Supporting Information

Photochemical Selective Difluoroalkylation reactions of Bicyclobutanes: Direct Sustainable Pathways to Functionalized Bioisosteres for Drug Discovery

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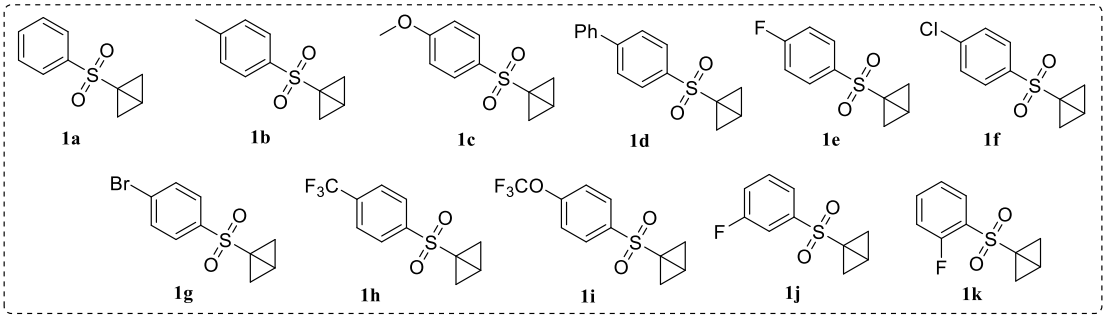
Contents

1. General information

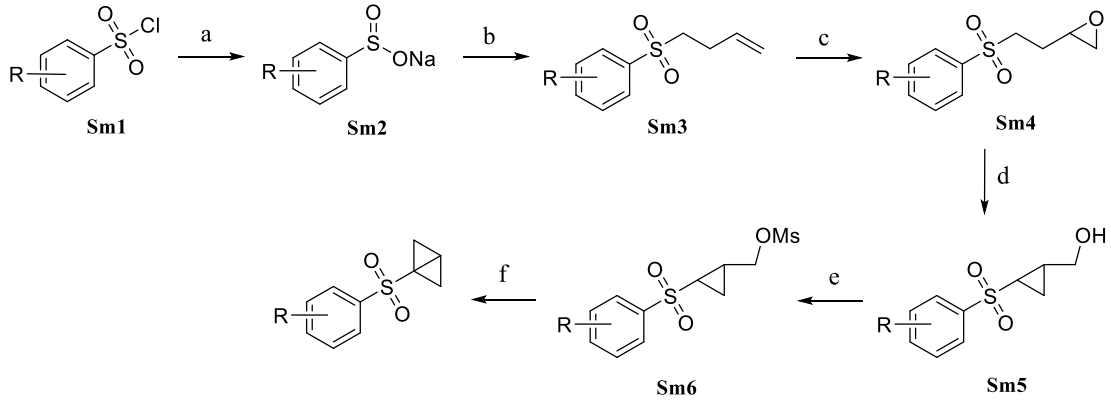
Unless otherwise noted, all reactants or reagents including dry solvents were obtained from commercial suppliers and used as received. All the reactions were conducted using reaction tube (10 mL). The reactions were performed under nitrogen atmosphere. Blue LEDs (25W, equipped with a thermotank) was used as light source. Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F25 plates. Column chromatograph was performed on silica gel 200~300 mesh. ^{1}H, ^{19}F and ^{13}C NMR spectra were obtained in $CDCl_3$, acetone-d_6, or DMSO-d_6 using 300 MHz, 400 MHz Varian NMR spectrometer. Chemical shifts in ^{1}H NMR and ^{19}F NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CDCl_3$ (7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant in Hertz (Hz). Chemical shifts in ^{13}C NMR spectra are reported in ppm on the δ scale from the central peak of residual $CDCl_3$ (77.16 ppm). High resolution mass spectrometry (HRMS) was recorded on TOF premier for ESI^{+}.

2. General procedures for the synthesis of substrates and products

2.1 Preparation of bicyclo[1.1.0]butane compounds



Scheme S1. Synthesis of bicyclo[1.1.0]butane compounds **1a-1k** [a]



[a] *Reagents and conditions*: (a) Na_2SO_3, $NaHCO_3$, H_2O, 80 °C, 12 h; (b) 4-bromo-1-butene, DMF,

60 °C, 12 h; (c) Oxone, $NaHCO_3$, acetone/H_2O, rt, 12 h; (d) *n*-BuLi, anhydrous THF, 0 °C; (e) MsCl, TEA, DCM, 0 °C to rt, 12 h; (f) *n*-BuLi, anhydrous THF, 0 °C.

The preparations of bicyclo[1.1.0]butane compounds **1a-1k** were outlined in **Scheme S1** according to the procedure disclosed by Baran et al.[1]

Step a: To a solution of **Sm1** (19.2 mmol, 1.0 equiv.), and Na_2SO_3 (38.4 mmol, 2.0 equiv.) in H_2O (60 mL) was slowly added $NaHCO_3$ (38.4 mmol, 2.0 equiv.). The reaction mixture was stirred at 80 °C for 12 h then cooled to room temperature and concentrated under reduced pressure. The crude product was obtained by drying for couple hours and could be used directly in the next step without further purification.

Step b: To a solution of **Sm2** (14.4 mmol, 1.0 equiv.) in DMF (60 mL) was slowly added 4-bromo-1-butene (28.8 mmol, 2.0 equiv.). The reaction was stirred at 60 °C for 12 h then cooled to room temperature. The mixture was extracted by EtOAc (100 mL x 3) and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (30:1 to 20:1, v/v) as eluents furnishing the desired product.

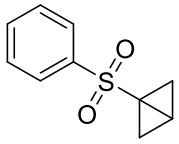
Step c: To a solution of **Sm3** (11.5 mmol, 1.0 equiv.), and Oxone (17.3 mmol, 1.5 equiv.) in acetone (50 mL) and H_2O (50 mL) was slowly added $NaHCO_3$ (57.5 mmol, 5.0 equiv.). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was evaporated to remove acetone then extracted by EtOAc (50 mL x 3) and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (6:1 to 4:1, v/v) as eluents furnishing the desired product.

Step d: To a solution of **Sm4** (5 mmol, 1.0 equiv.) in anhydrous THF (30 mL) was dropwise added *n*-BuLi (2.5 M in hexane, 2.2 mL, 1.1 equiv.) in an ice/water bath. The reaction mixture was stirred at 0 °C for 15 min under a nitrogen atmosphere then quenched with saturated NH_4Cl solution. The mixture was extracted by EtOAc (50 mL x 3) and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (5:1 to 3:1, v/v) as eluents furnishing the desired product.

Step e: To a solution of **Sm5** (5 mmol, 1.0 equiv.), and TEA (10 mmol, 2.0 equiv.) in DCM (30 mL) was dropwise added MsCl (7.5 mmol, 1.5 equiv.) in an ice/water bath. The reaction was stirred at room temperature for 12 h. The mixture was extracted by DCM (50 mL x 3) and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (3:1 to 1:1, v/v) as eluents furnishing the desired product.

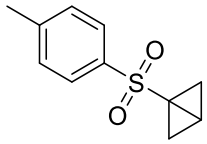
Step f: To a solution of **Sm6** (1 mmol, 1.0 equiv.) in anhydrous THF (20 mL) was dropwise added *n*-BuLi (2.5 M in hexane, 0.44 mL, 1.1 equiv.) in an ice/water bath. The reaction mixture was stirred at 0 °C for 15 min under a nitrogen atmosphere then quenched with saturated NH_4Cl solution. The mixture was extracted by EtOAc (50 mL x 3) and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (20:1 to 10:1, v/v) as eluents furnishing the desired product.

1-(phenylsulfonyl)bicyclo[1.1.0]butane (1a)



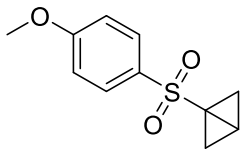
White solid. Yield: 44 %. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.95 – 7.87 (m, 2H), 7.78 – 7.71 (m, 1H), 7.71 – 7.63 (m, 2H), 2.87 – 2.78 (m, 1H), 2.40 – 2.30 (m, 2H), 1.46 – 1.37 (m, 2H). The spectroscopic data of **1a** was consistent with previously reported data.[2]

1-tosylbicyclo[1.1.0]butane (1b)



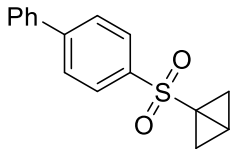
White solid. Yield: 54 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 2.54 – 2.47 (m, 3H), 2.44 (s, 3H), 1.37 – 1.34 (m, 2H). The spectroscopic data of **1b** was consistent with previously reported data.[2]

1-((4-methoxyphenyl)sulfonyl)bicyclo[1.1.0]butane (1c)



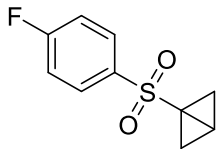
White solid. Yield: 58 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 2.48 (s, 3H), 1.35 (s, 2H). The spectroscopic data of **1c** was consistent with previously reported data.[2]

1-([1,1'-biphenyl]-4-ylsulfonyl)bicyclo[1.1.0]butane (1d)



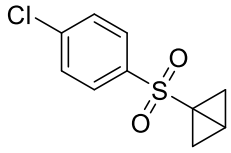
White solid. Yield: 60 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.65 – 7.59 (m, 2H), 7.53 – 7.39 (m, 3H), 2.63 – 2.58 (m, 1H), 2.56 (d, *J* = 3.3 Hz, 2H), 1.42 (d, *J* = 2.7 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 144.9, 140.1, 138.4, 129.2, 128.7, 127.8, 127.5, 127.2, 37.7, 22.9, 12.3. **HRMS** (ESI) for $C_{16}H_{15}O_2S$ $[M + H]^+$, calcd: 271.0787, found: 271.0791.

1-((4-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane (1e)



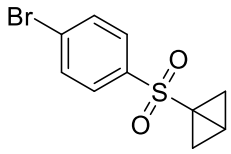
White solid. Yield: 56 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 2.68 – 2.62 (m, 1H), 2.57 (d, *J* = 3.6 Hz, 2H), 1.45 (d, *J* = 2.8 Hz, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -104.71. The spectroscopic data of **1e** was consistent with previously reported data.[2]

1-((4-chlorophenyl)sulfonyl)bicyclo[1.1.0]butane (1f)



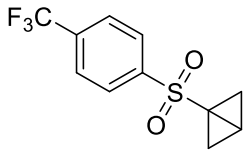
White solid. Yield: 52 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 2.65 – 2.58 (m, 1H), 2.52 (d, *J* = 3.9 Hz, 2H), 1.40 (s, 2H). The spectroscopic data of **1f** was consistent with previously reported data.[2]

1-((4-bromophenyl)sulfonyl)bicyclo[1.1.0]butane (1g)



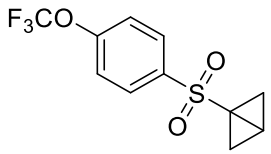
White solid. Yield: 40 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 2.66 – 2.58 (m, 1H), 2.52 (d, *J* = 3.6 Hz, 2H), 1.40 (s, 2H). The spectroscopic data of **1g** was consistent with previously reported data.[3]

1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[1.1.0]butane (1h)



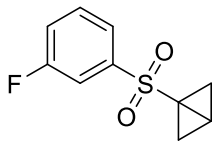
White solid. Yield: 60 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 2.72 – 2.65 (m, 1H), 2.55 (d, *J* = 3.8 Hz, 2H), 1.43 (d, *J* = 2.8 Hz, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -63.11. The spectroscopic data of **1h** was consistent with previously reported data.[2]

1-((4-(trifluoromethoxy)phenyl)sulfonyl)bicyclo[1.1.0]butane (1i)



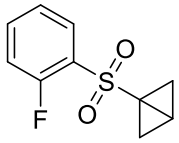
White solid. Yield: 54 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 – 7.96 (m, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 2.68 – 2.61 (m, 1H), 2.54 (d, *J* = 3.7 Hz, 2H), 1.42 (d, *J* = 2.8 Hz, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -57.68. The spectroscopic data of **1i** was consistent with previously reported data.[2]

1-((3-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane (1j)



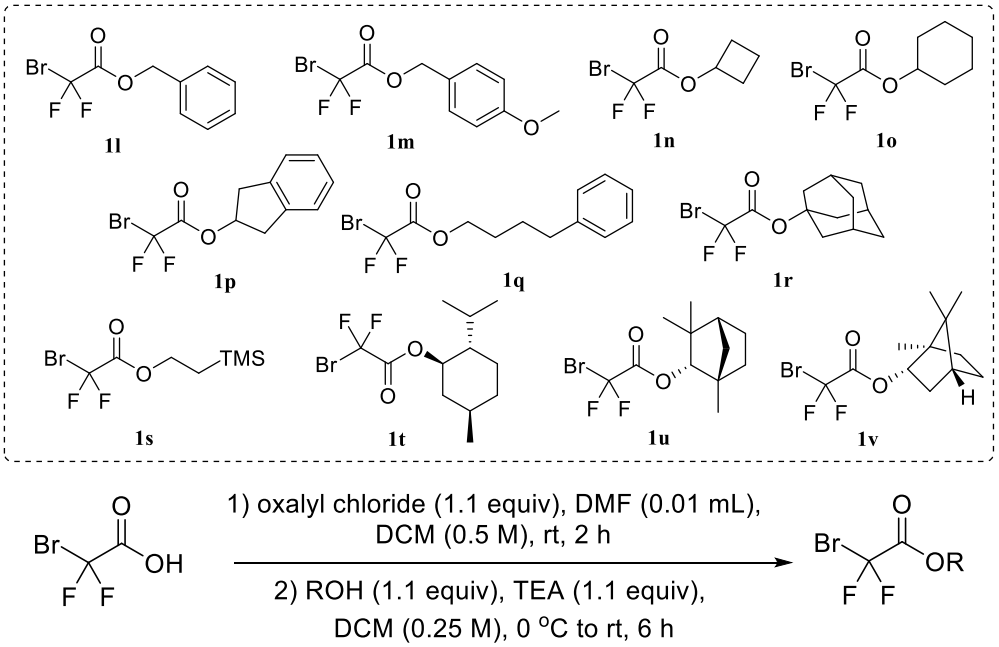
White solid. Yield: 42 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 1H), 7.67 – 7.61 (m, 1H), 7.59 – 7.51 (m, 1H), 7.36 – 7.28 (m, 1H), 2.66 – 2.60 (m, 1H), 2.53 (d, *J* = 3.8 Hz, 2H), 1.42 (d, *J* = 2.8 Hz, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -109.52. The spectroscopic data of **1j** was consistent with previously reported data.[2]

1-((2-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane (1k)



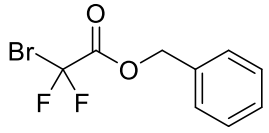
White solid. Yield: 35 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 1H), 7.67 – 7.57 (m, 1H), 7.36 – 7.20 (m, 2H), 2.71 – 2.64 (m, 1H), 2.60 (d, *J* = 4.7 Hz, 2H), 1.46 (d, *J* = 5.0 Hz, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.49. The spectroscopic data of **1k** was consistent with previously reported data.[3]

2.2 Preparation of 2-bromo-2,2-difluoroacetates



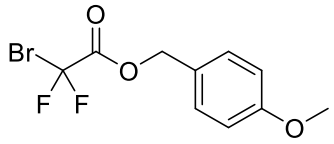
To a 2-bromo-2,2-difluoroacetic acid (5.00 mmol, 1.00 equiv.) in DCM (10.0 mL, 0.50 M) was slowly added oxalyl chloride (5.50 mmol, 1.10 equiv.) and DMF (0.01 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h then cooled to 0 °C, and then a mixture of ROH (5.50 mmol, 1.1 equiv.) and TEA (5.50 mmol, 1.10 equiv.) dissolved in DCM was added dropwise. The reaction mixture stirred at room temperature for 6 h then quenched with saturated $NaHCO_3$ solution, extracted with DCM (25 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (100:1, v/v) as eluents furnishing the desired product.

benzyl 2-bromo-2,2-difluoroacetate (1l)



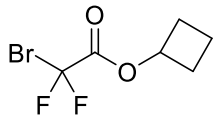
Colorless oil. Yield: 72 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (s, 5H), 5.37 (s, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.74. The spectroscopic data of **1l** was consistent with previously reported data.[4]

4-methoxybenzyl 2-bromo-2,2-difluoroacetate (1m)



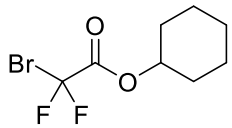
Colorless oil. Yield: 65 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.30 (s, 2H), 3.82 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.5, 159.6 (t, $^{2}J_{C\text{-}F}$ = 31.5 Hz), 130.8, 125.6, 114.3, 108.9 (t, $^{1}J_{C\text{-}F}$ = 312.8 Hz), 69.9, 55.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.75. **HRMS** (ESI) for $C_{10}H_{10}BrF_2O_3$ $[M + H]^+$, calcd: 294.9775, found: 294.9780.

cyclobutyl 2-bromo-2,2-difluoroacetate (1n)



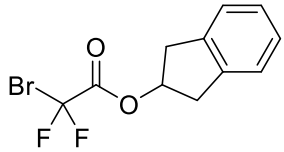
Colorless oil. Yield: 80 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.23 – 5.10 (m, 1H), 2.52 – 2.38 (m, 2H), 2.33 – 2.14 (m, 2H), 1.98 – 1.83 (m, 1H), 1.78 – 1.60 (m, 1H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.99. The spectroscopic data of **1n** was consistent with previously reported data.[4]

cyclohexyl 2-bromo-2,2-difluoroacetate (1o)



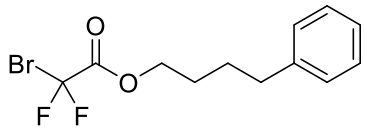
Colorless oil. Yield: 80 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.03 – 4.91 (m, 1H), 1.97 – 1.85 (m, 2H), 1.84 – 1.70 (m, 2H), 1.66 – 1.50 (m, 3H), 1.49 – 1.28 (m, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.92. The spectroscopic data of **1o** was consistent with previously reported data.[4]

2,3-dihydro-1*H*-inden-2-yl 2-bromo-2,2-difluoroacetate (1p)



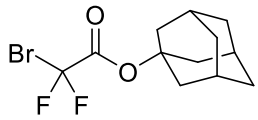
White solid. Yield: 72 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 4H), 5.74 (tt, *J* = 6.4, 3.0 Hz, 1H), 3.45 (dd, *J* = 17.3, 6.5 Hz, 2H), 3.17 (dd, *J* = 17.3, 3.0 Hz, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -61.03. The spectroscopic data of **1p** was consistent with previously reported data.[5]

4-phenylbutyl 2-bromo-2,2-difluoroacetate (1q)



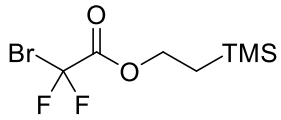
Colorless oil. Yield: 73 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.25 – 7.17 (m, 3H), 4.38 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 1.87 – 1.70 (m, 4H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.70. The spectroscopic data of **1q** was consistent with previously reported data.[6]

(*3s*,*5s*,*7s*)-adamantan-1-yl 2-bromo-2,2-difluoroacetate (1r)



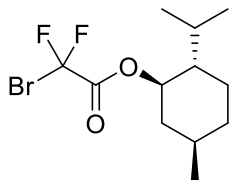
Colorless oil. Yield: 67 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.20 – 2.15 (m, 6H), 1.72 – 1.66 (m, 6H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.86. The spectroscopic data of **1r** was consistent with previously reported data.[4]

2-(trimethylsilyl)ethyl 2-bromo-2,2-difluoroacetate (1s)



Colorless oil. Yield: 58 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.49 – 4.39 (m, 2H), 1.18 – 1.08 (m, 2H), 0.08 (s, 9H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.74. The spectroscopic data of **1s** was consistent with previously reported data.[4]

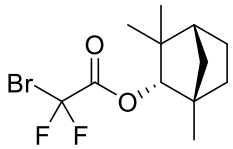
(*1R*,*2S*,*5R*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2,2-difluoroacetate (1t)



Colorless oil. Yield: 73 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.90 – 4.78 (m, 1H), 2.11 – 2.01 (m, 1H), 1.98 – 1.86 (m, 1H), 1.79 – 1.66 (m, 2H), 1.61 – 1.44 (m, 2H), 1.20 – 1.00 (m, 2H), 0.98 – 0.87 (m, 7H), 0.78 (d, *J* = 7.0 Hz, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.88 (d, *J* = 5.6 Hz). The

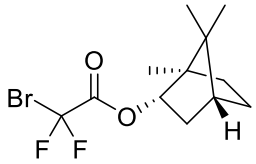
spectroscopic data of **1t** was consistent with previously reported data.[4]

(*1S*,*2S*,*4R*)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl 2-bromo-2,2-difluoroacetate (1u)



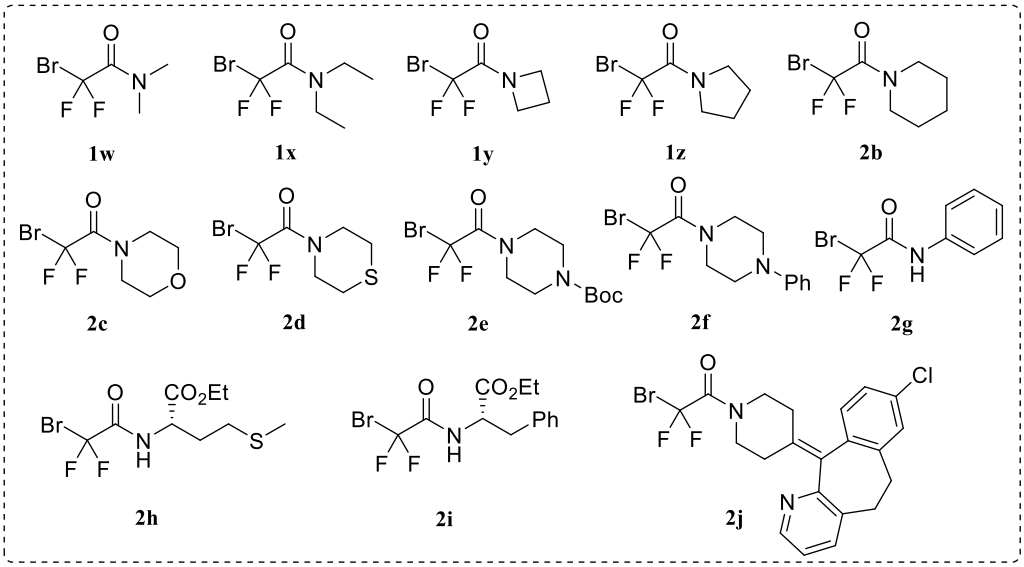
Colorless oil. Yield: 70 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.50 (d, *J* = 2.0 Hz, 1H), 1.83 – 1.68 (m, 3H), 1.62 (d, *J* = 8.3 Hz, 1H), 1.57 – 1.43 (m, 1H), 1.30 – 1.12 (m, 5H), 1.10 (s, 3H), 0.86 (s, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.19 (d, *J* = 9.2 Hz). The spectroscopic data of **1u** was consistent with previously reported data.[5]

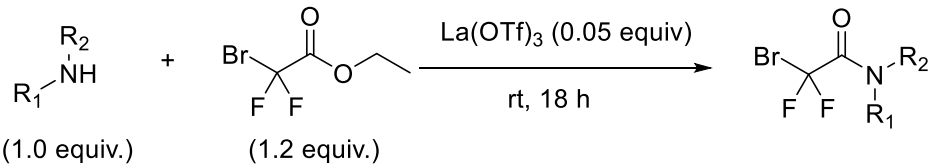
(*1R*,*2R*,*4R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-bromo-2,2-difluoroacetate (1v)



Colorless oil. Yield: 65 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.83 (t, *J* = 5.7 Hz, 1H), 1.91 – 1.67 (m, 4H), 1.66 – 1.55 (m, 1H), 1.22 – 1.06 (m, 2H), 0.99 (s, 3H), 0.92 (s, 3H), 0.86 (s, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.75 (d, *J* = 3.1 Hz). The spectroscopic data of **1v** was consistent with previously reported data.[7]

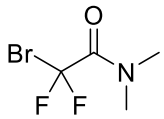
2.3 Preparation of 2-bromo-2,2-difluoroacetamides





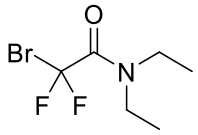
To a solution of ethyl 2-bromo-2,2-difluoroacetate (1.2 mmol, 1.2 equiv.), and amine (1.0 mmol, 1.0 equiv.) was slowly added $La(OTf)_3$ (0.05 mmol, 0.05 equiv.). The reaction was stirred at room temperature for 18 h, and was extracted by EtOAc (25 mL x 3) and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (50:1, v/v) as eluents furnishing the desired product.

2-bromo-2,2-difluoro-*N*,*N*-dimethylacetamide (1w)



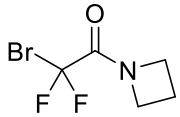
Colorless oil. Yield: 75 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.04 (s, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -54.38. The spectroscopic data of **1w** was consistent with previously reported data.[8]

2-bromo-*N*,*N*-diethyl-2,2-difluoroacetamide (1x)



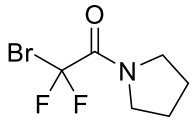
Colorless oil. Yield: 81 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.52 (q, J = 7.1 Hz, 2H), 3.42 (q, J = 7.1 Hz, 2H), 1.28 – 1.14 (m, 6H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -54.12. The spectroscopic data of **1x** was consistent with previously reported data.[8]

1-(azetidin-1-yl)-2-bromo-2,2-difluoroethan-1-one (1y)



Colorless oil. Yield: 70 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.44 – 4.32 (m, 2H), 4.20 – 4.08 (m, 2H), 2.47 – 2.31 (m, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -57.88. The spectroscopic data of **1y** was consistent with previously reported data.[8]

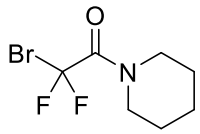
2-bromo-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-one (1z)



Colorless oil. Yield: 80 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.58 (dd, J = 25.9, 7.0 Hz, 4H), 1.93 (dd, J = 33.6, 6.8 Hz, 4H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -56.85. The spectroscopic data of **1z** was

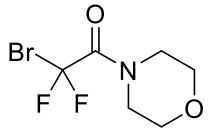
consistent with previously reported data.[8]

2-bromo-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (2b)



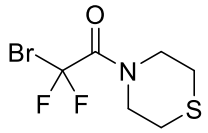
Colorless oil. Yield: 80 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.64 – 3.53 (m, 4H), 1.72 – 1.55 (m, 6H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -53.89. The spectroscopic data of **2b** was consistent with previously reported data.[9]

2-bromo-2,2-difluoro-1-morpholinoethan-1-one (2c)



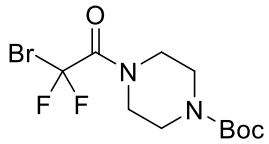
Colorless oil. Yield: 80 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.78 – 3.65 (m, 8H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -54.52. The spectroscopic data of **2c** was consistent with previously reported data.[8]

2-bromo-2,2-difluoro-1-thiomorpholinoethan-1-one (2d)



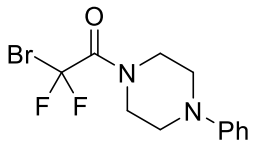
Colorless oil. Yield: 77 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.97 – 3.87 (m, 4H), 2.75 – 2.64 (m, 4H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -54.10. The spectroscopic data of **2d** was consistent with previously reported data.[8]

tert-butyl 4-(2-bromo-2,2-difluoroacetyl)piperazine-1-carboxylate (2e)



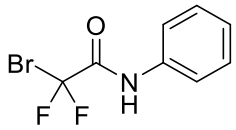
White solid. Yield: 74 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.71 – 3.62 (m, 4H), 3.56 – 3.47 (m, 4H), 1.47 (s, 9H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -54.38. The spectroscopic data of **2e** was consistent with previously reported data.[9]

2-bromo-2,2-difluoro-1-(4-phenylpiperazin-1-yl)ethan-1-one (2f)



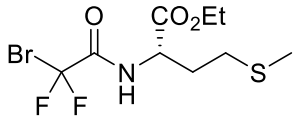
White solid. Yield: 74 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 6.98 – 6.91 (m, 3H), 3.90 – 3.82 (m, 4H), 3.29 – 3.21 (m, 4H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -54.20. The spectroscopic data of **2f** was consistent with previously reported data.[10]

2-bromo-2,2-difluoro-*N*-phenylacetamide (2g)



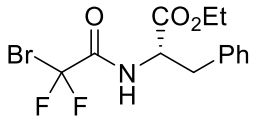
White solid. Yield: 60 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.61 – 7.54 (m, 2H), 7.44 – 7.36 (m, 2H), 7.28 – 7.20 (m, 1H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.61. The spectroscopic data of **2g** was consistent with previously reported data.[8]

ethyl (2-bromo-2,2-difluoroacetyl)-*L*-methioninate (2h)



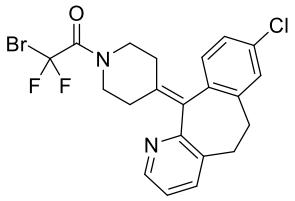
Colorless oil. Yield: 78 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 1H), 4.70 – 4.58 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.53 – 2.44 (m, 2H), 2.27 – 2.13 (m, 1H), 2.12 – 1.98 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.5, 159.7 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 111.2 (t, $^1J_{C\text{-}F}$ = 313.5 Hz), 62.2, 52.1, 30.7, 29.7, 15.3, 14.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -61.01. **HRMS** (ESI) for $C_9H_{15}BrF_2NO_3S$ $[M + H]^+$, calcd: 333.9916, found: 333.9924.

ethyl (2-bromo-2,2-difluoroacetyl)-*L*-phenylalaninate (2i)



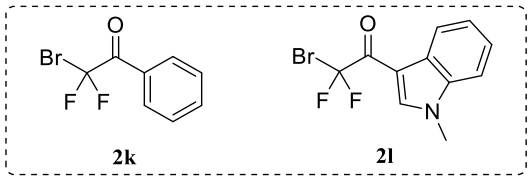
White solid. Yield: 75 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H), 7.15 – 7.07 (m, 2H), 6.77 – 6.63 (m, 1H), 4.89 – 4.78 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.30 – 3.13 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -60.82. The spectroscopic data of **2i** was consistent with previously reported data.[7]

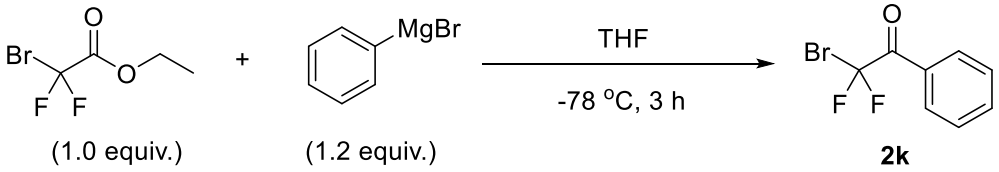
2-bromo-1-(4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene) piperidin-1-yl)-2,2-difluoroethan-1-one (2j)



White solid. Yield: 70 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 – 8.39 (m, 1H), 7.55 – 7.44 (m, 1H), 7.22 – 7.10 (m, 4H), 4.15 – 3.86 (m, 2H), 3.55 – 3.26 (m, 4H), 2.96 – 2.37 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 156.5, 146.7, 139.6, 137.9, 137.4, 135.5, 135.4, 133.4, 133.3, 130.3, 129.1, 126.3, 122.5, 110.7 (t, $^{1}J_{C\text{-}F}$ = 316.6 Hz), 47.2, 45.0, 31.6, 31.5, 30.7, 29.9. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -54.11. **HRMS** (ESI) for $C_{21}H_{19}BrClF_2N_2O$ $[M + H]^+$, calcd: 467.0331, found: 467.0341.

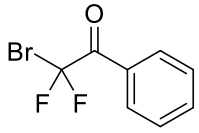
2.4 Preparation of 2-bromo-2,2-difluoroketones





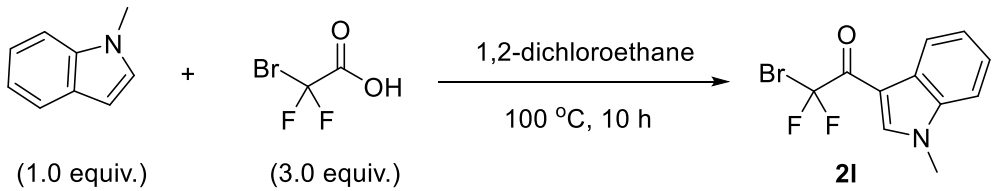
To a solution of ethyl 2-bromo-2,2-difluoroacetate (1.0 mmol, 1.0 equiv.) in anhydrous THF (10 mL) was dropwise added phenyl magnesium bromide (1.0 mol/l in THF, 1.2 mL, 1.2 equiv.) at -78 °C under nitrogen atmosphere. The reaction was stirred at -78 °C for 3 h and quenched with saturated NH_4Cl solution, extracted with EtOAc (25 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (100:1, v/v) as eluents furnishing the desired product.

2-bromo-2,2-difluoro-1-phenylethan-1-one (2k)



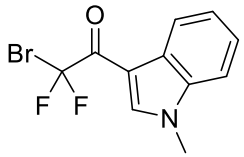
Colorless oil. Yield: 60 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.15 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 7.5 Hz, 1H), 7.58 – 7.49 (m, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -57.80. The spectroscopic data of **2k**

was consistent with previously reported data.[11]



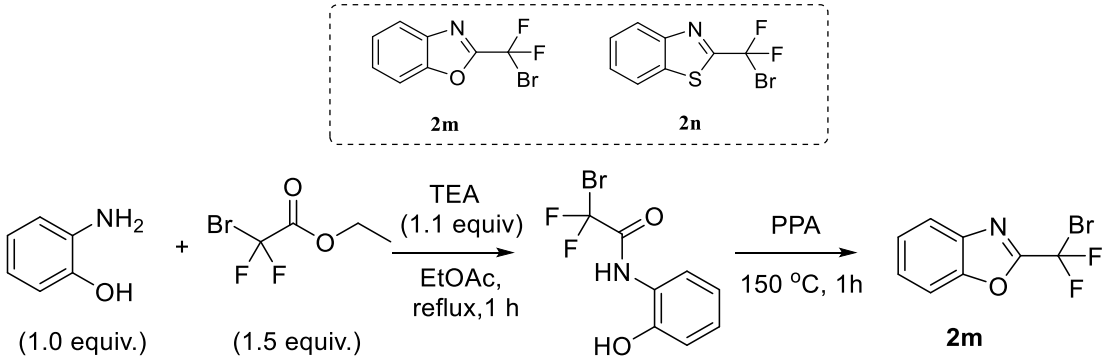
To a solution of 1-methyl-1*H*-indole (1.0 mmol, 1.0 equiv.) in 1,2-dichloroethane (30 mL) was added 2-bromo-2,2-difluoroacetic acid (3.0 mmol, 3.0 equiv.). The reaction was stirred at 100 °C for 10 h and cooled to room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with DCM (25 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (50:1, v/v) as eluents furnishing the desired product.

2-bromo-2,2-difluoro-1-(1-methyl-1*H*-indol-3-yl)ethan-1-one (2l)



Brown solid. Yield: 66 %. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 – 8.37 (m, 1H), 7.97 (s, 1H), 7.40 (d, *J* = 3.1 Hz, 3H), 3.92 (s, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -56.79. The spectroscopic data of **2l** was consistent with previously reported data.[12]

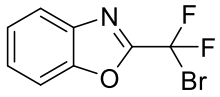
2.5 Preparation of bromodifluoromethyl substituted heterocycles



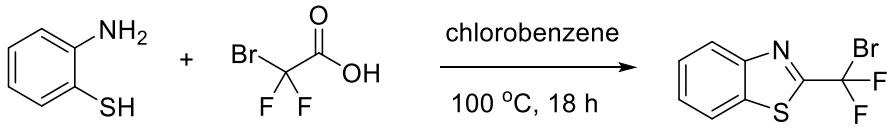
To a solution of 2-aminophenol (1.0 mmol, 1.0 equiv.), TEA (1.1 mmol, 1.1 equiv.) in EtOAc (10 mL) was added ethyl 2-bromo-2,2-difluoroacetate (1.5 mmol, 1.5 equiv.). The reaction was refluxed for 1 h and cooled to room temperature. The reaction mixture was extracted with EtOAc (25 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were

dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (10:1, v/v) as eluents furnishing the intermediate 2-bromo-2,2-difluoro-*N*-(2-hydroxyphenyl)acetamidet. Then placed the intermediate (2.08 g) and PPA (8.04 g) in a dry round-bottom flask. The reaction was stirred at 150 °C for 1 h and cooled to room temperature, then added moderate amount of ice and concentrated ammonia (6 mL, 30% $NH_3 \cdot H_2O$). The mixture was extracted with EtOAc (25 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (50:1, v/v) as eluents furnishing the desired product.

2-(bromodifluoromethyl)benzo[*d*]oxazole (2m)



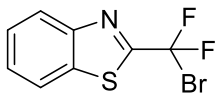
Colorless oil. Yield: 70%. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.01 – 7.91 (m, 2H), 7.68 – 7.61 (m, 1H), 7.60 – 7.52 (m, 1H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -51.42. The spectroscopic data of **2m** was consistent with previously reported data.[11]



(1.0 equiv.) (5.0 equiv.) **2n**

To the solution of 2-aminobenzenethiol (1.0 mmol, 1.0 equiv.) in chlorobenzene (10 mL) was added 2-bromo-2,2-difluoroacetic acid (5.0 mmol, 5.0 equiv.). The reaction mixture was stirred at 100 °C for 18 h, then cooled to room temperature and concentrated under reduced pressure. The mixture was extracted with EtOAc (25 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (50:1, v/v) as eluents furnishing the desired product.

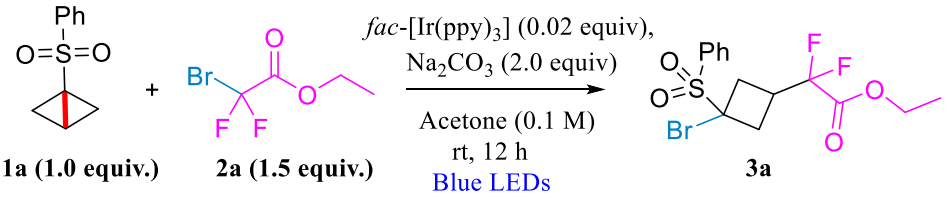
2-(bromodifluoromethyl)benzo[*d*]thiazole (2n)



Yellow oil. Yield: 75%. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.31 (dd, J = 7.3, 2.1 Hz, 1H), 8.23 (dd,

J = 7.5, 2.1 Hz, 1H), 7.74 – 7.62 (m, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -43.34. The spectroscopic data of **2n** was consistent with previously reported data.[11]

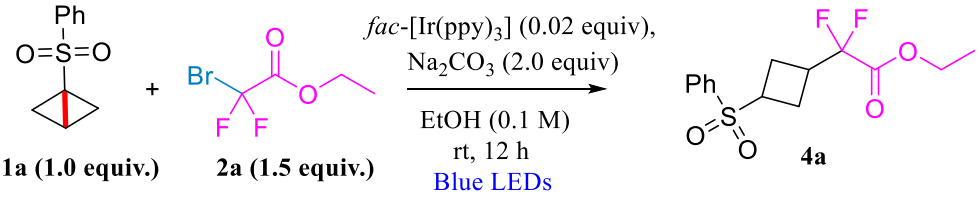
2.6 General procedure A for the synthesis of 3a



1a (1.0 equiv.) **2a (1.5 equiv.)** **3a**

A 10 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (0.2 mmol, 1.0 equiv.), Na_2CO_3 (0.4 mmol, 2.0 equiv.) and *fac*-[Ir(ppy)$_3$] (0.004 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (0.3 mmol, 1.5 equiv.) and anhydrous acetone (2.0 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 12 h. Upon completion of the reaction, the mixture was concentrated under vacuum and then extracted by ethyl acetate (10 mL) and washed with H_2O. The organic layers were concentrated and purified by silica gel column chromatography with petroleum ether/EtOAc (20:1, v/v) as eluents furnishing the product **3a**.

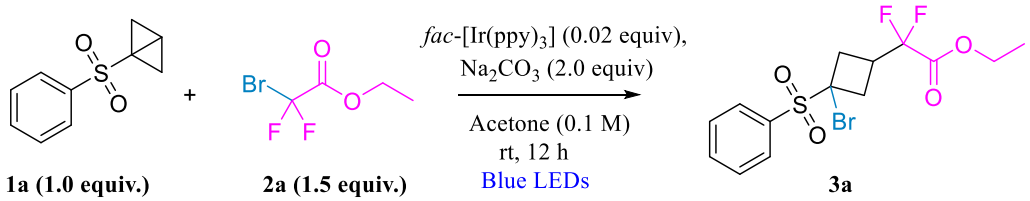
2.7 General procedure B for the synthesis of 4a



1a (1.0 equiv.) **2a (1.5 equiv.)** **4a**

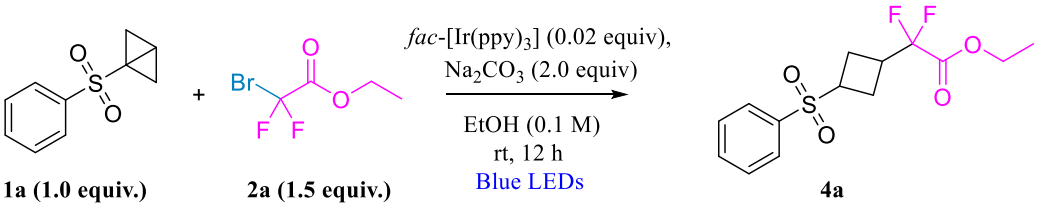
A 10 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (0.2 mmol, 1.0 equiv.), Na_2CO_3 (0.4 mmol, 2.0 equiv.) and *fac*-[Ir(ppy)$_3$] (0.004 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (0.3 mmol, 1.5 equiv.) and anhydrous EtOH (2.0 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 12 h. Upon completion of the reaction, the mixture was concentrated under vacuum and then extracted by ethyl acetate (10 mL) and washed with H_2O. The organic layers were concentrated and purified by silica gel column chromatography with petroleum ether/EtOAc (7:1, v/v) as eluents furnishing the product **4a**.

2.8 Gram-scale synthesis



1a (1.0 equiv.) **2a (1.5 equiv.)** **3a**

A 100 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (970 mg, 5 mmol, 1.0 equiv.), Na_2CO_3 (1.06 g, 10 mmol, 2.0 equiv.) and *fac*-[Ir(ppy)$_3$] (65 mg, 0.1 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (1.52 g, 7.5 mmol, 1.5 equiv.) and anhydrous acetone (50 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 12 h. Upon completion of the reaction, the mixture was concentrated under vacuum and then extracted by ethyl acetate (25 mL) and washed with H_2O. The organic layers were concentrated and purified by silica gel column chromatography with petroleum ether/EtOAc (20:1, v/v) as eluents furnishing the product **3a** (1.17 g, 59 % yield).

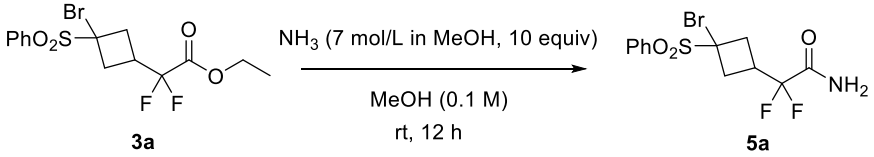


1a (1.0 equiv.) **2a (1.5 equiv.)** **4a**

A 100 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (970 mg, 5 mmol, 1.0 equiv.), Na_2CO_3 (1.06 g, 10 mmol, 2.0 equiv.) and *fac*-[Ir(ppy)$_3$] (65 mg, 0.1 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (1.52 g, 7.5 mmol, 1.5 equiv.) and anhydrous EtOH (50 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 12 h. Upon completion of the reaction, the mixture was concentrated under vacuum and then extracted by ethyl acetate (25 mL) and washed with H_2O. The organic layers were concentrated and purified by silica gel column chromatography with petroleum ether/EtOAc (7:1, v/v) as eluents furnishing the product **4a** (1.07 g, 67 % yield).

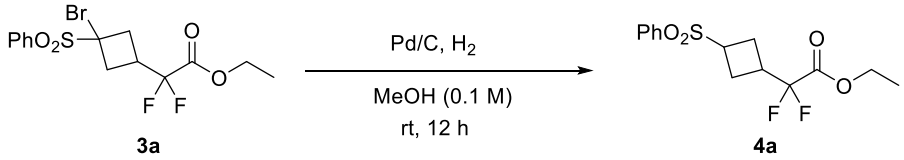
2.9 Late-stage functionalization

2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetamide (5a)



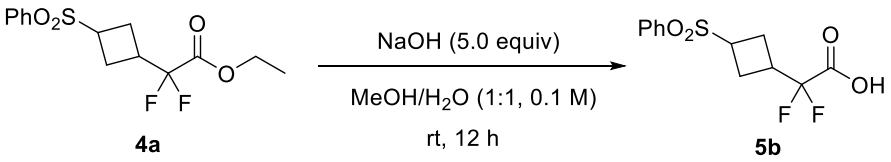
To a solution of compound **3a** (80 mg, 0.20 mmol, 1.0 equiv.) in MeOH (2.0 mL, 0.1 M) was added NH_3 (7.0 M in MeOH, 0.29 mL, 2.0 mmol, 10.0 equiv.). The reaction was stirred at room temperature for 12 h and quenched with saturated NH_4Cl solution. The reaction mixture was extracted with DCM (10 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with petroleum ether/EtOAc (5:1, v/v) as eluents furnishing the desired product as a white solid (58 mg, 78 % yield).

ethyl 2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetate (4a)



To a solution of compound **3a** (80 mg, 0.20 mmol, 1.0 equiv.) in MeOH (2.0 mL, 0.1 M) was added 10 % Pd/C (5 mg). The reaction was stirred at room temperature for 12 h under a hydrogen atmosphere. The desired product **4a** was obtained as a light-yellow solid by filtering mixture and evaporating the filtrate (58 mg, 90 % yield).

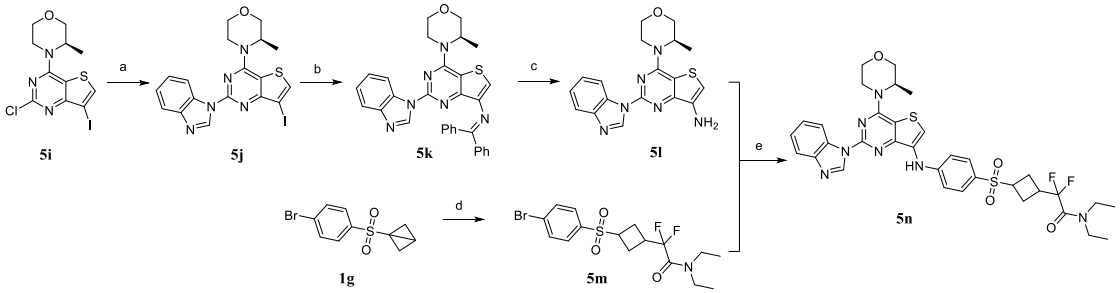
2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetic acid (5b)



To a solution of compound **4a** (63.6 mg, 0.20 mmol, 1.0 equiv.) in MeOH (1.0 mL) was added NaOH solution (1.0 M, 1.0 mL) at room temperature. The reaction was stirred at room temperature for 12 h and concentrated *in vacuo*, then neutralized to pH 6-7 with 1N HCl solution. The reaction mixture was extracted with DCM (10 mL x 3), and washed with H_2O followed by saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give residue, which was purified by silica gel column chromatography with DCM/MeOH/AcOH (30:1:0.1, v/v) as eluents furnishing the desired product as a white solid (38 mg, 66 % yield).

2.10 Applications in ATR inhibitors

Scheme S2. Synthesis of compound **5n** [a]



[a] *Reagents and conditions*: (a) benzimidazole, K_2CO_3, DMF, 110 °C, 12 h; (b) benzophenone imine, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, 1,4-dioxane, 105 °C, 12 h; (c) hydroxylamine hydrochloride, AcONa, rt, 24 h; (d) 2-bromo-*N*,*N*-diethyl-2,2-difluoroacetamide (**1x**), *fac*-[Ir(ppy)$_3$], Na_2CO_3, EtOH, Blue LEDs, rt, 12 h; (e) $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, 1,4-dioxane, 105 °C, 12 h.

(*R*)-4-(2-(1*H*-benzo[*d*]imidazol-1-yl)-7-iodothieno[3,2-*d*]pyrimidin-4-yl)-3-methylmorpholine (5j)

A mixture of benzimidazole (224 mg, 1.90 mmol) and K_2CO_3 (524 mg, 3.79 mmol) in DMF (15 mL) was added **5i** (500 mg, 1.26 mmol). The reaction mixture was stirred at 110 °C for 12 h and cooled to room temperature. Then extracted by EtOAc and washed with H_2O and brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **5j** as a white solid (yield, 74 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.93 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 4.86 – 4.73 (m, 1H), 4.58 – 4.45 (m, 1H), 4.21 – 4.10 (m, 1H), 3.96 – 3.82 (m, 2H), 3.79 – 3.59 (m, 2H), 1.51 (d, *J* = 6.8 Hz, 3H).

(*R*)-N-(2-(1*H*-benzo[*d*]imidazol-1-yl)-4-(3-methylmorpholino)thieno[3,2-*d*]pyrimidin-7-yl)-1,1-diphenylmethanimine (5k)

A mixture of **5j** (300 mg, 0.63 mmol), $Pd_2(dba)_3$ (29 mg, 0.031 mmol), Xantphos (36 mg, 0.062 mmol) and Cs_2CO_3 (614 mg, 1.89 mmol) in anhydrous 1,4-dioxane (15 mL) was added benzophenone imine (171 mg, 0.94 mmol). The reaction mixture was refluxed for 12 h under a nitrogen atmosphere then cooled to room temperature and concentrated under reduced pressure. Then extracted by EtOAc and washed with H_2O and brine. The combined organic layers were dried

over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **5k** as a yellow solid (yield, 62 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.08 (d, *J* = 7.9 Hz, 1H), 8.33 (d, *J* = 7.1 Hz, 2H), 8.26 (d, *J* = 7.9 Hz, 1H), 7.98 (t, *J* = 7.3 Hz, 1H), 7.90 (t, *J* = 7.6 Hz, 2H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.70 – 7.60 (m, 7H), 5.25 – 5.15 (m, 1H), 4.92 – 4.84 (m, 1H), 4.56 – 4.52 (m, 1H), 4.33 – 4.22 (m, 2H), 4.17 – 3.98 (m, 2H), 1.89 (d, *J* = 6.8 Hz, 3H).

(*R*)-2-(1*H*-benzo[*d*]imidazol-1-yl)-4-(3-methylmorpholino)thieno[3,2-*d*]pyrimidin-7-amine (5l)

A mixture of **5k** (250 mg, 0.47 mmol) and AcONa (97 mg, 1.18 mmol) in MeOH (15 mL) was added hydroxylamine hydrochloride (66 mg, 0.94 mmol). The reaction mixture was stirred at room temperature for 12 h. Then extracted by EtOAc and washed with H_2O and brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **5l** as a white solid (yield, 80 %). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.69 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.38 – 7.30 (m, 1H), 6.68 (s, 1H), 5.41 (s, 2H), 4.89 – 4.73 (m, 1H), 4.59 – 4.44 (m, 1H), 4.14 – 3.99 (m, 1H), 3.88 – 3.72 (m, 2H), 3.67 – 3.51 (m, 2H), 1.40 (d, *J* = 6.8 Hz, 3H).

2-(3-((4-bromophenyl)sulfonyl)cyclobutyl)-*N*,*N*-diethyl-2,2-difluoroacetamide (5m)

Compound **5m** was synthesized from **1g** and **1x** by general procedure B for the synthesis of **5m** as a white solid (yield, 71 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83 – 7.50 (m, 4H), 3.78 – 3.63 (m, 1H), 3.51 (q, *J* = 7.1 Hz, 2H), 3.33 (q, *J* = 7.1 Hz, 2H), 3.23 – 3.01 (m, 1H), 2.72 – 2.56 (m, 2H), 2.38 – 2.25 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.64.

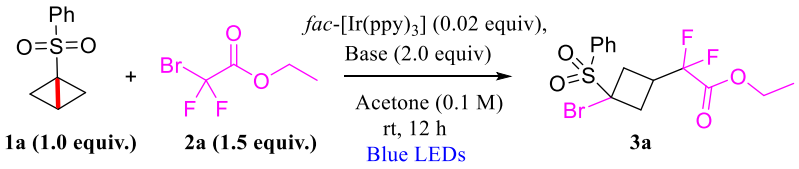
(*R*)-2-(3-((4-((2-(1*H*-benzo[*d*]imidazol-1-yl)-4-(3-methylmorpholino)thieno[3,2-*d*]pyrimidin-7-yl)amino)phenyl)sulfonyl)cyclobutyl)-*N*,*N*-diethyl-2,2-difluoroacetamide (5n)

Compound **5n** was synthesized from **5l** and **5m** by a synthetic procedure similar to that of **5n** as a beige solid (yield, 65 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.43 (d, *J* = 9.0 Hz, 1H), 7.88 – 7.77 (m, 3H), 7.46 – 7.29 (m, 5H), 7.27 (s, 1H), 4.92 – 4.75 (m, 1H), 4.63 – 4.47 (m, 1H), 4.22 – 4.10 (m, 1H), 3.99 – 3.81 (m, 2H), 3.79 – 3.60 (m, 3H), 3.51 (q, *J* = 7.1 Hz, 2H), 3.33 (q, *J* = 7.1 Hz, 2H), 3.21 – 2.99 (m, 1H), 2.75 – 2.57 (m, 2H), 2.40 – 2.23 (m, 2H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.23 – 1.15 (m, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.1 (t, $^2J_{C\text{-}F}$ =

29.3 Hz), 158.4, 154.5, 152.7, 147.0, 144.8, 142.4, 132.9, 132.0, 130.6, 128.4, 124.5, 123.7, 120.5, 117.9 (t, $^{1}J_{C\text{-}F}$ = 255.0 Hz), 115.6, 114.9, 110.1, 107.7, 71.0, 66.9, 52.9, 49.7, 41.6, 41.2, 33.1 (t, $^{2}J_{C\text{-}F}$ = 27.0 Hz), 23.6 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz), 15.5, 14.3, 12.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.48. **HRMS** (ESI) for $C_{34}H_{37}F_2N_7NaO_4S_2$ $[M + Na]^+$, calcd: 732.2188, found: 732.2209.

3. Reaction optimization

3.1 Optimization of reaction conditions for the preparation of 3a:



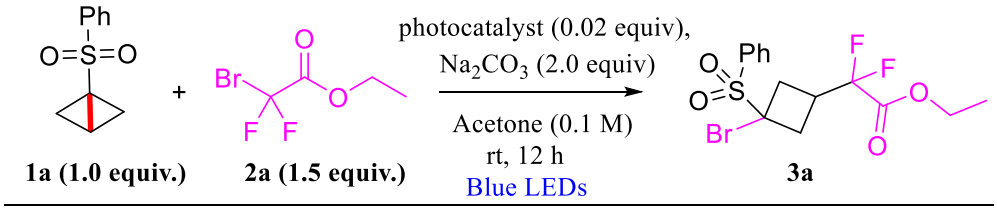
1a (1.0 equiv.) **2a (1.5 equiv.)** **3a**

Table S1. Screening of base [a]

Entry	Base	Yield (%) [b]
1	DBU	0
2	pyridine	0
3	DIPEA	0
4	**Na_2CO_3**	**62**
5	$NaHCO_3$	60
6	K_2CO_3	55
7	K_3PO_4	53
8	Cs_2CO_3	trace
9	*t*-BuONa	0
10	AcONa	52

[a] Reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), photocatalyst (0.004 mmol) and base (0.4 mmol) in acetone (2.0 mL) at room temperature under nitrogen atmosphere for 12 h.

[b] All yields are of isolated products.



1a (1.0 equiv.) **2a (1.5 equiv.)** **3a**

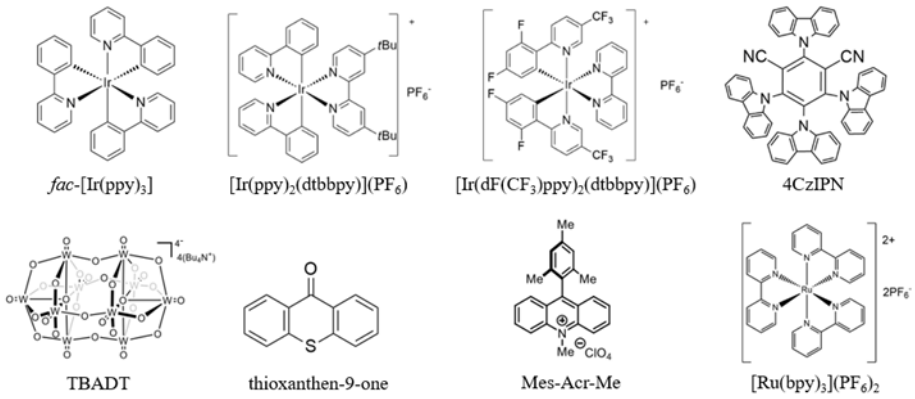


Table S2. Screening of photocatalyst [a]

Entry	Base	Yield (%) [b]
1	***fac*-[Ir(ppy)$_3$]**	**62**
2	[Ir(ppy)$_2$(dtbbpy)](PF$_6$)	0
3	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)](PF$_6$)	0
4	4CzIPN	0
5	TBADT	0
6	thioxanthen-9-one	N.R. [c]
7	Mes-Acr-Me	N.R.
8	[Ru(bpy)$_3$](PF$_6$)$_2$	trace

[a] Reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), photocatalyst (0.004 mmol) and base (0.4 mmol) in acetone (2.0 mL) at room temperature under nitrogen atmosphere for 12 h.

[b] All yields are of isolated products.

[c] N.R. = No Reaction.

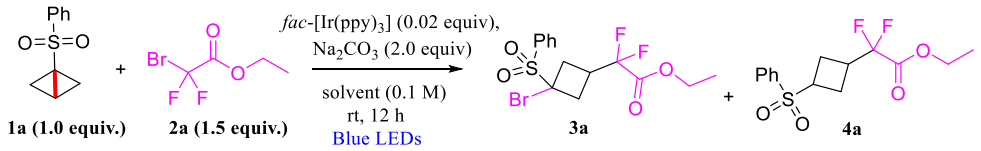


Table S3. Screening of solvent [a]

Entry	Solvent	Yield of **3a**/**4a** (%) [b]
1	**Acetone**	**62/0**
2	DCM	trace/0
3	EtOAc	10/0
4	THF	20/50
5	2-MeTHF	20/47
6	MeCN	58/0
7	toluene	43/22
8	MeOH	0/trace
9	EtOH	0/72
10	1,4-dioxane	trace/56
11	DMF	0/46
12	DMSO	0/0

[a] Reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), *fac*-[Ir(ppy)$_3$] (0.004 mmol) and base (0.4 mmol) in solvent (2.0 mL) at room temperature under nitrogen atmosphere for 12 h.

[b] All yields are of isolated products.

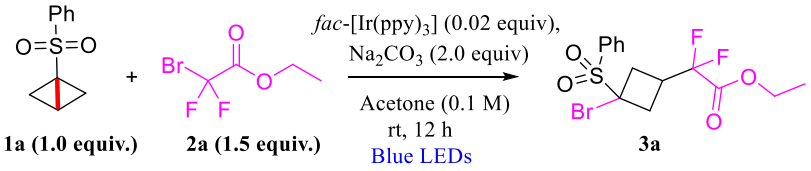


Table S4. Control experiments [a]

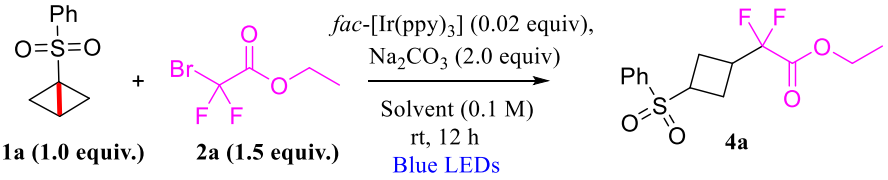
Entry	Deviation	Yield (%) [b]
1	without base	trace
2	without light	N.R. [c]
3	390 nm purple LEDs	26
4	without photocatalyst	N.R.
5	under air	0
6	with a drop of H_2O	34

[a] Reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), *fac*-[Ir(ppy)$_3$] (0.004 mmol) and base (0.4 mmol) in solvent (2.0 mL) at room temperature under nitrogen atmosphere for 12 h.

[b] All yields are of isolated products.

[c] N.R. = No Reaction.

3.2 Optimization of reaction conditions for the preparation of 4a:



1a (1.0 equiv.) **2a (1.5 equiv.)** **4a**

Table S5. Screening of solvent [a]

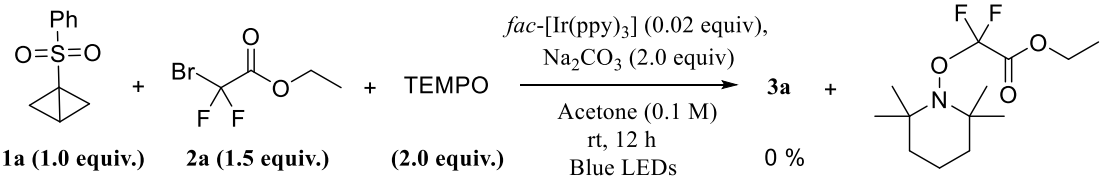
Entry	Solvent	Yield of **7a** (%) [b]
1	**EtOH**	**72**
2	*i*-PrOH	55
3	*n*-PrOH	56
4	*n*-BuOH	50
5	*s*-BuOH	67
6	*t*-BuOH	18

[a] Reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), *fac*-[Ir(ppy)$_3$] (0.004 mmol) and base (0.4 mmol) in solvent (2.0 mL) at room temperature under nitrogen atmosphere for 12 h.

[b] All yields are of isolated products.

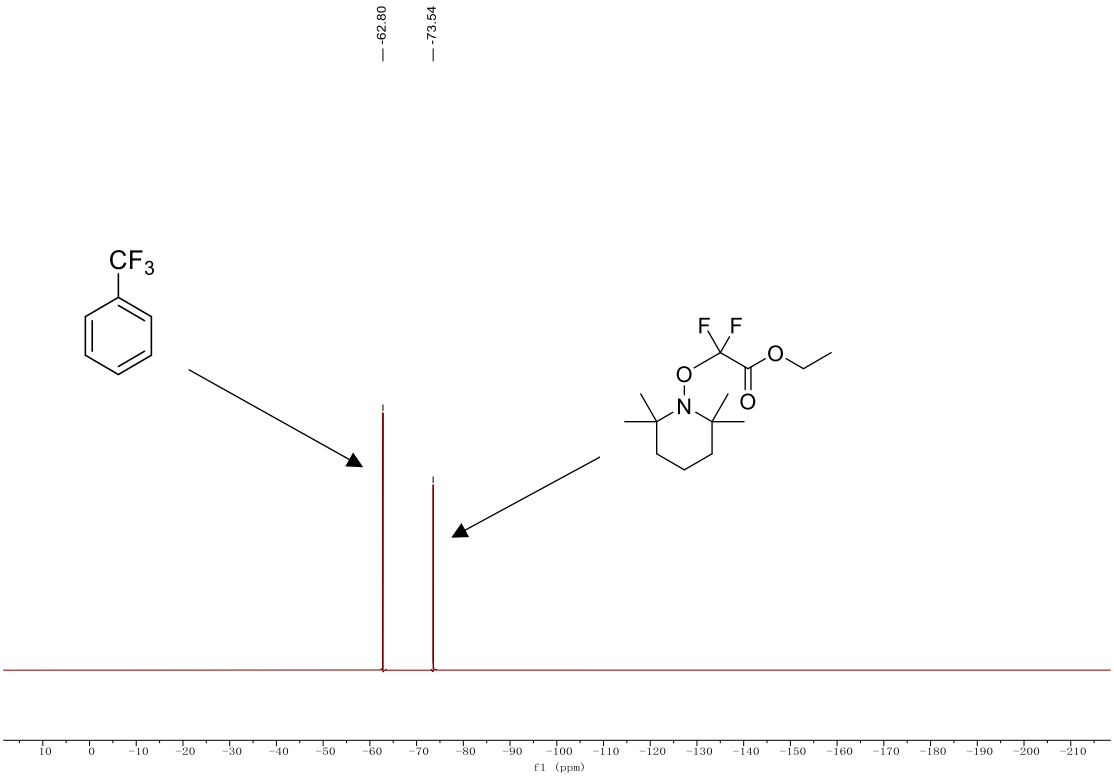
4. Mechanistic Studies

4.1 Radical trapping experiments

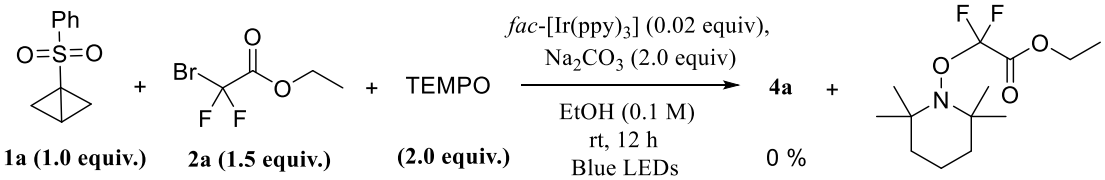


1a (1.0 equiv.) **2a (1.5 equiv.)** **(2.0 equiv.)** detected by ^{19}F NMR

A 10 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (0.2 mmol, 1.0 equiv.), TEMPO (0.4 mmol, 2.0 equiv.), Na_2CO_3 (0.4 mmol, 2.0 equiv.) and *fac*-[Ir(ppy)$_3$] (0.004 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (0.3 mmol, 1.5 equiv.) and anhydrous acetone (2 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 12 h. The reaction mixture was concentrated under vacuum then taken and monitored by ^{19}F NMR. ($PhCF_3$ was used as an internal standard.)[13]

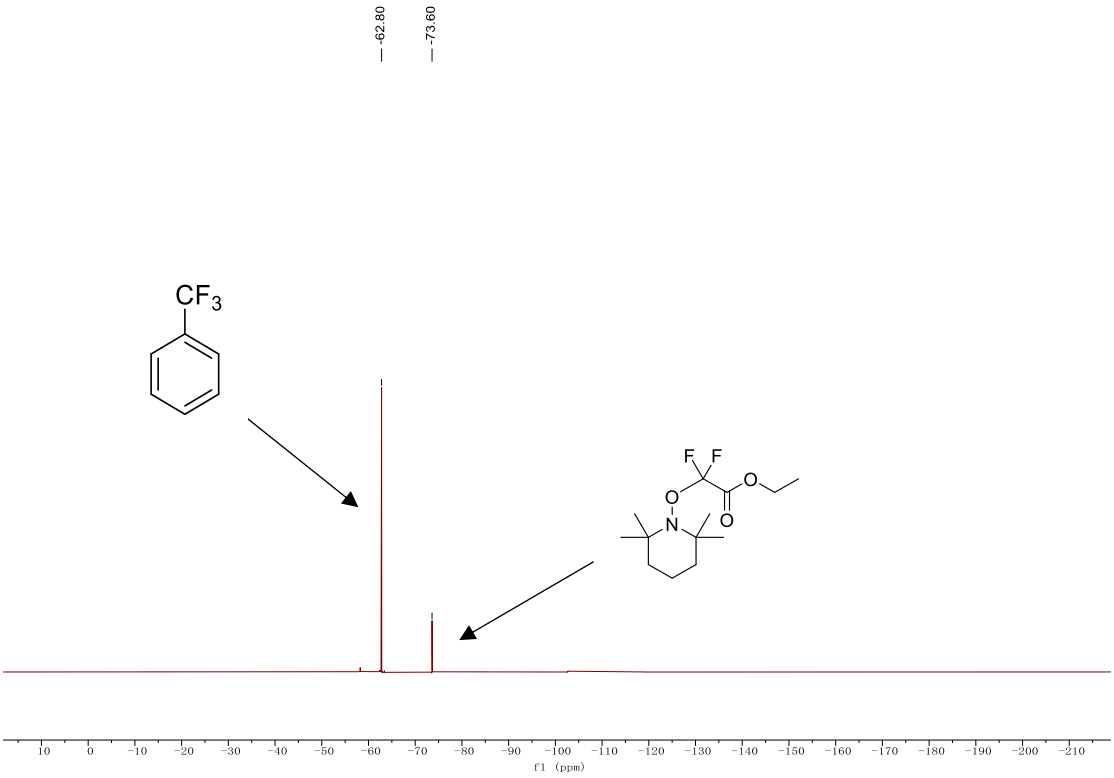


Results and Conclusion: TEMPO-adduct product was detected by ^{19}F NMR spectrum, no desired product was obtained in the presence of a radical scavenger. This experiment indicates that the reaction likely proceeds through a radical mechanism.



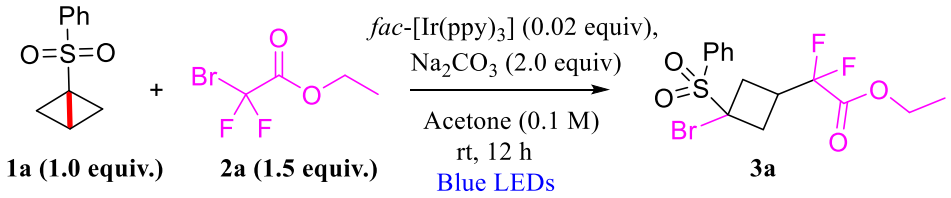
1a (1.0 equiv.) **2a (1.5 equiv.)** **(2.0 equiv.)**

A 10 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (0.2 mmol, 1.0 equiv.), TEMPO (0.4 mmol, 2.0 equiv.), Na_2CO_3 (0.4 mmol, 2.0 equiv.) and *fac*-[$Ir(ppy)_3$] (0.004 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (0.3 mmol, 1.5 equiv.) and anhydrous EtOH (2 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 12 h. The reaction mixture was concentrated under vacuum then taken and monitored by ^{19}F NMR. ($PhCF_3$ was used as an internal standard.)[13]



Results and Conclusion: TEMPO-adduct product was detected by ^{19}F NMR spectrum, no desired product was obtained in the presence of a radical scavenger. This experiment indicates that the reaction likely proceeds through a radical mechanism.

4.2 Light on/off experiments



1a (1.0 equiv.) **2a (1.5 equiv.)** **3a**

A 10 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (0.2 mmol, 1.0 equiv.), Na_2CO_3 (0.4 mmol, 2.0 equiv.) and *fac*-[Ir(ppy)$_3$] (0.004 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (0.3 mmol, 1.5 equiv.) and anhydrous acetone (2 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 0.5 h. The light was then removed for 0.5 h. Repeat those lights on and off operation for 3 h. The rection was tracked with LC-MS at each 0.5 hours.

Light condition		on	off	on	off	on	off
Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0
Yield	0	32	34	44	44	51	53

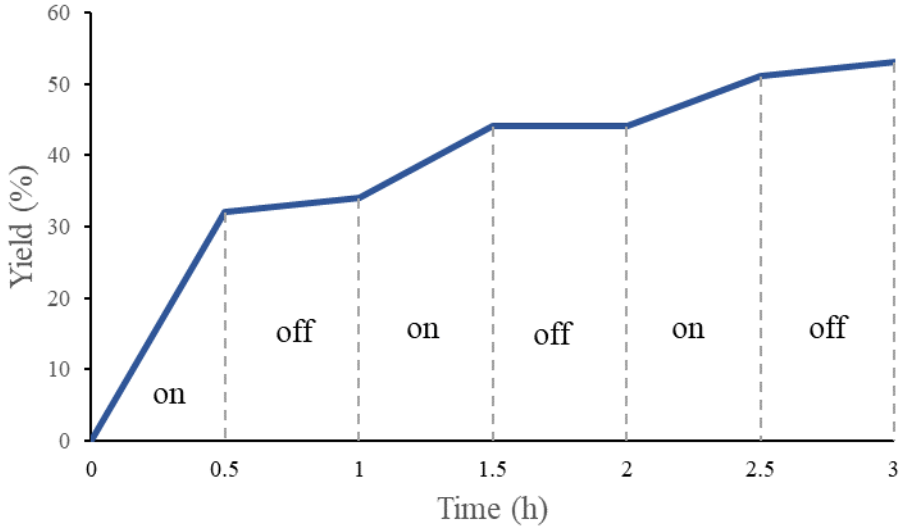
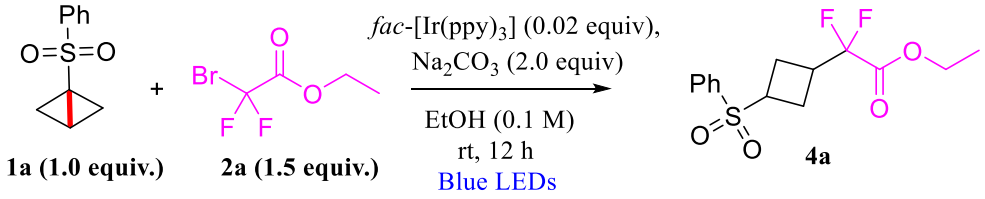


Fig. S2. Light on/off experiment.

Results and Conclusion: The light on/off experiment indicated that the reaction shows photo-irradiation dependence and may not follow a radical chain mechanism.



A 10 mL oven-dried reaction vessel was equipped with a magnetic stirrer bar and charged with **1a** (0.2 mmol, 1.0 equiv.), Na_2CO_3 (0.4 mmol, 2.0 equiv.) and *fac*-[Ir(ppy)$_3$] (0.004 mmol, 0.02 equiv.). The reaction vessel was sealed and degassed via vacuum evacuation and back-filled with nitrogen for three times, then added the **2a** (0.3 mmol, 1.5 equiv.) and anhydrous EtOH (2 mL). The reaction vessel was exposed to blue LEDs (450 nm, 25 W) irradiation and stirred at room temperature for 0.5 h. The light was then removed for 0.5 h. Repeat those lights on and off operation for 3 h. The rection was tracked with LC-MS at each 0.5 hours.

Light condition		on	off	on	off	on	off
Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0
Yield	0	37	37	47	47	59	59

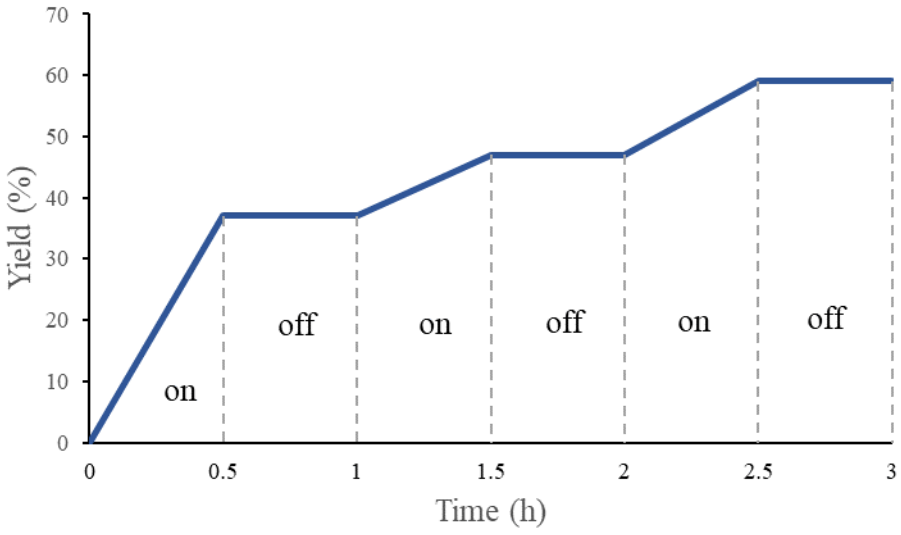
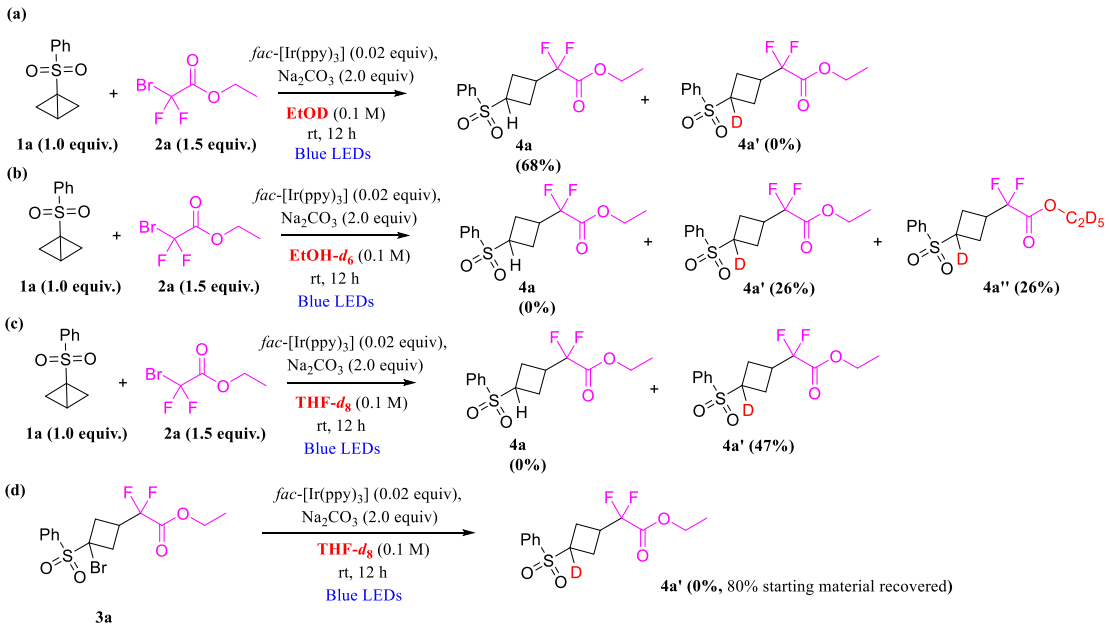


Fig. S3. Light on/off experiment.

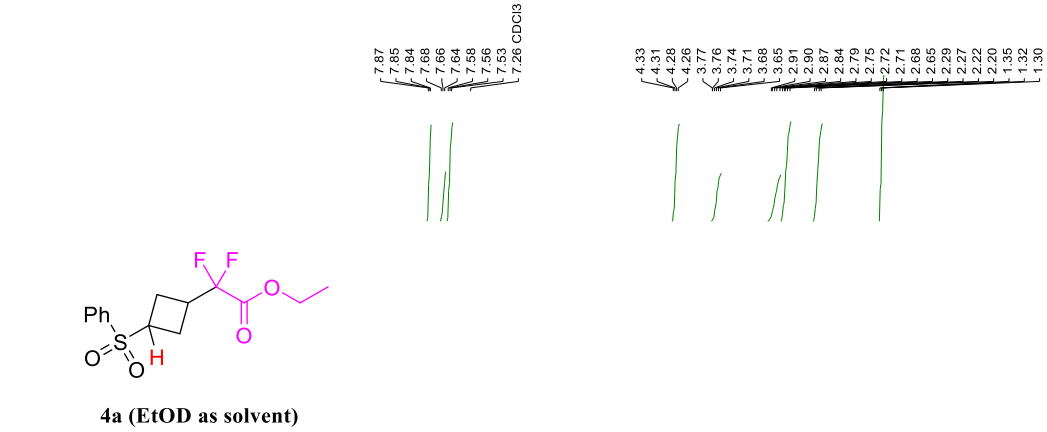
Results and Conclusion: The light on/off experiment indicated that the reaction shows photo-irradiation dependence and may not follow a radical chain mechanism.

4.3 Deuterium labeling experiments

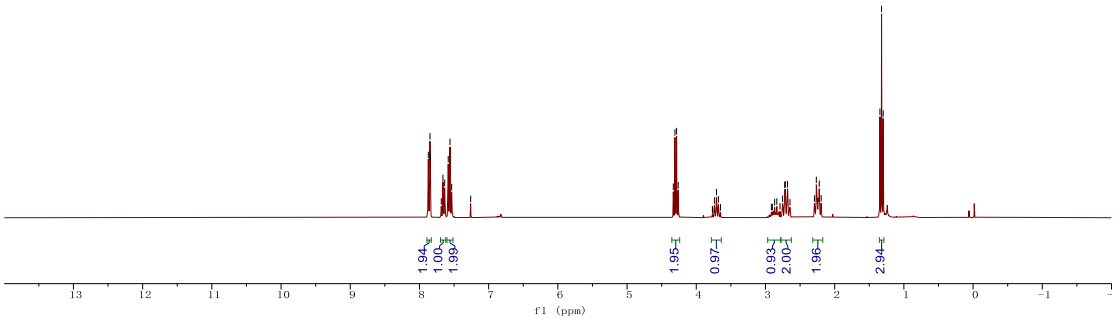


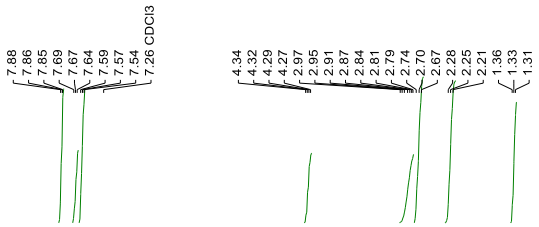
Results and Conclusion: When EtOD was used as solvent, no deuterated product **4a'** was tracked. While the deuterated product **4a'** and its transesterification product **4a''** were recorded with full deuterated EtOH-d_6. In the screening process, solvents bearing C-H bond adjacent to heteroatom were conductive to the formation of difluoromethylation product **4a**. The deuterated product **4a'** was produced in 47% yield using the THF-d_8, which further confirmed the

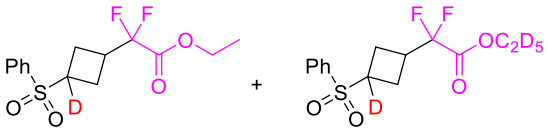
borrowed hydrogen coming from solvents.



4a (EtOD as solvent)

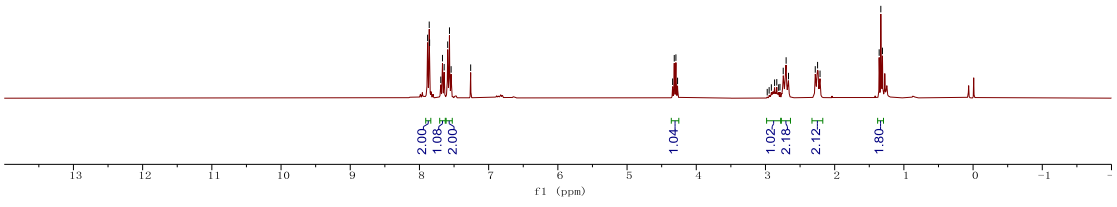


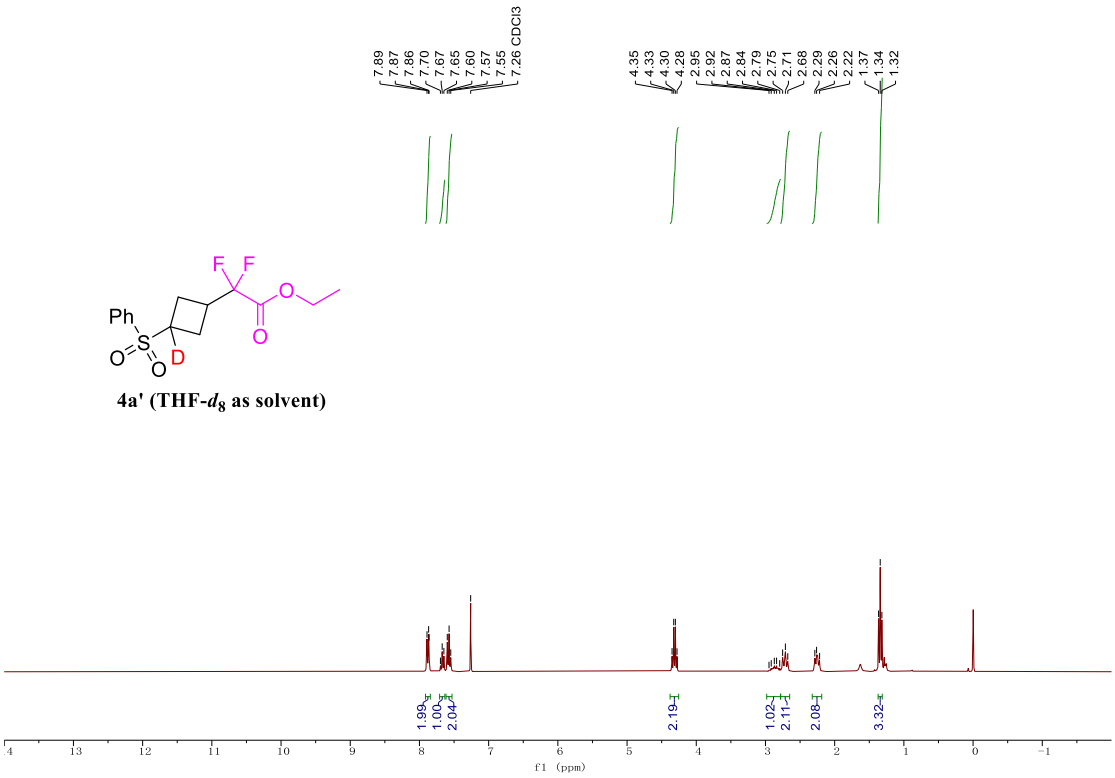




\+

4a' + 4a''(EtOH-d_6 as solvent)





4a' (THF-d_8 as solvent)

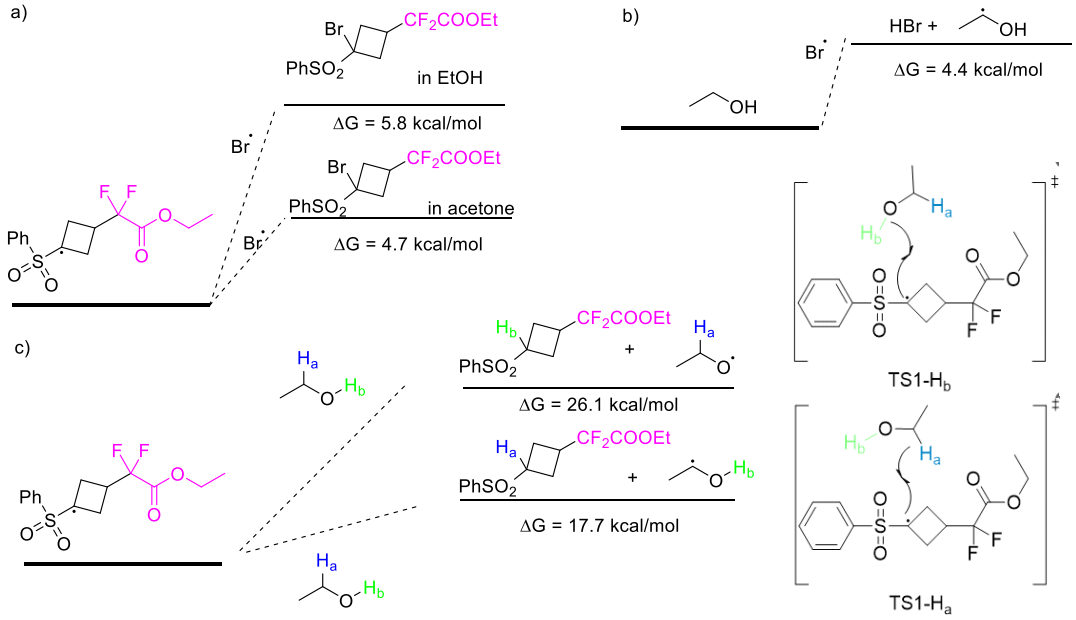
4.4 DFT calculations

All density functional theory (DFT) calculations were performed with the Gaussian 16 program package. [14]

Full geometry optimizations were operated to locate all of the stationary points, using (U)M06-2X density functional theory method [15-16] with def2SVP [17] basis for all atoms, and a polarized continuum model based on solute electron density (PCM) [18-19] was employed to simulate the solvent effect of acetone or ethanol solvent in optimization. The spin-restricted DFT method was used for closed-shell species and the spin-unrestricted DFT method for radical species and open-shell singlet species (TS1-Br, TS1-H_a, TS1-H_b) with the "guess (mix, always)" keyword. In the meantime, the stability of the density function theory (DFT) wave-function of the auxiliary Kohn–Sham determinant was examined.[20] Harmonic vibrational frequency calculations were conducted to characterize all stationary point. Herein, minima have zero imaginary frequencies, and transition states have only one imaginary vibrational frequency. Intrinsic reaction coordinate (IRC) calculations [21-22] were implemented to track minimum energy paths connecting each transition state structure to two corresponding minima. The single point energy calculations of all stationary points were performed at the (U)M06-2X/def2TZVP,SDD level using the PCM-SMD model with acetone or ethanol as solvent. This theoretical level is denoted as PCM-SMD (acetone/ethanol)-(U)M06-

2X/def2TZVP.

Unless mentioned otherwise, the Gibbs free energy of formation (ΔG) is obtained at the PCM-SMD (acetone/ethanol)-(U)M06-2X/def2TZVP level.



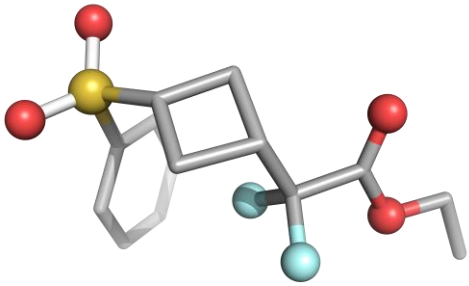
Scheme S3. **DFT calculations**

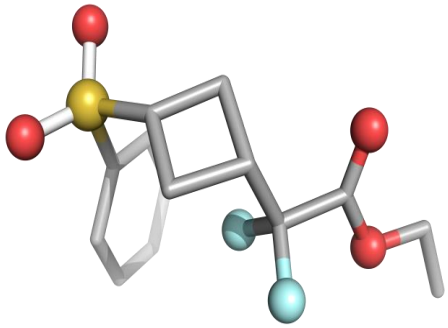
Table S6. Thermal correction to Gibbs free energy (G_0, hartree), single point energies (SP-E, hartree), sum of electronic and thermal free enaergies (G_c, hartree) with the addition of SP-E as well as thermal corrections, and relative Gibbs free energies (ΔG, kcal mol^{-1}) of various species with respect to TS1-Br for radical coupling and radical addition reactions at the PCM-SMD (acetone/ethanol)-(U)M06-2X/def2TZVP . IF represents imaginary frequencies (cm^{-1}).

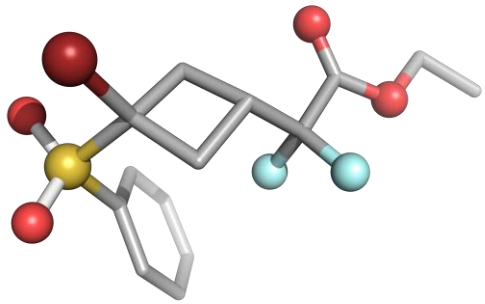
Species	G_0	SP-E	G_c(G_0+SP-E)	ΔG	IF
Solvent: EtOH					
Br	-0.01683	-2574.154372	-2574.171202		
EtOH	0.05507	-155.036443	-154.981373		
Int I	0.222813	-1441.228673	-1441.00586		
P1	0.224901	-4015.486781	-4015.26188		
TS1-Br	0.219643	-4015.387473	-4015.16783	5.79308	-86.59
TS1-H_b	0.291753	-1596.237465	-1595.945712	26.0544275	-1759.19
TS1-H_a	0.293404	-1596.252483	-1595.959079	17.666635	-1372.19
TS2	0.046353	-2729.191868	-2729.145515	4.43015	-175.25
Solvent: acetone					
Br	-0.01683	-2574.153976	-2574.170806		
Int I	0.22279	-1441.228974	-1441.006184		
P1	0.224895	-4015.487142	-4015.262247		
TS1-Br	0.219401	-4015.388964	-4015.169563	4.6604425	-87.73
Solvent: 1-propanol					
1-propanol	0.081307	-194.338495	-194.257188		
Int I	0.222818	-1441.228062	-1441.005244		
TS1-H_a	0.320068	-1635.542199	-1635.222131	25.268727	-1388.91
TS2	0.073001	-2768.499527	-2768.426526	1.17	-162.89
Solvent: 1-butanol					

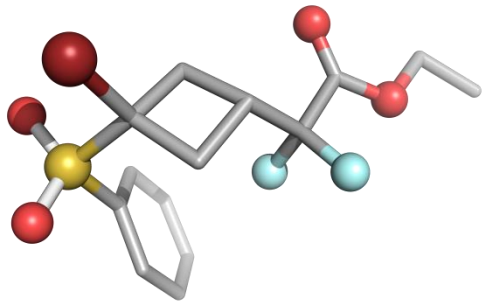
1-butanol	0.10751	-233.645252	-233.537742		
Int I	0.222845	-1441.227246	-1441.004401		
TS1-H_a	0.318263	-1635.568792	-1674.502717	24.720102	-1384.55
TS2	0.099024	-2807.807042	-2807.708018	0.43	-158.92
Solvent: 2-methyl-1-propanol					
2-methyl-1-Propanol	0.10756	-233.647572	-233.540012		
Int I	0.222848	-1441.227801	-1441.004953		
TS1-H_a	0.347655	-1674.850447	-1674.502792	26.442471	-1414.60
TS2	0.100245	-2807.808915	-2807.70867	1.649	-111.62

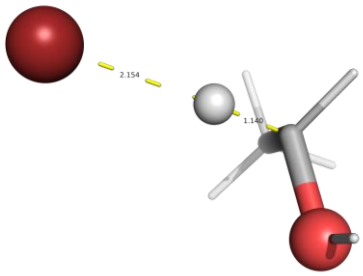
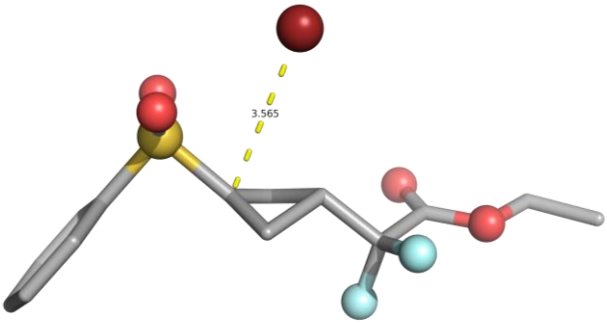
Table S7. Structure and Cartesian Coordinates of Optimized Geometries

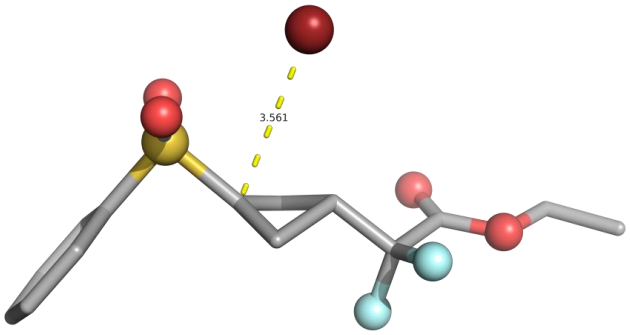
Structure Ethanol Solvent: Ethanol				
cartesian coordinates of stationary point structure [Å]	C	-2.75902300	0.01808400	0.00395400
	C	-1.24528500	0.01421100	-0.00269600
	H	-3.13670600	1.05033700	0.01082800
	H	-3.15589600	-0.49364900	-0.88315300
	H	-3.13685200	-0.49253000	0.90103000
	H	-0.87451500	-1.02645500	-0.02808400
	H	-0.87453600	0.51226500	-0.91680800
	O	-0.79673900	0.68369400	1.15640200
	H	0.16699100	0.68184700	1.15266800
Structure Int I Solvent: Ethanol				
cartesian coordinates of stationary point structure [Å]	C	-0.68165100	-0.29219100	2.28978200
	C	0.72479400	-0.79188000	1.84954500
	C	-0.07255800	1.07168300	2.38994000
	H	-1.49059500	-0.41268800	1.55205600
	H	-1.01788400	-0.70591600	3.25173800
	H	1.15080800	-1.60824600	2.44354600
	C	1.32726300	0.61678600	2.11550800
	H	1.99507900	0.65354800	2.98848800
	H	1.83709000	1.09697700	1.26536700
	S	-0.80221500	2.61615800	2.04821900
	O	0.15673000	3.65196500	2.43145800
	O	-2.14974200	2.60254900	2.61700600
	C	-0.94799000	2.62332500	0.27626700
	C	0.11736200	3.10368400	-0.48487800
	C	-2.09424600	2.08307400	-0.30634900
	C	0.03116100	3.02779700	-1.87338400

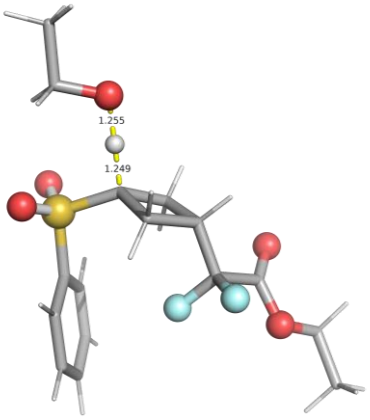
	H	0.98857300	3.53637400	0.00918900
	C	-2.16573700	2.01412900	-1.69594000
	H	-2.91338100	1.73407600	0.32420400
	C	-1.10422500	2.48035100	-2.47443300
	H	0.85075900	3.40049600	-2.48869200
	H	-3.05369700	1.59831900	-2.17325200
	H	-1.16492200	2.42154400	-3.56199300
	C	0.75269300	-1.17988500	0.39482000
	C	2.16817700	-1.49205300	-0.12468000
	F	0.24898700	-0.17426500	-0.37090100
	F	-0.03740500	-2.25502400	0.18174400
	O	3.15947600	-1.30278300	0.52560500
	O	2.12455000	-1.96585300	-1.35006800
	C	3.38815900	-2.28045500	-1.96640800
	C	3.10807700	-2.79305100	-3.35663200
	H	3.89760000	-3.02668300	-1.34077000
	H	4.00241100	-1.36912300	-1.97292800
	H	4.05448600	-3.04267000	-3.85316700
	H	2.48494600	-3.69622900	-3.31844800
	H	2.59089700	-2.03047700	-3.95372000
Structure Int I Solvent: acetone				
cartesian coordinates of stationary point structure [Å]	C	-0.68166900	-0.29233300	2.29050200
	C	0.72476200	-0.79216000	1.85037800
	C	-0.07251000	1.07154100	2.39013800
	H	-1.49073200	-0.41309600	1.55295100
	H	-1.01763100	-0.70575800	3.25267200
	H	1.15061800	-1.60846900	2.44453400
	C	1.32734500	0.61647900	2.11621900
	H	1.99474300	0.65321500	2.98951800
	H	1.83753500	1.09648900	1.26618900
	S	-0.80190100	2.61581200	2.04748000
	O	0.15677700	3.65198800	2.43080900
	O	-2.14951200	2.60304000	2.61636100
	C	-0.94763300	2.62283000	0.27560300
	C	0.11800600	3.10255500	-0.48558400
	C	-2.09416000	2.08299700	-0.30694200
	C	0.03167900	3.02675000	-1.87409700
	H	0.98966400	3.53456700	0.00827800
	C	-2.16577000	2.01417700	-1.69654300
	H	-2.91341300	1.73409000	0.32350300
	C	-1.10407200	2.47996000	-2.47509200
	H	0.85149600	3.39892000	-2.48942200
	H	-3.05394100	1.59876100	-2.17380000
	H	-1.16485700	2.42124300	-3.56264900

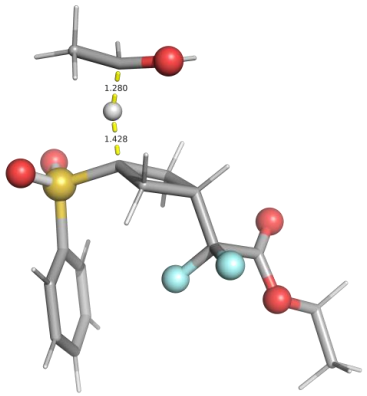
	C	0.75273000	-1.18017600	0.39569800
	C	2.16818400	-1.49205600	-0.12406200
	F	0.24872500	-0.17461600	-0.37003700
	F	-0.03725300	-2.25540200	0.18250100
	O	3.15956100	-1.30302200	0.52620900
	O	2.12433000	-1.96528400	-1.34961000
	C	3.38784400	-2.27962400	-1.96650200
	C	3.10737300	-2.79148000	-3.35690200
	H	3.89734900	-3.02624300	-1.34140300
	H	4.00200500	-1.36824700	-1.97278700
	H	4.05370000	-3.04076500	-3.85374100
	H	2.48436000	-3.69475900	-3.31904700
	H	2.59009900	-2.02856300	-3.95348400
Structure P1 Solvent: Ethanol				
cartesian coordinates of stationary point structure [Å]	C	-0.70958500	-0.23619100	2.08558300
	C	0.69093700	-0.68802900	1.61067700
	C	-0.06314000	1.03920800	2.65146300
	H	-1.38787500	-0.02612200	1.24716100
	H	-1.21994600	-0.87087800	2.81661300
	H	1.12212100	-1.48979900	2.22270600
	C	1.26046400	0.70836500	1.94190400
	H	2.15829500	0.74497600	2.56611200
	H	1.41786600	1.31891600	1.04253200
	S	-0.86025500	2.62990700	2.22911600
	O	0.06640300	3.68530900	2.62819400
	O	-2.21322100	2.58152900	2.77620700
	C	-0.97165900	2.62230000	0.45556000
	C	0.08002500	3.15782900	-0.28778700
	C	-2.11546400	2.09731900	-0.14546800
	C	-0.00505800	3.12828600	-1.67772500
	H	0.94014100	3.59733400	0.21963000
	C	-2.18585100	2.07518900	-1.53639800
	H	-2.93519900	1.72495800	0.47077600
	C	-1.13053600	2.58161900	-2.29716400
	H	0.80665700	3.53923800	-2.27857400
	H	-3.06976700	1.66703300	-2.02714600
	H	-1.19055800	2.55982600	-3.38607500
	C	0.75074500	-1.09364600	0.16115500
	C	2.18284900	-1.35805200	-0.33391600
	F	0.24160100	-0.10398200	-0.62419700
	F	-0.01891500	-2.18122900	-0.04652100
	O	3.14545300	-0.88701500	0.20870000
	O	2.19133000	-2.10657000	-1.41327400
	C	3.47863500	-2.37380600	-2.00334000
	C	3.25816000	-3.24305100	-3.21563300
	H	4.10662900	-2.86377800	-1.24630200

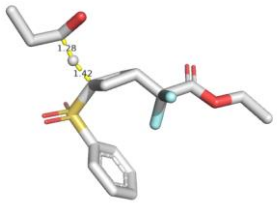
	H	3.94474000	-1.41156100	-2.25773000
	H	4.22350500	-3.46442600	-3.68855800
	H	2.78301400	-4.19113000	-2.93127200
	H	2.61951900	-2.73200100	-3.94804500
	Br	0.07655800	1.04062000	4.58760100
Structure P1 Solvent: acetone				
cartesian coordinates of stationary point structure [Å]	C	-0.70955300	-0.23628700	2.08706900
	C	0.69087800	-0.68824700	1.61196700
	C	-0.06311900	1.03960200	2.65185500
	H	-1.38834800	-0.02691100	1.24887500
	H	-1.21938300	-0.87064600	2.81874600
	H	1.12219100	-1.48976300	2.22419900
	C	1.26047400	0.70829600	1.94247600
	H	2.15817300	0.74504200	2.56687000
	H	1.41813500	1.31845800	1.04288200
	S	-0.86053700	2.62972300	2.22823100
	O	0.06521400	3.68593700	2.62775000
	O	-2.21371900	2.58141700	2.77514300
	C	-0.97120800	2.62172100	0.45481700
	C	0.08084400	3.15711900	-0.28816000
	C	-2.11465800	2.09628800	-0.14653800
	C	-0.00363800	3.12723000	-1.67812500
	H	0.94087500	3.59667800	0.21934000
	C	-2.18442500	2.07390200	-1.53750200
	H	-2.93458300	1.72363000	0.46926600
	C	-1.12883800	2.58033900	-2.29791600
	H	0.80836100	3.53800200	-2.27870100
	H	-3.06804900	1.66546700	-2.02853100
	H	-1.18837300	2.55831000	-3.38684500
	C	0.75041100	-1.09429700	0.16258700
	C	2.18242400	-1.35808600	-0.33310000
	F	0.24042200	-0.10512900	-0.62292700
	F	-0.01880900	-2.18232100	-0.04457900
	O	3.14509800	-0.88688600	0.20931300
	O	2.19062200	-2.10619500	-1.41265500
	C	3.47773900	-2.37291800	-2.00361100
	C	3.25661200	-3.24059500	-3.21688800
	H	4.10583700	-2.86405000	-1.24742400
	H	3.94379400	-1.41041700	-2.25704100
	H	4.22177800	-3.46150800	-3.69037600
	H	2.78147400	-4.18898400	-2.93353600
	H	2.61788600	-2.72844900	-3.94846900
	Br	0.07661600	1.04302400	4.58810300

Structure TS2 Solvent: Ethanol				
cartesian coordinates of stationary point structure [Å]	O	-2.33403900	-0.35429400	-0.03946300
	H	-2.73059600	0.49053000	0.20531000
	C	-0.95085700	-0.22540500	-0.04821200
	C	-0.31002700	-1.58550200	-0.18070500
	H	-0.57234600	0.32027800	0.83390300
	H	-0.62297400	0.41632400	-0.93128900
	H	0.78247100	-1.49369300	-0.23732400
	H	-0.57183600	-2.20730000	0.68691400
	H	-0.67015500	-2.08567200	-1.09053400
	Br	0.46454200	0.79603900	-2.75136800
Structure TS1-Br Solvent: Ethanol				
cartesian coordinates of stationary point structure [Å]	C	-0.79757400	-0.16070200	0.16742100
	C	0.73828700	-0.59994400	0.33250400
	C	-0.05295500	0.99228800	0.57019400
	H	-1.03549500	-0.27684900	-0.89793200
	H	-1.56309100	-0.51479100	0.86469200
	H	1.00355100	-0.95578400	1.33976500
	C	1.27045500	0.87953400	0.03316000
	H	2.07091300	1.30506400	0.64605000
	H	1.40124600	0.95992600	-1.05262800
	S	-0.53150800	2.07954000	1.97502900
	O	0.64414300	2.77443700	2.45318800
	O	-1.47917200	1.38050700	2.81790900
	C	-1.41531100	3.15087600	0.87113000
	C	-0.72031500	4.19592500	0.25495400
	C	-2.77787800	2.92161800	0.65803700
	C	-1.42081900	5.03343200	-0.60784200
	H	0.33929100	4.35069500	0.46244800
	C	-3.45986800	3.77163100	-0.20664000
	H	-3.28765700	2.10720000	1.17436900
	C	-2.78204400	4.81883500	-0.83711300
	H	-0.90500100	5.85909900	-1.09800000
	H	-4.52458900	3.62129000	-0.38520900
	H	-3.32430000	5.48013200	-1.51409300
	C	1.11883000	-1.57184000	-0.78432600
	C	2.63629900	-1.85988400	-0.75033900
	F	0.82576800	-1.05374400	-1.99544100

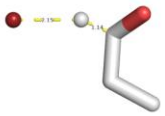
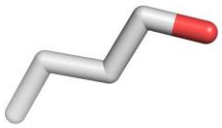
	F	0.40225000	-2.68898800	-0.64334600
	O	3.42623100	-0.99272700	-0.50094200
	O	2.89681000	-3.10394000	-1.05315400
	C	4.29255800	-3.47883600	-1.09933600
	C	4.36330200	-4.93783200	-1.47028000
	H	4.72809400	-3.27398900	-0.11186300
	H	4.79153600	-2.83257000	-1.83429500
	H	5.41416100	-5.25118800	-1.51354400
	H	3.84572000	-5.55345400	-0.72315700
	H	3.90648000	-5.11089800	-2.45340100
	Br	1.43448800	-0.28546900	3.54715800
Structure TS1-Br Solvent: acetone				
cartesian coordinates of stationary point structure [Å]	C	-0.79772300	-0.16296700	0.18509000
	C	0.73762000	-0.60253700	0.34931400
	C	-0.05494200	0.99308500	0.58351600
	H	-1.03623700	-0.28075000	-0.88008700
	H	-1.56390000	-0.51550400	0.88243700
	H	1.00309200	-0.95510500	1.35722800
	C	1.26843200	0.87588400	0.04643300
	H	2.06995700	1.30415800	0.65594100
	H	1.39720300	0.95452800	-1.03990200
	S	-0.53532400	2.08958400	1.97989400
	O	0.64003100	2.78584100	2.45728400
	O	-1.48478100	1.39661900	2.82598200
	C	-1.41537200	3.15452200	0.86754100
	C	-0.71848600	4.19679200	0.24863500
	C	-2.77698800	2.92305700	0.65022700
	C	-1.41616800	5.02930000	-0.62117900
	H	0.34033200	4.35303000	0.45900300
	C	-3.45602900	3.76807100	-0.22156200
	H	-3.28833500	2.11073300	1.16827900
	C	-2.77634800	4.81249200	-0.85471300
	H	-0.89893300	5.85260500	-1.11378500
	H	-4.51984400	3.61588200	-0.40384300
	H	-3.31629800	5.46972700	-1.53746300
	C	1.11832400	-1.57848600	-0.76342700
	C	2.63584300	-1.86641100	-0.72837000
	F	0.82410500	-1.06625800	-1.97656900
	F	0.40310000	-2.69618000	-0.61733500
	O	3.42540800	-1.00594900	-0.45544100
	O	2.89696600	-3.10343500	-1.05840100
	C	4.29268100	-3.47818000	-1.10797600
	C	4.36370300	-4.92997500	-1.50605300
	H	4.72587800	-3.29217000	-0.11576300
	H	4.79369800	-2.81846900	-1.82949200
	H	5.41449500	-5.24327000	-1.55117900

	H	3.84287700	-5.55907700	-0.77251900
	H	3.91053800	-5.08419300	-2.49398700
	Br	1.42426000	-0.26839400	3.56736900
Structure TS1-H_b Solvent: Ethanol				
cartesian coordinates of stationary point structure [Å]	C	-0.38268200	-0.93818300	2.26957200
	C	1.01554500	-1.21545500	1.66119500
	C	0.17075600	0.37167400	2.82254300
	H	-1.17488300	-0.80944900	1.51695900
	H	-0.72227300	-1.65097500	3.03038600
	H	1.55181000	-2.04913000	2.12976400
	C	1.50946900	0.18055300	2.11222200
	H	2.38845200	0.18474200	2.76744400
	H	1.68272300	0.87877100	1.28010200
	S	-0.75245500	1.88170800	2.64755200
	O	0.09190000	2.96198300	3.16350600
	O	-2.07587400	1.64266900	3.22776900
	C	-0.94946600	2.11374400	0.89763300
	C	0.03206300	2.81210300	0.19460900
	C	-2.06775900	1.56702300	0.26895500
	C	-0.10357900	2.94244300	-1.18570100
	H	0.87617800	3.25248600	0.72753200
	C	-2.18982400	1.70645600	-1.11181100
	H	-2.82919900	1.05457400	0.85882100
	C	-1.20742300	2.38556700	-1.83477500
	H	0.65139300	3.48496200	-1.75553300
	H	-3.05652500	1.28775100	-1.62413300
	H	-1.30728700	2.48950000	-2.91604100
	C	0.99685700	-1.43240600	0.17190700
	C	2.40399700	-1.52352800	-0.44482400
	F	0.35416900	-0.40576600	-0.44828900
	F	0.30373400	-2.55234500	-0.12747500
	O	3.39698000	-1.20506600	0.15071000
	O	2.35135600	-1.95841800	-1.68419000
	C	3.60388700	-2.05061100	-2.38980500
	C	3.31376300	-2.55805800	-3.77987900
	H	4.26424600	-2.72596700	-1.82807900
	H	4.06729400	-1.05406100	-2.39692800
	H	4.25177500	-2.63958100	-4.34385300
	H	2.84289800	-3.54912100	-3.74016500
	H	2.64495900	-1.86886900	-4.31209000
	O	0.49387600	0.23011600	5.30203400
	H	0.34280100	0.30421100	4.05793200
	C	-0.48367200	1.01638700	5.91955800

	C	-0.22127500	0.92739700	7.42084800
	H	-1.49851000	0.64894100	5.69206900
	H	-0.41397000	2.06743500	5.59086300
	H	-0.96627300	1.53129900	7.95587700
	H	-0.29641500	-0.11348200	7.76193100
	H	0.78143500	1.30677600	7.65734800
Structure TS1-H_a Solvent: Ethanol				
cartesian coordinates of stationary point structure [Å]	C	-0.24618500	-0.61492800	2.41209000
	C	1.13153300	-0.97188400	1.79599000
	C	0.32921900	0.74417600	2.77097700
	H	-1.07423700	-0.59644300	1.68662500
	H	-0.53115100	-1.23146800	3.27550100
	H	1.66815800	-1.77006300	2.32273900
	C	1.65858700	0.45452100	2.09487000
	H	2.53977600	0.50065800	2.74972700
	H	1.86087100	1.05467000	1.19392200
	S	-0.55316200	2.23289800	2.53099600
	O	0.34666700	3.33574900	2.88264600
	O	-1.83897800	2.09341500	3.22319500
	C	-0.88008000	2.32654600	0.78458400
	C	0.06666500	2.92289800	-0.04841000
	C	-2.04305600	1.74173700	0.28348600
	C	-0.15490500	2.91575200	-1.42405400
	H	0.95142600	3.39297700	0.38362800
	C	-2.25140400	1.74274300	-1.09424800
	H	-2.77220000	1.30802900	0.96945400
	C	-1.30712300	2.32248800	-1.94374200
	H	0.57140500	3.37926400	-2.09263600
	H	-3.15579900	1.29346600	-1.50604800
	H	-1.47456000	2.31863900	-3.02167500
	C	1.06151600	-1.31484300	0.33334500
	C	2.44467100	-1.49744500	-0.31697600
	F	0.41862100	-0.33183100	-0.35328600
	F	0.33835400	-2.44268200	0.14992700
	O	3.47159100	-1.22465200	0.24255100
	O	2.33293500	-1.96258900	-1.54224300
	C	3.55783000	-2.15199300	-2.27548500
	C	3.20077300	-2.68611600	-3.63983400
	H	4.19325400	-2.84664300	-1.70846900
	H	4.07865300	-1.18555400	-2.32859300
	H	4.11647300	-2.84097200	-4.22471600
	H	2.67440200	-3.64590700	-3.55454400
	H	2.55858800	-1.97636000	-4.17778300
	C	-0.61755400	0.40219900	6.02337300
	H	-1.33762000	-0.22137800	5.47353000

	H	-0.98845000	1.43509000	6.02409000
	C	0.73449200	0.33813100	5.37253200
	H	0.53896600	0.77010100	4.18325000
	H	1.48210200	1.03061900	5.78918600
	H	-0.56627800	0.03746500	7.06116900
	O	1.18712700	-0.96009800	5.23964100
	H	2.14251400	-0.95932700	5.10164200
Structure 1-propanol Solvent:1-propanol				
cartesian coordinates of stationary point structure [Å]	C	-3.50516200	1.37845200	0.01071100
	H	-3.16919100	0.33124900	-0.02609600
	H	-3.16830600	1.86990200	-0.91443300
	H	-4.60342500	1.37808300	0.00894900
	C	-2.95429100	2.08832800	1.24061600
	H	-3.31183500	3.12964600	1.27776800
	H	-3.31181700	1.59986300	2.16100300
	C	-1.43839900	2.10519300	1.27017600
	H	-1.06002200	2.60550100	0.35845400
	H	-1.06019300	1.06540400	1.24800100
	O	-1.01807800	2.77816000	2.43548300
	H	-0.05479400	2.78736200	2.45131800
Structure TS1-Ha Solvent:1-propanol				
cartesian coordinates of stationary point structure [Å]	C	-0.25366500	-0.62366900	2.40854800
	C	1.12326500	-0.98217500	1.79167900
	C	0.32428400	0.73380300	2.76974900
	H	-1.08133800	-0.60194900	1.68274700
	H	-0.54069200	-1.24060600	3.27098600
	H	1.65924900	-1.78086800	2.31830100
	C	1.65229700	0.44339800	2.09080700
	H	2.53448300	0.48782000	2.74451900
	H	1.85367800	1.04387600	1.18991400
	S	-0.55677100	2.22417500	2.53427000

	O	0.34188800	3.32470000	2.89594100
	O	-1.84590800	2.08136800	3.21939200
	C	-0.87554500	2.32715200	0.78682300
	C	0.07491200	2.92811800	-0.03857200
	C	-2.03627400	1.74525700	0.27726200
	C	-0.14038500	2.92853100	-1.41523900
	H	0.95757000	3.39593700	0.40018000
	C	-2.23836700	1.75382500	-1.10137000
	H	-2.76852800	1.30798300	0.95763300
	C	-1.29023100	2.33814100	-1.94337600
	H	0.58889700	3.39576700	-2.07796900
	H	-3.14089300	1.30686200	-1.51973700
	H	-1.45280300	2.34021300	-3.02206100
	C	1.05254200	-1.32449000	0.32892400
	C	2.43543000	-1.50805400	-0.32170700
	F	0.41032300	-0.34063100	-0.35701500
	F	0.32857500	-2.45175800	0.14509200
	O	3.46296700	-1.24047900	0.23918500
	O	2.32283300	-1.96795300	-1.54893000
	C	3.54742300	-2.15757200	-2.28244700
	C	3.18941100	-2.68401900	-3.64954200
	H	4.18054400	-2.85682800	-1.71849500
	H	4.07129900	-1.19251100	-2.33063200
	H	4.10487300	-2.83884600	-4.23481600
	H	2.66002500	-3.64256700	-3.56913000
	H	2.54957700	-1.96974700	-4.18429900
	C	-0.59752400	0.40947600	6.04113400
	H	-1.31551600	-0.19198100	5.45949600
	H	-0.94773600	1.45084000	5.98406000
	C	0.74685000	0.33135900	5.36684000
	H	0.53936300	0.75913100	4.17525300
	H	1.50526000	1.01849100	5.77597300
	O	1.18736600	-0.97129700	5.23552700
	H	2.14487200	-0.98383900	5.11510100
	C	-0.55348600	-0.07752500	7.48858600
	H	-1.55053400	-0.04036300	7.94817600
	H	-0.19096200	-1.11367600	7.53001300
	H	0.12424200	0.54492200	8.09108200

Structure TS2 Solvent:1-propanol				
cartesian coordinates of stationary point structure [Å]	O	-2.36533400	-0.39065600	-0.13050700
	H	-2.79943100	0.43264200	0.12290200
	C	-0.98791200	-0.22339000	-0.07181000
	C	-0.29722000	-1.56875700	-0.14061700
	H	-0.67093800	0.34681300	0.82057300
	H	-0.63127300	0.40756100	-0.95126800
	H	0.78830900	-1.39502100	-0.19359600
	H	-0.58861000	-2.05675700	-1.08450600
	Br	0.51217000	0.80508800	-2.72698200
	C	-0.64781200	-2.45886300	1.04661400
	H	-1.73248400	-2.62466400	1.09290500
	H	-0.15128200	-3.43543200	0.96861600
	H	-0.33453900	-1.99236300	1.99265800
Structure 1-butanol Solvent:1-butanol				
cartesian coordinates of stationary point structure [Å]	C	-3.50516200	1.37845200	0.01071100
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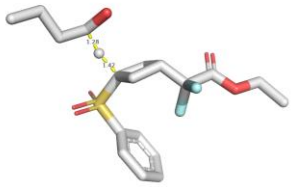
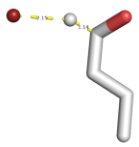
	H	-4.60342500	1.37808300	0.00894900
	C	-2.95429100	2.08832800	1.24061600
	H	-3.31183500	3.12964600	1.27776800
	H	-3.31181700	1.59986300	2.16100300
	C	-1.43839900	2.10519300	1.27017600
	H	-1.06002200	2.60550100	0.35845400
	H	-1.06019300	1.06540400	1.24800100
	O	-1.01807800	2.77816000	2.43548300
	H	-0.05479400	2.78736200	2.45131800

Structure TS1-Ha Solvent:1-butanol				
cartesian coordinates of stationary point structure [Å]	C	-0.24330700	-0.58285900	2.43118400
	C	1.12527500	-0.96252400	1.80829800
	C	0.35079800	0.77304800	2.77094500
	H	-1.07636000	-0.56225400	1.71152900
	H	-0.52954800	-1.18586400	3.30370600
	H	1.65739800	-1.76073000	2.33953000
	C	1.67102000	0.46101700	2.08670900
	H	2.55815700	0.50432200	2.73385200
	H	1.87251500	1.04880500	1.17748000
	S	-0.51602200	2.27000300	2.52493700
	O	0.39744200	3.36447800	2.86695900
	O	-1.80156100	2.14895400	3.22074100
	C	-0.84643800	2.35594500	0.77867500
	C	0.10388600	2.93749200	-0.06064600
	C	-2.01665800	1.77989000	0.28445800
	C	-0.12152300	2.92377000	-1.43562900
	H	0.99425600	3.40164700	0.36627900
	C	-2.22879100	1.77415300	-1.09266100
	H	-2.74819900	1.35819000	0.97534800
	C	-1.28103300	2.33877600	-1.94839000
	H	0.60745700	3.37585400	-2.10912400
	H	-3.13881800	1.33144300	-1.49913000
	H	-1.45144700	2.32968200	-3.02582900
	C	1.03998700	-1.32037400	0.35004000
	C	2.41614600	-1.52391500	-0.30889800
	F	0.40085400	-0.33874800	-0.34167300
	F	0.30527900	-2.44357800	0.18425300
	O	3.45080900	-1.26804600	0.24426200
	O	2.28943400	-1.98745100	-1.53342800
	C	3.50660300	-2.19762000	-2.27347800
	C	3.13272100	-2.72408100	-3.63633400

	H	4.13297300	-2.90379100	-1.71057200
	H	4.04424900	-1.24052800	-2.32860000
	H	4.04221700	-2.89448700	-4.22657100
	H	2.58989800	-3.67447000	-3.54896500
	H	2.50003400	-2.00267000	-4.17000400
	C	-0.54683800	0.50458700	6.05545000
	H	-1.27923400	-0.10607100	5.49936600
	H	-0.89304000	1.54752900	5.98057600
	C	0.78884700	0.39870800	5.37041800
	H	0.57655400	0.81275900	4.17595200
	H	1.56008800	1.08120400	5.76266200
	O	1.21112800	-0.91161700	5.25285300
	H	2.16723100	-0.93824600	5.12408800
	C	-0.50478000	0.05532400	7.51737500
	H	-0.11749900	-0.97446800	7.55464900
	H	0.21932800	0.68151200	8.06398400
	C	-1.87033500	0.13061700	8.18926400
	H	-1.82052000	-0.19348700	9.23809000
	H	-2.26161800	1.15886800	8.17132900
	H	-2.59830200	-0.51160200	7.67130300
Structure TS2 Solvent:1-butanol				
cartesian coordinates of stationary point structure [Å]	O	-2.37030700	-0.49963200	-0.20293200
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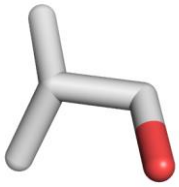
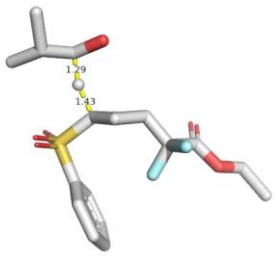
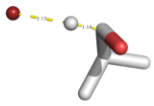
	C	-0.21335100	-1.49675500	-0.07225700
	H	-0.79315600	0.40836600	0.80149100
	H	-0.66905900	0.41672900	-0.96689800
	H	0.85785200	-1.23864500	-0.08774300
	H	-0.42230300	-2.04679300	-1.00535600
	Br	0.49303600	0.85240100	-2.72799000
	C	-0.52937800	-2.37995400	1.13215600
	H	-1.60985800	-2.58855900	1.13986000
	H	-0.31366200	-1.81824300	2.05637000

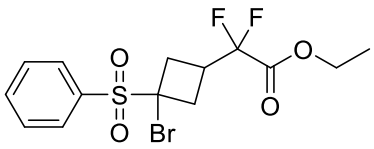
	C	0.25876600	-3.68416400	1.12113500
	H	1.34202300	-3.49081700	1.13296700
	H	0.01792500	-4.30711100	1.99371600
	H	0.03526200	-4.26952900	0.21660000
Structure 2-methyl-1-propanol Solvent:2-methyl-1-propanol				
cartesian coordinates of stationary point structure [Å]	C	-3.45930900	-0.04623800	0.00651800
	H	-3.07334700	-1.07382900	-0.01074400
	H	-3.12839100	0.45944200	-0.91547000
	H	-4.55835300	-0.08345600	-0.00391700
	C	-2.94646400	0.70330400	1.23315500
	H	-3.30726200	0.18203300	2.13702500
	C	-3.45191500	2.14270400	1.26340600
	H	-3.09164500	2.69781200	0.38243100
	H	-4.55075400	2.17251000	1.25060200
	H	-3.10763600	2.67396700	2.16303000
	C	-1.42603700	0.67833000	1.29159300
	H	-1.08559900	1.25049000	2.17492100
	H	-1.02627300	1.19136200	0.39448300
	O	-0.98715800	-0.65966400	1.35275900
	H	-0.02409800	-0.66670500	1.32934900
Structure TS1-Ha Solvent: 2-methyl-1-propanol				
cartesian coordinates of stationary point structure [Å]	C	-0.27693900	-0.65426600	2.38933200
	C	1.11305200	-0.96132000	1.77462100
	C	0.25101100	0.72268300	2.75488900
	H	-1.09957000	-0.65405900	1.65730600
	H	-0.54993100	-1.28289700	3.24730200

	H	1.68328700	-1.72669900	2.31482100
	C	1.57963300	0.49020000	2.05135700
	H	2.47398300	0.58705800	2.68153400
	H	1.72703300	1.08794500	1.13844600
	S	-0.71406900	2.16155200	2.50646100
	O	0.09269600	3.31672900	2.91717700
	O	-2.01960000	1.92575200	3.13273500
	C	-0.96613900	2.27097300	0.74817400
	C	-0.01937300	2.93712500	-0.03032600
	C	-2.07227700	1.63529500	0.18456100
	C	-0.17981400	2.94716700	-1.41438900
	H	0.81795100	3.44635100	0.44922600
	C	-2.22041400	1.65506900	-1.20080400
	H	-2.80560700	1.14813100	0.82885300
	C	-1.27366100	2.30310900	-1.99617000
	H	0.54808900	3.46426500	-2.04058900
	H	-3.08001100	1.16642000	-1.66082600
	H	-1.39363300	2.31331400	-3.08037700
	C	1.06026400	-1.33461400	0.31855000
	C	2.45145800	-1.47202000	-0.32563800
	F	0.37986900	-0.39221900	-0.38826700
	F	0.38439900	-2.49447800	0.15640300
	O	3.46410600	-1.14134600	0.22868500
	O	2.36326400	-1.97001300	-1.53991100
	C	3.59709100	-2.12293500	-2.26634800
	C	3.26704700	-2.70084600	-3.61964200
	H	4.25964700	-2.77772900	-1.68314100
	H	4.07701900	-1.13679800	-2.33906300
	H	4.19026100	-2.83030200	-4.19888300
	H	2.78035700	-3.67944100	-3.51475600
	H	2.59774000	-2.03018000	-4.17439700
	C	-0.59087500	0.56507300	6.07882500
	H	-1.40637900	0.19477300	5.43178600
	C	0.71204100	0.29893400	5.35607600
	H	0.50477200	0.74208700	4.16578100
	H	1.56268800	0.89181500	5.73319200
	O	0.98996300	-1.04553600	5.21991600
	H	1.93857700	-1.17524900	5.09883000

	C	-0.64186700	-0.18609000	7.41047400
	H	-1.60266000	-0.00833100	7.91476500
	H	-0.51876100	-1.26592700	7.25738700
	H	0.16304200	0.16160700	8.07732400
	C	-0.77130000	2.06851900	6.27437900
	H	-0.70215600	2.61396700	5.32334000
	H	-1.75394200	2.28373000	6.71701700
	H	0.00058000	2.45969500	6.95598200
Structure TS2 Solvent:2-methyl-1-propanol				
cartesian coordinates of stationary point structure [Å]	O	-2.41393700	-0.39536500	-0.07817300
	H	-2.82351200	0.43215700	0.20028500
	C	-1.03253300	-0.24374600	-0.09737600
	C	-0.35239000	-1.59939800	-0.20737900
	H	-0.65929200	0.31893500	0.77671600
	H	-0.72240100	0.37751500	-0.99953700
	H	0.72809100	-1.39258300	-0.28828700
	Br	0.64154700	1.06860700	-2.54484500
	C	-0.60625300	-2.42567200	1.05377000
	H	-1.68405400	-2.60571200	1.17627900
	H	-0.09857400	-3.39851600	0.98923200
	H	-0.24083300	-1.90681300	1.95207000
	C	-0.80692900	-2.34089900	-1.46280800
	H	-0.60074900	-1.74953000	-2.36791500
	H	-0.28573800	-3.30400100	-1.55651100
	H	-1.88807700	-2.53578800	-1.41869500

5 Product characterization

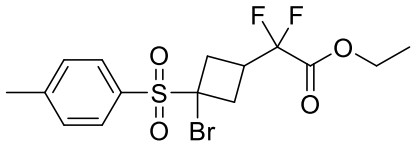
ethyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3a)



Prepared according to General Procedure A, compound **3a** was obtained as colorless oil (49

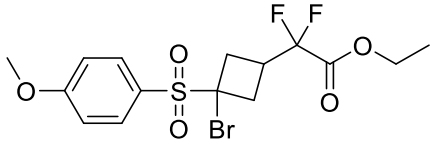
mg, 62 % yield, *dr* = 3.5:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 – 7.93 (m, 2H), 7.77 – 7.68 (m, 1H), 7.65 – 7.56 (m, 2H), 4.40 – 4.28 (m, 2H), 3.55 – 3.26 (m, 3H), 3.05 – 2.42 (m, 2H), 1.40 – 1.32 (m, 3H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 135.0, 133.6, 131.3, 129.1, 114.1 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 65.4, 63.4, 35.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.52. **HRMS** (ESI) for $C_{14}H_{15}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 418.9735, found: 418.9733. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 134.8, 134.0, 130.7, 129.2, 114.1 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 67.7, 63.5, 34.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.40. **HRMS** (ESI) for $C_{14}H_{15}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 418.9735, found: 418.9733.

ethyl 2-(3-bromo-3-tosylcyclobutyl)-2,2-difluoroacetate (3b)



Prepared according to General Procedure A, compound **3b** was obtained as colorless oil (53 mg, 65 % yield, *dr* = 3.5:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 – 7.81 (m, 2H), 7.42 – 7.35 (m, 2H), 4.39 – 4.28 (m, 2H), 3.53 – 3.26 (m, 3H), 3.04 – 2.40 (m, 5H), 1.39 – 1.32 (m, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 146.3, 130.9, 130.5, 129.8, 113.8 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 65.6, 63.4, 35.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 21.9, 14.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.53. **HRMS** (ESI) for $C_{15}H_{17}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 432.9891, found: 432.9888. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 146.1, 131.2, 130.6, 129.9, 114.2 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 67.9, 63.4, 34.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 31.8 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 21.9, 14.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.38. **HRMS** (ESI) for $C_{15}H_{17}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 432.9891, found: 432.9888.

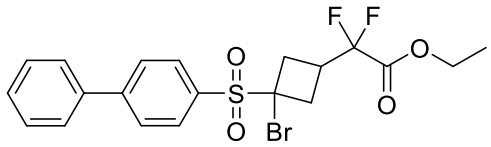
ethyl 2-(3-bromo-3-((4-methoxyphenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3c)



Prepared according to General Procedure A, compound **3c** was obtained as colorless oil (60 mg, 70 % yield, *dr* = 3.3:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.98 – 7.83 (m, 2H), 7.08 – 6.99 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.90 (d, *J* = 1.8 Hz, 3H), 3.51 – 3.26

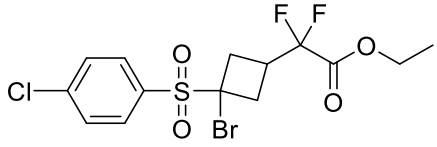
(m, 3H), 3.05 – 2.38 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.8, 163.2 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 133.5, 124.7, 114.4, 113.9 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 65.9, 63.4, 55.9, 35.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.51. **HRMS** (ESI) for $C_{15}H_{17}BrF_2NaO_5S$ $[M + Na]^+$, calcd: 448.9840, found: 448.9833. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7, 163.2 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 132.9, 125.1, 114.5, 114.2 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 68.3, 63.4, 55.9, 34.8 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 31.8 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.39. **HRMS** (ESI) for $C_{15}H_{17}BrF_2NaO_5S$ $[M + Na]^+$, calcd: 448.9840, found: 448.9833.

ethyl 2-(3-([1,1'-biphenyl]-4-ylsulfonyl)-3-bromocyclobutyl)-2,2-difluoroacetate (3d)



Prepared according to General Procedure A, compound **3d** was obtained as a beige solid (35 mg, 37 % yield, dr = 2.7:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 7.99 (m, 2H), 7.82 – 7.76 (m, 2H), 7.68 – 7.59 (m, 2H), 7.54 – 7.42 (m, 3H), 4.40 – 4.28 (m, 2H), 3.58 – 3.30 (m, 3H), 3.07 – 2.47 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 147.8, 138.9, 132.4, 132.0, 131.2, 129.3, 129.1, 127.6, 127.6, 113.8 ($^1J_{C\text{-}F}$ = 251.3 Hz), 65.5, 63.4, 35.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.50. **HRMS** (ESI) for $C_{20}H_{19}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 495.0048, found: 495.0043. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 147.7, 138.9, 132.4, 131.8, 131.2, 129.3, 129.0, 127.7, 127.6, 114.1 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 67.9, 63.5, 34.8 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.37. **HRMS** (ESI) for $C_{20}H_{19}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 495.0048, found: 495.0043.

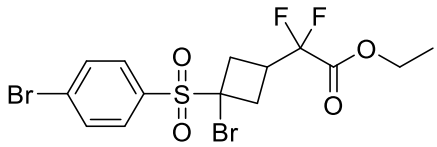
ethyl 2-(3-bromo-3-((4-chlorophenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3e)



Prepared according to General Procedure A, compound **3e** was obtained as colorless oil (51 mg, 59 % yield, dr = 2.6:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00 – 7.87 (m, 2H), 7.61 – 7.54 (m, 2H), 4.34 (qd, J = 7.2, 3.7 Hz, 2H), 3.54 – 3.27 (m, 3H), 3.05 – 2.43

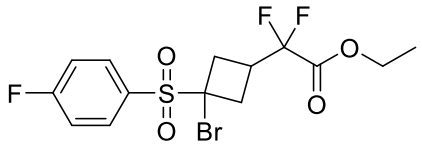
(m, 2H), 1.36 (td, J = 7.2, 1.7 Hz, 3H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 142.1, 132.4, 132.1, 129.5, 114.1 (t, $^1J_{C\text{-}F}$ = 224.3 Hz), 65.3, 63.5, 35.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 25.5 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.53. **HRMS** (ESI) for $C_{14}H_{14}BrClF_2NaO_4S$ $[M + Na]^+$, calcd: 452.9345, found: 452.9346. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 141.9, 132.6, 132.1, 129.7, 114.1 (t, $^1J_{C\text{-}F}$ = 224.3 Hz), 67.6, 63.5, 34.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 31.8 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.45. **HRMS** (ESI) for $C_{14}H_{14}BrClF_2NaO_4S$ $[M + Na]^+$, calcd: 452.9345, found: 452.9346.

ethyl 2-(3-bromo-3-((4-bromophenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3f)



Prepared according to General Procedure A, compound **3f** was obtained as colorless oil (50 mg, 52 % yield, *dr* = 2.2:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 2H), 7.77 – 7.69 (m, 2H), 4.38 – 4.27 (m, 2H), 3.53 – 3.26 (m, 3H), 3.07 – 2.41 (m, 2H), 1.39 – 1.31 (m, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 133.1, 132.6, 132.1, 130.7, 113.7 (t, $^1J_{C\text{-}F}$ = 251.5 Hz), 65.3, 63.4, 35.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.51. **HRMS** (ESI) for $C_{14}H_{14}Br_2F_2NaO_4S$ $[M + Na]^+$, calcd: 496.8840, found: 496.8847. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 132.6, 132.5, 132.1, 130.5, 114.1 (t, $^1J_{C\text{-}F}$ = 251.5 Hz), 67.6, 63.5, 34.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.45. **HRMS** (ESI) for $C_{14}H_{14}Br_2F_2NaO_4S$ $[M + Na]^+$, calcd: 496.8840, found: 496.8847.

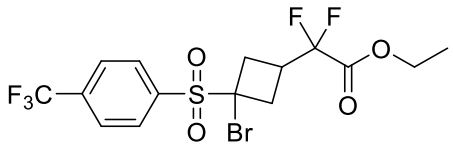
ethyl 2-(3-bromo-3-((4-fluorophenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3g)



Prepared according to General Procedure A, compound **3g** was obtained as colorless oil (62 mg, 75 % yield, *dr* = 2.8:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 – 7.93 (m, 2H), 7.32 – 7.22 (m, 2H), 4.40 – 4.26 (m, 2H), 3.54 – 3.25 (m, 3H), 3.04 – 2.41 (m, 2H), 1.39 – 1.30 (m, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.0 (d, $^1J_{C\text{-}F}$ = 259.6 Hz), 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 134.2 (d, $^3J_{C\text{-}F}$ = 9.1 Hz), 129.6 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 116.7 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 113.8

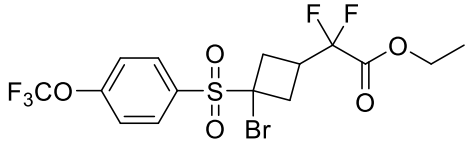
(t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 65.5, 63.4, 35.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -101.20, -114.52. **HRMS** (ESI) for $C_{14}H_{14}BrF_3NaO_4S$ $[M + Na]^+$, calcd: 436.9641, found: 436.9635. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9 (d, $^{1}J_{C\text{-}F}$ = 259.6 Hz), 163.1 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 133.6 (d, $^{3}J_{C\text{-}F}$ = 10.1 Hz), 130.0 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 116.8 (d, $^{2}J_{C\text{-}F}$ = 23.2 Hz), 114.1 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 67.8, 63.5, 34.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 31.8 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -101.48, -113.48. **HRMS** (ESI) for $C_{14}H_{14}BrF_3NaO_4S$ $[M + Na]^+$, calcd: 436.9641, found: 436.9635.

ethyl 2-(3-bromo-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3h)



Prepared according to General Procedure A, compound **3h** was obtained as colorless oil (56 mg, 60 % yield, *dr* = 7:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.21 – 8.07 (m, 2H), 7.91 – 7.82 (m, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.58 – 3.29 (m, 3H), 3.08 – 2.42 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 137.9, 136.9 (q, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 131.9, 126.4 (q, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 124.5 (q, $^{1}J_{C\text{-}F}$ = 274.7 Hz), 114.0 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 65.1, 63.5, 35.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 34.4 (t, $^{2}J_{C\text{-}F}$ = 28.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -63.30, -114.54. **HRMS** (ESI) for $C_{15}H_{14}BrF_5NaO_4S$ $[M + Na]^+$, calcd: 486.9609, found: 486.9619. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 137.9, 136.9 (q, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 131.3, 126.4 (q, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 124.5 (q, $^{1}J_{C\text{-}F}$ = 274.7 Hz), 114.0 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 67.3, 63.5, 34.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 32.0 (t, $^{2}J_{C\text{-}F}$ = 27.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -63.28, -113.52. **HRMS** (ESI) for $C_{15}H_{14}BrF_5NaO_4S$ $[M + Na]^+$, calcd: 486.9609, found: 486.9619.

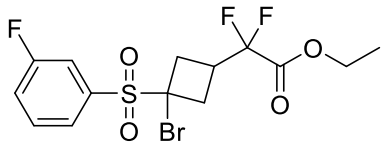
ethyl 2-(3-bromo-3-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3i)



Prepared according to General Procedure A, compound **3i** was obtained as colorless oil (61 mg, 63 % yield, *dr* = 2.2:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 8.00 (m, 2H), 7.44 – 7.38 (m, 2H), 4.38 – 4.28 (m, 2H), 3.53 – 3.30 (m, 3H), 3.07 – 2.45 (m, 2H),

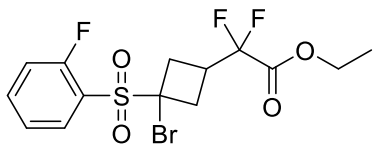
1.36 (t, J = 7.1 Hz, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 154.0, 133.6, 131.7, 121.6 (q, $^1J_{C\text{-}F}$ = 261.6 Hz), 120.6, 114.1 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 65.3, 63.5, 35.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -57.59, -114.54. **HRMS** (ESI) for $C_{15}H_{14}BrF_5NaO_5S$ $[M + Na]^+$, calcd: 502.9558, found: 502.9558. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 153.9, 133.0, 132.2, 121.6 (q, $^1J_{C\text{-}F}$ = 261.6 Hz), 120.7, 114.1 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 67.6, 63.5, 34.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 27.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -57.61, -113.49. **HRMS** (ESI) for $C_{15}H_{14}BrF_5NaO_5S$ $[M + Na]^+$, calcd: 502.9558, found: 502.9558.

ethyl 2-(3-bromo-3-((3-fluorophenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3j)



Prepared according to General Procedure A, compound **3j** was obtained as colorless oil (46 mg, 55 % yield, *dr* = 2.4:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.66 (m, 2H), 7.64 – 7.56 (m, 1H), 7.47 – 7.39 (m, 1H), 4.34 (qd, J = 7.1, 4.6 Hz, 2H), 3.55 – 3.30 (m, 3H), 3.06 – 2.46 (m, 2H), 1.36 (td, J = 7.1, 2.4 Hz, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{C\text{-}F}$ = 253.5 Hz), 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 135.7 (d, ^3J = 7.1 Hz), 130.9 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 127.1 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 122.4 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 118.7 (d, $^2J_{C\text{-}F}$ = 25.3 Hz), 113.7 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 65.2, 63.5, 35.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -109.07, -114.53. **HRMS** (ESI) for $C_{14}H_{14}BrF_3NaO_4S$ $[M + Na]^+$, calcd: 436.9641, found: 436.9638. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (d, $^1J_{C\text{-}F}$ = 253.5 Hz), 163.1 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 136.1 (d, ^3J = 6.1 Hz), 131.1 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 126.5 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 122.3 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 118.1 (d, $^2J_{C\text{-}F}$ = 24.2 Hz), 114.1 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 67.4, 63.5, 34.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.97, -113.46. **HRMS** (ESI) for $C_{14}H_{14}BrF_3NaO_4S$ $[M + Na]^+$, calcd: 436.9641, found: 436.9638.

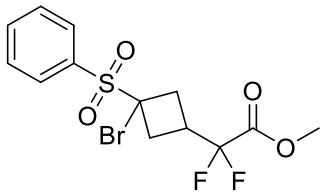
ethyl 2-(3-bromo-3-((2-fluorophenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (3k)



Prepared according to General Procedure A, compound **3k** was obtained as colorless oil (34

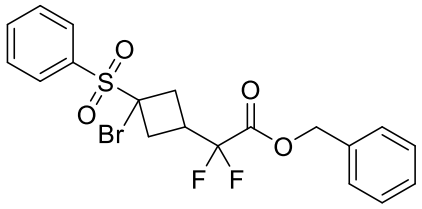
mg, 41 % yield, *dr* = 2.1:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 – 7.94 (m, 1H), 7.76 – 7.64 (m, 1H), 7.41 – 7.33 (m, 1H), 7.31 – 7.21 (m, 1H), 4.33 (qd, *J* = 7.2, 3.9 Hz, 2H), 3.65 – 3.22 (m, 3H), 3.14 – 2.52 (m, 2H), 1.35 (td, *J* = 7.2, 2.5 Hz, 3H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 161.1 (d, $^{1}J_{C\text{-}F}$ = 259.6 Hz), 137.4 (d, $^{3}J_{C\text{-}F}$ = 9.1 Hz), 134.0, 124.7 (d, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 122.9 (d, $^{2}J_{C\text{-}F}$ = 15.2 Hz), 117.8 (d, $^{2}J_{C\text{-}F}$ = 22.2 Hz), 113.9 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 66.2, 63.4, 35.5 (q, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 34.2 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -103.55, -114.52. **HRMS** (ESI) for $C_{14}H_{14}BrF_3NaO_4S$ $[M + Na]^+$, calcd: 436.9641, found: 436.9636. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 160.9 (d, $^{1}J_{C\text{-}F}$ = 258.6 Hz), 137.2 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 133.0, 124.8 (d, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 123.3 (d, $^{2}J_{C\text{-}F}$ = 15.2 Hz), 117.5 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 114.2 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 68.1, 63.4, 35.1 (q, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 32.1 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -105.35, -113.37. **HRMS** (ESI) for $C_{14}H_{14}BrF_3NaO_4S$ $[M + Na]^+$, calcd: 436.9641, found: 436.9636.

methyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3l)



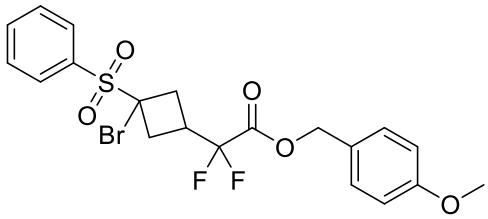
Prepared according to General Procedure A, compound **3l** was obtained as colorless oil (45 mg, 59 % yield, *dr* = 3:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 2H), 7.76 – 7.67 (m, 1H), 7.64 – 7.55 (m, 2H), 3.88 (d, *J* = 3.7 Hz, 3H), 3.54 – 3.26 (m, 3H), 3.06 – 2.41 (m, 2H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 135.0, 133.6, 131.3, 129.1, 113.8 (t, $^{1}J_{C\text{-}F}$ = 251.5 Hz), 65.3, 53.7, 35.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.29. **HRMS** (ESI) for $C_{13}H_{13}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 404.9578, found: 404.9573. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 134.8, 134.0, 130.7, 129.2, 114.2 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 67.7, 53.8, 34.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 31.8 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.15. **HRMS** (ESI) for $C_{13}H_{13}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 404.9578, found: 404.9573.

benzyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3m)



Prepared according to General Procedure A, compound **3m** was obtained as colorless oil (49 mg, 53 % yield, *dr* = 3.1:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 – 7.90 (m, 2H), 7.77 – 7.67 (m, 1H), 7.63 – 7.53 (m, 2H), 7.44 – 7.33 (m, 5H), 5.28 (d, *J* = 4.2 Hz, 2H), 3.54 – 3.24 (m, 3H), 3.04 – 2.37 (m, 2H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 134.9, 133.9, 131.2, 130.6, 129.2, 129.1, 128.9, 128.6, 113.8 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 68.7, 65.3, 35.6 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.36. **HRMS** (ESI) for $C_{19}H_{17}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 480.9891, found: 480.9889. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 134.8, 134.0, 131.2, 130.6, 129.2, 129.1, 128.9, 128.6, 114.2 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 68.8, 67.6, 34.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 31.8 (t, $^2J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.22. **HRMS** (ESI) for $C_{19}H_{17}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 480.9891, found: 480.9889.

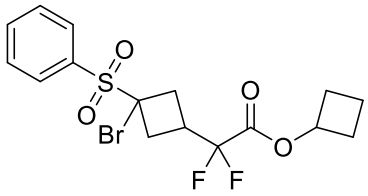
4-methoxybenzyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3n)



Prepared according to General Procedure A, compound **3n** was obtained as colorless oil (47 mg, 48 % yield, *dr* = 2.9:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 – 7.90 (m, 2H), 7.76 – 7.67 (m, 1H), 7.63 – 7.54 (m, 2H), 7.31 (dd, *J* = 8.8, 2.4 Hz, 2H), 6.91 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.22 (d, *J* = 3.9 Hz, 2H), 3.82 (d, *J* = 2.9 Hz, 3H), 3.54 – 3.21 (m, 3H), 3.01 – 2.35 (m, 2H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 160.4, 134.9, 133.6, 131.3, 130.7, 129.1, 126.2, 114.3, 114.2 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 68.7, 65.4, 55.5, 35.7 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 34.4 (t, $^2J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.54. **HRMS** (ESI) for $C_{20}H_{19}BrF_2NaO_5S$ $[M + Na]^+$, calcd: 510.9997, found: 510.9974. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 160.3, 134.8, 134.0, 130.7, 130.7, 129.2, 126.2, 114.3, 114.0 (t,

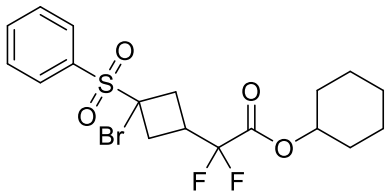
$^{1}J_{C\text{-}F}$ = 252.5 Hz), 68.8, 67.7, 55.5, 34.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 31.9 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.28. **HRMS** (ESI) for $C_{20}H_{19}BrF_2NaO_5S$ $[M + Na]^+$, calcd: 510.9997, found: 510.9974.

cyclobutyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3o)



Prepared according to General Procedure A, compound **3o** was obtained as colorless oil (56 mg, 66 % yield, *dr* = 2.4:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 – 7.93 (m, 2H), 7.77 – 7.68 (m, 1H), 7.65 – 7.55 (m, 2H), 5.18 – 5.04 (m, 1H), 3.56 – 3.23 (m, 3H), 3.05 – 2.35 (m, 4H), 2.26 – 2.06 (m, 2H), 1.94 – 1.81 (m, 1H), 1.75 – 1.62 (m, 1H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.3 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 134.9, 133.6, 131.3, 129.1, 113.7 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 71.6, 65.4, 35.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 34.3 (t, $^{2}J_{C\text{-}F}$ =26.3 Hz), 30.2, 13.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.59. **HRMS** (ESI) for $C_{16}H_{17}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 444.9891, found: 444.9882. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 134.8, 134.0, 130.7, 129.2, 114.0 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 71.7, 67.8, 34.7 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 31.9 (t, $^{2}J_{C\text{-}F}$ =26.3 Hz), 30.2, 13.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.55. **HRMS** (ESI) for $C_{16}H_{17}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 444.9891, found: 444.9882.

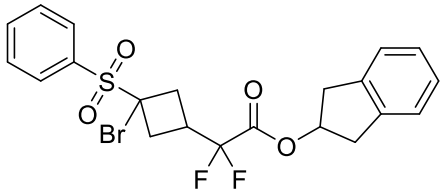
cyclohexyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3p)



Prepared according to General Procedure A, compound **3p** was obtained as colorless oil (52 mg, 58 % yield, *dr* = 2.6:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 2H), 7.76 – 7.67 (m, 1H), 7.64 – 7.54 (m, 2H), 4.97 – 4.84 (m, 1H), 3.54 – 3.23 (m, 3H), 3.05 – 2.40 (m, 2H), 1.94 – 1.81 (m, 2H), 1.78 – 1.70 (m, 2H), 1.58 – 1.30 (m, 6H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.5 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 134.9, 133.6, 131.2, 129.1, 114.1 (t, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 76.4, 65.4, 35.7 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz), 34.3 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 31.2, 25.1, 23.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.64. **HRMS** (ESI) for $C_{18}H_{21}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 473.0204,

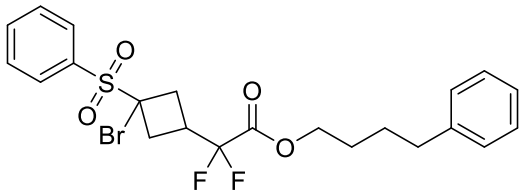
found: 473.0194. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.5 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 134.8, 134.0, 130.6, 129.2, 114.1 ($^1J_{C\text{-}F}$ = 250.5 Hz), 76.4, 67.8, 34.8 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 31.2, 25.1, 23.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.72. **HRMS** (ESI) for $C_{18}H_{21}BrF_2NaO_4S$ [M + Na]$^+$, calcd: 473.0204, found: 473.0194.

2,3-dihy*dr*o-1*H*-inden-2-yl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3q)



Prepared according to General Procedure A, compound **3q** was obtained as colorless oil (63 mg, 65 % yield, *dr* = 2.7:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 2H), 7.76 – 7.67 (m, 1H), 7.64 – 7.54 (m, 2H), 7.27 – 7.19 (m, 4H), 5.67 (t, *J* = 6.2, 3.0 Hz, 1H), 3.49 – 3.21 (m, 5H), 3.14 – 3.02 (m, 2H), 3.00 – 2.32 (m, 2H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 139.5, 134.9, 133.6, 131.2, 129.1, 127.3, 124.8, 114.1 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 78.8, 65.3, 39.5, 35.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 25.5 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.51. **HRMS** (ESI) for $C_{21}H_{19}BrF_2NaO_4S$ [M + Na]$^+$, calcd: 507.0048, found: 507.0039. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 139.5, 134.8, 134.0, 130.6, 129.2, 127.3, 124.8, 114.1 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 78.8, 67.7, 39.5, 34.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.38. **HRMS** (ESI) for $C_{21}H_{19}BrF_2NaO_4S$ [M + Na]$^+$, calcd: 507.0048, found: 507.0039.

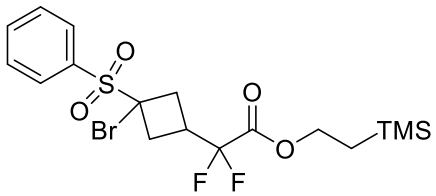
4-phenylbutyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3r)



Prepared according to General Procedure A, compound **3r** was obtained as colorless oil (68 mg, 68 % yield, *dr* = 2.4:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 – 7.92 (m, 2H), 7.77 – 7.66 (m, 1H), 7.64 – 7.53 (m, 2H), 7.35 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 4.38 – 4.17 (m, 2H), 3.53 – 3.26 (m, 3H), 3.05 – 2.38 (m, 4H), 1.82 – 1.67 (m, 4H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 141.7, 135.0, 133.6, 131.3, 129.1, 128.6, 128.5, 126.1, 114.2, 67.1, 65.4, 35.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 35.4, 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 27.9, 27.5. **^{19}F NMR**

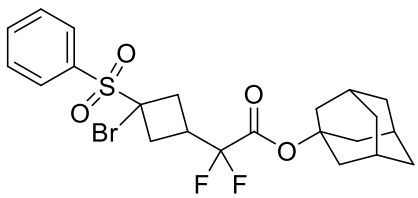
(282 MHz, $CDCl_3$) δ-114.36. **HRMS** (ESI) for $C_{22}H_{23}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 523.0361, found: 523.0358. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 141.7, 134.8, 134.0, 130.7, 129.2, 128.6, 128.5, 126.1, 114.2, 67.7, 67.2, 35.4, 34.7 (t, $^3J_{C\text{-}F}$ = 32.3 Hz), 31.86 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 27.9, 27.55. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.32. **HRMS** (ESI) for $C_{22}H_{23}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 523.0361, found: 523.0358.

2-(trimethylsilyl)ethyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3s)



Prepared according to General Procedure A, compound **3s** was obtained as colorless oil (54 mg, 59 % yield, *dr* = 4.4:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 – 7.92 (m, 2H), 7.76 – 7.68 (m, 1H), 7.65 – 7.55 (m, 2H), 4.41 – 4.30 (m, 2H), 3.56 – 3.26 (m, 3H), 3.05 – 2.40 (m, 2H), 1.13 – 1.01 (m, 2H), 0.06 (s, 9H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 135.0, 133.6, 131.3, 129.1, 114.1 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 67.8, 65.4, 35.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 17.5, -1.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.56. **HRMS** (ESI) for $C_{17}H_{23}BrF_2NaO_4SSi$ $[M + Na]^+$, calcd: 491.0130, found: 491.0133. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 134.8, 134.0, 130.7, 129.2, 114.1 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 67.8, 66.1, 34.8 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 17.5, -1.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.51. **HRMS** (ESI) for $C_{17}H_{23}BrF_2NaO_4SSi$ $[M + Na]^+$, calcd: 491.0130, found: 491.0133.

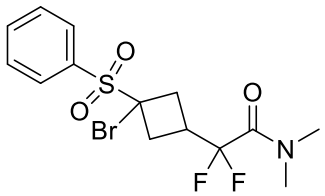
(*3s*,*5s*,*7s*)-adamantan-1-yl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (3t)



Prepared according to General Procedure A, compound **3t** was obtained as a white solid (51 mg, 51 % yield, *dr* = 2.8:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 2H), 7.76 – 7.67 (m, 1H), 7.64 – 7.54 (m, 2H), 3.52 – 3.18 (m, 3H), 3.02 – 2.38 (m, 2H), 2.21 (s, 3H), 2.13 (s, 6H), 1.66 (s, 6H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.6 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 134.9, 133.6, 131.2, 129.1, 113.8 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 85.5, 65.5, 41.1, 35.9, 35.8 (t, $^3J_{C\text{-}}$

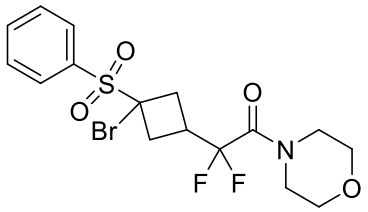
$_F$ = 5.3 Hz), 34.4 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 31.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.63. **HRMS** (ESI) for $C_{22}H_{25}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 525.0517, found: 525.0512. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.6 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 134.7, 134.1, 130.6, 129.2, 113.8 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 85.5, 68.0, 41.1, 35.9, 34.9 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 32.0 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 31.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.74. **HRMS** (ESI) for $C_{22}H_{25}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 525.0517, found: 525.0512.

2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoro-*N*,*N*-dimethylacetamide (3u)



Prepared according to General Procedure A, compound **3u** was obtained as colorless oil (36 mg, 46 % yield, *dr* = 3.7:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 – 7.92 (m, 2H), 7.75 – 7.66 (m, 1H), 7.63 – 7.53 (m, 2H), 3.74 – 3.36 (m, 3H), 3.19 (s, 3H), 2.98 (s, 3H), 2.94 – 2.49 (m, 2H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.3 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 134.8, 133.8, 131.3, 129.0, 117.8 (t, $^1J_{C\text{-}F}$ = 255.0 Hz), 66.3, 36.8, 36.3 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 34.7 (t, $^2J_{C\text{-}F}$ = 25.5 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.68. **HRMS** (ESI) for $C_{14}H_{16}BrF_2NNaO_3S$ $[M + Na]^+$, calcd: 417.9894, found: 417.9881. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.3 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 134.6, 134.3, 130.6, 129.1, 117.8 (t, $^1J_{C\text{-}F}$ = 255.0 Hz), 68.2, 36.7, 35.2 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 32.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.22. **HRMS** (ESI) for $C_{14}H_{16}BrF_2NNaO_3S$ $[M + Na]^+$, calcd: 417.9894, found: 417.9881.

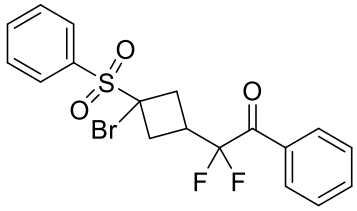
2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoro-1-morpholinoethan-1-one (3v)



Prepared according to General Procedure A, compound **3v** was obtained as a white solid (37 mg, 42 % yield, *dr* = 4.1:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 – 7.92 (m, 2H), 7.75 – 7.66 (m, 1H), 7.63 – 7.51 (m, 2H), 3.79 – 3.66 (m, 6H), 3.66 – 3.38 (m, 5H), 2.96 – 2.49 (m, 2H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 134.8, 133.8, 130.6, 129.1, 118.0 (t, $^1J_{C\text{-}F}$ = 257.6 Hz), 66.9, 66.7, 66.2, 46.4 (t, $^3J_{C\text{-}F}$ = 6.1 Hz), 43.3, 36.3

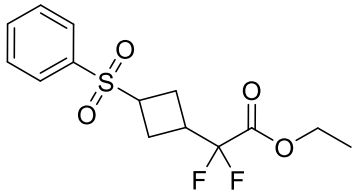
(t, $^{3}J_{C\text{-}F}$ = 6.1 Hz), 34.6 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.02. **HRMS** (ESI) for $C_{16}H_{18}BrF_2NNaO_4S$ $[M + Na]^+$, calcd: 460.0000, found: 459.9996. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0 (t, $^{2}J_{C\text{-}F}$ = 29.3 Hz), 134.7, 134.3, 131.3, 129.0, 118.0 (t, $^{1}J_{C\text{-}F}$ = 257.6 Hz), 68.1, 66.9, 66.7, 46.4 (t, $^{3}J_{C\text{-}F}$ = 6.1 Hz), 43.3, 35.2 (t, $^{3}J_{C\text{-}F}$ = 6.1 Hz), 32.2 (t, J = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -107.58. **HRMS** (ESI) for $C_{16}H_{18}BrF_2NNaO_4S$ $[M + Na]^+$, calcd: 460.0000, found: 459.9996.

2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoro-1-phenylethan-1-one (3w)



Prepared according to General Procedure A, compound **3w** was obtained as colorless oil (43 mg, 50 % yield, *dr* = 4:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 – 7.93 (m, 4H), 7.75 – 7.48 (m, 6H), 3.73 – 3.41 (m, 3H), 3.05 – 2.50 (m, 2H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 188.4 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 134.9, 134.7, 133.7, 131.4 (t, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 131.3, 130.3 (t, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 129.1, 128.9, 117.8 (t, $^{1}J_{C\text{-}F}$ = 254.3 Hz), 66.1, 36.1 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz), 33.8 (t, $^{2}J_{C\text{-}F}$ = 25.5 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.09. **HRMS** (ESI) for $C_{18}H_{15}BrF_2NaO_3S$ $[M + Na]^+$, calcd: 450.9786, found: 450.9785. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 188.4 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 134.9, 134.7, 134.2, 131.4 (t, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 130.6, 130.3 (t, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 129.2, 128.9, 117.8 (t, $^{1}J_{C\text{-}F}$ = 254.3 Hz), 68.3, 35.0 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz), 31.3 (t, $^{2}J_{C\text{-}F}$ = 25.5 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -107.30. **HRMS** (ESI) for $C_{18}H_{15}BrF_2NaO_3S$ $[M + Na]^+$, calcd: 450.9786, found: 450.9785.

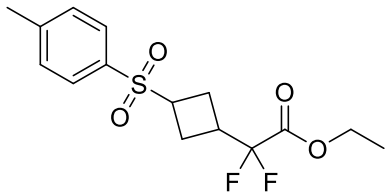
ethyl 2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetate (4a)



Prepared according to General Procedure B, compound **4a** was obtained as a light-yellow solid. (46 mg, 72 % yield, *dr* = 8:1). Isomer 1: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.5 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.8 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.85 – 3.73 (m, 1H), 3.24

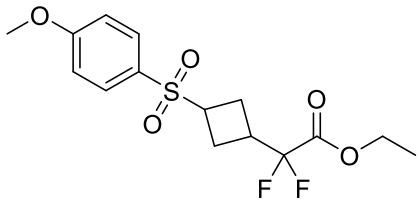
– 3.06 (m, 1H), 2.79 – 2.65 (m, 2H), 2.53 – 2.41 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.4 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 137.5, 134.1, 129.6, 128.4, 115.4 (t, $^2J_{C\text{-}F}$ = 249.8 Hz), 63.2, 54.2, 34.0 (t, $^2J_{C\text{-}F}$ = 24.8 Hz), 22.2 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.77. **HRMS** (ESI) for $C_{14}H_{16}F_2NaO_4S$ $[M + Na]^+$, calcd: 341.0630, found: 341.0616. Isomer 2: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.6 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.76 – 3.65 (m, 1H), 2.95 – 2.78 (m, 1H), 2.77 – 2.66 (m, 2H), 2.31 – 2.20 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.4 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 137.5, 134.1, 129.5, 128.5, 114.2 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 63.2, 52.2, 32.6 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.0 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -115.48. **HRMS** (ESI) for $C_{14}H_{16}F_2NaO_4S$ $[M + Na]^+$, calcd: 341.0630, found: 341.0616.

ethyl 2,2-difluoro-2-(3-tosylcyclobutyl)acetate (4b)



Prepared according to General Procedure B, compound **4b** was obtained as a light-yellow solid. (38 mg, 58 % yield, *dr* = 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H), 7.39 – 7.33 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.77 – 3.61 (m, 1H), 2.95 – 2.63 (m, 3H), 2.45 (s, 3H), 2.31 – 2.16 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 145.1, 134.5, 130.1, 128.4, 114.3 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 63.1, 52.2, 32.5 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.9 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 21.7, 14.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.72. **HRMS** (ESI) for $C_{15}H_{18}F_2NaO_4S$ $[M + Na]^+$, calcd: 355.0786, found: 355.0780.

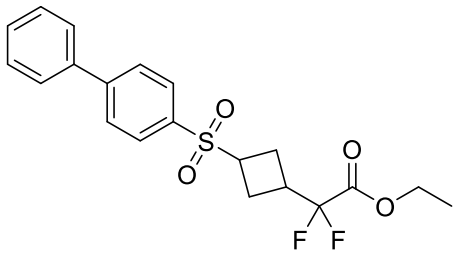
ethyl 2,2-difluoro-2-(3-((4-methoxyphenyl)sulfonyl)cyclobutyl)acetate (4c)



Prepared according to General Procedure B, compound **4c** was obtained as a light-yellow solid. (44 mg, 63 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.06 – 6.98 (m, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.75 – 3.60 (m, 1H), 2.94 – 2.61 (m, 3H), 2.31 – 2.17 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.1, 163.4 (t, $^2J_{C\text{-}F}$ = 32.3 Hz),

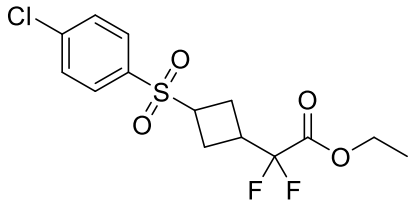
130.7, 128.9, 114.7, 114.3 (t, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 63.2, 55.8, 52.5, 32.5 (t, $^{2}J_{C\text{-}F}$ = 27.3 Hz), 23.1 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.73. **HRMS** (ESI) for $C_{15}H_{18}F_2NaO_5S$ [M + Na]$^+$, calcd: 371.0735, found: 371.0724.

ethyl 2-(3-([1,1'-biphenyl]-4-ylsulfonyl)cyclobutyl)-2,2-difluoroacetate (4d)



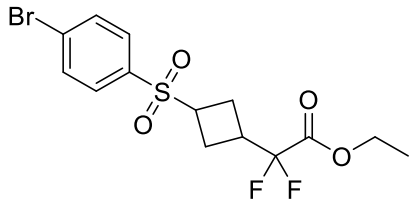
Prepared according to General Procedure B, compound **4d** was obtained as a beige solid. (32 mg, 41 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 2H), 7.81 – 7.73 (m, 2H), 7.66 – 7.58 (m, 2H), 7.53 – 7.40 (m, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.75 (t, *J* = 8.7 Hz, 1H), 2.98 – 2.68 (m, 3H), 2.36 – 2.22 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 147.0, 139.1, 136.1, 129.2, 129.0, 128.9, 128.1, 127.5, 114.3 (t, $^{1}J_{C\text{-}F}$ = 251.5 Hz), 63.2, 52.4, 32.6 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 23.1 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.70. **HRMS** (ESI) for $C_{20}H_{20}F_2NaO_4S$ [M + Na]$^+$, calcd: 417.0943, found: 417.0936.

ethyl 2-(3-((4-chlorophenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (4e)



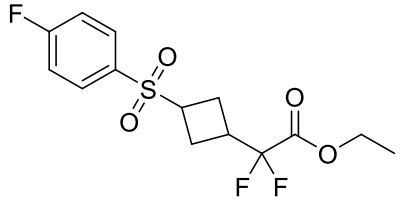
Prepared according to General Procedure B, compound **4e** was obtained as a beige solid. (43 mg, 61 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.58 – 7.51 (m, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.76 – 3.63 (m, 1H), 3.00 – 2.63 (m, 3H), 2.33 – 2.20 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 140.9, 136.0, 129.9, 129.9, 114.2 (t, $^{1}J_{C\text{-}F}$ = 249.8 Hz), 63.2, 52.2, 32.5 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 22.9 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz), 14.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.81. **HRMS** (ESI) for $C_{14}H_{15}ClF_2NaO_4S$ [M + Na]$^+$, calcd: 375.0240, found: 375.0231.

ethyl 2-(3-((4-bromophenyl)sulfonyl)cyclobutyl)-2,2-difluoroacetate (4f)



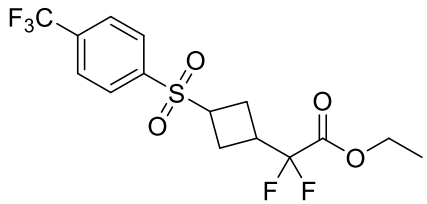
Prepared according to General Procedure B, compound **4f** was obtained as a light-yellow solid. (45 mg, 57 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 1.2 Hz, 4H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.77 – 3.62 (m, 1H), 3.00 – 2.64 (m, 3H), 2.35 – 2.19 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 136.6, 132.9, 130.0, 129.5, 114.2 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 63.3, 52.3, 32.6 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.0 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.80. **HRMS** (ESI) for $C_{14}H_{15}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 418.9735, found: 418.9727.

ethyl 2,2-difluoro-2-(3-((4-fluorophenyl)sulfonyl)cyclobutyl)acetate (4g)



Prepared according to General Procedure B, compound **4g** was obtained as a yellow solid. (44 mg, 66 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 2H), 7.29 – 7.21 (m, 2H, *overlapping with $CDCl_3$ signal*), 4.31 (q, *J* = 7.2 Hz, 2H), 3.78 – 3.62 (m, 1H), 2.99 – 2.62 (m, 3H), 2.33 – 2.20 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (d, $^1J_{C\text{-}F}$ = 255.0 Hz), 163.3 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 133.6 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 131.4 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 117.0 (t, $^2J_{C\text{-}F}$ = 22.5 Hz), 114.2 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 63.3, 52.4, 32.5 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.0 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -102.95, -113.85. **HRMS** (ESI) for $C_{14}H_{15}F_3NaO_4S$ $[M + Na]^+$, calcd: 359.0535, found: 359.0523.

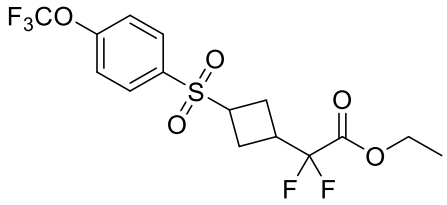
ethyl 2,2-difluoro-2-(3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)acetate (4h)



Prepared according to General Procedure B, compound **4h** was obtained as a light-yellow solid. (60 mg, 78 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 2H), 7.88 – 7.81 (m,

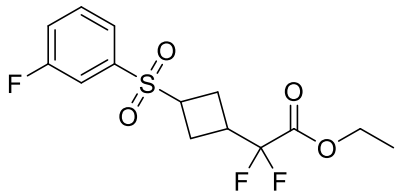
2H), 4.32 (q, J = 7.1 Hz, 2H), 3.80 – 3.66 (m, 1H), 3.01 – 2.67 (m, 3H), 2.35 – 2.22 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 141.2, 136.0 (d, $^2J_{C\text{-}F}$ = 33.0 Hz), 129.2, 126.7 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 125.0 (q, $^1J_{C\text{-}F}$ = 271.5 Hz), 114.1 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 63.3, 52.2, 32.6 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.9 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -63.23, -113.85. **HRMS** (ESI) for $C_{15}H_{15}F_5NaO_4S$ $[M + Na]^+$, calcd: 409.0503, found: 409.0500.

ethyl 2,2-difluoro-2-(3-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclobutyl)acetate (4i)



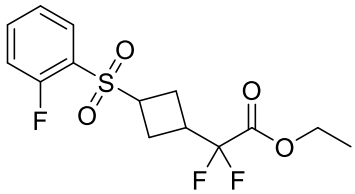
Prepared according to General Procedure B, compound **4i** was obtained as a beige solid. (66 mg, 82 % yield, dr > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H), 7.43 – 7.36 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.78 – 3.64 (m, 1H), 3.00 – 2.65 (m, 3H), 2.35 – 2.21 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 153.4, 135.8, 130.8, 122.0 (d, $^1J_{C\text{-}F}$ = 258.8 Hz), 121.3, 114.2 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 63.3, 52.3, 32.6 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.0 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -57.67, -113.85. **HRMS** (ESI) for $C_{15}H_{15}F_5NaO_5S$ $[M + Na]^+$, calcd: 425.0453, found: 425.0450.

ethyl 2,2-difluoro-2-(3-((3-fluorophenyl)sulfonyl)cyclobutyl)acetate (4j)



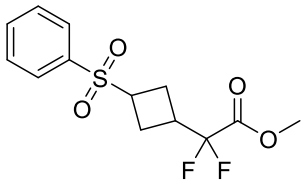
Prepared according to General Procedure B, compound **4j** was obtained as a light-yellow solid. (42 mg, 62 % yield, dr > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 – 7.50 (m, 3H), 7.42 – 7.31 (m, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.81 – 3.63 (m, 1H), 3.01 – 2.63 (m, 3H), 2.38 – 2.19 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.3 (d, $^1J_{C\text{-}F}$ = 251.3 Hz), 163.3 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 139.7 (d, $^3J_{C\text{-}F}$ = 6.8 Hz), 131.5 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 124.4, 121.6 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 116.0 (d, $^2J_{C\text{-}F}$ = 24.8 Hz), 114.2 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 63.3, 52.2, 32.6 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.0 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.1. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.77, -113.82. **HRMS** (ESI) for $C_{14}H_{15}F_3NaO_4S$ $[M + Na]^+$, calcd: 359.0535, found: 359.0526.

ethyl 2,2-difluoro-2-(3-((2-fluorophenyl)sulfonyl)cyclobutyl)acetate (4k)



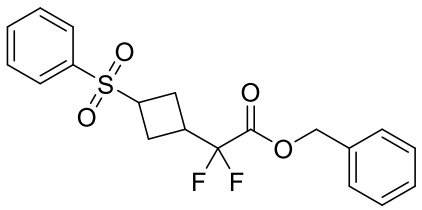
Prepared according to General Procedure B, compound **4k** was obtained as a yellow solid. (29 mg, 43 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 1H), 7.69 – 7.59 (m, 1H), 7.37 – 7.29 (m, 1H), 7.26 – 7.18 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 4.07 – 3.91 (m, 1H), 3.04 – 2.67 (m, 3H), 2.38 – 2.23 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 161.4 (d, $^1J_{C\text{-}F}$ = 254.3 Hz), 136.6 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 131.1, 125.7 (d, $^2J_{C\text{-}F}$ = 15.8 Hz), 125.0 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 117.5 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 114.2 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 63.2, 51.9, 32.6 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.6 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.0. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.38, -113.79. **HRMS** (ESI) for $C_{14}H_{15}F_3NaO_4S$ $[M + Na]^+$, calcd: 359.0535, found: 359.0529.

methyl 2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetate (4l)



Prepared according to General Procedure B (*s*-butanol (0.1M) as solvent instead of EtOH), compound **4l** was obtained as a light-yellow solid. (34 mg, 56 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.71 – 7.63 (m, 1H), 7.57 (ddt, J = 8.3, 6.6, 1.3 Hz, 2H), 3.87 (s, 3H), 3.79 – 3.64 (m, 1H), 2.98 – 2.63 (m, 3H), 2.32 – 2.19 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 137.5, 134.1, 129.5, 128.5, 114.3 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 53.6, 52.2, 32.5 (t, $^2J_{C\text{-}F}$ = 27.3 Hz), 22.9 (t, $^3J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.48. **HRMS** (ESI) for $C_{13}H_{14}F_2NaO_4S$ $[M + Na]^+$, calcd: 327.0473, found: 327.0462.

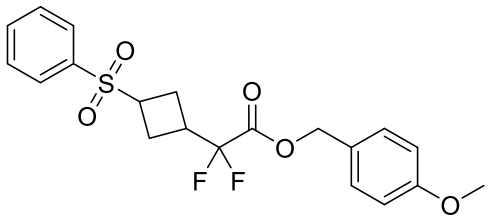
benzyl 2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetate (4m)



Prepared according to General Procedure B (*s*-butanol (0.1M) as solvent instead of EtOH), compound **4m** was obtained as a brown solid. (42 mg, 55 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz,

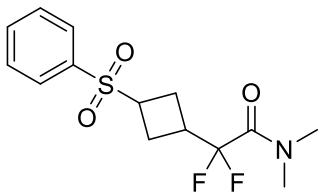
$CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.71 – 7.62 (m, 1H), 7.61 – 7.51 (m, 2H), 7.43 – 7.31 (m, 5H), 5.27 (s, 2H), 3.76 – 3.61 (m, 1H), 2.95 – 2.62 (m, 3H), 2.28 – 2.11 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 137.3, 134.1, 129.5, 129.1, 128.9, 128.6, 128.5, 128.4, 114.3 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 68.6, 52.2, 32.5 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.9 (t, $^3J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.67. **HRMS** (ESI) for $C_{19}H_{18}F_2NaO_4S$ $[M + Na]^+$, calcd: 403.0786, found: 403.0773.

4-methoxybenzyl 2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetate (4n)



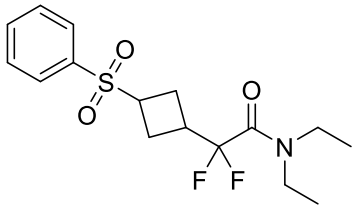
Prepared according to General Procedure B (*s*-butanol (0.1M) as solvent instead of EtOH), compound **4n** was obtained as a yellow solid. (41 mg, 50 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 2H), 7.70 – 7.63 (m, 1H), 7.60 – 7.52 (m, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.20 (s, 2H), 3.82 (s, 3H), 3.76 – 3.57 (m, 1H), 2.93 – 2.60 (m, 3H), 2.26 – 2.10 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{C\text{-}F}$ = 33.0 Hz), 160.2, 137.4, 134.1, 130.6, 129.5, 128.5, 126.3, 114.2, 114.0 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 68.5, 55.4, 52.2, 32.5 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.9 (t, $^3J_{C\text{-}F}$ = 4.5 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.77. **HRMS** (ESI) for $C_{20}H_{20}F_2NaO_5S$ $[M + Na]^+$, calcd: 433.0892, found: 433.0872.

2,2-difluoro-*N*,*N*-dimethyl-2-(3-(phenylsulfonyl)cyclobutyl)acetamide (4o)



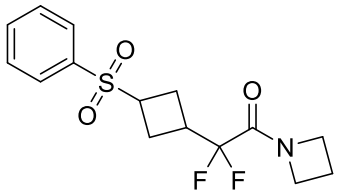
Prepared according to General Procedure B, compound **4o** was obtained as yellow oil. (38 mg, 59 % yield, *dr* = 13.7:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 – 7.82 (m, 2H), 7.70 – 7.61 (m, 1H), 7.61 – 7.50 (m, 2H), 3.73 (p, *J* = 8.5 Hz, 1H), 3.25 – 3.00 (m, 4H), 2.96 (s, 3H), 2.74 – 2.60 (m, 2H), 2.39 – 2.24 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.5 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 137.8, 133.9, 129.4, 128.4, 117.7 (t, $^1J_{C\text{-}F}$ = 255.0 Hz), 52.6, 36.8 (t, $^3J_{C\text{-}F}$ = 7.5 Hz), 36.6, 32.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.4 (t, $^3J_{C\text{-}F}$ = 5.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.55. **HRMS** (ESI) for $C_{14}H_{17}F_2NNaO_3S$ $[M + Na]^+$, calcd: 340.0789, found: 340.0781.

***N*,*N*-diethyl-2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetamide (4p)**



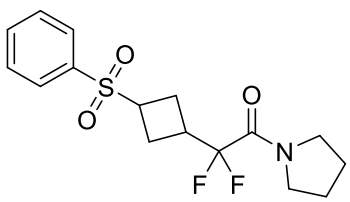
Prepared according to General Procedure B, compound **4p** was obtained as yellow oil. (40 mg, 58 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.69 – 7.61 (m, 1H), 7.60 – 7.51 (m, 2H), 3.80 – 3.65 (m, 1H), 3.57 – 3.45 (m, 2H), 3.33 (q, *J* = 7.1 Hz, 2H), 3.22 – 3.00 (m, 1H), 2.67 (qd, *J* = 9.8, 2.6 Hz, 2H), 2.37 – 2.23 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.9 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 137.8, 133.8, 129.4, 128.3, 117.8 (t, $^1J_{C\text{-}F}$ = 255.0 Hz), 52.6, 41.6 (t, $^3J_{C\text{-}F}$ = 6.0 Hz), 41.2, 33.1 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.4 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 14.2, 12.3. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.58. **HRMS** (ESI) for $C_{16}H_{21}F_2NNaO_3S$ $[M + Na]^+$, calcd: 368.1102, found: 368.1095.

1-(azetidin-1-yl)-2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)ethan-1-one (4q)



Prepared according to General Procedure B, compound **4q** was obtained as a light-yellow solid. (38 mg, 58 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.69 – 7.62 (m, 1H), 7.61 – 7.51 (m, 2H), 4.45 (t, *J* = 7.7 Hz, 2H), 4.09 (t, *J* = 7.8 Hz, 2H), 3.78 – 3.63 (m, 1H), 3.16 – 2.90 (m, 1H), 2.74 – 2.58 (m, 2H), 2.44 – 2.19 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1 (t, $^2J_{C\text{-}F}$ = 30.3 Hz), 137.7, 133.9, 129.4, 128.3, 117.1 (t, $^1J_{C\text{-}F}$ = 254.5 Hz), 52.4, 52.3, 48.9, 32.0 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.9 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 16.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -111.86. **HRMS** (ESI) for $C_{15}H_{17}F_2NNaO_3S$ $[M + Na]^+$, calcd: 352.0789, found: 352.0775.

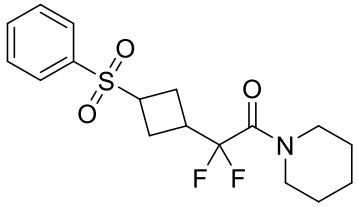
2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)-1-(pyrrolidin-1-yl)ethan-1-one (4r)



Prepared according to General Procedure B, compound **4r** was obtained as a light-yellow solid.

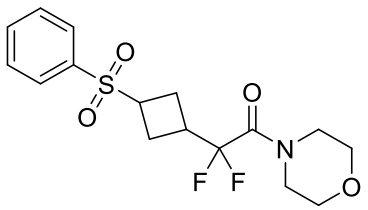
(38 mg, 55 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.69 – 7.61 (m, 1H), 7.60 – 7.51 (m, 2H), 3.79 – 3.65 (m, 3H), 3.47 (t, *J* = 7.0 Hz, 2H), 3.23 – 2.99 (m, 1H), 2.75 – 2.60 (m, 2H), 2.37 – 2.24 (m, 2H), 2.01 – 1.79 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3 (t, $^2J_{C\text{-}F}$ = 30.3 Hz), 137.8, 133.9, 129.4, 128.4, 117.2 (t, $^1J_{C\text{-}F}$ = 256.5 Hz), 52.6, 47.2, 46.3 (t, $^3J_{C\text{-}F}$ = 6.1 Hz), 32.5 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 26.5, 23.4, 23.3 (t, $^3J_{C\text{-}F}$ = 6.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -111.82. **HRMS** (ESI) for $C_{16}H_{19}F_2NNaO_3S$ $[M + Na]^+$, calcd: 366.0946, found: 366.0936.

2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)-1-(piperidin-1-yl)ethan-1-one (4s)



Prepared according to General Procedure B, compound **4s** was obtained as a light-yellow solid. (36 mg, 50 % yield, *dr* = 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.69 – 7.61 (m, 1H), 7.60 – 7.51 (m, 2H), 3.80 – 3.67 (m, 1H), 3.67 – 3.58 (m, 2H), 3.55 – 3.46 (m, 2H), 3.20 – 3.00 (m, 1H), 2.74 – 2.60 (m, 2H), 2.38 – 2.25 (m, 2H), 1.66 – 1.57 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.9 (t, $^2J_{C\text{-}F}$ = 28.5 Hz), 137.9, 133.9, 129.4, 128.4, 118.0 (t, $^1J_{C\text{-}F}$ = 255.8 Hz), 52.6, 46.7 (t, $^3J_{C\text{-}F}$ = 6.8 Hz), 44.2, 33.1 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 26.5, 25.7, 24.5, 23.4 (t, $^3J_{C\text{-}F}$ = 6.0 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.11. **HRMS** (ESI) for $C_{17}H_{21}F_2NNaO_3S$ $[M + Na]^+$, calcd: 380.1102, found: 380.1089.

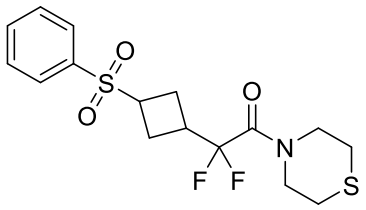
2,2-difluoro-1-morpholino-2-(3-(phenylsulfonyl)cyclobutyl)ethan-1-one (4t)



Prepared according to General Procedure B, compound **4t** was obtained as a white solid. (47 mg, 66 % yield, *dr* = 6:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.68 – 7.62 (m, 1H), 7.59 – 7.52 (m, 2H), 3.78 – 3.66 (m, 7H), 3.62 – 3.56 (m, 2H), 3.33 – 3.03 (m, 1H), 2.82 – 2.63 (m, 2H), 2.45 – 2.27 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.2 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 137.9, 133.9, 129.4, 128.4, 117.8 (t, $^1J_{C\text{-}F}$ = 255.0 Hz), 66.9, 66.7, 52.6, 46.4, 43.2, 32.8 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.3

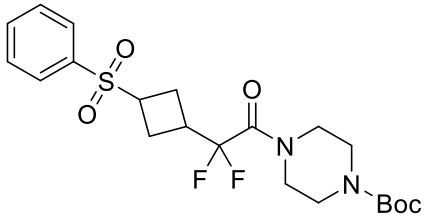
(t, $^{3}J_{C\text{-}F}$ = 5.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -107.88, -108.83. **HRMS** (ESI) for $C_{16}H_{19}F_2NNaO_4S$ $[M + Na]^+$, calcd: 382.0895, found: 382.0882.

2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)-1-thiomorpholinoethan-1-one (4u)



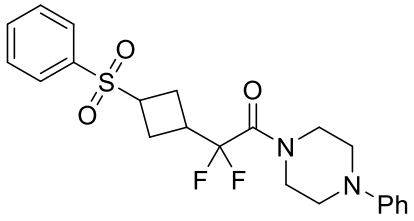
Prepared according to General Procedure B, compound **4u** was obtained as a beige solid. (43 mg, 57 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.69 – 7.62 (m, 1H), 7.61 – 7.51 (m, 2H), 4.01 – 3.91 (m, 2H), 3.89 – 3.80 (m, 2H), 3.80 – 3.66 (m, 1H), 3.22 – 2.99 (m, 1H), 2.76 – 2.55 (m, 6H), 2.38 – 2.23 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2 (t, $^{2}J_{C\text{-}F}$ = 29.3 Hz), 137.9, 133.9, 129.4, 128.4, 117.9 (t, $^{1}J_{C\text{-}F}$ = 257.6 Hz), 52.5, 48.6 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 45.8, 33.0 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 28.2, 27.4, 23.4 (t, $^{3}J_{C\text{-}F}$ = 6.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.02. **HRMS** (ESI) for $C_{16}H_{19}F_2NNaO_3S_2$ $[M + Na]^+$, calcd: 398.0667, found: 398.0656.

tert-butyl 4-(2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetyl)piperazine-1-carboxylate (4v)



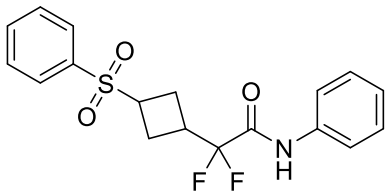
Prepared according to General Procedure B, compound **4v** was obtained as a light-yellow solid. (46 mg, 50 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.68 – 7.62 (m, 1H), 7.60 – 7.51 (m, 2H), 3.81 – 3.64 (m, 3H), 3.59 – 3.41 (m, 6H), 3.21 – 2.99 (m, 1H), 2.74 – 2.61 (m, 2H), 2.40 – 2.25 (m, 2H), 1.47 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.3 (t, $^{2}J_{C\text{-}F}$ = 29.3 Hz), 154.5, 137.8, 133.9, 129.4, 128.4, 117.8 (t, $^{1}J_{C\text{-}F}$ = 255.0 Hz), 80.6, 52.6, 45.6, 42.8, 32.9 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 28.5, 23.3 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -107.71. **HRMS** (ESI) for $C_{21}H_{28}F_2N_2NaO_5S$ $[M + Na]^+$, calcd: 481.1579, found: 481.1568.

2,2-difluoro-1-(4-phenylpiperazin-1-yl)-2-(3-(phenylsulfonyl)cyclobutyl)ethan-1-one (4w)



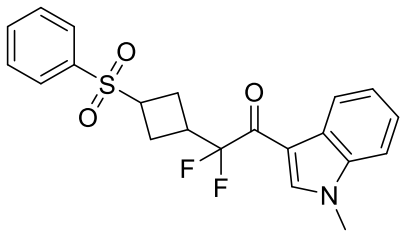
Prepared according to General Procedure B, compound **4w** was obtained as a beige solid. (56 mg, 65 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 – 7.83 (m, 2H), 7.70 – 7.50 (m, 3H), 7.35 – 7.27 (m, 2H), 7.04 – 6.88 (m, 3H), 3.95 – 3.66 (m, 5H), 3.29 – 3.03 (m, 5H), 2.77 – 2.62 (m, 2H), 2.41 – 2.25 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 150.8, 137.9, 133.9, 129.4, 128.4, 120.9, 117.9 (t, $^1J_{C\text{-}F}$ = 259.6 Hz), 116.9, 52.6, 49.9, 49.5, 45.6, 42.9, 32.9 (t, $^2J_{C\text{-}F}$ = 27.3 Hz), 23.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -107.62. **HRMS** (ESI) for $C_{22}H_{24}F_2N_2NaO_3S$ $[M + Na]^+$, calcd: 457.1368, found: 457.1359.

2,2-difluoro-*N*-phenyl-2-(3-(phenylsulfonyl)cyclobutyl)acetamide (4x)



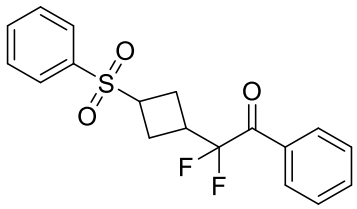
Prepared according to General Procedure B, compound **4x** was obtained as a yellow solid. (57 mg, 78 % yield, *dr* = 1.8:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 – 7.85 (m, 3H), 7.72 – 7.63 (m, 1H), 7.62 – 7.49 (m, 4H), 7.41 – 7.33 (m, 2H), 7.24 – 7.16 (m, 1H), 3.87 – 3.68 (m, 1H), 3.39 – 3.01 (m, 1H), 2.85 – 2.69 (m, 2H), 2.64 – 2.25 (m, 2H). Isomer 1: **^{13}C NMR** (101 MHz, Acetone-d_6) δ 162.3 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 138.9, 138.2, 134.8, 130.3, 129.7, 129.2, 129.0, 125.9, 121.4, 118.1 (t, $^1J_{C\text{-}F}$ = 254.5 Hz), 54.5, 34.8 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.8 (t, $^3J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.17. **HRMS** (ESI) for $C_{18}H_{17}F_2NNaO_3S$ $[M + Na]^+$, calcd: 388.0789, found: 388.0779. Isomer 2: **^{13}C NMR** (101 MHz, Acetone-d_6) δ 162.3 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 139.3, 138.2, 134.7, 130.3, 129.7, 129.2, 129.0, 125.9, 121.5, 117.1 (t, $^1J_{C\text{-}F}$ = 254.5 Hz), 52.5, 32.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.4 (t, $^3J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.49. **HRMS** (ESI) for $C_{18}H_{17}F_2NNaO_3S$ $[M + Na]^+$, calcd: 388.0789, found: 388.0779.

2,2-difluoro-1-(1-methyl-1*H*-indol-3-yl)-2-(3-(phenylsulfonyl)cyclobutyl)ethan-1-one (4y)



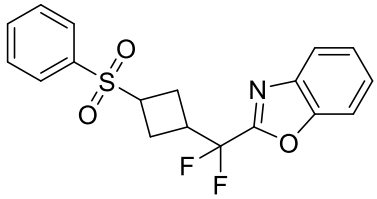
Prepared according to General Procedure B, compound **4y** was obtained as a light-yellow solid. (45 mg, 56 % yield, *dr* = 2.9:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.40 – 8.32 (m, 1H), 8.08 – 7.96 (m, 1H), 7.92 – 7.81 (m, 2H), 7.70 – 7.62 (m, 1H), 7.61 – 7.52 (m, 2H), 7.44 – 7.30 (m, 3H), 3.97 – 3.69 (m, 4H), 3.41 – 3.07 (m, 1H), 2.86 – 2.66 (m, 2H), 2.60 – 2.26 (m, 2H). Isomer 1: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 183.4 (t, $^{2}J_{C\text{-}F}$ = 30.3 Hz), 138.4 (t, $^{3}J_{C\text{-}F}$ = 9.1 Hz), 137.6, 137.1, 134.0, 129.4, 128.4, 127.2, 124.3, 123.6, 122.6, 119.2 (t, $^{1}J_{C\text{-}F}$ = 254.5 Hz), 110.5, 110.0, 54.5, 34.0 (t, $^{2}J_{C\text{-}F}$ = 25.3 Hz), 33.9, 22.6 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.25. **HRMS** (ESI) for $C_{21}H_{19}F_2NNaO_3S$ $[M + Na]^+$, calcd: 426.0946, found: 426.0932. Isomer 2: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 183.6 (t, $^{2}J_{C\text{-}F}$ = 30.3 Hz), 138.8 (t, $^{3}J_{C\text{-}F}$ = 9.1 Hz), 137.7, 137.1, 133.9, 129.4, 128.4, 127.3, 124.2, 123.6, 122.5, 118.1 (t, $^{1}J_{C\text{-}F}$ = 255.5 Hz), 110.6, 110.1, 52.7, 33.9, 32.1 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 23.2 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -109.61. **HRMS** (ESI) for $C_{21}H_{19}F_2NNaO_3S$ $[M + Na]^+$, calcd: 426.0946, found: 426.0932.

2,2-difluoro-1-phenyl-2-(3-(phenylsulfonyl)cyclobutyl)ethan-1-one (4z)



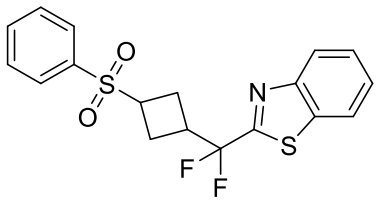
Prepared according to General Procedure B, compound **4z** was obtained as light-yellow oil (34 mg, 49 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 – 8.04 (m, 2H), 7.92 – 7.84 (m, 2H), 7.69 – 7.45 (m, 6H), 3.85 – 3.70 (m, 1H), 3.23 – 2.99 (m, 1H), 2.81 – 2.66 (m, 2H), 2.41 – 2.27 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 188.7 (t, $^{2}J_{C\text{-}F}$ = 31.5 Hz), 137.7, 134.8, 134.0, 131.7 (t, $^{3}J_{C\text{-}F}$ = 3.0 Hz), 130.3 (t, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 129.5, 128.9, 128.5, 117.8 (t, $^{1}J_{C\text{-}F}$ = 252.8 Hz), 52.8, 31.9 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 23.3 (t, $^{3}J_{C\text{-}F}$ = 6.0 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -107.69. **HRMS** (ESI) for $C_{18}H_{16}F_2NaO_3S$ $[M + Na]^+$, calcd: 373.0680, found: 373.0666.

2-(difluoro(3-(phenylsulfonyl)cyclobutyl)methyl)benzo[*d*]oxazole (4aa)



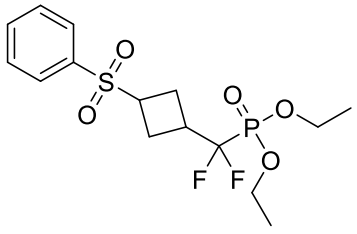
Prepared according to General Procedure B, compound **4aa** was obtained as a light-yellow solid. (49 mg, 67 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.79 – 7.74 (m, 1H), 7.70 – 7.52 (m, 4H), 7.50 – 7.37 (m, 2H), 3.87 – 3.72 (m, 1H), 3.42 – 3.19 (m, 1H), 2.91 – 2.76 (m, 2H), 2.49 – 2.33 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.8 (t, $^2J_{C\text{-}F}$ = 33.3 Hz), 150.7, 139.9, 137.5, 134.1, 129.5, 128.5, 127.2, 125.5, 121.4, 115.0 (t, $^1J_{C\text{-}F}$ = 242.4 Hz), 111.6, 52.3, 33.7 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 23.3 (t, $^3J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.46. **HRMS** (ESI) for $C_{18}H_{15}F_2NNaO_3S$ $[M + Na]^+$, calcd: 386.0633, found: 386.0620.

2-(difluoro(3-(phenylsulfonyl)cyclobutyl)methyl)benzo[*d*]thiazole (4ab)



Prepared according to General Procedure B, compound **4ab** was obtained as a yellow solid. (58 mg, 76 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 1H), 7.96 (d, *J* = 7.4 Hz, 1H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.69 – 7.62 (m, 1H), 7.61 – 7.45 (m, 4H), 3.84 – 3.69 (m, 1H), 3.51 – 3.29 (m, 1H), 2.91 – 2.76 (m, 2H), 2.44 – 2.29 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.9 (t, $^2J_{C\text{-}F}$ = 34.5 Hz), 152.6, 137.6, 135.1, 134.0, 129.5, 128.5, 126.9, 126.8, 124.4, 122.2, 118.1 (t, $^1J_{C\text{-}F}$ = 240.0 Hz), 52.4, 34.3 (t, $^2J_{C\text{-}F}$ = 27.0 Hz), 23.5 (t, $^3J_{C\text{-}F}$ = 5.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -98.56. **HRMS** (ESI) for $C_{18}H_{15}F_2NNaO_2S_2$ $[M + Na]^+$, calcd: 402.0405, found: 402.0392.

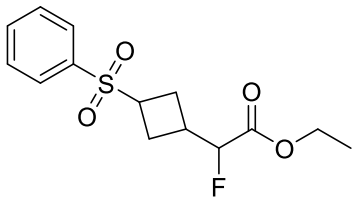
diethyl (difluoro(3-(phenylsulfonyl)cyclobutyl)methyl)phosphonate (4ac)



Prepared according to General Procedure B, compound **4ac** was obtained as light-yellow oil (44 mg, 58 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 2H), 7.68 – 7.59 (m, 1H), 7.58 – 7.49 (m, 2H), 4.29 – 4.16 (m, 4H), 3.76 – 3.61 (m, 1H), 2.98 – 2.76 (m, 1H), 2.75 – 2.60

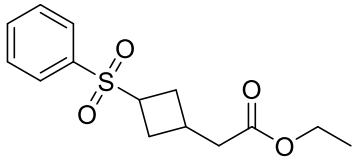
(m, 2H), 2.30 – 2.15 (m, 2H), 1.33 (t, J = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.6, 134.0, 129.4, 128.4, 119.6 (td, $^1J_{C\text{-}F}$ = 260.6, 214.1 Hz), 64.7, 64.6, 52.4, 32.1 (td, $^2J_{C\text{-}F}$ = 23.2, 15.2 Hz), 23.0 (q, $^3J_{C\text{-}F}$ = 4.3 Hz), 16.5, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -119.97, -120.36. **HRMS** (ESI) for $C_{15}H_{21}F_2NaO_5PS$ $[M + Na]^+$, calcd: 405.0708, found: 405.0695.

ethyl 2-fluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetate (4ad)



Prepared according to General Procedure B, compound **4ad** was obtained as light-yellow oil. (50 mg, 83 % yield, dr = 1.8:1). Isomer 1: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.70 – 7.62 (m, 1H), 7.61 – 7.52 (m, 2H), 4.84 (dd, J = 49.0, 6.1 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.77 – 3.65 (m, 1H), 2.84 – 2.53 (m, 3H), 2.37 – 2.16 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 137.7, 134.0, 129.5, 128.4, 90.5 (d, $^1J_{C\text{-}F}$ = 185.3 Hz), 61.8, 53.0, 31.5 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 24.6 (d, $^3J_{C\text{-}F}$ = 4.5 Hz), 24.5 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 14.3. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -197.46. **HRMS** (ESI) for $C_{14}H_{17}FNaO_4S$ $[M + Na]^+$, calcd: 323.0724, found: 323.0717. Isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.70 – 7.62 (m, 1H), 7.61 – 7.52 (m, 2H), 4.86 (dd, J = 49.4, 3.9 Hz, 1H), 4.23 (q, J = 6.9 Hz, 2H), 3.82 – 3.68 (m, 1H), 3.17 – 2.93 (m, 1H), 2.82 – 2.69 (m, 1H), 2.66 – 2.53 (m, 1H), 2.48 – 2.32 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (d, $^2J_{C\text{-}F}$ = 24.0 Hz), 137.8, 134.0, 129.5, 128.4, 90.5 (d, $^1J_{C\text{-}F}$ = 184.5 Hz), 61.9, 54.3, 32.9 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 24.0 (d, $^3J_{C\text{-}F}$ = 4.5 Hz), 22.9 (d, $^3J_{C\text{-}F}$ = 4.5 Hz), 14.3. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -202.80. **HRMS** (ESI) for $C_{14}H_{17}FNaO_4S$ $[M + Na]^+$, calcd: 323.0724, found: 323.0717.

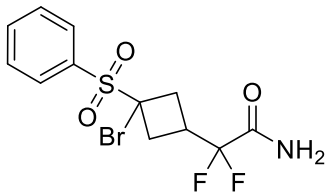
ethyl 2-(3-(phenylsulfonyl)cyclobutyl)acetate (4ae)



Prepared according to General Procedure B, compound **4ae** was obtained as yellow oil. (23 mg, 41 % yield, dr = 1.5:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 2H), 7.67 – 7.59 (m, 1H), 7.58 – 7.49 (m, 2H), 4.08 (qd, J = 7.2, 2.0 Hz, 2H), 3.83 – 3.62

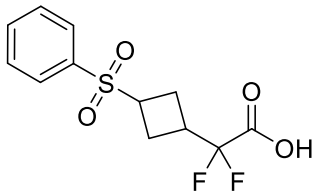
(m, 1H), 2.91 – 2.52 (m, 2H), 2.51 – 1.95 (m, 5H), 1.21 (td, *J* = 7.2, 3.7 Hz, 3H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.8, 138.0, 133.8, 129.4, 128.4, 60.6, 54.7, 40.0, 27.8, 27.3, 14.3. **HRMS** (ESI) for $C_{14}H_{18}NaO_4S$ $[M + Na]^+$, calcd: 305.0818, found: 305.0806. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.9, 138.2, 133.8, 129.4, 128.3, 60.6, 53.8, 40.3, 28.8, 26.2, 14.3. **HRMS** (ESI) for $C_{14}H_{18}NaO_4S$ $[M + Na]^+$, calcd: 305.0818, found: 305.0806.

2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetamide (5a)



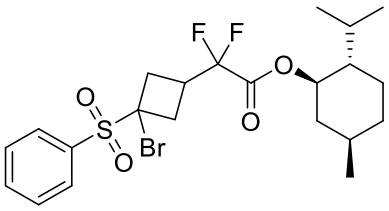
White solid. (58 mg, 78 % yield, *dr* = 3:1) Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 – 7.93 (m, 2H), 7.77 – 7.68 (m, 1H), 7.64 – 7.55 (m, 2H), 6.31 (s, 1H), 5.75 (s, 1H), 3.58 – 3.31 (m, 3H), 3.09 – 2.42 (m, 2H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.45 (t, $^{2}J_{C\text{-}F}$ = 30.0 Hz), 134.94, 133.51, 131.25, 129.10, 115.13 (t, $^{1}J_{C\text{-}F}$ = 252.8 Hz), 65.59, 35.82 (t, $^{2}J_{C\text{-}F}$ = 5.3 Hz), 33.98 (t, $^{3}J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.16. **HRMS** (ESI) for $C_{12}H_{12}BrF_2NNaO_3S$ $[M + Na]^+$, calcd: 389.9582, found: 389.9571. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.38 (t, $^{2}J_{C\text{-}F}$ = 30.0 Hz) 134.84, 133.93, 130.61, 129.22, 115.57 (t, $^{1}J_{C\text{-}F}$ = 252.8 Hz), 67.68, 34.66 (t, $^{2}J_{C\text{-}F}$ = 5.3 Hz), 31.27 (t, $^{3}J_{C\text{-}F}$ = 26.3 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.47. **HRMS** (ESI) for $C_{12}H_{12}BrF_2NNaO_3S$ $[M + Na]^+$, calcd: 389.9582, found: 389.9571.

2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetic acid (5b)



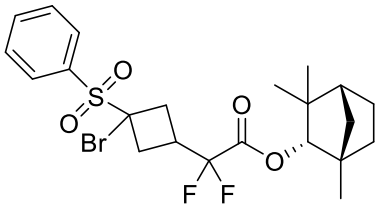
White solid. (38 mg, 66 % yield, *dr* > 20:1) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.72 – 7.64 (m, 1H), 7.62 – 7.53 (m, 2H), 3.82 – 3.65 (m, 1H), 3.02 – 2.64 (m, 3H), 2.38 – 2.20 (m, 2H). **^{13}C NMR** (101 MHz, Acetone-d_6) δ 165.3, 139.2, 134.7, 130.32, 129.0, 115.8 (t, $^{1}J_{C\text{-}F}$ = 249.5 Hz), 52.4, 33.0 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 23.4 (t, $^{3}J_{C\text{-}F}$ = 5.1 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.20. **HRMS** (ESI) for $C_{12}H_{12}F_2NaO_4S$ $[M + Na]^+$, calcd: 313.0316, found: 313.0320.

(*1R*,*2S*,*5R*)-2-isopropyl-5-methylcyclohexyl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl)-2,2-difluoroacetate (5c)



Prepared according to General Procedure A, compound **5c** was obtained as colorless oil (56 mg, 55 % yield, *dr* = 2.4:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 2H), 7.77 – 7.67 (m, 1H), 7.64 – 7.55 (m, 2H), 4.87 – 4.73 (m, 1H), 3.55 – 3.24 (m, 3H), 3.04 – 2.37 (m, 2H), 2.04 – 1.93 (m, 1H), 1.85 – 1.65 (m, 3H), 1.53 – 1.42 (m, 2H), 1.15 – 1.00 (m, 2H), 0.95 – 0.88 (m, 7H), 0.79 – 0.71 (m, 3H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$)δ 162.7 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 134.9, 133.6, 131.3, 129.1, 113.8 (t, $^{1}J_{C\text{-}F}$ = 249.8 Hz), 78.0, 65.4, 46.8, 41.7, 35.7 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz), 34.3 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 34.0, 31.5, 26.3, 23.4, 22.0, 20.8, 16.2. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.53 (d, *J* = 16.9 Hz). **HRMS** (ESI) for $C_{22}H_{29}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 529.0830, found: 529.0825. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.8 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 134.8, 134.0, 130.6, 129.2, 114.1 (t, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 78.1, 67.8, 46.8, 40.4, 34.7 (t, $^{3}J_{C\text{-}F}$ = 5.3 Hz), 34.0, 31.9 (t, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 31.5, 26.3, 23.4, 22.0, 20.8, 16.2. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.84 (d, *J* = 19.7 Hz). **HRMS** (ESI) for $C_{22}H_{29}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 529.0830, found: 529.0825.

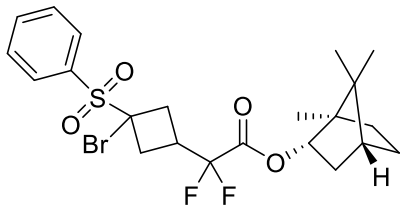
(*1S*,*2S*,*4R*)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl) -2,2-difluoroacetate (5d)



Prepared according to General Procedure A, compound **5d** was obtained as colorless oil (51 mg, 50 % yield, *dr* = 2.7:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 18.9, 7.1 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 4.46 (d, *J* = 2.0 Hz, 1H), 3.56 – 3.26 (m, 3H), 3.07 – 2.41 (m, 2H), 1.79 – 1.58 (m, 4H), 1.34 – 1.21 (m, 3H), 1.12 (s, 3H), 1.05 (s, 3H), 0.79 (s, 3H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 135.0, 133.5, 131.3, 129.1, 114.2 (t, $^{1}J_{C\text{-}F}$ = 249.8 Hz), 89.7, 65.4, 48.5, 48.3, 41.3, 39.7, 35.8, 34.3 (t, $^{2}J_{C\text{-}}$

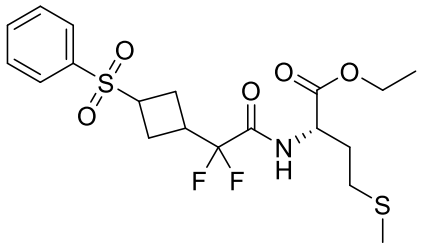
$_F$ = 25.5 Hz), 29.7, 26.6, 25.8, 20.1, 19.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.20 (d, *J* = 11.3 Hz). **HRMS** (ESI) for $C_{22}H_{27}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 527.0674, found: 527.0670. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.6 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 134.8, 134.0, 130.7, 129.2, 114.2 (t, $^1J_{C\text{-}F}$ = 249.8 Hz), 89.8, 67.8, 48.5, 48.3, 41.3, 39.7, 34.8, 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 29.7, 26.6, 25.8, 20.1, 19.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.52 (d, *J* = 11.3 Hz). **HRMS** (ESI) for $C_{22}H_{27}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 527.0674, found: 527.0670.

(*1R*,*2R*,*4R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(3-bromo-3-(phenylsulfonyl)cyclobutyl) -2,2-difluoroacetate (5e)



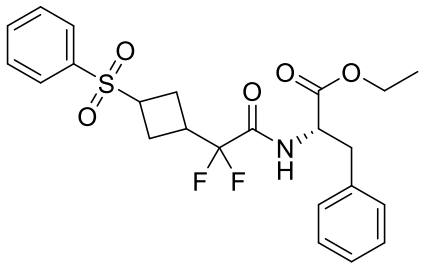
Prepared according to General Procedure A, compound **5e** was obtained as colorless oil (53 mg, 52 % yield, *dr* = 2.4:1). Mixture of isomer 1 and isomer 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 2H), 7.77 – 7.67 (m, 1H), 7.64 – 7.55 (m, 2H), 4.79 (dd, *J* = 7.3, 3.8 Hz, 1H), 3.52 – 3.25 (m, 3H), 3.03 – 2.40 (m, 2H), 1.90 – 1.65 (m, 4H), 1.64 – 1.55 (m, 1H), 1.20 – 1.04 (m, 2H), 0.97 (s, 3H), 0.85 (s, 6H). Isomer 1: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.6 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 135.0, 133.6, 131.3, 129.1, 113.8 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 84.5, 65.4, 49.2, 47.1, 45.0, 38.5, 35.7 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 34.3 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 33.6, 27.0, 20.1, 19.9, 11.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.55. **HRMS** (ESI) for $C_{22}H_{27}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 527.0674, found: 527.0671. Isomer 2: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{C\text{-}F}$ = 32.3 Hz), 134.8, 134.0, 130.7, 129.2, 114.1 (t, $^1J_{C\text{-}F}$ = 250.5 Hz), 84.5, 67.8, 49.2, 47.1, 45.0, 38.5, 34.8 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 33.6, 31.9 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 27.0, 20.1, 19.9, 11.5. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.76. **HRMS** (ESI) for $C_{22}H_{27}BrF_2NaO_4S$ $[M + Na]^+$, calcd: 527.0674, found: 527.0671.

ethyl (2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetyl)-*L*-methioninate (5f)



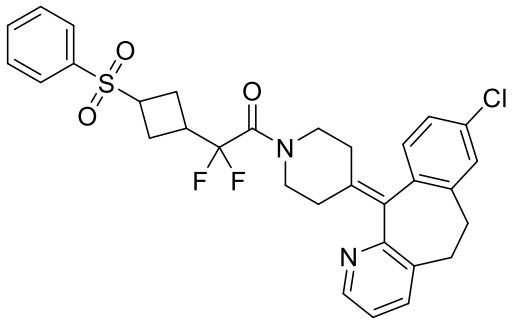
Prepared according to General Procedure B, compound **5f** was obtained as colorless oil (58 mg, 65 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.78 – 3.64 (m, 1H), 3.09 – 2.88 (m, 1H), 2.79 – 2.63 (m, 2H), 2.51 (t, *J* = 7.4 Hz, 2H), 2.33 – 2.14 (m, 3H), 2.13 – 1.99 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8, 163.2 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 137.5, 134.0, 129.5, 128.4, 115.7 (t, $^1J_{C\text{-}F}$ = 252.0 Hz), 62.2, 52.2, 51.7, 32.0 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 31.0, 29.9, 22.8 (t, $^3J_{C\text{-}F}$ = 4.5 Hz), 15.5, 14.2. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -113.17 – -115.72 (m, 2F). **HRMS** (ESI) for $C_{19}H_{25}F_2NNaO_5S_2$ $[M + Na]^+$, calcd: 472.1034, found: 472.1021.

ethyl (2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)acetyl)-*L*-phenylalaninate (5g)



Prepared according to General Procedure B, compound **5g** was obtained as a white solid. (63 mg, 68 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.71 – 7.63 (m, 1H), 7.61 – 7.53 (m, 2H), 7.33 – 7.26 (m, 3H), 7.14 – 7.06 (m, 2H), 6.75 (d, *J* = 7.8 Hz, 1H), 4.86 – 4.75 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.75 – 3.60 (m, 1H), 3.24 – 3.05 (m, 2H), 3.01 – 2.79 (m, 1H), 2.71 – 2.52 (m, 2H), 2.27 – 2.07 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.4, 162.9 (t, $^2J_{C\text{-}F}$ = 29.3 Hz), 137.6, 135.2, 134.0, 129.5, 129.3, 128.8, 128.5, 127.5, 115.7 (t, $^1J_{C\text{-}F}$ = 252.0 Hz), 62.1, 53.2, 52.2, 37.7, 32.0 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 22.8 (q, $^3J_{C\text{-}F}$ = 4.5 Hz), 14.2. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.74. **HRMS** (ESI) for $C_{23}H_{25}F_2NNaO_5S$ $[M + Na]^+$, calcd: 488.1314, found: 488.1299.

1-(4-(8-chloro-5,6-dihy*dro*-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidin-1-yl)-2,2-difluoro-2-(3-(phenylsulfonyl)cyclobutyl)ethan-1-one (5h)



Prepared according to General Procedure B, compound **5h** was obtained as a white solid. (48 mg, 41 % yield, *dr* > 20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.0 Hz, 1H), 7.87 (d, *J* = 7.1 Hz, 2H), 7.69 – 7.60 (m, 1H), 7.60 – 7.45 (m, 3H), 7.21 – 7.09 (m, 4H), 4.07 – 3.86 (m, 2H), 3.79 – 3.66 (m, 1H), 3.51 – 3.28 (m, 3H), 3.28 – 3.01 (m, 2H), 2.95 – 2.75 (m, 2H), 2.74 – 2.49 (m, 3H), 2.48 – 2.22 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1 (t, $^2J_{C\text{-}F}$ = 30.3 Hz), 156.7, 146.7, 139.6, 137.9, 137.8, 137.5, 136.3, 134.9, 133.9, 133.5, 133.2, 130.5, 129.4, 129.2, 128.4, 126.4, 122.6, 117.8 (t, $^1J_{C\text{-}F}$ = 257.6 Hz), 52.6, 46.2, 44.2, 33.2, 33.0 (t, $^2J_{C\text{-}F}$ = 27.3 Hz), 32.7, 31.7, 31.1, 30.3, 29.8, 23.3. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.57 – -109.31 (m, 2F). **HRMS** (ESI) for $C_{31}H_{29}ClF_2N_2NaO_3S$ $[M + Na]^+$, calcd: 605.1448, found: 605.1443.

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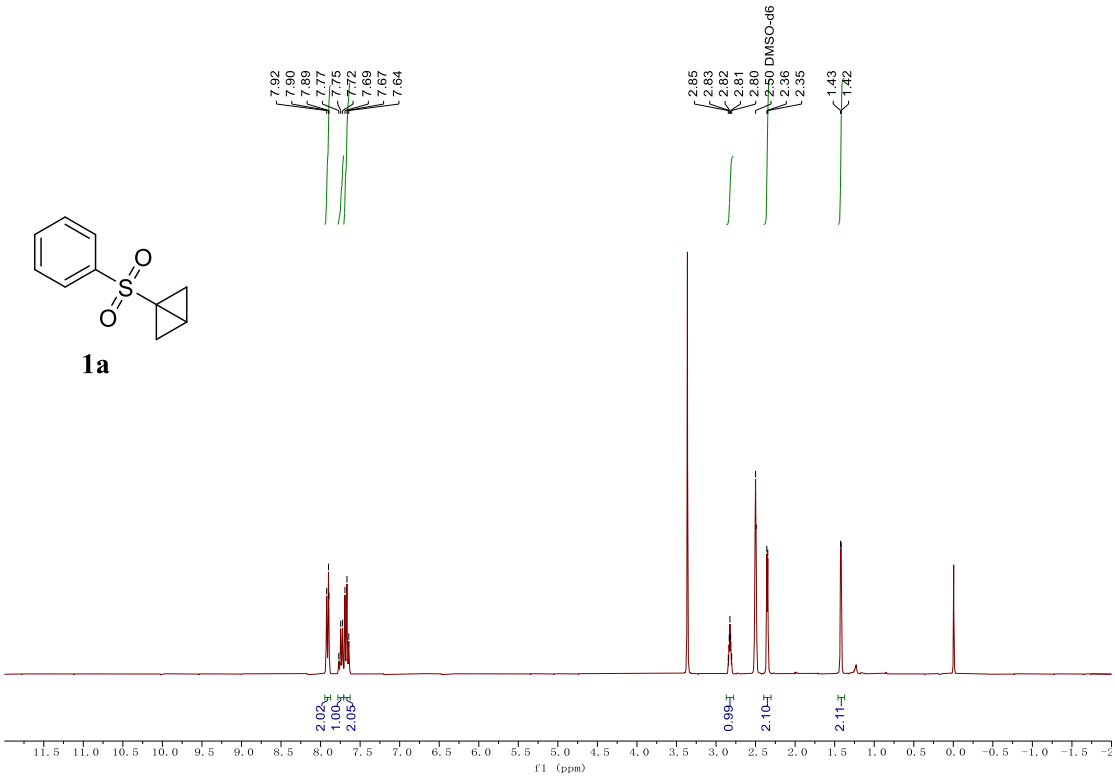
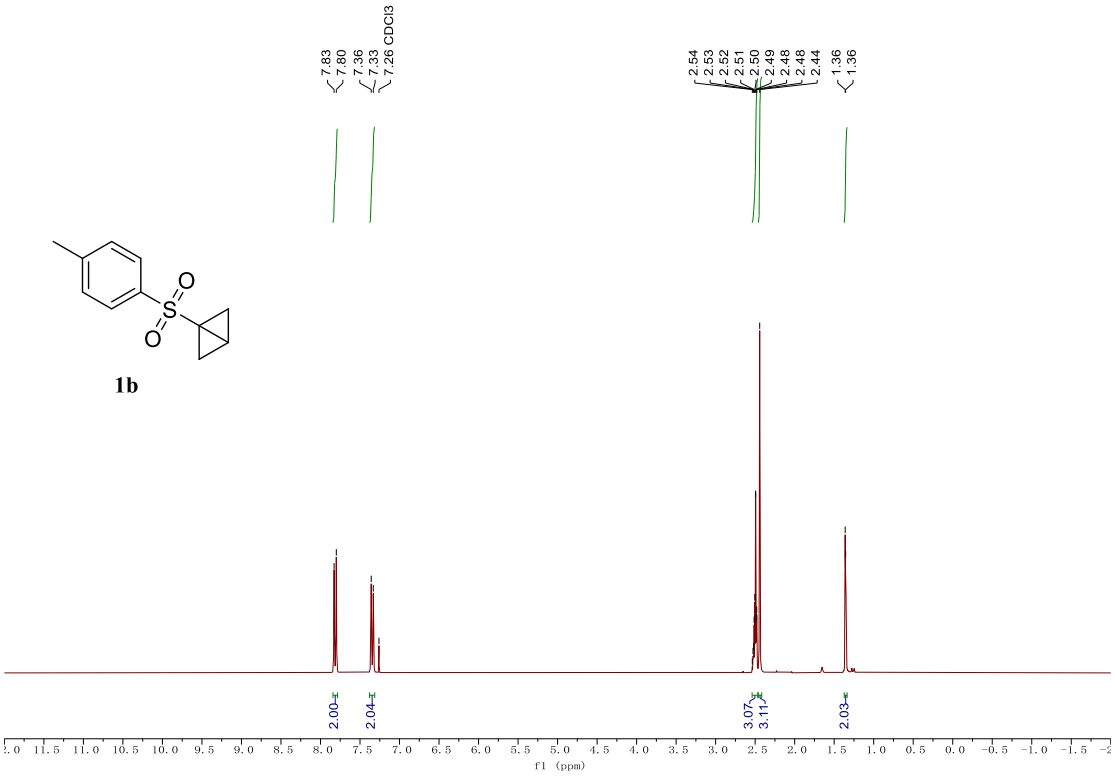
7 NMR spectra (^{1}H, ^{13}C and ^{19}F)

^{1}H NMR Spectrum of Compound **1a** (300 MHz, DMSO-d_6)



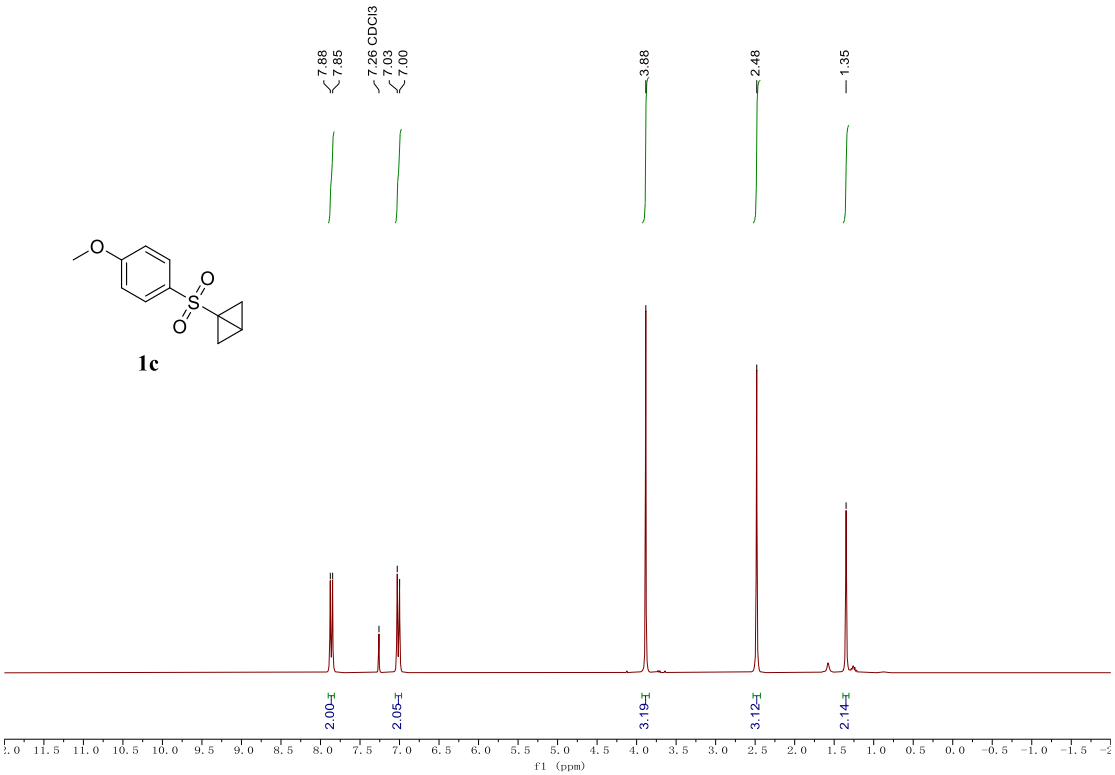
1a

^{1}H NMR Spectrum of Compound **1b** (300 MHz, $CDCl_3$)



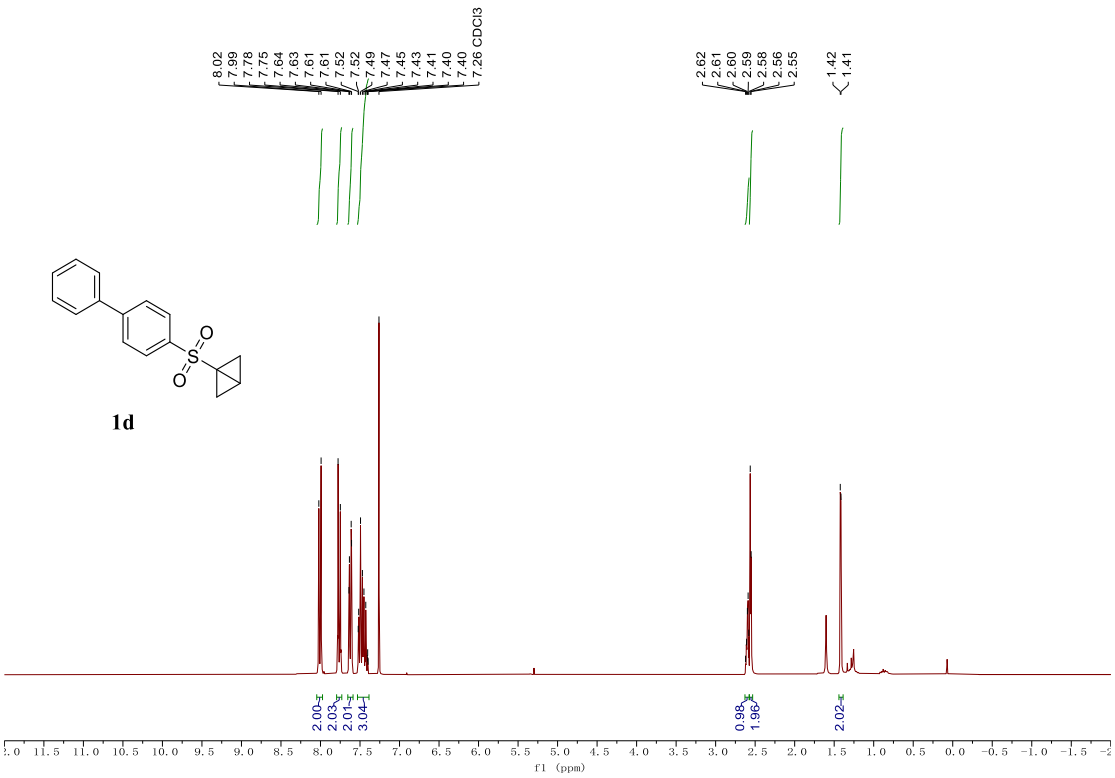
1b

^{1}H NMR Spectrum of Compound **1c** (300 MHz, $CDCl_3$)



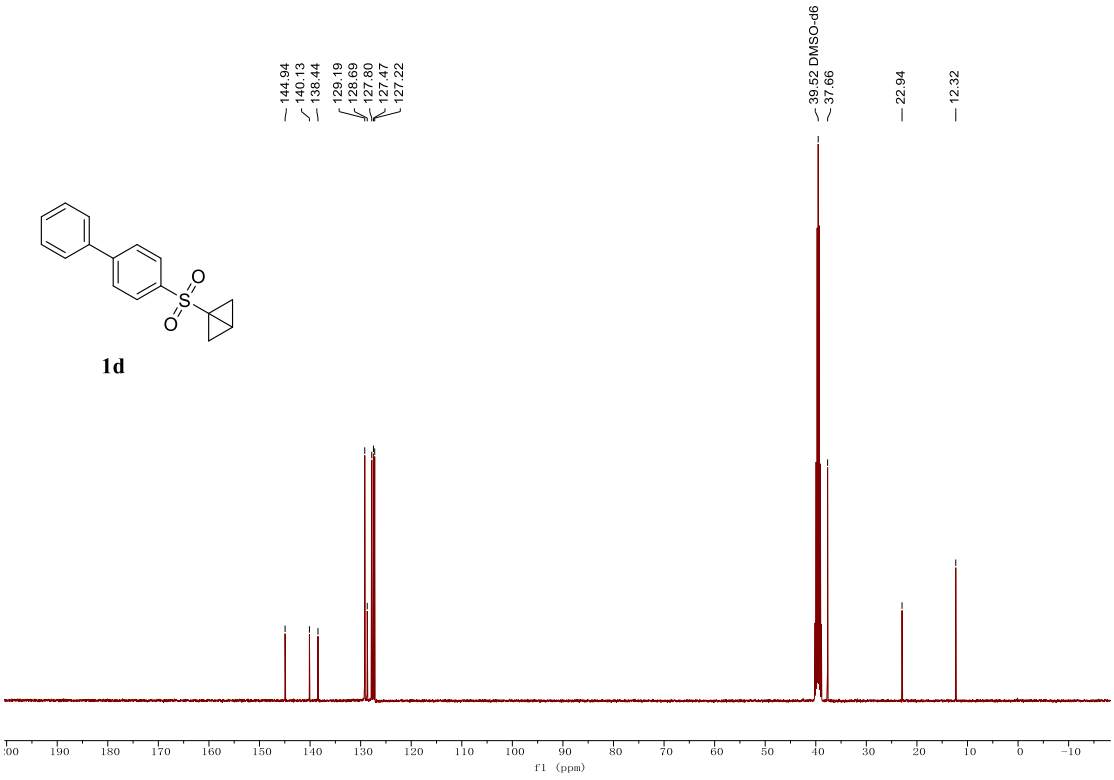
1c

^{1}H NMR Spectrum of Compound **1d** (300 MHz, $CDCl_3$)

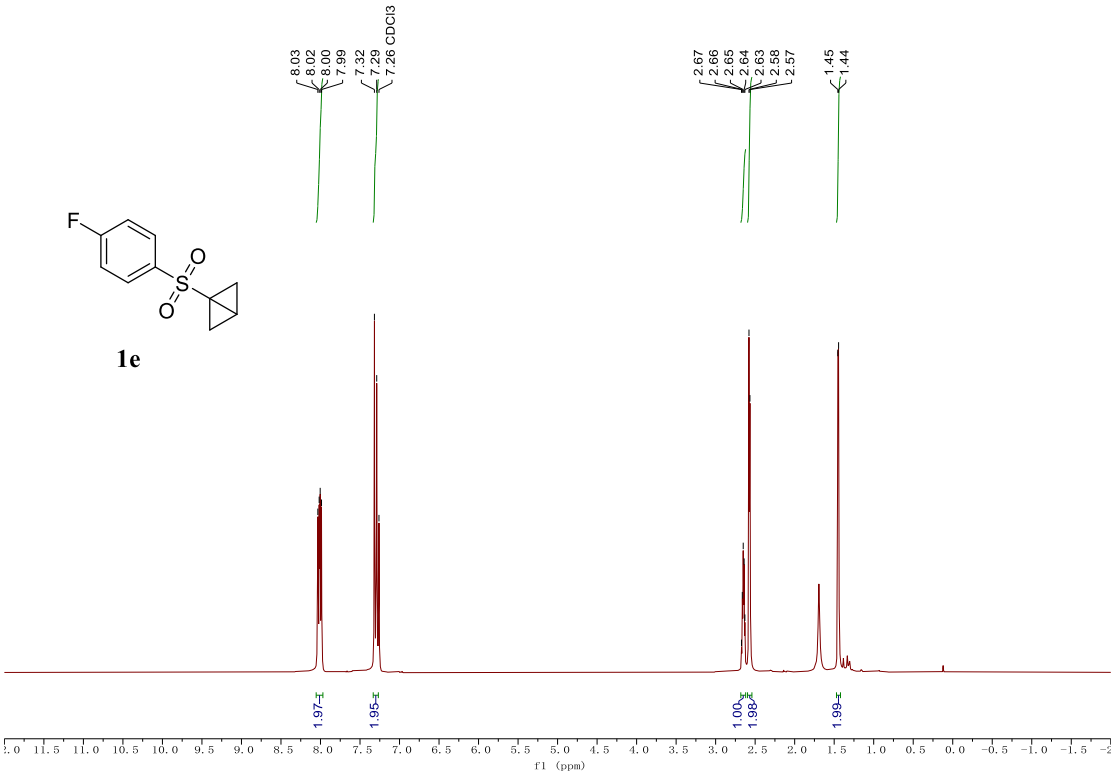


1d

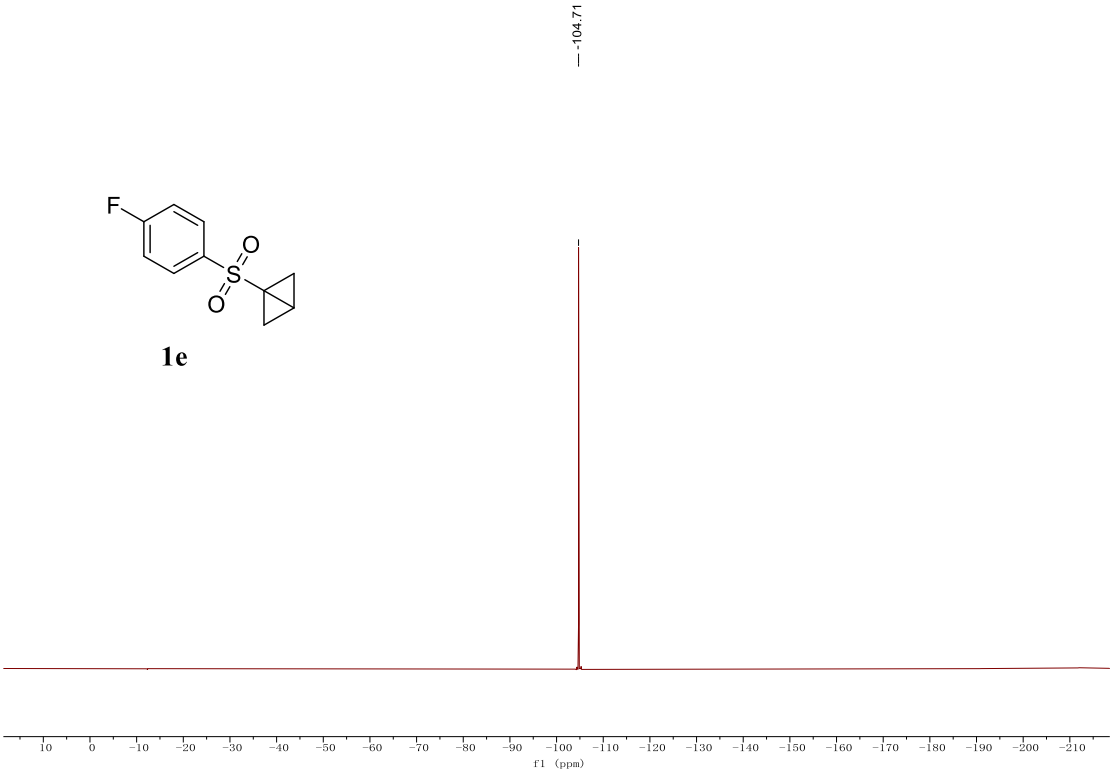
^{13}C NMR Spectrum of Compound **1d** (101 MHz, DMSO-d_6)



^{1}H NMR Spectrum of Compound **1e** (300 MHz, $CDCl_3$)

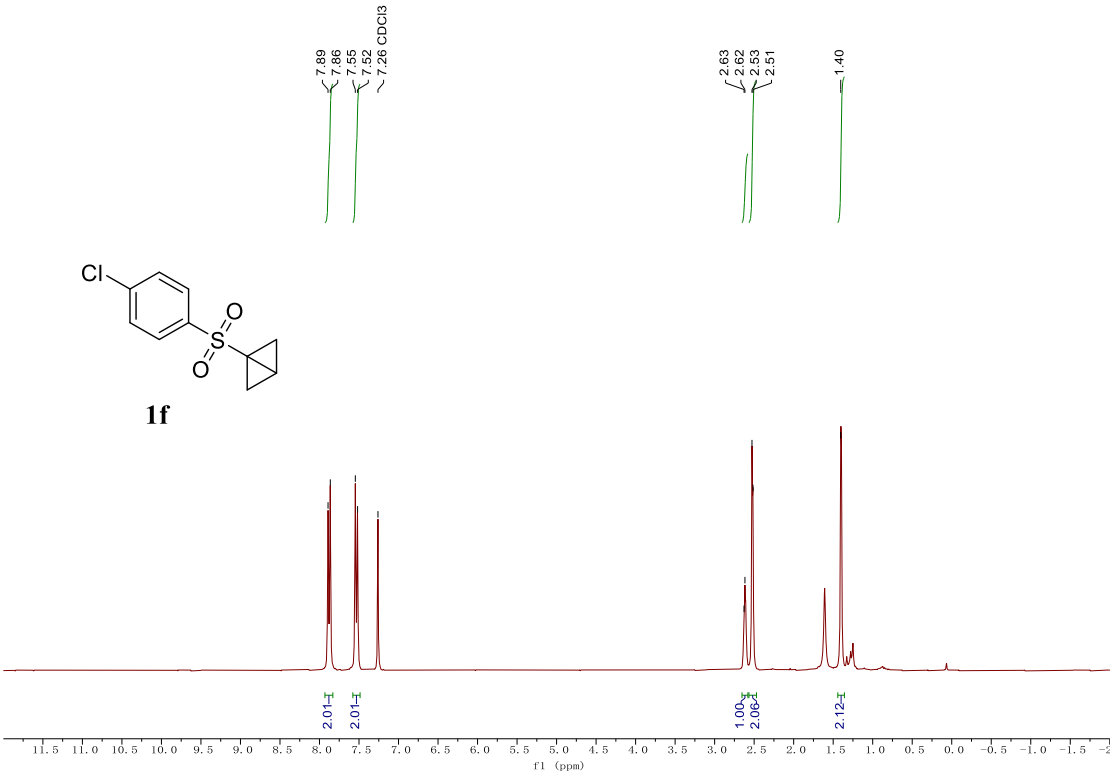


^{19}F NMR Spectrum of Compound **1e** (282 MHz, $CDCl_3$)



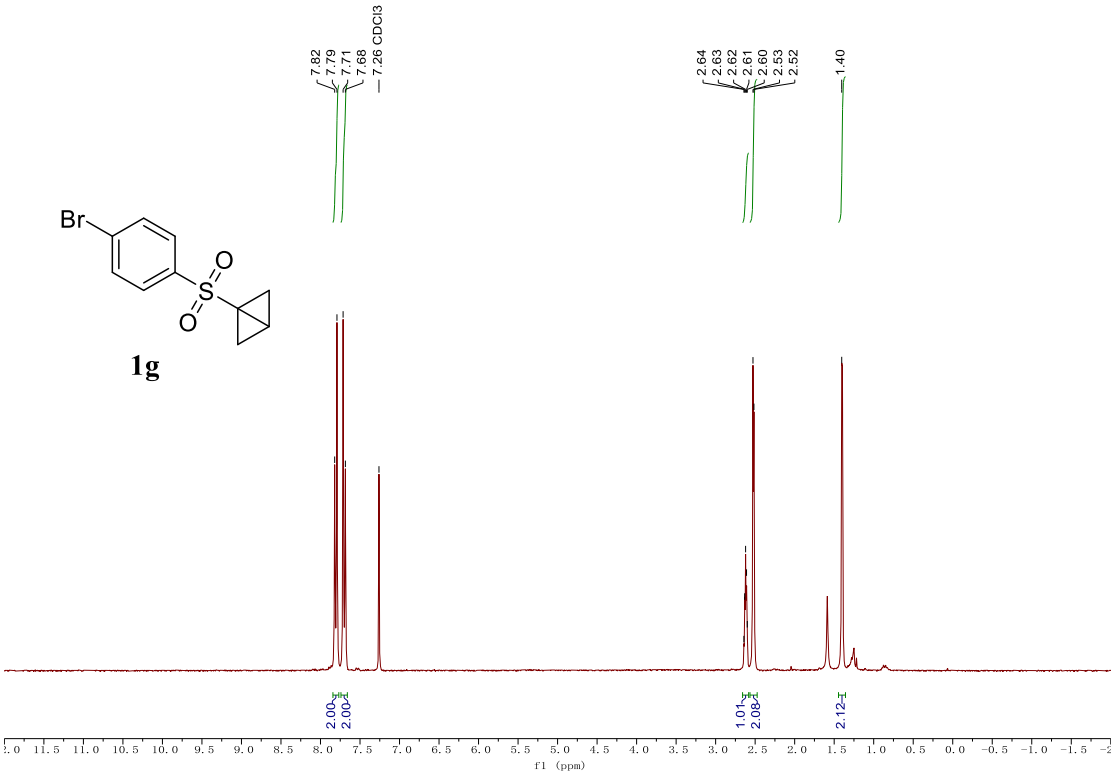
1e

^{1}H NMR Spectrum of Compound **1f** (300 MHz, $CDCl_3$)



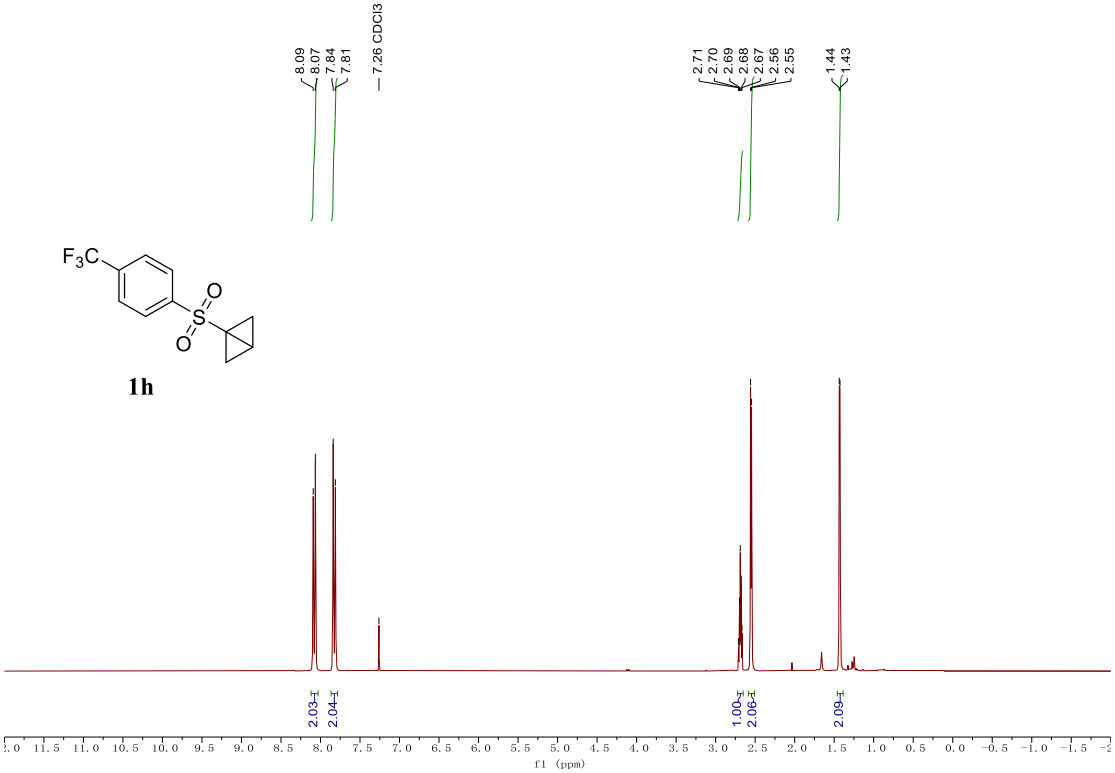
1f

^{1}H NMR Spectrum of Compound **1g** (300 MHz, $CDCl_3$)



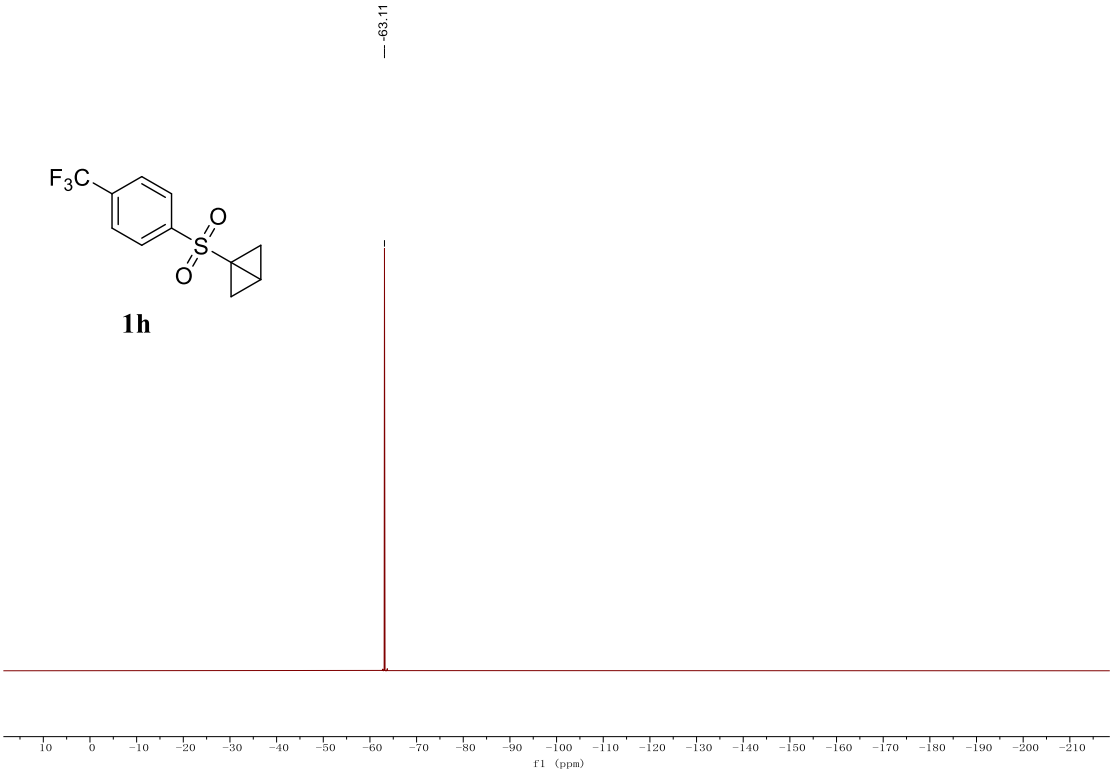
1g

^{1}H NMR Spectrum of Compound **1h** (300 MHz, $CDCl_3$)



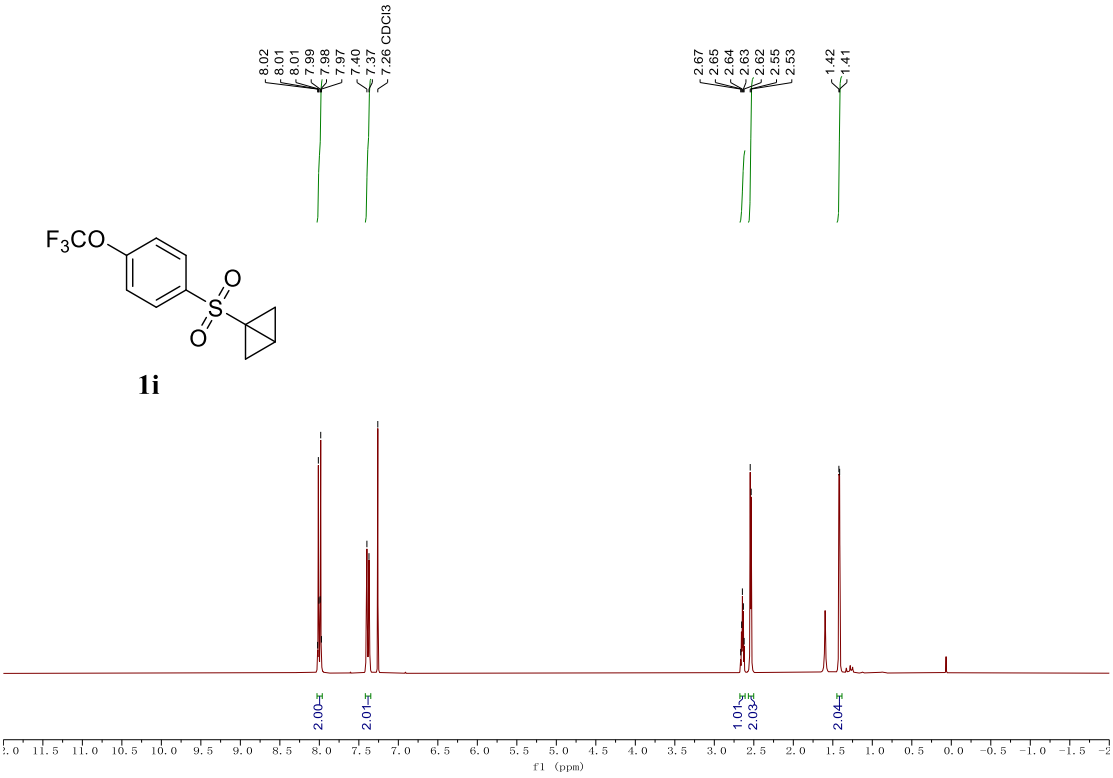
1h

^{19}F NMR Spectrum of Compound **1h** (282 MHz, $CDCl_3$)



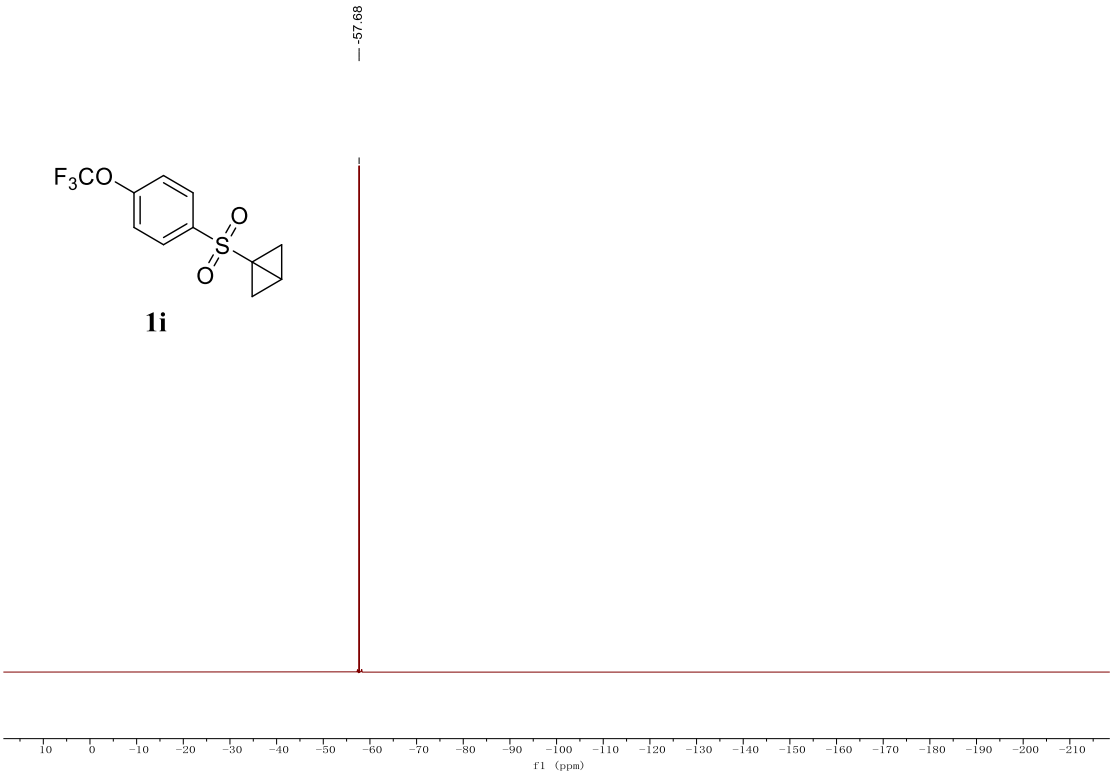
1h

^{1}H NMR Spectrum of Compound **1i** (300 MHz, $CDCl_3$)



1i

^{19}F NMR Spectrum of Compound **1i** (282 MHz, $CDCl_3$)



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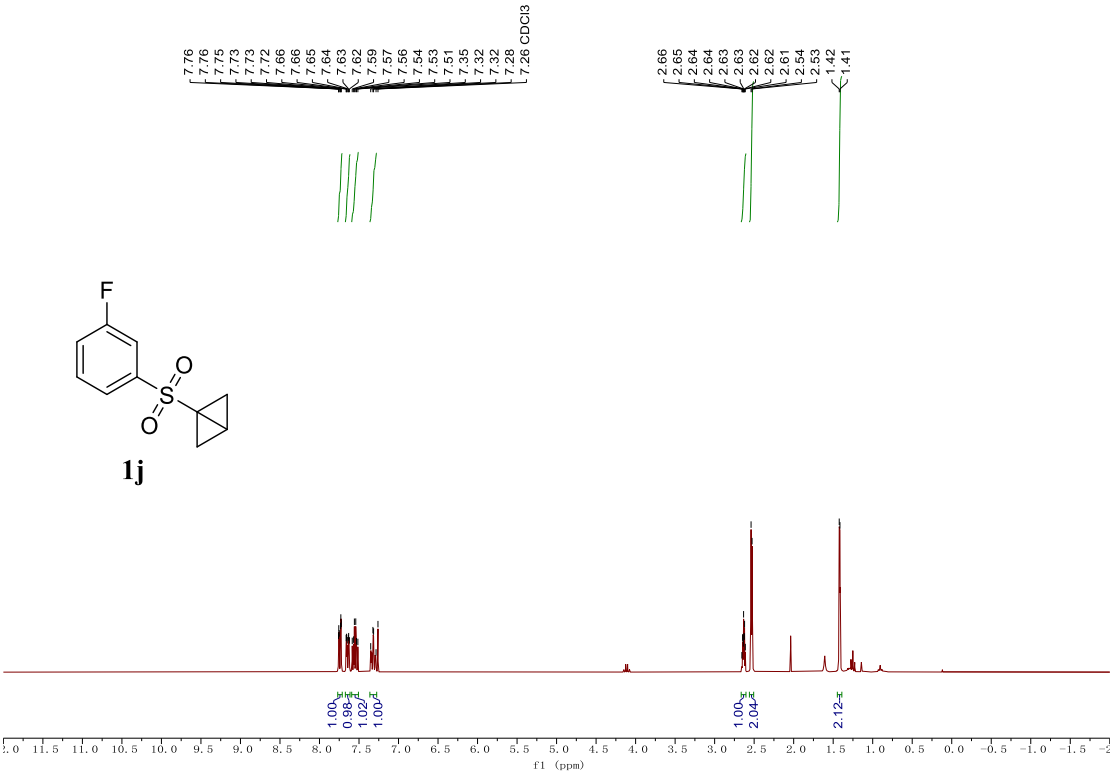
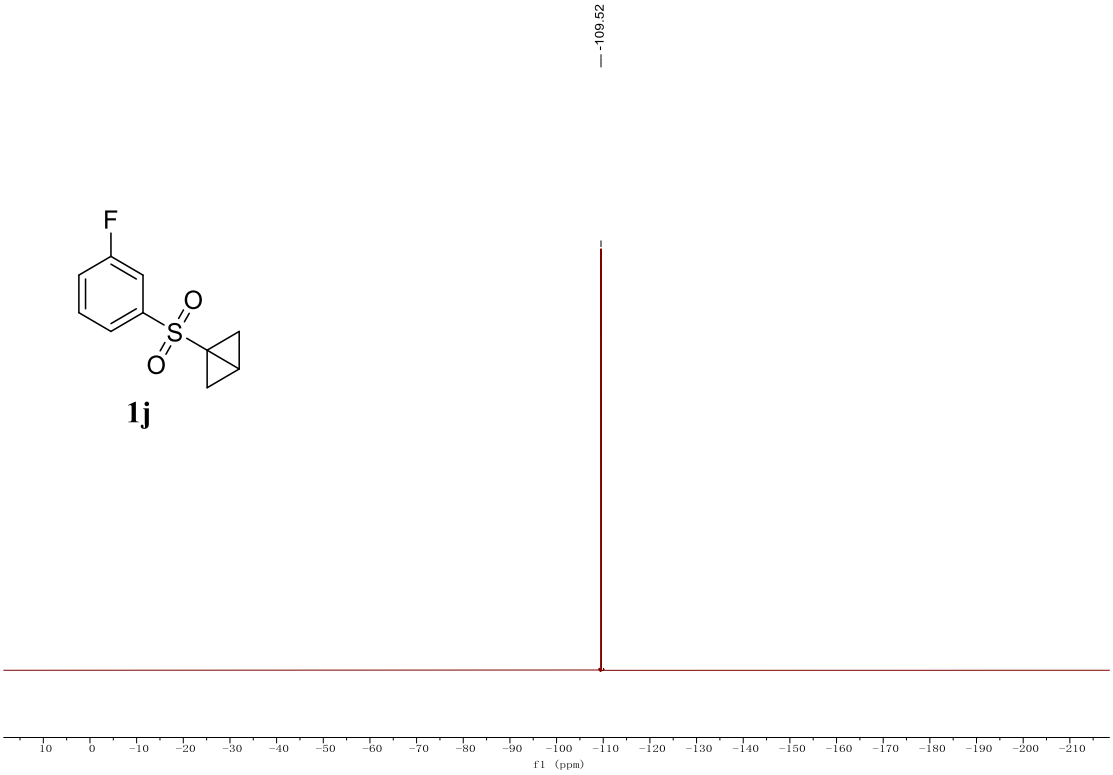
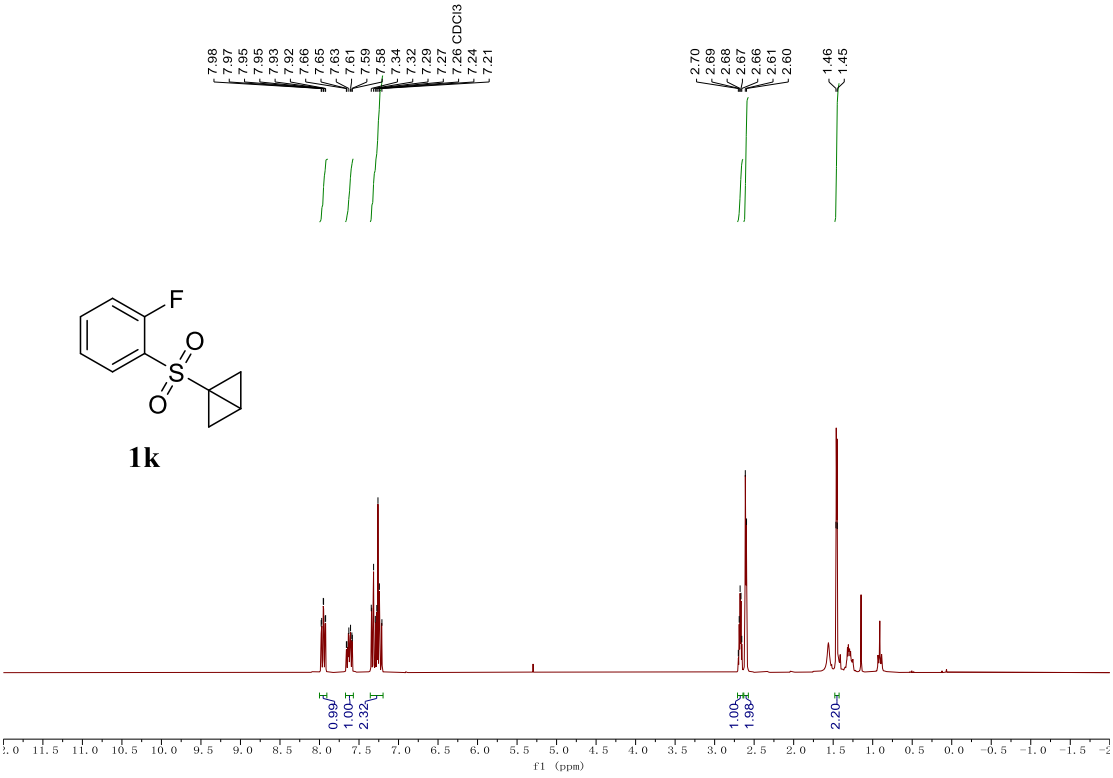


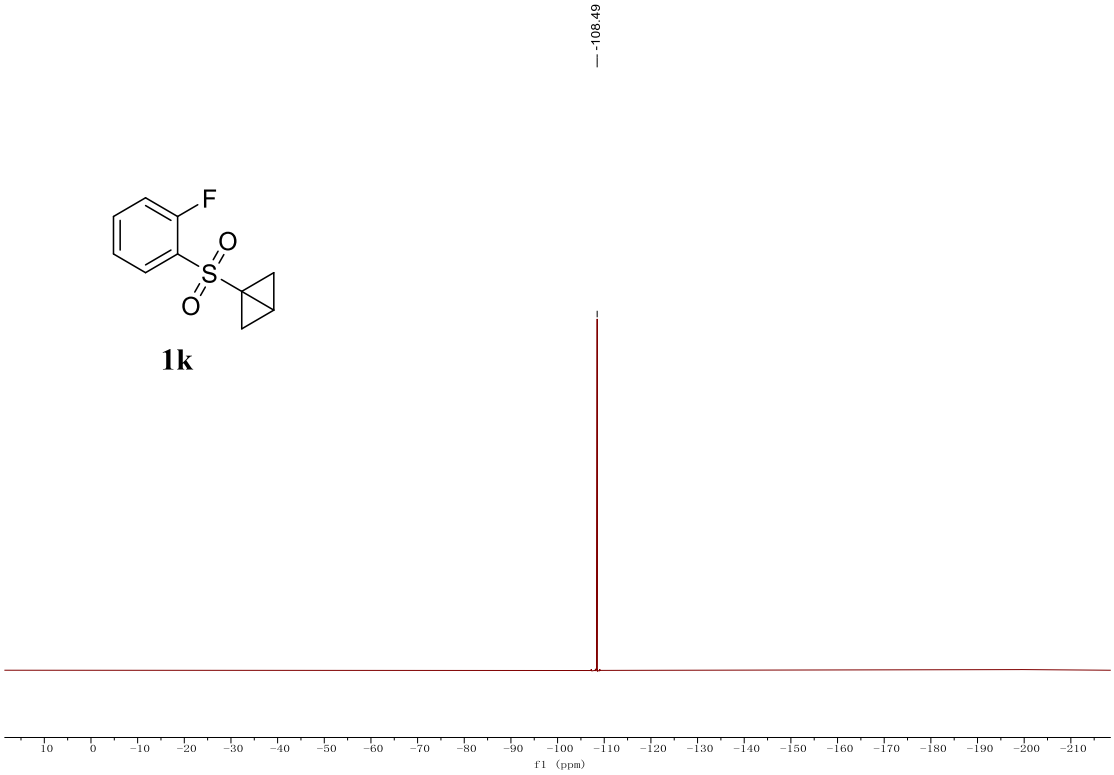
^{19}F NMR Spectrum of Compound **1j** (282 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound **1k** (300 MHz, $CDCl_3$)

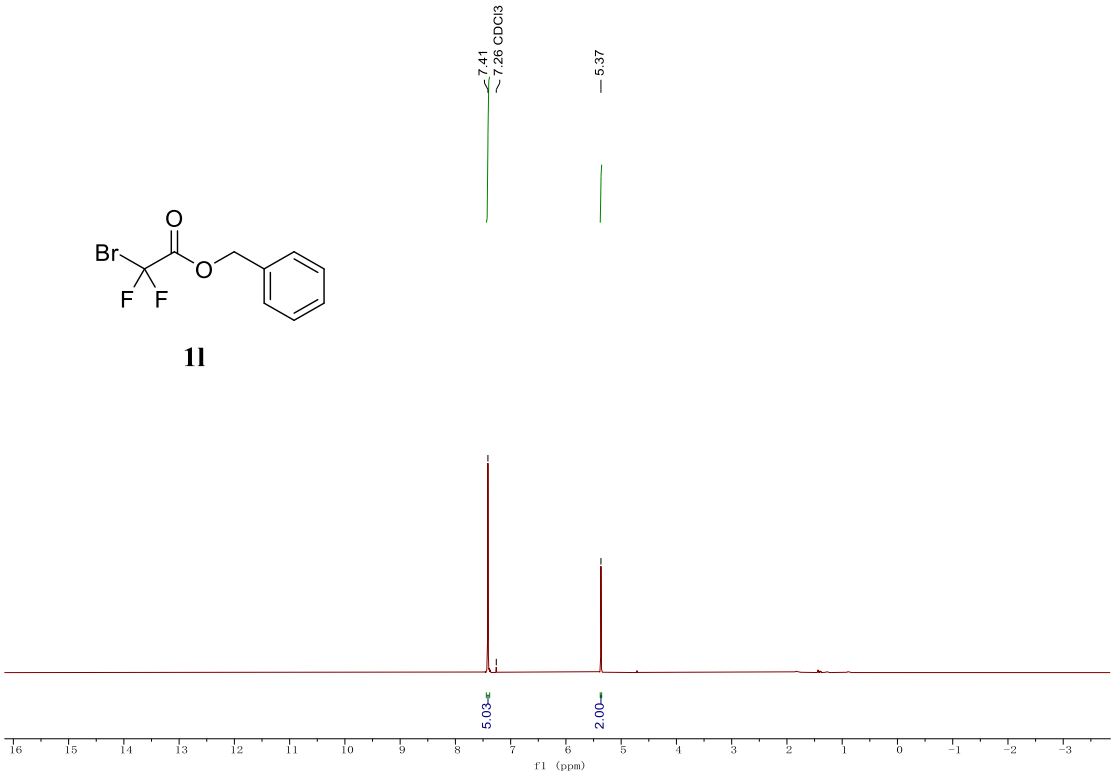


^{19}F NMR Spectrum of Compound **1k** (282 MHz, $CDCl_3$)



1k

^{1}H NMR Spectrum of Compound **1l** (300 MHz, $CDCl_3$)

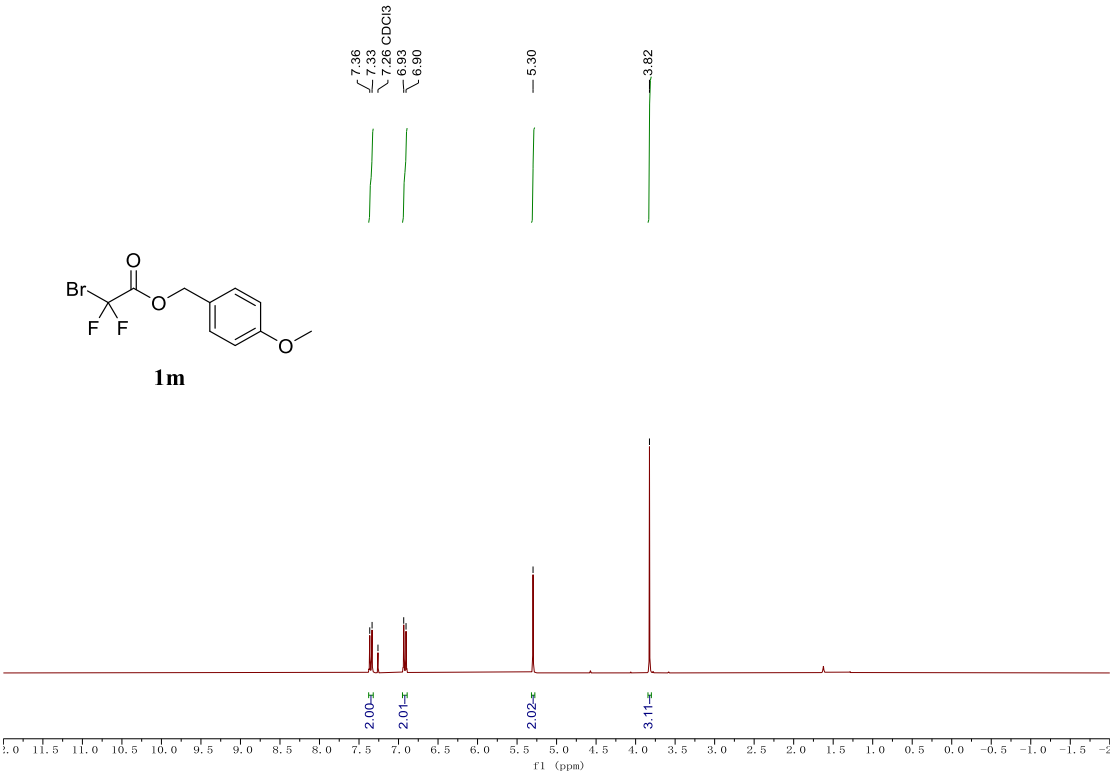


1l

^{19}F NMR Spectrum of Compound **1l** (282 MHz, $CDCl_3$)

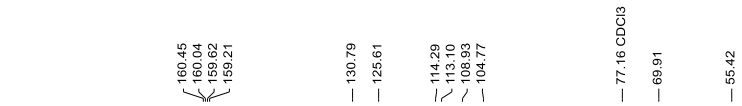
1l

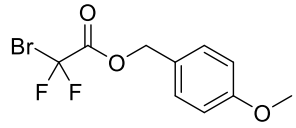
^{1}H NMR Spectrum of Compound **1m** (300 MHz, $CDCl_3$)



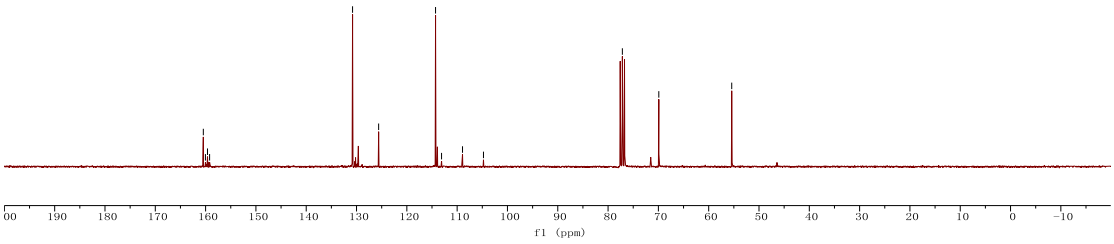
1m

^{13}C NMR Spectrum of Compound **1m** (75 MHz, $CDCl_3$)

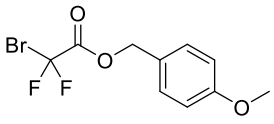




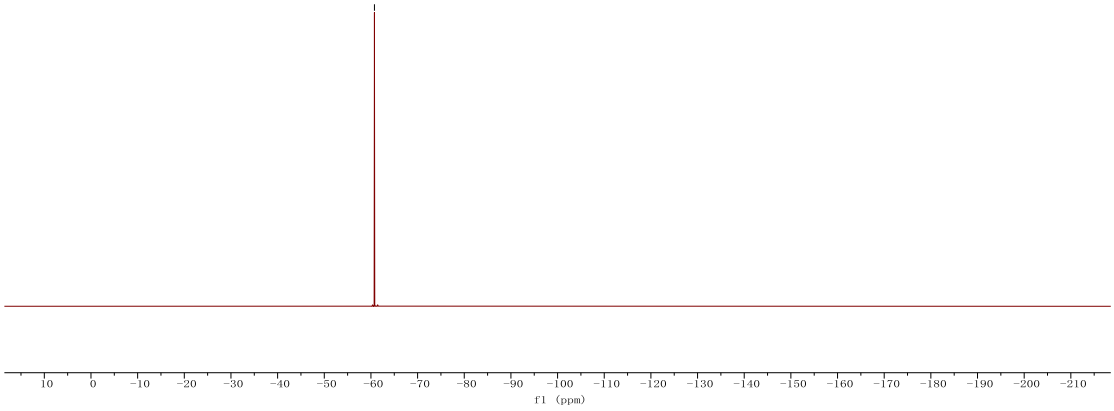
1m



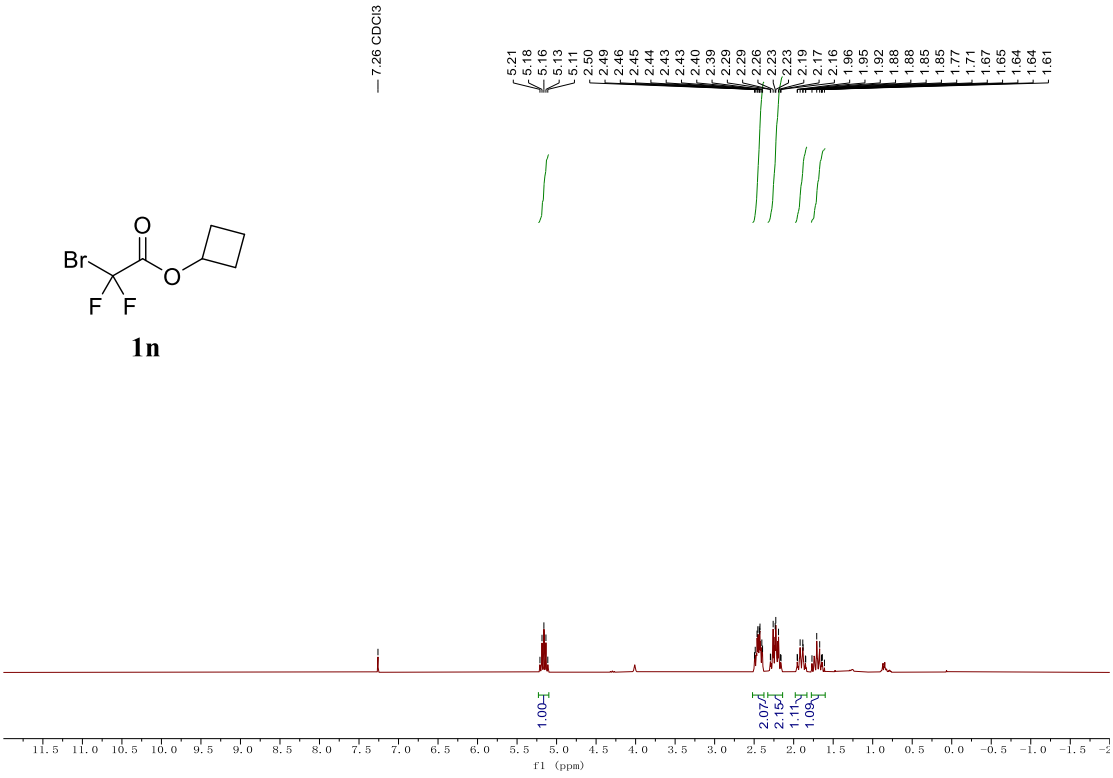
^{19}F NMR Spectrum of Compound **1m** (282 MHz, $CDCl_3$)



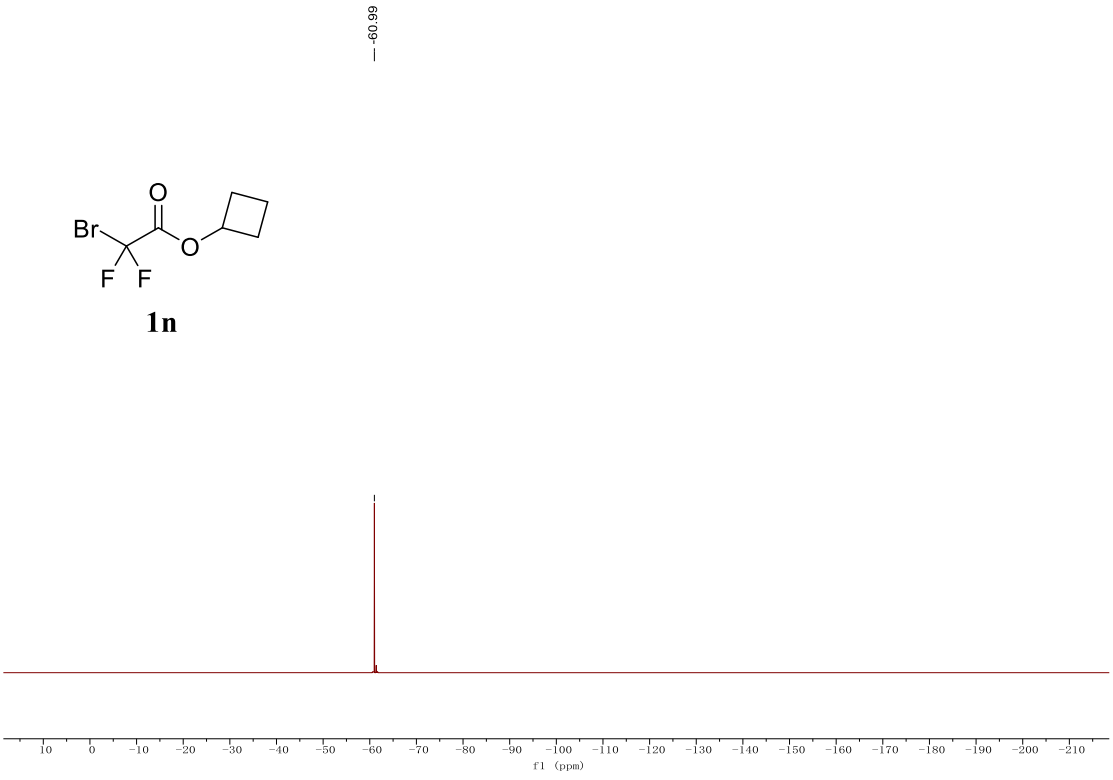
1m



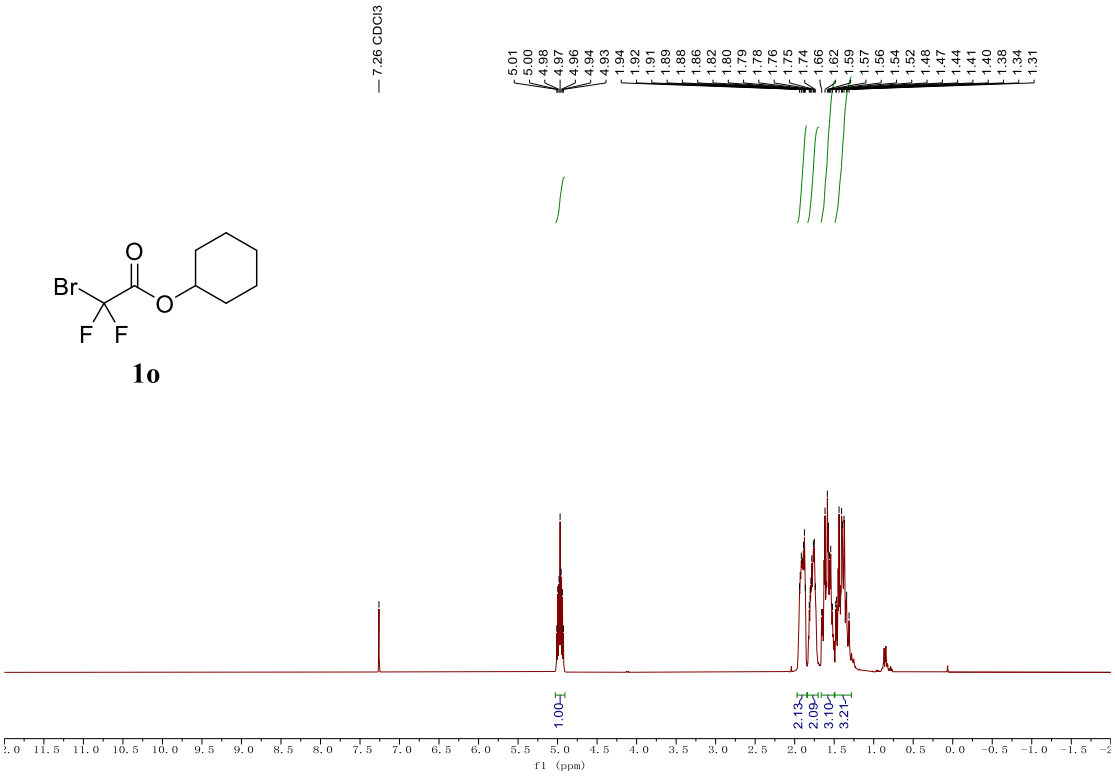
^{1}H NMR Spectrum of Compound **1n** (300 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **1n** (282 MHz, $CDCl_3$)

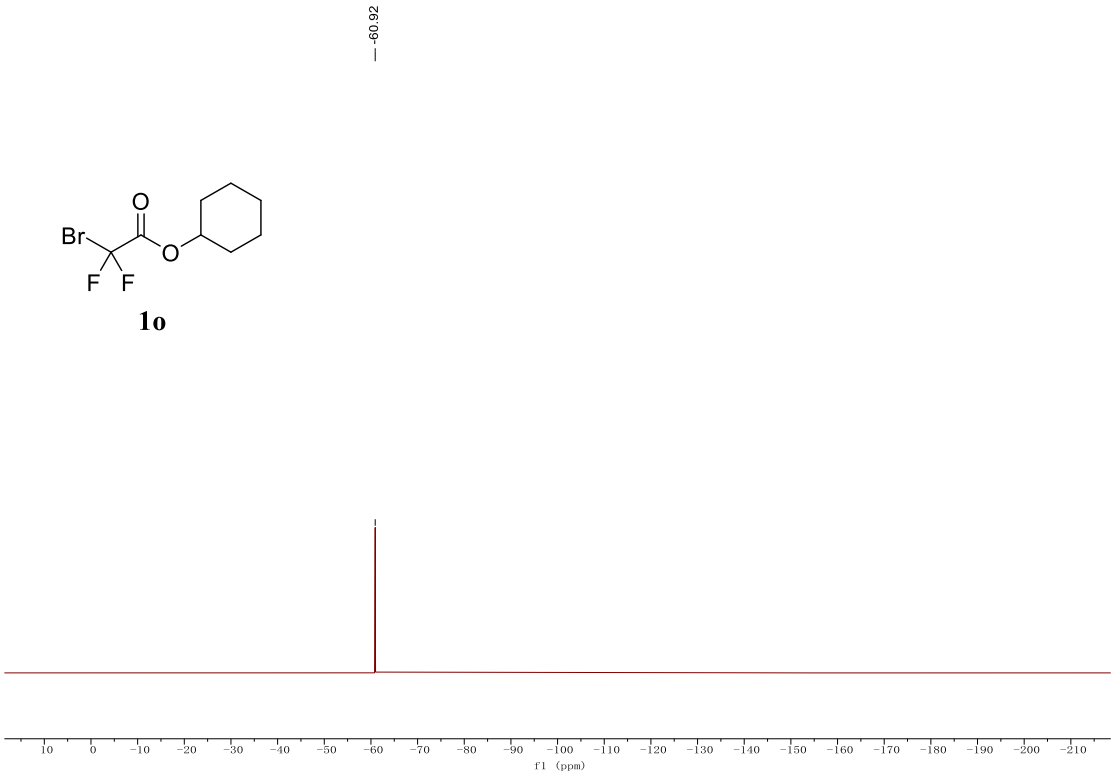


^{1}H NMR Spectrum of Compound **1o** (300 MHz, $CDCl_3$)



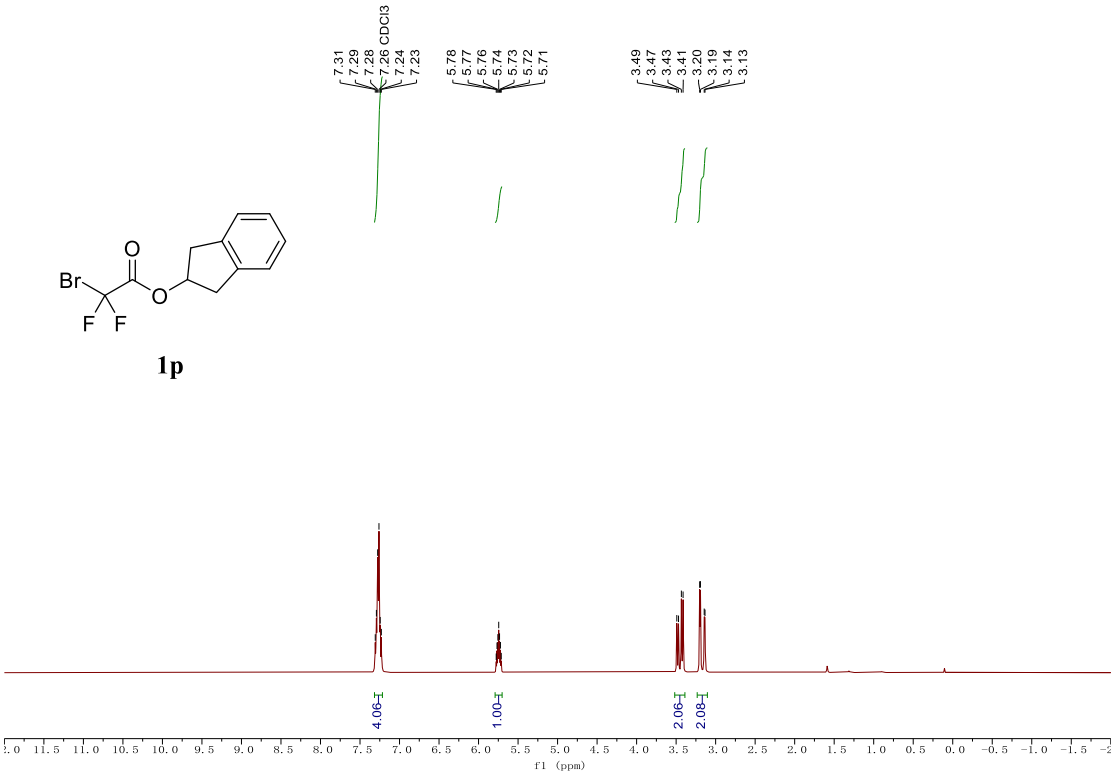
1o

^{19}F NMR Spectrum of Compound **1o** (282 MHz, $CDCl_3$)



1o

^{1}H NMR Spectrum of Compound **1p** (300 MHz, $CDCl_3$)

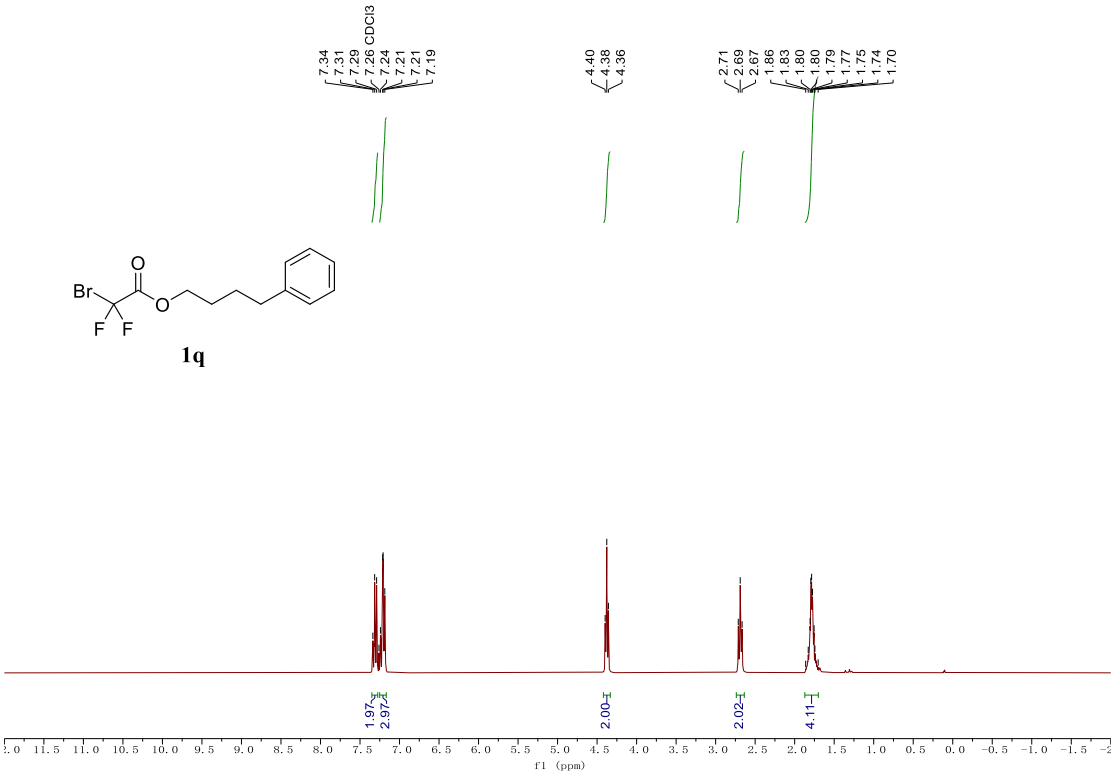


1p

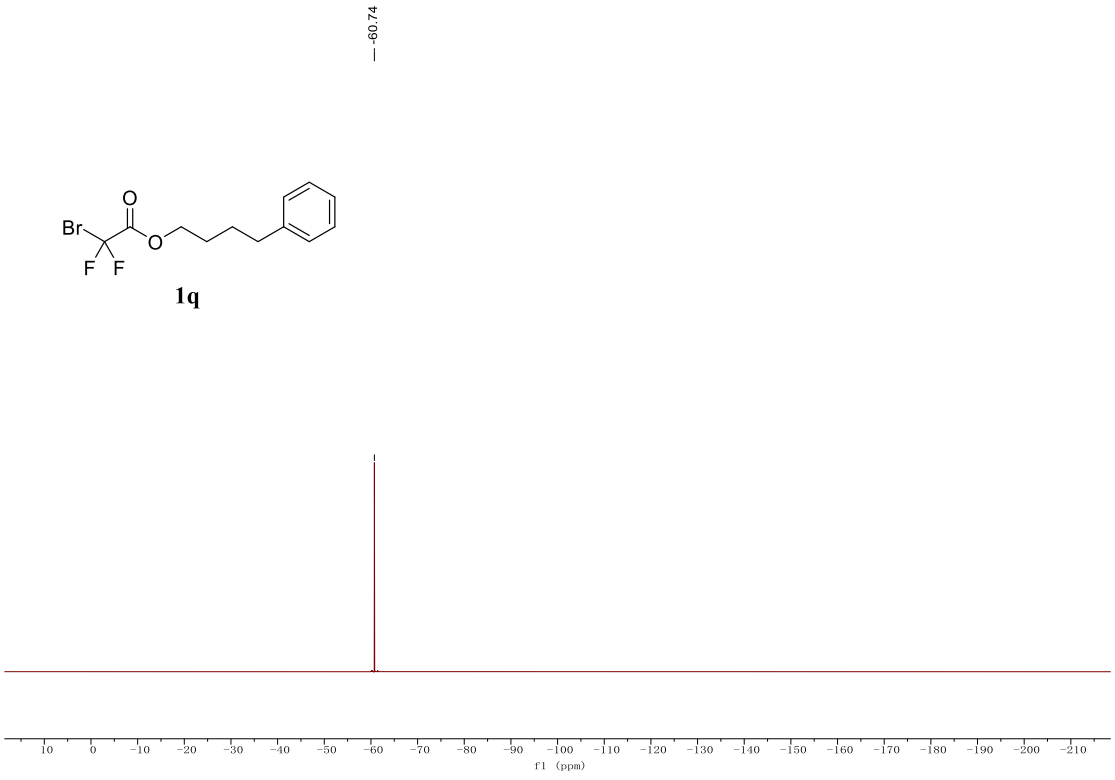
^{19}F NMR Spectrum of Compound **1p** (282 MHz, $CDCl_3$)

1p

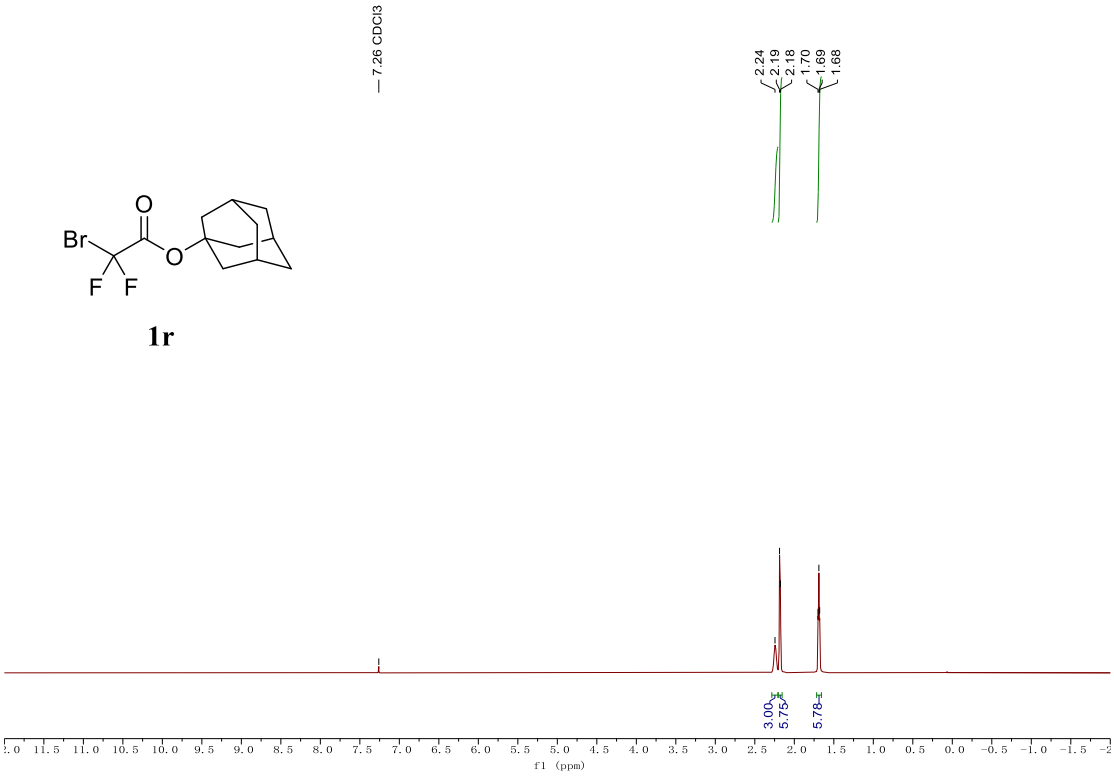
^{1}H NMR Spectrum of Compound **1q** (300 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **1q** (282 MHz, $CDCl_3$)

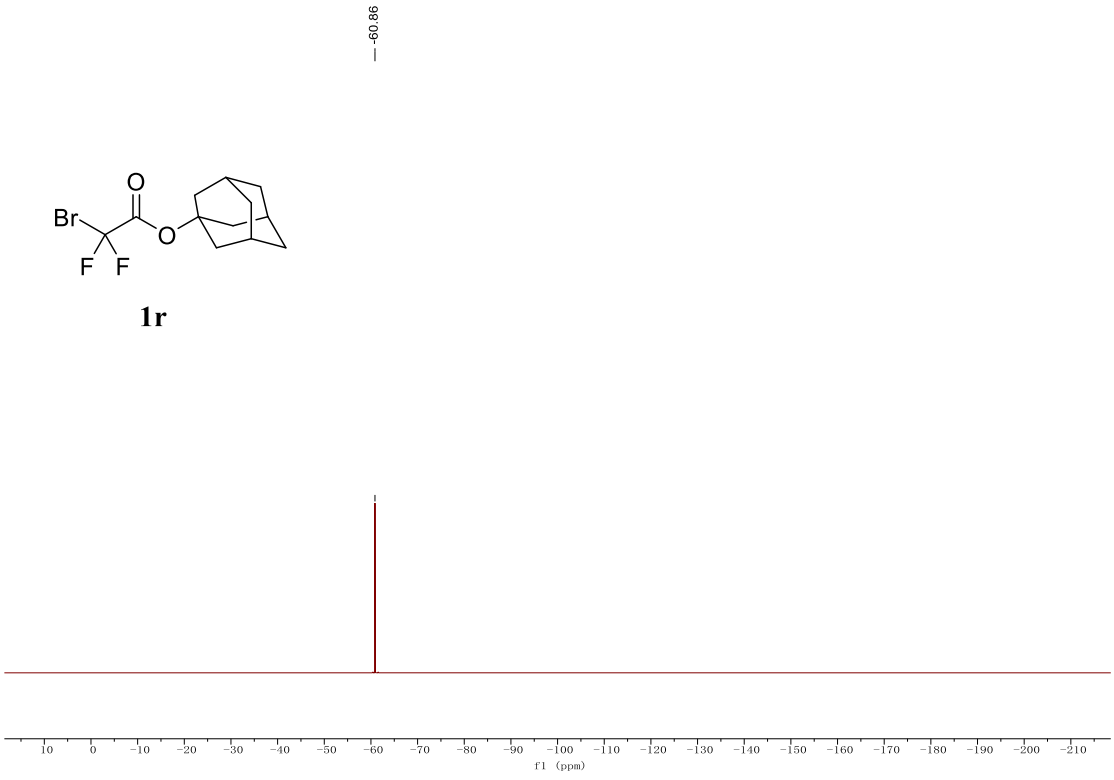


^{1}H NMR Spectrum of Compound **1r** (300 MHz, $CDCl_3$)



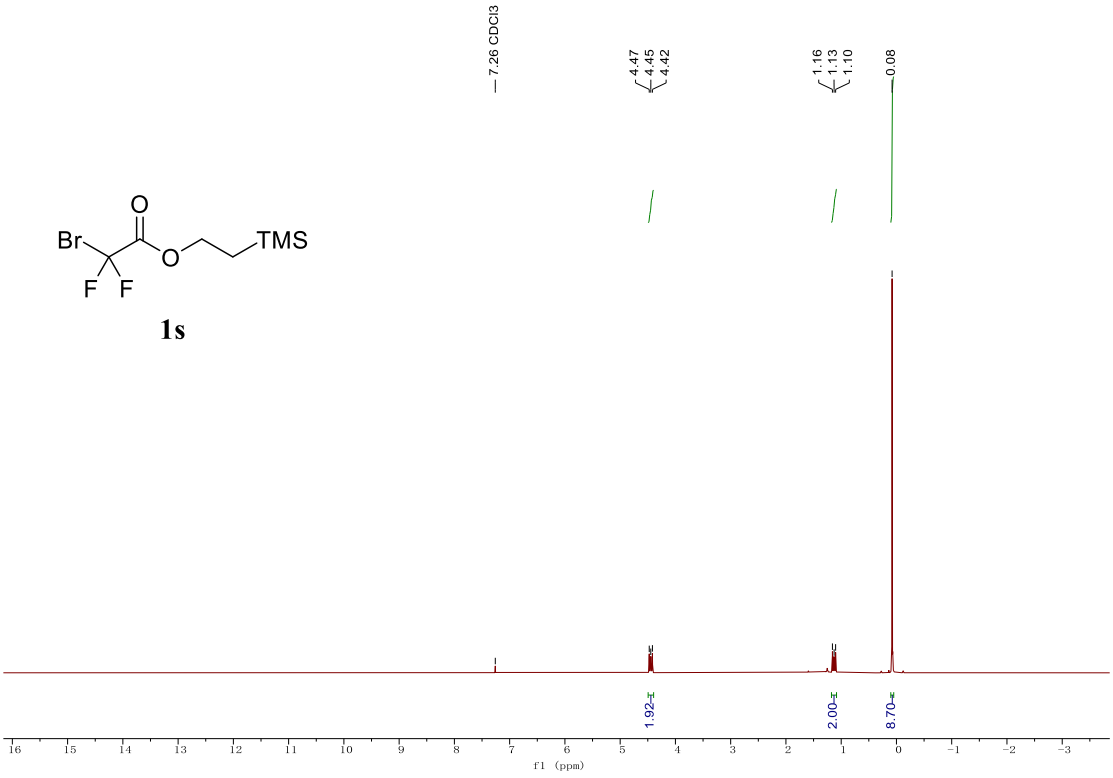
1r

^{19}F NMR Spectrum of Compound **1r** (282 MHz, $CDCl_3$)



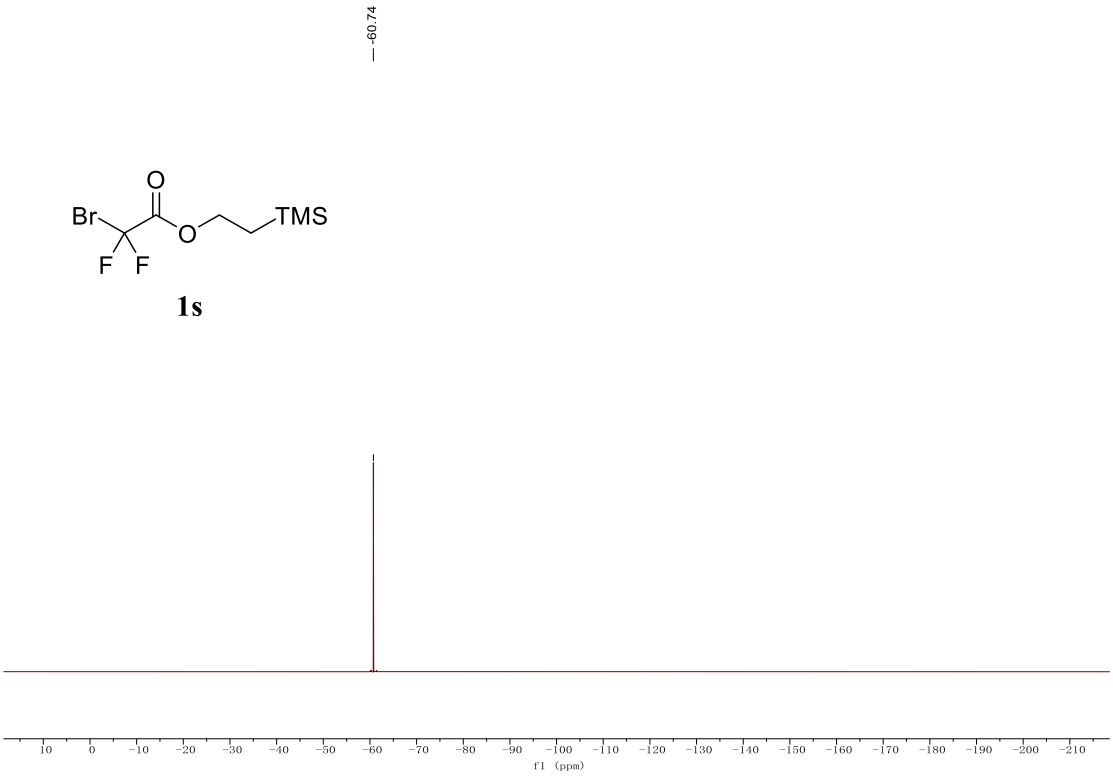
1r

^{1}H NMR Spectrum of Compound **1s** (300 MHz, $CDCl_3$)



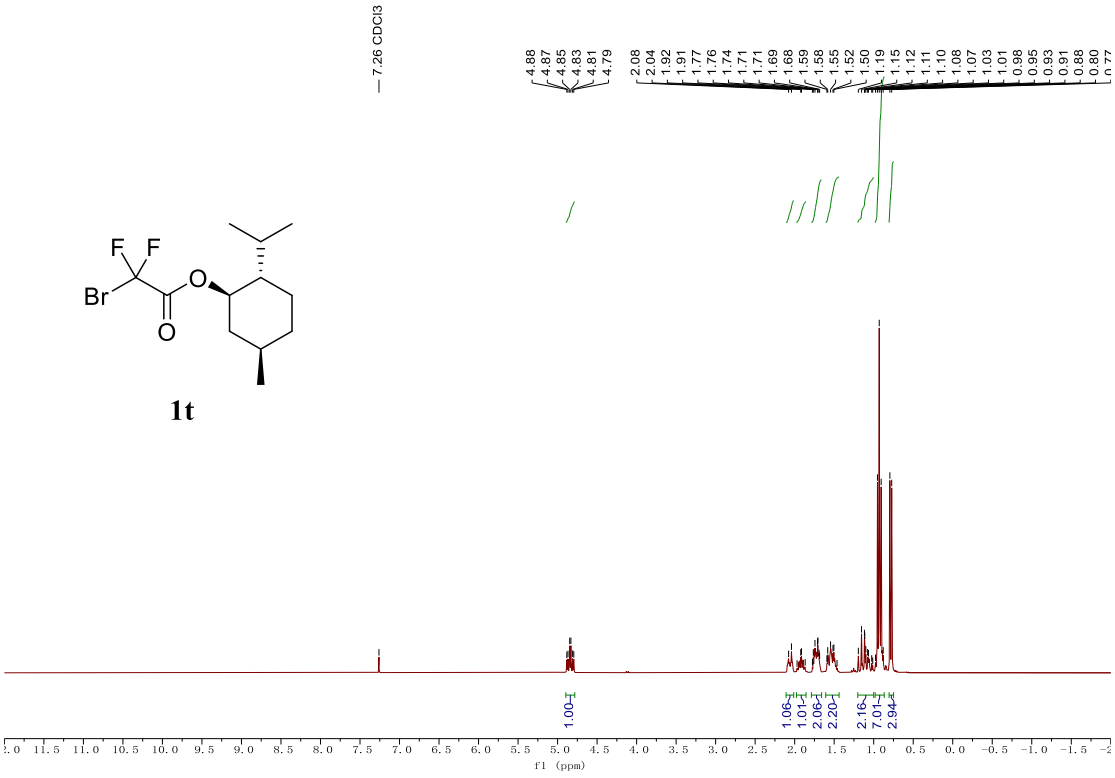
1s

^{19}F NMR Spectrum of Compound **1s** (282 MHz, $CDCl_3$)



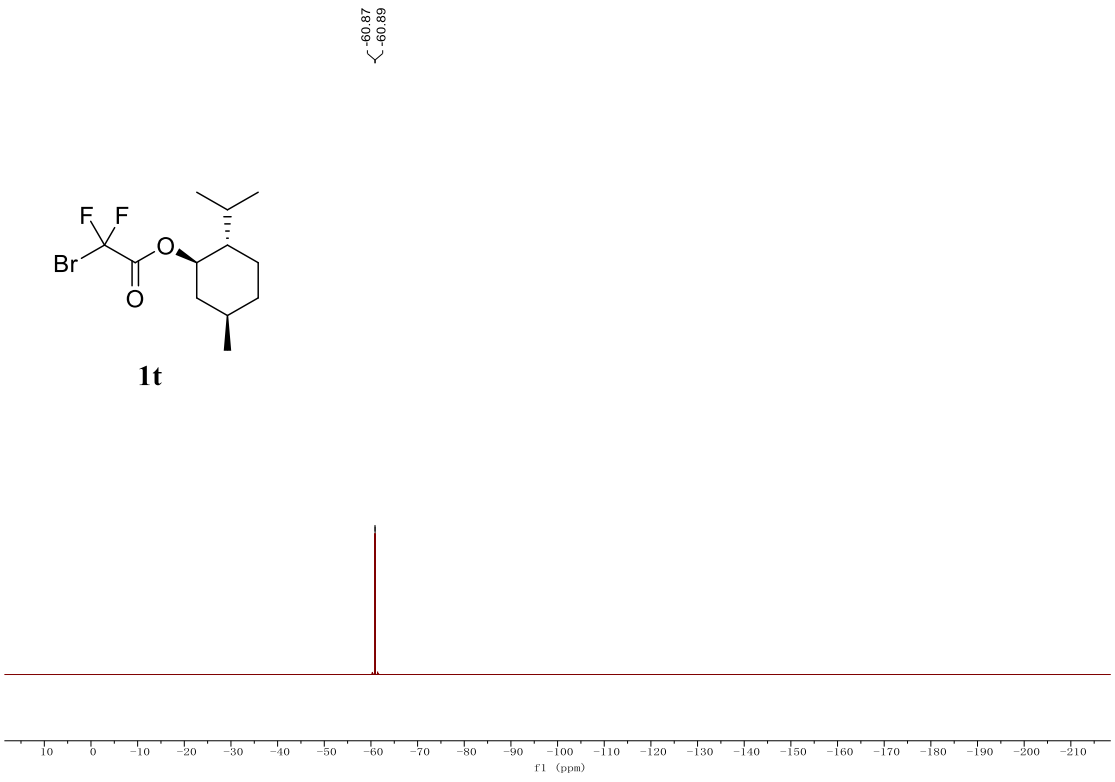
1s

^{1}H NMR Spectrum of Compound **1t** (300 MHz, $CDCl_3$)



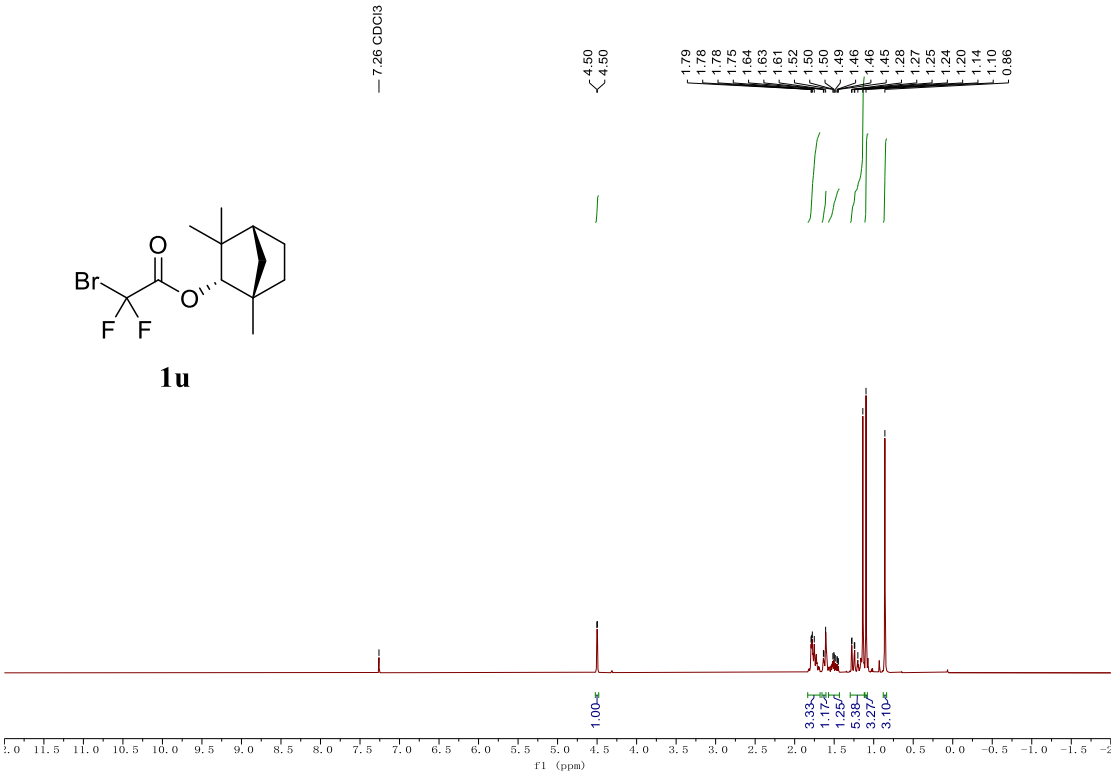
1t

^{19}F NMR Spectrum of Compound **1t** (282 MHz, $CDCl_3$)



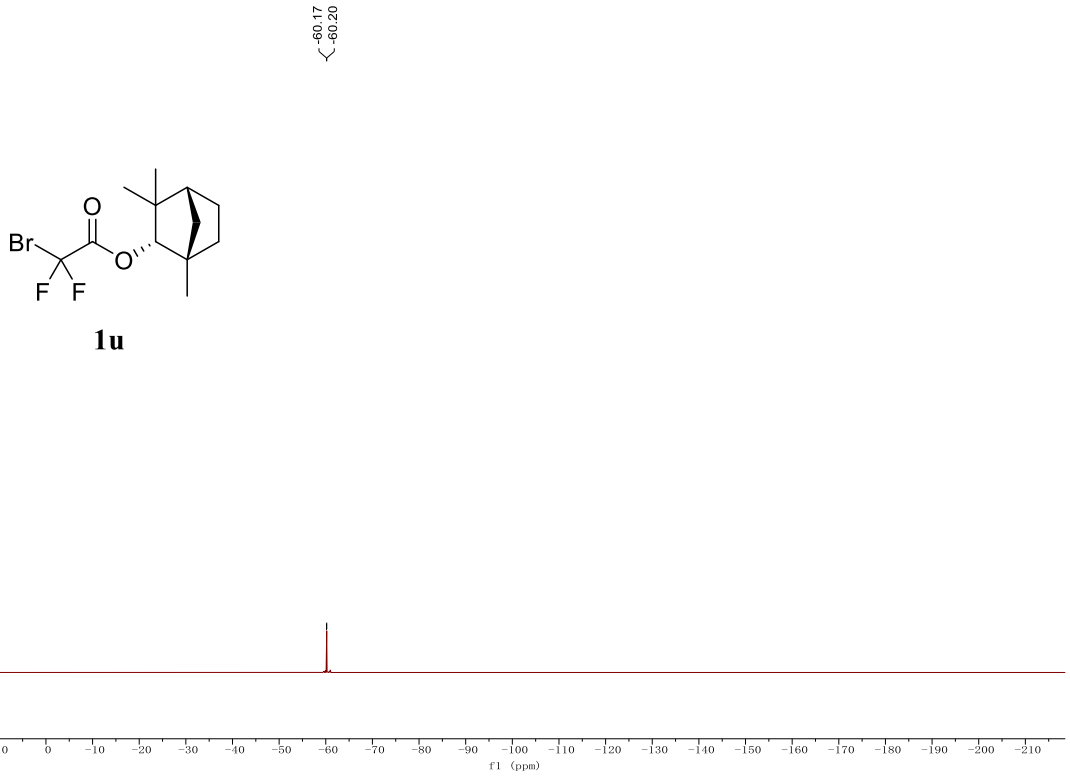
1t

^{1}H NMR Spectrum of Compound **1u** (300 MHz, $CDCl_3$)



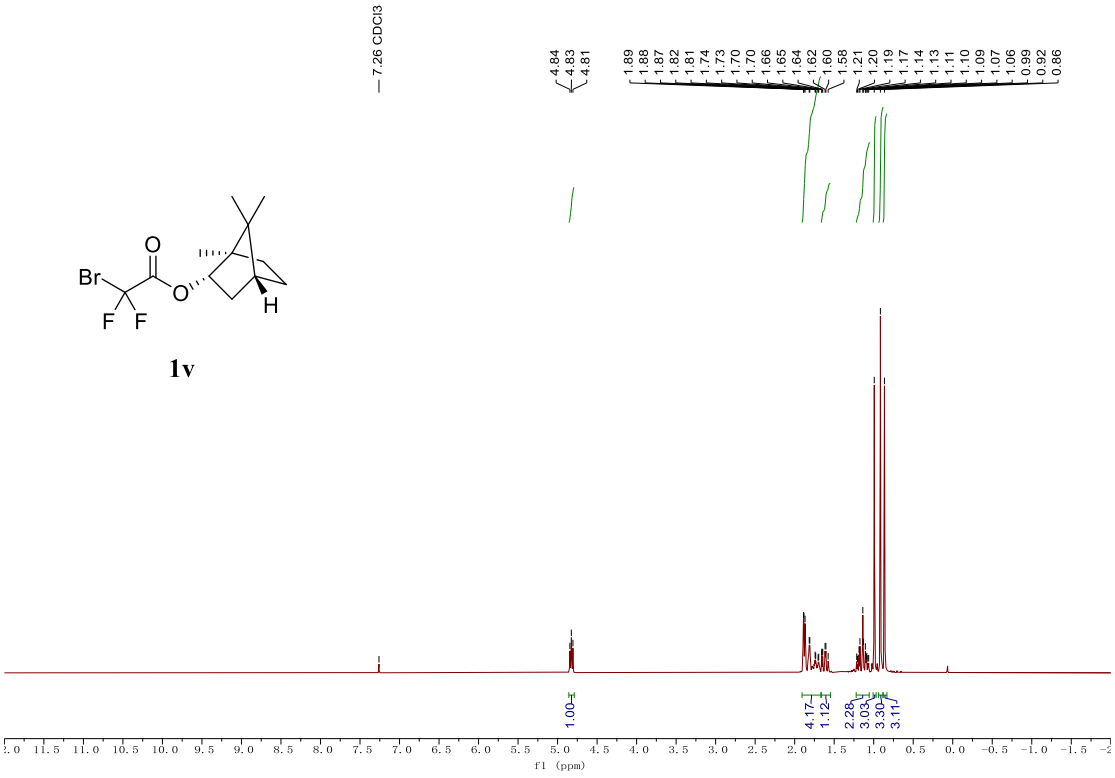
1u

^{19}F NMR Spectrum of Compound **1u** (282 MHz, $CDCl_3$)

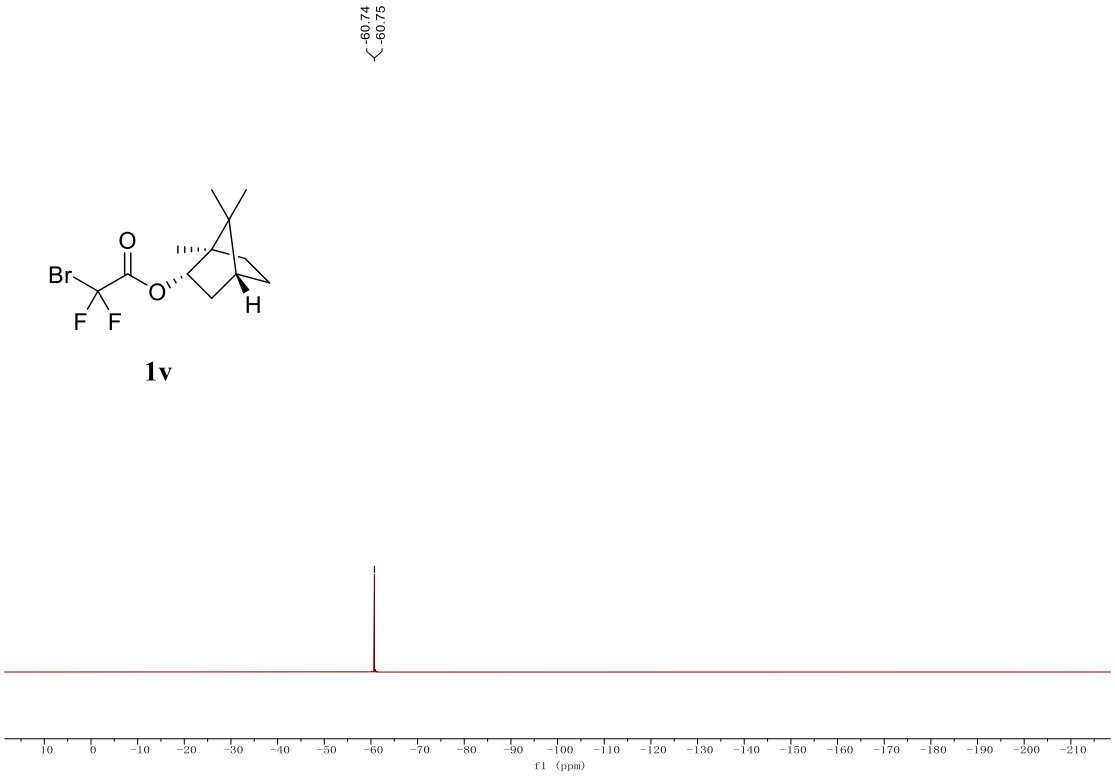


1u

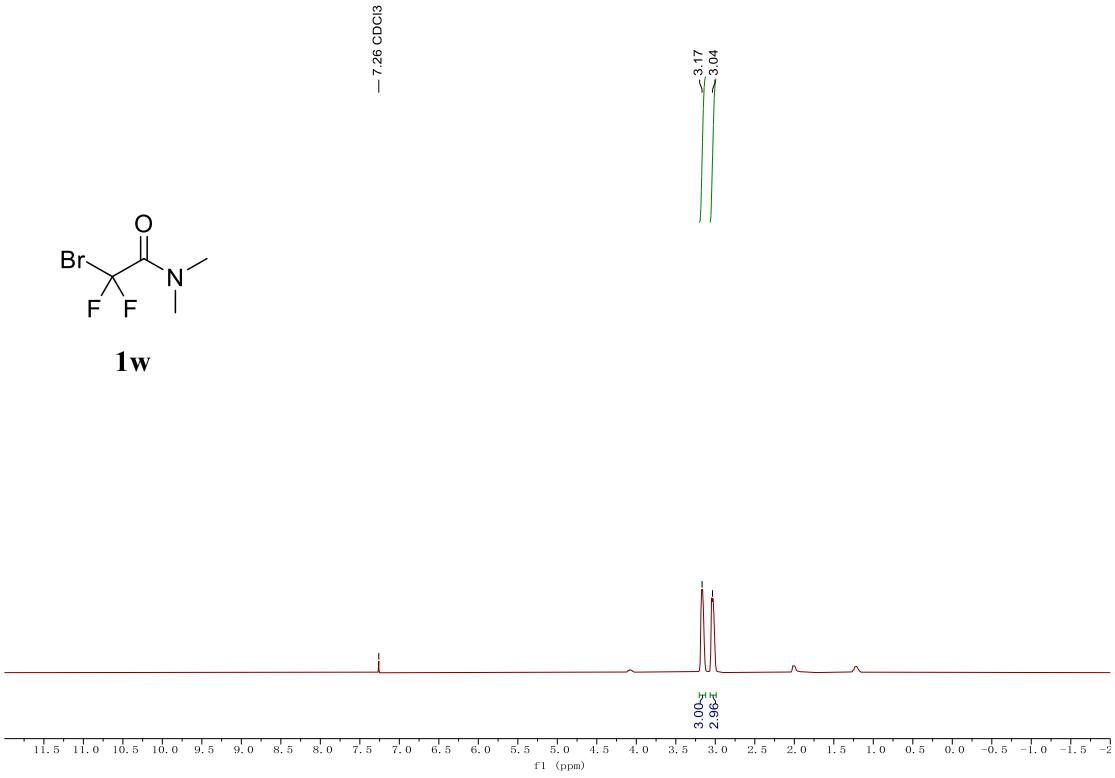
^{1}H NMR Spectrum of Compound **1v** (300 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **1v** (282 MHz, $CDCl_3$)

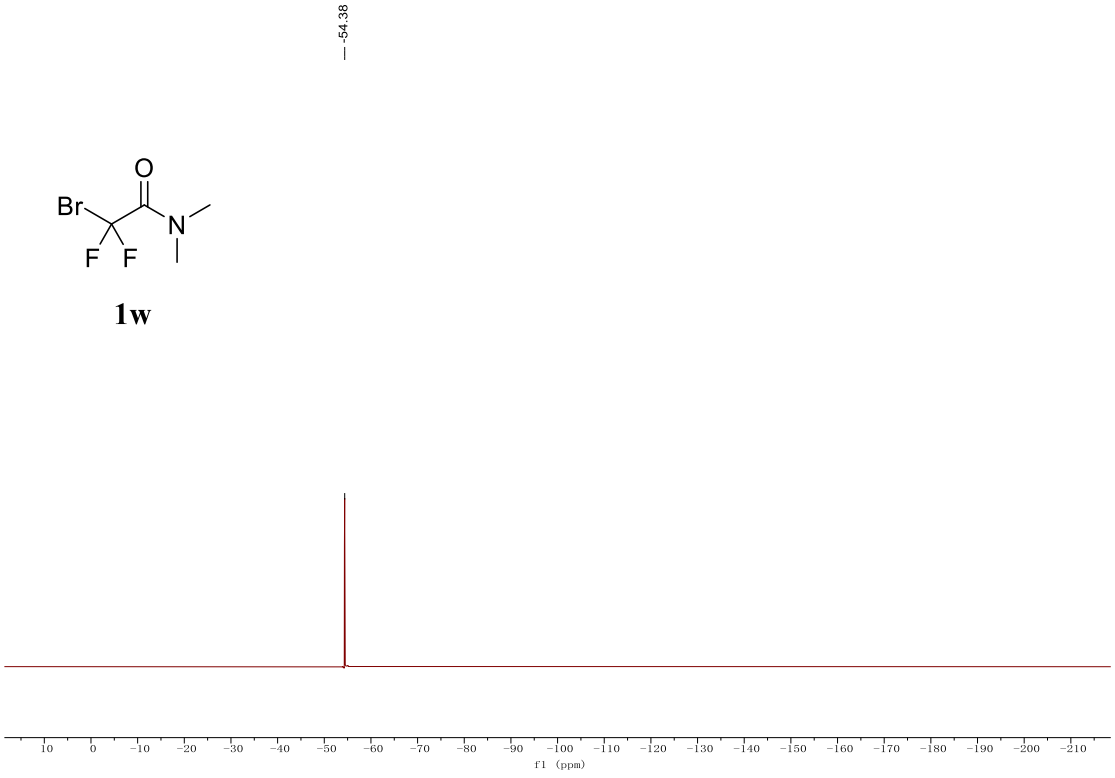


^{1}H NMR Spectrum of Compound **1w** (300 MHz, $CDCl_3$)



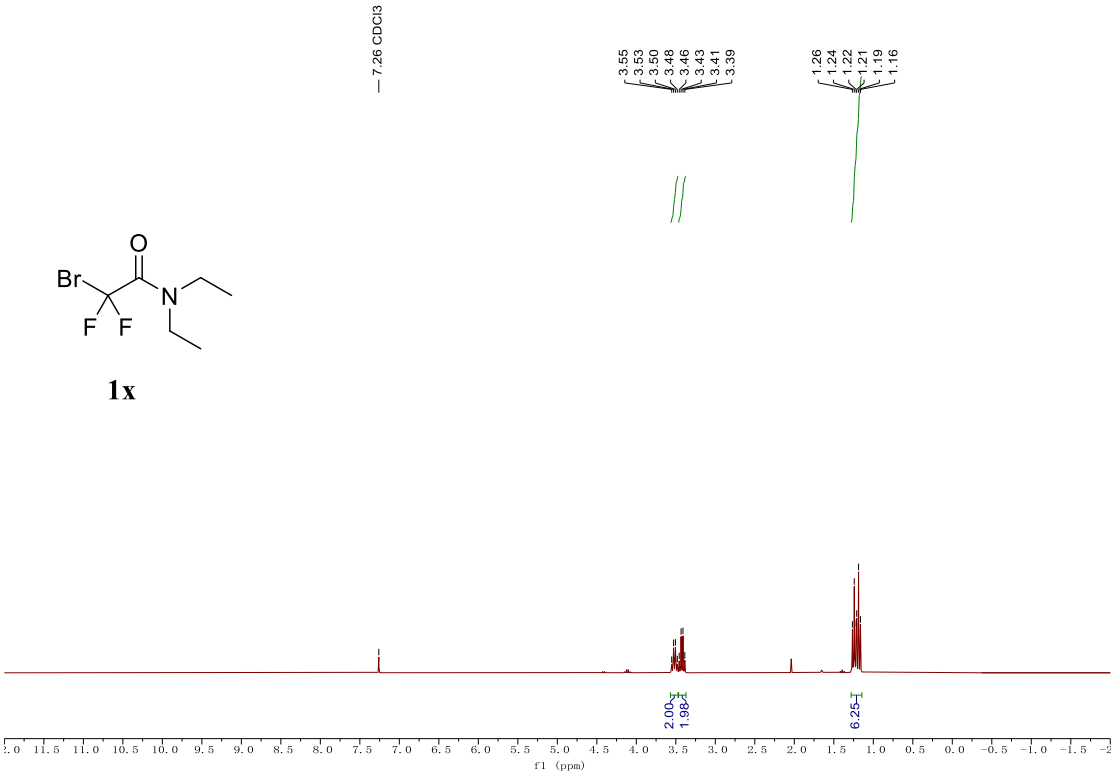
1w

^{19}F NMR Spectrum of Compound **1w** (282 MHz, $CDCl_3$)



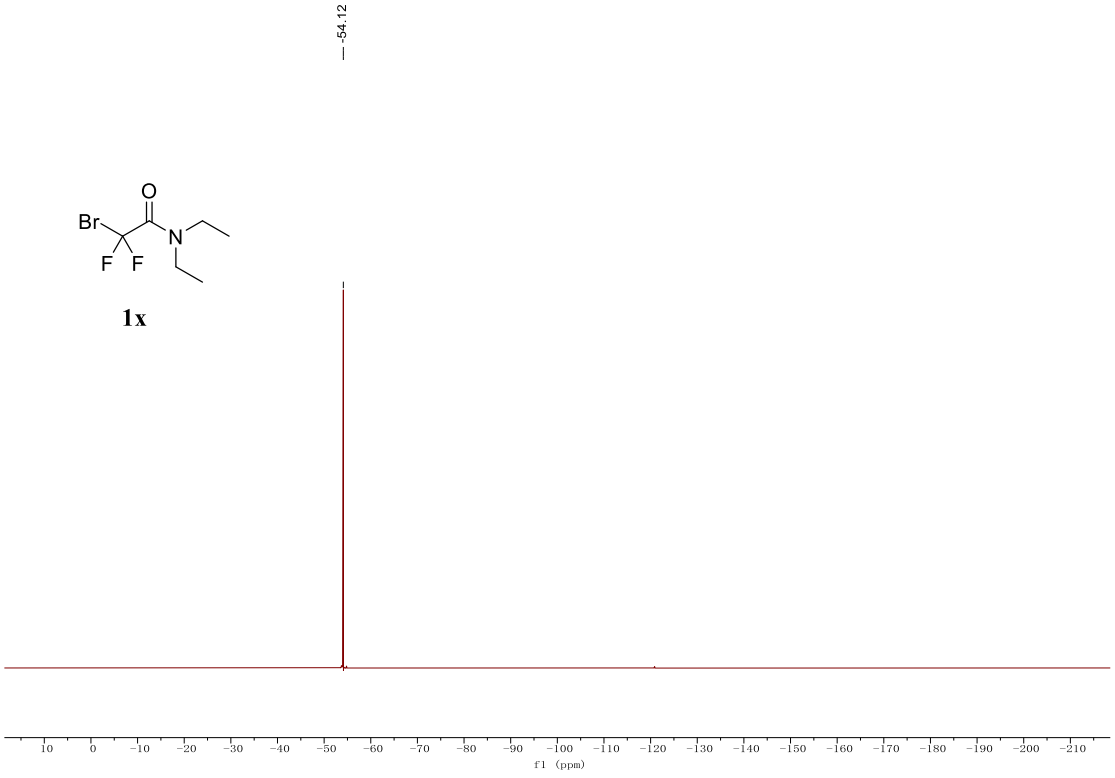
1w

^{1}H NMR Spectrum of Compound **1x** (300 MHz, $CDCl_3$)



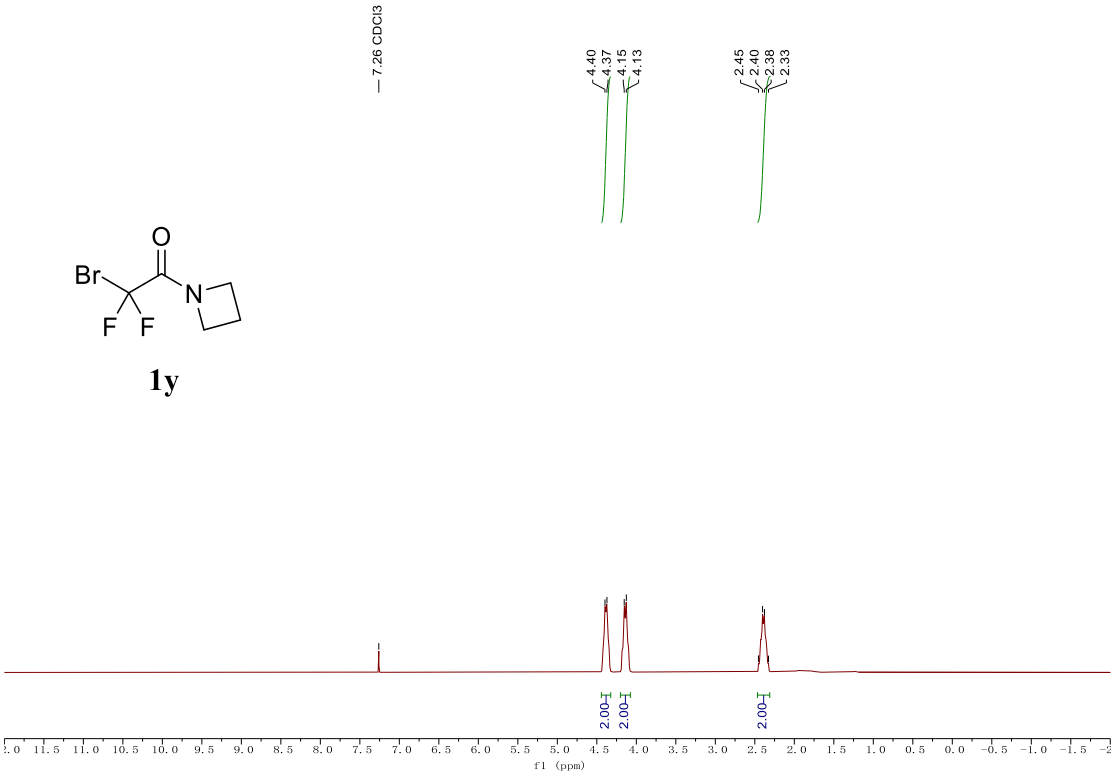
1x

^{19}F NMR Spectrum of Compound **1x** (282 MHz, $CDCl_3$)



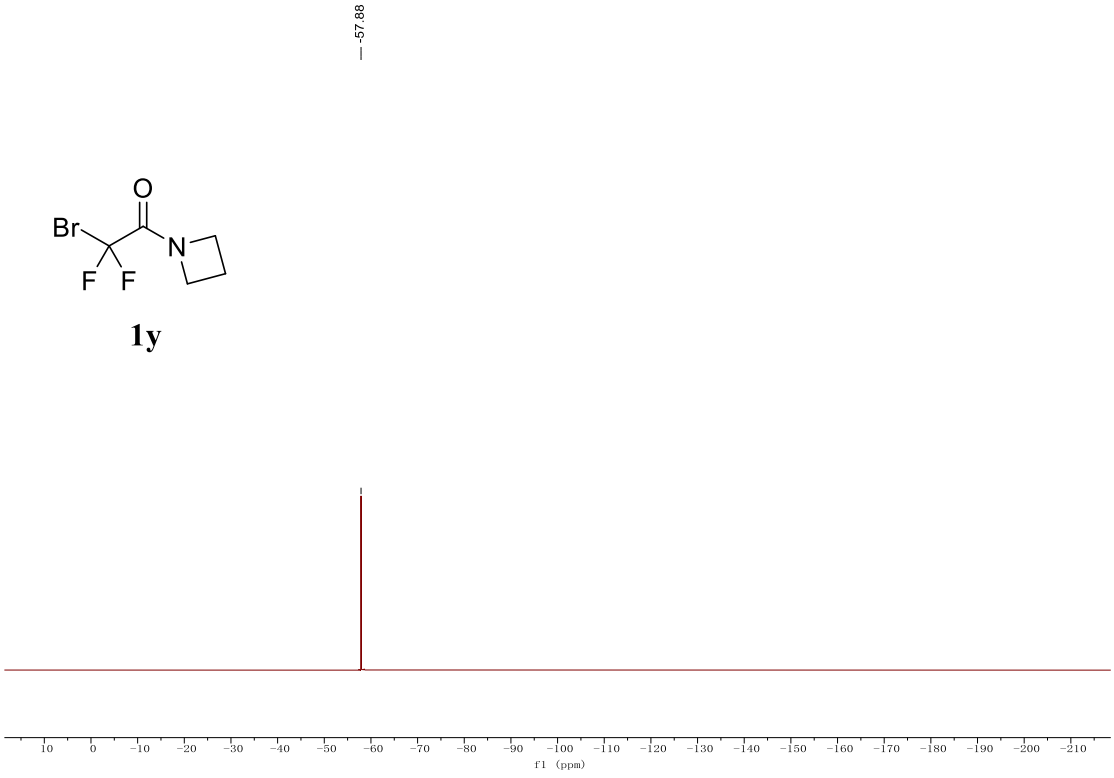
1x

^{1}H NMR Spectrum of Compound **1y** (300 MHz, $CDCl_3$)



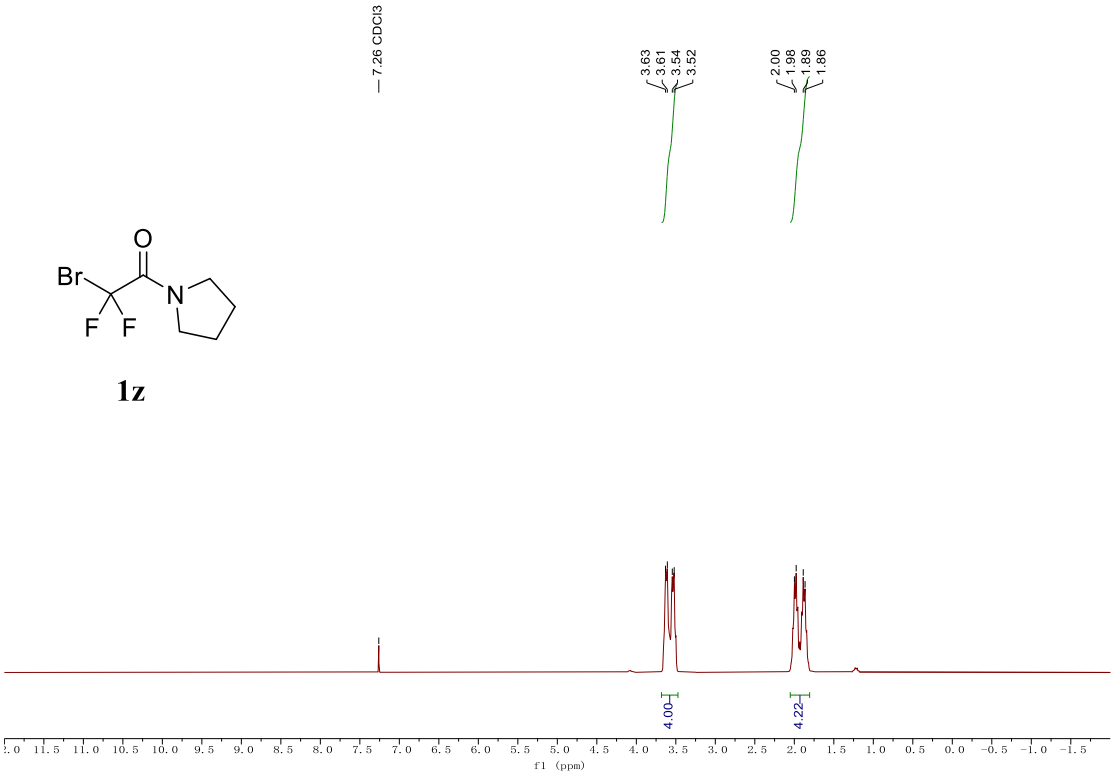
1y

^{19}F NMR Spectrum of Compound **1y** (282 MHz, $CDCl_3$)



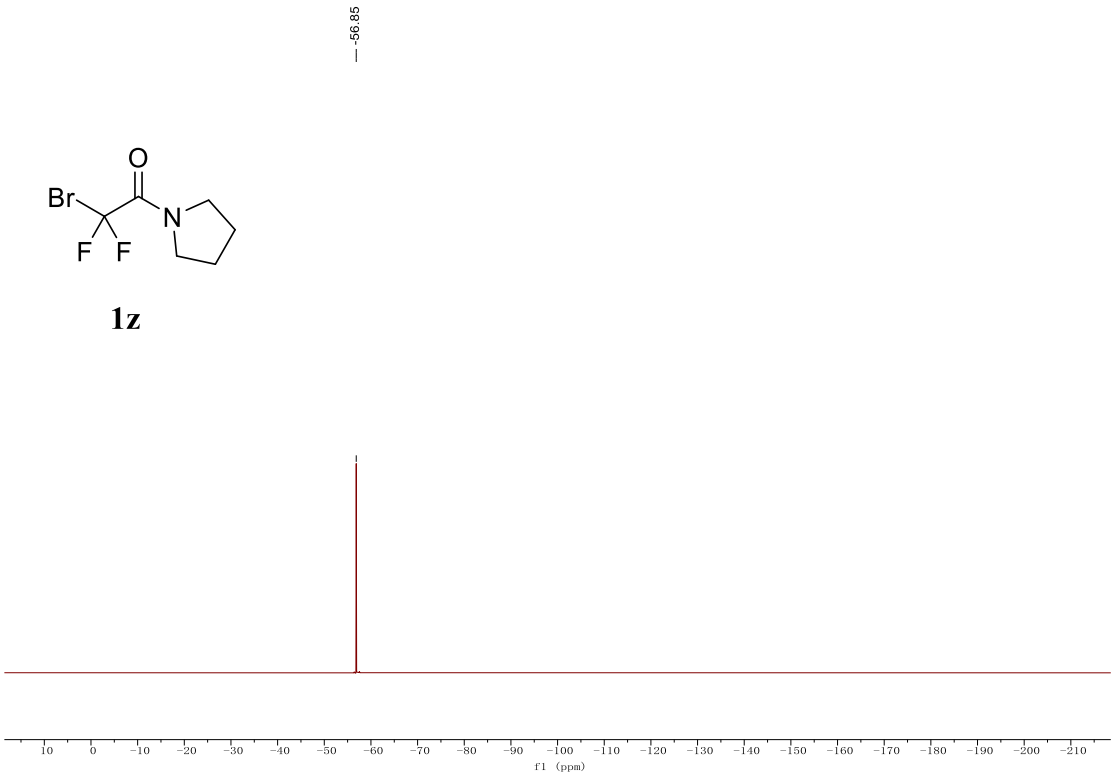
1y

^{1}H NMR Spectrum of Compound **1z** (300 MHz, $CDCl_3$)



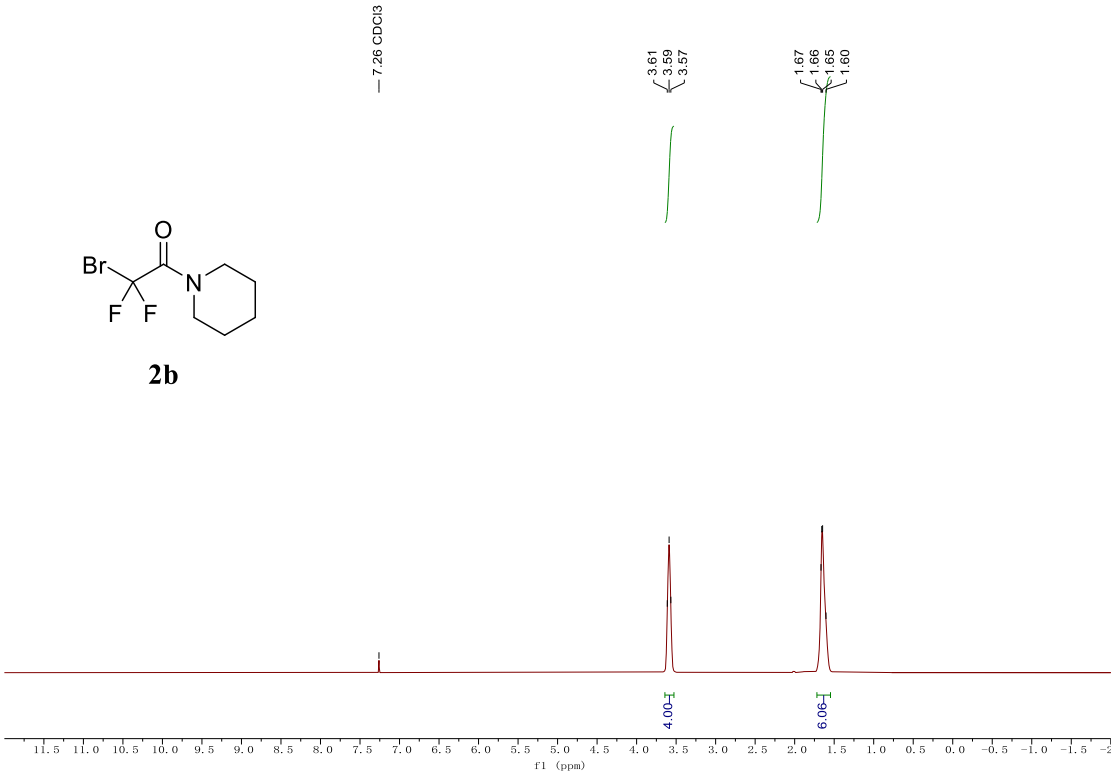
1z

^{19}F NMR Spectrum of Compound **1z** (282 MHz, $CDCl_3$)



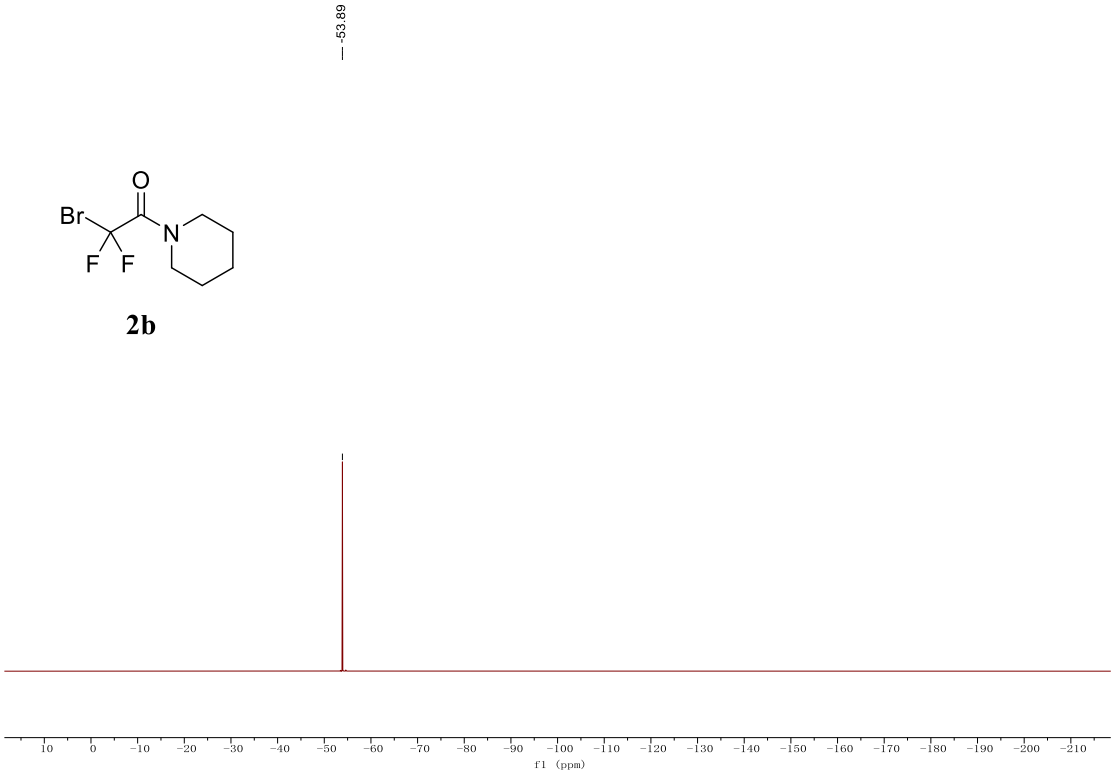
1z

^{1}H NMR Spectrum of Compound **2b** (300 MHz, $CDCl_3$)



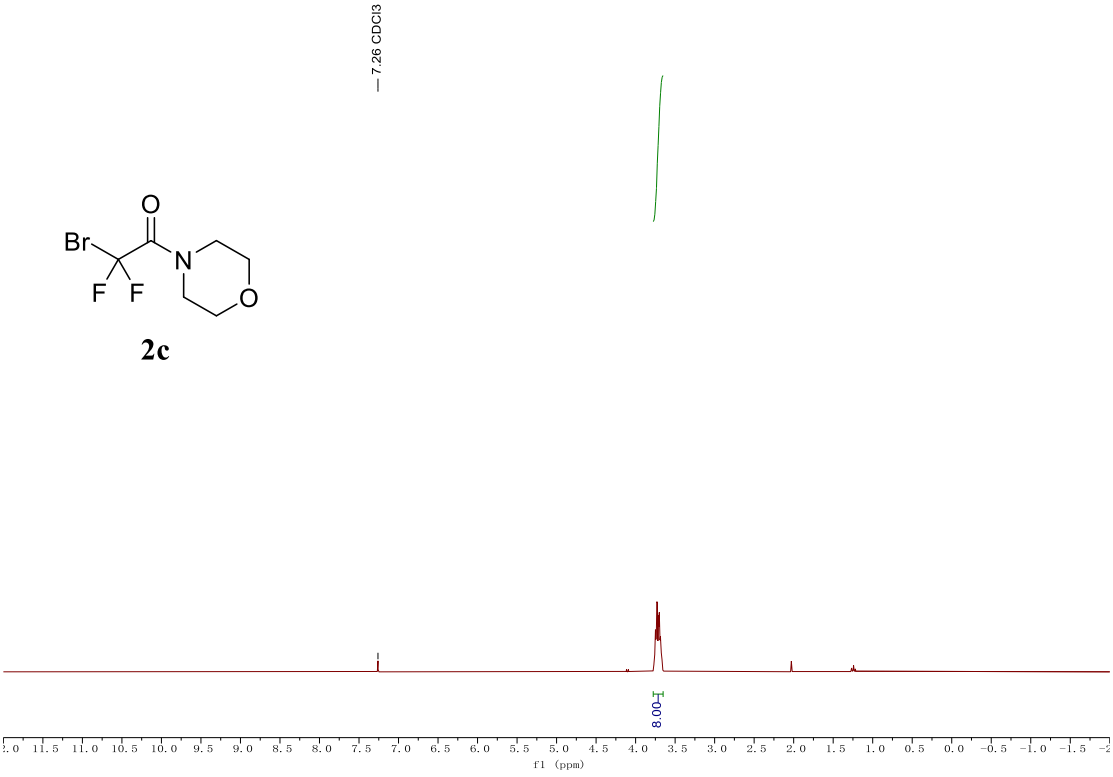
2b

^{19}F NMR Spectrum of Compound **2b** (282 MHz, $CDCl_3$)



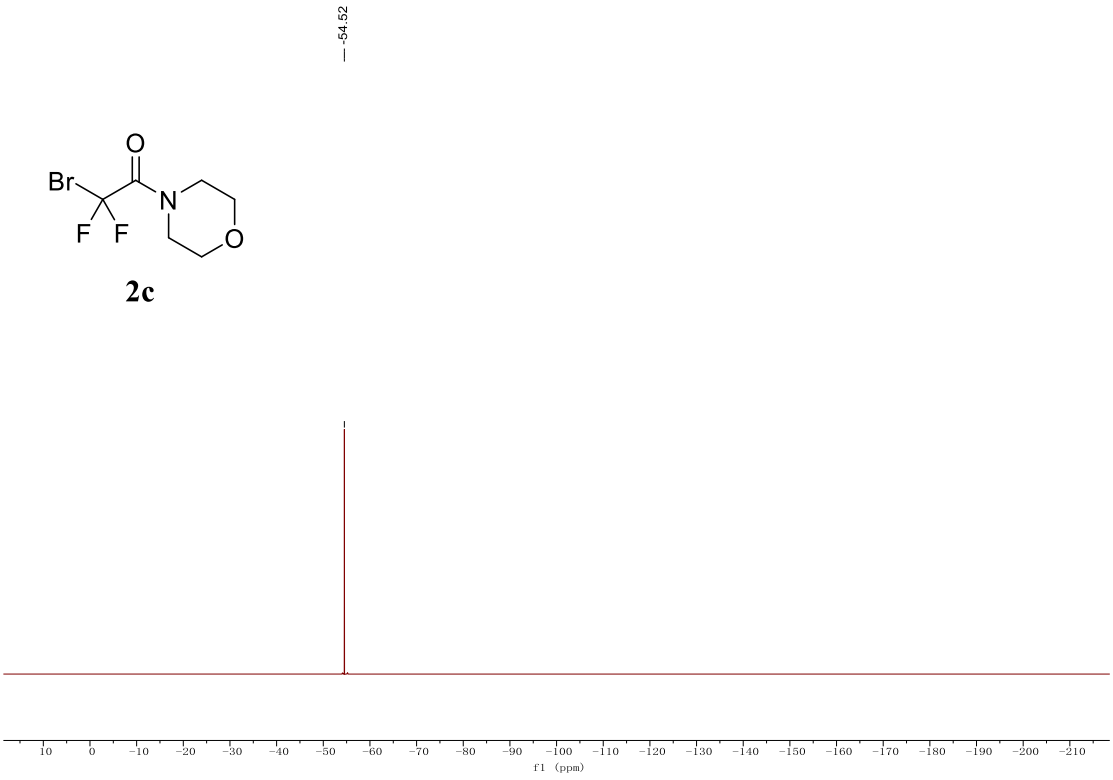
2b

^{1}H NMR Spectrum of Compound **2c** (300 MHz, $CDCl_3$)



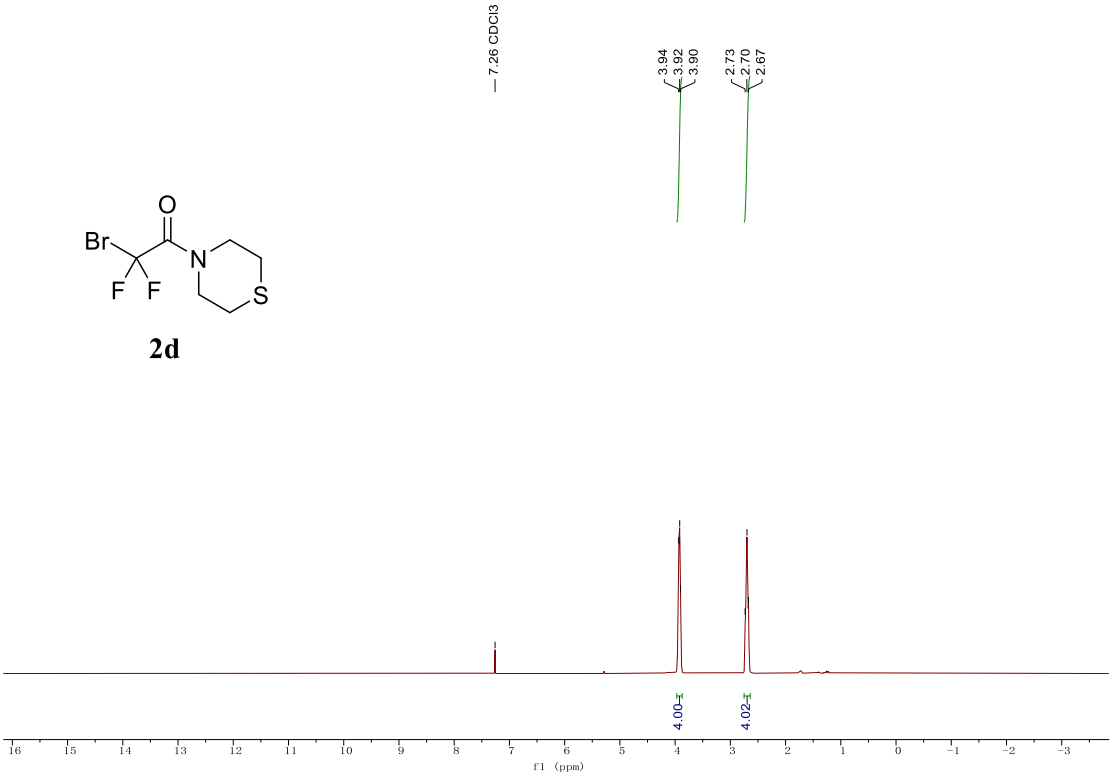
2c

^{19}F NMR Spectrum of Compound **2c** (282 MHz, $CDCl_3$)



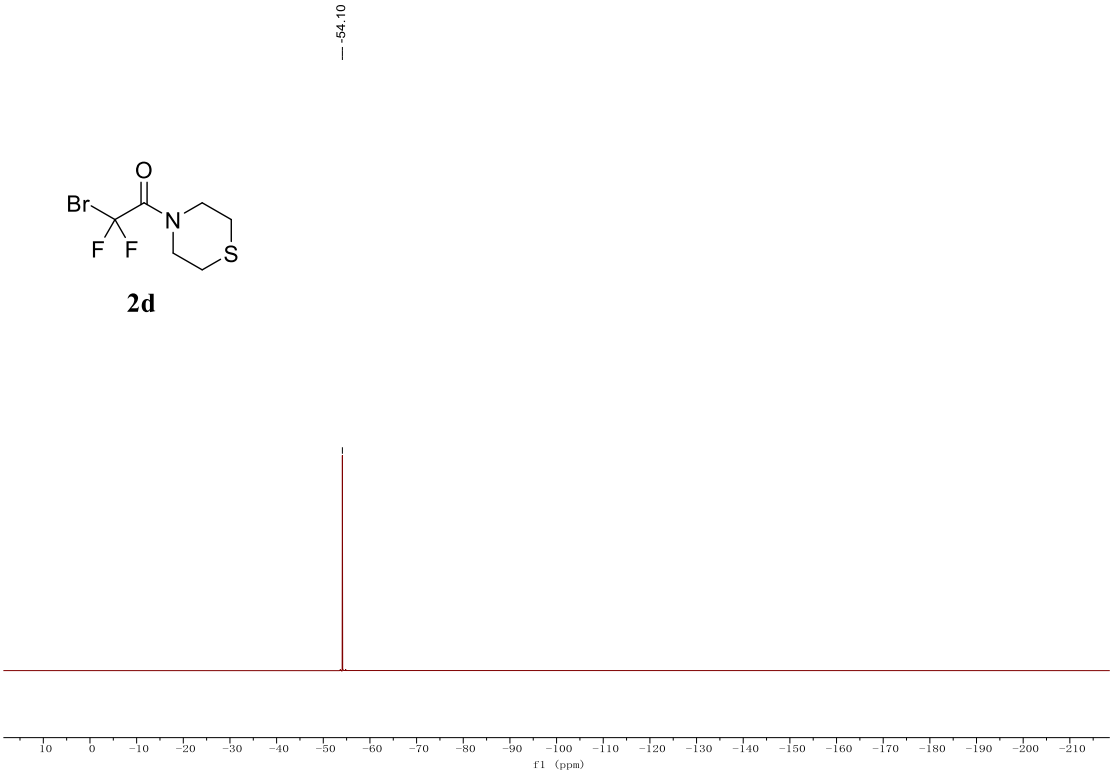
2c

^{1}H NMR Spectrum of Compound **2d** (300 MHz, $CDCl_3$)



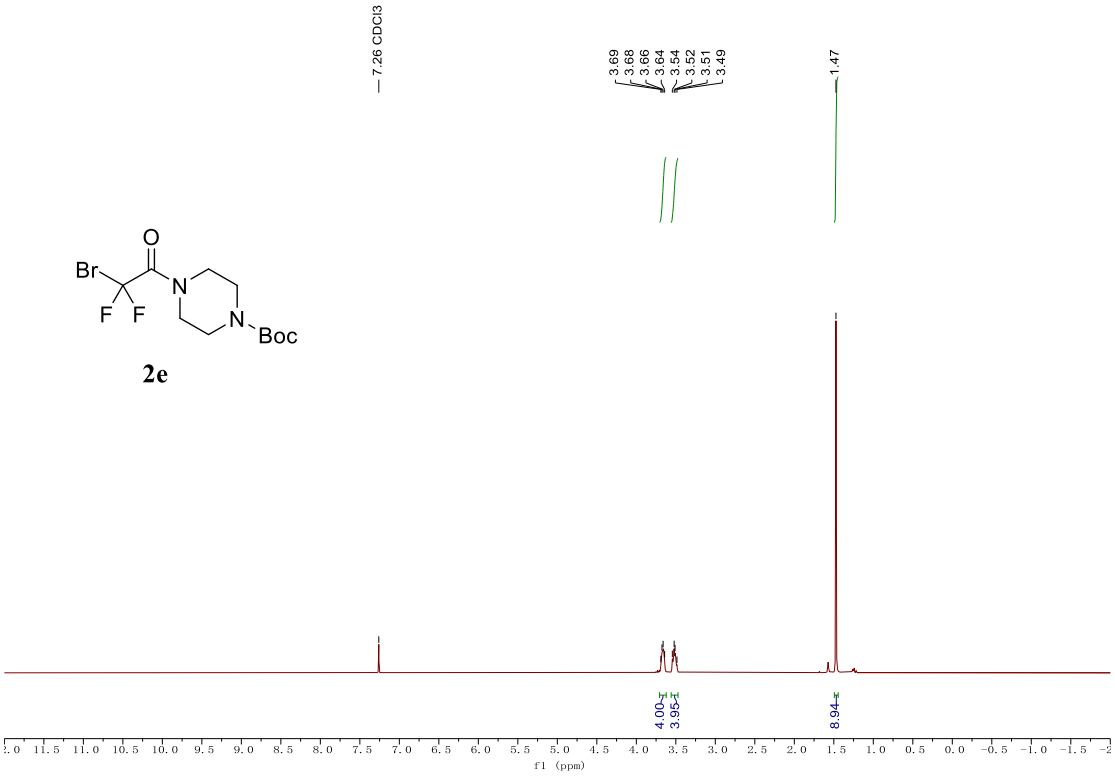
2d

^{19}F NMR Spectrum of Compound **2d** (282 MHz, $CDCl_3$)



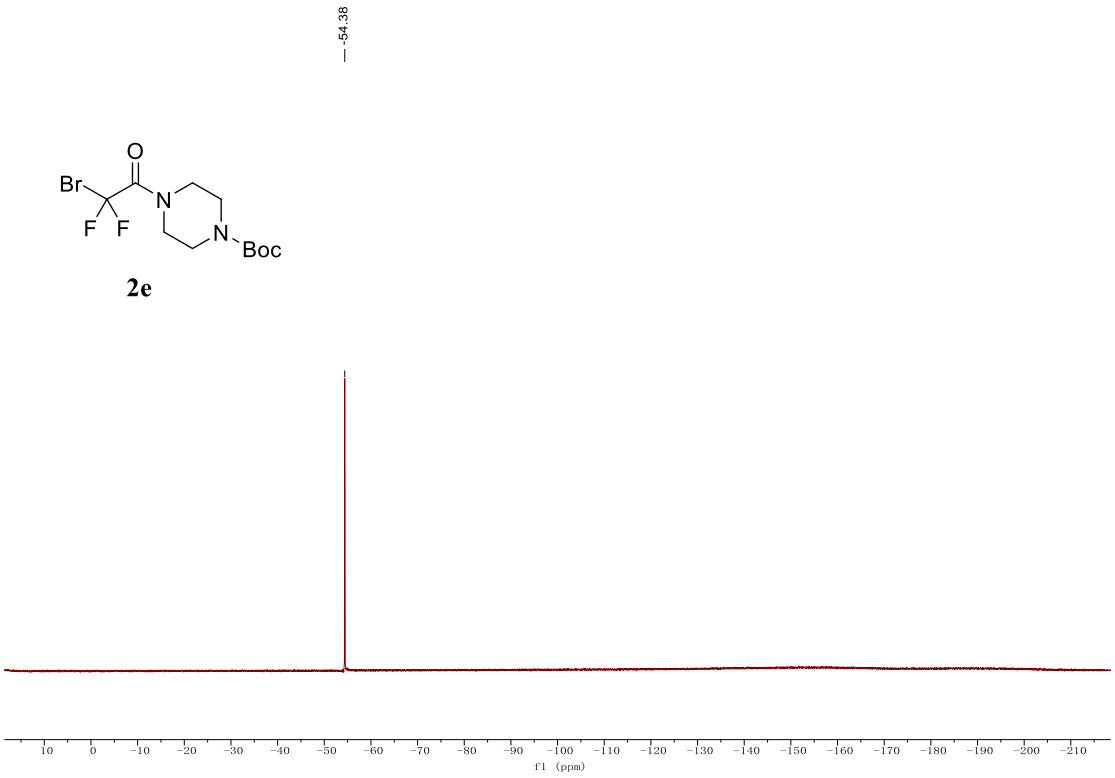
2d

^{1}H NMR Spectrum of Compound **2e** (300 MHz, $CDCl_3$)



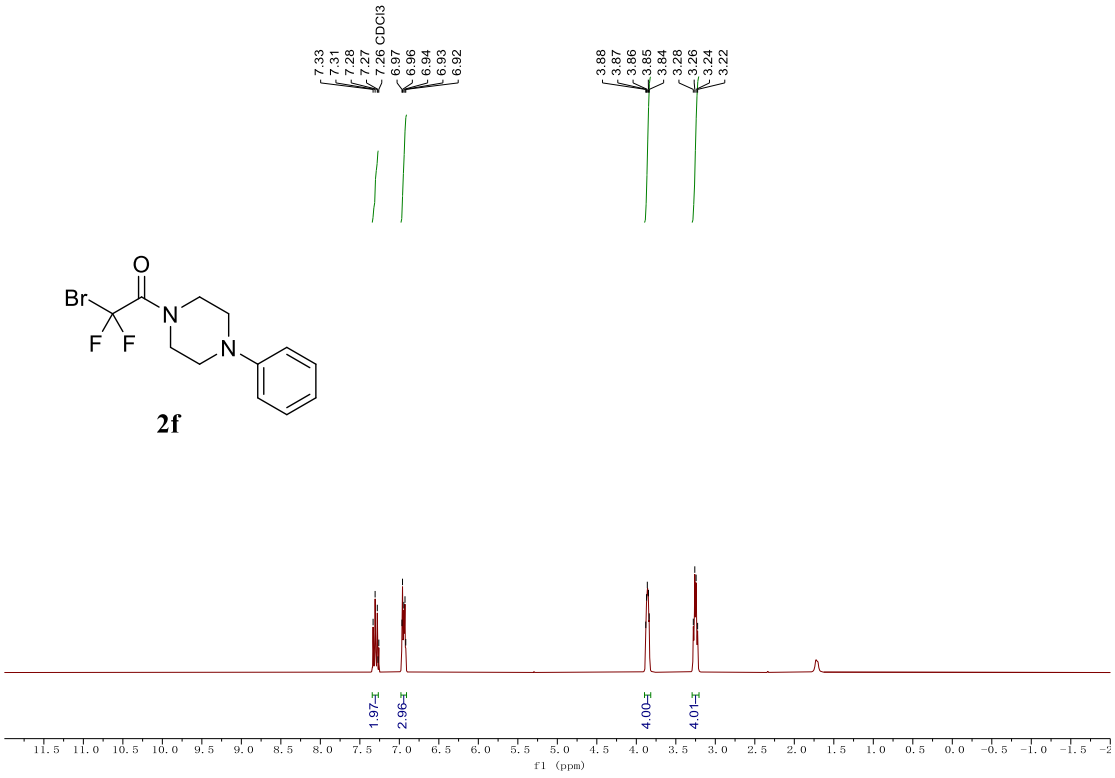
2e

^{19}F NMR Spectrum of Compound **2e** (282 MHz, $CDCl_3$)

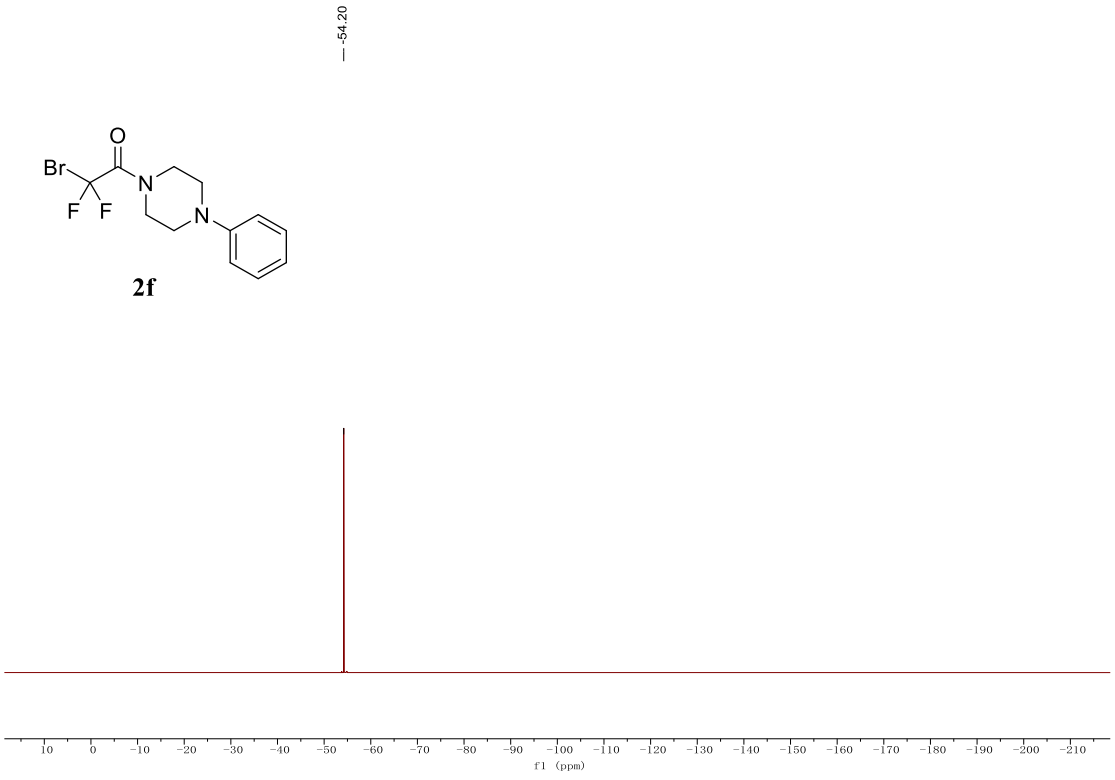


2e

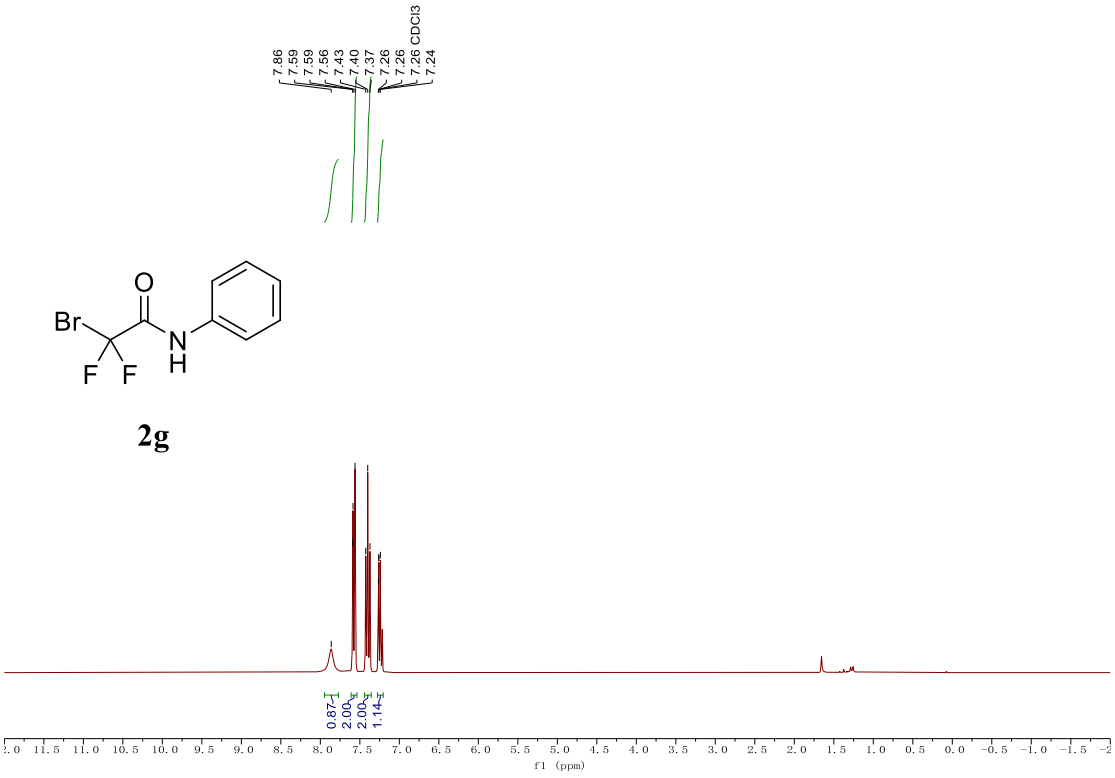
^{1}H NMR Spectrum of Compound **2f** (300 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **2f** (282 MHz, $CDCl_3$)

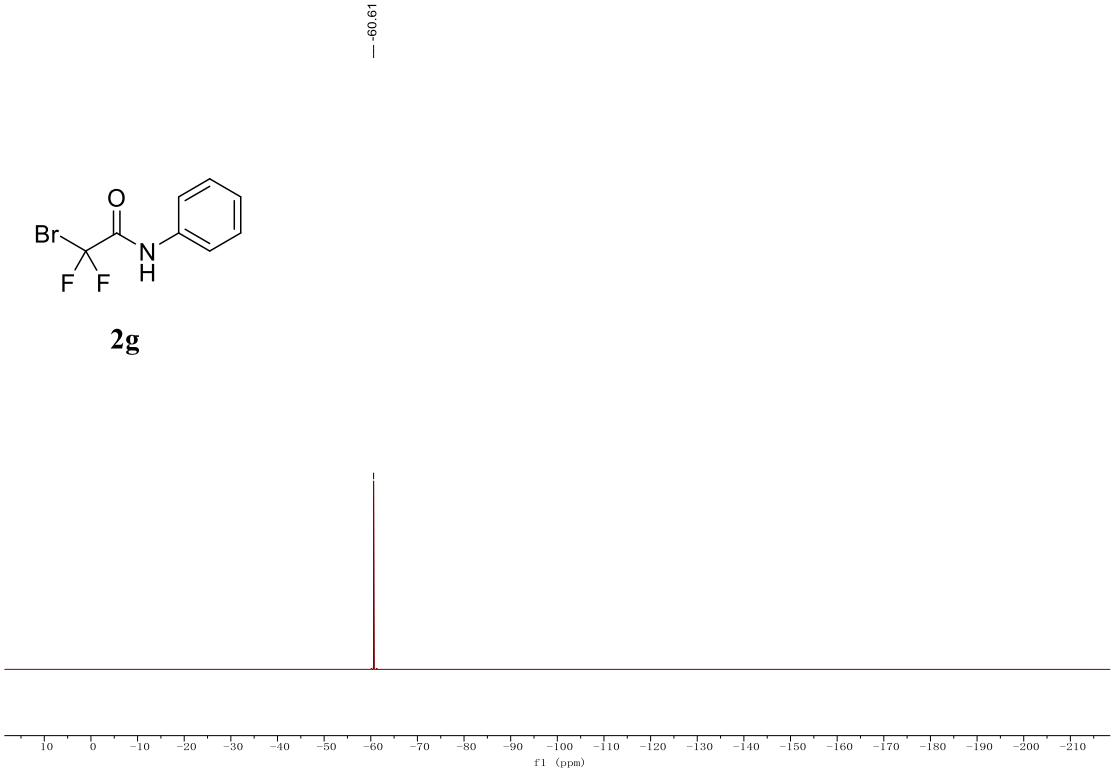


^{1}H NMR Spectrum of Compound **2g** (300 MHz, $CDCl_3$)



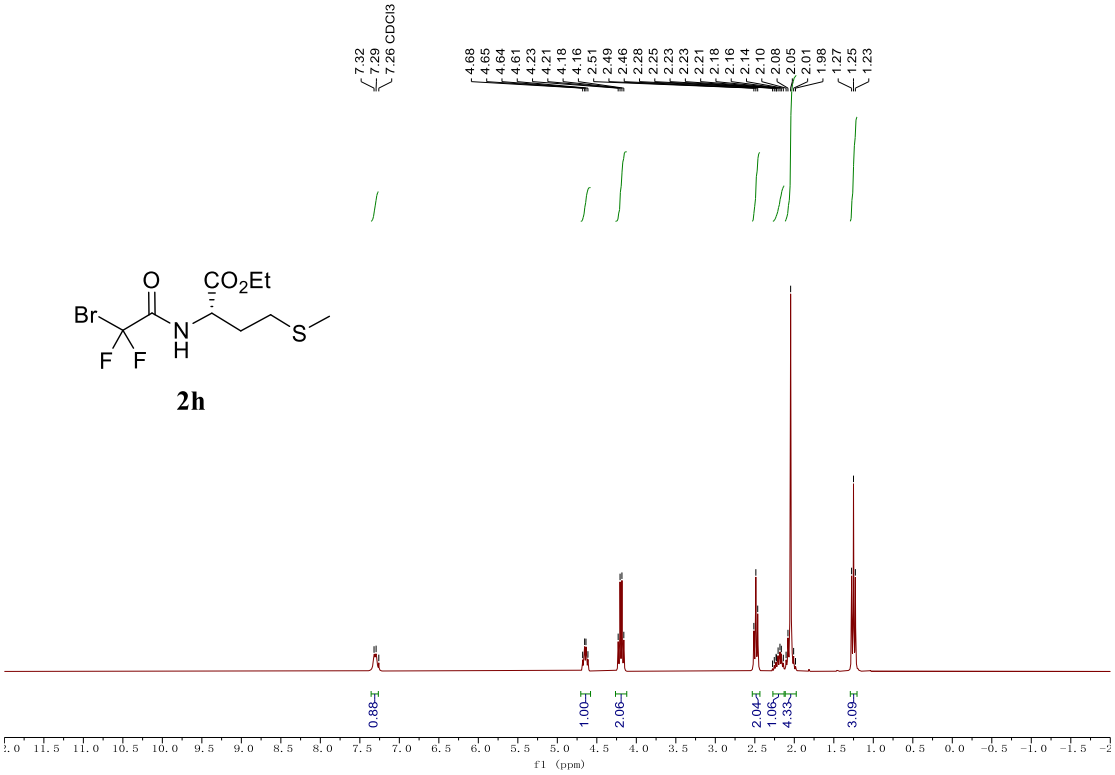
2g

^{19}F NMR Spectrum of Compound **2g** (282 MHz, $CDCl_3$)



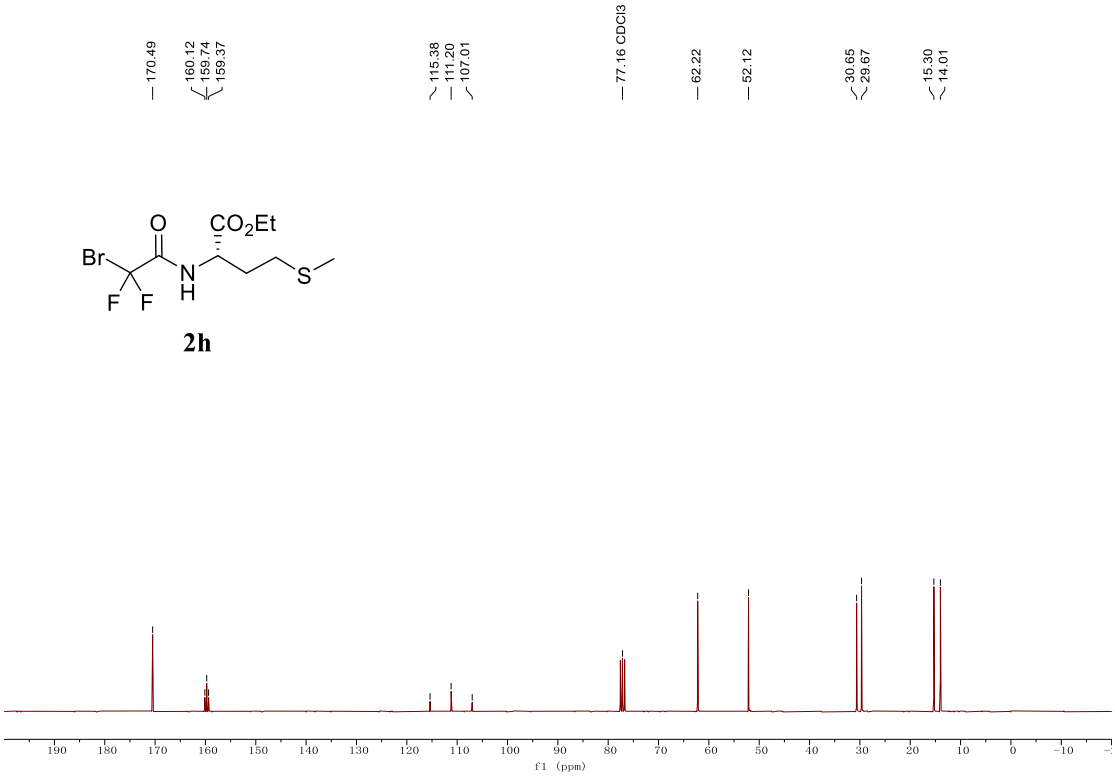
2g

^{1}H NMR Spectrum of Compound **2h** (300 MHz, $CDCl_3$)



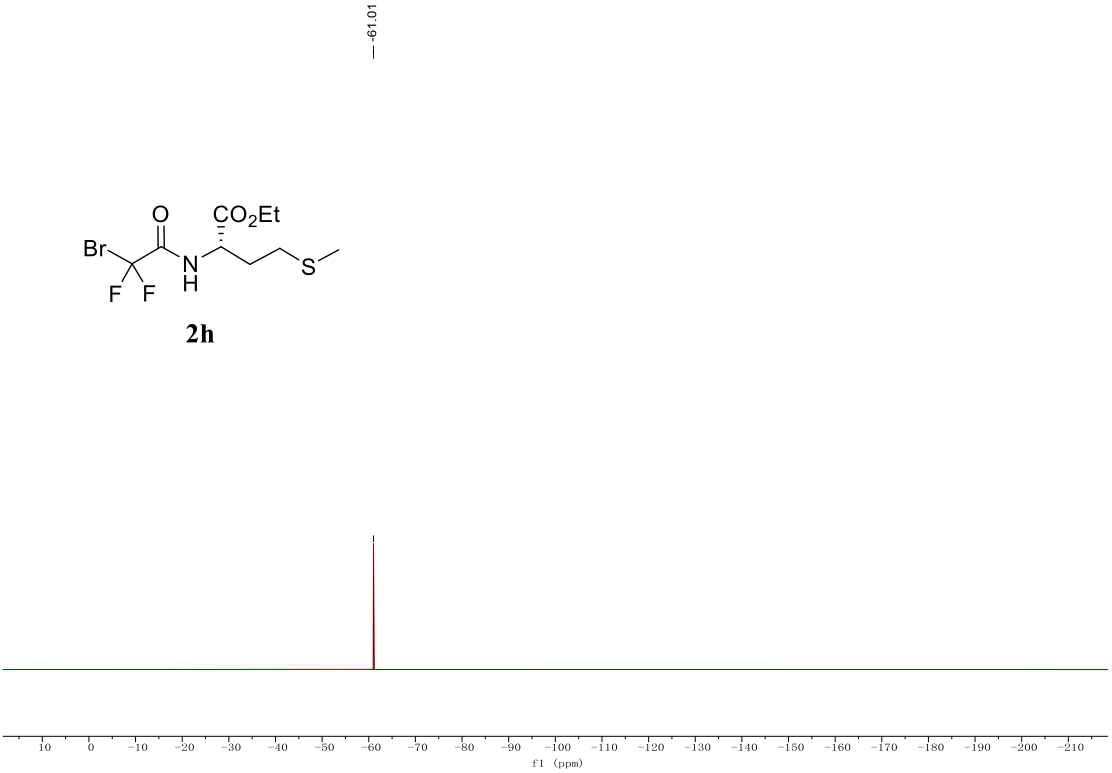
2h

^{13}C NMR Spectrum of Compound **2h** (75 MHz, $CDCl_3$)



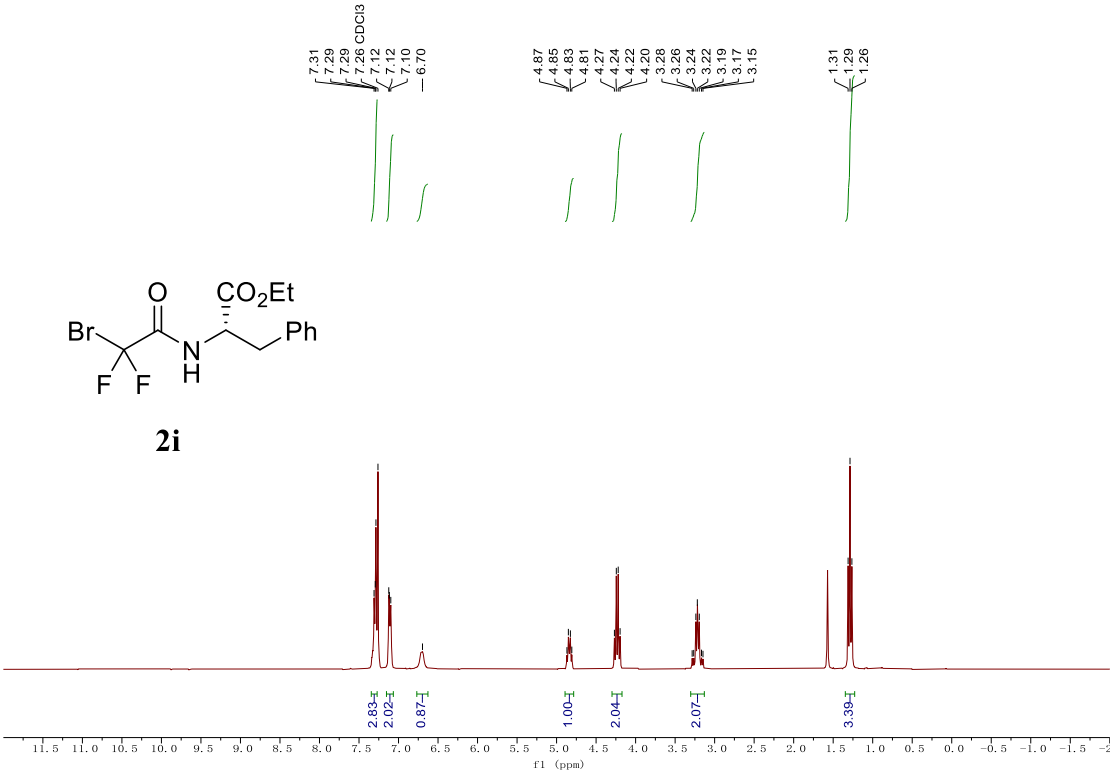
2h

^{19}F NMR Spectrum of Compound **2h** (282 MHz, $CDCl_3$)



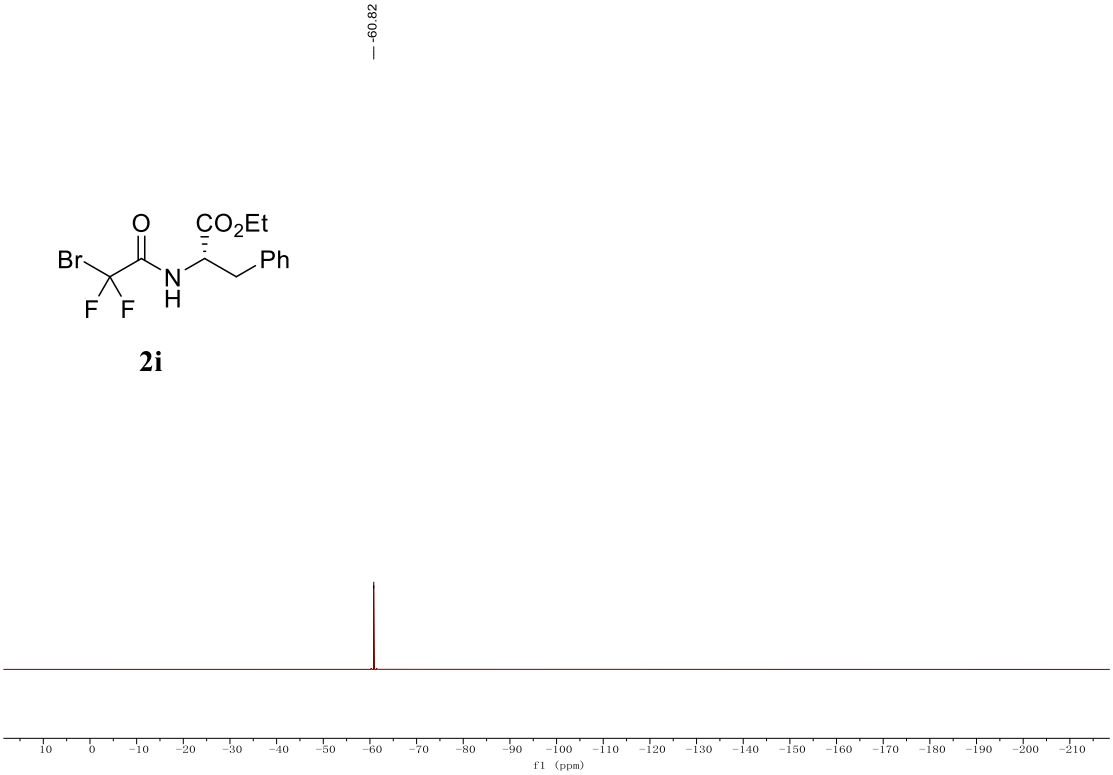
2h

^{1}H NMR Spectrum of Compound **2i** (300 MHz, $CDCl_3$)



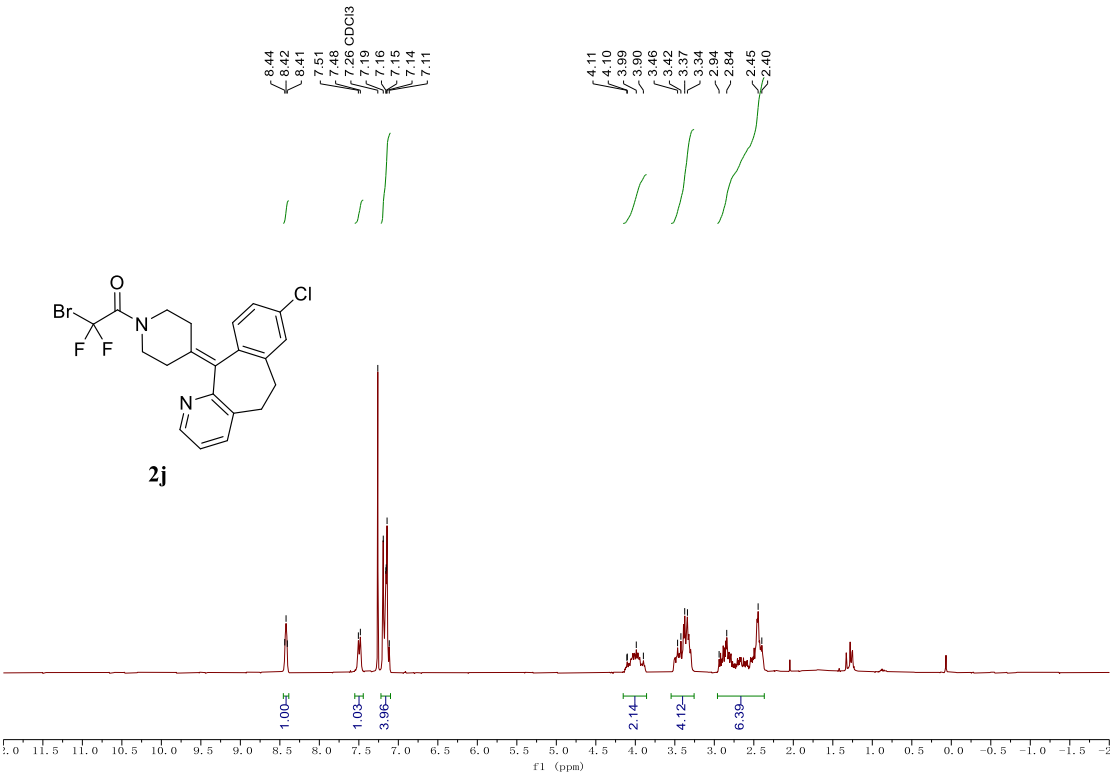
2i

^{19}F NMR Spectrum of Compound **2i** (282 MHz, $CDCl_3$)



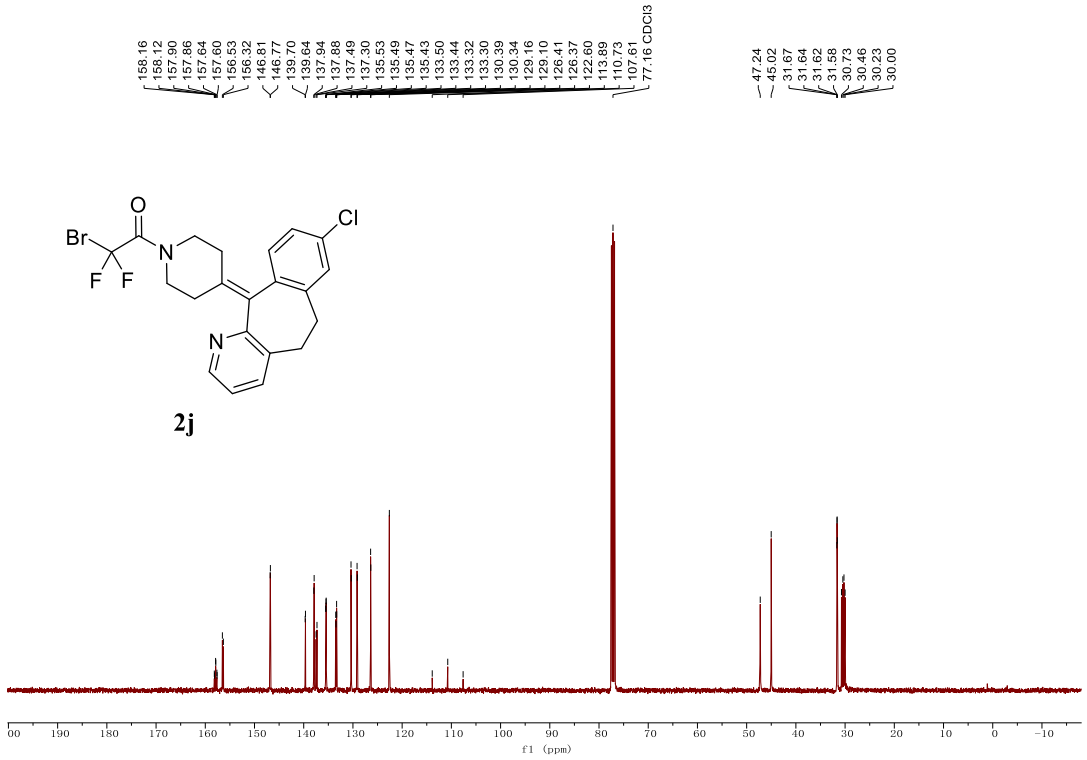
2i

^{1}H NMR Spectrum of Compound **2j** (300 MHz, $CDCl_3$)

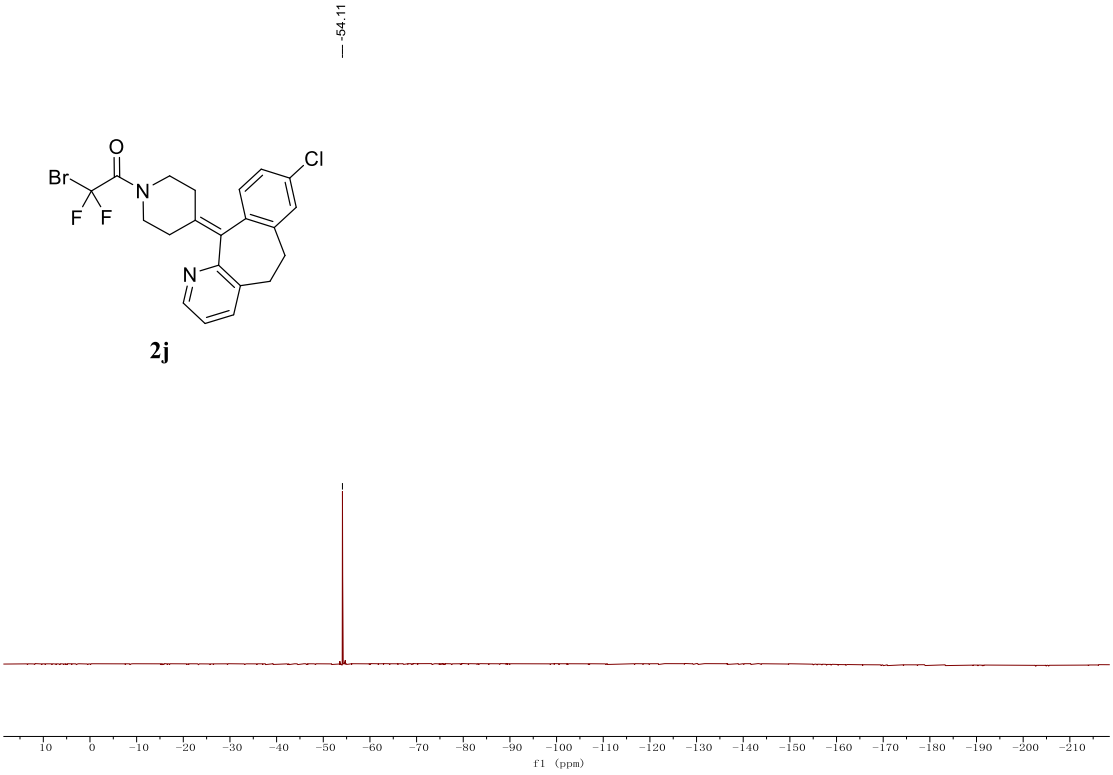


2j

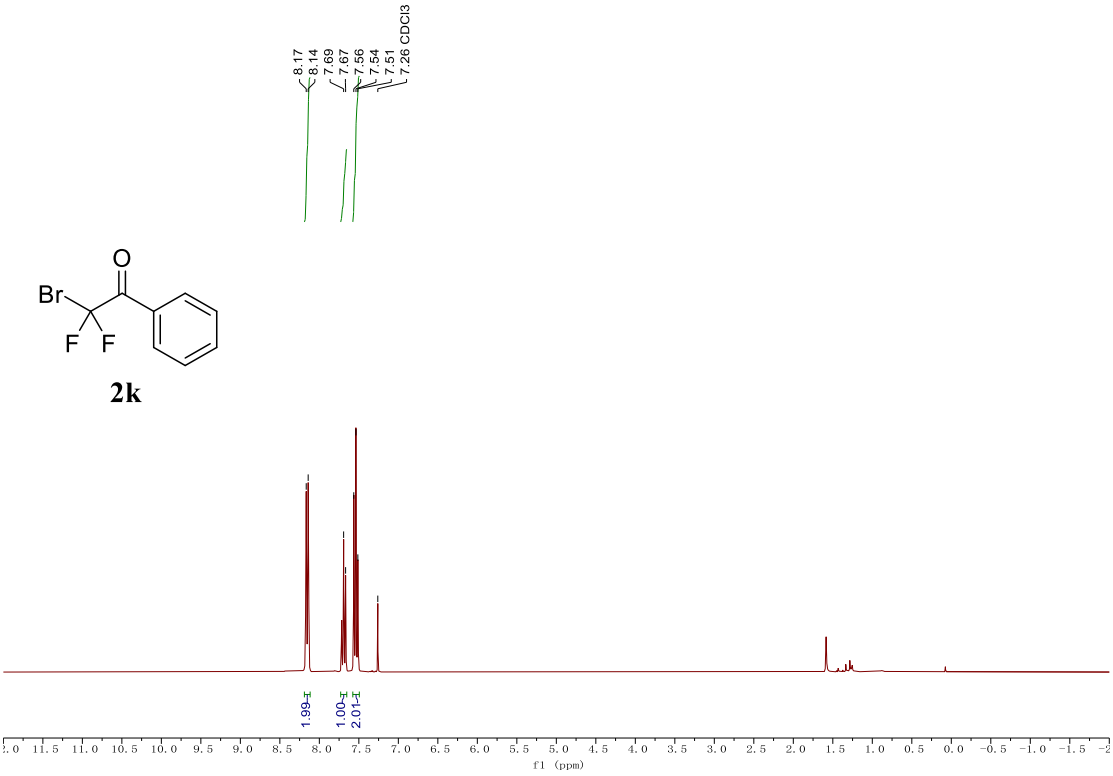
^{13}C NMR Spectrum of Compound **2j** (101 MHz, $CDCl_3$)



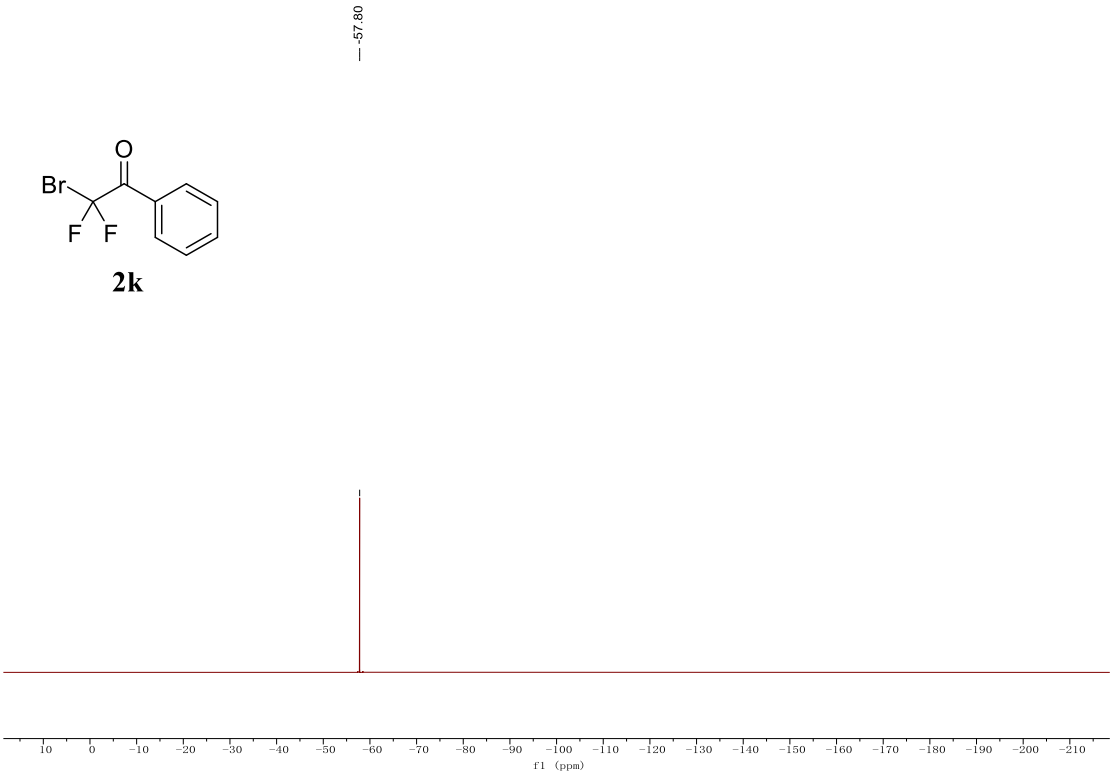
^{19}F NMR Spectrum of Compound **2j** (282 MHz, $CDCl_3$)



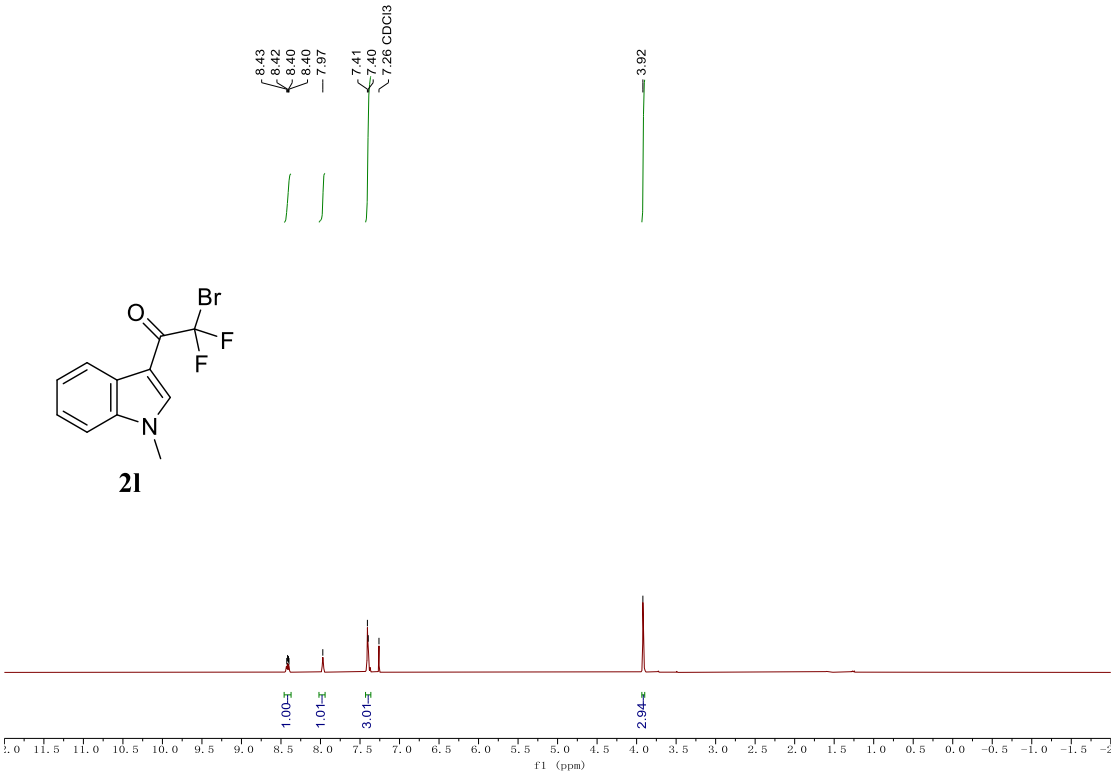
^{1}H NMR Spectrum of Compound **2k** (300 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **2k** (282 MHz, $CDCl_3$)

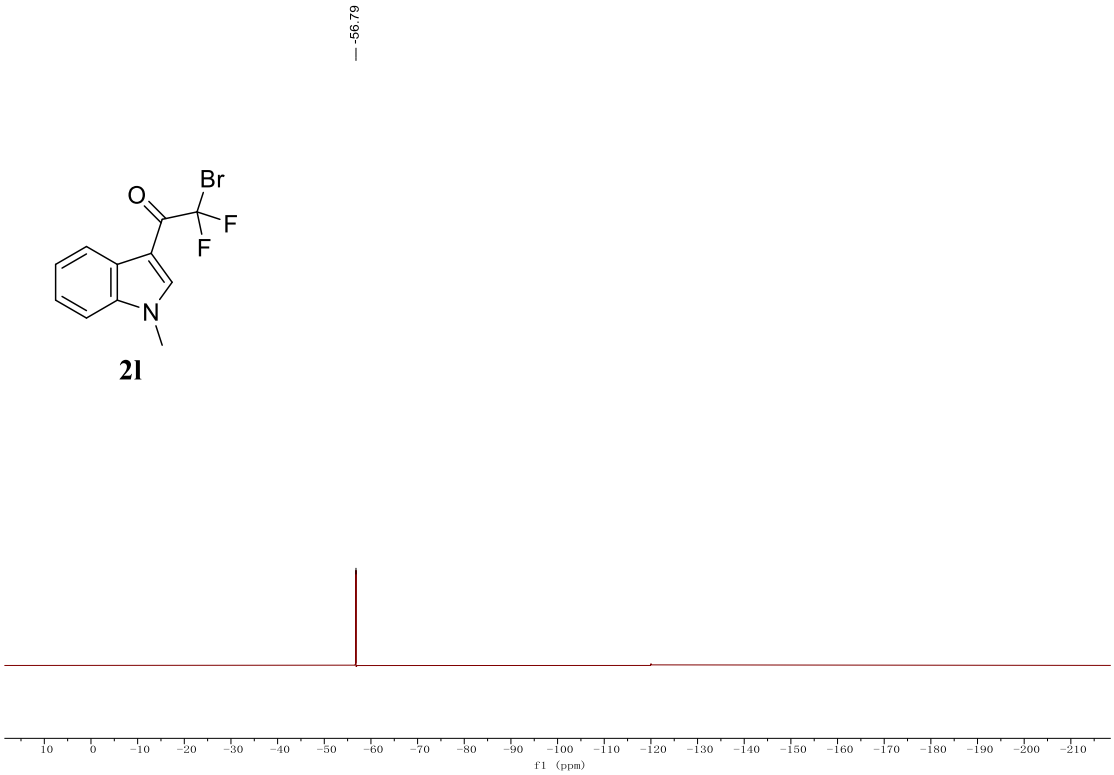


^{1}H NMR Spectrum of Compound **2l** (300 MHz, $CDCl_3$)



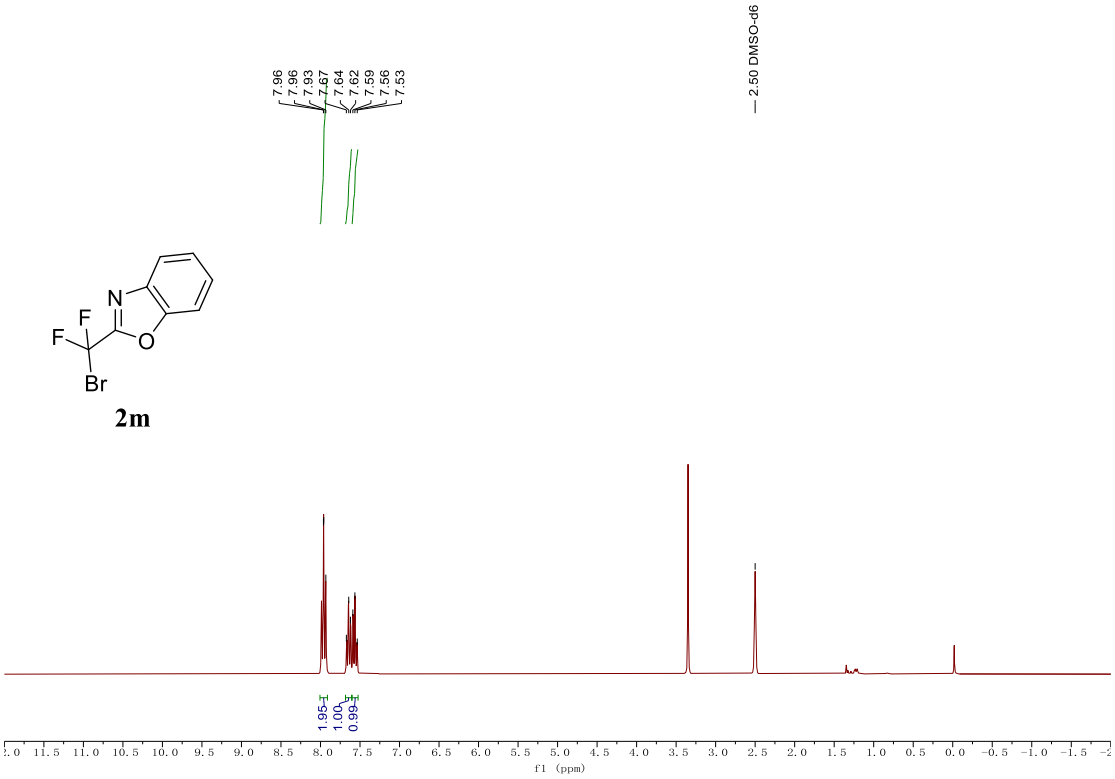
2l

^{19}F NMR Spectrum of Compound **2l** (282 MHz, $CDCl_3$)

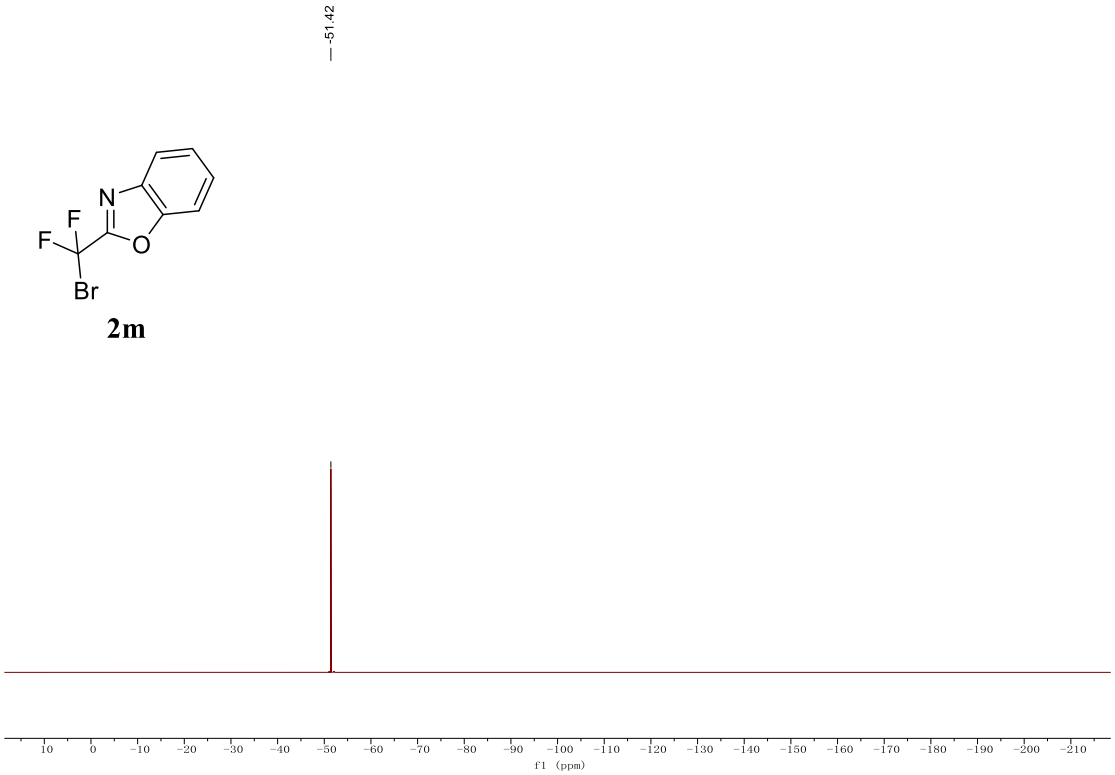


2l

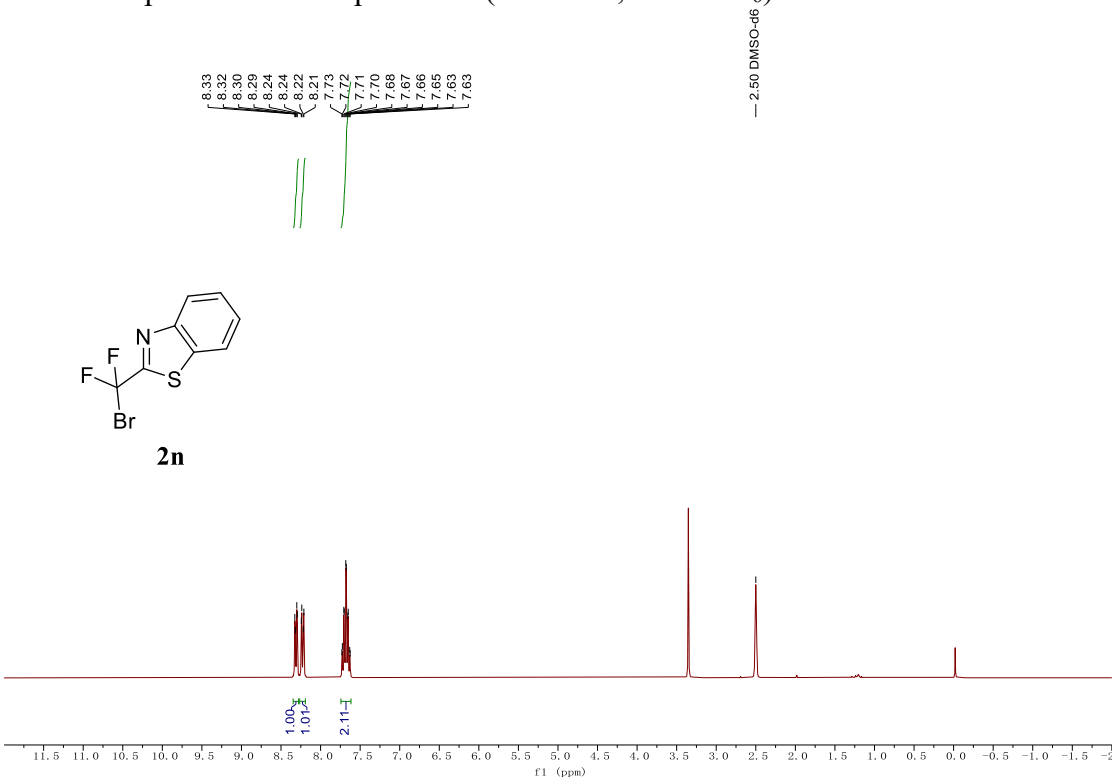
^{1}H NMR Spectrum of Compound **2m** (300 MHz, DMSO-d_6)



^{19}F NMR Spectrum of Compound **2m** (282 MHz, $CDCl_3$)

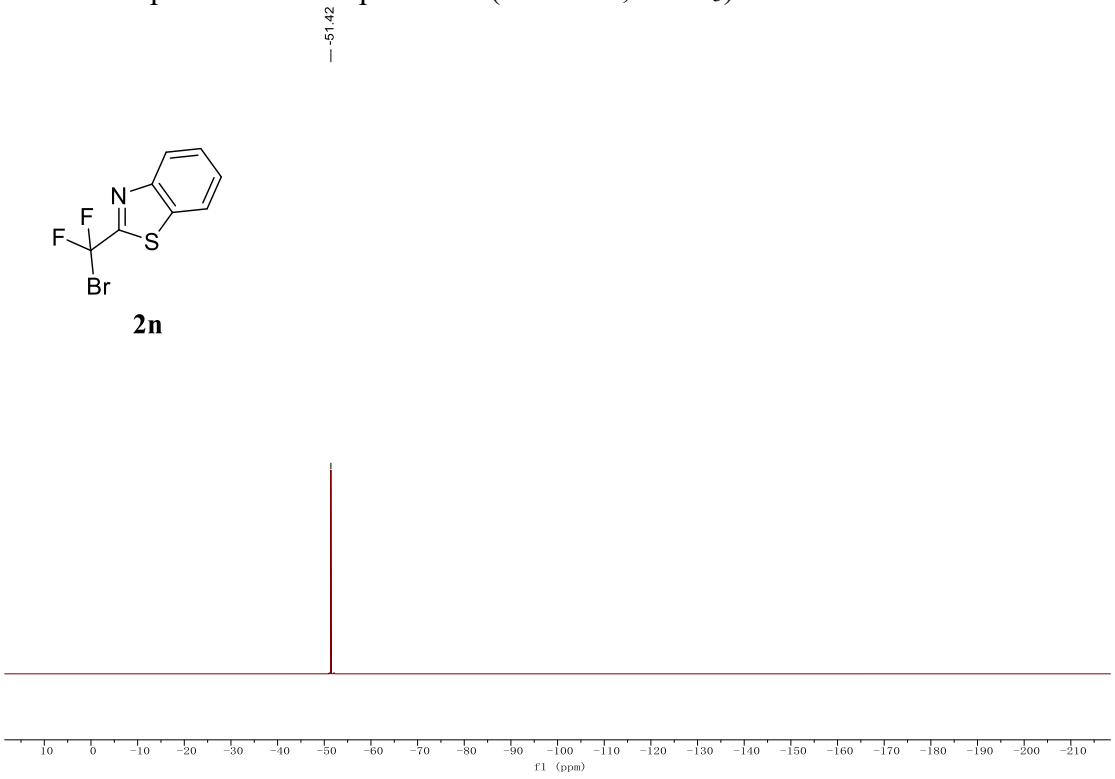


^{1}H NMR Spectrum of Compound **2n** (300 MHz, DMSO-d_6)



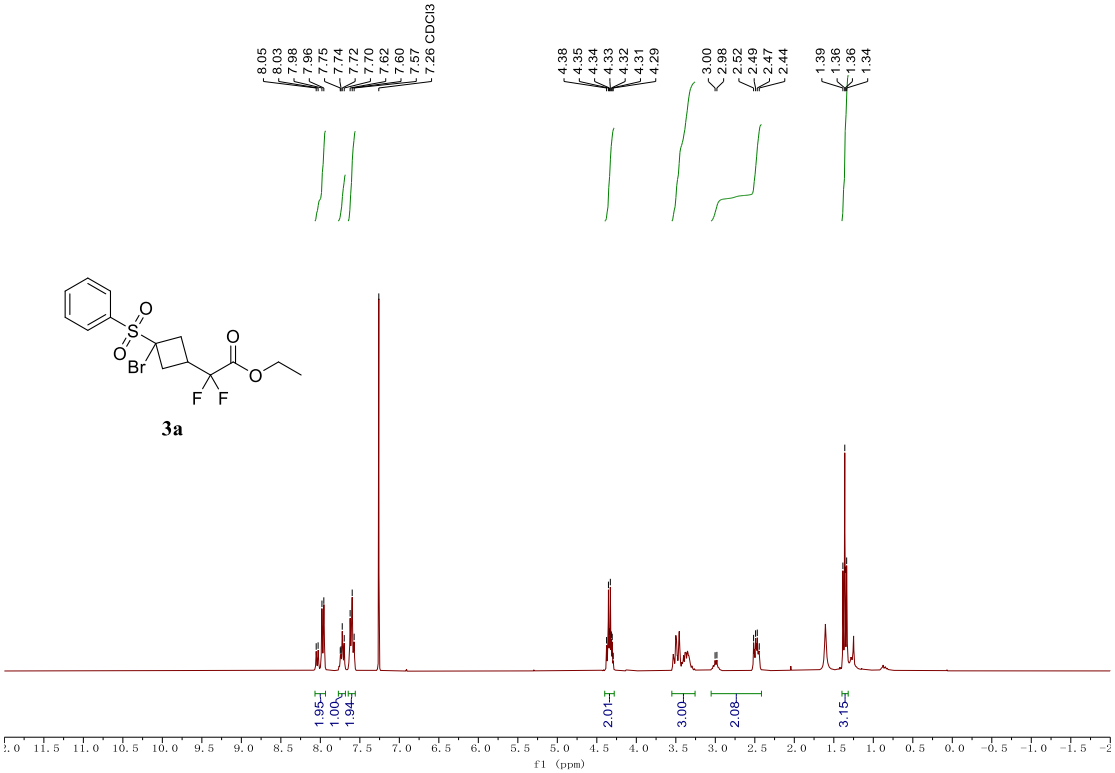
2n

^{19}F NMR Spectrum of Compound **2n** (282 MHz, $CDCl_3$)

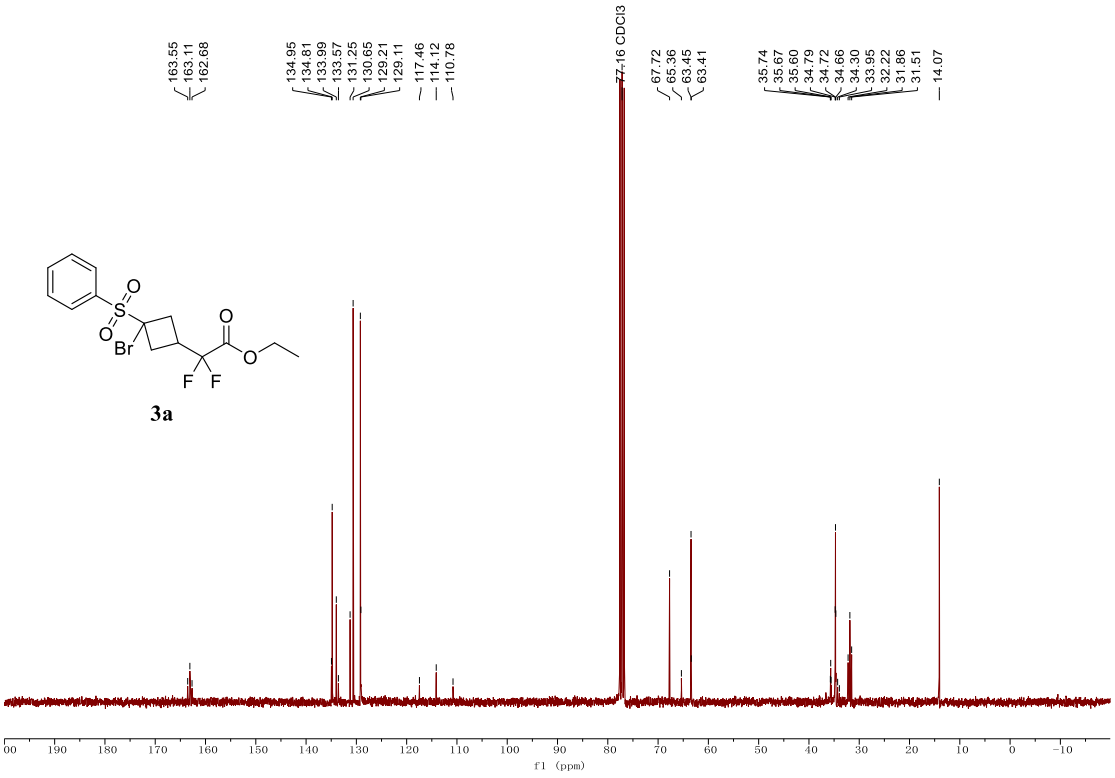


2n

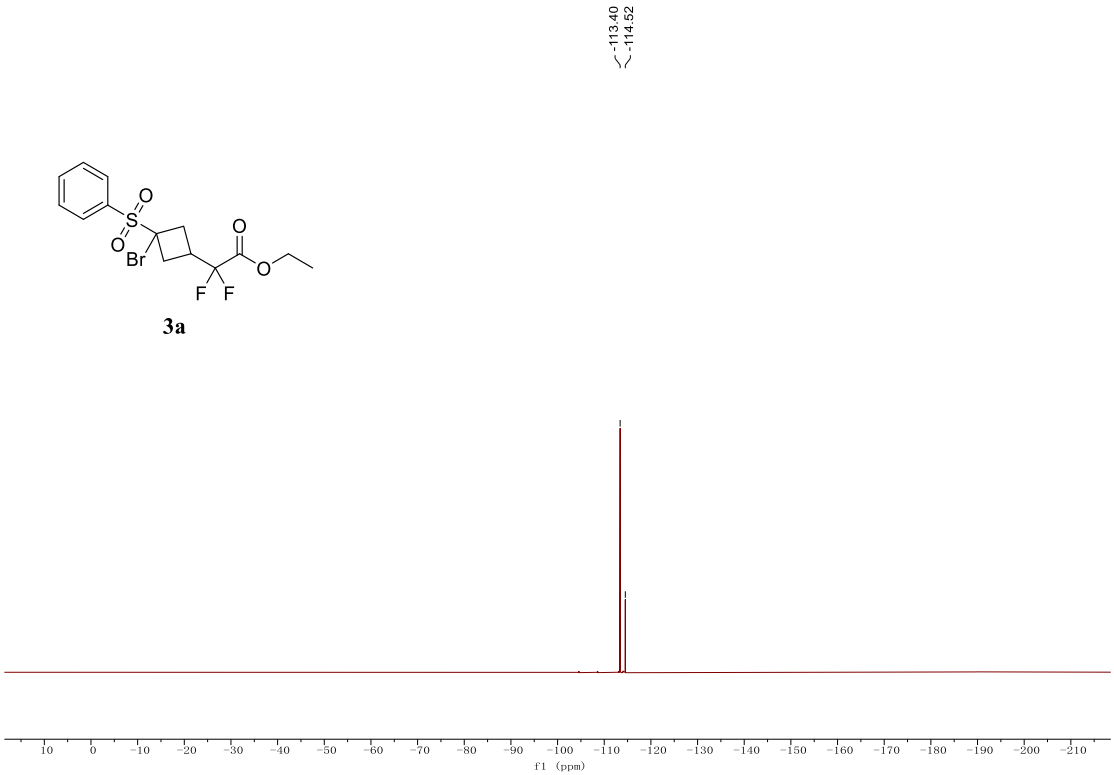
^{1}H NMR Spectrum of Compound **3a** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **3a** (75 MHz, $CDCl_3$)

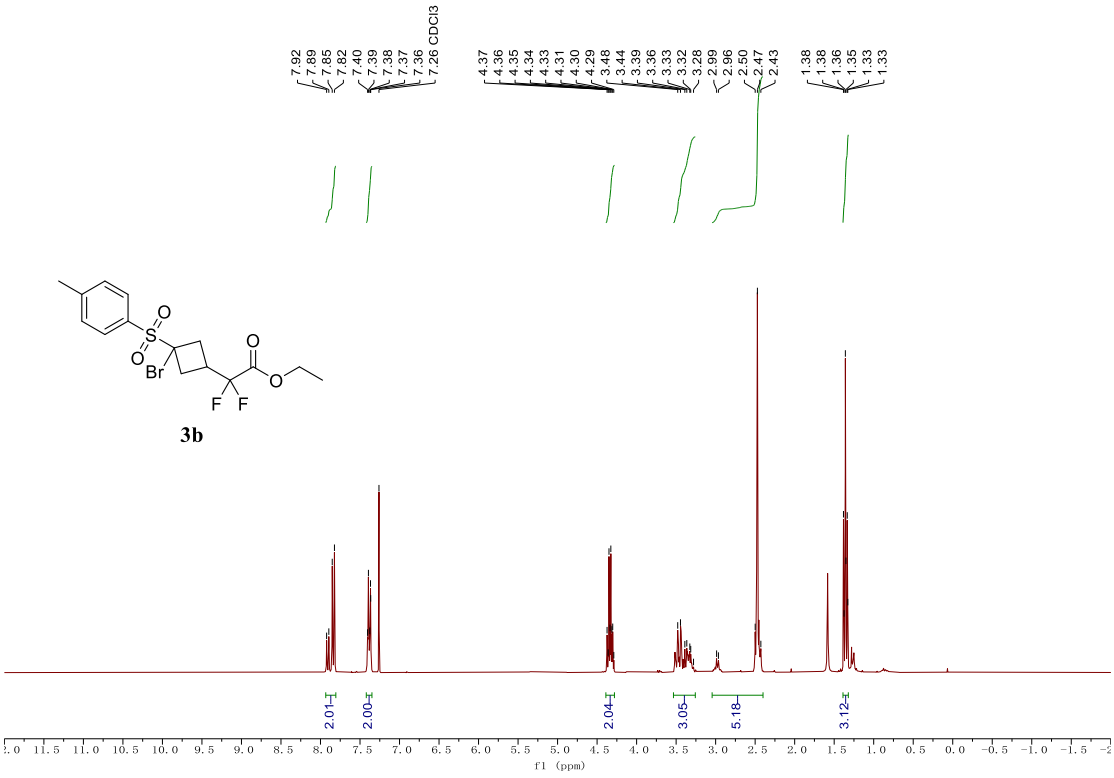


^{19}F NMR Spectrum of Compound **3a** (282 MHz, $CDCl_3$)



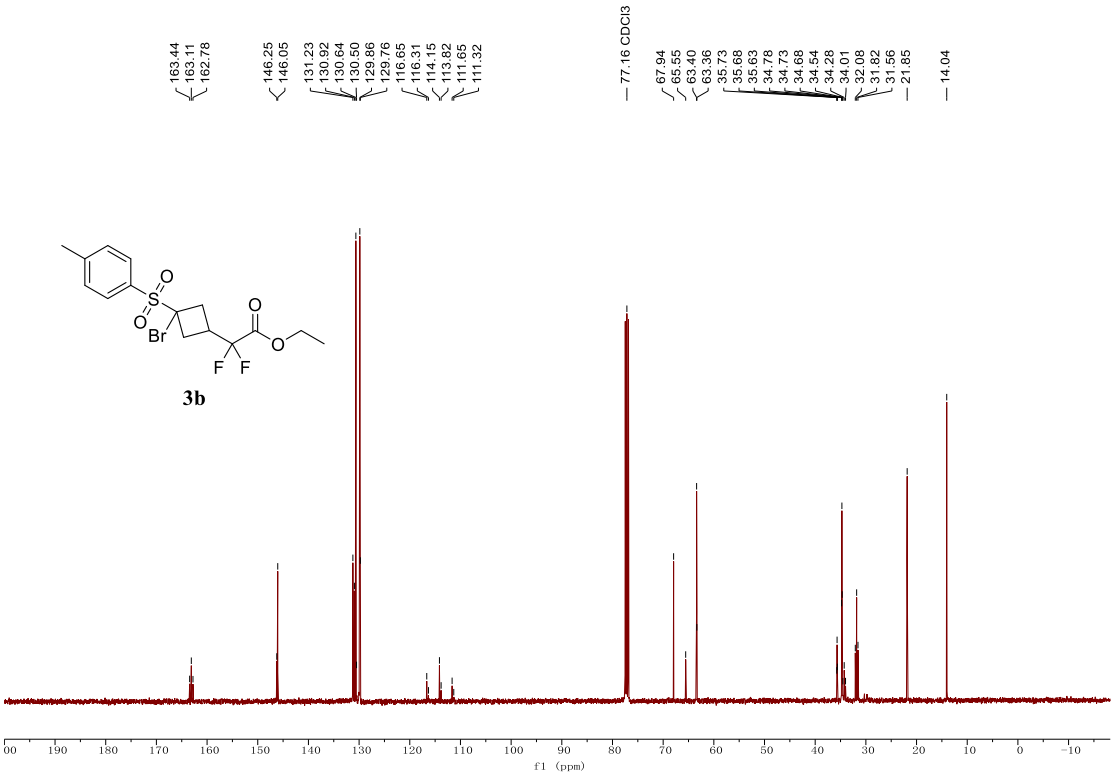
3a

^{1}H NMR Spectrum of Compound **3b** (300 MHz, $CDCl_3$)

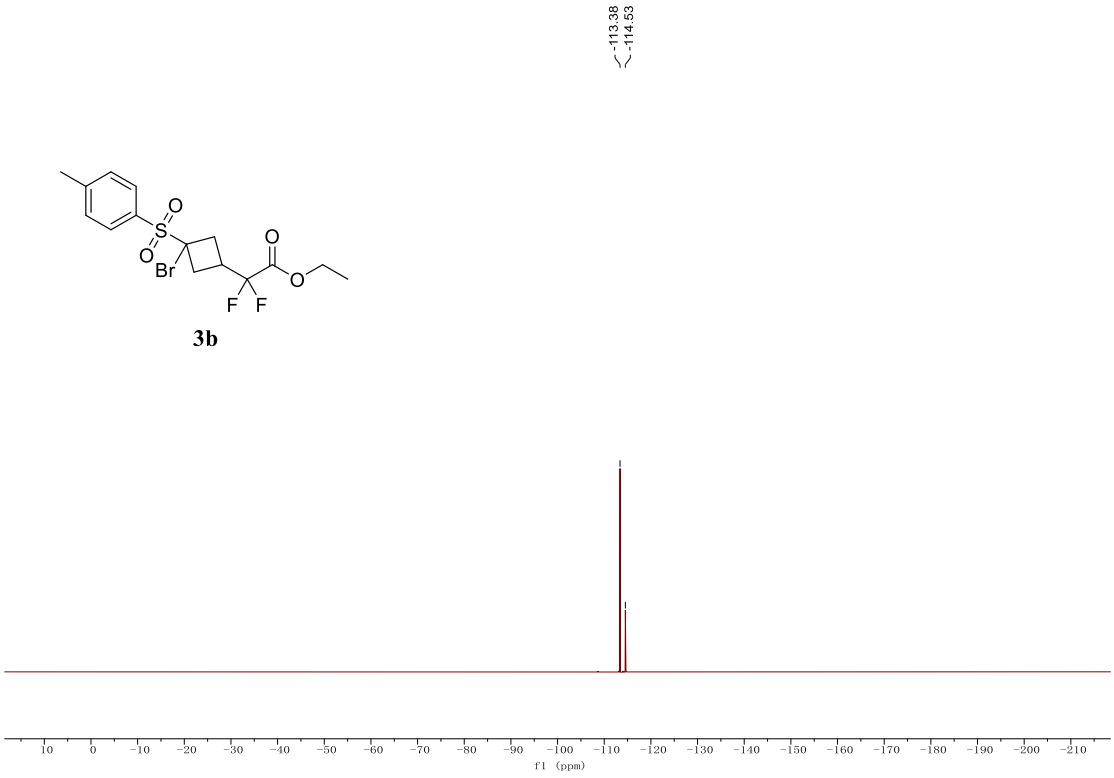


3b

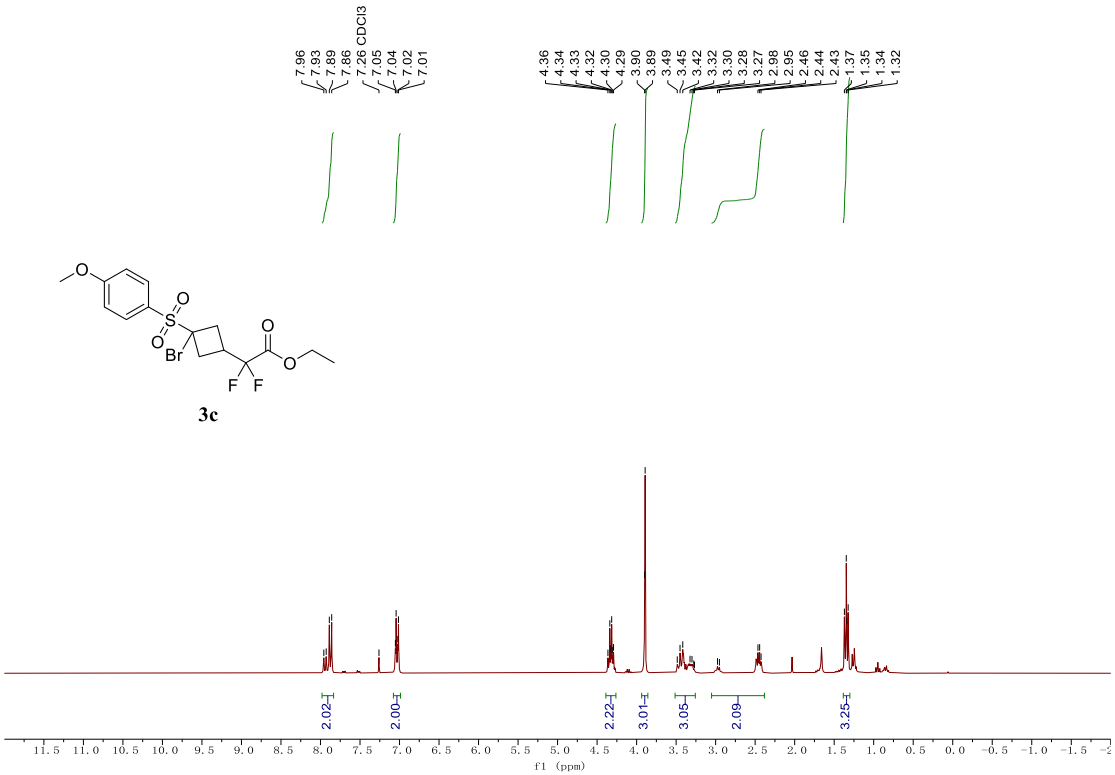
^{13}C NMR Spectrum of Compound **3b** (101 MHz, $CDCl_3$)



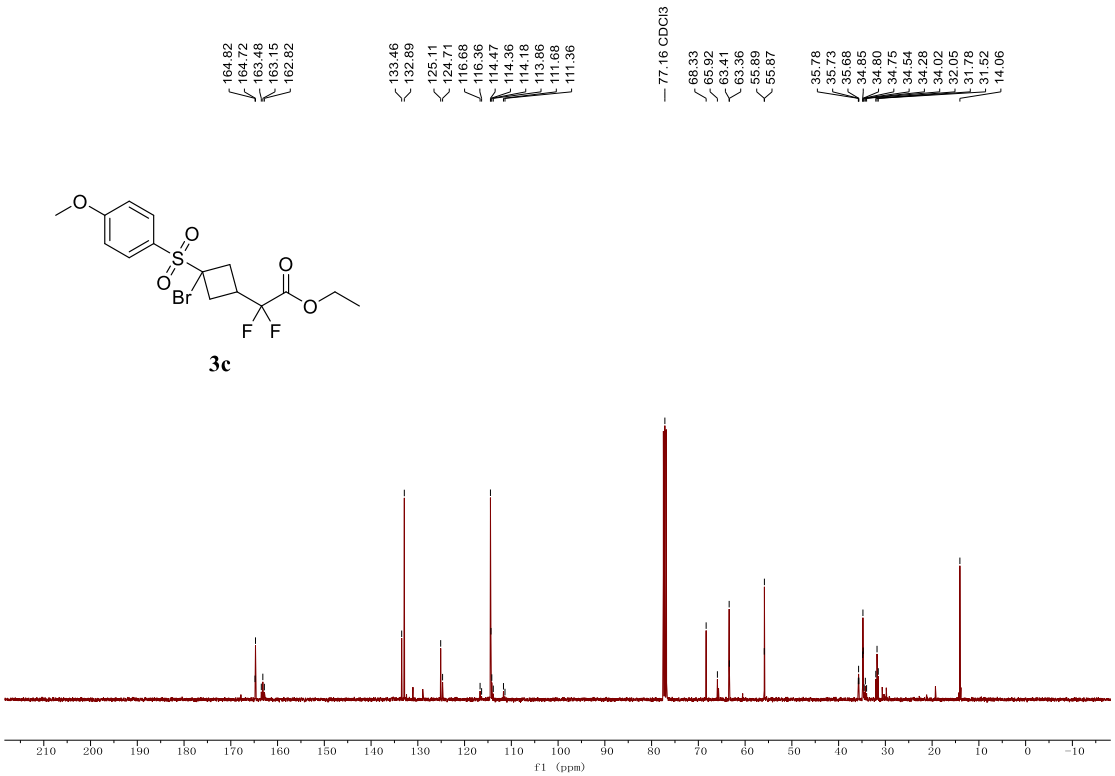
^{19}F NMR Spectrum of Compound **3b** (282 MHz, $CDCl_3$)



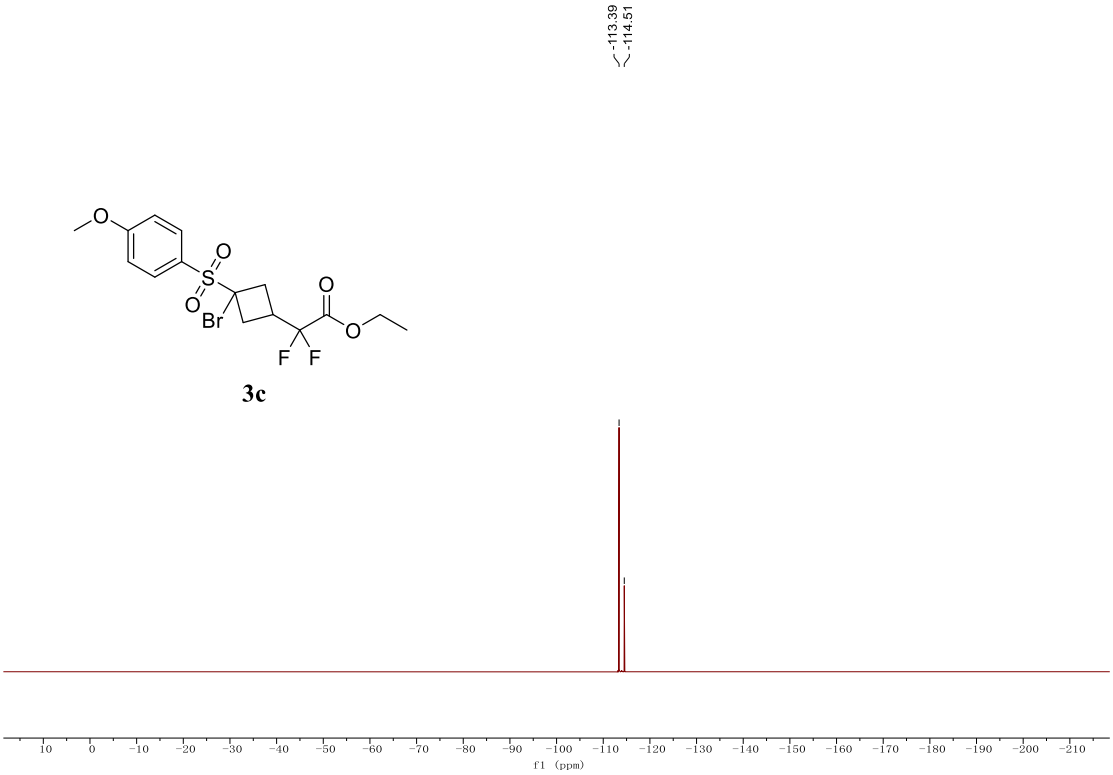
^{1}H NMR Spectrum of Compound **3c** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **3c** (101 MHz, $CDCl_3$)

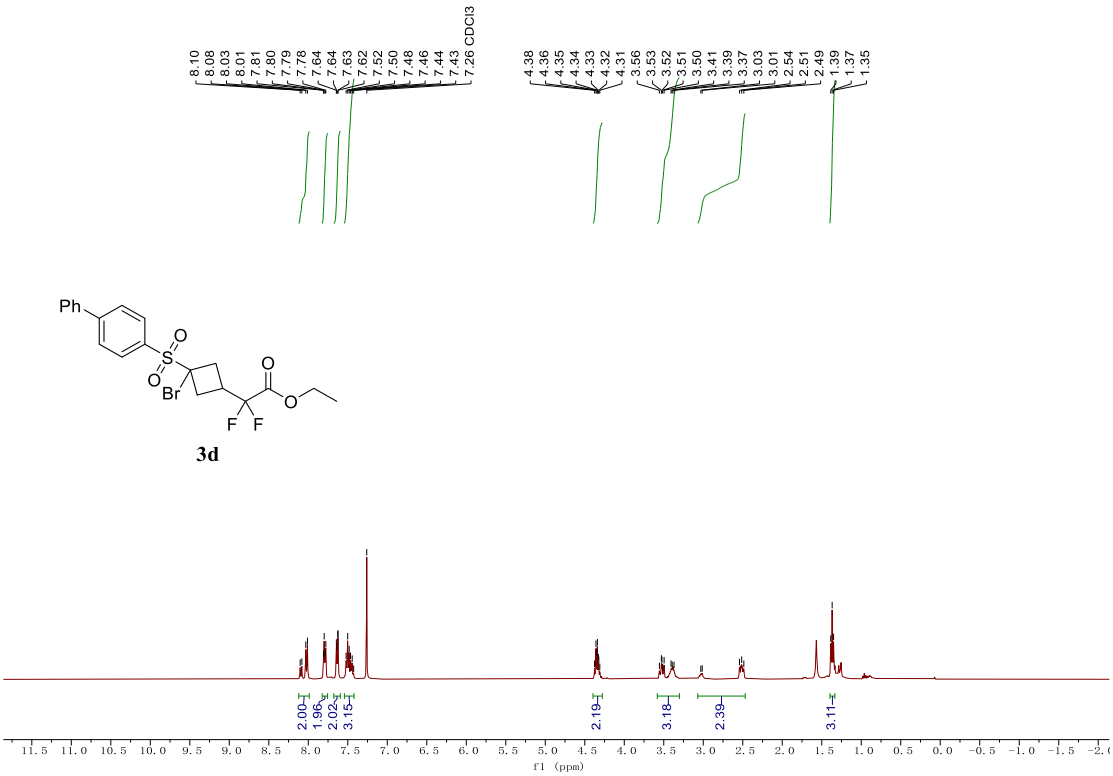


^{19}F NMR Spectrum of Compound **3c** (282 MHz, $CDCl_3$)



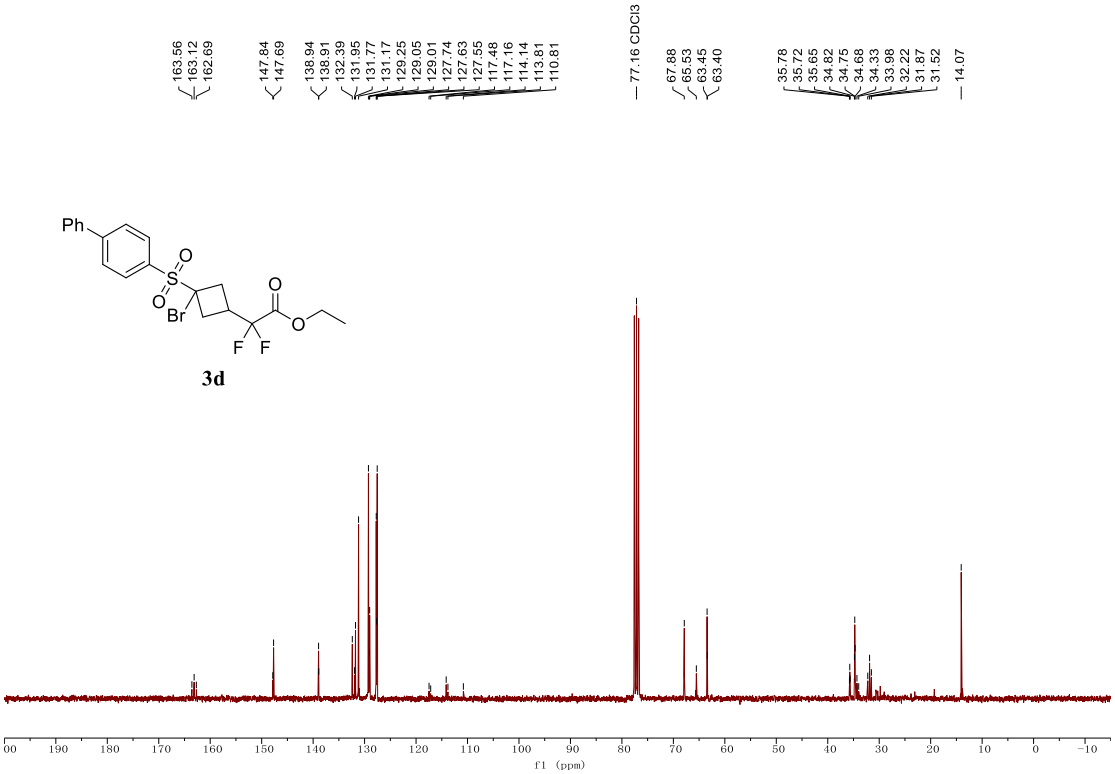
3c

^{1}H NMR Spectrum of Compound **3d** (400 MHz, $CDCl_3$)

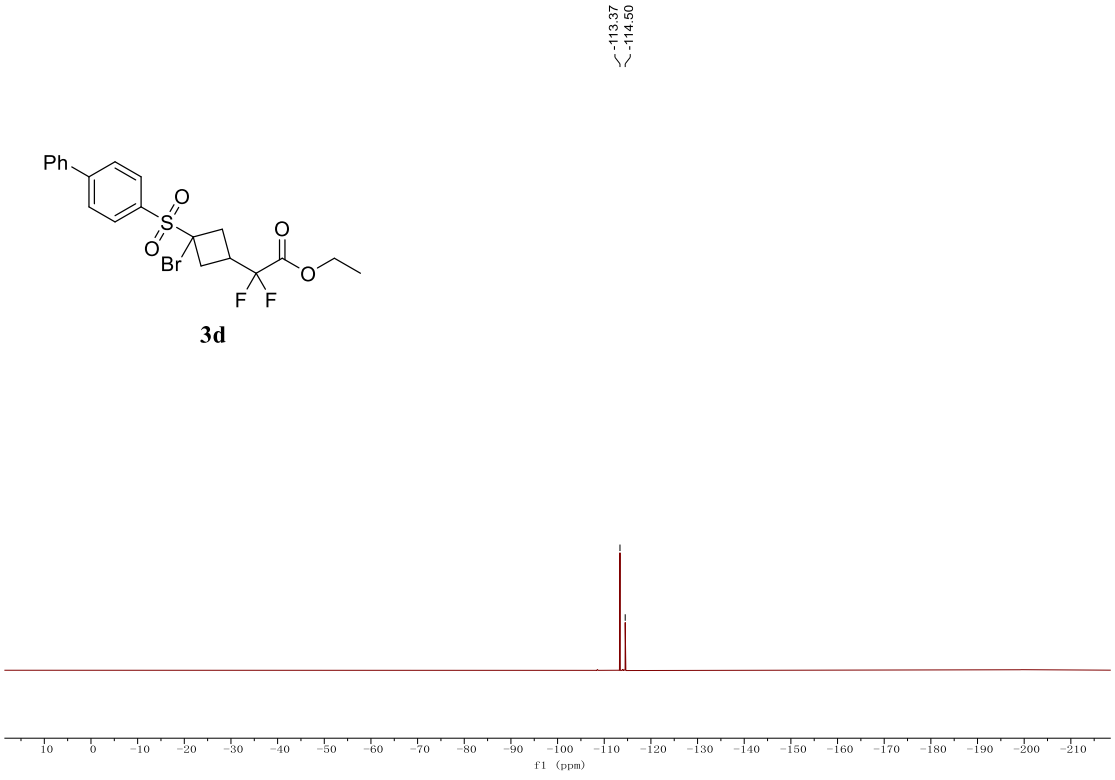


3d

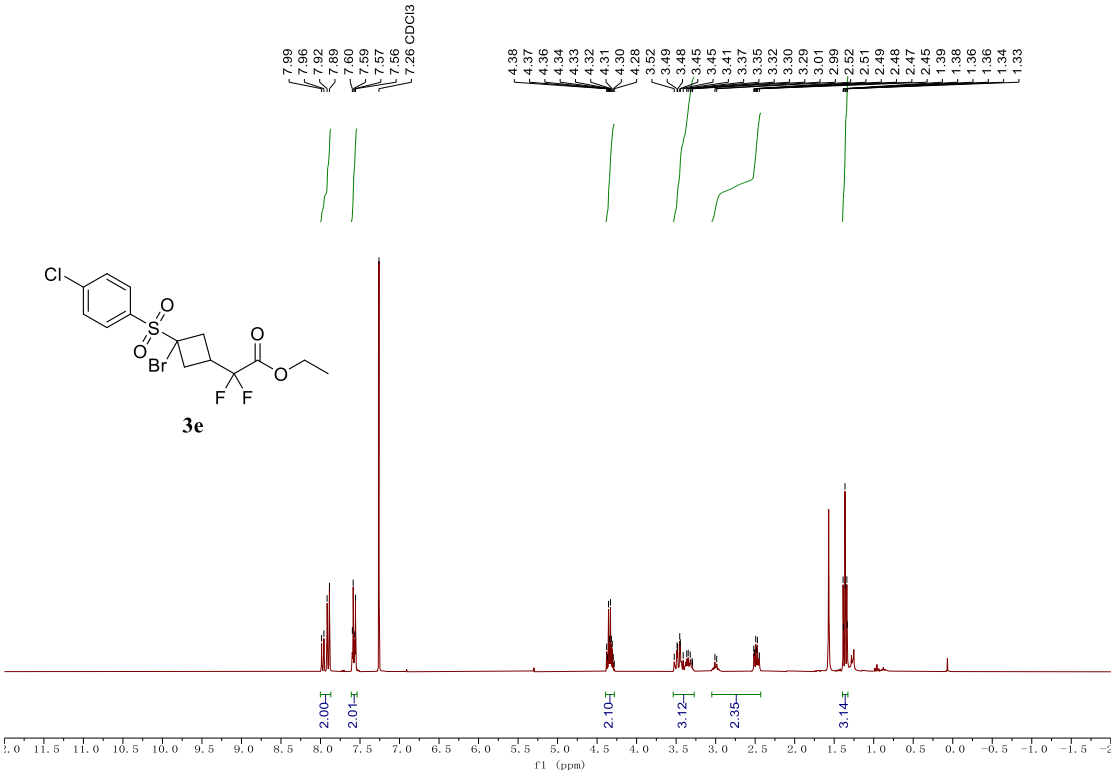
^{13}C NMR Spectrum of Compound **3d** (75 MHz, $CDCl_3$)



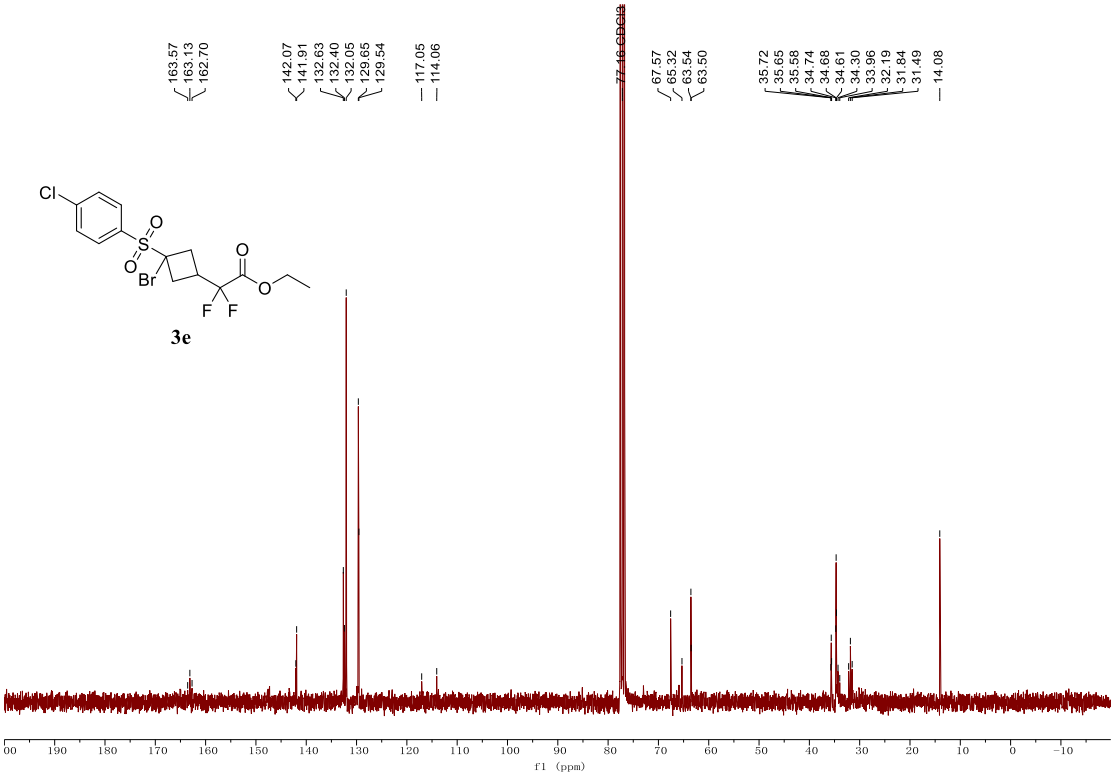
^{19}F NMR Spectrum of Compound **3d** (282 MHz, $CDCl_3$)



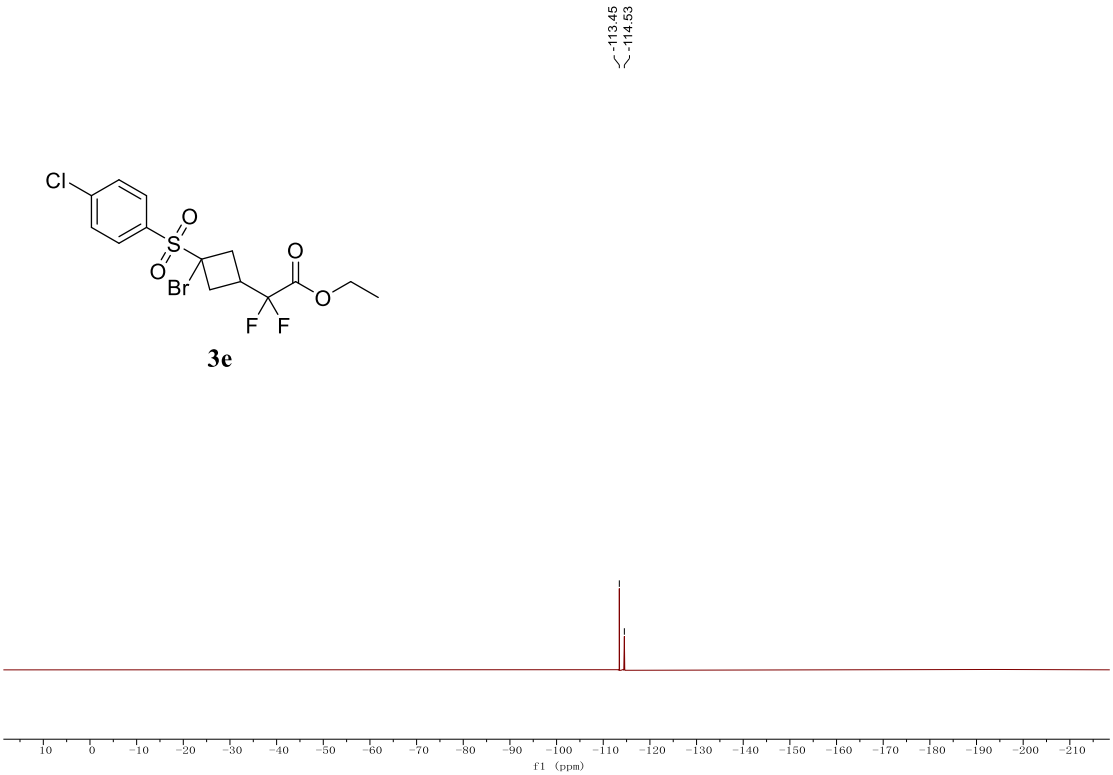
^{1}H NMR Spectrum of Compound **3e** (300 MHz, $CDCl_3$)



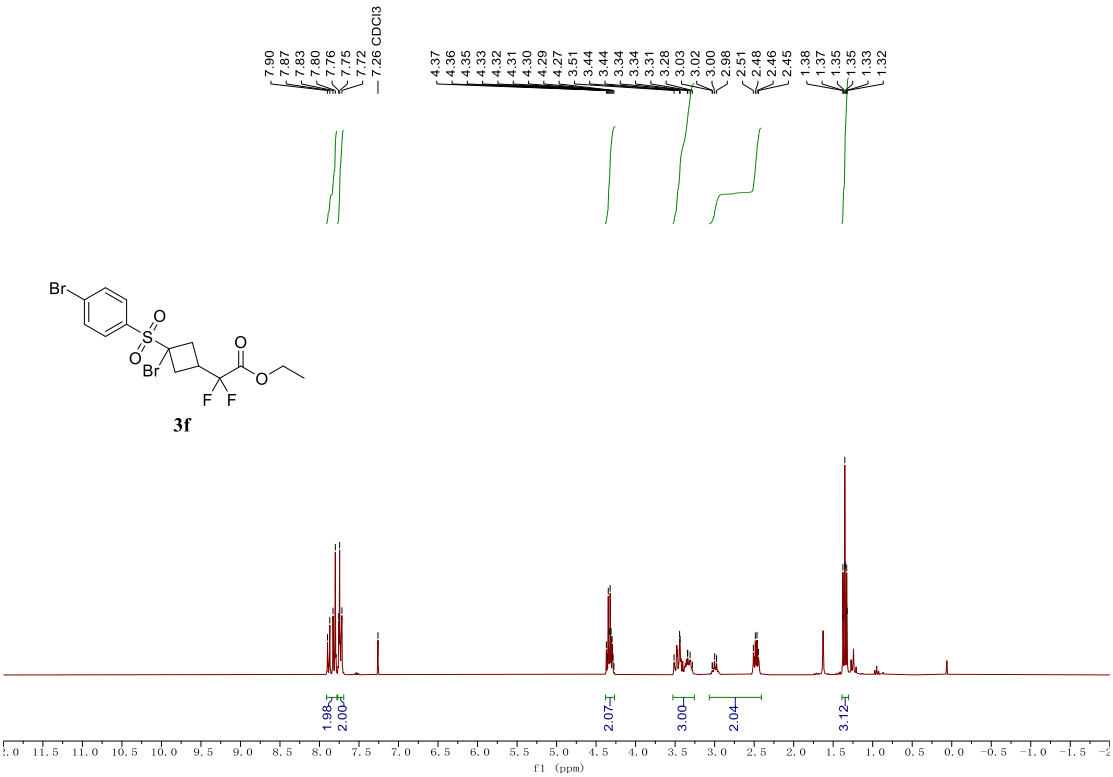
^{13}C NMR Spectrum of Compound **3e** (75 MHz, $CDCl_3$)



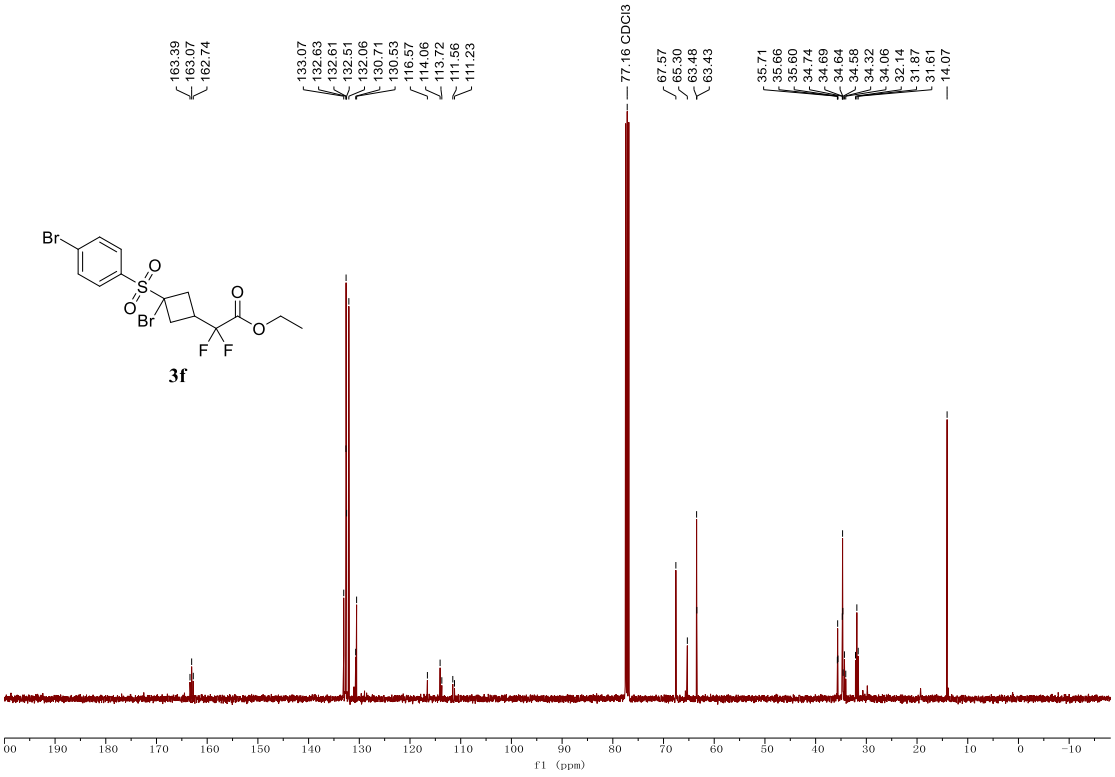
^{19}F NMR Spectrum of Compound **3e** (282 MHz, $CDCl_3$)



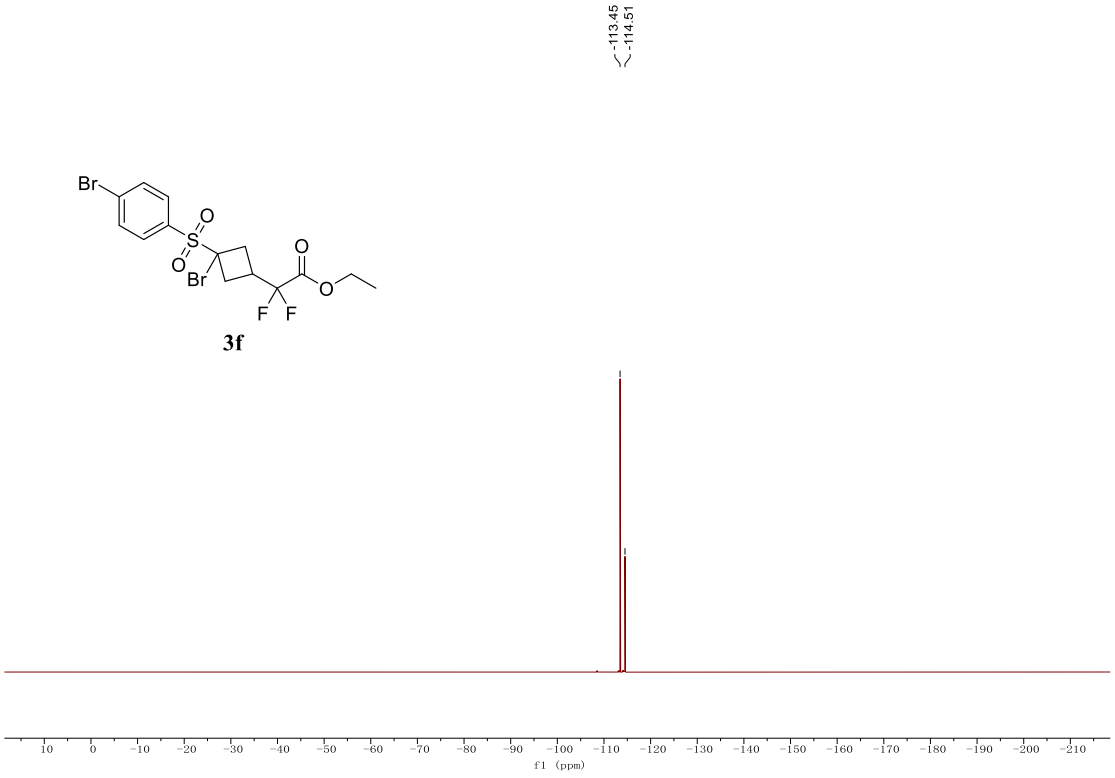
^{1}H NMR Spectrum of Compound **3f** (300 MHz, $CDCl_3$)



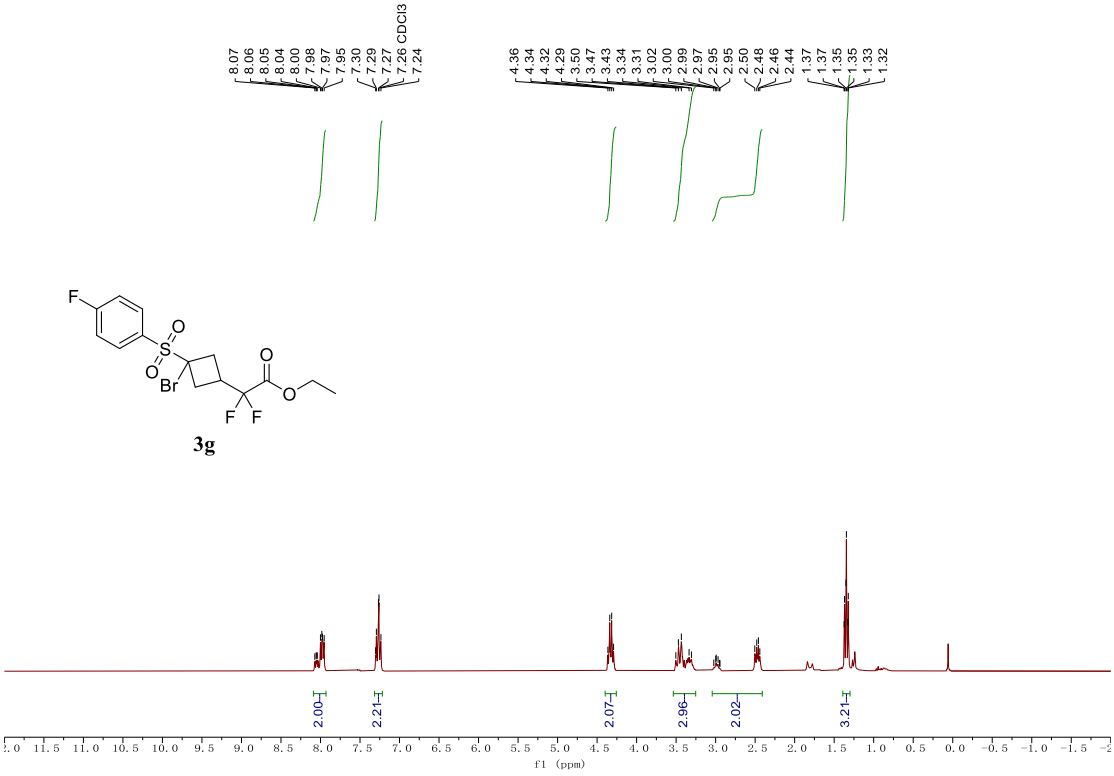
^{13}C NMR Spectrum of Compound **3f** (101 MHz, $CDCl_3$)



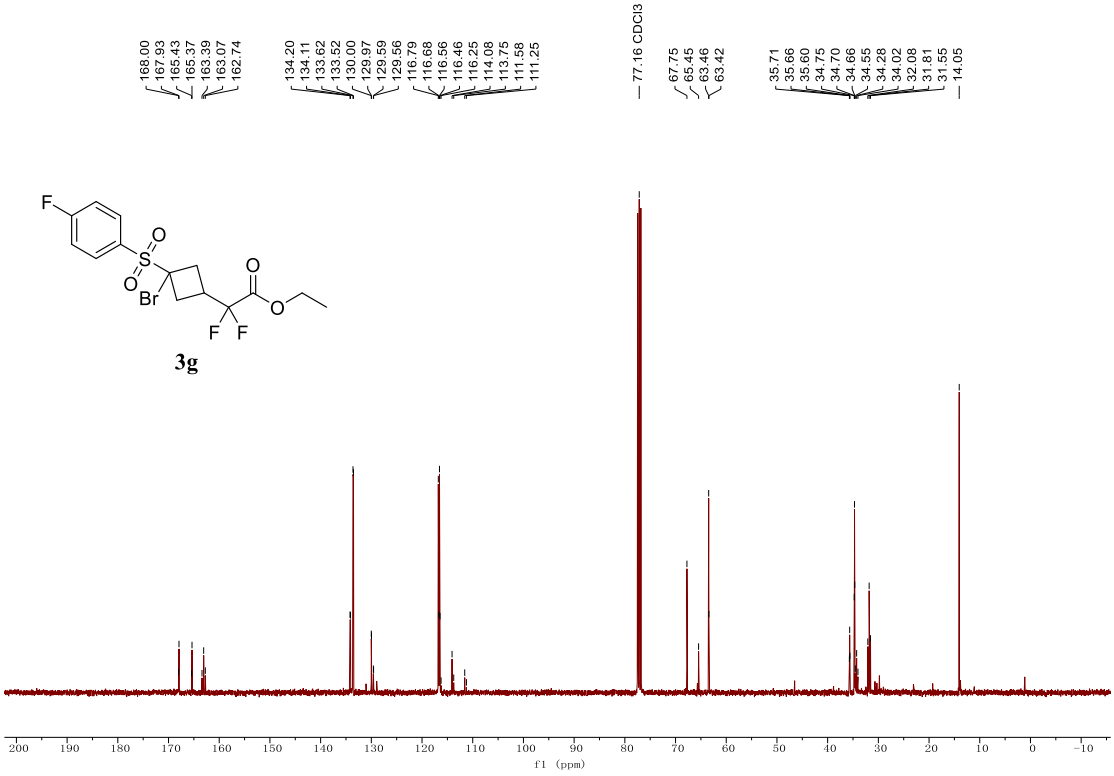
^{19}F NMR Spectrum of Compound **3f** (282 MHz, $CDCl_3$)



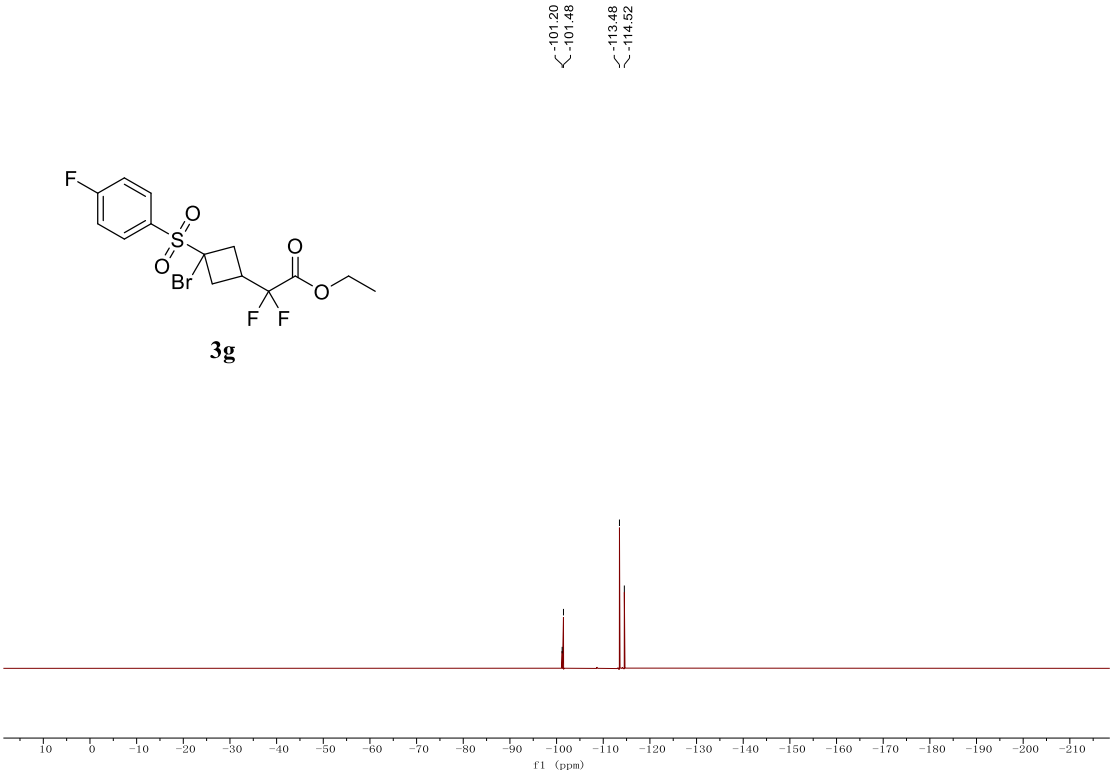
^{1}H NMR Spectrum of Compound **3g** (300 MHz, $CDCl_3$)



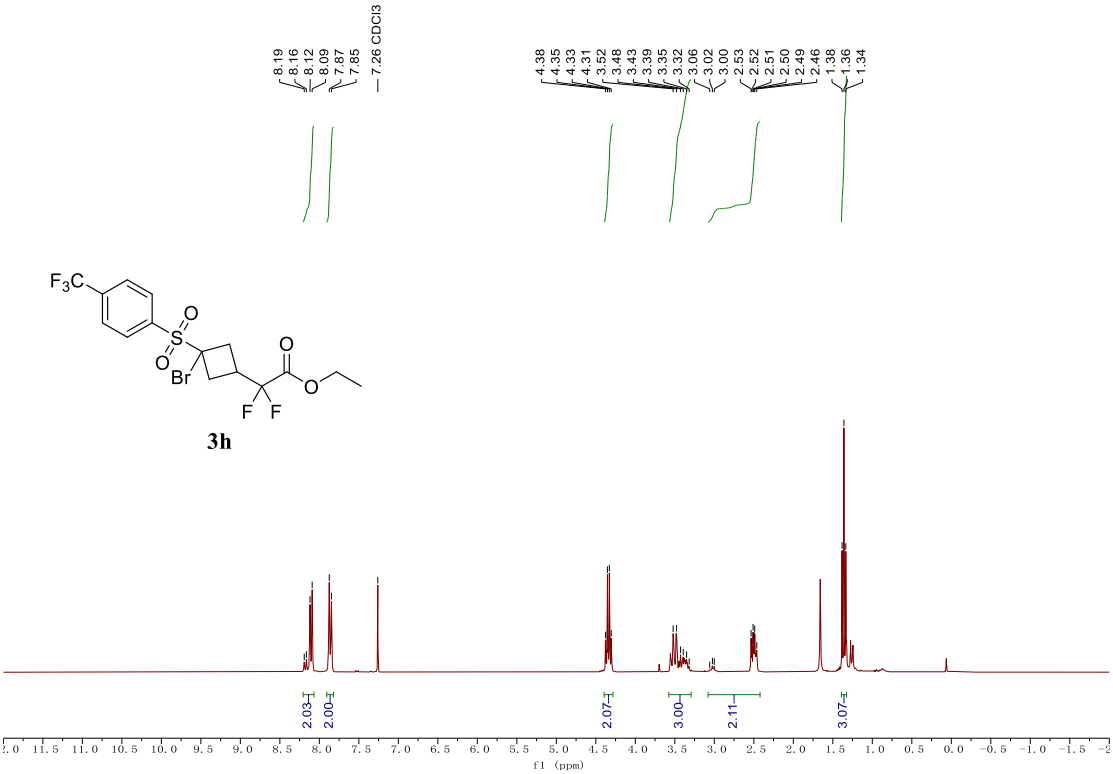
^{13}C NMR Spectrum of Compound **3g** (101 MHz, $CDCl_3$)



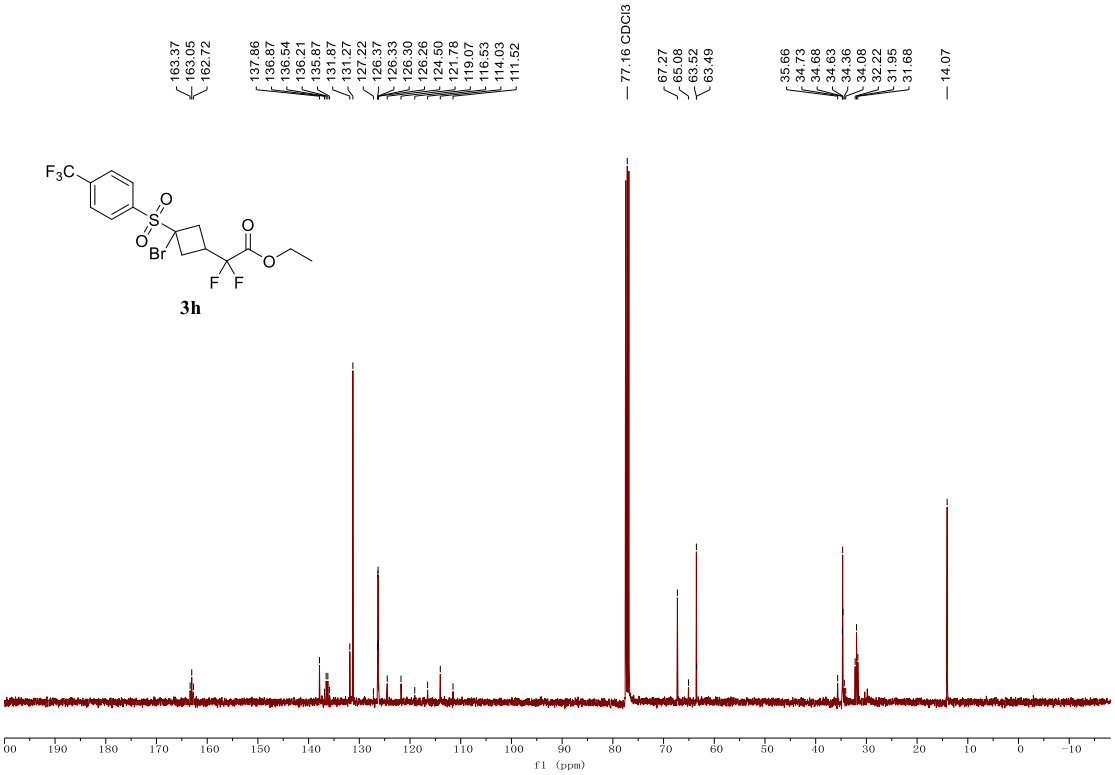
^{19}F NMR Spectrum of Compound **3g** (282 MHz, $CDCl_3$)



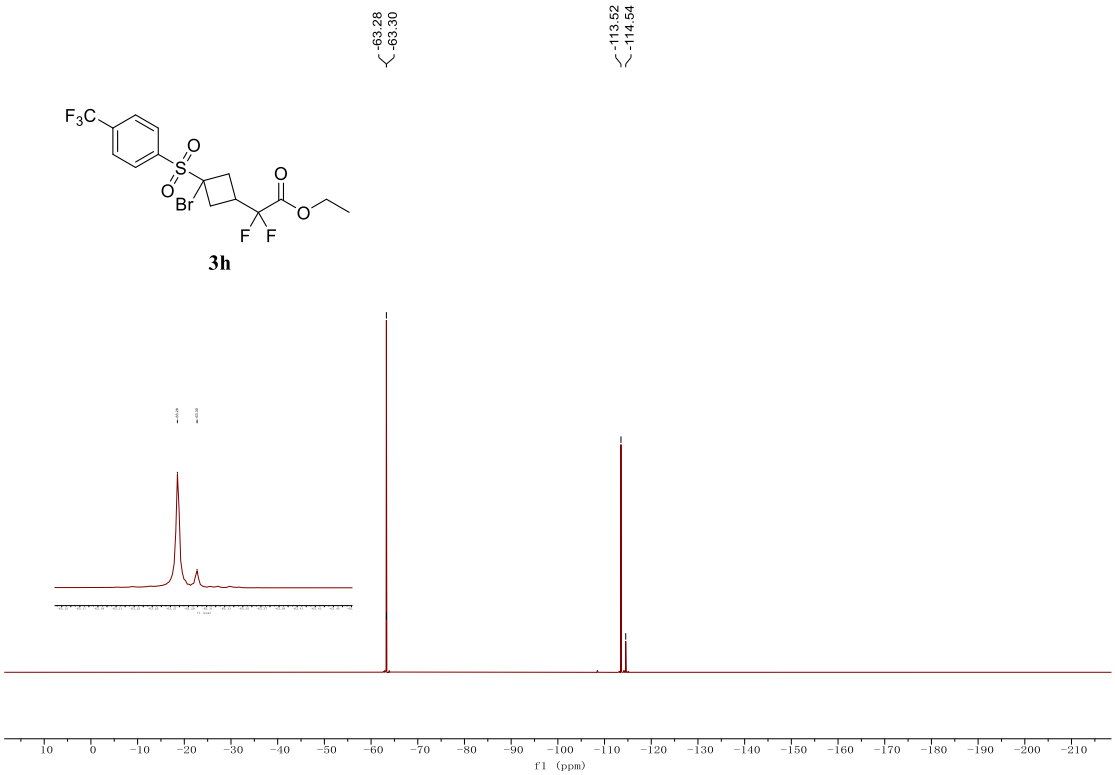
^{1}H NMR Spectrum of Compound **3h** (300 MHz, $CDCl_3$)



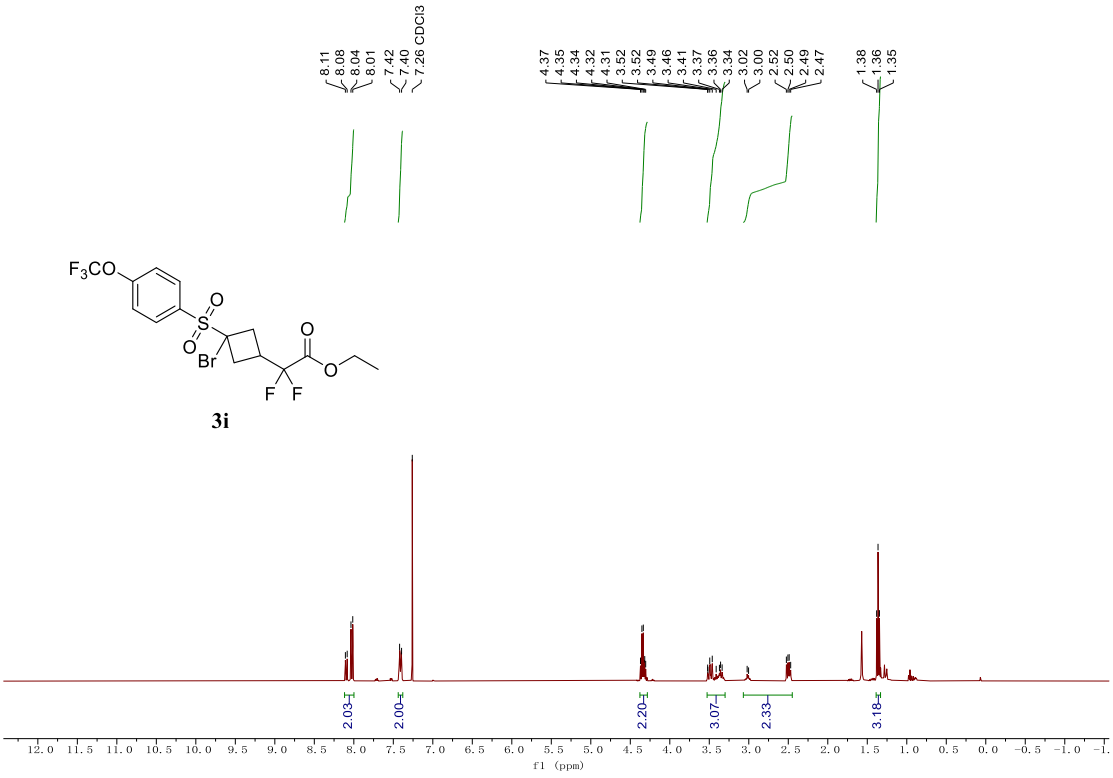
^{13}C NMR Spectrum of Compound **3h** (101 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **3h** (282 MHz, $CDCl_3$)

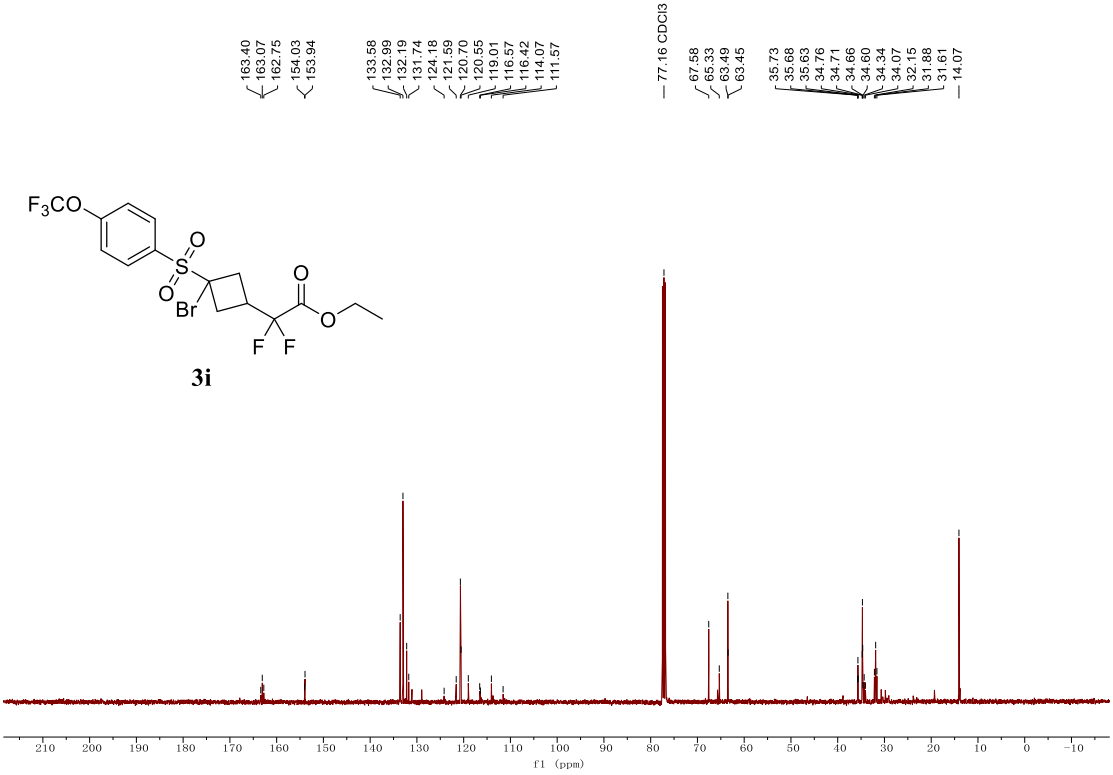


^{1}H NMR Spectrum of Compound **3i** (400 MHz, $CDCl_3$)



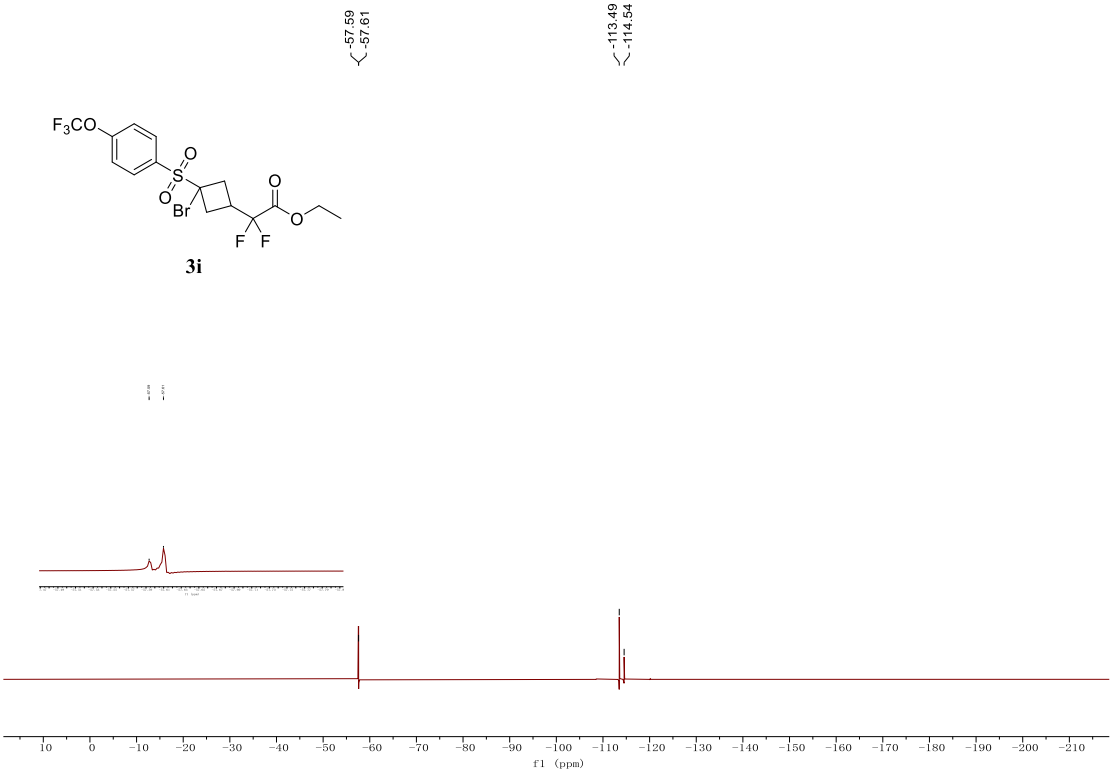
3i

^{13}C NMR Spectrum of Compound **3i** (101 MHz, $CDCl_3$)

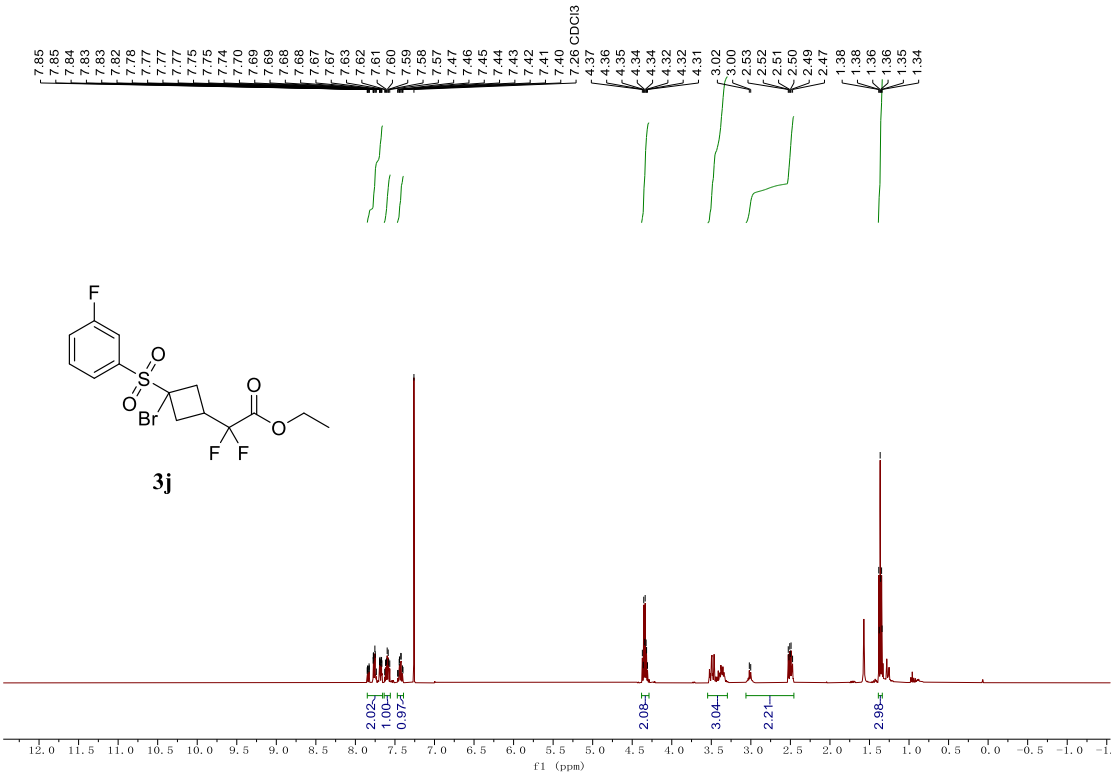


3i

^{19}F NMR Spectrum of Compound **3i** (282 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound **3j** (400 MHz, $CDCl_3$)



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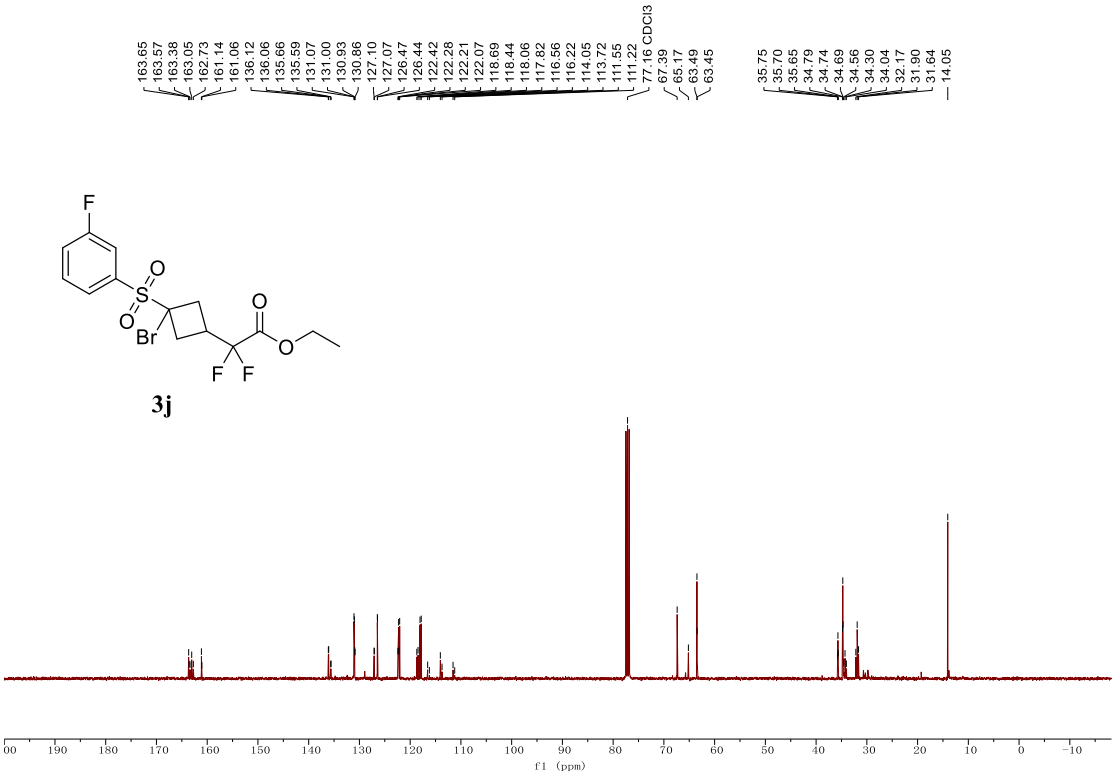
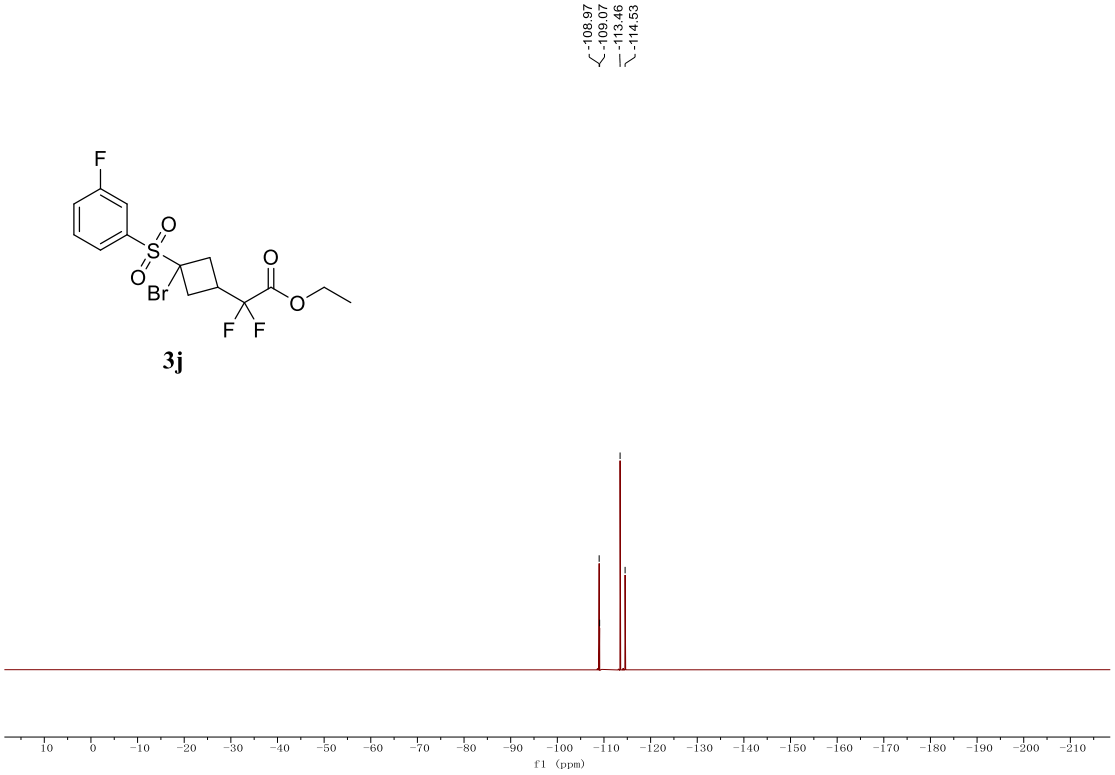
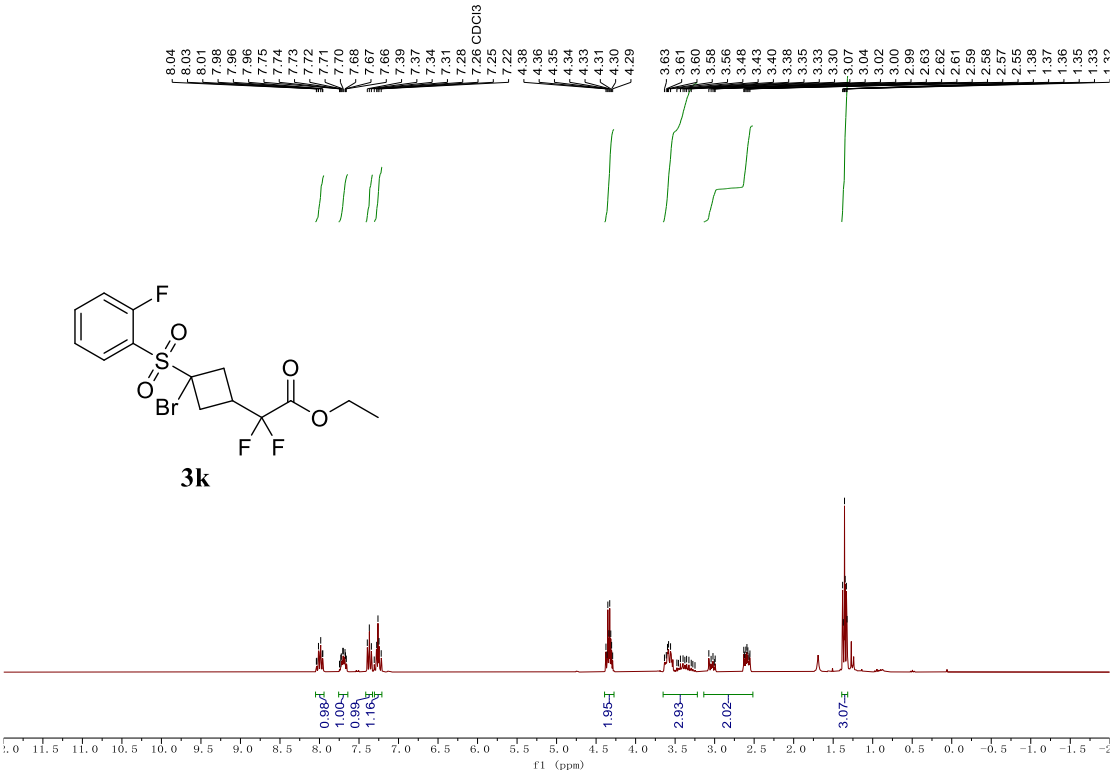
^{13}C NMR Spectrum of Compound **3j** (101 MHz, $CDCl_3$)



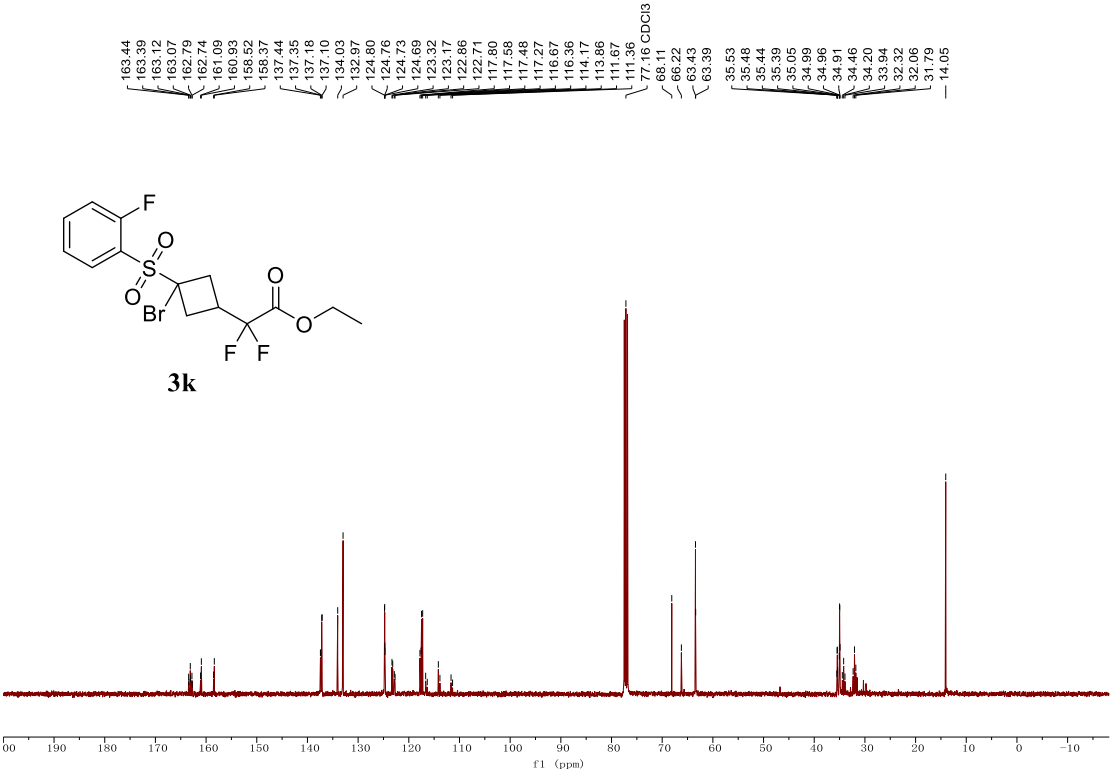
^{19}F NMR Spectrum of Compound **3j** (282 MHz, $CDCl_3$)



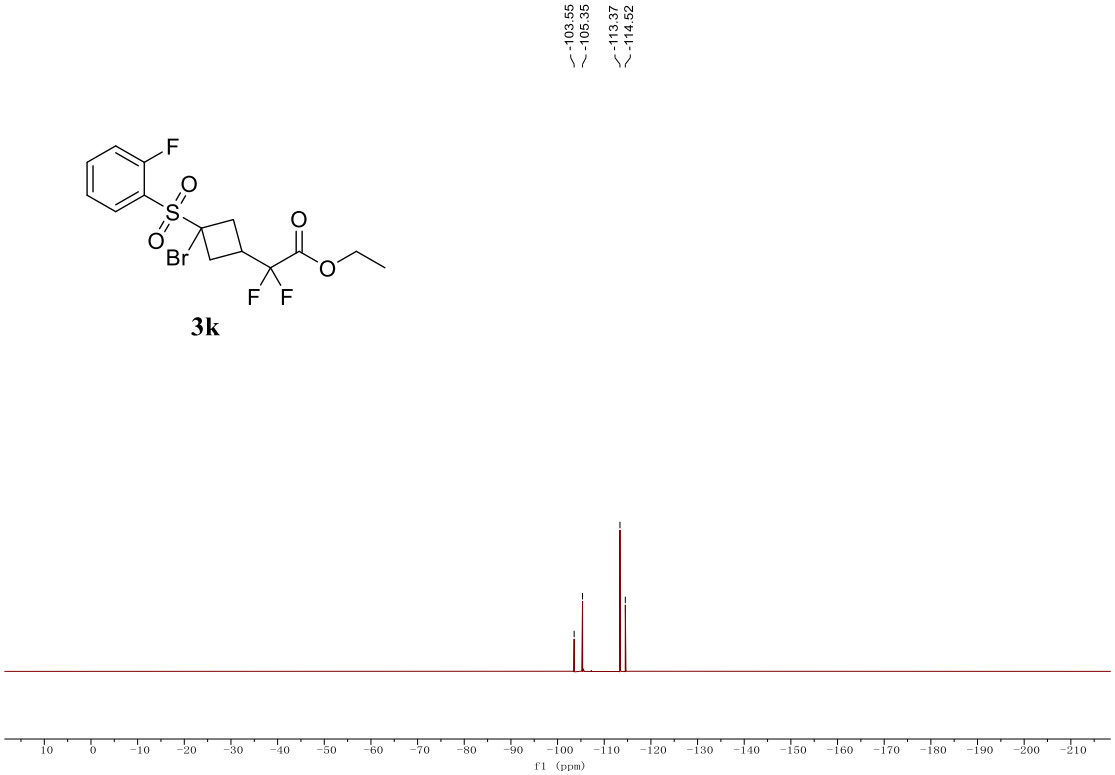
^{1}H NMR Spectrum of Compound **3k** (300 MHz, $CDCl_3$)



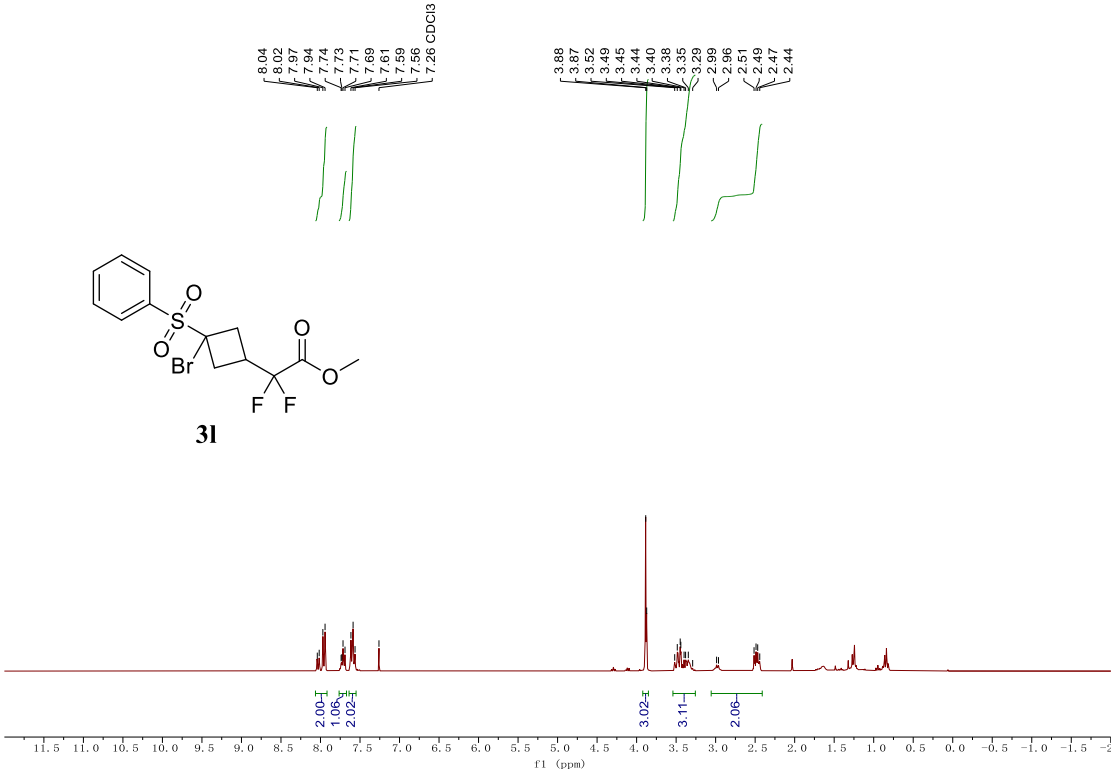
^{13}C NMR Spectrum of Compound **3k** (101 MHz, $CDCl_3$)



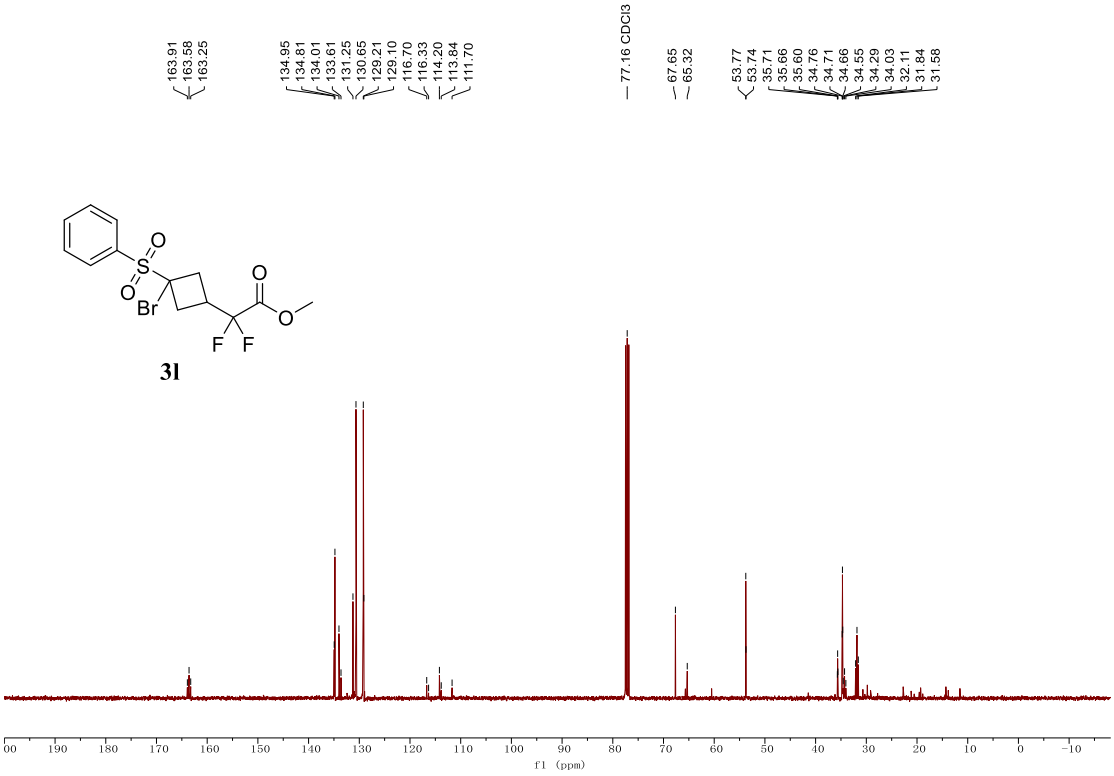
^{19}F NMR Spectrum of Compound **3k** (282 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound **3l** (300 MHz, $CDCl_3$)

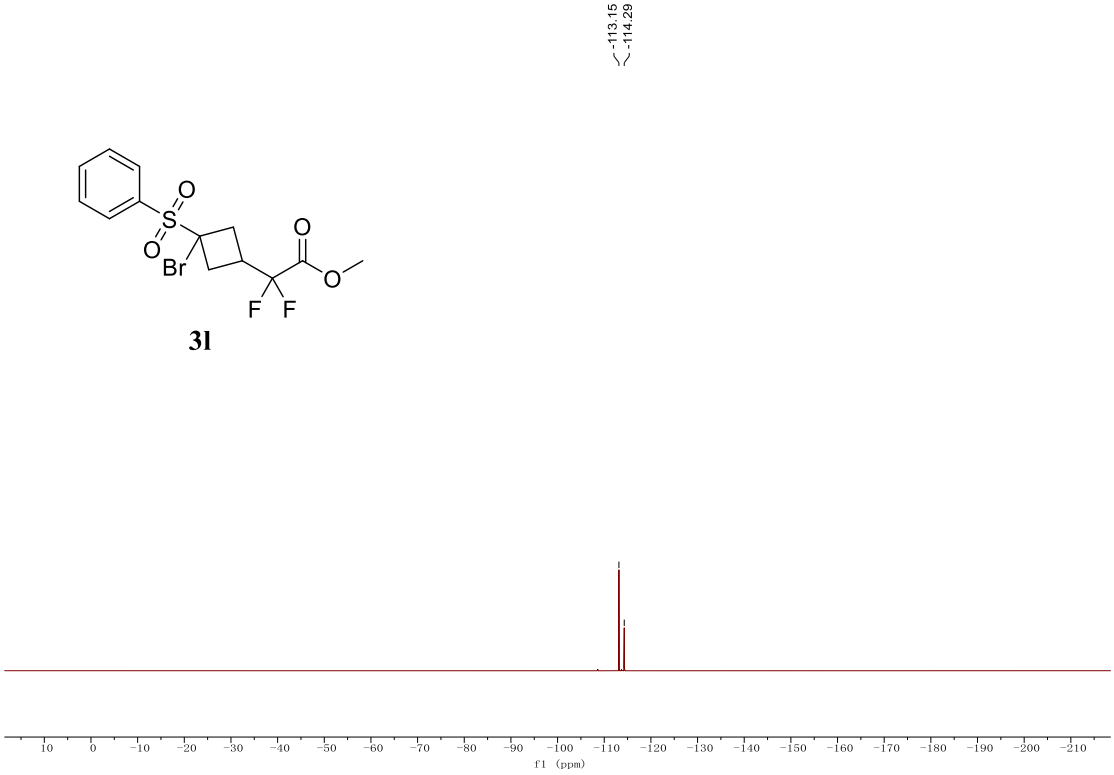


^{13}C NMR Spectrum of Compound **3l** (101 MHz, $CDCl_3$)



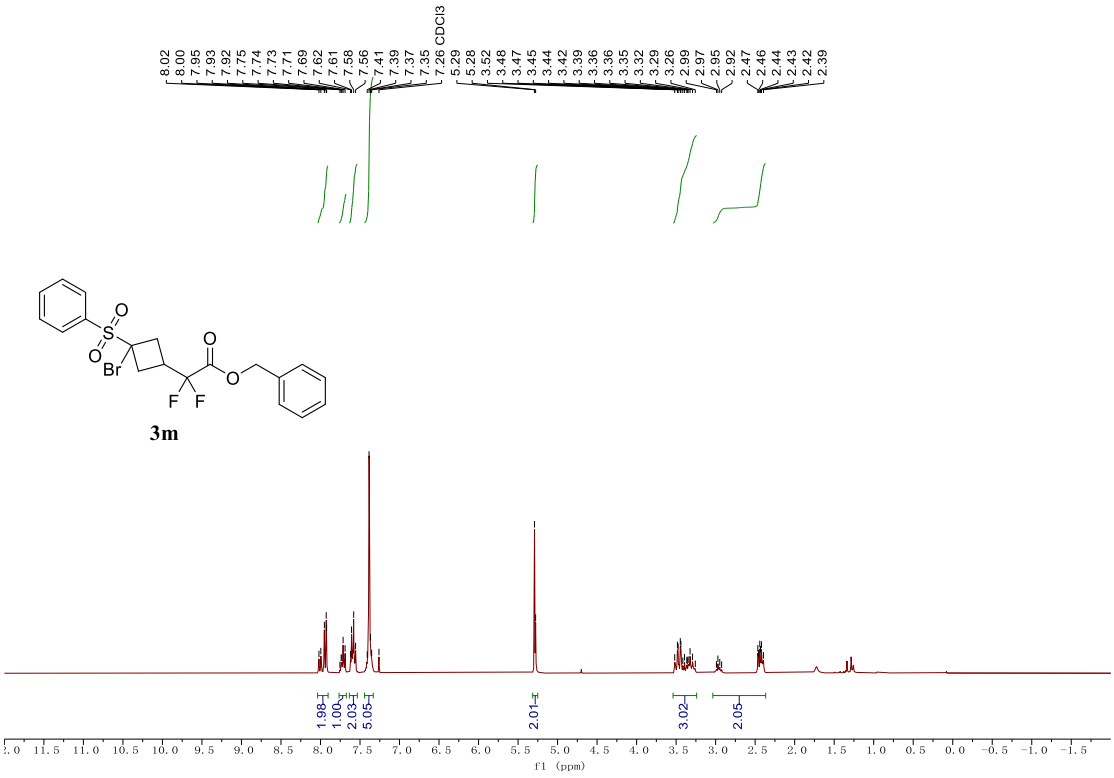
3l

^{19}F NMR Spectrum of Compound **3l** (282 MHz, $CDCl_3$)

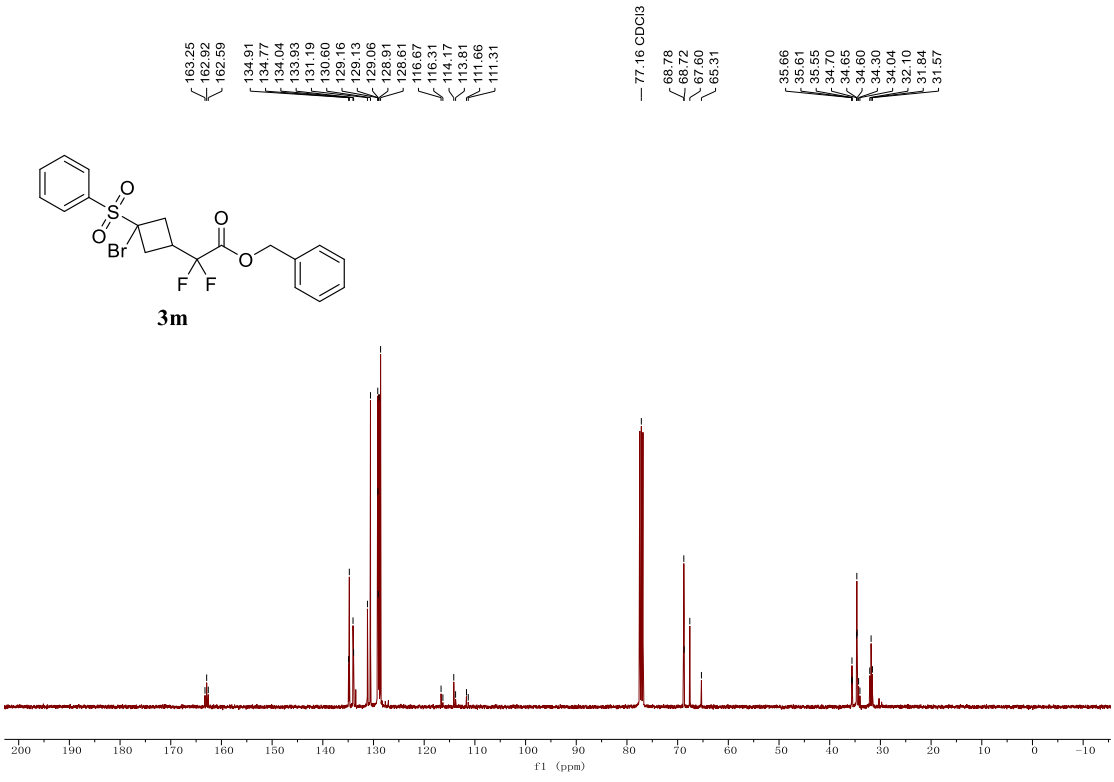


3l

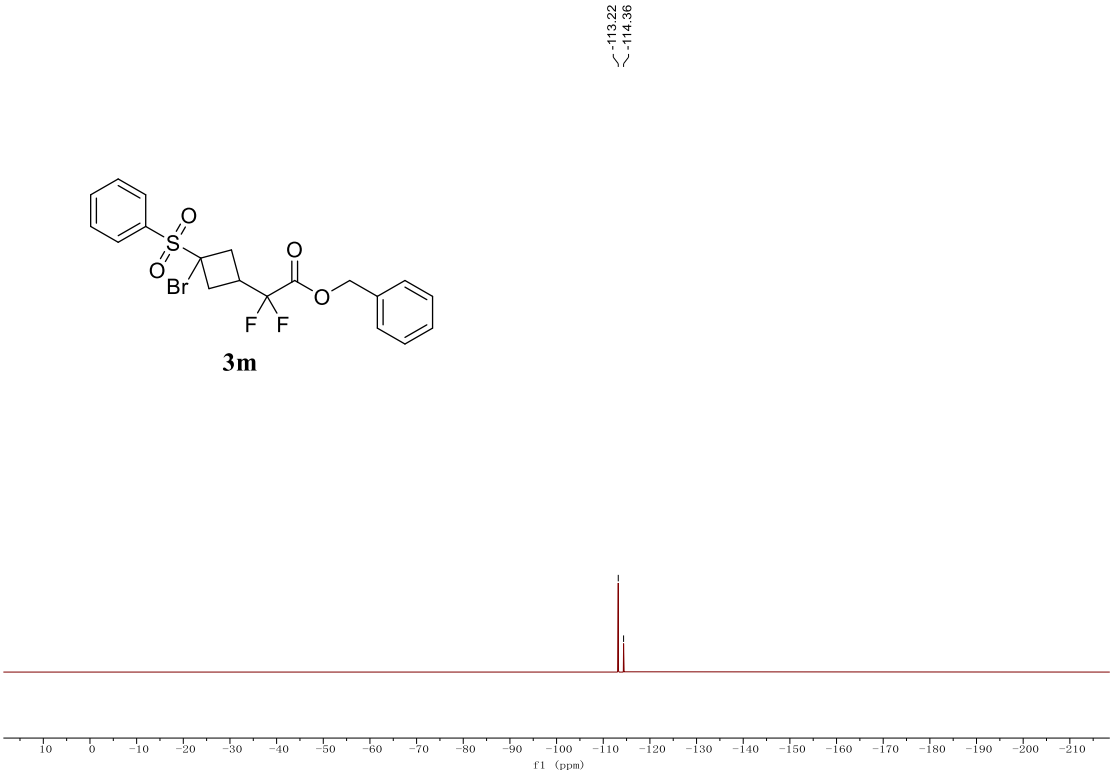
^{1}H NMR Spectrum of Compound **3m** (300 MHz, $CDCl_3$)



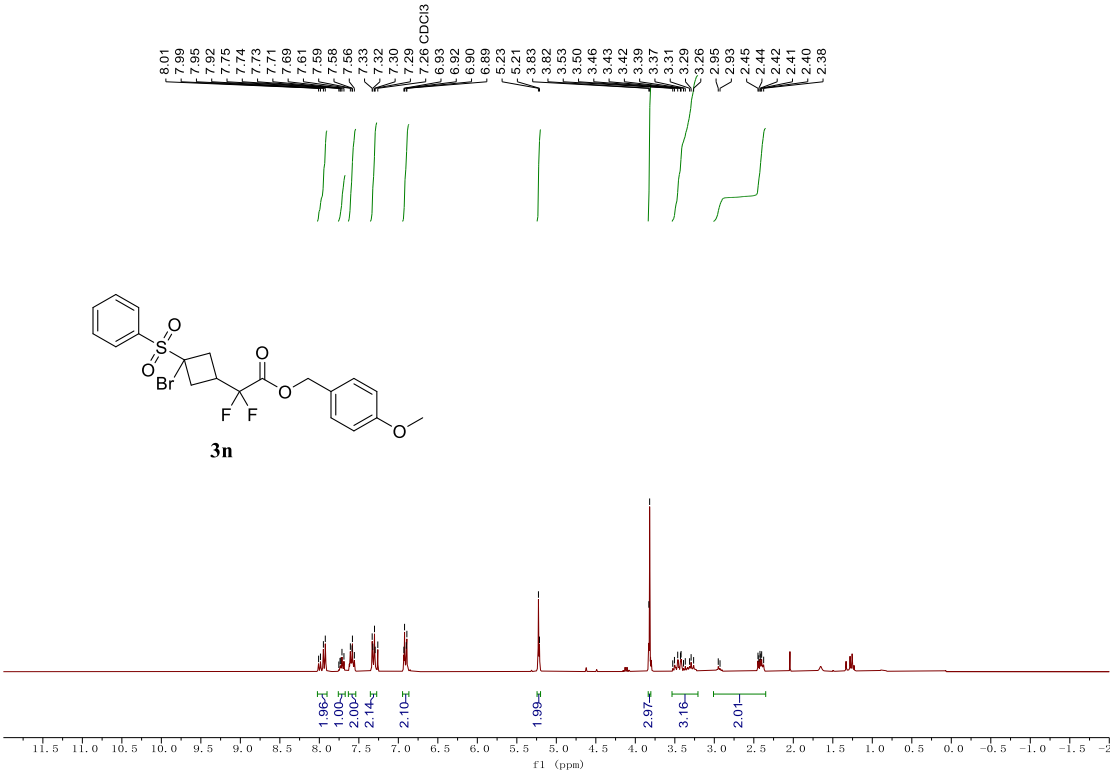
^{13}C NMR Spectrum of Compound **3m** (101 MHz, $CDCl_3$)



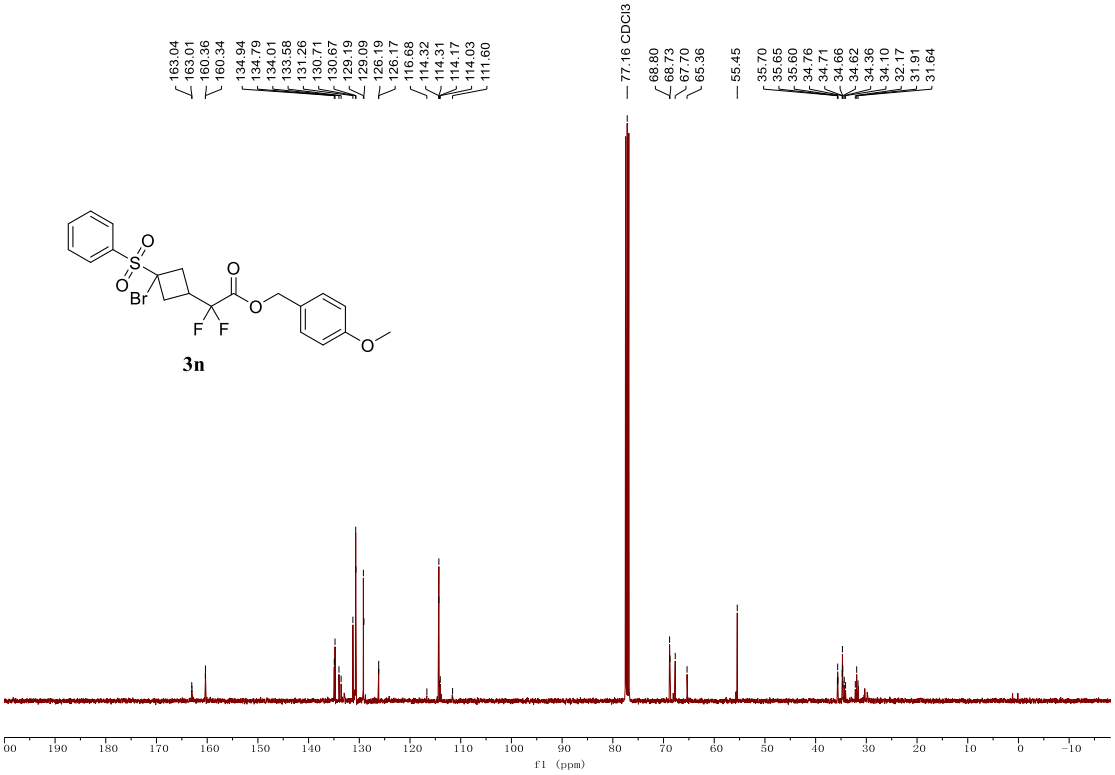
^{19}F NMR Spectrum of Compound **3m** (282 MHz, $CDCl_3$)



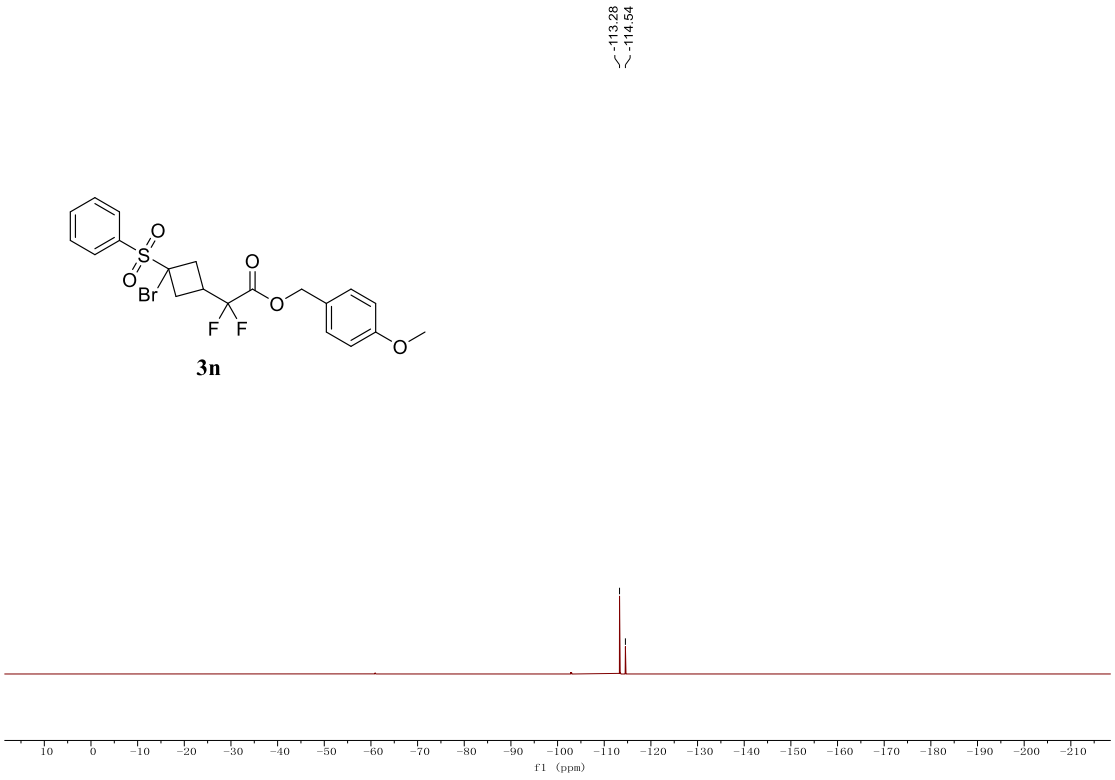
^{1}H NMR Spectrum of Compound **3n** (300 MHz, $CDCl_3$)



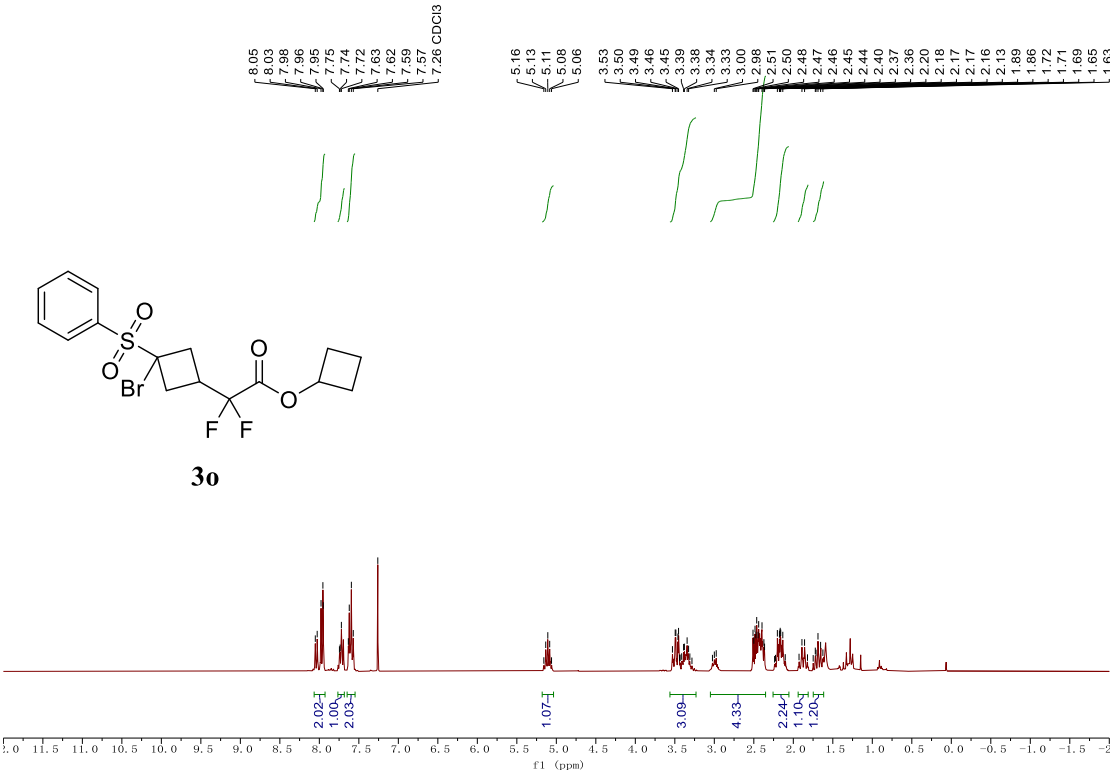
^{13}C NMR Spectrum of Compound **3n** (101 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **3n** (282 MHz, $CDCl_3$)

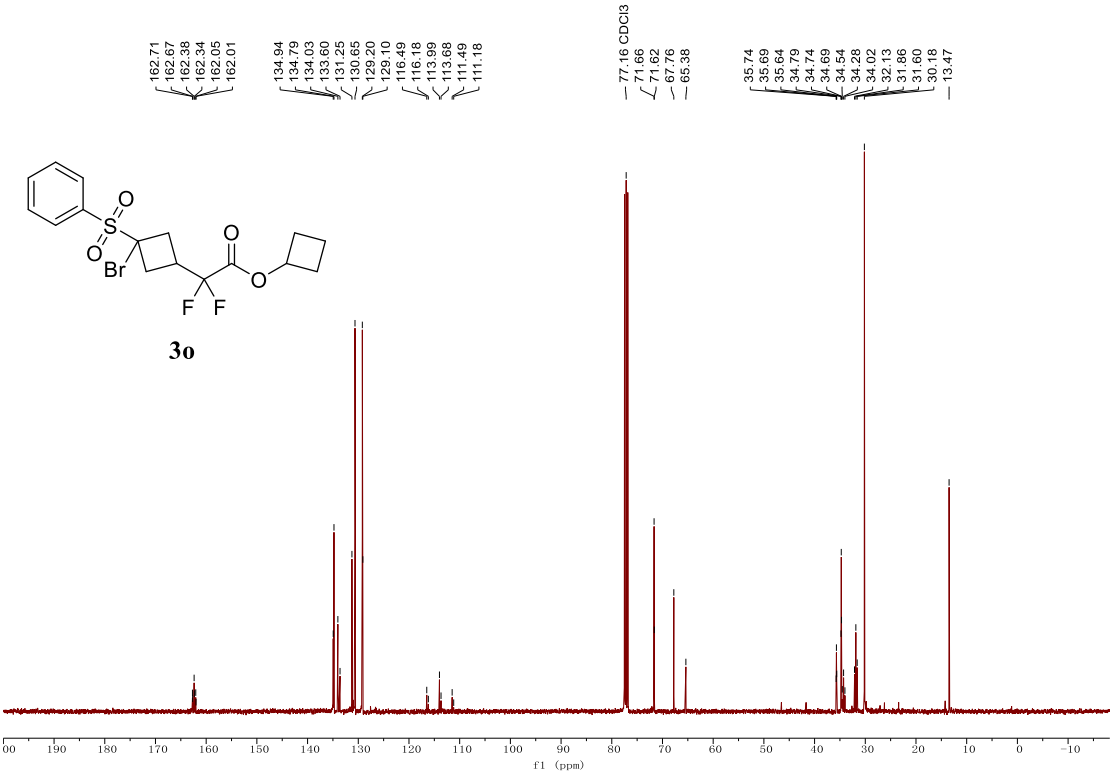


^{1}H NMR Spectrum of Compound **3o** (300 MHz, $CDCl_3$)



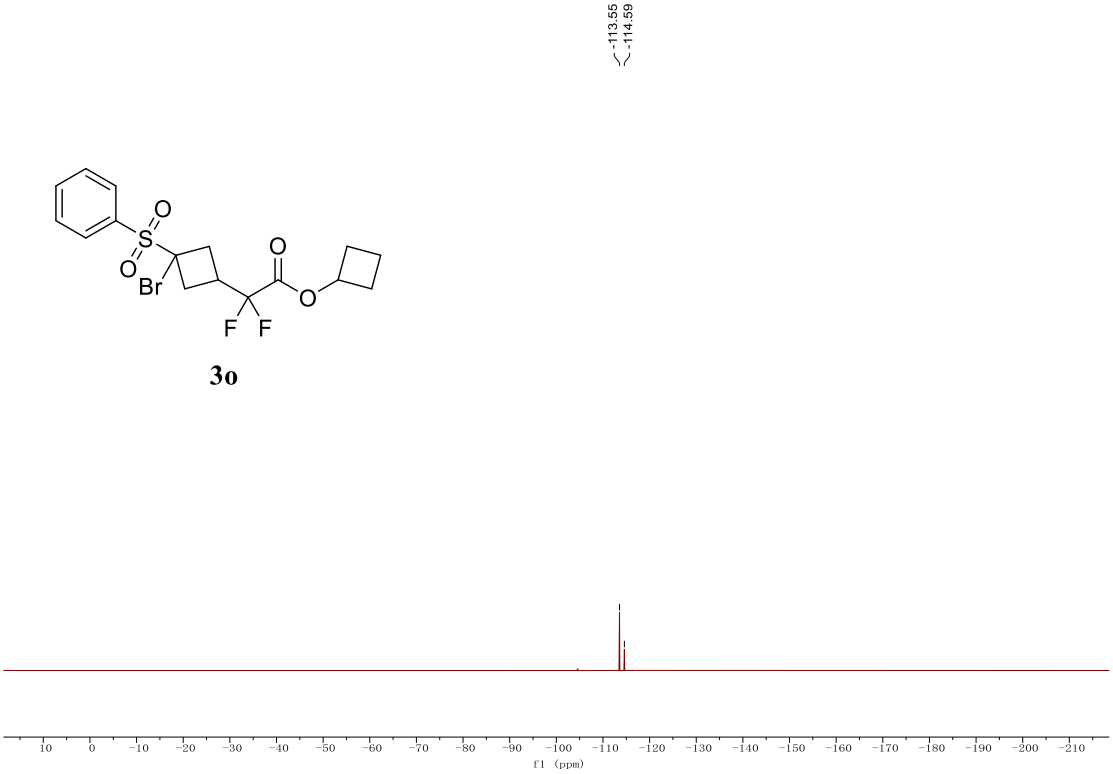
3o

^{13}C NMR Spectrum of Compound **3o** (101 MHz, $CDCl_3$)



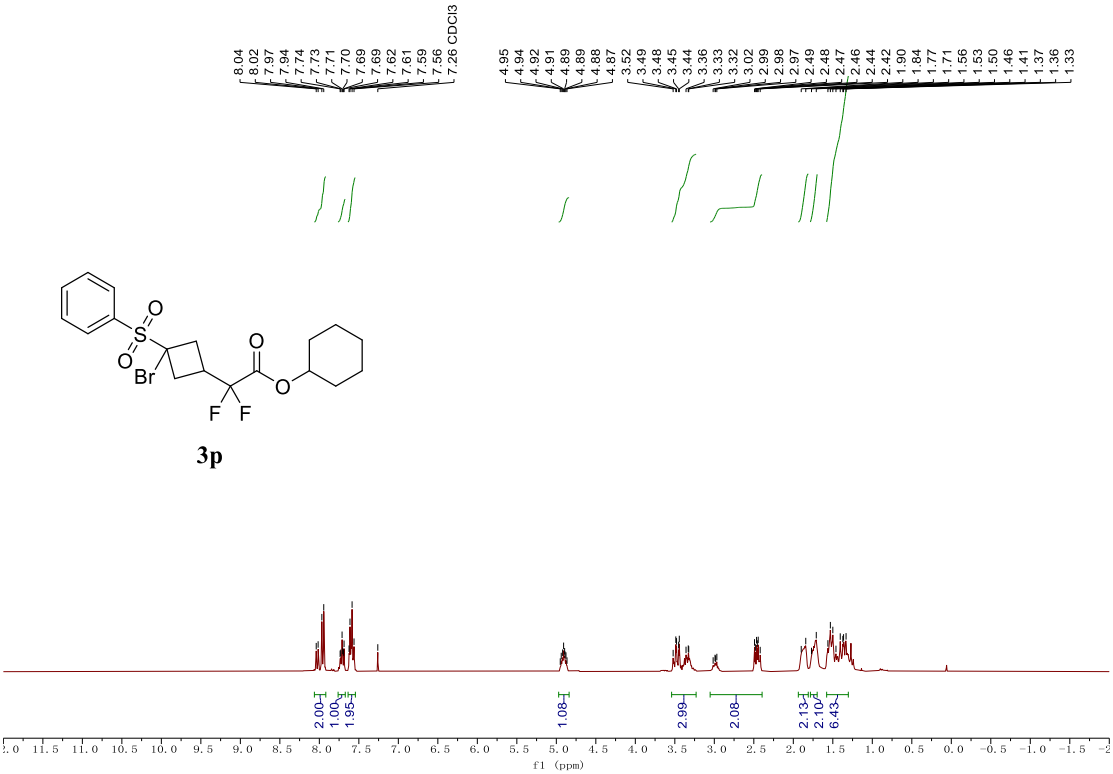
3o

^{19}F NMR Spectrum of Compound **3o** (282 MHz, $CDCl_3$)



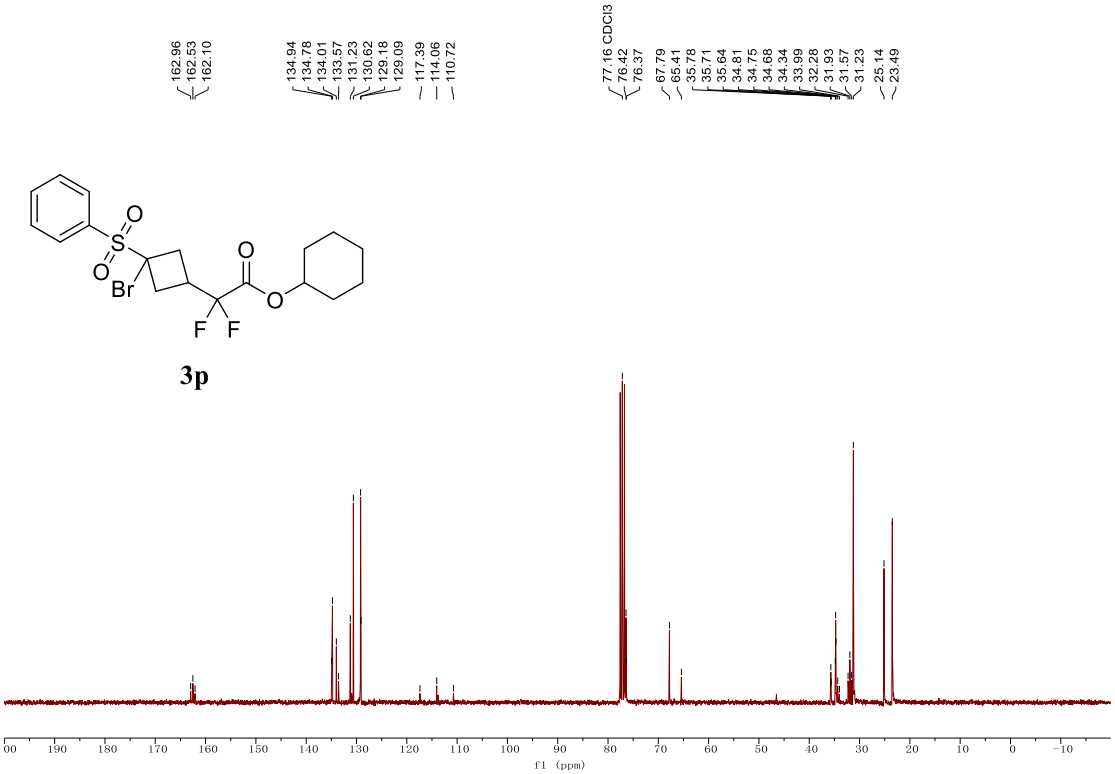
3o

^{1}H NMR Spectrum of Compound **3p** (300 MHz, $CDCl_3$)



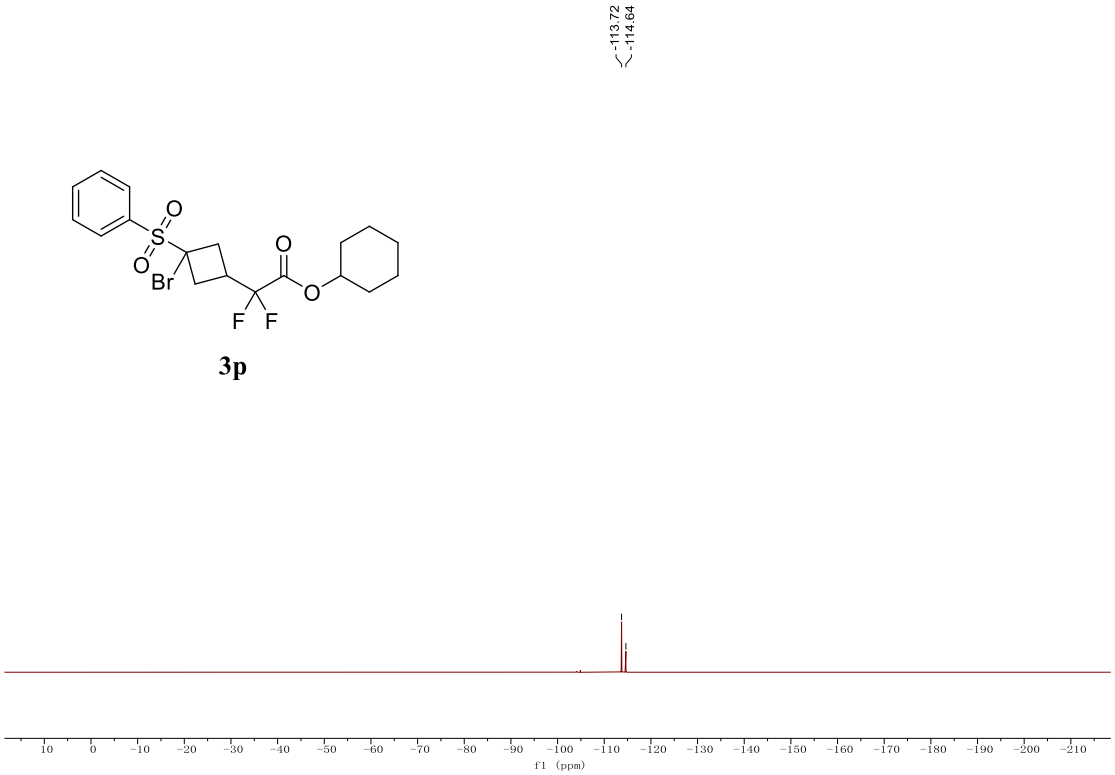
3p

^{13}C NMR Spectrum of Compound **3p** (101 MHz, $CDCl_3$)



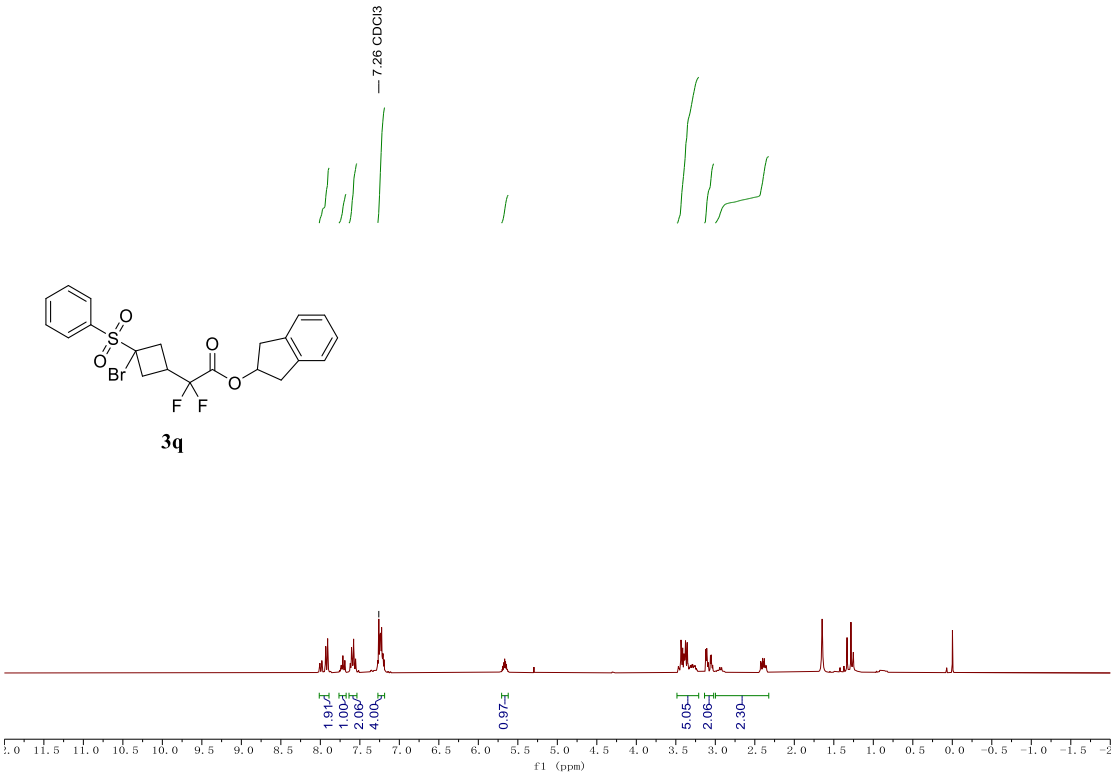
3p

^{19}F NMR Spectrum of Compound **3p** (282 MHz, $CDCl_3$)

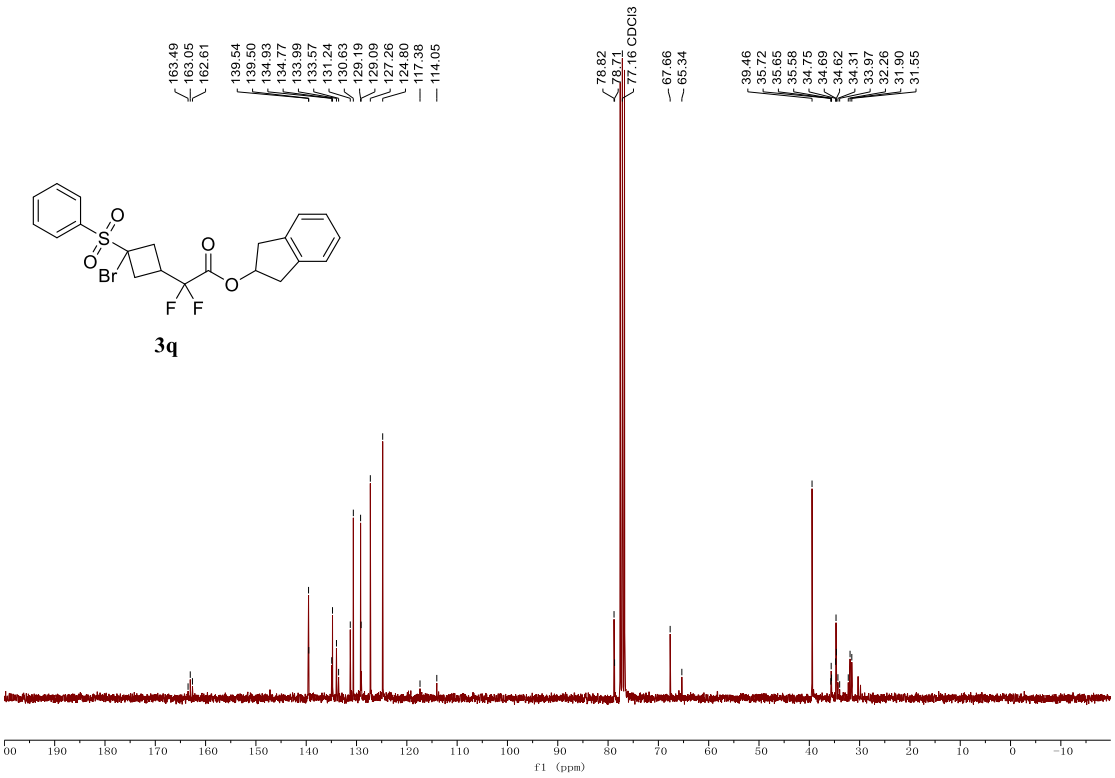


3p

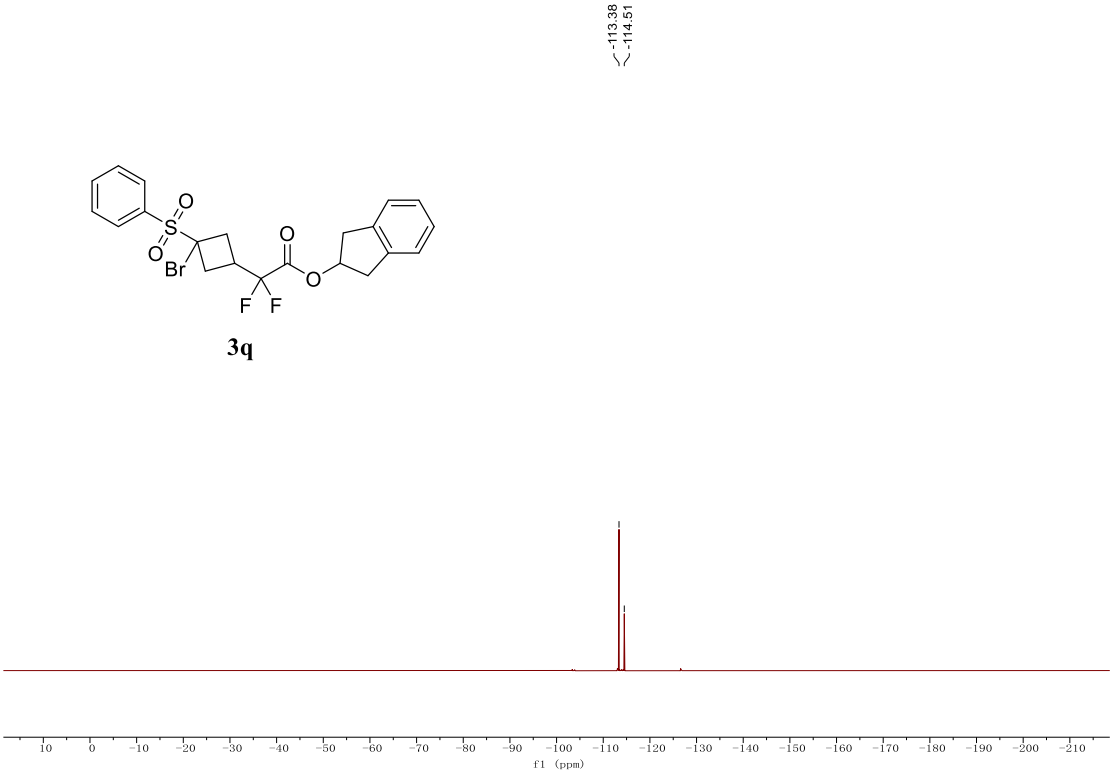
^{1}H NMR Spectrum of Compound **3q** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **3q** (75 MHz, $CDCl_3$)

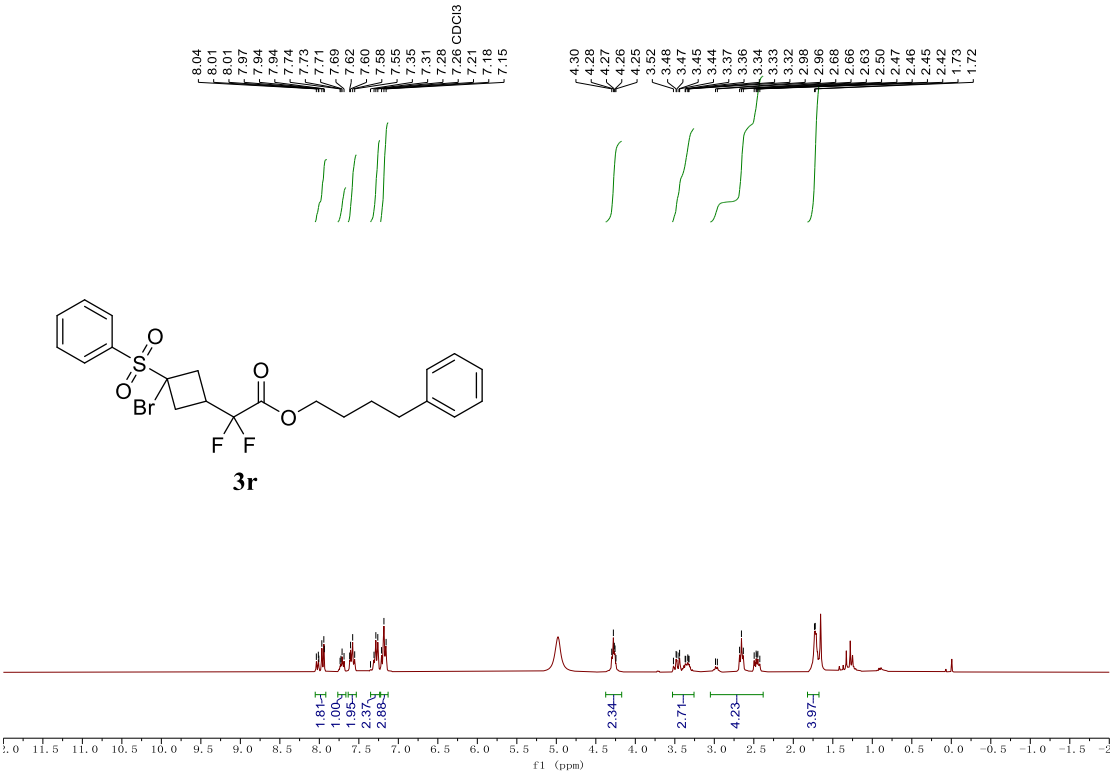


^{19}F NMR Spectrum of Compound **3q** (282 MHz, $CDCl_3$)



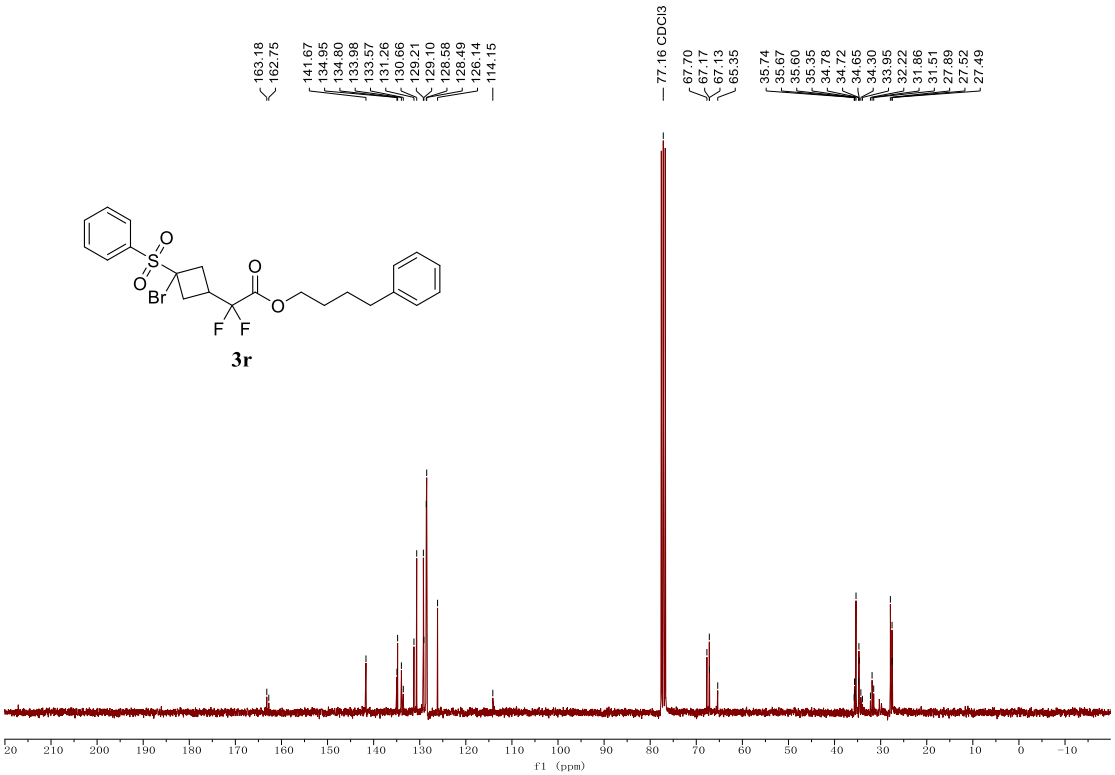
3q

^{1}H NMR Spectrum of Compound **3r** (300 MHz, $CDCl_3$)

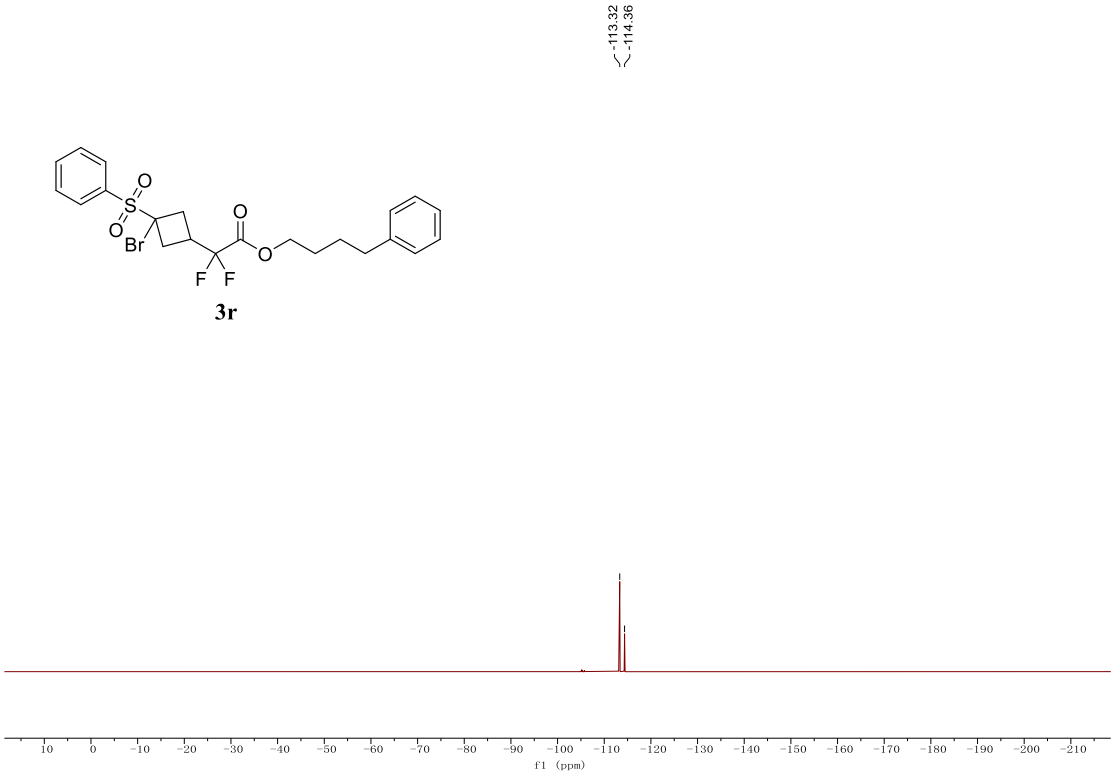


3r

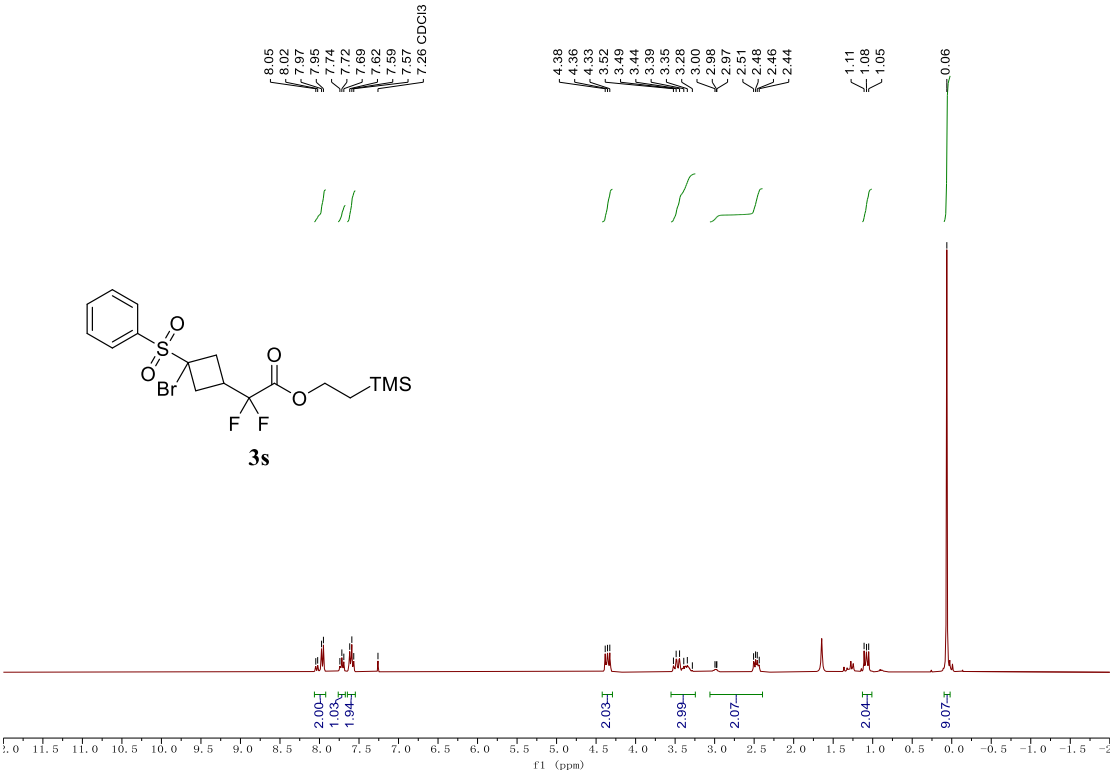
^{13}C NMR Spectrum of Compound **3r** (75 MHz, $CDCl_3$)



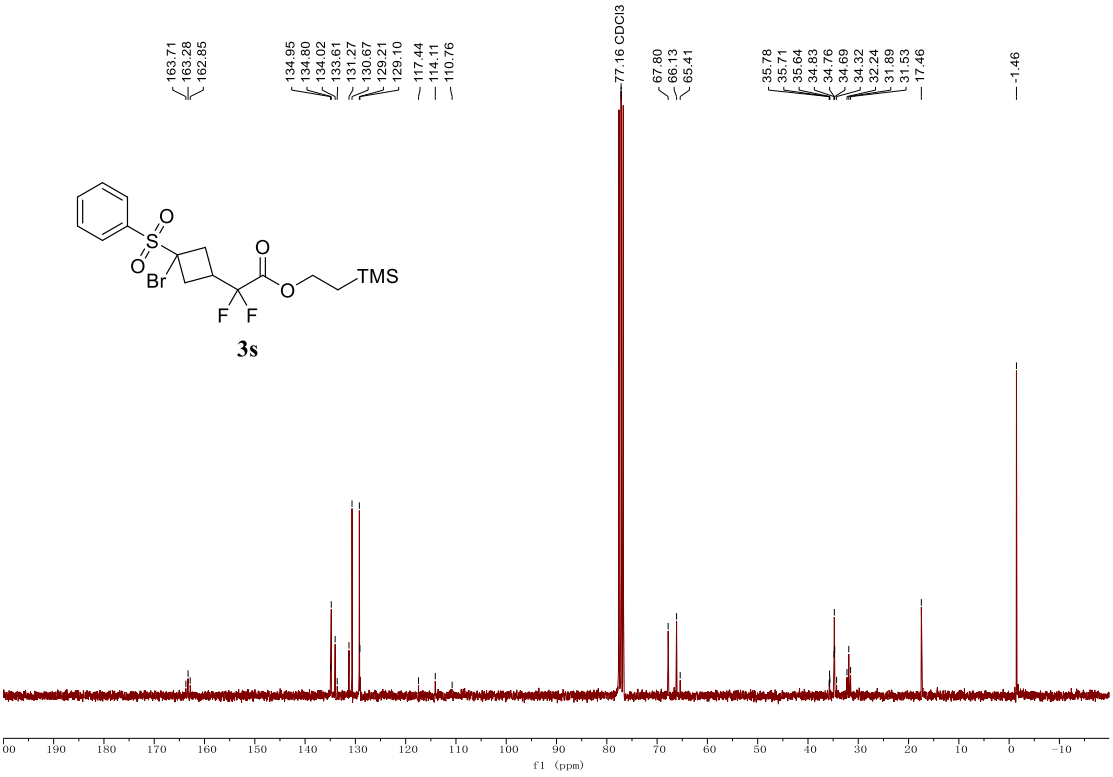
^{19}F NMR Spectrum of Compound **3r** (282 MHz, $CDCl_3$)



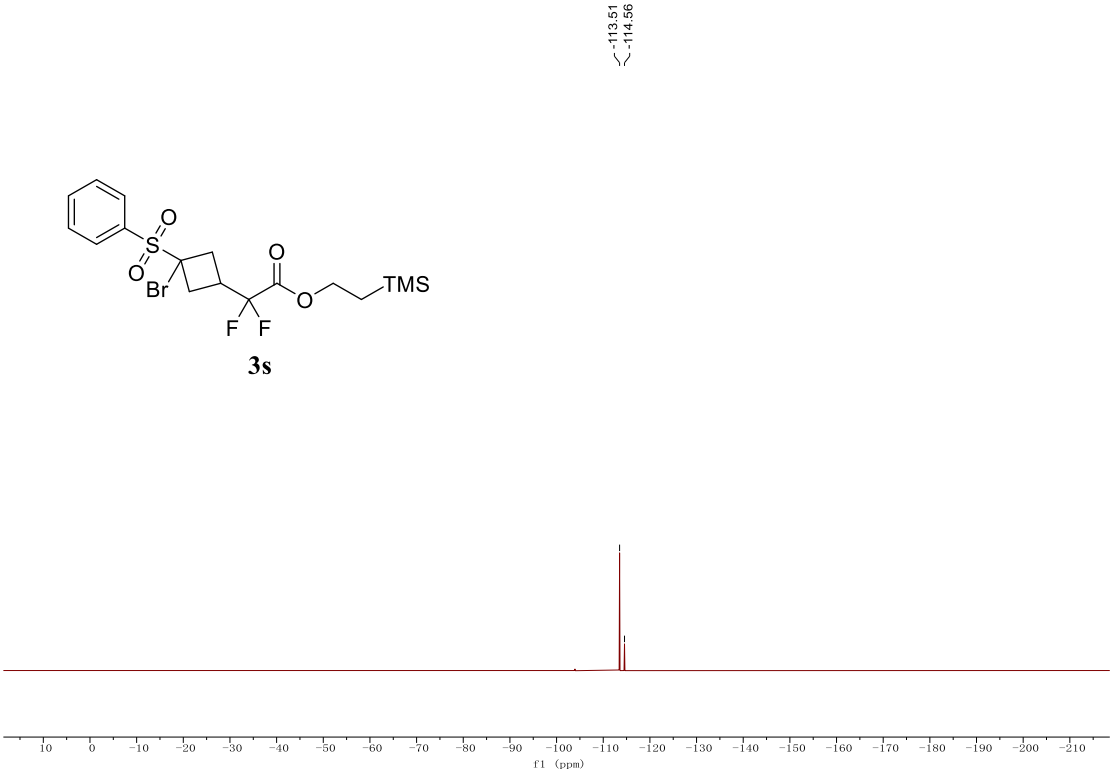
^{1}H NMR Spectrum of Compound **3s** (300 MHz, $CDCl_3$)



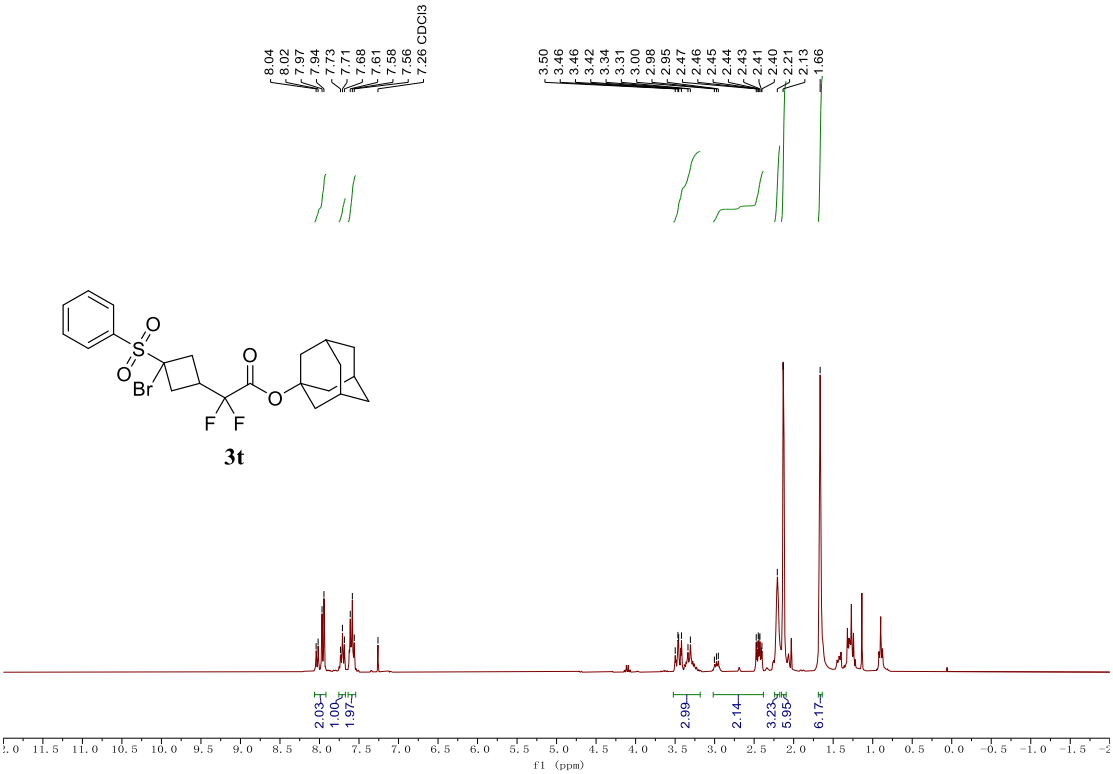
^{13}C NMR Spectrum of Compound **3s** (75 MHz, $CDCl_3$)



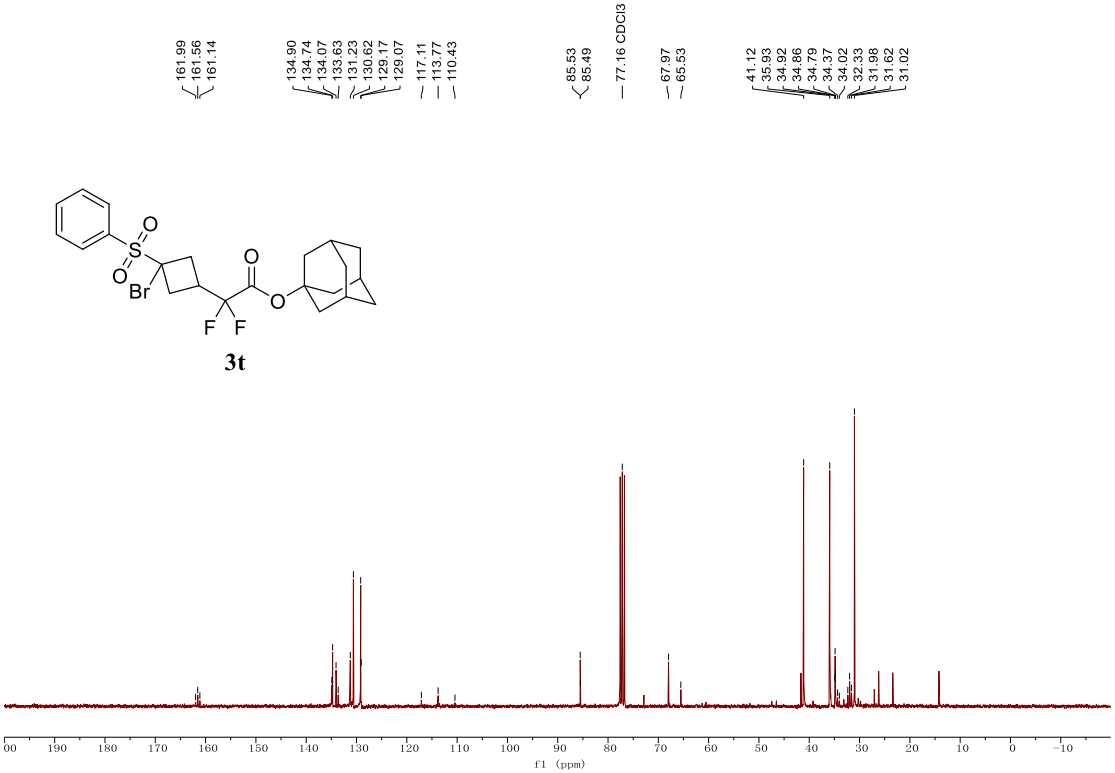
^{19}F NMR Spectrum of Compound **3s** (282 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound **3t** (300 MHz, $CDCl_3$)

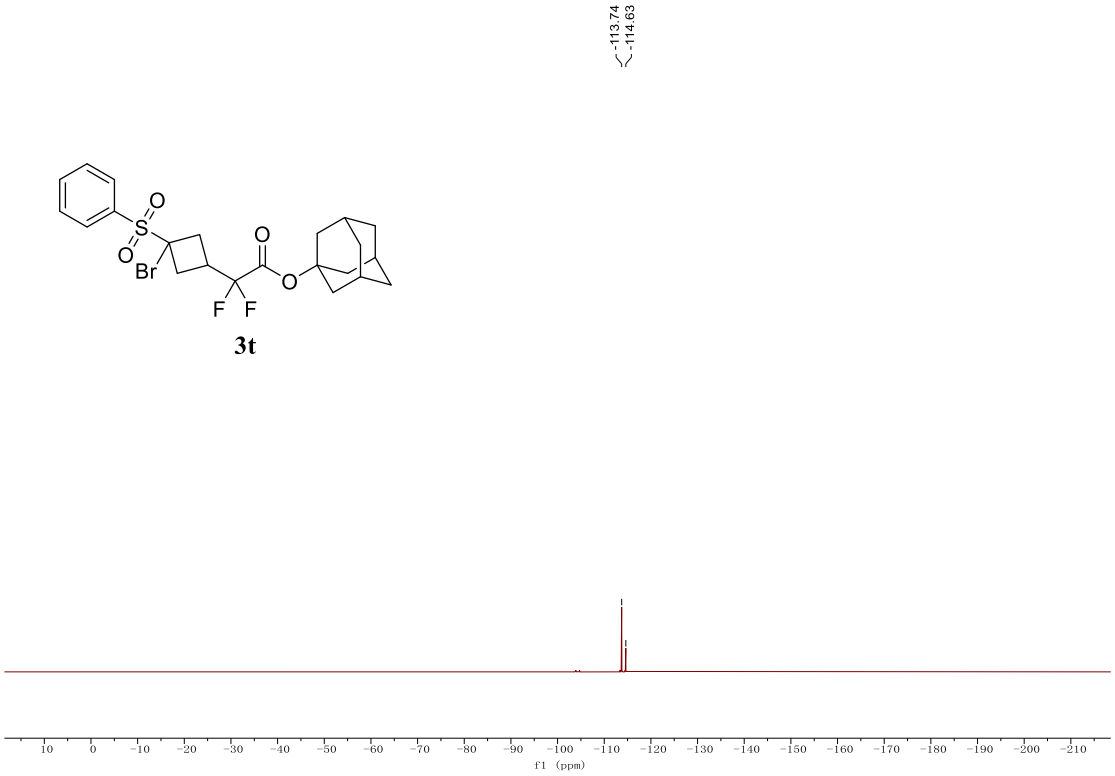


^{13}C NMR Spectrum of Compound **3t** (75 MHz, $CDCl_3$)



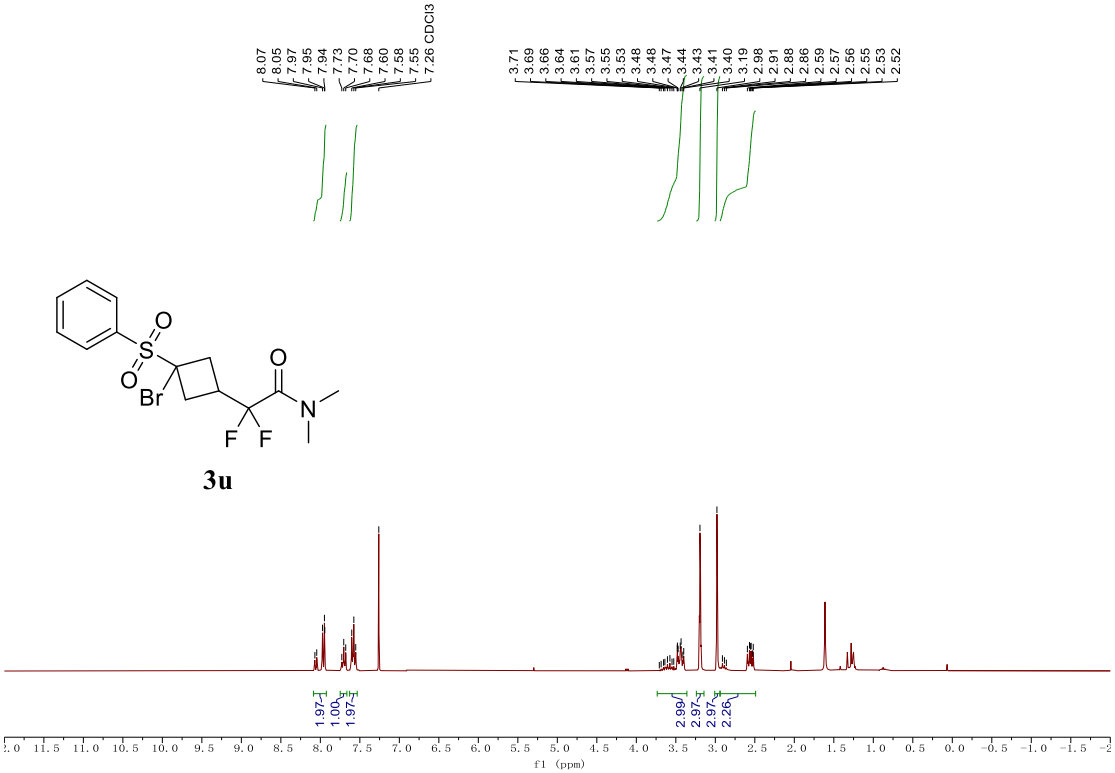
3t

^{19}F NMR Spectrum of Compound **3t** (282 MHz, $CDCl_3$)

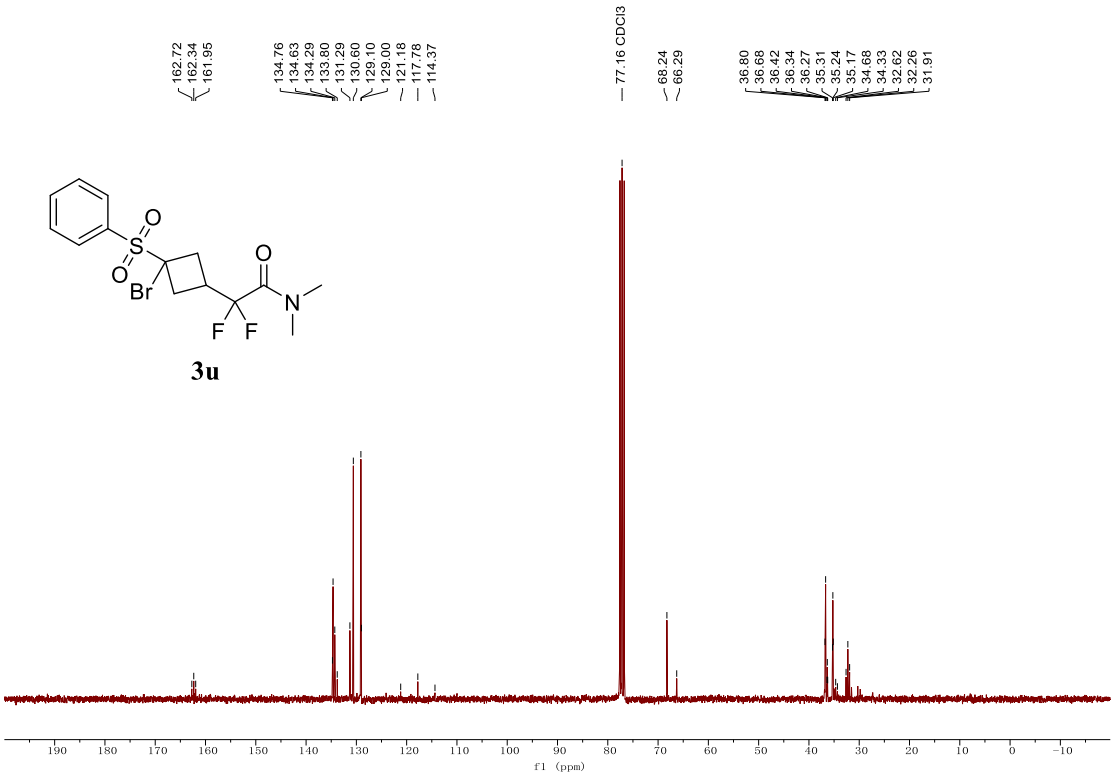


3t

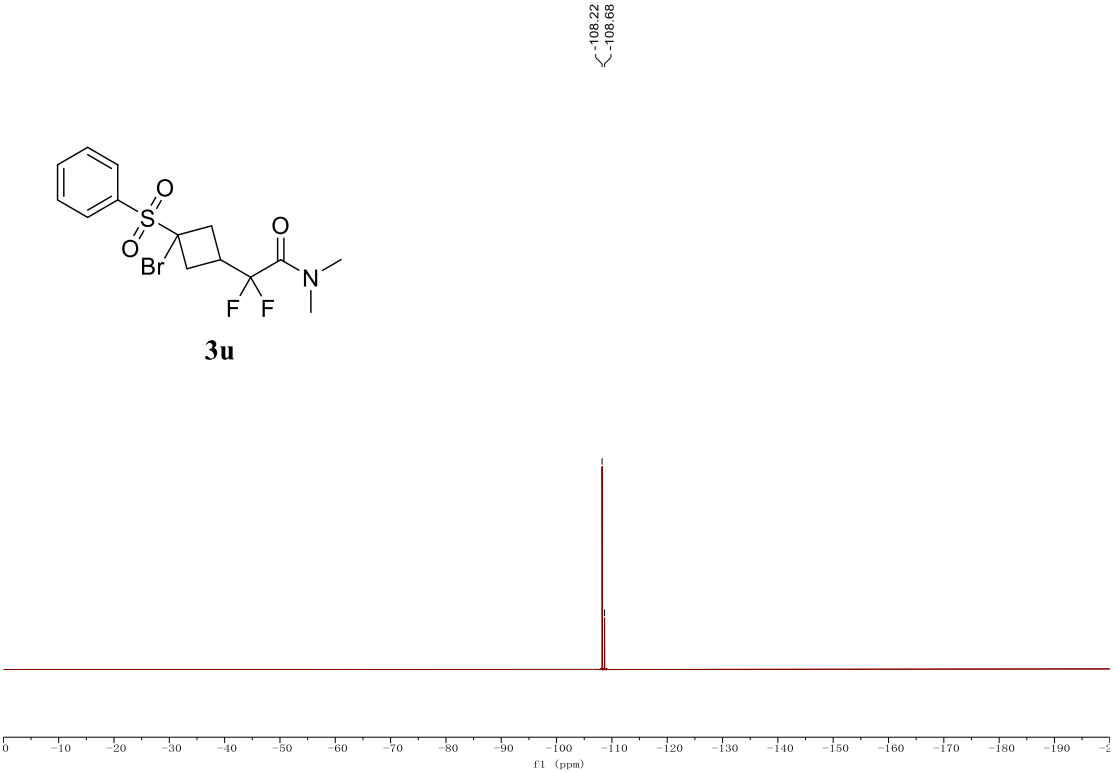
^{1}H NMR Spectrum of Compound **3u** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **3u** (75 MHz, $CDCl_3$)

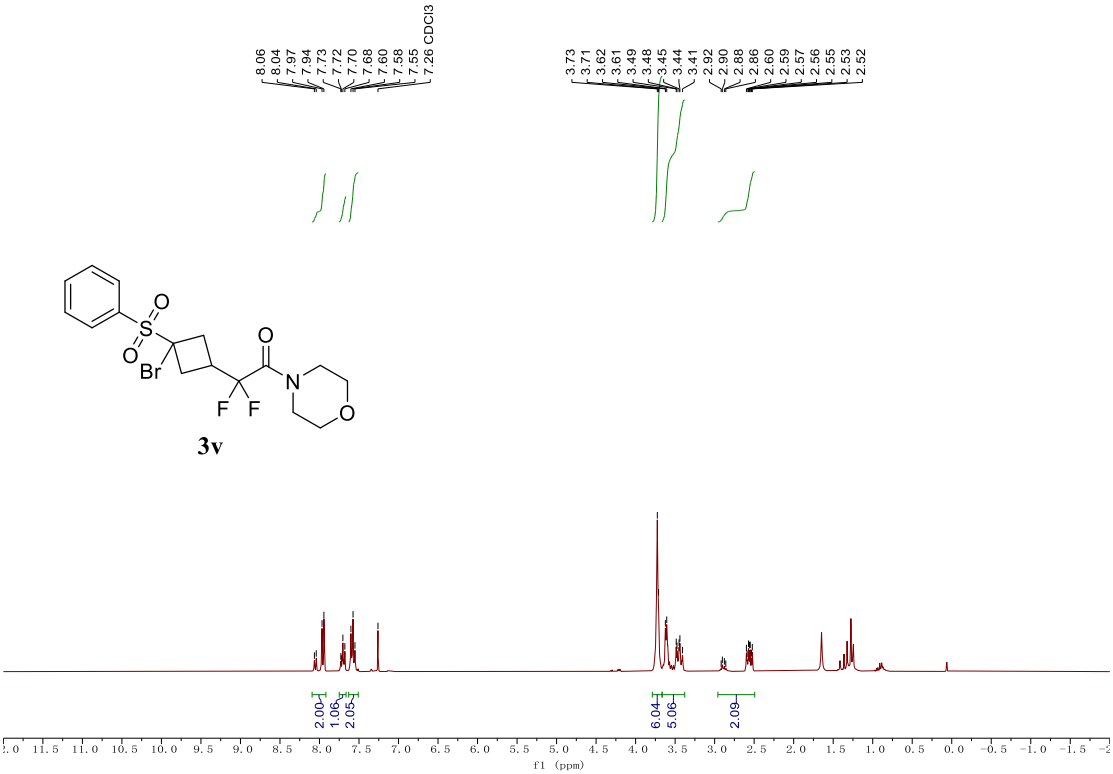


^{19}F NMR Spectrum of Compound **3u** (282 MHz, $CDCl_3$)



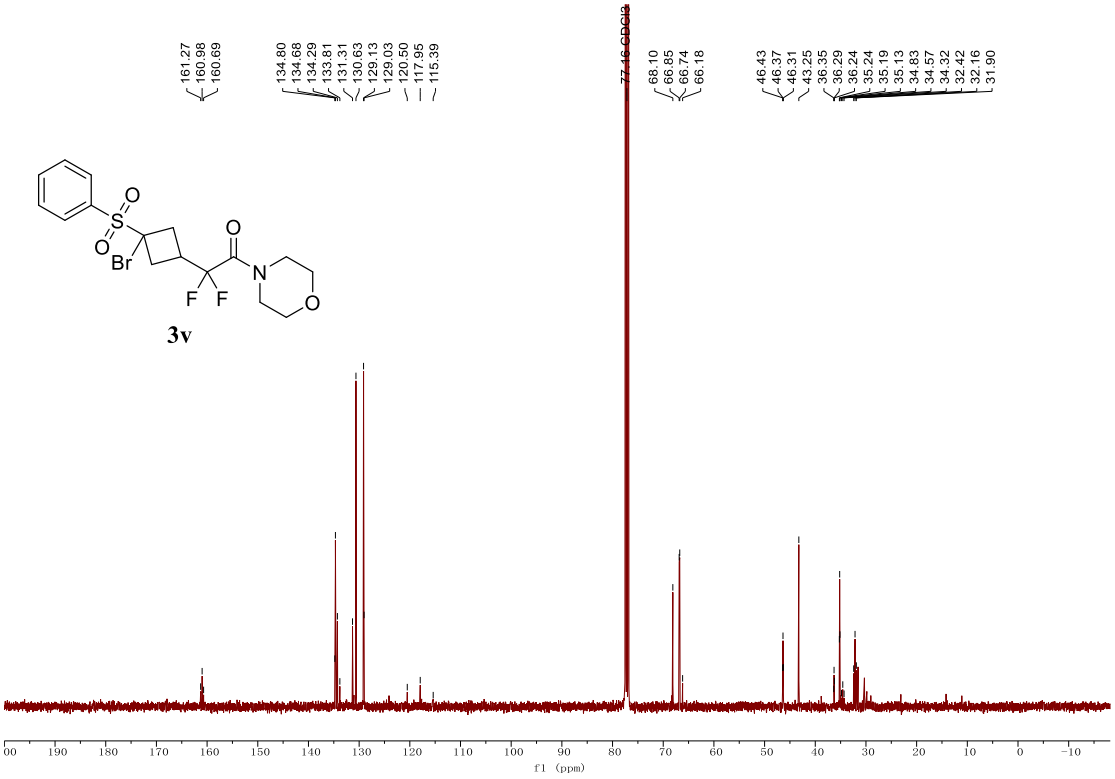
3u

^{1}H NMR Spectrum of Compound **3v** (300 MHz, $CDCl_3$)

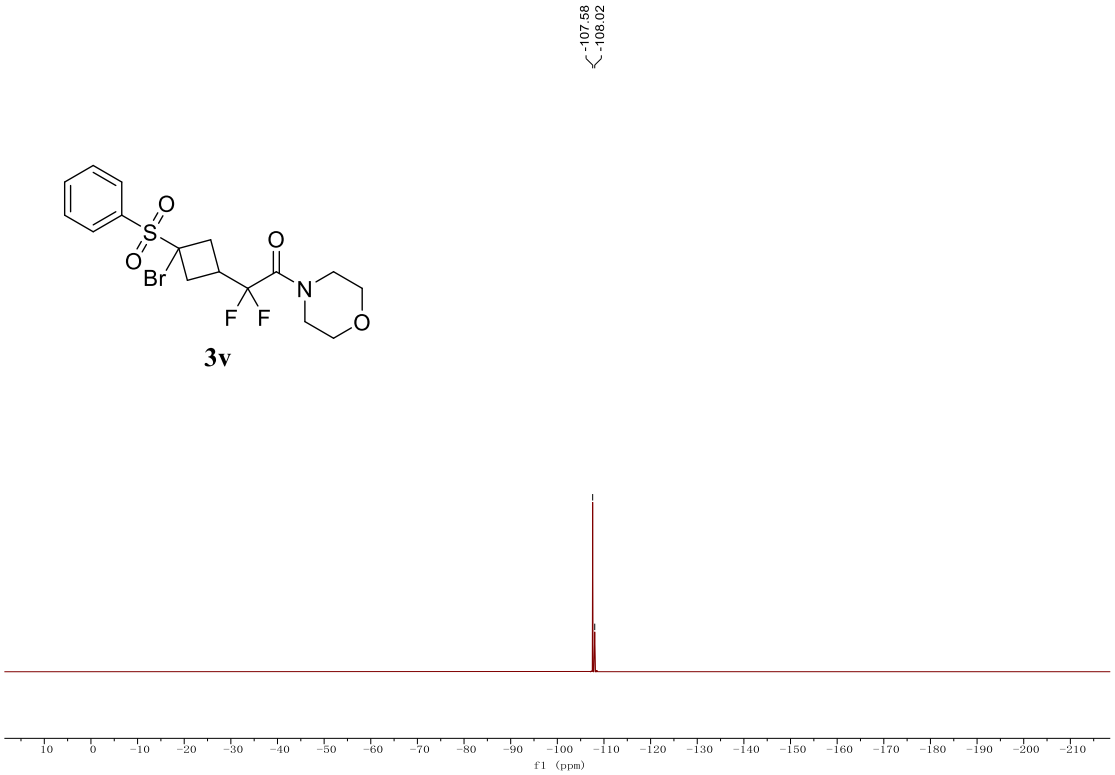


3v

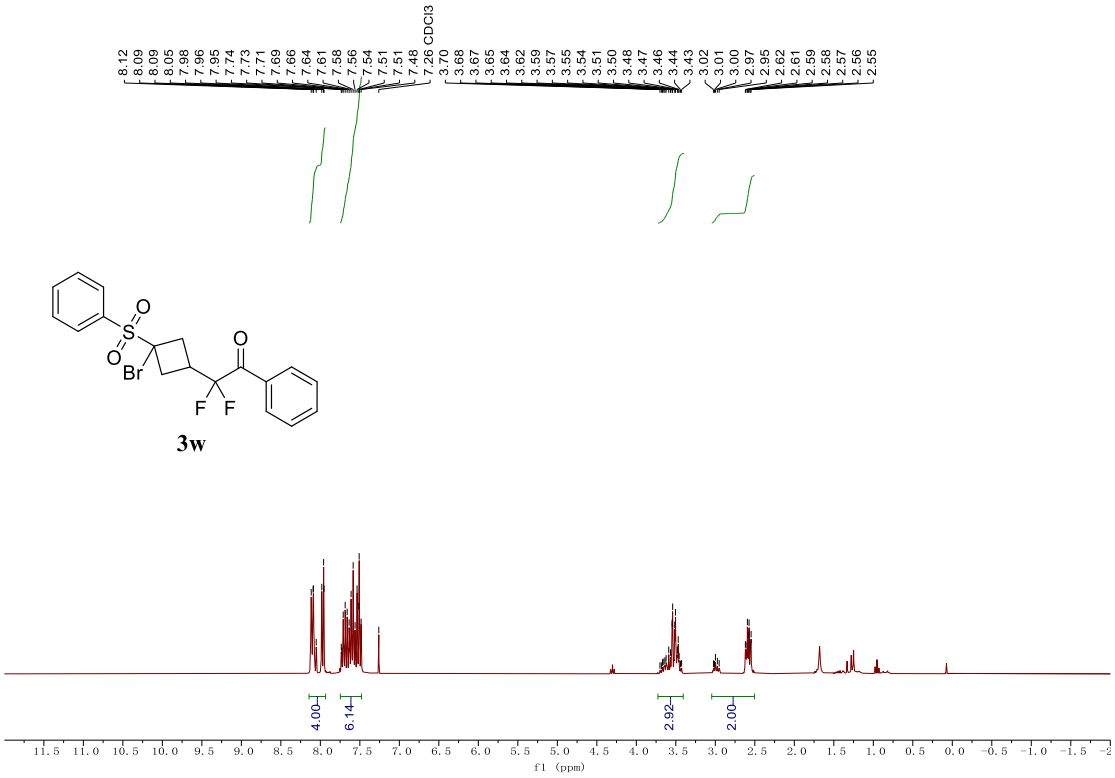
^{13}C NMR Spectrum of Compound **3v** (101 MHz, $CDCl_3$)



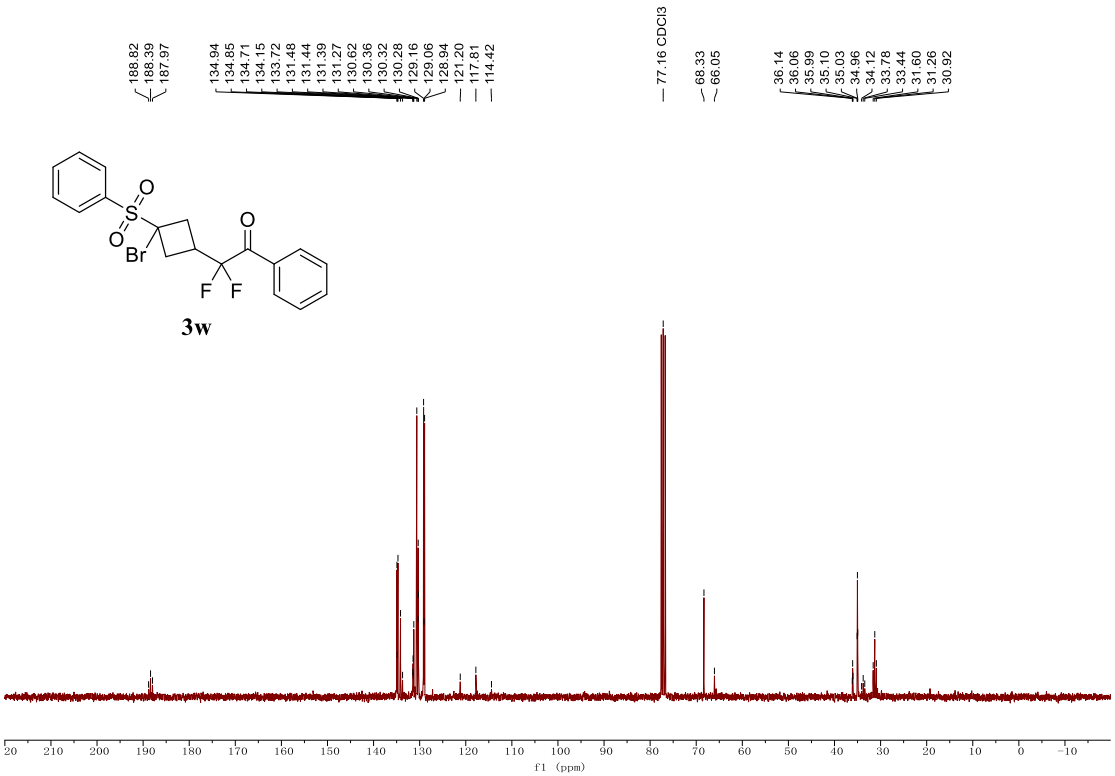
^{19}F NMR Spectrum of Compound **3v** (282 MHz, $CDCl_3$)



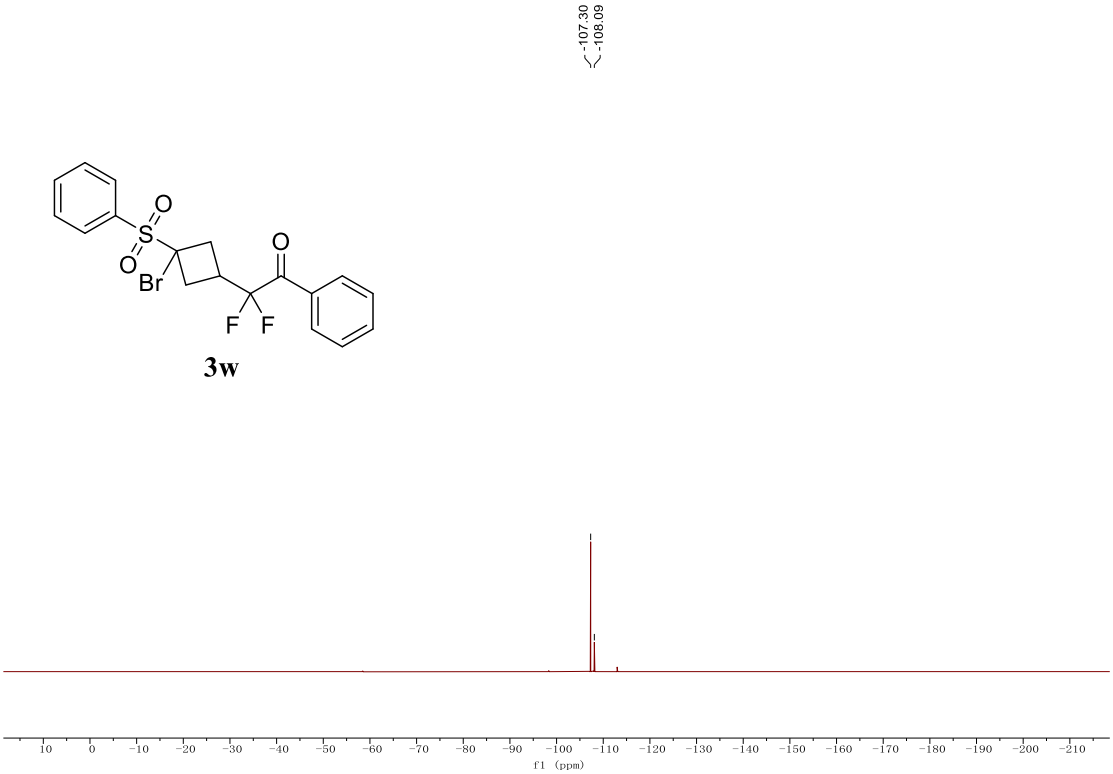
^{1}H NMR Spectrum of Compound **3w** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **3w** (75 MHz, $CDCl_3$)

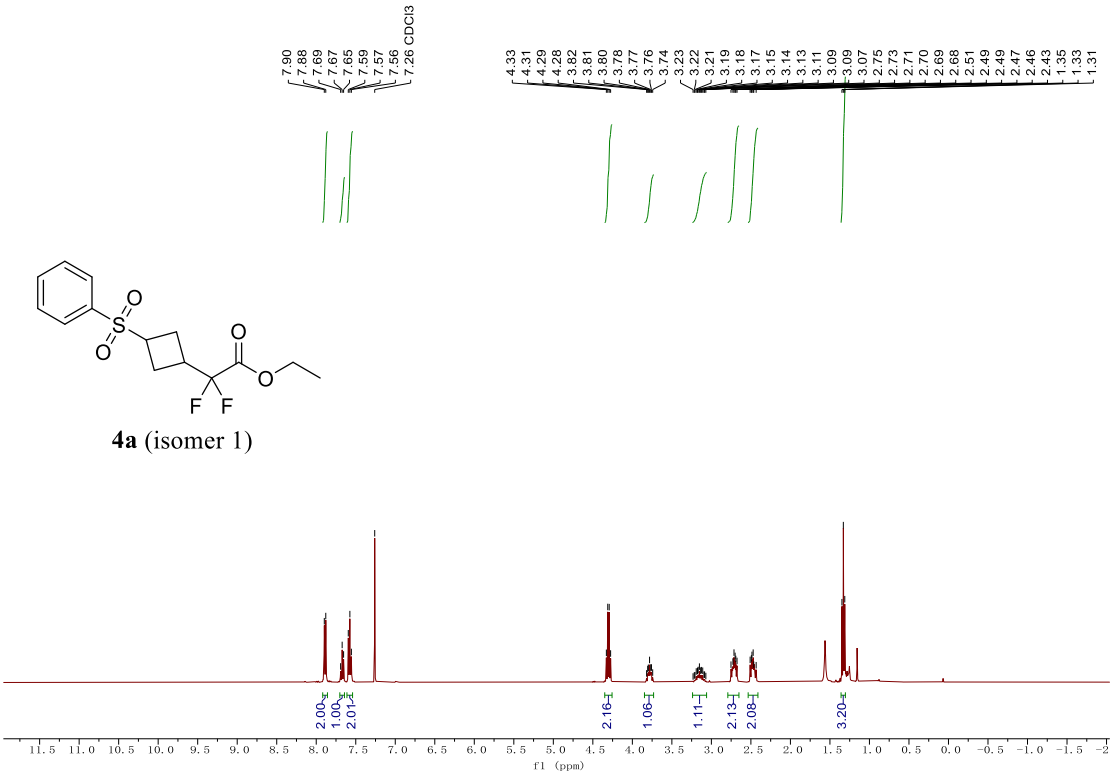


^{19}F NMR Spectrum of Compound **3w** (282 MHz, $CDCl_3$)



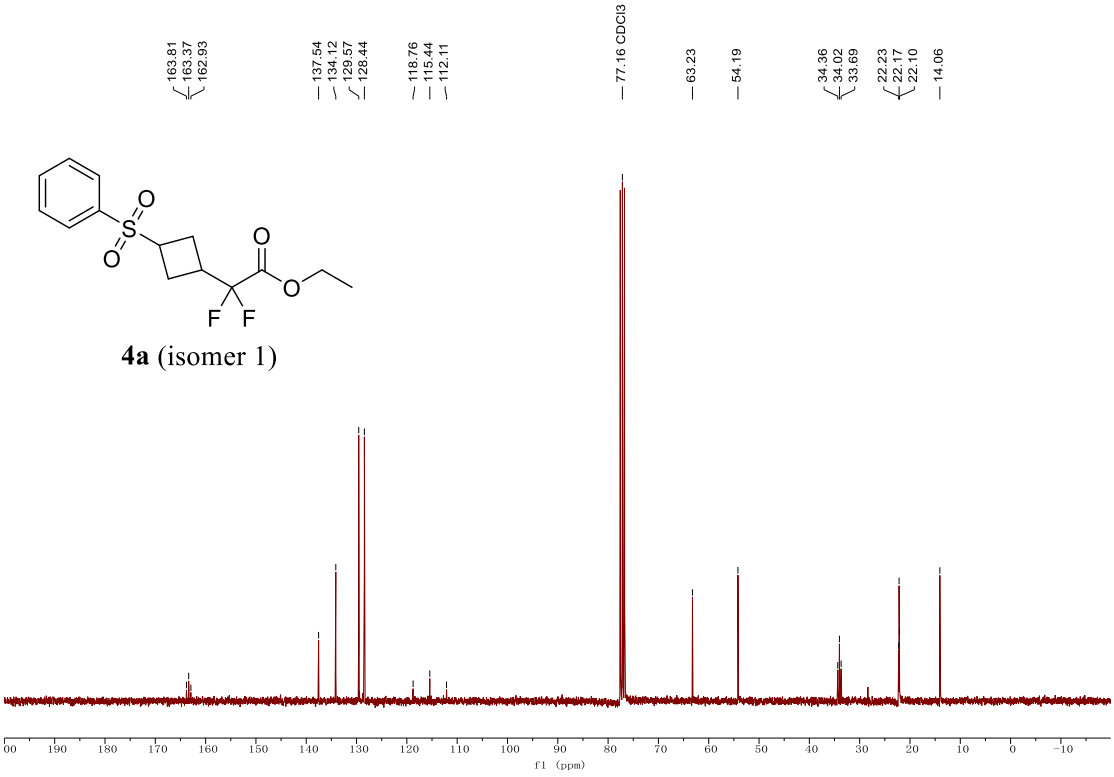
3w

^{1}H NMR Spectrum of Compound **4a** (isomer 1) (400 MHz, $CDCl_3$)



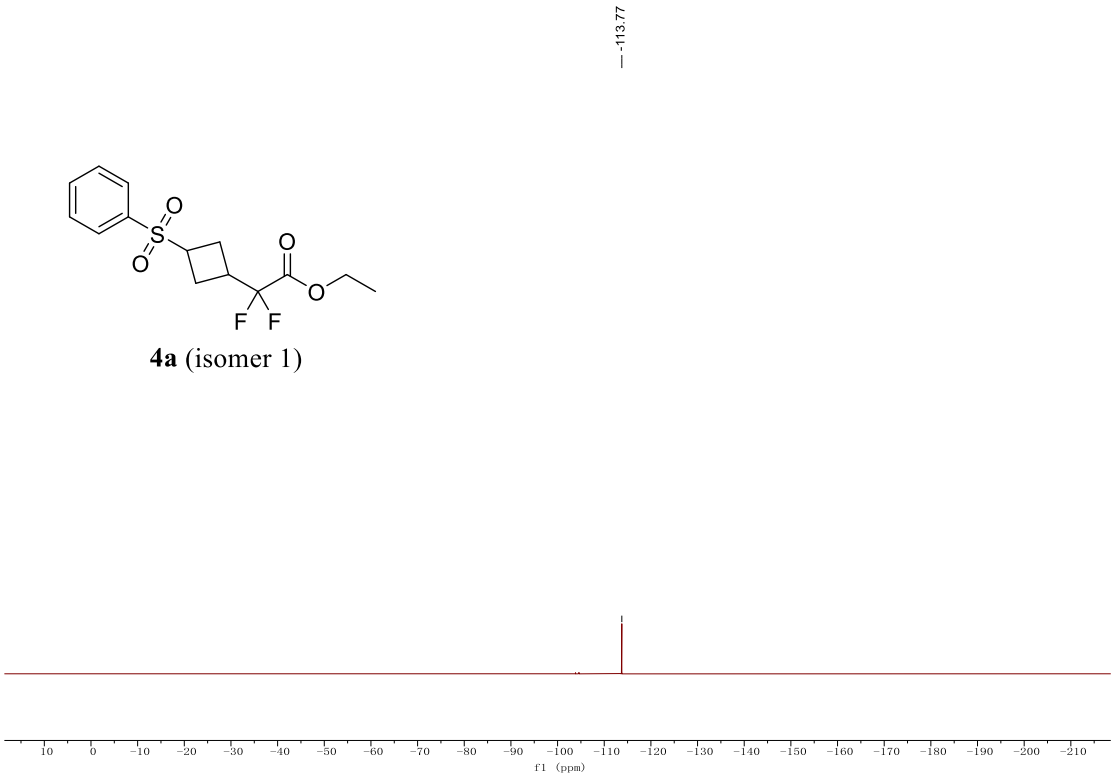
4a (isomer 1)

^{13}C NMR Spectrum of Compound **4a** (isomer 1) (75 MHz, $CDCl_3$)



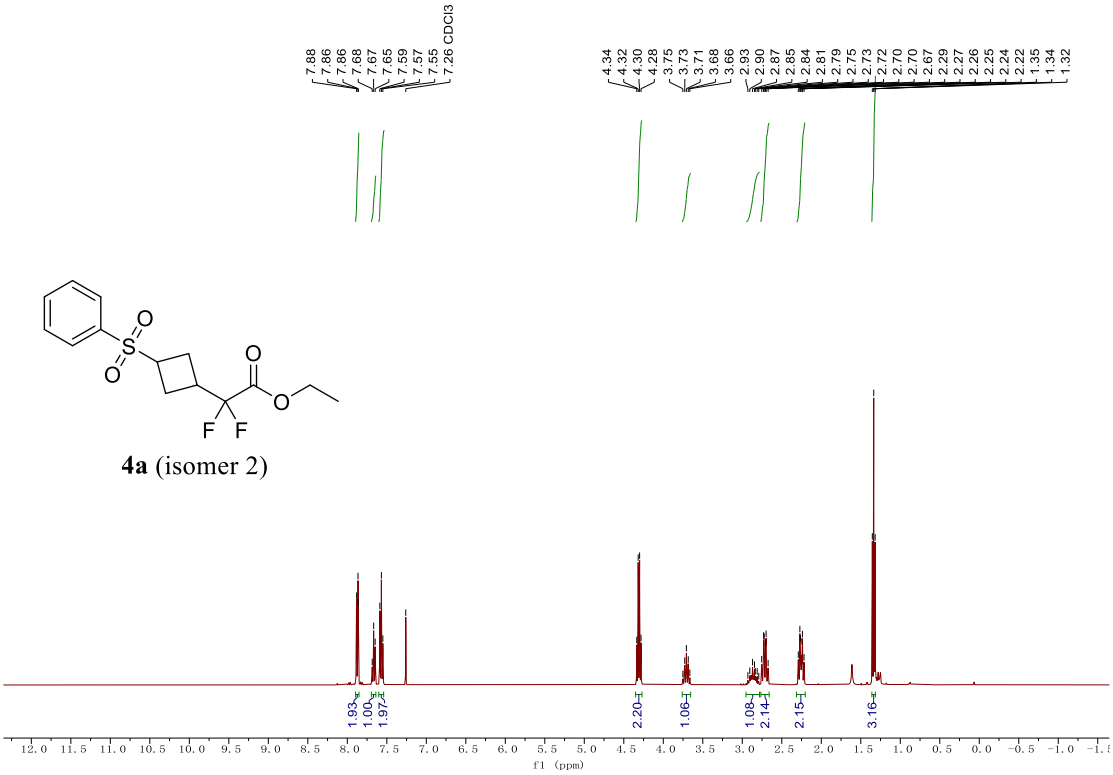
4a (isomer 1)

^{19}F NMR Spectrum of Compound **4a** (isomer 1) (282 MHz, $CDCl_3$)



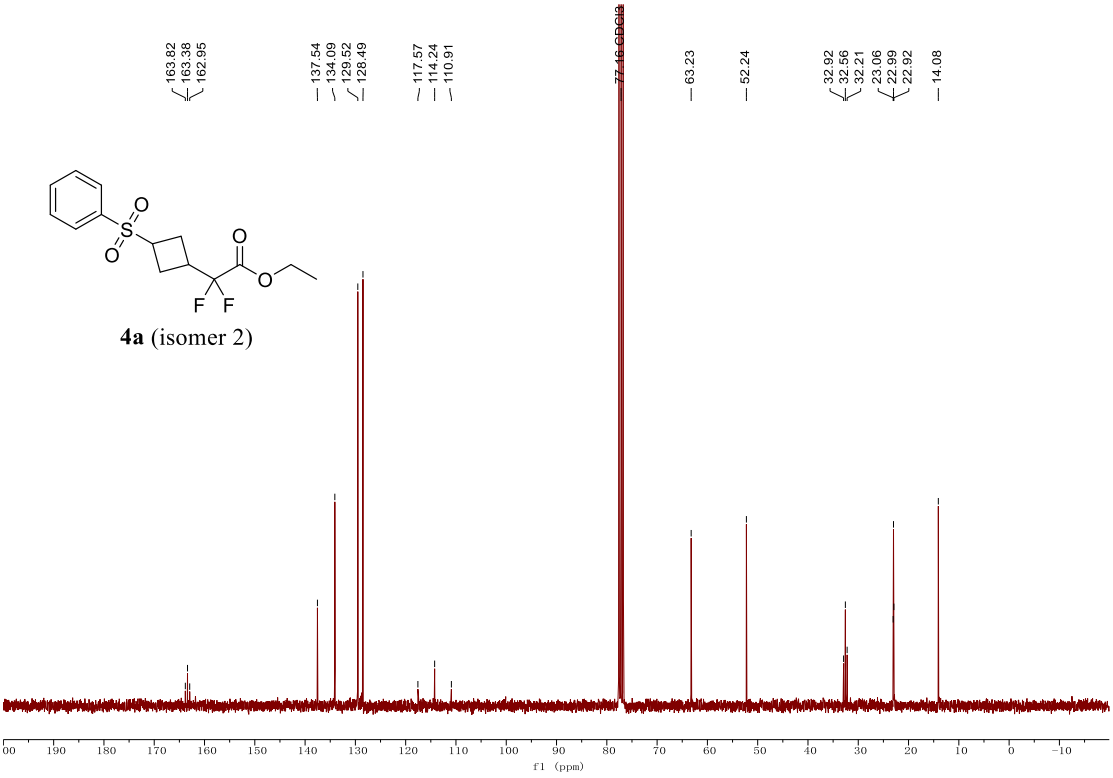
4a (isomer 1)

^{1}H NMR Spectrum of Compound **4a** (isomer 2) (400 MHz, $CDCl_3$)



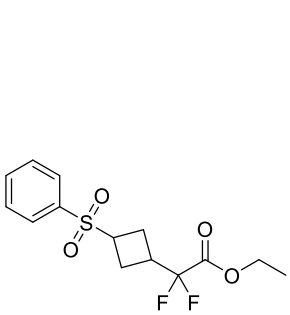
4a (isomer 2)

^{13}C NMR Spectrum of Compound **4a** (isomer 2) (75 MHz, $CDCl_3$)



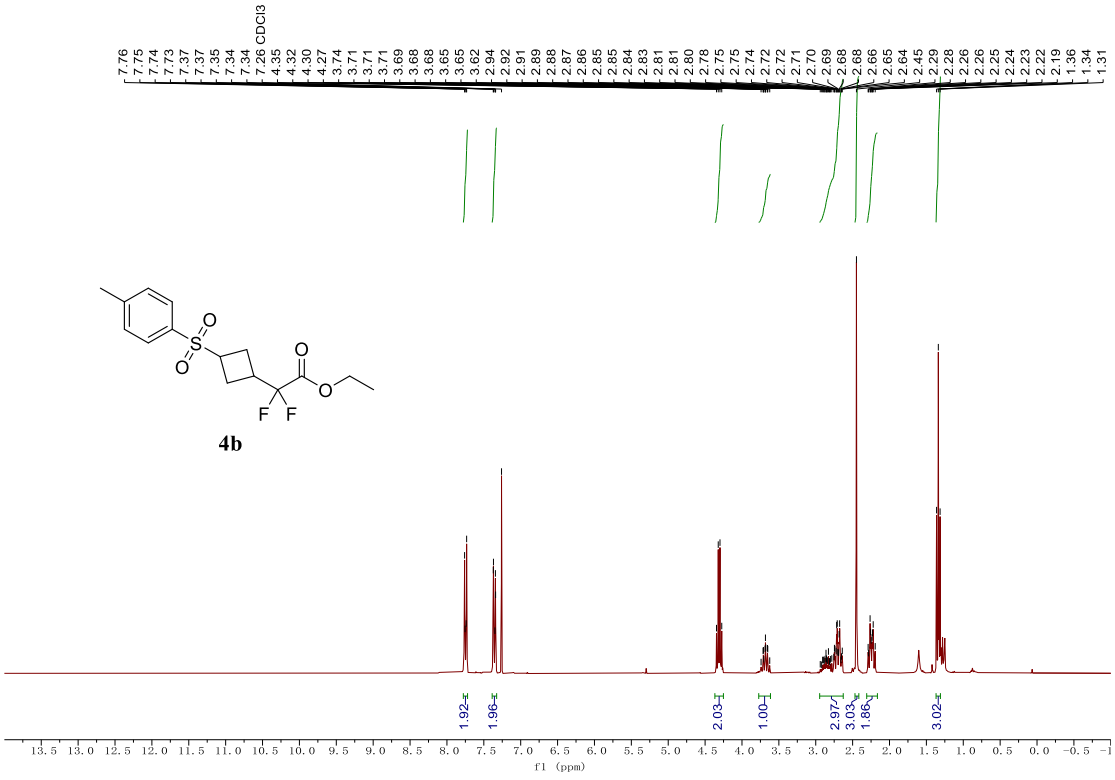
4a (isomer 2)

^{19}F NMR Spectrum of Compound **4a** (isomer 2) (282 MHz, $CDCl_3$)



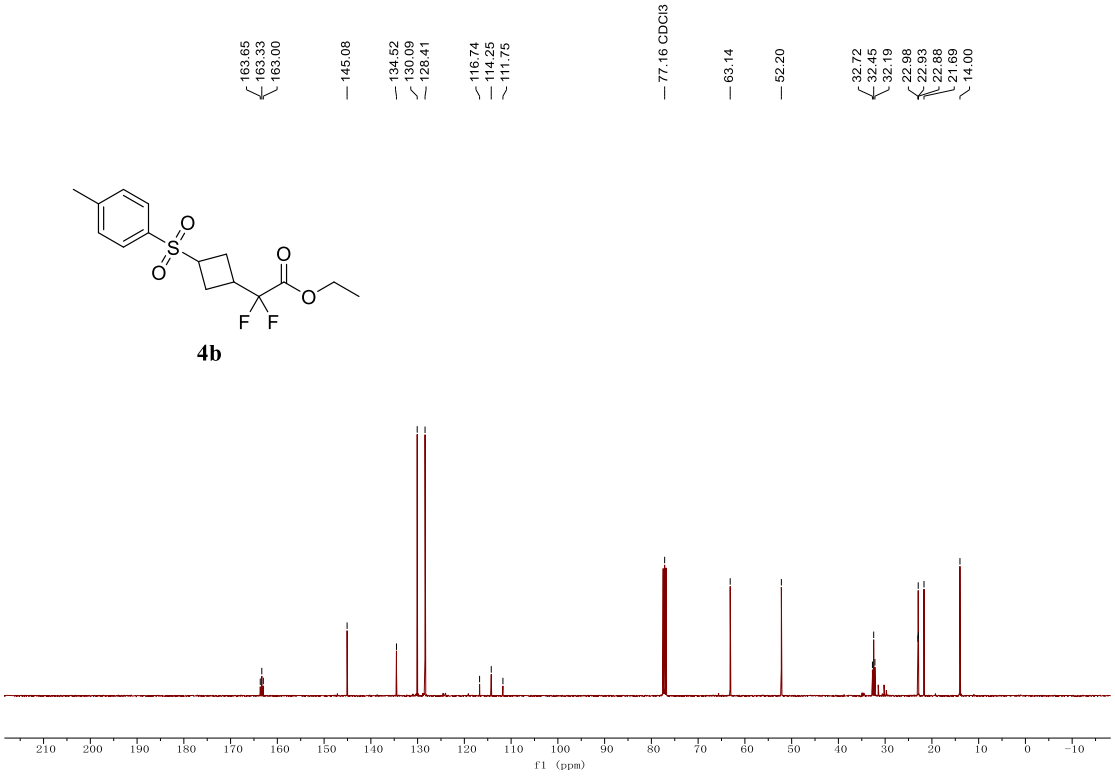
4a (isomer 2)

^{1}H NMR Spectrum of Compound **4b** (300 MHz, $CDCl_3$)

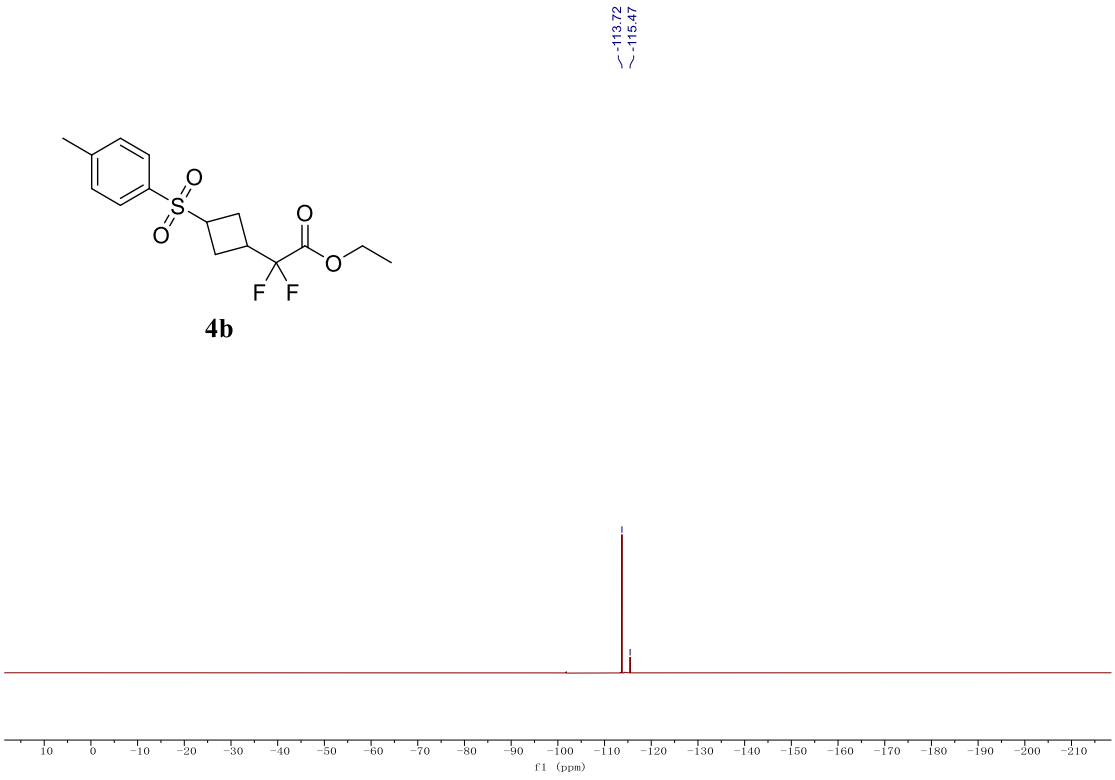


4b

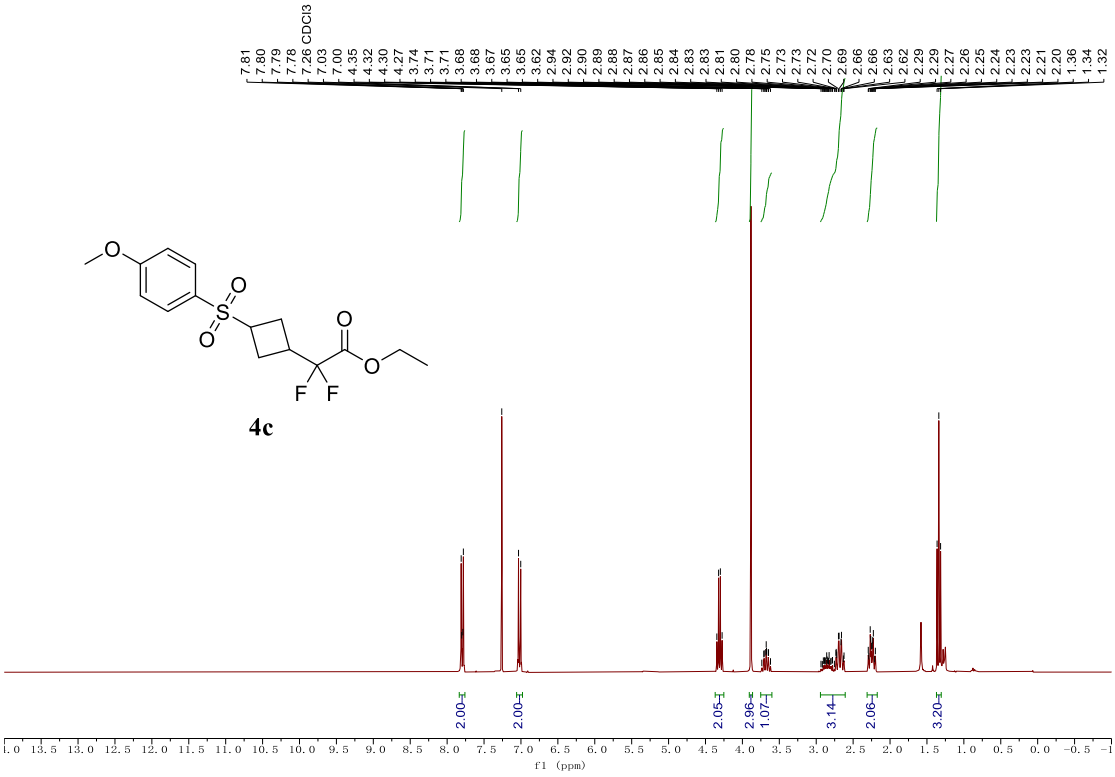
^{13}C NMR Spectrum of Compound **4b** (101 MHz, $CDCl_3$)



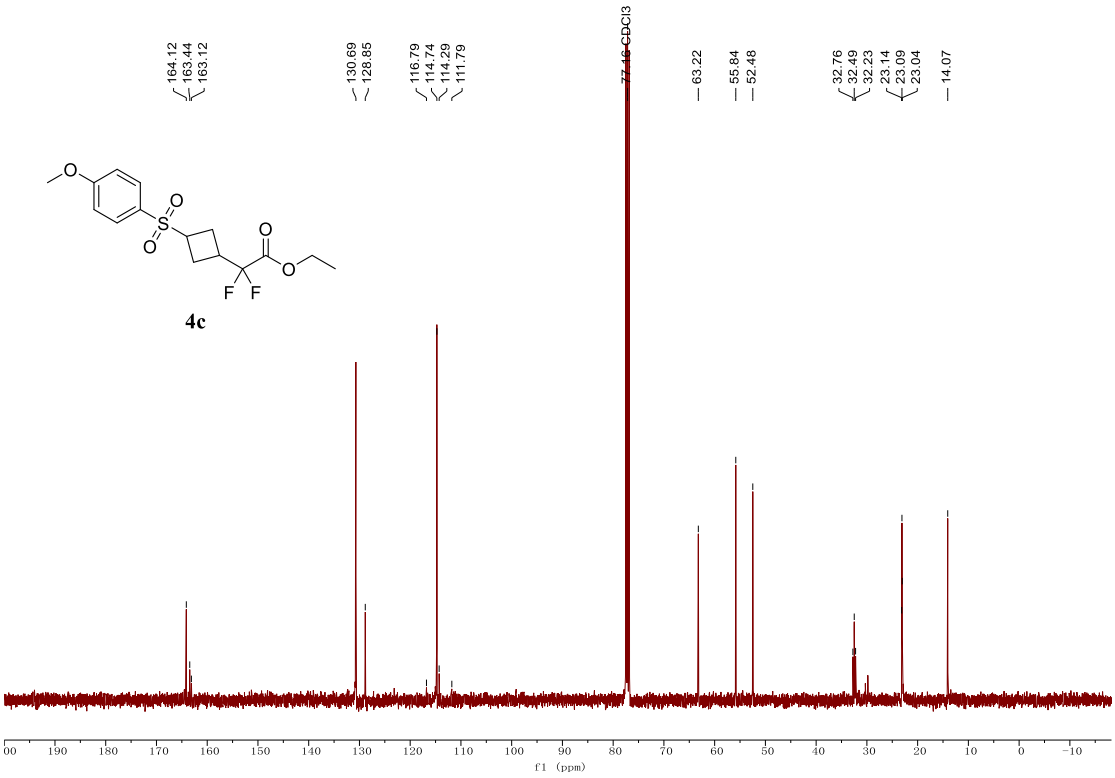
^{19}F NMR Spectrum of Compound **4b** (282 MHz, $CDCl_3$)



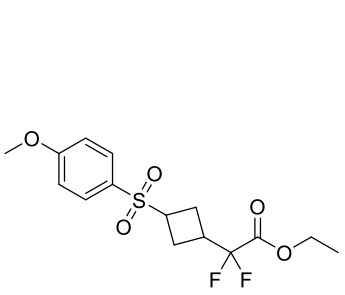
^{1}H NMR Spectrum of Compound **4c** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **4c** (101 MHz, $CDCl_3$)

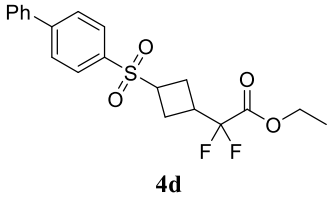


^{19}F NMR Spectrum of Compound **4c** (282 MHz, $CDCl_3$)



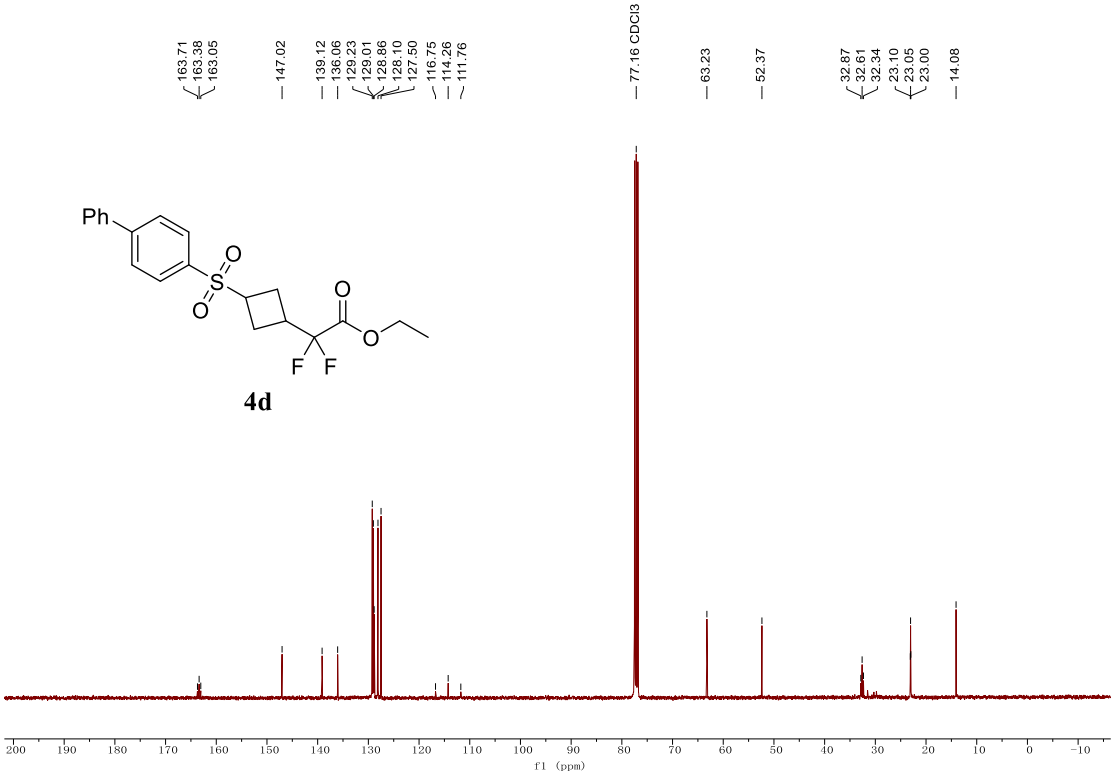
4c

^{1}H NMR Spectrum of Compound **4d** (300 MHz, $CDCl_3$)

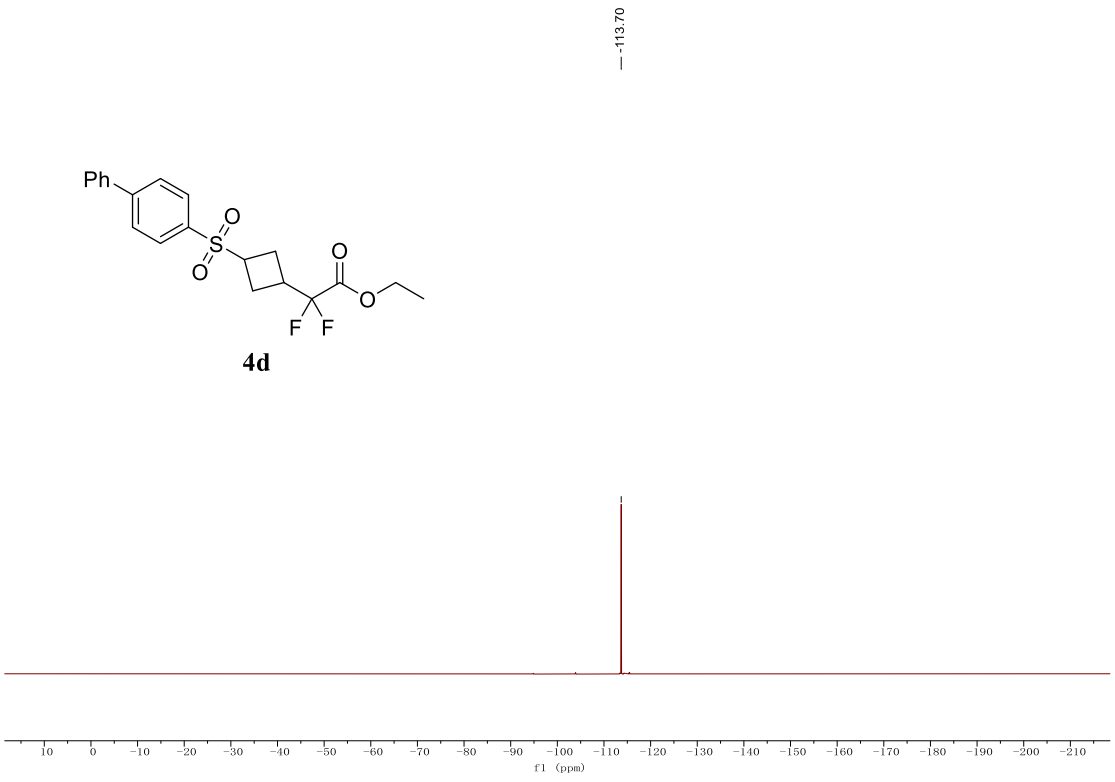


4d

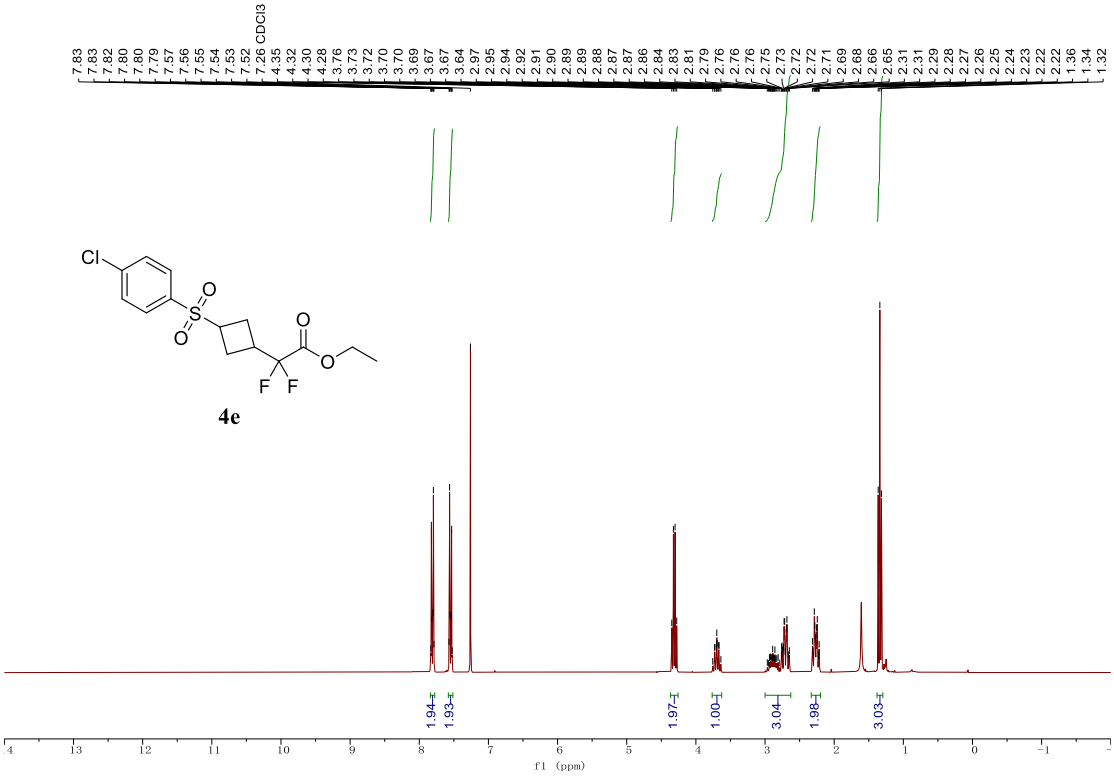
^{13}C NMR Spectrum of Compound **4d** (101 MHz, $CDCl_3$)



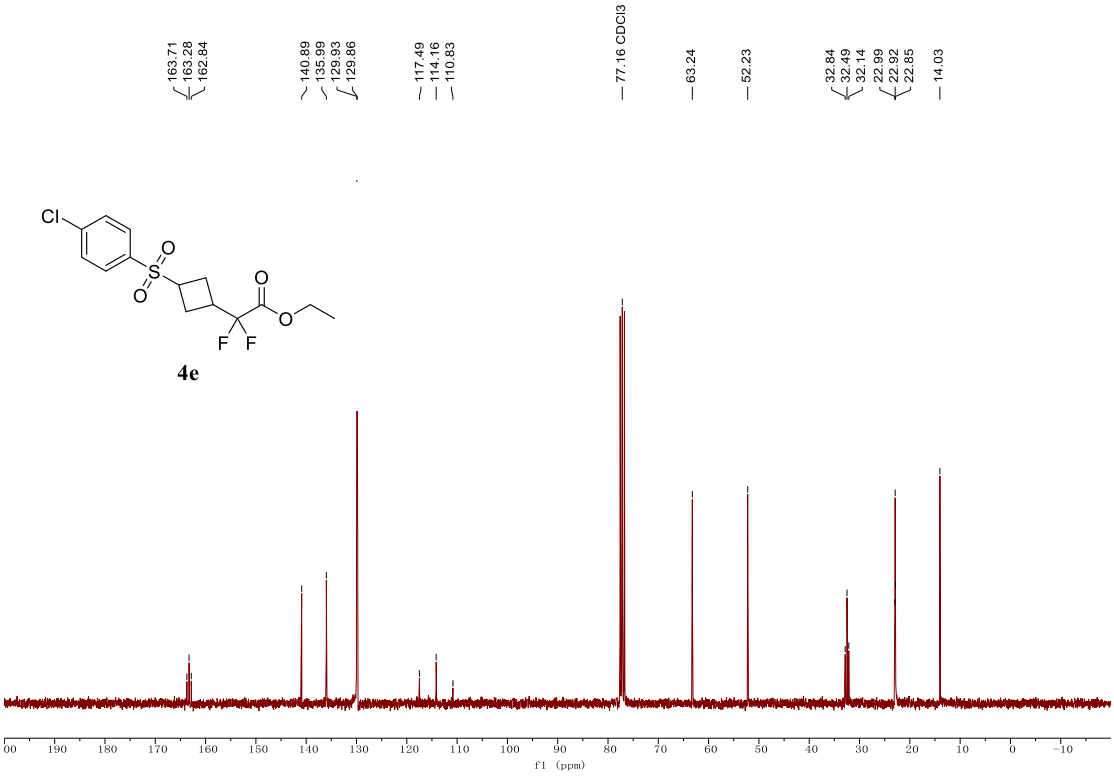
^{19}F NMR Spectrum of Compound **4d** (282 MHz, $CDCl_3$)



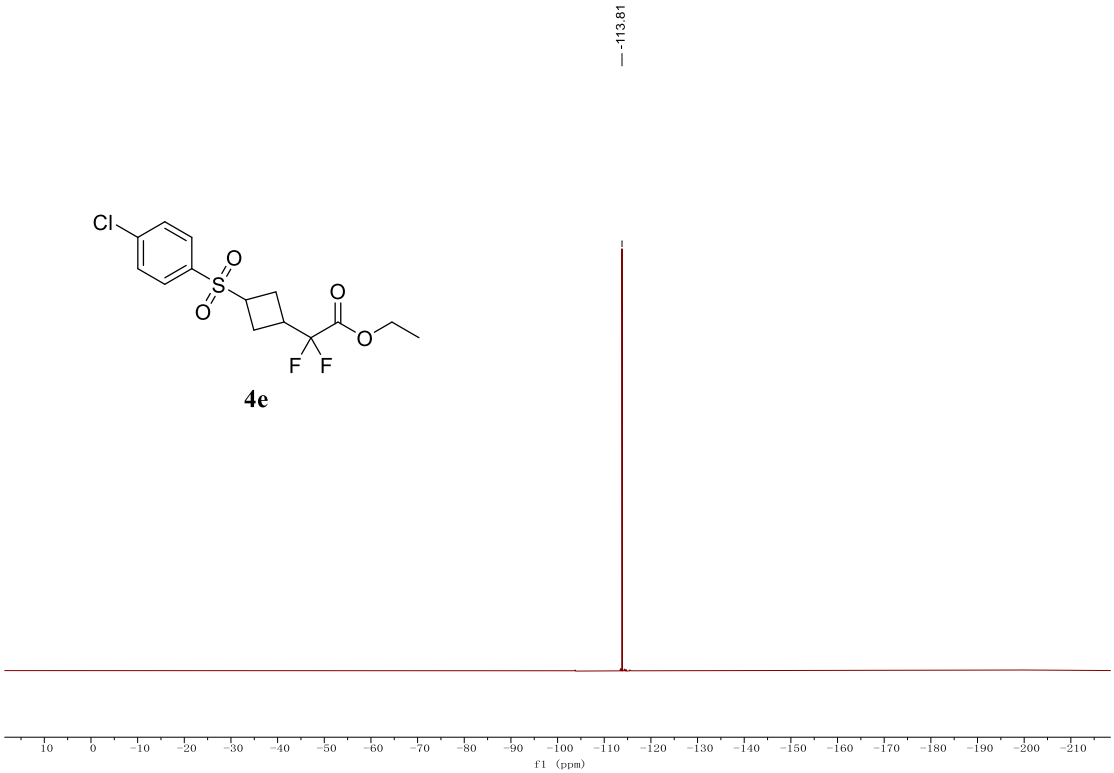
^{1}H NMR Spectrum of Compound **4e** (300 MHz, $CDCl_3$)



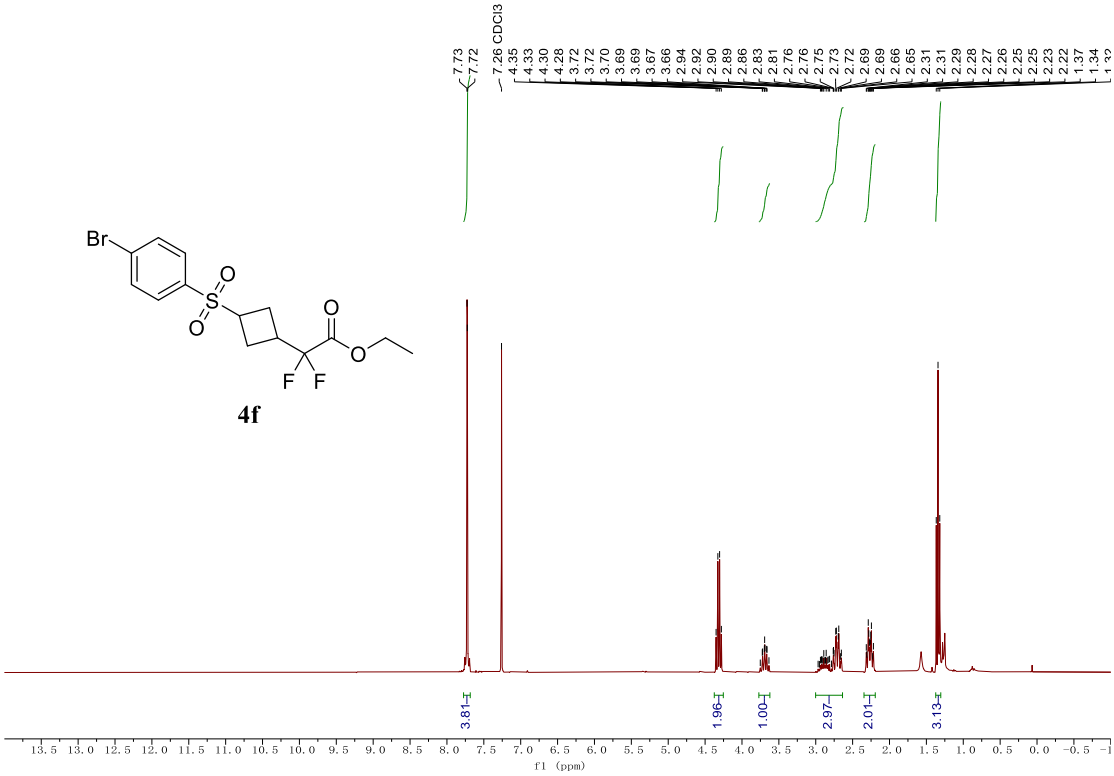
^{13}C NMR Spectrum of Compound **4e** (75 MHz, $CDCl_3$)



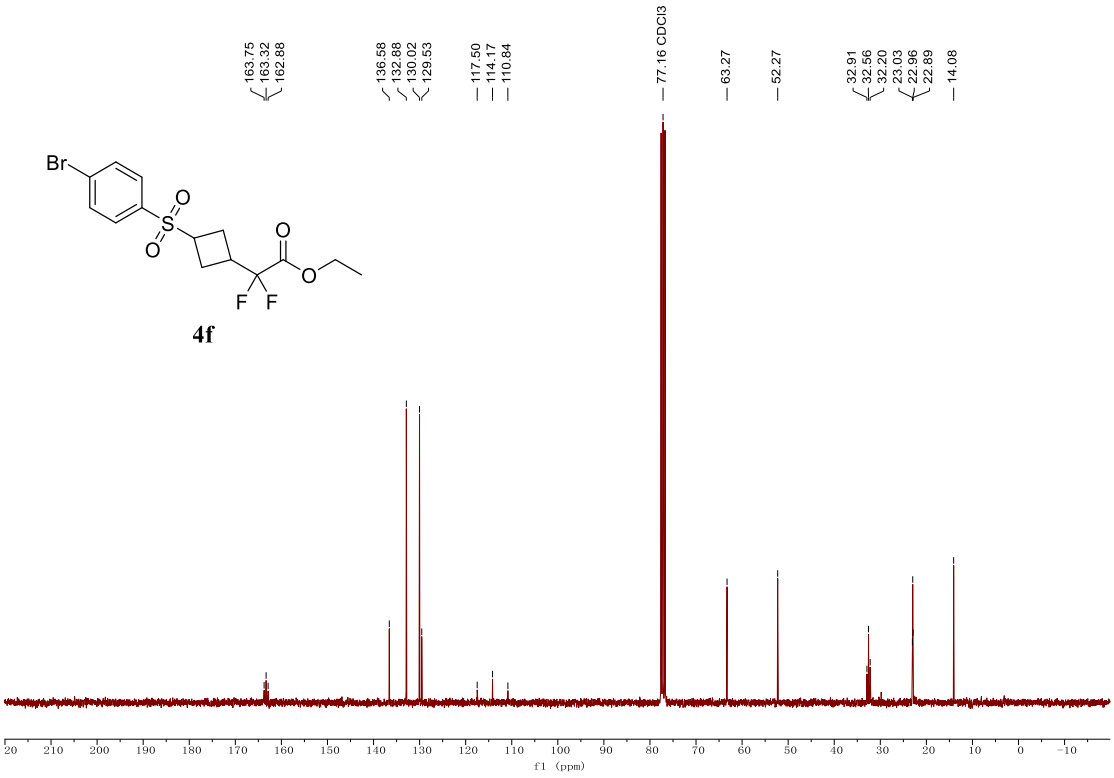
^{19}F NMR Spectrum of Compound **4e** (282 MHz, $CDCl_3$)



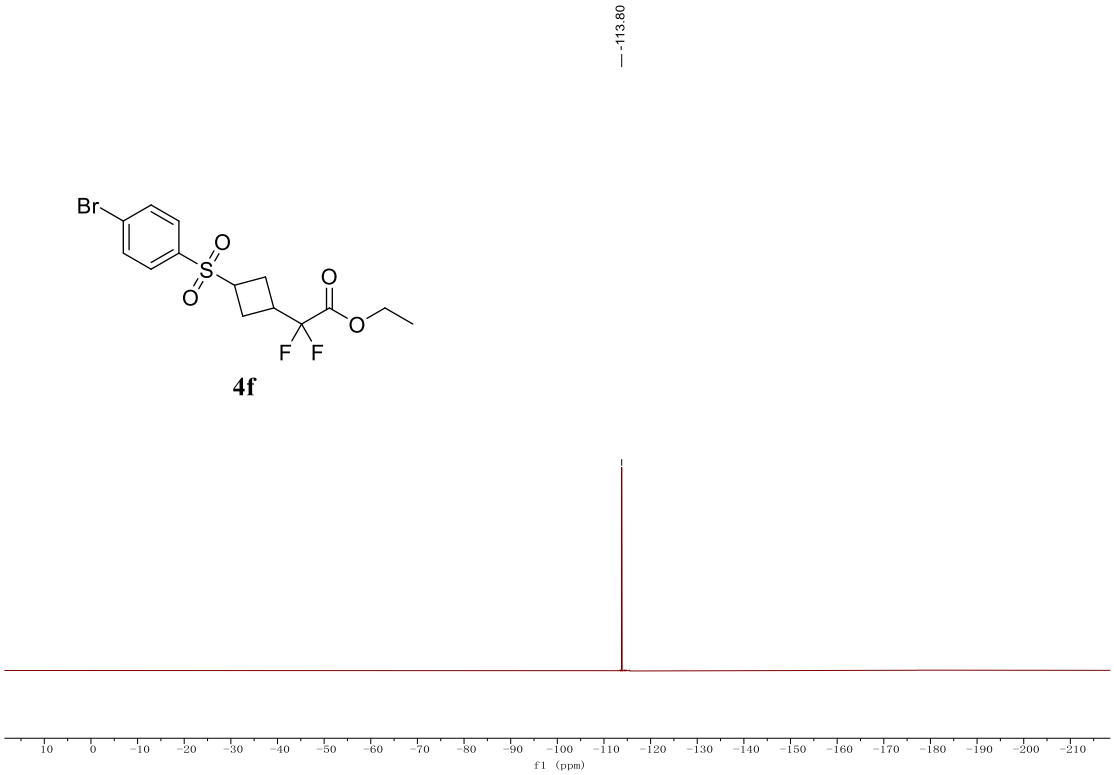
^{1}H NMR Spectrum of Compound **4f** (300 MHz, $CDCl_3$)



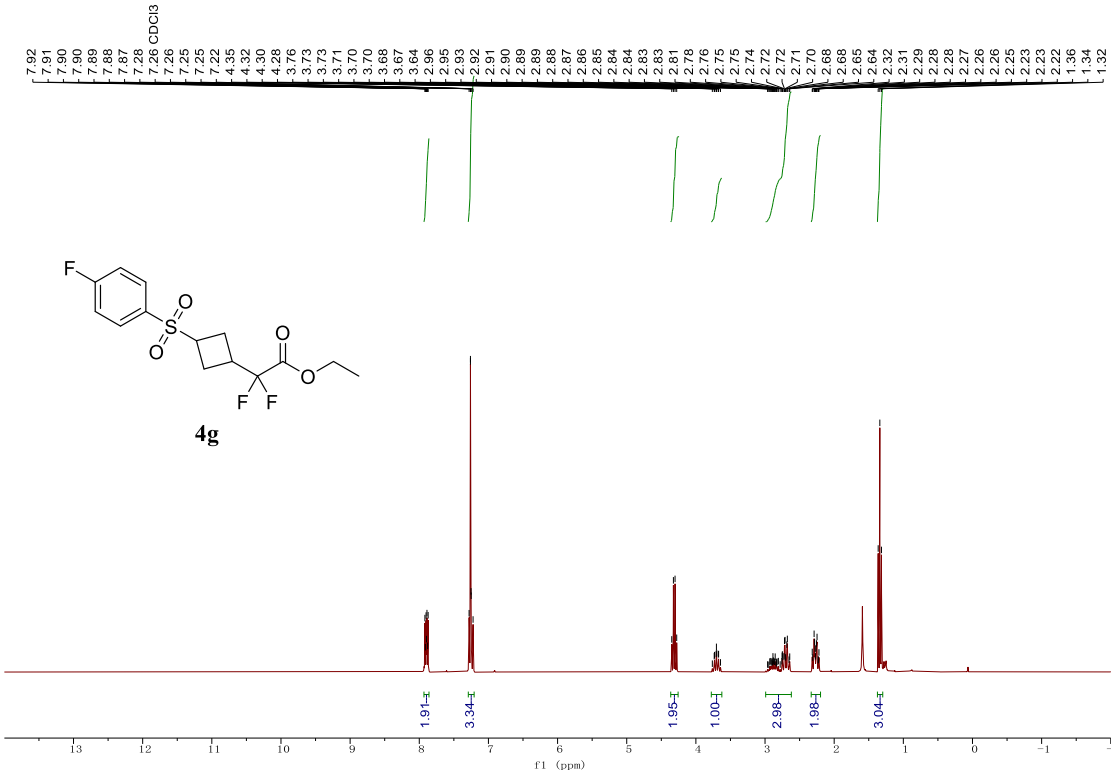
^{13}C NMR Spectrum of Compound **4f** (75 MHz, $CDCl_3$)



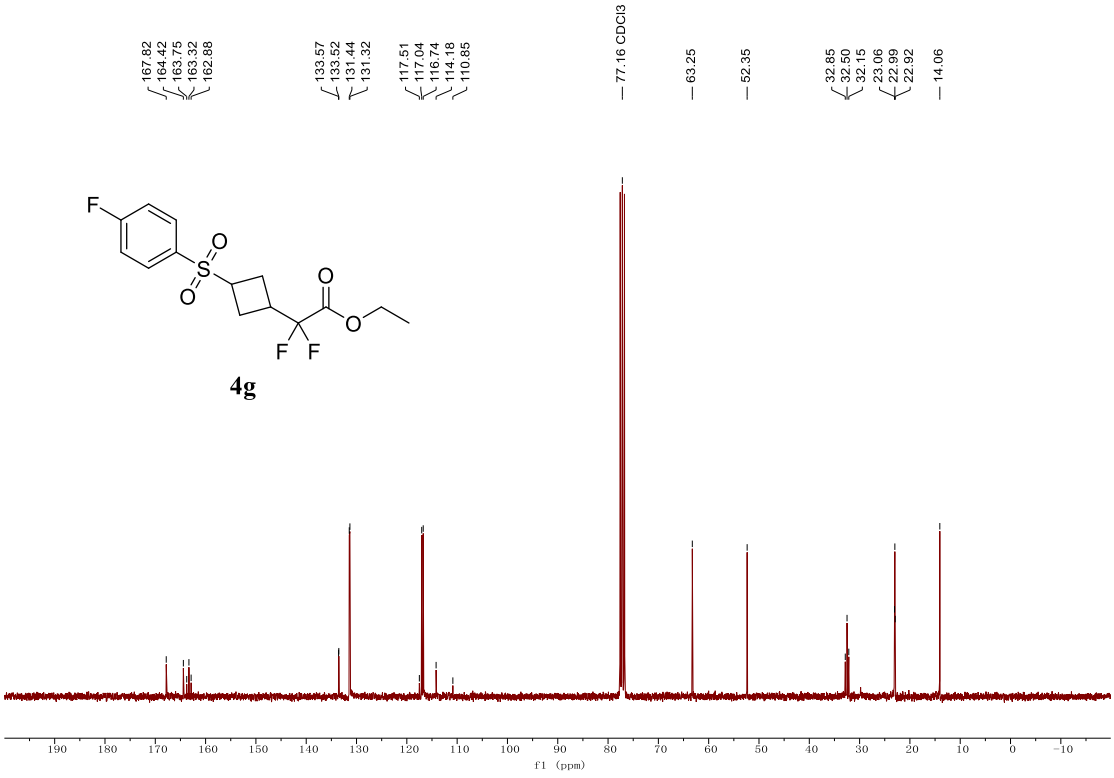
^{19}F NMR Spectrum of Compound **4f** (282 MHz, $CDCl_3$)



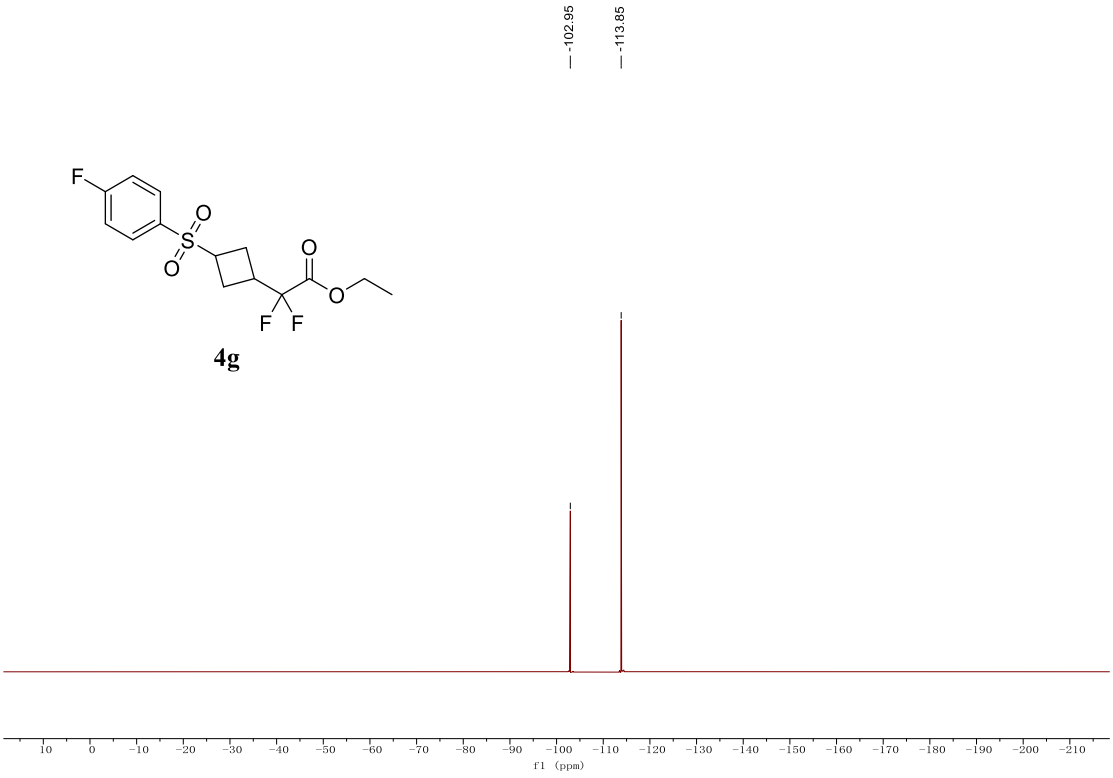
^{1}H NMR Spectrum of Compound **4g** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **4g** (75 MHz, $CDCl_3$)

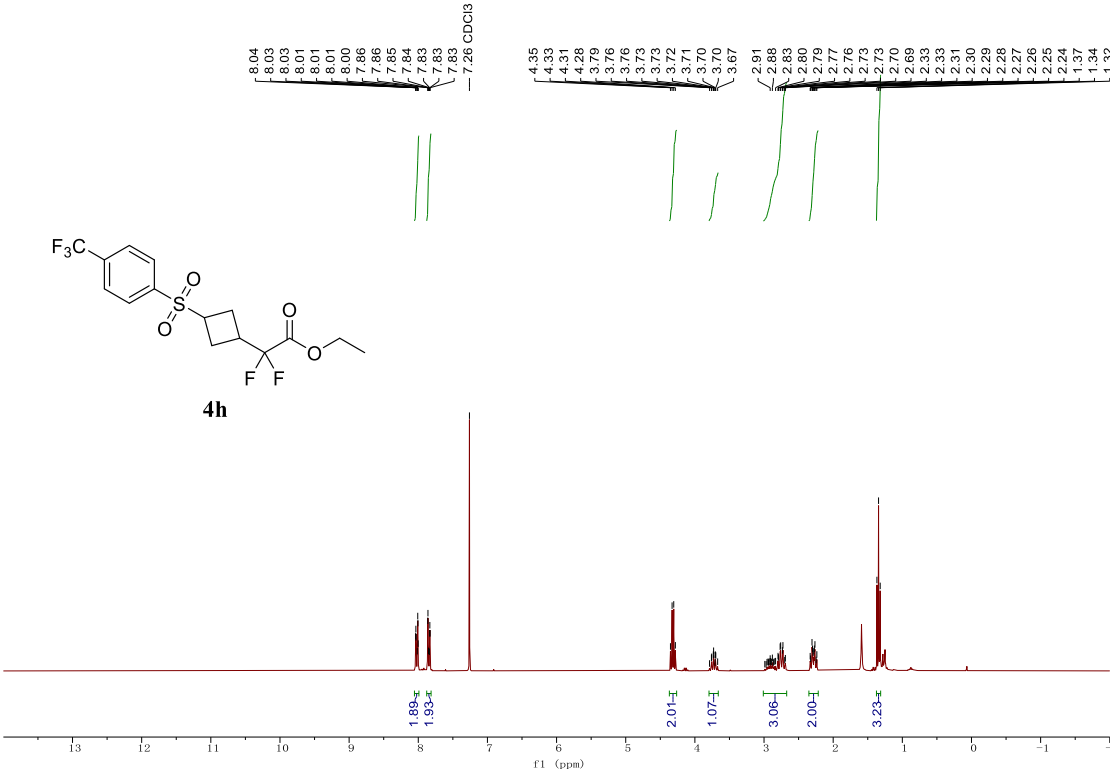


^{19}F NMR Spectrum of Compound **4g** (282 MHz, $CDCl_3$)



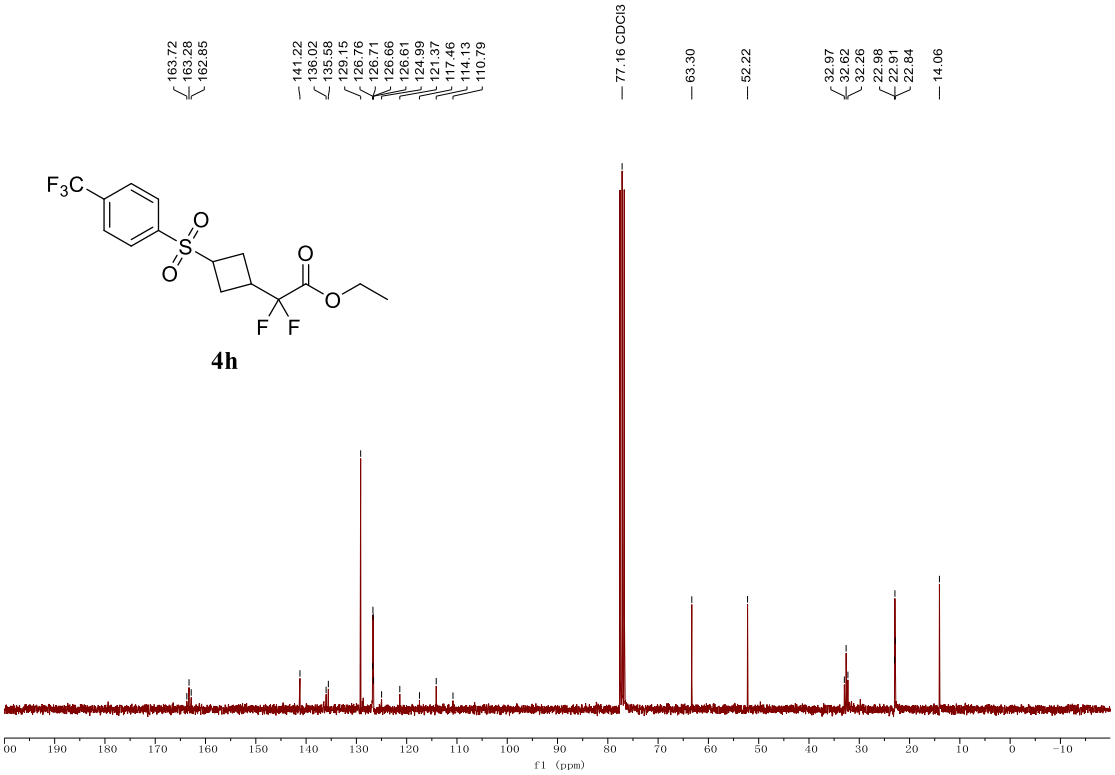
4g

^{1}H NMR Spectrum of Compound **4h** (300 MHz, $CDCl_3$)

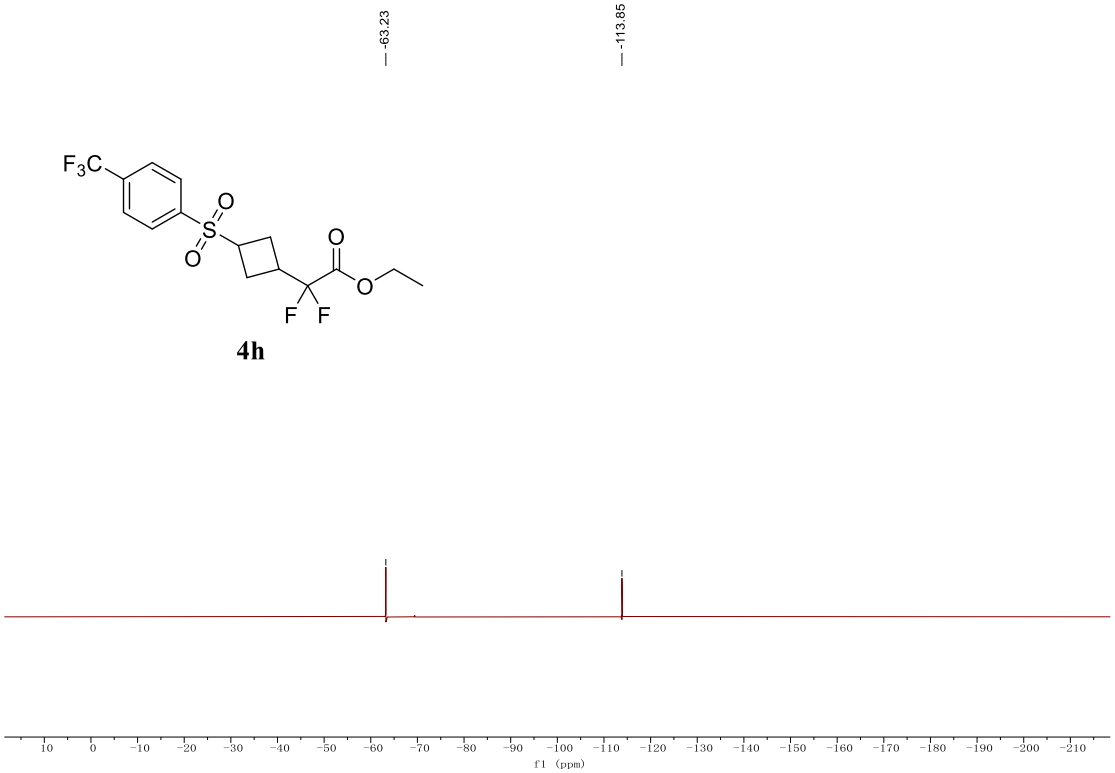


4h

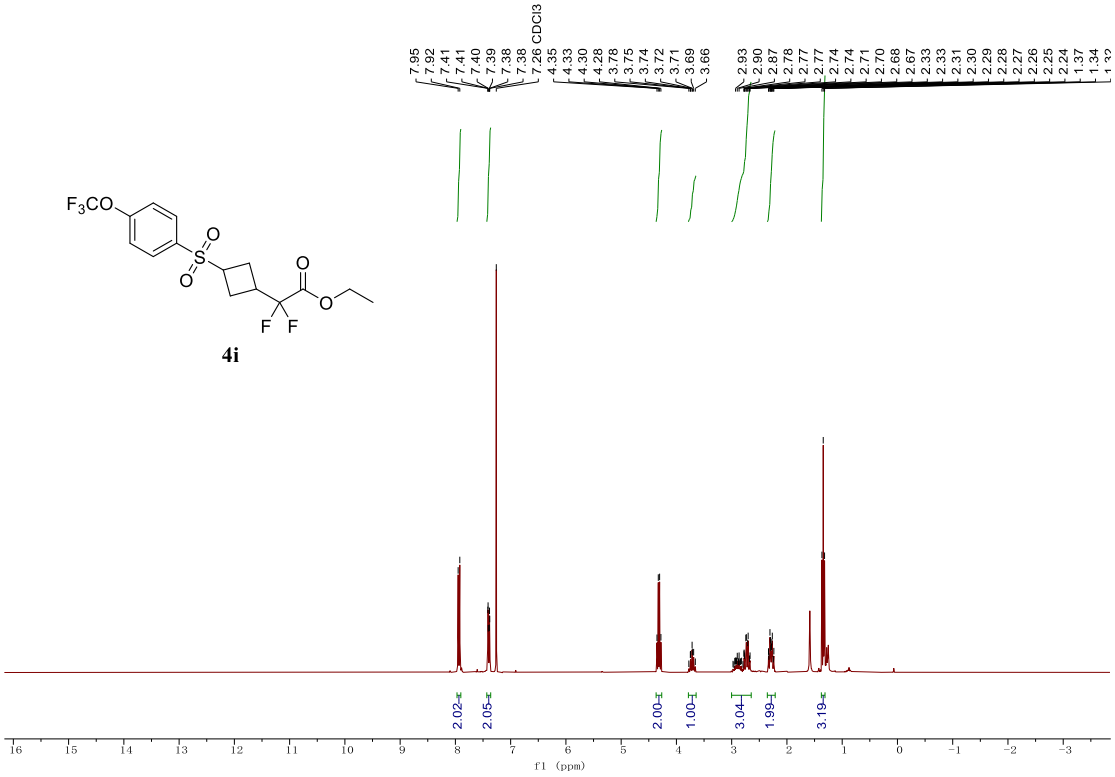
^{13}C NMR Spectrum of Compound **4h** (75 MHz, $CDCl_3$)



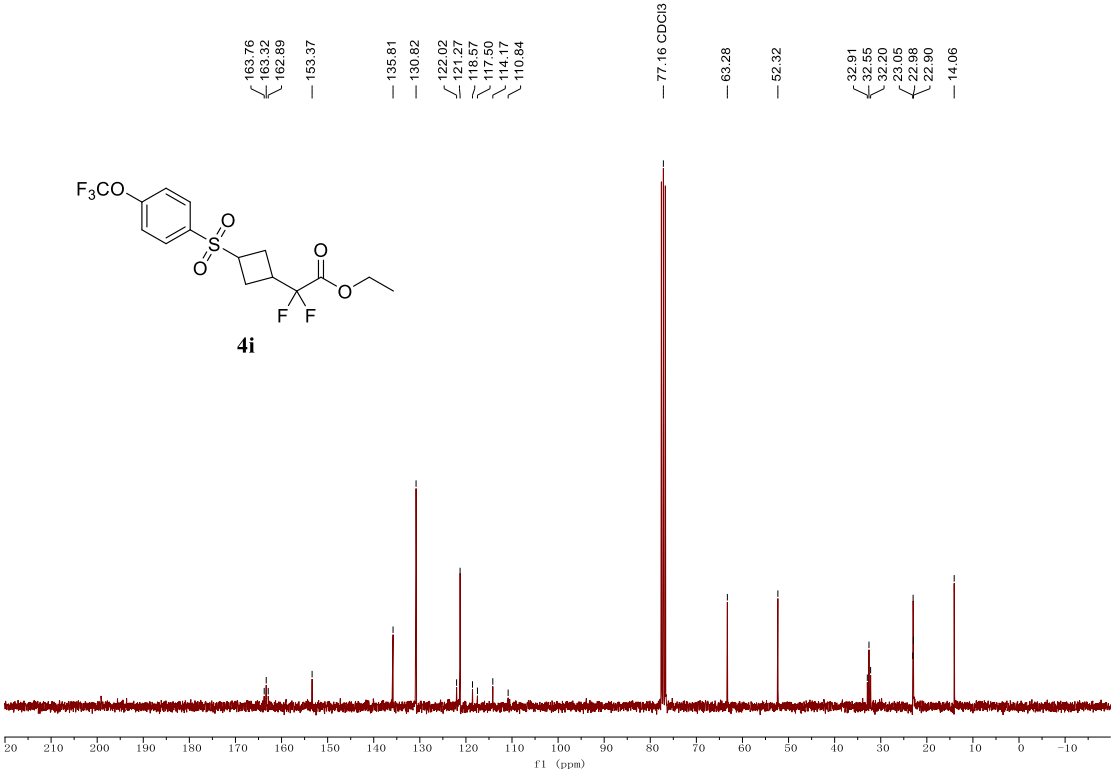
^{19}F NMR Spectrum of Compound **4h** (282 MHz, $CDCl_3$)



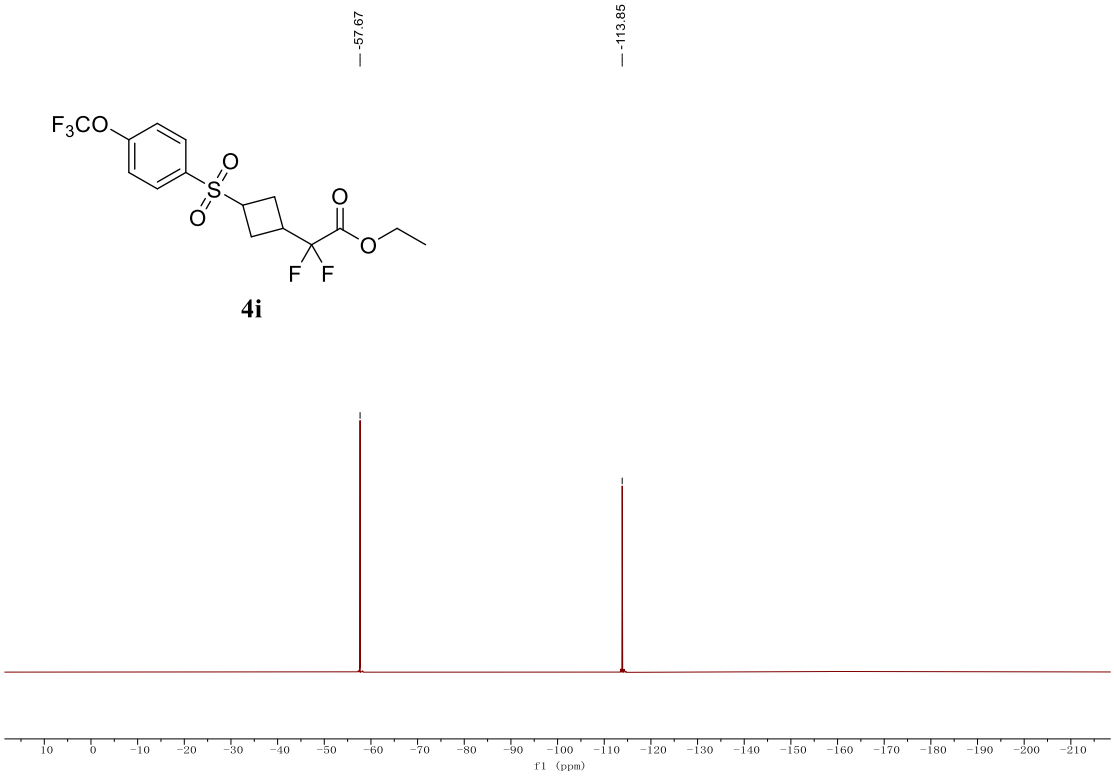
^{1}H NMR Spectrum of Compound **4i** (300 MHz, $CDCl_3$)



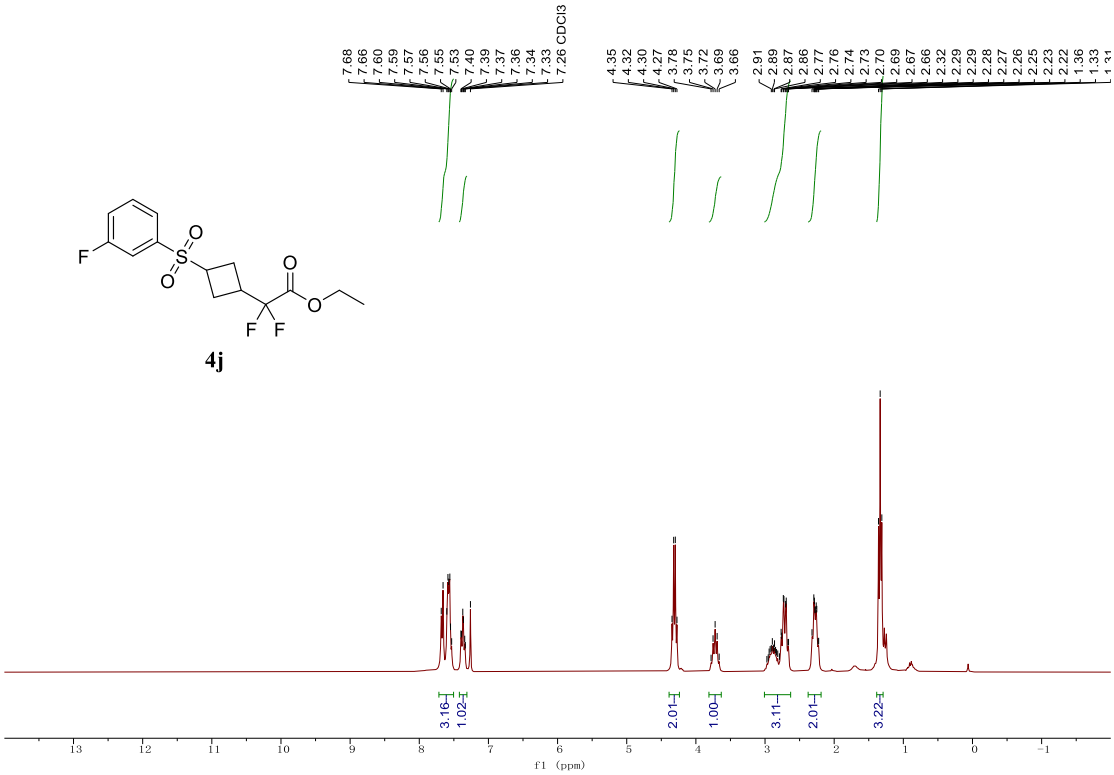
^{13}C NMR Spectrum of Compound **4i** (75 MHz, $CDCl_3$)



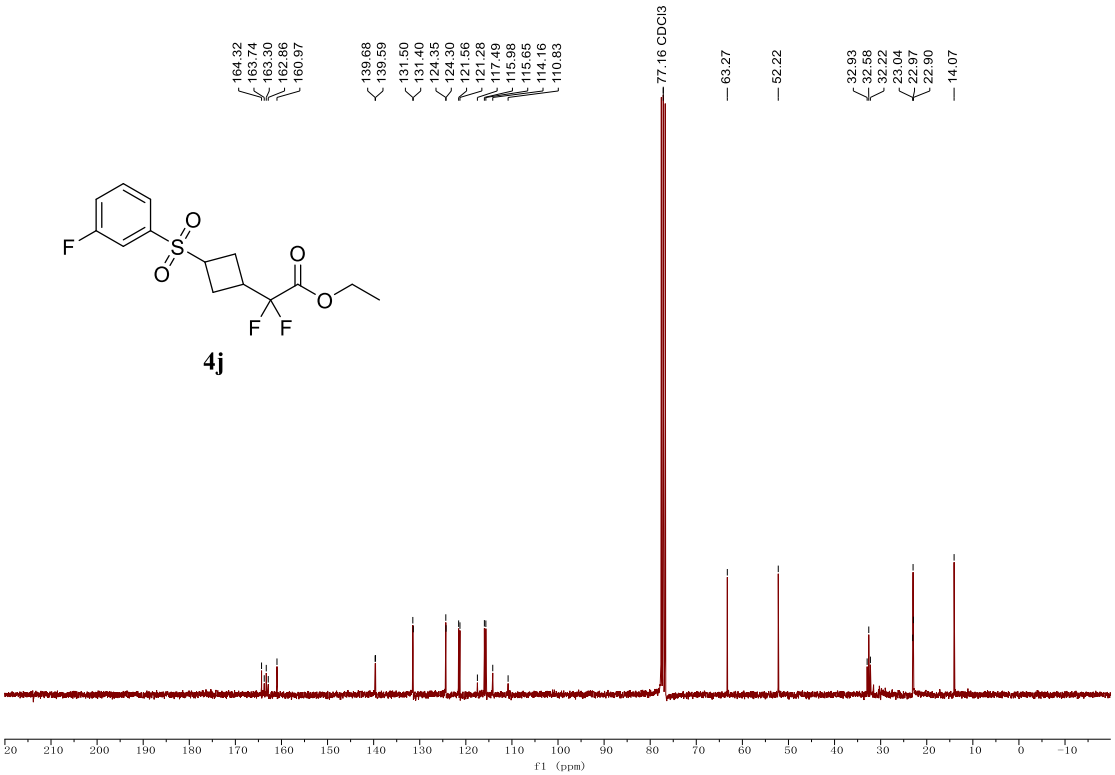
^{19}F NMR Spectrum of Compound **4i** (282 MHz, $CDCl_3$)



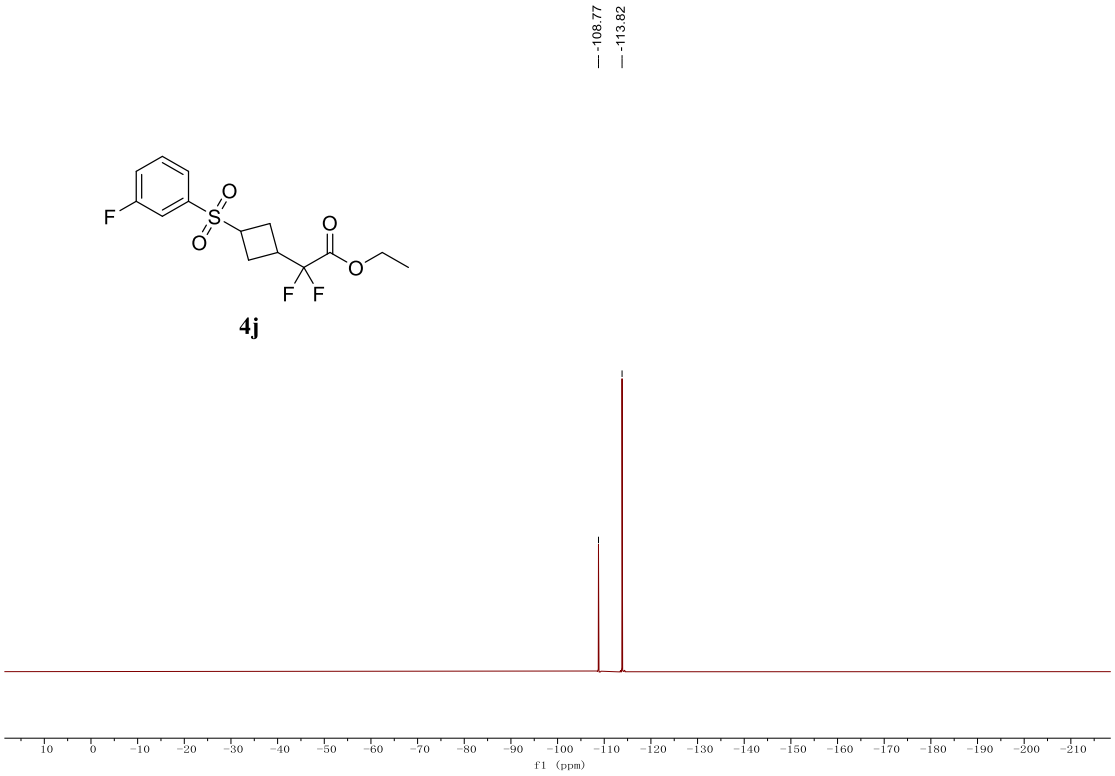
^{1}H NMR Spectrum of Compound **4j** (300 MHz, $CDCl_3$)



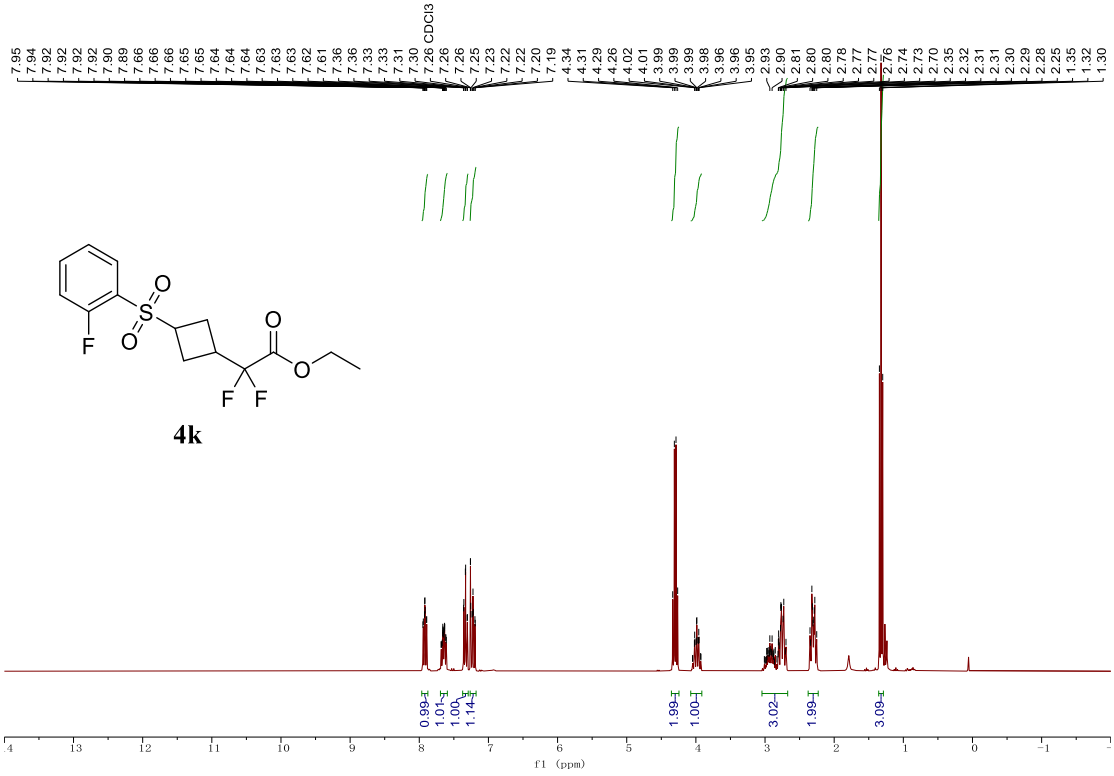
^{13}C NMR Spectrum of Compound **4j** (75 MHz, $CDCl_3$)



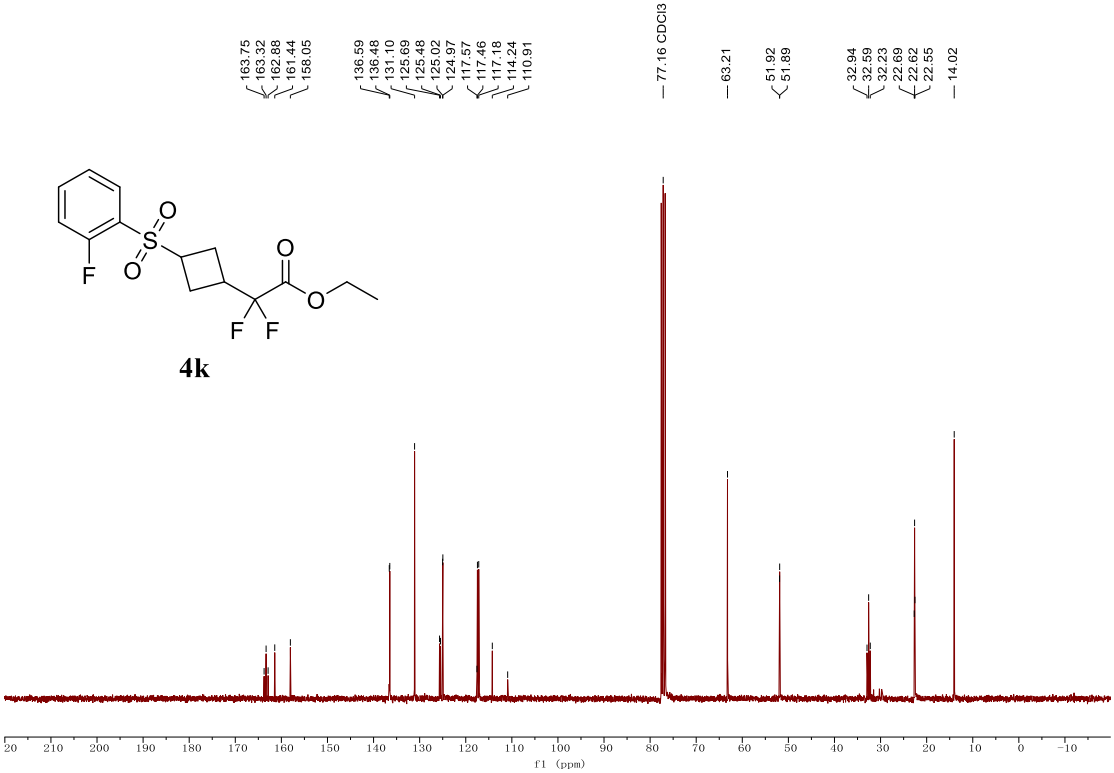
^{19}F NMR Spectrum of Compound **4j** (282 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound **4k** (300 MHz, $CDCl_3$)

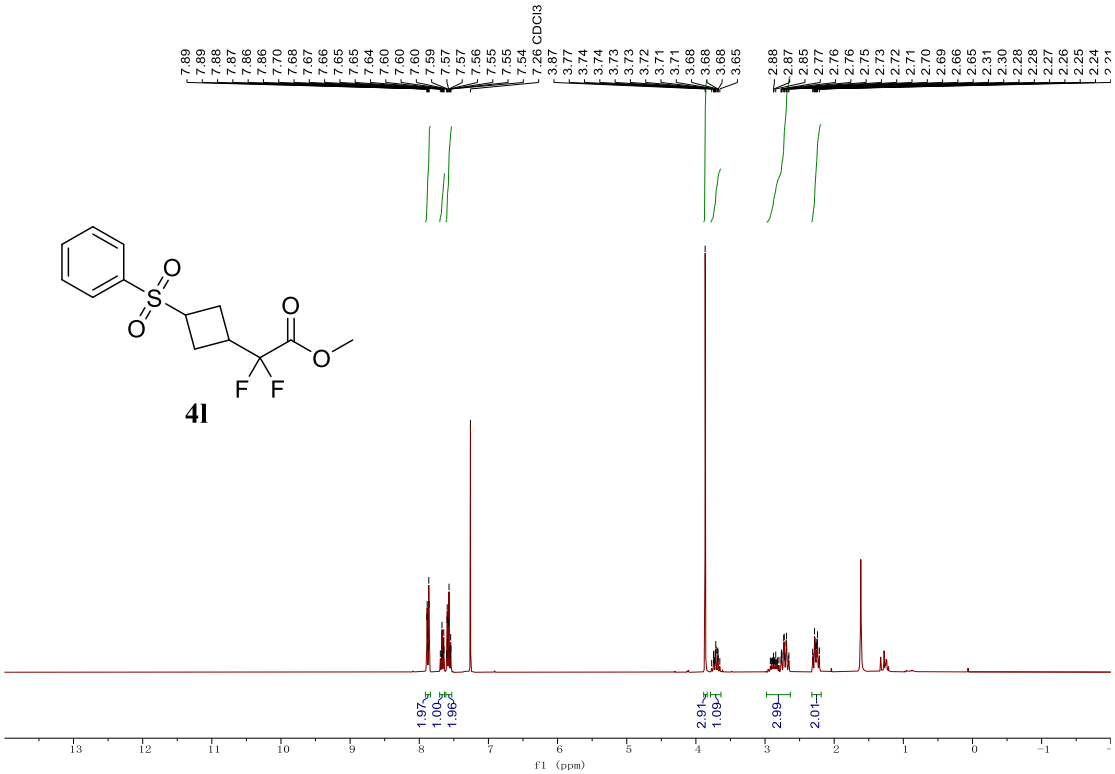


^{13}C NMR Spectrum of Compound **4k** (75 MHz, $CDCl_3$)

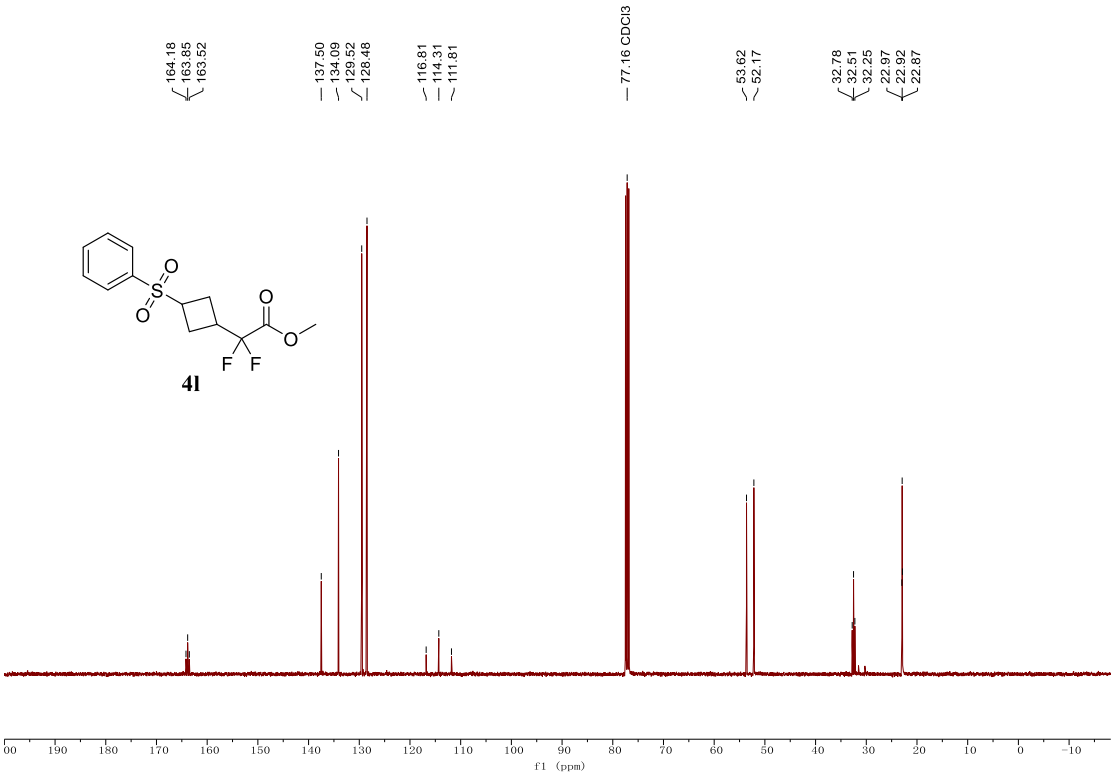


^{19}F NMR Spectrum of Compound **4k** (282 MHz, $CDCl_3$)

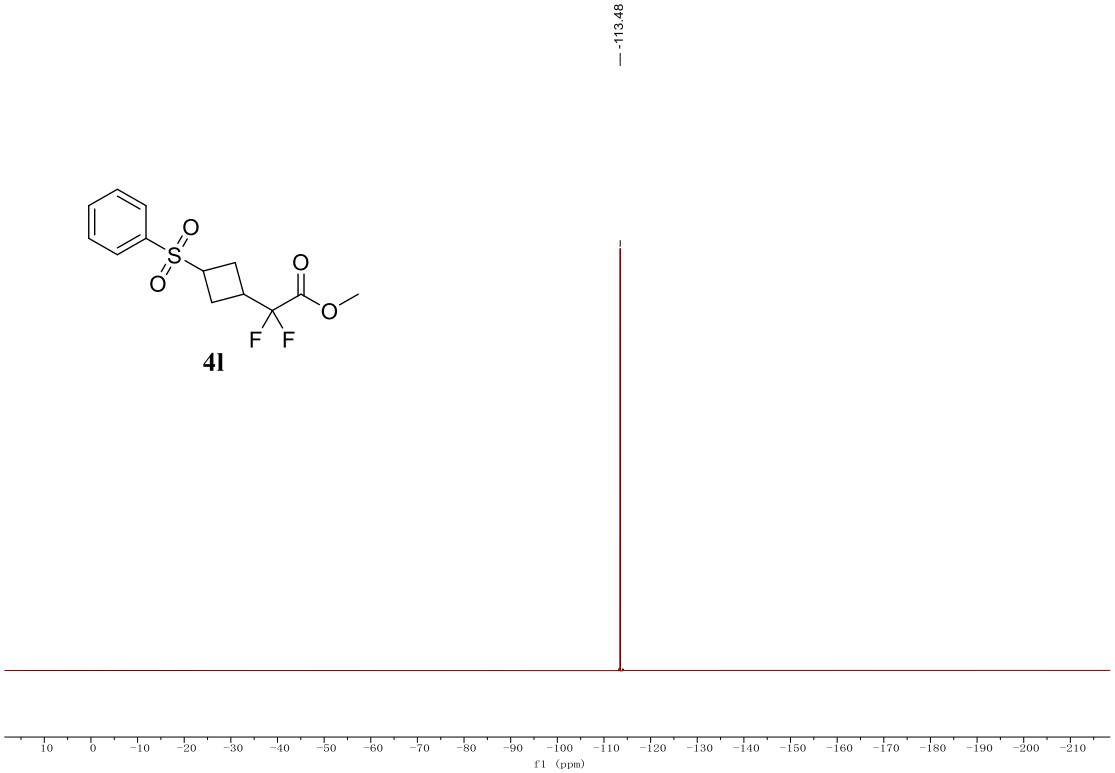
^{1}H NMR Spectrum of Compound **4l** (300 MHz, $CDCl_3$)



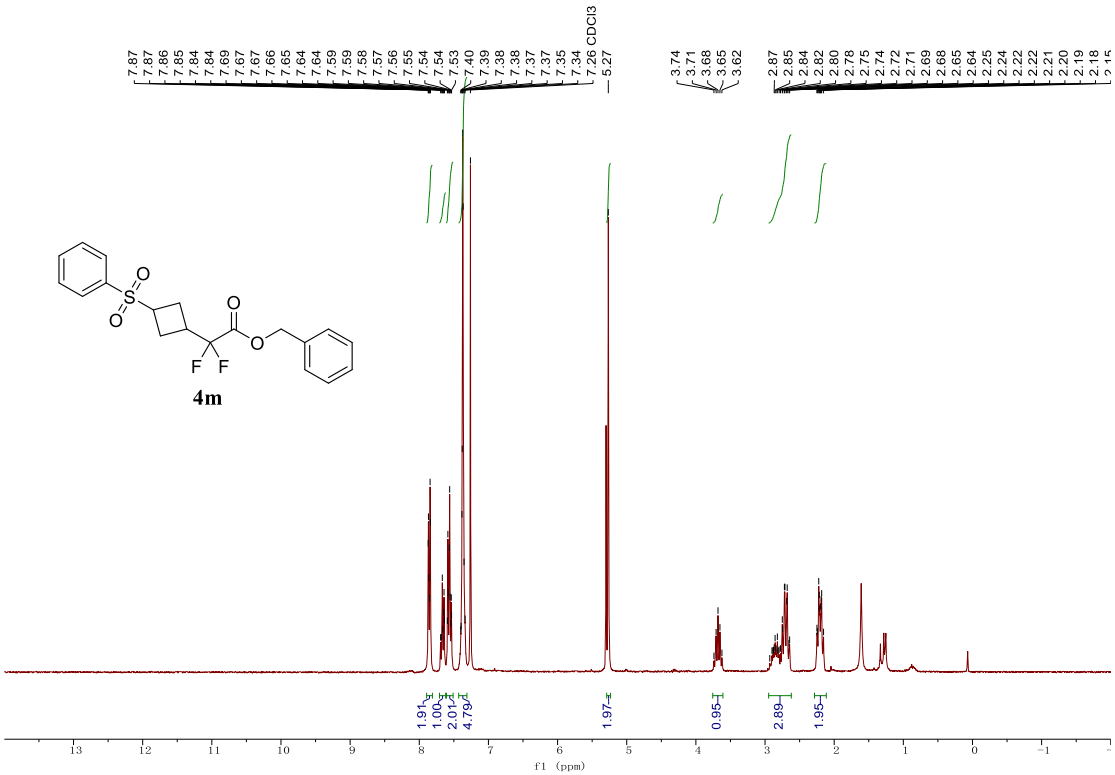
^{13}C NMR Spectrum of Compound **4l** (101 MHz, $CDCl_3$)



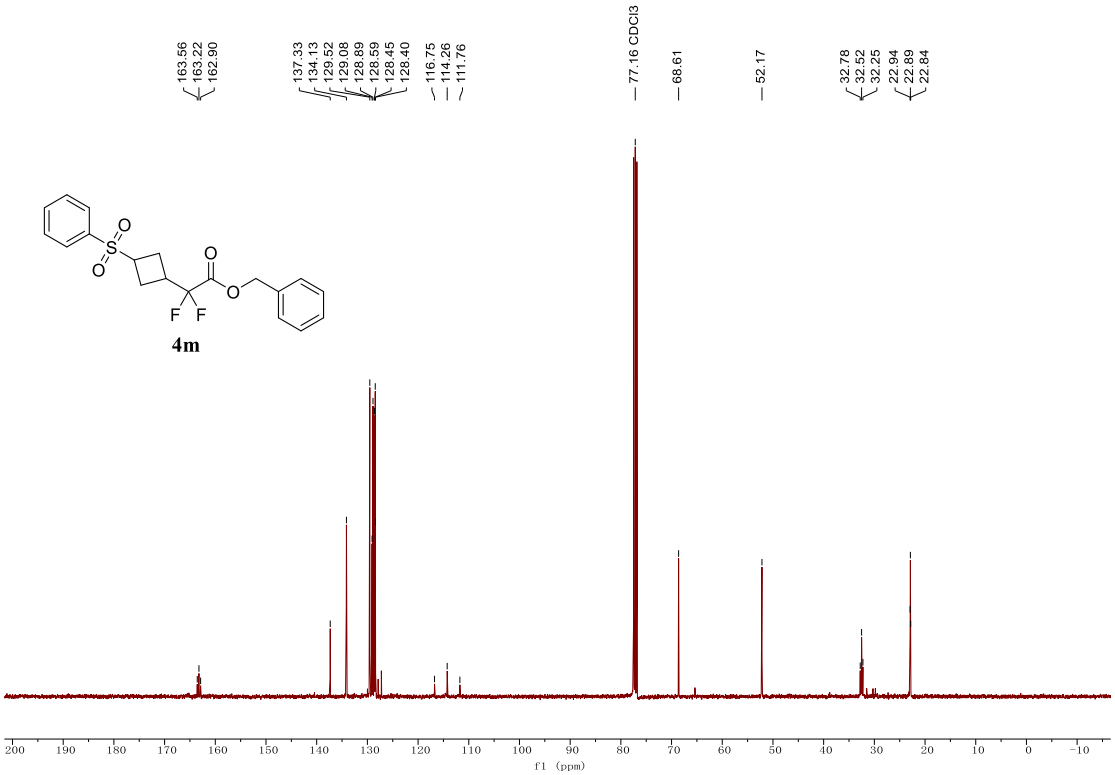
^{19}F NMR Spectrum of Compound **4l** (282 MHz, $CDCl_3$)



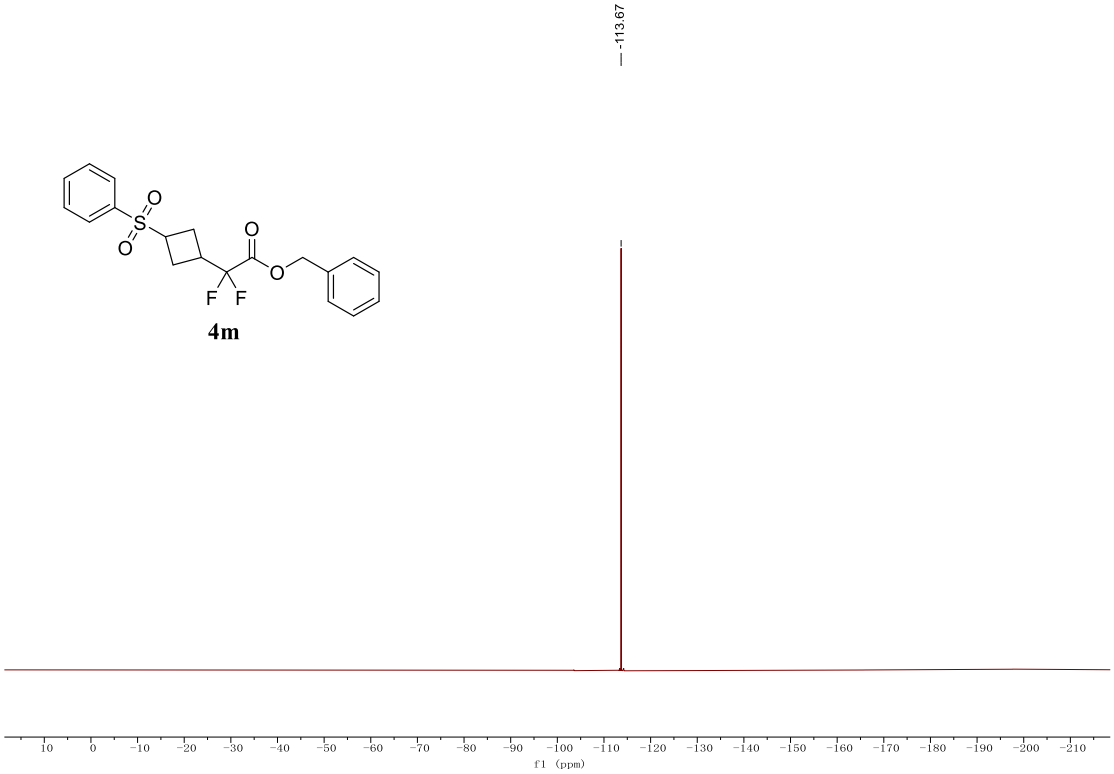
^{1}H NMR Spectrum of Compound **4m** (300 MHz, $CDCl_3$)



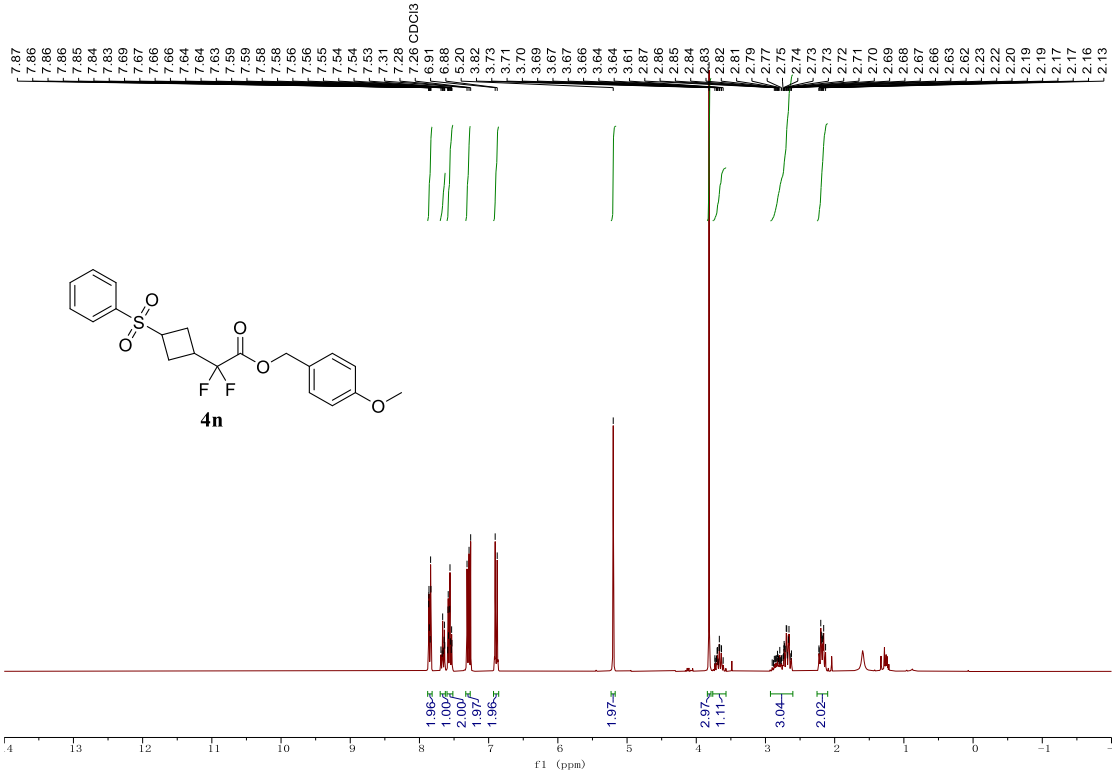
^{13}C NMR Spectrum of Compound **4m** (101 MHz, $CDCl_3$)



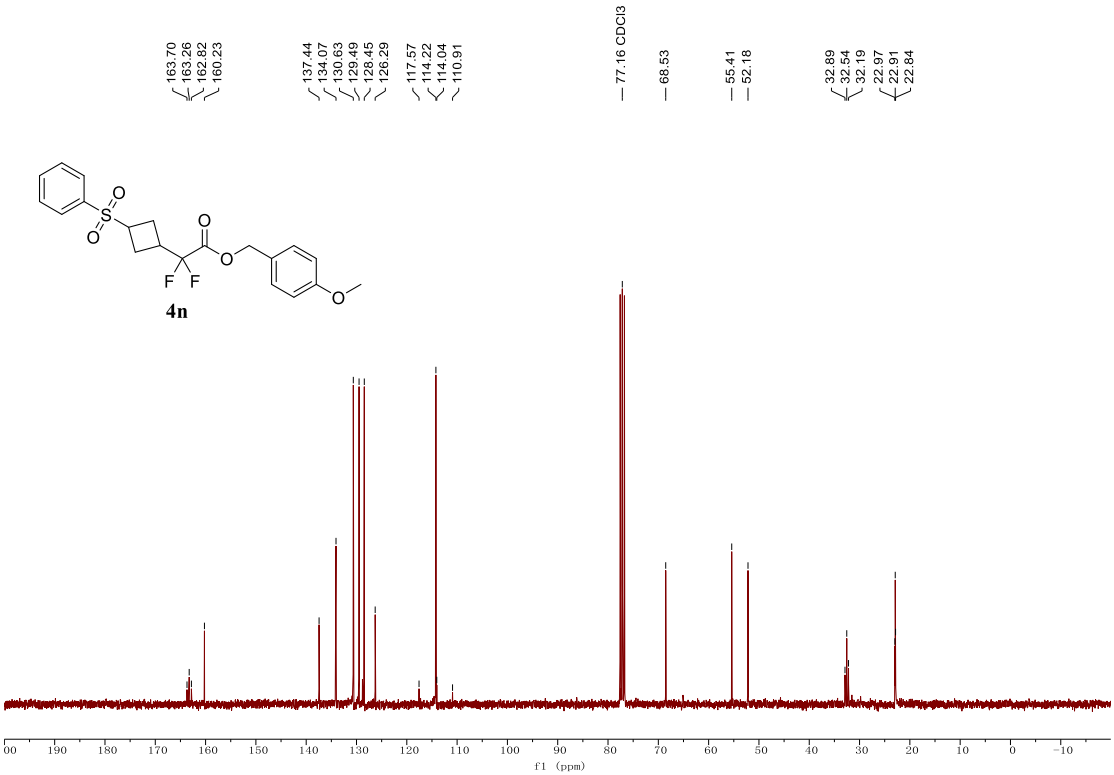
^{19}F NMR Spectrum of Compound **4m** (282 MHz, $CDCl_3$)



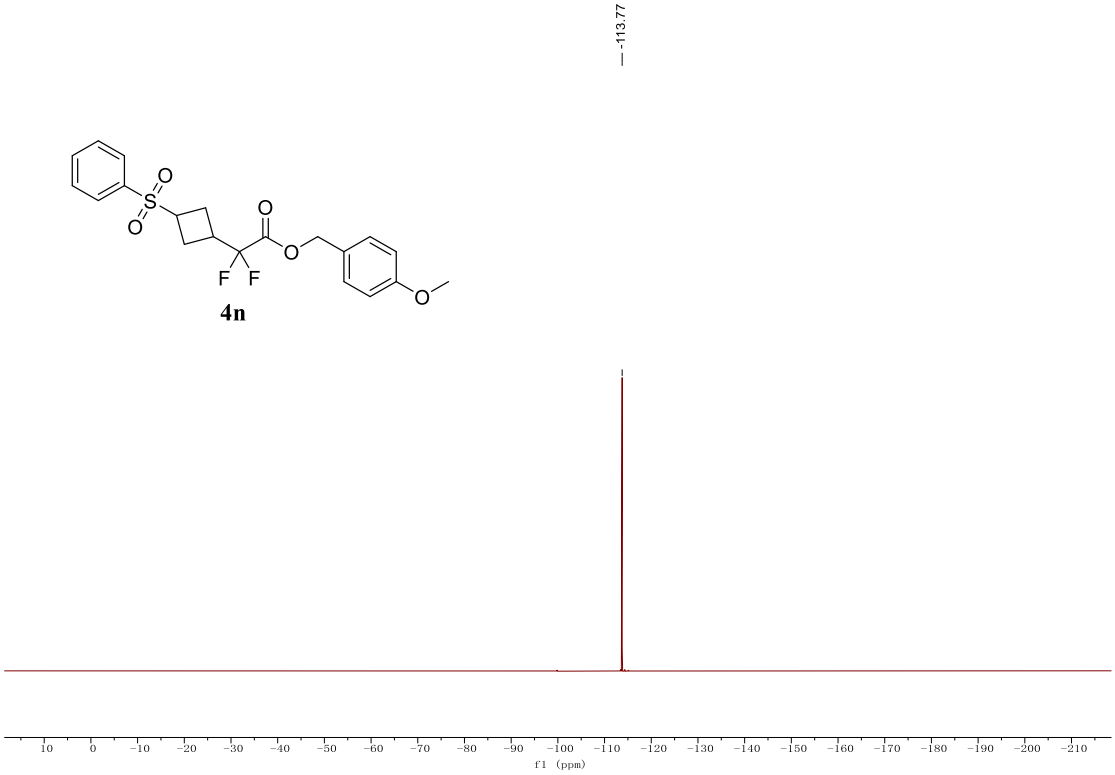
^{1}H NMR Spectrum of Compound **4n** (300 MHz, $CDCl_3$)



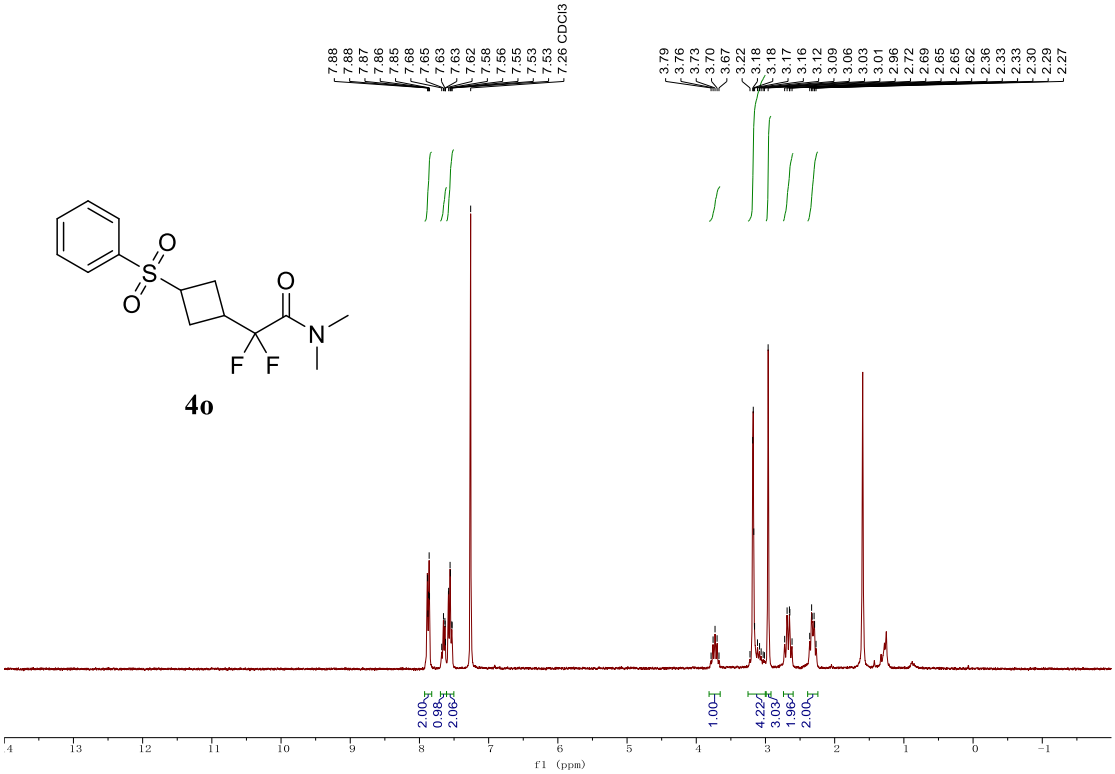
^{13}C NMR Spectrum of Compound **4n** (75 MHz, $CDCl_3$)



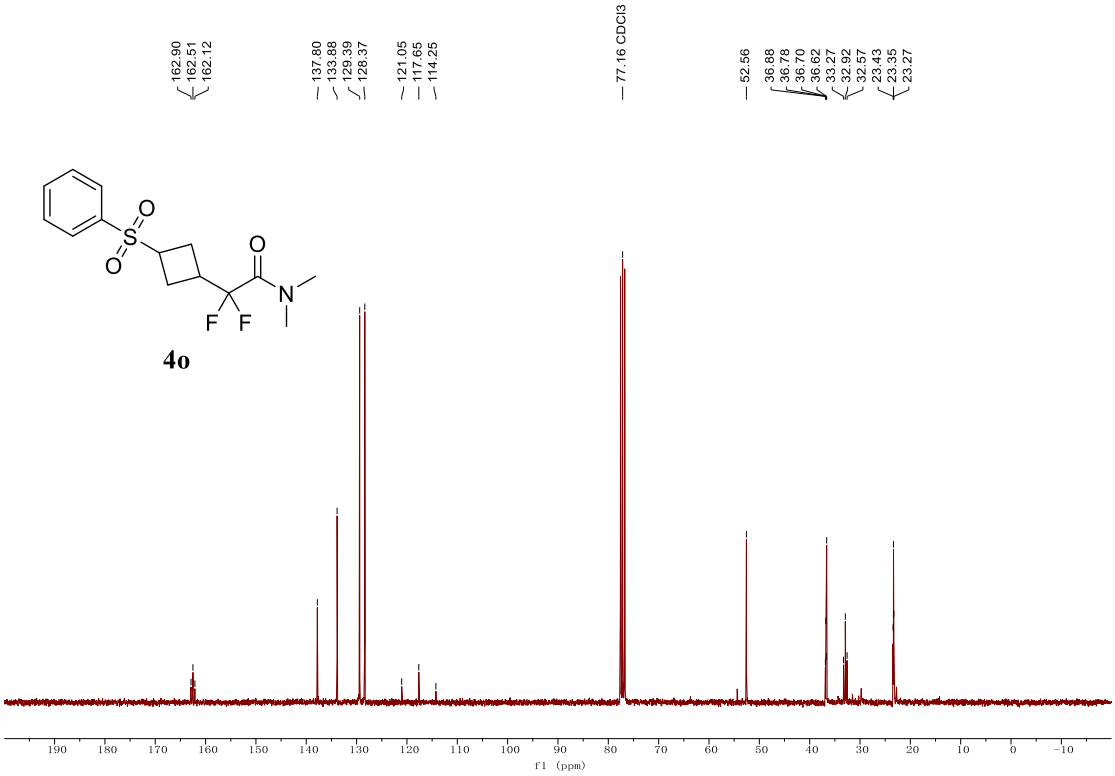
^{19}F NMR Spectrum of Compound **4n** (282 MHz, $CDCl_3$)



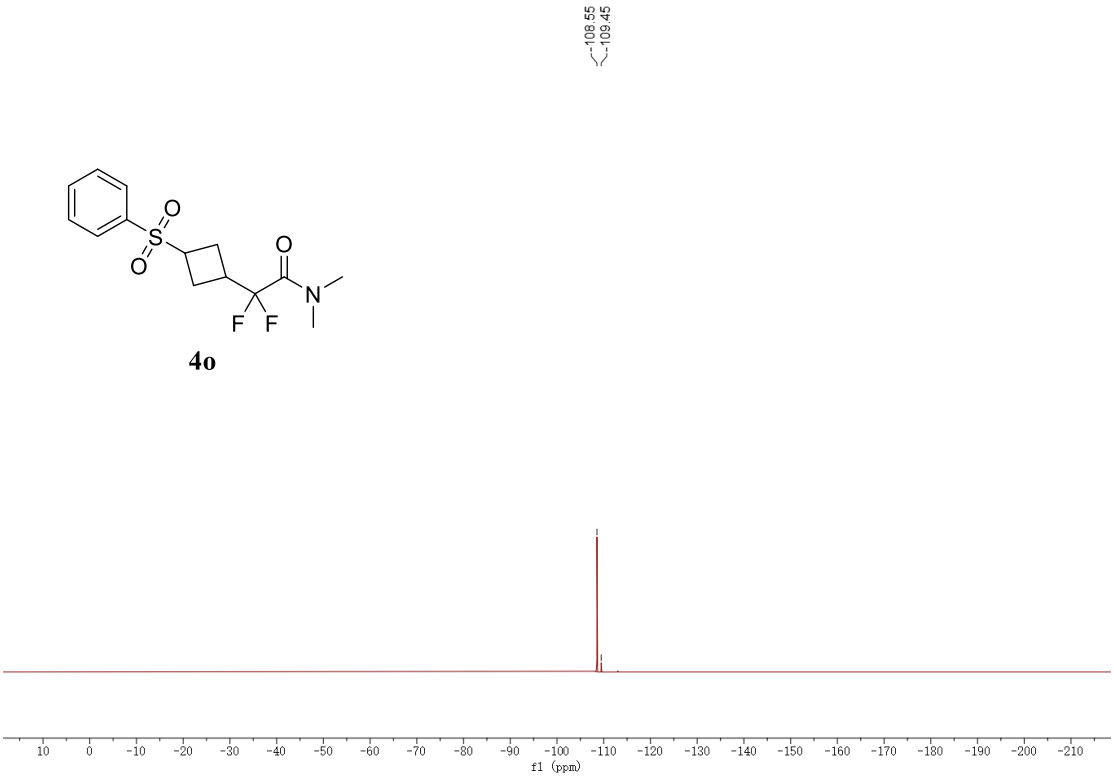
^{1}H NMR Spectrum of Compound **4o** (300 MHz, $CDCl_3$)



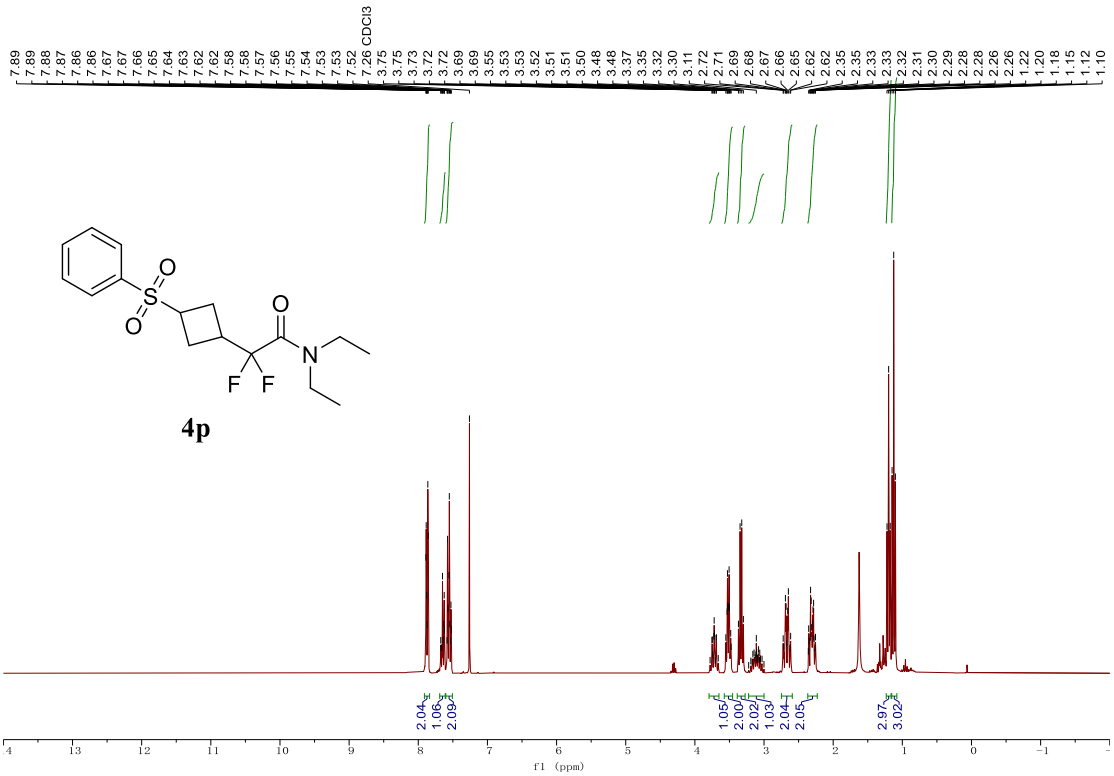
^{13}C NMR Spectrum of Compound **4o** (75 MHz, $CDCl_3$)



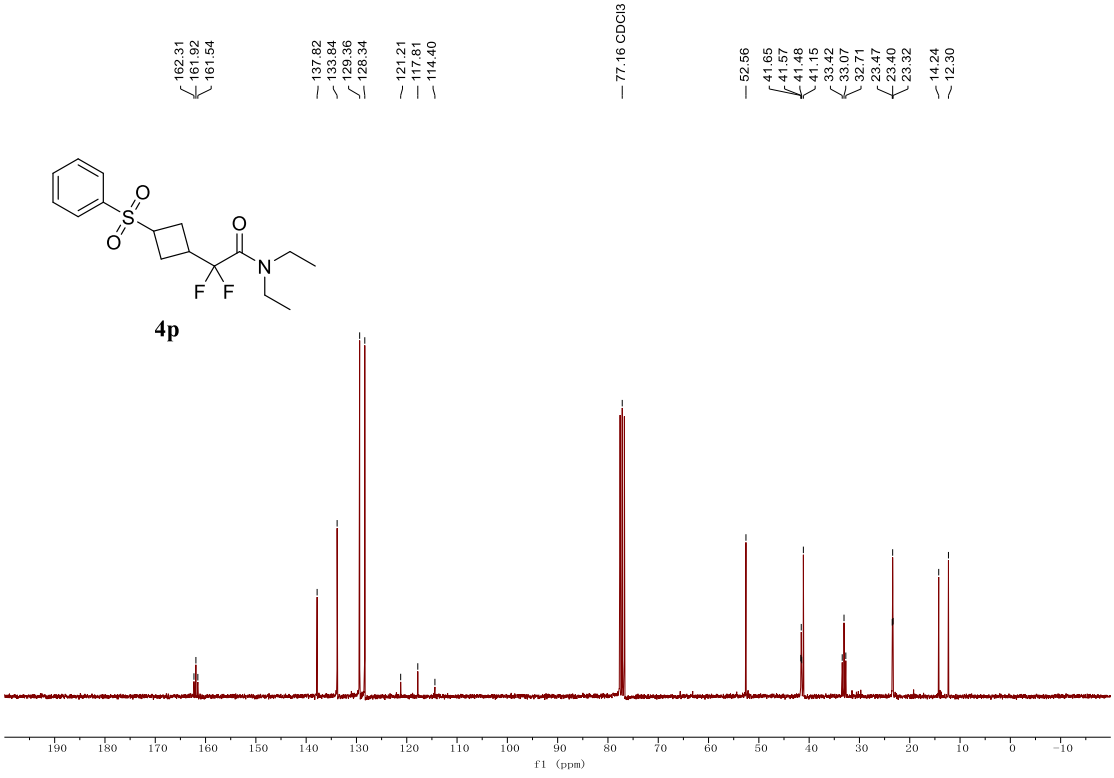
^{19}F NMR Spectrum of Compound **4o** (282 MHz, $CDCl_3$)



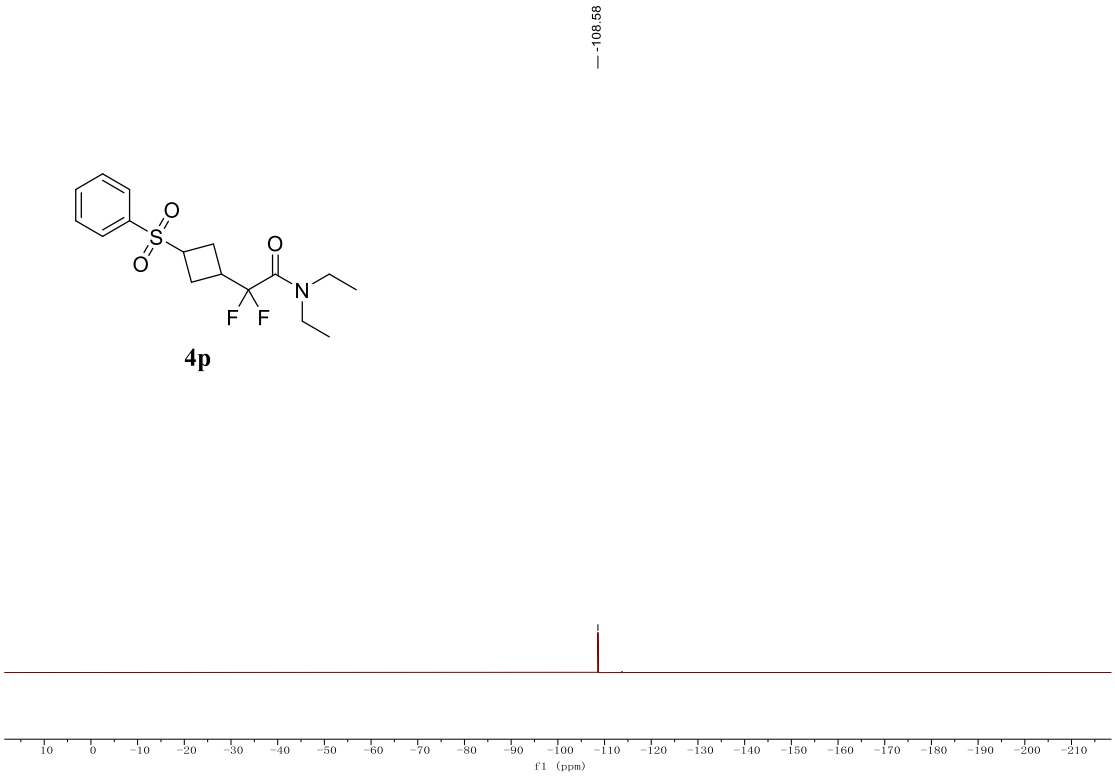
^{1}H NMR Spectrum of Compound **4p** (300 MHz, $CDCl_3$)



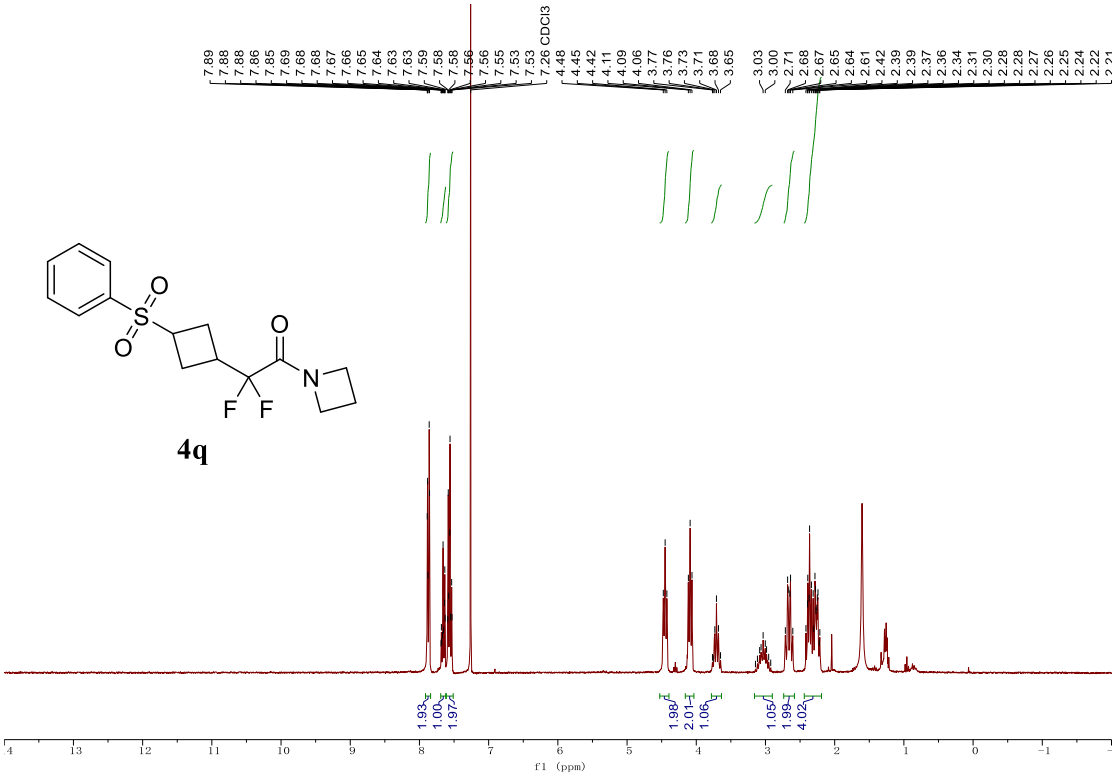
^{13}C NMR Spectrum of Compound **4p** (75 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **4p** (282 MHz, $CDCl_3$)

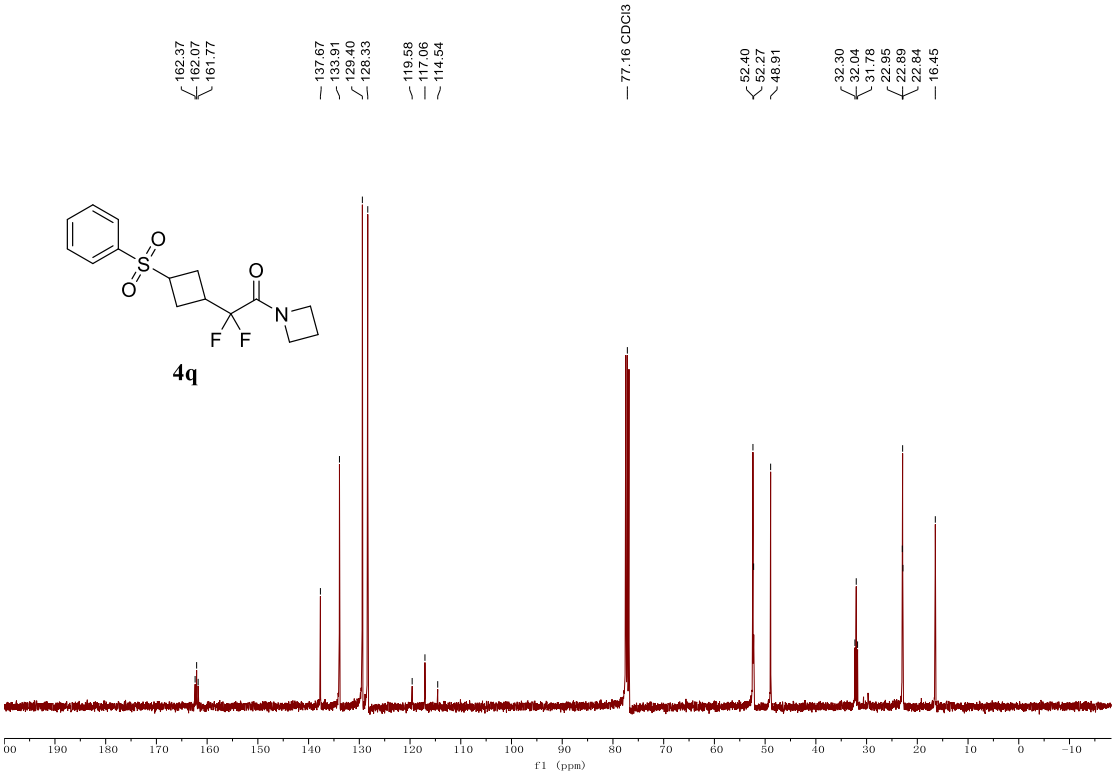


^{1}H NMR Spectrum of Compound **4q** (300 MHz, $CDCl_3$)



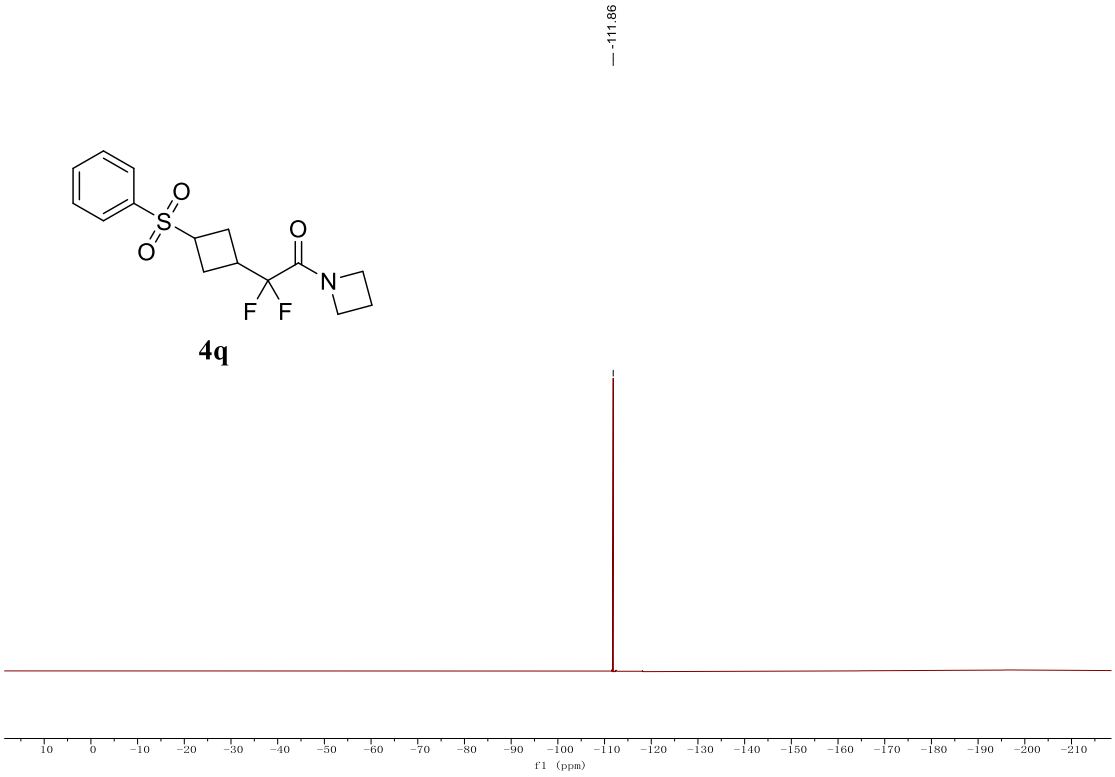
4q

^{13}C NMR Spectrum of Compound **4q** (101 MHz, $CDCl_3$)

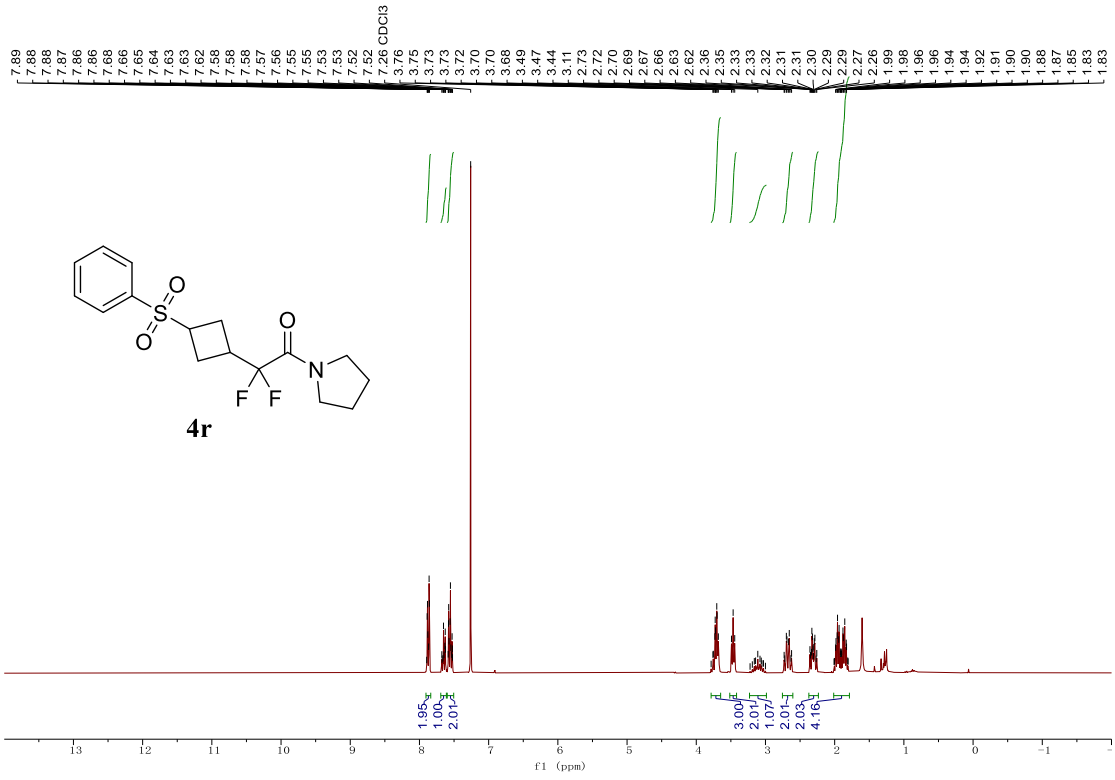


4q

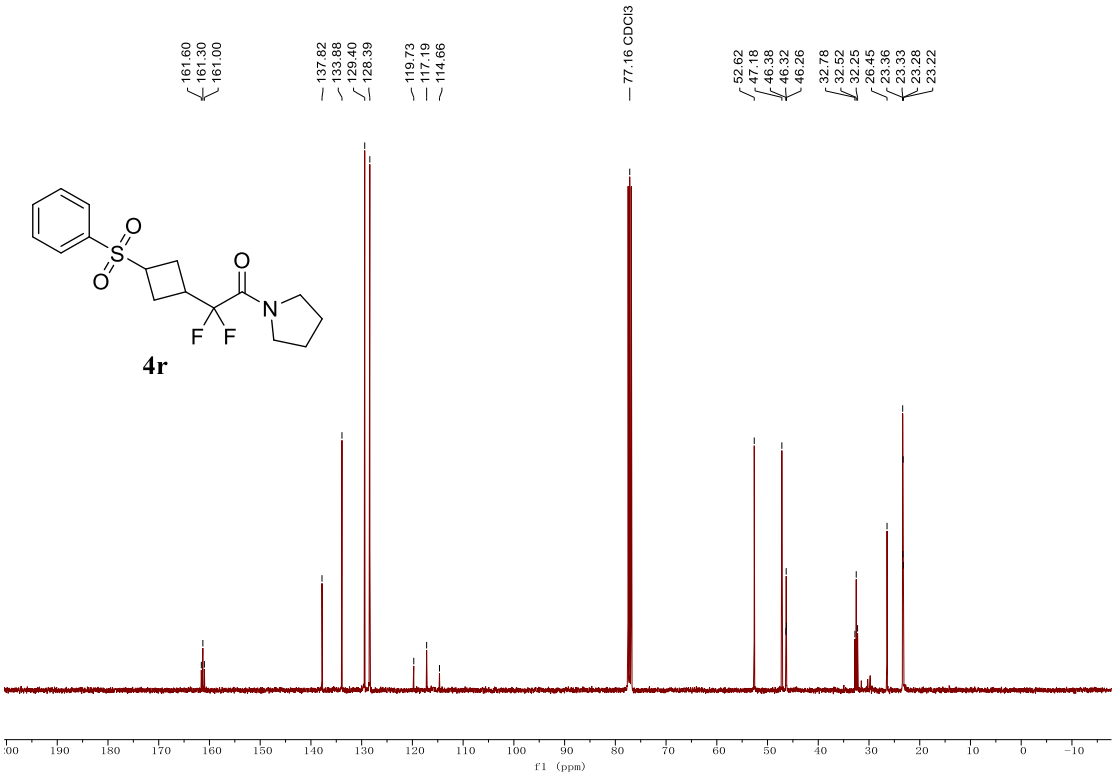
^{19}F NMR Spectrum of Compound **4q** (282 MHz, $CDCl_3$)



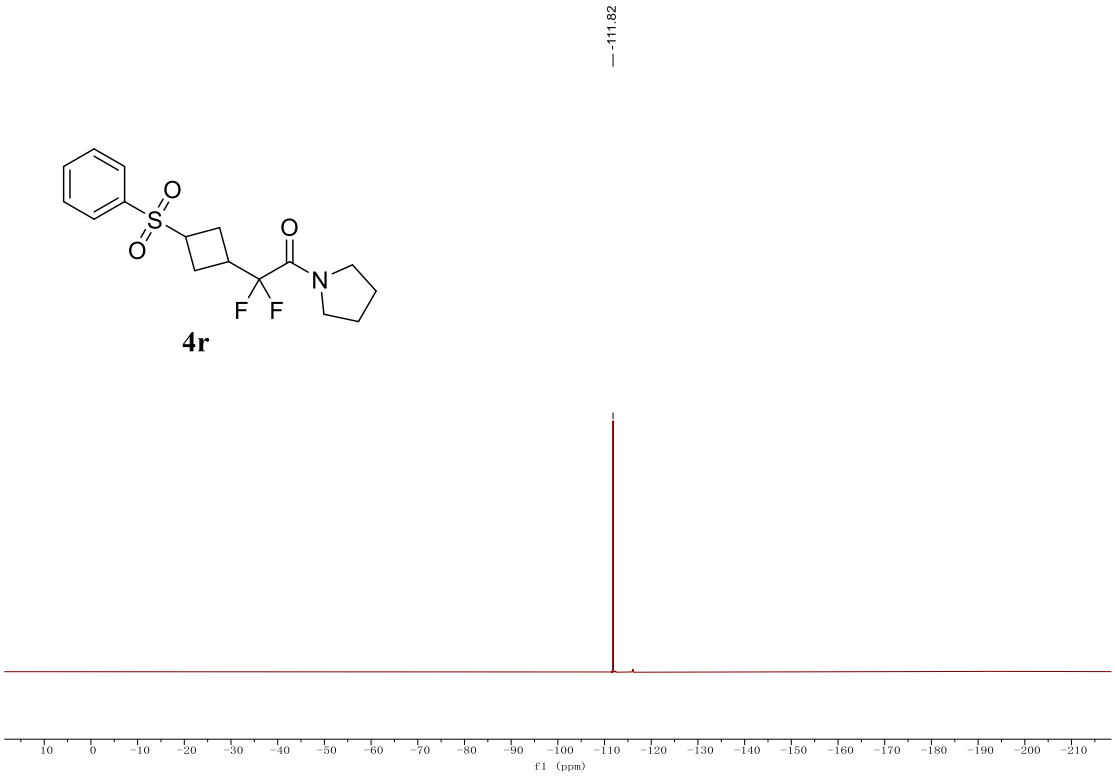
^{1}H NMR Spectrum of Compound **4r** (300 MHz, $CDCl_3$)



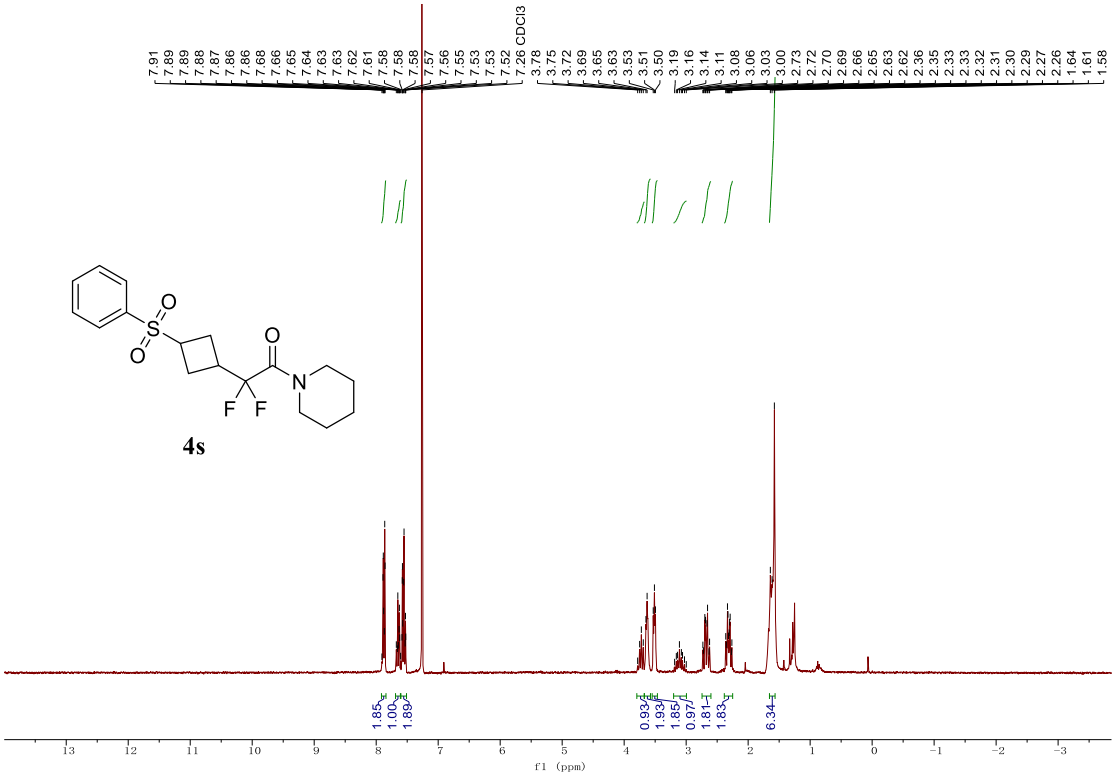
^{13}C NMR Spectrum of Compound **4r** (101 MHz, $CDCl_3$)



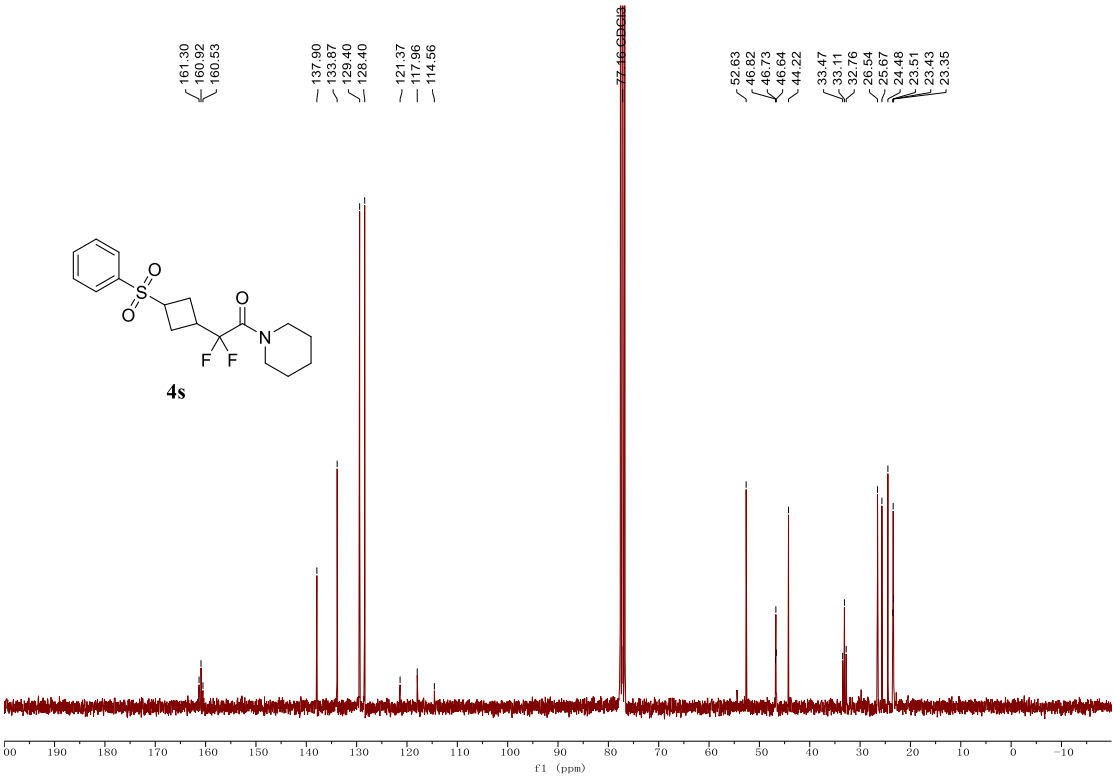
^{19}F NMR Spectrum of Compound **4r** (282 MHz, $CDCl_3$)



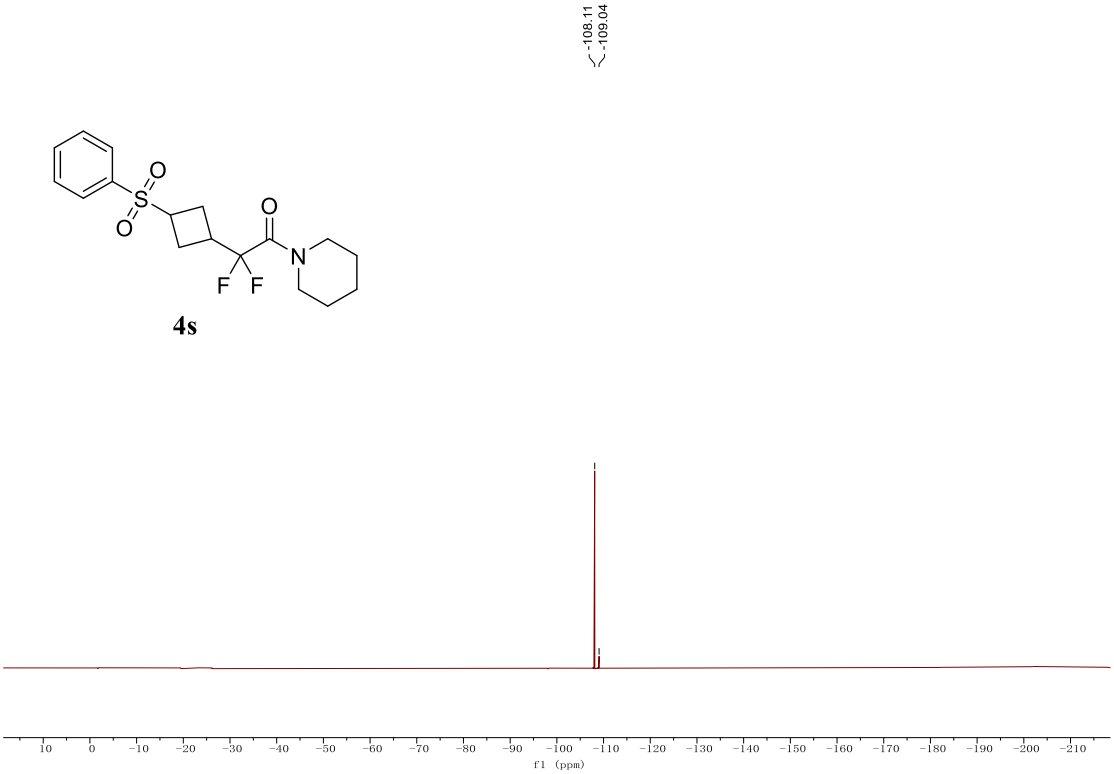
^{1}H NMR Spectrum of Compound **4s** (300 MHz, $CDCl_3$)



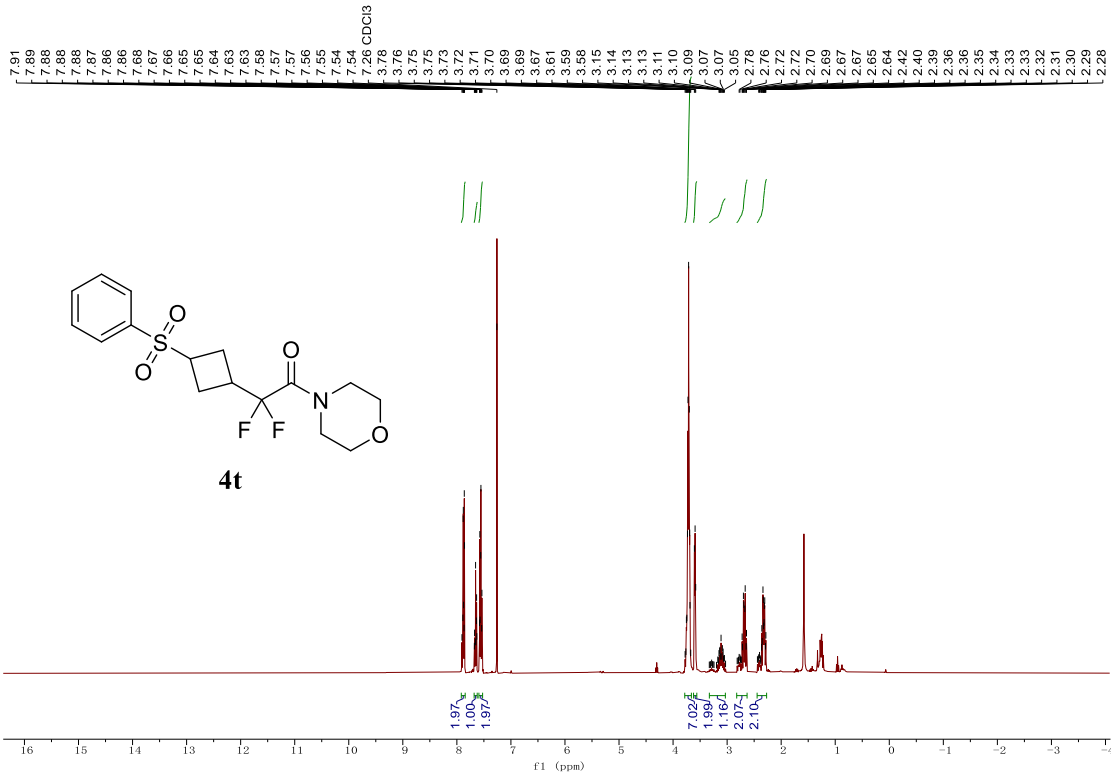
^{13}C NMR Spectrum of Compound **4s** (75 MHz, $CDCl_3$)



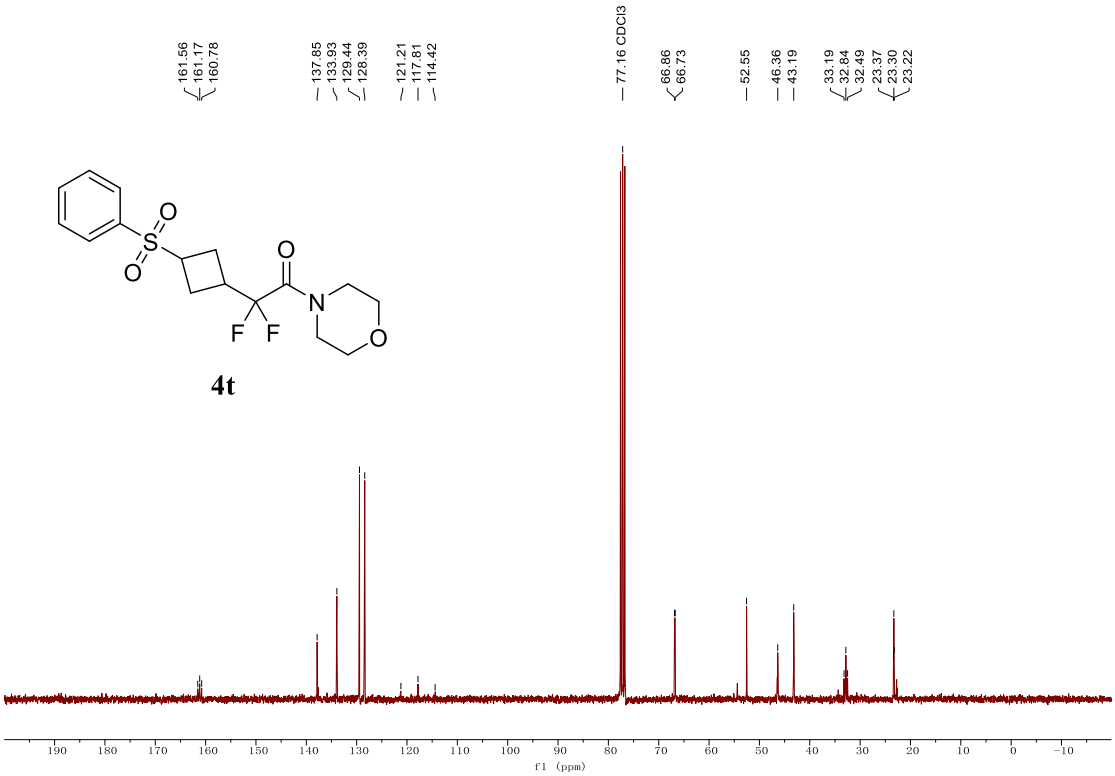
^{19}F NMR Spectrum of Compound **4s** (282 MHz, $CDCl_3$)



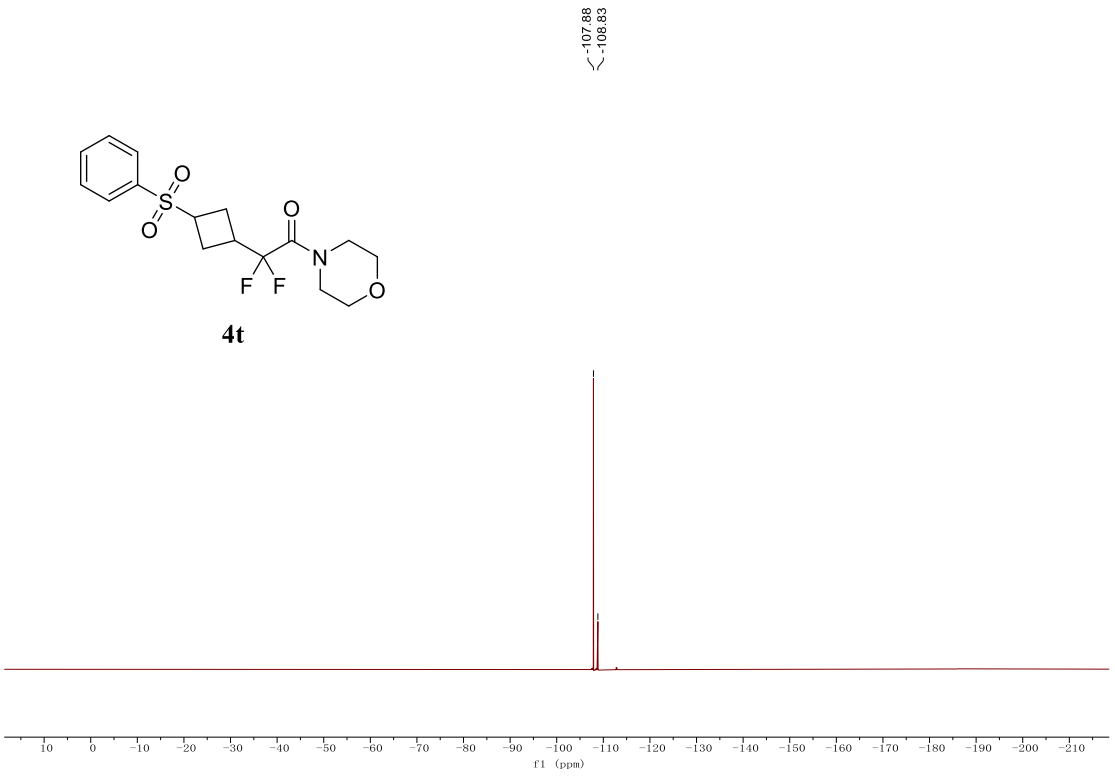
^{1}H NMR Spectrum of Compound **4t** (400 MHz, $CDCl_3$)



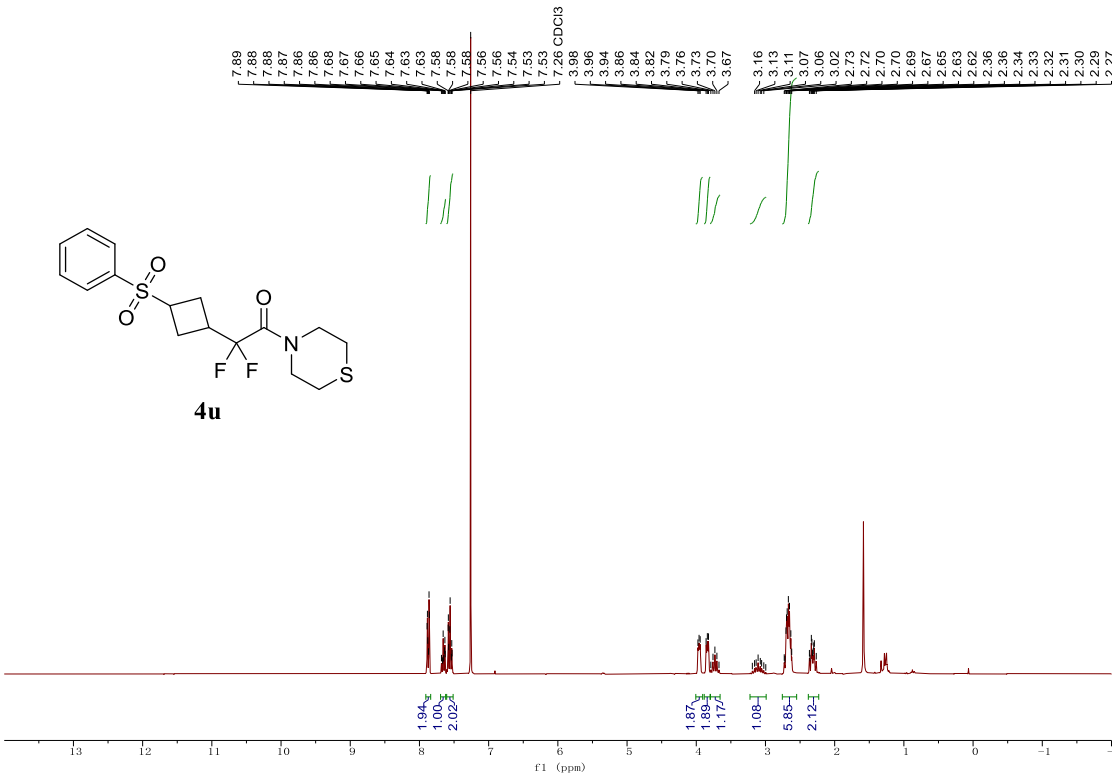
^{13}C NMR Spectrum of Compound **4t** (75 MHz, $CDCl_3$)



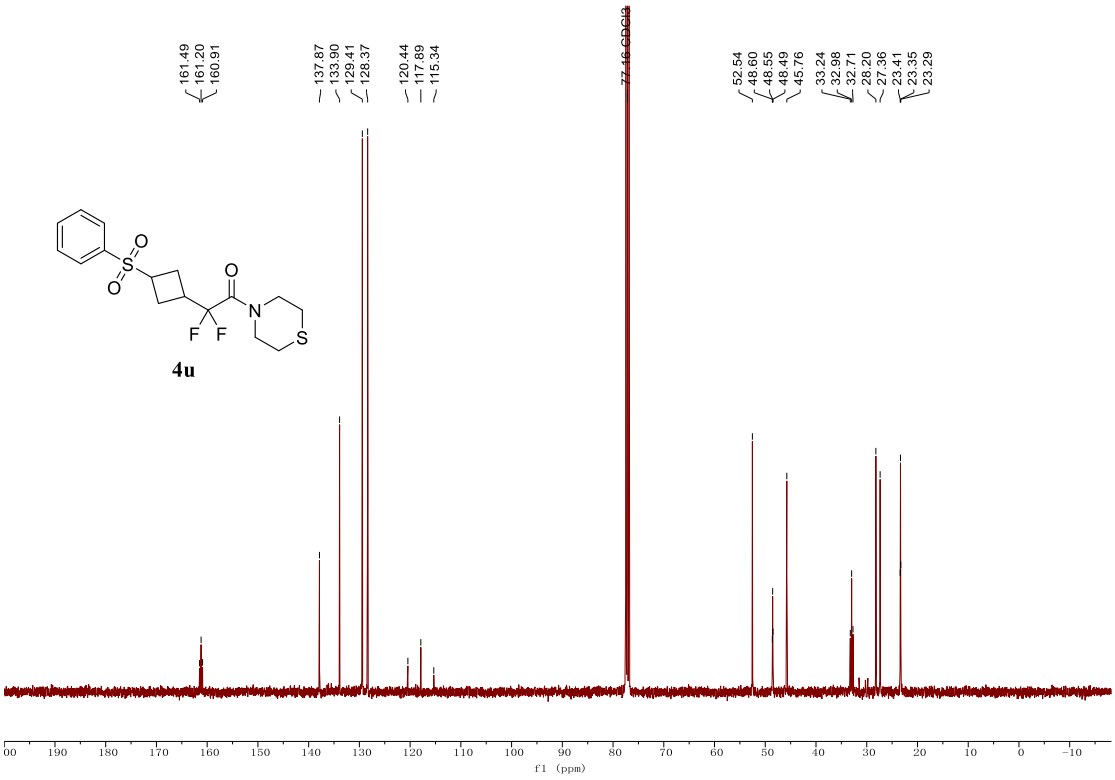
^{19}F NMR Spectrum of Compound **4t** (282 MHz, $CDCl_3$)



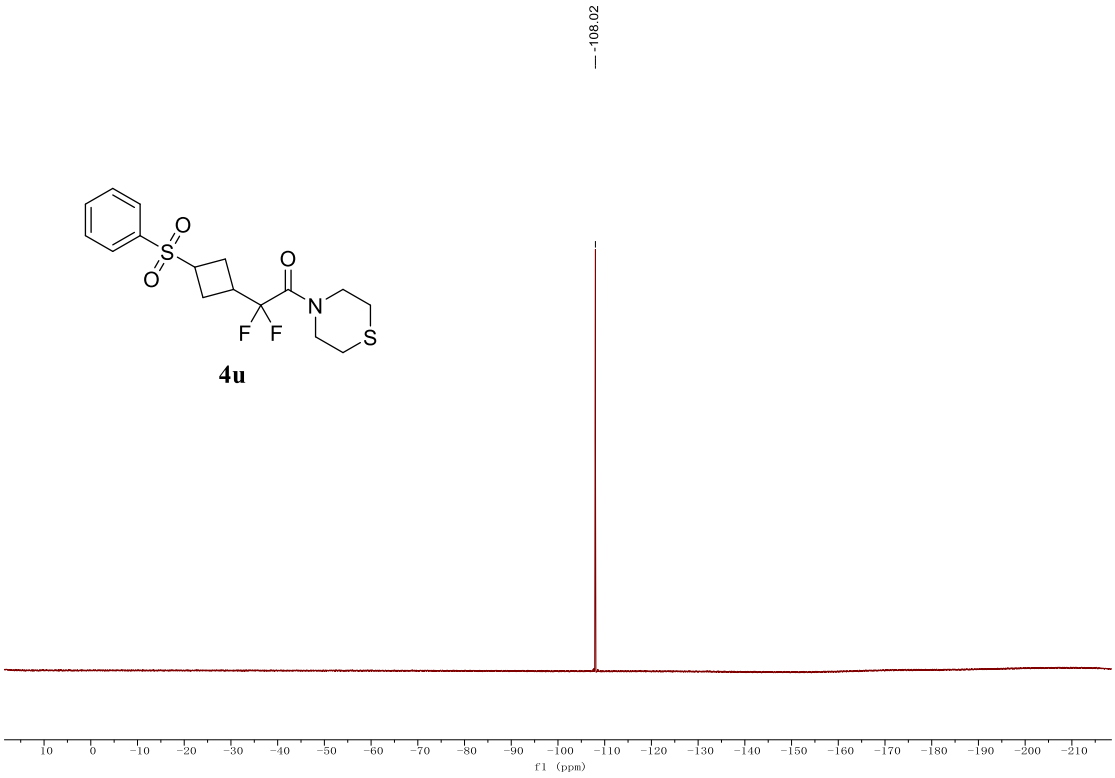
` ^{1}H NMR Spectrum of Compound **4u** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **4u** (101 MHz, $CDCl_3$)

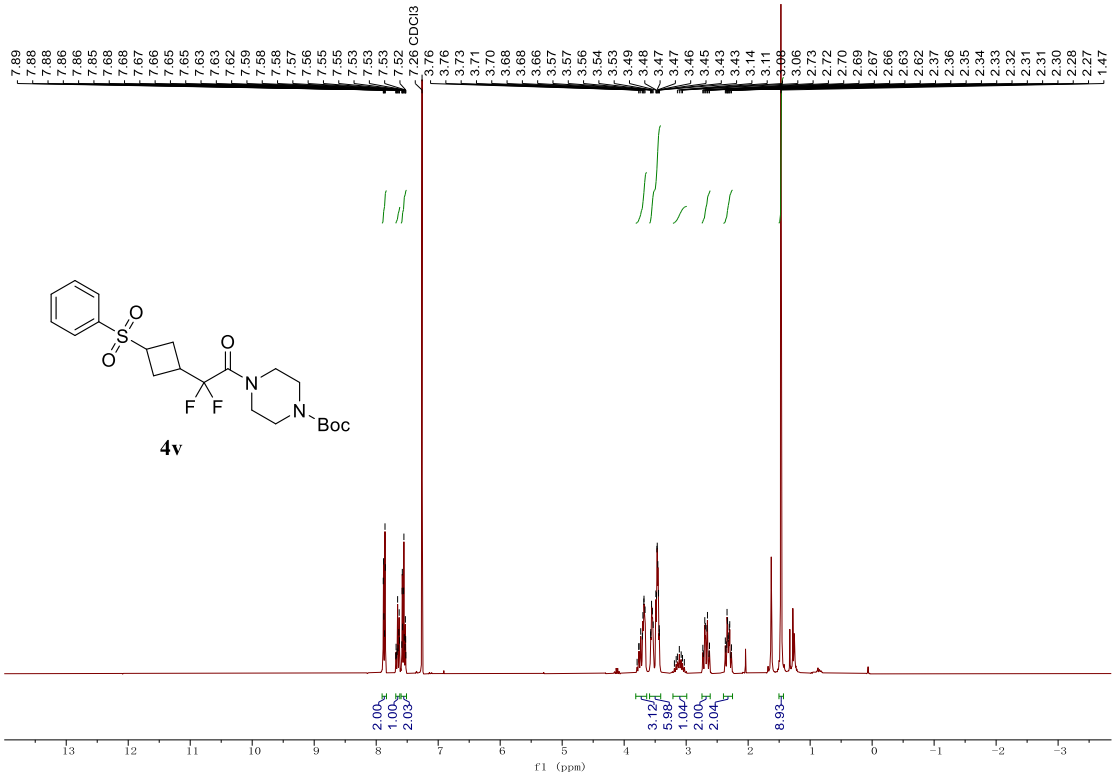


^{19}F NMR Spectrum of Compound **4u** (282 MHz, $CDCl_3$)



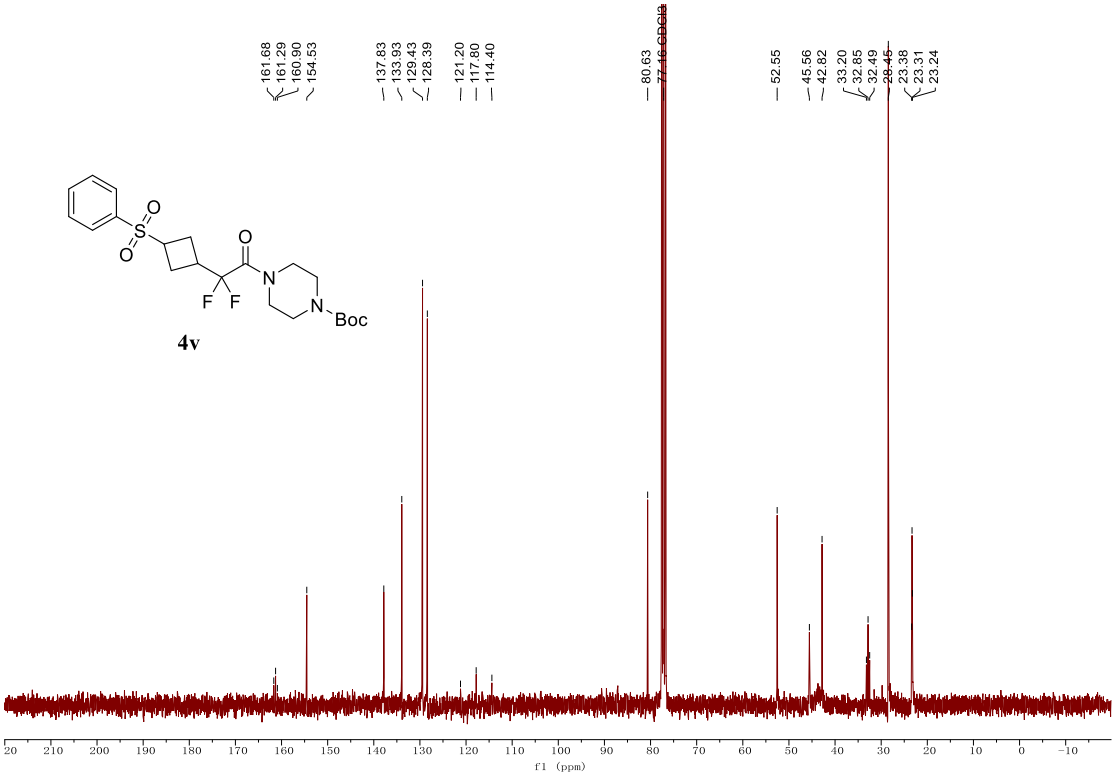
4u

^{1}H NMR Spectrum of Compound **4v** (300 MHz, $CDCl_3$)

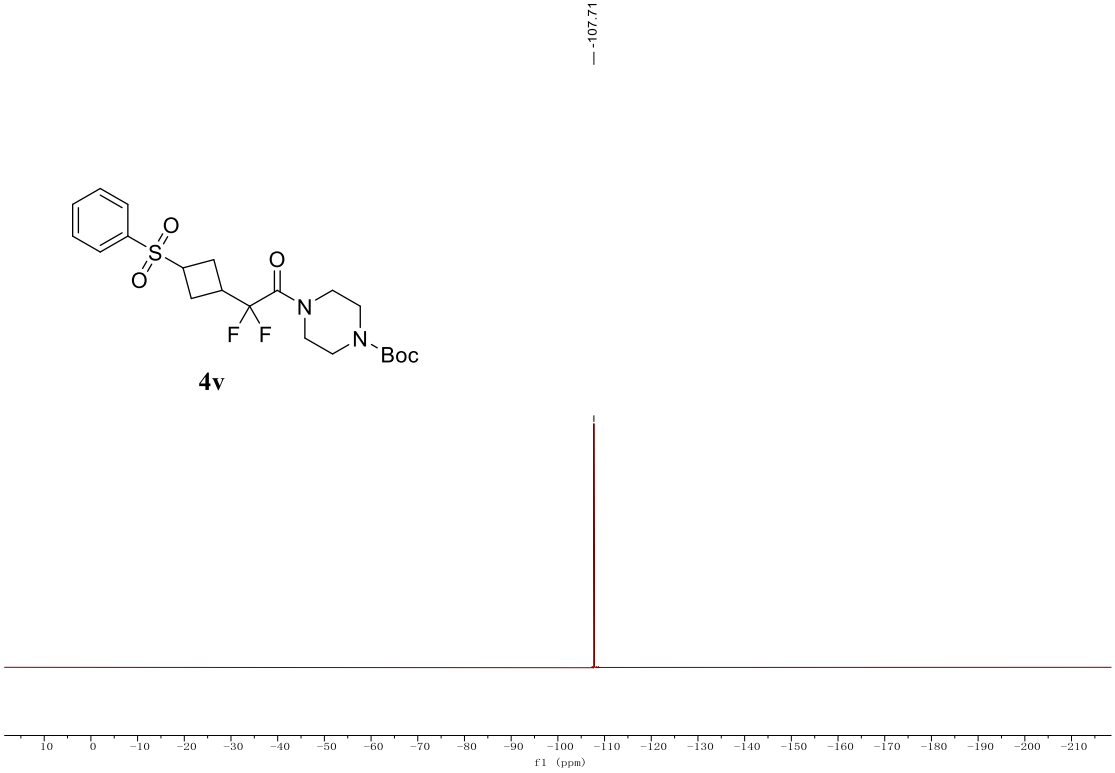


4v

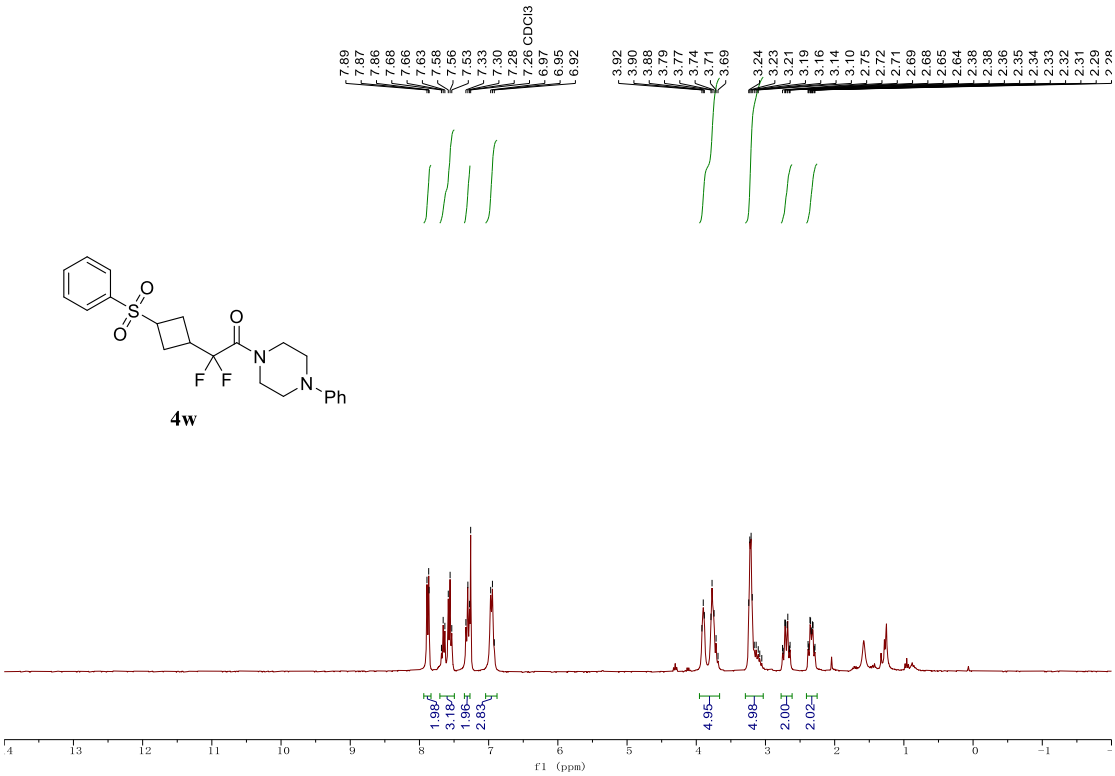
^{13}C NMR Spectrum of Compound **4v** (75 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **4v** (282 MHz, $CDCl_3$)

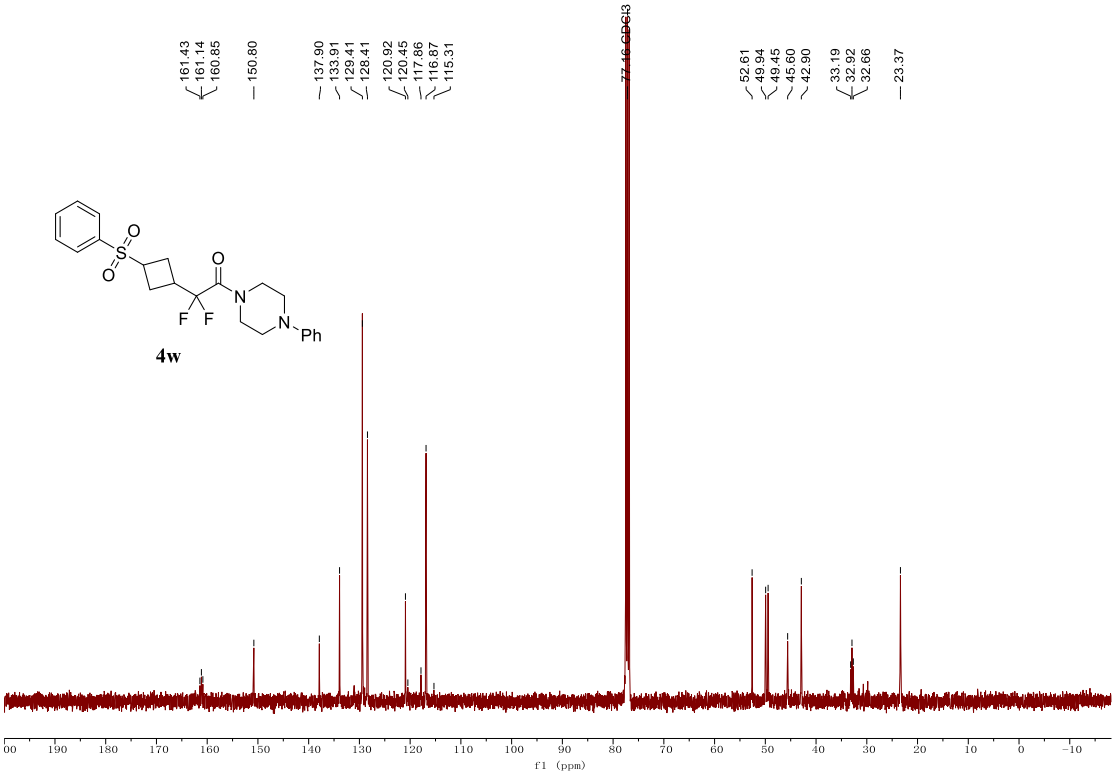


^{1}H NMR Spectrum of Compound **4w** (300 MHz, $CDCl_3$)



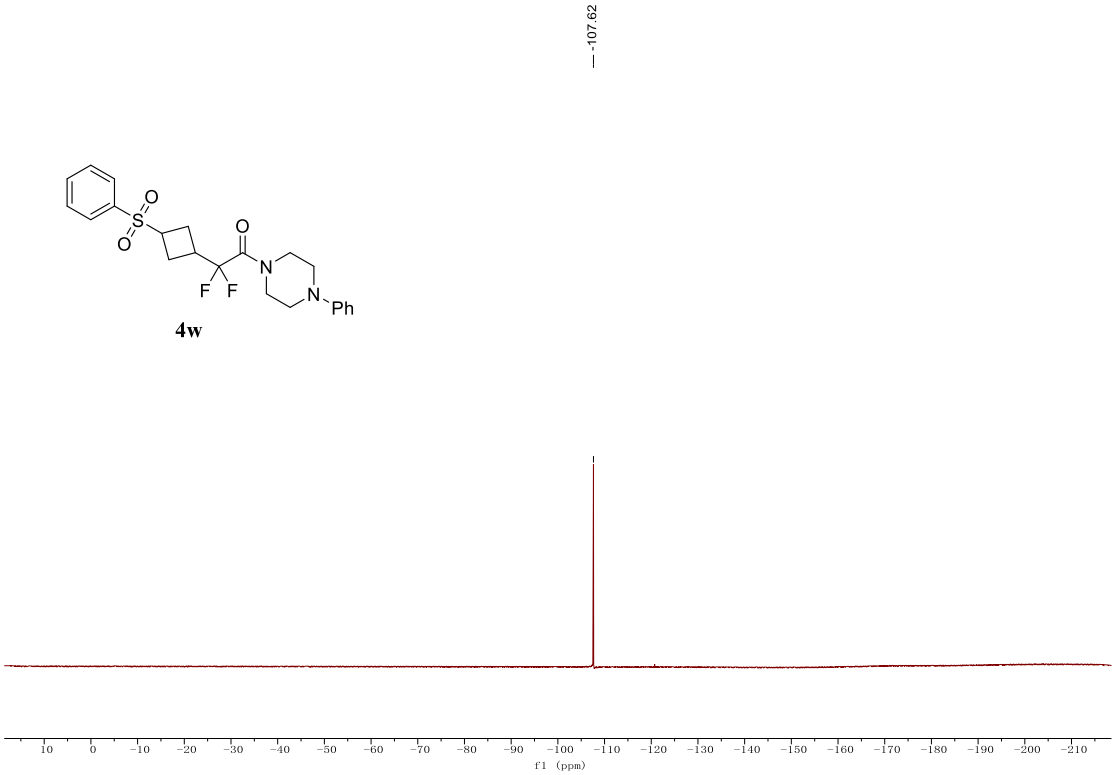
4w

^{13}C NMR Spectrum of Compound **4w** (101 MHz, $CDCl_3$)

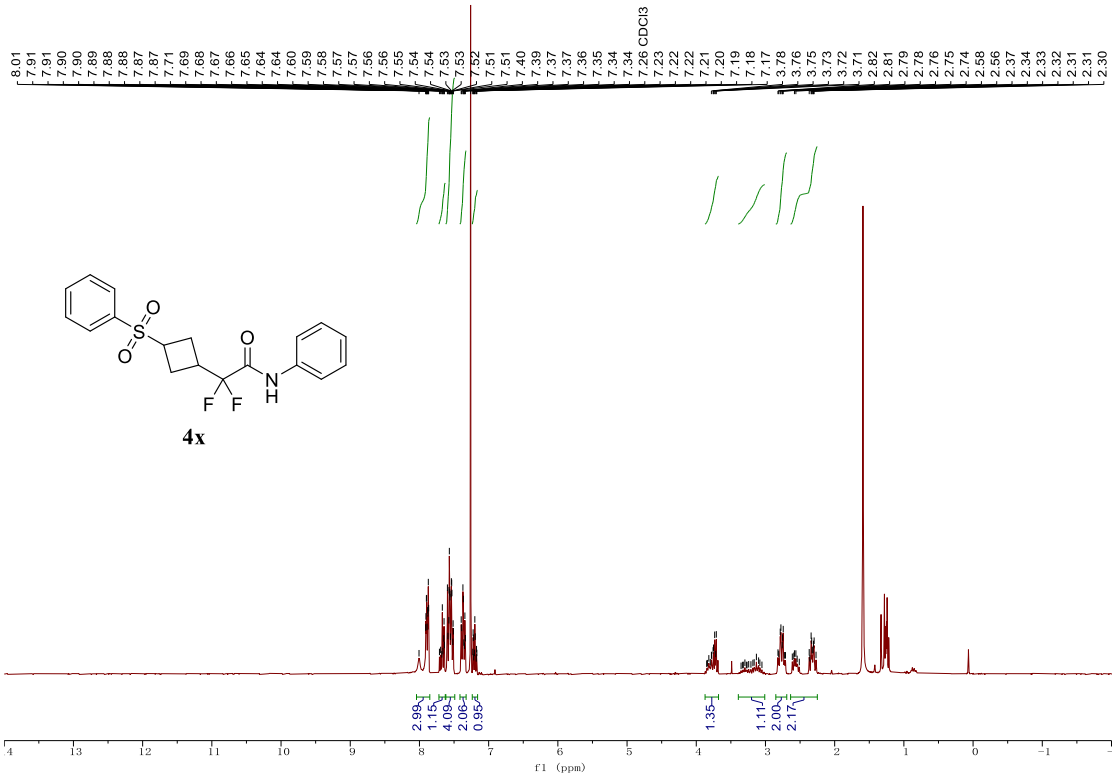


4w

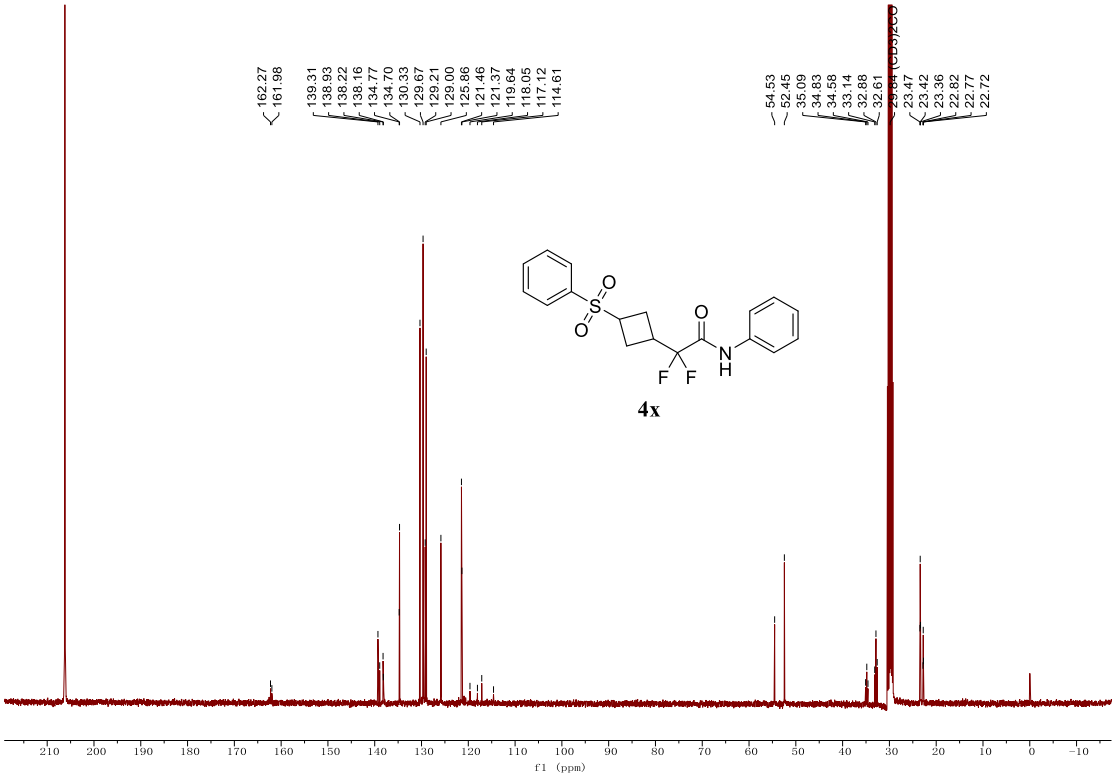
^{19}F NMR Spectrum of Compound **4w** (282 MHz, $CDCl_3$)



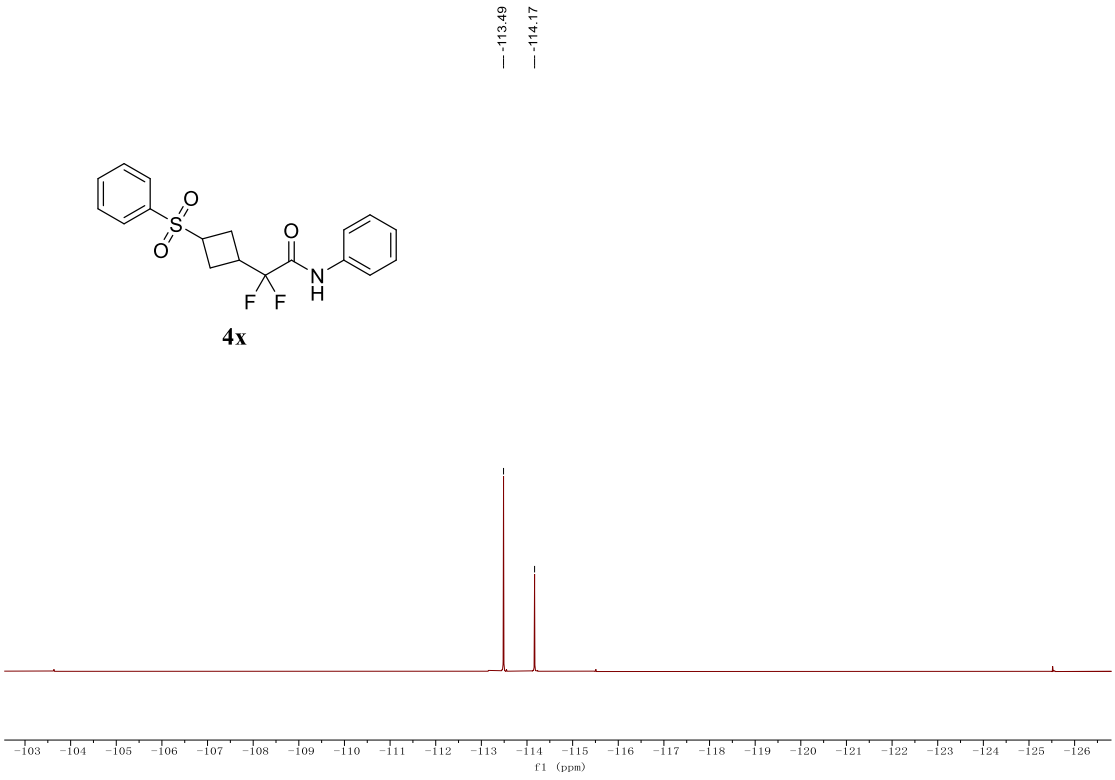
^{1}H NMR Spectrum of Compound **4x** (300 MHz, $CDCl_3$)



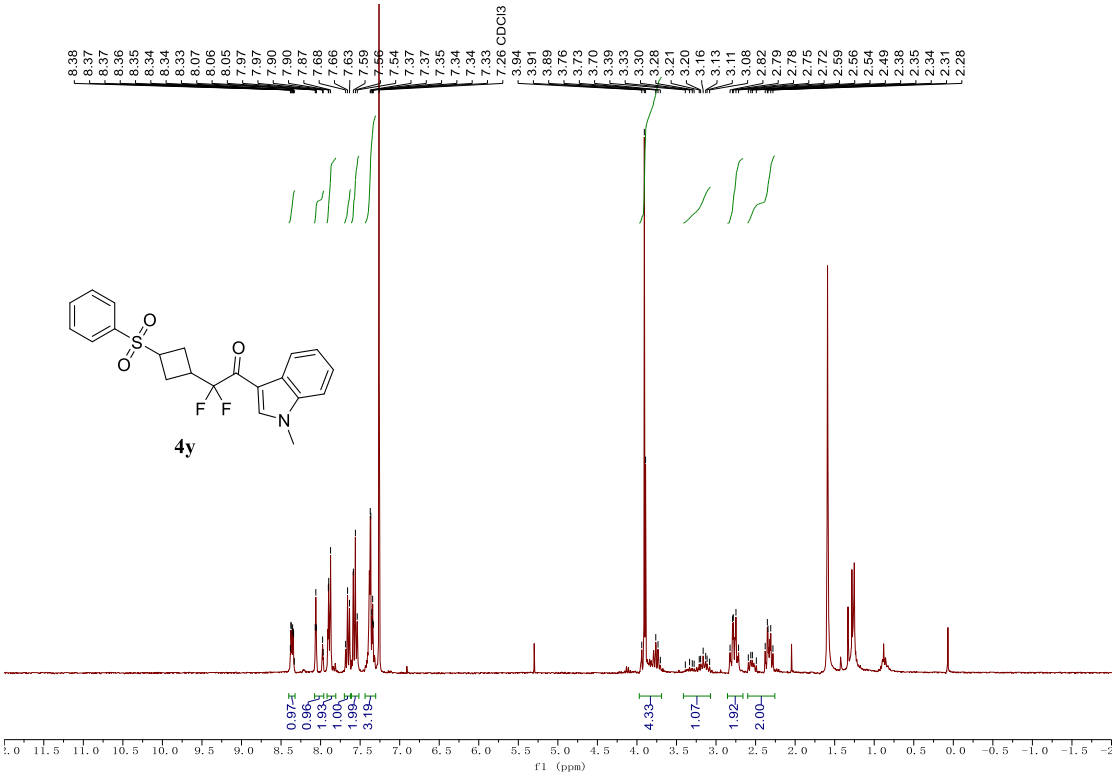
^{13}C NMR Spectrum of Compound **4x** (101 MHz, Acetone-d_6)



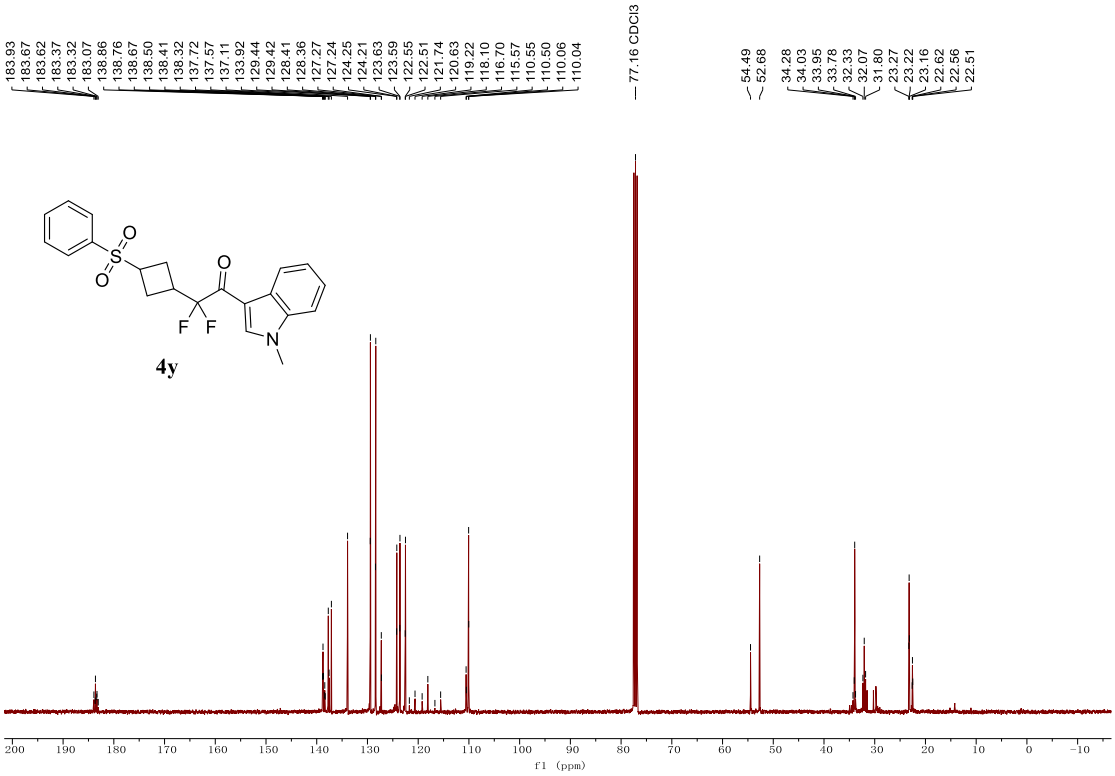
^{19}F NMR Spectrum of Compound **4x** (282 MHz, $CDCl_3$)



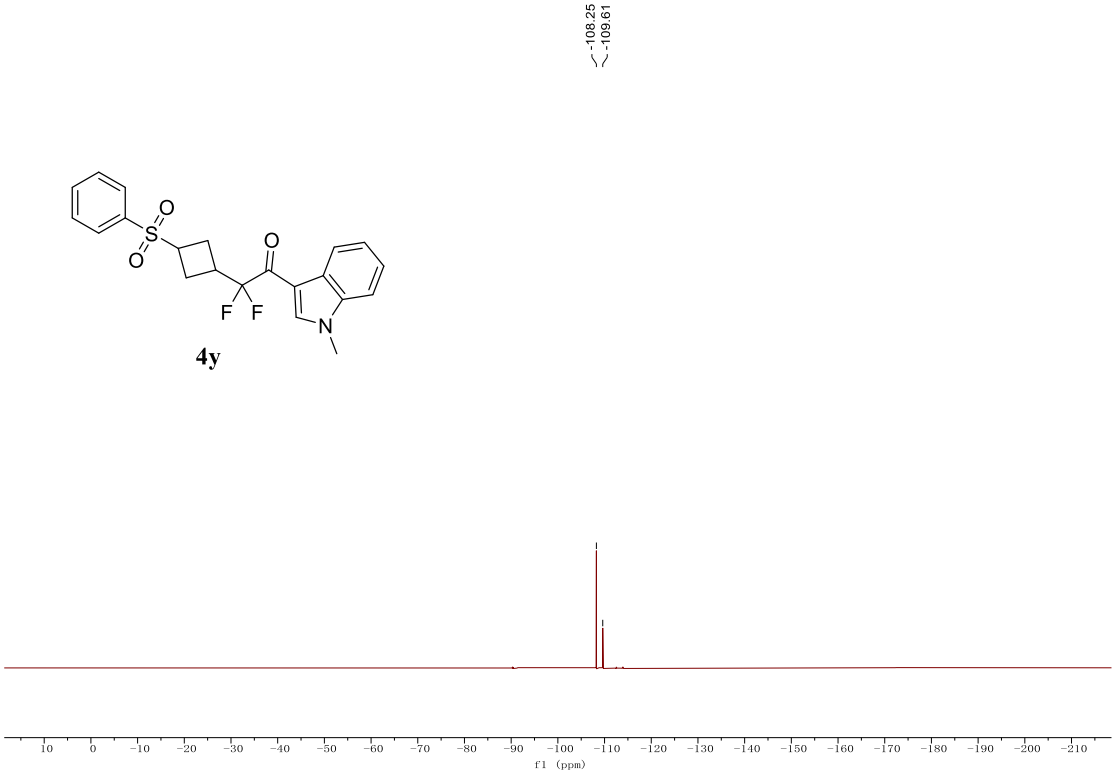
^{1}H NMR Spectrum of Compound **4y** (300 MHz, $CDCl_3$)



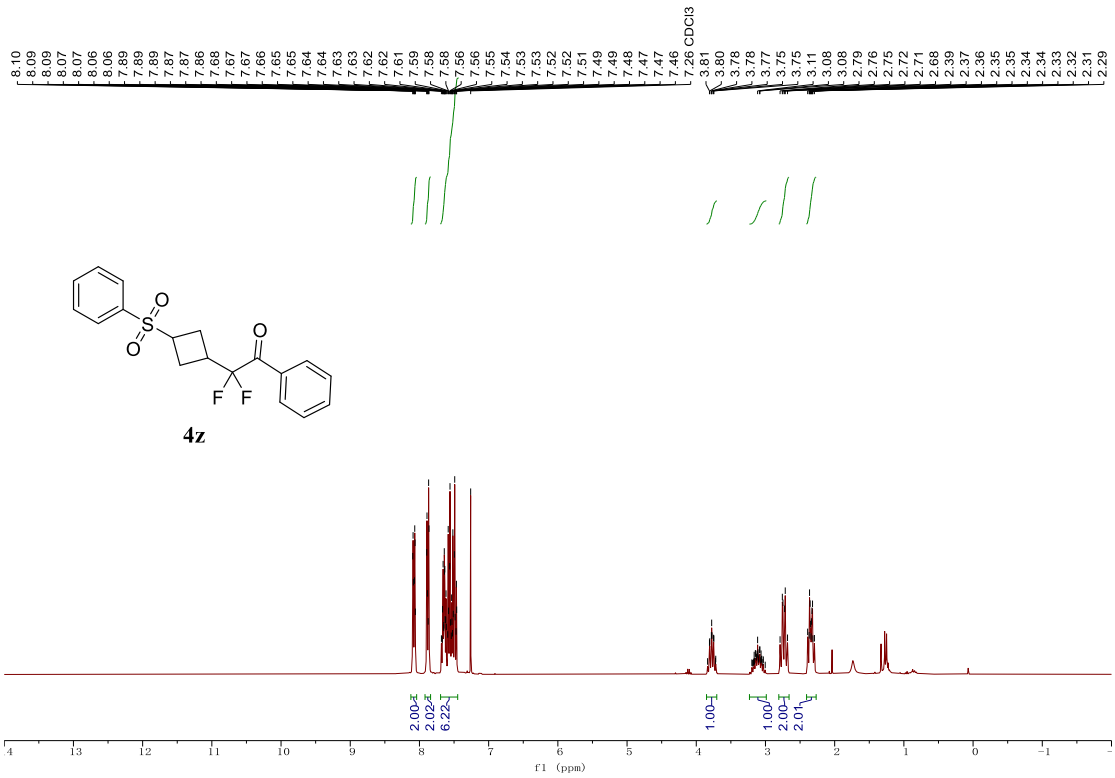
^{13}C NMR Spectrum of Compound **4y** (101 MHz, $CDCl_3$)



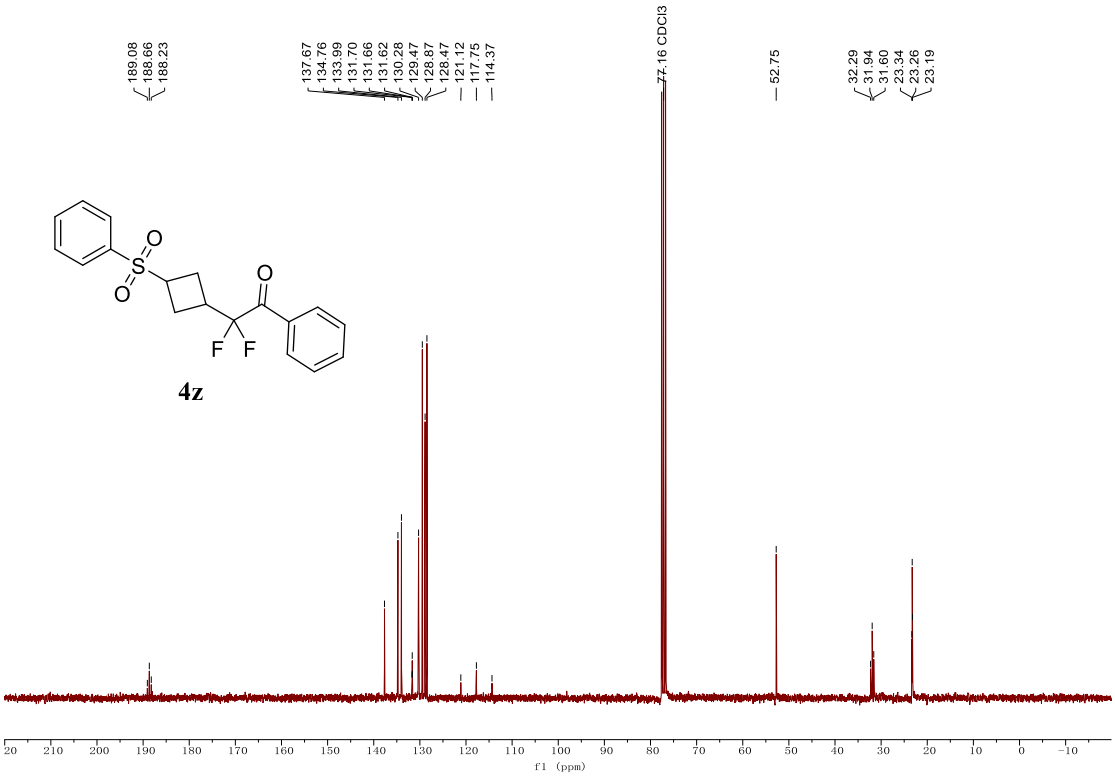
^{19}F NMR Spectrum of Compound **4y** (282 MHz, $CDCl_3$)



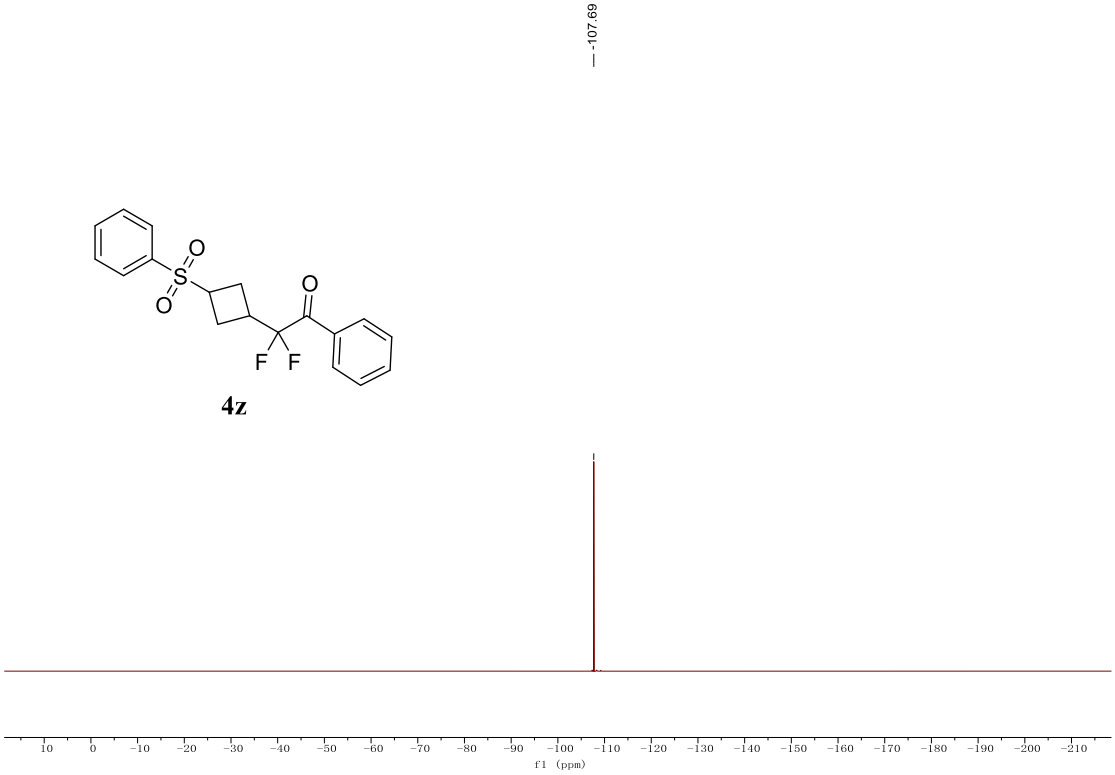
^{1}H NMR Spectrum of Compound **4z** (300 MHz, $CDCl_3$)



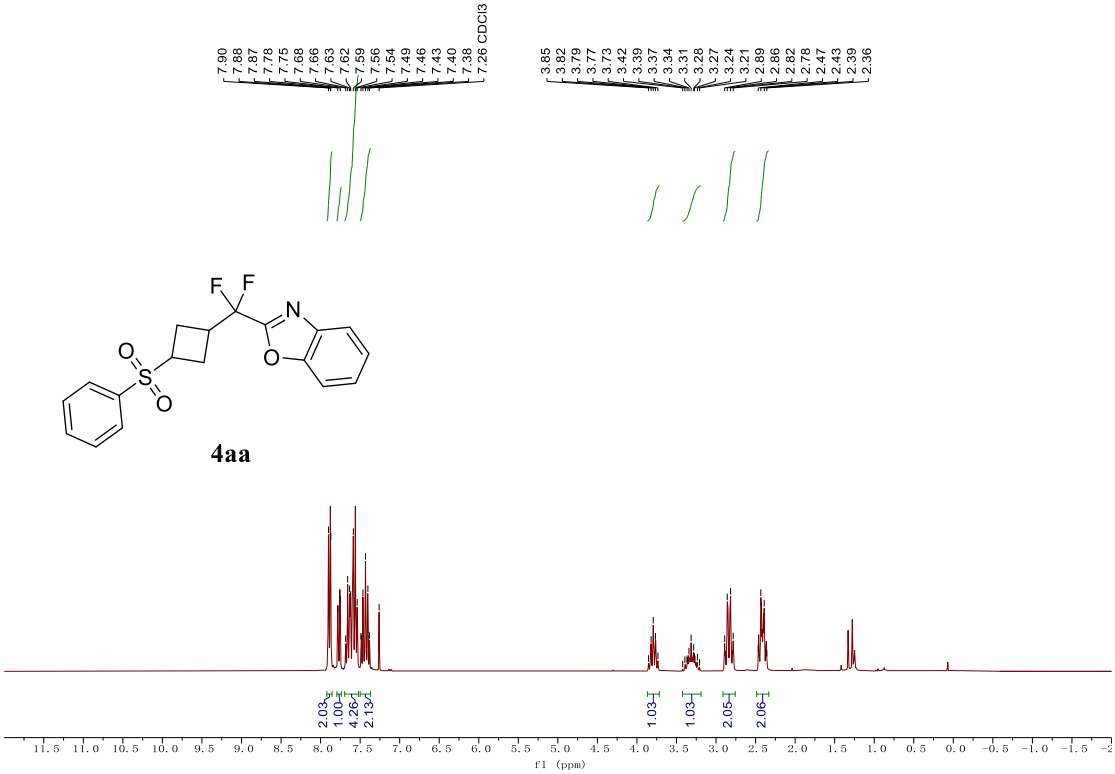
^{13}C NMR Spectrum of Compound **4z** (75 MHz, $CDCl_3$)



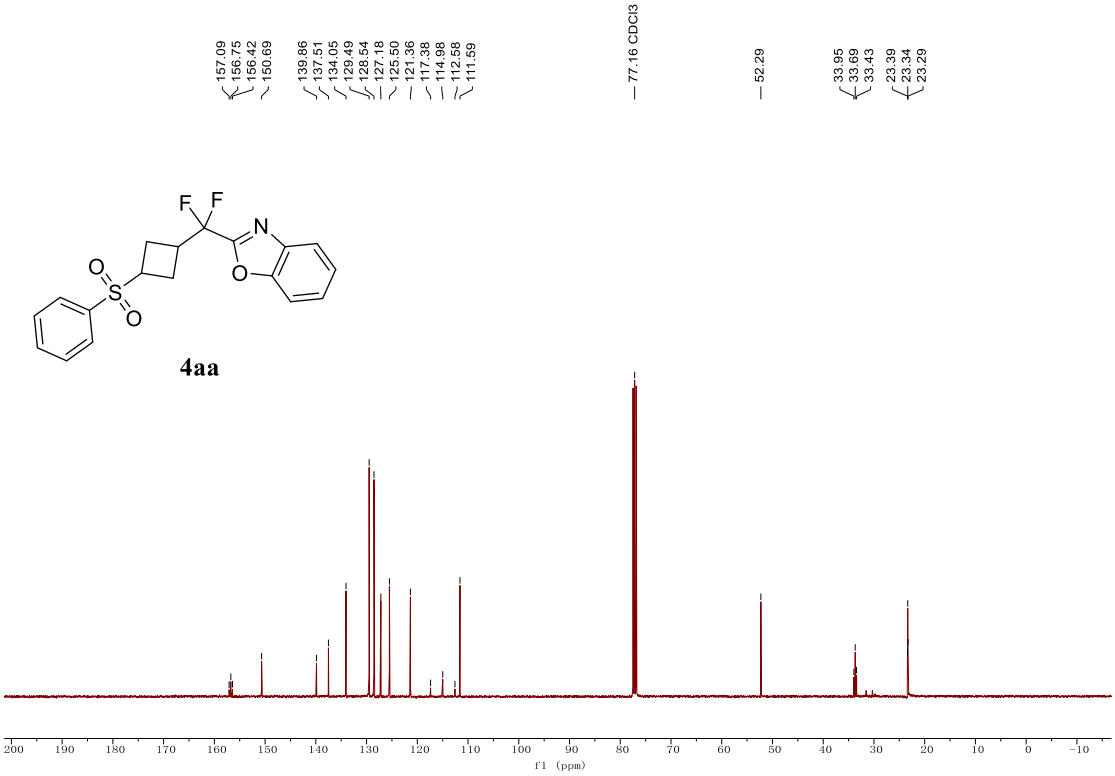
^{19}F NMR Spectrum of Compound **4z** (282 MHz, $CDCl_3$)



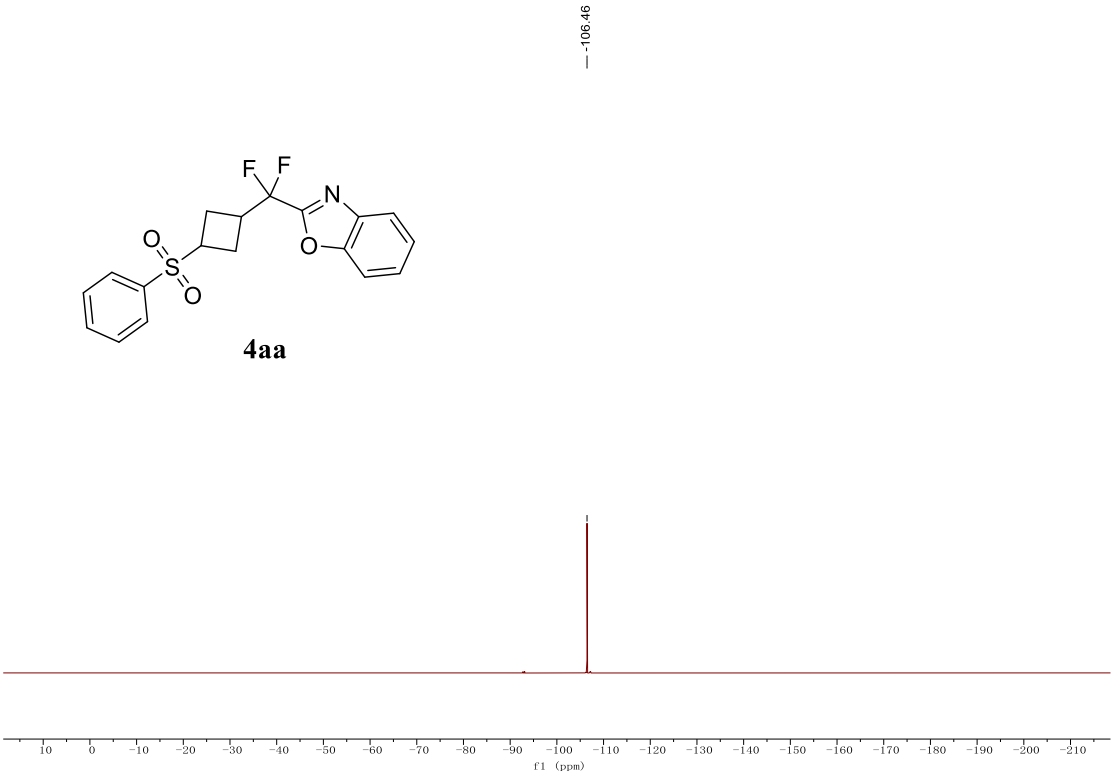
^{1}H NMR Spectrum of Compound **4aa** (300 MHz, $CDCl_3$)



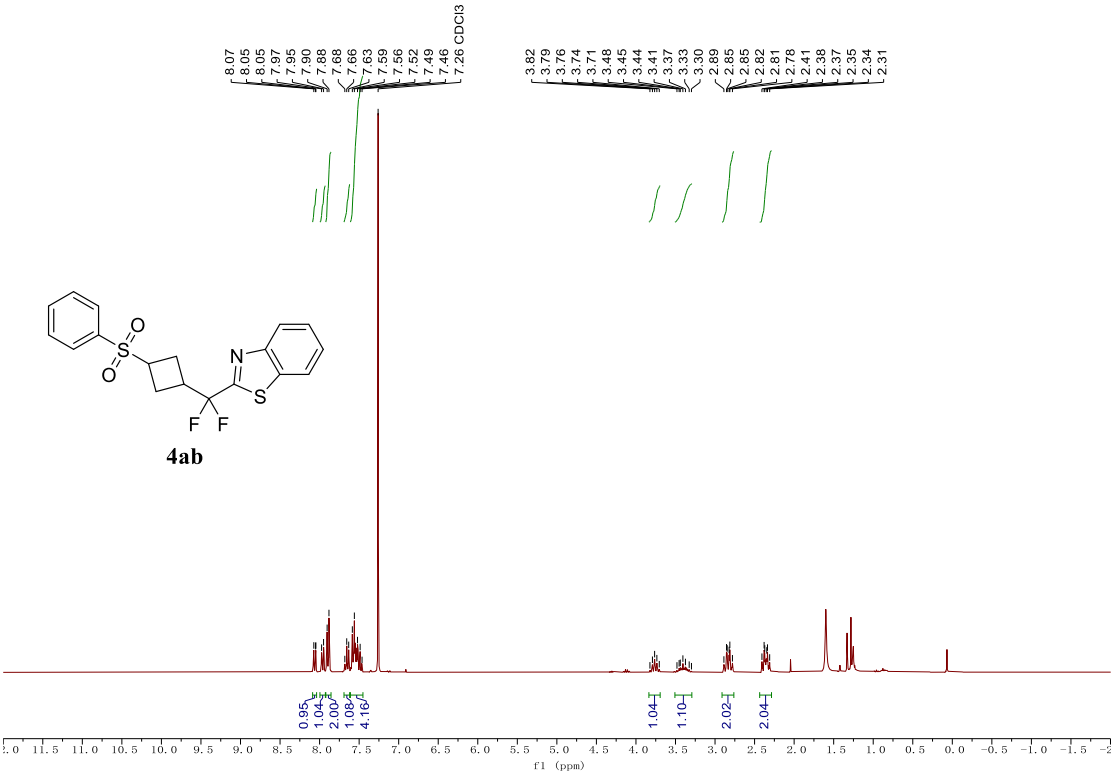
^{13}C NMR Spectrum of Compound **4aa** (101 MHz, $CDCl_3$)



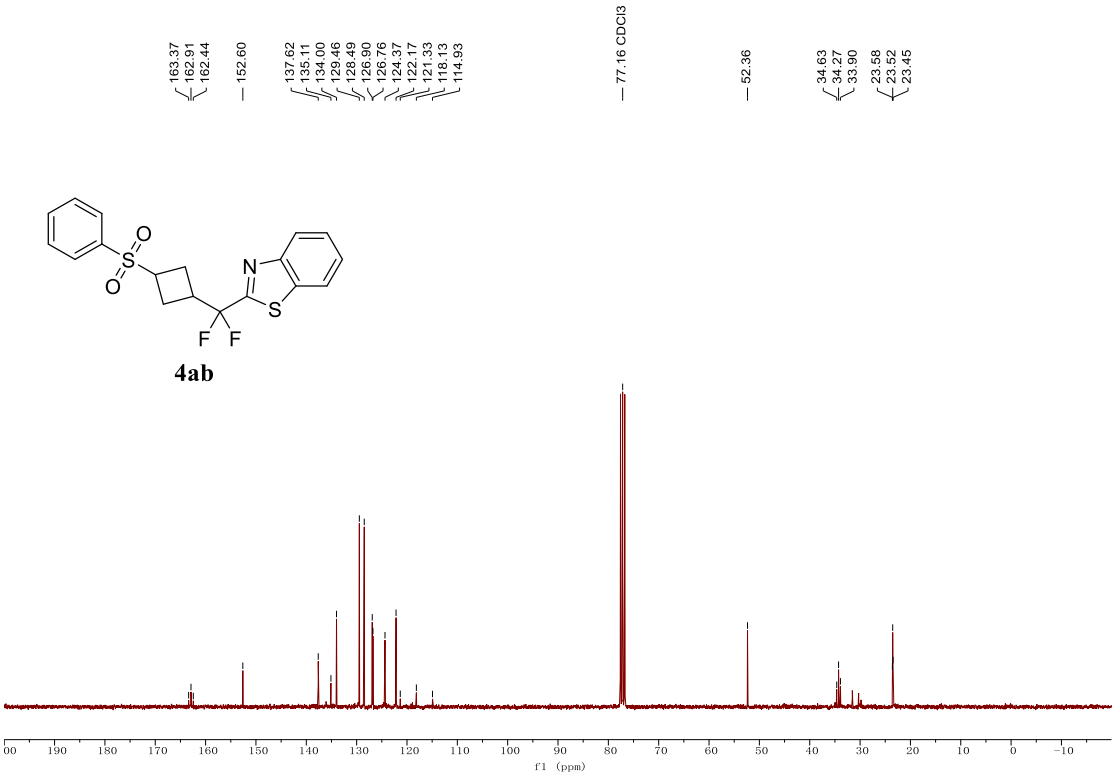
^{19}F NMR Spectrum of Compound **4aa** (282 MHz, $CDCl_3$)



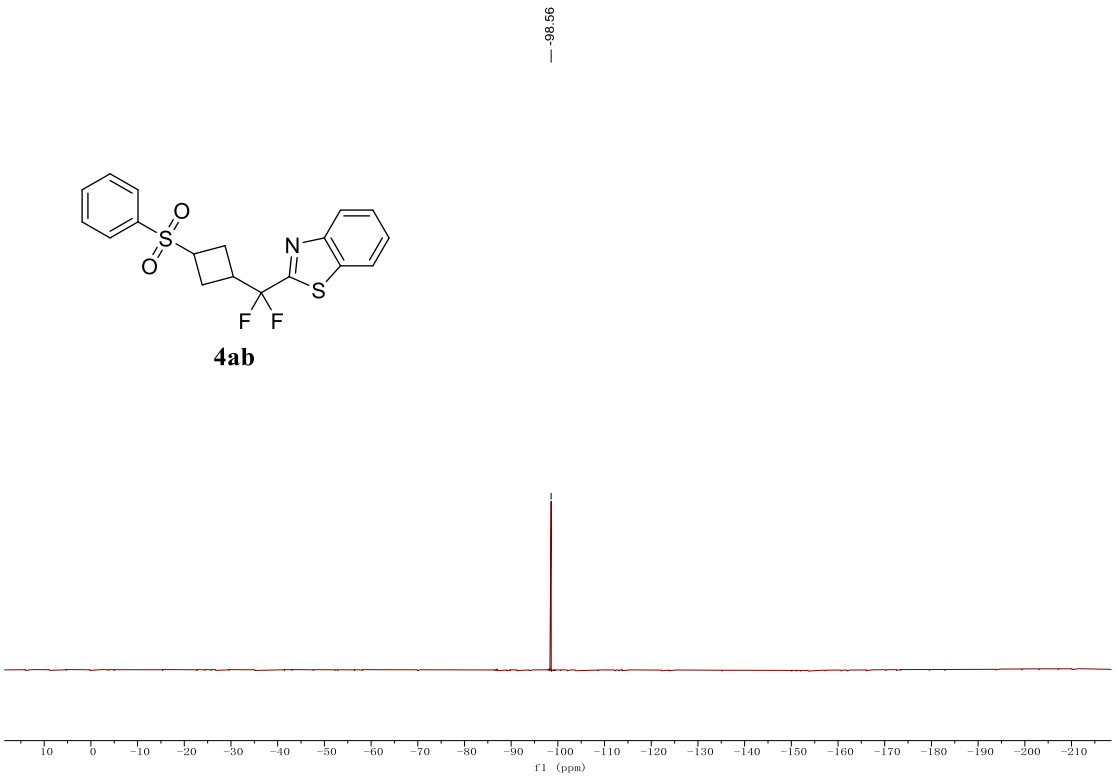
^{1}H NMR Spectrum of Compound **4ab** (300 MHz, $CDCl_3$)



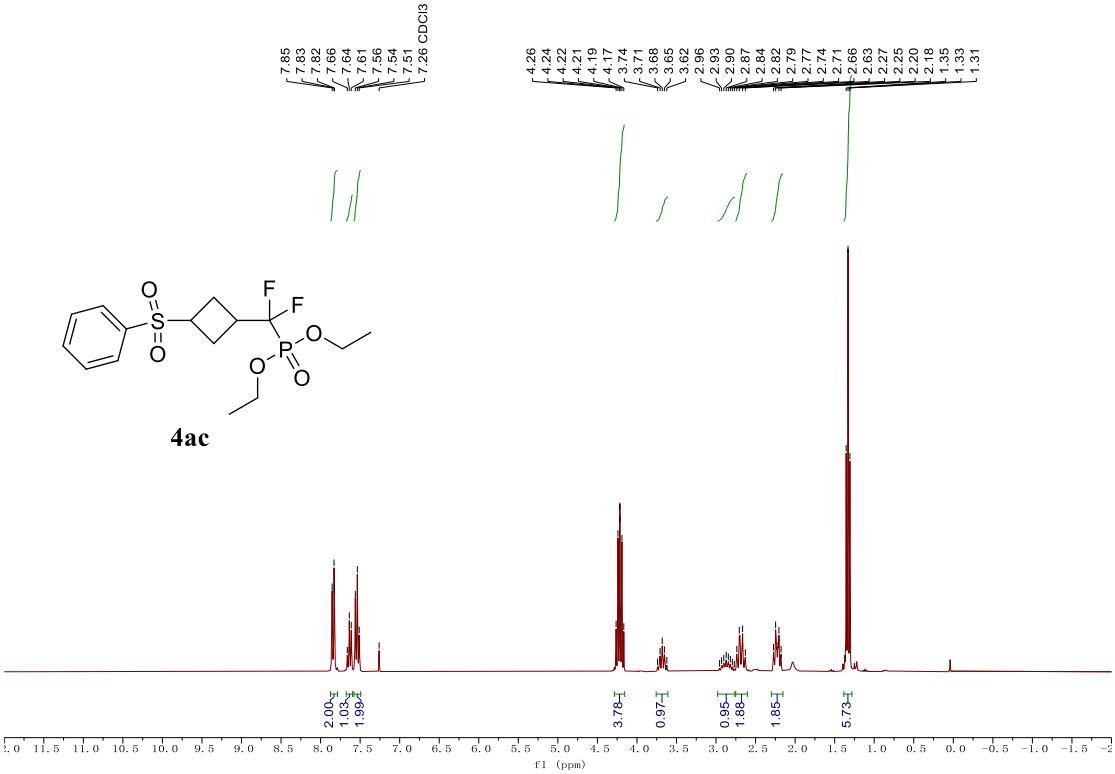
^{13}C NMR Spectrum of Compound **4ab** (75 MHz, $CDCl_3$)



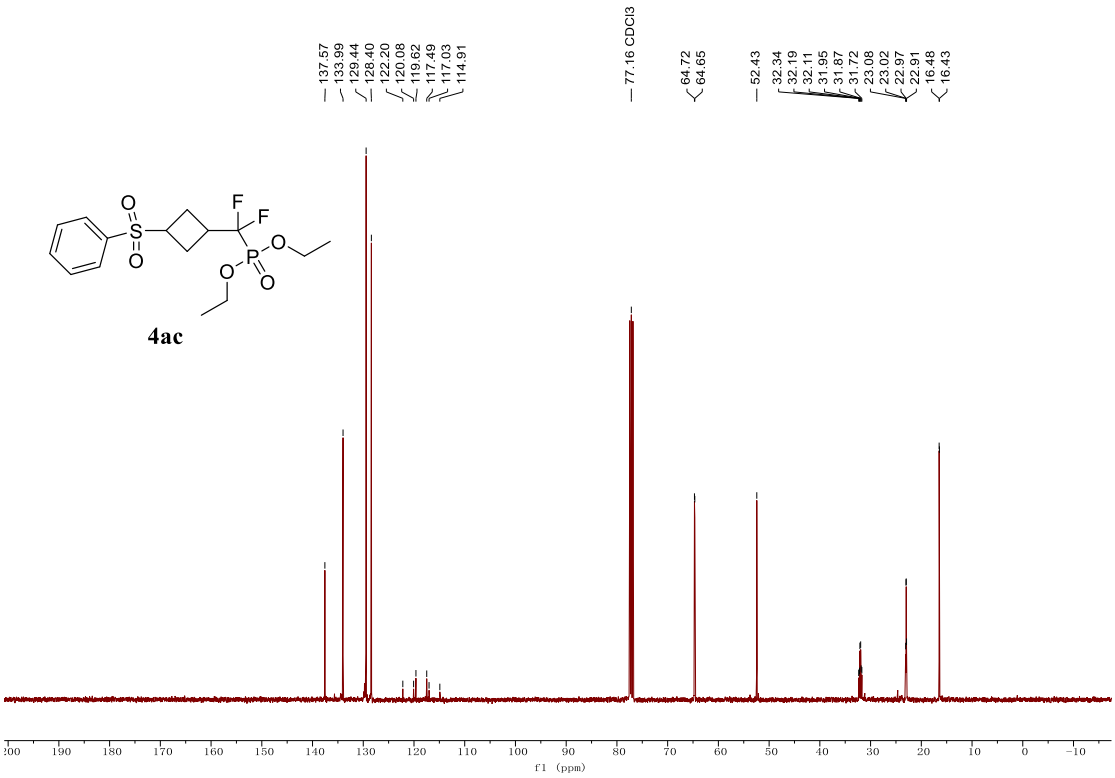
^{19}F NMR Spectrum of Compound **4ab** (282 MHz, $CDCl_3$)



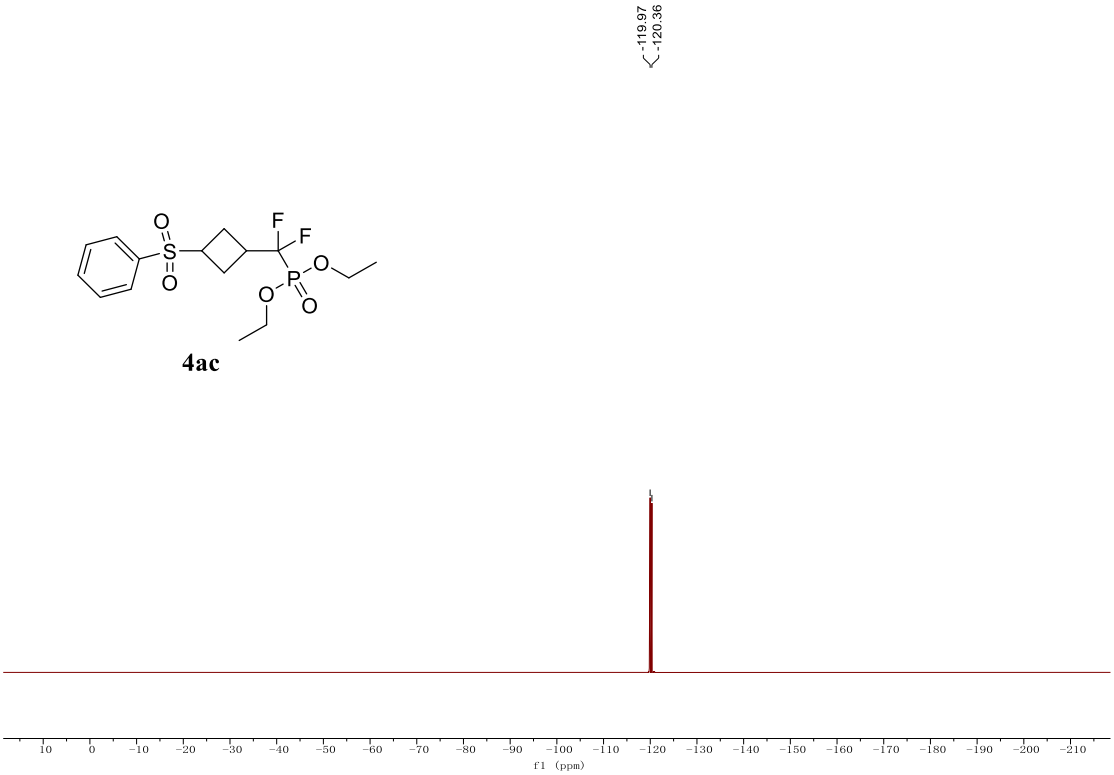
^{1}H NMR Spectrum of Compound **4ac** (300 MHz, $CDCl_3$)



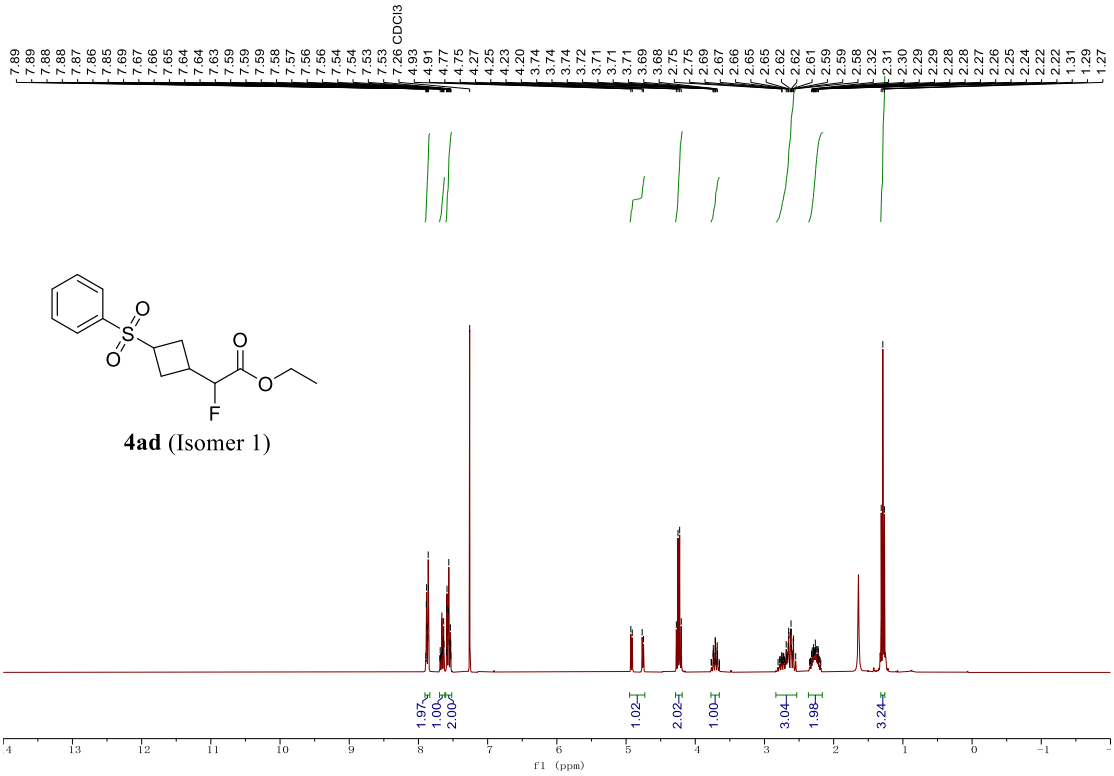
^{13}C NMR Spectrum of Compound **4ac** (101 MHz, $CDCl_3$)



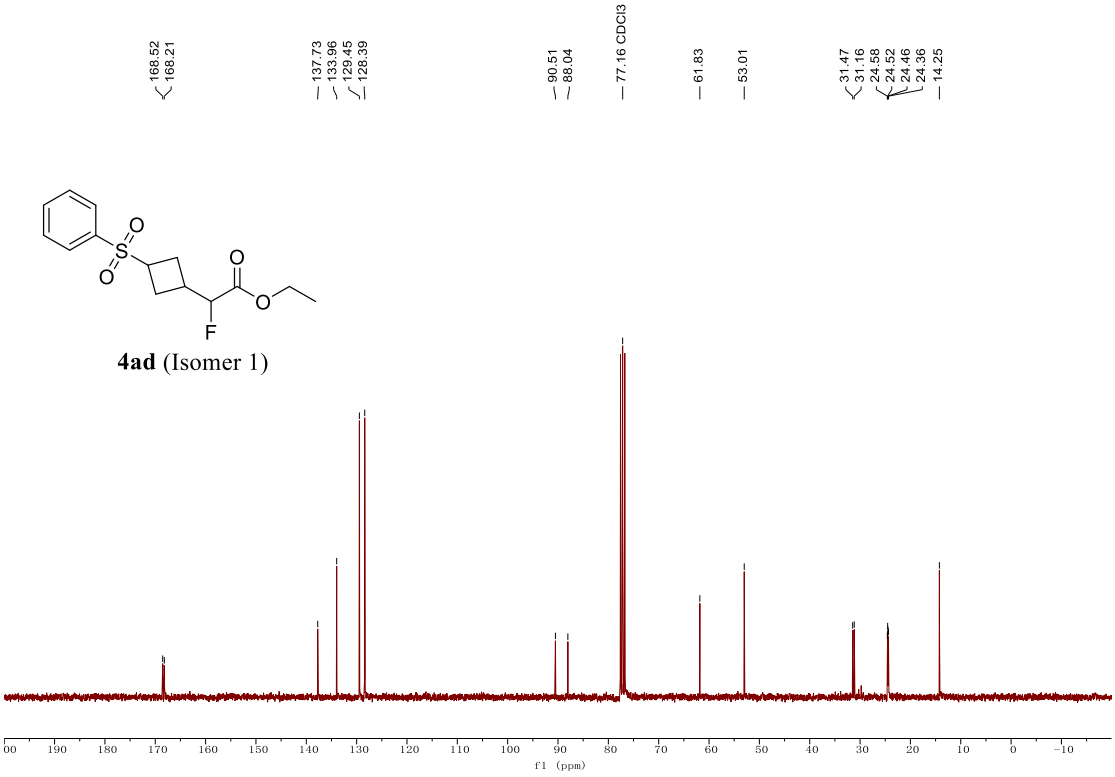
^{19}F NMR Spectrum of Compound **4ac** (282 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound **4ad** (isomer 1) (300 MHz, $CDCl_3$)

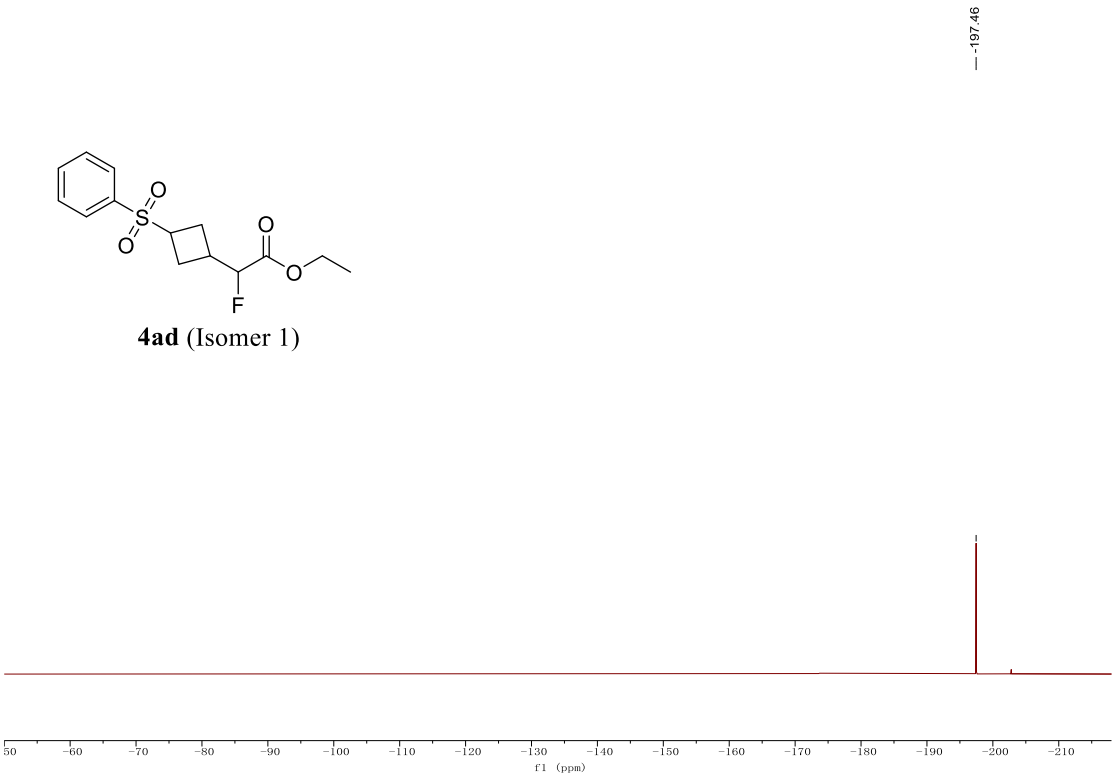


^{13}C NMR Spectrum of Compound **4ad** (isomer 1) (75 MHz, $CDCl_3$)



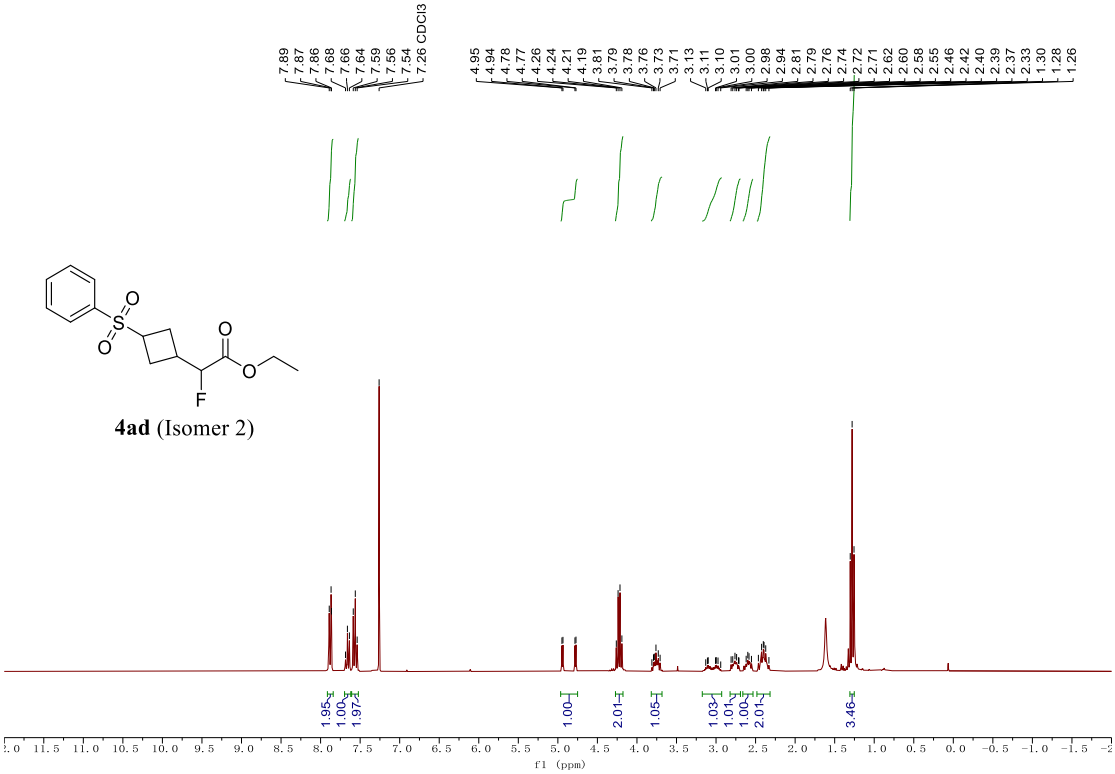
4ad (Isomer 1)

^{19}F NMR Spectrum of Compound **4ad** (isomer 1) (282 MHz, $CDCl_3$)

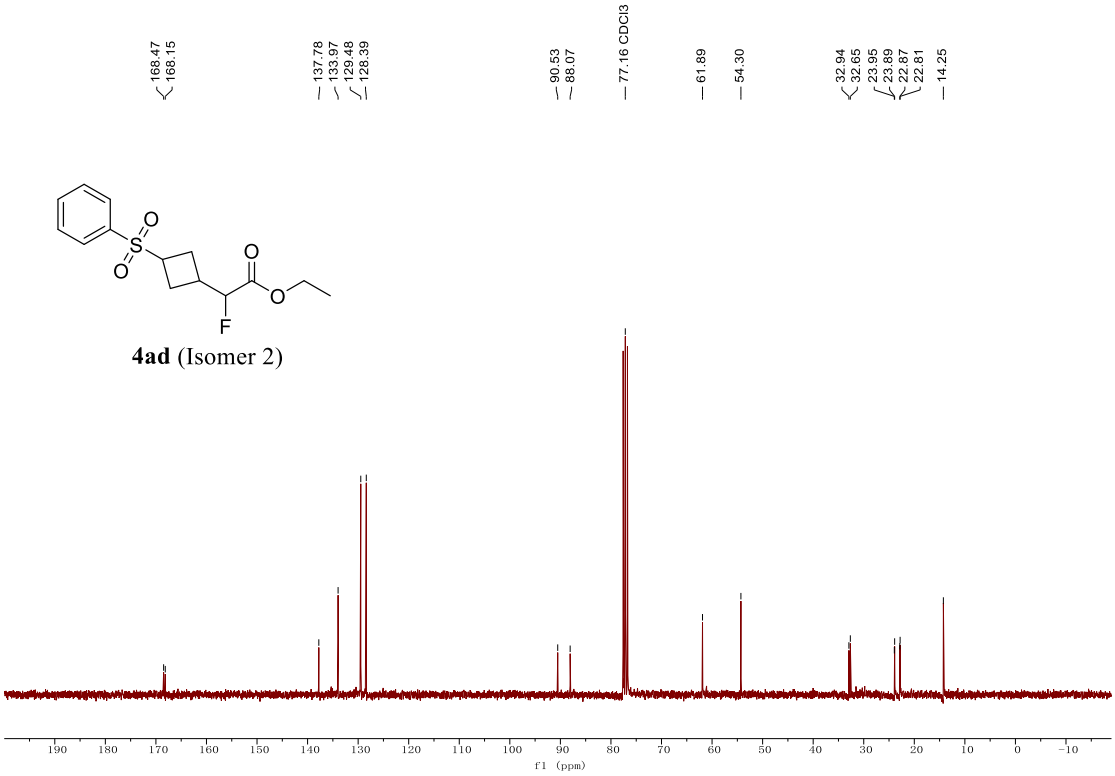


4ad (Isomer 1)

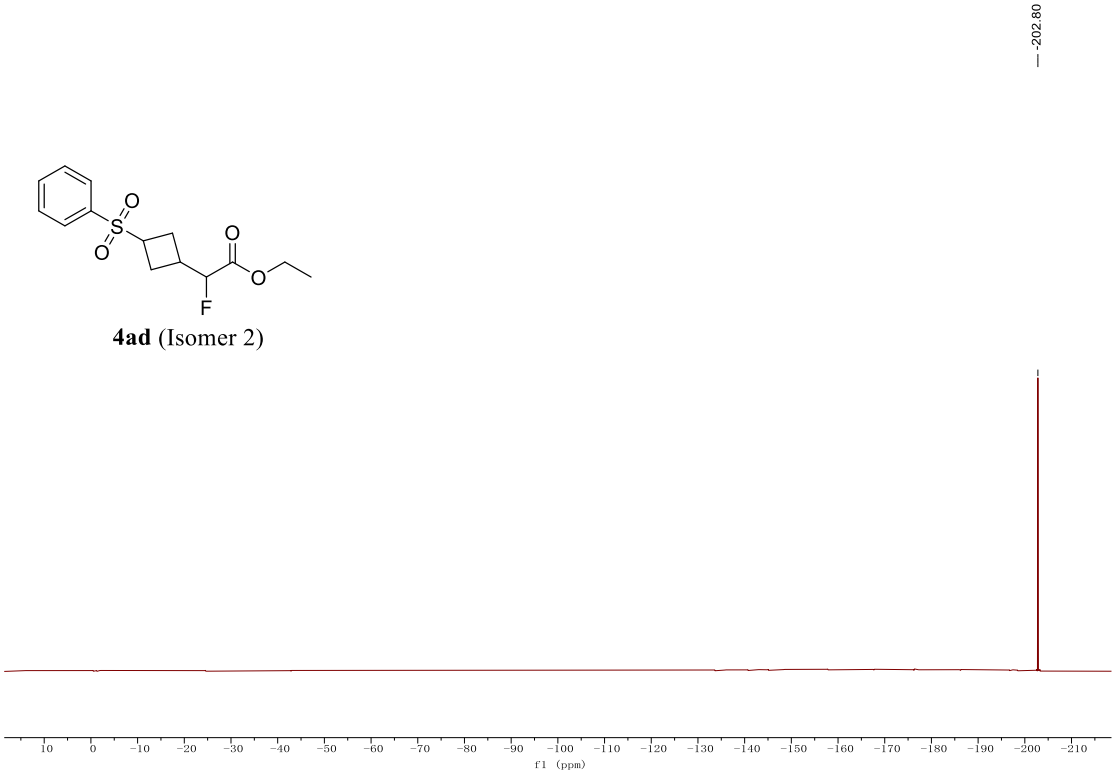
^{1}H NMR Spectrum of Compound **4ad** (isomer 2) (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **4ad** (isomer 2) (75 MHz, $CDCl_3$)

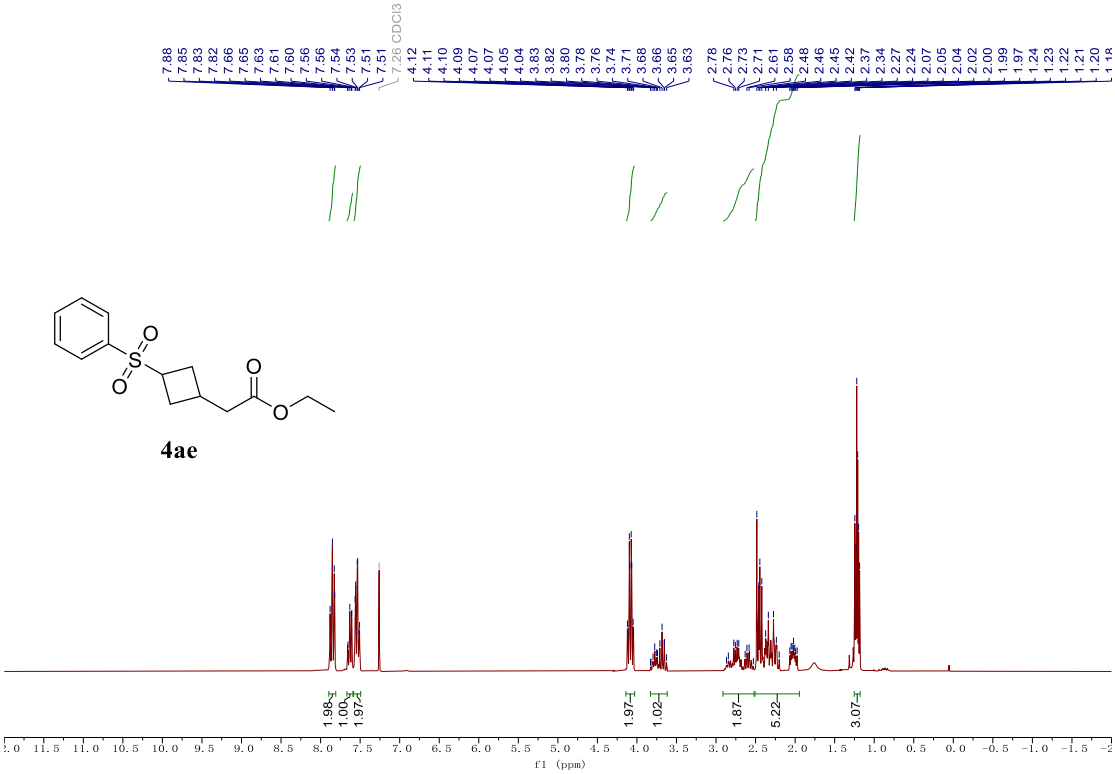


^{19}F NMR Spectrum of Compound **4ad** (isomer 2) (282 MHz, $CDCl_3$)



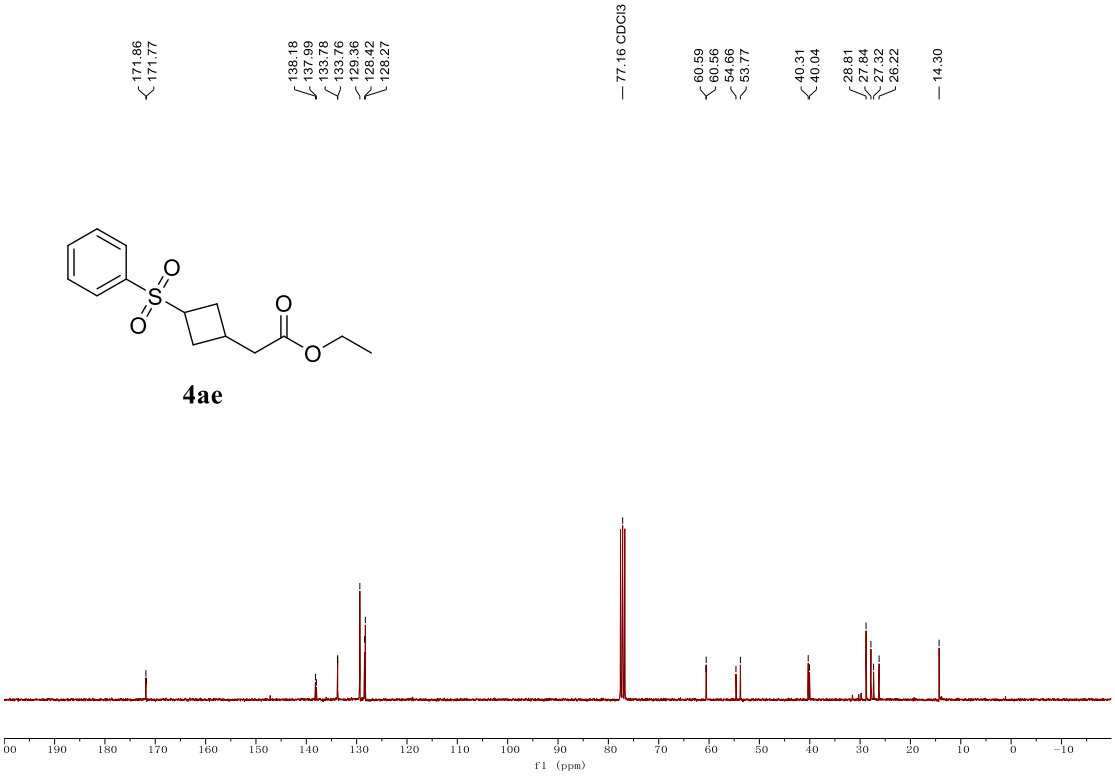
4ad (Isomer 2)

^{1}H NMR Spectrum of Compound **4ae** (300 MHz, $CDCl_3$)



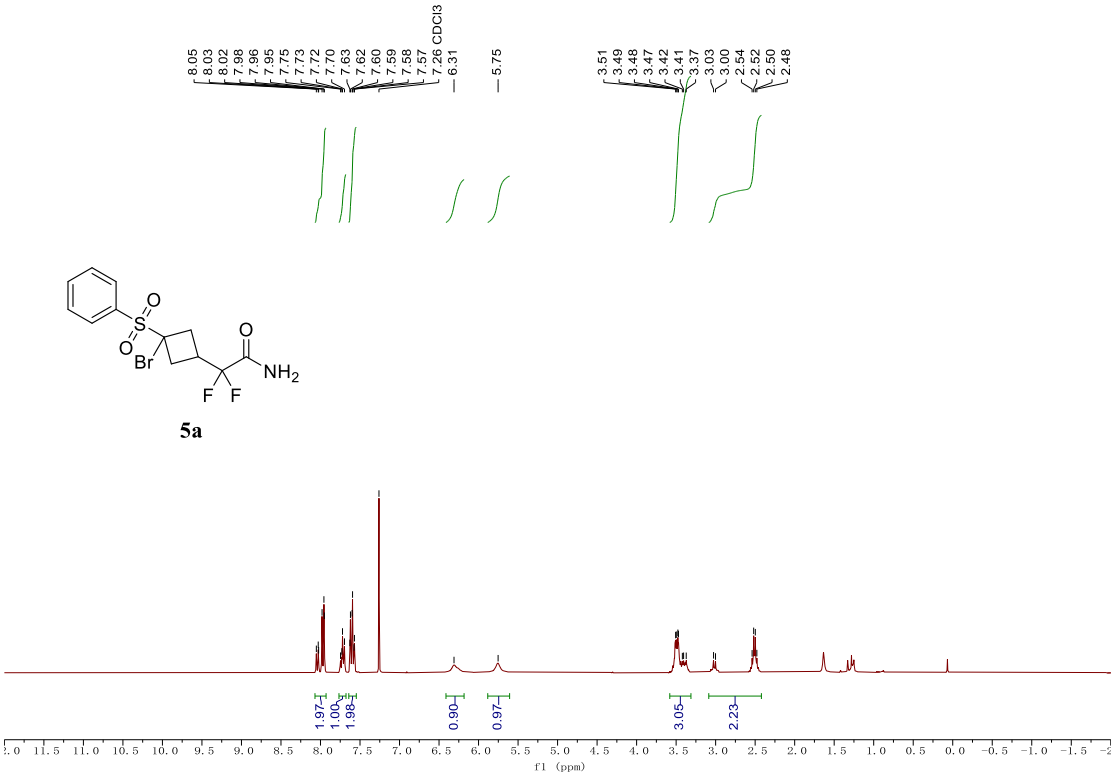
4ae

^{13}C NMR Spectrum of Compound **4ae** (75 MHz, $CDCl_3$)



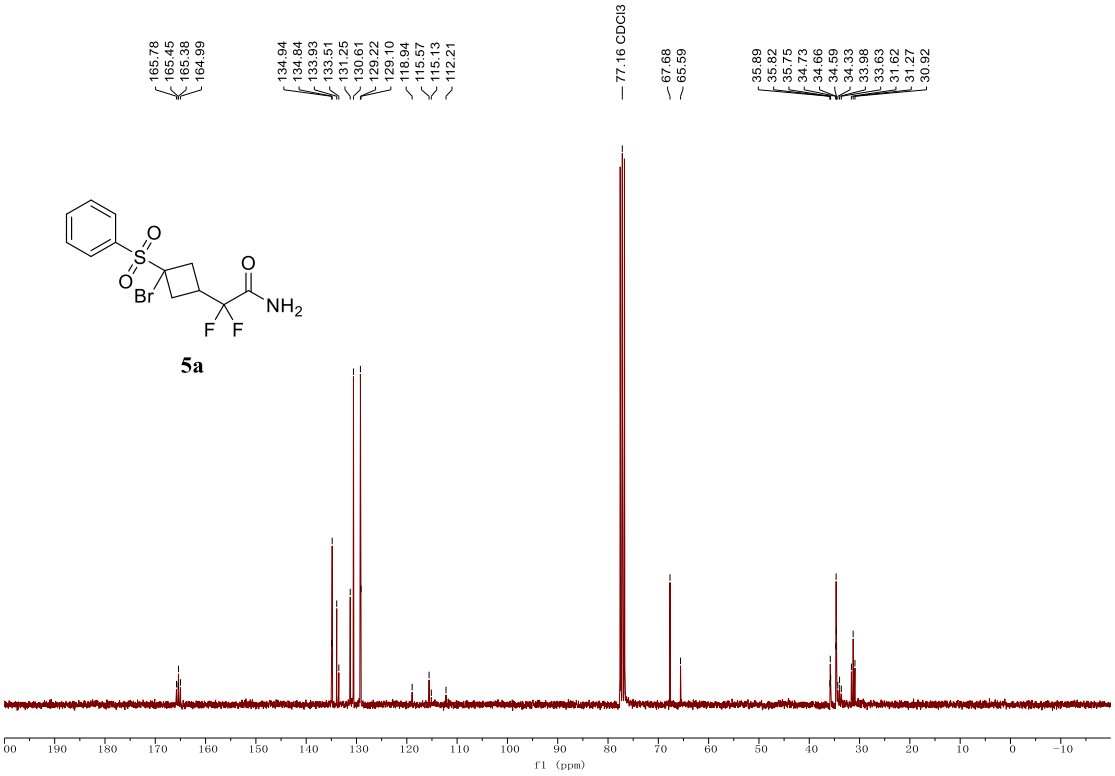
4ae

^{1}H NMR Spectrum of Compound **5a** (300 MHz, $CDCl_3$)

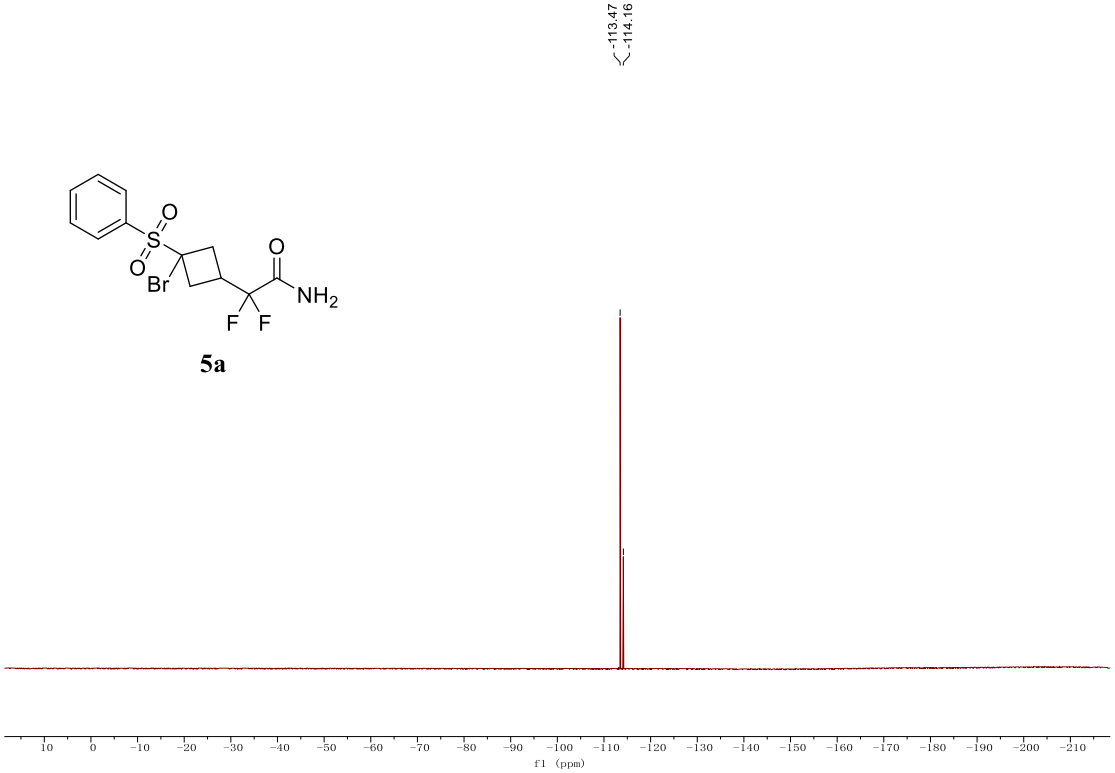


5a

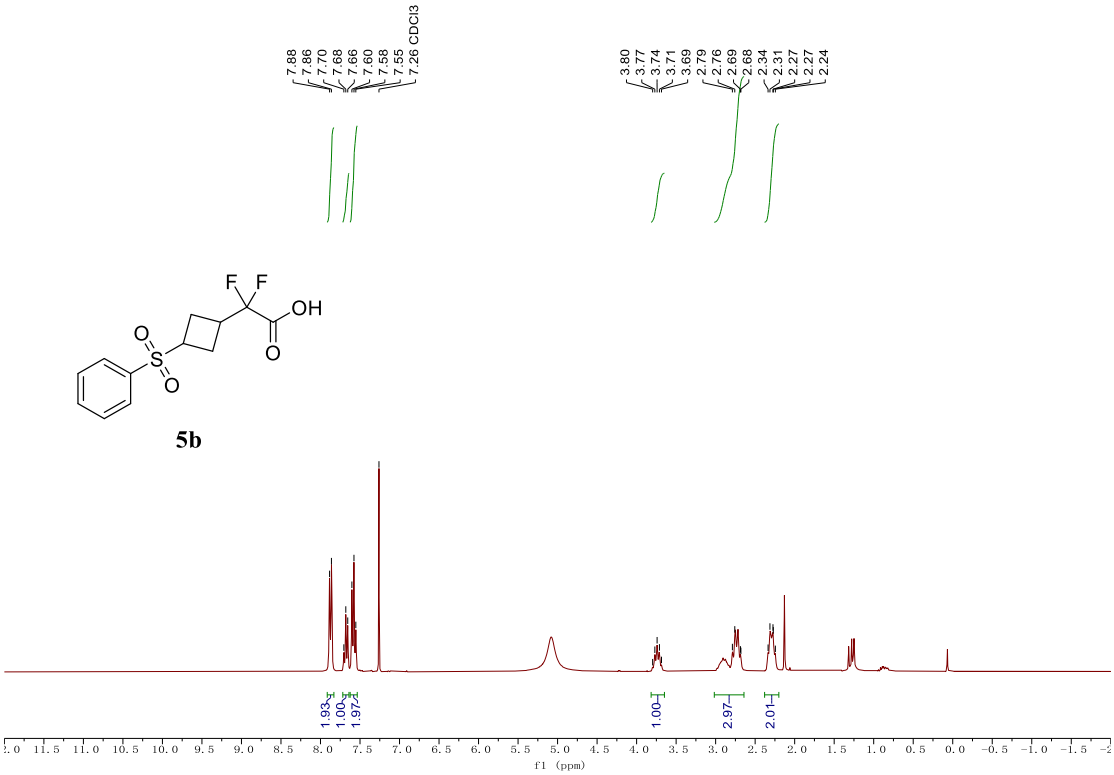
^{13}C NMR Spectrum of Compound **5a** (75 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **5a** (282 MHz, $CDCl_3$)

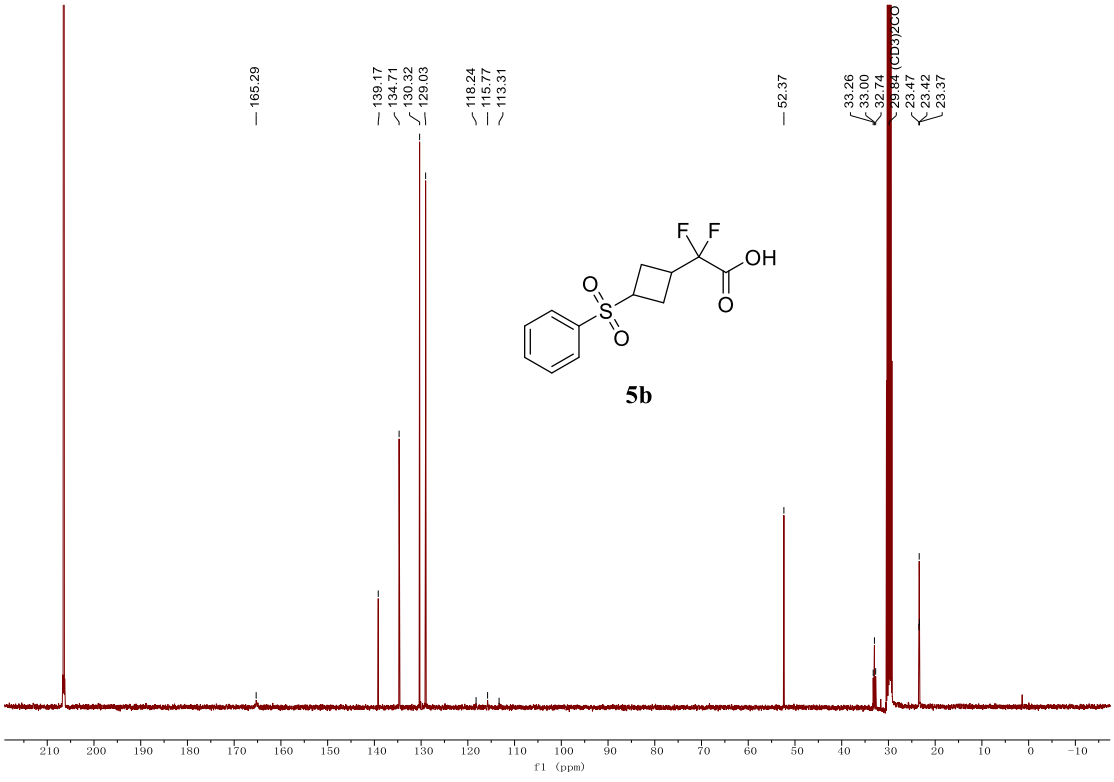


^{1}H NMR Spectrum of Compound **5b** (300 MHz, $CDCl_3$)



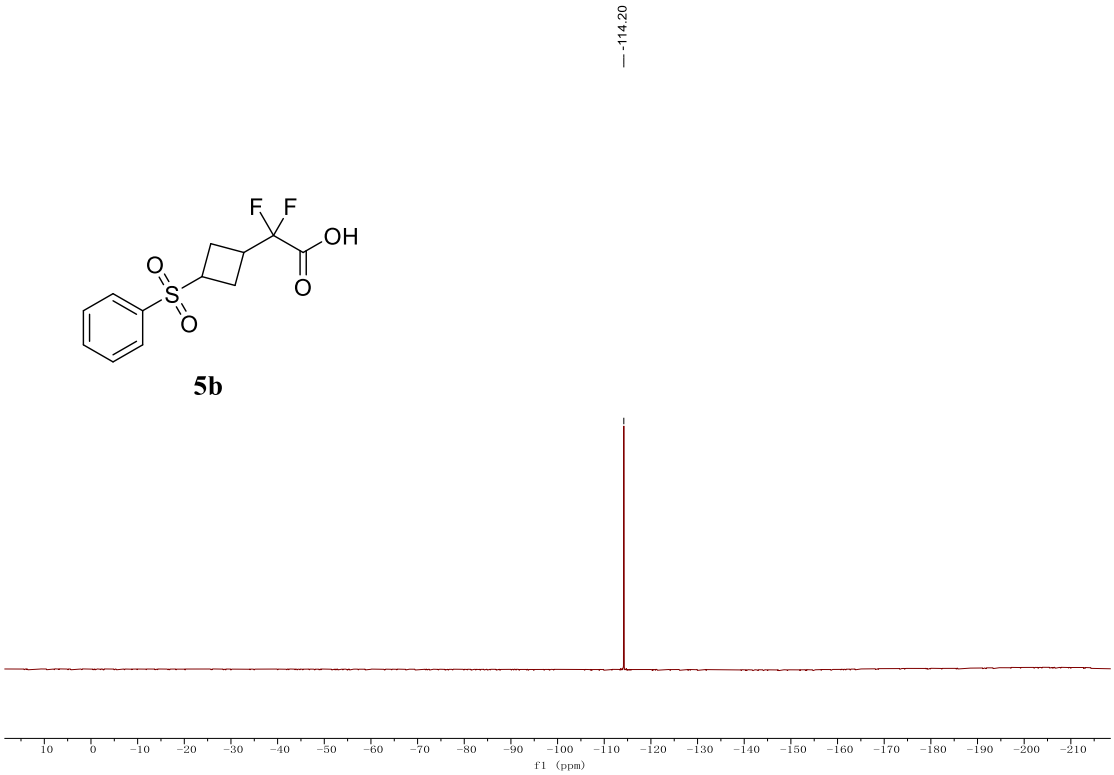
5b

^{13}C NMR Spectrum of Compound **5b** (101 MHz, Acetone-d_6)



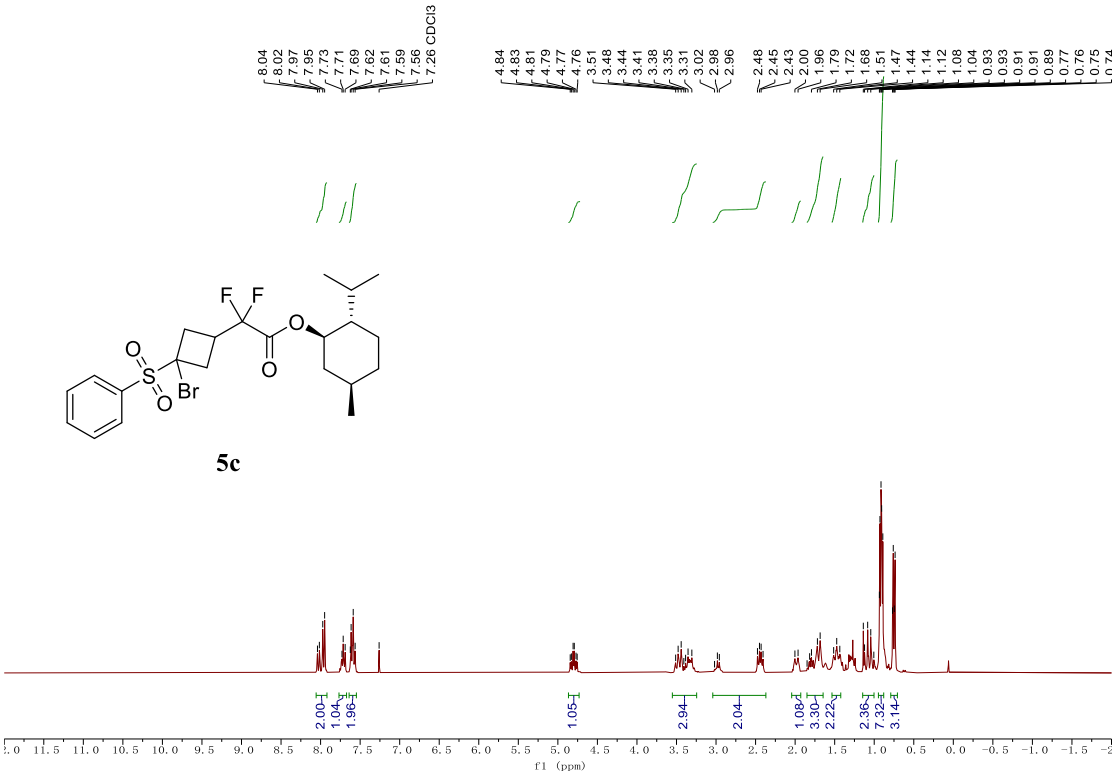
5b

^{19}F NMR Spectrum of Compound **5b** (282 MHz, $CDCl_3$)



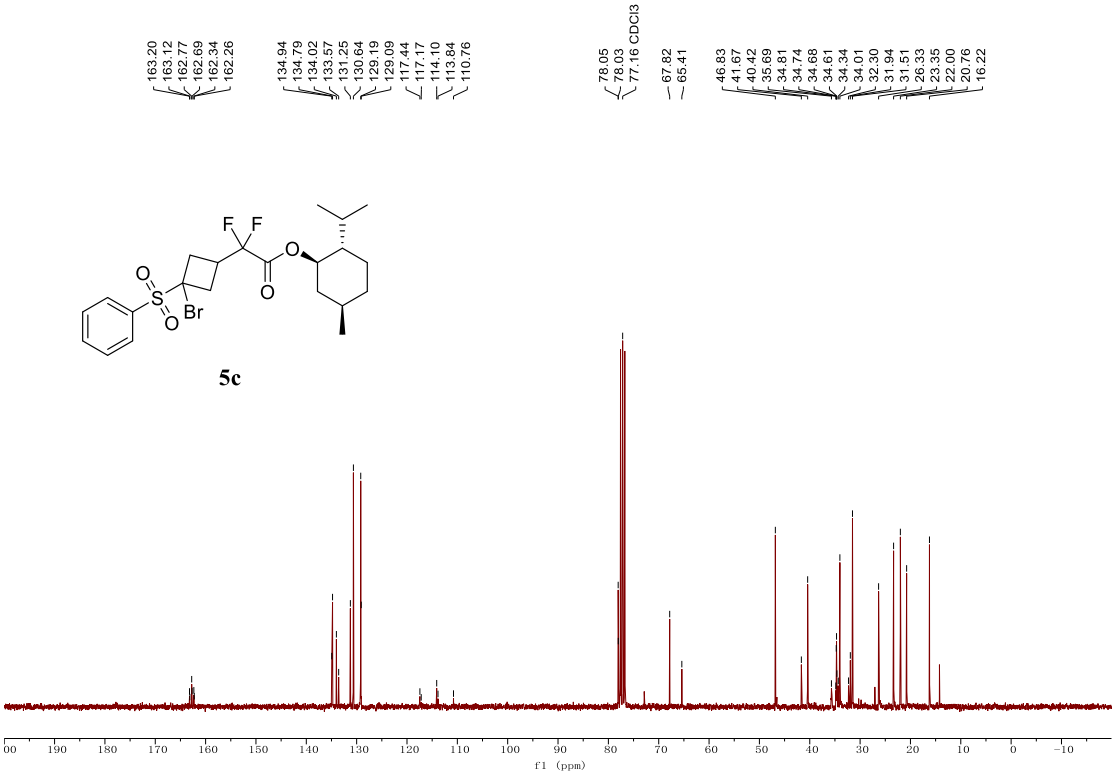
5b

^{1}H NMR Spectrum of Compound **5c** (300 MHz, $CDCl_3$)



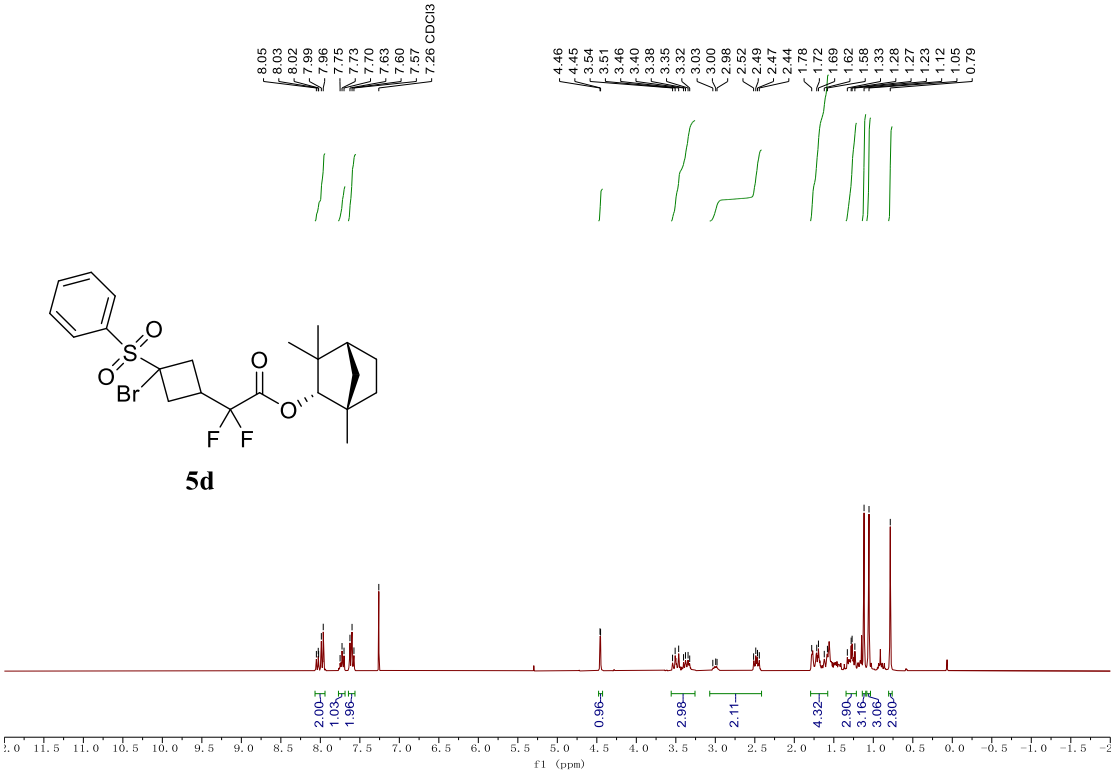
5c

^{13}C NMR Spectrum of Compound **5c** (75 MHz, $CDCl_3$)

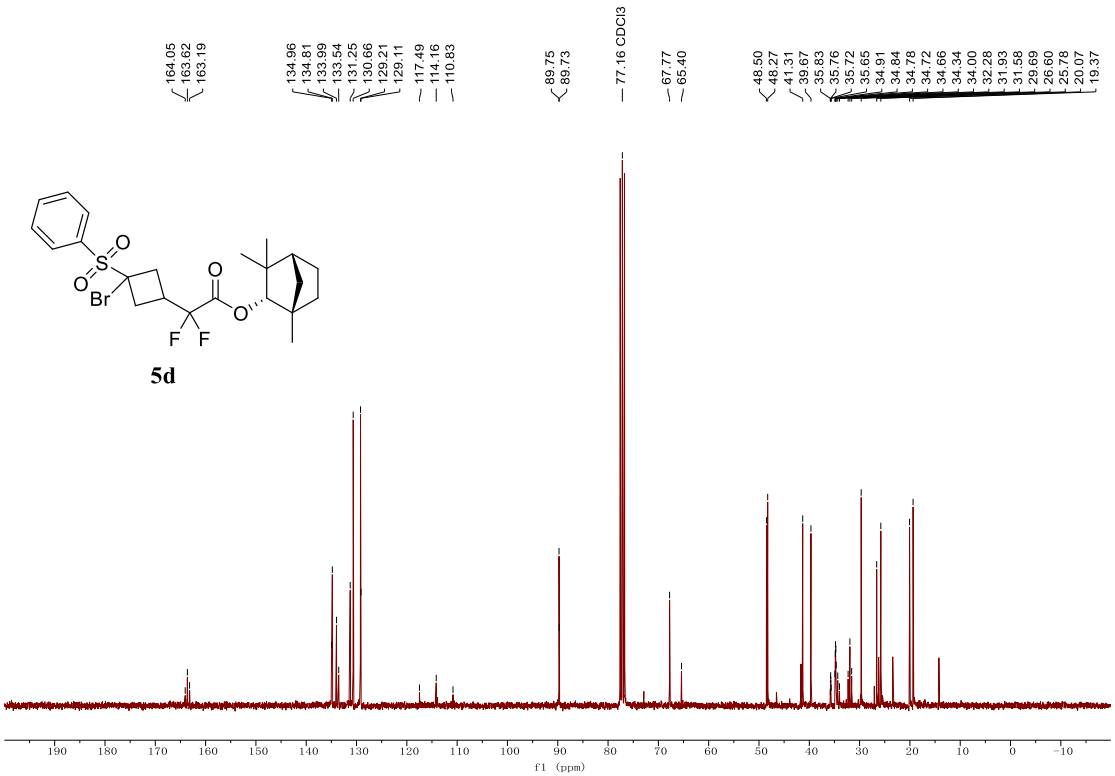


^{19}F NMR Spectrum of Compound **5c** (282 MHz, $CDCl_3$)

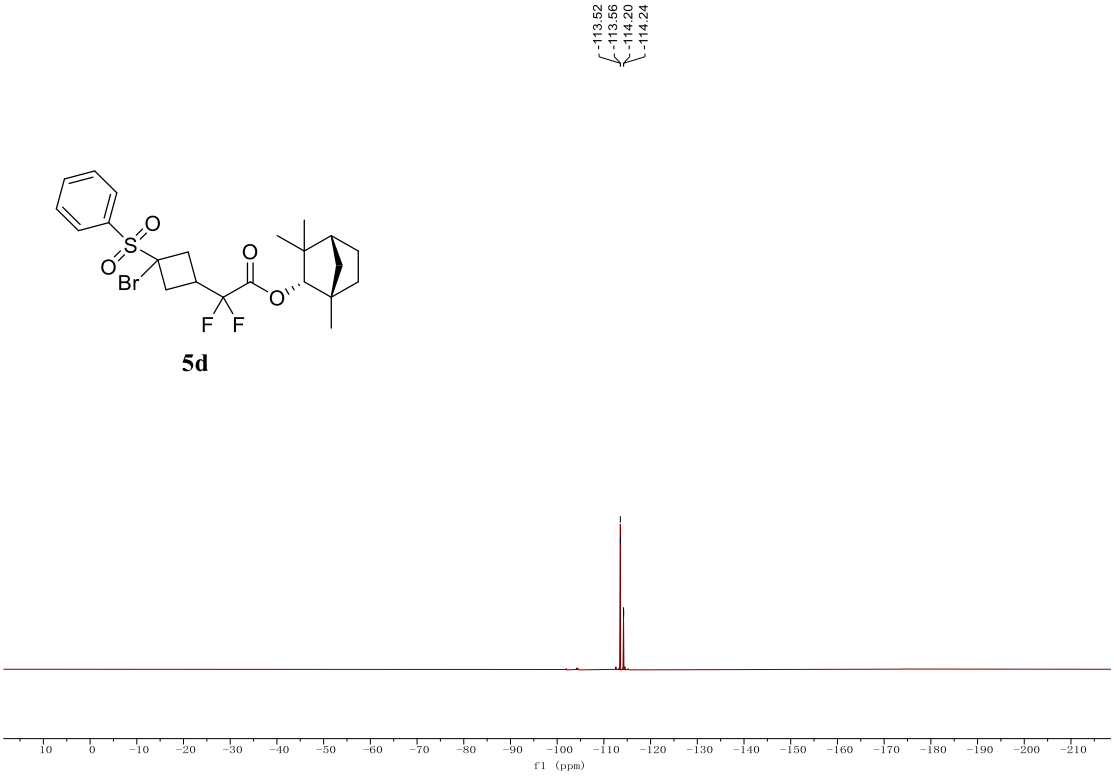
^{1}H NMR Spectrum of Compound **5d** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **5d** (75 MHz, $CDCl_3$)

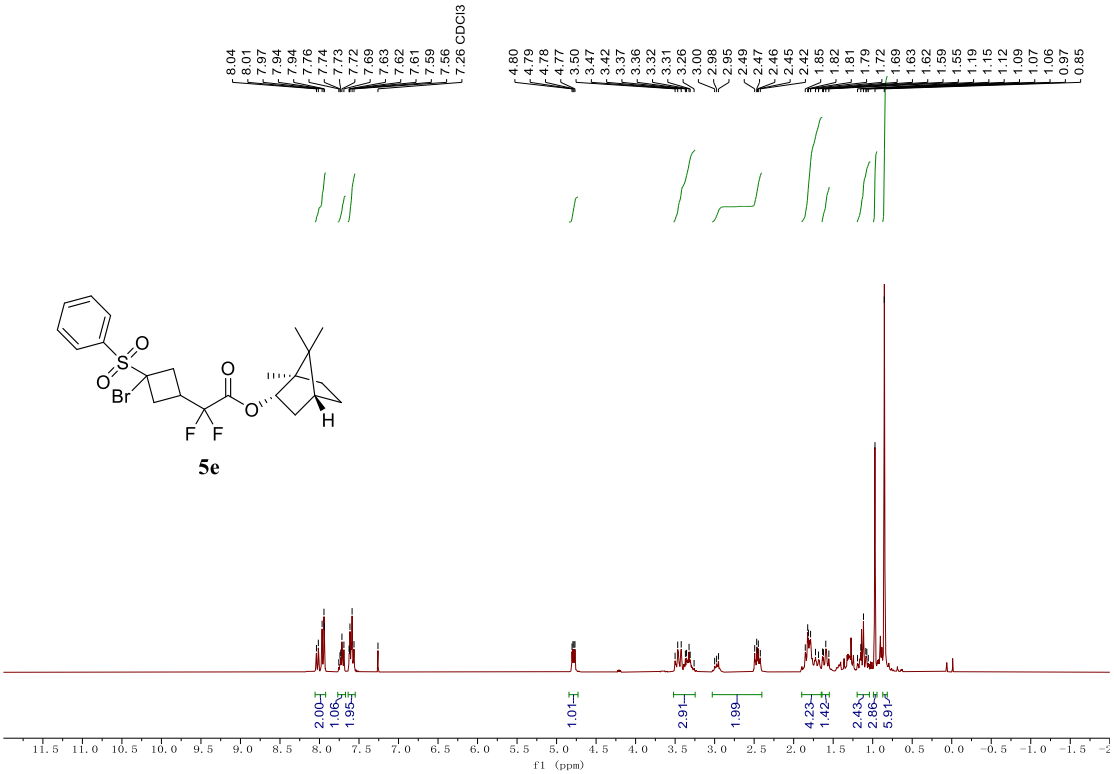


^{19}F NMR Spectrum of Compound **5d** (282 MHz, $CDCl_3$)



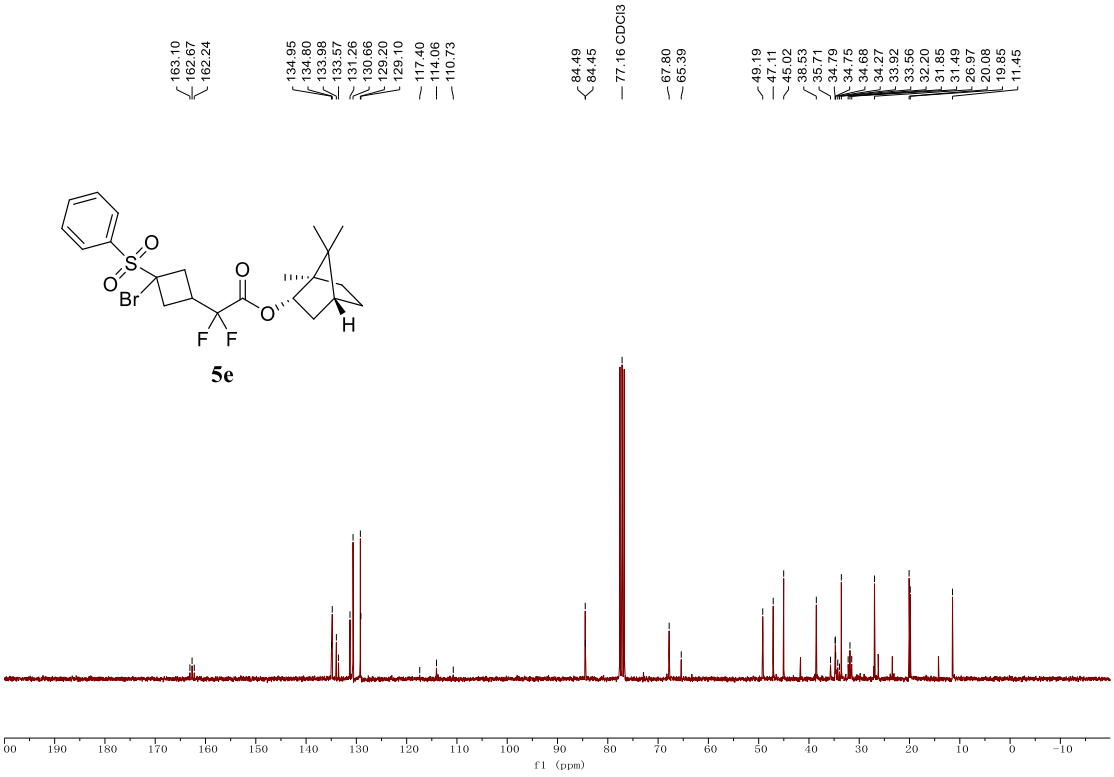
5d

^{1}H NMR Spectrum of Compound **5e** (300 MHz, $CDCl_3$)



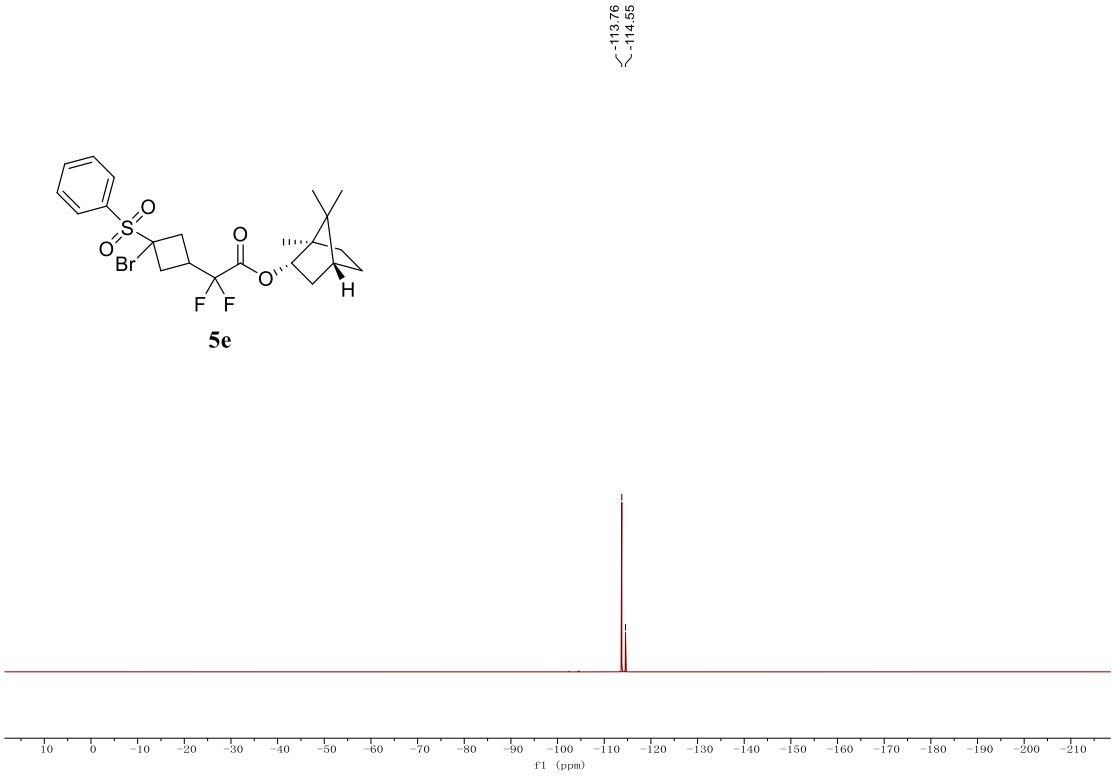
5e

^{13}C NMR Spectrum of Compound **5e** (75 MHz, $CDCl_3$)



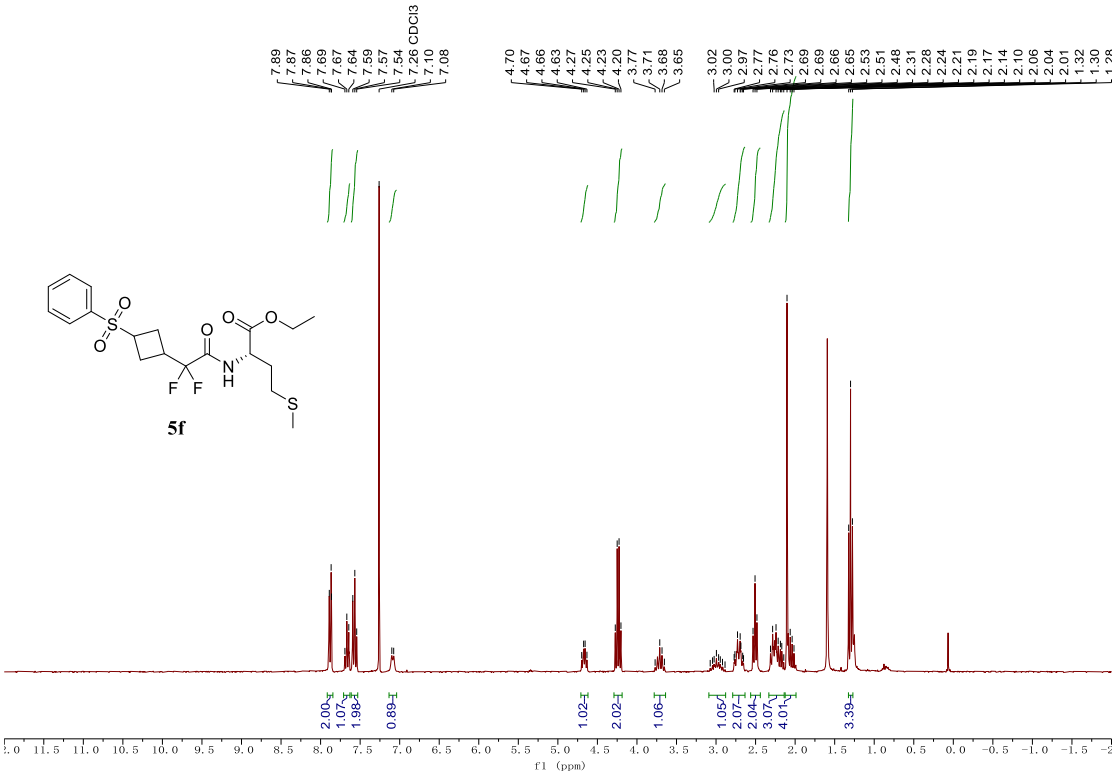
5e

^{19}F NMR Spectrum of Compound **5e** (282 MHz, $CDCl_3$)

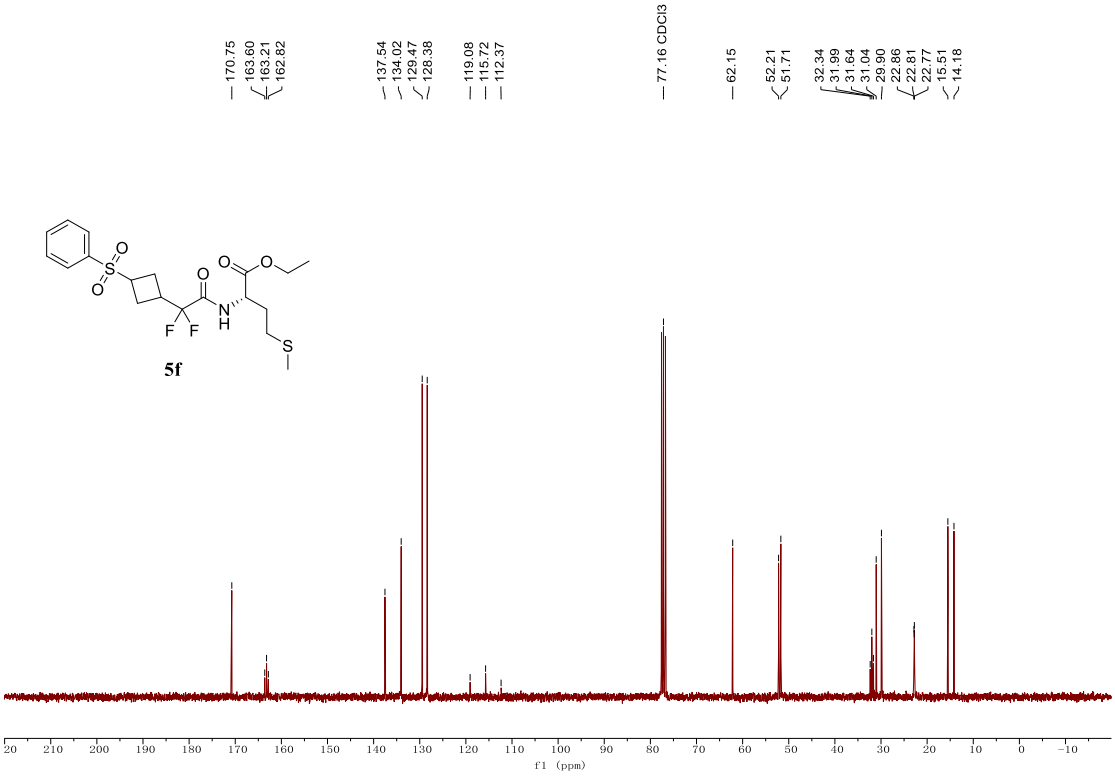


5e

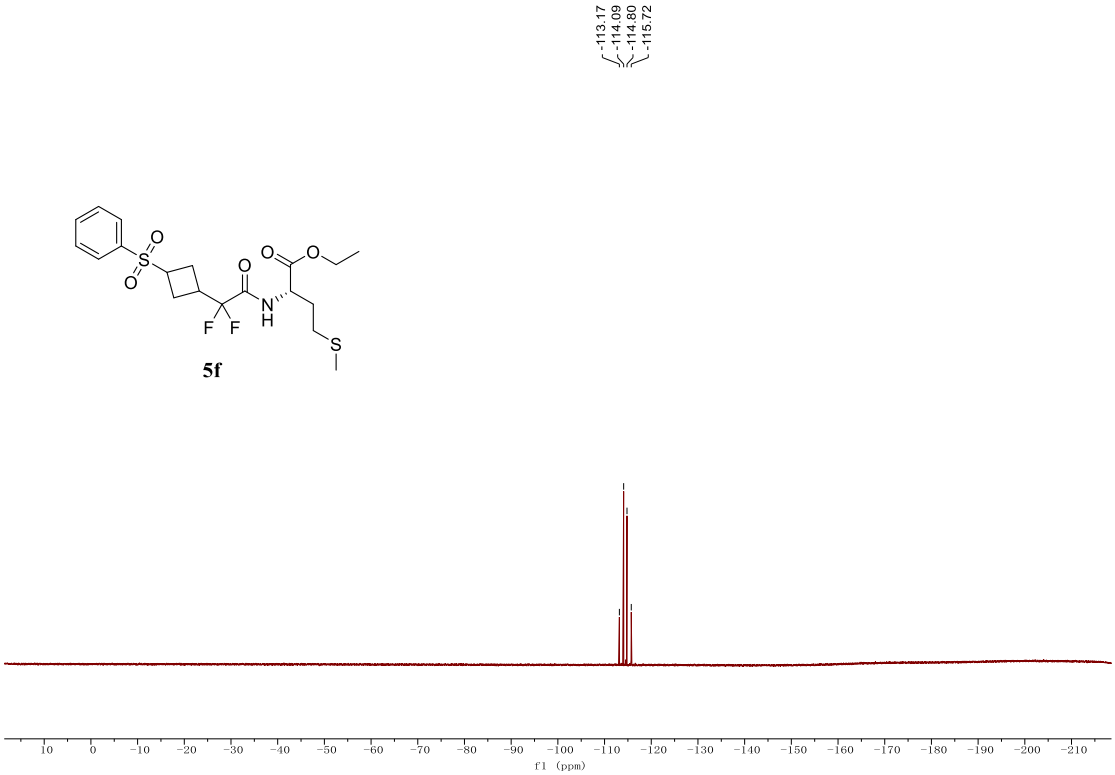
^{1}H NMR Spectrum of Compound **5f** (300 MHz, $CDCl_3$)



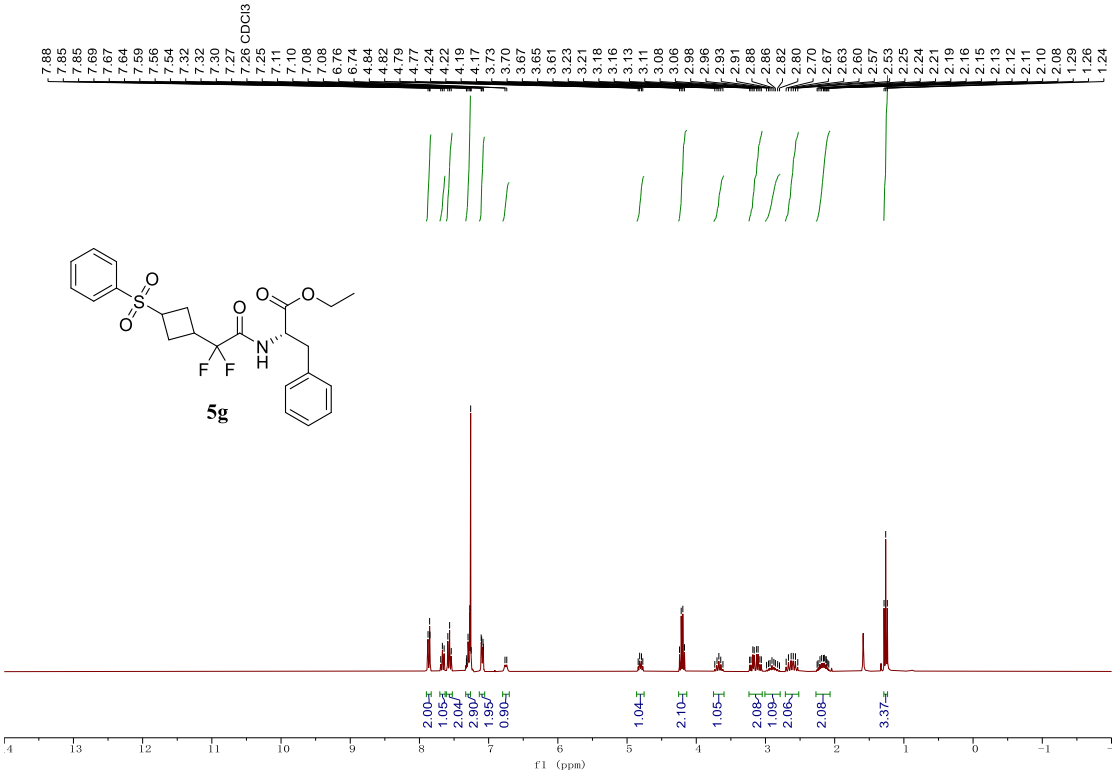
^{13}C NMR Spectrum of Compound **5f** (75 MHz, $CDCl_3$)



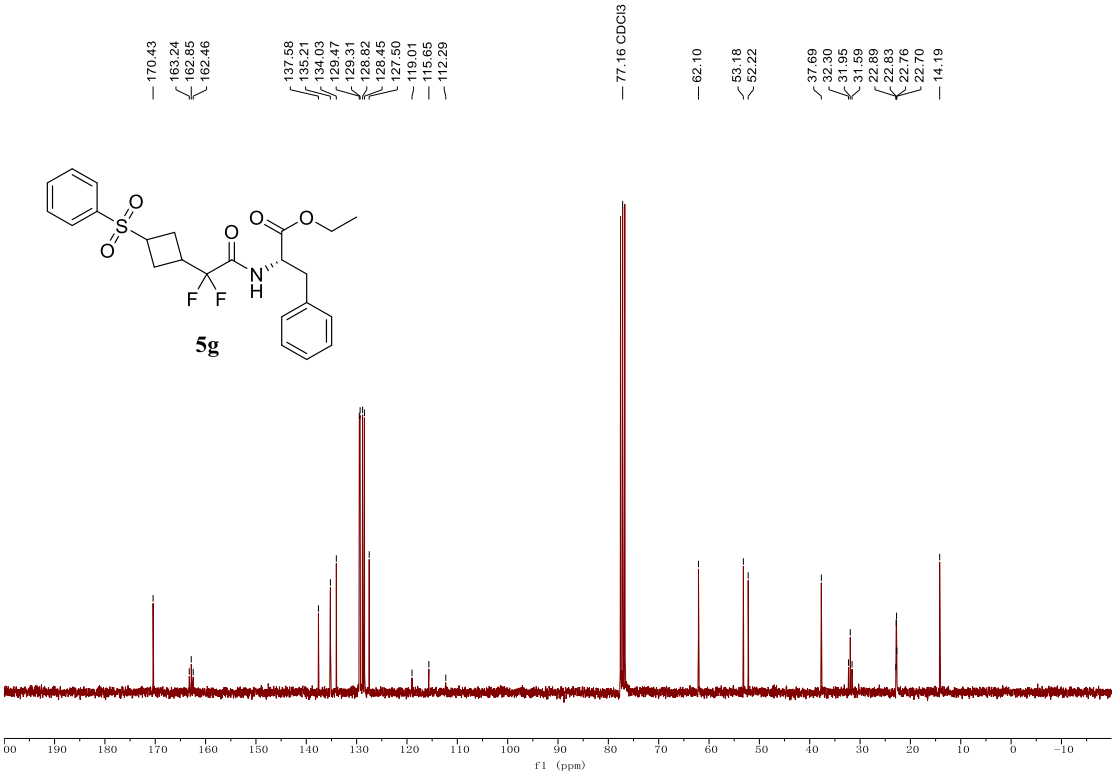
^{19}F NMR Spectrum of Compound **5f** (282 MHz, $CDCl_3$)



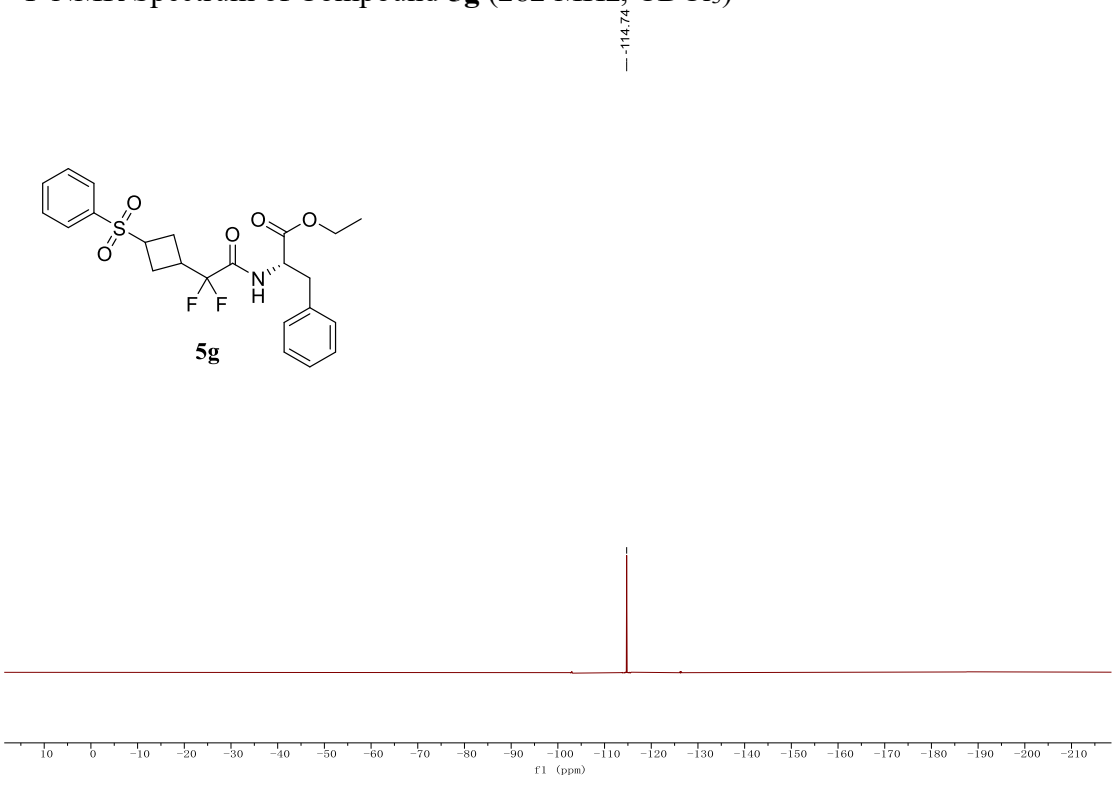
^{1}H NMR Spectrum of Compound **5g** (300 MHz, $CDCl_3$)



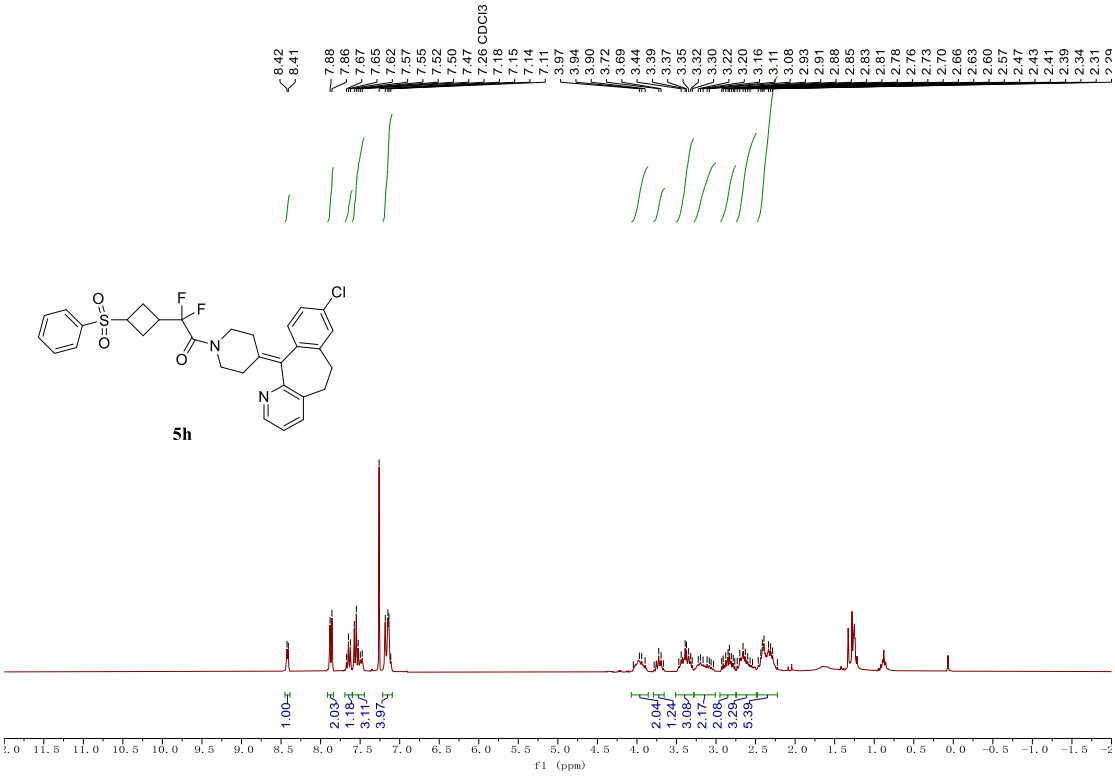
^{13}C NMR Spectrum of Compound **5g** (75 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **5g** (282 MHz, $CDCl_3$)

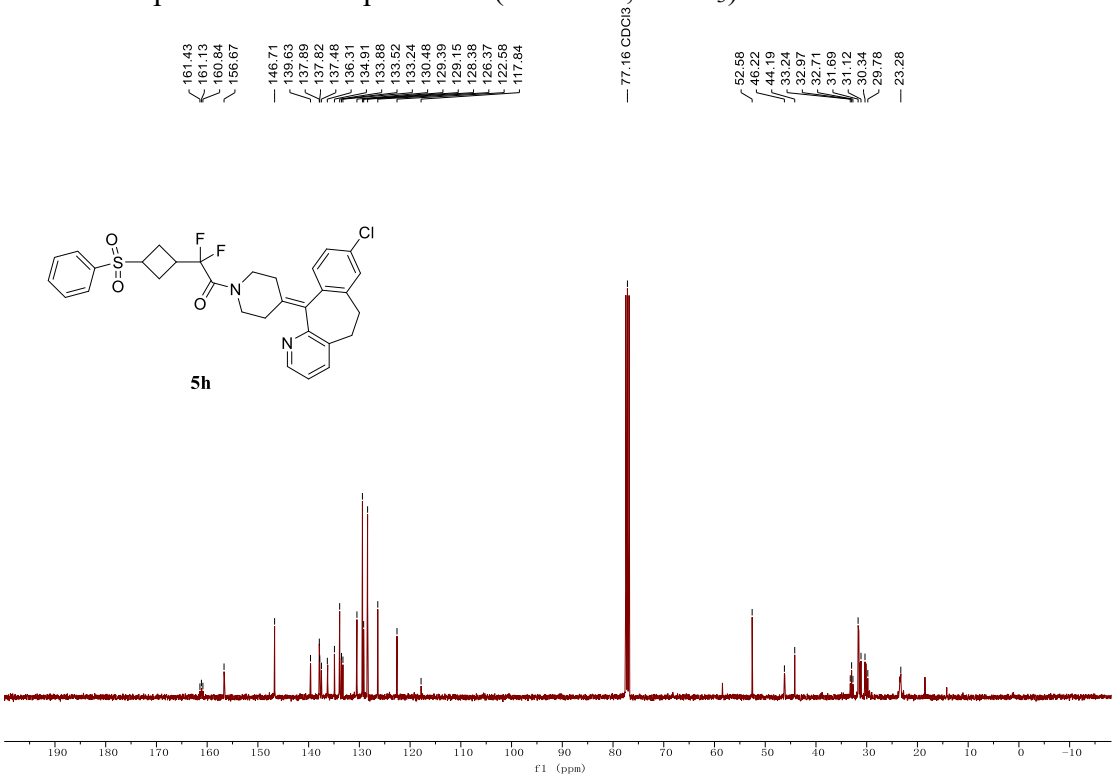


^{1}H NMR Spectrum of Compound **5h** (300 MHz, $CDCl_3$)



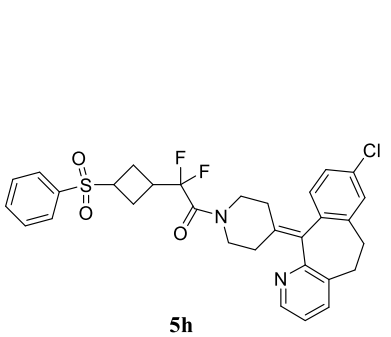
5h

^{13}C NMR Spectrum of Compound **5h** (101 MHz, $CDCl_3$)



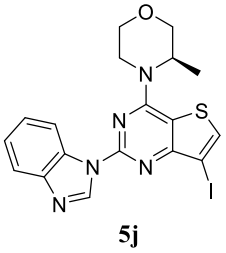
5h

^{19}F NMR Spectrum of Compound **5h** (282 MHz, $CDCl_3$)



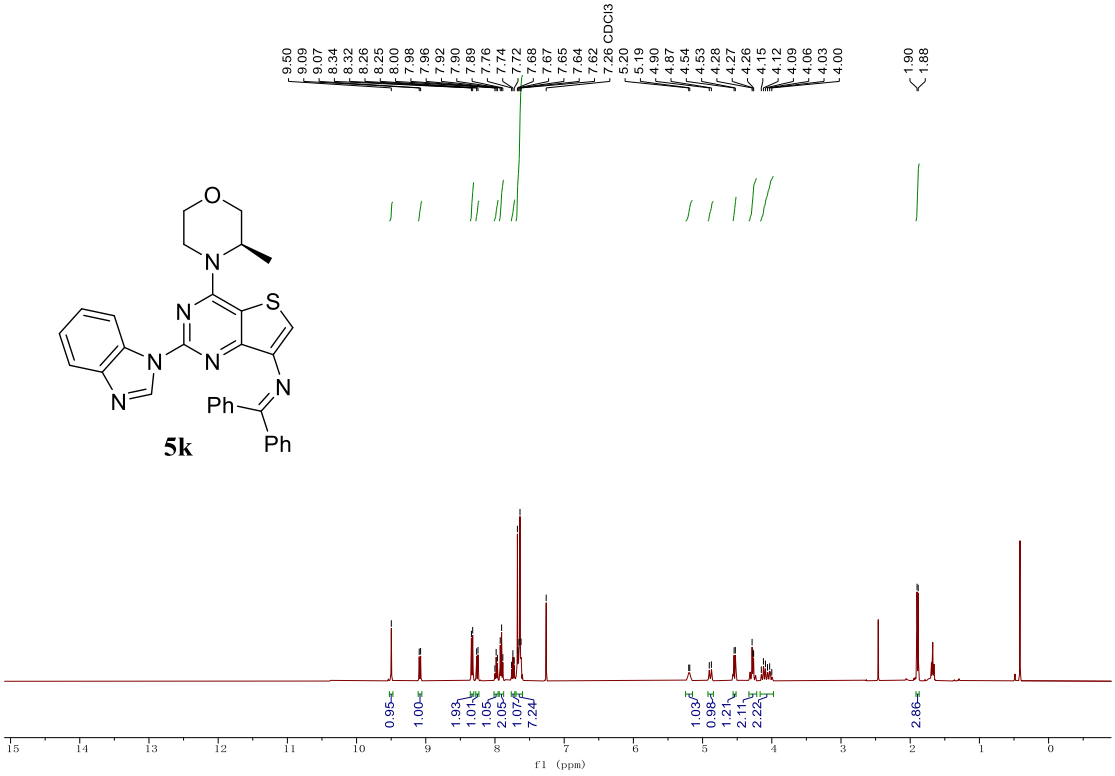
5h

^{1}H NMR Spectrum of Compound **5j** (300 MHz, $CDCl_3$)

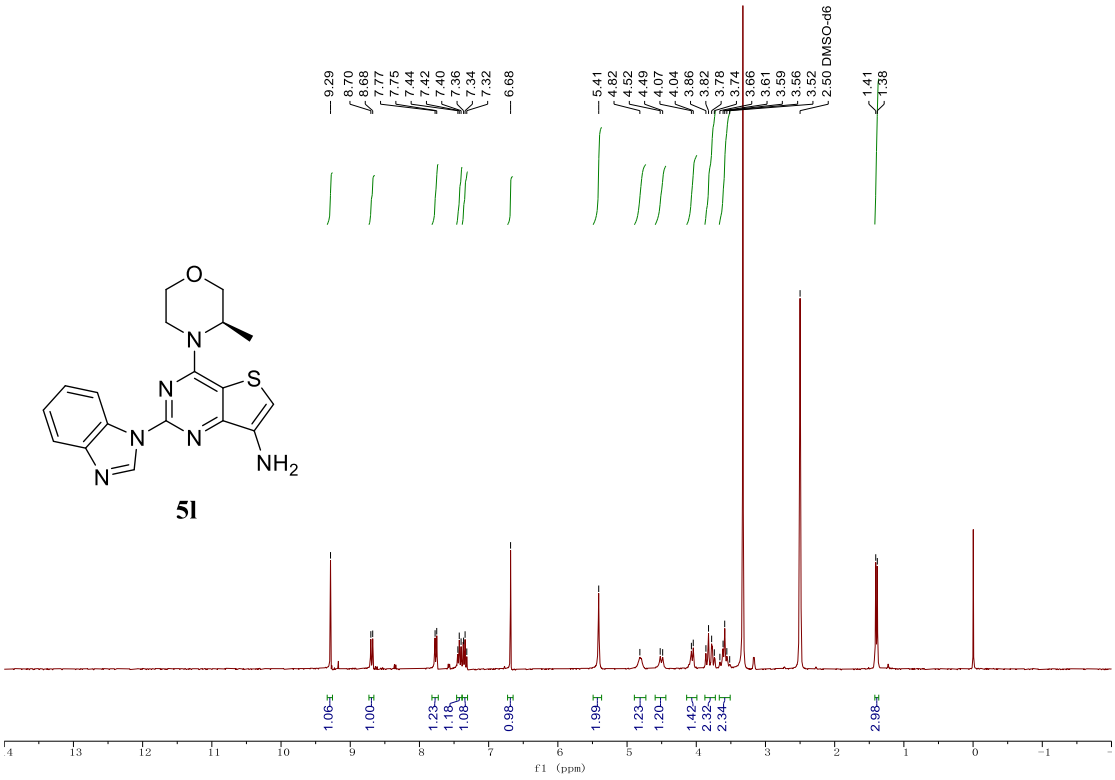


5j

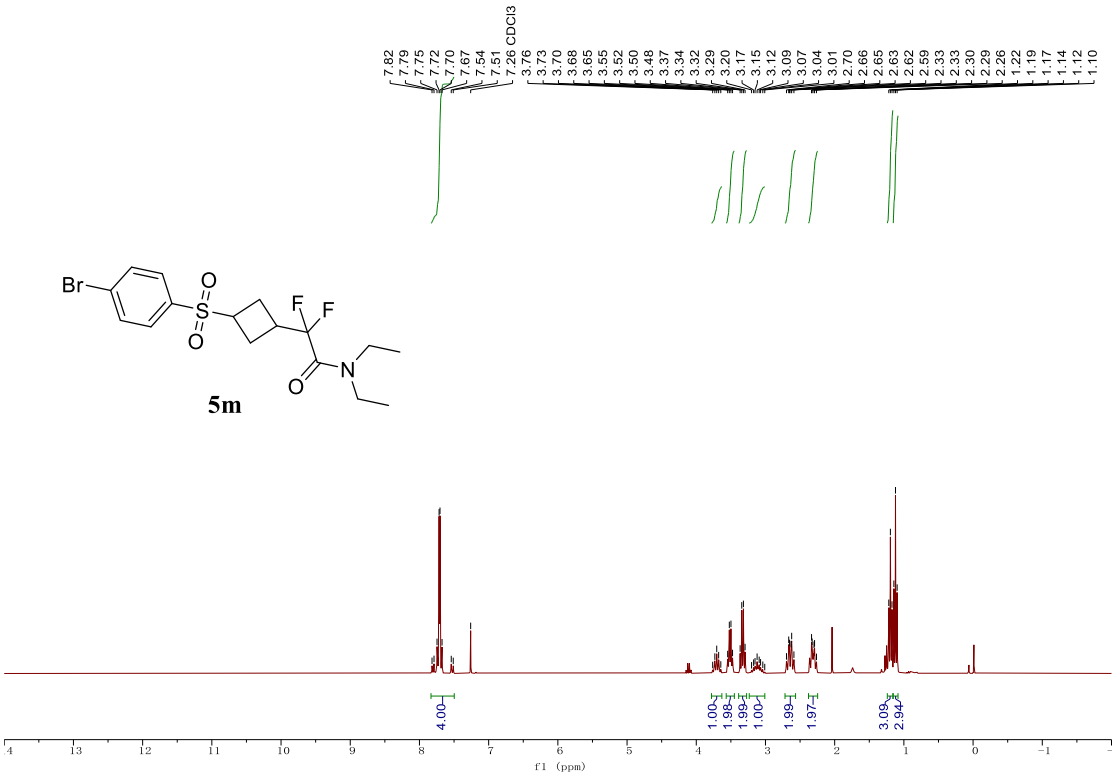
^{1}H NMR Spectrum of Compound **5k** (400 MHz, $CDCl_3$)



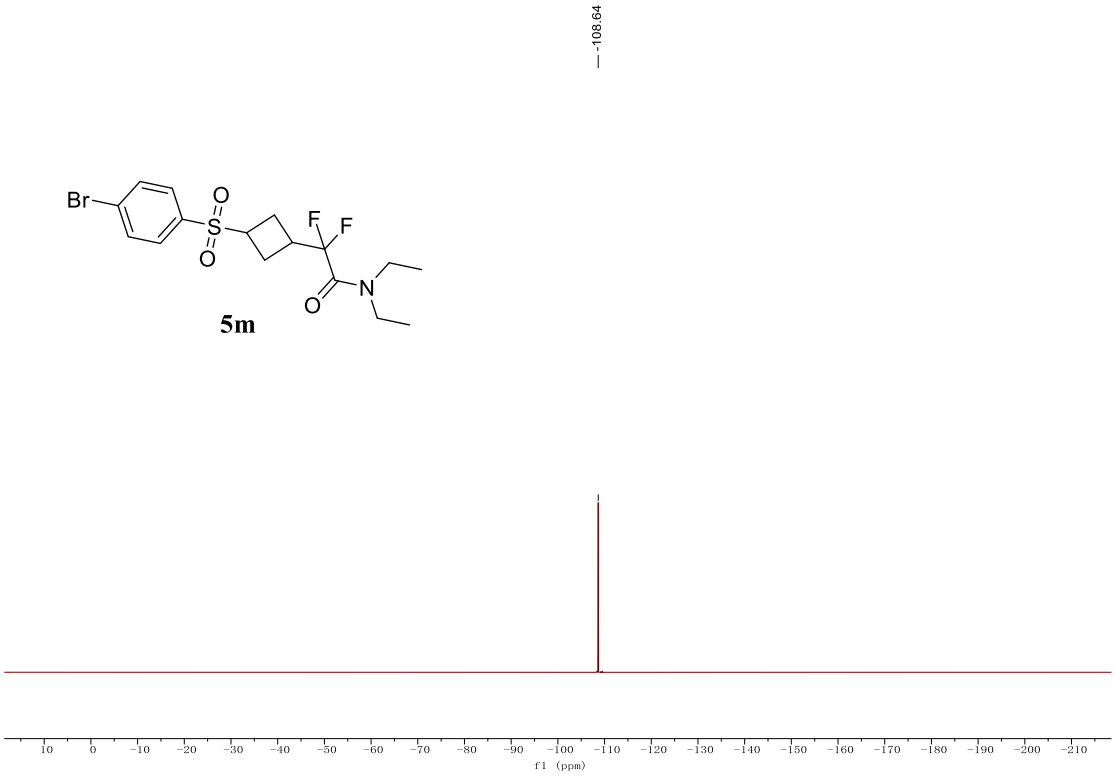
^{1}H NMR Spectrum of Compound **5l** (300 MHz, DMSO-d_6)



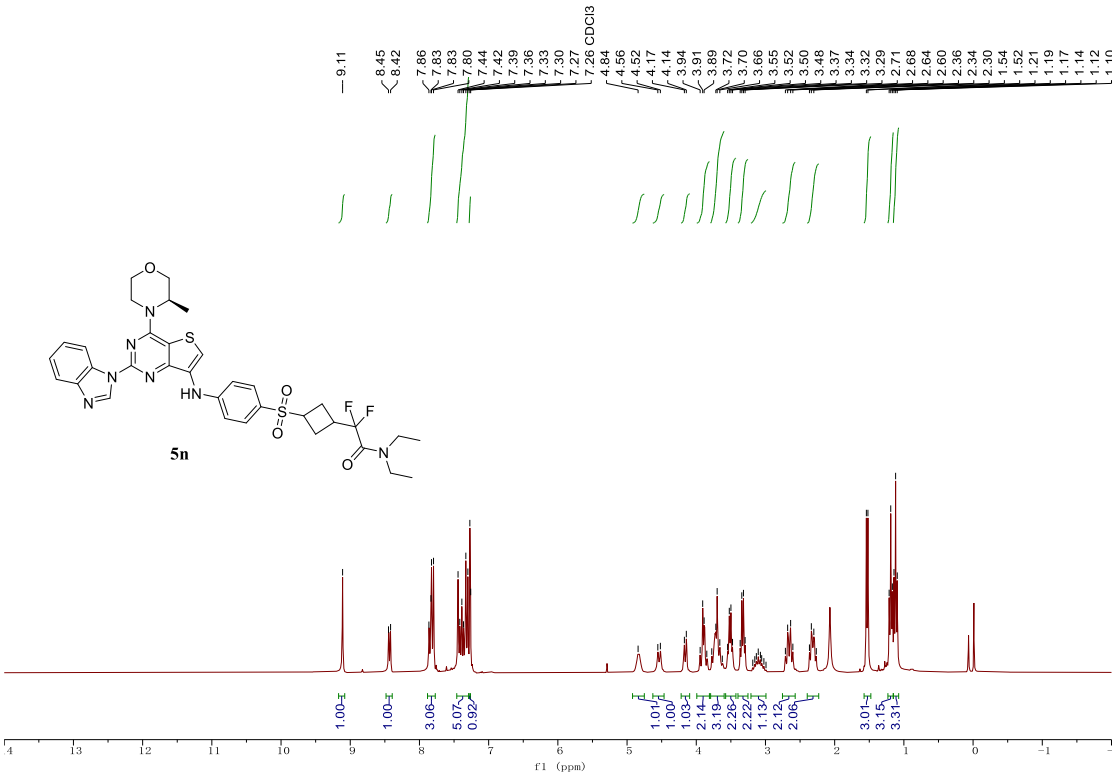
^{1}H NMR Spectrum of Compound **5m** (300 MHz, $CDCl_3$)



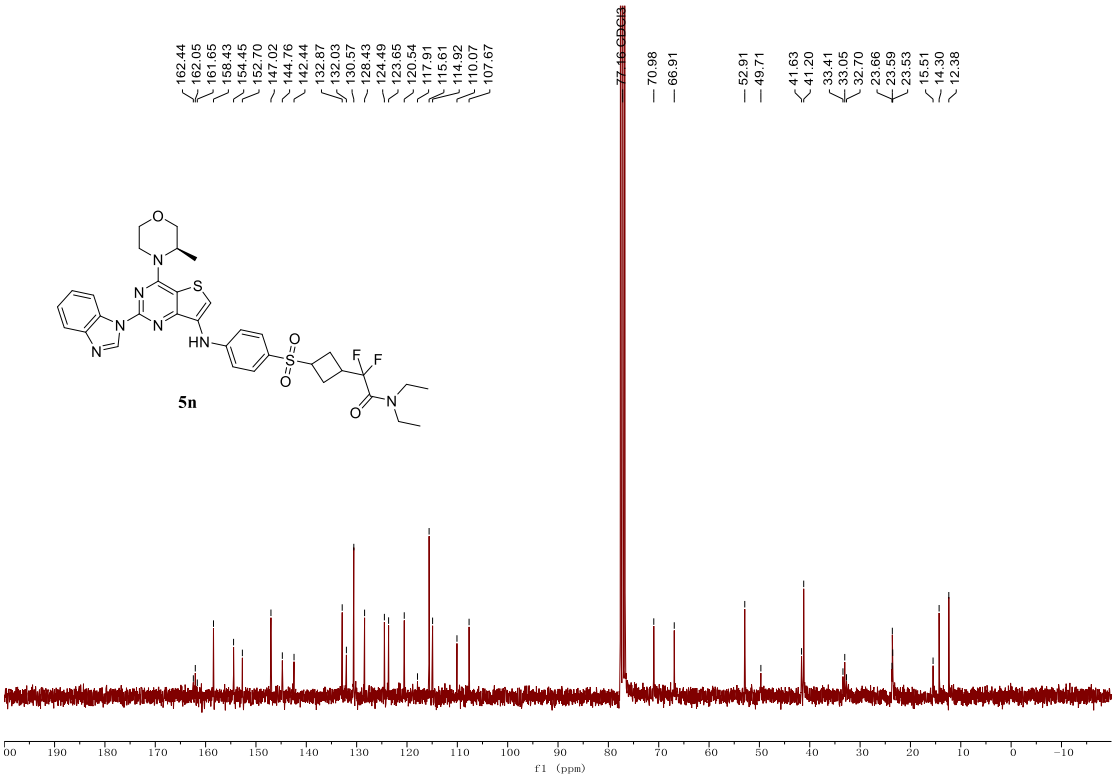
^{19}F NMR Spectrum of Compound **5m** (282 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound **5n** (300 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound **5n** (75 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **5n** (282 MHz, $CDCl_3$)