Diastereoselective construction of a library of structural bispiro[butyrolactone/valerolactone-pyrrolidine-indanedione] hybrids via 1,3-dipolar cycloaddition reactions

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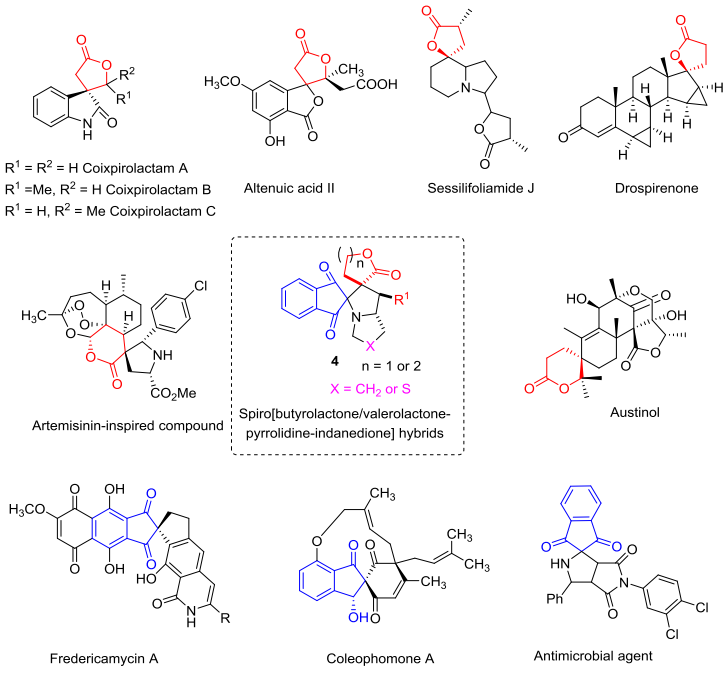
1. General information

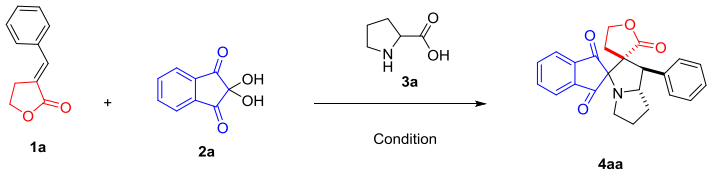
Reactions were monitored by thin layer chromatography using UV light to visualize the course of reaction. Purification of reaction products was carried out by flash chromatography on silica gel or just by simple filtration and washing. ^{1}H and ^{13}CNMR spectra were obtained using a Bruker DPX-400 spectrometer. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Melting points were measured on an electrothermal digital melting point apparatus.

All cell lines were purchased from the Chinese Academy of Sciences, Kunming Cell Bank. All of which were cultured in RPMI-1640 or DMEM medium (Gibco, USA) supplemented with 10% foetal bovine serum, 1% glutamine, 100 U/mL penicillin and 100 μg/mL streptomycin in a humidified atmosphere with 5% CO_2 at 37 ℃. The synthetic compounds were placed at -20℃ after dissolved in DMSO. Cisplatin purchased from Aladdin Company and bis-indole methane purchased from Macleans Reagent Company.

2. Figure S1: representative biological molecules and our target molecule



3. Table S1: optimization of reaction conditions for synthesis of compound 4aa



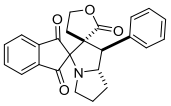
Entry [a]	Solvent	T (°C)	Time (h)	Yield[b] (%)	Dr[c]
1	toluene	65	6	81	>20:1
2	CH_3CN	65	6	69	>20:1
3	DCE	65	6	75	16:1
4	EtOAc	65	6	71	>20:1
5	EtOH	65	6	62	>20:1
6	THF	65	6	62	>20:1
7	toluene	80	5	87	>20:1
8	toluene	100	5	82	>20:1

[a] Unless noted, reactions were carried out with 0.2 mmol of compound **1a**, 0.3 mmol of compound **2a**, 0.5 mmol of compound **3a** in 2.5 mL of solvent. [b] Isolated yield after flash chromatography. [c] Determined by ^{1}H-NMR analysis of the crude products.

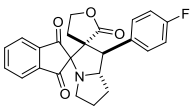
4. Synthesis of bispiro[butyrolactone/valerolactone-pyrrolidine-indanedione] hybrids 4

In a sealed tube equipped with a magnetic stirring bar, to 2.5 mL of toluene was added 3-benzylidenebutyrolactone **1** (0.2 mmol), ninhydrin **2** (0.3 mmol) and proline **3** (0.5 mmol). The reaction mixture was stirred at 80 °C for 5 h. After completion of the reaction, as indicated by TLC, purification by flash column chromatography (hexane/EtOAc, 5/1, v/v) was carried out to furnish the hybrids **4**.

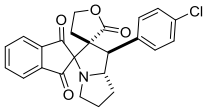
5. Characterization data of hybrids 4



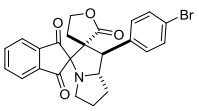
4aa: Light yellow solid, m.p. 237.9-238.6 °C; yield 87%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.88-2.04 (m, 3H), 2.16-2.29 (m, 2H), 2.57-2.63 (m, 1H), 2.76-2.80 (m, 1H), 2.83-2.90 (m, 1H), 3.18-3.24 (m, 1H), 3.64-3.70 (m, 1H), 4.25 (d, J = 10.0 Hz, 1H), 4.30-4.36 (m, 1H), 7.20-7.25 (m, 5H), 7.75-7.79 (m, 1H), 7.82-7.88 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.8, 28.3, 28.9, 45.3, 53.0, 63.6, 64.4, 65.3, 77.5, 121.5, 121.8, 126.4, 127.0, 127.3, 133.3, 134.4, 135.7, 138.4, 139.6, 173.1, 198.4, 198.9; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{21}NNaO_4$ $[M+Na]^+$: 410.1363; Found: 410.1366.



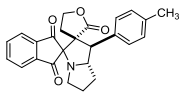
4ab: Light yellow solid, m.p. 240.1-241.0 ^{o}C; yield 81%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.88-2.03 (m, 3H), 2.16-2.23 (m, 2H), 2.57-2.63 (m, 1H), 2.76-2.81 (m, 1H), 2.85-2.92 (m, 1H), 3.31-3.37 (m, 1H), 3.66-3.72 (m, 1H), 4.21-4.29 (m, 2H), 6.93-6.97 (m, 2H), 7.17-7.20 (m, 2H), 7.76-7.80 (m, 1H), 7.83-7.89 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.2, 29.8, 30.5, 46.9, 53.8, 65.1, 66.1, 67.2, 79.0, 115.8 (d, J_{CF} = 21.3 Hz), 123.1, 123.5, 130.2 (d, J_{CF} = 8.1 Hz), 130.6, 136.2, 137.3, 140.0, 141.1, 162.9 (d, J_{CF} = 245.2 Hz), 174.6, 199.8, 200.4; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{20}FNNaO_4$ $[M+Na]^+$: 428.1269; Found: 428.1264.



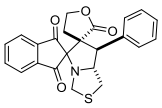
4ac: Light yellow solid, m.p. 235.7-236.4 ^{o}C; yield 86%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.87-2.03 (m, 3H), 2.15-2.21 (m, 2H), 2.57-2.63 (m, 1H), 2.76-2.80 (m, 1H), 2.86-2.92 (m, 1H), 3.35-3.41 (m, 1H), 3.66-3.72 (m, 1H), 4.20-4.28 (m, 2H), 7.14 (d, J = 7.6 Hz, 2H), 7.20-7.24 (m, 2H), 7.76-7.80 (m, 1H), 7.83-7.88 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.2, 29.8, 30.5, 46.9, 53.8, 65.0, 66.1, 67.0, 79.0, 123.1, 123.5, 129.1, 130.0, 133.5, 134.0, 136.2, 137.3, 140.0, 141.0, 174.5, 199.8, 200.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{20}ClNNaO_4$ $[M+Na]^+$: 444.0973; Found: 444.0976.



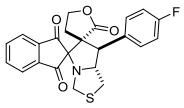
4ad: Light yellow solid, m.p. 235.9-236.6 ^{o}C; yield 89%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.87-2.03 (m, 3H), 2.13-2.20 (m, 2H), 2.56-2.63 (m, 1H), 2.75-2.80 (m, 1H), 2.85-2.92 (m, 1H), 3.36-3.42 (m, 1H), 3.66-3.72 (m, 1H), 4.19-4.28 (m, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.76-7.80 (m, 1H), 7.83-7.88 (m, 2H), 7.94 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.2, 28.8, 29.5, 45.9, 52.8, 63.9, 65.1, 65.9, 77.9, 121.1, 122.1, 122.5, 129.3, 131.0, 132.9, 135.2, 136.4, 139.0, 140.0, 173.4, 198.8, 199.2; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{20}BrNNaO_4$ $[M+Na]^+$: 488.0468; Found: 488.0471.



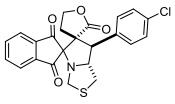
4ae: Light yellow solid, m.p. 245.1-245.7 ^{o}C; yield 82%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.88-2.03 (m, 3H), 2.15-2.29 (m, 5H), 2.56-2.62 (m, 1H), 2.75-2.87 (m, 2H), 3.19-3.24 (m, 1H), 3.64-3.70 (m, 1H), 4.20 (d, J = 10.0 Hz, 1H), 4.27-4.33 (m, 1H), 7.04-7.17 (m, 4H), 7.74-7.78 (m, 1H), 7.82-7.87 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.0, 25.4, 29.9, 30.5, 46.9, 54.3, 65.2, 66.1, 66.9, 79.2, 123.1, 123.4, 128.5, 129.6, 131.7, 136.0, 137.2, 137.8, 140.0, 141.3, 174.7, 200.0, 200.5; HRMS (ESI-TOF) m/z: Calcd. for $C_{25}H_{23}NNaO_4$ $[M+Na]^+$: 424.1519; Found: 424.1516.



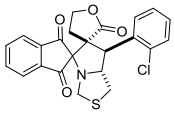
4ba: Light yellow solid, m.p. 250.7-251.0 ^{o}C; yield 83%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.22-2.30 (m, 1H), 2.83-2.90 (m, 1H), 2.95-2.99 (m, 1H), 3.18-3.28 (m, 2H), 3.54 (d, J = 7.6 Hz, 1H), 3.63-3.69 (m, 1H), 3.92 (d, J = 7.6 Hz, 1H), 4.31 (d, J = 8.8 Hz, 1H), 4.55-4.61 (m, 1H), 7.21-7.27 (m, 5H), 7.77-7.81 (m, 1H), 7.84-7.88 (m, 2H), 7.96 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.7, 34.2, 49.0, 51.8, 63.7, 64.2, 68.9, 77.4, 121.4, 121.8, 126.6, 126.9, 127.3, 132.3, 134.5, 135.7, 138.3, 139.6, 172.3, 196.5, 197.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{19}NNaO_4S$ $[M+Na]^+$: 428.0927; Found: 428.0923.



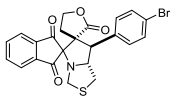
4bb: Light yellow solid, m.p. 242.4-244.4 ^{o}C; yield 82%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.17-2.25 (m, 1H), 2.85-2.98 (m, 2H), 3.22-3.26 (m, 1H), 3.32-3.38 (m, 1H), 3.54 (d, J = 7.6 Hz, 1H), 3.65-3.71 (m, 1H), 3.92 (d, J = 7.6 Hz, 1H), 4.30 (d, J = 8.8 Hz, 1H), 4.48-4.54 (m, 1H), 6.95-6.70 (m, 2H), 7.19-7.22 (m, 2H), 7.78-7.82 (m, 1H), 7.83-7.89 (m, 2H), 7.95-7.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.9, 34.5, 49.3, 51.4, 63.9, 64.6, 69.5, 77.6, 114.6 (d, J_{CF} = 21.2 Hz), 121.8, 122.2, 128.3, 128.4, 128.9 (d, J_{CF} = 8.0 Hz), 134.9, 136.1, 138.6, 139.8, 161.2 (d, J_{CF} = 247.2 Hz), 172.5, 196.7, 197.8; HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{18}FNNaO_4S$ $[M+Na]^+$: 446.0833; Found: 446.0835.



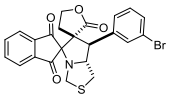
4bc: Light yellow solid, m.p. 236.2-237.0 ^{o}C; yield 88%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.15-2.22 (m, 1H), 2.86-2.98 (m, 2H), 3.22-3.26 (m, 1H), 3.37-3.42 (m, 1H), 3.54 (d, J = 7.6 Hz, 1H), 3.65-3.72 (m, 1H), 3.92 (d, J = 7.6 Hz, 1H), 4.29 (d, J = 8.8 Hz, 1H), 4.48-4.54 (m, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.79-7.82 (m, 1H), 7.86-7.89 (m, 2H), 7.96 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.3, 34.9, 49.7, 51.8, 64.3, 65.1, 69.8, 78.0, 122.2, 122.6, 128.3, 129.0, 131.6, 133.4, 135.4, 136.6, 139.0, 140.2, 172.8, 197.1, 198.2; HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{18}ClNNaO_4S$ $[M+Na]^+$: 462.0537; Found: 462.0537.



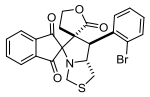
4bd: Light yellow solid, m.p. 237.4-238.1 ^{o}C; yield 76%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.45-2.51 (m, 1H), 2.79-2.87 (m, 1H), 2.90-2.94 (m, 1H), 2.98-3.04 (m, 1H), 3.33-3.37 (m, 1H), 3.57 (d, J = 8.0 Hz, 1H), 3.68-3.73 (m, 1H), 3.94 (d, J = 7.6 Hz, 1H), 4.51-4.56 (m, 1H), 5.05 (d, J = 8.4 Hz, 1H), 7.18-7.26 (m, 2H), 7.35-7.38 (m, 1H), 7.54-7.57 (m, 1H), 7.76-7.80 (m, 1H), 7.84-7.89 (m, 2H), 8.01 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.0, 35.2, 48.8, 50.0, 62.8, 65.0, 71.9, 78.1, 122.4, 122.5, 125.9, 128.5, 128.6, 129.8, 131.2, 135.0, 136.4, 139.2, 141.2, 172.6, 197.5, 198.5; HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{18}ClNNaO_4S$ $[M+Na]^+$: 462.0537; Found: 462.0539.



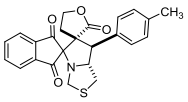
4be: Light yellow solid, m.p. 230.2-231.0 ^{o}C; yield 83%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.14-2.22 (m, 1H), 2.86-2.98 (m, 2H), 3.21-3.26 (m, 1H), 3.38-3.43 (m, 1H), 3.54 (d, J = 7.6 Hz, 1H), 3.65-3.72 (m, 1H), 3.92 (d, J = 7.6 Hz, 1H), 4.27 (d, J = 8.2 Hz, 1H), 4.47-4.53 (m, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.79-7.82 (m, 1H), 7.86-7.89 (m, 2H), 7.95-7.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.3, 35.9, 50.8, 52.9, 65.3, 66.1, 70.7, 79.1, 122.6, 123.3, 123.7, 130.4, 132.3, 133.2, 136.5, 137.6, 140.0, 141.2, 173.9, 198.1, 199.2; HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{18}BrNNaO_4S$ $[M+Na]^+$: 506.0032; Found: 506.0028.



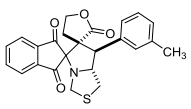
4bf: Light yellow solid, m.p. 240.7-241.5 ^{o}C; yield 82%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.17-2.25 (m, 1H), 2.89-2.99 (m, 2H), 3.22-3.27 (m, 1H), 3.42-3.47 (m, 1H), 3.53 (d, J = 7.6 Hz, 1H), 3.66-3.72 (m, 1H), 3.92 (d, J = 7.6 Hz, 1H), 4.28 (d, J = 9.2 Hz, 1H), 4.47-4.53 (m, 1H), 7.14-7.20 (m, 2H), 7.38-7.40 (m, 2H), 7.79-7.83 (m, 1H), 7.86-7.89 (m, 2H), 7.96 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.4, 34.9, 49.7, 51.9, 64.3, 65.1, 69.8, 78.0, 122.2, 122.6, 126.7, 129.6, 130.6, 135.4, 135.5, 136.5, 139.0, 140.2, 172.7, 197.0, 198.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{18}BrNNaO_4S$ $[M+Na]^+$: 506.0032; Found: 506.0032.



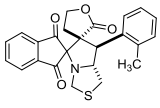
4bg: Light yellow solid, m.p. 235.8-236.2 ^{o}C; yield 79%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.47-2.53 (m, 1H), 2.77-2.84 (m, 1H), 2.90-2.94 (m, 1H), 3.02-3.08 (m, 1H), 3.34-3.39 (m, 1H), 3.58 (d, J = 7.6 Hz, 1H), 3.67-3.72 (m, 1H), 3.93 (d, J = 7.6 Hz, 1H), 4.45-4.51 (m, 1H), 5.09 (d, J = 7.6 Hz, 1H), 7.10-7.14 (m, 1H), 7.27-7.31 (m, 1H), 7.55-7.58 (m, 2H), 7.77-7.80 (m, 1H), 7.84-7.89 (m, 2H), 8.01 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.1, 35.1, 50.0, 51.1, 62.8, 64.9, 72.7, 78.1, 122.4, 122.6, 125.7, 126.5, 128.7, 128.8, 133.1, 133.3, 135.0, 136.4, 139.2, 141.2, 172.6, 197.5, 198.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{18}BrNNaO_4S$ $[M+Na]^+$: 506.0032; Found: 506.0027.



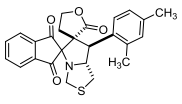
4bh: Light yellow solid, m.p. 238.5-239.3 ^{o}C; yield 81%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.23 (s, 3H), 2.26-2.30 (m, 1H), 2.80-2.87 (m, 1H), 2.94-2.98 (m, 1H), 3.19-3.27 (m, 2H), 3.52-3.55 (m, 1H), 3.63-3.69 (m, 1H), 3.91-3.93 (m, 1H), 4.27 (d, J = 8.8 Hz, 1H), 4.52-4.57 (m, 1H), 7.06-7.12 (m, 4H), 7.77-7.80 (m, 1H), 7.84-7.87 (m, 2H), 7.95-7.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.0, 24.5, 35.0, 49.8, 52.4, 64.5, 65.1, 69.8, 78.2, 122.2, 122.5, 127.5, 128.8, 129.9, 135.2, 136.5, 137.2, 139.0, 140.4, 173.1, 197.3, 198.4; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{21}NNaO_4S$ $[M+Na]^+$: 442.1083; Found: 442.1085.



4bi: Light yellow solid, m.p. 237.8-237.9 ^{o}C; yield 80%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.45 (s, 3H), 2.26-2.32 (m, 1H), 2.82-2.89 (m, 1H), 2.95-2.98 (m, 1H), 3.22-3.27 (m, 2H), 3.53 (d, J = 7.6 Hz, 1H), 3.63-3.70 (m, 1H), 3.92 (d, J = 7.6 Hz, 1H), 4.26 (d, J = 8.8 Hz, 1H), 4.53-4.59 (m, 1H), 7.02-7.06 (m, 3H), 7.14 (d, J = 7.6 Hz, 1H), 7.77-7.81 (m, 1H), 7.84-7.88 (m, 2H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.5, 24.6, 35.0, 49.8, 52.6, 64.5, 65.1, 69.8, 78.2, 122.2, 122.5, 124.6, 127.9, 128.1, 128.6, 133.0, 135.2, 136.4, 137.8, 139.0, 140.4, 173.1, 197.3, 198.4; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{21}NNaO_4S$ $[M+Na]^+$: 442.1083; Found: 442.1087.

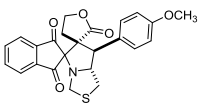


4bj: Light yellow solid, m.p. 245.7-246.5 ^{o}C; yield 79%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.30 (s, 3H), 2.58-2.65 (m, 1H), 2.82-2.88 (m, 1H), 2.90-2.94 (m, 1H), 3.11-3.17 (m, 1H), 3.26-3.31 (m, 1H), 3.55 (d, J = 7.6 Hz, 1H), 3.66-3.72 (m, 1H), 3.95 (d, J = 7.6 Hz, 1H), 4.45-4.51 (m, 1H), 4.77 (d, J = 8.8 Hz, 1H), 7.12-7.15 (m, 3H), 7.41-7.43 (m, 1H), 7.77-7.80 (m, 1H), 7.84-7.89 (m, 2H), 7.98 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.9, 25.5, 35.4, 48.3, 50.1, 63.4, 65.3, 72.7, 78.6, 122.3, 122.5, 124.9, 127.0, 127.2, 130.7, 131.2, 135.1, 136.4, 137.8, 139.2, 140.8, 173.5, 197.5, 198.7; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{21}NNaO_4S$ $[M+Na]^+$: 442.1083; Found: 442.1089.

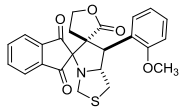


4bk: Light yellow solid, m.p. 234.3-234.6 ^{o}C; yield 81%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.22 (s, 3H), 2.25 (s, 3H), 2.57-2.64 (m, 1H), 2.80-2.85 (m, 1H), 2.89-2.93 (m, 1H), 3.12-3.18 (m, 1H), 3.24-3.29 (m, 1H), 3.54 (d, J = 8.0 Hz, 1H), 3.66-3.72 (m, 1H), 3.95 (d, J = 8.0 Hz, 1H), 4.43-4.49 (m, 1H), 4.72 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.76-7.79 (m, 1H), 7.83-7.88 (m, 2H), 7.97 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.8, 21.0, 26.5, 36.4, 49.2, 51.2, 64.5, 66.3, 73.6, 79.7, 123.3, 123.5, 126.7, 128.1, 129.1, 132.4,

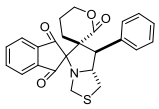
136.1, 137.3, 137.8, 138.6, 140.2, 141.9, 174.6, 198.6, 199.7; HRMS (ESI-TOF) m/z: Calcd. for $C_{25}H_{23}NNaO_4S$ $[M+Na]^+$: 456.1240; Found: 456.1245.



4bl: Light yellow solid, m.p. 237.6-238.9 ^oC; yield 78%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.23-2.31 (m, 1H), 2.80-2.87 (m, 1H), 2.94-2.98 (m, 1H), 3.22-3.27 (m, 2H), 3.54 (d, J = 7.6 Hz, 1H), 3.65-3.69 (m, 1H), 3.71 (s, 3H), 3.92 (d, J = 7.6 Hz, 1H), 4.25 (d, J = 8.2 Hz, 1H), 4.49-4.54 (m, 1H), 6.80 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.77-7.81 (m, 1H), 7.84-7.88 (m, 2H), 7.95-7.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.5, 35.0, 49.8, 52.1, 54.3, 64.5, 65.1, 70.0, 78.2, 113.4, 122.2, 122.5, 124.7, 128.7, 135.2, 136.4, 139.0, 140.4, 158.6, 173.2, 197.3, 198.4; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{21}NNaO_5S$ $[M+Na]^+$: 458.1033; Found: 458.1029.

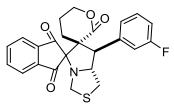


4bm: Light yellow solid, m.p. 232.7-232.9 ^oC; yield 81%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.29-2.33 (m, 1H), 2.74-2.80 (m, 2H), 2.95-2.98 (m, 1H), 3.28-3.33 (m, 1H), 3.53 (d, J = 7.6 Hz, 1H), 3.63 (s, 3H), 3.68-3.71 (m, 1H), 3.95 (d, J = 7.6 Hz, 1H), 4.70-4.75 (m, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.88-6.92 (m, 1H), 7.22-7.26 (m, 1H), 7.39 (d, J = 7.2 Hz, 1H), 7.74-7.77 (m, 1H), 7.83-7.87 (m, 1H), 8.00 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.1, 34.3, 46.3, 49.0, 52.8, 62.2, 64.2, 68.6, 77.1, 108.6, 118.6, 120.9, 121.2, 121.4, 126.4, 127.5, 133.7, 135.2, 138.2, 140.7, 156.4, 169.2, 172.1, 197.1, 198.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{21}NNaO_5S$ $[M+Na]^+$: 458.1033; Found: 458.1036.

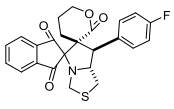


4ca: Light yellow solid, m.p. 248.6-248.9 ^oC; yield 80%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.20-1.22 (m, 1H), 1.28-1.35 (m, 1H), 1.87-1.95 (m, 1H), 2.84-2.91 (m, 1H), 2.92-2.96 (m, 1H), 3.26-3.31 (m, 1H), 3.32-3.38 (m, 1H), 3.53 (d, J = 7.2 Hz, 1H), 3.77-3.82 (m, 1H), 3.91 (d, J = 6.8 Hz, 1H), 4.43 (d, J = 9.2 Hz, 1H), 4.53-4.59 (m, 1H), 7.20-7.30 (m, 5H), 7.73-7.77 (m, 1H), 7.83-7.88 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.8, 23.2, 35.7, 50.2,

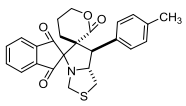
56.4, 67.0, 69.3, 69.9, 81.3, 123.0, 123.6, 128.2, 128.6, 129.0, 134.7, 135.6, 137.3, 140.2, 142.6, 169.4, 198.1, 199.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{21}NNaO_4S$ $[M+Na]^+$: 442.1083; Found: 442.1086.



4cb: Light yellow solid, m.p. 249.6-250.5 ^oC; yield 82%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.22-1.26 (m, 1H), 1.33-1.39 (m, 1H), 1.83-1.90 (m, 1H), 2.85-2.96 (m, 2H), 3.25-3.30 (m, 1H), 3.42-3.47 (m, 1H), 3.52 (d, J = 6.8 Hz, 1H), 3.81-3.84 (m, 1H), 3.90 (d, J = 6.8 Hz, 1H), 4.42-4.50 (m, 2H), 6.93-7.00 (m, 3H), 7.22-7.28 (m, 1H), 7.74-7.78 (m, 1H), 7.83-7.88 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.7, 22.3, 34.5, 49.1, 54.7, 65.7, 68.3, 69.0, 80.1, 114.1 (d, J_{CF} = 21.3 Hz), 114.6 (d, J_{CF} = 22.3 Hz), 122.0, 122.6, 123.4, 123.5, 129.5 (d, J_{CF} = 8.3 Hz), 134.7, 136.3, 139.2, 141.4, 161.9 (d, J_{CF} = 246.4 Hz), 168.1, 196.8, 198.0; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{20}FNNaO_4S$ $[M+Na]^+$: 460.0989; Found: 460.0989.

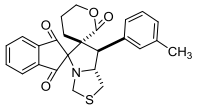


4cc: Light yellow solid, m.p. 242.5-243.8 ^oC; yield 82%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.22-1.24 (m, 1H), 1.31-1.38 (m, 1H), 1.82-1.90 (m, 1H), 2.84-2.94 (m, 2H), 3.24-3.29 (m, 1H), 3.38-3.44 (m, 1H), 3.52 (d, J = 7.2 Hz, 1H), 3.79-3.84 (m, 1H), 3.90 (d, J = 7.2 Hz, 1H), 4.41 (d, J = 9.2 Hz, 1H), 4.46-4.52 (m, 1H), 6.96-7.00 (m, 2H), 7.18-7.22 (m, 2H), 7.74-7.78 (m, 1H), 7.83-7.88 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.7, 21.1, 33.5, 48.1, 53.6, 64.8, 67.5, 67.9, 79.1, 113.8 (d, J_{CF} = 21.2 Hz), 121.0, 121.5, 128.2 (d, J_{CF} = 7.3 Hz), 133.6, 135.3, 138.2, 140.4, 160.4 (d, J_{CF} = 246.2 Hz), 167.2, 195.9, 197.0; HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{20}FNNaO_4S$ $[M+Na]^+$: 460.0989; Found: 460.0995.

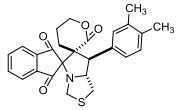


4cd: Light yellow solid, m.p. 237.9-238.1 ^oC; yield 75%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.22-1.24 (m, 1H), 1.30-1.35 (m, 1H), 1.88-1.92 (m, 1H), 2.26 (s, 3H), 2.82-2.88 (m, 1H), 2.91-2.95 (m, 1H), 3.24-3.29 (m, 1H), 3.34-3.40 (m, 1H), 3.52 (d, J = 7.2 Hz, 1H), 3.77-3.81 (m,

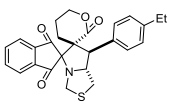
1H), 3.90 (d, *J* = 7.2 Hz, 1H), 4.40 (d, *J* = 9.2 Hz, 1H), 4.50-4.55 (m, 1H), 7.06-7.11 (m, 4H), 7.73-7.76 (m, 1H), 7.82-7.87 (m, 2H), 7.95 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 21.8, 23.2, 35.7, 50.2, 56.2, 67.0, 69.4, 69.9, 81.3, 123.0, 123.5, 128.5, 129.7, 131.5, 135.5, 137.2, 138.0, 140.2, 142.6, 169.5, 198.1, 199.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{25}H_{23}NNaO_4S$ $[M+Na]^+$: 456.1240; Found: 456.1241.



4ce: Light yellow solid, m.p. 248.1-249.2 ^{o}C; yield 80%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.21-1.26 (m, 1H), 1.31-1.35 (m, 1H), 1.89-1.96 (m, 1H), 2.26 (s, 3H), 2.83-2.89 (m, 1H), 2.92-2.96 (m, 1H), 3.25-3.30 (m, 1H), 3.34-3.39 (m, 1H), 3.52 (d, *J* = 7.2 Hz, 1H), 3.79-3.81 (m, 1H), 3.91 (d, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 9.2 Hz, 1H), 4.51-4.57 (m, 1H), 7.01-7.05 (m, 3H), 7.14-7.19 (m, 1H), 7.73-7.77 (m, 1H), 7.82-7.87 (m, 2H), 7.95 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 20.5, 20.8, 22.2, 34.7, 49.2, 55.4, 66.0, 68.4, 68.9, 80.3, 122.0, 122.5, 124.6, 127.8, 127.9, 128.4, 133.5, 134.5, 136.2, 137.7, 139.2, 141.6, 168.4, 197.1, 198.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{25}H_{23}NNaO_4S$ $[M+Na]^+$: 456.1240; Found: 456.1243.

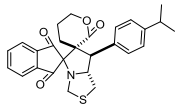


4cf: Light yellow solid, m.p. 234.4-235.9 ^{o}C; yield 81%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.24-1.28 (m, 1H), 1.31-1.36 (m, 1H), 1.90-1.97 (m, 1H), 2.16 (s, 6H), 2.82-2.88 (m, 1H), 2.91-2.95 (m, 1H), 3.24-3.29 (m, 1H), 3.35-3.41 (m, 1H), 3.52 (d, *J* = 6.8 Hz, 1H), 3.77-3.82 (m, 1H), 3.90 (d, *J* = 6.8 Hz, 1H), 4.36 (d, *J* = 9.2 Hz, 1H), 4.49-4.55 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.72-7.76 (m, 1H), 7.82-7.87 (m, 2H), 7.95 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 18.4, 18.9, 20.8, 22.2, 34.7, 49.2, 55.2, 66.0, 68.4, 68.9, 80.3, 122.0, 122.5, 124.9, 128.9, 129.1, 130.9, 134.5, 135.6, 136.2, 139.2, 141.6, 168.5, 197.2, 198.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{26}H_{25}NNaO_4S$ $[M+Na]^+$: 470.1397; Found: 470.1395.

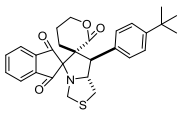


4cg: Light yellow solid, m.p. 236.1-236.7 ^{o}C; yield 75%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz)

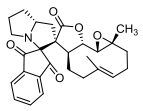
δ: 1.13-1.19 (m, 3H), 1.20-1.24 (m, 1H), 1.28-1.34 (m, 1H), 1.89-1.93 (m, 1H), 2.53-2.59 (m, 2H), 2.82-2.88 (m, 1H), 2.92-2.96 (m, 1H), 3.24-3.29 (m, 1H), 3.32-3.38 (m, 1H), 3.52 (d, J = 7.2 Hz, 1H), 3.78-3.80 (m, 1H), 3.90 (d, J = 7.2 Hz, 1H), 4.40 (d, J = 9.2 Hz, 1H), 4.51-4.57 (m, 1H), 7.09-7.14 (m, 4H), 7.72-7.76 (m, 1H), 7.82-7.87 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.4, 20.8, 22.2, 27.4, 34.7, 49.2, 55.2, 66.0, 68.4, 68.9, 80.3, 122.0, 122.5, 127.1, 127.4, 127.5, 129.4, 130.7, 134.5, 136.2, 139.2, 141.6, 143.2, 168.5, 197.1, 198.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{26}H_{25}NNaO_4S$ $[M+Na]^+$: 470.1397; Found: 470.1395.



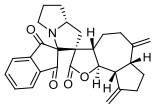
4ch: Light yellow solid, m.p. 240.8-241.5 ^{o}C; yield 81%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (s, 3H), 1.17 (s, 3H), 1.22-1.24 (m, 1H), 1.30-1.34 (m, 1H), 1.88-1.95 (m, 1H), 2.80-2.87 (m, 2H), 2.92-2.96 (m, 1H), 3.25-3.30 (m, 1H), 3.32-3.37 (m, 1H), 3.52 (d, J = 6.8 Hz, 1H), 3.78-3.81 (m, 1H), 3.91 (d, J = 7.2 Hz, 1H), 4.40 (d, J = 9.2 Hz, 1H), 4.51-4.57 (m, 1H), 7.13 (s, 4H), 7.72-7.76 (m, 1H), 7.82-7.87 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.8, 22.2, 22.9, 32.7, 34.7, 49.2, 55.2, 66.0, 68.4, 68.9, 80.3, 122.0, 122.5, 126.0, 127.5, 130.8, 134.5, 136.2, 139.2, 141.6, 147.9, 168.5, 197.1, 198.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{27}H_{27}NNaO_4S$ $[M+Na]^+$: 484.1553; Found: 484.1549.



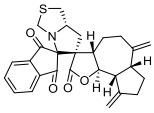
4ci: Light yellow solid, m.p. 246.2-246.7 ^{o}C; yield 75%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18-1.23 (m, 10H), 1.30-1.38 (m, 1H), 1.88-1.97 (m, 1H), 2.84-2.87 (m, 1H), 2.92-2.96 (m, 1H), 3.24-3.26 (m, 2H), 3.52 (d, J = 6.8 Hz, 1H), 3.78-3.81 (m, 1H), 3.90 (d, J = 6.8 Hz, 1H), 4.40 (d, J = 9.2 Hz, 1H), 4.51-4.57 (m, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.73-7.76 (m, 1H), 7.82-7.87 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.8, 22.2, 30.2, 33.5, 34.7, 49.2, 55.1, 66.0, 68.4, 68.9, 80.3, 122.0, 122.5, 124.8, 127.2, 130.4, 134.5, 136.2, 139.2, 141.6, 150.2, 168.5, 197.1, 198.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{29}NNaO_4S$ $[M+Na]^+$: 498.1710; Found: 498.1714.



4da: Light yellow solid, m.p. 243.7-244.5 ^{o}C; yield 81%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.10 (m, 1H), 1.22 (s, 3H), 1.59-1.64 (m, 4H), 1.87-2.13 (m, 6H), 2.25-2.47 (m, 6H), 2.55 (d, J = 8.8 Hz, 1H), 2.71-2.76 (m, 1H), 3.06-3.11 (m, 1H), 3.73-3.77 (m, 1H), 3.82-3.85 (m, 1H), 5.13 (d, J = 10.0 Hz, 1H), 7.73-7.77 (m, 1H), 7.80-7.84 (m, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.1, 15.0, 19.0, 22.3, 28.1, 30.8, 33.8, 34.8, 44.3, 49.6, 58.3, 59.9, 63.8, 64.1, 64.7, 77.1, 78.2, 121.1, 123.2, 133.0, 133.3, 135.0, 138.5, 140.5, 169.1, 171.8, 198.8, 198.9; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{31}NNaO_5$ $[M+Na]^+$: 484.2089; Found: 484.2084.

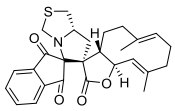


4ea: Light yellow solid, m.p. 240.3-241.1 ^{o}C; yield 79%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.42-1.46 (m, 1H), 1.69-1.75 (m, 1H), 1.83-1.92 (m, 4H), 2.05-2.13 (m, 2H), 2.27-2.51 (m, 7H), 2.58-2.62 (m, 1H), 2.69-2.73 (m, 1H), 2.78-2.86 (m, 2H), 3.77-3.82 (m, 2H), 4.71 (s, 1H), 4.83 (s, 1H), 4.91 (d, J = 12.8 Hz, 1H), 7.71-7.75 (m, 1H), 7.79-7.83 (m, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.8, 18.6, 26.4, 27.8, 29.8, 30.1, 34.6, 44.0, 44.5, 48.0, 49.0, 57.9, 63.4, 76.6, 79.9, 107.6, 109.0, 120.6, 120.8, 132.9, 134.5, 138.1, 140.1, 148.3, 148.6, 168.7, 172.1, 198.7, 198.8; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{30}NO_4$ $[M+H]^+$: 444.2169; Found: 444.2175.

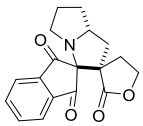


4eb: Light yellow solid, m.p. 241.1-241.9 ^{o}C; yield 78%, >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34-1.44 (m, 1H), 1.68-1.75 (m, 1H), 1.84-1.93 (m, 1H), 2.02-2.09 (m, 1H), 2.27-2.51 (m, 6H), 2.59-2.63 (m, 1H), 2.79-2.88 (m, 2H), 2.95-2.98 (m, 1H), 3.27-3.32 (m, 1H), 3.41-3.43 (m, 1H), 3.77-3.82 (m, 1H), 3.91-3.94 (m, 1H), 4.01-4.09 (m, 1H), 4.73 (s, 1H), 4.85 (s, 1H), 4.91 (d, J = 5.6 Hz, 2H), 7.73-7.77 (m, 1H), 7.81-7.89 (m, 2H), 7.95-7.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.6, 28.7, 31.2, 33.3, 35.7, 37.1, 46.0, 49.4, 49.9, 50.3, 64.3, 67.7, 77.9, 81.3, 109.2,

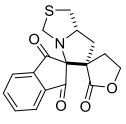
110.7, 122.3, 122.4, 134.5, 136.1, 139.5, 141.9, 149.5, 149.8, 173.0, 197.7, 199.1; HRMS (ESI-TOF) m/z: Calcd. for $C_{27}H_{27}NNaO_4S$ $[M+Na]^+$: 484.1548; Found: 484.1542.



4fa: Light yellow solid, m.p. 248.3-249.1 ^oC; yield 73%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (s, 3H), 1.59 (s, 3H), 1.63-1.66 (m, 1H), 1.84-1.88 (m, 1H), 2.09-2.23 (m, 5H), 2.28-2.33 (m, 1H), 2.44-2.49 (m, 1H), 2.52-2.57 (m, 1H), 2.95-3.03 (m, 2H), 3.30-3.35 (m, 1H), 3.43 (d, J = 8.0 Hz, 1H), 3.96 (d, J = 8.0 Hz, 1H), 4.10-4.14 (m, 1H), 4.40 (d, J = 10.0 Hz, 1H), 4.51-4.56 (m, 1H), 4.77 (d, J = 10.4 Hz, 1H), 7.73-7.77 (m, 1H), 7.81-7.84 (m, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.3, 17.3, 23.4, 26.2, 34.4, 38.4, 39.6, 40.3, 50.9, 53.9, 66.3, 68.9, 79.3, 123.4, 126.6, 126.8, 135.5, 137.1, 137.8, 140.5, 140.7, 143.1, 174.4, 198.7, 199.8; HRMS (ESI-TOF) m/z: Calcd. for $C_{27}H_{29}NNaO_4S$ $[M+Na]^+$: 486.1710; Found: 486.1713.



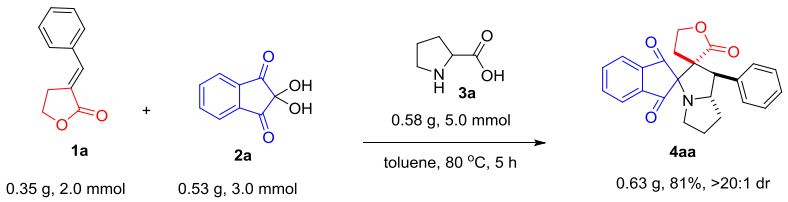
4ga: Light yellow solid, m.p. 249.6-250.1 ^oC; yield 80%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.93-2.06 (m, 4H), 2.11-2.22 (m, 2H), 2.48-2.57 (m, 2H), 2.69-2.73 (m, 1H), 2.93-3.00 (m, 1H), 3.90-4.01 (m, 2H), 4.10-4.16 (m, 1H), 7.74-7.78 (m, 1H), 7.80-7.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.2, 31.3, 31.6, 40.1, 46.6, 60.7, 64.9, 66.0, 77.7, 123.1, 123.2, 135.9, 137.1, 140.2, 141.3, 174.9, 200.3, 200.5; HRMS (ESI-TOF) m/z: Calcd. for $C_{18}H_{17}NNaO_4$ $[M+Na]^+$: 334.1050; Found: 334.1048.



4gb: Light yellow solid, m.p. 252.7-253.3 ^oC; yield 81%, >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.87-2.06 (m, 4H), 2.11-2.22 (m, 2H), 2.48-2.57 (m, 2H), 2.69-2.73 (m, 1H), 2.93-3.00 (m, 1H), 3.90-4.01 (m, 2H), 4.10-4.16 (m, 1H), 7.74-7.78 (m, 1H), 7.80-7.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.8, 37.1, 39.1, 50.7, 60.8, 65.9, 68.2, 77.8, 123.2, 123.4, 136.1, 137.3, 140.2, 141.7, 174.3, 198.4, 199.8; HRMS (ESI-TOF) m/z: Calcd. for $C_{17}H_{15}NNaO_4S$ $[M+Na]^+$: 352.0614;

Found: 352.0611.

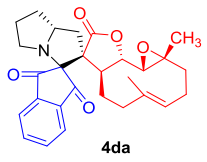
6. Scheme S1: gram scale synthesis of the products 4aa



In a sealed tube equipped with a magnetic stirring bar, to 20 mL of toluene was added 3-benzylidenebutyrolactone **1a** (0.35 g, 2.0 mmol), ninhydrin **2a** (0.53 g, 3.0 mmol) and proline **3a** (0.58 g, 5.0 mmol). The reaction mixture was stirred at 80 °C for 5 h. After completion of the reaction, as indicated by TLC, purification by flash column chromatography (hexane/EtOAc, 5/1, v/v) was carried out to furnish the hybrid **4aa** (0.63 g, 81%, >20:1 dr).

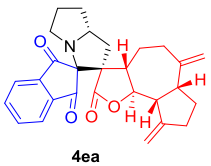
7. General experimental procedures for *in vitro* cytotoxicity assay

Two human cancer cell lines, K562 and A549 were purchased from Chinese Academy of Sciences. All the cells were cultured in RPMI-1640 medium (GIBICO, USA), supplemented with 10% fetal bovine serum (Hyclone, USA) and Penicillin-Streptomycin (respectively 100 U/mL) in 5% CO_2 at 37℃. The cytotoxicity assay was performed according to the MTT (3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide) method in 96-well microplates. Briefly, 5000 cells were seeded into each well of 96-well cell culture plates and allowed to grow for 24 h before drug addition. The K562 tumor cell line was exposed to test compounds **4** at the concentrations of 10, 20, 40, 80, and 100 μmol·L^{-1} in triplicates for 48 h, comparable to cisplatin (Aladdin, China). Then the MTT reagent was added to reaction with the cancer cells for 4 hours. At least, measure the OD value at 490 wavelengths. IC_{50} of all the compounds were calculated by IBM SPSS Statistics (version 19).



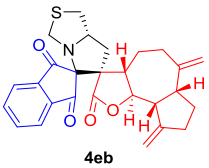
4da

A549 IC_{50} 41.23 μM,
K562 IC_{50} 18.81 μM



4ea

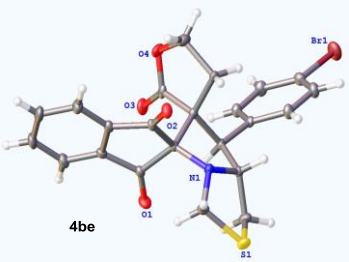
A549 IC_{50} 38.71 μM,
K562 IC_{50} 27.17 μM

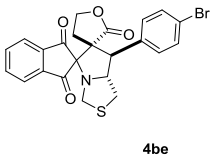


4eb

A549 IC_{50} >100.0 μM,
K562 IC_{50} >100.0 μM

8. X-ray crystal data for compounds 4be and 4ea



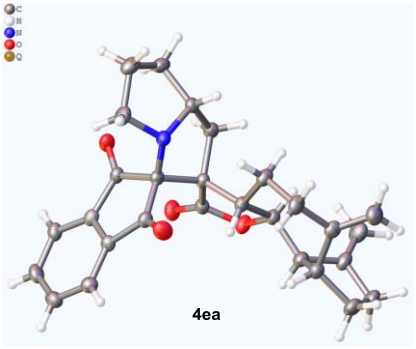


4be

Table S2 Crystal data and structure refinement for 4be

Identification code	**4be**
Empirical formula	$C_{24}H_{19}BrCl_3NO_4S$
Formula weight	603.72
Temperature/K	199.99(10)
Crystal system	triclinic
Space group	P-1
a/Å, b/Å, c/Å	10.2738(9), 11.6678(9), 12.4456(9)
α/°, β/°, γ/°,	99.949(6), 109.200(7), 108.757(7).
Volume/Å^3	1267.71(19)
Z	2
ρ_{calc}g/cm^3	1.582
μ/mm^{-1}	2.051
F(000)	608.0
Radiation	MoKα (λ = 0.71073)
Crystal size/mm^3	0.14 × 0.13 × 0.12
2Θ range for data collection/°	4.42 to 49.986
Index ranges	-12 ≤ h ≤ 10, -12 ≤ k ≤ 13, -14 ≤ l ≤ 14
Reflections collected	8237
Independent reflections	4445 [R_{int} = 0.0301, R_{sigma} = 0.0545]
Data/restraints/parameters	4445/0/271
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0451, wR_2 = 0.1218
Final R indexes [all data]	R_1 = 0.0589, wR_2 = 0.1288
Largest diff. peak/hole / e Å^{-3}	0.54/-0.47

Crystal Data for $C_{24}H_{19}BrCl_3NO_4S$ (*M* =603.72 g/mol): triclinic, space group P-1 (no. 2), *a* = 10.2738(9) Å, *b* = 11.6678(9) Å, *c* = 12.4456(9) Å, *α* = 99.949(6) °, *β* = 109.200(7) °, *γ* = 108.757(7) °, *V* = 1267.71(19) Å^3, *Z* = 2, *T* = 199.99(10) K, μ(MoKα) = 2.051 mm^{-1}, *Dcalc* = 1.582 g/cm^3, 8237 reflections measured (4.42° ≤ 2Θ ≤ 49.986°), 4445 unique (R_{int} = 0.0301, R_{sigma} = 0.0545) which were used in all calculations. The final R_1 was 0.0451 (I > 2σ(I)) and wR_2 was 0.1288 (all data).



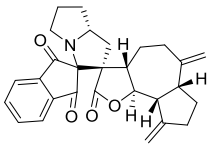


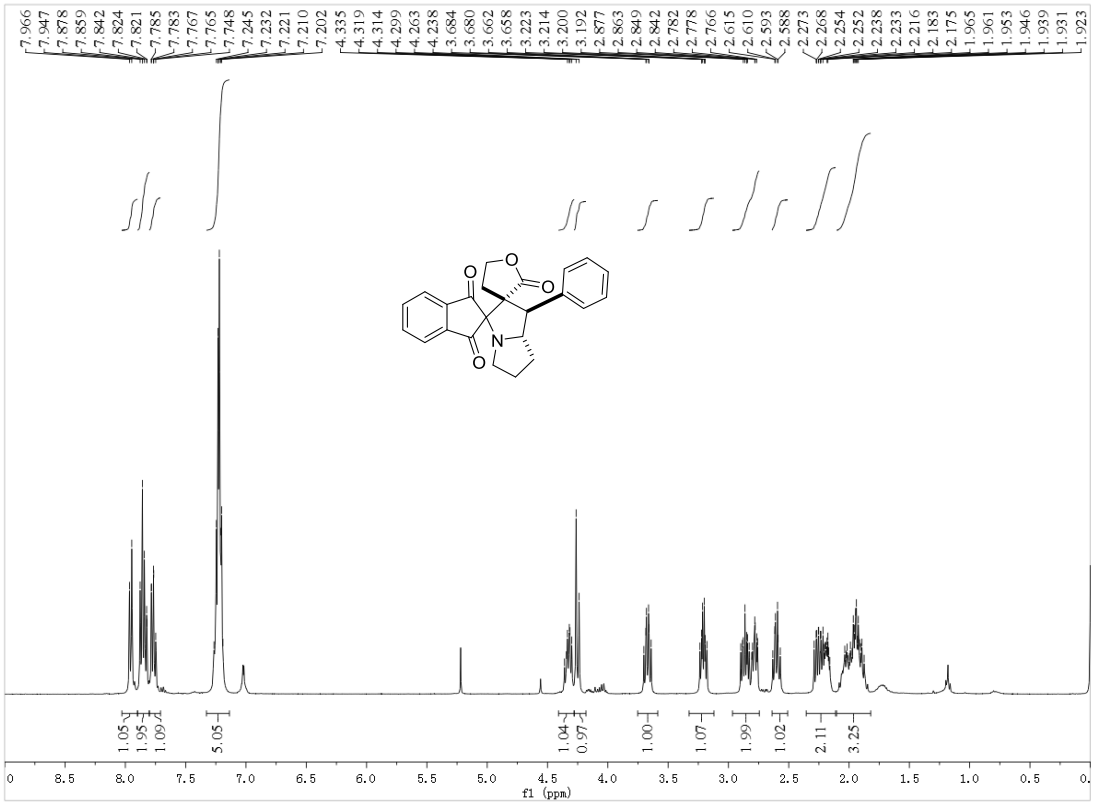
Table S3 Crystal data and structure refinement for 4ea

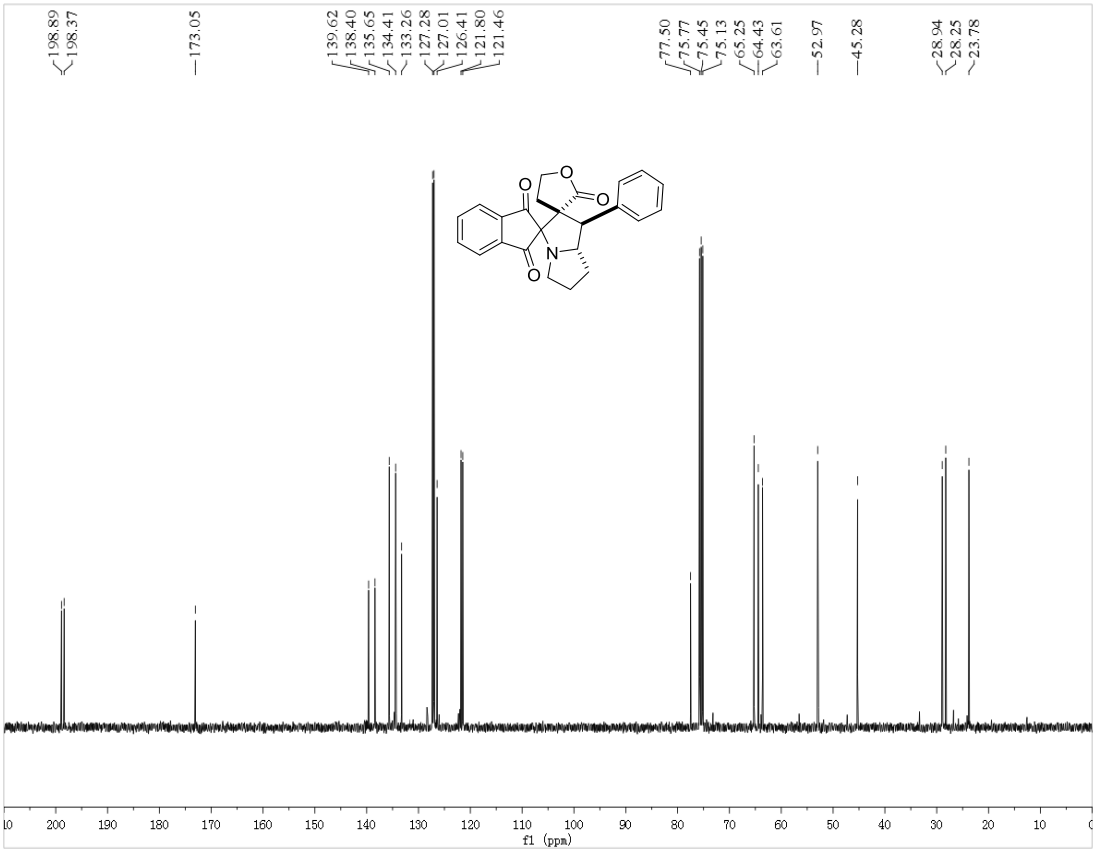
Identification code	**4ea**
Empirical formula	$C_{28}H_{29}NO_4$
Formula weight	443.52
Temperature/K	169.99(10)
Crystal system	tetragonal
Space group	$P4_12_12$
a/Å, b/Å, c/Å	8.1259(2), 8.1259(2), 67.712(2)
α/°, β/°, γ/°,	90, 90, 90.
Volume/Å^3	4471.0(3)
Z	8
ρ_{calc}g/cm^3	1.318
μ/mm^{-1}	0.702
F(000)	1888.0
Radiation	Cu Kα (λ = 1.54184)
Crystal size/mm^3	0.15 × 0.13 × 0.102
2Θ range for data collection/°	5.22 to 150.586
Index ranges	-6 ≤ h ≤ 9, -9 ≤ k ≤ 9, -84 ≤ l ≤ 78
Reflections collected	30219
Independent reflections	4505 [R_{int} = 0.0628, R_{sigma} = 0.0316]
Data/restraints/parameters	4505/0/315
Goodness-of-fit on F^2	1.241
Final R indexes [I>=2σ (I)]	R_1 = 0.0614, wR_2 = 0.1119
Final R indexes [all data]	R_1 = 0.0638, wR_2 = 0.1129
Largest diff. peak/hole / e Å^{-3}	0.26/-0.24
Flack/Hooft parameter	-0.05(11)/-0.04(10)

Crystal Data for $C_{28}H_{29}NO_4$ (*M* =443.52 g/mol): tetragonal, space group $P4_12_12$ (no. 92), *a* = 8.1259(2) Å, *c* = 67.712(2) Å, *V* = 4471.0(3) Å^3, *Z* = 8, *T* = 169.99(10) K, μ(CuKα) = 0.702 mm^{-1}, *Dcalc* = 1.318 g/cm^3, 30219 reflections measured (5.22° ≤ 2Θ ≤ 150.586°), 4505 unique (R_{int} = 0.0628, R_{sigma} = 0.0316) which were used in all calculations. The final R_1 was 0.0614 (I > 2σ(I)) and wR_2 was 0.1129 (all data).

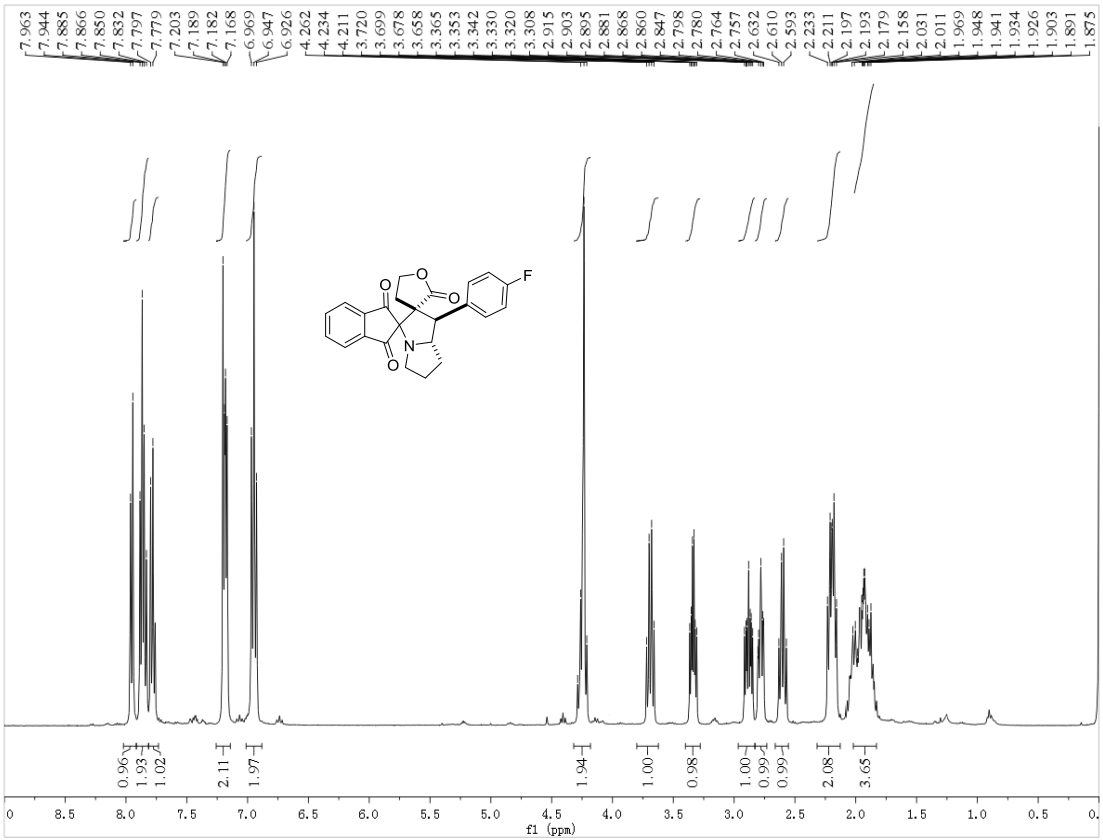
9. The copies of 1H NMR and 13C NMR spectra for compounds 4

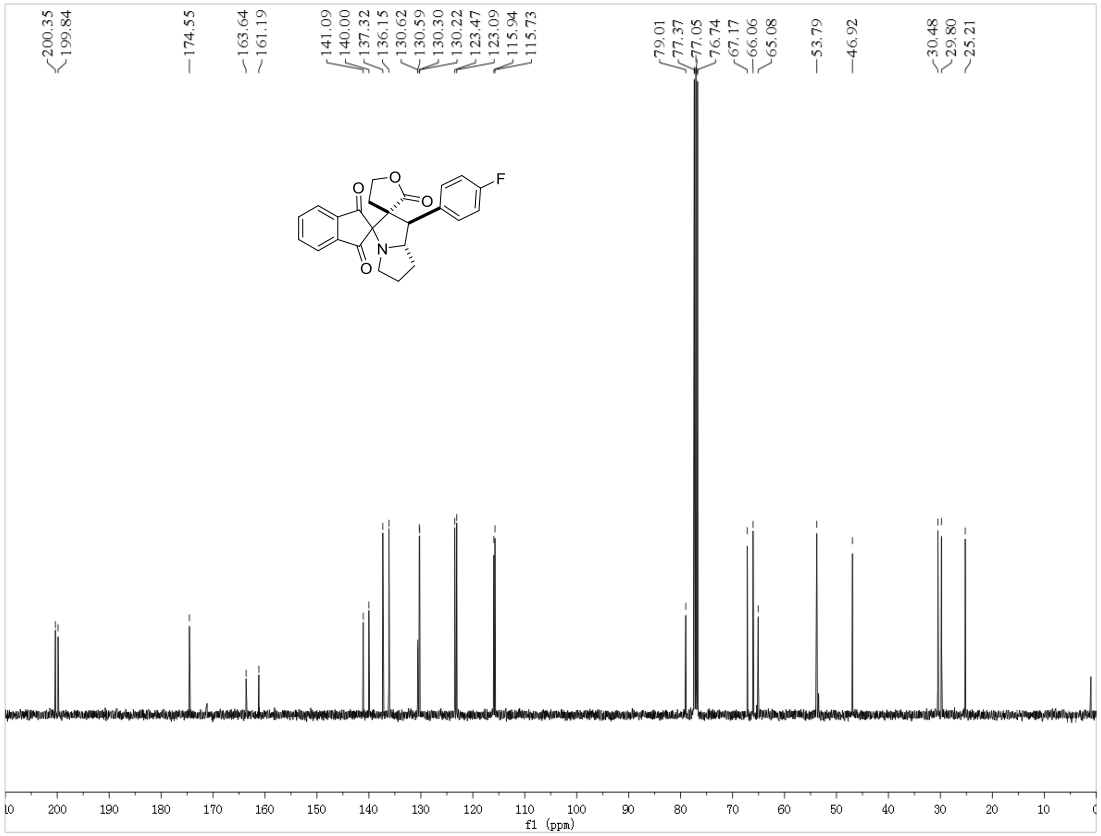
^{1}H and ^{13}C NMR of 4aa



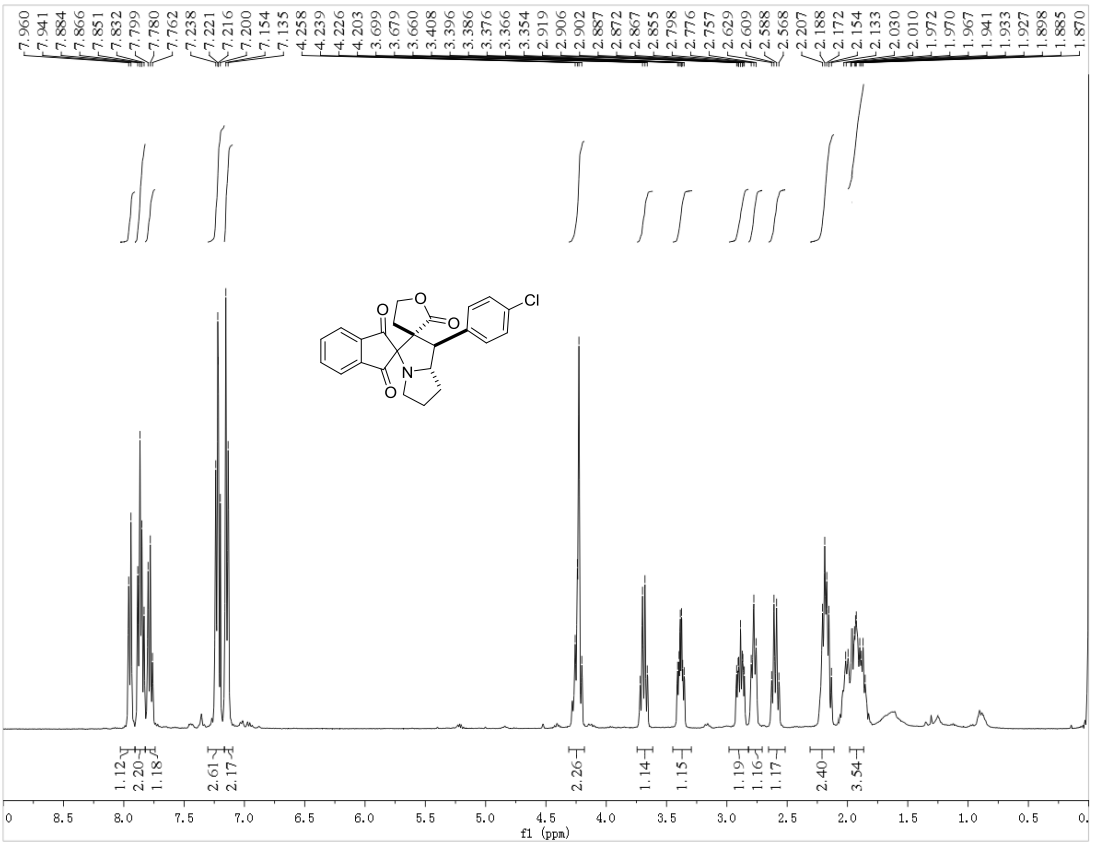


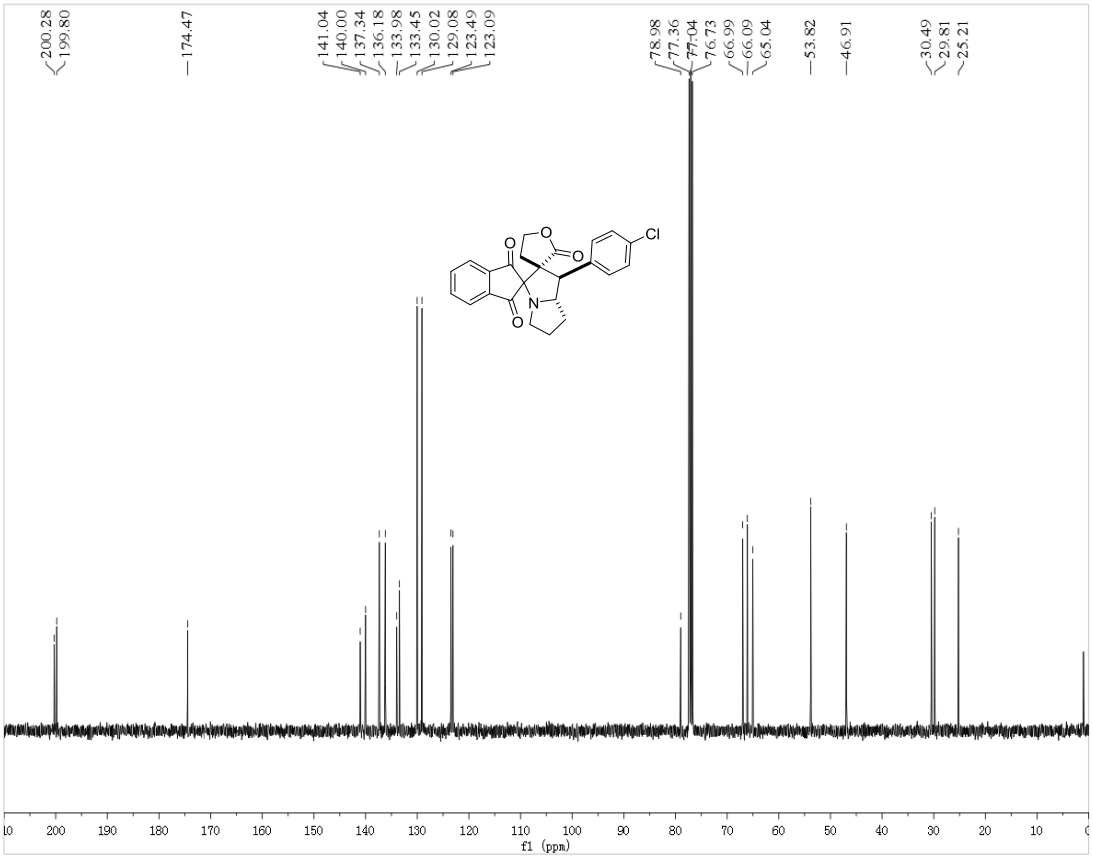
^{1}H and ^{13}C NMR of 4ab



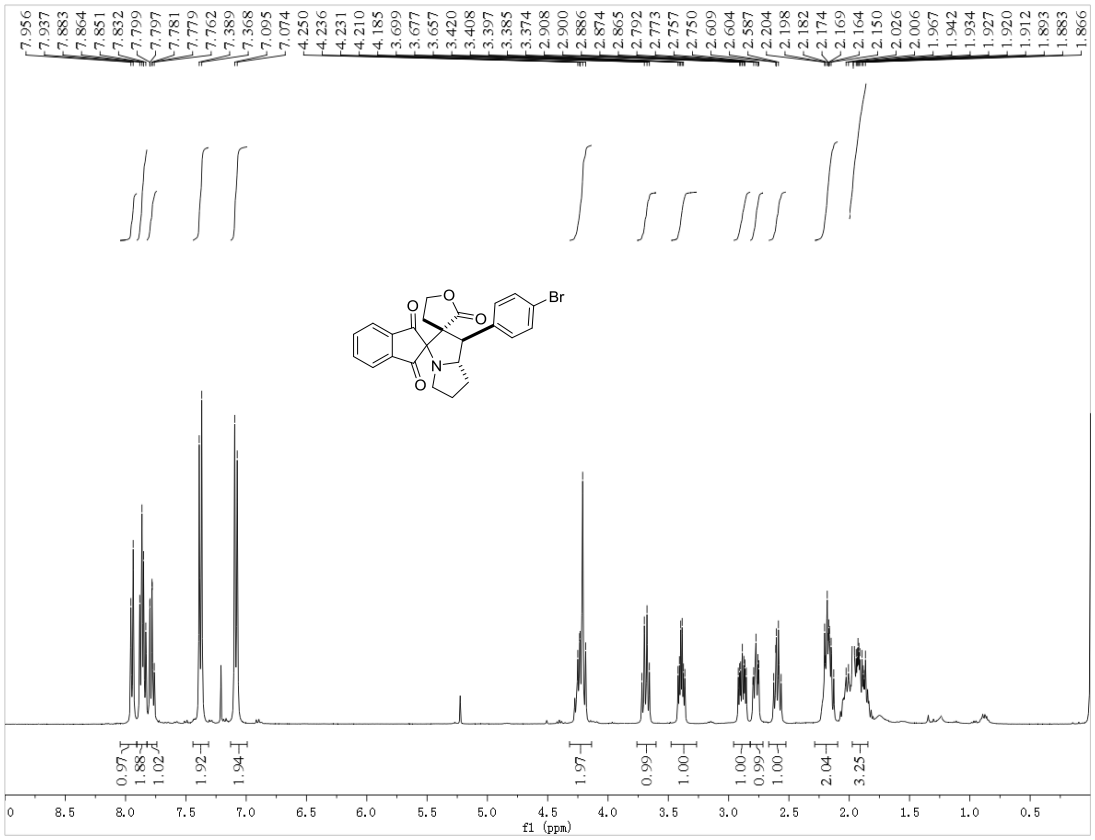


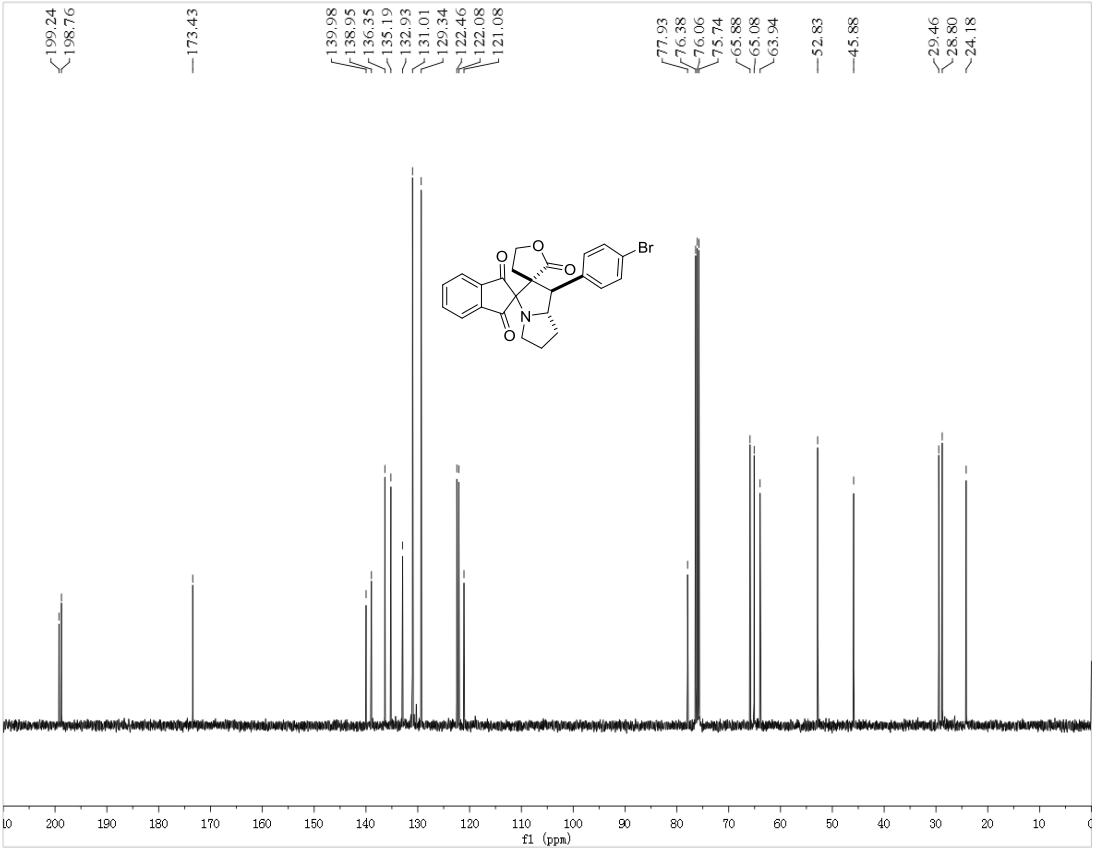
^{1}H and ^{13}C NMR of 4ac



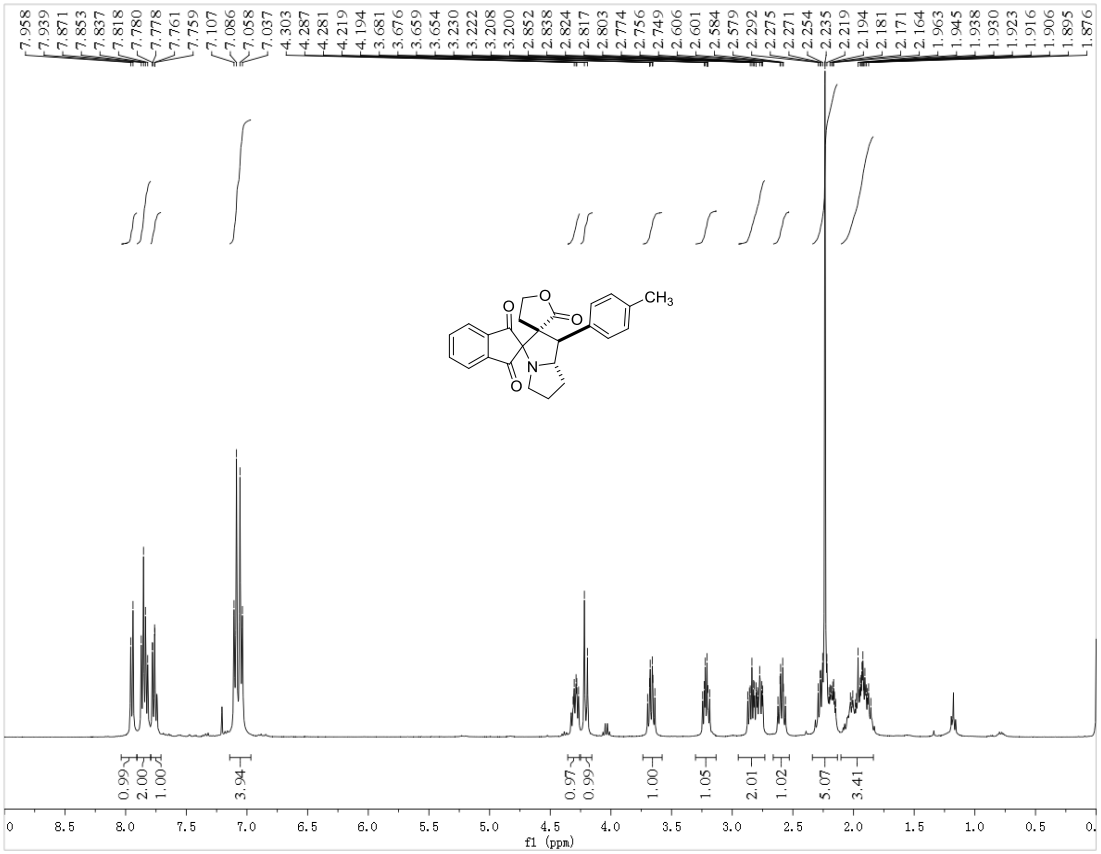


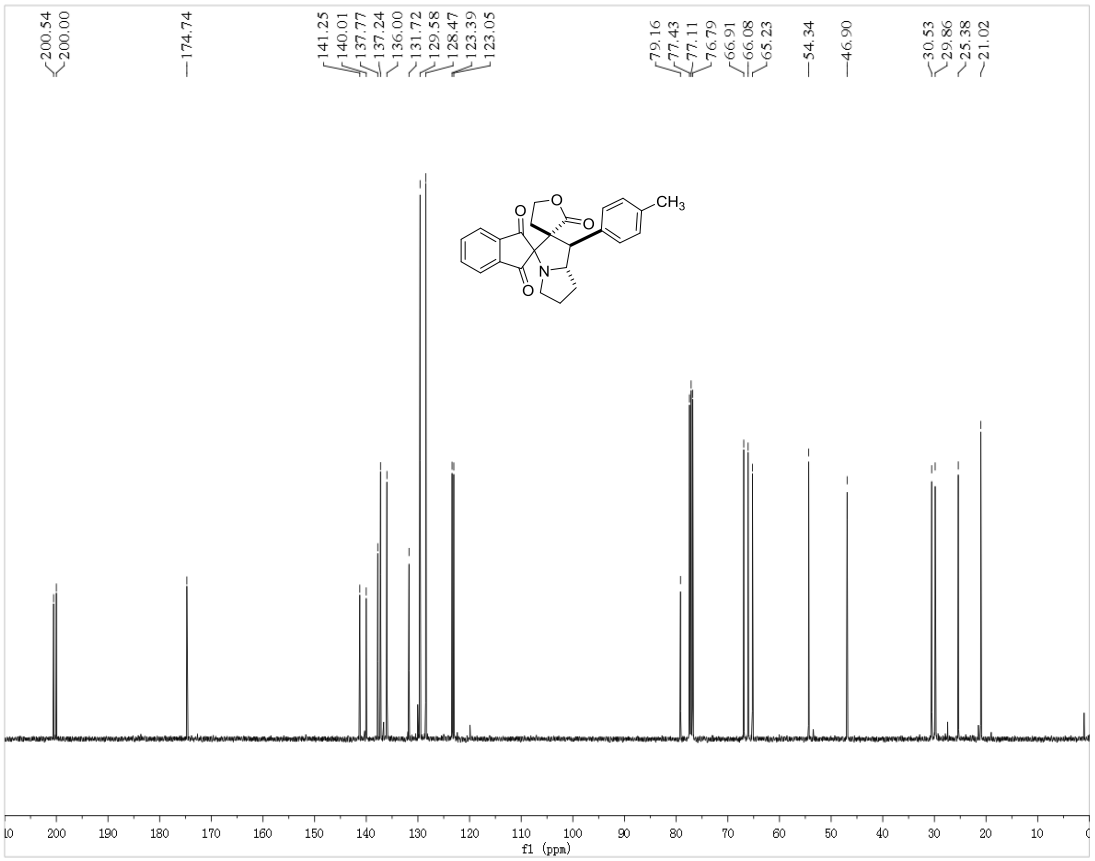
^{1}H and ^{13}C NMR of 4ad



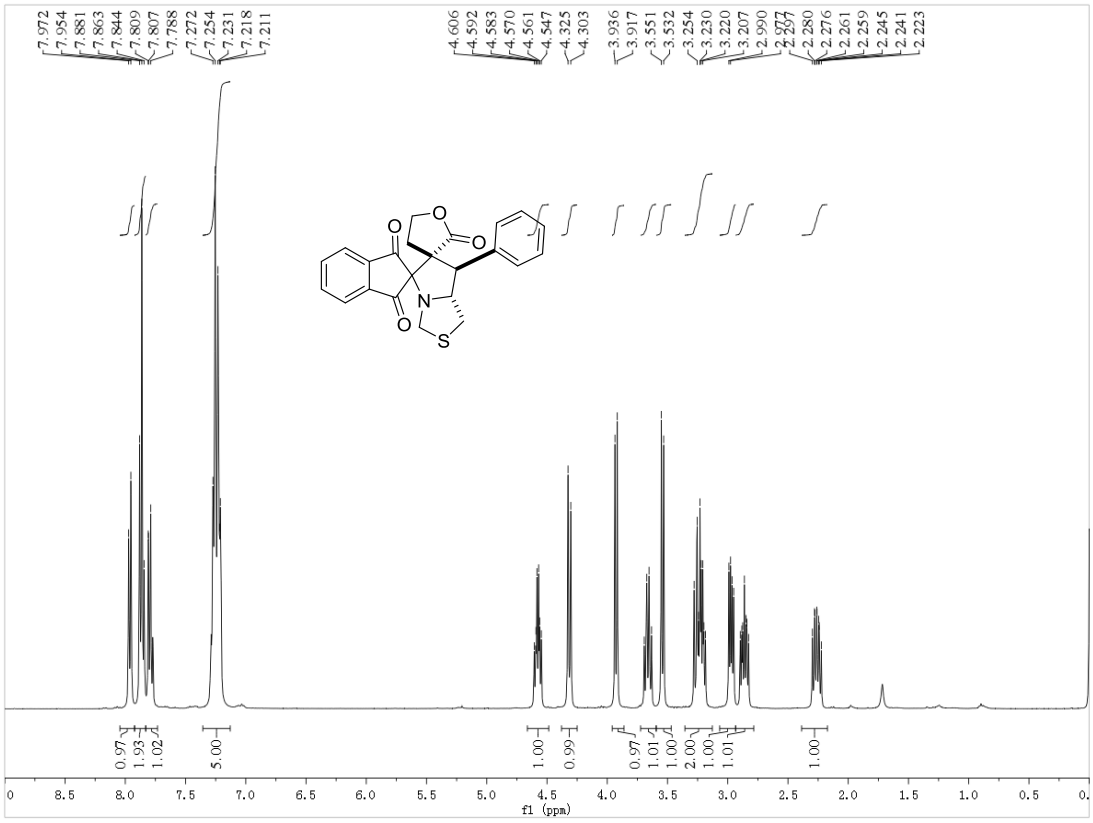


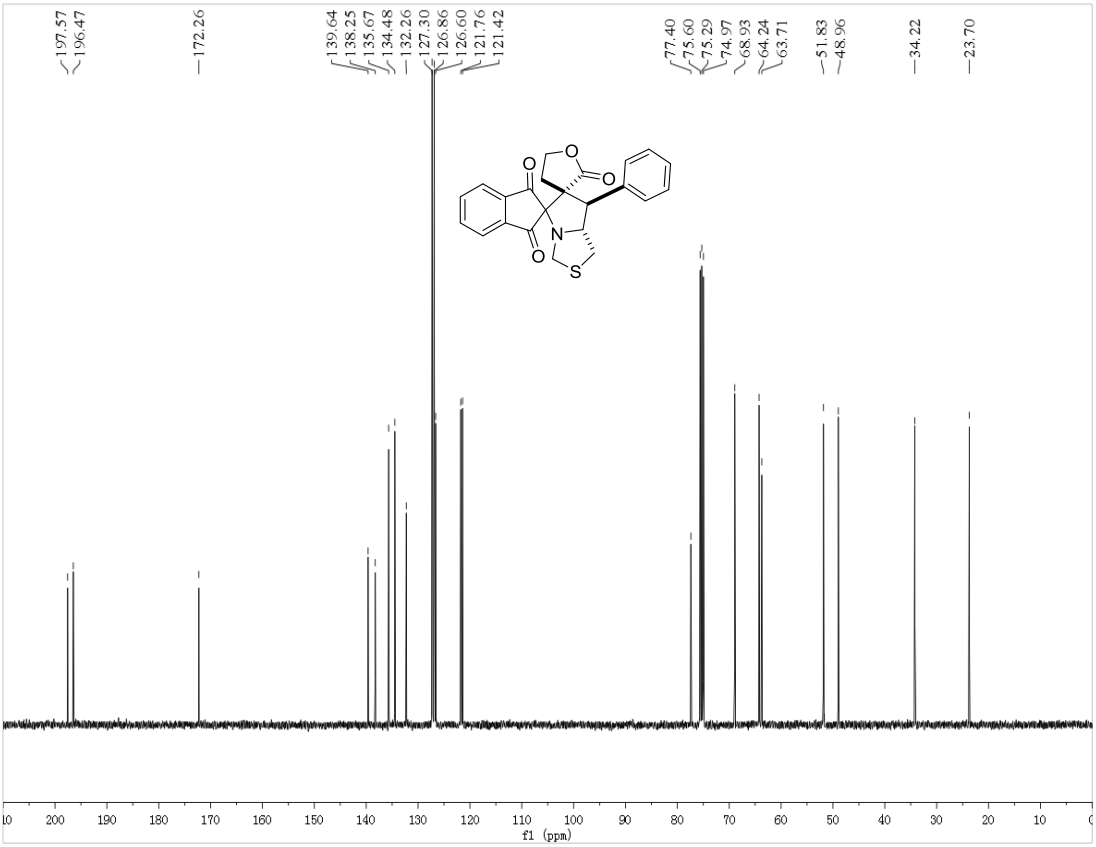
^{1}H and ^{13}C NMR of 4ae



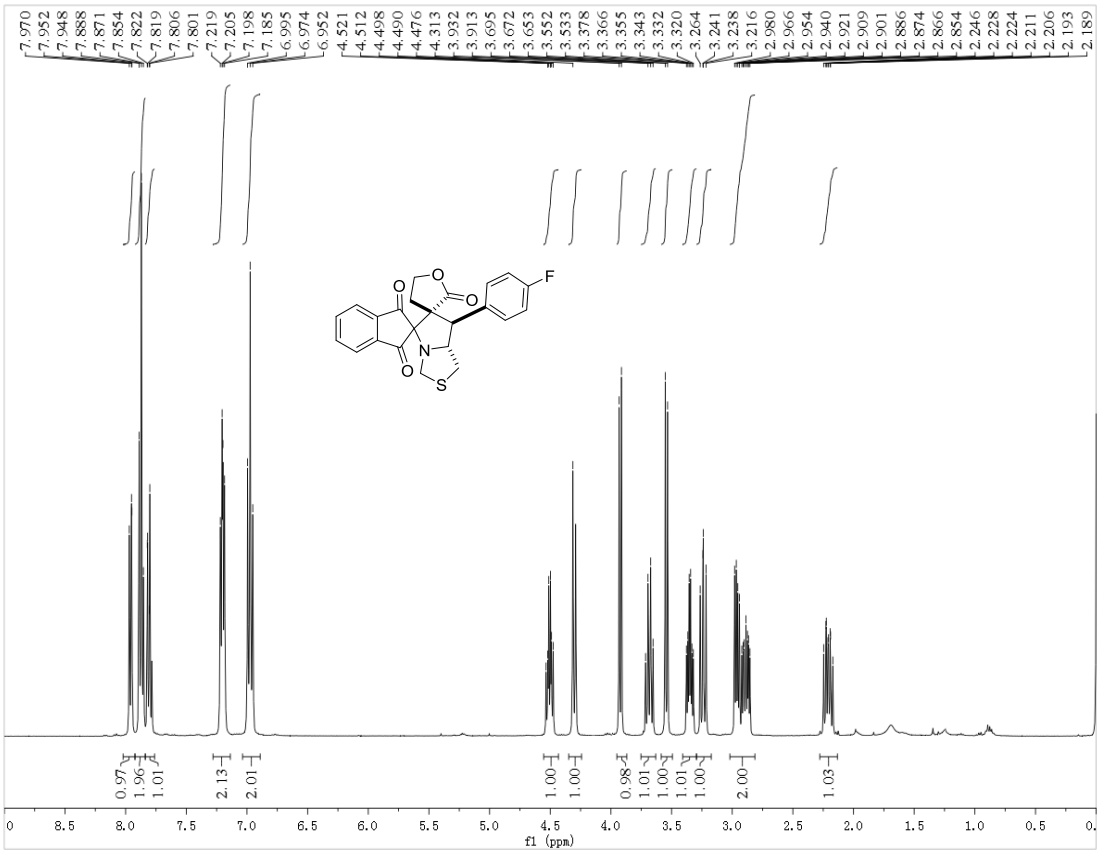


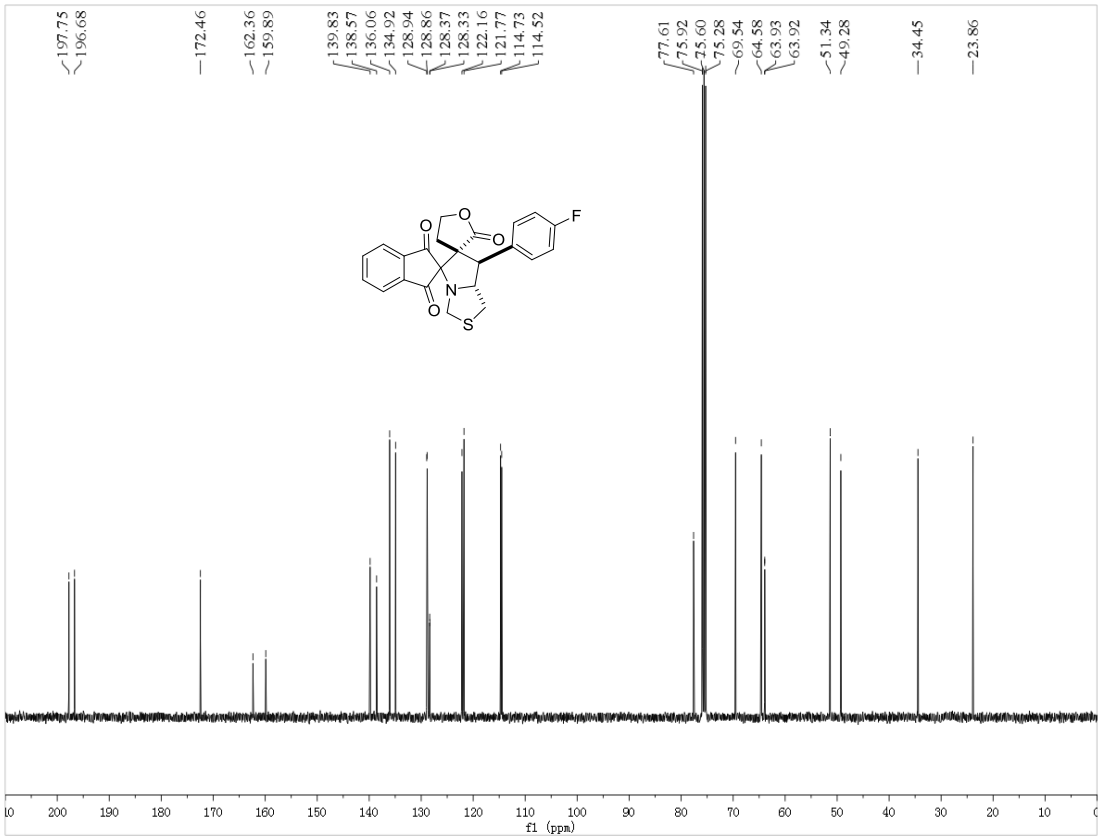
^{1}H and ^{13}C NMR of 4ba



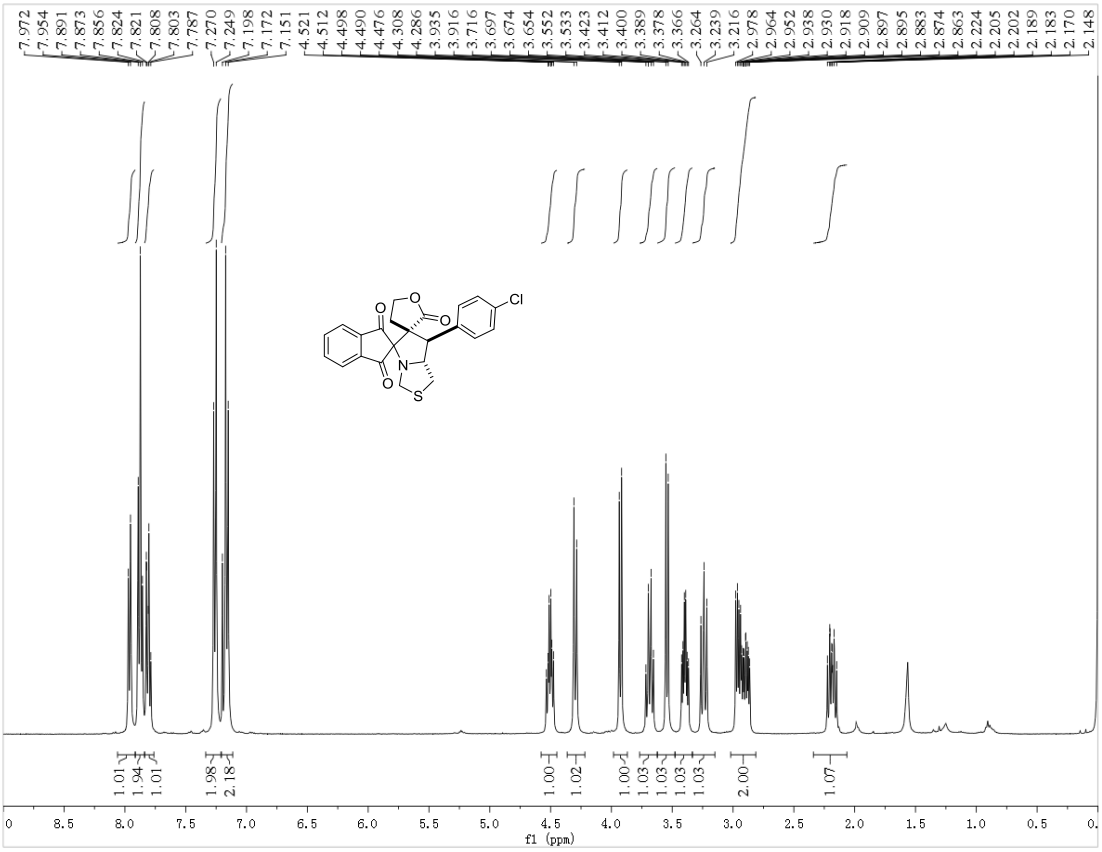


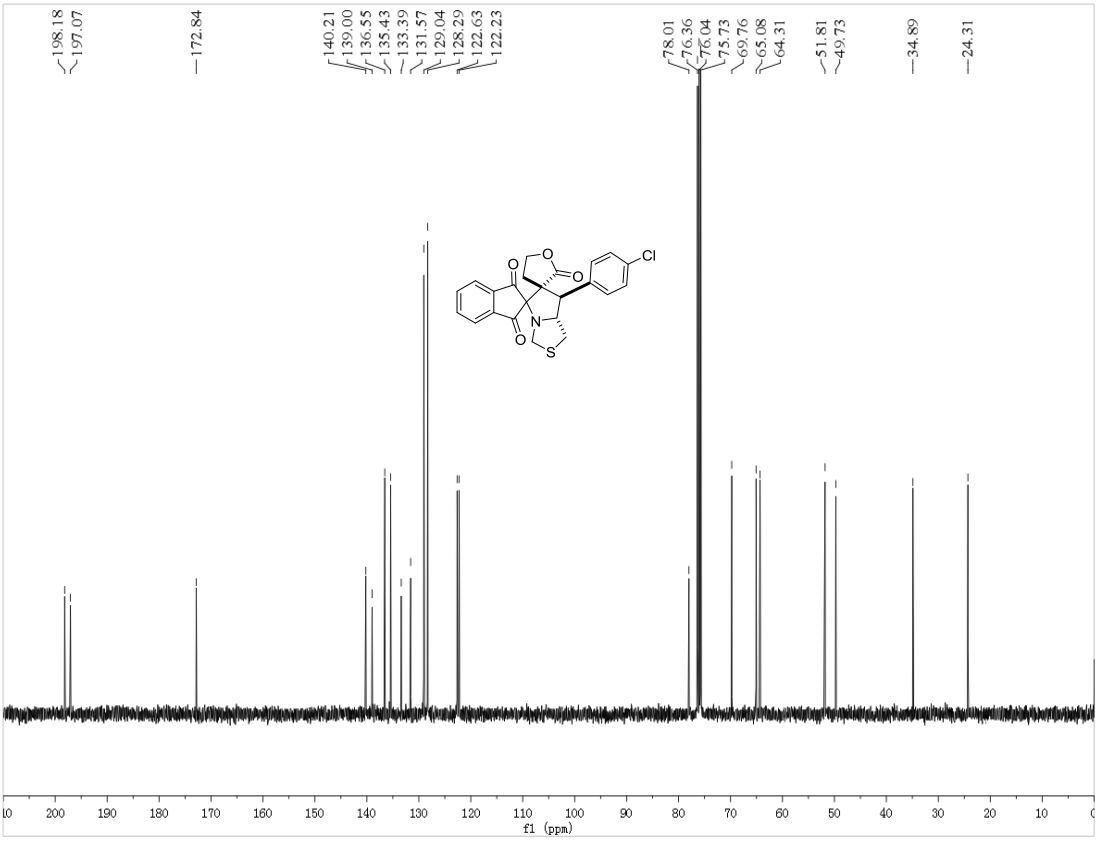
^{1}H and ^{13}C NMR of 4bb



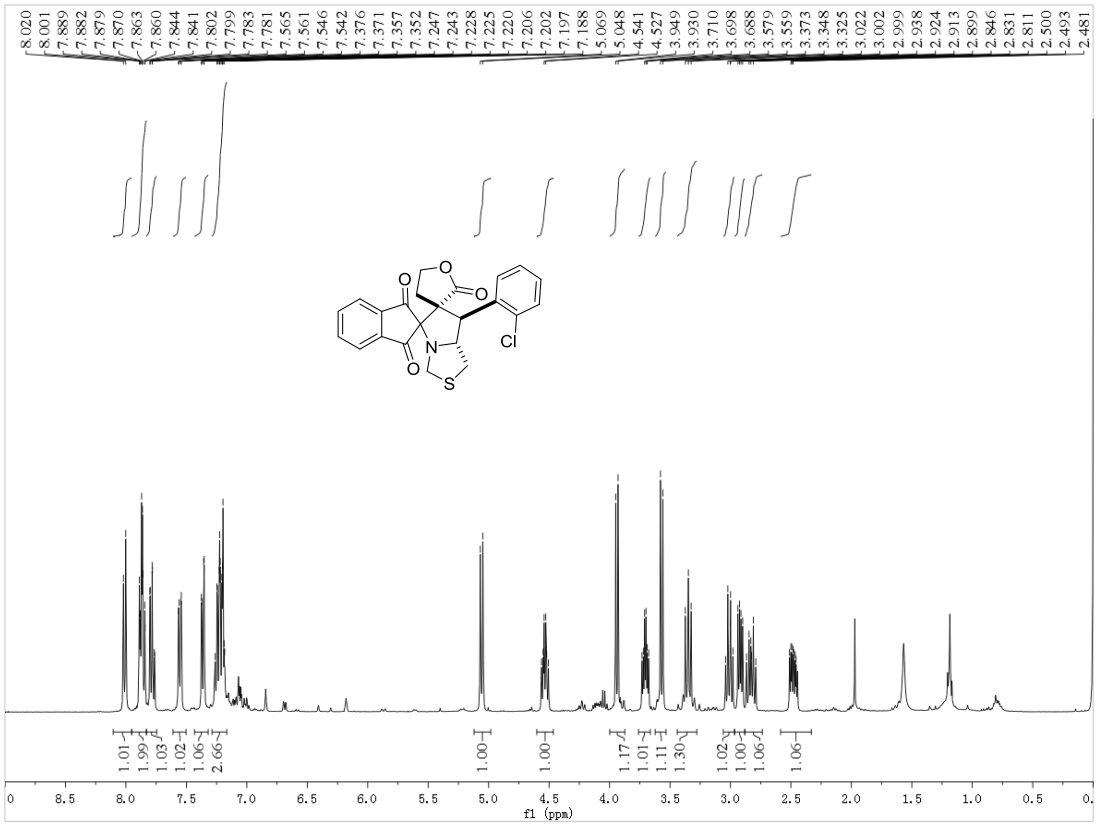


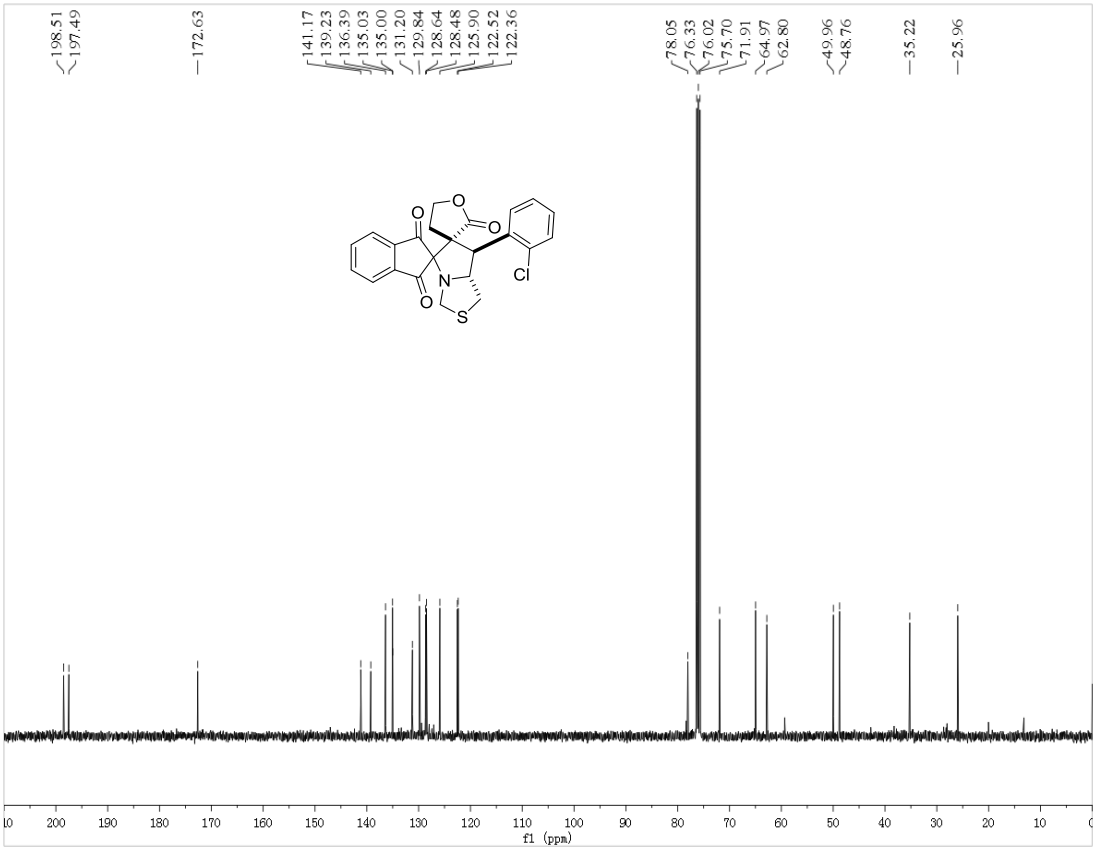
^{1}H and ^{13}C NMR of 4bc



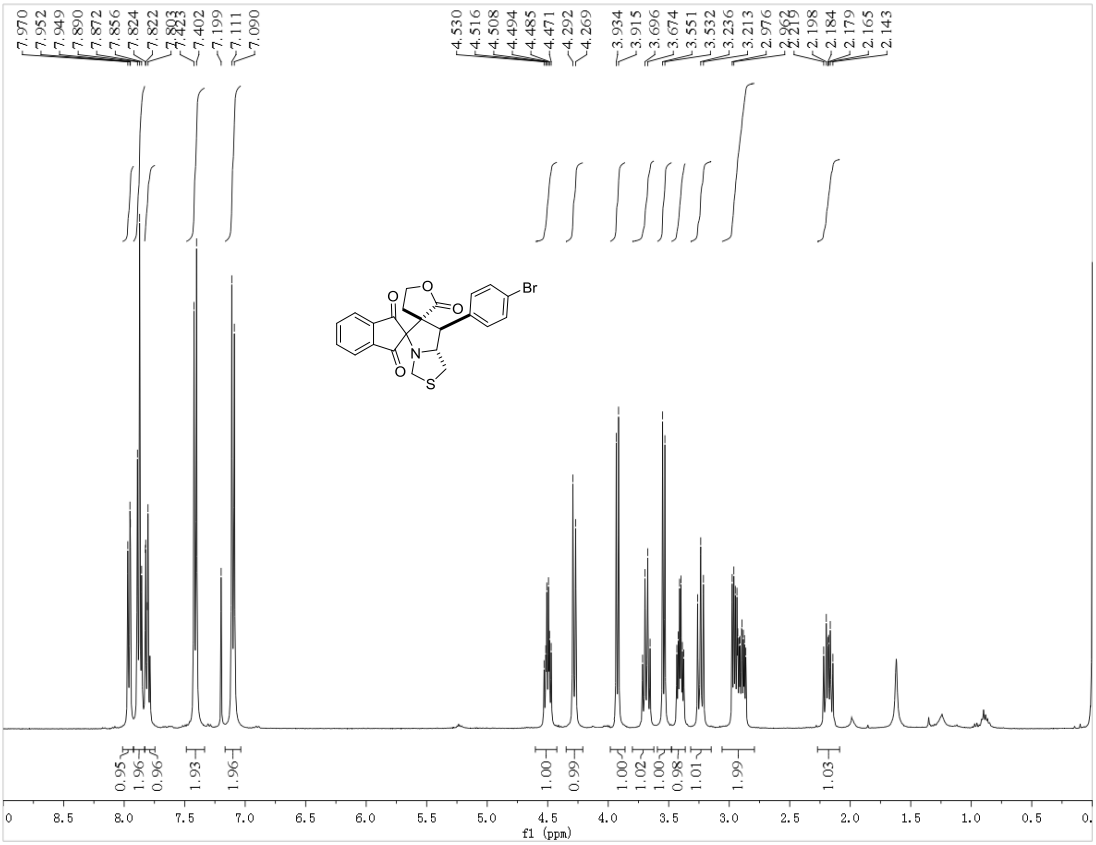


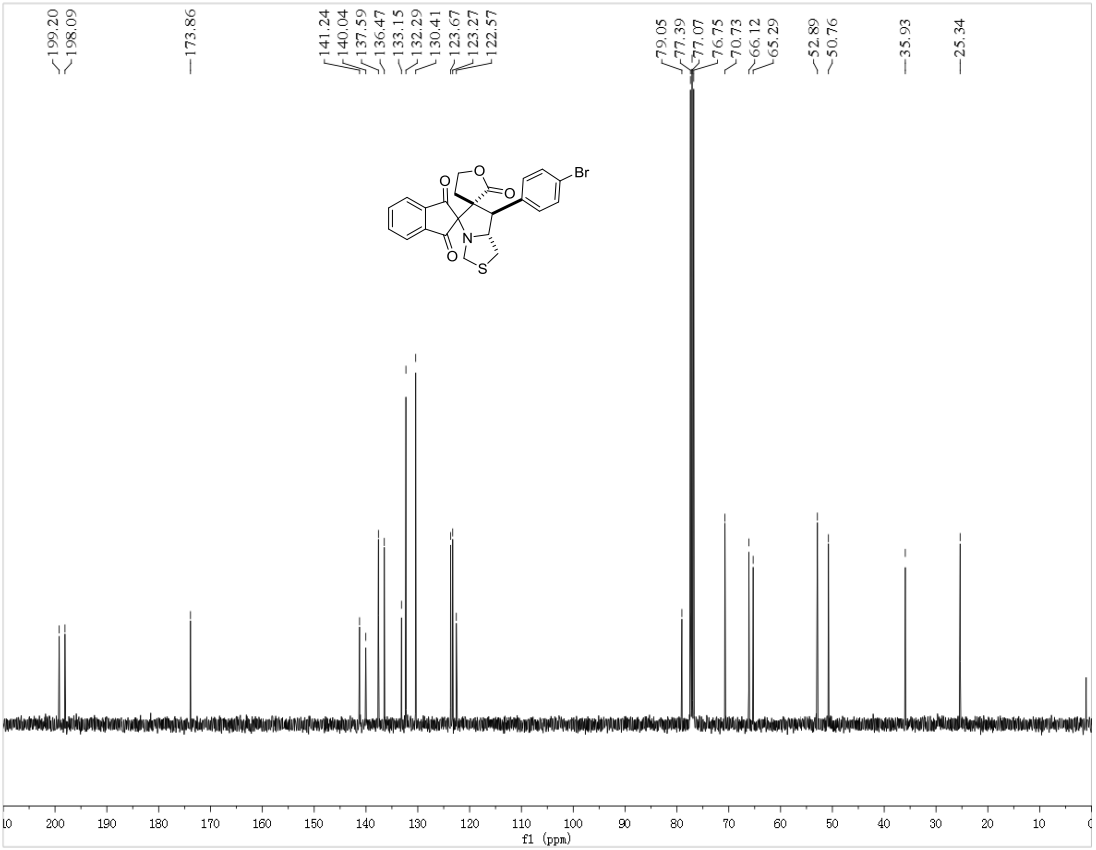
^{1}H and ^{13}C NMR of 4bd



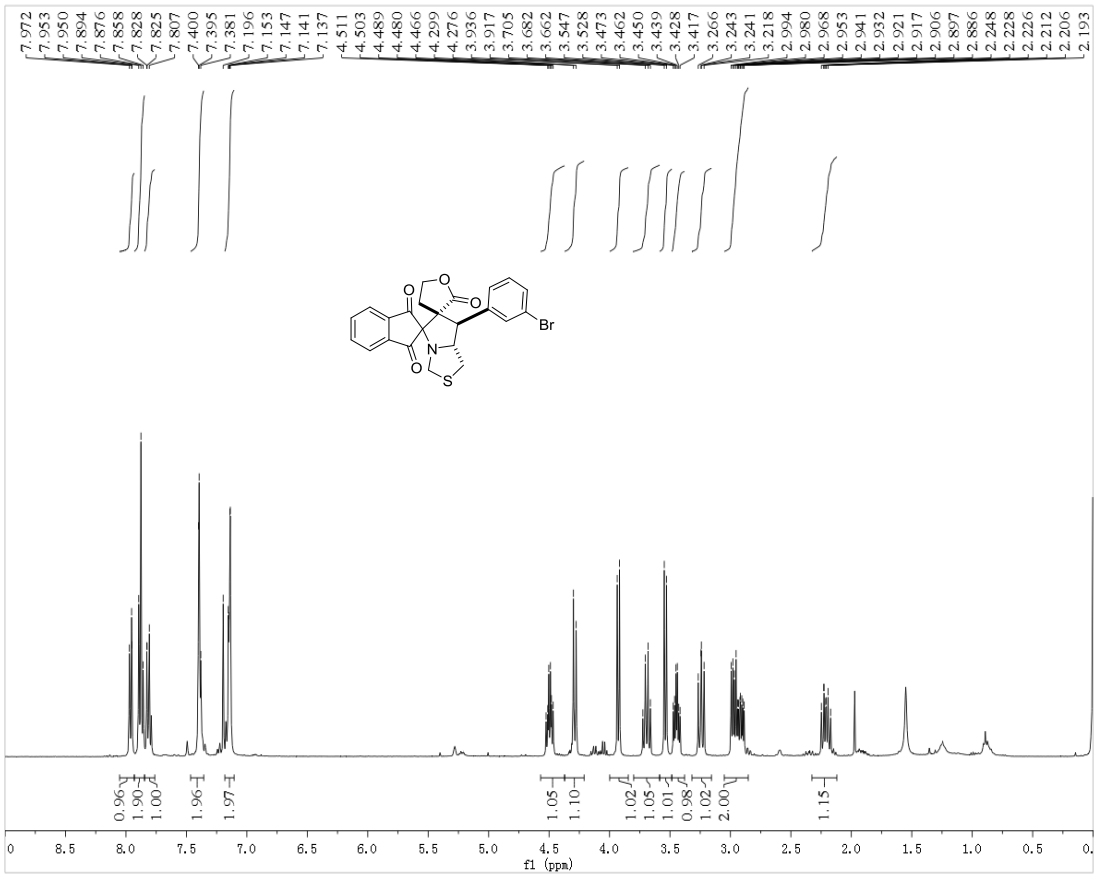


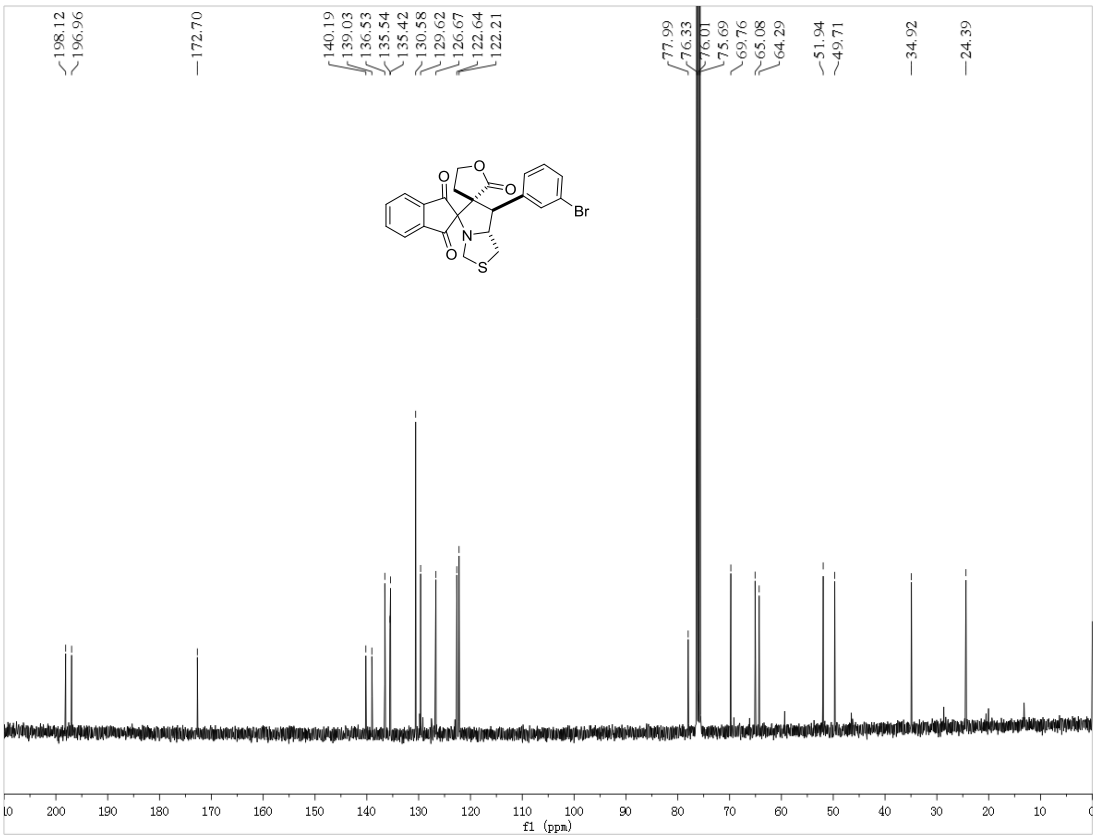
^{1}H and ^{13}C NMR of 4be



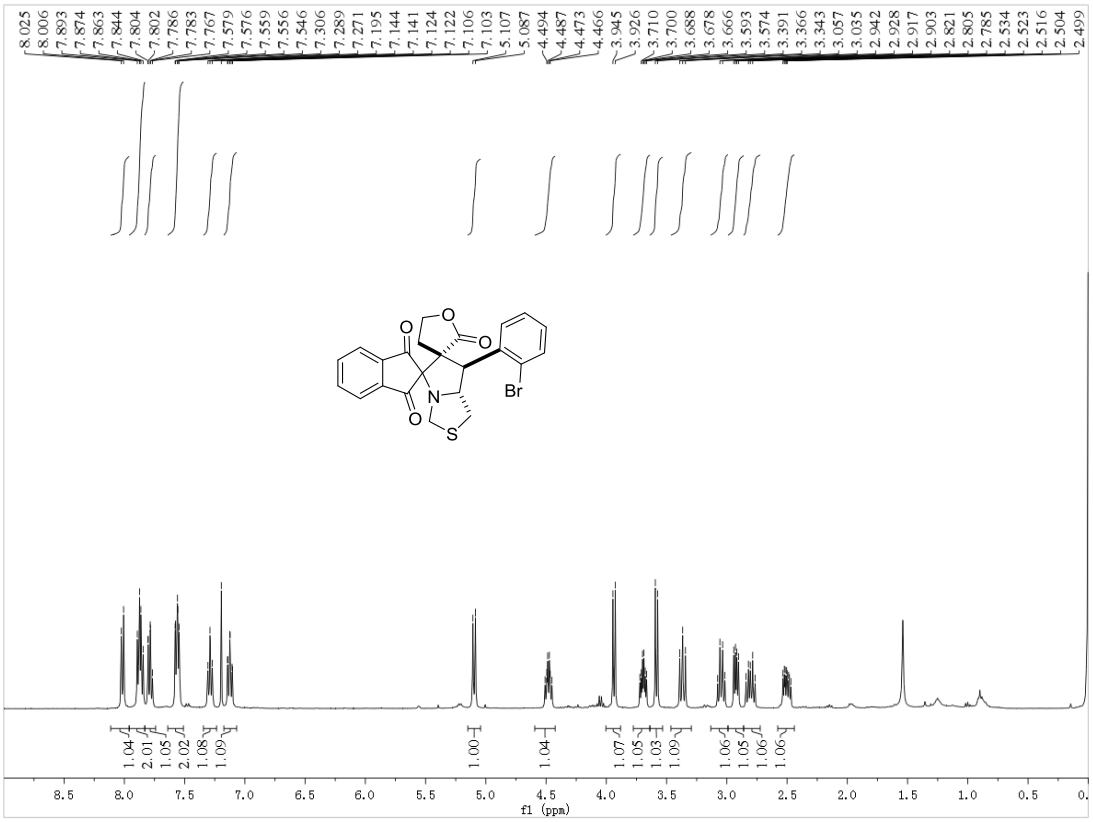


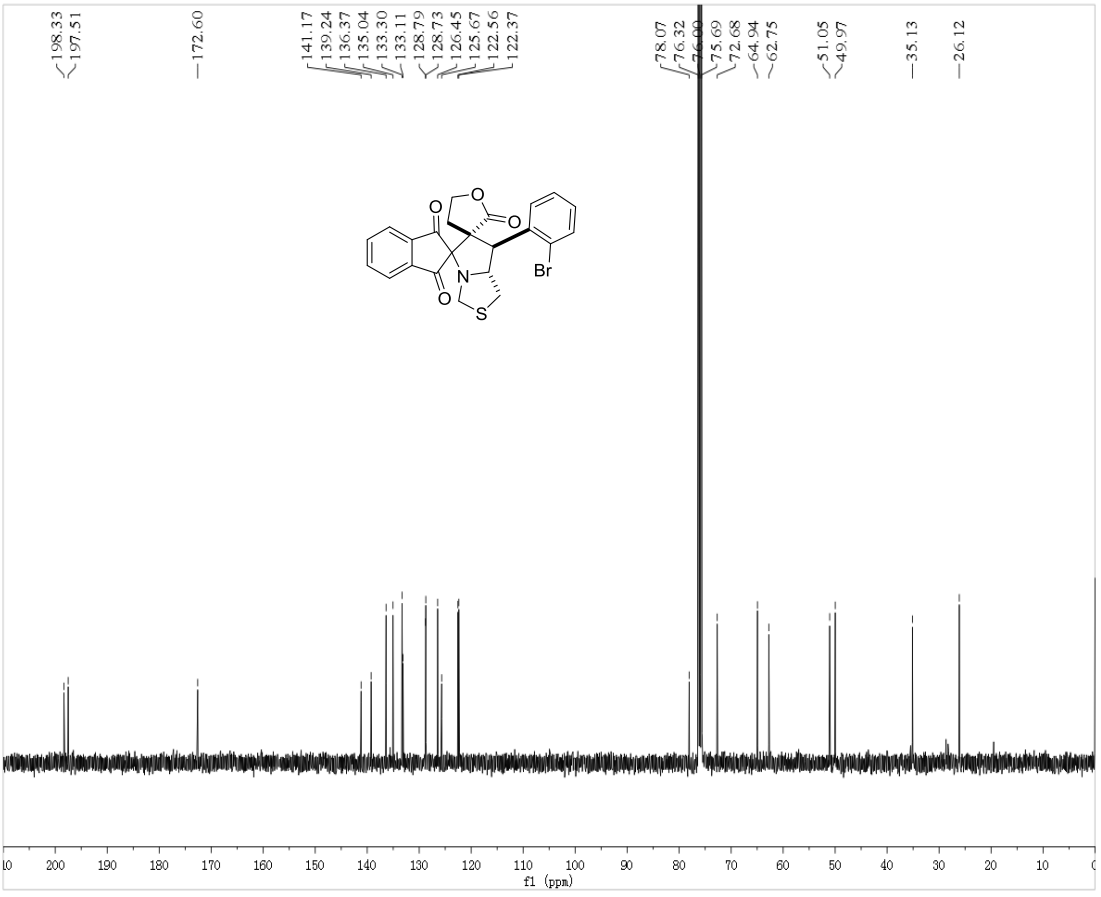
^{1}H and ^{13}C NMR of 4bf



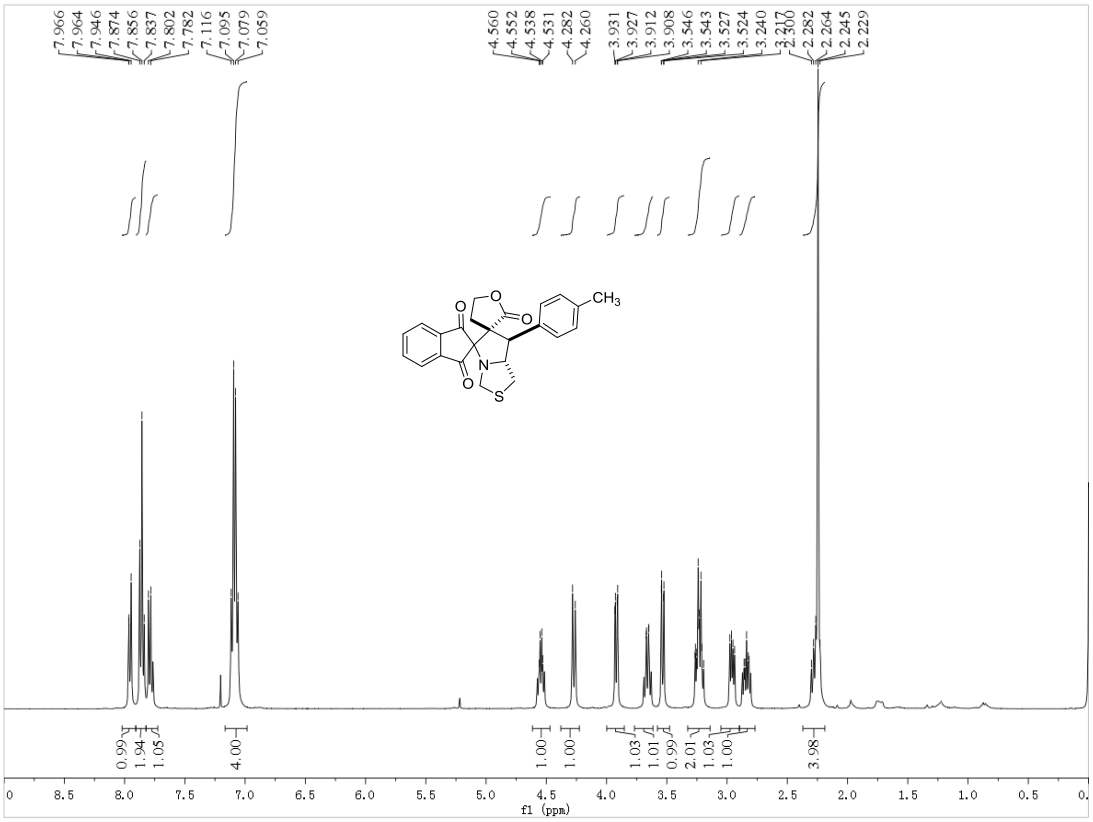


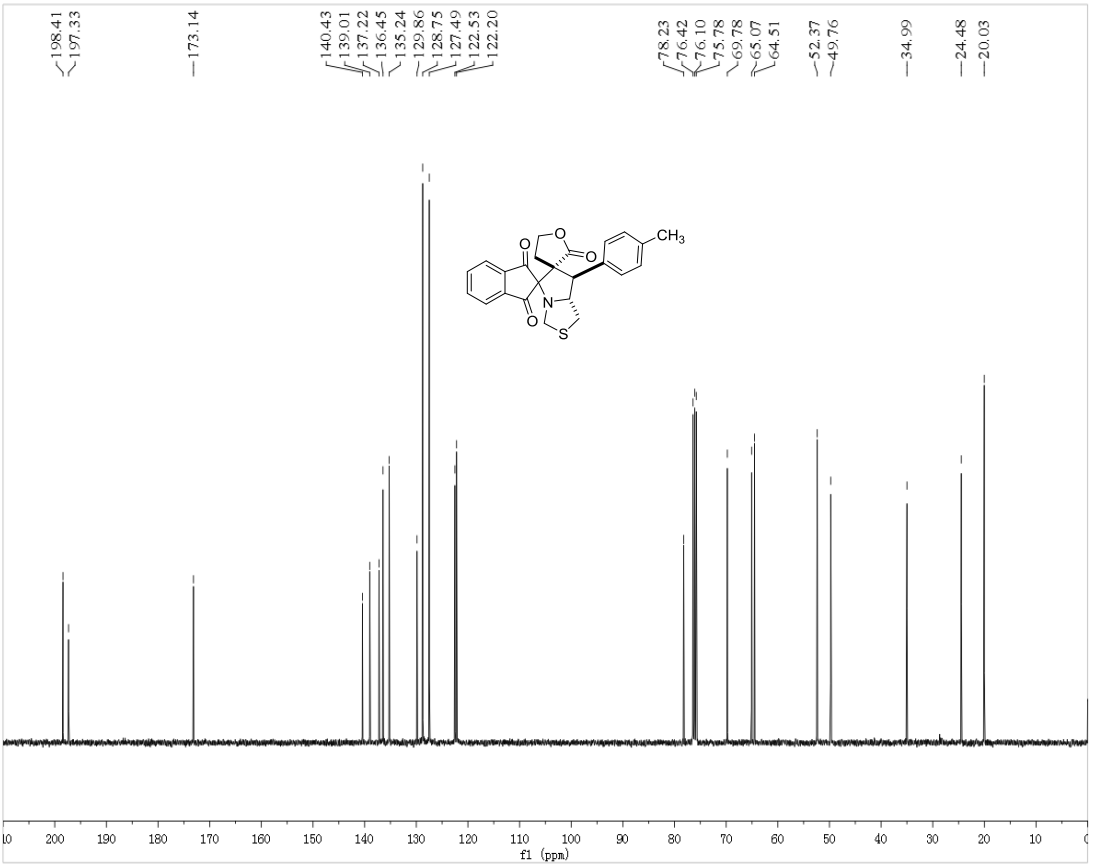
^{1}H and ^{13}C NMR of 4bg



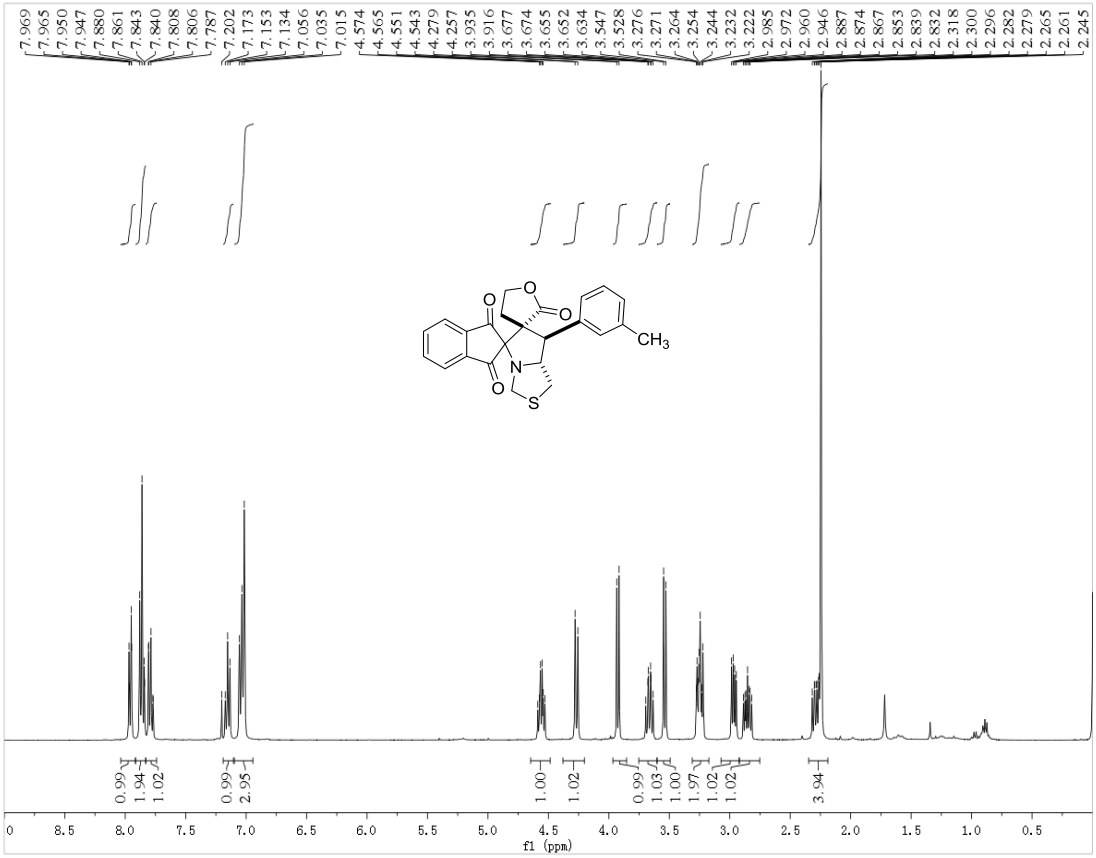


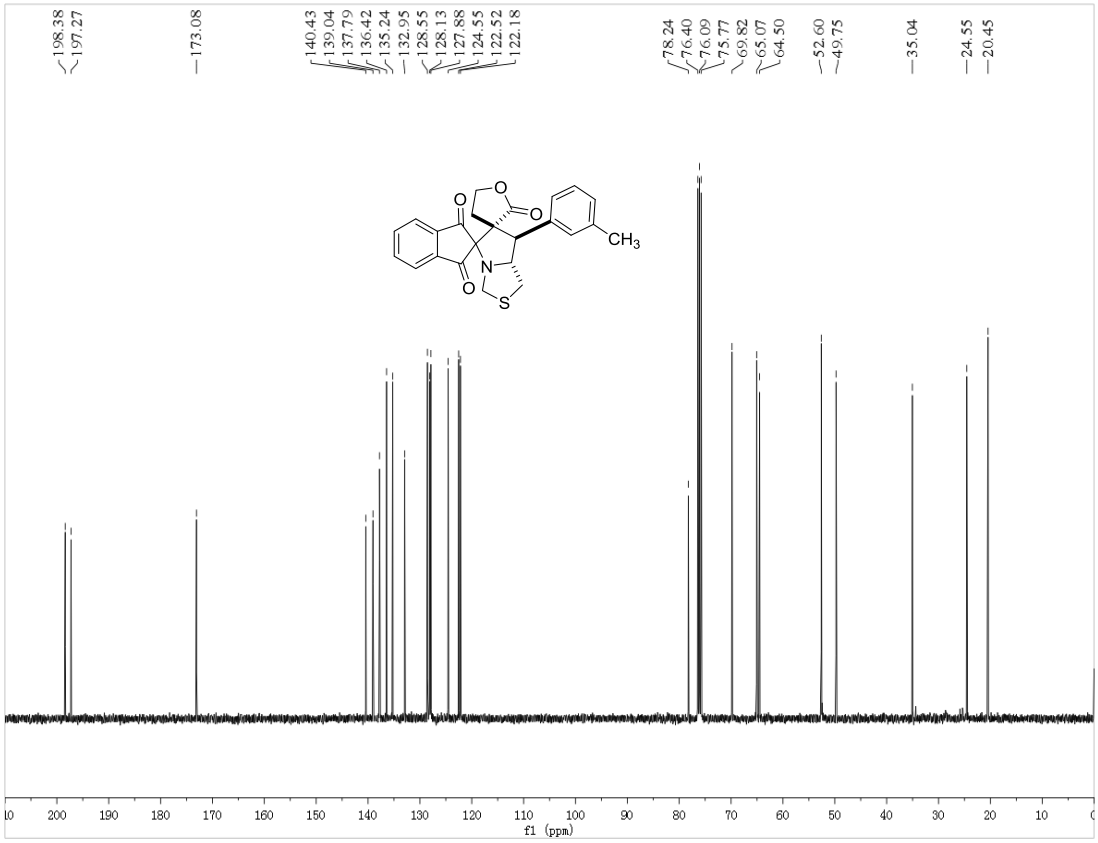
^{1}H and ^{13}C NMR of 4bh



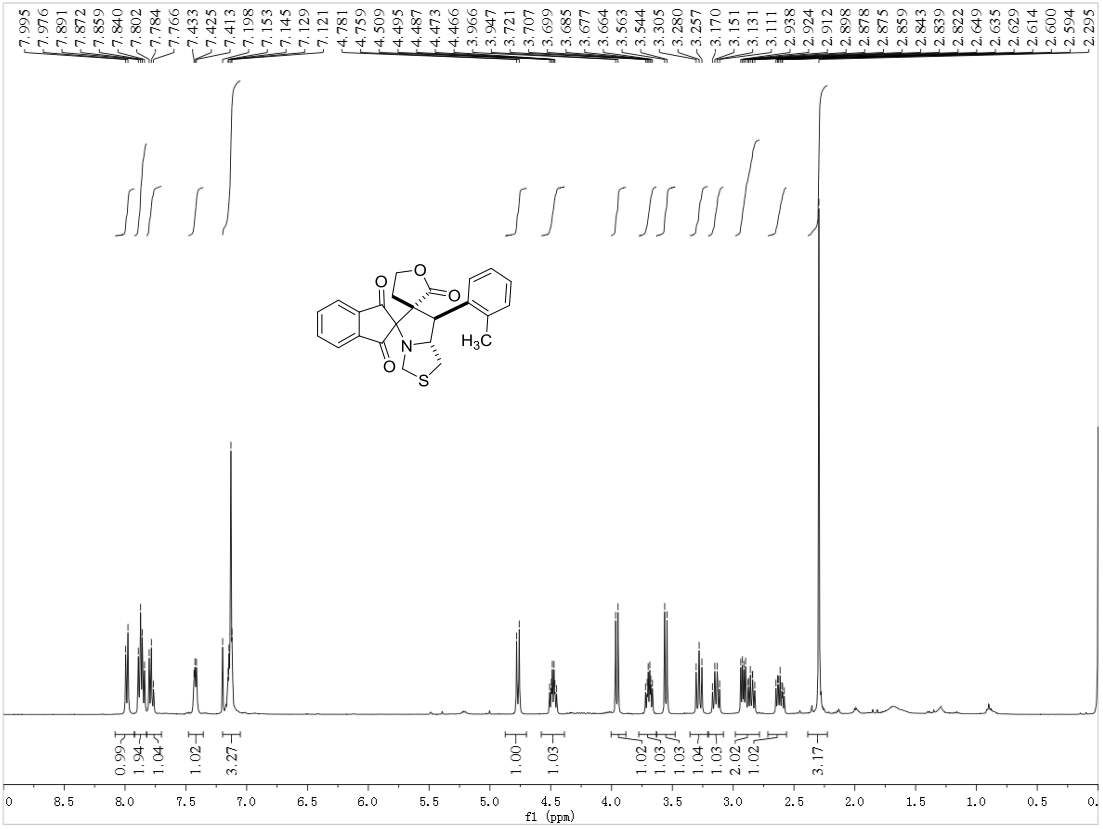


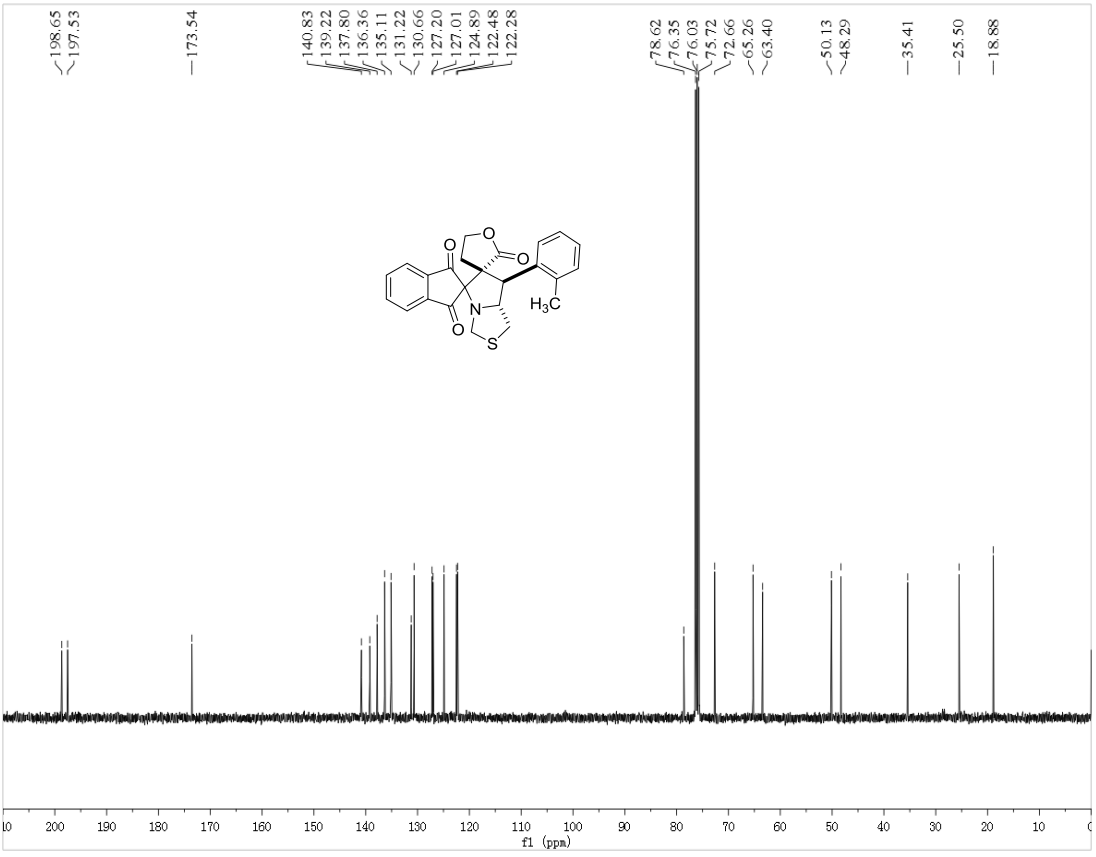
^{1}H and ^{13}C NMR of 4bi



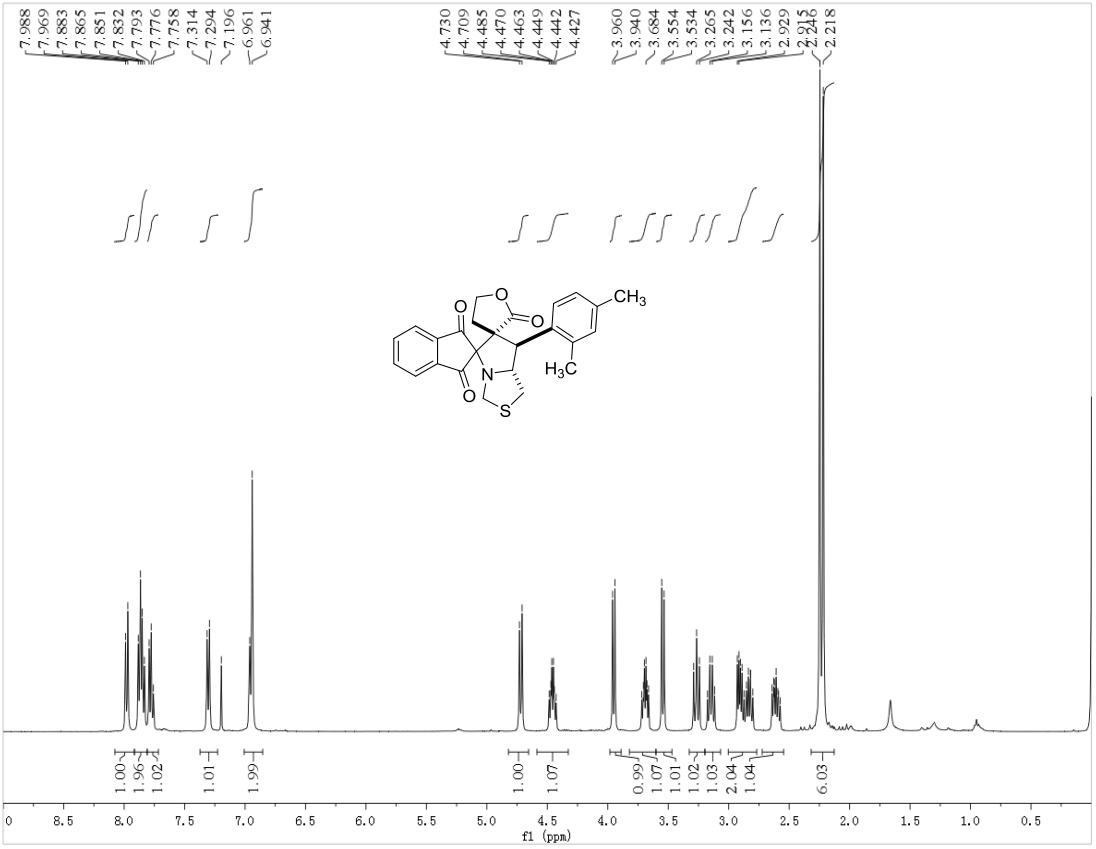


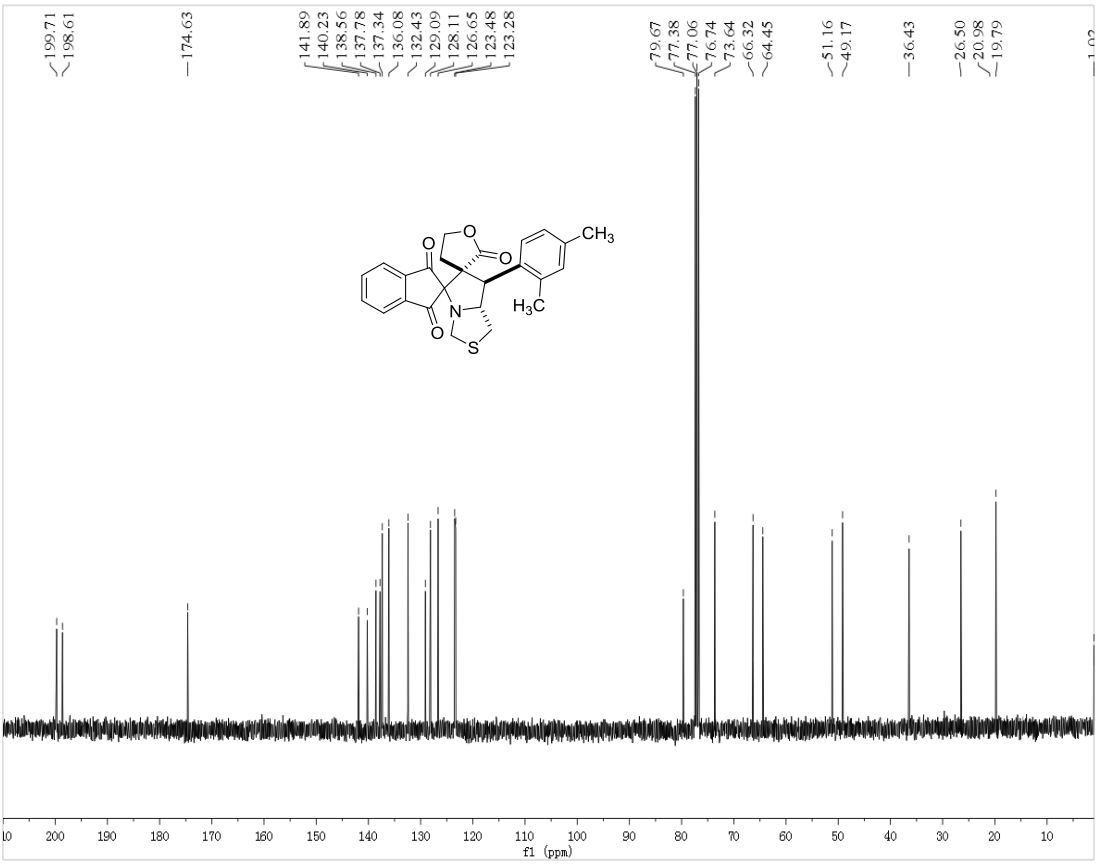
^{1}H and ^{13}C NMR of 4bj



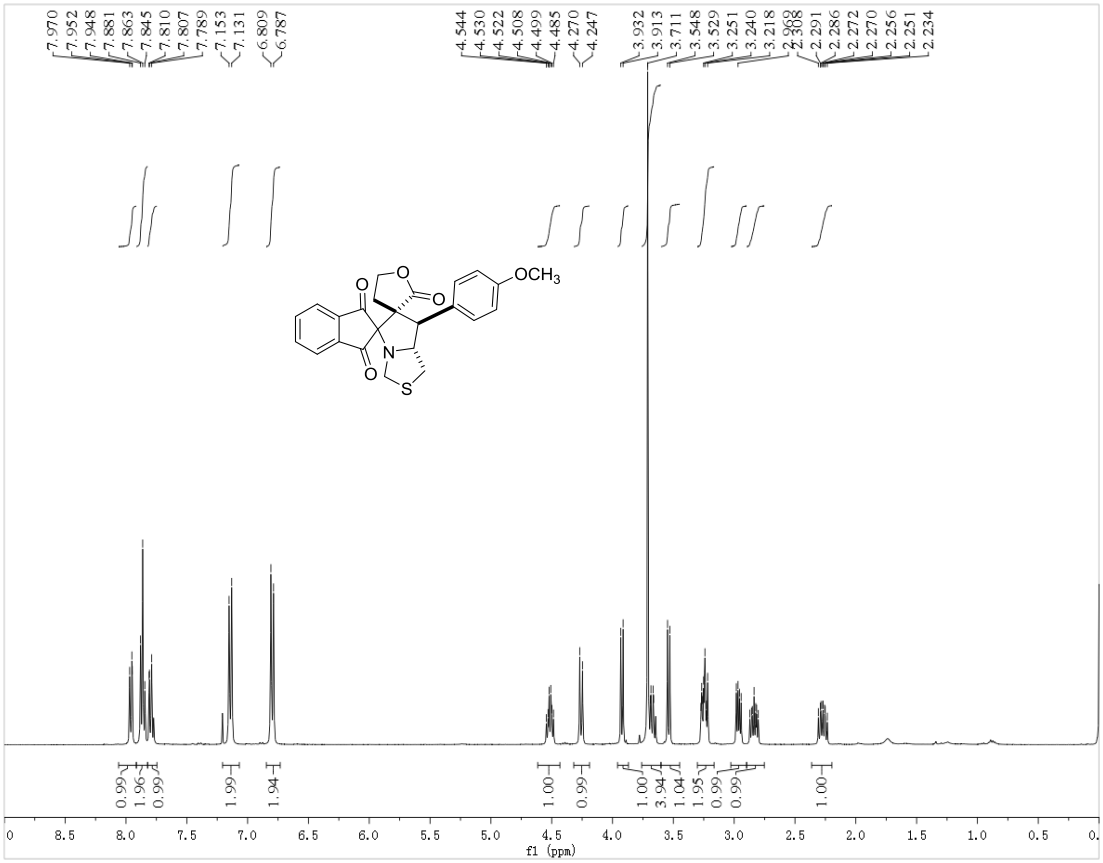


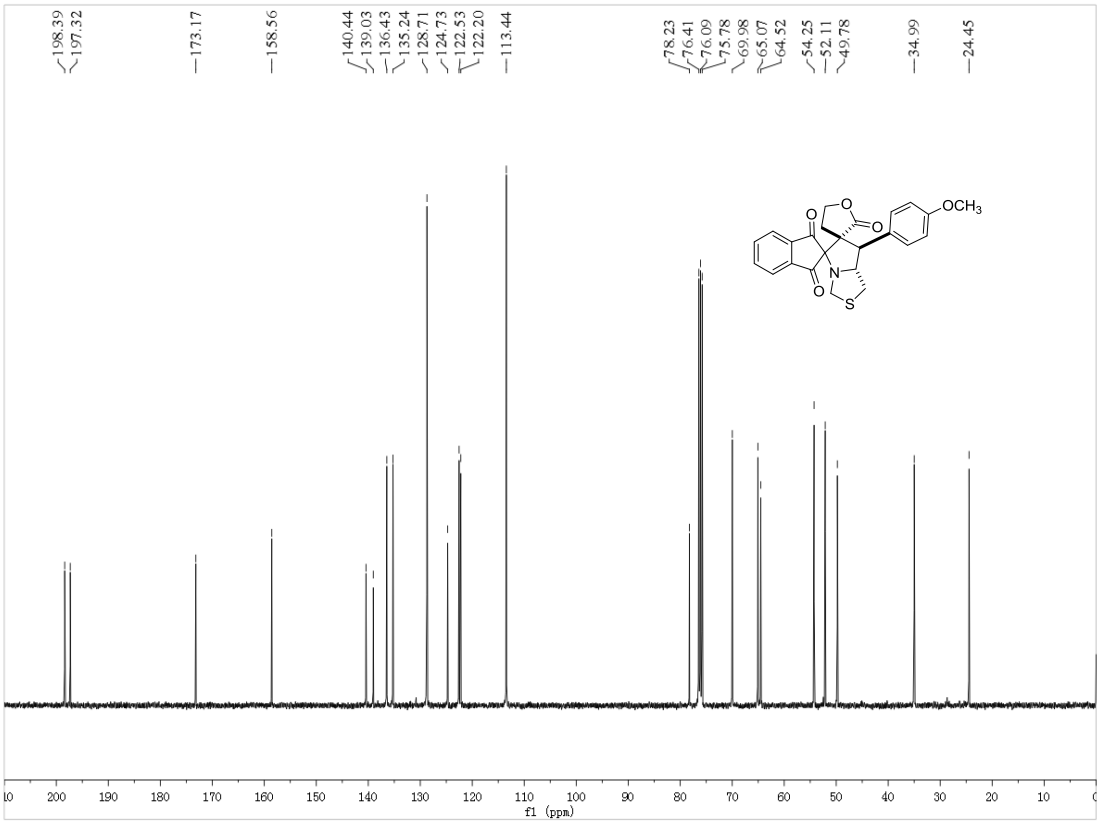
^{1}H and ^{13}C NMR of 4bk



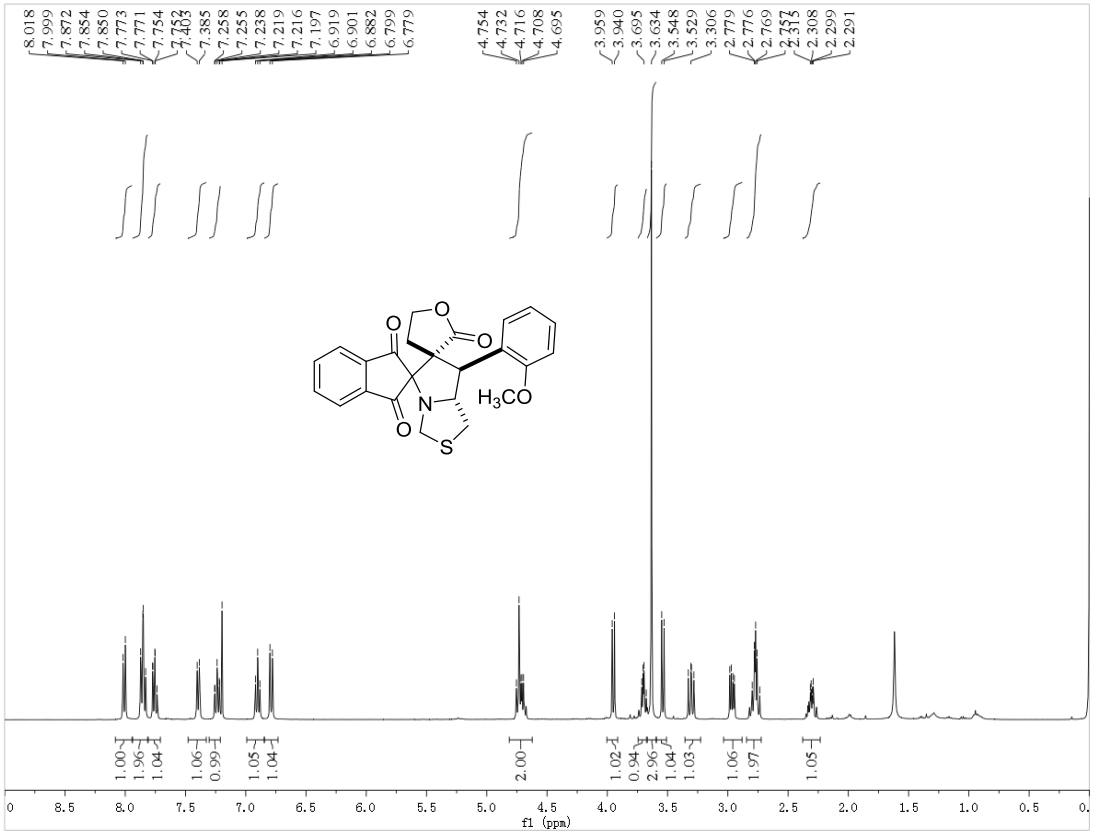


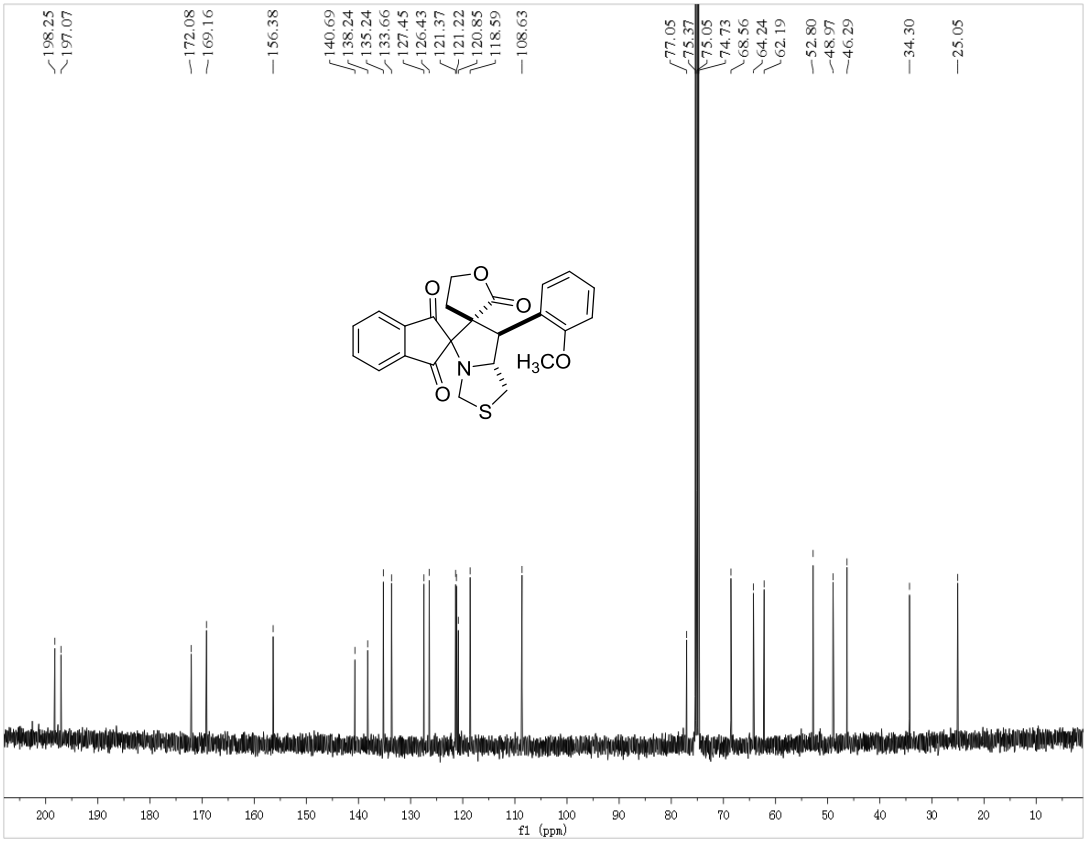
^{1}H and ^{13}C NMR of 4bl



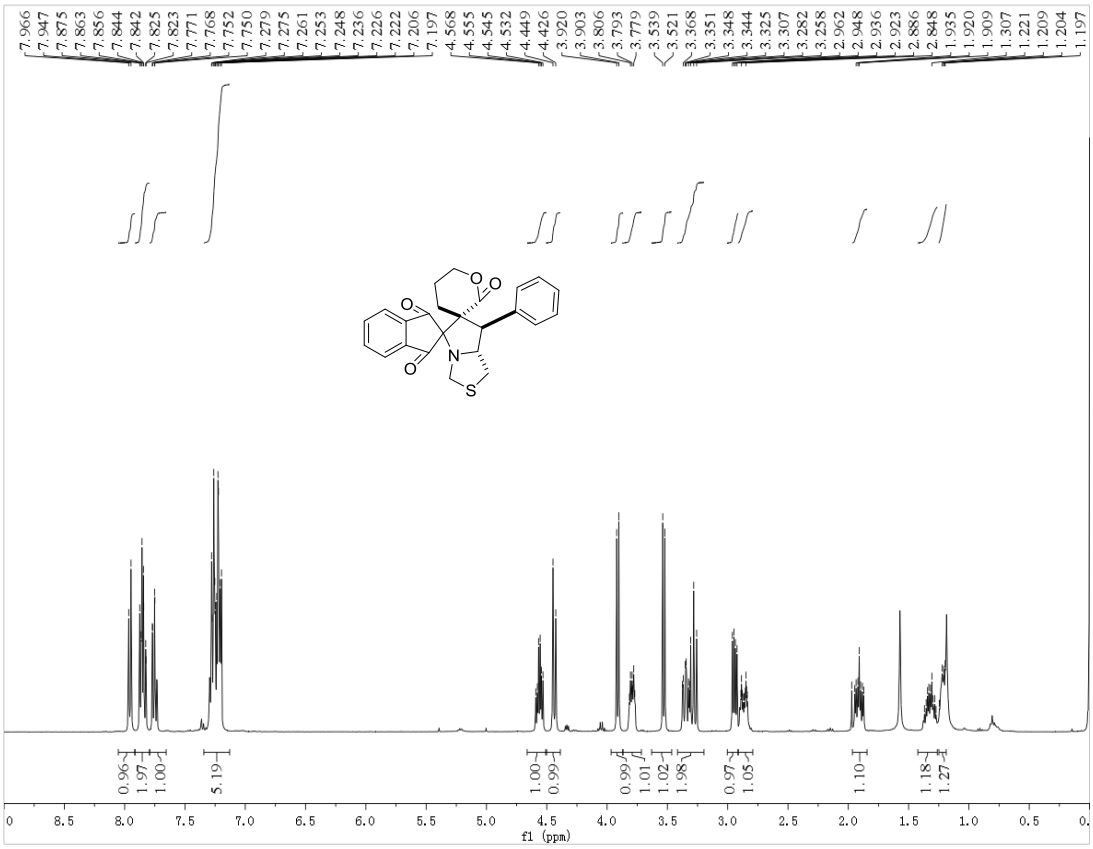


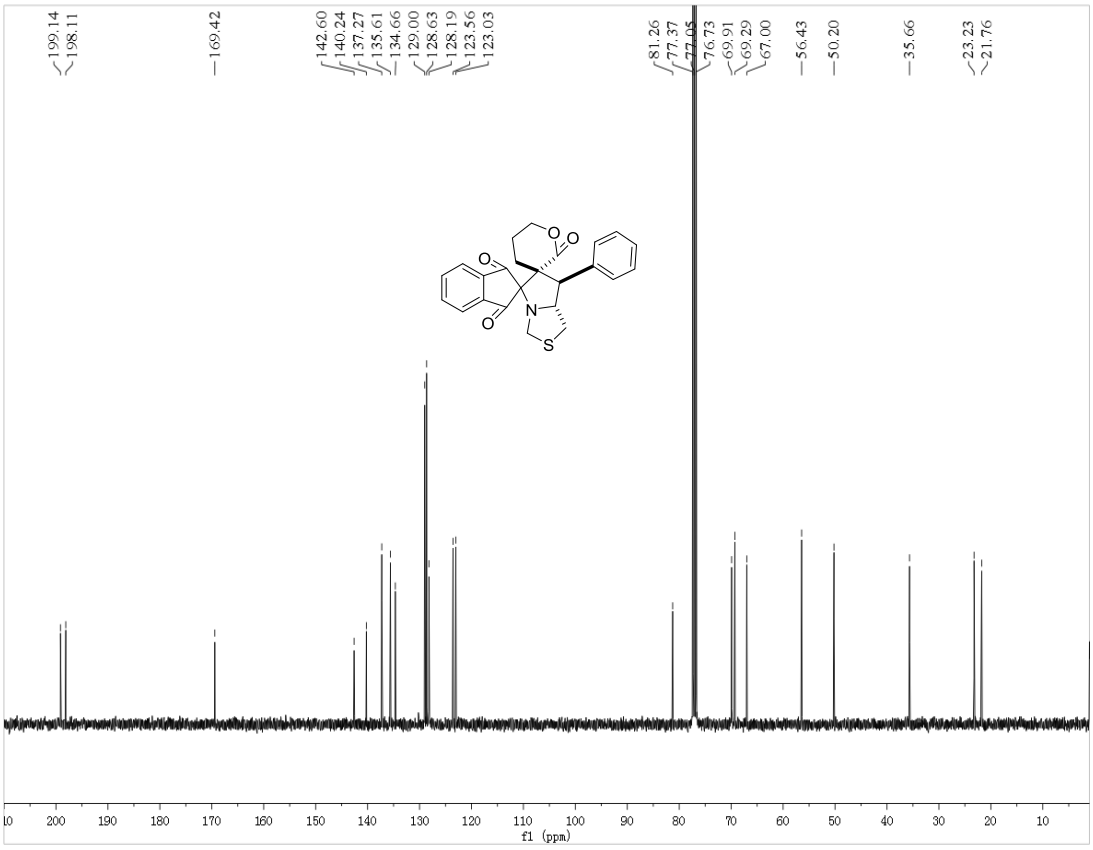
^{1}H and ^{13}C NMR of 4bm



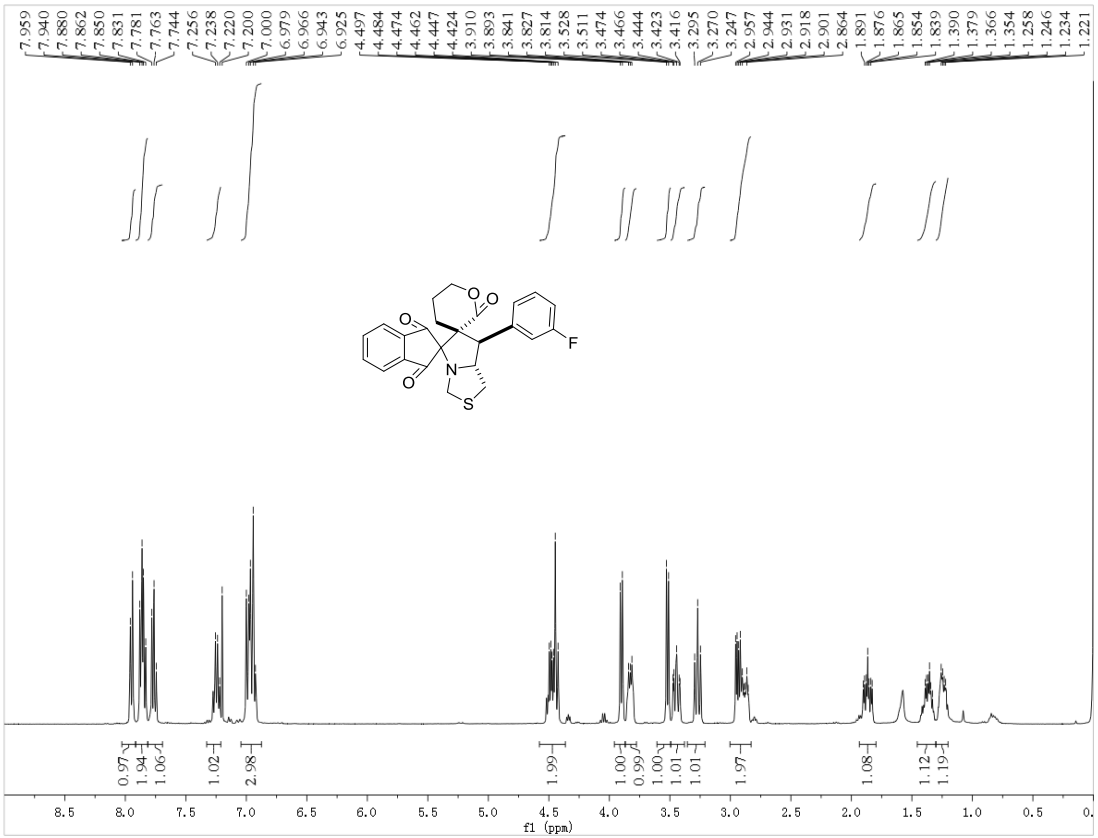


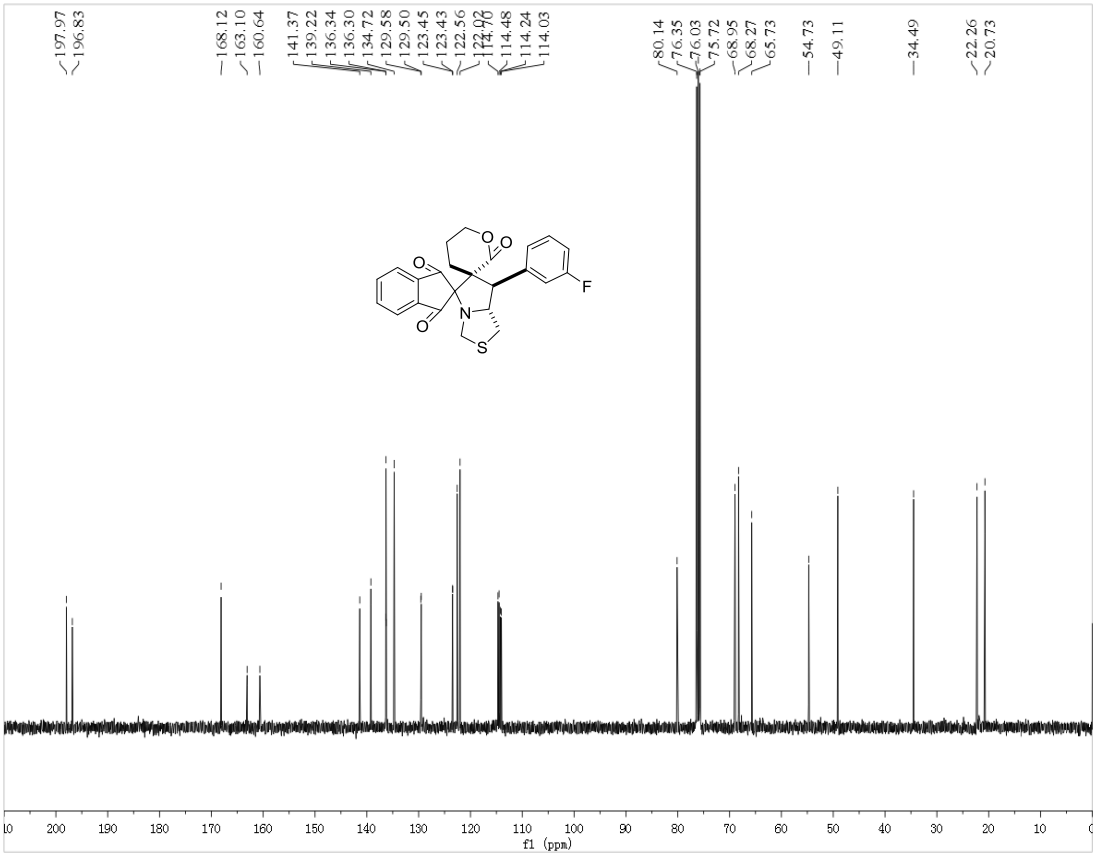
^{1}H and ^{13}C NMR of 4ca



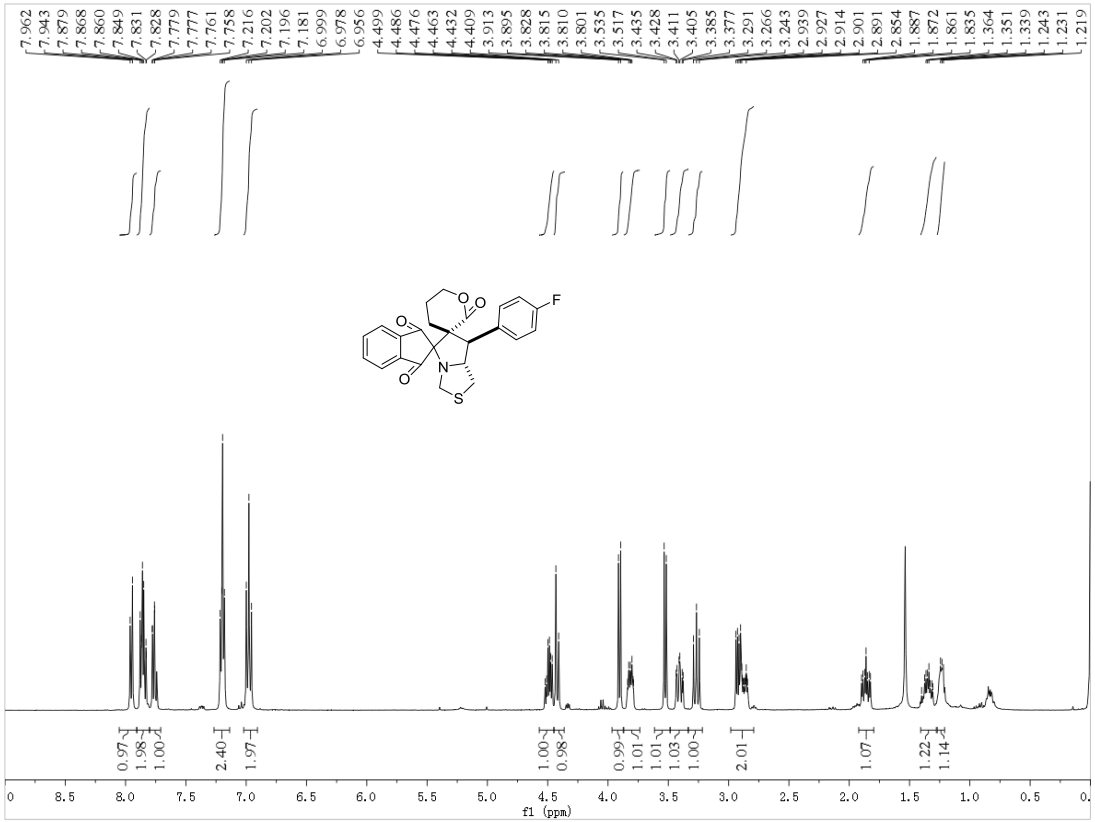


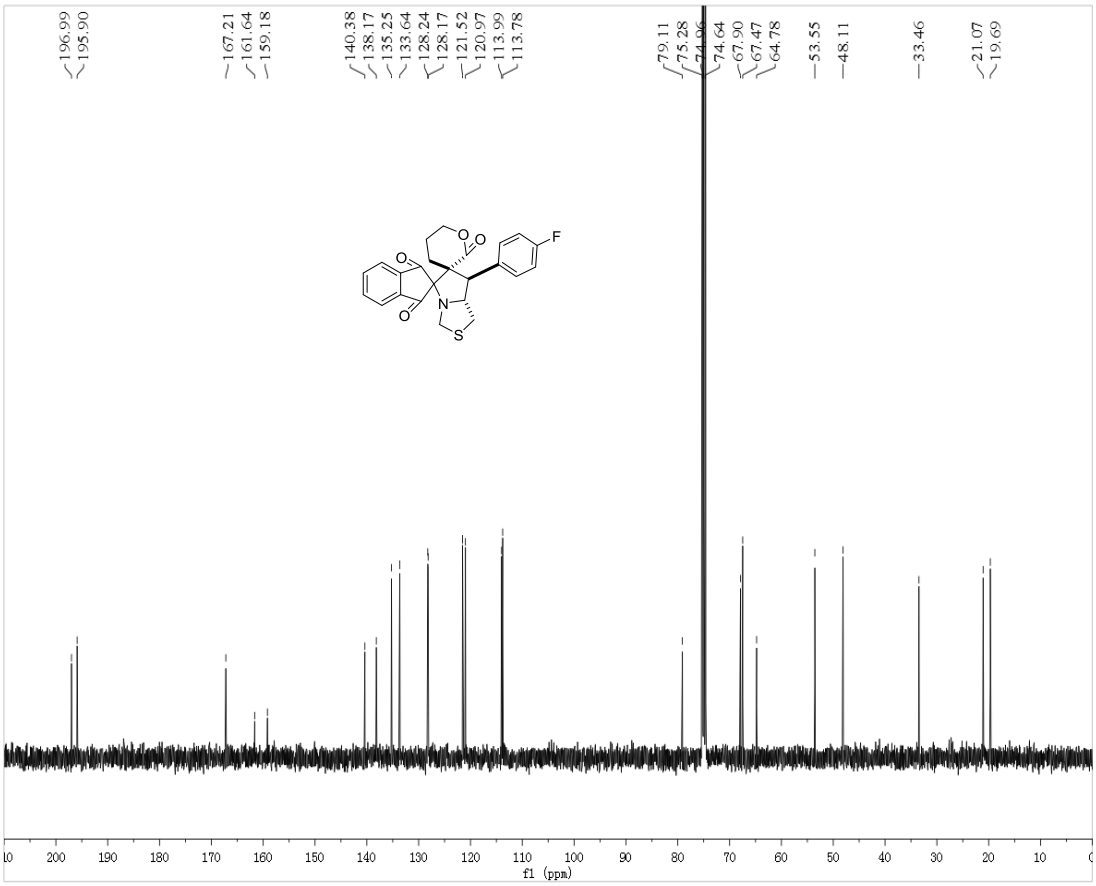
^{1}H and ^{13}C NMR of 4cb



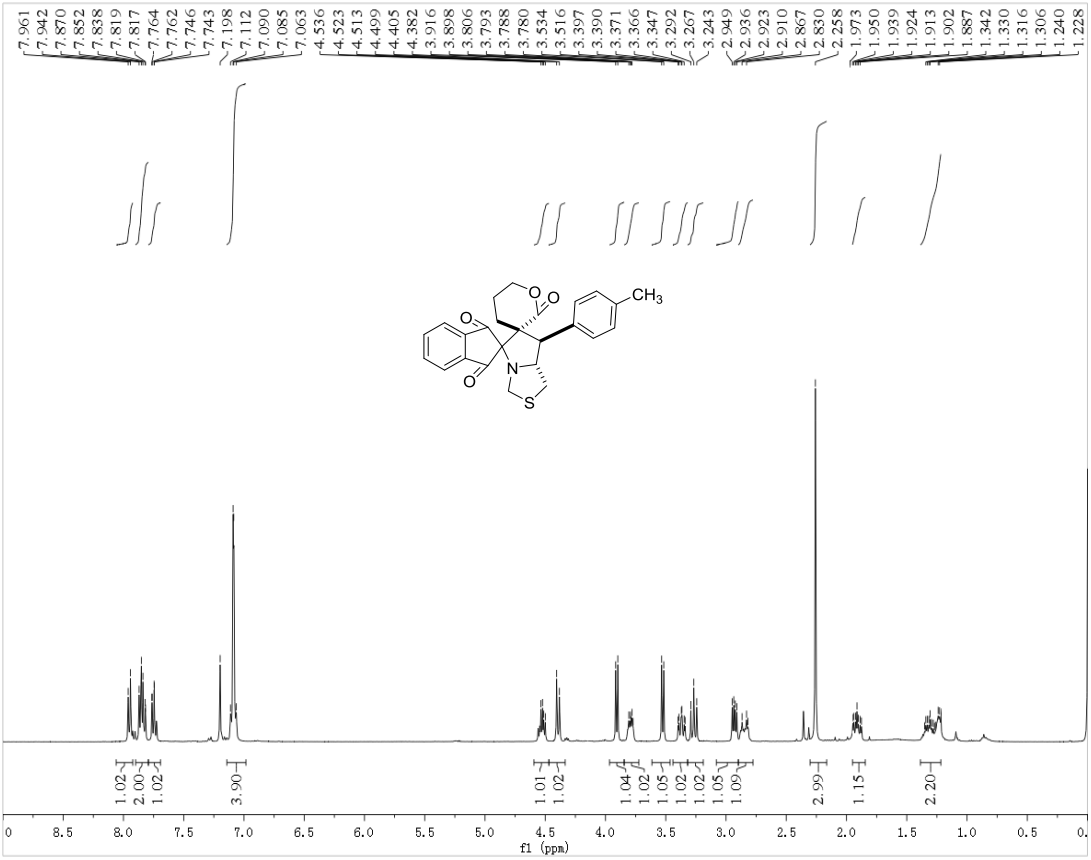


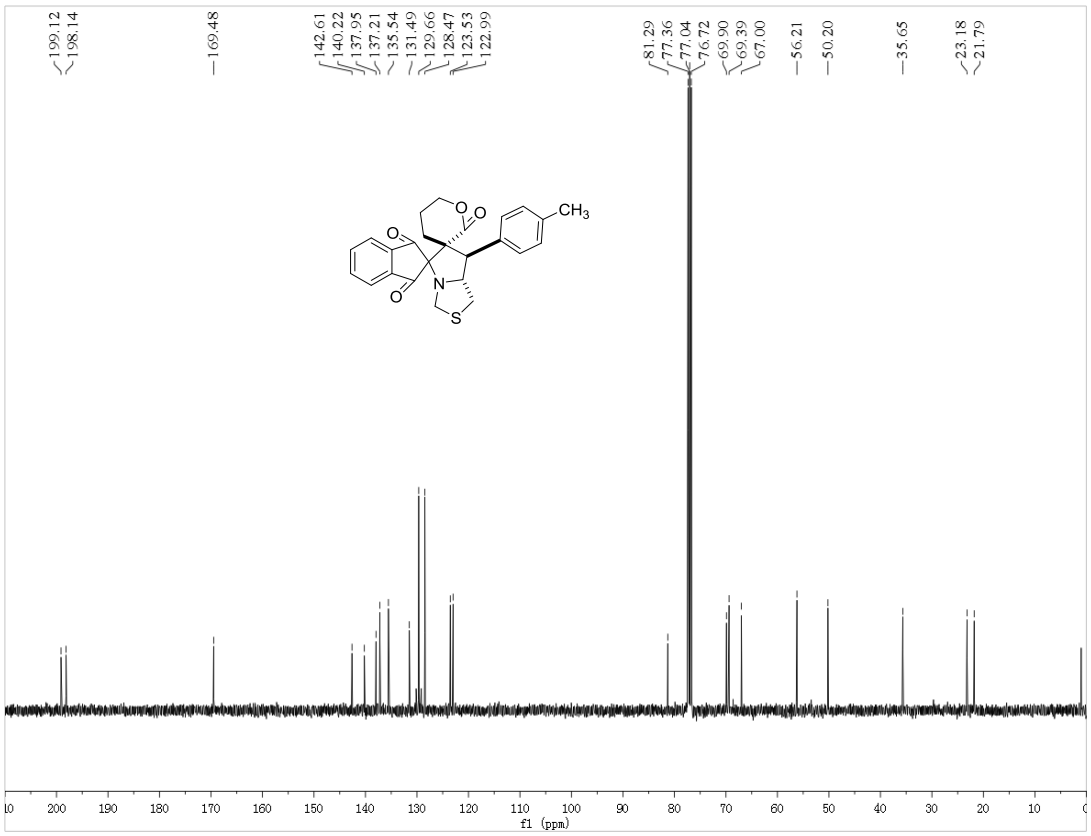
^{1}H and ^{13}C NMR of 4cc



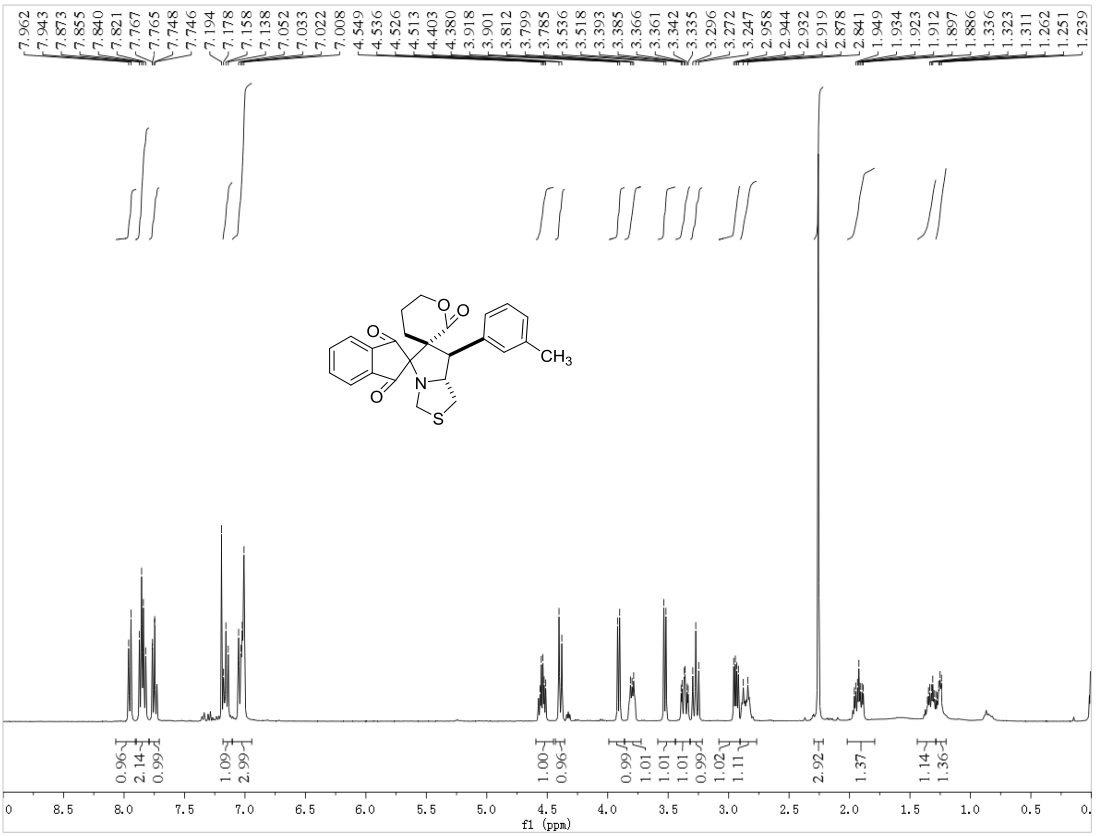


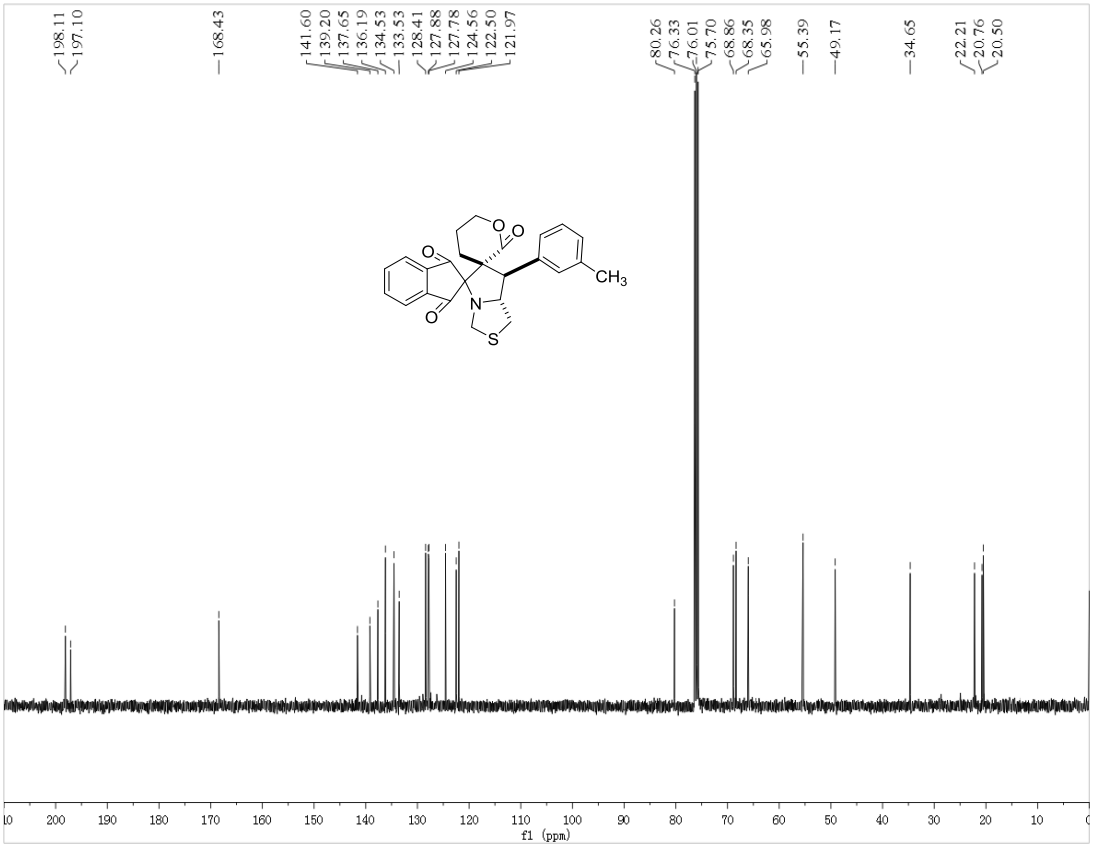
^{1}H and ^{13}C NMR of 4cd





^{1}H and ^{13}C NMR of 4ce





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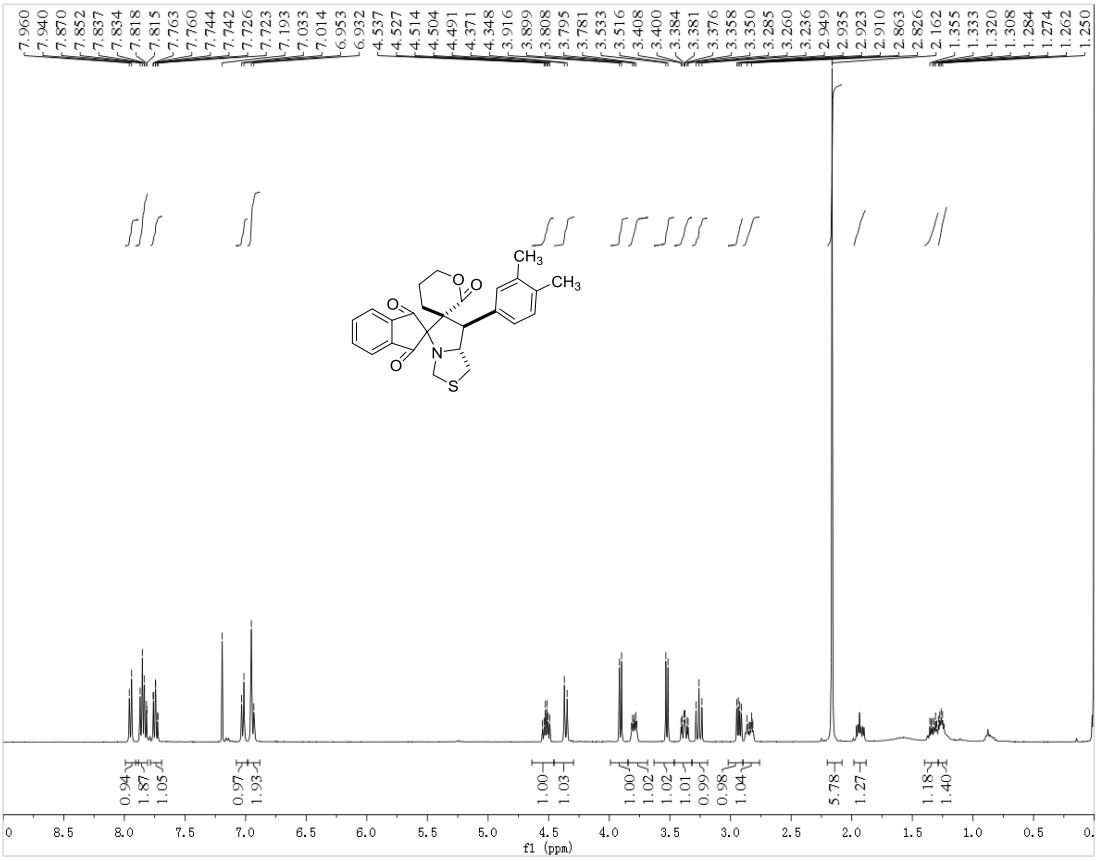
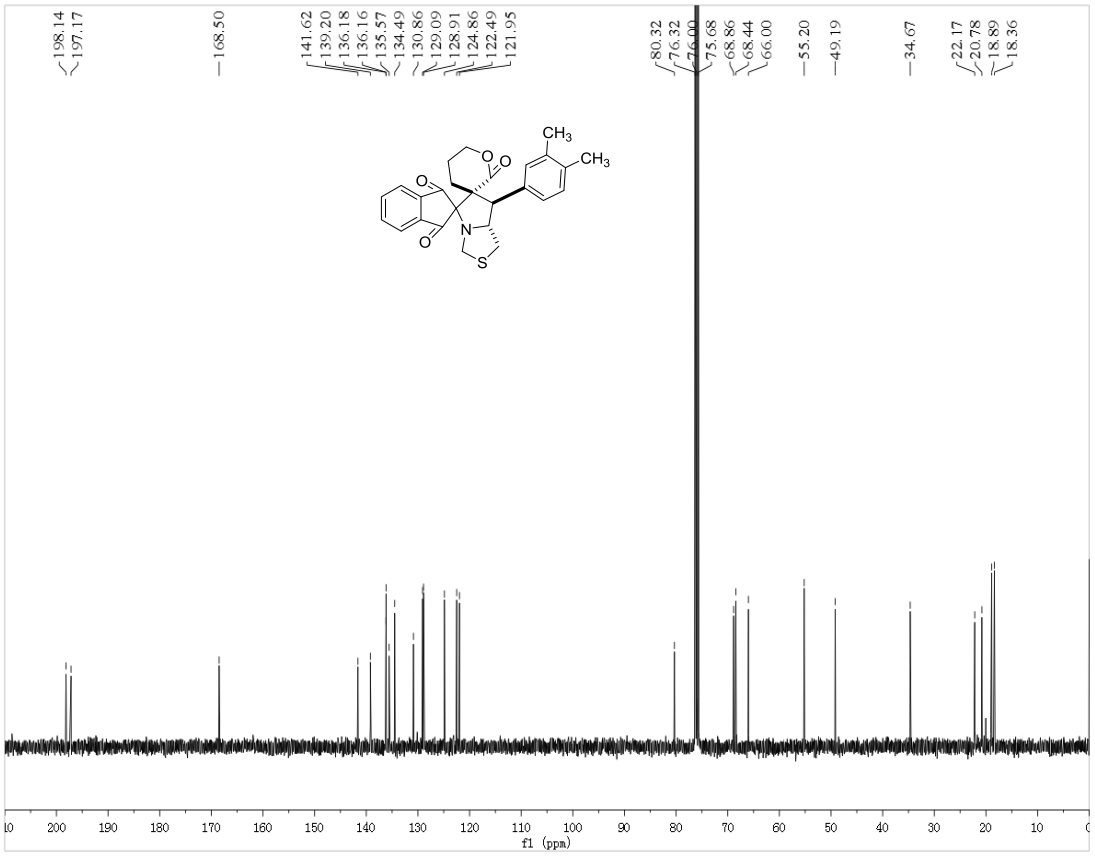
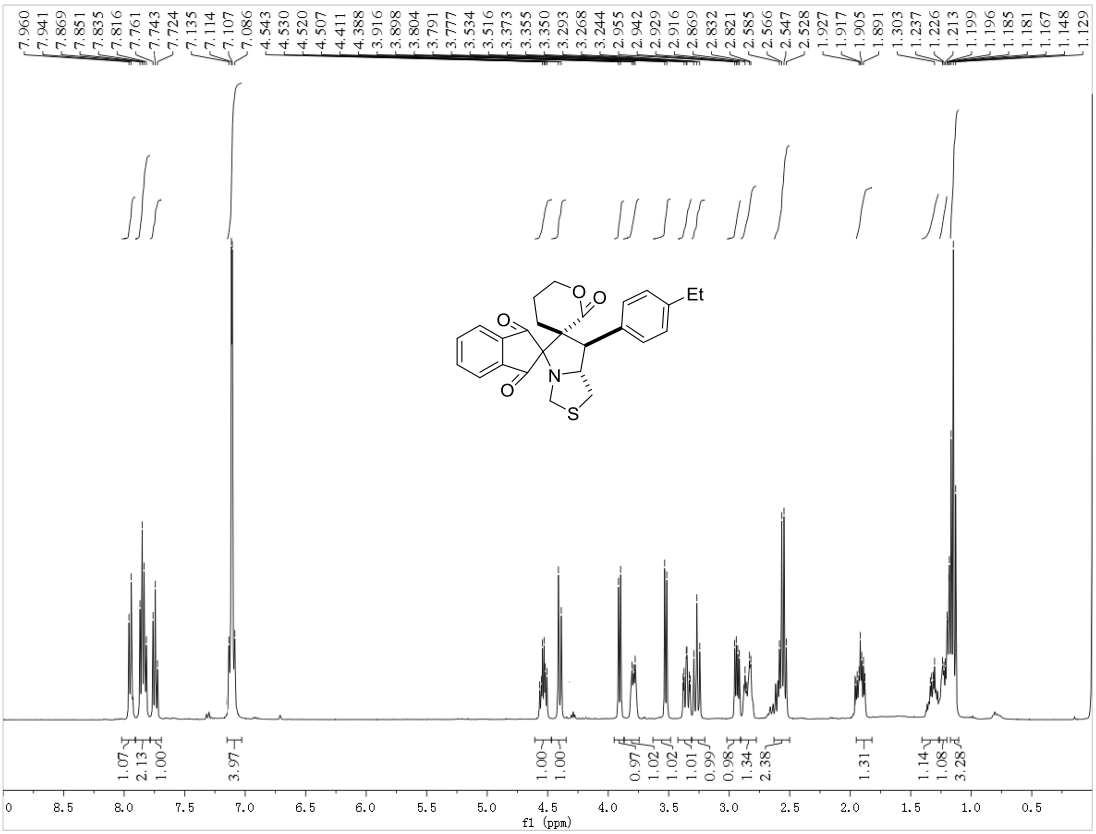
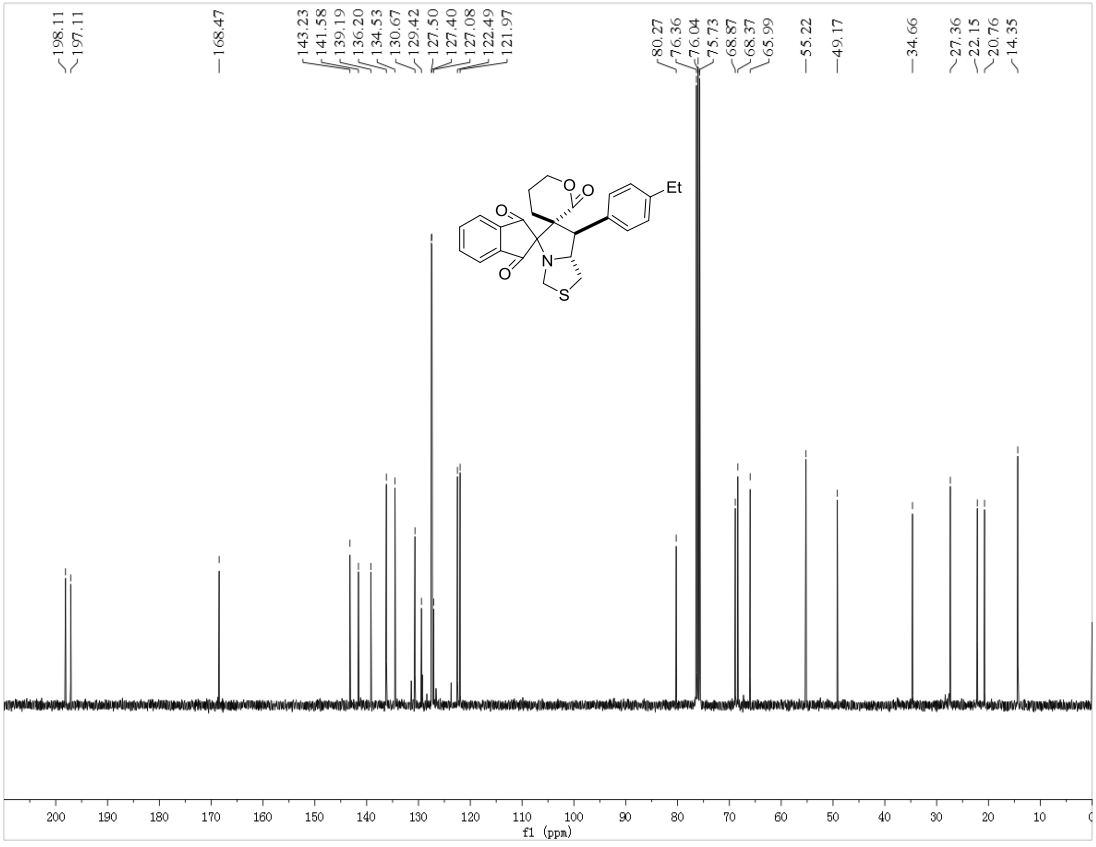


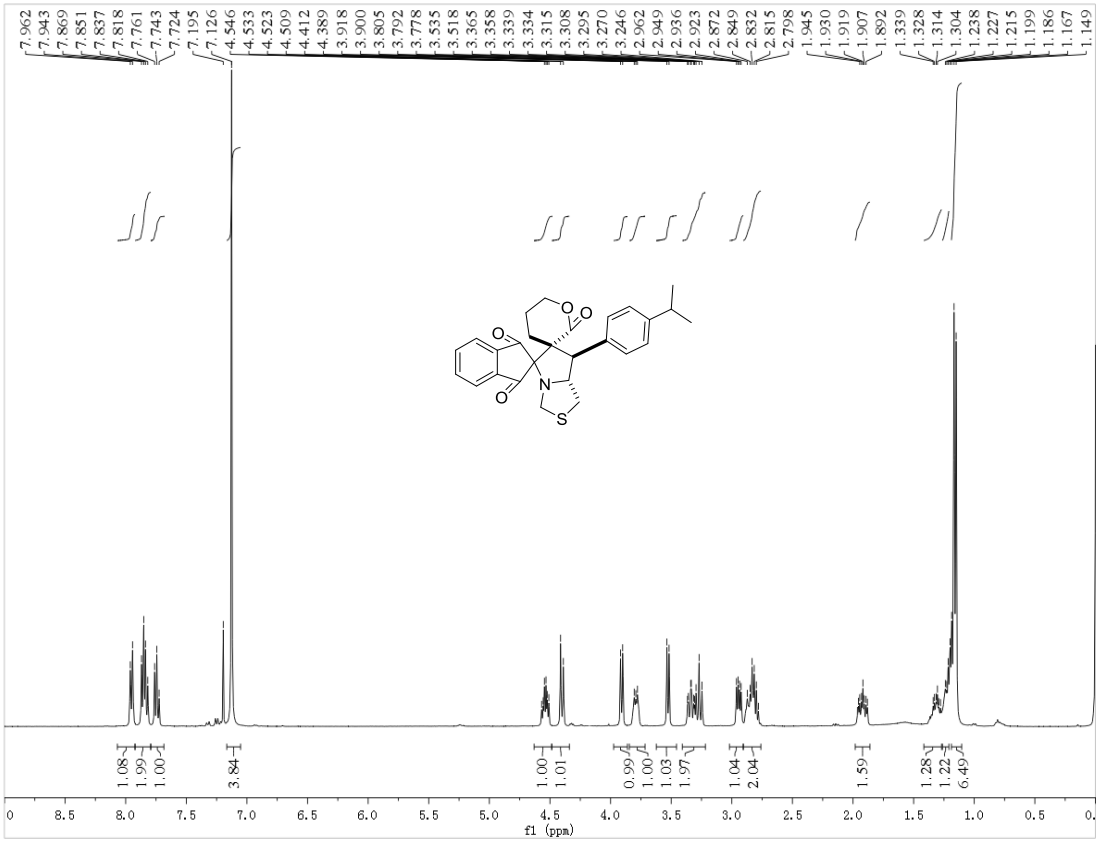


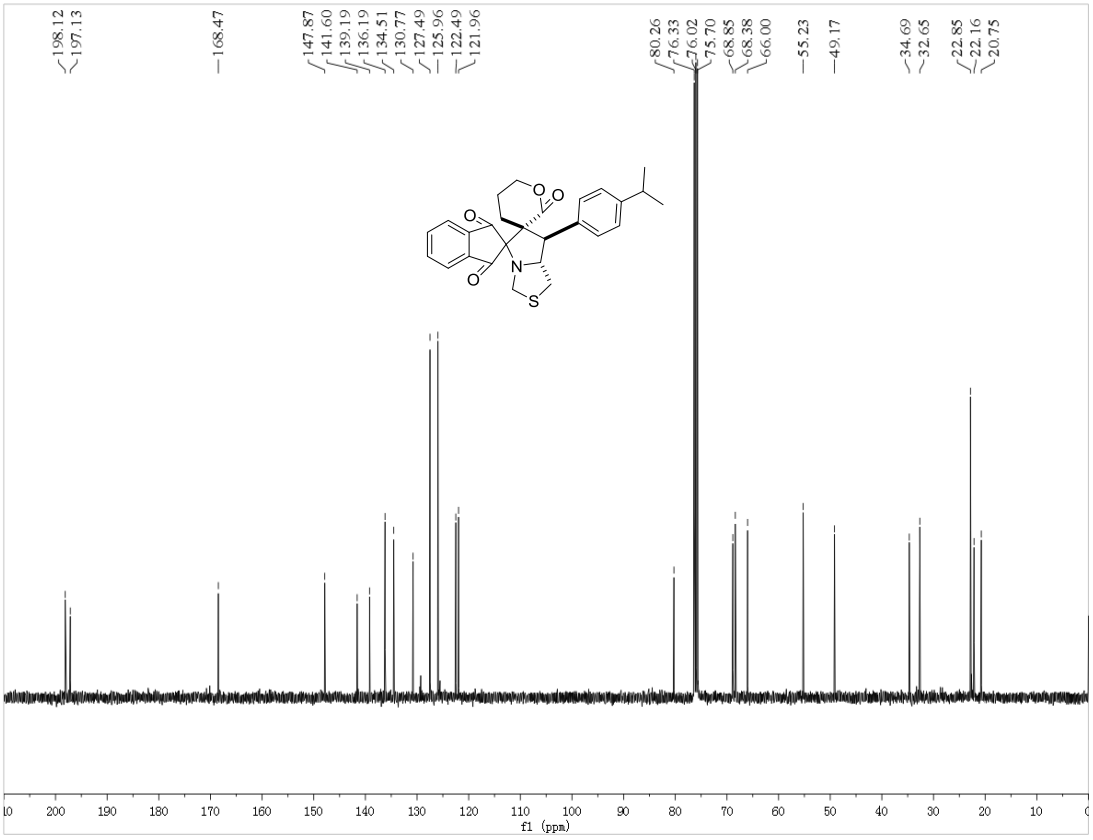
^{1}H and ^{13}C NMR of 4cg



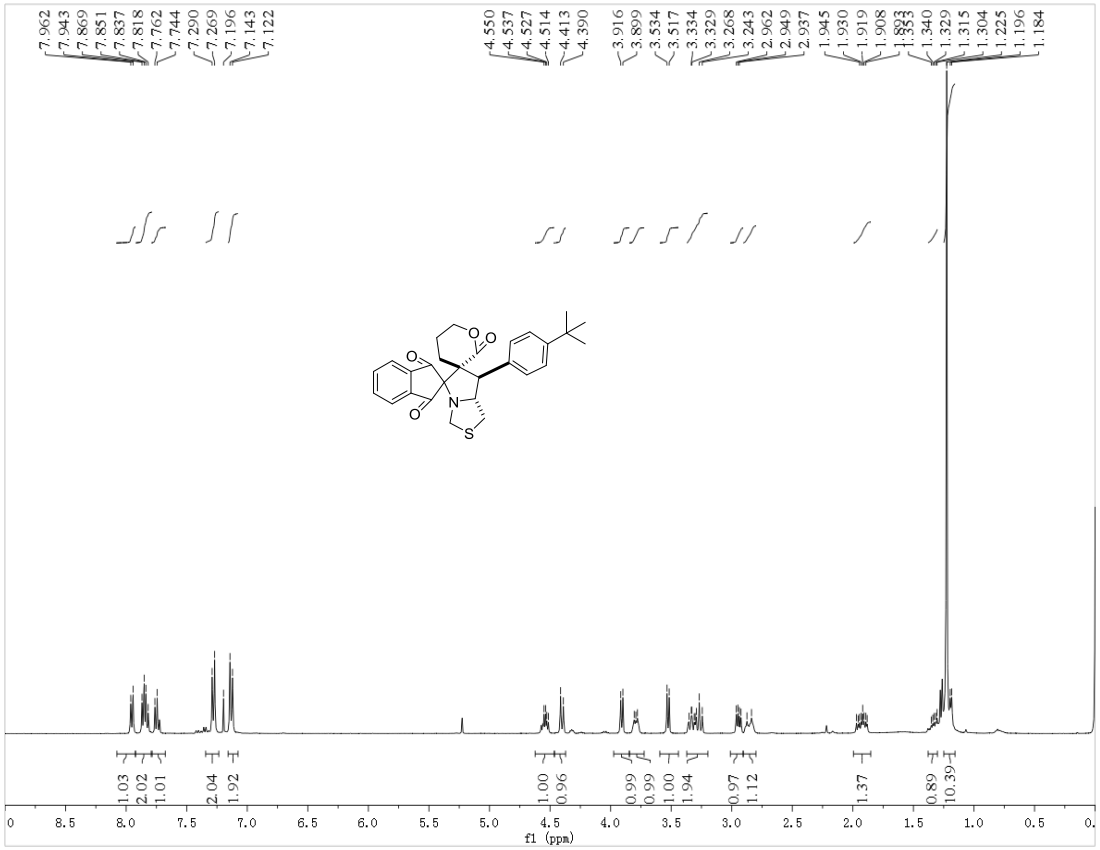


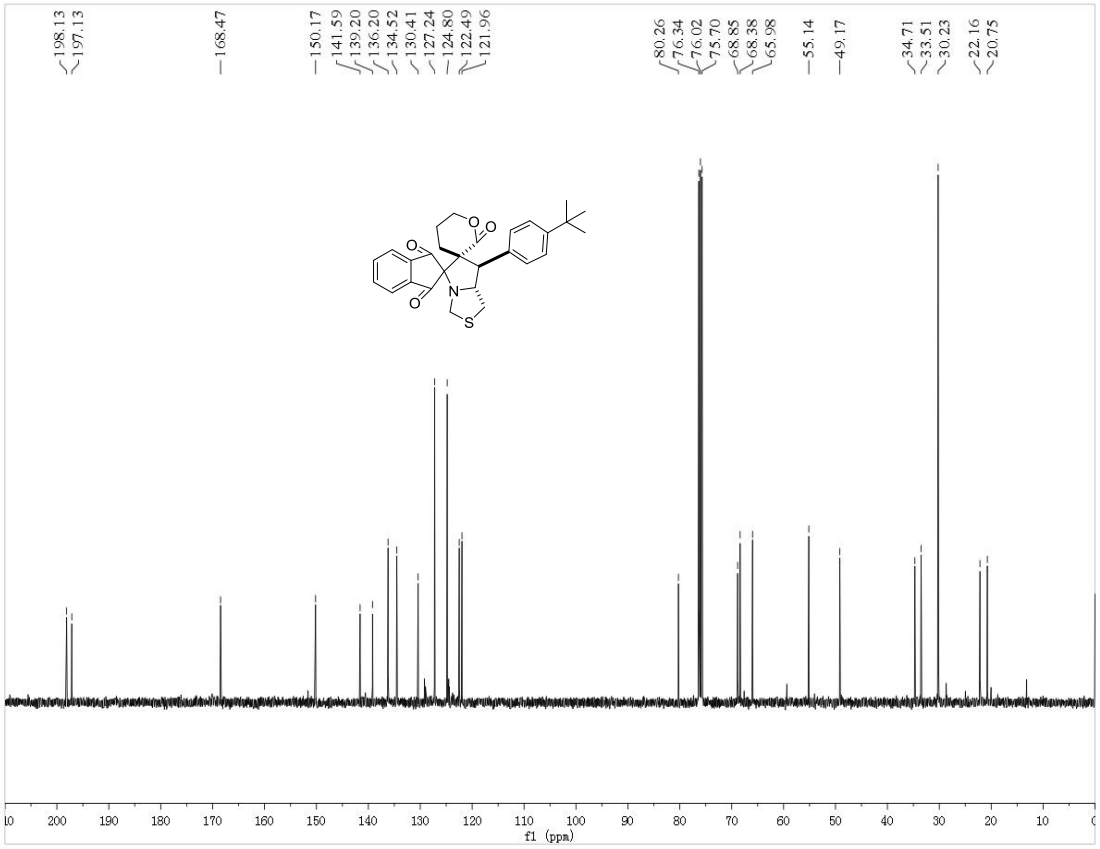
^{1}H and ^{13}C NMR of 4ch



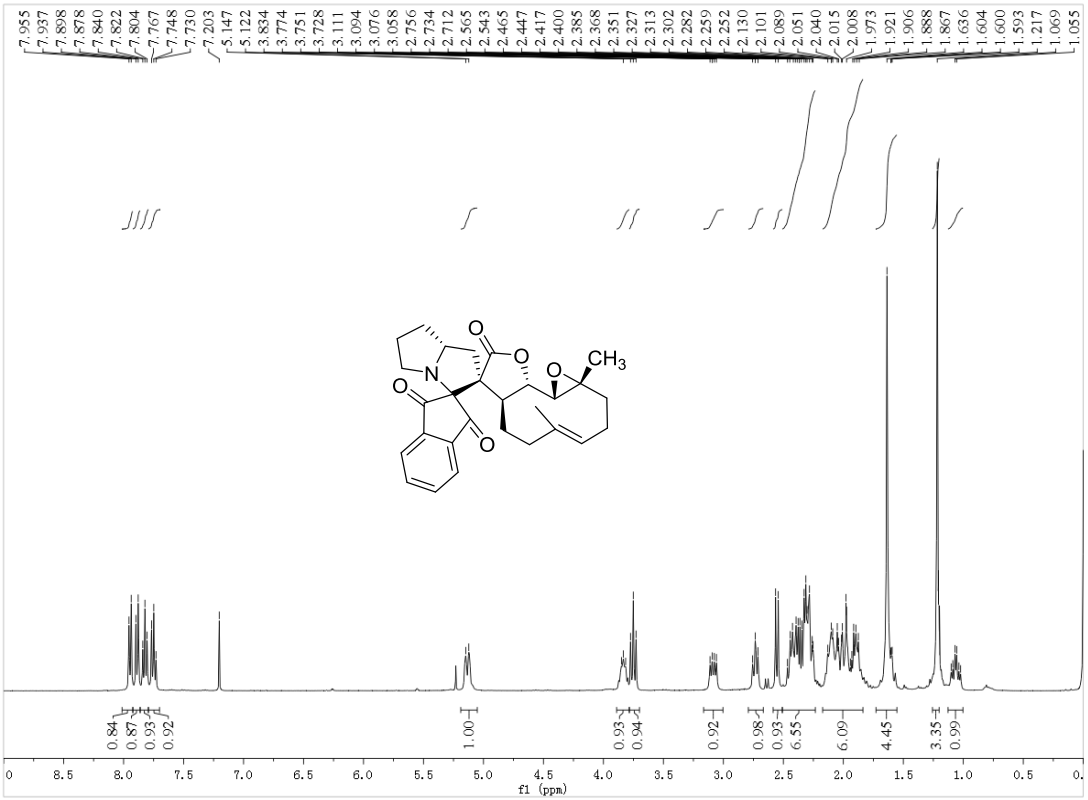


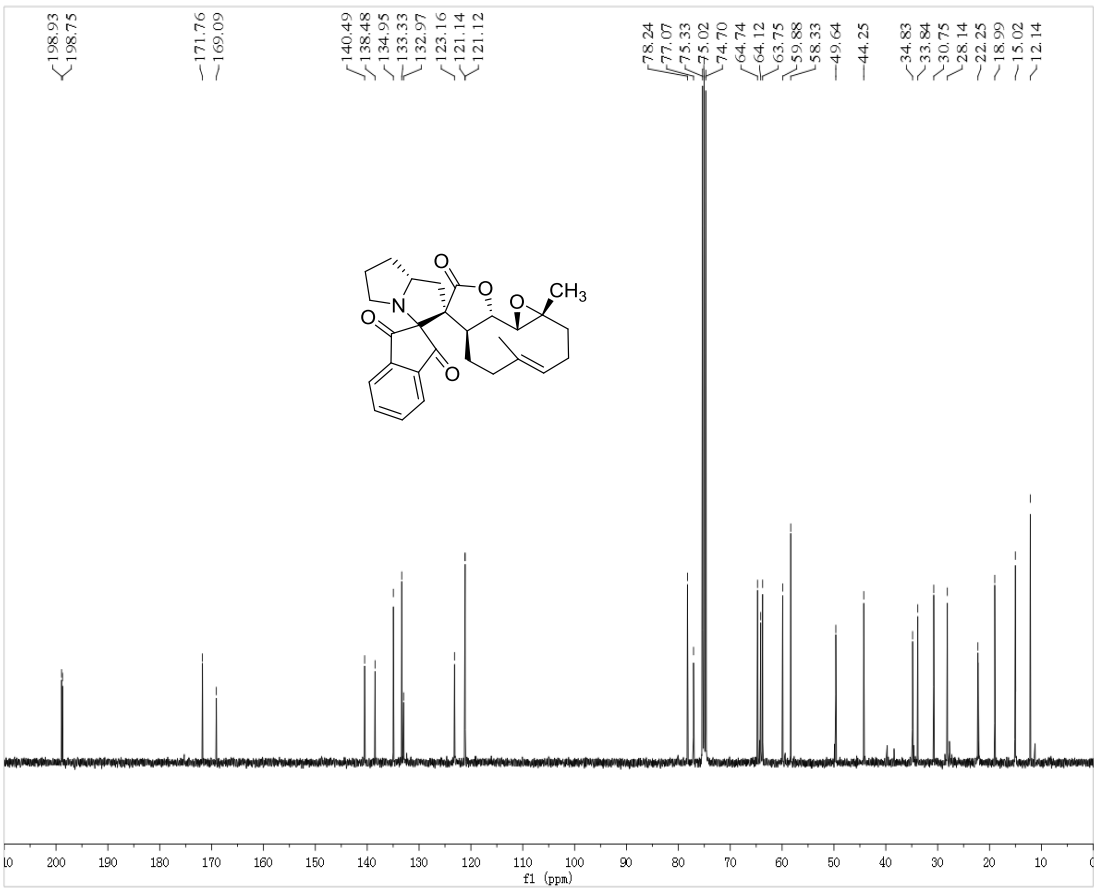
^{1}H and ^{13}C NMR of 4ci





^{1}H and ^{13}C NMR of 4da





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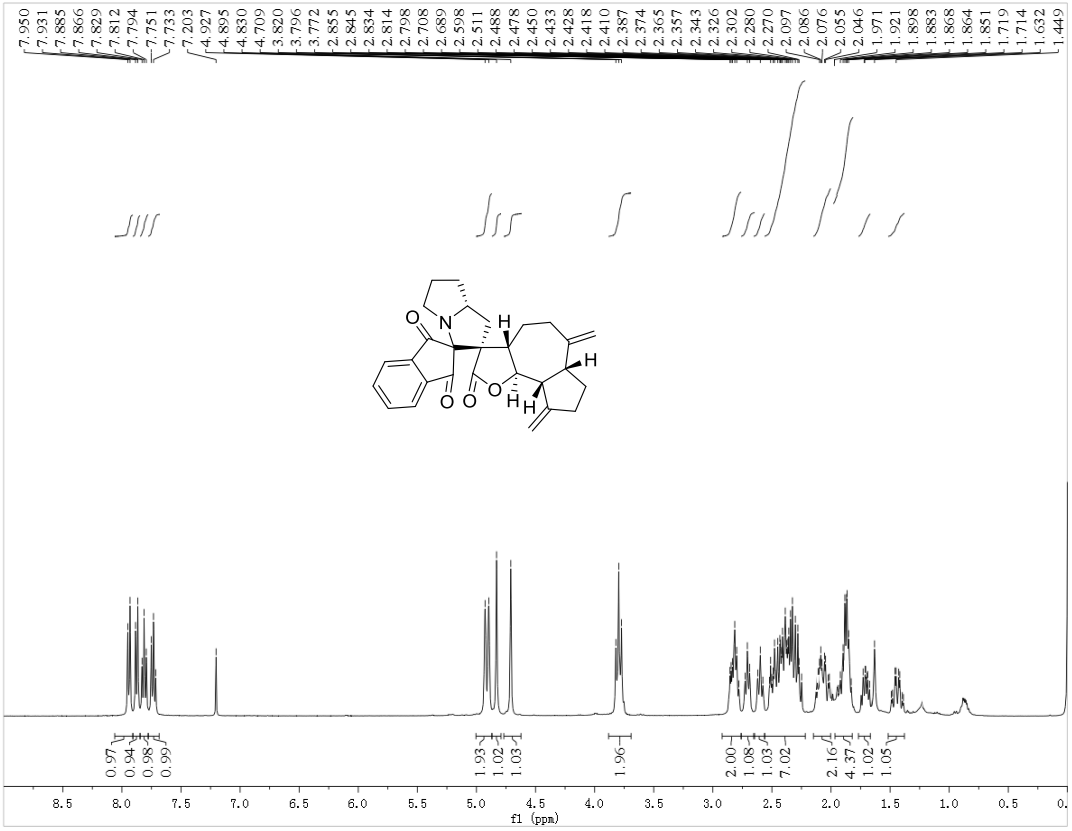
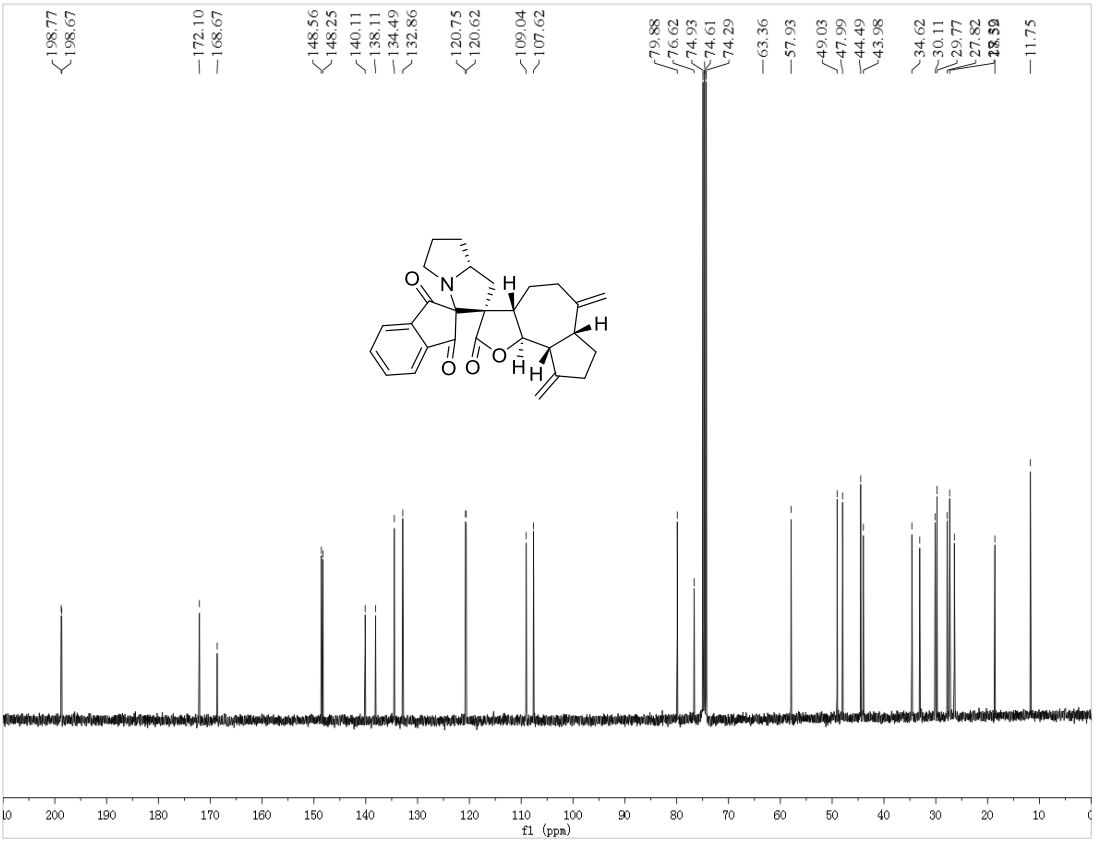
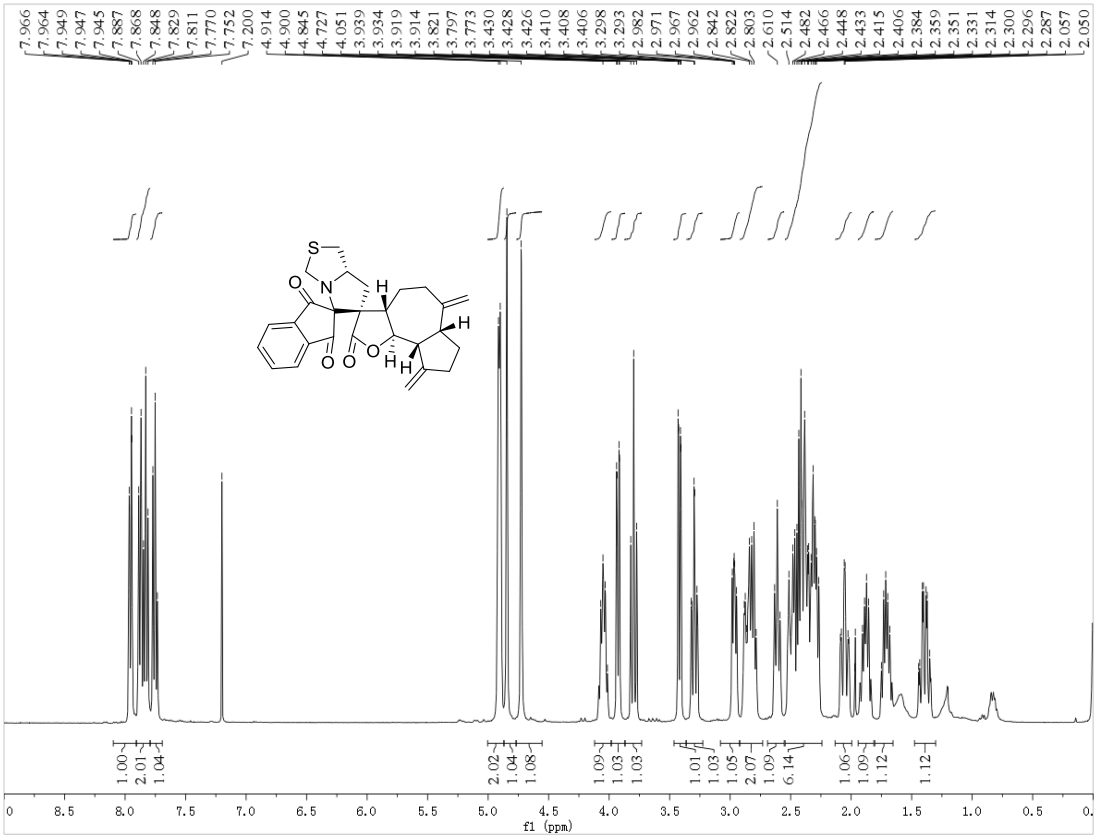
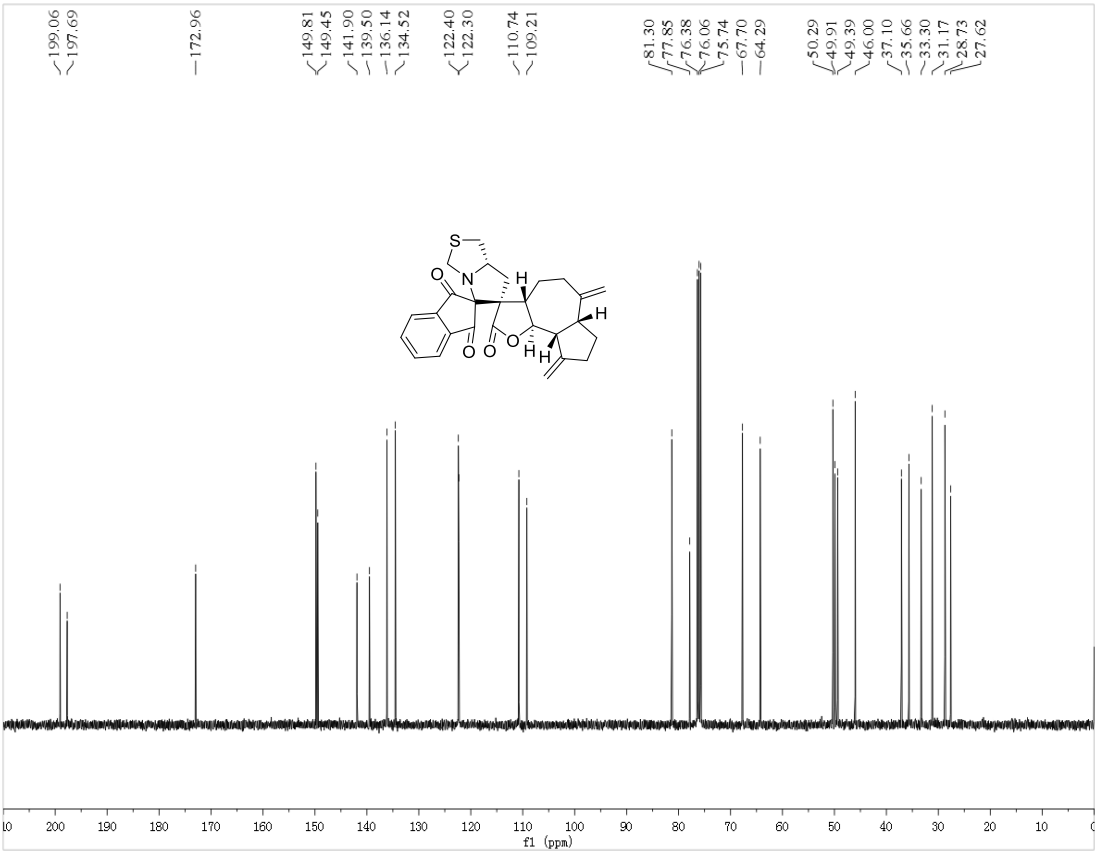


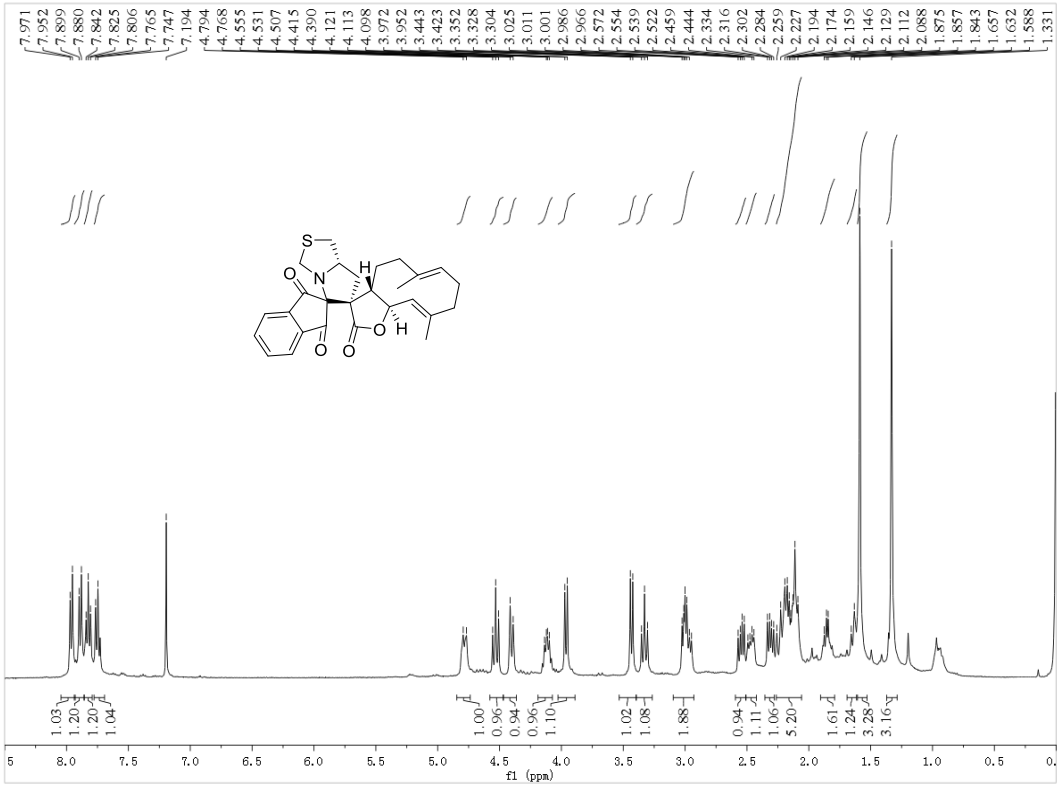


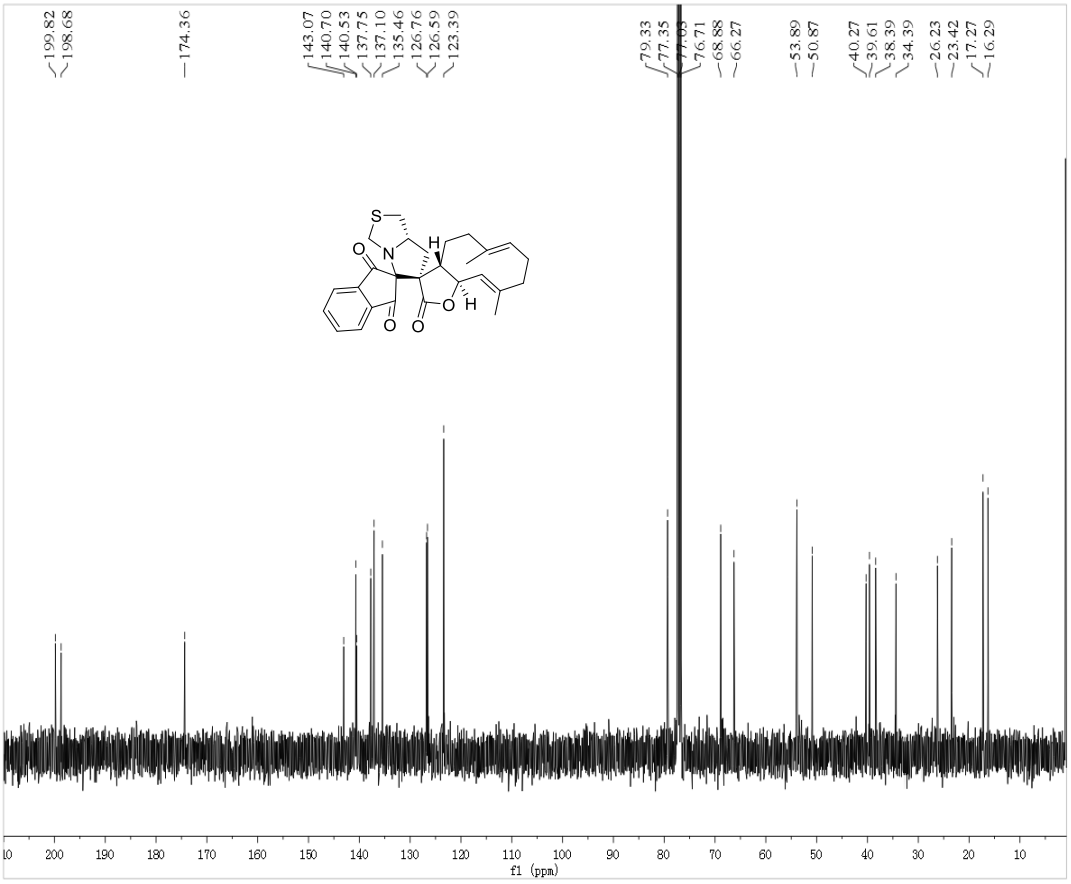
^{1}H and ^{13}C NMR of 4eb



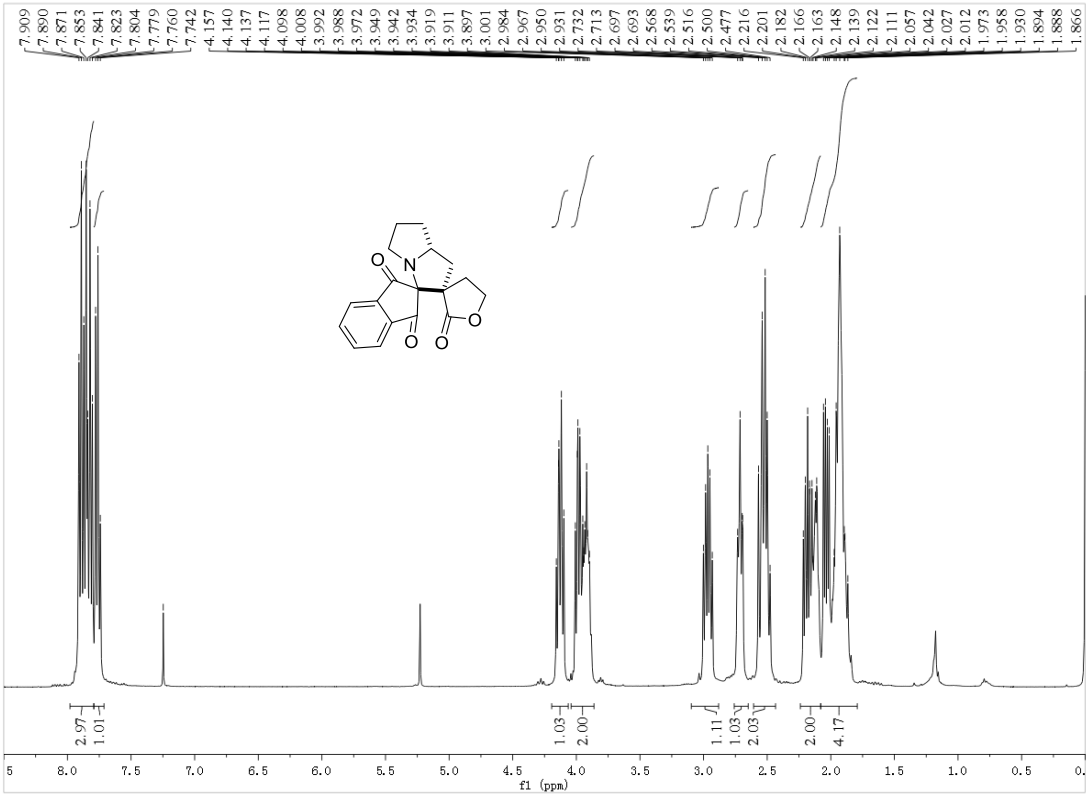


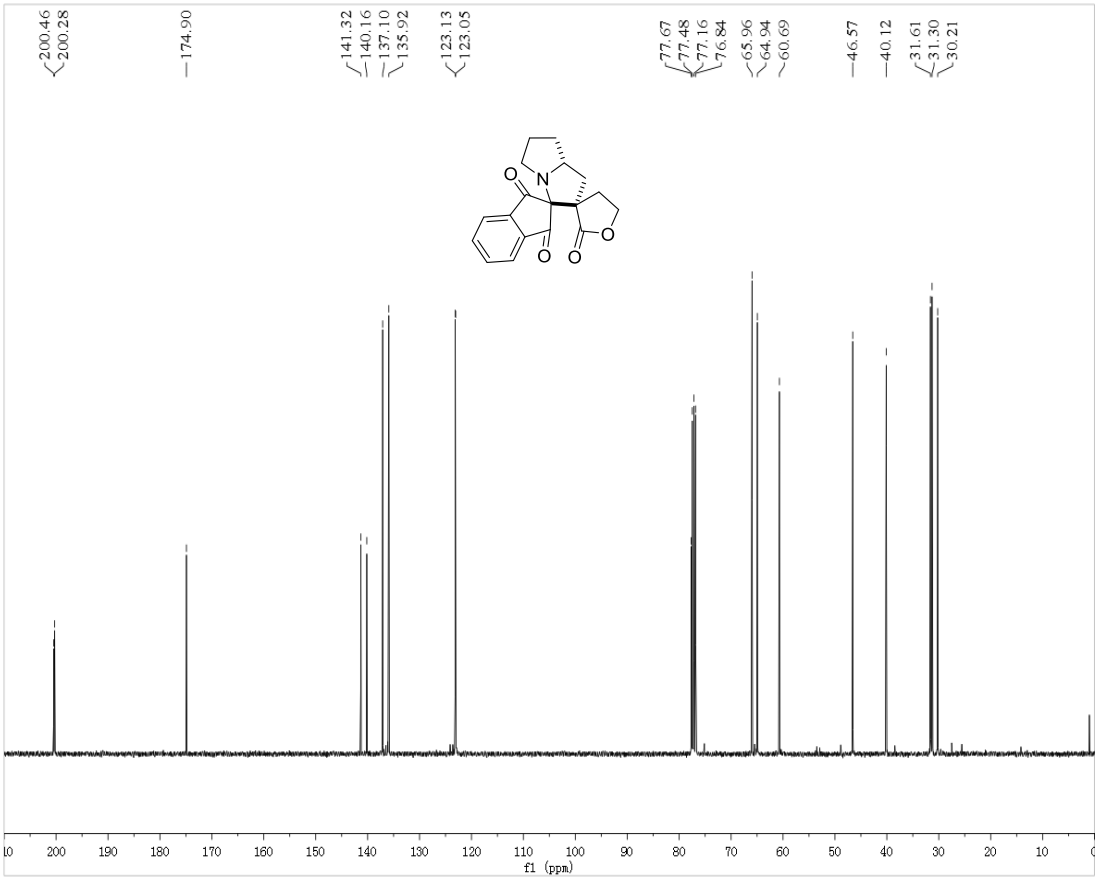
^{1}H and ^{13}C NMR of 4fa





^{1}H and ^{13}C NMR of 4ga





^{1}H and ^{13}C NMR of 4gb