Supporting Information

Carboxylation of C(sp^2)−H bonds in quinolone derivatives with CO_2: facile synthesis of quinolone carboxylic acids

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Table of contents

1 General information

All reactions were set up using standard Schlenk techniques and carried out under a CO_2 atmosphere with dry solvents. Commercially available chemicals were obtained from Adamas-beta, Energy Chemical, Bidepharm, TCI or J&K Scientific and used as received unless otherwise stated. 4-hydroxyquinolin-2(*1H*)-ones need further purification by silica gel column chromatography or recrystallization if purity less than 98%. Anhydrous *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc), and Dimethyl sulfoxide (DMSO) were purchased from J&K Scientific. Potassium *tert*-butoxide (KO^tBu) was purchased from Sigma-Aldrich. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.2±0.03 mm using UV light as a visualizing agent.

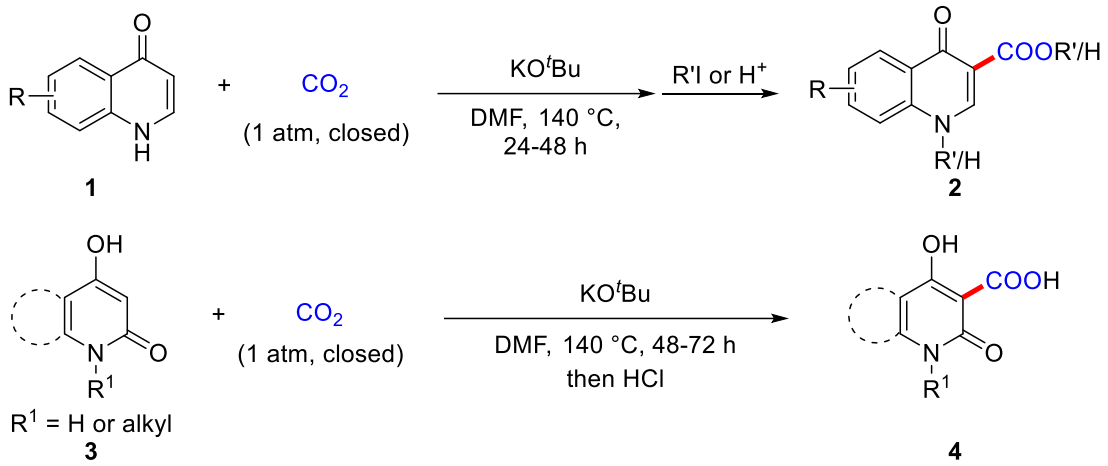
^1H NMR and ^{13}C NMR spectra were recorded on a Brüker Advance 400 or 600 spectrometer (^1H NMR: 400 MHz, ^{13}C: 101 or 151 MHz). Chemical shifts (δ) for ^1H and ^{13}C NMR spectra are given in ppm relative to TMS. The residual solvent signals were used as references for ^1H and ^{13}C NMR spectra and the chemical shifts converted to the TMS scale ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm, CD_3OD: δ H = 3.31 ppm, δ C = 49.00 ppm, DMSO-d_6: δ H = 2.50 ppm, δ C = 39.52 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

High-resolution mass spectra (HRMS) were recorded on a Shimadzu LCMS IT-TOF. ESI-MS were obtained on a Thermo-LTQ. TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was affected at 254 nm.

Human multiple myeloma cells line U266 and Human colorectal cancer cells line HCT116 were purchased from the Chinese Academy of Sciences (Shanghai, China).

2 General procedures

2.1 Experimental procedures



Procedure: To an oven-dried Schlenk (25 mL) tube equipped with a magnetic stir bar was charged with **1** or **3** (0.2 mmol), then transferred the tube to glovebox and added required KO^{t}Bu. The tube was sealed and removed from the glovebox, then evacuated and back-filled with CO_2 atmosphere for three times (*Note: During the initial evacuation and backfilling process, the tube was connected to the CO_2 line for at least 2 minutes to ensure that the tube's heat was released to room temperature*). Anhydrous DMF (4 mL or 6 mL) was added under CO_2 atmosphere and the tube was sealed at atmospheric pressure of CO_2 (1 atm). The reaction was stirred and heated at 140 °C for the indicated period of time.

Work-up Procedure A: The alkylated products require the sequential addition of Cs_2CO_3 (5 equiv.) and iodoalkane (5 equiv.) after the completion of the reaction. The mixture should then be heated at 80 °C for 2 h and subsequently cooled to room temperature. The crude reaction mixture was diluted with 10 mL EA. After adding 10 mL of H_2O, the mixture was extracted with EA ten times, and the combined organic phases were concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH 100/3 ~ 100/10) to give the alkylated products.

Work-up Procedure B: The alkylated products require the sequential addition of Cs_2CO_3 (5 equiv.) and iodoalkane (5 equiv.) after the completion of the reaction. The mixture should then be heated at 80 °C for 2 h and subsequently cooled to room temperature. The crude reaction mixture was concentrated under reduced pressure, and the residue was purified by reverse phase column chromatography (H_2O/MeOH 100/10

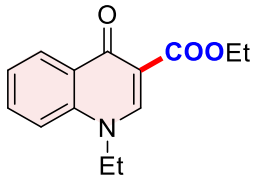
~ 100/40) using Biotage Isolera One® equipped with an Agela Technologies' Spherigel C_{18} column (25-35 μm, 100Å, 12 g).

Work-up Procedure C: Upon completion of the reaction, it was quenched by 10 mL 1 N HCl and stirred for 10 min. The reaction mixture was concentrated under reduced pressure, and the residue was purified by reverse phase column chromatography (H_2O/MeOH 100/10 ~ 100/40) using Biotage Isolera One® equipped with an Agela Technologies' Spherigel C_{18} column (25-35 μm, 100Å, 12 g).

Work-up Procedure D: Upon completion of the reaction, it was quenched with 10 mL 1 N HCl and stirred for 10 min. Then, the mixture was extracted by EA six times, and the combined organic phases were concentrated in vacuo, washed with 10 mL H_2O to remove residual salts, and then dried to yield the pure product without further purification.

Work-up Procedure E: Upon completion of the reaction, it was quenched with 10 mL 1 N HCl and stirred for 10 min. The mixture was then extracted with EA six times, and the combined organic phases were concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH 100/3).

Ethyl 1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (2a)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a white solid (43.1 mg, 87%).

R_f (DCM/MeOH 10:1): 0.6.

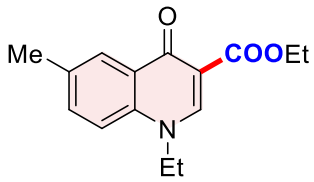
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 – 8.47 (m, 2H), 7.68 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6, 166.1, 148.8, 138.7, 132.8, 129.3, 128.2, 125.2, 115.8, 110.9, 61.1, 49.1, 14.7, 14.6.

HRMS (ESI+): calculated m/z for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1125, found 246.1130.

The spectra data was matched with the reported literature.[4]

Ethyl 1-ethyl-6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (2b)



Following **General Procedure B**, product was purified by reverse phase column to afford a white solid (47.1 mg, 91%).

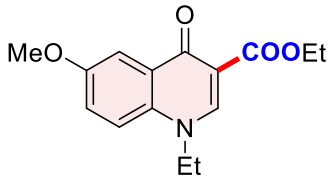
R_f (DCM/MeOH 10:1): 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.34 – 8.29 (m, 1H), 7.48 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.22 (q, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 166.2, 148.2, 136.7, 135.2, 133.9, 129.3, 127.7, 115.5, 110.8, 60.9, 48.9, 21.1, 14.7, 14.6.

HRMS (ESI+): calculated m/z for $C_{15}H_{17}NNaO_3$ $[M+Na]^+$ 282.1101, found 282.1104.

Ethyl 1-ethyl-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (2c)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a white solid (44.6 mg, 81%).

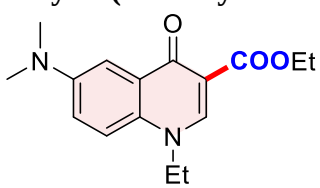
R_f (DCM/MeOH 20:1): 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.97 (d, *J* = 3.1 Hz, 1H), 7.41 (d, *J* = 9.3 Hz, 1H), 7.29 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 1.54 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 166.3, 157.3, 147.4, 133.0, 130.9, 122.8, 117.3, 110.1, 107.7, 60.9, 55.9, 49.1, 14.8, 14.5.

HRMS (ESI+): calculated m/z for $C_{15}H_{18}NO_4$ $[M+H]^+$ 276.1230, found 276.1237.

Ethyl 6-(dimethylamino)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (2d)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a yellow solid (48.4 mg, 84%).

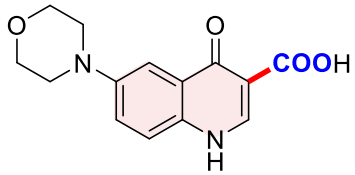
R_f (DCM/MeOH 10:1): 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.69 (s, 1H), 7.33 (d, *J* = 9.1 Hz, 1H), 7.09 (d, *J* = 9.3 Hz, 1H), 4.36 (q, *J* = 7.7, 7.2 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.01 (s, 6H), 1.48 (t, *J* = 7.5 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 166.7, 148.1, 146.4, 130.5, 129.8, 118.4, 116.7, 109.0, 107.9, 60.7, 48.9, 40.6, 14.8, 14.5.

HRMS (ESI+): calculated m/z for $C_{16}H_{21}N_2O_3$ $[M+H]^+$ 289.1547, found 289.1540.

6-Morpholino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2e)



Following **General Procedure C**, product was purified by reverse phase column to afford a yellow solid (43.0 mg, 78%).

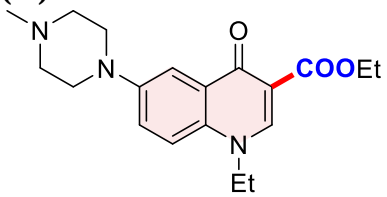
R_f (DCM/MeOH 10:1): 0.4.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.33 (s, 1H), 8.73 (s, 1H), 7.74 – 7.64 (m, 2H), 7.50 (d, *J* = 2.4 Hz, 1H), 3.81 – 3.74 (m, 4H), 3.26 – 3.19 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 177.6, 167.0, 149.4, 142.7, 133.0, 125.5, 123.9, 120.7, 106.7, 106.0, 66.0, 48.1.

HRMS (ESI+): calculated m/z for $C_{14}H_{15}N_2O_4$ $[M+H]^+$ 275.1026, found 275.1029.

Ethyl 1-ethyl-6-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (2f)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a yellow solid (46.0 mg, 67%).

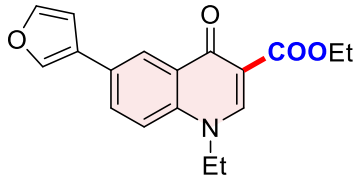
R_f (DCM/MeOH 10:1): 0.3.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (s, 1H), 7.69 (d, *J* = 9.4 Hz, 1H), 7.60 (d, *J* = 3.0 Hz, 1H), 7.51 (dd, *J* = 9.3, 3.0 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.26 – 3.19 (m, 4H), 2.50 – 2.45 (m, 4H), 2.23 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 172.5, 164.9, 148.2, 147.1, 131.5, 129.4, 122.0, 118.2, 108.9, 108.6, 59.5, 54.4, 47.9, 47.9, 45.8, 14.6, 14.4.

HRMS (ESI+): calculated m/z for $C_{19}H_{26}N_3O_3$ $[M+H]^+$ 344.1969, found 344.1973.

Ethyl 1-ethyl-6-(furan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (2g)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford an off-white solid (45.5 mg, 73%).

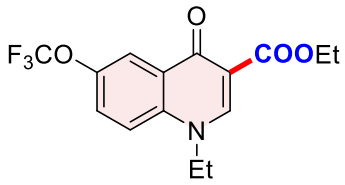
R_f (DCM/MeOH 10:1): 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.45 (s, 1H), 7.83 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.50 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 6.80 (s, 1H), 4.39 (q, *J* = 6.8 Hz, 2H), 4.24 (q, *J* = 7.3 Hz, 2H), 1.54 (t, *J* = 7.2 Hz, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 166.1, 148.3, 144.2, 139.3, 137.5, 130.2, 129.7, 129.6, 125.3, 124.5, 116.3, 111.2, 108.8, 61.0, 49.0, 14.7, 14.6.

HRMS (ESI+): calculated m/z for $C_{18}H_{18}NO_4$ $[M+H]^+$ 312.1230, found 312.1232.

Ethyl 1-ethyl-4-oxo-6-(trifluoromethoxy)-1,4-dihydroquinoline-3-carboxylate (2h)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a light brown solid (40.2 mg, 61%).

R_f (DCM/MeOH 20:1): 0.7.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.37 (s, 1H), 7.53 – 7.49 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.27 (q, *J* = 7.3 Hz, 2H), 1.55 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

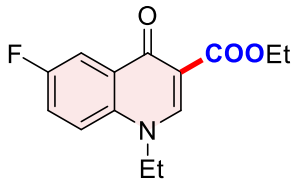
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 165.7, 148.9, 146.4, 137.1, 130.7, 125.9, 120.6 (q, *J* = 257 Hz), 119.6, 117.7, 111.4, 61.2, 49.3, 14.6, 14.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -58.06.

HRMS (ESI+): calculated m/z for $C_{15}H_{14}F_3NNaO_4$ $[M+Na]^+$ 352.0767, found 352.0778.

The spectra data was matched with the reported literature.[5]

Ethyl 1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (2i)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a white solid (35.7 mg, 72%).

R_f (DCM/MeOH 10:1): 0.6.

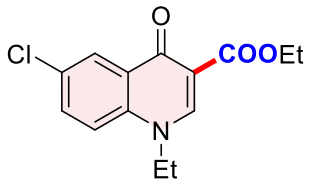
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.12 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.45 (dd, *J* = 9.3, 4.2 Hz, 1H), 7.43 – 7.33 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.3 Hz, 2H), 1.52 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (d, *J* = 2.3 Hz), 165.7, 160.0 (d, *J* = 247.7 Hz), 148.4 (d, *J* = 3.4 Hz), 135.1 (d, *J* = 1.8 Hz), 131.2 (d, *J* = 6.7 Hz), 121.0 (d, *J* = 25.2 Hz), 118.0, 113.1 (d, *J* = 23.0 Hz), 110.4, 61.0, 49.3, 14.6, 14.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.36.

HRMS (ESI+): calculated m/z for $C_{14}H_{15}FNO_3$ $[M+H]^+$ 264.1030, found 264.1033.

Ethyl 1-ethyl-6-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (2j)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a white solid (41.1 mg, 74%).

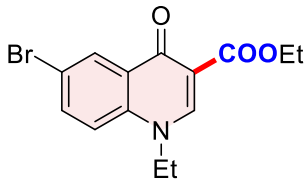
R_f (DCM/MeOH 10:1): 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 – 8.40 (m, 2H), 7.59 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.53 (t, *J* = 7.3 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2, 165.6, 148.6, 137.2, 132.9, 131.5, 130.5, 127.6, 117.4, 111.4, 61.1, 49.2, 14.6, 14.6.

HRMS (ESI+): calculated m/z for $C_{14}H_{15}ClNO_3$ $[M+H]^+$ 280.0735, found 280.0738.

Ethyl 1-ethyl-6-bromo-4-oxo-1,4-dihydroquinoline-3-carboxylate (2k)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a white solid (45.2 mg, 70%).

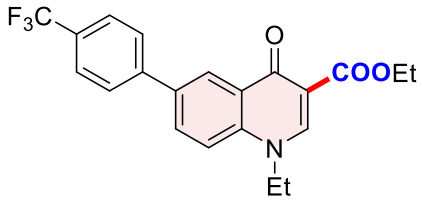
R_f (DCM/MeOH 10:1): 0.7.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 2.4 Hz, 1H), 8.47 (s, 1H), 7.75 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.3 Hz, 2H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 165.5, 148.7, 137.6, 135.6, 130.8, 130.7, 119.1, 117.6, 111.6, 61.1, 49.1, 14.6, 14.5.

HRMS (ESI+): calculated m/z for $C_{14}H_{14}BrNaNO_3$ $[M+Na]^+$ 346.0049, found 346.0058.

Ethyl 1-ethyl-4-oxo-6-(4-(trifluoromethyl)phenyl)-1,4-dihydroquinoline-3-carboxylate (2l)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a white solid (54.1mg, 70%).

R_f (DCM/MeOH 10:1): 0.6.

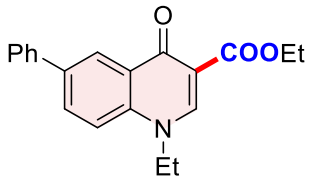
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.54 (d, *J* = 2.3 Hz, 1H), 8.16 (dd, *J* = 8.9, 2.4 Hz, 1H), 8.02 – 7.91 (m, 4H), 7.86 (d, *J* = 8.3 Hz, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.23 (d, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 173.0, 164.7, 149.3, 142.8, 138.7, 135.0, 131.5, 128.8, 128.3 (q, *J* = 31.9 Hz), 127.7, 126.2 (q, *J* = 3.7 Hz), 124.6, 124.4 (q, *J* = 271.7 Hz), 118.5, 110.6, 60.0, 48.3, 14.6, 14.4.

^{19}F NMR (376 MHz, DMSO-d_6): δ -60.95.

HRMS (ESI+): calculated m/z for $C_{21}H_{19}F_3NO_3$ $[M+H]^+$ 390.1312, found 390.1314.

Ethyl 1-ethyl-4-oxo-6-phenyl-1,4-dihydroquinoline-3-carboxylate (2m)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a white solid (57.8 mg, 90%).

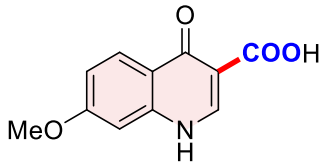
R_f (DCM/MeOH 20:1): 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 2.3 Hz, 1H), 8.46 (s, 1H), 7.88 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.52 – 7.42 (m, 3H), 7.37 (t, *J* = 7.3 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 166.0, 148.4, 139.3, 137.9, 137.8, 131.4, 129.6, 129.1, 127.9, 127.2, 125.8, 116.3, 111.2, 61.0, 49.0, 14.6, 14.5.

HRMS (ESI+): calculated m/z for $C_{20}H_{19}NaO_3$ $[M+Na]^+$ 344.1257, found 344.1259.

7-Methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2n)



Following **General Procedure C**, product was purified by reverse phase column to afford a white solid (40.0 mg, 91%).

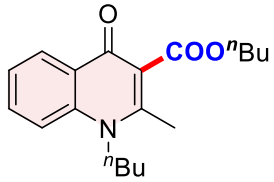
R_f (DCM/MeOH 10:1): 0.3.

^{1}H NMR (400 MHz, DMSO-d_6): δ 15.53 (s, 1H), δ 8.81 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.21 – 7.14 (m, 2H), 3.90 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 177.6, 166.6, 163.4, 145.1, 141.7, 126.9, 118.4, 116.4, 107.3, 100.5, 55.9.

HRMS (ESI-): calculated m/z for $C_{11}H_8NO_4$ $[M-H]^-$ 218.0459, found 218.0457.

Butyl 1-butyl-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (2o)



Following **General Procedure A** by iodobutane processed, product was purified by silica gel flash column chromatography to afford a colorless liquid (30.9 mg, 49%).

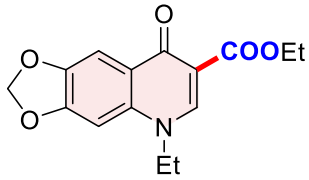
R_f (DCM/MeOH 10:1): 0.4.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 4.40 (t, *J* = 6.7 Hz, 2H), 4.22 (t, *J* = 6.5 Hz, 2H), 2.70 (s, 3H), 1.90 – 1.73 (m, 6H), 1.58 – 1.43 (m, 4H), 0.99 (td, *J* = 7.3, 6.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1, 160.5, 156.7, 130.9, 128.4, 126.1, 122.7, 121.7, 117.6, 74.6, 66.0, 32.4, 30.7, 23.8, 19.4, 19.3, 14.0, 13.8.

HRMS (ESI+): calculated m/z for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1907, found 316.1904.

Ethyl 1-ethyl-l,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (2p)



Following **General Procedure C**, product was purified by reverse phase column to afford a white solid (48.6 mg, 81%).

R_f (DCM/MeOH 10:1): 0.5.

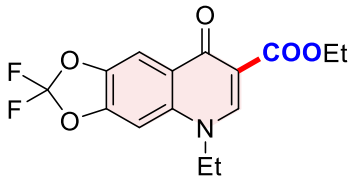
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.89 (s, 1H), 6.85 (s, 1H), 6.11 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.3 Hz, 2H), 1.52 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3, 166.3, 152.5, 147.3, 146.5, 135.7, 125.6, 110.8,

105.5, 102.5, 95.2, 61.0, 49.6, 14.6, 14.6.

HRMS (ESI+): calculated m/z for $C_{15}H_{15}NNaO_5$ $[M+Na]^+$ 312.0842, found 312.0845.

Ethyl 5-ethyl-2,2-difluoro-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (2q)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford an off-white solid (41.0 mg, 63%).

R_f (DCM/MeOH 10:1): 0.6.

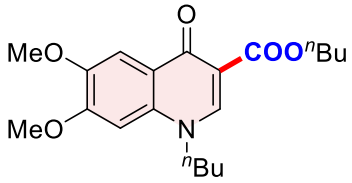
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 2H), 8.16 (s, 2H), 7.16 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 4H), 4.24 (q, *J* = 7.3 Hz, 4H), 1.55 (t, *J* = 7.2 Hz, 6H), 1.39 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 165.6, 148.3, 147.6, 142.0, 136.2, 131.8 (t, *J* = 259.6 Hz), 126.5, 111.2, 107.7, 96.9, 61.2, 49.8, 14.5, 14.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -50.21.

HRMS (ESI+): calculated m/z for $C_{15}H_{14}F_2NO_5$ $[M+H]^+$ 326.0835, found 326.0836.

Butyl 1-butyl-6,7-dimethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (2r)



Following **General Procedure A** by iodobutane processed, product was purified by silica gel flash column chromatography to afford a colorless liquid (51.3 mg, 71%).

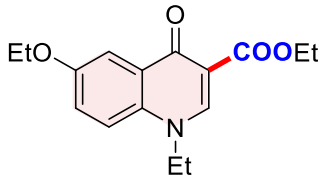
R_f (DCM/MeOH 10:1): 0.7.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.90 (s, 1H), 6.75 (s, 1H), 4.31 (t, *J* = 6.7 Hz, 2H), 4.13 (t, *J* = 7.3 Hz, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 1.86 (p, *J* = 7.4 Hz, 2H), 1.76 (dt, *J* = 14.5, 6.8 Hz, 2H), 1.55 – 1.34 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 166.5, 153.5, 147.8, 147.7, 134.2, 123.7, 110.3, 107.5, 97.4, 64.8, 56.4, 56.3, 54.0, 30.94, 30.90, 20.0, 19.4, 13.95, 13.93, 13.7.

HRMS (ESI+): calculated m/z for $C_{20}H_{28}NO_5$ $[M+H]^+$ 362.1962, found 362.1962.

Ethyl 6-ethoxy-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (2s)



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a pale yellow solid (17.4 mg, 30 %).

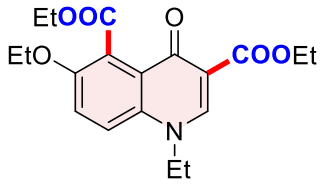
R_f (DCM/MeOH 10:1): 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.94 (d, *J* = 3.0 Hz, 1H), 7.40 (d, *J* = 9.2 Hz, 1H), 7.32 – 7.24 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.24 (p, *J* = 6.9 Hz, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 166.5, 156.7, 147.4, 132.9, 130.9, 123.2, 117.2, 110.1, 108.4, 64.2, 61.0, 49.1, 14.8, 14.8, 14.6.

HRMS (ESI+): calculated m/z for $C_{16}H_{20}NO_4$ $[M+H]^+$ 290.1387, found 290.1391.

Diethyl 6-ethoxy-1-ethyl-4-oxo-1,4-dihydroquinoline-3,5-dicarboxylate (2s')



Following **General Procedure A**, product was purified by silica gel flash column chromatography to afford a pale yellow solid (29.3 mg, 41%).

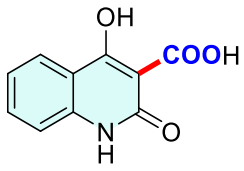
R_f (DCM/MeOH 10:1): 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.44 (d, *J* = 9.3 Hz, 1H), 7.26 (d, *J* = 9.3 Hz, 1H), 4.72 – 4.59 (m, 1H), 4.44 – 4.28 (m, 3H), 4.28 – 4.13 (m, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.42 – 1.33 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1, 167.9, 165.4, 153.4, 147.8, 132.7, 127.4, 123.6, 118.3, 118.0, 109.9, 65.5, 61.5, 60.9, 49.3, 14.8, 14.6, 14.5, 14.4.

HRMS (ESI+): calcd for $C_{19}H_{24}NO_6$ $[M+H]^+$ 362.1604, found 362.1606.

4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4a)



Following **General Procedure D**, an off-white solid product (41.0 mg, 99%) was obtained.

R_f (DCM/MeOH/HAc 10:1:0.1): 0.2.

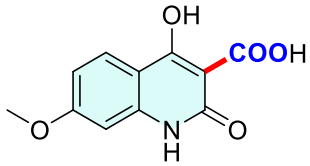
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.85 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 173.0, 171.6, 164.9, 138.3, 135.1, 124.3, 123.9, 117.0, 114.4, 94.6.

HRMS (ESI-): calculated m/z for $C_{10}H_6NO_4$ $[M-H]^-$ 204.0302, found 204.0301.

The spectra data was matched with the reported literature.[6]

4-Hydroxy-7-methoxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4b)



Following **General Procedure D**, a light brown solid product (44.7 mg, 95%) was obtained.

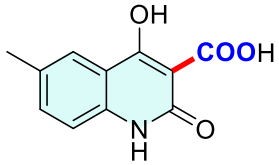
R_f (DCM/MeOH/HAc 10:1:0.1): 0.2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 15.80 (s, 1H), 14.28 (s, 1H), 12.60 (s, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 1H), 6.90 (s, 1H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 173.1, 171.1, 165.3, 164.6, 140.8, 126.2, 113.5, 107.9, 99.0, 92.8, 55.9.

HRMS (ESI-): calculated m/z for $C_{11}H_8NO_5$ $[M-H]^-$ 234.0408, found 234.0405.

4-Hydroxy-6-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4c)



Following **General Procedure D**, a white solid (43.0 mg, 98%) was obtained.

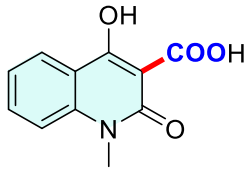
R_f (DCM/MeOH/HAc 10:1:0.1): 0.3.

^{1}H NMR (400 MHz, DMSO-d_6): δ 16.00 (s, 1H), 14.52 (s, 1H), 12.76 (s, 1H), 7.76 (s, 1H), 7.61 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 2.39 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 173.1, 171.4, 164.6, 136.4, 136.3, 133.3, 123.3, 116.9, 114.3, 94.4, 20.4.

HRMS (ESI+): calculated m/z for $C_{11}H_{10}NO_4$ $[M+H]^+$ 220.0604, found 220.0609.

4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4d)



Following **General Procedure D**, a yellowish-white solid (40.8 mg, 93%) was obtained.

R_f (DCM/MeOH 10:1): 0.4.

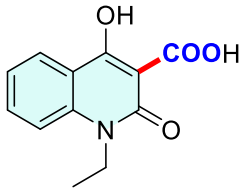
^{1}H NMR (400 MHz, $CDCl_3$): δ 15.57 (s, 1H), 14.53 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.80 (t, 1H), 7.51 – 7.38 (m, 2H), 3.76 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.5, 171.4, 164.8, 139.9, 135.3, 126.1, 123.9, 115.8, 115.0, 95.3, 29.7.

HRMS (ESI-): calculated m/z for $C_{11}H_8NO_4$ $[M-H]^-$ 218.0459, found 218.0458.

The spectra data was matched with the reported literature.[7]

1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4e)



Following **General Procedure D**, a yellowish-white solid (45.5 mg, 98%) was obtained.

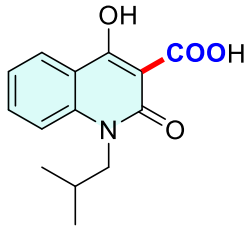
R_f (DCM/MeOH 10:1): 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.68 (s, 1H), 14.49 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 171.2, 164.4, 138.9, 135.2, 126.2, 123.7, 116.1, 114.9, 95.2, 37.9, 13.0.

HRMS (ESI+): calculated m/z for $C_{12}H_{12}NO_4$ $[M+H]^+$ 234.0761, found 234.0768.

4-Hydroxy-1-isobutyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4f)



Following **General Procedure D**, a light brown solid (50.2 mg, 96%) was obtained.

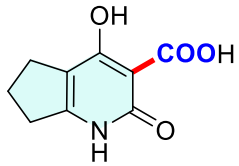
R_f (DCM/MeOH 10:1): 0.5.

^{1}H NMR (400 MHz, $CDCl_3$) δ 15.78 (s, 1H), 14.59 (s, 1H), 8.27 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.78 (ddd, *J* = 8.7, 7.1, 1.6 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 4.20 (d, *J* = 7.5 Hz, 2H), 2.24 (m, 1H), 1.02 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 171.2, 165.2, 139.4, 134.9, 126.2, 123.7, 116.1, 115.5, 95.1, 49.2, 27.5, 20.2.

HRMS (ESI+): calculated m/z for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1074, found 262.1070.

4-Hydroxy-2-oxo-2,5,6,7-tetrahydro-*1H*-cyclopenta[*b*]pyridine-3-carboxylic acid (4g)



Following **General Procedure D**, a light brown solid (38.2 mg, 98%) was obtained.

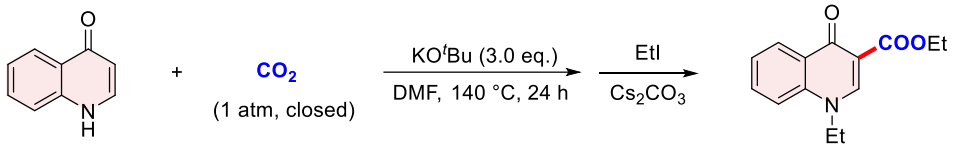
R_f (DCM/MeOH/HAc 10:1:0.1): 0.3.

^{1}H NMR (400 MHz, DMSO-d_6): δ 16.05 (s, 1H), 13.48 (s, 1H), 12.98 (s, 1H), 2.86 (t, *J* = 7.7 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.07 (p, *J* = 7.6 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 173.0, 170.4, 166.3, 157.2, 113.0, 94.2, 31.5, 26.0, 21.5.

HRMS (ESI+): calculated m/z for $C_9H_{10}NO_4$ $[M+H]^+$ 196.0604, found 196.0608.

2.2 Optimization of work-up process

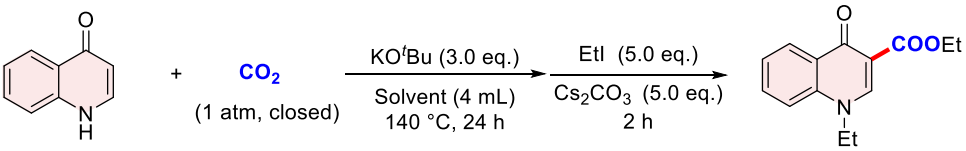


1a **2a**

entry	EtI	Cs_2CO_3	yield of **2a** (%) [a]
1	5 eq.	none	72
2	**5 eq.**	**5 eq.**	**92**
3	5 eq.	2 eq.	90
4	2 eq.	2 eq.	50

[a]The yield was determined by ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as the internal standard.

2.3 Optimization of mixed solvent

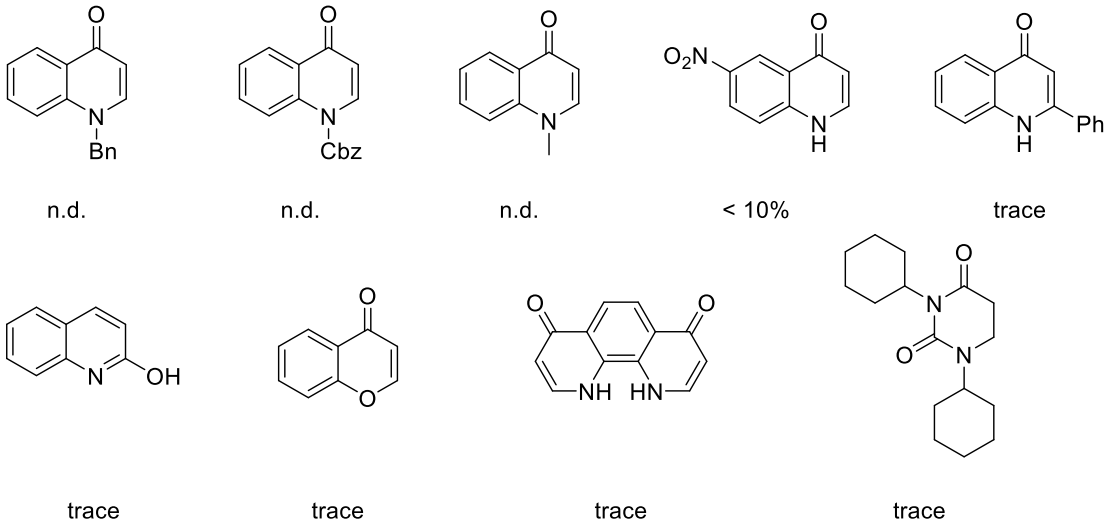


1a **2a**

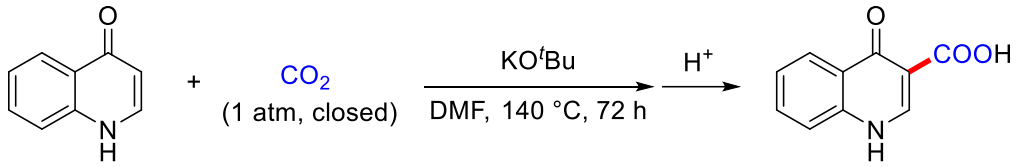
entry	Solvent	yield of **2a** (%) [a]
1	DMF/HO^{t}Bu 3:1	13%
2	DMF/DMSO 3:1	4%
3	**DMF/*p*-xylene 3:1**	**90**
4	DMF/Pyridine 3:1	19

[a]The yield was determined by ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as the internal standard.

2.4 Unsuccessful examples



2.5 Scale-up reaction of 1a

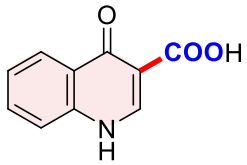


1a, 6 mmol

2a', 0.98 g, 87%

Procedure: An oven-dried Schlenk (250 mL) tube equipped with a magnetic stir bar was charged with **1a** (871 mg, 6.0 mmol), then transferred the tube to glovebox and added KO^{t}Bu (1.35g, 2.0 equiv.). The tube was sealed and removed from the glovebox, then evacuated and back-filled with CO_2 atmosphere for three times (*Note: The initial evacuation and backfilling process will generate a significant amount of heat due to the in situ formation of carbonates from KO^{t}Bu and CO_2. Therefore, this step must be conducted with caution, and CO_2 gas should be introduced slowly to prevent burns*). Anhydrous DMF (80 mL) was added under CO_2 atmosphere and the tube was sealed at atmospheric pressure of CO_2 (1 atm). The reaction was stirred and heated at 140 °C for 72 h. Upon completion, the reaction was quenched with 100 mL H_2O and the pH was adjusted to 2. The sediment was filtered and washed with 10 mL H_2O. Next, the filtrate mixture was extracted with EA five times, and the combined organic phases were concentrated under reduced pressure. The products were then washed with 10 mL of water and 10 mL of ethyl acetate, respectively. Finally, the two portions of the products were combined and dried under vacuum to obtain a white solid product (0.98 g, 87%).

4-Oxo-1,4-dihydroquinoline-3-carboxylic acid (2a')



^{1}H NMR (400 MHz, DMSO-d_6): δ 15.35(s, 1H), 13.45 (s, 1H), 8.89 (s, 1H), 8.29 (dd, J = 8.1, 1.5 Hz, 1H), 7.89 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.82 (dd, J = 8.5, 1.2 Hz, 1H), 7.60 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 178.4, 166.4, 145.2, 139.5, 134.0, 126.2, 125.1, 124.4, 119.7, 107.6.

HRMS (ESI+): calculated m/z for $C_{10}H_8NO_3$ $[M+H]^+$ 190.0499, found 190.0500.

The spectra data was matched with the reported literature.[8]

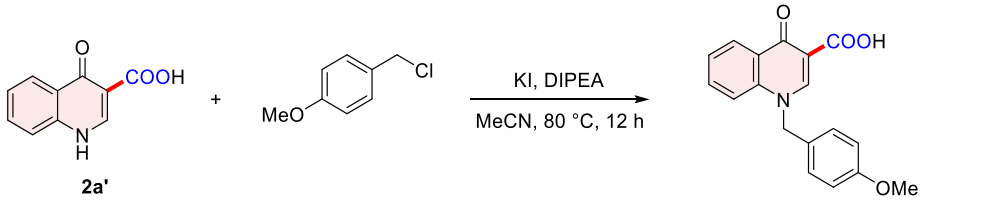
2.6 Conditions for crystal growing and crystallographic data

Crystals of compound **2b** and **4a** were prepared in same methods, compound **2b** or **4a** (20 mg) were put in appropriate amount of anhydrous ethanol, heated the mixture to 60 ºC and stirred until the solution was clear. The hot solution was filtered in time, and slowly evaporated solvent under room temperature, colorless crystals of **2b** or **4a** received for few days. Single crystal X-ray diffraction measurements were conducted on a Bruker APEX-II CCD diffractometer using Mo-Kα radiation (λ = 0.71073 Å) with a graphite monochromator at 300(2) K and 279(2) K in scan mode.

Crystallographic data of compound 2b and 4a

Compounds	**2b**	**4a**
Formula	$C_{15}H_{17}NO_3$	$C_{10}H_7NO_4$
Temperature (K)	300	279
Volume	1326.8(4)	853.20(9)
Space group	P 1 21/n 1	P 1 21/c 1
Hall group	-P 2yn	-P 2ybc
a (Å)	9.4468(15)	3.7486(2)
b (Å)	12.9259(17)	17.9200(11)
c (Å)	11.0202(19)	12.7162(8)
α (°)	90	90
β (°)	99.606(5)	92.790(2)
γ (°)	90	90
M_r	259.29	205.17
calc. density (g·cm^{-3})	1.298	1.597
Z	4	4
μ (mm^{-1})	0.091	0.126
F(000)	552.0	424.0
Reflections with	1607	1945
h, k, lmax	11, 15, 13	4,23,16
T_{min}, T_{max}	0.377, 0.746	0.684, 0.746
θ_{max} (°)	24.996	27.478
goodness-of-fit on F^2	1.010	1.044
R (reflections)	0.0562(1607)	0.0450(1316)
wR_2 (reflections)	0.1687(2325)	0.1232(1945)
CCDC	**2388494**	**2388495**

2.7 Synthetic applications



2a'

5, 81% (BQCA, M1 mAChR modulator)

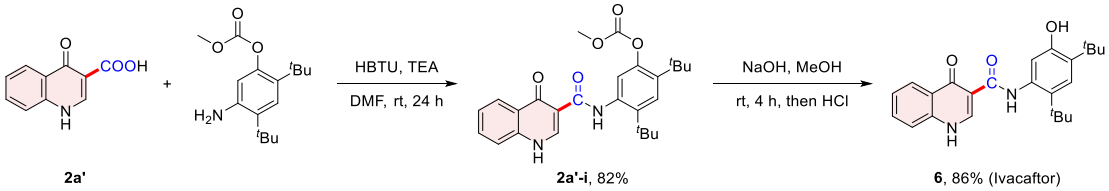
Procedure: According to the previous literature,[9] carboxylic acid **2a'** (1.0 mmol, 189 mg) and acetonitrile (15 mL) were placed in a round-bottomed flask and cooled to 0 °C in an ice bath. 4-Methoxybenzylchloride (2 equiv.), potassium iodide (1.1 equiv.) and *N*,*N*-diisopropylethylamine (DIPEA, 4 equiv.) were added and the reaction stirred at 80 °C for 12 h. Once complete, the reaction mixture was partitioned between EA (10 mL), 1 M HCl (aq.) (10 mL) and the aqueous layer extracted with EA (5 × 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated in vacuo to afford white solid (249 mg, 81% yield).

1-(4-Methoxybenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5).

^{1}H NMR (400 MHz, DMSO-d_6): δ 15.18 (s, 1H), 9.26 (s, 1H), 8.38 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.87 (ddd, *J* = 8.7, 6.9, 1.6 Hz, 1H), 7.62 (td, *J* = 7.4, 6.9, 1.0 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.78 (s, 2H), 3.71 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 177.9, 166.1, 159.1, 149.9, 139.5, 134.2, 128.4, 127.0, 126.4, 125.9, 125.7, 118.8, 114.3, 107.8, 56.0, 55.1.

HRMS (ESI+): calculated m/z for $C_{14}H_{16}NO_4$ $[M+H]^+$ 310.1074, found 310.1082.



2a'

2a'-i, 82%

6, 86% (Ivacaftor)

Procedure: To a 25 mL oven-dried Schlenk tube equipped with a magnetic stir bar was charged with carboxylic acid **2a'** (0.4 mmol, 1.0 equiv.) and HBTU (0.6 mmol, 1.5 equiv.), the tube was then evacuated and back-filled with N_2 atmosphere three times. Then TEA (1.2 mmol, 3.0 equiv.) and DMF (5 mL) was added under N_2 atmosphere

followed by 5-amino-2,4-di-*tert*-butylphenyl methyl carbonate (0.6 mmol, 1.5 equiv.) and the tube was sealed. The reaction mixture was then stirred at room temperature overnight. Once complete, the solvent was evaporated, and the crude residue was diluted with H_2O and extracted with EtOAc (5 × 10 mL), the organic layer was dried over anhydrous Na_2SO_4, following purified by silica gel chromatography column chromatography (DCM/MeOH 100:1) to afford white solid **2a'-i** (148 mg, 82% yield). Next, a solution of **2a'-i** (45.0 mg, 0.1 mmol), 2 N NaOH (1 mL) and MeOH (2 mL) were stirred at room temperature for 4 h. The completion of the reaction was monitored by TLC. The mixture was then quenched with ice 1N HCl to adjust the pH to 5~6. Subsequently, it was extracted with EA (5 × 10 mL), concentrated the solvent, the residue was purified by silica gel chromatography (ethyl acetate/hexane 1/3 ~ 1/1) to obtain Ivacaftor **6** (33.7 mg, 86% yield).

2,4-Di-*tert*-butyl-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenyl methyl carbonate (2a'-i)

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.83 (s, 1H), 8.39 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.78 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.44 (s, 1H), 3.88 (s, 3H), 1.49 (s, 9H), 1.36 (s, 9H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 178.8, 165.9, 155.8, 148.8, 145.5, 142.3, 140.6, 139.1, 134.8, 134.4, 127.6, 126.9, 126.7, 126.2, 126.2, 124.5, 124.4, 120.0, 111.9, 56.0, 35.9, 35.7, 31.0, 30.6.

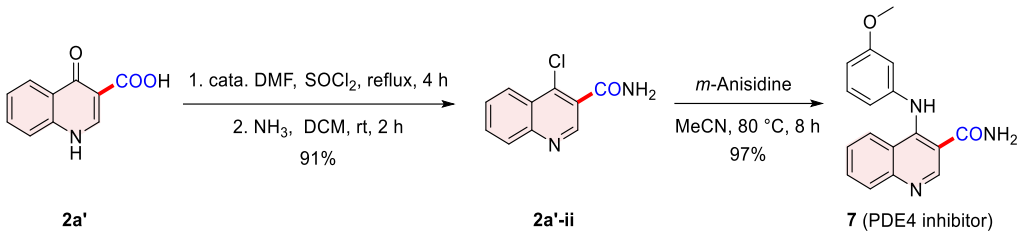
HRMS (ESI+): calculated m/z for $C_{26}H_{31}N_2O_5$ $[M+H]^+$ 451.2227, found 451.2245.

***N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3carboxamide (6)**

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 11.81 (s, 1H), 9.20 (s, 1H), 8.86 (d, *J* = 6.7 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.72 (m, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.16 (s, 1H), 7.10 (s, 1H), 1.37 (s, 9H), 1.36 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 176.4, 162.8, 153.3, 144.1, 139.2, 133.5, 132.9, 132.3, 131.5, 126.0, 125.6, 125.1, 123.7, 119.1, 116.0, 110.9, 34.3, 34.0, 30.6, 29.4.

HRMS (ESI-): calculated m/z for $C_{24}H_{27}N_2O_3$ $[M-H]^-$ 391.2027, found 391.2020.



Procedure: According to the previous literature,[10] 4-quinolone-3-carboxylic acid **2a'** (1.0 mmol, 189 mg), catalytic amount of DMF and $SOCl_2$ (4 mL) were placed in a 25 ml round-bottomed flask, and the mixture was refluxed to 80 °C for 4 h. The excess thionyl chloride was evaporated in vacuo, then added DCM (5 mL) and ammonia (3 mL, 0.4 M in Dioxane) to the flask, and the mixture was stirred at room temperature for 2 h. Next, the mixture was diluted with H_2O (10 × 10 mL) and extracted with EtOAc (6 × 10 mL), the organic layer was dried over anhydrous Na_2SO_4, dried under vacuum to give **2a'-ii** as a white solid (187 mg, 91% yield).

4-Chloroquinoline-3-carboxamide (2a'-ii)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.88 (s, 1H), 8.30 (d, *J* = 7.7 Hz, 1H), 8.20 (br. s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.97 (br. s, 1H), 7.93 (t, *J* = 7.7 Hz, 1H), 7.83 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.3, 148.6, 148.0, 137.7, 131.3, 130.1, 129.5, 128.9, 125.1, 124.3.

HRMS (ESI+): calculated m/z for $C_{10}H_8ClN_2NaO$ $[M+Na]^+$ 229.0139, found 229.0141.

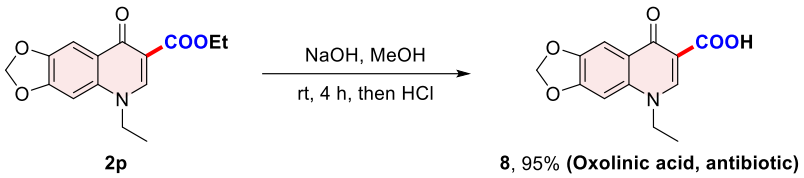
Next, a mixture of **2a'-ii** (62 mg, 0.3 mmol), *m*-Anisidine (40.6 mg, 1.1 equiv.) and MeCN (4 mL) were heated to 80 °C with stirring for 6 h under N_2 atmosphere. The reaction mixture was concentrated *in vacuo*, then purified by silica gel flash column chromatography MeOH/DCM (1:10) to give yellow solid **7** (86.0 mg, 97% yield).

4-((3-Methoxyphenyl)amino)quinoline-3-carboxamide (7)

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 9.02 (s, 1H), 8.29 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.56 (t, *J* = 2.2 Hz, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 3.67 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 169.7, 160.0, 149.7, 149.5, 148.6, 144.7, 130.6, 129.9, 129.4, 125.5, 124.9, 120.6, 113.2, 112.4, 108.6, 105.8, 55.0.

HRMS (ESI+): calculated m/z for $C_{17}H_{16}N_3O_2$ $[M+H]^+$ 294.1237, found 294.1238.



2p **8**, 95% **(Oxolinic acid, antibiotic)**

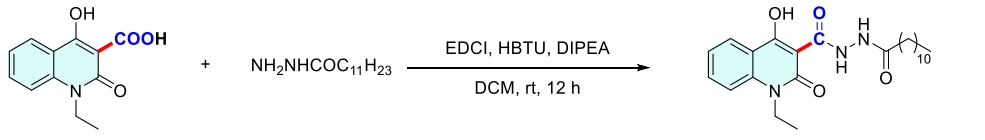
Procedure: A solution of **2p** (36.0 mg, 0.12 mmol), 2 N NaOH (1 mL) and MeOH (2 mL) were stirred at room temperature for 4 h. The reaction was monitored by TLC. Once the reaction was completed, the mixture was quenched with ice 1N HCl (5 mL) and stirred for 0.5 h to form a white precipitate. The precipitate was then extracted with EA (5 × 10 mL) the combined organic fractions were washed with H_2O (10 mL). The solvent was removed under reduced pressure to obtain the pure product **8** (29.8 mg, 95% yield).

5-Ethyl-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (8)

^{1}H NMR (400 MHz, DMSO-d_6): δ 15.69 (s, 1H), 8.90 (s, 1H), 7.64 (d, J = 4.9 Hz, 2H), 6.30 (s, 2H), 4.54 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 176.0, 166.3, 153.7, 147.1, 147.1, 137.0, 121.3, 107.3, 103.3, 101.9, 97.2, 49.6, 14.6.

HRMS (ESI+): calculated m/z for $C_{13}H_{12}NO_5$ $[M+H]^+$ 262.0710, found 262.0715.



4e **9**, 41% **(VP0.7, GSK-3β inhibitor)**

Procedure: According to reported literature,[11] EDCI (1.5 equiv.) was added to a solution of the **4e** (46.6 mg, 0.2 mmol, 1.0 equiv.), DIPEA (1.5 equiv.) and HBTU (1.5 equiv.) in DMF (2 mL) at room temperature and stirred for 30 min. Then, the hydrazide (64.3 mg, 1.5 equiv.) was added to the solution and the reaction mixture was stirred for 12 h at room temperature. The mixture was then extracted with dichloromethane, and the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated

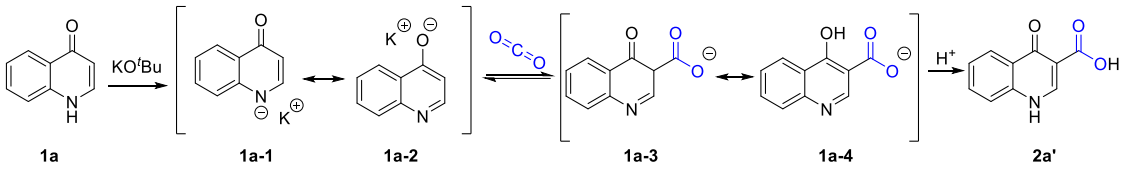
under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane 2/3), the target compound **9** was obtained as a white solid (35.2 mg, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.42 (s, 1H), 12.52 (d, *J* = 5.2 Hz, 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 8.19 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.70 (td, *J* = 7.8, 7.0, 1.6 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 1.25 – 1.35 (m, 21H), 0.87 (t, *J* = 6.7 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 169.4, 166.8, 161.7, 139.3, 134.3, 125.8, 122.5, 116.0, 114.4, 96.4, 37.5, 34.5, 32.0, 29.7, 29.6, 29.5, 29.5, 29.4, 25.6, 22.8, 14.3, 13.0.
HRMS (ESI-): calculated m/z for $C_{24}H_{34}N_3O_4$ $[M-H]^-$ 428.2555, found 428.2545.

2.8 Cell proliferation assay

U266 cell lines were cultured in RIPMI-1640 medium and HCT116 were cultured in DMEM medium supplemented with 10% fetal bovine serum (ZETA, Z7180FBS-500, USA). Cell proliferation was performed using the Cell Counting-Kit 8. U266 and HCT116 cells were seeded into 96-well culture plate at 8000 and 4000 cells/well respectively, and culture at 37 °C and 5% CO_2 for 24 h. The next day, cells were treated with vehicle or various concentrations of the tested compounds in medium for 48 h. Cell viability was measured with CCK-8 assay kit (BMU 106-CN, Abbkine, USA) which was performed according to manufacturer's instructions. The IC_{50} value was calculated m/z by using the SPASS software 20.0 package and figures were generated by using GraphPad Prism 8 software.

3 Proposed mechanism



The initial deprotonation of **1a** by KO^{t}Bu most likely occurred at the N-H proton to generate **1a-1** and its tautomeric form **1a-2**. This was followed by a nucleophilic attack with CO_2, resulting in the formation of the C-3 carboxylate intermediate **1a-3** and **1a-4**. The intermediate subsequently undergoes regioselective rearrangement and acidification to yield quinolone-3-carboxylic acid **2a'** as the final product.

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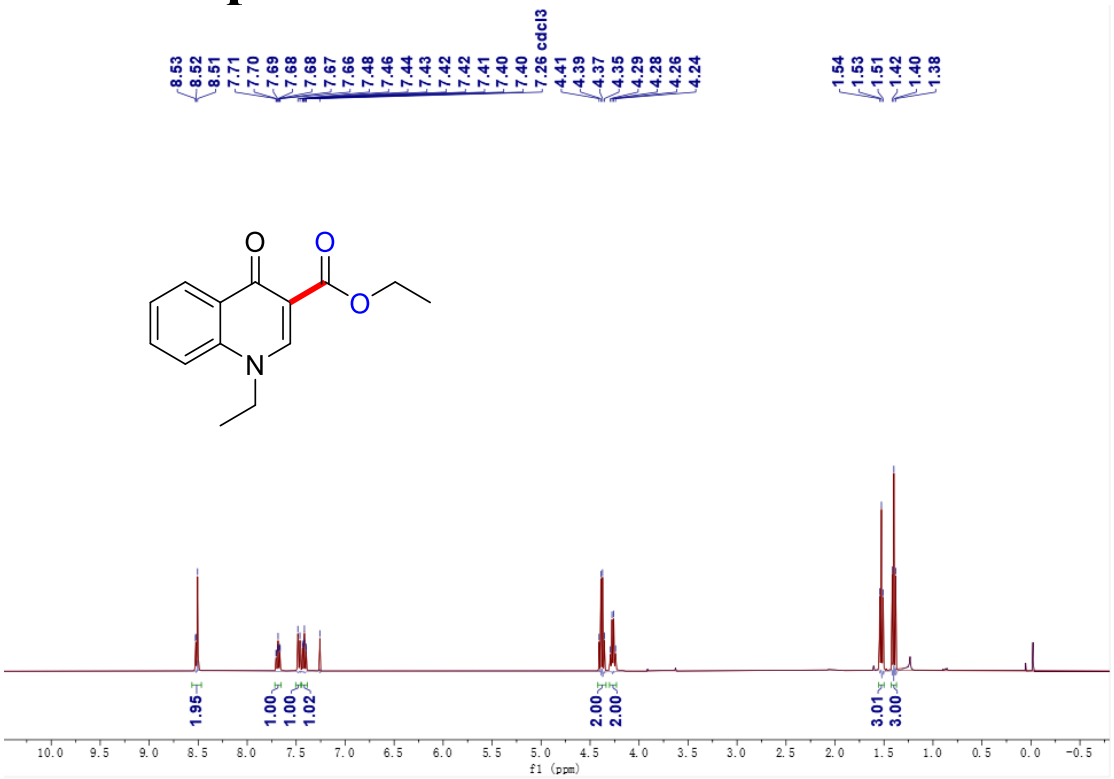
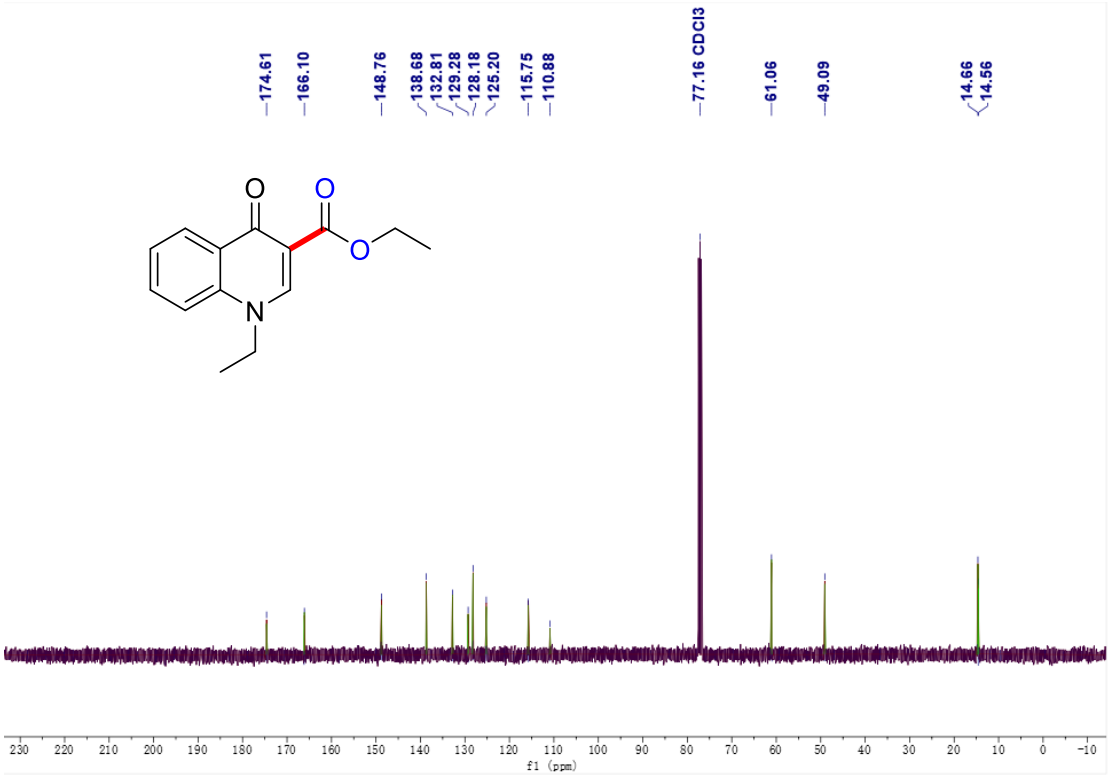
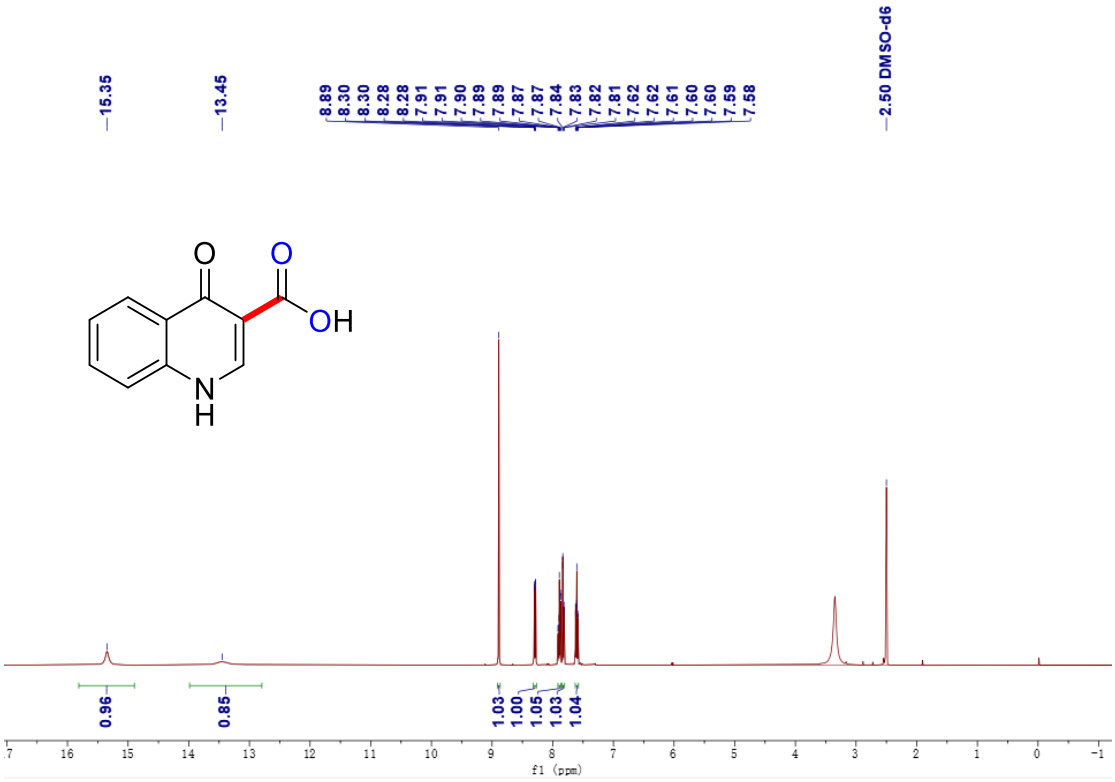
5 NMR spectra



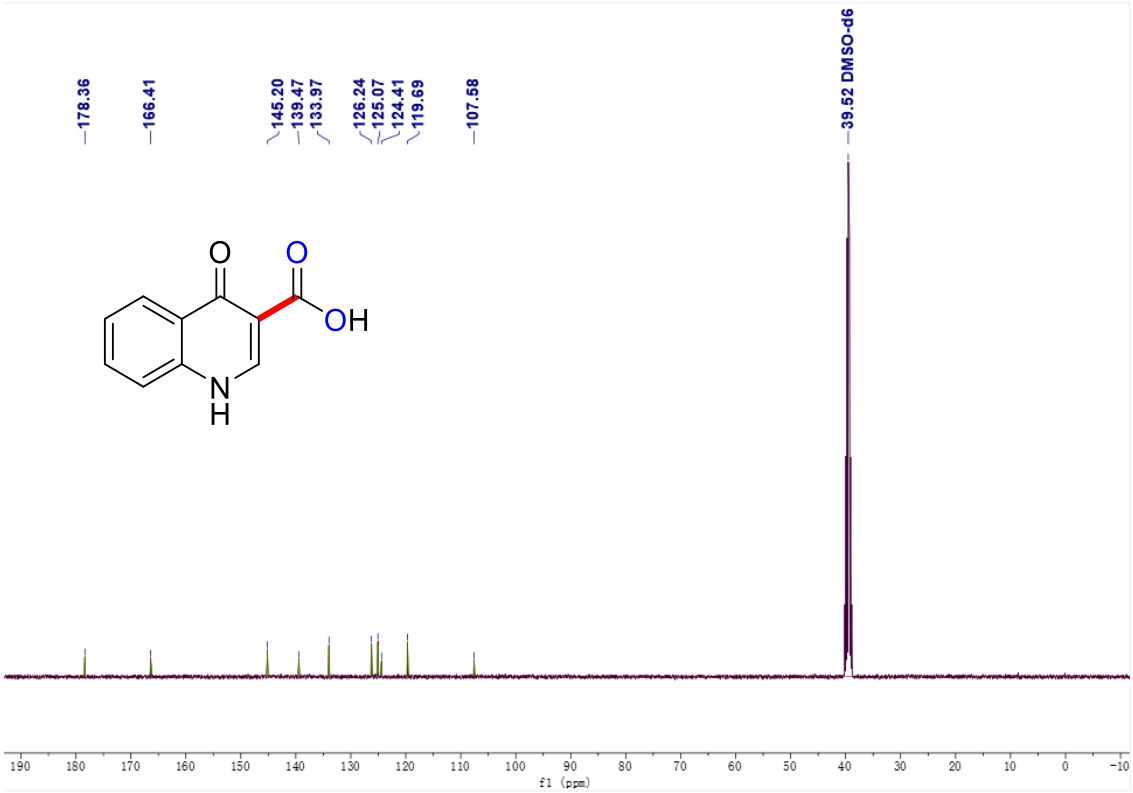
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2a**



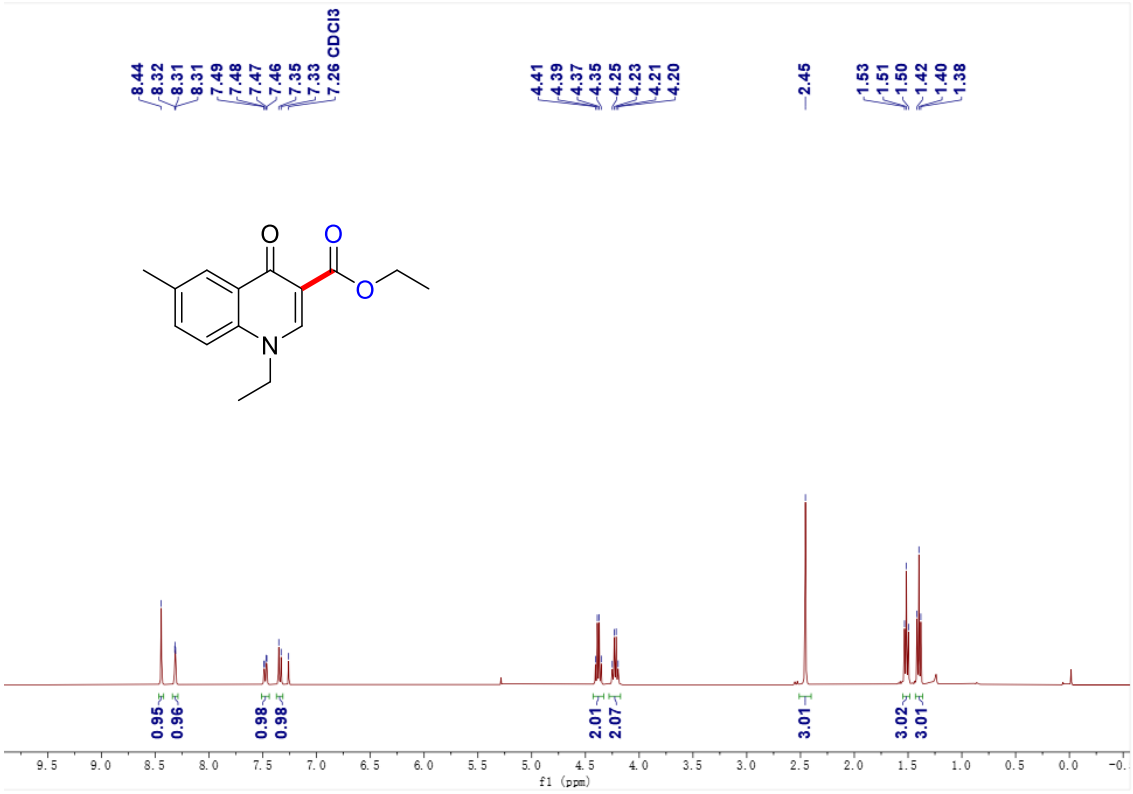
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2a**



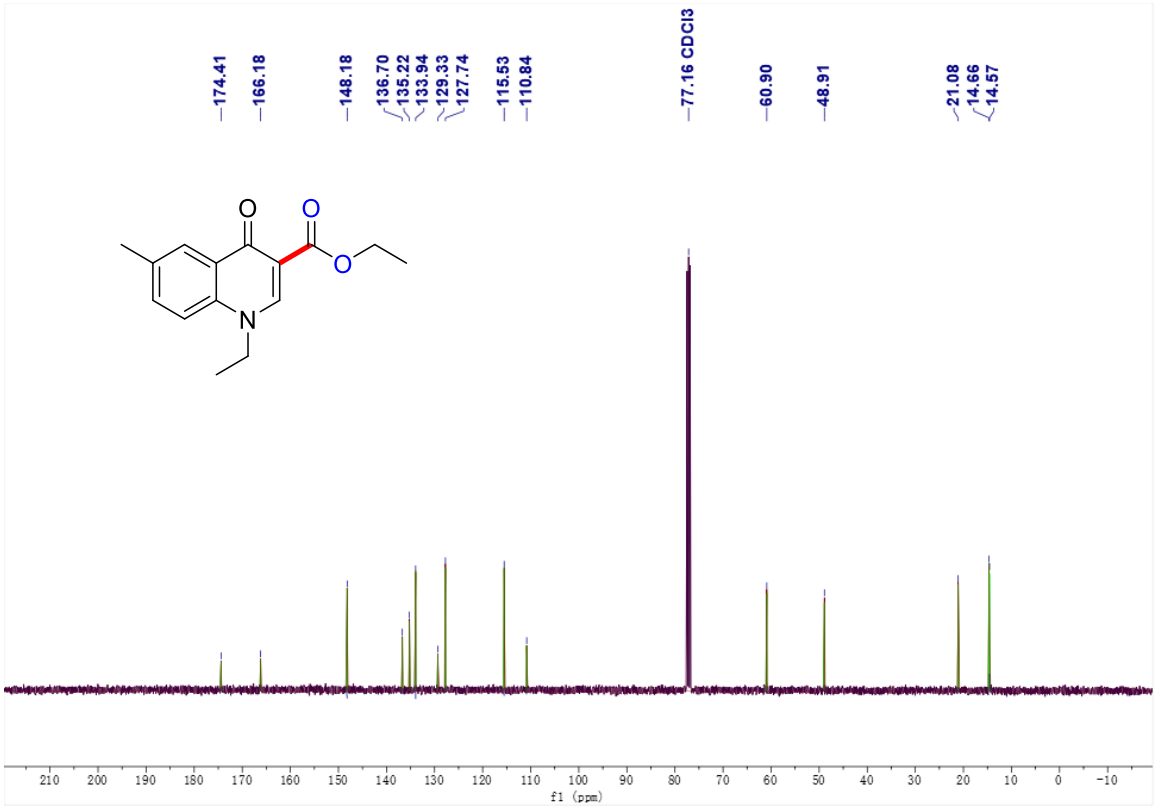
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **2a'**



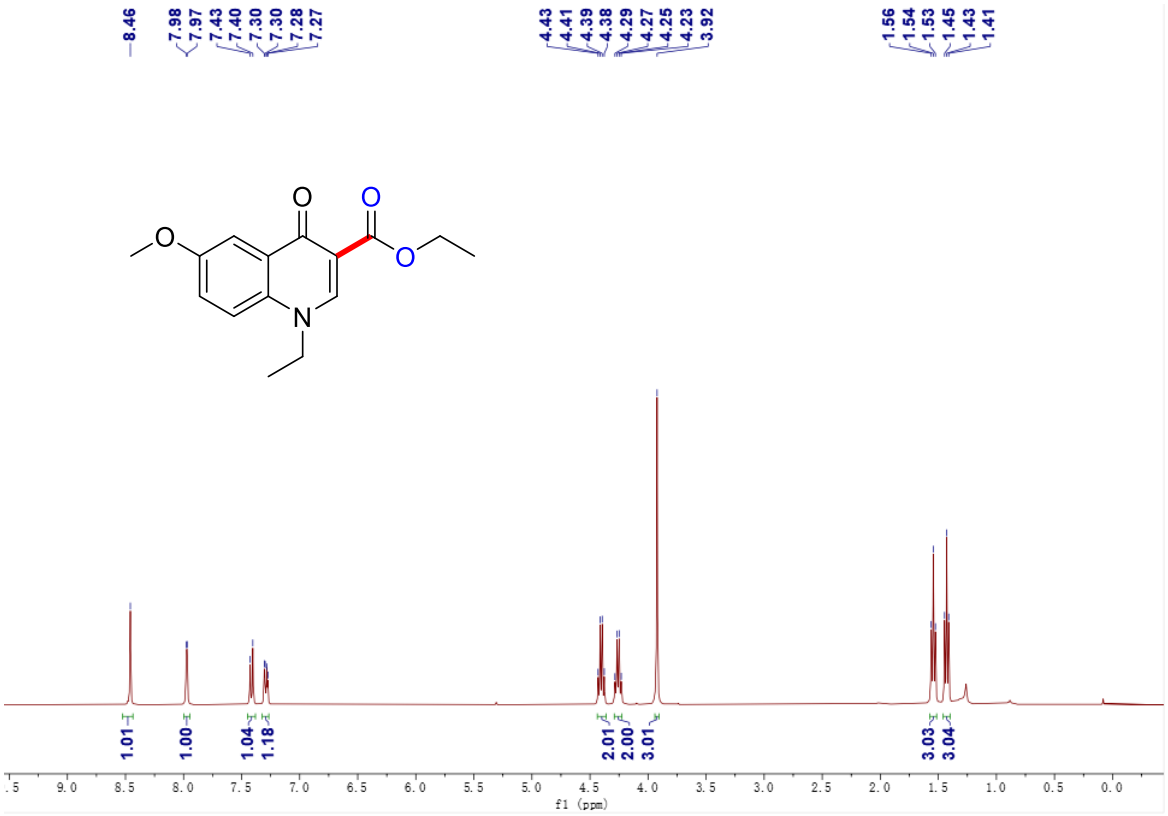
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **2a'**



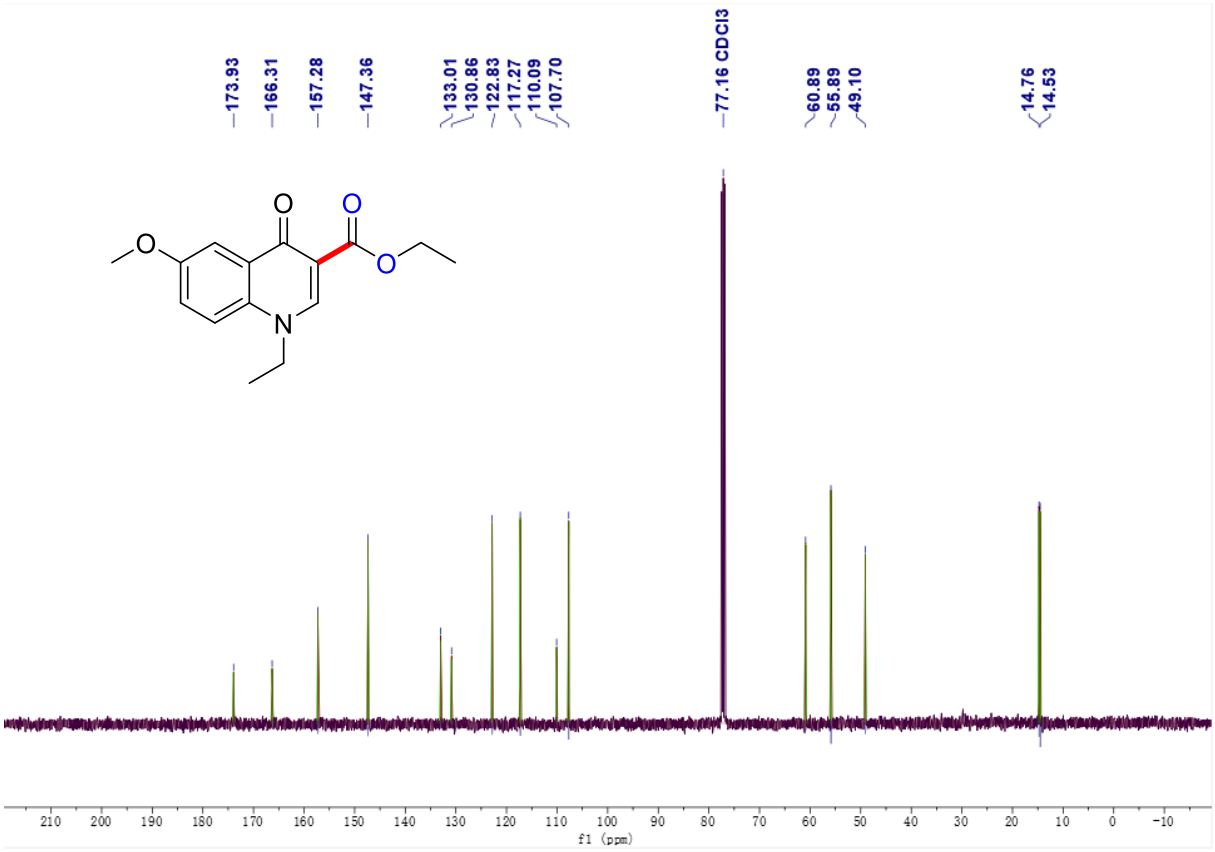
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2b**



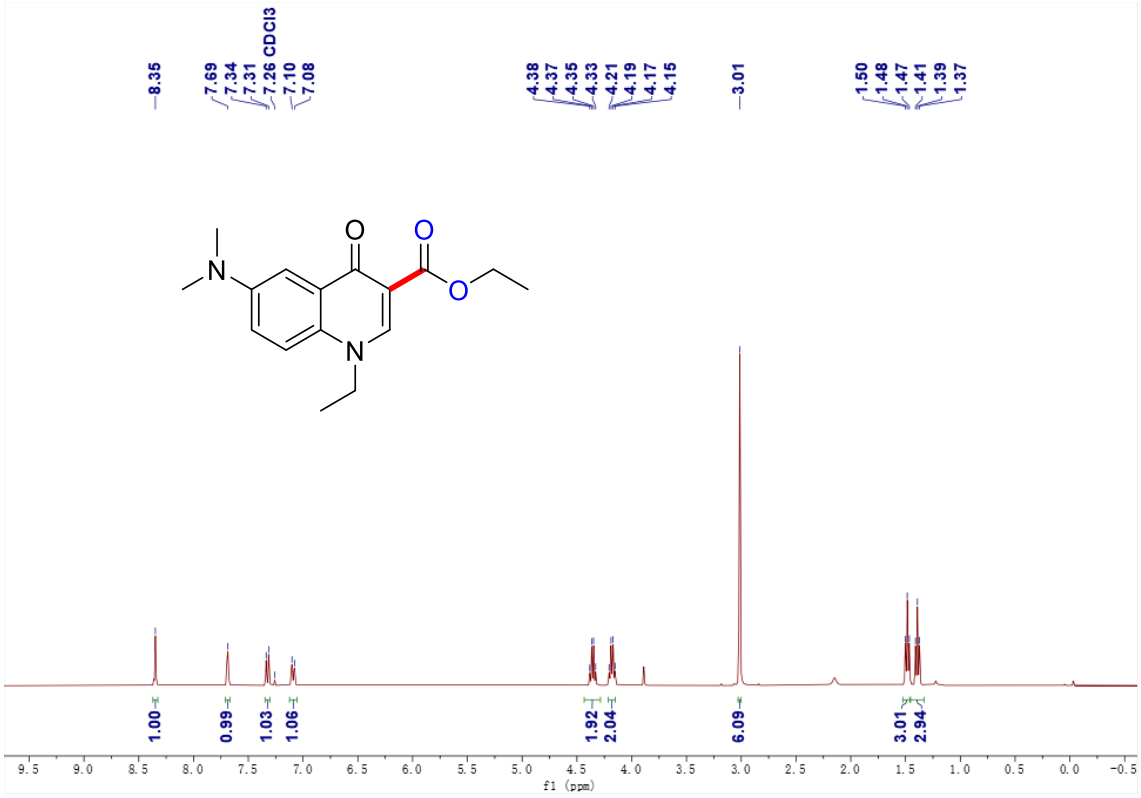
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2b**



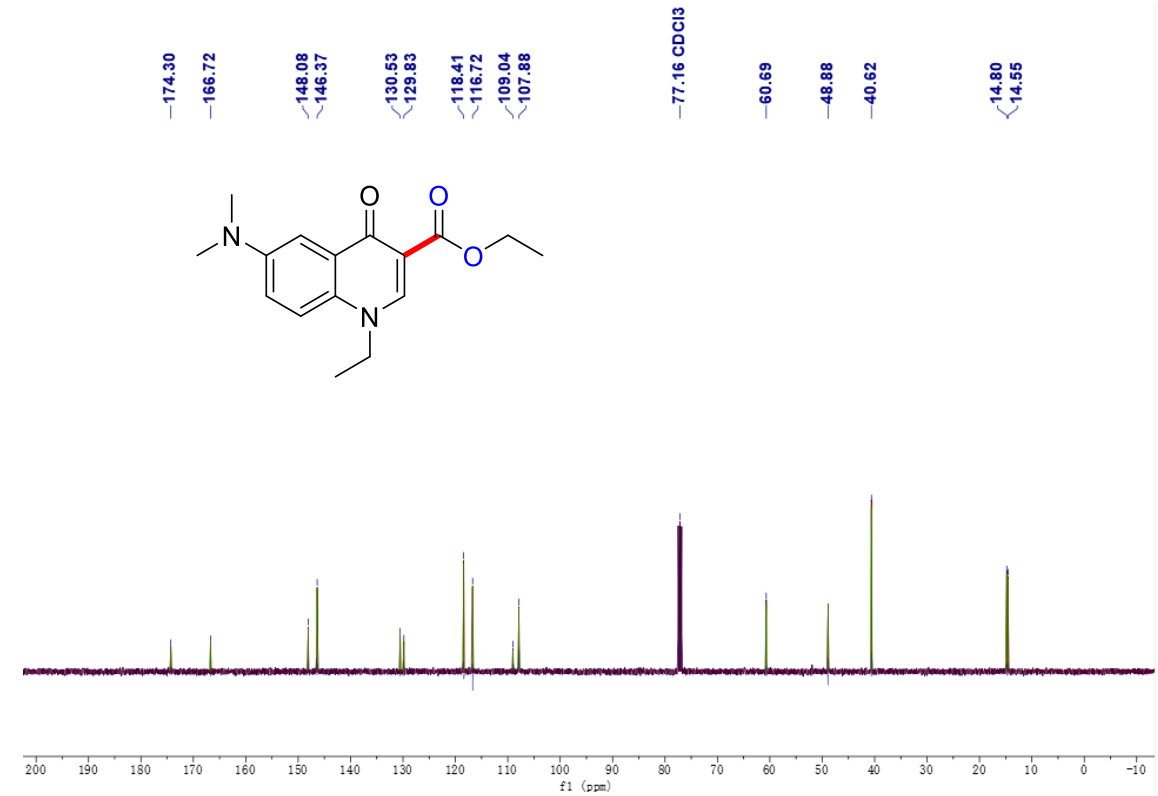
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2c**



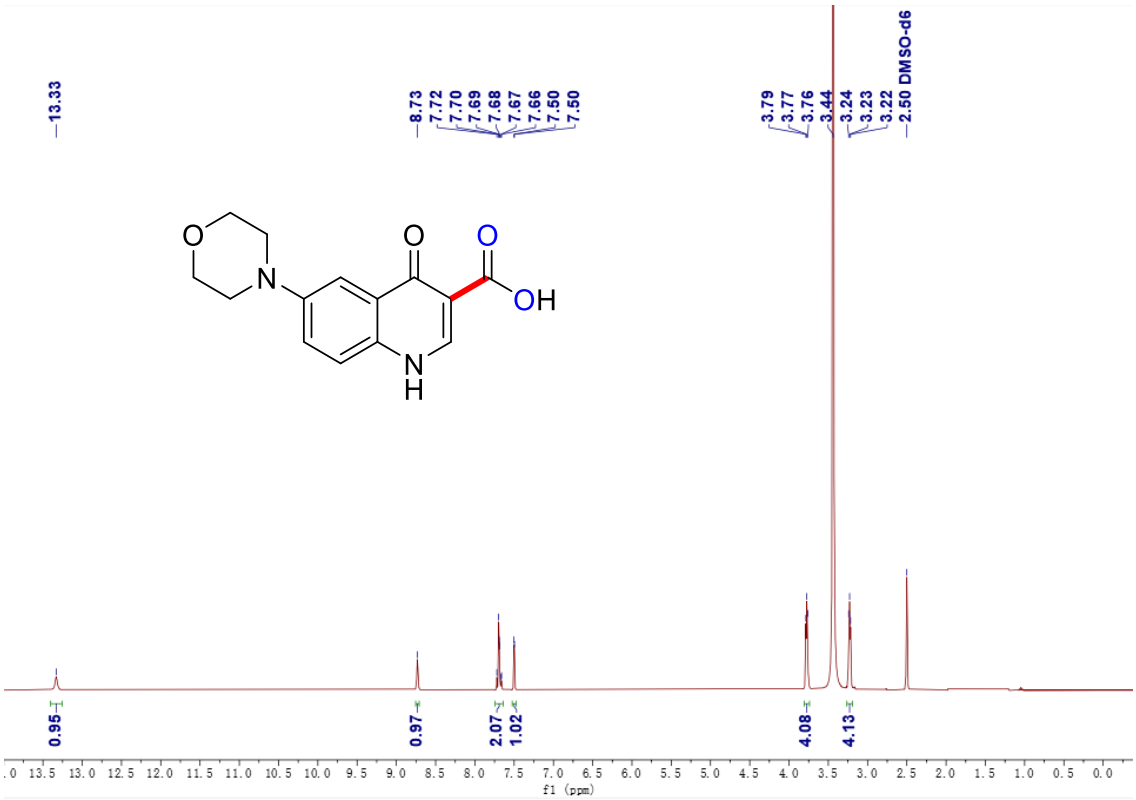
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2c**



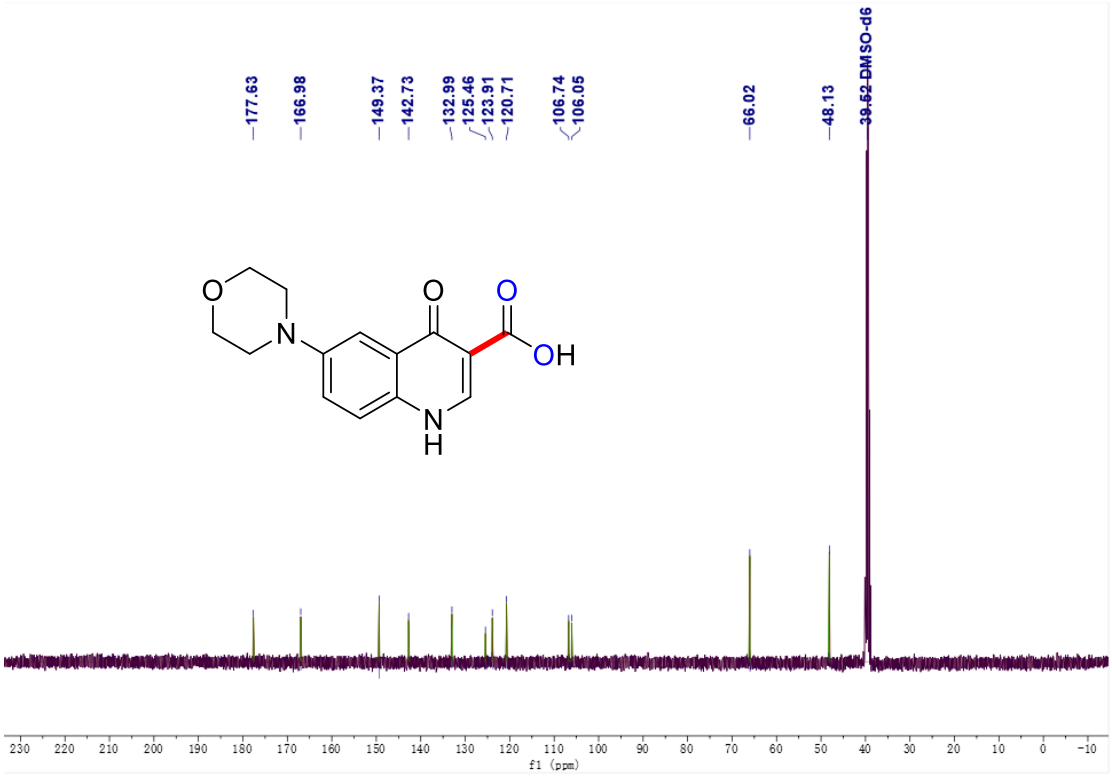
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2d**



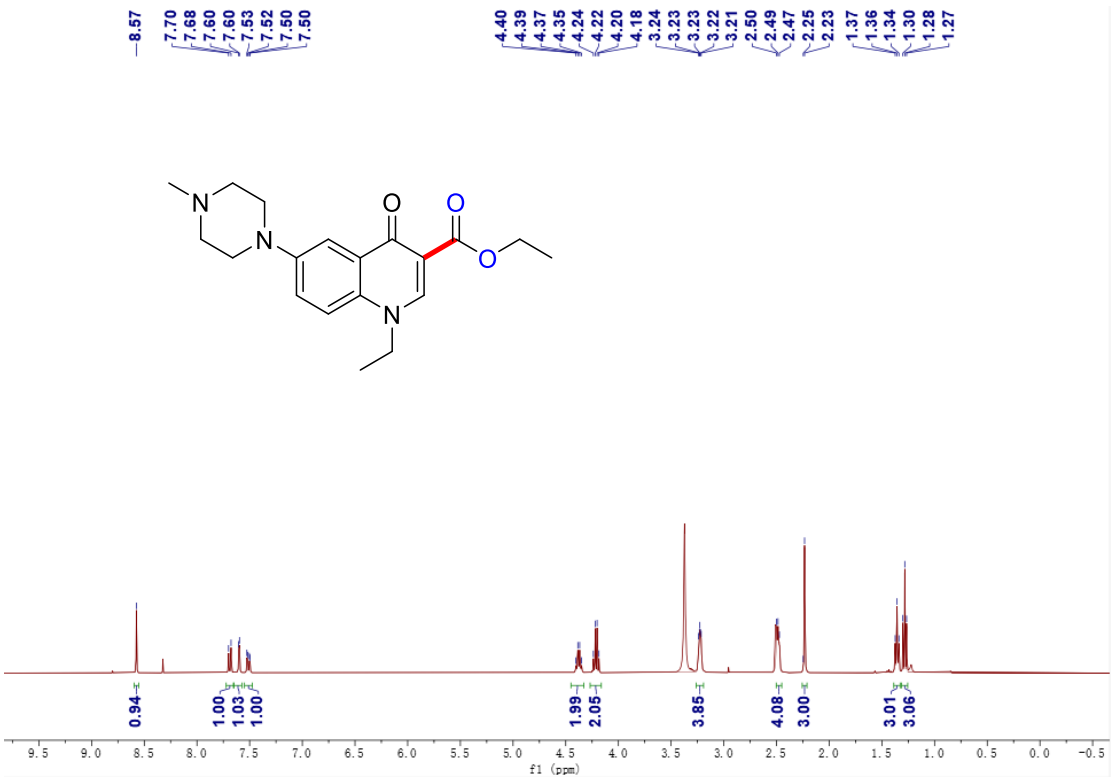
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2d**



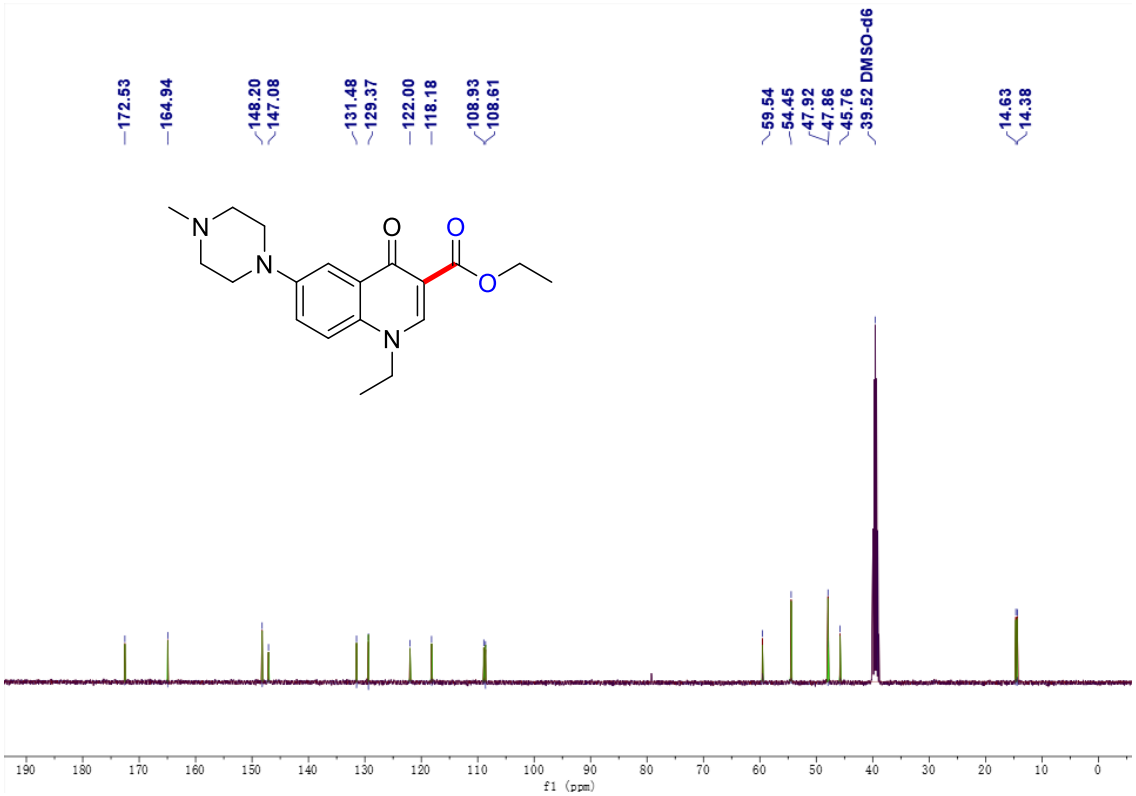
^{1}H NMR (400 MHz, DMSO-*d6*) spectrum of **2e**



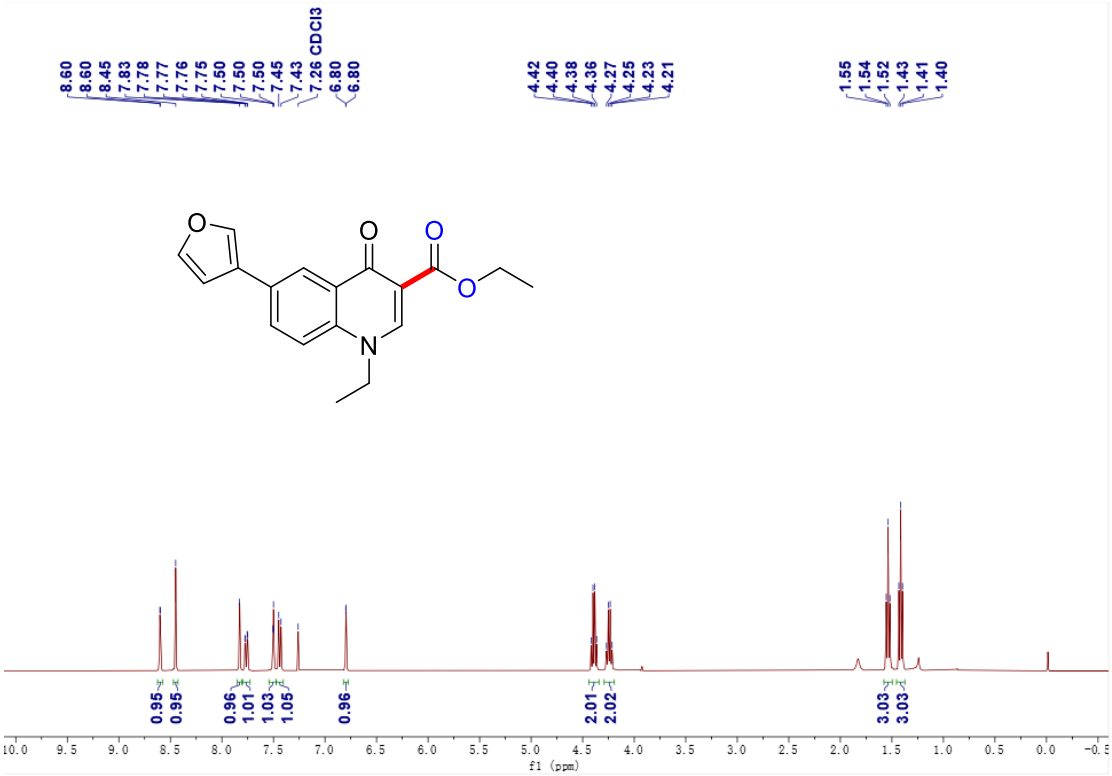
^{13}C NMR (101 MHz, DMSO-*d6*) spectrum of **2e**



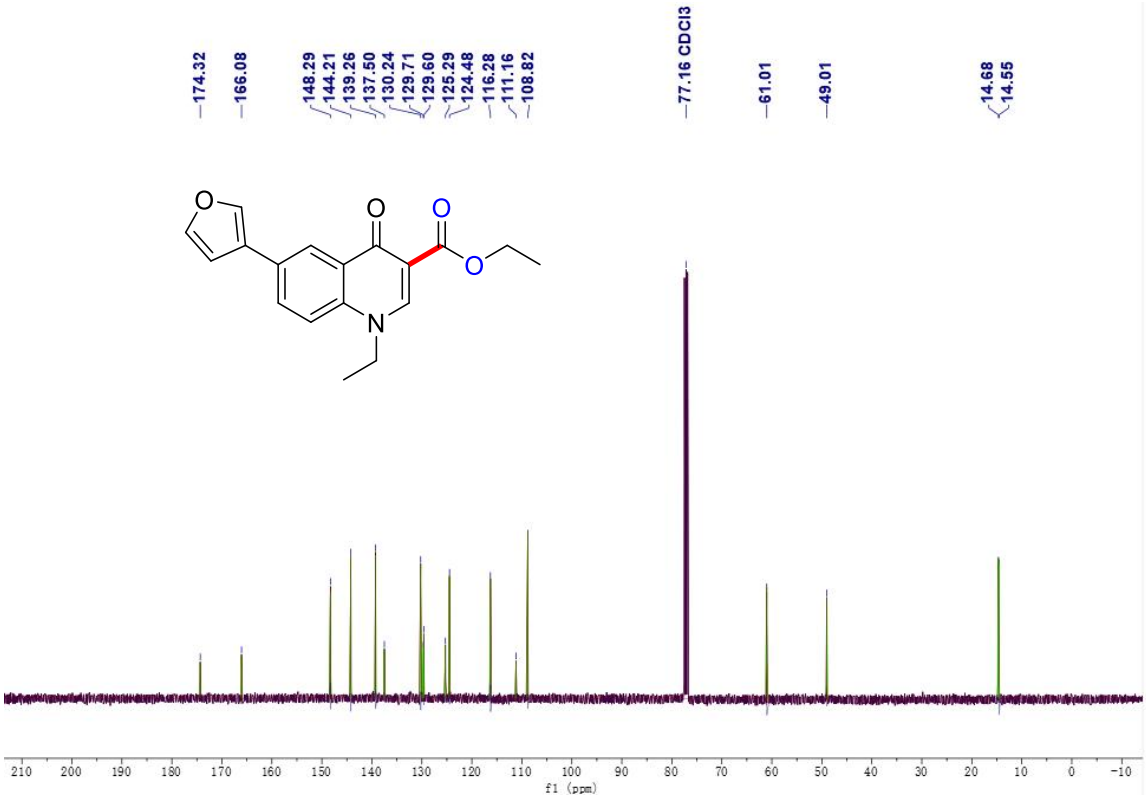
^{1}H NMR (400 MHz, DMSO-*d6*) spectrum of **2f**



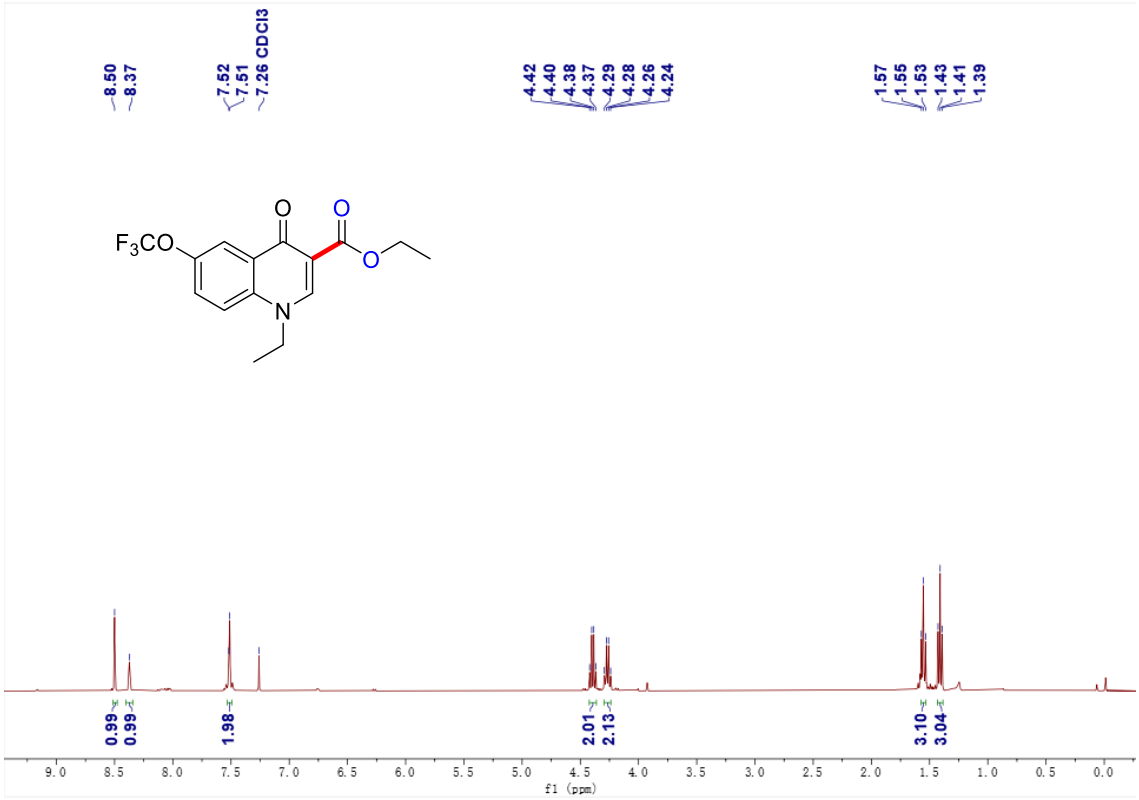
^{13}C NMR (101 MHz, DMSO-*d6*) spectrum of **2f**



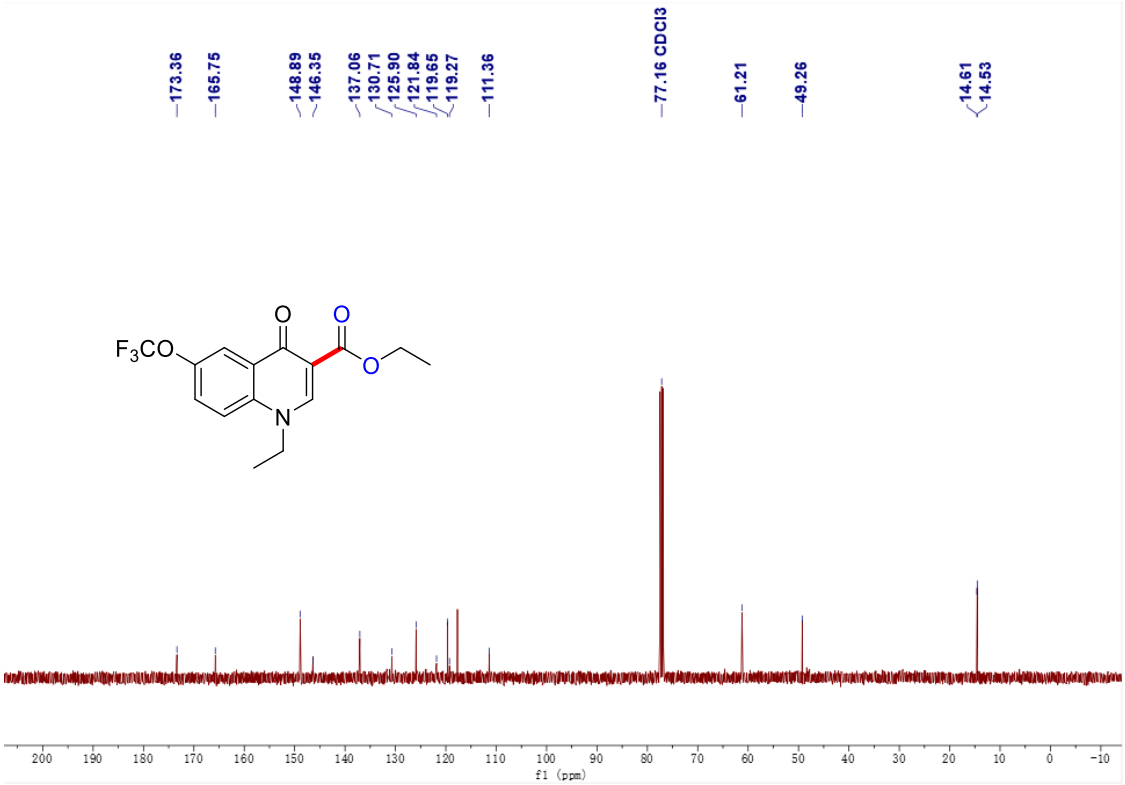
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2g**



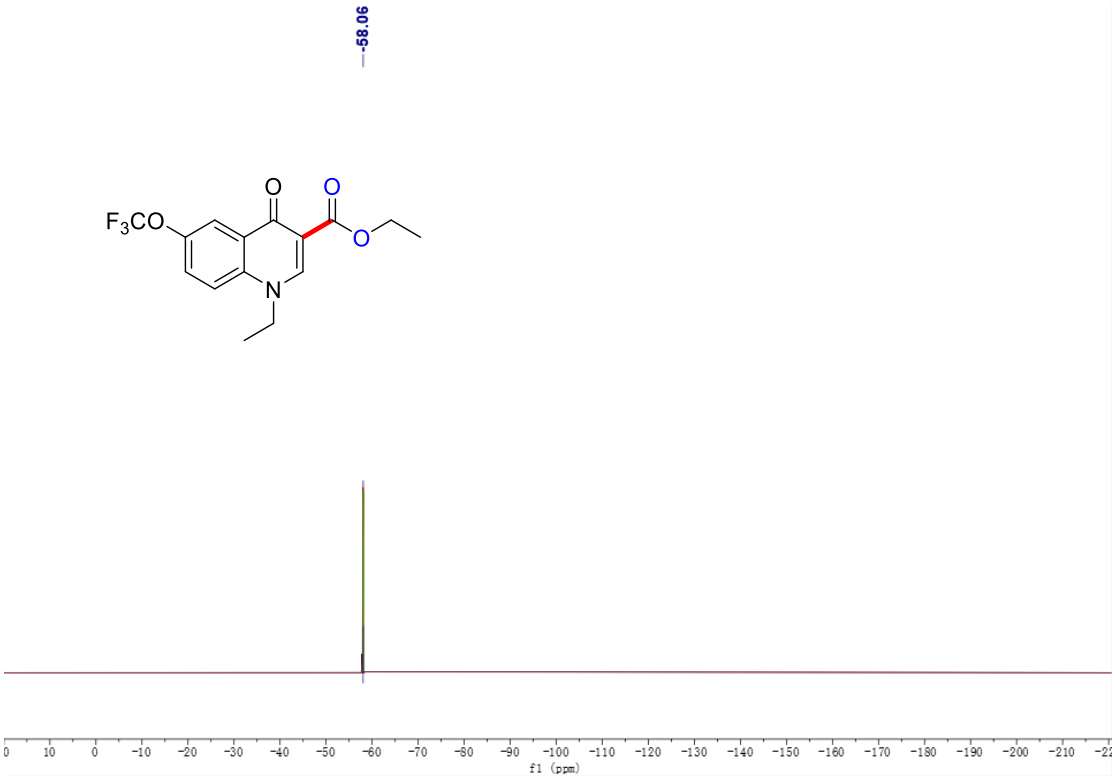
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2g**



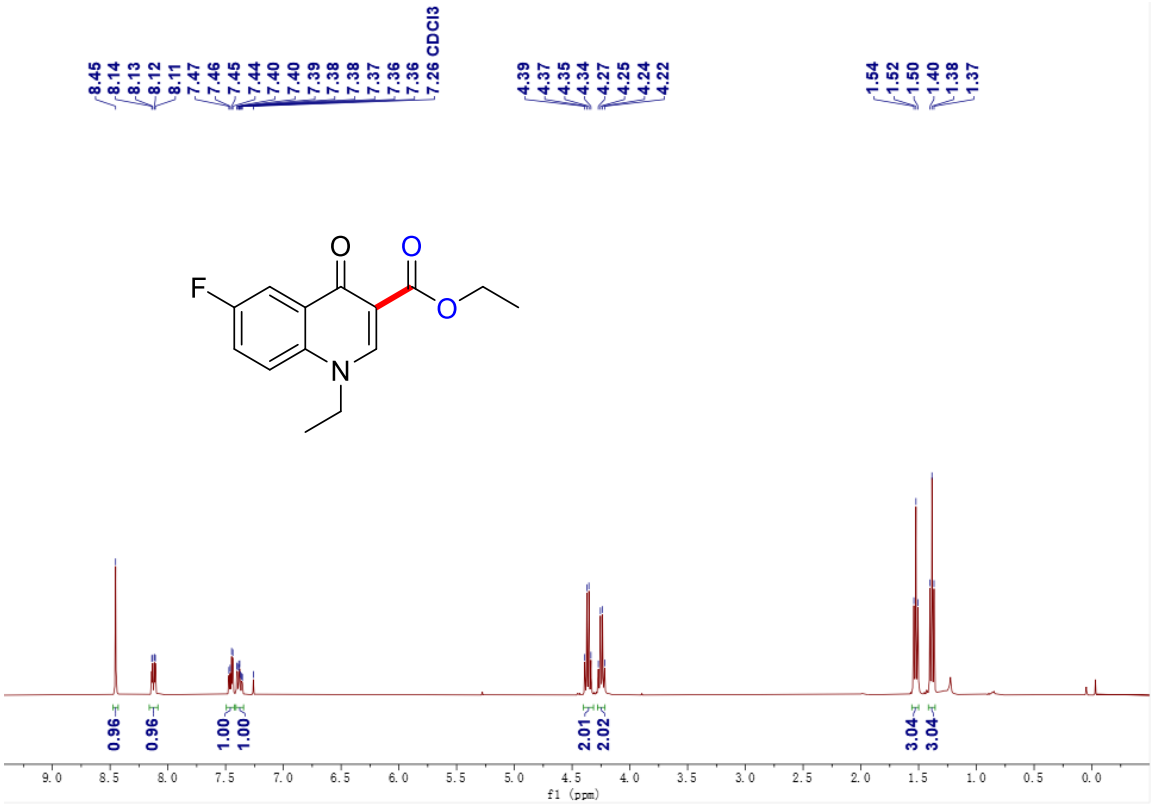
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2h**



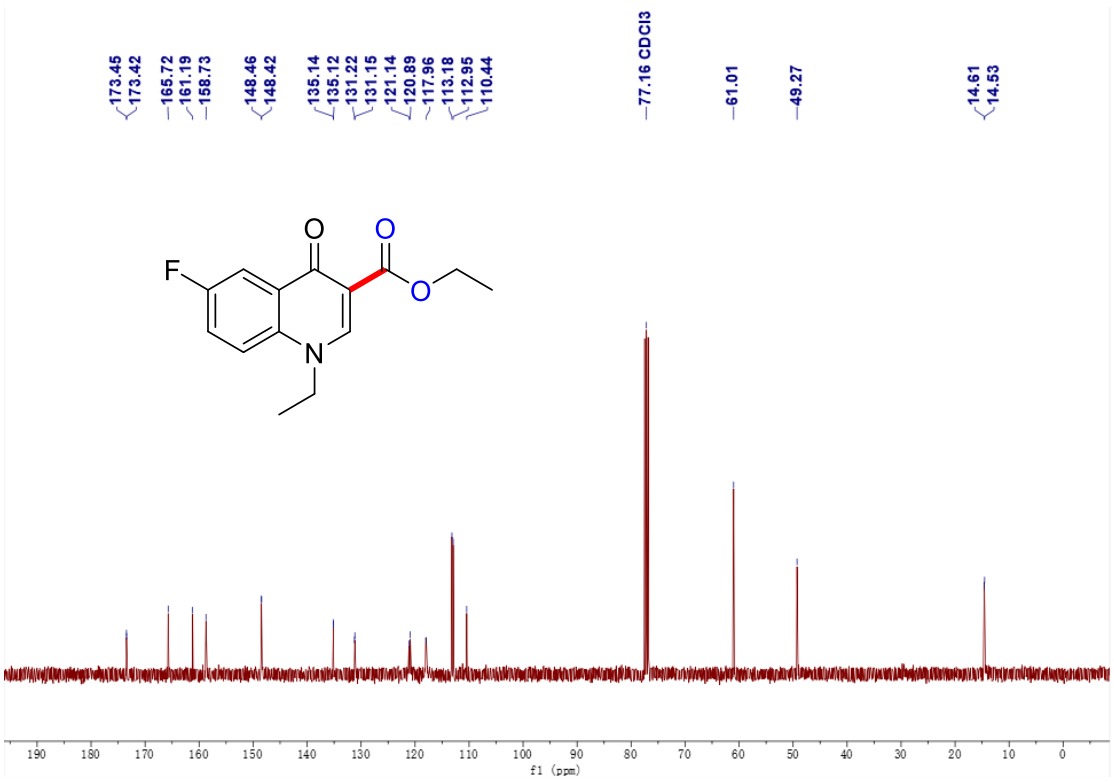
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2h**



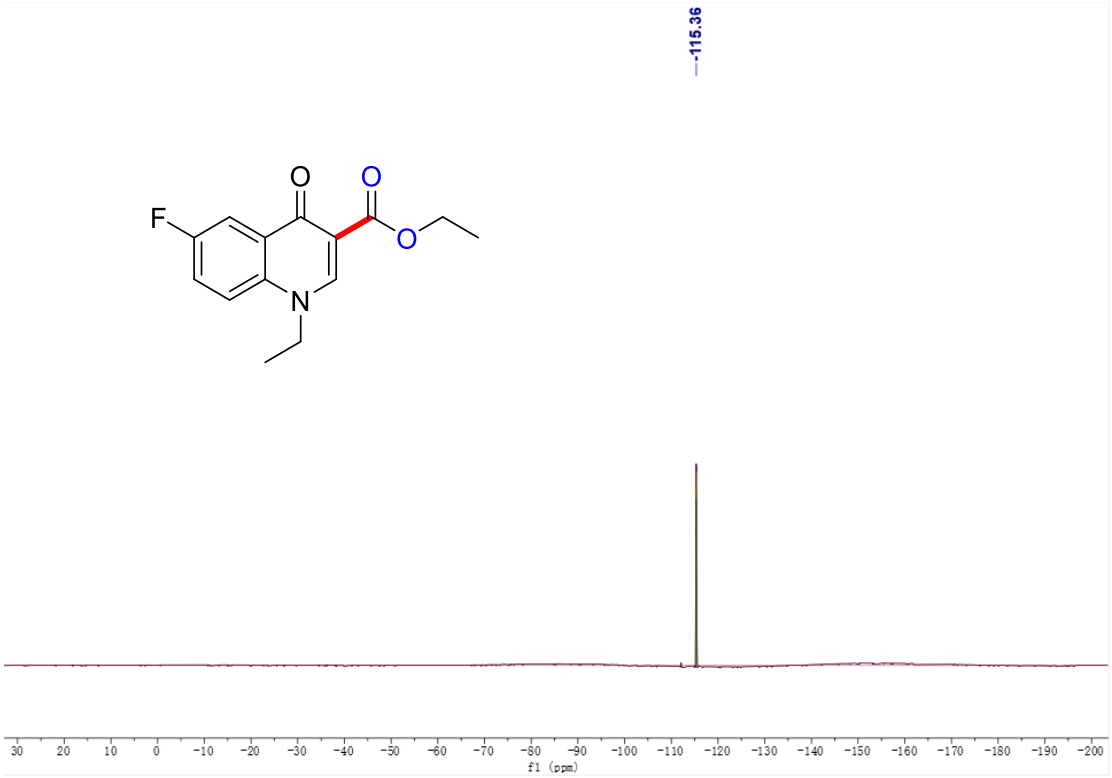
^{19}F NMR (101 MHz, $CDCl_3$) spectrum of **2h**



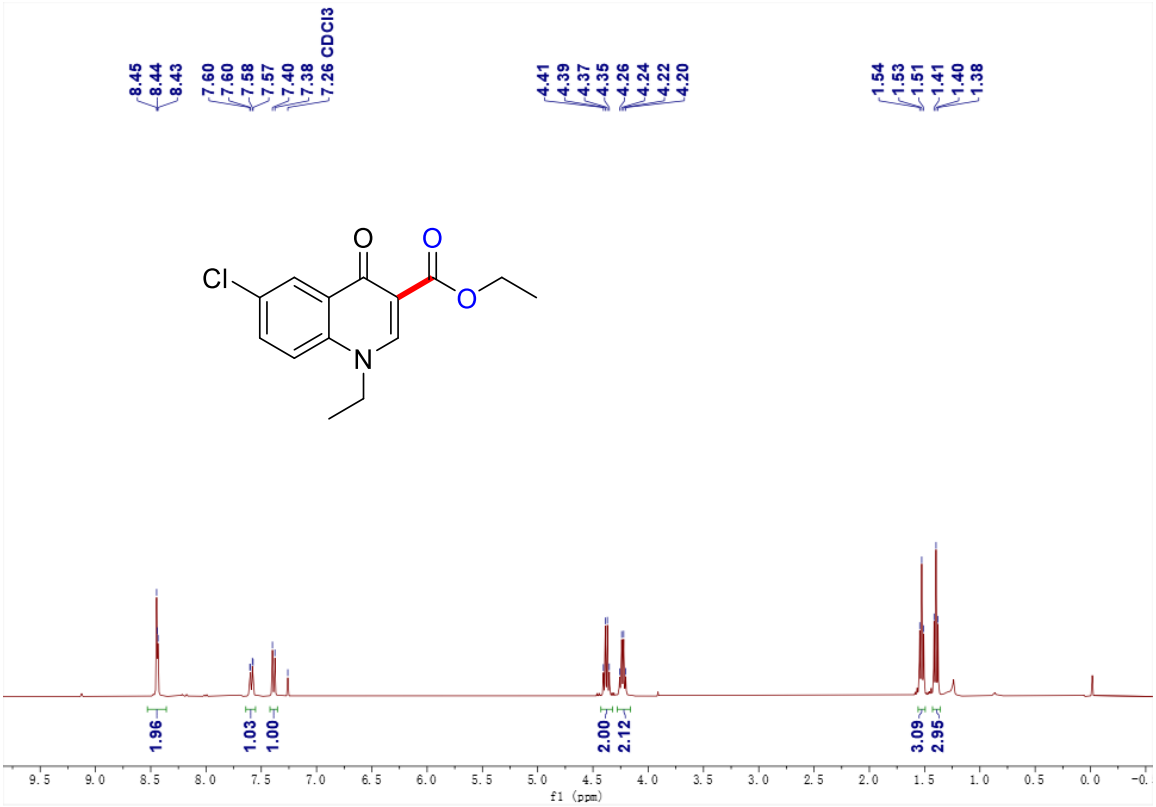
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2i**



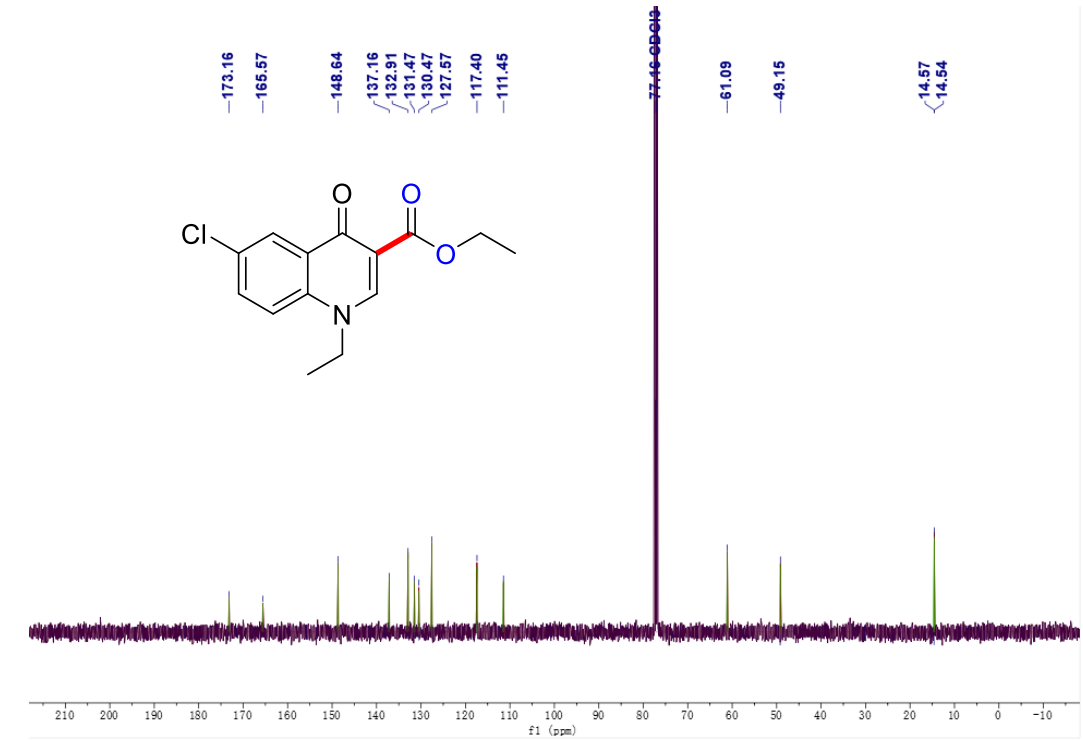
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2i**



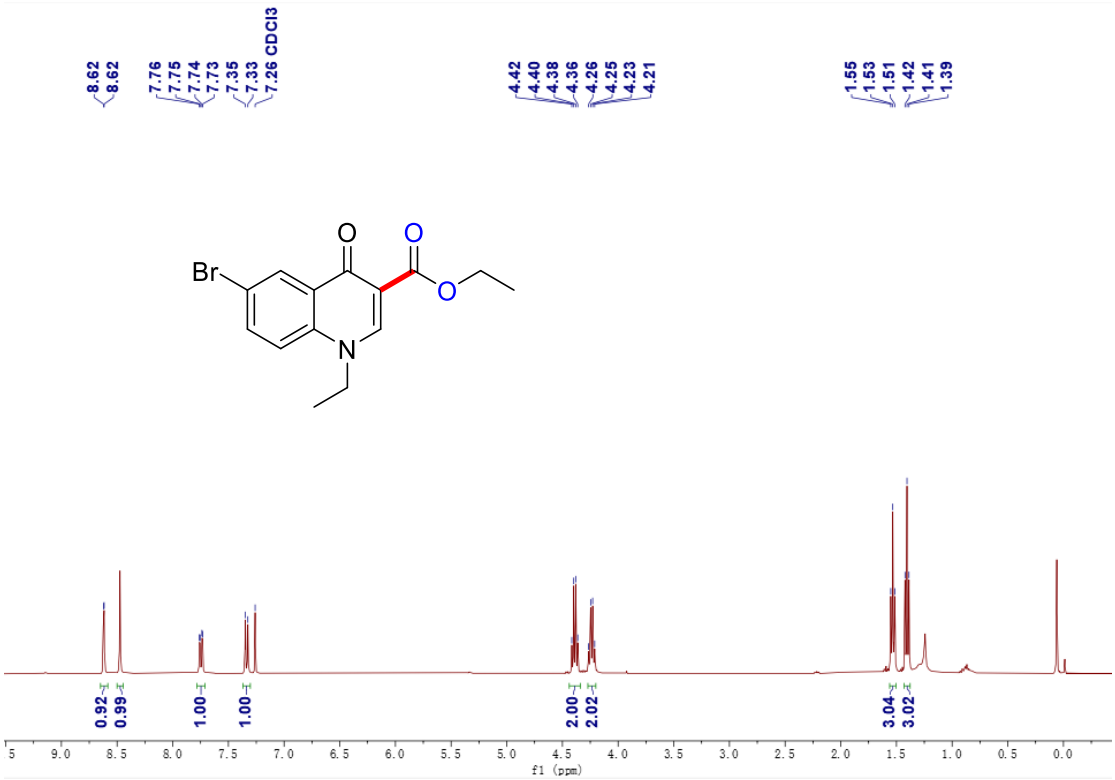
^{19}F NMR (101 MHz, $CDCl_3$) spectrum of **2i**



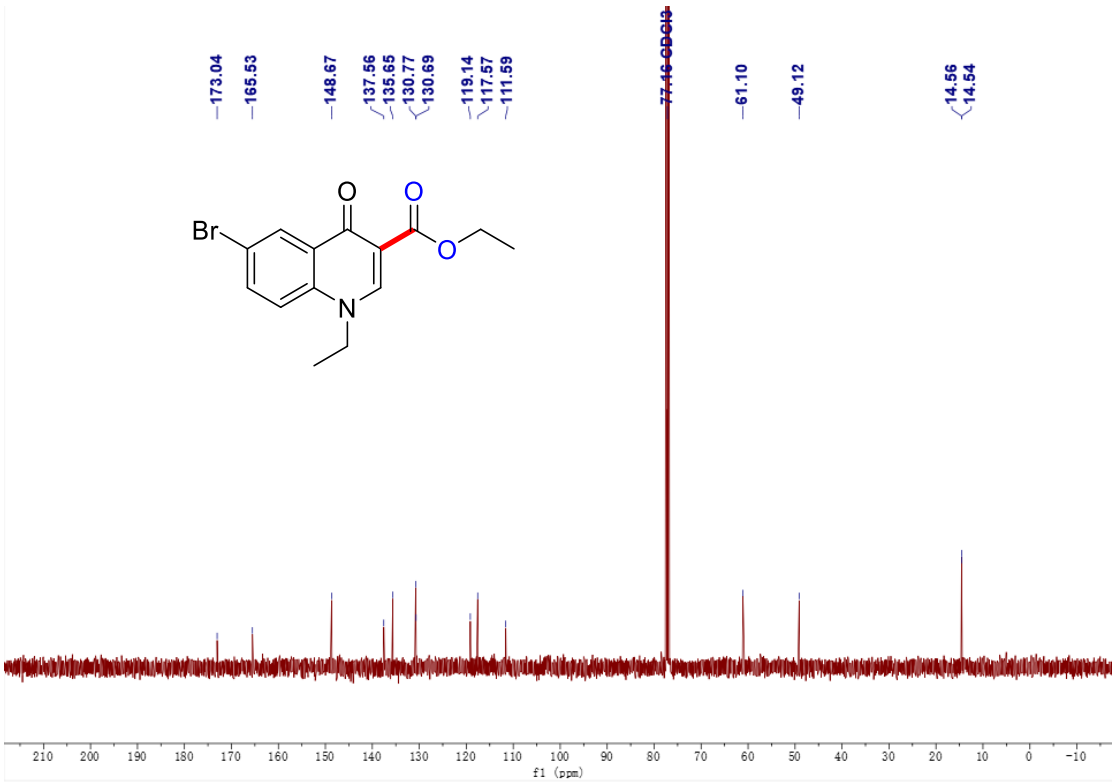
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2j**



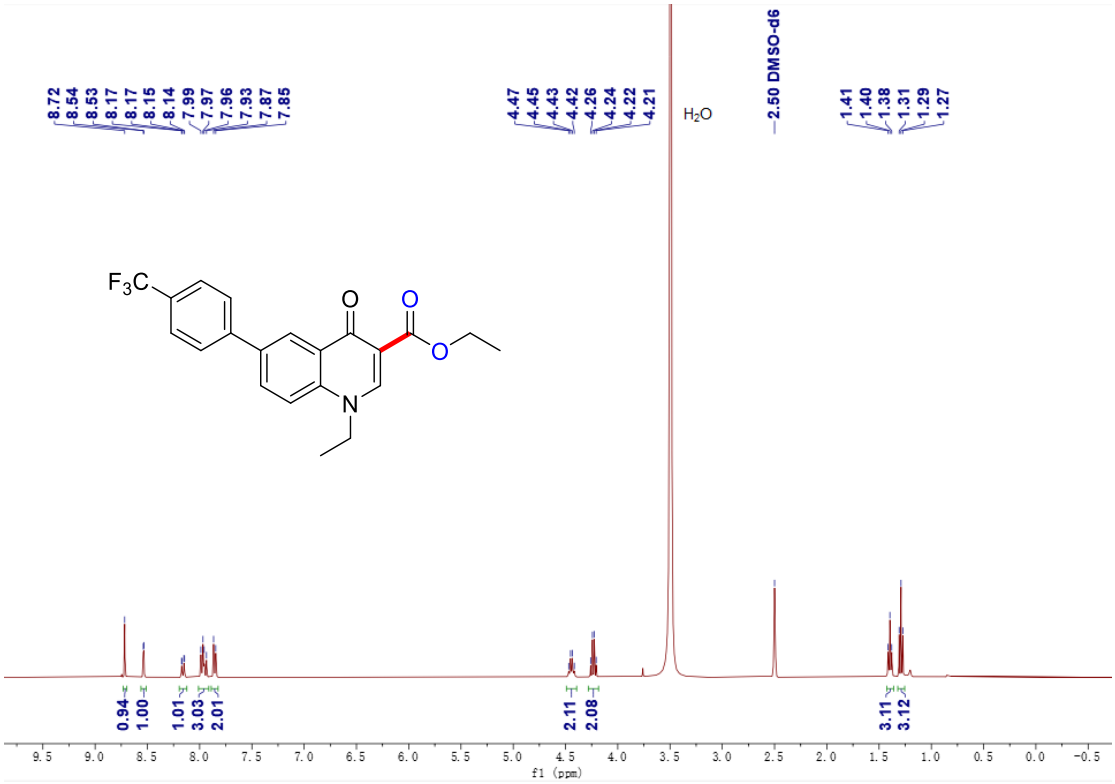
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2j**



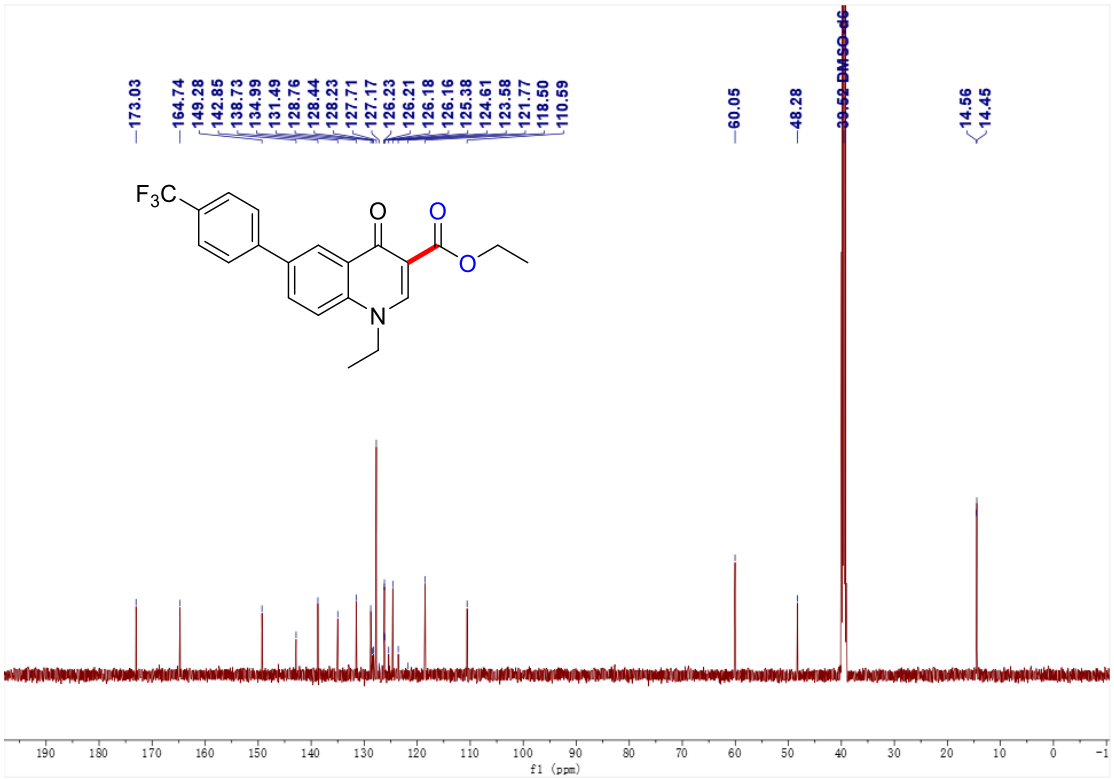
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2k**



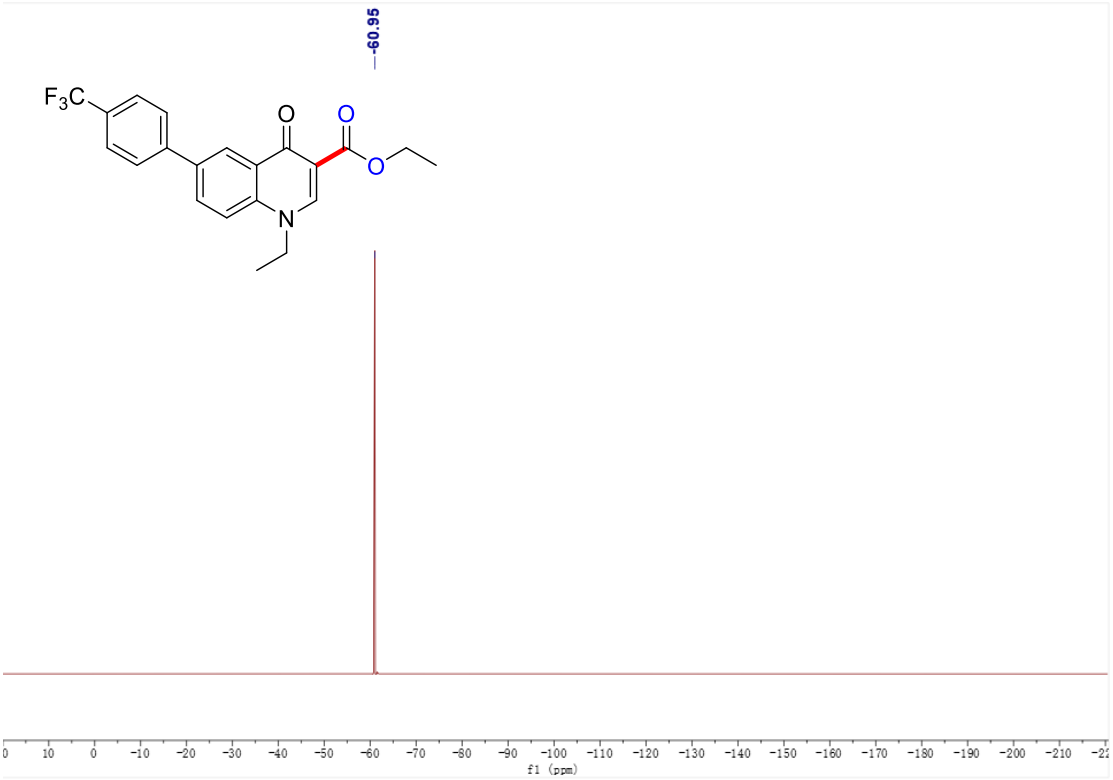
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2k**



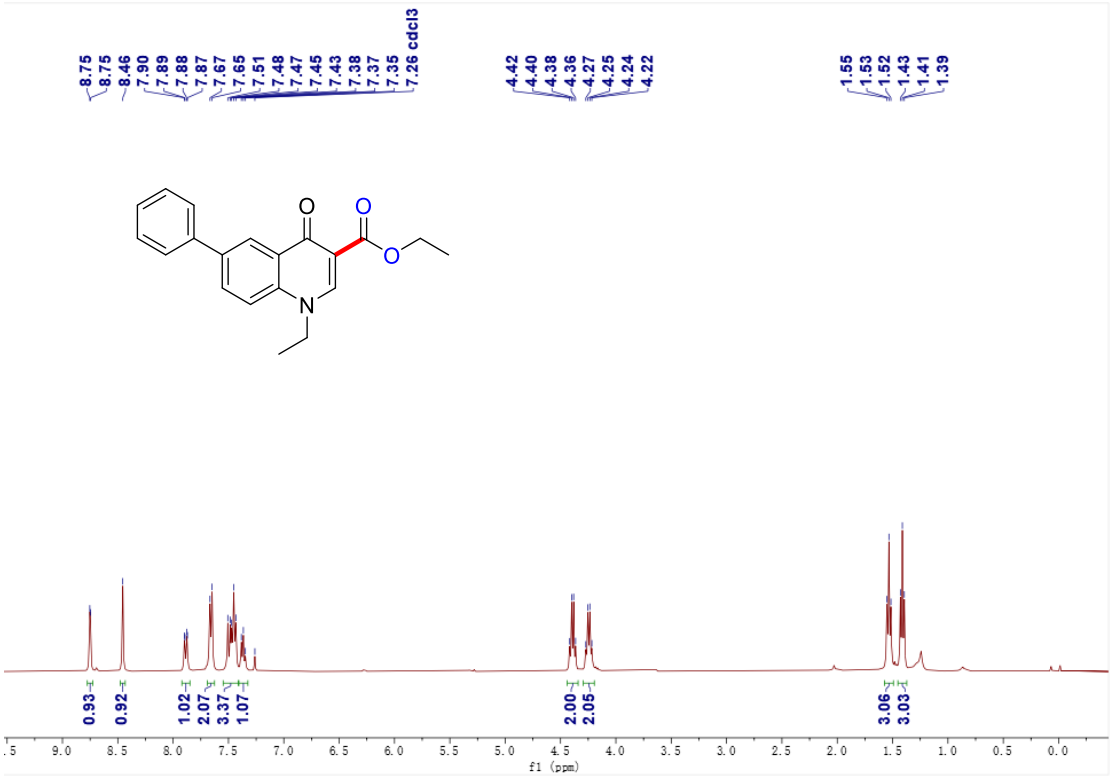
^{1}H NMR (400 MHz, DMSO-*d6*) spectrum of **2l**



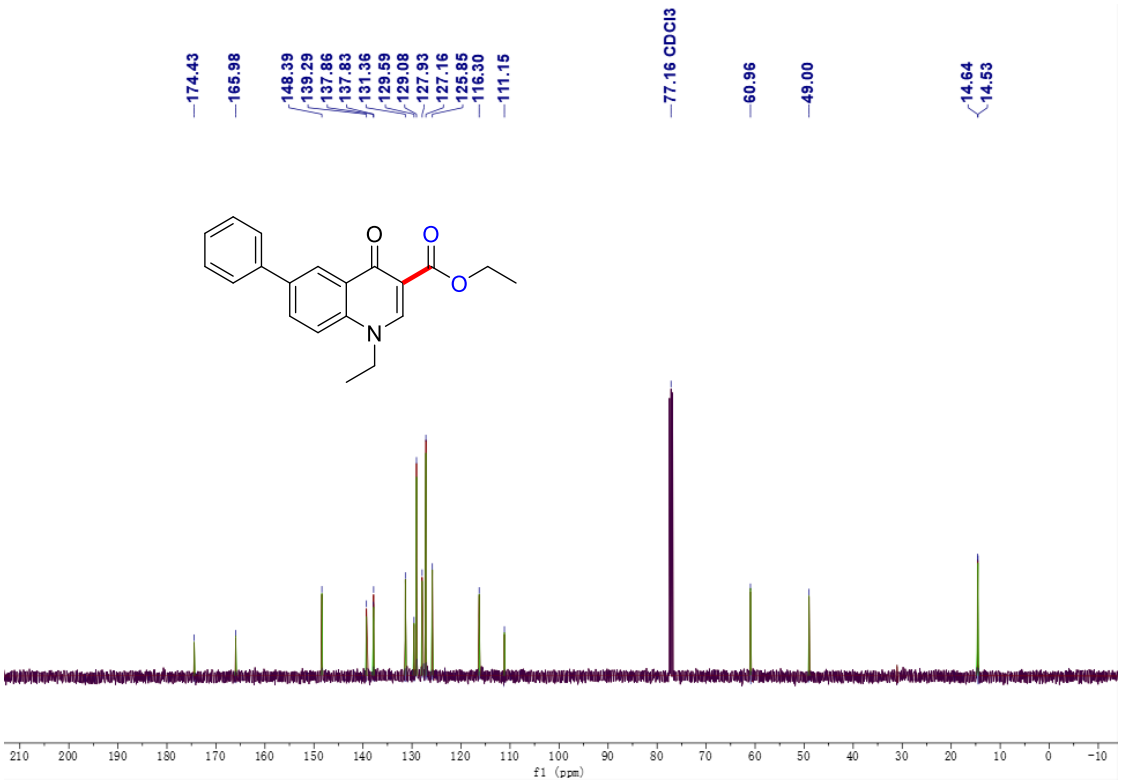
^{13}C NMR (101 MHz, DMSO-*d6*) spectrum of **2l**



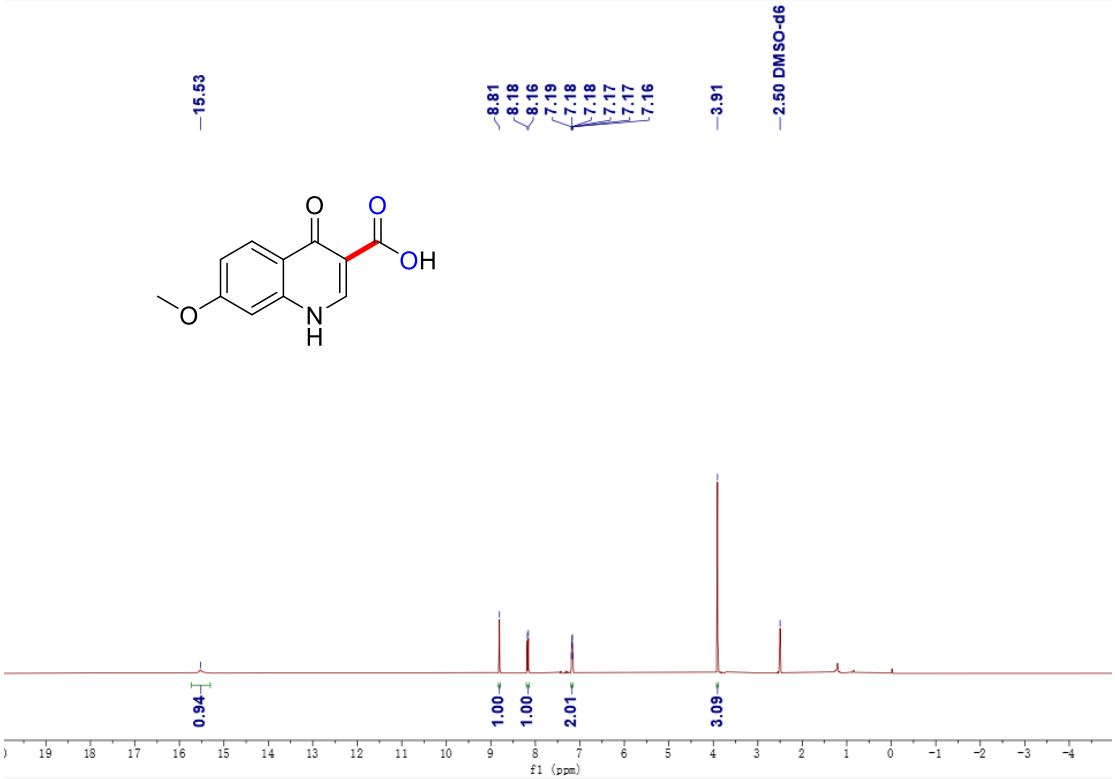
^{19}F NMR (101 MHz, DMSO-*d6*) spectrum of **2l**



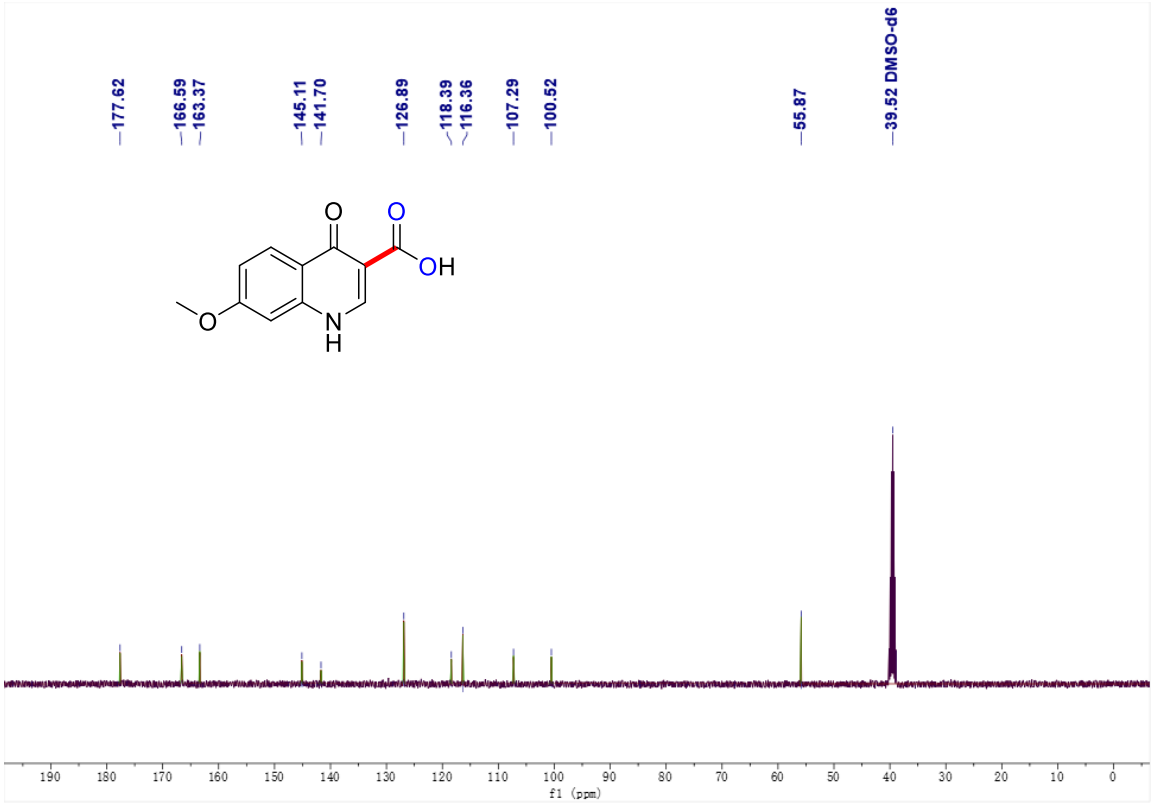
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2m**



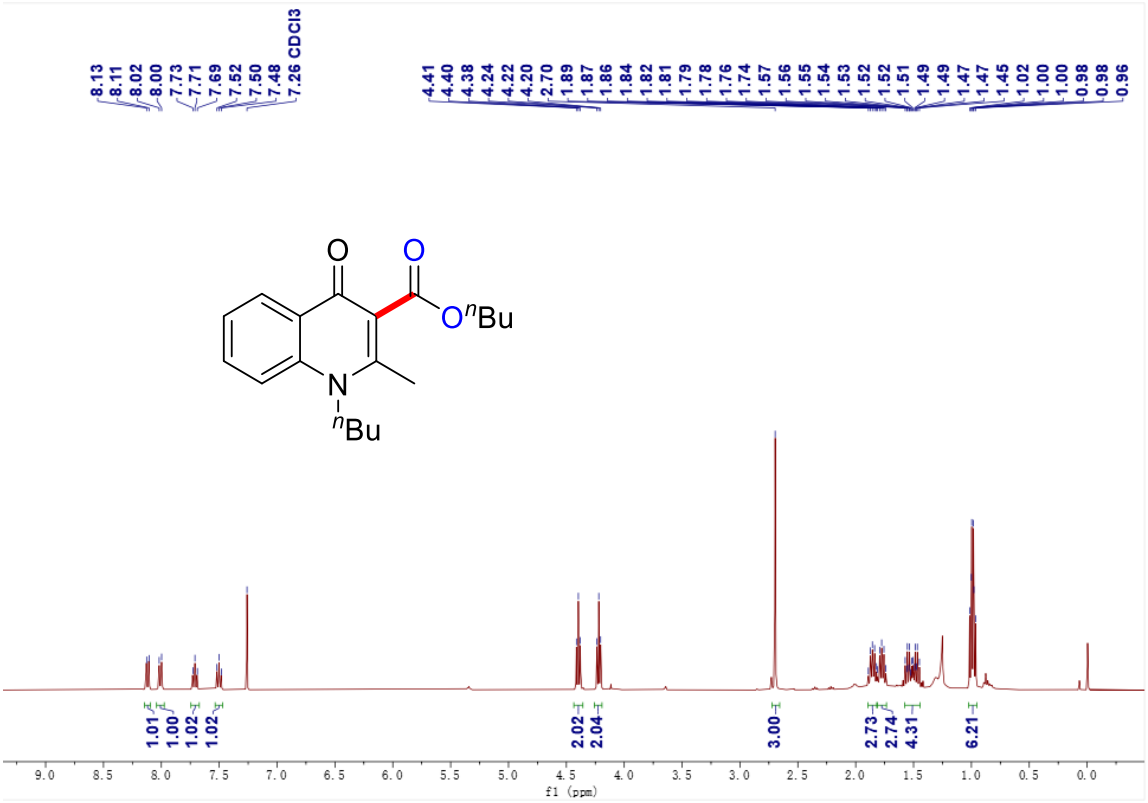
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2m**



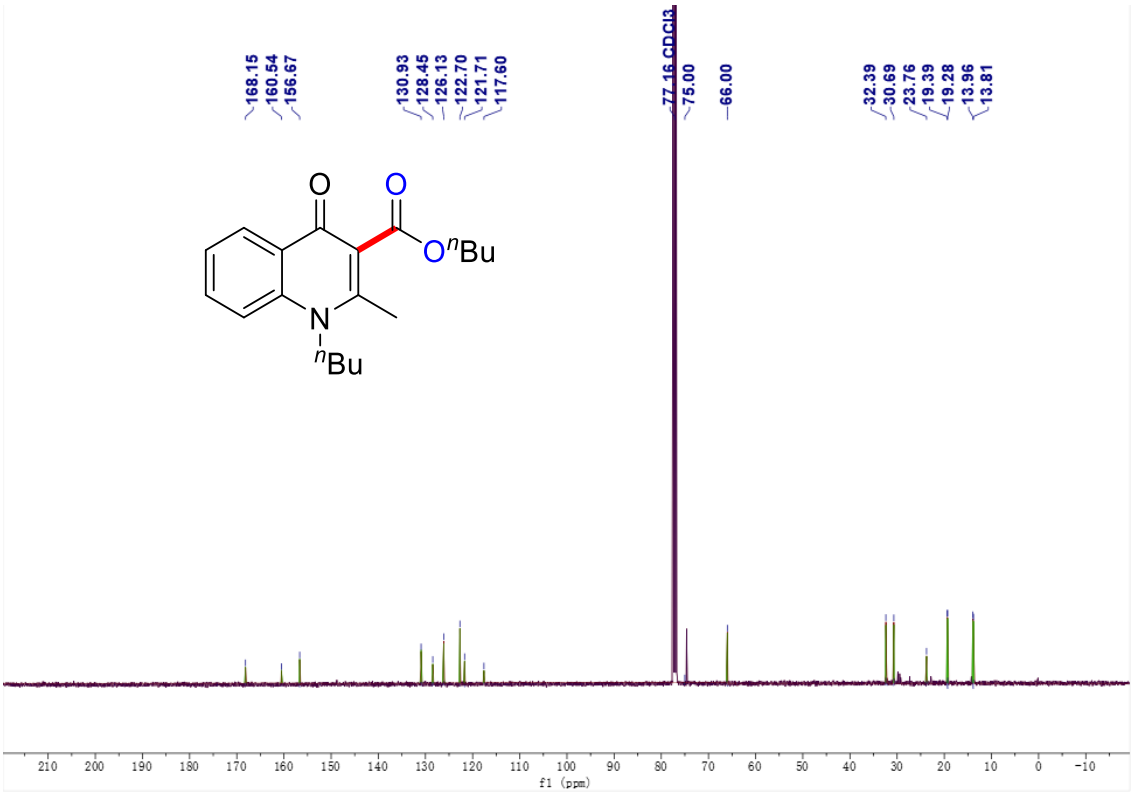
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2n**



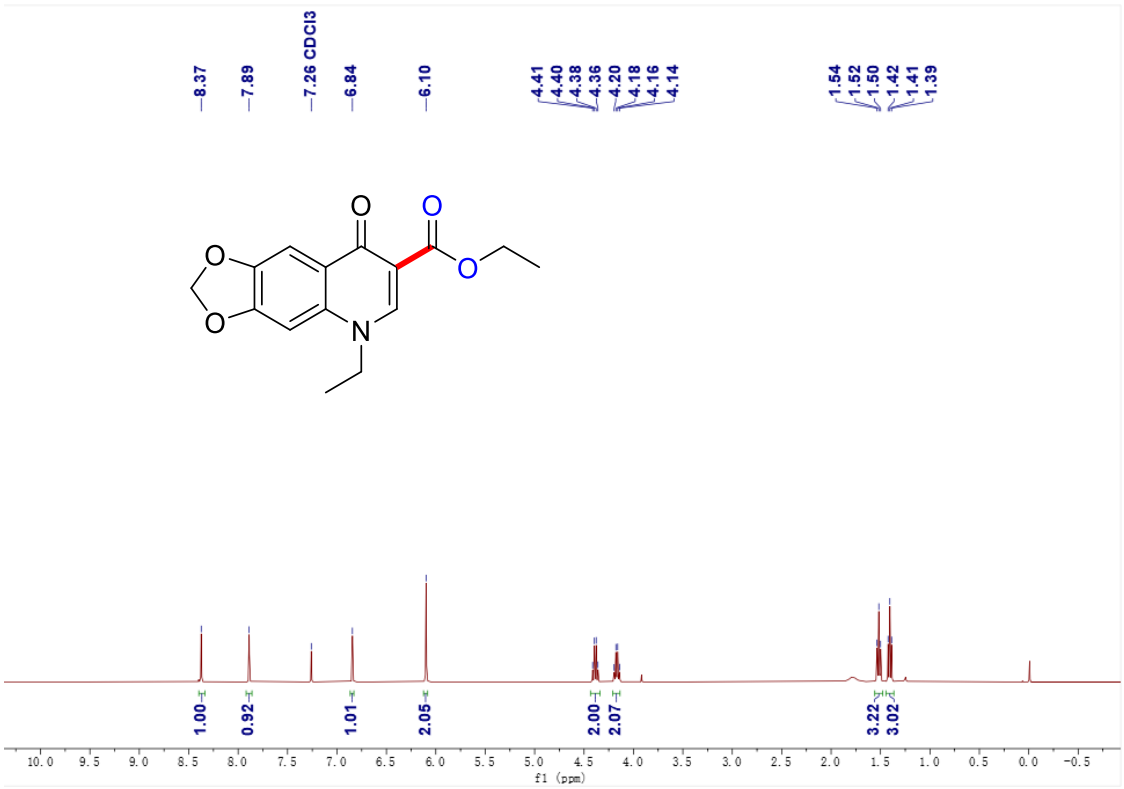
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2n**



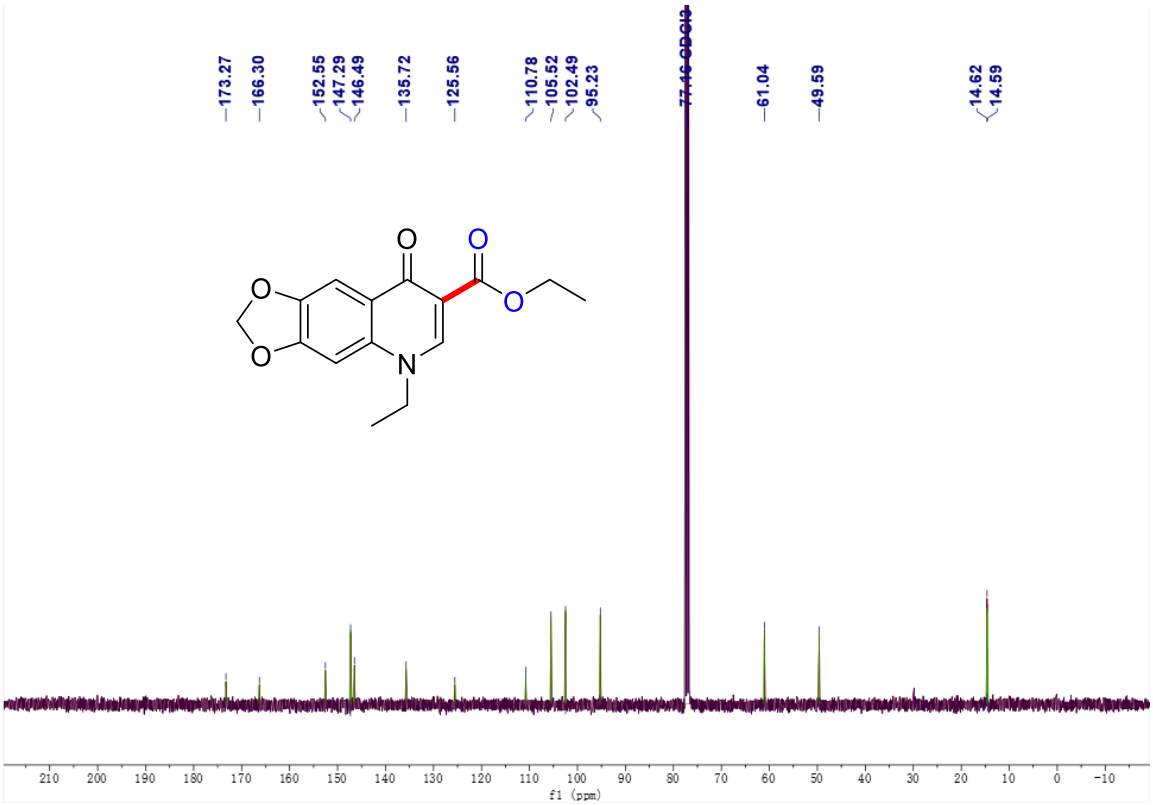
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2o**



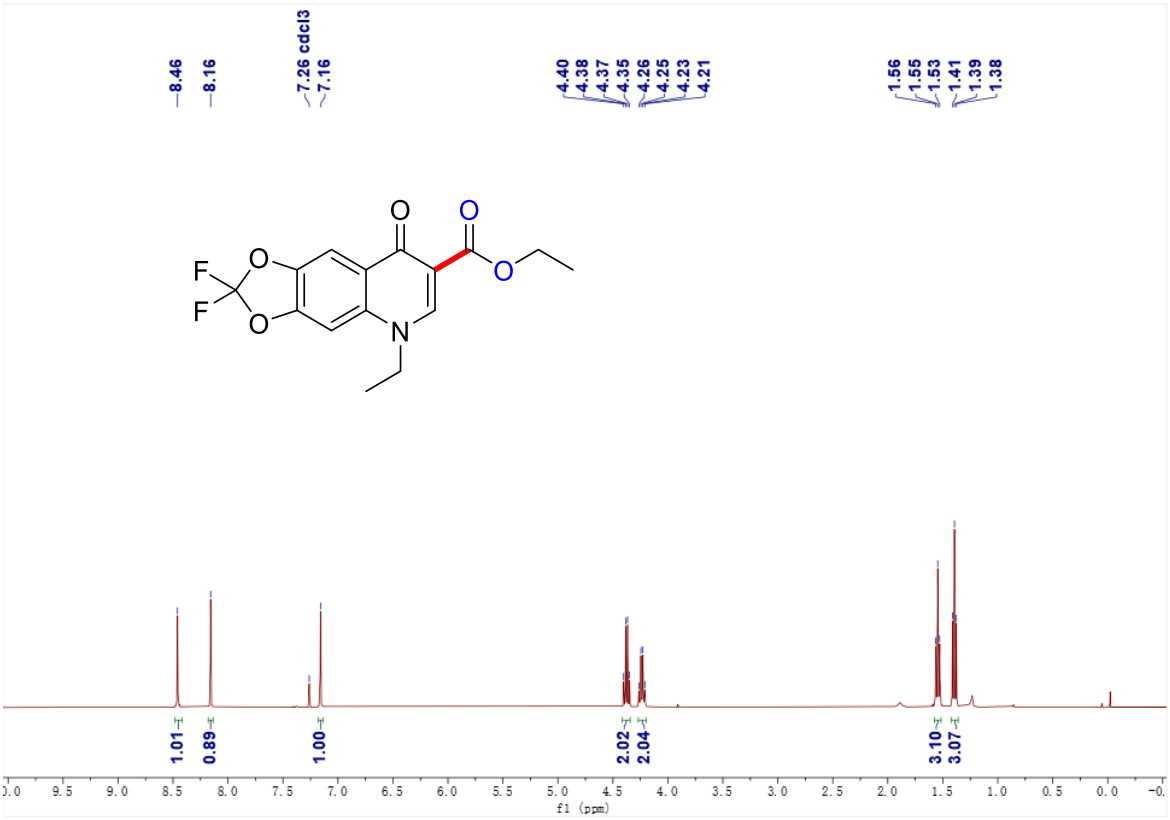
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2o**



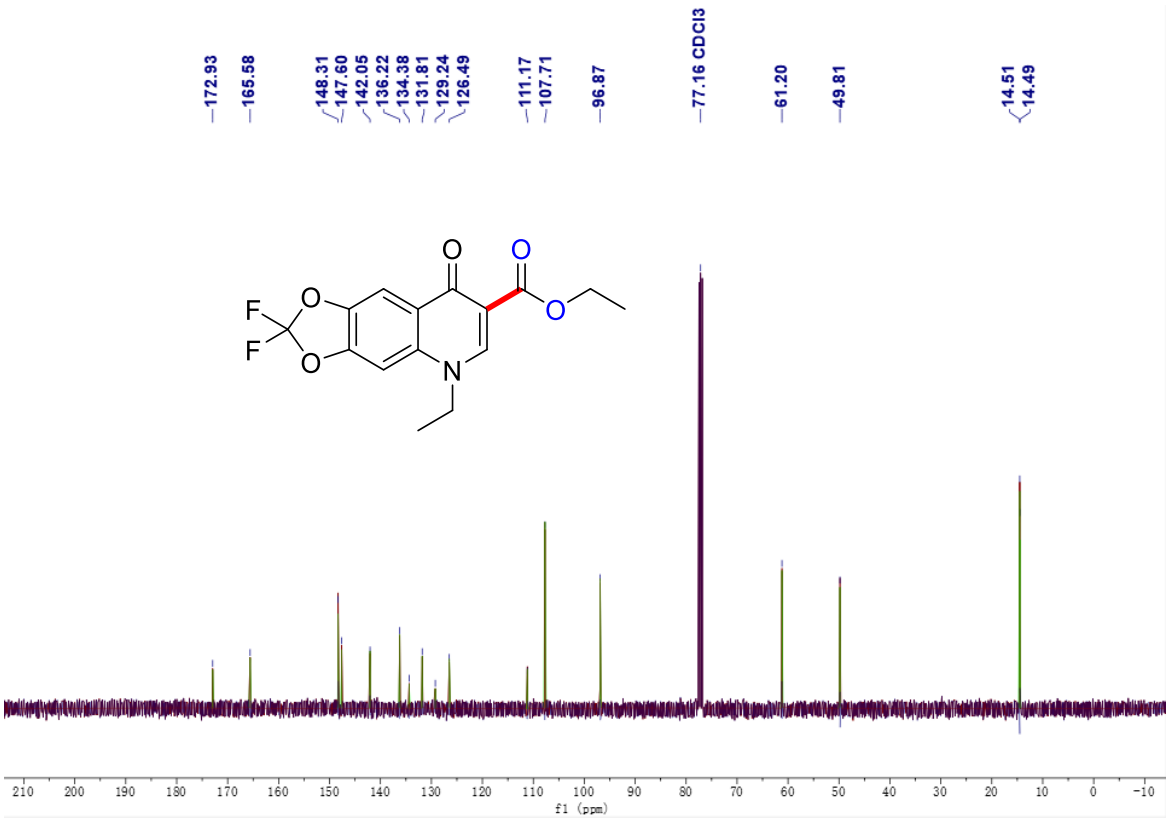
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2p**



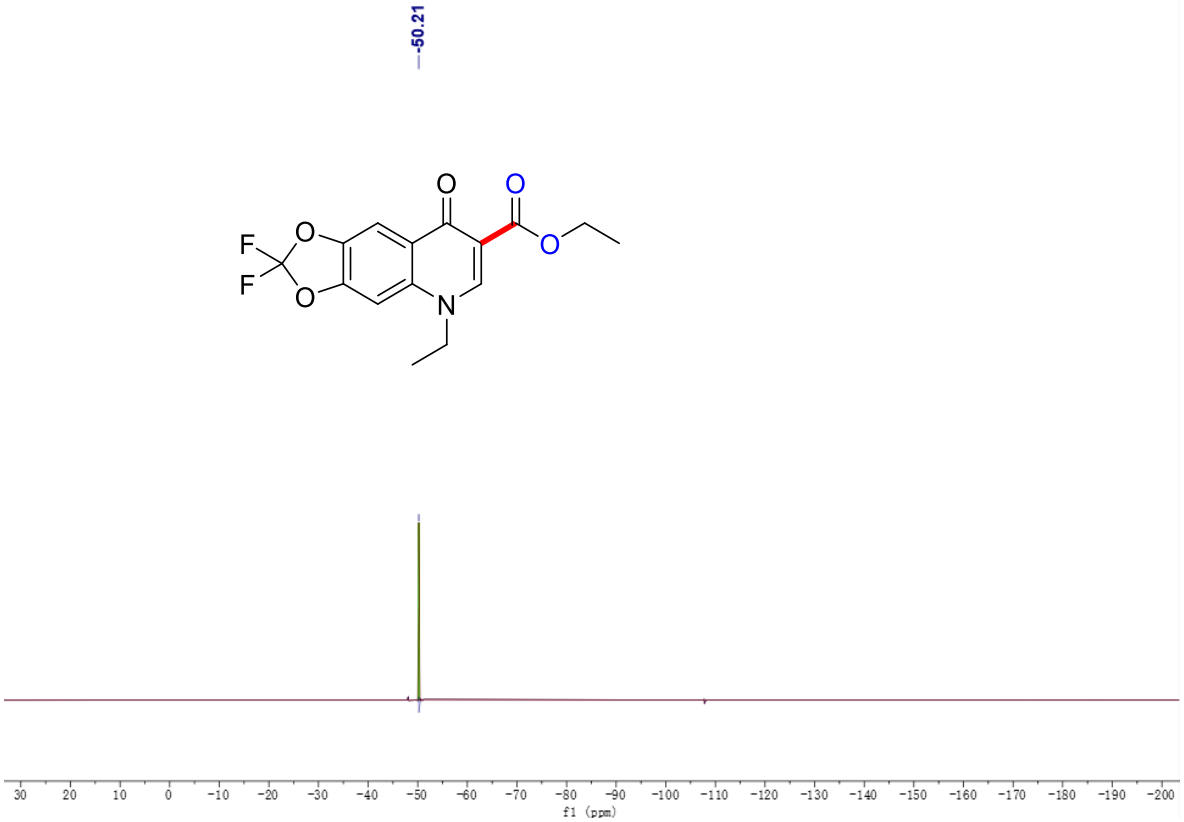
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2p**



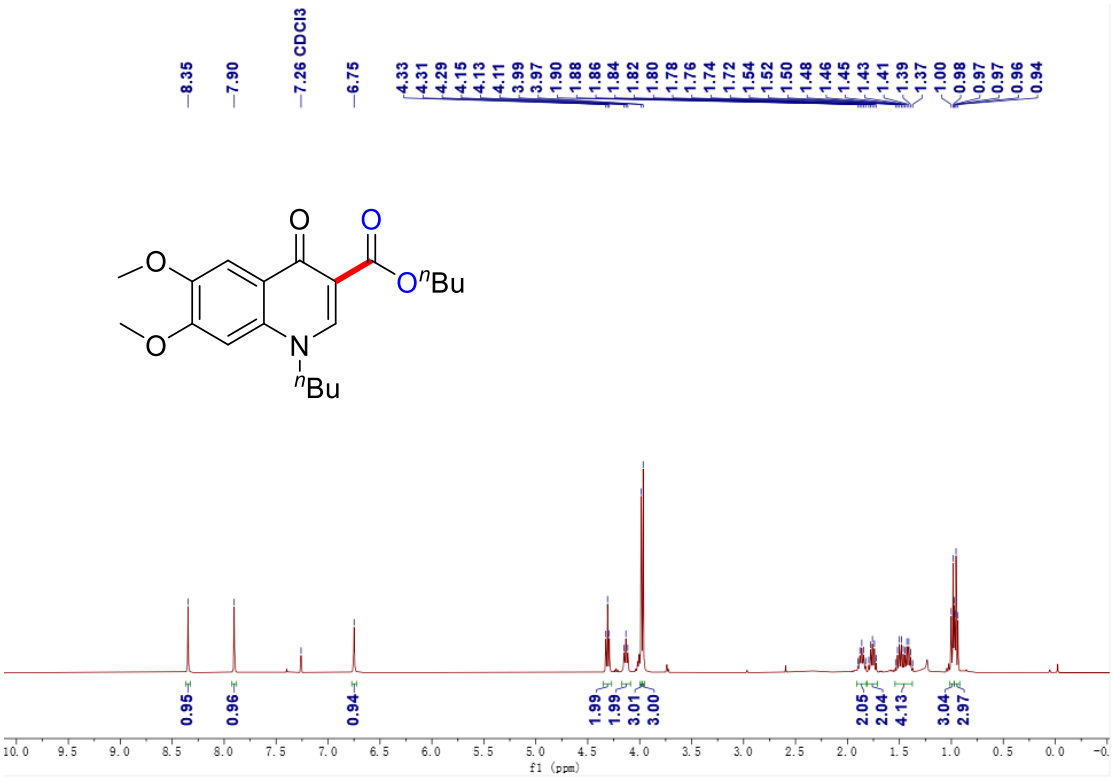
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2q**



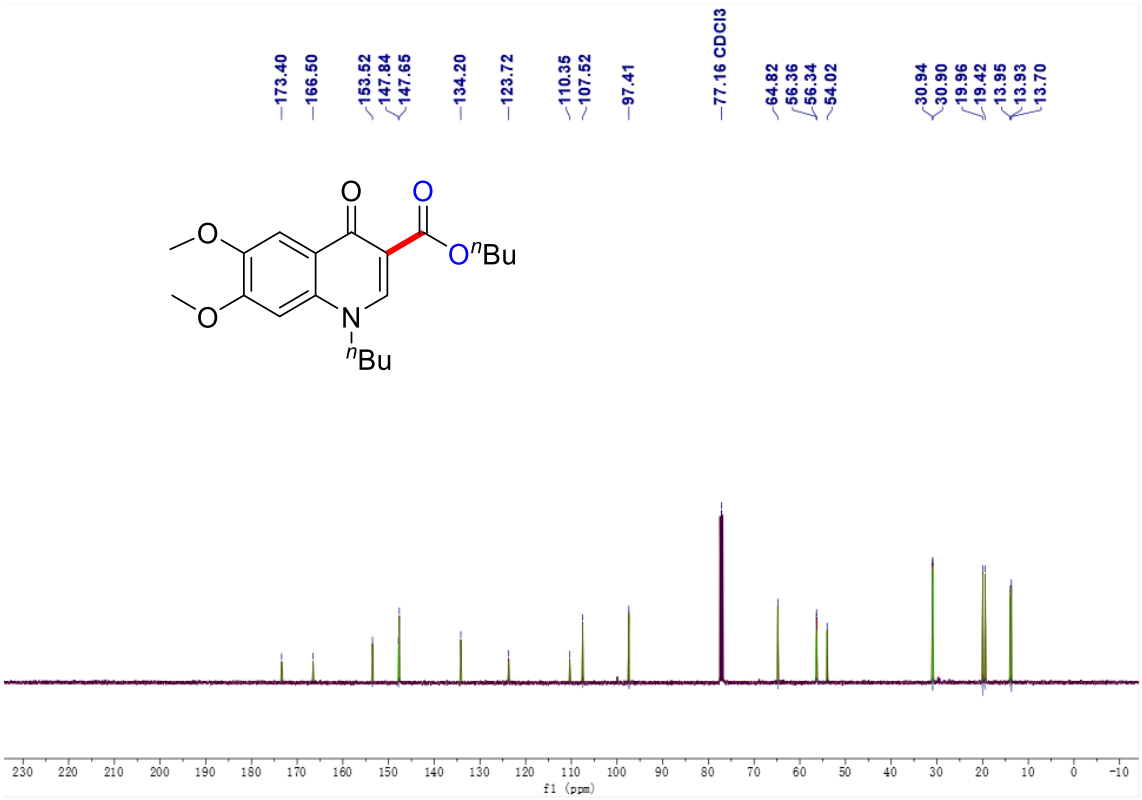
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2q**



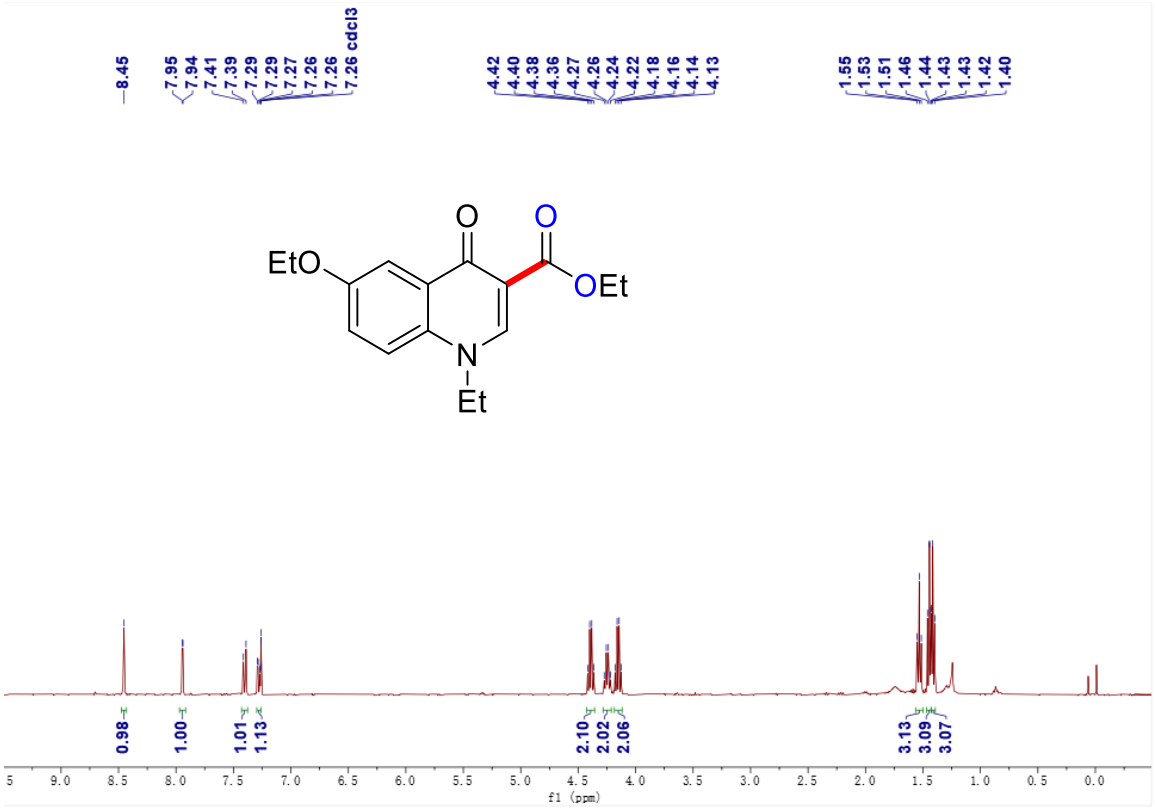
^{19}F NMR (101 MHz, $CDCl_3$) spectrum of **2q**



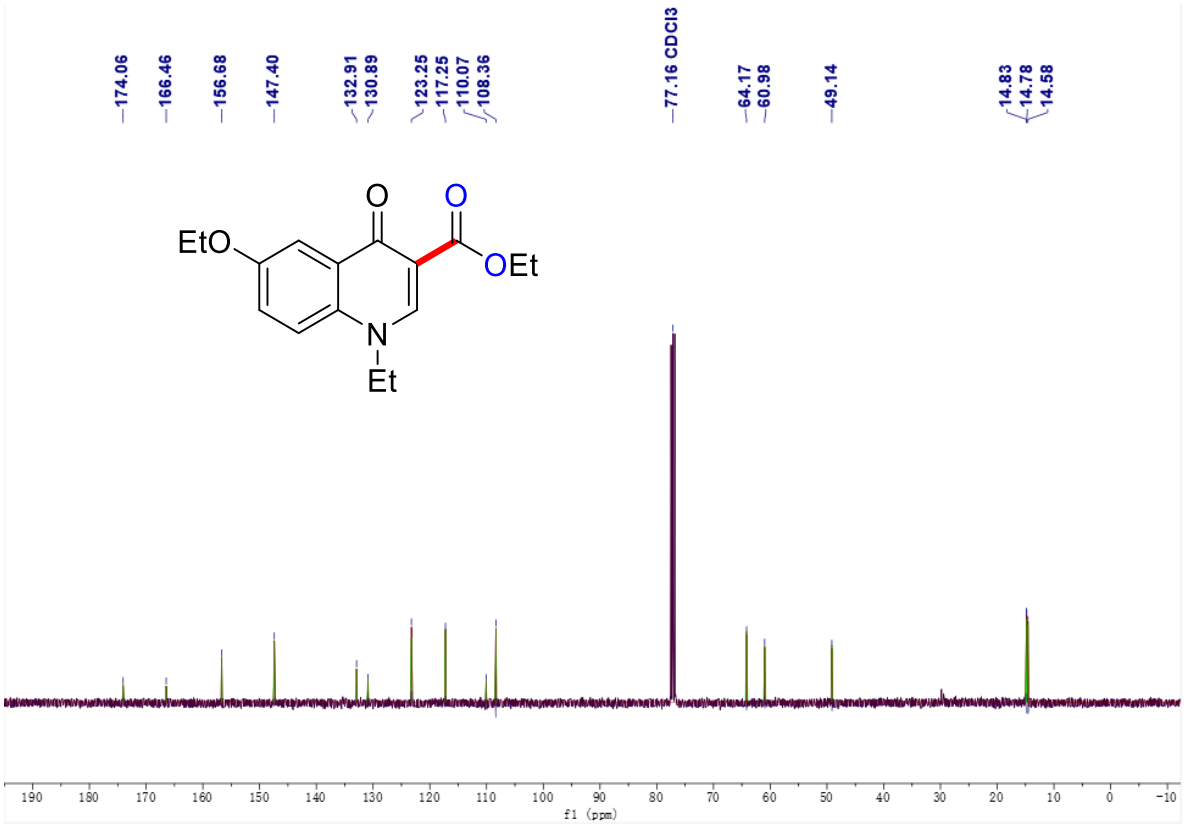
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2r**



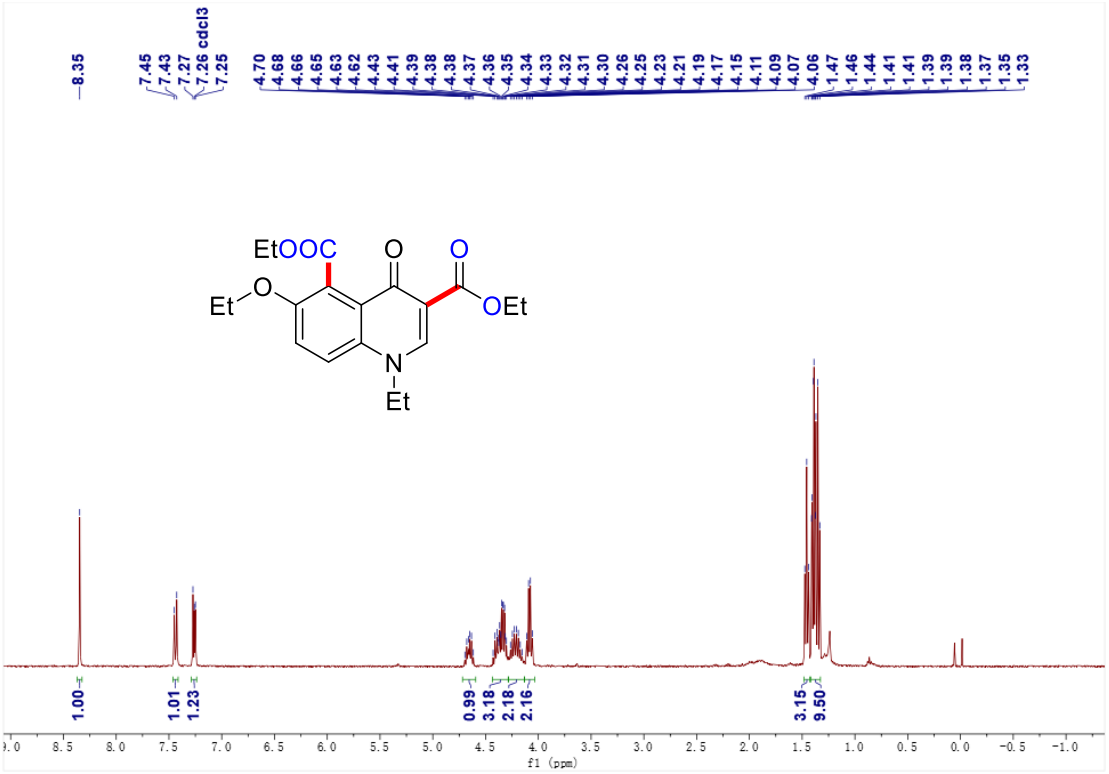
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2r**



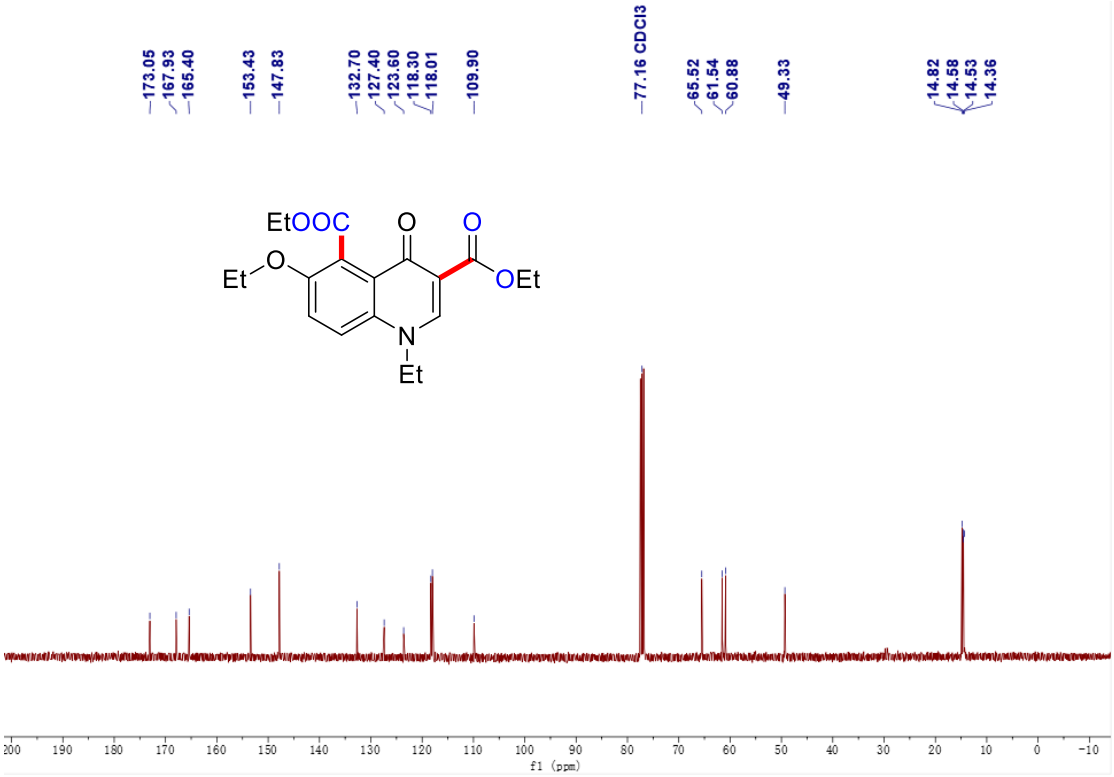
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2s**



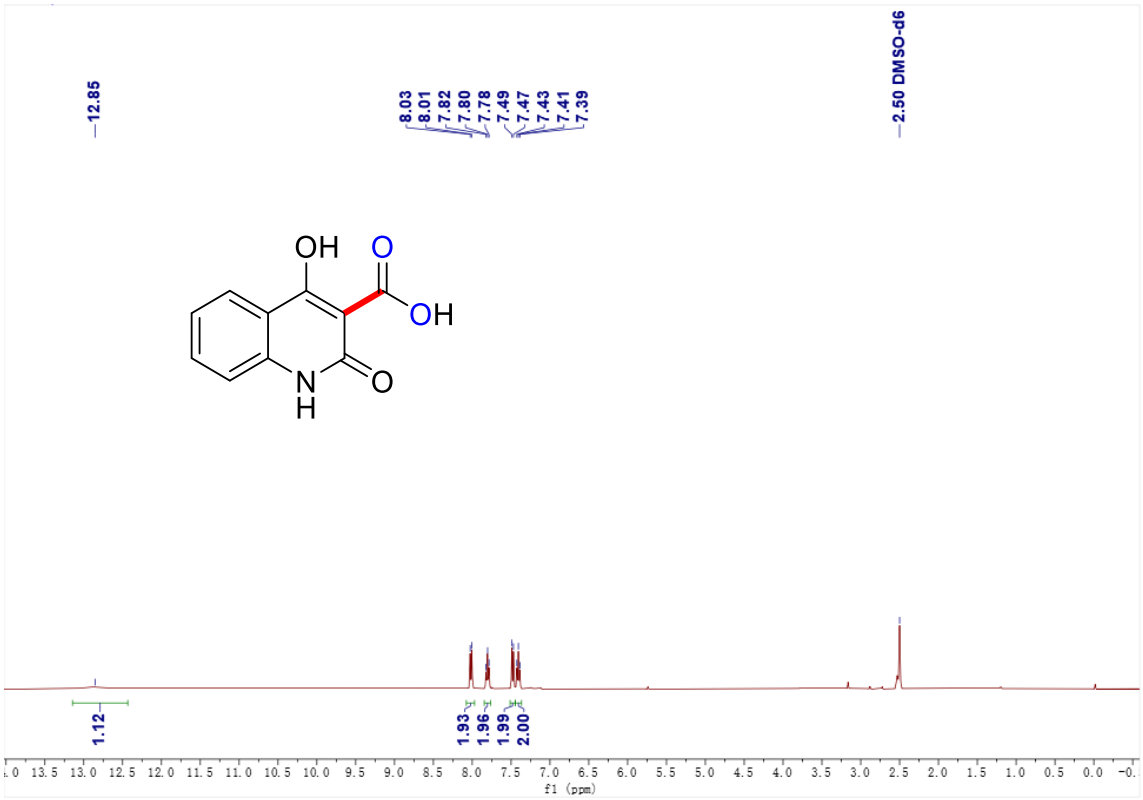
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2s**



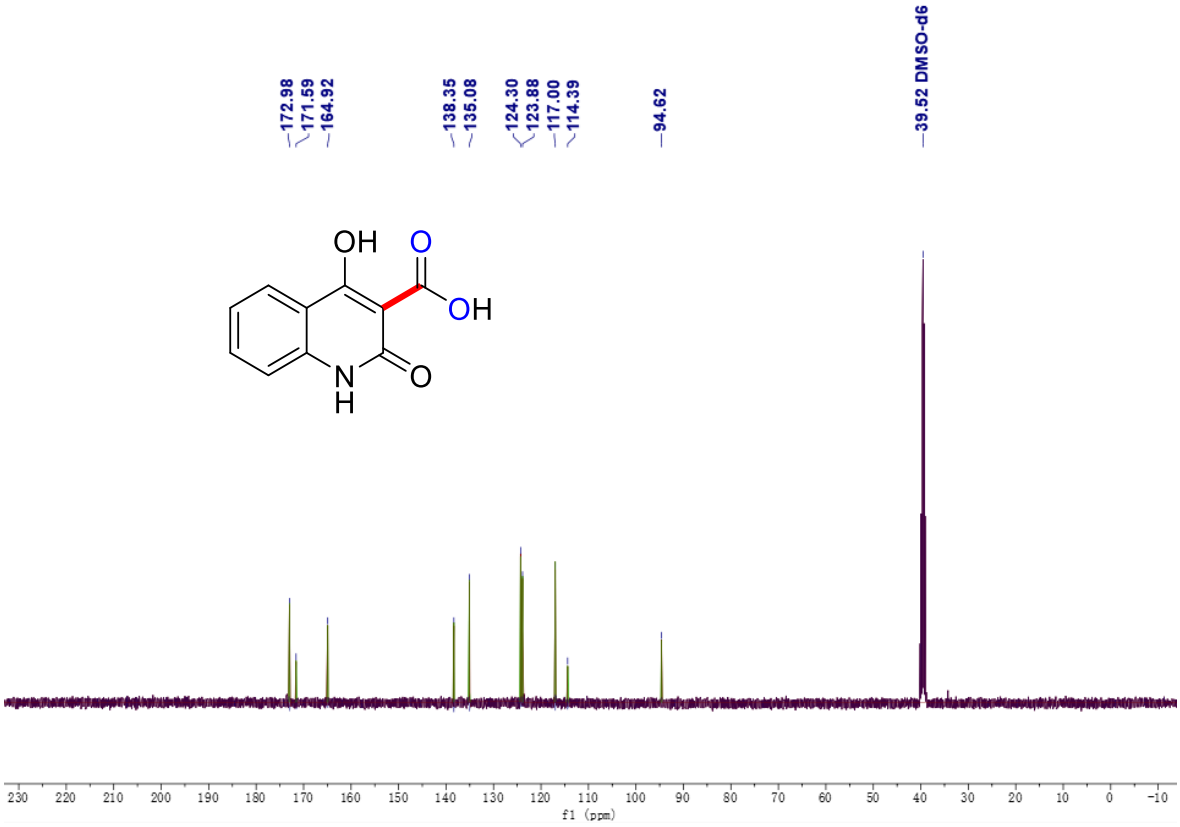
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2s'**



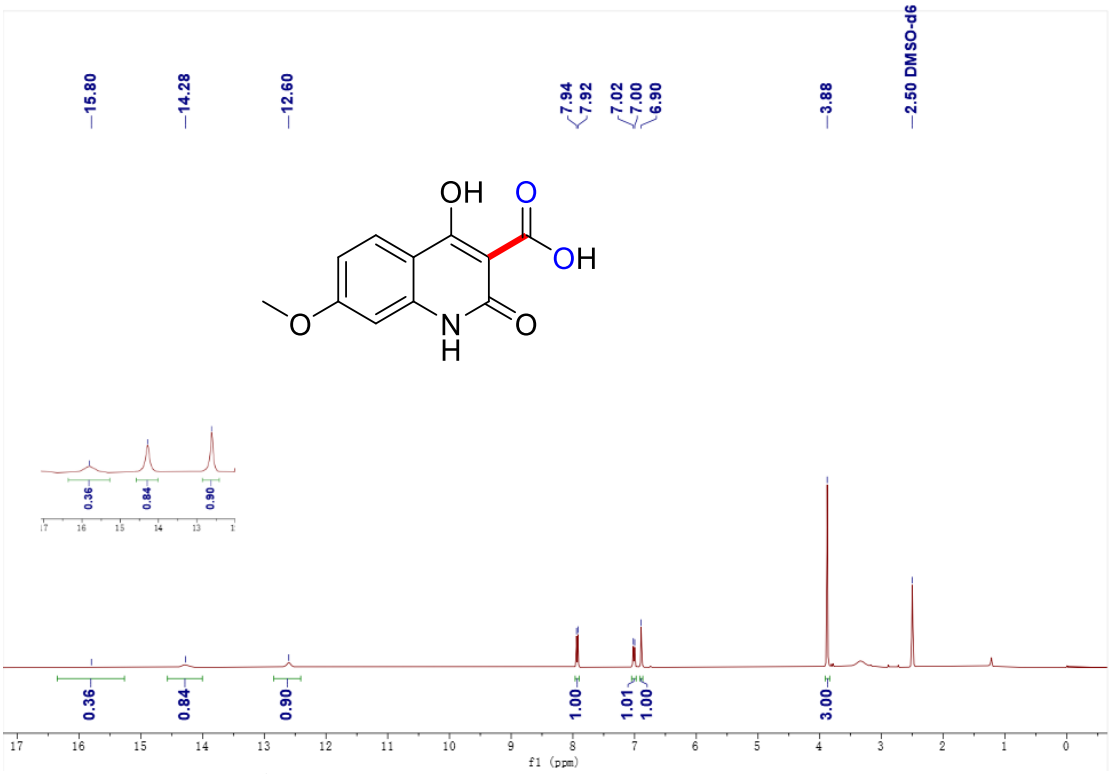
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **2s'**



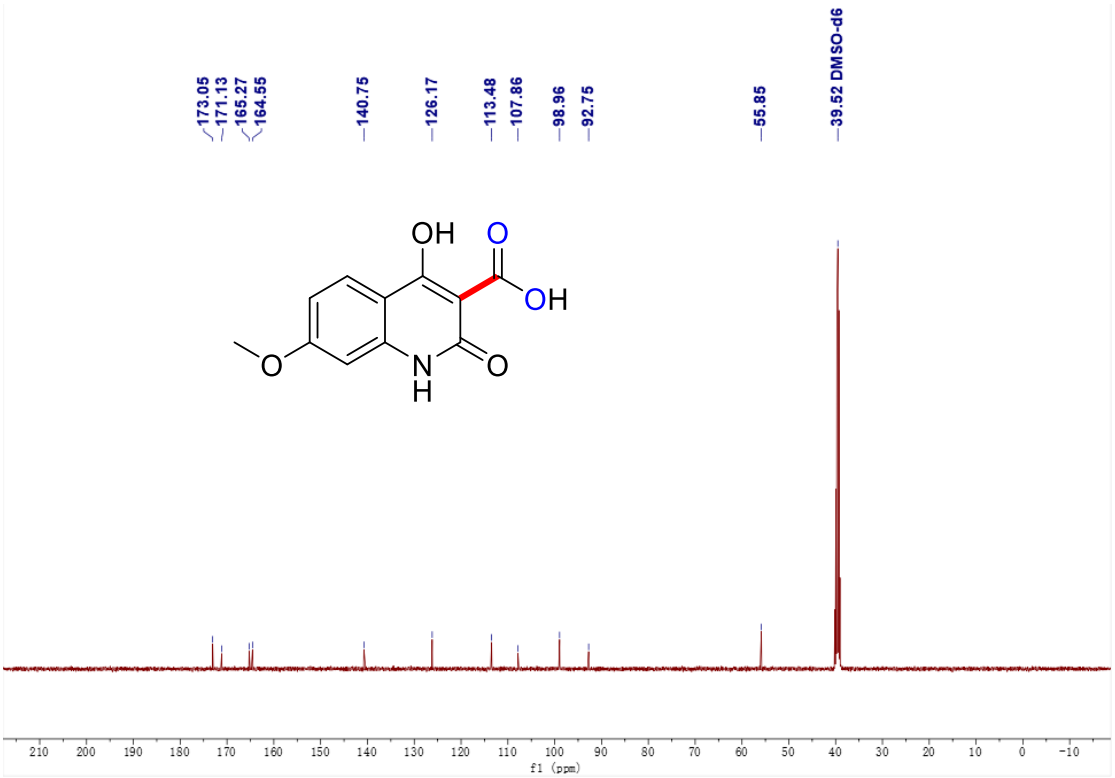
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4a**



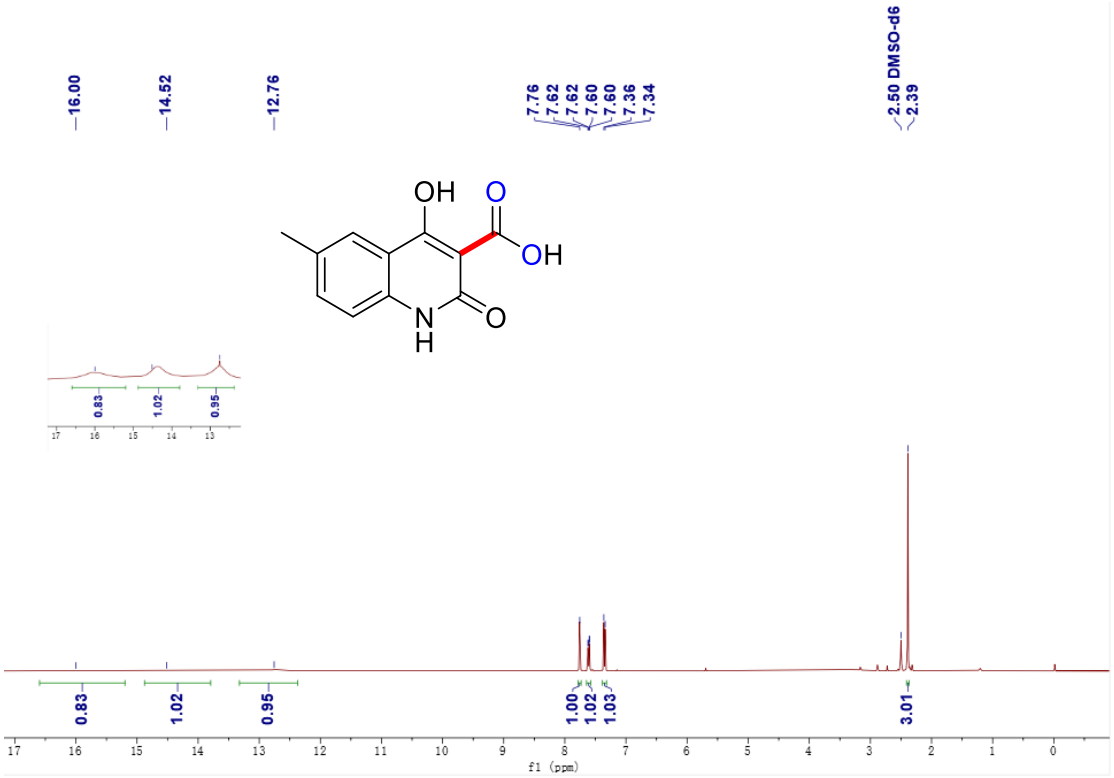
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **4a**



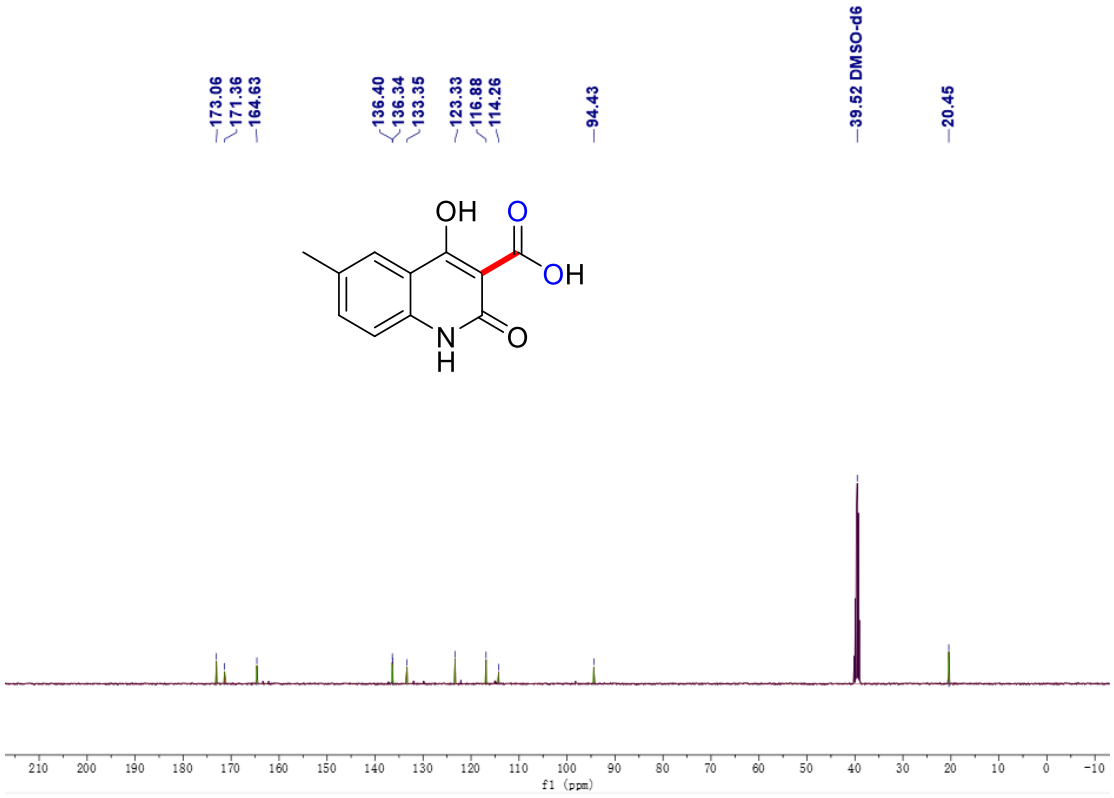
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4b**



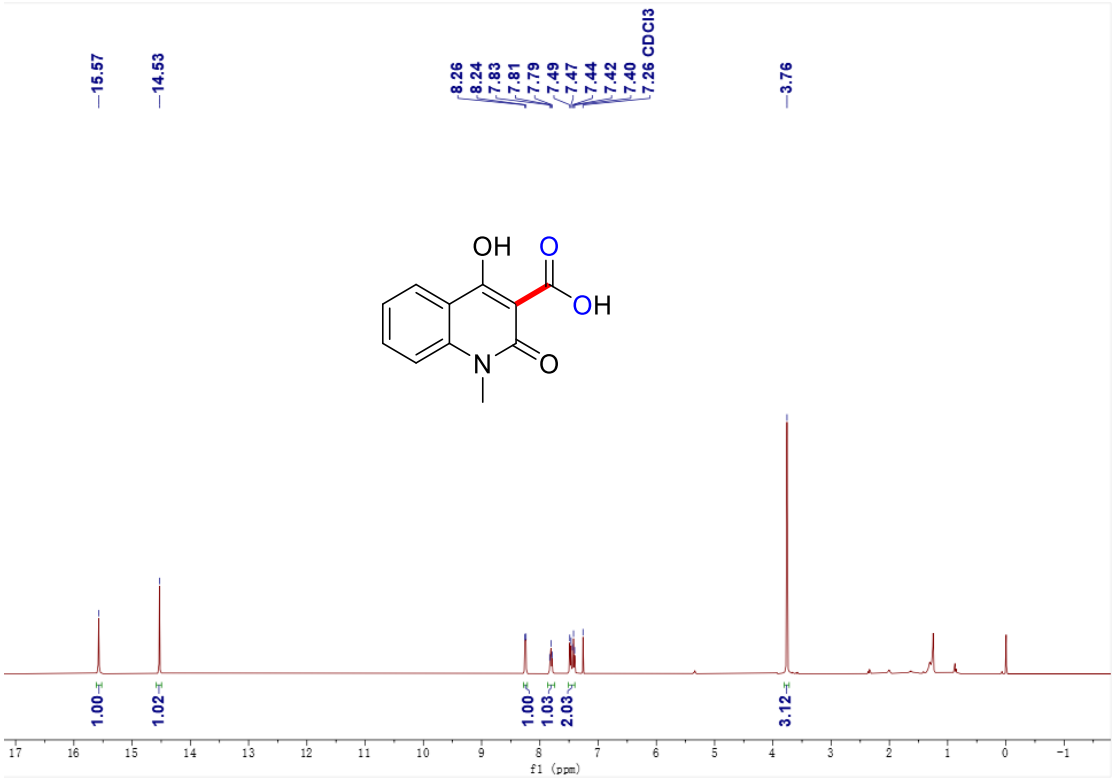
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **4b**



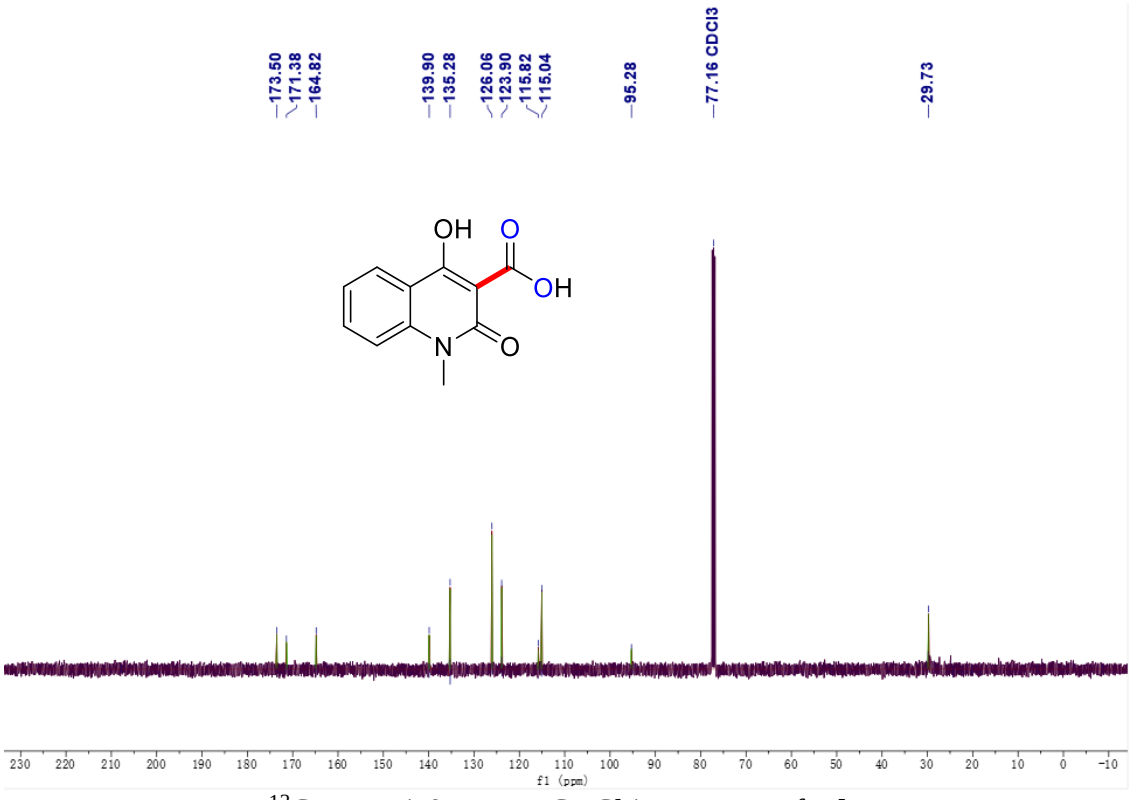
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4c**



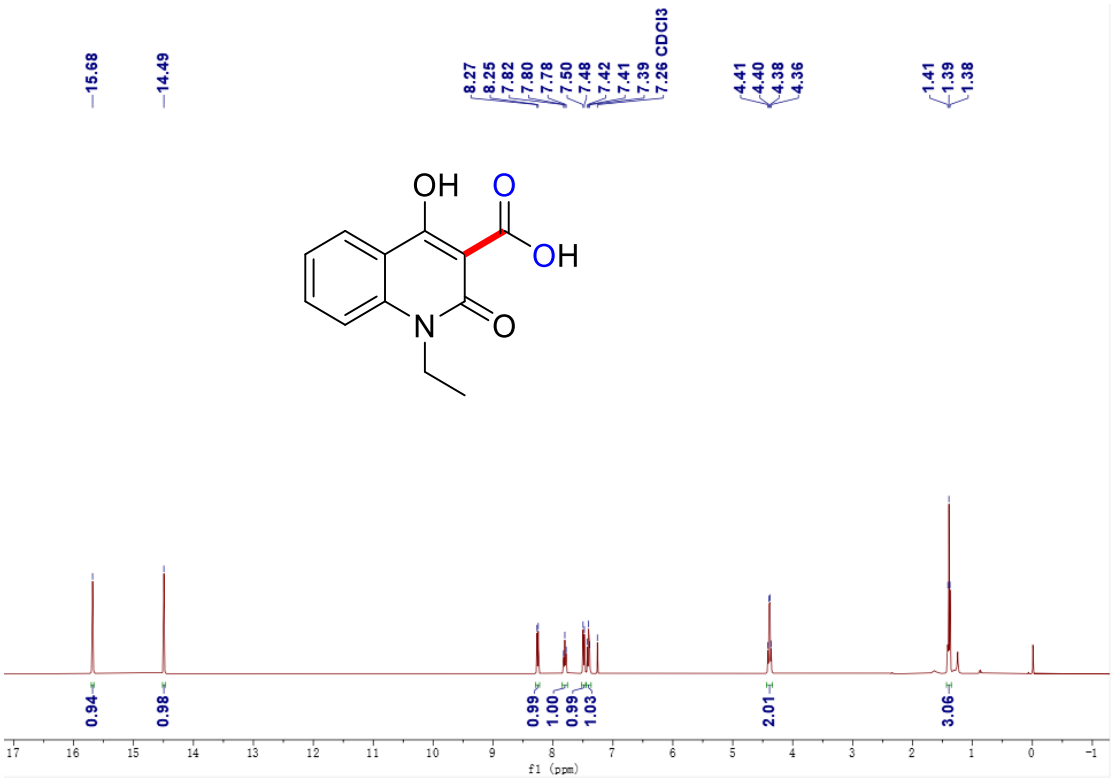
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **4c**



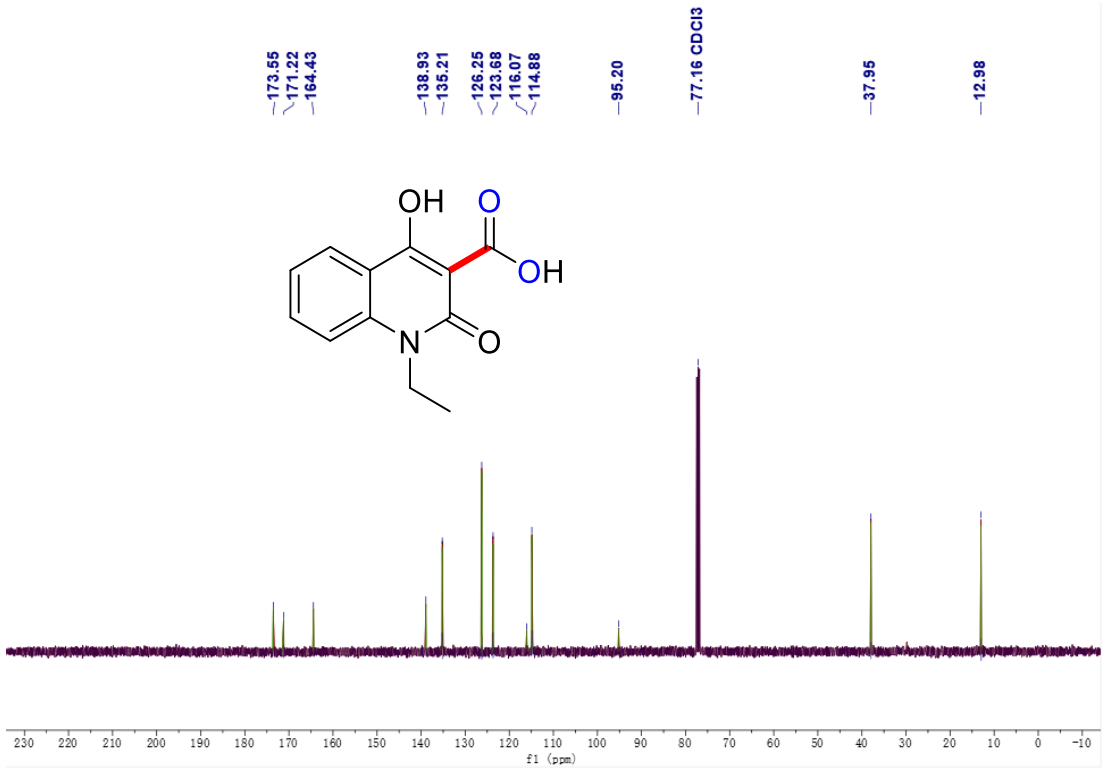
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4d**



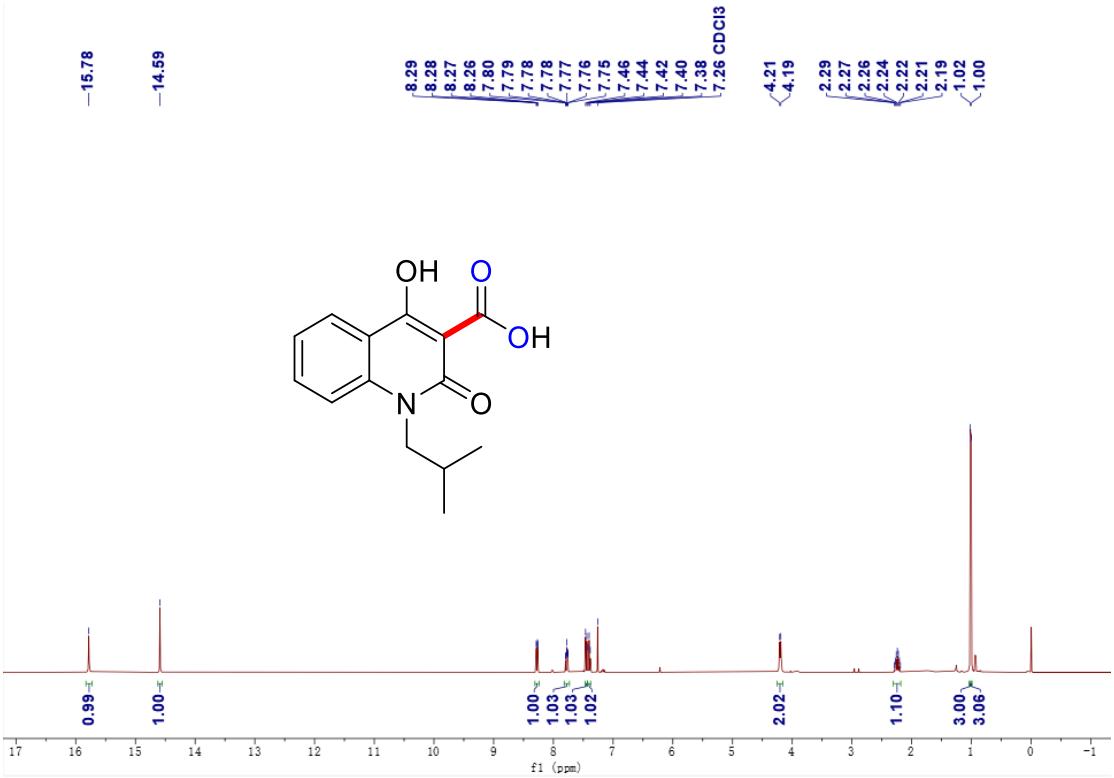
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **4d**



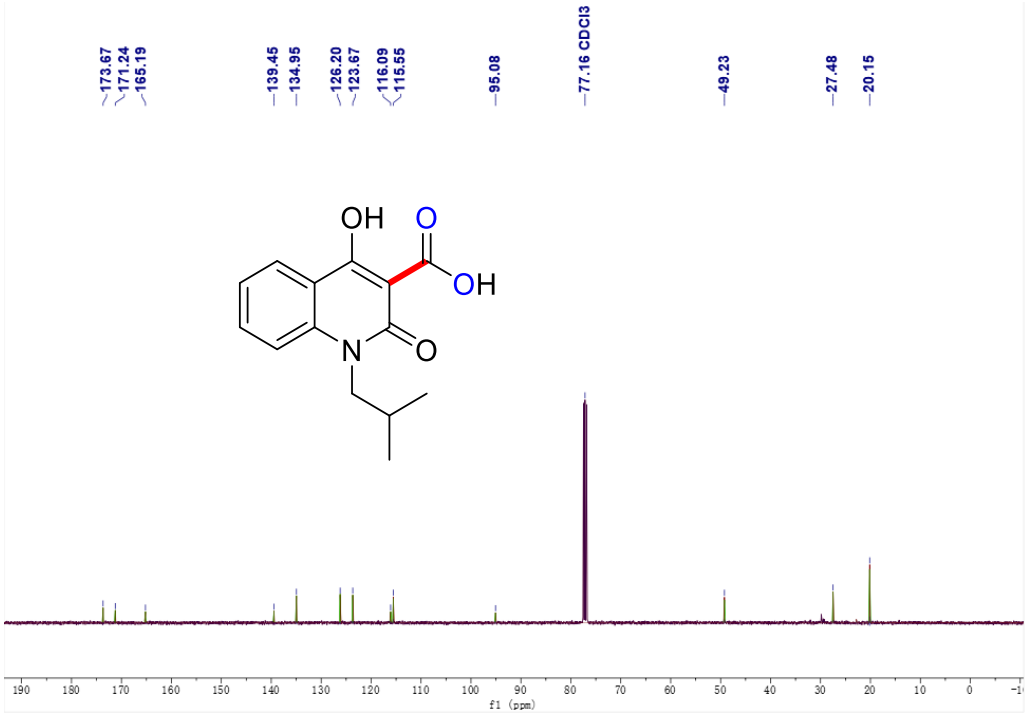
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4e**



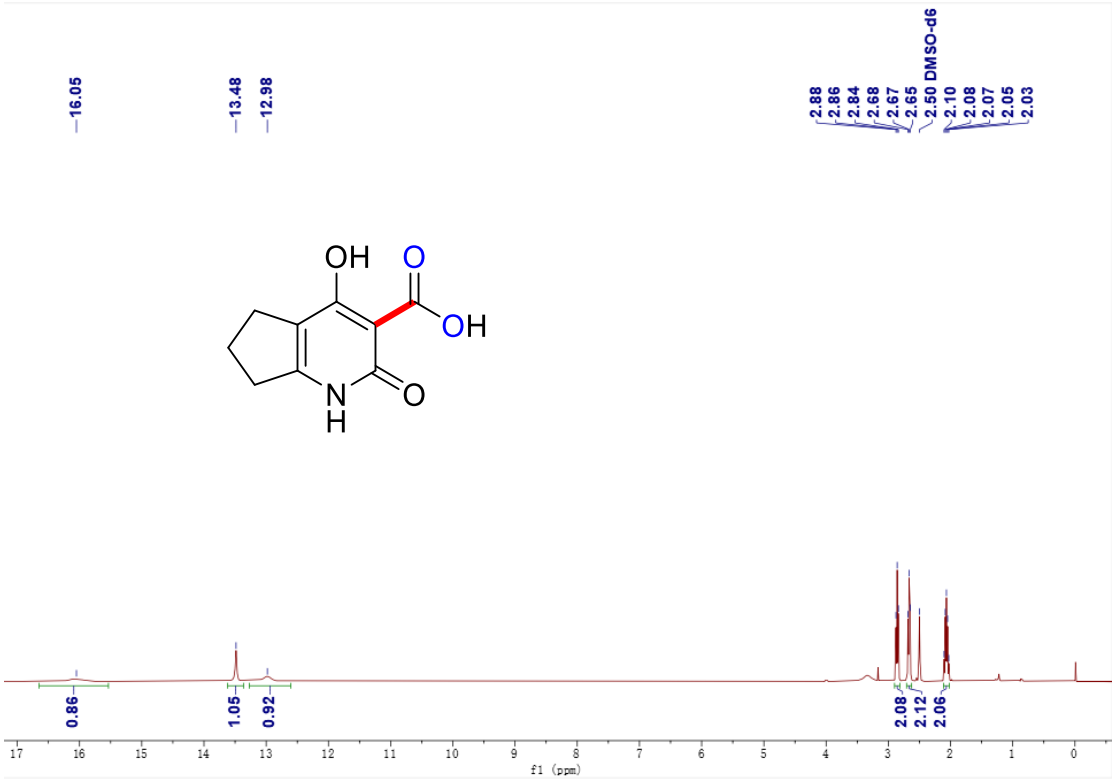
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **4e**



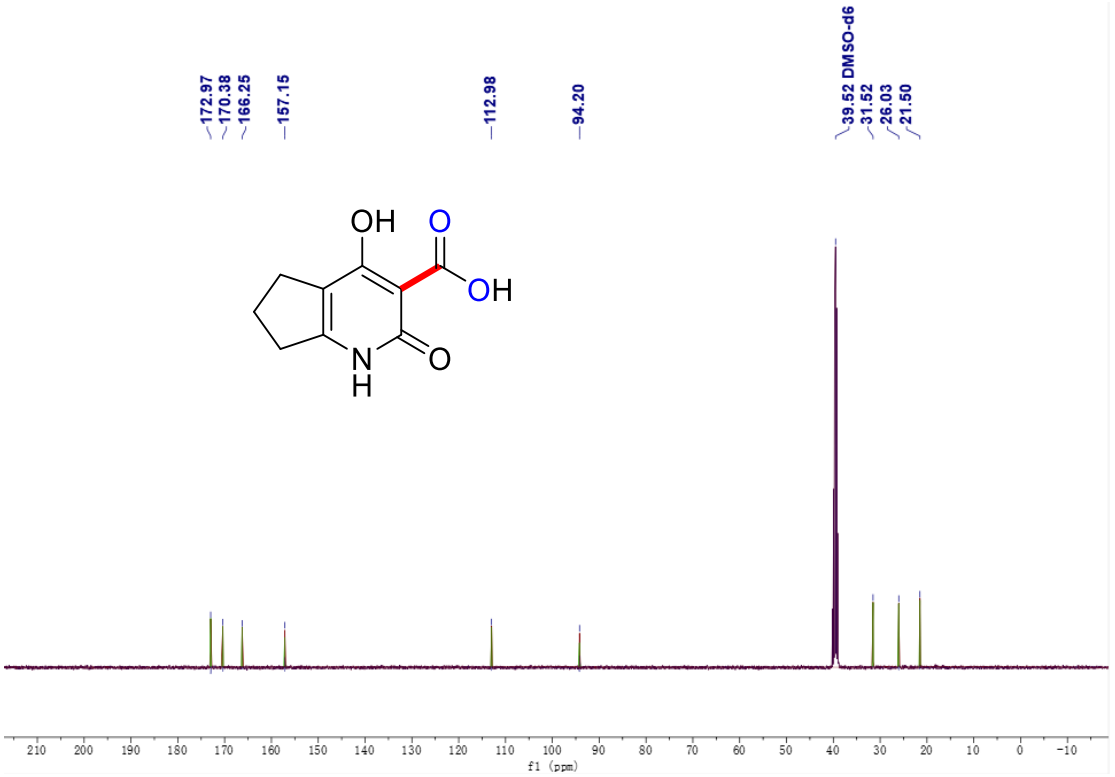
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4f**



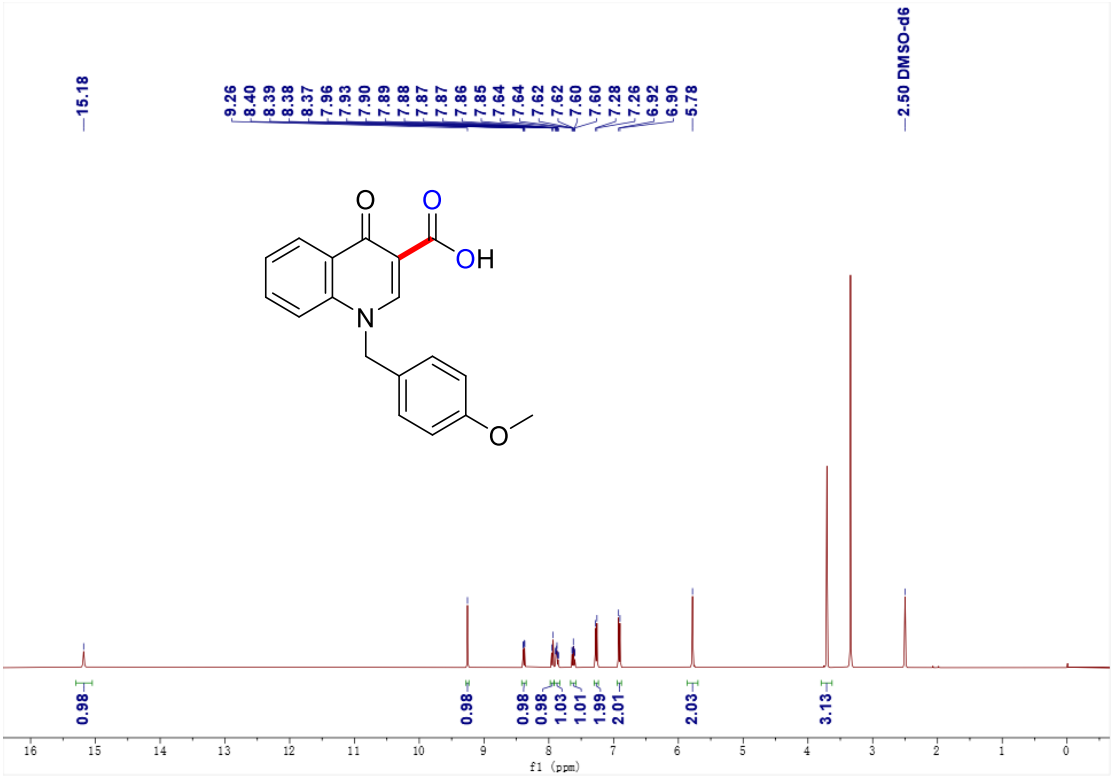
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4f**



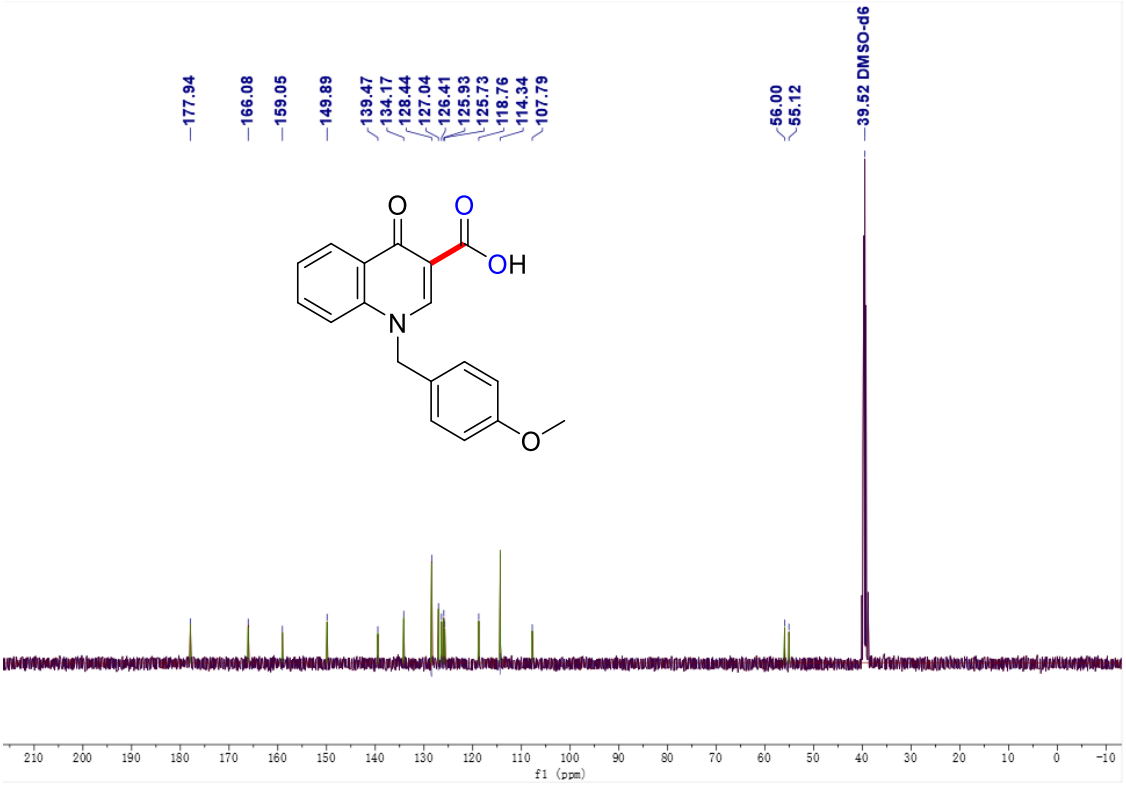
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4g**



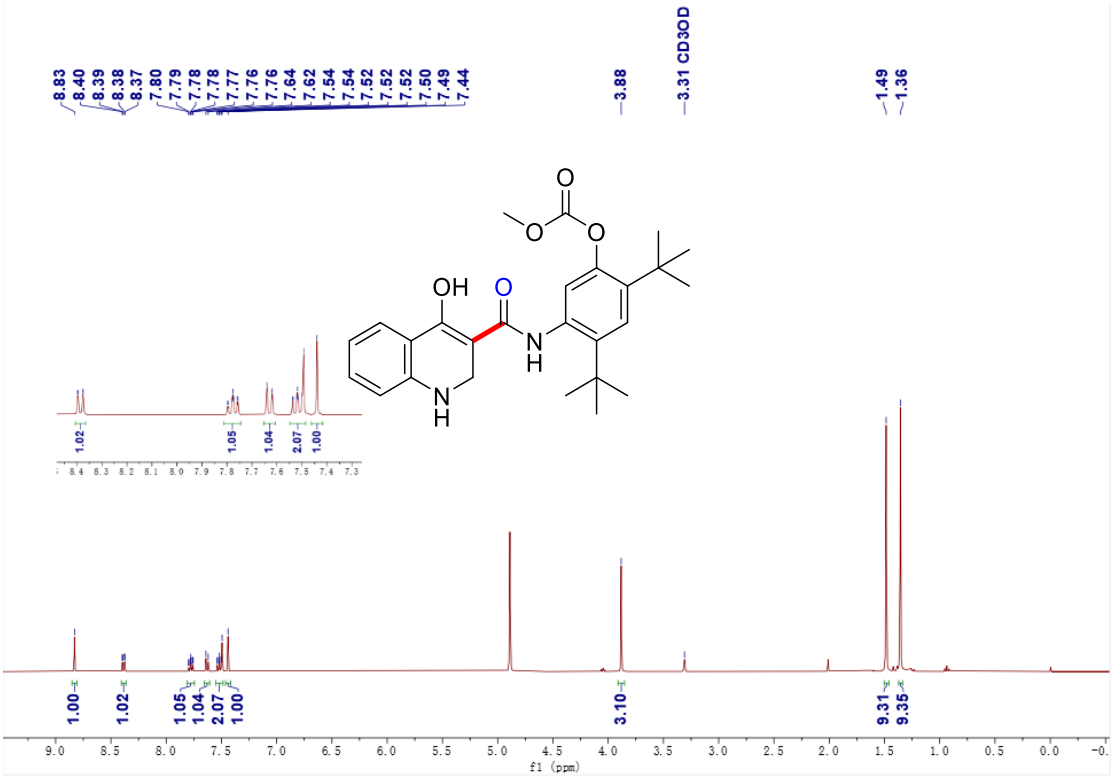
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **4g**



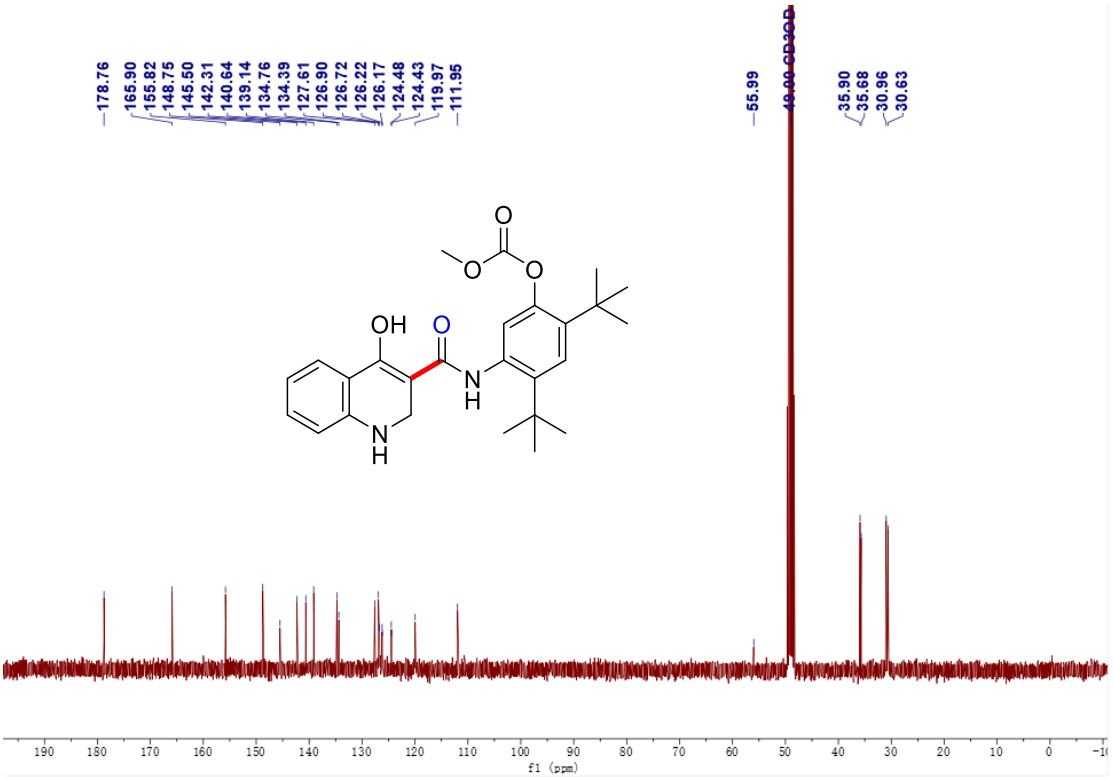
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **5**



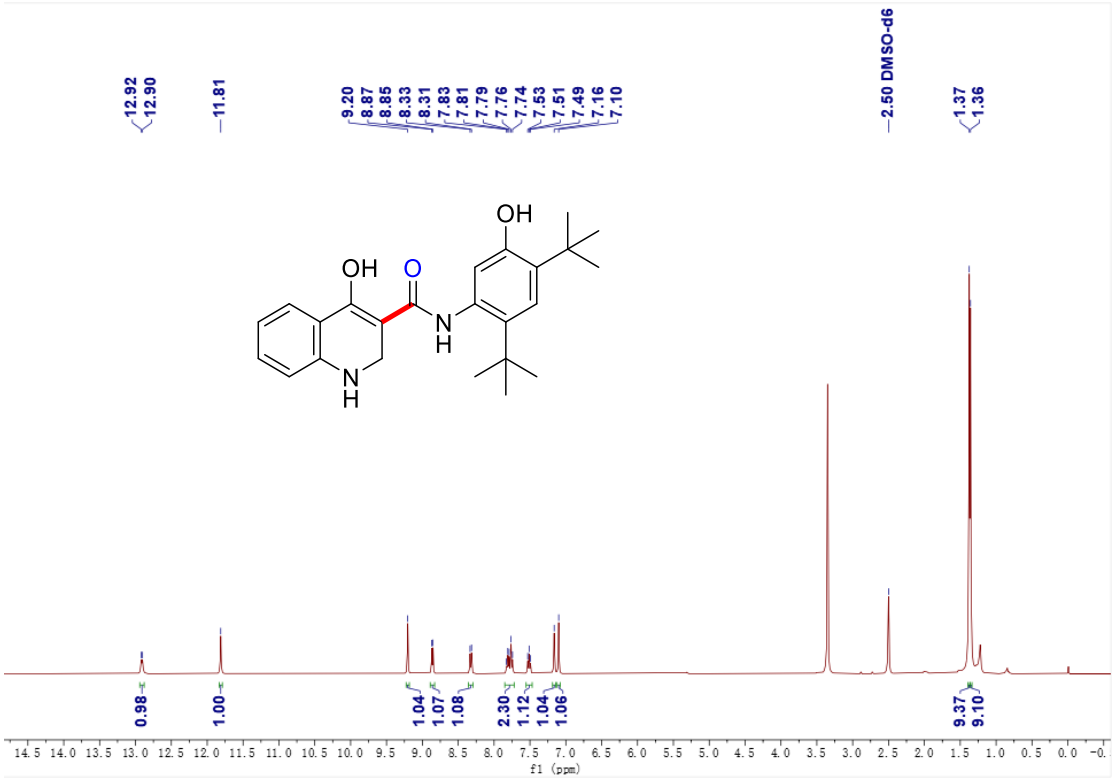
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **5**



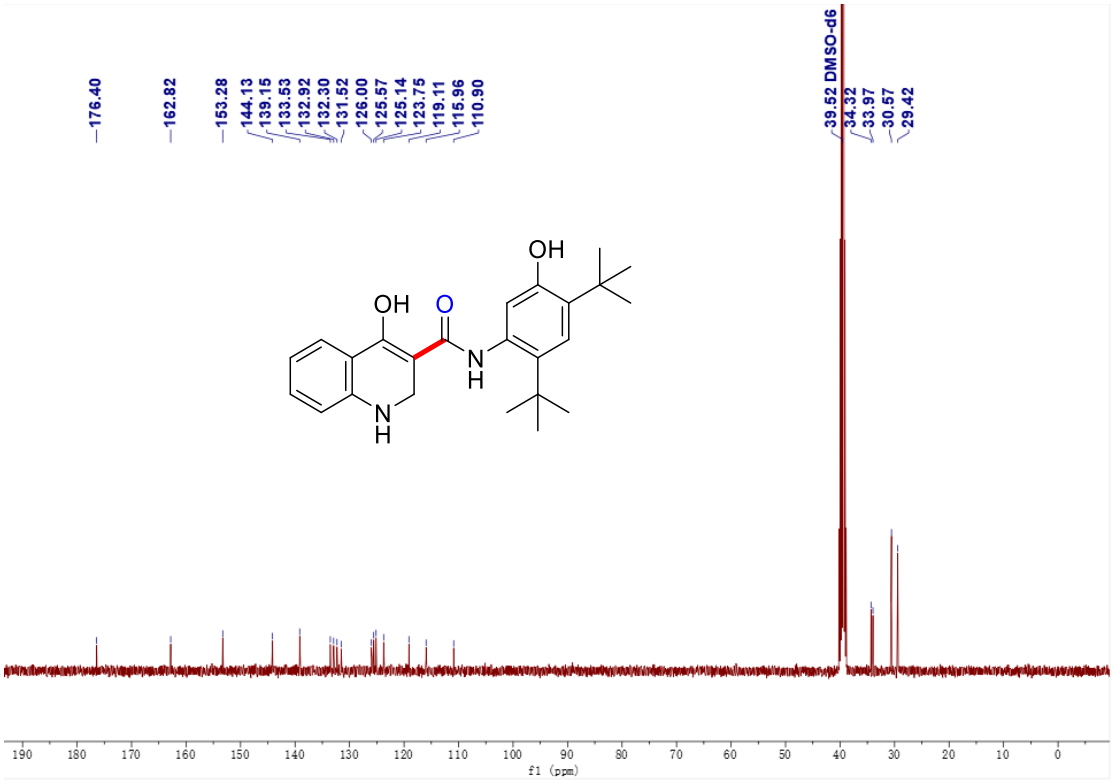
^{1}H NMR (400 MHz, CD_3OD) spectrum of **2a'-i**



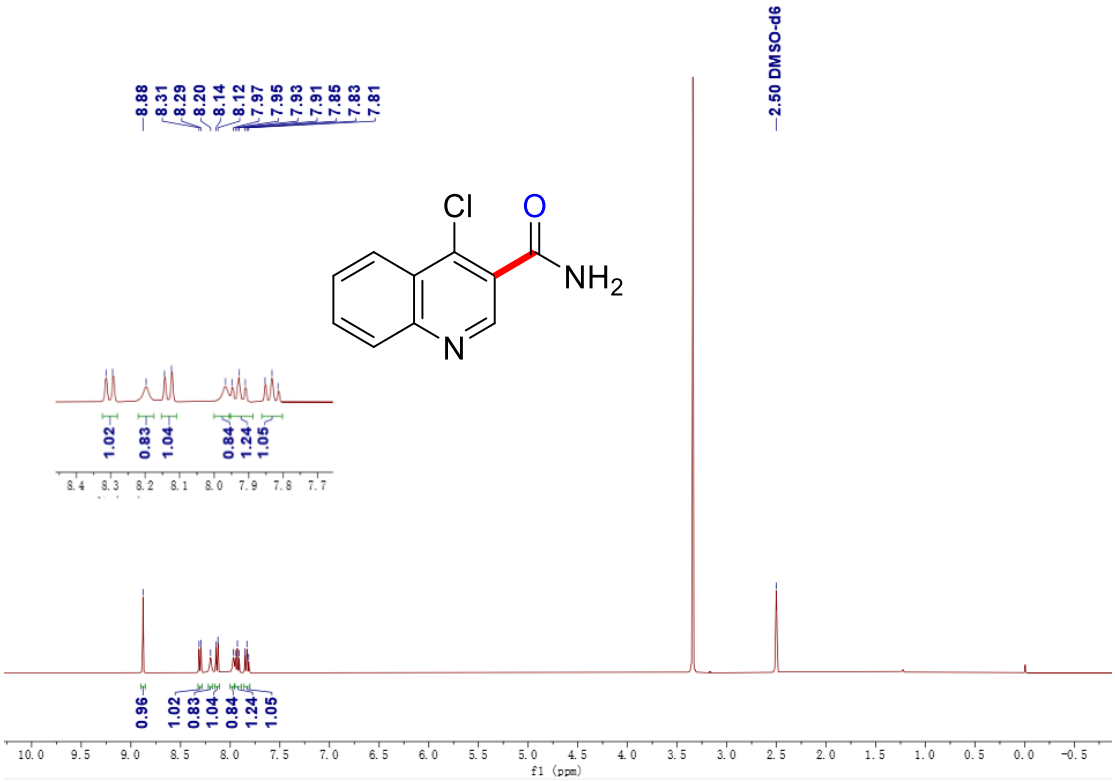
^{13}C NMR (101 MHz, CD_3OD) spectrum of **2a'-i**



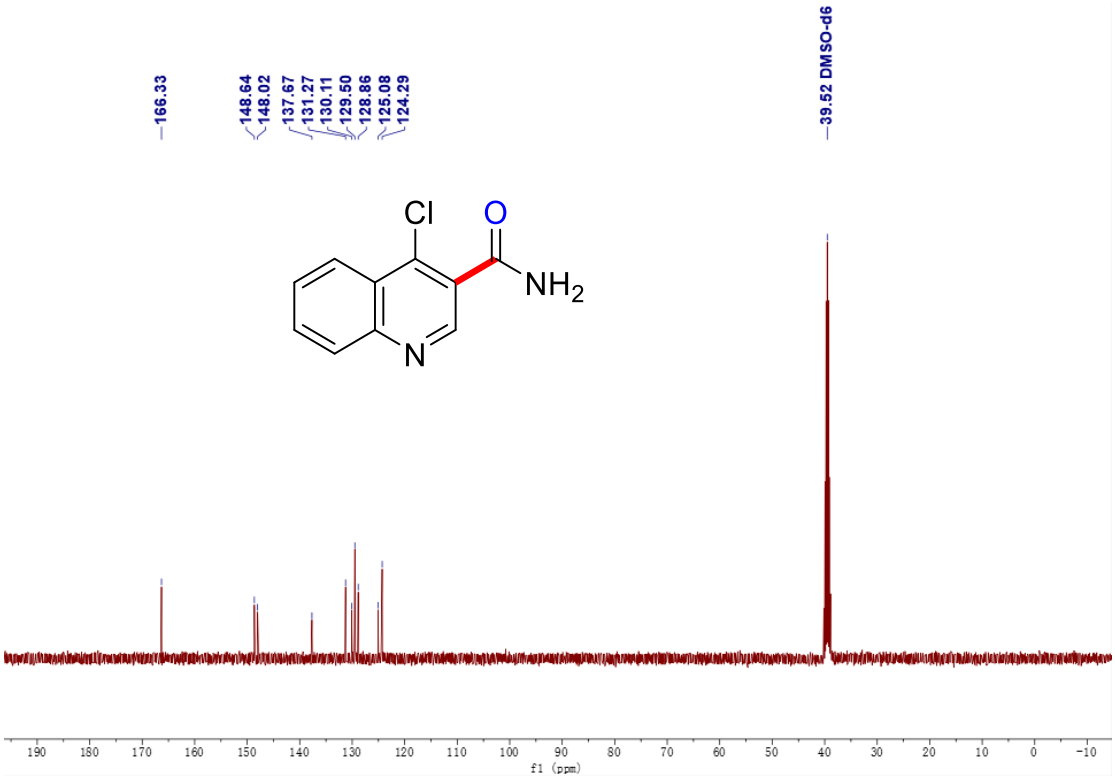
^{1}H NMR (400 MHz, DMSO-*d6*) spectrum of **6**



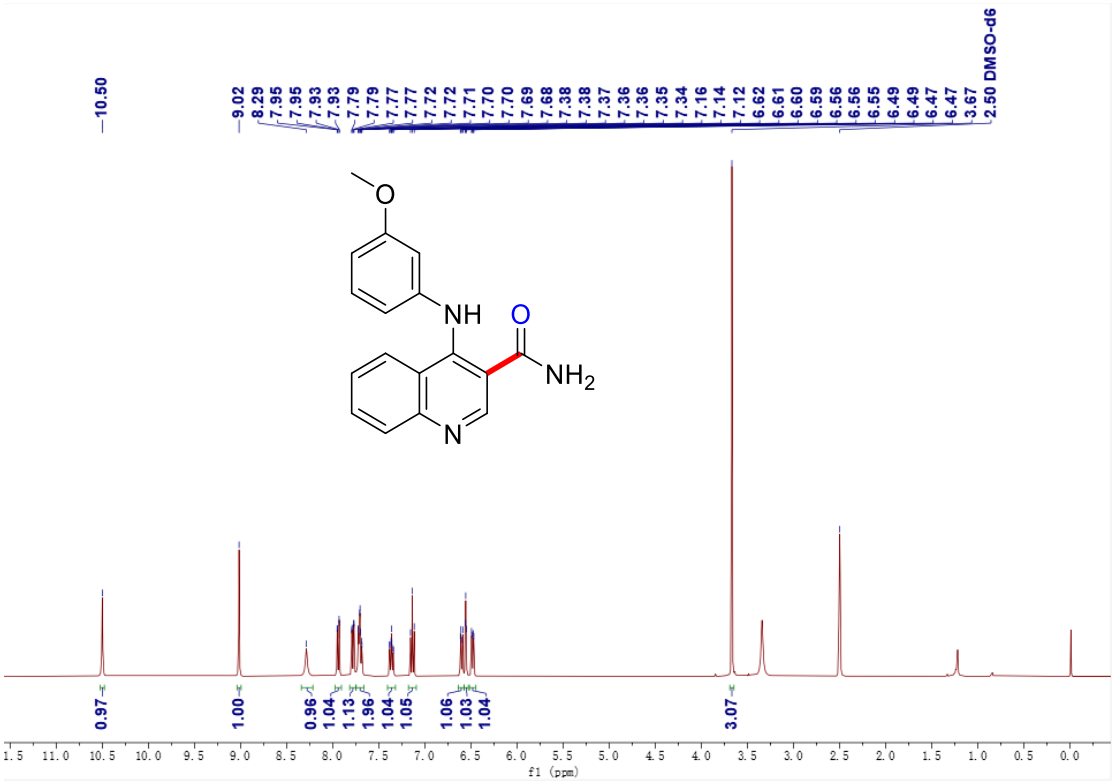
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6**



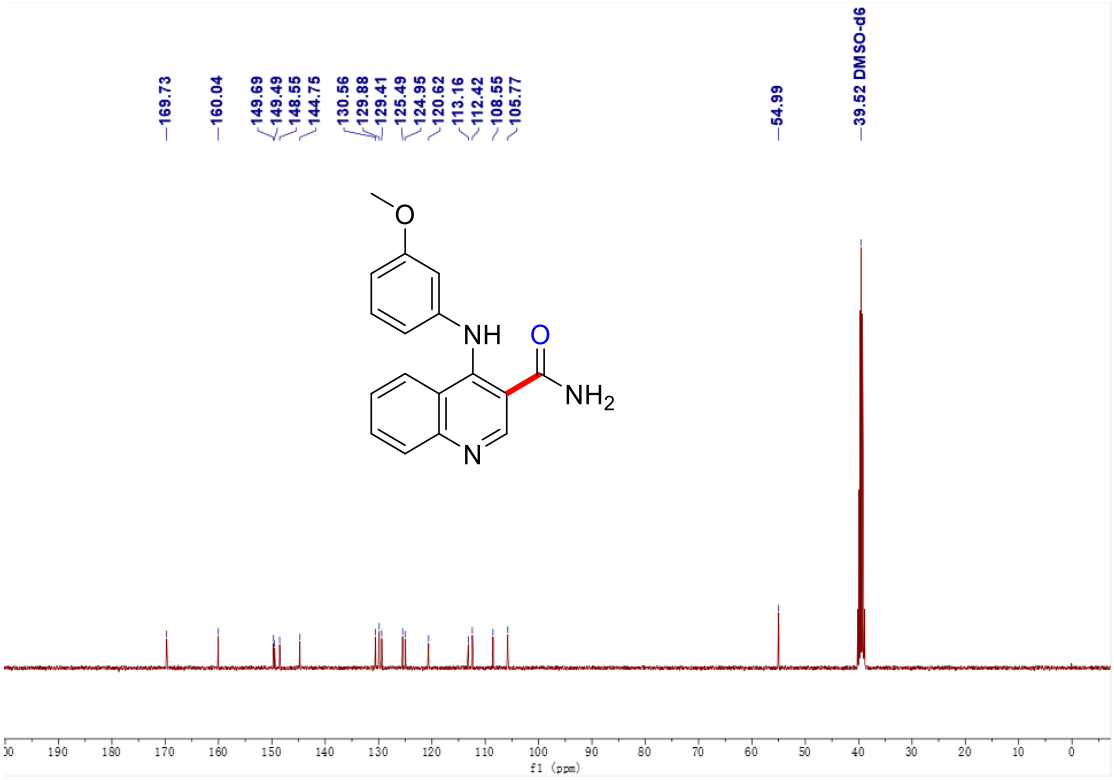
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **2a'-ii**



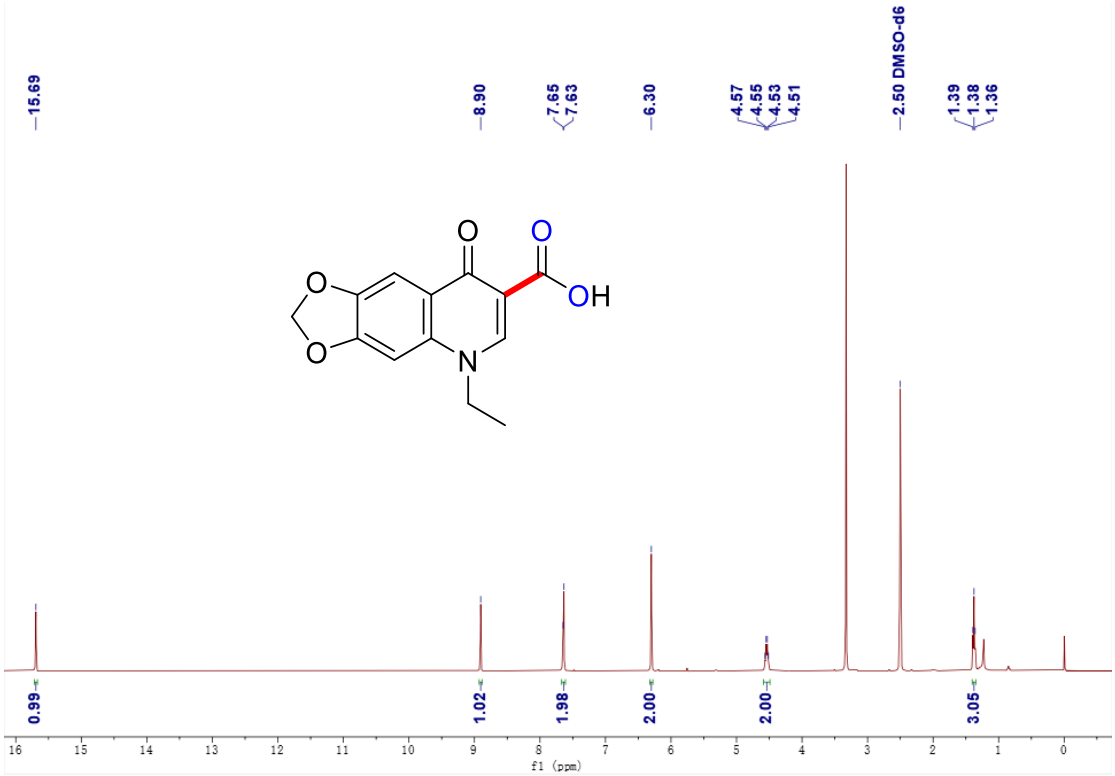
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **2a'-ii**



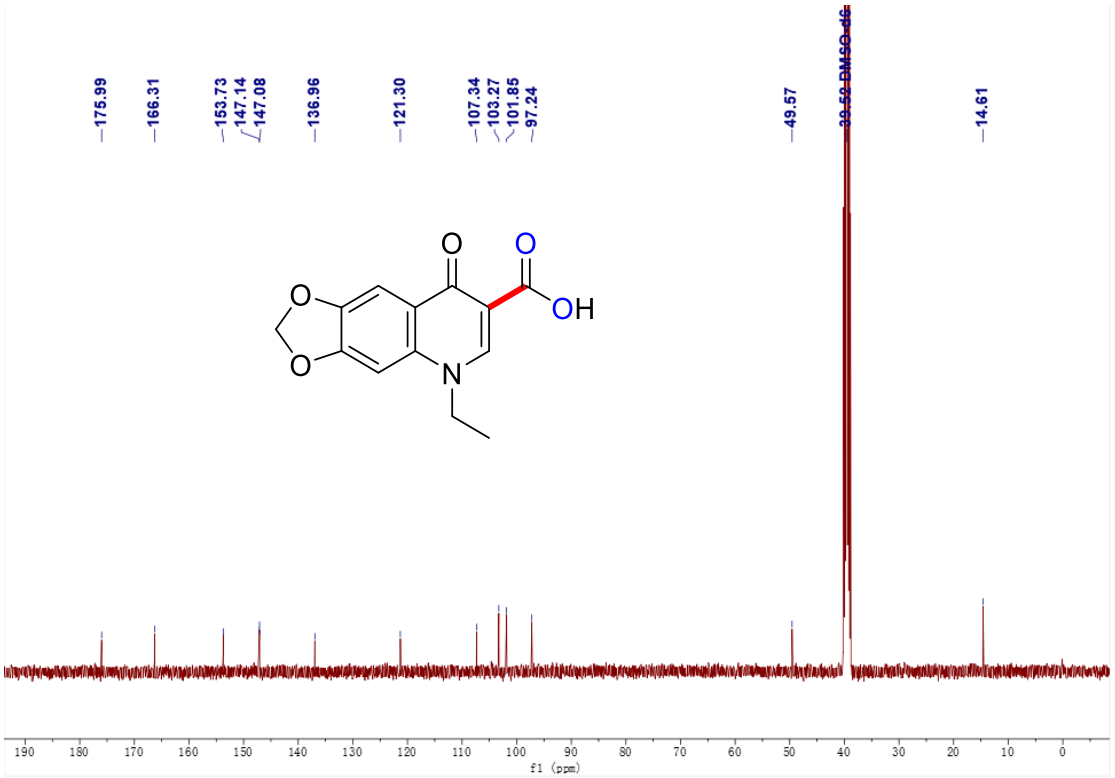
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **7**



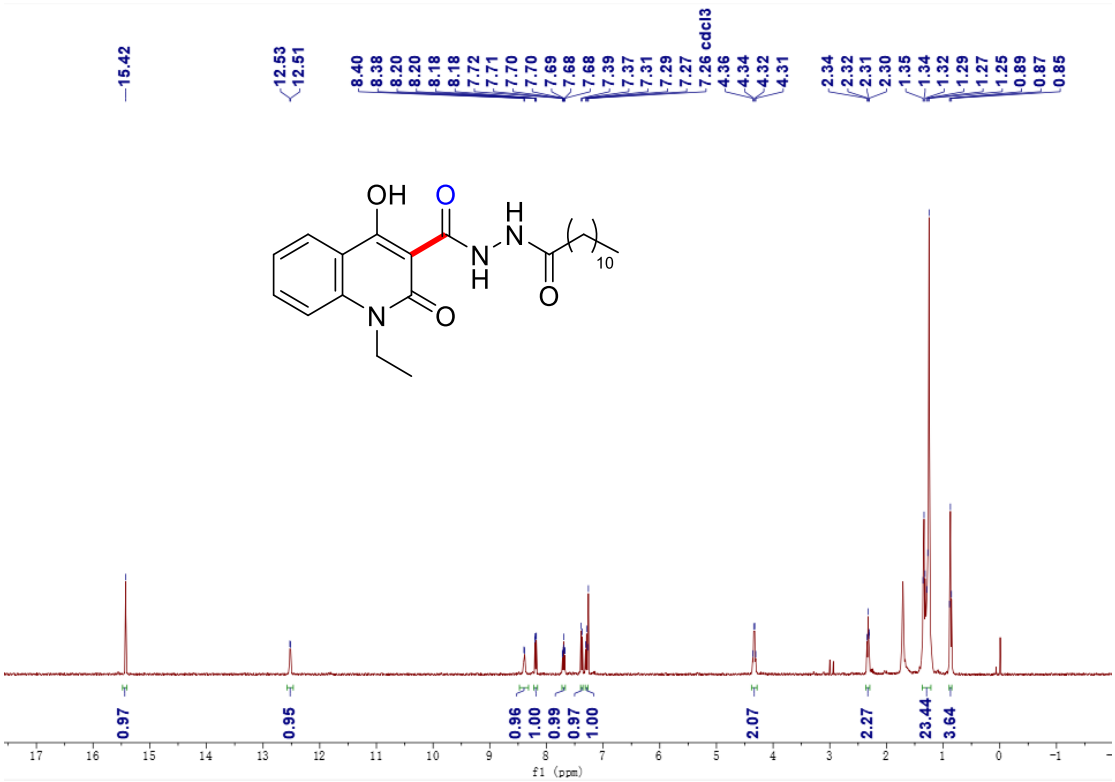
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **7**



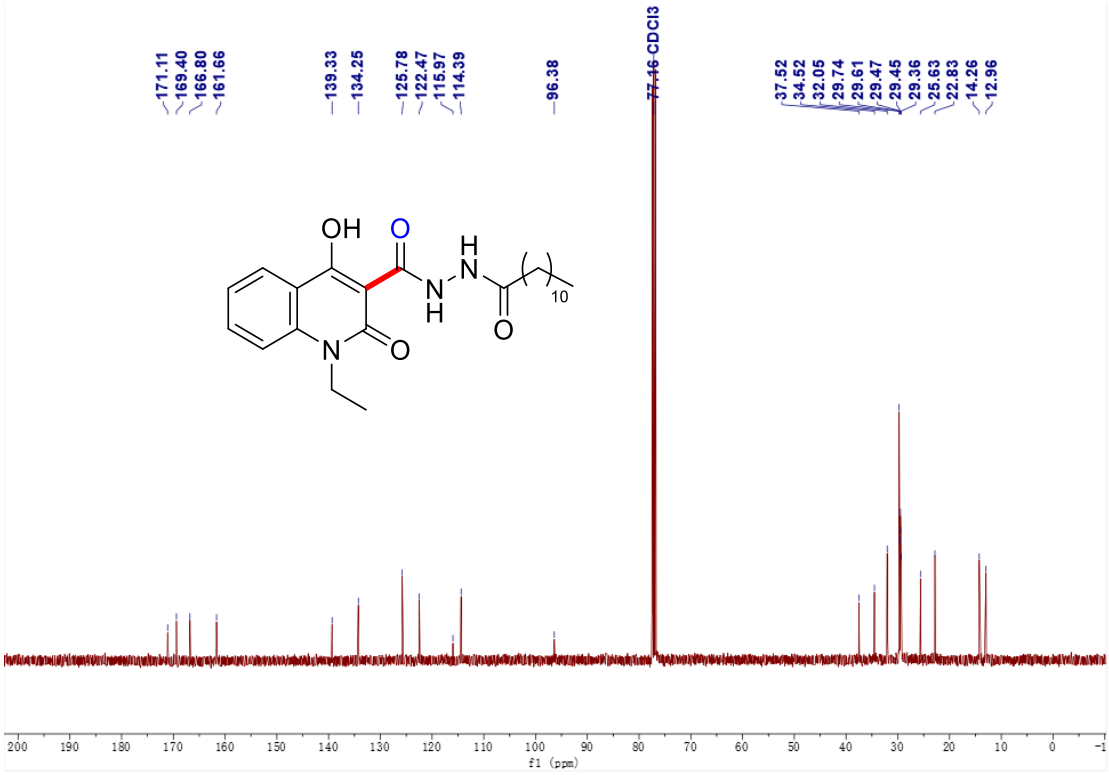
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **8**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **8**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **9**



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **9**