

Design, synthesis and evaluation of structurally diverse polycyclic harmaline scaffolds as anticancer agents

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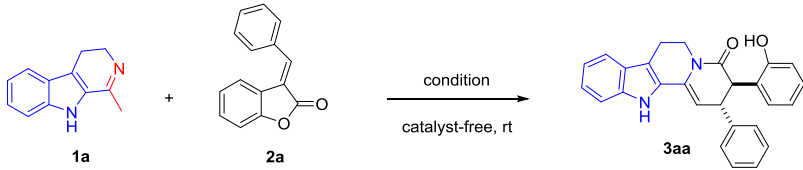
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1. General information

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. ^1H and ^{13}C NMR spectra were obtained using a Bruker DPX-400 spectrometer. ^1H 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 $\mu\text{g}/\text{mL}$ streptomycin in a humidified atmosphere with 5% CO_2 at 37°C. The synthetic compounds were placed at -20°C after dissolved in DMSO. Cisplatin purchased from Aladdin Company.

2. Table S1: optimization of reaction conditions for synthesis of product 3aa



| Entry | Solvent | Time (h) | Yield ^b (%) | Dr ^c |
|-------|------------------------|----------|------------------------|-----------------|
| 1 | toluene | 3 | 55 | 10:1 |
| 2 | DCM | 3 | 68 | 18:1 |
| 3 | DCE | 3 | 64 | 13:1 |
| 4 | CHCl_3 | 3 | 65 | 16:1 |
| 5 | CH_3CN | 3 | <10 | - |
| 6 | EtOH | 3 | <10 | - |
| 7 | THF | 3 | <10 | - |
| 8 | DCM | 4 | 70 | 18:1 |
| 9 | DCM | 7 | 69 | 18:1 |

^a Unless noted, reactions were carried out with 0.2 mmol of compound **1a** and 0.3 mmol of compound **2a** in 2.0 mL of solvent under catalyst-free condition at room temperature.

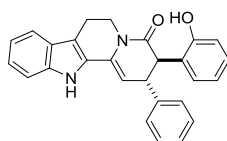
^b Isolated yield after flash chromatography.

^c Determined by ^1H -NMR analysis.

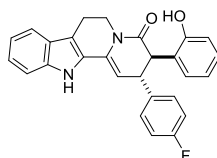
3. Synthesis of polycyclic harmaline scaffolds 3

In a sealed tube equipped with a magnetic stirring bar, to 2.0 mL of DCM was added harmaline scaffold **1** (0.2 mmol) and 3-vinyl benzofuranone **2** (0.3 mmol). The reaction mixture was stirred at rt for 4 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 polycyclic harmaline scaffold **3**.

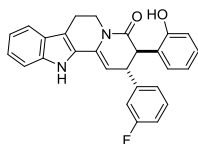
4. Characterization data of products 3



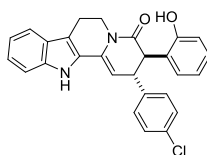
3aa: Light yellow solid, m.p. 138.7-139.4 °C; yield 70%, 18:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 2.97-3.00 (m, 2H), 3.87-3.93 (m, 1H), 4.08-4.11 (m, 1H), 4.21 (d, *J* = 8.4 Hz, 1H), 4.30-4.36 (m, 1H), 5.88 (d, *J* = 5.2 Hz, 1H), 6.61-6.64 (m, 1H), 6.84-6.91 (m, 2H), 6.99-7.06 (m, 2H), 7.14-7.23 (m, 2H), 7.30-7.35 (m, 5H), 7.53 (d, *J* = 8.0 Hz, 1H), 9.70 (br s, 1H), 11.32 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 20.9, 39.3, 43.0, 49.9, 103.0, 111.2, 111.7, 119.2, 119.3, 125.7, 126.5, 127.8, 128.5, 129.1, 130.9, 137.9, 143.4, 155.5, 168.9; HRMS (ESI-TOF) *m/z*: Calcd. for C₂₇H₂₂N₂NaO₂ [M+Na]⁺: 429.1573; Found: 429.1577.



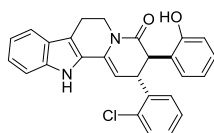
3ab: Light yellow solid, m.p. 140.8-141.5 °C; yield 62%, 17:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 2.97-2.99 (m, 2H), 3.93-4.00 (m, 1H), 4.11-4.18 (m, 2H), 4.23-4.29 (m, 1H), 5.86 (d, *J* = 4.8 Hz, 1H), 6.61-6.65 (m, 1H), 6.83-6.90 (m, 2H), 7.00-7.06 (m, 2H), 7.10-7.18 (m, 3H), 7.30-7.35 (m, 3H), 7.53 (d, *J* = 8.0 Hz, 1H), 9.68 (br s, 1H), 11.32 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 20.9, 39.3, 42.2, 50.1, 102.9, 111.3, 115.7 (d, *J*_{CF} = 21.1 Hz), 119.3, 125.5, 126.5, 128.3, 128.5 (d, *J*_{CF} = 25.2 Hz), 129.7 (d, *J*_{CF} = 8.3 Hz), 129.8, 131.0, 137.9, 139.5, 139.6, 155.5, 161.5 (d, *J*_{CF} = 240.1 Hz), 168.8; HRMS (ESI-TOF) *m/z*: Calcd. for C₂₇H₂₁FN₂NaO₂ [M+Na]⁺: 447.1479; Found: 447.1472.



3ac: Light yellow solid, m.p. 133.4-134.1 °C; yield 71%, 17:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.94-3.03 (m, 2H), 3.99-4.05 (m, 1H), 4.17-4.25 (m, 3H), 5.87 (d, $J = 4.8$ Hz, 1H), 6.62-6.66 (m, 1H), 6.84-6.86 (m, 1H), 6.90-6.92 (m, 1H), 7.00-7.06 (m, 3H), 7.09-7.19 (m, 3H), 7.31-7.37 (m, 2H), 7.54 (d, $J = 8.0$ Hz, 1H), 9.72 (br s, 1H), 11.33 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 39.3, 42.6, 49.7, 102.5, 111.4, 111.7, 113.9 (d, $J_{CF} = 21.0$ Hz), 114.5 (d, $J_{CF} = 21.1$ Hz), 115.7, 119.3, 119.4, 123.4, 125.4, 126.5, 128.4, 130.9 (d, $J_{CF} = 8.2$ Hz), 131.1, 137.9, 146.3 (d, $J_{CF} = 7.2$ Hz), 155.5, 162.7 (d, $J_{CF} = 242.3$ Hz), 168.7; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{27}\text{H}_{21}\text{FN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 447.1479; Found: 447.1484.

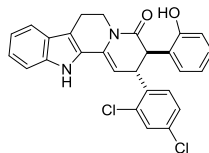


3ad: Light yellow solid, m.p. 135.5-136.6 °C; yield 60%, 10:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.98 (s, 2H), 3.94-4.04 (m, 1H), 4.14-4.16 (m, 2H), 4.23-4.26 (m, 1H), 5.85 (d, $J = 4.4$ Hz, 1H), 6.61-6.65 (m, 1H), 6.83-6.89 (m, 2H), 7.00-7.06 (m, 2H), 7.15-7.21 (m, 2H), 7.29-7.37 (m, 4H), 7.53 (d, $J = 8.0$ Hz, 1H), 9.70 (br s, 1H), 11.32 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 40.3, 42.3, 49.9, 102.6, 111.4, 111.7, 119.3, 125.3, 126.5, 128.4, 129.0, 129.8, 131.2, 131.7, 137.9, 142.3, 155.5, 168.7; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{27}\text{H}_{21}\text{ClN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 463.1184; Found: 463.1183.

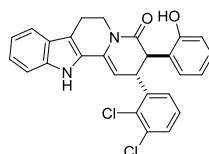


3ae: Light yellow solid, m.p. 141.2-141.9 °C; yield 58%, >20:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.90-3.00 (m, 2H), 4.00-4.04 (m, 1H), 4.17-4.21 (m, 1H), 4.38 (d, $J = 8.8$ Hz, 1H), 4.65-4.69 (m, 1H), 5.85 (d, $J = 4.8$ Hz, 1H), 6.60-6.64 (m, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.94-7.04 (m, 3H), 7.13-7.23 (m, 2H), 7.28-7.34 (m, 2H), 7.80 (d, $J = 7.6$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 9.59 (br s, 1H), 11.29 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8,

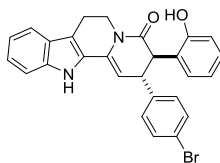
39.3, 40.4, 47.5, 102.9, 111.3, 111.7, 115.7, 119.2, 125.3, 126.4, 128.1, 128.4, 128.5, 128.7, 130.0, 130.5, 133.3, 137.9, 140.7, 155.6, 169.2; HRMS (ESI-TOF) m/z : Calcd. for $C_{27}H_{21}ClN_2NaO_2$ $[M+Na]^+$: 463.1184; Found: 463.1181.



3af: Light yellow solid, m.p. 142.5-143.3 °C; yield 62%, 15:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.89-3.01 (m, 2H), 3.90-3.96 (m, 1H), 4.24-4.30 (m, 1H), 4.35 (d, $J = 9.2$ Hz, 1H), 4.66-4.69 (m, 1H), 5.80 (d, $J = 4.4$ Hz, 1H), 6.60-6.64 (m, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 6.92-6.94 (m, 1H), 6.98-7.04 (m, 2H), 7.13-7.17 (m, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.38-7.41 (m, 1H), 7.47-7.54 (m, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 39.6, 40.4, 47.7, 102.4, 111.4, 111.7, 115.7, 119.1, 119.3, 124.9, 126.4, 128.2, 128.3, 128.4, 129.3, 130.8, 132.4, 134.3, 137.9, 139.8, 155.6, 169.0; HRMS (ESI-TOF) m/z : Calcd. for $C_{27}H_{20}Cl_2N_2NaO_2$ $[M+Na]^+$: 497.0794; Found: 497.0790.

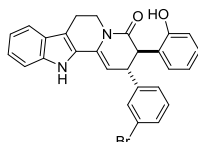


3ag: Light yellow solid, m.p. 134.8-135.3 °C; yield 57%, 10:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.89-3.03 (m, 2H), 3.95-4.04 (m, 1H), 4.21-4.25 (m, 1H), 4.38 (d, $J = 8.8$ Hz, 1H), 4.73-4.77 (m, 1H), 5.83 (d, $J = 4.4$ Hz, 1H), 6.61-6.64 (m, 1H), 6.78-6.80 (m, 1H), 6.94-7.05 (m, 3H), 7.13-7.17 (m, 1H), 7.31-7.35 (m, 2H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.48-7.53 (m, 2H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 39.3, 42.7, 47.5, 102.3, 111.4, 111.7, 115.7, 119.2, 119.3, 123.4, 125.0, 126.4, 128.3, 128.5, 128.9, 129.3, 130.8, 131.4, 132.5, 137.9, 155.6, 169.0; HRMS (ESI-TOF) m/z : Calcd. for $C_{27}H_{20}Cl_2N_2NaO_2$ $[M+Na]^+$: 497.0794; Found: 497.0795.

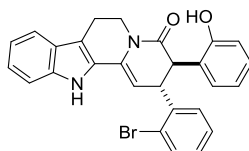


3ah: Light yellow solid, m.p. 136.4-137.3 °C; yield 67%, 18:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.96-2.99 (m, 2H), 3.92-3.98 (m, 1H), 4.11-4.16 (m, 2H), 4.21-4.27 (m, 1H), 5.83 (d, $J =$

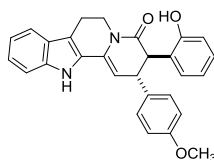
4.8 Hz, 1H), 6.61-6.64 (m, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.87 (d, $J = 6.4$ Hz, 1H), 6.99-7.06 (m, 2H), 7.14-7.18 (m, 1H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 1H), 9.69 (br s, 1H), 11.31 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 39.3, 42.3, 49.8, 102.5, 111.4, 111.7, 115.7, 119.3, 119.6, 120.2, 123.4, 125.3, 126.5, 128.3, 128.6, 130.1, 131.2, 131.9, 137.9, 142.8, 155.4, 168.6; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{27}\text{H}_{21}\text{BrN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 507.0679; Found: 507.0674.



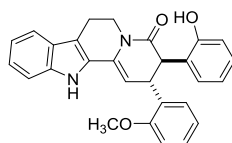
3ai: Light yellow solid, m.p. 135.7-136.2 °C; yield 61%, 15:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.97 (d, $J = 5.6$ Hz, 2H), 3.94-4.00 (m, 1H), 4.13-4.25 (m, 3H), 5.85 (d, $J = 4.4$ Hz, 1H), 6.62-6.66 (m, 1H), 6.83 (d, $J = 7.2$ Hz, 1H), 6.88-6.90 (m, 1H), 7.00-7.06 (m, 2H), 7.15-7.19 (m, 1H), 7.24-7.30 (m, 2H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.40-7.43 (m, 1H), 7.48 (s, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 9.73 (br s, 1H), 11.33 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 39.3, 42.6, 49.7, 102.3, 111.4, 111.7, 119.3, 122.3, 125.3, 126.5, 126.9, 128.3, 130.7, 131.3, 137.9, 146.2, 155.4, 168.6; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{27}\text{H}_{21}\text{BrN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 507.0679; Found: 507.0685.



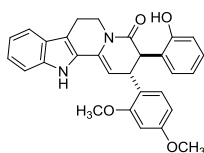
3aj: Light yellow solid, m.p. 141.6-142.3 °C; yield 64%, >20:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.92-3.00 (m, 2H), 3.97-4.03 (m, 1H), 4.19-4.23 (m, 1H), 4.38 (d, $J = 8.8$ Hz, 1H), 4.63-4.66 (m, 1H), 5.83 (d, $J = 4.4$ Hz, 1H), 6.60-6.64 (m, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.94-7.04 (m, 3H), 7.11-7.16 (m, 2H), 7.30-7.36 (m, 2H), 7.44 (d, $J = 7.2$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.55-7.57 (m, 1H), 9.58 (br s, 1H), 11.28 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 39.3, 42.2, 47.5, 103.0, 111.3, 111.7, 115.7, 119.2, 119.3, 119.6, 123.3, 125.3, 126.4, 128.3, 128.4, 128.7, 129.1, 130.3, 133.3, 137.9, 155.6, 169.2; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{27}\text{H}_{21}\text{BrN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 507.0679; Found: 507.0676.



3ak: Light yellow solid, m.p. 146.5-147.2 °C; yield 62%, 17:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 2.97-2.99 (m, 2H), 3.71 (s, 3H), 3.83-3.89 (m, 1H), 4.00-4.02 (m, 1H), 4.14 (d, *J* = 6.4 Hz, 1H), 4.31-4.37 (m, 1H), 5.85 (d, *J* = 5.6 Hz, 1H), 6.60-6.64 (m, 1H), 6.84-6.88 (m, 4H), 6.99-7.06 (m, 2H), 7.14-7.18 (m, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 9.67 (br s, 1H), 11.30 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 20.9, 39.3, 42.2, 50.1, 55.5, 103.3, 111.1, 111.7, 114.4, 115.7, 119.2, 119.3, 119.6, 123.3, 125.7, 126.5, 128.4, 128.5, 128.8, 130.7, 135.2, 137.9, 155.4, 158.5, 168.9; HRMS (ESI-TOF) *m/z*: Calcd. for C₂₈H₂₄N₂NaO₃ [M+Na]⁺: 459.1679; Found: 459.1671.

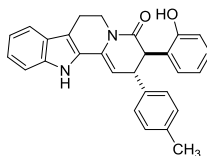


3al: Light yellow solid, m.p. 126.7-127.3 °C; yield 55%, >20:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 2.93-2.96 (m, 2H), 3.75 (s, 3H), 3.87-3.93 (m, 1H), 4.24-4.33 (m, 1H), 4.35 (s, 3H), 5.81-5.82 (m, 1H), 6.60-6.64 (m, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.87-6.91 (m, 1H), 6.94-7.04 (m, 3H), 7.11-7.22 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 9.49 (br s, 1H), 11.24 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 20.9, 37.4, 39.3, 46.6, 56.0, 106.3, 110.8, 111.6, 119.1, 119.2, 121.0, 126.2, 126.5, 128.7, 130.0, 131.4, 137.8, 155.5, 157.2, 169.6; HRMS (ESI-TOF) *m/z*: Calcd. for C₂₈H₂₄N₂NaO₃ [M+Na]⁺: 459.1679; Found: 459.1675.

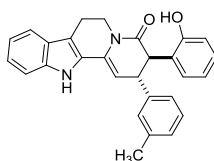


3am: Light yellow solid, m.p. 130.2-130.9 °C; yield 54%, >20:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 2.93-2.96 (m, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 4.22-4.28 (m, 3H), 5.78 (d, *J* = 4.8 Hz, 1H), 6.44-6.47 (m, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.59-6.63 (m, 1H), 6.77-6.79 (m, 1H), 6.92-7.04 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.11-7.15 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 9.46 (br s, 1H), 11.23 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 20.9, 37.0, 39.4, 46.9, 55.6,

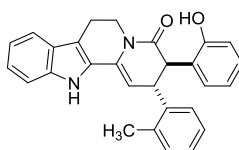
56.0, 99.2, 104.1, 105.2, 110.7, 111.6, 115.6, 119.1, 119.2, 119.5, 123.1, 123.6, 126.3, 126.5, 128.0, 128.3, 128.5, 128.7, 129.8, 137.8, 155.5, 158.1, 159.7, 169.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{29}H_{26}N_2NaO_4 [M+Na]^+$: 489.1785; Found: 489.1788.



3an: Light yellow solid, m.p. 137.6-137.9 °C; yield 64%, >20:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.25 (s, 3H), 2.96-2.99 (m, 2H), 3.83-3.90 (m, 1H), 4.03-4.06 (m, 1H), 4.19 (d, J = 6.0 Hz, 1H), 4.32-4.37 (m, 1H), 5.86 (d, J = 5.6 Hz, 1H), 6.60-6.64 (m, 1H), 6.84-6.91 (m, 2H), 6.99-7.06 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.14-7.21 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 9.69 (br s, 1H), 11.31 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 21.1, 39.3, 42.6, 50.0, 103.2, 111.2, 111.7, 115.6, 119.2, 119.3, 119.6, 123.3, 125.7, 126.5, 127.7, 128.5, 129.6, 130.8, 136.2, 137.9, 140.3, 155.5, 168.9; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{24}N_2NaO_2 [M+Na]^+$: 443.1730; Found: 443.1736.

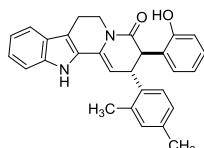


3ao: Light yellow solid, m.p. 132.2-133.0 °C; yield 66%, >20:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.27 (s, 3H), 2.97-3.00 (m, 2H), 3.84-3.90 (m, 1H), 4.03-4.06 (m, 1H), 4.21 (d, J = 6.4 Hz, 1H), 4.34-4.40 (m, 1H), 5.87 (d, J = 5.2 Hz, 1H), 6.61-6.65 (m, 1H), 6.84-6.91 (m, 2H), 7.00-7.06 (m, 3H), 7.09-7.21 (m, 4H), 7.35 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 9.72 (br s, 1H), 11.32 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 21.6, 39.3, 42.9, 49.8, 103.1, 111.2, 111.7, 119.2, 119.3, 124.9, 125.8, 126.5, 128.5, 129.0, 130.8, 137.9, 138.1, 143.3, 155.5, 168.9; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{24}N_2NaO_2 [M+Na]^+$: 443.1730; Found: 443.1737.

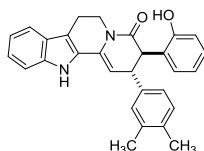


3ap: Light yellow solid, m.p. 135.1-136.2 °C; yield 64%, >20:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.33 (s, 3H), 2.95-2.98 (m, 2H), 4.02-4.08 (m, 1H), 4.16-4.19 (m, 1H), 4.22 (d, J = 7.6

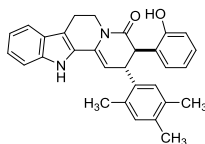
Hz, 1H), 4.32-4.35 (m, 1H), 5.84 (d, $J = 4.8$ Hz, 1H), 6.59-6.63 (m, 1H), 6.81-6.83 (m, 1H), 6.92-6.95 (m, 1H), 6.98-7.17 (m, 6H), 7.28 (d, $J = 9.6$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 9.67 (br s, 1H), 11.27 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 19.7, 20.9, 39.1, 39.4, 48.3, 103.9, 111.1, 111.7, 119.2, 119.3, 125.8, 126.5, 126.8, 126.9, 127.1, 128.6, 130.6, 130.9, 136.1, 137.9, 141.5, 155.5, 169.3; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 443.1730; Found: 443.1728.



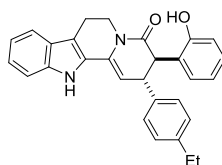
3aq: Light yellow solid, m.p. 128.6-129.2 °C; yield 70%, 20:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.20 (s, 3H), 2.30 (s, 3H), 2.95-2.98 (m, 2H), 3.98-4.04 (m, 2H), 4.25-4.29 (m, 1H), 5.81 (d, $J = 4.8$ Hz, 1H), 6.59-6.63 (m, 1H), 6.79-6.82 (m, 1H), 6.91-6.94 (m, 3H), 6.98-7.05 (m, 2H), 7.13-7.17 (m, 2H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 9.65 (br s, 1H), 11.25 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 19.6, 21.0, 38.8, 39.3, 40.5, 48.3, 104.1, 111.0, 111.7, 119.2, 119.3, 125.8, 126.5, 127.0, 127.3, 128.6, 130.5, 131.5, 135.7, 135.8, 137.8, 138.4, 155.5, 169.3; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 457.1886; Found: 457.1880.



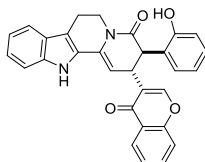
3ar: Light yellow solid, m.p. 127.9-128.7 °C; yield 62%, >20:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.16 (s, 3H), 2.18 (s, 3H), 2.96-2.99 (m, 2H), 3.98-4.01 (m, 1H), 4.18 (d, $J = 6.0$ Hz, 1H), 4.33-4.37 (m, 1H), 5.84 (d, $J = 5.2$ Hz, 1H), 6.60-6.64 (m, 1H), 6.82-6.84 (m, 1H), 6.88-6.90 (m, 1H), 6.99-7.08 (m, 5H), 7.13-7.17 (m, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 9.68 (br s, 1H), 11.29 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 19.4, 20.1, 20.9, 40.6, 42.5, 49.8, 103.3, 111.1, 111.7, 115.7, 119.2, 119.3, 119.6, 123.3, 125.1, 125.8, 126.5, 128.2, 128.5, 128.9, 130.1, 130.7, 134.9, 136.7, 137.9, 140.7, 155.5, 168.9; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 457.1886; Found: 457.1889.



3as: Light yellow solid, m.p. 131.5-132.2 °C; yield 55%, >20:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 2.11 (s, 6H), 2.23 (s, 3H), 2.97 (s, 2H), 4.03-4.08 (m, 1H), 4.16-4.19 (m, 2H), 4.24-4.27 (m, 1H), 5.81 (d, *J* = 4.8 Hz, 1H), 6.58-6.62 (m, 1H), 6.79-6.81 (m, 1H), 6.87 (s, 3H), 6.91-6.93 (m, 1H), 6.99-7.05 (m, 3H), 7.13-7.17 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 9.64 (br s, 1H), 11.25 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 19.1, 19.3, 19.7, 20.9, 39.4, 39.6, 48.6, 104.4, 111.0, 111.7, 119.2, 119.3, 125.9, 126.5, 128.3, 128.6, 130.4, 132.0, 133.1, 134.0, 134.4, 137.8, 138.7, 155.5, 169.3; HRMS (ESI-TOF) *m/z*: Calcd. for C₃₀H₂₈N₂NaO₂ [M+Na]⁺: 471.2043; Found: 471.2044.

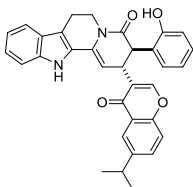


3at: Light yellow solid, m.p. 127.5-128.2 °C; yield 74%, 19:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 1.13-1.17 (m, 3H), 2.52-2.58 (m, 2H), 2.97-3.00 (m, 2H), 3.82-3.88 (m, 1H), 4.03-4.06 (m, 1H), 4.21 (d, *J* = 7.0 Hz, 1H), 4.36-4.39 (m, 1H), 5.87 (d, *J* = 5.6 Hz, 1H), 6.61-6.64 (m, 1H), 6.85-6.91 (m, 2H), 7.00-7.06 (m, 2H), 7.13-7.18 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 9.71 (br s, 1H), 11.31 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 16.1, 20.9, 28.3, 39.4, 42.6, 49.9, 103.2, 111.2, 111.7, 119.2, 119.3, 125.8, 126.5, 127.7, 128.3, 128.5, 130.8, 137.9, 140.6, 142.6, 155.5, 168.9; HRMS (ESI-TOF) *m/z*: Calcd. for C₂₉H₂₆N₂NaO₂ [M+Na]⁺: 457.1886; Found: 457.1890.

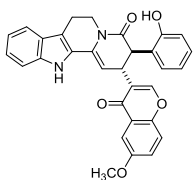


3au: Light yellow solid, m.p. 262.8-263.4 °C; yield 75%, >20:1 dr; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 2.91-3.00 (m, 2H), 3.90-3.96 (m, 1H), 4.22-4.31 (m, 2H), 4.43 (d, *J* = 9.2 Hz, 1H), 5.83 (d, *J* = 4.4 Hz, 1H), 6.64-6.67 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.99-7.04 (m, 3H), 7.12-7.16 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.47-7.53 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.76-7.81 (m, 1H),

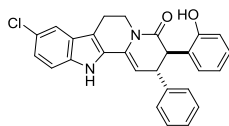
8.06-8.08 (m, 1H), 8.19 (s, 1H), 9.56 (br s, 1H), 11.29 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 35.3, 45.9, 55.4, 102.6, 111.0, 111.7, 115.8, 118.8, 119.2, 119.3, 119.5, 123.6, 124.5, 125.5, 125.6, 126.0, 126.4, 128.6, 137.8, 154.6, 155.6, 156.0, 169.2, 176.4; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{30}\text{H}_{22}\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 497.1472; Found: 497.1468.



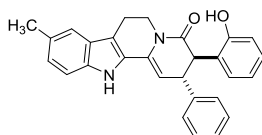
3av: Light yellow solid, m.p. 261.3-262.2 $^{\circ}\text{C}$; yield 71%, >20:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 1.22 (s, 3H), 1.24 (s, 3H), 2.88-3.06 (m, 3H), 3.92-3.97 (m, 1H), 4.20-4.29 (m, 2H), 4.43 (d, $J = 9.2$ Hz, 1H), 5.81 (d, $J = 4.4$ Hz, 1H), 6.64-6.68 (m, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.99-7.04 (m, 3H), 7.12-7.16 (m, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 2H), 7.67-7.70 (m, 1H), 7.89 (d, $J = 2.0$ Hz, 1H), 8.17 (s, 1H), 9.53 (br s, 1H), 11.27 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 24.1, 24.2, 33.4, 35.4, 45.9, 102.6, 110.9, 111.6, 115.8, 118.8, 119.3, 121.9, 123.4, 124.3, 125.6, 126.5, 128.6, 130.6, 137.8, 146.3, 154.5, 154.6, 155.6, 169.2, 176.5; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{33}\text{H}_{28}\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 539.1941; Found: 539.1943.



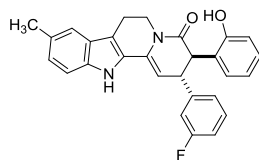
3aw: Light yellow solid, m.p. 263.1-264.0 $^{\circ}\text{C}$; yield 73%, >20:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.91-2.97 (m, 2H), 3.85 (s, 3H), 3.92-3.98 (m, 1H), 4.20-4.28 (m, 2H), 4.42 (d, $J = 8.8$ Hz, 1H), 5.80 (d, $J = 4.4$ Hz, 1H), 6.64-6.68 (m, 1H), 6.77-6.80 (m, 1H), 6.98-7.04 (m, 3H), 7.12-7.16 (m, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.37-7.43 (m, 2H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.57 (d, $J = 8.8$ Hz, 1H), 8.18 (s, 1H), 9.52 (br s, 1H), 11.27 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 35.4, 40.3, 45.8, 56.2, 102.8, 105.1, 110.9, 111.6, 115.8, 119.1, 119.3, 119.5, 120.5, 123.2, 123.7, 124.0, 124.3, 125.5, 126.4, 128.3, 128.6, 130.6, 137.8, 150.8, 154.4, 155.6, 157.0, 169.2, 176.1; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{31}\text{H}_{24}\text{N}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$: 527.1577; Found: 527.1585.



3ba: Light yellow solid, m.p. 126.4-127.2 °C; yield 77%, 10:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.96-2.99 (m, 2H), 3.90-3.95 (m, 1H), 4.11-4.14 (m, 1H), 4.21 (d, J = 6.4 Hz, 1H), 4.24-4.29 (m, 1H), 5.92 (d, J = 5.2 Hz, 1H), 6.60-6.64 (m, 1H), 6.83-6.90 (m, 2H), 7.00-7.04 (m, 1H), 7.14-7.22 (m, 2H), 7.30-7.36 (m, 5H), 7.61 (d, J = 2.0 Hz, 1H), 9.70 (br s, 1H), 11.54 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 39.4, 42.9, 49.8, 104.1, 111.0, 113.2, 118.6, 124.2, 125.6, 127.6, 127.9, 129.1, 130.1, 130.6, 136.3, 143.2, 155.5, 168.8; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{27}\text{H}_{21}\text{ClN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 463.1184; Found: 463.1183.

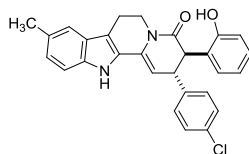


3ca: Light yellow solid, m.p. 127.6-128.3 °C; yield 57%, 15:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.37 (s, 3H), 2.88-2.97 (m, 2H), 3.95-4.02 (m, 1H), 4.18-4.24 (m, 1H), 4.36 (d, J = 9.2 Hz, 1H), 4.61-4.64 (m, 1H), 5.78 (d, J = 4.4 Hz, 1H), 6.59-6.63 (m, 1H), 6.76-6.78 (m, 1H), 6.92-7.01 (m, 3H), 7.11-7.15 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 7.33-7.36 (m, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.55-7.57 (m, 1H), 9.57 (br s, 1H), 11.13 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 21.6, 39.4, 42.1, 47.5, 102.7, 110.8, 115.6, 118.8, 119.1, 125.2, 126.6, 128.1, 128.4, 128.7, 129.0, 133.2, 136.2, 142.4, 155.6, 169.2; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 443.1730; Found: 443.1734.

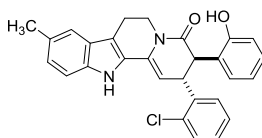


3cb: Light yellow solid, m.p. 132.1-132.9 °C; yield 54%, 12:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.38 (s, 3H), 2.93-2.96 (m, 2H), 3.97-4.03 (m, 1H), 4.14-4.20 (m, 3H), 5.82 (d, J = 4.4 Hz, 1H), 6.60-6.64 (m, 1H), 6.81-6.83 (m, 1H), 6.87-6.89 (m, 1H), 6.98-7.13 (m, 5H), 7.22 (d, J = 8.4 Hz, 1H), 7.31-7.34 (m, 2H), 9.68 (br s, 1H), 11.17 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 21.6, 39.4, 42.6, 49.7, 102.3, 110.9, 111.4, 113.9 (d, J_{CF} = 21.2 Hz), 114.5 (d, J_{CF} = 21.3 Hz), 115.6, 118.8, 119.2, 125.0, 125.3, 126.7, 128.2, 128.4, 131.0 (d, J_{CF} = 8.3 Hz), 131.2, 136.2,

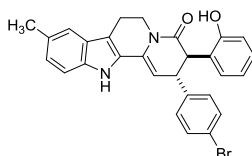
146.4 (d, $J_{CF} = 7.4$ Hz), 155.5, 162.7 (d, $J_{CF} = 242.3$ Hz), 168.7; HRMS (ESI-TOF) m/z : Calcd. for $C_{28}H_{23}FN_2NaO_2$ $[M+Na]^+$: 461.1636; Found: 461.1638.



3cc: Light yellow solid, m.p. 129.4-130.2 °C; yield 53%, 13:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.38 (s, 3H), 2.92-2.94 (m, 2H), 3.92-3.98 (m, 1H), 4.11-4.15 (m, 2H), 4.18-4.23 (m, 1H), 5.80 (d, $J = 4.8$ Hz, 1H), 6.60-6.64 (m, 1H), 6.81-6.87 (m, 2H), 6.97-7.03 (m, 2H), 7.18-7.23 (m, 1H), 7.28-7.31 (m, 3H), 7.35 (d, $J = 8.8$ Hz, 2H), 9.68 (br s, 1H), 11.17 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 21.6, 39.4, 42.2, 49.9, 102.3, 110.9, 111.4, 118.8, 125.3, 126.7, 128.2, 128.4, 129.0, 129.8, 131.2, 131.7, 136.2, 142.4, 155.4, 168.7; HRMS (ESI-TOF) m/z : Calcd. for $C_{28}H_{23}ClN_2NaO_2$ $[M+Na]^+$: 477.1340; Found: 477.1345.

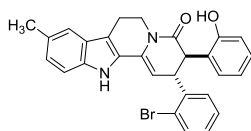


3cd: Light yellow solid, m.p. 131.4-131.9 °C; yield 50%, 18:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.37 (s, 3H), 2.89-2.97 (m, 2H), 3.96-4.04 (m, 1H), 4.15-4.21 (m, 1H), 4.35 (d, $J = 8.8$ Hz, 1H), 4.62-4.65 (m, 1H), 5.79 (d, $J = 4.8$ Hz, 1H), 6.58-6.62 (m, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.92-7.01 (m, 3H), 7.18-7.24 (m, 2H), 7.29-7.32 (m, 2H), 7.38-7.40 (m, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 9.56 (br s, 1H), 11.12 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 21.6, 39.4, 47.5, 102.6, 110.8, 111.4, 115.6, 118.8, 119.1, 125.2, 126.6, 128.1, 128.3, 128.4, 128.7, 130.0, 130.6, 133.3, 136.2, 140.7, 155.6, 169.2; HRMS (ESI-TOF) m/z : Calcd. for $C_{28}H_{23}ClN_2NaO_2$ $[M+Na]^+$: 477.1340; Found: 477.1344.



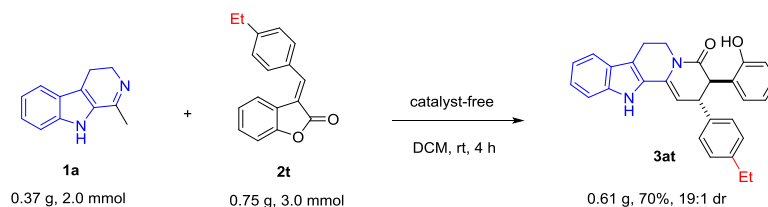
3ce: Light yellow solid, m.p. 138.5-139.2 °C; yield 51%, 11:1 dr; 1H NMR (DMSO- d_6 , 400 MHz) δ : 2.38 (s, 3H), 2.92-2.94 (m, 2H), 3.92-3.99 (m, 1H), 4.10-4.16 (m, 2H), 4.20-4.23 (m, 1H), 5.80 (d, $J = 4.8$ Hz, 1H), 6.60-6.64 (m, 1H), 6.81-6.83 (m, 1H), 6.86-6.88 (m, 1H), 6.97-7.03 (m,

2H), 7.21-7.25 (m, 3H), 7.31 (s, 1H), 7.48 (d, $J = 8.4$ Hz, 1H), 9.68 (br s, 1H), 11.17 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.9, 21.7, 39.4, 42.3, 49.9, 102.2, 110.9, 111.4, 118.8, 120.2, 125.3, 126.7, 128.2, 128.4, 130.2, 131.2, 131.9, 136.2, 142.8, 155.5, 168.6; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{28}\text{H}_{23}\text{BrN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 521.0835; Found: 521.0838.



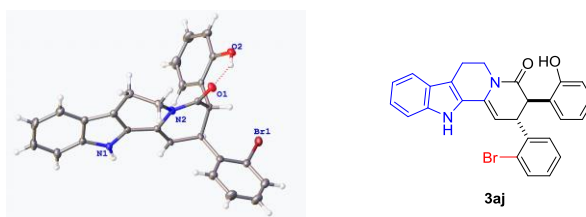
3cf: Light yellow solid, m.p. 130.5-131.2 °C; yield 54%, 12:1 dr; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 2.37 (s, 3H), 2.88-2.97 (m, 2H), 3.95-4.02 (m, 1H), 4.18-4.24 (m, 1H), 4.36 (d, $J = 9.2$ Hz, 1H), 4.61-4.64 (m, 1H), 5.78 (d, $J = 4.4$ Hz, 1H), 6.59-6.63 (m, 1H), 6.76-6.78 (m, 1H), 6.92-7.01 (m, 3H), 7.11-7.15 (m, 1H), 7.18 (d, $J = 8.4$ Hz, 1H), 7.29 (s, 1H), 7.33-7.36 (m, 1H), 7.43 (d, $J = 7.2$ Hz, 1H), 7.55-7.57 (m, 1H), 9.57 (br s, 1H), 11.13 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 20.8, 21.6, 39.4, 42.1, 47.5, 102.7, 110.8, 115.6, 118.8, 119.1, 125.2, 126.6, 128.1, 128.4, 128.7, 129.0, 133.2, 136.2, 142.4, 155.6, 169.2; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{28}\text{H}_{23}\text{BrN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 521.0835; Found: 521.0831.

5. Scheme S1: gram scale synthesis of the products 3at



In a sealed tube equipped with a magnetic stirring bar, to 20.0 mL of DCM was added harmaline scaffold **1a** (0.37 g, 2.0 mmol) and 3-(4-ethoxyphenyl)acryloyl benzofuranone **2t** (0.75 g, 3.0 mmol). The reaction mixture was stirred at rt for 4 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 polycyclic harmaline scaffold **3at** (0.61 g, 70%, 19:1 dr).

6. X-ray crystal data for compound 3aj



CCDC 2323856

Table S1 Crystal data and structure refinement for 3aj

| | |
|--|---|
| Identification code | 3aj |
| Empirical formula | $C_{27}H_{21}BrN_2O_2$ |
| Formula weight | 485.37 |
| Temperature/K | 169.99(10) |
| Crystal system | triclinic |
| Space group | P-1 |
| $a/\text{\AA}$, $b/\text{\AA}$, $c/\text{\AA}$ | 8.6905(5), 13.8209(8), 19.6302(11) |
| $\alpha/^\circ$, $\beta/^\circ$, $\gamma/^\circ$, | 80.159(5), 84.229(5), 72.876(5) |
| Volume/ \AA^3 | 2217.0(2) |
| Z | 4 |
| $\rho_{\text{calc}}/\text{g/cm}^3$ | 1.454 |
| μ/mm^{-1} | 2.742 |
| F(000) | 992.0 |
| Radiation | Cu K α ($\lambda = 1.54184$) |
| Crystal size/ mm^3 | 0.15 \times 0.13 \times 0.1 |
| 2 Θ range for data collection/ $^\circ$ | 4.576 to 147.798 |
| Index ranges | $-7 \leq h \leq 10$, $-16 \leq k \leq 17$, $-22 \leq l \leq 24$ |
| Reflections collected | 14977 |
| Independent reflections | 8678 [$R_{\text{int}} = 0.0648$, $R_{\text{sigma}} = 0.0794$] |
| Data/restraints/parameters | 8678/0/579 |
| Goodness-of-fit on F^2 | 1.089 |
| Final R indexes [$I > 2\sigma(I)$] | $R_1 = 0.0619$, $wR_2 = 0.1480$ |
| Final R indexes [all data] | $R_1 = 0.0853$, $wR_2 = 0.1557$ |
| Largest diff. peak/hole / $e \text{\AA}^{-3}$ | 1.06/-1.08 |

Crystal Data for $C_{27}H_{21}BrN_2O_2$ ($M = 485.37$ g/mol): triclinic, space group P-1 (no. 2), $a = 8.6905(5)$ \AA , $b = 13.8209(8)$ \AA , $c = 19.6302(11)$ \AA , $\alpha = 80.159(5)^\circ$, $\beta = 84.229(5)^\circ$, $\gamma = 72.876(5)^\circ$, $V = 2217.0(2)$ \AA^3 , $Z = 4$, $T = 169.99(10)$ K, $\mu(\text{Cu K}\alpha) = 2.742$ mm^{-1} , $D_{\text{calc}} = 1.454$ g/cm^3 , 14977 reflections measured ($4.576^\circ \leq 2\Theta \leq 147.798^\circ$), 8678 unique ($R_{\text{int}} = 0.0648$, $R_{\text{sigma}} = 0.0794$) which were used in all calculations. The final R_1 was 0.0619 ($I > 2\sigma(I)$) and wR_2 was 0.1557 (all data).

7. MTT assay

Cells were cultured in RPMI-1640 medium with 10% fetal beef serum (FBS), 100 U mL⁻¹ penicillin, 100 µg mL⁻¹ streptomycin, and 2 mm L-glutamine. A 96-well plate with the cell suspensions (80 µL, 5×10³ cells/well) was incubated at 37 °C with 5% CO₂ for 24 h. After that, the cells were exposed to various doses of compounds for 48 h. Subsequently, each well received 10 µL of MTT solution, which was then incubated for an extra 4 h. After incubation, the liquid in the 96-well plate was gently aspirated with a syringe and discarded. To completely dissolve the formazan, DMSO (150 µL) was filled in each well and oscillated for 10 min. At last, an iMark microplate reader (Bio-Rad Laboratories, Inc., Hercules, CA, USA) was used to measure the absorbance at 490 nm. IBM SPSS Statistics 23 software was used to calculate half maximal inhibitory concentration (IC₅₀).

8. Apoptosis analysis

The A549 cell suspension (2×10⁵ cells/well) was incubated in a six-well plate for 24 h. At the end of the incubation, the control group of the control experiment was 1/1000 DMSO solvent group, and the rest were treated with the corresponding concentration of **3at** solution for each treatment group. After 48 h incubation, we used related instruments for detection and analysis according to the manufacturer's instructions. The apoptosis detection-related kits are as follows: AO/EB (Hefei Biomei Biotechnology Co., Ltd., China), Hoechst 33258 (Beyotime Biotechnology, China), Reactive Oxygen Species (Beijing Solarbio Science & Technology Co., Ltd., China), JC-1(Beijing Solarbio Science & Technology Co., Ltd., China), Cell Cycle Staining (Multi Sciences Biotech Co., Ltd., China), Annexin V-PE/7-AAD apoptosis (Multi Sciences Biotech Co., Ltd., China).

9. Colony formation assay

A549 cells were counted, seeded at 200 cells per well in six-well plates, and cultured for 24 h. Subsequently, the **3at** solution (control, 0.625, 1.25, 2.5 µM) was added, and the cultivation was continued for 48 h. Afterward, we changed the medium containing the drug solution every two days for two weeks. Next, cells were stained as follows: removed medium, washed twice with PBS, fixed with 4% paraformaldehyde solution for 30 min, discarded fixative solution, stained

with 0.1% crystal violet solution for 15 min, cleaned with water, and dried for 24 h.

10. Cell migration assay

The A549 cell suspensions (2 mL, 1×10^5 cells/mL) were added to each well of six-well plates. Cells were incubated until they spread across the bottom of the six-well plate to form a monolayer of fused cells. Then, a straight line was drawn on the monolayer cells of each well with the tip of a 200 μ L pipette. Next, the floating cells were washed away with PBS, and then different concentrations of **3at** solutions (serum-free medium preparation, 2 mL) were added and incubated for 48 h. A Leica microscope was used to take pictures of the scratch at 0 and 48 h.

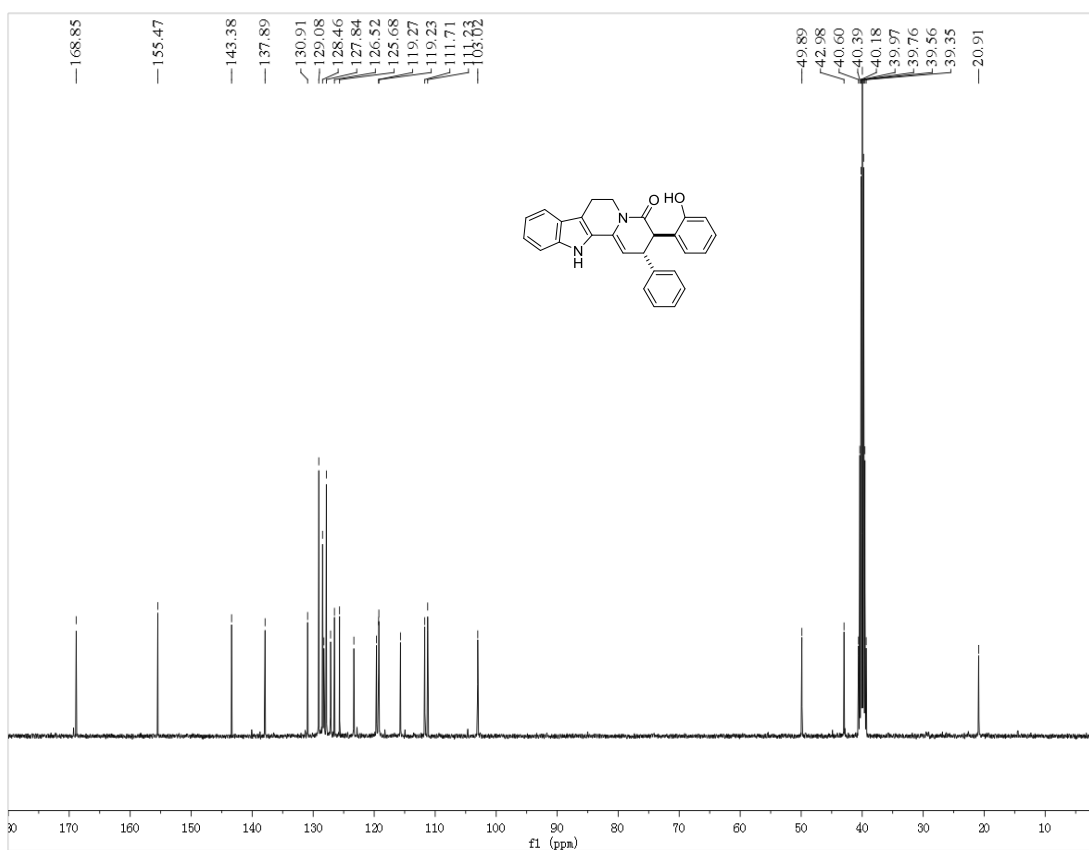
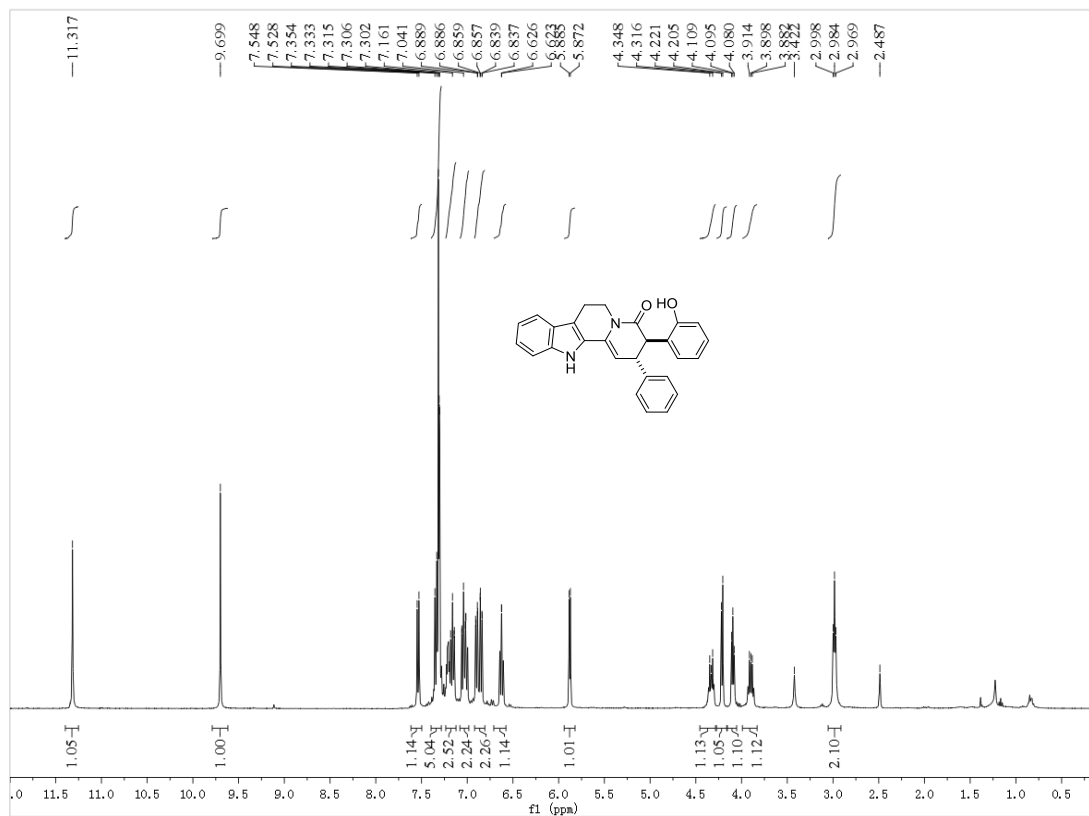
The Corning® Incorporated® migration chamber (Corning, New York, USA) was utilized for the transwell migration assay. The Corning® BioCoat™ Matrigel® invasion chamber (Corning, New York, USA) was used for the transwell invasion assay. The lower chamber was injected with 600 μ L of 10% FBS medium containing different concentrations of **3at**. The 1% FBS medium (200 μ L) containing A549 cells (5×10^4 cells per well) and various doses of **3at** solutions (dissolved in 1% FBS medium, 200 μ L) were loaded into the upper chamber. At the end of 48 h incubation, cells were fixed with 4% paraformaldehyde for 2 min, incubated with anhydrous methanol for 20 min, and colored with 0.1% crystal violet for 15 min. A Leica DMI8 microscope recorded the pictures after rinsing with PBS twice, and the count of migrated and invaded cells per field of view was performed using Image J software.

11. Western Blot assay

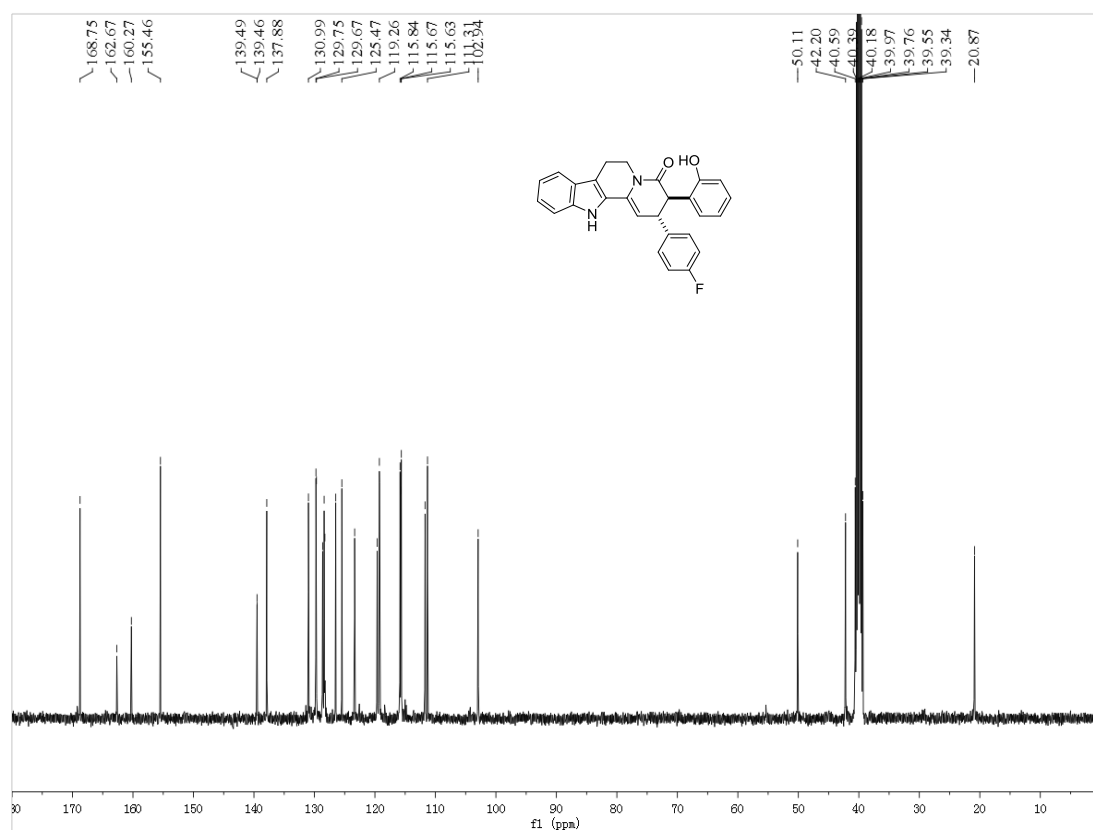
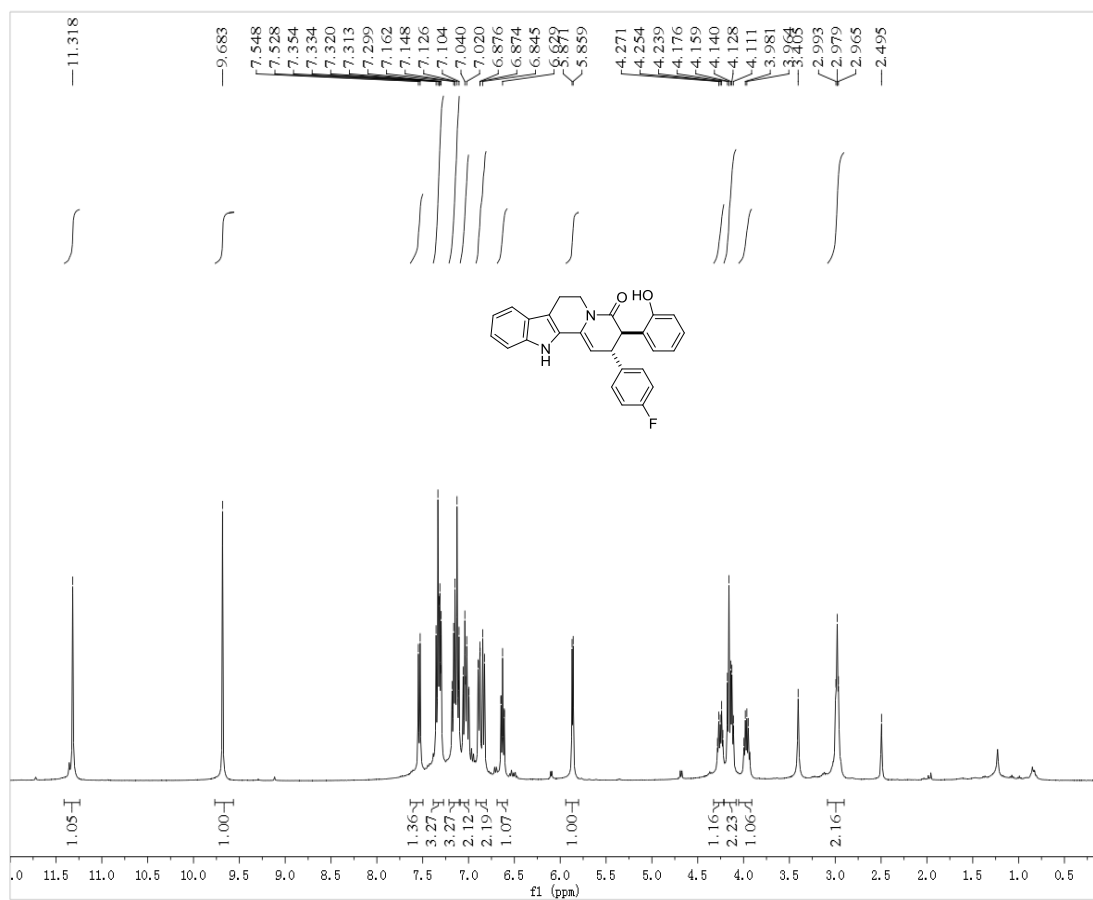
The A549 cell suspension (3×10^5 cells/well) was incubated for 24 h in the six-well plates. At the end of the incubation, the **3at** with different solutions was added, and the cultivation was continued for 48 h. The total protein concentration was determined using a BCA kit after extraction of total protein using radioimmunoprecipitation assay (RIPA) lysis buffer. The protein was then transferred to a PVDF membrane after being separated with 10% SDS-PAGE. The PVDF membranes were closed in TBST containing 5% skimmed milk powder for 1 h and incubated with the primary antibody overnight at 4 °C. Subsequently, the membranes were washed three times (5 min each) with TBST and incubated with secondary antibody for 1 h. After washing the membranes three times with TBST for 5 min each time, chemiluminescence was carried out, and the Image Lab software (Bio-Rad, CA, USA) was used for quantification.

12. The copies of ^1H NMR and ^{13}C NMR spectra for compounds 3

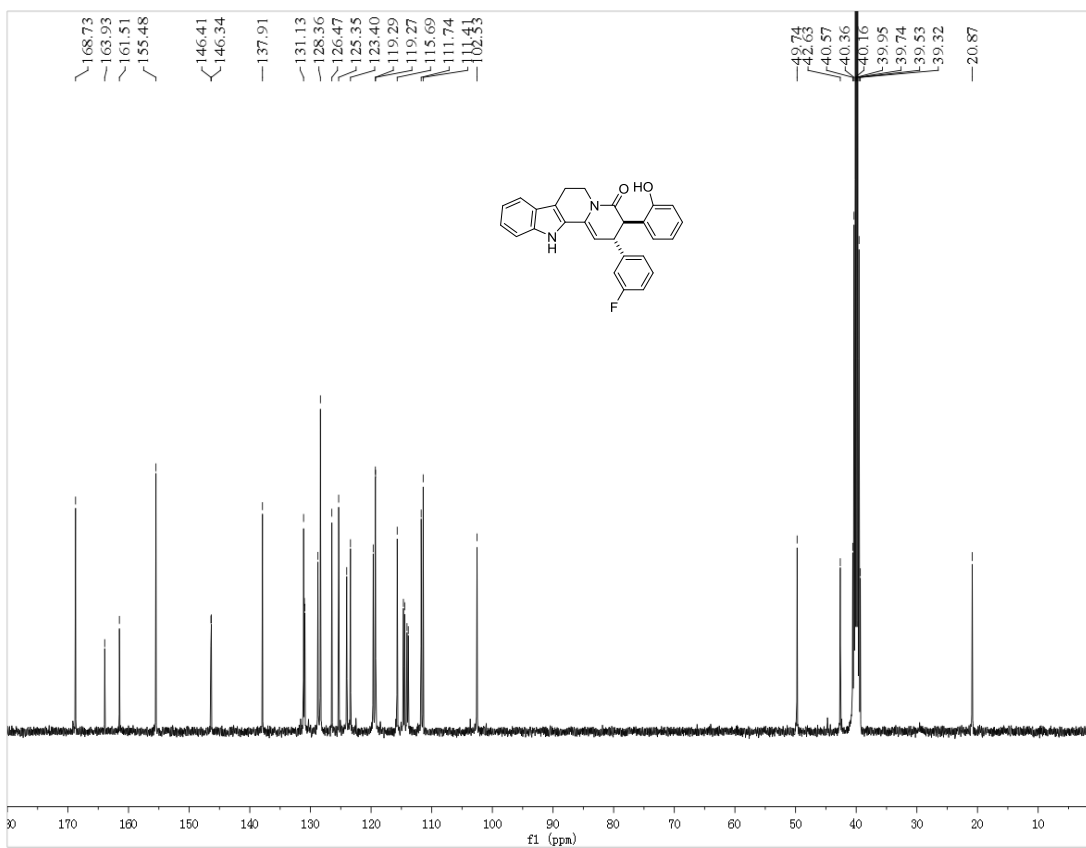
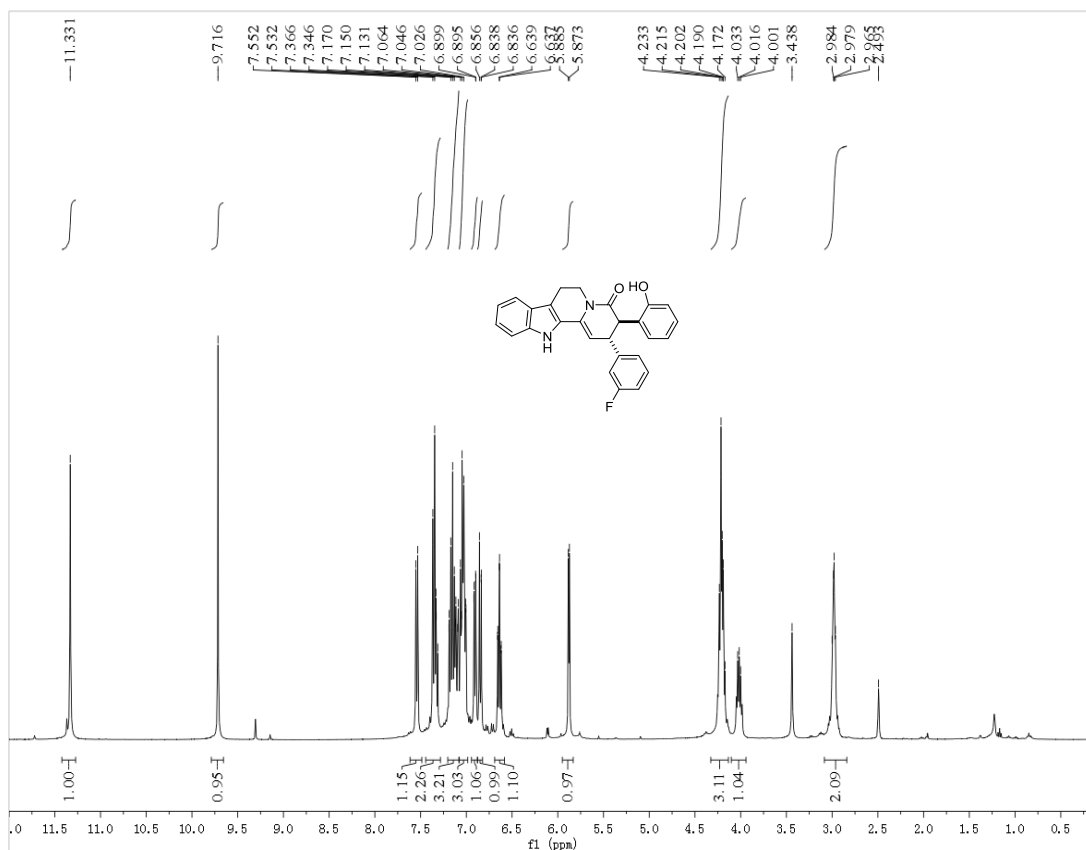
^1H and ^{13}C NMR of 3aa



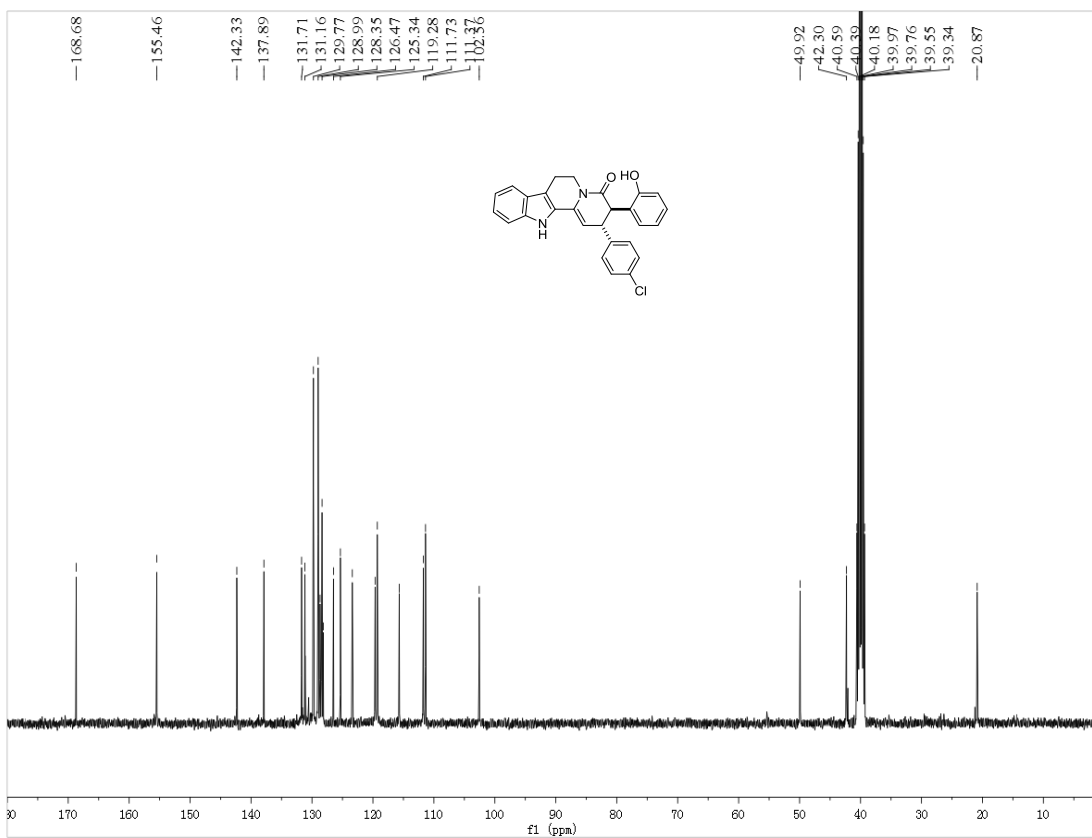
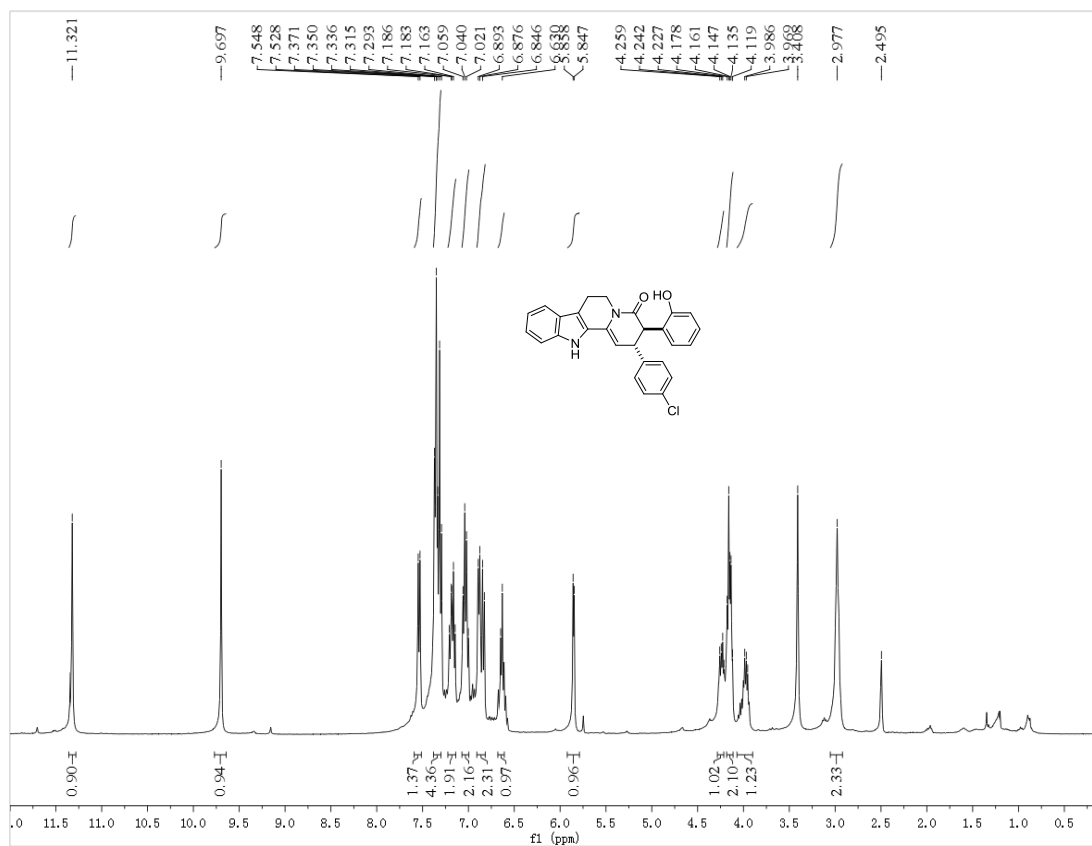
¹H and ¹³C NMR of 3ab



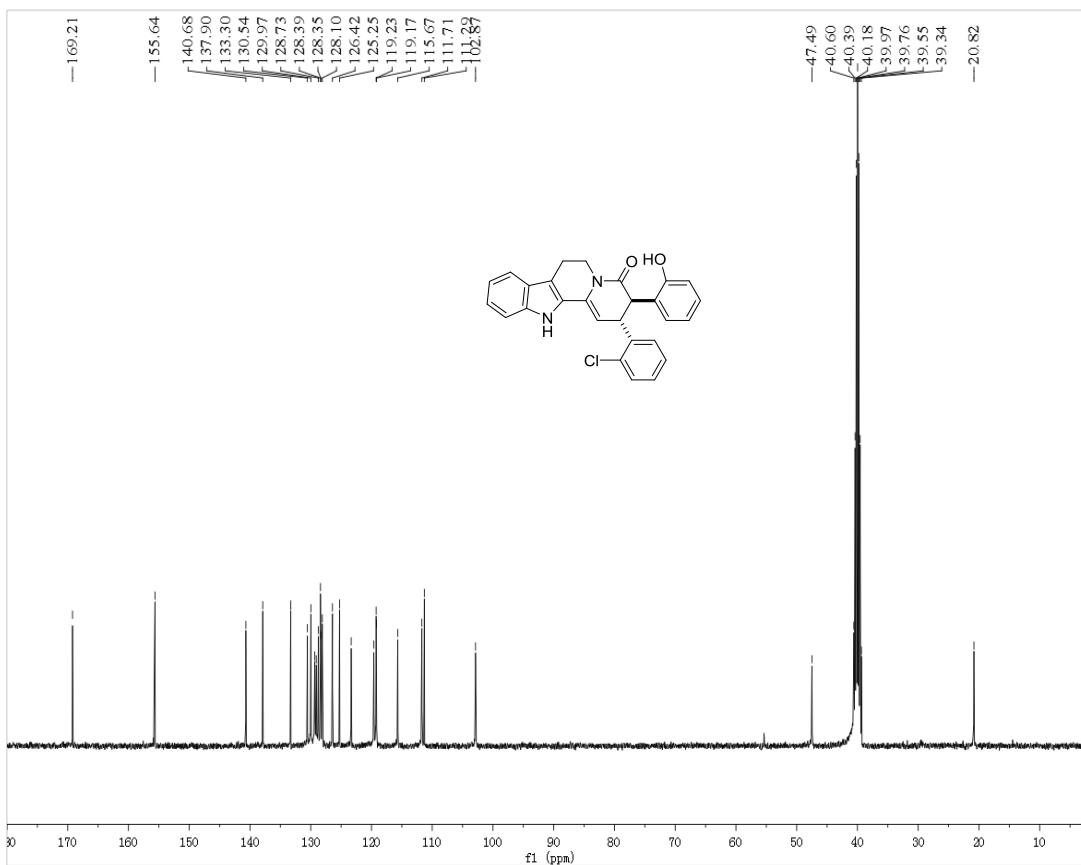
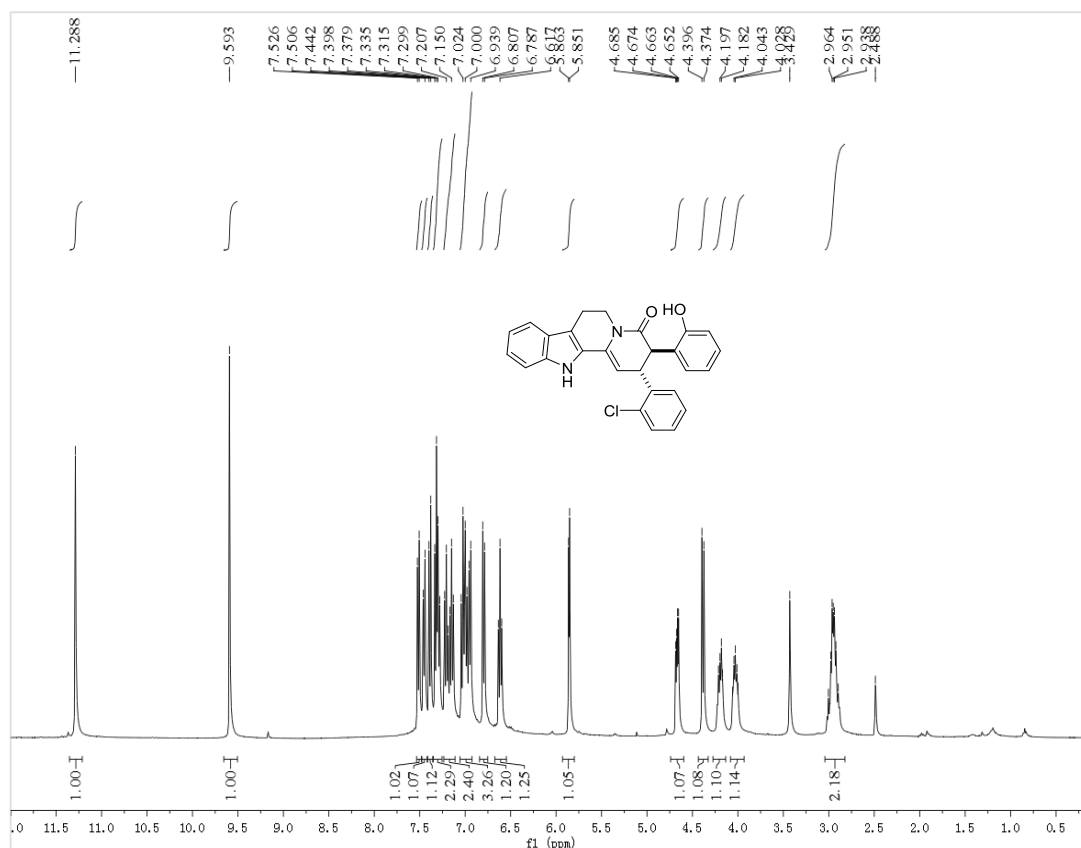
^1H and ^{13}C NMR of 3ac



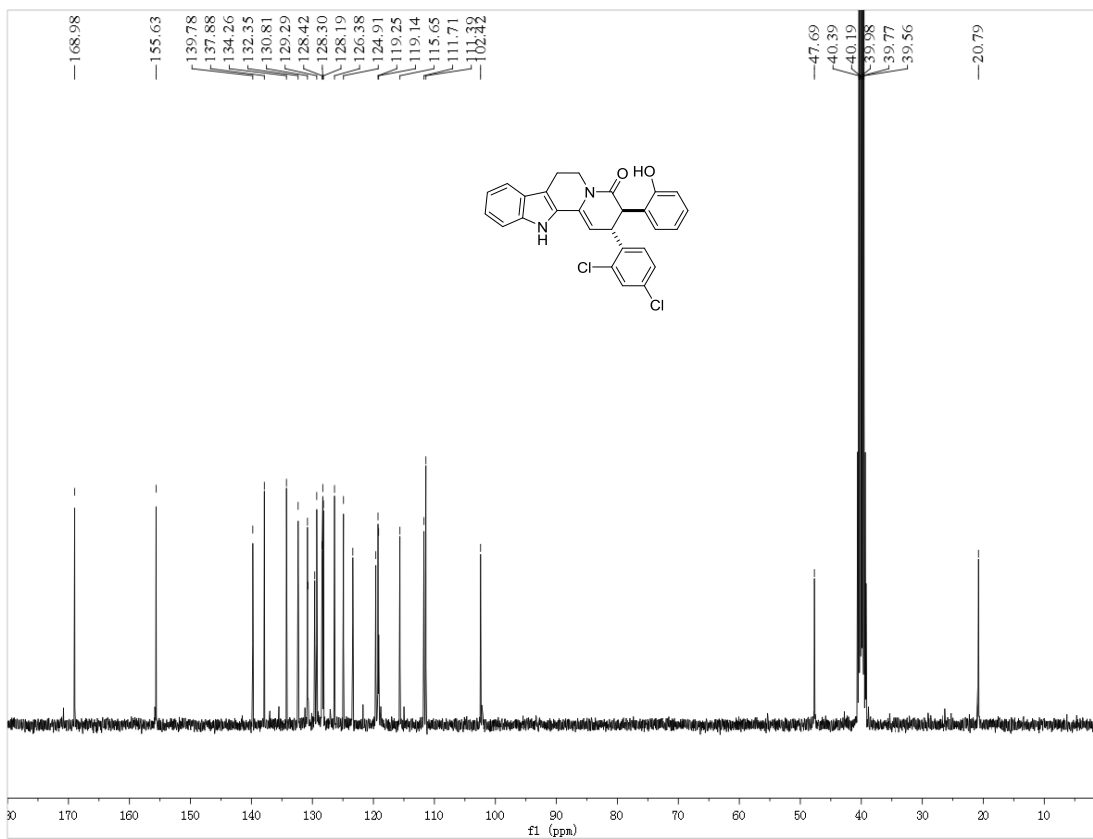
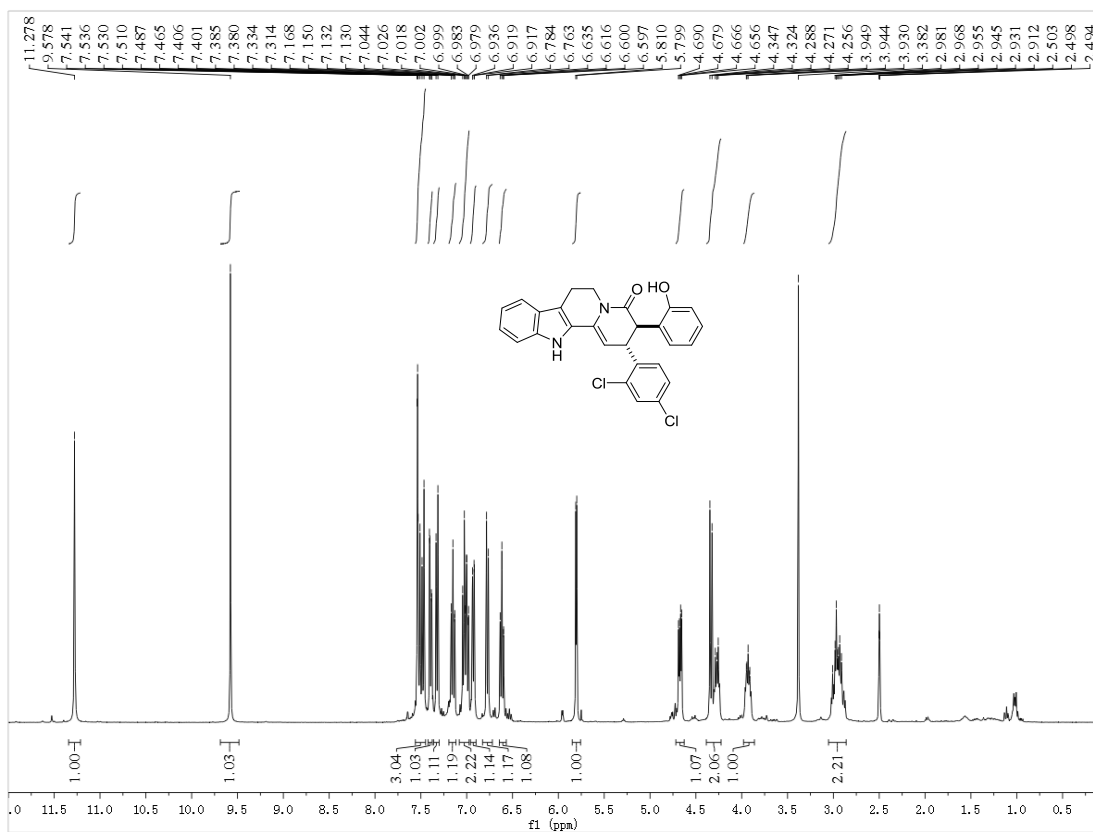
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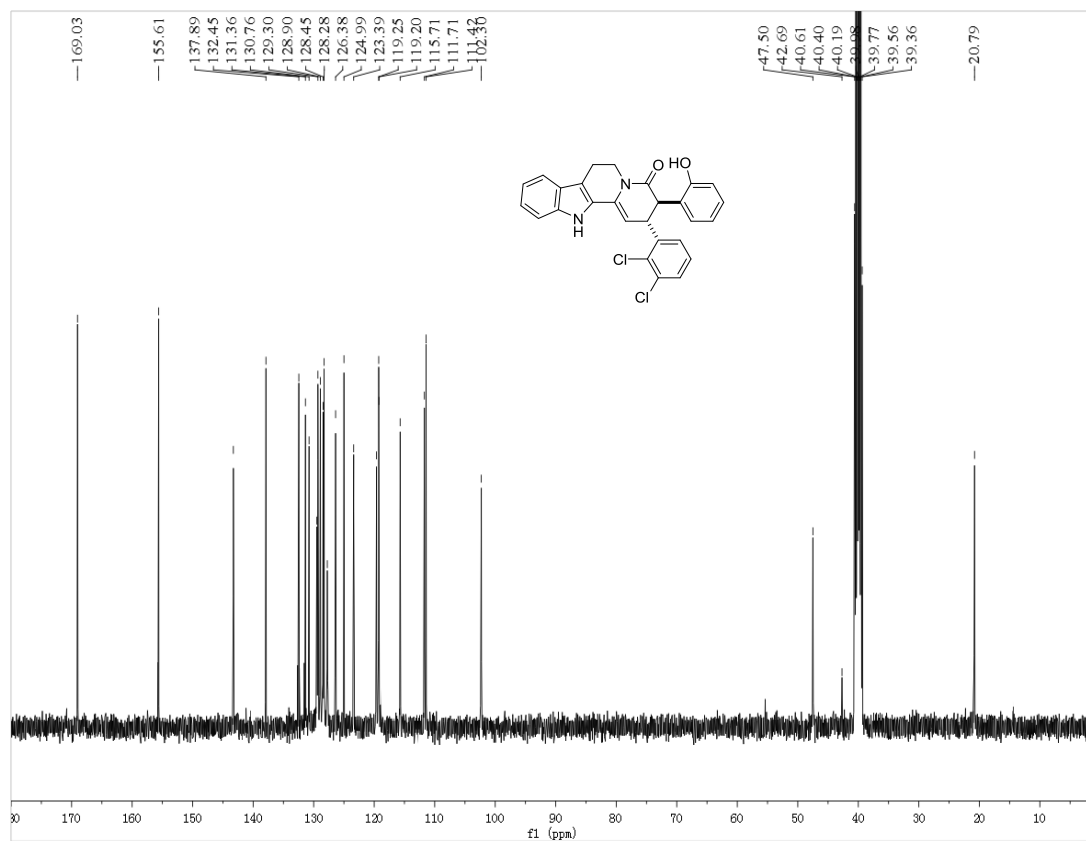
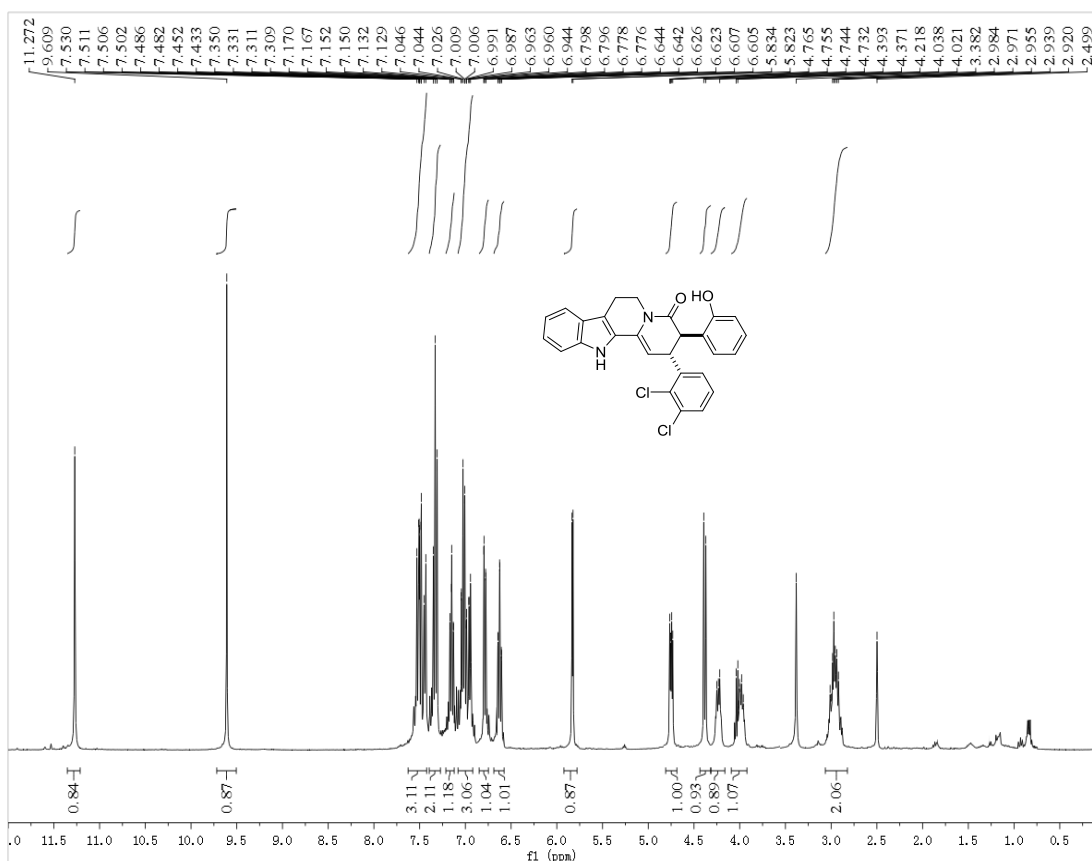
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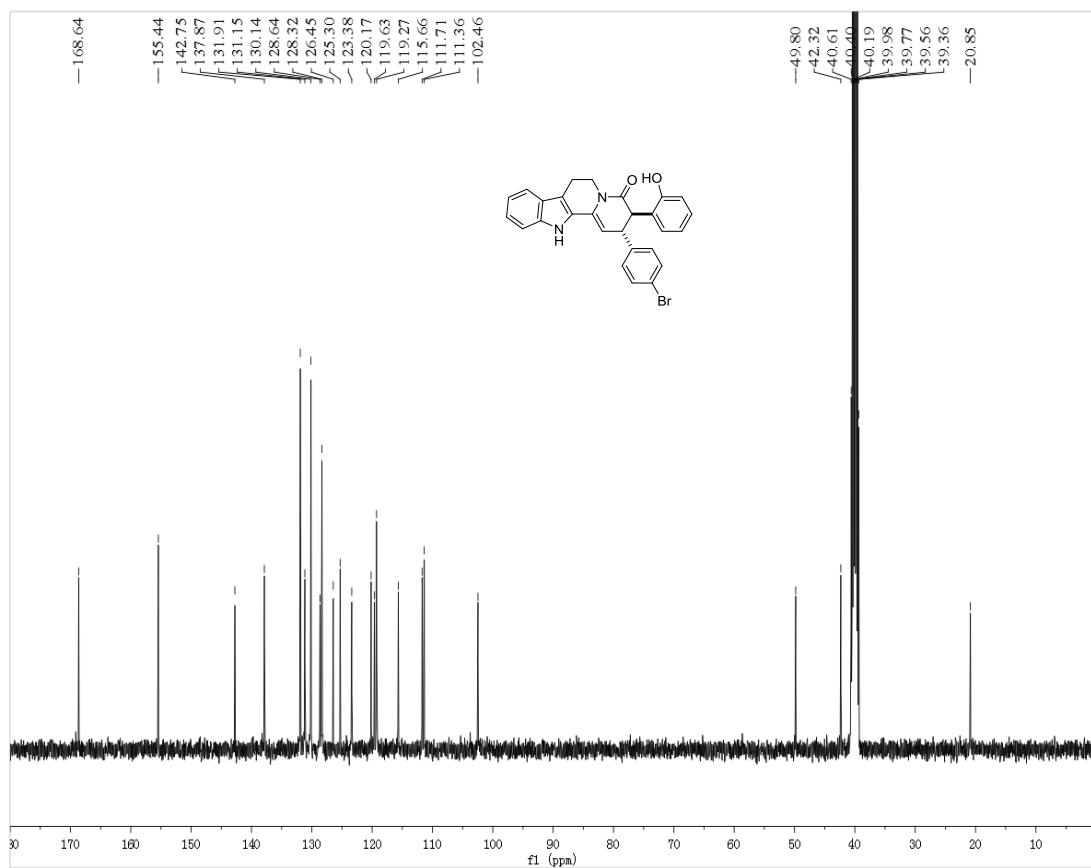
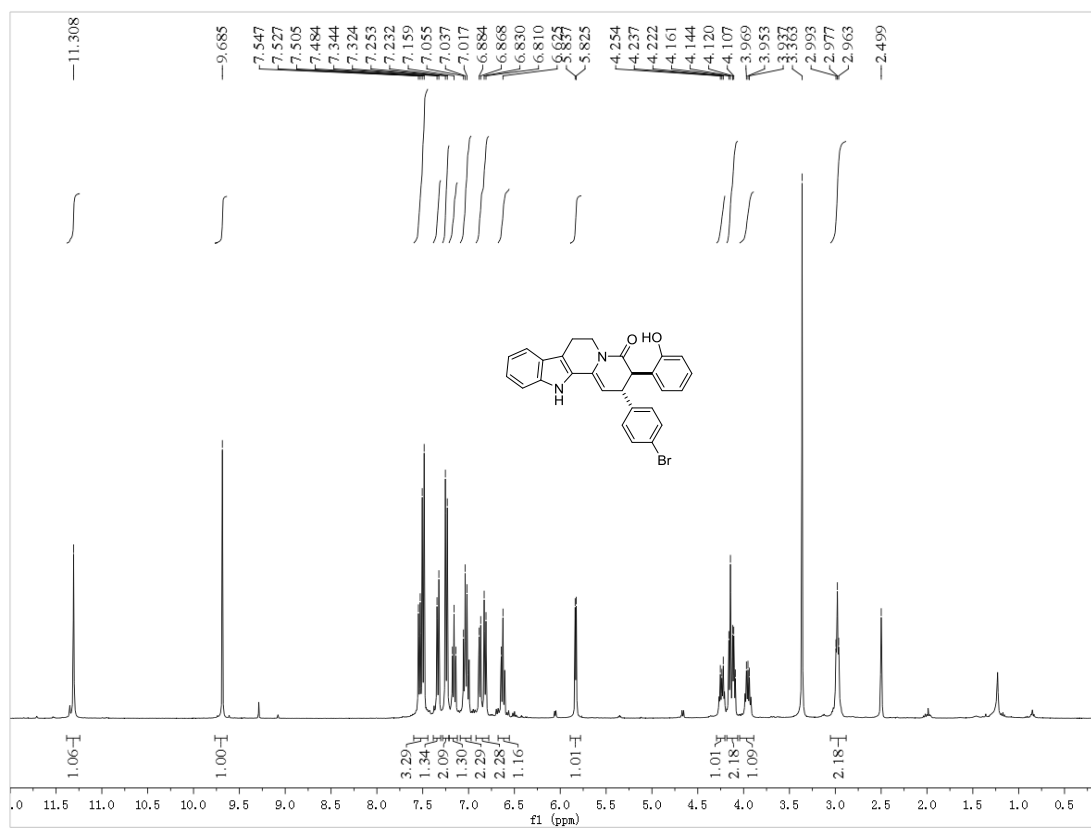
^1H and ^{13}C NMR of 3af



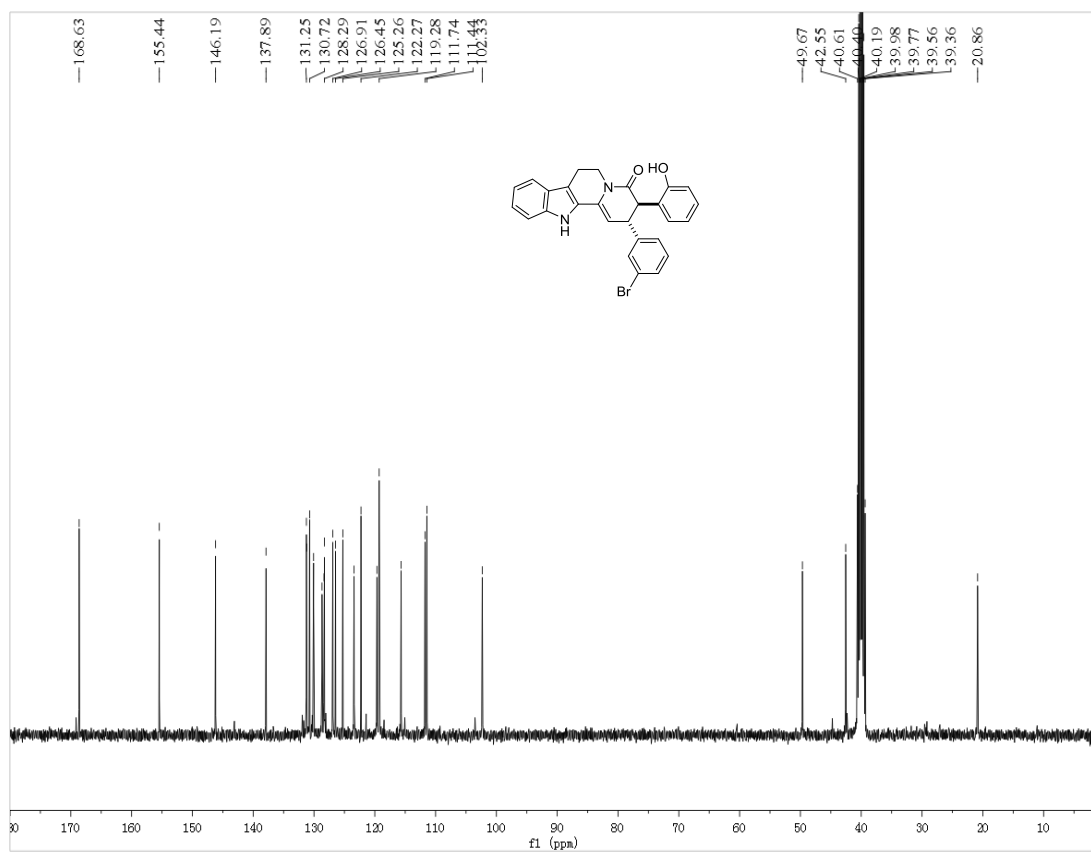
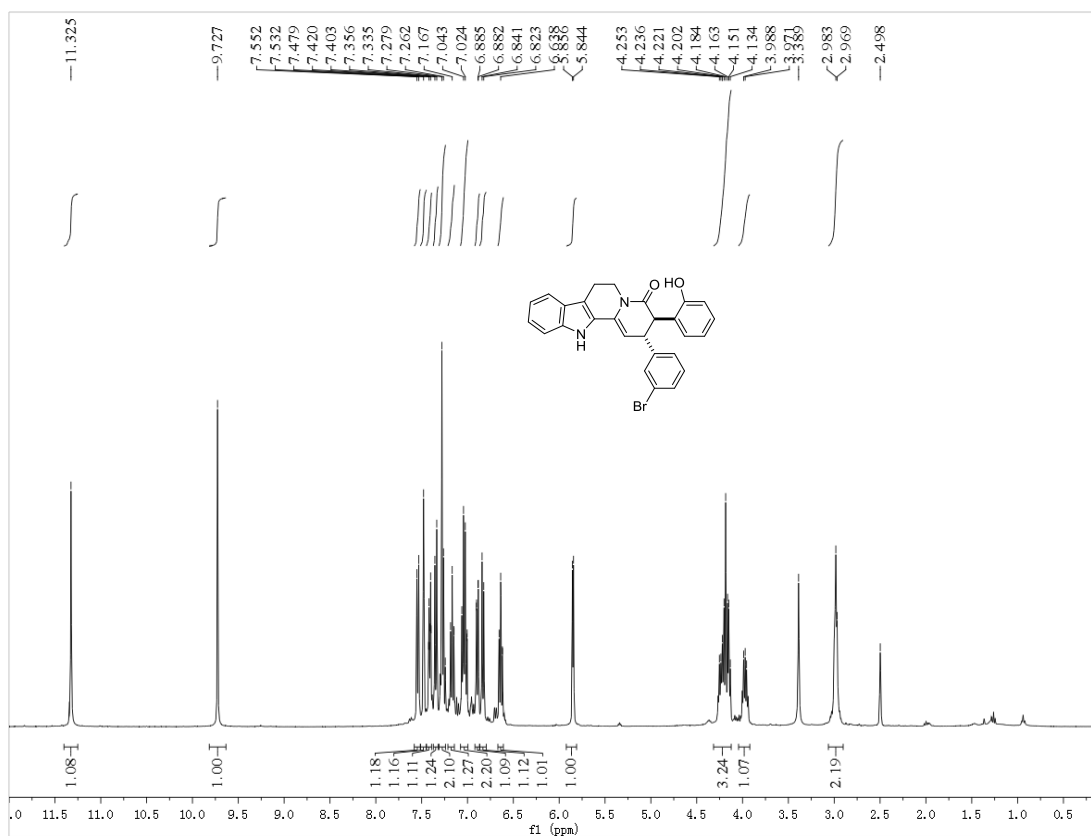
¹H and ¹³C NMR of 3ag



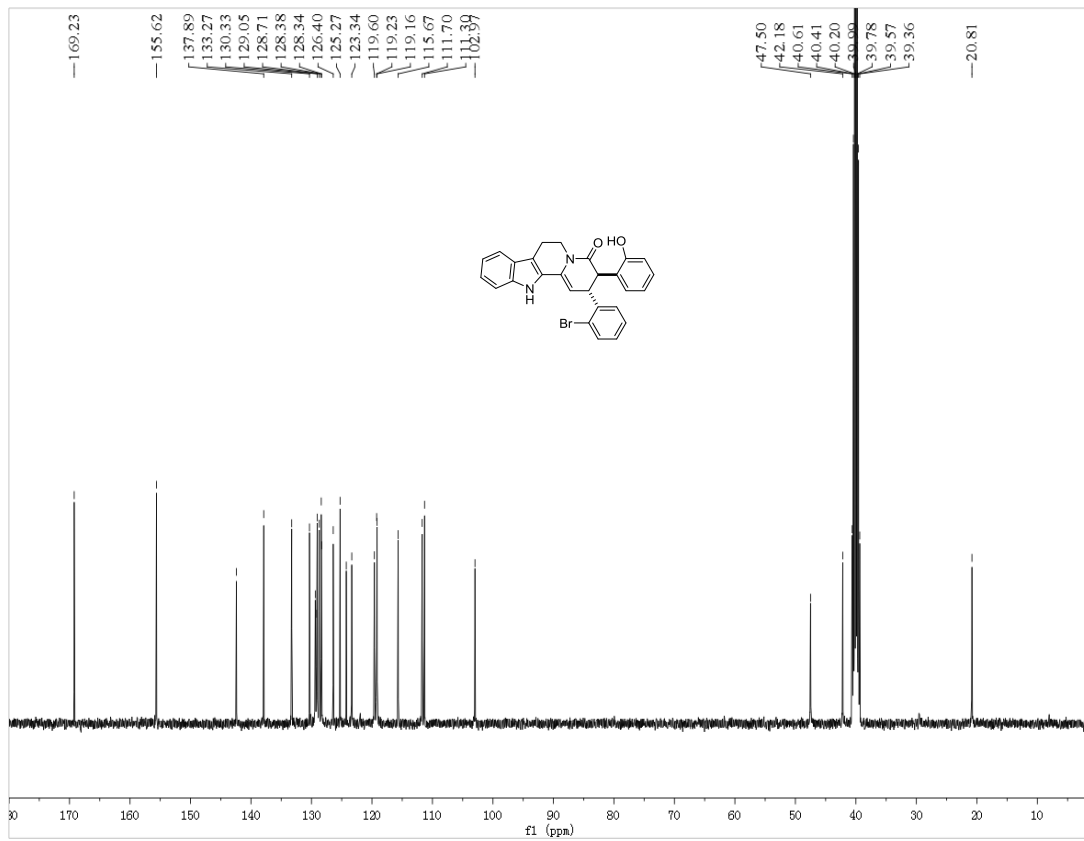
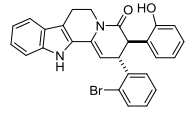
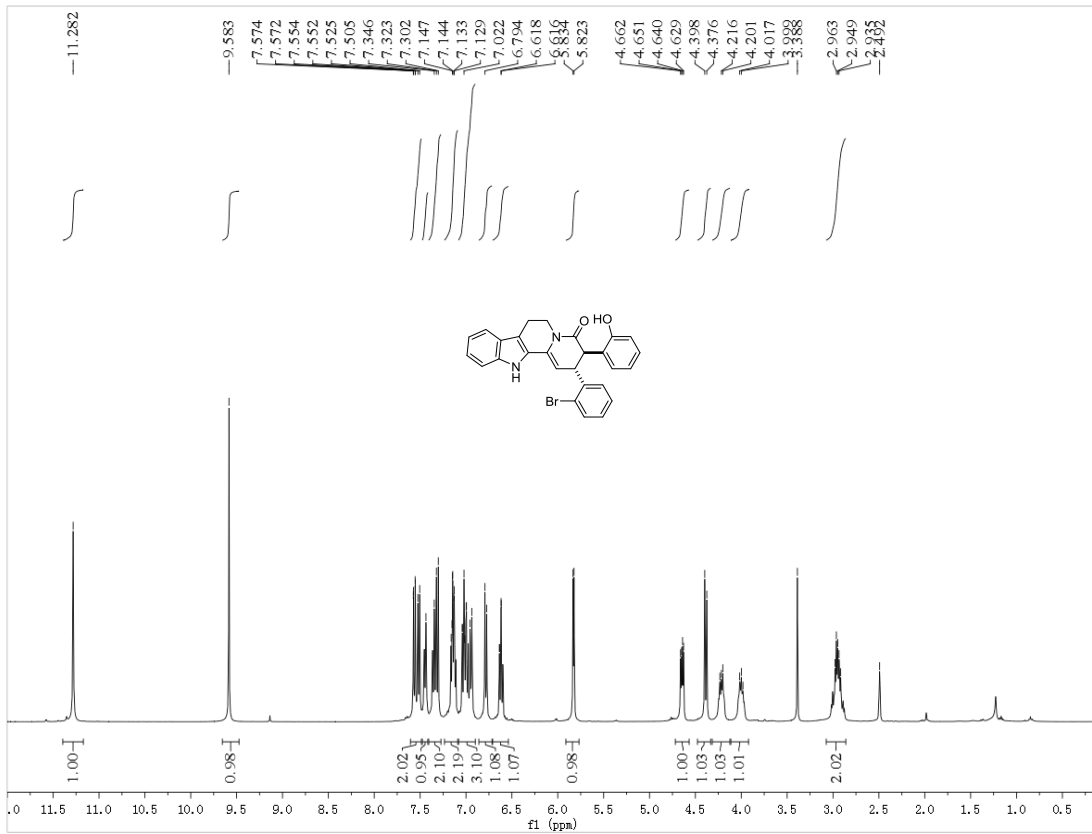
^1H and ^{13}C NMR of 3ah



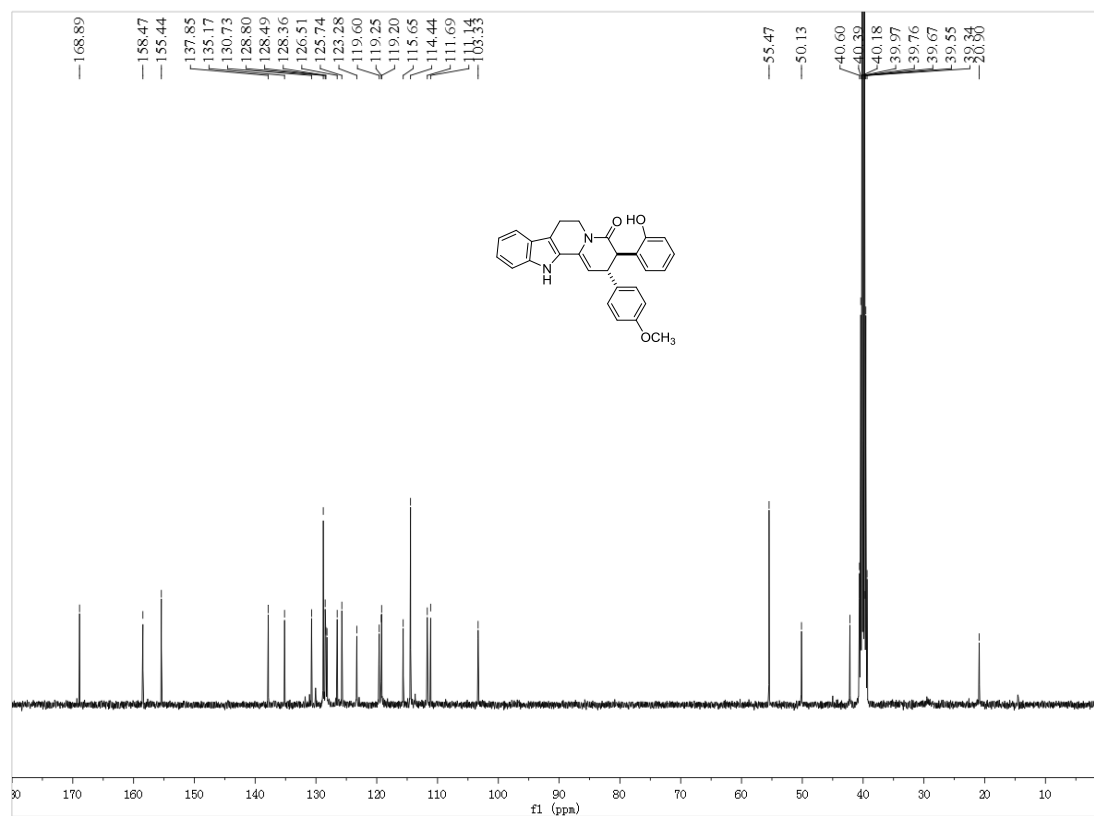
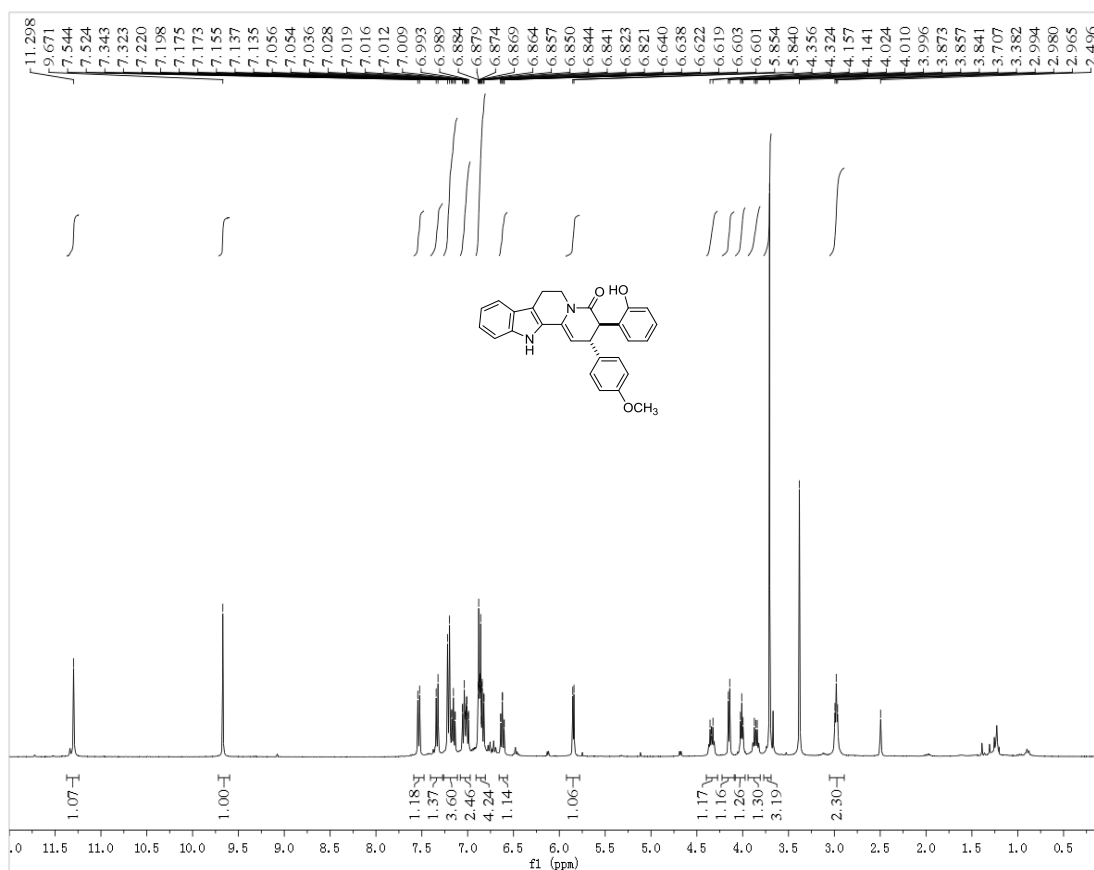
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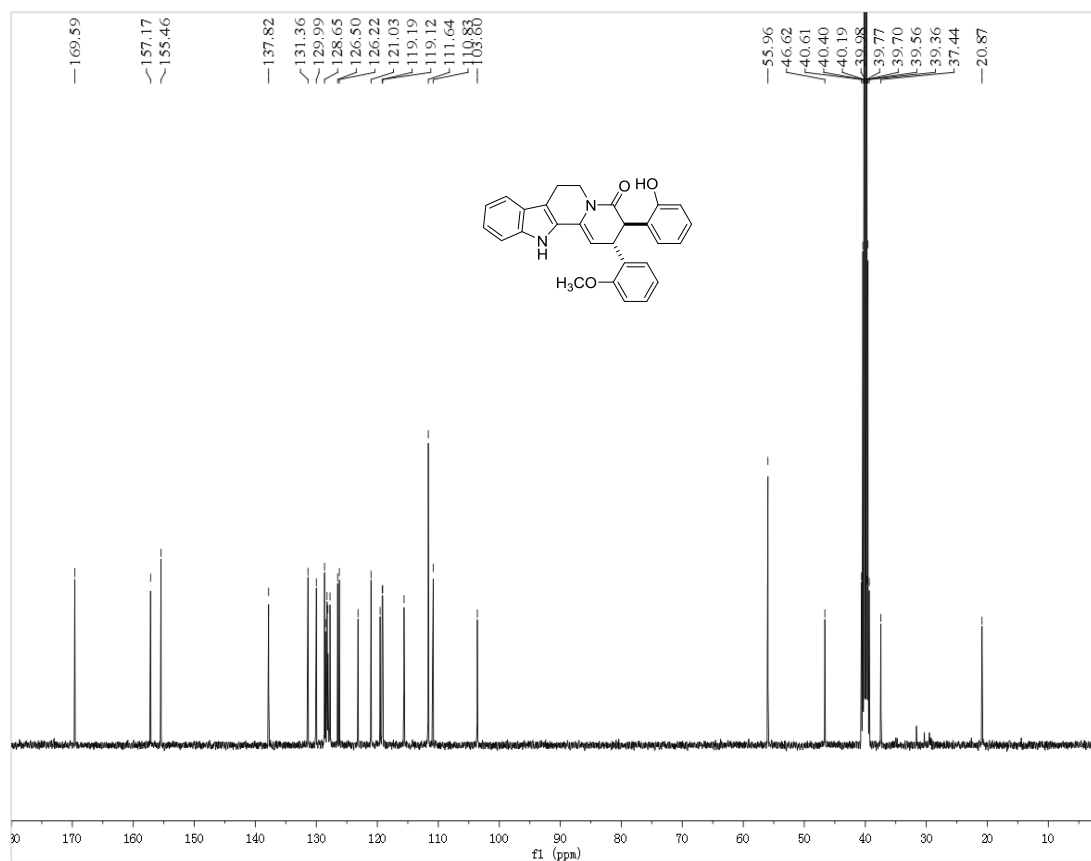
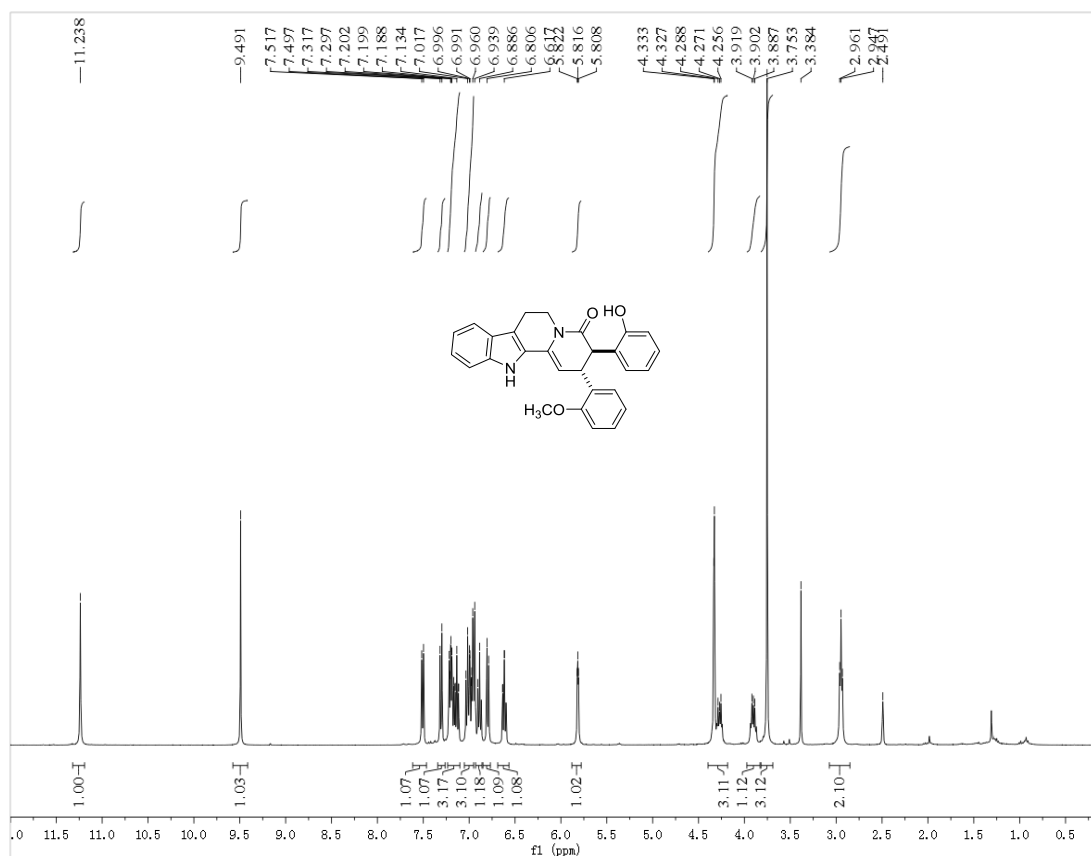
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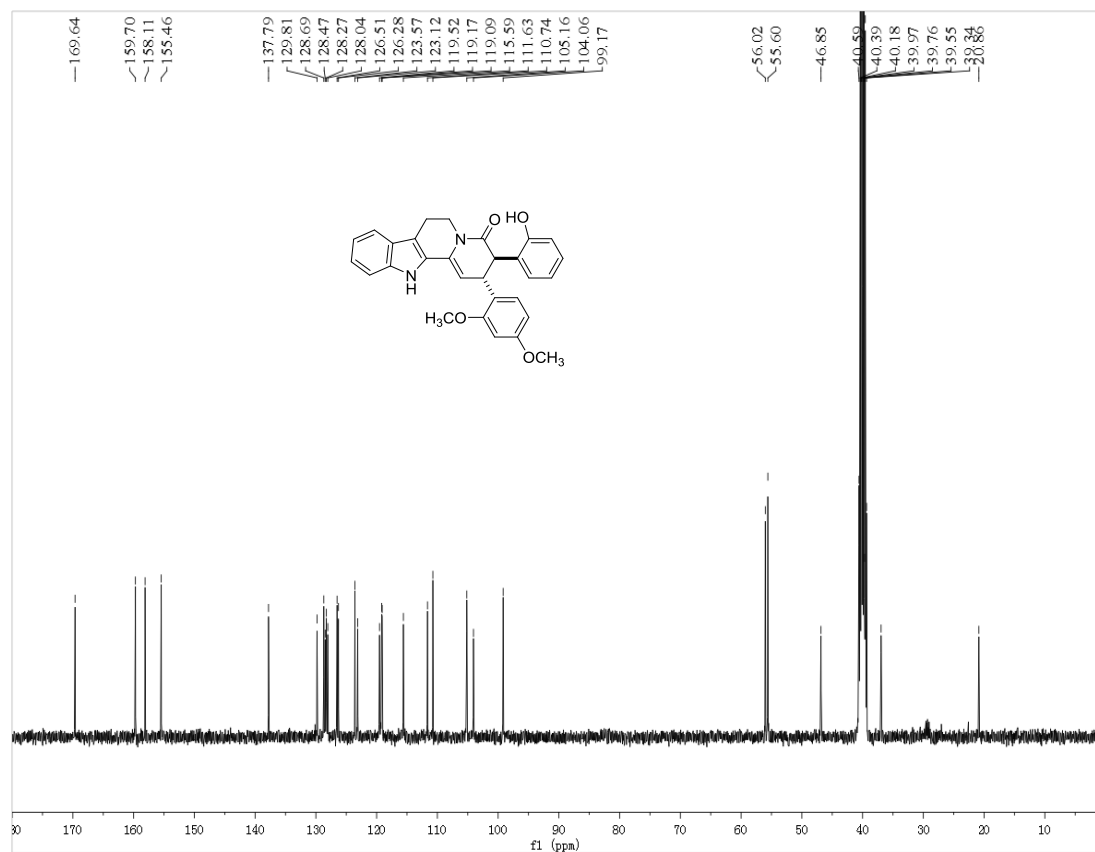
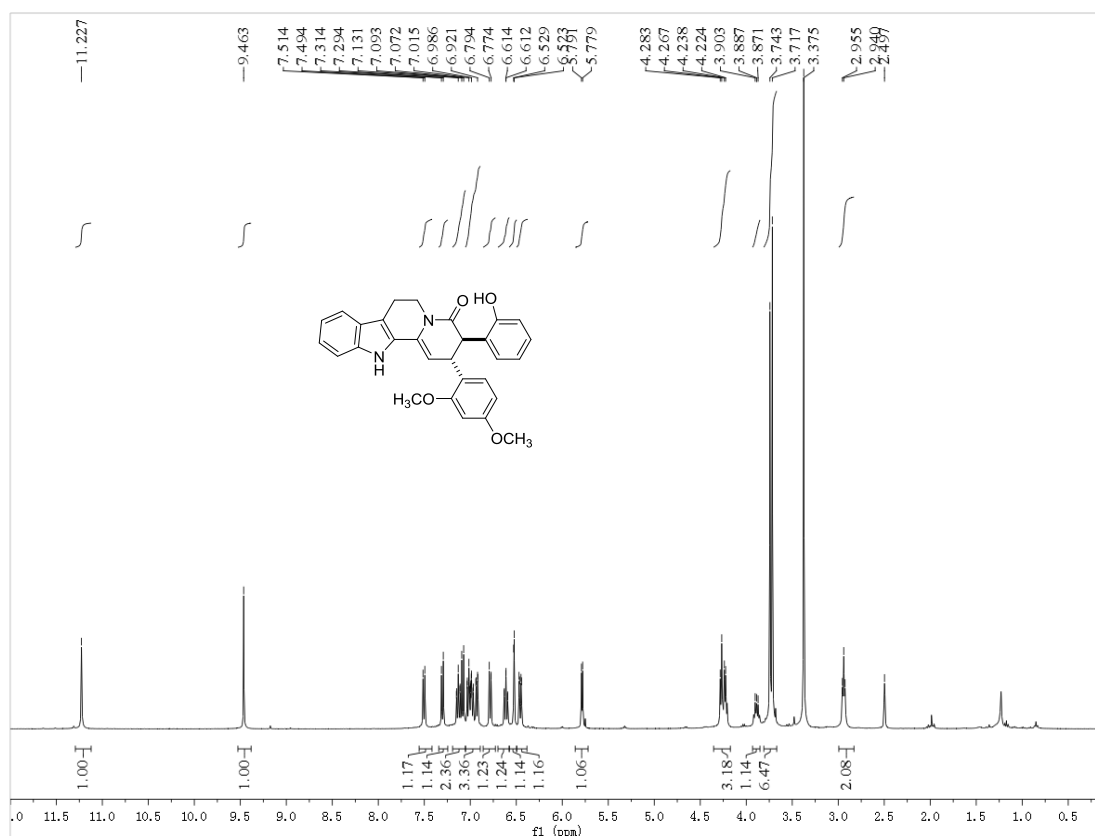
^1H and ^{13}C NMR of 3ak



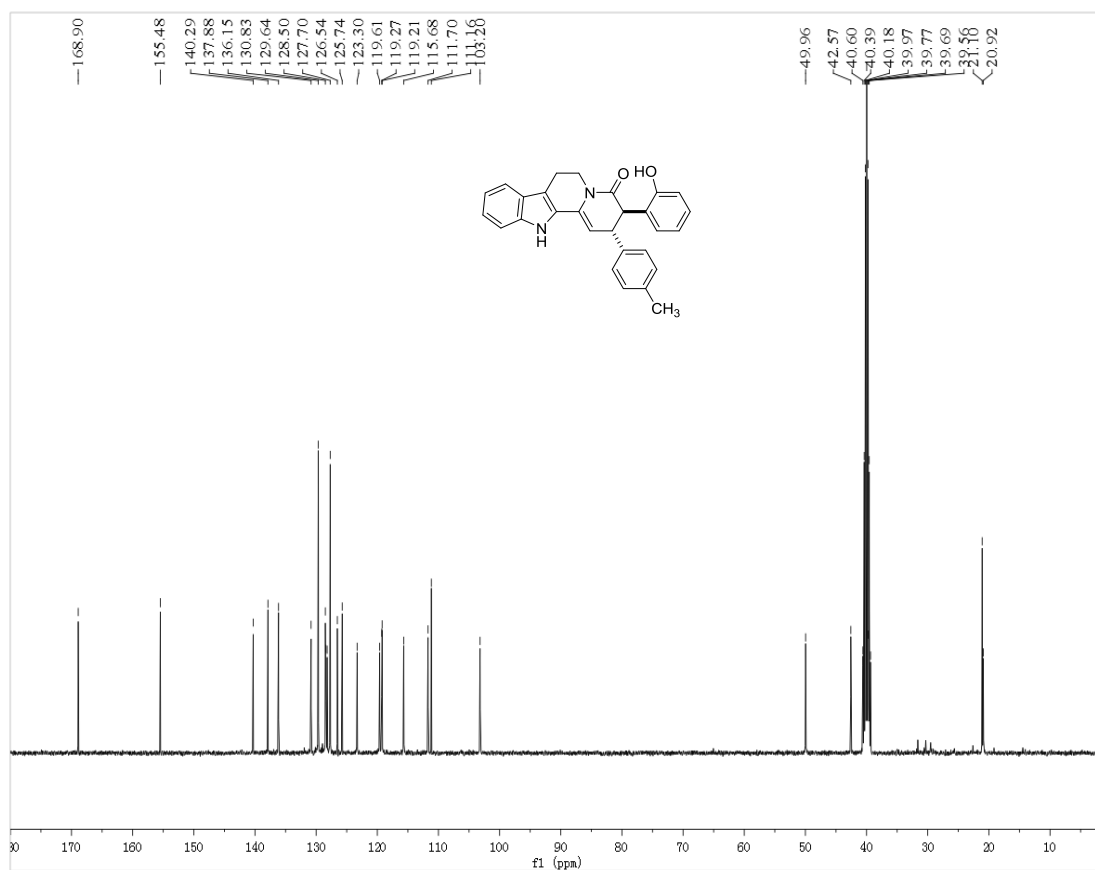
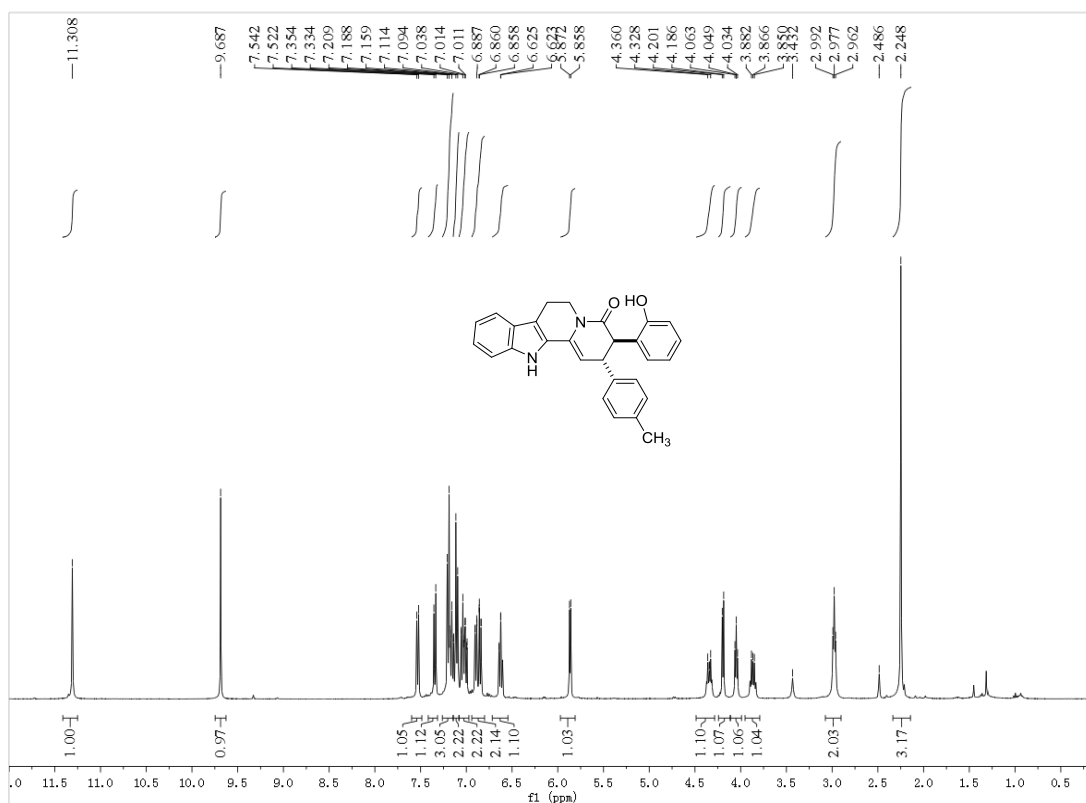
¹H and ¹³C NMR of 3al



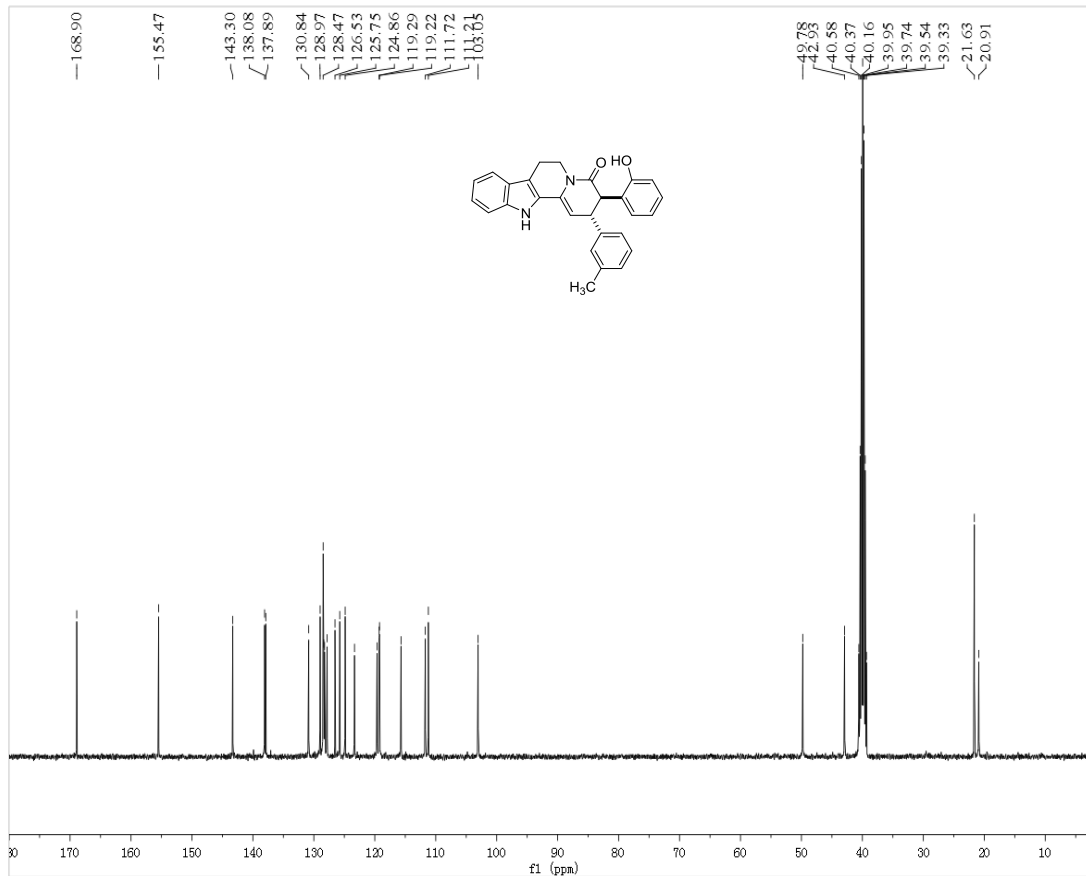
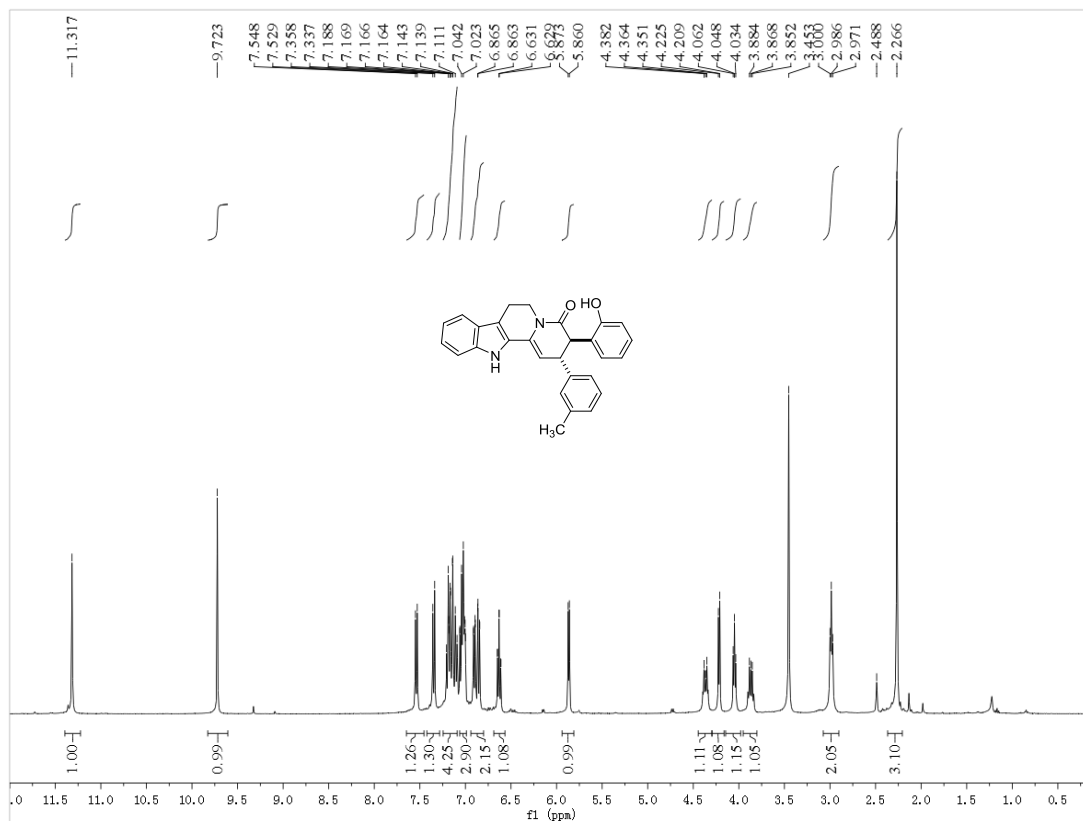
¹H and ¹³C NMR of 3am



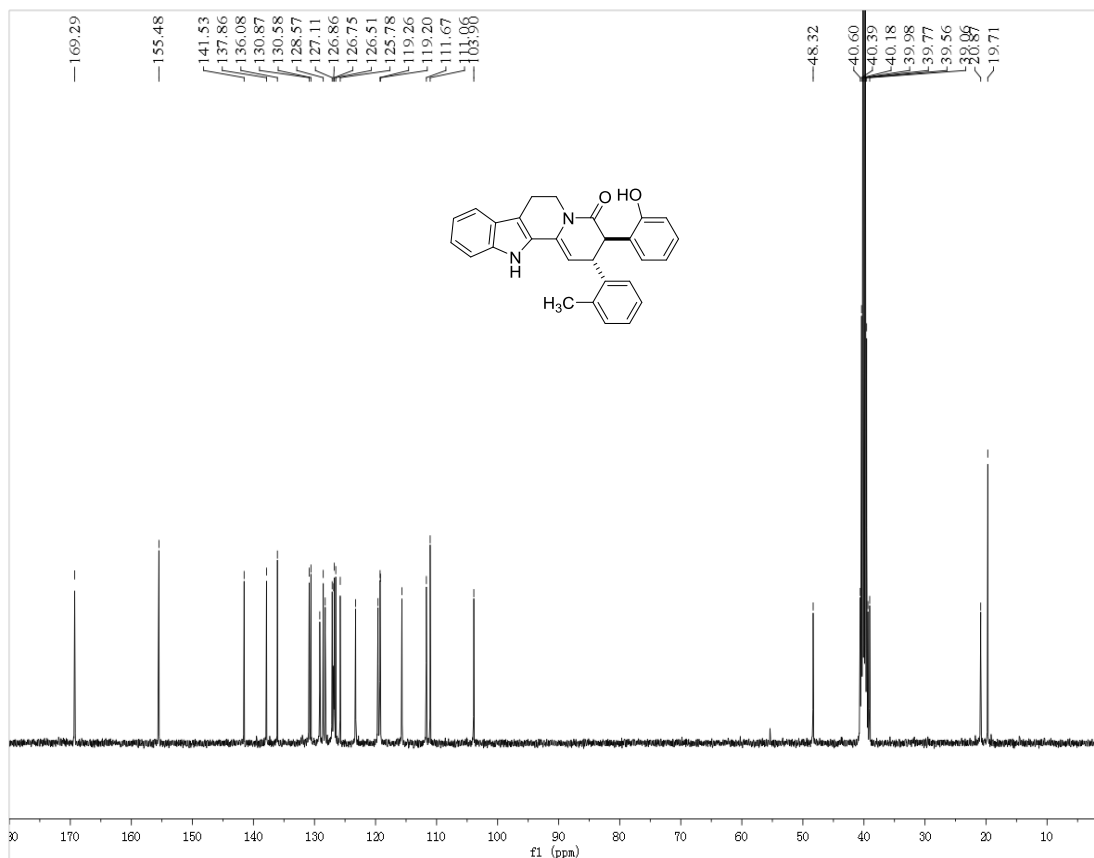
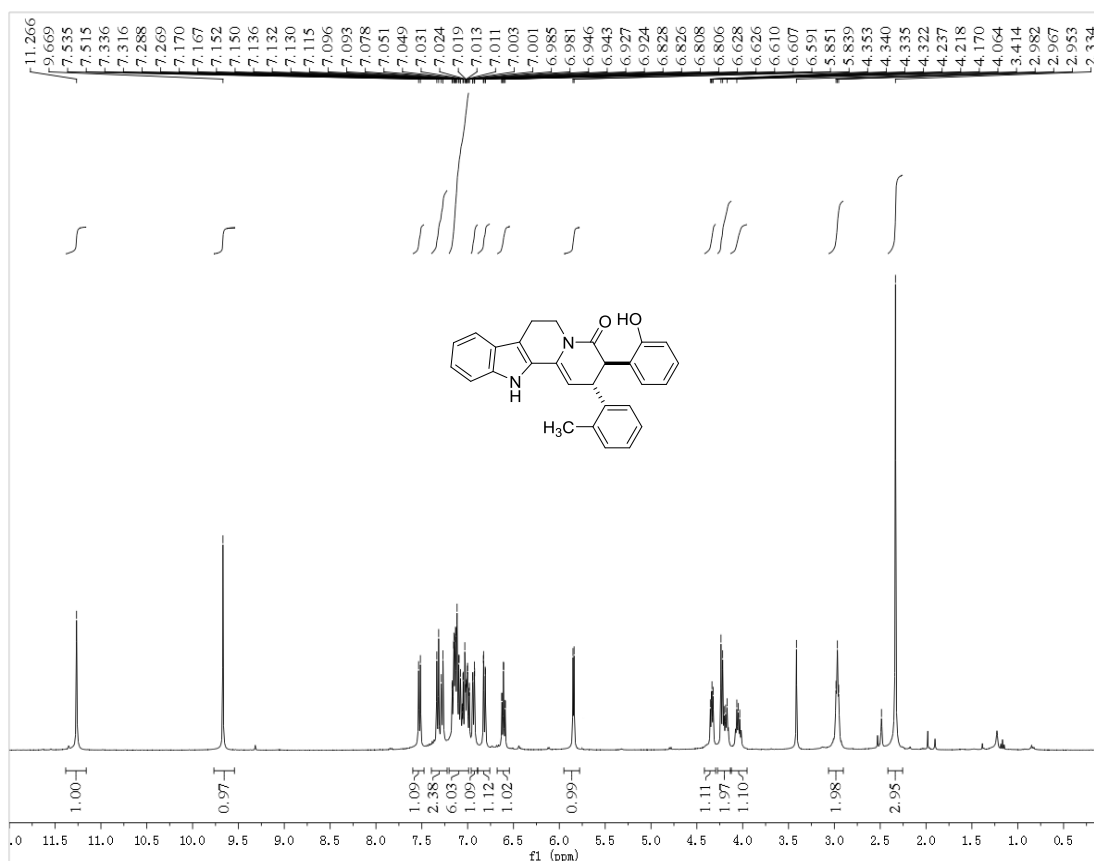
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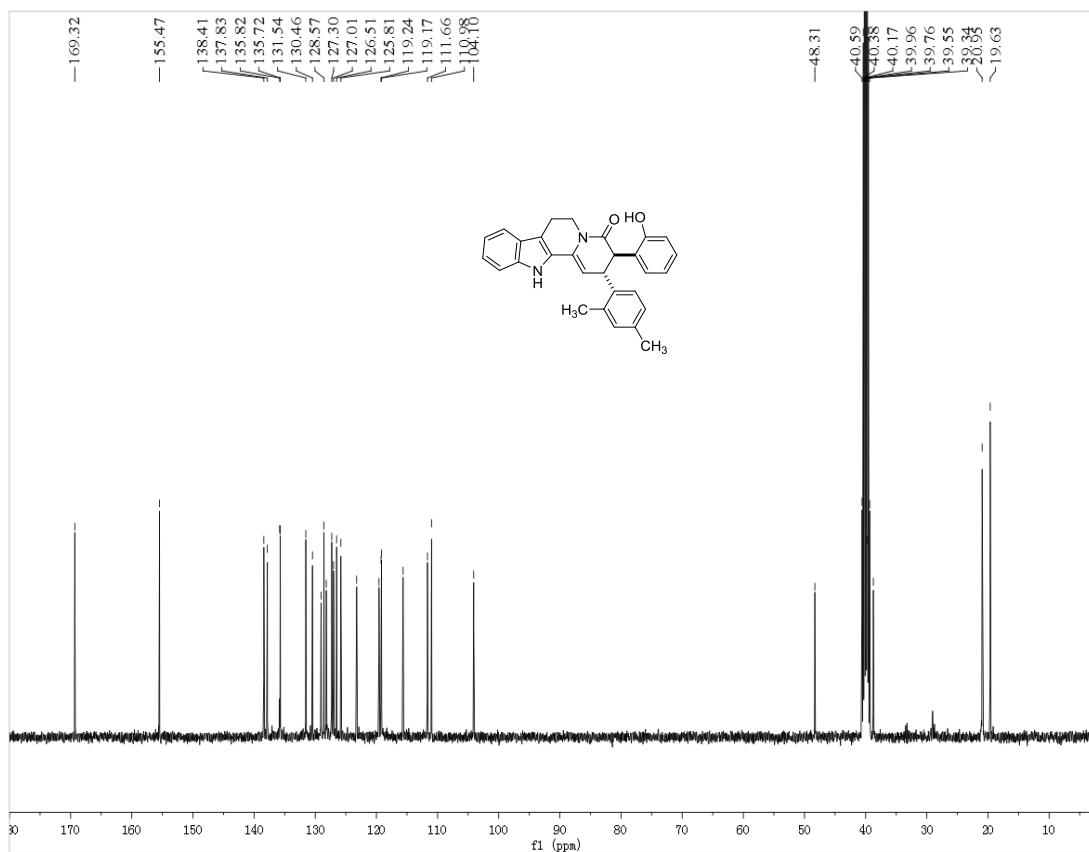
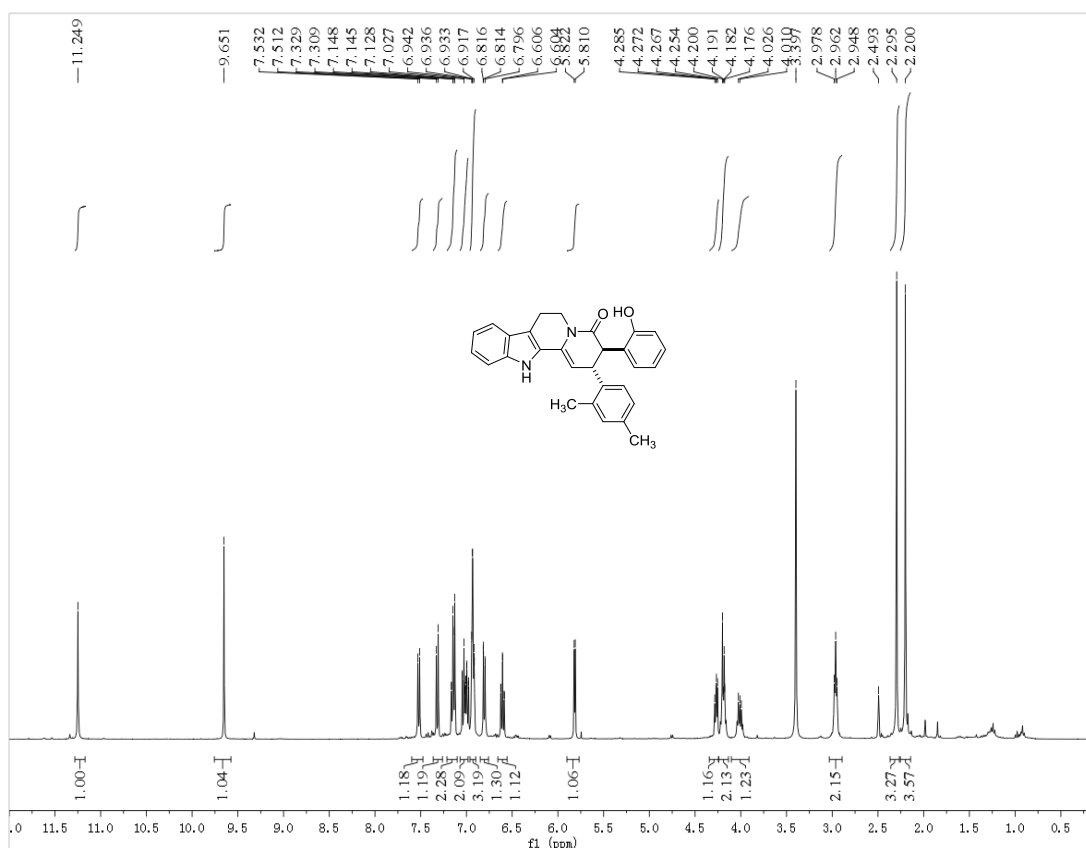
¹H and ¹³C NMR of 3ao



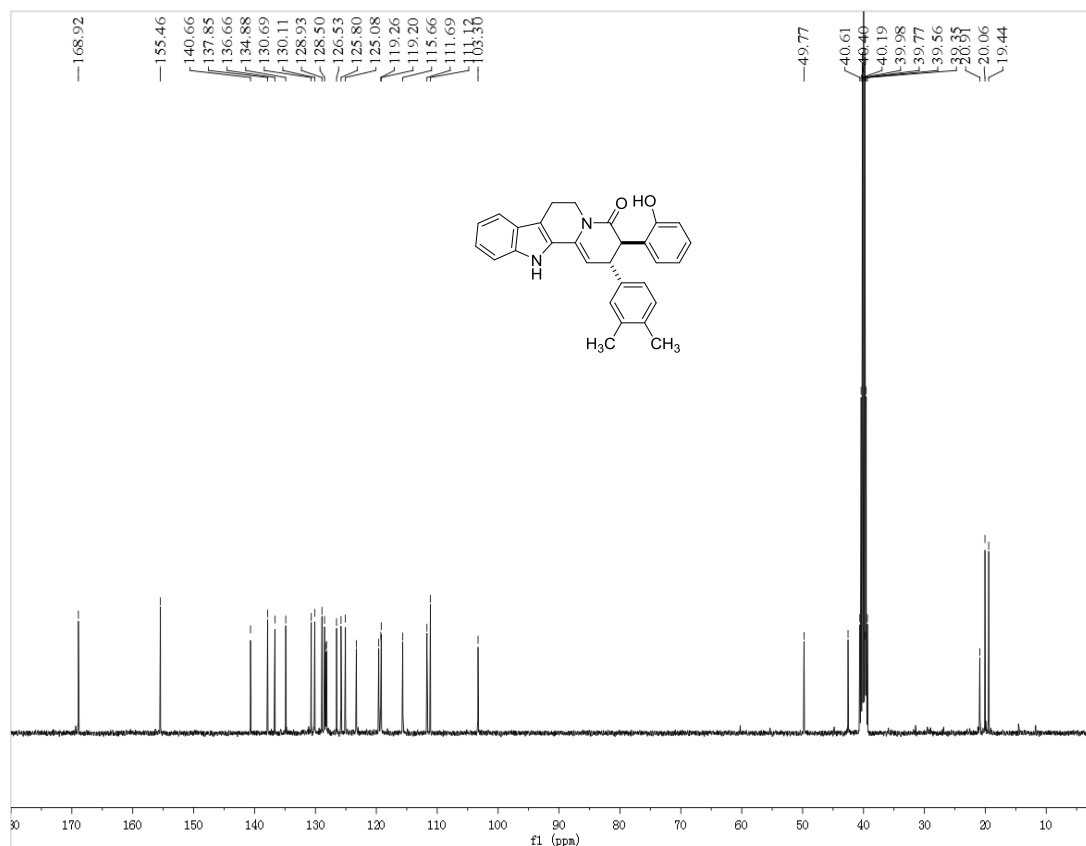
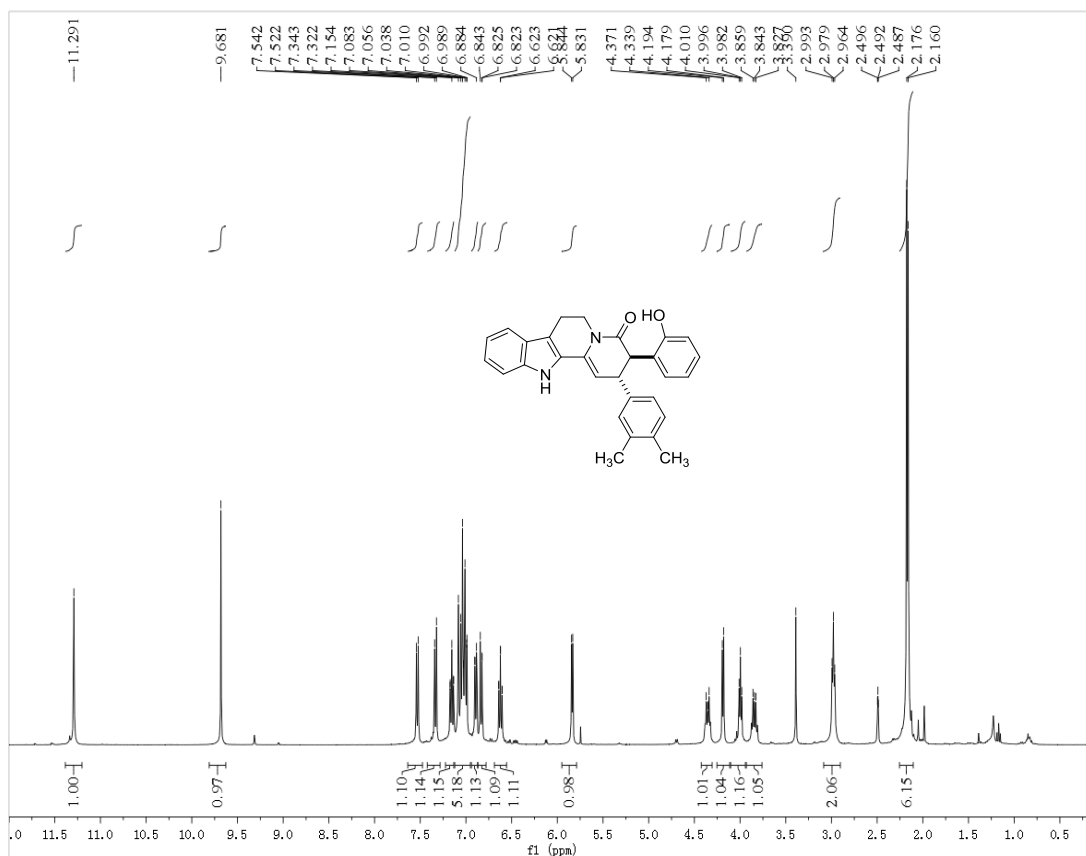
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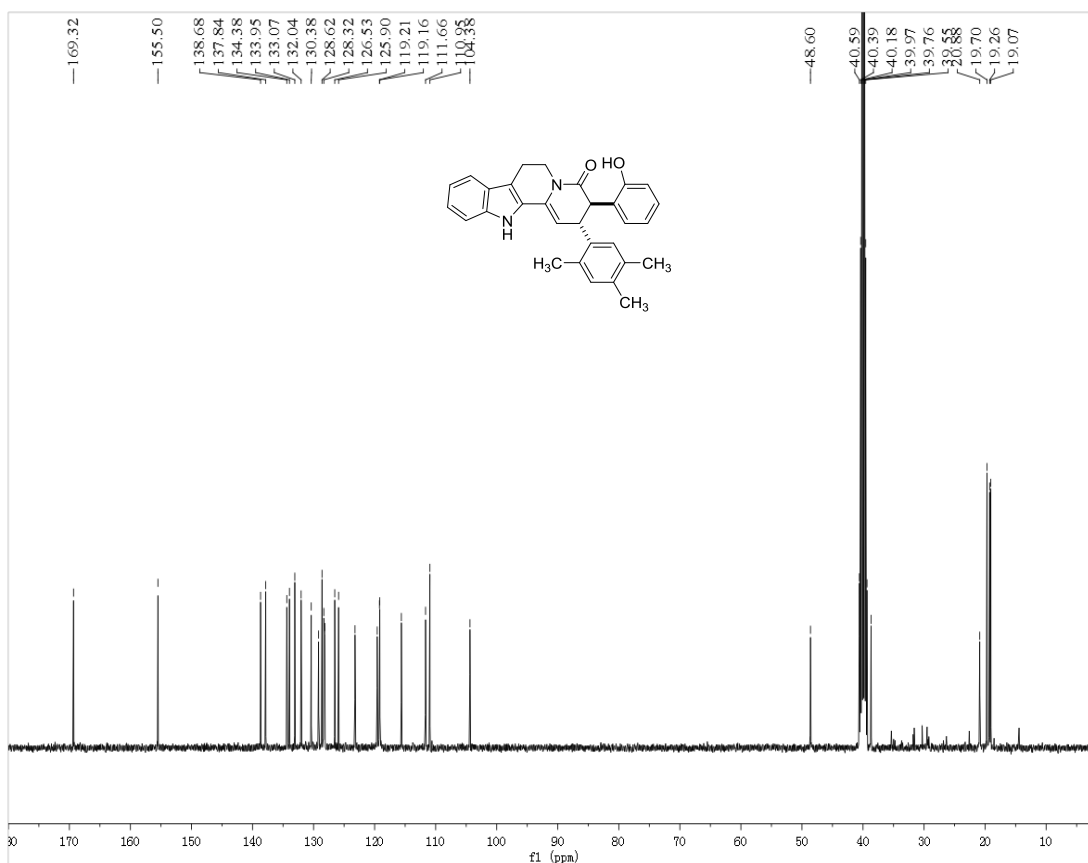
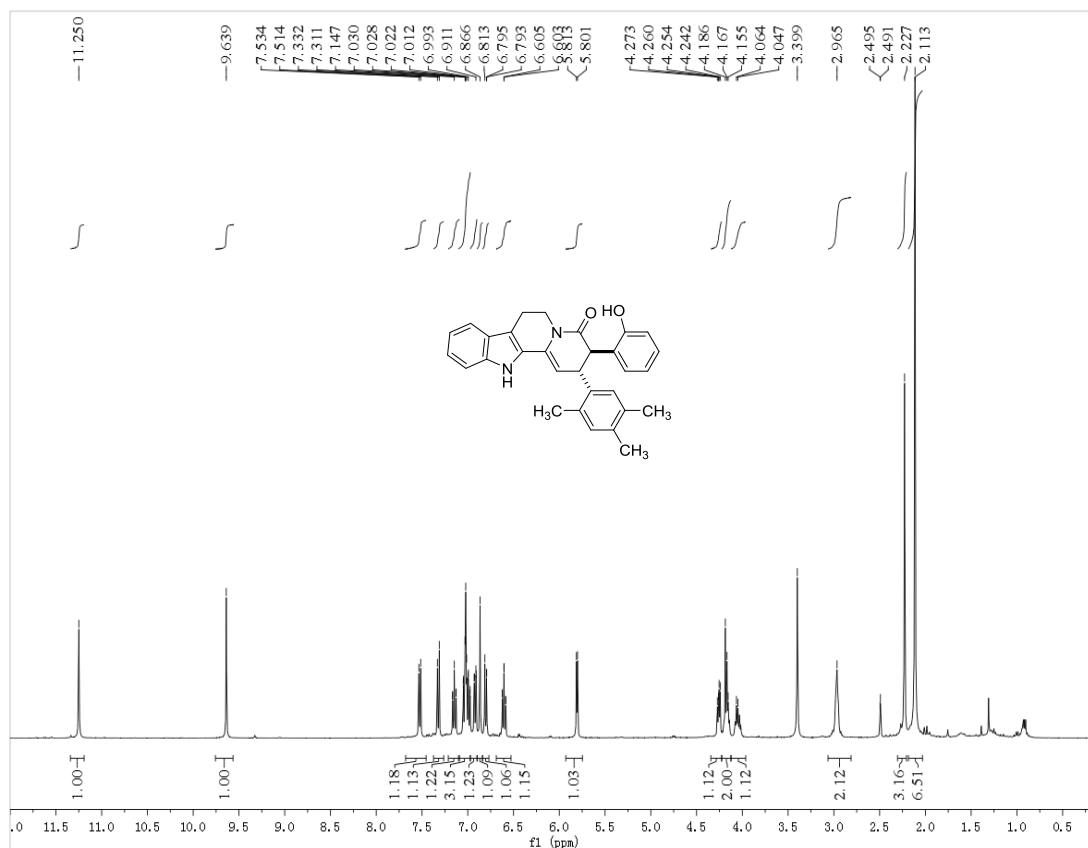
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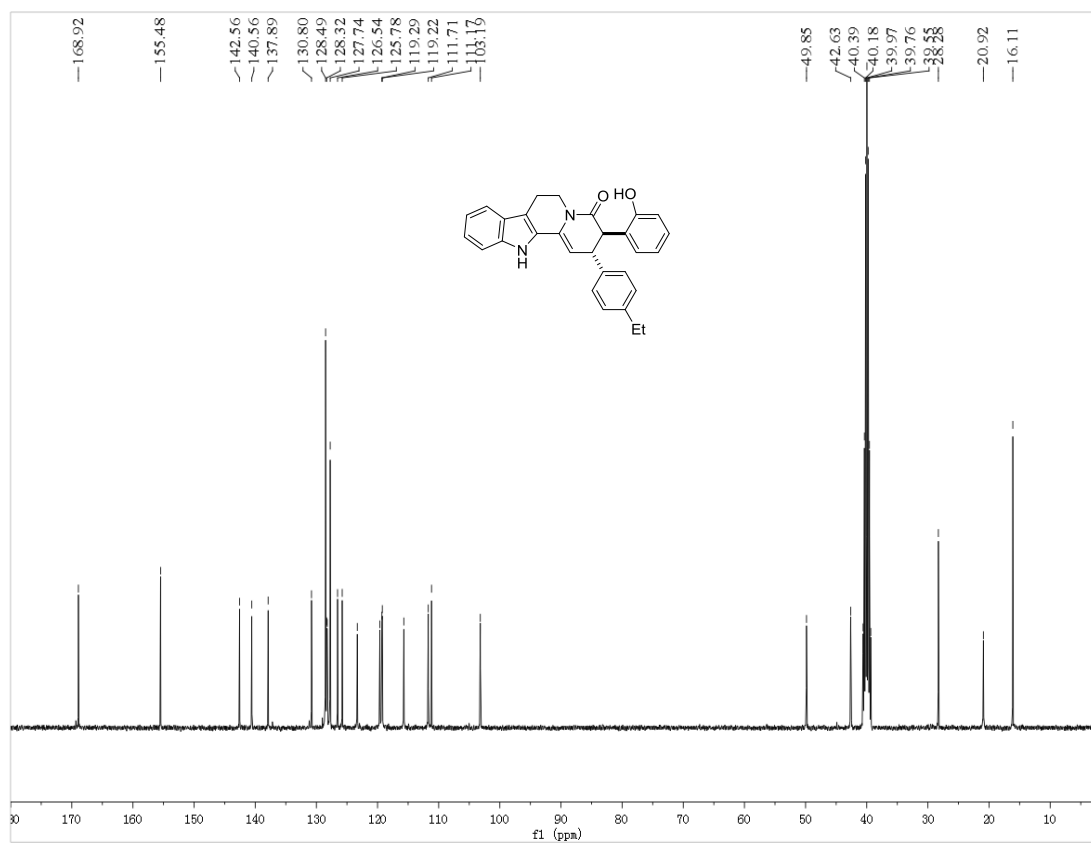
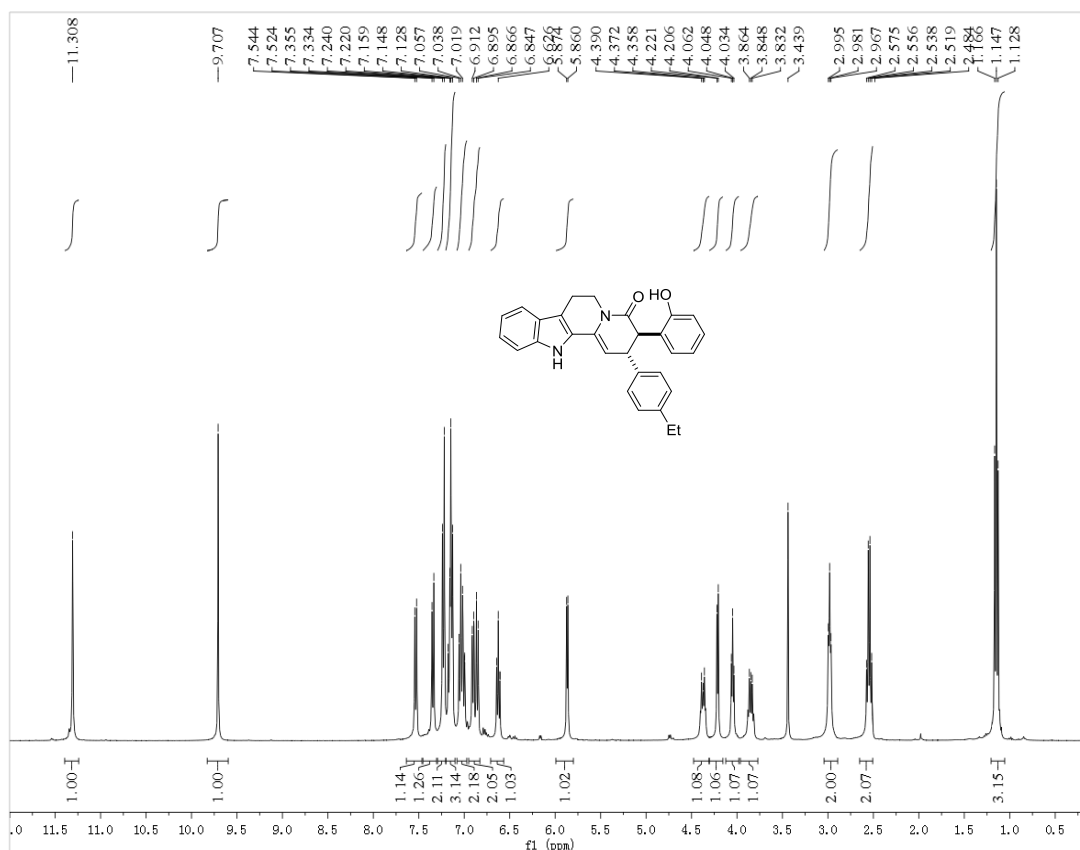
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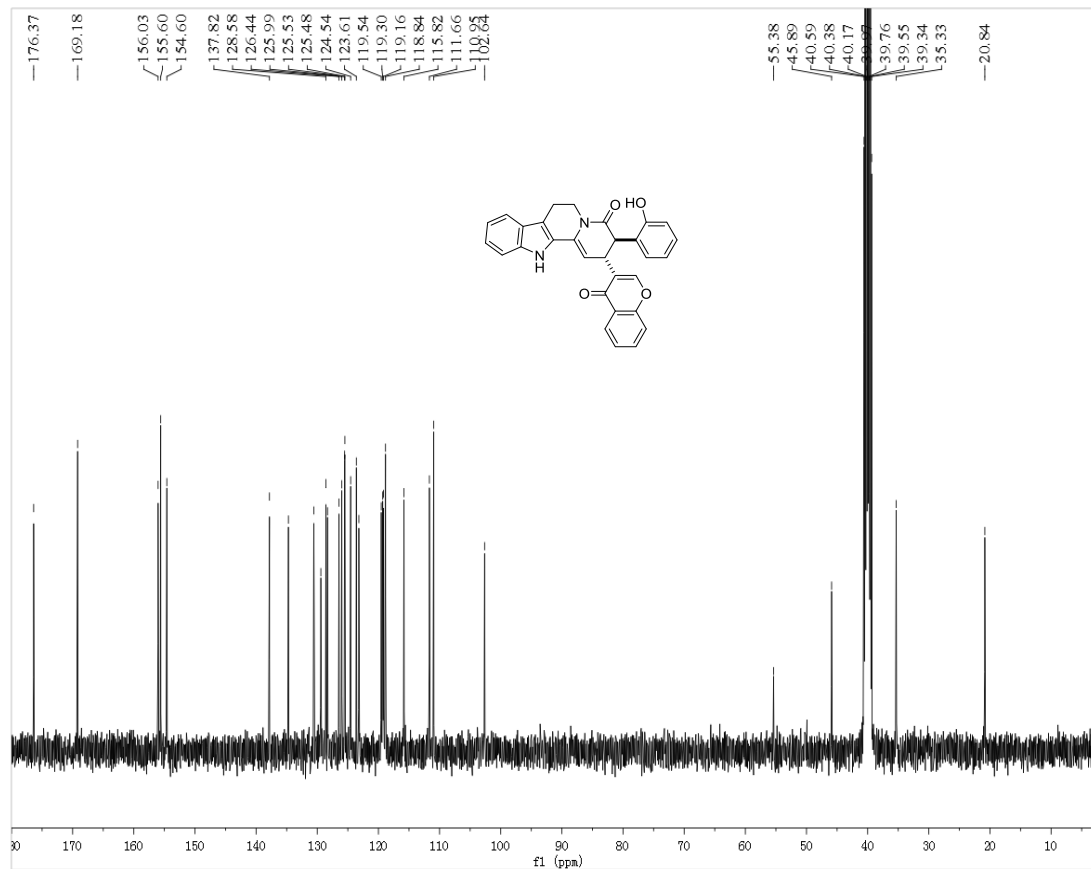
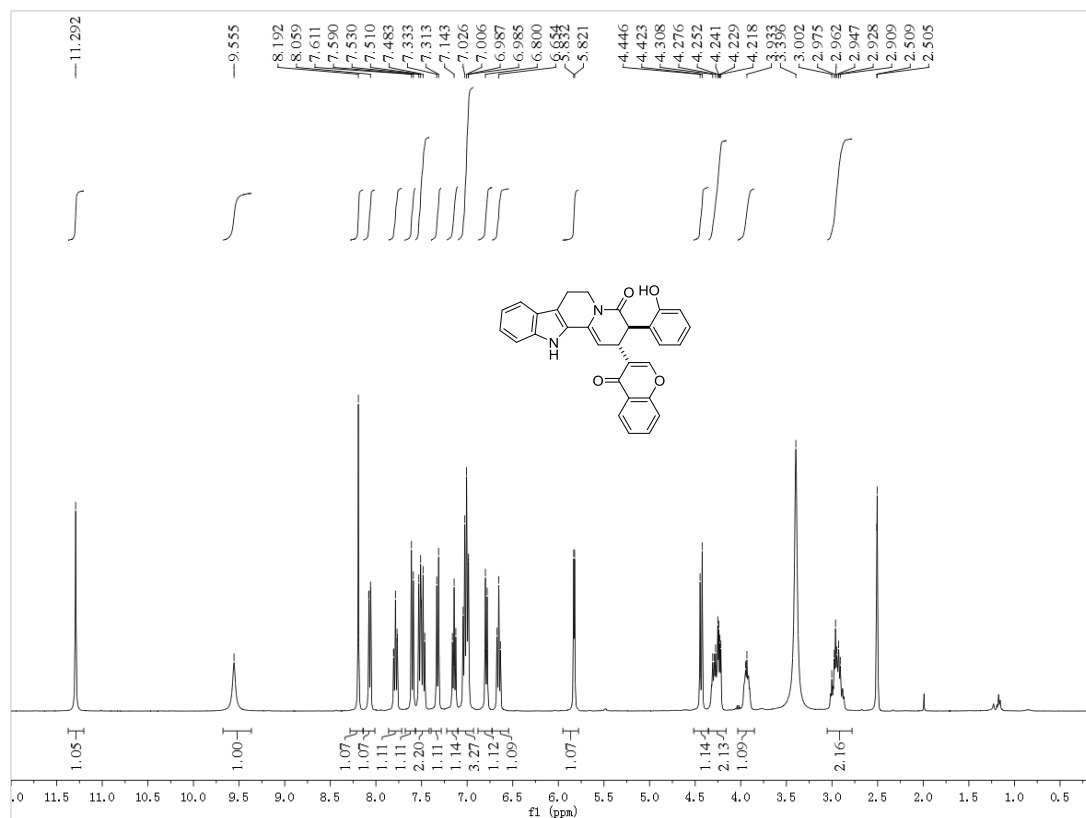
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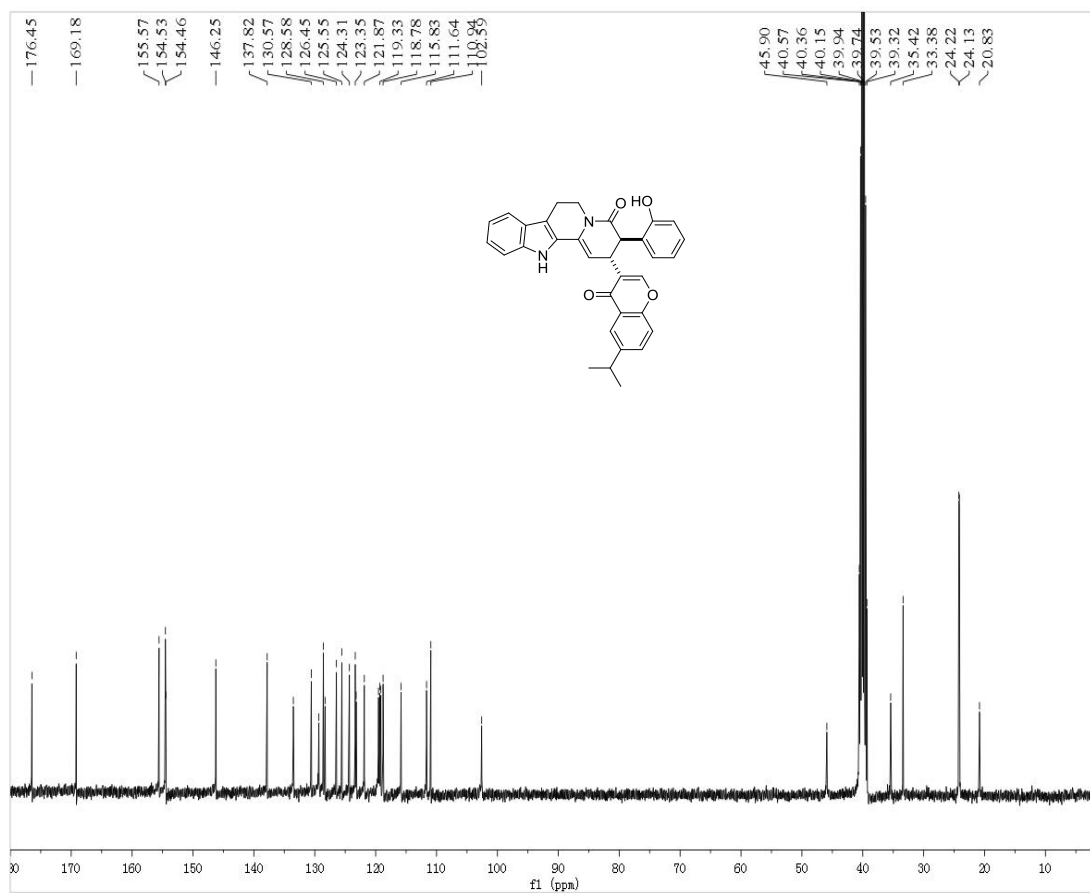
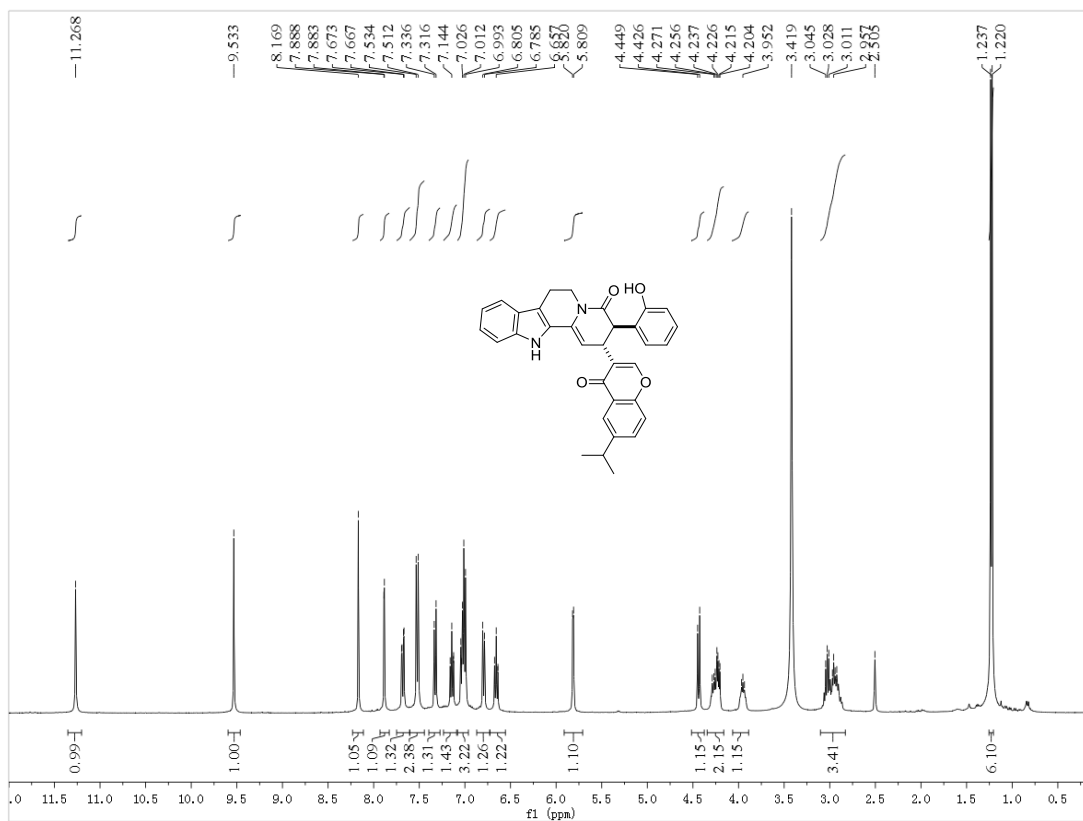
^1H and ^{13}C NMR of 3at



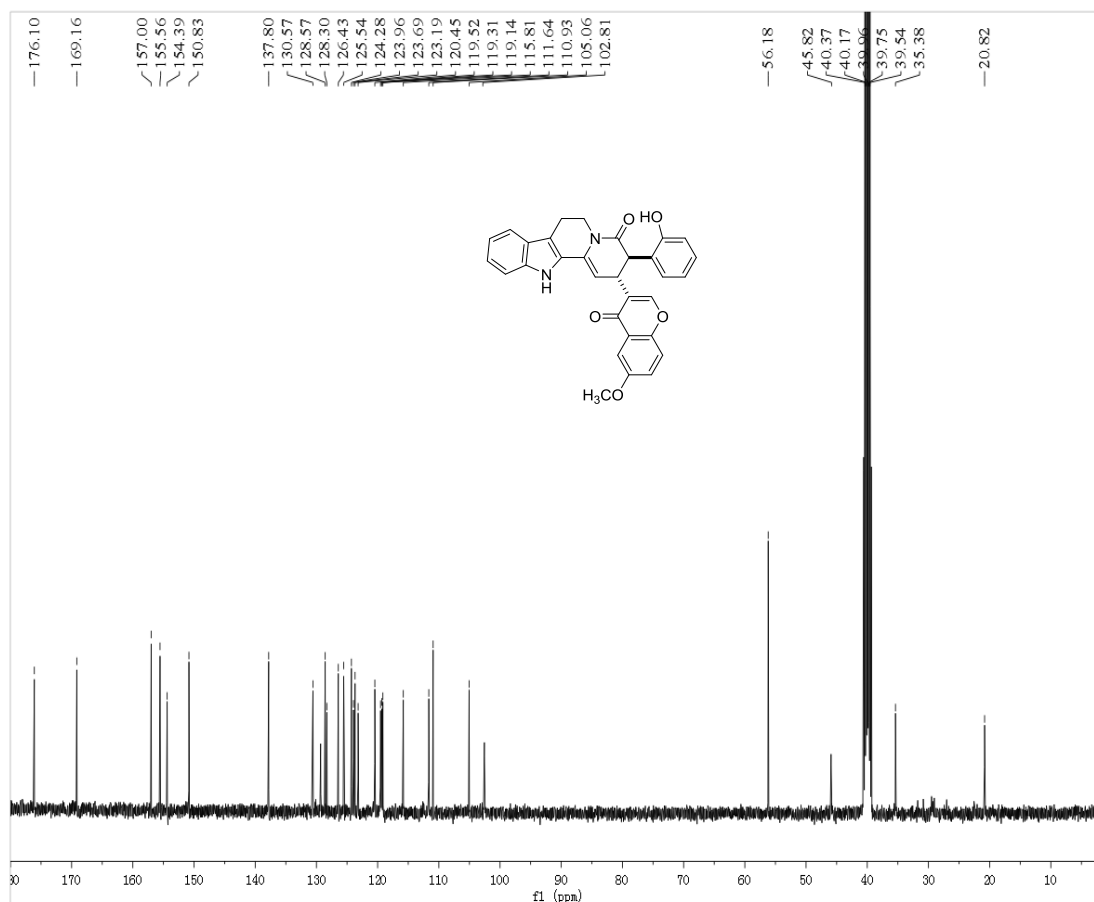
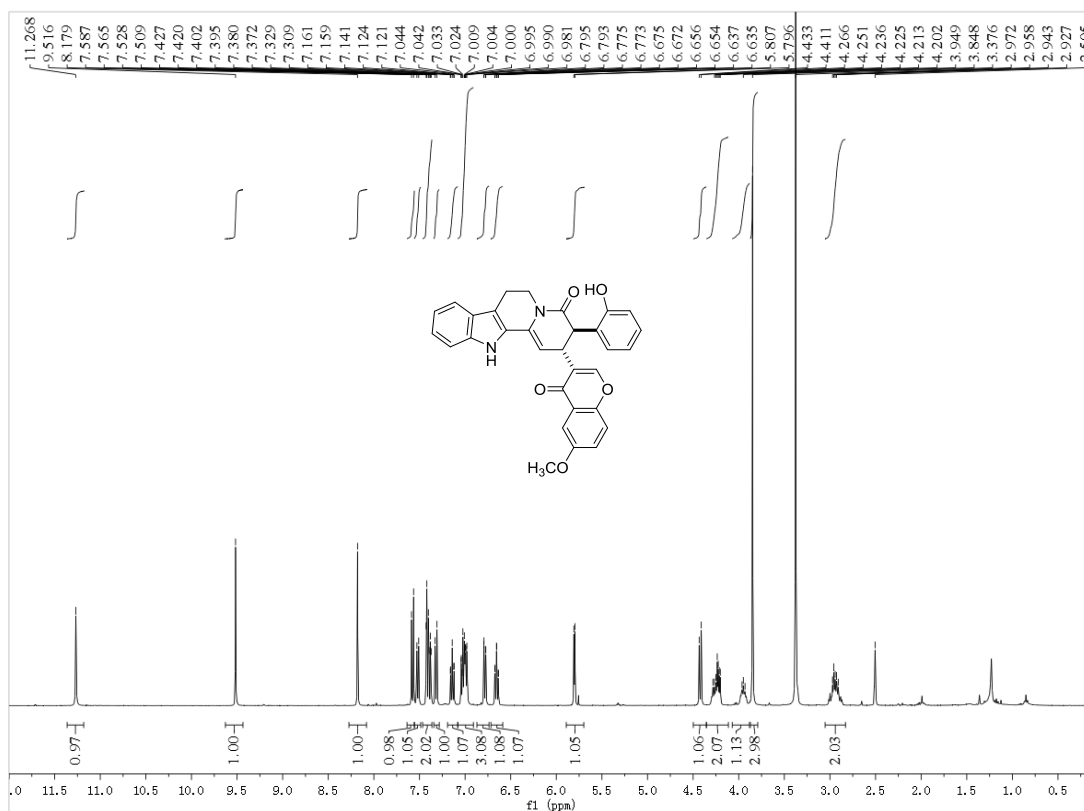
¹H and ¹³C NMR of 3au



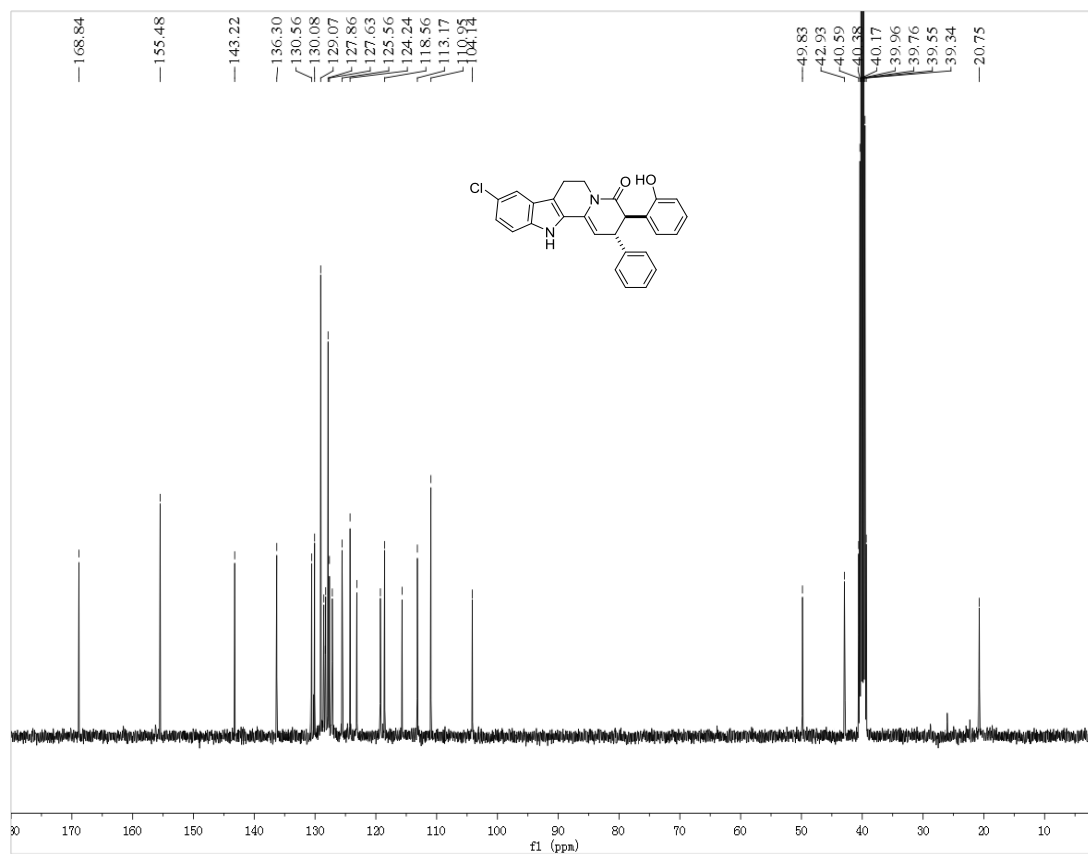
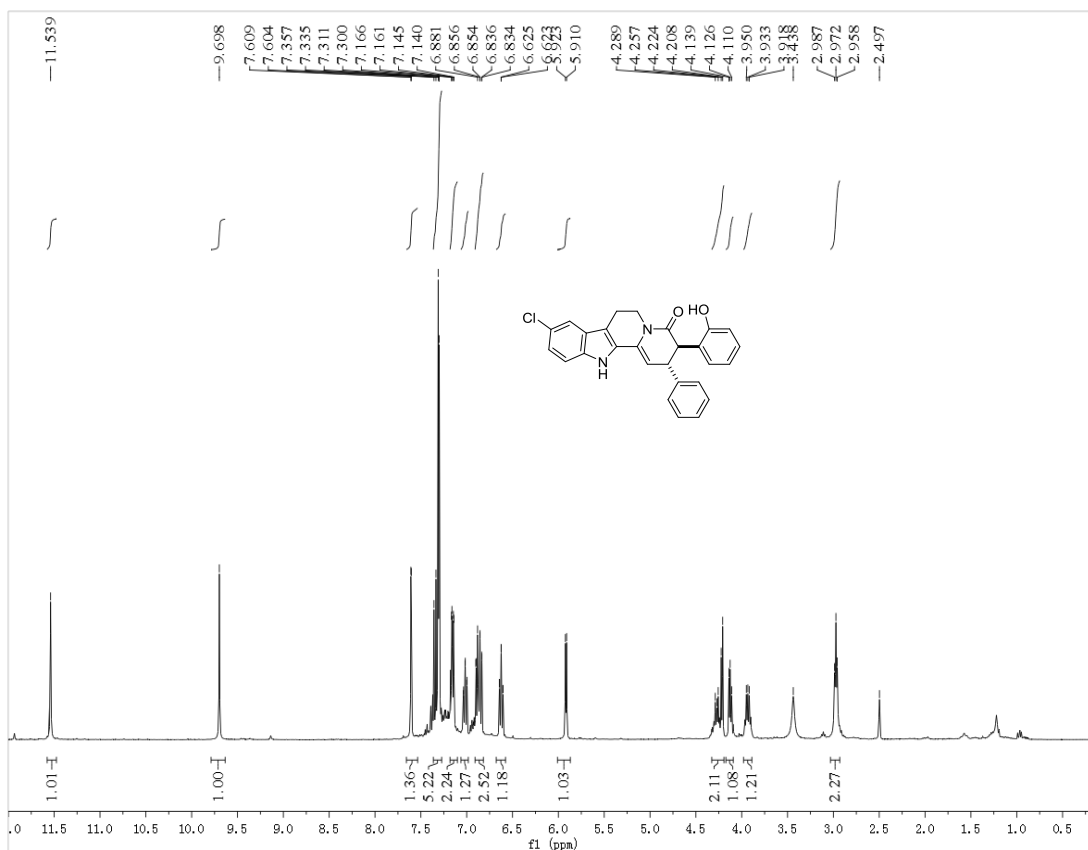
¹H and ¹³C NMR of 3av



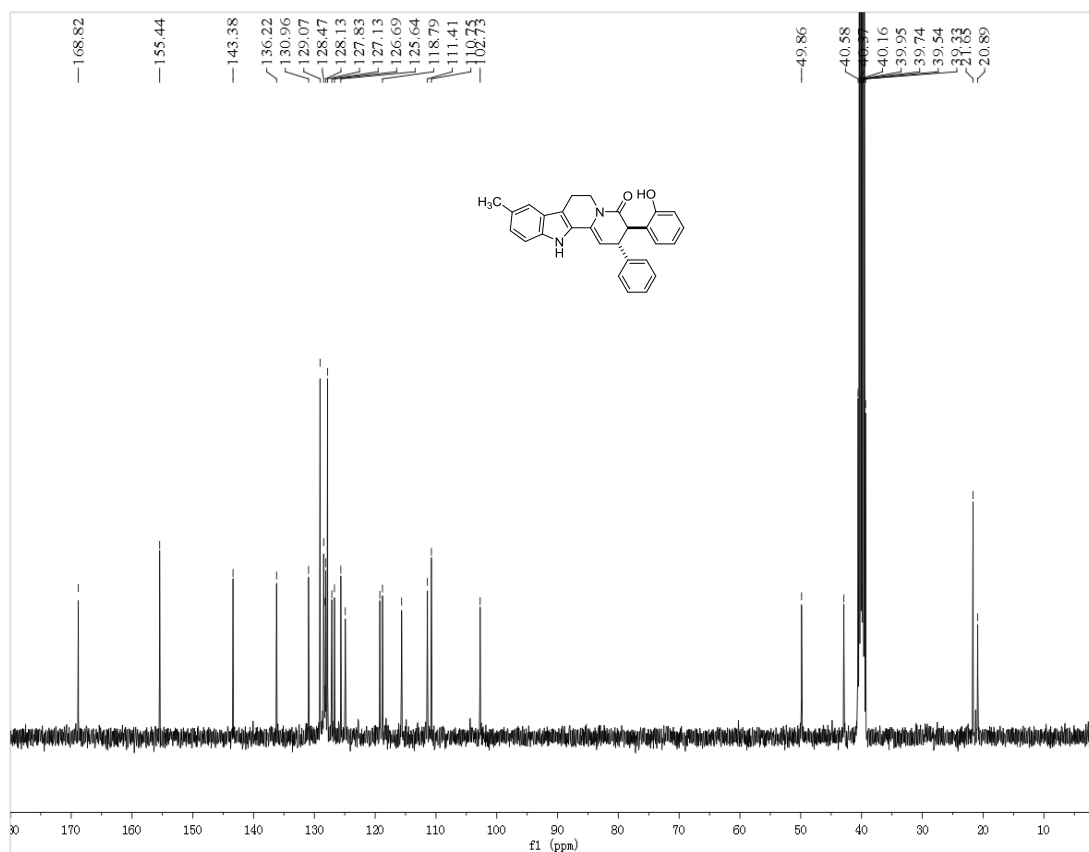
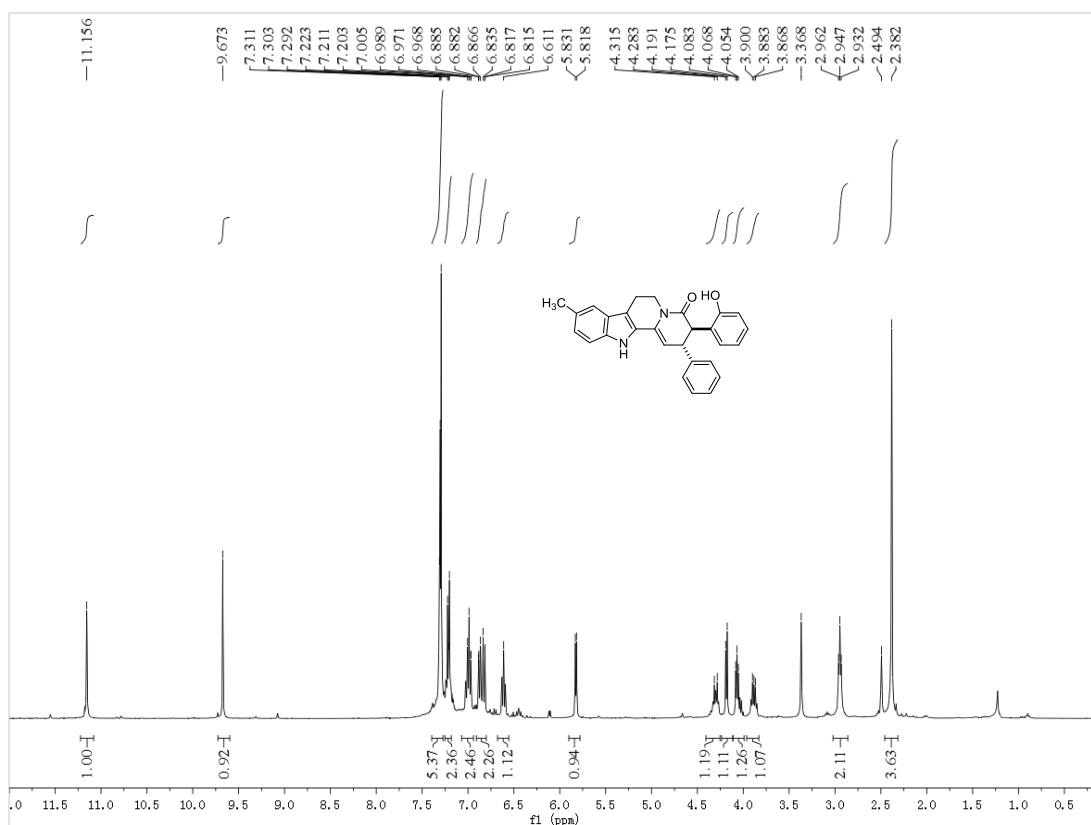
^1H and ^{13}C NMR of 3aw



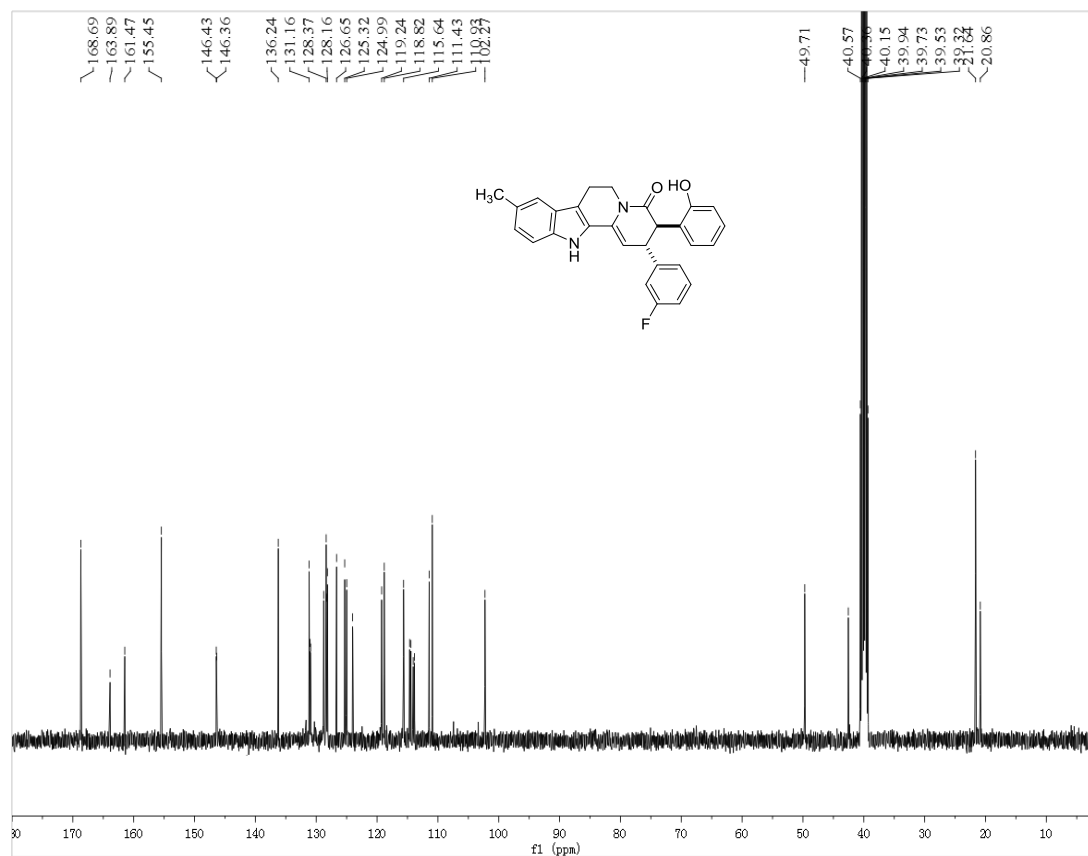
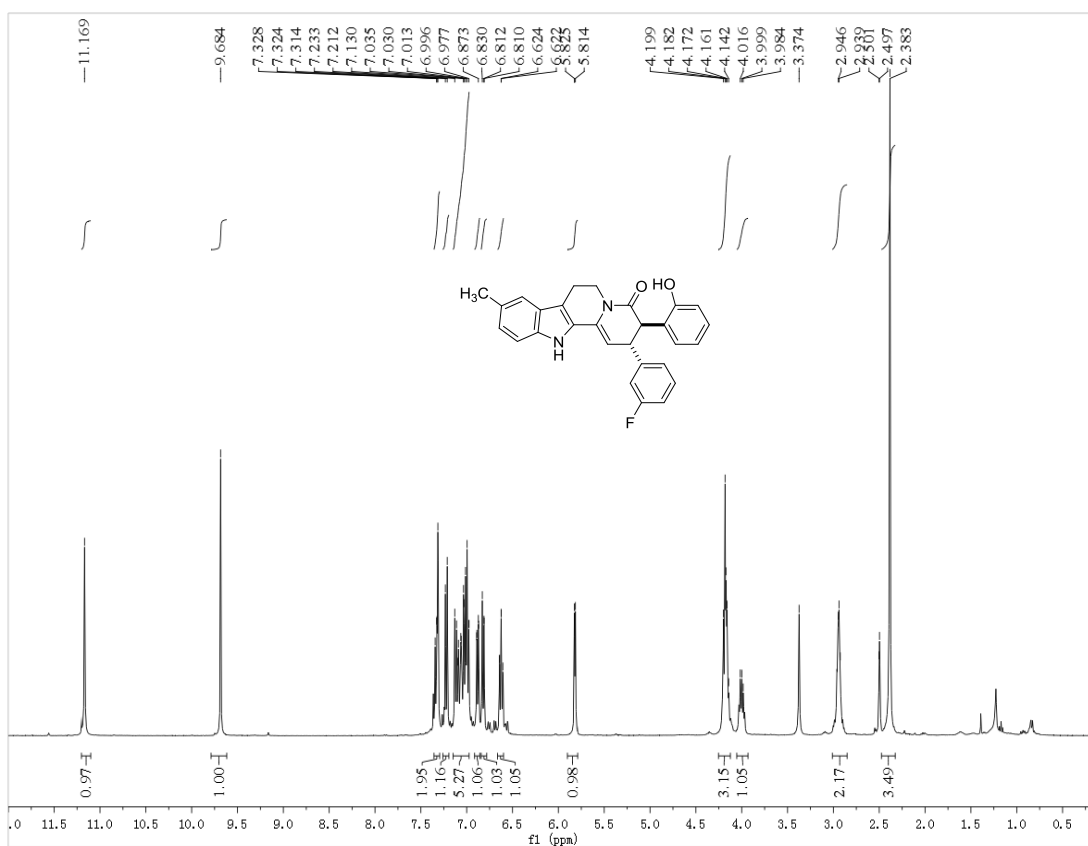
¹H and ¹³C NMR of 3ba



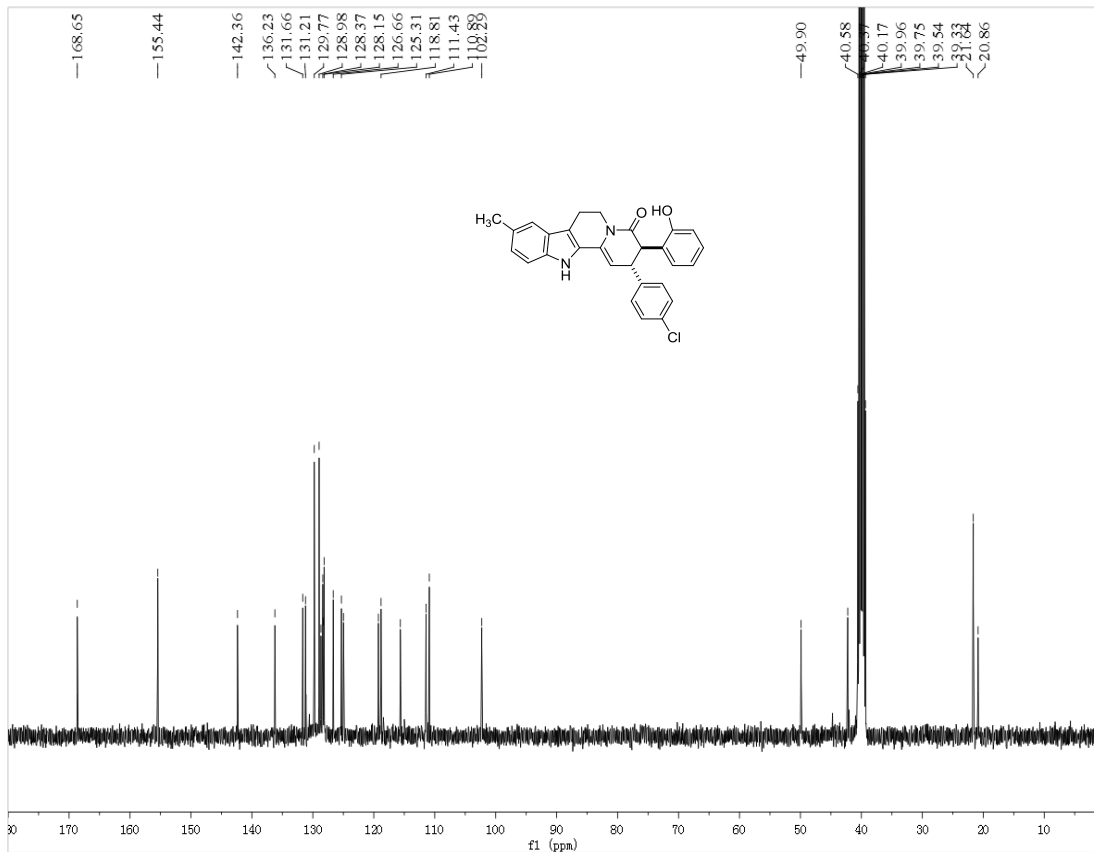
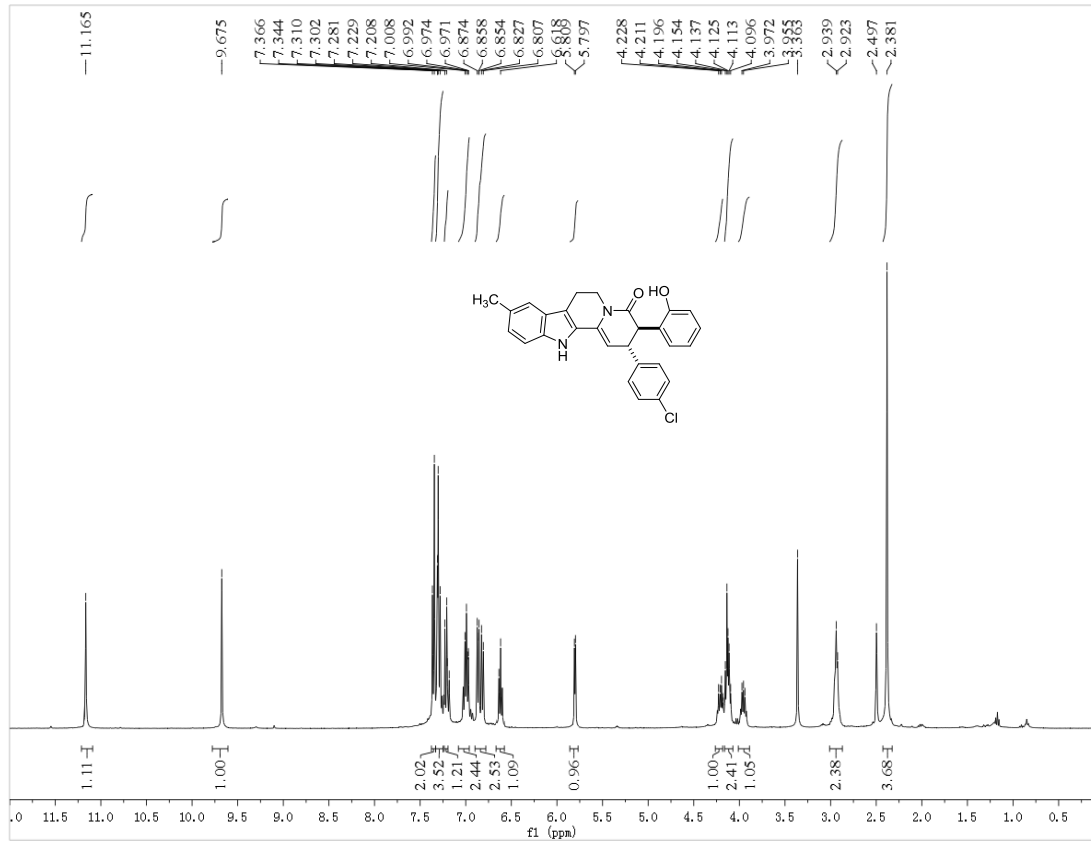
^1H and ^{13}C NMR of 3ca



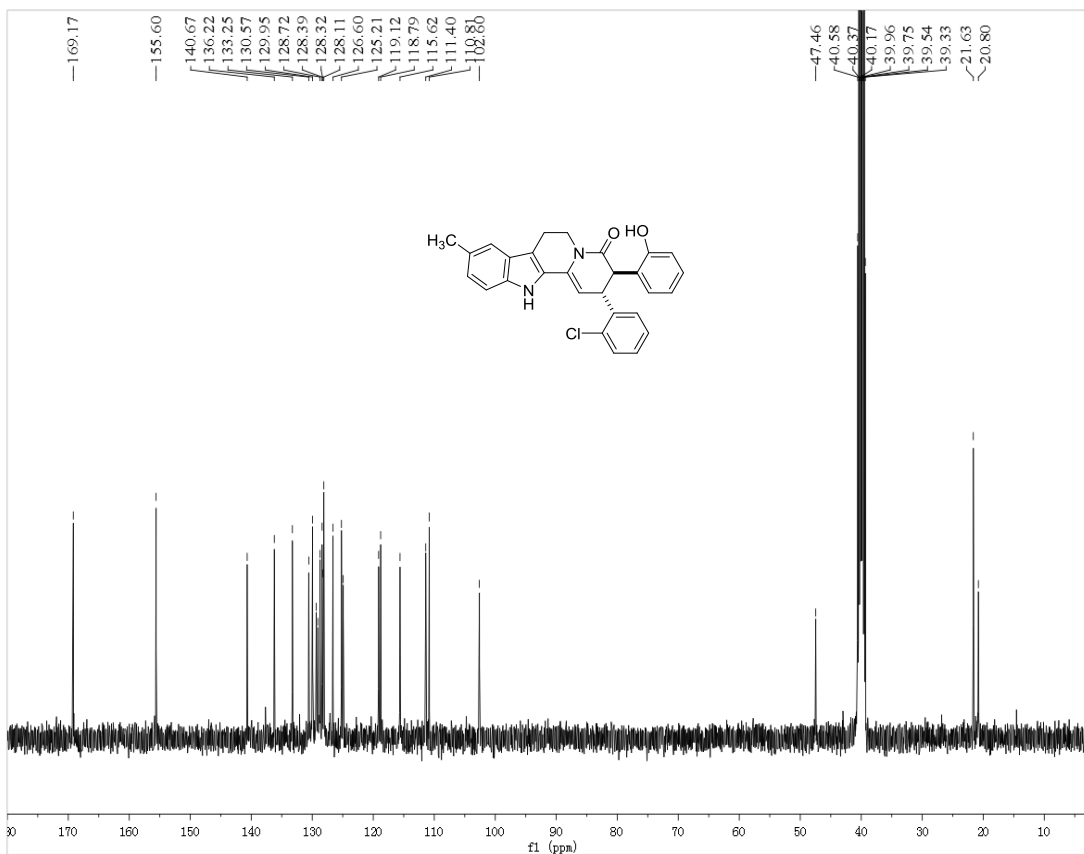
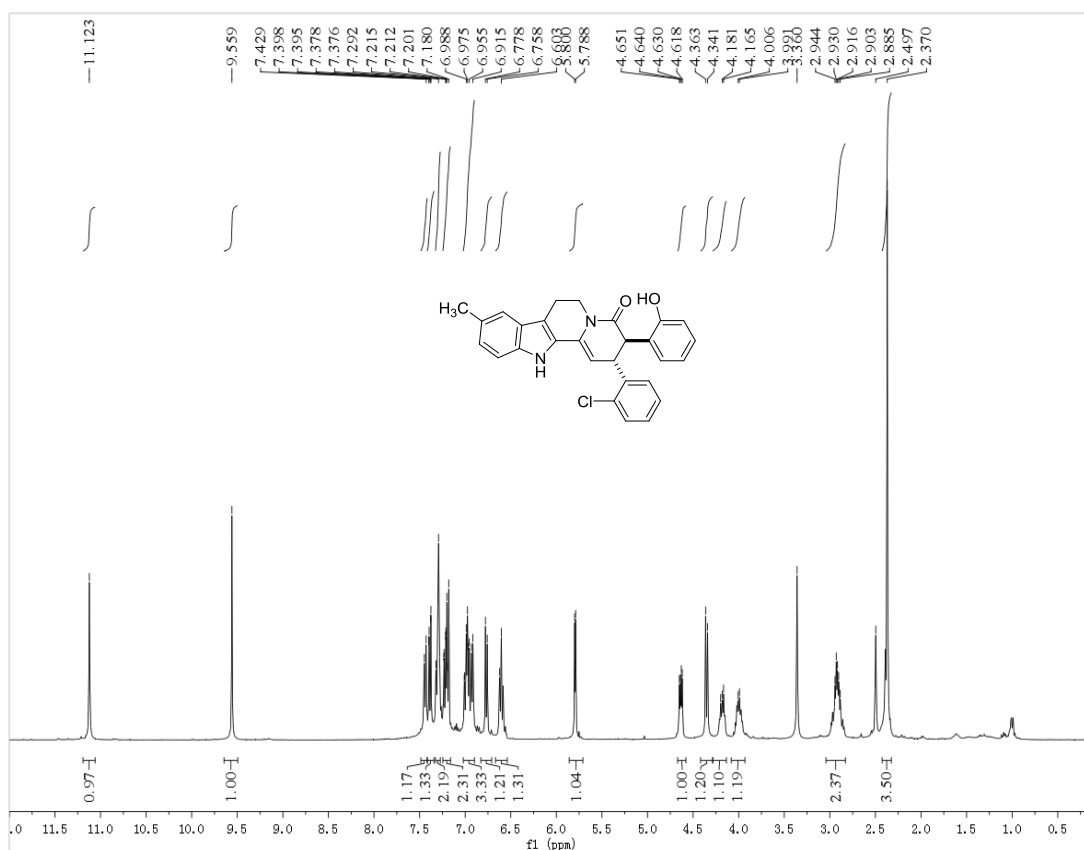
¹H and ¹³C NMR of 3cb



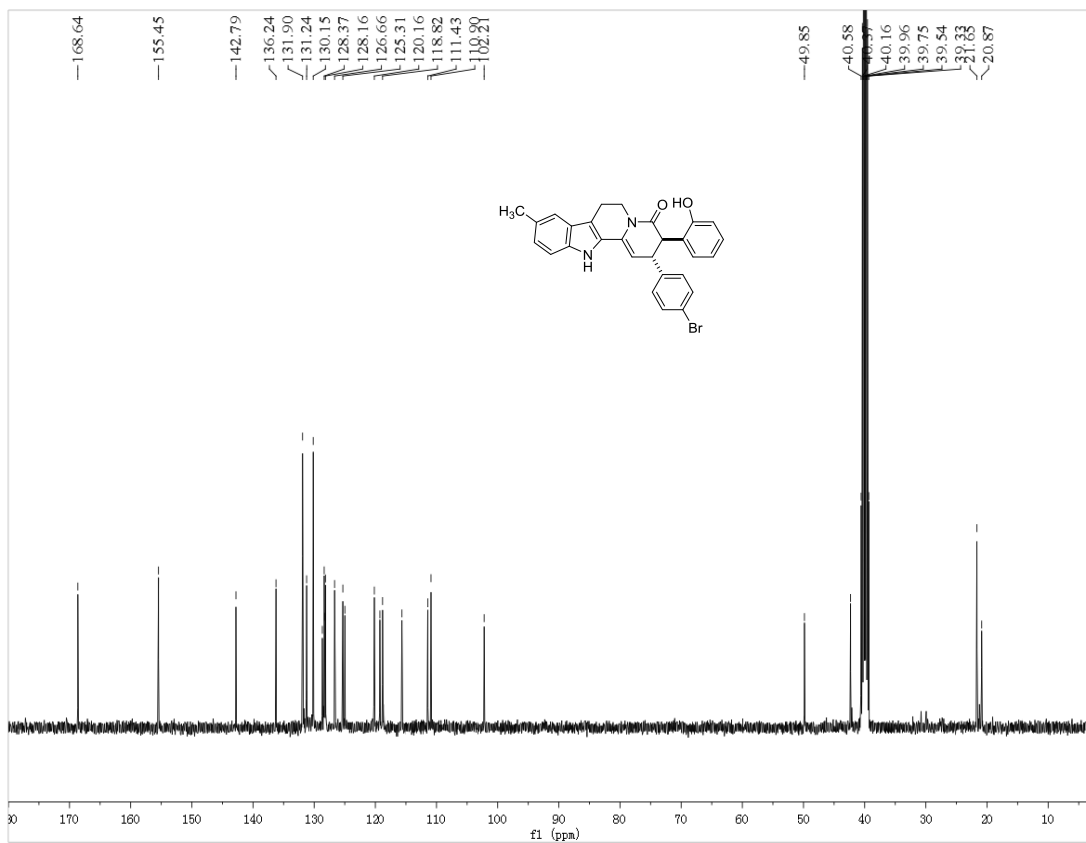
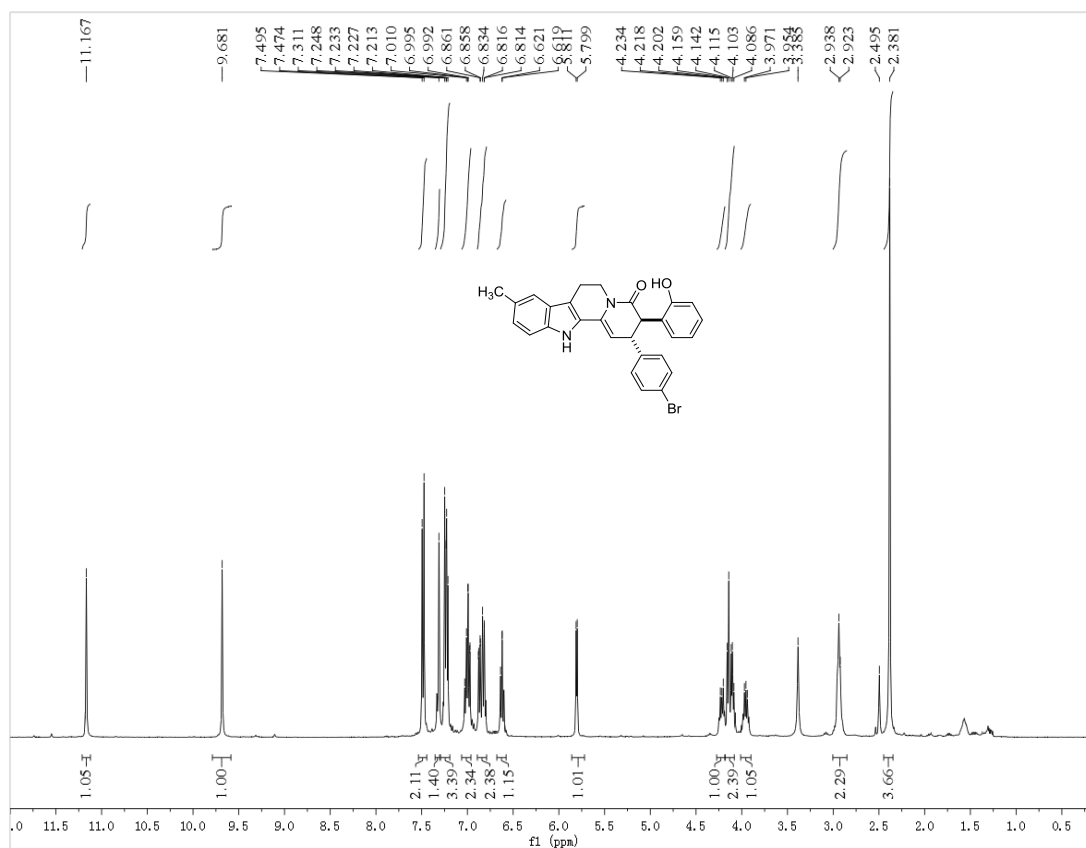
^1H and ^{13}C NMR of 3cc



^1H and ^{13}C NMR of 3cd



^1H and ^{13}C NMR of 3ce



^1H and ^{13}C NMR of 3cf

