Trisubstituted 1,3,5-Triazines: The First Ligands of the sY12-Binding Pocket on Chemokine CXCL12

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Experimental Section

Protein production and purification. Isotopically labeled $^{15}$N-CXCL12 wild type was expressed and purified as previously described. Briefly, E. coli cells were lysed by French press and centrifuged for 20 min at 15,000 × g. The insoluble fraction was resuspended in a 6 M guanidine buffer and purified via nickel chromatography. Fractions containing CXCL12 were pooled, and the protein was refolded by adding dropwise into a buffer containing 10 mM cysteine, 0.5 mM cystine, and 100 mM Tris (pH 8.0). Refolded CXCL12 was cleaved with recombinant ULP1 and the SUMO-His6 tag was separated from the recombinant protein by cation exchange chromatography. After exchange chromatography, the fractions containing CXCL12 were purified via HPLC and lyophilized. Purity and MW were confirmed by SDS/PAGE and mass spectrometry.

Ligand preparation. All small molecules were solubilized in 100% DMSO at a concentration of 100 mM.

NMR spectroscopy of HTS screening. NMR data was collected on a Bruker Avance 600 MHz spectrometer equipped with a TCI cryoprobe at 298 K. Lyophilized [U-$^{15}$N]-CXCL12 WT was reconstituted in a 25 mM deuterated MES, 10% v/v D2O, 0.02% w/v NaN3 buffer, pH 6.8. NMR samples of 50 μM CXCL12 WT and 0–1600 μM compound were made with a LEAP PAL robot, where each sample contained 2.0% DMSO. A Bruker SampleJet was used for automated sample handling and 1H, $^{15}$N heteronuclear multiple quantum coherence (HMQC) spectra were collected for each titration point. Spectral data was processed with in-house scripts, and chemical shift changes were tracked using CARA2 and NMRpipe3 Titrvew software. Total 1H and $^{15}$N chemical shift perturbations were calculated as previously shown. $^4$ $K_d$ values were calculated as in Veldkamp et al.$^5$

Procedure for Docking Experiments. Compound 5 was docked to all 20 conformations of the NMR structure ensemble of CXCL12 (PDB: 2KEE)$^6$ using Schrödinger Maestro suite v2019-3. Three-dimensional ligand structures were generated using the LigPrep module, hydrogen bonds were optimized at pH 7.0, and the structure was minimized in the OPLS3e forcefield. Compound 5 was docked into a 40×40×40 Å grid centered on centroid of the protein using Glide$^{7,8,9}$ (ver. 84013) in Standard Precision mode. The top 500 poses for each of the 20 conformations (10,000 total) were taken. Python scripts$^{10}$ obtained from the Merz laboratory (Michigan State University) were used to calculate chemical shift perturbations for each residue of CXCL12. The calculated and experimental shifts were compared by using a weighted linear regression and the poses were sorted by their weighted Pearson correlation coefficient. The top 20 poses were examined manually for qualitative information regarding protein-ligand interactions. The figure was generated using the PyMOL Molecular Graphics System, Version 2.3.0 Schrödinger, LLC.

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Calculation of cLogP, ligand efficiency (LE), and lipophilic ligand efficiency (LLE). cLogP was calculated using MarvinSketch (v. 21.11) with the default parameters. Ligand efficiency was calculated used the equations: \( LE = pKd/(\text{number of heavy atoms}) \). Lipophilic ligand efficiency (LLE) was calculated using the equation: \( LLE = pKd - cLogP \).

Synthetic Procedures

All reagents and solvents were commercial grade and purified prior to use when necessary. Small molecules 1-4, 6, and 10 are commercially available; 9j, 12 24b, 13 and 24j 12 were previously reported. Tetrahydrofuran and dichloromethane were dried by passage through a column of activated alumina as described by Grubbs. Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates. UV light, and/or the use of potassium permanganate, and bromoresol green stains were used to visualize products. Microwave reactions were run using a Biotage Initiator+ synthesizer at the temperature listed. MPLC was performed as described using Biotage Sfar HC-Duo or SNAP Ultra columns on a Biotage Isolera in conjunction with a Biotage Dalton 2000. Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker Avance NEO (800 MHz) equipped with a TCI cryoprobe with XYZ pulsed field gradients. Chemical shifts were measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 (CDCl3) or δ 2.50 and δ 39.5 (DMSO-d6). All reported compounds were >90% pure by 1H NMR analysis and/or HPLC tracing. HPLC analysis was performed on an Agilent 1100 HPLC equipped with a diode array detector on a Thermo Scientific Hypersil Gold column (250 × 4.6 mm, 5 μm particle size) with 0.1% v/v CF3COOH in H2O (Solvent A) and 100% methanol (solvent B) in the following gradient: 0-10 min = 5% v/v solvent B, 10-40 min 5-95% v/v solvent B, 40-50 min = 95% solvent B. Low-resolution mass spectra 15 were recorded on a Biotage Dalton 2000 or an Advion Expression Compact Mass Spectrometer using the indicated ionization method. High-resolution mass spectra 16 were recorded at the Indiana University Mass Spectrometry Facility on a Thermo Scientific Orbitrap XL spectrometer by use of the indicated ionization method. A post acquisition gain correction was applied using reserpine as a lock mass.

General Procedure A, for the Suzuki Coupling. A microwave vial was charged with the triazine, boronic acid, and Na2CO3, and 1,4-dioxane and H2O were added. Argon was bubbled through the mixture for 10 min, and then Pd(PPh3)4 was added to the vial under argon. The vial was capped and heated at 120 °C for 1 h under microwave conditions. After cooling to ambient temperature, the reaction was concentrated onto SiO2 and purified via MPLC.

General Procedure B, for the deprotection of tert-butyl esters: To a vial containing the triazine dissolved in CH2Cl2 was added CF3CO2H dropwise. The resulting mixture was stirred at ambient temperature for 2 h and then concentrated in vacuo to afford the desired bis(acid).

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15 LRMS was collected on all intermediates.
16 HRMS was collected for all final products used for NMR titrations.
2,2’-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (5). Following general procedure B, compound 7 (250 mg, 556 μmol) in CH_{2}Cl_{2} (3 mL) and CF_{3}CO_{2}H (3 mL), after concentration, afforded the bis(acid) as a colorless solid (188 mg, 99% yield). {H NMR (500 MHz, DMSO-d_{6}) δ 8.41 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.3 Hz, 1H), 7.58 (dd, J = 7.6, 7.3 Hz, 2H), 4.03 (s, 4H); 13C NMR (125 MHz, DMSO-d_{6}) ppm 180.5, 168.1, 167.7, 134.1, 129.3, 129.2, 81.9, 28.0; HRMS (APCI) m/z: [M+H]^{+} calcd for C_{13}H_{12}N_{3}O_{4}S_{2} 338.0264; found 338.0264.

Di-tert-butyl 2,2’-((6-phenyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetate (7). To a solution 6 (100 mg, 442 μmol) and the thiol (148 mg, 995 μmol) in 1,4-dioxane (2 mL) was added a solution of Na_{2}CO_{3} (597 mg, 4.32 mmol) in H_{2}O (1 mL), and the reaction was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction was poured into H_{2}O and extracted with CH_{2}Cl_{2}. The combined organic layers were washed with 10% aq citric acid and brine and then dried and concentrated. MPLC (Sfar HC-Duo, 10 g, 8-60% ethyl acetate in hexanes) afforded the product as a golden oil (263 mg, 84% yield). {H NMR (500 MHz, CDCl_{3}) δ 8.48 (d, J = 2.9 Hz, 2H), 7.86 (d, J = 5.1 Hz, 1H), 7.35 (dd, J = 5.1, 2.9 Hz, 2H), 3.84 (s, 4H), 1.45 (s, 18H); 13C NMR (125 MHz, CDCl_{3}) ppm 180.1, 167.6, 164.8, 138.8, 132.6, 127.7, 126.3, 82.3, 34.2, 28.0; HRMS (APCI) m/z: [M+H]^{+} calcd for C_{21}H_{28}N_{3}O_{4}S_{2} 450.1516; found 450.1513.

Di-tert-butyl 4,4’-((6-phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))dibutyrate (8). To a solution 6 (150 mg, 664 μmol) and the amine (292 mg, 1,49 mmol) in 1,4-dioxane (2 mL) was added a solution of Na_{2}CO_{3} (597 mg, 4.32 mmol) in H_{2}O (1 mL), and the reaction was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction was poured into H_{2}O and extracted with CH_{2}Cl_{2}. The combined organic layers were washed with 10% aq citric acid and brine and then dried and concentrated. MPLC (Sfar HC-Duo, 10 g, 15-85% ethyl acetate in hexanes) afforded the product as a golden oil (263 mg, 84% yield). LRMS (APCI) m/z: [M+H]^{+} calcd for C_{25}H_{38}N_{5}O_{4} 472.3; found 472.2. This product was used to synthesize 9e without further characterization.

2,2’-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))diacetic acid (9a). To a solution of 6 (225 mg, 955 μl) and Hünig’s base (1.04 mL, 5.97 mmol) in 1,4-dioxane (10 mL) was added tert-butyl glycinate hydrochloride (375 mg, 2.24 mmol), and the solution was stirred at 80 °C for 24 h. The reaction was concentrated, and the residue was dissolved in CH_{2}Cl_{2} (5 mL). Trifluoroacetic acid (5 mL) was added.

\[ \text{CO}_2\text{-H protons are exchangeable and not observed.} \]
added, and the reaction was stirred for 16 h at ambient temperature. Cold Et₂O was added to the reaction, and the precipitate was filtered, washed with Et₂O and dried to afford the product as a colorless solid (195 mg, 65% yield). Analytical spectra matched those previously reported.¹³ HRMS (ESI) m/z: [M+H]+ calcd for C₁₃H₁₄N₅O₄ 304.1040; found 304.1042.

1,1’-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))bis(propan-2-one) (9b). To a solution of 6 (225 mg, 995 μmol) and the amine (300 mg, 2.74 mmol) in DMF (1 mL) was added Hüning’s base (796 μL, 4.57 mmol), and the reaction was stirred at 80 °C for 18 h. After cooling to ambient temperature, the reaction was diluted with H₂O and EtOAc. The layers were separated, and the aq layer was extracted with EtOAc. The combined organic layers were washed with 1 M HCl and brine, and then dried and concentrated. MPLC (Sfar HC-Duo, 10 g, 10-80% ethyl acetate in hexanes) afforded the product as a colorless solid (176 mg, 59% yield).¹⁸ ¹H NMR (500 MHz, DMSO-d₆) δ 8.40 (br dd, J = 7.9, 7.9 Hz, 2H), 7.61-7.41 (br m, 3H), 4.42 (s, 4H), 2.29 (s, 6H); ¹³C NMR (125 MHz, DMSO-d₆) ppm 180.5, 175.2, 170.1, 136.7, 129.7, 128.9, 127.2, 44.5, 33.2; HRMS (ESI) m/z: [M+H]+ calcd for C₁₅H₁₈N₅O₂ 300.1455; found 300.1457.

3,3’-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))dipropionic acid (9c). Following general procedure B, compound S1 (103 mg, 216 μmol) in CHCl₃ (1 mL) and CF₃CO₂H (1 mL), after concentration, afforded the product as a colorless solid (77 mg, 98% yield).¹⁹ ¹H NMR (500 MHz, DMSO-d₆) δ 8.41 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.3 Hz, 1H), 7.58 (dd, J = 7.6, 7.3 Hz, 2H), 4.03 (m, 4H), 2.36 (m, 4H); HRMS (ESI) m/z: [M+Na]+ calcd for C₁₅H₁₅N₃NaO₄S 388.0396; found 388.0396.

4,4’-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))dibutyric acid (9d). To a solution 6 (150 mg, 664 μmol) and the thiol (175 mg, 1.46 mmol) in 1,4-dioxane (2 mL) was added a solution of Na₂CO₃ (597 mg, 4.32 mmol) in H₂O (1 mL), and the reaction was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction was acidified with 6 M HCl, and the resulting ppt was filtered and dried under vacuum to afford the product as a colorless solid (261 mg, 72% yield).¹⁰ ¹H NMR (500 MHz, CDCl₃) δ 8.48 (d, J = 2.9 Hz, 2H), 7.86 (d, J = 5.1 Hz, 1H), 7.35 (d, J = 5.1, 2.9 Hz, 2H), 3.84 (br m, 4H), 2.40 (br m, 4H), 2.00 (br m, 4H);¹⁰¹³C NMR (125 MHz, CDCl₃) ppm 179.1, 178.4, 169.8, 134.0, 130.9, 129.0, 126.6, 36.1, 34.9, 23.2; HRMS (APCI) m/z: [M+H]+ calcd for C₁₇H₂₀N₃NaO₄S₂ 394.0890; found 394.0893.

¹⁸ The N-H proton signals are exchangeable and not observed.

SI-I-8
4,4′-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))dibutyric acid (9e). Following general procedure B, compound 8 (100 mg, 212 μmol) in CH₂Cl₂ (5 mL) and CF₃CO₂H (5 mL), after concentration, afforded the product as a colorless solid (75 mg, 99% yield). 

$$\text{H NMR (500 MHz, DMSO-d₆) } \delta 8.36 (d, J = 7.5 \text{ Hz}, 2H), 7.68-7.58 (m, 3H), 3.35 (br t, 6.9 \text{ Hz}, 4H), 2.30 (br m, 4H), 1.89 (m, 4H)$$

$$\text{C NMR (125 MHz, DMSO-d₆) ppm 182.3, 164.6, 160.9, 134.7, 131.1, 129.2, 127.5, 44.4, 35.9, 25.5; HRMS (ESI) m/z: [M+H]+ calcd for C₁₇H₂₂N₅O₄ 360.1666; found 360.1666.}

(2S,2'S)-2,2′-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))dihexanoic acid (9f). To a solution of 6 (150 mg, 664 μmol) and the amine (195 mg, 1.49 mmol) in 1,4-dioxane (2 mL) was added a solution of Na₂CO₃ (597 mg, 4.32 mmol) in H₂O (1 mL), and the reaction was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction was acidified with 1 M HCl and extracted with CH₂Cl₂. The combined organic layers were washed with 1 M HCl and brine, and then dried and concentrated. This resulted in a colorless solid which was spectroscopically pure (227 mg, 82% yield). 

$$\text{H NMR (500 MHz, DMSO-d₆) } \delta 8.27 (br d, J = 7.4 \text{ Hz}, 2H), 7.56-7.38 (series of br m, 5H), 4.47-4.26 (br m, 2H), 1.88-1.64 (br m, 4H), 1.45-1.16 (br m, 8H), 0.86 (t, J = 6.9 \text{ Hz}, 6H); \text{C NMR (125 MHz, DMSO-d₆) ppm 175.2, 169.6, 165.9, 137.3, 131.9, 128.6, 128.2, 54.3, 33.8, 25.7, 22.3, 14.4; HRMS (ESI) m/z: [M+H]+ calcd for C₂₁H₃₀N₅O₄ 416.2292; found 416.2293.}

(2R,2'R)-2,2′-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))dihexanoic acid (9g). To a solution of 6 (150 mg, 664 μmol) and the amine (195 mg, 1.49 mmol) in 1,4-dioxane (2 mL) was added a solution of Na₂CO₃ (597 mg, 4.32 mmol) in H₂O (1 mL), and the reaction was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction was acidified with 1 M HCl and extracted with CH₂Cl₂. The combined organic layers were washed with 1 M HCl and brine, and then dried and concentrated. This resulted in a colorless solid which was pure by 

$$\text{H NMR (500 MHz, DMSO-d₆) } \delta 1.00 (t, J = 6.9 \text{ Hz}, 6H); \text{C NMR (125 MHz, DMSO-d₆) ppm 175.2, 169.6, 165.9, 137.3, 131.9, 128.6, 128.2, 54.3, 33.8, 25.7, 22.3, 14.4; HRMS (ESI) m/z: [M+H]+ calcd for C₂₁H₃₀N₅O₄ 416.2292; found 416.2292.}
2,2′-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))diacetamide (9h). To a solution of 6 (250 mg, 1.11 mmol) and the amine (368 mg, 3.33 mmol) in 1,4-dioxane (3 mL) was added a solution of Na₂CO₃ (706 mg, 6.66 mmol) in H₂O (1 mL), and the reaction was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction was concentrated. The residue was triturated with methanol to afford a colorless solid (237 mg, 71% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.36-8.22 (br m, 2H), 7.58-6.93 (series of br m, 3H), 3.87 (br s, 4H);¹³C NMR (125 MHz, DMSO-d₆) ppm 169.8, 164.6, 160.9, 134.7, 131.1, 129.2, 127.5, 57.8; HRMS (ESI) m/z: [M+Na]⁺ calcld for C₁₃H₁₅N₃NaO₂ 314.1179; found 324.1181.

3,3′-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))bis(1,1,1-trifluoropropan-2-ol) (9i). To a solution of 6 (225 mg, 995 μmol) and the amine (289 mg, 2.24 mmol) in 1,4-dioxane (3 mL) was added a solution of Na₂CO₃ (688 mg) in H₂O (1 mL), and the reaction was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction was concentrated, and the residue was dissolved in CH₂Cl₂ and washed with 1 M HCl and brine, and then dried and concentrated. MPLC (Si-économique HC₃) afforded the product as a colorless solid (299 mg, 73% yield).

2,2′-((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))bis(N-hydroxyacetamide) (9k). To a solution of 9a (125 mg, 412 μmol), hydroxylamine hydrochloride (115 mg, 1.65 mmol) and HATU (392 mg, 1.03 mmol) in DMF (1.5 mL) was added Hünig’s base (430 μL, 2.47 mmol) dropwise, and the bright yellow solution was stirred at ambient temperature for 16 h. The reaction was concentrated in vacuo, and the residue was dissolved in CH₂Cl₂, washed with H₂O, dried, and concentrated. Trituration with a mixture of EtO and MeOH followed by filtration afforded the product as a colorless solid (42 mg, 31% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.41-6.93 (series of br m, 5H), 3.83 (br s, 4H);¹³C NMR (125 MHz, DMSO-d₆) ppm 170.1, 162.6, 161.9, 131.7, 131.0, 129.0, 127.4, 53.0; HRMS (ESI) m/z: [M+H]⁺ calcld for C₁₃H₁₆N₆O₃ 348.1258; found 334.1260.

((6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl))dimethanesulfonic acid dipotassium salt (9l). To a suspension of the triazine (225 mg, 995 μmol) and aminomesylsulfonic acid (195 mg, 2.24 mmol) in DME (3 mL) and H₂O (1 mL) was added K₂CO₃ (1.38 g, 10 mmol). The mixture was stirred in the microwave at 125 °C for 6 h. After cooling to ambient temperature, the precipitate formed. The solid was filtered, and the colorless solid was washed with EtO and dried under vacuum. This afforded the desired bis(sulfonate) as a free-flowing colorless solid (198 mg, 44% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.51-7.61 (m, 2H), 5.65 (m, 2H), 4.65 (m, 4H);¹³C NMR (125 MHz, DMSO-d₆) ppm 170.1, 162.6, 161.9, 131.7, 131.0, 129.0, 127.4, 53.0; HRMS (ESI) m/z: [M−H]⁻ calcld for C₁₃H₁₆N₆O₃ 314.1258; found 334.1260.

¹⁹ The N-H and O-H protons are exchangeable and not observed.
$^{13}$C NMR (125 MHz, DMSO-$d_6$) ppm 169.9, 160.2, 135.0, 131.1, 128.9, 126.8, 76.6; HRMS (ESI) m/z: [M-H]$^-$ calcld for C$_{11}$H$_{12}$N$_5$O$_6$S$_2$ 374.0234; found 374.0234.

4,4'-(6-Phenyl-1,3,5-triazine-2,4-diyl)bis(azanediyl) dibenzoic acid (9m). 4-Aminobenzoic acid (410 mg, 2.99 mmol) was dissolved in H$_2$O (5 mL) containing Na$_2$CO$_3$ (633 mg, 5.97 mmol) and added to a solution of 6 (225 mg, 995 µl) in 1,4-dioxane (2.5 mL); the mixture was stirred at 80 °C for 18 hr. At the completion of the reaction, the solution was acidified to pH = 1 with concentrated HCl and the precipitate was filtered, washed with 1 M HCl, cold dioxane, and Et$_2$O. This afforded an amorphous solid which was dried under vacuum resulting in the desired product as a colorless solid (288 mg, 68% yield).

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.36 (br s, 2H), 8.42 (d, $J$ = 7.3 Hz, 2H), 8.10-7.88 (series of br m, 8H), 7.68-7.52 (series of m, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) ppm 167.1, 164.0, 143.5, 135.7, 132.3, 130.2, 128.7, 128.2, 124.6, 119.7, 66.4. HRMS (ESI) m/z: [M+H]$^+$ calcld for C$_{23}$H$_{18}$N$_5$O$_4$ 428.1353; found 428.1352.

Di-tert-butyl 2,2'-(6-chloro-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (11). To a solution of cyanuric chloride (10) (909 mg, 4.93 mmol) and Hünig’s base (1.81 mL, 10.4 mmol) in THF (50 mL), chilled to -20 °C in a dry ice bath, was added the thiol (1.50 g, 10.1 mmol). The reaction was stirred at -20 °C for 18 h and then concentrated in vacuo. MPLC (Sfar HC-Duo, 25 g, 10-80% ethyl acetate in hexanes) afforded the desired compound as a colorless oil which solidified upon standing (1.65 g, 82% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 3.80 (s, 4H), 1.47 (s, 18H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 181.7, 168.1, 166.7, 82.8, 34.1, 27.9. LRMS (APCI) m/z: [M+H]$^+$ calcld for C$_{15}$H$_{23}$ClN$_3$O$_4$S$_2$ 408.1; found 408.2.

Di-tert-butyl 2,2'-(6-(naphthalen-1-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12a). Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (33.7 mg, 196 µmol), and Na$_2$CO$_3$ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H$_2$O (250 µL) using Pd(PPh$_3$)$_4$ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10g, 3-30% ethyl acetate in hexanes), afforded the product as a colorless oil (17.6 mg, 36% yield). $R_f = 0.51$ (15% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.90 (d, $J$ = 8.6 Hz, 1H), 8.28 (d, $J$ = 7.1 Hz, 1H), 7.90 (d, $J$ = 8.2 Hz, 1H), 7.60-7.52 (m, 3H), 3.92 (s, 4H), 1.40 (s, 18H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 180.0, 171.0, 167.5, 134.0, 132.7, 132.2, 131.0$^{20}$, 128.6, 127.4, 126.1, 125.9, 124.9, 82.4, 34.0, 27.9; LRMS (APCI) m/z: [M+H]$^+$ calcld for C$_{25}$H$_{30}$N$_5$O$_5$S$_2$ 500.2; found 500.2.

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$^{20}$ It appears that a quaternary carbon may overlap with the methine carbon signal.
Di-tert-butyl 2,2′-((6-(naphthalen-2-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetate (12b). Following general procedure A, the triazine (150 mg, 507 µmol), boronic acid (131 mg, 761 µmol), and NaCO₃ (322 mg, 3.04 mmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (30.0 mg, 25 µmol), after MPLC (Sfar-HC Duo 10g, 3-30% ethyl acetate in hexanes), afforded the product as a colorless oil (195 mg, 77% yield). This product was then deprotected to afford 13b without further characterization or manipulation. LRMS (APCI) m/z: [M+H]+ calcd for C₂₅H₃₀N₅O₅S₂ 500.2; found 500.2.

Di-tert-butyl 2,2′-((6-(anthracen-9-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetate (12c). Following general procedure A, the triazine (150 mg, 426 µmol), boronic acid (142 mg, 639 µmol), and NaCO₃ (271 mg, 2.56 mmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar HC-Duo, 10 g, 3-30% ethyl acetate in hexanes), afforded the product as a colorless oil (86.1 mg, 41% yield). Rf = 0.52 (15% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.53 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 7.5 Hz, 2H), 7.48 (dd, J = 7.5, 7.5 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 3.90 (s, 4H), 1.47 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 180.1, 168.2, 167.6, 145.7, 140.1, 133.3, 129.9, 128.9, 128.1, 127.24, 127.17, 82.4, 34.2, 28.0; LRMS (APCI) m/z: [M+H]+ calcd for C₂₇H₂₂N₅O₅S₂ 526.2; found 526.2.

Di-tert-butyl 2,2′-((6-mesityl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetate (12d). Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (32.1 mg, 196 µmol), and NaCO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O (250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar HC-Duo, 10 g, 5-75% ethyl acetate in hexanes), afforded the product as a colorless oil (20.6 mg, 40% yield). ¹H NMR (800 MHz, CDCl₃) δ 6.89 (s, 2H), 3.86 (s, 4H), 2.30 (s, 3H), 2.17 (s, 6H), 1.41 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 180.0, 173.1, 167.4, 139.1, 135.9, 133.5, 128.7, 82.4, 33.9, 27.9, 21.2, 20.1; LRMS (APCI) m/z: [M+H]+ calcd for C₂₆H₃₂N₅O₄S₂ 492.2; found 492.2.

Di-tert-butyl 2,2′-((6-([1,1′-biphenyl]-4-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetate (12e). Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (38.8 mg, 196 µmol), and NaCO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O (250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar HC-Duo, 10 g, 10-75% ethyl acetate in hexanes), afforded the product as a colorless oil (20.6 mg, 40% yield). Rf = 0.52 (15% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.54 (br ddd, J = 8.3, 1.8, 1.8 Hz, 2H), 7.71 (br ddd, J = 8.3, 2.0, 2.0 Hz, 2H), 7.66 (br d, J = 7.5 Hz, 2H), 7.48 (br dd, J = 7.5 Hz, 7.5 Hz, 2H), 7.40 (br dd, J =
Di-tert-butyl 2,2'-(6-(perfluorophenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12f). Following general procedure A, the triazine (150 mg, 426 µmol), boronic acid (135 mg, 639 µmol), and Na₂CO₃ (271 mg, 2.56 mmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (24.0 mg, 21 µmol), after MPLC (Sfar HC-Duo, 10 g, 12-86% ethyl acetate in hexanes) afforded the product as a colorless solid (200 mg, 87% yield). 

\[ ^1H \text{ NMR (800 MHz, CDCl}_3 \delta 3.72 (s, 4H), 1.40 (s, 18H); } ^{13}C \text{ NMR (125 MHz, CDCl}_3 \) ppm 180.1, 168.2, 167.6, 145.7, 140.1, 133.3, 129.9, 128.9, 128.1, 127.24, 127.17, 82.4, 34.2, 28.0; LRMS (APCI) m/z: [M+H]\(^+\) calcd for C₂₁H₂₃F₅N₃O₄S₂ 540.1; found 540.2.}

Di-tert-butyl 2,2'-(6-(3,5-bis(trifluoromethyl)phenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12g). Following general procedure A, the triazine (150 mg, 426 µmol), boronic acid (165 mg, 639 µmol), and Na₂CO₃ (271 mg, 2.56 mmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (24.0 mg, 21 µmol), after MPLC (Sfar HC-Duo, 10 g, 12-86% ethyl acetate in hexanes) afforded the product as a colorless solid (225 mg, 90% yield). 

\[ ^1H \text{ NMR (800 MHz, CDCl}_3 \delta 8.91 (s, 2H), 8.06 (s, 1H), 3.90 (s, 4H), 1.45 (s, 18H); } ^{13}C \text{ NMR (125 MHz, CDCl}_3 \) ppm 181.1, 167.1, 165.9, 136.9, 132.2 (q, \( ^1J_{C,F} = 36 \text{ Hz} \)), 129.1 (q, \( ^1J_{C,F} = 2.5 \text{ Hz} \)), 128.4, 125.0 (q, \( ^1J_{C,F} = 271 \text{ Hz} \)), 82.6, 34.1, 27.9; LRMS (APCI) m/z: [M+H]\(^+\) calcd for C₂₃H₂₆F₆N₃O₄S₂ 586.1; found 586.2.}

Di-tert-butyl 2,2'-(6-(4-morpholinophenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12i). Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (40.6 mg, 196 µmol), and Na₂CO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O (250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar HC Duo 10 g, 10%-80% ethyl acetate in hexanes), afforded the product as a golden oil (37.7 mg, 72% yield). 

\[ R_f = 0.72 (50\% \text{ EtOAc/hexanes}); ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 8.38 (d, \( J = 8.9 \text{ Hz} \)), 6.93 (d, \( J = 8.9 \text{ Hz} \)), 3.88 (br dd, \( J = 4.6, 4.6, 4.4 \text{ Hz} \)), 3.85 (s, 4H), 3.34 (br dd, \( J = 4.6, 4.6, 4.4 \text{ Hz} \)), 1.45 (s, 18H); ^{13}C \text{ NMR (125 MHz, CDCl}_3 \) ppm 179.4, 167.9, 167.7, 154.2, 131.1 (2C), 113.7, 82.2, 66.5, 47.7, 34.1, 28.0; LRMS (APCI) m/z: [M+H]\(^+\) calcd for C₂₅H₃₅N₃O₅S₂ 535.2; found 535.2.}

\(^{21}\) The \(^{13}C\) spectrum in this case does not provide meaningful data without being \(^{19}F\)-decoupled; this is not a capability present at our institution.
Di-tert-butyl 2,2'-(6-(3-hydroxyphenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12j). Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (27.0 mg, 196 µmol), and Na₂CO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O (250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10 g, 15%-75% ethyl acetate in hexanes), afforded the product as a colorless oil (32.4 mg, 71% yield).

1H NMR (800 MHz, CDCl₃) δ 8.09 (d, J = 7.8 Hz, 1H), 7.92 (dd, J = 1.9, 1.9 Hz, 1H), 7.35 (dd, J = 7.8, 7.8 Hz, 1H), 7.05 (dd, J = 7.8, 1.9 Hz, 1H), 3.86 (s, 4H), 1.45 (s, 18H);

13C NMR (125 MHz, CDCl₃) ppm 180.2, 170.3, 167.7, 158.2, 135.7, 129.9, 121.8, 120.1, 115.6, 82.5, 34.2, 28.0;

LRMS (APCI) m/z: [M+H]+ calcd for C₂₁H₂₂N₃O₅S₂ 466.2; found 466.2.

Di-tert-butyl 2,2'-(6-(3-(tert-butoxycarbonyl)phenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12k). Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (27.0 mg, 196 µmol), and Na₂CO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O (250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10 g, 5%-40% ethyl acetate in hexanes), afforded the product as a colorless oil (34.5 mg, 64% yield).

1H NMR (800 MHz, CDCl₃) δ 9.03 (br dd, J = 1.8, 1.8 Hz, 1H), 8.62 (br dd, J = 7.7, 1.8 Hz, 1H), 8.17 (br dd, J = 7.7, 1.8 Hz, 1H), 7.54 (dd, J = 7.7, 7.7 Hz, 1H), 3.90 (s, 4H), 1.63 (s, 9H), 1.45 (s, 18H);

13C NMR (125 MHz, CDCl₃) ppm 180.4, 167.8, 167.4, 165.1, 134.9, 133.7, 133.1, 132.6, 130.2, 128.5, 82.5, 81.6, 34.1, 28.2, 28.0;

LRMS (APCI) m/z: [M+H]+ calcd for C₂₆H₃₆N₃O₆S₂ 550.2; found 550.2.

Di-tert-butyl 2,2'-(6-(quinolin-3-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12l). Following general procedure A, the triazine (150 mg, 426 µmol), boronic acid (111 mg, 639 µmol), and Na₂CO₃ (271 mg, 2.56 mmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (24.0 mg, 21 µmol), after MPLC (Sfar-HC Duo 10 g, 5-50% ethyl acetate in hexanes), afforded the product as a colorless solid (77 mg, 41% yield).

1H NMR (800 MHz, CDCl₃) δ 9.87 (br d, J = 1.7 Hz, 1H), 9.25 (br s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.83 (dd, J = 7.5, 7.5 Hz, 1H), 7.63 (dd, J = 7.5, 7.5 Hz, 1H), 3.93 (s, 4H), 1.47 (s, 18H);

13C NMR (125 MHz, CDCl₃) ppm 180.5, 167.4, 167.4, 165.1, 134.9, 133.7, 133.1, 132.6, 130.2, 128.5, 81.6, 34.1, 28.2, 28.0;

LRMS (APCI) m/z: [M+H]+ calcd for C₂₄H₂₉N₄O₄S₂ 501.2; found 501.2.

22 The phenolic O-H is exchangeable and not observed.
**Supporting Information I**

**Di-*tert*-butyl 2,2’-(6-(4-phenoxynaphenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12m).** Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (21.9 mg, 196 µmol), and Na₂CO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O (250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10g, 3-28% ethyl acetate in hexanes), afforded the product as a colorless oil (26.3 mg, 61% yield). Rᵣ = 0.55 (15% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.48 (br d, J = 2.9 Hz, 1H), 7.86 (d, J = 5.1 Hz, 1H), 7.45 (dd, J = 5.1, 2.9 Hz, 1H), 7.35 (s, 1H), 3.84 (s, 4H), 1.45 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 180.1, 167.6, 164.8, 138.8, 128.8, 124.8, 120.0, 117.6, 82.4, 34.1, 28.0; LRMS (APCI) m/z: [M+H]+ calculated for C₁₉H₂₆N₄O₅S₂: 440.2; found 440.2.

**Di-*tert*-butyl 2,2’-(6-(furan-3-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12n).** Following general procedure A, the triazine (150 mg, 426 µmol), boronic acid (72 mg, 639 µmol), and Na₂CO₃ (271 mg, 2.56 mmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10g, 3-28% ethyl acetate in hexanes), afforded the product as a golden oil (119 mg, 73% yield). Rᵣ = 0.50 (15% EtOAc/hexanes); ¹H NMR (800 MHz, CDCl₃) δ 7.67 (s, 1H), 7.50 (d, J = 3.5 Hz, 1H), 6.59 (br s, 1H), 3.84 (s, 4H), 1.46 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 180.1, 167.4, 160.5, 149.6, 147.1, 118.5, 112.7, 82.4, 34.1, 28.0; LRMS (APCI) m/z: [M+H]+ calculated for C₁₉H₂₆N₄O₅S₂: 440.1; found 440.2. LRMS (APCI) m/z: [M+H]+ calculated for C₁₉H₂₆N₄O₅S₂: 440.1; found 440.2.

**Di-*tert*-butyl 2,2’-(6-(furan-2-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12o).** Following general procedure A, the triazine (150 mg, 426 µmol), boronic acid (72 mg, 639 µmol), and Na₂CO₃ (271 mg, 2.56 mmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10g, 3-28% ethyl acetate in hexanes), afforded the product as a golden oil (119 mg, 73% yield). Rᵣ = 0.50 (15% EtOAc/hexanes); ¹H NMR (800 MHz, CDCl₃) δ 7.67 (s, 1H), 7.50 (d, J = 3.5 Hz, 1H), 6.59 (br s, 1H), 3.84 (s, 4H), 1.46 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 180.1, 167.4, 160.5, 149.6, 147.1, 118.5, 112.7, 82.4, 34.1, 28.0; LRMS (APCI) m/z: [M+H]+ calculated for C₁₉H₂₆N₄O₅S₂: 440.1; found 440.2. LRMS (APCI) m/z: [M+H]+ calculated for C₁₉H₂₆N₄O₅S₂: 440.1; found 440.2.

**Di-*tert*-butyl 2,2’-(6-(thiophen-3-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12p).** Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (25.1 mg, 196 µmol), and Na₂CO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O (250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10g, 3-28% ethyl acetate in hexanes), afforded the product as a golden oil (34.5 mg, 65% yield). Rᵣ = 0.50 (15% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.48 (br d, J = 2.9 Hz, 1H), 7.86 (d, J = 5.1 Hz, 1H), 7.35 (dd, J = 5.1, 2.9 Hz, 1H), 7.34 (s, 1H), 1.45 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 180.1, 167.6, 164.8, 138.8, 132.6, 127.7, 126.3, 82.3, 34.2, 28.0; LRMS (APCI): LRMS (APCI) m/z: [M+H]+ calculated for C₁₉H₂₆N₄O₅S₂: 456.1; found 456.2.

**Di-*tert*-butyl 2,2’-(6-(thiophen-2-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetate (12q).** Following general procedure A, the triazine (40.0 mg, 98.1 µmol), boronic acid (25.1 mg, 196 µmol), and Na₂CO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (1.0 mL) and H₂O...
(250 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar-HC Duo 10g, 3-30% ethyl acetate in hexanes), afforded the product as a golden oil (32.6 mg, 73% yield). Rₛ = 0.49 (15% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.14 (d, J = 3.7 Hz, 1H), 7.60 (d, J = 4.9 Hz, 1H), 7.15 (d, J = 4.3 Hz, 1H), 3.85 (s, 4H), 1.46 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) ppm 179.8, 167.4, 164.6, 140.1, 133.2, 132.7, 128.4, 82.4, 34.0, 28.0; LRMS (APCI) m/z: [M+H]⁺ calcd for C₁₉H₂₆N₃O₄S₄ 456.1; found 456.2.

2-((4-[(Carboxymethyl)sulfanyl]-6-(naphthalen-1-yl)-1,3,5-triazin-2-yl)sulfanyl)acetic acid (13a). Following general procedure B, the triazine (12.1 mg, 24.2 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the desired compound as a brown solid (10.3 mg, 99% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 12.96 (br s, 2H), 8.80 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 7.2 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.70-7.56 (series of m, 3H), 4.07 (s, 4H); ¹³C NMR (125 MHz, DMSO-d₆) ppm 179.8, 170.3, 169.5, 133.5, 132.9, 131.7, 130.8, 130.3, 128.6, 127.5, 126.3, 125.3, 125.1, 32.7; HRMS (ESI) m/z: [M+Na]⁺ calcd for C₁₇H₁₃N₃NaO₄S₂ 410.0240; found 410.0239.

2,2'-(6-(Naphthalen-2-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetic acid (13b). Following general procedure B, the triazine (21 mg, 42.0 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the desired compound as a tan solid (16.2 mg, 99% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.60-7.56 (series of br m, 7H), 4.04 (s, 4H); ¹³C NMR (125 MHz, DMSO-d₆) ppm 181.8, 171.0, 170.3, 133.9, 133.8, 133.1, 133.0, 131.9, 128.1, 126.2, 125.7, 125.1, 124.5, 34.6; HRMS (ESI) m/z: [M+Na]⁺ calcd for C₁₇H₁₃N₃NaO₄S₂ 410.0240; found 410.0241.
180.4, 172.8, 169.8, 139.0, 135.7, 133.7, 128.9, 27.9, 20.0, 19.3; HRMS (ESI) m/z: [M+H]⁺ calcd for C₁₆H₁₈N₃O₄S₂ 380.0733; found 380.0732.

2-[(4-[[1,1'-Biphenyl]-4-yl]-6-(carboxymethyl)sulfanyl]-1,3,5-triazin-2-yl)sulfanyl]acetic acid (13e). Following general procedure B, the triazine (14.4 mg, 27.4 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the desired compound as a pale-yellow solid (11.1 mg, 98% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 12.97 (br s, 2H), 8.47 (br d, J = 8.3 Hz, 2H), 7.87 (br d, J = 6.6 Hz, 2H), 7.78 (br d, J = 7.6 Hz, 2H), 7.51 (dd, J = 7.5, 7.5 Hz, 2H), 7.47-7.36 (br m, 1H), 4.06 (s, 4H); ¹³C NMR (125 MHz, DMSO-d₆) ppm 184.8, 174.4, 172.2, 149.7, 143.4, 137.7, 134.3, 134.1, 133.9, 133.2, 131.8, 37.6. HRMS (ESI) m/z: [M+H]⁺ calcd for C₁₉H₁₆N₃O₄S₂ 414.0577; found 414.0576.

2,2'-((6-(Perfluorophenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13f). Following general procedure B, the triazine (10.0 mg, 18.5 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the desired compound as a colorless solid (7.8 mg, 99% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 3.85 (s, 4H); ¹³C NMR (125 MHz, DMSO-d₆) ppm 181.4, 170.1, 165.6, 137.1, 131.5 (¹J_C-F = 66 Hz), 129.3, 127.2 (¹J_C-F = 3.3 Hz), 123.4 (¹J_C-F = 271 Hz), 33.6; HRMS (ESI) m/z: [M+H]⁺ calcd for C₁₉H₁₈F₅N₃O₄S₂ 427.9793; found 427.9794.

2,2'-((6-(3,5-Bis(trifluoromethyl)phenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13g). Following general procedure B, the triazine (14.4 mg, 24.6 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the desired compound as a colorless solid (11.4 mg, 98% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.90 (s, 2H), 8.46 (s, 1H), 4.05 (s, 4H); ¹³C NMR (125 MHz, DMSO-d₆) ppm 181.4, 170.1, 165.6, 137.1, 131.5 (¹J_C-F = 66 Hz), 129.3, 127.2 (¹J_C-F = 3.3 Hz), 123.4 (¹J_C-F = 271 Hz), 33.6; HRMS (ESI) m/z: [M-H]⁻ calcd for C₁₅H₁₇F₆N₃O₄S₂ 471.9866; found 471.9856.

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23 The ¹³C spectrum and ¹⁹F spectrum in this case does not provide meaningful, interpretable data without being ¹⁹F-decoupled; this is not a capability present at our institution.
**2,2’-((6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13h).** Following general procedure A, the triazine (11) (40.0 mg, 98.1 µmol), boronic acid (30.0 mg, 196 µmol), and Na₂CO₃ (20.7 mg, 196 µmol) in 1,4-dioxane (200 µl) and H₂O (55 µL) using Pd(PPh₃)₄ (7.0 mg, 4.9 µmol), after MPLC (Sfar HC-Duo, 10 g, 10-65% ethyl acetate in hexanes), afforded 12h as an amorphous solid that was directly deprotected (15.0 mg, 32% yield). LRMS (APCI) m/z: [M+H]⁺ calcd for C₂₂H₃₀N₃O₅S₂ 480.2; found 480.2.

Following general procedure B, the triazine (12.5 mg, 26.1 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the desired compound as a colorless solid (9.5 mg, 99% yield).

**1H NMR (500 MHz, DMSO-d₆) δ 8.34 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 4.01 (s, 4H), 3.86 (s, 3H);**
**13C NMR (125 MHz, DMSO-d₆) ppm 180.2, 170.2, 167.7, 164.1, 131.4, 126.5, 114.8, 56.0, 33.3; HRMS (ESI) m/z: [M+H]⁺ calcd for C₁₄H₁₄N₃O₅S₂ 368.0369; found 368.0371.**

**2,2’-((6-(4-Morpholinophenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13i).** Following general procedure B, the triazine (26.1 mg, 48.8 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the product as a yellow solid (20.0 mg, 97% yield).

**1H NMR (500 MHz, DMSO-d₆) δ 12.6 (br s, 2H), 7.98 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.81 (s, 4H), 3.74 (br dd, J = 5.1, 5.1 Hz, 4H), 3.11 (br dd, J = 5.1, 5.1 Hz, 4H);**
**13C NMR (125 MHz, DMSO-d₆) ppm 180.0, 171.3, 170.7, 151.2, 129.1, 124.2, 112.7, 66.3, 53.3, 33.9; HRMS (ESI) m/z: [M-H]⁻ calcd for C₁₇H₁₇N₄O₅S₂ 421.0646; found 421.0634.**

**2,2’-((6-(3-Hydroxyphenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13j).** Following general procedure B, the triazine (19.7 mg, 42.3 µmol) in CH₂Cl₂ (1.0 mL) and CF₃CO₂H (1.0 mL), after concentration, afforded the product as a colorless solid (14.3 mg, 96% yield).

**1H NMR (500 MHz, DMSO-d₆) δ 7.81 (d, J = 7.8 Hz, 1H), 7.77 (br s, 1H), 7.34 (dd, J = 7.8, 7.8 Hz, 1H), 7.04 (dd, J = 7.8, 2.0 Hz, 1H), 3.98 (s, 4H);**
**13C NMR (125 MHz, DMSO-d₆) ppm 180.7, 170.3, 168.1, 158.2, 158.2, 135.7, 130.4, 120.9, 120.1, 115.6, 33.5; HRMS (ESI) m/z: [M-H]⁻ calcd for C₁₃H₁₀N₃O₅S₂ 352.0067; found 352.0058.**

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24 The carboxylate and phenolic protons are exchangeable and not observed.

SI-I-18
2,2'-((6-(3-Carboxyphenyl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13k). Following general procedure B, the triazine (25.0 mg, 45.5 µmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the product as a colorless solid (17.2 mg, 99% yield). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.90 (br s, 1H), 8.58 (d, $J$ = 7.8 Hz, 1H), 8.19 (d, $J$ = 7.8 Hz, 1H), 7.70 (dd, $J$ = 7.8, 7.8 Hz, 1H), 4.03 (s, 4H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) ppm 180.9, 170.1, 167.4, 167.1, 134.8, 134.3, 133.3, 132.1, 129.9, 129.8, 33.4; HRMS (ESI) m/z: [M+Na]$^+$ calcd for C$_{14}$H$_{11}$N$_3$NaO$_6$S$_4$ 403.9981; found 403.9983.

2,2'-(6-(Quinolin-3-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13l). Following general procedure B, the triazine (13.7 mg, 27.4 µmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the product as a yellow solid (10.4 mg, 98% yield). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 9.67 (br s, 1H), 8.60 (br s, 1H), 8.24 (d, $J$ = 8.1 Hz, 1H), 7.94 (d, $J$ = 8.1 Hz, 1H), 7.83-7.73 (br m, 1H), 7.63-7.54 (br m, 1H), 4.14 (s, 4H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) ppm 180.5, 167.4, 167.1, 150.7, 149.8, 138.0, 132.1, 129.5, 128.7, 127.4, 127.0, 126.6, 34.2; HRMS (ESI) m/z: [M+H]$^+$ calcd for C$_{16}$H$_{13}$N$_4$O$_4$S$_2$ 389.0373; found 389.0373.

2-({4-[(Carboxymethyl)sulfanyl]-6-(4-phenoxyphenyl)-1,3,5-triazin-2-yl}sulfanyl)acetic acid (13m). Following general procedure B, the triazine (24.0 mg, 44.3 µmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the desired compound as a colorless solid (18.9 mg, 99% yield). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 12.93 (br s, 2H), 8.39 (br d, $J$ = 8.9 Hz, 2H), 8.70 (br d, $J$ = 8.0 Hz, 2H), 7.62 (br d, $J$ = 8.0 Hz, 2H), 7.26 (br d, $J$ = 7.4 Hz, 2H), 7.15 (d, $J$ = 8.0 Hz, 2H), 7.09 (br d, $J$ = 8.9 Hz, 2H), 4.03 (s, 4H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) ppm 179.9, 169.6, 167.1, 167.1, 150.7, 149.8, 138.0, 132.1, 129.5, 128.7, 127.4, 127.0, 126.6, 34.2; HRMS (ESI) m/z: [M+H]$^+$ calcd for C$_{19}$H$_{16}$N$_4$O$_5$S$_2$ 430.0526; found 430.0527.

2-({4-[(Carboxymethyl)sulfanyl]-6-(4-phenoxyphenyl)-1,3,5-triazin-2-yl}sulfanyl)acetic acid (13n). Following general procedure B, the triazine (18.1 mg, 41.2 µmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the desired compound as a tan solid (13.4 mg, 99% yield). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 12.90 (br s, 2H), 8.53 (br d, $J$ = 3.3 Hz, 1H), 7.88-7.83 (br m, 1H), 7.00
Supporting Information I

2,2'-((6-(Furan-2-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (13o). Following general procedure B, the triazine (21.0 mg, 47.8 μmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the desired compound as a colorless solid (15.5 mg, 99% yield). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.20 (br d, J = 5.3 Hz, 1H), 7.53 (d, J = 3.4 Hz, 1H), 6.98-6.88 (br m, 1H), 3.95 (s, 4H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) ppm 181.1, 174.1, 169.6, 154.0, 142.9, 112.0, 107.1, 33.1; HRMS (ESI) m/z: [M-H]$^-$ calcd for C$_{11}$H$_8$N$_3$O$_5$S$_2$ 325.9911; found 325.9903.

2,2'-((6-(Carboxymethyl)sulfanyl)-6-(thiophen-3-yl)-1,3,5-triazin-2-yl)sulfanyl)acetic acid (13p). Following general procedure B, the triazine (23.8 mg, 52.2 μmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the desired compound as a pale tan solid (17.7 mg, 99% yield). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.07 (br s, 1H), 7.54 (br d, J = 3.4 Hz, 1H), 6.80 (br s, 1H), 3.99 (s, 4H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) ppm 180.3, 170.0, 160.2, 149.2, 149.1, 119.4, 113.7, 33.2; HRMS (ESI) m/z: [M+H]$^+$ calcd for C$_{11}$H$_{10}$N$_3$O$_4$S$_3$ 343.9828; found 343.9829.

2,2'-((6-(Carboxymethyl)sulfanyl)-6-(thiophen-2-yl)-1,3,5-triazin-2-yl)sulfanyl)acetic acid (13q). Following general procedure B, the triazine (22.7 mg, 49.8 μmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the desired compound as a colorless solid (16.6 mg, 97% yield). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.11 (br d, J = 3.4 Hz, 1H), 8.01 (br d, J = 4.7 Hz, 1H), 7.29 (br dd, J = 4.5, 4.5 Hz, 1H), 4.00 (s, 4H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) ppm 179.7, 169.5, 163.9, 139.1, 135.0, 133.0, 129.1, 32.8; HRMS (ESI) m/z: [M+H]$^+$ calcd for C$_{11}$H$_{10}$N$_3$O$_4$S$_3$ 343.9828; found 343.9827.

2,2'-((6-Benzyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (15). A solution of 14$^{25}$ (100 mg, 417 μmol), thioglycolic acid (73 μL, 1.04 mmol), and Hünig’s base (435 μL, 2.50 mmol) in 1,4-dioxane (3 mL) was stirred in the microwave for 5 h at 150 °C. The

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25 Boy, K. M.; Guernon, J. M.; Zuev, D. S.; Xu, L.; Zhang, Y.; Shi, J.; Marcin, L. R.; Higgins, M. A.; Wu, Y. J.; Krishnananthan, S.; Li, J.; Trehan, A.; Smith, D.; Toyn, J. H.; Meredith, J. E.; Burton, C. R.; Kimura, S. R.; Žyvaga, T.; Zhuo, X.; Lentz, K. A.; Grace, J. E.; Denton, R.; Morrison, J. S.; Mathur, A.; Albright, C. F.; Ahlijanian, M. K.; Olson, R. E.; Thompson, L. A.; Macor, J. E.
reaction was cooled to ambient temperature, and concentrated. The residue was triturated with 1 M HCl and filtered to afford the product as a colorless solid (94 mg, 64% yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.48-7.10 (m, 5H), 4.20 (s, 2H), 4.00 (s, 4H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) ppm 179.9, 174.4, 169.9, 136.5, 129.0, 128.6, 124.9, 39.1, 34.9; HRMS (APCI) m/z: [M+H]$^+$ calecd for C$_{14}$H$_{14}$N$_2$O$_2$S$_2$ 352.0420; found 352.0422.

2,2'-(6-((1R,3r)-Adamantan-2-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (17). In a microwave vial, a solution of the triazine (150 mg, 367 µmol) in THF (2 mL) was degassed by bubbling argon through the solution for 10 min. The catalyst (13.5 mg, 18.4 µmol) was added, and the vial was sealed. The zincate (0.5 M in THF, 808 µL, 404 µmol) was added dropwise, and the resulting dark-red solution was stirred in the microwave at 100 °C for 4 h. After cooling to ambient temperature, the reaction was quenched with sat aq NH$_4$Cl, and the solution extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried, and concentrated. MPLC (Sifar HC-Duo, 10 g, 5-75% ethyl acetate in hexanes) afforded 16 as an amorphous solid (134 mg, 72% yield). LRMS (APCI) m/z: [M+H]$^+$ calecd for C$_{27}$H$_{33}$N$_5$O$_{22}$S$_{10}$ 508.2; found 508.2.

Following general procedure B, 16 (15.1 mg, 29.7 µmol) in CH$_2$Cl$_2$ (1.0 mL) and CF$_3$CO$_2$H (1.0 mL), after concentration, afforded the desired compound as an amorphous solid (11.5 mg, 98% yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 4.01 (s, 4H), 3.32-1.75 (series of br m, 6H), 0.88 (br t, J = 7.6 Hz, 2H), 1.73 (t, J = 7.3, 7.3 Hz, 2H), 1.44 (s, 18H), 1.20 (series of br m, 6H), 0.88 (br t, J = 6.3 Hz, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) ppm 180.3, 178.4, 170.0, 44.0, 41.1, 36.5, 35.5, 28.7; HRMS (ESI) m/z: [M+H]$^+$ calecd for C$_{14}$H$_{22}$N$_5$O$_{22}$S$_{10}$ 396.1046; found 396.1048.

Di-tert-butyl 2,2'-(6-hexyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetate (18). Adapted from Fürstner, to a solution of the triazine (100 mg, 246 µmol) and Fe(acac)$_3$ (4.2 mg, 12 µmol), in THF (1.6 mL) and NMP (150 µL) at ambient temperature was added hexylmagnesium bromide (2.0 M in Et$_2$O, 148 µL, 295 µmol). The reaction was stirred for 20 min and then diluted with EtOAc and quenched with 1 M aq HCl. The layers were separated and the aq layer was extracted with EtOAc. The combined layers were washed with 1 M HCl, sat aq NaHCO$_3$, and brine, and then dried and concentrated. MPLC (Sifar HC-Duo, 10 g, 5-50% ethyl acetate in hexanes) afforded the product as a colorless oil (104 mg, 92% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 3.81 (s, 4H), 2.66 (t, J = 7.6 Hz, 2H), 1.73 (t, J = 7.3, 7.3 Hz, 2H), 1.44 (s, 18H), 1.41-1.20 (series of br m, 6H), 0.88 (br t, J = 6.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 179.7, 177.1, 167.4, 82.3, 38.5, 33.8, 31.5, 29.0, 27.9, 27.2, 22.5, 14.0. LRMS (APCI) m/z: [M+H]$^+$ calecd for C$_{36}$H$_{54}$N$_3$O$_{24}$S$_{10}$ 458.6; found 458.6.

2,2'-(6-Hexyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (19). Following general procedure B, compound 18 (23 mg, 50 µmol) in CH$_2$Cl$_2$ (500 µL) and CF$_3$CO$_2$H (200 µL), after concentration, afforded the product as a brown solid (17.1 mg, 99% yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 3.94 (s, 4H), 2.62 (t, J = 7.5 Hz, 2H), 1.70-1.60 (br t, J = 6.7, 6.7 Hz, 2H), 1.33-1.16 (br m, 6H), 0.85 (br t, J = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) ppm 180.0, 176.9, 170.0, 38.0, 33.0, 31.4, 28.6, 26.7, 22.4, 14.4; HRMS (APCI) m/z: [M+H]$^+$ calecd for C$_{13}$H$_{20}$N$_2$O$_2$S$_2$ 346.0890; found 346.0892.

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Following general procedure A, the triazine (100 mg, 245 µmol), boronic acid (61.7 mg, 490 µmol), and Na₂CO₃ (104 mg, 980 µmol) in 1,4-dioxane (1.0 mL) and H₂O (200 µL) using Pd(PPh₃)₄ (14.2 mg, 12.3 µmol), after MPLC (Sfar-HC Duo 10g, 5-50% ethyl acetate in hexanes), afforded the product as a colorless oil (119 mg, 73% yield). LRMS (APCI) m/z: [M+H]⁺ calcd for C₂₁H₃₂N₃O₄S₂ 454.2; found 454.2.

Following general procedure B, the protected triazine (obtained above) (14.3 mg, 31.5 µmol) in CH₂Cl₂ (1 mL) and CF₃CO₂H (1 mL), after concentration, afforded the product as a gummy colorless solid (10.7 mg, 99% yield).

**1H NMR (500 MHz, DMSO-d₆) δ 5.32 (t, J = 3.9 Hz, 1H), 3.93 (s, 4H), 2.34 (br s, 2H), 2.27 (br s, 2H), 1.65 (br m, 2H), 1.60 (br m, 2H); 13C NMR (125 MHz, DMSO-d₆) ppm 179.7, 170.1, 169.0, 140.8, 134.3, 33.2, 26.3, 24.1, 22.2, 21.7; HRMS (ESI) m/z: [M+Na]⁺ calcd for C₁₃H₁₅N₃NaO₄S₂ 364.0396; found 364.0397.**

Following general procedure B, the protected triazine (obtained above) (21.2 mg, 31.5 µmol) in CH₂Cl₂ (1 mL) and CF₃CO₂H (1 mL), after concentration, afforded the product as a colorless solid (10.7 mg, 98% yield).

**1H NMR (500 MHz, DMSO-d₆) δ 12.8 (br s, 2H), 9.33 (s, 1H), 3.87 (s, 4H); 13C NMR (125 MHz, DMSO-d₆) ppm 179.7, 170.1, 140.8, 134.3, 33.2, 26.3, 24.1, 22.2, 21.7; HRMS (ESI) m/z: [M+H]⁺ calcd for C₇H₈N₃O₄S₂ 261.9951; found 261.9956.**

Despite reasonable stoichiometric and temperature control, the reaction was contaminated with overaddition.
**Di-tert-butyl 2,2'-(6-((pyridin-3-ylmethyl)amino)-1,3,5-triazine-2,4-diy)bis(sulfanediyl))diacetate (23g).** To a solution of the triazine (60.0 mg, 147 µmol) and Hünig’s base (51 µL, 294 µmol) in 1,4-dioxane (1 mL) was added 3-picolyamine (16.5 µL, 162 µmol), and the reaction was stirred at 120 °C in the microwave for 20 min. The reaction was concentrated directly onto SiO₂ and purified via MPLC (Sfar HC-Duo, 10 g, 1-5% methanol in dichloromethane) to afford the product as a colorless oil (34.9 mg, 50% yield).

**1H NMR (800 MHz, CDCl₃) δ 8.59 (d, J = 1.6 Hz, 1H), 8.54 (d, J = 4.3 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.8, 4.8 Hz, 1H), 5.90 (br s, 1H), 4.65 (s, 1H), 4.64 (s, 1H), 3.74 (s, 2H), 3.73 (s, 2H), 1.45 (s, 9H), 1.44 (s, 9H).**

**13C NMR (125 MHz, CDCl₃) ppm 179.3, 178.5, 167.8, 162.7, 148.9, 135.5, 133.7, 123.6, 82.2, 42.2, 33.8, 28.0; LRMS (APCI) m/z: [M+H]+ calcd for C₂₁H₃₀N₅O₄S₂ 480.2; found 480.2.

**Di-tert-butyl 2,2'-(6-((pyridin-4-ylmethyl)amino)-1,3,5-triazine-2,4-diy)bis(sulfanediyl))diacetate (23h).** To a solution of the triazine (60.0 mg, 147 µmol) and Hünig’s base (51 µL, 294 µmol) in 1,4-dioxane (1 mL) was added 3-picolyamine (16.5 µL, 162 µmol), and the reaction was stirred at 120 °C in the microwave for 20 min. The reaction was concentrated directly onto SiO₂ and purified via MPLC (Sfar HC-Duo, 10 g, 1-5% methanol in dichloromethane) to afford the product as a colorless oil (31.4 mg, 45% yield).

**1H NMR (800 MHz, CDCl₃) δ 8.57 (d, J = 6.0 Hz, 2H), 7.24 (d, J = 6.0 Hz, 2H), 4.66 (s, 1H), 4.65 (s, 1H), 3.76 (s, 2H), 3.67 (s, 2H), 1.46 (s, 9H), 1.43 (s, 9H);**

**13C NMR (125 MHz, CDCl₃) ppm 179.4, 178.7, 167.8, 162.9, 149.7, 122.2, 82.2, 43.5, 33.8, 27.9; LRMS (APCI) m/z: [M+H]+ calcd for C₂₁H₃₀N₅O₄S₂ 480.2; found 480.2.

**4-(4,6-Bis((2-tert-butoxy)-2-oxoethyl)thio)-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride (23l).** A solution of the triazine (100 mg, 245 µmol) and N-methylmorpholine (135 µL, 1.23 mmol), with Hünig’s base (128 µL, 735 µmol), in 1,4-dioxane (2 mL), was stirred at 120 °C in the microwave for 4 h and then concentrated. The residue was triturated in a 1:1 mixture of Et₂O and EtOAc, and the precipitate which formed was filtered and dried to afford the product as a colorless, free-flowing solid (76 mg, 61% yield).

**1H NMR (500 MHz, CDCl₃) δ 3.81 (s, 4H), 3.71 (t, J = 4.3 Hz, 4H), 3.62 (t, J = 4.3 Hz, 4H), 3.33 (s, 3H), 1.38 (s, 18H);**

**13C NMR (125 MHz, CDCl₃) ppm 178.4, 178.7, 167.8, 162.9, 149.7, 122.2, 82.2, 43.5, 33.8, 27.9; LRMS (ESI) m/z: [M-Cl]− calcd for C₂₀H₃₃N₂O₅S₂ 473.2; found 473.2.**
2.2′-((6-(Phenylthio)-1,3,5-triazine-2,4-diy)bis(sulfanediyl))diacetic acid (24a). A solution of the triazine \(^{28}\) (100 mg, 387 \(\mu\)mol), thiol (143 mg, 968 \(\mu\)mol), and Hünig’s base (202 \(\mu\)L, 1.16 mmol) in 1,4-dioxane (3 mL) was stirred at 120 °C in the microwave for 4 h and then dried and concentrated in vacuo. The residue was dissolved in EtOAc and washed with sat aq NH\(_4\)Cl, 1 M NaOH, and brine, and then dried and concentrated. MPLC (Sfär HC-Duo, 10 g, 10-80% ethyl acetate in hexanes) afforded the bis(ester) as a colorless oil (123 mg, 66% yield). LRMS (APCI) m/z: [M+H]\(^+\) \(\text{calcd for C}_{21}\text{H}_{33}\text{N}_{3}\text{O}_5\text{S}_{2} 482.2; \text{found} 482.2\). 

Following general procedure B, the protected triazine (obtained above) (14.0 mg, 29.1 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (1 mL) and CF\(_3\)CO\(_2\)H (1 mL), after concentration, afforded the product as a colorless solid (10.6 mg, 99% yield). \(^{1}\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.63-7.44 (series of br m, 5H), 3.80 (s, 4H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) ppm 179.2, 169.8, 135.5, 130.5, 130.1, 129.9, 126.6, 33.0; HRMS (ESI) m/z: [M+H]\(^+\) \(\text{calcd for C}_{12}\text{H}_{33}\text{N}_{3}\text{O}_5\text{S}_{2} 369.9984; \text{found} 369.9983\).

2.2′-((6-(Bicyclo[1.1.1]pentan-1-yl amino)-1,3,5-triazine-2,4-diy)bis(sulfanediyl))diacetic acid (24c). To a solution of the triazine (12.6 mg, 56 \(\mu\)mol) in 1,4-dioxane (500 \(\mu\)L) was added tert-butyl thioglycolate (25 mg, 168 \(\mu\)mol) and Hünig’s base (34 \(\mu\)L, 196 \(\mu\)mol). The resulting solution was stirred in the microwave for 8 h at 120 °C. After cooling to ambient temperature, the reaction was concentrated directly onto silica gel and purified via MPLC (Sfär HC-Duo, 10 g, 25%-100% ethyl acetate in hexanes) to afford the bis(ester) as a colorless oil (18.3 mg, 72% yield). LRMS (APCI) m/z: [M+H]\(^+\) \(\text{calcd for C}_{20}\text{H}_{31}\text{N}_{3}\text{O}_5\text{S}_{2} 455.2; \text{found} 455.2\).

Following general procedure B, the protected triazine (obtained above) (15.1 mg, 32.2 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (1 mL) and CF\(_3\)CO\(_2\)H (1 mL), after concentration, afforded the product as an amorphous solid (11.3 mg, 99% yield). \(^{1}\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 3.91 (s, 4H), 2.62 (s, 1H), 2.07 (s, 6H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) ppm 179.7, 171.8, 160.3, 61.1, 39.2, 35.8, 28.8; HRMS (ESI) m/z: [M+H]\(^+\) \(\text{calcd for C}_{12}\text{H}_{33}\text{N}_{3}\text{O}_5\text{S}_{2} 343.0529; \text{found} 343.0530\).

2.2′-((6-(Cyclohexylamino)-1,3,5-triazine-2,4-diy)bis(sulfanediyl))diacetic acid (24d). To a solution of the triazine \(^{29}\) (100 mg, 405 \(\mu\)mol) in 1,4-dioxane (2 mL) was added tert-butyl thioglycolate (150 mg, 1.01 mmol) and Hünig’s base (213 \(\mu\)L, 1.22 mmol). The resulting solution was stirred in the microwave for 8 h at 120 °C. After cooling to ambient temperature, the reaction was concentrated directly onto silica gel and purified via MPLC (Sfär HC-Duo, 10 g, 45%-100% ethyl acetate in hexanes) to afford the bis(ester) as a colorless oil (91.5 mg, 48% yield). LRMS (APCI) m/z: [M+H]\(^+\) \(\text{calcd for C}_{21}\text{H}_{35}\text{N}_{3}\text{O}_5\text{S}_{2} 471.2; \text{found} 471.2\).

Following general procedure B, the protected triazine (obtained above) (18.6 mg, 39.5 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (1 mL) and CF\(_3\)CO\(_2\)H (1 mL), after concentration, afforded the product as an amorphous solid (14.0 mg, 99% yield). \(^{1}\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 8.03 (d, \(J = 7.44\) Hz, 11H), 3.85 (s, 4H), 2.60-0.95 (series of br m, 11H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) ppm 178.5, 170.4, 161.5, 49.6, 32.9, 32.4, 25.4, 25.0; HRMS (ESI) m/z: [M-H]\(^-\) \(\text{calcd for C}_{13}\text{H}_{17}\text{N}_{3}\text{O}_5\text{S}_{2} 357.0697; \text{found} 357.0690\).

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\(^{29}\) Singh, P.; Kaur, S.; Kumari, P.; Kaur, B.; Kaur, M.; Singh, G.; Bhatti, R.; Bhatti, M. Tailoring the Substitution Pattern on 1,3,5-Triazine for Targeting Cyclooxygenase-2: Discovery and Structure-Activity Relationship of Triazine-4-Aminophenylmorpholin-3-one Hybrids that Reverse Algesia and Inflammation in Swiss Albino Mice. J Med Chem 2018, 61, 7929-7941.
2,2'-((6-(Dicyclohexylamino)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (24e). To a solution of the triazine\textsuperscript{30} (133 mg, 405 \(\mu\)mol) in 1,4-dioxane (2 mL) was added tert-butyl thioglycolate (150 mg, 1.01 mmol) and Hünig’s base (213 \(\mu\)L, 1.22 mmol). The resulting solution was stirred in the microwave for 8 h at 120 \(^{\circ}\)C. After cooling to ambient temperature, the reaction was concentrated directly onto silica gel and purified via MPLC (Sfar HC-Duo, 10 g, 25%-100% ethyl acetate in hexanes) to afford the bis(ester) as a colorless oil (162 mg, 72% yield). LRMS (APCI) m/z: [M+H]\(^+\) calcd for C\(_{27}\)H\(_{45}\)N\(_{4}\)O\(_{4}\)S\(_{5}\) 553.3; found 553.2.

Following general procedure B, the protected triazine (obtained above) (18.0 mg, 32.6 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (1 mL) and CF\(_3\)CO\(_2\)H (1 mL), after concentration, afforded the product as a colorless solid (14.4 mg, 99% yield).

1\(^{H}\) NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 8.03 (d, \(J = 8.1\) Hz, 1H), 3.85 (s, 4H), 2.60-0.95 (series of br m, 11H); 13\(^{C}\) NMR (125 MHz, DMSO-\(d_6\)) ppm 178.5, 170.4, 161.5, 49.6, 32.9, 32.4, 25.4, 25.0; HRMS (ESI) m/z: [M-H]\(^-\) calcd for C\(_{13}\)H\(_{17}\)N\(_{4}\)O\(_{4}\)S\(_{2}\) 357.0697; found 357.0690.

2,2'-((6-(Benzylamino)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (24f). To a solution of the triazine\textsuperscript{29} (103 mg, 405 \(\mu\)mol) in 1,4-dioxane (2 mL) was added tert-butyl thioglycolate (150 mg, 1.01 mmol) and Hünig’s base (213 \(\mu\)L, 1.22 mmol). The resulting solution was stirred in the microwave for 8 h at 120 \(^{\circ}\)C. After cooling to ambient temperature, the reaction was concentrated directly onto silica gel and purified via MPLC (Sfar HC-Duo, 10 g, 30%-100% ethyl acetate in hexanes) to afford the bis(ester) as a colorless oil (143 mg, 74% yield). LRMS (APCI) m/z: [M+H]\(^+\) calcd for C\(_{22}\)H\(_{31}\)N\(_{4}\)O\(_{4}\)S\(_{2}\) 479.2; found 479.2.

Following general procedure B, the protected triazine (obtained above) (16.5 mg, 34.5 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (1 mL) and CF\(_3\)CO\(_2\)H (1 mL), after concentration, afforded the product as a colorless solid (12.4 mg, 98% yield).

1\(^{H}\) NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.58 (br d, \(J = 7.2\) Hz, 2H), 7.54-7.44 (br m, 3H), 3.79 (s, 4H), 3.60 (s, 2H); 17\(^{C}\), 18\(^{13}\) C NMR (125 MHz, DMSO-\(d_6\)) ppm 179.3, 169.8, 135.6, 135.5, 130.5, 129.9, 126.6, 41.1, 33.0; HRMS (APCI) m/z: [M+H]\(^+\) calcd for C\(_{14}\)H\(_{15}\)N\(_{4}\)O\(_{4}\)S\(_{2}\) 367.0529; found 367.0531.

2,2'-((6-(Pyridin-3-ylmethyl)amino)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (24g). Following general procedure B, the bis(ester) (13.0 mg, 27.1 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (1 mL) and CF\(_3\)CO\(_2\)H (1 mL), after concentration, afforded the product as a colorless solid (9.7 mg, 97% yield).

1\(^{H}\) NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 8.67 (dd, \(J = 6.1, 6.1\) Hz, 1H), 8.61 (s, 1H), 8.56 (br d, \(J = 4.1\) Hz, 1H), 7.91 (d, \(J = 7.8\) Hz, 1H), 7.55 (br d, \(J = 7.3, 5.3\) Hz, 1H), 3.88 (s, 4H), 3.81 (br s, 2H); \(^{13}\) C NMR (125 MHz, DMSO-\(d_6\)) ppm 178.6, 170.2, 162.6, 146.9, 146.6, 138.4, 136.1, 125.0, 41.4, 32.6; HRMS (ESI) m/z: [M+H]\(^+\) calcd for C\(_{13}\)H\(_{14}\)N\(_{5}\)O\(_{4}\)S\(_{2}\) 368.0482; found 368.0482.

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2,2′-((6-(pyridin-4-ylmethyl)amino)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)diacetic acid (24h). Following general procedure B, the bis(ester) (17.4 mg, 36.3 µmol) in CHCl₃ (1 mL) and CF₂CO₂H (1 mL), after concentration, afforded the product as a colorless solid (14.5 mg, 99% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.57 (d, J = 6.0 Hz, 2H), 7.24 (d, J = 6.0 Hz, 2H), 3.89 (s, 4H), 3.75 (s, 2H);¹³C NMR (125 MHz, DMSO-d₆) ppm 178.9, 170.2, 164.0, 151.0, 146.9, 123.7, 43.2, 32.5; HRMS (ESI) m/z: [M+H]+ calcd for C₂₃H₂₃N₅O₇S₂ 434.1330; found 434.1337.

Following general procedure B, the triazine (38 mg, 78 µmol) in 1,4-dioxane (2 mL) was added tert-butyl thioglycolate (222 µL, 1.62 mmol) and Hünig’s base (329 µL, 1.89 mmol). The resulting solution was stirred in the microwave for 4 h at 120 °C. After cooling to ambient temperature, the reaction was concentrated directly onto silica gel and purified via MPLC (Sfar HC-Duo, 10 g, 30-100% ethyl acetate in hexanes) to afford the product as a colorless solid (9.1 mg, 98% yield). LRMS (APCI) m/z: [M+H]+ calcd for C₁₉H₁₅N₃O₇S₂ 308.0482; found 308.0480.

2,2′-((6-(Pyrrolidin-1-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (24i). To a solution of the triazine (39 mg, 52 µmol) in 1,4-dioxane (6 mL) was added tert-butyl thioglycolate (222 µL, 1.62 mmol) and Hünig’s base (329 µL, 1.89 mmol). The resulting solution was stirred in the microwave for 4 h at 120 °C. After cooling to ambient temperature, the reaction was concentrated directly onto silica gel and purified via MPLC (Sfar HC-Duo, 10 g, 30-100% ethyl acetate in hexanes) to afford the product as a colorless solid (9.1 mg, 98% yield). LRMS (APCI) m/z: [M+H]+ calcd for C₂₄H₂₄N₅O₇S₂ 424.1466; found 424.1464.

2,2′-((6-(3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)-1,3,5-triazine-2,4-diyl)bis(sulfanediyl))diacetic acid (24k). To a solution of the triazine (39 mg, 52 µmol) in 1,4-dioxane (6 mL) was added tert-butyl thioglycolate (222 µL, 1.62 mmol) and Hünig’s base (329 µL, 1.89 mmol). The resulting solution was stirred in the microwave for 4 h at 120 °C. After cooling to ambient temperature, the reaction was concentrated directly onto silica gel and purified via MPLC (Sfar HC-Duo, 10 g, 30-100% ethyl acetate in hexanes) to afford the product as an amorphous solid (100 mg, 51% yield). LRMS (APCI) m/z: [M+H]+ calcd for C₁₉H₁₅N₃O₇S₂ 434.1330; found 434.1337.

Following general procedure B, the triazine (38 mg, 78 µmol) in CHCl₃ (500 µL) and CF₂CO₂H (500 µL), after concentration, afforded the desired compound as a pale-yellow solid (28.4 mg, 98% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 12.9 (br s, 2H), 3.91 (s, 4H), 3.71-3.11 (series of br m, 6H), 1.91-1.84 (br m, 4H);¹³C NMR (125 MHz, DMSO-d₆) ppm 180.1, 179.1, 171.0, 71.1, 67.9, 38.4, 29.9; HRMS (ESI) m/z: [M+H⁺] calcd for C₂₃H₂₃N₅O₇S₂ 434.1330; found 434.1337.

4-(4,6-Bis((carboxymethyl)thio)-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride (24l). Following general procedure B, the triazine (25.0 mg, 49.1 µmol) in CH₂Cl₂ (500 µL) and CF₂CO₂H (500 µL), after concentration, afforded the desired compound as a colorless foam (19.1 mg, 98% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 12.9 (br s, 2H), 3.91 (s, 4H), 3.71-3.11 (series of br m, 6H).

31 Zask, A.; Verheijen, J. C.; Richard, D. J.; Kaplan, J.; Curran, K.; Toral-Barza, L.; Lucas, J.; Hollander, I.; Yu, K. Discovery of 2-ureidophenyltriazines bearing bridged morpholines as potent and selective ATP-competitive mTOR inhibitors. Bioorg Med Chem Lett 2010, 20, 2644-2647.
1.91-1.84 (br m, 4H); 'H NMR (500 MHz, DMSO-d6) δ 3.89 (s, 4H), 3.81 (t, J = 5.1 Hz, 4H), 3.41 (t, J = 5.1 Hz, 4H), 3.30 (br s, 3H); 'C NMR (125 MHz, DMSO-d6) ppm 178.9, 170.2, 160.8, 68.5, 60.7, 51.8, 34.6; HRMS (ESI) m/z: [M]+ calcd for C12H18N4O5S2 361.0635; found 361.0364.

**Di-tert-butyl 3,3'-(6-phenyl-1,3,5-triazine-2,4-diyl)bis(sulfanediyl)dipropionate (S1).** To a solution of the triazine (84 mg, 370 µmol) and Hünig’s base (193 µL, 1.11 mmol) in 1,4-dioxane (3 mL) was added the thiol (193 µL, 924 µmol), and the reaction was stirred in the microwave at 120 °C for 3 h, then concentrated onto SiO2. MPLC (Sfar HC-Duo, 10 g, 12-100% ethyl acetate in hexanes) afforded the product as a colorless oil (103 mg, 59% yield). 'H NMR (500 MHz, CDCl3) δ 8.44 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 3.41 (t, J = 7.0 Hz, 4H), 2.76 (t, J = 7.0 Hz, 4H), 1.48 (s, 18 H); 'C NMR (125 MHz, CDCl3) ppm 180.9, 170.9, 168.3, 134.8, 132.8, 129.0, 128.6, 81.1, 35.3, 28.1, 25.7. LRMS (APCI) m/z: [M+H]+ calcd for C23H32N3O4S2 478.2; found 478.2.
Table S1. Ligand Metrics of Compounds Binding CXCL12.

| Compound | $K_d$ (µM) | LE$^a$ | cLogP | LLE$^b$ |
|----------|-----------|--------|-------|---------|
| 1        | 169 ± 12  | 0.23   | 2.82  | 0.95    |
| 5        | 158 ± 66  | 0.24   | 2.41  | 1.39    |
| 9a       | 355 ± 89  | 0.21   | 1.73  | 1.72    |
| 9c       | 158 ± 73  | 0.22   | 3.11  | 0.69    |
| 9f       | 156 ± 76  | 0.17   | 4.91  | -1.10   |
| 9g       | 383 ± 199 | 0.16   | 4.91  | -1.49   |
| 13g      | 646 ± 23  | 0.15   | 4.34  | -1.15   |
| 13h      | 357 ± 101 | 0.20   | 2.61  | 0.84    |
| 13i      | 306 ± 128 | 0.17   | 2.82  | 0.69    |
| 13j      | 1798 ± 218| 0.16   | 1.77  | 0.98    |
| 13k      | 133 ± 12  | 0.21   | 1.82  | 2.06    |
| 13p      | 1344 ± 376| 0.19   | 2.36  | 0.51    |
| 13q      | 1640 ± 190| 0.18   | 2.31  | 0.48    |
| 24a      | 80 ± 18   | 0.24   | 3.05  | 1.05    |
| 24b      | 251 ± 99  | 0.21   | 2.14  | 1.46    |
| 24c      | 1355 ± 194| 0.18   | 1.80  | 1.07    |
| 24d      | 170 ± 44  | 0.22   | 2.45  | 1.32    |
| 24i      | 1030 ± 474| 0.19   | 2.11  | 0.88    |
| 24j      | 234 ± 4   | 0.23   | 1.56  | 2.07    |
| 24k      | 233 ± 34  | 0.21   | 2.01  | 1.62    |

$^a$LE = Ligand Efficiency; $^b$LLE = Lipophilic Ligand Efficiency
Figure S1. NMR Titration Data for Compound 5

Figure S2. NMR Titration Data for Compound 9a
Figure S3. NMR Titration Data for Compound 9c

Figure S4. NMR Titration Data for Compound 13h
Figure S5. NMR Titration Data for Compound 13i

Figure S6. NMR Titration Data for Compound 13k
Figure S7. NMR Titration Data for compound 24a

Figure S8. NMR Titration Data for compound 24b
Figure S9. NMR Titration Data for compound 24c

![Figure S9](image)

Figure S10. NMR Titration Data for compound 24d

![Figure S10](image)
Figure S11. NMR Titration Data for compound 24i

Figure S12. NMR Titration Data for compound 24k
Figure S13. Representative Data of Non-binding compounds (9h, 13a, 13d, 24f)
Figure S14. HPLC Chromatogram of Compound 5

| Peak | RetTime | Type | Width | Area   | Height | Area |
|------|---------|------|-------|--------|--------|------|
| 1    | 41.028  | MM   | 0.1039| 303.92783 | 48.77113 | 1.6986 |
| 2    | 41.643  | MM   | 0.1282| 1.75892e4 | 2286.11401 | 98.3014 |
Figure S15. HPLC Chromatogram of Compound 9a

| Peak | Ret Time | Type | Width | Area | Height (mAU) | Area (mAU²%) |
|------|----------|------|-------|------|--------------|--------------|
| 1    | 28.920   | VB   | 0.126 | 4728.83301 | 596.07275    | 100.0000     |
Figure S16. HPLC Chromatogram of Compound 9c.
Figure S17. HPLC Chromatogram of Compound 9f.

| Peak | RetTime | Type | Width  | Area     | Height   | Area %   |
|------|---------|------|--------|----------|----------|----------|
| 1    | 34.189  | MM   | 0.1270 | 127.4488 | 16.7305 | 3.4920   |
| 2    | 36.828  | MM   | 0.1833 | 3393.25391| 308.47519| 92.9731  |
| 3    | 37.347  | MM   | 0.0975 | 129.01343| 22.05939| 3.5349   |
**Figure S18. HPLC Chromatogram of Compound 9g.**

| Peak | RetTime | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------|---------|------|-------------|--------------|--------------|--------|
| 1    | 34.219  | MM   | 0.1120      | 86.14863     | 12.01444     | 2.5564 |
| 2    | 36.845  | MM   | 0.1819      | 3026.54517   | 277.32339    | 89.8093|
| 3    | 37.361  | MM   | 0.0942      | 147.28731    | 26.04626     | 4.3706 |
| 4    | 37.927  | MM   | 0.0906      | 109.98813    | 20.22254     | 3.2638 |
Figure S19. HPLC Chromatogram of Compound 13g.

| Peak | RetTime | Type | Width | Area   | Height | Area % |
|------|---------|------|-------|--------|--------|--------|
| 1    | 34.767  | MM   | 0.1031| 86.92754| 14.05089| 5.8557 |
| 2    | 38.224  | MM   | 0.1000| 1336.17627| 222.69012| 90.0083 |
| 3    | 39.781  | MM   | 0.1437| 61.39955| 7.12338| 4.1360  |
Figure S20. HPLC Chromatogram of Compound 13h.

![HPLC Chromatogram](image)

| Peak | RetTime | Type | Width | Area    | Height | Area % |
|------|---------|------|-------|---------|--------|--------|
| 1    | 38.631  | MM   | 0.1723| 2.1239e4| 2054.10815| 92.0505|
| 2    | 39.402  | MM   | 0.1871| 1185.93213| 105.66413| 5.1398 |
| 3    | 41.737  | MM   | 0.1852| 648.27985| 58.34878 | 2.6096 |
Figure S21. HPLC Chromatogram of Compound 13i.

| Peak | RetTime | Type | Width | Area  | Height | Area  |
|------|---------|------|-------|-------|--------|-------|
| 1    | 34.657  | MM   | 0.1027| 150.77827 | 24.46567 | 1.2419 |
| 2    | 36.890  | MM   | 0.1031| 1.15270e4 | 1863.35181 | 94.9394 |
| 3    | 37.970  | MM   | 0.0950| 463.64615  | 81.30899  | 3.8187  |
Figure S22. HPLC Chromatogram of Compound 13j.

| Peak | RetTime | Type | Width | Area    | Height | Area % |
|------|---------|------|-------|---------|--------|--------|
| 1    | 41.411  | MM   | 0.090 | 583.297 | 107.488 | 1.6284 |
| 2    | 41.809  | MM   | 0.306 | 1097.239 | 59.748 | 3.0631 |
| 3    | 42.604  | MM   | 0.179 | 3.41408 | 3169.511 | 95.3086 |
Figure S23. HPLC Chromatogram of Compound 13k.

| Peak RetTime Type | Width | Area | Height | Area |
|------------------|-------|------|--------|------|
| #                | [min] | [min] | [mAU*s] | [mAU] | %    |
| 1                | 39.780 | 0.2799 | 5.37590e4 | 3200.58496 | 100.0000 |
Figure S24. HPLC Chromatogram of Compound 13p.

| Peak | RetTime | Type | Width | Area      | Height   | Area %  |
|------|---------|------|-------|-----------|----------|---------|
| 1    | 25.102  | MM   | 0.2059| 72.92378  | 5.90382  | 2.6276  |
| 2    | 32.438  | MM   | 0.1013| 2520.28320| 414.77365| 90.8099 |
| 3    | 33.973  | MM   | 0.0889| 29.16709  | 5.47105  | 1.0509  |
| 4    | 34.170  | MM   | 0.0854| 37.63120  | 7.34215  | 1.3559  |
| 5    | 37.936  | MM   | 0.0906| 115.33356 | 21.22506 | 4.1557  |
Figure S25. HPLC Chromatogram of Compound 13q.

| Peak | RetTime | Type | Width | Area   | Height | Area  |
|------|---------|------|-------|--------|--------|-------|
| 1    | 25.207  | MM   | 0.1624| 50.55398| 5.18684| 1.8998|
| 2    | 32.623  | MM   | 0.0997| 2532.01050| 423.15704| 95.1498|
| 3    | 34.160  | MM   | 0.0949| 31.94049| 5.60794| 1.2003|
| 4    | 34.358  | MM   | 0.0998| 46.57405| 7.77551| 1.7502|
Figure S26. HPLC Chromatogram of Compound 24a.

| Peak | RetTime | Type  | Width | Area  | Height | Area % |
|------|---------|-------|-------|-------|--------|--------|
| 1    | 30.767  | MM    | 0.1244| 2.00731e4 | 2690.21631 | 100.0000 |

**Supporting Information I**
Figure S27. HPLC Chromatogram of Compound 24b.

| Peak # | Ret Time (min) | Type | Width (min) | Area (mAU*s) | Height (mAU) | Area % |
|--------|----------------|------|-------------|--------------|--------------|--------|
| 1      | 39.491         | MM   | 0.1025      | 225.66162    | 36.68227     | 1.1381 |
| 2      | 41.233         | MM   | 0.1427      | 1.96031e4    | 2288.83569   | 98.8619 |
Figure S28. HPLC Chromatogram of Compound 24c.

| Peak | RetTime | Type | Width | Area  | Height | Area % |
|------|---------|------|-------|-------|--------|--------|
| 1    | 30.185  | MM   | 0.098 | 2839.05713 | 481.04803 | 92.0931 |
| 2    | 37.003  | MM   | 0.133 | 139.50632  | 17.47621  | 4.5253  |
| 3    | 38.327  | MM   | 0.096 | 104.24736  | 17.98326  | 3.3816  |
Figure S29. HPLC Chromatogram of Compound 24d.

| Peak | RetTime | Type | Width | Area   | Height | %     |
|------|---------|------|-------|--------|--------|-------|
| 1    | 26.929  | MM   | 0.2393| 1475.00098 | 102.73867 | 6.4317 |
| 2    | 27.973  | MM   | 0.1414| 2.14585e4  | 2528.44458 | 93.5683 |
Figure S30. HPLC Chromatogram of Compound 24i.

| Peak Ret Time | Type | Width [min] | Area [mAU*] | Height [mAU] | Area % |
|---------------|------|-------------|-------------|--------------|-------|
| 1             | MM   | 0.1025      | 4294.96973  | 698.19489    | 93.2118 |
| 2             | MM   | 0.1682      | 212.21971   | 21.02605     | 4.6057  |
| 3             | MM   | 0.0913      | 100.56231   | 18.36167     | 2.1825  |
Figure S31. HPLC Chromatogram of Compound 24j.

| Peak | Ret Time | Type | Width | Area  | Height | Area % |
|------|----------|------|-------|-------|--------|--------|
| 1    | 32.030   | BB   | 0.1317| 2.43595e4 | 2970.32227 | 100.0000 |
Figure S32. HPLC Chromatogram of Compound 24k.

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
---|--------|---|--------|------------------|-----|-----|-----|
1  28.645 MM  0.0984  1109.07629  187.82170  96.9106
2  33.669 MM  0.1201  35.35566   4.90588   3.0894
Figure S33. HPLC Chromatogram of Compound 24L.

| Peak | RetTime | Type | Width | Area       | Height    | Area         |
|------|---------|------|-------|------------|-----------|--------------|
| 1    | 25.714  | MM   | 0.1974| 8616.85059 | 727.56097 | 95.7580      |
| 2    | 26.458  | MM   | 0.1495| 161.53978  | 18.00815  | 1.7952       |
| 3    | 27.547  | MM   | 0.1379| 220.17683  | 26.60641  | 2.4468       |