Hz, 1H), 2.55 (dd, *J* = 6.1, 1.1 Hz, 1H), 3.08 (m, 1H), 3.22 (dd, *J* = 14.3, 7.9 Hz, 1H), 3.57 (dd, *J* = 14.4, 5.6 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 7.4 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.1, 62.7, 123.1, 128.9, 130.4, 130.4, 134.4, 136.0, 155.6, 164.4;
HRMS (FAB)	calcd for $C_{16}H_{15}O_4S_2$ ($M+H^+$) 335.0412, found 335.0400
13	
Preparation Route	Scheme S4
Overall yield	51% from thiophenol
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.10 (dd, *J* = 5.0, 1.7 Hz, 1H), 2.49 (d, *J* = 6.1 Hz, 1H), 3.03 (m, 1H), 3.17 (dd, *J* = 14.4, 8.0 Hz, 1H), 3.54 (dd, *J* = 14.2, 5.4 Hz, 1H), 7.52 - 7.74 (m, 3H), 7.93 (d, *J* = 7.5 Hz, 2H)

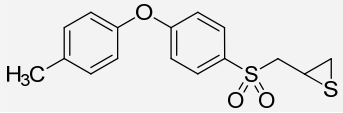
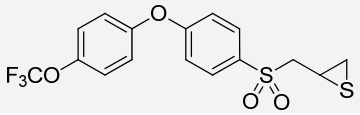
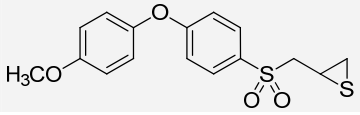
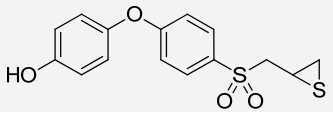
^{13}C NMR	(75 MHz, $CDCl_3$) δ 24.3, 26.1, 62.5, 128.5, 129.5, 134.3, 138.6
HRMS (FAB)	calcd for $C_9H_{10}O_2S_2$ (M^+) 214.0122, found 214.0118
14	
Preparation Route	Scheme S4
Overall yield	29% from **47**
^{1}H NMR	(500 MHz, 5% CD_3OD in $CDCl_3$) δ 2.05 (dd, *J* = 5.2, 2.1 Hz, 1H), 2.45 (dd, *J* = 6.2, 2.1 Hz, 1H), 2.94 - 3.01 (m, 1H), 3.11 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.47 (dd, *J* = 14.1, 5.5 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, 5% CD_3OD in $CDCl_3$) δ 24.2, 26.2, 62.7, 116.3, 128.2, 130.7, 162.6
HRMS (FAB)	calcd for $C_9H_{11}O_3S_2$ ($M+H^+$) 231.0150, found 231.0143.
15	
Preparation Route	Scheme S12
Overall yield	23% from **93**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.27 - 1.46 (m, 3H), 1.52 - 1.65 (m, 3H), 1.82 (dd, *J* = 9.4, 3.4 Hz, 2H), 1.95 - 2.05 (m, 2H), 2.14 (dd, *J* = 5.0, 1.6 Hz, 1H), 2.53 (dd, *J* = 6.2, 1.4 Hz, 1H), 3.05 (m, 1H), 3.12 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.54 (dd, *J* = 13.8, 5.0 Hz, 1H), 4.38 (td, *J* = 8.5, 4.2 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 23.7, 24.6, 25.6, 26.4, 31.6, 62.9, 76.1, 116.1, 129.5, 130.7, 162.8
HRMS (ESI)	calcd for $C_{15}H_{21}O_3S_2$ ($M+H^+$) 313.0927, found 313.0942
16	
Preparation Route	Scheme S1
Overall yield	35% from **57**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.18 (dd, *J* = 5.2, 1.6 Hz, 1H), 2.56 (m, 1H), 3.11 (m, 1H), 3.22 (dd, *J* = 14.4, 8.0 Hz, 1H), 3.60 (dd, *J* = 14.2, 5.4 Hz, 1H), 7.44 - 7.53 (m, 3H), 7.64 (d, *J* = 7.0 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.5, 26.2, 62.7, 127.6, 128.1, 129.0, 129.1, 129.3, 137.2, 139.1, 147.3
HRMS (ESI)	calcd for $C_{15}H_{15}O_2S_2$ ($M+H^+$) 291.0508, found 291.0518
17	
Preparation Route	Scheme S1
Overall yield	29% from 3-biphenylbromide
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.18 (m, 1H), 2.56 (d, *J* = 6.0 Hz, 1H), 3.12 (m, 1H), 3.25 (dd, *J* = 14.3, 7.9 Hz, 1H), 3.62 (dd, *J* = 14.2, 5.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.52 (t,

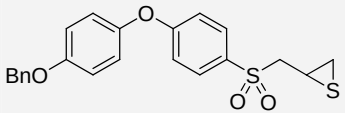
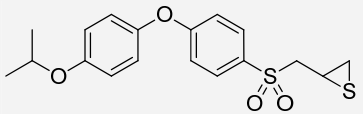
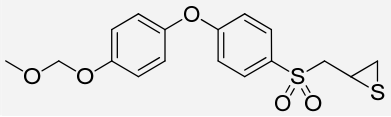
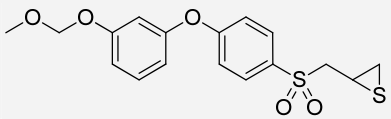
	J = 7.6 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 8.18 (s, 1H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.7, 127.0, 127.1, 127.4, 128.7, 129.3, 130.1, 132.9, 139.0, 139.4, 143.0
HRMS (FAB)	calcd for $C_{15}H_{14}O_2S_2$ (M^+) 290.0435, found 290.0430
18	
Preparation Route	Scheme S2
Overall yield	22% from **61**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.14 (dd, 1H, *J* = 1.7, 5.2 Hz), 2.51 (dd, 1H, *J* = 1.7, 6.2 Hz), 3.03 (m, 1H), 3.18 (dd, 1H, *J* = 7.7, 14.1 Hz), 3.51 (dd, 1H, *J* = 5.4, 14.3 Hz),7.05 (dd, 2H, *J* = 1.0, 8.9 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 7.29, 7.31 (2dd, 1H, *J* = 1.0, 2.5 Hz), 7.39 (dd, 2H, *J* = 7.4, 8.4 Hz), 7.52-7.55 (m, 2H), 7.64 (dt, 1H, *J* = 1.5, 7.9 Hz)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 20.0, 62.4, 117.7, 119.8, 122.6, 123.9, 124.8, 130.3, 131.0, 140.2, 155.7, 158.6
HRMS (FAB)	calcd for $C_{15}H_{15}O_3S_2$ (MH^+) 307.0463, found 307.0474
19a	
Preparation Route	Scheme S6
Overall yield	27% from 4-fluorophenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.14 (dd, *J* = 5.1, 1.5 Hz, 1H), 2.52 (m, 1H), 3.04 (m, 1H), 3.20 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.49 (dd, *J* = 14.3, 5.7 Hz, 1H), 7.04 - 7.13 (m, 6H), 7.86 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.2, 26.2, 62.5, 116.9 (d, *J* = 23.0 Hz), 122.1 (d, *J* = 8.2 Hz), 130.8, 132.0, 150.5 (m), 158.8, 160.7, 163.0
^{19}F NMR	^{19}F NMR (282 MHz, $CDCl_3$) δ -117.1 (m, 1F)
HRMS (FAB)	calcd for $C_{15}H_{14}FO_3S_2$ ($M+H^+$) 325.0368, found 325.0354
19b	
Preparation Route	Scheme S6
Overall yield	22% from 3-fluorophenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.16 (dd, *J* = 5.2, 1.6 Hz, 1H), 2.54 (m, 1H), 3.06 (m, 1H), 3.21 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.50 (dd, *J* = 14.4, 5.8 Hz, 1H), 6.81 (dd, *J* = 9.6, 2.2 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.94 (m, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.37 (m, 1H), 7.89 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.2, 62.6, 108.1 (d, *J* = 23.9 Hz), 112.2 (d, *J* = 21.4 Hz), 115.9 (d, *J* = 3.3 Hz), 118.4 (s, 4 C), 130.9 (m, 4 C), 131.2 (d, *J* = 9.1 Hz), 132.8, 156.2 (d, *J* = 10.7 Hz), 162.1, 162.6, 164.6
^{19}F NMR	^{19}F NMR (282 MHz, $CDCl_3$) δ -109.6 (m, 2F)
HRMS (FAB)	calcd for $C_{15}H_{14}FO_3S_2$ ($M+H^+$) 325.0368, found 325.0354

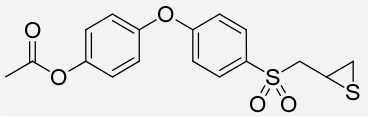
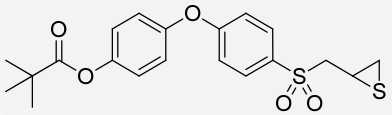
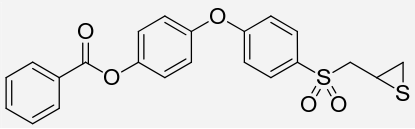
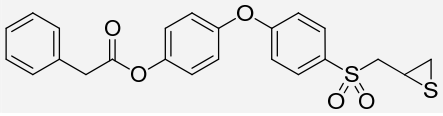
19c	
Preparation Route	Scheme S6
Overall yield	23% from 3,4-difluorophenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.15 - 2.21 (m, 1H), 2.53 - 2.59 (m, 1H), 3.04 - 3.11 (m, 1H), 3.24 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.51 (dd, *J* = 14.4, 5.8 Hz, 1H), 6.83 - 6.90 (m, 1H), 6.93 - 7.01 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.20 - 7.29 (m, 1H), 7.91 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.2, 62.7, 110.4 (d, *J* = 19.7 Hz), 116.4 (m), 117.9, 118.3 (d, *J* = 18.9 Hz), 131.0, 132.9, 146.9 (d, *J* = 12.3 Hz), 148.8 (d, *J* = 12.3 Hz), 149.8 (d, *J* = 14.0 Hz), 150.8 (dd, *J* = 8.2, 3.3 Hz), 151.8 (d, *J* = 14.0 Hz), 162.3;
^{19}F NMR	^{19}F NMR (282 MHz, $CDCl_3$) □ -141.3 (m, 1F), -133.0 (m, 1F)
HRMS (FAB)	calcd for $C_{15}H_{13}F_2O_3S_2$ ($M+H^+$) 343.0274, found 343.0252
20	
Preparation Route	Scheme S6
Overall yield	28% from 4-chlorophenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 5.0, 1.6 Hz, 1H), 2.55 (d, *J* = 6.0 Hz, 1H), 3.07 (m, 1H), 3.21 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.51 (dd, *J* = 14.3, 5.9 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.8, 118.0, 121.9, 130.5, 130.7, 131.0, 132.6, 153.6, 162.7
HRMS (FAB)	calcd for $C_{15}H_{14}ClO_3S_2$ ($M+H^+$) 341.0073, found 341.0088
21	
Preparation Route	Scheme S6
Overall yield	30% from 4-bromophenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 5.1, 1.7 Hz, 1H), 2.55 (dd, *J* = 6.1, 1.3 Hz, 1H), 3.08 (m, 1H), 3.21 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.51 (dd, *J* = 14.2, 5.8 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.8, 118.1, 122.3, 131.0, 132.7, 133.5, 154.2, 162.5;
HRMS (FAB)	calcd for $C_{15}H_{13}BrO_3S_2$ ($M+H^+$) 385.9568, found 385.9568
22a	
Preparation Route	Scheme S6
Overall yield	29% from 4-iodophenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (d, *J* = 5.0 Hz, 1H), 2.55 (d, *J* = 5.8 Hz, 1H), 3.07 (m, 1H), 3.21 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.51 (dd, *J* = 14.2, 5.8 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H)

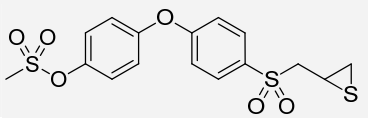
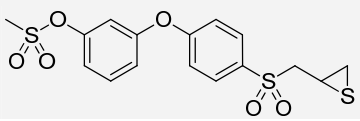
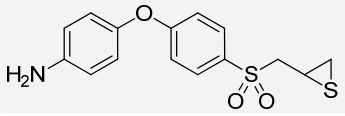
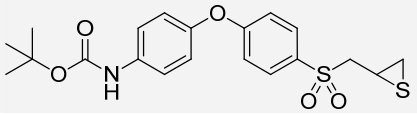
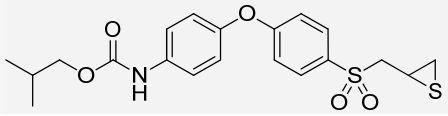
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.8, 88.9, 118.1, 122.6, 131.0, 132.6, 139.5, 155.0, 162.4;
HRMS (FAB)	calcd for $C_{15}H_{13}IO_3S_2$ (M^+) 431.9351, found 431.9375
22b	
Preparation Route	Scheme S6
Overall yield	25% from 3-iodophenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.19 (d, *J* = 4.0 Hz, 1H), 2.57 (d, *J* = 5.8 Hz, 1H), 3.10 (m, 1H), 3.23 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.54 (dd, *J* = 14.2, 5.8 Hz, 1H), 7.08 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.17 (t *J* = 8.0 Hz, 1H)), 7.47 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.8, 94.6, 118.3, 119.8, 129.5, 131.0, 131.7, 134.4, 155.6, 162.3
HRMS (FAB)	calcd for $C_{15}H_{14}IO_3S_2$ ($M+H^+$) 432.9429, found 432.9405
23	
Preparation Route	Scheme S5
Overall yield	55% from hexafluorobenzene
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.16 (dd, *J* = 5.1, 1.7 Hz, 1H), 2.55 (d, *J* = 6.2 Hz, 1H), 3.08 (m, 1H), 3.23 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.51 (dd, *J* = 14.4, 5.8 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.1, 62.8, 116.2, 128.5, 131.3, 134.1, 137.6, 139.5, 140.9, 142.9, 161.1
^{19}F NMR	^{19}F NMR (282 MHz, $CDCl_3$) δ -160.7 (dd, *J* = 22.0, 16.5 Hz, 2F), -157.6 (t, *J* = 22.0 Hz, 1F), -153.2 (d, *J* = 17.4 Hz, 2F)
HRMS (FAB)	calcd for $C_{15}H_{10}F_5O_3S_2$ ($M+H^+$) 396.9992, found 396.9983
24	
Preparation Route	Scheme S3
Overall yield	48% from hexafluorobenzene
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.16 (dd, *J* = 5.1, 1.7 Hz, 1H), 2.55 (m, 1H), 3.07 (m, 1H), 3.21 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.52 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.90 (s, 0.2H), 4.06 (s, 0.5H), 4.12 (s, 2.3H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 9.0 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.2, 26.1, 62.6 (t, *J* = 3.29 Hz), 62.7, 116.0, 131.1, 133.6, 140.8 (m, 1 C), 142.8 (m), 161.5
^{19}F NMR	(282 MHz, $CDCl_3$) δ -157.2 (d, *J* = 19.5 Hz),), -155.4 (d, *J* = 19.5 Hz)
HRMS (FAB)	calcd for $C_{16}H_{13}F_4O_4S_2$ ($M+H^+$) 409.0191, found 409.0173

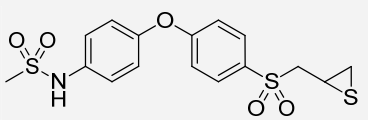
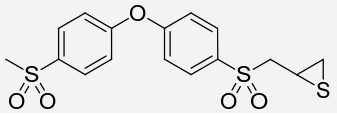
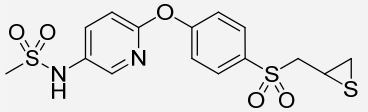
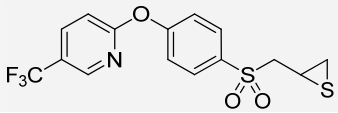
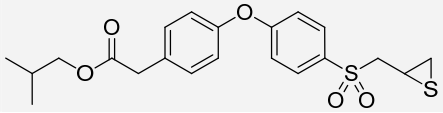
25	
Preparation Route	Scheme S3
Overall yield	43% from 1-iodopentafluorobenzene
^{1}H NMR	163 (500 MHz, $CDCl_3$) δ 2.2 (d, *J* = 5.0 Hz, 1H), 2.6 (d, *J* = 6.0 Hz, 1H), 3.1 (m, 1H), 3.2 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.5 (dd, *J* = 14.2, 5.8 Hz, 1H), 7.2 (d, *J* = 8.6 Hz, 2H), 8.0 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.1, 62.8, 116.4, 131.3, 134.1, 139.8, 146.9 (m), 148.7 (m), 160.9
^{19}F NMR	(282 MHz, $CDCl_3$) δ -151.4 (m), -118.8 (m)
HRMS (FAB)	calcd for $C_{15}H_{10}F_4IO_3S_2$ ($M+H^+$) 504.9052, found 504.9027
26	
Preparation Route	Scheme S6
Overall yield	29% from 4-hydroxymethylphenylboronic acid
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.14 (d, *J* = 4.1 Hz, 1H), 2.41 (br. s., 1H), 2.52 (d, *J* = 5.9 Hz, 1H), 3.00 - 3.07 (m, 1H), 3.18 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.49 (dd, *J* = 14.3, 5.7 Hz, 2H), 4.69 (s, 2H), 7.07 (dd, *J* = 8.6, 6.9 Hz, 4H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.2, 62.7, 64.5, 117.8, 120.6, 129.1, 130.8, 131.9, 138.2, 154.1, 163.0
HRMS (FAB)	calcd for $C_{16}H_{17}O_4S_2$ ($M+H^+$) 337.0568, found 337.0561
27	
Preparation Route	Scheme S6
Overall yield	31% from 4-cyanophenylboronic acid
^{1}H NMR	(500 MHz, 10% CD_3OD in $CDCl_3$) δ 2.10 (dd, *J* = 5.2, 1.6 Hz, 1H), 2.48 (dd, *J* = 6.2, 1.6 Hz, 1H), 2.99 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.26 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.40 (dd, *J* = 14.4, 6.2 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 2H)
^{13}C NMR	(126 MHz, 10% CD_3OD in $CDCl_3$) δ 23.9, 25.9, 62.5, 108.0, 118.3, 119.6, 119.9, 131.2, 133.8, 134.6, 159.3, 160.6
HRMS (ESI)	calcd for $C_{16}H_{14}NO_3S_2$ ($M+H^+$) 322.0410, found 322.0410
28a	
Preparation Route	Scheme S4
Overall yield	47% from **68**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 5.2, 1.6 Hz, 1H), 2.55 (dd, *J* = 6.2, 1.4 Hz, 1H),

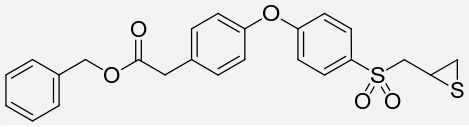
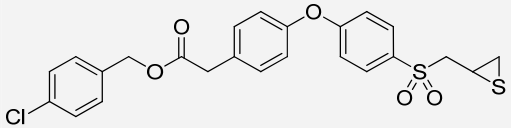
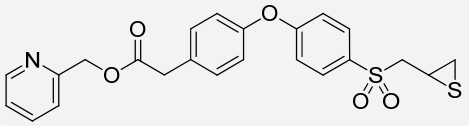
	3.07 (m, 1H), 3.25 (dd, *J* = 14.3, 7.5 Hz, 1H), 3.50 (dd, *J* = 14.4, 6.0 Hz, 1H), 7.17 (m, 4H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.2, 62.7, 118.9, 120.1, 127.8, 127.8, 131.1, 133.4, 158.1, 161.6
^{19}F NMR	^{19}F NMR (282 MHz, $CDCl_3$) δ -62.02 (s, 1F)
HRMS (FAB)	calcd for $C_{16}H_{14}F_3O_3S_2$ ($M+H^+$) 375.0336, found 375.0324
28b	
Preparation Route	Scheme S6
Overall yield	30% from *p*-tolylboronic acid
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.39 (s, 3H), 2.55 (m, 1H), 3.07 (m, 1H), 3.17 (dd, *J* = 14.1, 8.0 Hz, 1H), 3.54 (dd, *J* = 13.8, 5.2 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(75 MHz, $CDCl_3$) δ 21.1, 24.5, 26.3, 62.9, 117.5, 120.6, 130.9, 131.0, 131.7, 135.3, 152.5, 163.6
HRMS (ESI)	calcd for $C_{16}H_{17}NO_3S_2$ ($M+H^+$) 332.0614, found 321.0589
29a	
Preparation Route	Scheme S6
Overall yield	24% from **70**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.18 (dd, *J* = 5.1, 1.5 Hz, 1H), 2.55 (d, *J* = 6.2 Hz, 1H), 3.08 (m, 1H), 3.24 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.51 (dd, *J* = 14.3, 5.9 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 4H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 1H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.2, 62.7, 118.1, 121.6, 123.2, 131.0, 132.7, 153.4, 162.5;
^{19}F NMR	(282 MHz, $CDCl_3$) δ -58.2 (s, 1F)
HRMS (ESI)	calcd for $C_{16}H_{14}F_3O_4S_2$ ($M+H^+$) 391.0200, found 391.0280
29b	
Preparation Route	Scheme S13
Overall yield	53% from **30a**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.16 (d, *J* = 5.2 Hz, 1H), 2.53 (d, *J* = 5.5 Hz, 1H), 3.06 (m, 1H), 3.16 (dd, *J* = 13.8, 7.7 Hz, 1H), 3.53 (dd, *J* = 14.1, 5.5 Hz, 1H), 3.83 (s, 3H), 6.84 - 7.10 (m, 6H), 7.84 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(75 MHz, $CDCl_3$) δ 24.4, 26.3, 55.8, 62.8, 115.4, 117.1, 122.0, 130.8, 131.5, 148.0, 157.2, 163.9
HRMS (ESI)	calcd for $C_{16}H_{17}N_4O_4S_2$ ($M+H^+$) 337.0563, found 337.0543
30a	

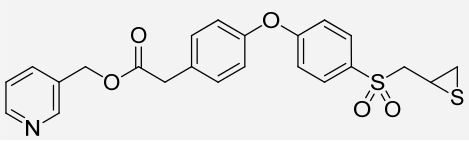
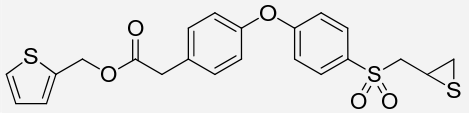
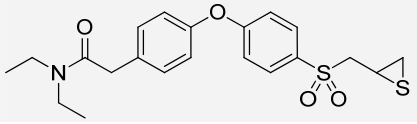
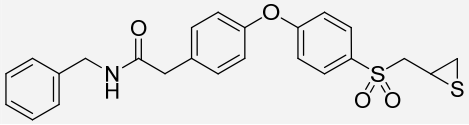
Preparation Route	Lit.[12]
31a	
Preparation Route	Scheme S1
Overall yield	35% from **90**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (m, *J* = 5.2, 1.4 Hz, 1H), 2.54 (d, *J* = 5.5 Hz, 1H), 3.07 (m, 1H), 3.17 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.53 (dd, *J* = 14.1, 5.5 Hz, 1H), 5.10 (s, 2H), 6.96 - 7.11 (m, 6H), 7.34 - 7.49 (m, 5H), 7.86 (d, *J* = 9.0 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.3, 62.8, 70.7, 116.5, 117.2, 121.9, 127.6, 128.2, 128.8, 130.8, 131.6, 136.8, 148.3, 156.4, 163.8
HRMS (FAB)	calcd for $C_{22}H_{21}O_4S_2$ ($M+H^+$) 413.0881, found 413.0869
32	
Preparation Route	Scheme S1
Overall yield	28% from 4-phenoxyphenol
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.0 Hz, 6H), 2.15 (d, *J* = 5.0 Hz, 1H), 2.52 (d, *J* = 6.0 Hz, 1H), 3.05 (m, 1H), 3.15 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.52 (dd, *J* = 14.2, 5.4 Hz, 1H), 4.52 (dt, *J* = 11.9, 5.9 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 22.2, 24.4, 26.3, 62.8, 70.7, 117.2, 117.4, 121.9, 130.8, 131.5, 147.8, 155.5, 163.9
HRMS (FAB)	calcd for $C_{18}H_{20}O_4S_2$ (M^+) 364.0803, found 364.0825
33a	
Preparation Route	Scheme S1
Overall yield	29% from 4-iodophenol
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 5.1, 1.3 Hz, 1H), 2.54 (d, *J* = 5.8 Hz, 1H), 3.06 (m, 1H), 3.17 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.48 (m, 1H), 3.52 (s, 3H), 5.19 (s, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.5, 26.3, 56.3, 62.9, 95.0, 117.3, 118.1, 122.0, 130.9, 131.7, 149.0, 154.9, 163.8
HRMS (FAB)	calcd for $C_{17}H_{19}O_5S_2$ ($M+H^+$) 367.0674, found 367.0665
33b	
Preparation Route	Scheme S4 and S8
Overall yield	19% from 3-iodophenol
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.15 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.53 (d, *J* = 5.0 Hz, 1H), 3.05 (m, 1H), 3.18 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.47 (s, 3H), 3.52 (dd, *J* = 14.2, 5.6 Hz, 1H), 5.16 (s, 2H), 6.71 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.79 (t, *J* = 2.1 Hz, 1H), 6.92 (dd, *J* = 8.3,

	2.1 Hz, 1H), 7.11 (m, *J* = 8.8 Hz, 2H), 7.31 (t, *J* = 8.3 Hz, 1H), 7.86 (m, *J* = 8.8 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 56.3, 62.7, 94.6, 108.8, 113.1, 113.6, 118.0, 130.8, 132.1, 155.9, 158.9, 162.8
HRMS (ESI)	calcd for $C_{17}H_{19}O_5S_2$ ($M+H^+$) 367.0668, found 367.0676
34a	
Preparation Route	Scheme S14
Overall yield	67% from **30a**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.15 (d, *J* = 4.1 Hz, 1H), 2.31 (s, 3H), 2.52 (d, *J* = 5.5 Hz, 1H), 3.05 (m, 1H), 3.18 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.50 (dd, *J* = 14.3, 5.7 Hz, 1H), 7.03 - 7.18 (m, 6H), 7.86 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 21.2, 24.3, 26.2, 62.7, 117.8, 121.4, 123.5, 130.9, 132.2, 147.7, 152.3, 162.8, 169.5
HRMS (FAB)	calcd for $C_{17}H_{16}O_5S_2$ (M^+) 364.0439, found 364.0420
34b	
Preparation Route	Scheme S14
Overall yield	75% from **30a**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.17 (dd, *J* = 5.0, 1.6 Hz, 1H), 2.55 (d, *J* = 6.2 Hz, 1H), 3.08 (m, 1H), 3.19 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.53 (dd, *J* = 14.3, 5.7 Hz, 1H), 7.06 - 7.17 (m, 6H), 7.87 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.3, 27.3, 62.8,, 117.8, 121.5, 123.5, 130.9, 132.2, 148.2, 152.1, 163.1, 177.3
HRMS (FAB)	calcd for $C_{20}H_{23}O_5S_2$ ($M+H^+$) 407.0987, found 407.0990
34c	
Preparation Route	Scheme S14
Overall yield	89% from **30a**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 4.8, 1.0 Hz, 1H), 2.54 (d, *J* = 5.5 Hz, 1H), 3.07 (m, 1H), 3.20 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.53 (dd, *J* = 14.3, 5.7 Hz, 1H), 7.15 (t, *J* = 8.4 Hz, 4H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 8.21 (d, *J* = 7.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.7, 117.8, 121.5, 123.7, 128.8, 130.3, 130.9, 132.3, 134.0, 148.0, 152.4, 162.9, 165.3
HRMS (FAB)	calcd for $C_{22}H_{19}O_5S_2$ ($M+H^+$) 427.0674, found 427.0634
34d	
Preparation Route	Scheme S14

Overall yield	85% from **30a**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.18 (m, 1H), 2.55 (t, *J* = 5.7 Hz, 1H), 3.08 (m, 1H), 3.19 (m, 1H), 3.53 (ddd, *J* = 14.4, 9.0, 5.9 Hz, 1H), 3.89 (s, 2H), 7.05 - 7.19 (m, 6H), 7.25 - 7.45 (m, 5H), 7.87 (d, *J* = 9.0 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.3, 41.6, 62.8, 117.9, 121.5, 123.5, 129.0, 130.4, 131.0, 132.3, 133.4, 147.8, 152.4, 163.0, 170.2
HRMS (FAB)	calcd for $C_{23}H_{21}O_5S_2$ ($M+H^+$) 441.0830, found 441.0841
35a	
Preparation Route	Lit.[12]
35a	
Preparation Route	Scheme S14
Overall yield	17% from 3-iodophenol
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.18 (dd, *J* = 5.0, 1.6 Hz, 1H), 2.56 (d, *J* = 6.0 Hz, 1H), 3.08 (m, 1H), 3.20 (s, 3H), 3.23 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.52 (m, *J* = 14.2, 5.8 Hz, 1H), 7.01 - 7.21 (m, 5H), 7.47 (t, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.4, 26.2, 38.0, 62.8, 114.6, 118.6, 118.6, 119.0, 131.1, 131.2, 131.3, 131.4, 133.2, 150.1, 156.3, 161.9
HRMS (FAB)	calcd for $C_{16}H_{17}O_6S_3$ ($M+H^+$) 400.0109, found 400.0113
36	
Preparation Route	Lit.[13]
37a	
Preparation Route	Lit.[13]
37b	
Preparation Route	Scheme S14
Overall yield	76% from **306**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.8 Hz, 6H), 2.00 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.17 (dd, *J* = 5.2, 1.6 Hz, 1H), 2.55 (dd, *J* = 6.1, 1.3 Hz, 1H), 3.07 (m, 1H), 3.17 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.53 (dd, *J* = 14.2, 5.6 Hz, 1H), 3.98 (d, *J* = 6.8 Hz, 2H), 6.69 (br. s., 1H), 7.06 (t, *J* = 9.2 Hz, 4H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 9.0 Hz, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 19.2, 24.4, 26.3, 28.1, 62.8, 71.7, 117.5, 120.6, 121.4, 130.9, 130.9, 131.8, 135.6, 150.2, 154.0, 163.5
HRMS (ESI)	calcd for $C_{20}H_{24}NO_5S_2$ ($M+H^+$) 422.1090, found 422.1117

38	
Preparation Route	Lit.[1]
39	
Preparation Route	Scheme S6
Overall yield	24% from 4-(methylthio)phenylboronic acid
^{1}H NMR	(300 MHz, 5% CD_3OD in $CDCl_3$) δ 2.12 (dd, *J* = 5.0, 1.7 Hz, 1H), 2.49 (dd, *J* = 6.1, 1.4 Hz, 1H), 3.01 (m, 1H), 3.04 (s, 3H), 3.26 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.43 (dd, *J* = 14.4, 6.4 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 4H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H)
^{13}C NMR	(75 MHz, 5% CD_3OD in $CDCl_3$) δ 24.0, 26.0, 44.6, 62.4, 119.6, 119.8, 130.1, 131.1, 133.9, 136.1, 160.0, 160.6
HRMS (ESI)	calcd for $C_{16}H_{16}NaO_5S_3$ ($M+H^+$) 407.0052, found 407.0044
40	
Preparation Route	Scheme S3
Overall yield	31% from 2-chloro-5-nitropyridine
^{1}H NMR	(500 MHz, CD_2Cl_2) δ 2.16 (dd, *J* = 5.2, 1.8 Hz, 1H), 2.53 (dd, *J* = 6.6, 1.8 Hz, 1H), 2.97 (s, 3H), 3.06 (m, 1H), 3.25 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.52 (dd, *J* = 14.4, 6.0 Hz, 1H), 7.04 (dd, *J* = 8.8, 0.4 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.79 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 2.8 Hz, 1H)
^{13}C NMR	(126 MHz, CD_2Cl_2) δ 24.5, 26.5, 39.8, 63.0, 113.8, 121.4, 131.0, 131.9, 134.4, 134.7, 141.1, 159.9, 160.1
HRMS (FAB)	calcd for $C_{15}H_{17}N_2O_5S_3$ ($M+H^+$) 401.0300, found 401.0290
41	
Preparation Route	Scheme S3
Overall yield	39% from **65**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 2.21 (dd, *J* = 5.1, 1.7 Hz, 1H), 2.58 (dd, *J* = 6.0, 1.2 Hz, 1H), 3.12 (m, 1H), 3.22 (dd, *J* = 14.3, 7.9 Hz, 1H), 3.59 (dd, *J* = 14.3, 5.5 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.97 - 8.04 (m, 3H), 8.47 (s, 1H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.1, 62.6, 112.4, 122.2, 130.5, 135.0, 137.4 (q, *J* = 2.5 Hz), 145.3 (q, *J* = 4.1 Hz), 158.0, 164.5
^{19}F NMR	(282 MHz, $CDCl_3$) δ -61.74 (s, 1F)
HRMS	calcd for $C_{15}H_{13}F_3NO_3S_2$ ($M+H^+$) 376.0289, found 376.0265
42a	

Preparation Route	Scheme S15
Overall yield	60% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 0.92 (d, 6H, J = 6.7 Hz), 1.94 (sep, 1H, J = 6.7 Hz), 2.17 (dd, 1H, J = 5.1, 1.8 Hz), 2.55 (dd, 1H, J = 6.3, 1.7 Hz), 3.07 (m, 1H), 3.18 (dd, 1H, J = 14.0, 7.8 Hz), 3.53 (dd, 1H, J = 13.9, 5.4 Hz), 3.66 (s, 2H), 3.91 (d, 2H, J = 6.6 Hz), 7.07 (m, 4H), 7.35 (m,2H), 7.87 (m, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 19.0, 24.3, 26.1, 27.7, 40.7, 62.7, 71.1, 117.4, 120.6, 130.7 (d), 131.2 (d), 131.3, 131.9, 153.7, 162.9, 171.4
HRMS (FAB)	calcd for $C_{21}H_{24}O_5S_2$ (M^+) 420.1065, found 420.1046
42b	
Preparation Route	Scheme S15
Overall yield	34% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.17 (dd, 1H, J = 5.1, 1.7 Hz), 2.55 (dd, 1H, J = 6.0, 1.1 Hz), 3.07 (m, 1H), 3.19 (dd, 1H, J = 14.1, 7.9 Hz), 3.53 (dd, 1H, J = 14.1, 5.4 Hz), 3.71 (s, 1H), 5.17 (s, 1H), 7.08 (m, 4H), 7.35 (m, 6H), 7.87 (m, 2H)
^{13}C NMR	(500 MHz, $CDCl_3$) δ 24.2, 26.1, 40.6, 62.7, 66.8, 117.7, 120.6, 128.2, 128.4, 128.6, 130.7, 130.8, 130.9, 131.2, 132.0, 135.7, 153.9, 162.9, 171.2
HRMS (FAB)	calcd for for $C_{24}H_{23}O_5S_2$ ($M+H^+$) 455.0987, found 455.0989
42c	
Preparation Route	Scheme S15
Overall yield	58% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.16 (dd, 1H, 5.1, 1.7 Hz), 2.54 (dd, 1H, 6, 1.4 Hz), 3.06 (m, 1H), 3.18 (dd, 1H, 14.1, 7.8 Hz), 3.52 (dd, 1H, 13.8, 5.4 Hz), 3.69 (s, 2H), 5.12 (s, 2H), 7.06 (m, 4H), 7.29 (m, 6H), 7.86 (m, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.1, 40.5, 62.7, 66.0, 117.4, 117.8, 120.6, 128.8, 129.6, 130.7, 130.8, 131.2 (d), 132.0, 134.2, 153.9, 162.8, 171.1
HRMS (FAB)	calcd for $C_{24}H_{22}ClO_5$ ($M+H^+$) 489.0597, found 489.0576
42d	
Preparation Route	Scheme S15
Overall yield	61% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.17 (dd, 1H, J = 5.1, 1.7 Hz), 2.54 (dd, 1H, J = 6.0, 1.4 Hz), 3.07 (m, 1H), 3.19 (dd, 1H, J = 13.8, 7.8 Hz), 3.53 (dd, 1H, J = 14.1, 5.4 Hz), 3.78 (s, 1H), 5.30 (s, 1H), 7.08 (m, 4H), 7.32 (m, 4H), 7.72 (d of t, 1H, J = 7.8, 1.5 Hz), 7.87 (m, 2H), 8.62 (d, 1H, J = 4.9 Hz)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.1, 40.4, 62.6, 67.3, 117.4, 117.8, 120.6, 121.9, 123.1, 130.8 (t), 131.3 (d), 132.0, 136.9, 149.5, 153.9, 155.4, 162.9, 171.1
HRMS (FAB)	calcd for $C_{23}H_{22}NO_5S_2$ ($M+H^+$) 456.0939, found 456.0943

42e	
Preparation Route	Scheme S15
Overall yield	40% from **42**
^{1}H NMR	(300 MHz, acetone-*d6*) δ 2.18 (dd, 1H, J = 5.0, 1.4 Hz), 2.55 (dd, 1H, J = 6.5, 1.2 Hz), 3.06 (quinett t,t, 1H, J = 6.2, 1.1 Hz), 3.41 (dd, 1H, J = 14.5, 7.3 Hz), 3.59 (dd, 1H, J = 14.5, 6.1 Hz), 3.79 (s, 2H), 5.21 (s, 2H), 7.15 (m, 4H), 7.37 (ddd, 1H, J = 5.0, 8.0, 0.8 Hz), 7.43 (m, 2H), 7.77 (m, 1H), 7.95 (m, 2H), 8.54 (dd, 1H, J = 4.5, 1.6 Hz), 8.59 (d, 1H, J = 1.8 Hz)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.1, 40.4, 62.6, 64.2, 117.5, 117.8, 120.6, 123.6, 130.5, 130.8 (d), 131.2 (d), 132.0, 136.2, 149.4, 149.5, 154.0, 162.8, 171.1
HRMS (FAB)	calcd for $C_{23}H_{22}NO_5S_2$ ($M+H^+$) 456.0939, found 456.0961
42f	
Preparation Route	Scheme S15
Overall yield	45% from **42**
^{1}H NMR	(300 MHz, acetone-*d6*) δ 2.18 (dd, 1H, J = 5.0, 1.4 Hz), 2.55 (dd, H, 6.0, 1.3 Hz), 3.06 (m, 1H), 3.40 (dd, 1H, 14.5, 7.3 Hz), 3.59 (dd, 1H, 14.5, 6.1 Hz), 3.74 (s, 2H), 5,33 (s, 2H), 7.01 (m, 1H), 7.14 (m, 5H), 7.41 (m, 2H), 7.48 (m, 1H), 7.94 (m, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.3, 26.1, 40.4, 61.1, 62.7, 117.4, 117.7, 120.6, 126.9, 127.0, 128.3, 130.7, 130.8 (d), 131.2 (d), 131.9, 137.6, 153.9, 162.9, 171.1
HRMS (FAB)	calcd for $C_{22}H_{20}O_5S_3$ (M^+) 460.0473, found 460.0468
43a	
Preparation Route	Scheme S15
Overall yield	28% from **42**
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.14 (t, 3H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.1 Hz) 2.16 (dd, 1H, J = 5.0, 1.8 Hz), 2.54 (dd, 1H, J = 6.0, 1.1 Hz), 3.06 (m, 1H), 3.17 (dd, 1H, 14.0, 7.9 Hz), 3.36 (q, 2H, J = 7.1 Hz), 3.41 (q, 2H, J = 7.1 Hz), 3.52 (dd, 1H, J = 14.0, 5.5 Hz), 3.71 (s, 2H), 7.06 (m, 4H), 7.31 (m, 2H), 7.85 (m, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 13.0, 14.4, 24.3, 26.1, 39.8, 40.4, 42.4, 62.6, 117.3, 117.6, 120.6, 130.7 (d), 130.8 (d), 131.8, 132.7, 153.4, 163.0, 169.8
HRMS (FAB)	calcd for $C_{21}H_{26}NO_4S_2$ ($M+H^+$) 420.1303, found 420.1306
43b	
Preparation Route	Scheme S15
Overall yield	13% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.17 (dd, 1H, J = 5.1, 1.8 Hz), 2.55 (dd, 1H, J = 6.0, 1.7 Hz), 3.07 (m, 1H), 3.19 (dd, 1H, J = 14.0, 7.8 Hz), 3.52 (dd, 1H, J = 14.1, 5.7 Hz), 3,63 (s, 2H), 4.46 (d, 2H, J = 5.7 Hz), 5.80 (m, 1H), 7.08 (m, 4H), 7.29 (m, 7H), 7.87 (m, 2H)

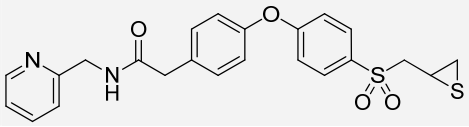
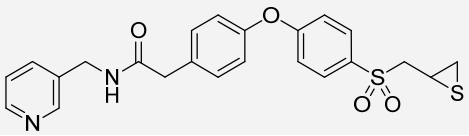
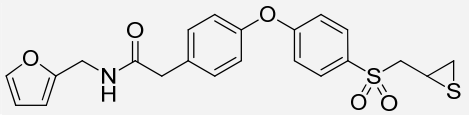
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.2, 26.1, 43.0, 43.8, 62.6, 117.5, 117.8, 117.9, 120.8, 127.7, 128.8, 130.8 (d), 131.2 (d), 131.8, 132.1, 138.0, 154.1, 162.7, 170.4
HRMS (FAB)	calcd for $C_{24}H_{24}NO_4S_2$ ($M+H^+$) 454.1147, found 454.1162
43c	
Preparation Route	Scheme S15
Overall yield	16% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.16 (dd 1H, J = 5.0, 1.8 Hz), 2.54 (dd 1H, J = 6.0, 1.5 Hz), 3.06 (m, 1H), 3.18 (dd, 1H, J = 14.5, 7.8 Hz), 3.52 (dd, 1H, J = 14.5, 5.6 Hz), 3.66 (s, 2H), 4.59 (d, 2H, J = 5.0 Hz), 7.07 (m, 4H), 7.32 (m, 4H), 7.80 (m, 3H), 8.51 (d, 1H, J = 5.0 Hz)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.2, 26.1, 42.8, 44.1, 62.7, 117.4, 117.8 (d), 120.8, 122.8, 122.9, 130.8, 131.3 (d), 131.9 (d), 137.9, 148.0, 153.9, 155.7, 162.9, 170.8
HRMS (FAB)	calcd for $C_{23}H_{23}O_4N_2S_2$ ($M+H^+$) 455.1099, found 455.1100
43d	
Preparation Route	Scheme S15
HRMS (FAB)	calcd for $C_{23}H_{23}O_4N_2S_2$ ($M+H^+$) 455.1099, found 455.1101
Overall yield	27% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.16 (dd, 1H, J = 5.0, 1.7 Hz), 2.54 (dd, 1H, J = 6.0, 1.8 Hz), 3.06 (m, 1H), 3.19 (dd, 1H, J = 14.5, 7.7 Hz), 3.50 (dd, 1H, J = 14.0, 5.7 Hz), 3.63 (s, 2H), 4.46 (d, 2H, J = 6.06 Hz), 5.98 (m, 1H), 7.07 (m, 4H), 7.30 (m, 3H), 7.60 (m, 1H), 7.83 (m, 2H), 8.47 (d, 1H, J = 2.1 Hz), 8.51 (dd, 1H, J = 5.0, 1.5 Hz)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.2, 26.1, 41.2, 42.8, 62.6, 117.6, 117.9 (d), 120.8, 123.7, 130.8 (d), 131.2 (d), 131.5, 132.2, 133.9, 135.7, 148.8, 154.2, 162.6, 170.7
43e	
Preparation Route	Scheme S15
Overall yield	15% from **42**
^{1}H NMR	(300 MHz, $CDCl_3$) δ 2.17 (dd, 1H, J = 4.8, 1.8 Hz), 2.55 (dd, 1H, J = 6.0, 1.7 Hz), 3.07 (m, 1H), 3.20 (dd, 1H, J = 13.8, 7.7 Hz), 3.52 (dd, 1H, J = 14.1, 5.6 Hz), 3.61 (s, 2H), 4.45 (d, 2H, J = 5.6 Hz), 5.80 (m, 1H), 6.20 (d, 1H, J = 3.3 Hz), 6.32 (m, 1H), 7.09 (m, 4H), 7.33 (m, 3H), 7.87 (m, 2H)
^{13}C NMR	(126 MHz, $CDCl_3$) δ 24.2, 26.1, 36.7, 42.8, 62.7, 107.5, 110.4, 117.5, 117.8, 120.8, 130.8 (d), 131.2 (d), 131.6, 132.1, 142.3, 150.9, 154.1, 162.7, 170.3
HRMS (FAB)	calcd for $C_{22}H_{22}NO_5S_2$ ($M+H^+$) 444.0939, found 444.0920

Figure S1. High-throughput screening of synthetic compounds at 30 μM (in blue), 3 μM (in orange), and 0.3 μM (in turquoise) with MMP-2.

A. SAR-1 Compounds at 30 μM.

[I] = 30 μM

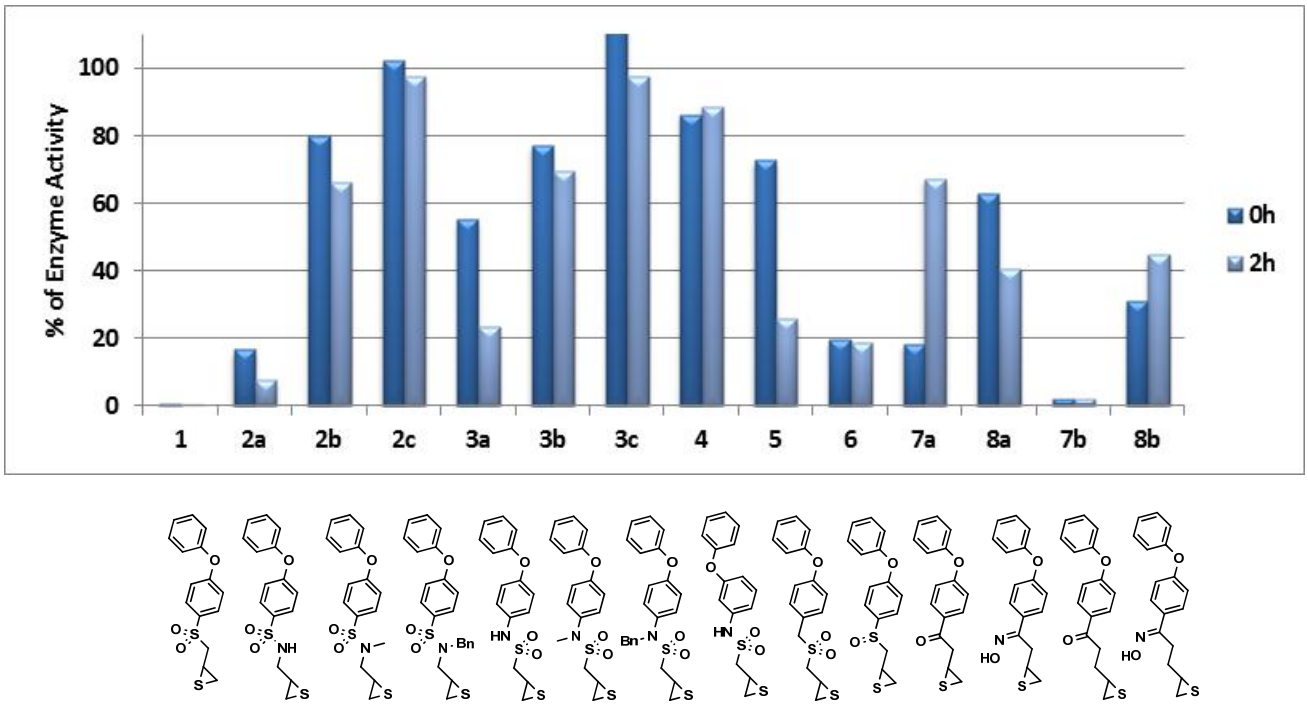
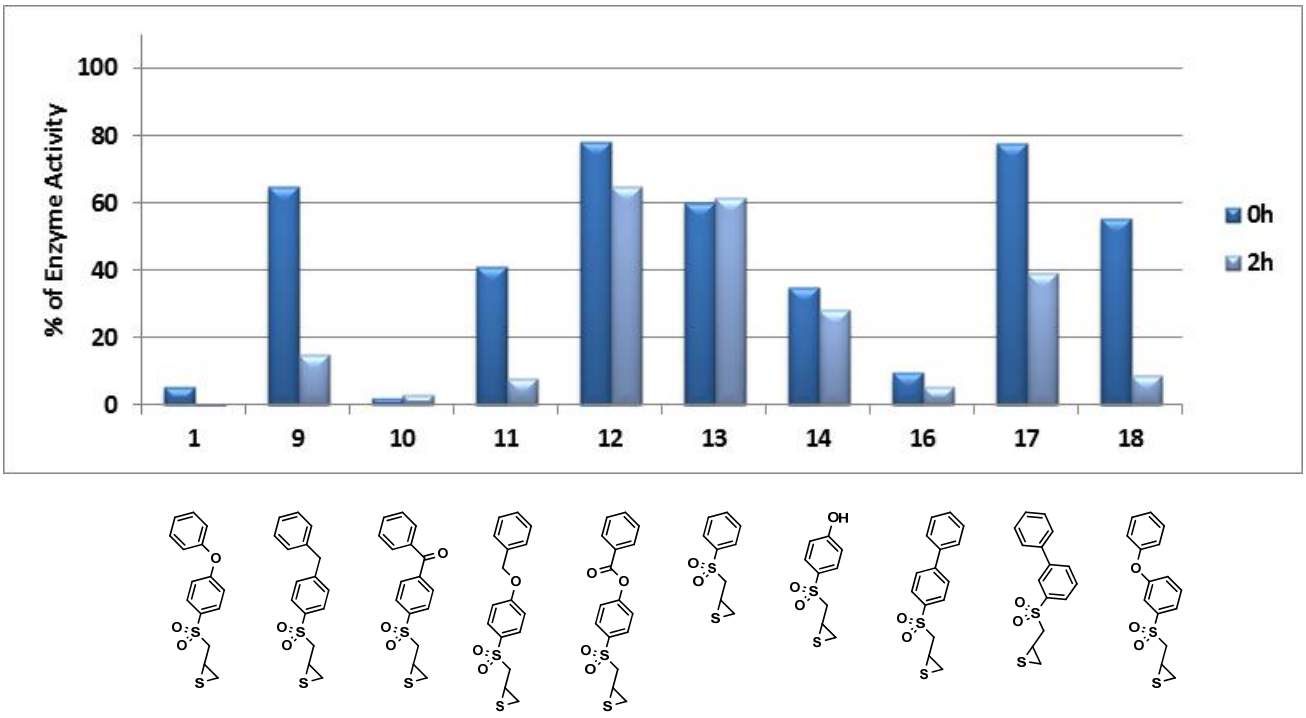
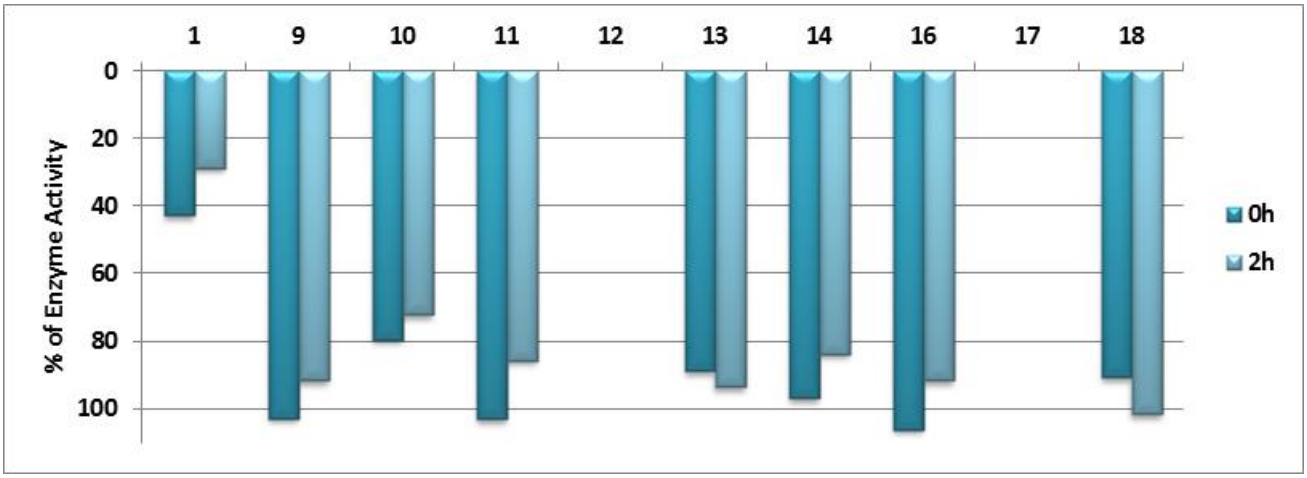


Figure S1. continued

B. SAR-2 Compounds at 30 μM and 0.3 μM.

[I] = 30 μM



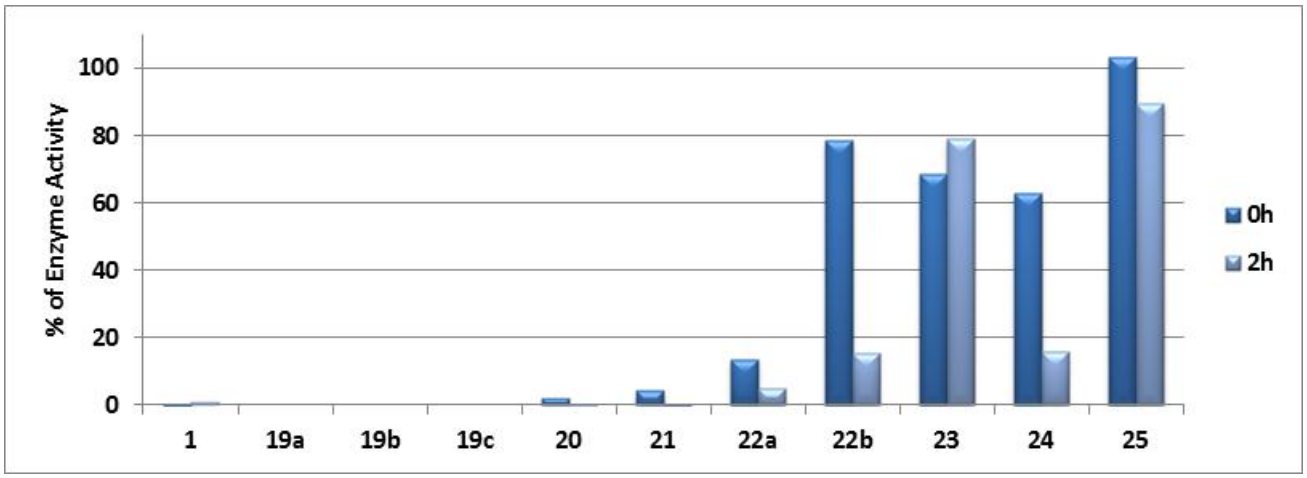


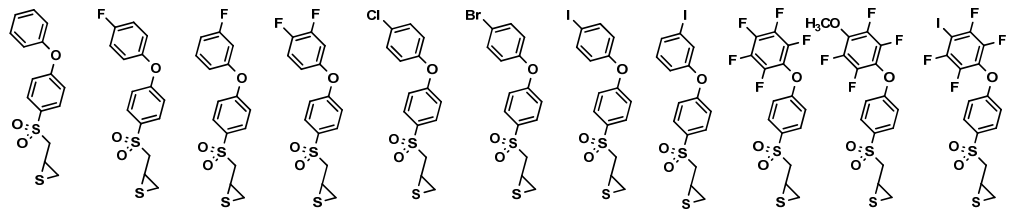
[I] = 0.3 μM

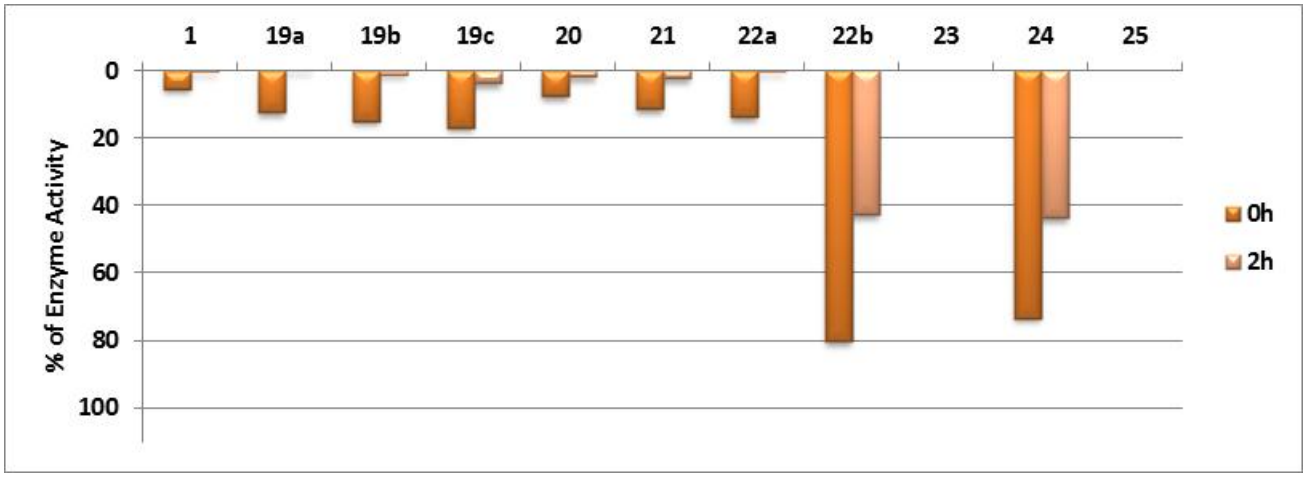
Figure S1. continued

C. Halogen substituted compounds at 30 μM and 3 μM.

[I] = 30 μM





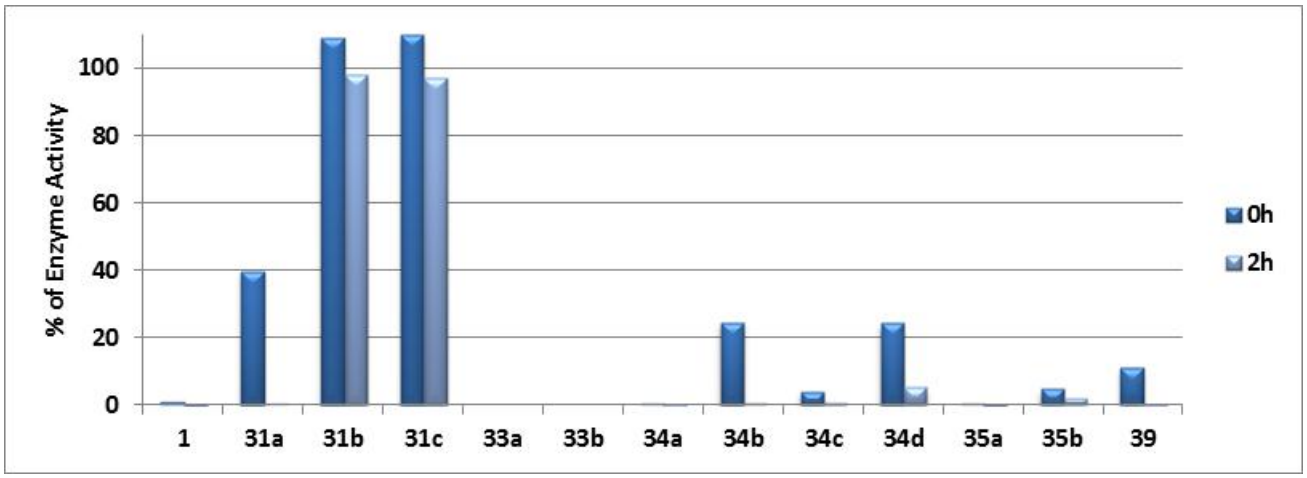


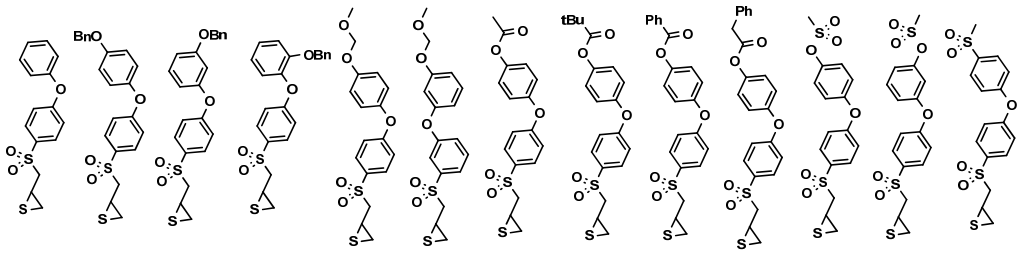
[I] = 3 μM

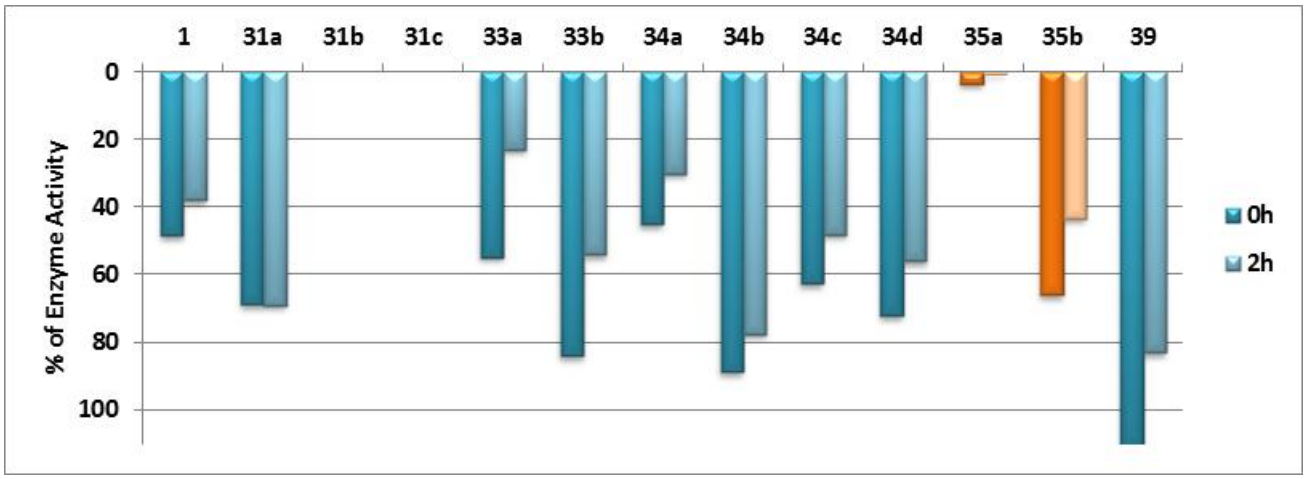
Figure S1. continued

D. SAR-3 Compounds at 30 μM, 3 μM, and 0.3 μM.

[I] = 30 μM





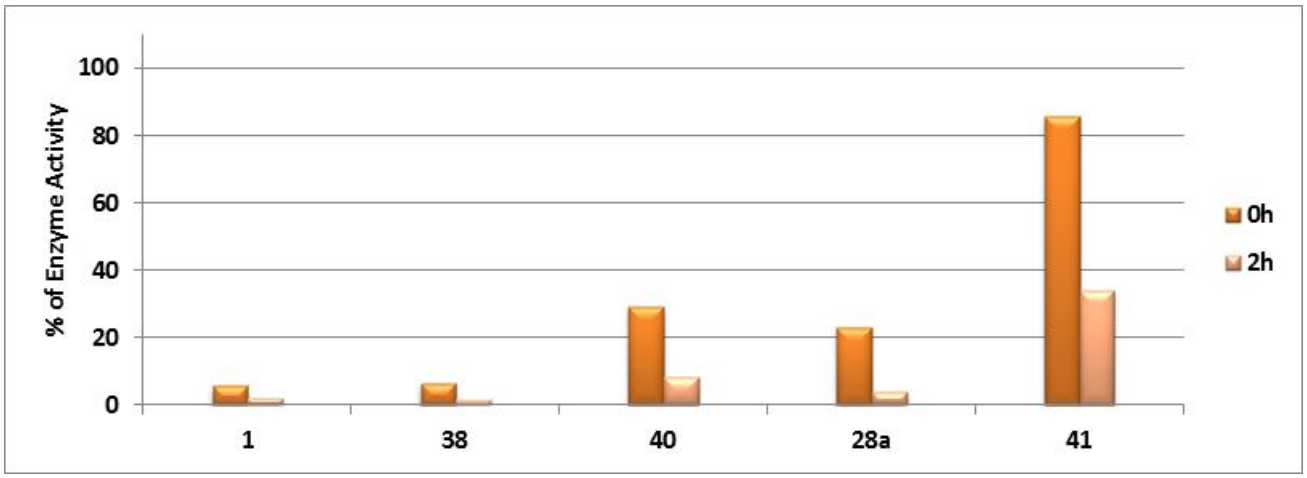


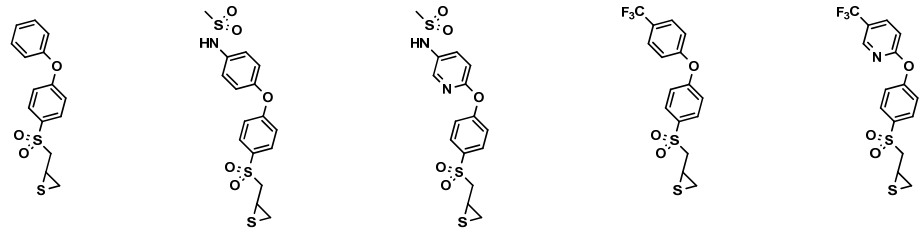
[I] = 0.3 μM ([I] = 3 μM in orange)

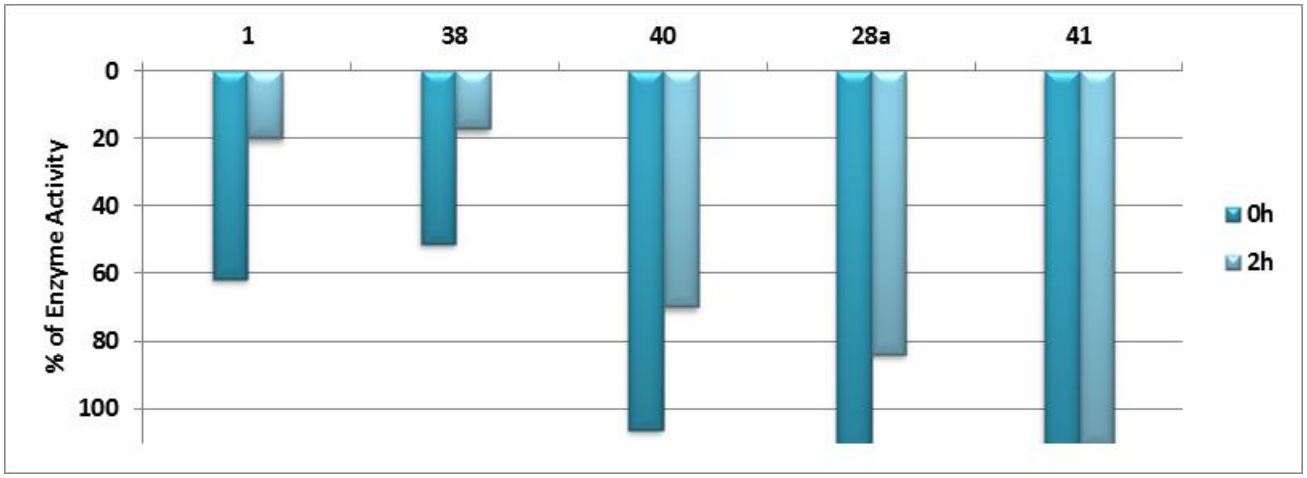
Figure S1. continued

E. Pyridine containing compounds at 3 μM and 0.3 μM.

[I] = 3 μM





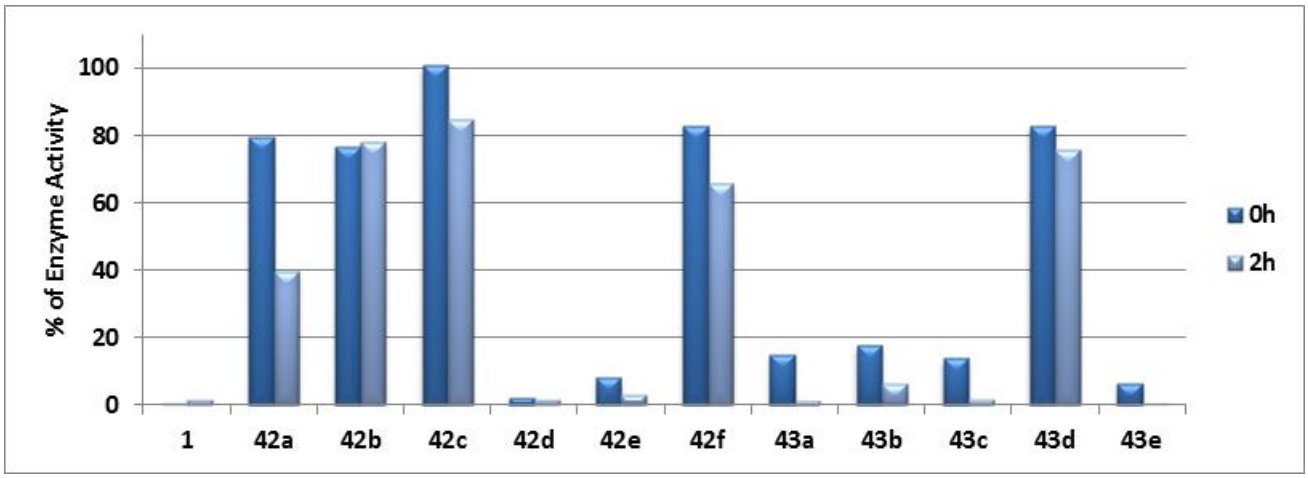


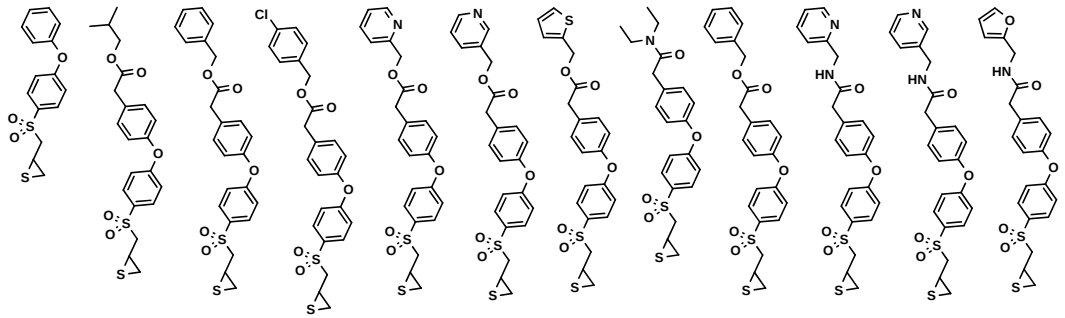
[I] = 0.3 μM

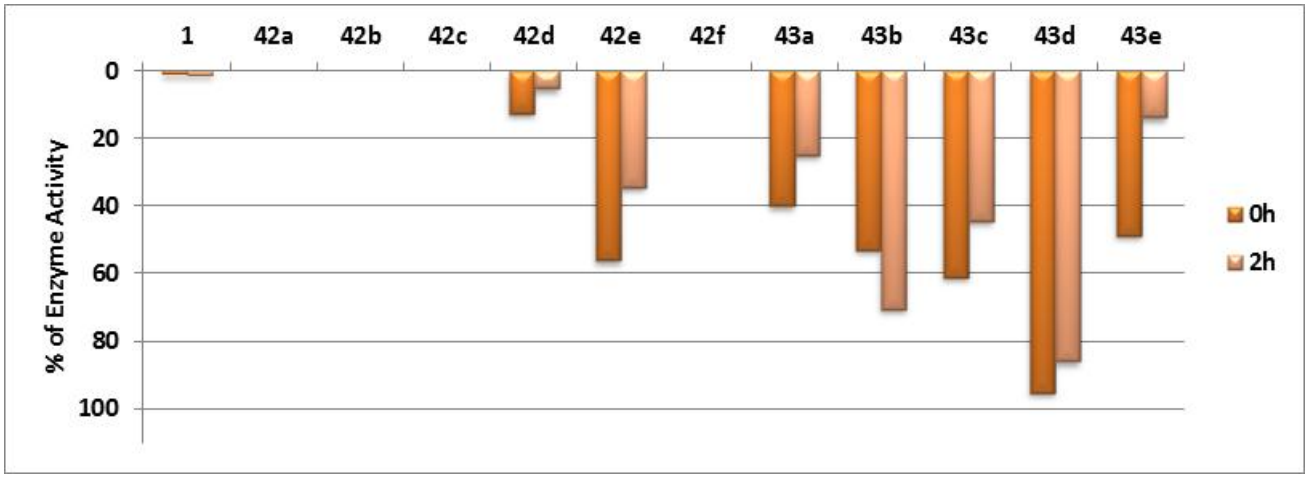
Figure S1. continued

F. Ester (**42a – 42e**) and amide (**43a – 43e**) derivatives of compound **42** at 30 μM and 3 μM.

[I] = 30 μM







[I] = 3 μM

Figure S1. continued

G. Figure 2 (in the main manuscript). High-throughput screening of synthetic compounds at 30 μM (in blue) and at 300 nM (in turquoise) with MMP-2.

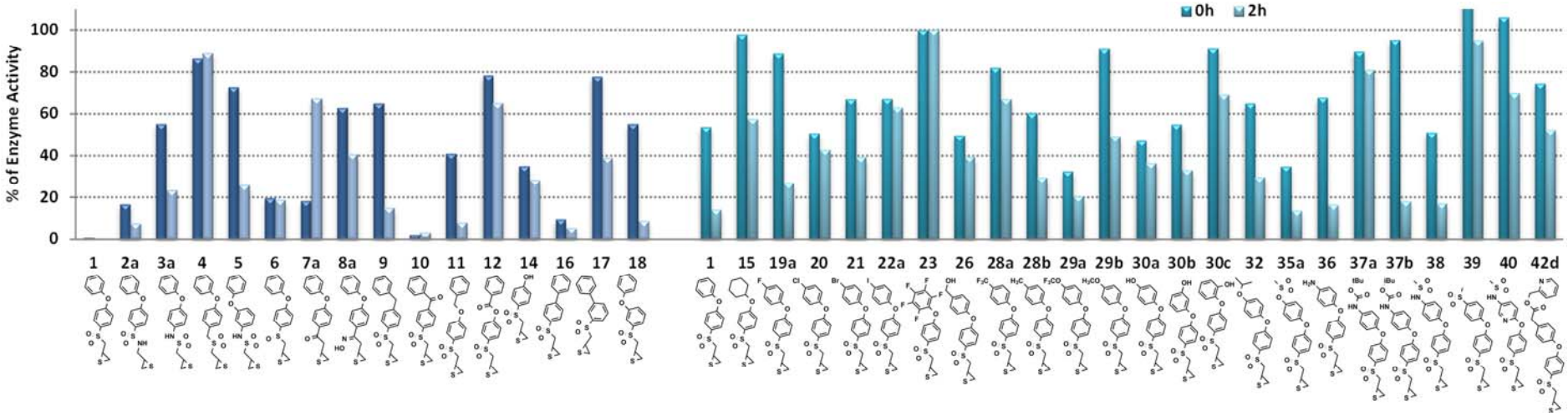
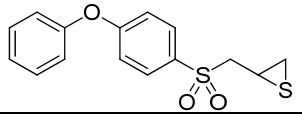
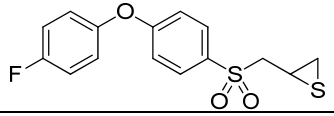
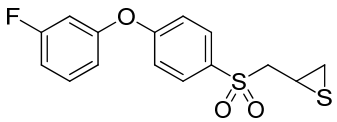
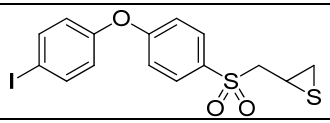
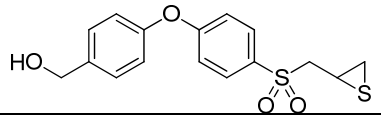
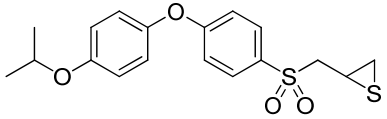
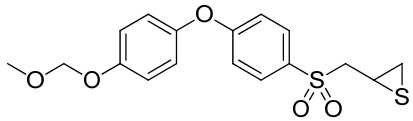
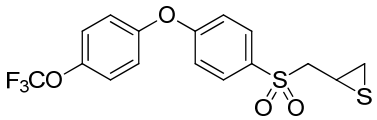


Table S2. Full slow-binding kinetic parameters for inhibition of MMPs by selected compounds.

Inhibitor	Structure	Enzyme	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_i (μM)
1 [a]		MMP-2	$(11 \pm 1) \times 10^4$	$(1.8 \pm 0.1) \times 10^{-3}$	0.0139 ± 0.0004
		MMP-9	$(1.4 \pm 0.3) \times 10^4$	$(1.5 \pm 0.1) \times 10^{-3}$	0.6 ± 0.2
19a		MMP-2	$(1.5 \pm 0.1) \times 10^4$	$(9.1 \pm 0.8) \times 10^{-4}$	0.061 ± 0.007
		MMP-14 $_{cat}$	$(4.6 \pm 0.4) \times 10^3$	$(2.7 \pm 0.6) \times 10^{-3}$	0.58 ± 0.14
19b		MMP-2	$(1.3 \pm 0.1) \times 10^3$	$(0.6 \pm 0.1) \times 10^{-3}$	0.45 ± 0.1
		MMP-9	$(0.5 \pm 0.05) \times 10^3$	$(1.5 \pm 0.1) \times 10^{-3}$	3.0 ± 0.3
		MMP-14 $_{cat}$	$(3.0 \pm 0.2) \times 10^3$	$(0.6 \pm 0.1) \times 10^{-3}$	0.19 ± 0.04
22a		MMP-2	$(1.9 \pm 0.3) \times 10^3$	$(1.1 \pm 0.1) \times 10^{-3}$	0.60 ± 0.11
		MMP-9	$(2.9 \pm 0.3) \times 10^3$	$(0.83 \pm 0.20) \times 10^{-3}$	0.29 ± 0.07
26		MMP-2	$(1.5 \pm 0.2) \times 10^4$	$(1.2 \pm 0.2) \times 10^{-3}$	0.078 ± 0.013
		MMP-9	$(2.6 \pm 0.4) \times 10^3$	$(1.0 \pm 0.2) \times 10^{-3}$	0.390 ± 0.085
32		MMP-2	$(2.1 \pm 0.4) \times 10^3$	$(0.6 \pm 0.1) \times 10^{-3}$	0.30 ± 0.09
		MMP-9	$(1.9 \pm 0.2) \times 10^3$	$(0.9 \pm 0.2) \times 10^{-3}$	0.47 ± 0.10
		MMP-14 $_{cat}$	$(2.0 \pm 0.3) \times 10^3$	$(0.6 \pm 0.2) \times 10^{-3}$	0.28 ± 0.10
33a		MMP-2	$(2.0 \pm 0.3) \times 10^3$	$(0.4 \pm 0.1) \times 10^{-3}$	0.18 ± 0.05
		MMP-9	$(3.8 \pm 0.3) \times 10^3$	$(0.6 \pm 0.2) \times 10^{-3}$	0.16 ± 0.05
		MMP-14 $_{cat}$	$(2.3 \pm 0.2) \times 10^3$	$(0.3 \pm 0.09) \times 10^{-3}$	0.14 ± 0.04
38a		MMP-2	$(1.1 \pm 0.2) \times 10^4$	$(1.2 \pm 0.4) \times 10^{-3}$	0.110 ± 0.040
		MMP-9	$(2.4 \pm 0.2) \times 10^3$	$(2.3 \pm 0.1) \times 10^{-3}$	0.930 ± 0.090
		MMP-14 $_{cat}$	$(1.2 \pm 0.1) \times 10^2$	$(6 \pm 0.4) \times 10^{-4}$	5.08 ± 0.510

[a] Reported earlier,[4] and given here for the sake of side-by-side comparison.

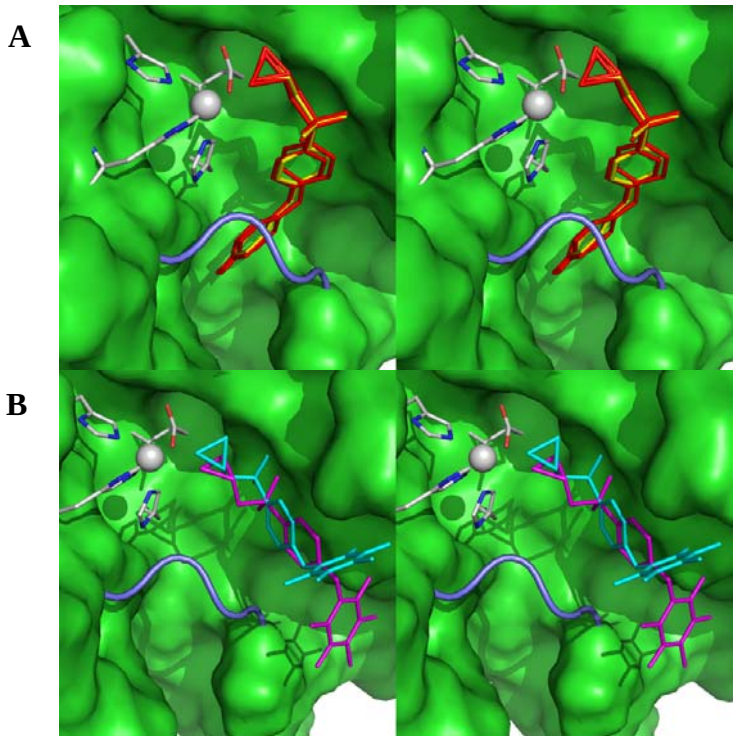


Figure S2. Glide (Schrödinger) software with the glidescore scoring function in the standard precision mode was used for docking of compounds **1**, **19a**, **22a**, **23** and **25** into the active site of MMP-2. Zn^{2+} is depicted as a gray sphere with coordinating histidines and glutamic acid as capped sticks. The rest of the protein is shown as a green Connolly surface with part of the loop that encompasses the S1 binding site as a slate ribbon. (A) The docked conformation of compounds showing activity, with **1** in yellow, and **19a** and **22a** in red. (B) The docked conformation for **23** (cyan) and **25** (magenta). Note that the terminal phenyl ring is not in the S1 loop, but is exposed to the solvent. The backbones of the molecules in the two binding conformations are distinct.

References

(1) Ikejiri, M.; Bernardo, M. M.; Bonfil, R. D.; Toth, M.; Chang, M.; Fridman, R.; Mobashery, S., Potent mechanism-based inhibitors for matrix metalloproteinases. *J. Biol. Chem.* **2005,** *280*, 33992-34002.

(2) Barbero, M.; Degani, I.; Dughera, S.; Fochi, R., An improved, general procedure to S-aryl thiol esters: A new synthetic application of dry arenediazonium *o*-benzenedisulfonimides. *Synthesis* **2003**, 1225-1230.

(3) Barbero, M.; Crisma, M.; Degani, I.; Fochi, R.; Perracino, P., New dry arenediazonium salts, stabilized to an exceptionally high degree by the anion of *o*-benzenedisulfonimide. *Synthesis* **1998**, 1171-1175.

(4) Brown, S.; Bernardo, M. M.; Li, Z. H.; Kotra, L. P.; Tanaka, Y.; Fridman, R.; Mobashery, S., Potent and selective mechanism-based inhibition of gelatinases. *J. Am. Chem. Soc.* **2000,** *122*, 6799-6800.

(5) Ma, D. W.; Cai, Q., N,N-Dimethyl glycine-promoted Ullmann coupling reaction of phenols and aryl halides. *Org. Lett.* **2003,** *5*, 3799-3802.

(6) Evans, D. A.; Katz, J. L.; West, T. R., Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine. *Tetrahedron Lett.* **1998,** *39*, 2937-2940.

(7) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P., New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998,** *39*, 2933-2936.

(8) Ikejiri, M.; Bernardo, M. M.; Meroueh, S. O.; Brown, S.; Chang, M.; Fridman, R.; Mobashery, S., Design, synthesis, and evaluation of a mechanism-based inhibitor for gelatinase a. *J. Org. Chem.* **2005,** *70*, 5709-5712.

(9) Lee, M.; Bernardo, M. M.; Meroueh, S. O.; Brown, S.; Fridman, R.; Mobashery, S., Synthesis of chiral 2-(4-phenoxyphenylsulfonylmethyl)thiiranes as selective gelatinase inhibitors. *Org. Lett.* **2005,** *7*, 4463-4465.

(10) Lim, I. T.; Brown, S.; Mobashery, S., A convenient synthesis of a selective gelatinase inhibitor as an antimetastatic agent. *J. Org. Chem.* **2004,** *69*, 3572-3573.

(11) Forbes, C.; Shi, Q. C.; Fisher, J. F.; Lee, M.; Hesek, D.; Llarrull, L. I.; Toth, M.; Gossing, M.; Fridman, R.; Mobashery, S., Active site ring-opening of a thiirane moiety and picomolar inhibition of gelatinases. *Chem. Biol. Drug Des.* **2009,** *74*, 527-534.

(12) Lee, M.; Celenza, G.; Boggess, B.; Blase, J.; Shi, Q.; Toth, M.; Bernardo, M. M.; Wolter, W. R.; Suckow, M. A.; Hesek, D.; Noll, B. C.; Fridman, R.; Mobashery, S.; Chang, M., A potent gelatinase inhibitor with anti-tumor-invasive activity and its metabolic disposition. *Chem. Biol. Drug Des.* **2009,** *73*, 189-202.

(13) Gooyit, M.; Lee, M.; Ikejiri, M.; Wolter, W. R.; Suckow, M. A.; Mobashery, S.; Chang, M., Selective water-soluble gelatinase inhibitor prodrugs. *J. Med. Chem.* **2011,** *54*, 6676-6690.