Supporting Information
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Supporting Information

Practical synthesis of fluorinated piperidine analogs based on the 2-azaspiro[3.3]heptane scaffold

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General. Solvents were purified according to the standard procedures. Compound 14 was prepared according to reported procedure. Melting points were measured on an automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. $^1$H, $^{13}$C, $^{19}$F NMR spectra were recorded at 499.9 or 400.4 MHz for $^1$H, 124.9 or 100.4 MHz for $^{13}$C, and 470 or 377 MHz for $^{19}$F. Chemical shifts are reported in ppm downfield from TMS ($^1$H, $^{13}$C) or CFCl$_3$ ($^{19}$F) as an internal standard. MS analyzes were done on an LCMS instrument with chemical ionization (CI) or a GCMS instrument with electron impact ionization (EI). HRMS spectra were recorded on Finnigan MAT 95 mass spectrometer equipped with Sector Field Analyzer and electrospray (EI) ion source. All compound names were generated using ChemBioDraw.

**Tert-butyl 3-cyclopropylideneazetidine-1-carboxylate 2.** NaHMDS (1 M solution in THF, 312 mL, 312 mmol) was added to a suspension of (3-bromopropyl)triphenylphosphonium bromide (69.00 g, 148.70 mmol) in toluene (600 mL) under an Ar atmosphere at -30 ºC. The orange solution was stirred for 2 h at room temperature, and then the solution of compound 1 (23.00 g, 134.35 mmol) in THF (100 mL) was slowly added dropwise to the reaction mixture at -78 ºC. The reaction mixture was stirred at -78 °C for 1 h, slowly warmed up to room temperature overnight, refluxed for 3 h, and poured into cold saturated aq. NH$_4$Cl. The mixture was extracted with EtOAc. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated. The resulting solid was washed with hexanes–EtOAc (7:1, 3×100 mL), and the combined organic extracts were evaporated. The residue was purified by column chromatography (Hexanes:EtOAc=7:1). 13.90 g (71.19 mmol, 53%); white solid; m.p. 90–93 ºC; TLC: $R_f$ = 0.37 (hexanes:EtOAc=7:1); $^1$H NMR (500 MHz, CDCl$_3$), δ: 4.55–4.50 (m, 4H), 1.44 (s, 9H), 1.08–1.03 (m, 4H); $^{13}$C NMR (126 MHz, CDCl$_3$), δ: 156.7, 116.9, 113.4, 91.4, 79.6, 28.5, 2.4; HRMS (EI): C$_{11}$H$_{17}$O$_2$N (M$^+$), calc. 195.1254, found 195.1253.

**Tert-butyl 8-oxa-6-azadispiro[2.0.3.4]octane-6-carboxylate.** Meta-chloroperoxybenzoic acid (15.53 g, 76.52 mmol) was added portionwise to a solution of compound 2 (11.50 g, 58.90 mmol) in CH$_2$Cl$_2$ (400 mL) at ambient temperature. The reaction mixture was stirred for 48 h, washed with 10% aq. Na$_2$SO$_3$ (2×100 mL), saturated aq. NaHCO$_3$, dried over Na$_2$SO$_4$, filtered, and evaporated to give crude epoxide. It was used in the next step without additional purification. 10.93 g (51.74 mmol, 88%); colorless oil; 1H NMR (500 MHz, CDCl$_3$), δ: 4.32 (d, $J$ =10.7 Hz, 2H), 4.21 (d, $J$ =10.8 Hz, 2H), 1.45 (s, 9H), 1.16 (t, $J$ =6.1 Hz, 2H), 1.01 (t, $J$ =6.6 Hz, 2H); 13C NMR (126 MHz, CDCl$_3$), δ: 156.2, 80.2, 62.7, 60.8, 28.4, 27.7, 3.0; HRMS (EI, +3NBA): C$_{11}$H$_{18}$O$_3$N (MH$^+$), calc. 212.1281, found 212.1283.

**Tert-butyl 5-oxo-2-azaspiro[3.3]heptane-2-carboxylate 3.** Anhydrous lithium iodide (3.17 g, 45.3 mmol, 0.5 eq.) was added to a solution of tert-butyl 8-oxa-6-azadispiro[2.0.3.4]octane-6-carboxylate (10.00 g, 47.36 mmol) in THF (200 mL) under argon atmosphere. The reaction mixture was heated at 50 ºC overnight, cooled to ambient temperature, and water (250 mL) was added. The mixture was extracted with EtOAc. Combined organic phase was washed with water, dried over Na$_2$SO$_4$, and evaporated. The crude product was purified by column chromatography (Hexanes:EtOAc=7:1). 8.15 g (38.58 mmol, 81%); white solid; m.p. 51–56 ºC; TLC: $R_f$ = 0.45 (hexanes:EtOAc=7:1); $^1$H NMR (500 MHz, CDCl$_3$), δ: 4.12 (d, $J$ =8.7 Hz, 2H), 3.88 (d, $J$ =8.7 Hz, 2H), 2.96 (t, $J$ =8.6 Hz, 2H), 2.23 (t, $J$ =8.6 Hz, 2H), 1.36 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$), δ: 209.2, 155.9, 91.3, 79.9, 56.8, 44.4, 28.3, 23.6; HRMS (EI, +3NBA): C$_{11}$H$_{18}$O$_3$N (MH$^+$), calc. 212.1281, found 212.1282.

**Tert-butyl 5,5-difluoro-2-azaspiro[3.3]heptane-2-carboxylate 4.** Morpholinosulfur trifluoride (4.00 g, 22.73 mmol) was added dropwise to an ice-cold solution of compound 3 (2.00 g, 9.47 mmol) in anhydrous DCM (20 mL). The resulting solution was stirred for 24 h while being gradually warmed to ambient temperature, and was then diluted with aq. NaHCO$_3$ and extracted with EtOAc. The organic phase was dried over Na$_2$SO$_4$, filtered and evaporated. The crude product was purified by column chromatography (Hexanes:EtOAc=4:1). 1.99 g (8.53 mmol, 90%); colorless oil; TLC: $R_f$ = 0.38 (Hexanes:EtOAc=4:1); $^1$H NMR (500 MHz, CDCl$_3$), δ: 4.22 (d, $J$ =9.2 Hz, 2H), 3.76 (d, $J$ =9.2 Hz, 2H), 2.49–2.37 (m, 2H), 2.03–1.95 (m, 2H), 1.43 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$), δ: 156.2, 120.4 (t, $J$ =284.1 Hz), 79.8, 54.2, 45.7 (t, $J$ =23.8 Hz), 32.1 (t, $J$ =22.8 Hz), 28.4, 23.2 (t, $J$ =7.9 Hz), $^{19}$F NMR (376 MHz, CDCl$_3$), δ: -102.76; MS (GCMS) 233 (M$^+$), 132 (M$^+$ - t-BuCO).
**5,5-Difluoro-2-azaspiro[3.3]heptan-2-ium 2,2,2-trifluoroacetate 5.** TFA (5 mL) was added to a solution of compound 4 (0.40 g, 1.72 mmol) in DCM (5 mL). The reaction mixture was stirred at ambient temperature for 2 h and the solvents were removed in vacuum. The residue was taken up in ether and the resulting solid was filtered to give 0.35 g (1.42 mmol, 82%) of compound 5. White solid; m.p. 100–102 °C; 1H NMR (500 MHz, D2O), δ: 4.17 (d, J=11.9 Hz, 2H), 3.95 (d, J=11.7 Hz, 2H), 2.31 (tt, J=13.2, 8.9 Hz, 2H), 1.98–1.86 (m, 2H); 13C NMR (126 MHz, D2O), δ: 162.5 (q, J=35.4 Hz), 119.4 (t, J=286.5 Hz), 116.0 (q, J=291.9 Hz), 49.8 (t, J=5.0 Hz), 47.4 (t, J=24.0 Hz), 30.7 (t, J=22.1 Hz), 21.0 (t, J=7.7 Hz); 19F NMR (376 MHz, CDCl3), δ: -75.95, -103.07 (t, J=13.0 Hz); HRMS (EI, +3NBA): C16H10F2N2 (MH+), calc. 288.0863, found 288.0864.

**Tert-butyl 5-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate 6.** Sodium borohydride (1.53 g, 40.26 mmol) was added to a solution of ketone 3 (3.00 g, 14.20 mmol) in a mixture of THF (100 mL) and water (10 mL). The reaction mixture was stirred at ambient temperature overnight, diluted with EtOAc (2×30 mL), and organic phase was washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (Hexanes:EtOAc:Et3N=2:1:0.15). 2.55 g (11.96 mmol, 84%); white solid; m.p. 100–102 ºC; TLC: Rf=0.50 (Hexanes:EtOAc:Et3N=2:1:0.15); 1H NMR (500 MHz, CDCl3), δ: 4.37 (d, J=8.5 Hz, 1H), 4.07–3.90 (m, 2H), 3.81 (d, J=9.0 Hz, 1H), 3.72 (d, J=9.0 Hz, 1H), 3.65 (d, J=8.5 Hz, 1H), 2.15–2.04 (m, 1H), 1.87–1.78 (m, 1H), 1.66–1.56 (m, 2H), 1.38 (s, 9H); 13C NMR (126 MHz, CDCl3), δ: 156.6, 79.4, 70.1, 57.6, 43.7, 28.5, 27.8, 24.5; HRMS (EI): C11H19O2NF (M+), calc. 216.1394, found 216.1393.

**Tert-butyl 5-(methylsulfonyl)oxy-2-azaspiro[3.3]heptane-2-carboxylate 7.** Methanesulfonyl chloride (0.32 g, 2.80 mmol) was added to a cooled solution of compound 6 (0.50 g, 2.34 mmol) and triethylamine (0.65 mL, 4.66 mmol) in DCM (10 mL) under Ar at -30 °C. The reaction mixture was gradually warmed to ambient temperature with water, aq. NaHCO3, dried over Na2SO4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (Hexanes:EtOAc=2:1) and triethylamine (0.65 mL, 4.66 mmol) in DCM (10 mL) under Ar at -30 °C. The reaction mixture was gradually warmed to ambient temperature with water, aq. NaHCO3, dried over Na2SO4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (Hexanes:EtOAc=7:1). Colorless oil; TLC: Rf=0.31 (Hexane:EtOAc=7:1); 1H NMR (500 MHz, CDCl3), δ: 3.93 (dd, J=20.9, 10.0 Hz, 2H), 3.76 (dd, J=17.7, 10.0 Hz, 2H), 1.40 (s, 9H), 1.29–1.19 (m, 1H), 0.66–0.53 (m, 2H), 0.48–0.34 (m, 2H); 13C NMR (126 MHz, CDCl3), δ: 156.3, 92.3 (d, J=205.0 Hz), 79.9, 59.1, 28.3, 14.8 (d, J=29.5 Hz), 1.2 (d, J=4.8 Hz); 19F NMR (376 MHz, CDCl3), δ: -148.46—149.03 (m); HRMS (EI, +3NBA): C11H19O2NF (M+), calc. 219.1359, found 219.1361.

**Tert-butyl 3-cyclopropyl-3-fluoroazetidine-1-carboxylate 8.** Compound 9 (0.45 g, 2.09 mmol, 89%) was obtained from 6 (0.50 g, 2.34 mmol) analogously to 5. The crude product was purified by column chromatography (Hexanes:EtOAc=7:1). Colorless oil; TLC: Rf=0.31 (Hexane:EtOAc=7:1); 1H NMR (500 MHz, CDCl3), δ: 3.93 (dd, J=20.9, 10.0 Hz, 2H), 3.76 (dd, J=17.7, 10.0 Hz, 2H), 1.40 (s, 9H), 1.29–1.19 (m, 1H), 0.66–0.53 (m, 2H), 0.48–0.34 (m, 2H); 13C NMR (126 MHz, CDCl3), δ: 156.3, 92.3 (d, J=205.0 Hz), 79.9, 59.1, 28.3, 14.8 (d, J=29.5 Hz), 1.2 (d, J=4.8 Hz); 19F NMR (376 MHz, CDCl3), δ: -148.46—149.03 (m); HRMS (EI, +3NBA): C11H19O2NF (M+), calc. 216.1394, found 216.1393.

**3-Cyclopropyl-3-fluoroazetidin-1-ium 2,2,2-trifluoroacetate 10.** Compound 10 (0.19 g, 0.83 mmol, 71%) was obtained from 9 (0.25 g, 1.16 mmol) analogously to 5. White solid; m.p. 69–71 °C; 1H NMR (500 MHz, D2O), δ: 4.21–3.97 (m, 4H), 1.33–1.22 (m, 1H), 0.64–0.55 (m, 2H), 0.43–0.35 (m, 2H); 13C NMR (126 MHz, D2O), δ: 162.5 (q, J=35.7 Hz), 116.0 (q, J=292.0 Hz), 94.6 (d, J=200.5 Hz), 55.1 (d, J=30.8 Hz), 13.1 (d, J=29.6 Hz), 0.2 (d, J=4.0 Hz); 19F NMR (376 MHz, D2O), δ: -76.35, -143.91—144.30 (m); HRMS (EI): C6H16F3N (M–H+), calc. 164.0776, found 164.0776.

**6,6-Difluoro-2-azaspiro[3.3]heptane 15.** Compound 15 (4.36 g, 15.17 mmol, 81%) was obtained from 14 (5.00 g, 18.85 mmol) analogously to 4. The crude product was recrystallized from ethanol. White solid; m.p. 95–96 °C; 1H NMR (500 MHz, CDCl3), δ: 7.71 (d, J=7.3 Hz, 2H), 7.37 (d, J=7.2 Hz, 2H), 3.81 (s, 4H), 2.57 (t, J=11.6 Hz, 4H), 2.46 (s, 3H); 13C NMR (126 MHz, CDCl3), δ: 144.5, 131.5, 129.9, 128.5, 118.3 (t, J=278.4 Hz), 61.1, 45.6 (t, J=23.4 Hz), 27.1 (t, J=10.3 Hz), 21.7; 19F NMR (376 MHz, CDCl3), δ: -93.08 (p, J=11.6 Hz); HRMS (EI, +3NBA): C16H10F2S (MH+), calc. 288.0864, found 288.0863.

**6,6-Difluoro-2-azaspiro[3.3]heptan-2-ium chloride 16.** Compound 15 (2.00 g, 6.96 mmol) was dissolved in methanol (20 mL), and solid sodium amalgam (10 g) was added to the resulting solution in one portion. The reaction mixture was refluxed for 12 h and was then allowed to cool to ambient temperature. The solution was decanted from the liquid amalgam, and the residue was washed with methanol (10 mL). The
The solvent was evaporated in vacuum. Water (20 mL) was added to dissolve the residue. pH of the solution was adjusted to 1 with 3 N HCl. The resulting aqueous solution was extracted with diethyl ether (2×10 mL). NaHCO₃ was added to the aqueous solution to neutralize the acid. The resulting mixture was extracted with diethyl ether (3×10 mL). The organic phase was dried over MgSO₄ and filtered. A solution of 2 M HCl in diethyl ether was added to the residue. The precipitated hydrochloride salt was filtered and washed with diethyl ether. 0.95 g (5.60 mmol, 80%); white solid; m.p. 175–177 ºC; ¹H NMR (500 MHz, D₂O), δ: 4.12 (s, 4H), 2.80 (t, J=12.2 Hz, 4H); ¹³C NMR (126 MHz, D₂O), δ: 117.7 (t, J=76.0 Hz), 54.9, 43.5 (t, J=23.6 Hz), 28.7 (t, J=11.2 Hz); ¹⁹F NMR (376 MHz, D₂O), δ: -93.35 (p, J=12.2 Hz); HRMS (EI): C₆H₉NF₂ (M⁺), calc. 133.0698, found 133.0698.

2-Tosyl-2-azaspiro[3.3]heptan-6-ol 17. NaBH₄ (3.00 g, 79.15 mmol) was added portionwise to a mixture of 14 (20.00 g, 75.38 mmol) in propan-2-ol (250 mL) at 5 ºC. The reaction mixture was stirred overnight at ambient temperature and evaporated. The resulting solid was dissolved in a mixture of EtOAc–water (200 mL/200 mL). The organic phase was separated, dried over Na₂SO₄, filtered, and evaporated. The crude product was recrystallized from a mixture of EtOAc-Hexane to yield 19.52 g (73.02 mmol, 97%) of compound 17. White solid; m.p. 99 –101 ºC; ¹H NMR (500 MHz, CDCl₃), δ: 7.65 (d, J=7.5 Hz, 2H), 7.34 (d, J=7.5 Hz, 2H), 4.08–3.96 (m, 1H), 3.65 (d, J=5.6 Hz, 4H), 2.49 (s, 1H), 2.43 (s, 3H), 2.32–2.20 (m, 2H), 1.93–1.82 (m, 2H); ¹³C NMR (126 MHz, CDCl₃), δ: 144.3, 131.2, 129.8, 128.3, 62.5, 62.0, 61.4, 43.3, 29.6, 21.7; HRMS (EI, +3NBA): C₁₃H₁₈O₃NS (MH⁺), calc. 268.1002, found 268.1003.

6-Fluoro-2-tosyl-2-azaspiro[3.3]heptane 18. Methanesulfonyl chloride (2.67 g, 23.34 mmol) was added dropwise to a cooled solution of compound 17 (5.20 g, 19.45 mmol) and triethylamine (5.40 mL, 38.74 mmol) in DCM (100 mL) under Ar at -30 ºC. The reaction mixture was allowed to warm to the ambient temperature, washed with water, aq. NaHCO₃, dried over Na₂SO₄, filtered, and evaporated. The crude mesylate was dissolved THF (50 mL), and a solution of TBAF in THF (1 M, 100.00 mL, 0.1 mol) was added. The reaction mixture was heated at reflux under Ar for 3 h, cooled to ambient temperature, diluted with EtOAc (250 mL), and washed with water. The organic phase was dried over Na₂SO₄, filtered, and evaporated to give a crude mixture of compound 18 and corresponding alkene at about 3: 2 ratio (according to NMR). Separation of compounds by column chromatography (Hexane:EtOAc=3:1) yielded alkene (eluted first) (1.72 g, 6.82 mmol, 35%) and compound 18 (eluted second) (2.63 g, 9.77 mmol, 50%). 2-Tosyl-2-azaspiro[3.3]hept-5-ene: White solid; m.p. 95–97 ºC; TLC: Rf=0.51 (Hexane:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃), δ: 7.73 (d, J=8.0 Hz, 2H), 7.37 (d, J=7.7 Hz, 2H), 6.05 (s, 1H), 5.82 (s, 1H), 3.90 (d, J=8.3 Hz, 2H), 3.84 (d, J=8.4 Hz, 2H), 2.54 (s, 2H), 2.46 (s, 3H); ¹³C NMR (126 MHz, CDCl₃), δ: 144.1, 138.1, 131.6, 129.8, 128.5, 58.5, 44.4, 42.9, 21.7; HRMS (EI, +3NBA): C₁₃H₁₆O₂NS (MH⁺), calc. 250.0896, found 250.0898.

6-Fluoro-2-tosyl-2-azaspiro[3.3]heptane 18. Methanesulfonyl chloride (2.67 g, 23.34 mmol) was added dropwise to a cooled solution of compound 17 (5.20 g, 19.45 mmol) and triethylamine (5.40 mL, 38.74 mmol) in DCM (100 mL) under Ar at -30 ºC. The reaction mixture was allowed to warm to the ambient temperature, washed with water, aq. NaHCO₃, dried over Na₂SO₄, filtered, and evaporated. The crude mesylate was dissolved THF (50 mL), and a solution of TBAF in THF (1 M, 100.00 mL, 0.1 mol) was added. The reaction mixture was heated at reflux under Ar for 3 h, cooled to ambient temperature, diluted with EtOAc (250 mL), and washed with water. The organic phase was dried over Na₂SO₄, filtered, and evaporated to give a crude mixture of compound 18 and corresponding alkene at about 3: 2 ratio (according to NMR). Separation of compounds by column chromatography (Hexane:EtOAc=3:1) yielded alkene (eluted first) (1.72 g, 6.82 mmol, 35%) and compound 18 (eluted second) (2.63 g, 9.77 mmol, 50%). 2-Tosyl-2-azaspiro[3.3]hept-5-ene: White solid; m.p. 95–97 ºC; TLC: Rf=0.51 (Hexane:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃), δ: 7.73 (d, J=8.0 Hz, 2H), 7.37 (d, J=7.7 Hz, 2H), 6.05 (s, 1H), 5.82 (s, 1H), 3.90 (d, J=8.3 Hz, 2H), 3.84 (d, J=8.4 Hz, 2H), 2.54 (s, 2H), 2.46 (s, 3H); ¹³C NMR (126 MHz, CDCl₃), δ: 144.1, 138.1, 131.6, 129.8, 128.5, 58.5, 44.4, 42.9, 21.7; HRMS (EI, +3NBA): C₁₃H₁₆O₂NS (MH⁺), calc. 250.0896, found 250.0898.

6-Fluoro-2-tosyl-2-azaspiro[3.3]heptan-2-ium chloride 19. Compound 19 (1.08 g, 7.12 mmol, 78%) was obtained from 18 (2.47 g, 9.17 mmol) analogously to 16. White solid; m.p. 107–110 ºC; TLC: Rf=0.36 (Hexane:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃), δ: 7.69 (d, J=8.1 Hz, 2H), 7.36 (d, J=7.9 Hz, 2H), 4.92–4.68 (m, 1H), 3.74 (s, 2H), 3.70 (s, 2H), 2.44 (s, 3H), 2.42–2.33 (m, 2H), 2.27–2.12 (m, 2H); ¹³C NMR (126 MHz, CDCl₃), δ: 144.3, 131.4, 129.8, 128.4, 82.8 (d, J=211.6 Hz), 61.7 (d, J=56.2 Hz), 41.3 (d, J=21.2 Hz), 29.4 (d, J=16.4 Hz), 21.7. ¹⁹F NMR (376 MHz, CDCl₃), δ: -170.14–-170.57 (m); HRMS (EI, +3NBA): C₁₃H₁₀O₂NFS (MH⁺), calc. 270.0959, found 270.0960.
**X-Ray diffraction:** For compound 5 data sets were collected with a Bruker APEX II Kappa CCD diffractometer. For compound 19 data sets were collected with a D8 Venture Dual Source 100 CMOS diffractometer. Programs used: data collection: APEX2 V2014.5-0 (Bruker AXS Inc., 2014); cell refinement: SAINT V8.34A (Bruker AXS Inc., 2013); data reduction: SAINT V8.34A (Bruker AXS Inc., 2013); absorption correction, SADABS V2014/2 (Bruker AXS Inc., 2014); structure solution SHELXT-2014 (Sheldrick, 2014); structure refinement SHELXL-2014 (Sheldrick, 2014) and graphics, XP (Bruker AXS Inc., 2014). Data sets for the compound 15 were collected with a Nonius Kappa CCD diffractometer. Programs used: data collection, COLLECT (R. W. W. Hooft, Bruker AXS, 2008, Delft, The Netherlands); data reduction Denzo-SMN (Z. Otwinowski, W. Minor, Methods Enzymol. 1997, 276, 307-326); absorption correction, Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, Acta Crystallogr. 2003, A59, 228-234); structure solution SHELXS-97 (G. M. Sheldrick, Acta Crystallogr. 1990, A46, 467-473); structure refinement SHELXL -97 (G. M. Sheldrick, Acta Crystallogr. 2008, A64, 112-122) and graphics, XP (BrukerAXS, 2000). R-values are given for observed reflections, and wR2 values are given for all reflections.

** Exceptions and special features:** For compound 5 one CF3 group and for compound 15 two fluorine atoms and one methyl group were found disordered over two positions. Several restraints (SADI, SAME, ISOR and SIMU) were used in order to improve refinement stability. Compound 19 present one four membered-ring partial disordered over two positions (CH-F unit). Several restraints (SADI, SAME, ISOR and SIMU) were used in order to improve refinement stability of the compound.

**X-ray crystal structure analysis of 5 (haf7984):** formula C8H10F5NO2, M = 247.17, colourless crystal, 0.30 x 0.18 x 0.18 mm, a = 14.9508(4), b = 10.9720(3), c = 12.4040(3) Å, β = 104.767(1) °, V = 1967.5(1) Å3, ρcalc = 1.669 gcm−3, μ = 1.625 mm−1, empirical absorption correction (0.641 ≤ T ≤ 0.759), Z = 8, monoclinic, space group P21/c (No. 14), λ = 1.54178 Å, T = 100(2) K, ω and φ scans, 35737 reflections collected (±h, ±k, ±l), 3537 independent (Rint = 0.041) and 3138 observed reflections [I >2σ(I)], 333 refined parameters, R = 0.033, wR2 = 0.093, max. (min.) residual electron density 0.29 (-0.19) e.Å−3. The hydrogen atoms at N1A and N1B were refined freely others were calculated and refined as riding atoms.

**X-ray crystal structure analysis of 15 (haf7982):** formula C13H15F2NO2S, M = 287.32, pale yellow crystal, 0.12 x 0.12 x 0.05 mm, a = 5.7810(2), b = 11.2525(3), c = 12.1297(3) Å, α = 62.437(2), β = 79.960(1), γ = 76.786(2)°, V = 678.8(1) Å3, ρcalc = 1.406 gcm−3, μ = 0.259 mm−1, empirical absorption correction (0.969 ≤ T ≤ 0.987), Z = 2, triclinic, space group P21 (No. 2), λ = 0.71073 Å, T = 223(2) K, ω and φ scans, 6835 reflections collected (±h, ±k, ±l), 2305 independent (Rint = 0.047) and 2019 observed reflections [I >2σ(I)], 203 refined parameters, R = 0.054, wR2 = 0.132, max. (min.) residual electron density 0.21 (-0.36) e.Å−3, hydrogen atoms were calculated and refined as riding atoms.

**X-ray crystal structure analysis of 19 (haf7910):** formula C6H11ClFN, M = 151.61, colourless crystal, 0.26 x 0.11 x 0.10 mm, a = 11.0759(4), b = 10.3228(3), c = 13.2018(5) Å, V = 1509.4(1) Å3, ρcalc = 1.334 gcm−3, μ = 0.437 mm−1, empirical absorption correction (0.892 ≤ T ≤ 0.955), Z = 8, orthorhombic, space group Pbcα (No. 61), λ = 0.71073 Å, T = 102(2) K, ω and φ scans, 17440 reflections collected (±h, ±k, ±l), 1378 independent (Rint = 0.035) and 1247 observed reflections [I>2σ(I)], 100 refined parameters, R = 0.026, wR2 = 0.069, max. (min.) residual electron density 0.29 (-0.23) e.Å−3. The hydrogens at N1 atom were refined freely; others were calculated and refined as riding atoms.
Figure xx. Crystal structure of compound 5.
Thermals ellipsoids are shown with 30% probability.

Figure xx. Crystal structure of compound 15.
Thermals ellipsoids are shown with 15% probability.

Figure xx. Crystal structure of compound 19.
Thermals ellipsoids are shown with 30% probability.