Supporting Information

Anthranilic Amide and Imidazobenzothiadiazole Compounds Disrupt Mycobacterium tuberculosis Membrane Potential: Relationship to Bactericidal Activity and Mammalian Cytotoxicity

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1. *M. tuberculosis* Membrane Potential - pH 4.5

![Graphs showing membrane potential changes with concentration](image)

Figure S1. Disruption of *M. tuberculosis* membrane potential by anthranilic amide compounds at pH 4.5. Compounds were tested for their ability to disrupt membrane potential at pH 4.5 in *M. tuberculosis*. DMSO (negative control) and CCCP (positive control) were included. Reported values are a representative from two independent runs. MBC<sub>4.5</sub> is reported as the median of two or more replicates.
Figure S2. Disruption of *M. tuberculosis* Membrane potential by benzothiadiazole compounds at pH 4.5. Compounds were tested for their ability to disrupt membrane potential at pH 4.5 in *M. tuberculosis*. DMSO (negative control) and CCCP (positive control) were included. Reported values are a representative from two independent runs. MBC$_{4.5}$ is reported as the median of two or more replicates.
## 2. *M. tuberculosis* Minimum Inhibitory Concentrations

| Cpd | ID          | MIC pH 5.6 (µM) | MIC pH 6.8 (µM) |
|-----|-------------|----------------|-----------------|
| 1   | IDR-0019306 | 20 ± 0 (2)     | 182 ± 35 (4)    |
| 2   | IDR-0099118 | 115 ± 15 (2)   | >200 (2)        |
| 3   | IDR-0597329 | 26 ± 5.7 (2)   | 110 ± 0 (2)     |
| 4   | IDR-0484542 | 63 ± 3.5 (2)   | 185 ± 21 (2)    |
| 5   | IDR-0597554 | 78 ± 4.2 (2)   | >200 (5)        |
| 6   | IDR-0597555 | 71 ± 12 (2)    | >200 (4)        |
| 7   | IDR-0596462 | 19 ± 0.71 (2)  | >200 (2)        |
| 8   | IDR-0596461 | 46 ± 7.1 (2)   | >200 (1)        |
| 9   | IDR-0597928 | >200 (2)       | >200 (3)        |
| 10  | IDR-0596465 | 85 ± 3.5 (2)   | 175 ± 35 (2)    |
| 11  | IDR-0597268 | 115 ± 21 (2)   | 115 ± 7.1 (2)   |
| 12  | IDR-0597556 | >200 (2)       | >200 (5)        |
| 13  | IDR-0596464 | >200 (2)       | >200 (2)        |
| 14  | IDR-0596463 | >200 (2)       | >200 (2)        |
| 15  | IDR-0597330 | 19 ± 12 (2)    | >200 (2)        |
| 16  | IDR-0600849 | 136 ± 91 (2)   | >200 (3)        |
| 17  | IDR-0597328 | 96 ± 20 (2)    | >200 (2)        |
| 18  | IDR-0600848 | 77 ± 9.9 (2)   | >200 (3)        |
| 19  | IDR-0600851 | 106 ± 91 (2)   | >200 (3)        |

| Cpd | ID          | MIC pH 5.6 (µM) | MIC pH 6.8 (µM) |
|-----|-------------|----------------|-----------------|
| 20  | IDR-0600850 | >200 (2)       | >200 (2)        |
| 21  | IDR-0600833 | 170 ± 42 (2)   | >200 (2)        |
| 22  | IDR-0600834 | >200 (2)       | >200 (2)        |
| 23  | IDR-0600866 | >200 (2)       | >200 (3)        |
| 24  | IDR-0597331 | 44 ± 32 (3)    | >200 (2)        |
| 25  | IDR-0597270 | 154 ± 72 (3)   | >200 (2)        |
| 26  | IDR-0600899 | 95 ± 7.8 (2)   | >200 (2)        |
| 27  | IDR-0597462 | >200 (2)       | >200 (2)        |
| 28  | IDR-0597332 | >200 (4)       | >200 (3)        |
| 29  | IDR-0597269 | 112 ± 78 (3)   | 170 ± 42 (2)    |
| 30  | IDR-0597937 | >200 (2)       | >200 (3)        |
| 31  | IDR-0597557 | >200 (5)       | >200 (2)        |
| 32  | IDR-0597558 | 120 ± 113 (2)  | 53 ± 11 (5)     |
| 33  | IDR-0597589 | >200 (2)       | >200 (5)        |
| 34  | IDR-0107334 | 145 ± 7.1 (2)  | >200 (2)        |
| 35  | IDR-0697786 | >200 (2)       | >200 (2)        |
| 36  | IDR-0697784 | >200 (2)       | >200 (2)        |
| 37  | IDR-0050636 | 4.2 ± 0.21 (2) | 30.5 ± 0.71 (2) |
| 38  | IDR-0033566 | 8.1 ± 0.071 (2)| 24 ± 2.6 (2)    |

Table S1. Minimum Inhibitory Concentrations. Compounds were tested for inhibitory activity against *M. tuberculosis* at pH 5.6 and pH 6.8. MIC are reported as the mean ± standard deviation. The number of replicates is in parentheses.
### 3. Intracellular *M. tuberculosis* Minimum Inhibitory Concentrations and RAW 264.7 Cytotoxicity

| Cpd | ID            | Intracellular IC₅₀ (µM) | RAW IC₅₀ (µM) |
|-----|---------------|------------------------|--------------|
| 1   | IDR-0019306   | >11 (6)                | 2.8 ± 0.68 (6) |
| 2   | IDR-0099118   | >33 (4)                | 35 ± 14 (4)   |
| 3   | IDR-0597329   | >3.7 (1)               | 7.0 ± 3.3 (2) |
| 4   | IDR-0484542   | >11 (1)                | 13 (1)        |
| 5   | IDR-0597554   | >100 (3)               | 85 ± 17 (3)   |
| 6   | IDR-0597555   | >100 (3)               | >100 (3)      |
| 7   | IDR-0596462   | >3.7 (2)               | 9.8 ± 0.28 (2) |
| 8   | IDR-0596461   | >33 (2)                | 47 ± 6.4 (2)  |
| 9   | IDR-0597928   | >33 (6)                | 49 ± 36 (6)   |
| 10  | IDR-0596465   | >100 (2)               | 61 ± 40 (2)   |
| 11  | IDR-0597268   | 3.9 ± 0.53 (3)         | 22 ± 9.2 (3)  |
| 12  | IDR-0597556   | >100 (3)               | >100 (3)      |
| 13  | IDR-0596464   | >100 (2)               | >100 (2)      |
| 14  | IDR-0596463   | >100 (2)               | 98 ± 2.8 (2)  |
| 15  | IDR-0597330   | >11 (1)                | 11 ± 0 (2)    |
| 16  | IDR-0600849   | >33 (2)                | 30 ± 1.4 (2)  |
| 17  | IDR-0597328   | >100 (2)               | >100 (2)      |
| 18  | IDR-0600848   | >100 (2)               | 94 ± 9.2 (2)  |
| 19  | IDR-0600851   | >11 (2)                | 11 ± 0.71 (2) |

| Cpd | ID            | Intracellular IC₅₀ (µM) | RAW IC₅₀ (µM) |
|-----|---------------|------------------------|--------------|
| 20  | IDR-0600850   | >11 (2)                | 12 ± 2.8 (2) |
| 21  | IDR-0600833   | >100 (4)               | 73 ± 30 (4)  |
| 22  | IDR-0600834   | >100 (4)               | >100 (4)     |
| 23  | IDR-0600866   | >100 (2)               | >100 (2)     |
| 24  | IDR-0597331   | >11 (2)                | 29 ± 0 (2)   |
| 25  | IDR-0597270   | >100 (3)               | 30 ± 0.58 (3) |
| 26  | IDR-0600899   | >11 (2)                | 14 ± 4.9 (2) |
| 27  | IDR-0597462   | >33 (4)                | 53 ± 8.5 (4) |
| 28  | IDR-0597332   | >3.7 (2)               | 9.9 ± 0.14 (2) |
| 29  | IDR-0597269   | 8.7 (1)                | 11 ± 0.69 (3) |
| 30  | IDR-0597937   | >100 (5)               | 82 ± 17 (5)  |
| 31  | IDR-0597557   | >100 (3)               | 30 ± 2.5 (3) |
| 32  | IDR-0597558   | >1.2 (3)               | 1.0 ± 0.092 (3) |
| 33  | IDR-0597589   | >11 (2)                | 10 ± 0 (2)   |
| 34  | IDR-0107334   | >100 (3)               | 92 ± 2.3 (3) |
| 35  | IDR-0697786   | >100 (4)               | >100 (4)     |
| 36  | IDR-0697784   | >100 (4)               | >100 (4)     |
| 37  | IDR-0050636   | >3.7 (3)               | 2.9 ± 0.68 (3) |
| 38  | IDR-0033566   | >3.7 (3)               | 0.81 ± 0.77 (3) |

Table S2. Minimum Inhibitory Concentrations. Compounds were tested for inhibitory activity against *M. tuberculosis* in infected RAW 264.7 cells and cytotoxicity against RAW 264.7 cells. IC₅₀ are reported as the mean ± standard deviation. The number of replicates is in parentheses.
4. Chemical Methods

**General Methods**
Reagents and solvents were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, Matrix Scientific, Enamine, or Fisher Scientific and used without further purification. NMR spectra were collected on a 300 MHz Bruker AVANCE 300 system with 5 mm BBI probe. LC-MS was performed on an Agilent 1100 system with Phenomenex Gemini 5 µM C18 column and 0.5% formic acid buffered acetonitrile/water gradient elution.

**Abbreviations**
DCM – dichloromethane
DMF – N,N-dimethylformamide
DMSO – dimethylsulfoxide
EDC – N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride
EtOAc – ethyl acetate
HATU – 1-(bis(dimetylamino)methylene)-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
MeCN – acetonitrile
MeOH – methanol
THF – tetrahydrofuran

**N-(2,4-dichlorophenyl)-2-nitrobenzamide (S1)**

![Chemical structure](image)

Thionyl chloride (1.89 mL, 26 mmol) was added slowly to a solution of 2-nitrobenzoic acid (3.34 g, 20 mmol) and DMF (2.0 mL, 26 mmol) in DCM (100 mL). The resulting solution was refluxed for 4 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to provide the crude acid chloride which was used without further purification.

A solution of the acid chloride prepared above in DCM (100 mL) was added to a solution of 2,4-dichloroaniline (4.21 g, 26 mmol) in DCM (100 mL) and pyridine (20 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with 1 M HCl (aq) and the layers separated. The aqueous layer was back-extracted with one portion of EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (24 g) eluting with a gradient from 0-20% EtOAc in hexanes then 100% EtOAc to give 5.45 g (88%) off-white solid.
2-amino-N-(2,4-dichlorophenyl)benzamide (9)

\[
\begin{align*}
\text{Stannous chloride dihydrate (14.1 g, 62.5 mmol) was added to a solution of } & N-(2,4\text{-dichlorophenyl})-2\text{-nitrobenzamide (3.90 g, 12.5 mmol) in EtOAc (62.5 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with 1 M NaOH (aq) (100 mL) and the layers separated. The organic layer was dried over Na}_2\text{SO}_4 \text{ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (40 g) eluting first with DCM then a gradient from 0-20% EtOAc in DCM to give 2.42 g (69%) off-white solid.} ^1\text{H NMR (300 MHz, DMSO-d}_6\text{) } \delta = 9.82 \text{ (bs, 1H), 7.71 (dd, 8.0, 1.5 Hz, 1H), 7.70 (d, 2.5 Hz, 1H), 7.61 (d, 8.5 Hz, 1H), 7.45 (dd, 8.5, 2.5 Hz, 1H), 7.22 (ddd, 8.5, 7.0, 1.5 Hz, 1H), 6.45 (b, 2H).} & \text{LC-MS (ESI) calculated for } C_{13}H_{10}Cl_2N_2O ([M+H]^+): 281.02; found: 281.0.
\end{align*}
\]

2-amino-N-(4-chlorophenyl)benzamide (S2)

\[
\begin{align*}
\text{Thionyl chloride (0.55 mL, 7.6 mmol) was added to a suspension of anthranilic acid (0.25 g, 1.8 mmol) in toluene (2.75 mL). The resulting mixture was heated to reflux for 1 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to provide the crude acid chloride which was used without further purification. 4-chloroaniline (0.70 g, 5.5 mmol) was added to a solution of the acid chloride prepared above in THF (2.75 mL). The resulting mixture was heated to reflux for 2 h. The reaction mixture was cooled to room temperature, diluted with 10% K}_2\text{CO}_3 \text{ (aq) (10 mL), and stirred for 15 min. The mixture was diluted further with H}_2\text{O and extracted with three portions of EtOAc. The combined organic layers were dried over Na}_2\text{SO}_4 \text{ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g silica) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 0.208 g (46%) yellow solid.}
\end{align*}
\]

2-(4-bromophenylsulfonamido)-N-(4-chlorophenyl)benzamide (3)
4-bromophenylsulfonyl chloride (236 mg, 0.92 mmol) was added to a solution of 2-amino-N-(4-chlorophenyl)benzamide (208 mg, 0.84 mmol) and pyridine (0.203 mL, 2.5 mmol) in DCM (4.2 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of 1 M HCl (aq) and one portion of sat. NaHCO$_3$ (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 223 mg (57%) white solid.

**1H NMR** (300 MHz, CDCl$_3$) $\delta = 10.19$ (bs, 1H), 7.73 (d, 8.0 Hz, 1H), 7.59 (d, 8.5 Hz, 2H), 7.47 (m, 6H), 7.37 (d, 9.0 Hz, 2H), 7.19 (ddd, 8.5, 8.0, 1.0 Hz, 1H).

**LC-MS** (ESI) calculated for C$_{19}$H$_{14}$BrClN$_2$O$_3$S ([M+H]$^+$): 466.97; found: 466.9.

**2-nitro-N-phenylbenzamide (S3)**

![Image of reaction](image)

Thionyl chloride (0.47 mL, 6.5 mmol) was added slowly to a solution of 2-nitrobenzoic acid (0.84 g, 5 mmol) and DMF (0.5 mL, 6.5 mmol) in DCM (25 mL). The resulting solution was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo to provide the crude acid chloride which was used without further purification.

A solution of the acid chloride prepared above in DCM (25 mL) was added to a solution of aniline (0.59 mL, 6.5 mmol) in DCM (25 mL) and pyridine (5 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with 1 M HCl (aq) and the layers separated. The aqueous layer was back-extracted with one portion of EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting with a gradient from 0-20% EtOAc in hexanes to give an orange-white solid that was used without further purification.

**2-amino-N-phenylbenzamide (S4)**

![Image of reaction](image)

Stannous chloride dihydrate (5.64 g, 25 mmol) was added to a solution of 2-nitro-N-phenylbenzamide (1.21 g, 5 mmol) in EtOAc (25 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with 1 M NaOH (aq) (50 mL), stirred to give a suspension, and extracted with EtOAc (100 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (24 g) eluting first with hexanes then a gradient from 0-25% EtOAc in hexanes to give 0.888 g (84%) white powder.
2-(4-bromophenylsulfonamido)-N-phenylbenzamide (4)

![Chemical structure](image)

4-bromophenylsulfonyl chloride (132 mg, 0.52 mmol) was added to a solution of 2-amino-N-phenylbenzamide (100 mg, 0.47 mmol) and pyridine (114 µL, 1.4 mmol) in DCM (2.35 mL). The resulting solution was stirred for 3 h. The reaction mixture was diluted with DCM, washed with three portions of 1 M HCl (aq) and one portion of sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 198 mg (97%) white powder.

**¹H NMR** (300 MHz, CDCl₃) δ = 10.29 (bs, 1H), 7.74 (dd, 8.5, 1.0 Hz, 1H), 7.60 (d, 8.5 Hz, 2H), 7.45 (m, 8H), 7.21 (m, 2H).

**LC-MS** (ESI) calculated for C₁₉H₁₅BrN₂O₃S ([M+H]⁺): 433.00; found: 432.9.

2-(4-bromophenylsulfonamido)benzoic acid (S5)

![Chemical structure](image)

A solution of anthranilic acid (2.74 g, 20 mmol) and Na₂CO₃ (5.09 g, 48 mmol) in H₂O (30 mL) was heated to 60°C. 4-bromophenylsulfonyl chloride (6.13 g, 24 mmol) was added, and the resulting suspension was stirred for 7 h. The reaction mixture was cooled to room temperature, 6 M HCl (aq) (10 mL) added slowly, and the resulting suspension stirred overnight. The precipitate was collected by vacuum filtration, washed with water, and dried in vacuo at 40°C to give 7.07 g (99%) tan solid.

2-(4-bromophenylsulfonamido)-N-ethylbenzamide (5)

![Chemical structure](image)

N,N-diisopropylethylamine (146 µL, 0.84 mmol) was added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol) and HATU (128 mg, 0.34 mmol) in DMF (2.8 mL). The resulting solution was stirred 10 min. Ethylamine (2 M in THF) (0.7 mL, 1.4 mmol) was added,
and the mixture was stirred overnight. The reaction mixture was diluted with DCM, washed with 1 M HCl (aq), water, sat. NaHCO₃ (aq), and brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-50% EtOAc in hexanes to give 56 mg yellow oil. The material was further purified by semi-preparative HPLC (C18) eluting with a gradient from 25-65% MeCN in H₂O buffered with 0.5% formic acid to give 28.3 mg (26%) white powder. ³¹H NMR (300 MHz, CDCl₃) δ = 10.83 (bs, 1H), 7.72 (d, 8.5 Hz, 1H), 7.66 (d, 8.5 Hz, 2H), 7.55 (d, 8.5 Hz, 2H), 7.44 (t, 7 Hz, 1H), 7.35 (d, 9.0 Hz, 1H), 5.94 (b, 1H), 3.38 (qd, 7.5, 5.5 Hz, 2H), 1.22 (t, 7 Hz, 3H).

2-(4-bromophenylsulfonamido)benzamide (6)

\[ \text{NH}_{3}, \text{MeOH} \quad \text{HATU, DIEA} \quad \text{DMF} \]

\[ \text{N,N-diisopropylethylamine (146 µL, 0.84 mmol) was added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol) and HATU (128 mg, 0.34 mmol) in DMF (2.8 mL). The resulting solution was stirred 10 min. Ammonia (7 M in MeOH) (0.2 mL, 1.4 mmol) was added, and the mixture was stirred overnight. The reaction mixture was diluted with DCM, washed with 1 M HCl (aq), water, sat. NaHCO₃ (aq), and brine, dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-50% EtOAc in hexanes to give 46.2 mg off-white solid. The material was further purified by semi-preparative HPLC (C18) eluting with a gradient from 5-95% MeCN in H₂O buffered with 0.5% formic acid. The material was further purified by semi-preparative HPLC to (C18) eluting with a gradient from 25-65% MeCN in H₂O buffered with 0.5% formic acid to give 9.8 mg (10%) white powder. ³¹H NMR (300 MHz, CDCl₃) δ = 11.02 (bs, 1H), 7.73 (d, 7.5 Hz, 1H), 7.69 (d, 8.5 Hz, 2H), 7.55 (d, 8.5 Hz, 2H), 7.47 (d, 8.5 Hz, 1H), 7.43 (t, 7.5 Hz, 1H), 7.10 (t, 7.5 Hz, 3H). LC-MS (ESI) calculated for C₁₅H₁₅BrN₂O₃S ([M+H]+): 384.27; found: 384.9.

N-(2,4-dichlorophenyl)-2-(phenylsulfonamido)benzamide (7)

\[ \text{Benzenesulfonyl chloride (21.5 µL, 0.17 mmol) was added to a solution of 2-amino-N-(2,4-dichlorophenyl)benzamide (43 mg, 0.15 mmol) and pyridine (37 µL, 0.46 mmol) in DCM (0.77 mL). The} \]
resulting solution was stirred for 2.5 h. The reaction mixture was diluted with DCM, washed with three portions of 1 M HCl (aq) and one portion of sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then with a gradient from 0-25% EtOAc in hexanes. The material was further purified by semi-preparative HPLC on C18 eluting with a gradient from 5-95% MeCN in H₂O buffered with 0.1% formic acid to give 20.7 mg (32%) white powder. ¹H NMR (300 MHz, CDCl₃) δ = 10.19 (bs, 1H), 8.35 (d, 9.0 Hz, 1H), 8.00 (b, 1H), 7.76 (m, 3H), 7.51 (m, 2H), 7.43 (m, 2H), 7.32 (m, 3H), 7.19 (td, 8.0, 1.0 Hz, 1H).

**LC-MS** (ESI) calculated for C₁₉H₁₄Cl₂N₂O₃S ([M+H]+): 421.02; found: 420.9.

**N-(2,4-dichlorophenyl)-2-(methylsulfonamido)benzamide (8)**

Methanesulfonyl chloride (15.2 µL, 0.2 mmol) was added to a solution of 2-amino-N-(2,4-dichlorophenyl)benzamide (50 mg, 0.18 mmol) and pyridine (43 µL, 0.53 mmol) in DCM (0.89 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of 1 M HCl (aq) and one portion of sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by semi-preparative HPLC on C18 eluting with a gradient from 5-95% MeCN in H₂O buffered with 0.1% formic acid. The material was further purified by semi-preparative HPLC on C18 eluting with a gradient from 25-60% MeCN in H₂O buffered with 0.1% formic acid to give 15.9 mg white powder. ¹H NMR (300 MHz, CDCl₃) δ = 10.34 (bs, 1H), 8.41 (dd, 9.0, 2.5 Hz, 1H), 7.82 (dd, 8.5, 1.0 Hz, 1H), 7.70 (d, 8.0 Hz, 1H), 7.59 (ddd, 8.0, 7.5, 1.0 Hz, 1H), 7.47 (d, 2.5 Hz, 1H), 7.34 (dd, 9.0, 2.5 Hz, 1H), 7.24 (t, 8.0 Hz, 1H), 3.09 (s, 3H).

**LC-MS** (ESI) calculated for C₁₄H₁₂Cl₂N₂O₃S ([M+H]+): 359.00; found: 358.9.

**N-(2,4-dichlorophenyl)-2-(ethylamino)benzamide (10)**

Acetaldehyde (5 M in THF) (0.43 mL, 2.15 mmol) was added to 2-amino-N-(2,4-dichlorophenyl)benzamide (200 mg, 0.71 mmol) and acetic acid (30.6 µL, 0.53 mmol) in MeOH (2.8 mL). Sodium cyanoborohydride (145 mg, 2.3 mmol) was added portionwise. The resulting mixture was stirred overnight. The reaction mixture was diluted with water and extracted with three portions of EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 73.2 mg (22%) amorphous solid. ¹H NMR (300 MHz, CDCl₃) δ = 8.39
Formaldehyde (37 wt% in H2O) (29.2 µL, 0.39 mmol) was added to 2-amino-N-(2,4-dichlorophenyl)benzamide (100 mg, 0.36 mmol) and acetic acid (15.3 µL, 0.27 mmol) in MeOH (1.78 mL). Sodium cyanoborohydride (44.6 mg, 0.71 mmol) was added portionwise. The resulting mixture was stirred overnight. LC-MS showed incomplete conversion. Additional formaldehyde (37 wt% in H2O) (29.2 µL, 0.39 mmol) and sodium cyanoborohydride (44.6 mg, 0.71 mmol) were added. The resulting mixture was stirred overnight. The reaction mixture was diluted with water and extracted with three portions of EtOAc. The combined organic layers were dried over Na2SO4 and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 63 mg (60%) amorphous solid.

N-(2,4-dichlorophenyl)-2-(ethyl(methyl)amino)benzamide (11)

Acetaldehyde (5 M in THF) (126 µL, 0.63 mmol) was added to N-(2,4-dichlorophenyl)-2-(methylamino)benzamide (63 mg, 0.21 mmol) and acetic acid (9.0 µL, 0.16 mmol) in MeOH (4.2 mL). Sodium cyanoborohydride (39.6 mg, 0.63 mmol) was added, and the resulting mixture was stirred overnight. LC-MS showed incomplete conversion. Additional acetaldehyde (5 M in THF) (0.42 mL, 2.1 mmol) and sodium cyanoborohydride (132 mg, 2.1 mmol) were added. The resulting mixture was stirred overnight. The reaction mixture was diluted with water and extracted with three portions of EtOAc. The combined organic layers were dried over Na2SO4 and concentrated in vacuo. The crude residue was purified by semi-preparative HPLC (C18) eluting with a gradient from 5-95% MeCN in H2O to give 10.8 mg (16%) yellow oil. 1H NMR (300 MHz, CDCl3) δ = 13.61 (bs, 1H), 8.73 (d, 9.0 Hz, 1H), 8.34 (dd, 8.0, 1.5 Hz, 1H), 7.53 (ddd, 8.0, 6.5, 1.5 Hz, 1H), 7.40 (d, 2.5 Hz, 1H), 7.33 (m, 2H), 3.11 (q, 7.0 Hz, 2H), 2.80 (s, 3H), 1.04 (t, 7.0 Hz, 3H). LC-MS (ESI) calculated for C16H17Cl2N2O ([M+H]+): 323.07; found: 323.1.
2-((4-bromobenzyl)amino)-N-(2,4-dichlorophenyl)benzamide (12)

![Chemical structure of 2-((4-bromobenzyl)amino)-N-(2,4-dichlorophenyl)benzamide (12)]

2-amino-N-(2,4-dichlorophenyl)benzamide (100 mg, 0.36 mmol) and 4-bromobenzaldehyde (100 mg, 0.54 mmol) were dissolved in MeOH (1.8 mL). The resulting suspension was stirred overnight, during which time a precipitate formed. Additional MeOH (1.8 mL) was added to give a slurry followed by NaOH (2.9 mg, 0.07 mmol), H₂O (180 µL), and sodium borohydride (23.8 mg, 0.63 mmol). The resulting mixture was stirred 1.5 h. The reaction mixture was diluted with water and extracted with three portions of DCM. The combined organic layers were washed with sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo to give 128.8 mg (80%) white powder. **¹H NMR** (300 MHz, DMSO-d₆) δ = 7.75 (s, 0.8H), 7.71 (d, 7.0 Hz, 1.2H), 7.61-7.46 (m, 3.4H), 7.44-7.30 (m, 4.6H), 6.99 (d, 8.0 Hz, 0.6H), 6.86-6.74 (m, 1.4H), 6.49 (s, 0.4H), 6.11 (s, 0.6H), 3.34 (s, 2H). **LC-MS** (ESI) calculated for C₂₀H₁₅BrCl₂N₂O ([M+H]⁺): 450.98; found: 448.9.

2-acetamido-N-(2,4-dichlorophenyl)benzamide (13)

![Chemical structure of 2-acetamido-N-(2,4-dichlorophenyl)benzamide (13)]

A solution of 2-amino-N-(2,4-dichlorophenyl)benzamide (100 mg, 0.36 mmol) in DCM (0.75 mL) was cooled in an ice/water bath. Triethylamine (99 µL, 0.71 mmol) and acetic anhydride (67 µL, 0.71 mmol) were added sequentially. The resulting mixture was heated to 40°C for 2 h. The reaction mixture was diluted with sat. NH₄Cl (aq) and extracted with three portions of DCM. The combined organic layers were washed with sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then with a gradient from 0-20% EtOAc in hexanes to give 37 mg white solid. The material was further purified by semi-preparative HPLC (C18) eluting with a gradient from 5-95% MeCN in H₂O buffered with 0.05% formic acid to give 12 mg (10%) white solid. **¹H NMR** (300 MHz, CDCl₃) δ = 10.73 (bs, 1H), 8.65 (d, 8.5 Hz, 1H), 8.37 (d, 8.5 Hz, 1H), 8.33 (b, 1H), 7.66 (dd, 8.0, 1.0 Hz, 1H), 7.57 (ddd, 8.5, 8.0, 1.5 Hz, 1H), 7.47 (d, 2.5 Hz, 1H), 7.34 (dd, 9.0, 2.5 Hz, 1H), 7.18 (td, 7.5, 1.5 Hz, 1H), 2.22 (s, 3H). **LC-MS** (ESI) calculated for C₁₅H₁₂Cl₂N₂O₂ ([M+2H]²⁺):162.02; found: 162.0.
2-(4-bromobenzamido)-N-(2,4-dichlorophenyl)benzamide (14)

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\text{N, N-diisopropylethylamine (121 µL, 0.89 mmol) was added to a solution of 2-amino-N-(2,4-dichlorophenyl)benzamide (100 mg, 0.36 mmol), 4-bromobenzoic acid (86 mg, 0.43 mmol), and HATU (162 mg, 0.43 mmol) in DMF (1.78 mL). The resulting solution was stirred for 2 h. LC-MS showed the reaction was not proceeding past activation of the acid. 4-dimethylaminopyridine (4.5 mg, 0.036 mmol) was added, and the mixture was heated to 50°C overnight. LC-MS showed incomplete conversion. A solution of additional 4-bromobenzoic acid (86 mg, 0.43 mmol) and HATU (162 mg, 0.43 mmol) in DMF (1 mL) was added, and heating to 50°C continued for 3 h. The reaction mixture was diluted with EtOAc, washed with water, 1 M HCl (aq), water, and sat. NaHCO}_3 (aq), dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 63.3 mg (38%) white solid. ^{1}H NMR (300 MHz, CDCl_3) \delta = 11.88 (bs, 1H), 8.86 (dd, 8.5, 1.5 Hz, 1H), 8.43 (s, 1H), 8.41 (d, 9.0 Hz, 1H), 7.90 (d, 8.5 Hz, 2H), 7.73 (dd, 8.0, 1.0 Hz, 1H), 7.66 (d, 8.5 Hz, 2H), 7.63 (dd, 7.0, 1.5 Hz, 1H), 7.47 (d, 2.0 Hz, 1H), 7.35 (dd, 9.0, 2.5 Hz, 1H), 7.24 (td, 7.5, 1.0 Hz, 1H). LC-MS (ESI) calculated for C_{20}H_{13}BrCl_2N_2O_2 ([M+Na]^+): 486.94; found: 486.8.
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N-(2,4-dichlorophenyl)-2-(4-methylphenylsulfonamido)benzamide (15)

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\text{Toluenesulfonyl chloride (75 mg, 0.39 mmol) was added to a solution of 2-amino-N-(2,4-dichlorophenyl)benzamide (100 mg, 0.36 mmol) and pyridine (86 µL, 1.07 mmol) in DCM (1.8 mL). The resulting solution was stirred for 3 h. The reaction mixture was diluted with DCM, washed with 1 M HCl (aq) and sat. NaHCO}_3 (aq), dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then with a gradient from 0-20% EtOAc in hexanes to give 51.1 mg (33%) white powder. ^{1}H NMR (300 MHz, CDCl_3) \delta = 10.07 (bs, 1H), 8.37 (d, 9 Hz, 1H), 8.00 (b, 1H), 7.75 (dd, 8.5, 1 Hz, 1H), 7.63 (d, 8.5 Hz, 2H), 7.51 (m, 2H), 7.44 (d, 2.5 Hz, 1H), 7.34 (dd, 9, 2 Hz, 1H), 7.20 (td, 7.5, 1 Hz, 1H), 7.10 (d, 8 Hz, 2H), 2.26 (s, 3H). LC-MS (ESI) calculated for C_{20}H_{16}Cl_2N_2O_3S ([M+H]^+): 435.03; found: 435.0.}
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2-(4-bromophenylsulfonamido)-N-butylbenzamide (16)

n-Butylamine (55 µL, 0.56 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol), EDC (80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (67 mg, 0.42 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with EtOAc, washed with three portions of half-saturated brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g silica) eluting with a gradient from 0-25% EtOAc in hexanes to give 49.0 mg (43%) white solid. ¹H NMR (300 MHz, CDCl₃) δ = 10.89 (s, 1H), 7.68 (dd, 8.5, 1.0 Hz, 1H), 7.63 (d, 9.0 Hz, 2H), 7.52 (d, 8.5 Hz 2H), 7.41 (td, 7.5, 1.5 Hz, 1H), 7.08 (td, 8.0, 1.0 Hz, 1H), 3.31 (q, 7.0 Hz, 2H), 1.53 (quint, 8.0 Hz, 2H), 1.38 (quint, 7.5 Hz, 2H), 0.96 (t, 7.5 Hz, 3H). LC-MS (ESI) calculated for C₁₇H₁₉BrN₂O₃S ([M+H]+): 411.04; found: 413.0.

2-(4-bromophenylsulfonamido)-N-cyclopropylbenzamide (17)

Cyclopropylamine (29.1 µL, 0.42 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol) and HATU (128 mg, 0.34 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with 1 M HCl (aq), water, sat. NaHCO₃ (aq), and brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-40% EtOAc in hexanes to give 87.9 mg (51%) orange oil. The material was further purified by semi-preparative HPLC (C18) eluting with a gradient from 5-95% MeCN in H₂O buffered with 0.05% formic acid to give 44.3 mg (40%) less pure white solid and 9.1 mg (8%) more pure white solid. ¹H NMR (300 MHz, CDCl₃) δ = 10.86 (bs, 1H), 7.69 (d, 8.5 Hz, 1H), 7.65 (d, 8.5 Hz, 2H), 7.54 (d, 8.5 Hz, 2H), 7.41 (t, 7.5 Hz, 1H), 7.29 (d, 7.5 Hz, 1H), 7.06 (t, 7.5 Hz, 1H), 6.18 (s, 1H), 2.76 (m, 1H), 0.88 (dd, 13, 6.5 Hz, 2H), 0.55 (dd, 9.5, 7.5 Hz, 2H). LC-MS (ESI) calculated for C₁₆H₁₅BrN₂O₃S ([M+H]+): 397.00; found: 397.1.
2-(4-bromophenylsulfonamido)-N-(pro-2-yn-1-yl)benzamide (18)

Propargylamine (36 µL, 0.56 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol), EDC (80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (67 mg, 0.42 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of half-saturated brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting with a gradient from 0-25% EtOAc in hexanes to give 54.4 mg (49%) white solid. ¹H NMR (300 MHz, CDCl₃) δ = 10.66 (s, 1H), 7.70 (d, 8.5, 1.0 Hz, 1H), 7.65 (d, 9.0 Hz, 2H), 7.54 (d, 9.0 Hz, 2H), 7.45 (t, 7.5, 1.5 Hz, 1H), 7.38 (dd, 8.0, 1.5 Hz, 1H), 7.11 (td, 7.5, 1.0 Hz, 1H), 6.16 (b, 1H), 4.14 (d, 2.5 Hz, 1H), 4.12 (d, 2.5 Hz, 1H), 2.33 (t, 2.5 Hz, 1H).

LC-MS (ESI) calculated for C₁₆H₁₃BrN₂O₃S ([M+H]⁺): 394.99; found: 394.9.

2-(4-bromophenylsulfonamido)-N-cycloheptylbenzamide (19)

Cycloheptylamine (71 µL, 0.56 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol), EDC (80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (67 mg, 0.42 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of half-saturated brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting with a gradient from 0-25% EtOAc in hexanes to give 64.3 mg (51%) white solid. ¹H NMR (300 MHz, CDCl₃) δ = 10.89 (s, 1H), 7.69 (dd, 8.0, 1.0 Hz, 1H), 7.63 (d, 9.0 Hz, 2H), 7.51 (d, 9.0 Hz, 2H), 7.41 (ddd, 8.0, 7.5, 1.5 Hz, 1H), 7.33 (dd, 8.0, 1.5 Hz, 1H), 7.09 (td, 7.5, 1.5 Hz, 1H), 5.95 (d, 7.5 Hz, 1H), 5.97 (t, 13.0, 4.0 Hz, 1H), 1.91 (m, 2H), 1.54 (m, 10H).

LC-MS (ESI) calculated for C₂₀H₂₃BrN₂O₃S ([M+H]⁺): 451.07; found: 453.0.
**N-(adamantan-2-yl)-2-(4-bromophenylsulfonamido)benzamide (20)**

2-adamantylamine hydrochloride (105 mg, 0.56 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol), EDC (80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (67 mg, 0.42 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of half-saturated brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting with a gradient from 0-25% EtOAc in hexanes to give 70.4 mg (51%) white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 10.84 (s, 1H), 7.72 (dd, 8.0, 1.0 Hz, 1H), 7.63 (d, 9.0 Hz, 2H), 7.51 (d, 9.0 Hz, 2H), 7.44 (t, 7.5 Hz, 1H), 7.37 (d, 8.5, 1.5 Hz, 1H), 7.11 (td, 7.5, 1.0 Hz, 1H), 6.25 (b, 1H), 4.07 (bd, 8.0 Hz), 1.95-1.87 (m, 7H), 1.80-1.76 (m, 2H), 1.73-1.69 (m, 3H).

**4-bromo-N-(2-(piperidine-1-carbonyl)phenyl)benzenesulfonamide (21)**

Piperidine (55 µL, 0.56 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol), EDC (80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (67 mg, 0.42 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of half-saturated brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then with a gradient from 0-20% EtOAc in hexanes to give 54.5 mg (46%) colorless film. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 8.69 (bs, 1H), 7.68-7.62 (m, 3H), 7.56 (d, 9.0 Hz, 2H), 7.36 (ddd, 9.0, 6.0, 3.0 Hz, 1H), 7.15-7.07 (m, 2H), 3.63-2.93 (b, 4H), 1.63 (b, 2H), 1.48 (b, 2H). LC-MS (ESI) calculated for C$_{25}$H$_{25}$BrN$_2$O$_3$S ([M+H]$^+$): 491.08; found: 491.0.
4-bromo-N-(2-(morpholine-4-carbonyl)phenyl)benzenesulfonamide (22)

Morpholine (49 µL, 0.56 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol), EDC (80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (67 mg, 0.42 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of half-saturated brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then with a gradient from 0-20% EtOAc in hexanes to give 60.7 mg (51%) colorless film. ¹H NMR (300 MHz, CDCl₃) δ = 7.69 (d, 9.0 Hz, 2H), 7.64-7.57 (m, 3H), 7.38 (ddd, 9.0, 5.5, 3.5 Hz, 1H), 7.15-7.11 (m, 2H), 3.73-3.27 (b, 8H). LC-MS (ESI) calculated for C₁₇H₁₇BrN₂O₄S ([M+H]+): 427.02; found: 427.0.

4-bromo-N-(2-(4-methylpiperizine-1-carbonyl)phenyl)benzenesulfonamide (23)

1-methylpiperazine (62 µL, 0.56 mmol) and N,N-diisopropylethylamine (146 µL, 0.84 mmol) were added to a suspension of 2-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol), EDC (80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (67 mg, 0.42 mmol) in DMF (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with three portions of half-saturated brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with a gradient from 0-100% EtOAc in hexanes then with a gradient from 0-5% MeOH in EtOAc. The material was further purified by flash column chromatography on silica gel (4 g) eluting with a gradient from 0-2% MeOH in DCM to give 13.8 mg colorless film. ¹H NMR (300 MHz, CDCl₃) δ = 7.67 (d, 8.5 Hz, 2H), 7.66 (m, 1H), 7.58 (d, 8.5 Hz, 2H), 7.38 (ddd, 8.5, 6.5, 2.0 Hz, 1H), 7.13 (m, 2H), 3.66 (b, 2H), 3.30 (b, 2H), 2.32 (s, 3H). LC-MS (ESI) calculated for C₁₈H₂₀BrN₃O₃S ([M+H]+): 438.05; found: 440.0.
2-nitro-N-(pyridin-2-yl)benzamide (S7)

![Chemical structure]

Thionyl chloride (0.47 mL, 6.5 mmol) was added slowly to a solution of 2-nitrobenzoic acid (0.84 g, 5 mmol) and DMF (0.5 mL, 6.5 mmol) in DCM (25 mL). The resulting solution was refluxed for 4 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to provide the crude acid chloride which was used without further purification.

A solution of the acid chloride prepared above in DCM (25 mL) was added to a solution of 2-aminopyridine (0.61 g, 6.5 mmol) in DCM (25 mL) and pyridine (5 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with 1 M HCl (aq) and the layers separated. The aqueous layer was back-extracted with one portion of EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting with a gradient from 0-50% EtOAc in hexanes to give 0.82 g (67%) white solid.

2-amino-N-(2-pyridyl)benzamide (S8)

![Chemical structure]

Stannous chloride dihydrate (3.8 g, 16.9 mmol) was added to a solution of 2-nitro-N-(pyridin-2-yl)benzamide (0.82 g, 3.4 mmol) in EtOAc (16 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with 1 M NaOH (aq), water, and brine. The resulting emulsion was filtered through a celite plug, washing with DCM, to remove insoluble material. The layers were separated, and the aqueous layer back-extracted with one portion of DCM. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-50% EtOAc in hexanes to give 0.512 g (71%) yellow solid.

2-(4-bromophenylsulfonamido)-N-(pyridin-2-yl)benzamide (24)

![Chemical structure]
4-bromophenylsulfonyl chloride (132 mg, 0.52 mmol) was added to a solution of 2-amino-N-(2-pyridyl)benzamide (100 mg, 0.47 mmol) and pyridine (0.114 mL, 1.4 mmol) in DCM (2.35 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM, washed with 1 M HCl (aq) and sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then a gradient from 0-25% EtOAc in hexanes to give 154 mg (76%) white solid.

\[ ^1H \text{NMR} (300 \text{ MHz, CDCl}_3) \delta = 10.30 (\text{bs, } 1\text{H}), 8.31 (\text{b, } 1\text{H}), 8.21 (\text{d, } 9.0 \text{ Hz, } 1\text{H}), 7.80 (\text{ddd, } 9.0, 7.5, 2.0 \text{ Hz, } 1\text{H}), 7.60 (\text{d, } 8.5 \text{ Hz, } 2\text{H}), 7.56 (\text{d, } 7.0 \text{ Hz, } 1\text{H}), 7.51 (\text{ddd, } 8.5, 8.0, 1.5 \text{ Hz, } 1\text{H}), 7.41 (\text{d, } 8.5 \text{ Hz, } 2\text{H}), 7.19 (\text{td, } 8.0, 1.0 \text{ Hz, } 1\text{H}), 7.14 (\text{dd, } 7.5, 5.0 \text{ Hz, } 1\text{H}). \]

\[ \text{LC-MS (ESI) calculated for C}_{18}\text{H}_{14}\text{BrN}_{3}\text{O}_{3}\text{S ([M+H]})^+: 434.00; \text{found: 433.9.} \]

\[ N-(2,4\text{-dichlorophenyl})-N\text{-methyl-2-nitrobenzamide (S9)} \]

\[
\begin{align*}
\text{N} & \quad \text{O} \\
& \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{N} \\
\end{align*}
\]

Sodium hydride (60 wt% in mineral oil) (96 mg, 2.4 mmol) was added to a solution of 2-amino-N-(2,4-dichlorophenyl)benzamide (0.5 g, 1.6 mmol) in THF (12.3 mL) cooled in an ice/water bath. The bath was removed and the mixture stirred 15 min. Methyl iodide (0.2 mL, 3.2 mmol) was added, and the mixture was heated to 35°C overnight. The reaction mixture was cooled to room temperature and the volatiles removed in vacuo. The residue was diluted with 1 M HCl (aq) and extracted with three portions of DCM. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude material was used without further purification.

\[ 2\text{-amino-N-(2,4\text{-dichlorophenyl})-N-methylbenzamide (S10)} \]

\[
\begin{align*}
\text{N} & \quad \text{O} \\
& \quad \text{O} \\
\text{O} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

Stannous chloride dihydrate (1.8 g, 8 mmol) was added to a solution of \(N\)-(2,4-dichlorophenyl)-N-methyl-2-nitrobenzamide (0.52 g, 1.6 mmol) in EtOAc (8 mL). The resulting mixture was stirred overnight. The reaction mixture was diluted with 1 M NaOH (aq) and extracted with three portions of EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting with a gradient from 0-50% EtOAc in DCM to give 0.44 g (94%) colorless film.
4-bromophenylsulfonyl chloride (0.42 g, 1.7 mmol) was added to a solution of 2-amino-N-(2,4-
dichlorophenyl)-N-methylbenzamide (0.44 g, 1.5 mmol) and pyridine (0.36 mL, 4.5 mmol) in DCM (7.5 mL). The resulting solution was stirred for 1.5 h. The reaction mixture was diluted with DCM, washed with three portion of 1 M HCl (aq) and one portion of sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 0.62 g (80%) white solid. ¹H NMR (300 MHz, CDCl₃) δ = 9.29 (bs, 1H), 7.81 (d, 8.0 Hz, 2H), 7.64 (d, 8.5 Hz, 2H), 7.56 (d, 8.0 Hz, 1H), 7.38 (s, 1H), 7.20 (t, 7.5 Hz, 1H), 6.98 (d, 7.0 Hz, 1H), 6.74 (m, 2H), 6.23 (d, 9.0 Hz, 1H), 3.32 (s, 3H). LC-MS (ESI) calculated for C₂₀H₁₅BrCl₂N₂O₃S ([M+H]+): 514.94; found: 514.8.

3-(4-bromophenylsulfonamido)benzoic acid (S11)

A solution of 3-aminobenzoic acid (0.274 g, 2 mmol) and Na₂CO₃ (0.51 g, 4.8 mmol) in H₂O (3 mL) was heated to 60°C. 4-bromophenylsulfonyl chloride (0.61 g, 2.4 mmol) was added, and the resulting suspension was stirred overnight. The reaction mixture was cooled to room temperature, 6 M HCl (aq) (1 mL) added slowly, and the resulting suspension stirred overnight. The precipitate was collected by vacum filtration, washed with water, and dried in vacuo at 40°C to give 0.388 g (54%) tan solid.
**3-(4-bromophenylsulfonamido)-N-(2,4-dichlorophenyl)benzamide (26)**

Thionyl chloride (26.4 µL, 0.36 mmol) was added slowly to a solution of 3-(4-bromophenylsulfonamido)benzoic acid (100 mg, 0.28 mmol) and DMF (28 µL, 34 µmol) in DCM (1.4 mL). The resulting solution was refluxed for 4 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to provide the crude acid chloride which was used without further purification.

2,4-dichloroaniline (59 mg, 0.36 mmol) and pyridine (0.28 mL) were added to a solution of the acid chloride prepared above in DCM (2.8 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with DCM washed with 1 M HCl (aq), water, and sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (4 g) eluting with a gradient from 0-20% EtOAc in hexanes to give 13 mg (9%) off-white solid.

**H NMR** (300 MHz, DMSO-d₆) δ = 10.64 (bs, 1H), 10.11 (bs, 1H), 7.80 (d, 9.0 Hz, 2H), 7.73 (d, 2.5 Hz, 1H), 7.70 (d, 9.0 Hz, 2H), 7.67 (m, 1H), 7.60 (d, 8.5 Hz, 1H), 7.47 (dd, 8.5, 2.5 Hz, 1H), 7.43 (t, 7.5 Hz, 1H), 7.32 (8.0, 2.0, 1.0 Hz, 1H). **LC-MS** (ESI) calculated for C₁₉H₁₄BrCl₂N₂O₃S ([M+H]+): 500.93; found: 485.8.

**N-(2,4-dichlorophenyl)-2-iodobenzamide (S12)**

Thionyl chloride (0.47 mL, 6.5 mmol) was added slowly to a solution of 2-iodobenzoic acid (1.24 g, 5 mmol) and DMF (0.5 mL, 6.5 mmol) in DCM (25 mL). The resulting solution was refluxed for 4 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to provide the crude acid chloride which was used without further purification.

A solution of the acid chloride prepared above in DCM (25 mL) was added to a solution of 2,4-dichloroaniline (1.05 g, 6.5 mmol) in DCM (25 mL) and pyridine (5 mL). The resulting solution was stirred overnight. The reaction mixture was diluted with 1 M HCl (aq) and the layers separated. The aqueous layer was back-extracted with one portion of EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography on...
silica gel (12 g) eluting with a gradient from 0-20% EtOAc in hexanes to give a mixture of product and 2,4-dichloroaniline which was used without further purification.

**2-((4-bromophenyl)sulfonyl)-N-(2,4-dichlorophenyl)benzamide (27)**

![Chemical structure of 2-((4-bromophenyl)sulfonyl)-N-(2,4-dichlorophenyl)benzamide](image)

Cupric iodide (4.8 mg, 0.025 mmol) was added to a mixture of N-(2,4-dichlorophenyl)-2-iodobenzamide (~30%) (300 mg, 0.25 mmol), sodium 4-bromobenzene-1-sulfinate (124 mg, 0.51 mmol) (prepared per Du et al, Org Lett, 18 (16), 4144-4147, 2016), and 1,2-dimethylethlenediamine (2.7 µL, 0.025 mmol) in DMSO (2.5 mL). The resulting mixture was heated to 110°C overnight. LC-MS showed incomplete conversion. Additional sodium 4-bromobenzene-1-sulfinate (31 mg, 0.13 mmol) and cupric iodide (4.8 mg, 0.025 mmol) were added, and the mixture was heated back to 110°C overnight. The reaction mixture was cooled to room temperature, diluted with water, and extracted with two portions of EtOAc. The combined organic layers were washed with 1 M HCl (aq), sat. NaHCO₃ (aq), and two portions of brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column concentration on silica gel (12 g) eluting first with hexanes then a gradient from 0-25% EtOAc in hexanes to give 160 mg purple-white solid which was pure by LC-MS.

A portion of the material was taken up in a 6:1:1 mixture of THF, 8 M Na₂SO₃ (aq), and 8 M NaHCO₃ (aq). The resulting mixture was heated to 80°C overnight, during which time the volatiles evaporated. The residue was partitioned between H₂O and EtOAc, the layers separated, and the aqueous layer extracted with one portion of EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give a white solid. **H NMR** (300 MHz, CDCl₃) δ = 8.39 (d, 9.0 Hz, 1H), 8.18 (dd, 7.0, 2.0 Hz, 1H), 7.94 (b, 1H), 7.86 (d, 8.5 Hz, 2H), 7.67 (td, 7.0, 1.5 Hz, 1H), 7.63 (d, 8.5 Hz, 2H), 7.60 (dd, 6.0, 2.0 Hz, 1H), 7.45 (d, 2.5 Hz, 1H), 7.34 (dd, 9.0, 2.5 Hz, 1H). **LC-MS** (ESI) calculated for C₁₉H₁₂BrCl₂NO₃S ([M+H]⁺): 485.92; found: 485.8.

**N-(2-aminobenzyl)-2,4-dichloroaniline (S13)**

Borane-tetrahydrofuran (2 M in THF) (3.6 mL, 7.2 mmol) was added dropwise to a solution of 2-amino-N-(2,4-dichlorophenyl)benzamide (0.25 g, 0.89 mmol) in THF (1.8 mL) cooled in an ice/water bath. The resulting mixture was stirred for 15 min then heated to reflux overnight. LC-MS showed incomplete
conversion. Additional borane-tetrahydrofuran (2 M in THF) (0.88 mL, 1.76 mmol) was added and reflux was continued for 2 h. The reaction mixture was cooled in a water bath, slowly quenched with 1 M NaOH (aq) (5 mL), and stirred for 15 min. The reaction mixture was partitioned between half-saturated brine and DCM, the layers separated, and the aqueous layer extracted with one portion of DCM. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 0.204 g (86%) white solid.

**4-bromo-N-(2-(((2,4-dichlorophenyl)amino)methyl)phenyl)benzenesulfonamide (28)**

![Chemical structure](image)

4-bromophenylsulfonyl chloride (0.21 g, 0.84 mmol) was added to a solution of N-(2-aminobenzyl)-2,4-dichloroaniline (0.20 g, 0.76 mmol) and pyridine (0.18 mL, 2.3 mmol) in DCM (3.8 mL). The resulting solution was stirred for 4.5 h. The reaction mixture was diluted with DCM, washed with three portion of 1 M HCl (aq) and one portion of sat. NaHCO$_3$ (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-25% EtOAc in hexanes to give 0.27 g (74%) white powder.

**1H NMR** (300 MHz, DMSO-d$_6$) $\delta$ = 9.96, (s, 1H), 7.81 (d, 8.5 Hz, 2H), 7.62 (d, 8.5 Hz, 2H), 7.35 (d, 2.5 Hz, 1H), 7.15 (m, 3H), 6.99 (d, 2.5 Hz, 1H), 6.96 (d, 2.5 Hz, 1H), 6.28 (t, 5.0, 1H), 5.89 (d, 9.0 Hz, 1H), 4.26 (d, 5.5 Hz, 2H).

**LC-MS** (ESI) calculated for C$_{19}$H$_{15}$BrCl$_2$N$_2$O$_2$S ($[M+H]^+$): 486.95; found: 486.9.

**2-((2,4-dichlorophenoxy)methyl)aniline (S14)**

![Chemical structure](image)

Potassium carbonate (0.42 g, 3 mmol) was added to a solution of 2,4-dichlorophenol (0.25 g, 1.5 mmol) and 2-nitrobenzyl bromide (0.33 g, 1.5 mmol) in MeCN (2.3 mL). The resulting mixture was heated to 70°C for 2 h then cooled to room temperature. The reaction mixture was diluted with water and extracted with three portions of EtOAc. The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to give the crude ether which was used without further purification.

Stannous chloride dihydrate (1.73 g, 7.6 mmol) was added to a solution of the crude ether prepared above in EtOAc (7.5 mL). The resulting mixture was stirred overnight. The reaction mixture was diluted
with 1 M NaOH (aq) and extracted with three portions of EtOAc. The combined organic layers were washed with water, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting with a gradient from 0-20% EtOAc in hexanes to give 88.7 mg (22%) material.

**4-bromo-N-((2,4-dichlorophenoxy)methyl)phenyl)benzenesulfonamide (29)**

![Chemical structure of 4-bromo-N-((2,4-dichlorophenoxy)methyl)phenyl)benzenesulfonamide (29)](image)

4-bromophenylsulfonyl chloride (93 mg, 0.36 mmol) was added to a solution of 2-((3,4-dichlorophenoxy)methyl)aniline (88.7 mg, 0.33 mmol) and pyridine (80 µL, 0.99 mmol) in DCM (1.65 mL). The resulting solution was stirred for 1.5 h. The reaction mixture was cooled to room temperature, diluted with water, washed with three portions of 1 M HCl (aq) and one portion of sat. NaHCO₃ (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then a gradient from 0-20% EtOAc in hexanes to give 64.8 mg (40%) white powder. **¹H NMR** (300 MHz, CDCl₃) δ = 7.60 (d, 9.0 Hz, 2H), 7.61-7.59 (m, 1H), 7.53 (d, 8.5 Hz, 2H), 7.42 (d, 2.5 Hz, 1H), 7.41 (dt, 8.0, 1.5 Hz, 1H), 7.33 (td, 7.0, 2.0 Hz, 1H), 7.26 (dd, 7.0, 1.5 Hz, 1H), 7.19 (dd, 9.0, 2.5 Hz, 1H), 7.18 (td, 7.5, 1.5 Hz, 1H), 6.84 (d, 8.5 Hz, 1H), 4.81 (s, 2H). **LC-MS** (ESI) calculated for C₁₉H₁₄BrCl₂NO₃S ([M+Na]+): 509.91; found: 509.8.

**cis-2-((4-bromophenylsulfonamido)-cyclohexanecarboxylic acid (S15)**

![Chemical structure of cis-2-((4-bromophenylsulfonamido)-cyclohexanecarboxylic acid (S15)](image)

NaOH (60 mg, 1.5 mmol) in H₂O (1 mL) and 4-bromophenylsulfonyl chloride (197 mg, 0.77 mmol) in toluene (1 mL) were added sequentially to a solution of cis-2-aminocyclohexanecarboxylic acid (100 mg, 0.7 mmol) in H₂O (1 mL). The resulting mixture was stirred overnight. The reaction mixture was washed with two portions of toluene, acidified to approximately pH 4 with 1 M HCl (aq), and extracted with three portions of EtOAc. The combined EtOAc extracts were dried over Na₂SO₄ and concentrated in vacuo to give 132.6 mg (52%) white solid.
cis-2-(4-bromophenylsulfonamido)-N-(4-chlorophenyl)cyclohexanecarboxamide (30)

\[
\begin{align*}
\text{cis-2-(4-bromophenylsulfonamido)-N-(4-chlorophenyl)cyclohexanecarboxamide (30)}
\end{align*}
\]

\[
\begin{align*}
N,N\text{-diisopropylethylamine (128 µL, 0.73 mmol) was added to a suspension of cis-2-}
\text{(4-bromophenylsulfonamido)-cyclohexanecarboxylic acid (132.6 mg, 0.37 mmol), 4-chloroaniline (93 mg,}
\text{0.73 mmol), EDC (105 mg, 0.55 mmol), and 1-hydroxybenzotriazole hydrate (87 mg, 0.55 mmol) in DMF}
\text{(3.7 mL). The resulting solution was heated to 45°C overnight. The reaction mixture was cooled to}
\text{room temperature, diluted with DCM, washed with 1 M HCl (aq), water, sat. NaHCO}_3\text{ (aq), and brine,}
\text{dried over Na}_2\text{SO}_4\text{, and concentrated in vacuo. The crude material was purified by flash column}
\text{chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-20% EtOAc in}
\text{hexanes to give 51.6 mg tan solid. The material was further purified by preparative HPLC (C18) eluting}
\text{with a gradient from 10-90% MeCN in H}_2\text{O buffered with 1% formic acid to give 25.6 mg (15%) white}
\text{powder.} \\
\text{^1H NMR (300 MHz, DMSO-d}_6\text{) }\delta = 9.79\text{ (bs, 1H), 7.78\text{ (b, 1H), 7.64\text{ (d, 9.0 Hz, 2H), 7.55\text{ (d, 9.0 Hz, 2H), 7.47\text{ (d, 9.0 Hz, 2H), 7.30\text{ (d, 9.0 Hz, 2H), 3.70\text{ (b, 1H), 2.57\text{ (b, 1H), 1.76\text{ (b, 2H), 1.54\text{ (b, 3H), 1.26\text{ (b, 3H).} LC-MS (ESI) calculated for C}_{19}\text{H}_{20}\text{BrClN}_2\text{O}_3\text{S ([M+H]^+): 473.01; found: 473.0.}}}
\end{align*}
\]

trans-2-(4-bromophenylsulfonamido)-cyclohexanecarboxylic acid (S16)

\[
\begin{align*}
\text{trans-2-(4-bromophenylsulfonamido)-cyclohexanecarboxylic acid (S16)}
\end{align*}
\]

NaOH (30 mg, 0.75 mmol) in H$_2$O (0.5 mL) and 4-bromophenylsulfonyl chloride (98 mg, 0.39 mmol) in toluene (0.5 mL) were added sequentially to a solution of trans-2-aminocyclohexanecarboxylic acid (50 mg, 0.35 mmol) in H$_2$O (0.5 mL). The resulting mixture was stirred overnight. The reaction mixture was washed with two portions of toluene, acidified to approximately pH 4 with 1 M HCl (aq), and extracted with three portions of EtOAc. The combined EtOAc extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was taken up in toluene and concentrated in vacuo to give 46.2 mg (36%) white solid.
trans-2-(4-bromophenylsulfonamido)-N-(4-chlorophenyl)cyclohexanecarboxamide (31)

\[
\begin{align*}
&\text{OH} \quad \text{Cl} \\
&\text{N} \quad \text{H} \\
&\text{O} \quad \text{N} \\
&\text{H} \\
&\text{N} \quad \text{H} \\
&\text{O} \\
&\text{N} \quad \text{H} \\
&\text{Br} \\
&\text{Cl}
\end{align*}
\]

\[\text{(+/-)}\]

\[\text{(+/-)}\]

\(N,N\text{-diisopropylethylamine (44.6 µL, 0.26 mmol) was added to a suspension of trans-2-(4-bromophenylsulfonamido)-cyclohexanecarboxylic acid (46.2 mg, 0.13 mmol), 4-chloroaniline (32.7 mg, 0.26 mmol), EDC (36.8 mg, 0.19 mmol), and 1-hydroxybenzotriazole hydrate (30.5 mg, 0.19 mmol) in DMF (1.3 mL). The resulting solution was heated to 45°C overnight. The reaction mixture was cooled to room temperature, diluted with DCM, washed with 1 M HCl (aq), water, sat. NaHCO}_3 (aq), and brine, dried over Na}_2\text{SO}_4, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (4 g) eluting first with hexanes then a gradient from 0-25% EtOAc in hexanes to give 3.5 mg (6%) tan solid.}\]

\(\text{^1H NMR (300 MHz, DMSO-d}_6\) δ = 9.82 (s, 1H), 7.92 (bs, 1H), 7.58 (d, 8.5 Hz, 2H), 7.52 (d, 8.5 Hz, 2H), 7.41 (d, 8.5 Hz, 2H), 7.30 (d, 8.5 Hz, 2H), 7.39 (b, 1H), 2.26 (td, 11.0, 3.5 Hz, 1H), 1.77 (m, 2H), 1.62 (m, 2H), 1.38 (q, 12.0 Hz, 1H), 1.21 (t, 9.5 Hz, 1H), 1.15 (m, 2H).}\]

\(\text{LC-MS (ESI) calculated for C}_{19}\text{H}_{20}\text{BrClN}_2\text{O}_3\text{S ([M+H]}^+)\): 473.01; found: 472.9.\]

3-amino-N-(4-chlorophenyl)picolinamide (S17)

\[
\begin{align*}
&\text{NH}_2 \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]

\[\text{(+/-)}\]

\[\text{(+/-)}\]

\(N,N\text{-diisopropylethylamine (0.25 mL, 1.4 mmol) was added to a suspension of 3-amino-2-pyridinecarboxylic acid (100 mg, 0.72 mmol), 4-chloroaniline (184 mg, 1.4 mmol), EDC (207 mg, 1.1 mmol), and 1-hydroxybenzotriazole hydrate (172 mg, 1.1 mmol) in DMF (6 mL). The resulting solution was heated to 45°C overnight. The reaction mixture was cooled to room temperature, diluted with DCM, washed with half-saturated brine, sat. NaHCO}_3 (aq), and half-saturated brine, dried over Na}_2\text{SO}_4, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting first with hexanes then a gradient from 0-50% EtOAc in hexanes to give a mixture of product and excess 4-chloroaniline which was used without further purification.}\)
3-(4-bromophenylsulfonamido)-N-(4-chlorophenyl)picolinamide (32)

4-bromophenylsulfonyl chloride (184 mg, 0.72 mmol) was added to a solution of crude 3-amino-N-(4-chlorophenyl)picolinamide (178 mg, 0.72 mmol) in pyridine (7.2 mL). The resulting solution was heated to 60°C overnight. Additional 4-bromophenylsulfonyl chloride (184 mg, 0.72 mmol) was added, and the solution was heated to 60°C overnight. LC-MS showed the reaction not progressing. The solution was heated to 90°C overnight, during which time the volatiles boiled off. The residue was taken up in DCM, washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting with a gradient from 0-25% EtOAc in hexanes to give 21.6 mg (6%) white solid. \(^1\)H NMR (300 MHz, CDCl₃) δ = 11.86 (bs, 1H), 10.18 (bs, 1H), 8.26 (dd, 4.5, 1.5 Hz, 1H), 8.15 (dd, 8.5, 1.5 Hz, 1H), 7.76 (d, 8.5 Hz, 2H), 7.64 (d, 8.5 Hz, 2H), 7.59 (d, 8.5 Hz, 2H), 7.43 (dd, 8.5, 4.5 Hz, 1H), 7.37 (d, 9.0 Hz, 2H). LC-MS (ESI) calculated for C₁₈H₁₃BrClIN₃O₃S ([M+H]+): 467.96; found: 467.8.

2-amino-N-(4-chlorophenyl)nicotinamide (S18)

\(N,N\)-diisopropylethylamine (0.25 mL, 1.4 mmol) was added to a suspension of 2-aminonicotinic acid (100 mg, 0.72 mmol), 4-chloroaniline (184 mg, 1.4 mmol), EDC (207 mg, 1.1 mmol), and 1-hydroxybenzotriazole hydrate (172 mg, 1.1 mmol) in DMF (6 mL). The resulting solution was heated to 45°C overnight. The reaction mixture was cooled to room temperature, diluted with DCM, washed with half-saturated brine, sat. NaHCO₃ (aq), and half-saturated brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting with a gradient from 0-50% EtOAc in hexanes to give 130 mg (73%) yellow solid.
2-(4-bromophenylsulfonamido)-N-(4-chlorophenyl)nicotinamide (33)

4-bromophenylsulfonyl chloride (0.4 g, 1.6 mmol) was added to a solution of 2-amino-N-(4-chlorophenyl)nicotinamide (130 mg, 0.53 mmol) in pyridine (5.25 mL). The resulting solution was heated to 90°C overnight. The reaction mixture was cooled to room temperature, diluted with water, and extracted with three portions of DCM. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (12 g) eluting with a gradient from 0-100% EtOAc in hexanes to give 46.3 mg (19%) white solid. ³¹H NMR (300 MHz, CDCl₃) δ = 11.85 (bs, 1H), 8.92 (d, 7.0 Hz, 1H), 7.84 (d, 8.5 Hz, 2H), 7.74 (d, 5.5 Hz, 1H), 7.66 (d, 9.0 Hz, 2H), 7.52 (d, 9.0 Hz, 2H), 7.30 (d, 8.5 Hz, 1H), 6.94 (t, 7.0 Hz, 1H). LC-MS (ESI) calculated for C₁₈H₁₃BrClN₃O₃S ([M+H]⁺): 467.96; found: 468.0.
5. NMR Spectra of Final Compounds

Compound 3 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))
Compound 4 (1H NMR, 300 MHz)

![Image of compound 4 NMR spectrum]

![Image of chemical structure of compound 4]
Compound 5 (\textsuperscript{1}H NMR, 300 MHz, CDCl\textsubscript{3})

![Chemical Structure](image_url)
Compound 6 (¹H NMR, 300 MHz, CDCl₃)
Compound 7 (¹H NMR, 300 MHz)
Compound 8 (¹H NMR, 300 MHz, CDCl₃)
Compound 9 \( (^{1}H\text{ NMR, 300 MHz, DMSO-}d_{6}) \)
Compound 10 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))
Compound 11 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))
Compound 12 ($^1$H NMR, 300 MHz, DMSO-$d_6$)
Compound 13 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 14 (¹H NMR, 300 MHz, CDCl₃)
Compound 15 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))
Compound 16 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 17 (\textsuperscript{1}H NMR, 300 MHz, CDCl\textsubscript{3})
Compound 18 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 19 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

\[
\begin{align*}
&\text{O} \\
&\text{N} \\
&\text{O} \\
&\text{Br}
\end{align*}
\]
Compound 20 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 21 (\( ^1H \) NMR, 300 MHz, CDCl\(_3\))

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{Br}
\end{align*}
\]
Compound 22 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 23 (\(^1\text{H NMR, 300 MHz, CDCl}_3\))

![NMR spectrum for Compound 23]
Compound 24 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

\[
\begin{array}{c}
\text{N}
\end{array}
\]

\[
\begin{array}{c}
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{Br}
\end{array}
\]
Compound 25 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 26 (¹H NMR, 300 MHz, DMSO-d₆)
Compound 27 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 28 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 29 (¹H NMR, 300 MHz, CDCl₃)
Compound 30 ($^1$H NMR, 300 MHz, DMSO-$d_6$)
Compound 31 (\(^1\)H NMR, 300 MHz, DMSO-\(d_6\))
Compound 32 ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 33 ($^1$H NMR, 300 MHz, CDCl$_3$)

![NMR spectrum]

![Chemical structure]

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