# Supporting Information

## Optimization of $P2Y_{12}$ Antagonist Ethyl 6-(4-((Benzylsulfonyl) -carbamoyl)piperidin-1-yl)-5-cyano-2-methylnicotinate (AZD1283) Led to the Discovery of an Oral Antiplatelet Agent with Improved Drug-Like Properties

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**General Chemical Methods.** All solvents and chemicals were used as purchased without further purification. Room temperature refers to 20−25 °C. Intermediates not described below were purchased from commercial vendors and were used as supplied unless stated otherwise. All reactions were monitored using thin-layer chromatography (TLC) on silica gel F-254 TLC plates. Column chromatography was carried out using silica gel (200−300 mesh). $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker 400, a Bruker 500 or a Bruker 600 NMR spectrometer using solvent residual as an internal standard. Chemical shifts ($\delta$) are reported in parts per million (ppm), and coupling constants ($J$) are reported in Hertz (Hz). EI-MS spectra were obtained on a Finnigan MAT95 spectrometer, and ESI-MS spectra were obtained on a Krats MS 80 mass spectrometer. All final compounds were purified to >96% purity as determined by analytical HPLC (PLATISIL ODS 250 mm × 4.6 mm, particle size 5 $\mu$m) with acetonitrile/buffer (0.1% $CF_3COOH$ and 0.1% $NH_4OH$ in water, pH 3.5) as the mobile phase.

***tert*-Butyl 4-((Benzylsulfonyl)carbamoyl)piperidine-1-carboxylate (7a).** A suspension of **5a** (3 g, 13.10 mmol ) and TBTU (4.4 g, 13.76 mmol) in THF (50 mL) and TEA (5.46 ml, 39.30 mmol) was stirred at rt for 40 min. 1-Phenylmethanesulfonamide **6** (2.46 g, 14.41 mmol) and LiCl (0.14 g, 3.33 mmol) were added, and the reaction mixture was stirred at rt for **7a**. The mixture was concentrated, diluted with EtOAc (100 mL), dried ($Na_2SO_4$), and concentrated.

Addition of petroleum ether (50 mL) facilitated precipitation. The mixture was stirred at rt for 0.5 h and filtered, and the solids were washed with diluted HCl (50 mL). Yield: 9.34 g (72%).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42–7.37 (m, 3H), 7.34–7.31 (m, 2H), 4.64 (s, 2H), 4.08 (d, $J$ = 11.2 Hz, 2H), 2.76–2.64 (m, 2H), 2.33–2.24 (m, 1H), 1.74–1.70 (m, 2H), 1.65–1.58 (m, 2H), 1.46 (s, 9H). MS (ESI) *m/z*: 383.0 $[M + H]^+$.

***N*-(Benzylsulfonyl)piperidine-4-carboxamide (8a)**. Compound **7a** (5.0 g, 13.09 mmol) in formic acid (40 ml, 39.27 mmol) was stirred at rt for 18 h, concentrated and Water (15 mL) was added, and the pH was adjusted to 6 with $NH_4OH$ (saturated, aq solution). The mixture was stirred at rt for 2 h and filtered, and the solids were washed with cold water (35 mL) and dried in vacuo. Yield: 3.0 g (80%) of **8a** as a white powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.57−1.72 (2H, m), 1.72−1.84 (2H, m), 2.08−2.19 (1H, m), 2.72−2.85 (2H, m), 3.07−3.17 (2H, m), 4.24 (2H, s), 7.19−7.29 (5H, m), 8.12 (1H, br s). MS (ESI) *m/z*: 283 $[M + H]^+$.

***tert*-Butyl 4-((Benzylsulfonyl)carbamoyl)piperidine-1-carboxylate (7b).** Compound **7b** (0.32 g, 65%) was prepared from **5b** (0.31 g, 1.29 mmol) and Phenylmethanesulfonamide **6** (0.22 g, 1.29 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.51–7.48 (m, 3H), 7.41–7.35 (m, 2H), 4.27 (s, 2H), 3.52–3.43 (m, 2H), 3.02–2.91 (m, 2H), 2.04–1.98 (m, 2H), 1.95–1.84 (m, 2H), 1.39 (s, 9H), 1.10 (s, 3H). MS (ESI) *m/z*: 397.1 $[M + H]^+$.

***N*-(Benzylsulfonyl)-4-methylpiperidine-4-carboxamide (8b).** Compound **8b** (0.22 g, 90%) was prepared from **7b** (0.32 g, 0.8 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.13 (s, 1H), 7.27–7.10 (m, 5H),

4.14 (s, 2H), 3.12–3.05 (m, 2H), 2.79–2.70 (m, 2H), 2.12 (d, *J* = 14.6 Hz, 2H), 1.34–1.27 (m, 2H), 0.99 (s, 3H). MS (ESI) *m/z*: 297.2 $[M + H]^+$.

***tert*-Butyl 3-((Benzylsulfonyl)carbamoyl)azetidine-1-carboxylate (7c).** Compound **7c** (0.45 g, 45%) was prepared from **5c** (0.50 g, 2.49 mmol) and Phenylmethanesulfonamide **6** (0.50 g, 2.6 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.73 (s, 1H), 7.42–7.38 (m, 3H), 7.34–7.28 (m, 2H), 4.73 (s, 2H), 3.91 (t, *J* = 8.9 Hz, 2H), 3.85–3.78 (m, 2H), 2.03–1.95 (m, 1H), 1.39 (s, 9H). MS (ESI) *m/z*: 353.1$[M - H]^-$.

***N*-(Benzylsulfonyl)azetidine-3-carboxamide (8c).** Compound **8c** (0.17 g, 93%) was prepared from **8b** (0.25 g, 0.70 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.46 (s, 1H), 7.31–7.20 (m, 5H), 4.28 (s, 2H), 4.00–3.88 (m, 4H), 3.22 (ddd, *J* = 17.1, 9.4, 8.0 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 174.89, 133.15, 130.43, 127.78, 126.87, 56.93, 48.67, 38.22. MS (ESI) *m/z*: 253.4$[M - H]^-$.

***tert*-Butyl 3-((Benzylsulfonyl)carbamoyl)pyrrolidine-1-carboxylate (7d).** Compound **7d** (0.50 g, 37%) was prepared from **5d** (0.50 g, 2.3 mmol) and phenylmethanesulfonamide **6** (0.55 g, 2.9 mmol) in the same manner as described for **7d**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.70 (s, 1H), 7.40 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.32–7.26 (m, 2H), 4.70 (s, 2H), 3.46–3.33 (m, 2H), 3.27–3.16 (m, 2H), 3.03–2.92 (m, 1H), 2.06–1.94 (m, 2H), 1.41 (s, 9H). MS (ESI) *m/z*: 369.1 $[M + H]^+$.

***N*-(Benzylsulfonyl)pyrrolidine-3-carboxamide (8d).** Compound **8d** (0.36 g, 91%) was prepared from **7d** (0.50 g, 1.49 mmol) in the same manner as described for **8a**. $^1$H

NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.57 (s, 1H), 7.30–7.20 (m, 5H), 4.26 (s, 2H), 3.29–3.25 (m, 2H), 3.12–3.05 (m, 2H), 2.82–2.74 (m, 1H), 1.99–1.90 (m, 2H). MS (ESI) *m/z*: 269.1 $[M + H]^+$.

***tert*-Butyl 4-(((5-Chlorothiophen-2-yl)sulfonyl)carbamoyl)piperidine -1-carboxylate (10a).** Compound **10a** (11.3 g, 90%) was prepared from **5a** (7.00 g, 30.5 mmol) and 5-chlorothiophene-2-sulfonamide **9** (6.28 g, 32.02 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.45 (9H, s), 1.55–1.65 (2H, m), 1.79–1.82 (2H, m), 2.92–2.37 (1H, m), 2.73–2.80 (2H, m), 4.06–4.11 (2H, m), 6.96 (1H, d, $J$ = 4.1 Hz), 7.69 (1H, d, $J$ = 4.1 Hz), 8.11 (1H, br s). MS (ESI) *m/z*: 409.1 $[M + H]^+$.

***N*-((5-Chlorothiophen-2-yl)sulfonyl)piperidine-4-carboxamide (11a).** Compound **11a** (5.9 g, 78%) was prepared from **10a** (10.0 g, 24.50 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.58–1.68 (2H, m), 1.87–1.90 (2H, m), 2.52–2.59 (1H, m), 2.80–2.88 (2H, m), 3.22–3.25 (2H, m), 7.29 (1H, d, $J$ = 4.1 Hz), 7.67 (1H, d, $J$ = 4.1 Hz), 8.51 (1H, br s), 8.82 (1H, br s). MS (ESI) *m/z*: 309.01 $[M + H]^+$.

***tert*-Butyl 4-(((5-Chlorothiophen-2-yl)sulfonyl)carbamoyl)-4-methylpiperidine -1-carboxylate (10b).** Compound **10b** (0.43 g, 43%) was prepared from **5b** (0.60 g, 2.45 mmol) and 5-chlorothiophene-2-sulfonamide **9** (0.53 g, 2.36 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.67 (d, $J$ = 4.1 Hz, 1H), 7.28 (d, $J$ = 4.1 Hz, 1H), 3.53–3.45 (m, 2H), 2.95–2.85 (m, 2H), 1.92–1.84 (m, 2H), 1.37 (s, 9H), 1.34–1.26 (m, 2H), 1.11 (s, 3H). MS (ESI) *m/z*: 423.1 $[M + H]^+$.

***N*-((5-Chlorothiophen-2-yl)sulfonyl)-4-methylpiperidine-4-carboxamide (11b).** Compound **11b** (0.30 g, 95%) was prepared from **10a** (0.40 g, 1.0 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.22 (d, $J$ = 3.9 Hz, 1H), 6.98 (d, $J$ = 3.9 Hz, 1H), 3.10 (dt, $J$ = 6.5, 3.6 Hz, 2H), 2.73 (td, $J$ = 12.4, 2.8 Hz, 2H), 2.10 (d, $J$ = 14.1 Hz, 2H), 1.33 (td, $J$ = 14.1, 4.1 Hz, 2H), 0.99 (s, 3H). MS (ESI) *m/z*: 323.0 $[M + H]^+$.

***tert*-Butyl 3-(((5-Chlorothiophen-2-yl)sulfonyl)carbamoyl)azetidine-1-carboxylate (10c).** Compound **10c** (0.25 g, 26%) was prepared from **5c** (0.50 g, 2.49 mmol) and 5-chlorothiophene-2-sulfonamide **9** (0.50 g, 2.6 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.61 (s, 1H), 7.70 (d, $J$ = 4.2 Hz, 1H), 7.30 (d, $J$ = 4.2 Hz, 1H), 3.91 (t, $J$ = 8.5 Hz, 2H), 3.79–3.72 (m, 2H), 3.37–3.34 (m, 1H), 1.36 (s, 9H). MS (ESI) *m/z*: 381.0 $[M + H]^+$.

***N*-((5-Chlorothiophen-2-yl)sulfonyl)azetidine-3-carboxamide (11c).** Compound **11c** (0.18 g, 96%) was prepared from **10c** (0.25 g, 0.66 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.47 (s, 1H), 7.27 (d, $J$ = 3.9 Hz, 1H), 7.00 (d, $J$ = 3.9 Hz, 1H), 3.97 (t, $J$ = 10.1 Hz, 2H), 3.93–3.87 (m, 2H), 3.29–3.22 (m, 1H). MS (ESI) *m/z*: 281.0 $[M + H]^+$.

**Ethyl 4-(Benzyloxy)-3-oxobutanoate (13a).** To a suspension of 60% NaH (15.0 g, 366 mmol) in THF (300 mL) at 0 °C was added benzyl alcohol (26.0 g, 238 mmol), and the resulting mixture was stirred at rt for 2 h. To this mixture was then added ethyl 4-chloroacetoacetate **12a** (30.0 g, 183 mmol) dropwise over 30 min, and the resulting clear yellow solution was stirred at rt overnight before it was cooled to 5°C,

acidified to pH = 4 using 5% HCl and extracted with the EtOAc (2 × 150 mL). The combined organics were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo to yield the desired product (**13a**) as orange oil. The crude material was used for next step without further purification. Yield: 92% (39.7 g). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39–7.29 (m, 5H), 4.59 (s, 2H), 4.17 (q, $J$ = 7.1 Hz, 2H), 3.54 (s, 2H), 1.25 (t, $J$ = 7.1 Hz, 3H). MS (ESI) *m/z*: 235.08 $[M - H]^-$.

**Ethyl 4-Hydroxy-3-oxobutanoate (14a).** Pd/C (10%, 0.60 g) was added to a solution of **1b** (5.0 g, 27.51 mmol) in MeOH (70 mL), which was placed in a 150 mL autoclave. The autoclave was purged and then filled with $H_2$ (10 bar). The mixture was stirred at rt for 5 h. The catalyst was filtrated with a clarifying pad and the filtrate was condensed in vacuo to give the product **14a** (3.95 g, 98%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.39 (d, $J$ = 3.6 Hz, 2H), 4.22 (q, $J$ = 7.1 Hz, 2H), 3.50 (s, 2H), 3.00 (s, 1H), 1.29 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.8, 166.6, 68.3, 61.5, 45.1, 13.8.

**Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-3-oxobutanoate (15a).** To a solution of ethyl **14a** (3.89 g, 26.66 mmol) in 50 mL of THF were added imidazole (2.72 g, 39.98 mmol) and DMAP (100 mg); the resulting solution was cooled to 0 °C. TBSCl (4.82 g, 31.99 mmol) in 10 mL of THF was added portion-wise to the solution. The reaction was allowed to warm to rt and stirred for an additional 12 h. The mixture was diluted with DCM (150 mL) and washed with 1 M HCl (20 mL × 2), saturated $NaHCO_3$ (20 mL × 2) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes/ethyl acetate = 10:1) to provide

**15a** (1.5 g, 84%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.22 (s, 2H), 4.19 (q, $J$ = 7.1 Hz, 2H), 3.56 (s, 2H), 1.28 (t, $J$ = 7.1 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 204.1, 167.2, 68.8, 61.2, 45.5, 25.6, 18.1, 14.0, 5.7. MS (ESI) *m/z*: 261.1$[M + H]^+$.

**Ethyl (E)-4-((*tert*-Butyldimethylsilyl)oxy)-2-((dimethylamino)methylene)-3-oxobutanoate (16a).** Compound **15a** (100 mg, 0.384 mmol) in toluene (5 mL) were added 1,1-dimethoxy-N,N-dimethylmethanamine (0.5 mL, 3.76 mmol). The mixture was heated to 80° C. After 12 h, the mixture was concentrated and diluted with DCM (100 mL) and washed with water (20 mL ), saturated $NaHCO_3$ (10 mL × 2) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes/ethyl acetate = 5:1) gave the **16a** as a yellow color oil (0.10 g, 83%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 (s, 1H), 4.58 (s, 2H), 4.19 (q, $J$ = 7.1 Hz, 2H), 2.96 (s, 6H), 1.30 (t, $J$ = 7.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H). MS (ESI) *m/z*: 315.2 $[M + H]^+$.

**Ethyl-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-cyano-6-oxo-1,6-dihydropyridine-3-carboxylate (17a).** Compound **16a** (1.5 g，4.75 mmol) and cyanoacetamide (0.40 g, 4.75 mmol) were mixed in EtOH (5 mL) and 20% NaOEt (1.94 g, 5.7 mmol) was added. The reaction mixture was stirred at rt for 1h and concentrated. The crude was dissolved in EtOAc (50 mL) and washed with $NH_4Cl$ (2 × 40 mL, saturated, aq solution). The organic phase were dried ($MgSO_4$) and concentrated. The crude was purified by silica gel chromatography (hexanes/ethyl acetate = 5:1) gave the **17a** as a white solid (1.3 g, 81%). $^1$H NMR (400 MHz, $CDCl_3$)

δ 8.42 (s, 1H), 5.12 (s, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.97 (s, 9H), 0.20 (s, 6H). MS (ESI) *m/z*: 337.3 $[M + H]^+$.

**Ethyl 5-Cyano-2-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (18a).** Compound **17a** (1.25 g，0.37 mmol) was dissolved in THF (100 mL). A solution of TBAF (1M, 4.5ml) in THF (5 mL) was added and the reaction mixture was stirred at rt for 1 h. The mixture was concentrated and diluted with DCM (100 mL) and washed with water (20 mL), saturated $NaHCO_3$ (10 mL × 2) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 5:1) gave the **18a** as a white solid (0.78 g, 84%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.83 (s, 1H), 8.47 (s, 1H), 6.07 (s, 1H), 4.85 (d, *J* = 3.2 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). MS (ESI) *m/z*: 323.0 $[M + H]^+$ .

**5-Cyano-2-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (19a).** Compound **18a** (1.0 g, 4.5 mmol) was dissolved in THF (10 mL). LiOH (1 M in water, 21.6 mL, 21.6 mmol) was added and the reaction mixture was stirred at rt for 3 h. HCl (1M) was added until pH = 5-6. The aq phase was extracted with EtOAc (3 × 50 mL) and the combined organic phases were washed with brine (2 × 150 mL), dried ($Na_2SO_4$), and concentrated in vacuo. Yield: 0.80 g (92%) as a solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.98 (s, 1H), 4.33 (s, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 170.2, 164.9, 147.2, 121.4, 114.8, 91.3, 66.2. MS (ESI) *m/z*: 193.0 $[M - H]^-$ .

**2-Chloro-5-oxo-5,7-dihydrofuro[3,4-b]pyridine-3-carbonitrile (20a).** A reaction mixture of **19a** (0.80 g，4.0 mmol) and phosphorus(V) oxychloride (4.14 g, 2.52 mL,

27.0 mmol) was heated at 110 °C for 4 h. The mixture was cooled, poured onto ice, stirred for 1 h, and then extracted with EtOAc. The organic phase was washed with water, brine, dried ($MgSO_4$) and concentrated. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:5) gave the **20a** as a yellow solid (0.44 g, 55%). $^1$H NMR (400MHz, DMSO-$d_6$) $\delta$ 8.17(s, 1H), 5.03 (s, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 170.8, 166.6, 156.8, 141.8, 119.0, 114.5, 110.3, 70.5. MS (ESI) *m/z*: 195.2 $[M + H]^+$.

**Methyl 4-(Benzyloxy)-3-oxopentanoate (13b).** Compound **13b** (21.0 g, 91%) was prepared from **12b** (16.0 g, 97.6 mmol) in the same manner as described for **13a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39–7.29 (m, 5H), 4.63 (s, 2H), 4.32(q, $J$ = 6.8 Hz, 1H), 3.84 (d, $J$ = 16.3 Hz, 1H), 3.74 (s, 3H), 3.62 (s, 2H), 1.74 (d, $J$ = 6.8 Hz, 3H). MS (ESI) *m/z*: 237.1 $[M + H]^+$ .

**Methyl 4-Hydroxy-3-oxopentanoate (14b).** Compound **14b** (9.5 g, 86%) was prepared from **13b** (18.0 g, 76.27 mmol) in the same manner as described for **14a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.28 (q, $J$ = 6.8 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 2H). 1.28 (d, $J$ = 6.8 Hz, 3H). MS (ESI) *m/z*: 147.1 $[M + H]^+$ .

**Methyl 4-((*tert*-Butyldimethylsilyl)oxy)-3-oxopentanoate (15b).** Compound **15b** (12.0 g, 70%) was prepared from **14b** (9.5 g, 65.07 mmol) in the same manner as described for **15a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.25 (q, $J$ = 6.8 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 2H), 1.34 (d, $J$ = 6.8 Hz, 3H), 0.93 (s, 9H), 0.11 (d, $J$ = 2.8 Hz, 6H). MS (ESI) *m/z*: 260.1 $[M + H]^+$.

**Methyl (E)-4-((*tert*-Butyldimethylsilyl)oxy)-2-((dimethylamino)methylene)-3-**

**oxopentanoate (16b).** Compound **16b** (10.5 g, 72%) was prepared from **15b** (12.0 g, 46.15 mmol) in the same manner as described for **16a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 5.04 – 4.85 (m, 1H), 3.71 (s, 3H), 3.00 (s, 6H), 1.34 (d, $J$ = 6.7 Hz, 3H), 0.88 (s, 9H), 0.08 – 0.04 (m, 6H). MS (ESI) *m/z*: 316.4 $[M + H]^+$ .

**Methyl 2-(1-((*Tert*-Butyldimethylsilyl)oxy)ethyl)-5-cyano-6-oxo-1,6-dihydropyridine-3-carboxylate (17b).** Compound **17b** (9.0 g, 81%) was prepared from **16b** (10.5 g, 33.33 mmol) in the same manner as described for **17a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.04 (s, 1H), 8.44 (s, 1H), 4.33 (q, $J$ = 7.3 Hz, 1H), 3.70 (s, 3H), 1.39 (d, $J$ = 7.1 Hz, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H). MS (ESI) *m/z*: 337.2 $[M + H]^+$.

**Methyl 5-Cyano-2-(1-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (18b).** Compound **18b** (8.2 g, 91%) was prepared from **17b** (9.0 g, 26.79 mmol) in the same manner as described for **18a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.47 (s, 1H), 5.84 (q, $J$ = 8.8, 2.4 Hz, 1H), 3.91 (s, 3H), 1.58 (d, $J$ = 6.4 Hz, 3H). MS (ESI) *m/z*: 223.1 $[M + H]^+$ .

**5-Cyano-2-(1-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (19b).** Compound **19b** (1.8 g, 96%) was prepared from **18b** (2.0 g, 9 mmol) in the same manner as described for **19a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.82 (s, 1H), 8.44 (s, 1H), 5.57 (q, $J$ = 6.6 Hz, 1H), 1.36 (d, $J$ = 6.4 Hz, 3H). MS (ESI) *m/z*: 209.2 $[M + H]^+$.

**2-Chloro-7-methyl-5-oxo-5,7-dihydrofuro[3,4-b]pyridine-3-carbonitrile (20b).** Compound **20b** (0.14 g, 56%) was prepared from **19b** (0.25 g, 1.2 mmol) in the same

manner as described for **20a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.34 (s, 1H), 4.78 (q, 6.5 Hz, 1H), 1.32 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 173.1, 165.7, 157.0, 142.0, 118.9, 114.5, 110.6, 78.3, 17.6. MS (ESI) *m/z*: 209.0 $[M + H]^+$.

**Ethyl 5-(Benzyloxy)-3-oxopentanoate (25).** To sodium hydride (60 % dispersion in mineral oil, 3.23 g, 80.17 mmol) in a three-necked flask was added 50 mL of THF under an argon atmosphere. The mixture was stirred at 0 °C, a solution of ethyl acetoacetate (10.0 g, 76.84 mmol) in 50 mL of THF was added dropwise over 15 min. The mixture was stirred for 15 min, 2.5 M of *n*-butyllithium (33.8 mL, 1.1 equiv) was added dropwise, and the dianion solution was stirred for 15 min at 0 °C. A solution of benzyl chloromethyl ether (9.63 g，61.47 mmol) in 10 mL of THF was then added, and the mixture was stirred at 0 °C for 1 h and then 15 mL of cold water was added. The mixture was acidified with cold 1 N HCl and the organic layer was separated. The aqueous solution was extracted twice with ether, and the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:10) gave the **25** as a colorless oil (8.3 g, 43%). $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37–7.28 (m, 5H), 4.51 (s, 2H), 4.18 (q, $J$ = 7.1 Hz, 2H), 3.75 (t, $J$ = 6.2 Hz, 2H), 3.18 (t, $J$ = 6.2 Hz, 2H), 3.49 (s, 2H), 2.83 (t, $J$ = 6.2 Hz, 2H), 1.27 (t, $J$ = 7.1 Hz, 3H). MS (ESI) *m/z*: 251.02 $[M + H]^+$.

**Ethyl 5-Hydroxy-3-oxopentanoate (26).** Compound **26** (5.02 g, 98%) was prepared from **25** (8.0 g, 31.96 mmol) in the same manner as described for **14a**. $^{1}$H NMR (400 MHz, CDCl3) δ 6.97 (s, 1H), 4.19 (q, $J$ = 14.4, 7.2 Hz, 2H), 3.83 (t, $J$ = 6.2 Hz, 2H), 3.48 (s, 2H), 2.80 (t, $J$ = 5.4 Hz, 2H), 1.23 (t, $J$ = 7.0 Hz, 3H). MS (ESI)

*m/z*:159.1 $[M-H]^-$ .

**Ethyl 5-((*tert*-Butyldimethylsilyl)oxy)-3-oxopentanoate (27).** Compound **27** (6.3 g, 81%) was prepared from **26** (5.5 g，28.2 mmol) in the same manner as described for **15a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.18 (q, *J* = 7.0, 2.3 Hz, 2H), 3.89 (t, *J* = 6.2 Hz, 2H), 3.48 (s, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 1.27 (t, *J* = 7.1Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H). MS (ESI) *m/z*: 275.2 $[M+H]^+$ .

**Ethyl (E)-5-((*Tert*-Butyldimethylsilyl)oxy)-2-((dimethylamino)methylene)-3-oxopentanoate (28).** Compound **28** (7.9 g, 96%) was prepared from **27** (6.86 g, 25.0 mmol) in the same manner as described for **16a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.90 (t, *J* = 6.3 Hz, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 2.96 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H). MS (ESI) *m/z*: 330.1 $[M+H]^+$.

**Ethyl 2-(2-((*Tert*-Butyldimethylsilyl)oxy)ethyl)-5-cyano-6-oxo-1,6-dihydropyridine-3-carboxylate (29).** Compound **29** (6.44 g, 81%) was prepared from **28** (7.5 g, 22.76 mmol) in the same manner as described for **17a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.71 (s, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H). MS (ESI) *m/z*: 351.23 $[M+H]^+$.

**Ethyl 5-Cyano-2-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30).** Compound **30** (4.23 g, 98%) was prepared from **28** (6.4 g, 27.02 mmol) in the same manner as described for **18a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.45 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 1.28 (t, *J* =

7.1 Hz, 3H). MS (ESI) *m/z*: 235.1 $[M - H]^-$.

**5-Cyano-2-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (31).** Compound **31** (1.67 g, 94%) was prepared from **30** (2.0 g, 8.47 mmol) in the same manner as described for **19a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.90 (s, 1H), 4.64 (t, *J* = 6.1 Hz, 2H), 3.30 (t, *J* = 6.1 Hz, 2H). MS (ESI) *m/z*: 209.16 $[M + H]^+$.

**2-Chloro-5-oxo-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile (32).** Compound **32** (0.52 g, 35%) was prepared from **31** (1.5 g, 7.2 mmol) in the same manner as described for **20a**. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.90 (s, 1H), 4.64 (t, *J* = 6.1 Hz, 2H), 3.30 (t, *J* = 6.1 Hz, 2H). 13C NMR (126 MHz, DMSO-$d_6$) $\delta$ 164.22, 162.0,154.4, 144.7, 120.9, 114.2, 109.1, 66.2, 30.0. MS(ESI) *m/z*: 209.10 $[M + H]^+$.

**2-((Dimethylamino)methylene)cyclohexane-1,3-dione (36).** Compound **36** (7.45 g, 98%) was prepared from **35** (5.0 g, 45.59 mmol) in the same manner as described for **16a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (s, 1H), 3.39 (s, 3H), 3.16 (s, 3H), 2.46 (t, *J* = 6.4 Hz, 4H), 1.97–1.90 (m, 2H). MS (ESI) m/z: 166.1$[M - H]^-$.

**2,5-Dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (37).** A suspension of **36** (7.23 g, 43.2 mmol), malononitrile (2.86 g, 43.2 mmol) and ammonium acetate (3.33 g, 4.32 mmol) was refluxed in acetonitrile (150 mL) for 2 h. The solvent was reduced to deposit a solid that was crystallized from acetonitrile. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.98 (s, 1H), 8.36 (s, 1H), 2.87 (t, *J* = 6.1 Hz, 2H), 2.49–2.43 (m, 2H), 2.05–1.98 (m, 2H). MS (ESI) *m/z*: 189.1$[M + H]^+$ .

**6-Fluoro-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (38b).** To a solution of **37** (0.42 g, 2.66 mmol) in MeOH (15 mL) were successively added

SelectFluor (1.0 g, 3.19 mmol) and $H_2SO_4$ (26 mg, 0.266 mmol). The resulting mixture was stirred under argon at 50 °C for 16 hours. EtOAc was added and the mixture was successively washed with water (15 mL) and brine (10 mL), then dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:1) gave the **38b** as a yellow solid (0.45 g, 70%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 13.15 (s, 1H), 8.43 (s, 1H), 5.68–4.78 (m, 1H), 3.18–3.03 (m, 1H), 2.99–2.89 (m, 1H), 2.48–2.41 (m, 1H), 2.31–2.25 (m, 1H). MS (ESI) *m/z*: 207.1$[M + H]^+$.

**6-Chloro-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (38c).** To a solution of **37** (1.5 g, 7.9 mmol) and N-chlorosuccinimide in MeCN (15 mL) were added together with ptoluenesulfonicacid (PTSA, 0.23 g, 0.15 mmol). The reaction mixture was then heated to 80 °C for 15 h, turning into a dense paste. Water was then added (5.0 mL) followed by extraction with EtOAc (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL), then dried over $Na_2SO_4$ and solvent evaporated under reduced pressure. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:1) gave the **38c** as a yellow solid (1.15 g, 65%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 13.20 (s, 1H), 8.44 (s, 1H), 4.94 (dd, $J$ = 5.8, 3.7 Hz, 1H), 2.39–2.29 (m, 2H), 2.03–1.94 (m, 2H). MS (ESI) *m/z*: 223.0$[M + H]^+$ .

**2-Chloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (39a).** 2,5-Dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile **37** (2.5 g, 13.28 mmol) was suspended in DCM (30 mL). Thionyl chloride (2.1 g, 17.6 mmol) and DMF (2 drops) were added dropwise (careful, gas evolution!) at rt under a nitrogen atmosphere. The

reaction mixture was refluxed for 16 h under a nitrogen atmosphere. The solvents were removed in vacuo and the crude material was partitioned between EtOAc (200 mL) and water (100 mL). The organic layer was separated and washed with cold water (500 mL) and $NaHCO_3$ (2 x 500 mL). The organic layer was dried with sodium sulphate and concentrated. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:3) gave the **20a** as a yellow solid (1.97 g, 72 %). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.71 (s, 1H), 3.13 (t, $J$ = 6.2 Hz, 2H), 2.73–2.67 (m, 2H), 2.17–2.08 (m, 2H). MS (ESI) *m/z*: 207.1$[M + H]^+$ .

**2-Chloro-6-fluoro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (39b).** Compound **39b** (56 mg, 51%) was prepared from **38b** (0.10 g, 0.49 mmol) in the same manner as described for **39a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.84 (s, 1H), 5.54 (dd, $J$ = 13.1, 5.6 Hz, 1H), 3.44–3.36 (m, 1H), 3.26–3.21 (m, 1H), 2.60–2.56 (m, 1H), 2.40–2.33 (m, 1H). MS (ESI) *m/z*: 225.0 $[M + H]^+$.

**2,6-Dichloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (39c).** Compound **39c** (65 mg, 62%) was prepared from **38c** (0.10 g, 0.45 mmol) in the same manner as described for **39a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.84 (s, 1H), 5.54 (dd, $J$ = 13.1, 5.6 Hz, 1H), 2.39–2.29 (m, 2H), 2.03–1.94 (m, 2H). MS (ESI) *m/z*: 225.0$[M + H]^+$.

**Ethyl 2-(Chloromethyl)-5-cyano-6-oxo-1,6-dihydropyridine-3-carboxylate (42).** A mixture of ethyl 4-chloro-3-oxobutanoate **41** (3.0 g, 30.38 mmol), acetic anhydride (13.65 g, 133.67 mmol) and triethylorthoformate was heated at 120 °C (bath temperature) for 3 h. The dark mixture was concentrated in vacuo and co-evaporated

once with toluene (25 mL). Heptane (25 mL) was added to precipitate the product and then removed in vacuo. The crude material was dissolved in EtOH (50 mL). In a separate flask, 20%NaOEt/EtOH (2.07 g, 30.38 mmol) was added dropwise to a cold (< 5 °C) solution of 2-cyanoacetamide (2.55 g, 30.38 mmol) in EtOH (25 mL) and the mixture was stirred for 30 minutes after which the solution of the crude material from above was added over 5 minutes and the stirring was contiued at rt over night. The solid formed was isolated by filtration and washed with MTBE (50mL). Drying of the filtrate gave **42** as a beige solid. Yield: 9.1 g (62 %). $^1$H NMR (500 MHz, DMSO-$d_6$ ) $\delta$ 1.27 (t, $J$ = 7.0 Hz, 3H), 4.16 (q, $J$ = 7.0 Hz, 2H), 4.75 (s, 2H), 8.02 (s, 1H). MS (ESI) *m/z*: 241.0 $[M + H]^+$.

**Ethyl 6-Chloro-2-(chloromethyl)-5-cyanonicotinate (43).** Compound **43** (1.15 g, 54%) was prepared from **42** (1.98 g, 8.25 mmol) in the same manner as described for **39a**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (s, 1H), 5.10 (s, 2H), 4.49 (q, $J$ = 7.2 Hz, 2H), 1.47 (t, $J$ = 7.1 Hz, 3H). MS (ESI) *m/z*: 259.0 $[M + H]^+$.

**Ethyl 6-(4-((Benzylsulfonyl)carbamoyl)piperidin-1-yl)-2-(chloromethyl)-5 -cyanonicotinate (44).** Compound **44** (0.43 g, 84%) was prepared from **43** (0.26 g, 1.02 mmol) and N-(benzylsulfonyl)piperidine-4-carboxamide (0.30 g, 1.07 mmol) in the same manner as described for **21a**. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 11.63 (s, 1H), 7.43–7.39 (m, 3H), 7.29 (dd, $J$ = 7.3, 1.8 Hz, 2H), 4.98 (s, 2H), 4.70 (s, 2H), 4.59 (d, $J$ = 13.5 Hz, 2H), 4.28 (q, $J$ = 7.1 Hz, 2H), 3.22–3.16 (m, 2H), 2.63–2.58 (m, 1H), 1.86 (dd, $J$ = 12.9, 2.4 Hz, 2H), 1.65 (ddd, $J$ = 15.5, 12.8, 3.8 Hz, 2H), 1.32 (t, $J$ = 7.1

Hz, 3H). $^{13}$C NMR (126MHz, DMSO-$d_6$) $\delta$ 174.6, 163.8, 160.0, 158.3, 148.7, 131.2, 129.6, 129.2, 129.1, 117.8, 113.9, 90.9, 61.6, 57.9, 46.6, 45.9, 41.9, 27.9, 14.5.

***N, N*-Bis(2,4-dimethoxybenzyl)-1-phenylmethanesulfonamide (47).** To a stirred 0 ℃ solution of bis(2,4-dimethoxybenzyl)amine (14.0 g, 44.16 mmol), DMAP (6.0 g, 48.57 mmol) and THF (150 mL) was added a solution of benzylsulfonyl chloride **46** (8.4 g, 44.16 mmol) and THF. The ice bath was removed and the resulting mixture stirred overnight at room temperature. The mixture was filtered, washed with EtOAc. The filtrate was washed with aq. $NH_4Cl$, brine, dried over $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:5) gave the **47** as a white solid (10.0 g, 50%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.37–7.32 (m, 3H), 7.21 (dd, $J$ = 6.5, 3.0 Hz, 2H), 7.08 (d, $J$ = 8.3 Hz, 2H), 6.53–6.46 (m, 4H), 4.27 (s, 2H), 4.11 (s, 4H), 3.74 (s, 6H), 3.72 (s, 6H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 160.3, 158.2, 131.1, 130.6, 129.3, 128.3, 128.1, 117.1, 103.8, 98.1, 58.9, 55.2, 54.9, 45.3. MS (ESI) *m/z*: 470.2[ M − H]$^-$.

***N*,*N*-Bis(2,4-dimethoxybenzyl)-1,1-difluoro-1-phenylmethanesulfonamide (48a).** To a cooled -78 ℃ solution of *N*, *N*-bis(2,4-dimethoxybenzyl)-1 -phenylmethanesulfonamide **47** (3.0 g, 6.37 mmol), NSFI (4.4 g, 14 mmol), and THF (40 mL) was added NaHMDS (9.0 mL, 2 M) in THF (50 mL) dropwise over 0.5 h via syringe pump. The reaction was stirred at -78℃ for 2 hrs further then warmed to rt and stirred another 2 h. The reaction was quenched with aq $NH_4Cl$ (20 mL), and separated. The aqueous was extracted with EtOAc (100 mLx3), and the combined organics were washed with aq. $NaHCO_3$, brine, dried $MgSO_4$, filtered, and

concentrated. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:5) gave the **48a** as a white solid (2.1 g, 66%). $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.70–7.57 (m, 5H), 7.02 (d, $J$ = 8.2 Hz, 2H), 6.43 (d, $J$ = 2.4 Hz, 1H), 6.41 (dd, $J$ = 4.3, 2.3 Hz, 3H), 4.28 (s, 4H), 3.71 (s, 6H), 3.63 (s, 6H). $^{13}$C NMR (75 MHz): $\delta$ 160.2, 158.0, 131.6, 130.2, 129.3), 128.3, 127.0, 122.2, 116.4, 103.7, 97.5, 55.2, 54.8, 46.6; $^{19}$F NMR (282 MHz): $\delta$ -100.7; HRMS (EI) *m/z* calculated for $C_{25}H_{27}F_2NO_6S$: 507.152716, found 507.152685.

***N*,*N*-Bis(2,4-dimethoxybenzyl)-1-phenylethane-1-sulfonamide (48b).** Compound **48b** (2.3 g, 77%) was prepared from **47** (3.0 g, 6.37 mmol) and methyl iodide (2.17 g, 15.3 mmol) in the same manner as described for **48a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.36–7.32 (m, 3H), 7.24–7.19 (m, 2H), 7.03 (d, $J$ = 8.3 Hz, 2H), 6.48 (dd, $J$ = 6.1, 2.4 Hz, 3H), 6.46 (d, $J$ = 2.4 Hz, 1H), 4.20 (q, $J$ = 7.0 Hz, 1H), 3.74 (s, 6H), 3.70 (s, 6H), 1.61 (d, $J$ = 7.0 Hz, 3H). MS (ESI) *m/z*: 484.2 [ M − H]$^{-}$.

***N*,*N*-Bis(2,4-dimethoxybenzyl)-1-phenylcyclopropane-1-sulfonamide (48c).** Compound **48c** (2.65 g, 74%) was prepared from **47** (3.4 g, 7.2 mmol) and 1,3,2-dioxathiolane 2,2-dioxide (1.16 g, 9.4 mmol) in the same manner as described for **48a**. $^{1}$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.44–7.36 (m, 5H), 6.96–6.92 (m, 2H), 6.39–6.35 (m, 4H), 3.88 (s, 4H), 3.70 (s, 6H), 3.61 (s, 6H), 1.57–1.52 (m, 2H), 1.19 –1.14 (m, 2H). MS(ESI) *m/z*: 298.2 [M + H]$^{+}$.

**Difluoro(phenyl)methanesulfonamide (49a).** To a cooled 0 °C solution of N,N-bis(2,4-dimethoxybenzyl)-1-phenylcyclopropane-1-sulfonamide **48c** (0.50 g, 1.0 mmol)and $CH_2Cl_2$ was added TFA (5 mL). The reaction mixture immediately turned

pink. The reaction was stirred at 0 °C for 4.5 h then the solvent was removed in vacuo to yield a pink solid. The solid was suspended in acetone and filtered thru a plug of cotton (acetone rinse). The filtrate was evaporated and the residue purified by silica gel chromatography (EtOAc/hexanes = 1/5) gave the **48a** as a white solid (0.14 g, 70%). $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.12 (s, 2H), 7.66–7.54 (m, 5H). $^{19}$F NMR (471 MHz, DMSO-$d_6$) $\delta$ -102.42. $^{1}$H NMR (acetone-$d_6$, 300 MHz): δ 7.69 (2H, d, *J*= 7.4 Hz), 7.63 (1H, t, *J*= 7.2 Hz), 7.55 (2H, t, *J*= 7.6 Hz), 7.26 (2H, bs); $^{13}$C NMR (acetone-$d_6$, 75 MHz): $\delta$ 132.6, 130.0, 129.3, 128.0, 121.4; MS (ESI) *m/z*: 206.0 [ M − H]$^{-}$.

**1-Phenylethane-1-sulfonamide (49b).** Compound **49b** (0.25 g, 65%) was prepared from **48b** (1.0 g, 2.06 mmol) in the same manner as described for **49a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.40–7.31 (m, 5H), 6.79 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 1H), 1.62 (d, *J* = 7.1 Hz, 3H). MS (ESI) *m/z*: 184.1[ M − H]$^{-}$.

**1-Phenylcyclopropane-1-sulfonamide (49c).** Compound **49c** (1.13 g, 78%) was prepared from **48c** (2.50 g, 5.77 mmol) in the same manner as described for **49a**. $^{1}$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.50 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.38–7.33 (m, 3H), 6.81 (s, 2H), 1.54 (q, *J* = 4.6 Hz, 2H), 1.14 (q, *J* = 4.9 Hz, 2H). MS (ESI) *m/z*:198.1 [M + H]$^{+}$.

**1-(3-Cyano-5-oxo-5,7-dihydrofuro[3,4-b]pyridin-2-yl)piperidine-4-carboxylic Acid (50).** A suspension of **20a** (0.20 g, 1.0 mmol), piperidine-4-carboxylic acid (0.15 g, 1.13 mmol), and DIPEA (0.5 mL, 3 mmol) in EtOH (10 mL) was heated at reflux

for 1 h. The solvents were removed in vacuo and the crude material was partitioned between EtOAc (50 mL) and water (20 mL). The organic layer was separated and washed with cold water (10 mL) and $NaHCO_3$ (2 x 15 mL). The organic layer was dried with sodium sulphate and concentrated. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:2) gave the **50** as a white solid (0.20 g, 70%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.21 (s, 1H), 5.12 (s, 2H), 4.56 (d, $J$ = 13.8 Hz, 2H), 3.42 (dd, $J$ = 17.8, 6.8 Hz, 2H), 2.79–2.69 (m, 1H), 2.13 (d, $J$ = 11.2 Hz, 2H), 1.95–1.89 (m, 2H). MS(ESI) *m/z*: 288.1 $[M + H]^+$.

**(4-Fluorophenyl)methanesulfonamide (55a).** A suspension of 1-(chloromethyl)-4-fluorobenzene **52a** (3.0 g, 20.8 mmol) and thiourea (1.9 g, 24.96 mmol) in EtOH (50 mL) was heated at reflux for 1 h. The solvent was removed in vacuo and the crude material **53a** was used for next step without further purification.

The obtained solid **53a**, NCS (2.67 g, 83.2 mmol) and 2 M HCl (4.7 mL) in MeCN (50 mL) was stirred in a 10 °C water bath to maintain the internal temperature between 10 and 20 °C. When the reaction was complete (~20 min), EtOAc (50 mL) was added and the resulting solution was partitioned by addition of $H_2O$ (15 mL). The organic phase was separated, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude material **54a** was used for next step without further purification. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.49–7.46 (m, 2H), 7.17–7.13 (m, 2H), 4.84 (s, 2H).

The crude material **54a** was dissolved in THF (50 mL), then to this solution was added concentrated aqueous ammonia (10 mL) saturated with ammonium carbonate and the reaction mixture was vigorously stirred for 1 h at room temperature. The

solvents were removed in vacuo and the crude material was partitioned between EtOAc (50 mL) and aturated $NH_4Cl$ (2 × 20 mL). The organic layer was separated and washed with cold water (10 mL) and $NaHCO_3$ (2 x 15 mL). The organic layer was dried with sodium sulphate and concentrated. The crude was purified by silica gel chromatography (EtOAc/hexanes = 1:5) gave **55a** as a white solid (1.9 g, 50% for three steps). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.44–7.38 (m, 2H), 7.25–7.18 (m, 2H), 6.85 (s, 2H), 4.27 (s, 2H). MS (ESI) *m/z*: 190.1 $[M + H]^+$

**(2-Fluorophenyl)methanesulfonamide (55b).** Compound **55b** (1.8 g, 51% for three steps) was prepared from **52b** (3.0 g, 20.8 mmol) and in the same manner as described for **55a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.48–7.38 (m, 2H), 7.27–7.20 (m, 2H), 7.02 (s, 2H), 4.32 (s, 2H). MS(ESI) *m/z*: 190.0 $[M + H]^+$.

**(3-Fluorophenyl)methanesulfonamide (55c).** Compound **55c** (1.5 g, 39% for three steps) was prepared from **52c** (3.0 g, 20.8 mmol) and in the same manner as described for **55a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.46–7.39 (m, 1H), 7.24–7.15 (m, 3H), 6.90 (s, 2H), 4.30 (s, 2H). MS(ESI) *m/z*:190.1 $[M + H]^+$.

**(2,4-Difluorophenyl)methanesulfonamide (55d).** Compound **55d** (1.6 g, 40% for three steps) was prepared from **52d** (3.0 g, 18.52 mmol) and in the same manner as described for **55a**. $^1$H NMR (400MHz, DMSO-$d_6$) $\delta$ 7.48 (td, $J$ = 8.6, 6.7 Hz, 1H), 7.33–7.25 (m, 1H), 7.17–7.10 (m, 1H), 7.01 (s, 2H), 4.35 (s, 2H). MS (ESI) *m/z*: 208.1 $[M + H]^+$.

**(4-(Trifluoromethyl)phenyl)methanesulfonamide (55e).** Compound **55e** (0.80 g, 67% for three steps) was prepared from **52e** (1.0 g, 5.15mmol) and in the same

manner as described for **55a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.76 (d, $J$ = 8.0 Hz, 2H), 7.59 (d, $J$ = 8.0 Hz, 2H), 6.94 (s, 2H), 4.39 (s, 2H). MS (ESI) m/z: 238.1[M - H]$^-$.

**(4-Cyanophenyl)methanesulfonamide (55f).** Compound **55f** (0.80 g, 67% for three steps) was prepared from **52f** (1.0 g, 5.15mmol) and in the same manner as described for **55a**. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.88–7.83 (m, 2H), 7.58–7.55 (m, 2H), 6.93 (s, 2H), 4.39 (s, 2H). MS (ESI) *m/z*: 195.0 [ M − H]$^-$.

***p*-Tolylmethanesulfonamide (55g).** Compound **55g** (2.5 g, 25% for three steps) was prepared from **52g** (5.0 g, 35.75 mmol) and in the same manner as described for **55a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.25 (d, $J$ = 8.0 Hz, 2H), 7.18 (d, $J$ = 7.9 Hz, 2H), 6.80 (s, 2H), 4.21 (s, 2H), 2.31 (s, 3H). MS(ESI) *m/z*:186.1 [M + H]$^+$.

**(4-Chlorophenyl)methanesulfonamide (55h).** Compound **55h** (0.80 g, 88% for three steps) was prepared from **52h** (1.0 g, 44.6 mmol) and in the same manner as described for **55a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.44–7.40 (m, 2H), 7.35–7.31 (m, 2H), 6.91 (s, 2H), 4.30 (s, 2H). MS(ESI) *m/z*: 206.1 [M + H]$^+$.

**(3,5-Dichlorophenyl)methanesulfonamide (55i).** Compound **55i** (1.88 g, 57% for three steps) was prepared from **52i** (3.0 g, 15.46 mmol) and in the same manner as described for **55a**.$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.62 (t, $J$ = 1.9 Hz, 1H), 7.43 (d, $J$ = 1.9 Hz, 2H), 6.96 (s, 2H), 4.34 (s, 2H). MS(ESI) *m/z*: 240.1 [M + H]$^+$.

***tert*-Butyl 4-(((4-Fluorobenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56a).** Compound **56a** (0.26 g, 75%) was prepared from **55a** (0.22 g, 1.14 mmol) and **5a** (0.20 g, 0.87 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz,

DMSO-$d_6$) $\delta$ 11.57 (s, 1H), 7.35–7.29 (m, 2H), 7.25 (m, 2H), 4.69 (s, 2H), 3.93 (d, *J* = 13.0 Hz, 2H), 2.75–.59 (m, 2H), 2.43–2.31 (m, 1H), 2.03 – 1.92 (m, 2H), 1.67 (d, *J* = 11.0 Hz, 2H), 1.40 (s, 9H). MS (ESI) *m/z* : 401.2 $[M + H]^+$.

***tert*-Butyl 4-(((2-Fluorobenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56b).** Compound **56b** (0.30 g, 72%) was prepared from **55b** (0.20 g, 1.04 mmol) and **5a** (0.24 g, 1.04 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.49 (s, 1H), 7.33–7.27 (m, 2H), 7.23–7.19 (m, 2H), 4.63 (s, 2H), 3.89 (m, 2H), 2.73–2.65 (m, 2H), 2.39–2.31 (m, 1H), 2.12–1.99 (m, 2H), 1.63–1.57 (m, 2H), 1.38 (s, 9H). MS (ESI) *m/z* : 401.2 $[M + H]^+$.

***tert*-Butyl 4-(((3-Methylbenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56c).** Compound **56c** (0.42 g, 65%) was prepared from **55c** (0.31 g, 1.62 mmol) and **5a** (0.37 g, 1.04 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.52 (s, 1H), 7.42–7.37 (m, 1H), 7.18–7.11 (m, 3H), 4.52 (s, 2H), 3.82 (d, *J* = 13.0 Hz, 2H), 2.69–2.50 (m, 2H), 2.40–2.38 (m, 1H), 2.11–1.99 (m, 2H), 1.71–1.68 (m, 2H), 1.36 (s, 9H). MS (ESI) *m/z* : 401.1 $[M + H]^+$.

***tert*-Butyl 4-(((2,4-Difluorobenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56d).** Compound **56d** (0.75 g, 83%) was prepared from **55d** (0.59 g, 2.84 mmol) and **5a** (0.50 g, 2.81 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.22 (dt, *J* = 10.0, 5.5 Hz, 1H), 7.14–7.09 (m, 1H), 7.02 (td, *J* = 8.7, 2.7 Hz, 1H), 3.21 (dt, *J* = 12.4, 3.8 Hz, 2H), 2.95(dt, *J* = 12.0, 3.3 Hz, 2H), 2.49–2.38 (m, 1H), 1.84–1.77 (m, 2H), 1.75–1.59(m, 2H), 1.35 (s, 9H). MS (ESI) *m/z*: 419.2$[M + H]^+$.

***tert*-Butyl 4-(((4-(Trifluoromethyl)benzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56e).** Compound **56e** (0.87 g, 62%) was prepared from **55e** (0.80 g, 3.36 mmol) and **5a** (0.70 g, 3.06 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.64 (s, 1H), 7.76 (d, $J$ = 8.0 Hz, 2H), 7.59 (d, $J$ = 8.0 Hz, 2H), 4.39 (s, 2H), 3.99–3.83 (m, 2H), 2.79–2.57 (m, 2H), 2.46–2.27 (m, 2H), 2.05–1.87 (m, 1H), 1.73–1.61 (m, 2H), 1.39 (s, 9H). MS (ESI) *m/z*: 449.1[ M − H]$^-$.

***tert*-Butyl 4-(((4-Cyanobenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56f).** Compound **56f** (0.78 g, 63%) was prepared from **55f** (0.60 g, 3.06 mmol) and **5a** (0.77 g, 3.37 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.66 (s, 1H), 7.91 (d, $J$ = 8.2 Hz, 2H), 7.49 (d, $J$ = 8.1 Hz, 2H), 4.84 (s, 2H), 3.99–3.88 (m, 2H), 2.76–2.62 (m, 2H), 2.43–2.31 (m, 1H), 2.05–1.93 (m, 1H), 1.72–1.62 (m, 2H), 1.40 (s, 9H). MS (ESI) *m/z*: 460.1 [ M − H]$^-$.

***tert*-Butyl 4-(((4-Methylbenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56g).** Compound **56g** (0.50 g, 68%) was prepared from **55g** (0.34 g, 1.85 mmol) and **5a** (0.42 g, 1.85 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.10 (s, 1H), 7.71 (d, $J$ = 8.1Hz, 2H), 7.52 (d, $J$ = 8.1 Hz, 2H), 4.74 (s, 2H), 3.86–3.78 (m, 2H), 2.74–2.62 (m, 2H), 2.45 (s, 3H), 2.43–2.31 (m, 1H), 2.05–1.93 (m, 2H), 1.72–1.62 (m, 2H), 1.40 (s, 9H). MS (ESI) *m/z*: 395.2 [ M − H]$^-$.

***tert*-Butyl 4-(((4-Chlorobenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56h).** Compound **56h** (0.44 g, 73%) was prepared from **55g** (0.30 g, 1.46 mmol) and **5a** (0.44 g, 1.90 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.67 (s, 1H), 7.91 (d, $J$ = 8.1 Hz, 2H), 7.49 (d, $J$ = 8.0 Hz, 2H), 4.84 (s,

2H), 3.93 (d, *J* = 11.2 Hz, 2H), 2.76–2.61 (m, 2H), 2.43–2.34 (m, 2H), 2.05–1.92 (m, 1H), 1.71–1.63 (m, 2H), 1.41 (s, 9H). MS (ESI) m/z: 415.1 [ M − H]$^{-}$.

***tert*-Butyl 4-(((3,5-Dichlorobenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56i).** Compound **56i** (0.41 g, 73%) was prepared from **55i** (0.30 g, 1.25 mmol) and **5a** (0.55 g, 1.74 mmol) in the same manner as described for **7a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.68 (s, 1H), 7.71–7.69 (m, 1H), 7.58–7.51 (m, 1H), 7.48–7.38 (m, 1H), 4.78 (s, 2H), 3.95–3.88 (m, 2H), 2.43–2.35 (m, 2H), 2.18–2.10 (m, 1H), 1.82–1.71 (m, 2H), 1.66–1.59 (m, 2H), 1.39 (s, 9H). MS(ESI) M/Z:451.1 [M + H]$^{+}$.

***tert*-Butyl 4-(((2,4-Difluorobenzyl)sulfonyl)carbamoyl)-4-methylpiperidine-1-carboxylate (56j).** Compound **56j** (0.25 g, 60%) was prepared from **55d** (0.20 g, 1.0 mmol) and **5b** (0.30 g, 1.25 mmol) in the same manner as described for **7a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.22 (s, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 4.69 (s, 2H), 3.72–3.55 (m, 2H), 2.98–2.92 (m, 2H), 1.94–1.89 (m, 2H), 1.39 (s, 9H), 1.31–1.28 (m, 2H), 1.10 (s, 3H). MS(ESI) *m/z*: 433.1 [M + H]$^{+}$.

***tert*-Butyl 4-(((4-Fluorobenzyl)sulfonyl)carbamoyl)-4-methylpiperidine-1-carboxylate (56k).** Compound **56k** (0.28 g, 62%) was prepared from **55a** (0.21 g, 1.1 mmol) and **5b** (0.35 g, 1.44 mmol) in the same manner as described for **7a**. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.29 (s, 1H), 7.38–7.33 (m, 1H), 7.27–7.21 (m, 1H), 4.76 (s, 2H), 3.52–3.44 (m, 2H), 3.02–2.92 (m, 2H), 1.94–1.88 (m, 2H), 1.39 (s, 9H), 1.32–1.28 (m, 2H), 1.10 (s, 3H). MS (ESI) *m/z*: 415.1 [M + H]$^{+}$

***tert*-Butyl 4-Methyl-4-(((4-methylbenzyl)sulfonyl)carbamoyl)piperidine-1-carboxylate (56l).** Compound **56l** (0.22 g, 48%) was prepared from **55g** (0.21 g, 1.1 mmol) and **5b** (0.35 g, 1.44 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.21 (s, 1H), 7.99 (d, $J$ = 8.5 Hz, 2H), 7.72 (d, $J$ = 8.2 Hz, 2H), 4.68 (s, 2H), 3.52–3.44 (m, 2H), 3.00–2.89 (m, 2H), 2.30 (s, 3H), 1.91 (d, $J$ = 14.1 Hz, 2H), 1.39 (s, 9H), 1.33–1.25 (m, 2H), 1.10 (s, 3H). MS (ESI) *m/z*: 309.1 [M + H]$^+$.

***tert*-Butyl 4-(((4-Chlorobenzyl)sulfonyl)carbamoyl)-4-methylpiperidine-1-carboxylate (56m).** Compound **56m** (0.44 g, 64%) was prepared from **55h** (0.33 g, 1.58 mmol) and **5b** (0.50 g, 2.05 mmol) in the same manner as described for **7a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.51–7.42 (m, 2H), 7.41–7.30 (m, 2H), 4.27 (s, 2H), 3.52–3.43 (m, 2H), 3.02–2.91 (m, 2H), 2.04–1.98 (m, 2H), 1.95–1.84 (m, 2H), 1.39 (s, 3H). MS (ESI) *m/z*: 431.1 [M + H]$^+$.

***N*-((4-Fluorobenzyl)sulfonyl)piperidine-4-carboxamide (57a).** Compound **57a** (0.14 g, 91%) was prepared from **56a** (0.21 g, 0.53 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.16 (s, 1H), 7.24 (dd, $J$ = 8.7, 5.7 Hz, 2H), 7.11–7.05 (m, 2H), 4.23 (s, 2H), 3.15 (dt, $J$ = 12.4, 4.1 Hz, 2H), 2.83 (td, $J$ = 12.2, 3.1 Hz, 2H), 2.18–2.09 (m, 1H), 1.84–1.75 (m, 2H), 1.70–1.57 (m, 2H). MS (ESI) *m/z* :301.1 [M + H]$^+$.

***N*-((2-Fluorobenzyl)sulfonyl)piperidine-4-carboxamide (57b).** Compound **57b** (0.19 g, 85%) was prepared from **56b** (0.30 g, 0.75 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.32 (s, 1H), 8.16 (s, 1H),

7.23–7.19 (m, 2H), 7.18–7.04 (m, 2H), 4.33 (s, 2H), 3.79 (m, 2H), 2.63–2.61 (m, 2H), 2.30–2.27 (m, 1H), 2.10–1.79 (m, 2H), 1.62–1.56 (m, 2H). MS (ESI) *m/z* : 301.3 [M + H]$^+$.

***N*-((3-Fluorobenzyl)sulfonyl)piperidine-4-carboxamide (57c).** Compound **57c** (0.25 g, 88%) was prepared from **56c** (0.40 g, 1.0 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.41 (s, 1H), 7.39–7.28 (m, 1H), 7.09–7.04 (m, 3H), 4.32 (s, 2H), 3.72 (d, *J* = 13.0 Hz, 2H), 2.62–2.51(m, 2H), 2.45–2.39 (m, 1H), 2.07–1.99 (m, 2H), 1.69–1.67 (m, 2H). MS (ESI) *m/z* : 301.1 [M + H]$^+$.

***N*-((2,4-Difluorobenzyl)sulfonyl)piperidine-4-carboxamide (57d).** Compound **57d** (0.43 g, 75%) was prepared from **56d** (0.74 g, 1.78 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-*d*$_6$) $\delta$ 8.20 (s, 1H), 7.32 (dt, *J* = 10.0, 5.5 Hz, 1H), 7.18–7.11 (m, 1H), 7.01 (td, *J* = 8.7, 2.7 Hz, 1H), 3.18 (dt, *J* = 12.4, 3.8 Hz, 2H), 2.86 (dt, *J* = 12.0, 3.3 Hz, 2H), 1.87–1.79 (m, 2H), 1.73–1.61 (m, 2H). MS(ESI) *m/z*: 319.1 [M + H]$^+$.

***N*-((4-(Trifluoromethyl)benzyl)sulfonyl)piperidine-4-carboxamide (57e).** Compound **57e** (0.47 g, 87%) was prepared from **56e** (0.70 g, 1.56 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-*d*$_6$) $\delta$ 8.20 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 2H), 4.36 (s, 2H), 3.22–3.10 (m, 2H), 2.89–2.78 (m, 2H), 2.21–2.10 (m, 1H), 1.87–1.75 (m, 2H), 1.71–1.57 (m, 2H). MS (ESI) *m/z*:351.1 [M + H]$^+$.

***N*-((4-Cyanobenzyl)sulfonyl)piperidine-4-carboxamide (57f).** Compound **57f**

(0.26 g, 88%) was prepared from **56f** (0.40 g, 0.98 mmol) in the same manner as described for **8a**.$^1$H NMR (400 MHz, $D_2O$) $\delta$ 7.69 (d, $J$ = 7.6 Hz, 2H), 7.42 (d, $J$ = 7.8 Hz, 2H), 4.51 (s, 2H), 3.38 – 3.29 (m, 2H), 2.91 (t, $J$ = 12.7 Hz, 2H), 2.33 (d, $J$ = 11.4 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.73–1.61 (m, 2H). MS (ESI) *m/z*: 306.1 $[M - H]^-$.

***N*-((4-Methylbenzyl)sulfonyl)piperidine-4-carboxamide (57g).** Compound **57g** (0.37 g, 88%) was prepared from **56g** (0.50 g, 1.26 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 8.12 (1H, s), 7.35−7.27 (5H, m), 7.35−7.27 (5H, m), 4.35 (2H, s), 3.37−3.17 (2H, m), 2.92−2.84 (2H, m), 2.28−2.18 (1H, m), 1.82−1.74 (2H, m), 1.77−1.62 (2H, m). MS (ESI) *m/z*: 295.2$[M - H]^-$.

***N*-((4-Chlorobenzyl)sulfonyl)piperidine-4-carboxamide (57h).** Compound **57h** (0.28g, 92%) was prepared from **56h** (0.40 g, 0.96 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 1H), 7.82(d, $J$ = 8.1 Hz, 2H), 7.39 (d, $J$ = 8.0 Hz, 2H), 3.17 (dt, $J$ = 12.7, 4.0 Hz, 1H), 2.89–2.79 (m, 1H), 2.15 (ddd, $J$ = 14.4, 10.3, 3.9 Hz, 1H), 1.80 (dd, $J$ = 14.5, 3.4 Hz, 2H), 1.72–1.60 (m, 2H). MS (ESI) *m/z*: 315.0$[M - H]^-$.

***N*-((3,5-Dichlorobenzyl)sulfonyl)piperidine-4-carboxamide (57i).** Compound **57i** (0.27 g, 83%) was prepared from **56i** (0.41 g, 0.91 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.25 (s, 1H), 7.51–7.45 (m, 1H), 7.23 (d, $J$ = 1.9 Hz, 2H), 4.29 (s, 2H), 3.18 (dt, $J$ = 7.8, 3.5 Hz, 2H), 2.86 (dd, $J$ = 11.9, 2.9 Hz, 2H), 2.15 (tt, $J$ = 10.9, 4.0 Hz, 1H), 1.85–1.74 (m, 2H), 1.72–1.58 (m, 2H). MS(ESI) *m/z*: 351.0$[M + H]^+$.

***N*-((2,4-Difluorobenzyl)sulfonyl)piperidine-4-carboxamide (57j).** Compound

**57g** (0.43 g, 75%) was prepared from **56g** (0.74 g, 1.78 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 1H), 7.32 (dt, $J$ = 10.0, 5.5 Hz, 1H), 7.18–7.11 (m, 1H), 7.01 (td, $J$ = 8.7, 2.7 Hz, 1H), 3.18 (dt, $J$ = 12.4, 3.8 Hz, 2H), 2.86 (dt, $J$ = 12.0, 3.3 Hz, 2H), 1.87–1.79 (m, 2H), 1.73–1.61 (m, 2H). MS(ESI) *m/z*: 319.1 $[M + H]^+$.

***N*-((4-Fluorobenzyl)sulfonyl)-4-methylpiperidine-4-carboxamide (57k).** Compound **57k** (0.14 g, 74%) was prepared from **56k** (0.25 g, 0.6 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.13 (s, 1H), 7.27 (dd, $J$ = 8.4, 5.8 Hz, 2H), 7.10 (t, $J$ = 8.9 Hz, 2H), 4.27 (s, 2H), 3.12–3.05 (m, 2H), 2.79–2.70 (m, 2H), 2.12 (d, $J$ = 14.6 Hz, 2H), 1.34–1.27 (m, 2H), 0.99 (s, 3H). MS (ESI) *m/z*: 315.1 $[M + H]^+$.

**4-Methyl-*N*-((4-Methylbenzyl)sulfonyl)piperidine-4-carboxamide (57l).** Compound **57l** (0.15 g, 95%) was prepared from **56k** (0.20 g, 0.50 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.12 (s, 1H), 7.12 (d, $J$ = 8.0 Hz, 2H), 7.06 (d, $J$ = 8.0 Hz, 2H), 4.22 (s, 2H), 3.11–3.05 (m, 2H), 2.82–2.72 (m, 2H), 2.26 (s, 3H), 2.12 (d, $J$ = 13.0 Hz, 2H), 1.35–1.25 (m, 2H), 0.99 (s, 3H). MS(ESI) *m/z* :311.2 $[M + H]^+$.

***N*-((4-Chlorobenzyl)sulfonyl)-4-methylpiperidine-4-carboxamide (57m).** Compound **57m** (0.18 g, 79%) was prepared from **56m** (0.30 g, 0.70 mmol) in the same manner as described for **8a**. $^1$H NMR (400 MHz, $D_2O$) $\delta$ 7.25 (d, $J$ = 2.7 Hz, 2H), 7.19 (d, $J$ = 2.6 Hz, 2H), 4.34 (s, 2H), 3.12–3.04 (m, 2H), 2.81–2.71 (m, 2H), 2.06–1.98 (m, 2H), 1.45–1.34 (m, 2H), 0.95 (s, 3H). MS (ESI) *m/z*: 331.1 $[M + H]^+$.

**1-(3-Cyano-5-oxo-5,7-dihydrofuro[3,4-b]pyridin-2-yl)-4-fluoropiperidine-4-carboxylic Acid (59).** Compound **21a** (0.15 g, 0.77 mmol) and 4-fluoropiperidine-4-carboxylic acid (0.13 g, 0.85 mmol) were suspended in EtOH (15 mL). DIPEA (0.24 g, 2.31 mmol) was added, and the reaction mixture was heated at 72 °C for 12 h. The mixture was cooled to rt and concentrated. The crude material was dissolved in DCM (20 mL), and the solution was washed with 1 N HCl (15 mL), dried ($MgSO_4$ ), and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes/ethyl acetate = 1:1) to provide **59** (0.19 g, 80%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.21 (s, 1H), 5.12 (s, 2H), 4.65 (d, $J$ = 13.6 Hz, 2H), 3.55 (d, $J$ = 12.0 Hz, 2H), 2.24–2.21 (m, 2H), 2.02–1.99 (m, 2H). MS(ESI) *m/z*: 306.1 $[M + H]^+$.

**1-(3-Cyano-5-oxo-5,7-dihydrofuro[3,4-b]pyridin-2-yl)-4-fluoropiperidine-4-carbonyl Chloride (60).** To a solution of **59** (0.10 g, 0.33 mmol) in dichloromethane (5.0 mL) was added thionyl chloride (0.18 g, 1.0 mmol) and dimethylformamide (2 drops) and the mixture was refluxed for 1 h. The solvent was removed in vacuo to give **60 (**0.10 g, 98%) as a yellow solid which was used without further purification.