Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting information

Synthesis of Tricyclic 3-Hydroxyisoindolin-1-onesvia Triethylamine-Catalyzed Domino Reactions of Electron-Deficient Alkynes with Phthalimidomalonate Derivatives

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Contents

I. Instrumentation and chemicals

All reactions were performed under N_2 unless otherwise indicated. Reagents and solvents were purchased as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel (200 - 300 m) using a mixture of ethyl acetate (EA) and petroleum ether (PE).

^1H NMR and ^{13}C NMR spectra were obtained at room temperature using a Bruker Avance 300 spectrometer. DMSO-d_6 containing 0.03% tetramethylsilane (TMS) (99.8%D, Adamas, Inc.) was used as a solvent for NMR measurements. Chemical shifts (δ) for ^1H NMR are given in parts per million (ppm) relative to residual DMSO (δ 2.50 ppm) or H_2O (δ 3.33 ppm). Chemical shifts (δ) for ^{13}C NMR are given in ppm relative to DMSO (δ 39.50 ppm). The abbreviations s, d, t, q and m signify singlet, doublet, triplet, quartet and multiplet, respectively.

High resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro spectrometer. Melting points were determined with a Micro melting point apparatus. TLC plates were visualized by exposure to ultraviolet light.

II. Optimization study of Triethylamine - Catalyzed Domino Reactions of 3a

General procedure for Optimization study of Triethylamine - Catalyzed Domino Reactions of 3a

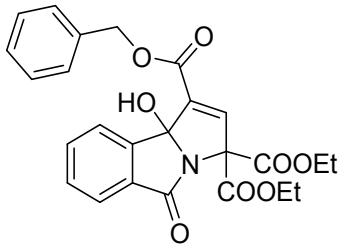
To a mixture of **1a** (122 mg, 0.4 mmol) and **2a** (128 mg, 0.8 mmol) in solvent (5 mL) catalyst was added. The resulting solution was stirred at different temperature until the TLC indicated that the total consumption of **1a**. After removal of solvent, the residue was column chromatographed on silica and eluted with PE/EA (5:1) to give **3a**.

III. Synthetic procedures and characterization data

General procedure for synthesis of Tricyclic 3-Hydroxyisoindolin-1-ones (3)

To a mixture of phthalimidomalonate derivative **1** (0.4 mmol) and electron - deficient alkyne **2** (0.8 mmol) in CH_3CN (5 mL) Et_3N (8.0 mg, 0.08 mol) was added. The resulting solution was stirred at 0 °C for 100 h. After removal of solvent, the residue was column chromatographed on silica and eluted with PE/EA (5:1) to give tricyclic 3-hydroxyisoindolin-1-ones (**3**).

1-benzyl3,3-diethyl9b-hydroxy-5-oxo-5,9b-hydroxy-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3a)



Yield: 55% (102.2 mg, 0.220 mmol);

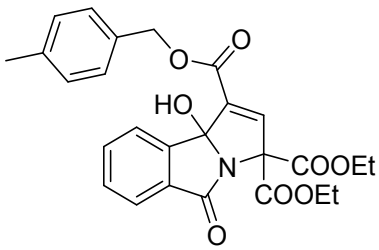
White solid (mp 119-121 °C);

^{1}H NMR (DMSO) δ 7.95 (d, *J* = 7.5 Hz, 1H), 7.73 - 7.55 (m, 3H), 7.55 - 7.30 (m, 6H), 7.16 (s, 1H), 5.41 - 5.25 (m, 2H), 4.47 - 4.01 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 14.52 (1C), 14.71 (1C), 63.01 (1C), 63.61 (1C), 67.49 (1C), 75.21 (1C), 99.93 (1C), 124.18 (1C), 126.69 (1C), 129.26 (1C), 129.37 (2C), 129.42 (2C), 131.12 (1C), 132.22 (1C), 134.34 (1C), 136.30 (1C), 137.00 (1C), 143.05 (1C), 146.33 (1C), 161.92 (1C), 165.38 (1C), 166.52 (1C), 169.52 (1C);

HRMS (ESI$^+$) *m/z* 488.1326 (488.1321 calcd for $C_{25}H_{23}NO_8Na^+$, $[M+Na]^+$).

3,3-diethyl1-(4-methylbenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3b)



Yield: 39% (74.8 mg, 0.156 mmol);

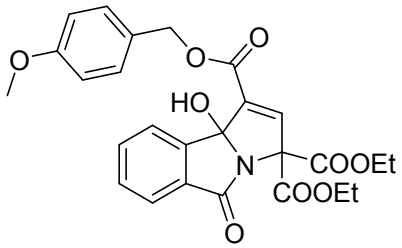
White solid (mp 137-139 °C);

^{1}H NMR (DMSO) δ 7.97 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.70 (td, *J* = 7.4, 6.0 Hz, 2H), 7.61 (td, *J* = 7.5, 1.1 Hz, 1H), 7.43 - 7.35 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.15 (s, 1H), 5.35 - 5.25 (m, 2H), 4.40 - 4.07 (m, 4H), 2.34 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 14.13 (1C), 14.32 (1C), 21.24 (1C), 62.60 (1C), 63.21 (1C), 67.04 (1C), 74.81 (1C), 99.53 (1C), 123.76 (1C), 126.31 (1C), 129.19 (2C), 129.56 (2C), 130.71 (1C), 131.84 (1C), 132.88 (1C), 133.92 (1C), 136.70 (1C), 138.30 (1C), 142.53 (1C), 145.95 (1C), 161.54 (1C), 164.98 (1C), 166.13 (1C), 169.11 (1C);

HRMS (ESI$^+$) *m/z* 502.1473 (502.1478 calcd for $C_{26}H_{25}NO_8Na^+$, $[M+Na]^+$).

3,3-diethyl1-(4-methoxybenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3c)



Yield: 24% (47.6 mg, 0.096 mmol);

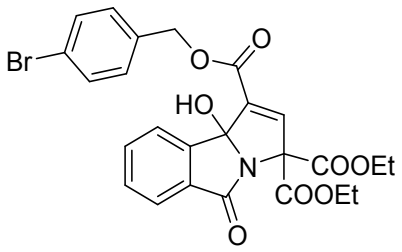
White solid (mp 46-48 ^{o}C);

^{1}H NMR (DMSO) δ 7.94 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.73 - 7.62 (m, 2H), 7.62 - 7.53 (m, 1H), 7.49 - 7.32 (m, 3H), 7.11 (s, 1H), 7.02 - 6.89 (m, 2H), 5.33 - 5.16 (m, 2H), 4.38 - 4.03 (m, 4H), 3.76 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 13.64 (1C), 13.82 (1C), 55.11 (1C), 62.11 (1C), 62.71 (1C), 66.48 (1C), 74.24 (1C), 98.99 (1C), 113.89 (2C), 123.26 (1C), 125.82 (1C),127.24 (1C), 130.22 (1C), 130.57 (2C), 131.28 (1C), 133.43 (1C), 136.20 (1C), 141.97 (1C), 145.40 (1C), 159.41 (1C), 161.03 (1C), 164.47 (1C), 165.60 (1C), 168.59 (1C);

HRMS (ESI$^+$) *m/z* 518.1436 (518.1427 calcd for $C_{26}H_{25}NO_9Na^+$, $[M+Na]^+$).

1-(4-bromobenzyl)3,3-diethyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3d)



Yield: 60% (130.6 mg, 0.240 mmol);

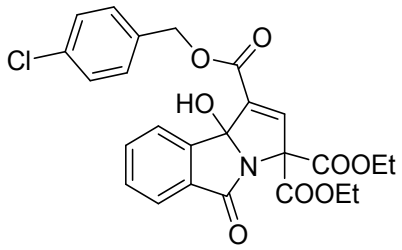
White solid (mp 154-156 °C);

^{1}H NMR (DMSO) δ 7.95 (d, *J* = 6.9 Hz, 1H), 7.75 - 7.54 (m, 5H), 7.52 - 7.38 (m, 3H), 7.19 (s, 1H), 5.30 (s, 2H), 4.40 - 4.01 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 13.64 (1C), 13.83 (1C), 62.13 (1C), 62.74 (1C), 65.81 (1C), 74.30 (1C), 99.00 (1C), 121.60 (1C), 123.30 (1C), 125.75 (1C), 130.26 (1C), 130.66 (1C), 131.27 (1C), 131.45 (1C), 133.48 (1C), 134.84 (1C), 135.92 (1C), 142.31 (1C), 145.38 (1C), 160.93 (1C), 164.45 (1C), 165.59 (1C), 168.62 (1C);

HRMS (ESI^{+}) *m/z* 566.0438 (566.0426 calcd for $C_{25}H_{22}NO_8Na^{79}Br^{+}$, $[M+Na]^{+}$).

1-(4-chlorobenzyl)3,3-diethyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3e)



Yield: 47% (94.0 mg, 0.188 mmol);

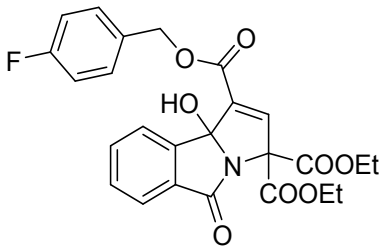
White solid (mp 149-151 °C);

^{1}H NMR (DMSO) δ 7.98 (d, *J* = 5.0 Hz, 1H), 7.74 - 7.67 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.57 - 7.48 (m, 4H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.20 (d, *J* = 1.7 Hz, 1H), 5.40 - 5.30 (m, 2H), 4.41 - 4.07 (m, 4H), 1.30 (td, *J* = 7.1, 1.2 Hz, 3H), 1.13 (td, *J* = 7.1, 1.2 Hz, 3H);

^{13}C NMR (DMSO) δ 14.13 (1C), 14.32 (1C), 62.62 (1C), 63.23 (1C), 66.27 (1C), 74.85 (1C), 99.54 (1C), 123.79 (1C), 126.26 (1C), 129.03 (2C),130.74 (1C), 130.85 (1C), 131.84 (1C), 133.56 (1C), 133.95 (1C), 134.96 (1C), 136.52 (1C), 142.78 (1C), 145.94 (1C), 161.47 (1C), 164.97 (1C), 166.12 (1C), 169.12 (1C);

HRMS (ESI^{+}) *m/z* 522.0941 (522.0932 calcd for $C_{25}H_{22}NO_8NaCl^{+}$, $[M+Na]^{+}$).

3,3-diethyl1-(4-fluorobenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3f)



Yield: 40% (77.4 mg, 0.160 mmol);

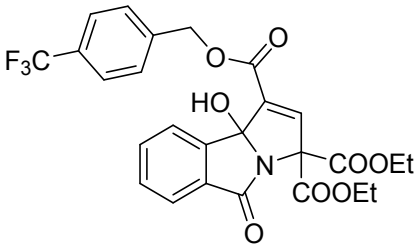
White solid (mp 131-133 °C);

^{1}H NMR (DMSO) δ 7.95 (d, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 2H), 7.64 - 7.49 (m, 3H), 7.42 (s, 1H), 7.25 (dd, *J* = 8.7, 8.6 Hz, 2H), 7.18 (s, 1H), 5.31 (s, 2H), 4.41 - 4.00 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 13.63 (1C), 13.82 (1C), 62.12 (1C), 62.73 (1C), 65.88 (1C), 74.29 (1C), 99.00 (1C), 115.51(d, $J_{C\text{-}F}$ = 21.7 Hz, 2C), 123.29 (1C), 125.77 (1C), 130.25 (1C), 130.89 (d, $J_{C\text{-}F}$ = 8.3 Hz, 2C), 131.00 (1C), 131.28 (1C), 131.68(d, $J_{C\text{-}F}$ = 3.0 Hz, 1C), 133.46 (1C), 136.01 (1C), 142.23 (1C), 145.39 (1C), 160.97(1C), 163.66(d, $J_{C\text{-}F}$ = 243.0 Hz, 1C), 164.46 (1C), 165.60 (1C), 168.61 (1C);

HRMS (ESI$^+$) *m/z* 506.1222 (506.1227 calcd for $C_{25}H_{22}NO_8FNa^+$, $[M+Na]^+$).

3,3-diethyl1-(4-(trifluoromethyl)benzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3g)



Yield: 70% (149.4 mg, 0.280 mmol);

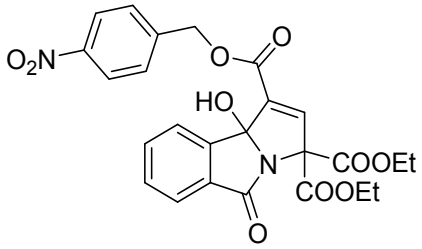
White solid (mp 179-181 °C);

^{1}H NMR (DMSO) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.76 - 7.65 (m, 4H), 7.60 (ddd, *J* = 8.4, 6.4, 1.1 Hz, 1H), 7.45 (s, 1H), 7.25 (s, 1H), 5.43 (s, 2H), 4.41 - 4.02 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 13.63 (1C), 13.82 (1C),62.14 (1C), 62.74 (1C), 65.66 (1C), 74.35 (1C),99.02 (1C), 123.31 (1C), 125.36 (2C), 125.42 (1C), 125.72 (1C), 128.80 (2C), 130.27 (1C), 131.29 (1C), 133.49 (1C), 135.82 (1C), 140.21 (1C), 142.48 (1C), 145.39 (1C), 160.90 (1C), 164.44 (1C), 165.60 (1C), 168.63 (1C);

HRMS (ESI$^+$) *m/z* 556.1201 (556.1195 calcd for $C_{26}H_{22}NO_8NaF_3^+$, $[M+Na]^+$).

3,3-diethyl1-(4-nitrobenzyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3h)



Yield: 45% (91.9 mg, 0.180 mmol);

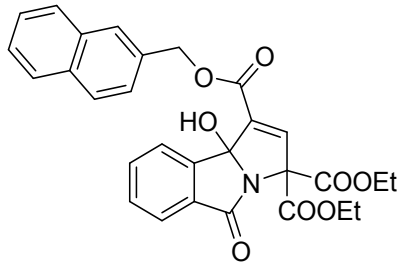
White solid (mp 169-171 °C);

^{1}H NMR (DMSO) δ 8.27 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 6.9 Hz, 2H), 7.60 (t, *J* = 6.6 Hz, 1H), 7.46 (s, 1H), 7.28 (s, 1H), 5.48 (s, 2H), 4.37 - 4.07 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 13.65 (1C), 13.83 (1C), 62.16 (1C), 62.76 (1C), 65.33 (1C), 74.37 (1C), 99.02 (1C), 123.33 (1C), 123.62 (2C), 125.72 (1C), 129.01 (1C), 130.29 (1C), 131.26 (1C), 133.56 (1C), 135.72 (1C), 142.62 (1C), 143.11 (1C), 145.37 (1C), 147.25 (1C), 160.84 (1C), 164.44 (1C), 165.59 (1C), 168.63 (1C);

HRMS (ESI$^+$) *m/z* 533.1180 (533.1172 calcd for $C_{25}H_{22}N_2O_{10}Na^+$, $[M+Na]^+$).

3,3-diethyl1-(naphthalen-2-ylmethyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3i)



Yield: 54% (111.4 mg, 0.216 mmol);

White solid (mp 64-66 °C);

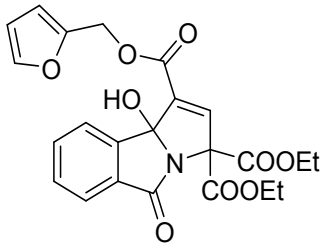
^{1}H NMR (DMSO) δ 8.33 - 7.88 (m, 6H), 7.75 - 7.54 (m, 5H), 7.41 (s, 1H), 7.22 (s, 1H), 5.59 - 5.47 (m, 2H), 4.73 - 3.78 (m, 4H), 1.30 (t, *J* = 4.5 Hz, 3H), 1.11 (t, *J* = 4.6 Hz, 3H);

^{13}C NMR (DMSO) δ 14.12 (1C), 14.32 (1C), 62.61 (1C), 63.21 (1C), 67.27 (1C), 74.85 (1C), 99.56 (1C), 123.78 (1C), 126.30 (1C), 126.76 (1C), 126.93 (2C), 128.04 (1C), 128.10 (1C), 128.34 (1C), 128.70 (1C), 130.72 (1C), 131.85 (1C), 133.18 (1C), 133.21 (1C), 133.45 (1C), 133.91 (1C), 136.64 (1C), 142.72 (1C), 145.95 (1C), 161.59 (1C), 164.98 (1C),

166.13 (1C), 169.12 (1C);

HRMS (ESI$^+$) *m/z* 538.1488 (538.1478 calcd for $C_{29}H_{25}NO_8Na^+$, $[M+Na]^+$).

3,3-diethyl1-(furan-2-ylmethyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3j)



Yield: 55% (100.2 mg, 0.220 mmol);

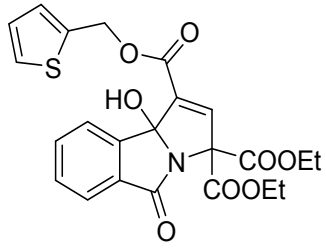
White solid (mp 136-138 ^oC);

^1H NMR (DMSO) δ 7.96 - 7.88 (m, 1H), 7.76 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.73 - 7.64 (m, 2H), 7.59 (ddd, *J* = 8.3, 6.5, 1.2 Hz, 1H), 7.41 (s, 1H), 7.13 (s, 1H), 6.65 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.51 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.41-5.20 (m, 2H), 4.37 - 4.03 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz);

^{13}C NMR (DMSO) δ 13.63 (1C), 13.82 (1C), 58.41 (1C), 62.13 (1C), 62.74 (1C), 74.27 (1C), 98.97 (1C), 110.85 (1C), 111.70 (1C), 123.29 (1C), 125.70 (1C), 130.24 (1C), 131.27 (1C), 133.46 (1C), 135.85 (1C), 142.32 (1C), 144.09 (1C), 145.34 (1C), 148.60 (1C), 160.72 (1C), 164.40 (1C), 165.55 (1C), 168.59 (1C);

HRMS (ESI$^+$) *m/z* 478.1121 (396.1059 calcd for $C_{23}H_{21}NO_9Na^+$, $[M+Na]^+$).

3,3-diethyl1-(thiophen-2-ylmethyl)9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3k)



Yield: 39% (73.6 mg, 0.156 mmol);

White solid (mp 146-148 ^oC);

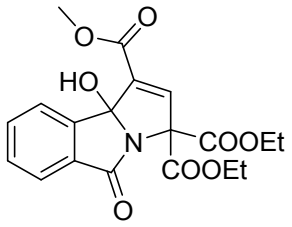
^1H NMR (DMSO) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.74 - 7.65 (m, 2H), 7.65 - 7.53 (m, 2H), 7.40 (s, 1H), 7.29 (d, *J* = 3.5, 1H), 7.12 (s, 1H), 7.06 (t, *J* = 4.4 Hz, 1H), 5.60-5.40 (m, 2H), 4.37 - 4.03 (m, 4H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* =

7.1 Hz);

^{13}C NMR (DMSO) δ 13.64 (1C), 13.82 (1C), 60.86 (1C), 62.13 (1C), 62.74 (1C), 74.27 (1C), 98.96 (1C), 123.29 (1C), 125.76 (1C), 126.98 (1C), 128.05 (1C), 129.44 (1C), 130.25 (1C), 131.26 (1C), 133.48 (1C), 135.91 (1C), 136.96 (1C), 142.26 (1C), 145.35 (1C), 160.85 (1C), 164.42 (1C), 165.55 (1C), 168.59 (1C);

HRMS (ESI$^+$) *m/z* 494.0878 (494.0886 calcd for $C_{23}H_{21}NO_8NaS^+$, $[M+Na]^+$).

3,3-diethyl1-methyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3l)



Yield: 53% (82.5 mg, 0.212 mmol);

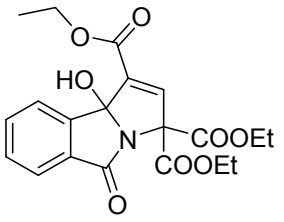
White solid (mp 153-155 ^{o}C);

^{1}H NMR (DMSO) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.79 - 7.66 (m, 2H), 7.60 (t, *J* = 7.4, 1H), 7.39 (s, 1H), 7.13 (s, 1H), 4.40 - 4.02 (m, 4H), 3.82 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 13.63 (1C), 13.83 (1C), 52.23 (1C), 62.12 (1C), 62.70 (1C), 74.29 (1C), 99.00 (1C), 123.28 (1C), 125.72 (1C), 130.23 (1C), 131.27 (1C), 133.59 (1C), 135.95 (1C), 141.82 (1C), 145.48 (1C), 161.61 (1C), 164.48 (1C), 165.60 (1C), 168.65 (1C);

HRMS (ESI$^+$) *m/z* 412.1001 (412.1008 calcd for $C_{19}H_{19}NO_8Na^+$, $[M+Na]^+$).

Triethyl 9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3m)



Yield: 50% (80.7 mg, 0.200 mmol);

White solid (mp 169-171 ^{o}C);

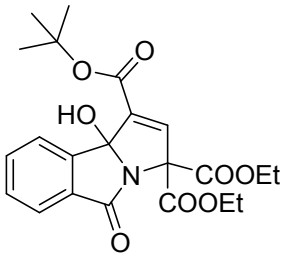
^{1}H NMR (DMSO) δ 8.02 (d, *J* = 7.0 Hz, 1H), 7.74 (ddd, *J* = 7.6, 7.4, 1.4 Hz, 1H), 7.69 (d, 7.4Hz, 1H), 7.60 (dd, 7.5, 1.1 Hz, 1H), 7.38 (s, 1H), 7.10 (s, 1H), 4.40 - 4.01 (m, 6H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J*

= 7.1Hz, 3H);

^{13}C NMR (DMSO) δ 14013 (1C), 14.32 (1C), 14.46 (1C), 61.69 (1C), 62.62 (1C), 63.22 (1C), 74.73 (1C), 99.50 (1C), 123.76 (1C), 126.28 (1C), 130.73 (1C), 131.79 (1C), 134.05 (1C), 136.79 (1C), 142.14 (1C), 146.00 (1C), 161.67 (1C), 165.05 (1C), 166.15 (1C), 169.15 (1C);

HRMS (ESI$^+$) *m/z* 426.1169 (426.1165 calcd for $C_{20}H_{21}NO_8Na^+$, $[M+Na]^+$).

1-(tert-butyl)3,3-diethyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3n)



Yield: 16% (27.6 mg, 0.064 mmol);

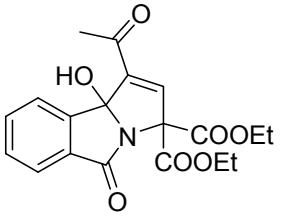
White solid (mp 164-166 ^{o}C);

^{1}H NMR (DMSO) δ 8.03 (d, *J* = 7.6 Hz, 1H), 7.75 (dd, *J* = 7.4, 7.5 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.34 (s, 1H), 6.97 (s, 1H), 4.41 - 4.03 (m, 4H), 1.52 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 13.65 (1C), 13.82 (1C), 27.70 (3C), 62.09 (1C), 62.73 (1C), 74.04 (1C), 82.18 (1C), 98.93 (1C), 123.25 (1C), 125.77 (1C), 130.15 (1C), 131.30 (1C), 133.49 (1C), 137.65 (1C), 140.92 (1C), 145.61 (1C), 160.47 (1C), 164.69 (1C), 165.76 (1C), 168.59 (1C);

HRMS (ESI$^+$) *m/z* 454.1465 (454.1478 calcd for $C_{22}H_{25}NO_8Na^+$, $[M+Na]^+$).

Diethyl1-acetyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-3,3-dicarboxylate (3p)



Yield: 87% (129.9 mg, 0.348 mmol);

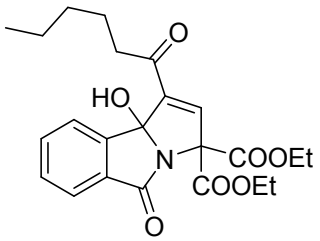
White solid (mp 153-155 °C);

^{1}H NMR (DMSO) δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.77 - 7.62 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (s, 1H), 7.14 (s, 1H), 4.44 - 4.03 (m, 4H), 2.42 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 14.55 (1C), 14.75 (1C), 28.67 (1C), 62.95 (1C), 63.53 (1C), 75.30 (1C), 100.52 (1C), 123.99 (1C), 127.21 (1C), 130.87 (1C), 132.32 (1C), 134.29 (1C), 143.59 (1C), 143.78 (1C), 146.80 (1C), 165.66 (1C), 166.73 (1C), 169.51 (1C), 194.75 (1C);

HRMS (ESI$^+$) *m/z* 396.1049 (396.1059 calcd for $C_{19}H_{19}NO_7Na^+$, $[M+Na]^+$).

Diethyl1-hexanoyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-3,3-dicarboxylate (3q)



Yield: 48% (82.5 mg, 0.192 mmol);

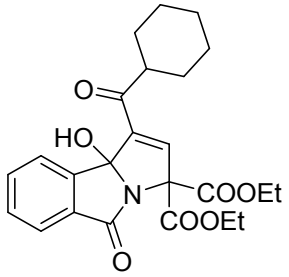
White solid (mp 157-159 °C);

^{1}H NMR (DMSO) δ 8.05 (d, *J* = 7.7 Hz, 1H), 7.77 - 7.63 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (s, 1H), 7.15 (s, 1H), 4.41 - 4.22 (m, 2H), 4.20 - 4.06 (m, 2H), 2.80 (td, *J* = 7.3, 2.3 Hz, 2H), 1.59 - 1.46 (m, 2H), 1.35 - 1.19 (m, 7H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (DMSO) δ 13.65 (1C), 13.74 (1C), 13.87 (1C), 21.84 (1C), 23.39 (1C), 30.53 (1C), 62.02 (1C), 62.58 (1C), 74.38 (1C), 99.76 (1C), 123.08 (1C), 126.30 (1C), 129.96 (1C), 131.37 (1C), 133.39 (1C), 141.85 (1C), 142.14 (1C), 145.90 (1C), 164.78 (1C), 165.84 (1C), 168.61 (1C), 196.48 (1C);

HRMS (ESI$^+$) *m/z* 452.1689 (452.1685 calcd for $C_{23}H_{27}NO_7Na^+$, $[M+Na]^+$).

Diethyl1-(cyclohexanecarbonyl)-9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-3,3-dicarboxylate (3r)



Yield: 53% (93.6 mg, 0.212 mmol);

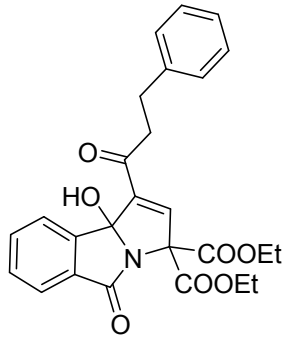
White solid (mp 171-173 °C);

^{1}H NMR (DMSO) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.76 - 7.62 (m, 2H), 7.56 (t, *J* = 7.4Hz, 1H), 7.48 (s, 1H), 7.15 (s, 1H), 4.42 - 4.19 (m, 2H), 4.19 - 4.06 (m, 2H), 3.26 - 3.06 (m, 1H), 1.84 - 1.67 (m, 2H), 1.65 - 1.58 (m, 2H), 1.42 - 1.22 (m, 6H), 1.19 - 0.92 (m, 6H);

^{13}C NMR (DMSO) δ 13.65 (1C), 13.88 (1C), 24.74 (1C), 24.82 (1C), 25.42 (1C), 28.51 (1C), 29.13 (1C), 46.22 (1C), 61.99 (1C), 62.55 (1C), 74.35 (1C), 99.86 (1C), 123.09 (1C), 126.22 (1C), 129.95 (1C), 131.39 (1C),133.40 (1C), 140.91 (1C), 141.59 (1C), 145.91 (1C), 164.81 (1C), 165.89 (1C), 168.56 (1C), 199.57 (1C);

HRMS (ESI$^+$) *m/z* 464.1677 (464.1685 calcd for $C_{24}H_{27}NO_7Na^+$, $[M+Na]^+$).

Diethyl9b-hydroxy-5-oxo-1-(3-phenylpropanoyl)-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-3,3-dicarboxylate (3s)



Yield: 62% (114.9 mg, 0.248 mmol);

White solid (mp 163-165 °C);

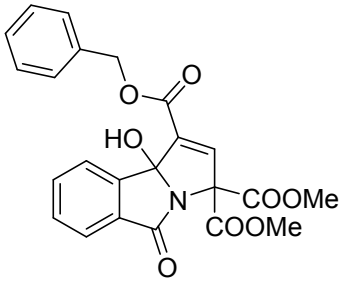
^{1}H NMR (DMSO) δ 8.04 (d, *J* = 7.6 Hz, 1H), 7.77 - 7.62 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.51 (s, 1H), 7.29 - 7.20 (m, 4H), 7.20 - 7.03 (m, 2H), 4.37 - 4.05 (m, 4H), 3.24 - 3.05 (m, 2H), 2.85 (t, *J* = 7.6 Hz), 1.27 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.1 Hz);

^{13}C NMR (DMSO) δ 13.67 (1C), 13.86 (1C), 29.21 (1C), 40.92 (1C), 62.01 (1C), 62.58 (1C), 74.44 (1C), 99.79 (1C), 123.08 (1C), 125.84 (1C), 126.31 (1C), 128.14 (2C), 128.36 (2C), 129.96 (1C), 131.38 (1C), 133.39 (1C), 140.70 (1C),

141.96 (1C), 142.17 (1C), 145.85 (1C), 164.75 (1C), 165.81 (1C), 168.60 (1C), 195.37 (1C);

HRMS (ESI$^+$) *m/z* 486.1533 (486.1529 calcd for $C_{26}H_{25}NO_7Na^+$, $[M+Na]^+$).

1-benzyl3,3-dimethyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3u)



Yield: 40% (70.0 mg, 0.160 mmol);

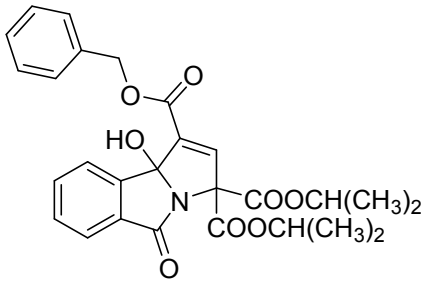
White solid (mp 96-98 ^oC);

1H NMR (DMSO) δ 7.95 (d, *J* = 7.5 Hz, 2H), 7.75 - 7.55 (m, 3H), 7.49 - 7.34 (m, 5H), 7.22 (s, 1H), 5.2 - 5.43 (m, 2H), 3.80 (s, 3H), 3.64 (s, 1H);

^{13}C NMR (DMSO) δ 53.29 (1C), 53.51 (1C), 66.62 (1C), 74.08 (1C), 99.02 (1C), 123.42 (1C), 125.82 (1C), 128.38 (1C), 128.53 (2C), 128.55 (2C), 130.28 (1C), 131.14 (1C), 133.54 (1C), 135.36 (1C), 136.11 (1C), 142.12 (1C), 145.37 (1C), 160.96 (2C), 165.00 (1C), 166.18 (1C).

HRMS (ESI$^+$) *m/z* 460.1003 (460.1008 calcd for $C_{23}H_{19}NO_8Na^+$, $[M+Na]^+$).

1-benzyl3,3-dipropyl9b-hydroxy-5-oxo-5,9b-dihydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (3v)



Yield: 48% (94.8 mg, 0.192 mmol);

White solid (mp 164-166 ^oC);

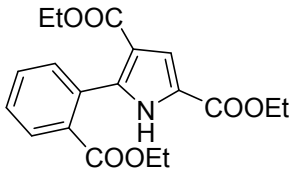
^1H NMR (DMSO) δ 7.93 (d, *J* = 7.4 Hz, 1H), 7.72 - 7.54 (m, 3H), 7.52 - 7.32 (m, 6H), 7.10 (s, 1H), 5.33 (s, 2H), 5.10 - 4.99 (m, 1H), 4.99 - 4.88 (m, 1H), 1.27 (d, *J* = 6.3 Hz, 6H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.11 (d, *J* = 6.2 Hz);

^{13}C NMR (DMSO) δ 21.15 (1C), 21.17 (1C), 21.19 (1C), 21.35 (1C), 66.53 (1C), 69.94 (1C), 71.01 (1C), 74.47 (1C), 98.98 (1C), 123.22 (1C), 125.74 (1C), 128.34 (1C), 128.38 (1C), 128.42 (1C), 128.51 (2C), 130.18 (1C), 131.39 (1C),

133.36 (1C), 135.44 (1C), 135.99 (1C), 142.35 (1C), 145.40 (1C), 161.04 (1C), 164.01 (1C), 165.09 (1C), 168.55 (1C)

HRMS (ESI$^+$) *m/z* 516.1650 (516.1634calcd for $C_{27}H_{27}NO_8Na^+$, $[M+Na]^+$).

Diethyl5-(2-(ethoxycarbonyl)phenyl)-1H-pyrrole-2,4-dicarboxylate (4)



To a solution of **3m** (81.0mg, 0.2mmol) in EtOH (5.0mL), NaOH (48.0mg, 1.2mmol) was added at room temperature. After stirring for 12h, the reaction mixture was concentrated and purified by column chromatography on silica gel (50% EA/PE) to afford **4**.

Yield: 89% (127.9 mg, 0.356 mmol);

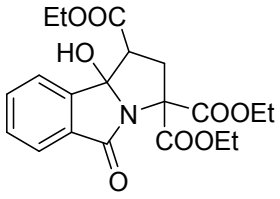
White solid (mp 103-105 ^oC);

^1H NMR (DMSO) δ 12.61 (s, 1H), 7.93 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.68 - 7.51 (m, 2H), 7.41 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.14 (s, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 6H);

^{13}C NMR (DMSO) δ 13.58 (1C), 13.75 (1C), 14.24 (1C), 59.06 (1C), 59.92 (1C), 60.27 (1C), 113.75 (1C), 116.30 (1C), 121.77 (1C), 128.72 (1C), 129.31 (1C), 131.19 (1C), 131.35 (1C), 131.91 (1C), 132.03 (1C), 140.33 (1C), 159.99 (1C), 163.01 (1C), 165.97 (1C);

HRMS (ESI$^+$) *m/z* 382.0915 (382.1267 calcd for $C_{19}H_{21}NO_6Na^+$, $[M+Na]^+$).

Triethyl9b-hydroxy-5-oxo-1,2,5,9b-tetrahydro-3*H*-pyrrolo[2,1-*a*]isoindole-1,3,3-tricarboxylate (5)



To a solution of **3m** (81.0 mg, 0.2 mmol) in MeOH (5.0 mL), Pd/C (8.1 mg) was added. The mixture was stirred at room temperature under H_2 atmosphere until TLC analysis showed a complete consumption of the starting material. The reaction mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (20% EA/PE) to afford **5**.

Yield: 74% (120.0 mg, 0.296 mmol);

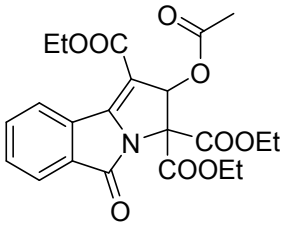
White solid (mp 145-147 °C);

^{1}H NMR (DMSO) δ 7.86 - 7.68 (m, 2H), 7.68 - 7.51 (m, 2H), 7.16 (d, *J* = 1.7 Hz, 1H), 4.37 - 4.17 (m, 4H), 4.17 - 4.02 (m, 2H), 3.37 (dd, *J* = 13.4, 12.2 Hz, 2H), 3.13 (ddd, *J* = 12.2, 7.1, 1.8 Hz, 1H), 2.84 (dd, *J* = 13.4, 7.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (DMSO) δ 14.53 (1C), 14.77 (1C), 14.94 (1C), 50.64 (1C), 61.59(1C), 62.44 (1C), 62.80 (1C), 67.71 (1C), 96.38 (1C), 115.00 (1C), 123.80 (1C), 125.47 (1C), 130.96 (1C), 132.17 (1C), 133.96 (1C), 146.57 (1C), 167.33 (1C), 168.74 (1C), 168.89 (1C), 169.20 (1C);

HRMS (ESI$^+$) *m/z* 428.1309 (428.1321 calcd for $C_{20}H_{23}NO_8Na^+$, $[M+Na]^+$).

Tetraethyl5-oxo-2,5-dihydro-3H-pyrrolo[2,1-a]isoindole-1,2,3,3-tetracarboxylate (6)



To a solution of **3m** (81.0 mg, 0.2 mmol) in CH_2Cl_2 (10.0 mL), Et_3N (67.1 mg, 0.6 mmol), Acetyl chloride (23.6 mg, 0.3 mmol) were added at room temperature. The mixture was stirred at room temperature until TLC analysis showed a complete consumption of the starting material. The reaction mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10% EA/PE) to afford **6**.

Yield: 91% (167.2 mg, 0.364 mmol);

White solid (mp 113-117 °C);

^{1}H NMR (DMSO) δ 8.59 (d, *J* = 7.38 Hz, 1H), 7.99 - 7.85 (m, 3H), 7.15 (s, 1H), 4.59 - 3.97 (m, 8H), 2.06 (s, 3H), 1.51 - 0.87 (m, 12H);

^{13}C NMR (DMSO) δ 13.64 (1C), 13.79 (1C), 13.94 (1C), 20.22 (1C), 60.74 (1C), 62.88 (1C), 63.02 (1C), 72.31 (1C), 79.98 (1C), 104.80 (1C), 124.17 (1C), 127.21 (1C), 128.28 (1C), 133.55 (1C), 133.81 (1C), 134.33 (1C), 151.26 (1C), 160.91 (1C), 162.05 (1C), 164.10 (1C), 167.86 (1C);

HRMS (ESI$^+$) *m/z* 468.1262 (468.1271 calcd for $C_{22}H_{23}NO_9Na^+$, $[M+Na]^+$).

Gram-scale preparation of Triethyl 9b-hydroxy-5-oxo-5,9b-dihydro-3H-pyrrolo[2,1-a]isoindole-1,3,3-tricarboxylate (3m)

To a mixture of phthalimidomalonate derivative **1** (1.22 g, 4 mmol) and electron - deficient alkyne **2a** (0.78 g, 8

mmol) in CH_3CN (50 mL) Et_3N (0.08 g, 0.8 mol) was added. The resulting solution was stirred at 0 °C for 100 h. After removal of solvent, the residue was column chromatographed on silica and eluted with PE/EA (5:1) to afford **3m**. Yield: 47% (0.76 g, 1.88 mmol).

IV.X-Ray crystallographic analysis of 3m

Crystallographic data for **3m** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1493448. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

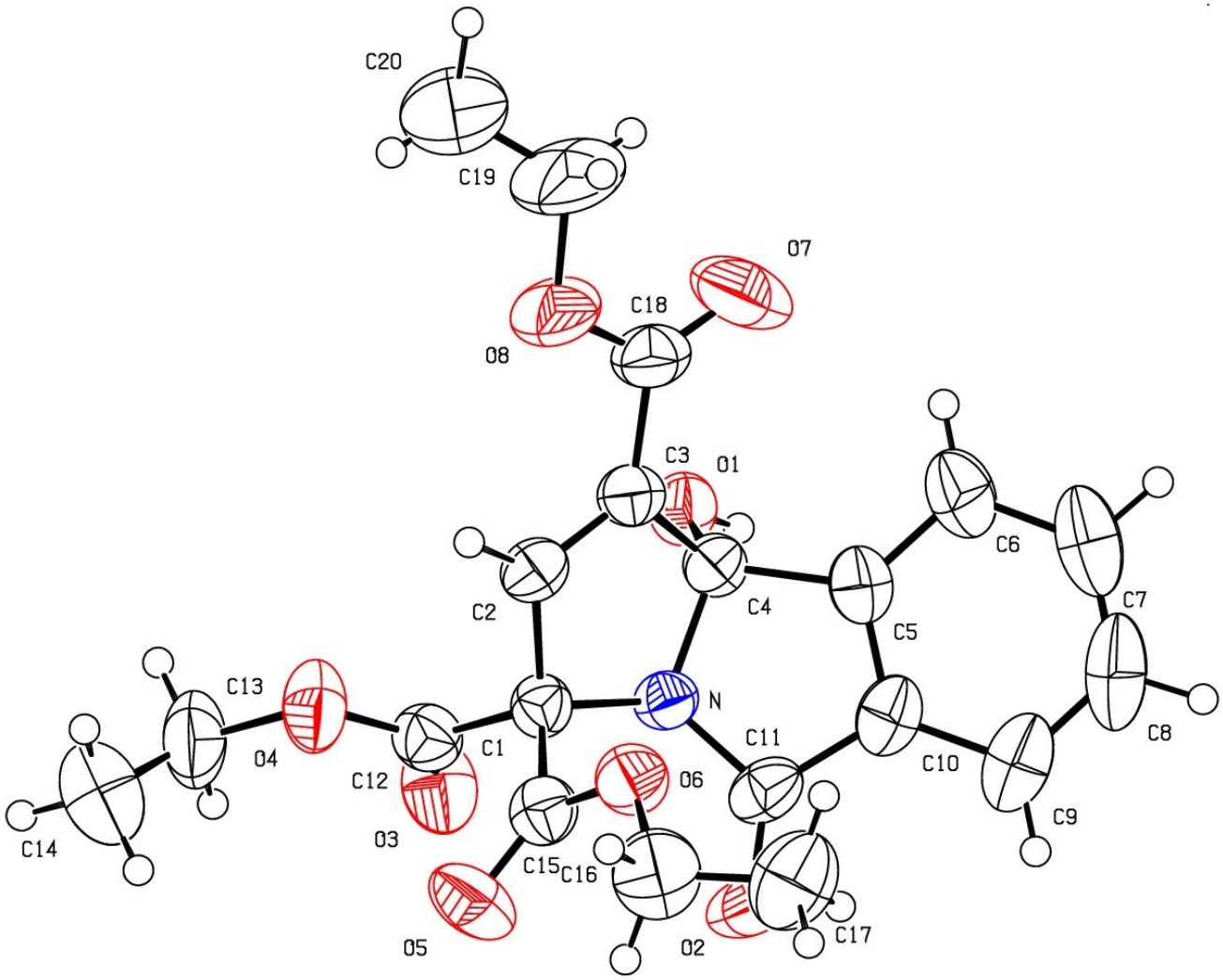
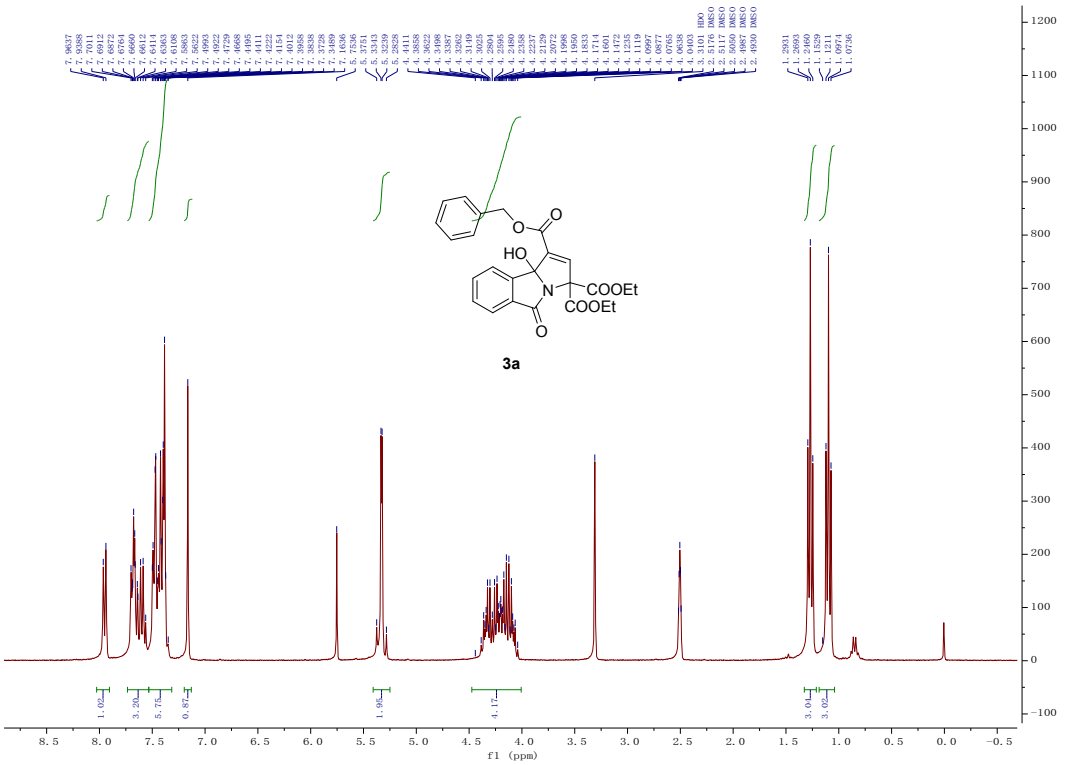


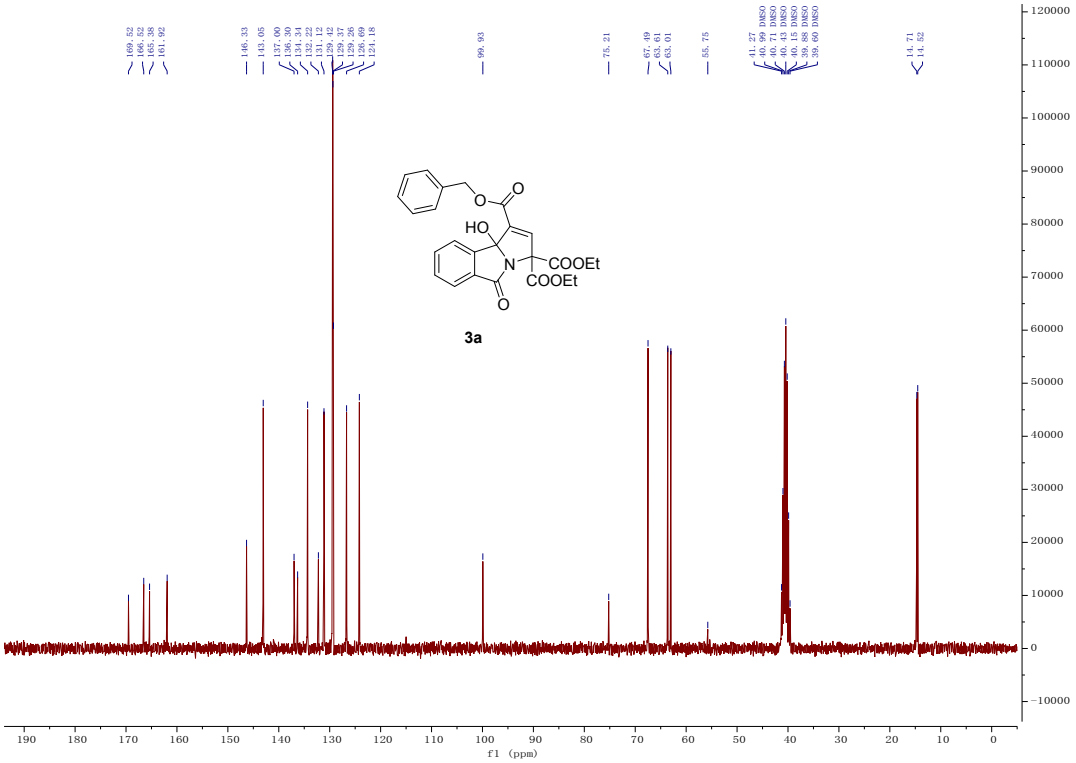
Table S1 Crystal data and structure refinement for 3

Chemical formula	$C_{20}H_{21}NO_8$
M_r	403.38
Crystal system, space group	Monoclinic, $P2_1/C$
Temperature (K)	293
a, b, c (Å)	8.1010 (16), 19.041 (4), 13.693 (3)
β (°)	107.19 (3)
V (Å^3)	2017.8 (7)
Z	4

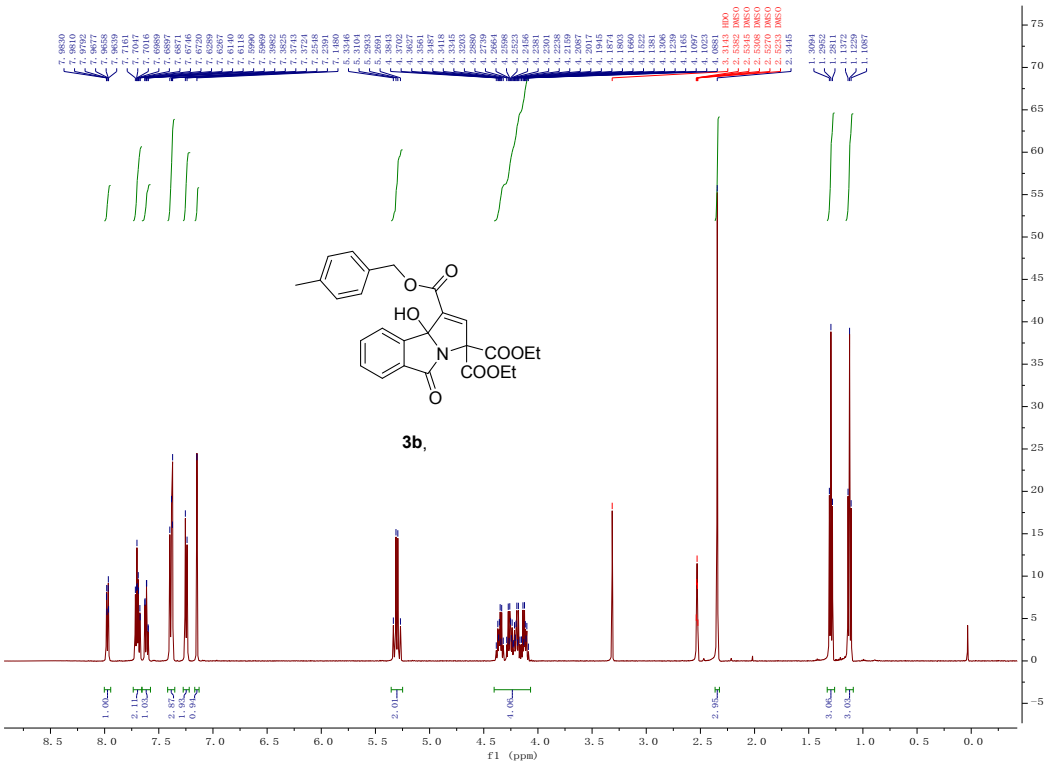
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.10
Crystal size (mm)	0.30 × 0.20 × 0.10
Data collection	
Diffractometer	Nonius CAD4 diffractometer
Absorption correction	ψ scan
T_{min}, T_{max}	0.970, 0.990
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	7831, 3714, 1841
R_{int}	0.135
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.604
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.068, 0.181, 1.01
No. of reflections	3714
No. of parameters	262
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.35, −0.35

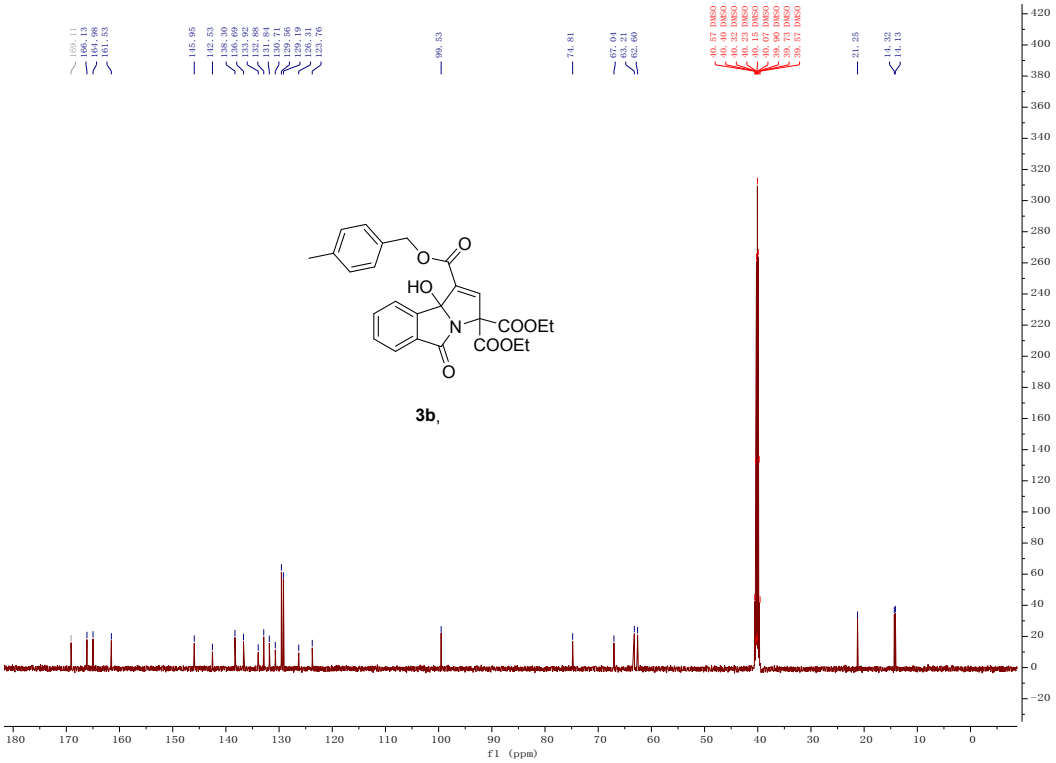
^{1}H NMR (300 MHz) and^{13}C NMR (300 MHz) spectra of **3a** (DMSO)



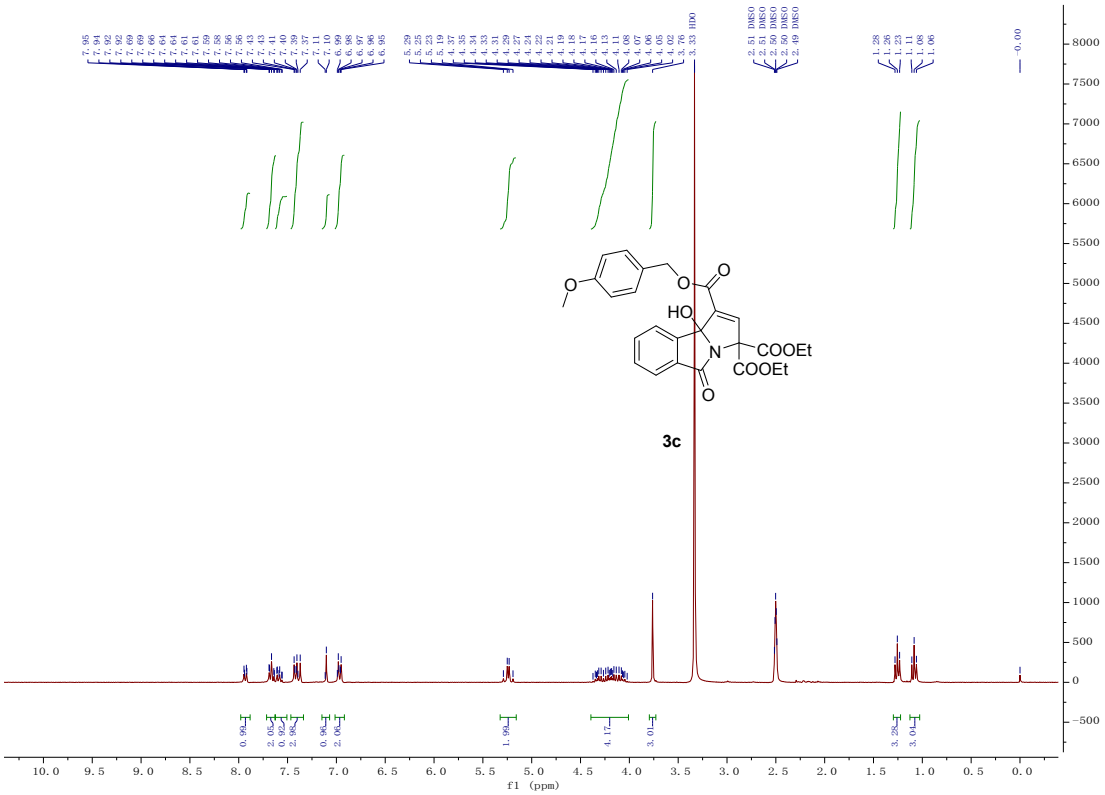


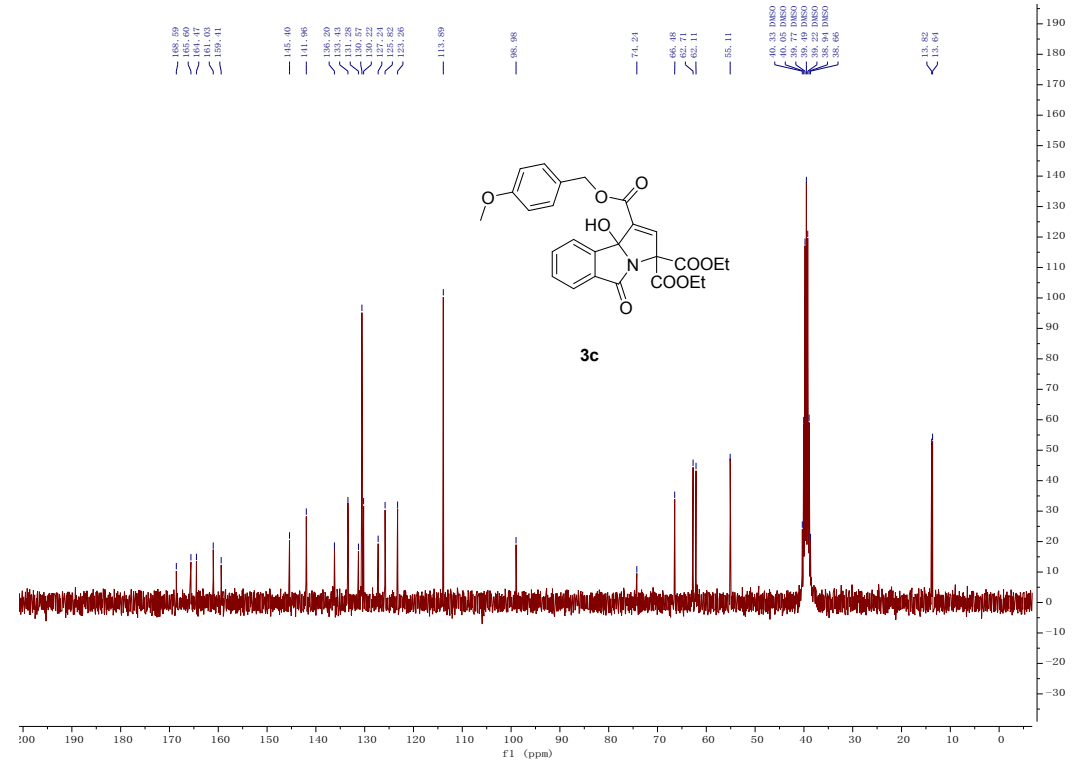
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3b** (DMSO)



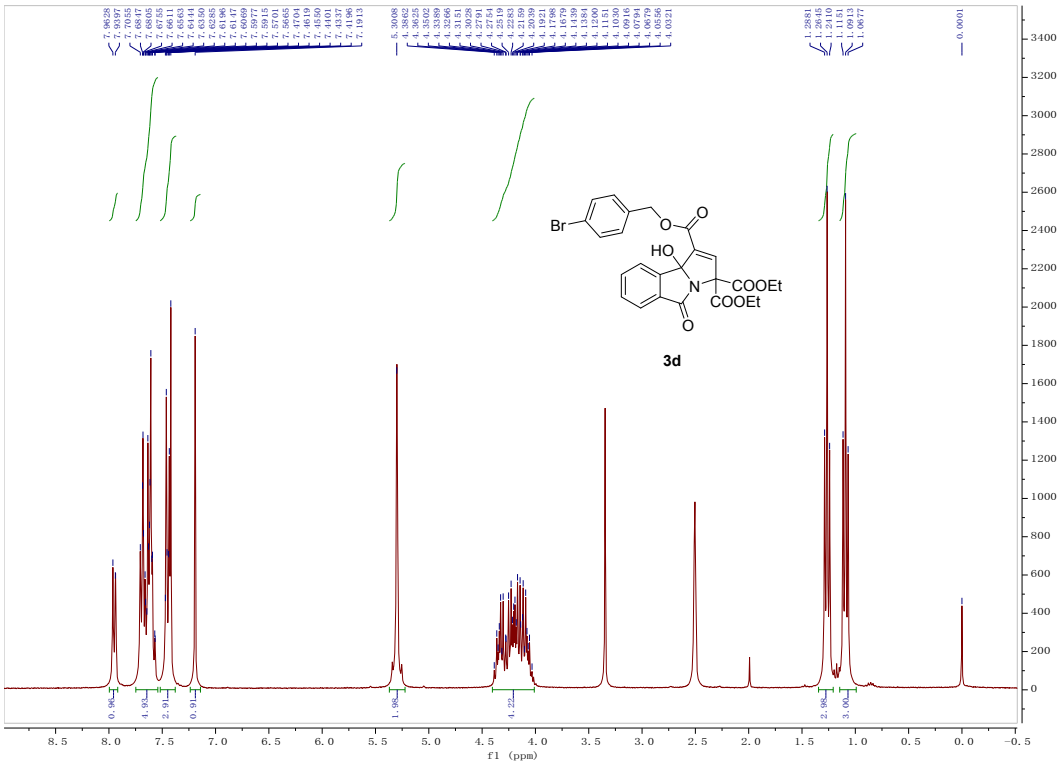


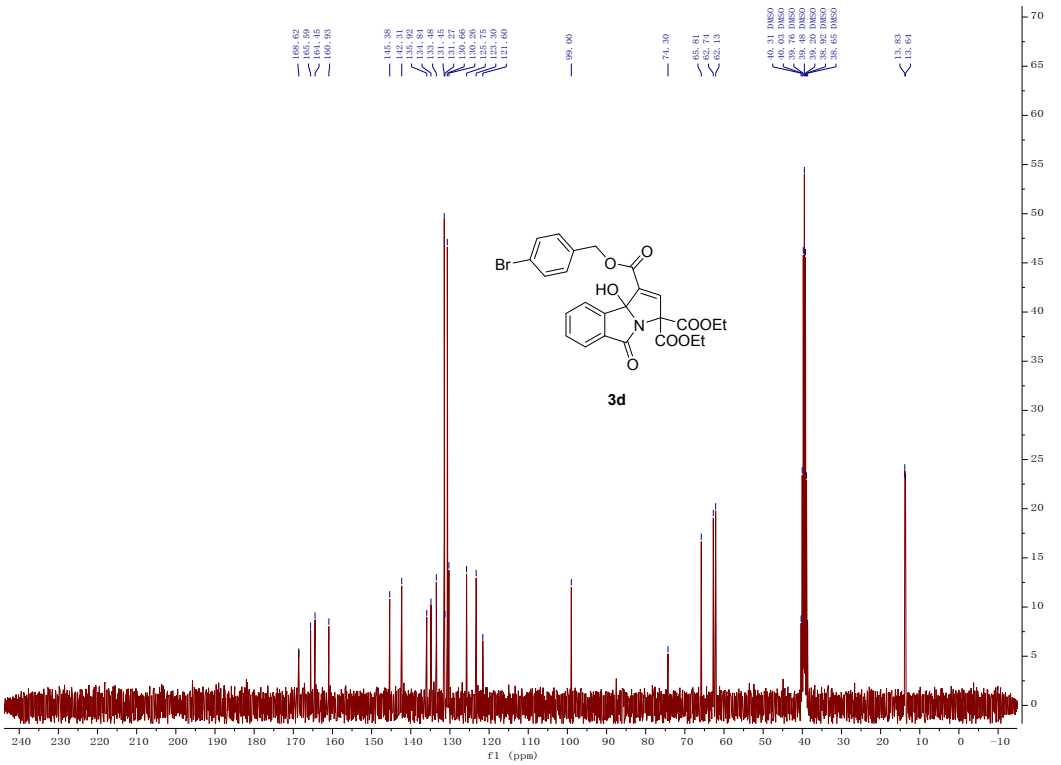
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3c** (DMSO)



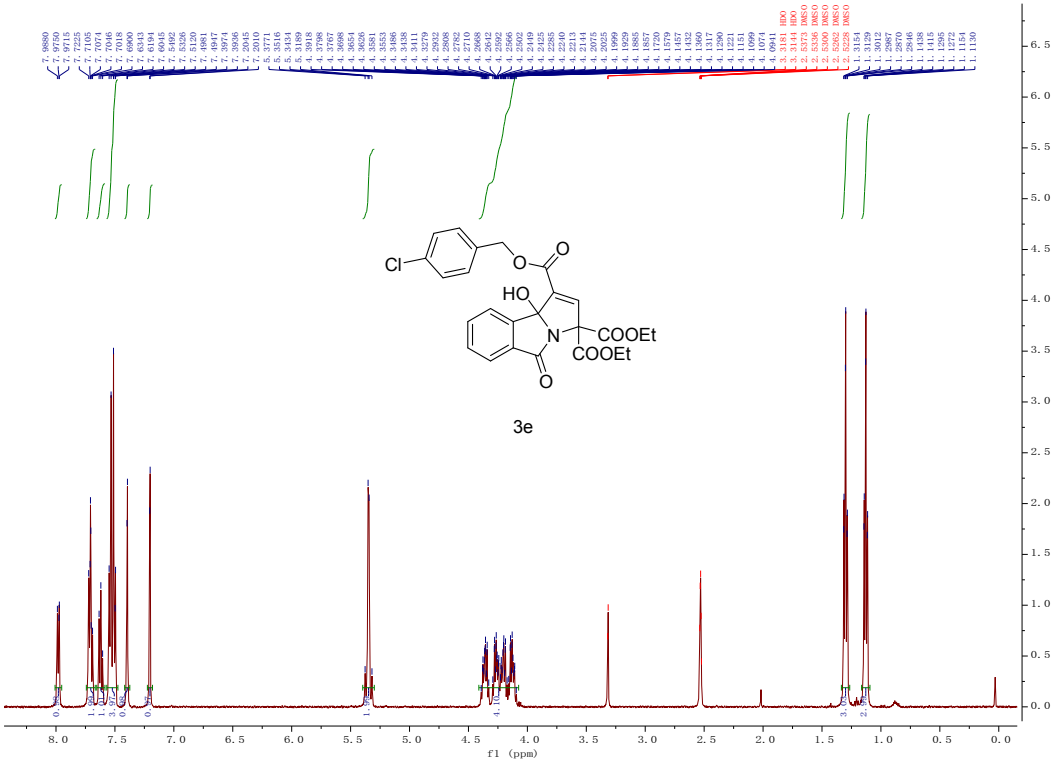


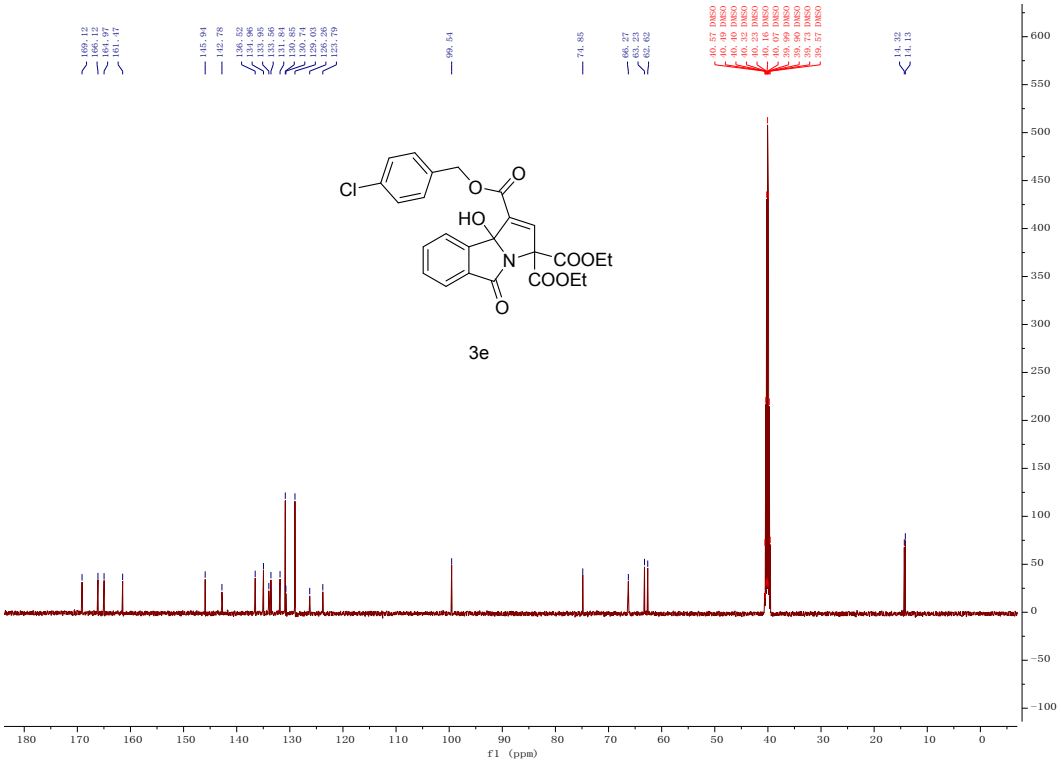
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3d** (DMSO)



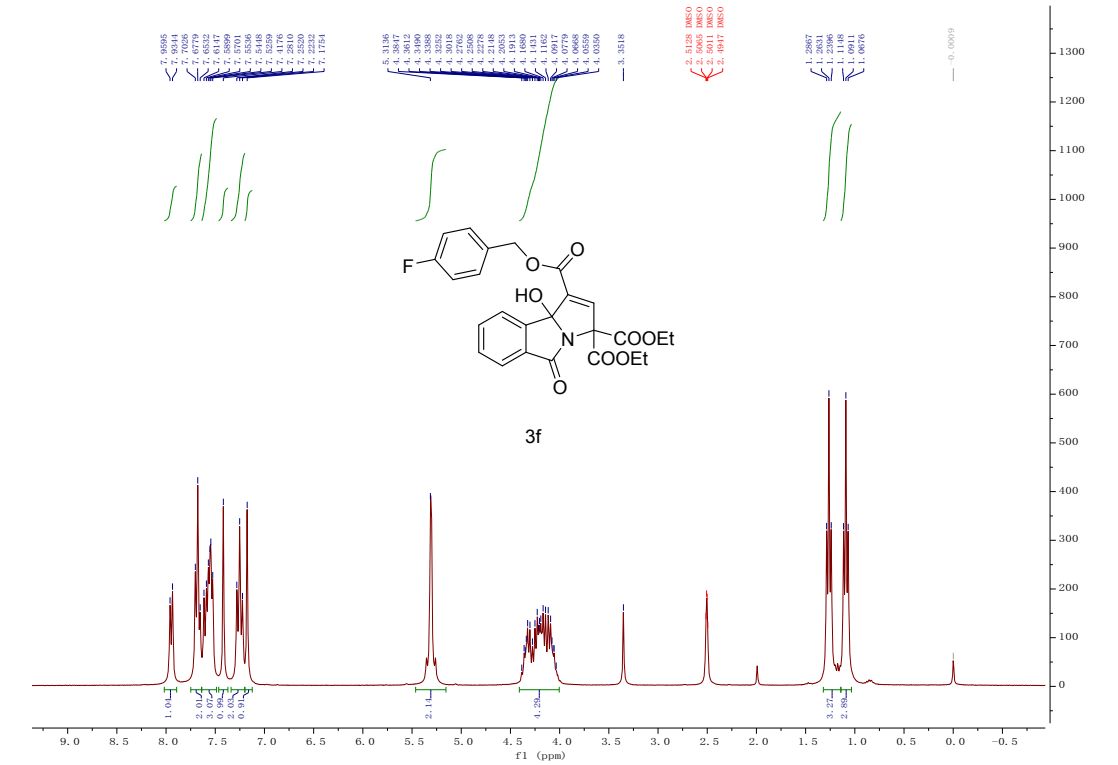


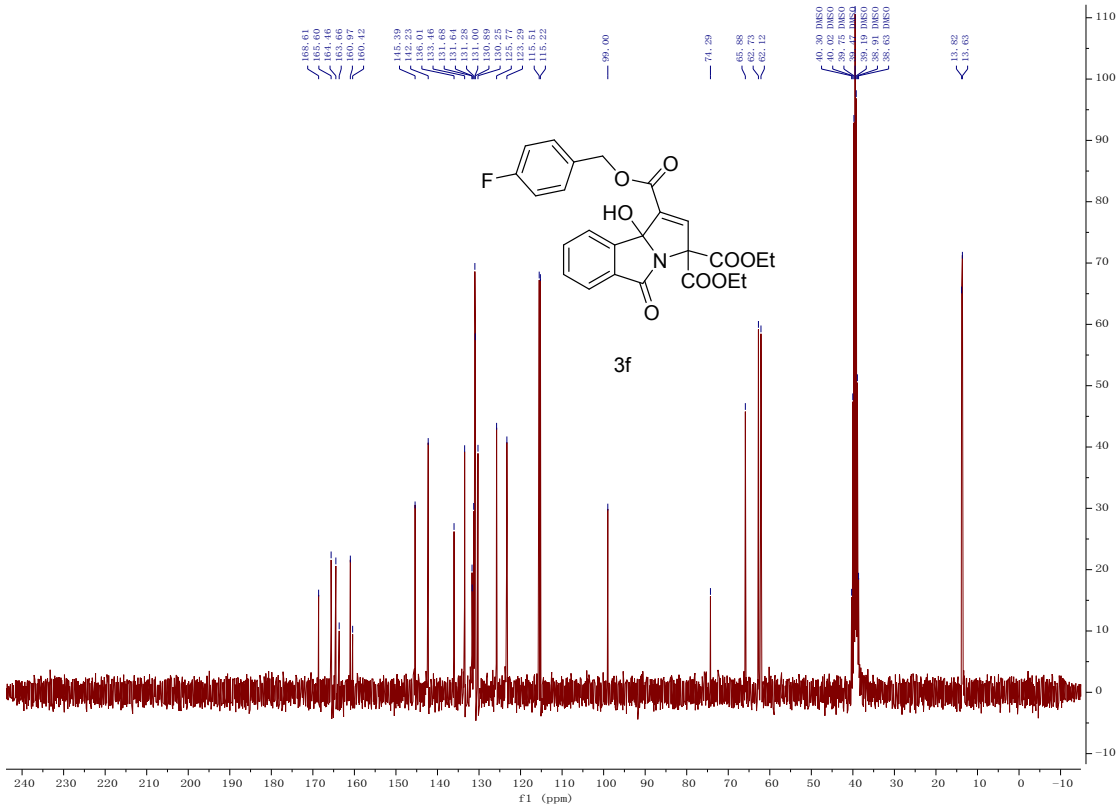
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3e** (DMSO)



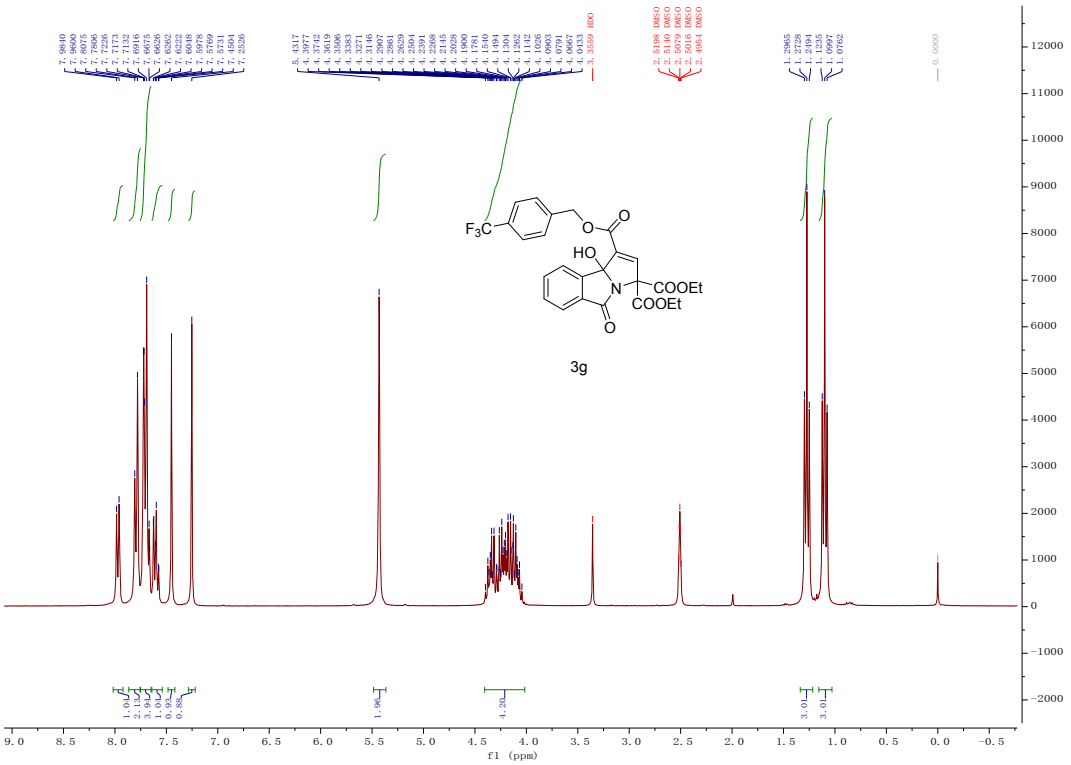


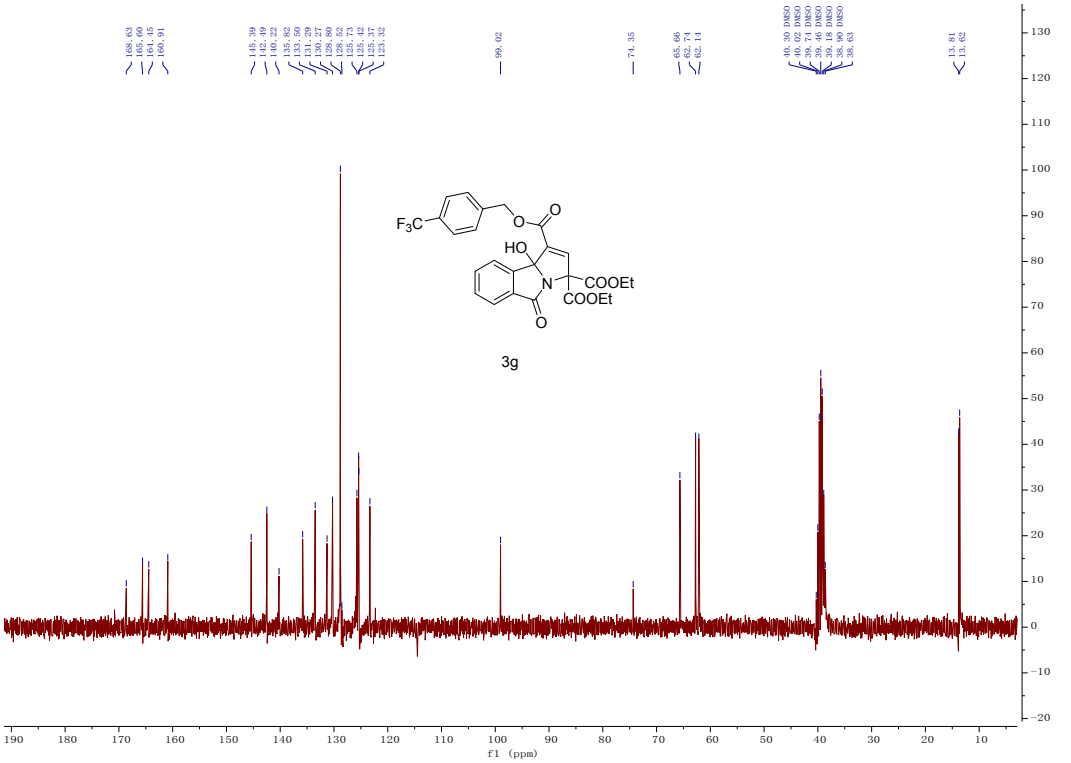
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3f** (DMSO)



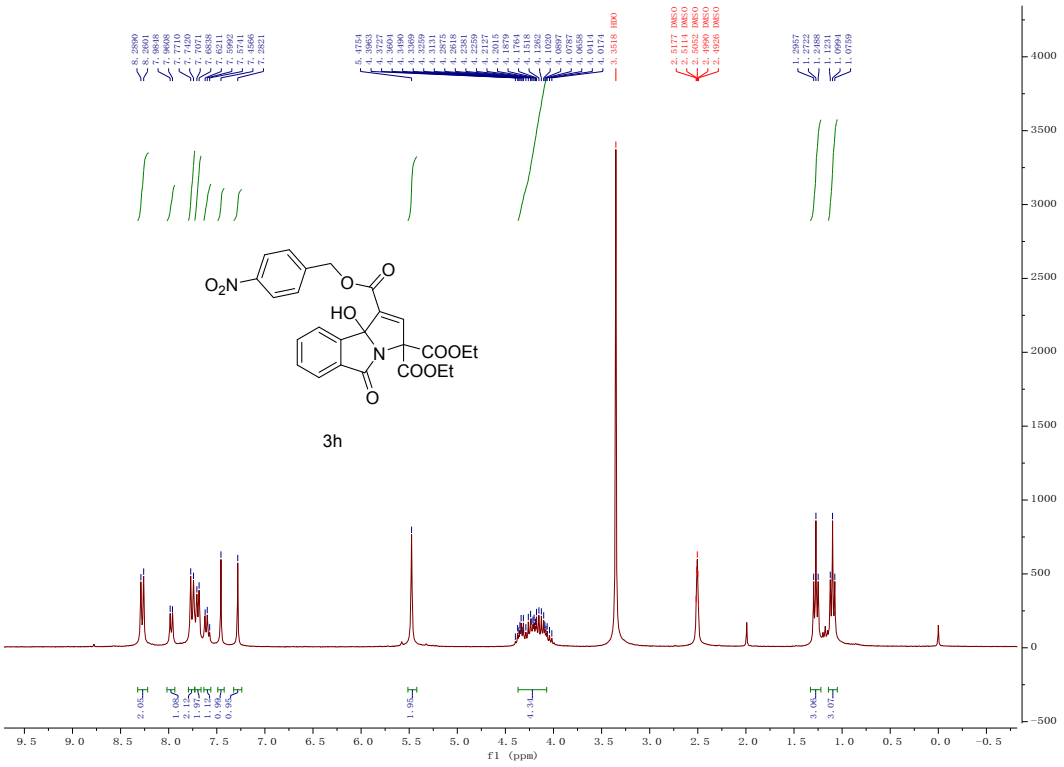


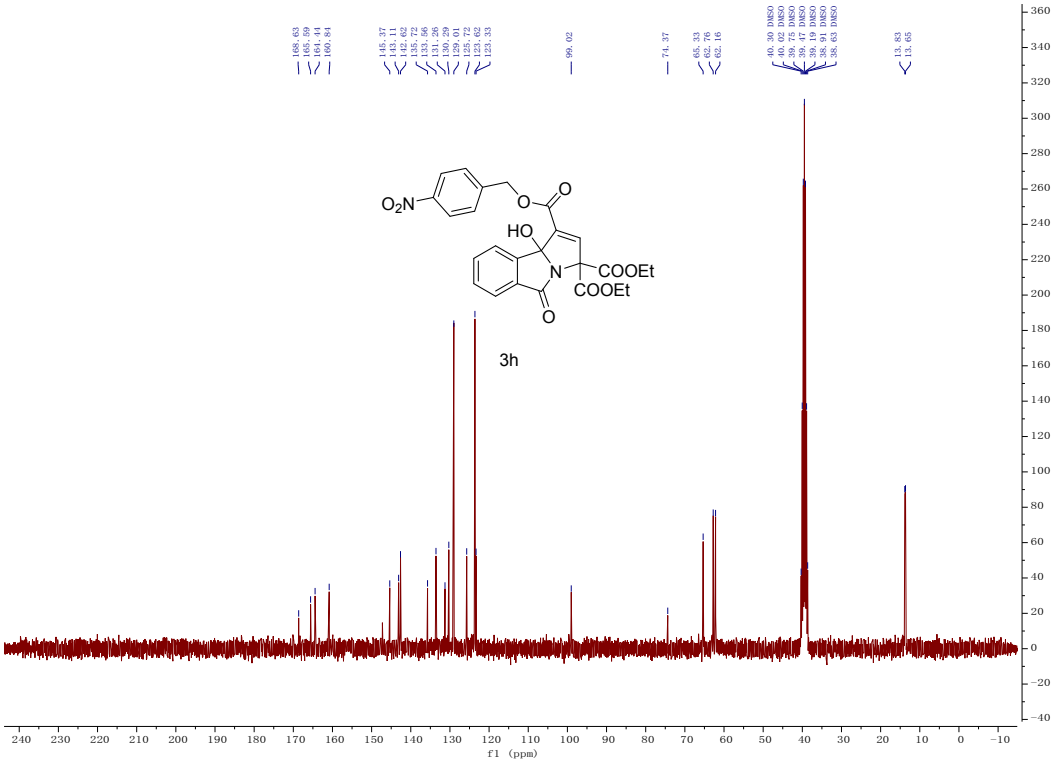
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3g** (DMSO)



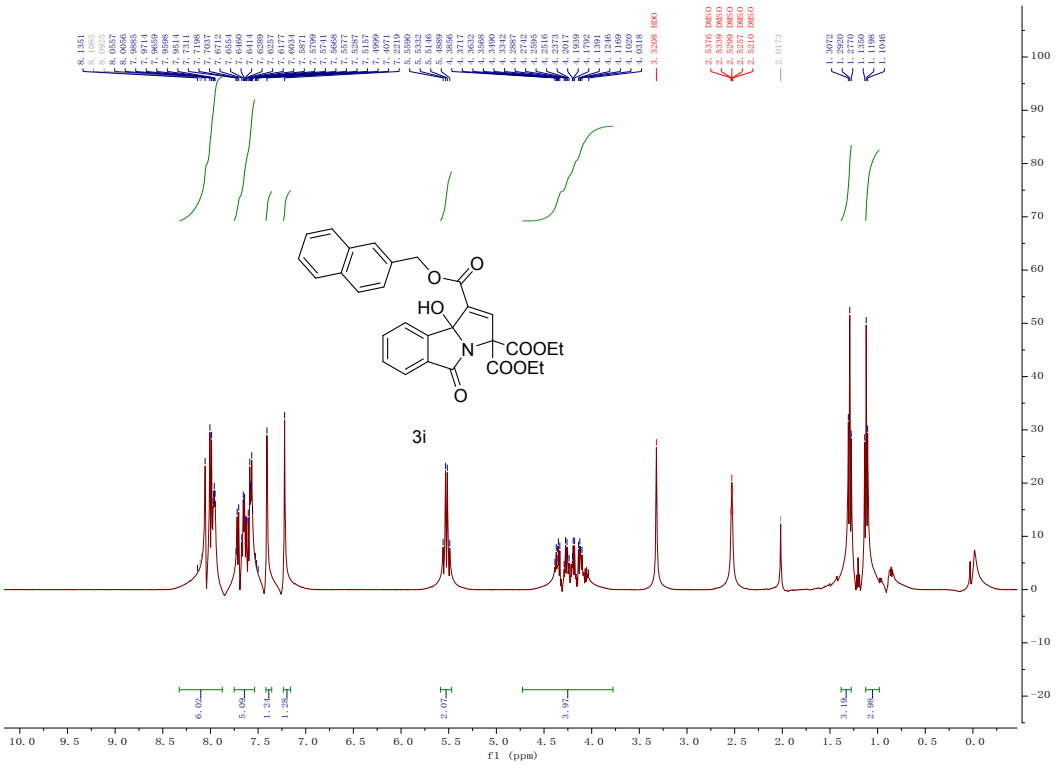


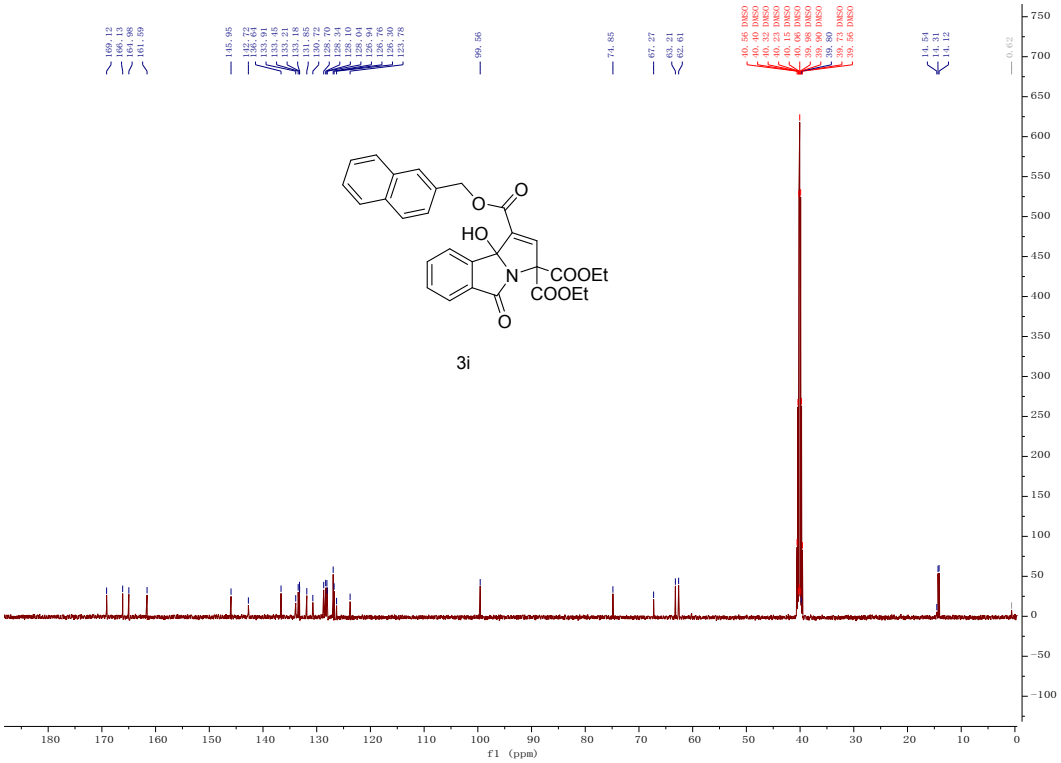
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3h** (DMSO)



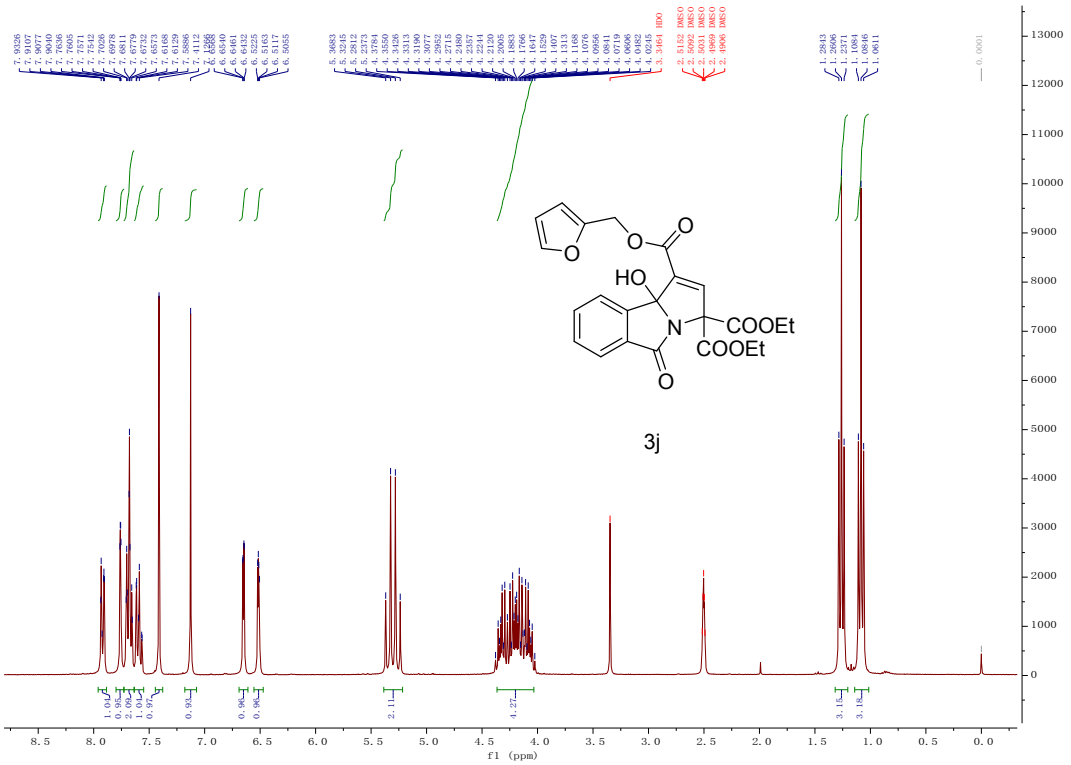


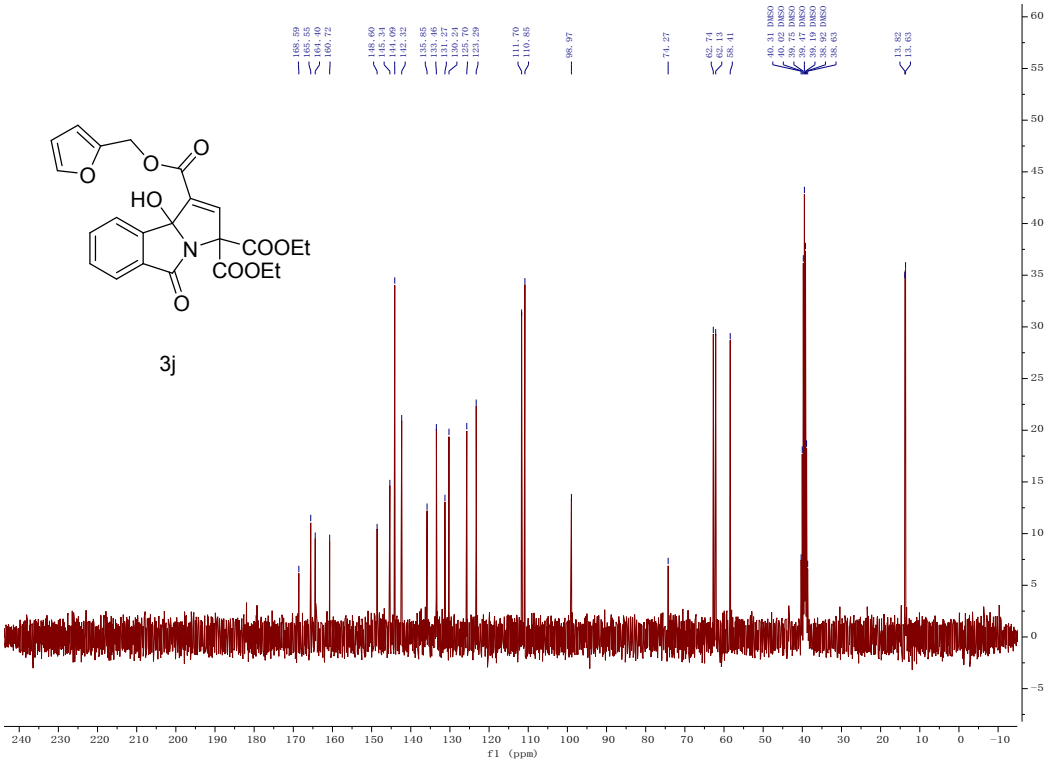
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3i** (DMSO)



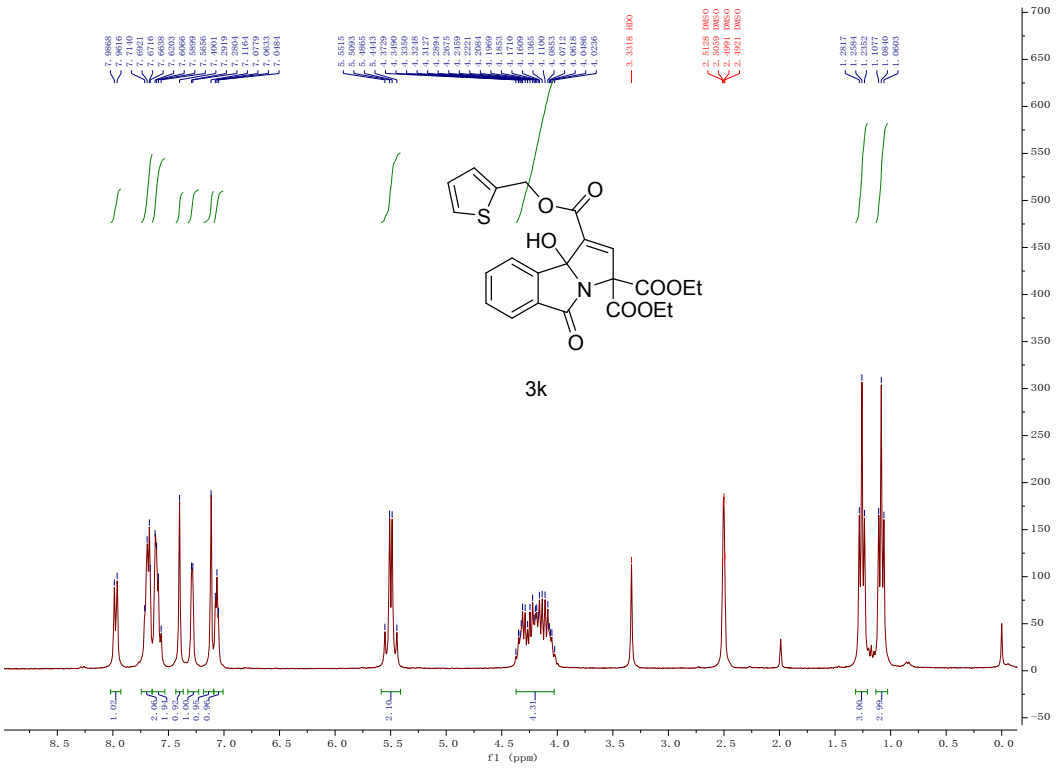


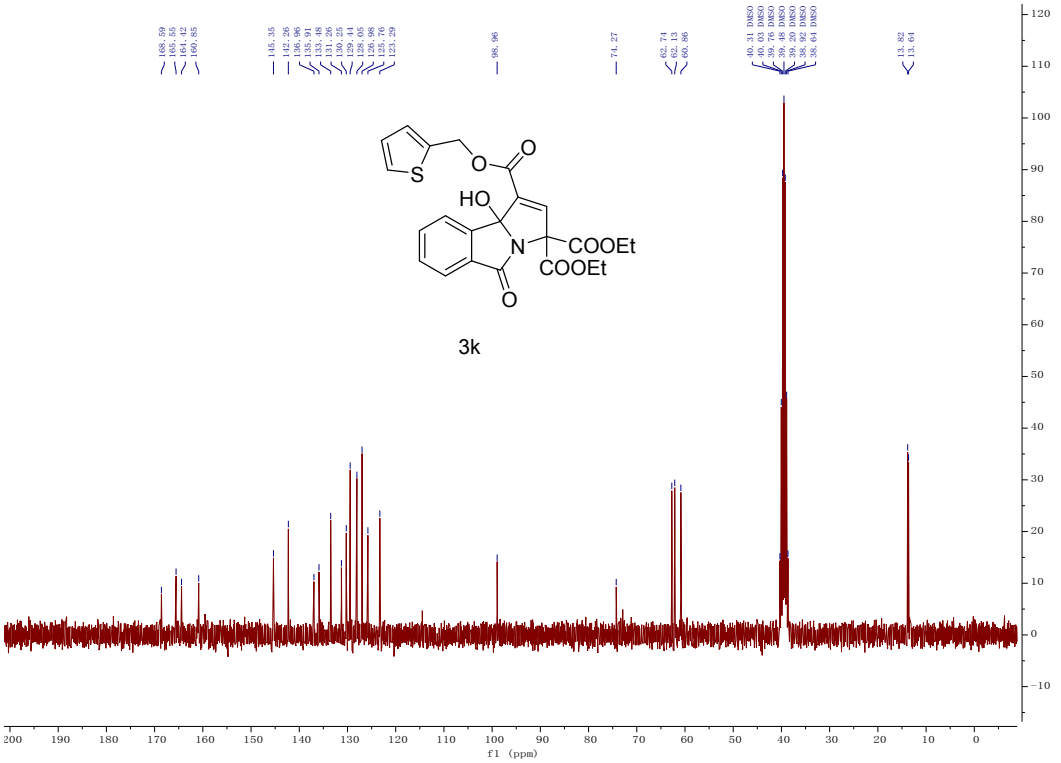
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3j** (DMSO)



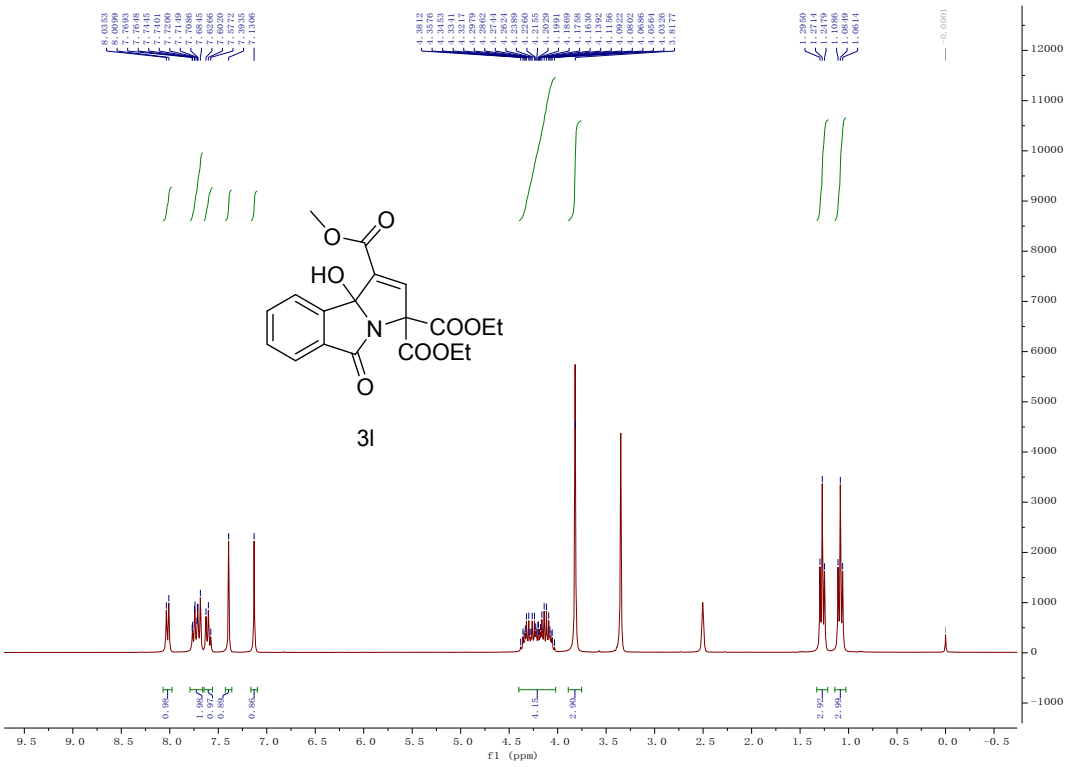


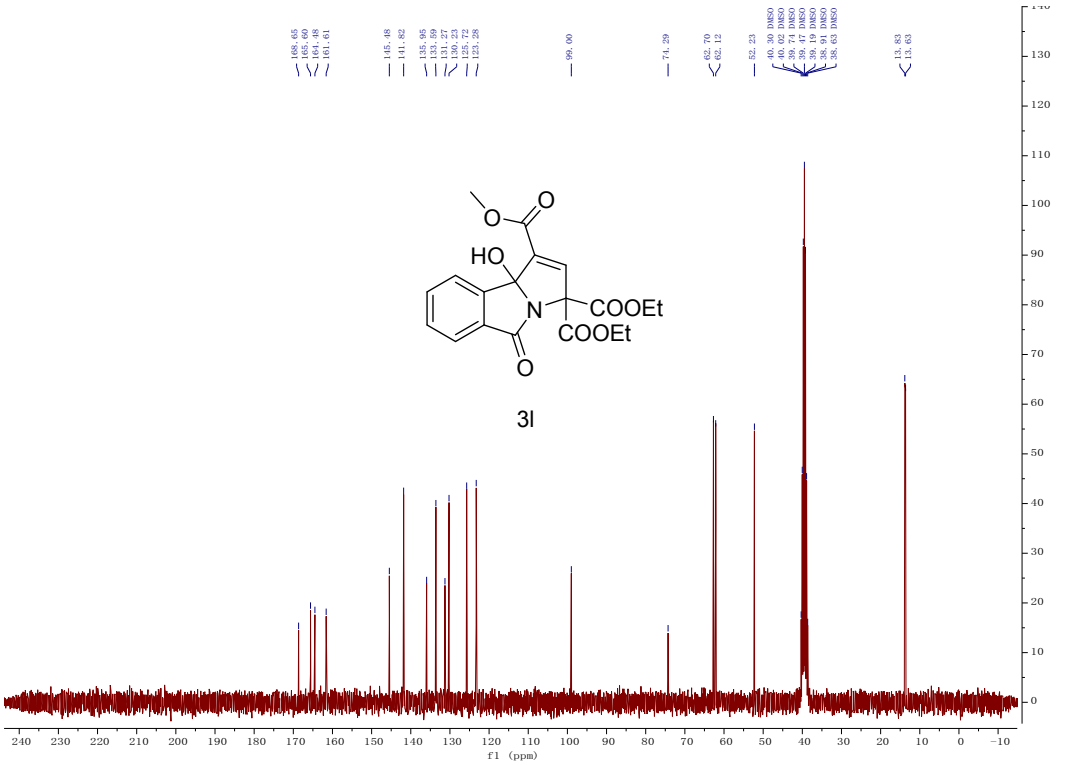
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3k** (DMSO)



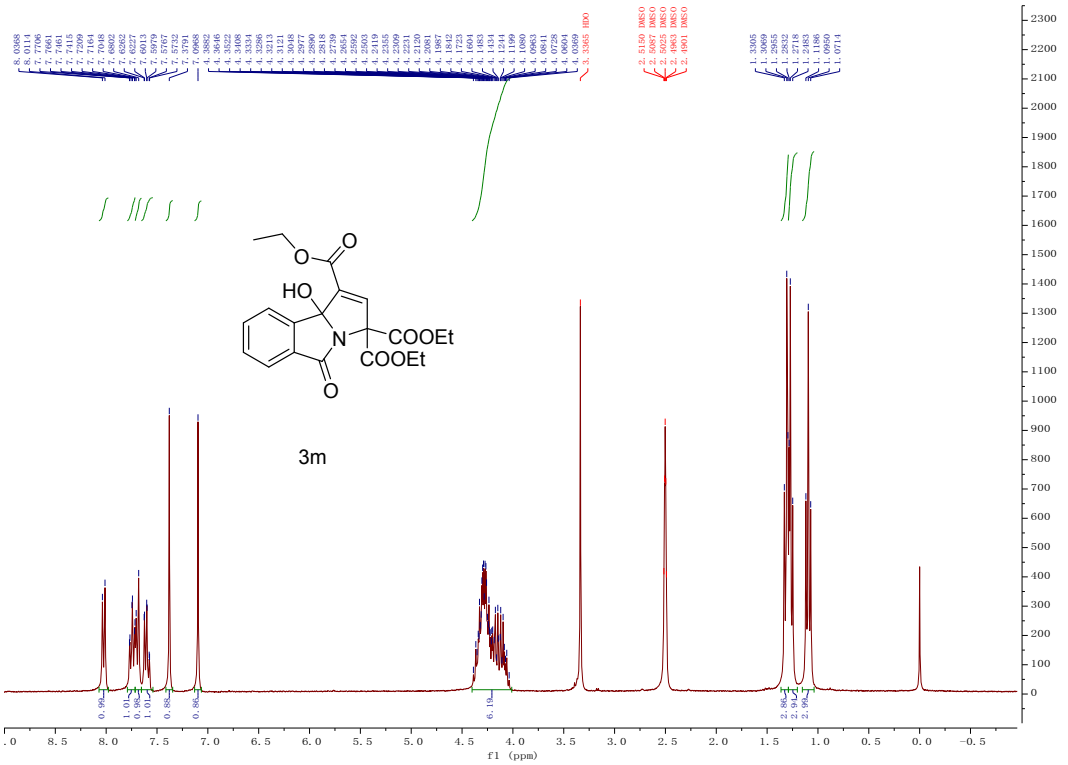


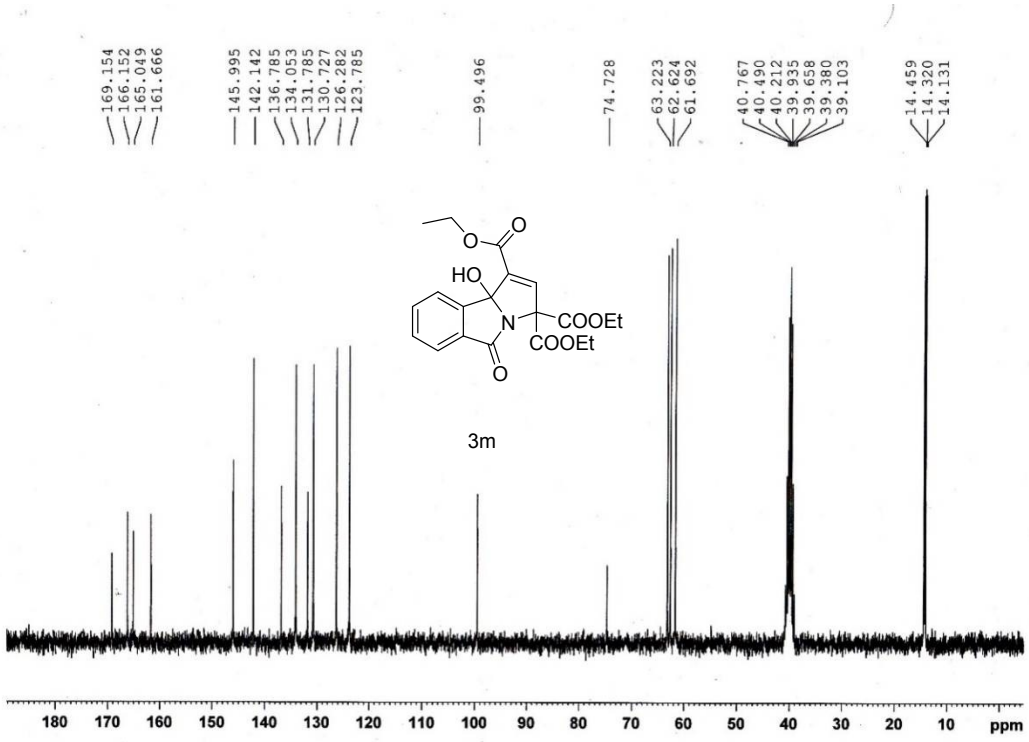
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3l** (DMSO)



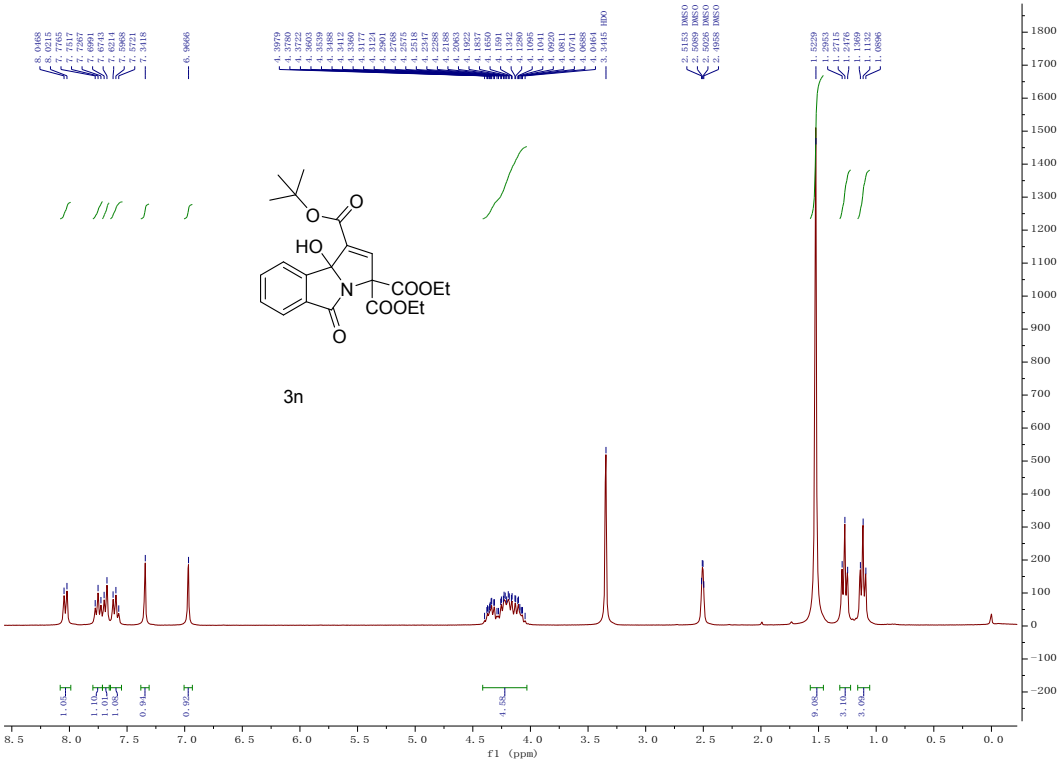


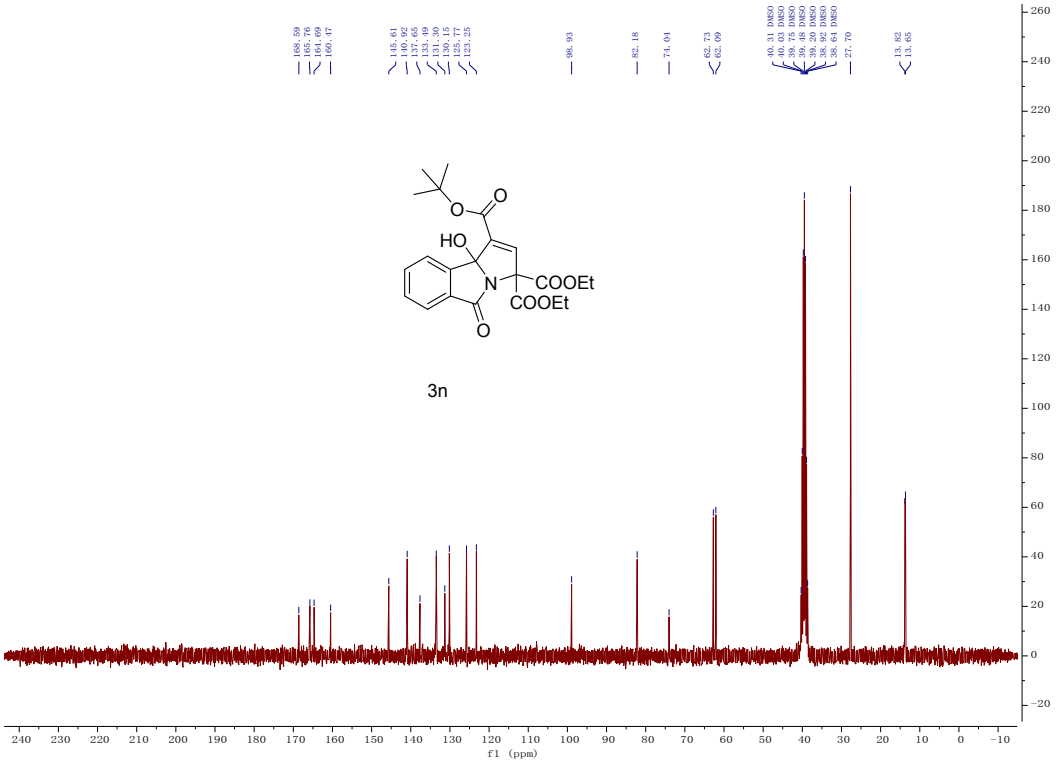
^{1}H NMR (300 MHz) and^{13}C NMR (300 MHz) spectra of **3m** (DMSO)



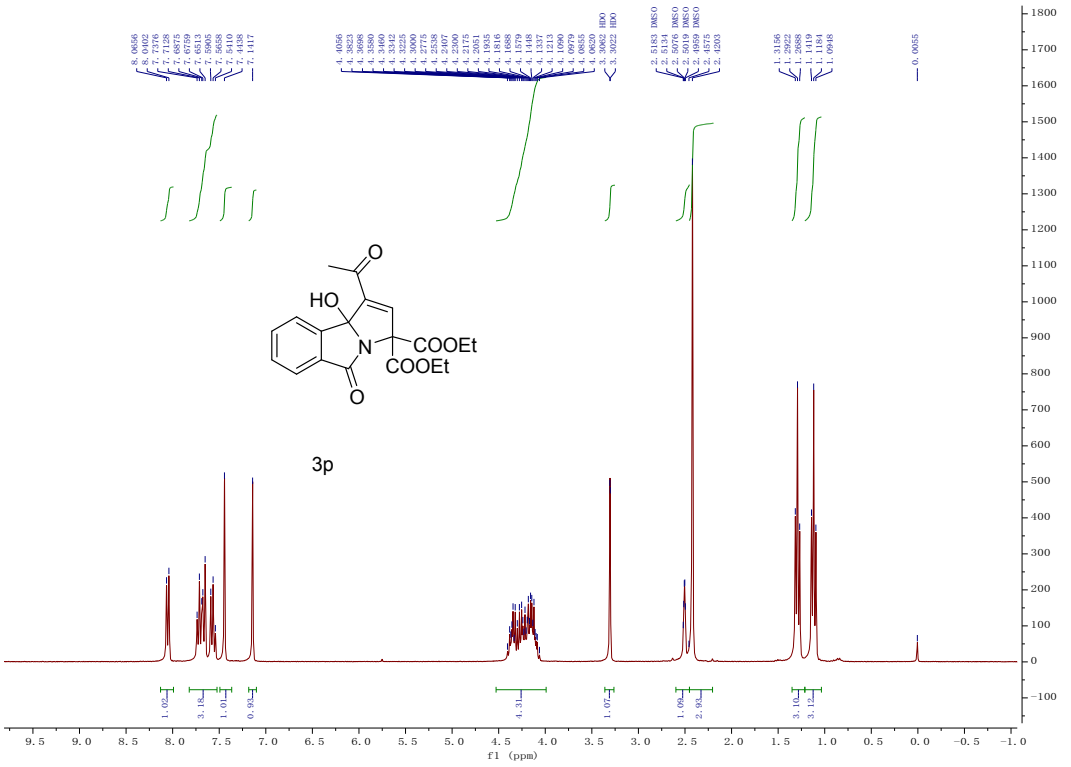


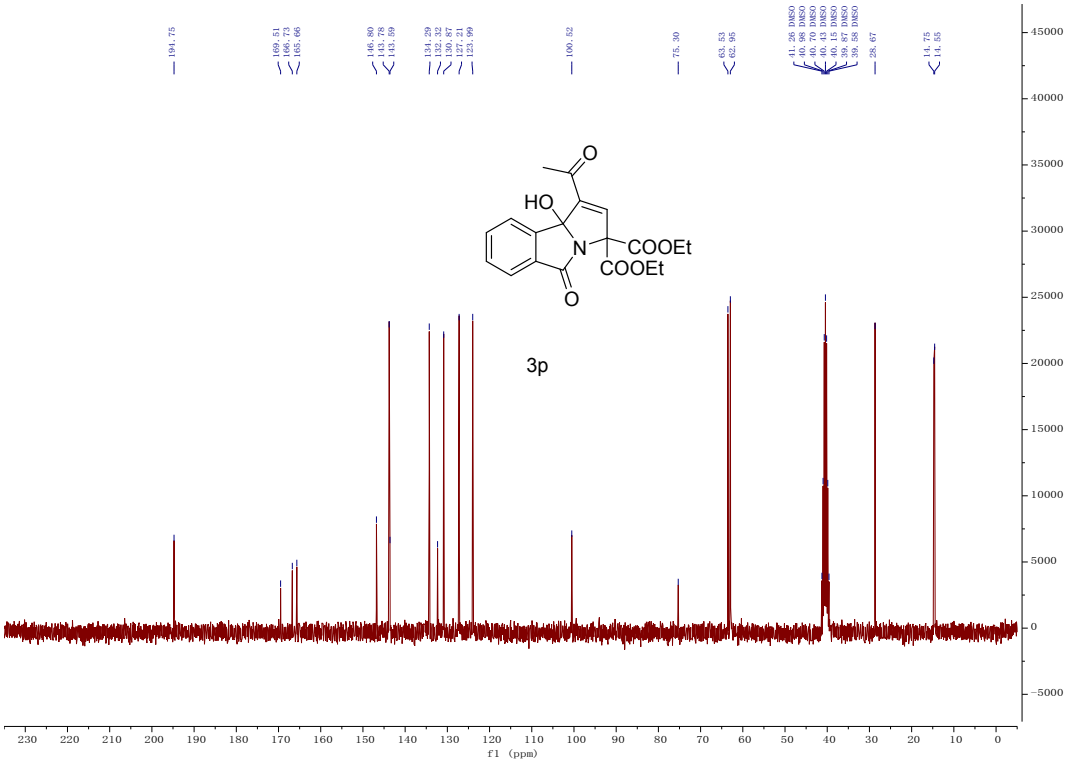
^{1}H NMR (300 MHz) and^{13}C NMR (300 MHz) spectra of **3n** (DMSO)



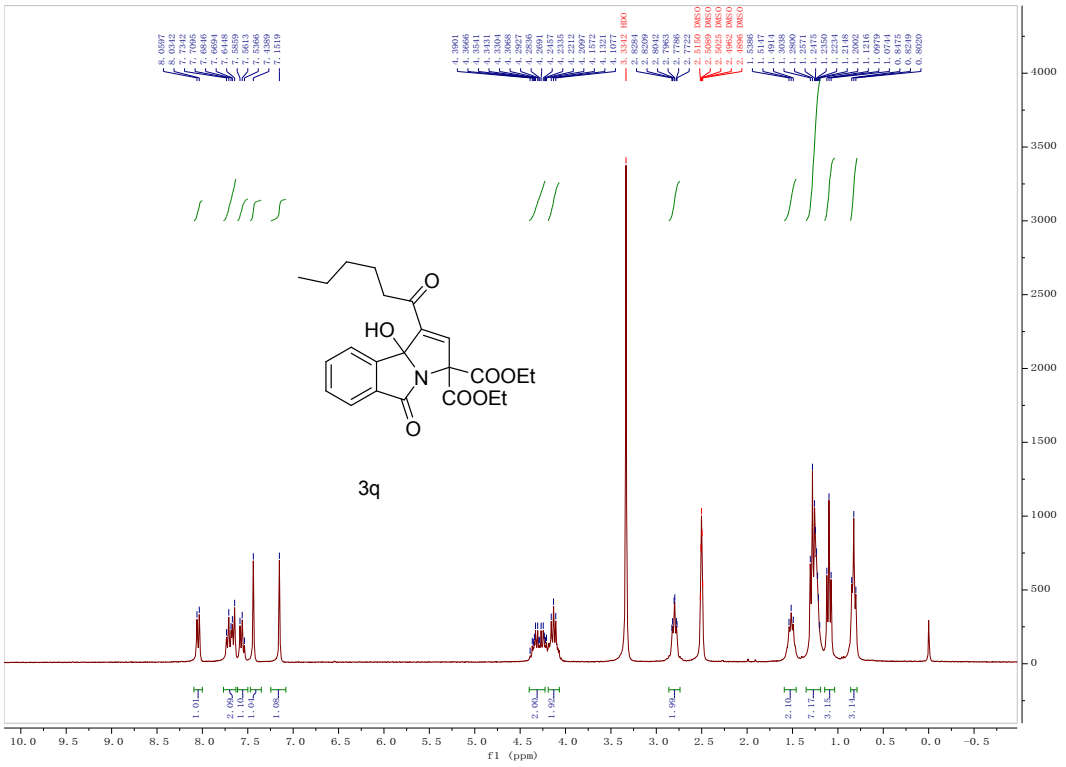


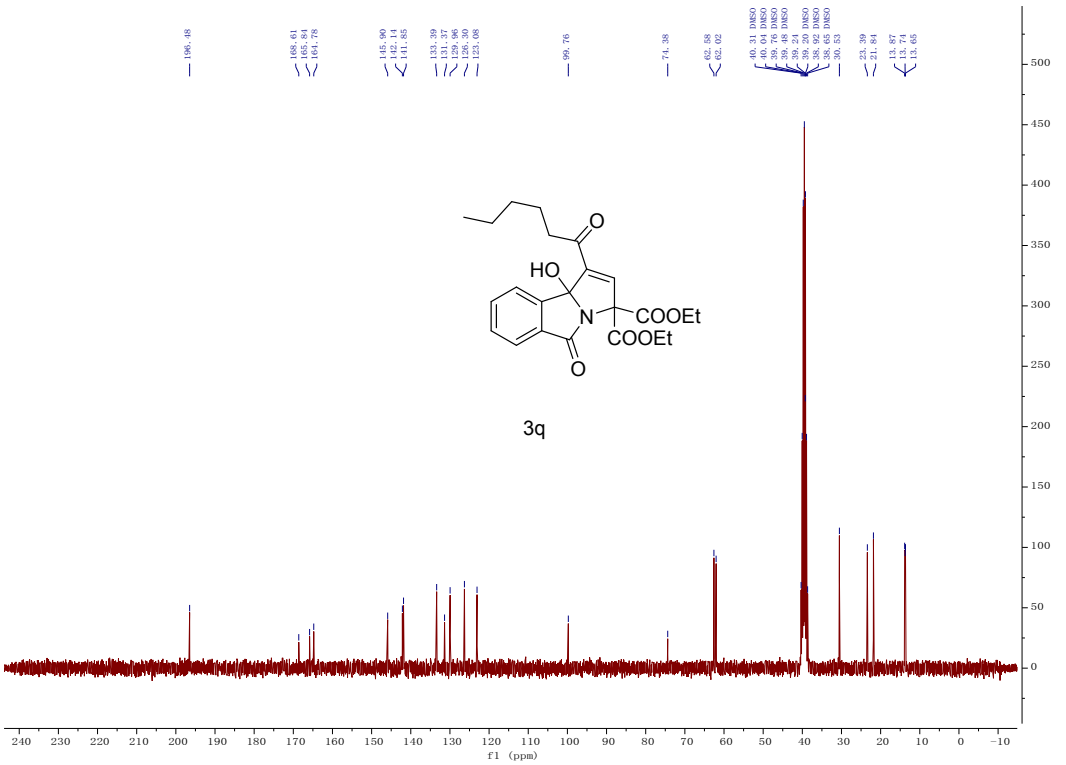
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3p** (DMSO)



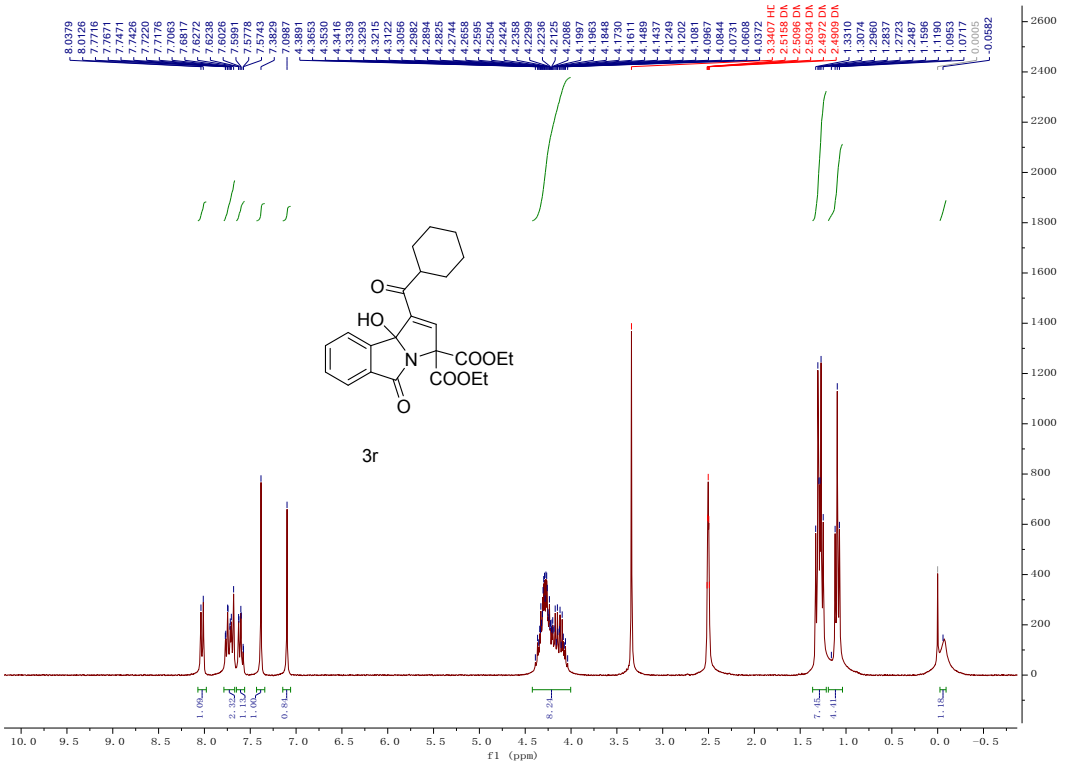


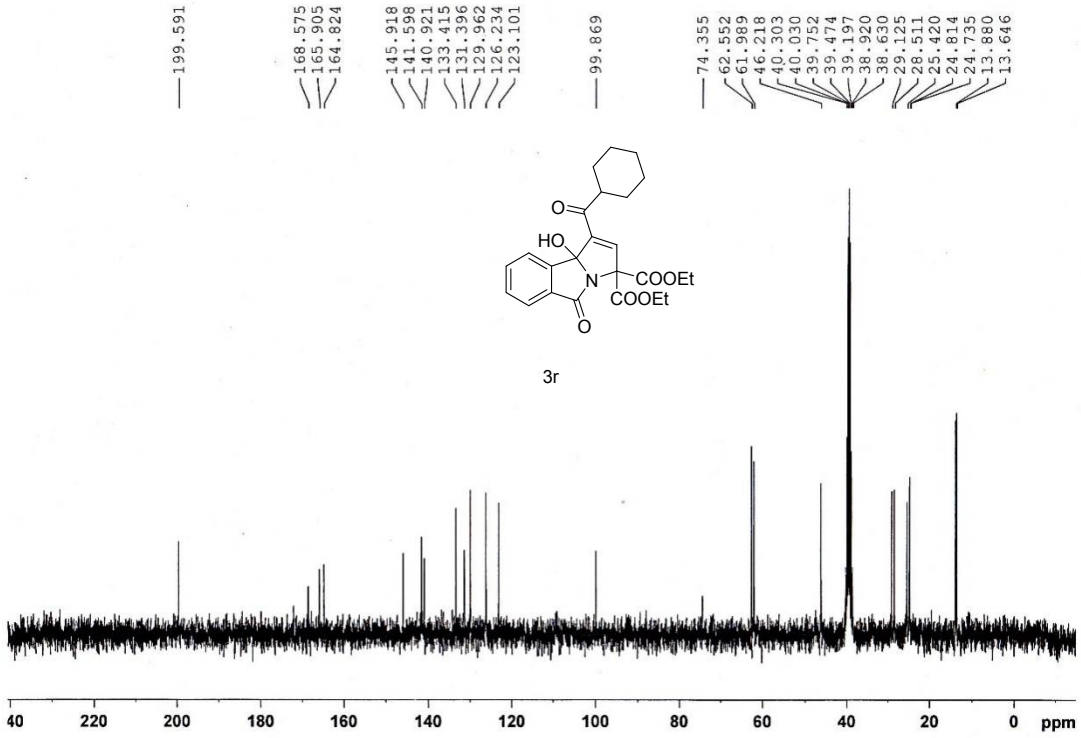
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3q** (DMSO)



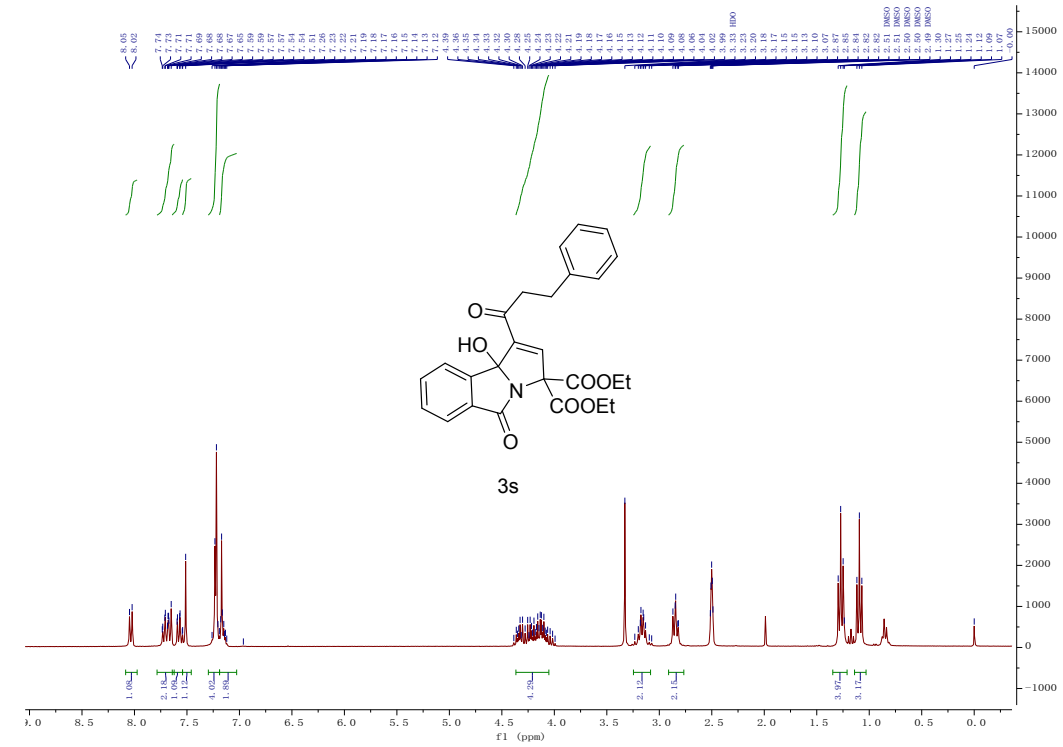


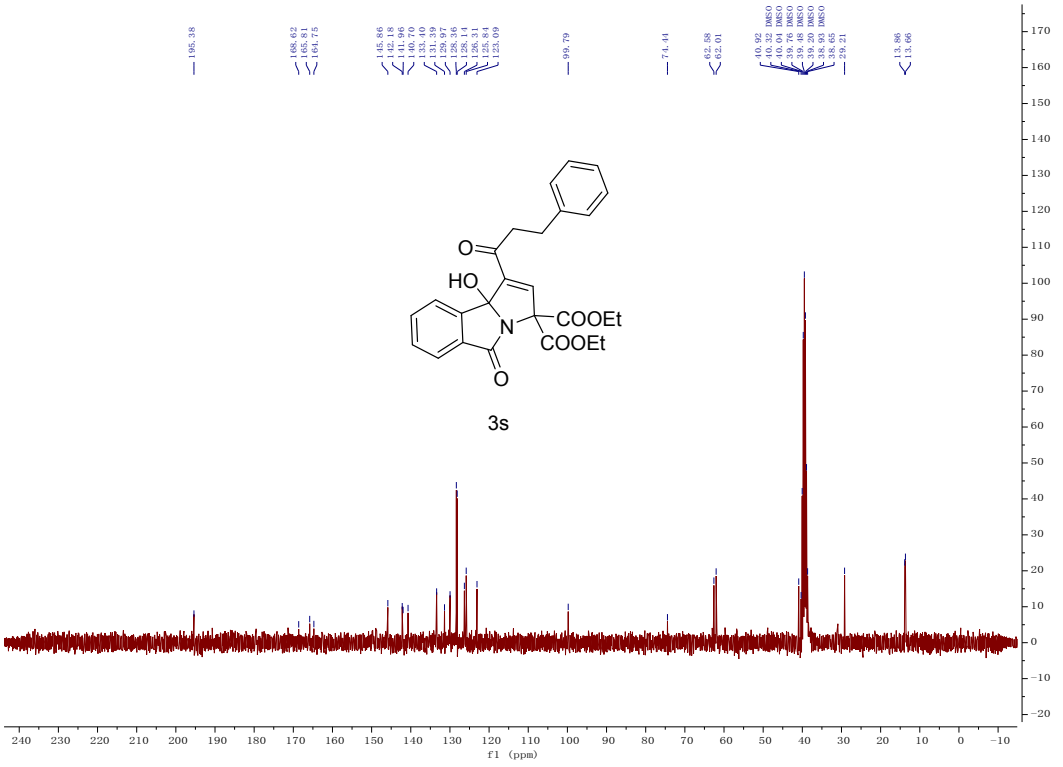
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3r** (DMSO)



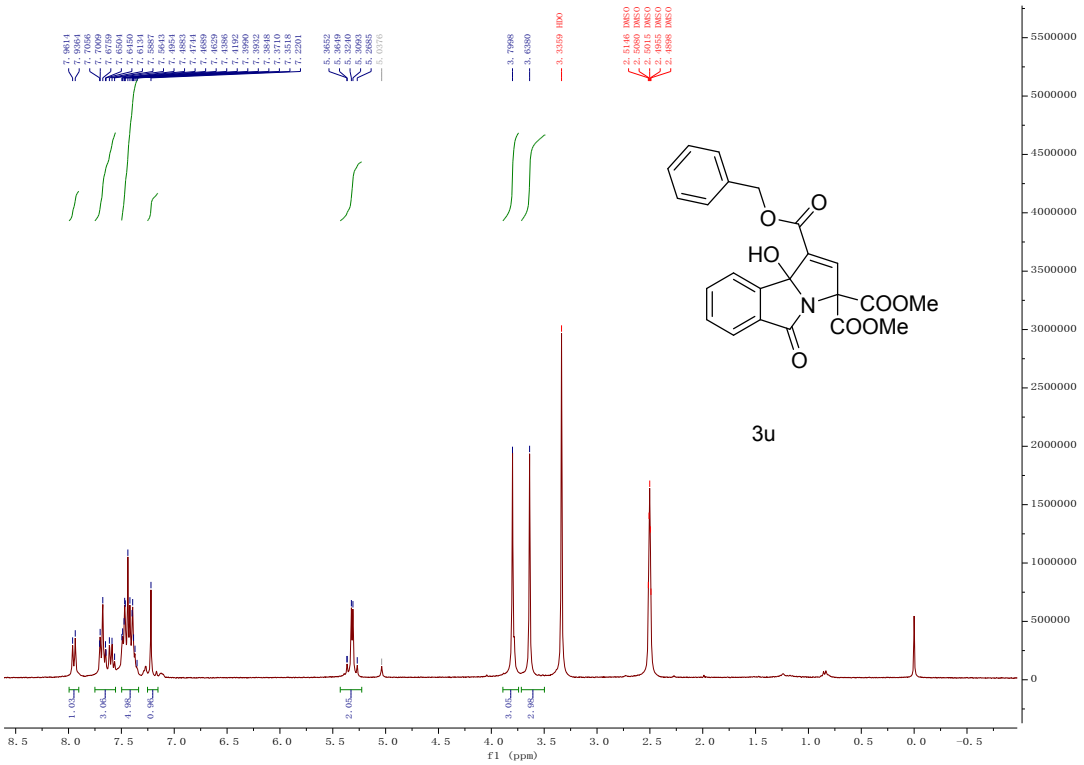


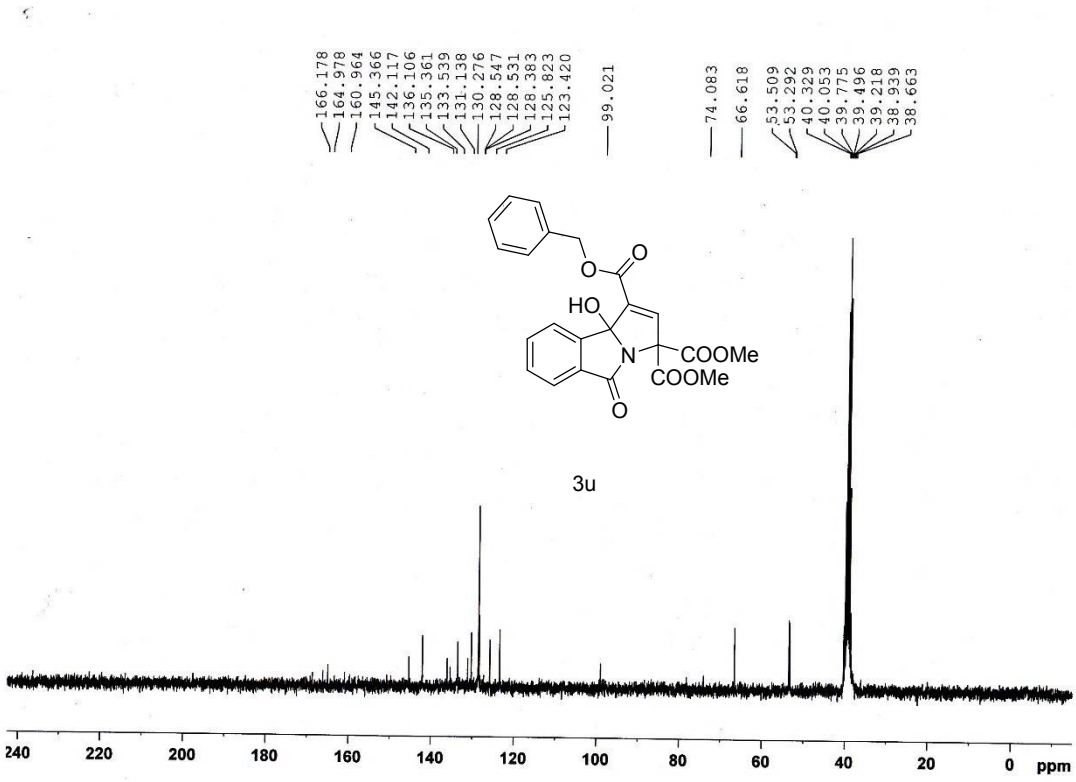
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3s** (DMSO)



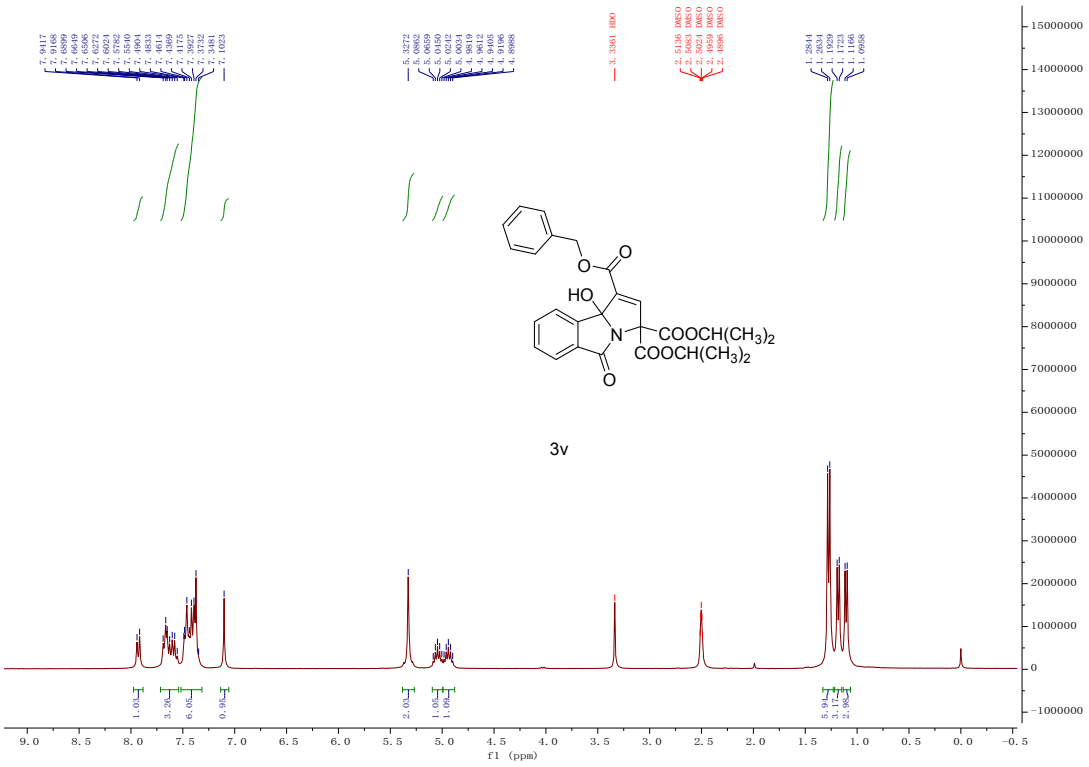


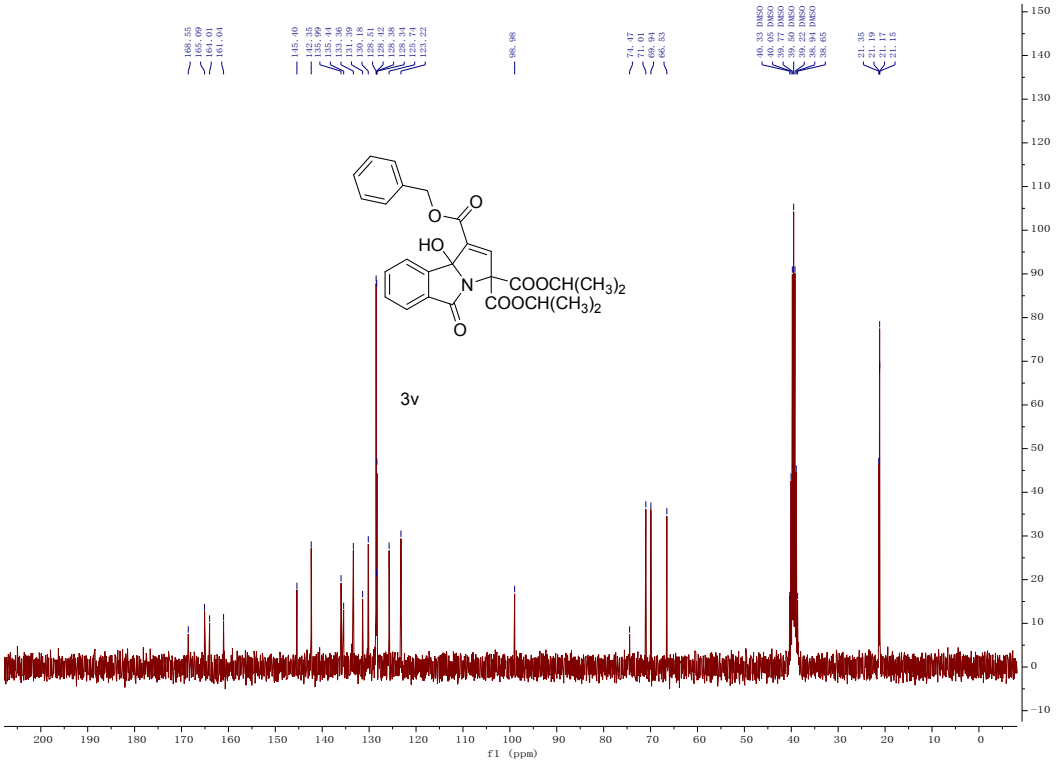
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3u** (DMSO)



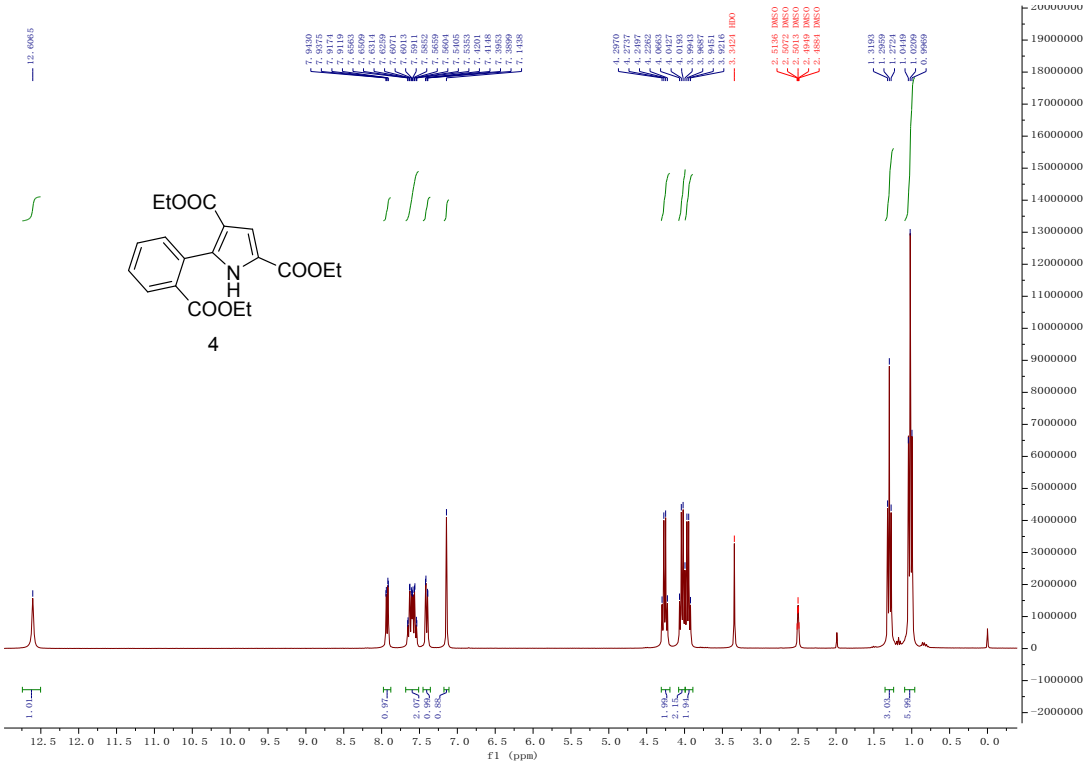


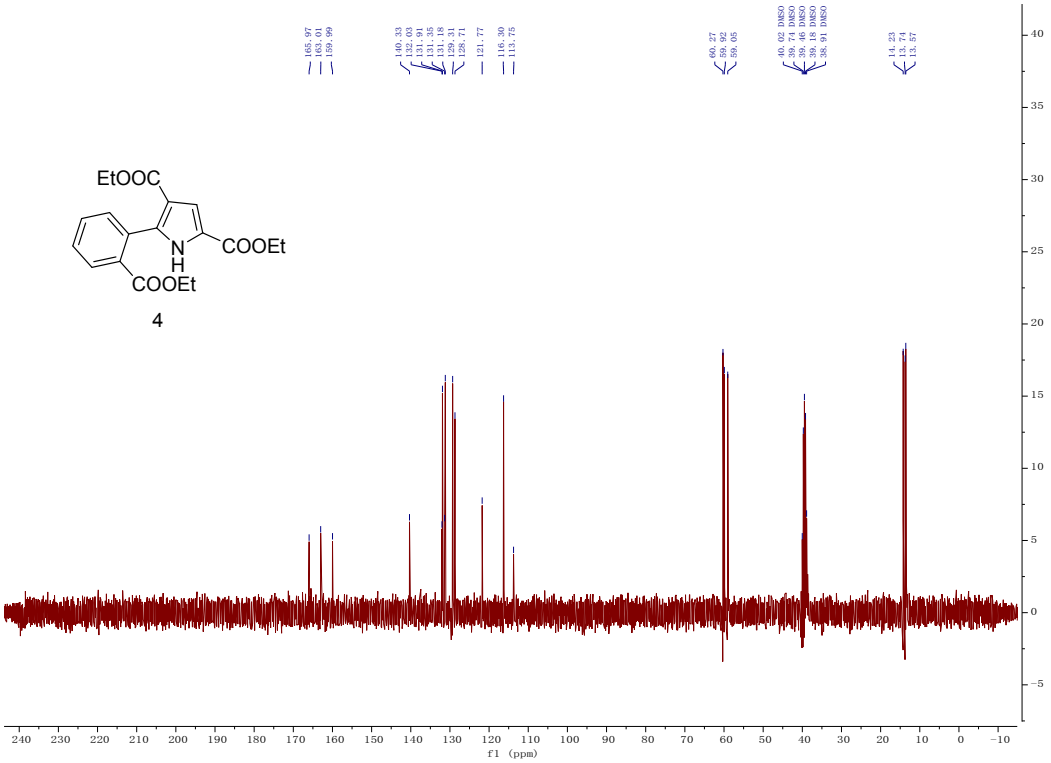
^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **3v** (DMSO)



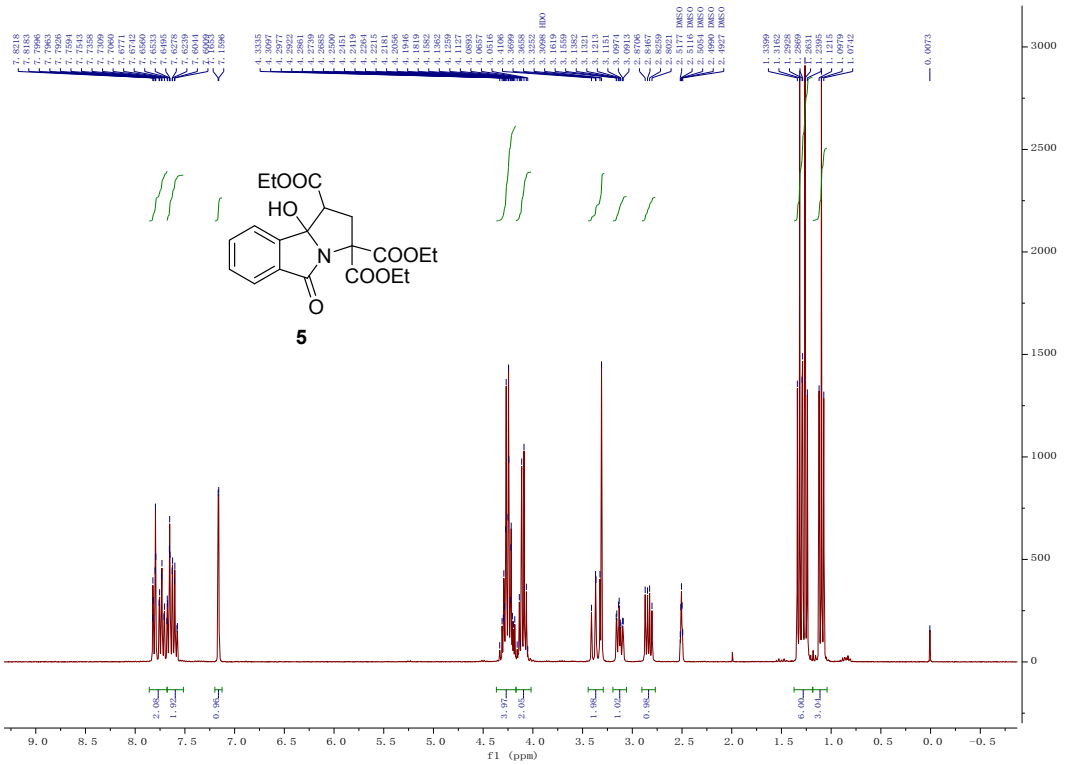


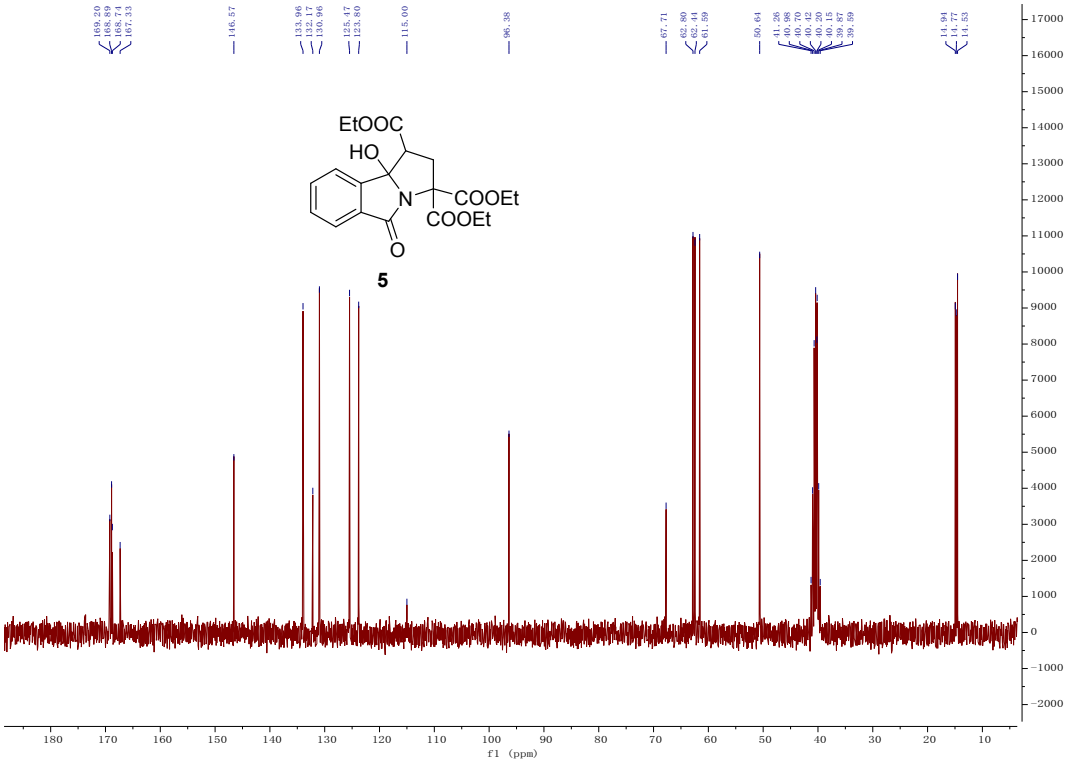
^{1}H NMR (300 MHz) and^{13}C NMR (300 MHz) spectra of **4** (DMSO)





^{1}H NMR (300 MHz) and ^{13}C NMR (300 MHz) spectra of **5** (DMSO)





^{1}H NMR (300 MHz) and^{13}C NMR (300 MHz) spectra of **6**(DMSO)