

Py-2NO ligand enabled Ni(II)-catalyzed asymmetric Michael addition reaction of indoles with β,γ -unsaturated α -keto esters

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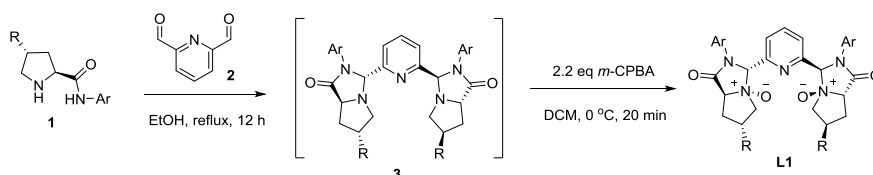
Table of Contents

Table of contents.....	S1
1. General experimental information.....	S2
2. General procedure for preparation of chiral Py-2NO ligands L1	S2
3. Characterization data of ligands L1 , L3g , L4g and 5	S2
4. Catalytic asymmetric synthesis of compounds 8	S6
5. Characterization data of compounds 8	S6
6. Control experiments and HPLC spectra for compound 8a	S12
7. X-ray crystal data for compounds 3h , L1g , 4 and 5	S16
8. References.....	S18
9. The copies of ¹ H NMR, ¹³ C NMR and HPLC spectra for compounds L , 4 , 5 and 8	S19

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. ^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.

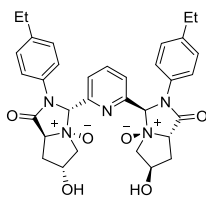
2. General procedure for preparation of chiral Py-2NO ligands L1



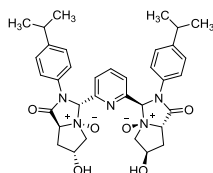
General procedure A—In a sealed tube equipped with a magnetic stirring bar, pyridine-2,6-dicarbaldehyde **2** (1.0 mmol) and optically pure 4-hydroxyprolinamide or prolinamide **1** (2.4 mmol, 2.4 equiv) were added. Then, ethanol (6.0 mL) was added and the reaction was heated with stirring at reflux for 12 h. After completion of the reaction, as indicated by TLC, the aftertreatment residue was purified by flash column chromatography to give the intermediate **3**.

For the oxidation step, see: X. Liu, L. Lin and X. Feng, Chiral *N,N'*-dioxide ligands: synthesis, coordination chemistry and asymmetric catalysis, *Org. Chem. Front.*, 2014, **1**, 298-302. In a sealed tube equipped with a magnetic stirring bar, to the intermediate **3** was added 3.0 mL of DCM and *m*-CPBA (2.2 eq). The reaction mixture was stirred at 0 °C for 20 min. After completion of the reaction, as indicated by TLC, the aftertreatment residue was purified by flash column chromatography to furnish the Py-2NO ligand L1.

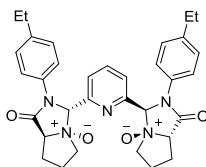
3. Characterization data of ligands L1, L3g, L4g 4 and 5



L1a (Prepared according to general procedure A): White solid, m.p. 237.5-238.1 °C; overall yield 55%, >20:1 dr; ¹H NMR (CD₃OD, 400 MHz) δ: 1.05-1.09 (m, 6H), 2.29-2.35 (m, 2H), 2.46-2.52 (m, 4H), 2.61-2.67 (m, 2H), 3.78-3.81 (m, 2H), 4.13-4.16 (m, 2H), 4.19-4.24 (m, 2H), 4.46-4.50 (m, 2H), 6.66 (s, 2H), 7.06 (d, *J* = 8.8 Hz, 4H), 7.28 (d, *J* = 8.8 Hz, 4H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.84-7.88 (m, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ: 14.6, 27.9, 35.1, 70.0, 76.2, 76.4, 87.5, 123.0, 128.4, 129.1, 132.9, 137.4, 143.4, 149.9, 168.0; HRMS (ESI-TOF) *m/z*: Calcd. for C₃₃H₃₇N₅NaO₆ [M+Na]⁺: 622.2636; Found: 622.2636.

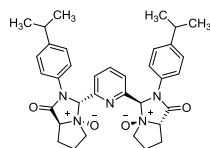


L1b (Prepared according to general procedure A): White solid, m.p. 248.3-248.9 °C; overall yield 51%, >20:1 dr; ¹H NMR (CD₃OD, 400 MHz) δ: 1.07 (s, 6H), 1.09 (s, 6H), 2.29-3.35 (m, 2H), 2.60-2.67 (m, 2H), 2.71-2.78 (m, 2H), 3.81 (d, *J* = 12.0 Hz, 2H), 4.15-4.24 (m, 4H), 4.48 (s, 2H), 6.67 (s, 2H), 7.09 (d, *J* = 8.8 Hz, 4H), 7.29 (d, *J* = 8.8 Hz, 4H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.81-7.85 (m, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ: 22.9, 33.5, 35.2, 70.0, 76.1, 76.4, 87.5, 123.1, 127.0, 129.1, 132.9, 137.4, 148.0, 149.9, 168.0; HRMS (ESI-TOF) *m/z*: Calcd. for C₃₅H₄₁N₅NaO₆ [M+Na]⁺: 650.2949; Found: 650.2952.

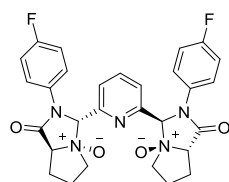


L1c (Prepared according to general procedure A): White solid, m.p. 223.5-223.9 °C; overall yield 53%, 19:1 dr; ¹H NMR (CD₃OD, 400 MHz) δ: 1.15-1.19 (m, 6H), 2.13-2.21 (m, 2H), 2.33-2.46 (m, 6H), 2.55-2.61 (m, 4H), 3.84-3.88 (m, 2H), 3.98-4.01 (m, 2H), 4.07-4.14 (m, 2H), 6.77 (s, 2H), 7.16 (d, *J* = 8.8 Hz, 4H), 7.41 (d, *J* = 8.8 Hz, 4H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.94-7.98 (m, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ: 14.6, 22.1, 24.1, 27.9, 71.0, 76.7, 87.2, 122.8, 128.4, 129.0, 133.1,

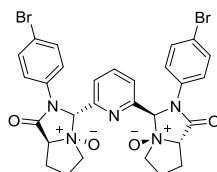
137.1, 143.1, 150.2, 168.6; HRMS (ESI-TOF) m/z : Calcd. for $C_{33}H_{37}N_5NaO_4$ $[M+Na]^+$: 590.2738; Found: 590.2734.



L1d (Prepared according to general procedure A): White solid, m.p. 210.3-211.0 °C; overall yield 53%, 19:1 dr; 1H NMR (CD_3OD , 400 MHz) δ : 1.07 (s, 6H), 1.08 (s, 6H), 2.02-2.07 (m, 2H), 2.22-2.27 (m, 4H), 2.30-2.39 (m, 2H), 2.70-2.77 (m, 2H), 3.73-3.78 (m, 2H), 3.91-4.01 (m, 4H), 6.66 (s, 2H), 7.09 (d, $J = 8.8$ Hz, 4H), 7.31 (d, $J = 8.4$ Hz, 4H), 7.65 (d, $J = 7.6$ Hz, 2H), 7.82-7.86 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ : 22.2, 22.9, 23.0, 24.2, 33.6, 71.0, 76.8, 87.2, 122.9, 127.0, 129.0, 133.2, 137.2, 147.8, 150.3, 168.6; HRMS (ESI-TOF) m/z : Calcd. for $C_{35}H_{41}N_5NaO_4$ $[M+Na]^+$: 618.3051; Found: 618.3051.

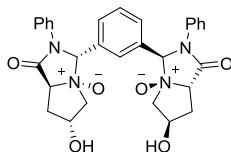


L1e (Prepared according to general procedure A): White solid, m.p. 248.5-249.1 °C; overall yield 54%, >20:1 dr; 1H NMR (CD_3OD , 400 MHz) δ : 2.06-2.12 (m, 2H), 2.23-2.40 (m, 6H), 3.76-3.80 (m, 2H), 4.01-4.09 (m, 4H), 6.66 (s, 2H), 6.94-6.98 (m, 4H), 7.38-7.41 (m, 4H), 7.64 (d, $J = 7.6$ Hz, 2H), 7.85-7.88 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ : 22.3, 24.3, 71.3, 76.9, 87.5, 115.8 (d, $J_{CF} = 23.2$ Hz), 125.7 (d, $J_{CF} = 9.0$ Hz), 129.0, 131.4 (d, $J_{CF} = 3.1$ Hz), 137.5, 150.5, 161.6 (d, $J_{CF} = 245.0$ Hz), 168.9; HRMS (ESI-TOF) m/z : Calcd. for $C_{29}H_{27}F_2N_5NaO_4$ $[M+Na]^+$: 570.1923; Found: 570.1925.

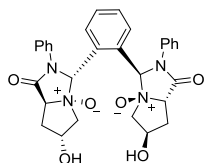


L1f (Prepared according to general procedure A): White solid, m.p. 239.5-239.4 °C; overall yield 57%, >20:1 dr; 1H NMR (CD_3OD , 400 MHz) δ : 2.14-2.20 (m, 2H), 2.33-2.38 (m, 4H), 2.41-2.48

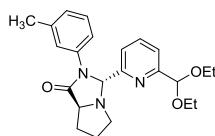
(m, 2H), 3.78-3.87 (m, 4H), 4.05-4.12 (m, 2H), 6.85 (s, 2H), 7.47 (s, 8H), 7.81 (d, $J = 7.6$ Hz, 2H), 7.99-8.03 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ : 22.2, 24.1, 70.9, 76.5, 86.4, 119.4, 123.8, 129.4, 132.1, 134.9, 137.3, 149.7, 168.4; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{29}\text{H}_{27}\text{Br}_2\text{N}_5\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 690.0322; Found: 690.0322.



L3g (Prepared according to general procedure A): White solid, m.p. 227.1-228.0 °C; overall yield 29%, 15:1 dr; ^1H NMR (CD_3OD , 400 MHz) δ : 2.52-2.58 (m, 2H), 2.77-2.83 (m, 2H), 3.77 (d, $J = 12.4$ Hz, 2H), 4.25-4.30 (m, 2H), 4.50-4.53 (m, 2H), 4.66 (s, 2H), 6.76 (s, 2H), 7.18-7.21 (m, 2H), 7.27-7.31 (m, 5H), 7.41 (d, $J = 7.6$ Hz, 4H), 7.49-7.50 (m, 1H), 7.63-7.67 (m, 2H); ^{13}C NMR (CD_3OD , 100 MHz) δ : 35.1, 69.9, 75.8, 76.3, 88.3, 122.9, 123.7, 126.6, 128.6, 128.9, 129.8, 131.9, 135.3, 167.2; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_4\text{NaO}_6$ $[\text{M}+\text{Na}]^+$: 565.2058; Found: 565.2049.

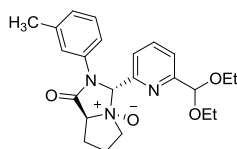


L4g (Prepared according to general procedure A): White solid, m.p. 268.2-269.0 °C; overall yield 34%, 17:1 dr; ^1H NMR (CD_3OD , 400 MHz) δ : 2.56-2.63 (m, 2H), 2.88-2.94 (m, 2H), 4.22 (d, $J = 11.6$ Hz, 2H), 4.34-4.38 (m, 2H), 4.58 (d, $J = 8.4$ Hz, 2H), 4.65 (s, 2H), 7.16-7.19 (m, 2H), 7.30-7.34 (m, 4H), 7.48-7.52 (m, 2H), 7.57-7.59 (m, 2H), 7.75 (d, $J = 8.0$ Hz, 4H), 8.07 (s, 2H); ^{13}C NMR (CD_3OD , 100 MHz) δ : 35.2, 70.2, 74.5, 76.6, 85.3, 122.1, 126.1, 127.9, 128.6, 130.6, 133.4, 135.6, 167.3; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_4\text{NaO}_6$ $[\text{M}+\text{Na}]^+$: 565.2058; Found: 565.2054.



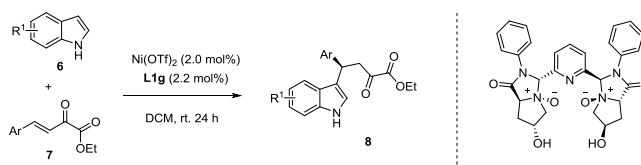
4: Light yellow oil; yield 70%, 15:1 dr; ^1H NMR (CDCl_3 , 400 MHz) δ : 1.11-1.15 (m, 6H), 1.79-1.84 (m, 2H), 2.11-2.21 (m, 5H), 2.86-2.93 (m, 1H), 3.35-3.40 (m, 1H), 3.45-3.61 (m, 4H),

4.11-4.14 (m, 1H), 5.35 (s, 1H), 5.70 (s, 1H), 6.81 (d, $J = 7.6$ Hz, 1H), 7.02-7.14 (m, 3H), 7.27 (s, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.59-7.63 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 15.2, 15.3, 21.5, 24.8, 27.9, 56.4, 61.9, 62.5, 64.9, 84.8, 102.5, 118.6, 120.0, 120.7, 122.2, 126.1, 128.7, 137.2, 137.9, 138.8, 157.5, 158.6, 175.0; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$: 418.2101; Found: 418.2091.



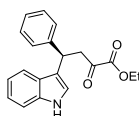
5 (Prepared according to general procedure A): White solid, m.p. 253.3-254.5 °C; yield 71%, >20:1 dr; ^1H NMR (CD_3OD , 400 MHz) δ : 1.11-1.15 (m, 3H), 1.22-1.25 (m, 3H), 2.21-2.25 (m, 4H), 2.41-2.59 (m, 3H), 3.53-3.58 (m, 2H), 3.62-3.66 (m, 1H), 3.74-3.81 (m, 1H), 3.88-3.92 (m, 1H), 4.11-4.16 (m, 1H), 4.70-4.73 (m, 1H), 5.45 (s, 1H), 6.69 (s, 1H), 7.01-7.03 (m, 1H), 7.15-7.20 (m, 2H), 7.29 (s, 1H), 7.56-7.63 (m, 2H), 7.84-7.87 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ : 14.2, 14.3, 20.0, 22.3, 24.2, 61.9, 62.6, 70.8, 76.7, 87.9, 102.4, 120.3, 122.0, 123.8, 126.7, 127.5, 128.7, 135.3, 137.3, 139.1, 149.6, 158.7, 169.1; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 434.2050; Found: 434.2057.

4. Catalytic asymmetric synthesis of compounds **8**

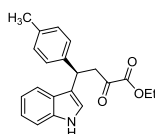


In a sealed tube equipped with a magnetic stirring bar, to the mixture of $\text{Ni}(\text{OTf})_2$ (2.0 mol %), **L1a** (2.2 mol %) in 2.0 mL of CH_2Cl_2 was added **6** (0.30 mmol), and **7** (0.20 mmol). The reaction mixture was stirred at room temperature for 24 h and was directly loaded onto a silica gel and purified by flash chromatography to give the desired product **8**, using hexane/EtOAc (10/1, v/v) as the eluent.

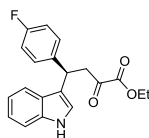
5. Characterization data of compounds **8**



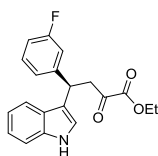
8a: Product in accordance with literature characterization data^{1a}. 91%, 98% ee, $[\alpha]_D^{20} = -25.1$ (c 0.720, CHCl₃); The ee was determined by HPLC analysis using a Chiralpak IA column (95/5 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 38.22$ min; $\tau_{minor} = 49.46$ min); ¹H NMR (CDCl₃, 400 MHz) δ : 1.18-1.21 (m, 3H), 3.49-3.64 (m, 2H), 4.11-4.16 (m, 2H), 4.82-4.86 (m, 2H), 6.93-6.97 (m, 2H), 7.05-7.12 (m, 2H), 7.17-7.21 (m, 2H), 7.23-7.26 (m, 3H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.96 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 13.9, 37.8, 45.6, 62.5, 111.2, 119.4, 119.5, 122.3, 126.6, 127.8, 128.6, 136.6, 143.3, 161.0, 193.1.



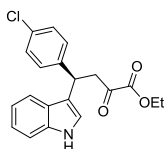
8b: Product in accordance with literature characterization data^{1b}. 90%, 98% ee, $[\alpha]_D^{20} = -74.5$ (c 0.6, CHCl₃); The ee was determined by HPLC analysis using a Chiralpak IA column (90/10 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 15.96$ min; $\tau_{minor} = 21.32$ min); ¹H NMR (CDCl₃, 400 MHz) δ : 1.15-1.19 (m, 3H), 2.19 (s, 3H), 3.45-3.60 (m, 2H), 4.09-4.14 (m, 2H), 4.77-4.81 (m, 1H), 6.89-6.99 (m, 4H), 7.03-7.07 (m, 1H), 7.12 (d, $J = 7.6$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.95 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 13.9, 21.0, 37.5, 45.8, 62.5, 111.2, 119.4, 119.5, 122.2, 127.7, 129.3, 136.1, 136.6, 140.3, 161.1, 193.3.



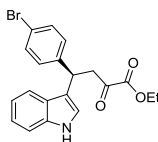
8c: 92%, 91% ee; The ee was determined by HPLC analysis using a Chiralpak IA column (90/10 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 16.91$ min; $\tau_{minor} = 24.98$ min); ¹H NMR (CDCl₃, 400 MHz) δ : 1.18-1.22 (m, 3H), 3.46-3.61 (m, 2H), 4.12-4.17 (m, 2H), 4.80-4.84 (m, 1H), 6.83-6.89 (m, 2H), 6.94-6.96 (m, 2H), 7.06-7.10 (m, 1H), 7.17-7.25 (m, 3H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.99 (br s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 12.9, 36.0, 44.6, 61.5, 110.2, 114.3 (d, $J_{CF} = 21.3$ Hz), 117.1, 118.4 (d, $J_{CF} = 29.0$ Hz), 120.4, 121.3, 125.2, 128.2 (d, $J_{CF} = 8.3$ Hz), 135.6, 137.9, 138.0, 159.9, 160.5 (d, $J_{CF} = 244.2$ Hz), 191.9; HRMS (ESI-TOF) m/z : Calcd. for C₂₀H₁₈FNNaO₃ [M+Na]⁺: 362.1163; Found: 362.1168.



8d: Product in accordance with literature characterization data^{1b}. 89%, 90% ee, $[\alpha]_D^{20} = -64.4$ (c 0.45, CHCl_3); The ee was determined by HPLC analysis using a Chiralpak ID column (95/5 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{\text{major}} = 17.04$ min; $\tau_{\text{minor}} = 20.74$ min); ^1H NMR ($\text{DMSO-}d_6$, 400 MHz) δ : 1.21-1.24 (m, 3H), 3.59-3.65 (m, 1H), 3.72-3.79 (m, 1H), 4.16-4.22 (m, 2H), 4.74-4.78 (m, 1H), 6.90-6.98 (m, 2H), 7.03-7.06 (m, 1H), 7.18-7.34 (m, 5H), 7.43 (d, $J = 8.0$ Hz, 1H), 10.95 (br s, 1H); ^{13}C NMR ($\text{DMSO-}d_6$, 100 MHz) δ : 14.2, 37.1, 45.2, 62.3, 111.9, 113.3 (d, $J_{\text{CF}} = 21.2$ Hz), 114.8 (d, $J_{\text{CF}} = 21.3$ Hz), 117.1, 118.9, 119.0, 119.1, 121.7, 122.7, 124.3, 124.4, 126.5, 130.5 (d, $J_{\text{CF}} = 9.1$ Hz), 136.8, 148.0, 161.0, 162.6 (d, $J_{\text{CF}} = 241.5$ Hz), 193.0.

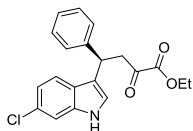


8e: Product in accordance with literature characterization data^{1b}. 90%, 92% ee, $[\alpha]_D^{20} = -43.1$ (c 0.55, CHCl_3); The ee was determined by HPLC analysis using a Chiralpak IC column (95/5 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{\text{major}} = 26.09$ min; $\tau_{\text{minor}} = 20.87$ min); ^1H NMR (CDCl_3 , 400 MHz) δ : 1.18-1.22 (m, 3H), 3.45-3.61 (m, 2H), 4.12-4.18 (m, 2H), 4.79-4.83 (m, 1H), 6.93-6.97 (m, 2H), 7.06-7.10 (m, 1H), 7.13-7.19 (m, 4H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.99 (br s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 13.9, 37.2, 45.4, 62.6, 111.3, 117.9, 119.3, 119.7, 121.6, 122.5, 126.2, 128.7, 129.2, 132.3, 136.6, 141.9, 160.9, 192.9.

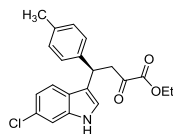


8f: Product in accordance with literature characterization data^{1b}. 93%, 92% ee, $[\alpha]_D^{20} = -27.1$ (c 0.55, CHCl_3); The ee was determined by HPLC analysis using a Chiralpak IA column (90/10 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{\text{major}} = 18.75$ min; $\tau_{\text{minor}} = 30.34$ min); ^1H NMR (CDCl_3 , 400 MHz) δ : 1.18-1.21 (m, 3H), 3.45-3.60 (m, 2H), 4.11-4.17 (m, 2H), 4.77-4.80

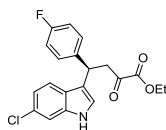
(m, 1H), 6.91-6.96 (m, 2H), 7.05-7.12 (m, 3H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 8.8$ Hz, 3H), 8.00 (br s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 14.0, 37.2, 45.4, 62.7, 111.4, 117.7, 119.3, 119.7, 120.4, 121.6, 122.5, 126.2, 129.7, 131.7, 136.6, 142.4, 160.9, 192.9.



8g: Product in accordance with literature characterization data^{1b}. 85%, 91% ee, $[\alpha]_{\text{D}}^{20} = -58.7$ (c 0.89, CHCl_3); The ee was determined by HPLC analysis using a Chiralpak ID column (95/5 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{\text{major}} = 16.53$ min; $\tau_{\text{minor}} = 18.29$ min); ^1H NMR (CDCl_3 , 400 MHz) δ : 1.18-1.22 (m, 3H), 3.46-3.61 (m, 2H), 4.12-4.17 (m, 2H), 4.77-4.81 (m, 1H), 6.88-6.93 (m, 2H), 7.09-7.12 (m, 1H), 7.16-7.22 (m, 6H), 8.03 (br s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 12.7, 36.4, 44.3, 61.4, 109.9, 119.1, 121.0, 123.8, 125.6, 126.5, 127.4, 135.7, 141.8, 159.7, 191.8.

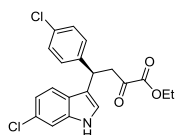


8h: 85%, 92% ee; The ee was determined by HPLC analysis using a Chiralpak IC column (93/7 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{\text{major}} = 19.72$ min; $\tau_{\text{minor}} = 18.35$ min); ^1H NMR ($\text{DMSO-}d_6$, 400 MHz) δ : 1.20-1.24 (m, 3H), 2.21 (s, 3H), 3.50-3.56 (m, 1H), 3.66-3.72 (m, 1H), 4.16-4.21 (m, 2H), 4.64-4.68 (m, 1H), 6.90-6.92 (m, 1H), 7.04 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.32-7.37 (m, 3H), 11.04 (br s, 1H); ^{13}C NMR ($\text{DMSO-}d_6$, 100 MHz) δ : 14.2, 21.0, 36.9, 45.4, 62.3, 111.5, 118.1, 119.1, 120.5, 123.6, 125.5, 126.3, 127.9, 129.3, 135.6, 137.2, 141.6, 161.0, 193.2; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{21}\text{H}_{20}\text{ClNNaO}_3$ $[\text{M}+\text{Na}]^+$: 392.1024; Found: 392.1024.

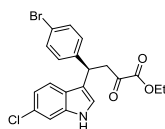


8i: Product in accordance with literature characterization data^{1d}. 87%, 90% ee; The ee was determined by HPLC analysis using a Chiralpak IE column (95/5 hexane/*i*-PrOH; flow rate: 1.0

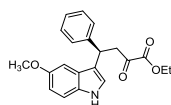
mL/min; $\lambda = 254$ nm; $\tau_{major} = 16.25$ min; $\tau_{minor} = 18.56$ min); ^1H NMR (DMSO- d_6 , 400 MHz) δ : 1.21-1.25 (m, 3H), 3.54-3.60 (m, 1H), 3.70-3.76 (m, 1H), 4.17-4.22 (m, 2H), 4.71-4.75 (m, 1H), 6.92-6.95 (m, 1H), 7.04-7.09 (m, 2H), 7.36-7.40 (m, 5H), 11.09 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 14.2, 36.5, 45.4, 62.3, 111.5, 115.4 (d, $J_{CF} = 21.0$ Hz), 117.9, 119.2, 120.4, 123.7, 125.4, 126.5, 129.9 (d, $J_{CF} = 3.0$ Hz), 137.2, 140.8, 160.8 (d, $J_{CF} = 240.3$ Hz), 161.0, 193.0.



8j: 88%, 94% ee; The ee was determined by HPLC analysis using a Chiralpak IE column (95/5 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 17.06$ min; $\tau_{minor} = 21.81$ min); ^1H NMR (DMSO- d_6 , 400 MHz) δ : 1.21-1.25 (m, 3H), 3.55-3.61 (m, 1H), 3.69-3.76 (m, 1H), 4.17-4.22 (m, 2H), 4.69-4.73 (m, 1H), 6.92-6.94 (m, 1H), 7.29-7.39 (m, 7H), 11.09 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 14.2, 36.6, 45.1, 62.3, 111.5, 117.6, 119.2, 120.4, 123.8, 125.3, 126.5, 128.6, 128.8, 130.0, 131.2, 137.2, 143.7, 160.9, 192.9; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{20}\text{H}_{17}\text{Cl}_2\text{NNaO}_3$ $[\text{M}+\text{Na}]^+$: 412.0478; Found: 412.0484.

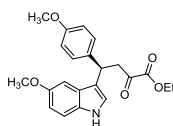


8k: 89%, 99% ee; The ee was determined by HPLC analysis using a Chiralpak IE column (95/5 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 20.82$ min; $\tau_{minor} = 26.38$ min); ^1H NMR (DMSO- d_6 , 400 MHz) δ : 1.21-1.25 (m, 3H), 3.55-3.61 (m, 1H), 3.69-3.75 (m, 1H), 4.17-4.22 (m, 2H), 4.67-4.71 (m, 1H), 6.92-6.94 (m, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.36-7.44 (m, 5H), 11.09 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 14.2, 36.6, 45.0, 62.3, 111.5, 117.5, 119.2, 119.6, 120.4, 123.8, 125.3, 126.5, 130.4, 130.5, 131.6, 131.7, 144.1, 160.9, 192.8; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{20}\text{H}_{17}\text{BrClNNaO}_3$ $[\text{M}+\text{Na}]^+$: 455.9973; Found: 455.9980.

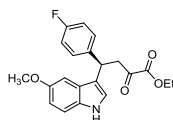


8l: Product in accordance with literature characterization data^{1b}. 92%, 96% ee, $[\alpha]_D^{20} = -51.0$ (c

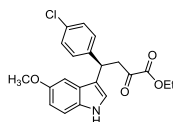
0.55, CHCl₃); The ee was determined by HPLC analysis using a Chiralpak IE column (95/5 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 34.27$ min; $\tau_{minor} = 41.07$ min); ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 1.20-1.23 (m, 3H), 3.53-3.59 (m, 1H), 3.67-3.75 (m, 4H), 4.15-4.21 (m, 2H), 4.66-4.70 (m, 1H), 6.68-6.71 (m, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 7.11-7.15 (m, 1H), 7.20-7.27 (m, 4H), 7.36 (d, $J = 7.2$ Hz, 2H), 10.74 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ : 14.2, 37.5, 45.4, 55.8, 62.3, 101.2, 111.4, 112.5, 117.4, 123.2, 126.5, 127.0, 128.1, 128.7, 132.0, 144.8, 153.4, 161.1, 193.3.



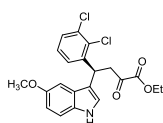
8m: 90%, 97% ee; The ee was determined by HPLC analysis using a Chiralpak IB column (90/10 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 31.68$ min; $\tau_{minor} = 27.02$ min); ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 1.20-1.23 (m, 3H), 3.48-3.54 (m, 1H), 3.64-3.70 (m, 7H), 4.15-4.21 (m, 2H), 4.62-4.65 (m, 1H), 6.68-6.71 (m, 1H), 6.80-6.84 (m, 3H), 7.19-7.27 (m, 4H), 10.71 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ : 14.2, 36.8, 45.8, 55.4, 55.8, 62.3, 101.3, 111.3, 112.5, 114.0, 117.7, 123.1, 127.0, 129.1, 132.1, 136.7, 153.3, 158.0, 161.1, 193.5; HRMS (ESI-TOF) *m/z*: Calcd. for C₂₂H₂₃NNaO₅ [M+Na]⁺: 404.1468; Found: 404.1471.



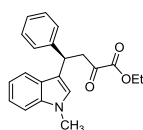
8n: 92%, 94% ee; The ee was determined by HPLC analysis using a Chiralpak IC column (90/10 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 41.90$ min; $\tau_{minor} = 35.41$ min); ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 1.21-1.24 (m, 3H), 3.53-3.59 (m, 1H), 3.66-3.75 (m, 4H), 4.16-4.22 (m, 2H), 4.68-4.72 (m, 1H), 6.69-6.72 (m, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 7.05-7.09 (m, 2H), 7.21-7.23 (m, 2H), 7.38-7.42 (m, 2H), 10.76 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ : 14.2, 36.7, 45.4, 55.8, 62.3, 101.2, 111.5, 112.5, 115.3 (d, $J_{CF} = 21.1$ Hz), 117.3, 123.2, 126.9, 129.9 (d, $J_{CF} = 3.2$ Hz), 141.0, 153.4, 161.0, 161.5 (d, $J_{CF} = 240.4$ Hz), 193.2; HRMS (ESI-TOF) *m/z*: Calcd. for C₂₁H₂₀FNNaO₄ [M+Na]⁺: 392.1269; Found: 392.1275.



8o: 93%, 90% ee; The ee was determined by HPLC analysis using a Chiralpak ID column (90/10 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 15.06$ min; $\tau_{minor} = 22.54$ min); ^1H NMR (DMSO- d_6 , 400 MHz) δ : 1.21-1.24 (m, 3H), 3.55-3.61 (m, 1H), 3.66-3.76 (m, 4H), 4.17-4.22 (m, 2H), 4.68-4.72 (m, 1H), 6.70-6.73 (m, 1H), 6.87 (d, $J = 2.4$ Hz, 1H), 7.22 (d, $J = 8.8$ Hz, 2H), 7.28-7.31 (m, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 10.78 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 14.2, 36.8, 45.2, 55.8, 62.3, 101.2, 111.5, 112.6, 117.0, 123.3, 126.9, 128.6, 128.8, 130.0, 131.1, 132.0, 143.9, 153.4, 161.0, 193.1; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{21}\text{H}_{20}\text{ClNNaO}_4$ $[\text{M}+\text{Na}]^+$: 408.0973; Found: 408.0974.



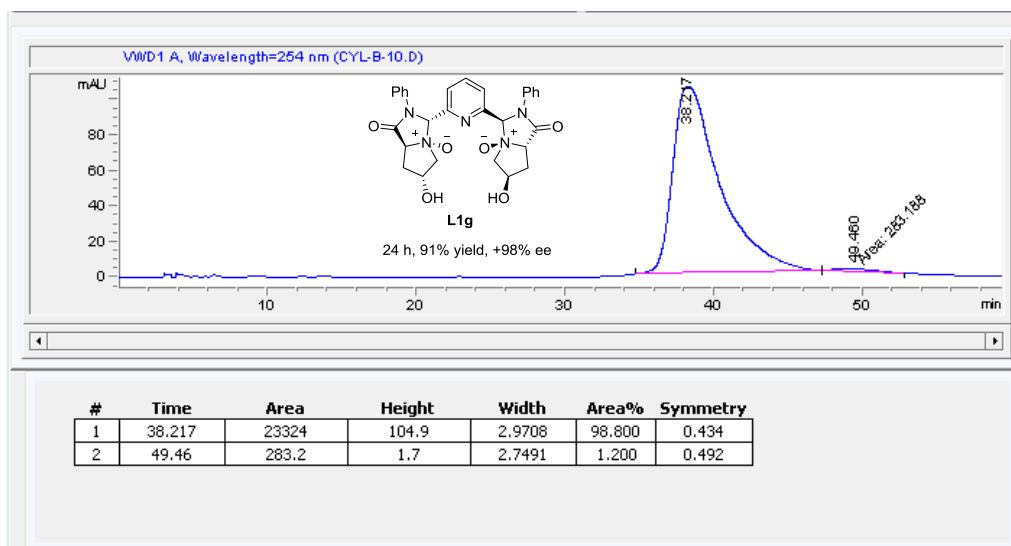
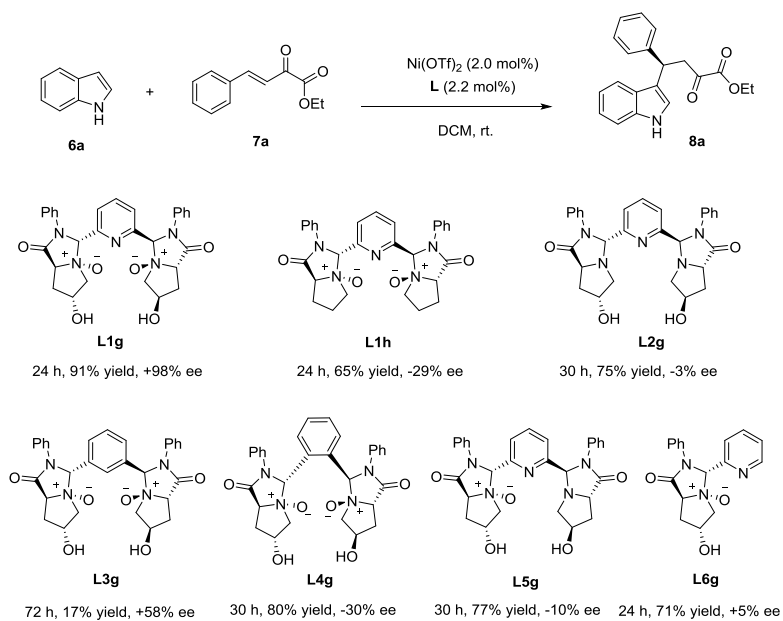
8p: 93%, 91% ee; The ee was determined by HPLC analysis using a Chiralpak IA column (85/15 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 10.68$ min; $\tau_{minor} = 17.62$ min); ^1H NMR (DMSO- d_6 , 400 MHz) δ : 1.22-1.26 (m, 3H), 3.54-3.61 (m, 1H), 3.69 (s, 3H), 3.76-3.82 (m, 1H), 4.18-4.23 (m, 2H), 5.17-5.20 (m, 1H), 6.71-6.74 (m, 1H), 6.87 (d, $J = 2.4$ Hz, 1H), 7.18 (d, $J = 2.4$ Hz, 1H), 7.23-7.28 (m, 2H), 7.39-7.47 (m, 2H), 10.84 (br s, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 14.2, 34.7, 44.6, 55.7, 62.3, 100.8, 111.6, 112.7, 115.8, 124.0, 128.2, 128.5, 128.8, 131.9, 132.2, 144.5, 153.5, 160.7, 192.6; HRMS (ESI-TOF) m/z : Calcd. for $\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$: 442.0583; Found: 442.0577.

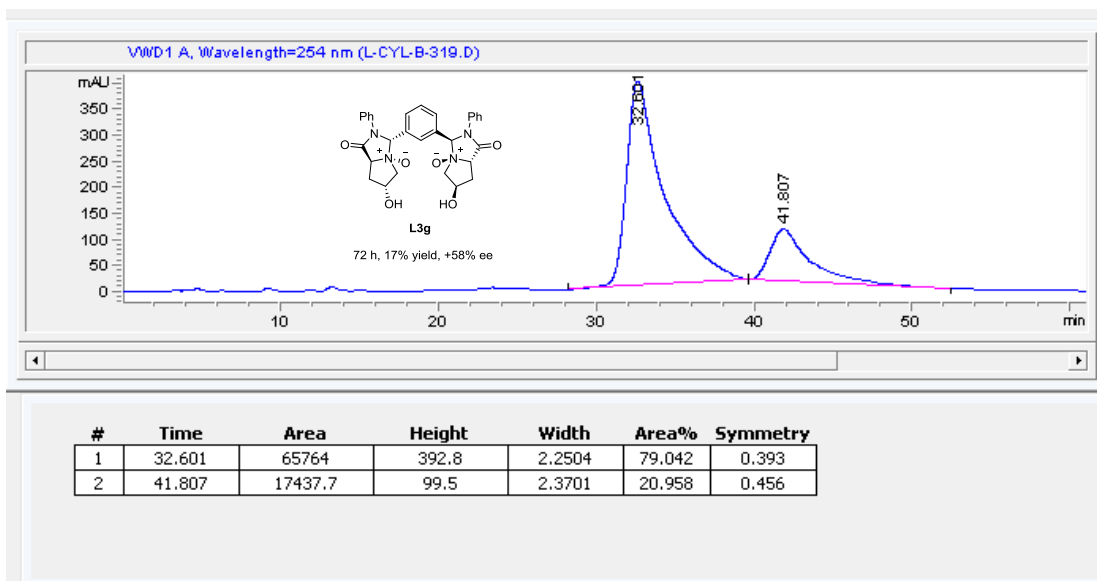
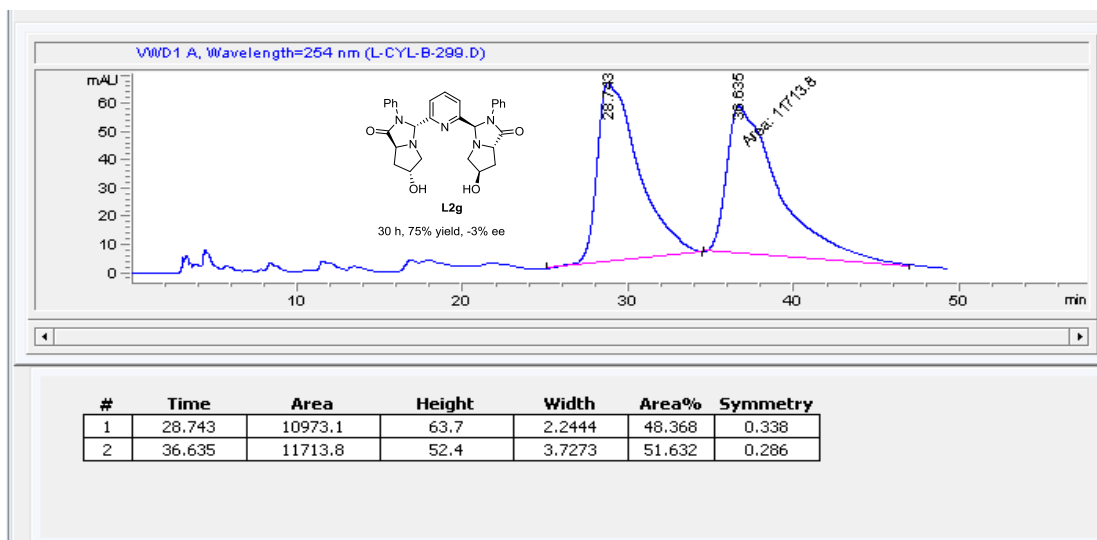
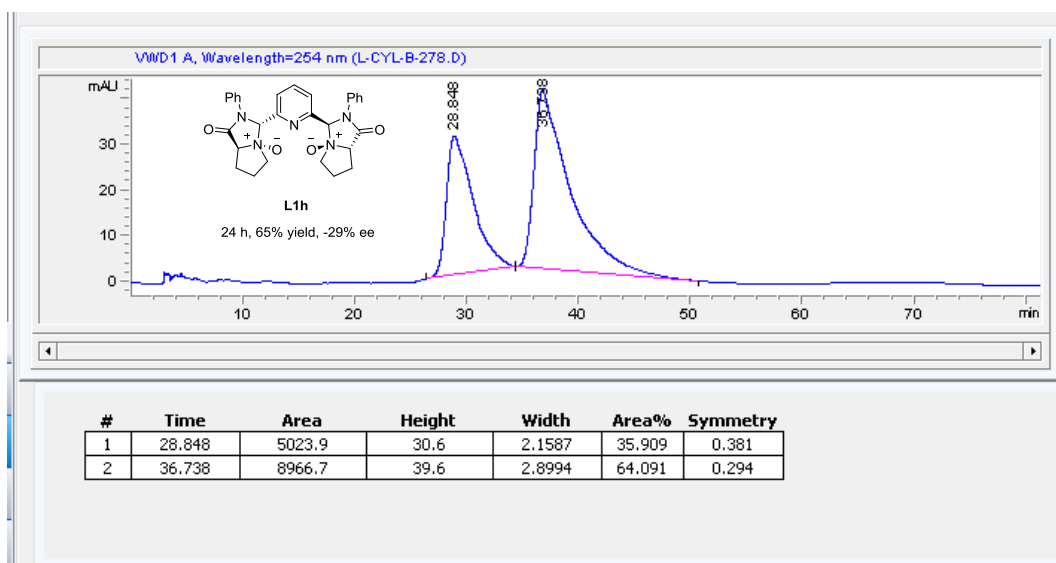


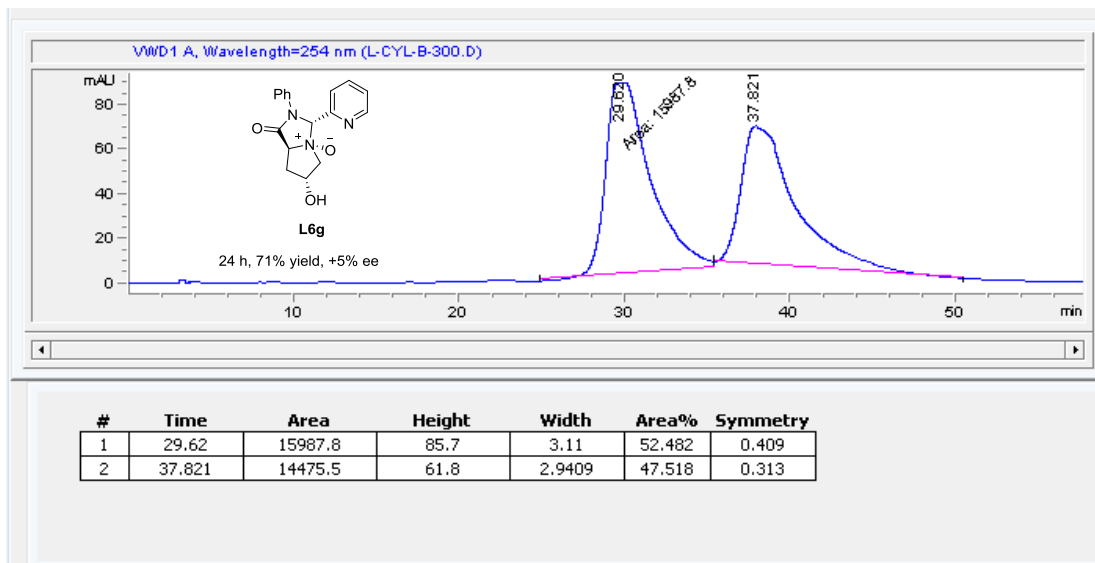
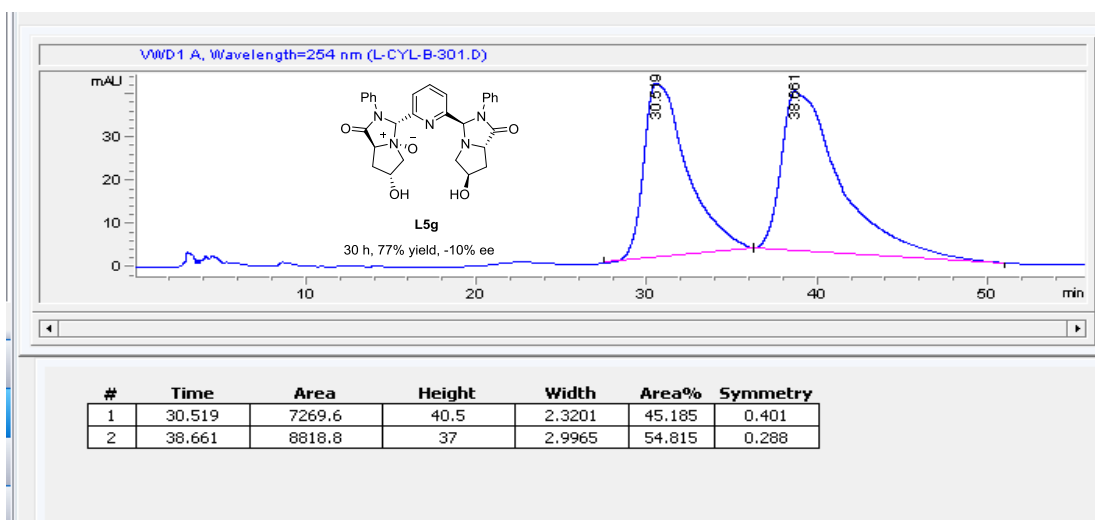
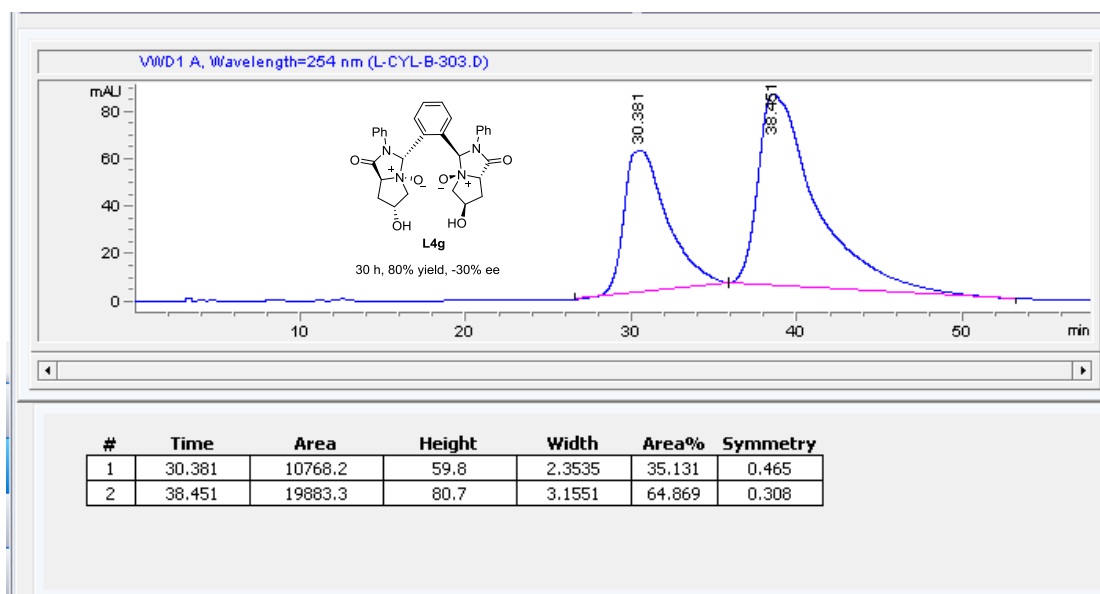
8q: Product in accordance with literature characterization data^{1b}. 70% yield, 55% ee, $[\alpha]_{\text{D}}^{20} = -16.7$ (c 4.2, CHCl_3); The ee was determined by HPLC analysis using a Chiralpak IA column (85/15 hexane/*i*-PrOH; flow rate: 1.0 mL/min; $\lambda = 254$ nm; $\tau_{major} = 15.54$ min; $\tau_{minor} = 14.59$ min); ^1H NMR (DMSO- d_6 , 400 MHz) δ : 1.20-1.24 (m, 3H), 3.55-3.61 (m, 1H), 3.67-3.74 (m, 4H), 4.16-4.21 (m, 2H), 4.70-4.73 (m, 1H), 6.91-6.95 (m, 1H), 7.08-7.15 (m, 2H), 7.22-7.26 (m, 3H), 7.33-7.36 (m, 3H), 7.41 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ : 14.2, 32.8, 37.3, 45.4, 62.3, 110.1, 117.0, 118.9, 119.3, 121.7, 126.6, 126.9, 127.0, 128.1, 128.7, 137.2, 144.8, 160.9, 193.0.

6. Control experiments and HPLC spectra for compound **8a**

In a sealed tube equipped with a magnetic stirring bar, to the mixture of Ni(OTf)₂ (2.0 mol %), **L** (2.2 mol %) in 2.0 mL of CH₂Cl₂ was added **6a** (0.30 mmol), and **7a** (0.20 mmol). The reaction mixture was stirred at room temperature for 24 h and was directly loaded onto a silica gel and purified by flash chromatography to give the desired product **8a**, using hexane/EtOAc (10/1, v/v) as the eluent.







7. X-ray crystal data for compounds 3h, L1g, and 5

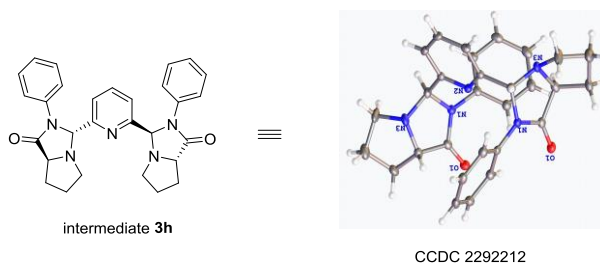


Table S1 Crystal data and structure refinement for 3h

Identification code	3h
Empirical formula	C ₂₉ H ₃₁ N ₅ O ₃
Formula weight	497.59
Temperature/K	162(18)
Crystal system	trigonal
Space group	P3 ₂ 21
a/Å, b/Å, c/Å	9.35380(10), 9.35380(10), 24.4673(3)
α/°, β/°, γ/°	90, 90, 120
Volume/Å ³	1853.93(5)
Z	3
ρ _{calc} /cm ³	1.337
μ/mm ⁻¹	0.713
F(000)	792.0
Radiation	Cu Kα (λ = 1.54184)
Crystal size/mm ³	0.15 × 0.12 × 0.1
2θ range for data collection/°	10.848 to 142.81
Index ranges	-11 ≤ h ≤ 7, -8 ≤ k ≤ 11, -29 ≤ l ≤ 29
Reflections collected	8924
Independent reflections	2390 [R _{int} = 0.0195, R _{sigma} = 0.0136]
Data/restraints/parameters	2390/0/172
Goodness-of-fit on F ²	1.085
Final R indexes [I ≥ 2σ(I)]	R ₁ = 0.0378, wR ₂ = 0.1036
Final R indexes [all data]	R ₁ = 0.0380, wR ₂ = 0.1037
Largest diff. peak/hole / e Å ⁻³	0.45/-0.34
Flack parameter	0.02(7)

Crystal Data for C₂₉H₃₁N₅O₃ (*M* = 497.59 g/mol): trigonal, space group P3₂21 (no. 154), *a* = 9.35380(10) Å, *c* = 24.4673(3) Å, *V* = 1853.93(5) Å³, *Z* = 3, *T* = 162(18) K, μ(Cu Kα) = 0.713 mm⁻¹, *D*_{calc} = 1.337 g/cm³, 8924 reflections measured (10.848° ≤ 2θ ≤ 142.81°), 2390 unique (*R*_{int} = 0.0195, *R*_{sigma} = 0.0136) which were used in all calculations. The final *R*₁ was 0.0378 (*I* > 2σ(*I*)) and *wR*₂ was 0.1037 (all data).

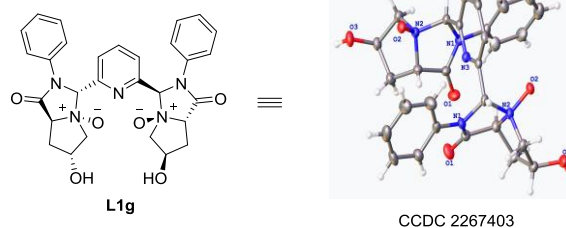
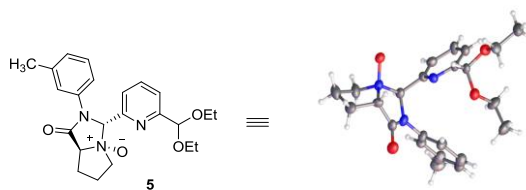


Table S2 Crystal data and structure refinement for L1g

Identification code	L1g
Empirical formula	$C_{29}H_{41}N_5O_{12}$
Formula weight	651.67
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	I2
$a/\text{\AA}$, $b/\text{\AA}$, $c/\text{\AA}$	10.5408(7), 8.9758(5), 16.0958(7)
$\alpha/^\circ$, $\beta/^\circ$, $\gamma/^\circ$,	90, 98.351(5), 90
Volume/ \AA^3	1506.70(14)
Z	2
$\rho_{\text{calc}}/\text{cm}^3$	1.436
μ/mm^{-1}	0.949
F(000)	692.0
Radiation	Cu K α ($\lambda = 1.54184$)
Crystal size/ mm^3	0.14 \times 0.13 \times 0.1
2 Θ range for data collection/ $^\circ$	9.438 to 149.61
Index ranges	-13 $\leq h \leq$ 12, -10 $\leq k \leq$ 10, -19 $\leq l \leq$ 19
Reflections collected	4899
Independent reflections	2755 [$R_{\text{int}} = 0.0253$, $R_{\text{sigma}} = 0.0306$]
Data/restraints/parameters	2755/1/224
Goodness-of-fit on F^2	1.050
Final R indexes [$I > 2\sigma(I)$]	$R_1 = 0.0647$, $wR_2 = 0.1763$
Final R indexes [all data]	$R_1 = 0.0710$, $wR_2 = 0.1830$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.44/-0.77
Flack parameter	-0.06(18)/-0.03(9)

Crystal Data for $C_{29}H_{41}N_5O_{12}$ ($M = 651.67$ g/mol): monoclinic, space group I2 (no. 5), $a = 10.5408(7)$ \AA , $b = 8.9758(5)$ \AA , $c = 16.0958(7)$ \AA , $\beta = 98.351(5)^\circ$, $V = 1506.70(14)$ \AA^3 , $Z = 2$, $T = 150.00(10)$ K, $\mu(\text{Cu K}\alpha) = 0.949$ mm^{-1} , $D_{\text{calc}} = 1.436$ g/cm^3 , 4899 reflections measured ($9.438^\circ \leq 2\Theta \leq 149.61^\circ$), 2755 unique ($R_{\text{int}} = 0.0253$, $R_{\text{sigma}} = 0.0306$) which were used in all calculations. The final R_1 was 0.0647 ($I > 2\sigma(I)$) and wR_2 was 0.1830 (all data).



CCDC 2285109

Table S3 Crystal data and structure refinement for 5

Identification code	5
Empirical formula	C ₂₃ H ₂₉ N ₃ O ₄
Formula weight	411.49
Temperature/K	170.00(10)
Crystal system	hexagonal
Space group	P6 ₁
a/Å, b/Å, c/Å	25.6308(19), 25.6308(19), 13.8132(12)
α/°, β/°, γ/°	90, 90, 120
Volume/Å ³	7858.7(14)
Z	12
ρ _{calc} /cm ³	1.043
μ/mm ⁻¹	0.584
F(000)	2640.0
Radiation	Cu Kα (λ = 1.54184)
Crystal size/mm ³	0.13 × 0.12 × 0.1
2θ range for data collection/°	6.898 to 150.376
Index ranges	-31 ≤ h ≤ 23, -21 ≤ k ≤ 31, -16 ≤ l ≤ 15
Reflections collected	56884
Independent reflections	9885 [R _{int} = 0.1950, R _{sigma} = 0.1617]
Data/restraints/parameters	9885/487/548
Goodness-of-fit on F ²	0.816
Final R indexes [I >= 2σ(I)]	R ₁ = 0.0868, wR ₂ = 0.2073
Final R indexes [all data]	R ₁ = 0.1523, wR ₂ = 0.2298
Largest diff. peak/hole / e Å ⁻³	0.81/-0.29
Flack parameter	0.8(4)

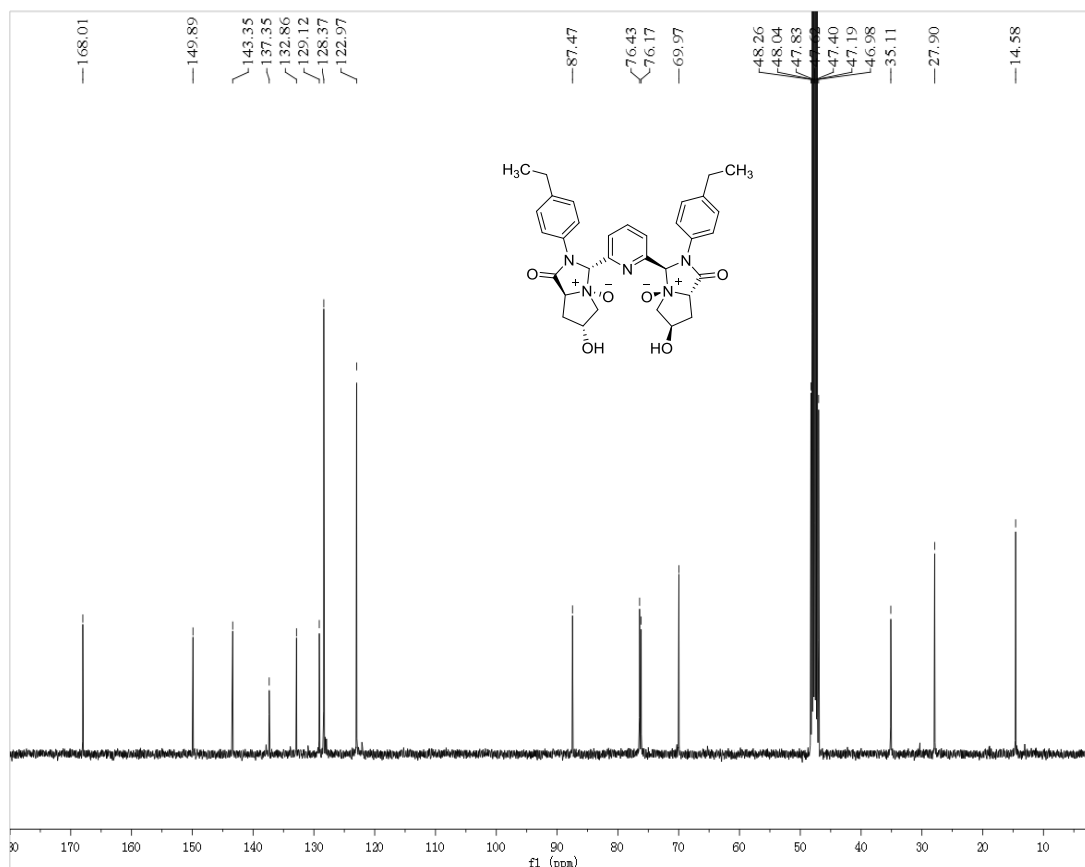
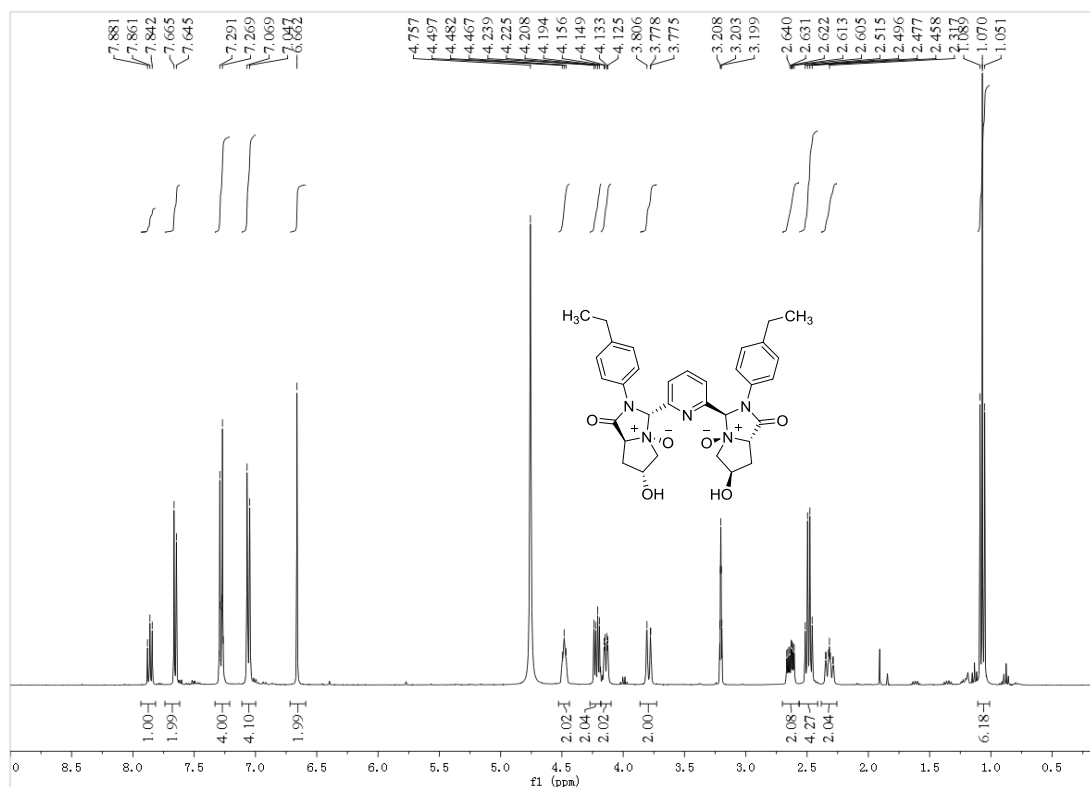
Crystal Data for C₂₃H₂₉N₃O₄ (*M* = 411.49 g/mol): hexagonal, space group P6₁ (no. 169), *a* = 25.6308(19) Å, *c* = 13.8132(12) Å, *V* = 7858.7(14) Å³, *Z* = 12, *T* = 170.00(10) K, μ(Cu Kα) = 0.584 mm⁻¹, *D*_{calc} = 1.043 g/cm³, 56884 reflections measured (6.898° ≤ 2θ ≤ 150.376°), 9885 unique (*R*_{int} = 0.1950, *R*_{sigma} = 0.1617) which were used in all calculations. The final *R*₁ was 0.0868 (*I* > 2σ(*I*)) and *wR*₂ was 0.2298 (all data).

8. References

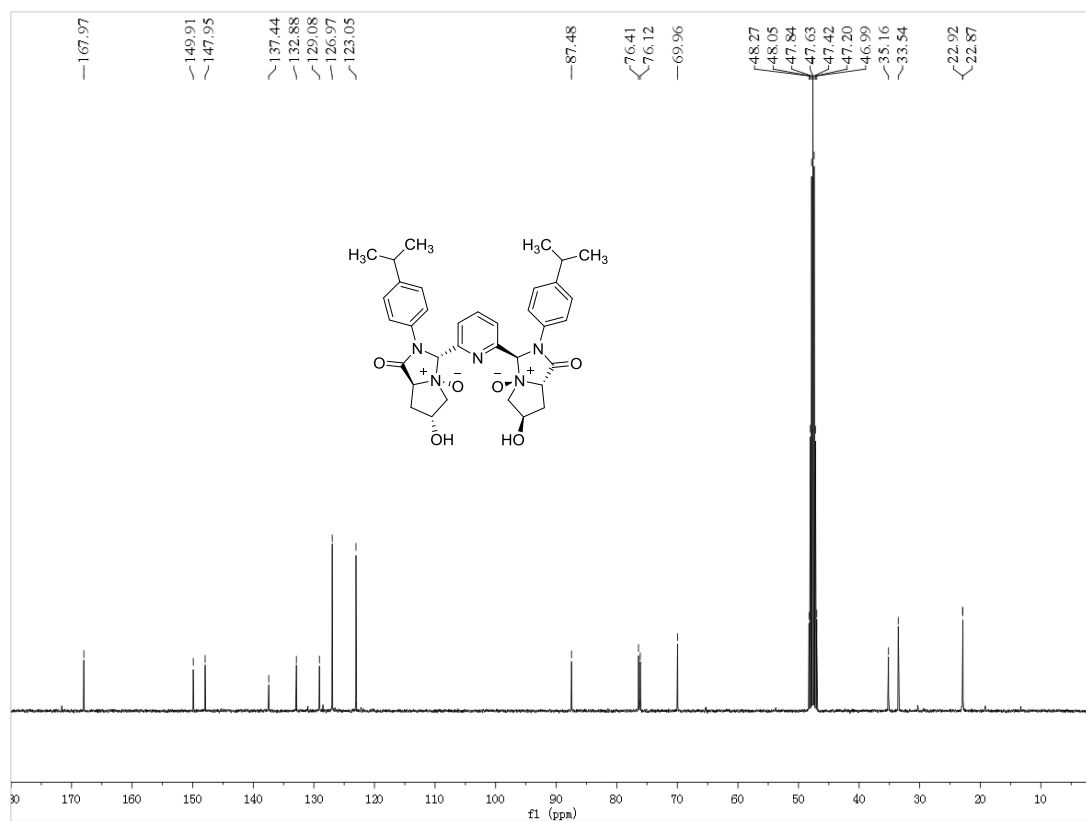
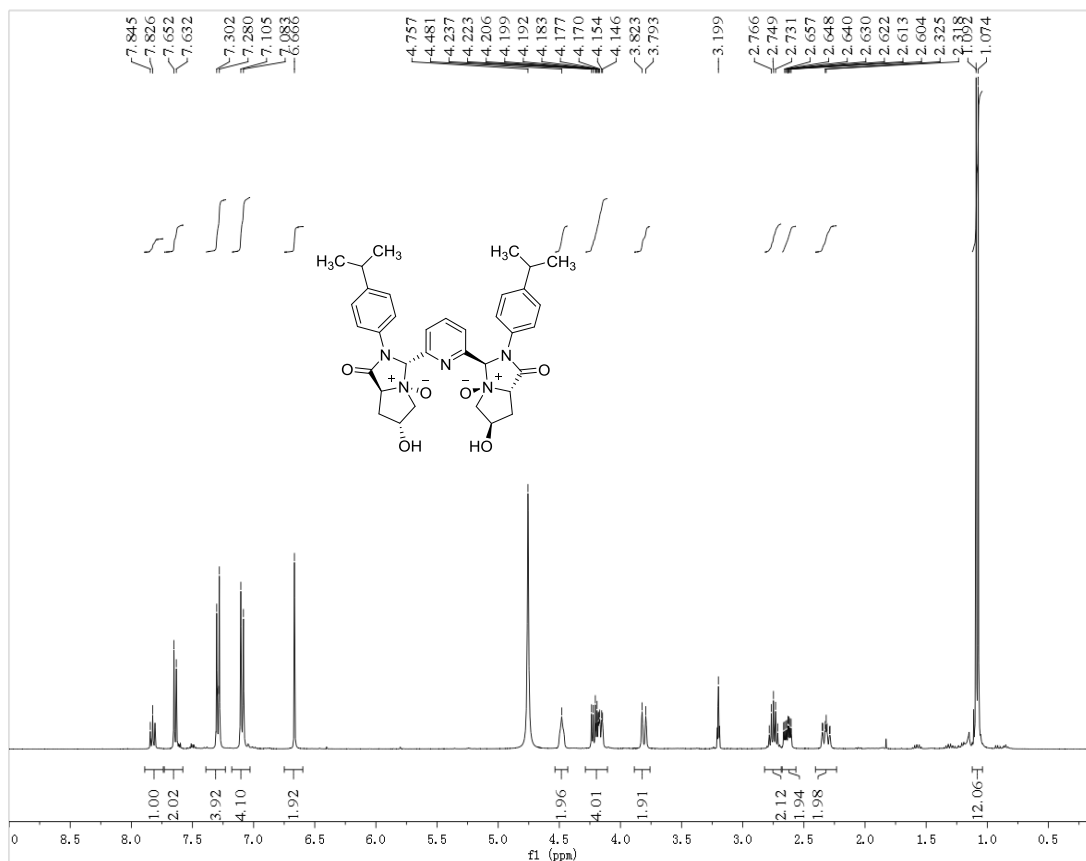
- (a) Y. Liu, D. Shang, X. Zhou, Y. Zhu, L. Lin, X. Liu and X. Feng, *Org. Lett.*, 2010, **12**, 180-183; (b) S. Yu, Q. Cai, C. Wang, J. Hou, J. Liang, Z. Jiao, C. Yao and Y. M. Li, *J. Org. Chem.*, 2023, **88**, 3046-3053; (c) V. Juste-Navarro, E. Marqués-López and R. P. Herrera, *Asian J. Org. Chem.*, 2015, **4**, 884-889; (d) M. Wang, M. Li, L. Zhang, R. Song, D. Yang and J. Lv, *Org. Chem. Front.*, 2022, **9**, 1875-1883.

9. The copies of ^1H NMR, ^{13}C NMR and HPLC spectra for compounds L, 4, 5 and 8

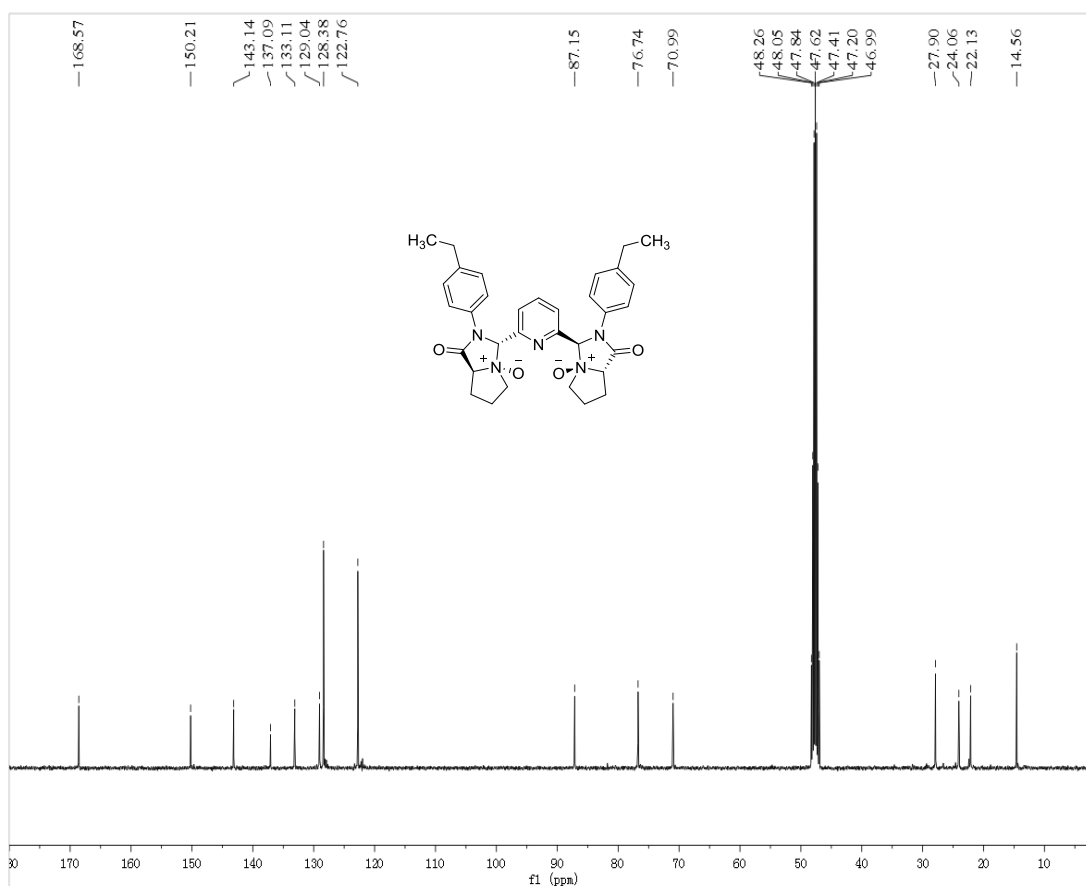
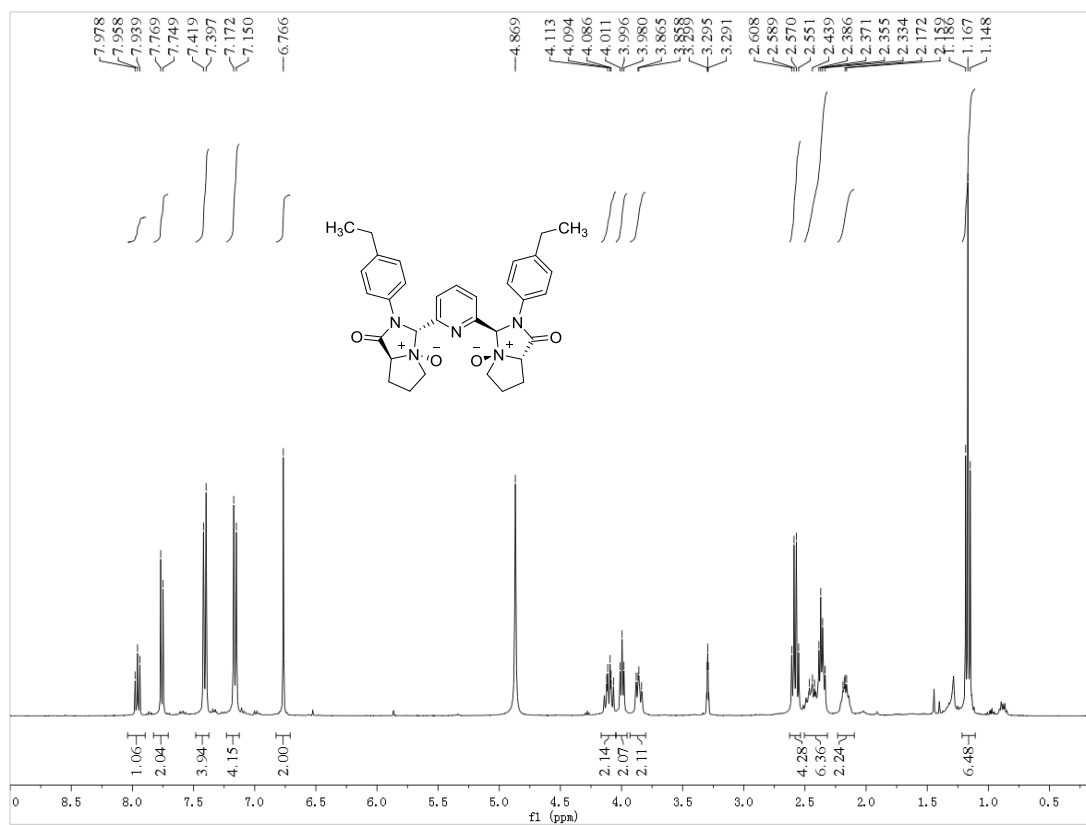
^1H and ^{13}C NMR of L1a



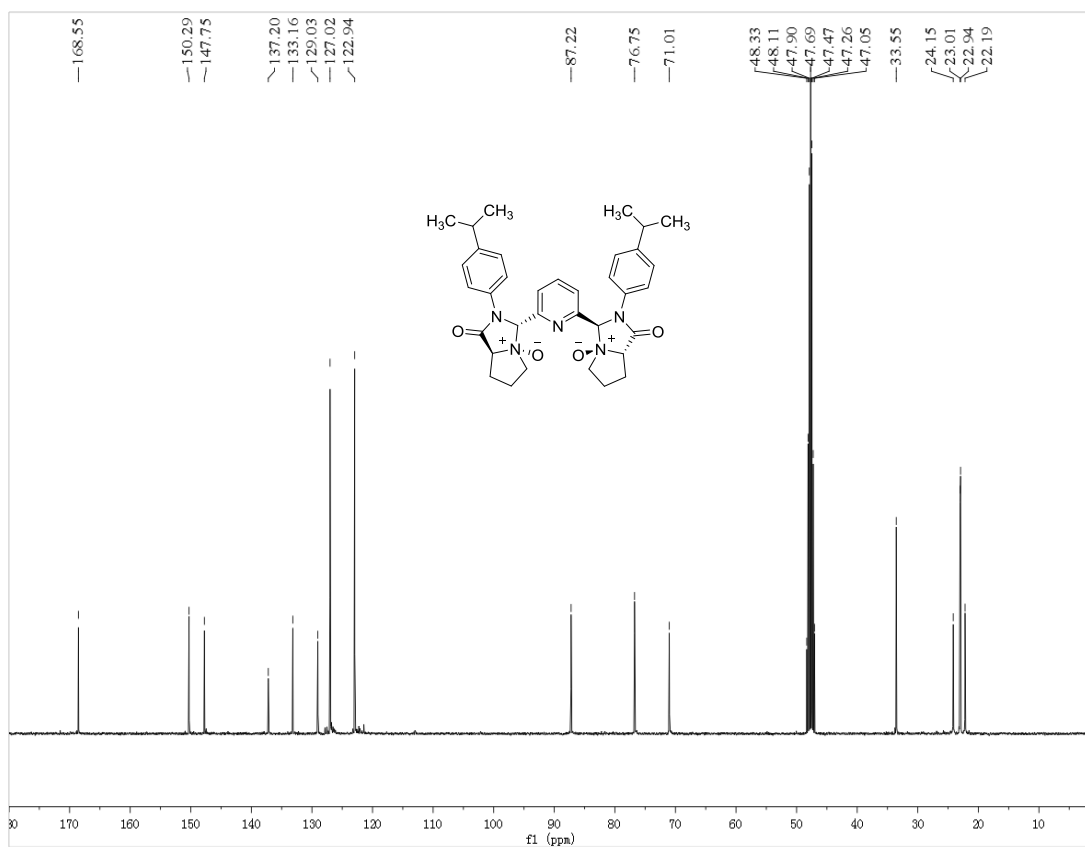
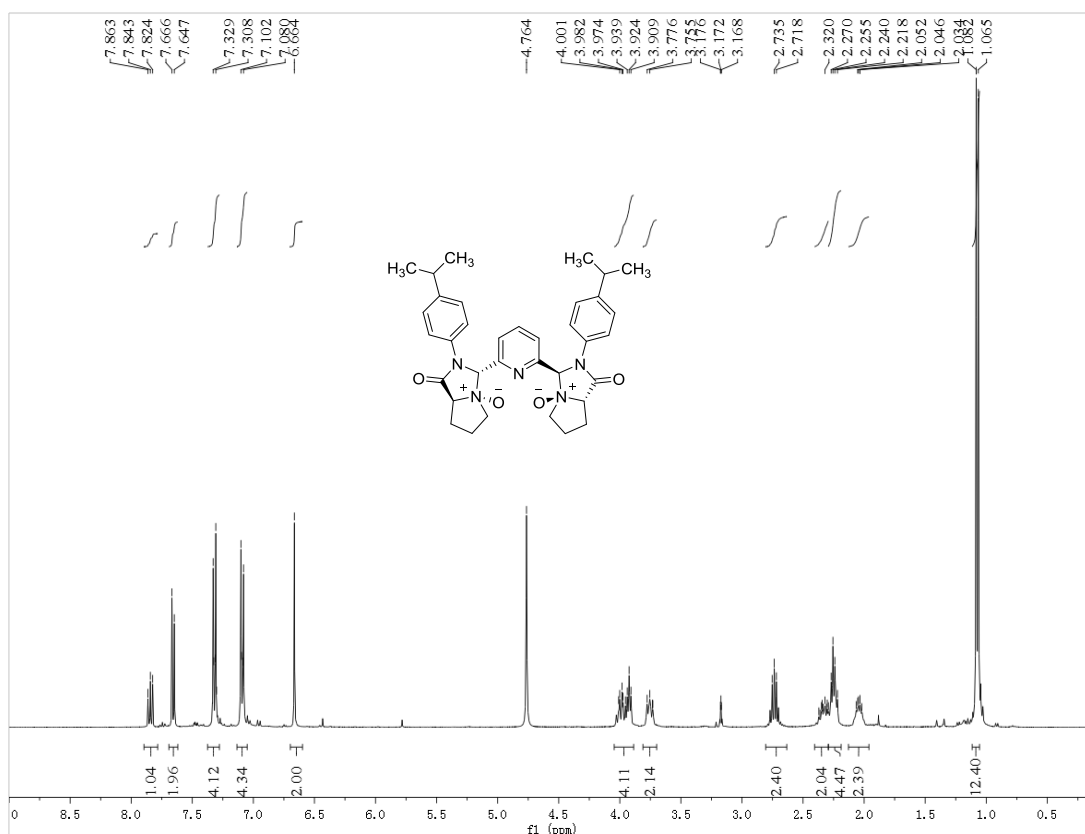
^1H and ^{13}C NMR of L1b



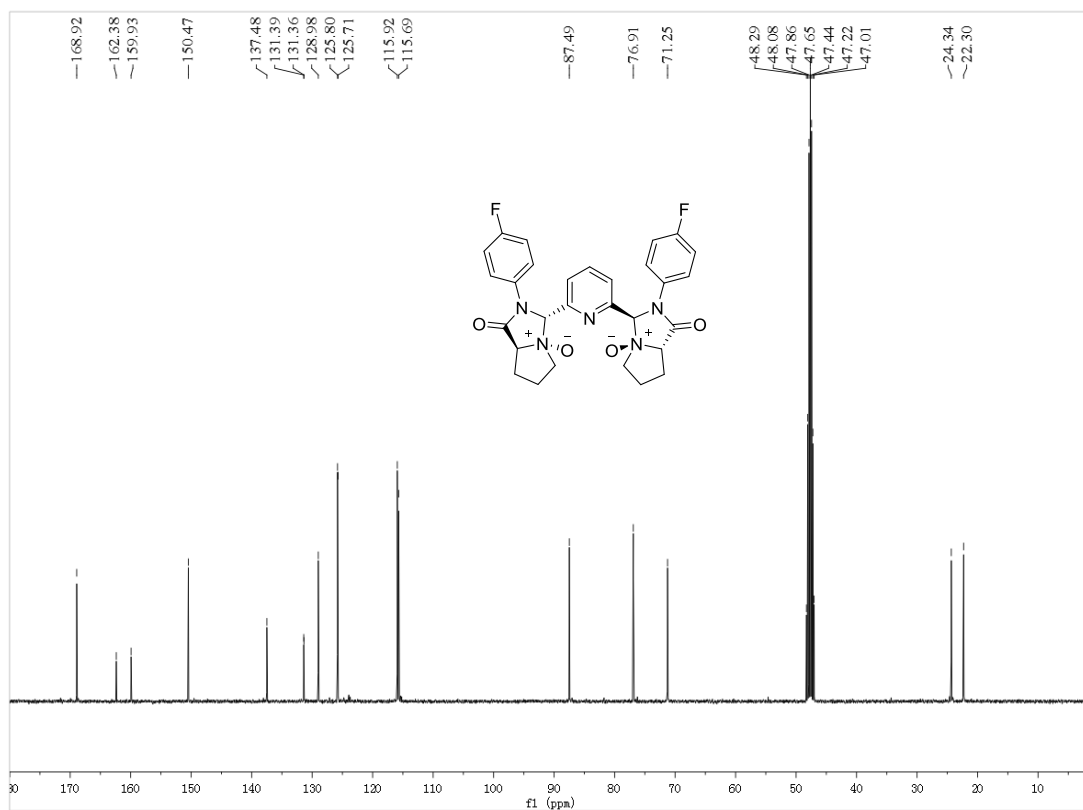
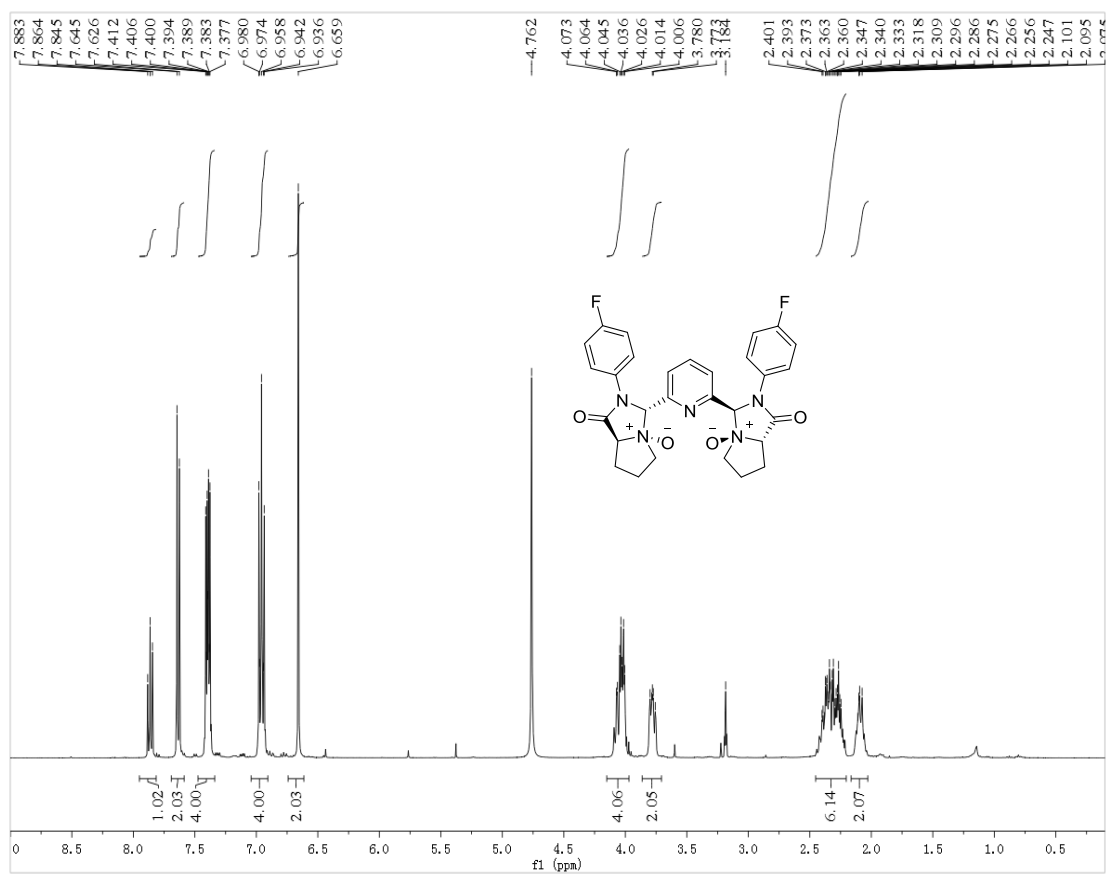
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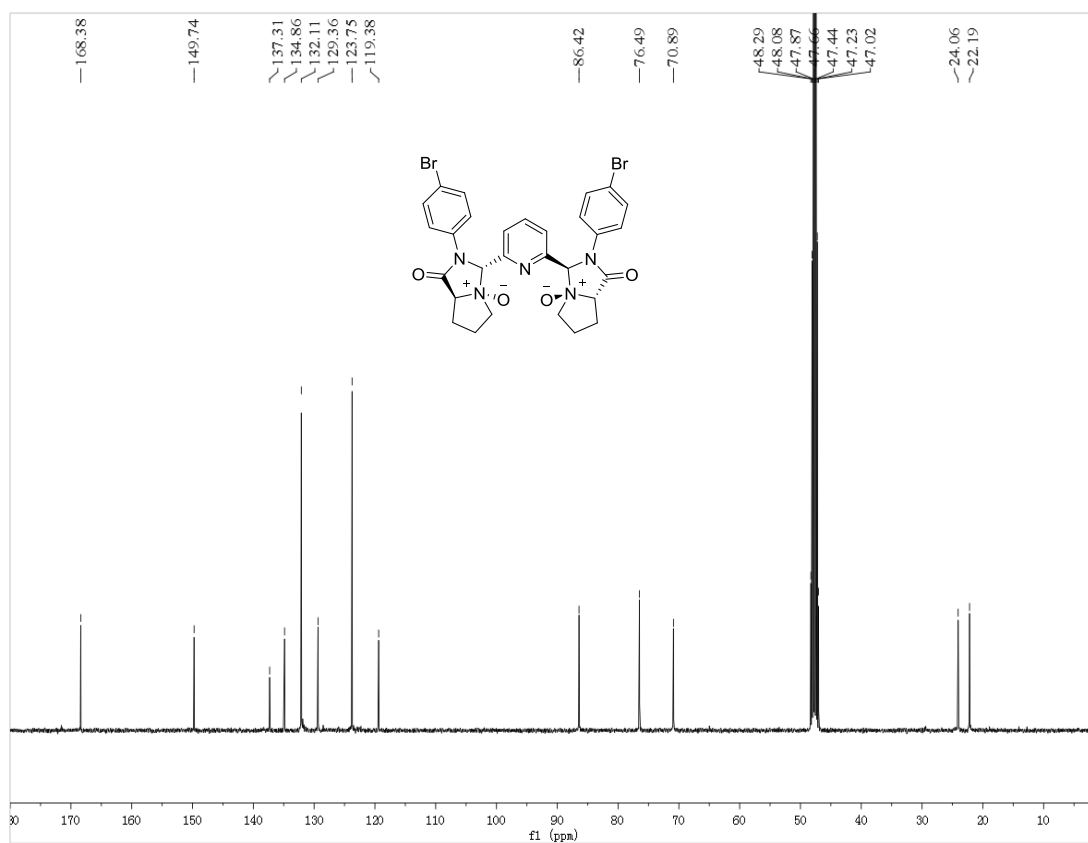
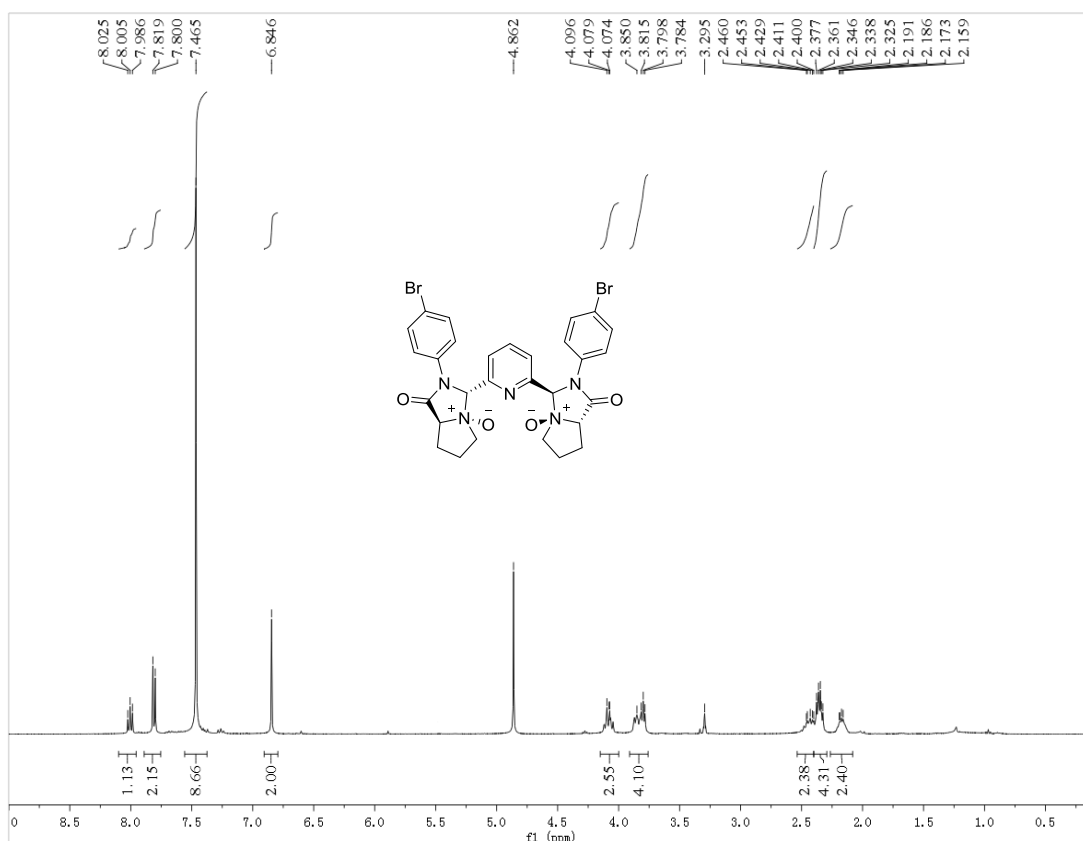
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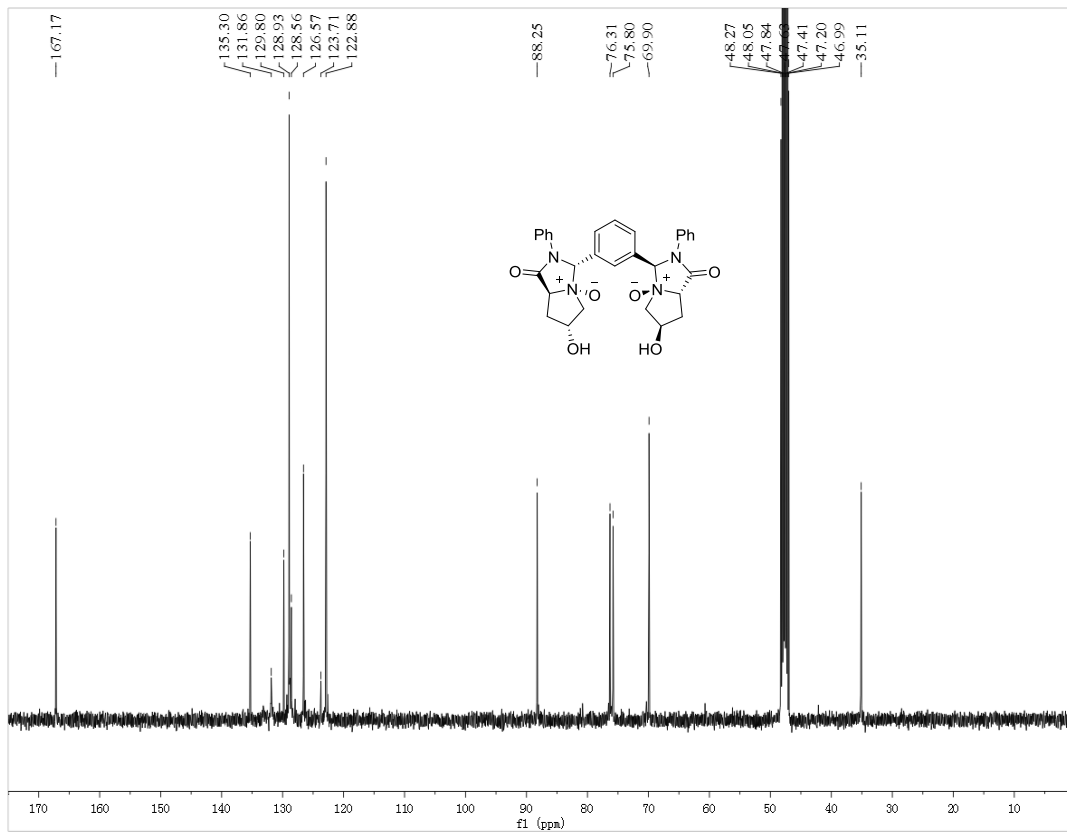
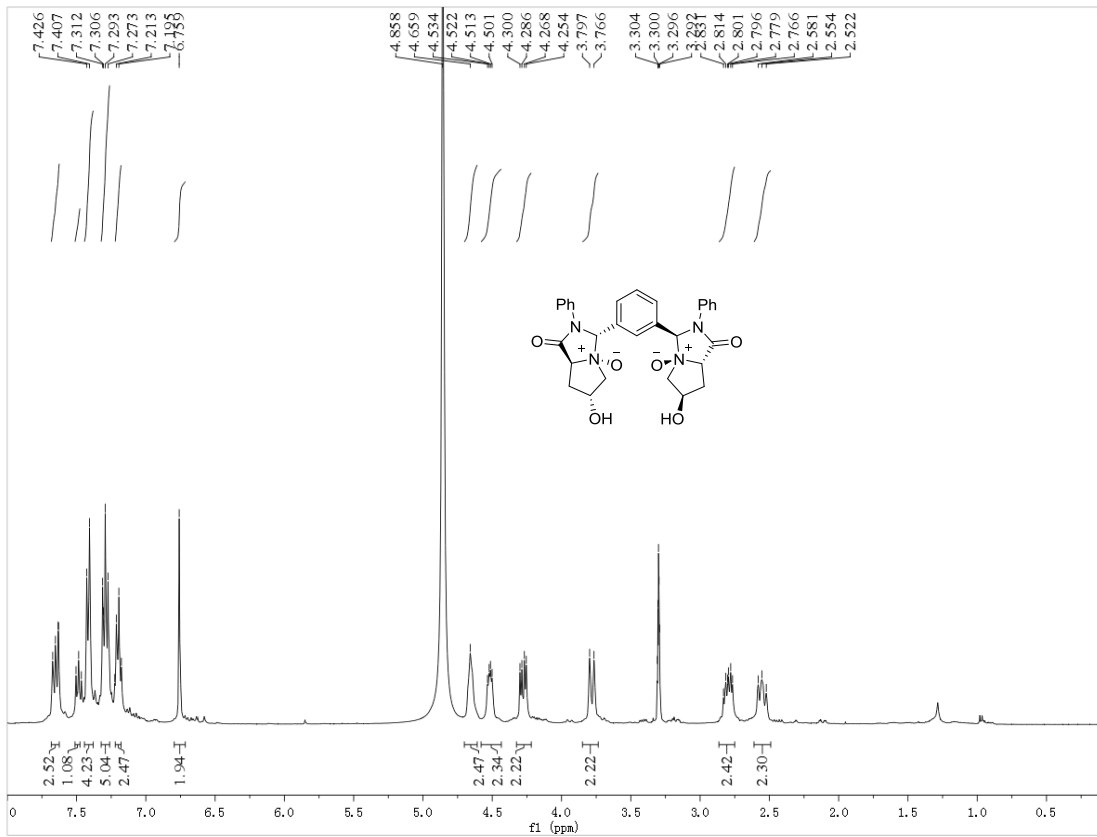
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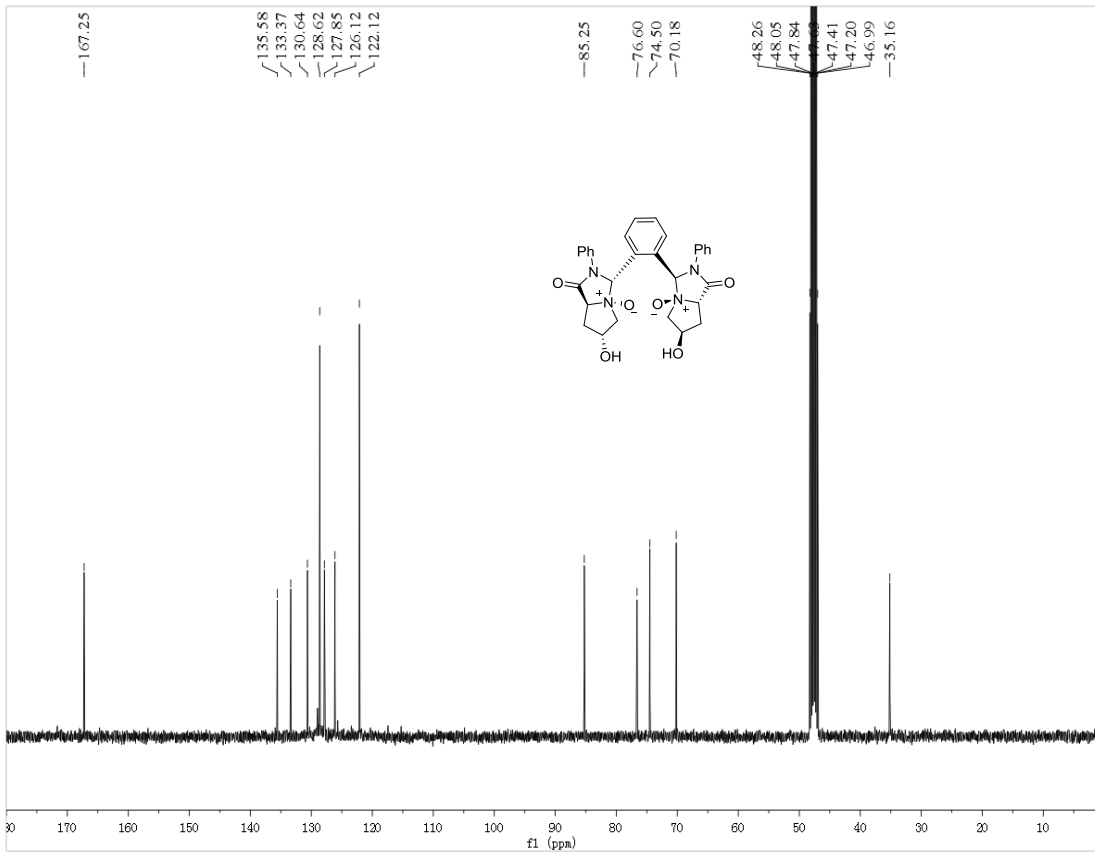
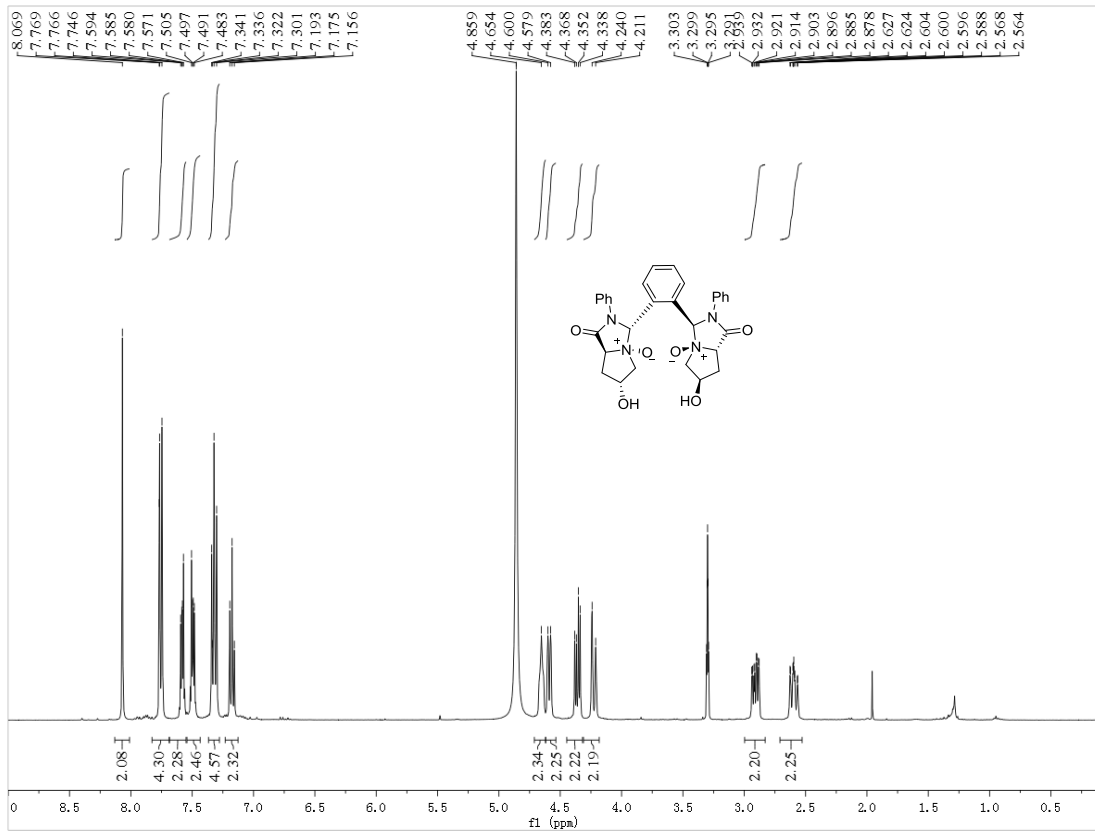
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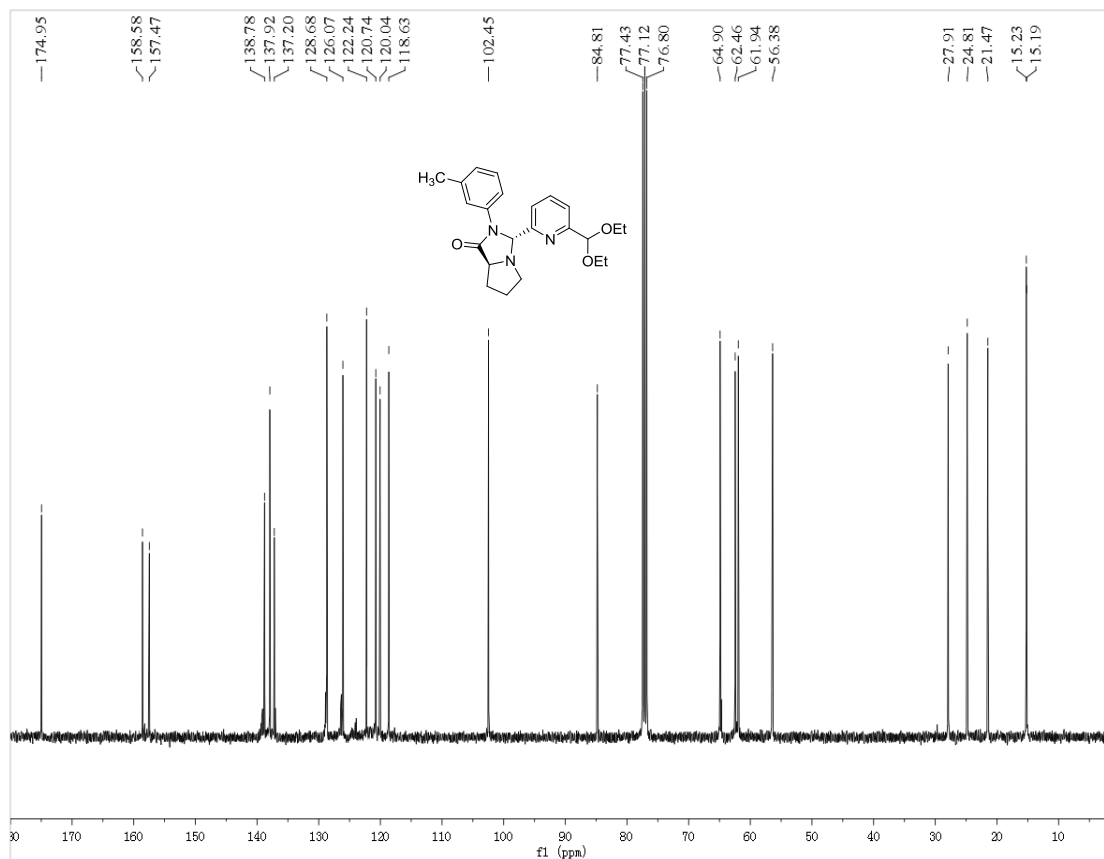
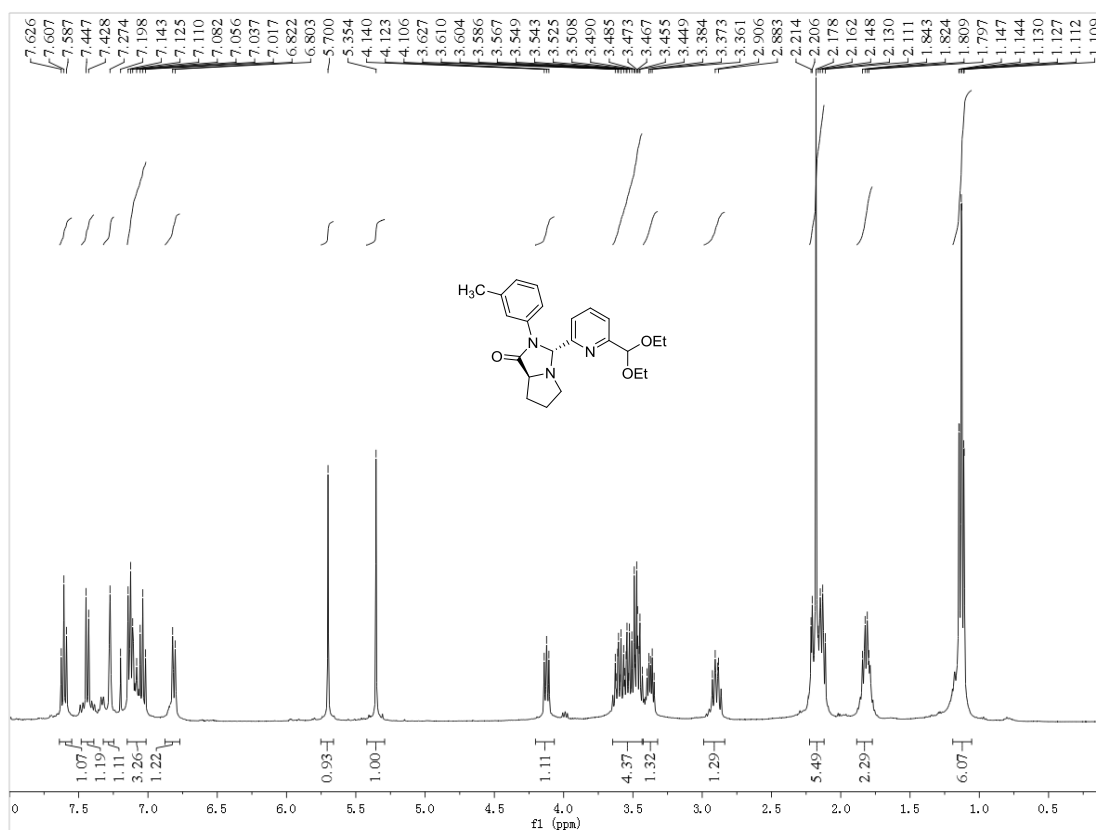
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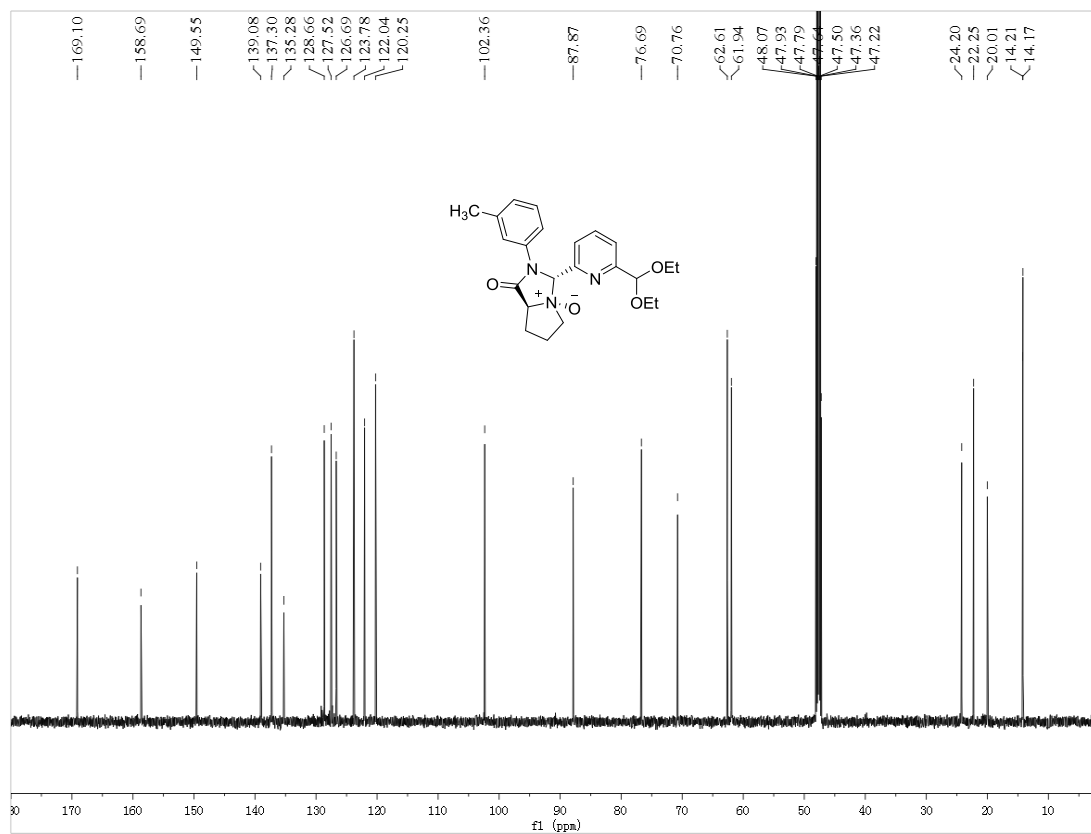
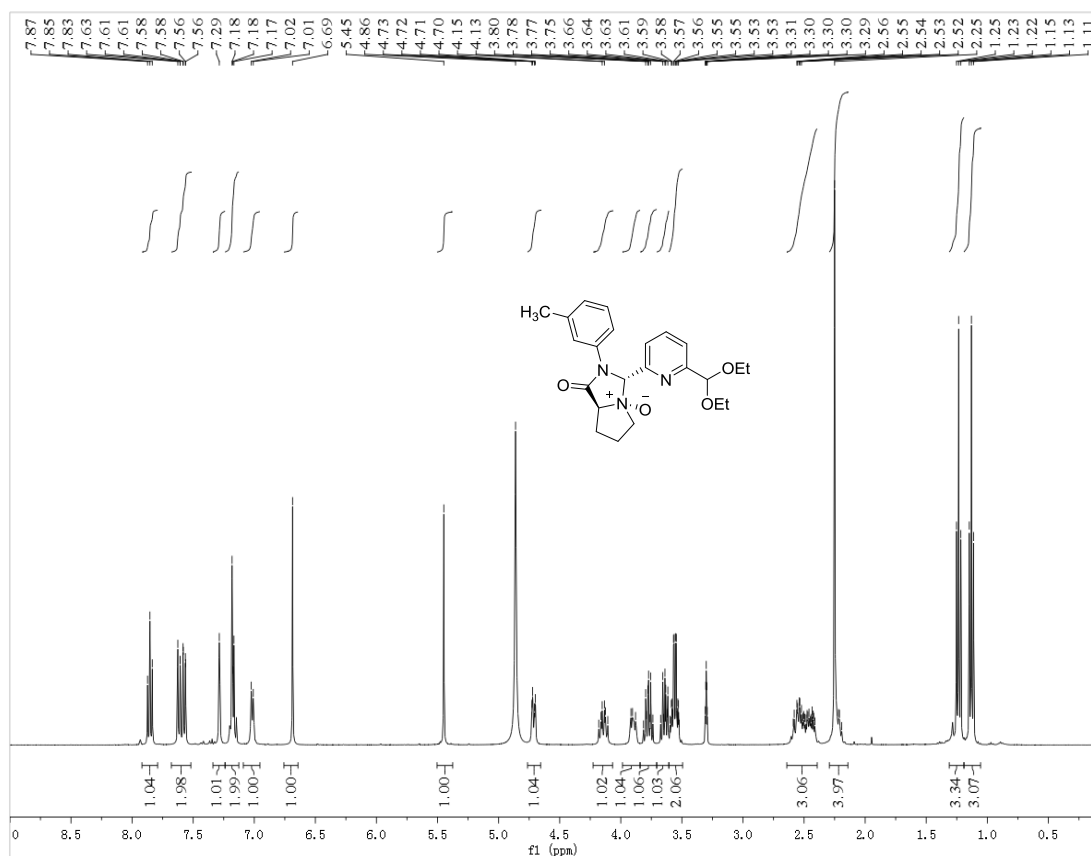
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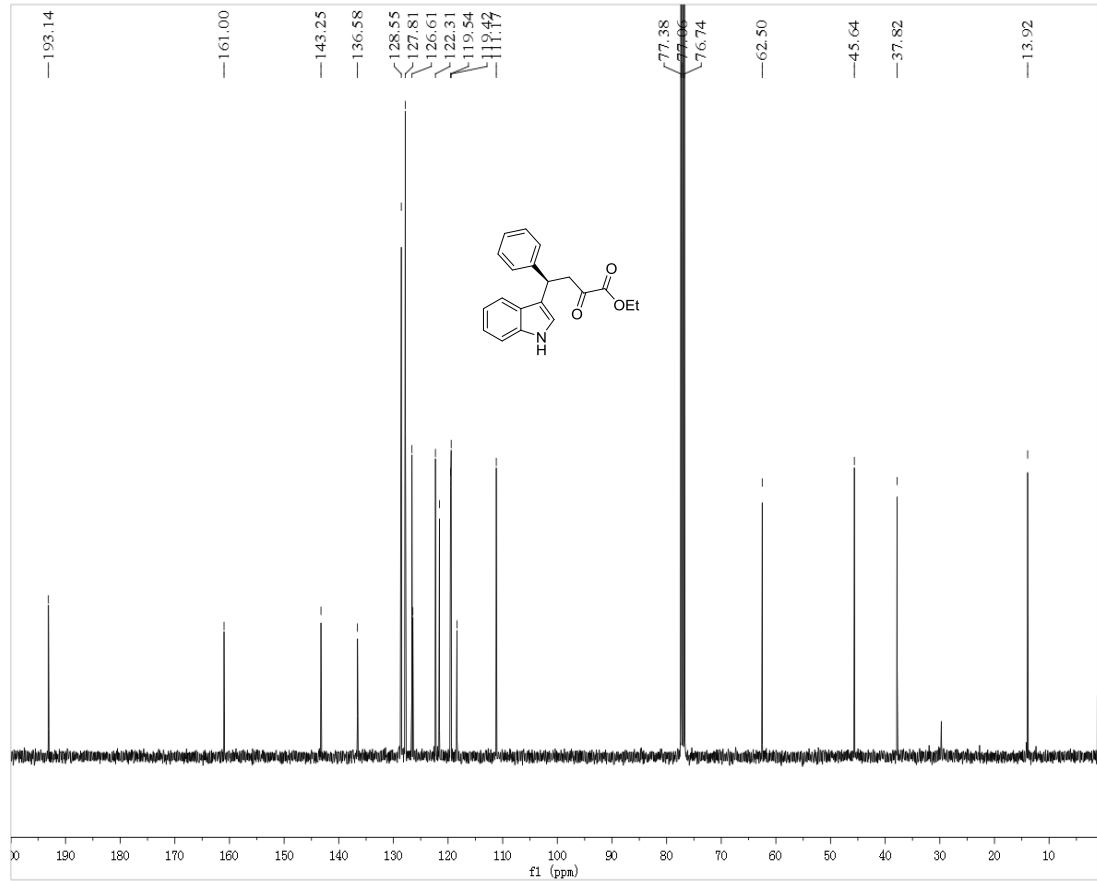
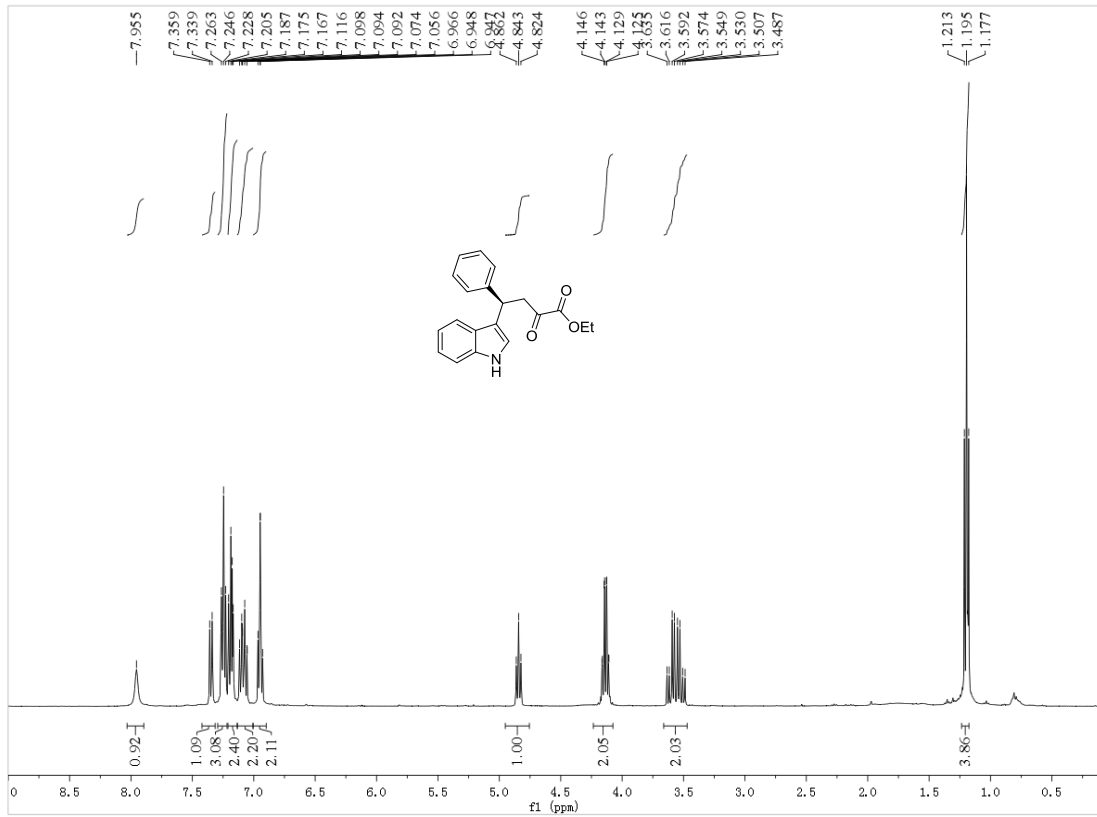
¹H and ¹³C NMR of 4



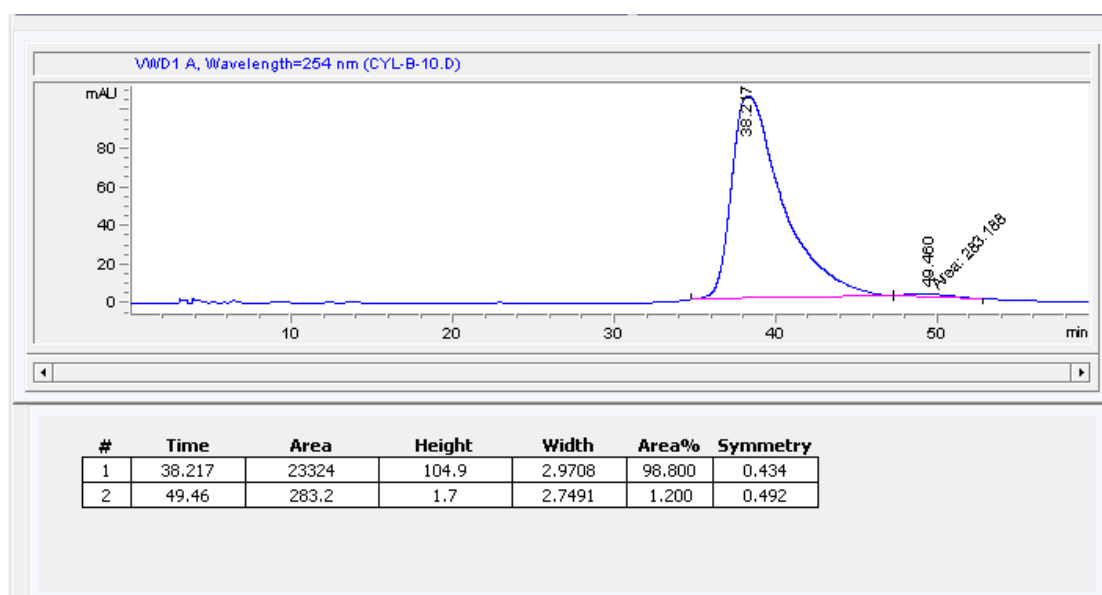
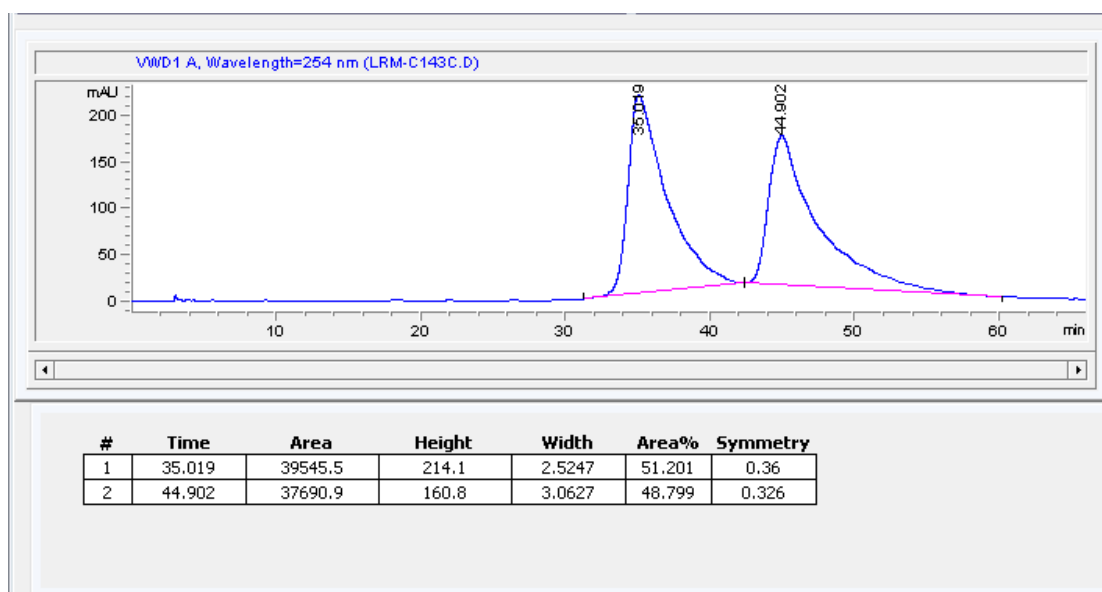
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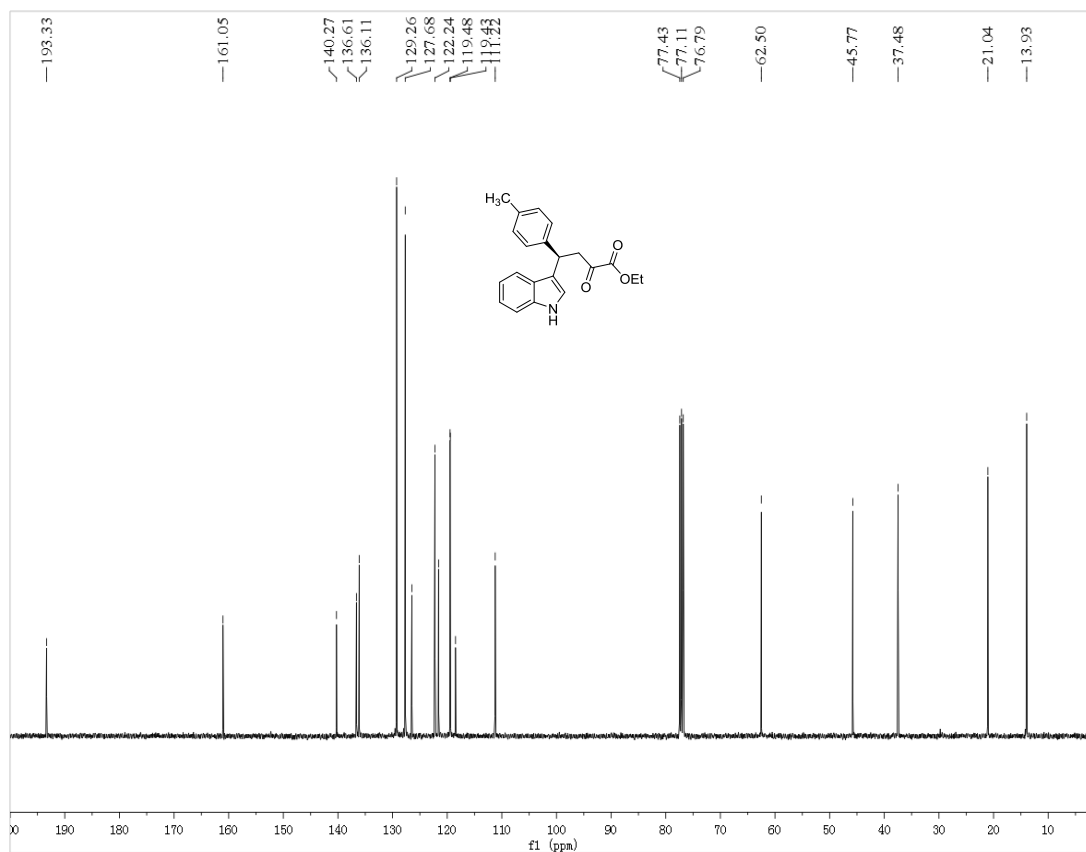
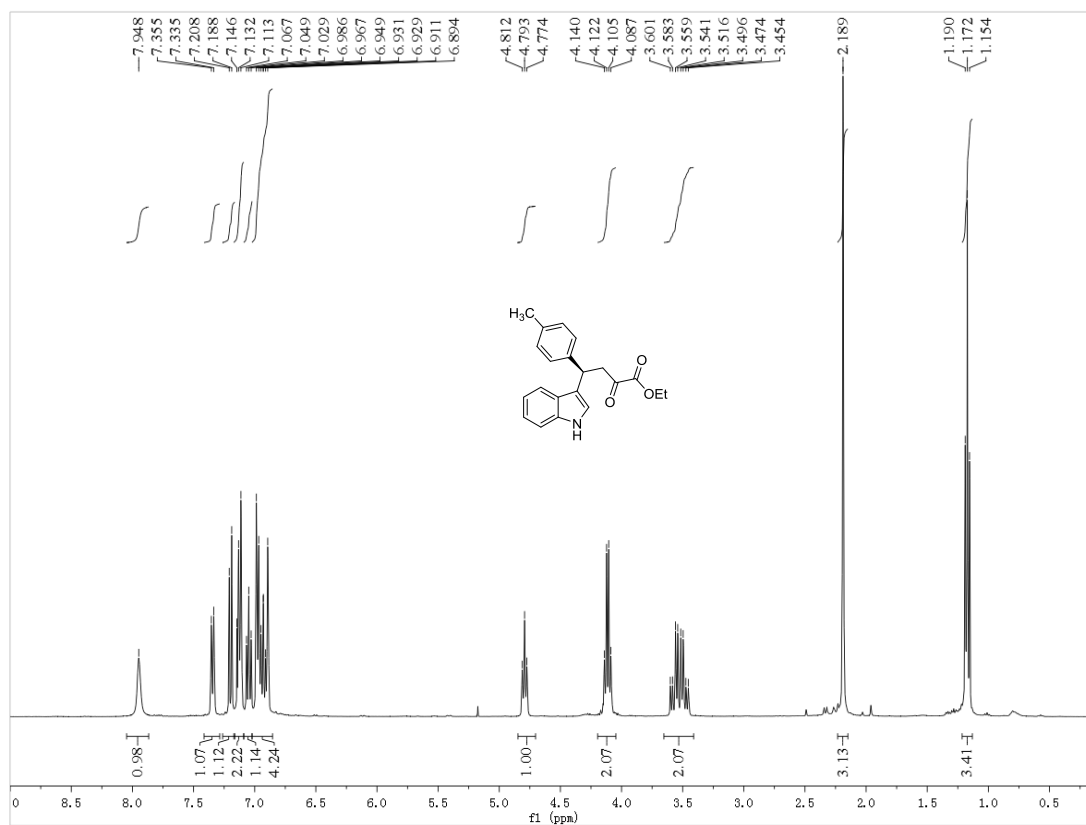
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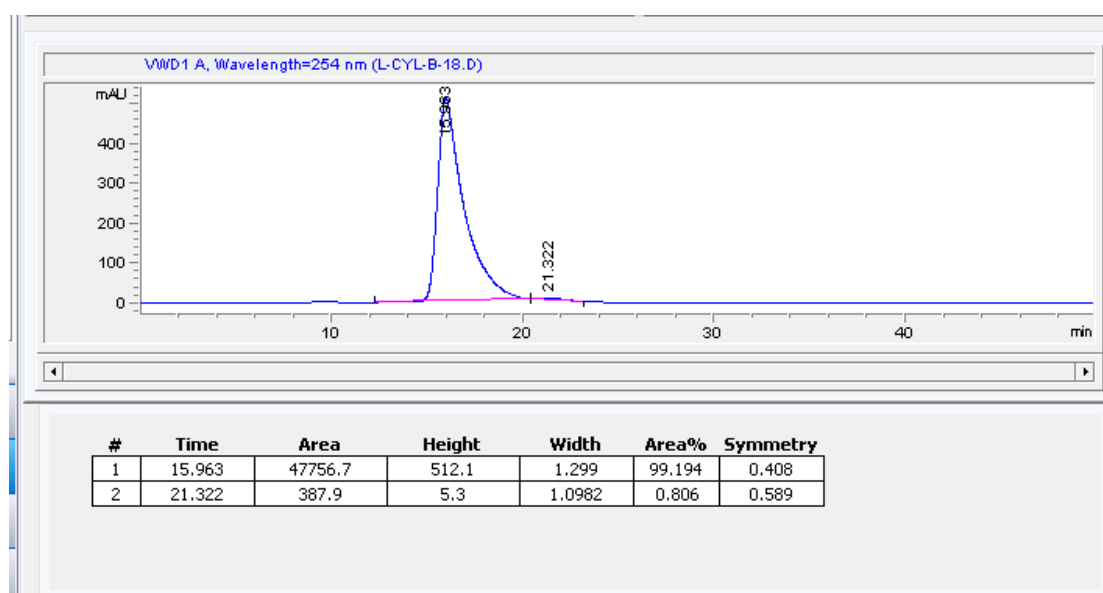
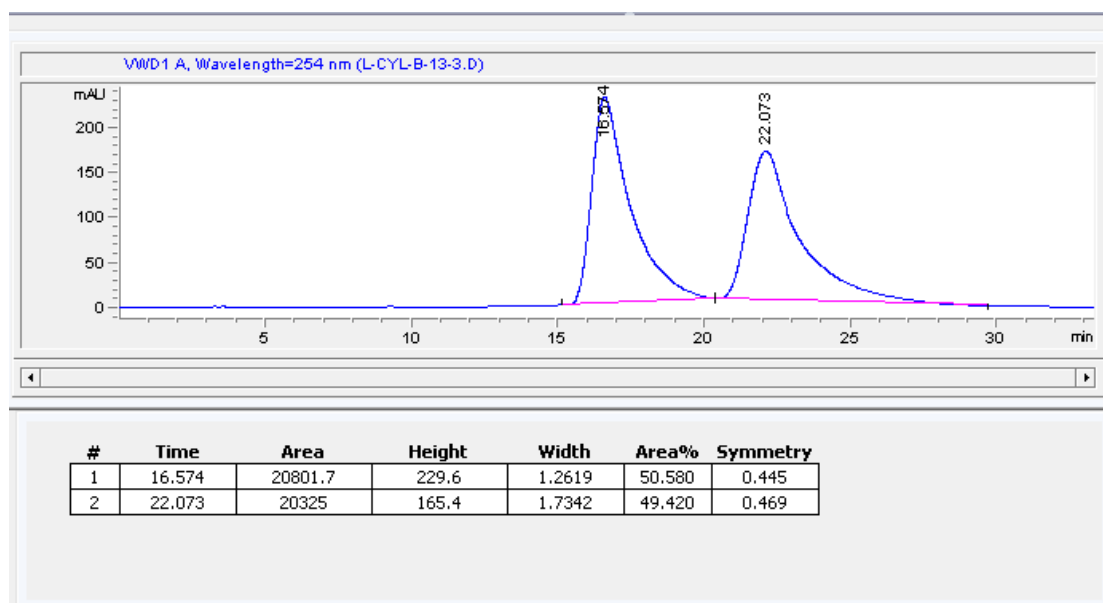
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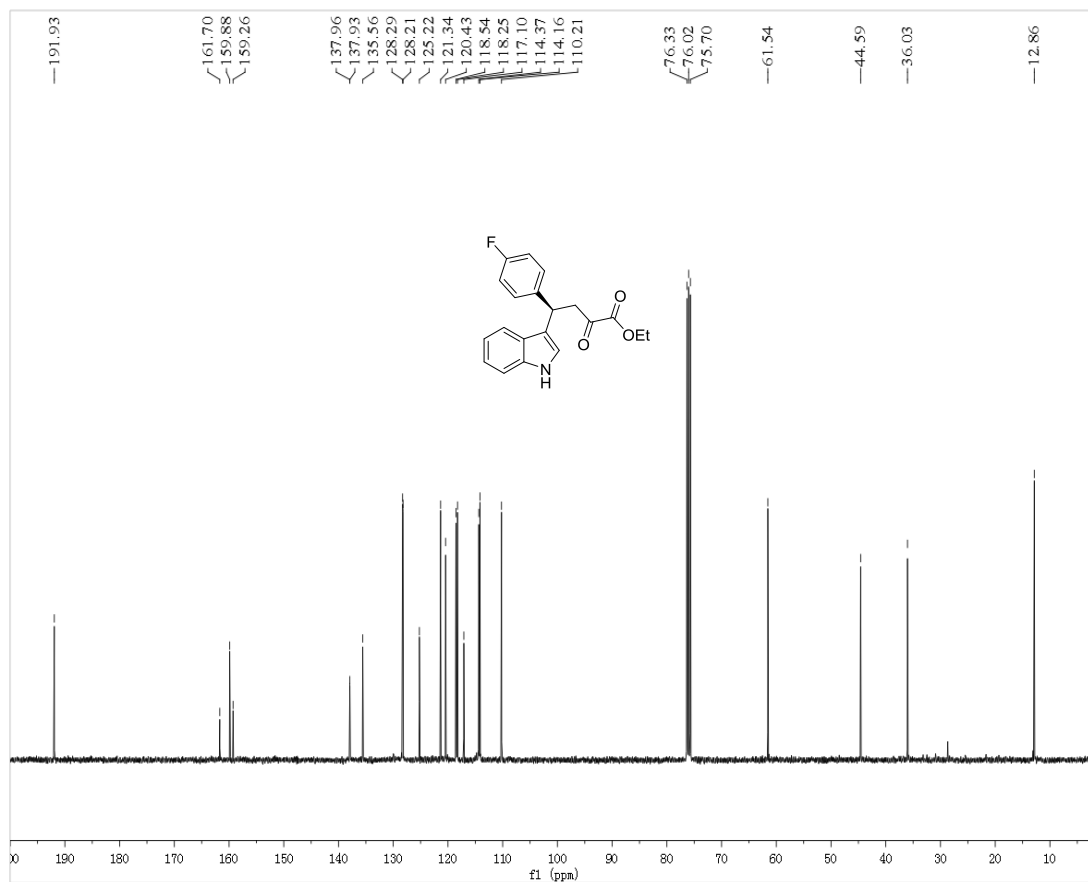
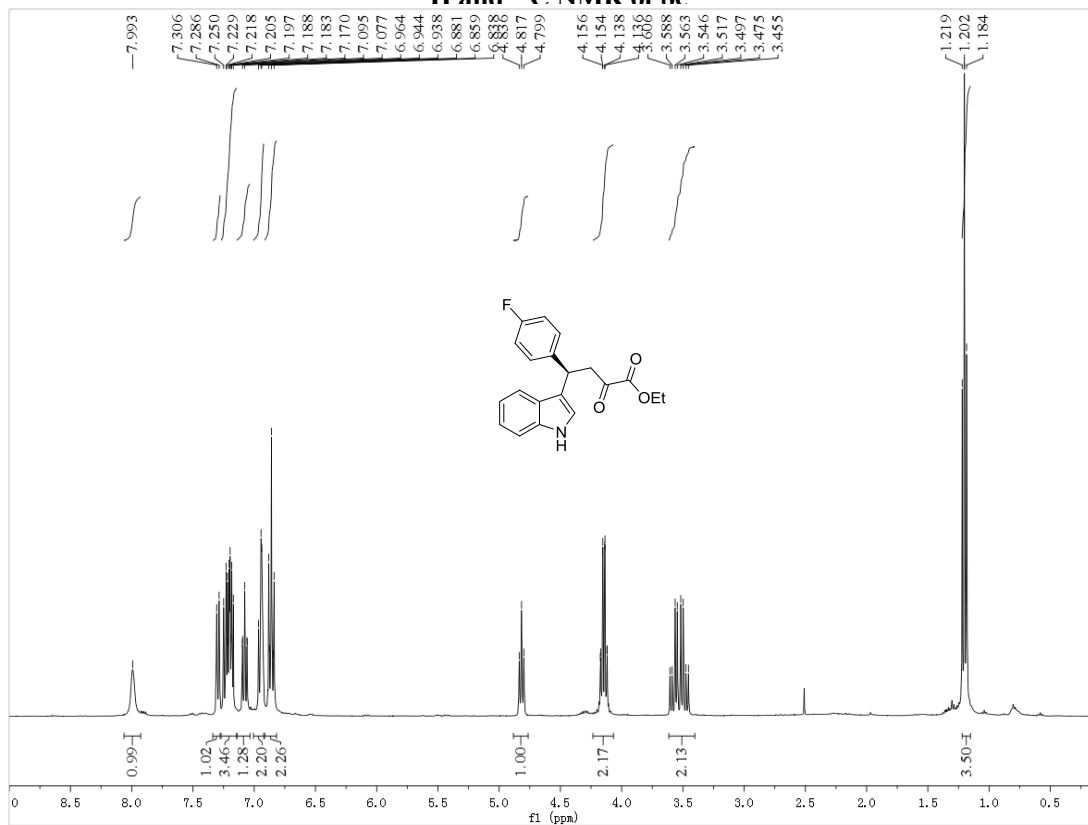
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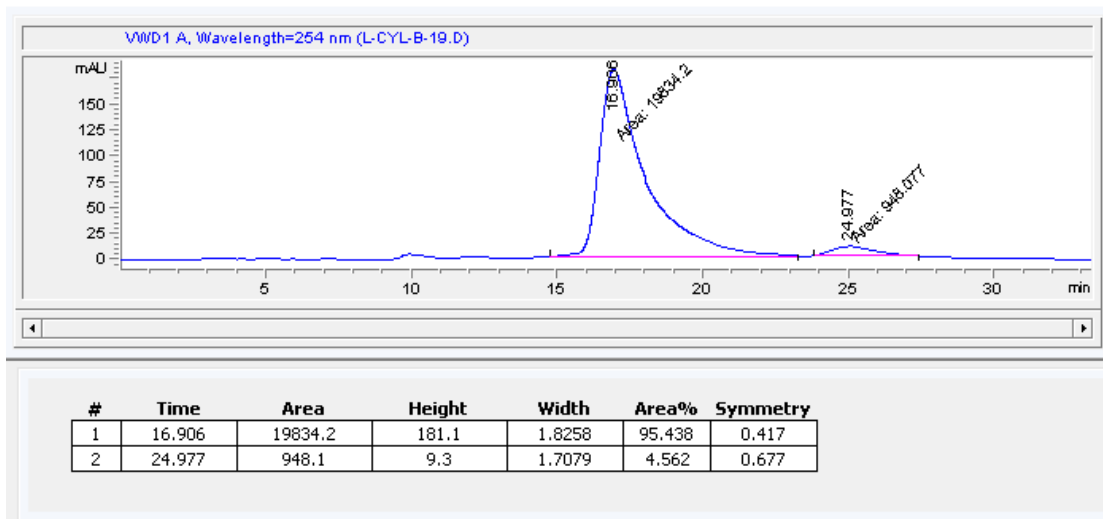
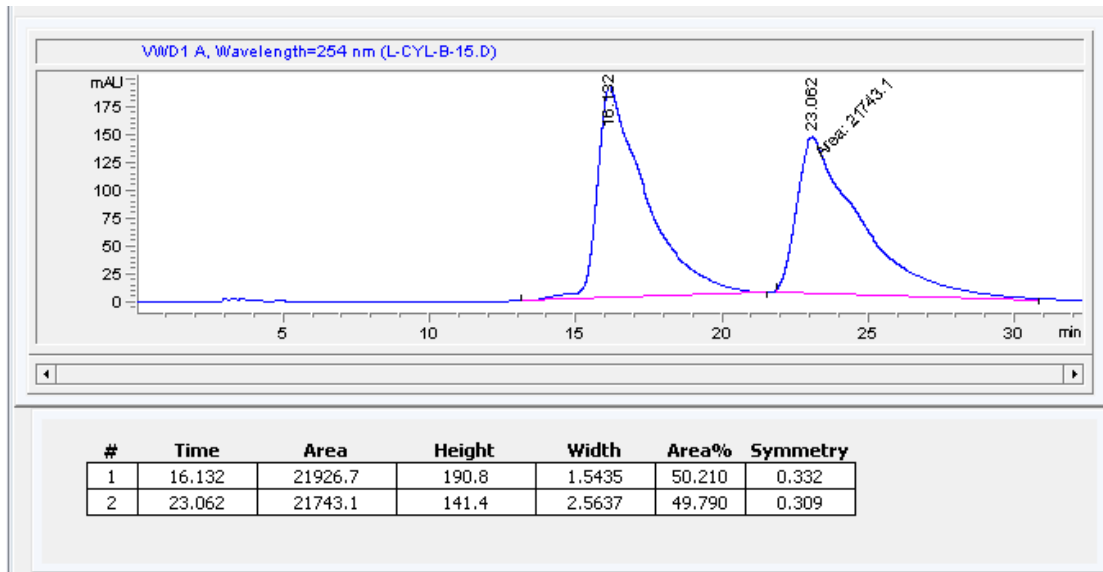
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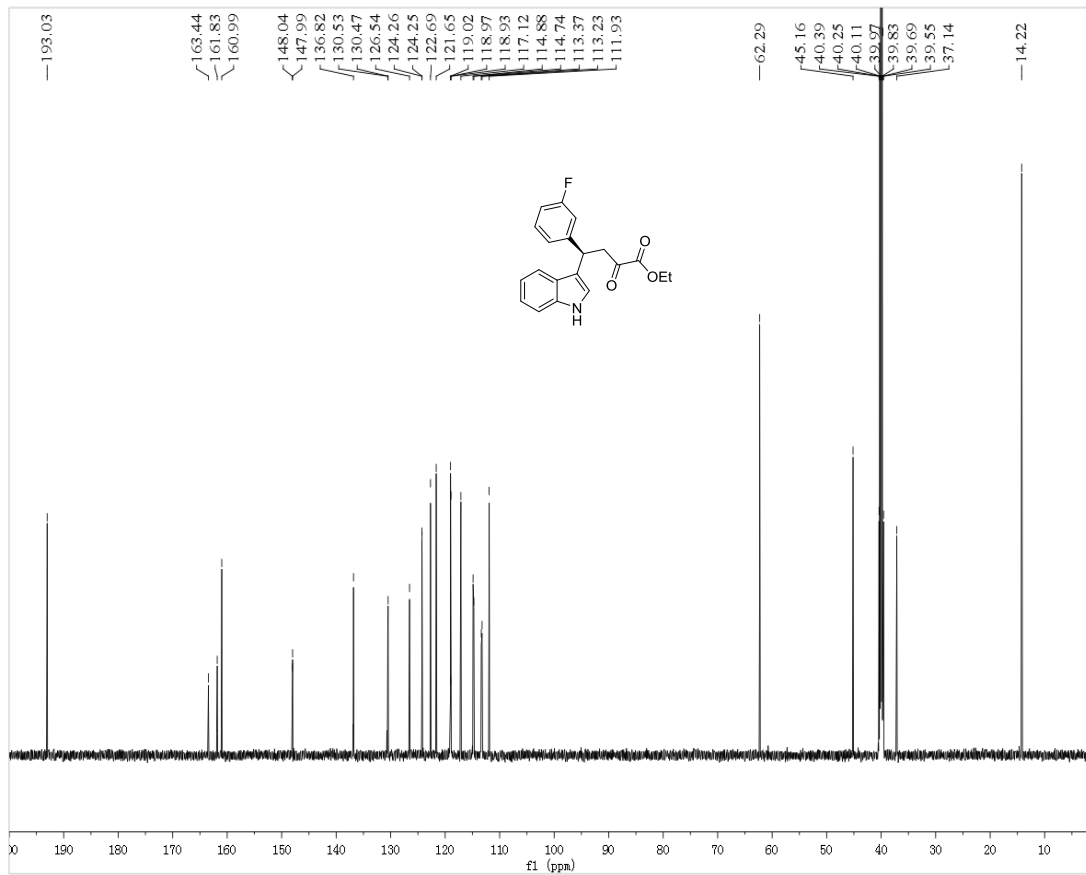
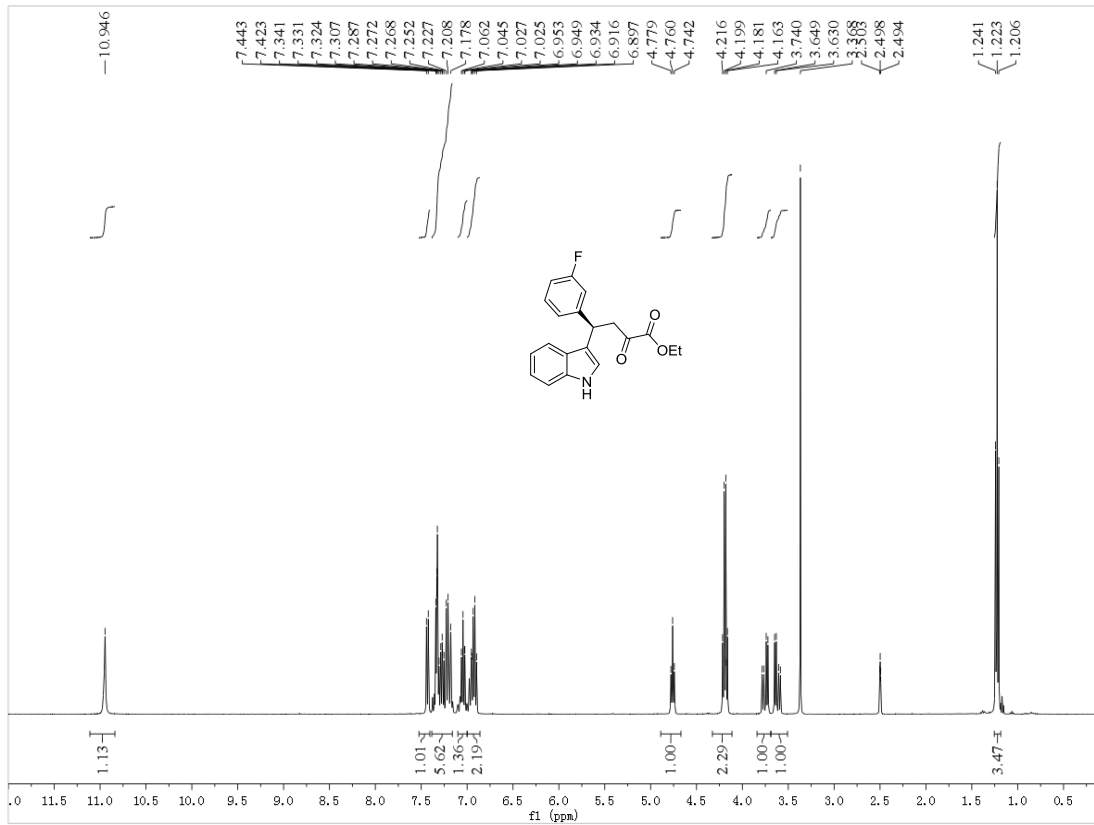
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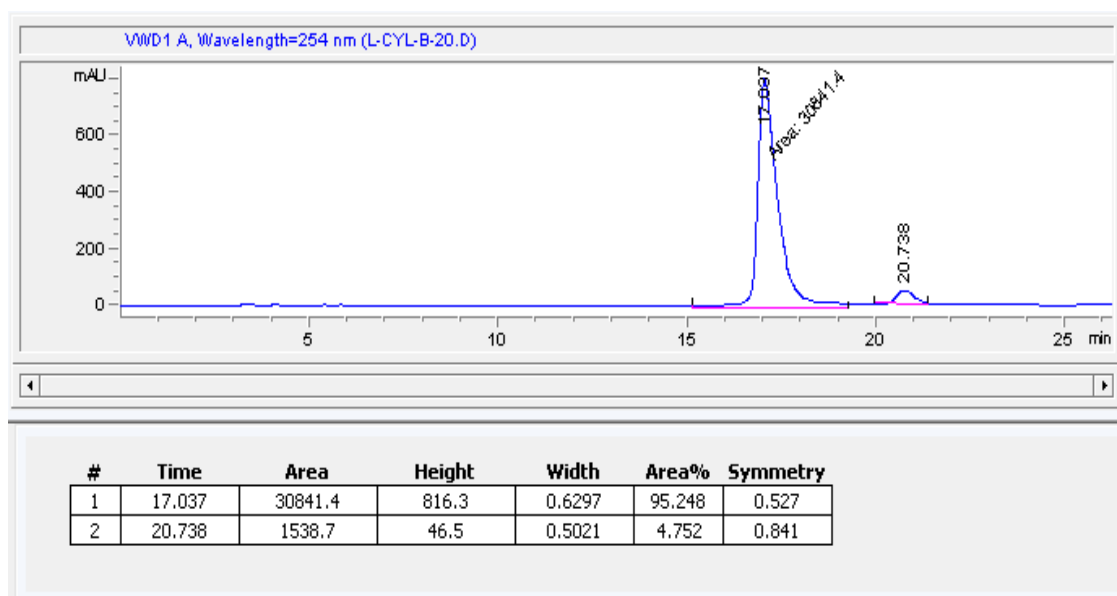
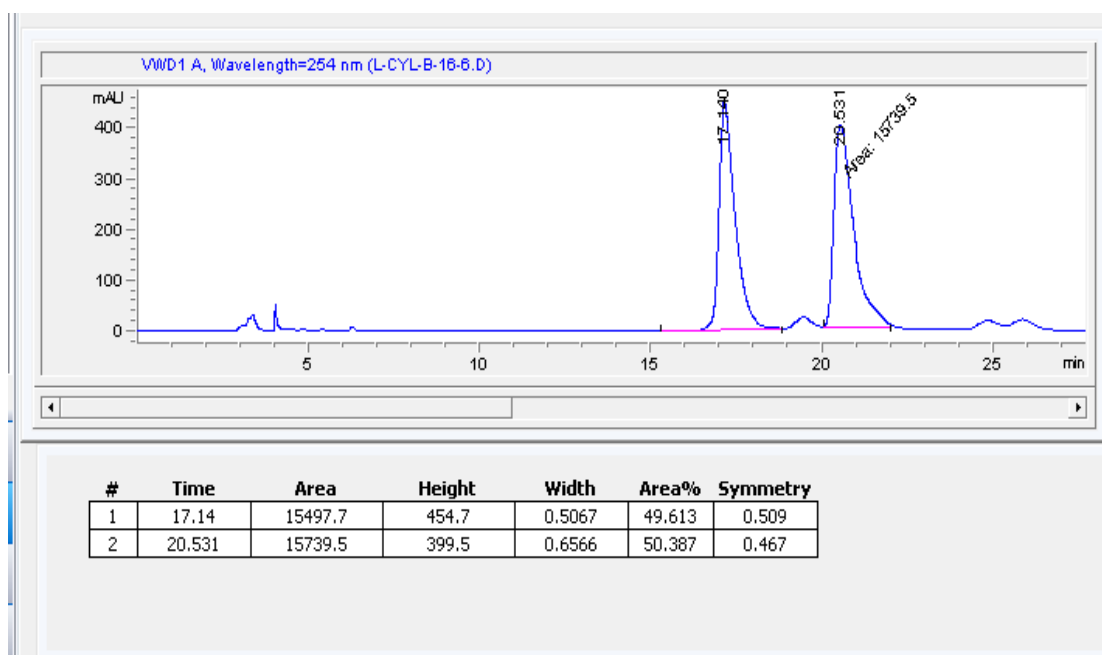
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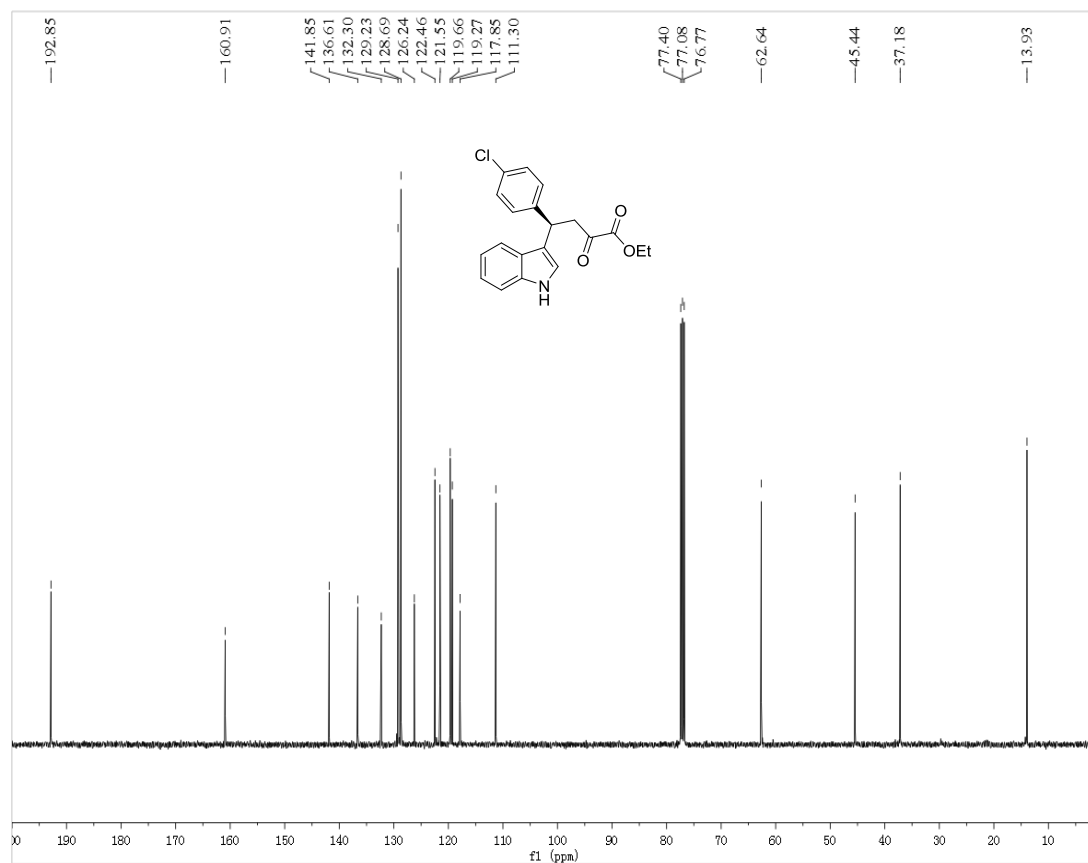
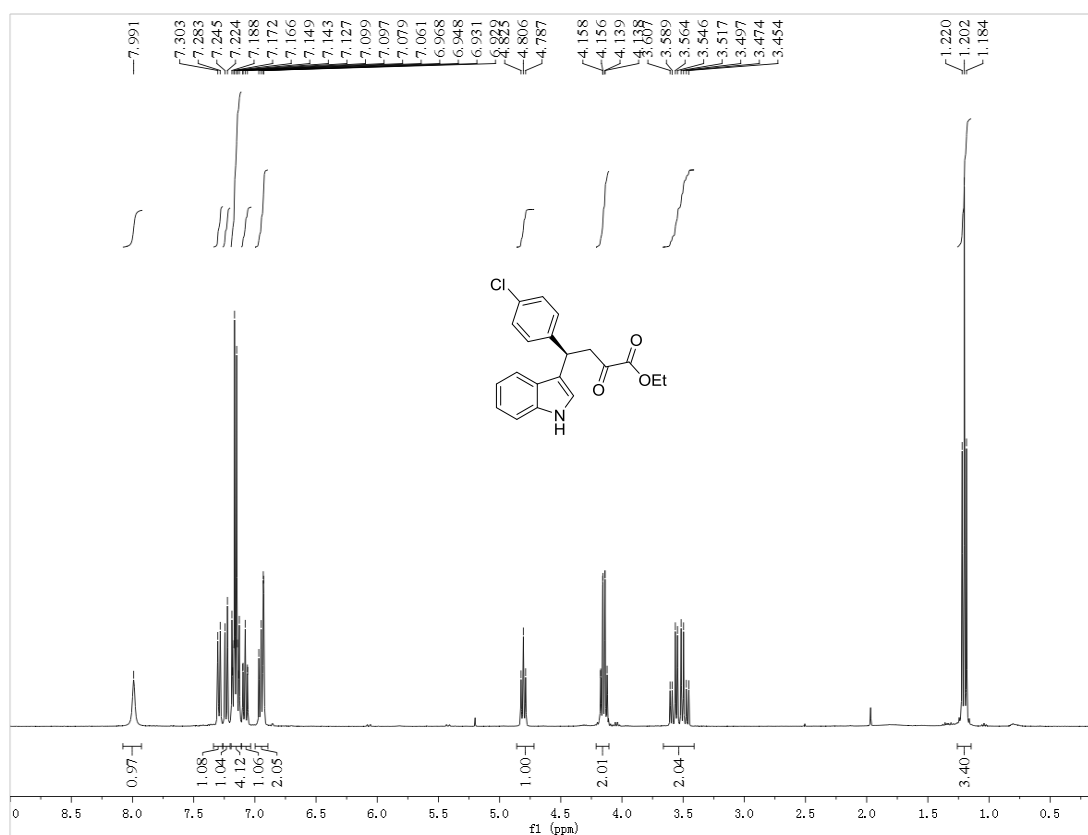
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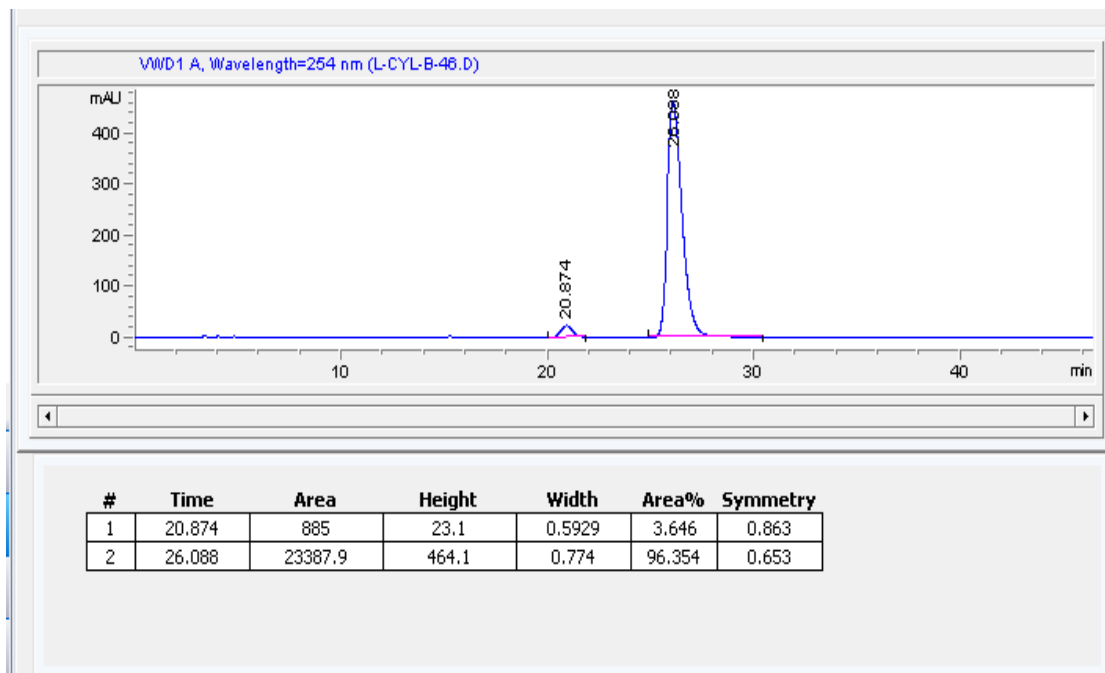
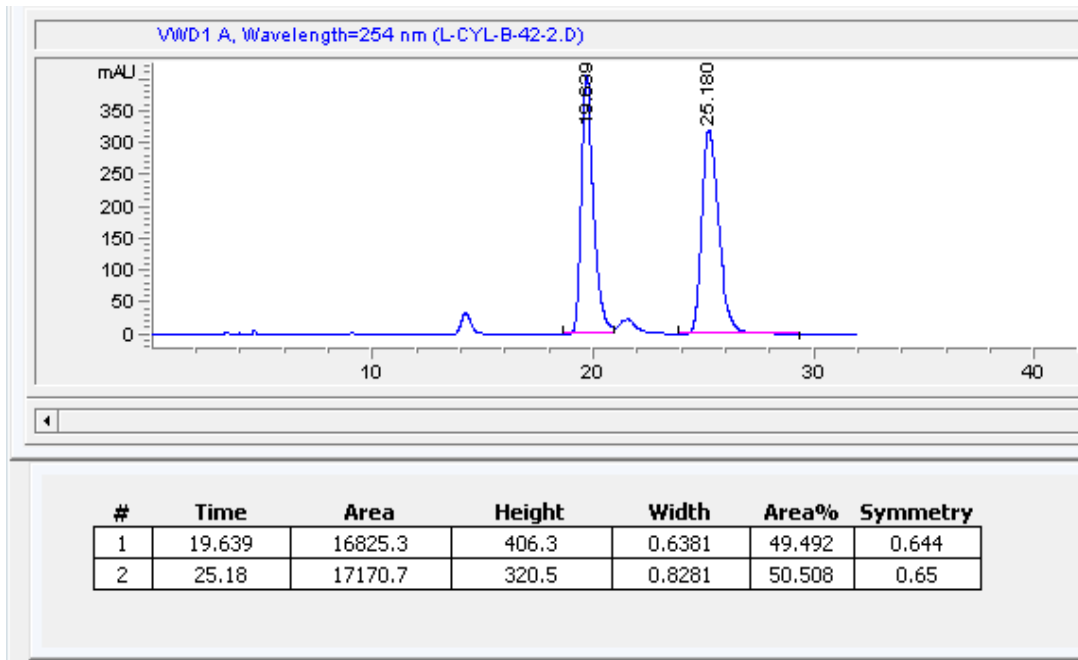
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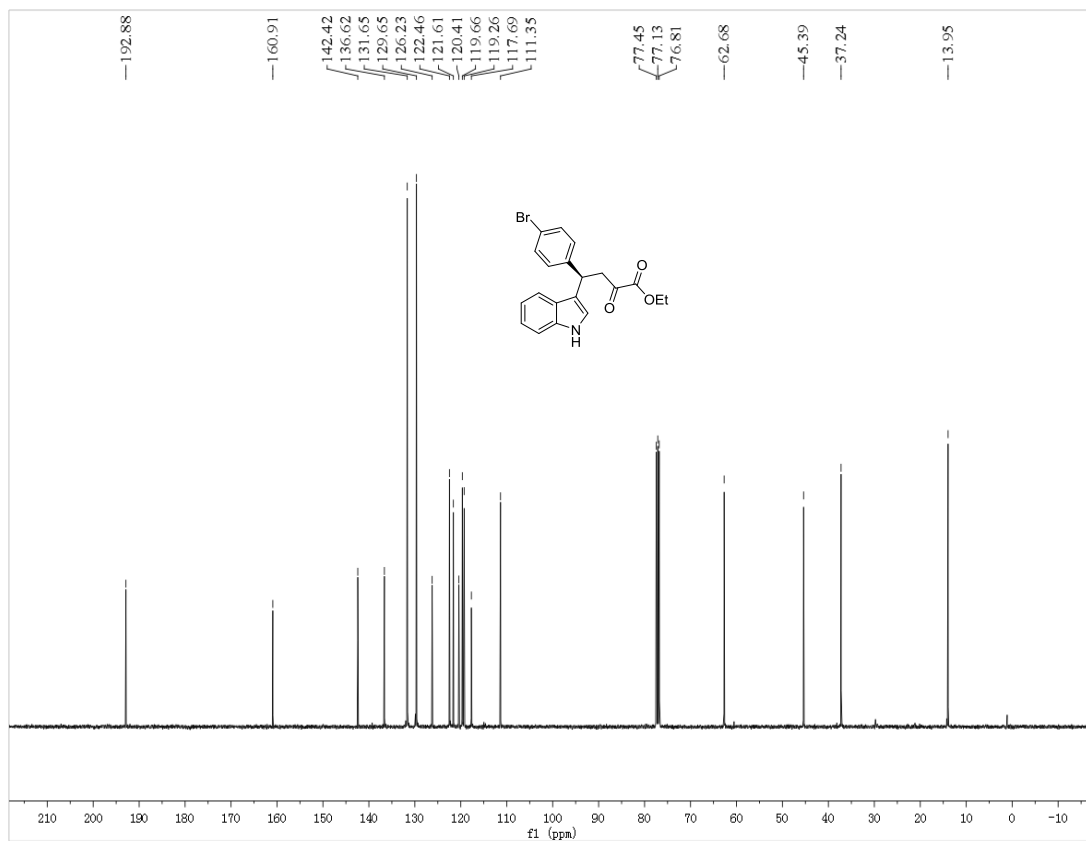
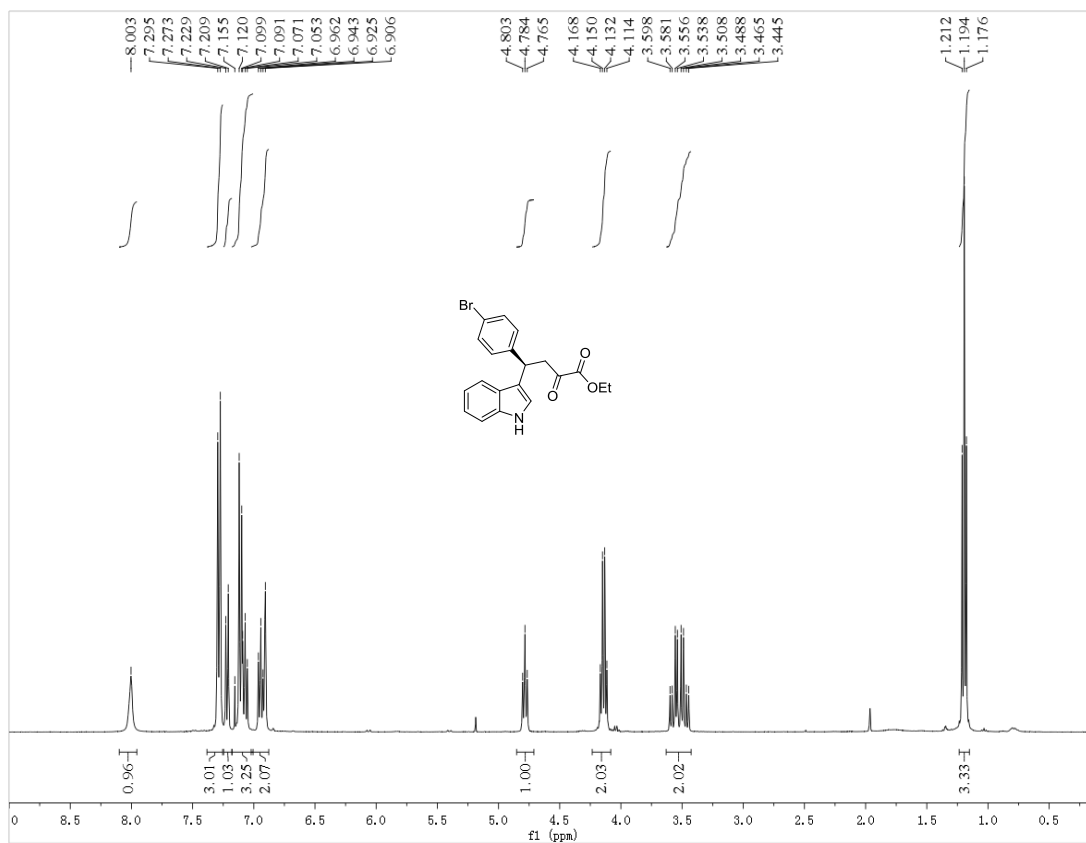
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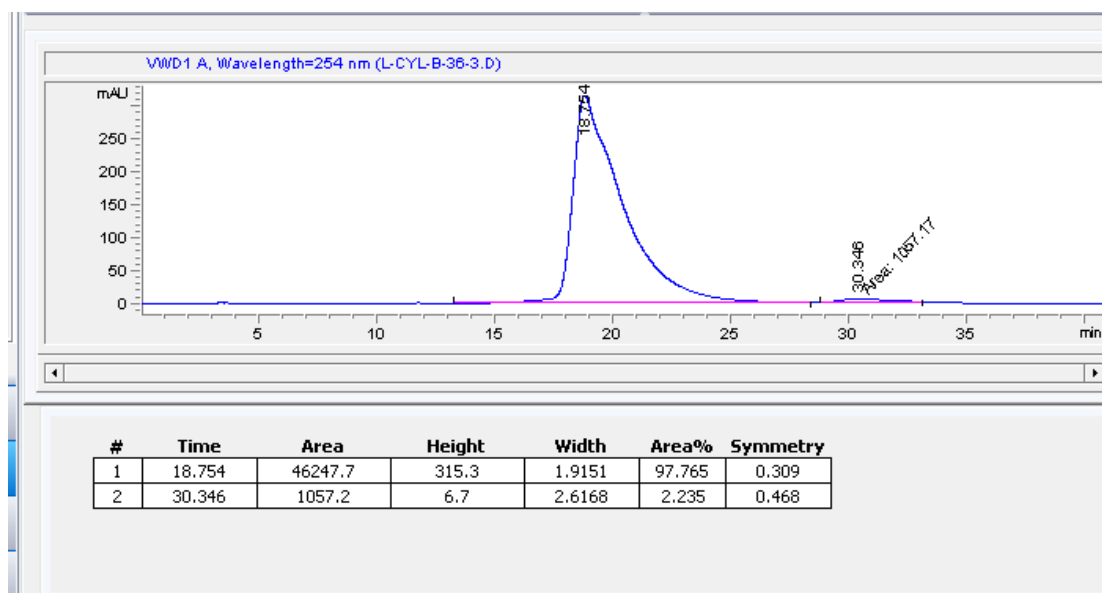
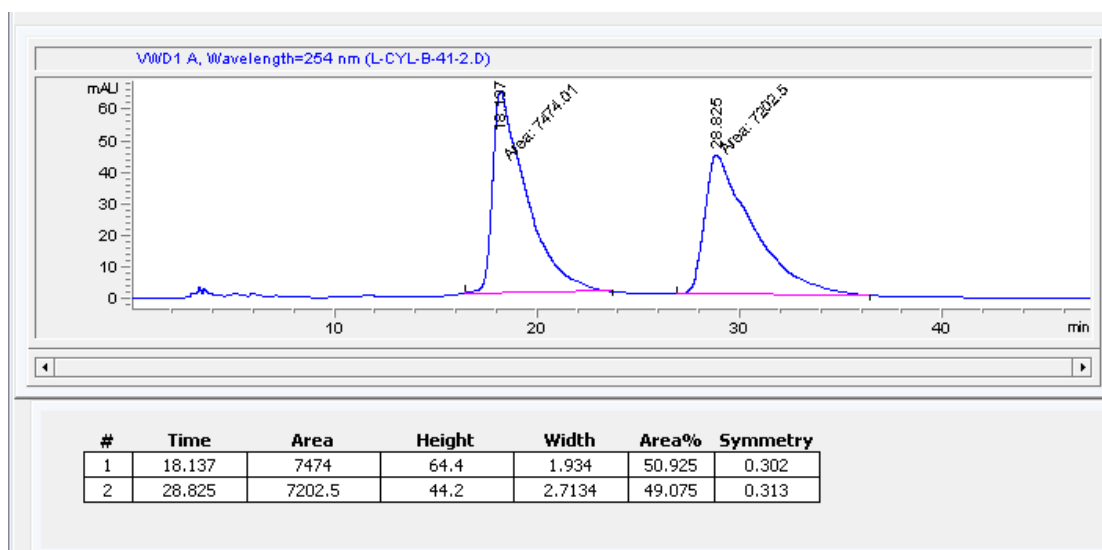
HPLC of 8e



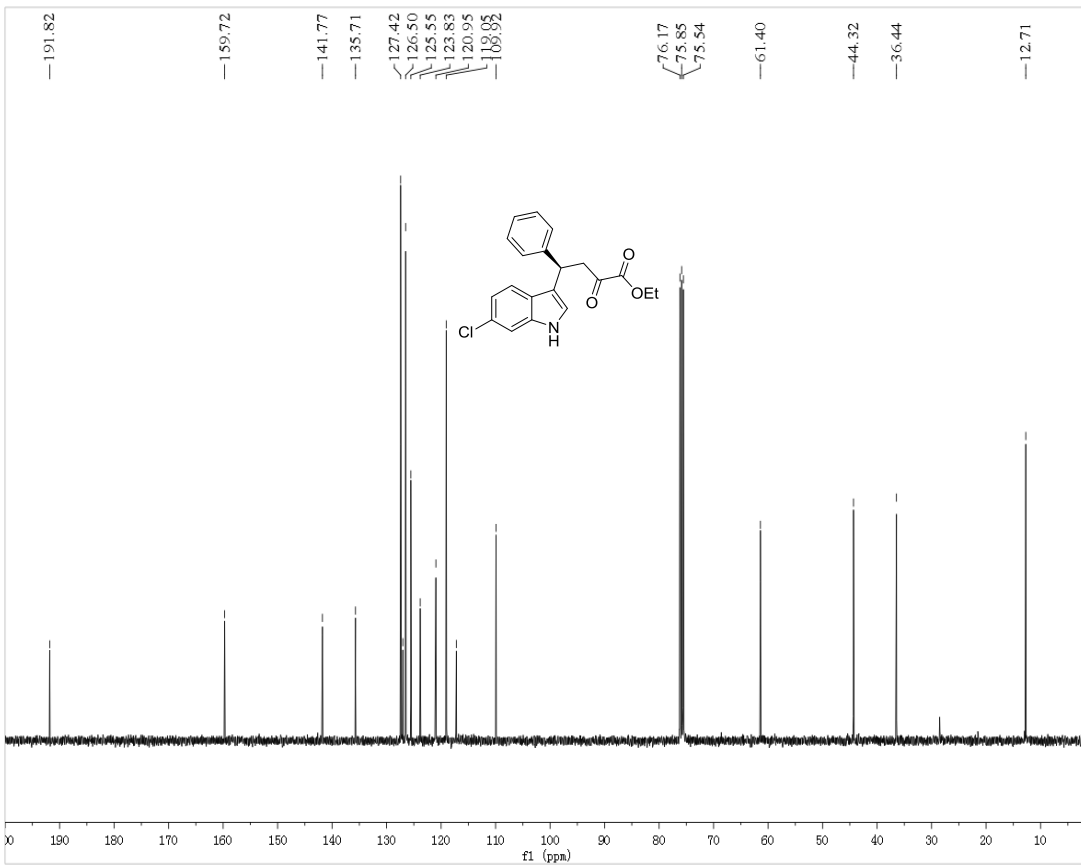
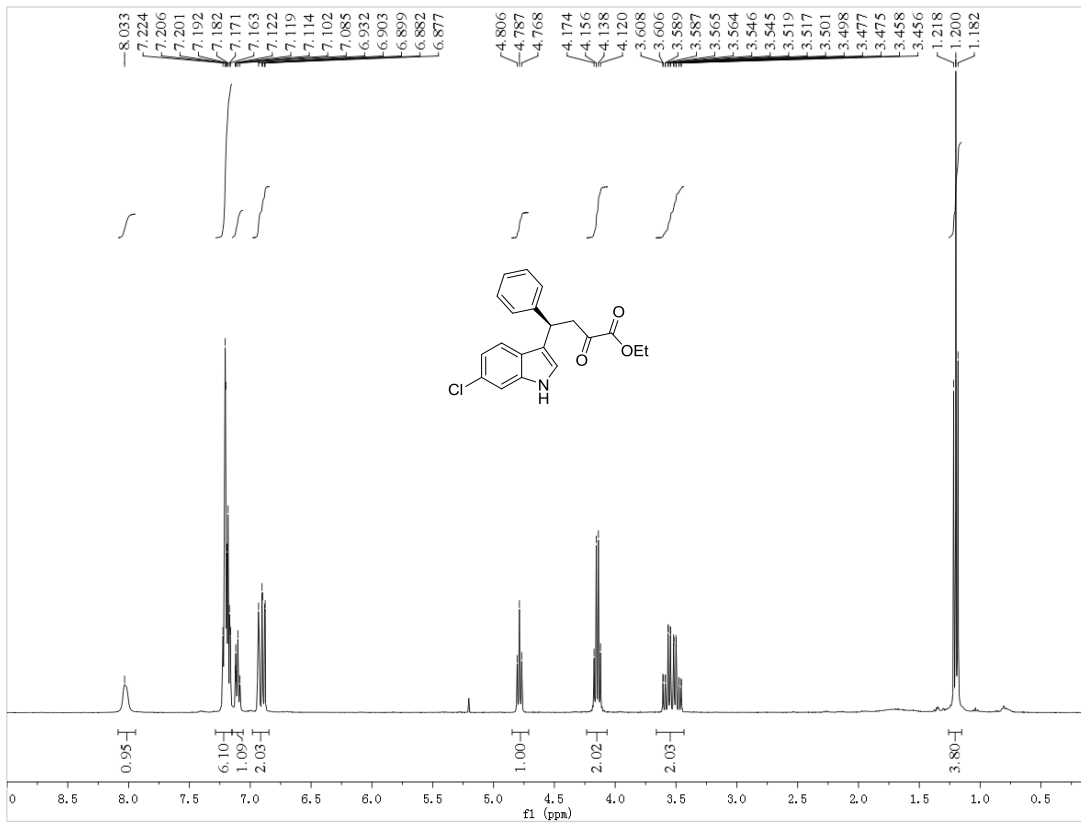
¹H and ¹³C NMR of 8f



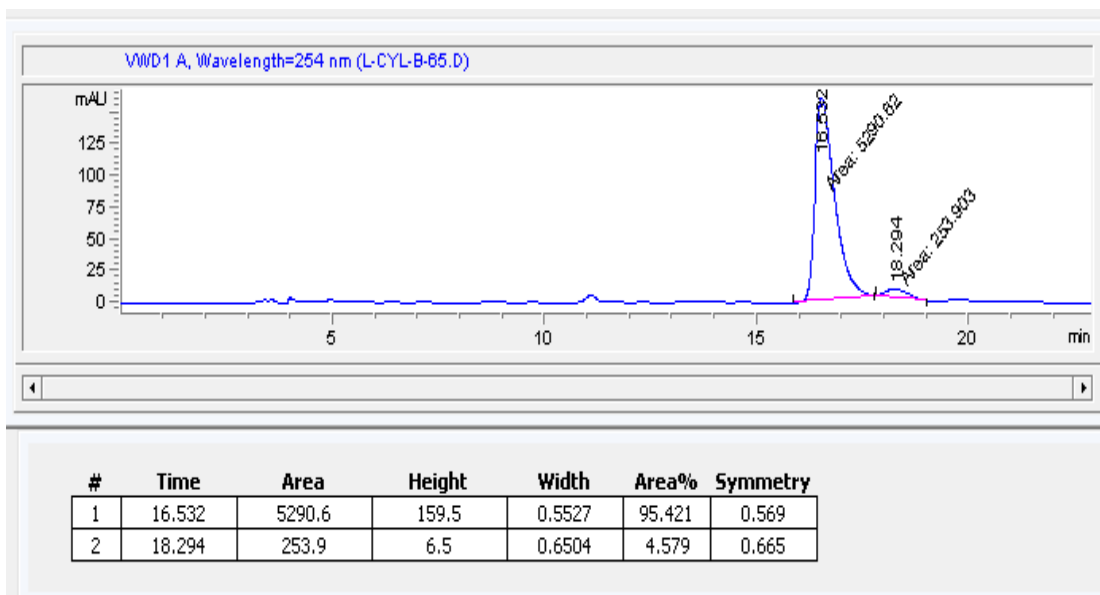
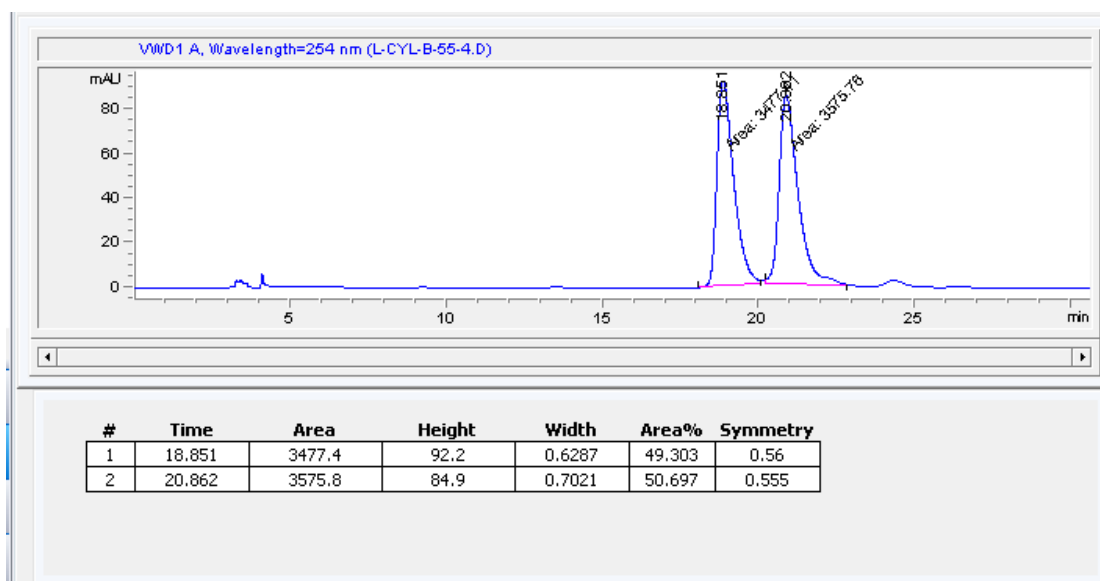
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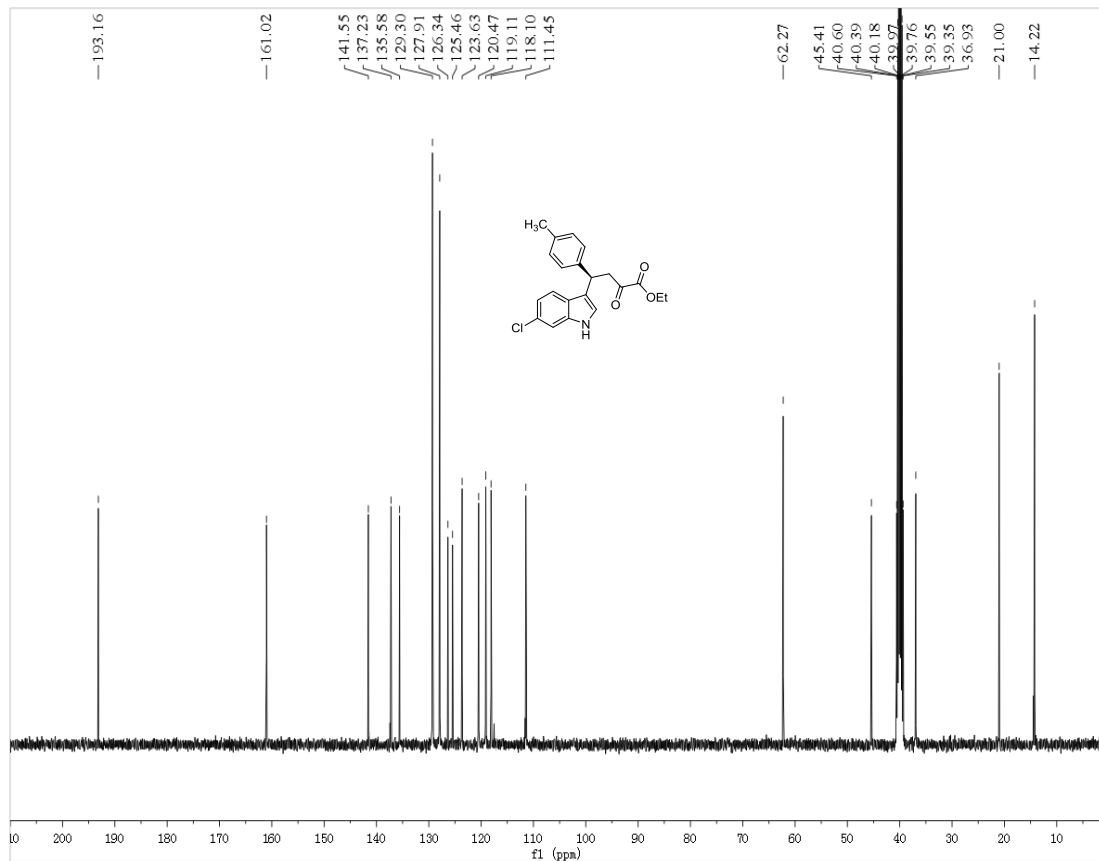
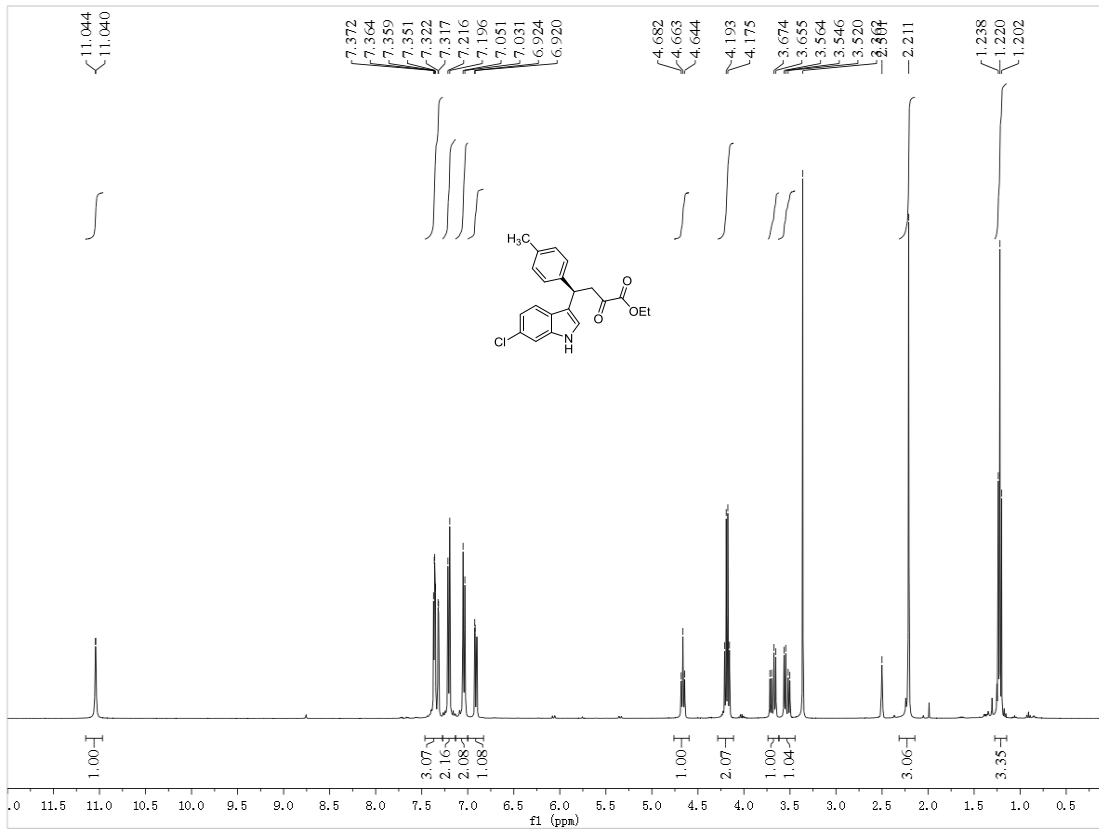
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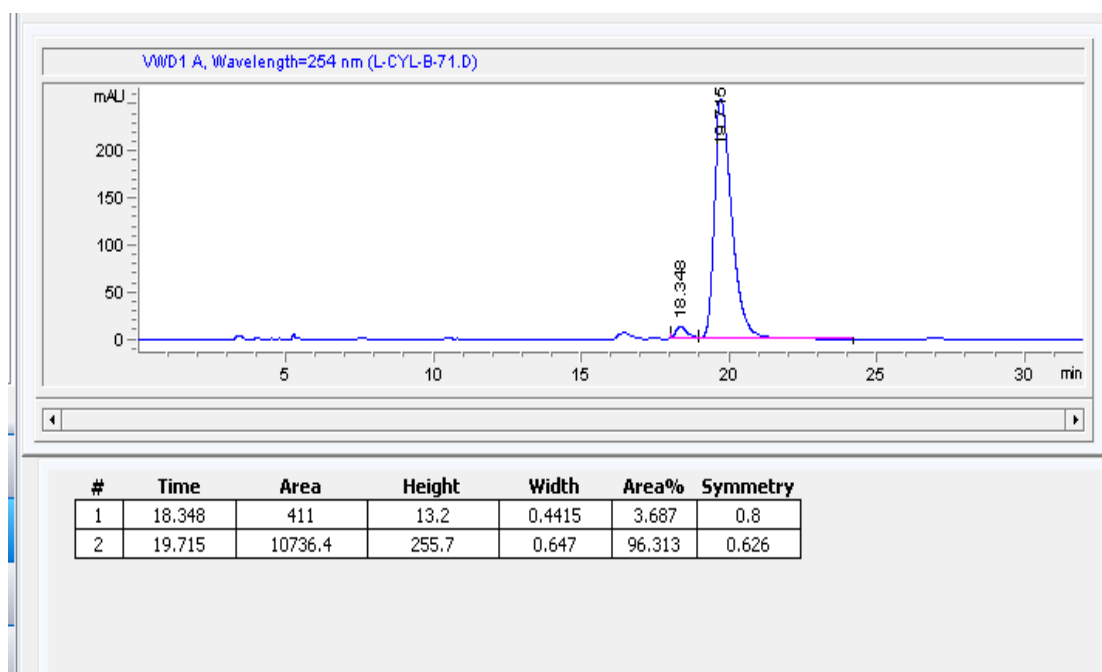
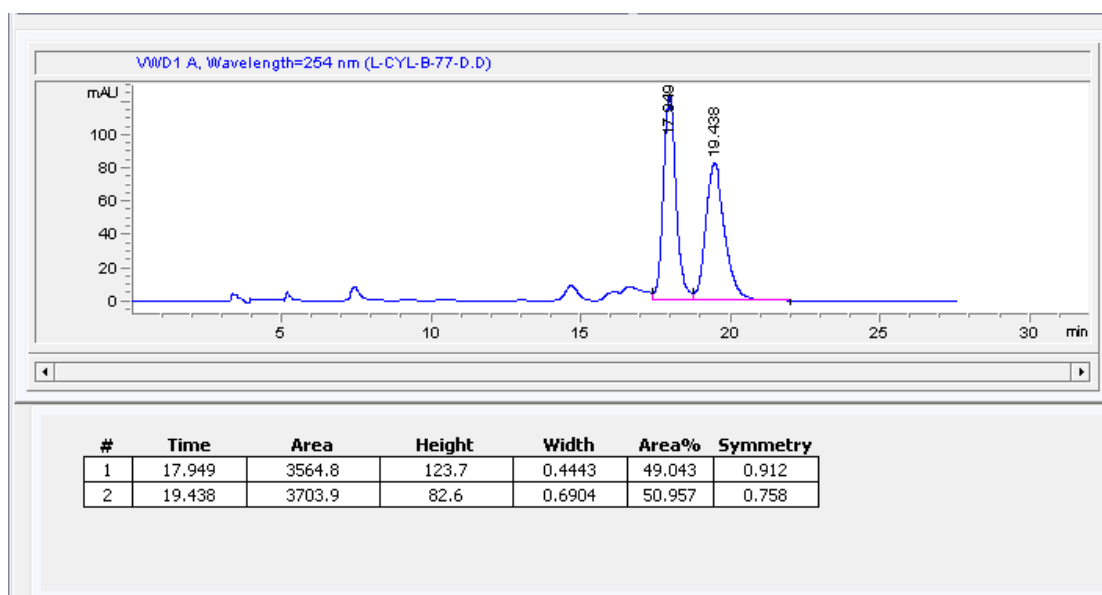
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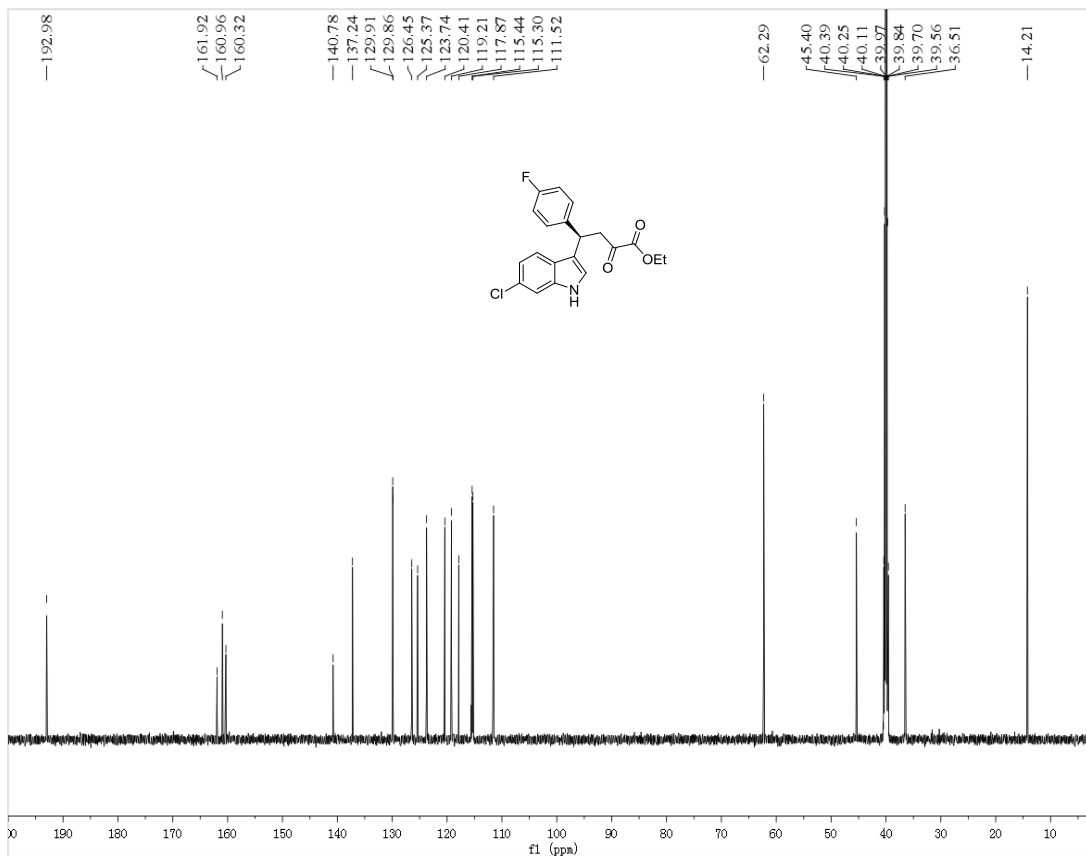
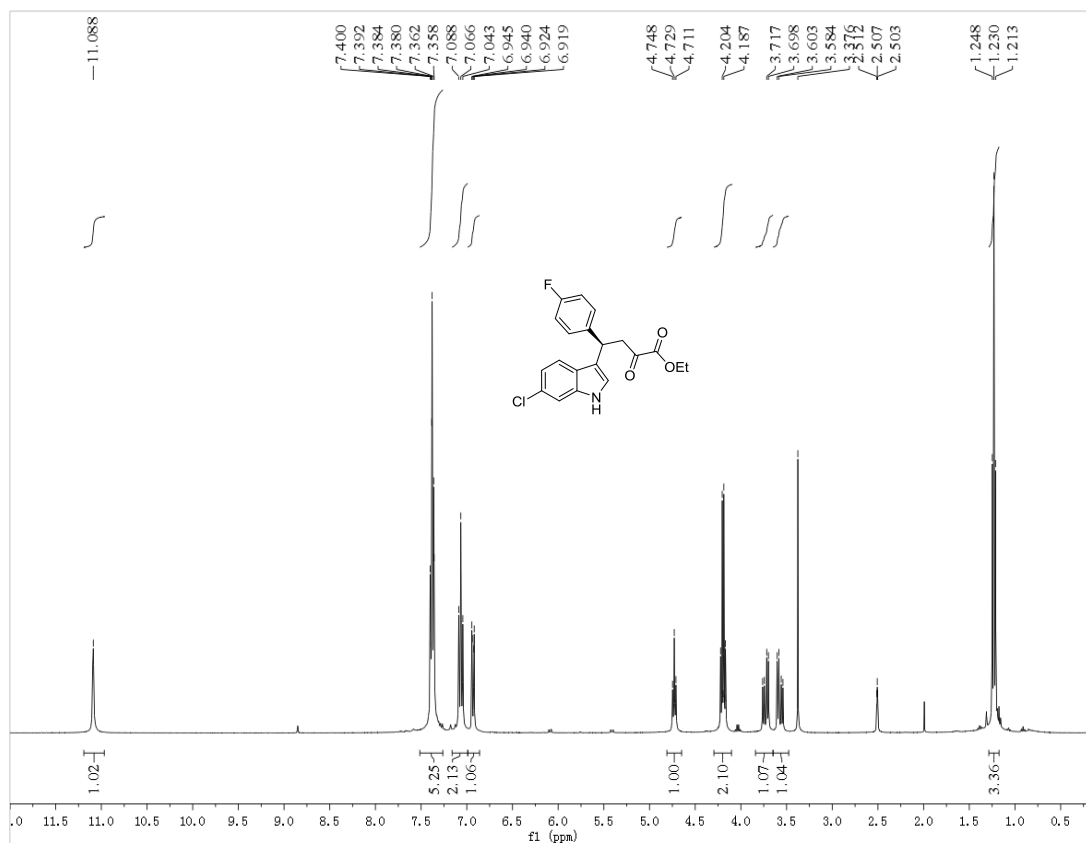
¹H and ¹³C NMR of 8h



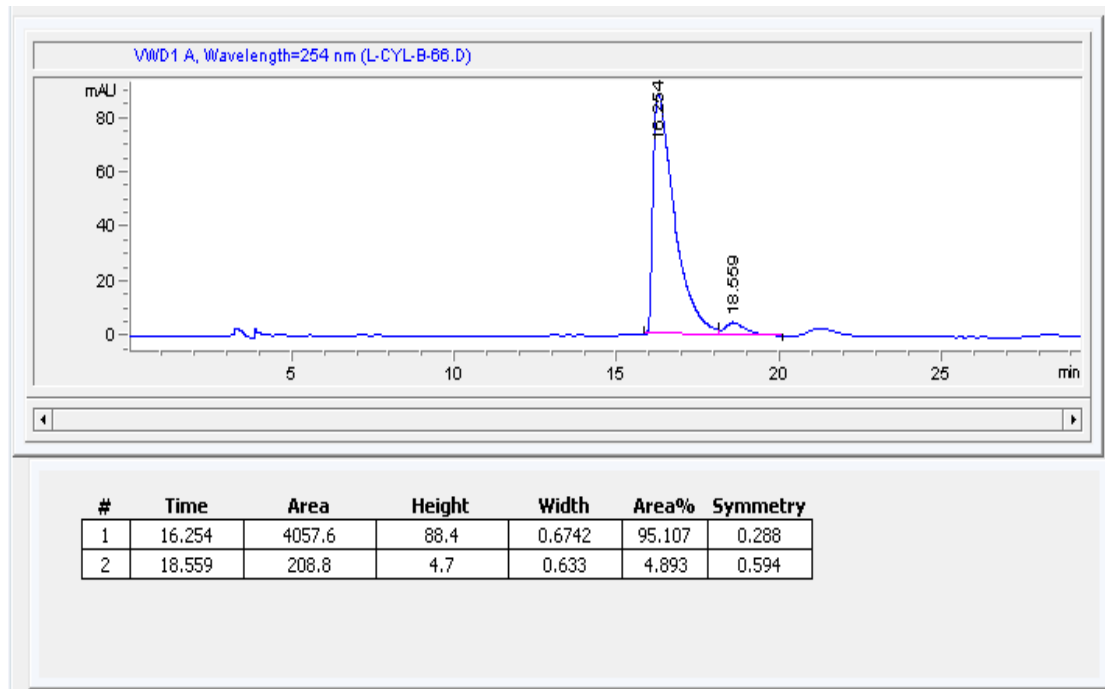
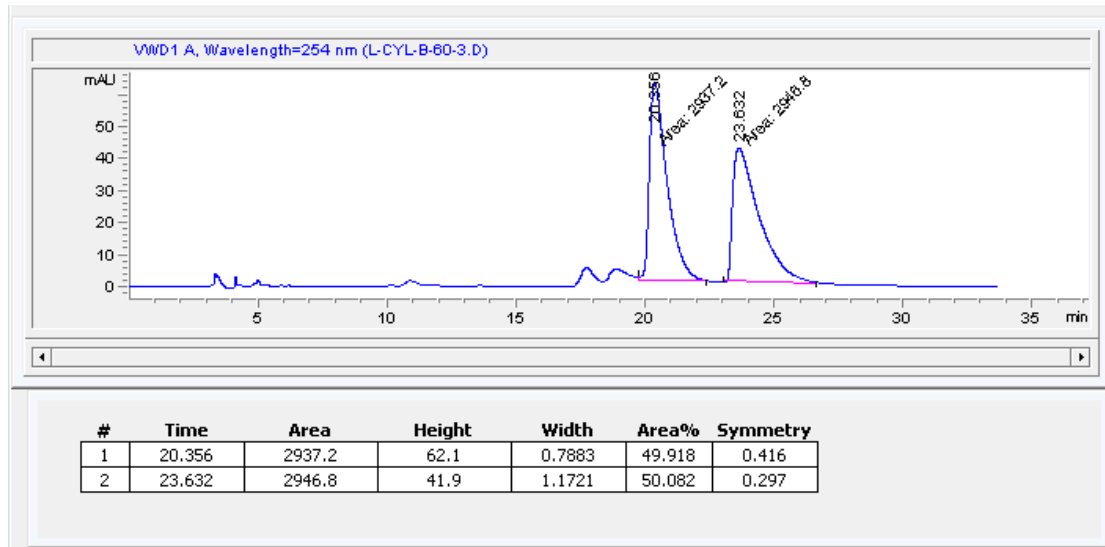
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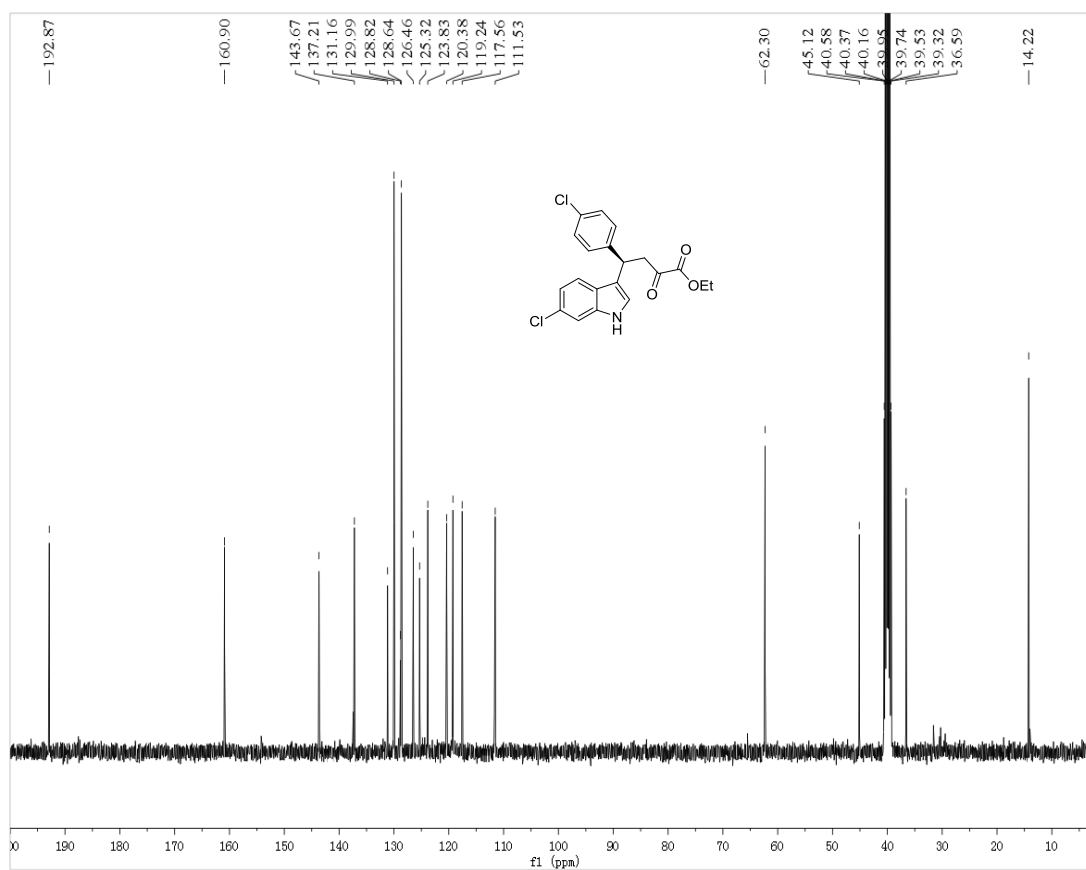
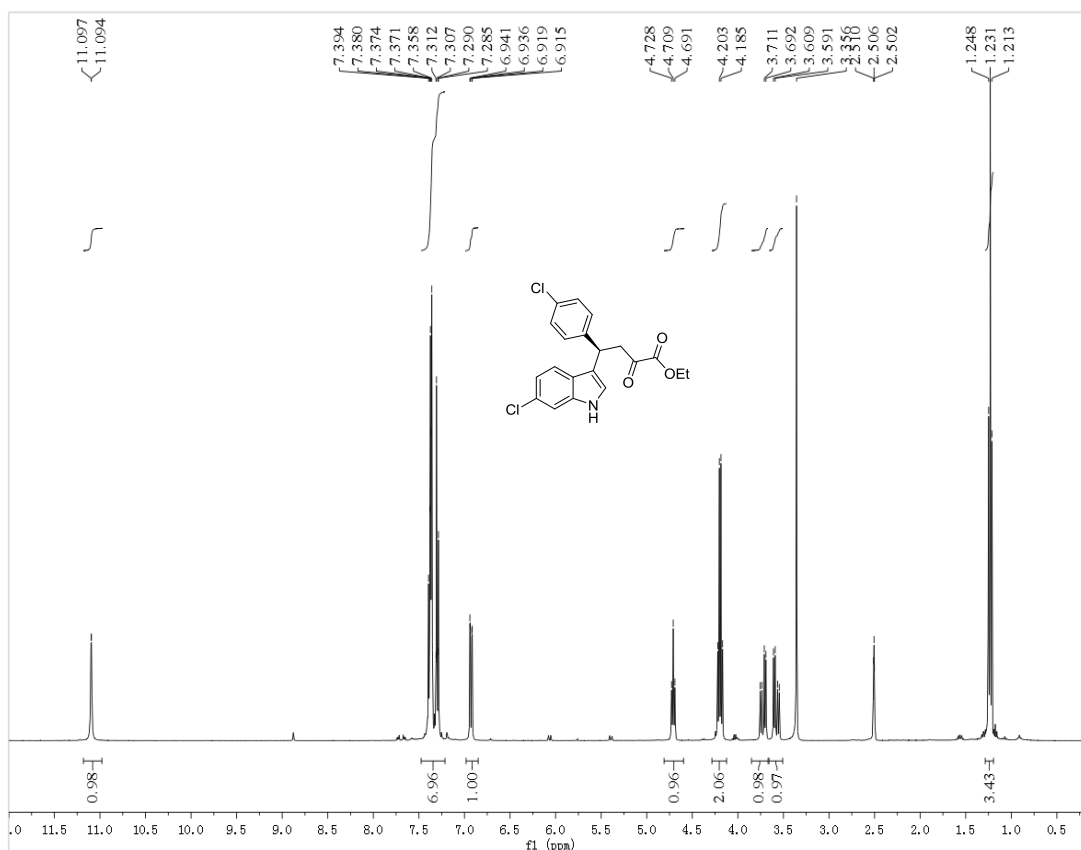
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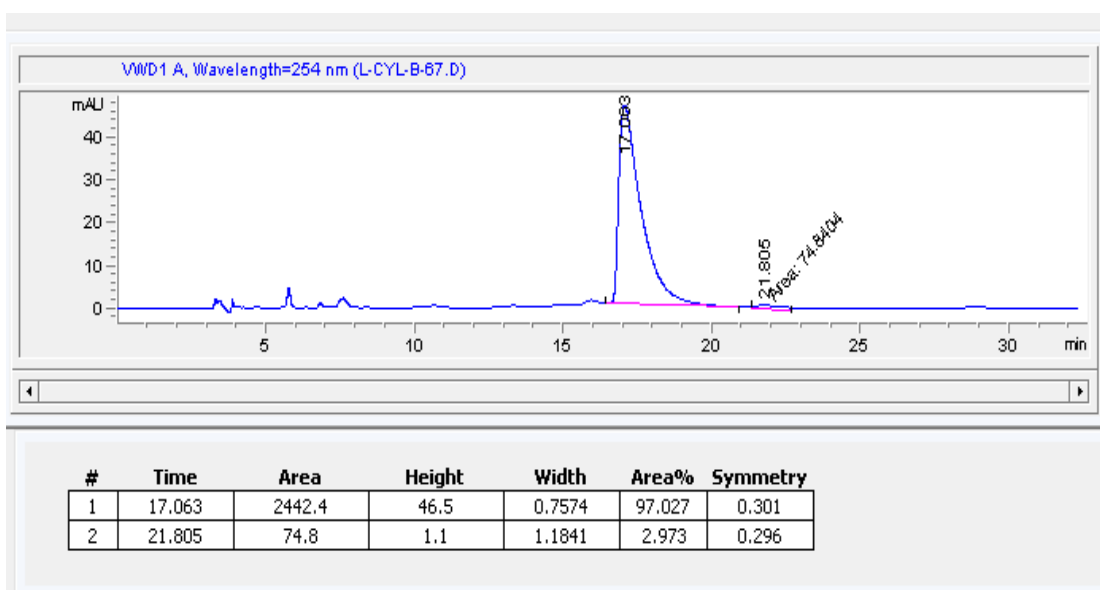
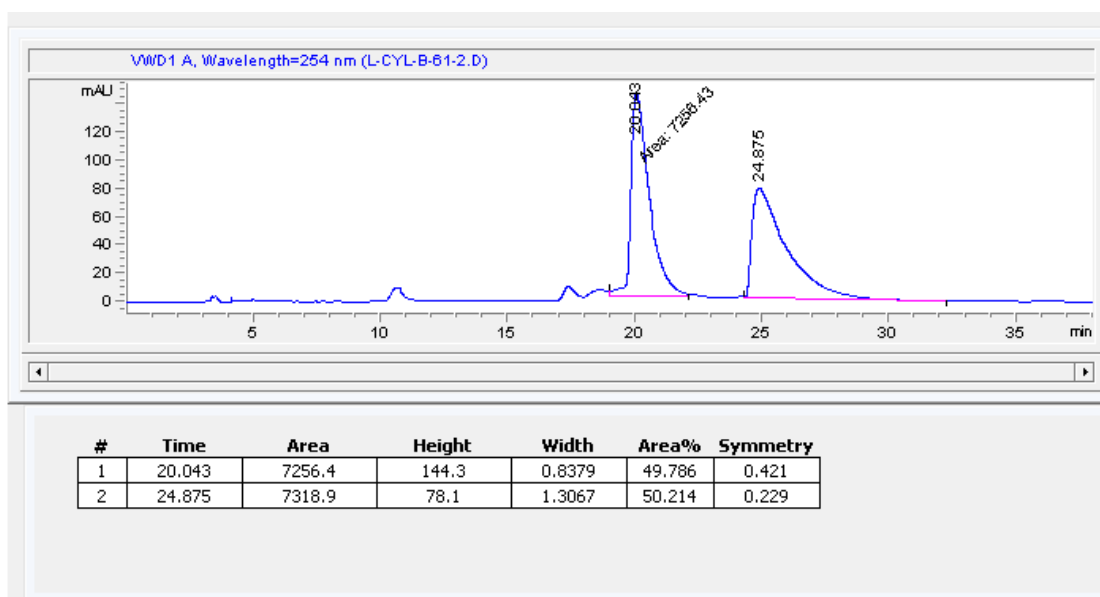
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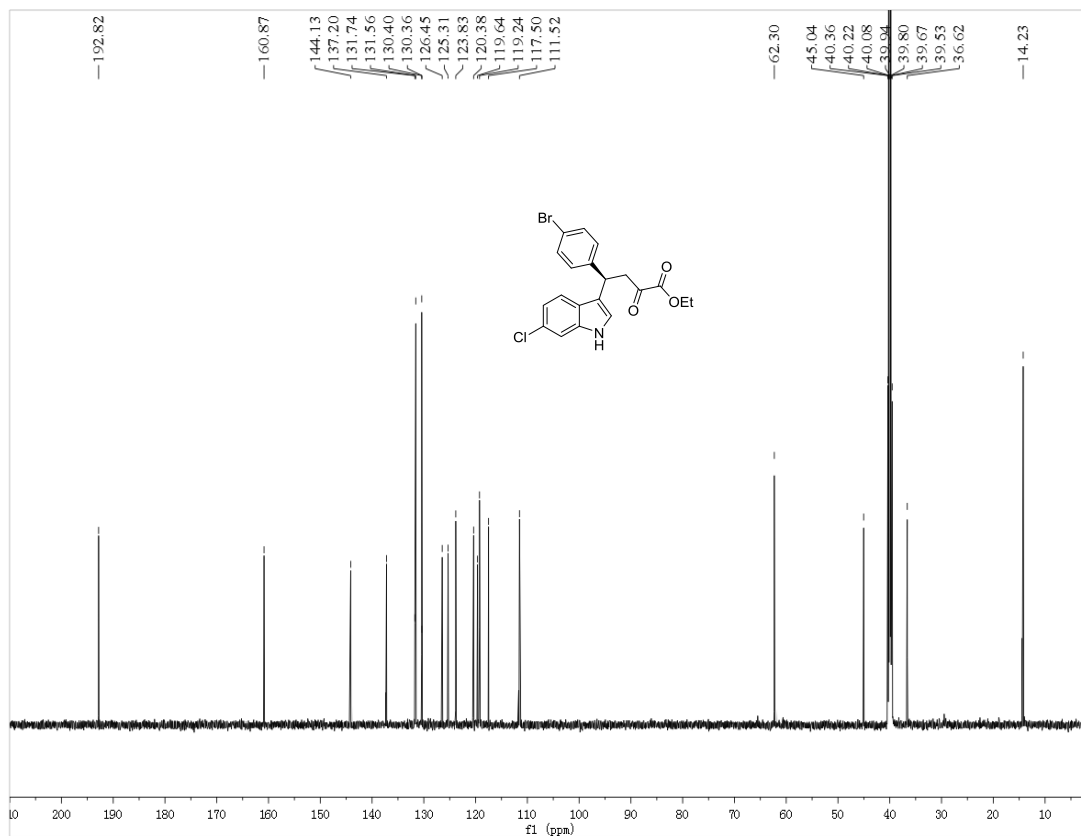
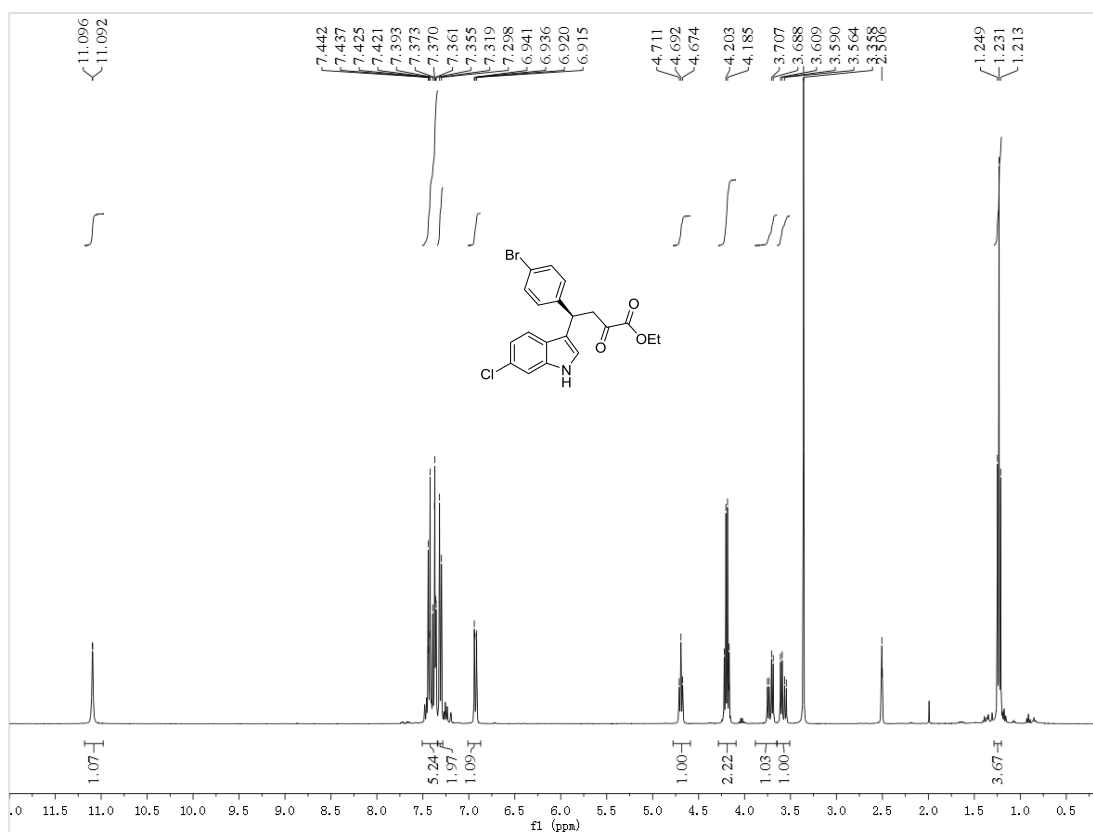
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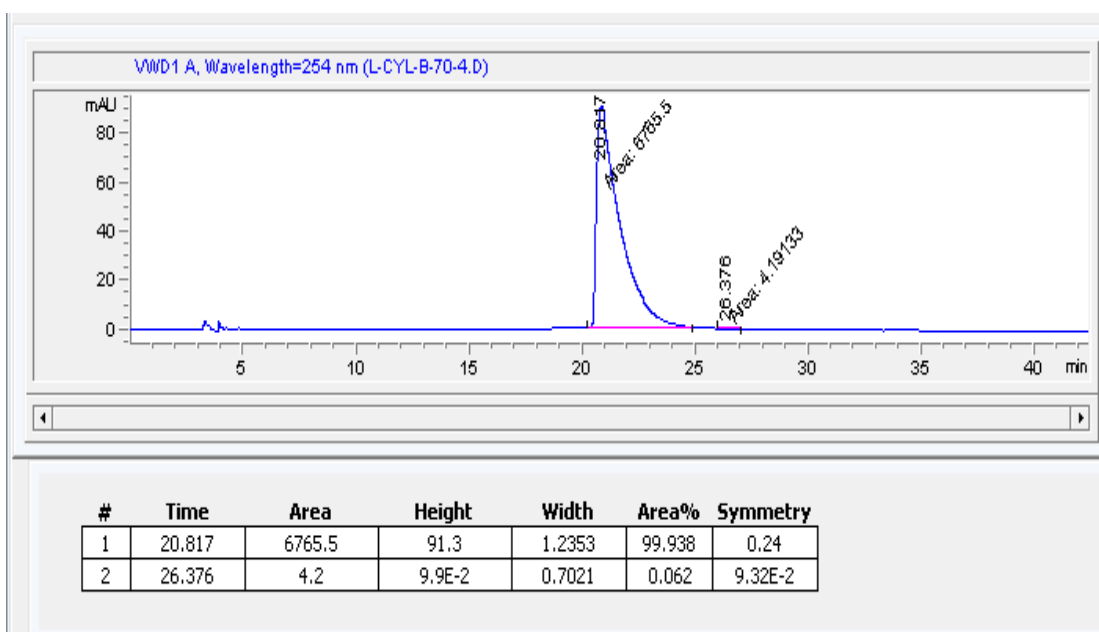
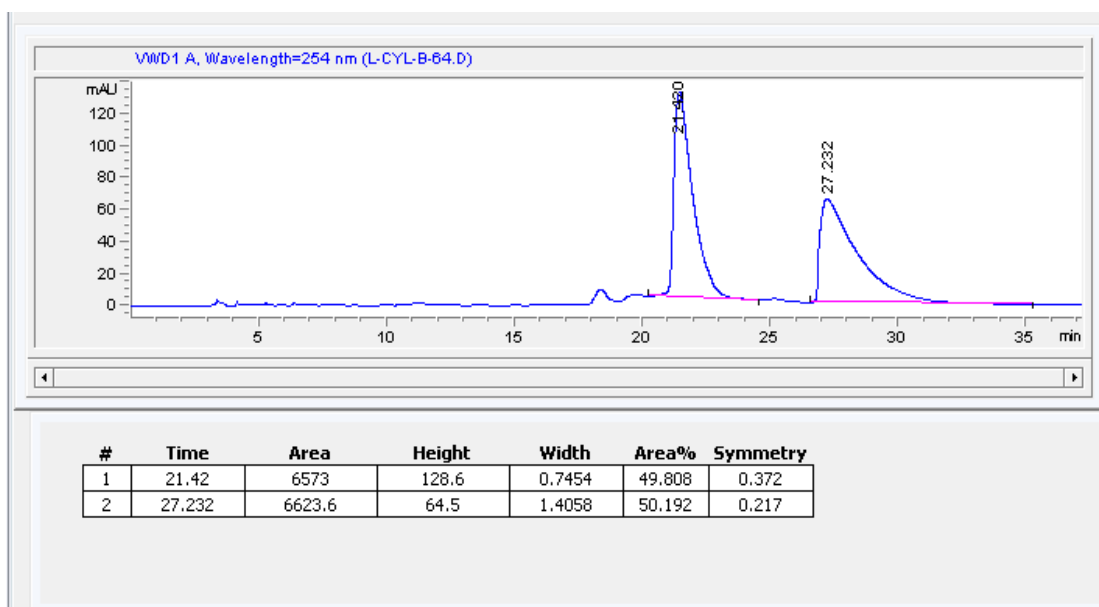
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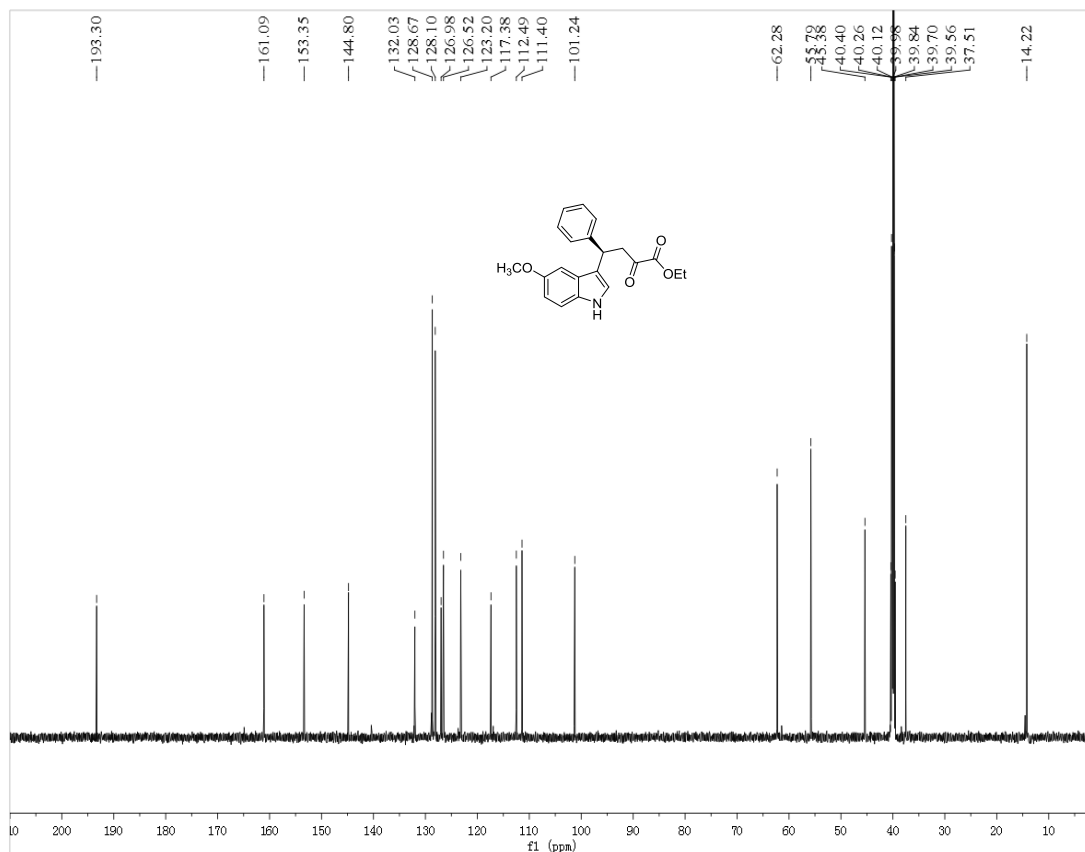
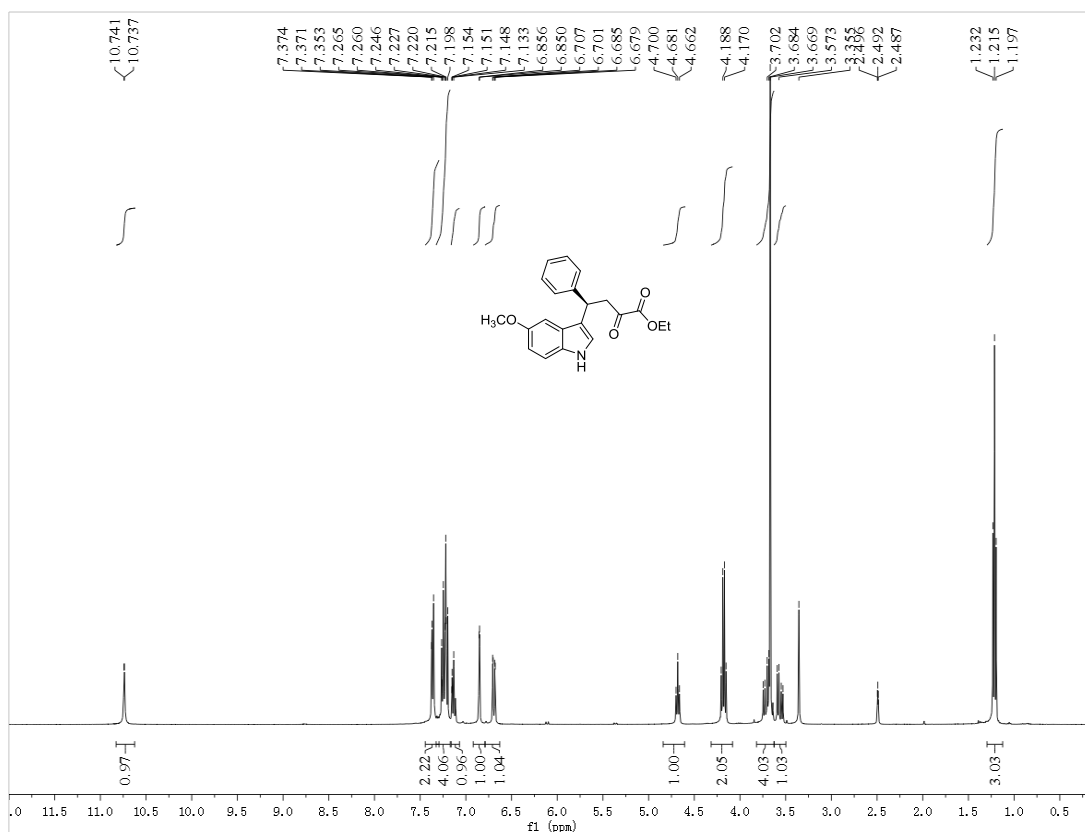
^1H and ^{13}C NMR of 8k



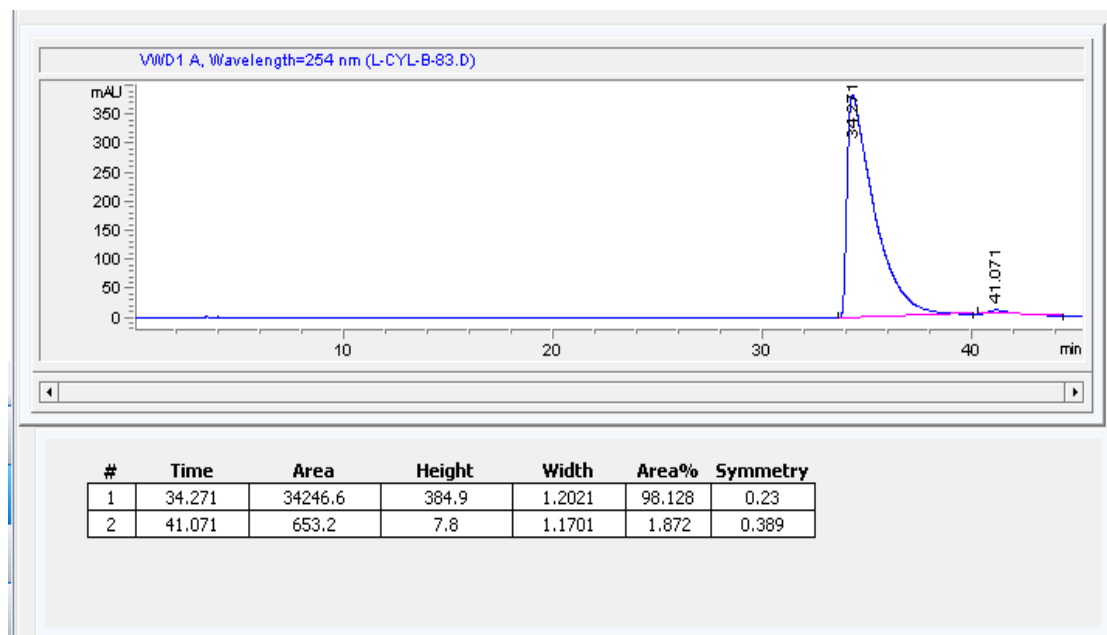
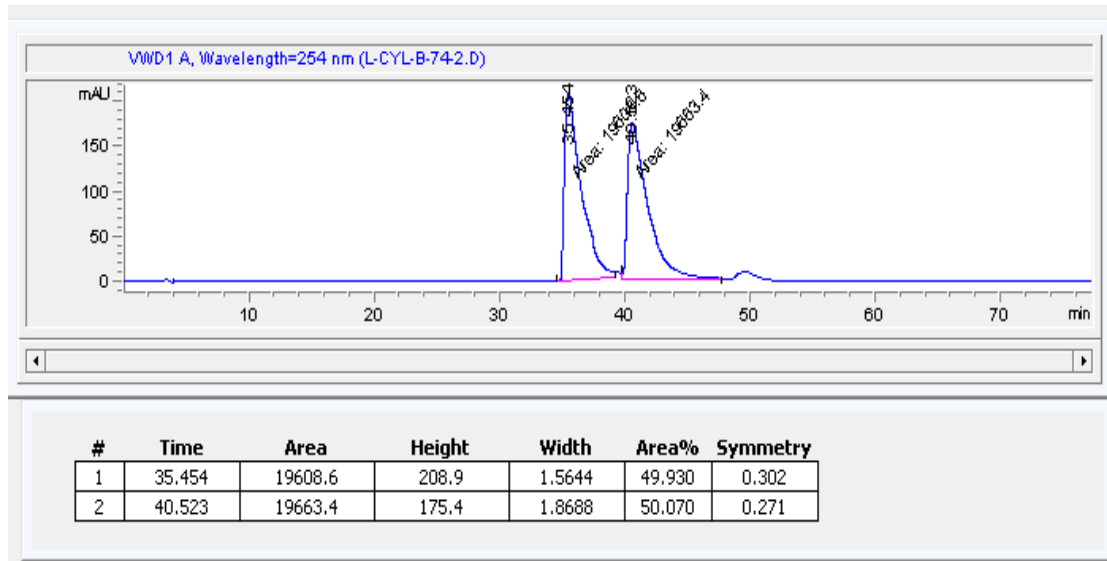
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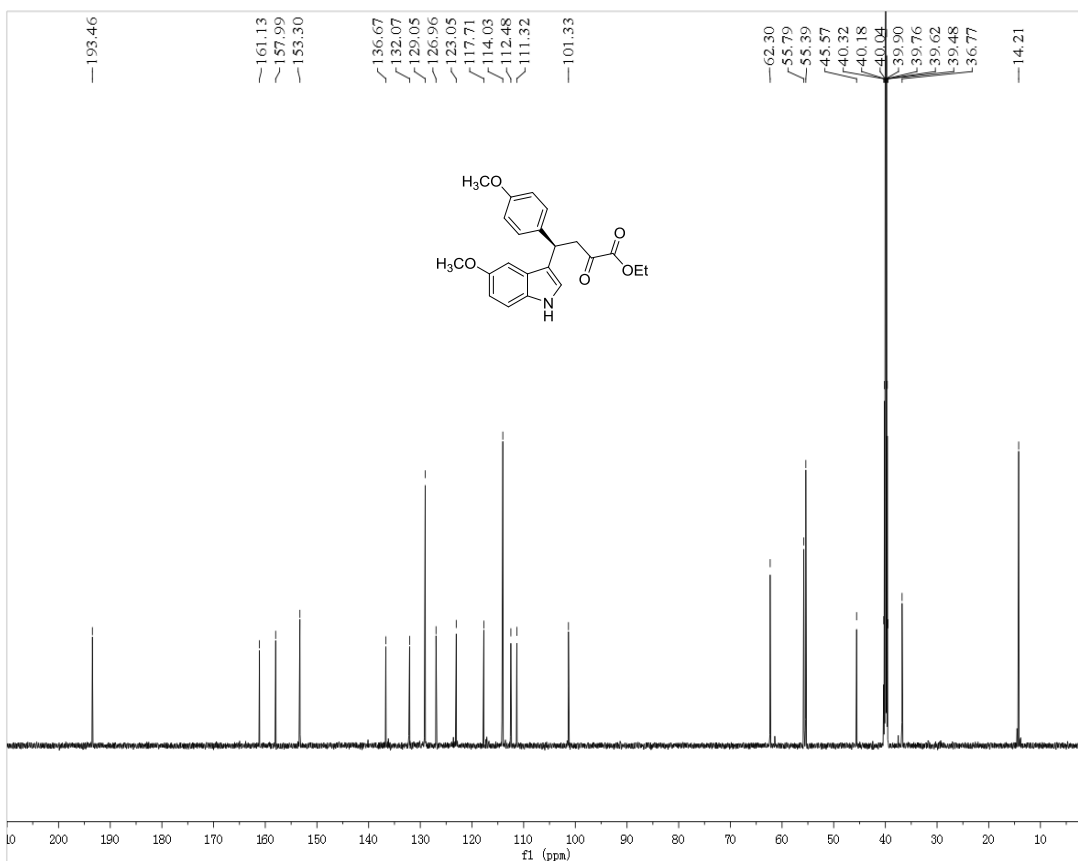
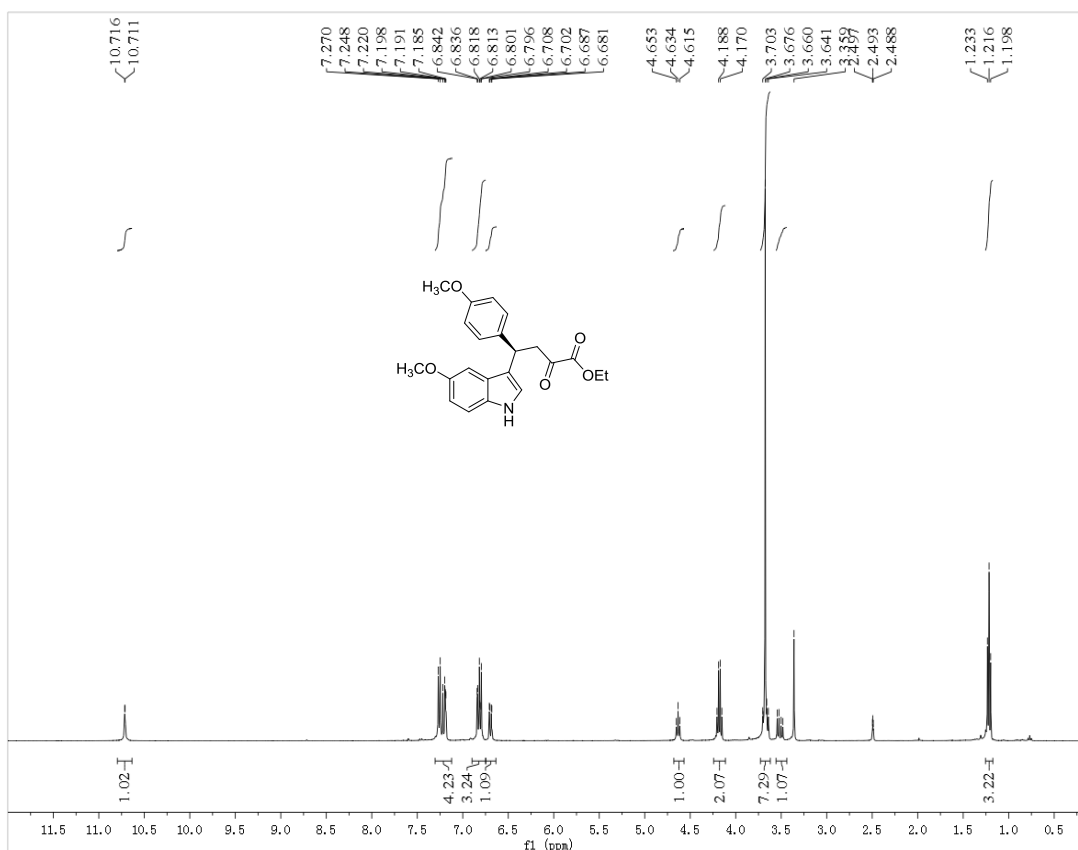
^1H and ^{13}C NMR of 81



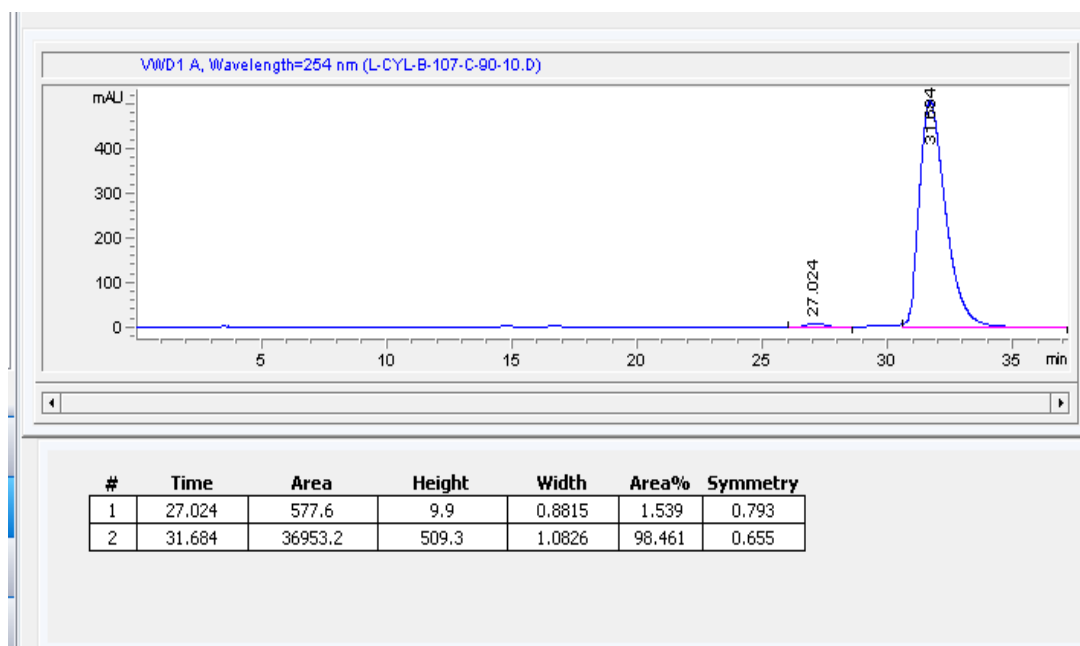
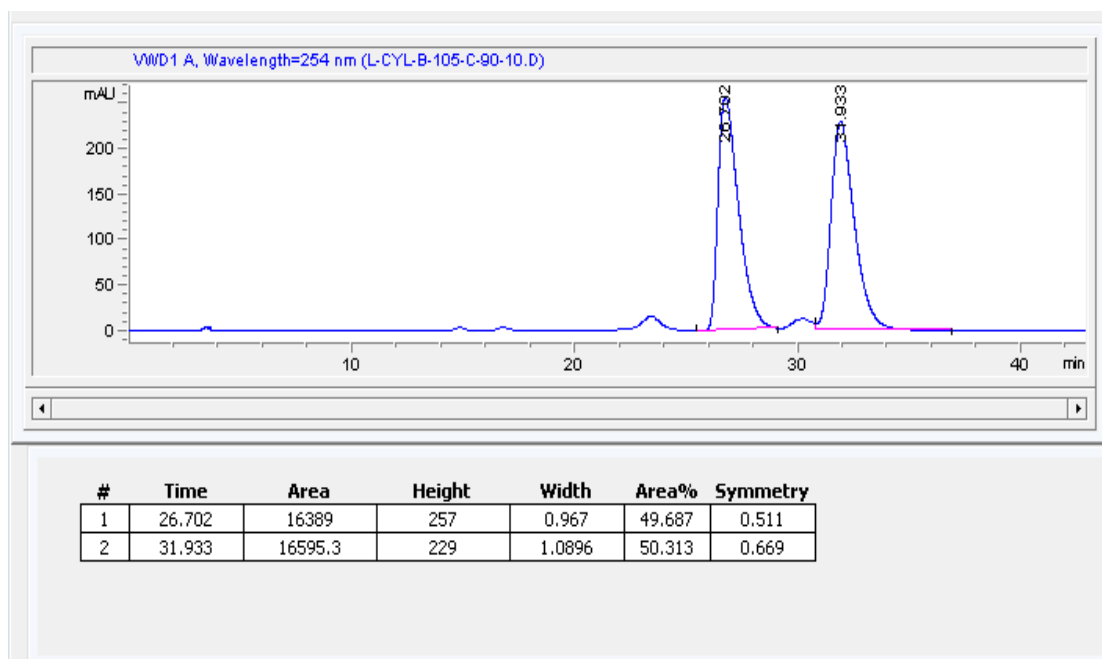
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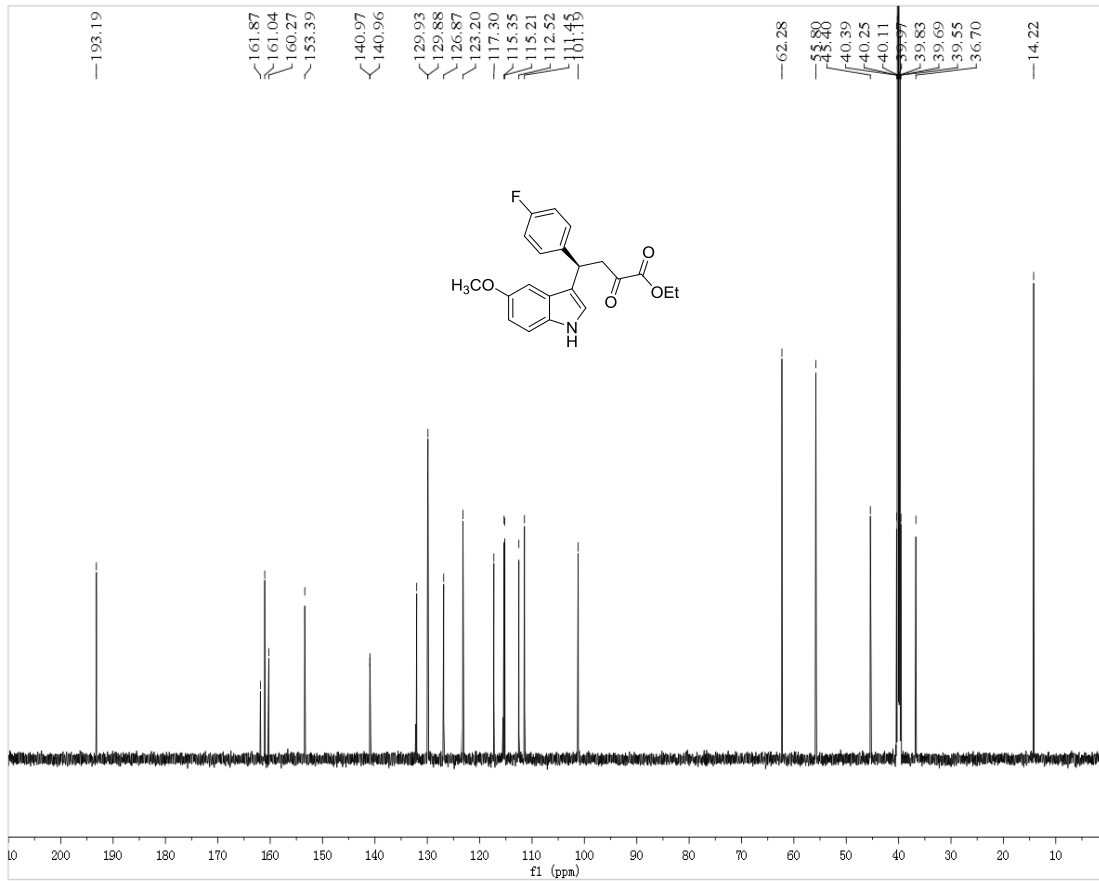
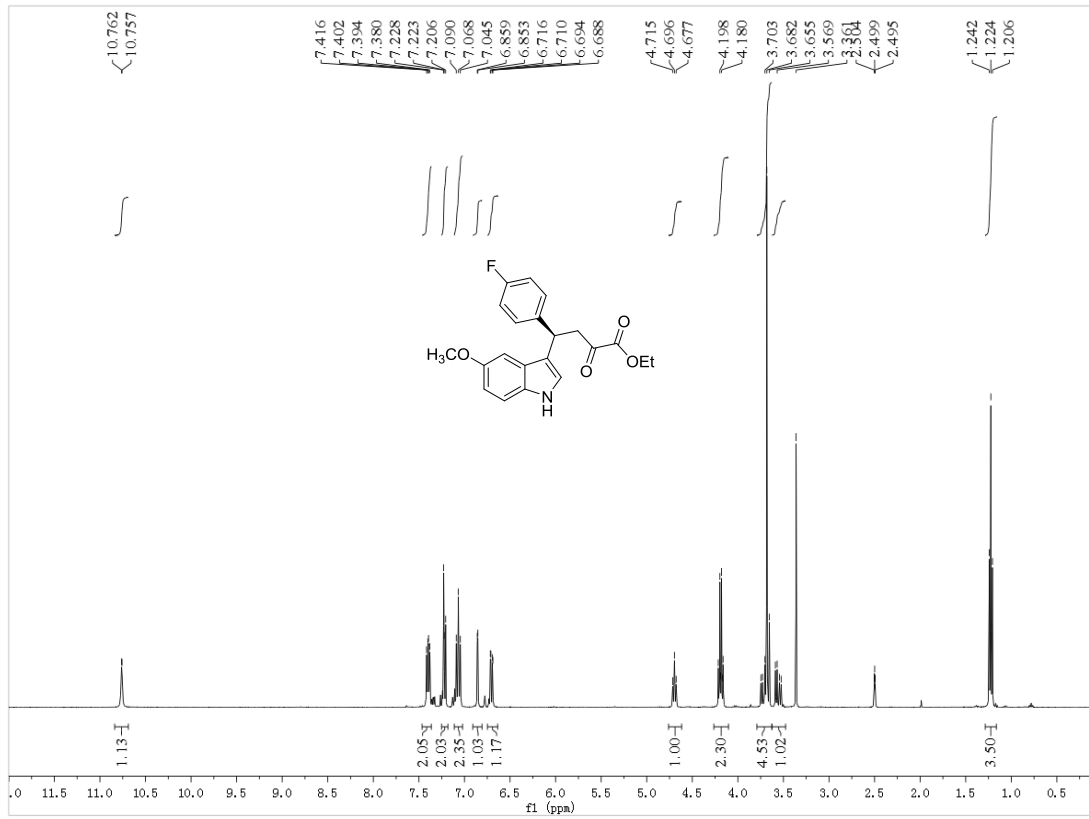
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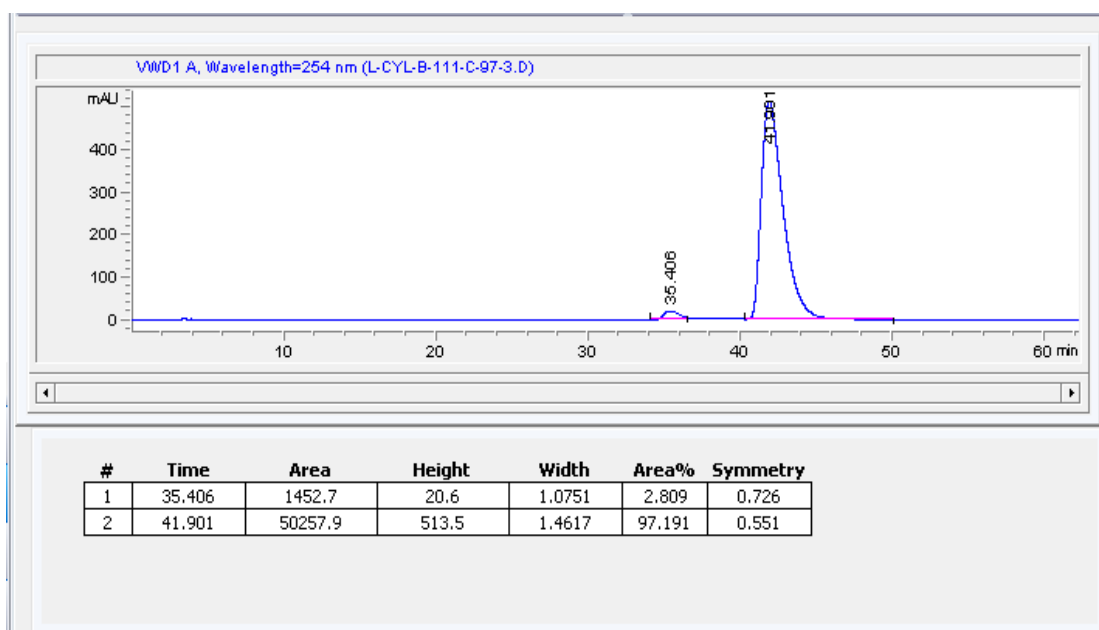
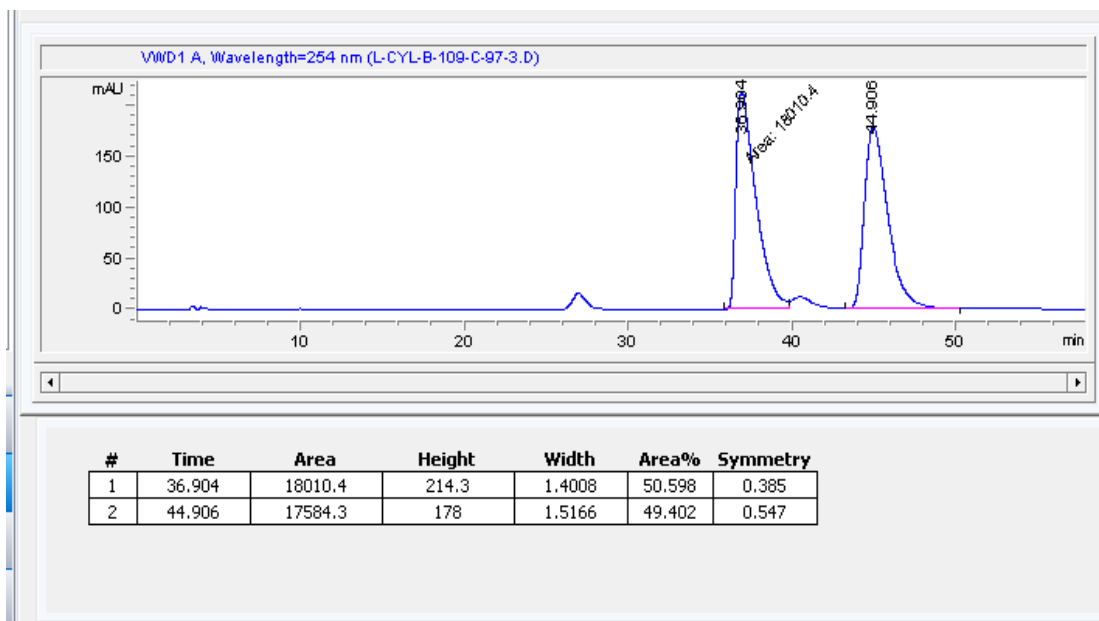
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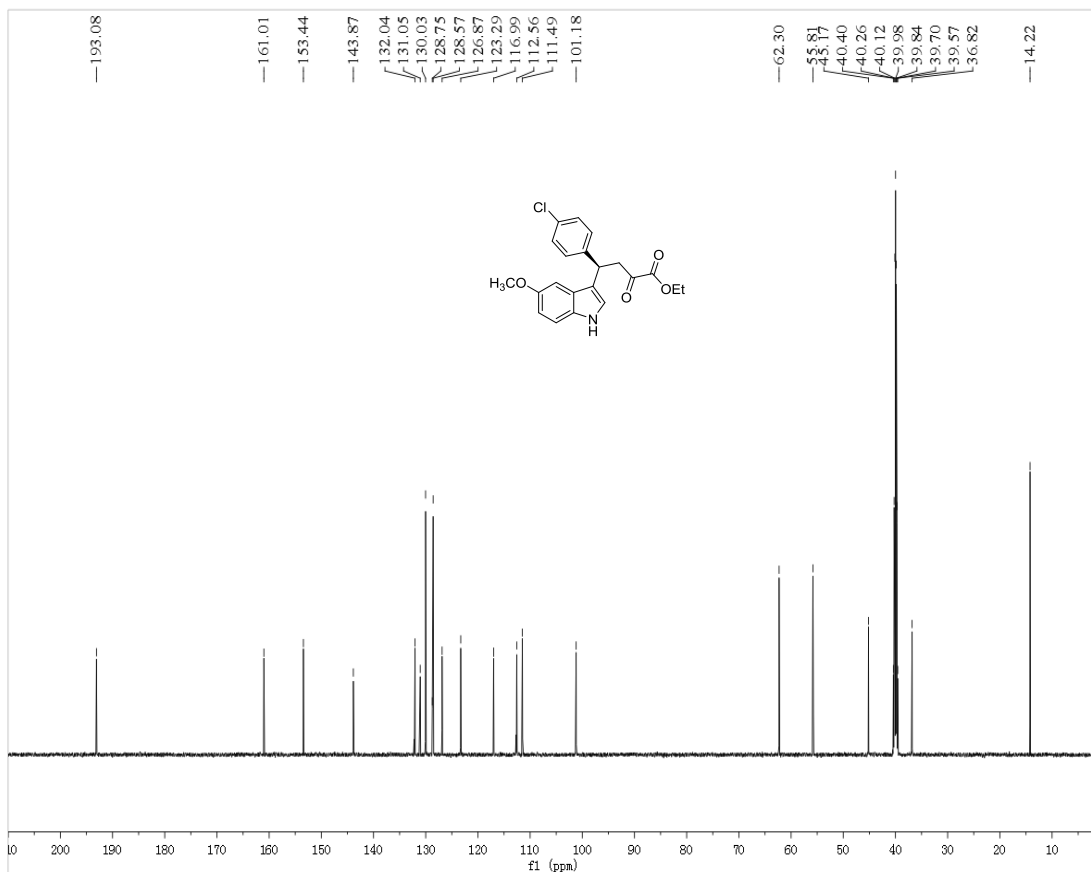
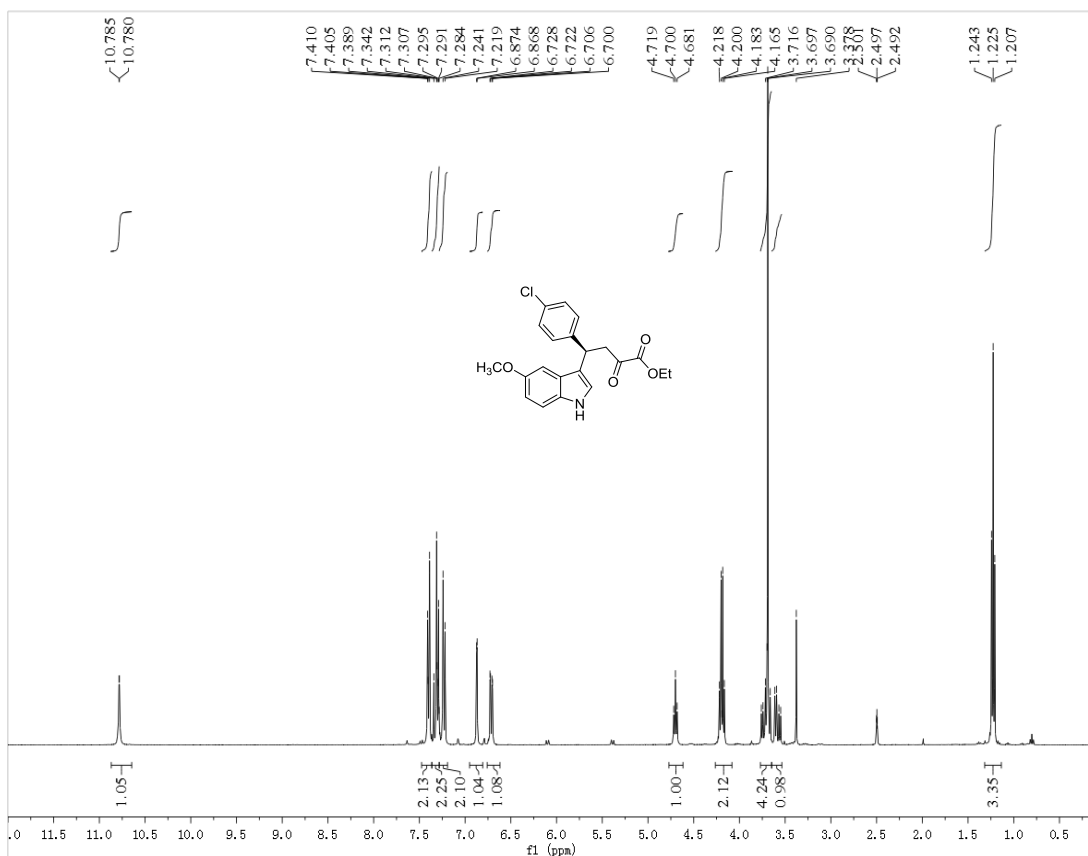
¹H and ¹³C NMR of 8n



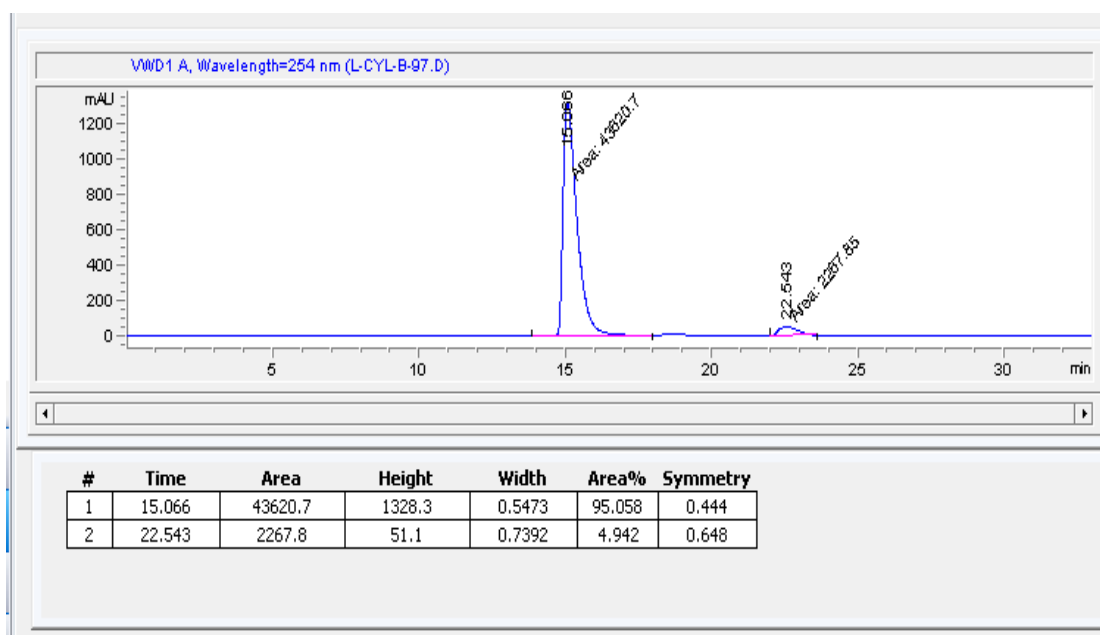
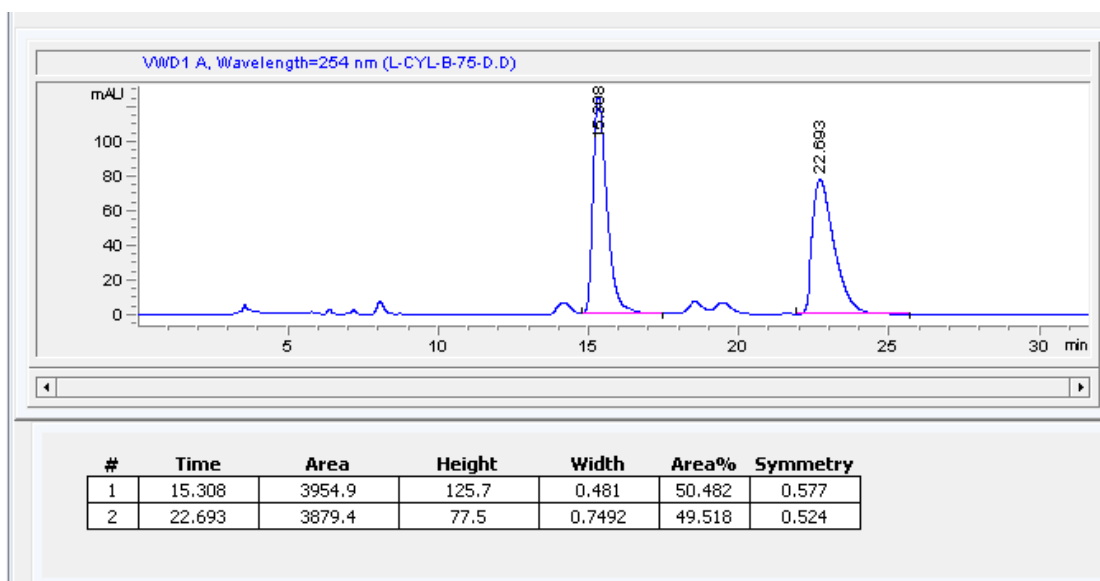
HPLC of 8n



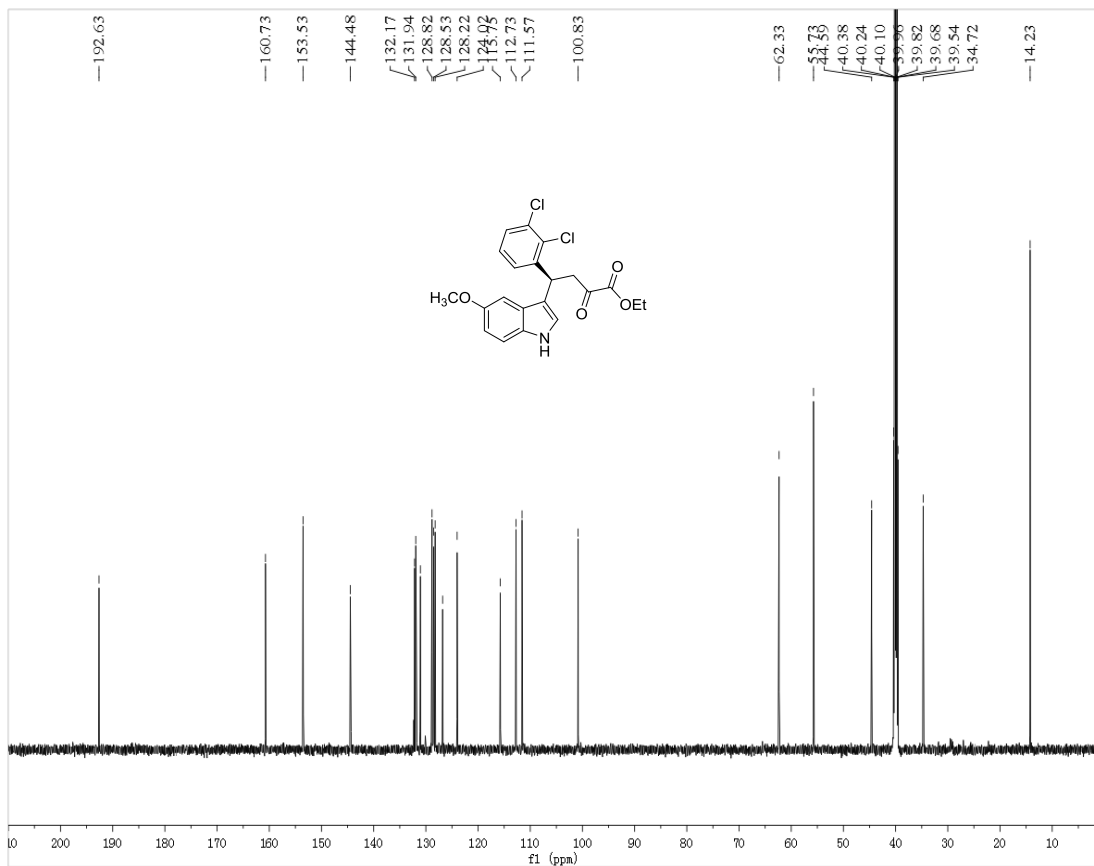
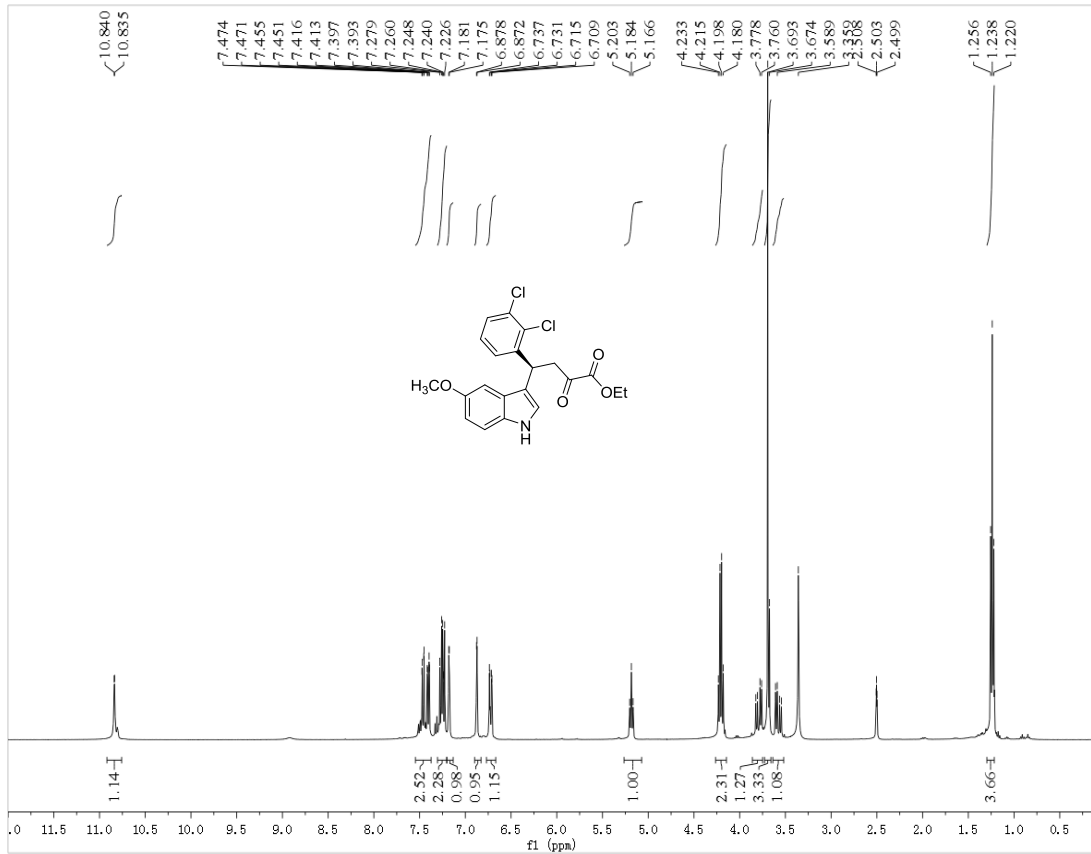
^1H and ^{13}C NMR of 8o



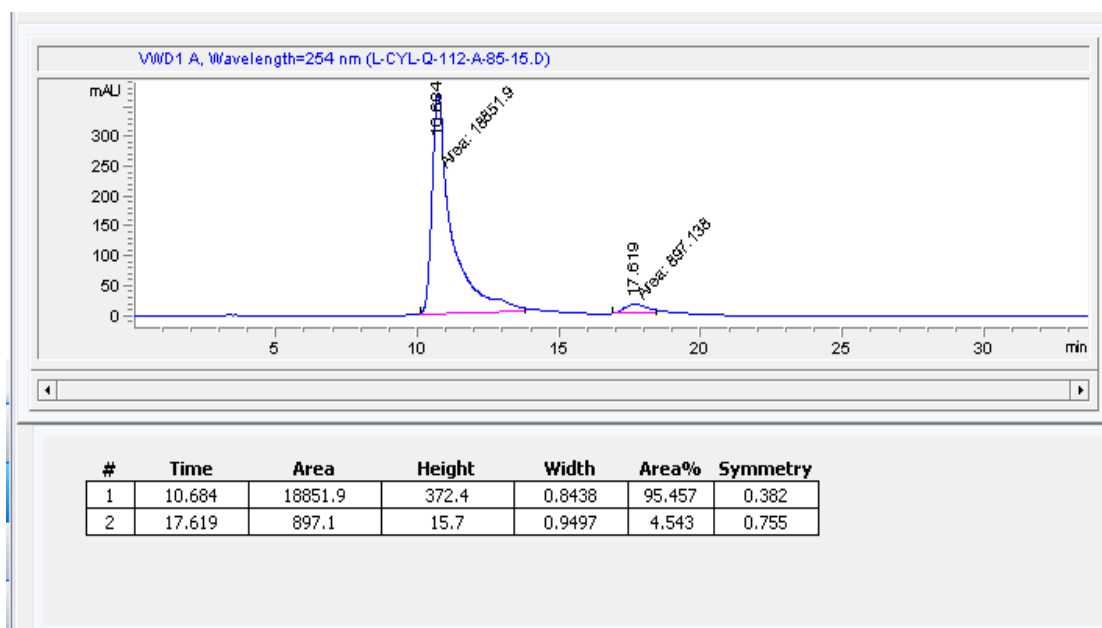
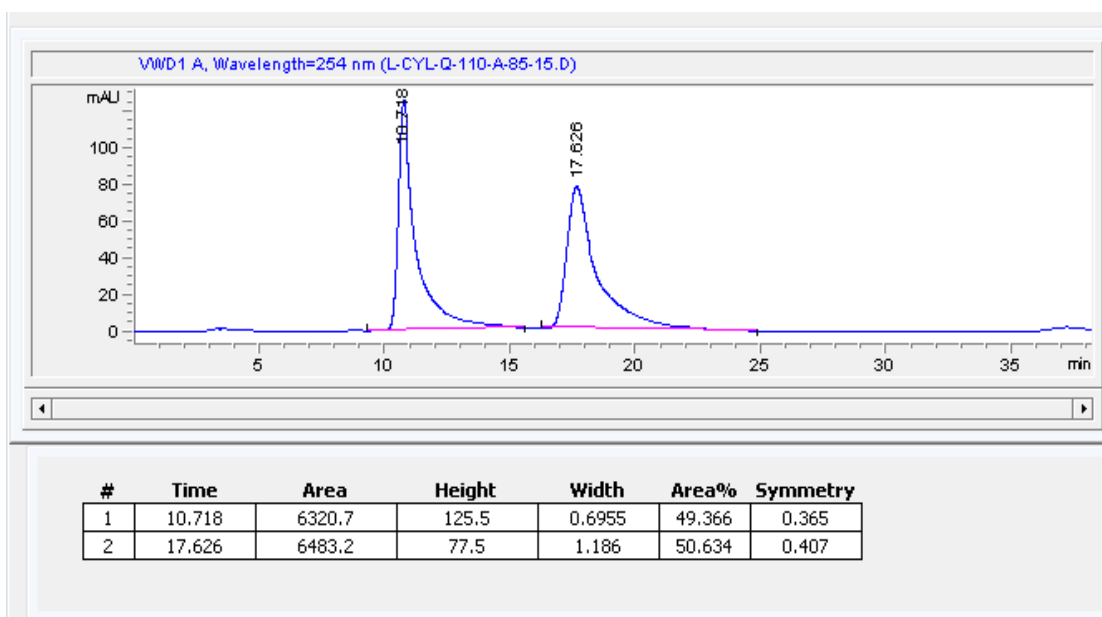
HPLC of 8o



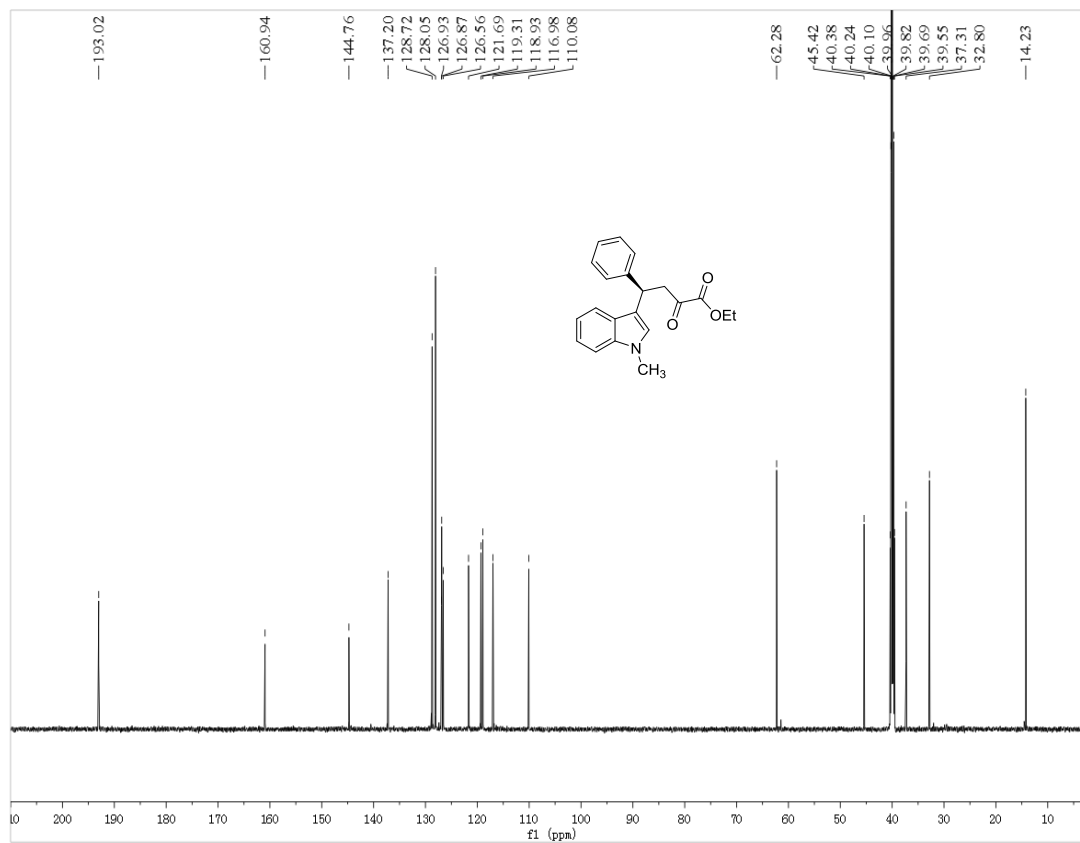
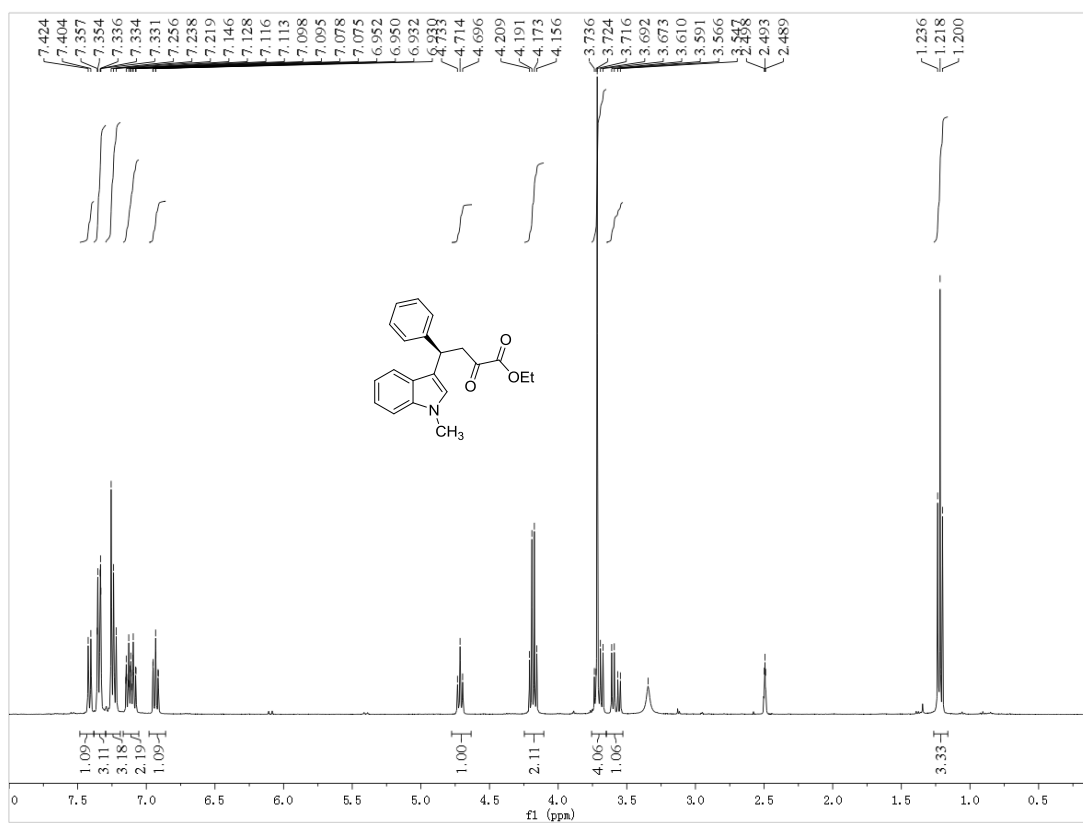
¹H and ¹³C NMR of 8p



HPLC of 8p



^1H and ^{13}C NMR of 8q



HPLC of 8q

