Rapid Access to Difluoroalkylated Pyrrolobenzodiazepines via a Pd-catalyzed C-H Difluoroalkylation/Cyclization Cascade Reaction

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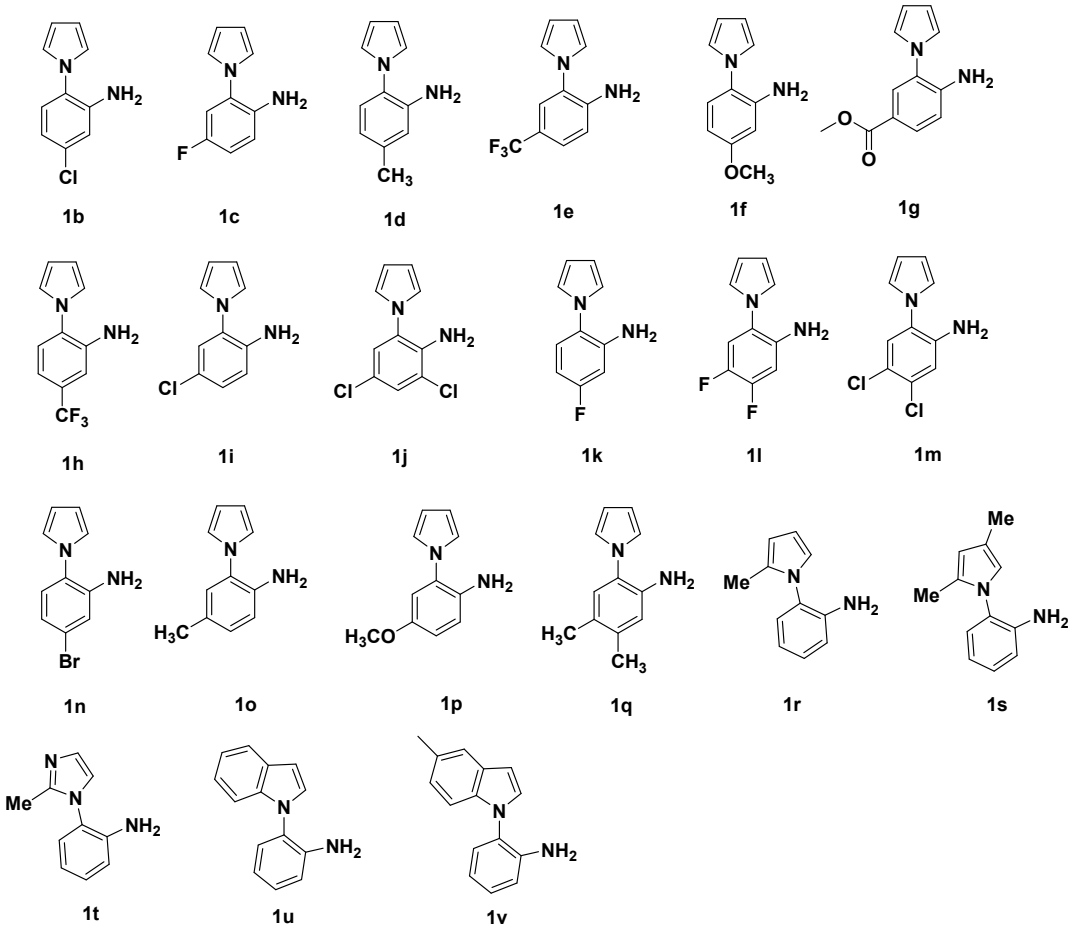
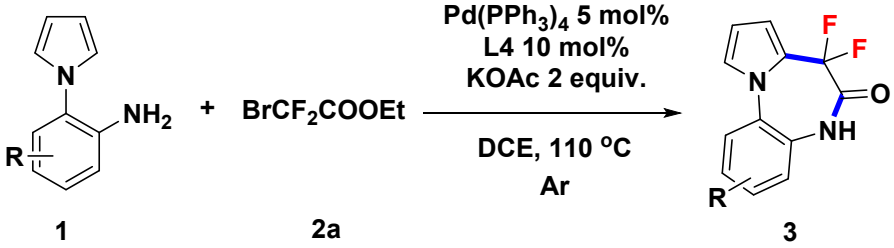
1. General Information

Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness). Preparative thin layer chromatography (PTLC) was HSGF 254 (0.4-0.5 mm thickness). All products were characterized by their NMR and MS spectra. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz, 500 MHz or 600 MHz instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd) and broad (br). High-resolution mass spectra (HRMS) were measured on Micromass Ultra Q-TOF spectrometer. Other reagents (chemicals) were purchased from Alfa Aesar, Acros organics, TCI, J&K Chemicals, Energy Chemical and Adamas and used without further purification. Compounds **1b-1d, 1f**, **1i, 1k** were known compounds, compounds **1e**, **1j** were new compounds and all of them were prepared according to literature.[1] Compounds **1g**, **1o** were known compounds and were prepared according to literature.[2] Compounds **1m, 1n**, **1s, 1u** and **1v** were known compounds and were prepared according to literature.[3] Compounds **1l**, **1h**, **1p**, **1q** were known compounds and were prepared according to literature.[4] Compound **1r** was known compounds and were prepared according to literature.[7] Compound **1t** was known compounds and were prepared according to literature.[8]



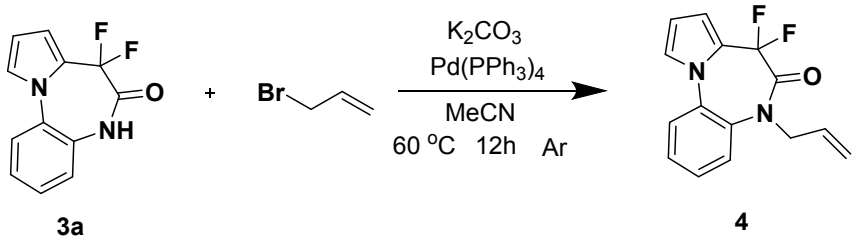
2. General procedures



To a 25 mL of Schlenk tube was added 1-(2-aminophenyl)pyrrole (0.2 mmol), $Pd(PPh_3)_4$ (5.0 mol %), **L4** (10.0 mol %), and CH_3COOK (2.0 equiv) under air. The mixture was then evacuated and backfilled with Ar (3 times). Ethyl bromodifluoroacetate (0.8 mmol), 1,2-dichloroethane (DCE, 4.0 mL) were added subsequently. The tube was screw capped and stirred at 110 °C for 14 h. After the solution was cooled to room temperature, the crude reaction mixture was diluted with EA (5 mL) and washed with saturated aqueous NaCl (3 x 5 mL). The aqueous layers were extracted with EA (3 x 5 mL) and the combined organic layers dried over anhydrous Na_2SO_4. Then, the solvents were removed under vacuo, and the residue was purified by a silica gel column chromatography (PE/EA = 10:1) to give the desired products **3**.

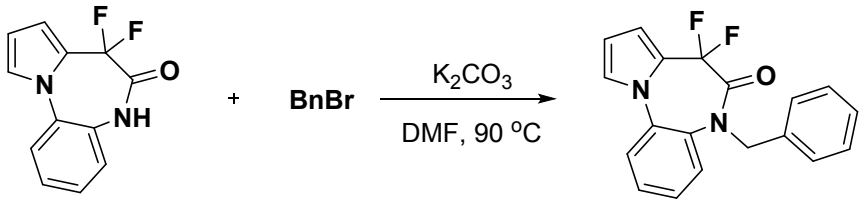
3. Synthetic Transformations

5-Allyl-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (4)



To a solution of **3a** (70.0 mg, 0.3 mmol) in MeCN (10.0 mL) was added bromoallylene (72.3 mg, 0.6 mmol), $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol) and K_2CO_3 (206.5 mg, 1.5 mmol). The mixture was then evacuated and backfilled with Ar (3 times). The reaction mixture was stirred for 12 h at 60 °C, then diluted with water (20 mL), extracted with EA (20 mL x 3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA=6:1) to obtain **4** (53 mg, 65%) as a yellow oil.[5]

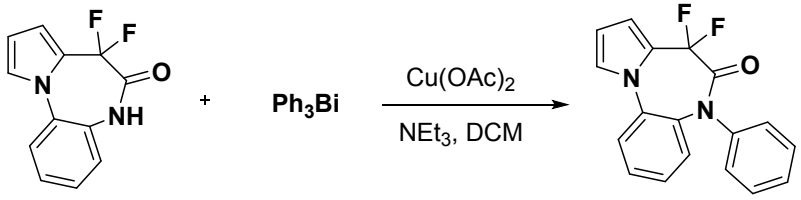
5-Benzyl-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (5)



3a **5**

To a solution of **3a** (70.5 mg, 0.3 mmol) in DMF (5.0 mL) was added BnBr (103 mg, 0.6 mmol) and K_2CO_3 (83.2 mg, 0.6 mmol) sequentially. The reaction mixture was stirred for 12 h at 90 °C. Then the reaction was diluted with H_2O (10 mL), extracted with EA (30 mL), the organic layer was washed with H_2O for three times, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA, 8:1) to obtain **5** (70 mg, 72%) as a yellow solid.

7,7-Difluoro-5-phenyl-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (6)

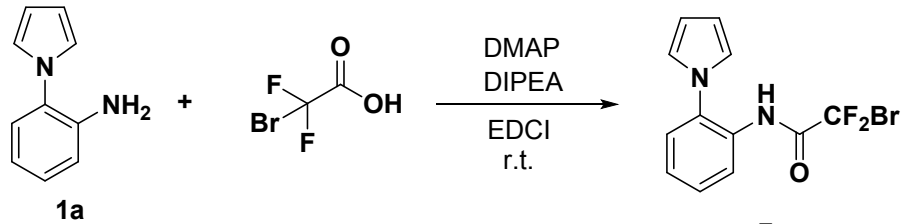


3a **6**

To a solution of **3a** (70.5 mg, 0.3 mmol) in dry DCM (3.0 mL) was added Ph_3Bi (265 mg, 0.6 mmol), $Cu(OAc)_2$ (109.4 mg, 0.6 mmol) and NEt_3 (91.4 mg, 0.9 mmol) sequentially. The reaction mixture was stirred at room temperature overnight. Then the reaction was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA, 10:1) to obtain **6** (70 mg, 75%) as a yellow solid.

4. Mechanistic Investigations

***N*-(2-(1*H*-pyrrol-1-yl)phenyl)-2-bromo-2,2-difluoroacetamide (7)**



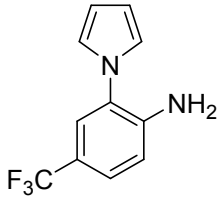
1a **7**

To a flask charged with a solution of difluorobromoacetic acid (1 g, 5.72 mmol) in DCM/THF (4/1, 37.5 mL) was added DMAP (139.7 mg, 1.14 mmol), **1a** (994.8 mg, 6.29 mmol) and EDCI (1.53 g, 8.0 mmol). The mixture was stirred at room temperature. After 3 h, DIPEA (1.03 g, 8.0 mmol) was added to the mixture. The

reaction was stirred at room temperature for 6 h. The crude mixture was washed with HCl (1 M), saturated aqueous $NaHCO_3$ (3 x 20 mL) and NaCl (3 x 20 mL) in turn, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE/EA, 10:1) to obtain **7** (970 mg, 54 %) as a white solid.[6]

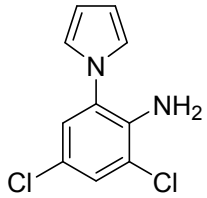
5. Analytical Characterization Data of Compounds

2-(1*H*-Pyrrol-1-yl)-4-(trifluoromethyl)aniline (1e)



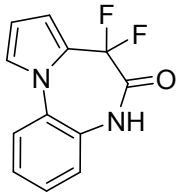
White solid (272 mg, 60%). M.p. 97-98 °C. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.27 (d, *J* = 2.1 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.94 (t, *J* = 2.1 Hz, 2H), 6.27 (t, *J* = 2.1 Hz, 2H), 5.52 (s, 2H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 147.26, 125.64, 125.13 (q, *J* = 270.9 Hz), 124.15 (q, *J* = 3.6 Hz), 121.91, 116.41 (q, *J* = 32.7 Hz), 115.94, 109.97. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -61.25 .HRMS (ESI) m/z: calculated for $C_{11}H_8F_3N_2$ $[M - H]^-$: 225.0645, found: 225.064.

2,4-Dichloro-6-(1*H*-pyrrol-1-yl)aniline (1j)



Colorless oil (491 mg, 54%). ^{1}H NMR (500 MHz, Acetone-*d6*) δ 7.24 (d, *J* = 2.4 Hz, 2H), 7.06 (dd, *J* = 8.7, 2.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.08 (s, 2H).^{13}C NMR (126 MHz, Chloroform-*d*) δ 138.36, 128.36, 128.25, 125.80, 121.80, 121.50, 120.12, 110.40. HRMS (ESI) m/z: calculated for $C_{10}H_9Cl_2N_2$ $[M + H]^+$: 227.0137, found: 227.0134.

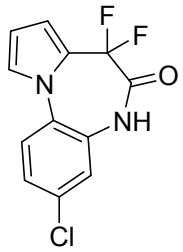
7,7-Difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3a)



White solid (34 mg, 73%). M.p. 148-149 °C. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.18 (s, 1H), 7.66 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.61 (dd, *J* = 2.9, 1.8 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.38 – 7.31 (m, 2H), 6.72 (dt, *J* = 3.8, 1.5 Hz, 1H), 6.51 (dd, *J* = 3.8, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 162.05 (t, *J* = 33.4 Hz), 130.65, 128.97, 128.03,

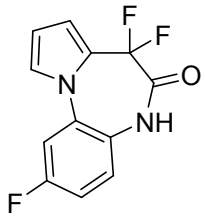
126.62, 125.36, 125.30 (t, *J* = 34.1 Hz), 124.11, 123.35, 111.64, 110.64, 110.16 (t, *J* = 243.8 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_7F_2N_2O$ [M - H]$^-$: 233.0532, found: 233.0532.

3-Chloro-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3b)



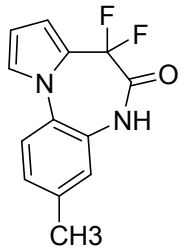
Yellow solid (38 mg, 71%). M.p. 205-207 ^{o} C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.30 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 2.9, 1.7 Hz, 1H), 6.77 – 6.69 (m, 1H), 6.48 (dd, *J* = 3.8, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.69 (t, *J* = 34.7 Hz), 132.54, 129.34, 128.54, 126.43, 125.13 (t, *J* = 34.0 Hz), 124.27, 123.32, 122.19, 111.42, 110.92 (t, *J* = 3.0 Hz), 108.87 (t, *J* = 246.9 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_6ClF_2N_2O$ [M - H]$^-$: 267.0142, found: 267.0143.

2,7,7-Trifluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3c)



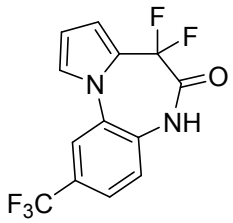
Yellow solid (34 mg, 68%). M.p. 190-192 ^{o}C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 7.24 – 7.19 (m, 2H), 7.18 (dd, *J* = 3.0, 1.7 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.76 – 6.72 (m, 1H), 6.49 (dd, *J* = 3.7, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.05 (t, *J* = 34.5 Hz), 160.24 (d, *J* = 247.9 Hz), 132.15 (d, *J* = 10.0 Hz), 125.81 (t, *J* = 34.1 Hz), 124.45 – 124.24 (m), 123.64, 114.66 (d, *J* = 22.6 Hz), 112.04, 111.45 (t, *J* = 3.2 Hz), 110.76 (d, *J* = 26.1 Hz), 109.30 (t, *J* = 245.8 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_6F_3N_2O$ [M - H]$^-$: 251.0438, found: 251.044.

7,7-Difluoro-3-methyl-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3d)



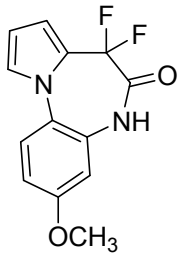
Yellow solid (32 mg, 64%). M.p. 247-248 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.18 (dd, *J* = 2.9, 1.8 Hz, 1H), 7.14 – 7.11 (m, 1H), 7.00 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.73 – 6.69 (m, 1H), 6.44 (dd, *J* = 3.8, 2.8 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.16 (t, *J* = 34.6 Hz), 138.03, 128.92, 127.80, 127.74, 125.69, 123.76, 123.58, 123.05, 111.39, 110.95 (t, *J* = 3.2 Hz), 109.75 (t, *J* = 245.7 Hz), 20.99. HRMS (ESI) m/z: calculated for $C_{13}H_{11}F_2N_2O$ [M - H]$^-$: 249.0834, found: 249.0832.

7,7-Difluoro-2-(trifluoromethyl)-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3e)



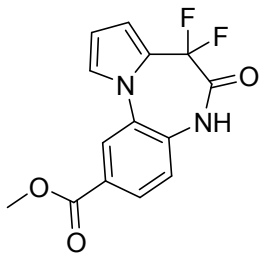
Yellow solid (52 mg, 75%). M.p. 222-223 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.78 – 7.73 (m, 1H), 7.65 – 7.58 (m, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.25 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.80 – 6.75 (m, 1H), 6.52 (dd, *J* = 3.8, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.15 (t, *J* = 35.3 Hz), 131.22 (d, *J* = 33.4 Hz), 129.23 (q, *J* = 34.2 Hz), 125.89 (t, *J* = 34.1 Hz), 124.52 (d, *J* = 4.1 Hz), 124.39, 124.17, 123.39, 122.22, 121.18 (d, *J* = 3.9 Hz), 112.48, 111.94 (t, *J* = 3.1 Hz), 109.31 (t, *J* = 245.9 Hz). HRMS (ESI) m/z: calculated for $C_{13}H_6F_5N_2O$ [M - H]$^-$: 301.0406, found: 301.0402.

7,7-Difluoro-3-methoxy-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3f)



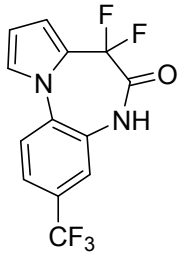
Yellow solid (29 mg, 55%). M.p. 162-163 °C. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.10 (s, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.52 (dd, *J* = 2.8, 1.8 Hz, 1H), 6.93 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.88 (d, *J* = 2.8 Hz, 1H), 6.67 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.46 (dd, *J* = 3.8, 2.7 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.40 (t, *J* = 34.7 Hz), 158.79, 129.05, 125.46 (t, *J* = 34.1 Hz), 124.81, 124.72, 123.72, 112.80, 111.19, 110.68 (t, *J* = 3.2 Hz), 109.77 (t, *J* = 245.4 Hz), 107.55, 55.93. HRMS (ESI) m/z: calculated for $C_{13}H_9F_2N_2O_2$ [M - H]$^-$: 263.0638, found: 263.0642.

Methyl 7,7-difluoro-6-oxo-6,7-dihydro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepine-2-carboxylate (3g)



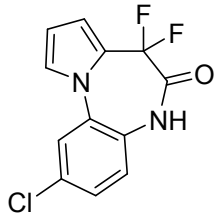
White solid (34 mg, 60%). M.p. 257-258 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.57 (s, 1H), 8.13 (d, *J* = 1.9 Hz, 1H), 7.98 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.74 (dd, *J* = 2.9, 1.7 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 6.78 (dt, *J* = 3.7, 1.4 Hz, 1H), 6.55 (dd, *J* = 3.8, 2.9 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 165.86, 162.57 (t, *J* = 34.73 Hz), 133.82, 131.57, 129.20, 128.85, 126.46 (t, *J* = 34.2 Hz), 125.68, 123.92, 112.51, 111.44 (t, *J* = 2.8 Hz), 111.31 (d, *J* = 134.1 Hz), 110.65 (t, *J* = 243.9 Hz), 52.74. HRMS (ESI) m/z: calculated for $C_{14}H_9F_2N_2O_3$ [M - H]$^-$: 291.0587, found: 291.0592.

7,7-Difluoro-3-(trifluoromethyl)-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3h)



Brown solid (48 mg, 79%). M.p. 190-191 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.44 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.74 – 7.68 (m, 3H), 6.80 (dt, *J* = 3.7, 1.5 Hz, 1H), 6.58 (dd, *J* = 3.8, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 162.53 (t, *J* = 33.9 Hz), 134.59, 130.48, 129.69 (q, *J* = 33.3 Hz), 126.68 (t, *J* = 34.0 Hz), 125.72 (d, *J* = 3.8 Hz), 125.46, 123.73 (q, *J* = 3.8 Hz), 123.66, 121.07 (q, *J* = 4.0 Hz), 112.78, 111.83 (t, *J* = 3.3 Hz), 110.55 (t, *J* = 244.1 Hz). HRMS (ESI) m/z: calculated for $C_{13}H_6F_5N_2O$ [M - H]$^-$: 301.0406, found: 301.0404.

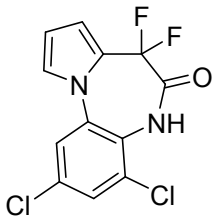
2-Chloro-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3i)



White solid (33 mg, 63%). M.p. 222-223 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 7.81 (d, *J* = 2.3 Hz, 1H), 7.70 (dd, *J* = 2.9, 1.7 Hz, 1H), 7.50 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 6.75 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.56 – 6.49 (m, 1H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 162.48 (t, *J* = 33.8 Hz), 132.71, 131.49, 128.86, 128.38,

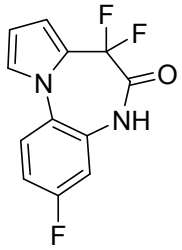
126.54 (t, *J* = 34.1 Hz), 125.57, 125.30, 124.34, 112.42, 111.45 (t, *J* = 3.1 Hz), 110.65 (t, *J* = 243.9 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_6ClF_2N_2O$ [M - H]$^-$: 267.0142, found: 267.0141.

2,4-Dichloro-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one(3j)



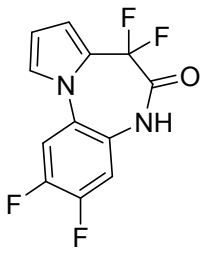
Yellow solid (41 mg, 74%). M.p. 208-210 ^{o} C. ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.76 (d, *J* = 2.3 Hz, 1H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.64 (dd, *J* = 3.0, 1.7 Hz, 1H), 6.80 – 6.76 (m, 1H), 6.56 (t, *J* = 3.4 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 162.06 (t, *J* = 33.6 Hz), 134.67, 132.14, 129.23, 128.70, 127.03, 126.69 (t, *J* = 15.1 Hz), 126.08 (t, *J* = 2.4 Hz), 123.92, 112.77, 112.09 (t, *J* = 3.3 Hz), 109.69 (t, *J* = 244.62 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_5Cl_2F_2N_2O$ [M - H]$^-$:300.9752, found: 300.9762.

3,7,7-Trifluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3k)



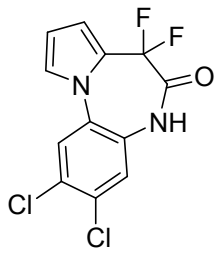
Yellow solid (41 mg, 81%). M.p. 183-184 ^{o} C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.32 (s, 1H), 7.73 (dd, *J* = 9.0, 5.5 Hz, 1H), 7.60 (dd, *J* = 2.9, 1.7 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.18 (dd, *J* = 9.6, 2.9 Hz, 1H), 6.73 (dt, *J* = 4.0, 1.5 Hz, 1H), 6.51 (dd, *J* = 3.8, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 162.81 (t, *J* = 19.4 Hz), 160.86, 131.43 (d, *J* = 11.5 Hz), 128.52, 126.45 (d, *J* = 9.7 Hz), 125.50, 113.90 (d, *J* = 22.9 Hz), 112.11, 111.09 (t, *J* = 2.5 Hz), 110.77 (t, *J* = 244.3 Hz), 110.44 (d, *J* = 7.2 Hz), 110.23 (d, *J* = 7.2 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_6F_3N_2O$ [M - H]$^-$: 251.0438, found: 251.0438.

2,3,7,7-Tetrafluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3l)



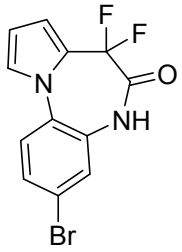
Yellow solid (46 mg, 85%). M.p. 194-195 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.29 (s, 1H), 7.95 (dd, *J* = 11.4, 7.8 Hz, 1H), 7.63 (dd, *J* = 2.9, 1.7 Hz, 1H), 7.40 (dd, *J* = 11.3, 7.8 Hz, 1H), 6.75 (dt, *J* = 3.7, 1.5 Hz, 1H), 6.53 (dd, *J* = 3.8, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 161.59 (t, *J* = 34.0 Hz), 148.77 (dd, *J* = 148.6, 13.5 Hz), 146.81 (dd, *J* = 147.4, 13.4 Hz), 127.58, 125.86, 125.65 (t, *J* = 34.1 Hz), 124.77 (t, *J* = 2.7 Hz), 112.92 (d, *J* = 21.8 Hz), 111.69 (d, *J* = 21.4 Hz), 111.54, 110.54 (t, *J* = 3.3 Hz), 109.72 (t, *J* = 244.1 Hz). HRMS (EI) m/z: calculated for $C_{12}H_6F_4N_2O$ [M] :270.0411, found: 270.0406.

2,3-Dichloro-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3m)



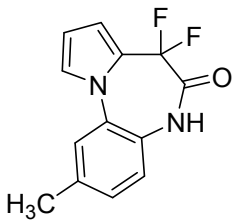
Yellow solid (44 mg, 69%). M.p. 254-256 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.38 (s, 1H), 8.05 (s, 1H), 7.71 (dd, *J* = 2.9, 1.7 Hz, 1H), 7.58 (s, 1H), 6.77 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.54 (t, *J* = 3.4 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 162.34 (t, *J* = 34.2 Hz), 131.49, 131.16, 129.79, 129.59, 126.37 (t, *J* = 34.0 Hz), 126.11, 125.80, 125.06, 112.61, 111.77 (t, *J* = 3.1 Hz), 110.54 (t, *J* = 244.2 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_5Cl_2F_2N_2O$ [M - H]$^{-}$:300.9752, found: 300.9752.

3-Bromo-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3n)



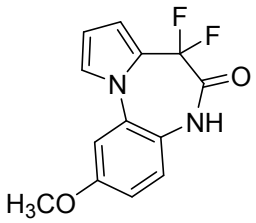
Yellow solid (56 mg, 80%). M.p. 218-219 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.92 (s, 1H), 7.45 (d, *J* = 10.8 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.17 (s, 1H), 6.74 (s, 1H), 6.48 (s, 1H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 162.54 (t, *J* = 34.1 Hz), 131.24, 131.12, 129.87, 126.38 (t, *J* = 33.9 Hz), 126.31, 125.40 (t, *J* =3.02 Hz), 120.56, 112.36, 111.36 (t, *J* = 3.2 Hz), 110.64 (t, *J* = 244.0 Hz). HRMS (ESI) m/z: calculated for $C_{12}H_6BrF_2N_2O$ [M - H]$^{-}$: 310.9637, found: 310.9642.

7,7-Difluoro-2-methyl-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3o)



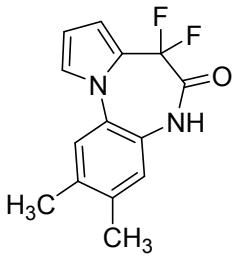
Yellow solid (43 mg, 86%). M.p. 217-218 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.06 (s, 1H), 7.60 (dd, *J* = 2.9, 1.8 Hz, 1H), 7.49 (t, *J* = 1.1 Hz, 1H), 7.21 (d, *J* = 1.1 Hz, 2H), 6.70 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.49 (dd, *J* = 3.8, 2.9 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 162.65 (t, *J* = 33.8 Hz), 137.29, 131.50, 129.08, 127.26, 126.54 (t, *J* = 33.9 Hz), 125.06, 124.74, 123.61, 111.84, 110.89 (t, *J* = 241.6 Hz), 110.85 (t, *J* = 4.53 Hz), 20.70. HRMS (ESI) m/z: calculated for $C_{13}H_{11}F_2N_2O$ [M - H]$^-$: 249.0834, found: 249.0831.

7,7-Difluoro-2-methoxy-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3p)



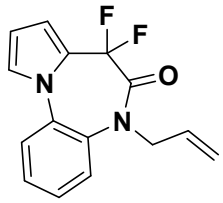
Yellow solid (30 mg, 57%). M.p. 223-224 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.98 (s, 1H), 7.68 (dd, *J* = 2.9, 1.7 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.18 (d, *J* = 2.8 Hz, 1H), 7.00 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.70 (dt, *J* = 3.7, 1.4 Hz, 1H), 6.50 (dd, *J* = 3.8, 2.9 Hz,1H), 3.84 (s, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 162.57 (t, *J* = 33.2 Hz), 158.66, 132.61, 126.65 (t, *J* = 34.1 Hz), 125.14, 125.02 (t, *J* = 9.1 Hz), 122.92, 122.81 (t, *J* = 30.2 Hz), 114.58, 111.89, 110.89 (t, *J* = 3.0 Hz), 109.08, 56.17. HRMS (ESI) m/z: calculated for $C_{13}H_{11}F_2N_2O_2$ [M - H]$^-$: 265.0783, found: 265.0784.

7,7-Difluoro-2,3-dimethyl-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (3q)



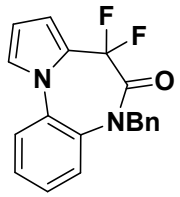
White solid (40 mg, 77%). M.p. 269-270 °C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.01 (s, 1H), 7.56 (dd, *J* = 2.9, 1.8 Hz, 1H), 7.44 (s, 1H), 7.07 (s, 1H), 6.67 (dt, *J* = 3.7, 1.5 Hz, 1H), 6.47 (dd, *J* = 3.8, 2.8 Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 162.74 (t, *J* = 33.6 Hz), 137.20, 135.92, 129.44, 127.28, 126.46 (t, *J* = 34.1 Hz), 125.03, 124.86, 124.40, 111.63, 110.00 (t, *J* = 244.4 Hz), 110.60 (t, *J* = 3.1 Hz), 19.21, 19.13. HRMS (ESI) m/z: calculated for $C_{14}H_{11}F_2N_2O$ [M - H]$^-$: 261.0845, found: 261.0849.

5-Allyl-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (4)



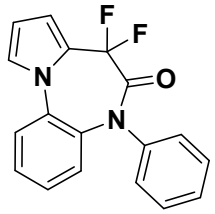
Yellow oil. (51 mg, 65%). ^{1}H NMR (500 MHz, Acetone-*d6*) δ 7.72 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.59 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.52 – 7.38 (m, 3H), 6.71 – 6.65 (m, 1H), 6.53 – 6.46 (m, 1H), 5.89 – 5.75 (m, 1H), 5.12 – 5.06 (m, 1H), 5.01 (dt, *J* = 17.3, 1.7 Hz, 1H), 4.69 – 4.55 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.10 (dd, *J* = 36.4, 29.4 Hz), 133.83, 132.67 (d, *J* = 2.5 Hz), 132.39, 127.64, 127.30, 127.12 (dd, *J* = 41.7, 27.2 Hz), 124.20, 123.96, 123.13 (d, *J* = 2.5 Hz), 117.35, 111.72 (d, *J* = 2.2 Hz), 110.87 (d, *J* = 4.2 Hz), 110.11 (dd, *J* = 250.2, 241.8 Hz), 53.58. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -95.02 (d, *J* = 262.9 Hz), -118.00 (d, *J* = 262.8 Hz). HRMS (ESI) m/z: calculated for $C_{15}H_{13}F_2N_2O$ $[M + H]^+$: 275.099, found: 275.0986.

5-Benzyl-7,7-difluoro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one (5)



White solid (70 mg, 72%). M.p. 110-111 °C. ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.70 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.21 – 7.14 (m, 3H), 6.99 – 6.92 (m, 2H), 6.74 – 6.69 (m, 1H), 6.54 – 6.48 (m, 1H), 5.47 (d, *J* = 15.8 Hz, 1H), 5.11 (d, *J* = 15.8 Hz, 1H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 162.82 (dd, *J* = 36.0, 29.1 Hz), 137.39, 133.99, 129.38, 128.67, 128.40, 128.16, 127.83 – 127.20 (m), 127.49, 125.69, 125.08, 124.78 – 124.61 (m), 112.23 (d, *J* = 2.2 Hz), 111.54 (dd, *J* = 249.6, 240.7 Hz), 111.15 (d, *J* = 4.3 Hz), 53.54. ^{19}F NMR (471 MHz, Acetone-d_6) δ -95.27 (d, *J* = 260.9 Hz), -117.89 (d, *J* = 260.4 Hz). HRMS (ESI) m/z: calculated for $C_{19}H_{15}F_2N_2O$ $[M + H]^+$: 325.1147, found: 325.1152.

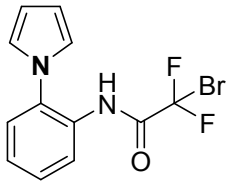
7,7-Difluoro-5-phenyl-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepin-6(7*H*)-one(6)



White solid (70 mg, 75%). M.p. 166-167 °C. ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.66 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.49 – 7.44 (m, 2H), 7.44 – 7.36 (m, 2H), 7.36 – 7.30 (m, 1H), 7.30 – 7.23 (m, 2H), 7.10 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.76 – 6.72 (m, 1H), 6.58 – 6.52 (m, 1H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 161.05 (dd, *J*

= 36.6, 29.2 Hz), 141.93, 134.10 (d, *J* = 2.4 Hz), 132.72 (d, *J* = 2.5 Hz), 129.39, 128.36, 127.86, 127.49, 127.28, 126.95, 126.41 (dd, *J* = 41.5, 27.1 Hz), 124.26, 124.15 (d, *J* = 3.9 Hz), 111.51 (d, *J* = 2.2 Hz), 110.54 (dd, *J* = 240.8 Hz), 110.50 (d, *J* = 4.4 Hz). ^{19}F NMR (471 MHz, Acetone-d_6) δ -95.56 (d, *J* = 260.0 Hz), -117.93 (d, *J* = 260.1 Hz). HRMS (ESI) m/z: calculated for $C_{18}H_{13}F_2N_2O$ $[M + H]^+$: 311.099, found: 311.0992.

***N*-(2-(1*H*-pyrrol-1-yl)phenyl)-2-bromo-2,2-difluoroacetamide (7)**



White solid. (970 mg, 54 %). M.p. 71-72 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.35 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.76 (s, 1H), 7.50 – 7.43 (m, 1H), 7.37 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.29 (td, *J* = 7.7, 1.4 Hz, 1H), 6.80 (t, *J* = 2.1 Hz, 2H), 6.44 (t, *J* = 2.1 Hz, 2H).^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.46 (t, *J* = 28.0 Hz), 131.79, 131.47, 129.08, 127.19, 126.29, 122.01, 121.43, 111.34, 111.20 (t, *J* = 317.5 Hz). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -60.81 (s). HRMS (ESI) m/z: calculated for $C_{12}H_8F_2N_2OBr$ $[M - H]^-$: 312.9794, found: 312.9794.

6. Reference

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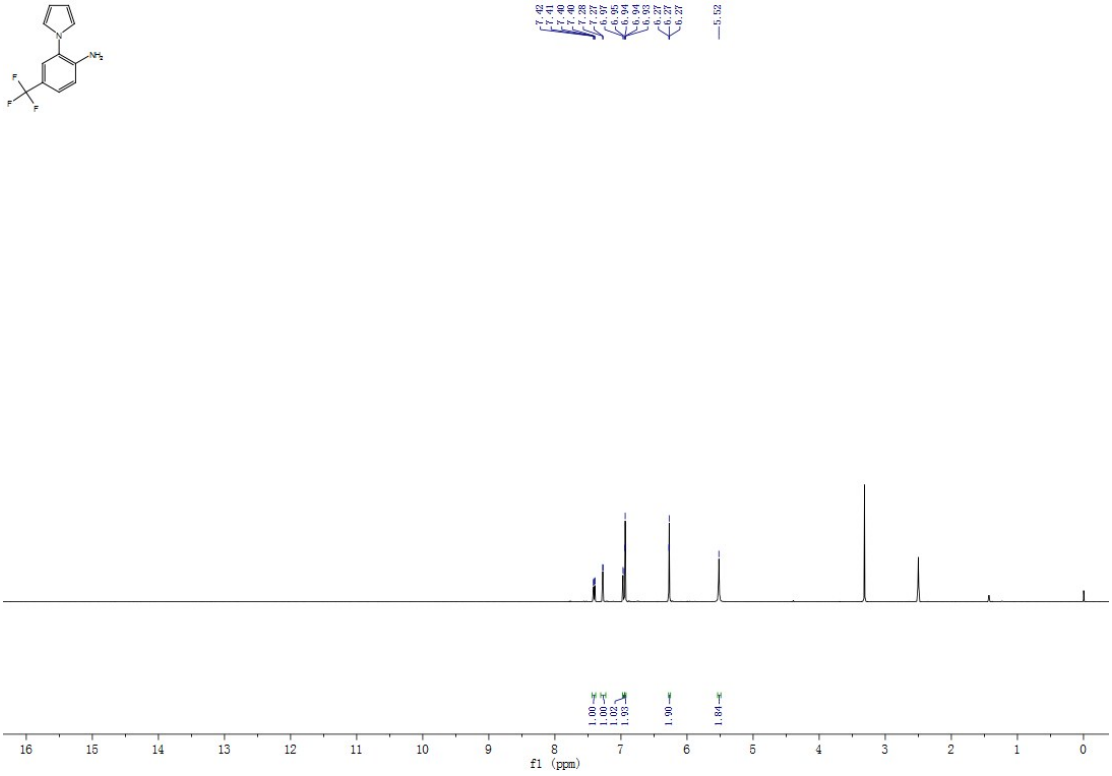
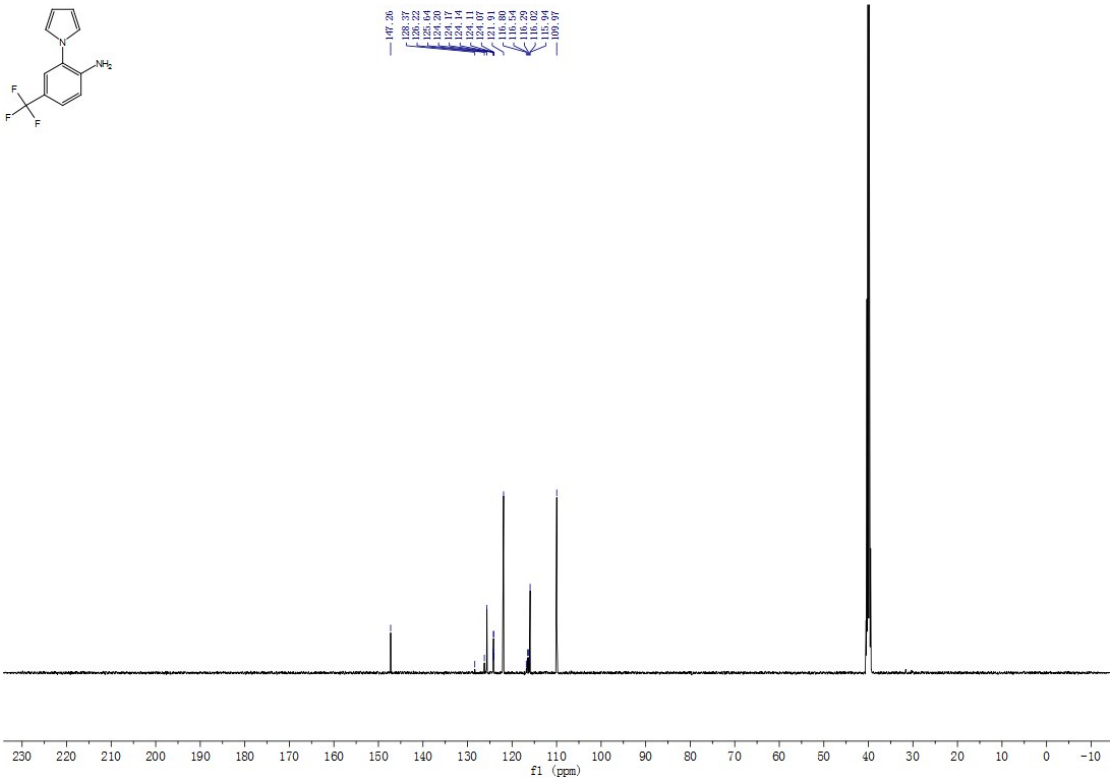
2. N.T. Patil, *et al. J. Org. Chem.,* 2009, **74**, 6315-6318.
3. Z. An, *et al. Chem. Commun.,* 2017, **53**, 11572-11575.
4. H. Liu, *et al. Org. Biomol. Chem.,* 2017, **15**, 7157-7164.
5. S. Cacchi, *et al. J. Org. Chem.,* 1998, **63**, 1001-1011.
6. W. Huang, *et al. ACS Catal.* 2016, **6**, 7471-7474.
7. K. Yonekura, et al. *Adv. Syn. Catal*., 2016, 358, 2895-2902.
8. C. Xie, *et al. J. Org. Chem.,* 2017, **82**, 3491-3499

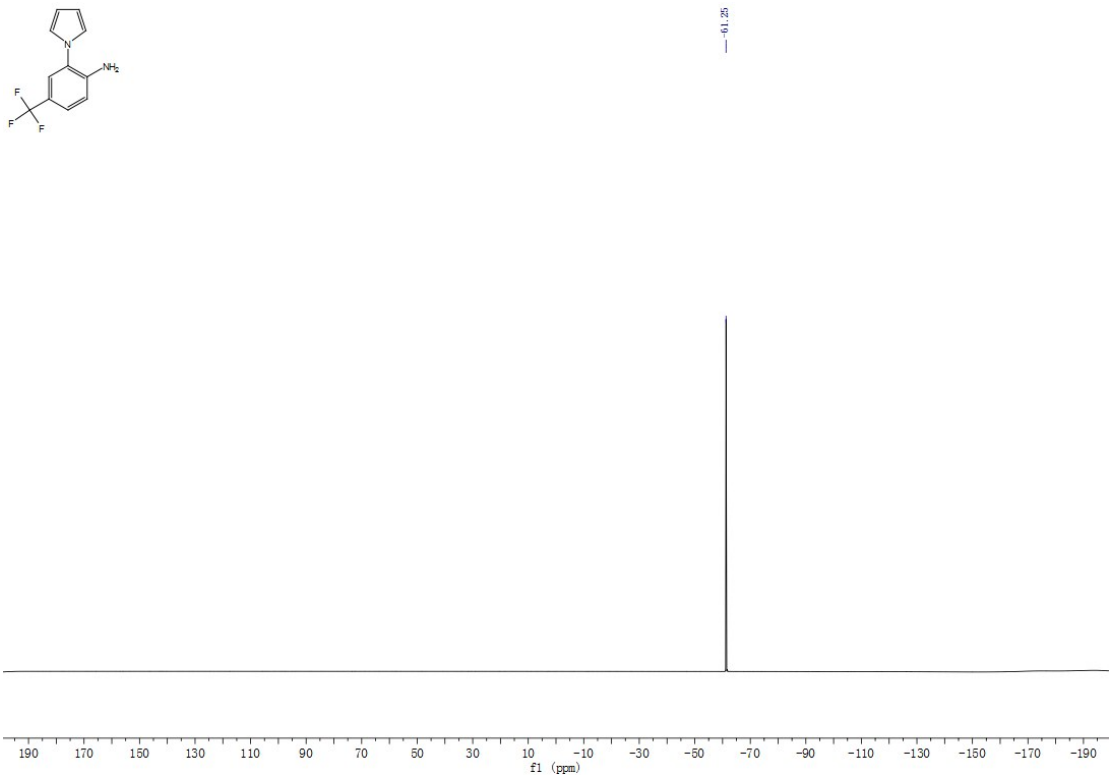
7. NMR spectra of the products



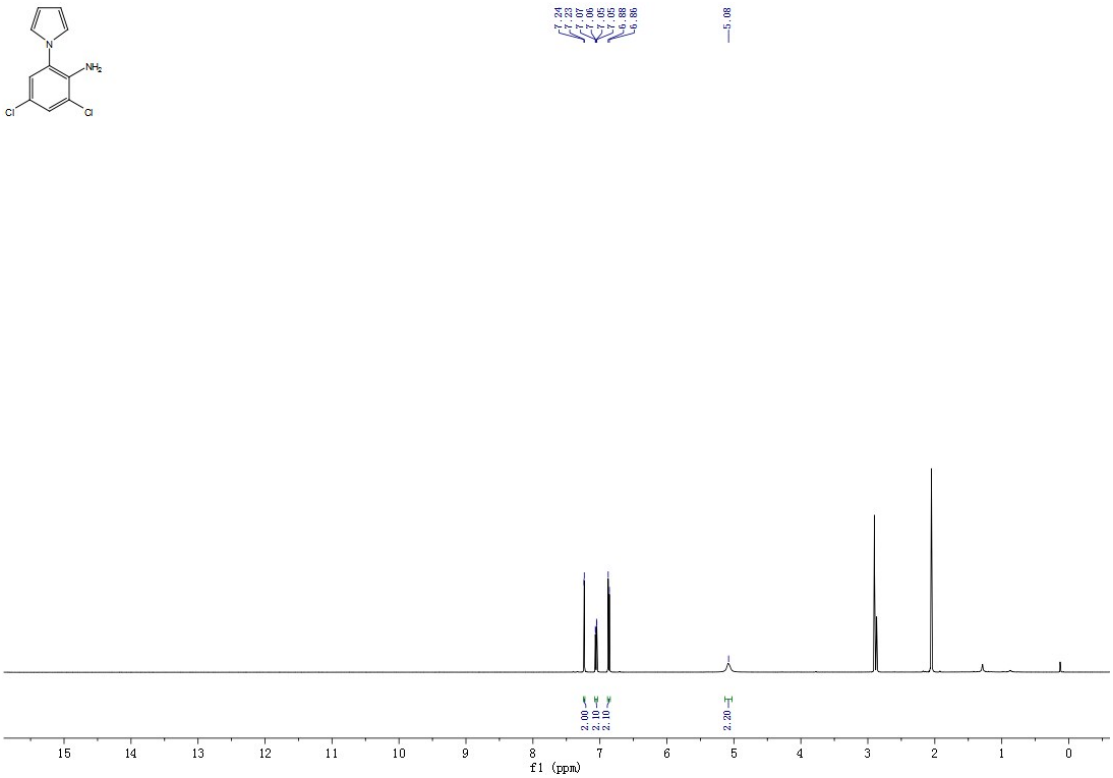
^{1}H NMR spectrum of compound **1e**



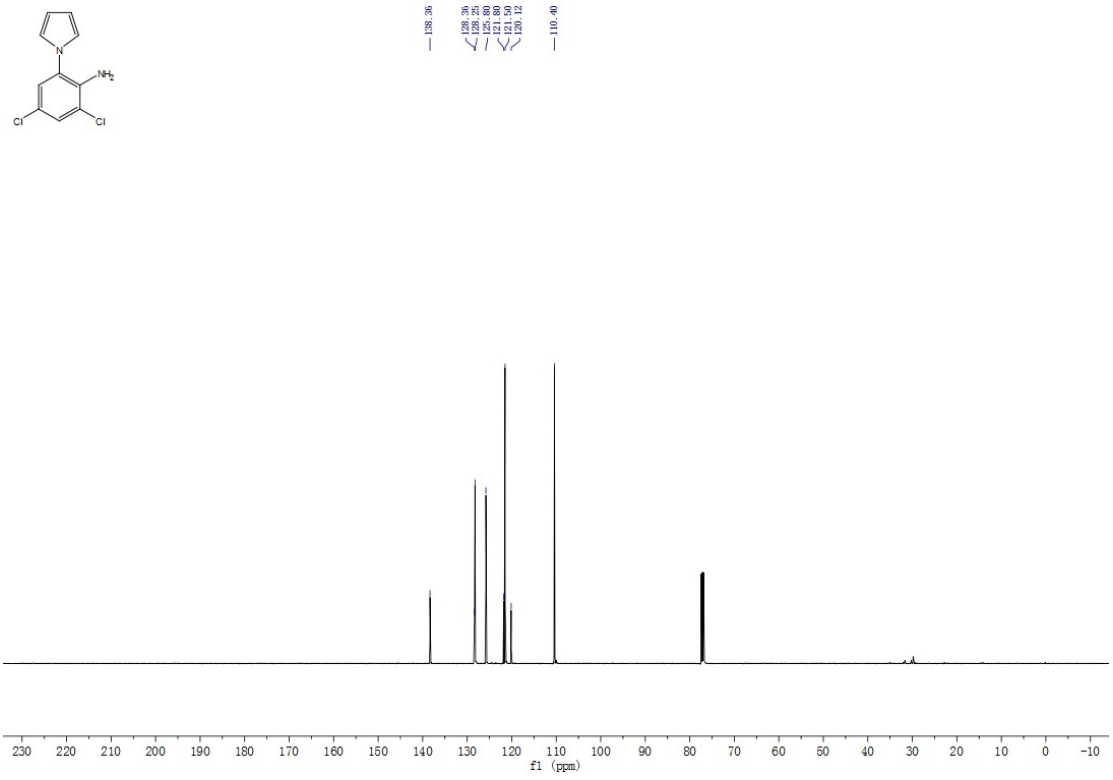
^{13}C NMR spectrum of compound **1e**



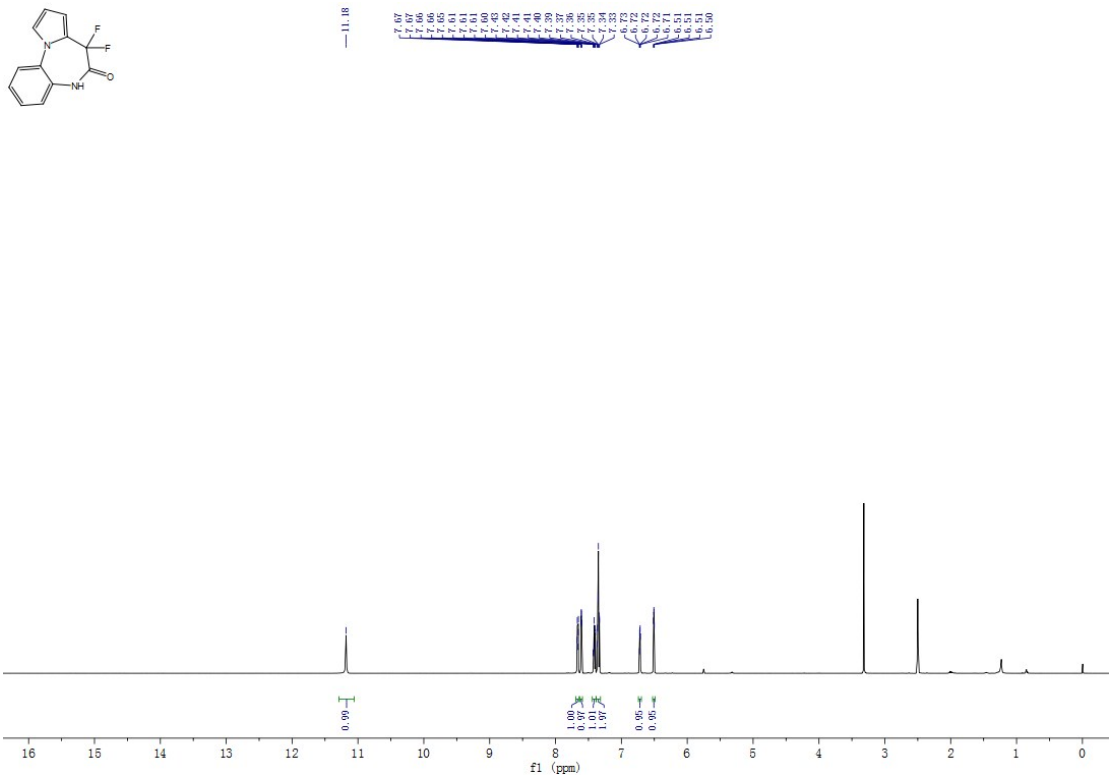
^{19}F NMR spectrum of compound **1e**



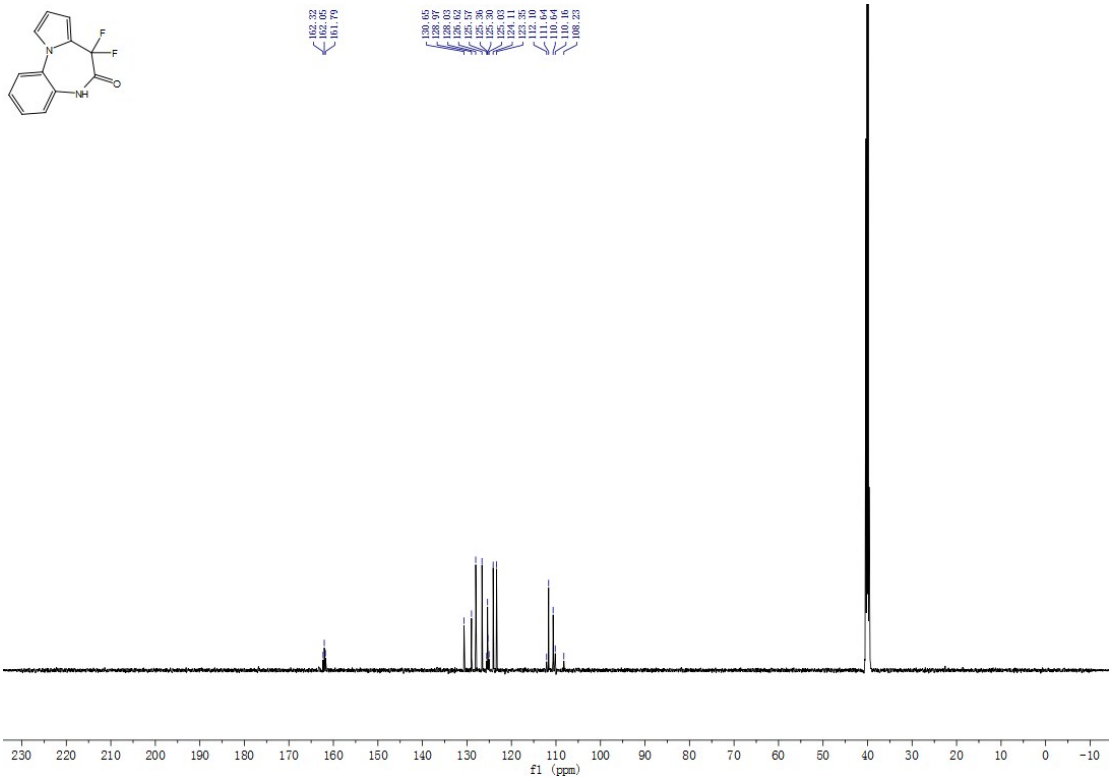
^{1}H NMR spectrum of compound **1j**



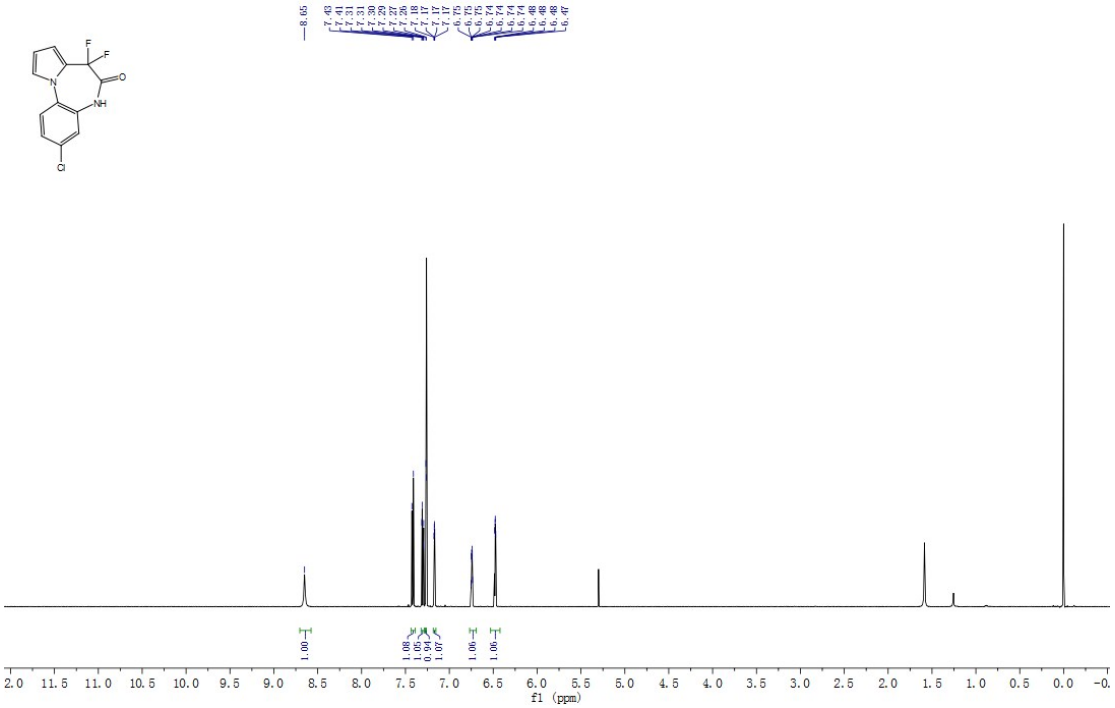
^{13}C NMR spectrum of compound **1j**



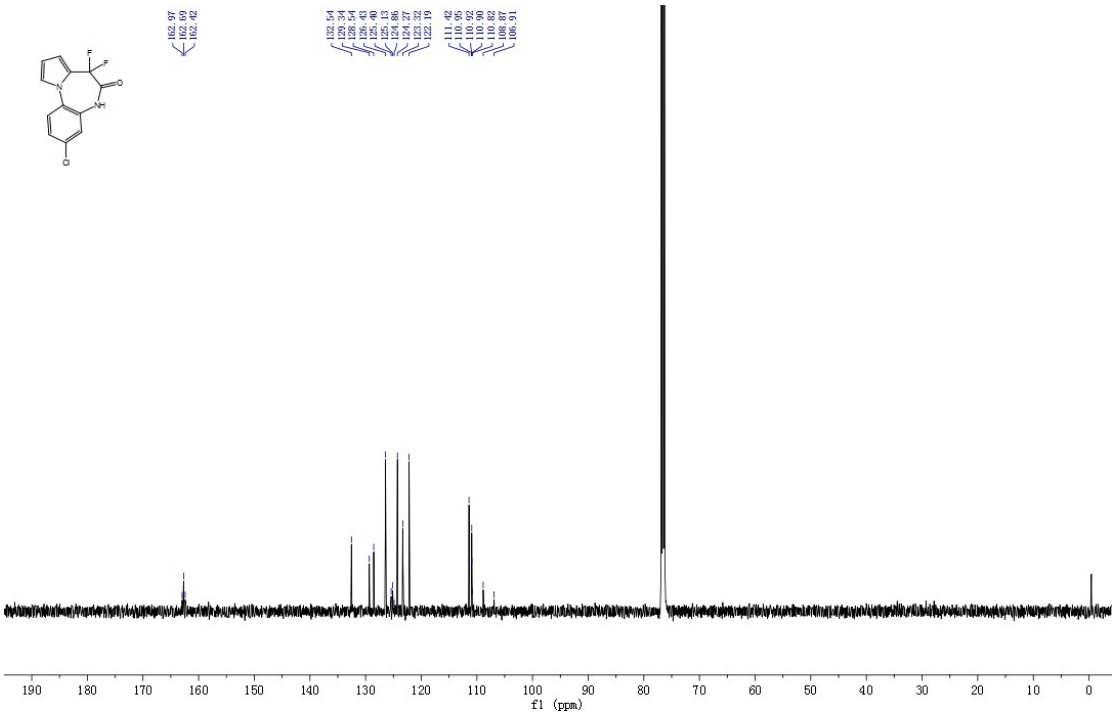
^{1}H NMR spectrum of compound **3a**



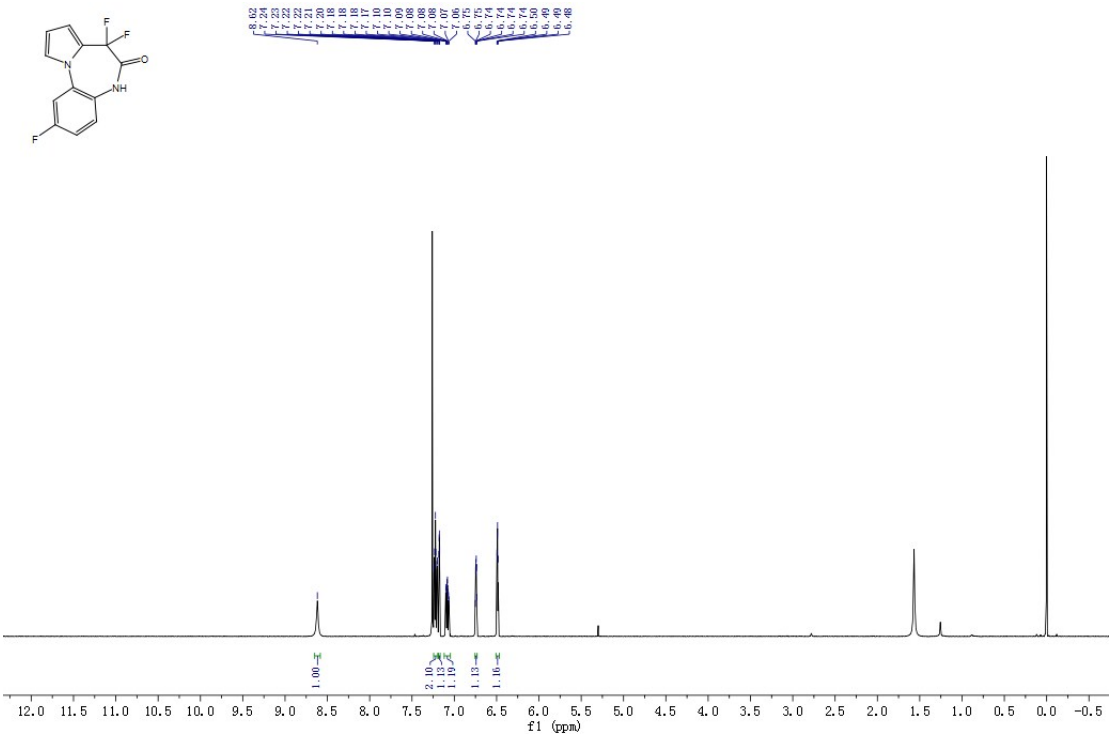
^{13}C NMR spectrum of compound **3a**



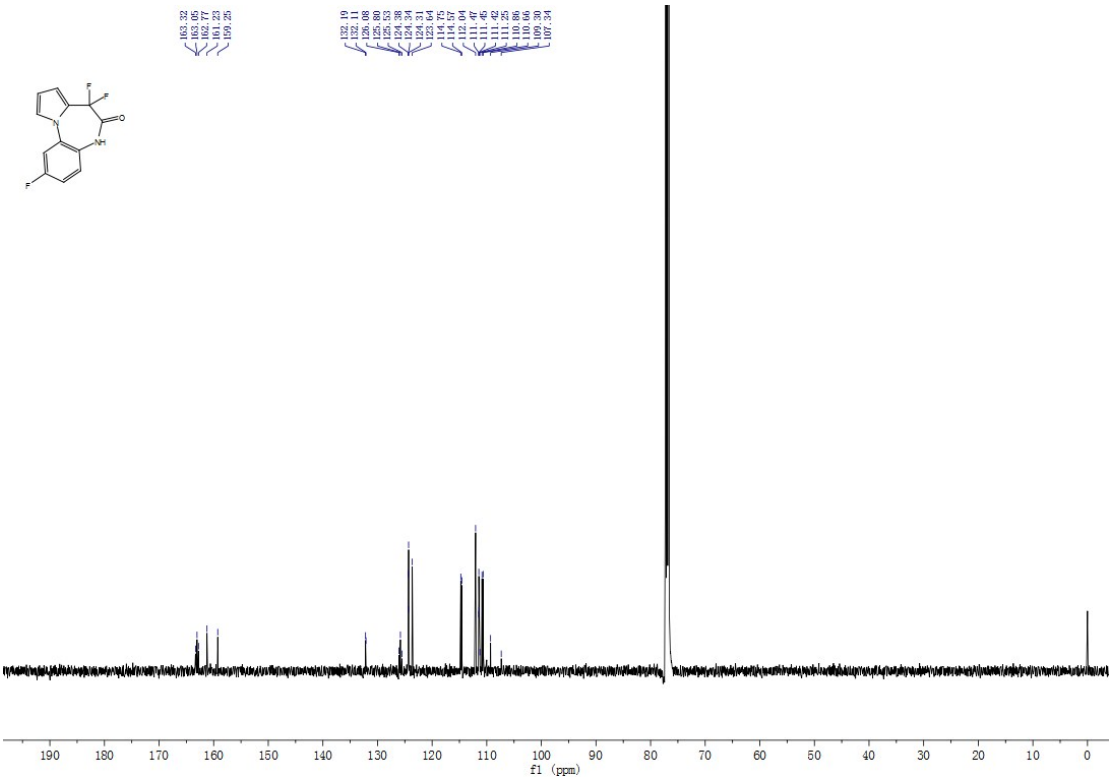
^{1}H NMR spectrum of compound **3b**



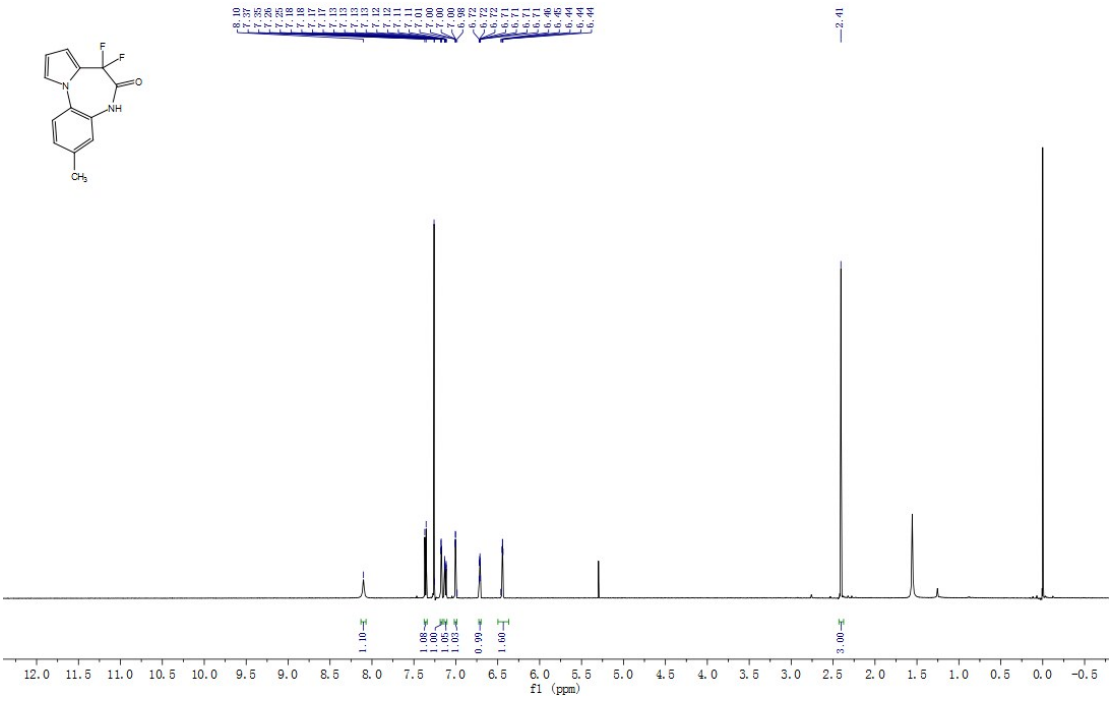
^{13}C NMR spectrum of compound **3b**



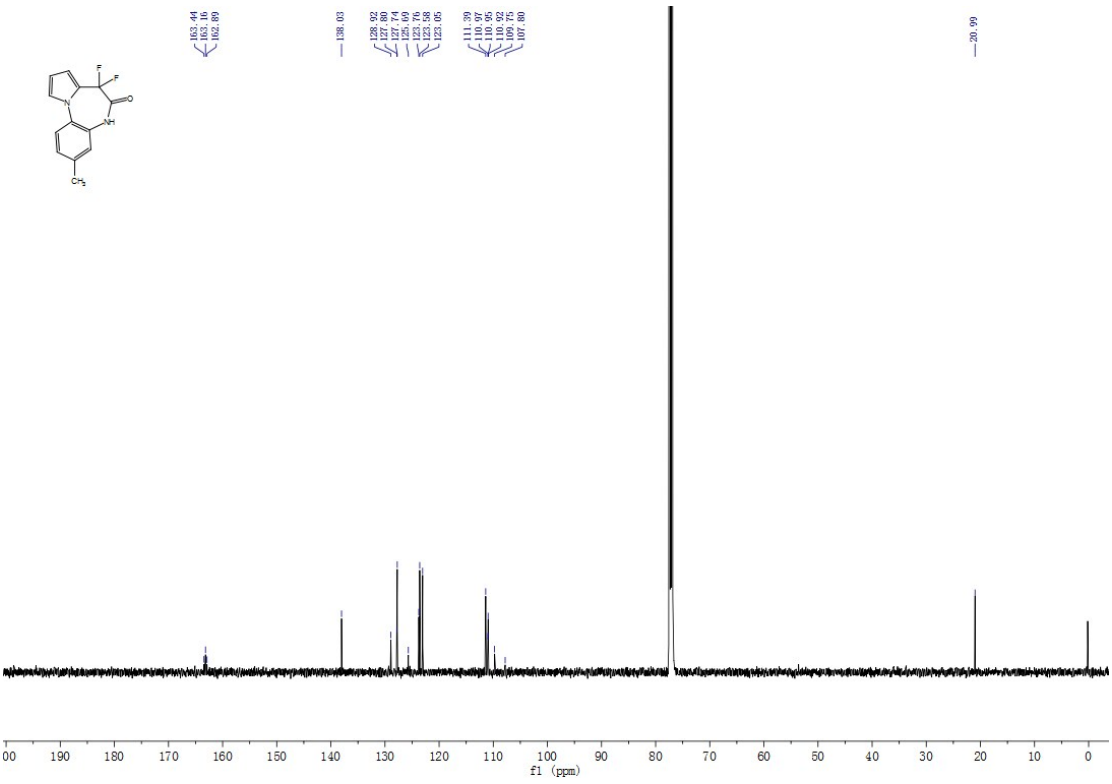
^{1}H NMR spectrum of compound **3c**



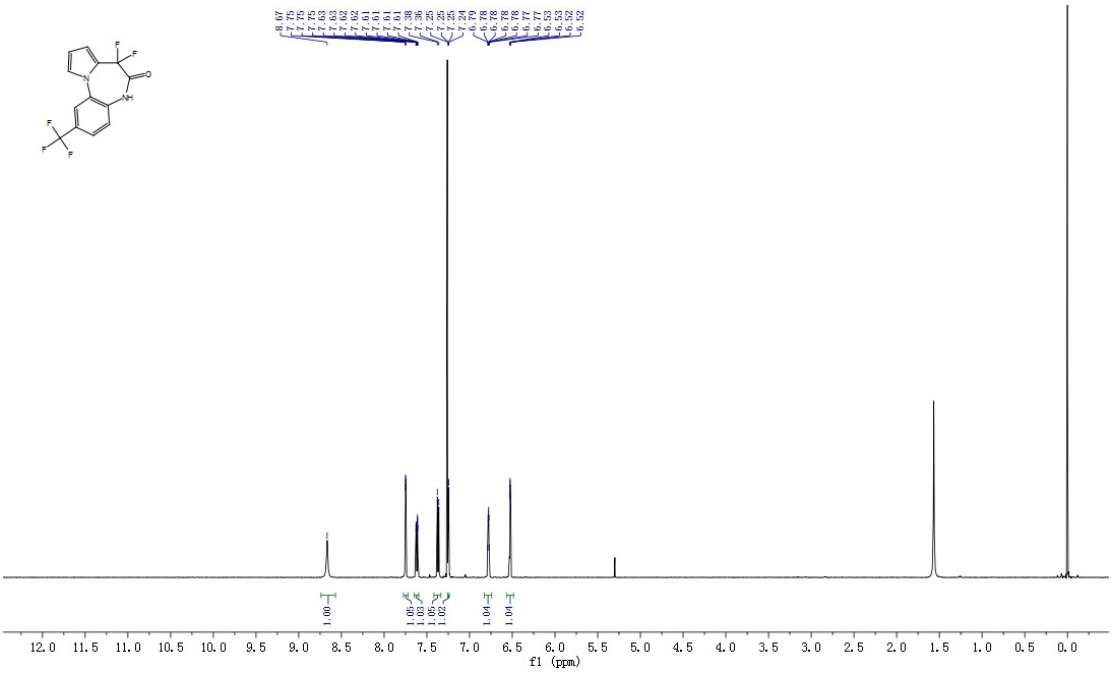
^{13}C NMR spectrum of compound **3c**



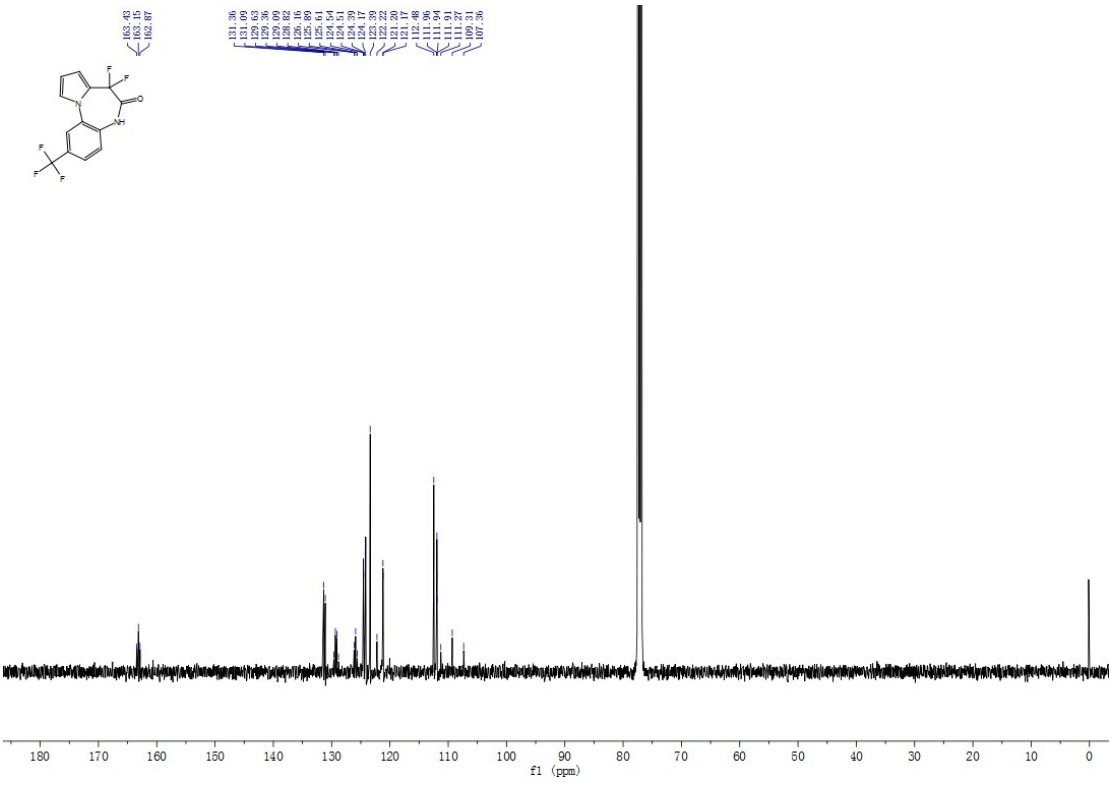
^{1}H NMR spectrum of compound **3d**



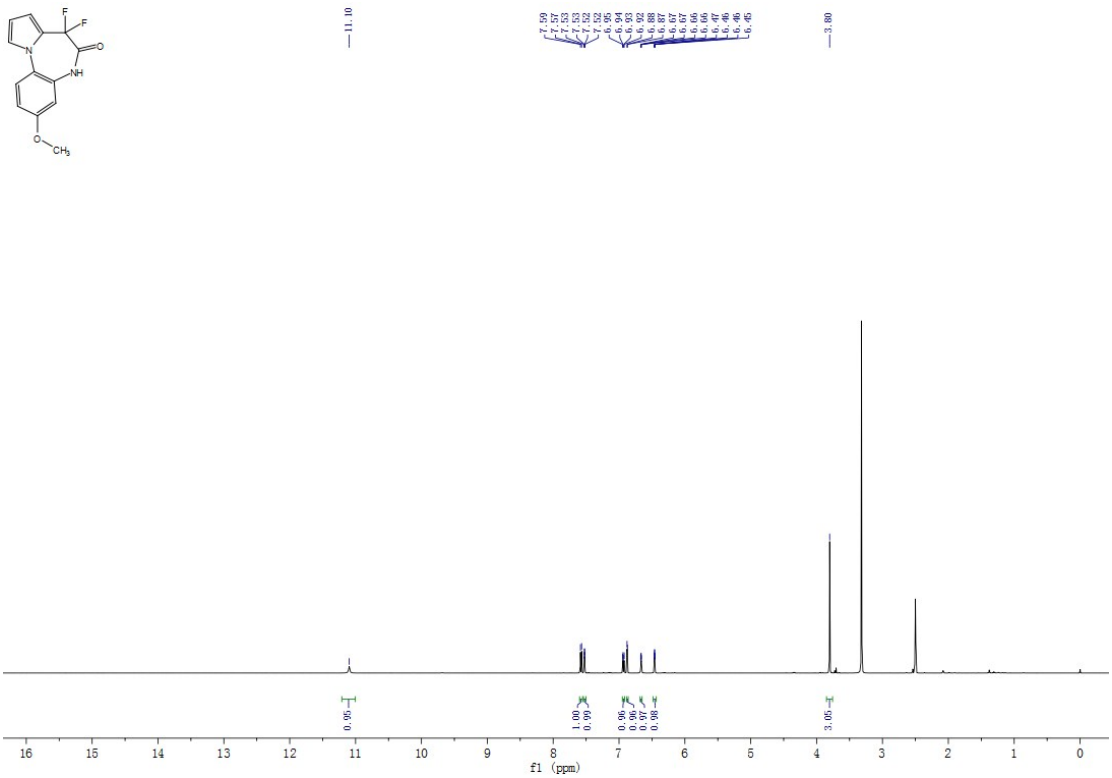
^{13}C NMR spectrum of compound **3d**



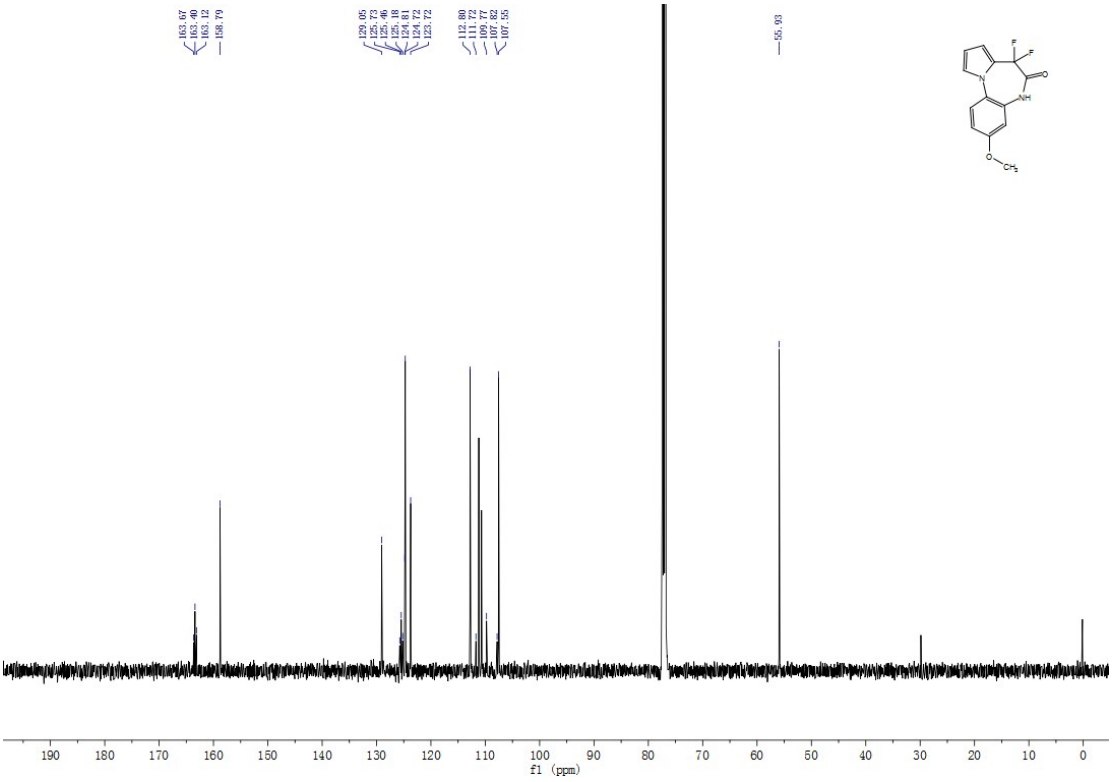
^{1}H NMR spectrum of compound **3e**



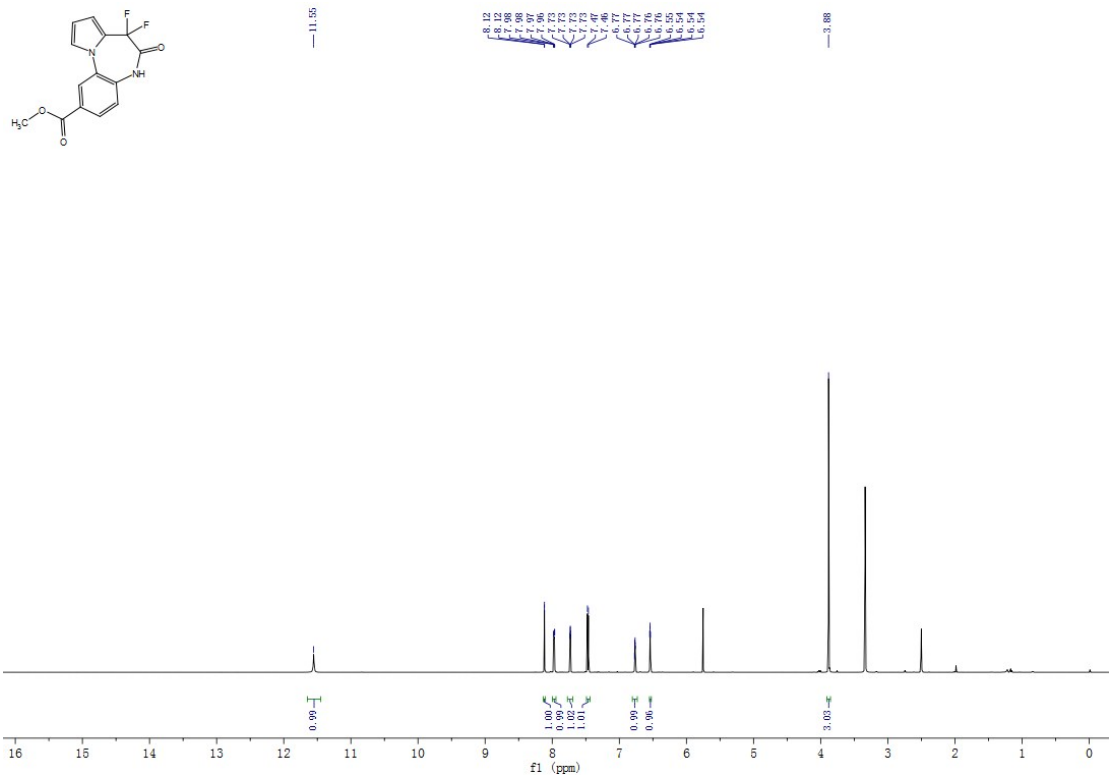
^{13}C NMR spectrum of compound **3e**



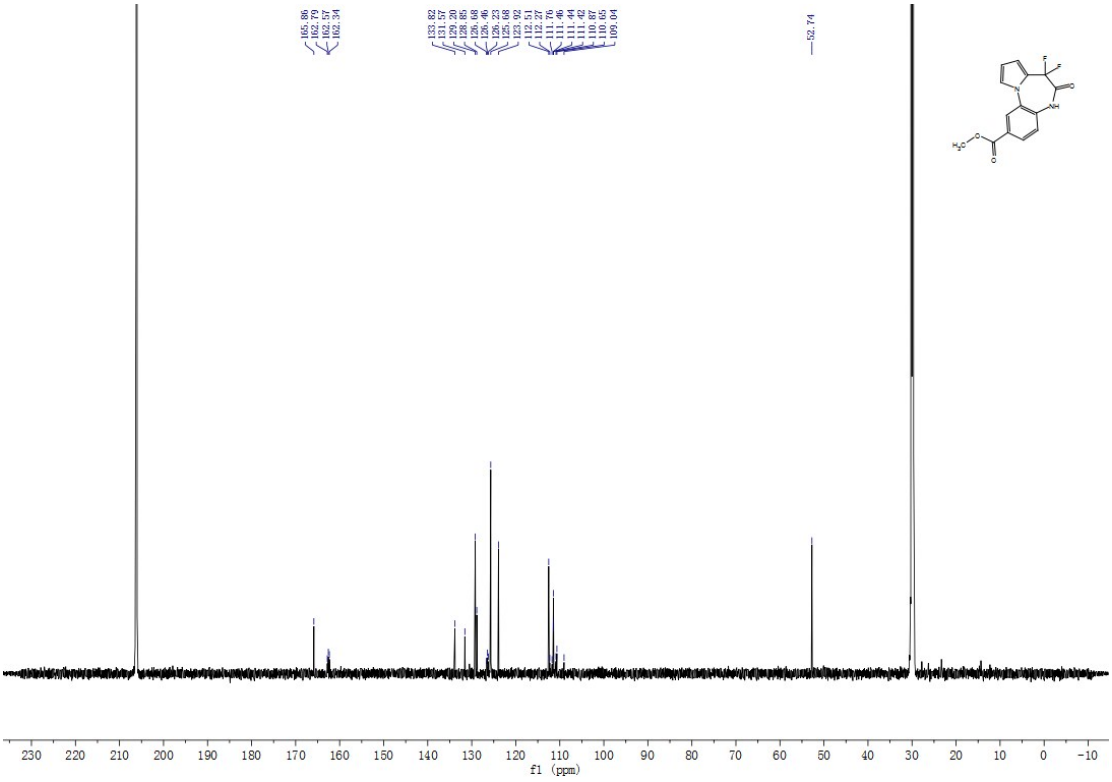
^{1}H NMR spectrum of compound **3f**



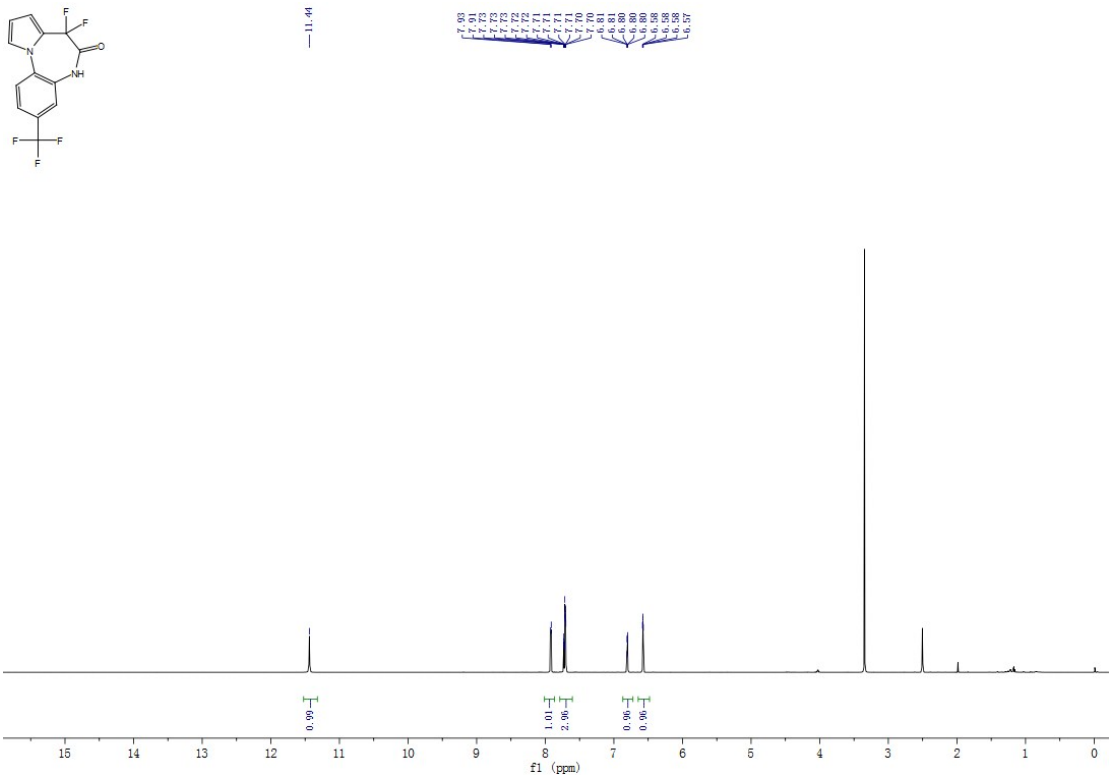
^{13}C NMR spectrum of compound **3f**



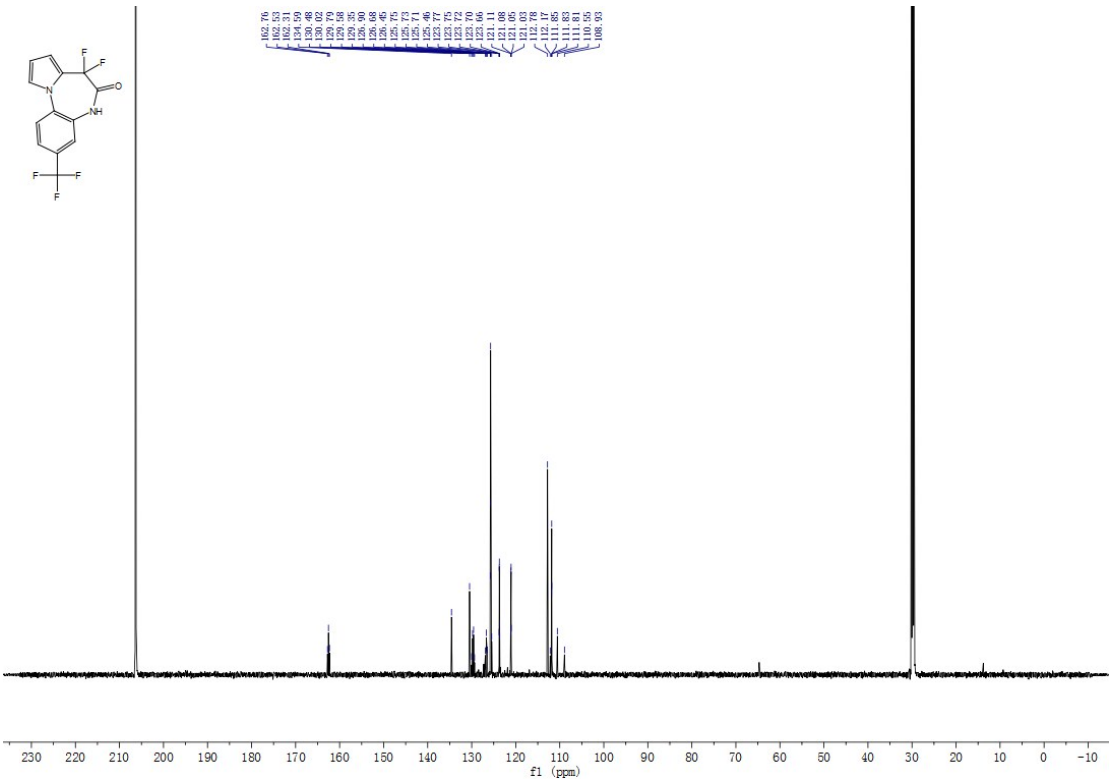
^{1}H NMR spectrum of compound **3g**



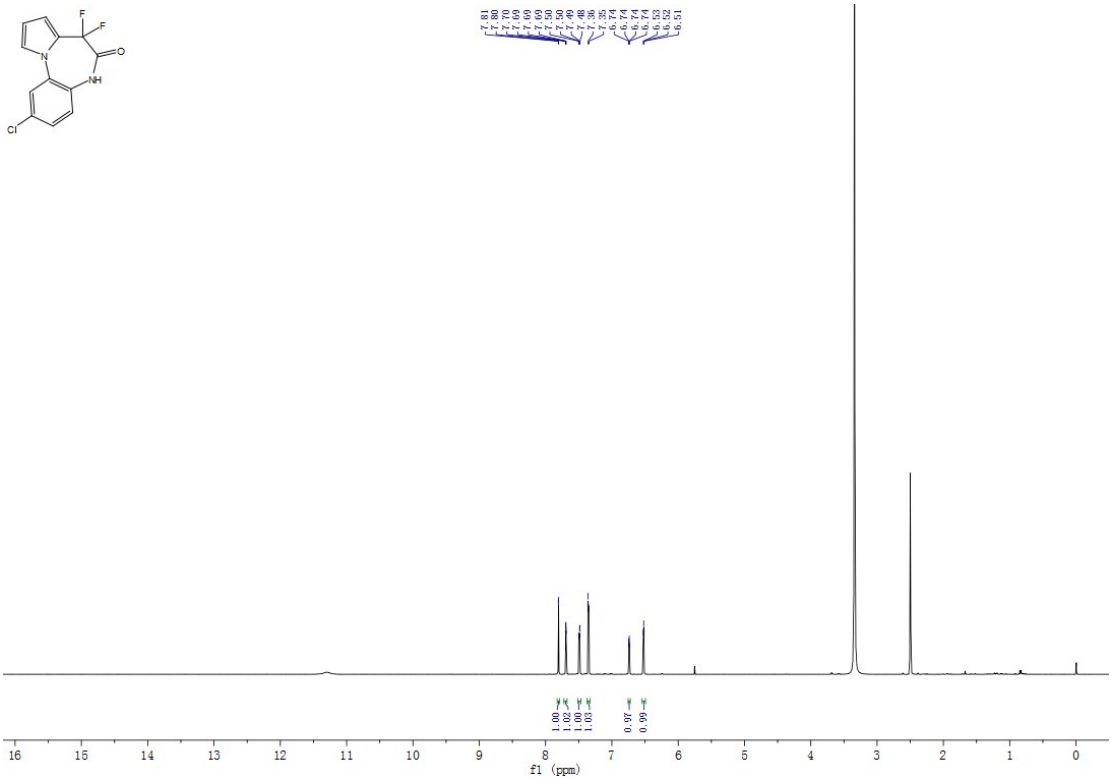
^{13}C NMR spectrum of compound **3g**



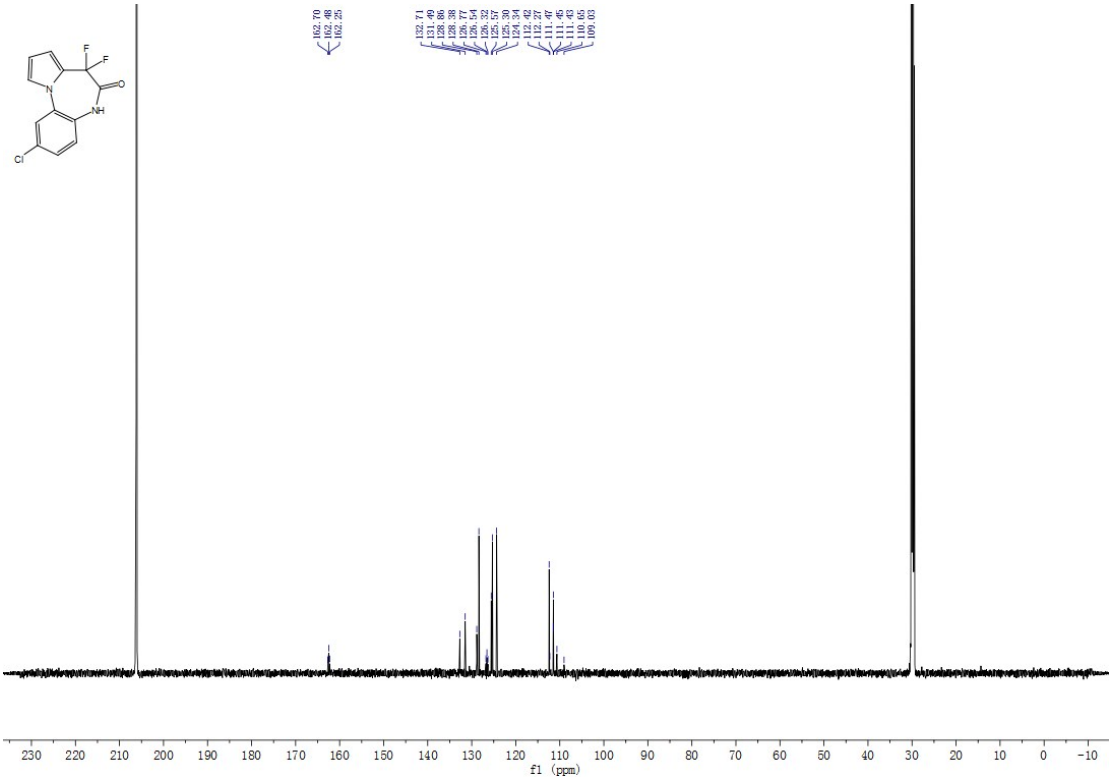
^{1}H NMR spectrum of compound **3h**



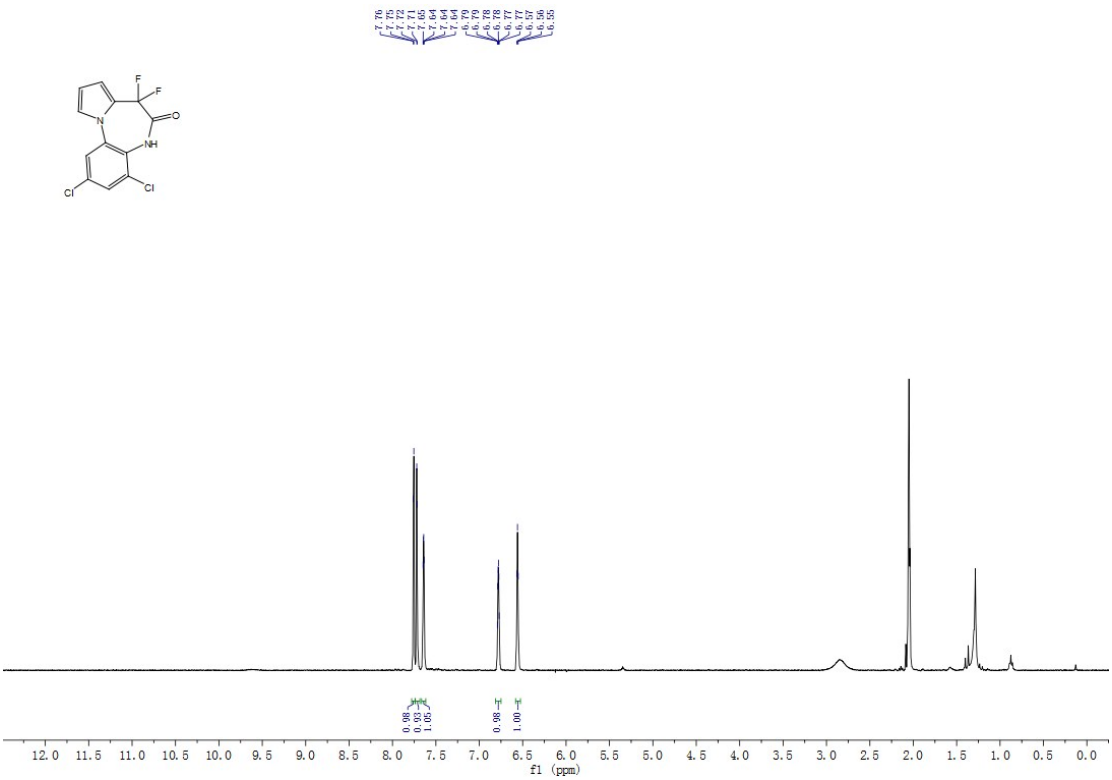
^{13}C NMR spectrum of compound **3h**



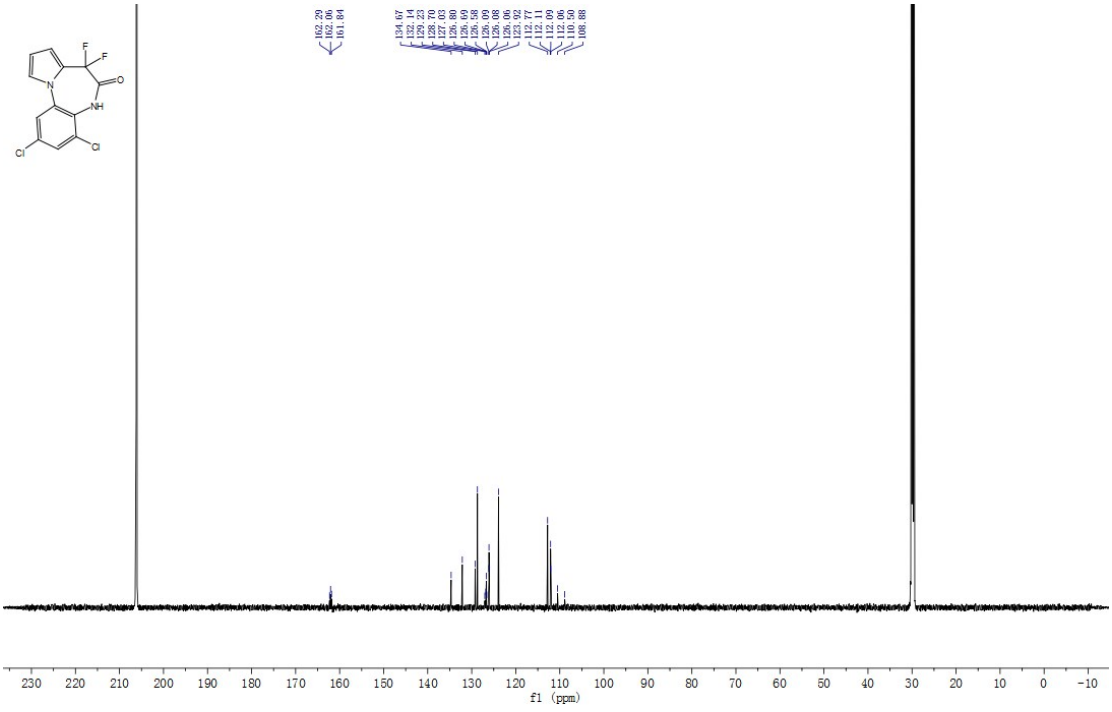
^{1}H NMR spectrum of compound **3i**



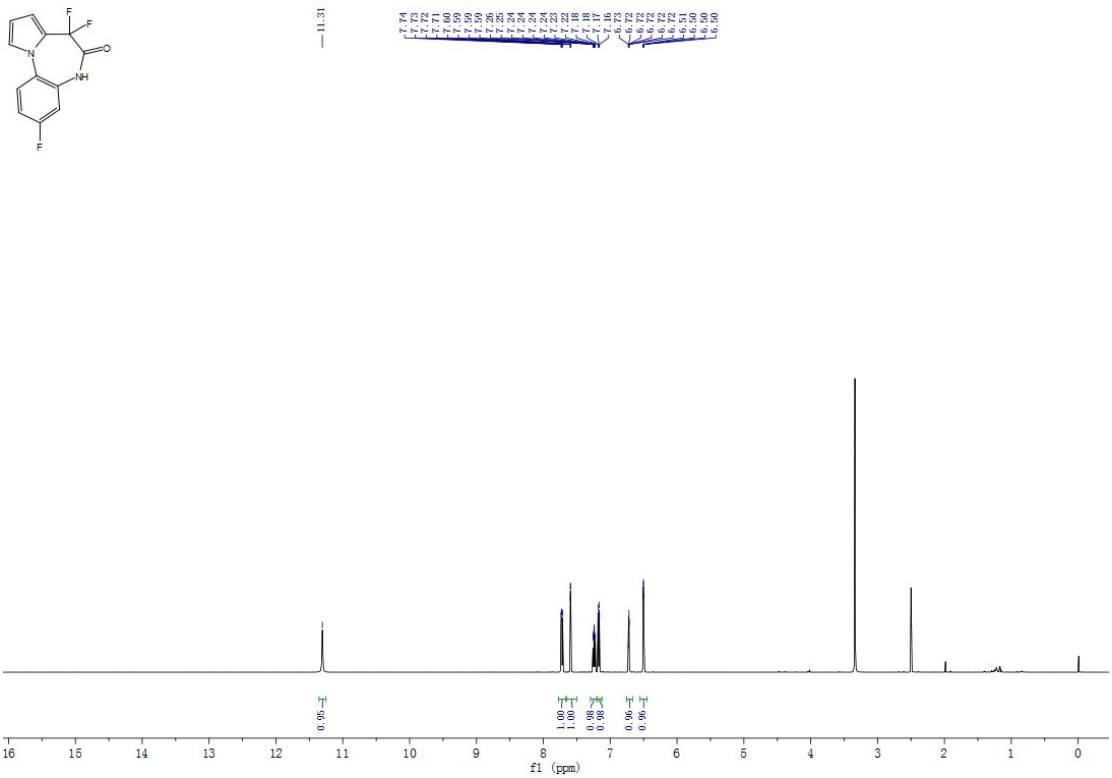
^{13}C NMR spectrum of compound **3i**



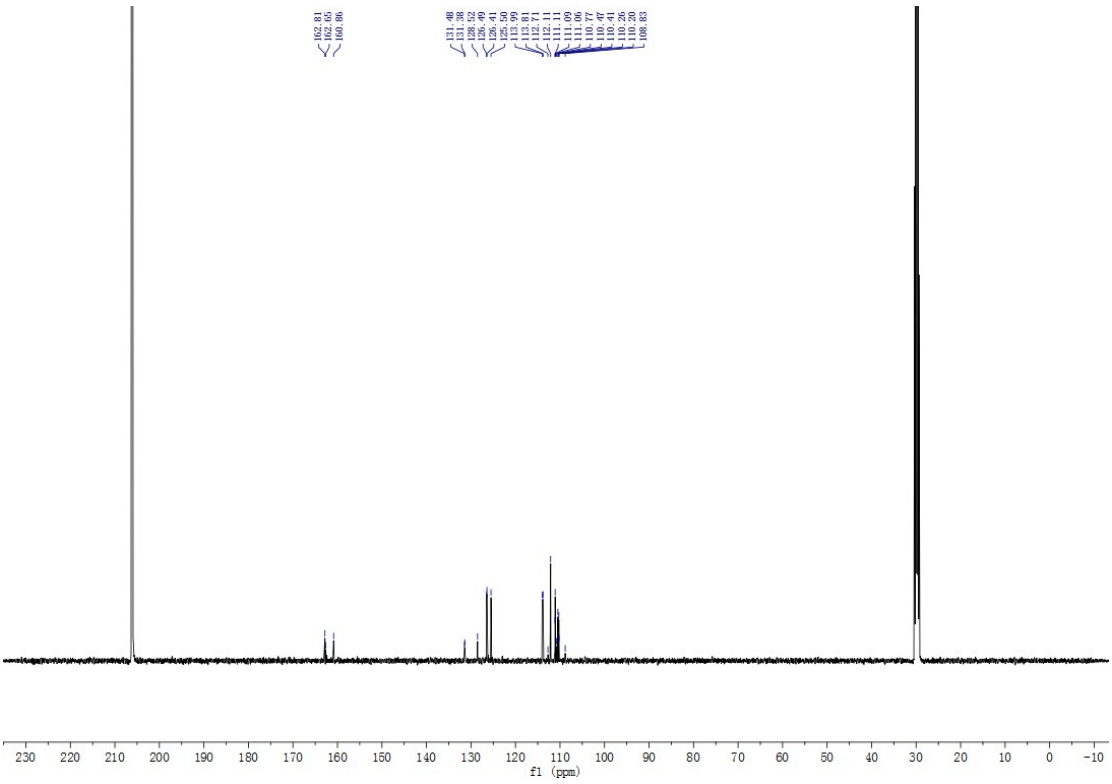
^{1}H NMR spectrum of compound **3j**



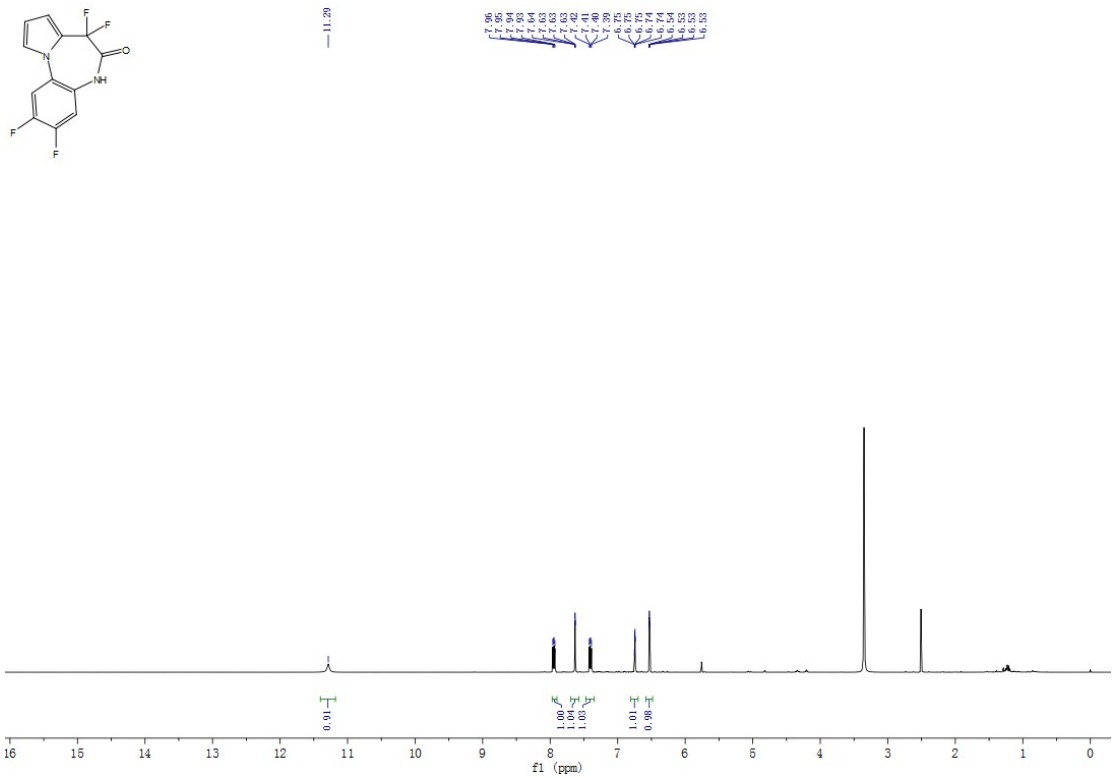
^{13}C NMR spectrum of compound **3j**



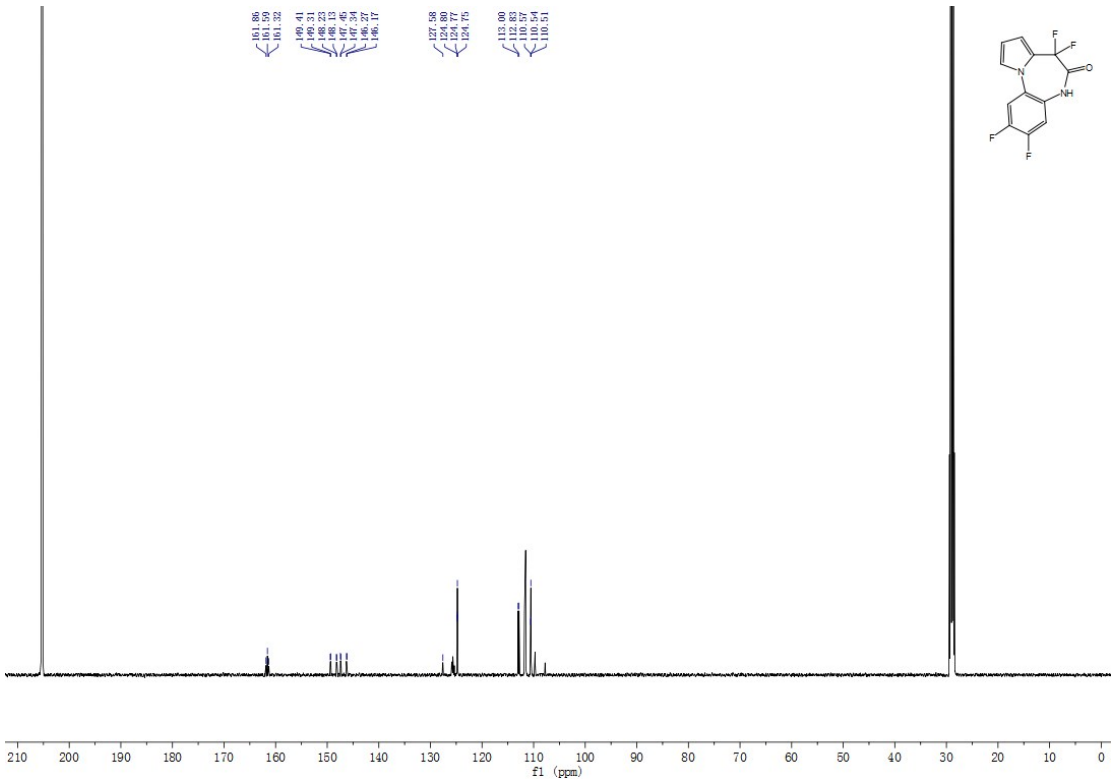
^{1}H NMR spectrum of compound **3k**



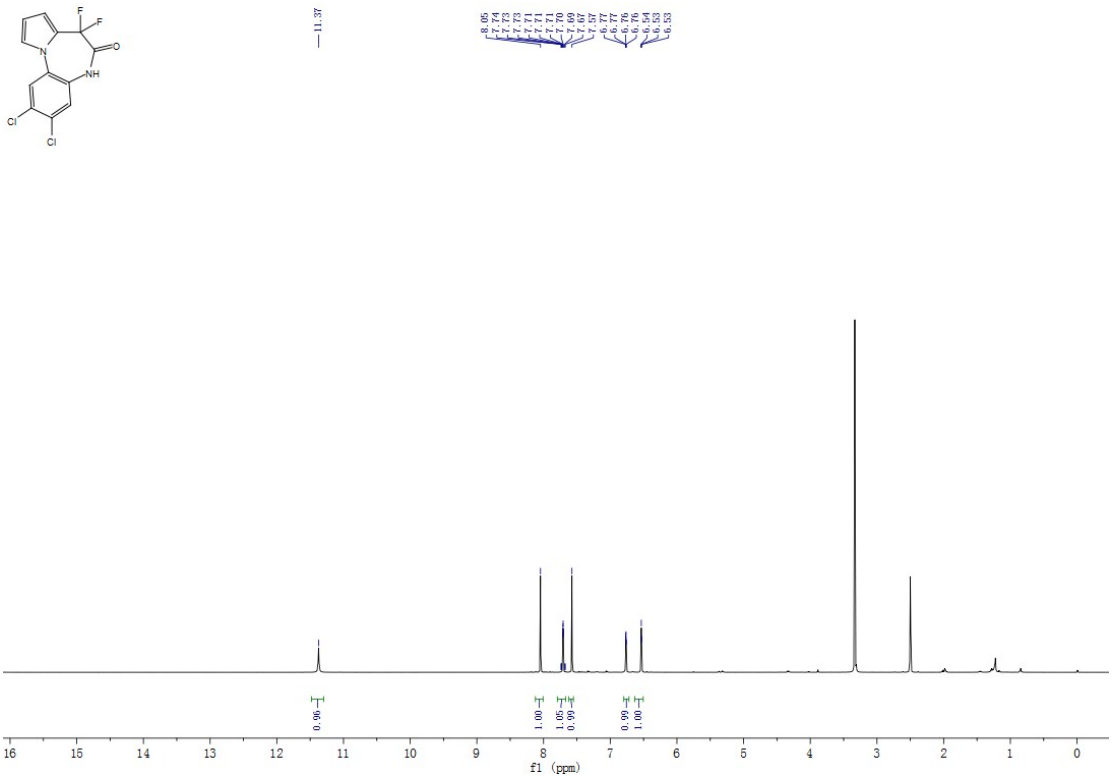
^{13}C NMR spectrum of compound **3k**



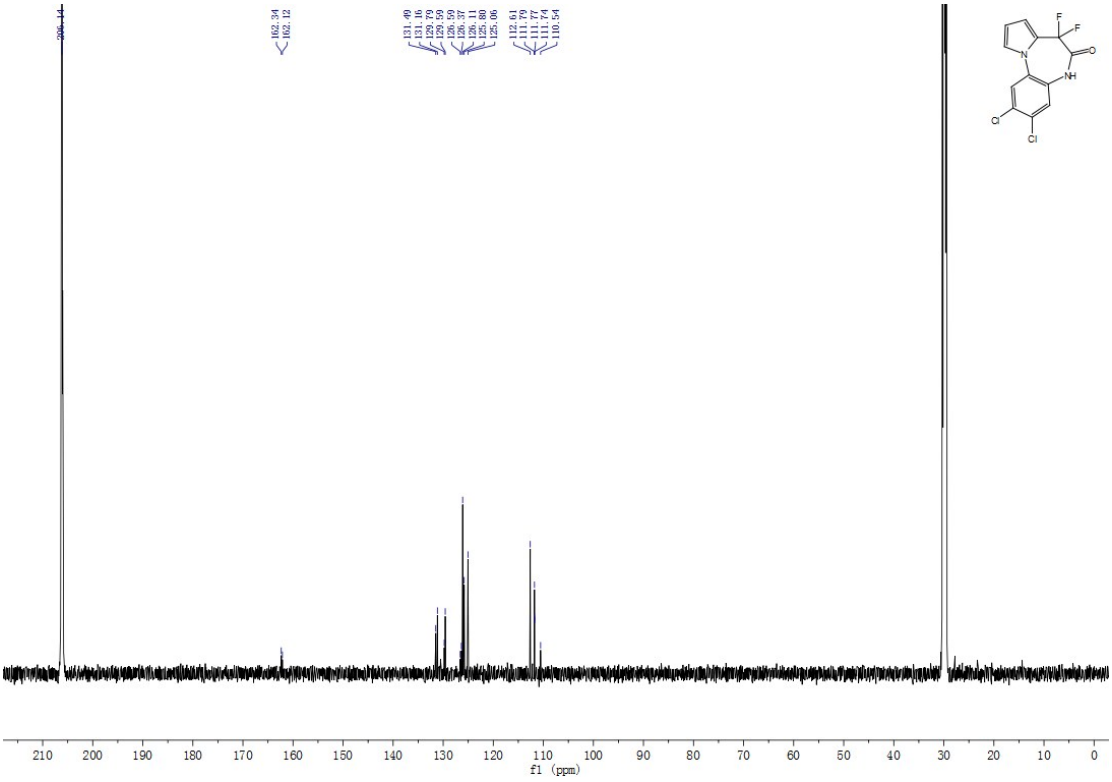
^{1}H NMR spectrum of compound **3l**



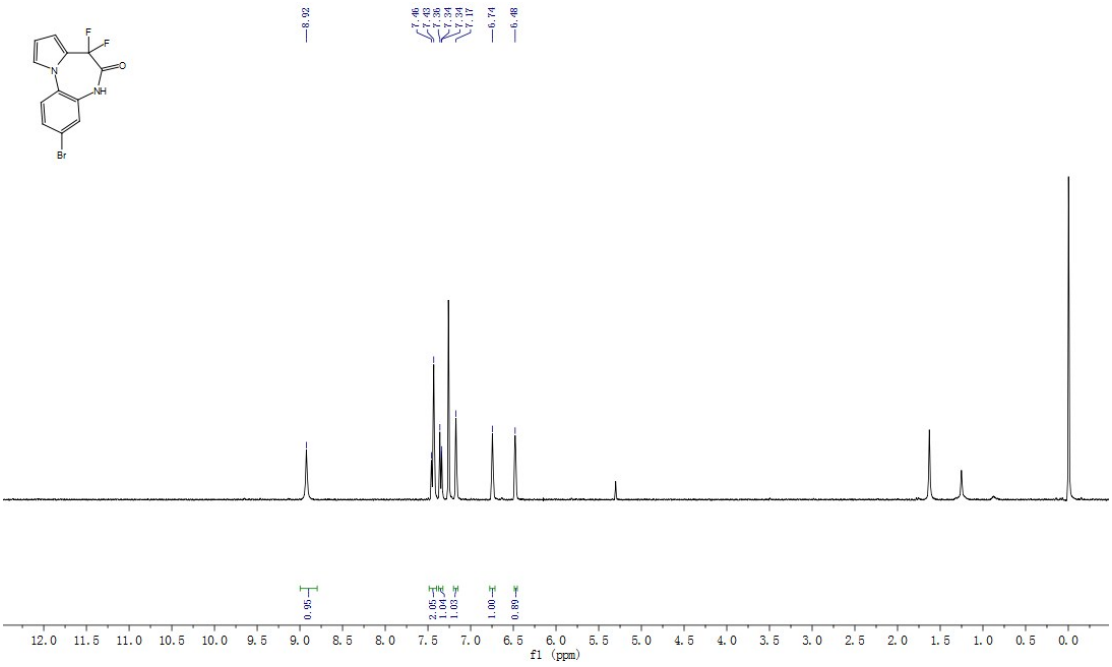
^{13}C NMR spectrum of compound **3l**



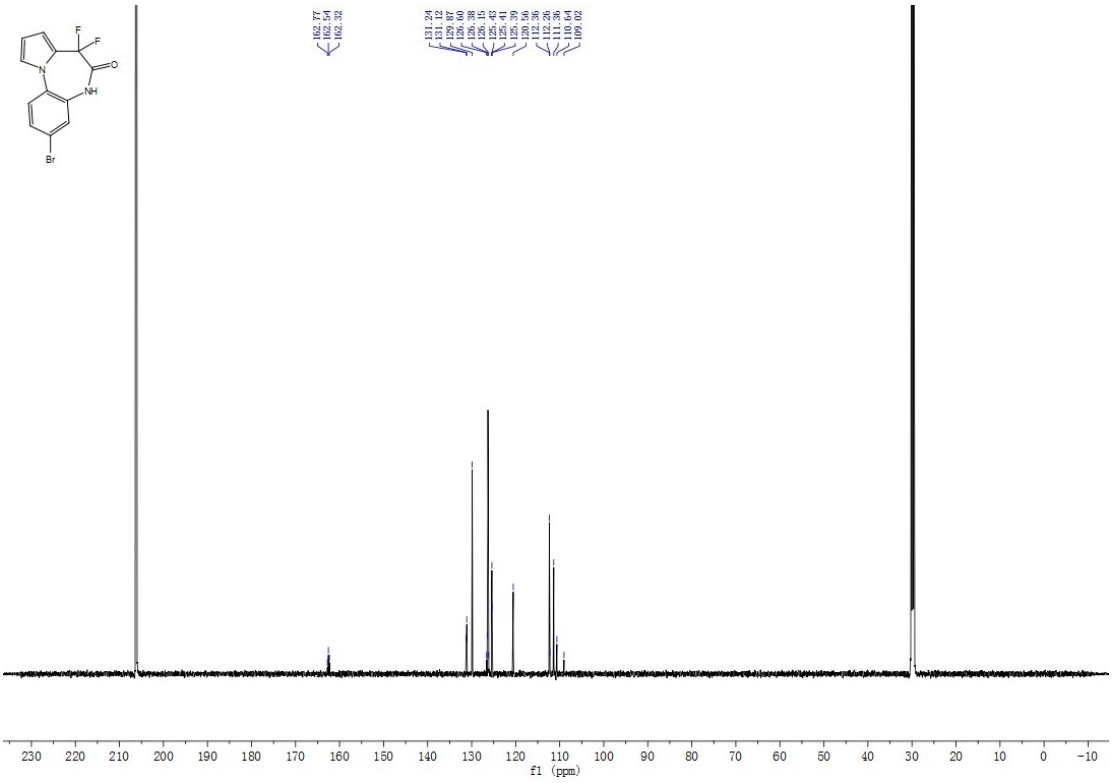
^{1}H NMR spectrum of compound **3m**



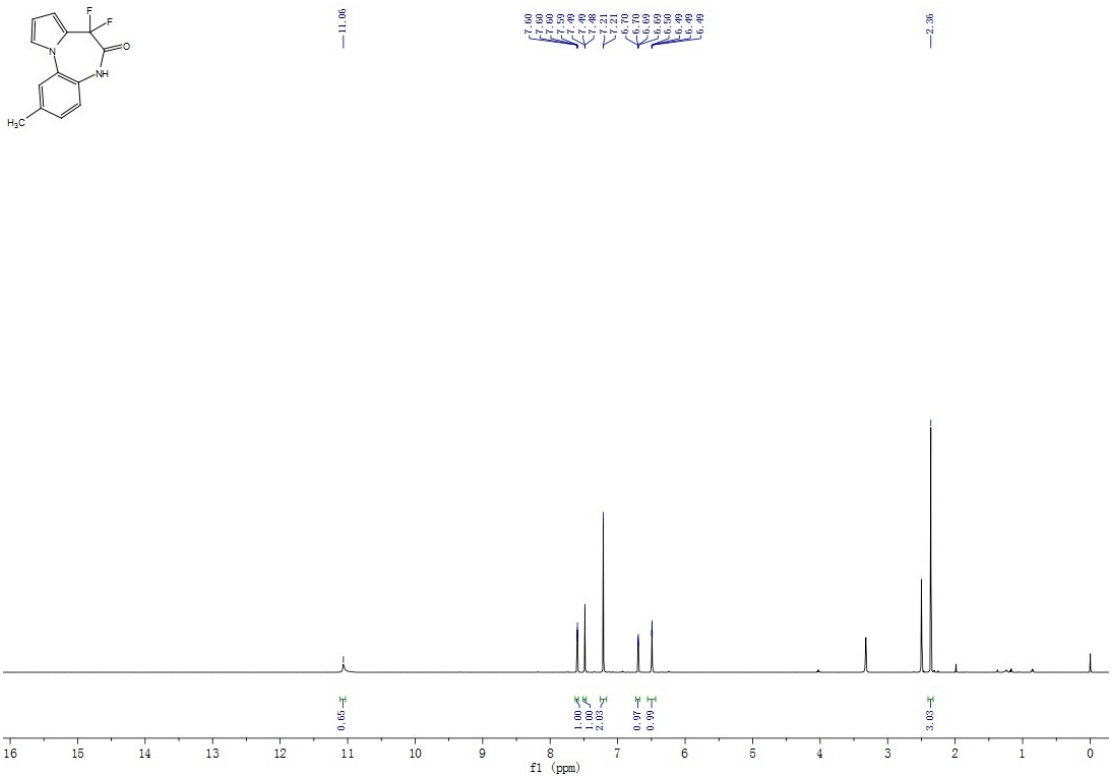
^{13}C NMR spectrum of compound **3m**



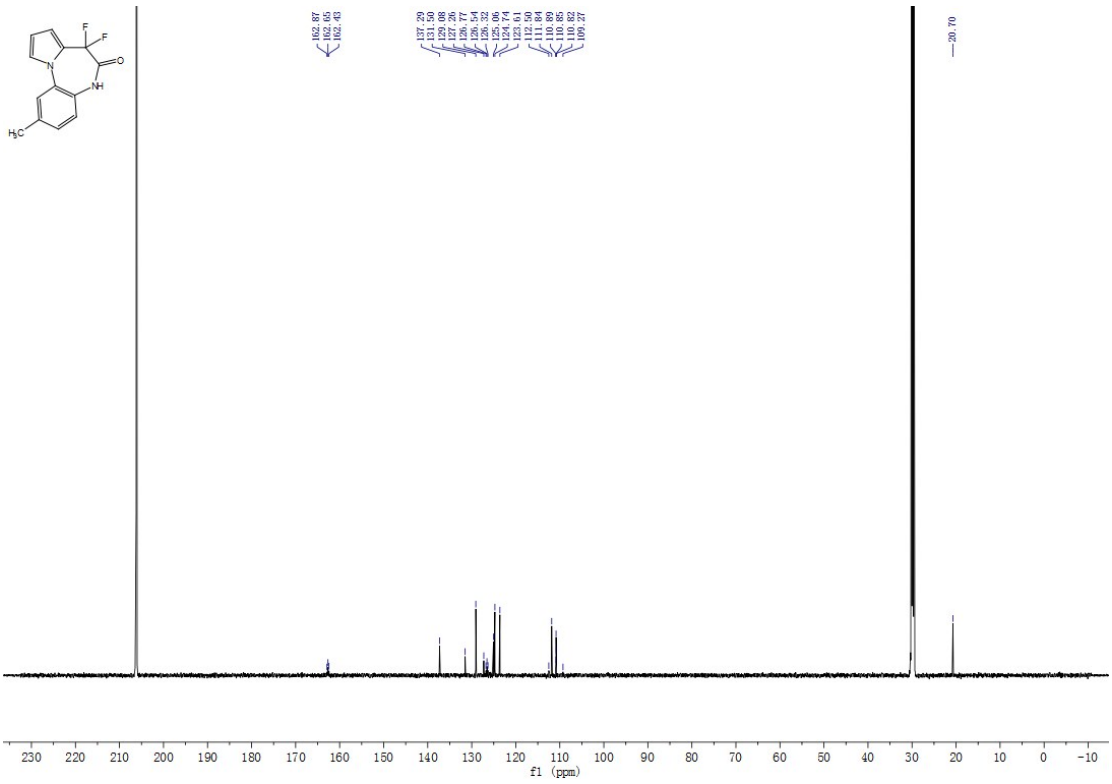
^{1}H NMR spectrum of compound **3n**



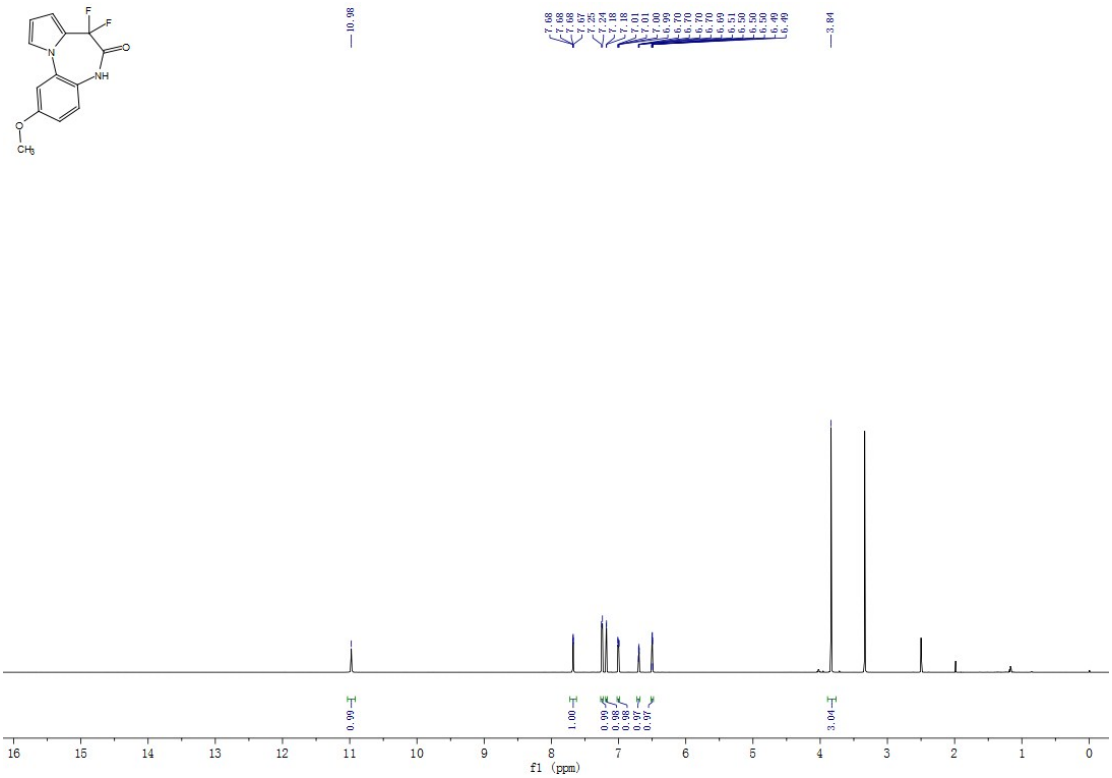
^{13}C NMR spectrum of compound **3n**



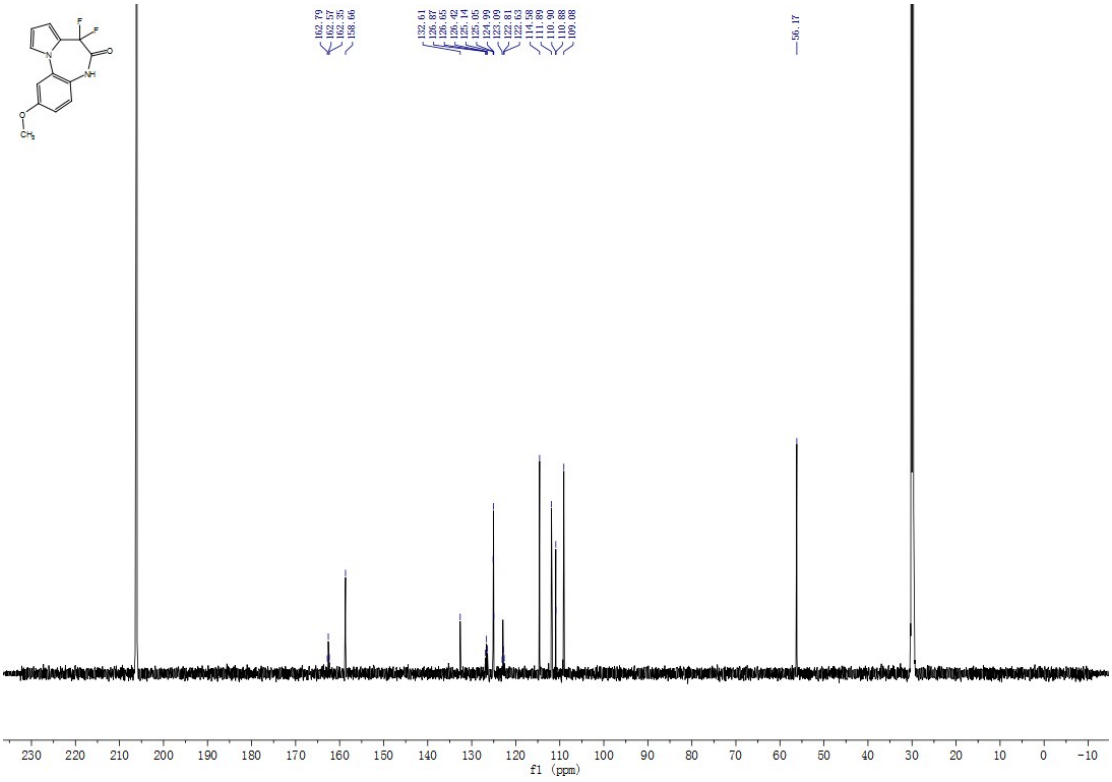
^{1}H NMR spectrum of compound **3o**



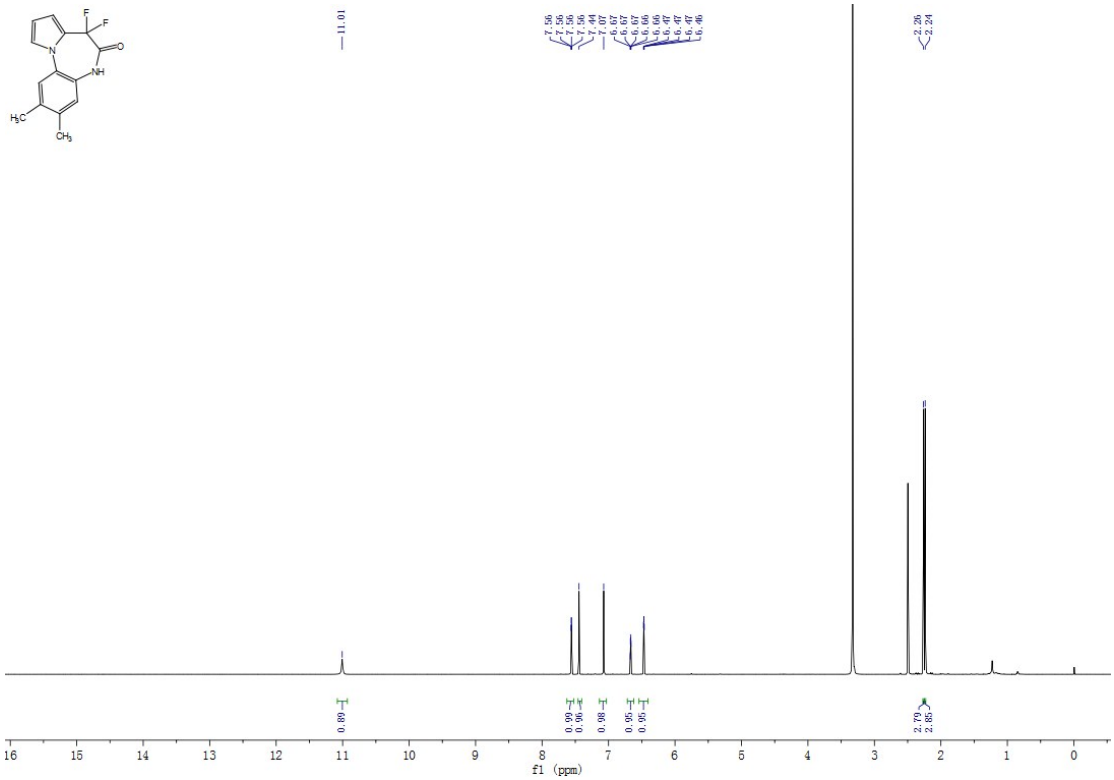
^{13}C NMR spectrum of compound **3o**



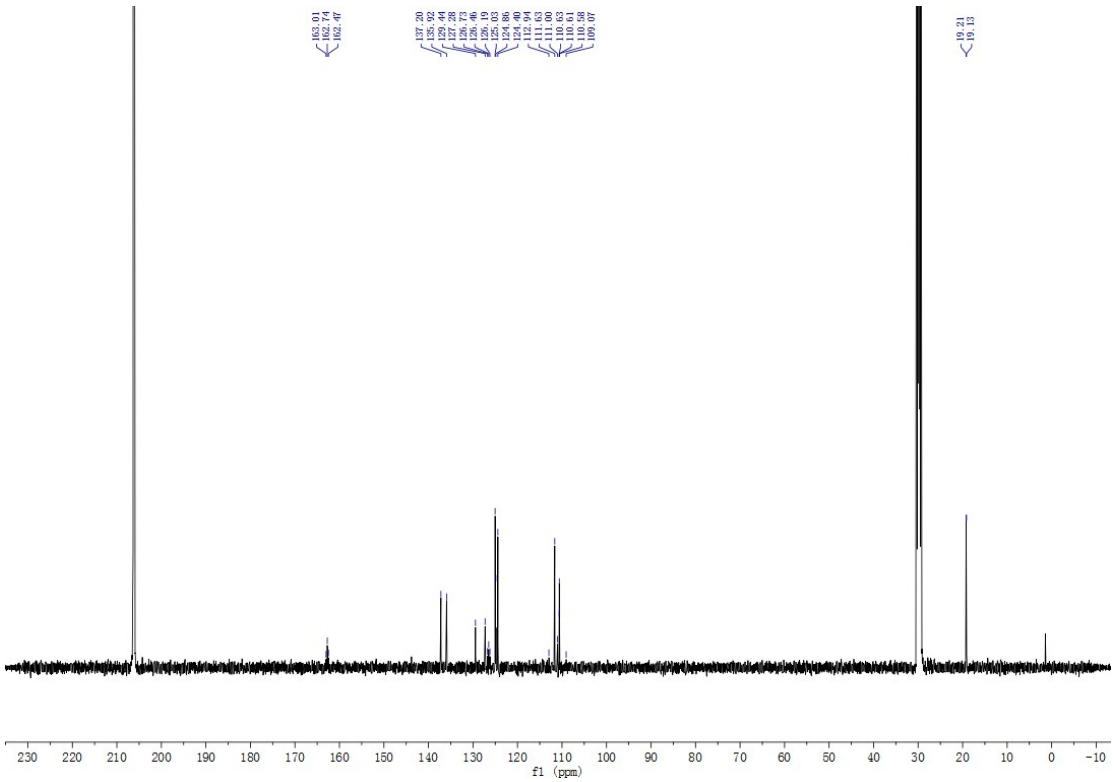
^{1}H NMR spectrum of compound **3p**



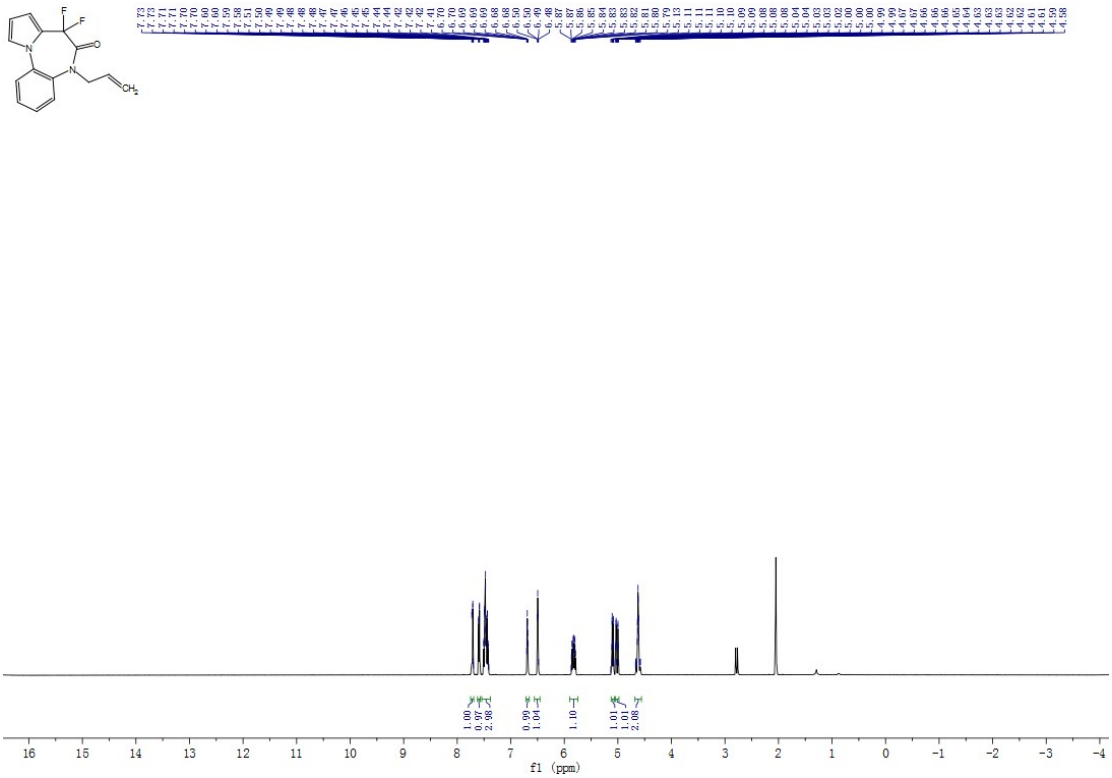
^{13}C NMR spectrum of compound **3p**



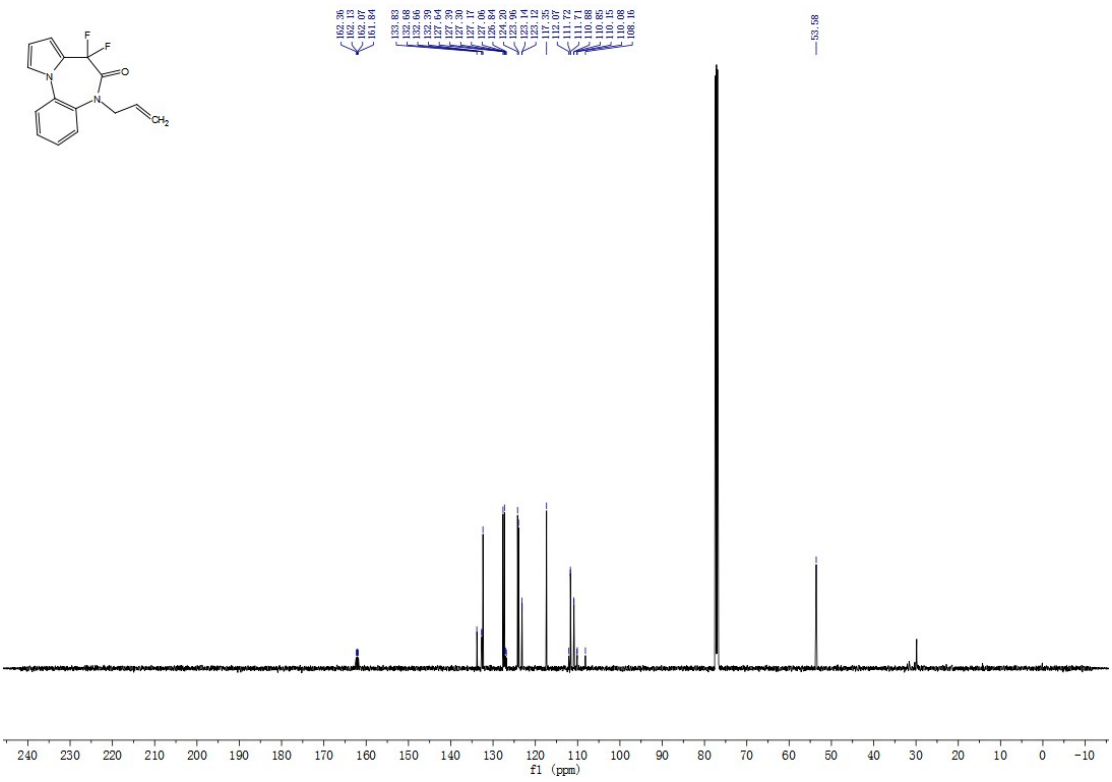
^{1}H NMR spectrum of compound **3q**



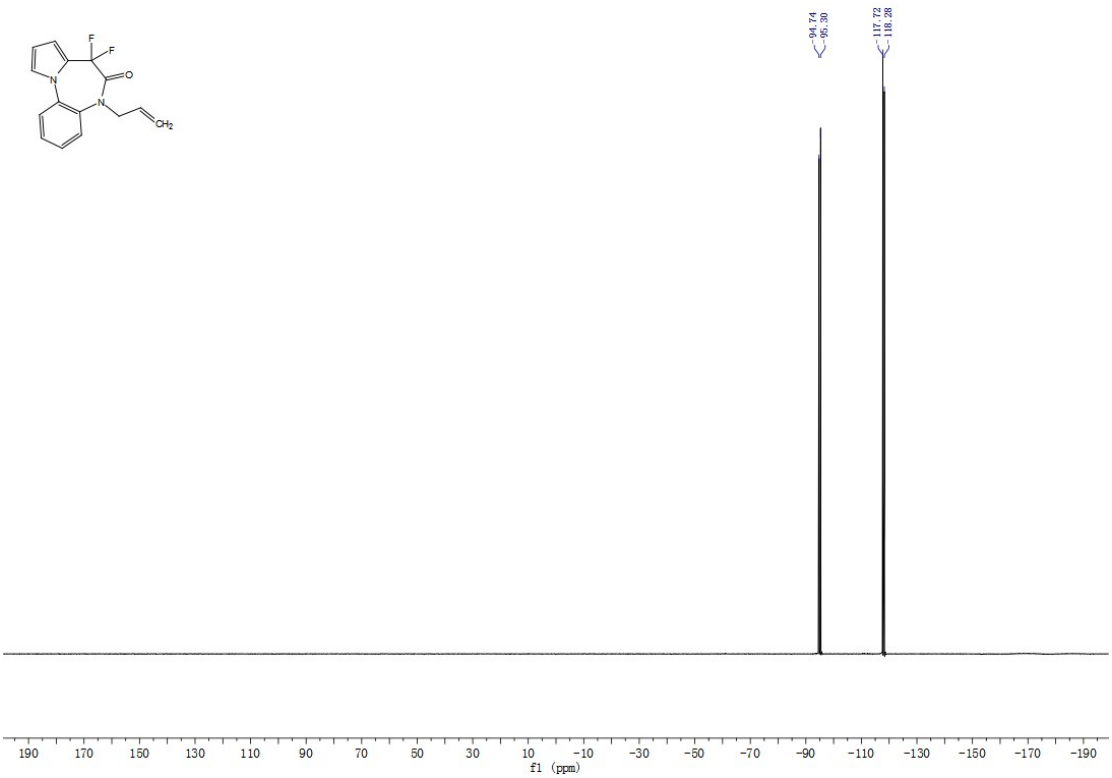
^{13}C NMR spectrum of compound **3q**



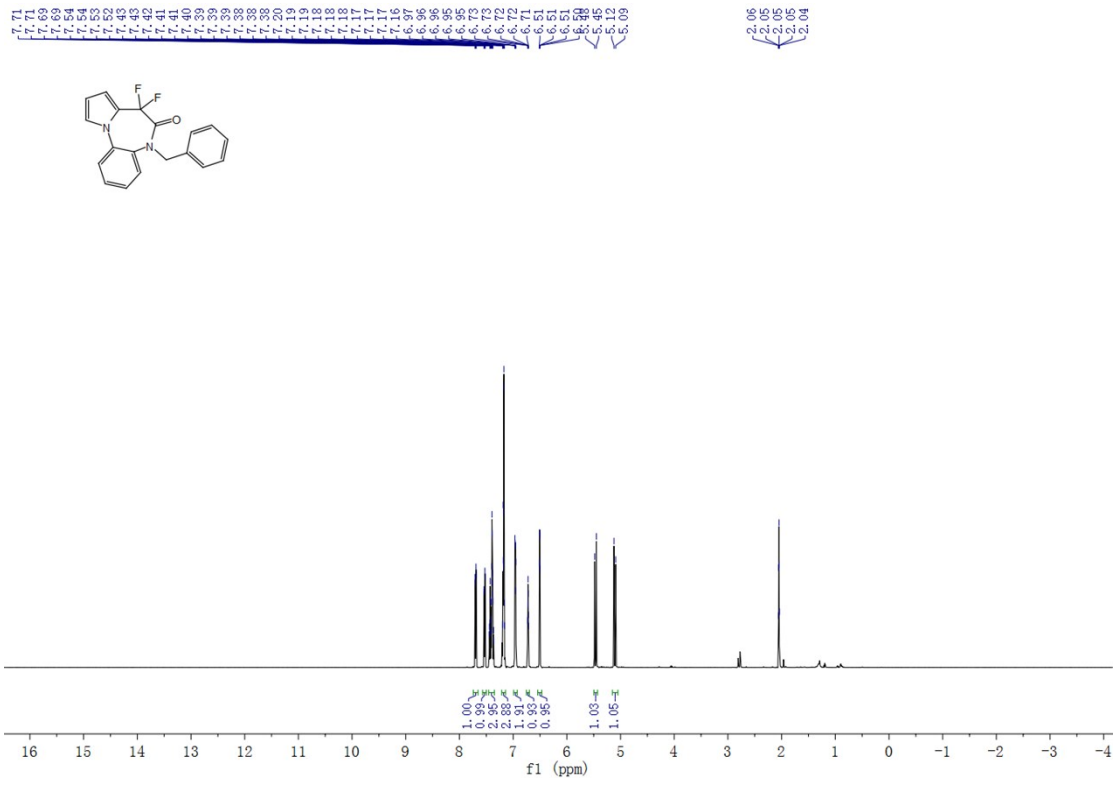
^{1}H NMR spectrum of compound **4**



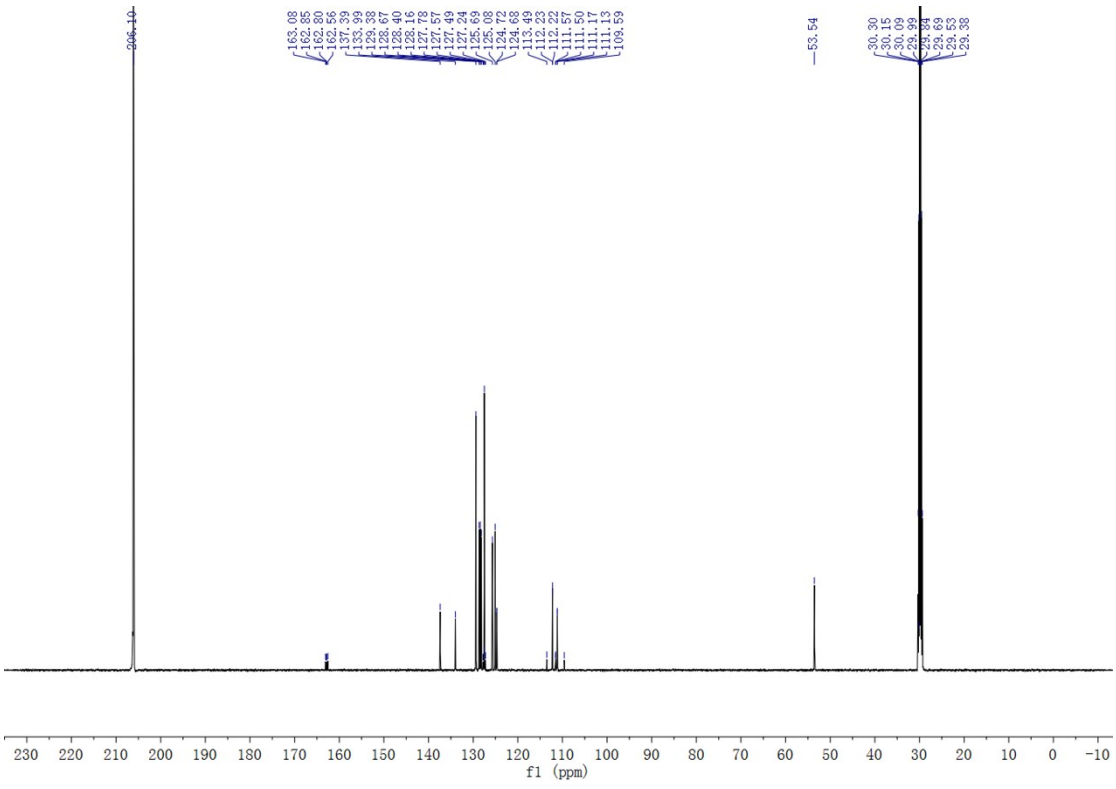
^{13}C NMR spectrum of compound **4**



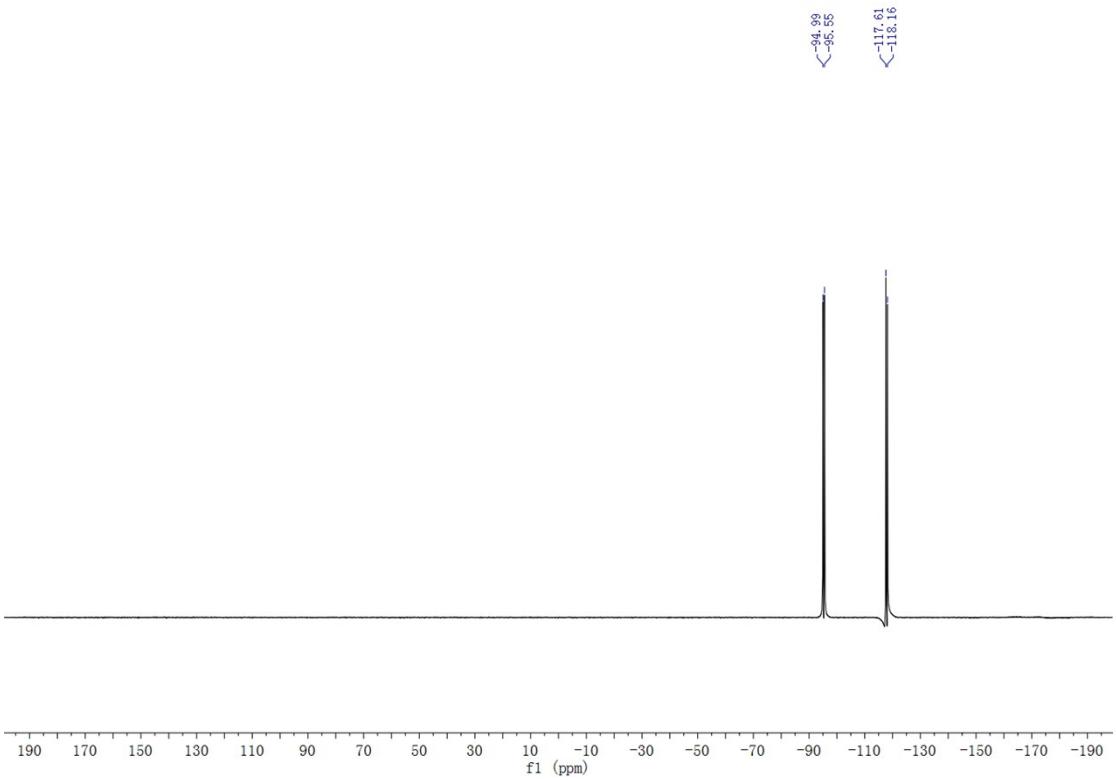
^{19}F NMR spectrum of compound **4**



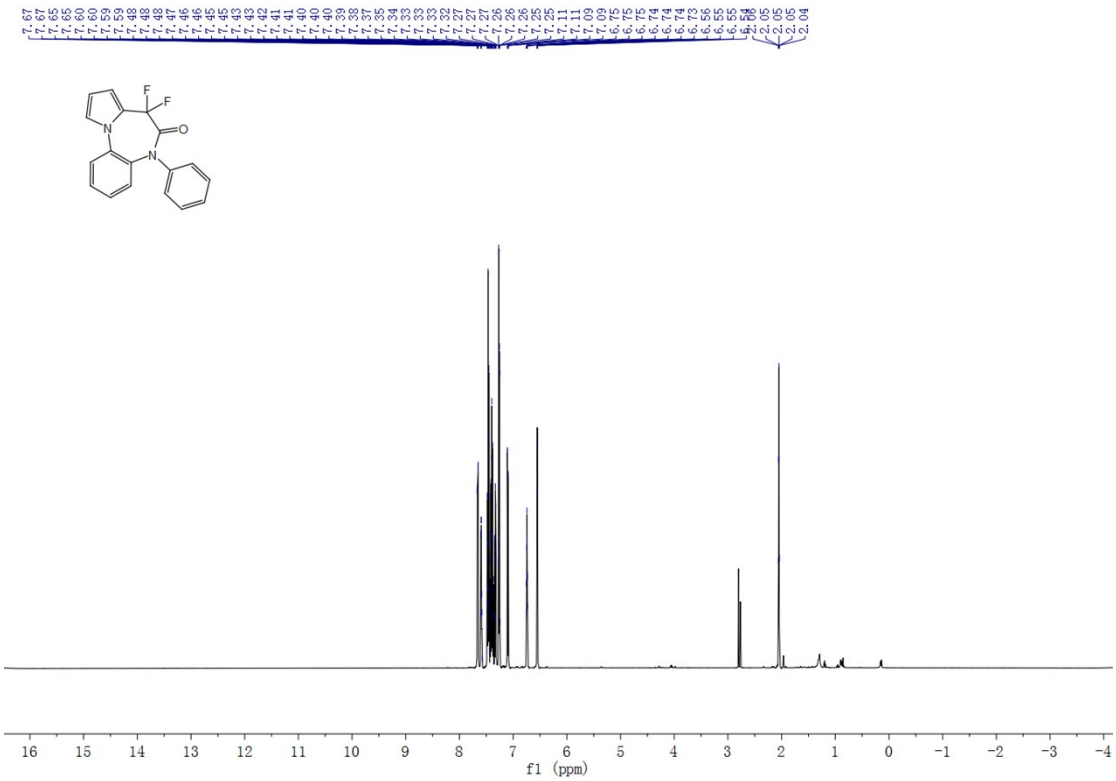
^{1}H NMR spectrum of compound **5**



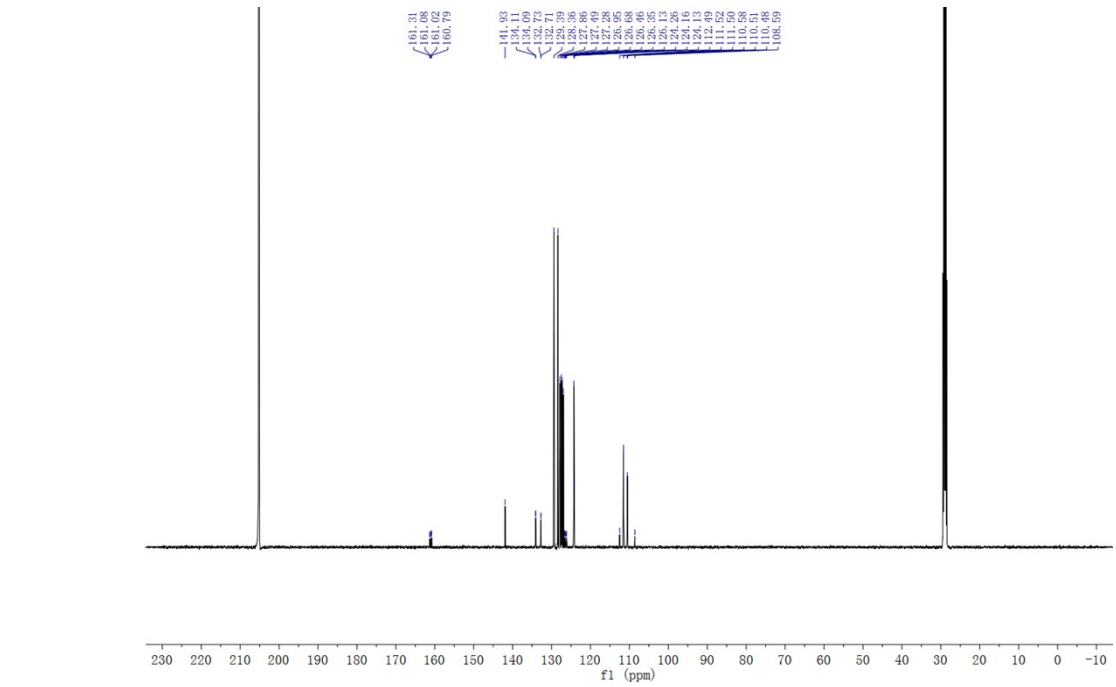
^{13}C NMR spectrum of compound **5**



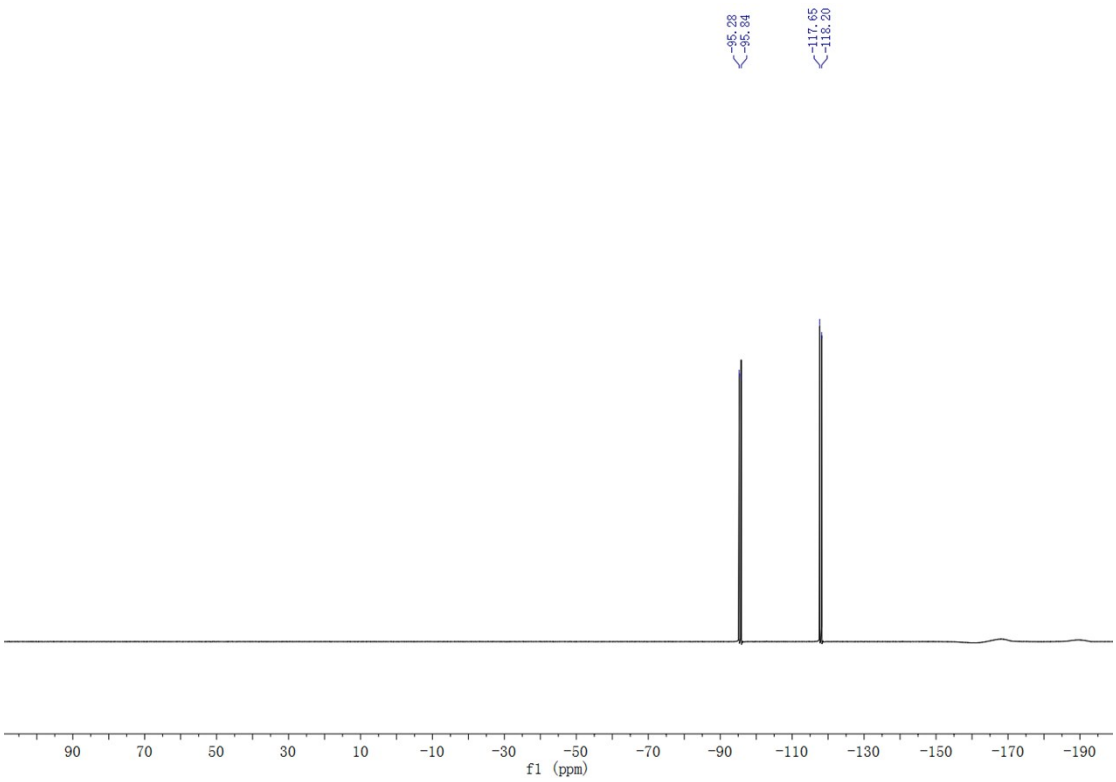
^{19}F NMR spectrum of compound **5**



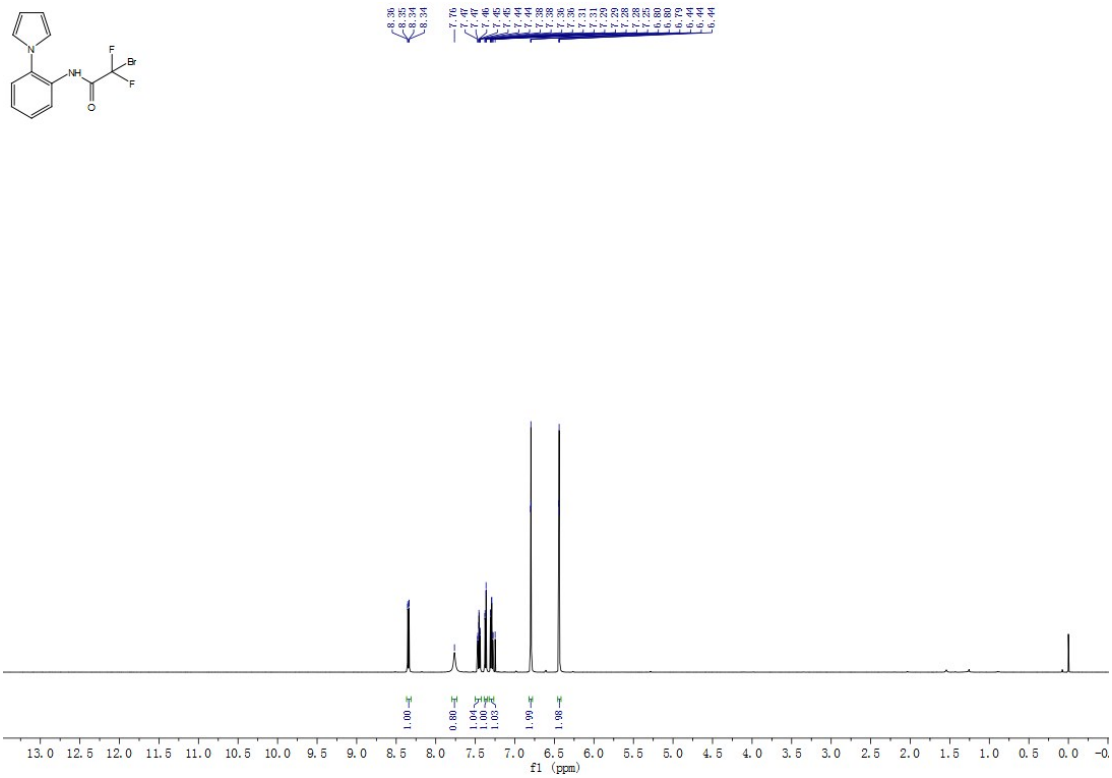
^{1}H NMR spectrum of compound **6**



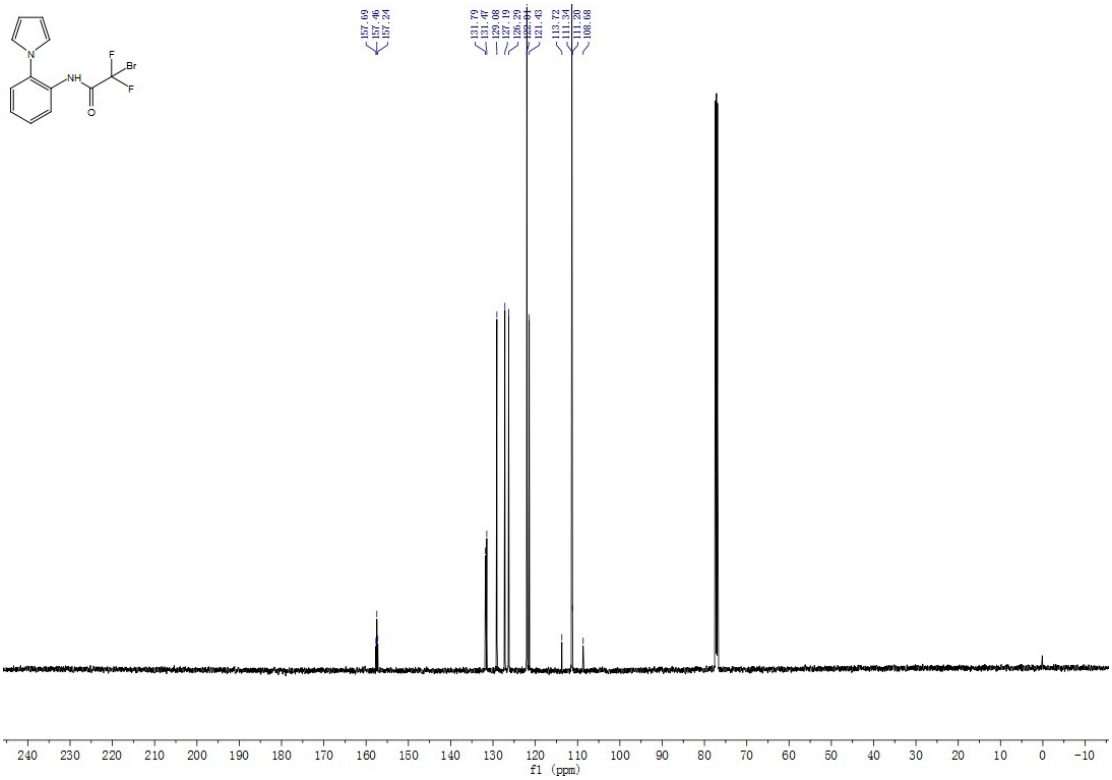
^{13}C NMR spectrum of compound **6**



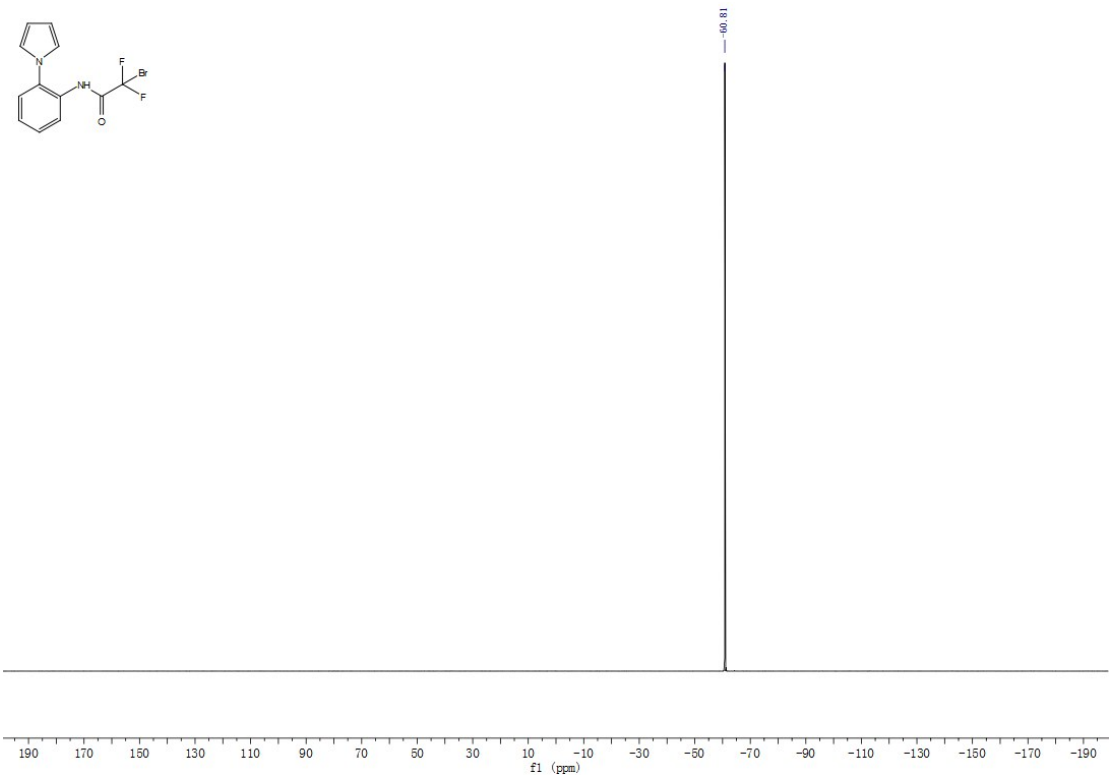
^{19}F NMR spectrum of compound **6**



^{1}H NMR spectrum of compound **7**



^{13}C NMR spectrum of compound **7**



^{19}F NMR spectrum of compound **7**