One-Pot Synthesis of Thio-Augmented Sulfonylureas via a Modified Bunte’s Reaction

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EXPERIMENTAL SECTION (Materials and Methods)

Reagents available commercially were purchased and used as is. The starting materials were synthesized based on literature procedures. Proton (^1H NMR) spectra were recorded on a Bruker 500 or 800 MHz spectrometer in CDCl$_3$ or DMSO-d$_6$ (unless otherwise noted) with the values given in ppm (TMS as internal standard) and J (Hz) assignments of ^1H resonance coupling. Time of Flight (TOF) High Resolution Mass spectra (HRMS) were recorded on a VG 7070E spectrometer or a JEOL SX102a mass spectrometer. Thin layer chromatography (TLC) analyses were carried out on prescored silica gel GHLF 0.25 mm plates (Miles Scientific) using various gradients of CHCl$_3$/MeOH containing 1% NH$_4$OH or gradients of EtOAc:n-hexane (30-50%). Visualization was accomplished under UV light or by staining in an iodine chamber. Flash column chromatography was performed on Teledyne ISCO Combiflash system with and without Purilon mass detect or. For reaction that required heating, commercially available heating block, pie-block, stir-plate was used. Product yields are un-optimized unless indicated. All compounds characterized had ≥ 95% purity unless indicated. Purity and structural confirmation were analyzed by a combination of TLC, ^1H-NMR, ^13C-NMR (where available), LC/MS (available upon request), high-resolution mass spec and X-ray (where indicated). LC-MS detection was carried out on Agilent 1200 using Poroshell 120 EC-C18, (3 x 50 mm/2.7 uM). The mobile phase was 50% to 98% acetonitrile (1% formic acid) over 8 mins standard gradient. The LC-MS chromatogram showed the correct molecular (MH$^+$) ion as well as a single peak at UV (254 nm). Chiral HPLC was carried using Whelko ($R, R$) chiral column using method as indicated for specific compounds. Melting point (for crystalline compounds) are reported and carried out using Stanford Research Systems (MPA100) apparatus. X-ray results were obtained utilizing the X-ray facility at Georgetown University.
Table S1. Screening of Reaction Conditions using 1a (1 mmol scale/solvent 5 mL/mmol)

| Entry | Reagent       | Solventa | Temp (°C) | Time/ conversionb |
|-------|---------------|-----------|-----------|-------------------|
| 1.    | POCl₃ /DIPEA  | Toluene   | 110       | 1.5 h/complete (<5% decomp) |
| 2.    | POCl₃ /DIPEA  | Toluene   | 95        | 2 h/complete clean (>95%) |
| 3.    | POBr₃ /DIPEA  | Toluene   | 110       | 1.5h/complete with ~50% decomposition |
| 4.    | POBr₃ /DIPEA  | Toluene   | 85        | 2h/complete with ~30% decomposition |
| 5.    | PCl₅         | Chlorobenzene | 140   | 1.5 h/up to 15% decomposition |

(b)Conversion checked by LCMS

Table S2. Screening of Reaction Conditions using 1a (product 2a obtained from entry 2 Table S1) (100 mg scale/ 0.2 mmol scale)

| Entry | Reagent/equiv | Solventa | Temp (°C) | Time to complete conversionb/ % Yield from 1ac,d |
|-------|---------------|-----------|-----------|-----------------------------------------------|
| 1.    | Na₂S₂O₃ (5 eq)| MeOH-H₂O  | RT        | 12 h<sup>c</sup> 85% |
| 2.    | Na₂S₂O₃ (5 eq)| MeOH-H₂O  | 55        | 2 h<sup>c</sup> 80% |
| 3.    | Na₂S₂O₃ (3 eq)| MeOH-H₂O  | 65        | 2 h/ NA |
| 4.    | Na₂S₂O₃ (2 eq)| MeOH-H₂O  | 85        | 30 mins<sup>c</sup> 78% |
| 5.    | K₂S₂O₃ (2 eq)| MeOH-H₂O  | 85        | 20 mins<sup>c</sup> NA |
| 6.    | Na₂S₂O₃ (2 eq)| MeOH-H₂O  | 90        | 20 mins<sup>d</sup> 91% |
| 7.    | Na₂S₂O₃ (5 eq)| MeOH      | 55        | 3 h<sup>c</sup> 70% |
| 8.    | Na₂S₂O₃ (2 eq)| MeOH      | 85        | 1 h<sup>c</sup> 84% |
| 9.    | Na₂S₂O₃ (2 eq)| IPA-H₂O   | 90        | 30 mins<sup>c</sup> NA |
| 10.   | Na₂S₂O₃ (2 eq)| EtOH-H₂O  | 90        | 20 mins<sup>c</sup> NA |
| 11.   | Na₂S₂O₃ (5 eq)| Dioxane-H₂O | 55    | 3 h<sup>c</sup> NA |
| 12.   | Na₂S₂O₃ (2 eq)| Dioxane-H₂O | 85    | 30 mins<sup>d</sup> 72% |
| 13.   | Na₂S₂O₃ (2 eq)| Toluene-H₂O | 90    | -/traces |
| 14.   | Na₂S₂O₃ (2 eq)| DMF-H₂O   | 85        | 30 mins<sup>d</sup> 68% |
| 15.   | Na₂S₂O₃ (2 eq)| Acetonitrile-H₂O | 85    | 1h<sup>c</sup> 68% |
| 16.   | Na₂S₂O₃ (2 eq)| Water     | 95        | Solubility issues/NA |

a Water was used at maximum 10% solvent combination (Solvent:water total volume, 10 mL/mmol or as indicated)
b Conversion based on LCMS comparison with intermediate imidoylchloride 1b
c Yield based on work-up/MeOH-IPA (1:1) trituration
d Yield based on work-up/flash chromatography (40% hex/EtOAc)
General Procedure A for the Synthesis of STUs
3-(4-chlorophenyl)-4-phenyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3a):

To a mixture of compound 1a (100 mg, 0.20 mmol) in toluene (5 mL), POCl₃ (0.03 mL, 1.5 mmol), was added, followed by the addition of N, N-diisopropylethylamine (DIPEA) (0.03 mL, 1.5 mmol) and the mixture was refluxed for 1.5 h under N₂ atmosphere. The reaction mixture was then cooled, and the excess reagents in toluene were evaporated in vacuo. The imidoyl chloride intermediate was dissolved in methanol (10 mL), to this solution was added dropwise, sodium thiosulfate (2 eq, 63 mg, 0.4 mmol) dissolved in 0.5 mL water and the reaction was heated to 90 °C. Upon completion of reaction as seen by TLC, the reaction mixture was cooled to room temperature and methanol was evaporated. The organic mixture was the extracted into dichloromethane, washed with brine and dried over Na₂SO₄. The sticky solid was purified by flash chromatography (40% hexanes in EtOAc) to compound 3a as a pale white powder (94 mg, 91% yield). Mp 146-148 °C; ¹H-NMR (800 MHz, CDCl₃): δ 9.62 (s, 1H), 8.30 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.60-7.59 (m, 2H), 7.32-7.28 (m, 5H), 7.11-7.10 (m, 2H), 4.78-4.74 (m, 1H), 4.60-4.56 (m, 1H), 4.20-4.17 (m, 1H). ¹³C{¹H} NMR (201 MHz, CDCl₃): δ 169.3, 159.5, 142.2, 138.8, 137.8, 135.49, 135.35, 130.1, 129.8, 129.41, 129.30, 128.5, 127.7, 127.4, 125.9, 58.1, 51.4. LRMS 524.1, HRMS (ESI) m/z: [M+H]+ (C₉H₈ClN₃O₂F₃S₂) 524.0481; Found 524.0480.

General Procedure B for the Synthesis of STUs
3-(4-chlorophenyl)-4-phenyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3a):

To a mixture of compound 1a (100 mg, 0.20 mmol) in toluene (5 mL), POCl₃ (0.03 mL, 1.5 mmol), was added, followed by the addition of N, N-diisopropylethylamine (DIPEA) (0.03 mL, 1.5 mmol) and the mixture was refluxed for 1.5 h under N₂ atmosphere. The reaction mixture was then cooled, and the excess reagents in toluene were evaporated in vacuo. The imidoyl chloride intermediate was dissolved in methanol (5 mL), to this solution was added dropwise, sodium thiosulfate (5 eq, 158 mg, 1 mmol) dissolved in 0.5 mL water and the reaction was heated to 55 °C for 2h. Upon completion of reaction as seen by TLC, the reaction mixture was cooled to room temperature and methanol was evaporated. The organic mixture was the extracted into dichloromethane, washed with brine and dried over Na₂SO₄. The sticky solid was triturated with (50-50/mix of MeOH/IPA) to give compound 3a as a pale white powder (82 mg, 80 % yield).

General Procedure C for the Synthesis of STUs
Carboxamide Compound (1 equiv.) was dissolved in dry toluene (5 mL). To the solution was added N, N-diisopropylethylamine (1.5 equiv.) under N₂ atmosphere. POCl₃ (1.5 equiv.) was added to the reaction mixture under ice cold condition, and it was refluxed for 1 hour. Completion of the reaction was confirmed by thin layer chromatography. Toluene was evaporated and intermediate was taken to the next step as is. A solution of sodium thiosulfate (2 equiv.) dissolved in a 9 mL mixture of dioxane and water (8:1) was added dropwise to the reaction mixture. The reaction mixture was heated at 85 °C for 2 hours. The solvent was removed under vacuum, extracted with
DCM, and washed with brine solution. The residue was purified by silica gel column chromatography to provide compounds as white solid.

**General Procedure D for Synthesis of SU**

To a solution of appropriate sulfonyl carbamate\(^1\) (1.2 eq) in toluene was added amino component (1 eq) and the resulting slurry was refluxed for 4 h. After cooling to room temperature, the toluene solution was evaporated, and the slurry was triturated with isopropyl alcohol to obtain white slurry. The solution was filtered and washed with a mixture of cold IPA and hexanes (1:1) to give sulfonyl urea compounds as a white solid/powder.

**General Procedure E for alkylation of STU**

To a mixture of sulfonylurea compound (e.g. 1a) (1eq) in toluene (8 mL), POCl\(_3\) (1.5 eq), was added, followed by the addition of N, N-diisopropylethylamine (DIPEA) (1.5 eq) and the mixture was heated to 95 °C for 1.5 h under \(\text{N}_2\) atmosphere. The reaction mixture was then cooled, and the excess reagents in toluene were evaporated in vacuo. The imidoyl chloride intermediate was dissolved in methanol (10 ml), to this solution was added dropwise, sodium thiosulfate (2 eq, dissolved in 0.5 ml water and the reaction was heated to 90 °C. Upon completion of reaction as seen by TLC/LCMS, alkylation agent was added dropwise to the reaction mixture and reaction continued until all the thiourea is consumed as seen by TLC/LCMS. The reaction was cooled to room temperature and methanol was evaporated. The organic mixture was the extracted into dichloromethane, washed with brine and dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo and dried thoroughly to afford thio-alkylated sulfonyl compounds.

**Gram scale synthesis of 3a**

To a mixture of compound 1a (2.02 g, 4.00 mmol) in toluene (20 mL), POCl\(_3\) (0.56 mL, 6 mmol), was added, followed by the addition of N, N-diisopropylethylamine (DIPEA) (1.05 mL, 6 mmol) and the mixture was refluxed for 2 h under \(\text{N}_2\) atmosphere. The reaction mixture was then cooled, and the excess reagents in toluene were chased off in vacuo. The pale yellow imidoyl chloride intermediate (LCMS showing no traces of urea) was dissolved in methanol (20 ml), to this solution was added dropwise, sodium thiosulfate (2 eq, 1.3 g, 8 mmol) dissolved in 2 ml water and the reaction was heated to 90 °C. Upon completion of the reaction as seen by TLC, the reaction mixture was cooled to room temperature and methanol was evaporated. The organic mixture was then extracted into dichloromethane (30 mL) washed with brine and dried over Na\(_2\)SO\(_4\). The solvent removed in vacuo and dried thoroughly to afford 3a as a yellow sticky solid (up to 90% pure). The sticky solid was run through a filter silica column and washed with 50% hexanes/ethyl acetate to give compound 3a as an off-white powder (1.49 g, 71 % yield).
Sulfonylureas (SU) (1a-1w, 11a-11d, 13a-13d, 15a) were synthesized according to General Procedure B and as reported in the literature or procured commercially when available.

3-(4-chlorophenyl)-4-phenyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1a)<sup>2,3</sup>

3-(4-chlorophenyl)-4-phenyl-N-((2-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1b)

Using General Procedure D, ethyl ((2-trifluoromethylphenyl)sulfonyl)carbamate<sup>4</sup> (1.2 eq) and 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (2.56 g, 10.0 mmol) gave 1b which was purified by flash chromatography (40% hexanes in EtOAc) to give a white solid (3.7 g, 73%). Mp 230-232 °C; <sup>1</sup>H-NMR (800 MHz, CDCl<sub>3</sub>): δ 8.91 (s, 1H), 8.57 (d, <i>J</i> = 7.3 Hz, 1H), 7.90 (d, <i>J</i> = 6.9 Hz, 1H), 7.78 (t, <i>J</i> = 7.5 Hz, 2H), 7.52 (d, <i>J</i> = 8.1 Hz, 2H), 7.29 (td, <i>J</i> = 17.3, 9.4 Hz, 5H), 7.11 (d, <i>J</i> = 7.2 Hz, 2H), 4.71 (dd, <i>J</i> = 11.2, 4.9 Hz, 1H), 4.28 (t, <i>J</i> = 11.5 Hz, 1H), 3.87 (dd, <i>J</i> = 10.8, 4.8 Hz, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (201 MHz, CDCl<sub>3</sub>): δ 156.6, 147.6, 139.1, 137.4, 136.9, 134.3, 133.9, 132.5, 129.7, 129.2, 128.8, 128.35, 128.29, 128.17, 127.3, 54.1, 51.7. LRMS 508.1, HRMS (ESI) m/z: [M + H]<sup>+</sup> Calcd for (C<sub>23</sub>H<sub>18</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S) 508.0709; Found 508.0707.

3-(4-chlorophenyl)-4-phenyl-N-((3-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1c)<sup>3</sup>

3-(4-chlorophenyl)-N-((3-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1d)<sup>5</sup>

3-(4-chlorophenyl)-4-phenyl-N-((4-(trifluoromethoxy)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1e)<sup>2</sup>

N-((4-bromophenyl)sulfonyl)-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1f)<sup>2</sup>

3-(4-chlorophenyl)-4-phenyl-N-tosyl-4,5-dihydro-1H-pyrazole-1-carboxamide (3g)<sup>2,3</sup>

3-(4-chlorophenyl)-N-((4-isopropylphenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1h)<sup>2</sup>

N-((4-(tert-butyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1i)<sup>2</sup>

3-(4-chlorophenyl)-N-((napthalen-2-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1j)<sup>2</sup>

3-(4-chlorophenyl)-N-((4-fluorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1k)<sup>1,3</sup>

3-(4-chlorophenyl)-N-((4-iodophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1l)<sup>2</sup>

3-(4-chlorophenyl)-N-((4-cyanophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1m)<sup>1</sup>

3-(4-chlorophenyl)-N-((phenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1n)<sup>1</sup>

3-(4-chlorophenyl)-N-((2,4-difluorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1o)<sup>5</sup>
3-(4-chlorophenyl)-N-((2-fluorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1p)

Using General Procedure D, methyl ((2-fluorophenyl)sulfonyl)carbamate (1.3 eq) and 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (1.0 g, 3.9 mmol) gave 1p which was purified by flash chromatography (35% hexanes in EtOAc) to give a white solid (720 mg, 40%). Mp 265-267 °C; ¹H-NMR (800 MHz, CDCl₃): δ 8.94 (s, 1H), 8.15 (t, J = 7.1 Hz, 1H), 7.64 (d, J = 4.8 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.30 (td, J = 16.0, 8.1 Hz, 4H), 7.23 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 7.3 Hz, 2H), 4.71 (dd, J = 11.5, 5.3 Hz, 1H), 4.30 (t, J = 11.6 Hz, 1H), 3.89 (dd, J = 11.5, 5.4 Hz, 1H). ¹³C{¹H} NMR (201 MHz, CDCl₃): δ 159.8, 158.5, 156.6, 147.8, 139.2, 136.8, 136.6, 136.3, 132.17, 132.00, 129.7, 129.2, 128.8, 128.28, 128.20, 127.4, 124.7, 117.25, 117.13, 54.1, 51.7. LRMS 458.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₂₂H₁₈ClFN₃O₃S) 458.0741; Found 458.0735.

3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1q)²,³

R-3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1r)

¹H-NMR (800 MHz; CDCl₃): δ 8.09 (d, J = 7.4 Hz, 2H), 7.52 (d, J = 7.9 Hz, 4H), 7.29 (d, J = 6.9 Hz, 2H), 7.26 (d, J = 7.3 Hz, 3H), 7.10 (d, J = 7.4 Hz, 2H), 4.70-4.69 (m, 1H), 4.30-4.28 (m, 1H), 3.89-3.88 (m, 1H) (known parent racemic compound).

S-3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1s)

¹H-NMR (800 MHz; CDCl₃): δ 8.10 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 5H), 7.30 (t, J = 7.4 Hz, 6H), 7.11 (d, J = 7.5 Hz, 2H), 4.71 (dd, J = 11.5, 5.4 Hz, 1H), 4.31 (t, J = 11.6 Hz, 1H), 3.90 (dt, J = 14.2, 3.9 Hz, 1H) (known parent racemic compound).

3-(4-chlorophenyl)-N-((4-methoxyphenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1t)²

3-(4-chlorophenyl)-N-(N,N-diethylsulfamoyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1u)⁵

3-(4-chlorophenyl)-4-phenyl-N-(piperidin-1-ylsulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1v)⁶

3-(4-chlorophenyl)-4-phenyl-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1w)⁶

3-(4-Chlorophenyl)-N-((4-cyanophenyl)sulfonyl)-4-phenyl-5,6-dihydropyridazine-1(4H)-carboxamide (11a)⁷

Using General Procedure D, methyl ((4-cyanophenyl)sulfonyl)carbamate (1.2 eq, 1.06g, 4.43 mmol) and (3-(4-chlorophenyl)-4-phenyl-1,4,5,6-tetrahydropyridazine)⁷ (1.0 g, 3.69 mmol) gave 11a which was purified by flash chromatography (40% hexanes in EtOAc) to give a white solid (1.2 g, 68%). Mp 100-104 °C decom.; ¹H-NMR (800 MHz; CDCl₃): δ 9.33 (s, 1H), 8.30 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 7.30 (dt, J = 14.4, 7.5 Hz, 4H), 7.26 (d, J = 9.0 Hz, 1H), 7.06 (d, J = 7.3 Hz, 2H), 4.21-4.16 (m, 2H), 3.04 (td, J = 13.1, 4.0 Hz, 1H), 2.14-2.08 (m, 2H). ¹³C{¹H} NMR (201 MHz; CDCl₃): δ 149.4, 148.3, 143.1, 140.2, 136.1, 134.1, 133.1, 132.8, 129.4, 129.0,
127.9, 127.7, 127.5, 117.5, 117.3, 38.3, 35.3, HRMS (ESI) m/z: [M + H]^+ Calcd for (C_{24}H_{20}ClN_4O_3S) 479.0945; Found m/z 479.0939.

3-(4-Chlorophenyl)-4-phenyl-N-((3-(trifluoromethyl)phenyl)sulfonyl)-5,6-dihydropyridazine-1(4H)-carboxamide (11b) Using General Procedure D methyl ((3-trifluoromethylphenyl)sulfonyl)carbamate (1.2 eq, 1.26 g, 4.43 mmol) and amino component (3-(4-chlorophenyl)-4-phenyl-1,4,5,6-tetrahydropyridazine) (1.0 g, 3.69 mmol) afforded 11b which was purified by flash chromatography (35% hexanes in EtOAc) to give a white solid (1.2 g, 60%). Mp 150-155 °C; ^1H-NMR (800 MHz; CDCl_3): δ 9.31 (s, 1H), 8.42 (d, J = 9.3 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 7.0 Hz, 2H), 7.32-7.29 (m, 4H), 7.26 (d, J = 9.6 Hz, 1H), 7.07 (d, J = 7.4 Hz, 2H), 4.19 (d, J = 15.6 Hz, 2H), 3.05 (td, J = 12.9, 2.6 Hz, 1H), 2.15-2.07 (m, 2H). ^13C{^1H} NMR (201 MHz; CDCl_3): δ 149.5, 148.0, 140.3, 136.0, 134.2, 132.4, 131.8, 130.5, 129.8, 129.4, 129.0, 128.0, 127.73, 127.55, 125.6, 38.3, 35.3, 25.8. LRMS 522.1, HRMS (ESI) m/z: [M + H]^+ Calcd for (C_{24}H_{20}ClF_3N_3O_3S) 522.0866; Found m/z 522.0865.

3-(4-Chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-5,6-dihydropyridazine-1(4H)-carboxamide (11c)^7

3-(4-Chlorophenyl)-N-(naphthalen-2-ylsulfonyl)-4-phenyl-5,6-dihydropyridazine-1(4H)-carboxamide (11d)

Using General Procedure D methyl ((naphthalen-2-ylsulfonyl)sulfonyl)carbamate (1.2 eq, 1.18g, 4.43 mmol) and amino component (3-(4-chlorophenyl)-4-phenyl-1,4,5,6-tetrahydropyridazine) (1.0 g, 3.69 mmol) gave 11d which was purified by flash chromatography (30% hexanes in EtOAc) to give a white solid (1.5 g, 81%). Mp 197-200 °C; ^1H-NMR (800 MHz; CDCl_3): δ 9.34 (s, 1H), 8.76 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.29 (dd, J = 7.3, 4.2 Hz, 4H), 7.24 (t, J = 7.1 Hz, 1H), 7.05 (d, J = 7.4 Hz, 2H), 4.17 (d, J = 12.3 Hz, 2H), 3.01 (td, J = 13.1, 3.7 Hz, 1H), 2.11-2.03 (m, 2H). ^13C{^1H} NMR (201 MHz; CDCl_3): δ 149.7, 147.3, 140.4, 136.0, 135.9, 135.5, 134.3, 132.1, 130.6, 129.8, 129.3, 129.2, 129.0, 128.0, 127.6, 127.5, 123.3, 122.0, 38.3, 35.1, 25.8. LRMS 504.1, HRMS (ESI) m/z: [M + H]^+ Calcd for (C_{27}H_{23}ClN_3O_3S) 504.1149; Found 504.1146.

N-(Adamant-1-yl)carbamoyl)-4-(trifluoromethoxy)benzenesulfonamide (13a)

Utilizing General procedure D, methyl ((4-trifluoromethoxy)sulfonyl)carbamate (5.0 g 16.7 mmol) and amino component (1-adamantyl amine) (1.9 g, 12.9 mmol) gave 13a which was purified by flash chromatography (35% hexanes in EtOAc) to give a white solid (3.1 g, 58%). Mp 164-166 °C; ^1H NMR (800 MHz; CDCl_3): δ 7.94 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 2.04 (s, 6H), 1.92 (s, 1H), 1.88 (s, 3H), 1.64-1.63 (m, 6H).
$^{13}$C-1H NMR (200 MHz; CDCl$_3$): $\delta$ 145.5, 142.3, 130.6, 122.0, 113.7, 45.0, 34.3, 28.8, 22.0. LRMS 419.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{18}$H$_{22}$F$_3$N$_2$O$_4$S) 419.1252; Found 419.1250.

**N-(Adamantan-1-yl)carbamoyl)benzenesulfonamide (13b)$^8$**

**N-(-Adamantan-1-yl)carbamoyl)-4-methoxybenzenesulfonamide (13c)$^8$**

**N-(Adamantan-1-yl)carbamoyl)-4-(tert-butyl)benzenesulfonamide (13d)**

Utilizing General procedure D, methyl ((4-t-butyl)sulfonyl)carbamate (5 g, 18.4 mmol) and amino component (1adamantyl amine) (2.23 g, 14.7 mmol) 13d which was purified by flash chromatography (35% hexanes in EtOAc) to give a white solid (3.63 g, 63%). Mp 188-190 °C; $^1$H NMR (800 MHz; CDCl$_3$): $\delta$ 7.79 (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 8.0$ Hz, 2H), 2.02 (s, 3H), 1.87 (s, 6H), 1.62 (s, 6H), 1.32 (s, 9H). $^{13}$C-1H NMR (200 MHz; CDCl$_3$): $\delta$ 157.6, 150.3, 137.2, 127.0, 126.4, 52.1, 41.8, 36.4, 36.0, 31.3, 29.6. LRMS 391.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{21}$H$_{13}$N$_2$O$_3$S) 391.0555; Found 391.0561.

**N-(Cyclohexyl)carbamoyl)-4-(trifluoromethyl)benzenesulfonamide (15)**

Utilizing General procedure D, methyl ((4-trifluoromethyl)sulfonyl)carbamate (2.9 g 10.3 mmol) and cyclohexylamine (853 mg, 8.8 mmol) compound 15 which was purified by flash chromatography (35% hexanes in EtOAc) to give a white solid (1.5 g, 51%). Mp 168-170 °C; $^1$H NMR (800 MHz; CDCl$_3$): $\delta$ 8.03 (d, $J = 8.1$ Hz, 3H), 7.82 (d, $J = 8.3$ Hz, 2H), 6.41 (s, 1H), 3.61 (s, 1H), 1.86-1.85 (m, 2H), 1.69 (t, $J = 0.3$ Hz, 2H), 1.61-1.57 (m, 5H), 1.34 (s, 2H), 1.22-1.20 (m, 3H). $^{13}$C-1H NMR (201 MHz, CDCl$_3$): $\delta$ 150.7, 143.2, 135.5, 127.7, 126.6, 49.4, 33.0, 25.4, 24.6; LRMS 351.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{14}$H$_{18}$N$_2$O$_3$SF$_3$) 351.0990; Found 351.0987.

**3-(4-Chlorophenyl)-4-phenyl-N-((2-(trifluoromethyl)phenyl) sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3b):**

Following General procedure A, Compound (urea) 1b (220 mg, 0.43 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3b which was purified by flash chromatography (35% hexanes in EtOAc) to give a white solid (184 mg, 88% yield). Mp 195 °C; $^1$H-NMR (800 MHz, CDCl$_3$): $\delta$ 9.78 (d, $J = 0.5$ Hz, 1H), 8.63 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 7.3$ Hz, 1H), 7.77 (q, $J = 7.9$ Hz, 2H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.33-7.30 (m, 4H), 7.27 (d, $J = 7.3$ Hz, 1H), 7.10 (d, $J = 7.7$ Hz, 2H), 4.74 (dd, $J = 11.3$, 5.4 Hz, 1H), 4.56 (t, $J = 12.0$ Hz, 1H), 4.19 (dd, $J = 12.7$, 5.3 Hz, 1H). $^{13}$C-1H NMR (201 MHz, CDC$_3$): $\delta$ 169.1, 159.3, 138.9, 137.7, 136.8, 135.9, 133.9, 131.9, 129.8, 129.4, 129.3, 128.5, 127.4, 58.0, 51.4. LRMS 524.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{23}$H$_{18}$ClN$_3$O$_2$F$_3$S$_2$) 524.0481; Found 524.0480.

**3-(4-Chlorophenyl)-4-phenyl-N-((3-(trifluoromethyl)phenyl) sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3c):**

Following General procedure A, Compound (urea) 1c (136 mg, 0.27 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3c which
was purified by flash chromatography (40% hexanes in EtOAc) to give an off-white solid (110 mg, 78% yield). Mp 202 °C decomp; 1H-NMR (800 MHz, CDCl3): δ 9.62 (s, 1H), 8.42-8.40 (m, 2H), 7.89 (d, J = 7.8 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.33-7.27 (m, 5H), 7.11 (d, J = 7.4 Hz, 2H), 4.76 (dd, J = 11.4, 5.6 Hz, 1H), 4.59 (t, J = 12.1 Hz, 1H), 4.20 (dd, J = 12.8, 5.6 Hz, 1H). 13C{1H} NMR (201 MHz, CDCl3): δ 169.3, 159.4, 139.9, 138.9, 137.8, 133.1, 130.5, 129.9, 129.4, 129.3, 128.5, 127.7, 127.4, 126.6, 58.1, 51.4. LRMS 524.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C23H18ClN3O2F3S2) 524.0481; Found 524.0480.

3-(4-Chlorophenyl)-N-((3-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3d):

Following General procedure A, Compound (urea) 1d (104 mg, 0.22 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3d which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (78 mg, 73% yield). Mp 235 °C decomp; 1H-NMR (800 MHz, CDCl3): δ 9.62 (s, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.60-7.59 (m, 3H), 7.49 (s, 1H), 7.30 (td, J = 18.5, 8.1 Hz, 5H), 7.12 (d, J = 7.5 Hz, 2H), 4.76 (dd, J = 11.1, 5.1 Hz, 1H), 4.61-4.58 (m, 1H), 4.21-4.19 (m, 1H). 13C{1H} NMR (201 MHz, CDCl3): 169.3, 159.3, 140.2, 138.9, 137.7, 134.9, 134.0, 129.95, 129.81, 129.3, 128.4, 127.84, 127.73, 127.4, 58.1, 51.3 LRMS 490.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C22H18ClN3O2S2) 490.0217; Found m/z 490.0222.

3-(4-Chlorophenyl)-4-phenyl-N-((4-(trifluoromethoxy)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3e):

Following General procedure A, Compound (urea) 1e (300 mg, 0.57 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3e which was purified by flash chromatography (45% hexanes in EtOAc) to give a pale solid (257 mg, 83% yield). Mp 199-201 °C; 1H-NMR (800 MHz, CDCl3): δ 9.60 (s, 1H), 8.23 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.30 (q, J = 9.1 Hz, 5H), 7.11 (d, J = 7.4 Hz, 2H), 4.75 (dd, J = 11.2, 5.4 Hz, 1H), 4.59 (t, J = 12.1 Hz, 1H), 4.20 (dd, J = 12.6, 5.3 Hz, 1H). 13C{1H} NMR (201 MHz, CDCl3): δ 169.5, 159.3, 153.1, 138.9, 137.8, 136.8, 131.9, 129.9, 129.4, 129.3, 128.5, 127.4, 120.32, 58.1, 51.3. LRMS 540.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C23H18ClN3O2F3S2) 540.0430; Found 540.0425.

N-((4-Bromophenyl)sulfonyl)-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3f):
Following General procedure A, Compound (urea) 1f (96 mg, 0.18 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3f which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (62 mg, 52% yield) as a pale white solid. Mp 206-208 °C decom; \( ^1H\)-NMR (800 MHz; CDCl\(_3\)): \( \delta \) 9.59 (s, 1H), 8.04 (s, 2H), 7.68 (d, \( J = 8.3 \) Hz, 2H), 7.59 (d, \( J = 8.3 \) Hz, 2H), 7.31 (dt, \( J = 16.8 \), 9.0 Hz, 6H), 7.11 (d, \( J = 7.4 \) Hz, 2H), 4.76 (t, \( J = 5.7 \) Hz, 1H), 4.59 (t, \( J = 12.0 \) Hz, 1H), 4.20 (dd, \( J = 12.7 \), 5.4 Hz, 1H). \( ^{13}C \{ ^1H \} \) NMR (201 MHz, CDCl\(_3\)): \( \delta \) 159.3, 154.8, 138.9, 137.8, 132.1, 131.1, 130.0, 129.9, 129.3, 129.2, 128.5, 127.8, 127.4, 126.55, 118.9, 58.1, 51.3. LRMS 534.0, HRMS (ESI) m/z: [M + H]\(^+\) Calcd for \((C_{22}H_{15}ClBrN_3O_2S_2)\) 533.9712; Found 533.9718.

3-(4-Chlorophenyl)-4-phenyl-N-tosyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3g):

Following General procedure A, Compound (urea) 1g (240 mg, 0.53 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3g which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (109 mg, 56% yield). Mp 226-228 °C; \( ^1H\)-NMR (800 MHz, CDCl\(_3\)): \( \delta \) 9.59 (s, 1H), 8.05 (d, \( J = 8.1 \) Hz, 2H), 7.59 (d, \( J = 8.3 \) Hz, 2H), 7.34 (d, \( J = 8.0 \) Hz, 2H), 7.31 (d, \( J = 5.6 \) Hz, 5H), 7.10 (d, \( J = 7.5 \) Hz, 2H), 4.74 (dd, \( J = 11.4 \), 5.5 Hz, 1H), 4.58 (t, \( J = 12.1 \) Hz, 1H), 4.20 (dd, \( J = 12.6 \), 5.5 Hz, 1H), 2.44 (s, 3H). \( ^{13}C \{ ^1H \} \) NMR (201 MHz, CDCl\(_3\)): \( \delta \) 169.8, 158.9, 145.0, 139.0, 137.6, 135.7, 129.8, 129.6, 129.33, 129.26, 128.4, 127.9, 127.4, 58.1, 51.2, 21.9. LRMS 470.1, HRMS (ESI) m/z: [M + H]\(^+\) Calcd for \((C_{23}H_{21}ClN_3O_2S_2)\) 470.0764; Found 470.0769.

3-(4-Chlorophenyl)-N-((4-isopropylphenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3h):

Following General procedure A, Compound (urea) 1h (300 mg, 0.62 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3h which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale solid (191 mg, 62 % yield). Mp 228-230 °C; \( ^1H\)-NMR (800 MHz; CDCl\(_3\)): \( \delta \) 9.61 (s, 1H), 8.08 (d, \( J = 7.8 \) Hz, 2H), 7.59 (d, \( J = 8.0 \) Hz, 2H), 7.39 (d, \( J = 7.8 \) Hz, 2H), 7.30 (t, \( J = 8.6 \) Hz, 4H), 7.11 (d, \( J = 7.2 \) Hz, 2H), 4.74 (dd, \( J = 11.2 \), 5.2 Hz, 1H), 4.59 (t, \( J = 12.1 \) Hz, 1H), 4.20 (dd, \( J = 12.5 \), 5.1 Hz, 1H), 2.99 (t, \( J = 6.7 \) Hz, 1H), 1.28 (d, \( J = 6.7 \) Hz, 6H). \( ^{13}C \{ ^1H \} \) NMR (201 MHz, CDCl\(_3\)): \( \delta \) 169.8, 158.9, 155.5, 138.9, 137.5, 135.9, 129.8, 129.6, 129.2, 128.4, 127.9, 127.4, 126.9, 58.1, 51.2, 34.4, 23.7. LRMS 498.1, HRMS (ESI) m/z: [M + H]\(^+\) Calcd for \((C_{25}H_{25}ClN_3O_2S_2)\) 498.1077; Found 498.1083.

N-((4-(tert-Butyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3i):
Following General procedure A, Compound (urea) 1i (100 mg, 0.20 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3i which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale solid (52 mg, 50% yield). Mp 178-180 °C decomp; 1H-NMR (800 MHz; CDCl3): δ 9.61 (s, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 8.5 Hz, 4H), 7.27 (s, 1H), 7.11 (d, J = 7.7 Hz, 2H), 4.74 (dd, J = 11.4, 5.5 Hz, 1H), 4.59 (t, J = 12.1 Hz, 1H), 4.21 (dd, J = 12.6, 5.5 Hz, 1H), 1.35 (s, 9H). HRMS (ESI) m/z: [M + H]+ Calcd for (C28H27ClN3O2S2) 512.1233; Found 512.1234.

3-(4-Chlorophenyl)-N-(naphthalen-2-ylsulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3j): Following General procedure A, Compound (urea) 1j (90 mg, 0.18 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3j which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale solid (72 mg, 77% yield). Mp 224-226 °C; 1H-NMR (800 MHz; CDCl3): δ 9.68 (s, 1H), 8.78 (s, 1H), 8.09 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.61 (dd, J = 14.2, 7.3 Hz, 3H), 7.30 (t, J = 8.4 Hz, 4H), 7.25 (s, 1H), 7.10 (d, J = 7.5 Hz, 2H), 4.72 (t, J = 5.7 Hz, 1H), 4.56 (t, J = 12.1 Hz, 1H), 4.19-4.17 (m, 1H). 13C{1H} NMR (201 MHz, CDCl3): δ 169.8, 158.8, 157.8, 139.0, 137.5, 135.6, 129.8, 129.2, 127.4, 125.8, 58.1, 51.2, 51.1, 51.2. LRMS 512.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C26H22ClIN3O2S2) 506.0769; Found 506.0769.

3-(4-Chlorophenyl)-N-((4-fluorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3k): Following General procedure A, Compound (urea) 1k (32 mg, 0.07 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3k which was purified by flash chromatography (35% hexanes in EtOAc) to give a off-white solid (15 mg, 45% yield). Mp 177-180 °C; 1H-NMR (800 MHz, CDCl3): δ 9.58 (s, 1H), 8.21-8.19 (m, 2H), 7.60-7.59 (m, 2H), 7.33-7.29 (m, 4H), 7.28 (d, J = 7.4 Hz, 1H), 7.21 (t, J = 8.6 Hz, 2H), 7.11 (d, J = 7.2 Hz, 2H), 4.75 (dd, J = 11.5, 5.6 Hz, 1H), 4.59 (t, J = 12.1 Hz, 1H), 4.20 (dd, J = 12.7, 5.6 Hz, 1H). 13C{1H} NMR (201 MHz, CDCl3): δ 169.6, 159.2, 138.9, 137.9, 132.6, 129.8, 129.3, 128.9, 128.4, 128.1, 127.7, 127.4, 123.7, 58.1, 51.3. LRMS 474.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C22H18ClFN3O2S2) 474.0513; Found 474.0520.

3-(4-Chlorophenyl)-N-((4-iodophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3l):
Following General procedure A, Compound (urea) 11 (85 mg, 0.15 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3l which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale solid (48 mg, 55% yield). Mp 230-232 °C; $^1$H-NMR (800 MHz, CDCl$_3$): $\delta$ 9.59 (s, 1H), 7.91-7.87 (m, 4H), 7.59 (dd, $J = 8.6, 2.1$ Hz, 2H), 7.31 (dd, $J = 8.5, 7.0$ Hz, 4H), 7.28 (s, 1H), 7.11 (d, $J = 7.5$ Hz, 2H), 4.77-4.75 (m, 1H), 4.60-4.57 (m, 1H), 4.20 (ddd, $J = 12.7, 5.5, 2.0$ Hz, 1H). $^{13}$C{1H} NMR (201 MHz, CDCl$_3$): $\delta$ 169.3, 159.2, 138.8, 138.51, 138.37, 138.26, 130.8, 129.8, 129.37, 129.26, 128.4, 127.7, 127.4, 58.1, 51.3. LRMS 582.0, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{22}$H$_{16}$ClIN$_3$O$_2$S$_2$) 581.9574; Found 581.9570.

3-(4-Chlorophenyl)-N-((4-cyanophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3m):

Following General procedure A, Compound (urea) 1m (1.0 g, 2.2 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3m which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale yellow solid (820 mg, 79% yield). Mp 176-178 °C; $^1$H-NMR (800 MHz, CDCl$_3$): $\delta$ 8.28 (d, $J = 8.1$ Hz, 2H), 7.83 (d, $J = 8.2$ Hz, 2H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.32 (dd, $J = 13.6, 7.7$ Hz, 5H), 7.28 (d, $J = 7.3$ Hz, 1H), 7.11-7.10 (m, 2H), 4.77 (dd, $J = 11.3, 5.4$ Hz, 1H), 4.58 (t, $J = 12.1$ Hz, 1H), 4.19 (dd, $J = 12.7, 5.6$ Hz, 1H). $^{13}$C{1H} NMR (201 MHz, CDCl$_3$): $\delta$ 169.0, 159.7, 142.7, 138.7, 132.5, 130.2, 129.8, 129.41, 129.30, 128.5, 127.4, 117.4, 58.1, 51.3. LRMS 481.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{22}$H$_{16}$ClIN$_4$O$_2$S$_2$) 481.0560; Found 481.0557.

3-(4-Chlorophenyl)-N-(phenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3n):

Following General procedure A, Compound (urea) 1n (150 mg, 0.34 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3n which was purified by flash chromatography (40% hexanes in EtOAc) to give a pale solid (58 mg, 37% yield). Mp 229-231 °C; $^1$H-NMR (800 MHz, CDCl$_3$): $\delta$ 8.18-8.17 (m, 2H), 7.65-7.63 (m, 1H), 7.59 (d, $J = 8.1$ Hz, 2H), 7.56-7.54 (m, 2H), 7.32-7.28 (m, 5H), 7.11-7.10 (m, 2H), 4.75-4.73 (m, 1H), 4.60-4.57 (m, 1H), 4.21-4.19 (m, 1H). $^{13}$C{1H} NMR (201 MHz, CDCl$_3$): $\delta$ 169.7, 159.0, 139.0, 138.7, 133.9, 129.8, 129.48, 129.36, 129.26, 128.8, 128.4, 127.4, 58.1, 51.3. LRMS 456.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{22}$H$_{16}$ClIN$_3$O$_2$S$_2$) 456.0607; Found 456.0609.

3-(4-Chlorophenyl)-N-((2,4-Difluorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3o):

Following General procedure A, Compound (urea) 1o (200 mg, 0.42 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3o which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (82 mg, 40% yield). Following General procedure B, Compound (urea) 1o (100 mg, 0.21 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3o (78 mg, 76% yield) as a pale solid. Mp 230-232 °C; $^1$H-NMR (800 MHz, CDCl$_3$): $\delta$ 8.20 (q, $J = 7.3$ Hz, 1H), 7.61 (d, $J = 8.6$ Hz, 2H), 7.32 (dd, $J = 16.8, 8.0$ Hz, 5H), 7.28 (d, $J = 7.4$ Hz, 2H), 7.12 (d, $J = 7.1$ Hz, 2H), 7.07-7.05 (m,
1H), 6.96-6.94 (m, 1H), 4.77 (dd, J = 11.4, 5.5 Hz, 1H), 4.59 (dd, J = 12.5, 11.6 Hz, 1H), 4.20 (dd, J = 12.7, 5.5 Hz, 1H). $^{13}$C{1H} NMR (201 MHz, CDCl$_3$): δ 169.2, 159.5, 135.6, 129.8, 129.35, 129.28, 128.5, 127.7, 127.4, 111.92, 111.81, 105.6, 58.0, 51.3. LRMS 492.1, HRMS (ESI) m/z: [M + H]$^+$ Caled for (C$_{22}$H$_{17}$ClN$_3$O$_2$F$_2$S$_2$) 492.0419; Found m/z 492.0415.

3-(4-Chlorophenyl)-N-((2-fluorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3p):

Following General procedure A, Compound (urea) 1p (50 mg, 0.11 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3p which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (16 mg, 31% yield).

$^1$H-NMR (800 MHz, CDCl$_3$): δ 8.19 (t, J = 7.3 Hz, 1H), 7.65-7.62 (m, 3H), 7.34 (dd, J = 15.9, 8.1 Hz, 8H), 7.14 (d, J = 7.6 Hz, 2H), 4.78-4.76 (m, 1H), 4.61 (d, J = 12.5 Hz, 1H), 4.22 (dd, J = 12.3, 5.1 Hz, 1H). $^{13}$C{1H} NMR (201 MHz, CDCl$_3$): δ 169.4, 158.5, 138.9, 137.7, 136.2, 133.6, 129.8, 129.4, 128.5, 128.1, 127.8, 127.4, 124.3, 120.3, 117.01, 116.95, 58.1, 51.3. LRMS 474.1, HRMS (ESI) m/z: [M + H]$^+$ Caled for (C$_{22}$H$_{18}$ClF$_2$N$_3$O$_2$S$_2$) 474.0513; Found 474.0520.

3-(4-Chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3q):

Following General procedure A, Compound (urea) 1q (500 mg, 1.05 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3q which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (385 mg, 75% yield). Mp 232-235 ºC; $^1$H-NMR (800 MHz; CDCl$_3$): δ 9.55 (s, 1H), 8.06-8.05 (m, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.46-7.45 (m, 2H), 7.26-7.24 (m, 3H), 7.21-7.20 (m, 2H), 7.05 (d, J = 6.8 Hz, 2H), 4.70 (dq, J = 8.6, 2.7 Hz, 1H), 4.53 (t, J = 12.1 Hz, 1H), 4.14 (dq, J = 9.7, 2.9 Hz, 1H). $^{13}$C{1H} NMR (201 MHz, CDCl$_3$): δ 169.4, 159.3, 140.6, 138.9, 137.7, 137.0, 131.0, 129.8, 129.4, 129.3, 128.9, 128.4, 127.4, 58.1, 51.3. LRMS 490.1, HRMS (ESI) m/z: [M + H]$^+$ Caled for (C$_{22}$H$_{18}$Cl$_2$N$_3$O$_2$S$_2$) 490.0217; Found 490.0222. Analytical Chiral HPLC (R,R)-Whelk-O1 chiral column (250 mm x 4.6 mm/5µm) : 40% hexanes:60% CH$_2$Cl$_2$ (254 nm) Peak 1 = 4.2 min. Peak 2 = 5.5 min.

$R$-3-(4-Chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3r):

Following General procedure A, Compound (urea) 1r (50 mg, 0.10 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3r which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid as a pale white solid (37 mg, 71 % yield). Mp 207-209 ºC; $^1$H-NMR (800 MHz, CDCl$_3$): δ 9.59 (d, J = 0.5 Hz, 1H), 8.11 (d, J = 7.3 Hz, 2H), 7.60 (t, J = 8.5 Hz, 3H), 7.52 (d, J = 7.4 Hz, 2H), 7.34-7.29 (m, 5H), 7.13-7.10 (m, 2H), 4.77-4.74 (m, 1H), 4.61-4.57 (m, 1H), 4.21-4.18 (m, 1H). LRMS 490.1, HRMS (ESI) m/z: [M + H]$^+$ Caled for (C$_{22}$H$_{18}$Cl$_2$N$_3$O$_2$S$_2$) 490.0217; Found 490.0222. Analytical Chiral HPLC (R,R)-Whelk-O1 chiral column (250 mm x 4.6 mm/5µm) : 40% hexanes:60% CH$_2$Cl$_2$ (254 nm) Peak 1 = NA. Peak 2 = 5.7 min (ee >99.99%)
S-3-(4-Chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3s)

Following General procedure A, Compound (urea) 1s (60 mg, 0.13 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3s which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid. (43 mg, 69% yield) as a pale solid. Mp 208-210 °C; 1H-NMR (800 MHz, CDCl3): δ 8.11 (dd, J = 8.9, 2.4 Hz, 2H), 7.60-7.58 (m, 2H), 7.51 (dd, J = 8.9, 2.3 Hz, 2H), 7.32-7.30 (m, 6H), 7.11-7.10 (m, 2H), 4.75-4.74 (m, 1H), 4.59-4.58 (m, 1H), 4.20 (d, J = 12.7 Hz, 1H). LRMS 490.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C22H18Cl2N4O2S2) 490.0217; Found 490.0222. Analytical Chiral HPLC (R,R)-Whelk-O1 chiral column (250 mm x 4.6 mm/5μm) : 40% hexanes: 60% CH2Cl2 (254 nm) Peak 1 = 4.3 min. Peak 2 = 5.6 min (ee >97%).

3-(4-Chlorophenyl)-N-((4-methoxyphenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3t)

Following General procedure A, Compound (urea) 1t (110 mg, 0.23 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3t which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid. (40 mg, 35% yield). Following General procedure B, Compound (urea) 1t (50 mg, 0.11 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3t (41 mg, 79% yield) as a white solid. Mp 216 °C decomp; 1H-NMR (800 MHz, CDCl3): δ 8.11-8.10 (m, 2H), 7.59-7.58 (m, 2H), 7.32-7.29 (m, 5H), 7.10 (d, J = 7.7 Hz, 2H), 7.00 (dd, J = 7.2, 1.3 Hz, 2H), 4.74-4.72 (m, 1H), 4.60-4.57 (m, 1H), 4.22-4.19 (m, 1H), 3.90-3.87 (m, 3H). 13C{1H} NMR (201 MHz, CDCl3): δ 169.8, 163.9, 158.8, 139.0, 137.5, 131.9, 129.91, 129.76, 129.2, 128.4, 127.9, 127.4, 113.9, 58.1, 55.8, 51.1. LRMS 486.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C23H21ClN3O2S2) 486.0713; Found 486.0710.

3-(4-Chlorophenyl)-N-(N,N-diethylysulfamoyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (3u)

Following General procedure B, Compound (urea) 1u (63 mg, 0.15 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3u which was purified by flash chromatography (40% hexanes in EtOAc) to give a pale solid (47 mg, 72% yield). Mp 156-158 °C; 1H-NMR (800 MHz, CDCl3): δ 9.43 (s, 1H), 7.58-7.57 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 8.4 Hz, 3H), 7.13 (d, J = 8.0 Hz, 2H), 4.75 (s, 1H), 4.67 (s, 1H), 4.29 (dd, J = 12.4, 5.5 Hz, 1H), 3.55 (tt, J = 15.3, 7.9 Hz, 4H), 1.27 (t, J = 7.1 Hz, 6H). 13C{1H} NMR (201 MHz, CDCl3): δ 170.9, 158.5, 139.1, 137.4, 129.8, 129.3, 129.2, 128.4, 128.1, 127.4, 58.2, 51.2, 44.3, 14.3. LRMS 451.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C20H24ClN4O2S2) 451.1029; Found 451.1030.

3-(4-Chlorophenyl)-4-phenyl-N-(piperidin-1-ylsulfonfonyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3v)
Following General procedure B, Compound (urea) 1v (55 mg, 0.12 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3w which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (36 mg, 63% yield). Mp 165-167 °C; 1H-NMR (800 MHz, CDCl3): δ 9.38 (s, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 7.3 Hz, 2H), 7.29-7.28 (m, 3H), 7.14 (d, J = 7.8 Hz, 2H), 4.77-4.75 (m, 1H), 4.68 (t, J = 12.0 Hz, 1H), 4.31-4.28 (m, 1H), 3.53 (s, 2H), 1.69 (d, J = 2.9 Hz, 4H), 1.61-1.59 (m, 2H). 13C{1H} NMR (201 MHz, CDCl3): 170.9, 158.7, 139.1, 137.4, 129.8, 129.30, 129.15, 128.3, 127.9, 127.4, 58.2, 51.18, 51.07, 48.2, 25.7, 23.9. LRMS 463.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C21H24ClN4O2S2) 463.1029; Found 463.1033.

3-(4-Chlorophenyl)-4-phenyl-N-((4-(trifluoromethyl)piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3w)

Following General procedure B, Compound (urea) 1w (75 mg, 0.15 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 3w which was purified by flash chromatography (40% hexanes in EtOAc) to give a pale white solid (40 mg, 52% yield).

1H-NMR (800 MHz, CDCl3): δ 9.41 (s, 1H), 7.58-7.57 (m, 2H), 7.34-7.30 (m, 3H), 7.29 (d, J = 8.4 Hz, 3H), 7.14 (d, J = 7.3 Hz, 2H), 4.78 (dd, J = 11.4, 5.4 Hz, 1H), 4.67 (t, J = 12.0 Hz, 1H), 4.28 (dd, J = 12.5, 5.5 Hz, 1H), 4.08 (t, J = 15.1 Hz, 2H), 3.16 (dt, J = 38.9, 12.7 Hz, 2H), 2.18 (s, 1H), 1.96 (d, J = 11.3 Hz, 2H), 1.77-1.74 (m, 2H). 13C{1H} NMR (201 MHz, CDCl3): δ 160.2, 138.8, 137.4, 130.2, 129.96, 129.80, 129.2, 128.6, 127.99, 127.84, 127.4, 58.3, 52.0, 46.0, 40.10, 39.96, 39.85, 23.8. LRMS 531.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C22H23ClN4O2F3S2) 531.0903; Found 531.0903.

4-Chloro-N-(propylcarbamothioyl)benzenesulfonamide (7)

Following General procedure B, chloropropamide (1.0 g, 3.6 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 7 which was purified by flash chromatography (25% hexanes in EtOAc) to give a pale solid (735 mg, 69 % yield). 1H-NMR (800 MHz; CDCl3): δ 8.13 (s, 1H), 7.81 (d, J = 6.7 Hz, 2H), 7.54-7.53 (m, 2H), 3.54 (d, J = 5.4 Hz, 2H), 1.63 (d, J = 7.2 Hz, 2H), 0.95-0.93 (m, 3H). 13C{1H} NMR (201 MHz, CDCl3): δ 177.9, 141.2, 137.1, 130.1, 128.5, 47.9, 21.8, 11.4. LRMS 293.0, HRMS (ESI) m/z: [M + H]+ Calcd for (C10H14ClN3O2S2) 293.0185; Found 293.0190.

N-(Butylcarbamothioyl)-4-methylbenzenesulfonamide (10)

Following General procedure A, Tolbutamide (1.0 g, 3.7 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 10 which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (695 mg, 66% yield). Mp 174-176 °C; 1H-NMR (800 MHz, CDCl3): δ 8.11 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 3.57-3.57 (m, 1H), 2.45 (s, 2H), 1.57 (t, J = 7.4 Hz, 1H), 1.33 (q, J = 7.5 Hz, 1H), 0.93 (s, 2H). 13C{1H} NMR (201 MHz, CDCl3): δ 178.0, 145.7, 135.7, 130.4, 127.1, 46.0, 30.5, 21.9, 20.1. LRMS 287.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C12H15N2O2S2) 287.0888; Found 287.0893.
3-(4-Chlorophenyl)-N-(4-cyanophenyl)sulfonyl)-4-phenyl-5,6-dihydropyridazine-1(4H)-carbothioamide (12a)

Following General procedure C, Compound (urea) 11a (100 mg, 0.21 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 12a which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (49 mg, 48% yield). Mp 114–118 °C; 1H-NMR (800 MHz; CDCl3): δ 10.43 (s, 1H), 8.28 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 7.8 Hz, 4H), 7.28 (d, J = 7.4 Hz, 1H), 7.07 (d, J = 7.2 Hz, 2H), 4.92 (d, J = 12.1 Hz, 1H), 4.27 (s, 1H), 3.20 (t, J = 13.4 Hz, 1H), 2.17 (dd, J = 36.2, 15.7 Hz, 2H). 13C {1H} NMR (201 MHz; CDCl3): δ 173.80, 149.7, 140.60, 139.69, 137.03, 133.49, 132.5, 130.2, 129.6, 129.4, 129.0, 127.9, 117.5, 39.2, 38.5, 26.4. LRMS 495.0, HRMS (ESI) m/z: [M + H]+ Calcd for (C24H18Cl3N2O2S2) 495.0716; Found m/z 495.0714.

3-(4-Chlorophenyl)-4-phenyl-N-((3-(trifluoromethyl)phenyl)sulfonyl)-5,6-dihydropyridazine-1(4H)-carbothioamide (12b)

Following General procedure C, Compound (urea) 11b (100 mg, 0.19 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 12b which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (44.5 mg, 43% yield). Mp 100–104 °C; 1H-NMR (800 MHz; CDCl3): δ 10.43 (s, 1H), 8.42 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.71 (t, J = 7.9 Hz, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.34–7.32 (m, 4H), 7.28 (d, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 2H), 4.94 (d, J = 13.8 Hz, 1H), 4.26 (s, 1H), 3.20 (d, J = 13.6, 4.0 Hz, 1H), 2.22–2.14 (m, 2H). 13C {1H} NMR (201 MHz; CDCl3): δ 173.80, 149.41, 140.60, 139.69, 137.03, 133.78, 129.56, 129.34, 129.08, 127.95, 39.13, 38.47, 26.41. LRMS 538.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C24H20ClF3N3O2S2) 538.0638; Found m/z 538.0643.

3-(4-Chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-5,6-dihydropyridazine-1(4H)-carbothioamide (12c)

Following General procedure C, Compound (urea) 11c (50 mg, 0.05 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 12c which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale solid (19 mg, 38% yield). Mp 100–104 °C; 1H-NMR (800 MHz; CDCl3): δ 10.39 (s, 1H), 8.10 (t, J = 9.2 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 7.3 Hz, 5H), 7.06 (d, J = 7.7 Hz, 2H), 4.94 (d, J = 12.2 Hz, 1H), 4.25 (s, 1H), 3.19 (t, J = 15.4 Hz, 1H), 2.16 (dd, J = 32.2, 8.1 Hz, 2H). 13C {1H} NMR (201 MHz; CDCl3): δ 173.7, 149.7, 139.78, 139.80, 139.65, 136.9, 133.7, 133.2, 130.5, 129.56, 129.40, 128.0, 126.7, 39.2, 38.5, 26.4. LRMS 504.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C23H20Cl2N3O2S2) 504.0374; Found m/z 504.0368.

3-(4-Chlorophenyl)-N-(naphthalen-2-ylsulfonyl)-4-phenyl-5,6-dihydropyridazine-1(4H)-carbothioamide (12d)
Following General procedure C, Compound (urea) 11d (100 mg, 0.198 mmol) was converted in a two-step, one-pot protocol to title compound thiourea 12d which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale solid (55 mg, 53% yield). Mp 196-201 °C; 1H NMR (800 MHz; CDCl3): δ 10.48 (s, 1H), 8.78 (s, 1H), 8.09-7.91 (m, 4H), 7.67-7.61 (m, 5H), 7.34-7.30 (m, 4H), 7.06 (d, J = 7.8 Hz, 2H), 4.93 (d, J = 12.5 Hz, 1H), 4.24 (s, 1H). 3.17 (td, J = 13.6, 3.2 Hz, 1H), 2.19-2.10 (m, 2H). 13C{1H} NMR (201 MHz; CDCl3): δ 174.0, 149.1, 139.8, 136.7, 135.6, 135.3, 133.9, 132.1, 129.8, 129.52, 129.34, 128.9, 128.10, 127.96, 127.89, 127.70, 123.8, 39.1, 38.5, 26.4. LRMS 520.0, HRMS (ESI) m/z: [M + H]+ Calcd for (C27H23ClN3O2S2) 520.0920; Found m/z 520.0922.

**N-(Adamantan-1-yl)carbamothioyl)-4-(trifluoromethoxy)benzenesulfonamide (14a):**

Following General procedure C, Compound 13a (0.5 g, 1.19 mmol) was converted to title compound 14a which was purified by flash chromatography (35% hexanes in EtOAc) to give an off-white solid (170 mg, 33% yield). Mp 152-154 °C; 1H NMR (800 MHz; CDCl3): δ 7.91 (d, J = 8.0 Hz, 2H), 7.87 (s, 1H), 7.84 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 2.09 (s, 6H), 2.02 (s, 1H), 1.92 (s, 3H), 1.64 (d, J = 16.0 Hz, 6H). 13C{1H} NMR (200 MHz; CDCl3): δ 175.1, 153.4, 136.8, 129.6, 121.3, 42.8, 40.6, 36.7, 36.3, 29.6. LRMS 435.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C18H22F3N2O3S2) 435.1024; Found 435.1029.

**N-(Adamantan-1-yl)carbamothioyl)benzenesulfonamide (14b):** Following General procedure C, Compound 13b (0.5 gm, 1.50 mmol) was A to form compound 14b which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale solid (210 mg, 41% yield). Mp 144–146 °C; 1H NMR (800 MHz; CDCl3): δ 7.92 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 8.0 Hz, 1H), 7.60-7.58 (m, 2H), 2.12 (s, 6H), 2.10 (s, 3H), 1.67 (s, 6H). 13C{1H} NMR (200 MHz; CDCl3): δ 175.2, 138.6, 134.4, 129.7, 127.3, 55.9, 40.6, 36.3, 29.6. LRMS 351.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C18H22N2O3S2) 351.1201; Found m/z 351.1199.

**N-(Adamantan-1-yl)carbamothioyl)-4-methoxybenzenesulfonamide (14c):** Following General procedure C, Compound 13c (0.5 gm, 1.37 mmol) was converted to title compound 14c which was purified by flash chromatography (35% hexanes in EtOAc) to give a pale white solid (160 mg, 31% yield). Mp 172–174 °C; 1H NMR (800 MHz; CDCl3): δ 7.93 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H), 2.14 (s, 6H), 2.10 (s, 3H), 1.67 (s, 6H). 13C{1H} NMR (200 MHz; CDCl3): δ 175.5, 164.3, 130.0, 129.6, 114.9, 56.0, 55.9, 40.6, 36.4, 29.6. LRMS 381.1, HRMS (ESI) m/z: [M + H]+ Calcd for (C18H22N2O3S2) 381.1307; Found 381.1314.

**N-(Adamantan-1-yl)carbamothioyl)-4-(tert-butyl)benzenesulfonamide (14d):** Following General procedure A, Compound 13d (0.5 gm, 1.28 mmol) was converted to title compound 14d which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale solid (180 mg, 35% yield). Mp 171–173 °C; 1H NMR (800 MHz; CDCl3): δ 7.93 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 2.11 (s, 6H), 2.09 (s, 3H), 1.66 (s, 6H), 1.35 (s, 9H). 13C{1H}
NMR (200 MHz; CDCl₃): δ 175.4, 158.6, 135.6, 127.2, 126.7, 55.9, 40.5, 36.3, 31.2, 29.6. 381.1307. LRMS 407.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₂₁H₃₁N₂O₂S₂) 407.1827, Found 407.1833.

N-(Cyclohexylcarbamothioyl)-4-(trifluoromethyl)benzenesulfonamide (16)

Following General procedure A, (100 mg, 0.37 mmol) compound 15 was converted in a two-step, one-pot protocol to title compound thiourea 16 which was purified by flash chromatography (30% hexanes in EtOAc) to give a pale white solid (55 mg, 52% yield). ¹H-NMR (800 MHz, CDCl₃): δ 8.01 (d, J = 8.2 Hz, 4H), 7.85 (d, J = 8.2 Hz, 2H), 4.14-4.10 (m, 1H), 1.97-1.96 (m, 2H). 1.71 (dd, J = 9.4, 4.0 Hz, 2H), 1.63 (dt, J = 8.5, 4.1 Hz, 1H), 1.39 (dd, J = 11.0, 2.5 Hz, 2H), 1.28-1.26 (m, 3H). ¹³C{¹H} NMR (200 MHz; CDCl₃): δ 176.0, 142.1, 136.2, 127.7, 126.9, 54.9, 31.8, 25.4, 24.5. LRMS 367.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₁₄H₁₈N₂O₂F₃S₂) 367.0762; Found 367.0764.

Methyl 3-(4-chlorophenyl)-4-phenyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbimidothioate (17)

Following General procedure E, compound 1a (200 mg, 0.39 mmol) was reacted in a three-step one-pot procedure using Mel (2 eq) as an alkylating agent to afford compound 17 which was purified by flash chromatography (25% hexanes in EtOAc) to give a pale orange powder (138 mg, 65% yield). ¹H-NMR (800 MHz, CDCl₃): δ 8.10 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.4 Hz, 2H), 7.28 (t, J = 6.4 Hz, 3H), 7.17 (d, J = 7.4 Hz, 2H), 4.98-4.93 (m, 1H), 4.83 (dd, J = 11.1, 5.3 Hz, 1H), 4.54-4.51 (m, 1H), 5.34 (s, 3H). ¹³C{¹H} NMR (200 MHz; CDCl₃): δ 163.6, 160.2, 147.6, 137.4, 129.8, 129.4, 129.2, 128.5, 128.1, 127.5, 126.8, 125.9, 60.3, 60.2, 52.5, 16.3. LRMS 538.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₂₃H₂₀ClN₃O₂F₃S₂) 538.0638; Found 538.0644.

But-3-yn-1-yl (Z)-3-(4-chlorophenyl)-4-phenyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carbimidothioate (18)

Following General procedure E, Compound (urea) 1b (300 mg, 0.59 mmol) was converted in a three-step, one-pot protocol using 1-Butynyl bromide (2 eq) to afford title compound 18 which was purified by flash chromatography (25% hexanes in EtOAc) to give a pale, yellow solid (185 mg, 54% yield). ¹H-NMR (800 MHz, CDCl₃): δ 8.09 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 7.1 Hz, 3H), 7.61 (d, J = 6.6 Hz, 3H), 7.34 (d, J = 6.7 Hz, 2H), 7.27 (dd, J = 9.2, 2.0 Hz, 4H), 7.17 (d, J = 6.5 Hz, 2H), 5.04 (s, 1H), 4.87-4.85 (m, 1H), 4.60 (s, 1H), 2.95 (d, J = 7.7 Hz, 2H), 2.39 (t, J = 3.2 Hz, 2H), 1.92 (d, J = 2.4 Hz, 1H). ¹³C{¹H} NMR (200 MHz; CDCl₃): δ 161.6, 160.3, 147.3, 138.6, 137.5, 133.5, 129.5, 129.4, 129.2, 128.5, 127.9, 127.5, 126.8, 126.0, 81.6, 69.9, 60.4, 52.6, 31.6, 19.4. LRMS 576.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₂₇H₂₂ClN₃O₂F₃S₂) 576.0794; Found 576.0786.

Methyl 3-(((3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)((4-(trifluoromethyl)phenyl)sulfonylimino)methyl)thio)-2-methylpropanoate (19)
Following General procedure E, Compound (urea) \(1a\) (300 mg, 0.60 mmol) was converted in a three-step, one-pot protocol using methyl (S)-3-bromo-2-methylpropanoate (2 eq) as alkylation agent to afford title compound \(19\) which was purified by flash chromatography (25% hexanes in EtOAc) to give a pale yellow solid (197 mg, 55%). \(^1\)H-NMR (800 MHz, CDCl\(_3\)) : \(\delta\) 8.07 (d, \(J = 7.3\) Hz, 4H), 7.74 (d, \(J = 8.1\) Hz, 4H), 7.58 (s, 4H), 7.31 (d, \(J = 7.5\) Hz, 5H), 7.25 (t, \(J = 9.7\) Hz, 7H), 7.15 (s, 5H), 5.05 (s, 1H), 4.84 (dd, \(J = 7.2, 3.5\) Hz, 2H), 4.61 (s, 1H), 3.59 (d, \(J = 10.5\) Hz, 7H), 3.05 (ddd, \(J = 22.1, 13.9, 8.1\) Hz, 2H), 2.78 (s, 2H), 2.61 (d, \(J = 6.5\) Hz, 2H), 0.94 (dd, \(J = 10.9, 7.2\) Hz, 7H). \(^13\)C{H} NMR (200 MHz; CDCl\(_3\)) : \(\delta\) 175.1, 162.1, 160.2, 147.2, 138.6, 137.4, 133.6, 129.8, 129.4, 129.2, 128.4, 127.8, 127.5, 126.8, 125.9, 60.5, 52.6, 52.3, 52.0, 39.5, 35.3, 16.9. LRMS 624.1, HRMS (ESI) m/z: [M + H]\(^+\) Calcd for (C\(_{38}\)H\(_{31}\)Cl\(_2\)N\(_2\)O\(_4\)F\(_2\)S\(_2\)) 624.1005; Found 624.1006. (R,R)-Whelk-O1 chiral column (250 mm x 4.6 mm/5\(\mu\)m): 100% EtOH (254 nm) (1.5 mL/min) Peak 1 = 4.7 min. Peak 2 = 6.1 min.

2-Methylbutyl ((3-(4-chlorophenyl))-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioate (20)

Following General procedure E, Compound (urea) \(1q\) (200 mg, 0.42 mmol) was converted in a three-step, one-pot protocol using (S)-1-bromo-2-methylbutane (2 eq) as the alkylation agent to afford title compound \(3\) which was purified by flash chromatography (20% hexanes in EtOAc) to give (103 mg, 43% yield) as a pale brown powder.

\(^1\)H-NMR (800 MHz, CDCl\(_3\)) : \(\delta\) 7.90 (d, \(J = 8.2\) Hz, 2H), 7.62 (d, \(J = 7.4\) Hz, 2H), 7.44 (d, \(J = 8.5\) Hz, 3H), 7.33 (t, \(J = 7.5\) Hz, 3H), 7.31-7.27 (m, 3H), 7.17 (d, \(J = 6.9\) Hz, 2H), 4.97 (s, 1H), 4.82 (dd, \(J = 10.8, 5.1\) Hz, 1H), 4.52 (s, 1H), 2.89-2.85 (m, 1H), 2.67-2.64 (m, 1H), 1.06 (dt, \(J = 10.7, 5.2\) Hz, 1H), 0.84 (t, \(J = 3.2\) Hz, 4H), 0.75 (d, \(J = 4.1\) Hz, 4H). \(^13\)C{H} NMR (200 MHz; CDCl\(_3\)) : \(\delta\) 138.8, 137.9, 137.2, 129.8, 129.4, 129.2, 128.4, 128.2, 127.9, 127.5, 52.3, 47.9, 40.1, 34.7, 28.8, 18.7, 11.3. LRMS 560.1, HRMS (ESI) m/z: [M + H]\(^+\) Calcd for (C\(_{28}\)H\(_{24}\)Cl\(_2\)N\(_2\)O\(_4\)F\(_2\)S\(_2\)) 560.1000; Found 560.1006. (R,R)-Whelk-O1 chiral column (250 mm x 4.6 mm/5\(\mu\)m): 100% EtOH (254 nm) (1.0 mL/min) Peak 1 = 4.6 min. Peak 2 = 6.2 min.

2-Amino-2-oxoethyl ((3-(4-chlorophenyl))-4-phenyl-N-((4-(cyano)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioate (21)

Following General procedure E, Compound (urea) \(1m\) (50 mg, 0.11 mmol) was converted in a three-step, one-pot protocol using bromoacetamide (2 eq) as the alkylation agent to afford title compound \(21\) which was purified by flash chromatography (40% hexanes in EtOAc) to give (22 mg, 38% yield) a pale brown solid. Mp 170-172 °C; \(^1\)H-NMR (800 MHz, CDCl\(_3\)) : \(\delta\) 8.05 (d, \(J = 7.7\) Hz, 2H), 7.79 (d, \(J = 8.0\) Hz, 2H), 7.60 (d, \(J = 8.2\) Hz, 2H), 7.35 (t, \(J = 7.1\) Hz, 3H), 7.30 (t, \(J = 6.1\) Hz, 3H), 7.15 (d, \(J = 7.1\) Hz, 2H), 6.58 (s, 1H), 5.34 (t, \(J = 1.4\) Hz, 1H), 4.94-4.92 (m, 1H), 4.87-4.85 (m, 1H), 4.47 (s, 1H), 3.70-3.68 (m, 1H), 3.62 (d, \(J = 16.3\) Hz, 1H). \(^13\)C{H} NMR (200 MHz; CDCl\(_3\)) : \(\delta\) 169.2, 161.6, 138.7, 132.8, 130.0, 129.48, 129.37, 128.6, 127.4, 127.2, 117.7, 116.0, 111.1, 60.2, 52.5, 36.1.
2-((3-(4-Chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)((4-(trifluoromethoxy)phenyl)sulfonyl)imino)methyl)thio)acetic acid (22)

Following General procedure E, Compound (urea) 1e (200 mg, 0.38 mmol) was converted in a three-step, one-pot protocol using bromoacetic acid (2eq) as the alkylating agent to afford title compound 22 which was purified by flash chromatography (45% hexanes in EtOAc) to give (139 mg, 61% yield) an off-white solid. Mp 184-186 °C; \( ^1 \)H-NMR (800 MHz, CDCl\(_3\)): \( \delta \) 7.98 (d, \( J = 8.7 \) Hz, 2H), 7.61 (d, \( J = 8.4 \) Hz, 2H), 7.34 (t, \( J = 7.5 \) Hz, 2H), 7.29 (dd, \( J = 13.3, 10.8 \) Hz, 5H), 7.18 (d, \( J = 7.3 \) Hz, 2H), 5.11 (t, \( J = 0.8 \) Hz, 1H), 4.90 (dd, \( J = 11.1, 5.6 \) Hz, 1H), 4.66-4.66 (m, 1H), 3.58 (q, \( J = 14.3 \) Hz, 2H). \( ^{13} \)C\{1H\} NMR (200 MHz; CDCl\(_3\)): \( \delta \) 172.4, 160.5, 151.8, 141.9, 139.3, 138.5, 137.7, 129.9, 129.5, 129.7, 128.7, 128.5, 127.7, 127.6, 120.7, 60.7, 53.1, 34.5. LRMS 598.1, HRMS (ESI) m/z: [M + H]\(^+\) Calcd for (C\(_{25}\)H\(_{21}\)ClN\(_3\)O\(_3\)S\(_2\)) 598.0485, Found 598.0488.

But-3-yn-1-yl (Z)-N’-((4-chlorophenyl)sulfonyl)-N-propylcarbamimidothioate (23)

Following General procedure E, chlorpropamide (50 mg, 0.18 mmol) was converted in a three-step, one-pot protocol using methyl iodide (2 eq) as the alkylating agent to afford title compound 23 which was purified by flash chromatography (30% hexanes in EtOAc) to give (20 mg, 32% yield) a pale white sticky solid. \( ^1 \)H-NMR (800 MHz, CDCl\(_3\)): \( \delta \) 8.19 (s, 1H), 7.84 (d, \( J = 7.9 \) Hz, 2H), 7.45 (d, \( J = 8.1 \) Hz, 2H), 3.26 (t, \( J = 5.4 \) Hz, 2H), 3.12 (d, \( J = 6.6 \) Hz, 2H), 2.45 (d, \( J = 5.5 \) Hz, 2H), 2.01 (s, 1H), 1.66 (d, \( J = 6.8 \) Hz, 2H), 0.98 (d, \( J = 7.1 \) Hz, 3H). \( ^{13} \)C\{1H\} NMR (200 MHz; CDCl\(_3\)): \( \delta \) 168.6, 141.1, 138.6, 129.2, 127.7, 81.7, 70.2, 46.2, 30.3, 22.6, 19.4, 11.3. LRMS 345.0. HRMS (ESI) m/z: [M + H]\(^+\) Calcd for (C\(_{14}\)H\(_{18}\)ClN\(_2\)O\(_3\)S\(_2\)) 345.0498; Found m/z 345.0504.

Cyclopropylmethyl N’-((4-chlorophenyl)sulfonyl)-N-propylcarbamimidothioate (24)

Following General procedure E, Chlorpropamide (100 mg, 0.36 mmol) was converted in a three-step, one-pot protocol to title compound 24 which was purified by flash chromatography (25% hexanes in EtOAc) to give (60 mg, 48% yield) as an off-white sticky solid. \( ^1 \)H-NMR (800 MHz, CDCl\(_3\)): \( \delta \) 8.18 (s, 1H), 7.83 (d, \( J = 8.3 \) Hz, 2H), 7.44 (d, \( J = 8.5 \) Hz, 2H), 3.26 (t, \( J = 6.2 \) Hz, 2H), 2.93 (d, \( J = 7.3 \) Hz, 2H), 1.66 (d, \( J = 7.2 \) Hz, 2H), 0.98 (t, \( J = 7.3 \) Hz, 4H), 0.55 (d, \( J = 7.2 \) Hz, 2H). \( ^{13} \)C\{1H\} NMR (200 MHz; CDCl\(_3\)): \( \delta \) 169.9, 141.5, 138.5, 129.1, 127.8, 46.2, 37.9, 29.8, 22.7, 11.3, 10.1, 6.0. LRMS 347.1, HRMS (ESI) m/z: [M + H]\(^+\) Calcd for (C\(_{18}\)H\(_{20}\)ClN\(_2\)O\(_3\)S\(_2\)) 347.0655; Found 347.0659.

2-Hydroxyethyl N’-((4-chlorophenyl)sulfonyl)-N-propylcarbamimidothioate (25)
Following General procedure E, chlorpropamide (100mg, 0.36 mmol) was converted in a three-step, one-pot protocol to yield title compound 25 which was purified by flash chromatography (40% hexanes in EtOAc) to give (51mg, 42% yield) as a sticky solid. ¹H-NMR (800 MHz, CDCl₃): δ 8.23 (s, 1H), 7.82 (d, J = 4.4 Hz, 2H), 7.45 (d, J = 4.3 Hz, 2H), 3.75 (d, J = 5.2 Hz, 2H), 3.28 (d, J = 4.9 Hz, 2H), 3.17 (d, J = 4.6 Hz, 2H), 1.66 (t, J = 5.9 Hz, 2H), 0.97 (d, J = 4.9 Hz, 3H). ¹³C{¹H} NMR (200 MHz; CDCl₃): δ 169.5, 140.8, 138.8, 129.3, 127.7, 61.7, 46.3, 34.1, 22.6, 11.3. LRMS 337.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₁₉H₁₈ClN₂O₃S₂) 337.0047; Found 337.0443.

**Methyl N-(Adamantan-1-yl)-N'-(4-(trifluoromethoxy)phenyl)sulfonyl)carbamimidothioate (26):**

Following General procedure E, Compound 13a (0.5 g, 11.9 mmol) was converted in a three-step, one-pot protocol to title compound 26 which was purified by flash chromatography (25% hexanes in EtOAc) to give a white sticky solid (180 mg, 34% yield). Mp 108–110 °C; ¹H-NMR (800 MHz; CDCl₃): δ 7.92 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H), 2.10 (s, 3H), 2.01 (s, 6H), 1.67-1.62 (m, 6H). ¹³C{¹H} NMR (200 MHz; CDCl₃): δ 151.8, 141.5, 128.9, 128.5, 121.3, 120.9, 41.9, 36.3, 36.04, 29.7, 15.3. LRMS 449.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₁₉H₂₃F₃N₂O₃S₂) 449.1180; Found 449.1180.

**Methyl-3-(4-chlorophenyl)-N-(naphthalen-2-ylsulfonyl)-4-phenyl-5,6-dihydropyridazine-1(4H)-carbimidothioate (27):**

Following General procedure E, Compound 11d (100 mg, 0.19 mmol) was converted in a three-step, one-pot protocol to give title compound 27 which was purified by flash chromatography (25% hexanes in EtOAc) to give a white sticky solid (30 mg, 29% yield). Mp 103–105 °C; ¹H-NMR (800 MHz, CDCl₃): δ 8.51 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.94 (dd, J = 19.2, 8.2 Hz, 2H), 7.89 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.59 (td, J = 15.4, 7.5 Hz, 2H), 7.33 (t, J = 7.1 Hz, 2H), 7.27 (s, 2H), 7.26 (t, J = 1.9 Hz, 1H), 7.14 (d, J = 7.7 Hz, 2H), 4.59 (d, J = 12.9 Hz, 1H), 4.24 (s, 1H), 3.62 (td, J = 13.3, 2.7 Hz, 1H), 2.34 (s, 3H), 2.28-2.13 (m, 2H). ¹³C{¹H} NMR (201 MHz; CDCl₃): δ 168.6, 150.3, 141.5, 139.9, 136.2, 134.5, 134.2, 132.2, 129.4, 129.0, 128.3, 128.0, 127.7, 127.3, 126.3, 122.6, 42.3, 37.8, 26.6, 16.8. LRMS 534.1, HRMS (ESI) m/z: [M + H]⁺ Calcd for (C₂₉H₂₅ClN₃O₂S₂) 534.1077; Found m/z 534.1075.

**(S,S)-Methyl(3-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)((4-(trifluoromethyl)phenyl)sulfonyl)imino)methyl)thio)-2-methylpropanoate (28):**

Successive crystallizations of 19 (200 mg batch) from ethanol gave the S, S-diastereomer (92-94% de.) This was followed by recrystallization with isopropyl alcohol to afford the compound 31 (>99.8% de, 64 mg, 32%). The preferential crystallization of the diastereomeric compound could be expedited by generating seed crystals from chiral separation of a small sample on (R, R)-Whelk O chiral column. Mp 116-118°C; ¹H-NMR (500 MHz, CDCl₃): δ 8.10 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.28 (s, 2H), 7.18-7.17 (m, 2H), 5.07 (s, 1H), 4.86 (dt, J = 7.7, 4.7 Hz, 1H), 4.61
(s, 1H), 3.61 (s, 3H), 3.06 (dd, J = 13.8, 8.1 Hz, 1H), 2.84-2.78 (m, 1H), 2.65-2.62 (m, 1H), 0.96 (d, J = 7.1 Hz, 3H). $^{13}$C{1H} NMR (201 MHz, CDCl$_3$): δ 175.1, 160.3, 147.5, 138.6, 129.9, 129.5, 129.2, 128.5, 128.0, 127.6, 126.9, 125.9, 60.6, 52.7, 52.0, 39.7, 35.4, 17.0. LRMS 624.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{28}$H$_{26}$ClN$_3$O$_4$F$_3$S$_2$) 624.1005; Found m/z 624.1006. ($R, R$)-Whelk-O1 chiral column (250 mm x 4.6 mm/5µm) : 100% EtOH (254 nm) Peak 1 = 6.7 min, Peak 2= NA (8.7 min).

**SLV326 (S-enantiomer)**

To a solution of Compound 31 in DCM (5 mL) (20 mg, 0.03 mmol) cooled to 0 °C, methylamine (1.5 eq) dissolved in DCM:MeOH (9:1) was added followed by Et$_3$N (1.5 eq). The reaction was warmed to room temperature and allowed to run until completion of the reaction (4 h). The organic layer was then extracted in DCM washed with water, dried over Na$_2$SO$_4$. Purification on a silica gel column using hexanes-ethyl acetate (1:1) yielded compound SLV326 as a pale white solid (14 mg, 84%). SLV326 was confirmed as the desired product with 97.9% ee by the comparison of all spectroscopic data with racemic sample.

$^1$H-NMR (800 MHz, CDCl$_3$): δ 8.04 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 7.5 Hz, 2H), 7.25 (s, 3H), 7.12 (d, J = 7.1 Hz, 2H), 4.65 (d, J = 1.1 Hz, 1H), 4.54-4.53 (m, 1H), 4.10 (s, 1H), 3.23 (s, 3H). LRMS 531.1, HRMS (ESI) m/z: [M + H]$^+$ Calcd for (C$_{24}$H$_{21}$ClN$_4$O$_2$F$_3$S$_2$) 531.1026; Found m/z 521.1031. ($R, R$)-Whelk-O1 chiral column (250 mm x 4.6 mm/5µm) : 100% EtOH (0.5 mL/min) (254 nm) Peak 1 = 11.1 min, Peak 2 = NA (11.8 min). Racemic sample was utilized for ee calculations.
**X-ray Crystal Structure data for 3m.**

**Crystallization Method:** Compound 3m was crystallized by slow evaporation of Isopropyl alcohol (2.0 mg in 1mL IPA) to yield crystals suitable for X-ray.

A single crystal of 3m (CCDC 2158144) was mounted under mineral oil on a Mitegen micromount and immediately placed in a cold nitrogen stream at 100(2) K prior to data collection. Data were collected on a Bruker D8 Quest equipped with a Photon100 CMOS detector and Mo ImS source. A series of 0.5° φ- and ω-scans were collected with monochromatic Mo Kα radiation, λ = 0.71073 Å and integrated with the Bruker SAINT program. Structure solution and refinement was performed using the SHELXTL/PC suite and ShelXle. Intensities were corrected for Lorentz and polarization effects and an empirical absorption correction was applied using Blessing’s method as incorporated into the program SADABS. Non-hydrogen atoms were refined with anisotropic thermal parameters. Further comments on each compound:

3m. The molecule crystallized in the Monoclinic P2₁/n space group. The amine H atom was located in the difference map and its position was allowed to freely refine. Remaining H atoms were included as riding idealized contributors. Amine H atom U's were assigned as 1.5 times U(eq) of the carrier atom; remaining H atom U's were assigned as 1. 2 times carrier U(eq).

![Figure S1. Ellipsoid contour at 50 % probability levels](image-url)
Table S3. Crystal data and structure refinement for 3m.

| Parameter                                      | Value                                      |
|------------------------------------------------|--------------------------------------------|
| Identification code                            | MRI3208                                    |
| Empirical formula                              | C23 H17 Cl N4 O2 S2                       |
| Formula weight                                  | 480.98                                     |
| Temperature                                     | 100(2) K                                   |
| Wavelength                                      | 0.71073 Å                                  |
| Crystal system                                  | Monoclinic                                 |
| Space group                                     | P21/n                                      |
| Unit cell dimensions                           | a = 5.7807(5) Å                           |
|                                                 | b = 24.0953(18) Å                         |
|                                                 | c = 15.7069(12) Å                         |
| Volume                                          | 2168.2(3) Å                               |
| Z                                               | 4                                          |
| Density (calculated)                           | 1.473 Mg/m³                                |
| Absorption coefficient                         | 0.399 mm⁻¹                                 |
| F(000)                                         | 992                                        |
| Crystal size                                    | 0.622 x 0.056 x 0.018 mm³                  |
| Theta range for data collection                | 2.138 to 25.437°                           |
| Index ranges                                    | -6<=h<=6, -29<=k<=29, -18<=l<=18            |
| Reflections collected                           | 50440                                      |
| Independent reflections                         | 3971 [R(int) = 0.2226]                     |
| Completeness to theta = 25.242°                | 99.9 %                                     |
| Absorption correction                          | Semi-empirical from equivalents           |
| Max. and min. transmission                     | 0.99558 and 0.87253                        |
| Refinement method                              | Full-matrix least-squares on F²           |
| Data / restraints / parameters                  | 3971 / 0 / 292                            |
| Goodness-of-fit on F²                           | 1.062                                      |
| Final R indices [I>2sigma(I)]                  | R1 = 0.0563, wR2 = 0.1083                 |
| R indices (all data)                            | R1 = 0.0919, wR2 = 0.1204                 |
| Extinction coefficient                         | n/a                                        |
| Largest diff. peak and hole                    | 0.325 and -0.460 e.Å⁻³                    |
**X-ray crystal data for compound 28**

**Crystallization Method:** Compound 28 (2 mg) was re-crystallized from isopropyl alcohol (1.5 mL) by slow evaporation to afford a single diastereomer crystal required for X-ray.

Single crystals of each compound, 28 (CCDC 2158143) were mounted under mineral oil on a Mitegen micromount and immediately placed in a cold nitrogen stream at 100(2) K prior to data collection. Data were collected on a Bruker DUO equipped with an APEXII CCD detector and Cu ImS source. A series of 0.5° φ- and ω-scans were collected with monochromatic Cu Kα radiation, λ = 1.54178 Å and integrated with the Bruker SAINT program. Structure solution and refinement was performed using the SHELXTL/PC suite and ShelXle. Intensities were corrected for Lorentz and polarization effects and an empirical absorption correction was applied using Blessing’s method as incorporated into the program SADABS. Non-hydrogen atoms were refined with anisotropic thermal parameters. Further comments on each compound:

**31.** The molecule crystallized in the Monoclinic P2₁ space group. Methyl H atom positions, R-CH₃, were optimized by rotation about R-C bonds with idealized C-H, R--H and H--H distances. Remaining H atoms were included as riding idealized contributors. Methyl H atom U's were assigned as 1.5 times U(eq) of the carrier atom; remaining H atom U's were assigned as 1.2 times carrier U(eq).

![Figure S2. Ellipsoid contour at 50 % probability levels](image-url)
Table S4. Crystal data and structure refinement for 28.

| Identification code         | MRI2941E1 |
|-----------------------------|-----------|
| Empirical formula           | C28 H25 Cl F3 N3 O4 S2 |
| Formula weight              | 624.08    |
| Temperature                 | 100(2) K  |
| Wavelength                  | 1.54178 Å |
| Crystal system              | Monoclinic|
| Space group                 | P2₁      |
| Unit cell dimensions        |           |
| \( a = 9.0363(3) \) Å     | \( \alpha = 90^\circ \) |
| \( b = 8.4186(3) \) Å     | \( \beta = 92.351(2)^\circ \) |
| \( c = 18.2914(7) \) Å    | \( \gamma = 90^\circ \) |
| Volume                      | 1390.31(9) Å³ |
| \( Z \)                     | 2         |
| Density (calculated)        | 1.491 Mg/m³ |
| Absorption coefficient      | 3.157 mm⁻¹ |
| \( F(000) \)                | 644       |
| Crystal size                | 0.209 x 0.114 x 0.030 mm³ |
| Theta range for data collection | 2.417 to 68.337°. |
| Index ranges                | -10≤h≤10, -9≤k≤9, -22≤l≤22 |
| Reflections collected       | 28434     |
| Independent reflections     | 4933 [R(int) = 0.0503] |
| Completeness to theta       | 98.8 %    |
| Absorption correction       | Semi-empirical from equivalents |
| Max. and min. transmission  | 0.94315 and 0.68238 |
| Refinement method           | Full-matrix least-squares on \( F^2 \) |
| Data / restraints / parameters | 4933 / 1 / 372 |
| Goodness-of-fit on \( F^2 \) | 1.054     |
| Final R indices [I>2σ(I)]   | \( R_1 = 0.0295 \), \( wR_2 = 0.0770 \) |
| R indices (all data)        | \( R_1 = 0.0308 \), \( wR_2 = 0.0780 \) |
| Absolute structure parameter| -0.006(9) |
| Extinction coefficient      | n/a       |
| Largest diff. peak and hole | 0.286 and -0.452 e.Å⁻³ |
Mechanistic Insights, control experiments and explanation

1. Additional insight into sulfonyl Bunte salt formation and in situ alkylation (Main Scheme 3)

As described in Table S2, the conversion of 1a to 3a proceeds under flexible temperature conditions and decreasing equivalents of Na$_2$S$_2$O$_3$ at higher temperatures without a significant loss of yield. The alkylation conditions are optimum at 90-95 °C with thiosulfate displacement carried out under 90-95 °C 2 eq of Na$_2$S$_2$O$_3$.

**Figure S3.** Schematic mechanistic depiction

In general, for substrates 1a-1w, chlorpropamide, tolbutamide and 15, aq. Methanol is the solvent of choice. For SUs, chlorpropamide, tolbutamide and 15 <10% of the products arising from MeOH displacement is seen (LCMS) at 90°C with 2 eq of Na$_2$S$_2$O$_3$.

For the alkylation procedure, in situ trapping of Bunte salt without thiourea isolation (Step C/D) is the method of choice. The alkylation of thiourea of the type 3a proceeds to give products in good yields even under aq. methanol or dioxane. When the thiourea was isolated and alkylation attempted in methanol/95°C (Step E) the reaction proceeded sluggishly (MeI) or barely traces of product are seen in case of alkylating agents like above (Step F).
Chiral HPLC data

1. Chiral HPLC data for 3q, 3r, 3s
2. Chiral HPLC data for 20 (diastereomeric mix), 19 (diastereomeric mix), and 28 (single diastereomer)
3. Chiral HPLC data for SLV326 (rac) and SLV326 (enantiopure) (S)
4. Chiral HPLC data for 1q, 1s, 1r (CRO)
NMR Spectra of Compounds

NMR spectra of 1b

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 1p

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 1r/s

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{$^1$H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3a

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3b

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3c

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3d

$^1$H-NMR (800 MHz; CDCl₃)

$^{13}$C{¹H} NMR (201 MHz; CDCl₃)
NMR of compound $3e$

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{$^1$H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3f

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{$_1$H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3g

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3h

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3i

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3j

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3k

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 31

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C($^1$H) NMR (201 MHz; CDCl$_3$)
NMR of compound 3m

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3n

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3o

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3p

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3q

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
Proton NMR of compound 3r/3s

$^1$H-NMR (800 MHz; CDCl₃)

$^1$H-NMR (800 MHz; CDCl₃)
NMR of compound 3t

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3u

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3v

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{$_1^1$H} NMR (201 MHz; CDCl$_3$)
NMR of compound 3w

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 7

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 10

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)

10
NMR of compound 11a

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound **11b**

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 11d

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 12a

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 12b

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 12c

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 12d

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 13a

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 13d

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 14a

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 14b

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 14c

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{$_1^1$H} NMR (201 MHz; CDCl$_3$)
NMR of compound 14d

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{$^1$H} NMR (201 MHz; CDCl$_3$)
NMR of compound 15

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 16

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 17

\(^1\)H-NMR (800 MHz; CDCl\(_3\))

\(^{13}\)C\{\(^1\)H\} NMR (201 MHz; CDCl\(_3\))
NMR of compound 18

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 19

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 20

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
NMR of compound 21

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C$\{^1$H$\}$ NMR (201 MHz; CDCl$_3$)
NMR of compound 22

$^1$H-NMR (500 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 23

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 24

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 25

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 26

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{H} NMR (201 MHz; CDCl$_3$)
NMR of compound 27

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C$\{^1$H$\}$ NMR (201 MHz; CDCl$_3$)
NMR of compound 28

$^1$H-NMR (800 MHz; CDCl$_3$)

$^{13}$C{1H} NMR (201 MHz; CDCl$_3$)
1H-NMR of SLV326

$^1$H-NMR (800 MHz; CDCl$_3$)
LCMS Data for select compounds

Compound 17

Compound 3m
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