Supplementary Material

Novel 4,4-Disubstituted Piperidine-Based C-C Chemokine Receptor -5 Inhibitors with High Potency Against Human Immunodeficiency Virus-1 and an Improved human Ether-à-go-go Related Gene (hERG) Profile

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■ EXPERIMENTAL SECTION
General procedures. Unless stated otherwise, the reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. The reactions were carried out at ambient temperature unless otherwise indicated. Silica gel (EM Science, 230-400 mesh) was used for chromatographic purification unless otherwise indicated. Anhydrous solvents were obtained from Aldrich (Sure Seal).

1H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometers; the chemical shifts are reported in parts per million (ppm) relative to TMS. The following abbreviations are used to describe peak patterns when appropriate: b) broad, s) singlet, d) doublet, t) triplet, q) quartet, m) multiplet. 1H NMR analyses were carried out in deuterated chloroform unless otherwise indicated. Mass spectra (ms) were obtained using electrospray (positive or negative ion). All compounds were >95% pure as determined by LC/MS (equipped with UV and Evaporative Light Scattering Detectors) in both acid- and base-modified acetonitrile/water gradients and 1H NMR.

Compound 107
a) ethylcyanoacetate, NH₄OAc, AcOH, benzene; b) ArMgBr, CuI, THF, 2h; c) 2M NaOH, rt, 2h; d) Cu₂O/MeCN, reflux 30 min; e) DIBAL-H, DCM, -40 °C, 1h; f) DCE, 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole, sodium triacetoxyborohydride; g) 4M HCl in dioxane, rt, 1h.

106a

A mixture of tert-butyl 4-oxo-1-piperidinecarboxylate (25.25 g, 127 mmol), ethyl cyanoacetate (13.8 ml, 130 mmol), ammonium acetate (2.73 g, 35.4 mmol), glacial acetic acid (6.3 ml) and benzene (250 ml) was heated for 4 hours at reflux under Dean Stark conditions. The reaction mixture was cooled to room temperature and washed successively with water, sodium bicarbonate solution and brine. Drying, filtration and evaporation of the organic phase provided tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate as an oil that crystallized on standing (37 g, 99%). ¹H NMR (400 MHz, CDCl₃): δ 4.28 (q, 2H, J = 7 Hz), 3.60 (br t, 2H, J = 6 Hz), 3.54 (br t, 2H, J = 6 Hz), 3.12 (t, 2H, J = 6 Hz), 2.76 (t, 2H, J = 6 Hz), 1.47 (s, 9H), and 1.35 (t, 3H, J = 7 Hz). ES-LCMS m/z 293 (M-1).

106b [Y=Cl]

A solution of 1-chloro-3-iodobenzene (14.1 g, 59.28 mmol) in diethyl ether (12 ml) was added dropwise to a mixture of magnesium turnings (1.59 g, 65.4 mmol) in diethyl ether (50 ml) at
room temperature. When the Grignard reaction was complete, the resulting organomagnesium reagent was added dropwise to a stirred mixture of compound 106a (5.0 g, 17 mmol) and cuprous iodide (800 mg, 4.2 mmol) in tetrahydrofuran (30 mL) cooled to 0°C. The reaction mixture was stirred 1 hour at 0°C and then quenched with saturated ammonium chloride solution. Ethyl acetate (500 ml) was added and the mixture was washed successively with saturated ammonium chloride, water and brine. The organic layer was dried and concentrated and the resulting crude material was purified by column chromatography on silica gel eluting with 4:1 hexane:ethyl acetate, affording 106b [Y=Cl] as an oil (5.2 g, 75%). 1H NMR (400 MHz, CDCl₃): δ 7.37-7.26 (m, 4H), 3.99 (br.q, 2H, J=6Hz), 3.91 (br m, 2H), 3.58 (s, 1H), 2.88 (br.m, 2H), 2.52 (ddd, 2H, J=6, 4, 3Hz), 2.04 (m, 2H), 1.43 (s, 9H), and 1.06 (t, 3H, J = 6 Hz). ES-LCMS m/z 429 (M+Na⁺).

106c [Y=Cl]

A solution of 106b [Y=Cl] (5.2 g, 12.8 mmol) was dissolved in ethanol (30 ml) and 4 M aqueous sodium hydroxide (30 ml, 120 mmol) was added. The resulting solution was stirred at room temperature for 6.5 hours and then stored at 0°C overnight. Concentrated hydrochloric acid (10 ml) was added dropwise at 0°C and the mixture was then adjusted to pH~4 with 1 M hydrochloric acid. The solution was extracted with ethyl acetate (500 ml) and the aqueous phase was acidified to pH~3 and re-extracted with ethyl acetate. Both ethyl acetate layers were combined and washed with water and brine and then dried and concentrated to afford [1-(tert-butoxycarbonyl)-4-(3-chlorophenyl) piperidin-4-yl](cyano)acetic acid 106c [Y=Cl] as a rigid foam (3.75 g, 77%).

106d [Y=Cl]
**106c [Y=Cl]** (3.75 g, 9.90 mmol) was dissolved in acetonitrile (30 ml) and cupric oxide (355 mg, 0.025 mmol) was added. This mixture was heated at reflux with stirring for 30 minutes and then cooled to room temperature and filtered through celite. Evaporation of the filtrate gave tert-butyl 4-(3-chlorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate **106d [Y=Cl]** as an oil that crystallized on standing (3.0 g, 91%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.37-7.27 (m, 4H), 3.74 (br.m, 2H), 3.08 (br.t, 2H, $J=11$Hz), 2.55 (s, 2H), 2.27 (br.dd, 2H, $J = 11, 3$Hz), 1.86 (ddd, 2H, $J=14, 11, 4$Hz), and 1.44 (s, 9H).

**23 [Y=Cl]**

A solution of **106d [Y=Cl]** (1.96 g, 5.85 mmol) in dichloromethane (25 mL) was cooled to -30°C and a 1M solution of diisobutyl aluminum hydride in dichloromethane (15.5 ml, 17.5 mmol) was added dropwise. During this addition the internal temperature was maintained at or below –35°C. When the addition was complete, the reaction mixture was stirred 30 min and then quenched at –35°C with methanol (0.7 ml) followed by saturated citric acid solution (50 ml). The mixture was allowed to warm to room temperature and then extracted with dichloromethane. Combined dichloromethane layers were dried, filtered and evaporated to provide **23 [Y=Cl]** as an oil (1.3 g, 66%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.40 (t, 1H, $J = 3$ Hz), 7.34-7.22 (m, 4H), 3.61 (m, 2H), 3.26 (ddd, 2H, $J=13, 9, 3$Hz), 2.66 (d, 2H, $J=3$Hz), 2.19 (m, 2H), 1.86 (ddd, 2H, $J=13, 9, 3$Hz), and 1.44 (s, 9H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 201.4 (CH), 154.97 (C), 145.8 (C), 135.2 (C), 130.4 (CH), 127.3 (CH), 127.0 (CH), 124.9 (CH), 79.9 (C), 54.6 (2CH$_2$), 53.3 (C), 39.2 (CH$_2$), 35.5 (2CH$_2$), and 28.6 (3CH$_3$).

**106e [Y=Cl]**
Sodium triacetoxyborohydride (286 mg, 1.35 mmol) was added in one portion to a stirred mixture of 3-endo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1\textit{H}-benzimidazole dihydrochloride 23 [\textit{Y=Cl}] (250 mg, 0.90 mmol), 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1\textit{H}-benzimidazole (304 mg, 0.90 mmol), triethylamine (0.25 ml, 1.79 mmol) and powdered molecular sieves (250 mg) in dichloromethane (3 ml). After stirring 1 hour at room temperature, the reaction was quenched with saturated sodium bicarbonate solution and the dichloromethane layer was removed. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried, filtered and concentrated to afford 106\textit{e} [\textit{Y=Cl}] as a rigid foam (500 mg, 99%). $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.47 (dd, 1H, J = 7, 2 Hz), 7.40 (br s, 1H), 7.39-7.35 (m, 3H), 7.27 (d, 1H, J = 7 Hz), 7.11 (dd, 1H, J = 7, 6 Hz), 7.08 (dd, 1H, J = 7, 6 Hz), 4.50 (m, 1H, J = 8 Hz), 3.48 (m, 2H); 3.24 (m, 2H), 3.11 (m, 2H), 2.48 (s, 3H), 2.35 (br dd, 2H, J = 15, 9 Hz), 1.98 (m, 2H), 1.90-1.70 (m, 10H), 1.59 (d, 2H, J = 8 Hz), and 1.36 (s, 9H). ES-LCMS $m/\text{z}$ 585 (M+Na$^+$).

107 [\textit{Y=Cl}]

To a solution of 106\textit{e} [\textit{Y=Cl}] (500 mg, 0.888 mmol) in dichloromethane (6 ml) was added a 4 M solution of hydrogen chloride in 1,4-dioxane (7 ml, 28 mmol). After stirring 15 minutes at room temperature, the supernatant was decanted. The remaining precipitate was triturated with ethyl acetate and dried under high vacuum to afford the dihydrochloride salt 107 [\textit{Y=Cl}] as a pink solid (548 mg, 100%). ES-LCMS $m/\text{z}$ 463 (M+H).

\textbf{Compound 84}
106b [Z=i-Pr] 4-((1-cyano-2-ethoxy-2-oxoethyl)-4-(4-isopropylphenyl)piperidine-1-carboxylate was prepared as described for 106b [Y=Cl] in 56% yield. ES-LCMS m/z 413 (M+Na)+.

106c [Z=i-Pr] [1-(Tert-butoxycarbonyl)-4-(4-isopropylphenyl)piperidin-4-yl](cyano)acetic acid was prepared as described for 106c [Y=Cl] in 100% yield. ES-LCMS m/z 409 (M+Na)+.

106d [Z=i-Pr] t-butyl 4-(cyanomethyl)-4-(4-isopropyl phenyl)piperidine-1-carboxylate was prepared as described for 106d [Y=Cl] in 78% yield. 1H-NMR (300 MHz, CDCl3) δ 7.26-7.29 (m, 4H), 3.80-3.72 (m, 2H), 3.17-3.05 (m, 2H), 2.94-2.90 (m, 1H), 2.54 (s, 2H), 2.46-2.32 (m, 2H), 1.91-1.81 (m, 2H), 1.46 (s, 9H), 1.28 (s, 3H), 1.26 (s, 3H).

23 [Z=i-Pr] Tert-butyl 4-(4-isopropylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate was prepared as described for 23 [Y=Cl] in 58% yield. 1H-NMR (300 MHz, CDCl3) δ 9.40 (t, 1H, J=2.9 Hz), 7.30-7.20 (m, 4H) 3.66-3.61 (br m, 2H), 3.35-3.22 (m, 2H), 2.96-2.87 (m, 1H), 2.64 (d, 2H, J=2.9 Hz), 2.26-2.21 (br m, 2H), 1.90-1.81 (m, 2H), 1.46 (s, 9H) 1.27 (s, 3H), 1.25 (s, 3H). ES-LCMS m/z 368 (M+Na)+.

106e [Z=i-Pr] t-butyl endo 4-(4-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate was prepared as described for 106e [Y=Cl] in 60% yield. 1H-NMR (300 MHz, CDCl3) δ 7.69 (d, 1H, J=7 Hz), 7.33-7.19 (m, 7H), 4.75-4.65 (m, 1H), 3.84-3.65 (m, 2H), 3.39-3.22 (m, 4H), 2.96-2.85 (m, 1H), 2.60 (s, 3H), 2.47-2.37 (m, 2H), 2.16-2.09 (m, 2H), 2.05-1.87 (m, 10H), 1.85-1.80 (m, 2H), 1.45 (s, 9H) 1.29 (s, 3H), 1.27 (s, 3H). ES-LCMS m/z 571 (M+H)+.

107 [Z=i-Pr] endo 1-(((1R,5S)-8-{2-[4-(4-isopropylphenyl) piperidin-4-yl]ethyll}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride was prepared as described for 107 [Y=Cl] in 100% yield. ES-LCMS m/z 443 (M+H)+.

Inhibitor 84 was prepared from 107 [Z=i-Pr], similarly to compound 89, in 34% yield. 1H-NMR (300 MHz, CDCl3) δ 8.13 (s, 1H), 7.67 (d, 1H, J=7 Hz), 7.61-7.52 (m, 3H), 7.33-7.13 (m, 6H), 5.42 (br s, 2H), 4.67-4.61 (m, 1H), 4.24-4.18 (br m, 1H), 3.55-3.42 (br m, 1H), 3.38-3.20 (br m,
4H), 3.00-2.91 (m, 1H), 2.57 (s, 3H), 2.45-2.35 (m, 4H), 2.27-2.21 (br m, 1H), 1.98-1.70 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H). HRMS m/z (M+H)+ 688.3088 Cal., 688.3079 Obs.

**Compound 89**

106b [Y=Me] t-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(3-methylphenyl)piperidine-1-carboxylate was prepared as described for 106b [Y=Cl] in 93.4% yield. ES-LCMS m/z 287 (M-BOC+H)+.

106c [Y=Me] 1-(Tert-butoxycarbonyl)-4-(3-methylphenyl)piperidin-4-yl](cyano)acetic acid was prepared as described for 106c [Y=Cl] in 100% yield. ES-LCMS m/z 259 (M-BOC+H)+

106d [Y=Me] t-butyl 4-(cyanomethyl)-4-(3-methylphenyl) piperidine-1-carboxylate was prepared analogously to 106d [Y=Cl] in 53.3% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.34-7.28 (m, 1H), 7.18-7.12 (m, 3H) 3.82-3.72 (m, 2H), 3.13-3.04 (m, 2H), 2.55 (s, 2H), 2.39 (s, 3H) 2.37-2.31 (m, 2H), 1.91-1.82 (m, 2H), 1.46 (s, 9H). ES-LCMS m/z 215 (M-BOC+H)+.

23 [Y=Me] t-butyl 4-(3-methylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate was prepared analogously to 23 [Y=Cl] in 83% yield. $^1$H-NMR (300 MHz, CDCl$_3$) δ 9.39 (t, 1H, J=2.9 Hz), 7.31-7.28 (m, 1H), 7.20-7.07 (m, 3H), 3.68-3.60 (m, 2H), 3.31-3.22 (m, 2H), 2.64 (s, 2H), 2.38 (s, 3H), 2.27-2.21 (m, 2H), 1.90-1.81 (m, 2H), 1.46 (s, 9H).

106e [Y=Me] t-butyl endo-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)piperidine-1-carboxylate was prepared analogously to 106e [Y=Cl] in 57% yield. $^1$H-NMR (300 MHz, CDCl$_3$) δ 7.70-7.68 (d, 1H, J=7 Hz), 7.34-7.04 (m, 7H), 4.73-4.63 (m, 1H), 3.70-3.66 (m, 2H), 3.30-3.21 (m, 4H), 2.60 (s, 3H), 2.46-2.32 (m, 2H), 2.39 (s, 3H), 2.18-2.09 (m, 2H), 2.00-1.90 (m, 6H), 1.85-1.75 (m, 4H), 1.73-1.60 (m, 2H), 1.44 (s, 9H). ES-LCMS m/z 543 (M+H)+.

107 [Y=Me] Endo 2-methyl-1-{(1R,5S)-8-2-[4-(3-methyl phenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazol dihydrochloride was prepared analogously to 107 [Y=Cl] in 100% yield. ES-LCMS m/z 443 (M+H)+.
Compound 89: To a solution of endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride 107 [Y=Me] (200 mg, 0.3879 mmol) in N,N-dimethylformamide (1.5 ml) was added 4-chloro-3-sulfamoylbenzoic acid (91.4 mg, 0.3879 mmol), triethylamine (0.163 ml, 1.1637 mmol) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (162.2 mg, 0.4267). The reaction mixture was stirred at room temperature for 2h. Water was added until a precipitate formed, after filtration the resulting solid was washed with saturated sodium bicarbonate solution (10 ml) and water (10 ml). The product was purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane with 0.5% ammonium hydroxide to afford the title compound as a white solid (115 mg, 45%). ¹H-NMR (300 MHz, CDCl₃) δ 7.92-7.83 (m, 1H), 7.74-7.66 (m, 1H), 7.57-7.49 (m, 1H), 7.33-7.07 (m, 8H), 5.44 (br s, 2H), 4.69-4.62 (m, 1H), 4.35-4.23 (m, 1H), 3.42-3.16 (m, 6H), 2.55 (s, 3H), 2.45-2.30 (m, 2H), 2.35 (s, 3H), 2.28-2.18 (m, 2H), 2.05-1.60 (m, 12H). HRMS m/z (M+H)+ 660.2775 Cal., 660.2772 Obs.

Compound 93

106b [Y=Cl, Z=F] t-butyl 4-(3-chloro-4-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate was prepared from 1-fluoro-2-chloro-4-bromobenzene as described for 106b [Y=Cl] in 100% yield. ES-LCMS m/z 423 (M-H)+

106c [Y=Cl, Z=F] 1-(t-butoxycarbonyl)-4-(3-chloro-4-fluorophenyl)piperidin-4-yl(cyano)acetic acid was prepared as described for 106c [Y=Cl] in 100% yield.

106d [Y=Cl, Z=F] t-butyl endo 4-(3-chloro-4-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate was prepared as described for 106d [Y=Cl] in 51% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.41 (dd, 1H, J=2.3, 2.5 Hz) 7.30-7.21 (m, 2H), 3.76-3.72 (m, 2H), 3.13 (br t, 2H, J=10.4 Hz), 2.57 (s, 2H), 2.29-2.24 (br m, 2H), 1.93-1.84 (m, 2H), 1.46 (s, 9H). ES-LCMS m/z 253 (M-BOC+H)+

23 [Y=Cl, Z=F] t-butyl 4-(3-chloro-4-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate was prepared as described for 23 [Y=Cl] in 76.2% yield. ¹H-NMR (300 MHz, CDCl₃) δ 9.45 (t, 1H, J=2.6 Hz), 7.40(dd, 1H, J=2.4 Hz), 7.28-7.20 (m, 2H), 3.66-3.60 (m, 2H), 3.33-3.25 (m, 2H), 2.68 (s, 2H), 2.24-2.17 (br m, 2H), 1.95-1.82 (m, 2H), 1.45 (s, 9H).

106e [Y=Cl, Z=F] t-butyl 4-(3-chloro-4-fluorophenyl)-4-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl)piperidine-1-carboxylate was prepared as
described for 106b \([Y=Cl]\) in 61.2% yield. \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.70 (dd, 1H, \(J=2, 2.7\) Hz), 7.35-7.31 (m, 2H), 7.23-7.11 (m, 4H), 4.72-4.63 (m, 1H), 3.90-3.81 (m, 2H), 3.68-3.63 (br m, 2H), 3.38-3.19 (m, 4H), 3.15-3.00 (m, 1H), 2.61 (s, 3H), 2.55-2.40 (m, 2H), 2.10-1.65 (m, 11H), 1.45 (s, 9H). ES-LCMS \(m/z\) 581 (M+H). 

107 \([Y=Cl, Z=F]\) Endo 1-((1R,5S)-8-{2-[4-(3-chloro-4-fluoro phenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride was prepared as described for 107 \([Y=Cl]\) in 100% yield. ES-LCMS \(m/z\) 481 (M+H). 

Compound 93 was prepared from 107 \([Y=Cl, Z=F]\) (200 mg, 0.36 mmol) as described for 89, purified by column chromatography on silica gel, eluting with a gradient of 0-5% methanol in dichloromethane to afford the 37 mg of the product (14.6%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.14 (s, 1H), 7.69-7.54 (m, 3H), 7.35-7.29 (m, 2H), 7.20-7.15 (m, 4H), 5.41 (br s, 2H), 4.66-4.60 (m, 1H), 4.18-4.10 (m, 1H), 3.51-3.29 (m, 4H), 2.58 (s, 3H), 2.48-2.37 (m, 2H), 2.03-1.67 (m, 15H). HRMS \(m/z\) (M+H)\(^+\) 698.2135 Cal., 698.2132 Obs.

**Compound 94**

106b \([Y=F, Z=Cl]\) t-Butyl-4-(4-chloro-3-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate. Using the procedure from 106b \([Y=Cl]\), and 1-bromo-4-chloro-5-fluorobenzene used in place of 1-chloro-3-iodobenzene, 106b \([Y=F, Z=Cl]\) was obtained as an amber foam that was used without further purification.

106c \([Y=F, Z=Cl]\) [1-(tert-Butoxycarbonyl)-4-(4-chloro-3-fluorophenyl)piperidin-4-yl](cyano)acetic Acid. 106b \([Y=F, Z=Cl]\) was hydrolyzed using the same procedure as in 106b \([Y=Cl]\) to give as an amber solid 106c \([Y=F, Z=Cl]\).

106d \([Y=F, Z=Cl]\) t-Butyl 4-(4-chloro-3-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate. 106c \([Y=F, Z=Cl]\) was subjected to the same decarboxylation conditions used in 106d \([Y=Cl]\) and chromatographed on silica gel eluting with a gradient of ethyl acetate:hexane 1:20 to 1:1 to give 106d \([Y=F, Z=Cl]\) in 38% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 (m,
1H), 7.09–7.16 (m, 2H), 3.69–3.75 (m, 2H), 3.09 (m, 2H), 2.54 (s, 2H), 2.20–2.25 (m, 2H), 1.85 (m, 2H), 1.43 (s, 9H).  ES-LCMS m/z 253 (M-99).

23 [Y=F, Z=Cl] t-Bu-4-(4-chloro-3-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate.
Using the same procedure as for 23 [Y=Cl], 23 [Y=F, Z=Cl] was obtained in 65% yield. 1H NMR (400 MHz, CDCl3) δ 9.43 (t, 1H), 7.40 (m, 1H), 7.07–7.16 (m, 2H), 3.57–3.63 (m, 2H), 3.22–3.29 (m, 2H), 2.66 (s, 2H), 2.11–2.17 (m, 2H), 1.86 (m, 2H), 1.43 (s, 9H).  ES-LCMS m/z 354 (M-1).

106e [Y=F, Z=Cl] t-Butyl 4-(4-chloro-3-fluorophenyl)-4-\{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl\}piperidine-1-carboxylate was obtained as described for 106e [Y=Cl] in 59% yield. 1H NMR (400 MHz, CDCl3) δ 7.66 (m, 1H), 7.38 (m, 1H), 7.28 (m, 1H), 7.17 (m, 2H), 7.02–7.09 (m, 2H), 4.66 (m, 2H), 3.83 (m, 2H), 3.62 (m, 2H), 3.23 (m, 4H), 3.01 (m, 1H), 2.60 (s, 3H), 2.43 (m, 2H), 1.65–2.01 (m, 10H), 1.43 (s, 9H).  ES-LCMS m/z 581 (M+1).

107 [Y=F, Z=Cl] 1-(8-{2-[4-(4-Chloro-3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride was obtained similarly to 106e [Y=Cl] in 93% yield. 1H NMR (400 MHz, DMSO-d6) δ 11.22 (s, 1H), 9.03 (s, 2H), 7.88 (m, 1H), 7.80 (m, 1H), 7.46–7.62 (m, 4H), 7.26 (m, 1H), 6.03 (m, 1H), 4.08 (m, 2H), 3.23 (m, 2H), 3.11 (m, 1H), 2.87 (s, 3H), 2.75–2.90 (m, 4H), 2.30 (m, 2H), 2.10–2.25 (m, 8H), 2.08 (m, 2H).  ES-LCMS m/z 481 (M+1).

A mixture of 1-(8-{2-[4-(4-chloro-3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride 107 [Y=F, Z=Cl] (0.40 g, 0.78 mmol), triethylamine (0.35 mL, 2.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (184 mg, 0.78 mmol) in dimethylformamide (2.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (327 mg, 0.86 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution, with water, dried and purified by chromatography on silica gel eluting with a 400:15:1 to 200:15:1 gradient of
chloroform:methanol:ammonium hydroxide to give the inhibitor 94 as a solid (0.24 g, 43%). $^1$H NMR (400 MHz, CD$_3$OD) δ 8.09 (s, 1H), 7.68 (m, 1H), 7.61 (m, 1H), 7.34–7.54 (m, 4H), 7.17–7.26 (m, 3H), 4.73 (m, 1H), 4.09 (m, 1H), 3.59 (m, 1H), 3.43 (m, 1H), 3.30 (m, 3H), 2.53 (s, 3H), 2.40–2.48 (m, 4H), 2.28 (m, 1H), 2.16 (m, 1H), 1.83–2.04 (m, 10H), 1.70 (m, 2H). HRMS C$_{35}$H$_{38}$Cl$_2$FN$_5$O$_3$S m/z 698.2135 (M+H)$^+$ Cal., 698.2142 (M+H)$^+$ Obs.

**Compound 98**

$^{106b}$ [Y=O-Et] t-Butyl 4-((1-cyano-2-ethoxy-2-oxoethyl)-4-(3-ethoxyphenyl)piperidine-1-carboxylate. Using the same procedure as $^{106b}$ [Y=Cl], 3-bromophenetole (10.2 g, 51 mmol) was used in place of 1-chloro-3-iodobenzene. Yield 77%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (m, 1H), 6.81–6.91 (m, 3H), 3.90–4.04 (m, 4H), 3.55 (s, 1H), 2.86 (m, 2H), 2.54 (m, 2H), 1.95–2.05 (m, 4H), 1.43 (s, 9H), 1.40 (t, 3H), 1.04 (t, 3H). ES-LCMS m/z 317 (M-99).

$^{106d}$ [Y=O-Et] t-Butyl 4-(cyanomethyl)-4-(3-ethoxyphenyl) piperidine-1-carboxylate. $^{106c}$ [Y=O-Et] was subjected to the same decarboxylation conditions used in $^{106d}$ [Y=Cl] and purified by chromatography on silica gel eluting with a 1:9 to 1:2 ethyl acetate:hexane gradient to give $^{106d}$ [Y=O-Et] as a solid, yield 72%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 (m, 1H), 6.80–6.94 (m, 3H), 4.04 (m, 2H), 3.74–3.80 (m, 2H), 3.06 (m, 2H), 2.53 (s, 2H), 2.30 (m, 2H), 1.83 (m, 2H), 1.43 (s, 9H), 1.40 (t, 3H). ES-LCMS m/z 245 (M-99).

$^{23}$ [Y=O-Et] t-Butyl-4-(3-ethoxyphenyl)-4-(2-oxoethyl) piperidine-1-carboxylate. Using the same procedure as in $^{106b}$ [Y=Cl] t-butyl 4-(cyanomethyl)-4-(3-ethoxyphenyl piperidine-1-carboxylate $^{106d}$ [Y=O-Et] gave $^{23}$ [Y=O-Et] as a solid (Yield 68%). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.37 (t, 1H), 7.30 (m, 1H), 6.89–6.92 (m, 2H), 6.76 (m, 1H), 4.02 (m, 2H), 3.59–3.65 (m, 2H), 3.19–3.26 (m, 2H), 2.60 (s, 2H), 2.17–2.22 (m, 2H), 1.85 (m, 2H), 1.43 (s, 9H), 1.40 (m, 3H).

$^{106e}$ [Y=O-Et] t-Butyl 4-(3-ethoxyphenyl)-4-{2-[(3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)ethyl]piperidine-1-carboxylate. Using the same procedure as in $^{106e}$ [Y=Cl], $^{23}$ [Y=O-Et] gave $^{106e}$ [Y=O-Et], yield 88%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.66 (m, 1H), 7.26 (m, 2H), 7.13–7.19 (m, 2H), 6.85 (m, 2H), 6.75 (m, 1H), 4.66 (m, 2H), 4.03 (m, 2H), 3.65 (m, 2H), 3.30 (m, 2H), 3.17 (m, 4H), 2.60 (s, 3H), 2.40 (m, 2H), 1.65–2.16 (m, 11H), 1.43 (s, 9H), 1.40 (m, 3H). ES-LCMS m/z 573 (M+1).
107 [Y=O-Et] 1-(8-{2-[4-(3-Ethoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride. Using the same procedure as in 107 [Y=Cl], 106e [Y=O-Et] gave 1-(8-{2-[4-(3-ethoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride 107 [Y=O-Et] as a solid, yield 100%. 1H NMR (400 MHz, DMSO-d$_6$) δ 11.21 (s, 1H), 9.04 (s, 2H), 7.88 (m, 1H), 7.80 (m, 1H), 7.55 (m, 2H), 7.31 (m, 1H), 6.83--6.94 (m, 3H), 6.02 (m, 1H), 4.07 (m, 2H), 3.21 (m, 2H), 2.88 (s, 3H), 2.75--2.83 (m, 4H), 2.52 (m, 2H), 2.18--2.34 (m, 8H), 2.08 (m, 4H), 1.33 (t, 3H). ES-LCMS m/z 473 (M+1).

A mixture of 1-(8-{2-[4-(3-ethoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride 107 [Y=O-Et] (0.40 g, 0.78 mmol), triethylamine (0.35 mL, 2.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (184 mg, 0.78 mmol) in dimethylformamide (2.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (327 mg, 0.86 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution and water, dried and purified by chromatography on silica gel eluting with a chloroform:methanol:ammonium hydroxide 400:15:1 to 200:15:1 gradient to give compound 98 as a solid (0.34 g, 62%). 1H NMR (400 MHz, CD$_3$OD) δ 8.08 (s, 1H), 7.67 (m, 1H), 7.59 (m, 1H), 7.51 (m, 1H), 7.41 (m, 1H), 7.29 (m, 1H), 7.17 (m, 2H), 6.93--6.98 (m, 2H), 6.81 (m, 1H), 4.74 (m, 1H), 4.17 (m, 1H), 4.04 (m, 2H), 3.54 (m, 1H), 3.30 (m, 4H), 2.52 (s, 3H), 2.40--2.48 (m, 4H), 2.27 (m, 1H), 2.14 (m, 1H), 1.83--2.04 (m, 10H), 1.70 (m, 2H), 1.40 (t, 3H). HRMS C$_{37}$H$_{44}$ClN$_5$O$_4$S m/z 690.2881 (M+H)$_{\text{Cal.}}$ 690.2901 (M+H)$_{\text{Obs.}}$.

**Compound 99**
106b [Y=O-iPr] t-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(3-isopropoxyphenyl)piperidine-1-carboxylate was prepared as described for 106b [Y=Cl] from 1-bromo-3-isopropoxybenzene in 70% yield. ES-LCMS m/z 453 (M+Na)+.

106c [Y=O-iPr] 1-t-butoxycarbonyl)-4-(3-isopropoxyphenyl)piperidin-4-yl](cyano)acetic acid was prepared as described for 106b [Y=Cl] in 100% yield. ES-LCMS m/z 303 (M-BOC+H)+.

106d [Y=O-iPr] t-butyl 4-(cyanomethyl)-4-(3-isopropoxyphenyl)piperidine-1-carboxylate was prepared from 106c [Y=O-iPr] as described for 106d [Y=Cl] in 63% yield. 1H-NMR (300 MHz, CDCl3) δ 7.32 (t, 1H, J=8 Hz), 6.93 (d, 1H, J=7.9 Hz), 6.89 (s, 1H), 6.83 (d, 1H, J=5.9 Hz), 4.61-4.53 (m, 1H), 3.81-3.72 (br m, 2H), 3.12-3.04 (m, 2H), 2.54 (s, 2H), 2.34-2.29 (m, 2H), 1.89-1.80 (m, 2H), 1.46 (s, 9H), 1.37 (s, 3H), 1.35 (s, 3H). ES-LCMS m/z 259 (M-BOC+H)⁺.

23 [Y=O-iPr] t-butyl 4-(3-isopropoxyphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate was prepared as described for 23 [Y=Cl] in 79.3% yield.

106e [Y=O-iPr] t-butyl endo 4-(3-isopropoxyphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate was prepared from 23 [Y=O-iPr] as described for 106e [Y=Cl] in 46.4% yield. 1H-NMR (300 MHz, CDCl3) δ 7.70 (d, 1H, J=7.2 Hz), 7.30-7.15 (m, 3H), 6.93-6.70 (m, 4H), 4.74-4.61 (br m, 1H), 4.59-4.53 (m, 1H), 3.68-3.64 (br m, 2H), 3.35-3.00 (m, 4H), 2.61 (s, 3H), 2.57-2.41 (m, 2H), 2.20-2.15 (m, 2H), 2.05-1.60 (m, 12H), 1.46 (s, 9H), 1.37 (s, 3H), 1.35 (s, 9H).

107 [Y=O-iPr] endo 1-((1R,5S)-8-{2-[4-(3-isopropoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride was prepared from 106e [Y=O-iPr] as described in 106e [Y=Cl], yield 97.5%. ES-LCMS m/z 487 (M +H)⁺

Compound 99 was prepared from 107 [Y=O-iPr] as described for 89. 1H-NMR (300 MHz, CDCl3) δ 8.41 (br s, 1H), 8.13 (s, 1H), 7.70 (d, 1H, J=7.2 Hz), 7.62-7.53 (m, 1H), 7.59 (s, 1H), 7.34-7.24 (m, 2H), 7.20-7.15 (m, 2H), 6.87-6.80 (m, 3H), 4.83-4.77 (m, 1H), 4.65-4.52 (m ,1H),
4.22-4.19 (br m, 1H), 3.50-3.27 (m, 4H), 2.59 (s, 3H), 2.56-2.46 (m, 2H), 2.20-1.83 (m, 15H), 1.80-1.75 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H). HRMS m/z (M+H)+ 704.3037 Cal., 704.3055 Obs.

**Compound 103**

106e [Z=S-Me] t-butyl endo 4-{2-{[1R,5S]-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[4-(methylthio)phenyl]piperidine-1-carboxylate was prepared in 73.5% yield as described for 106e [Y=Cl]. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.70 (d, 1H, J=7 Hz), 7.33-7.15 (m, 7H), 4.78-4.65 (m, 1H), 3.75-3.62 (br m, 2H), 3.38-3.31 (br m, 2H), 3.23-3.15 (m, 2H), 2.60 (s, 3H), 2.51 (s, 3H), 2.48-2.39 (m, 4H), 2.21-2.15 (m, 2H), 1.99-1.66 (m, 10H), 1.46 (s, 9H). ES-LCMS m/z 575 (M+H)+.

107 [Z=S-Me] Endo 2-methyl-1-[(1R,5S)-8-[2-{4-[4-(methyl thio)phenyl]piperidin-4-yl}ethyl]-8-azabicyclo[3.2.1] oct-3-yl]-1H-benzimidazole dihydrochloride was prepared as described for 107 [Y=Cl] in 78% yield. ES-LCMS m/z 475 (M+H)+.

Inhibitor 103 was prepared from 107 [Z=S-Me] (200 mg, 0.365 mmol) as described for 89, in 24.3% yield. \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.41 (s, 1H), 7.70 (d, 1H, J=7.1 Hz,), 7.61-7.53 (m, 2H), 7.31-7.17 (m, 7H), 4.93-4.86 (m, 1H), 4.19-4.15 (m, 1H), 3.57-3.44 (m, 4H), 3.37-3.27 (m, 2H), 2.59 (s, 3H), 2.52 (s, 3H), 2.46-2.00 (m, 8H), 1.96-1.78 (m, 7H). HRMS m/z (M+H)+ 692.2496 Cal., 692.2498 Obs.

**Compound 104**

23 [Y=S-Me] t-butyl 4-[3-(methylthio)phenyl]-4-(2-oxoethyl)piperidine-1-carboxylate was prepared as described for 23 [Y=Cl] in 53.5% yield. \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.41(t, 1H, J=3 Hz), 7.36-7.26 (m, 1H), 7.17-7.04 (m, 3H), 3.66-3.61 (br m, 2H), 3.32-3.24 (m, 2H), 2.66 (s, 2H), 2.51 (s, 3H), 2.27-2.21 (br m, 2H), 1.91-1.82 (m, 2H), 1.46 (s, 9H).
**106e [Y=S-Me]** t-butyl endo 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[3-(methylthio)phenyl]piperidine-1-carboxylate was prepared as described for **23 [Y=Cl]** in 37.3% yield. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.70 (d, 1H, J=7 Hz), 7.34-7.08 (m, 7H), 4.70-4.65 (m, 1H), 3.75-3.65 (br m, 2H), 3.35-3.21 (m, 4H), 2.61 (s, 3H), 2.52 (s, 3H), 2.49-2.41 (m, 2H), 2.24-2.18 (m, 2H), 1.99-1.66 (m, 12H), 1.47 (s, 9H). ES-LCMS m/z 575 (M+H)$^+$.  

**107 [Y=S-Me]** endo 2-methyl-1-[(1R,5S)-8-(2-{4-[3-(methylthio)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole dihydrochloride was prepared as described for **107 [Y=Cl]** in 100% yield.

![Chemical structure](image)

Compound **104** was prepared as described for **89** in 44% yield. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.13 (s, 1H), 7.67 (d, 1H, J=6.9Hz), 7.62-7.52 (m, 2H), 7.37-7.32 (m, 2H), 7.28-7.15 (m, 4H), 7.08 (d, 1H, J=7.6 Hz), 5.44 (br s, 2H), 4.71-4.60 (m, 1H), 4.25-4.18 (br m, 1H), 3.58-3.50 (br m, 1H), 3.40-3.27 (br m, 4H), 2.57 (s, 3H), 2.52 (s, 3H), 2.46-2.36 (m, 3H), 2.25-2.16 (br m, 1H), 2.06-1.62 (m, 12H). HRMS m/z (M+H)$^+$ 692.2496 Cal., 692.2520 Obs.

**Compound 105**

Intermediates were obtained in a similar fashion to intermediates **Y=Cl**.  
1-bromo-3-chloro-5-fluorobenzene (10.7 g, 51 mmol) was used in place of 1-chloro-3-iodobenzene to give tert-butyl 4-(3-chloro-5-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate **106c [Y=Cl, W=F]** as an amber foam that was used without further purification.

**106d [Y=C, W=F]** tert-butyl 4-(3-chloro-5-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate was prepared with yield of 38%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 (s, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 3.71 (m, 2H), 3.11 (m, 2H), 2.55 (s, 2H), 2.20 (m, 2H), 1.86 (m, 2H), 1.43 (s, 9H). ES-LCMS m/z 253 (M-99).
23 [Y=Cl, W=F] tert-Butyl 4-(3-chloro-5-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate. Using the same procedure as in 23 [Y=Cl], tert-butyl 4-(3-chloro-5-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate (2.3 g, 6.5 mmol) gave 23 [Y=Cl, W=F] as an amber foam (1.5 g, 65%). 1H NMR (400 MHz, CDCl3) δ 9.43 (t, 1H), 7.12 (s, 1H), 6.95–7.01 (m, 2H), 3.55–3.62 (m, 2H), 3.24–3.30 (m, 2H), 2.63 (s, 2H), 2.04–2.17 (m, 2H), 1.80–1.91 (m, 2H), 1.42 (s, 9H). ES-LCMS m/z 354 (M-1).

106e [Y=Cl, W=F] tert-Butyl 4-(3-chloro-5-fluorophenyl)-4-[2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl]piperidine-1-carboxylate. Using the same procedure as in example 106e [Y=Cl] tert-butyl 4-(3-chloro-5-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate (1.5 g, 4.2 mmol) gave 106e [Y=Cl, W=F] (1.7 g, 71%). 1H NMR (400 MHz, CDCl3) δ 7.66 (m, 1H), 7.29 (m, 1H), 7.17 (m, 2H), 7.08 (s, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 4.66 (m, 2H), 3.83 (m, 2H), 3.62 (m, 2H), 3.25 (4H), 3.01 (m, 1H), 2.60 (s, 3H), 2.44 (m, 2H), 2.02 (m, 4H), 1.71–1.86 (m, 6H), 1.43 (s, 9H). ES-LCMS m/z 581 (M+1).

107 [Y=Cl, W=F] 1-((1R,5S)-8-{2-[4-(3-Chloro-5-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride. Using the same procedure as in example 107 [Y=Cl], tert-butyl 4-(3-chloro-5-fluorophenyl)-4-[2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl]piperidine-1-carboxylate (1.7 g, 2.9 mmol) gave 1-((1R,5S)-8-{2-[4-(3-chloro-5-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride 107 [Y=Cl, W=F] as a solid, yield 100%. 1H NMR (400 MHz, DMSO-d6) δ 11.26 (s, 1H), 9.14 (s, 2H), 7.89 (m, 1H), 7.80 (m, 1H), 7.55 (m, 2H), 7.37 (m, 1H), 7.30 (m, 2H), 6.03 (m, 1H), 4.11 (m, 2H), 3.22 (m, 2H), 3.11 (m, 1H), 2.88 (s, 3H), 2.75–2.90 (m, 4H), 2.30 (m, 2H), 2.10–2.25 (m, 8H), 2.08 (m, 2H). ES-LCMS m/z 481 (M+1).

A mixture of 1-((1R,5S)-8-{2-[4-(3-chloro-5-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride 107 [Y=Cl, W=F] (0.40 g, 0.78 mmol), triethylamine (0.35 mL, 2.5 mmol) and 4-chloro-3-sulfamoylbenzoic acid (184 mg, 0.78 mmol) in dimethylformamide (2.5 mL) was treated with O-(7-azabenzotriazol-1-yl)-
1,1,3,3-tetramethyluronium hexafluorophosphate (327 mg, 0.86 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution and water, dried and purified by chromatography on silica gel eluting with a gradient of chloroform:methanol:ammonium hydroxide 400:15:1 to 200:15:1 to give compound 105 as a solid (0.20 g, 36%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 8.09 (s, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.42 (m, 1H) 7.30 (s, 1H), 7.10–7.21 (m, 4H), 4.72 (m, 1H), 4.06 (m, 1H), 3.57 (m, 1H), 3.47 (m, 1H), 3.30 (m, 3H), 2.52 (s, 3H), 2.40–2.48 (m, 4H), 2.27 (m, 1H), 2.14 (m, 1H), 1.83–2.04 (m, 10H), 1.70 (m, 2H).

HRMS C$_{35}$H$_{38}$Cl$_2$FN$_5$O$_3$S $m/z$ 698.2134 (M+H)$^+$ Cal.: 698.2161 (M+H)$^+$ Obs.

**Analytical data for selected compounds**

**Compound 26**

![Compound 26](image)

$^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 7.48-7.40 (m, 9H), 7.28 (m, 3H), 7.13 (m, 2H), 4.61 (pent, 1H), 4.19 (m, 1H), 3.59 (m, 1H), 3.39-3.27 (m, 4H), 2.48-1.65 (m, 16H). HRMS C$_{34}$H$_{39}$N$_5$O $m/z$ 534.3233 (M+H)$^+$ Cal.: 534.3241 (M+H)$^+$ Obs.

**Compound 32**

![Compound 32](image)

$^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 7.49-7.39 (m, 10H), 7.32 (m, 1H), 7.24 (m, 1H), 7.16 (m, 2H), 4.81 (pent, 1H), 4.25 (m, 1H), 4.17 (s, 3H), 3.75 (m, 2H), 3.63 (m, 1H), 3.35-3.27 (m, 2H), 2.65-1.79 (m, 16H). ES-LCMS $m/z$ 549.38 (M+H). HRMS C$_{35}$H$_{40}$N$_4$O$_2$ $m/z$ 549.3230 (M+H)$^+$ Cal.: 549.3217 (M+H)$^+$ Obs.
**Compound 33**

\[
\text{H NMR (300 MHz, CD}_3\text{OD) } \delta 7.51-7.39 (m, 10H), 7.32 (m, 1H), 7.24 (m, 1H), 7.16 (m, 2H), 4.85 (pent, 1H), 4.57 (q, 2H, J = 7.0 Hz), 4.23 (m, 1H), 3.73 (m, 2H), 3.63 (m, 1H), 3.35-3.27 (m, 2H), 2.65-1.79 (m, 16H). ES-LCMS } m/z 563.40 (M+H). HRMS C_{36}H_{42}N_4O_2 m/z 563.3386 (M+H)_{Cal.}; 563.3368 (M+H)_{Obs.}
\]

**Compound 85**

Prepared analogously to 89. \(^1\)H NMR (400 MHz, CD$_3$OD) \( \delta 7.79–7.94 (m, 2H), 7.57–7.71 (m, 5H), 7.40–7.54 (m, 2H), 7.15–7.21 (m, 2H), 4.73 (m, 1H), 4.15 (m, 1H), 3.39–3.55 (m, 4H), 3.16–3.22 (m, 1H), 2.52 (s, 3H), 2.34–2.50 (m, 3H), 2.22–2.32 (m, 1H), 1.94–2.12 (m, 10H), 1.68–1.74 (m, 2H). HRMS C$_{36}$H$_{39}$ClF$_3$N$_5$O$_3$S \( m/z \) 714.2492 (M+H)$_{Cal.}$; 714.2496 (M+H)$_{Obs.}$.

**Compound 86**

Prepared analogously to 89. \(^1\)H NMR (300 MHz, CD$_3$OD) \( \delta 7.93 (\text{app d, 2H, J=9.6 Hz}), 7.78-7.64 (m, 1H), 7.53-7.39 (m, 3H), 7.24-7.15 (m, 4H), 6.99 (\text{app t, 1H, J=8.0 Hz}), 4.73 (\text{app quint, 1H, J=9.6 Hz}), 4.20-4.15 (\text{br m, 1H}), 3.48-3.29 (m, 3H), 3.22-3.14 (m, 1H), 2.52 (s, 3H), 2.48-2.34 (m, 3H), 2.10-1.88 (m, 11H), \text{NH}_2 \text{(not observed).} \)
**Compound 88**

Prepared analogously to 89. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.93 (s, 1H), 7.68 (d, 1H, J=8 Hz), 7.63 (br, 2H), 7.61 (d, 1H, J=8Hz), 7.48 (d, 1H, J=7 Hz), 7.34 (d, 1H, J=7 Hz), 7.27 (t, 1H, J=8 Hz), 7.23 (s, 1H), 7.18 (d, 1H, J=7 Hz), 7.09 (m, 3H), 4.49 (m, 1H), 3.89 (m, 1H), 3.50-3.30 (m, 2H), 3.20 (m, 4H), 2.89 (m, 1H, J=7 Hz), 2.43 (s, 3H), 2.35 (br.dd, 2H, J=22, 10 Hz), 2.17 (m, 1H), 2.07 (m, 1H), 1.90-1.70 (m, 9H), 1.56 (br.d, 2H, J=8Hz), 1.20 (d, 6H, J=7 Hz). HRMS C$_{38}$H$_{46}$ClN$_5$O$_3$S $m/z$ 688.3088 (M+H)$_{Cal.}$, 688.3075 (M+H)$_{Obs.}$

**Compound 100.**

Prepared analogously to 89. $^1$H NMR (400 MHz, CD$_3$OD) δ 7.95-7.78 (m, 2H), 7.71 (d, 2H, J=8Hz), 7.67 (m, 1H), 7.64 (d, 2H, J=8Hz), 7.52 (br.d, 1H, J=7 Hz), 7.42 (br. D, 1H, J=7 Hz), 7.20 (t, 1H, J=7 Hz), 7.17 (t, 1H, J=7 Hz), 4.74 (m, 1H), 4.19 (m, 1H), 3.40 (m, 4H), 3.18 (m, 1H), 2.52 (s, 3H), 2.43 (m, 3H), 2.25 (m, 1H), 1.99 (m, 10H), 1.71 (d, 2H, J=7 Hz). HRMS C$_{36}$H$_{39}$Cl$_3$N$_5$O$_3$S $m/z$ 714.2492 (M+H)$_{Cal.}$, 714.2492 (M+H)$_{Obs.}$

**Amine 37**
Amine 47 (2.5 g, 7.88 mmol) was treated with BrCN (0.92 g, 8.66 mmol) in CH$_3$OH (30 mL) at reflux for 3h and concentrated to give 2.30 g of the product (6.73 mmol, 85%, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.15 (d, 2H, $J = 7.6$ Hz), 6.97-6.86 (m, 2H), 6.21 (s, 2H), 4.34 (m, 2H), 4.22 (pent, 1H), 2.42-2.32 (m, 2H), 1.98-1.85 (m, 6H), 1.44 (s, 9H). ES-LCMS $m/z$ 343.12 (M+H)), which was suspended in DCM (2 mL) and treated with TFA (2 mL) at ambient temperature for 30 min. The reaction mixture was concentrated to dryness to give the di-TFA salt of 37 (320 mg, 0.681 mmol, 95%) as a white solid. $^1$H NMR (300 MHz, D$_2$O) $\delta$ 7.40-7.20 (m, 4H), 4.66-4.49 (m, 1H), 4.16 (m, 2H), 2.71-2.60 (m, 2H), 2.29-2.11 (m, 6H). ES-LCMS $m/z$ 243.04 (M+H).

Amine 47 (900 mg, 2.83 mmol) in THF was treated with methyl isothiocyanate (230 mg, 3.15 mmoles, 1.1 eq.) at 0$^\circ$C for 1h followed by 16h at ambient temperature. The reaction mixture was concentrated, redissolved in 7 mL DMF and treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (815 mg, 1.5 eq.) at ambient temperature for 16h. The reaction mixture was concentrated, dissolved in EtOAc, washed successively with saturated aqueous NaHCO$_3$, water (3x), and brine. The organic phase was separated, dried over MgSO$_4$ and concentrated to give the desired product (ES-LCMS $m/z$ 357.15 (M+H)), which was dissolved in 3 mL CH$_3$OH, treated with 3 mL 4N HCl in dioxane at ambient temperature for 30 minutes, concentrated and triturated with EtOH, filtered, and dried to give the di-HCl salt of 38 (201 mg, 0.61 mmoles) as a pink solid. ES-LCMS $m/z$ 257.04 (M+H).

Amine 38

Amine 47 (900 mg, 2.83 mmol) in THF was treated with methyl isothiocyanate (230 mg, 3.15 mmoles, 1.1 eq.) at 0$^\circ$C for 1h followed by 16h at ambient temperature. The reaction mixture was concentrated, redissolved in 7 mL DMF and treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (815 mg, 1.5 eq.) at ambient temperature for 16h. The reaction mixture was concentrated, dissolved in EtOAc, washed successively with saturated aqueous NaHCO$_3$, water (3x), and brine. The organic phase was separated, dried over MgSO$_4$ and concentrated to give the desired product (ES-LCMS $m/z$ 357.15 (M+H)), which was dissolved in 3 mL CH$_3$OH, treated with 3 mL 4N HCl in dioxane at ambient temperature for 30 minutes, concentrated and triturated with EtOH, filtered, and dried to give the di-HCl salt of 38 (201 mg, 0.61 mmoles) as a pink solid. ES-LCMS $m/z$ 257.04 (M+H).

Amine 39
To a solution of trifluoroacetic acid (496 mg, 4.35 mmoles) in 5 mL DMF was added CDI (4.35 mmoles, 1 eq.) and the mixture was then stirred for 30 min at ambient temperature, until CO₂ evolution ceased. The reaction mixture was then cooled in an ice bath and 47 (1.38 g, 4.35 mmoles, 1 eq.) dissolved in 10mL DMF was added slowly. The reaction mixture was stirred for 30 min at 0°C and then at ambient temperature for 30 min, followed by heating at 80°C for 16h, then concentrated and partitioned between DCM, saturated aqueous NaHCO₃ and water (3x). The organic phase was dried, concentrated and purified by normal phase flash chromatography (SiO₂, 10→40% EtOAc/Hexanes) to give the product (0.36 g, 0.91 mmoles, 21%). ES-LCMS m/z 396.27 (M+H). Next, 330 mg, 0.84 mmoles was dissolved in 6 mL DCM and treated with 4 mL 4N HCl in dioxane at ambient temperature for 30 minutes. A solid precipitated from the reaction mixture and was filtered off to give the HCl salt of 39 (260 mg, 0.78 mmoles, 94%) as a pink solid. ES-LCMS m/z 295.67 (M+H).

**Amine 40**

![Amine 40](image)

Amine 46 (1.5 g, 6.66 mmoles) was treated with 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene (1.46 g, 1 eq.) in 10 mL NMP with DIPEA (947 mg, 1.1 eq.) at 70°C for 3h. The reaction mixture was diluted with 5 mL NMP, cooled to ambient temperature, and water added to incipient cloudiness. The reaction mixture was stirred until a heavy precipitate formed. The precipitate was filtered off, washed successively with NMP/water (1:1) and water, and air dried to give the above product (2.21 g, 78%) as a yellow solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.90 (d, 1H, J=7.0Hz), 8.53 (d, 1H, J=2.0Hz), 7.94 (dd, 1H, J=9.2, 2.0Hz), 7.17 (d, 1H, J=9.3Hz), 4.11 (m, 3H), 3.21 (s, 3H), 2.16 (m, 2H), 1.94 (m, 4H), 1.80 (m, 2H), 1.42 (s, 9H). The nitro product (2.21 g, 5.19 mmoles) was then subjected to catalytic hydrogenation with 10% Pd/C (260 mg) in EtOH/EtOAc (1:1, 100 mL) under 1atm H₂(g) for 16h. The catalyst was filtered off and the filtrate concentrated to a purple oil further treated with 1,1,1-triethoxyethane.
at reflux for 2h. The reaction mixture was concentrated to dryness, redissolved in CH$_3$OH (10 mL), and treated with 6 N HCl at reflux for 1h. The reaction mixture was concentrated to dryness to give the di-HCl salt of 40. $^1$H NMR (300 MHz, D$_2$O) $\delta$ 8.27 (m, 1H), 7.98-7.89 (m, 2H), 5.00 (m, 1H), 4.20 (m, 2H), 3.21 (s, 3H), 2.77 (s, 3H), 2.79-2.70 (m, 2H), 2.35-2.15 (6H).

Amine 41

Amine 46 (2.0 g, 8.88 mmoles) was treated with 1,4-difluoro-2-nitrobenzene (1.41 g, 1 eq.) in 10 mL NMP with DIPEA (1.26 g, 1.1 eq.) at 70 °C for 16h. The reaction mixture was cooled to ambient temperature, and water (4 mL) added to incipient cloudiness. The reaction mixture was stirred until a heavy precipitate formed. The precipitate was filtered off, washed successively with NMP/water (1:1) and water, and air dried to give the desired product as an orange solid (2.74 g, 7.50 mmoles, 84%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.66 (d, 1H, $J$=5.7Hz), 7.93 (m, 1H), 7.27 (m, 1H), 6.72 (m, 1H), 4.29 (m, 3H), 3.91 (m, 1H), 2.40-2.29 (m, 2H), 2.15-2.01 (m, 4H), 1.80 (m, 2H), 1.50 (s, 9H). The product (2.74 g, 7.50 mmoles) was catalytically hydrogenated in presence of 10% Pd/C (300 mg) in EtOH/EtOAc (1:1, 80 mL) under 1atm H$_2$(g) for 16h. The catalyst was filtered off and the filtrate concentrated to give the title compound (2.57 g, 100%) as a white foam. ES-LCMS $m/z$ 336.26 (M+H). To the residue was added 1,1,1-triethoxyethane and a catalytic amount of camphor sulphonic acid and the mixture refluxed for 3h. The reaction mixture was concentrated to dryness, redissolved in CH$_3$OH (10 mL), and treated with 6N HCl at reflux for 1h, resulting in the di-HCl salt amine 41 as a solid, after all solvents were removed. ES-LCMS $m/z$ 260.27 (M+H).

Amine 42
Amine 46 (8.64 g, 38.3 mmoles) was treated with 2-chloro-3-nitropyridine (6.08 g, 1 eq.) in 50 mL NMP with DIPEA (10.9 g, 2.2 eq.) at 70°C for 16h. The reaction mixture was cooled to ambient temperature, water (60 mL) added and precipitate filtered off, to give 11.5 g (33.0 mmoles, 86%) of the product. Catalytic hydrogenation of this product with 10% Pd/C (500 mg) in EtOH/EtOAc (1:1, 200 mL) under 1 atm H₂(g) for 16h was subsequently followed by the treatment with 1,1,1-triethoxyethane in presence of catalytic amount of camphor sulphonic acid at reflux for 3h (ES-LCMS m/z 411.08 (M+Na)). Catalytic amount of camphor sulphonic acid in NMP was added to the residue and the mixture was heated at 150 °C for 12h. The reaction mixture was purified by normal phase flash chromatography to give 42 (1.60 g, 4.67 mmoles). ES-LCMS m/z 343.24 (M+H).

Amine 43

Amine 47 was treated with 5 mL tetramethyl orthocarbonate at reflux for 40h. The reaction mixture was concentrated to dryness and purified by flash chromatography on silica gel eluted with 20% EtOAc in hexanes to give the desired product (0.50 g, 1.40 mmol, 44%, ES-LCMS m/z 358.11, M+H), which was then suspended in DCM (2 mL) was treated with TFA (1 mL) at ambient temperature for 5 min. The reaction mixture was concentrated to dryness to give the di-TFA salt 43 (340 mg, 0.722 mmol, 51%) as a tan solid. ¹H NMR (300 MHz, D₂O) δ 7.35 (m, 1H), 7.26 (m, 1H), 7.12 (m, 2H), 4.65 (m, 1H), 4.08-4.00 (m, 2H), 4.03 (s, 3H), 2.55-2.45 (m, 2H), 2.17-2.02 (m, 6H). ES-LCMS m/z 258.02 (M+H).

Amine 44
Amine 47 (1.7 g, 5.36 mmol) was treated with 10 mL tetraethyl orthocarbonate at reflux for 16h. The reaction mixture was concentrated to dryness and purified by flash chromatography on silica gel eluted with DCM followed by 20% EtOAc in hexanes to give 1.15 g (3.10 mmol, 58%) of an amber oil product (ES-LCMS m/z 372.19 (M+H)), which was suspended in DCM (4 mL) was treated with TFA (1 mL) at ambient temperature for 5 min. The reaction mixture was concentrated to dryness to give the di-TFA salt of 44 (715 mg, 1.43 mmol, 46%) as a white powder. $^1$H NMR (300 MHz, D$_2$O) δ 7.36 (m, 1H), 7.27 (m, 1H), 7.12 (m, 2H), 4.65 (m, 1H), 4.43 (q, 2H, J=7.1 Hz), 4.00 (m, 2H), 2.54-2.43 (m, 2H), 2.16-2.00 (m, 6H). ES-LCMS m/z 272.05 (M+H).

Amine 45

Amine 47 (2.5 g, 7.80 mmol) was treated with 20 mL 1,1,1-triethoxypropane at reflux for 3h. The reaction mixture was concentrated to dryness, redissolved in CH$_3$OH (10 mL), treated with 6 N HCl at reflux for 1h, concentrated to dryness and triturated with EtOH to give a solid residue as HCl salt of the above product (1.35 g, 4.11 mmol, 53%). $^1$H NMR (300 MHz, D$_2$O) δ 7.72-7.65 (m, 2H), 7.49-7.46 (m, 2H), 4.99 (m, 1H) 4.19 (m, 2H), 3.10 (q, 2H, J=7.6Hz), 2.76-2.70 (m, 2H), 2.40-2.18 (m, 6H), 1.35 (t, 3H, J=7.6Hz). ES-LCMS m/z 256.07 (M+H).

**Preparation of selected meta- and para- N-substituted sulfonamides**

**4-Chloro-3-(chlorosulfonyl)benzoic acid**
To a stirred chlorosulfonic acid (200 mL) was added 4-chlorobenzoic acid (78 g, 0.5 mol) at 5-10 °C, and the reaction was carried on for 5 hrs at 150°C. After cooling down, the reaction mixture was poured onto ice and extracted with ether. The combined organic extracts were washed with ice water and dried over anhydrous magnesium sulfate. Evaporation of solvents afforded 4-chloro-3-(chlorosulfonyl)benzoic acid as a solid (76 g).

4-(aminosulfonyl)-2-fluorobenzoic acid

To ~20 mL of liquid ammonia at -78°C was added 2.1g (10 mmol) of 3-fluoro-4-methyl benzenesulfonyl chloride. The excess ammonia was then naturally evaporated to dryness overnight at room temperature. The crude sulfonamide was partitioned between methylene chloride (100mL) and water (100 mL), aqueous phase was further extracted with methylene chloride and the combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvents afforded 1.9 g of 3-fluoro-4-methylbenzenesulfonamide, which was dissolved in 50 mL water, added sodium carbonate (0.53g, 5 mmol) and potassium permanganate (3.16g, 20 mmol) portionwise over three hours at 50~60 °C. The resulting mixture was stirred for further 8 hours at this temperature before 0.2 mL of formic acid was added to quench the excess of potassium permanganate. The hot mixture was then filtered through celite, the filtrate concentrated to ~30 mL and adjusted to pH 9~10. The final filtrate was acidified with concentrated HCl to ~ pH 1 and 4-(aminosulfonyl)-2-fluorobenzoic acid was precipitated and collected by filtration as white solid (1.10g, 50%).