

Supporting Information

Synthesis and Biochemical Evaluation of Thiochromanone Thiosemicarbazone Analogues as Inhibitors of Cathepsin L

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General Details:

Chemicals and reagents used in the synthetic procedures were obtained from various suppliers (Sigma Aldrich Chem. Co., Acros Chem. Co., Alfa Aesar, Fisher Scientific, EMD Chemicals, Fluorochem, Ltd., and VWR). Thin layer chromatography (TLC) plates (pre-coated glass plates with silica gel 60 F254, 0.25 mm thickness, EMD Chemicals, VWR) were used to monitor reactions. Silica gel (200 – 400 mesh, 60Å) used for column chromatography was obtained from either Silicycle Inc. or VWR. Purification of intermediates and products was carried out using manual flash column chromatography with silica gel or with a Biotage® Isolera™ flash purification system using Biotage® KP-Sil SNAP columns. Intermediates and products were characterized by ¹H-NMR (Varian operating at 500 MHz or Bruker operating at 300 MHz) and ¹³C-NMR (Varian operating at 125 MHz or Bruker operating at 75 MHz). Deuterated CDCl₃ (with 0.03 % TMS as internal standard), acetone-d₆, and DMSO-d₆ were used as common solvents for the NMR studies. Each of the chemical shifts is expressed in ppm (δ). The coupling constants (*J*) are expressed in Hz and peak patterns are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). High-resolution mass spectra (HRMS) were obtained using Electron Impact (EI) ionization on a VG Prospec Micromass spectrometer or Electrospray Ionization (ESI) technique on a Thermo Scientific LTQ Orbitrap Discovery Mass Spectrometer in the Baylor University Mass Spectrometry Center. Purity of the final compounds was further analyzed using an Agilent Technologies 1200 series HPLC system with a Diode Array and Multiple Wavelength Detector SL, equipped with an Agilent Eclipse XDB-C18 column (4.6 mm ID X 250 mm (5 μm) 80 Å), *T* = 30 °C; eluents solvent A, water, solvent B, acetonitrile; gradient 90 % A 10 % B → 0 % A 100 % B over 0 to 20 min, hold for 2 min; flow rate 1.5 mL/min; injection volume 20 μL; monitored at 300 and 320 nm wavelength.

Biochemical Assays:

Cathepsin B Assay for IC₅₀ Determination: Human liver Cathepsin B (Calbiochem) was pre-incubated with inhibitors at various concentrations for 5 minutes at 37 °C. The assay was initiated by addition of substrate Z-Arg-Arg-aminomethylcoumarin (Bacchem) and the final assay conditions were 1.1 nM cathepsin B, 60 μM Z-R-R-AMC, 126 mM sodium potassium phosphate pH 6.0 (Fisher), 0.3 mM EDTA (Omnipure), 2.7 mM DTT (Omnipure), 0.004%

Brij 35 (Sigma), and 2.0% DMSO (Acros) in a final volume of 200 μ L. Inhibitors were serially diluted with DMSO and 0.01% Brij 35 to include a final concentration range of 20 μ M to 10 pM. The reaction was monitored fluorometrically for 5 minutes at 37 °C using black 96 well Corning 3686 assay microplates with a Thermo Fluoroskan Ascent FL microplate reader at excitation and emission filter wavelengths of 355 nm and 460 nm, respectively. Data were analyzed to determine IC₅₀ values utilizing GraphPad Prism 4.03 software with a minimum of a triplicate on the same microplate.

Several samples (**16**, **23**, **29**, and **34**) were analyzed on the Fluoromax2. The assay conditions followed those noted for the microplate assay with the following modifications: 6 μ M Z-R-R-AMC substrate and 250 μ l final volume.

Cathepsin L Assay for IC₅₀ Determination: Human liver Cathepsin L (Sigma) was pre-incubated with inhibitors at various concentrations for 5 minutes at 25 °C. The assay was initiated by addition of substrate Z-Phe-Arg-aminomethylcoumarin (Bacchem) and the final assay conditions were 1 nM cathepsin L, 50 μ M Z-F-R-AMC, 100 mM sodium acetate pH 5.5, 1 mM EDTA (Omnipure), 3 mM DTT (EMD), 0.01 % Brij 35 (Sigma), and 2.0 % DMSO (Acros). Inhibitors were serially diluted with DMSO and water to include a final concentration range of 10 μ M to 10 pM. The reaction was monitored fluorometrically for 5 minutes at 25 °C using black 96 well Corning 3686 assay microplates with a Thermo Fluoroskan Ascent FL microplate reader at excitation and emission filter wavelengths of 355 nm and 460 nm, respectively. Data were analyzed to determine IC₅₀ values utilizing GraphPad Prism 4.03 software with a minimum of a triplicate on the same microplate.

Molecular Modeling:

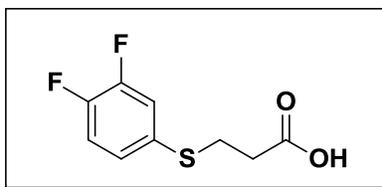
The crystal structure of PDB code 1ICF with two cathepsin L molecules complexed with thyroglobulin type-1 was used as the starting point for the modeling study. Insight II 2005 (Accelrys, San Diego, CA) was used for structure manipulation and visualization. A single cathepsin L molecule was extracted, hydrogen atoms were added, the pH was set to 5.5, and then the protein was subjected to conjugate gradient energy minimization and molecular dynamics. This complex served as the template for the docking of compound 4. Residues of the protein around the active site including the S3'- S3 subsites, were allowed to relax during the minimization, and frames of cathepsin L - compound 4

inhibitor complexes were collected in groups of 200 and examined for hydrogen bonding, total energy, interaction energy, and distances of the thiocarbonyl of the thiosemicarbazone functional group from the Cys-25 thiolate, among other parameters, and then ranked by the interaction energies. Manual visualization was used to examine the frames with the best interaction energies and best Cys-25 thiolate-thiocarbonyl carbon (inhibitor) distances.

X-ray Crystallographic Analysis:

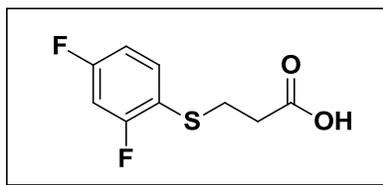
X-ray crystallographic analysis of compound **27**.^[S1] Crystallographic data were collected on a crystal of **27** with dimensions 0.15 °— 0.17 °— 0.20 mm³. Data were collected at 110 K on a Bruker X8 Apex using Mo KR radiation ($\lambda = 0.71073 \text{ \AA}$). The structure was solved by direct methods after correction of the data using SADABS.^[S2] Crystallographic data and refinement details for the complexes mentioned herein are found in the Supporting Information (Table S1). The thermal ellipsoid plots at 50% probability for compound xx is displayed in Figure S2. All data were processed using the Bruker AXS SHELXTL software, version 6.10.^[S3] All hydrogen atoms were placed in calculated positions except for the amine (N₃) hydrogens which were located in the difference map and refined isotropically. All non-hydrogen atoms were refined anisotropically.

Experimental Procedures:

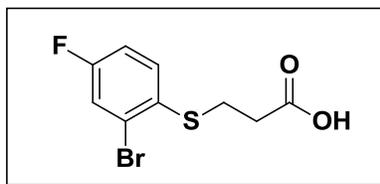


3-((3,4-Difluorophenyl)thio)propanoic acid (4a) (*also commercially available*): A solution of sodium carbonate (0.425 g, 4.01 mmol) and 3-bromopropionic acid (0.599 g, 3.91 mmol) in ice-cold water (15 mL) was added to a solution of sodium hydroxide (0.203 g, 5.08 mmol) and 3,4-difluorobenzenethiol (0.584 g, 3.99 mmol) in ice-cold water (15 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room

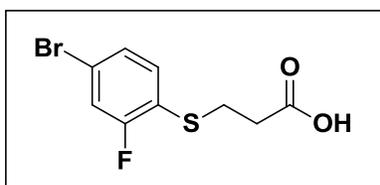
temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (30 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed once with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **4a** was obtained as a white solid (0.637 g, 2.92 mmol, 73% yield). ¹H NMR (300 MHz, CDCl₃) : δ 7.04-7.24 (3H, m), 3.11(2H, t, *J* = 7.2 Hz), 2.65 (2H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 177.62, 150.3 (dd, *J*_{C-F} = 250.0 Hz, 13.1Hz), 149.8 (dd, *J*_{C-F} = 247.7 Hz, 13.1 Hz), 131.2 (dd, *J*_{C-F} = 5.8 Hz, 4.0 Hz), 127.3 (dd, *J*_{C-F} = 6.1 Hz, 3.5 Hz), 119.9 (d, *J*_{C-F} = 17.9 Hz), 117.9 (d, *J*_{C-F} = 17.6 Hz), 34.07, 29.65; HRMS (ESI) calculated for C₉H₈F₂O₂S 218.0213, found 218.0212.



3-((2,4-Difluorophenyl)thio)propanoic acid (5a) (also commercially available): A solution of sodium carbonate (0.725 g, 6.84 mmol) and 3-bromopropionic acid (1.05 g, 6.86 mmol) in ice-cold water (20 mL) was added to a solution of sodium hydroxide (0.274 g, 6.85 mmol) and 2,4-difluorobenzenethiol (1.00 g, 6.80 mmol) in ice-cold water (20 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (40 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed once with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **5a** was obtained as a white solid (1.06 g, 4.84 mmol, 71% yield). ¹H NMR (300 MHz, CDCl₃) : δ 7.41-7.49 (2H, m), 6.82-6.90 (2H, m), 3.08 (2H, t, *J* = 7.2 Hz), 2.63 (2H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 177.7, 163.1 (dd, *J*_{C-F} = 249.8 Hz, 11.3 Hz), 162.8 (dd, *J*_{C-F} = 247.5 Hz, 11.3 Hz), 135.9 (dd, *J*_{C-F} = 9.8 Hz, 3.0 Hz), 116.7 (dd, *J*_{C-F} = 18.8 Hz, 4.5 Hz), 111.9 (dd, *J*_{C-F} = 21.8 Hz, 4.5 Hz), 104.7(t, *J*_{C-F} = 26.3Hz), 34.4, 29.2.

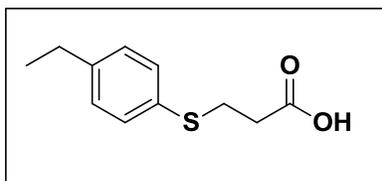


3-((2-Bromo-4-fluorophenyl)thio)propanoic acid (6a): A solution of sodium carbonate (0.550 g, 5.19 mmol) and 3-bromopropionic acid (0.745 g, 4.87 mmol) in ice-cold water (20 mL) was added to a solution of sodium hydroxide (0.293 g, 7.33 mmol) and 2-bromo,4-fluorothiophenol (1.00 g, 4.83 mmol) in ice-cold water (20 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (50 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed once with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **6a** was obtained as a white solid (0.860 g, 3.09 mmol, 64% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.35-7.42 (2H, m), 7.03 (1H, m), 3.15 (2H, t, *J* = 7.5 Hz), 2.69 (2H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 177.5, 161.4 (d, *J*_{C-F} = 249.8 Hz), 132.9 (d, *J*_{C-F} = 8.3 Hz), 131.3 (d, *J*_{C-F} = 3.8 Hz), 126.9 (d, *J*_{C-F} = 9.8 Hz), 120.9 (d, *J*_{C-F} = 24.8 Hz), 115.5 (d, *J*_{C-F} = 21.8 Hz), 33.8, 28.9; HRMS (ESI) calculated for C₉H₇BrFO₂S(M-H)⁻ 276.9340, found 276.9345.

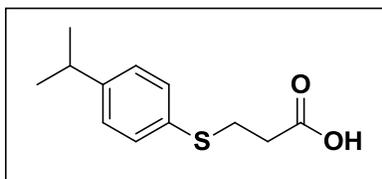


3-((4-Bromo-2-fluorophenyl)thio)propanoic acid (7a):^{S4} A solution of sodium carbonate (0.547g, 5.16 mmol) and 3-bromopropionic acid (0.752 g, 4.92 mmol) in ice-cold water (20 mL) was added to a solution of sodium hydroxide (0.250 g, 6.25 mmol) and 2-fluoro,4-bromothiophenol (1.00 g, 4.83 mmol) in ice-cold water (20 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (40 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers

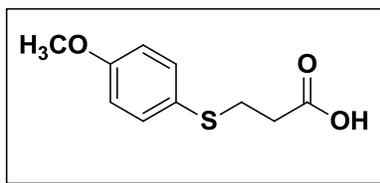
were washed once with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **7a** was obtained as a white solid (0.689 g, 2.48 mmol, 51% yield). ^1H NMR (500 MHz, CDCl_3): 7.23-7.30 (3H, m), 3.12 (2H, t, $J = 7.0$ Hz), 2.65 (2H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3): 177.63, 161.71 (d, $J_{\text{C-F}} = 249.0$ Hz), 134.36 (d, $J_{\text{C-F}} = 2.4$ Hz), 127.89 (d, $J_{\text{C-F}} = 4.13$ Hz), 121.86 (d, $J_{\text{C-F}} = 9.3$ Hz), 121.06 (d, $J_{\text{C-F}} = 18.1$ Hz), 119.6 (d, $J_{\text{C-F}} = 26$ Hz), 34.30, 28.38; HRMS (ESI) calculated for $\text{C}_9\text{H}_7\text{BrFO}_2\text{S}(\text{M-H})^-$ 276.9340, found 276.9346.



3-((4-Ethylphenyl)thio)propanoic acid (9a):^{S5} A solution of sodium carbonate (0.383 g, 3.61 mmol) and 3-bromopropionic acid (0.554 g, 3.62 mmol) in ice-cold water (20 mL) was added to a solution of sodium hydroxide (0.142 g, 3.55 mmol) and 4-ethylbenzenethiol (0.489 g, 3.54 mmol) in ice-cold water (20 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (25 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3×25 mL). The combined organic layers were washed once with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **9a** was obtained as a white solid (0.598 g, 2.84 mmol, 80% yield). ^1H NMR (500 MHz, CDCl_3): δ 7.31 (1H, dt, $J_1 = 8.5$ Hz, 2 Hz), 7.14 (1H, dt, $J = 8.5$ Hz, 2 Hz), 3.11 (2H, t, $J = 7.5$ Hz), 2.63 (4H, m), 1.22 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 177.7, 143.4, 131.3, 131.2, 128.7, 34.3, 29.5, 28.4, 15.5; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{14}\text{O}_2\text{S}$ 210.0715, found 210.0717.

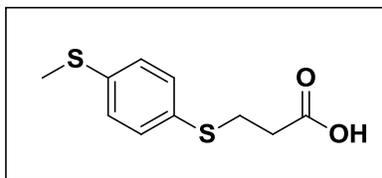


3-((4-Isopropylphenyl)thio)propanoic acid (10a) (also commercially available): A solution of sodium carbonate (0.696 g, 6.57 mmol) and 3-bromopropionic acid (1.01 g, 6.57 mmol) in ice-cold water (10 mL) was added to a solution of sodium hydroxide (0.262 g, 6.57 mmol) and 4-isopropylthiophenol (1.02 mL, 6.57 mmol) in ice-cold water (10 mL). The reaction was heated at reflux for 1 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (25 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine, dried over MgSO₄ and the solvent was removed under reduced pressure. After drying by house vacuum, propanoic acid **10a** was obtained as a white solid (1.29 g, 5.76 mmol, 88% yield). ¹H NMR (CDCl₃, 500 MHz) δ 7.33 (2H, dd, *J* = 8.0 Hz, 2.5 Hz), 7.17 (2H, dd, *J* = 9.0 Hz, 2.5 Hz), 3.12 (2H, t, *J* = 7.0 Hz), 2.89 (1H, m), 2.67 (2H, t, *J* = 7.0 Hz), 1.24 (6H, d, *J* = 7.0 Hz); ¹³C NMR (125 MHz, CDCl₃-d): δ 178.0, 148.1, 131.4, 131.2, 127.3, 34.3, 33.7, 29.4, 23.9

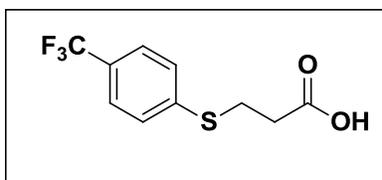


3-((4-Methoxyphenyl)thio)propanoic acid (11a):^{S6} A solution of sodium carbonate (1.07 g, 10.1 mmol) and 3-bromopropionic acid (1.54 g, 10.1 mmol) in ice-cold water (20 mL) was added to a solution of sodium hydroxide (0.405 g, 10.1 mmol) and 4-methoxybenzenethiol (1.48 g, 10.6 mmol) in ice-cold water (20 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (40 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq), and the product was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed once with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **11a** was obtained as a colorless white crystalline compound (1.63 g, 7.69 mmol, 77% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.39 (1H, d, *J* = 9.0 Hz), 6.86 (1H, d, *J* = 9.0 Hz), 3.80 (3H, s), 3.04 (2H, t, *J* = 6 Hz),

2.61 (2H, t, $J = 6$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 177.6, 159.5, 134.4, 124.8, 114.7, 55.4, 34.3, 30.8; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{12}\text{O}_3\text{S}$ 212.0507, found 212.0494.

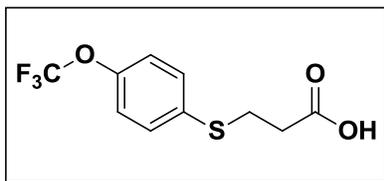


3-((4-(Methylthio)phenyl)thio)propanoic acid (12a):^{S7} A solution of sodium carbonate (0.678 g, 6.39 mmol) and 3-bromopropionic acid (0.980 g, 6.40 mmol) in ice-cold water (20 mL) was added to a solution of sodium hydroxide (0.256 g, 6.40 mmol) and 4-methylthiobenzenethiol (1.00 g, 6.40 mmol) in ice-cold water (20 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (50 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3 \times 50 mL). The combined organic layers were washed once with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. After the crude product was purified by flash chromatography (silica gel, hexanes: ethyl acetate, 50:50), propanoic acid **12a** was obtained as a white solid (0.667 g, 4.38 mmol, 68 % yield). ^1H NMR (300 MHz, CDCl_3): δ 7.30-7.34 (2H, m), 7.17-7.20 (2H, m), 3.11 (2H, t, $J = 7.2$ Hz), 2.650 (2H, t, $J = 7.2$ Hz), 2.48 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 177.5, 137.8, 131.7, 130.9, 127.2, 34.2, 29.5, 15.8; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{11}\text{O}_2\text{S}_2$ (M-H)⁻ 227.0206, found 227.0181.

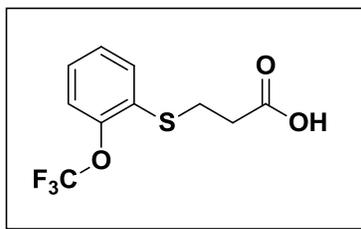


3-((4-(Trifluoromethyl)phenyl)thio)propanoic acid (13a):^{S4} A solution of sodium carbonate (0.595 g, 5.61 mmol) and 3-bromopropionic acid (0.880 g, 5.75 mmol) in ice-cold water (20 mL) was added to a solution of sodium hydroxide (0.290 g, 7.25 mmol) and 4-trifluoromethylbenzenethiol (1.00 g, 5.62 mmol) in ice-cold water (20 mL). This mixture was heated at reflux for 1.5 h, and then cooled to room temperature. In a

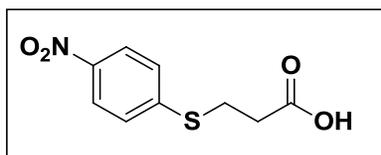
separatory funnel, the reaction mixture was washed with ethyl acetate (50 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed once with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **13a** was obtained as a white solid (1.10 g, 4.39 mmol, 78% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.54 (2H, d, *J* = 8.5 Hz), 7.41 (2H, d, *J* = 8.5 Hz), 3.24 (2H, t, *J* = 7.5 Hz), 2.73 (2H, t, *J* = 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 177.0, 140.6, 128.6, 128.2(q, *J*_{C-F} = 27.8 Hz), 125.87 (q, *J*_{C-F} = 2.3 Hz), 124.08 (q, *J*_{C-F} = 162.8 Hz), 33.8, 27.5; HRMS (ESI) calculated for C₁₀H₉F₃O₂S 250.0275, found 250.0275.



3-((4-(Trifluoromethoxy)phenyl)thio)propanoic acid (14a):^{S4} A solution of sodium carbonate (0.273 g, 2.58 mmol) and 3-bromopropionic acid (0.395 g, 2.58 mmol) in ice-cold water (10 mL) was added to a solution of sodium hydroxide (0.103 g, 2.58 mmol) and 4-trifluoromethoxythiophenol (0.500 g, 2.58 mmol) in ice-cold water (10 mL). The reaction heated at reflux for 2 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (25 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine, dried over MgSO₄, and the solvent was removed under reduced pressure. After drying under house vacuum, propanoic acid **14a** was obtained as a white solid (0.600 g, 2.25 mmol, 87% yield). ¹H-NMR (CDCl₃, 500 MHz) δ 7.40 (2H, d, *J* = 9.0 Hz), 7.16 (2H, d, *J* = 8.0 Hz), 3.16 (2H, t, *J* = 7.0 Hz), 2.68 (2H, t, *J* = 7.0 Hz).

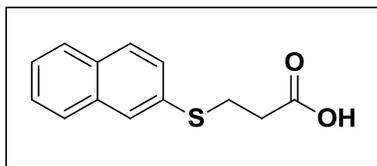


3-((2-(Trifluoromethoxy)phenyl)thio)propanoic acid (15a): A solution of sodium carbonate (0.273 g, 2.58 mmol) and 3-bromopropionic acid (0.395 g, 2.58 mmol) in ice-cold water (10 mL) was added to a solution of sodium hydroxide (0.103 g, 2.58 mmol) and 2-trifluoromethoxythiophenol (0.500 g, 2.58 mmol) in ice-cold water (10 mL). The reaction was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (25 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and the solvent was removed under reduced pressure. After drying under house vacuum, propanoic acid **15a** was obtained as a white solid (0.355 g, 1.33 mmol, 52% yield). $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 11.22 (1H, bs), 7.43-7.41 (1H, m), 7.27-7.25 (3H, m), 3.20-3.16 (2H, m), 2.71-2.68 (2H, m).

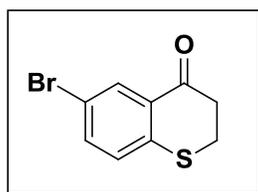


3-((4-Nitrophenyl)thio)propanoic acid (17a):^{S8} A solution of sodium carbonate (0.274 g, 2.59 mmol) and 3-bromopropionic acid (0.394 g, 2.58 mmol) in ice-cold water (15 mL) was added to a solution of sodium hydroxide (0.104 g, 2.60 mmol) and 4-nitrobenzenethiol (0.400 g, 2.58 mmol) in ice-cold water (15 mL). This mixture was heated at reflux for 2 h, after cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (25 mL) to remove the unreacted starting material. The water layer was acidified with hydrochloric acid (10% aq) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed once with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. After drying by house vacuum, propanoic acid **17a** was obtained as a yellow solid (0.506 g, 2.22 mmol,

85% yield). ^1H NMR (300 MHz, CDCl_3): δ 8.13-8.18 (2H, m), 7.35-7.40 (2H, m), 3.31 (2H, t, $J = 7.2$ Hz), 2.79 (2H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 175.8, 145.8, 126.9, 124.2, 33.2, 26.8; HRMS (ESI) calculated for $\text{C}_9\text{H}_8\text{NO}_4\text{S}$ (M-H) $^-$ 226.0180, found 226.0179.

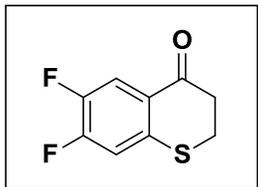


3-(Naphthalen-2-ylthio)propanoic acid (20a):^{S8} A solution of sodium carbonate (0.265 g, 2.50 mmol) and 3-bromopropionic acid (0.383 g, 2.50 mmol) and in ice-cold water (4 mL) was added to a solution of sodium hydroxide (0.100 g, 2.50 mmol) and 2-thionaphthol (0.400 g, 2.50 mmol) in ice-cold water (5 mL). The reaction was heated at reflux for 1.5 h, and then cooled to room temperature. In a separatory funnel, the reaction mixture was washed with ethyl acetate (25 mL) to remove unreacted starting material. The water layer was then acidified with hydrochloric acid (10% aq) and was extracted with ethyl acetate (2 \times 25 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and the solvent was removed under reduced pressure. After drying under house vacuum, propanoic acid **20a** was obtained as a white solid (0.480 g, 2.07 mmol, 83% yield). ^1H -NMR (CDCl_3 , 300 MHz) δ 7.82-7.75 (4H, m), 7.50-7.43 (3H, m), 3.25 (2H, t, $J = 7.0$ Hz), 2.71 (2H, t, $J = 7.0$ Hz).

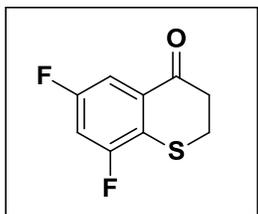


6-Bromothiochroman-4-one (3b):^{S9} Aluminum trichloride (1.62 g, 12.2 mmol) was added to an oven dried flask and diluted with dry dichloromethane (5 mL). The suspension was stirred under nitrogen at 0 $^\circ\text{C}$ for 10 min. A solution of thiochroman-4-one (1.00 g, 6.09 mmol) in dry dichloromethane (2 mL) was added and allowed to stir for 10 min. A solution of bromine (0.328 mL, 6.39 mmol) in dry dichloromethane (2 mL) was added over 30 min. The reaction was stirred for 4.5 h. Ice cold water was added, first

a few drops slowly and then 40 mL. The product was extracted with dichloromethane (3 x 30 mL), washed with brine, and dried over Na₂SO₄. Solvent was removed under reduced pressure. Purification of the crude mixture by flash column chromatography (silica gel, hexanes: ethyl acetate, gradient 95:5 to 80:20) provided a mixture of 6-bromothiochromanone and 8-bromothiochromanone, as a pale yellow oil.

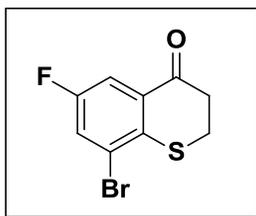


6,7-Difluorothiochroman-4-one (4b):^{S10} Polyphosphoric acid (10.0 g) was added to a flask containing propanoic acid **4a** (0.207 g, 0.948 mmol). The reaction mixture was heated at 60 °C for 1 h with overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed once with water, followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying under house vacuum overnight, ketone **4b** was obtained as a white solid (0.109 g, 0.545 mmol, 57% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.90-7.96 (1H, m), 7.06-7.12 (1H, m), 3.24-3.28 (2H, m), 2.94-2.99 (2H, m); ¹³C NMR (75 MHz, CDCl₃): δ 191.8, 153.5 (dd, *J*_{C-F} = 258.8 Hz, 14.3 Hz), 148.4 (dd, *J*_{C-F} = 248.3 Hz, 13.5 Hz), 139.3 (m), 127.80, 118.0 (dd, *J*_{C-F} = 18.8 Hz, 2.3 Hz), 116.0 (d, *J*_{C-F} = 19.5 Hz), 38.85, 26.92; HRMS (ESI) calculated for C₉H₆F₂OS 200.0107, found 200.0099.

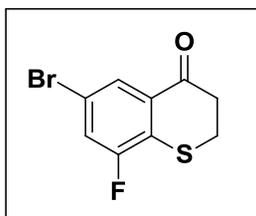


6,8-Difluorothiochroman-4-one (5b):^{S10} Polyphosphoric acid (10.0 g) was added to a flask containing propanoic acid **5a** (0.450 g, 2.06 mmol). The reaction mixture was heated at 60 °C for 1 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers

were washed once with water, followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. The organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying under house vacuum overnight, ketone **5b** was obtained as a white solid (0.278 g, 1.10 mmol, 53% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.65-7.69 (1H, m), 6.97-7.04 (1H, m), 3.24-3.28 (2H, m), 2.98-3.03 (2H, m); HRMS (ESI) calculated for C₉H₅F₂OS⁻ 199.0035, found 199.0033.

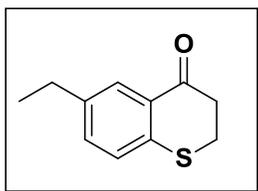


8-Bromo-6-fluorothiochroman-4-one (6b):^{S10} Polyphosphoric acid (10.0 g) was added to a flask containing propanoic acid **6a** (0.398g, 1.43 mmol). The reaction mixture was heated at 50 °C for 1 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed once with water, followed by a sodium hydroxide (5% aq), and then repeatedly with water until neutral pH was obtained. The organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying under house vacuum overnight, ketone **6b** was obtained as a light yellow solid (0.19 g, 0.73 mmol, 51% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.84 (1H, dd, *J* = 9.0 Hz, 3.0 Hz), 7.47 (1H, dd, *J* = 7.2 Hz, 3.0 Hz), 3.23-3.27 (2H, m), 2.95-2.99 (2H, m); ¹³C NMR (75 MHz, CDCl₃): 192.4, 159.4 (d, *J*_{C-F} = 248.3 Hz), 139.02 (d, *J*_{C-F} = 3 Hz), 133.36(d, *J*_{C-F} = 5.3 Hz), 125.17 (d, *J*_{C-F} = 25.5 Hz), 121.97 (d, *J*_{C-F} = 8.3 Hz), 114.93 (d, *J*_{C-F} = 22.5 Hz) 38.1, 26.18.

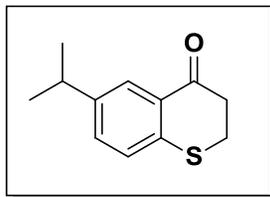


6-Bromo-8-fluorothiochroman-4-one (7b):^{S4} Polyphosphoric acid (10.0 g) was added to a flask containing propanoic acid **7a** (0.287g, 1.03 mmol). The reaction mixture was

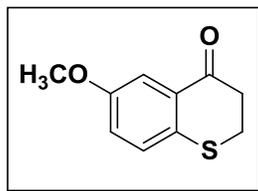
heated at 55 °C for 1 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed once with water, followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. The organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying under house vacuum overnight, ketone **7b** was obtained as a yellow solid (0.195g, 0.748 mmol, 73% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.03-8.06 (1H, m), 7.35 (1H, dd, *J* = 8.7 Hz, 2.1 Hz), 3.24-3.29 (2H, m), 2.97-3.01 (2H, m); ¹³C NMR (75 MHz, CDCl₃): 191.52, 158.2 (d, *J*_{C-F} = 248.3 Hz), 133.03 (d, *J*_{C-F} = 2.3 Hz), 129.63 (d, *J*_{C-F} = 18 Hz), 127.65 (d, *J*_{C-F} = 3 Hz), 122.55 (d, *J*_{C-F} = 24 Hz), 117.77(d, *J*_{C-F} = 9 Hz) 39.02, 25.68.



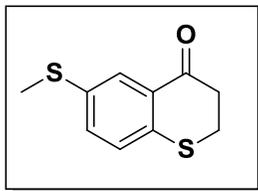
6-Ethylthiochroman-4-one (9b):^{S5} Polyphosphoric acid (7.00 g) was added to a flask containing propanoic acid **9a** (0.343g, 1.63 mmol). The reaction mixture was heated at 70 °C for 1 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed once with water (50 mL), followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. After the combined organic layers were washed with brine, dried over Na₂SO₄, and then concentrated under reduced pressure. After drying under house vacuum overnight, ketone **9b** was obtained as yellow oil (0.283 g, 1.47 mmol, 90% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.95 (1H, dd, *J* = 2 Hz, 0.5 Hz), 7.25 (1H, dd, *J* = 8 Hz, 2 Hz), 7.20 (1H, d, *J* = 8 Hz), 3.22 (2H, m), 2.97 (2H, m), 2.63 (2H, q, *J* = 7.5 Hz), 1.22 (3H, t, *J* = 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 194.4, 141.3, 139.1, 133.4, 130.8, 128.2, 127.6, 39.8, 28.2, 26.7, 15.4; HRMS (ESI) calculated for C₁₁H₁₂OS 192.0609, found 192.0606.



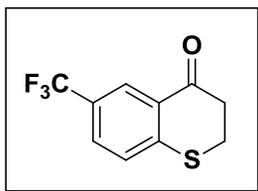
6-Isopropylthiochroman-4-one (10b):^{S11} Polyphosphoric acid (10.0 g) was added to a flask containing propanoic acid **10a** (1.00 g, 4.46 mmol). The reaction mixture was heated at 50 °C for 2 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. Purification of the crude mixture by flash column chromatography (silica gel, hexanes: ethyl acetate, gradient 95:5 to 60:40) afforded pure ketone **10b** as a yellow oil (0.351 g, 1.70 mmol, 38% yield). ¹H NMR (CDCl₃, 500 MHz) δ 7.99 (1H, d, *J* = 2.0 Hz), 7.27 (1H, dd, *J* = 8.0 Hz, 2.0 Hz), 7.21 (1H, d, *J* = 8.5 Hz), 3.22 (2H, dd, *J* = 7.5 Hz, 6.5 Hz), 2.97 (2H, dd, *J* = 8.0 Hz, 6 Hz), 2.90 (1H, m), 1.24 (6H, d, *J* = 7.5 Hz).



6-Methoxythiochroman-4-one (11b):^{S6} Polyphosphoric acid (20.0 g) was added to a flask containing propanoic acid **11a** (1.01 g, 4.72 mmol). The reaction mixture was heated at 60 °C for 1 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed once with water, followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. The organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying under house vacuum overnight, ketone **11b** was obtained as a white solid (0.580 g, 2.99 mmol, 63% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.63 (1H, d, *J* = 3.0 Hz), 7.20 (1H, d, *J* = 9.0 Hz), 7.01 (1H, dd, *J* = 9.0 Hz, 3.0 Hz), 3.83 (3H, s), 3.19-3.24 (2H, m), 2.95-2.99 (2H, m); ¹³C NMR (75 MHz, CDCl₃): δ 194.1, 157.4, 133.6, 131.7, 128.9, 122.3, 111.3, 55.6, 39.7, 26.9; HRMS (ESI) calculated for C₁₀H₁₀O₂S 194.0402, found 194.0394

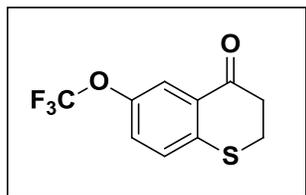


6-(Methylthio)thiochroman-4-one (12b):^{S7} Polyphosphoric acid (31.0 g) was added to a flask containing propanoic acid **12a** (0.202 g, 0.888 mmol). The reaction mixture was heated at 50 °C for 1 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed once with water, followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. The organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. After drying under house vacuum overnight, ketone **12b** was obtained as a yellow solid (0.07 g, 0.33 mmol, 37% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.95 (1H, d, *J* = 2.1 Hz), 7.27 (1H, dd, *J* = 8.4 Hz, 2.1 Hz), 7.17 (1H, d, *J* = 3 Hz), 3.20-3.24 (2H, m), 2.90-2.99 (2H, m), 2.49 (3H, s); ¹³C NMR (75 MHz, CDCl₃): δ 193.6, 138.7, 135.8, 132.0, 131.2, 128.0, 126.3, 39.6, 26.6, 16.0; HRMS (ESI) calculated for C₁₀H₁₀OS₂ H (M+H)⁺ 211.0246, found 211.0243.

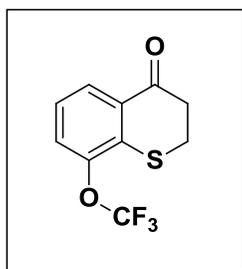


6-Trifluoromethylthiochroman-4-one (13b):^{S4} Polyphosphoric acid (12.0 g) was added to a flask containing propanoic acid **13a** (0.582 g, 2.33 mmol). The reaction mixture was heated at 60 °C for 1 h using overhead stirring. The reaction was quenched with ice and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed once with water, followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. After drying under house vacuum overnight, ketone **13b** (0.271 g, 1.17 mmol, 50% yield) was obtained. ¹H NMR (500 MHz, CDCl₃): δ 8.37 (1H, dd, *J* = 1.5 Hz, 0.5 Hz), 7.59

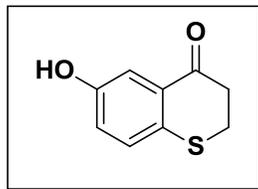
(1H, dd, $J = 8.5$ Hz, 2H), 7.40 (1H, d, $J = 8.5$ Hz), 3.28-3.31 (2H, m), 3.01-3.04 (2H, m); ^{13}C NMR (125 MHz, CDCl_3): δ 192.6, 146.8 (d, $J_{\text{C-F}} = 0.88$ Hz), 130.7, 129.1 (q, $J_{\text{C-F}} = 3.1$ Hz), 128.2, 127.3 (q, $J_{\text{C-F}} = 33.3$ Hz), 126.1 (q, $J_{\text{C-F}} = 3.8$ Hz), 123.6 (q, $J_{\text{C-F}} = 270.8$ Hz), 38.9, 26.3; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_7\text{F}_3\text{OS}$ 232.0170, found 232.0172.



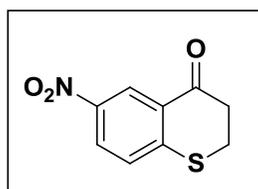
6-(Trifluoromethoxy)thiochroman-4-one (14b):^{S4} Polyphosphoric acid (6.00 g) was added to a flask containing propanoic acid **14a** (0.600 g, 2.26 mmol). The reaction mixture was heated at 60 °C for 3.5 h using overhead stirring. The reaction was quenched with ice and the product was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and the solvent was removed under reduced pressure. Purification of the crude mixture by flash column chromatography (silica gel, hexanes: ethyl acetate, gradient 95:5 to 70:30), afforded pure ketone **14b** (0.211 g, 0.851 mmol, 63% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.97 (1H, d, $J = 2.0$ Hz), 7.33 (1H, d, $J = 7.0$ Hz), 7.26-7.23 (1H, m), 3.28-3.24 (2H, m), 3.02-2.97 (2H, m).



8-(Trifluoromethoxy)thiochroman-4-one (15b): Polyphosphoric acid (3.00 g) was added to a flask containing propanoic acid **15a** (0.285 g, 1.07 mmol). The reaction mixture was heated at 60 °C for 1 h using overhead stirring. The reaction was quenched with ice and a solid crashed out. After filtration, pure ketone **15b** was obtained as a white solid (0.178 g, 0.715 mmol, 67% yield). ^1H NMR (CDCl_3 , 500 MHz) δ 8.08 (1H, d, $J = 8.0$ Hz), 7.39 (1H, d, $J = 7.0$ Hz), 7.21 (1H, td, $J = 8.0$ Hz, 1.0 Hz), 3.25 (2H, t, $J = 5.5$ Hz), 2.99 (2H, t, $J = 5.5$ Hz).

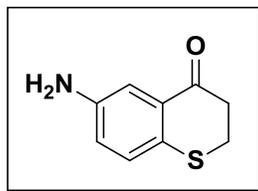


6-Hydroxythiochroman-4-one (16b):^{S12} Ketone **11b**, (0.121 g, 0.620 mmol) was dissolved in dichloromethane (20 mL), and aluminum chloride (0.250 g, 1.86 mmol) was added. The reaction mixture was stirred under nitrogen for 12 h. The reaction was quenched with water. Sodium bicarbonate (10% aq, 30 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were concentrated under reduced pressure. After purification by flash chromatography (silica gel, hexanes: ethyl acetate, gradient 90:10 to 70:30), ketone **16b** was obtained as a yellow solid (0.030 g, 0.167 mmol, 27% yield). ¹H NMR(500 MHz, CDCl₃): δ 7.70 (1H, d, *J* = 3 Hz), 7.19 (1H, d, *J* = 9.0 Hz), 7.00 (1H, dd, *J* = 9.0 Hz, 3.0 Hz), 6.04 (1H, s), 3.21(2H, t, *J* = 13 Hz), 2.96 (2H, t, *J* = 13.0 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 194.9, 153.8, 133.5, 131.6, 129.2, 122.3, 114.8, 39.8, 26.8; HRMS (ESI) calculated for C₉H₇O₂S (M-H)⁻ 179.0172, found 179.0175.

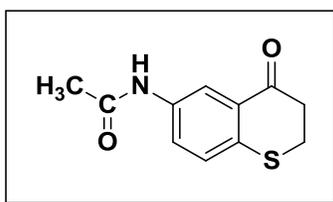


6-Nitrothiochroman-4-one (17b):^{S12} Polyphosphoric acid (10.0 g) was added to a flask containing propanoic acid **17a** (0.274 g, 1.20 mmol). The reaction mixture was heated at 60 °C for 1 h using overhead stirring. The reaction was quenched with ice and the product was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed once with water, followed by a sodium hydroxide solution (5% aq), and then repeatedly with water until neutral pH was obtained. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. After purification by flash chromatography (silica gel, hexanes: ethyl acetate, gradient 90:10 to 75:25), ketone **17b** was obtained as a yellow solid (0.271 g, 1.17 mmol, 50% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.93 (1H, s), 8.20 (1H, d, *J* = 8.7 Hz), 7.44 (1H, d, *J* = 8.7 Hz), 3.35

(2H, t, $J = 5.7$ Hz), 3.06 (2H, t, $J = 5.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3): 191.7, 150.6, 145.3, 130.9, 128.6, 126.8, 124.4, 38.5, 26.4.

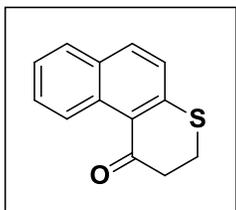


6-Aminothiochroman-4-one (18b):^{S12} Ketone **17b** (1.00 g, 4.78 mmol) was dissolved in tetrahydrofuran (75 mL). Tin (3.40 g, 28.6 mmol) and hydrochloric acid (16 mL) were added. After stirring under nitrogen for 4 h, water was added, followed by a saturated sodium bicarbonate solution (450 mL) which neutralized the mixture to a pH of 7. The mixture was extracted with ethyl acetate (4×300 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. After purification by flash chromatography (silica gel, hexanes: ethyl acetate, 70:30), ketone **18b** was obtained as a yellow solid (0.120 g, 0.609 mmol, 13% yield). ^1H NMR (500 MHz, CDCl_3): 7.43, (1H, d, $J = 2.5$ Hz), 7.08 (1H, d, $J = 8.5$ Hz), 6.78 (1H, dd, $J_1 = 8.5$ Hz, 3.0 Hz), 3.72 (2H, bs), 3.19-3.17 (2H, m), 2.93-2.95 (2H, m); ^{13}C NMR (125 MHz, CDCl_3): 194.5, 144.2, 131.7, 130.5, 128.7, 121.4, 114.4, 40.1, 27.0; HRMS (ESI) calculated for $\text{C}_9\text{H}_{10}\text{NOS}$ ($\text{M}+\text{H}$)⁺ 180.0478, found 180.0479.

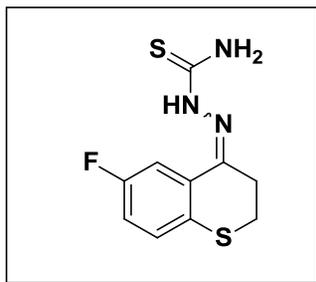


N-(4-Oxothiochroman-6-yl)acetamide (19b):^{S13} Ketone **18b** (0.100 g, 0.560 mmol) was dissolved in dry dichloromethane (5 mL), and acetic anhydride (0.200 mL, 2.10 mmol) and triethylamine (0.300 mL, 2.15 mmol) were added. The mixture was stirred under nitrogen for 30 min, and then concentrated under reduced pressure. After purification using flash chromatography (silica gel, hexanes: ethyl acetate, 60:40), ketone **19b** was obtained as a light yellow solid (0.100 g, 0.450 mmol, 81% yield). ^1H NMR (500 MHz, CDCl_3): 8.12 (1H, bs), 8.04 (1H, dd, $J = 8.5$ Hz, 2.5 Hz), 7.93 (1H, d, $J = 2.5$ Hz), 7.24

(1H, d, $J = 9.0$ Hz), 3.22-3.24 (2H, m), 2.96-2.99 (2H, m), 2.20 (3H, s); ^{13}C NMR (125 MHz, CDCl_3): 194.4, 169.0, 137.3, 135.8, 130.9, 128.5, 126.1, 119.7, 39.6, 26.7, 24.4.

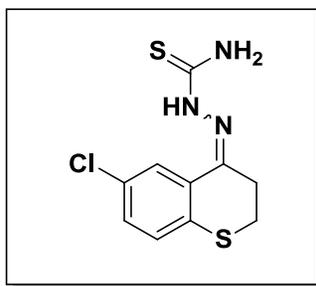


2,3-Dihydro-1H-benzo[f]thiochromen-1-one (20b):^{S14} Polyphosphoric acid (4.00 g) was added to a flask containing propionic acid **20a** (0.450 g, 1.94 mmol). The reaction mixture was heated at 60 °C for 2 h using overhead stirring. The reaction was quenched with ice and the product was collected by filtration. Purification of the crude product by flash column chromatography (silica gel, hexanes: ethyl acetate, gradient 90:10 to 0:100) afforded pure ketone **20b** as a white solid (0.200 g, 0.935 mmol, 48% yield). ^1H NMR (500 MHz, CDCl_3): 9.16 (1H, d, $J = 9.0$ Hz), 7.77 (1H, d, $J = 8.5$ Hz), 7.74 (1H, d, $J = 8.0$ Hz), 7.60 (1H, td, $J = 7.0$ Hz, 1.5 Hz), 7.46-7.43 (1H, m), 7.28 (1H, d, $J = 9.0$ Hz), 3.31-3.28 (2H, m), 3.12-3.10 (2H, m).

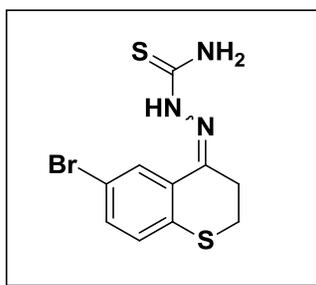


6-Fluorothiochroman-4-one thiosemicarbazone (1):^{S15} 6-fluoro-1-thiochroman-4-one (0.101 g, 0.556 mmol, commercially available) was dissolved in anhydrous methanol (10 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.0615 g, 0.674 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected through filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **1** was obtained as an off-white solid (0.032 g, 0.125 mmol, 22% yield). ^1H NMR (500 MHz, DMSO-d_6) δ 10.23 (1H, s) 8.37 (1H, s), 8.29 (1H, dd, $J = 11.5$, Hz, 3.0 Hz), 7.26 (1H, dd, $J = 9.0$ Hz, 6.0

Hz), 7.11 (1H, td, $J = 8.0$ Hz, 3.0 Hz), 3.01 (4H, bs); ^{13}C NMR (75 MHz, DMSO- d_6): δ 179.5, 160.7 (d, $J_{\text{C-F}} = 239.6$ Hz), 144.6 (d, $J_{\text{C-F}} = 2.8$ Hz), 133.4 (d, $J_{\text{C-F}} = 7.4$ Hz), 132.0 (d, $J_{\text{C-F}} = 2.8$ Hz), 130.1 (d, $J_{\text{C-F}} = 7.9$ Hz), 117.1 (d, $J_{\text{C-F}} = 23.1$ Hz), 113.9 (d, $J_{\text{C-F}} = 24.1$ Hz), 28.1, 25.6; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{FN}_3\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 256.0373, found 256.0372; HPLC retention time: 9.37 min.

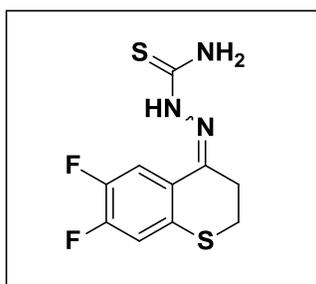


6-Chlorothiochroman-4-one thiosemicarbazone (2):^{S16} 6-chlorothiochroman-4-one (0.099 g, 0.500 mmol) was dissolved in anhydrous methanol (8 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.055 g, 0.604 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected through filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **2** was obtained as a white solid (0.093 g, 0.343 mmol, 69% yield). ^1H NMR (300 MHz, DMSO- d_6): δ 10.24 (1H, s), 8.47 (1H, s), 8.40 (1H, s), 8.30 (1H, s), 7.23-7.26 (2H, m), 3.03 (4H, bs); ^{13}C NMR (75 MHz, DMSO- d_6): δ 179.0, 144.1, 134.9, 132.6, 130.1, 129.5, 128.8, 126.5, 27.5, 24.9; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{ClN}_3\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 272.0077, found 272.0076; HPLC retention time: 7.85 min.

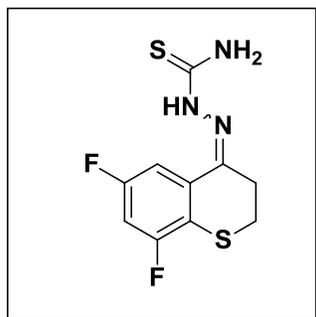


6-bromothiochroman-4-one thiosemicarbazone (3):^{S17} Ketone **3b** (0.050 g, 0.202 mmol) was dissolved in anhydrous methanol (3 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.038g, 0.410 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 3 h at reflux, solvent was removed under

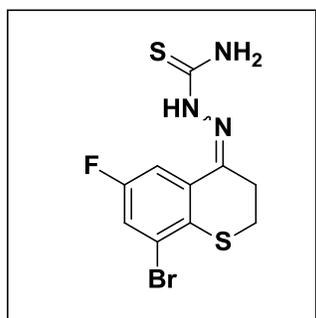
reduced pressure. Water was added and the product was extracted with ethyl acetate. The combined organic phase was washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. Purification of the crude mixture by flash column chromatography (silica gel, hexanes: ethyl acetate, gradient 70:30) afforded pure thiosemicarbazone **3** (0.055 g, 0.174 mmol, 87% yield). ¹H NMR (500 MHz, DMSO-d₆) : δ 10.21 (1H, s, NH) 8.55 (1H, s, ArH) 8.36 (1H, s, NH₂) 8.28 (1H, s, NH₂) 7.37 (1H, dd, *J* = 8.5 and 2 Hz, ArH) 7.16 (1H, d, *J* = 8.5 Hz, ArH) 3.03-2.98 (4H, m, CH₂CH₂); ¹³C NMR (125 MHz, DMSO-d₆): 179.5, 144.6, 135.9, 133.4, 132.1, 130.2, 129.7, 118.8, 27.9, 25.3; HRMS (ESI) calculated for C₁₀H₁₀BrN₃S₂ 314.9500, found 314.9497; HPLC retention time: 10.7 min.



6,7-Difluorothiochroman-4-one thiosemicarbazone (4): Ketone **4b** (0.060 g, 0.300 mmol) was dissolved in anhydrous methanol (15 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.058g, 0.637 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected through filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **4** was obtained as a light yellow solid (0.052 g, 0.194 mmol, 63% yield). ¹H NMR (300 MHz, DMSO-d₆): δ 10.25 (1H, bs), 8.51-8.59 (1H, m), 8.39 (1H, bs), 8.29 (1H, bs), 7.33-7.40 (1H, m), 3.00-3.05 (4H, m); ¹³C NMR (75 MHz, DMSO-d₆): δ 178.99, 149.55 (dd, *J*_{C-F} = 249.0 Hz, 14.3 Hz), 147.55 (dd, *J*_{C-F} = 241.5 Hz, 12.8 Hz), 143.3, 133.01 (dd, *J*_{C-F} = 6.75 Hz, 3.0 Hz), 128.3 (dd, *J*_{C-F} = 8.8 Hz, 6.3 Hz), 116.04 (d, *J*_{C-F} = 18.8 Hz), 27.13, 25.08 HRMS (ESI) calculated for C₁₀H₉F₂N₃S₂ 273.0206, found 273.0207; HPLC retention time 9.19 min.

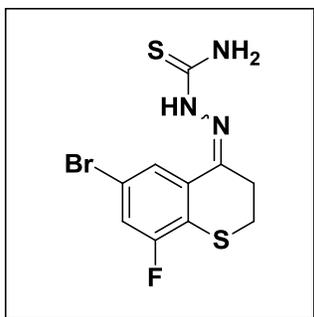


6,8-Difluoro-thiochroman-4-one thiosemicarbazone (5): Ketone **5b** (0.079 g, 0.395 mmol) was dissolved in anhydrous methanol (15 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.044 g, 0.483 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **5** was obtained as a white solid (0.063 g, 0.23 mmol, 58% yield). ¹H NMR (300 MHz, DMSO-d₆): δ 10.34 (1H, s), 8.44 (1H, s), 8.31 (1H, s), 8.25 (1H, d, *J* = 11.1 Hz), 7.27-7.32 (1H, m), 3.05 (4H, bs); ¹³C NMR (75 MHz, DMSO-d₆): δ 179.1, 159.7 (dd, *J*_{C-F} = 240.5 Hz, 13.4 Hz), 158.0 (dd, *J*_{C-F} = 239.8 Hz, 13.3 Hz), 142.8 (d, *J*_{C-F} = 3.0 Hz), 133.8 (dd, *J*_{C-F} = 9.0 Hz, 4.5 Hz), 119.7 (d, *J*_{C-F} = 16.2 Hz), 109.5 (d, *J*_{C-F} = 26.8 Hz), 104.3 (t, *J*_{C-F} = 26.8 Hz), 27.3, 24.0; HRMS (ESI) calculated for C₁₀H₈F₂N₃S₂ (M-H)⁻ 272.0133, found 272.0134; HPLC retention time 7.66 min.

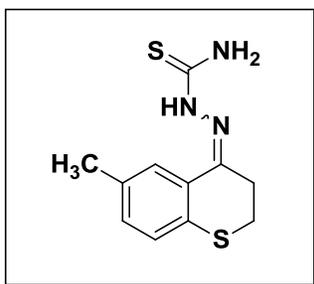


8-Bromo-6-fluorothiochroman-4-one thiosemicarbazone (6): Ketone **6b** (0.061 g, 0.230 mmol) was dissolved in anhydrous methanol (15 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.025 g, 0.279 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **6** was obtained as a light brown solid (0.030 g, 0.09

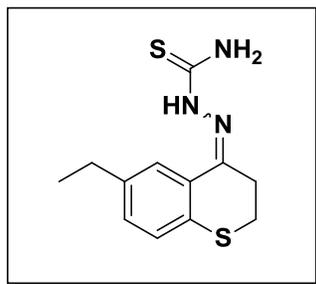
mmol, 39% yield). ^1H NMR (300 MHz, DMSO- d_6): δ 10.33 (1H, s), 8.40-8.44 (2H, m, NH_2), 8.31 (1H, s), 7.62 (1H, dd, $J = 7.8$ Hz, 2.4 Hz), 2.98-3.08 (4H, m); ^{13}C NMR (75 MHz, DMSO- d_6): 179.10, 159.23 (d, $J_{\text{C-F}} = 243$ Hz), 143.68 (d, $J_{\text{C-F}} = 3$ Hz), 134.52 (d, $J_{\text{C-F}} = 8.3$ Hz), 133.15 (d, $J_{\text{C-F}} = 3.8$ Hz), 121.66 (d, $J_{\text{C-F}} = 9.8$ Hz), 120.43 (d, $J_{\text{C-F}} = 26.3$ Hz), 113.14 (d, $J_{\text{C-F}} = 23.3$ Hz), 26.71, 25.09; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_9\text{BrFN}_3\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 333.9478, found 333.9311; HPLC retention time 1.52 min.



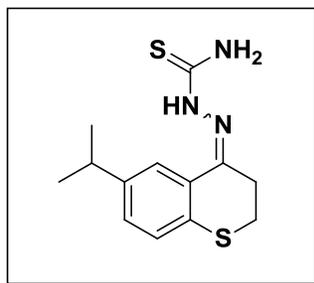
6-Bromo-8-fluorothiochroman-4-one thiosemicarbazone (7): Ketone **7b** (0.060 g, 0.230 mmol) was dissolved in anhydrous methanol (10 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.025 g, 0.275 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 20 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **7** (0.062 g, 0.186 mmol, 81% yield) was obtained. ^1H NMR (300 MHz, DMSO- d_6): δ 10.32 (1H, s), 8.49-8.50 (1H, m), 8.44 (1H, s), 8.36 (1H, s), 7.51 (1H, dd, $J = 9.0$ Hz, 2.1 Hz), 3.01-3.09 (4H, m); ^{13}C NMR (75 MHz, DMSO- d_6): δ 179.10, 157.80 (d, $J_{\text{C-F}} = 242.3$ Hz), 142.78 (d, $J_{\text{C-F}} = 4.5$ Hz), 134.16 (d, $J_{\text{C-F}} = 3.8$ Hz), 125.31 (d, $J_{\text{C-F}} = 3$ Hz), 123.72 (d, $J_{\text{C-F}} = 19.5$ Hz), 118.09 (d, $J_{\text{C-F}} = 24.8$ Hz), 117.35 (d, $J_{\text{C-F}} = 10.5$ Hz), 26.92, 23.86; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_9\text{BrFN}_3\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 333.9478, found 333.9479; HPLC retention time: 8.10 min.



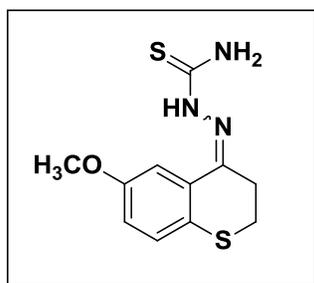
6-Methylthiochroman-4-one thiosemicarbazone (8):^{S16} 6-methylthiochroman-4-one (0.104 g, 0.583 mmol) was dissolved in anhydrous methanol (15 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.064 g, 0.703 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **8** was obtained as a white solid (0.113 g, 0.449 mmol, 77% yield). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.19 (1H, bs), 8.36 (1H, bs), 2.28 (3H, s), 8.19 (1H, bs), 8.05 (1H, bs), 7.11 (1H, d, *J* = 7.8 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 3.00 (4H, bs); ¹³C NMR (75 MHz, DMSO-*d*₆): 178.9, 145.4, 134.6, 132.7, 130.7, 130.1, 127.7, 127.4, 28.0, 25.2, 20.5; HRMS (ESI) calculated for C₁₁H₁₃N₃S₂H (M+H)⁺ 252.0624, found 252.0623; HPLC retention time 6.01 min.



6-Ethylthiochroman-4-one thiosemicarbazone (9): Ketone **9b** (0.090 g, 0.468 mmol) was dissolved in anhydrous methanol (9 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.052 g, 0.57 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **9** was obtained as a white solid (0.079 g, 0.298 mmol, 64% yield). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.19 (1H, s), 8.38 (1H, s), 8.18 (1H, d, *J* = 1.2 Hz), 8.05 (1H, s), 7.08-7.15 (2H, m), 3.00 (4H, m), 2.59 (2H, q, *J* = 7.5 Hz), 1.16 (3H, t, *J* = 7.5 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 178.9, 143.6, 141.1, 133.0, 130.8, 128.9, 127.8, 126.1, 28.0, 27.7, 25.1, 15.9; HRMS (ESI) calculated for C₁₂H₁₅N₃S₂H (M+H)⁺ 266.0780, found 266.0780; HPLC retention time 9.15 min.

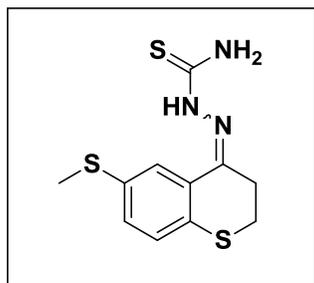


6-Isopropylthiochroman-4-one thiosemicarbazone (10): Ketone **10b** (0.100 g, 0.485 mmol) was dissolved in anhydrous methanol (12 mL). The reaction was heated at reflux under nitrogen for 30 min, and then thiosemicarbazide (0.0463 g, 0.509 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 36 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **10** was obtained as a white solid (0.0357g, 0.128 mmol, 26% yield). ^1H NMR (500 MHz, CDCl_3): δ 8.66 (1H, s), 7.80 (1H, d, $J = 1.5$ Hz), 7.36 (1H, bs), 7.22 (1H, d, $J = 8.5$ Hz), 7.16 (1H, dd, $J = 8.0$ Hz, 2.0 Hz), 6.34 (1H, bs), 3.05-3.02 (2H, m), 2.96-2.94 (2H, m), 2.93-2.87 (1H, m), 1.25 (6H, d, $J = 6.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 179.3, 146.7, 145.8, 134.2, 130.6, 128.7, 128.2, 124.5, 33.9, 28.4, 25.9, 23.9; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 280.4242, found 280.0937; HPLC retention time 12.7 min.

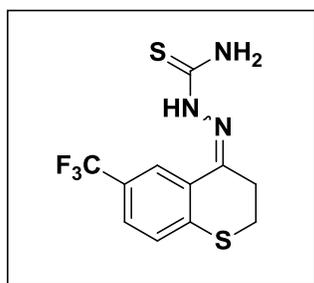


6-Methoxythiochroman-4-one thiosemicarbazone (11): Ketone **11b** (0.747 g, 3.85 mmol) was dissolved in anhydrous methanol (20 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.428 g, 4.67 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 12 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **11** was obtained as a light yellow solid (0.574 g, 2.15 mmol, 56% yield). ^1H NMR (500 MHz, DMSO-d_6): δ 10.17 (1H, bs), 8.36 (1H, bs), 8.07 (1H, bs),

7.16 (1H, d, $J = 3$ Hz), 6.88 (1H, dd, $J = 8.5$ Hz, 2.5 Hz), 3.78 (3H, s), 2.95-3.00 (4H, m); ^{13}C NMR (125 MHz, DMSO- d_6): δ 179.9, 162.9, 140.7, 135.1, 130.7, 125.3, 116.6, 111.6, 56.4, 46.5, 25.3; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{OS}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 268.0573, found 268.0572; HPLC retention time: 8.88 min.

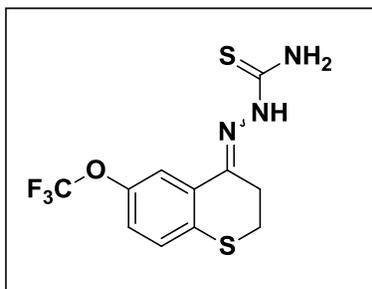


6-(Methylthio)thiochroman-4-one thiosemicarbazone (12): Ketone **12b** (0.115 g, 0.546 mmol) was dissolved in anhydrous methanol (15 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.060 g, 0.659 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 12 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **12** was obtained as a yellow solid (0.0895 g, 0.3145 mmol, 58% yield). ^1H NMR (300 MHz, DMSO- d_6): δ 10.21 (1H, s), 8.36 (1H, s), 8.16 (1H, d, $J = 1.5$ Hz), 8.14 (1H, s), 7.11-7.21 (2H, m), 3.01 (4H, bs), 2.49 (3H, s); ^{13}C NMR (75 MHz, DMSO- d_6): δ 179.0, 145.1, 135.1, 132.6, 131.5, 128.4, 127.1, 124.7, 28.0, 25.1; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{S}_3\text{H}$ ($\text{M}+\text{H}$) $^+$ 284.0350, found 284.0343; HPLC retention time: 9.58 min.

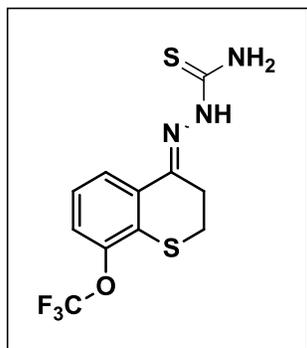


6-Trifluoromethylthiochroman-4-one thiosemicarbazone (13): Ketone **13b** (0.104 g, 0.583 mmol) was dissolved in anhydrous methanol (15 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.064 g, 0.703 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting

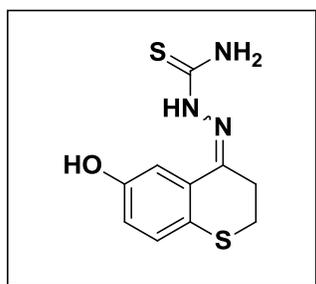
precipitate was collected by filtration and washed with methanol. After drying under house vacuum, thiosemicarbazone **13** was obtained as a white solid (0.113 g, 0.449 mmol, 77% yield). ^1H NMR (300 MHz, DMSO- d_6): δ 10.31 (1H, s), 8.63 (1H, s), 8.42 (1H, s), 8.31 (1H, s), 7.53 (1H, dd, $J = 8.4, 1.5$ Hz), 7.45 (1H, d, $J = 8.4$ Hz), 3.12-3.05 (4H, m); ^{13}C NMR (125 MHz, DMSO- d_6): δ 179.6, 144.8, 141.8 (d, $J_{\text{C-F}} = 0.88$ Hz), 132.0, 129.1, 126.4 (q, $J_{\text{C-F}} = 32$ Hz), 125.3 (q, $J_{\text{C-F}} = 3.6$ Hz) 124.6 (q, $J_{\text{C-F}} = 270.6$ Hz), 124.5 (q, $J_{\text{C-F}} = 3.6$ Hz), 27.7, 25.2; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{N}_3\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 306.0341, found 306.0340; HPLC retention time: 10.3 min.



6-(Trifluoromethoxy)thiochroman-4-one thiosemicarbazone (14): Ketone **14b** (0.041 g, 0.165 mmol) was dissolved in anhydrous methanol (10 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.0157 g, 0.173 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 24 h at reflux, the solvent was removed under reduced pressure. Purification of the crude mixture by flash column chromatography (silica gel, hexanes: ethyl acetate, gradient 95:5 to 80:20) afforded thiosemicarbazone **14** as a white solid (0.016 g, 0.041 mmol, 30% yield). ^1H NMR (CDCl_3 , 500 MHz) δ 8.80 (1H, s), 7.82 (1H, d, $J = 2.0$ Hz), 7.32 (1H, s), 7.29 (1H, d, $J = 8.5$ Hz), 7.13 (1H, dd, $J = 8.5$ Hz, 1.0 Hz), 6.51 (1H, s), 3.07 (2H, t, $J = 6.0$ Hz), 2.98 (2H, t, $J = 6.5$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6): 179.5, 147.1, 143.9, 135.7, 132.3, 130.0, 122.4, 120.4 (1C, q, $J_{\text{C-F}} = 256.4$ Hz), 118.9, 27.7, 25.7; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{N}_3\text{OS}_2\text{H}$ ($\text{M} + \text{H}$) $^+$ 322.0290, found 322.0290; HPLC retention time 11.8 min.

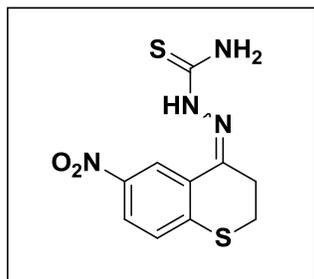


8-(Trifluoromethoxy)thiochroman-4-one thiosemicarbazone (15): Ketone **15b** (0.150 g, 0.604 mmol) was dissolved in anhydrous methanol (10 mL). The reaction was heated at reflux for 15 min, and then thiosemicarbazide (0.057 g, 0.634 mmol) and a catalytic amount of *p*-toluenesulfonic acid was added. After 12 h at reflux, the resulting precipitate was filtered, and pure thiosemicarbazone **15** was obtained as a white solid (0.020 g, 0.062 mmol, 10% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 10.34 (1H, s), 8.44 (1H, d, *J* = 8.5 Hz), 8.41 (1H, s), 8.09 (1H, s), 7.35 (1H, d, *J* = 8.0 Hz), 7.21 (1H, t, *J* = 8.0 Hz), 3.07-3.02 (4H, m); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 179.62, 145.06, 144.32, 133.81, 131.11, 126.68, 125.64, 121.64, 120.68 (q, *J*_{C-F} = 256.4 Hz) 27.47, 24.62; HRMS (ESI) calculated for C₁₁H₁₀F₃N₃OS₂H (M + H)⁺ 322.0290, found 322.0291; HPLC retention time 11.6 min.

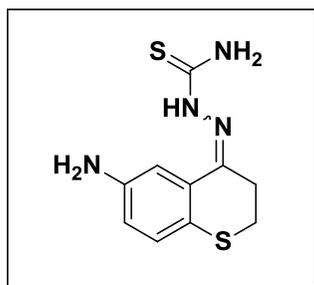


6-Hydroxythiochroman-4-one thiosemicarbazone (16): Ketone **16b** (0.030 g, 0.170 mmol) was dissolved in anhydrous methanol (10 mL). The solution was heated to reflux for 15 min, and then thiosemicarbazide (0.019 g, 0.206 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 12 h at reflux, purification using flash chromatography (silica gel, hexanes: ethyl acetate, 50:50) afforded thiosemicarbazone **16** as a brown solid (0.017 g, 0.67 mmol, 40% yield). ¹H NMR (500 MHz, acetone-*d*₆): δ 9.34 (1H, bs), 8.34 (1H, bs), 7.91 (1H, bs), 7.68 (1H, d, *J* = 3.0 Hz), 7.64 (1H, bs), 7.11

(1H, d, $J = 8.5$ Hz), 6.84 (1H, dd, $J = 8.5$ Hz, 2.5 Hz), 3.15-3.18 (2H, m), 3.06-3.10 (2H, m); ^{13}C NMR (75 MHz, DMSO- d_6): 179.5, 155.6, 146.3, 132.6, 129.4, 125.3, 118.0, 113.7, 28.9, 25.9; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{OS}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 254.0416, found 254.0416; HPLC retention time: 6.68 min.

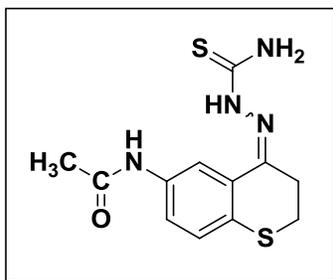


6-Nitrothiochroman-4-one thiosemicarbazone (17): Ketone **17b** (0.100 g, 0.478 mmol) was dissolved in 15 mL anhydrous methanol (15 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.053 g, 0.580 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and then with methanol several times. After drying under house vacuum, thiosemicarbazone **17** was obtained as an orange solid (0.110g, 0.392 mmol, 82% yield). ^1H NMR(500 MHz, DMSO- d_6): δ 10.43 (1H, s), 8.97 (1H, d, $J = 2.0$ Hz), 8.44 (1H, s), 8.25 (1H, s), 7.99 (1H, dd, $J = 8.5$ Hz, 2.0 Hz), 7.49 (1H, d, $J = 9.0$ Hz), 3.16-3.14 (2H, m), 3.09-3.06 (2H, m); ^{13}C NMR (125 MHz, DMSO- d_6): δ 179.7, 145.7, 145.5, 144.2, 132.1, 129.3, 123.3, 122.4, 27.1, 25.3; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_9\text{N}_4\text{O}_2\text{S}_2$ ($\text{M}-\text{H}$) $^-$ 281.0172, found 281.0174 ; HPLC retention time: 8.42 min.

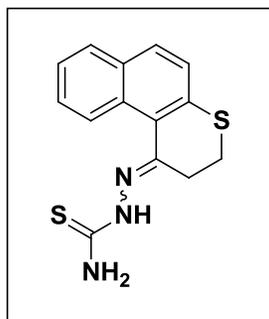


6-Aminothiochroman-4-one thiosemicarbazone (18): Ketone **18b** (0.100 g, 0.559 mmol) was dissolved in anhydrous methanol (12 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.080g, 0.879 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, purification using flash chromatography (silica gel, hexanes: ethyl acetate, 50:50) afforded thiosemicarbazone **18**

as a yellow solid (0.110 g, 0.392 mmol, 82% yield). ^1H NMR(500 MHz, acetone- d_6): 9.32 (1H, bs), 7.81 (1H, bs), 7.62 (1H, bs), 7.60 (1H, d, $J=2.5$ Hz), 6.98 (1H, d, $J=8.5$ Hz), 6.69 (1H, dd, $J=8.5$ Hz, 2.5 Hz), 4.61 (2H, bs), 3.12-3.14 (2H, m), 3.02-3.04 (2H, m); ^{13}C NMR (125 MHz, acetone- d_6): δ 180.3, 146.4, 145.3, 132.1, 128.8, 123.4, 116.7, 112.1, 28.6, 26.0; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 253.0576, found 253.0574; HPLC retention time: 2.16 min.

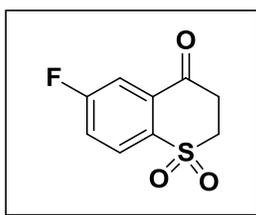


***N*-(4-oxothiochroman-6-yl)acetamide thiosemicarbazone (19)** : Ketone **19b** (0.100 g, 0.450 mmol) was dissolved in anhydrous methanol (10 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.050 g, 0.549 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, purification using flash chromatography (silica gel, hexanes: ethyl acetate, 60:40) afforded thiosemicarbazone **19** as a yellow solid (0.050 g, 0.170 mmol, 38% yield). ^1H NMR (500 MHz, DMSO- d_6): 10.44 (1H, s), 9.83 (1H, s), 8.56 (1H, s), 8.16 (1H, d, $J=2.5$ Hz), 7.67 (1H, dd, $J=8.5$ Hz, 2.5 Hz), 7.56 (1H, s), 7.16 (1H, d, $J=8.5$ Hz), 3.01-2.99 (4H, m), 2.03 (3H, s); ^{13}C NMR(500 MHz, DMSO- d_6): 179.7, 168.7, 145.7, 137.3, 131.7, 130.6, 128.6, 121.2, 117.6, 28.6, 25.8, 24.4 ; HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{OS}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 295.0682, found 295.0683; HPLC retention time: 6.12 min.

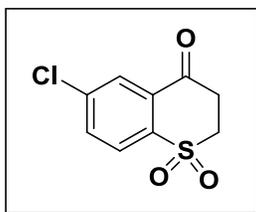


2,3-Dihydro-1H-benzo[f]thiochromen-1-one thiosemicarbazone (20):^{S14} Ketone **20b** (0.107 g, 0.500 mmol) was dissolved in anhydrous methanol (10 mL). The solution was

heated to reflux for 15 min, and then thiosemicarbazide (0.048 g, 0.525 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. The reaction was refluxed for 18 h and then cooled to room temperature. The precipitate was filtered and recrystallized from methanol, affording pure thiosemicarbazone **20** as a white solid (0.035 g, 0.122 mmol, 25% yield). ¹H NMR (CDCl₃, 500 MHz) δ 8.93 (1H, s), 8.55 (1H, d, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 7.5 Hz), 7.70 (1H, d, *J* = 8.5 Hz), 7.49 (1H, td, *J* = 6.5 Hz, 1.0 Hz), 7.46-7.43 (1H, m), 7.37 (1H, d, *J* = 8.5 Hz), 7.30 (1H, s), 6.41 (1H, s), 3.19 (2H, t, *J* = 6.5 Hz), 3.05 (2H, t, *J* = 6.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 179.5, 145.8, 138.6, 133.1, 131.7, 129.6, 128.5, 128.0, 127.4, 126.6, 125.9, 125.6, 32.1, 26.9; HRMS (ESI) calcd for C₁₄H₁₃N₃S₂H (M + H)⁺ 288.0624, found 288.0624; HPLC retention time 1.61 min.

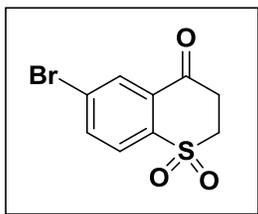


6-Fluorothiochroman-4-one 1,1-dioxide (1c):^{S15} 6-Fluorothiochroman-4-one (0.500 g, 2.74 mmol) was dissolved in glacial HOAc (5 mL) and 35% w/w solution of H₂O₂ (1.36 mL, 44.5 mmol). After 1 h at reflux, the solution was cooled to room temperature. The resulting precipitate was collected by filtration to obtain pure sulfone **1c** (0.343 g, 1.60 mmol, 59% yield). ¹H-NMR (DMSO-d₆, 500 MHz) δ 8.04 (1H, dd, *J* = 8.5 and 4.5 Hz, ArH) 7.78 (1H, td, *J* = 8 and 2 Hz, ArH) 7.73 (1H, dd, *J* = 9 and 2 Hz, ArH) 4.02 (2H, t, *J* = 6.5 Hz, CH₂) 3.27 (2H, t, *J* = 6.5 Hz, CH₂).

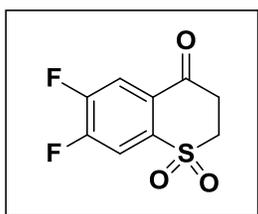


6-Chloro-1,1-dioxothiochroman-4-one (2c):^{S18} 6-chlorothiochroman-4-one (1.01 g, 5.08 mmol) was dissolved in glacial acetic acid (20 mL) and a 35% w/w solution of hydrogen peroxide (7 mL). After 2 h at reflux, the solution was cooled to room temperature, and concentrated under reduced pressure. Recrystallization using

methanol/ethanol (1:1) afforded sulfone **2c** as a white solid (0.710 g, 3.08 mmol, 61% yield). ^1H NMR (300 MHz, DMSO- d_6): 7.95-8.03 (3H, m), 4.06 (2H, t, $J = 6.0$ Hz), 3.29 (2H, t, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, DMSO- d_6): δ 198.8, 139.9, 138.3, 134.7, 132.0, 127.4, 125.4, 48.1, 36.5.

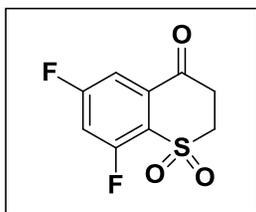


6-bromo-1,1-dioxothiochroman-4-one (3c):^{S9} The crude mixture of ketone **3b** (0.287 g, 1.18 mmol) was dissolved in glacial acetic acid (9 mL) and 35% w/w hydrogen peroxide solution (0.202 mL). After 2 h at reflux, the solution was cooled to room temperature, water (6 mL) was added and the product was extracted with dichloromethane (3×25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, gradient 80:20 to 40:60) afforded pure sulfone **3c** as a white solid (0.107 g, 0.390 mmol, 6%, calculated for two steps, beginning with bromination of thiochroman-4-one. See ketone **3b**). ^1H NMR (300 MHz, CDCl_3): δ 8.25 (1H, d, $J = 1.9$ Hz), 7.95 (1H, dd, $J = 8.4$ Hz, 2.0 Hz), 7.88 (1H, d, $J = 8.3$ Hz), 3.72-3.68 (2H, m), 3.46-3.41 (2H, m).

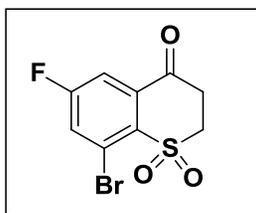


6,7-Difluoro-1,1-dioxothiochroman-4-one (4c) (*also commercially available*): Ketone **4b** (0.12 g, 0.6 mmol) was dissolved in glacial acetic acid (22 mL) and 35% w/w hydrogen peroxide solution (6 mL). After 2 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl

acetate, gradient 90:10 to 50:50) afforded sulfone **4c** as a white solid (0.070 g, 0.300 mmol, 50 % yield). ^1H NMR (300 MHz, CDCl_3): δ 7.92-7.97 (1H, m), 7.81-7.86 (1H, m), 3.71-3.75 (2H, m), 3.42-3.46 (2H, m); ^{13}C NMR (75 MHz, CDCl_3): δ 187.92, 154.15 (dd, $J_{\text{C-F}} = 264.2$ Hz, 13.7 Hz), 153.31 (dd, $J_{\text{C-F}} = 259.1$ Hz, 12.8 Hz), 138.91 (t, $J_{\text{C-F}} = 5.6$ Hz), 128.31 (t, $J_{\text{C-F}} = 5.3$ Hz), 118.54 (dd, $J_{\text{C-F}} = 19.4$ Hz, 2.0 Hz), 114.08 (d, $J_{\text{C-F}} = 20.8$ Hz), 49.45, 36.64; HRMS (ESI) calculated for $\text{C}_9\text{H}_6\text{F}_2\text{O}_3\text{S}$ 232.0006, found 232.0002.

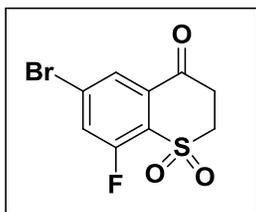


6,8-Difluoro-1,1-dioxothiochroman-4-one (5c) (also commercially available): Ketone **5b** (0.174 g, 0.870 mmol) was dissolved in glacial acetic acid (20 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 2 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 50:50) afforded sulfone **5c** as a white solid (0.050 g, 0.216 mmol, 25% yield). ^1H NMR (300 MHz, CDCl_3): 7.62-7.66 (1H, m), 7.23-7.29 (1H, m), 3.74-3.78 (2H, m), 3.40-3.44 (2H, m); ^{13}C NMR (75 MHz, CDCl_3): 188.16, 164.91 (dd, $J_{\text{C-F}} = 258.8$ Hz, 12 Hz), 159.87 (dd, $J_{\text{C-F}} = 250.5$ Hz, 11.3 Hz), 133.45 (d, $J_{\text{C-F}} = 8.3$ Hz), 126.15 (dd, $J_{\text{C-F}} = 13.5$ Hz, 3.8 Hz), 111.91 (dd, $J_{\text{C-F}} = 24.0$ Hz, 3.8 Hz), 111.49 (t, $J_{\text{C-F}} = 25.5$ Hz), 50.65, 36.27.

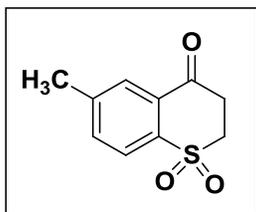


8-Bromo-6-fluoro-1,1-dioxothiochroman-4-one (6c): Ketone **6b** (0.100 g, 0.385 mmol) was dissolved in glacial acetic acid (20 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 2 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined

organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 50:50) afforded sulfone **6c** as a white solid (0.017 g, 0.058 mmol, 15% yield). ^1H NMR (300 MHz, CDCl_3): 7.81 (1H, dd, $J = 8.1$ Hz, 2.4 Hz), 7.72 (1H, dd, $J = 7.2$ Hz, 2.7 Hz), 3.74-3.78 (2H, m), 3.40-3.44 (2H, m); ^{13}C NMR (75 MHz, CDCl_3): 188.34, 163.5 (d, $J_{\text{C-F}} = 259.5$ Hz), 136.83 (d, $J_{\text{C-F}} = 3.8$ Hz), 134.67 (d, $J_{\text{C-F}} = 7.5$ Hz), 128.48 (d, $J_{\text{C-F}} = 24.8$ Hz), 120.32 (d, $J_{\text{C-F}} = 9$ Hz), 115.34 (d, $J_{\text{C-F}} = 7.2$ Hz), 50.44, 36.24.

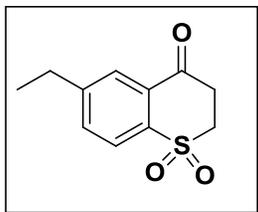


6-Bromo-8-fluoro-1,1-dioxothiochroman-4-one (7c): Ketone **7b** (0.125 g, 0.480 mmol) was dissolved in glacial acetic acid (20 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 2 h at reflux, the solution was cooled to room temperature, water (25 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 60:40) afforded sulfone **7c** as a white solid (0.050 g, 0.171 mmol, 36% yield). ^1H NMR (500 MHz, CDCl_3): 8.06 (1H, bs), 7.69 (1H, dd, $J = 9.0$ Hz, 2 Hz), 3.74-3.76 (2H, m), 3.39-3.41 (2H, m); ^{13}C NMR (125 MHz, CDCl_3): 188.15, 158.41 (d, $J_{\text{C-F}} = 263.75$ Hz), 132.09, 128.43 (d, $J_{\text{C-F}} = 9.3$ Hz), 128.32 (d, $J_{\text{C-F}} = 13.5$ Hz), 127.86 (d, $J_{\text{C-F}} = 3.8$ Hz), 126.45 (d, $J_{\text{C-F}} = 23.5$ Hz), 50.62, 36.32.

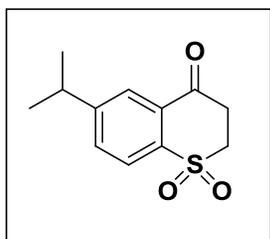


6-Methyl-1,1-dioxothiochroman-4-one (8c):^{S18} 6-methylthiochroman-4-one (0.449 g, 2.52 mmol) was dissolved in glacial acetic acid (19.7 mL) and a 35% w/w solution of hydrogen peroxide solution (3.27 mL) After 2 h at reflux, the solution was cooled to room temperature, and concentrated under reduced pressure. Recrystallization from methanol/ethanol (1:1) afforded sulfone **8c** as a white solid (0.301 g, 1.43 mmol, 57%

yield). ^1H NMR(300 MHz, DMSO- d_6): 7.84-7.87 (2H, m), 7.76 (1H, d, $J = 9.0$ Hz), 3.99 (2H, t, $J = 6.0$ Hz), 3.24 (2H t, $J = 6.0$ Hz), 2.51 (3H, s); ^{13}C NMR (75 MHz, DMSO- d_6): δ 190.9, 144.0, 138.7, 135.4, 130.2, 128.1, 123.1, 48.2, 36.6, 21.0.

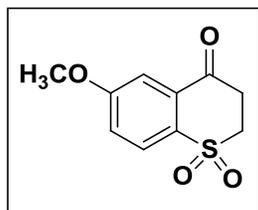


6-Ethyl-1,1-dioxothiochroman-4-one (9c): Ketone **9b** (0.283 g, 1.47 mmol) was dissolved in glacial acetic acid (25 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 2 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were concentrated. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 60:40) afforded sulfone **9c** as a white solid (0.128 g, 0.574 mmol, 39% yield). ^1H NMR (500 MHz, CDCl_3): δ 7.94 (1H, d, $J = 1.5$ Hz), 7.92 (1H, d, $J = 8.0$ Hz), 7.65 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz), 3.70-3.67 (2H, m), 3.42-3.40 (2H, m), 2.78 (2H, q, $J = 7.5$ Hz), 1.28 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 190.5, 150.6, 138.8, 134.5, 130.2, 128.0, 123.8, 49.3, 36.8, 28.9, 15.0; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{S}$ 224.0507, found 224.0501.

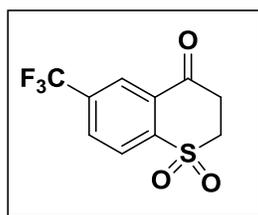


6-Isopropyl-1,1-dioxothiochroman-4-one (10c) (*also commercially available*): Ketone **10b** (0.238 g, 1.15 mmol) was dissolved in glacial acetic acid (6 mL) and 35% w/w hydrogen peroxide solution (0.197 mL). After 2 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, gradient 80:20 to 40:60) afforded pure sulfone **10c** as a white solid (0.180 g, 0.754 mmol, 65% yield). ^1H NMR(500 MHz,

CDCl₃): δ 7.98 (1H, d, $J = 1.5$ Hz), 7.94 (1H, d, $J = 8.0$ Hz), 7.68 (1H, dd, $J = 8.5$ Hz, 2.0 Hz), 3.68 (2H, dd, $J = 7.5$ Hz, 6.0 Hz), 3.42 (2H, dd, $J = 7.0$ Hz, 5.5 Hz), 3.06-3.03 (1H, m), 1.29 (6H, d, $J = 7.0$ Hz).

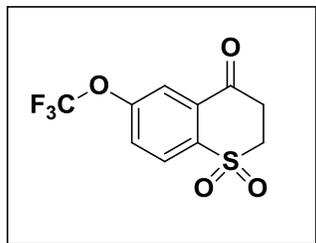


6-Methoxy-1,1-dioxothiochroman-4-one (11c):^{S19} Ketone **11b** (0.412 g, 2.12 mmol) was dissolved in glacial acetic acid (25 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 2 h at reflux, the solution was cooled to room temperature, and concentrated under reduced pressure. Recrystallization from methanol/ethanol (1:1) afforded sulfone **11c** as a white solid (0.121 g, 0.540 mmol, 25% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.94 (1H, d, $J = 8.7$ Hz), 7.56 (1H, d, $J = 2.7$ Hz), 7.29 (1H, dd, $J = 8.7$ Hz, 2.7 Hz), 3.93 (3H, s), 3.65-3.69 (2H, m), 3.40-3.45 (2H, m); ¹³C NMR (75 MHz, CDCl₃): δ 190.3, 163.2, 133.6, 132.2, 125.8, 121.6, 112.0, 56.0, 49.4, 36.9; HRMS (ESI) calculated for C₁₀H₁₀O₄S 226.0300, found 226.0299

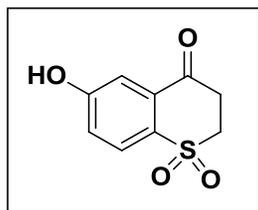


6-Trifluoromethyl-1,1-dioxothiochroman-4-one (13c): Ketone **13b** (0.208 g, 0.897 mmol) was dissolved in glacial acetic acid (25 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 2 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2 \times 25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 60:40) afforded sulfone **13c** as a white solid (0.053 g, 0.200 mmol, 22% yield). ¹H NMR (500 MHz, CDCl₃): δ 8.4 (1H, dd, $J_I = 1.5$ Hz, 0.5 Hz), 8.17 (1H, d, $J = 8.0$ Hz), 8.08 (1H, dd, $J_I = 7.0$ Hz, 1.0 Hz), 3.48 (2H, m), 3.75 (2H, m); ¹³C NMR (125 MHz, CDCl₃): δ 188.8, 144.3, (d, $J_{C-F} =$

1.4 Hz), 135.6 (q, J_{C-F} = 34.3 Hz), 131.5 (q, J_{C-F} = 3.8 Hz), 130.9, 126.2 (q, J_{C-F} = 4.3 Hz), 124.9, 122.4 (q, J_{C-F} = 272.1 Hz), 49.1, 36.6; HRMS (ESI) calculated for $C_{10}H_7F_3O_3S$ 264.0068, found 264.0061.

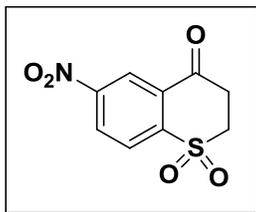


6-(Trifluoromethoxy)-1,1-dioxothiochroman-4-one (14c): Ketone **14b** (0.162 g, 0.653 mmol) was dissolved in glacial acetic acid (5 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 3 h at reflux, the solution was cooled to room temperature, water (10 mL) was added, and the product was extracted by dichloromethane (2×25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 60:40) afforded sulfone **14c** (0.142 g, 0.507 mmol, 78% yield). 1H NMR (500 MHz, $CDCl_3$): δ 8.10 (1H, d, J = 8.5 Hz), 7.94 (1H, dd, J = 2.0 Hz, 1.0 Hz), 7.64 (1H, ddd, J = 8.5 Hz, 2.5 Hz, 0.5 Hz), 3.73-3.71 (2H, m), 3.48-3.46 (2H, m).

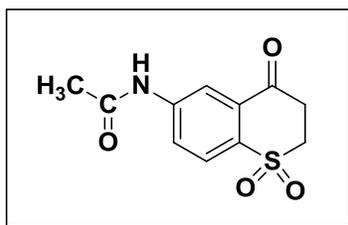


6-Hydroxy-1,1-dioxothiochroman-4-one (16c): Ketone **16b** (0.090 g, 0.500 mmol) was dissolved in glacial acetic acid (20 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 2 h at reflux, the solution was cooled to room temperature, water (10 mL) was added, and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 50:50) afforded sulfone **16c** as a white solid (0.060 g, 0.283 mmol, 57 % yield). 1H NMR (300 MHz, acetone- d_6): δ 9.70 (1H, s), 7.85 (1H, d, J = 8.4 Hz), 7.45 (1H, d, J = 2.7 Hz), 7.35 (1H, dd, J = 8.4 Hz, 2.7 Hz), 3.85 (2H, t, J = 6.0 Hz), 3.35 (2H, t, J = 6.3 Hz); ^{13}C NMR (75 MHz, acetone- d_6): δ 191.4,

162.1, 134.3, 133.7, 126.6, 122.2, 114.7, 49.8, 37.7; HRMS (ESI) calculated for $C_9H_7O_4S(M-H)^-$ 211.0071, found 211.0061.

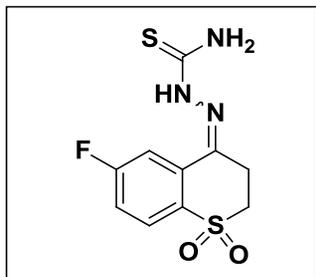


6-Nitro-1,1-dioxothiochroman-4-one (17c):^{S20} Ketone **17b** (0.067 g, 0.287 mmol) was dissolved in glacial acetic acid (20 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 12 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 60:40) afforded sulfone **17c** as a white solid (0.036 g, 0.149 mmol, 52% yield). 1H NMR (300 MHz, $CDCl_3$): δ 8.94 (1H, d, $J = 2.1$ Hz), 8.64 (1H, dd, $J = 8.4$ Hz, 2.4 Hz), 8.25 (1H, d, $J = 8.4$ Hz), 3.76-3.80 (2H, m), 3.50-3.54 (2H, m); ^{13}C NMR (75 MHz, acetone- d_6): δ 189.9, 147.3, 133.2, 129.9, 126.6, 123.9, 49.5, 37.6; HRMS (ESI) calculated for $C_9H_7NO_5S$ 241.0045, found 241.0044.

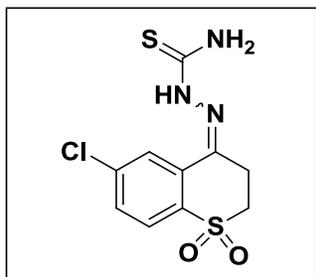


N-(1,1-dioxido-4-oxothiochroman-6-yl)acetamide (19c): Ketone **19b** (0.116 g, 0.527 mmol) was dissolved in glacial acetic acid (20 mL) and 35% w/w hydrogen peroxide solution (5 mL). After 1.5 h at reflux, the solution was cooled to room temperature, water (10 mL) was added and the product was extracted with dichloromethane (2×25 mL). The combined organic layers were concentrated under reduced pressure. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 50:50) afforded sulfone **19c** as a white solid (0.100 g, 0.234 mmol, 45% yield). 1H NMR (500 MHz, acetone- d_6): δ 8.18 (1H, dd, $J = 8.5$ Hz, 2 Hz), 8.31 (1H, d, $J = 2.5$ Hz), 7.91 (1H, d, $J = 8.5$ Hz), 3.87-

3.90 (2H, m), 3.35-3.38 (2H, m); ^{13}C NMR (125 MHz, acetone- d_6): δ 190.4, 168.9, 143.7, 136.0, 131.7, 124.4, 123.9, 117.4, 48.9, 36.8, 23.5.

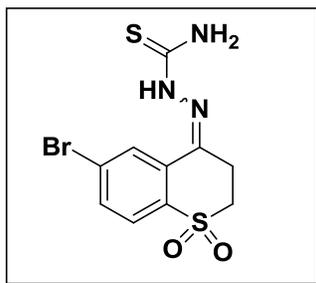


6-Fluoro-1,1-dioxothiochroman-4-one thiosemicarbazone (21):^{S15} 6-fluorothiochroman-4-one 1,1-dioxide (0.214 g, 1.00 mmol) was dissolved in anhydrous methanol (5 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.182 g, 2.00 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 7 h at reflux, the solvent was removed under reduced pressure. Water was added and the product was extracted with ethyl acetate. Purification using flash chromatography (silica gel, hexanes: ethyl acetate, 50:50 to 0:100) afforded pure thiosemicarbazone **21** (0.055 g, 0.19 mmol, 19% yield). ^1H NMR (500 MHz, DMSO- d_6): δ 10.62 (1H, s), 8.56 (1H, s), 8.45 (1H, d, $J = 13.5$ Hz), 8.44 (1H, s), 7.88 (1H, dd, $J = 8.5$ Hz, 5.5 Hz), 7.44 (1H, td, $J = 8.5$ Hz, 2 Hz), 3.67 (2H, t, $J = 6.0$ Hz), 3.28 (2H, t, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6): δ 180.0, 165.0 (d, $J_{\text{C-F}} = 248.5$ Hz) 139.3, 136.5 (d, $J_{\text{C-F}} = 9.25$ Hz) 134.7, 126.4 (d, $J_{\text{C-F}} = 9.25$ Hz) 117.8 (d, $J_{\text{C-F}} = 23.5$) 114.0 (d, $J_{\text{C-F}} = 24.8$ Hz) 46.2, 25.1; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{FN}_3\text{O}_2\text{S}$ 287.0198, found 287.0198; HPLC retention time 5.90 min.

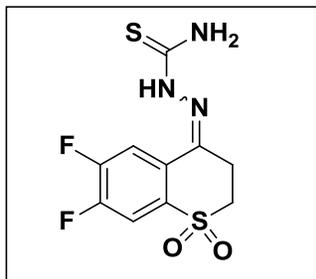


6-Chloro-1,1-dioxothiochroman-4-one thiosemicarbazone (22): Sulfone **2c** (0.700 g, 3.03 mmol) was dissolved in anhydrous methanol (56 mL). The solution was heated at reflux for 15 min, and thiosemicarbazide (0.34 g, 3.73 mmol) and a catalytic amount of

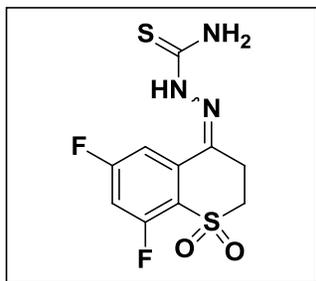
p-toluenesulfonic acid were added. After 12 h at reflux, the resulting precipitate was collected by filtration and washed by methanol. After drying under high vacuum, thiosemicarbazone **22** was obtained as a white solid (0.800 g, 2.64 mmol, 87% yield). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.62(1H, s), 8.68 (1H, d, *J* = 3 Hz), 8.60 (1H, bs), 8.52 (1H, bs), 7.85 (1H, d, *J* = 9.0 Hz), 7.67 (1H, dd, *J* = 9.0 Hz, 3.0 Hz), 3.71 (2H, t, *J* = 6.0 Hz), 3.30 (2H, t, *J* = 6.0 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 179.5, 138.8, 138.2, 136.3, 134.6, 129.9, 126.4, 124.7, 45.6, 24.5; HRMS (ESI) calculated for C₁₀H₁₀ClN₃O₂S 302.9903, found 302.9910; HPLC retention time 7.27 min.



6-Bromo-1,1-dioxothiochroman-4-one thiosemicarbazone (23):^{S17} Sulfone **3c** (0.400 g, 1.45 mmol) was dissolved in anhydrous methanol (25 mL). The solution was heated at reflux for 15 min, and thiosemicarbazide (0.138 g, 1.52 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 12 h at reflux, the resulting precipitate was collected by filtration and washed by methanol. After drying under high vacuum, thiosemicarbazone **23** was obtained as a white solid (0.218 g, 0.630 mmol, 43% yield). ¹H NMR (500 MHz, DMSO-*d*₆): δ 10.59 (1H, s), 8.78 (1H, d, *J* = 2.0 Hz), 8.57 (1H, s), 8.52 (1H, s), 7.81 (1H, dd, *J* = 8.5 Hz, 2.0 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 3.69 (2H, t, *J* = 6.0 Hz), 3.28 (2H, t, 6.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 180.0, 139.3, 137.2, 135.0, 133.3, 129.7, 127.7, 125.1, 46.1, 25.0; HRMS (ESI) calculated for C₁₀H₉BrN₃O₂S₂ (M-H)⁻ 345.9325, found 345.9332; HPLC retention time 7.21 min.

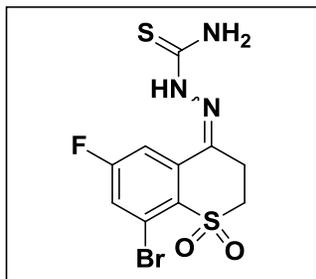


6,7-Difluoro-1,1-dioxothiochroman-4-one thiosemicarbazone (24): Sulfone **4c** (0.044 g, 0.190 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at reflux for 15 min, and thiosemicarbazide (0.037 g, 0.406 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **24** was obtained as a white solid (0.022 g, 0.072 mmol, 38% yield). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.66 (1H, s), 8.76 (1H, dd, *J* = 12.6 Hz, 7.8 Hz), 8.60 (1H, s), 8.48 (1H, s), 7.92-7.97 (1H, m), 3.74 (2H, t, *J* = 6.3 Hz), 3.30 (2H, t, *J* = 6.3 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 179.52, 152.31 (dd, *J*_{C-F} = 250.5 Hz, 12.8 Hz), 149.99 (dd, *J*_{C-F} = 253.5 Hz, 14.3 Hz), 138.22, 134.80 (t, *J*_{C-F} = 4.5 Hz), 131.38 (dd, *J*_{C-F} = 7.5 Hz, 3.8 Hz), 116.50 (d, *J*_{C-F} = 20.3 Hz), 112.62 (d, *J*_{C-F} = 21.00 Hz), 45.84, 24.46; HRMS (ESI) calculated for C₁₀H₈F₂N₃O₂S₂ (M-H)⁻ 304.0031, found 304.0033 ; HPLC retention time 3.71 min.

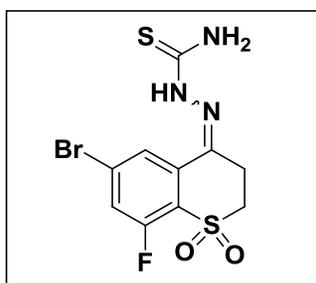


6,8-Difluoro-1,1-dioxothiochroman-4-one thiosemicarbazone (25): Sulfone **5c** (0.028 g, 0.129 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.015 g, 0.16 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **25** was obtained as a white solid (0.020 g, 0.065 mmol, 51 % yield). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.74 (1H, s), 8.62 (1H, s), 8.47 (1H, s), 8.41 (1H, d, *J* = 10.8 Hz), 7.54-7.61 (1H, m), 3.77 (2H, t, *J* = 6.0 Hz), 3.28 (2H, t, *J* = 6.0 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): 179.55, 164.07 (dd, *J*_{C-F} = 250.5 Hz, 14.3 Hz), 159.16 (dd, *J*_{C-F} = 253.5 Hz, 12.8 Hz), 138.4, 136.94 (d, *J*_{C-F} = 12.8 Hz), 123.23 (d, *J*_{C-F} = 14.3 Hz), 109.74 (d, *J*_{C-F} = 21.8 Hz), 106.48 (t, *J*_{C-F} = 27.0 Hz), 47.62, 23.45; HRMS (ESI)

calculated for $C_{10}H_8F_2N_3O_2S_2(M-H)^-$ 304.0031, found 304.0033 ; HPLC retention time: 1.55 min.

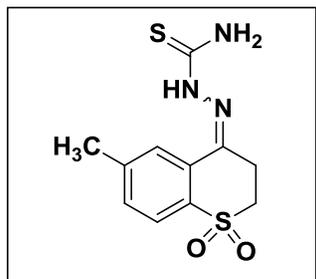


8-Bromo-6-fluoro-1,1-dioxothiochroman-4-one thiosemicarbazone (26): Sulfone **6c** (0.039 g, 0.130 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at reflux for about 15 min, and thiosemicarbazide (0.015 g, 0.165 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **26** was obtained as a white solid (0.034 g, 0.072 mmol, 51 % yield). 1H NMR (300 MHz, DMSO- d_6): 10.73 (1H, s), 8.55-8.60 (2H, m), 8.46 (1H, s), 7.86 (1H, dd, $J = 7.8$ Hz, 2.7 Hz), 3.76 (2H, t, $J = 6.0$ Hz), 3.27 (2H, t, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, DMSO- d_6): 179.53, 164.52, 161.16, 139.31, 137.93, 133.53, 133.48, 123.69, 123.34, 118.51, 118.37, 113.47, 118.15, 47.6, 23.08; HRMS (ESI) calculated for $C_{10}H_9BrFN_3O_2S_2H (M+H)^+$ 365.9376, found 365.9209; HPLC retention time 3.06 min.

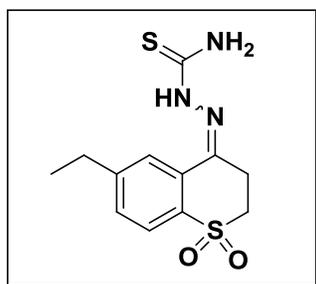


6-Bromo-8-fluoro-1,1-dioxothiochroman-4-one thiosemicarbazone (27): Sulfone **7c** (0.031 g, 0.106 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.012 g, 0.132 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 12 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **27** was obtained as a solid (0.010 g, 0.0274 mmol, 26 % yield). 1H NMR (300 MHz, DMSO- d_6): 9.83 (1H, s), 8.50-8.51 (1H, m), 8.33 (1H, s),

7.85 (1H, s), 7.69 (1H, dd, $J = 9.9$ Hz, 1.8 Hz), 3.76-3.80 (2H, m), 3.53-3.58 (2H, m); ^{13}C NMR (75 MHz, DMSO- d_6): 180.0, 158.4 (d, $J_{\text{C-F}} = 256.4$ Hz), 139.0 (d, $J_{\text{C-F}} = 3.6$ Hz), 136.4, 127.4 (d, $J_{\text{C-F}} = 10.6$ Hz), 126.0, 125.9 (d, $J_{\text{C-F}} = 2.8$ Hz), 121.3 (d, $J_{\text{C-F}} = 24$ Hz), 48.0, 24.0 ; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_9\text{BrFN}_3\text{O}_2\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 365.9376, found 365.9377; HPLC retention time 3.47 min.

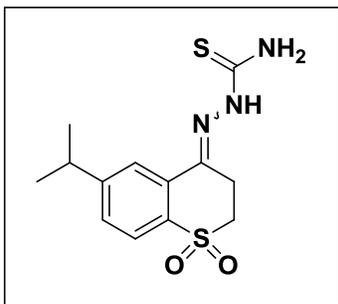


6-Methyl-1,1-dioxothiochroman-4-one thiosemicarbazone (28): Sulfone **8c** (0.274 g, 1.30 mmol) was dissolved in anhydrous methanol (30 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.160 g, 1.73 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 12 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **28** was obtained as a white solid (0.215 g, 0.758 mmol, 58 % yield). ^1H NMR (300 MHz, DMSO- d_6): 10.58 (1H, s), 8.59 (1H, s), 8.37 (1H, s), 8.27 (1H, s), 7.72 (1H, d, $J = 9.0$ Hz), 7.44 (1H, d, $J = 9.0$ Hz), 3.63 (2H, t, $J = 6.0$ Hz), 3.28 (2H, t, $J = 6.0$ Hz), 2.42 (3H, s); ^{13}C NMR (75 MHz, DMSO- d_6): 179.5, 143.3, 140.1, 135.1, 132.4, 130.6, 127.0, 122.5, 45.9, 24.5, 21.0; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_2\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 284.0522, found 284.0524, HPLC retention time 5.36 min.

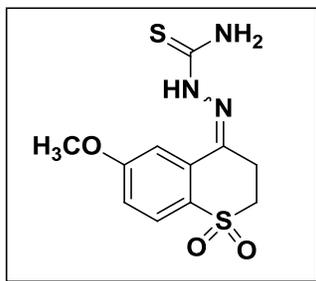


6-Ethyl-1,1-dioxothiochroman-4-one-thiosemicarbazone (29): Sulfone **9b** (0.067 g, 0.300 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at reflux for 15 min, then thiosemicarbazide (0.033 g, 0.36 mmol) a catalytic amount of *p*-toluenesulfonic acid were added. After 16 h at reflux, the resulting precipitate was

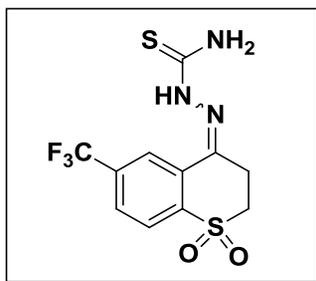
collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **29** was obtained as a light yellow solid (0.043 g, 0.15 mmol, 48% yield). ^1H NMR (500 MHz, DMSO- d_6): δ 10.56 (1H, s), 8.57 (1H, bs), 8.35 (1H, bs), 8.26 (1H, bs), 7.74 (1H, d, $J = 8.5$ Hz), 7.48 (1H, dd, $J = 1.5$ Hz, 1.0 Hz), 3.63 (2H, t, $J = 6.5$ Hz), 3.28 (2H, t, $J = 6.5$ Hz), 2.71 (2H, q, $J = 7.5$ Hz), 1.20 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6): δ 180.0, 150.0, 140.7, 135.8, 133.0, 129.9, 126.7, 123.2, 46.4, 28.6, 25.1, 16.1; HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2\text{S}_2$ 297.0606, found 297.0606; HPLC retention time 7.73 min.



6-Isopropyl-1,1-dioxothiochroman-4-one thiosemicarbazone (30): Sulfone **10c** (0.180 g, 0.754 mmol) was dissolved in anhydrous methanol (12 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.072 g, 0.791 mmol) and a catalytic amount of *p*-toluenesulfonic acid was added. After 36 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **30** was obtained as a white solid (0.113 g, 0.362 mmol, 48% yield). ^1H NMR (500 MHz, DMSO- d_6): δ 10.54 (1H, s), 8.57 (1H, s), 8.31 (1H, s), 8.25 (1H, s), 7.76 (1H, d, $J = 8.0$ Hz), 7.53 (1H, d, $J = 8.0$ Hz), 3.63 (2H, t, $J = 6.0$ Hz), 3.28 (2H, t, $J = 6.5$ Hz), 3.07 (1H, m), 1.23 (6H, d, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6): δ 179.9, 154.5, 140.9, 135.9, 133.0, 128.1, 125.6, 123.3, 46.3, 34.0, 25.1, 23.9; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_2\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 312.0835, found 312.0836; HPLC retention time 9.19 min.

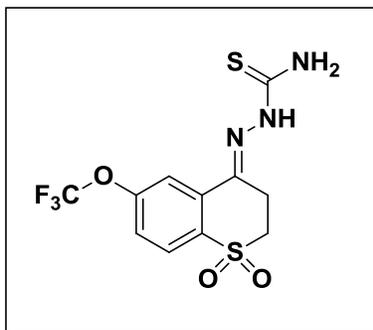


6-Methoxy-1,1-dioxothiochroman-4-one thiosemicarbazone (31): Sulfone **11c** (0.091 g, 0.400 mmol) was dissolved in anhydrous methanol (10 mL). The mixture was heated at reflux for 15 min, and then thiosemicarbazide (0.053 g, 0.580 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **31** was obtained as a white solid (0.092 g, 0.31 mmol, 77% yield). ¹H NMR (500 MHz, DMSO-*d*₆): δ 10.54 (1H, s), 8.54 (1H, bs), 8.30 (1H, bs), 7.88 (1H, d, *J* = 3 Hz), 7.77 (1H, d, *J* = 9 Hz), 7.18 (1H, dd, *J* = 8.5 Hz, 2.5 Hz), 3.89 (3H, s), 3.60 (2H, t, *J* = 6.5 Hz), 3.28 (2H, t, *J* = 6.5 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 179.5, 162.4, 140.2, 134.6, 130.2, 124.8, 116.1, 111.2, 55.9, 46.0, 24.8; HRMS (ESI) calculated for C₁₁H₁₃N₃O₃S₂ 299.0398, found 299.0401; HPLC retention time 5.50 min.

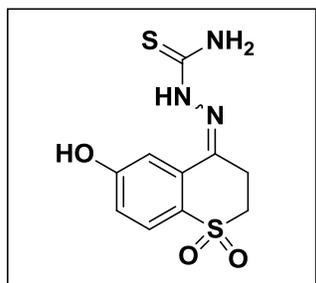


6-Trifluoromethyl-1,1-dioxothiochroman-4-one thiosemicarbazone (32): Sulfone **13c** (0.043 g, 0.160 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at reflux for 15 min, and thiosemicarbazide (0.017 g, 0.19 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **32** was obtained as a light yellow solid (0.032 g, 0.090 mmol, 58 % yield). ¹H NMR (500 MHz, DMSO-*d*₆): δ 10.63 (1H, s), 8.83 (1H, bs), 8.61 (1H, bs), 8.56 (1H, bs), 8.05 (1H, d, *J* = 8.0 Hz), 7.96 (1H, d, *J* = 7.5 Hz), 3.77 (2H, t, *J* =

6.5 Hz), 3.33 (2H, t, $J_1 = 6.5$ Hz); ^{13}C NMR (125 MHz, acetone- d_6): δ 180.8, 141.5 (d, $J_{C-F} = 0.88$ Hz), 138.4, 134.3, 134.0 (q, $J_{C-F} = 32.4$ Hz), 126.3 (q, $J_{C-F} = 3.6$ Hz), 124.4, 123.8 (q, $J_{C-F} = 4.1$ Hz), 123.5 (q, $J_{C-F} = 271.2$ Hz), 46.0, 24.3; HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{N}_3\text{O}_2\text{S}_2$ 337.0167, found 337.0166; HPLC retention time 8.40 min.

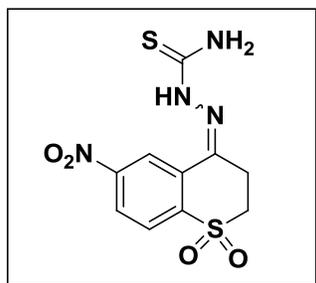


6-(Trifluoromethoxy)-1,1-dioxothiochroman-4-one thiosemicarbazone (33): Sulfone **14c** (0.060 g, 0.214 mmol) was dissolved in anhydrous methanol (10 mL). The solution was heated to reflux for 15 min, and then thiosemicarbazide (0.021 g, 0.225 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 36 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **33** was obtained as a white solid (0.005 g, 0.014 mmol, 7% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ 10.65 (1H, s), 8.61 (1H, s), 8.59 (1H, d, $J = 2.5$ Hz), 8.49 (1H, s), 7.97 (1H, d, $J = 8.5$ Hz), 7.61 (1H, dd, $J = 8.5$ Hz, 1 Hz), 3.73 (2H, t, $J = 5.0$ Hz), 3.30 (2H, t, $J = 5.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 180.1, 151.8, 139.3, 137.1, 136.2, 126.1, 122.6, 120.36 (1C, q, $J = 258$, CF_3), 120.35, 46.1, 25.1; HRMS (ESI) calculated for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_3\text{S}_2$ (M-H)- 352.0043, found 352.0049; HPLC retention time 9.11 min.

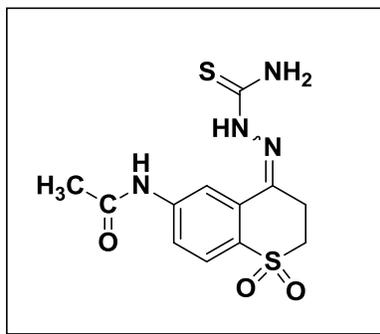


6-Hydroxy-1,1-dioxothiochroman-4-one thiosemicarbazone (34): Sulfone **16c** (0.045 g, 0.212 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at

reflux for 15 min, and thiosemicarbazide (0.05 g, 0.545 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 16 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **34** was obtained as a white solid (0.023 g, 0.081 mmol, 38% yield). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.43 (1H, s), 10.59 (1H, s), 8.53 (2H, s), 8.10 (2H, s), 7.74 (1H, s), 7.67 (1H, d, *J* = 8.4 Hz), 7.00 (1H, d, *J* = 8.1 Hz), 3.57 (2H, m), 3.26 (2H, m); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 179.5, 161.1, 140.4, 134.7, 128.7, 124.9, 117.1, 112.6, 46.1, 24.8; HRMS (ESI) calculated for C₁₀H₁₀N₃O₃S₂ (M-H)⁻ 284.0169, found 284.0170; HPLC retention time 3.59/3.74 min. (possibly E/Z isomers, although the LCMS showed only one peak)



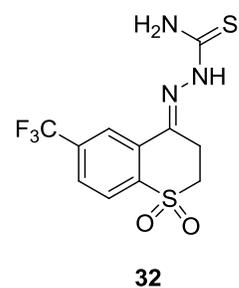
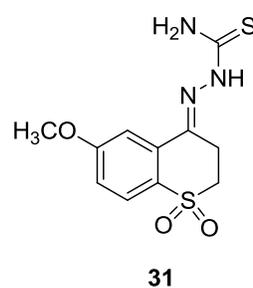
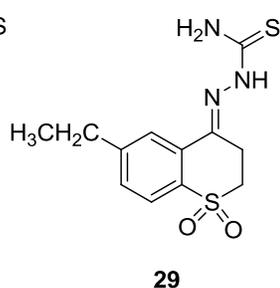
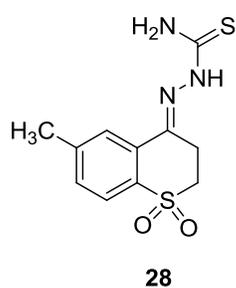
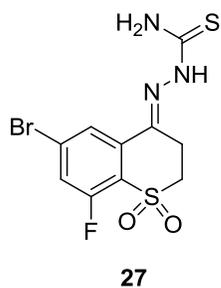
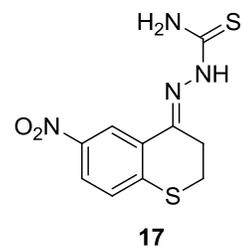
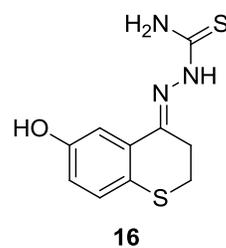
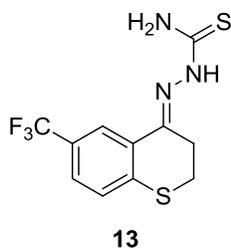
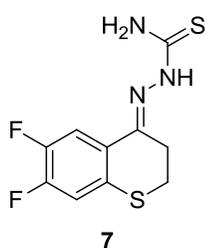
6-Nitro-1,1-dioxothiochroman-4-one thiosemicarbazone (35): Sulfone **17c** (0.033 g, 0.137 mmol) was dissolved in anhydrous methanol (8 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.015 g, 0.160 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **35** was obtained as an orange solid (0.026 g, 0.083 mmol, 60% yield). ¹H NMR (300 MHz, DMSO-*d*₆): 10.76 (1H, s), 9.13 (1H, d), 8.66 (1H, s), 8.55 (1H, s), 8.34 (1H, dd, *J* = 8.7 Hz, 2.1 Hz), 8.11 (1H, d, *J* = 8.7 Hz), 3.82 (2H, t, *J* = 6.0 Hz), 3.35 (2H, t, *J* = 6.3 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): 190.9, 179.7, 150.6, 141.8, 138.7, 134.8, 124.9, 124.2, 122.0, 45.4, 24.5; HRMS (ESI) calculated for C₁₀H₉N₄O₄S₂ (M-H)⁻ 313.0071, found 313.0074; HPLC retention time 6.10 min.



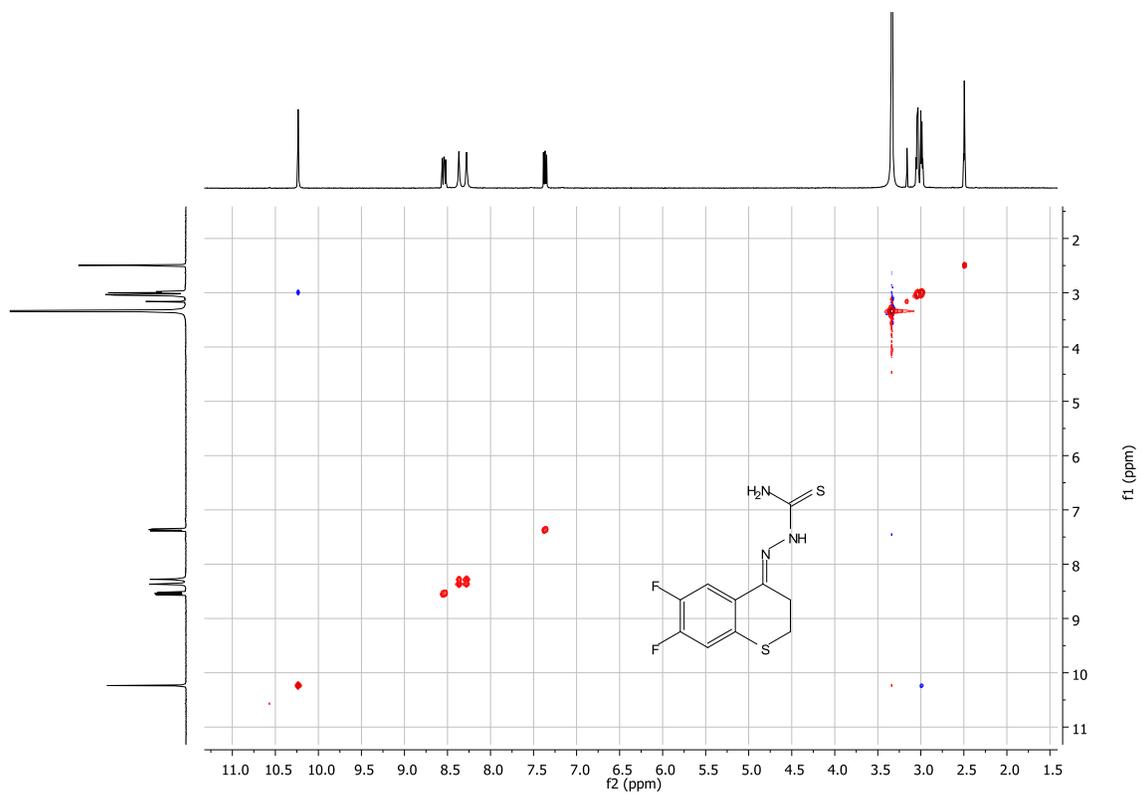
***N*-(1,1-dioxido-4-oxothiochroman-6-yl)acetamide thiosemicarbazone (36):** Sulfone **19c** (0.100 g, 0.395 mmol) was dissolved in anhydrous methanol (20 mL). The solution was heated at reflux for 15 min, and then thiosemicarbazide (0.0435 g, 0.479 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 10 h at reflux, the resulting precipitate was collected by filtration and washed with methanol. After drying under high vacuum, thiosemicarbazone **36** was obtained as a light yellow solid (0.091 g, 0.279 mmol, 71 % yield). ^1H NMR (500 MHz, DMSO- d_6): 10.82 (1H, s), 10.23 (1H, s), 8.75 (1H, s), 8.23 (1H, d, $J = 2.5$ Hz), 8.01 (1H, dd, $J = 8.5$ Hz, 2.0 Hz), 7.78 (1H, d, $J = 8.0$ Hz), 7.72 (1H, s), 3.63 (2H, t, $J = 6.5$ Hz), 3.28 (2H, t, $J = 6.5$ Hz), 2.09 (3H, s); ^{13}C NMR (75 MHz, DMSO- d_6): 180.2, 169.5, 143.5, 140.6, 134.0, 132.5, 124.4, 120.5, 116.4, 46.5, 25.2, 24.6; HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_3\text{S}_2\text{H}$ ($\text{M}+\text{H}$) $^+$ 327.0580, found 327.0579 ; HPLC retention time 4.25 min.

Summary of NOESY Experiments

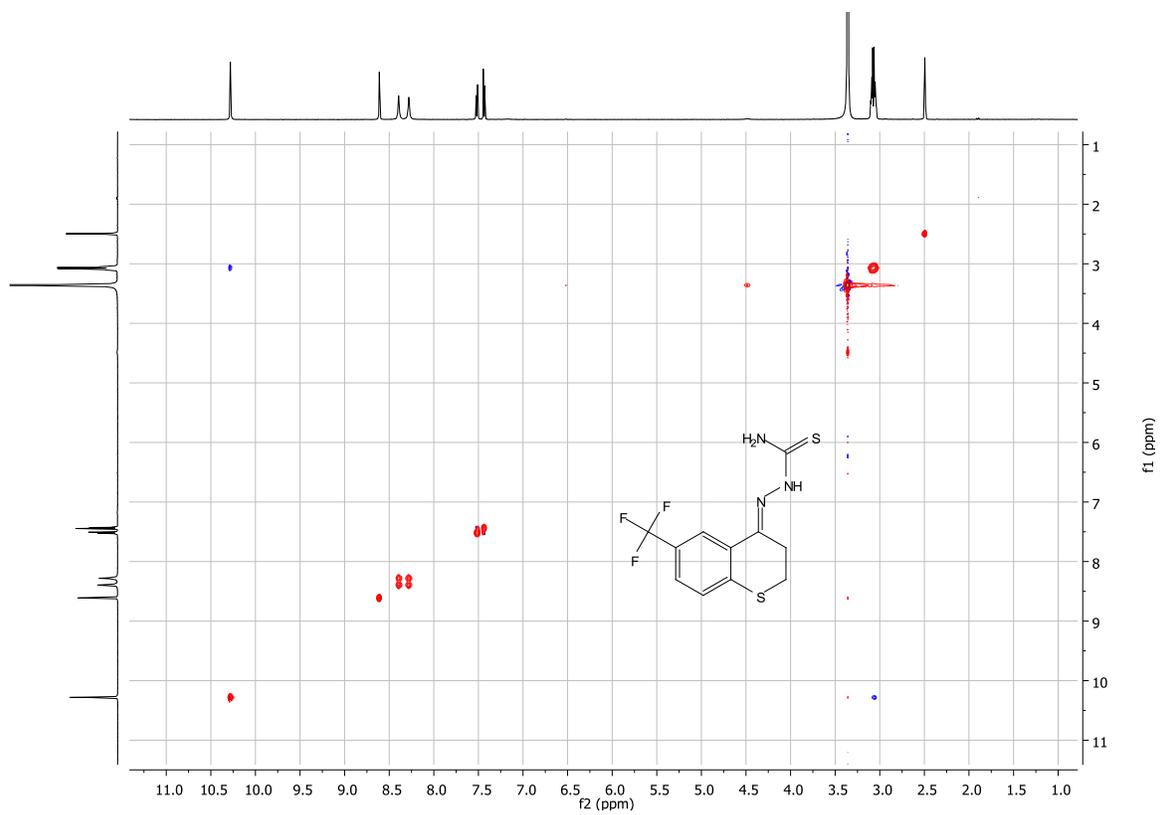
Non-symmetrical thiosemicarbazone derivatives can exist as geometrical isomers (*E* and *Z*). NOESY (Nuclear Overhauser Effect Spectroscopy) experiments can provide through-space molecular proximity information (within approximately 5 angstroms). NOESY data for nine compounds (structures below) confirmed a correlation between the N-H proton and the methylene (CH₂) protons at C-3, thus indicating the *E*-configuration for each of these compounds.



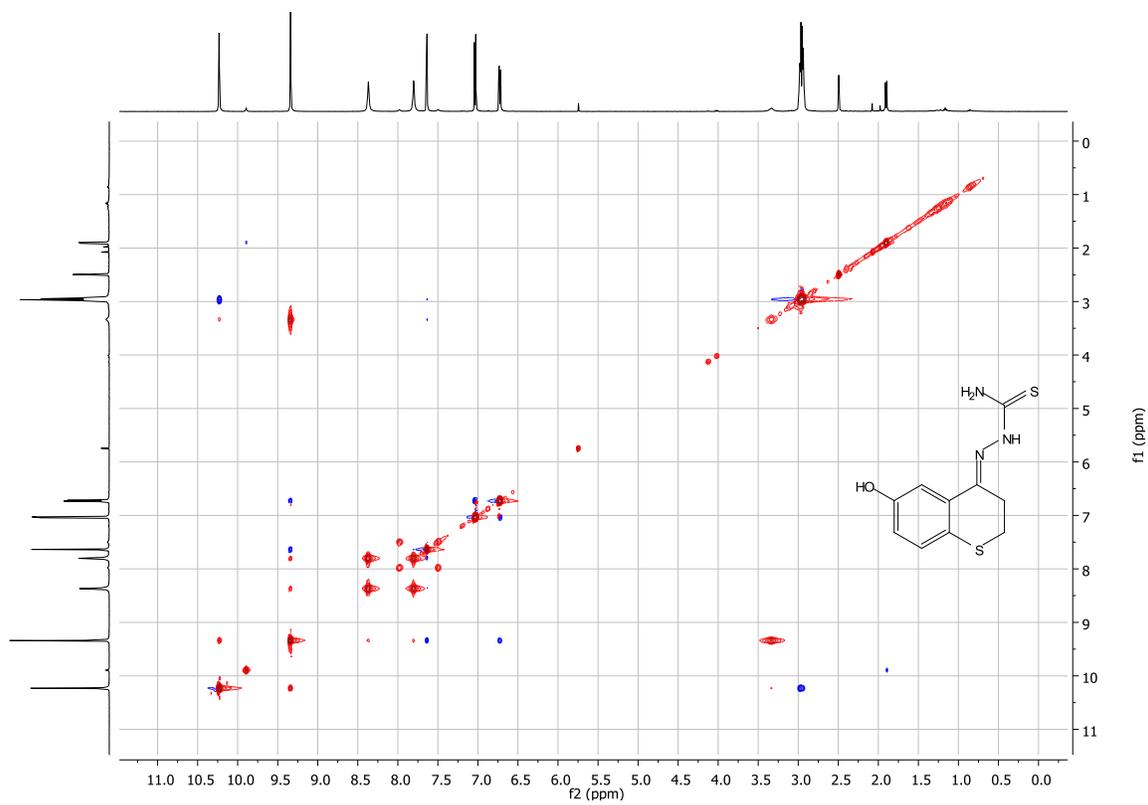
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 4



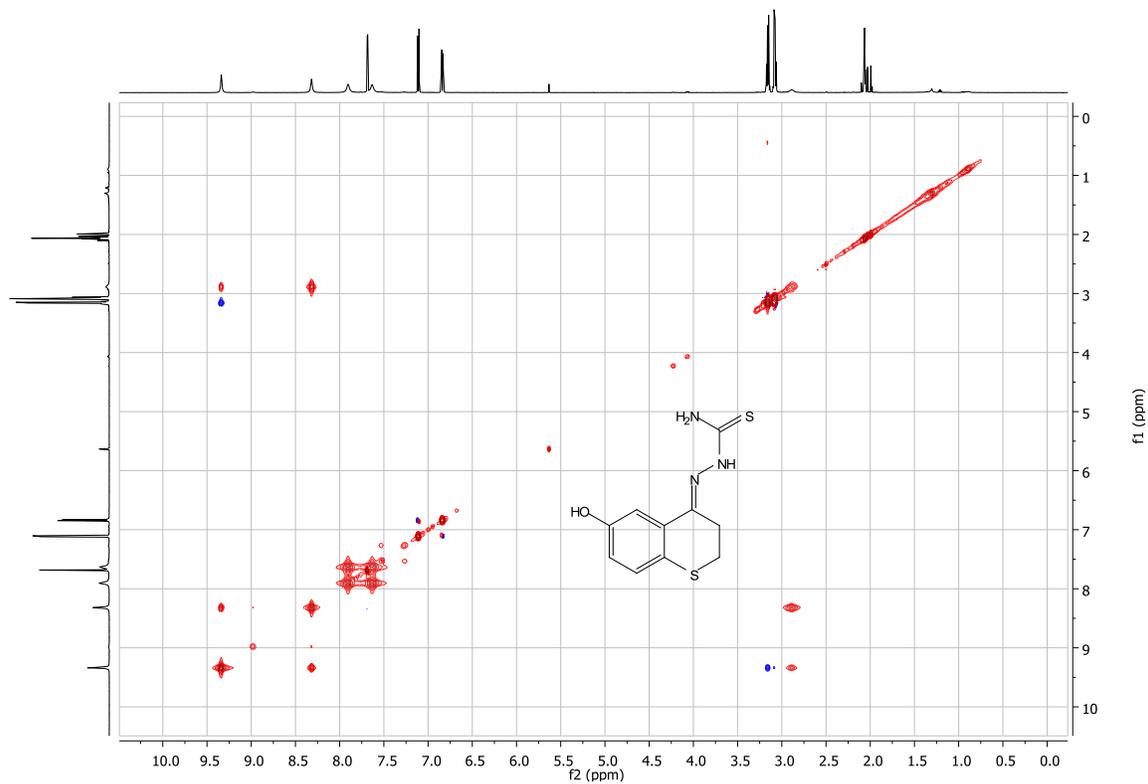
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 13



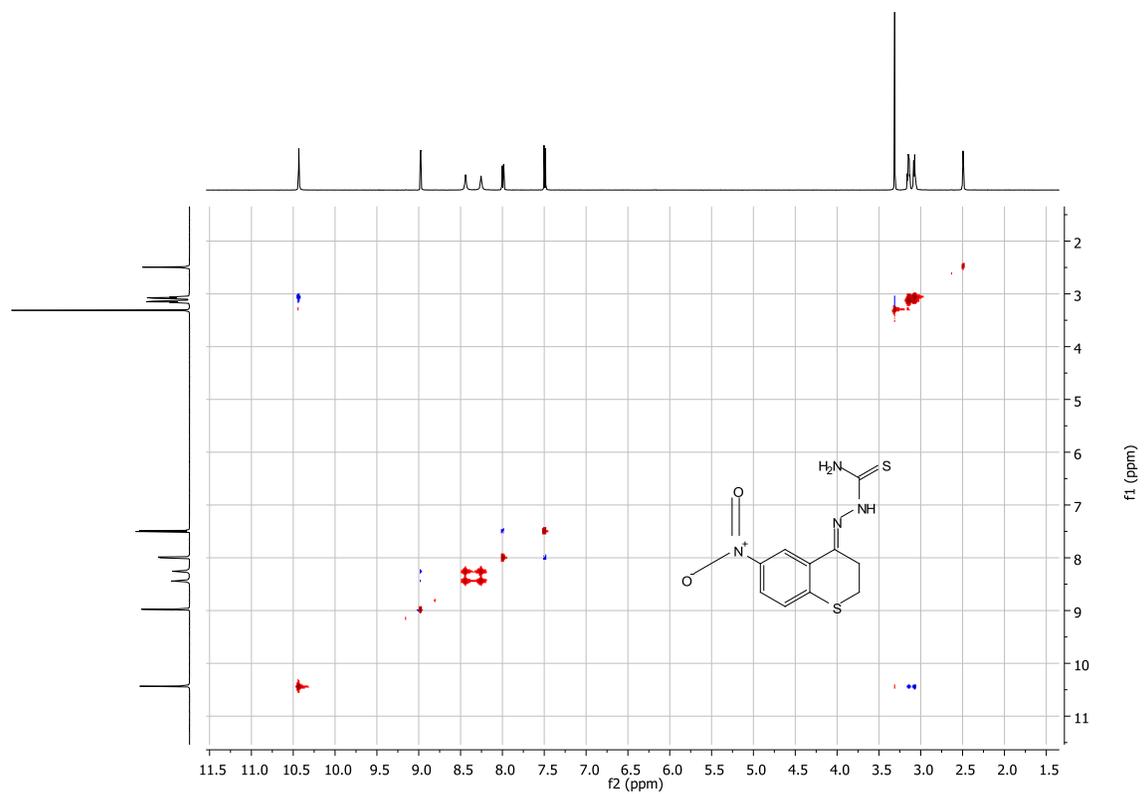
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 16



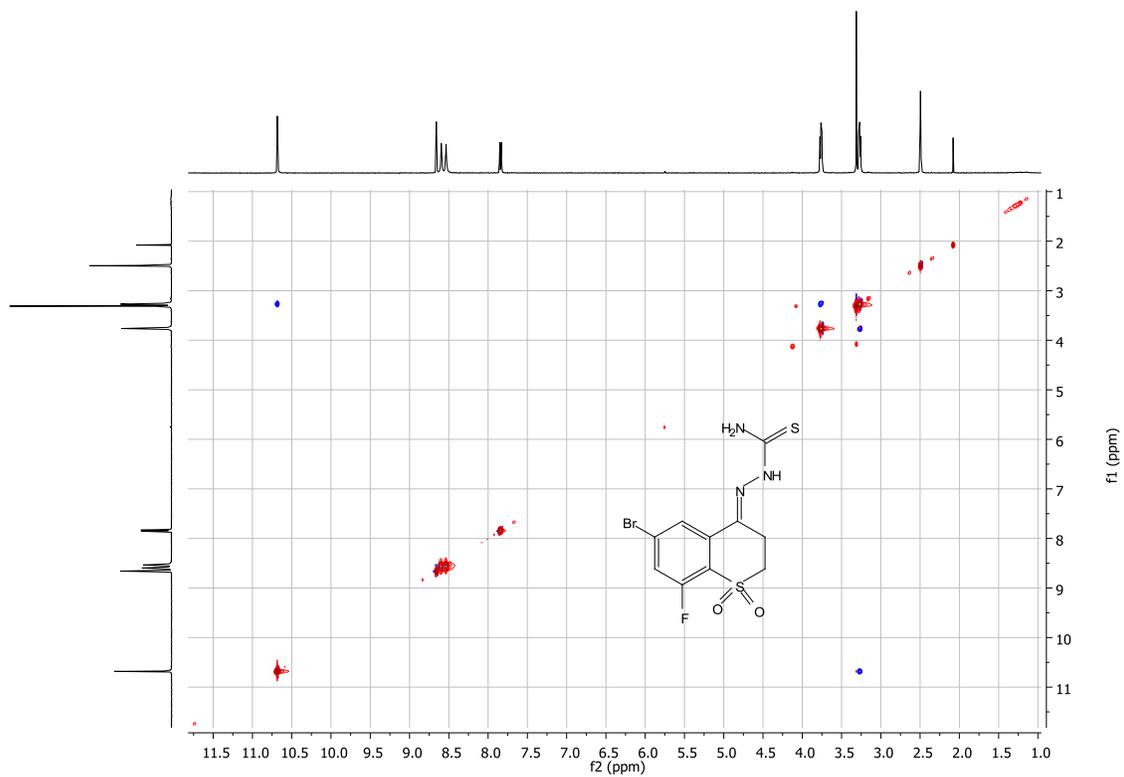
Noesy ^1H - ^1H (500 MHz, Acetone- d_6) of Compound 16



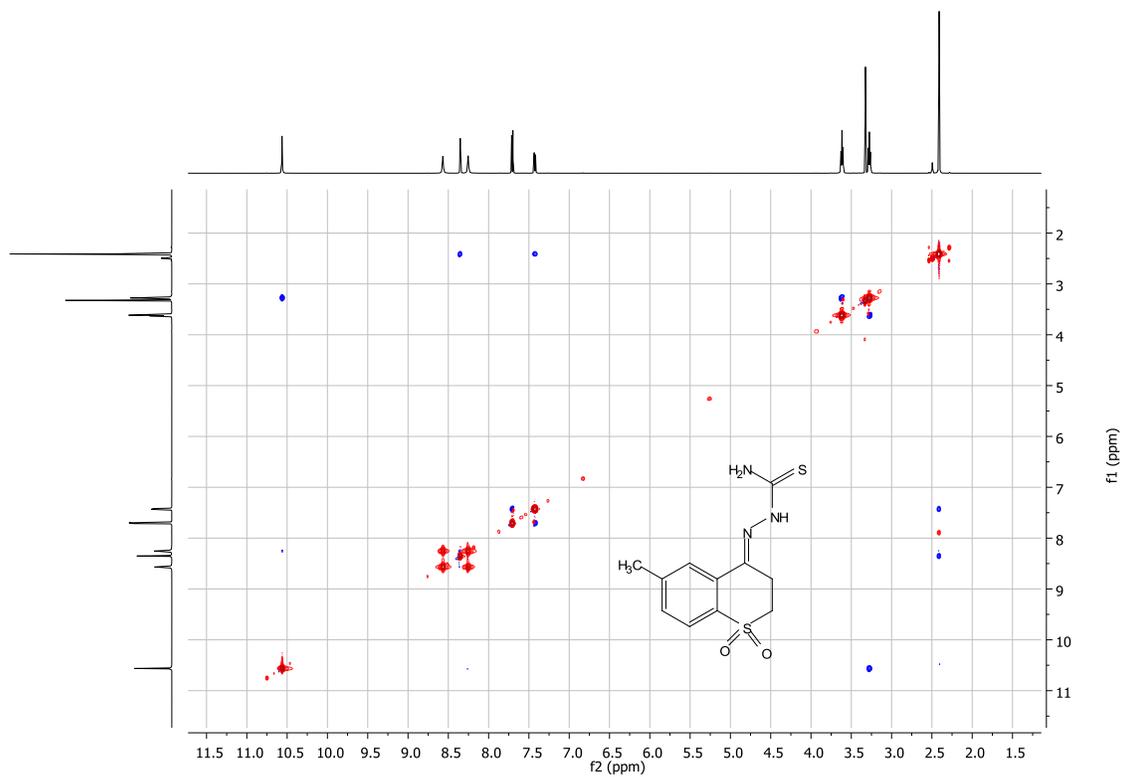
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 17



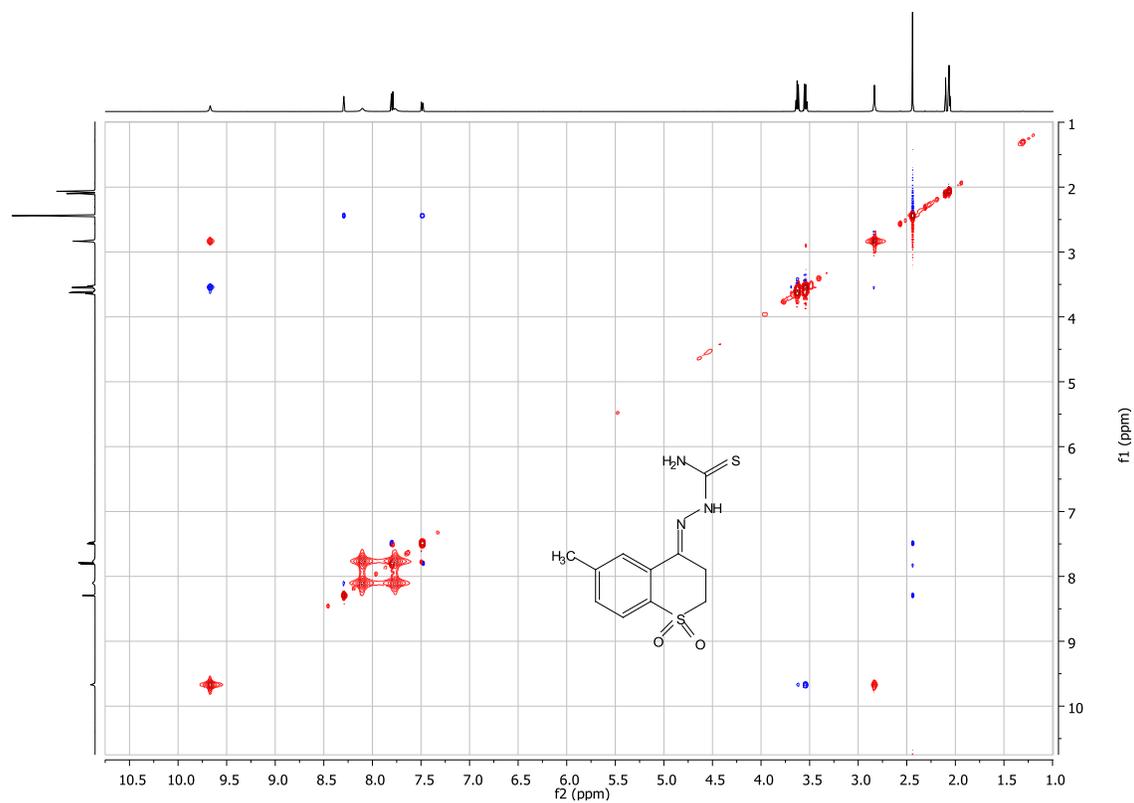
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 27



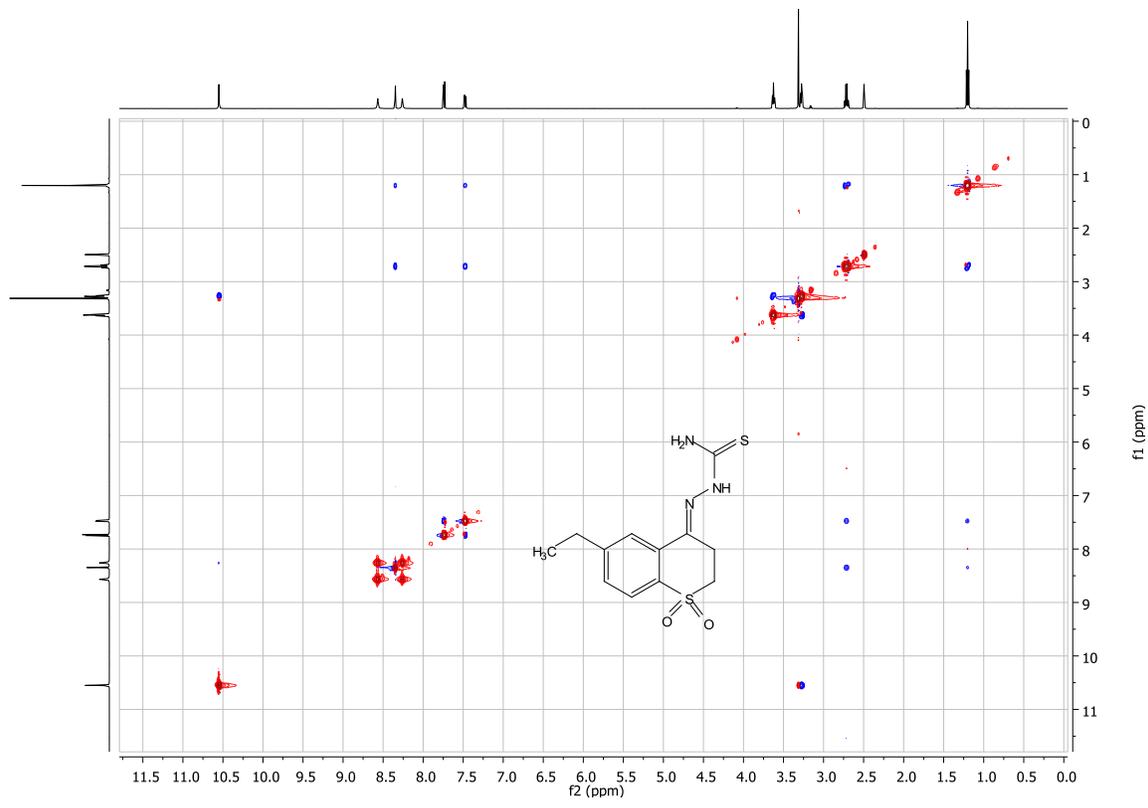
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 28



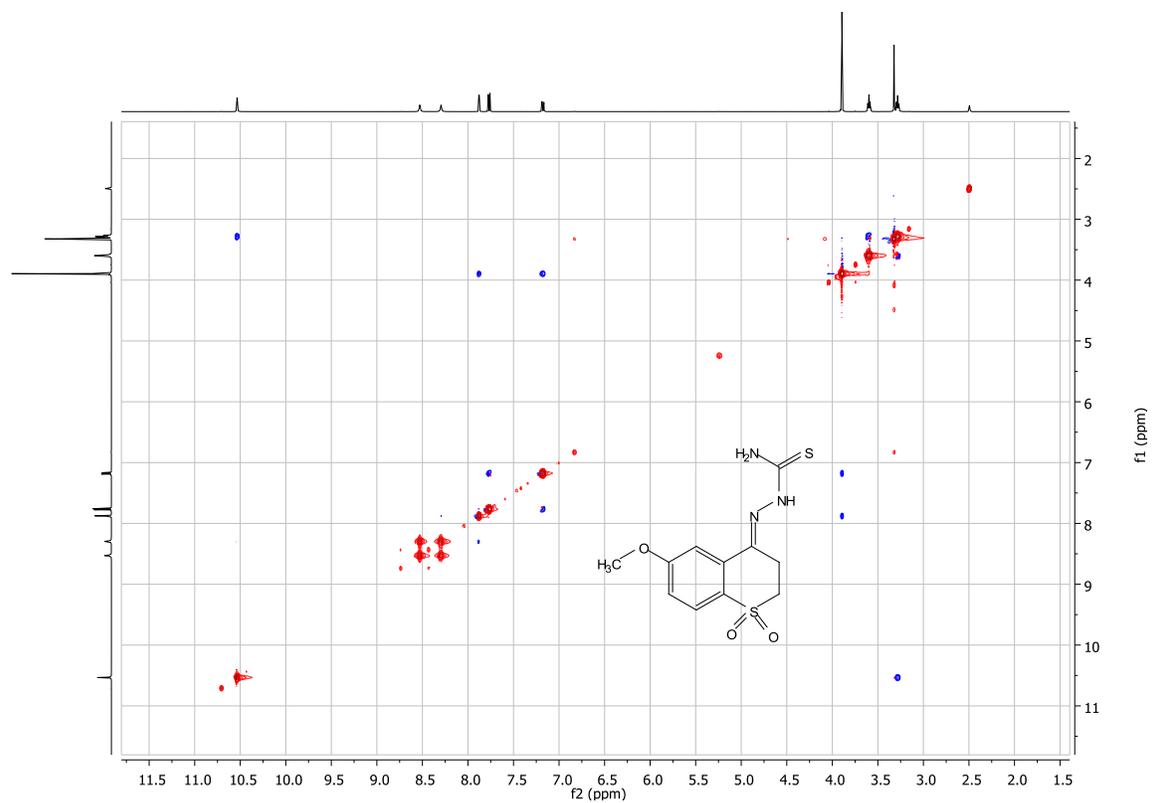
Noesy ^1H - ^1H (500 MHz, Acetone- d_6) of Compound 28



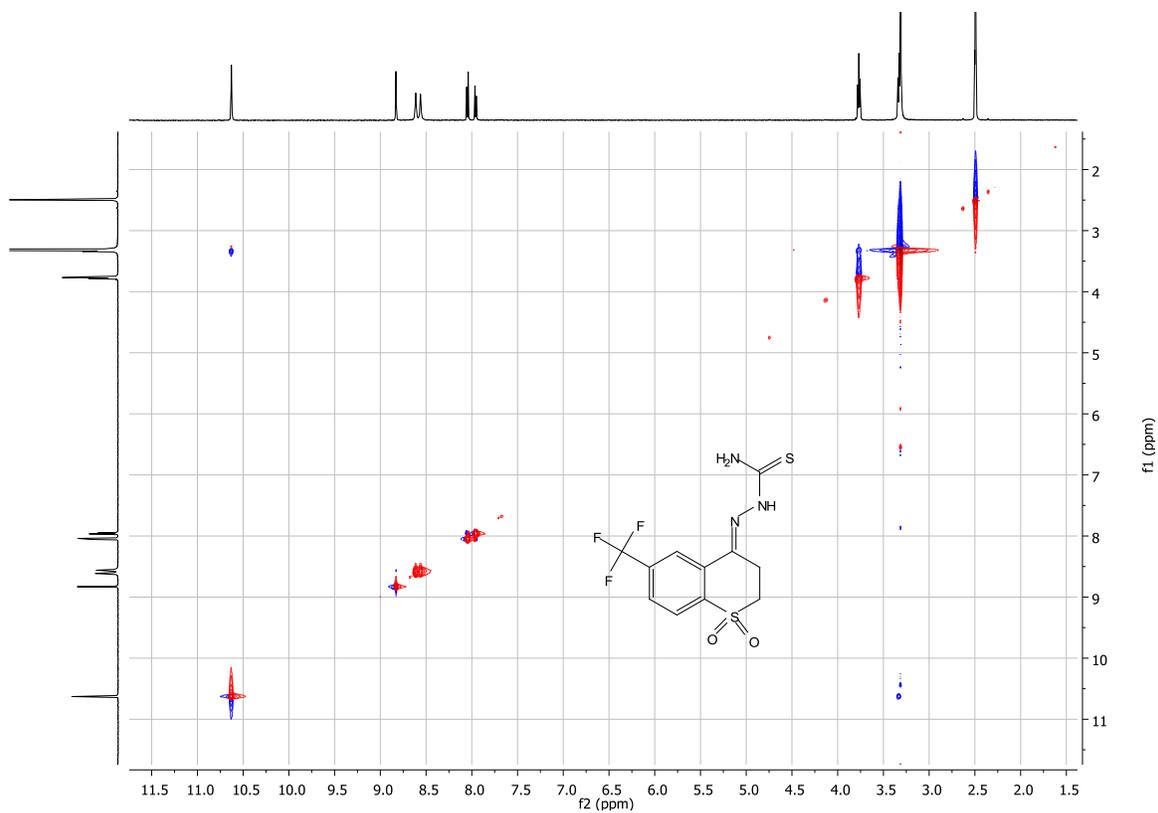
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 29



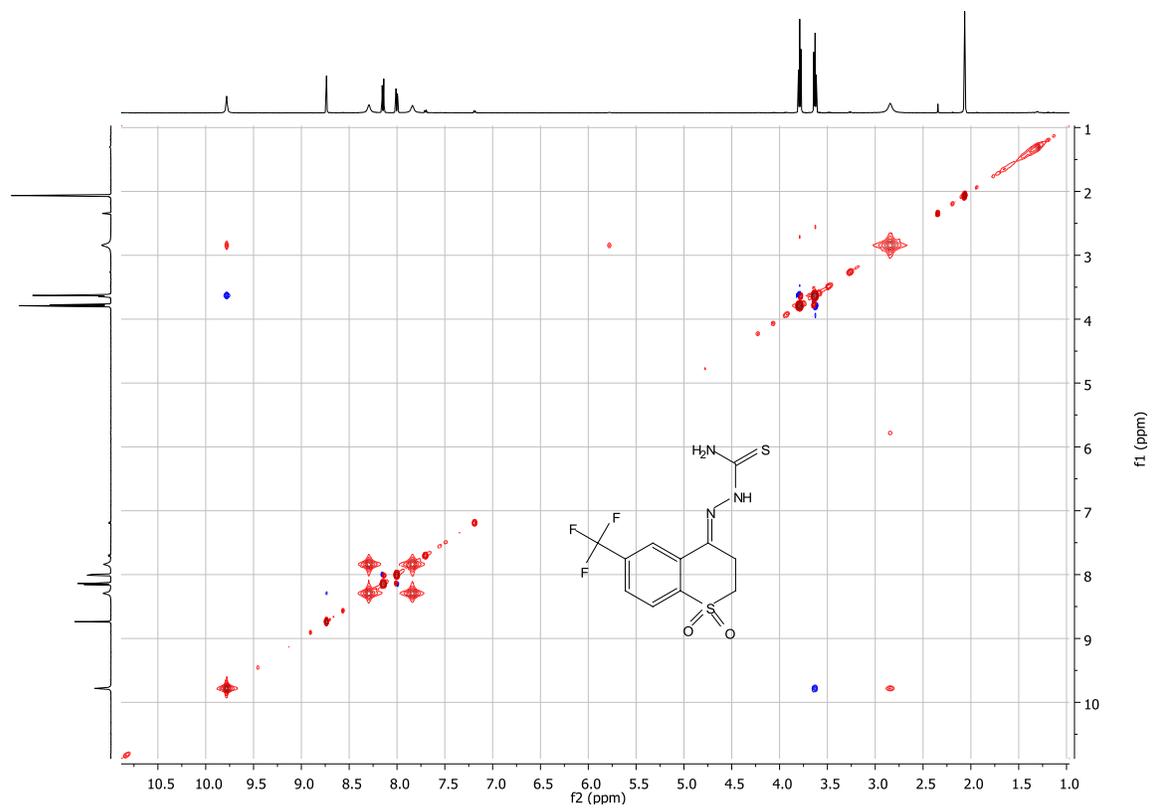
Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 31



Noesy ^1H - ^1H (500 MHz, DMSO- d_6) of Compound 32



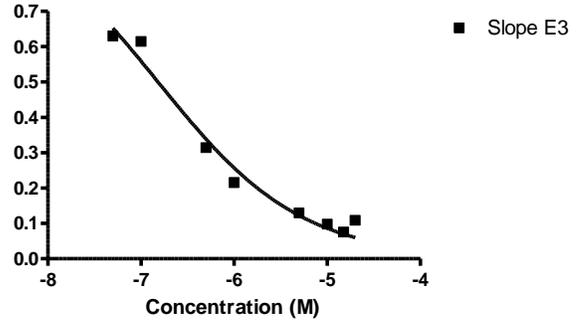
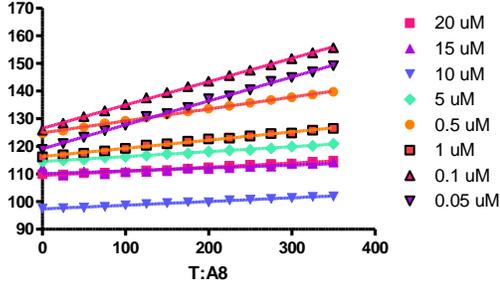
Noesy ^1H - ^1H (500 MHz, Acetone- d_6) of Compound 32



Cathepsin L IC₅₀ ± Standard Error:

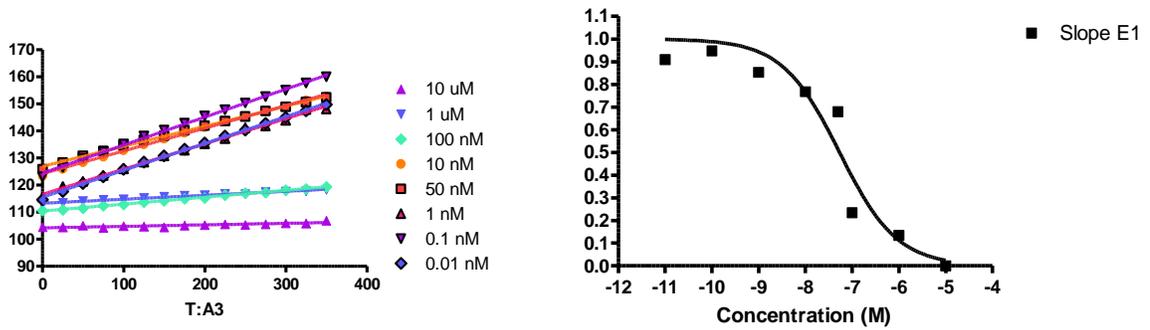
compound	R	X	IC ₅₀ (nM) ^a Cat L	compound	R	X	IC ₅₀ (nM) ^a Cat L
1	6-F	S	741±23.3	19	6-NHAc	S	>10,000
2	6-Cl	S	228±11.58	20	fused 5,6-phenyl	S	>10,000
3	6-Br	S	152±2.7	21	6-F	SO ₂	>10,000
4	6,7-F	S	46±7.6	22	6-Cl	SO ₂	>10,000
5	6,8-F	S	1,500±100.1	23	6-Br	SO ₂	574±37.43
6	6-F,8-Br	S	>10,000	24	6,7-F	SO ₂	3,650±378
7	6-Br,8-F	S	434±14.78	25	6,8-F	SO ₂	>10,000
8	6-CH ₃	S	214±16.42	26	6-F,8-Br	SO ₂	>10,000
9	6-CH ₂ CH ₃	S	2,720±240	27	6-Br,8-F	SO ₂	1,117±102.7
10	6- <i>i</i> -Pr	S	>10,000	28	6-CH ₃	SO ₂	>10,000
11	6-OCH ₃	S	>10,000	29	6-CH ₂ CH ₃	SO ₂	6,521±490
12	6-SCH ₃	S	>10,000	30	6- <i>i</i> -Pr	SO ₂	>10,000
13	6-CF ₃	S	284±10.71	31	6-OCH ₃	SO ₂	>10,000
14	6-OCF ₃	S	256±26.4	32	6-CF ₃	SO ₂	260±34.4
15	8-OCF ₃	S	>10,000	33	6-OCF ₃	SO ₂	3,960±40
16	6-OH	S	>10,000	34	6-OH	SO ₂	>10,000
17	6-NO ₂	S	68±4.46	35	6-NO ₂	SO ₂	112±4
18	6-NH ₂	S	>10,000	36	6-NHAc	SO ₂	>10,000

Compound 3



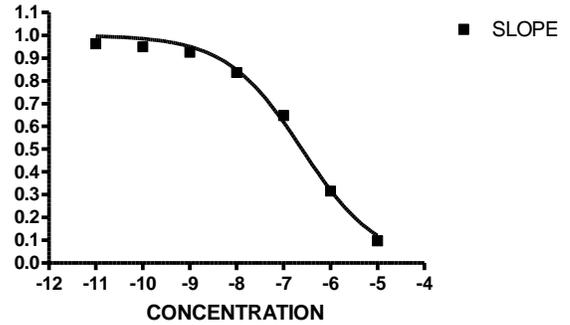
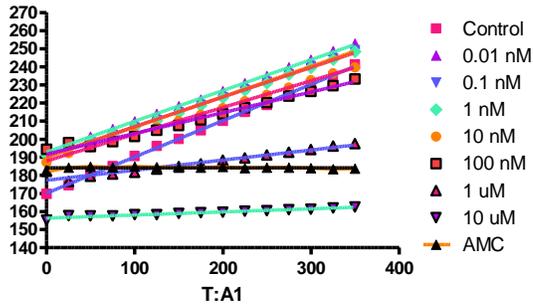
	Slope E3
Sigmoidal dose-response (variable slope)	
Best-fit values	
Bottom	= 0.0
Top	= 1.000
LogEC50	-6.816
HillSlope	-0.5644
EC50	1.526e-007
Std. Error	
LogEC50	0.06579
HillSlope	0.04878
95% Confidence Intervals	
LogEC50	-6.977 to -6.655
HillSlope	-0.6838 to -0.4450
EC50	1.053e-007 to 2.211e-007
Goodness of Fit	
Degrees of Freedom	6
R square	0.9769
Absolute Sum of Squares	0.008461
Sy.x	0.03755
Constraints	
Bottom	Bottom = 0.0
Top	Top = 1.000
Number of points	
Analyzed	8

Compound 4



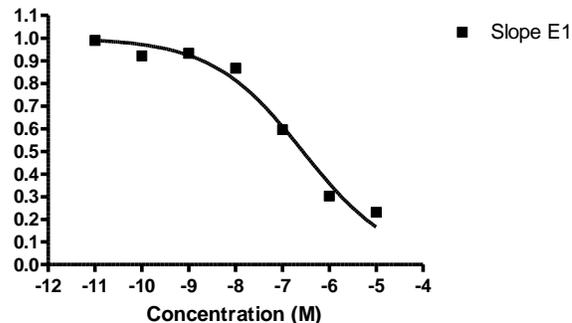
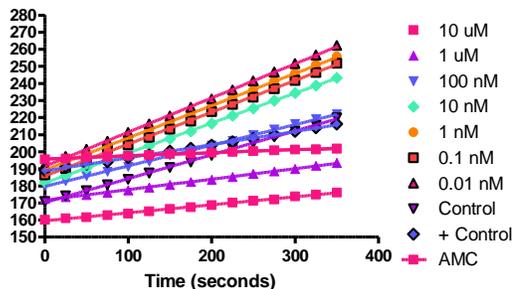
	Slope E1
Sigmoidal dose-response (variable slope)	
Best-fit values	
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Top	= 1.000
LogEC50	-7.267
HillSlope	-0.7054
EC50	5.404e-008
Std. Error	
LogEC50	0.1656
HillSlope	0.2121
95% Confidence Intervals	
LogEC50	-7.673 to -6.862
HillSlope	-1.224 to -0.1865
EC50	2.126e-008 to 1.374e-007
Goodness of Fit	
Degrees of Freedom	6
R square	0.9296
Absolute Sum of Squares	0.07157
Sy.x	0.1092
Constraints	
Bottom	Bottom = 0.0
Top	Top = 1.000
Number of points	
Analyzed	8

Compound 8



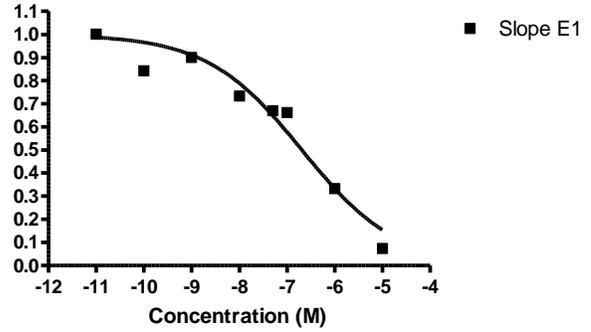
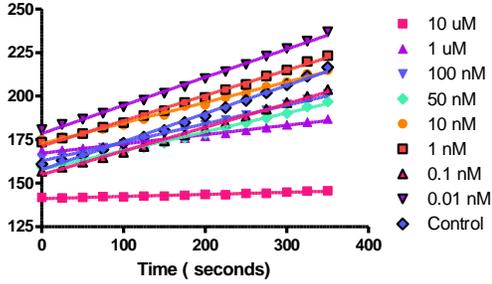
Sigmoidal dose-response (variable slope)	
Best-fit values	
Bottom	= 0.0
Top	= 1.000
LogEC50	-6.608
HillSlope	-0.5365
EC50	2.465e-007
Std. Error	
LogEC50	0.06685
HillSlope	0.04084
95% Confidence Intervals	
LogEC50	-6.780 to -6.436
HillSlope	-0.6415 to -0.4315
EC50	1.659e-007 to 3.662e-007
Goodness of Fit	
Degrees of Freedom	5
R square	0.9936
Absolute Sum of Squares	0.004543
Sy.x	0.03014
Constraints	
Bottom	Bottom = 0.0
Top	Top = 1.000
Number of points	
Analyzed	7

Compound 13



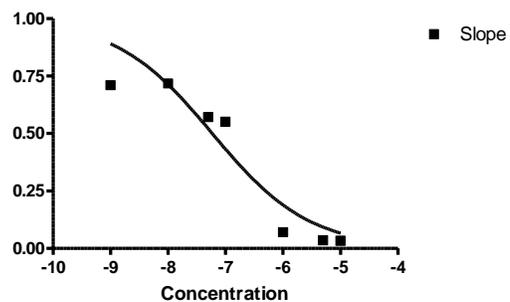
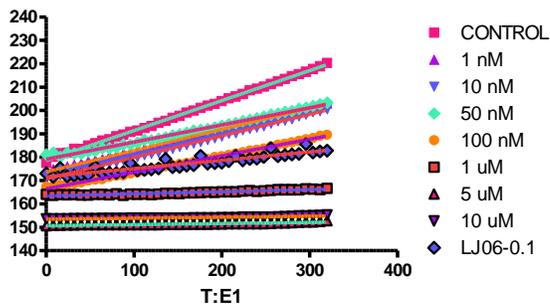
	Slope E1
Sigmoidal dose-response (variable slope)	
Best-fit values	
Bottom	= 0.0
Top	= 1.000
LogEC50	-6.565
HillSlope	-0.4457
EC50	2.726e-007
Std. Error	
LogEC50	0.1250
HillSlope	0.05483
95% Confidence Intervals	
LogEC50	-6.886 to -6.243
HillSlope	-0.5867 to -0.3047
EC50	1.300e-007 to 5.713e-007
Goodness of Fit	
Degrees of Freedom	5
R square	0.9786
Absolute Sum of Squares	0.01290
Sy.x	0.05080
Constraints	
Bottom	Bottom = 0.0
Top	Top = 1.000
Number of points	
Analyzed	7

Compound 14



	Slope E1
Sigmoidal dose-response (variable slope)	
Best-fit values	
Bottom	= 0.0
Top	= 1.000
LogEC50	-6.689
HillSlope	-0.4370
EC50	2.047e-007
Std. Error	
LogEC50	0.1621
HillSlope	0.07406
95% Confidence Intervals	
LogEC50	-7.086 to -6.292
HillSlope	-0.6182 to -0.2557
EC50	8.208e-008 to 5.103e-007
Goodness of Fit	
Degrees of Freedom	6
R square	0.9510
Absolute Sum of Squares	0.03255
Sy.x	0.07365
Constraints	
Bottom	Bottom = 0.0
Top	Top = 1.000
Number of points	
Analyzed	8

Compound 17



Sigmoidal dose-response (variable slope)

Best-fit values

Bottom

= 0.0

Top

= 1.000

LogEC50

-7.228

HillSlope

-0.5147

EC50

5.911e-008

Std. Error

LogEC50

0.2157

HillSlope

0.1360

95% Confidence Intervals

LogEC50

-7.783 to -6.674

HillSlope

-0.8643 to -0.1651

EC50

1.648e-008 to 2.120e-007

Goodness of Fit

Degrees of Freedom

5

R square

0.8915

Absolute Sum of Squares

0.06771

Sy.x

0.1164

Constraints

Bottom

Bottom = 0.0

Top

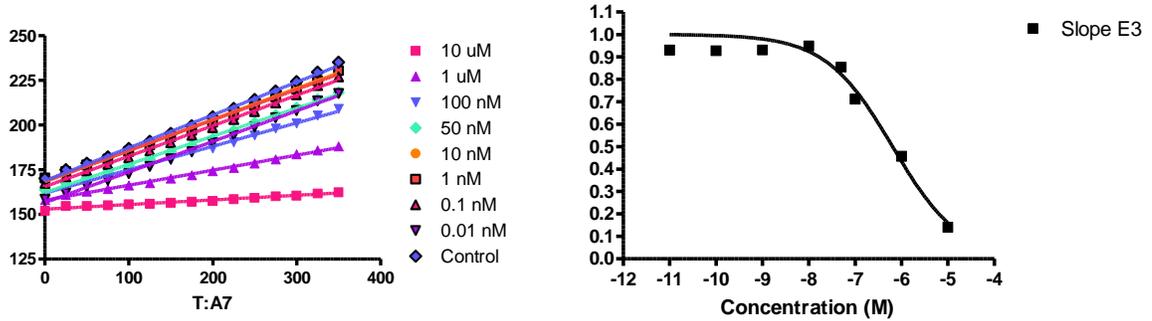
Top = 1.000

Number of points

Analyzed

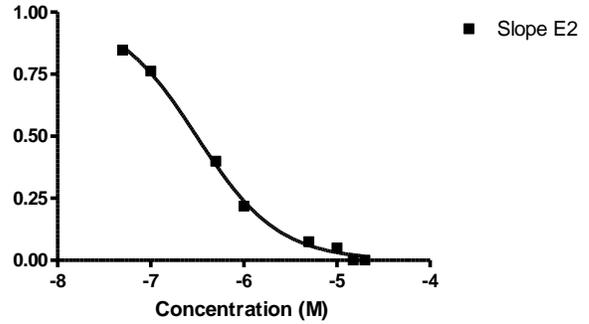
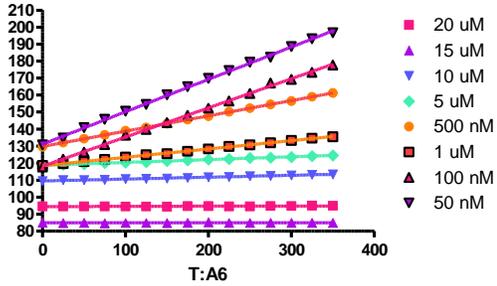
7

Compound 23



	Slope E3
Sigmoidal dose-response (variable slope)	
Best-fit values	
Bottom	= 0.0
Top	= 1.000
LogEC50	-6.191
HillSlope	-0.5997
EC50	6.435e-007
Std. Error	
LogEC50	0.1031
HillSlope	0.07438
95% Confidence Intervals	
LogEC50	-6.444 to -5.939
HillSlope	-0.7817 to -0.4177
EC50	3.598e-007 to 1.151e-006
Goodness of Fit	
Degrees of Freedom	6
R square	0.9735
Absolute Sum of Squares	0.01603
Sy.x	0.05170
Constraints	
Bottom	Bottom = 0.0
Top	Top = 1.000
Number of points	
Analyzed	8

Compound 32



	Slope E2
Sigmoidal dose-response (variable slope)	
Best-fit values	
Bottom	= 0.0
Top	= 1.000
LogEC50	-6.507
HillSlope	-0.9907
EC50	3.113e-007
Std. Error	
LogEC50	0.02184
HillSlope	0.04243
95% Confidence Intervals	
LogEC50	-6.560 to -6.453
HillSlope	-1.095 to -0.8869
EC50	2.753e-007 to 3.521e-007
Goodness of Fit	
Degrees of Freedom	6
R square	0.9974
Absolute Sum of Squares	0.002110
Sy.x	0.01875
Constraints	
Bottom	Bottom = 0.0
Top	Top = 1.000
Number of points	
Analyzed	8

Molecular Modeling of compound **4** in the active site of cathepsin L

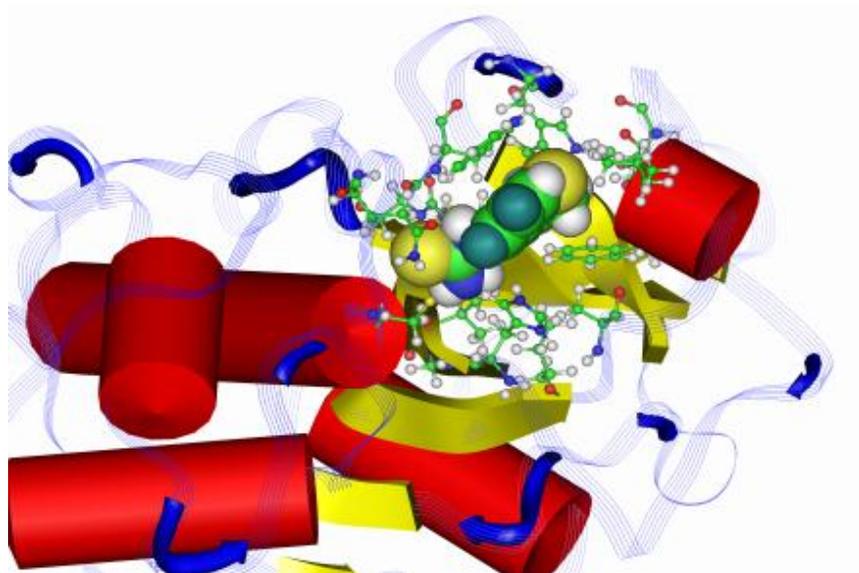


Figure S1. Compound **4** modeled at the active site of cathepsin L: oxygen (red), carbon (green), nitrogen (blue), hydrogen (white), sulfur (yellow), fluorine (teal). This represents a frame with one of the best interaction energies. The Cys25 thiolate - thiocarbonyl carbon of compound **4** has distance of 3.51 Å, close enough to allow covalent interaction. The inhibitor is in the S_1 - S_1' subsites.

X-ray crystallography

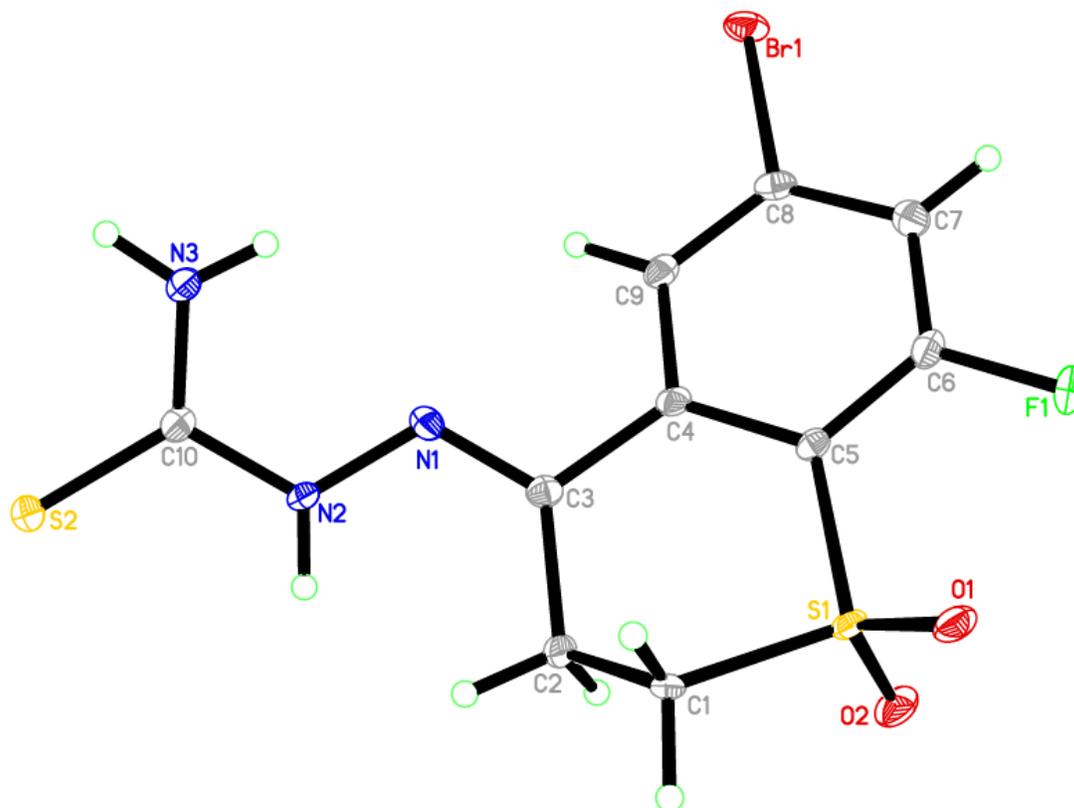


Figure S2. X-ray crystallography of compound **27**

Table S1. Crystal data and structure refinement for compound **27**.

Identification code	kp18	
Empirical formula	C ₁₀ H ₉ Br F N ₃ O ₂ S ₂	
Formula weight	366.23	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.1795(5) Å	a = 90°.
	b = 7.0816(4) Å	b = 103.820(3)°.
	c = 18.5193(11) Å	g = 90°.
Volume	1296.36(12) Å ³	
Z	4	

Density (calculated)	1.876 Mg/m ³
Absorption coefficient	3.505 mm ⁻¹
F(000)	728
Crystal size	0.21 x 0.17 x 0.15 mm ³
Theta range for data collection	2.06 to 26.38°.
Index ranges	-12<=h<=12, -8<=k<=8, -22<=l<=23
Reflections collected	12991
Independent reflections	2599 [R(int) = 0.0415]
Completeness to theta = 26.38°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6196 and 0.5307
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2599 / 0 / 172
Goodness-of-fit on F ²	1.180
Final R indices [I>2sigma(I)]	R1 = 0.0269, wR2 = 0.0692
R indices (all data)	R1 = 0.0314, wR2 = 0.0716
Largest diff. peak and hole	0.819 and -0.682 e.Å ⁻³

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound 27. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	-1944(1)	5438(1)	9186(1)	16(1)
S(1)	3153(1)	6381(1)	7739(1)	10(1)
S(2)	4141(1)	-3075(1)	9961(1)	14(1)
O(1)	3783(2)	8204(2)	7914(1)	14(1)
O(2)	2636(2)	5940(2)	6962(1)	17(1)
C(5)	1813(2)	6115(3)	8183(1)	9(1)
C(2)	3586(2)	2724(3)	8172(1)	12(1)
C(3)	2579(2)	2823(3)	8646(1)	10(1)
C(4)	1629(2)	4432(3)	8557(1)	10(1)
C(1)	4296(2)	4627(3)	8167(1)	11(1)
F(1)	1083(1)	9185(2)	7796(1)	15(1)
C(7)	-220(2)	7469(3)	8447(1)	13(1)
C(9)	489(2)	4294(3)	8850(1)	12(1)
C(6)	890(2)	7568(3)	8148(1)	12(1)
N(1)	2460(2)	1634(2)	9155(1)	12(1)
N(2)	3222(2)	41(3)	9252(1)	12(1)
C(10)	3296(2)	-1022(3)	9872(1)	12(1)
C(8)	-410(2)	5782(3)	8791(1)	12(1)
N(3)	2696(2)	-327(2)	10375(1)	22(1)

Table S3. Bond lengths [\AA] and angles [$^\circ$] for compound 27.

Br(1)-C(8)	1.891(2)
S(1)-O(1)	1.4437(15)
S(1)-O(2)	1.4437(16)
S(1)-C(1)	1.756(2)
S(1)-C(5)	1.763(2)
S(2)-C(10)	1.678(2)
C(5)-C(6)	1.385(3)
C(5)-C(4)	1.413(3)
C(2)-C(3)	1.502(3)
C(2)-C(1)	1.530(3)
C(3)-N(1)	1.292(3)
C(3)-C(4)	1.478(3)
C(4)-C(9)	1.397(3)
F(1)-C(6)	1.355(2)
C(7)-C(6)	1.373(3)
C(7)-C(8)	1.390(3)
C(9)-C(8)	1.383(3)
N(1)-N(2)	1.357(2)
N(2)-C(10)	1.359(3)
C(10)-N(3)	1.325(3)
O(1)-S(1)-O(2)	116.93(9)
O(1)-S(1)-C(1)	108.69(10)
O(2)-S(1)-C(1)	109.94(10)
O(1)-S(1)-C(5)	110.07(9)
O(2)-S(1)-C(5)	107.69(10)
C(1)-S(1)-C(5)	102.55(10)
C(6)-C(5)-C(4)	118.8(2)
C(6)-C(5)-S(1)	119.38(16)
C(4)-C(5)-S(1)	121.76(16)
C(3)-C(2)-C(1)	110.58(17)
N(1)-C(3)-C(4)	114.25(19)
N(1)-C(3)-C(2)	126.34(18)
C(4)-C(3)-C(2)	119.39(18)

C(9)-C(4)-C(5)	117.94(19)
C(9)-C(4)-C(3)	119.03(18)
C(5)-C(4)-C(3)	123.0(2)
C(2)-C(1)-S(1)	111.28(16)
C(6)-C(7)-C(8)	116.6(2)
C(8)-C(9)-C(4)	120.8(2)
F(1)-C(6)-C(7)	117.65(18)
F(1)-C(6)-C(5)	118.5(2)
C(7)-C(6)-C(5)	123.89(19)
C(3)-N(1)-N(2)	119.27(19)
N(1)-N(2)-C(10)	119.14(19)
N(3)-C(10)-N(2)	116.55(19)
N(3)-C(10)-S(2)	124.33(17)
N(2)-C(10)-S(2)	119.11(17)
C(9)-C(8)-C(7)	121.9(2)
C(9)-C(8)-Br(1)	117.62(17)
C(7)-C(8)-Br(1)	120.46(17)

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound 27.

The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^* U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
Br(1)	13(1)	19(1)	19(1)	-2(1)	9(1)	1(1)
S(1)	14(1)	10(1)	8(1)	0(1)	6(1)	-1(1)
S(2)	17(1)	12(1)	14(1)	2(1)	6(1)	4(1)
O(1)	19(1)	12(1)	16(1)	0(1)	11(1)	-4(1)
O(2)	25(1)	18(1)	9(1)	0(1)	6(1)	-2(1)
C(5)	10(1)	12(1)	6(1)	0(1)	1(1)	-1(1)
C(2)	17(1)	8(1)	13(1)	1(1)	7(1)	1(1)
C(3)	11(1)	10(1)	9(1)	-2(1)	3(1)	-1(1)
C(4)	13(1)	11(1)	6(1)	-1(1)	3(1)	0(1)
C(1)	12(1)	12(1)	13(1)	2(1)	8(1)	3(1)
F(1)	19(1)	11(1)	16(1)	6(1)	3(1)	0(1)
C(7)	13(1)	14(1)	12(1)	-1(1)	2(1)	2(1)
C(9)	14(1)	12(1)	8(1)	0(1)	3(1)	-1(1)
C(6)	17(1)	10(1)	10(1)	1(1)	3(1)	-2(1)
N(1)	12(1)	10(1)	13(1)	0(1)	4(1)	2(1)
N(2)	16(1)	11(1)	9(1)	2(1)	7(1)	3(1)
C(10)	13(1)	12(1)	11(1)	1(1)	4(1)	-1(1)
C(8)	10(1)	17(1)	9(1)	-2(1)	3(1)	-1(1)
N(3)	38(1)	17(1)	15(1)	7(1)	16(1)	13(1)

Supporting Information References

- S1. Crystallographic data for structure 27 (deposition number CCDC 869693) reported in this paper has been deposited with the Cambridge Crystallographic data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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