Supporting Information

Eco-friendly Decarboxylative Cyclization in Water: Practical Access to Anti-malarial 4-Quinolones

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Contents

1. *General Information*

Reagents and Solvents: All the reagents and solvents were commercially available and were used without further purification unless otherwise stated. DMSO refers to dimethyl sulfoxide, DCM refers to dichloromethane and EA refers to ethyl acetate.

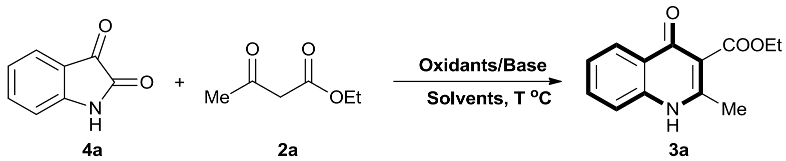
Chromatography: Flash column chromatography was carried out using commercially available 200-300 mesh under pressure unless otherwise indicated. Gradient flash chromatography was conducted eluting with PE/EA, they are listed as volume/volume ratios.

Data collection: ^{1}H and ^{13}C NMR spectra were collected on BRUKER AV-600 (600 MHz) spectrometer using DMSO-d_6 as solvent. Chemical shifts of ^{1}H NMR were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00 ppm) with the solvent resonance as the internal standard (DMSO-d_6: δ = 2.50 ppm). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Chemical shifts of ^{13}C NMR were reported in ppm with the solvent as the internal standard (DMSO-d_6: δ = 40.5 ppm). High Resolution Mass measurement was performed on Agilent QTOF 6520 mass spectrometer with electron spray ionization (ESI) as the ion source. Melting point (mp) was measured on a microscopic melting point apparatus.

2. *Optimization of Reaction Conditions*

The reaction conditions were screened as shown in **Table S1**.

Table S1. Optimization of Reaction Conditions.[a]

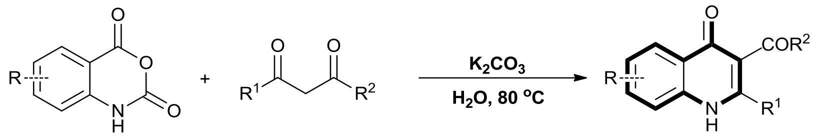


Entry	Oxidant	Base	T (°C)	solvent	Yield (%)[b]
1	TBHP	K_3PO_4	25	DMSO	53
2	TBPB	K_3PO_4	25	DMSO	0
3	DTBP	K_3PO_4	25	DMSO	0
4	TBHP	K_2CO_3	25	DMSO	85
5	TBHP	Cs_2CO_3	25	DMSO	83
6	TBHP	NaOH	25	DMSO	80
7	TBHP	KO^{t}Bu	25	DMSO	78
8	TBHP	K_2CO_3	25	DMF	65
9	TBHP	K_2CO_3	25	DCE	44
10	TBHP	K_2CO_3	25	MeOH	0
11	TBHP	K_2CO_3	25	MeCN	49
12	TBHP	K_2CO_3	25	Tolune	51
13	TBHP	K_2CO_3	25	Dioxane	39
14	TBHP	K_2CO_3	25	THF	17
15	TBHP	K_2CO_3	25	TFE	0
16	TBHP	K_2CO_3	25	H_2O	0
17[c]	TBHP	K_2CO_3	25	DMSO	77
18[d]	TBHP	K_2CO_3	25	DMSO	81
19[e]	TBHP	K_2CO_3	25	DMSO	75
20[f]	TBHP	K_2CO_3	25	DMSO	83
21	TBHP	K_2CO_3	50	DMSO	82
22	TBHP	K_2CO_3	100	DMSO	80

[a] Reaction conditions: **4a** (0. 5 mmol, 1.0 equiv); **2a** (1.0 mmol, 2.0 equiv); oxidant (1.0 mmol, 2.0 equiv); base (1.0 mmol, 2.0 equiv), solvent (2 mL), 12 hours under air atmosphere. [b] Isolated yield; [c] 1.5 equiv base were used; [d] 2.5 equiv base were used; [e] 1.5 equiv oxidant were used; [f] 2.5 equiv oxidant were used.

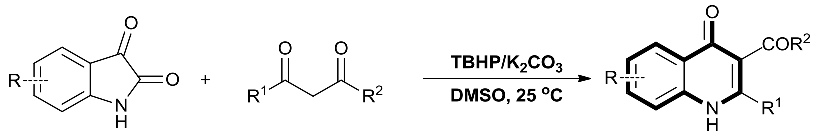
3. *General Procedure for The Decarboxylative Cyclization*

a) *General Procedure:*



1a 2a 3a

Conditions A: A sealed tube was charged with isatoic anhydrides (0.50 mmol, 1.0 equiv), 1,3-dicarbonyl compounds (1.0 mmol, 2.0 equiv), K_2CO_3 (1.0 mmol, 2.0 equiv) and 2 mL H_2O. The reaction mixture was vigorously stirred at 80 ^oC for 12 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL). The organic phase was combined and washed with water and brine respectively. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the desired product.

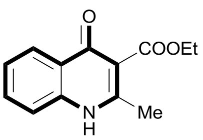


4a 2a 3a

Conditions B: A sealed tube was charged with isatins (0.50 mmol, 1.0 equiv), 1,3-dicarbonyl compounds (1.0 mmol, 2.0 equiv), K_2CO_3 (1.0 mmol, 2.0 equiv), TBHP (1.0 mmol, 2.0 equiv) and 2 mL DMSO. The reaction mixture was vigorously stirred at 25 ^oC for 12 hours. Next, the reaction mixture was diluted with ethyl acetate (20 mL). The organic phase was combined and washed with water and brine respectively. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the desired product.

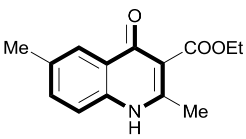
b) *Characterization of theProducts*

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



White solid, mp 230-231 ^oC; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ 11.85 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 173.8, 167.2, 149.3, 139.6, 132.7, 125.5, 125.0, 124.2, 118.4, 115.2, 60.7, 18.6, 14.6 ppm; HRMS (ESI) calcd for $[C_{13}H_{13}NO_3+H]^+$ 232.0975, found 232.1048.

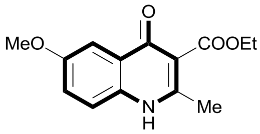
ethyl 2,6-dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3b)



White solid, m.p. 249-250 ^oC; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ 11.78 (s, 1H), 7.85 (s, 1H), 7.49 (dd, J = 8.4, 1.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.23 (d, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 173.7, 167.4, 148.8, 137.7, 134.0, 133.5, 125.0, 124.7, 118.4, 115.0, 60.7, 21.2, 18.6, 14.6 ppm; HRMS (ESI) calcd for $[C_{14}H_{15}NO_3+H]^+$ 246.1132, found

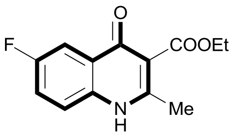
246.1239.

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



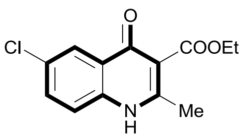
Light yellow solid, m.p. 277-278 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.84 (s, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 2.9 Hz, 1H), 7.31 (dd, J = 9.0, 3.0 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 173.2, 167.4, 156.3, 148.2, 134.1, 126.2, 122.8, 120.2, 114.2, 105.1, 60.7, 55.8, 18.5, 14.6 ppm; HRMS (ESI) calcd for $[C_{14}H_{15}NO_4+H]^+$ 262.1081, found 262.1187.

ethyl 6-fluoro-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3d)



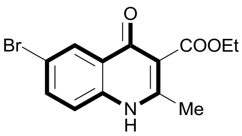
Light yellow solid, m.p. 269-271 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 12.02 (s, 1H), 7.70 (dd, J = 9.1, 2.7 Hz, 1H), 7.60 (dt, J = 8.2, 3.4 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 171.9, 171.9, 166.0, 158.7, 157.1, 148.5, 135.3, 125.2, 125.2, 120.4, 120.3, 120.2, 120.2, 113.5, 108.7, 108.5, 59.7, 17.5, 13.5 ppm; HRMS (ESI) calcd for $[C_{13}H_{12}FNO_3+H]^+$ 250.0881, found 250.0980.

ethyl 6-chloro-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3e)



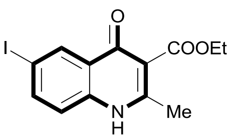
Light yellow solid, m.p. 277-278 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 12.04 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.71 (dd, J = 8.8, 2.3 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 172.6, 166.9, 149.9, 138.2, 132.8, 128.8, 126.1, 124.4, 120.9, 115.4, 60.9, 18.7, 14.6 ppm; HRMS (ESI) calcd for $[C_{13}H_{12}ClNO_3+H]^+$ 266.0586, found 266.0692.

ethyl 3-methyl-6-(trifluoromethoxy)cinnoline-4-carboxylate (3f)



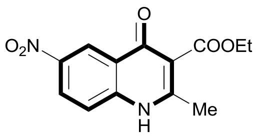
White solid, m.p. 281-282 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 12.03 (s, 1H), 8.13 (d, J = 2.2 Hz, 1H), 7.89 – 7.70 (m, 1H), 7.50 (dd, J = 8.8, 3.8 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 172.5, 166.9, 149.9, 138.5, 135.4, 127.6, 126.5, 121.1, 116.8, 115.5, 60.9, 18.7, 14.6 ppm; HRMS (ESI) calcd for $[C_{13}H_{12}BrNO_3+H]^+$ 310.0081, found 310.0231.

ethyl 6-iodo-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3g)



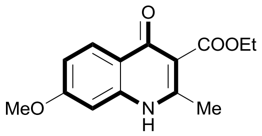
Light yellow solid, m.p. 274-275 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.99 (s, 1H), 8.34 (s, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 4.25 (dd, J = 13.9, 6.9 Hz, 2H), 2.39 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 171.9, 166.4, 149.4, 140.2, 138.4, 133.4, 126.3, 120.4, 115.1, 88.2, 60.4, 18.2, 14.1 ppm; HRMS (ESI) calcd for $[C_{13}H_{12}INO_3+H]^+$ 357.9942, found 358.0086.

ethyl 2-methyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (3h)



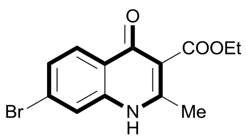
Light yellow solid, m.p. 299-301 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.84 (s, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 2.9 Hz, 1H), 7.31 (dd, J = 9.0, 3.0 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 172.2, 165.3, 165.3, 149.9, 142.4, 142.3, 125. 9, 123.1, 121.0, 119.3, 115.5, 60.1, 17.6, 13.5 ppm; HRMS (ESI) calcd for $[C_{13}H_{12}N_2O_5+H]^+$ 277.0826, found 277.0923.

ethyl 7-methoxy-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3i)



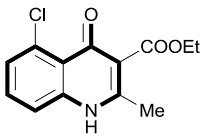
Light yellow solid, m.p. 243-244 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.68 (s, 1H), 7.95 (d, J = 8.9 Hz, 1H), 6.94 (dd, J = 8.9, 2.4 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 2.35 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 172.3, 166.2, 161.5, 147.8, 140.3, 126.3, 118.1, 114.0, 112.8, 98.5, 59.6, 54.8, 17.4, 13.5 ppm; HRMS (ESI) calcd for $[C_{14}H_{15}NO_4+H]^+$ 262.1081, found 262.1220.

ethyl 7-bromo-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3j)



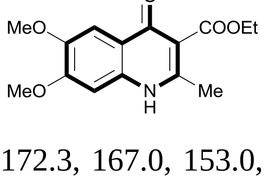
Light yellow solid, m.p. 310-311 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.90 (s, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.49 (dd, J = 8.6, 1.7 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 171.6, 165.1, 148.1, 138.8, 126.1, 125.4, 124.2, 122.1, 118.9, 114.0, 59.1, 16.9, 12.8 ppm; HRMS (ESI) calcd for $[C_{13}H_{12}BrNO_3+H]^+$ 310.0081, found 310.0213.

ethyl 5-chloro-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3k)



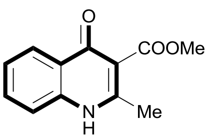
Light yellow solid, m.p. 218-219 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.84 (s, 1H), 7.63 – 7.52 (m, 1H), 7.52 – 7.41 (m, 1H), 7.38 – 7.19 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.34 (s, 3H), 1.27 (td, J = 7.1, 1.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 173.2, 167.1, 148.1, 142.2, 132.5, 132.4, 126.7, 121.0, 118.0, 117.3, 60.8, 18.1, 14.6. 166.6 ppm; HRMS (ESI) calcd for $[C_{13}H_{12}ClNO_3+H]^+$ 266.0586, found 266.0692.

ethyl 6,7-dimethoxy-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3l)



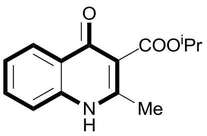
Yield 93%; Light yellow solid, m.p. 268-269 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.69 (s, 1H), 7.42 (s, 1H), 6.93 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.36 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 172.3, 167.0, 153.0, 147.0, 146.8, 134.7, 118.4, 113.9, 104.4, 99.0, 60.1, 55.6, 55.5, 17.9, 14.1 ppm; HRMS (ESI) calcd for $[C_{15}H_{17}NO_5+H]^+$ 291.1107, found 291.1112.

methyl 2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3m)



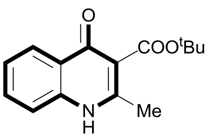
White solid, m.p. 53-55 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.90 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.1 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.35 (t, J = 7.3 Hz, 1H), 3.77 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 173.9, 167.8, 149.8, 139.6, 132.7, 125.5, 125.0, 124.2, 118.4, 114.9, 52.1, 18.7 ppm; HRMS (ESI) calcd for $[C_{12}H_{11}NO_3+H]^+$ 218.0819, found 218.0947.

isopropyl 2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3n)



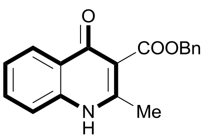
White solid, m.p. 230-231 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.85 (s, 1H), 8.09 – 8.04 (m, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 5.19 – 5.01 (m, 1H), 2.39 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 173.8, 166.7, 148.8, 139.6, 132.6, 125.5, 125.0, 124.1, 118.4, 115.6, 68.2, 22.1, 18.5 ppm; HRMS (ESI) calcd for $[C_{14}H_{15}NO_3+H]^+$ 246.1132, found 246.1239.

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



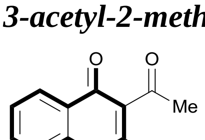
White solid, m.p. 249-250 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.77 (s, 1H), 8.05 (dd, J = 8.0, 1.1 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.33 (dd, J = 11.4, 4.3 Hz, 1H), 2.38 (s, 3H), 1.51 (s, 9H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 178.5, 171.3, 152.9, 144.4, 137.3, 137.3, 130.2, 130.2, 129.8, 128.7, 123.1, 121.8, 85.7, 33.1, 23.1 ppm; HRMS (ESI) calcd for $[C_{15}H_{17}NO_3+H]^+$ 260.1288, found 260.1380.

benzyl 2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (3p)



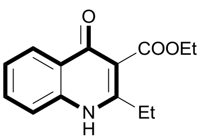
Light yellow solid, m.p. 223-224 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.91 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.37 – 7.29 (m, 2H), 5.30 (s, 2H), 2.40 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 178.7, 171.9, 154.8, 144.3, 141.5, 137.5, 137.5, 133.6, 133.1, 133.1, 130.3, 129.9, 129.0, 123.2, 119.4, 71.1, 23.5 ppm; HRMS (ESI) calcd for $[C_{18}H_{15}NO_3+H]^+$ 294.1132, found 294.1253.

3-acetyl-2-methylquinolin-4(1H)-oneethyl (3q)



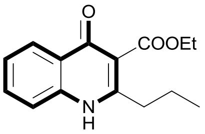
Light yellow solid, m.p. 255-256 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.91 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.73 – 7.64 (m, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 2.52 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 199.8, 173.6, 149.8, 137.1, 130.6, 123.8, 123.4, 122.3, 118.5, 116.3, 30.3, 17.3 ppm; HRMS (ESI) calcd for $[C_{12}H_{11}NO_2+H]^+$ 202.0870, found 202.0960.

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



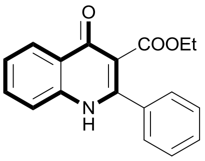
Light yellow solid, m.p. 212-213 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.80 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 1.32 – 1.22 (m, 6H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 178.9, 178.9, 172.0, 172.0, 158.6, 158.6, 144.6, 137.4, 130.2, 130.2, 129.7, 128.9, 123.3, 119.6, 65.6, 30.7, 19.3, 19.0 ppm; HRMS (ESI) calcd for $[C_{14}H_{15}NO_3+H]^+$ 246.1132, found 245.1239.

ethyl 2-(n-butyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (3s)



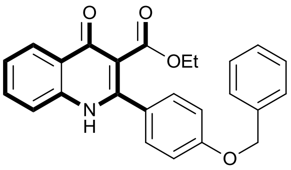
Light yellow solid, m.p. 215-216 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.78 (s, 1H), 8.07 (dd, J = 8.0, 0.9 Hz, 1H), 7.78 – 7.64 (m, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.44 – 7.29 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.69 – 2.56 (m, 2H), 1.71 (dd, J = 15.3, 7.6 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H) ppm ; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 174.1, 167.3, 152.4, 139.8, 132.7, 125.4, 125.0, 124.1, 118.6, 115.4, 60.8, 34.2, 22.8, 14.6, 14.0 ppm; HRMS (ESI) calcd for $[C_{15}H_{17}NO_3+H]^+$ 260.1045, found 260.1413.

ethyl 4-oxo-2-phenyl-1,4-dihydroquinoline-3-carboxylate (3t)



Light yellow solid, m.p. 268-269 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 12.07 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 9.0 Hz, 2H), 7.58 (s, 5H), 7.41 (t, J = 7.1 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 0.92 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 174.1, 166.7, 149.9, 140.0, 134.2, 132.9, 130.7, 129.10, 128.7, 125.4, 125.1, 124.5, 119.3, 116.0, 60.6, 14.1 ppm; HRMS (ESI) calcd for $[C_{18}H_{15}NO_3+H]^+$ 294.1132, found 294.1253.

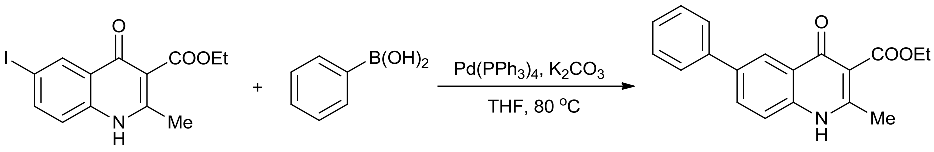
ethyl 2-(4-(benzyloxy)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (3u)



White solid, m.p. 288-289 °C; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 12.14 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.72 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.52 (td, J = 8.5, 1.7 Hz, 1H), 7.43 – 7.35 (m, 4H), 7.29 – 7.21 (m, 4H), 7.10 (td, J = 7.5, 0.5 Hz, 1H), 5.17 (s, 2H), 3.91 (q, J = 7.1 Hz, 2H), 2.00 (s, 1H), 0.83 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 174.1, 166.2, 156.2, 148.0, 139.8, 137.2, 132.8, 132.0, 130.5, 129.4, 128.7, 128.2, 127.6, 125.5, 125.2, 124.3, 123.6, 120.9, 118.9, 116.4, 115.8, 113.5, 70.2, 60.2, 14.0 ppm; HRMS (ESI) calcd for $[C_{25}H_{21}NO_4+H]^+$ 400.1471, found 400.1463.

4.Further Functionalization of Generated quinolones

4.1 Cross Coupling of 3la with phenylboronic acid

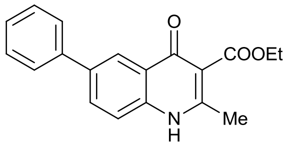


3g 3v

Scheme S1. Cross Coupling of 3g with *phenylboronic acid*

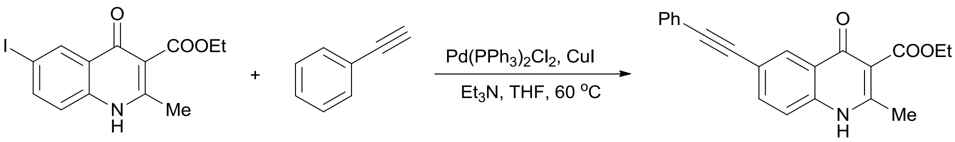
To expand the application of the method, the generated iodo vinylsulfone product **3g** was functionalized as shown in Scheme S1. A sealed tube was charged with **3g** (0.2 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (0.002 mmol, 1 mol %), K_2CO_3 (0.4 mmol, 2.0 equiv), phenylboronic acid (0.4 mmol, 2.0 equiv). The reaction mixture was then vigorously stirred at 80 ^oC (oil temperature) for 4 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of celite. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the desired product **3v** in 76% yield.

ethyl 2-methyl-4-oxo-6-phenyl-1,4-dihydroquinoline-3-carboxylate



Yield 76%; White solid, m.p. 294-285 ^oC; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ 12.04 (s, 1H), 8.18 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 19.4, 5.9 Hz, 3H), 7.44 (d, J = 1.9 Hz, 3H), 4.26 (d, J = 7.0 Hz, 2H), 2.41 (s, 3H), 1.28 (dd, J = 9.4, 4.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 172.6, 166.4, 149.2, 139.0, 134.5, 131.4, 128.8, 128.7, 128.2, 124.4, 122.1, 118.8, 117.4, 115.3, 89.4, 88.8, 60.4, 18.2, 14.1 ppm; HRMS (ESI) calcd for $[C_{19}H_{17}NO_3+H]^+$ 308.1208, found 308.1213.

4.2 Cross Coupling of 3la with phenylacetylene

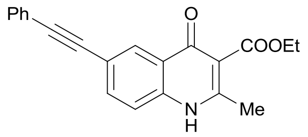


3g 3w

Scheme S4. Cross Coupling of 3g with phenylacetylene

A sealed tube was charged with **3g** (0.2 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.002 mmol, 1 mol %), CuI (0.004 mmol, 2 mol %), phenylacetylene (0.4 mmol, 2.0 equiv) and Et_3N (2 mL). The reaction mixture was then vigorously stirred at 60 ^oC (oil temperature) for 4 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of celite. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the desired product **3w** in 80% yield.

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



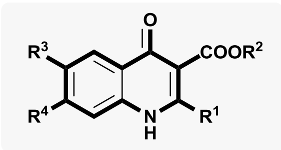
Yield 80%; White solid, 327-328 ºC; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ 11.97 (s, 1H), 8.30 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.5, 1.9 Hz, 1H), 7.73 (d, J = 7.4 Hz, 2H), 7.64 (d, J = 8.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ 173.3, 166.7, 148.8, 139.2, 138.5, 135.5, 130.8, 129.1, 127.6, 126.6, 124.8, 122.3, 118.8, 114.9, 60.3, 18.2, 14.1 ppm; HRMS (ESI) calcd for $[C_{21}H_{17}NO_3+H]^+$ 332.1208, found 332.1205.

5. *Anti-malarial Study*

Parasites were routinely cultured by the methods of Trager and Jensen[1] with minor modifications. *P falciparum*3D7 were maintained at 2% haematocrit. Parasies were synchronized by 5% D-Sorbitol at ring stage for each essay. The IC_{50} of the selected products was estimated using the methods as described by Forkuo[2] with minor modifications. Stock solutions of drugs were diluted with Malaria Culture Medium. Each well was seeded with 100 μL of parasite culture in array of different drug concentration ratio. RBCs and iRBCs with no treatment were plated in the last array as comparison. After the 72-h incubation, *P falciparum* 3D7 were above 90% in the stage of trophozoite. The supernatant of the plates was abandoned with 110 μL and thoroughly mixed with 10 μL malaria 10*lysis buffer with 200-fold dilution of 10000*SYBR Green I.

The results of the evaluation were summarized in Table S2.

Table S2 Anti-malarial study.

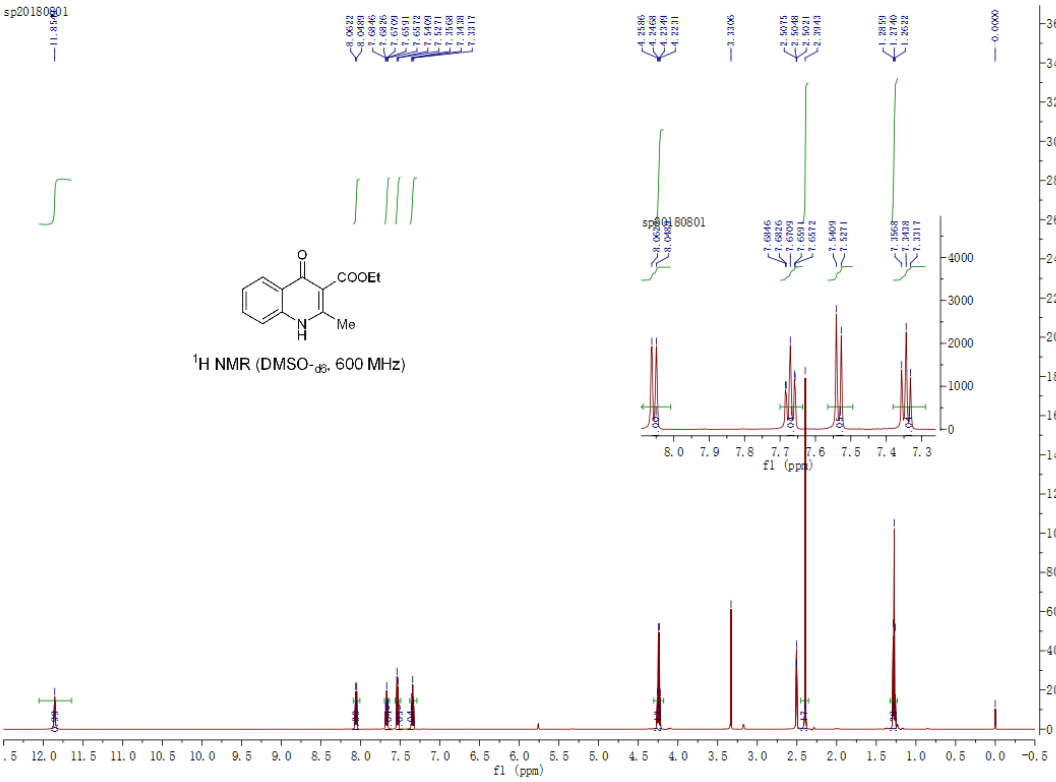


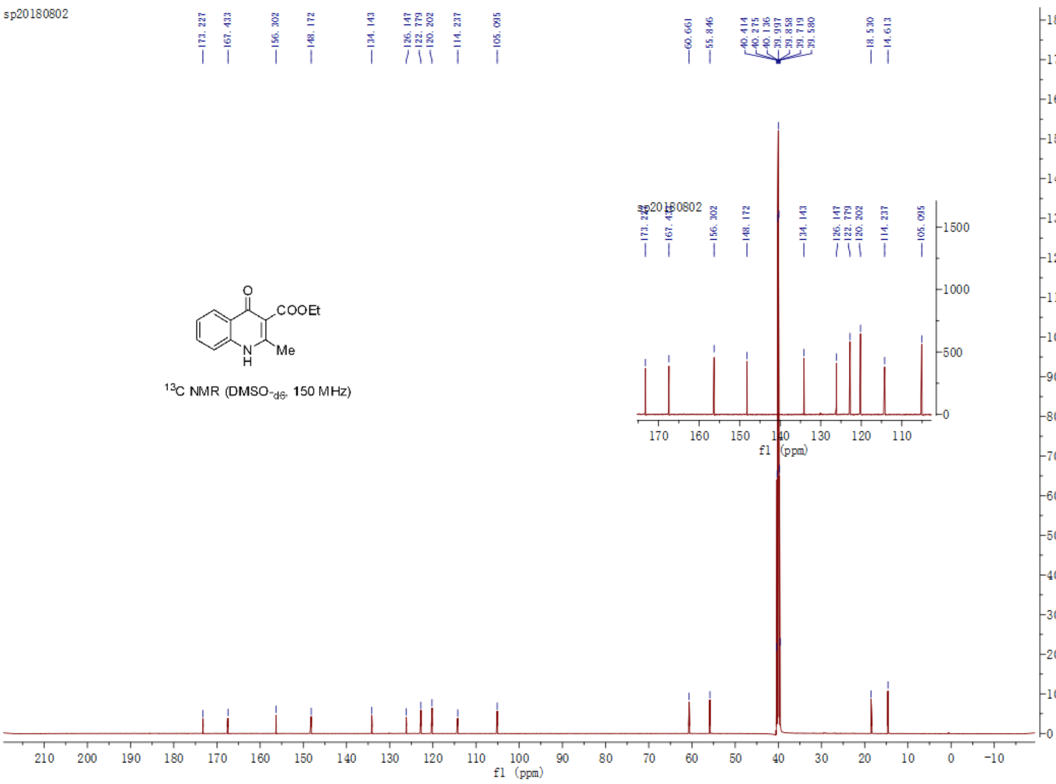
	R^1	R^2	R^3	R^4	IC_{50}
3d	Me	Et	F	H	1.2 μm
3l	Me	Et	OMe	OMe	> 400 μm
3o	Me	^{t}Bu	H	H	131.9 nm
3u	2-(4-benzyloxyphenyl)	Et	H	H	33 nm
3v	Me	Et	Ph	H	17 μm
3w	Me	Et	phenylethynyl	H	> 400 μm

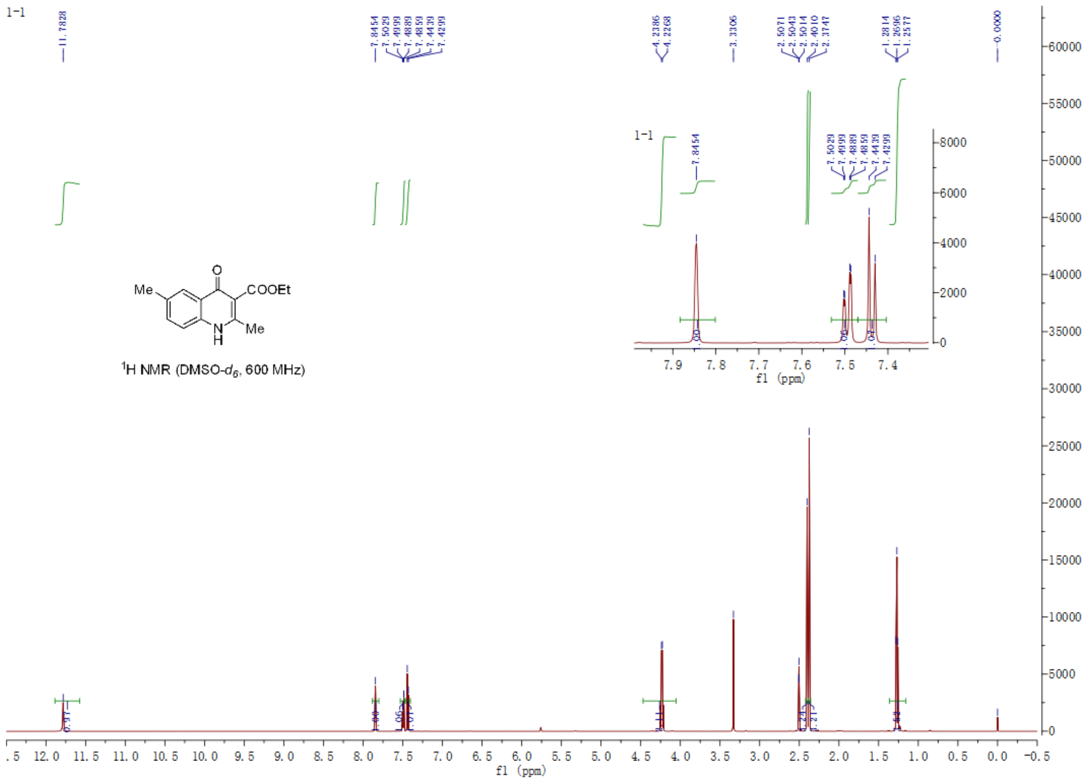
6. *References*

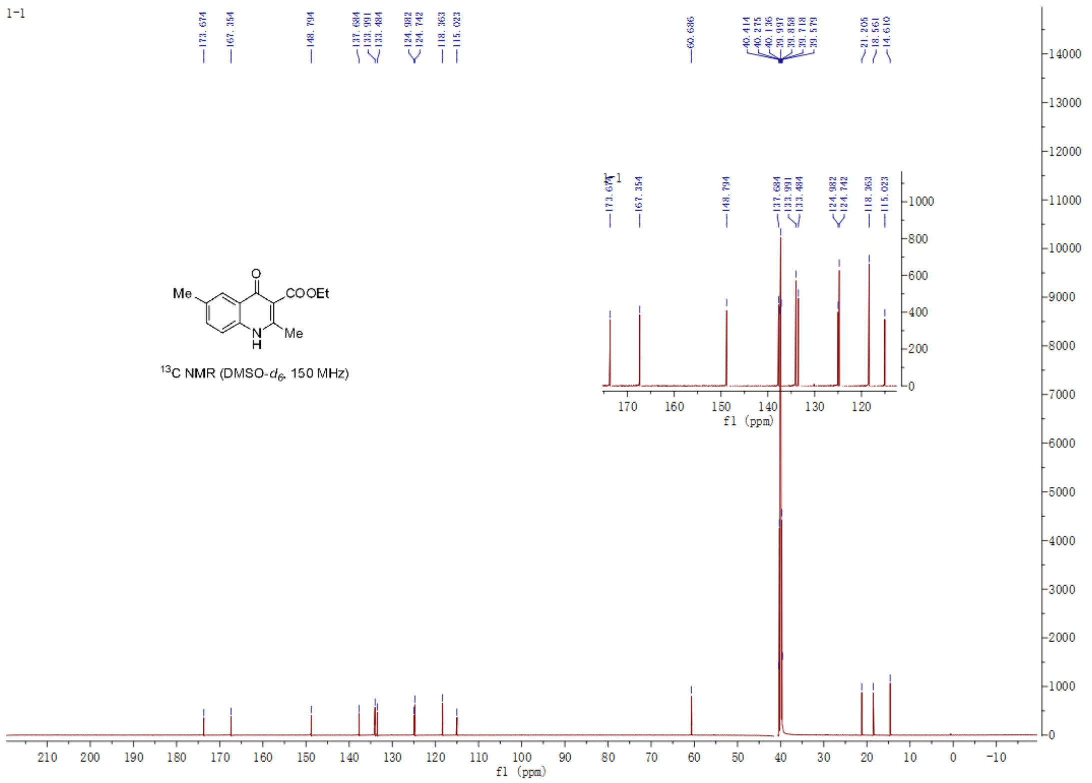
1) W. Trager, J. B. Jensen. *Science,* 1976, **193**, 673.
2) A. D. Forkuo, C. Ansah, K. M. Boadu, K. M. Boadu, J. N. Boampong, E. O. Ameyaw, B. A. Gyan, A. T. Arku, M. F. Ofori, *Malaria Journal*, 2016, **15**, 89.

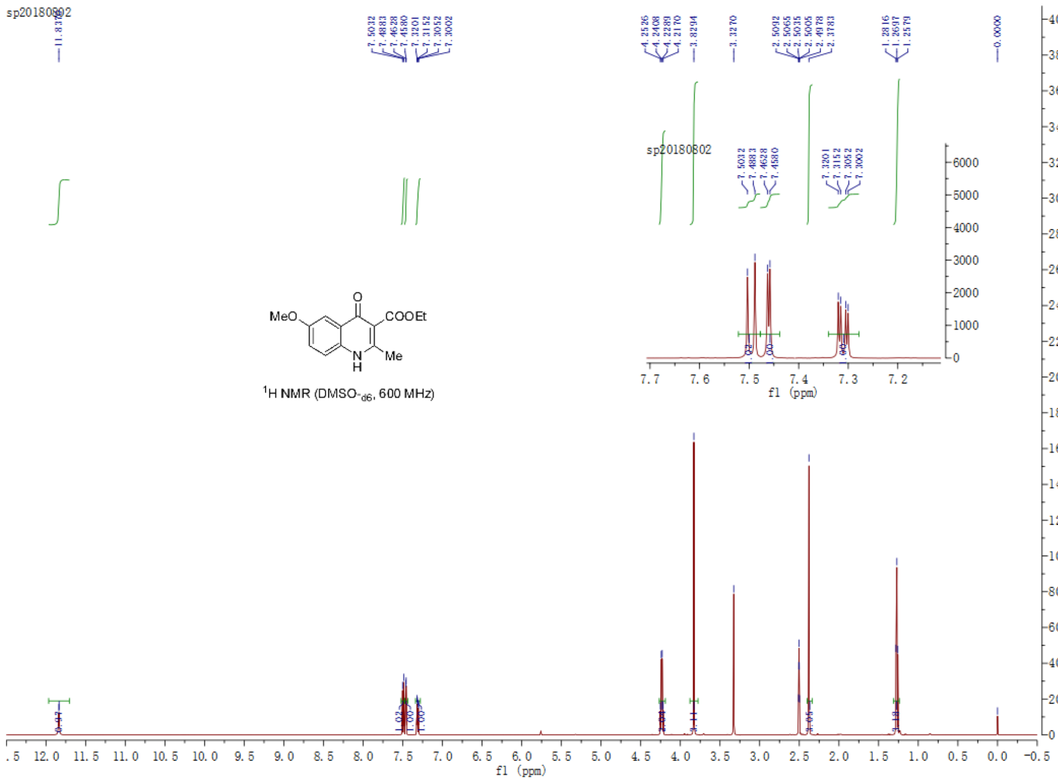
7. [1]H and [13]C-NMR Spectra of Title Compounds

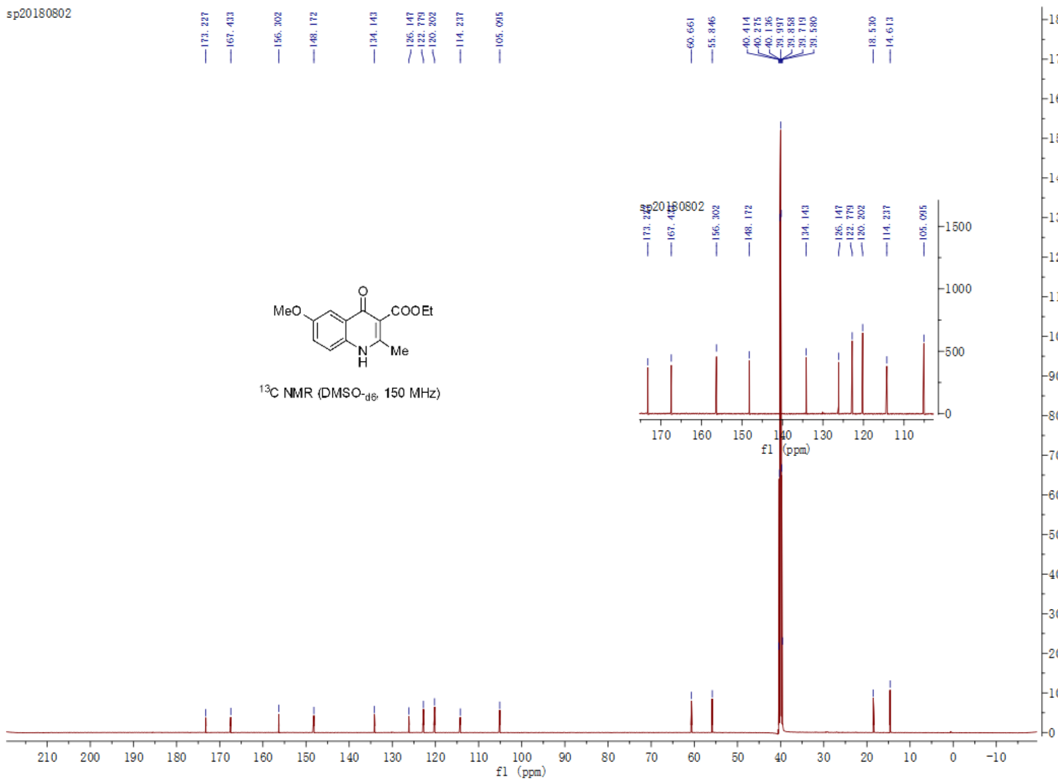





1-1
11.7828
7.8454
7.5029
7.4999
7.4889
7.4859
7.4439
7.4299
4.2386
4.2268
3.3306
2.5071
2.5041
2.5014
2.4010
2.3747
1.2814
1.2696
1.2577
0.0000
Me
O
COOEt
N
H
Me
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)


1-1
173.674
167.354
148.794
137.684
133.991
133.484
124.982
124.742
118.363
115.023
60.686
40.414
40.275
40.136
39.997
39.858
39.718
39.579
21.205
18.561
14.610
Me
O
COOEt
N
H
Me
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)


sp20180802
MeO
O
COOEt
N
H
Me
¹H NMR (DMSO-d6, 600 MHz)
f1 (ppm)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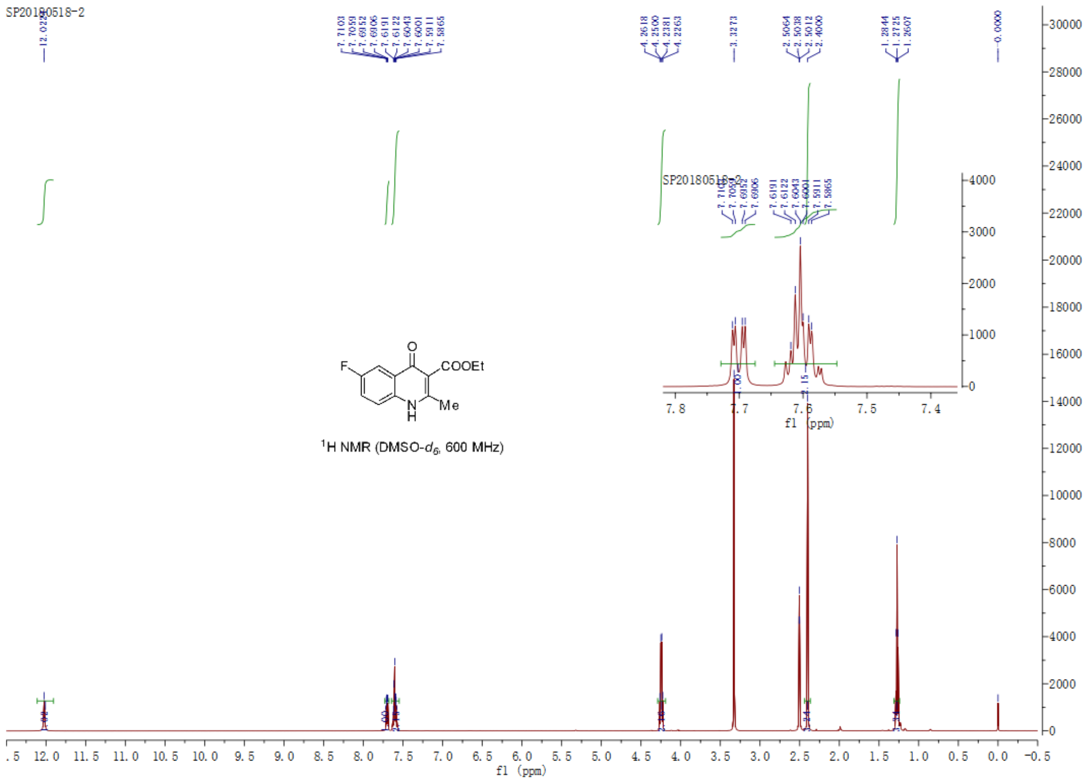
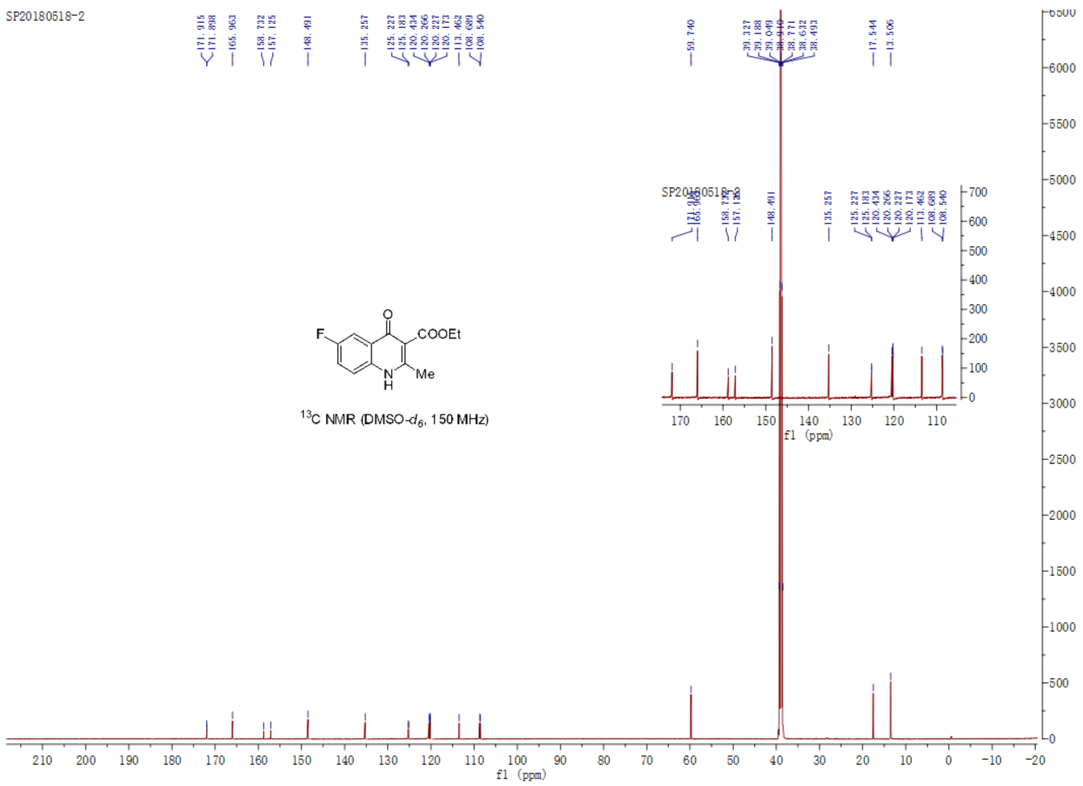
MeO
O
COOEt
N
H
Me
¹³C NMR (DMSO-d6, 150 MHz)
f1 (ppm)


SP20180518-2
COOEt
Me
^{1}H NMR (DMSO-d_6, 600 MHz)
f1 (ppm)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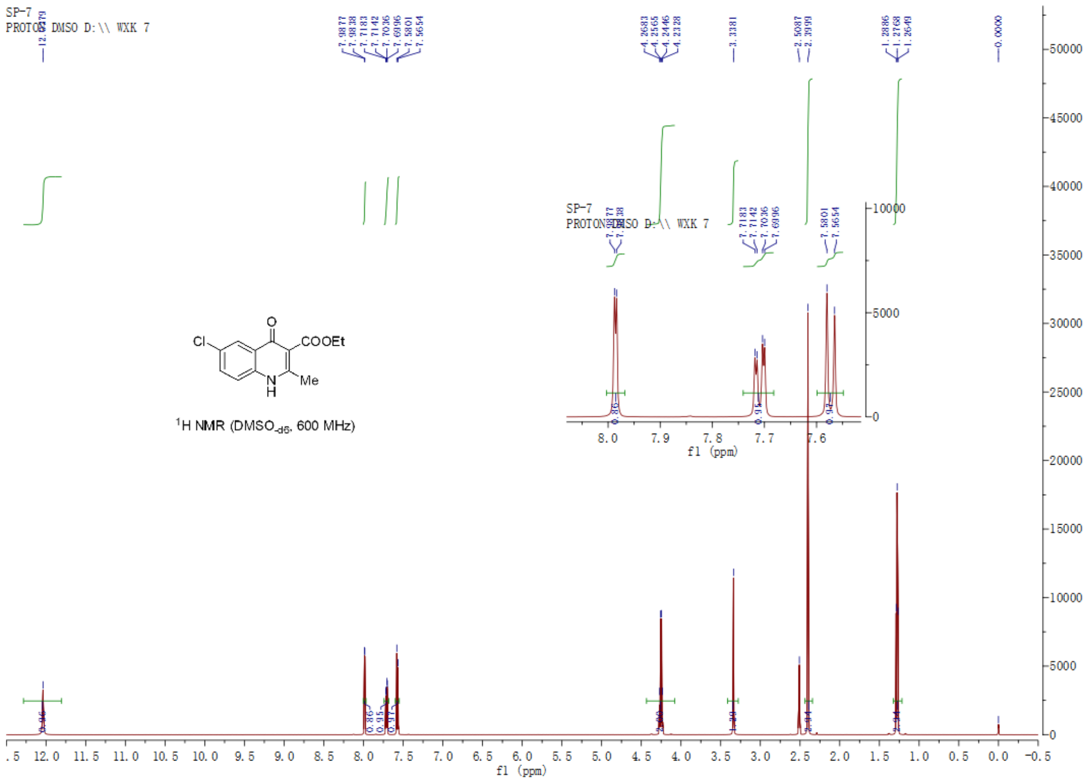
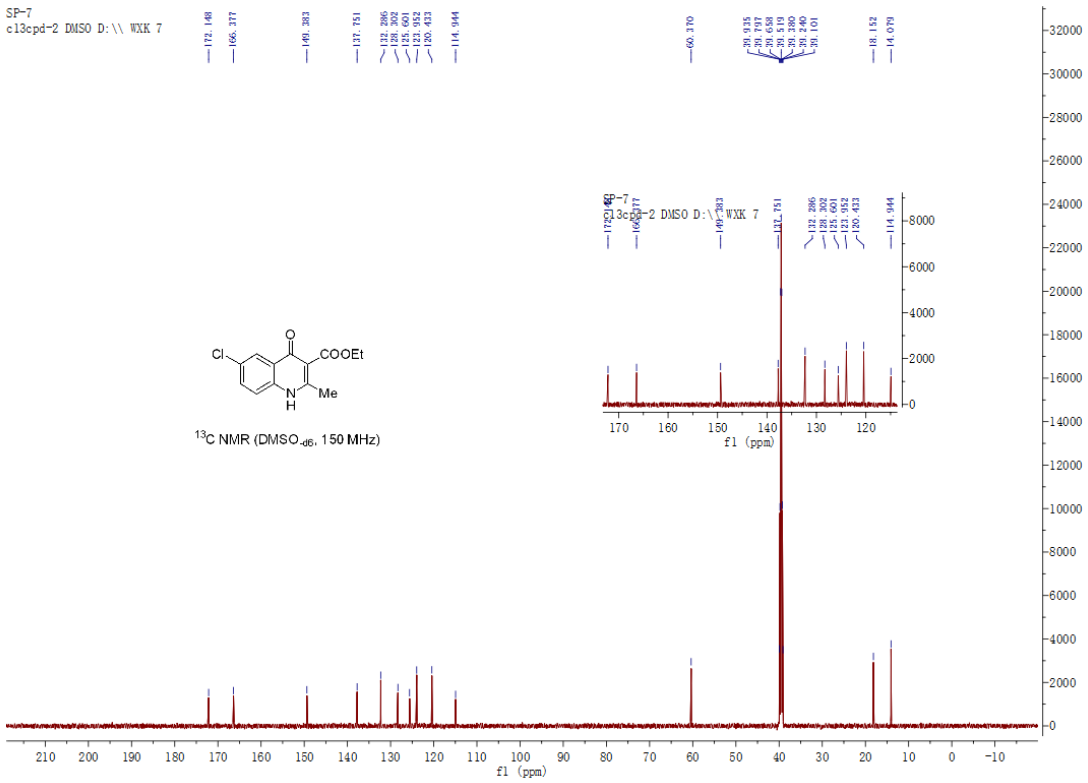
Me
^{13}C NMR (DMSO-d_6, 150 MHz)
f1 (ppm)


SP-7
PROTON DMSO D:\\ WXK 7
COOEt
Cl
Me
N
H
O
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)


SP-7
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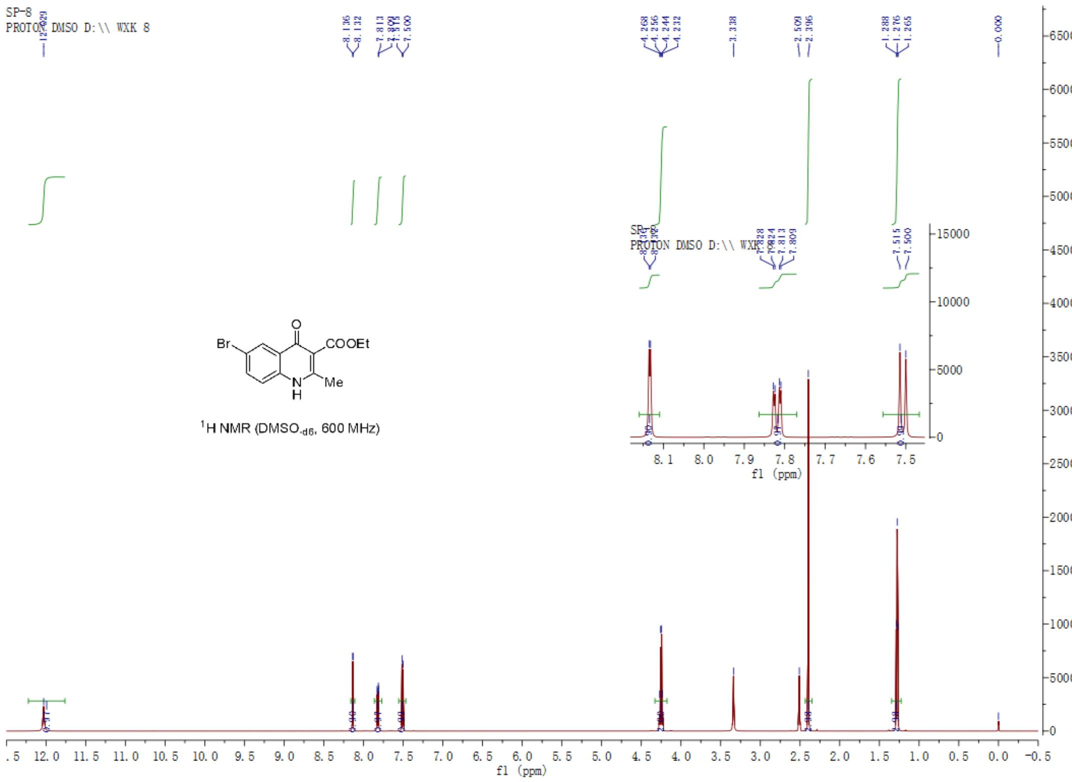
COOEt
Cl
Me
N
H
O
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)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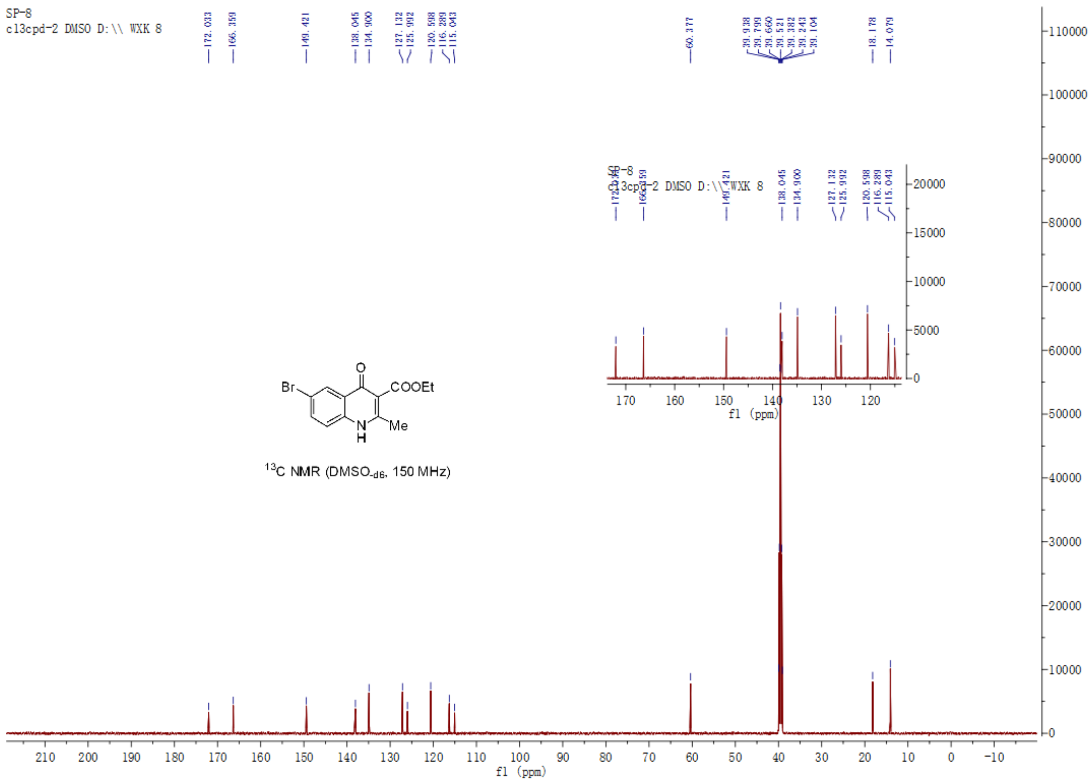
8.132
7.828
7.824
7.813
7.809
7.515
7.500
4.268
4.256
4.244
4.232
3.338
2.509
2.396
1.288
1.276
1.265
0.000
Br
O
COOEt
N
H
Me
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)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149.421
138.045
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115.043
60.377
39.938
39.799
39.660
39.521
39.382
39.243
39.104
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14.079
Br
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COOEt
N
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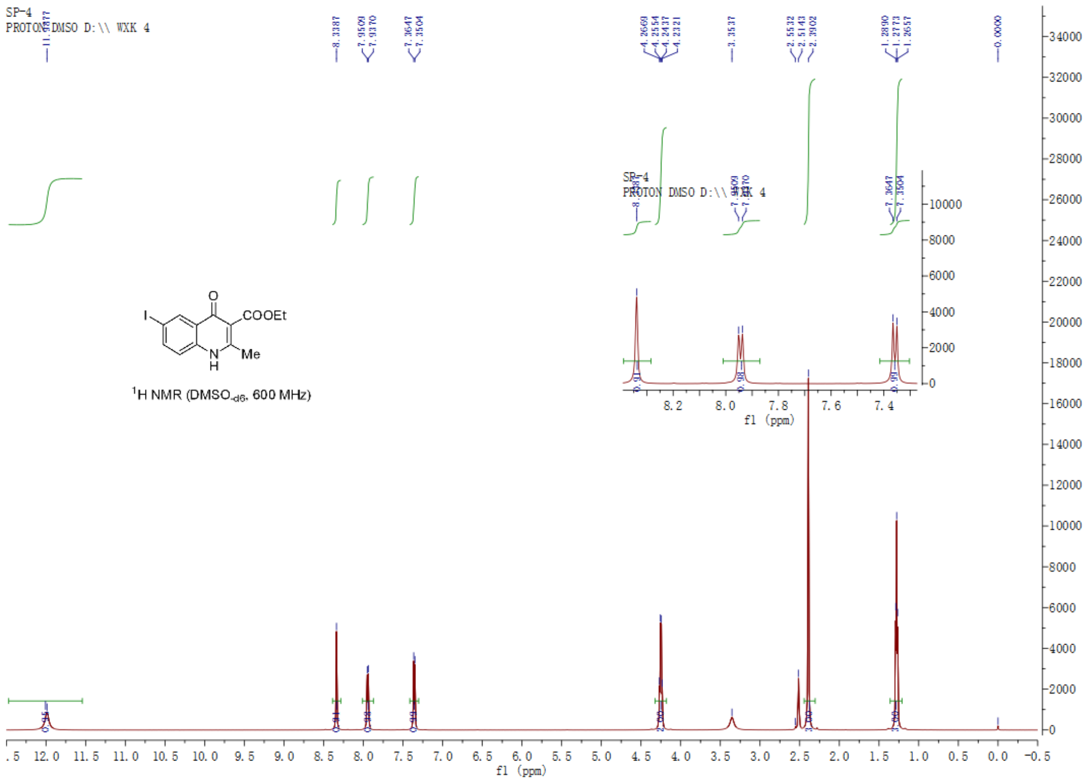
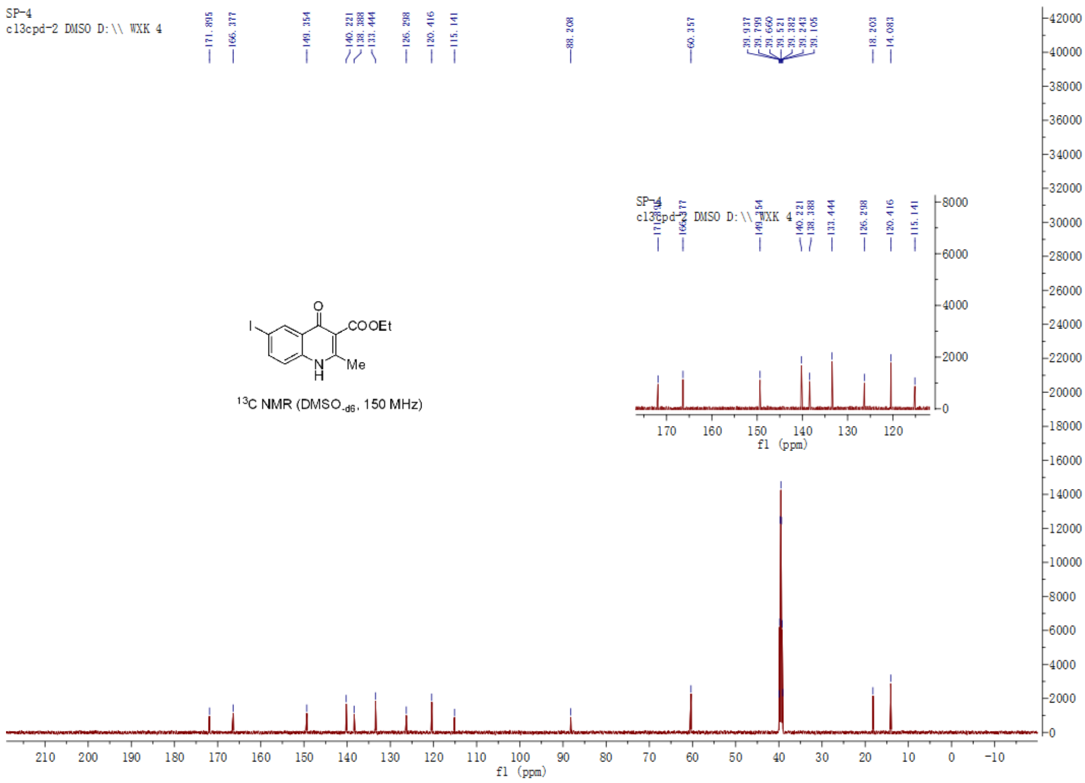
Me
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)


SP-4
PROTON DMSO D:\\ WXK 4
COOEt
Me
H
^{1}H NMR (DMSO-$_{d6}$, 600 MHz)
f1 (ppm)


SP-4
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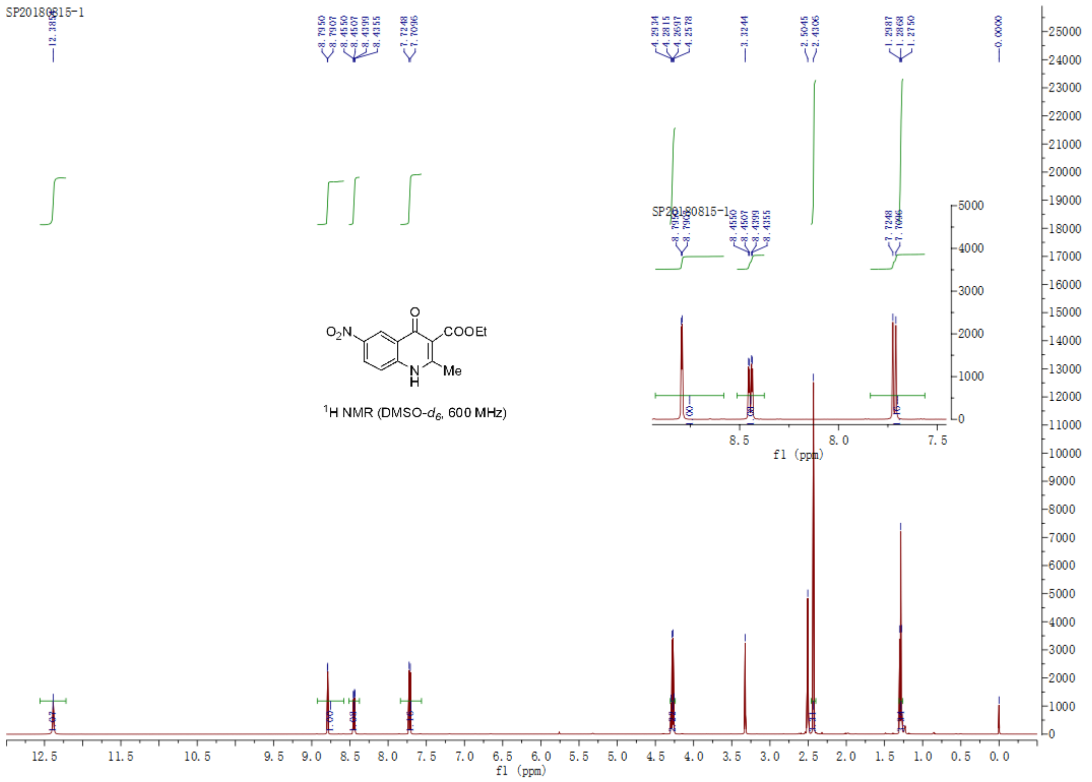
COOEt
Me
H
^{13}C NMR (DMSO-$_{d6}$, 150 MHz)
f1 (ppm)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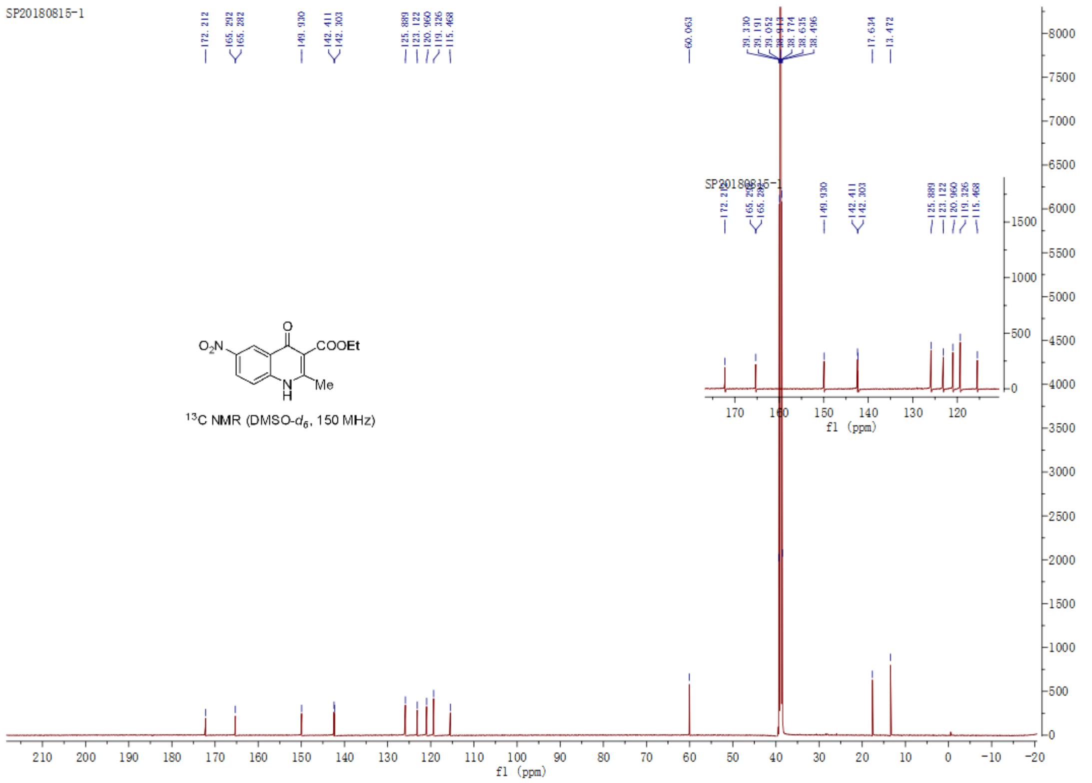
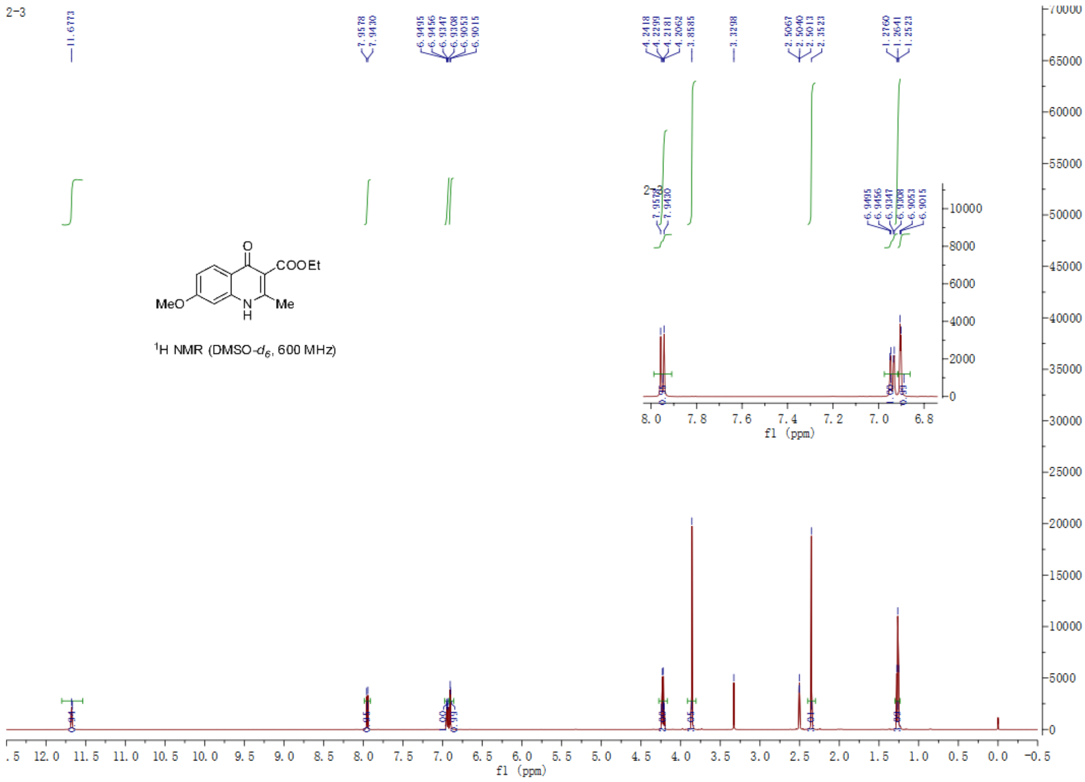
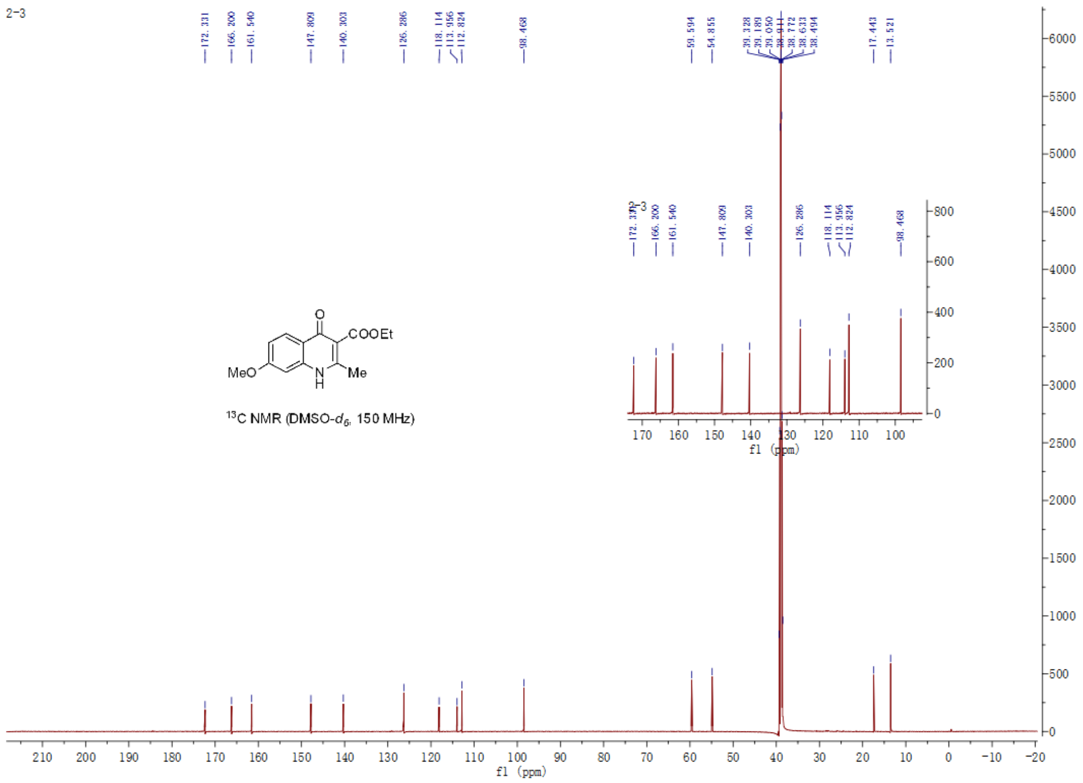
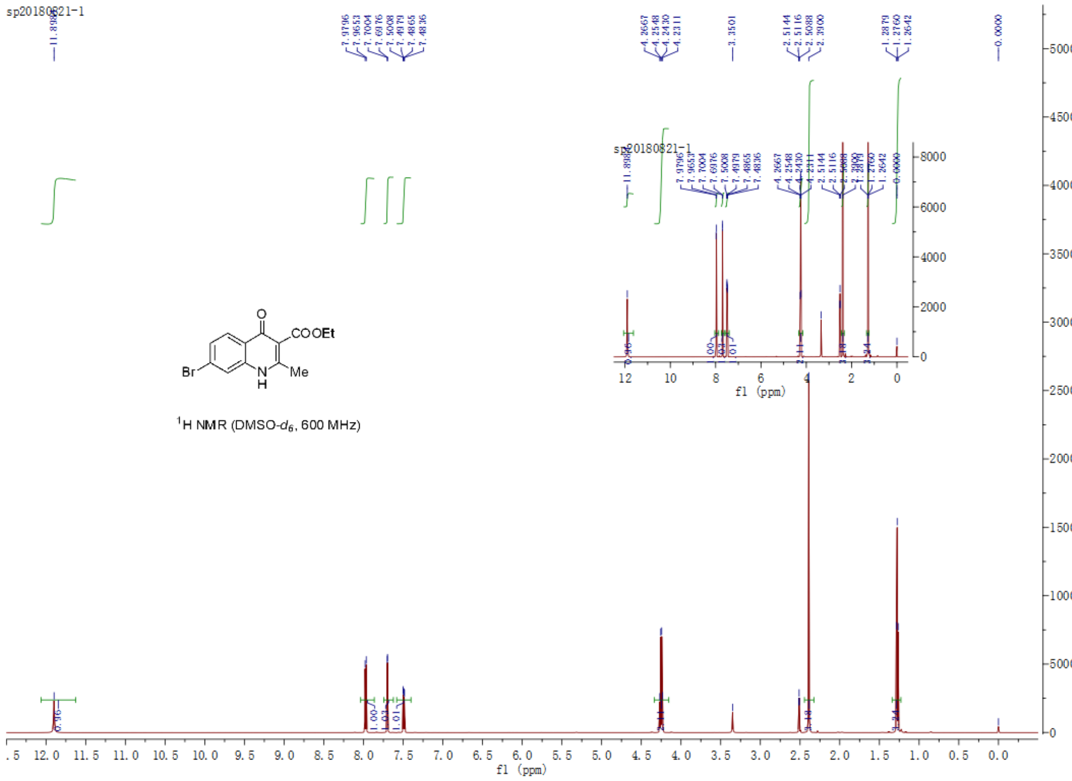
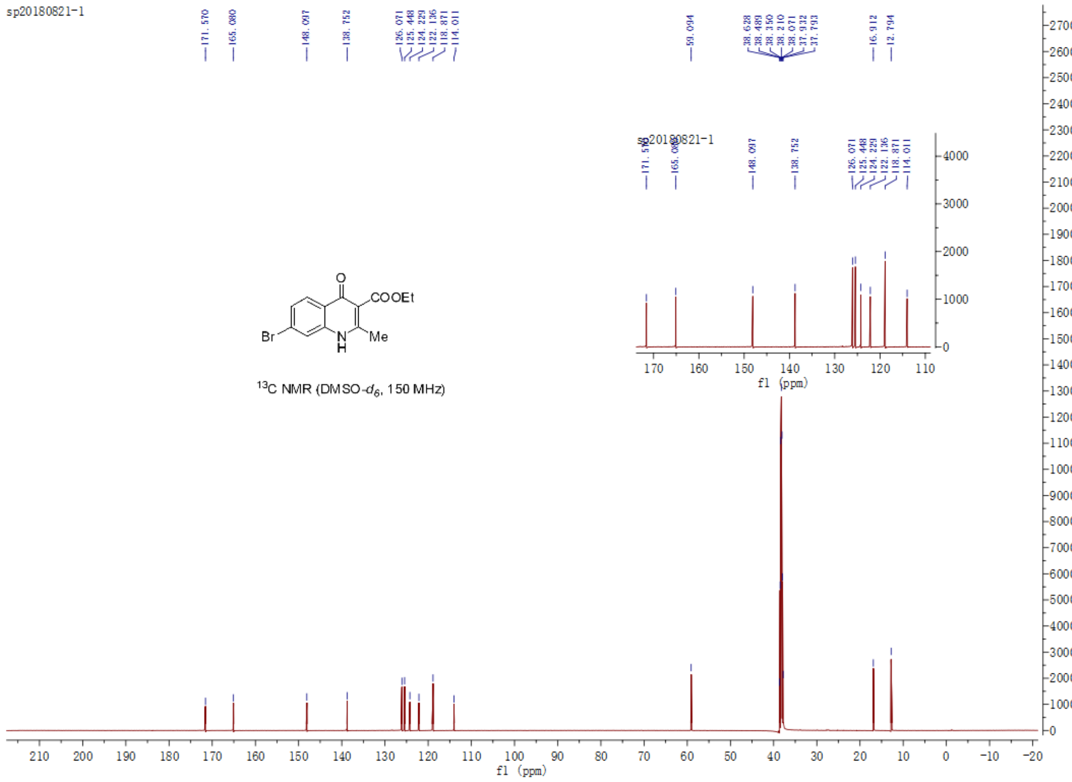
f1 (ppm)

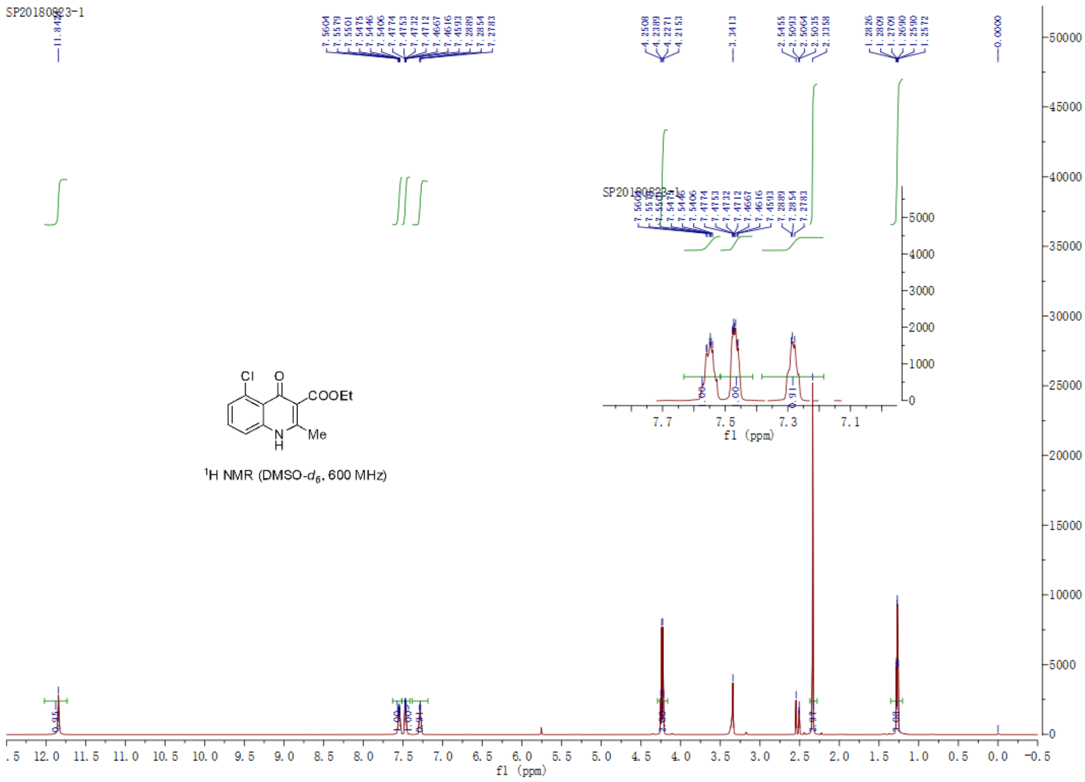

SP20180815-1
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)


2-3
MeO
COOEt
Me
^{1}H NMR (DMSO-d_6, 600 MHz)
f1 (ppm)


2-3
MeO
COOEt
Me
^{13}C NMR (DMSO-d_6, 150 MHz)
f1 (ppm)



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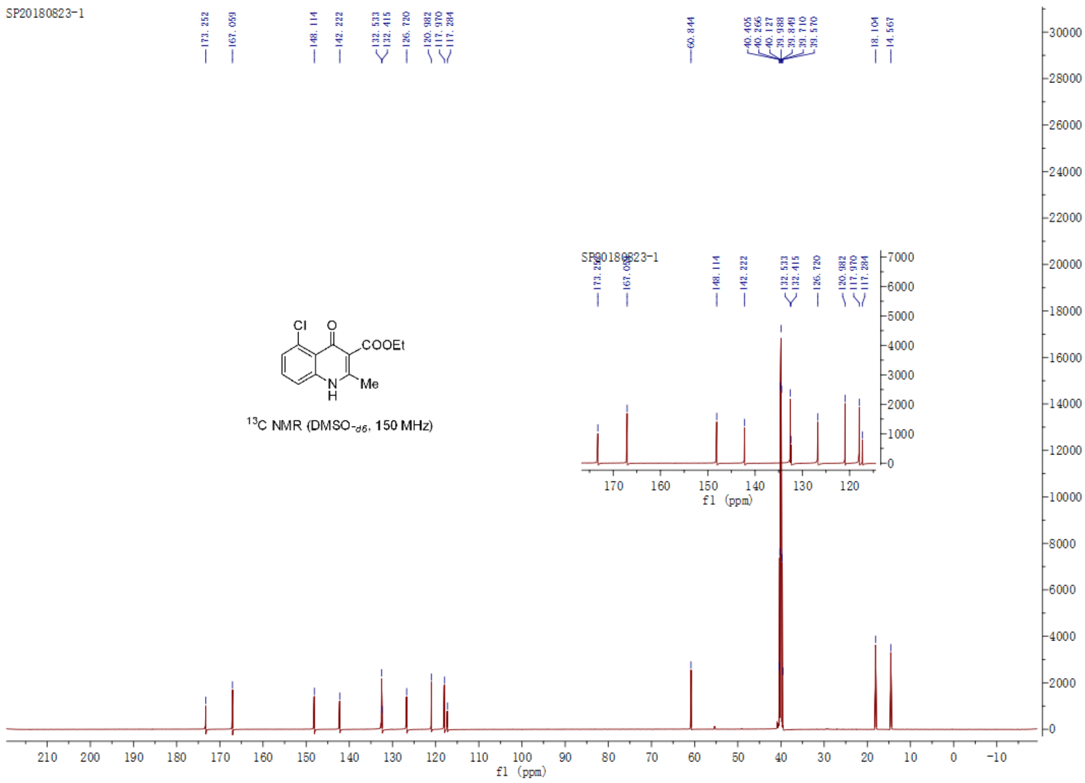
N
H
Me
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)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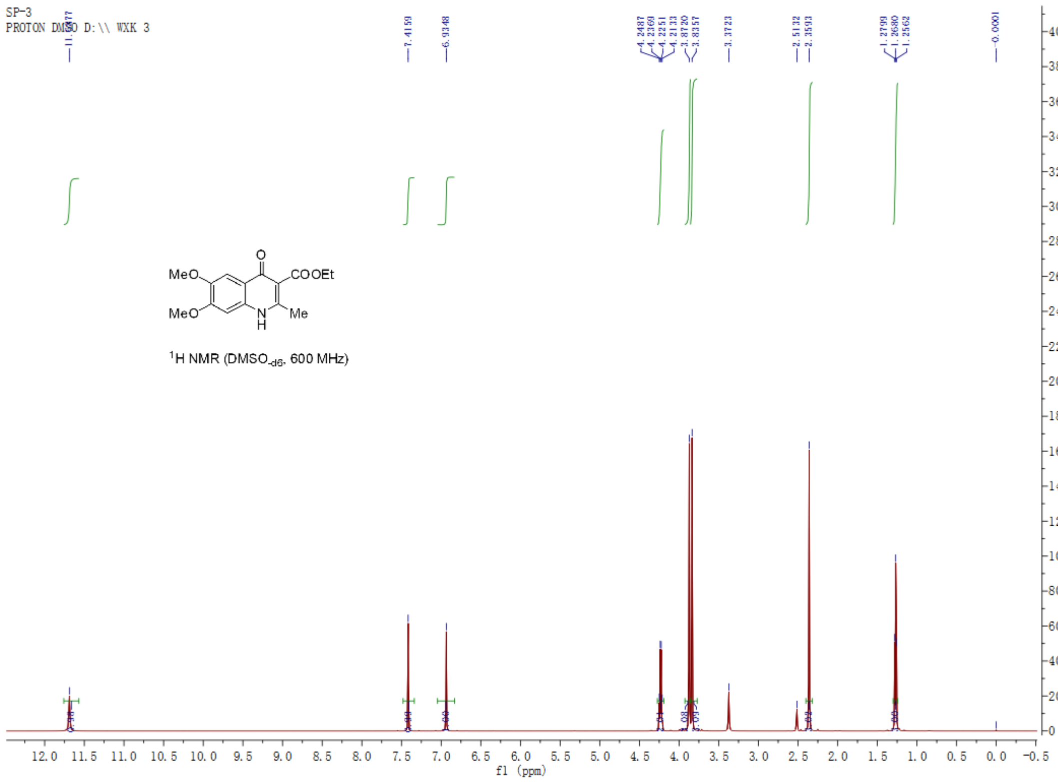
COOEt
N
H
Me
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)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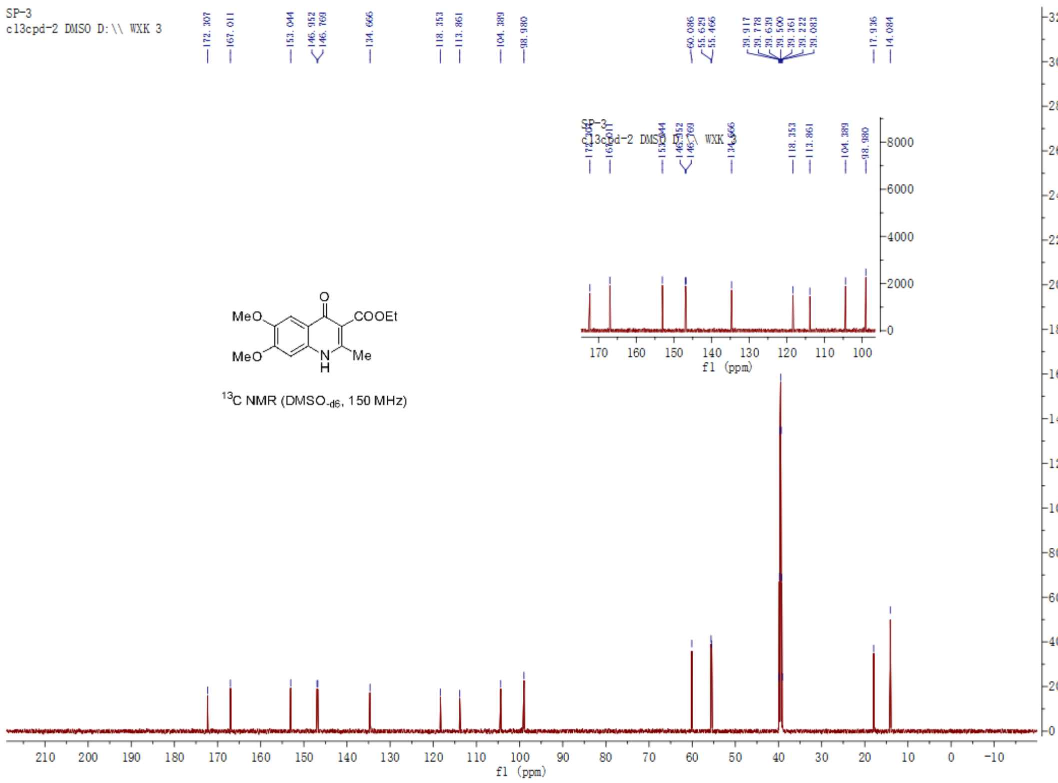
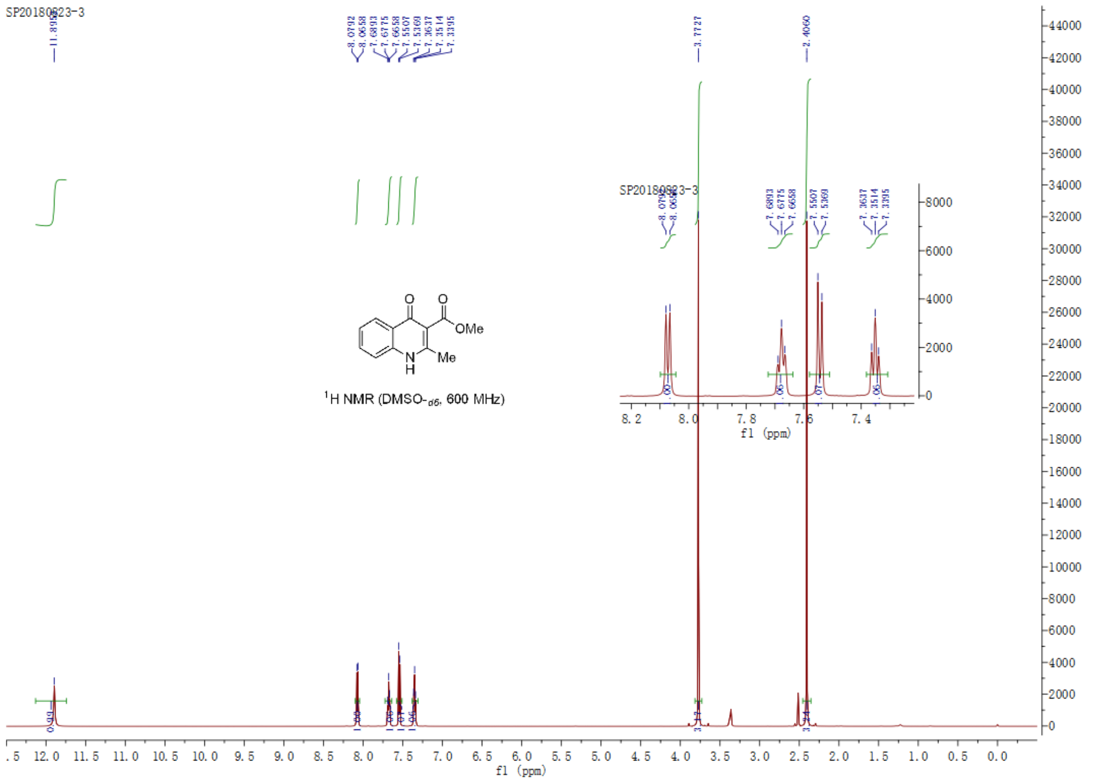
3.8720
3.8357
3.3723
2.5132
2.3593
1.2799
1.2680
1.2562
0.0001
MeO
MeO
O
COOEt
N
H
Me
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)


SP-3
c13cpd-2 DMSO D:\\ WXK 3
172.307
167.011
153.044
146.952
146.769
134.666
118.353
113.861
104.389
98.980
60.086
55.629
55.466
39.917
39.778
39.639
39.500
39.361
39.222
39.083
17.936
14.084
MeO
MeO
O
COOEt
N
H
Me
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)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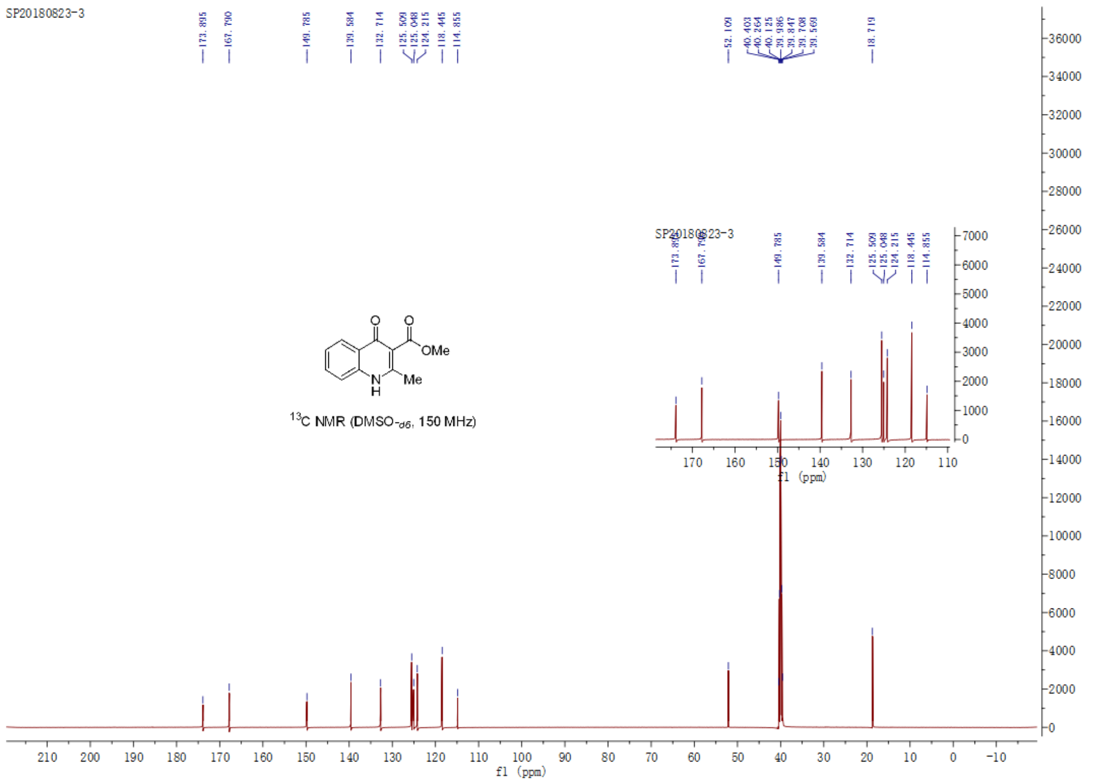
8.0792
8.0658
7.6893
7.6775
7.6658
7.5507
7.5369
7.3637
7.3514
7.3395
3.7727
2.4060
OMe
Me
N
H
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)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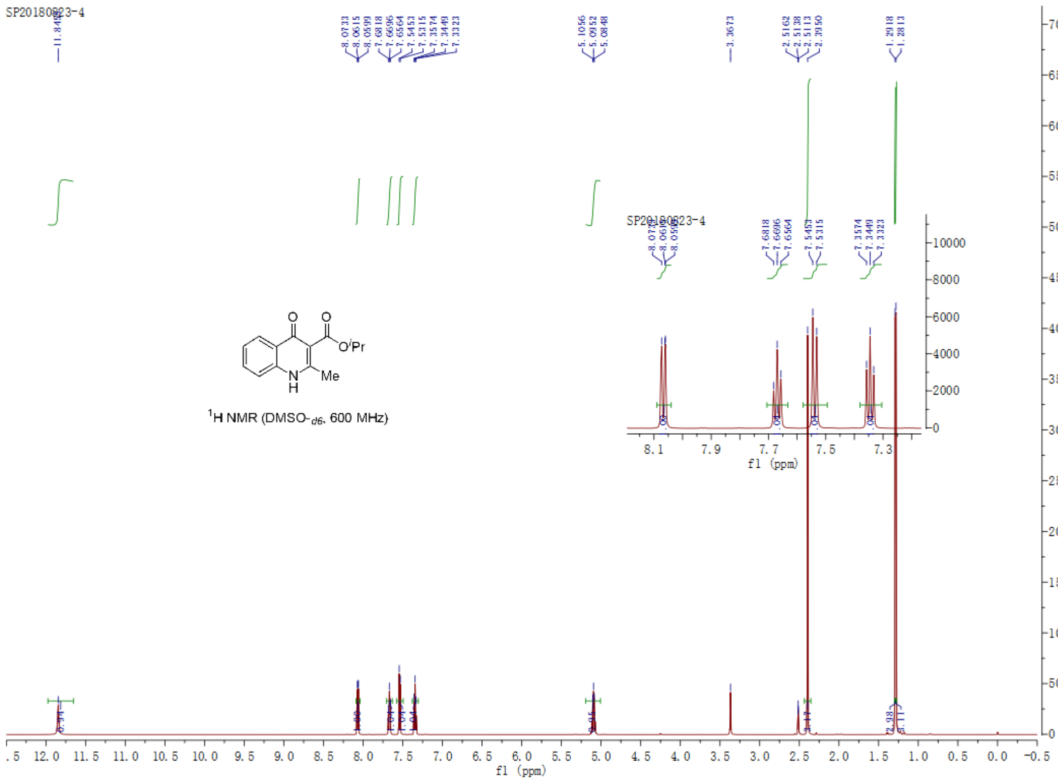
167.790
149.785
139.584
132.714
125.509
125.048
124.215
118.445
114.855
52.169
40.403
40.264
40.125
39.986
39.847
39.708
39.569
18.719
OMe
Me
N
H
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)


SP20180823-4
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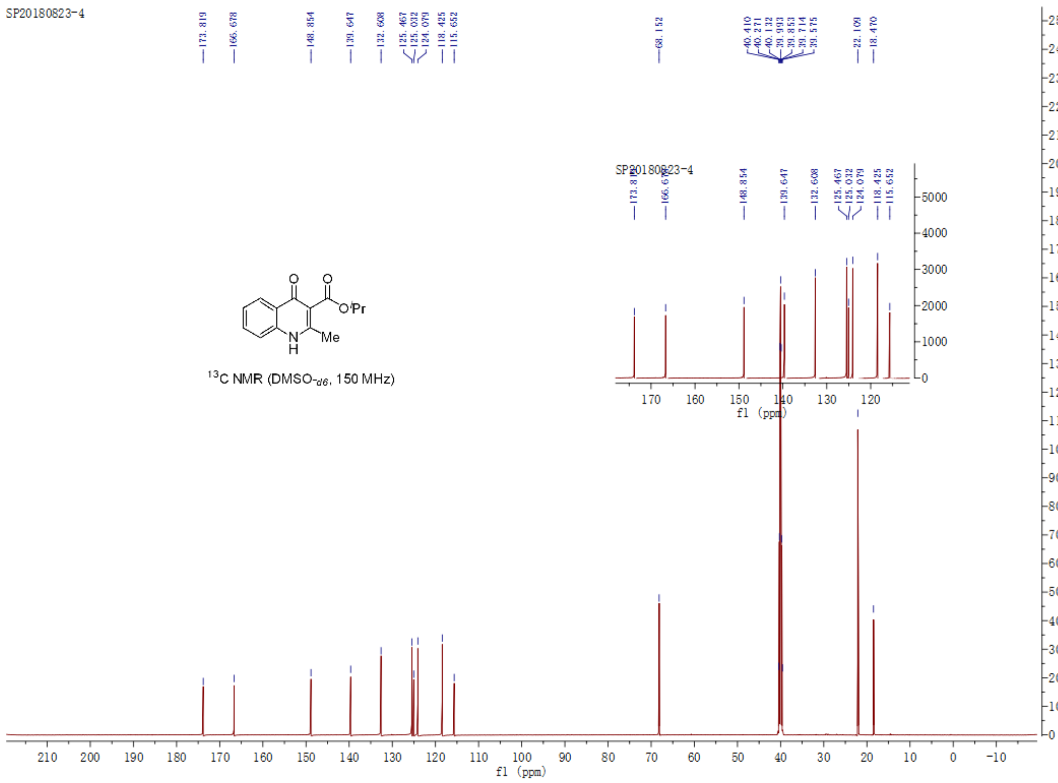
8.0615
8.0599
7.6818
7.6696
7.6564
7.5453
7.5315
7.3574
7.3449
7.3323
5.1056
5.0952
5.0848
3.3673
2.5162
2.5138
2.5113
2.3950
1.2918
1.2813
O
O
O^{i}Pr
N
H
Me
^{1}H NMR (DMSO-d_6, 600 MHz)
f1 (ppm)


SP20180823-4
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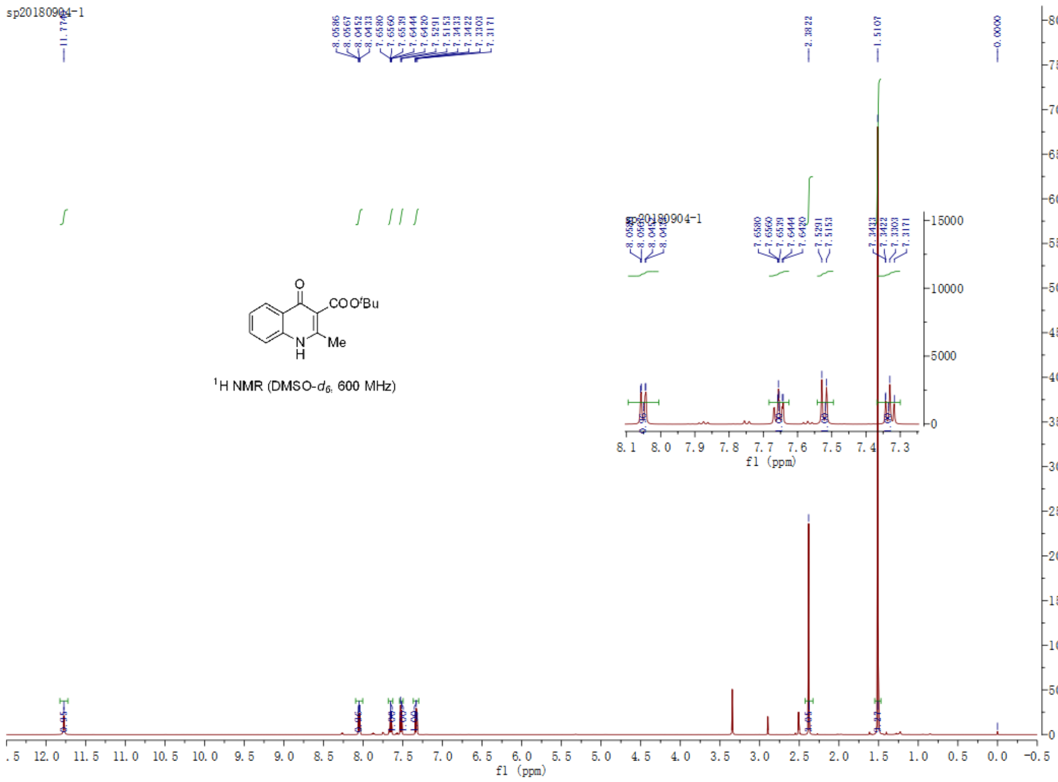
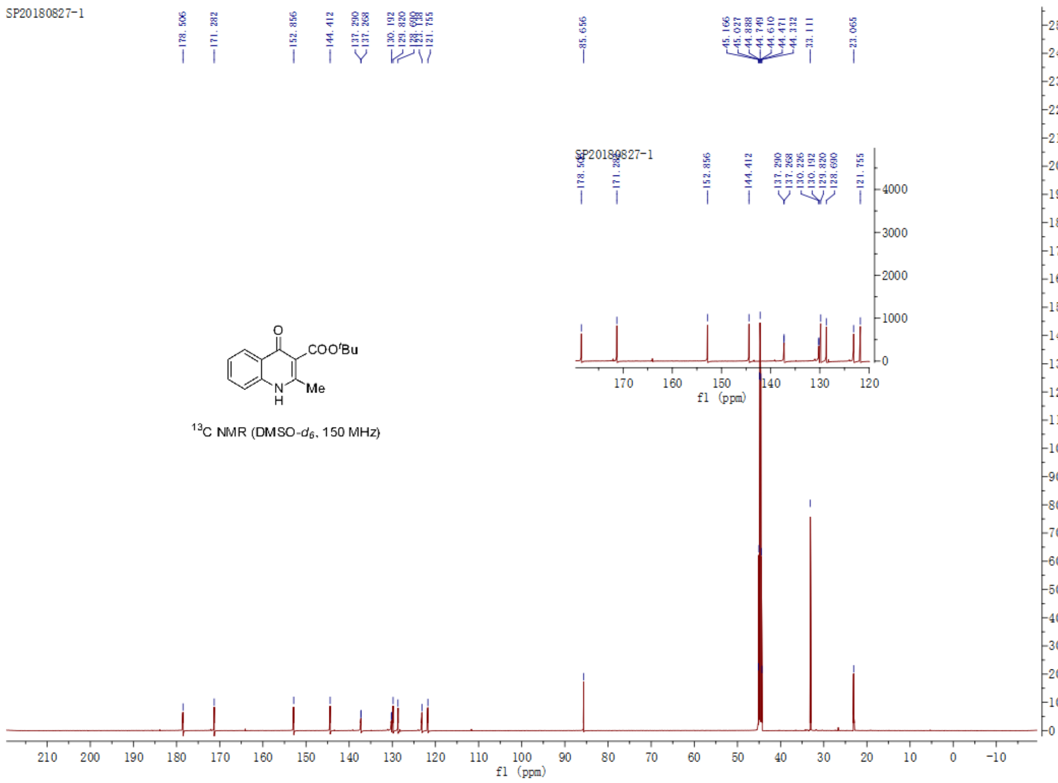
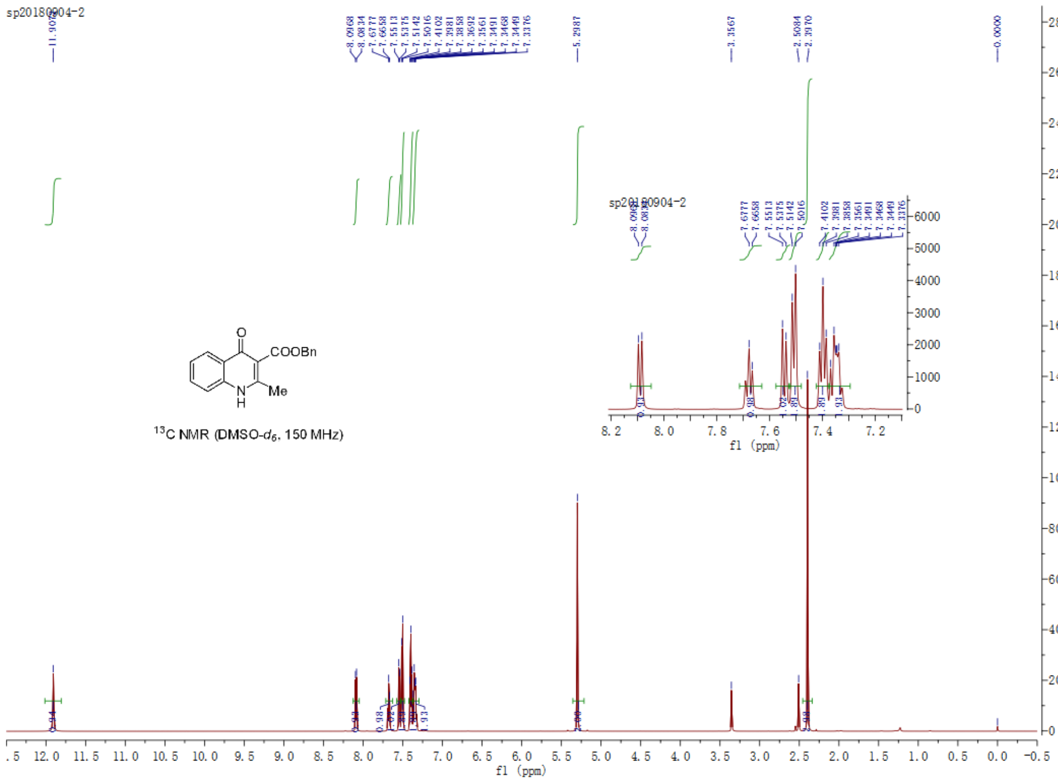
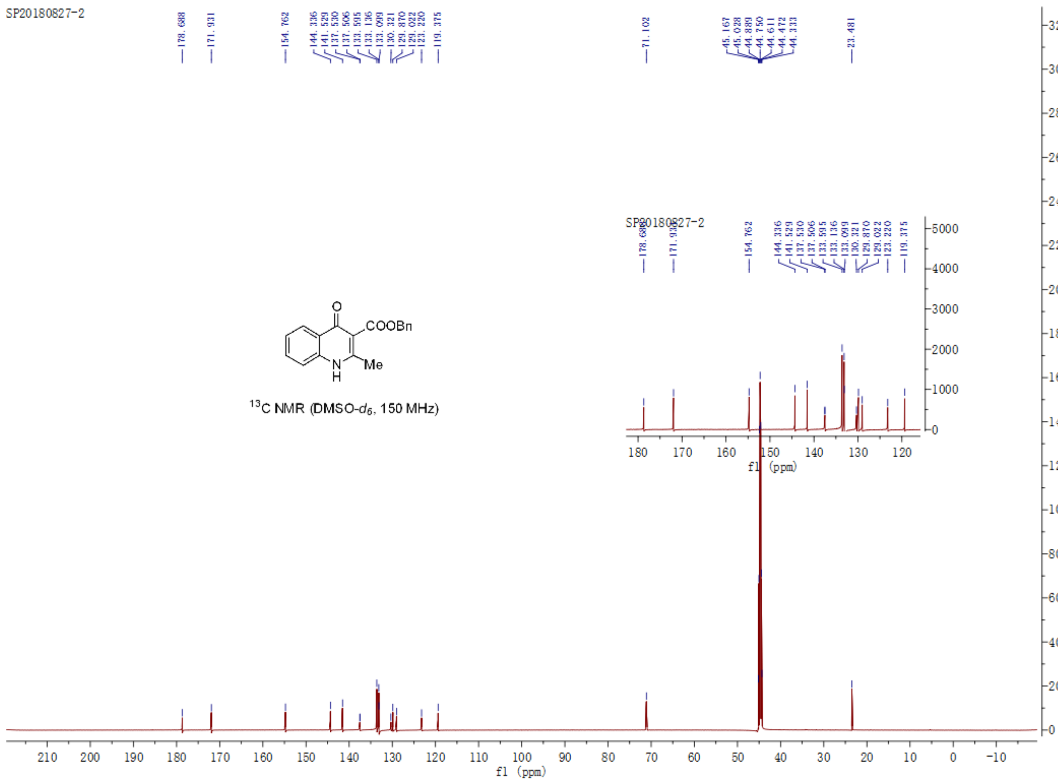
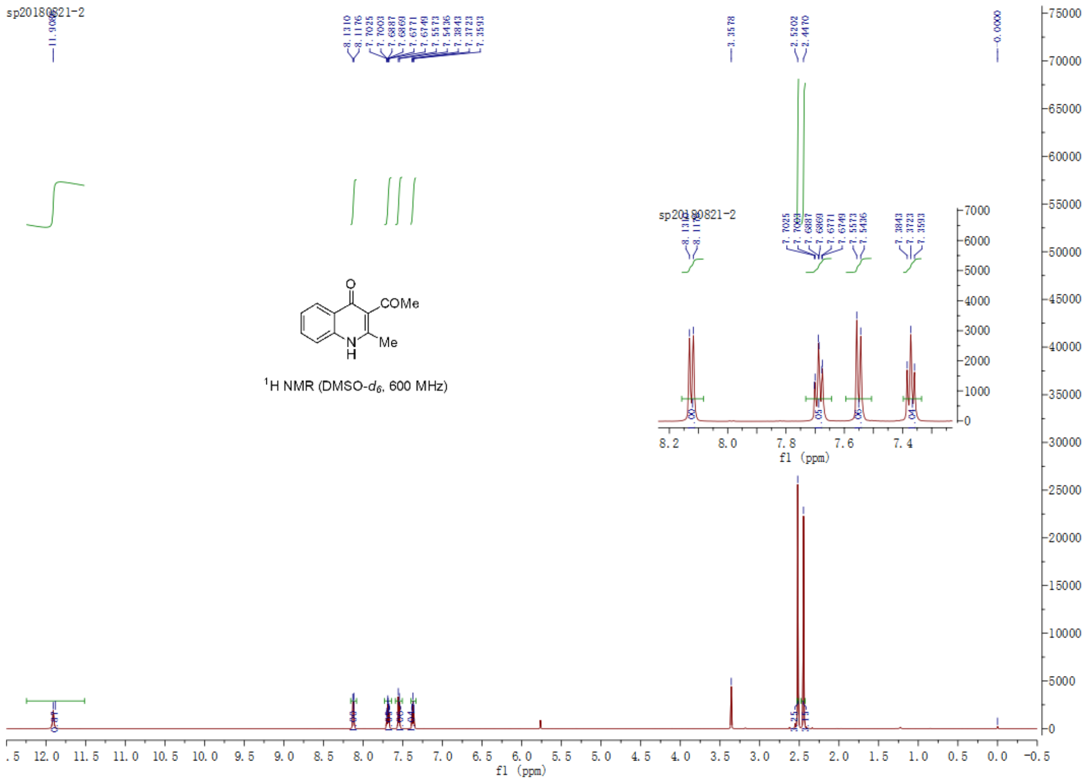
166.678
148.854
139.647
132.608
125.467
125.032
124.079
118.425
115.652
68.152
40.410
40.271
40.132
39.993
39.853
39.714
39.575
22.109
18.470
O
O
O^{i}Pr
N
H
Me
^{13}C NMR (DMSO-d_6, 150 MHz)
f1 (ppm)


sp20180904-1
COO^{t}Bu
Me
^{1}H NMR (DMSO-d_6, 600 MHz)
f1 (ppm)

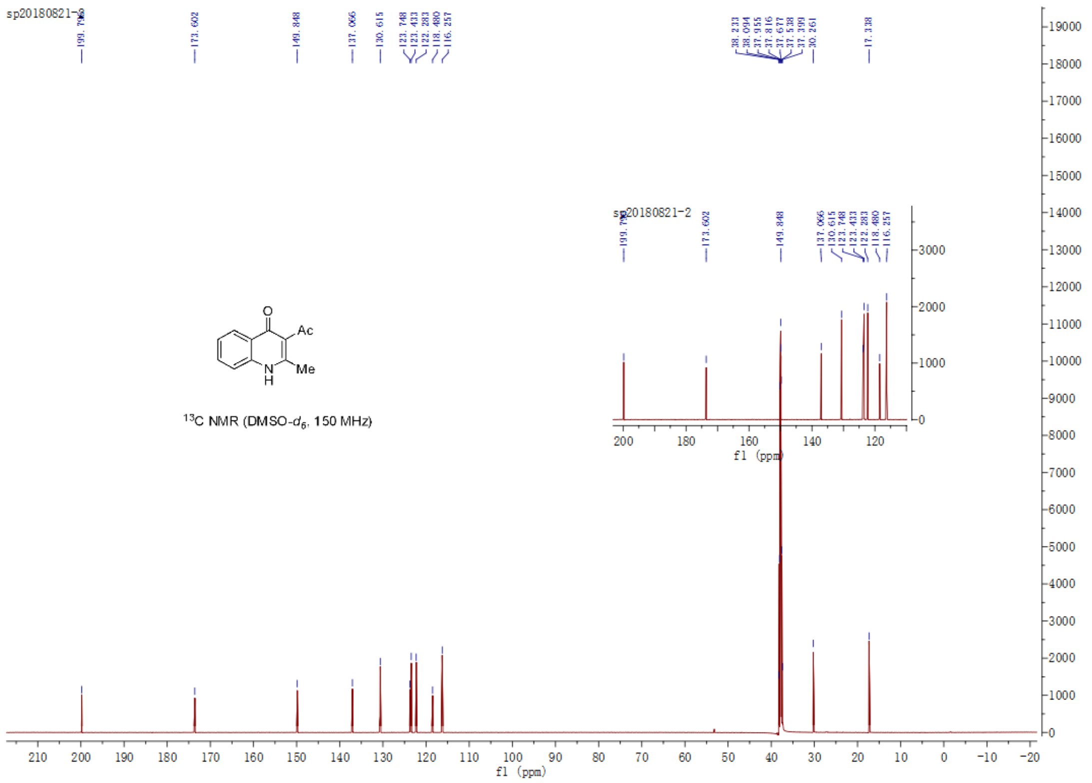

SP20180827-1
COO^{t}Bu
Me
^{13}C NMR (DMSO-d_6, 150 MHz)
f1 (ppm)



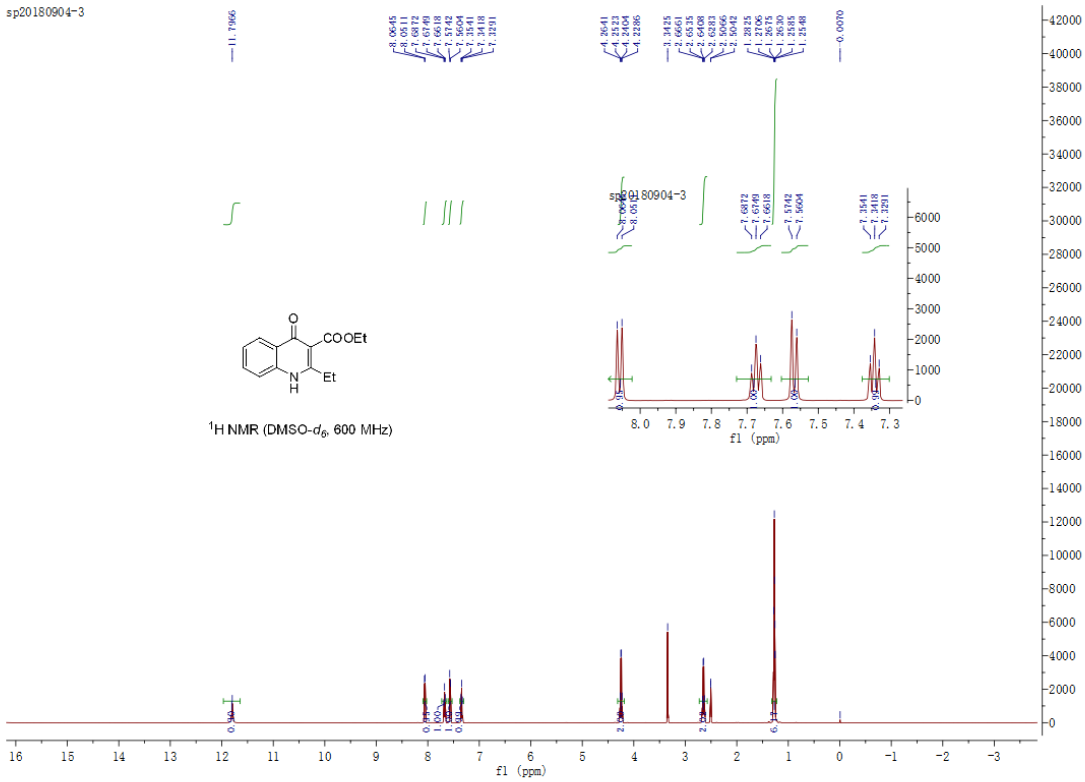


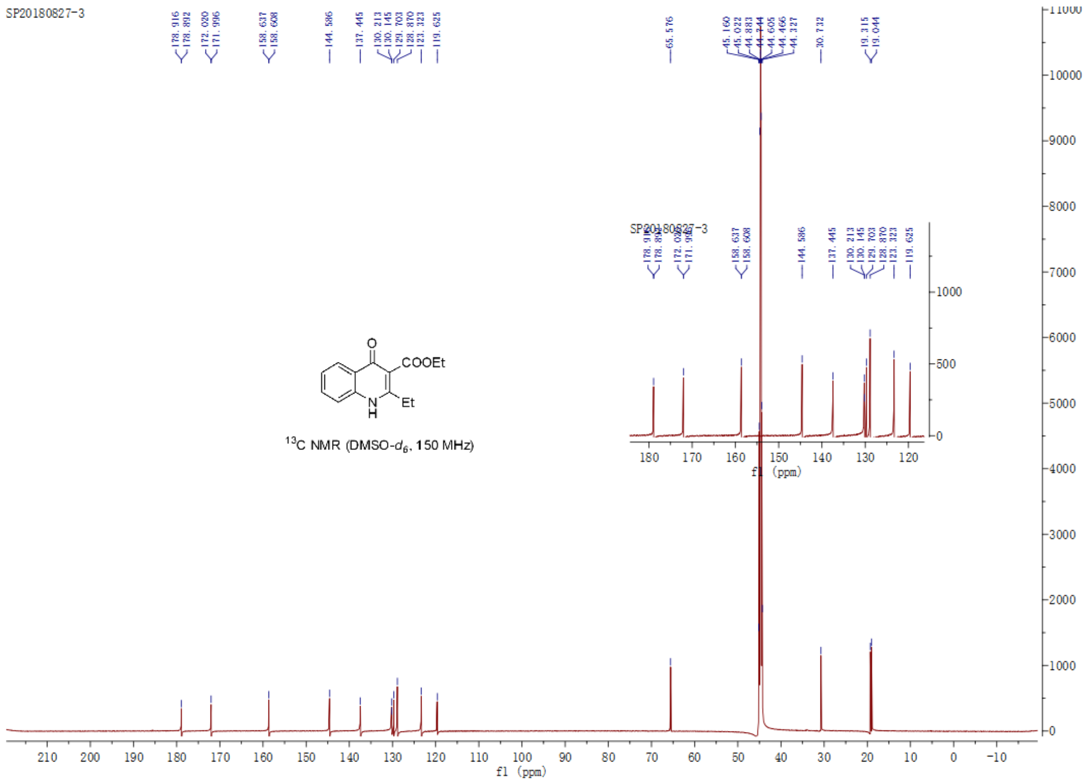


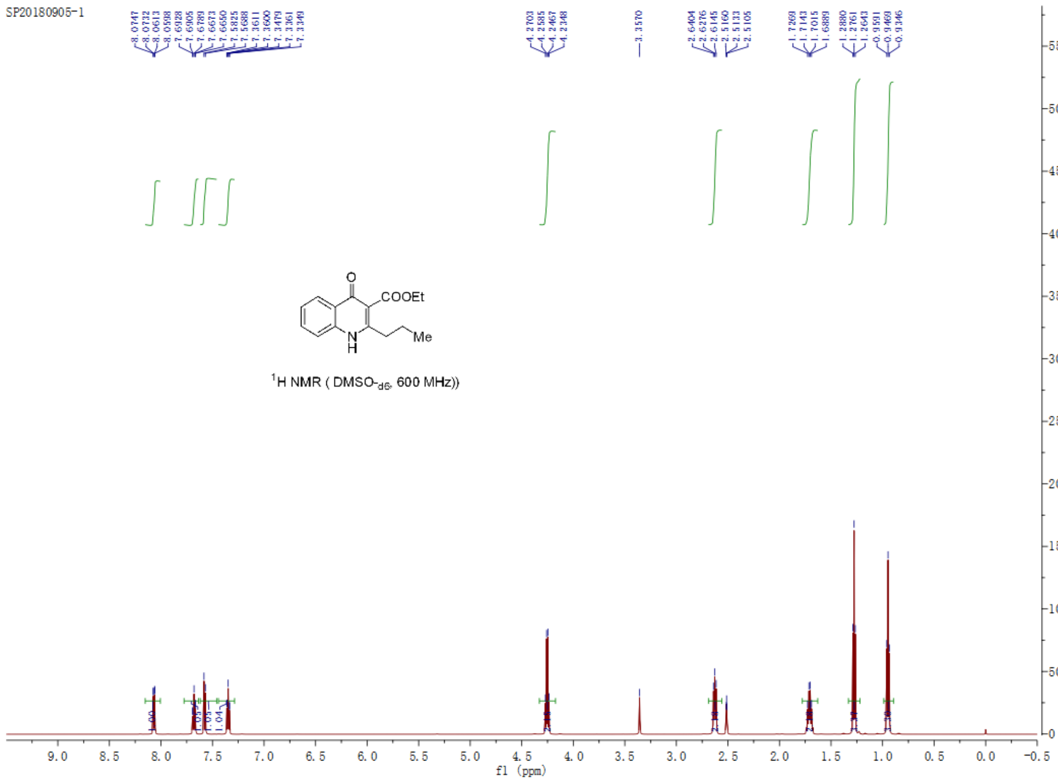
sp20180821-2
1H NMR (DMSO-d6, 600 MHz)
COMe
Me
f1 (ppm)

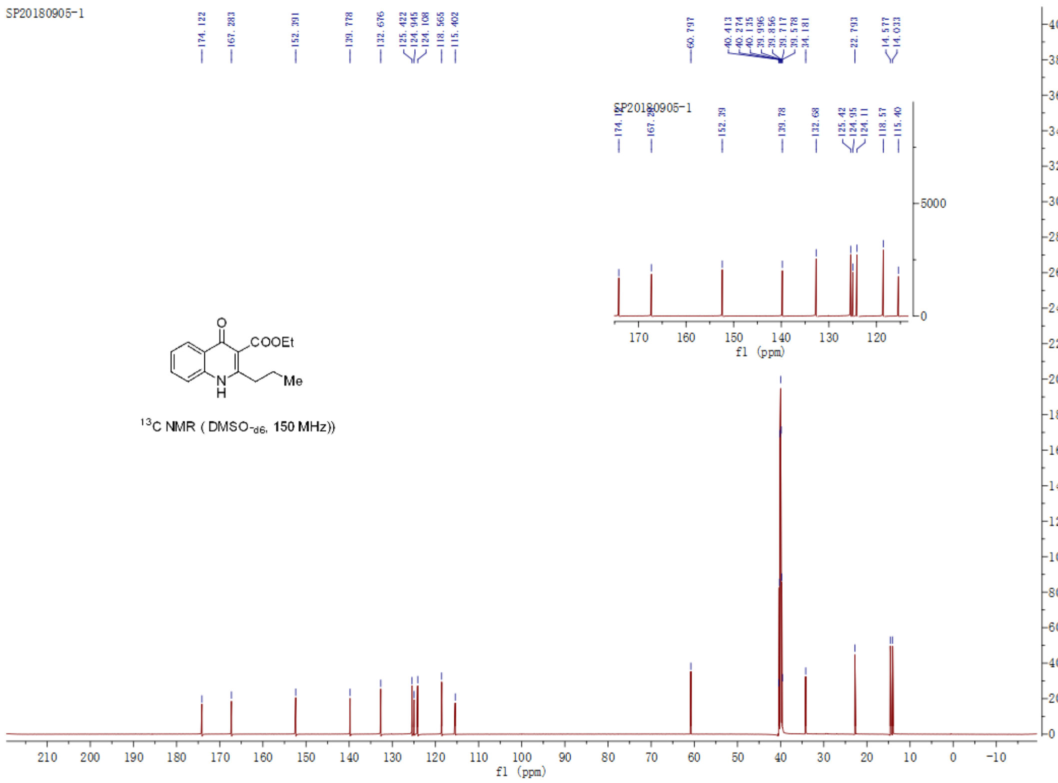


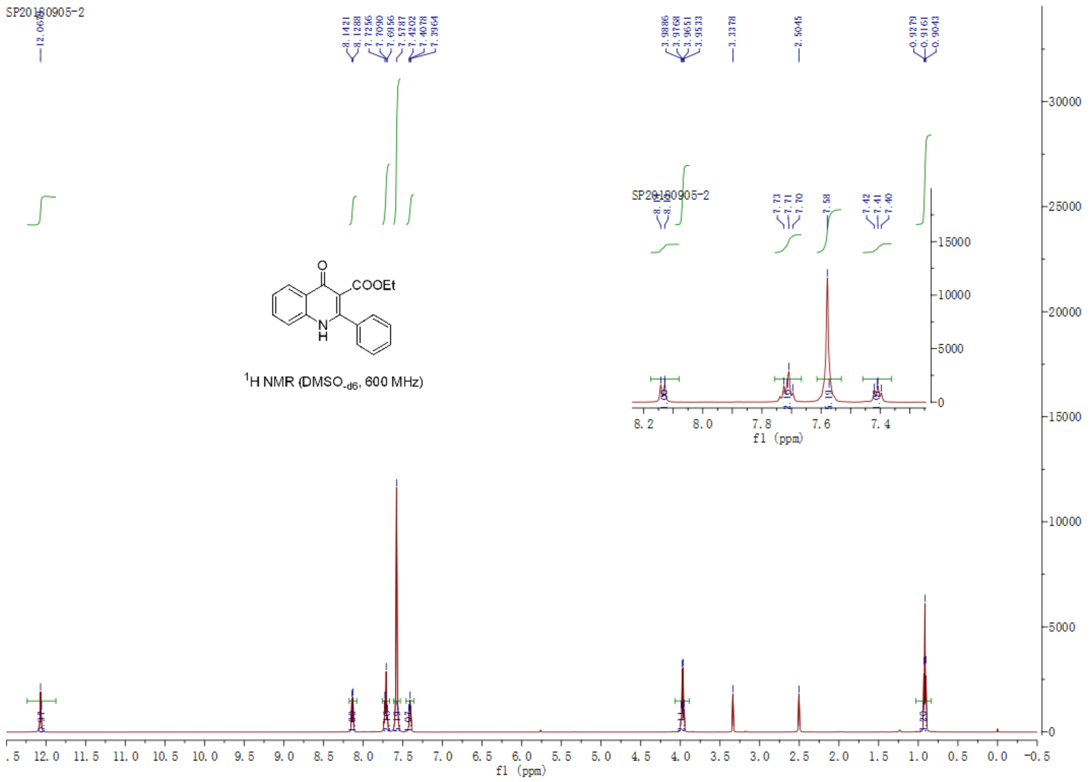
sp20180821-2
13C NMR (DMSO-d6, 150 MHz)
Ac
Me
f1 (ppm)

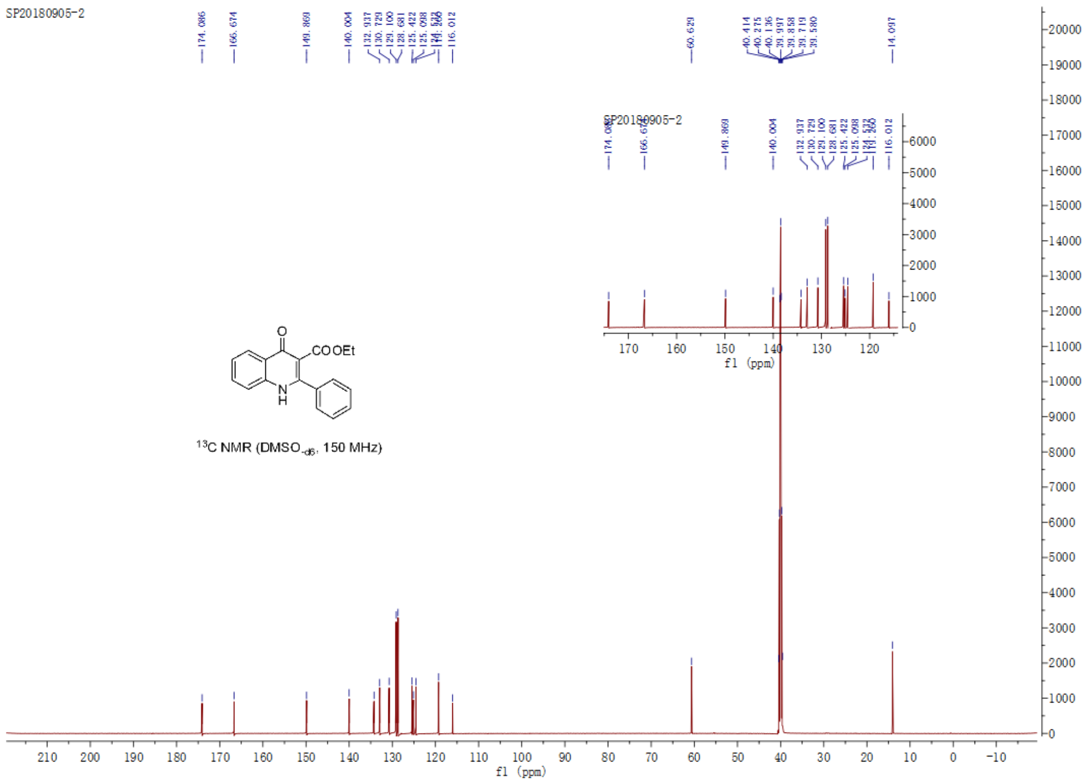

sp20180904-3
11.7966
8.0645 8.0511 7.6872 7.6749 7.6618 7.5742 7.5604 7.3541 7.3418 7.3291
4.2641 4.2523 4.2404 4.2286
3.3425 2.6661 2.6535 2.6408 2.6283 2.5066 2.5042 1.2825 1.2706 1.2675 1.2630 1.2585 1.2548
0.0070
O
COOEt
N
H
Et
^{1}H NMR (DMSO-d_6, 600 MHz)
f1 (ppm)

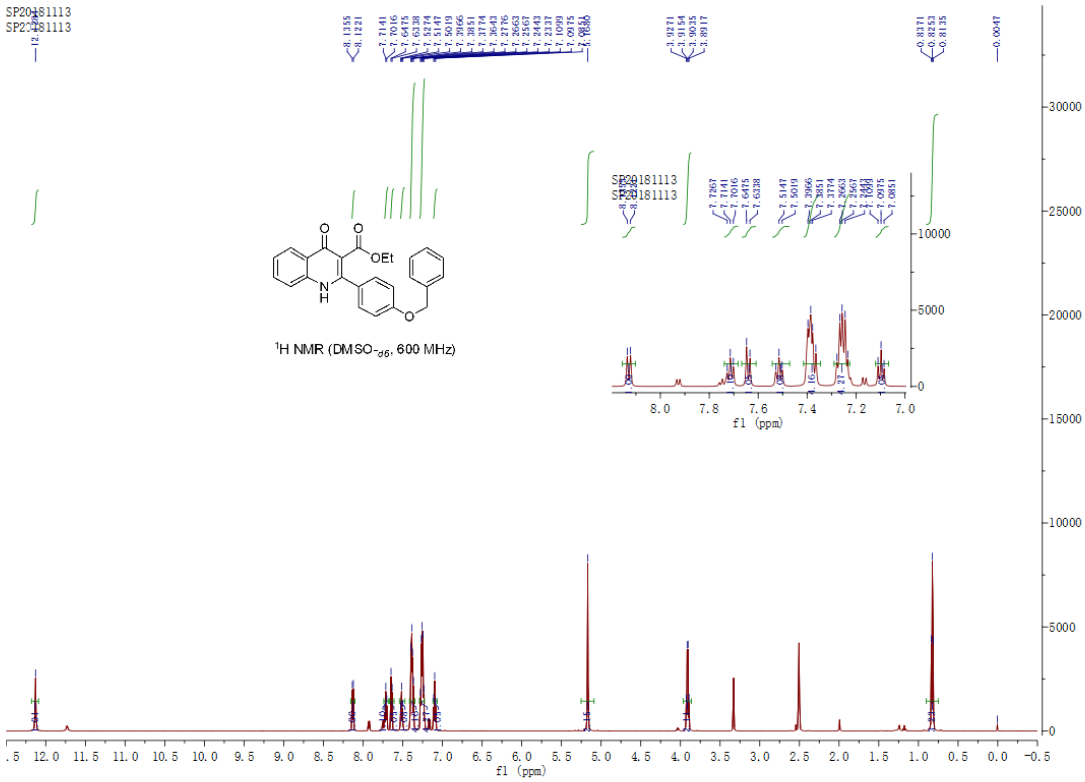

SP20180827-3
178.916 178.892 172.020 171.996 158.637 158.608 144.586 137.445 130.213 130.145 129.703 128.870 123.323 119.625
65.576
45.160 45.022 44.883 44.744 44.605 44.466 44.327 30.732 19.315 19.044
O
COOEt
N
H
Et
^{13}C NMR (DMSO-d_6, 150 MHz)
f1 (ppm)

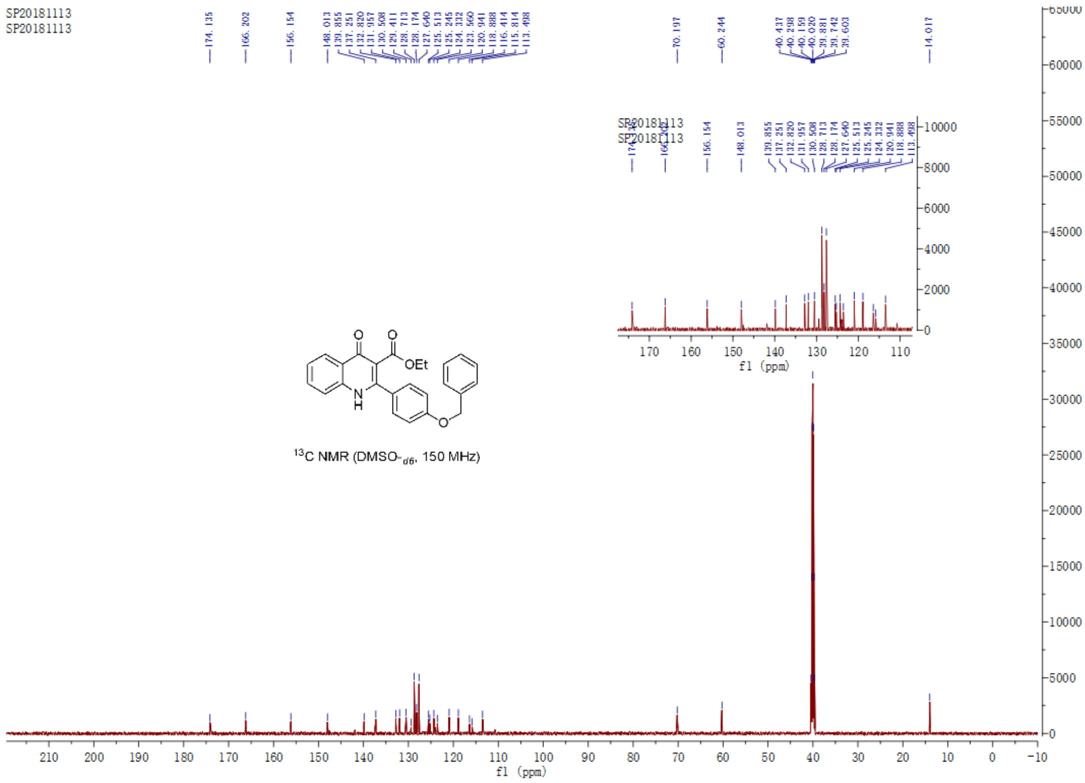


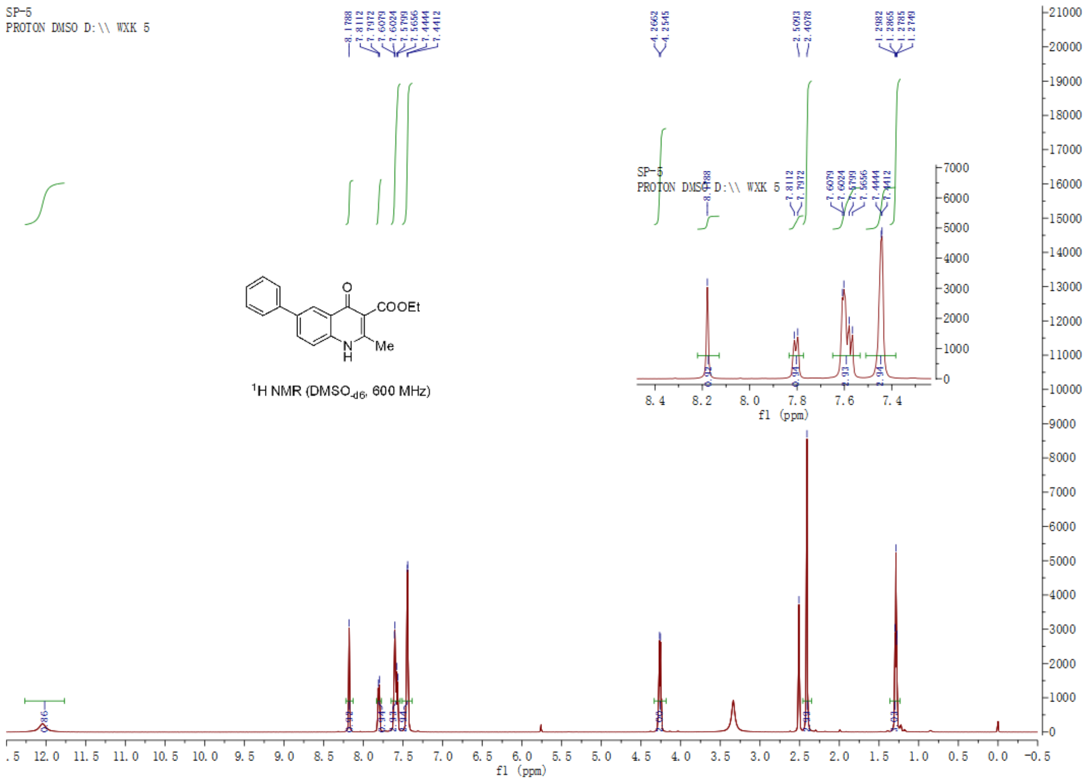


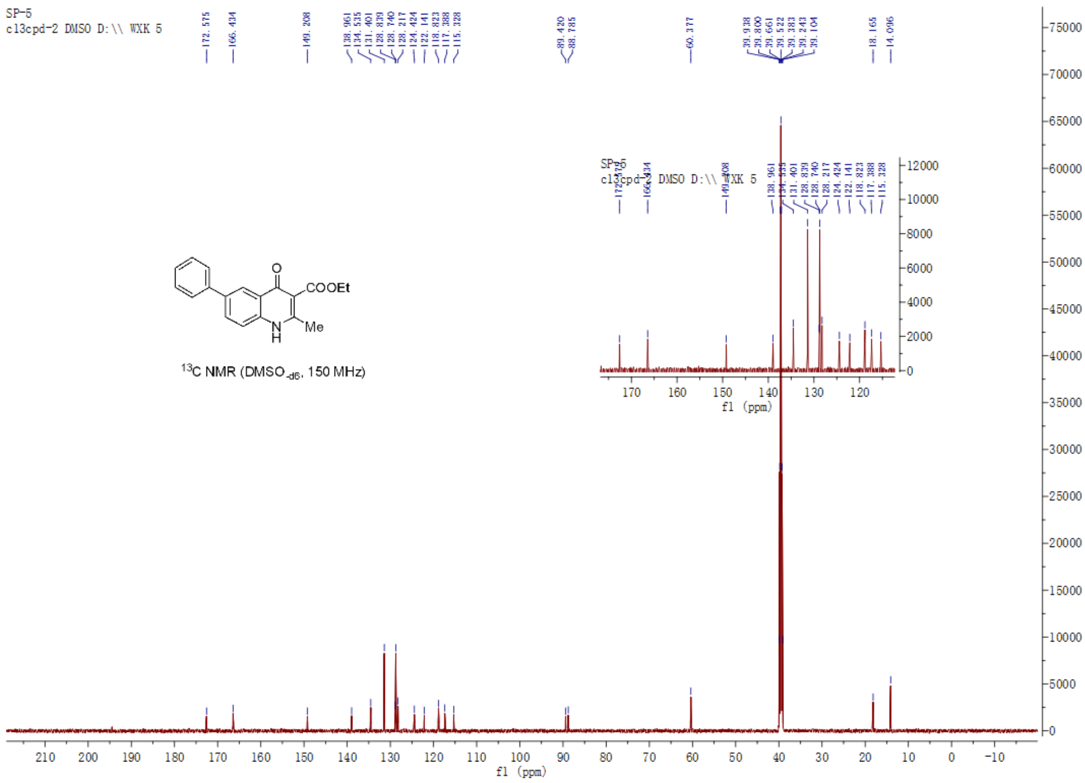

SP20180905-2
COOEt
O
N
H
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)

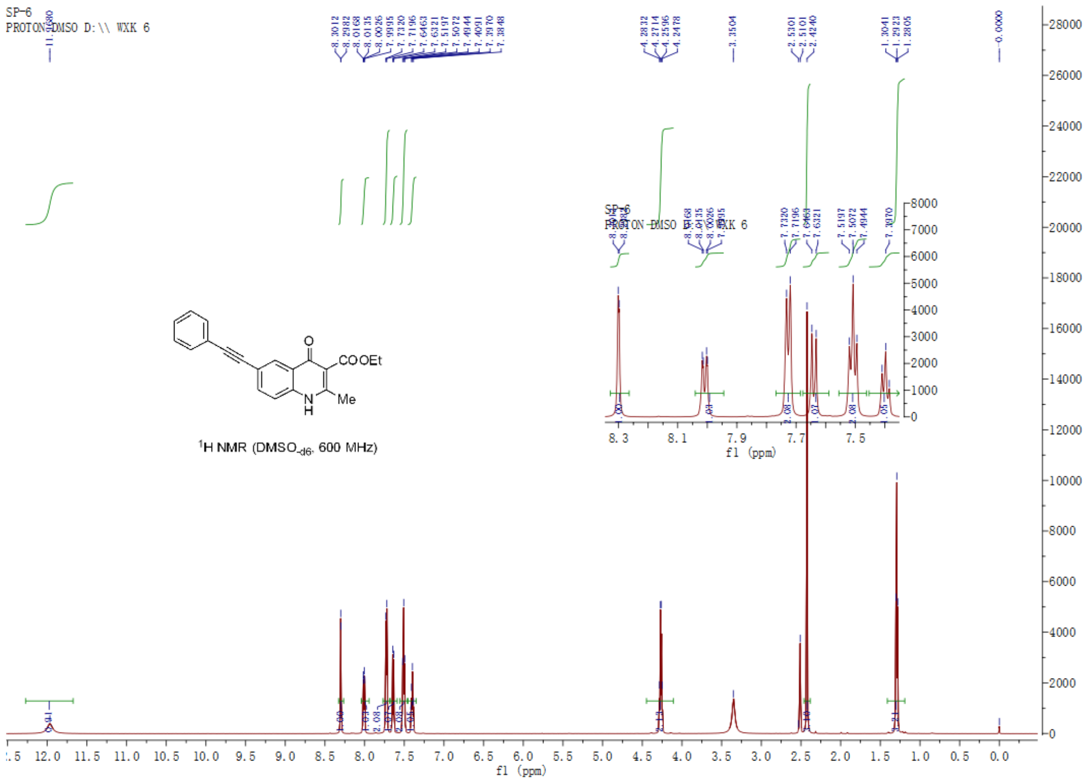

SP20180905-2
O
COOEt
N
H
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)

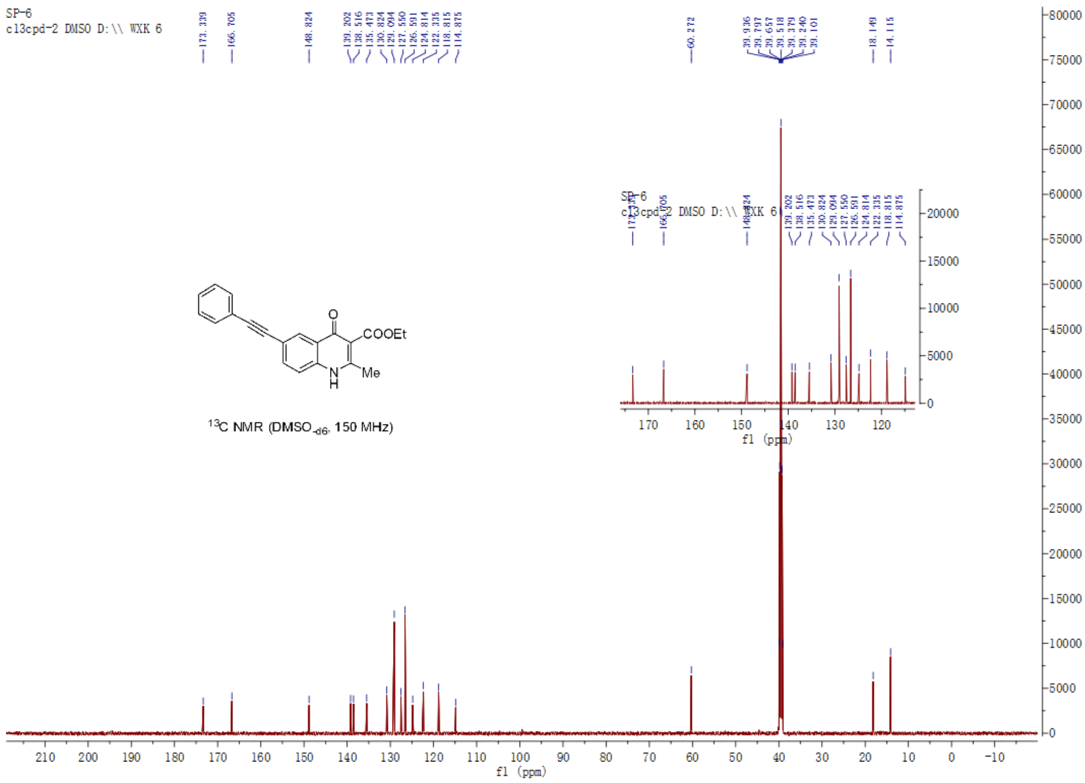

SP20181113
OEt
H
1H NMR (DMSO-d6, 600 MHz)
f1 (ppm)


SP20181113
OEt
H
13C NMR (DMSO-d6, 150 MHz)
f1 (ppm)


SP-5
PROTON DMSO D:\\ WXK 5
COOEt
Me
^{1}H NMR (DMSO$_{-d6}$, 600 MHz)
f1 (ppm)


SP-5
cl3cpd-2 DMSO D:\\ WXK 5
COOEt
Me
^{13}C NMR (DMSO$_{-d6}$, 150 MHz)
f1 (ppm)


SP-6
PROTON-DMSO D:\\ WXK 6
COOEt
Me
N
H
O
^{1}H NMR (DMSO$_{-d6}$, 600 MHz)
f1 (ppm)


SP-6
c13cpd-2 DMSO D:\\ WXK 6
173.339
166.705
148.824
139.202
138.516
135.473
130.824
129.094
127.550
126.591
124.814
122.335
118.815
114.875
60.272
18.149
14.115
COOEt
Me
^{13}C NMR (DMSO$_{-d6}$, 150 MHz)
f1 (ppm)