Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Silver-Catalyzed Decarboxylative Radical Relay Difluoroalkylation-Carbocyclization: Convenient Access to CF_2-Containing Quinolinones

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Supporting Information

I. General Conditions

All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra were recorded on a Bruker Ascend™ 400 or Bruker Ascend™ 500 or a Bruker Ascend™ 600 spectrometer or a Ascend 400 in deuterated solvents containing TMS as an internal reference standard. All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization orthogonal acceleration time-of-flight (ESI-OA-TOF), and the purity of all samples used for HRMS (>95%) was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) using GF254 silica gel-coated TLC plates. Purification by flash column chromatography was performed over SiO_2 (silica gel 200−300 mesh).

II. Typical Experimental Procedures

In the reaction tube, acrylamides **1** (0.2 mmol), *α,α*-difluoroarylacetic acids **2** (3.0 equiv., 0.6 mmol), $AgNO_3$ (20 mol%, 0.04 mmol), $K_2S_2O_8$ (2.0 equiv., 0.4 mmol,) and DBU (2.0 equiv., 0.4 mmol) were mixed in DMSO/H_2O (2:1, 3 mL). The mixture was heated in an oil bath at 60 °C until complete consumption of starting material as monitored by TLC analysis. Upon completion of the reaction, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and filtered. Then the organic solvent was concentrated in vacuo. The residue was purified by flash column chromatography with Ethyl acetate and Petroleum ether as eluent to give **3**.

III. Application Experiments

3.1 Procedure for the Gram-Scale Synthesis of 3a

To a reaction tube, acrylamide **1a** (5 mmol), 2,2-difluoro-2-phenylacetic acid **2a** (3.0 equiv., 15 mmol), $AgNO_3$ (20 mol%, 1 mmol), $K_2S_2O_8$ (2.0 equiv., 10 mmol) and DBU (2.0 equiv., 10 mmol) were mixed in DMSO/H_2O (2:1, 30 mL). The mixture was heated in an oil bath at 60 °C for 6 h. Upon completion of the reaction, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and filtered. Then the organic solvent was concentrated in vacuo. The residue was purified by flash column chromatography with Ethyl acetate and Petroleum ether as eluent to product **3a** in 80% yield (1.317g).

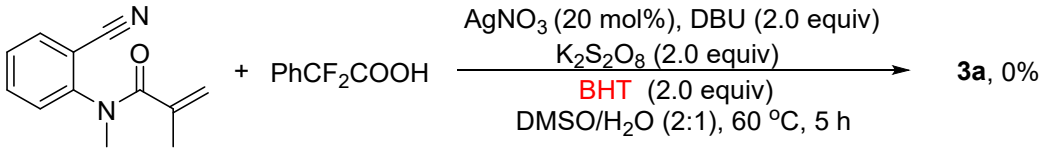
3.2 Procedure for the Gram-Scale Synthesis of 3v

To a reaction tube, acrylamide **1a** (5 mmol), 2,2-difluoropropanoic acid (3.0 equiv., 15 mmol), $AgNO_3$ (20 mol%, 1 mmol), $K_2S_2O_8$ (2.0 equiv., 10 mmol) and DBU (2.0 equiv., 10 mmol) were mixed in DMSO/H_2O (2:1, 30 mL). The mixture was heated in an oil bath at 60 °C for 10 h. Upon completion of the reaction, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and filtered. Then the organic solvent was concentrated in vacuo. The residue was

purified by flash column chromatography with Ethyl acetate and Petroleum ether as eluent to product **3v** in 54 % yield (0.721g).

IV. Control Experiments

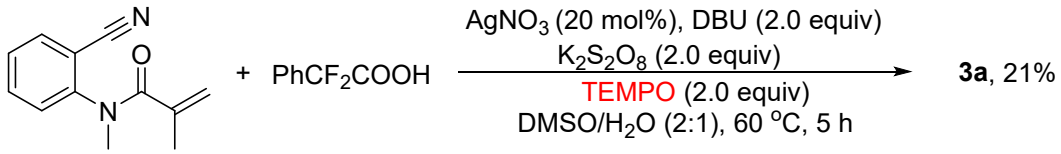
4.1 Control experiment in the presence of BHT



1a, 0.2 mmol **2a**

To a reaction tube, acrylamides **1a** (0.2 mmol), 2,2-difluoro-2-phenylacetic acid **2a** (3.0 equiv., 0.6 mmol, 103 mg), $AgNO_3$ (20 mol%, 0.04 mmol, 7 mg), $K_2S_2O_8$ (2.0 equiv., 0.4 mmol, 108 mg), DBU (2.0 equiv., 0.4 mmol, 60 μL) and the radical scavenger BHT (2.0 equiv., 88 mg) were mixed in DMSO/H_2O (2:1, 3 mL). Then the mixture was stirred at 60 °C for 5 h and monitored by TLC. No desired product **3a** was obtained.

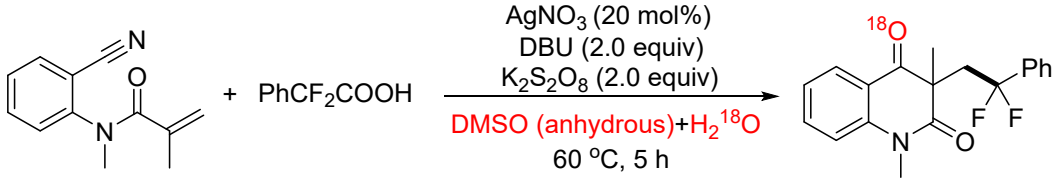
4.2 Control experiment in the presence of TEMPO



1a, 0.2 mmol **2a**

To a reaction tube, acrylamides **1a** (0.2 mmol), 2,2-difluoro-2-phenylacetic acid **2a** (3.0 equiv., 0.6 mmol, 103 mg), $AgNO_3$ (20 mol%, 0.04 mmol, 7 mg), $K_2S_2O_8$ (2.0 equiv., 0.4 mmol, 108 mg), DBU (2.0 equiv., 0.4 mmol, 60 μL) and the radical scavenger TEMPO (2.0 equiv., 62.5 mg) were mixed in DMSO/H_2O (2:1, 3 mL). Then the mixture was stirred at 60 °C for 5 h and monitored by TLC. Upon completion of the reaction, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and filtered. Then the organic solvent was concentrated in vacuo. The residue was purified by flash column chromatography with Ethyl acetate and Petroleum ether as eluent to product **3a** in 21% yield.

4.3 Mechanistic experiments

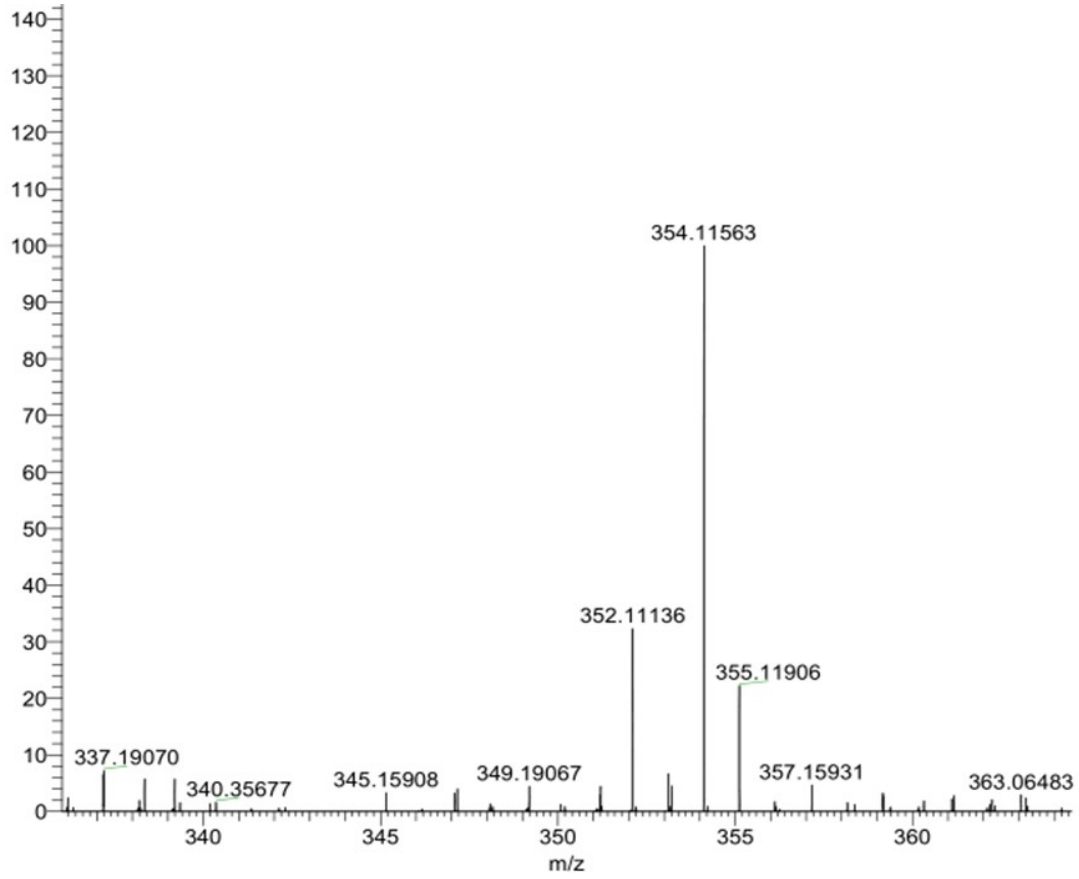


1a, 0.2 mmol **2a** **3a'**
detected by HRMS analysis

To a reaction tube, acrylamides **1a** (0.2 mmol), 2,2-difluoro-2-phenylacetic acid **2a** (3.0 equiv., 0.6 mmol, 103 mg), $AgNO_3$ (20 mol%, 0.04 mmol, 7 mg), $K_2S_2O_8$ (2.0 equiv., 0.4 mmol, 108 mg) and DBU (2.0 equiv., 0.4 mmol, 60 μL) were mixed in DMSO/$H_2{}^{18}O$ (2:1, 1.5 mL). The mixture

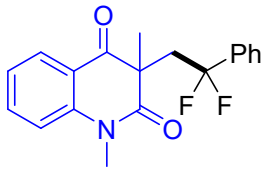
was heated in an oil bath at 60 °C for 5 h, we successfully detected the desired **3a'** by HRMS analysis.

HRMS (ESI) calcd for $C_{19}H_{17}F_2N^{18}OO$ $[M+Na]^+$: 354.1162, found: 354.1156.



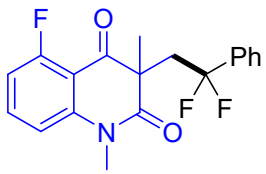
V. Products Characterization

3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3a)



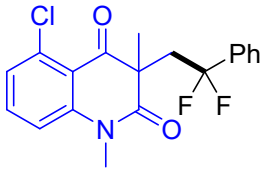
White soild (54 mg, 82% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.15. mp 74-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.09 (m, 1H), 7.68-7.63 (m, 1H), 7.38-7.32 (m, 5H), 7.22-7.16 (m, 2H), 3.45 (s, 3H), 3.12-3.02 (m, 2H), 1.50 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.62, 172.65, 143.35, 136.71 (t, J = 26.3 Hz), 136.34, 129.88, 128.51, 128.28, 128.14, 124.89 (t, J = 6.5 Hz), 123.09, 119.53, 114.88, 52.18, 47.81 (t, J = 26.4 Hz), 29.79, 27.12. ^{19}F NMR (377 MHz, $CDCl_3$) δ -88.89 (d, J = 244.8 Hz), -92.88 (d, J = 244.2 Hz). HRMS (ESI) calcd for $C_{19}H_{17}F_2NO_2$ $[M+Na]^+$: 352.1120, found: 352.1112.

3-(2,2-difluoro-2-phenylethyl)-5-fluoro-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3b)



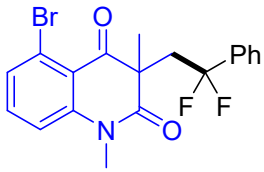
Yellow liquid (35 mg, 50% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.08. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55(m,1H), 7.42-7.31 (m, 5H), 6.98 (d, J = 8.5 Hz, 1H), 6.91-6.87 (m, 1H), 3.46 (s, 3H), 3.07-3.98 (m, 2H), 1.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.08, 172.42, 162.73 (d, J = 267.5 Hz), 144.54, 136.83 (d, J = 26.0 Hz), 136.42 (d, J = 12.0 Hz), 129.93, 128.34, 124.87 (t, J = 6.3 Hz), 121.61 (t, J = 245.0 Hz), 111.35 (d, J = 21.7 Hz), 110.64 (d, J = 3.7 Hz), 53.02, 47.76 (t, J = 26.3 Hz), 30.70, 26.58. ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.23 (d, J = 244.2 Hz), -92.71 (d, J = 244.2 Hz), -109.34. HRMS (ESI) calcd for $C_{19}H_{16}F_3NO_2$ $[M+Na]^+$: 370.1025, found: 370.1029.

5-chloro-3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3c)



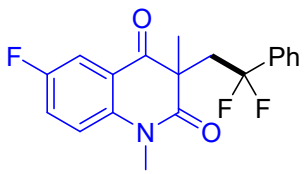
Yellow liquid (38 mg, 52% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.13. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, J = 8.2 Hz, 1H), 7.42-7.33 (m, 5H), 7.25-7.23 (m, 1H), 7.11 (d, J = 8.5 Hz, 1H), 3.44 (s, 3H), 3.04-2.93 (m, 2H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.58, 172.09, 144.99, 136.79 (t, J = 26.1 Hz), 136.21, 134.52, 129.93, 128.36, 126.74, 124.86 (t, J = 6.3 Hz), 121.53 (t, J = 245.1 Hz), 117.76, 113.71, 53.56, 47.46 (t, J = 26.6 Hz), 30.84, 25.29. ^{19}F NMR (376 MHz, $CDCl_3$) δ -87.46 (d, J = 248.2 Hz), -93.53 (d, J = 248.2 Hz). HRMS (ESI) calcd for $C_{19}H_{16}ClF_2NO_2$ $[M+Na]^+$: 386.0730, found: 386.0737.

5-bromo-3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3d)



Yellow liquid (51 mg, 63 % yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.13. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 1H), 7.41-7.35 (m, 6H), 7.16-7.14 (m, 1H), 3.43 (s, 3H), 3.03-2.93 (m, 2H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.71, 171.99, 145.10, 136.79 (t, J = 26.0 Hz), 134.67, 130.42, 129.93, 128.36, 124.86 (t, J = 6.3 Hz), 123.77, 121.51, 118.81, 114.40, 53.34, 47.42 (t, J = 26.7 Hz), 30.77, 25.11. ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.41 (d, J = 244.4 Hz), -92.33 (d, J = 244.4 Hz). HRMS (ESI) calcd for $C_{19}H_{16}BrF_2NO_2$ $[M+Na]^+$: 430.0025, found: 430.0021.

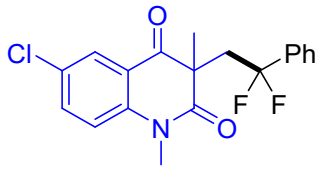
3-(2,2-difluoro-2-phenylethyl)-6-fluoro-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3e)



Colourless liquid (43 mg, 62% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.18. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.74(m, 1H), 7.42-7.29 (m, 6H), 7.17-7.14 (m, 1H), 3.45 (s, 3H), 3.15-2.97 (m, 2H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.07, 172.41, 162.73 (d, J = 267.4 Hz), 144.54, 136.74 (t, J = 20.1 Hz), 136.41 (d, J = 11.9 Hz), 129.93, 128.34, 124.87 (t, J = 6.3

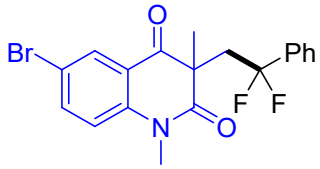
Hz), 121.61, 111.35 (d, J = 21.6 Hz), 110.64 (d, J = 3.6 Hz), 109.49, 53.02, 47.76 (t, J = 26.1 Hz), 30.70, 26.58. ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.95 (d, J = 244.1 Hz), -92.90 (d, J = 244.1 Hz), -119.72. HRMS (ESI) calcd for $C_{19}H_{16}F_3NO_2$ $[M+Na]^+$: 370.1025, found: 370.1031.

6-chloro-3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3f)



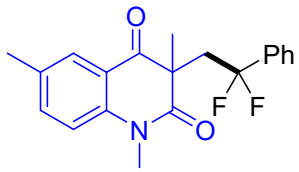
White soild (40 mg, 55% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.23. mp 83-84 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 2.6 Hz, 1H), 7.60-7.58 (m, 1H), 7.42-7.30 (m, 5H), 7.13 (d, J = 8.9 Hz, 1H), 3.44 (s, 3H), 3.15-2.97 (m, 2H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.67, 172.33, 141.86, 136.49 (t, J = 26.0 Hz), 135.92, 129.97, 128.97, 128.33, 127.90, 124.85 (t, J = 6.3 Hz), 121.57, 120.54, 116.53, 52.19, 48.04 (t, J = 26.4 Hz), 29.97, 26.97. ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.98 (d, J = 244.2 Hz), -92.73 (d, J = 244.2 Hz). HRMS (ESI) calcd for $C_{19}H_{16}ClF_2NO_2$ $[M+Na]^+$: 386.0730, found: 386.0736.

6-bromo-3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3g)



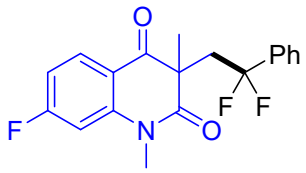
White soild (50 mg, 61% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.23. mp 98-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 2.5 Hz, 1H), 7.74-7.72 (m, 1H), 7.38-7.34 (m, 5H), 7.07 (d, J = 8.9 Hz, 1H), 3.43 (s, 3H), 3.15-2.98 (m, 2H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.57, 172.33, 142.31, 138.80, 136.47 (t, J = 25.8 Hz), 130.93, 129.98, 128.34, 124.85 (t, J = 6.4 Hz), 121.57, 120.81, 116.83, 116.21, 52.21, 48.03 (t, J = 26.4 Hz), 29.95, 26.98. ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.99 (d, J = 244.3 Hz), -92.67 (d, J = 244.5 Hz). HRMS (ESI) calcd for $C_{19}H_{16}BrF_2NO_2$ $[M+Na]^+$: 430.0025, found: 430.0028.

3-(2,2-difluoro-2-phenylethyl)-1,3,6-trimethylquinoline-2,4(1*H*,3*H*)-dione (3h)



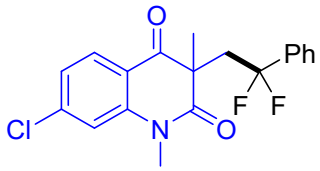
White soild (51 mg, 74 % yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.23. mp 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 1.9 Hz, 1H), 7.47-7.45 (m, 1H), 7.38-7.32 (m, 5H), 7.07 (d, J = 8.5 Hz, 2H), 3.42 (s, 3H), 3.11-3.00 (m, 2H), 2.38 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.85, 172.50, 141.22, 137.16, 136.78 (t, J = 26.1 Hz), 132.82, 129.82, 128.39, 128.26, 128.07, 124.89 (t, J = 6.4 Hz), 121.37 (t, J = 205.0 Hz), 114.87, 52.09, (t, J = 26.3 Hz), 29.75, 27.13, 20.34. ^{19}F NMR (377 MHz, $CDCl_3$) δ -88.98 (d, J = 244.1 Hz), -93.15 (d, J = 244.0 Hz). HRMS (ESI) calcd for $C_{20}H_{19}F_2NO_2$ $[M+Na]^+$: 366.1276, found: 366.1282.

3-(2,2-difluoro-2-phenylethyl)-7-fluoro-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3i)



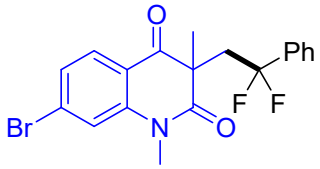
Colourless liquid (32 mg, 46 % yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.10 (m, 1H), 7.39-7.32 (m, 5H), 6.91-6.85 (m, 2H), 3.42 (s, 3H), 3.11-3.00 (m, 2H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.12, 172.80, 167.77 (d, J = 256.1 Hz), 145.62 (d, J = 11.7 Hz), 1136.56 (t, J = 26.0 Hz), 131.50 (d, J = 11.1 Hz), 129.96, 128.31, 124.85 (t, J = 6.3 Hz), 121.59 (t, J = 244.7 Hz), 116.20, 110.53 (d, J = 22.3 Hz), 102.49 (d, J = 27.6 Hz), 52.06, 47.91 (t, J = 26.3 Hz), 29.96, 27.09. ^{19}F NMR (377 MHz, $CDCl_3$) δ -89.18 (d, J = 244.0 Hz), -92.92 (d, J = 243.9 Hz), -98.87. HRMS (ESI) calcd for $C_{19}H_{16}F_3NO_2$ $[M+Na]^+$: 370.1025, found: 370.1020.

7-chloro-3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3j)



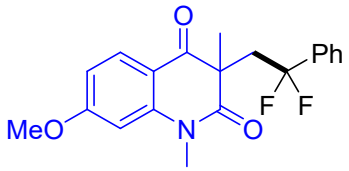
White soild (48 mg, 66% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.33. mp 79-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.37-7.34 (m, 5H), 7.21-7.16 (m, 2H), 3.42 (s, 3H), 3.11-2.98 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.55, 172.66, 144.26, 142.68, 136.53 (t, J = 24.0 Hz), 133.52, 129.89, 128.33, 124.84 (t, J = 6.3 Hz), 123.86, 123.38, 117.87 (t, J = 131.7 Hz), 115.24, 52.19, 47.96 (t, J = 26.3 Hz), 29.91, 27.03. ^{19}F NMR (377 MHz, $CDCl_3$) δ -88.98 (d, J = 244.1 Hz), -92.87 (d, J = 244.1 Hz). HRMS (ESI) calcd for $C_{19}H_{16}ClF_2NO_2$ $[M+Na]^+$: 386.0730, found: 386.0738.

7-bromo-3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3k)



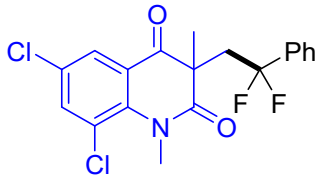
White soild (51 mg, 63% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.33. mp 92-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.3 Hz, 1H), 7.36-7.33 (m, 6H), 7.23-7.17 (m, 1H), 3.42 (s, 3H), 3.11-2.98 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.77, 172.62, 144.14, 1136.52 (t, J = 26.0 Hz), 133.43, 131.48, 129.81, 128.34, 126.98, 126.35, 124.84 (t, J = 6.3 Hz), 121.58 (t, J = 244.9 Hz), 118.17, 52.23, 47.97 (t, J = 26.3 Hz), 29.93, 27.02. ^{19}F NMR (377 MHz, $CDCl_3$) δ -88.98 (d, J = 244.0 Hz), -92.89 (d, J = 244.0 Hz). HRMS (ESI) calcd for $C_{19}H_{16}BrF_2NO_2$ $[M+Na]^+$: 430.0025, found: 430.0019.

3-(2,2-difluoro-2-phenylethyl)-7-methoxy-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3l)



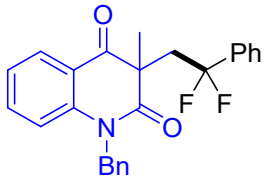
White soild (39.5 mg, 55% yield). R_f(Petroleum ether: Ethyl acetate=10:1): 0.11. mp 101-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 6.7 Hz, 5H), 6.74-6.71 (m, 2.2 Hz, 1H), 6.61 (d, J = 2.2 Hz, 1H), 3.93 (s, 3H), 3.41 (s, 3H), 3.12-2.98 (m, 2H), 1.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.98, 173.15, 166.16, 145.26, 136.79 (t, J = 26.0 Hz), 131.02, 129.83, 128.24, 124.89 (t, J = 6.3 Hz), 121.65 (t, J = 244.9 Hz), 113.53, 108.34, 100.86, 55.78, 51.71, 47.70 (t, J = 26.3 Hz), 29.74, 27.28. ^{19}F NMR (376 MHz, $CDCl_3$) δ -89.58 (d, J = 244.0 Hz), -93.23 (d, J = 244.1 Hz). HRMS (ESI) calcd for $C_{20}H_{19}F_2NO_3$ $[M+Na]^+$: 382.1225, found: 382.1230.

6,8-dichloro-3-(2,2-difluoro-2-phenylethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (2m)



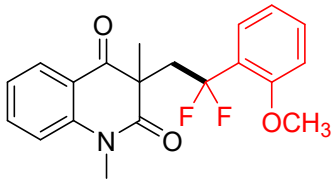
Colourless liquid (22 mg, 28% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 2.6 Hz, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.40-7.36 (m, 5H), 3.60 (s, 3H), 3.08-2.91 (m, 2H), 1.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.41, 173.35, 140.49, 137.79, 136.69 (t, J = 26.2 Hz), 130.04, 129.80, 128.44, 126.69, 124.83 (t, J = 6.4 Hz), 123.04 (t, J = 163.3 Hz), 118.96, 53.26, 47.26 (t, J = 26.9 Hz), 37.89, 24.85. ^{19}F NMR (377 MHz, $CDCl_3$) δ -88.67 (d, J = 246.6 Hz), -90.98 (d, J = 246.4 Hz). HRMS (ESI) calcd for $C_{19}H_{15}Cl_2F_2NO_2$ $[M+Na]^+$: 420.0340, found: 420.0344.

1-benzyl-3-(2,2-difluoro-2-phenylethyl)-3-methylquinoline-2,4(1*H*,3*H*)-dione (3n)



Colourless liquid (38 mg, 47% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.51-7.44 (m, 3H), 7.39-7.26 (m, 8H), 7.15 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 5.32 (q, J = 16.0 Hz, 2H), 3.26-3.10 (m, 2H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.39, 173.14, 142.61, 137.06 (t, J = 26.0 Hz), 136.25, 136.00, 129.91, 128.95, 128.64, 128.38, 127.38, 126.32, 124.86 (t, J = 6.3 Hz), 121.77 (t, J = 245.1 Hz), 123.20, 119.63, 116.01, 52.56, 47.28 (t, J = 26.1 Hz), 46.31, 27.64. ^{19}F NMR (377 MHz, $CDCl_3$) δ -89.48 (d, J = 243.4 Hz), -91.49 (d, J = 243.3 Hz). HRMS (ESI) calcd for $C_{25}H_{21}F_2NO_2$ $[M+Na]^+$: 428.1433, found: 428.1439.

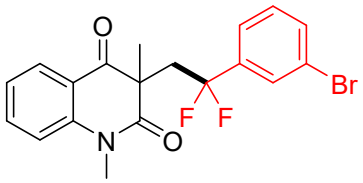
3-(2,2-difluoro-2-(2-methoxyphenyl)ethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3o)



White soild (33.7 mg, 47% yield). R_f(Petroleum ether: Ethyl acetate=10:1): 0.11. mp 107-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 1H), 7.64-7.59 (m, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.17-7.08 (m, 3H), 6.89 (d, J = 8.3 Hz, 1H), 6.73 (t, J = 7.6 Hz, 1H), 3.89 (s, 3H), 3.32 (s, 3H),

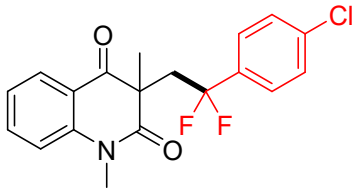
3.30-3.12 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.73, 172.60, 157.04, 143.28, 136.06, 131.55, 128.37, 126.07 (t, J = 18.1 Hz), 124.08 (t, J = 25.2 Hz), 123.34, 122.88, 120.91, 119.79, 114.71, 111.62, 55.78, 46.23 (t, J = 26.0 Hz), 29.71, 29.64, 26.77. ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.00 (d, J = 249.8 Hz), -91.23 (d, J = 249.7 Hz). HRMS (ESI) calcd for $C_{20}H_{19}F_2NO_3$ $[M+Na]^+$: 382.1225, found: 382.1229.

3-(2-(3-bromophenyl)-2,2-difluoroethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3p)



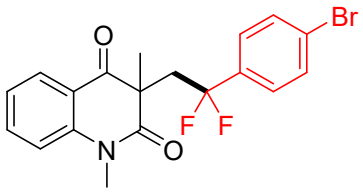
Colourless liquid (58.6 mg, 72 % yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 1H), 7.70-7.64 (m, 1H), 7.49 (d, J = 1.8 Hz, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.25-7.17 (m, 3H), 3.45 (s, 3H), 3.10-3.00 (m, 2H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.45, 172.50, 143.30, 138.80 (t, J = 26.5 Hz), 136.55, 133.12 (t, J = 1.6 Hz), 130.05, 128.58, 128.34, 128.18 (t, J = 6.7 Hz), 123.91 (t, J = 6.2 Hz), 123.28, 122.43, 119.55 (t, J = 123.0 Hz), 115.05, 52.27, 47.39 (t, J = 26.2 Hz), 29.87, 27.32. ^{19}F NMR (377 MHz, $CDCl_3$) δ -89.24 (d, J = 245.7 Hz), -92.82 (d, J = 245.7 Hz). HRMS (ESI) calcd for $C_{19}H_{16}BrF_2NO_2$ $[M+Na]^+$: 430.0025, found: 430.0031.

3-(2-(4-chlorophenyl)-2,2-difluoroethyl)-1,3-dimethylquinoline-2,4(1H,3H)-dione (3q)



White soild (54.4 mg, 75% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.23. mp 89-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 1H), 7.70-7.63 (m, 1H), 7.30 (s, 4H), 7.22-7.17 (m, 2H), 3.44 (s, 3H), 3.10-3.01 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.52, 172.57, 143.34, 136.51, 136.14 (t, J = 2.2 Hz), 135.28 (t, J = 26.7 Hz), 128.60, 126.58 (t, J = 6.3 Hz), 123.73, 123.24, 121.29 (t, J = 245.3 Hz), 119.51, 114.96, 52.31, 47.49 (t, J = 26.4 Hz), 29.86, 27.26. ^{19}F NMR (377 MHz, $CDCl_3$) δ -88.91 (d, J = 245.8 Hz), -92.31 (d, J = 245.9 Hz). HRMS (ESI) calcd for $C_{19}H_{16}ClF_2NO_2$ $[M+Na]^+$: 386.0730, found:386.0723.

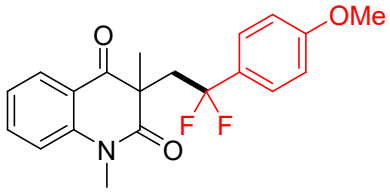
3-(2-(4-bromophenyl)-2,2-difluoroethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3r)



White soild (57 mg, 70% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.22. mp 94-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.05 (m, 1H), 7.67-7.63 (m, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.25-7.15 (m, 4H), 3.43 (s, 3H), 3.09-3.00 (m, 2H), 1.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.51, 172.56, 143.33, 136.53, 135.76 (t, J = 26.7 Hz), 131.56, 128.57, 126.83 (t, J = 6.3 Hz), 124.43 (t, J = 2.3 Hz), 123.76, 123.25, 119.90 (t, J = 122.6 Hz), 114.96, 52.30, 47.44 (t, J = 26.4 Hz), 29.86, 27.27. ^{19}F NMR (471 MHz, $CDCl_3$) δ -89.08 (d, J = 245.9 Hz), -92.43 (d, J = 246.2 Hz). HRMS

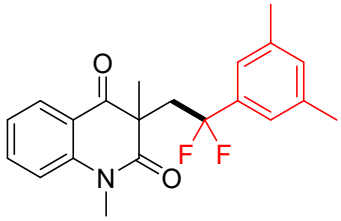
(ESI) calcd for $C_{19}H_{16}BrF_2NO_2$ $[M+Na]^+$: 430.0025, found: 430.0017.

3-(2,2-difluoro-2-(4-methoxyphenyl)ethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3s)



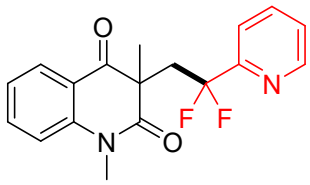
Yellow liquid (51 mg, 71% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.06 (m, 1H), 7.67-7.62 (m, 1H), 7.30-7.26 (m, 2H), 7.21-7.15 (m, 2H), 6.81 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 3.44 (s, 3H), 3.11-3.02 (m, 2H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.69, 172.70, 160.65, 143.34, 136.29, 129.11, 128.85 (t, J = 26.6 Hz), 126.50 (t, J = 6.3 Hz), 123.03, 121.74 (t, J = 244.4 Hz), 114.84, 113.99, 113.52, 55.31, 52.17, 48.05 (t, J = 27.1 Hz), 29.77, 27.06.^{19}F NMR (377 MHz, $CDCl_3$) δ -87.33 (d, J = 243.9 Hz), -90.92 (d, J = 243.9 Hz). HRMS (ESI) calcd for $C_{20}H_{19}F_2NO_3$ $[M+Na]^+$: 382.1225, found: 382.1219.

3-(2-(3,5-dimethylphenyl)-2,2-difluoroethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3t)



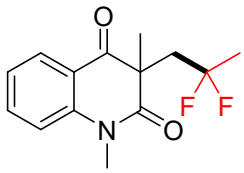
Colourless liquid (45.7 mg, 64 % yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.15. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 1H), 7.66-7.61 (m, 1H), 7.20-7.14 (m, 2H), 6.95 (s, 3H), 3.43 (s, 3H), 3.08-2.96 (m, 2H), 2.24 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.72, 172.79, 143.42, 138.08, 136.49 (t, J = 25.5 Hz), 136.33, 131.46 (t, J = 1.6 Hz), 128.52, 124.26, 123.10, 122.71 (t, J = 6.3 Hz), 121.82, 119.66, 114.91, 52.15, 48.21 (t, J = 26.6 Hz), 29.82, 27.22, 21.29. ^{19}F NMR (471 MHz, $CDCl_3$) δ -89.27 (d, J = 241.8 Hz), -92.83 (d, J = 242.5 Hz). HRMS (ESI) calcd for $C_{21}H_{21}F_2NO_2$ $[M+Na]^+$: 380.1433, found: 380.1437.

3-(2,2-difluoro-2-(pyridin-2-yl)ethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3u)



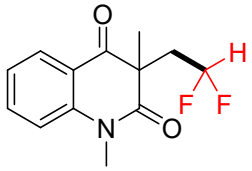
Colourless liquid (23 mg, 35% yield). R_f (Petroleum ether: Ethyl acetate=5:1): 0.09. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.7 Hz, 1H), 8.07-8.05 (m, 1H), 7.73-7.63 (m, 2H), 7.44 (d, J = 7.9 Hz, 1H), 7.32-7.27 (m, 1H), 7.19 (t, J = 7.4 Hz, 2H), 3.46 (s, 3H), 3.35-3.25 (m, 2H), 1.53 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.54, 172.80, 149.17, 143.36, 136.98, 136.24, 128.58, 124.77, 123.09, 120.08, 119.64 (t, J = 4.8 Hz), 114.87, 77.41, 77.09, 76.78, 52.40, 44.45 (t, J = 24.4 Hz), 29.88, 27.08. ^{19}F NMR (471 MHz, $CDCl_3$) δ -92.22 (d, J = 254.8 Hz), -93.91 (d, J = 254.9 Hz). HRMS (ESI) calcd for $C_{18}H_{16}F_2N_2O_2$ $[M+Na]^+$: 353.1072, found: 353.1077.

3-(2,2-difluoropropyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3v)



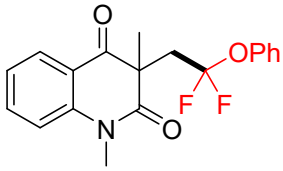
White soild (31 mg, 56% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.13. mp 118-119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09-8.07 (m, 1H), 7.66-7.61 (m, 1H), 7.21-7.17 (m, 2H), 3.49 (s, 3H), 2.88-2.81 (m, 2H), 1.55 (t, J = 18.7 Hz, 3H), 1.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.78, 172.91, 143.28, 136.31, 128.48, 123.11, 122.91, 119.41, 114.91, 52.30, 45.85 (t, J = 24.0 Hz), 29.81, 26.88, 25.07 (t, J = 27.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -84.09 (d, J = 241.3 Hz), -86.61 (d, J = 241.1 Hz). HRMS (ESI) calcd for $C_{14}H_{15}F_2NO_2$ $[M+Na]^+$: 290.0963, found: 290.0957.

3-(2,2-difluoroethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3w)



Yellow liquid (14.6 mg, 29% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.18. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07-8.05 (m, 1H), 7.69 -7.64 (m, 1H), 7.23-7.18 (m, 2H), 5.91 (tt, J = 56.9, 5.1 Hz, 1H), 3.49 (s, 3H), 2.78-2.68 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.54, 172.49, 143.06, 136.47, 128.56, 123.38, 119.35, 115.33 (t, J = 239.9 Hz), 114.96, 53.15, 39.54 (t, J = 22.4 Hz), 26.85, 19.19. ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.17 (d, J = 18.8 Hz). HRMS (ESI) calcd for $C_{13}H_{13}F_2NO_2$ $[M+Na]^+$: 276.0807, found: 276.0812.

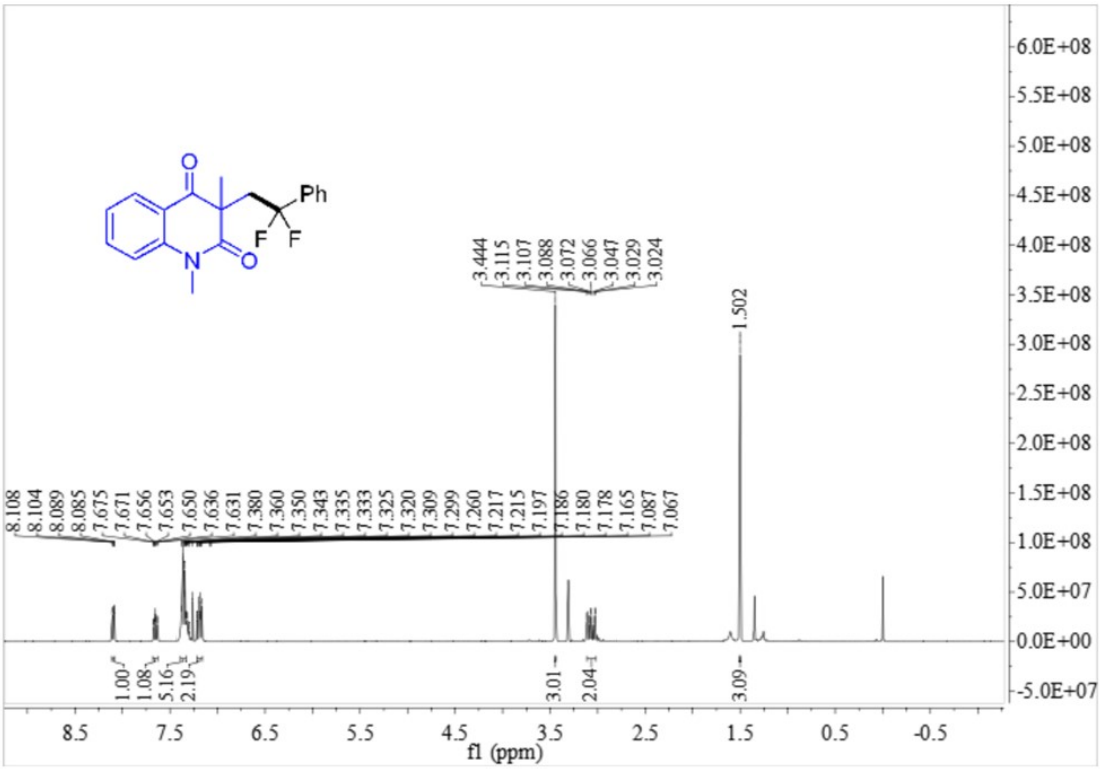
3-(2,2-difluoro-2-phenoxyethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (3x)



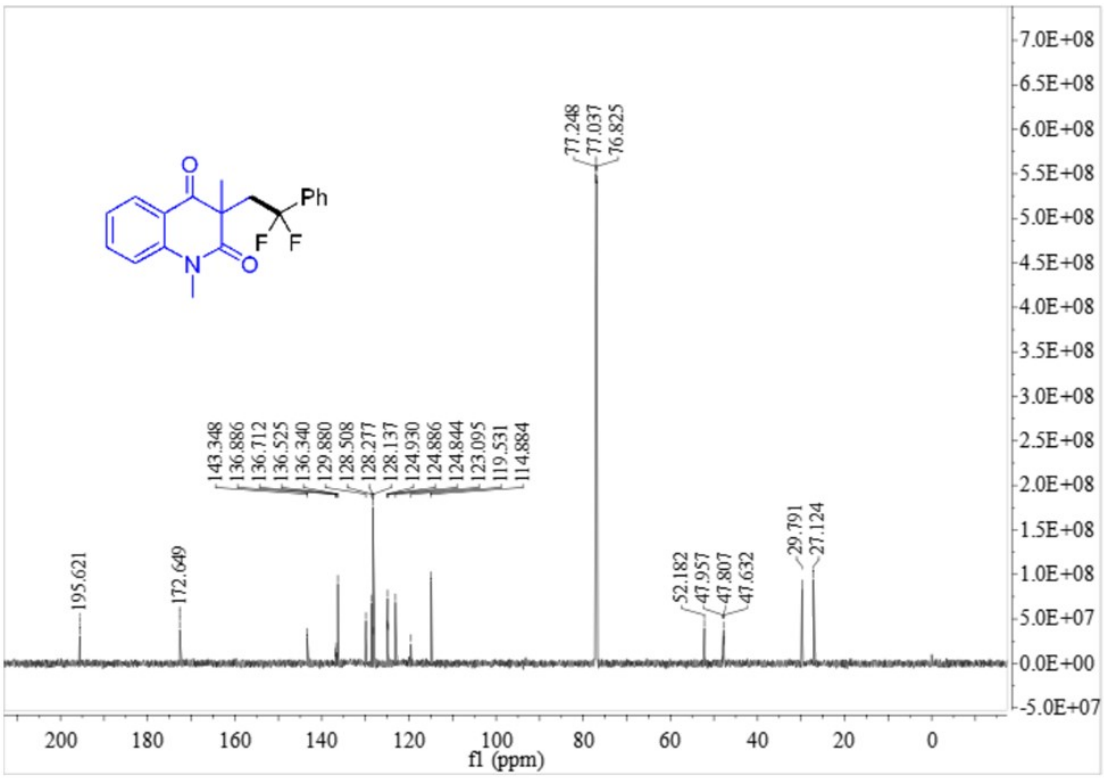
Colourless liquid (31 mg, 45% yield). R_f (Petroleum ether: Ethyl acetate=10:1): 0.15. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.68-7.60 (m, 1H), 7.22-7.15 (m, 4H), 7.12-7.07 (m, 1H), 6.77 (d, J = 7.7 Hz, 2H), 3.49 (s, 3H), 3.17-3.11 (m, 2H), 1.54 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.22, 172.52, 149.71, 143.30, 136.38, 129.15, 128.53, 125.53, 123.22, 121.58, 119.71, 114.90, 52.26, 44.22 (t, J = 29.7 Hz)., 29.84, 26.42. ^{19}F NMR (565 MHz, $CDCl_3$) δ -64.08 (d, J = 108.1 Hz). HRMS (ESI) calcd for $C_{19}H_{17}F_2NO_3$ $[M+Na]^+$: 368.1069, found: 368.1075.

VI. NMR Spectra of Products

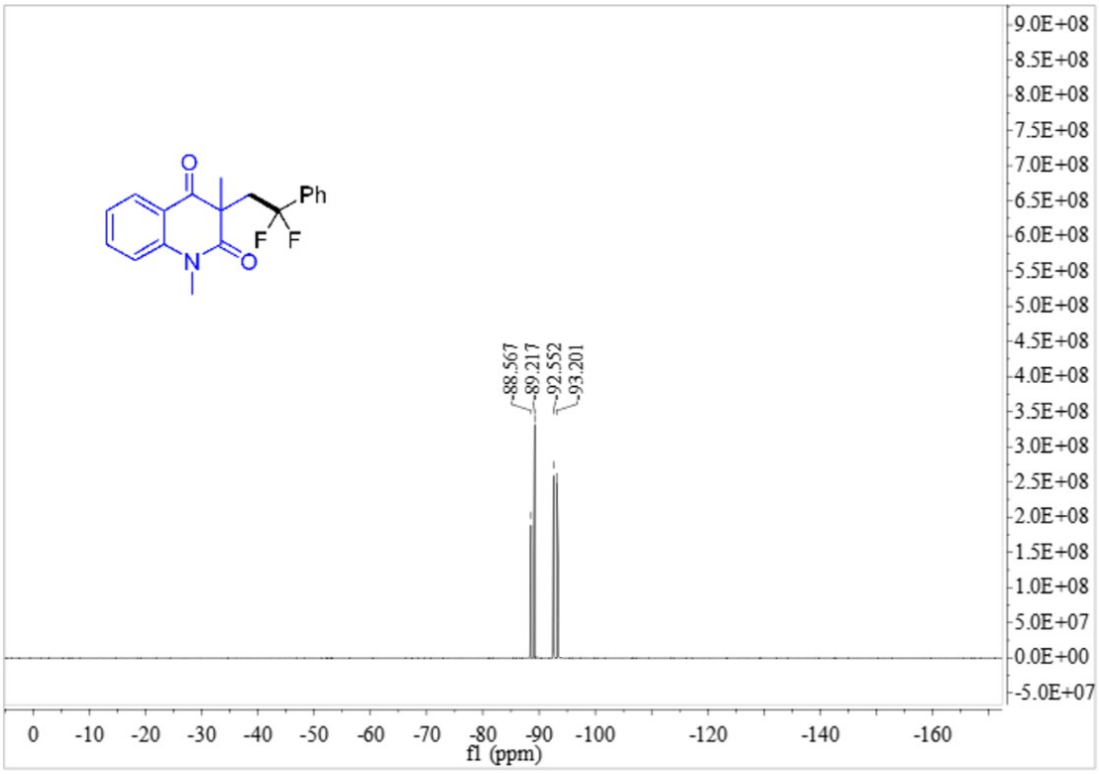
^{1}H NMR spectrum of **3a** (400 MHz, $CDCl_3$)



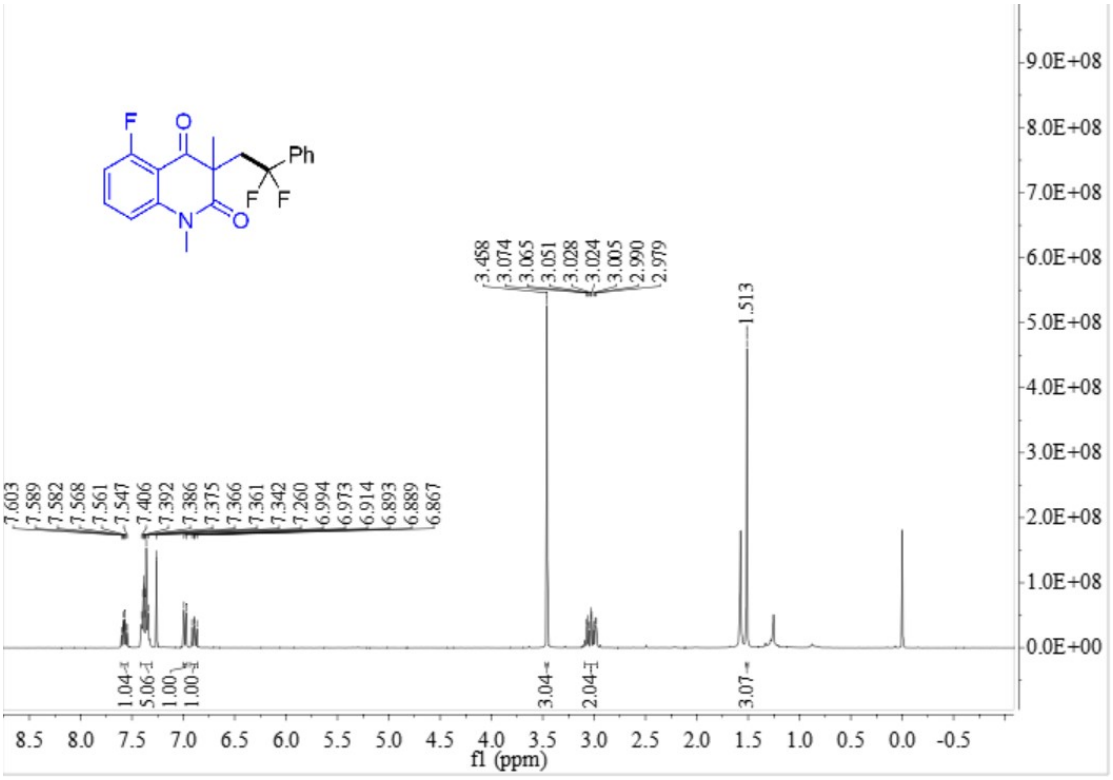
^{13}C NMR spectrum of **3a** (150 MHz, $CDCl_3$)



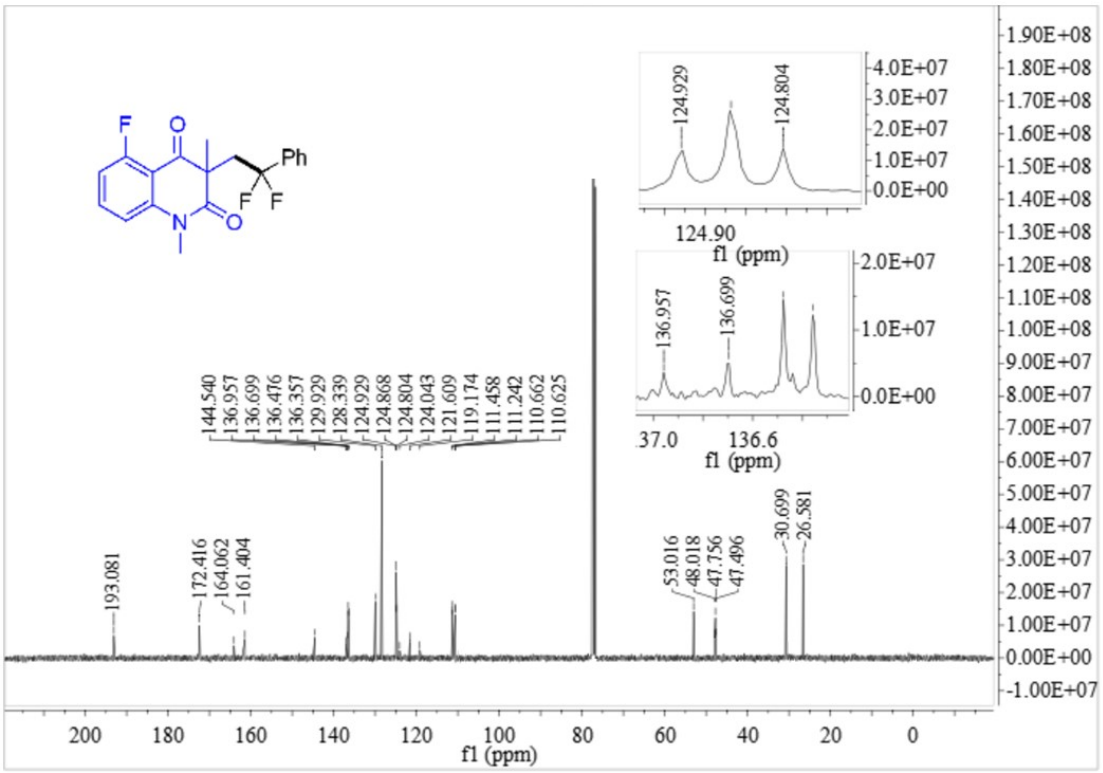
^{19}F NMR spectrum of **3a** (377 MHz, $CDCl_3$)



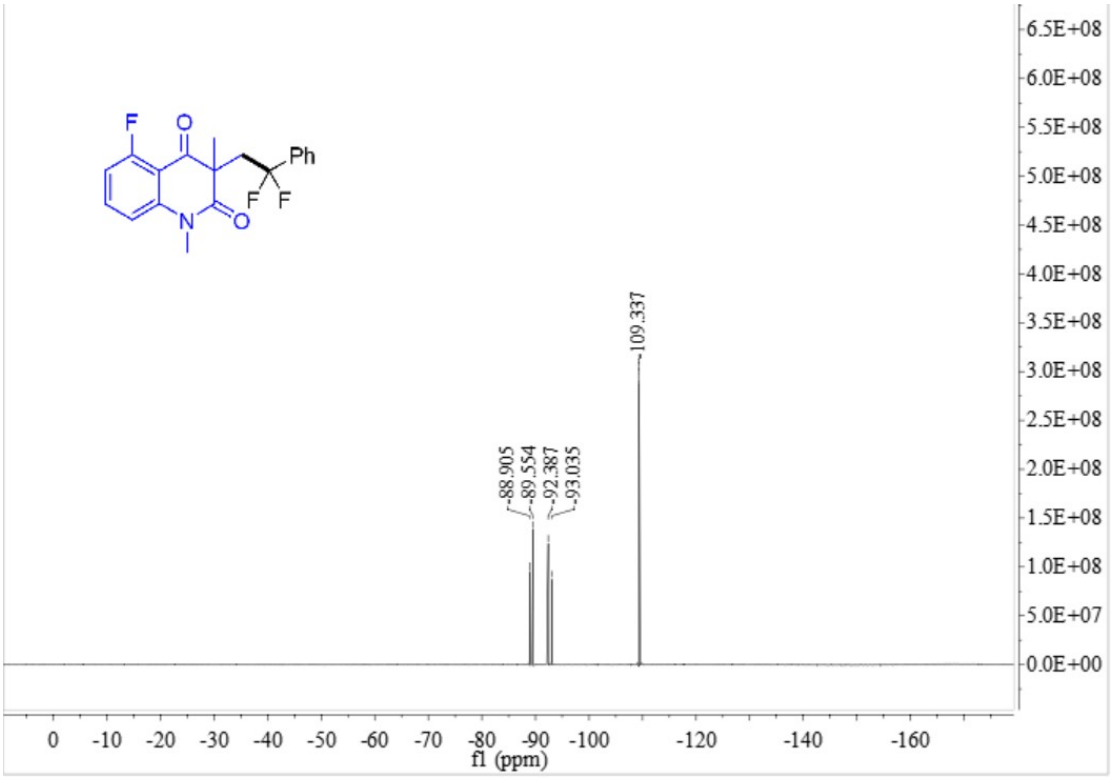
^{1}H NMR spectrum of **3b** (400 MHz, $CDCl_3$)



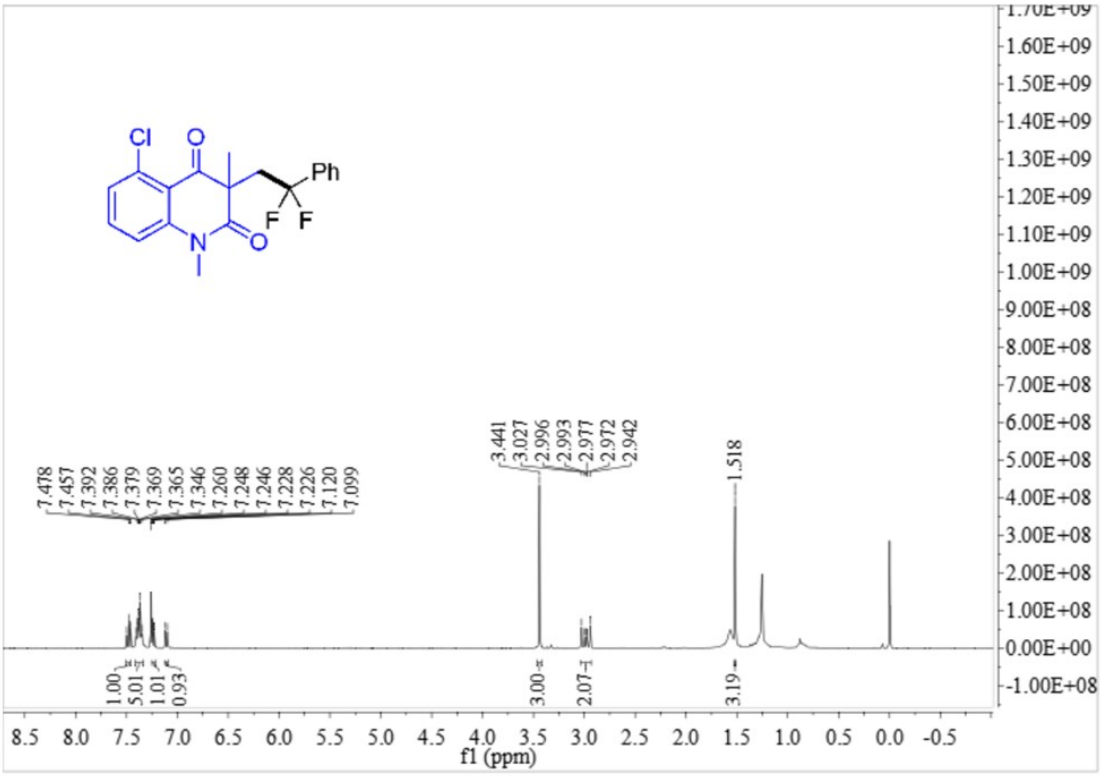
^{13}C NMR spectrum of **3b** (100 MHz, $CDCl_3$)



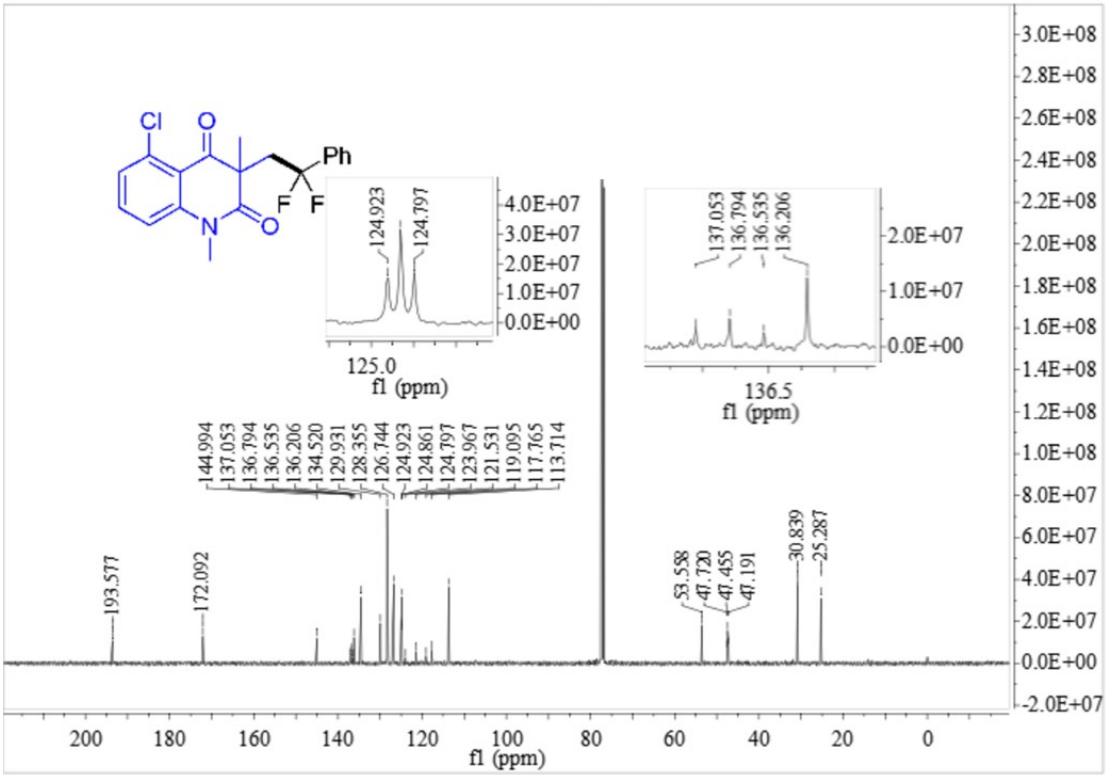
^{19}F NMR spectrum of **3b** (376 MHz, $CDCl_3$)



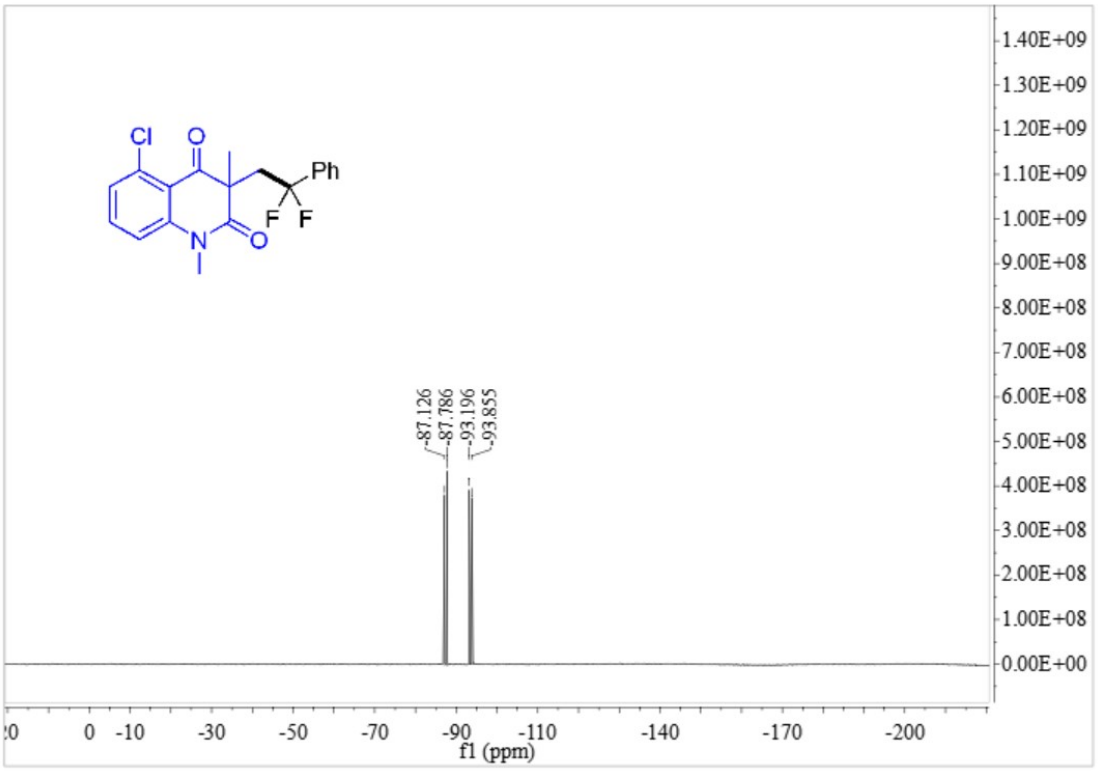
^{1}H NMR spectrum of **3c** (400 MHz, $CDCl_3$)



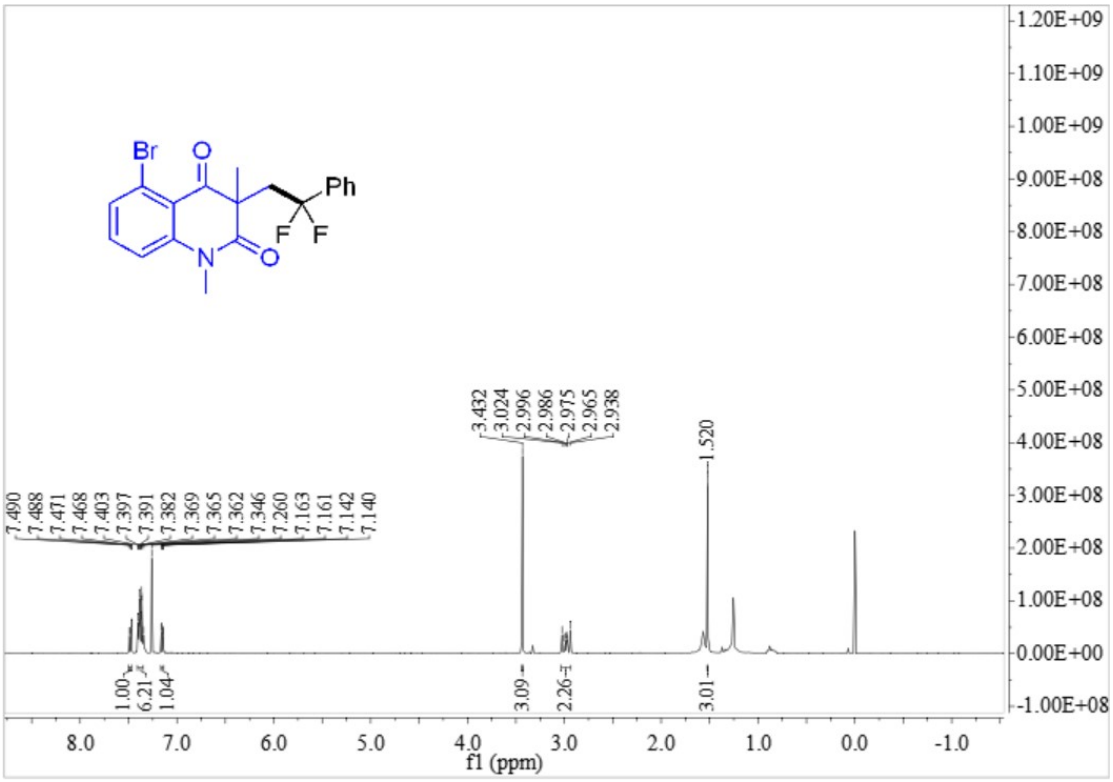
^{13}C NMRpectrum of **3c** (100 MHz, $CDCl_3$)



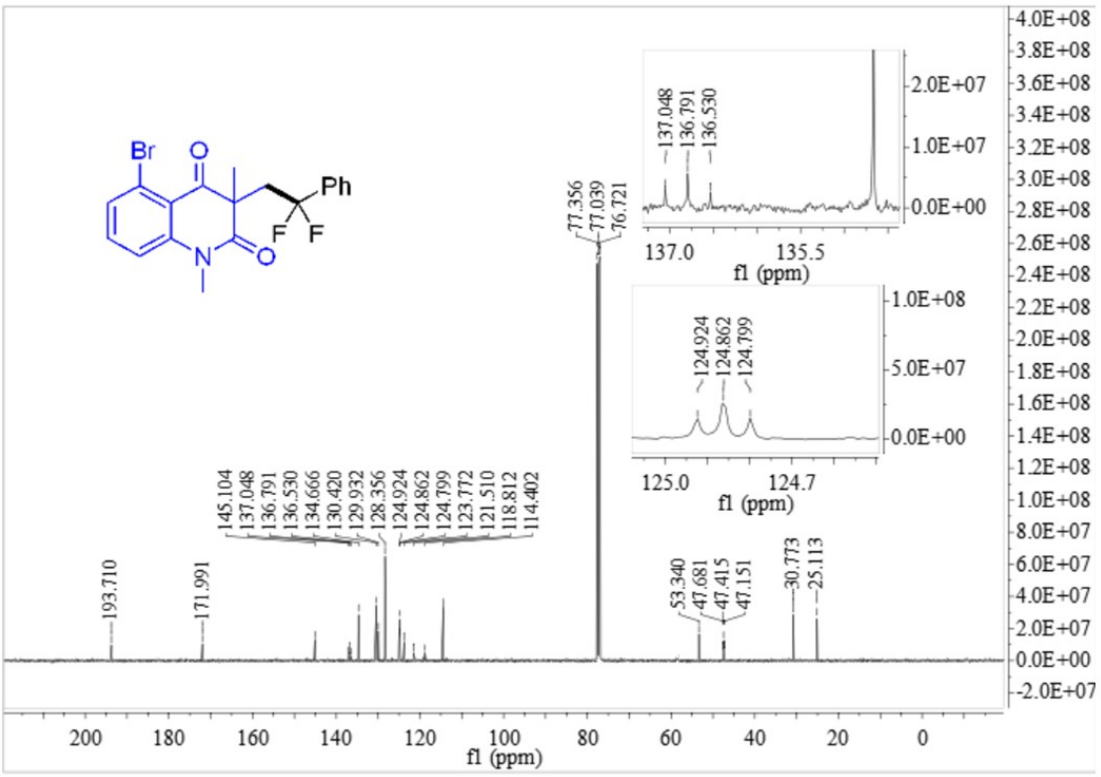
^{19}F NMR spectrum of **3c** (376 MHz, $CDCl_3$)



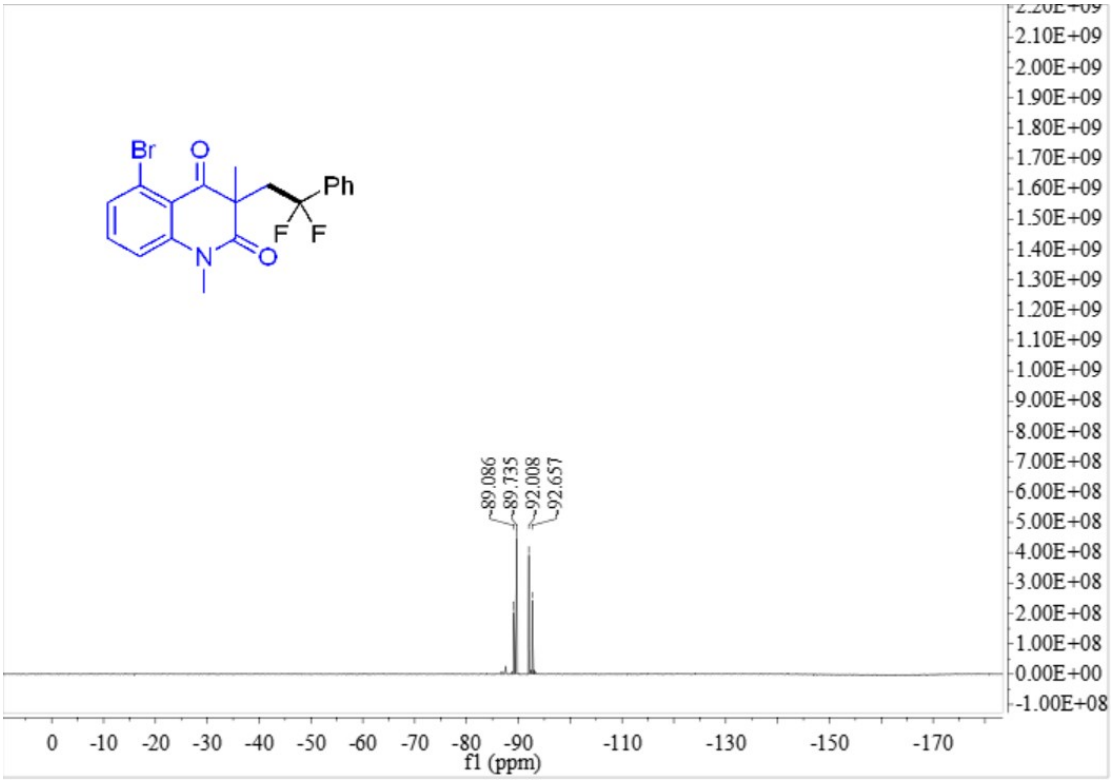
^{1}H NMR spectrum of **3d** (400 MHz, $CDCl_3$)



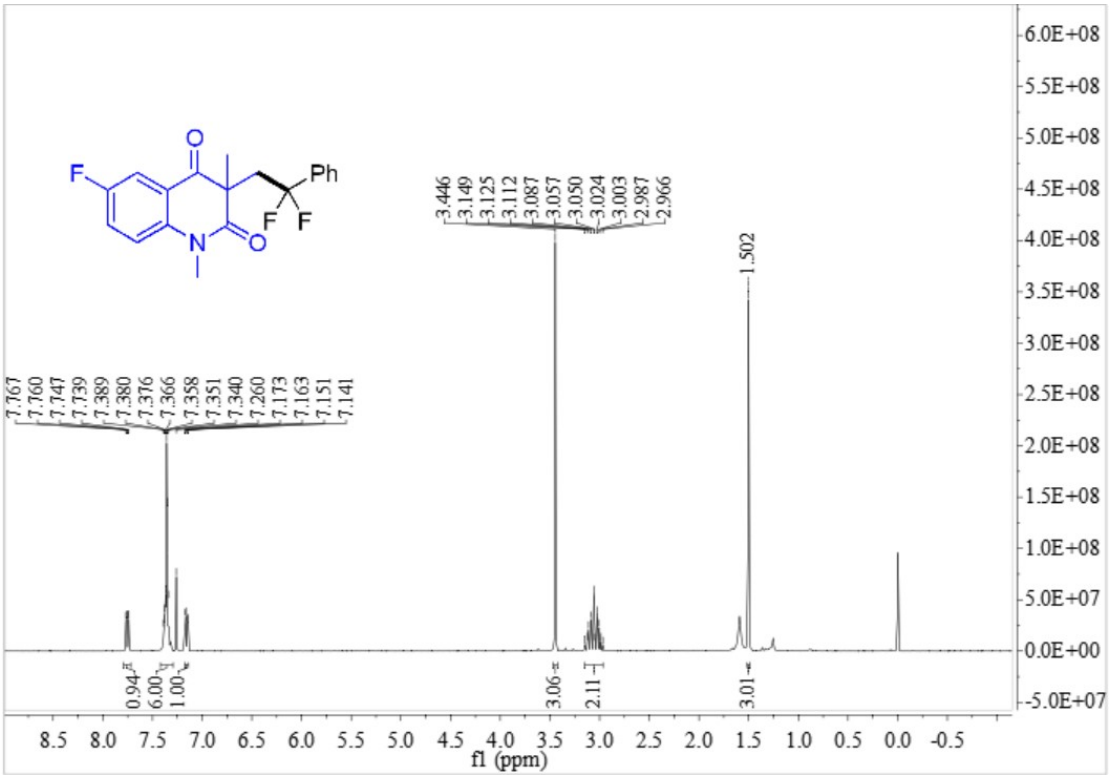
^{13}C NMR spectrum of **3d** (100 MHz, $CDCl_3$)



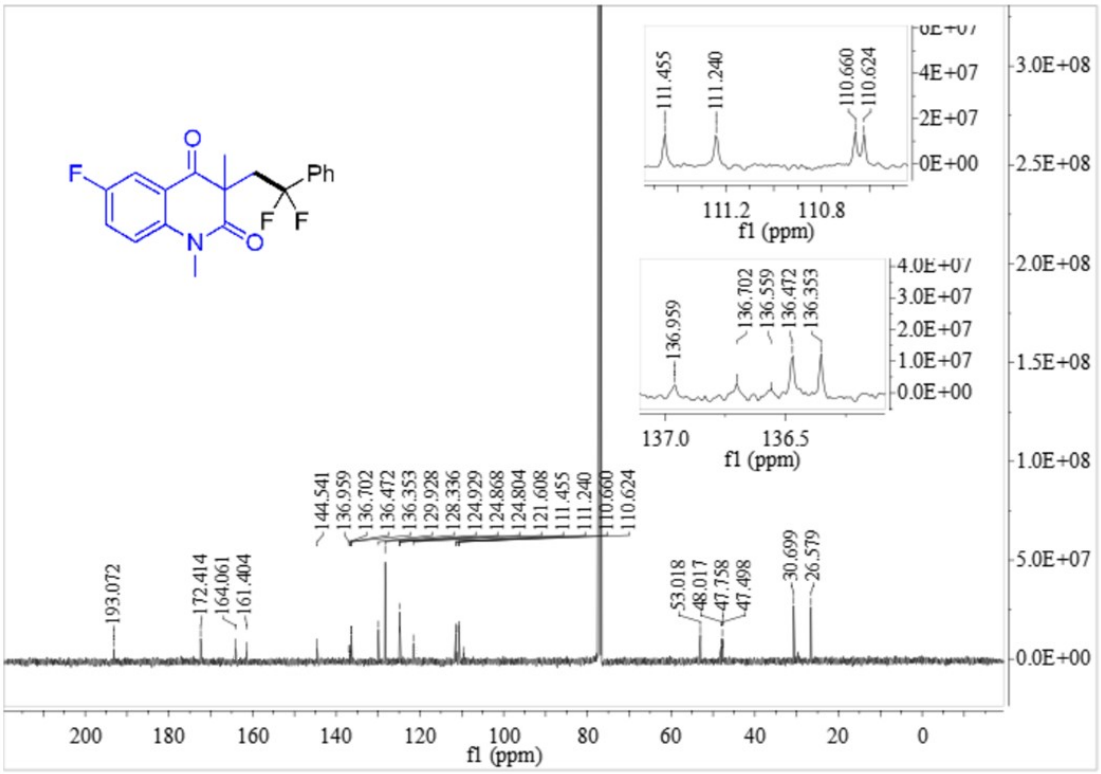
^{19}F NMR spectrum of **3d** (376 MHz, $CDCl_3$)



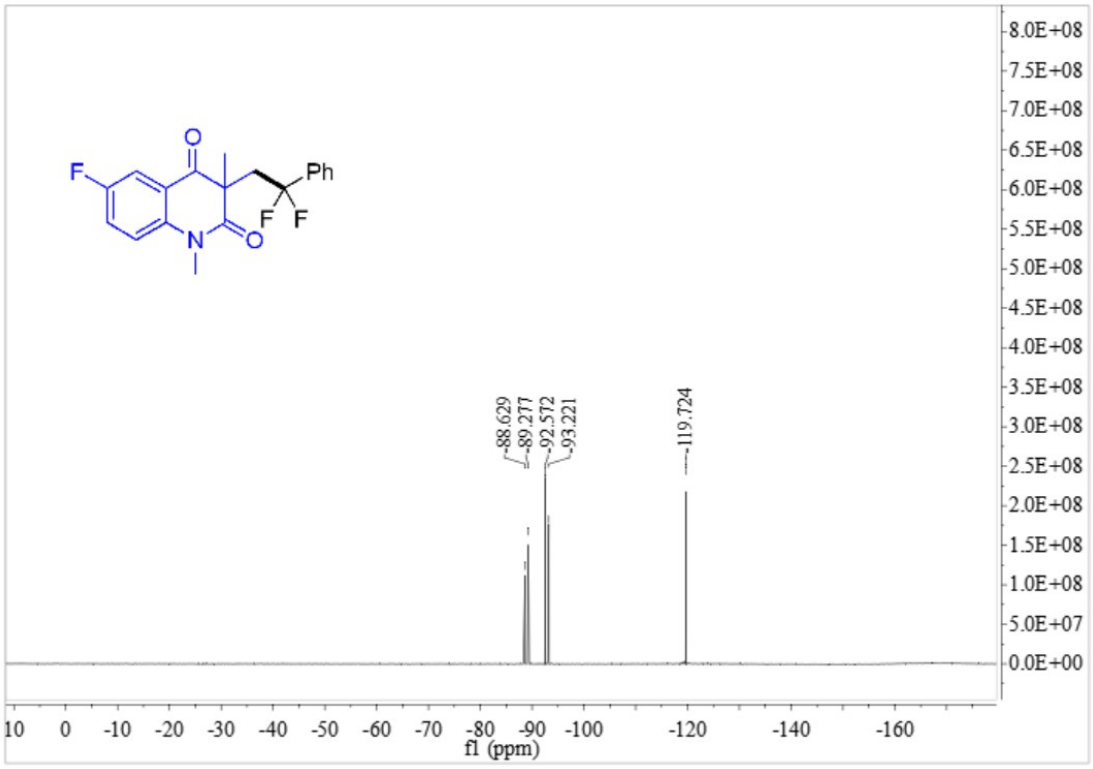
^{1}H NMR spectrum of **3e** (400 MHz, $CDCl_3$)



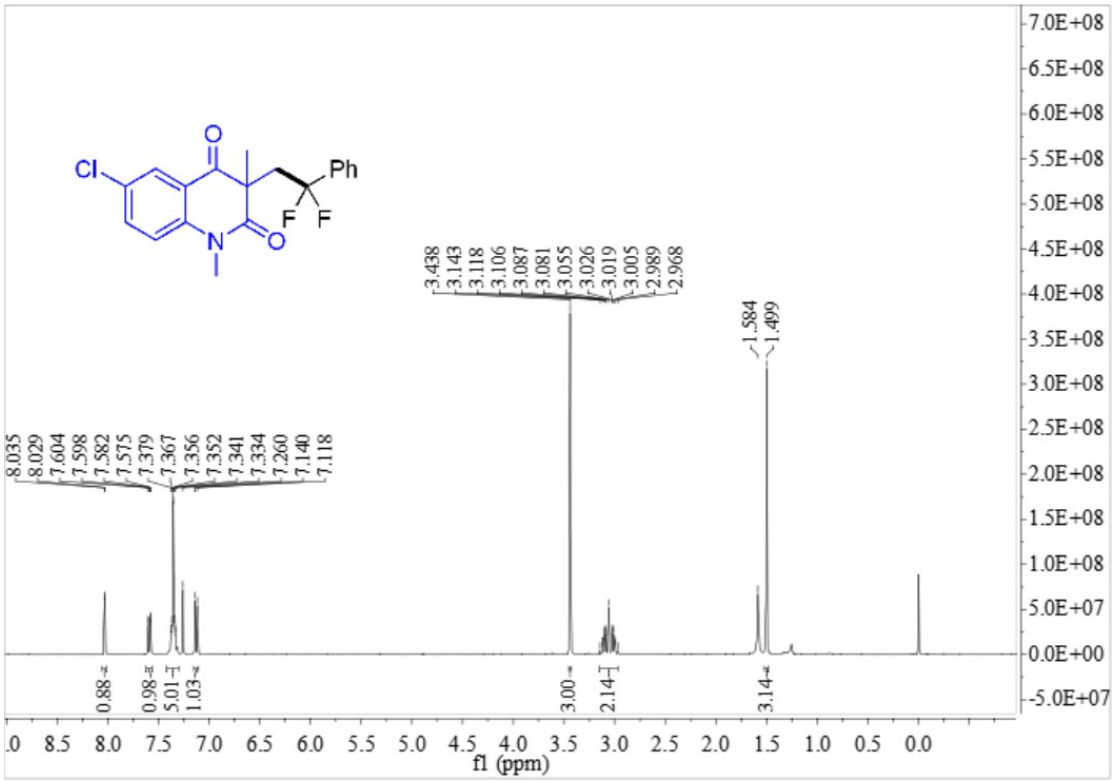
^{13}C NMR spectrum of **3e** (100 MHz, $CDCl_3$)



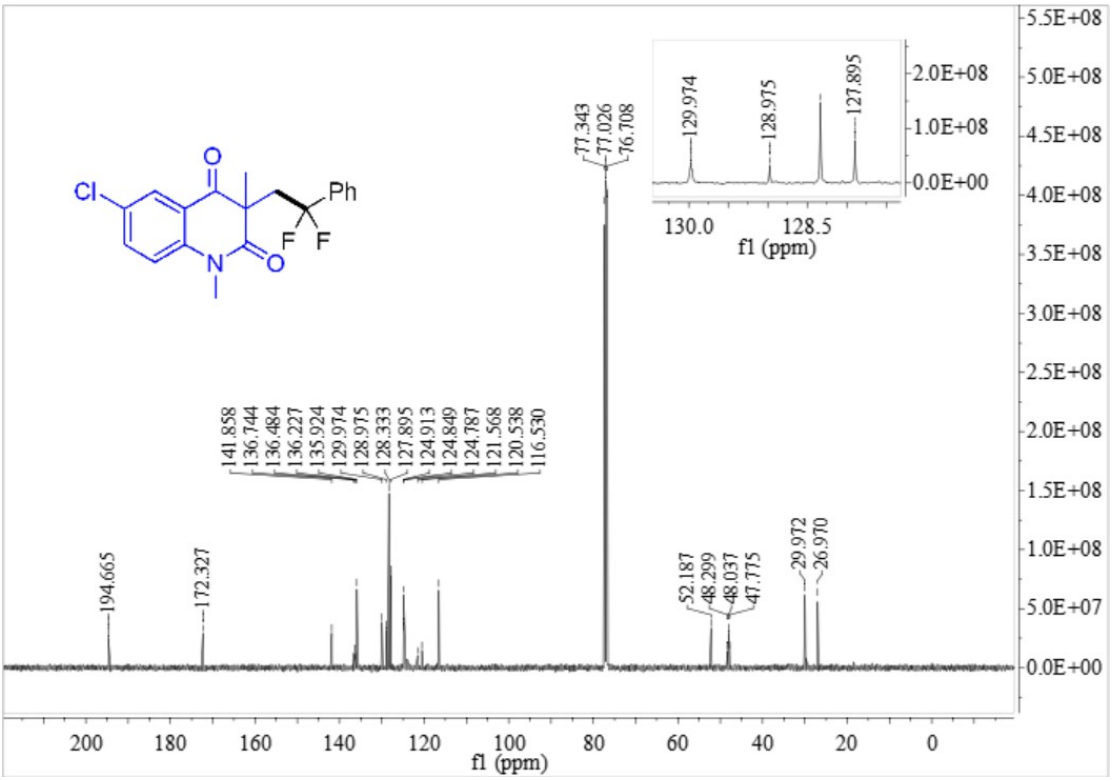
^{19}F NMR spectrum of **3e** (376 MHz, $CDCl_3$)



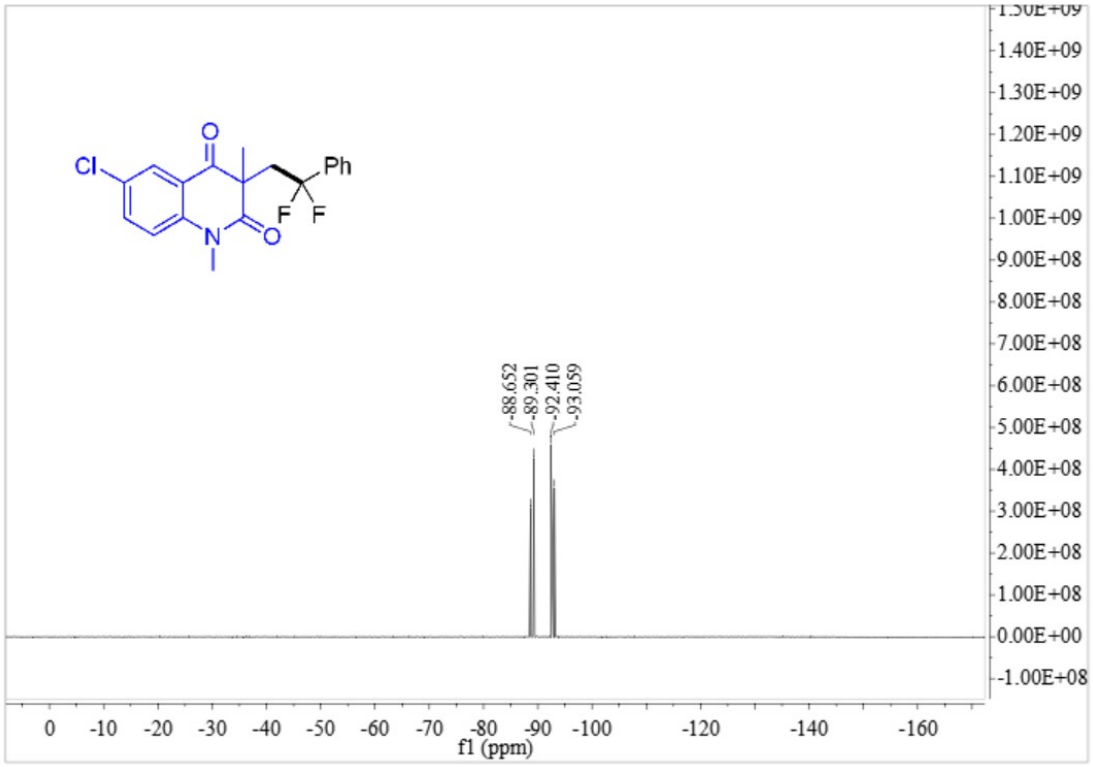
^{1}H NMR spectrum of **3f** (400 MHz, $CDCl_3$)



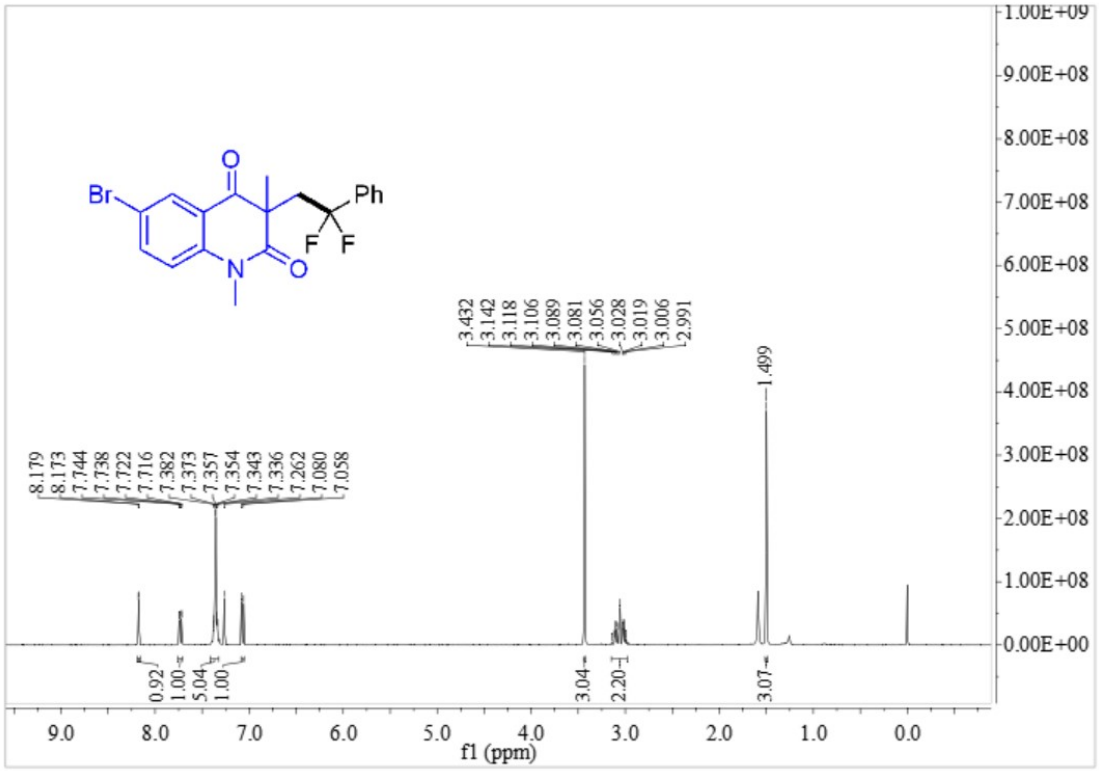
^{13}C NMR spectrum of **3f** (100 MHz, $CDCl_3$)



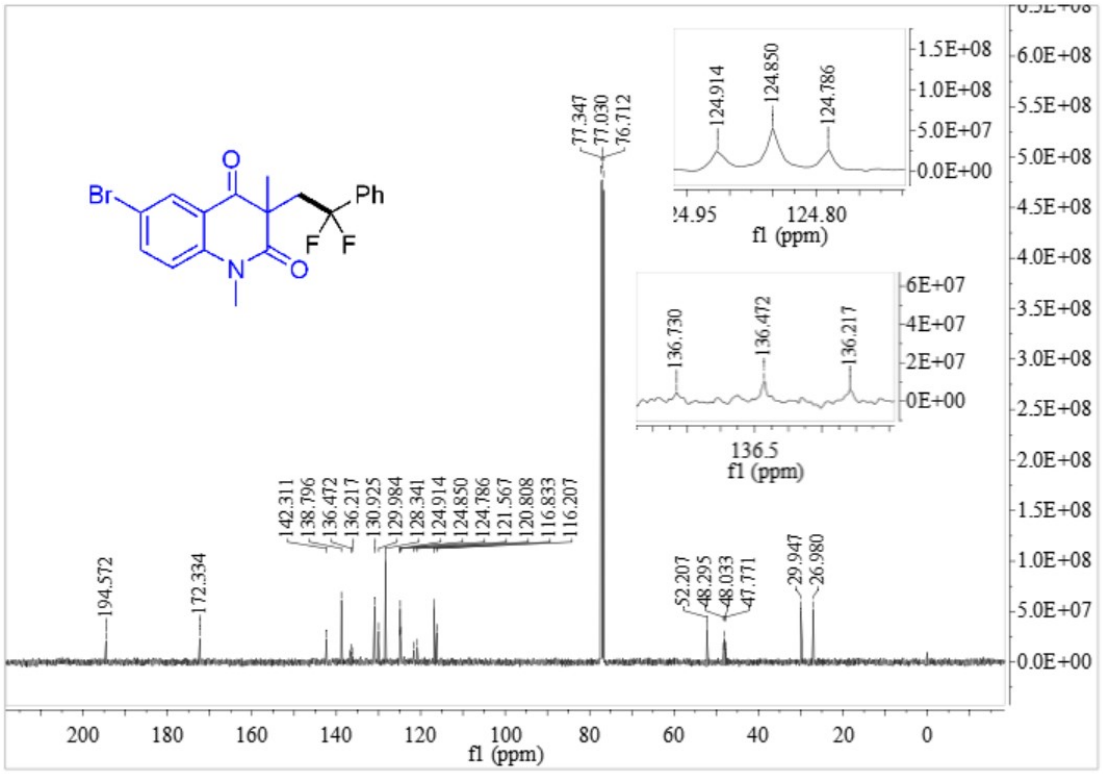
^{19}F NMR spectrum of **3f** (376 MHz, $CDCl_3$)



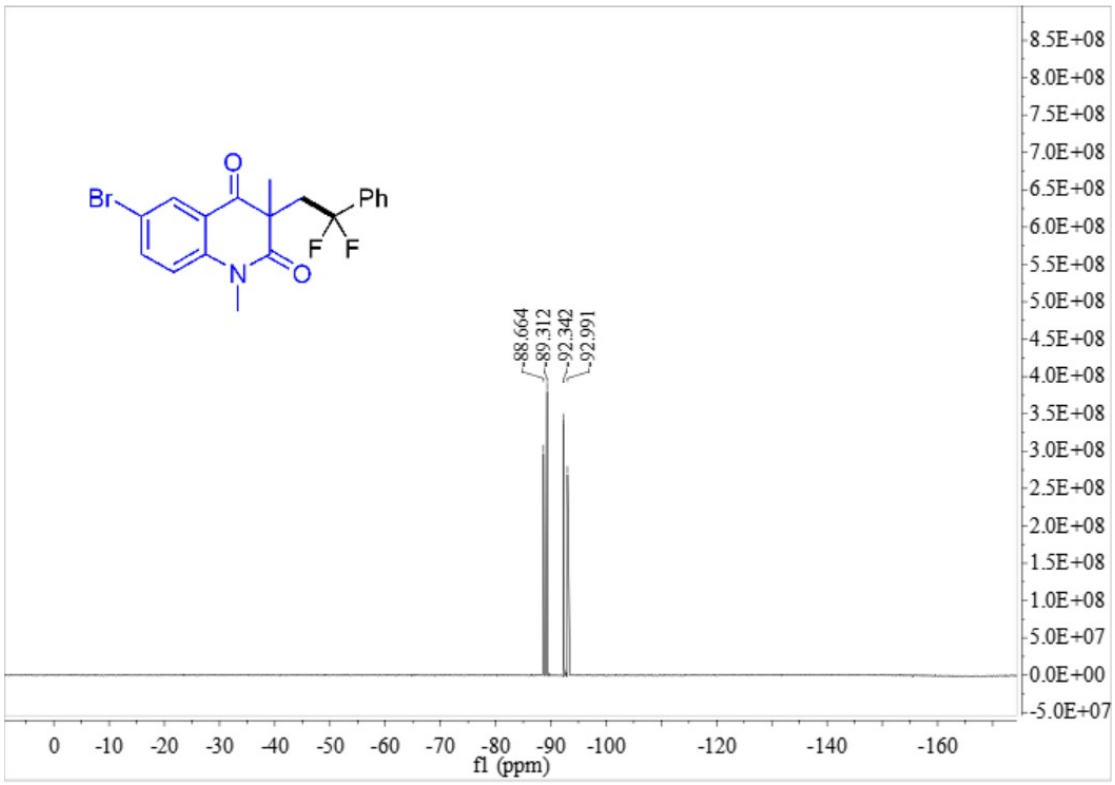
^{1}H NMR spectrum of **3g** (400 MHz, $CDCl_3$)



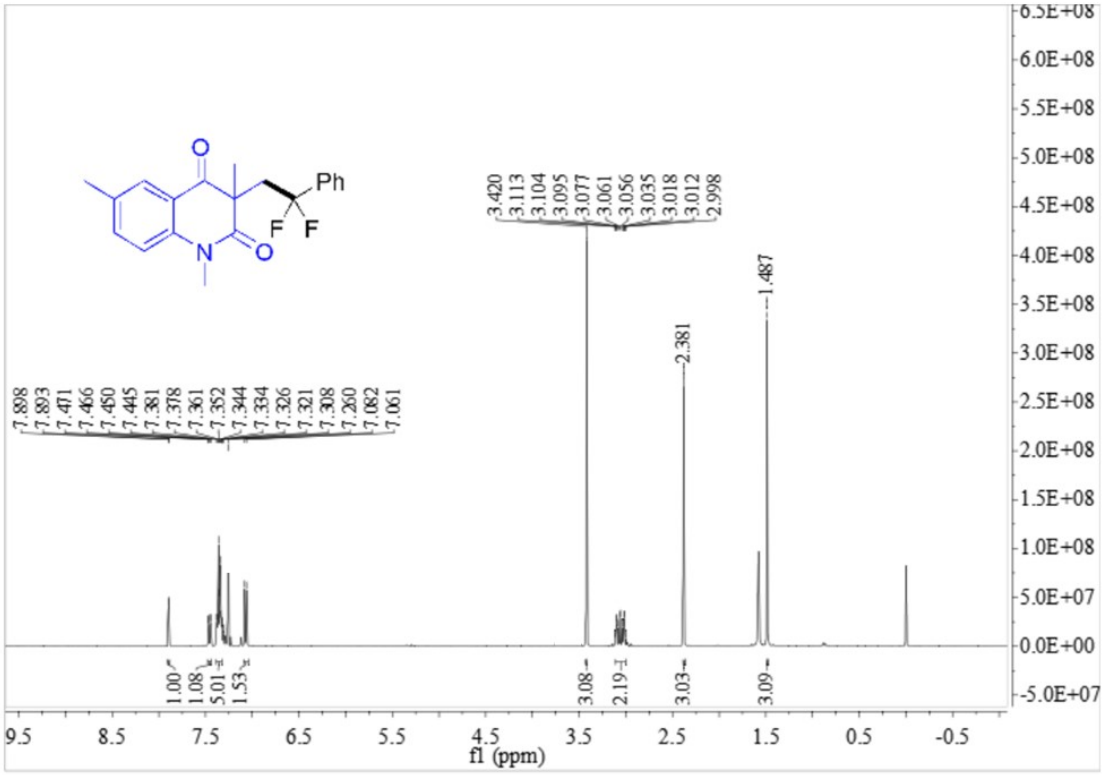
^{13}C NMR spectrum of **3g** (100 MHz, $CDCl_3$)



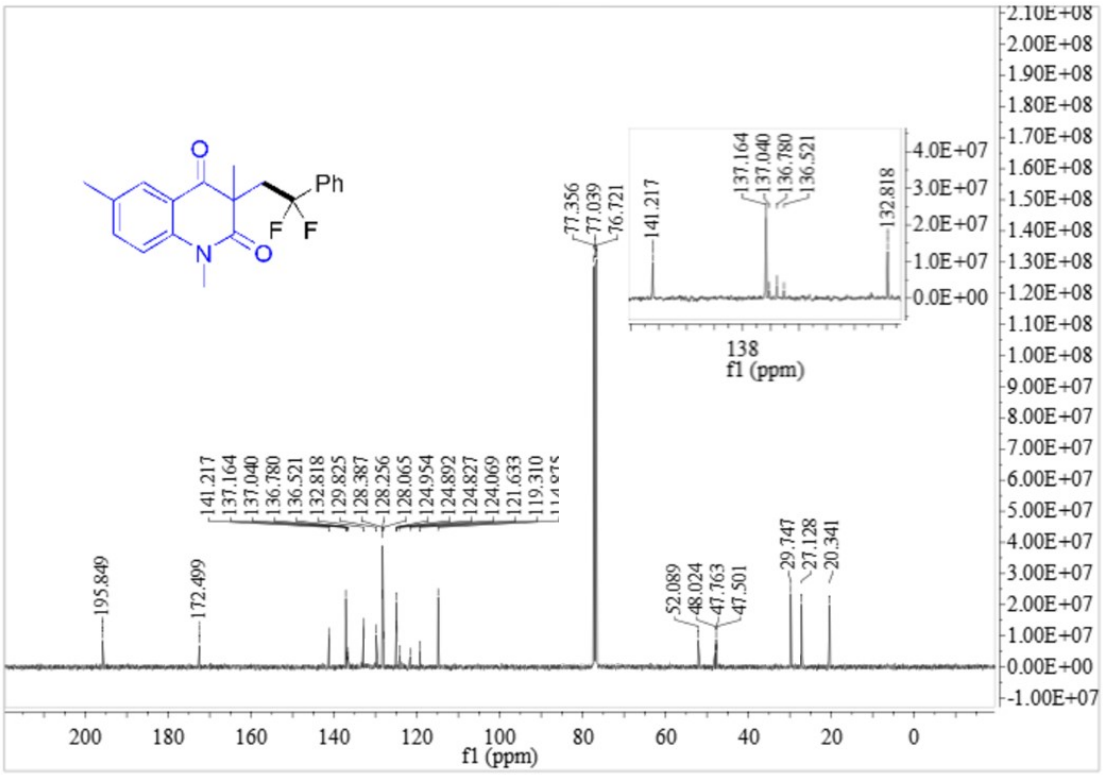
^{19}F NMR spectrum of **3g** (376 MHz, $CDCl_3$)



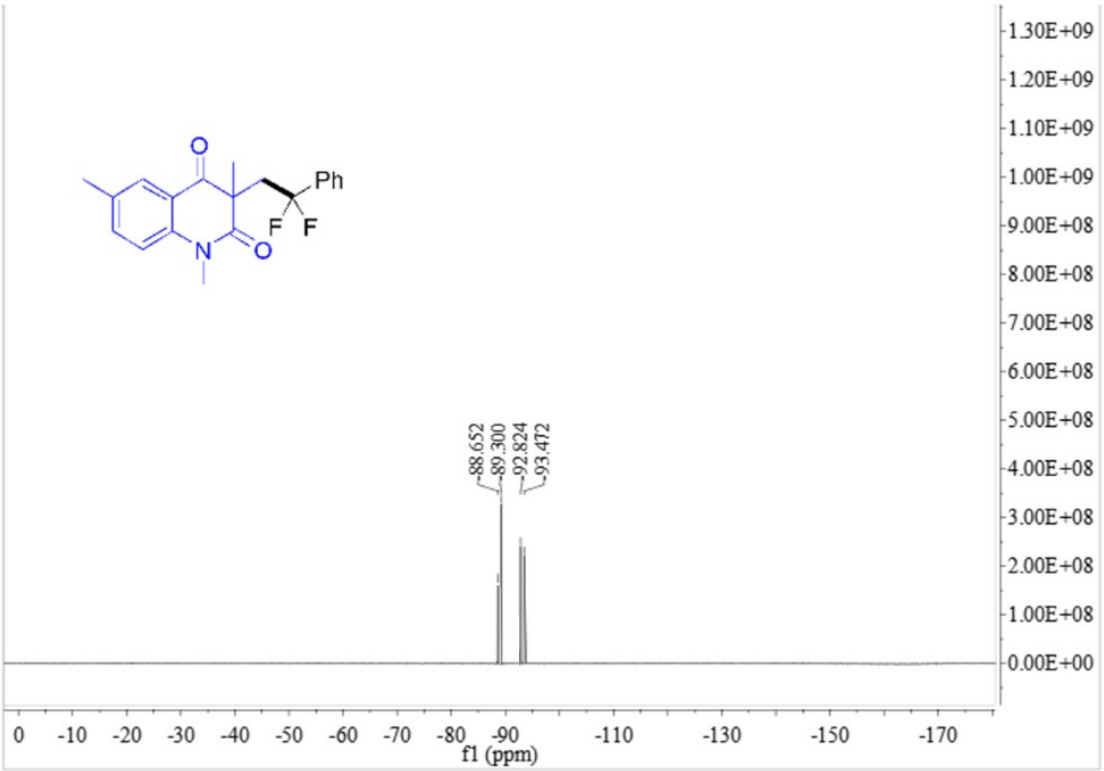
^{1}H NMR spectrum of **3h** (400 MHz, $CDCl_3$)



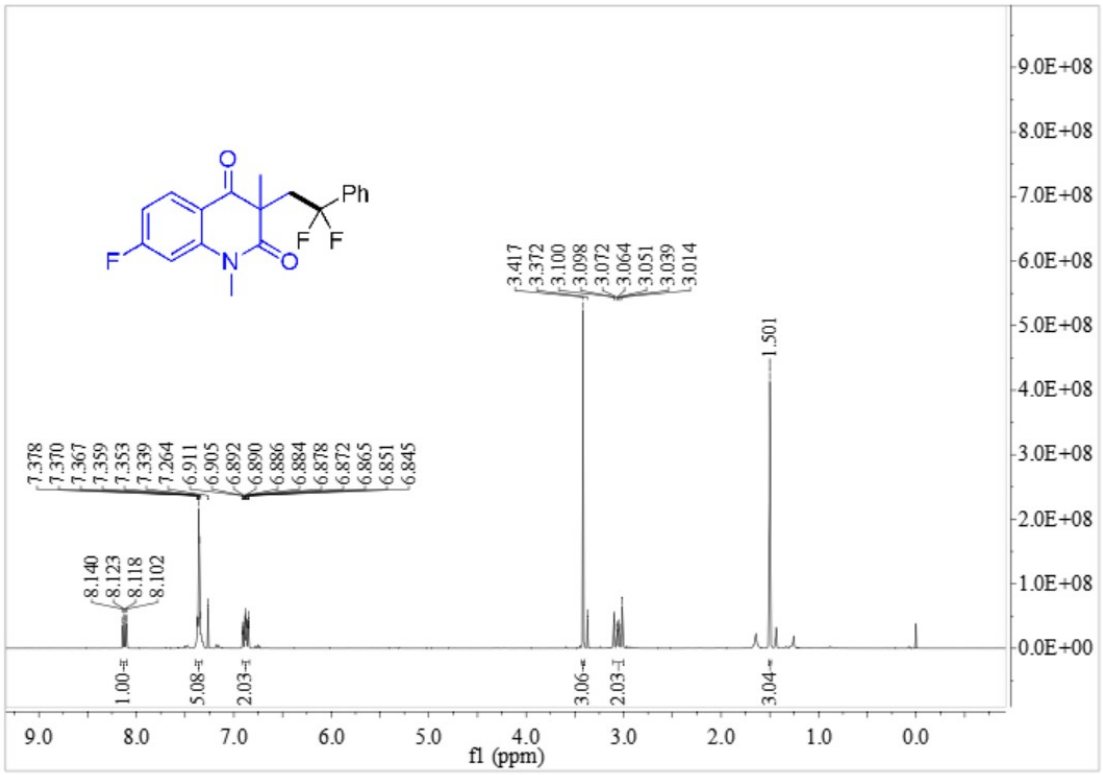
^{13}C NMR spectrum of **3h** (100 MHz, $CDCl_3$)



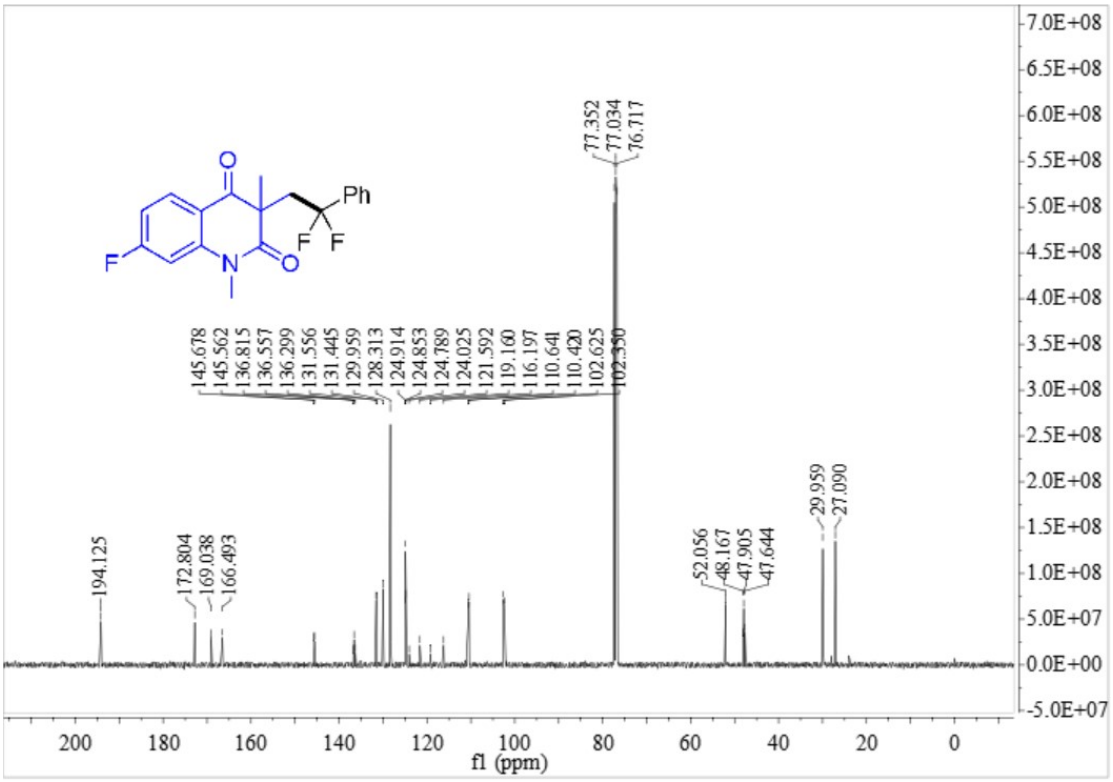
^{19}F NMR spectrum of **3h** (377 MHz, $CDCl_3$)



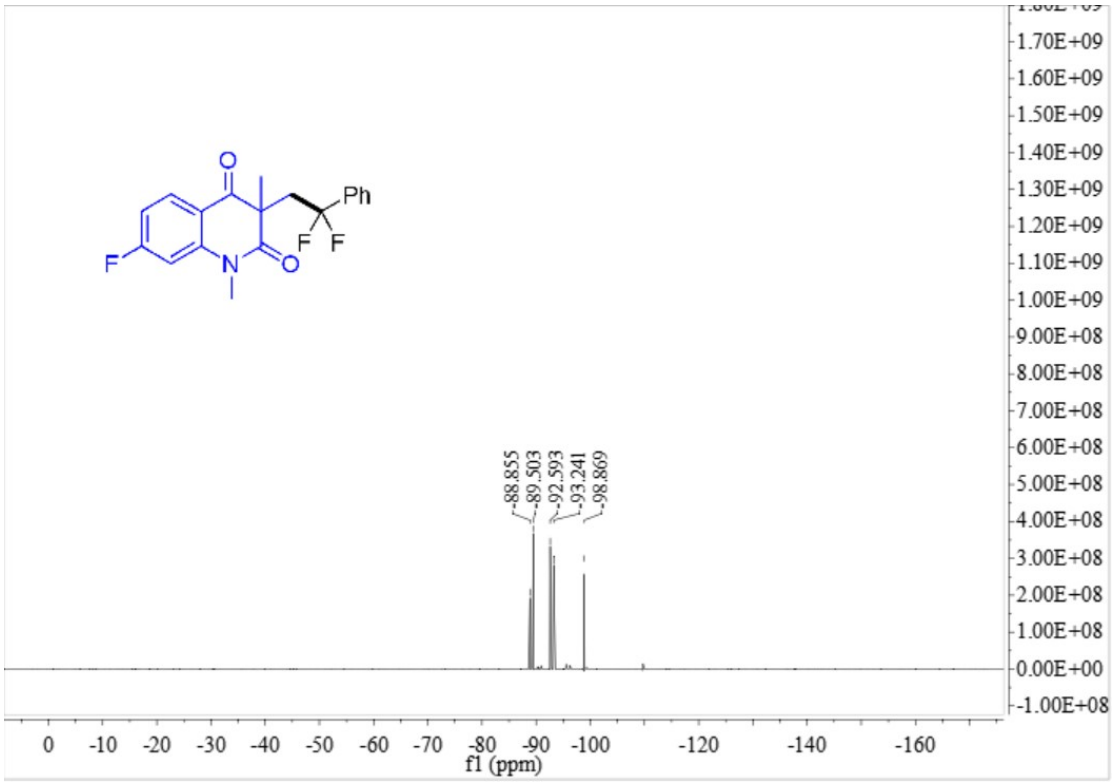
^{1}H NMR spectrum of **3i** (400 MHz, $CDCl_3$)



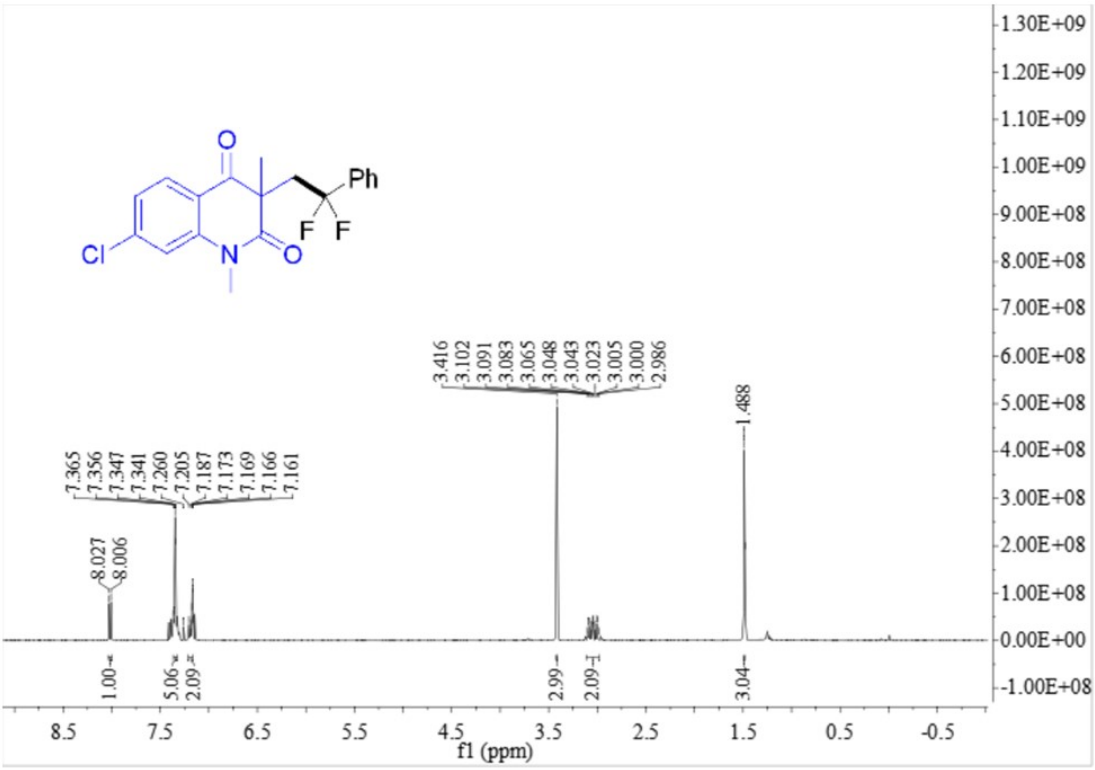
^{13}C NMR spectrum of **3i** (100 MHz, $CDCl_3$)



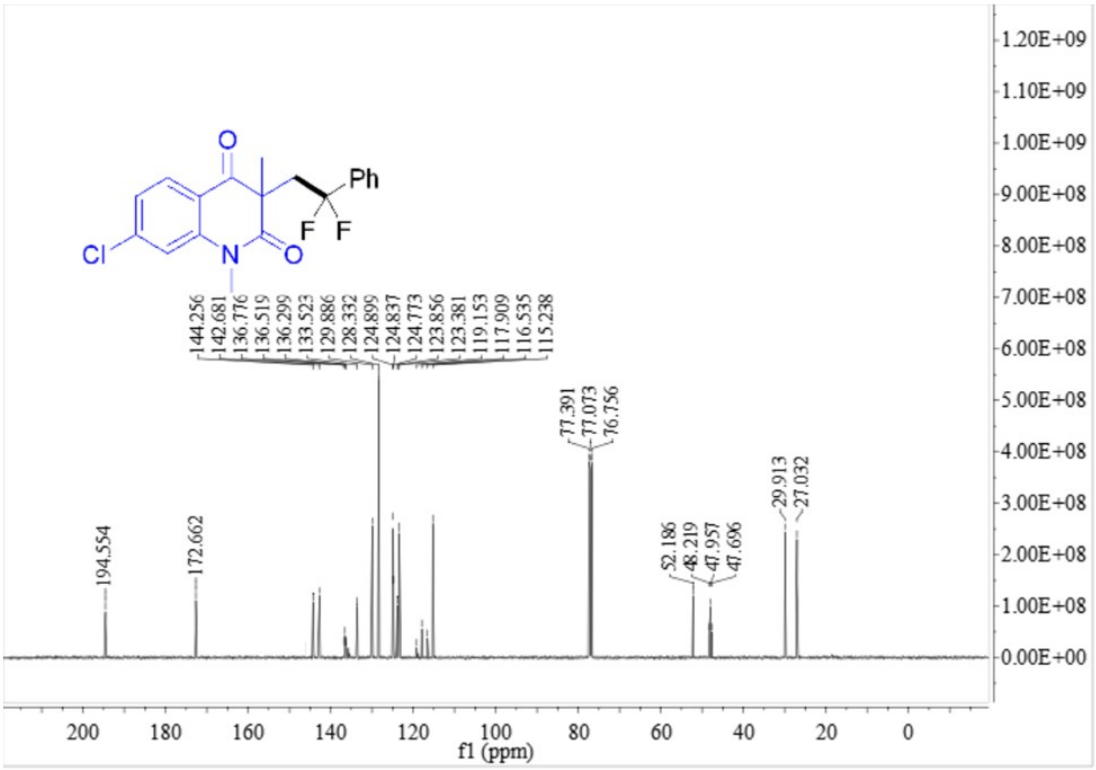
^{19}F NMR spectrum of **3i** (377 MHz, $CDCl_3$)



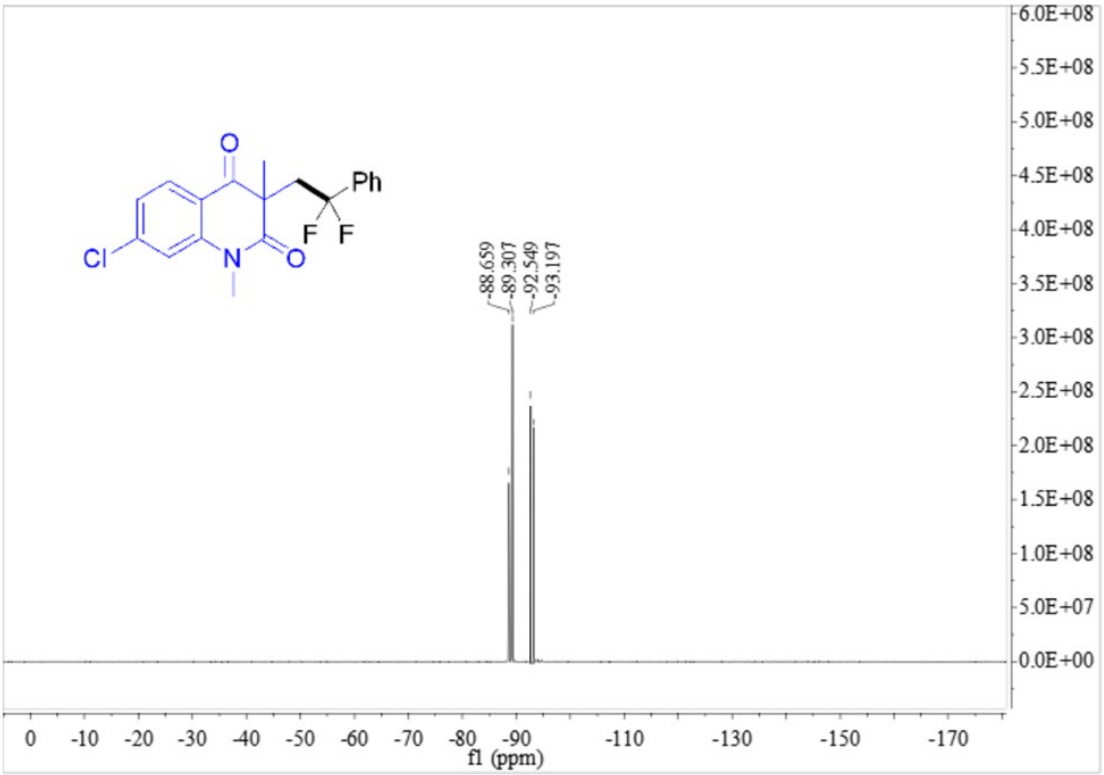
^{1}H NMR spectrum of **3j** (400 MHz, $CDCl_3$)



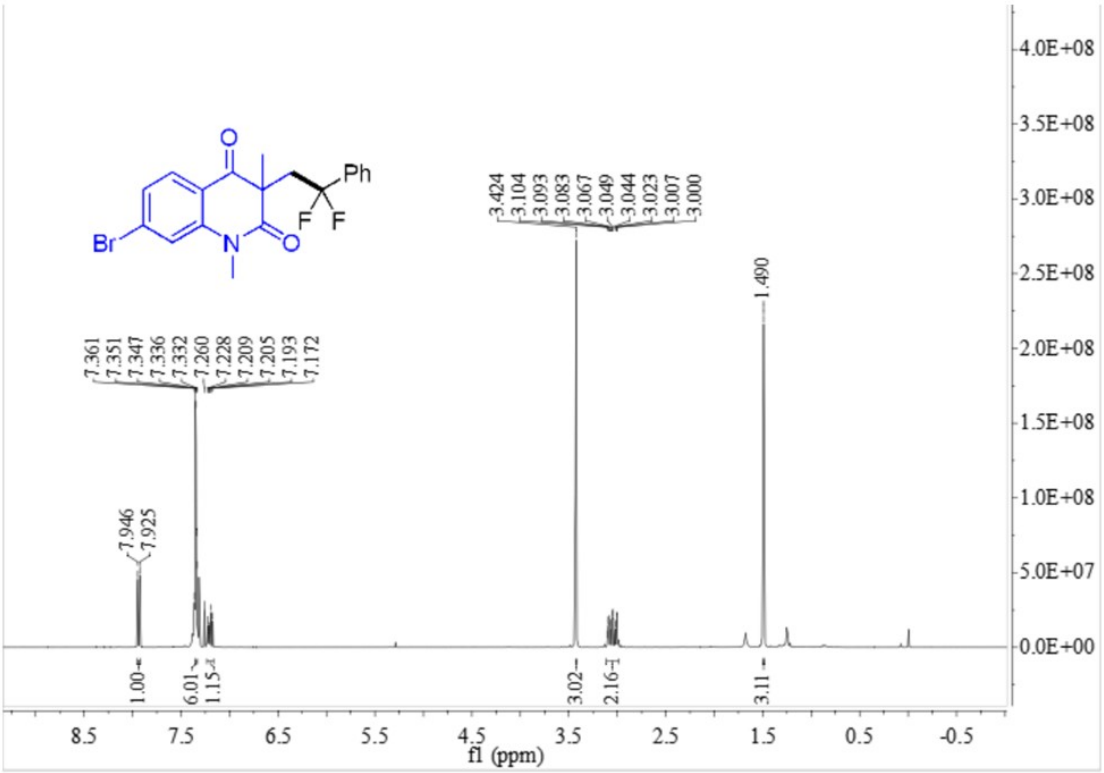
^{13}C NMR spectrum of **3j** (100 MHz, $CDCl_3$)



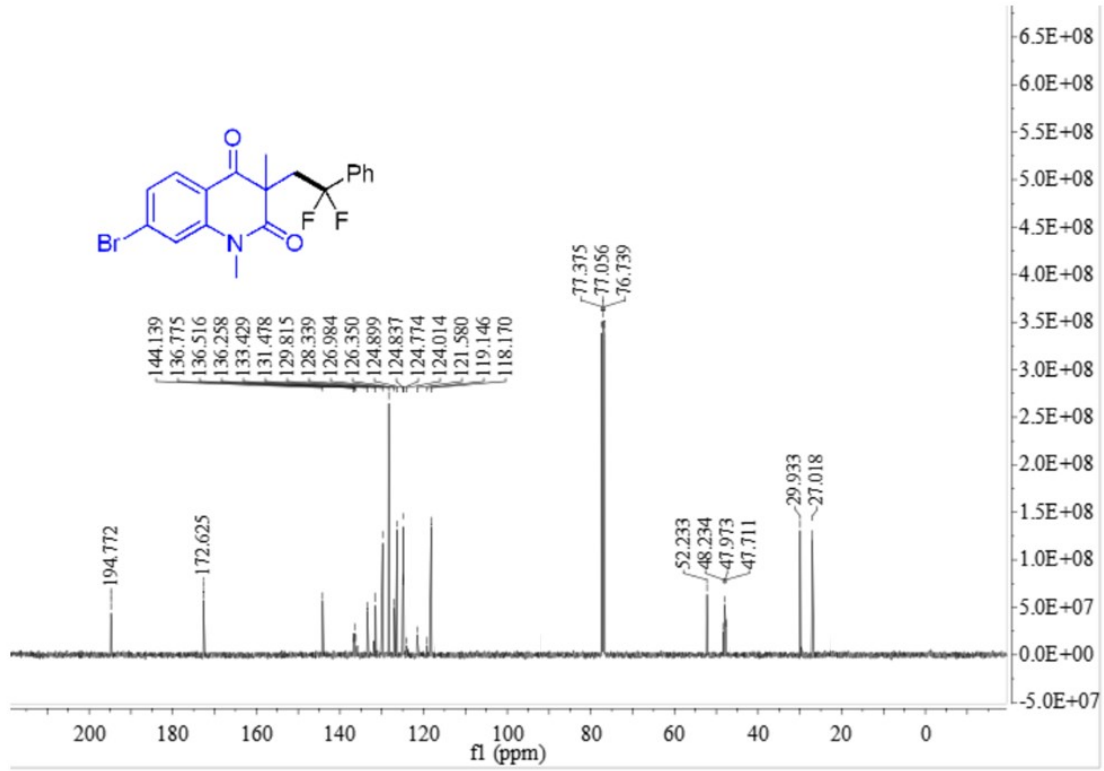
^{19}F NMR spectrum of **3j** (377 MHz, $CDCl_3$)



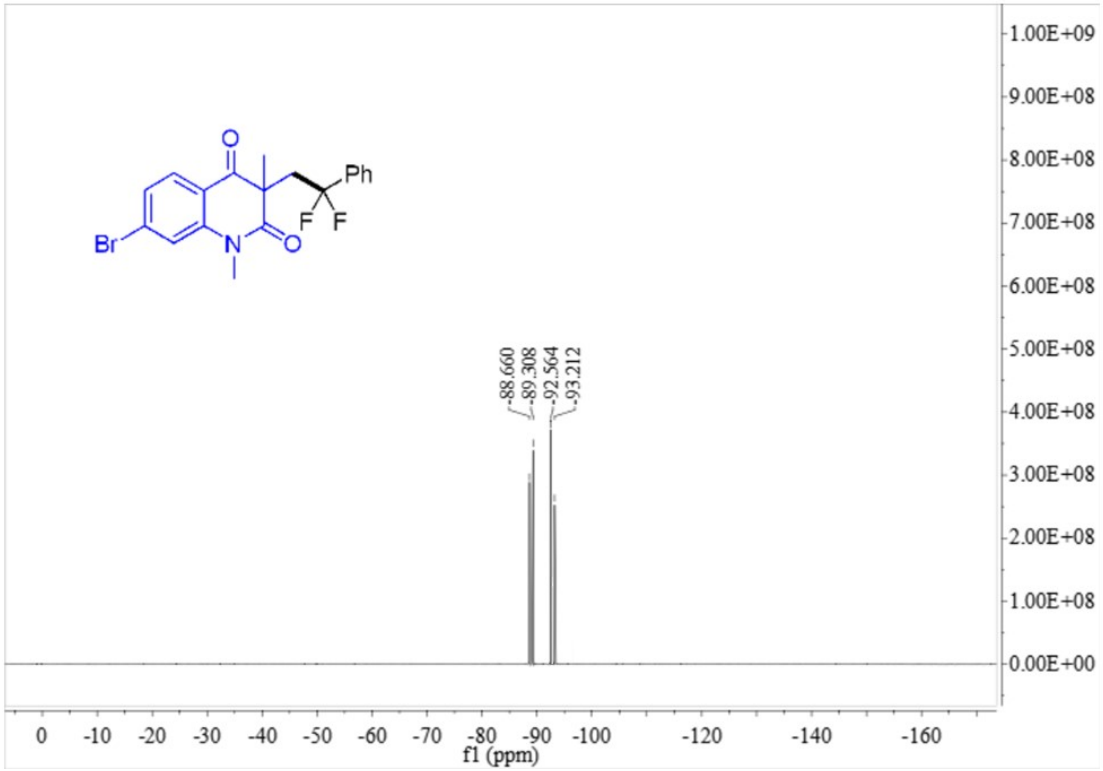
^{1}H NMR spectrum of **3k** (400 MHz, $CDCl_3$)



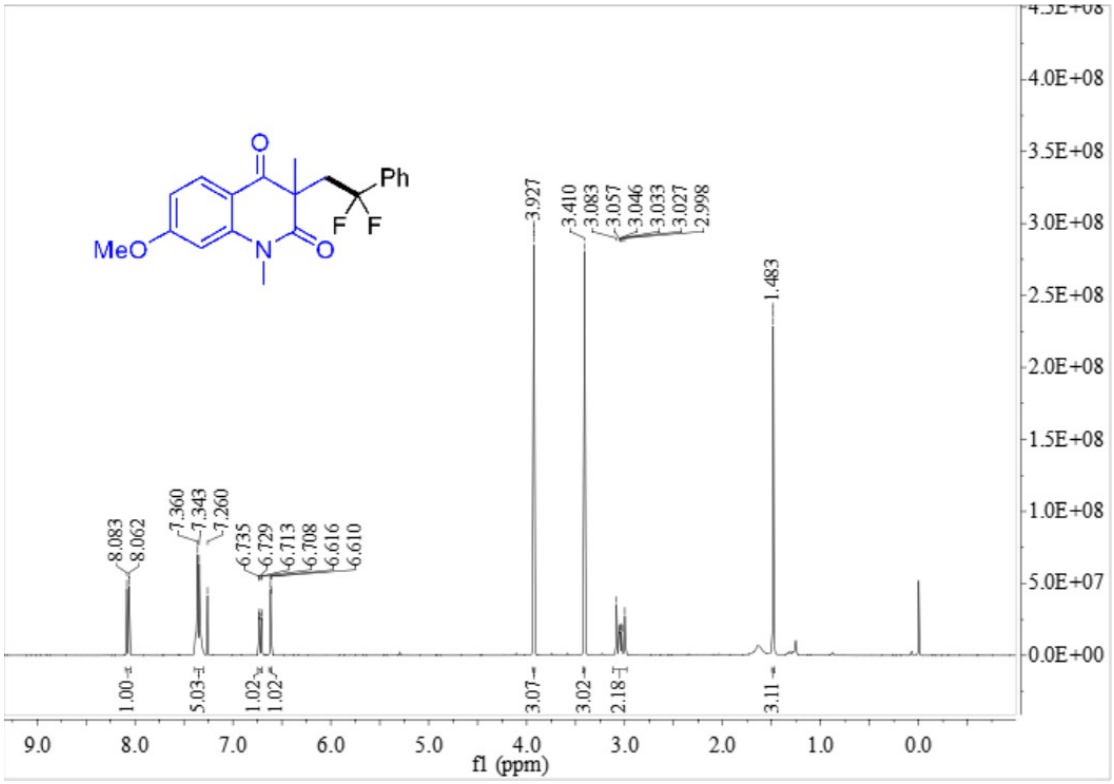
^{13}C NMR spectrum of **3k** (100 MHz, $CDCl_3$)



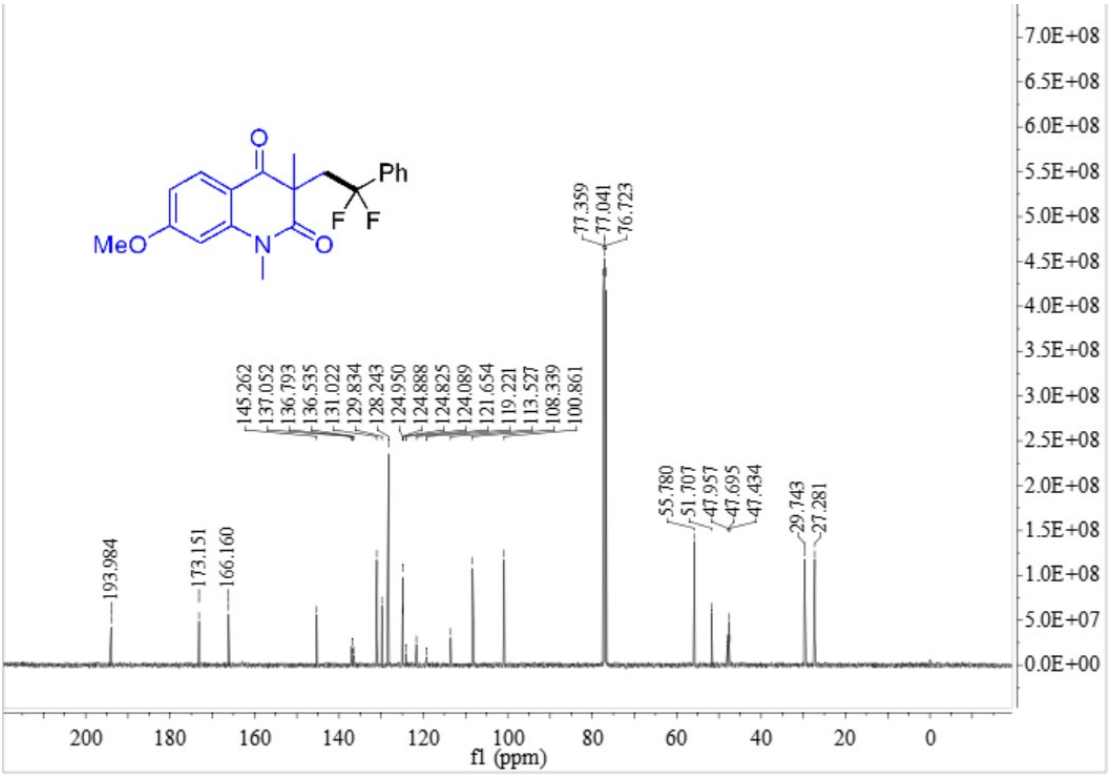
^{19}F NMR spectrum of **3k** (377 MHz, $CDCl_3$)



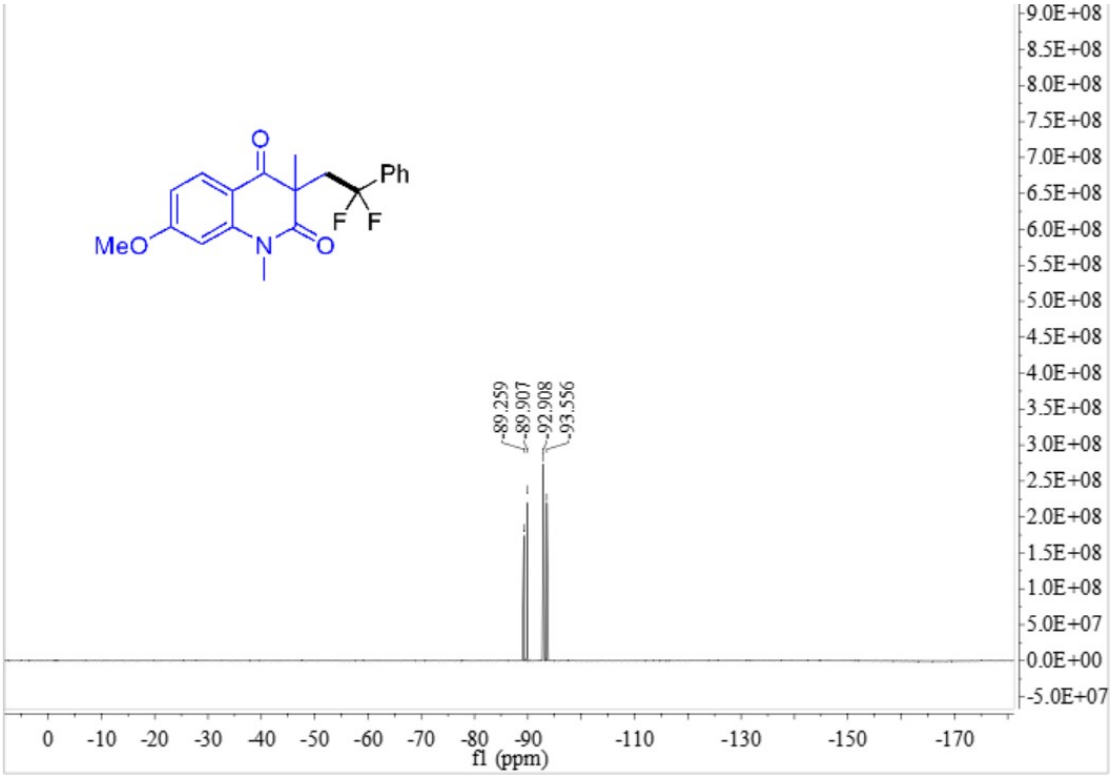
^{1}H NMR spectrum of **3l** (400 MHz, $CDCl_3$)



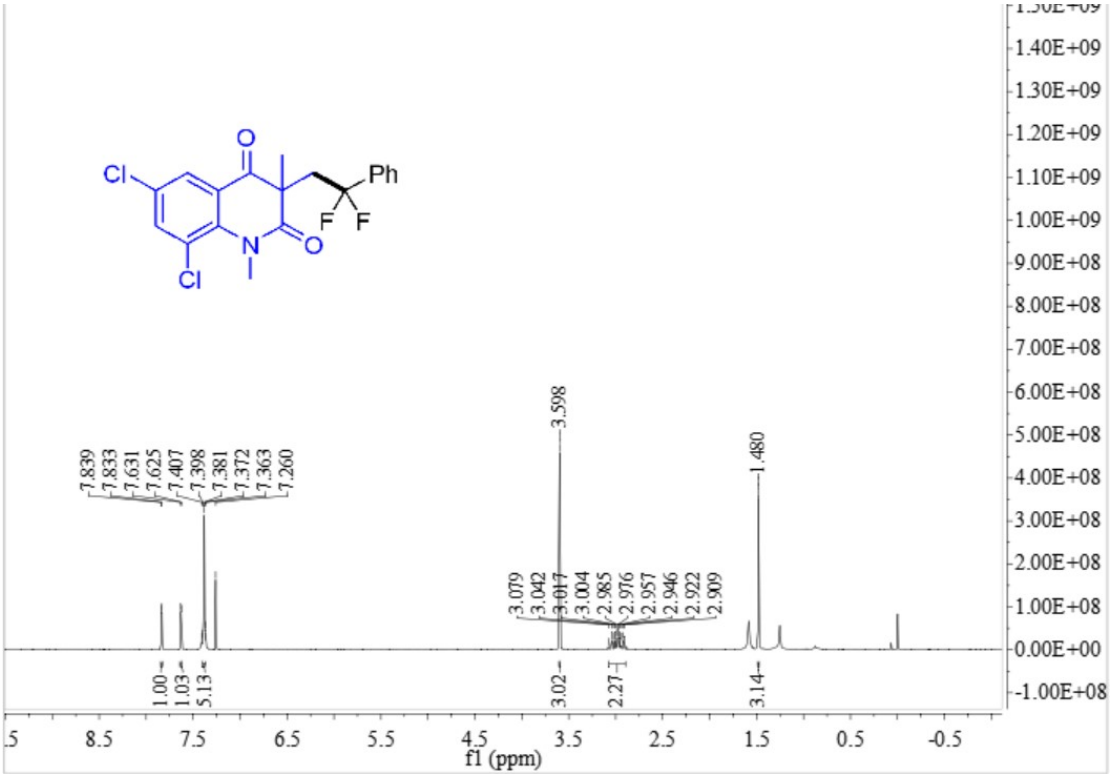
^{13}C NMR spectrum of **3l** (100 MHz, $CDCl_3$)



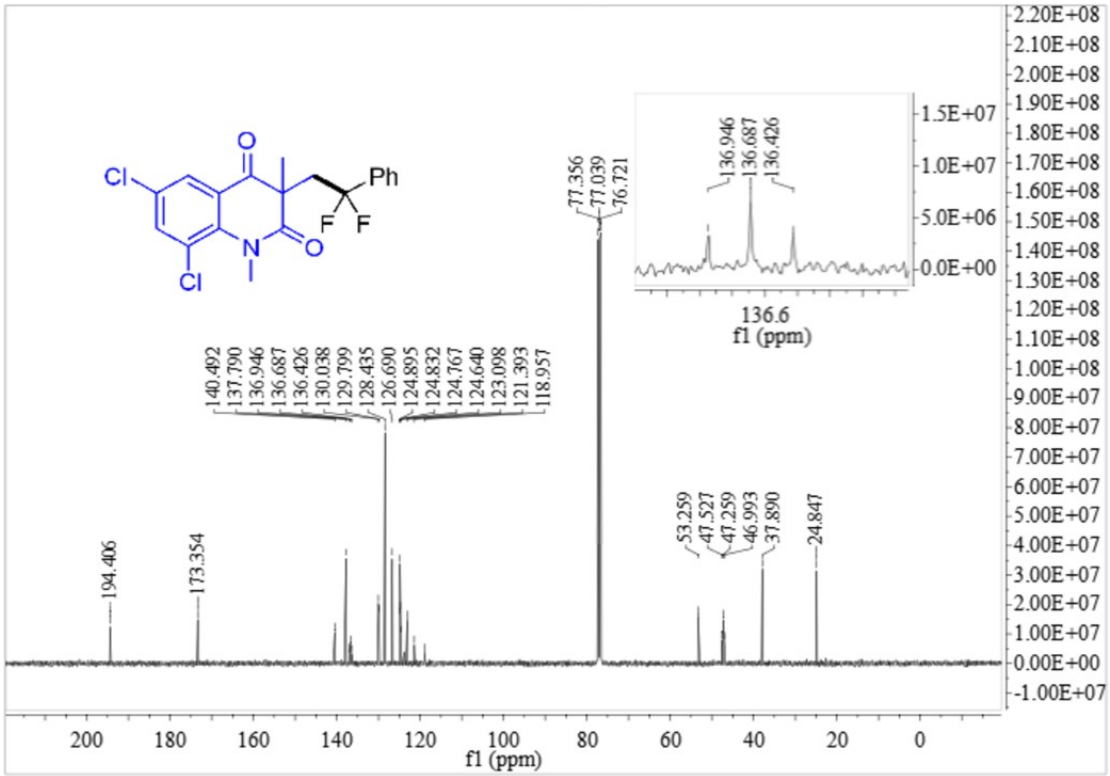
^{19}F NMR spectrum of **3l** (376 MHz, $CDCl_3$)



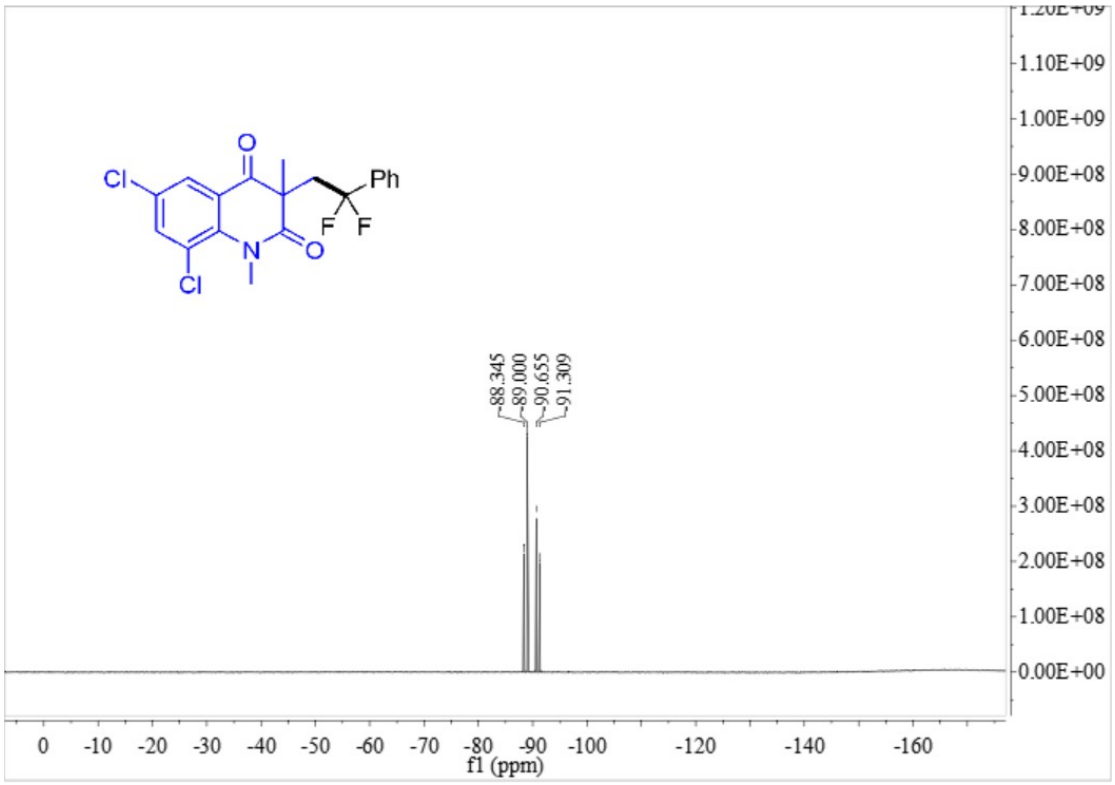
^{1}H NMR spectrum of **3m** (400 MHz, $CDCl_3$)



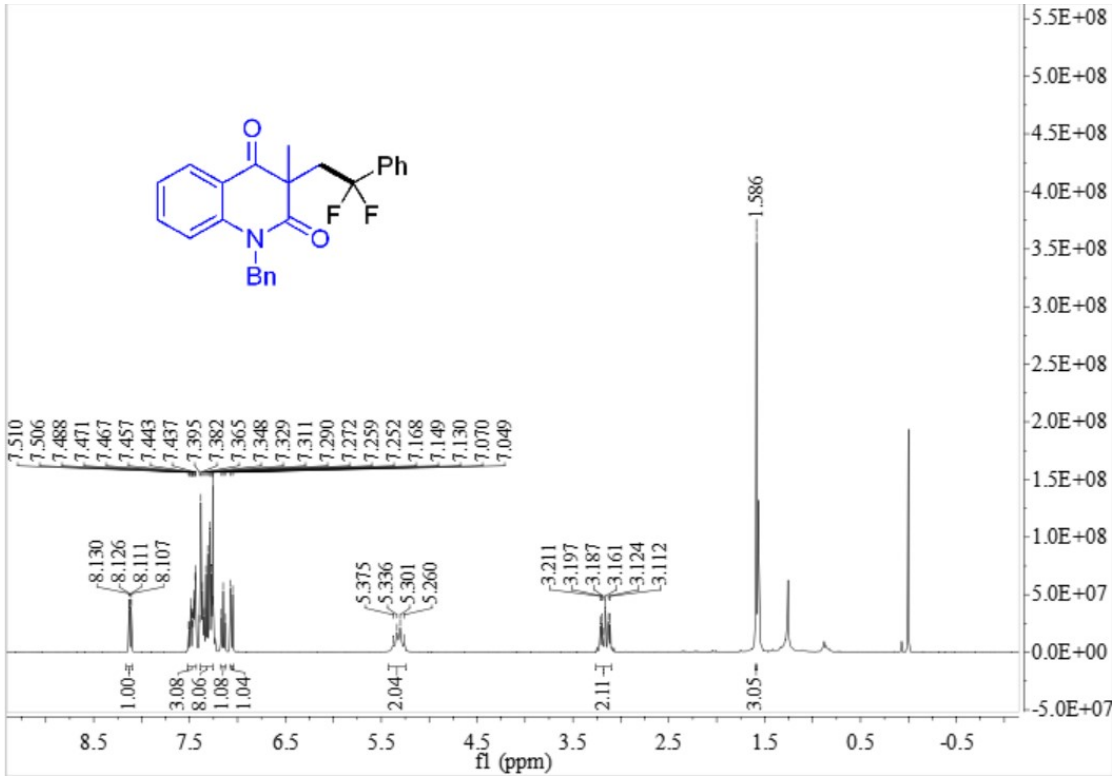
^{13}C NMR spectrum of **3m** (100 MHz, $CDCl_3$)



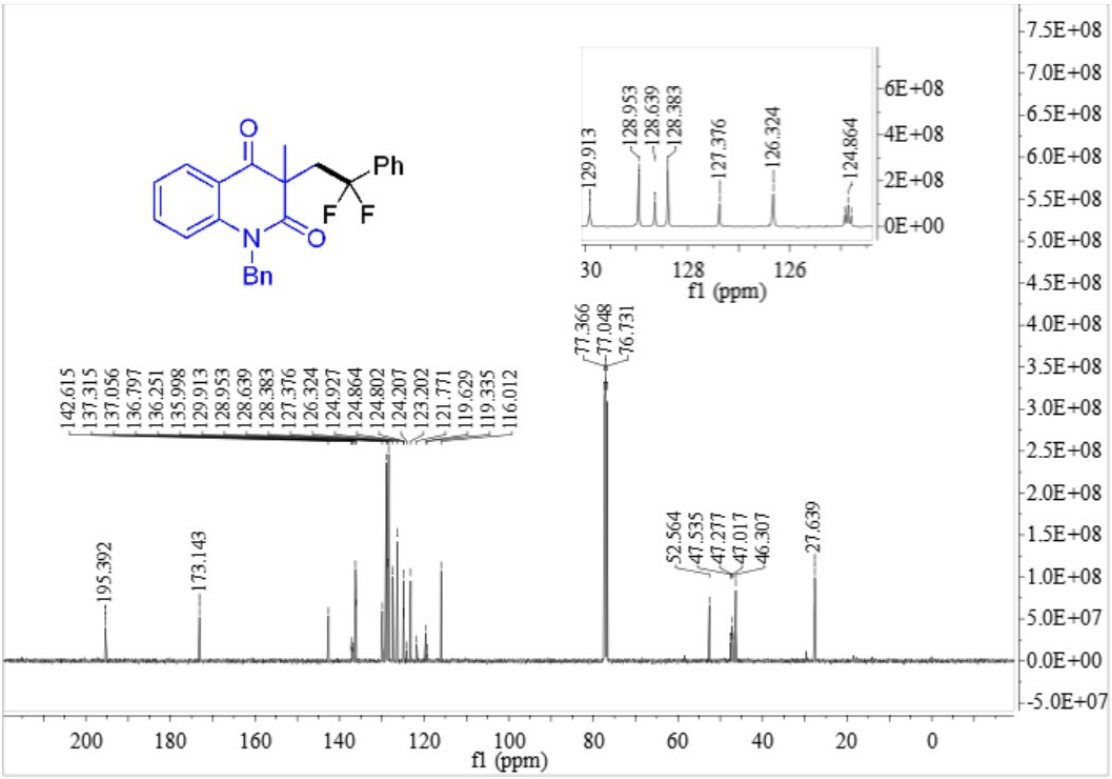
^{19}F NMR spectrum of **3m** (377 MHz, $CDCl_3$)



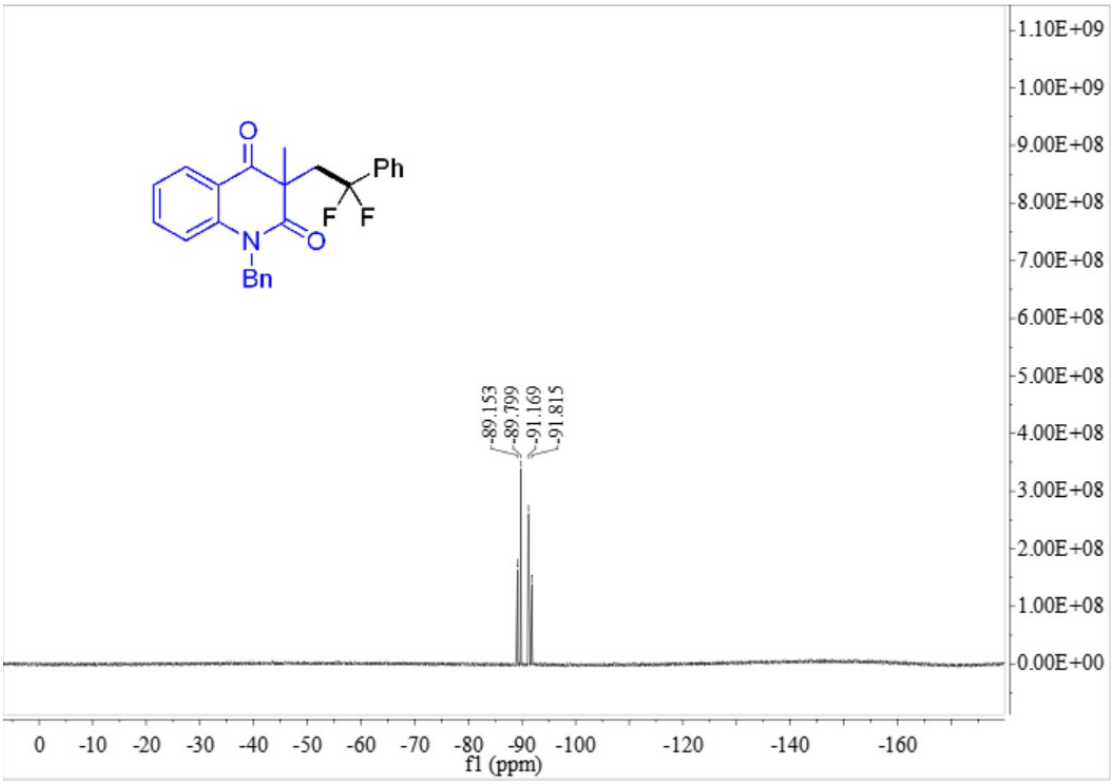
^{1}H NMR spectrum of **3n** (400 MHz, $CDCl_3$)



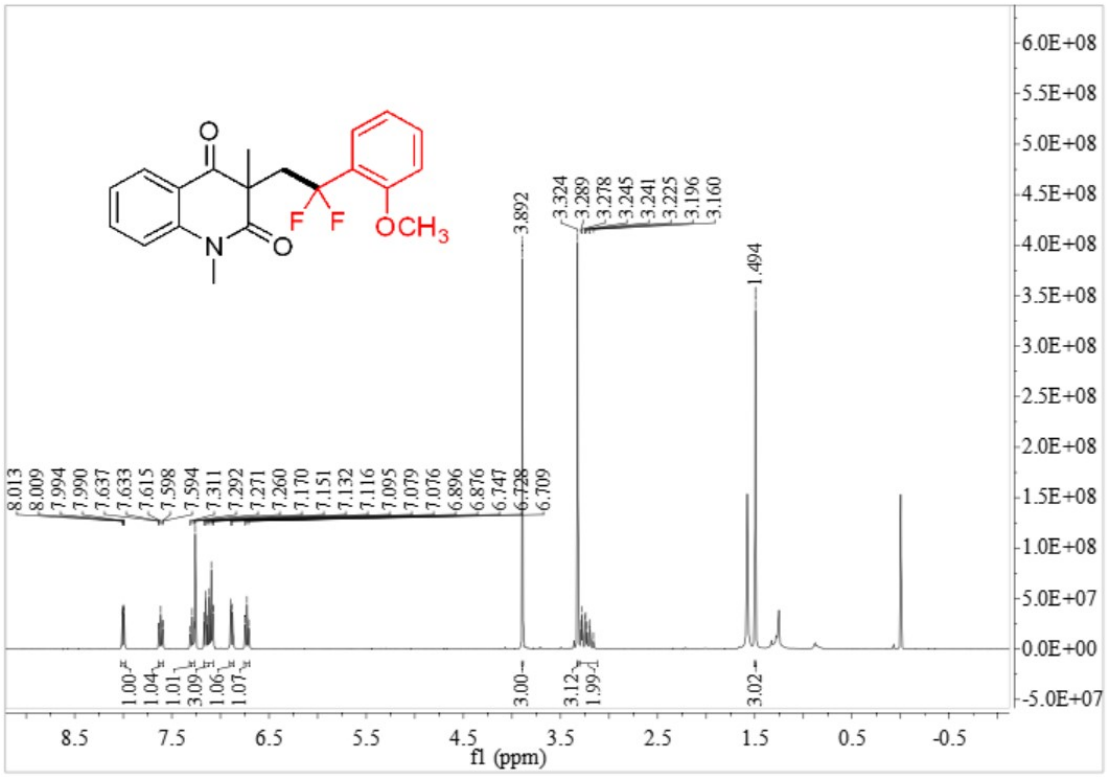
^{13}C NMR spectrum of **3n** (100 MHz, $CDCl_3$)



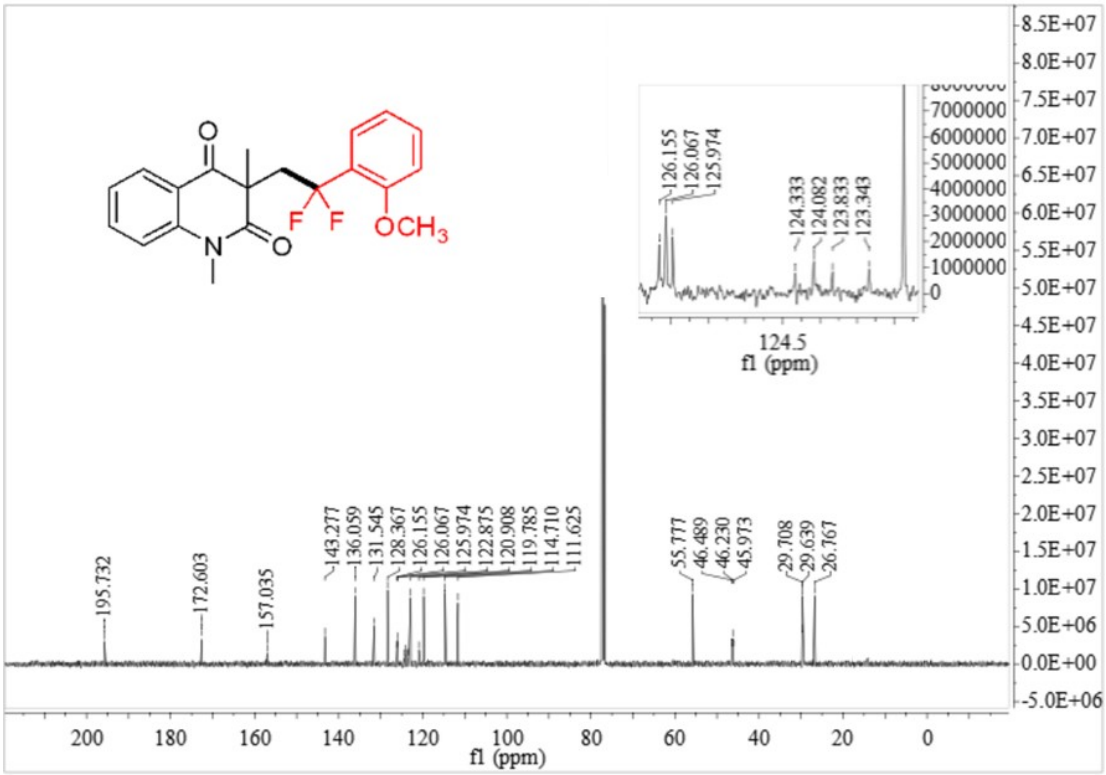
^{19}F NMR spectrum of **3n** (377 MHz, $CDCl_3$)



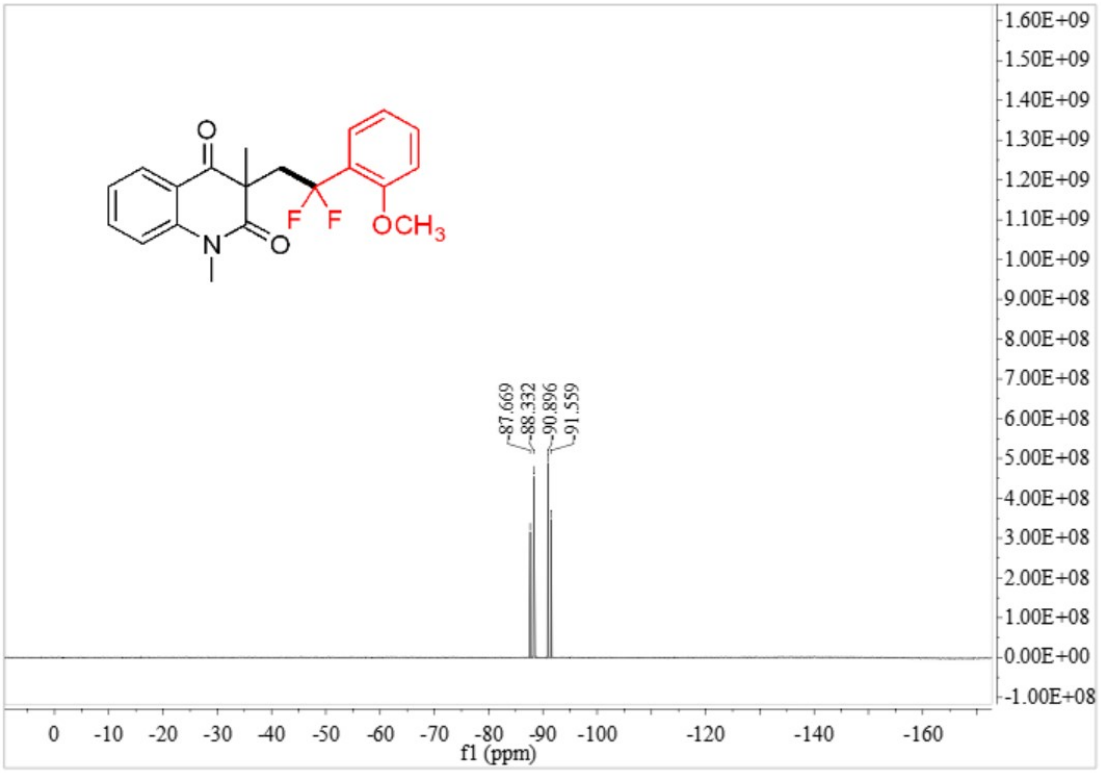
^{1}H NMR spectrum of **3o** (400 MHz, $CDCl_3$)



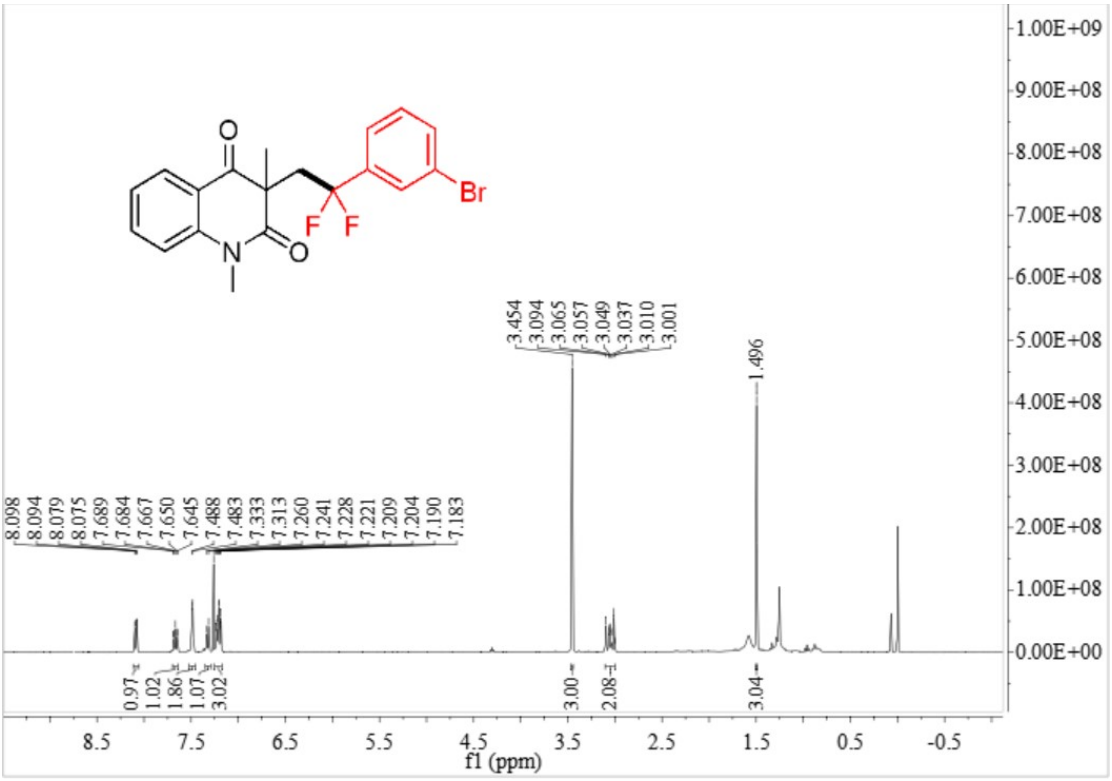
^{13}C NMR spectrum of **3o** (100 MHz, $CDCl_3$)



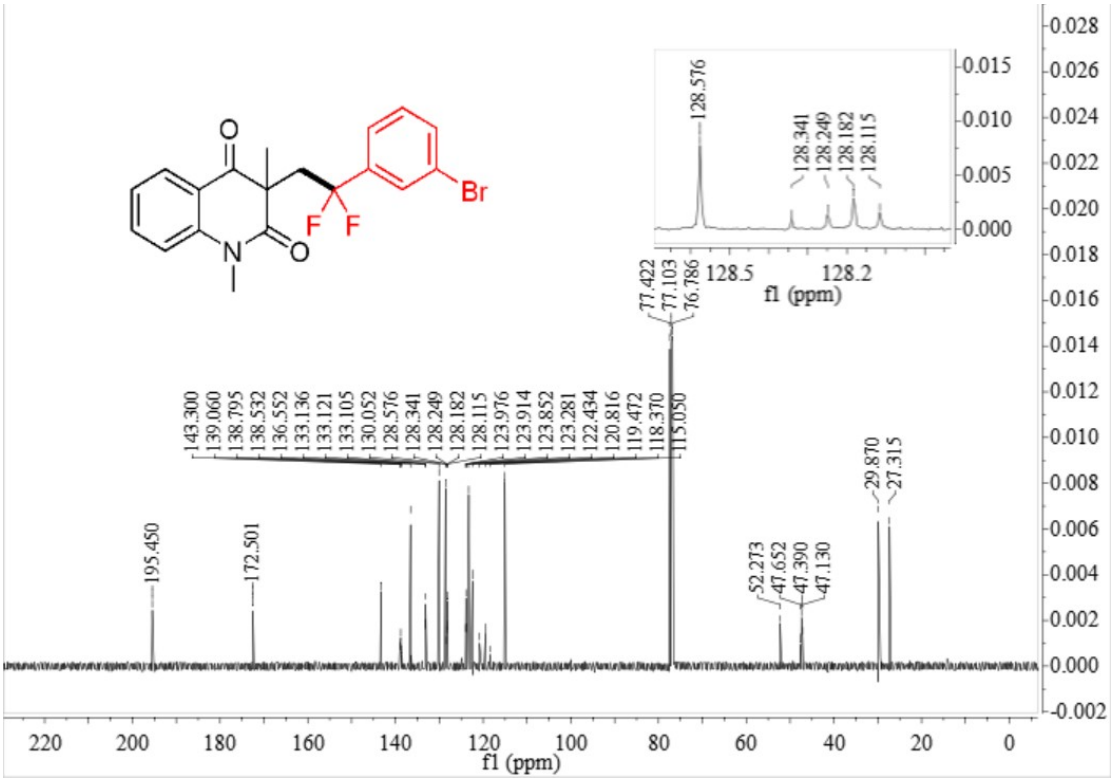
^{19}F NMR spectrum of **3o** (376 MHz, $CDCl_3$)



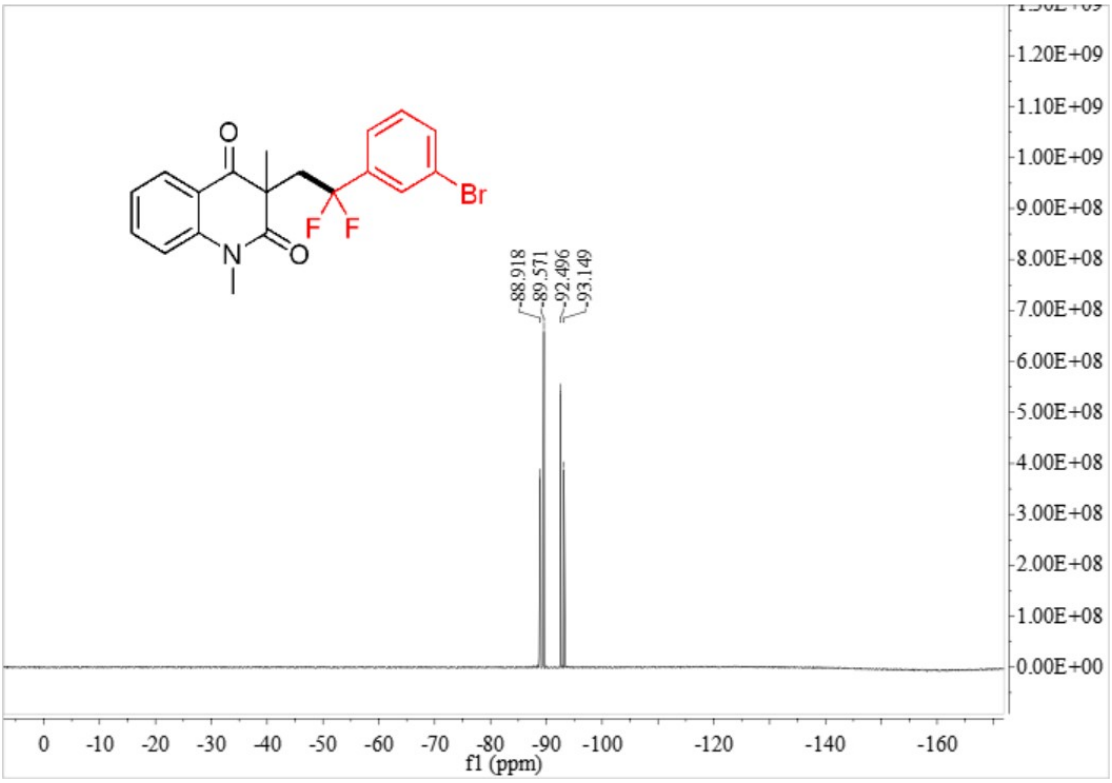
^{1}H NMR spectrum of **3p** (400 MHz, $CDCl_3$)



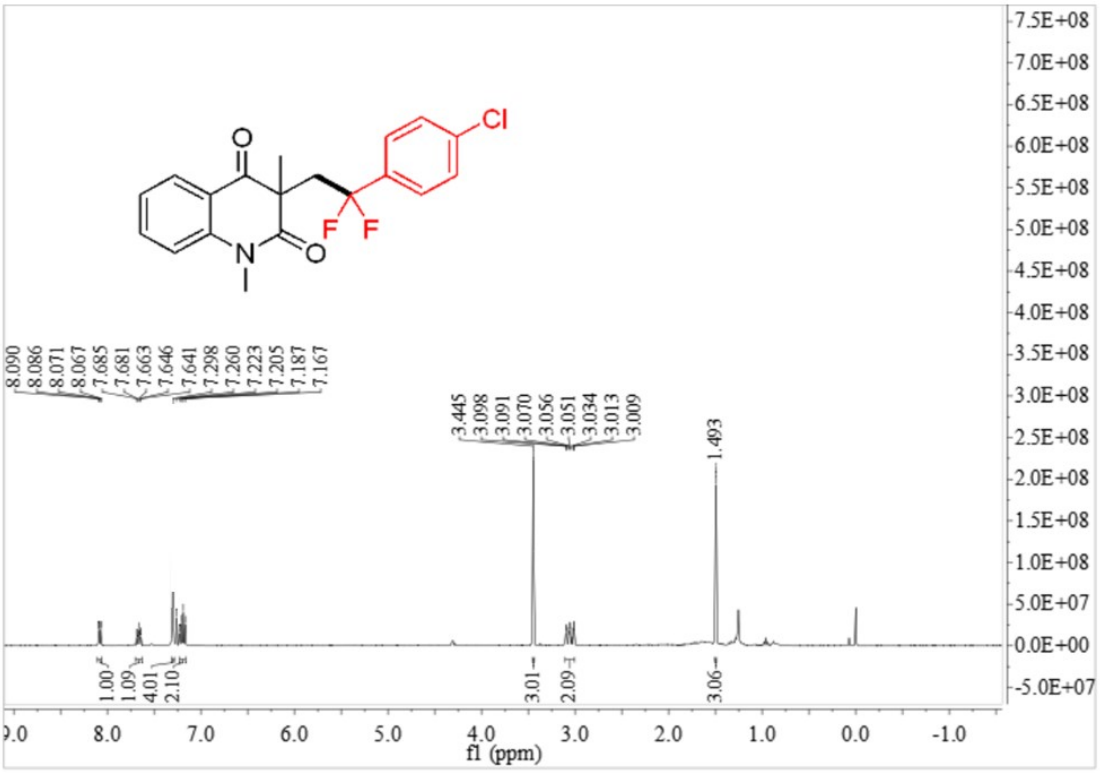
^{13}C NMR spectrum of **3p** (100 MHz, $CDCl_3$)



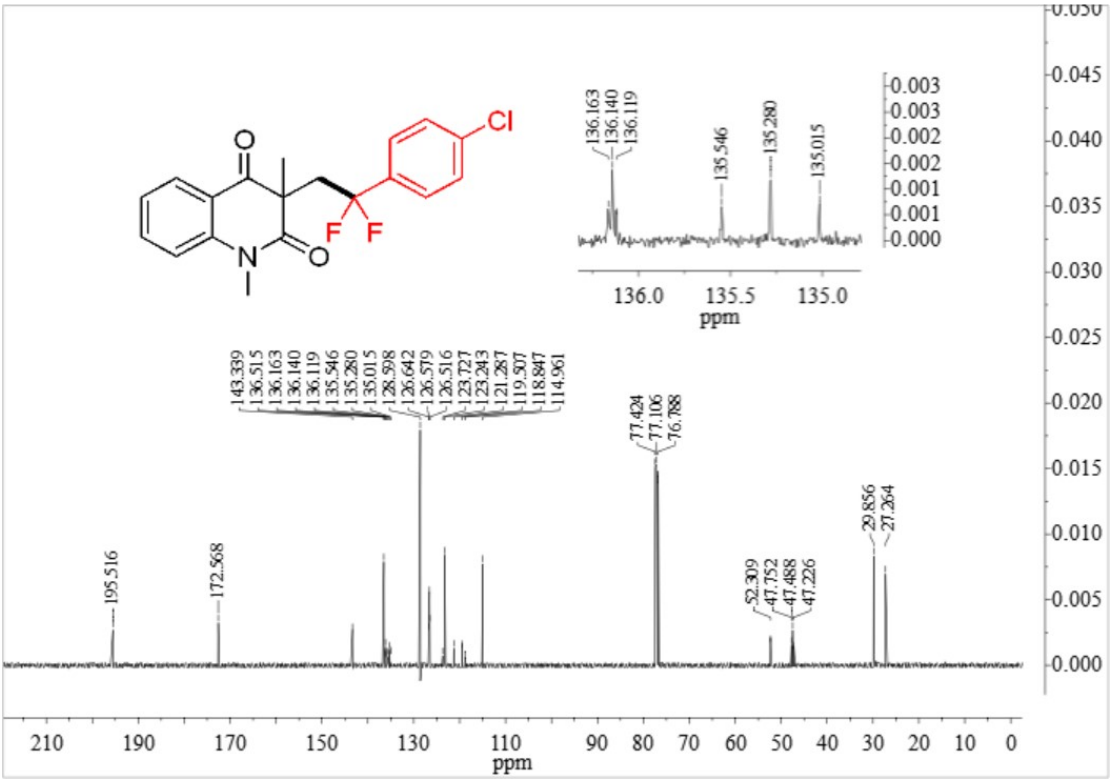
^{19}F NMR spectrum of **3p** (377 MHz, $CDCl_3$)



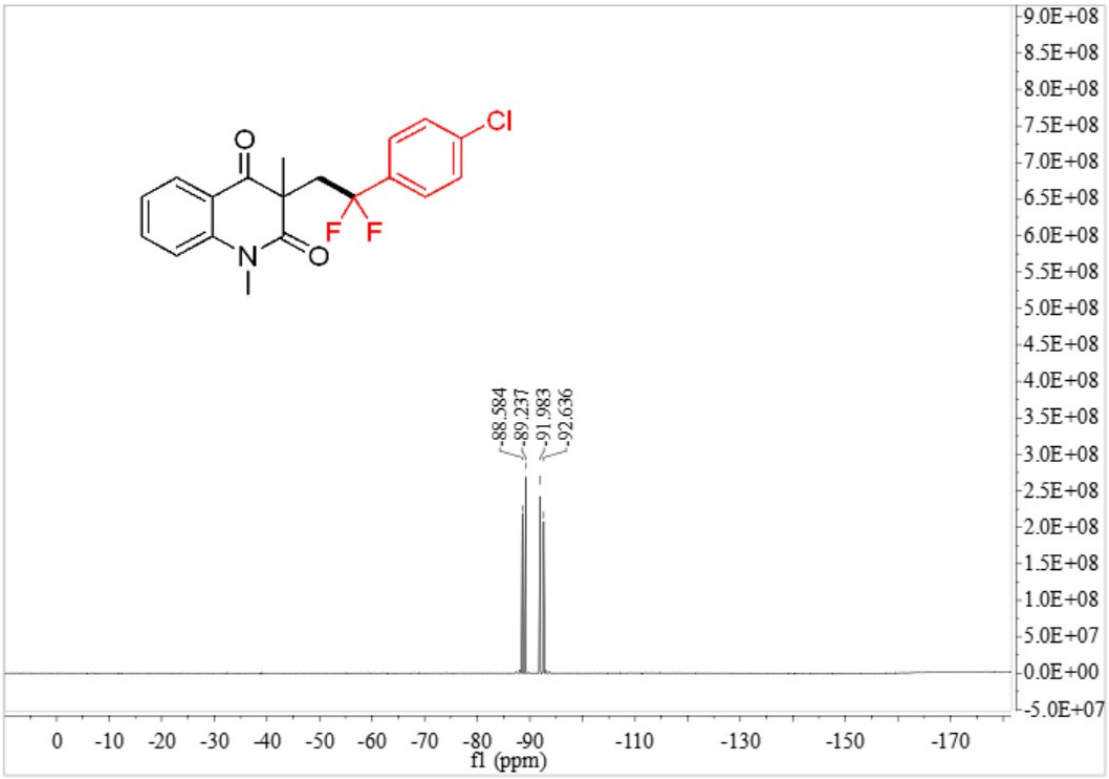
^{1}H NMR spectrum of **3q** (400 MHz, $CDCl_3$)



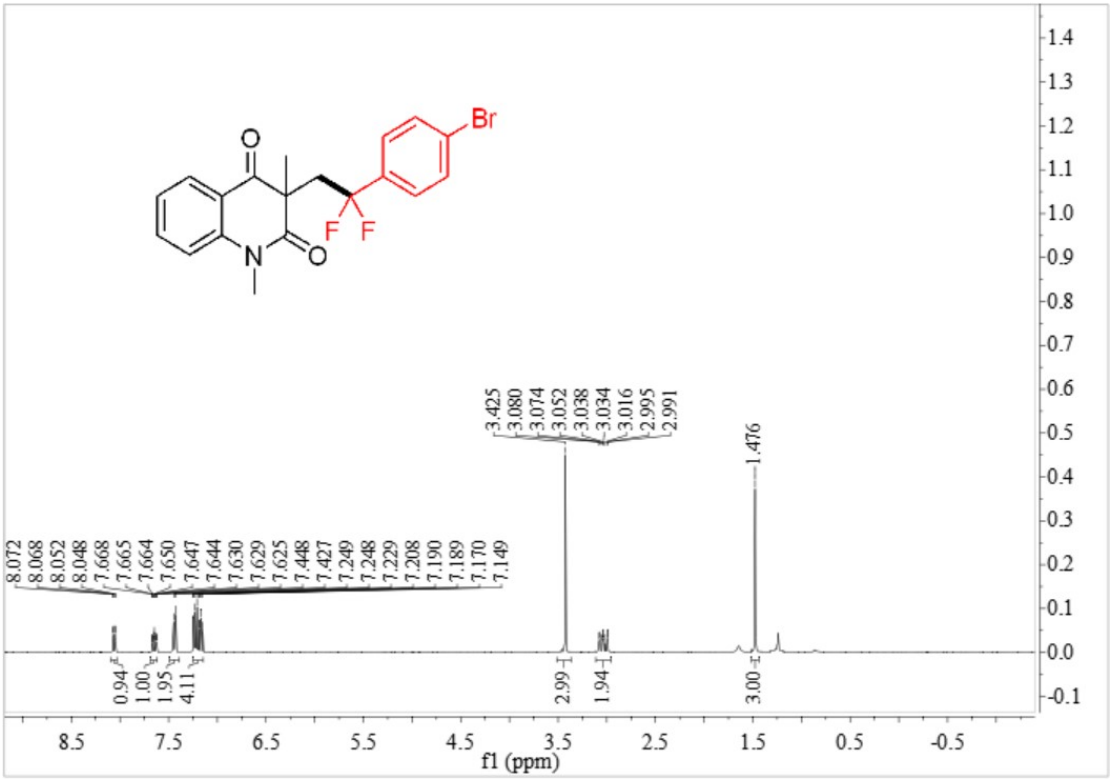
^{13}C NMR spectrum of **3q** (100 MHz, $CDCl_3$)



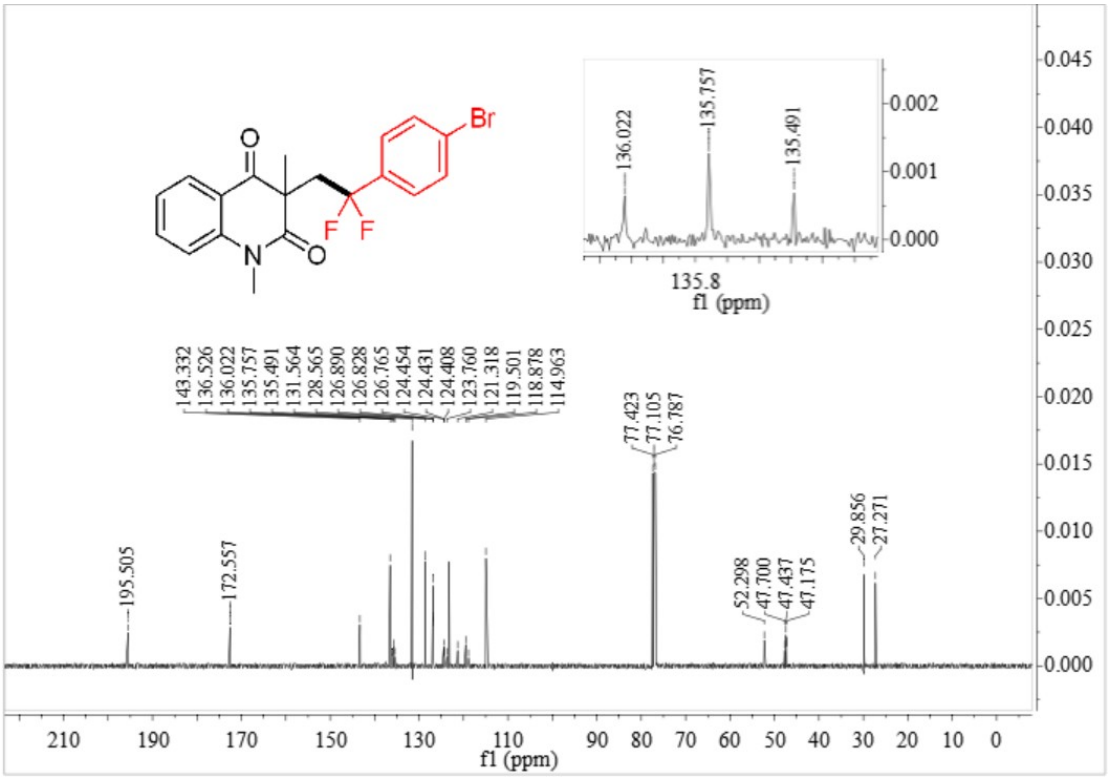
^{19}F NMR spectrum of **3q** (377 MHz, $CDCl_3$)



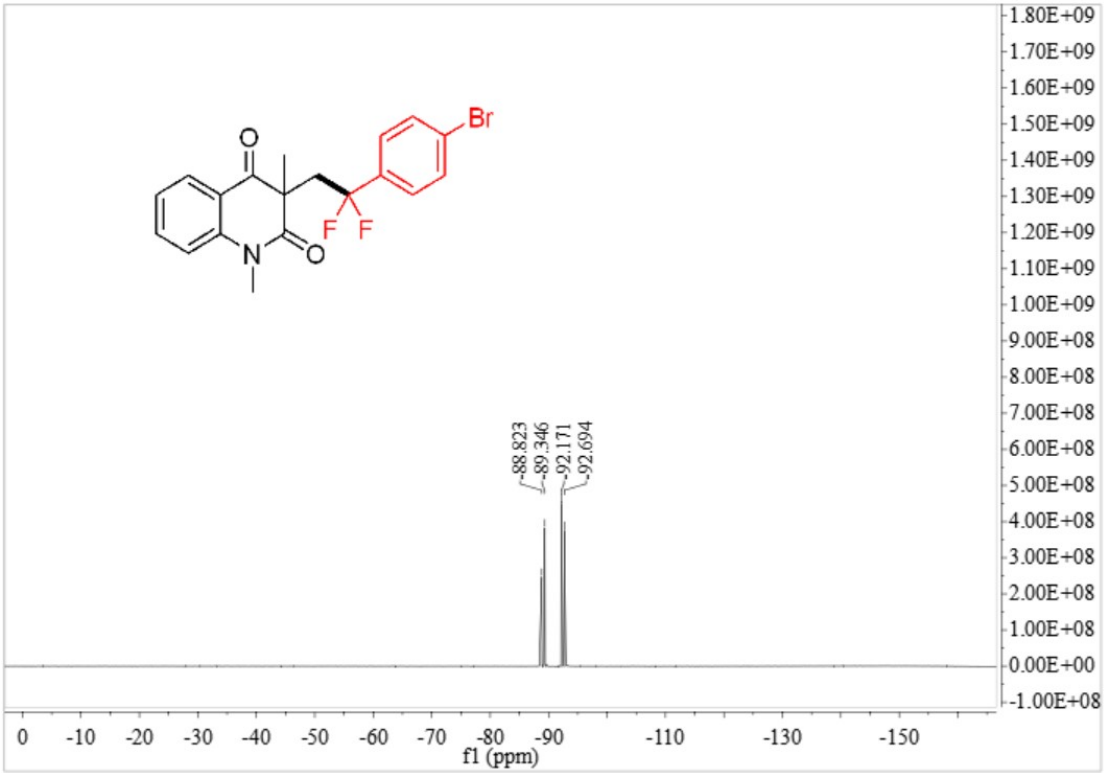
^{1}H NMR spectrum of **3r** (400 MHz, $CDCl_3$)



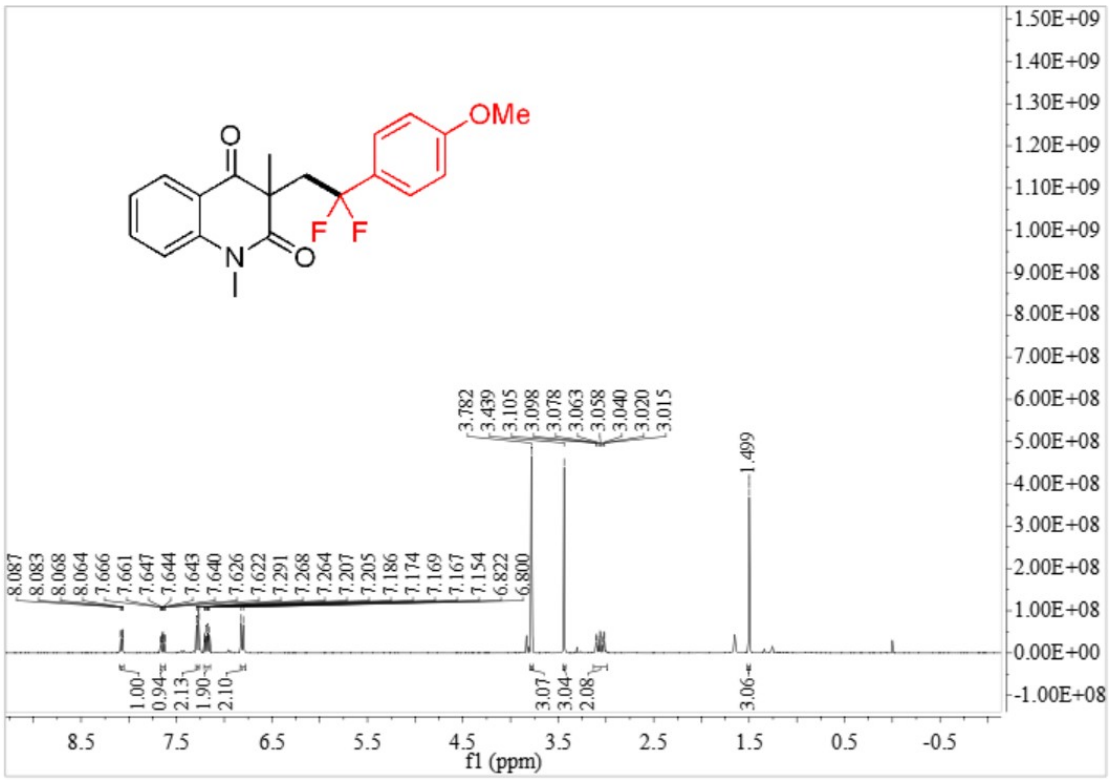
^{13}C NMR spectrum of **3r** (100 MHz, $CDCl_3$)



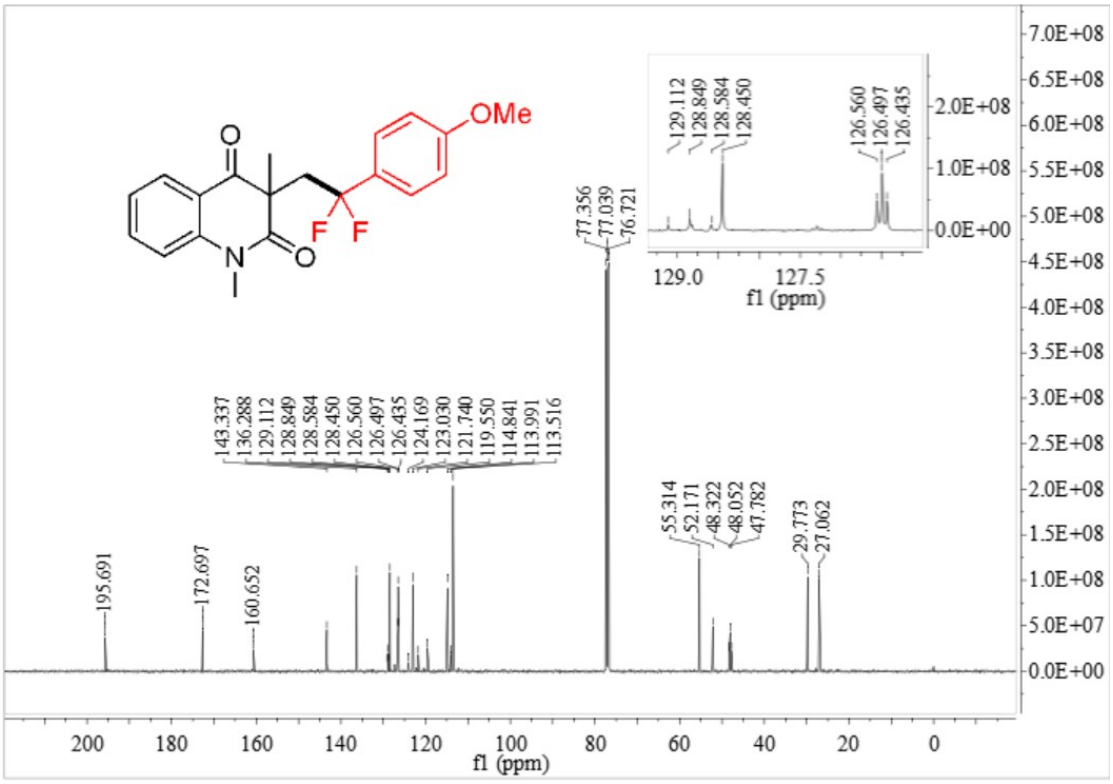
^{19}F NMR spectrum of **3r** (471 MHz, $CDCl_3$)



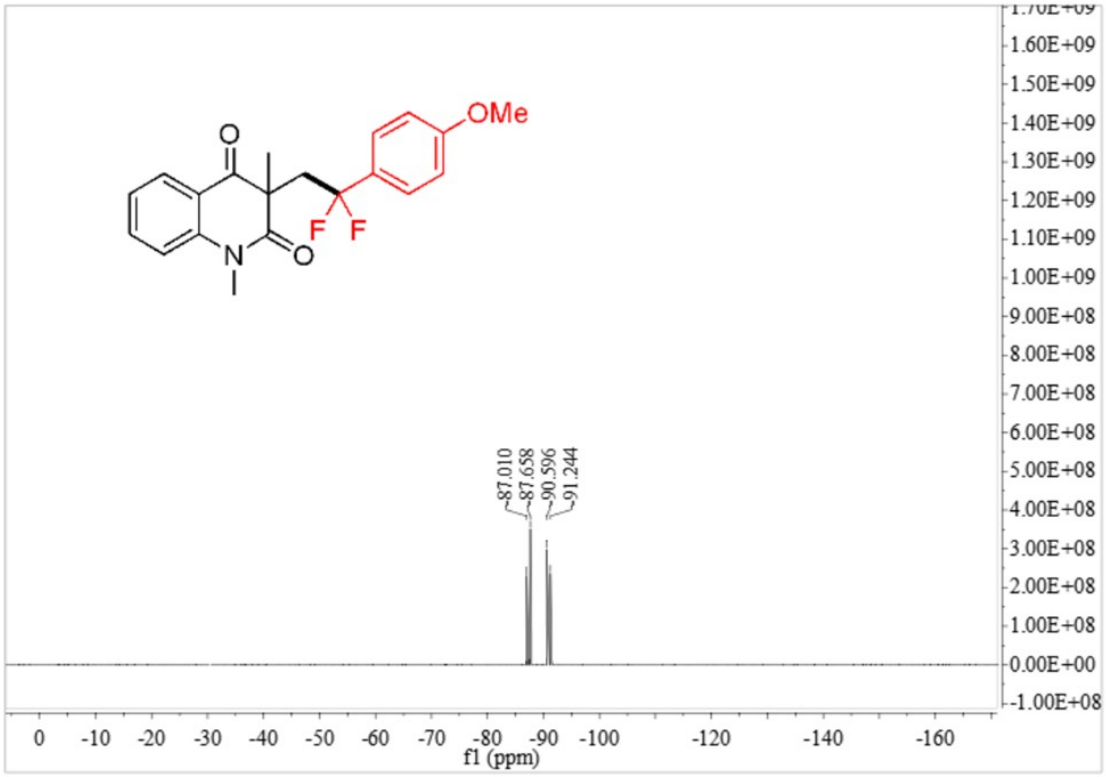
^{1}H NMR spectrum of **3s** (400 MHz, $CDCl_3$)



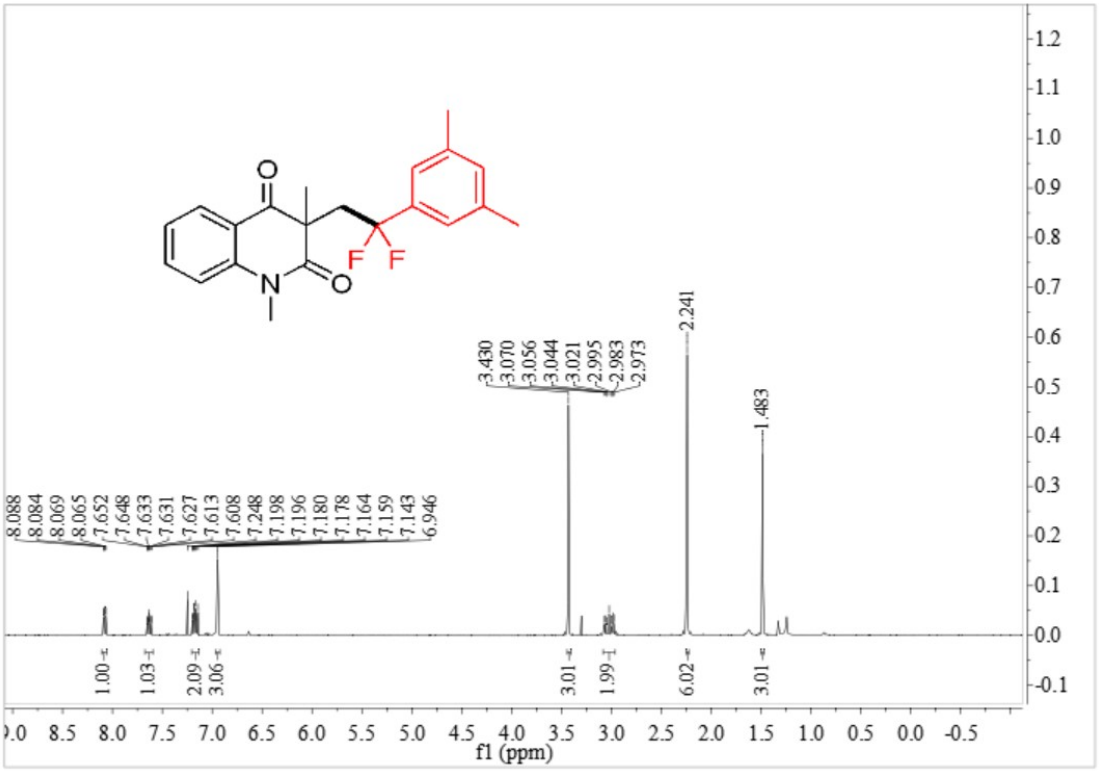
^{13}C NMR spectrum of **3s** (100 MHz, $CDCl_3$)



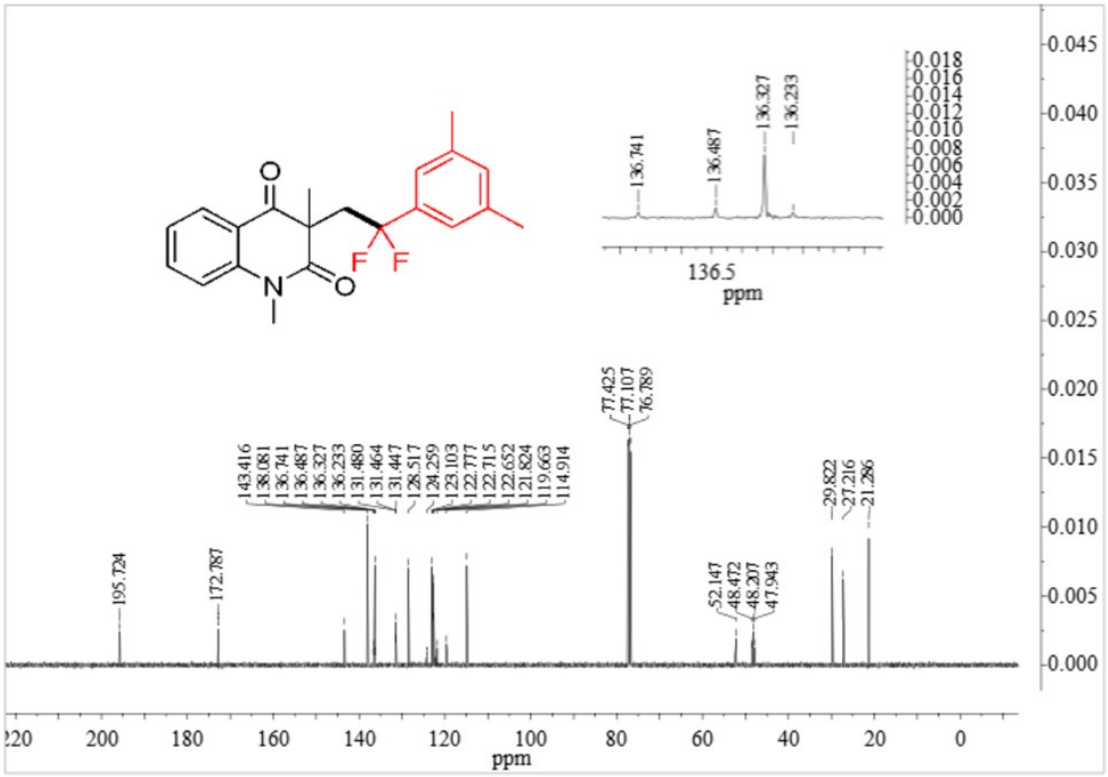
^{19}F NMR spectrum of **3s** (377 MHz, $CDCl_3$)



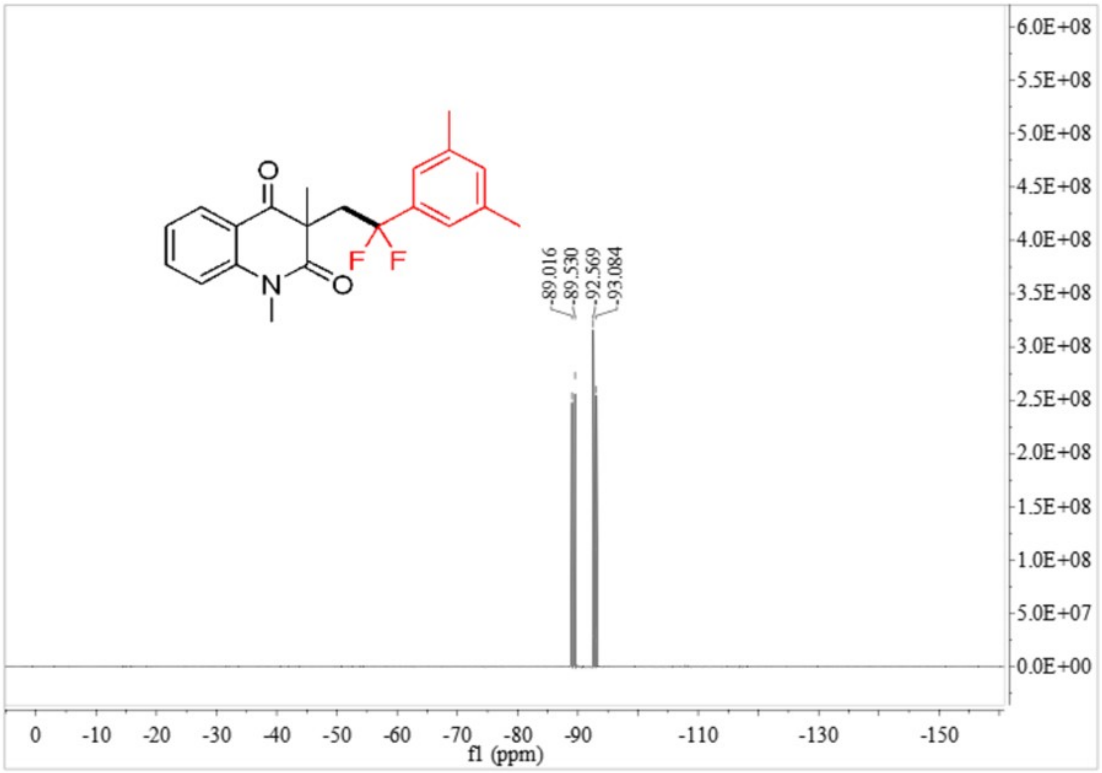
^{1}H NMR spectrum of **3t** (400 MHz, $CDCl_3$)



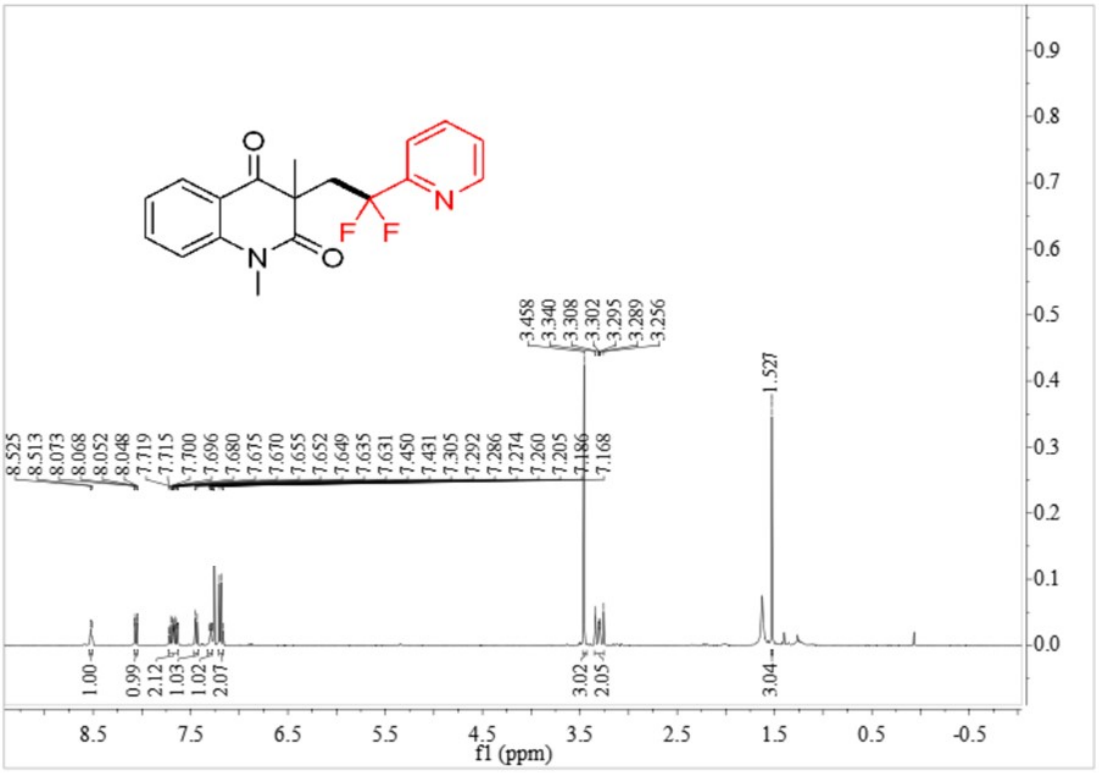
^{13}C NMR spectrum of **3t** (100 MHz, $CDCl_3$)



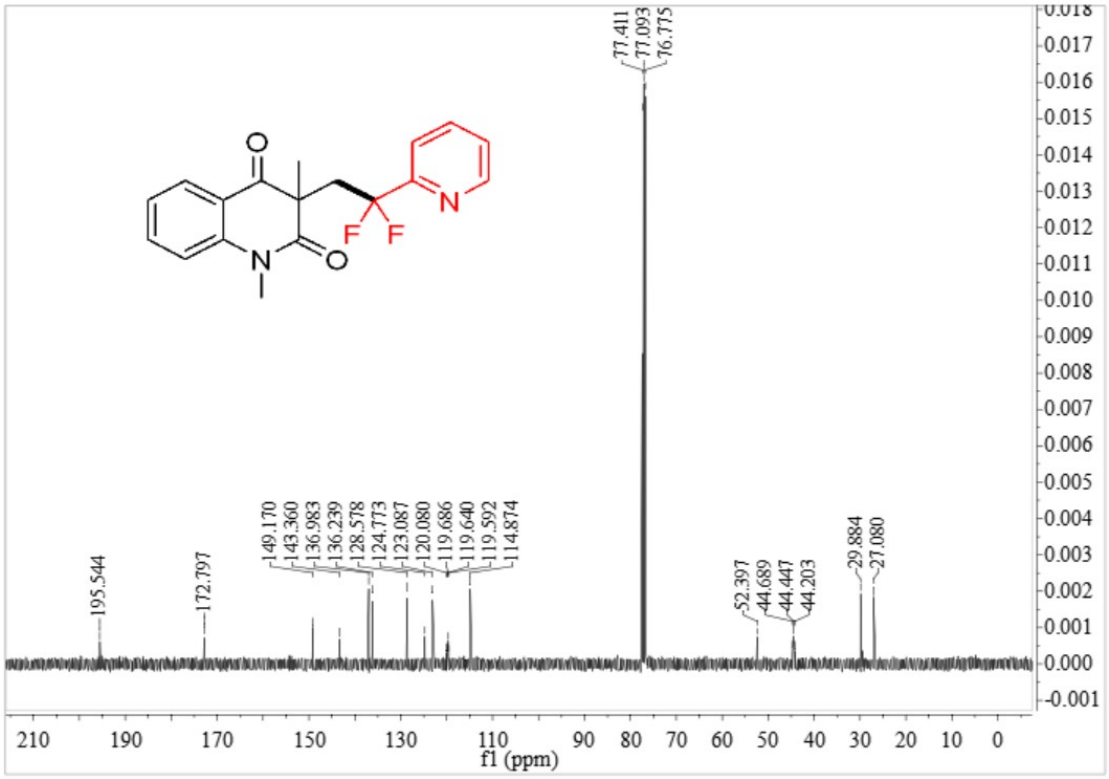
^{19}F NMR spectrum of **3t** (471 MHz, $CDCl_3$)



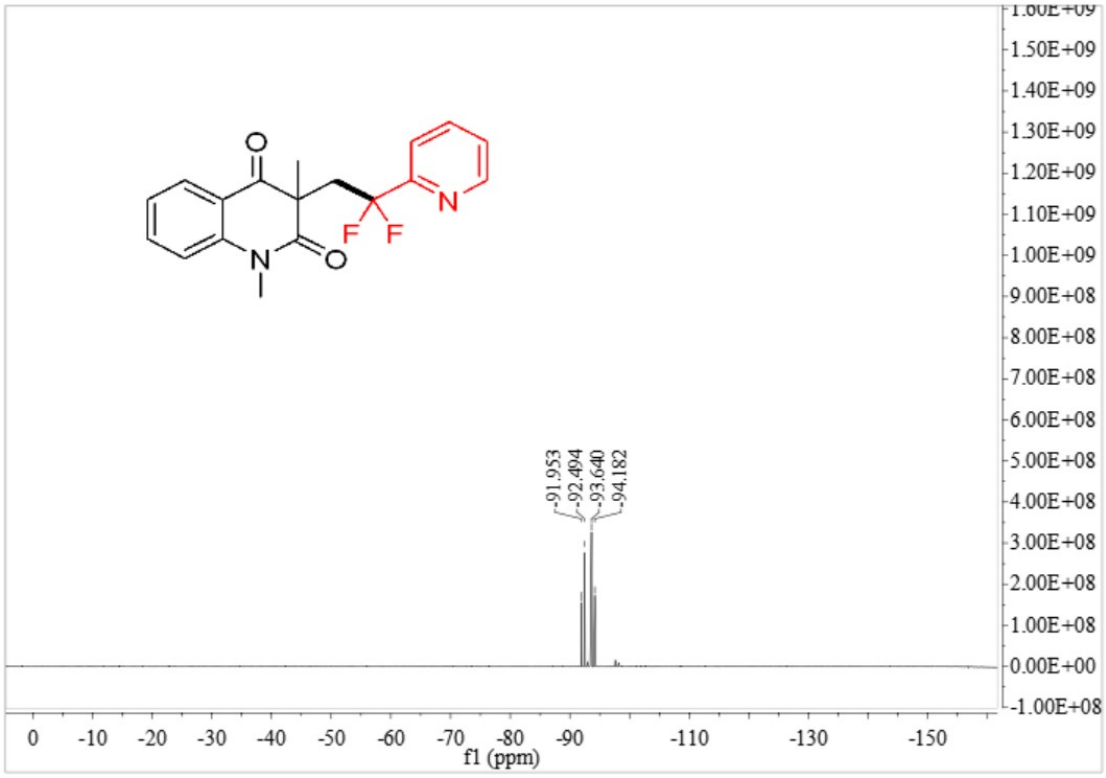
^{1}H NMR spectrum of **3u** (400 MHz, $CDCl_3$)



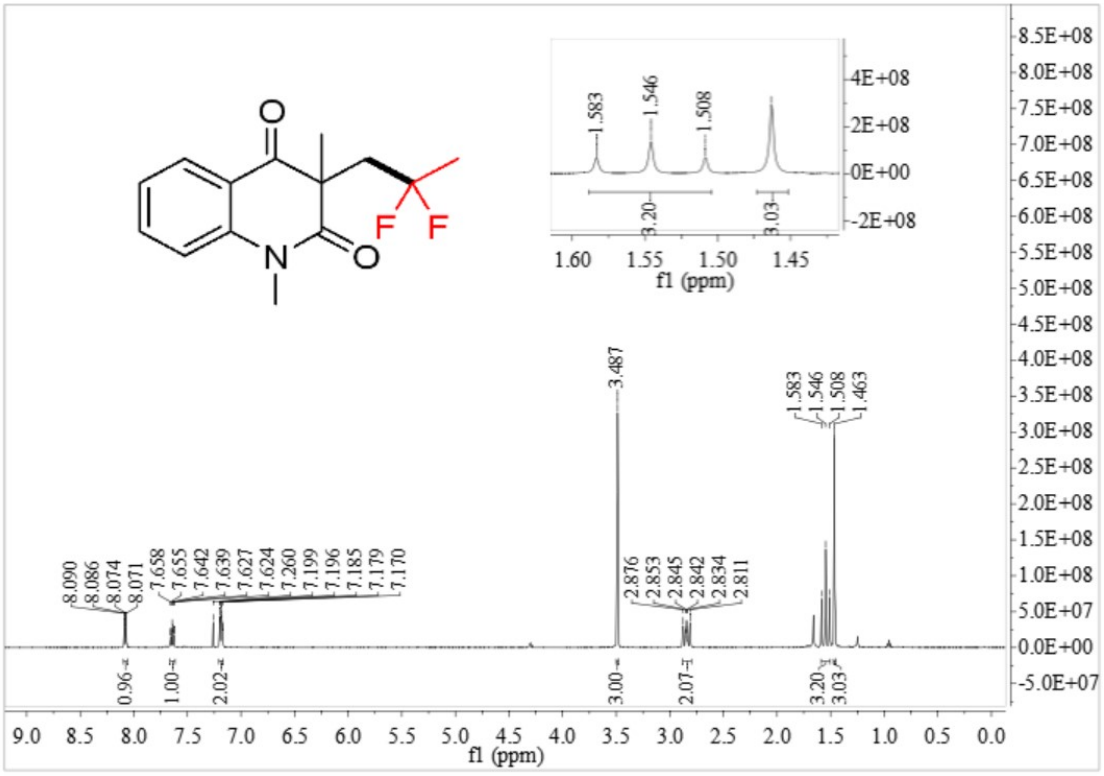
^{13}C NMR spectrum of **3u** (100 MHz, $CDCl_3$)



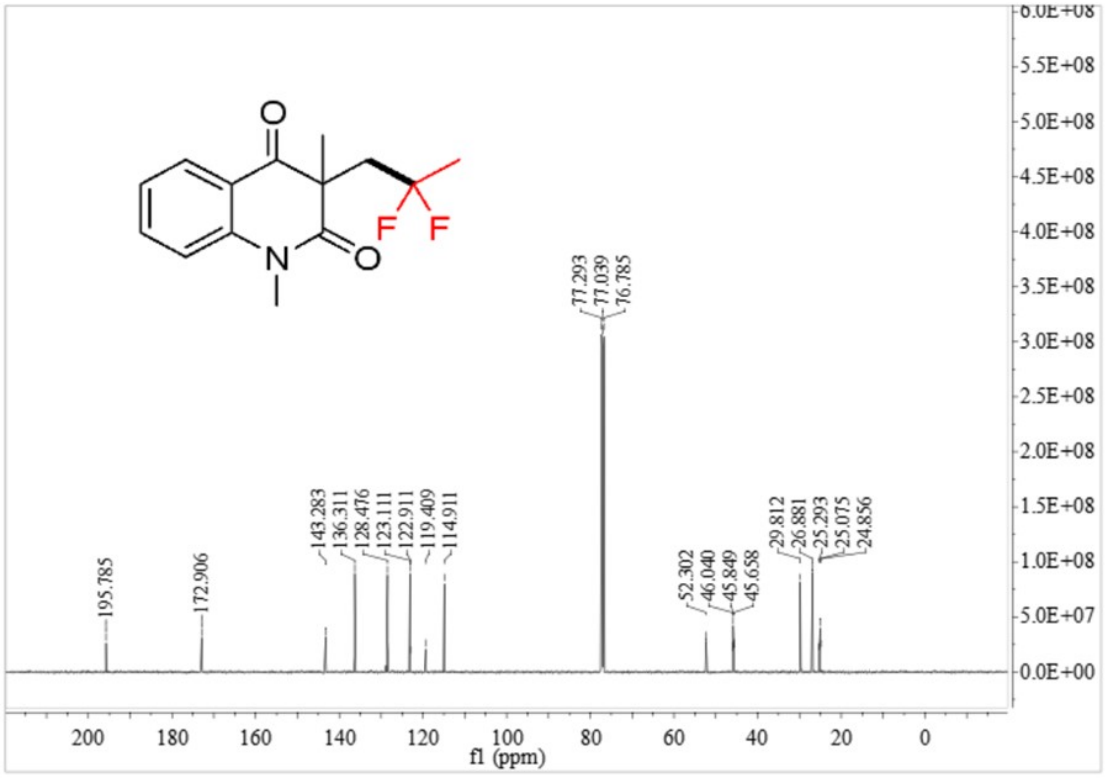
^{19}F NMR spectrum of **3u** (471 MHz, $CDCl_3$)



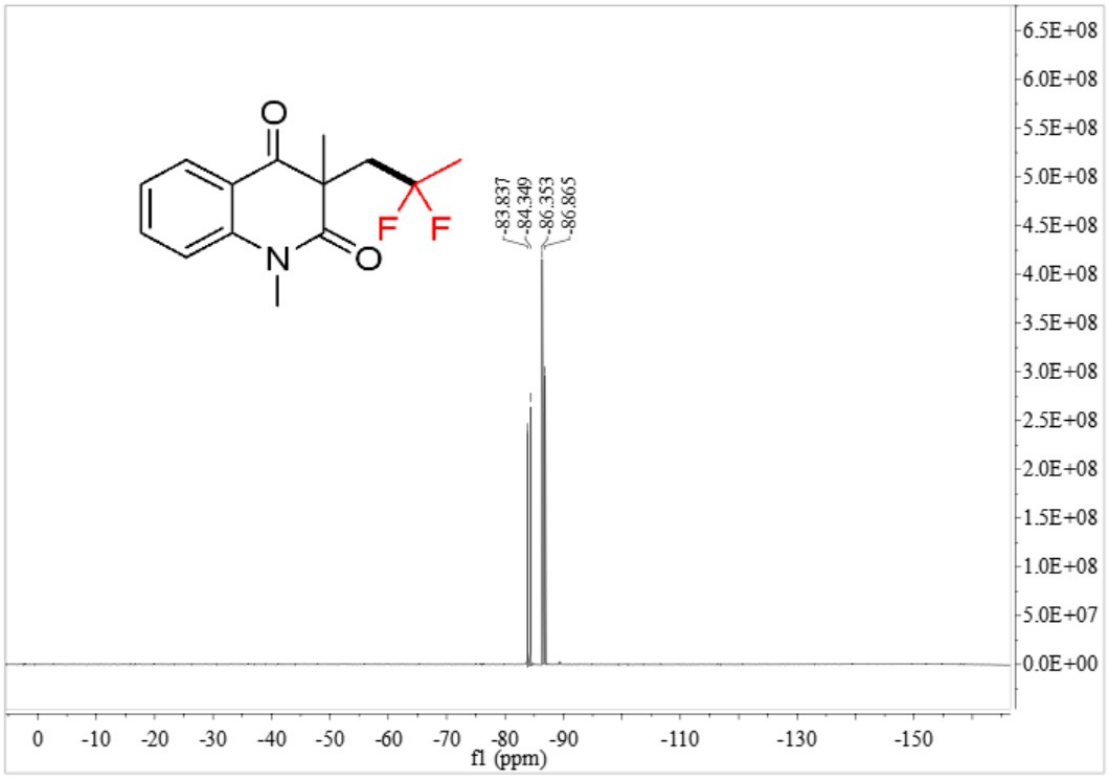
^{1}H NMR spectrum of **3v** (500 MHz, $CDCl_3$)



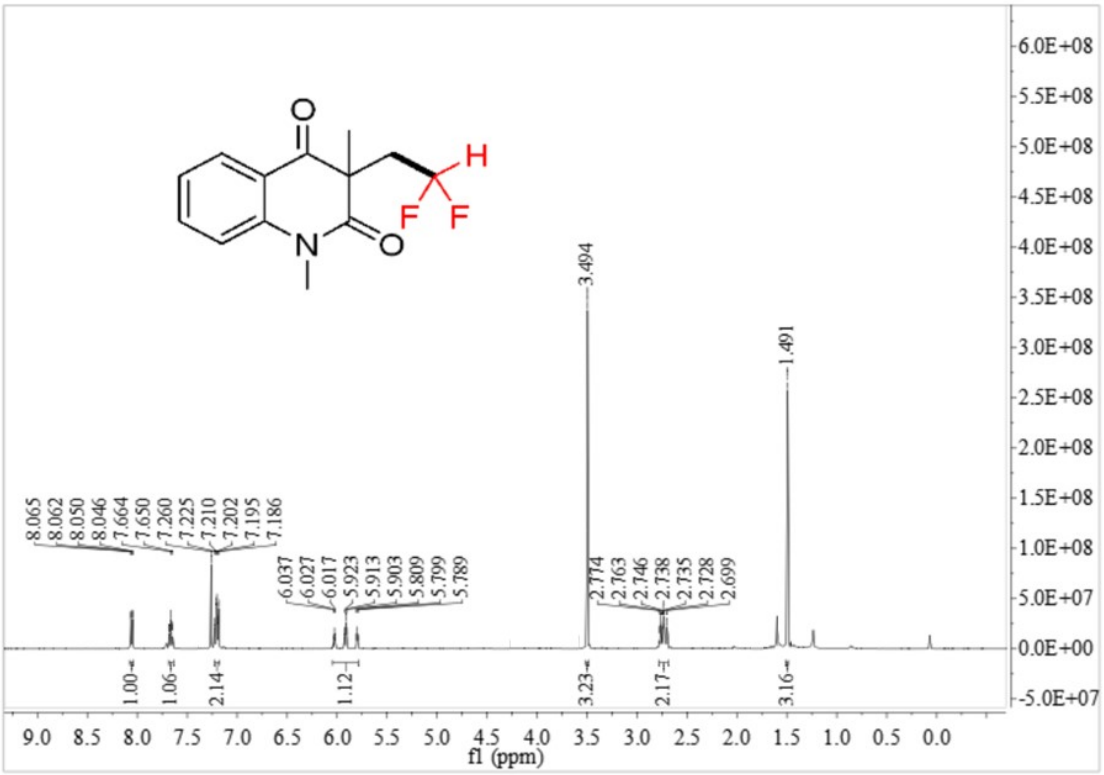
^{13}C NMR spectrum of **3v** (125 MHz, $CDCl_3$)



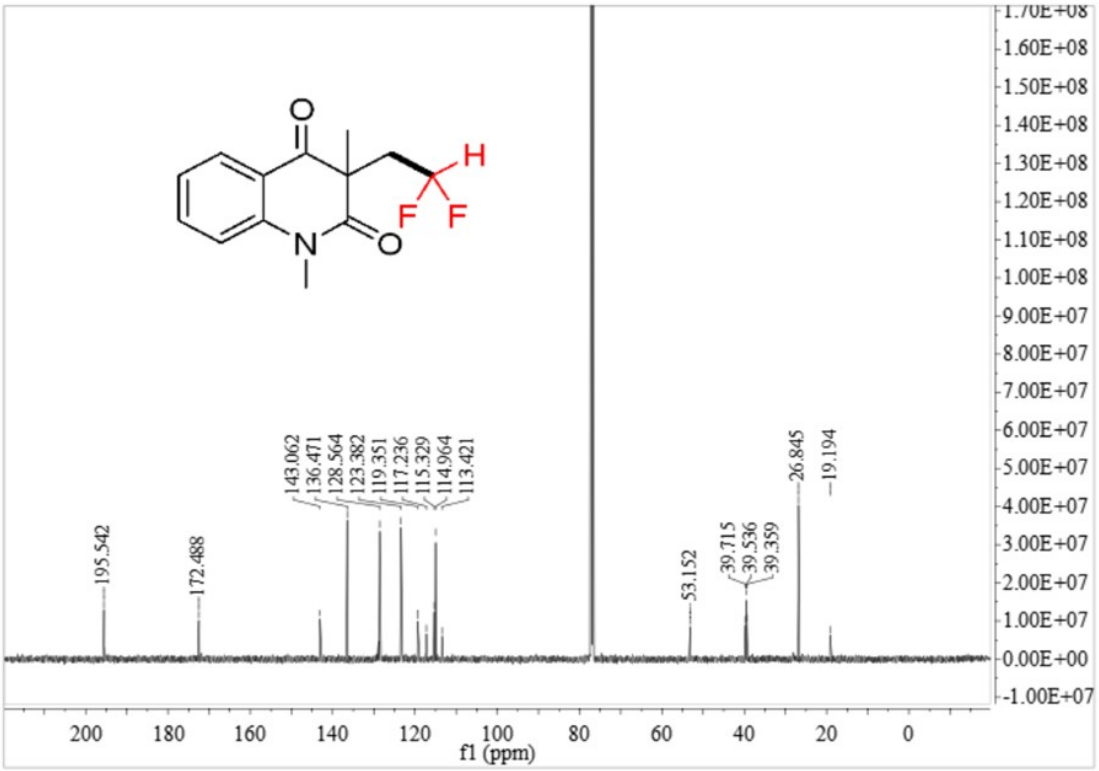
^{19}F NMR spectrum of **3v** (471 MHz, $CDCl_3$)



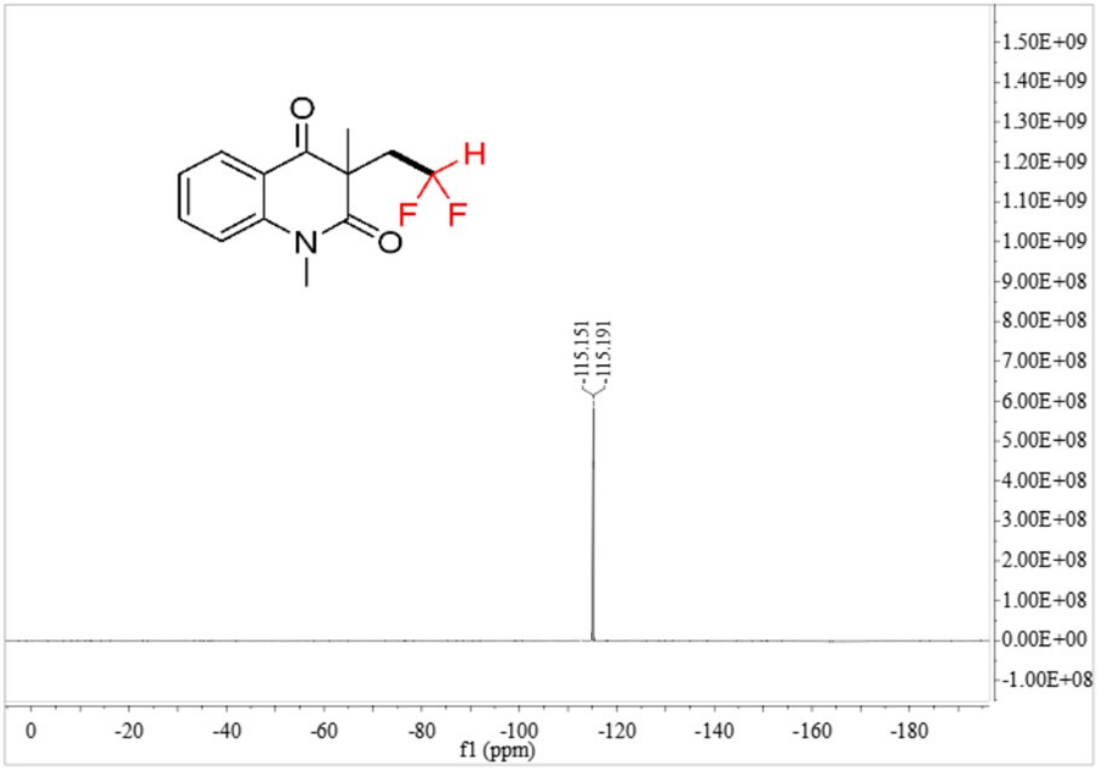
^{1}H NMR spectrum of **3w** (500 MHz, $CDCl_3$)



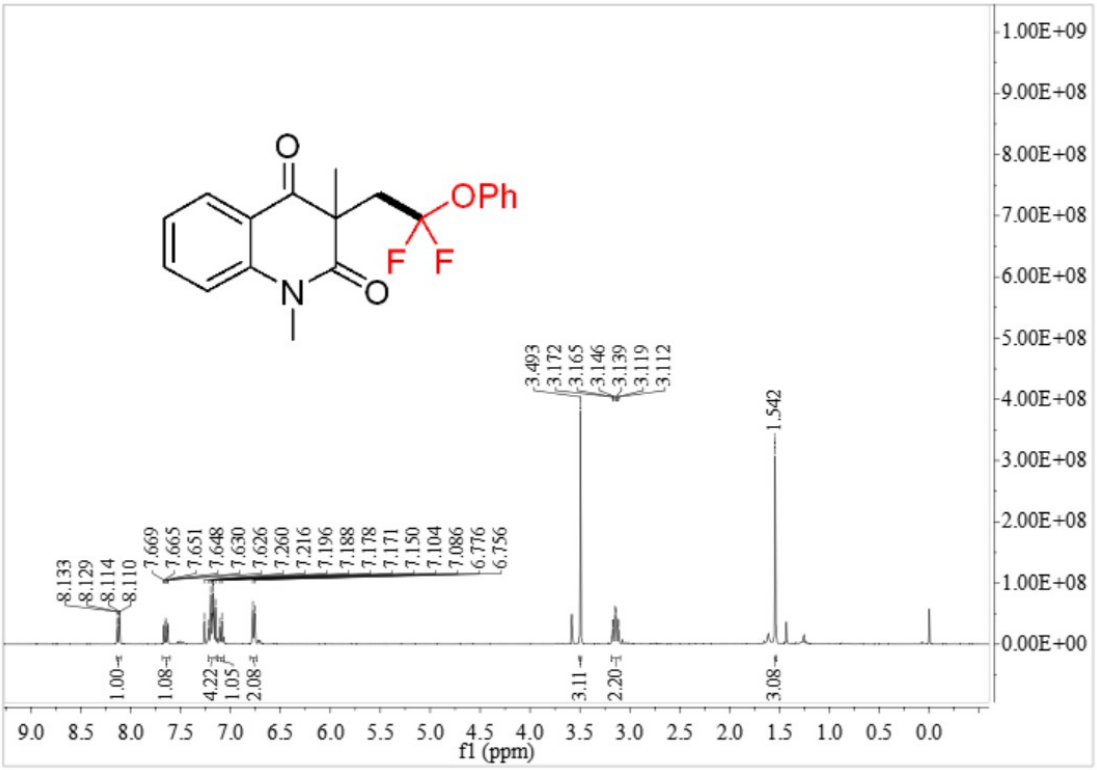
^{13}C NMR spectrum of **3w** (125 MHz, $CDCl_3$)



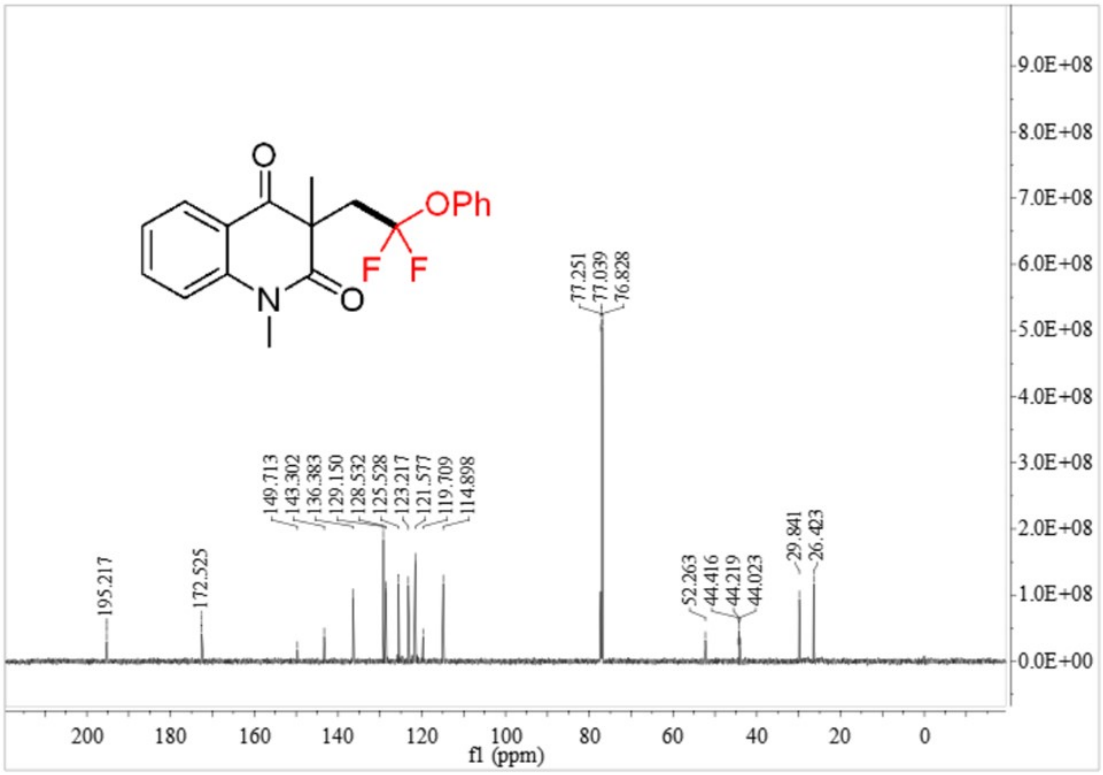
^{19}F NMR spectrum of **3w** (471 MHz, $CDCl_3$)



^{1}H NMR spectrum of **3x** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3x** (150 MHz, $CDCl_3$)



^{19}F NMR spectrum of **3x** (565 MHz, $CDCl_3$)