Supporting Information

Sustainable synthesis of long-acting local anesthetics ropivacaine and levobupivacaine under batch and continuous flow via asymmetric hydrogenation

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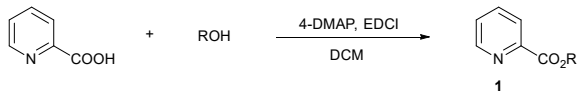
1. General Information

All commercially available reagents were used without further purification. Tetrahydrofuran and toluene were dried with sodium chips and indicated by benzophenone, other anhydrous solvents were purchased from Aladdin. Chromatography was conducted by using 300−400 mesh silica gel. All new compounds were characterized by NMR spectroscopy, high resolution mass spectrometry (HRMS), FT-IR spectroscopy and melting point (if solids). NMR spectra were recorded on a 400 MHz NMR spectrometer. Reference values for residual solvents were taken as δ = 7.26 ($CDCl_3$) ppm, δ = 2.50 (DMSO-d_6) ppm for ^{1}H NMR and δ = 77.16 ($CDCl_3$) ppm, δ = 49.00 (MeOH-d_4) ppm, δ = 39.52 (DMSO-d_6) ppm for ^{13}C NMR. Coupling constants (*J*) were given in Hz and multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and dd = double doublet etc. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF Q III by the ESI method. Melting points (m.p.) were recorded on an SRS-optic melting point apparatus. Chiral HPLC was performed using a Daicel Chiralcel IC column, Chiralcel OJ-H column, Chiralcel AD-H column and Chiralcel OD-H column.

2. Experimental Procedures

2.1 General Procedures for Picolinate esters

2-ester–substituted pyridines were synthesized from 2-carboxypyridines with the corresponding alcohols via esterification. Methyl picolinate **1a** was commercially available.



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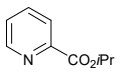
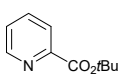
picolinic acid (500.0 mg, 4.1 mmol, 1.0 equiv.), 4-DMAP (248.1 mg, 2.0 mmol, 0.5 equiv.) and EDCI (1.2 g, 6.1 mmol, 1.5 equiv.) were dissolved in dichloromethane (15 mL) and stirred at 0 ℃ for 15 min. Alcohol (4.5 mmol, 1.1 equiv.) was added to the reaction mixture that was then stirred at 25 ℃ for 12 h. Water was added and the solution was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 100:1) to give the desired products.



Isopropyl picolinate (1b): 590.4 mg, 88% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 – 8.72 (m, 1H), 8.09 – 8.06 (m, 1H), 7.81 – 7.62 (m, 1H), 7.43 – 7.40 (m, 1H), 5.35 – 5.26 (m, 1H), 1.38 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.8, 149.9, 148.7, 136.9, 126.7, 125.1, 69.6, 21.9. HRMS (ESI) m/z calcd for $C_9H_{11}NNaO_2$ $[M + Na]^+$: 188.0682, found: 188.0680.



***tert*-Butyl picolinate (1c):** 727.9 mg, 93% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.75 – 8.73 (m, 1H), 8.05 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.83 – 7.78 (m, 1H), 7.44 – 7.41 (m, 1H),

1.64 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.4, 149.9, 149.8, 136.9, 126.5, 124.9, 82.4, 28.3. HRMS (ESI) m/z calcd for $C_{10}H_{13}NNaO_2$ $[M + Na]^+$: 202.0838, found: 202.0837.

Cyclopropylmethyl picolinate (1d): 618.9 mg, 86% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (t, *J* = 3.6 Hz, 1H), 8.10 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.44 – 7.40 (m, 1H), 4.20 (d, *J* = 7.6 Hz, 2H), 1.31 – 1.26 (m, 1H), 058 – 0.56 (m, 2H), 0.39 – 0.29 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.4, 149.9, 148.4, 137.0, 126.8, 125.2, 70.8, 10.0, 3.6. HRMS (ESI) m/z calcd for $C_{10}H_{11}NNaO_2$ $[M + Na]^+$: 200.0682, found: 200.0684.

Cyclopentylmethyl picolinate (1e): 758.6 mg, 91% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.78 – 8.68 (m, 1H), 8.07 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.47 – 7.38 (m, 1H), 4.27 (d, *J* = 7.6 Hz, 2H), 2.42 – 2.34 (m, 1H), 1.87 – 1.72 (m, 2H), 1.66 – 1.50 (m, 4H), 1.39 – 1.25 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.3, 150.0, 148.4, 137.0, 126.8, 125.1, 69.8, 38.7, 29.5, 25.3. HRMS (ESI) m/z calcd for $C_{12}H_{15}NNaO_2$ $[M + Na]^+$: 228.0995, found: 228.0998.

Cyclohexylmethyl picolinate (1f): 801.5 mg, 90% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 – 8.71 (m, 1H), 8.07 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.84 – 7.74 (m, 1H), 7.46 – 7.38 (m, 1H), 4.18 (d, *J* = 4.0 Hz, 2H), 1.86 – 1.58 (m, 6H), 1.28 – 0.93 (m, 5H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.3, 150.0, 148.4, 136.9, 126.8, 125.1, 70.9, 37.1, 29.8, 26.4, 25.7. HRMS (ESI) m/z calcd for $C_{13}H_{17}NNaO_2$ $[M + Na]^+$: 242.1151, found: 242.1149.

Benzyl picolinate (1g): 831.4 mg, 96% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.76 – 8.74 (m, 1H), 8.17 – 8.06 (m, 1H), 7.87 – 7.72 (m, 1H), 7.53 – 7.24 (m, 6H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.0, 149.9, 148.0, 137.0, 135.6, 128.6, 128.5, 128.4, 126.9, 125.2, 67.5. HRMS (ESI) m/z calcd for $C_{13}H_{11}NNaO_2$ $[M + Na]^+$: 236.0682, found: 236.0681.

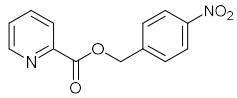
4-(Trifluoromethyl)benzyl picolinate (1h): 993.7 mg, 87% yield, white solid, m.p. = 70.2 – 72.4 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 – 8.61 (m, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.50 – 7.45 (m, 4H), 7.35 – 7.32 (m, 1H), 5.36 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.7, 149.8, 147.5, 139.5, 136.9, 130.2 (q, *J* = 32.2 Hz), 128.3, 127.0, 125.4 (q, *J* = 3.7 Hz), 125.2, 123.9 (q, *J* = 270.5 Hz), 66.2. HRMS (ESI) m/z calcd for $C_{14}H_{10}F_3NNaO_2$ $[M + Na]^+$: 304.0556, found: 304.0553.

4-Cyanobenzyl picolinate (1i): 822.5 mg, 85% yield, white solid, m.p. = 94.0 – 95.4 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.77 – 8.69 (m, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.64 – 7.61 (m, 2H), 7.57 – 7.52 (m, 2H), 7.49 – 7.46 (m, 1H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.8, 150.0, 147.5, 140.9, 137.2, 132.4, 128.6, 127.3, 125.4, 118.5, 112.1, 66.2. HRMS (ESI) m/z calcd for $C_{14}H_{10}N_2NaO_2$ $[M + Na]^+$: 261.0634, found: 261.0634.

4-(Methoxycarbonyl)benzyl picolinate (1j): 980.6 mg, 89% yield, white solid, m.p. = 60.3 – 62.6 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 – 8.72 (m, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.41 (m, 1H), 5.46 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz,

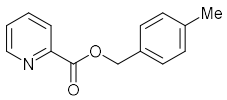
Chloroform-*d*) δ 166.7, 164.9, 150.0, 147.7, 140.7, 137.1, 130.1, 129.9, 128.0, 127.1, 125.3, 66.7, 52.2. HRMS (ESI) m/z calcd for $C_{15}H_{13}NNaO_4$ $[M + Na]^+$: 294.0737, found: 294.0740.

4-Nitrobenzyl picolinate (1k): 943.9 mg, 90% yield, white solid, m.p. = 126.1 – 127.8 ℃. ^{1}H NMR



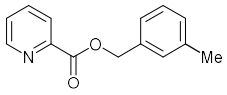
(400 MHz, Chloroform-*d*) δ 8.84 – 8.75 (m, 1H), 8.24 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.91 – 7.87 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.58 – 7.49 (m, 1H), 5.56 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.8, 150.1, 147.8, 147.5, 142.9, 137.2, 128.7, 127.4, 125.5, 123.9, 65.9. HRMS (ESI) m/z calcd for $C_{13}H_{10}N_2NaO_4$ $[M + Na]^+$: 281.0533, found: 281.0535.

4-Methylbenzyl picolinate (1l): 784.6 mg, 85% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-



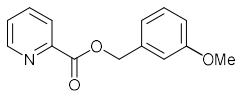
d) δ 8.71 – 8.59 (m, 1H), 8.02 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.41 – 7.24 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.32 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.0, 149.9, 148.1, 138.3, 137.0, 132.7, 129.3, 128.8, 126.9, 125.2, 67.5, 21.2. HRMS (ESI) m/z calcd for $C_{14}H_{13}NNaO_2$ $[M + Na]^+$: 250.0838, found: 250.0834.

3-Methylbenzyl picolinate (1m): 803.0 mg, 87% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-



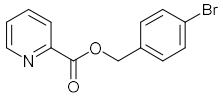
d) δ 8.68 – 8.66 (m, 1H), 8.03 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.39 – 7.32 (m, 1H), 7.20 – 7.16 (m, 3H), 7.05 (d, *J* = 7.2 Hz, 1H), 5.33 (s, 2H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.0, 150.0, 148.1, 138.3, 137.0, 135.5, 129.4, 129.2, 128.5, 126.9, 125.7, 125.3, 67.6, 21.4. HRMS (ESI) m/z calcd for $C_{14}H_{13}NNaO_2$ $[M + Na]^+$: 250.0838, found: 250.0842.

3-Methoxybenzyl picolinate (1n): 879.3 mg, 89% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-



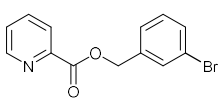
d) δ 8.71 – 8.58 (m, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.77 – 7.67 (m, 1H), 7.44 – 7.31 (m, 1H), 7.21 – 7.17 (m, 1H), 7.02 – 6.91 (m, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 5.33 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.0, 159.7, 149.9, 147.9, 137.1, 137.0, 129.7, 127.0, 125.3, 120.7, 114.0, 114.0, 67.3, 55.2. HRMS (ESI) m/z calcd for $C_{14}H_{13}NNaO_3$ $[M + Na]^+$: 266.0788, found: 266.0784.

4-Bromobenzyl picolinate (1o): 1.0 g, 87% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ



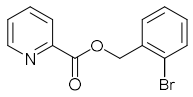
8.71 – 8.64 (m, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.21 (m, 1H), 7.42 – 7.38 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.31 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.0, 150.0, 147.8, 137.1, 134.7, 131.8, 130.3, 127.1, 125.3, 122.5, 66.7. HRMS (ESI) m/z calcd for $C_{13}H_{10}BrNNaO_2$ $[M + Na]^+$: 313.9787, found: 313.9786.

3-Bromobenzyl picolinate (1p): 1.0 g, 85% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ



8.72 – 8.62 (m, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.55 (s, 1H), 7.43 – 7.30 (m, 3H), 7.18 – 7.14 (m, 1H), 5.33 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.9, 150.0, 147.8, 137.9, 137.1, 131.6, 131.5, 130.3, 127.2, 127.2, 125.4, 122.7, 66.6. HRMS (ESI) m/z calcd for $C_{13}H_{10}BrNNaO_2$ $[M + Na]^+$: 313.9787, found: 313.9792.

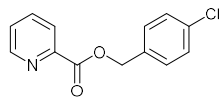
2-Bromobenzyl picolinate (1q): 996.6 mg, 84% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-



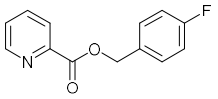
d) δ 8.83 – 8.75 (m, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.35 – 7.31 (m, 1H), 722 – 7.18 (m, 1H), 5.54 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.8, 150.1, 147.9, 137.1, 135.0, 132.9,

130.1, 129.9, 127.7, 127.1, 125.5, 123.5, 67.0. HRMS (ESI) m/z calcd for $C_{13}H_{10}BrNNaO_2$ $[M + Na]^+$: 313.9787, found: 313.9791.

4-Chlorobenzyl picolinate (1r): 865.1 mg, 86% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.77 – 8.69 (m, 1H), 8.10 (d, *J* = 8.0Hz, 1H), 7.83 – 7.78 (m, 1H), 7.46 – 7.39 (m, 3H), 7.33 – 7.26 (m, 2H), 5.39 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.9, 149.9, 147.7, 137.0, 134.3, 134.1, 129.9, 128.7, 127.0, 125.2, 66.6. HRMS (ESI) m/z calcd for $C_{13}H_{10}ClNNaO_2$ $[M + Na]^+$: 270.0292, found: 270.0291.



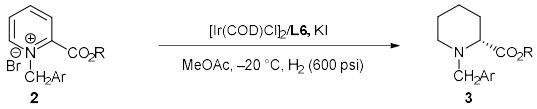
4-Fluorobenzyl picolinate (1s): 854.6 mg, 91% yield, colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.75 – 8.73 (m, 1H), 8.12 – 8.09 (m, 1H), 7.83 – 7.79 (m, 1H), 7.51 – 7.41 (m, 3H), 7.10 – 6.98 (m, 2H), 5.40 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.1, 162.9 (d, *J* = 245.5 Hz), 150.1, 148.0, 137.1, 131.6 (d, *J* = 3.3 Hz), 130.8 (d, *J* = 8.3 Hz), 127.1, 125.4, 115.6 (d, *J* = 21.6 Hz), 66.9. HRMS (ESI) m/z calcd for $C_{13}H_{10}FNNaO_2$ $[M + Na]^+$: 254.0588, found: 254.0592.



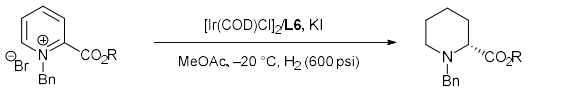
2.2 General Procedures for the synthesis of pyridinium salts

A mixture of 2-substituted pyridine (1.0 mmol), benzyl bromide (1.2 mmol) and 10.0 mL acetone or methanol was stirred at 0 ℃ for 12-96 h. Ether was added, the resulting precipitate was collected and rinsed with ethyl acetate to give the solid product which was directly used for the hydrogenation. If the desired product was not precipitated, the reaction mixture was purified by column chromatography on silica gel using DCM/MeOH (20:1) to give the desired products (35%–96% yield).

2.3 General Procedure for Hydrogenation of pyridinium salts



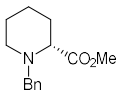
A mixture of $[Ir(COD)Cl]_2$ (1.3 mg, 2.0 μmol, 2.0 mol%) and (*R*,*R*)-BDPP (**L6**) (1.8 mg, 4.0 μmol, 4.0 mol%) were dissolved in degassed MeOAc (2.0 mL) at argon atmosphere, and the resulting solution was allowed to stirred for 20 min, followed by the addition of the substrate **2** (0.1 mmol, 1.0 equiv.) and KI (16.6 mg, 0.1 mmol, 1.0 equiv.). The resulting mixture was transferred to an autoclave, which was purged (3 × 5 atm) and charged with H_2 (600 psi), then the reaction mixtures were stirred at −20 °C for 72 h. After careful release of the hydrogen gas, the reaction mixture was filtrated and concentrated in vacuo. Flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluent gave the products. The enantiomeric excesses were determined by chiral HPLC.



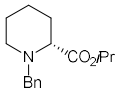
Asymmetric hydrogenation of *N*-benzyl-2-(methoxycarbonyl)pyridinium salts (**2a**) at gram scale: A mixture of $[Ir(COD)Cl]_2$ (5.5 mg, 8.0 μmol, 0.25 mol%) and (*R*,*R*)-BDPP (**L6**) (7.0 mg, 16.0 μmol, 0.5 mol%) were dissolved in degassed MeOAc (30.0 mL) at argon atmosphere, and the resulting solution

was allowed to stirred for 20 min, followed by the addition of the substrate **2a** (1.0 g, 3.2 mmol, 1.0 equiv.). The resulting mixture was transferred to an autoclave, which was purged (3 × 5 atm) and charged with H_2 (600 psi), then the reaction mixtures were stirred at −20 °C for 72 h. After careful release of the hydrogen gas, the reaction mixture was filtrated and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 150:1) to give the desired product **3a** (711.6 mg, 94% yield, 95% *ee*) as a pale-yellow oil.

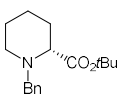
Asymmetric hydrogenation of *N*-benzyl-2-((benzyloxy)carbonyl)pyridinium salts (**2g**) at gram scale: A mixture of $[Ir(COD)Cl]_2$ (4.2 mg, 6.5 μmol, 0.25 mol%) and (*R*,*R*)-BDPP (**L6**) (5.8 mg, 13.0 μmol, 0.5 mol%) were dissolved in degassed MeOAc (30.0 mL) at argon atmosphere, and the resulting solution was allowed to stirred for 20 min, followed by the addition of the substrate **2g** (1.0 g, 2.6 mmol, 1.0 equiv.). The resulting mixture was transferred to an autoclave, which was purged (3 × 5 atm) and charged with H_2 (600 psi), then the reaction mixtures were stirred at −20 °C for 72 h. After careful release of the hydrogen gas, the reaction mixture was filtrated and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 150:1) to give the desired product **3g** (773.0 mg, 96% yield, 93% *ee*) as a pale-yellow oil.

(*R*)-1-Benzylpiperidine-2-carboxylate methyl ester (3a): 21.7 mg, 93% yield, 95% *ee*, $[\alpha]_D^{20}$ = 80.7 (c = 1.0, $CHCl_3$), colorless oil. 

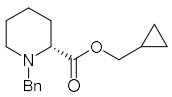
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.18 (m, 5H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.73 (s, 3H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.17 (dd, *J* = 7.6, 4.4 Hz, 1H), 2.96 – 2.91 (m, 1H), 2.19 – 2.13 (m, 1H), 1.90 – 1.77 (m, 2H), 1.66 – 1.50 (m, 3H), 1.42 – 1.32 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.5, 138.3, 129.3, 128.2, 127.1, 64.5, 60.7, 51.6, 50.2, 29.7, 25.4, 22.6. HRMS (ESI) m/z calcd for $C_{14}H_{20}NO_2$ $[M + H]^+$: 234.1489, found: 234.1490. HPLC: Chiralcel OD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 8.8 min and 11.4 min (maj).

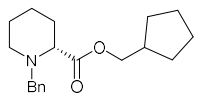
(*R*)-1-Benzylpiperidine-2-carboxylate isopropyl ester (3b)[1]: 23.0 mg, 88% yield, 91% *ee*, $[\alpha]_D^{20}$ = 80.1 (c = 0.5, $CHCl_3$), colorless oil. 

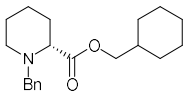
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.23 (m, 5H), 5.16 – 5.06 (m, 1H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.09 (t, *J* = 6.4 Hz, 1H), 2.96 – 2.90 (m, 1H), 2.16 – 2.10 (m, 1H), 1.90 – 1.46 (m, 6H), 1.30 – 1.26 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.7, 138.5, 129.4, 128.2, 127.1, 67.8, 64.8, 60.6, 50.3, 29.7, 25.4, 22.7, 22.1, 22.0. HRMS (ESI) m/z calcd for $C_{16}H_{24}NO_2$ $[M + H]^+$: 262.1802, found: 262.1805. HPLC: Chiralcel OD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 8.6 min and 9.6 min (maj).

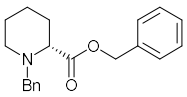
***(R)*-1-Benzylpiperidine-2-carboxylate tert-butyl ester (3c)[2]:** 25.6 mg, 93% yield, 96% *ee*, $[\alpha]_D^{20}$ = 76.1 (c = 0.5, $CHCl_3$), colorless oil. 

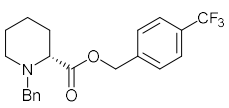
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.21 (m, 5H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.01 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.03 – 2.89 (m, 1H), 2.15 – 2.09 (m, 1H), 1.86 – 1.76 (m, 2H), 1.66 – 1.53 (m, 3H), 1.49 (s, 9H), 1.40 – 1.32 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.4, 138.9, 129.3, 128.2, 127.0, 80.6, 65.1, 60.5, 50.2, 29.8, 28.3, 25.5, 22.7. HRMS (ESI) m/z calcd for $C_{17}H_{26}NO_2$ $[M + H]^+$: 276.1958, found: 276.1960. HPLC: Chiralcel OJ-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 7.7 min and 8.2 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate cyclopropylmethyl ester (3d): 23.5 mg, 86% yield, 92% *ee*, 
$[\alpha]_D^{20}$ = 69.4 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.24 (m, 5H), 4.09 – 3.92 (m, 2H), 3.82 (d, *J* = 13.2 Hz, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.15 (dd, *J* = 8.0, 4.4 Hz, 1H), 2.97 – 2.92 (m, 1H), 2.20 – 2.11 (m, 1H), 1.91 – 1.79 (m, 2H), 1.58 – 1.53 (m, 3H), 1.42 – 1.32 (m, 1H), 1.24 – 1.15 (m, 1H), 0.59 – 0.55 (m, 2H), 0.35 – 0.29 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.3, 138.3, 129.5, 128.3, 127.2, 69.3, 64.8, 60.7, 50.4, 29.8, 25.4, 22.7, 10.1, 3.48, 3.46. HRMS (ESI) m/z calcd for $C_{17}H_{24}NO_2$ $[M + H]^+$: 274.1802, found: 274.1802. HPLC: Chiralcel OJ-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 9.0 min and 10.5 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate cyclopentylmethyl ester (3e): 27.4 mg, 91% yield, 92% *ee*, 
$[\alpha]_D^{20}$ = 61.3 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.26 (m, 4H), 7.25 – 7.21 (m, 1H), 4.04 (d, *J* = 7.2 Hz, 2H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.44 (d, *J* = 13.6 Hz, 1H), 3.17 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.96 – 2.91 (m, 1H), 2.30 – 2.11 (m, 2H), 1.85 – 1.72 (m, 4H), 1.61 – 1.55 (m, 8H), 1.46 – 1.32 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.3, 138.5, 129.4, 128.3, 127.1, 68.5, 64.5, 60.7, 50.2, 38.8, 29.9, 29.6, 25.51, 25.50, 22.6. HRMS (ESI) m/z calcd for $C_{19}H_{28}NO_2$ $[M + H]^+$: 302.2115, found: 302.2119. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 8.7 min and 9.3 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate cyclohexylmethyl ester (3f): 28.4 mg, 90% yield, 94% *ee*, 
$[\alpha]_D^{20}$ = 78.1 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.27 (m, 4H), 7.25 – 7.24 (m, 1H), 3.95 (d, *J* = 6.4 Hz, 2H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.44 (d, *J* = 13.2 Hz, 1H), 3.17 (t, *J* = 6.4 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.20 – 2.15 (m, 1H), 1.85 – 1.80 (m, 2H), 1.80 – 1.64 (m, 6H), 1.57 – 1.52 (m, 3H), 1.42 – 1.34 (m, 1H), 1.25 – 1.11 (m, 3H), 1.03 – 0.94 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.3, 138.5, 129.3, 128.3, 127.1, 69.7, 64.5, 60.7, 50.2, 37.3, 29.92, 29.89, 26.5, 25.8, 25.5, 22.7. HRMS (ESI) m/z calcd for $C_{20}H_{30}NO_2$ $[M + H]^+$: 316.2271, found: 316.2272. HPLC: Chiralcel OJ-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 7.5 min and 8.0 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate benzyl ester (3g)[3]: 29.7 mg, 96% yield, 93% *ee*, $[\alpha]_D^{20}$ = 64.9 
(c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.18 (m, 10H), 5.18 (s, 2H), 3.79 (dd, *J* = 13.2, 2.0 Hz, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.21 (t, *J* = 6.0 Hz, 1H), 2.98 – 2.92 (m, 1H), 2.25 – 2.11 (m, 1H), 1.86 – 1.82 (m, 2H), 1.69 – 1.47 (m, 3H), 1.42 – 1.33 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.8, 138.4, 136.1, 129.3, 128.7, 128.5, 128.4, 128.2, 127.1, 66.2, 64.2, 60.6, 50.2, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{24}NO_2$ $[M + H]^+$: 310.1802, found: 310.1805. HPLC: Chiralcel OJ-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 19.3 min and 21.8 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate-4-(trifluoromethyl)benzyl ester (3h)[4]: 32.8 mg, 87% yield, 93% 
ee, $[\alpha]_D^{20}$ = 86.3 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.24 (m, 5H), 5.21 (s, 2H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.25 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.23 – 2.18 (m, 1H), 1.88 – 1.82 (m, 2H), 1.62 – 1.53 (m, 3H), 1.44 – 1.35 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.6, 140.1, 138.3, 130.6 (q, *J* = 32.1 Hz), 129.2, 128.4, 128.3, 127.2, 125.7 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 270.4 Hz), 65.2, 64.2, 60.7, 50.2, 29.7, 25.4,

22.5. HRMS (ESI) m/z calcd for $C_{21}H_{23}F_3NO_2$ $[M + H]^+$: 378.1675, found: 378.1673. HPLC: Chiralcel OJ-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 17.8 min and 22.0 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 4-cyanobenzyl ester (3i): 28.4 mg, 85% yield, 92% *ee*, $[\alpha]_D^{20}$ = 93.1 (c = 1.0, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.20 (m, 5H), 5.20 (s, 2H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.43 (d, *J* = 13.6 Hz, 1H), 3.25 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.24 – 2.18 (m, 1H), 1.87 – 1.84 (m, 2H), 1.62 – 1.53 (m, 3H), 1.48 – 1.36 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.5, 141.4, 138.3, 132.5, 129.1, 128.6, 128.3, 127.2, 118.6, 112.2, 65.0, 64.2, 60.7, 50.2, 29.7, 25.3, 22.5. HRMS (ESI) m/z calcd for $C_{21}H_{23}N_2O_2$ $[M + H]^+$: 335.1754, found: 335.1750. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 23.7 min and 30.1 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 4-(methoxycarbonyl)benzyl ester (3j)[5]: 32.7 mg, 89% yield, 92% *ee*, $[\alpha]_D^{20}$ = 79.8 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.19 (m, 5H), 5.14 (s, 2H), 3.85 (s, 3H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.37 (d, *J* = 13.6 Hz, 1H), 3.20 – 3.17 (m, 1H), 2.95 – 2.83 (m, 1H), 2.20 – 2.10 (m, 1H), 1.80 – 1.76 (m, 2H), 1.54 – 1.47 (m, 3H), 1.34 – 1.31 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.6, 166.9, 141.2, 138.3, 130.1, 130.0, 129.3, 128.3, 128.0, 127.2, 65.5, 64.1, 60.6, 52.3, 50.2, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{22}H_{26}NO_4$ $[M + H]^+$: 368.1856, found: 368.1851. HPLC: Chiralcel AD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 17.7 min and 19.2 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 4-nitrobenzyl ester (3k): 31.9 mg, 90% yield, 92% *ee*, $[\alpha]_D^{20}$ = 89.1 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.22 (m, 5H), 5.25 (s, 2H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.44 (d, *J* = 13.6 Hz, 1H), 3.27 (dd, *J* = 7.2, 4.4 Hz, 1H), 2.99 – 2.93 (m, 1H), 2.25 – 2.19 (m, 1H), 1.88 – 1.83 (m, 2H), 1.59 – 1.55 (m, 3H), 1.46 – 1.34 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.5, 147.9, 143.4, 138.3, 129.1, 128.7, 128.3, 127.3, 124.0, 64.7, 64.1, 60.7, 50.2, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{23}N_2O_4$ $[M + H]^+$: 355.1652, found: 355.1652. HPLC: Chiralcel AD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 22.7 min and 24.0 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 4-methylbenzyl ester (3l)[5]: 27.5 mg, 85% yield, 93% *ee*, $[\alpha]_D^{20}$ = 71.9 (c = 0.6, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.14 (m, 9H), 5.13 (s, 2H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.41 (d, *J* = 13.2 Hz, 1H), 3.20 – 3.17 (m, 1H), 2.97 – 2.91 (m, 1H), 2.34 (s, 3H), 2.19 – 2.14 (m, 1H), 1.85 – 1.80 (m, 2H), 1.60 – 1.52 (m, 3H), 1.40 – 1.32 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.9, 138.4, 138.2, 133.2, 129.4, 129.3, 128.6, 128.2, 127.1, 66.2, 64.3, 60.6, 50.2, 29.7, 25.4, 22.6, 21.3. HRMS (ESI) m/z calcd for $C_{21}H_{26}NO_2$ $[M + H]^+$: 324.1958, found: 324.1963. HPLC: Chiralcel OJ-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 16.7 min and 22.1 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 3-methylbenzyl ester (3m): 28.1 mg, 87% yield, 92% *ee*, $[\alpha]_D^{20}$ = 61.9 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.11 (m, 9H), 5.14 (s, 2H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.21 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.34 (s, 3H), 2.25 – 2.13 (m, 1H), 1.89 – 1.81 (m, 2H), 1.63 – 1.54 (m, 3H), 1.43 – 1.34 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.9, 138.4, 136.0, 129.3, 129.2, 129.1, 128.6, 128.3, 128.3, 127.1, 125.5, 66.3, 64.3, 60.6, 50.2, 29.7, 25.4, 22.6, 21.5. HRMS (ESI) m/z calcd for $C_{21}H_{26}NO_2$ $[M + H]^+$: 324.1958, found: 324.1958. HPLC: Chiralcel OJ-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 16.1 min and 17.9 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 3-methoxybenzyl ester (3n): 30.2 mg, 89% yield, 92% *ee*, $[\alpha]_D^{20}$ = 76.4 (c = 0.6, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.23 (m, 6H), 6.97 – 6.84 (m, 3H), 5.15 (s, 2H), 3.82 – 3.80 (m, 1H), 3.79 (s, 3H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.24 – 3.21 (m, 1H), 2.99 – 2.93 (m, 1H), 2.24 – 2.16 (m, 1H), 1.89 – 1.82 (m, 2H), 1.60 – 1.53 (m, 3H), 1.42 – 1.34 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.8, 159.9, 138.3, 137.7, 129.8, 129.3, 128.3, 127.2, 120.6, 114.0, 113.8, 66.1, 64.3, 60.6, 55.4, 50.2, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{21}H_{26}NO_3$ $[M + H]^+$: 340.1907, found: 340.1904. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 12.6 min and 13.7 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 4-bromobenzyl ester (3o)[5]: 33.8 mg, 87% yield, 93% *ee*, $[\alpha]_D^{20}$ = 61.3 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.39 (m, 2H), 7.29 – 7.20 (m, 7H), 5.11 (s, 2H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.21 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.97 – 2.92 (m, 1H), 2.21 – 2.16 (m, 1H), 1.85 – 1.81 (m, 2H), 1.57 – 1.53 (m, 3H), 1.39 – 1.34 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.7, 138.3, 135.2, 131.9, 130.2, 129.2, 128.3, 127.2, 122.5, 65.4, 64.2, 60.7, 50.2, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{23}BrNO_2$ $[M + H]^+$: 388.0907, found: 388.0909. HPLC: Chiralcel OJ-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 12.1 min and 13.8min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 3-bromobenzyl ester (3p): 33.0 mg, 85% yield, 92% *ee*, $[\alpha]_D^{20}$ = 67.7 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (t, *J* = 1.9 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.31 – 7.19 (m, 7H), 5.13 (s, 2H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.23 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.28 – 2.14 (m, 1H), 1.86 – 1.81 (m, 2H), 1.63 – 1.54 (m, 3H), 1.44 – 1.35 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.7, 138.4, 138.3, 131.5, 131.3, 130.3, 129.3, 128.3, 127.2, 126.9, 122.7, 65.2, 64.1, 60.7, 50.2, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{23}BrNO_2$ $[M + H]^+$: 388.0907, found: 388.0906. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 11.3 min and 12.8 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 2-bromobenzyl ester (3q): 32.6 mg, 84% yield, 91% *ee*, $[\alpha]_D^{20}$ = 61.0 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.27 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.18 – 7.03 (m, 7H), 5.10 (s, 2H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.32 (d, *J* = 13.6 Hz, 1H), 3.13 (t, *J* = 6.0 Hz, 1H), 2.85 – 2.79 (m, 1H), 2.10 – 2.04 (m, 1H), 1.76 – 1.72 (m, 2H), 1.48 – 1.39 (m, 3H), 1.28 – 1.22 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.6, 138.5, 135.5, 133.1, 130.3, 130.0, 129.3, 128.3, 127.7, 127.1,

123.8, 65.9, 64.0, 60.6, 50.0, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{23}BrNO_2$ [M + H]$^+$: 388.0907, found: 388.0908. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 11.0 min and 11.7 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 4-chlorobenzyl ester (3r): 29.6 mg, 86% yield, 88% *ee*, $[\alpha]_D^{20}$ = 67.1 (c = 0.6, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.19 (m, 9H), 5.13 (s, 2H), 3.77 (d, *J* = 13.6 Hz, 1H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.21 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.97 – 2.92 (m, 1H), 2.21 – 2.15 (m, 1H), 1.85 – 1.78 (m, 2H), 1.57 – 1.52 (m, 3H), 1.41 – 1.34 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.7, 138.3, 134.7, 134.3, 129.9, 129.3, 128.9, 128.3, 127.2, 65.4, 64.3, 60.6, 50.2, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{23}ClNO_2$ [M + H]$^+$: 344.1412, found: 344.1415. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 15.2 min and 15.9 min (maj).

(*R*)-1-Benzylpiperidine-2-carboxylate 4-fluorobenzyl ester (3s): 29.8 mg, 91% yield, 92% *ee*, $[\alpha]_D^{20}$ = 90.5 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.32 (m, 2H), 7.28 – 7.21 (m, 5H), 7.05 – 7.01 (m, 2H), 5.14 (s, 2H), 3.76 (d, *J* = 13.2 Hz, 1H), 3.40 (d, *J* = 13.2 Hz, 1H), 3.19 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.97 – 2.92 (m, 1H), 2.22 – 2.15 (m, 1H), 1.84 – 1.81 (m, 2H), 1.61 – 1.54 (m, 3H), 1.43 – 1.32 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.8, 162.8 (d, *J* = 245.4 Hz), 138.3, 132.0 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 8.2 Hz), 129.3, 128.3, 127.2, 115.6 (d, *J* = 21.4 Hz), 65.5, 64.3, 60.6, 50.2, 29.7, 25.4, 22.6. HRMS (ESI) m/z calcd for $C_{20}H_{23}FNO_2$ [M + H]$^+$: 328.1707, found: 328.1708. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 10.1 min and 11.4 min (maj).

(*R*)-1-(4-(Trifluoromethyl)benzyl)piperidine-2-carboxylate benzyl ester (3t): 31.7 mg, 84% yield, 90% *ee*, $[\alpha]_D^{20}$ = 99.6 (c = 1.0, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.30 (m, 5H), 5.23 – 5.12 (m, 2H), 3.83 (d, *J* = 14.0 Hz, 1H), 3.47 (d, *J* = 14.0 Hz, 1H), 3.26 (t, *J* = 5.6 Hz, 1H), 2.96 – 2.90 (m, 1H), 2.23 – 2.18 (m, 1H), 1.90 – 1.85 (m, 2H), 1.60 – 1.54 (m, 3H), 1.45 – 1.38 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.6, 143.0, 136.0, 130.9 (q, *J* = 32.2 Hz), 129.2, 128.7, 128.5, 128.5, 127.1 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 270.2 Hz), 66.3, 64.2, 60.1, 50.1, 29.6, 25.4, 22.4. HRMS (ESI) m/z calcd for $C_{21}H_{23}F_3NO_2$ [M + H]$^+$: 378.1675, found: 378.1678. HPLC: Chiralcel AD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 9.5 and 10.1 min (maj).

(*R*)-1-(4-(Chlorobenzyl)benzyl)piperidine-2-carboxylate benzyl ester (3u): 30.6 mg, 89% yield, 91% *ee*, $[\alpha]_D^{20}$ = 61.2 (c = 0.65, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 5H), 7.25 – 7.17 (m, 4H), 5.20 – 5.13 (m, 2H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.37 (d, *J* = 13.2 Hz, 1H), 3.21 (t, *J* = 5.6 Hz, 1H), 2.94 – 2.89 (m, 1H), 2.23 – 2.10 (m, 1H), 1.88 – 1.80 (m, 2H), 1.60 – 1.52 (m, 3H), 1.40 – 1.36 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.7, 137.1, 136.1, 132.8, 130.5, 128.7, 128.5, 128.5, 128.4, 66.3, 64.2, 59.9, 50.1, 29.7, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{23}ClNO_2$ [M + H]$^+$: 344.1412, found: 344.1407. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 10.8 and 11.7 min (maj).

(*R*)-1-(4-(Methoxycarbonyl)benzyl)piperidine-2-carboxylate benzyl ester (3v): 33.8 mg, 92% yield, 92% *ee*, $[\alpha]_D^{20}$ = 70.3 (c = 0.65, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.28 (m, 7H), 5.25 – 5.09 (m, 2H), 3.90 (s, 3H), 3.82 (d, *J* = 14.0 Hz, 1H), 3.46 (d, *J* = 13.6 Hz, 1H), 3.23 (t, *J* = 6.0 Hz, 1H), 2.97 – 2.86 (m, 1H), 2.25 – 2.12 (m, 1H), 1.88 – 1.84 (m, 2H), 1.62 – 1.53 (m, 3H), 1.43 – 1.35 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.6, 167.2, 144.2, 136.1, 129.6, 129.0, 129.0, 128.7, 128.5, 128.4, 66.3, 64.2, 60.3, 52.1, 50.2, 29.6, 25.4, 22.4. HRMS (ESI) m/z calcd for $C_{22}H_{26}NO_4$ $[M + H]^+$: 368.1856, found: 368.1854 HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 15.4 and 16.1 min (maj).

(*R*)-1-(2,4-Difluorobenzyl)piperidine-2-carboxylate benzyl ester (3w): 30.7 mg, 89% yield, 98% *ee*, $[\alpha]_D^{20}$ = 59.1 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.25 (m, 6H), 6.86 – 6.69 (m, 2H), 5.27 – 5.12 (m, 2H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.22 (dd, *J* = 7.6, 4.4 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.24 – 2.18 (m, 1H), 1.87 – 1.80 (m, 2H), 1.62 – 1.53 (m, 3H), 1.41 – 1.31 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.7, 163.0 (dd, *J* = 78.4, 11.8 Hz), 160.6 (dd, *J* = 79.6, 12.0 Hz), 136.1, 132.4 (dd, *J* = 9.0, 6.3 Hz), 128.7, 128.5, 128.4, 121.0 (dd, *J* = 16.3 Hz), 111.1 (dd, *J* = 20.8, 3.7 Hz), 103.5 (dd, *J* = 26.0, 25.5Hz), 66.4, 64.2, 52.5, 50.2, 29.8, 25.4, 22.5. HRMS (ESI) m/z calcd for $C_{20}H_{22}F_2NO_2$ $[M + H]^+$: 346.1613, found: 346.1609. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 95/5, flow = 0.5 mL/min, retention time 27.6 min and 29.0 min (maj).

(*R*)-1-benzyl-2-phenylpiperidine (3x): 14.4 mg, 76% yield, 33% *ee*, $[\alpha]_D^{20}$ = 13.4 (c = 0.5, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.15 (m, 5H), 3.99 (d, *J* = 13.6 Hz, 1H), 3.18 (d, *J* = 13.6 Hz, 1H), 2.75 – 2.69 (m, 1H), 2.31 – 2.27 (m, 1H), 1.97 – 1.91 (m, 1H), 1.65 – 1.61 (m, 2H), 1.56 – 1.21 (m, 4H), 1.15 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 139.7, 129.1, 128.1, 126.7, 58.6, 56.5, 52.3, 34.9, 26.2, 24.1, 19.6. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 10.1 min and 11.5 min (maj).

(*R*)-1-benzyl-2-phenylpiperidine (3y): 20.6 mg, 82% yield, 60% *ee*, $[\alpha]_D^{20}$ = 24.9 (c = 1.0, $CHCl_3$), colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.15 (m, 6H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.10 (dd, *J* = 11.2, 2.8 Hz, 1H), 2.99 – 2.94 (m, 1H), 2.80 (d, *J* = 13.6 Hz, 1H), 1.96 – 1.90 (m, 1H), 1.80 – 1.74 (m, 2H), 1.66 – 1.55 (m, 3H), 1.42 – 1.33 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 145.9, 140.0, 128.8, 128.6, 128.1, 127.6, 127.0, 126.6, 69.4, 59.9, 53.5, 37.2, 26.2, 25.4. HRMS (ESI) m/z calcd for $C_{18}H_{22}N$ $[M + H]^+$: 252.1747, found: 252.1743. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 13.6 min and 15.1 min (maj).

2.4 General procedure for asymmetric hydrogenation under continuous flow

All process parts, including fittings, tubes, valves and junctions that hold pressure were purchased from SHENZHEN INSFTECH CO,. Ltd. The specification of the reaction coil is 0.5 ml/m. The information of other main components is summarized in Table S1.

Table S1 Components details of reactor system

Name	Information
Pump	Sanotac high pressure HPLC pump AP0030 (0-10 mL/min; 20 MPa)
MFC	SHENZHEN INSFTECH CO,. Ltd. FCM-1050 (0-500sccm,10MPa)
BPR	SHENZHEN INSFTECH CO,. Ltd. FAV-1500B (0-500mL/min, 10MPa)
Mixer	SHENZHEN INSFTECH CO,. Ltd. MGL-2000（200*250μm，2000Psi）

A mixture of $[Ir(COD)Cl]_2$ (2.0 mol%) and (*R*,*R*)-BDPP (4.0 mol%) was dissolved in a degassed solvent EA/MeOH at argon atmosphere, and the resulting solution was allowed to be stirred at room temperature for 30.0 min. Then, *N*-benzyl-2-methylpyridinium salt **2a** (1.0 equiv.) and KI (1.0 equiv.) were added. The process was washed by EA/MeOH at a liquid flow rate of 5 mL/min and gas flow rate of 10.0 sccm (avoid back flow of liquid to gas flow meter) for 10.0 minutes and then pressurized the BPR. After the reactor was pressurized to 8.0 MPa, the aforehand reaction medium was pumped instead of solvent. Liquid flow rate was set at 0.2 mL/min and gas flow rate was keeping 20.0 sccm. The liquid holding capacity of the reaction coil can be adjusted according to the needs. When reaction finished, system was depressurized by releasing the gas slowly, and washed the whole system by pumping ethanol for 10.0 minutes. The reaction mixture was filtrated and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 150:1) to give the desired product **3a** (94% yield, 92% *ee*) as a pale-yellow oil.

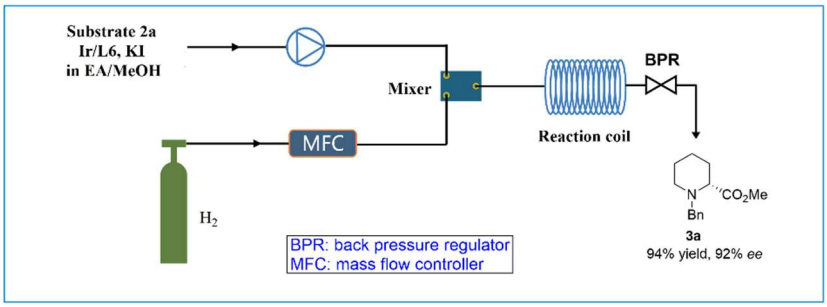
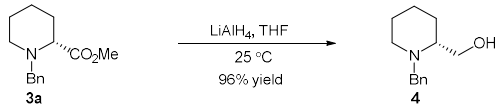


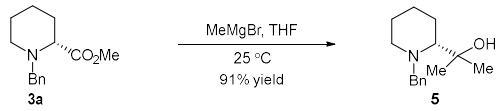
Figure S1 AH of **2a** under continuous flow.

Figure S2 Set-up for asymmetric hydrogenation under continuous flow.

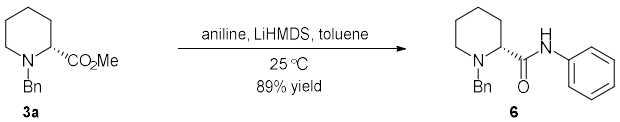
2.5 Procedures for Products Transformations



A solution of the methyl ester **3a** (100.0 mg, 0.43 mmol, 1.0 equiv.) in THF (2.5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (24.4 mg, 0.64 mmol, 1.5 equiv.) in THF (2.5 mL) at 0 °C under an argon atmosphere. The resulting mixture was stirred at 25 °C for 8 h and then 2 M NaOH(aq) (1 μL per 1 mg of $LiAlH_4$), Et_2O (5 mL) and Na_2SO_4 were carefully added. The solids were removed by filtration through Celite and evaporated under reduced pressure to give the crude product. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 100:1) to give compound **4** (84.5 mg, 96%, 97% *ee*) as a pale-yellow oil. $[\alpha]_D^{20}$ = 34.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.19 (m, 5H), 4.06 (d, *J* = 13.2 Hz, 1H), 3.86 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.52 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.32 (d, *J* = 13.2 Hz, 1H), 2.89 – 2.84 (m, 1H), 2.53 (s, 1H), 2.47 – 2.37 (m, 1H), 2.17 – 2.12 (m, 1H), 1.79 – 1.49 (m, 4H), 1.39 – 1.31 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 139.1, 129.0, 128.5, 127.1, 62.4, 61.0, 57.8, 50.9, 27.4, 24.2, 23.5. HRMS (ESI) m/z calcd for $C_{13}H_{20}NO$ $[M + H]^+$: 206.1539, found: 206.1537. HPLC: Chiralcel OD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 12.1 min and 12.8 min (maj).

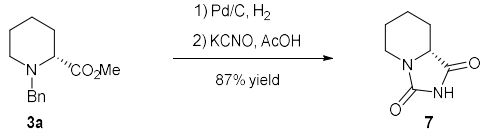


To a solution of the methyl ester **3a** (100.0 mg, 0.43 mmol, 1.0 equiv.) in anhydrous THF (5.0 mL) was added methyl magnesium bromide (1.0 M in THF, 1.3 mL, 1.29 mmol, 3.0 equiv.) dropwise under argon atmosphere at 0 °C. The resulting mixture was stirred at room temperature for 4 h and then quenched with aqueous NH_4Cl solution, extracted with ethyl acetate. Organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 50:1) to give compound **5** (91.0 mg, 91% yield, 93% *ee*) as a pale-yellow oil. $[\alpha]_D^{20}$ = −5.41 (c = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.21 (m, 5H), 3.96 – 3.84 (m, 2H), 2.87 – 2.80 (m, 1H), 2.59 – 2.53 (m, 2H), 1.87 – 1.59 (m, 4H), 1.59 – 1.49 (m, 2H), 1.43 – 1.36 (m, 1H), 1.26 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 140.1, 128.8, 128.5, 127.2, 72.4, 68.5, 58.6, 46.0, 29.5, 26.7, 21.5, 21.1, 18.7. HRMS (ESI) m/z calcd for $C_{15}H_{24}NO$ $[M + H]^+$: 234.1852, found: 234.1847. HPLC: Chiralcel OJ-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 11.9 min (maj) and 13.6 min.



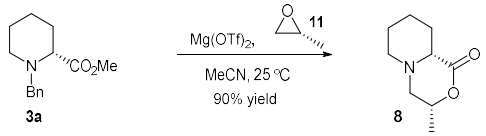
An oven-dried vial equipped with a stir bar was charged with the methyl ester **3a** (100.0 mg, 0.43 mmol, 1.0 equiv.), aniline (46.9 μL, 0.51 mmol, 1.2 equiv.) placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles. Toluene (5.0 mL) and LiHMDS (1.0 M in THF, 0.9 mL, 0.86 mmol, 2.0 equiv.) were sequentially added with vigorous stirring at 25 °C, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with aqueous NH_4Cl solution, diluted with ethyl acetate (5.0 mL), the organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to give compound **6** (112.3 mg, 89% yield, 96% *ee*) as a white solid, m.p. = 113.0 – 115.1 °C. $[\alpha]_D^{20}$ = 43.1 (c = 1.0, $CHCl_3$). ^{1}H NMR

(400 MHz, Chloroform-d) δ 8.84 (s, 1H), 7.56 – 7.54 (m, 2H), 7.36 – 7.24 (m, 7H), 7.10 – 7.06 (m, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.28 (d, *J* = 13.6 Hz, 1H), 3.00 – 2.95 (m, 2H), 2.11 – 2.06 (m, 2H), 1.77 – 1.62 (m, 3H), 1.51 – 1.26 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-d) δ 172.7, 138.0, 137.9, 129.1, 128.63, 128.59, 127.4, 124.1, 119.4, 68.1, 61.0, 51.5, 29.9, 24.6, 23.4. HRMS (ESI) m/z calcd for $C_{19}H_{23}N_2O$ $[M + H]^+$: 295.1805, found: 295.1807. HPLC: Chiralcel OD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 15.7 min (maj) and 19.0 min.



To a stirred solution of the methyl ester **3a** (100.0 mg, 0.43 mmol, 1.0 equiv.) in MeOH (5.0 mL) was added 10% Pd/C (10.0 mg, 10.0 wt%). The resulting mixture was stirred overnight at 25 °C under H_2 (1 atm, balloon) and then filtered, washed with water and concentrated under reduced pressure.

The crude was dissolved in acetic acid (5.0 mL), potassium cyanate (69.8 mg, 0.86 mmol, 1.0 equiv.) was added and the reaction mixture was allowed to stir at 25 °C for 12 h. The reaction mixture was quenched with aqueous $NaHCO_3$ solution, extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **7** (57.5 mg, 87% over 2 steps, 98% *ee*) as a white solid, m.p. = 131.3 – 133.3 °C. $[\alpha]_D^{20}$ = 77.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 4.13 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.82 – 3.78 (m, 1H), 2.83 – 2.76 (m, 1H), 2.21 – 2.17 (m, 1H), 2.01 – 1.98 (m, 1H), 1.75 – 1.72 (m, 1H), 1.54 – 1.31 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.8, 154.4, 58.8, 39.3, 27.7, 25.0, 22.8. HRMS (ESI) m/z calcd for $C_7H_{11}N_2O_2$ $[M + H]^+$: 155.0815, found: 155.0817. HPLC: Chiralcel IC column, 210 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 29.2 min (maj) and 33.7 min.



To a stirred solution of the methyl ester **3a** (100.0 mg, 0.43 mmol, 1.0 equiv.) in MeOH (5.0 mL) was added 10% Pd/C (10.0 mg, 10.0 wt%). The resulting mixture was stirred overnight at 25 °C under H_2 (1 atm, balloon) and then filtered, washed with water and concentrated under reduced pressure. The crude was dissolved in acetonitrile (6.0 mL), (*R*)-propylene oxide (39.0 µL, 0.56 mmol, 1.3 equiv.) was added. Next magnesium trifluoromethanesulfonate (37.8 mg, 0.21 mmol, 0.5 equiv.) was added and the reaction was stirred and heated at 75 °C for 17 h. After this time, the reaction was cooled to room temperature and sodium carbonate solution (2 M) was added. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 50:1) to give compound **8** (65.3 mg, 90% yield, 97% *ee*) as a pale-yellow oil. $[\alpha]_D^{20}$ = 45.5 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.58 – 4.51 (m, 1H), 2.88 – 2.79 (m, 1H), 2.70 – 2.57 (m, 3H), 2.24 – 2.19 (m, 1H), 2.15 – 2.08 (m, 1H), 1.92 – 1.81 (m, 1H), 1.65 – 1.49 (m, 3H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.37 – 1.21 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.3, 74.4, 64.6, 55.73, 55.68, 27.6, 24.8, 24.6, 20.8. HRMS (ESI) m/z calcd for $C_9H_{16}NO_2$ $[M + H]^+$: 170.1176, found:

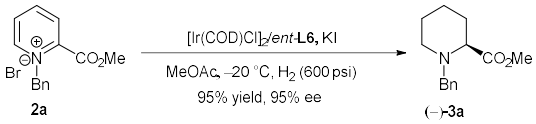
170.1173. HPLC: Chiralcel IC column, 210 nm, 30 ℃, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 44.3 min (maj) and 48.7 min.

To a stirred solution of the methyl ester **3a** (100.0 mg, 0.43 mmol, 1.0 equiv.) in MeOH (5.0 mL) were added 10% Pd/C (10.0 mg, 10.0 wt%). The resulting mixture was stirred overnight at 25 ℃ under H_2 (1 atm, balloon) and then filtered, washed with MeOH and concentrated under reduced pressure. The crude was dissolved in DMSO, 1-Fluoro-2-nitrobenzene (22.6 μL, 0.21 mmol, 0.5 equiv.) was added. The mixture was heated to 110 ℃ for 24 hours. After cooled to room temperature, The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was next dissolved in methanol (5.0 mL), zinc powder (420.4 mg, 6.43 mmol, 15.0 equiv.) and ammonium chloride (343.9 mg, 6.43 mmol, 15.0 equiv.) was added to this solution, and the mixture was stirred at 25 ℃ overnight. The mixture solution was then filtered, concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to give compound **9** (68.5 mg, 79% yield over 3 steps, 92% *ee*) as a white solid, m.p. = 181.2 – 183.1 ℃. $[\alpha]_D^{20}$ = 4.8 (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.36 (s, 1H), 7.03 – 6.94 (m, 1H), 6.80 – 6.77 (m, 3H), 3.78 (d, *J* = 12.0 Hz, 1H), 3.57 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.24 – 2.20 (m, 1H), 1.99 – 1.93 (m, 1H), 1.79 – 1.57 (m, 3H), 1.55 – 1.44 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 169.8, 135.7, 126.5, 124.2, 119.5, 115.6, 112.2, 59.9, 46.7, 26.9, 23.9, 23.4. HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O$ $[M + H]^+$: 203.1179, found: 203.1182. HPLC: Chiralcel IC column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 36.7 min and 40.3 min (maj).

2.6 The synthesis of ropivacaine and levobupivacaine under batch and flow

Synthesis of (−)-3a

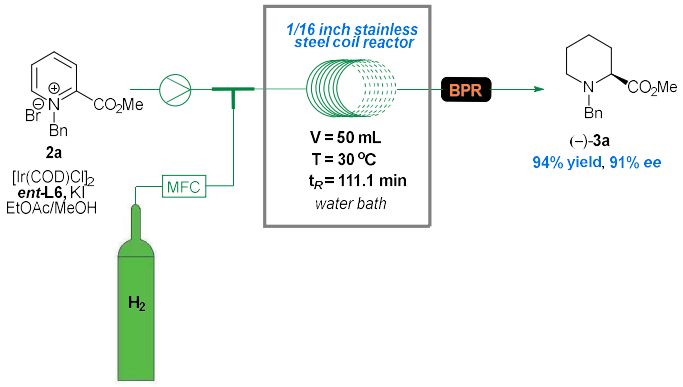
Batch Reaction



A mixture of $[Ir(COD)Cl]_2$ (2.2 mg, 2.0 μmol, 0.1 mol%) and (*S*,*S*)-BDPP (*ent*-**L6**) (2.6 mg, 4.0 μmol, 0.2 mol%) were dissolved in degassed MeOAc (30.0 mL) at argon atmosphere, and the resulting solution was allowed to stirred for 20 min, followed by the addition of the substrate **2a** (1.0 g, 3.25 mmol, 1.0 equiv.) and KI (539.5 mg, 3.25 mmol, 1.0 equiv.). The resulting mixture was transferred to an autoclave, which was purged (3 × 5 atm) and charged with H_2 (600 psi), then the reaction mixtures were stirred at −20 °C for 72 h. After careful release of the hydrogen gas, the reaction mixture was filtrated and concentrated in vacuo. Flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluent gave the products. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 100:1) to give compound (–)-**3a** (0.72 g, 95% yield, 95% *ee*) as a pale-yellow oil.

$[\alpha]_D^{20}$ = −75.1 (c = 1.0, $CHCl_3$). HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 8.8 min (maj) and 11.5 min.

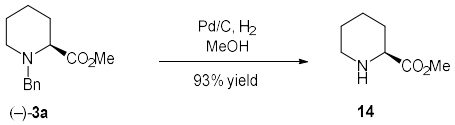
Continuous Flow Reaction



A mixture of $[Ir(COD)Cl]_2$ (2.0 mol%) and (*R*,*R*)-BDPP (4.0 mol%) was dissolved in a degassed solvent EtOAc/MeOH at argon atmosphere, and the resulting solution was allowed to be stirred at room temperature for 30 min. Then, *N*-benzyl-2-methylpyridinium salt **2a** (1.0 equiv.) was added. The process was washed by EA/MeOH at a liquid flow rate of 5 mL/min and gas flow rate of 10.0 sccm (avoid back flow of liquid to gas flow meter) for 10.0 minutes and then pressurized the BPR. After the reactor was pressurized to 8 MPa, the aforehand reaction medium was pumped instead of solvent. Liquid flow rate was set at 0.2 mL/min and gas flow rate was keeping 20 sccm. The liquid holding capacity of the reaction coil can be adjusted according to the needs. When reaction finished, system was depressurized by releasing the gas slowly, and washed the whole system by pumping ethanol for 10.0 minutes. the reaction mixture was filtrated and concentrated in vacuo. Flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluent gave the products. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 100:1) to give compound (–)-**3a** (94% yield, 91% *ee*) as a pale-yellow oil. HPLC: Chiralcel OD-H column, 254 nm, 30 ℃, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 8.8 min (maj) and 11.5 min.

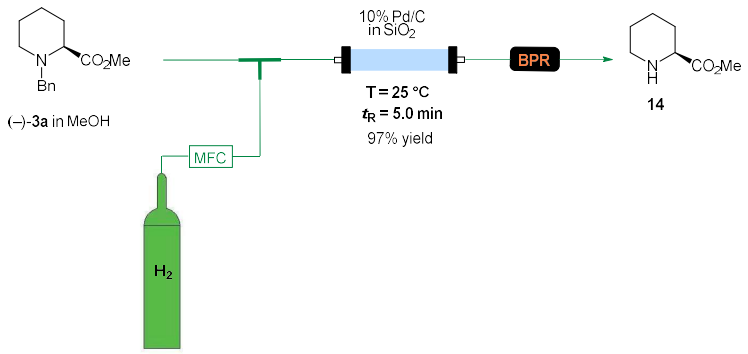
Synthesis of 14

Batch Reaction



To a stirred solution of the methyl ester (–)-**3a** (200.0 mg, 5.8 mmol, 1.0 equiv.) in MeOH (25.0 mL) were added 10% Pd/C (180.0 mg, 10.0 wt%). The resulting mixture was stirred overnight at 25 ℃ under H_2 (1 atm, balloon) and then filtered, washed with water and concentrated under reduced pressure to afford compound **13** (114.2 mg, 93% yield) as a yellow oil, which was directly used in the next step without further purification.

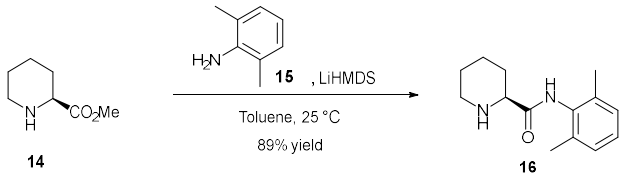
Continuous Flow Reaction



A solution of (−)-**3a** in MeOH (0.8 M) was pumped at a flow rate of 1.8 mL/min, which combined with hydrogen stream at 100 sccm in a T-shape mixer. The gas-liquid mixed solution was passed through a fixed bed reactor containing 10% Pd/C (2.0 g) and SiO_2 (18.0 g) (9.0 mL internal volume) at 25 °C with a 5.0 min residence time. The outlet of the fixed bed reactor was connected to a back-pressure regulator to control a stable system pressure at 1.0 MPa. The output of the reaction mixture was concentrated in vacuo to afford crude secondary amine **14** (97% yield) without further purification.

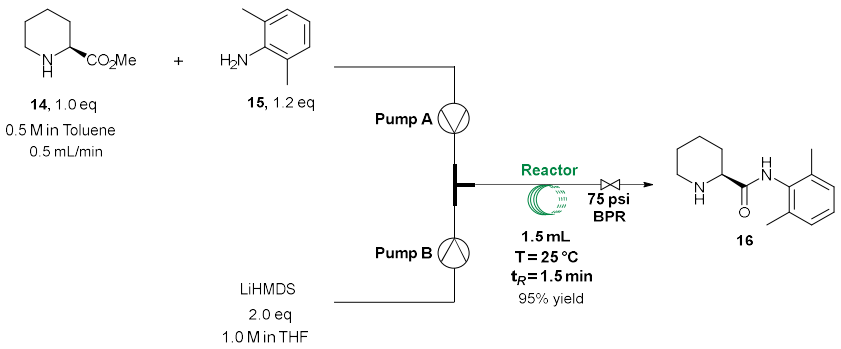
Synthesis of 16

Batch Reaction



An oven-dried vial equipped with a stir bar was charged with the methyl ester **14** (100.0 mg, 0.70 mmol, 1.0 equiv.), aniline (103.2 µL, 0.84 mmol, 1.2 equiv.) placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles. Toluene (5.0 mL) and LiHMDS (1.0 M in THF, 1.4 mL, 1.40 mmol, 2.0 equiv.) were sequentially added with vigorous stirring at 25 °C, and the reaction mixture was stirred overnight. The reaction mixture was quenched with aqueous NH_4Cl solution, diluted with ethyl acetate (5.0 mL), the organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 100:1) to give compound **16** (144.4 mg, 89% yield, 92% *ee*). HPLC: Chiralcel OJ-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 12.6 min and 14.6 min (maj).

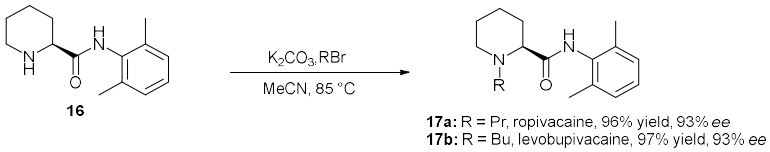
Continuous Flow Reaction



The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with toluene. The syringe pump A was used to introduce the solution of compound **14** (0.5 M, 1.0 equiv.) and **15** (1.2 equiv.) in toluene (0.5 mL/min), the syringe pump B was used to introduce the solution of LiHMDS (1.0 M in THF, 2.0 equiv., 0.5 mL /min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 1.5 min) at 25 °C. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, quenched by addition of water. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **16** (95% yield, 91% *ee*) as a white solid, m.p. = 121.1 – 123.2 °C. $[\alpha]_D^{20}$ = 38.6 (c = 2.0, HCl 1.0 M) [Lit.[6] $[\alpha]_D^{22}$ = 33.0 (c = 2.0, HCl 1.0 M)]. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (s, 1H), 7.13 – 6.95 (m, 3H), 3.41 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.14 – 3.09 (m, 1H), 2.85 – 2.70 (m, 1H), 2.22 (s, 6H), 2.10 – 2.05 (m, 1H), 1.86 – 1.82 (m, 2H), 1.65 – 1.58 (m, 2H), 1.57 – 1.41 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.5, 135.2, 133.8, 128.3, 127.1, 60.8, 46.0, 30.5, 26.1, 24.2, 18.6. HRMS (ESI) m/z calcd for $C_{14}H_{21}N_2O$ [M + H]$^+$: 233.1648, found: 233.1644. HPLC: Chiralcel OJ-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 11.9 min and 13.9 min (maj).

Synthesis of 17

Batch Reaction

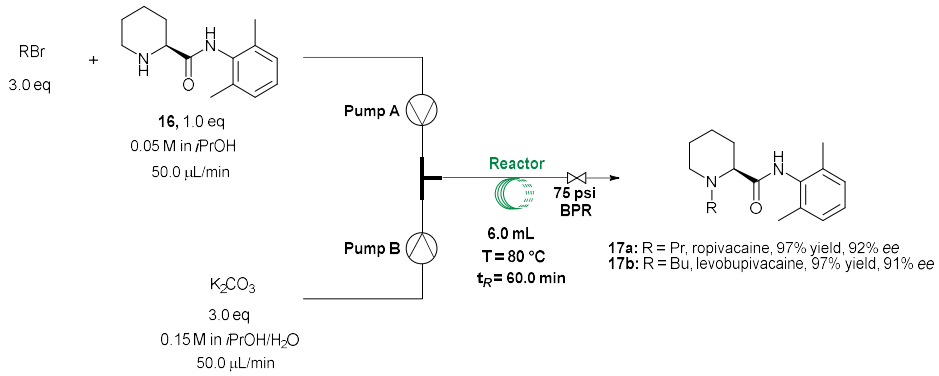


To a stirred solution of the amide **16** (50.0 mg, 0.22 mmol, 1.0 equiv.) in isopropyl alcohol (2.0 mL) were added potassium carbonate (89.3 mg, 0.65 mmol, 3.0 equiv.) and alkyl halide (0.65 mmol, 3.0 equiv.). Water (0.5 mL) was added and the mixture was stirred at 100 °C overnight, the solvent was evaporated and water was added. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to

give desired compound **17a**: 56.7 mg, 96% yield, 93% *ee*. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 13.8 min and 14.6 min (maj).

17b: 60.2 mg, 97% yield, 93% *ee*. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 19.7 min and 22.4 min (maj).

Continuous Flow Reaction



The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 6.0 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with *i*PrOH/H_2O. The syringe pump A was used to introduce the solution of compound **16** (0.05 M, 1.0 equiv.) and RBr (3.0 equiv.) in *i*PrOH (50.0 μL/min), the syringe pump B was used to introduce the solution of K_2CO_3 (0.15 M in *i*PrOH/H_2O, 3.0 equiv., 50.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (6.0 mL, internal volume, t_R = 60.0 min) at 80 °C. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, the solvent was evaporated and water was added. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to give desired compound **17a**: 97% yield, 92% *ee*, white solid, m.p. = 138.3 – 140.1 °C. $[\alpha]_D^{25}$ = −72.6 (c = 2.0, MeOH) [Lit.[6] $[\alpha]_D^{25}$ = −80.0 (c = 2.0, MeOH), m.p. = 145.0 – 147.0 °C]. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.10 – 7.04 (m, 3H), 3.22 – 3.17 (m, 1H), 2.87 (dd, *J* = 10.4, 3.6 Hz, 1H), 2.83 – 2.72 (m, 1H), 2.24 (s, 6H), 2.21 – 1.98 (m, 3H), 1.81 – 1.63 (m, 4H), 1.59 – 1.44 (m, 2H), 1.41 – 1.27 (m, 1H), 0.91 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.1, 135.4, 133.8, 128.4, 127.1, 68.7, 59.5, 51.7, 30.8, 25.0, 23.6, 20.8, 18.8, 11.7. HRMS (ESI) m/z calcd for $C_{17}H_{27}N_2O$ [M + H]$^+$: 275.2118, found: 275.2117. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 14.1 min and 14.9 min (maj). **17b:** 97% yield, 91% *ee*, white solid, m.p. = 133.1 – 135.3 °C. $[\alpha]_D^{20}$ = −89.5 (c = 1.0, MeOH) [Lit.[7] $[\alpha]_D^{20}$ = −77.0 (c = 1.0, MeOH), m.p. = 135.0 – 137.0 °C]. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.10 – 7.05 (m, 3H), 3.23 – 3.18 (m, 1H), 2.94 – 2.76 (m, 2H), 2.30 – 2.26 (m, 1H), 2.25 (s, 6H), 2.16 – 2.00 (m, 2H), 1.83 – 1.42 (m, 6H), 1.41 – 1.22 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.1, 135.4, 133.9, 128.4, 127.2, 68.7, 57.7, 51.8, 30.8, 29.9, 25.0, 23.7, 20.8, 18.9, 14.3. HRMS (ESI) m/z calcd for $C_{18}H_{29}N_2O$ [M + H]$^+$: 289.2274, found: 289.2277. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 90/10, flow = 0.5 mL/min, retention time 20.4 min and 23.1 min (maj).

3. References

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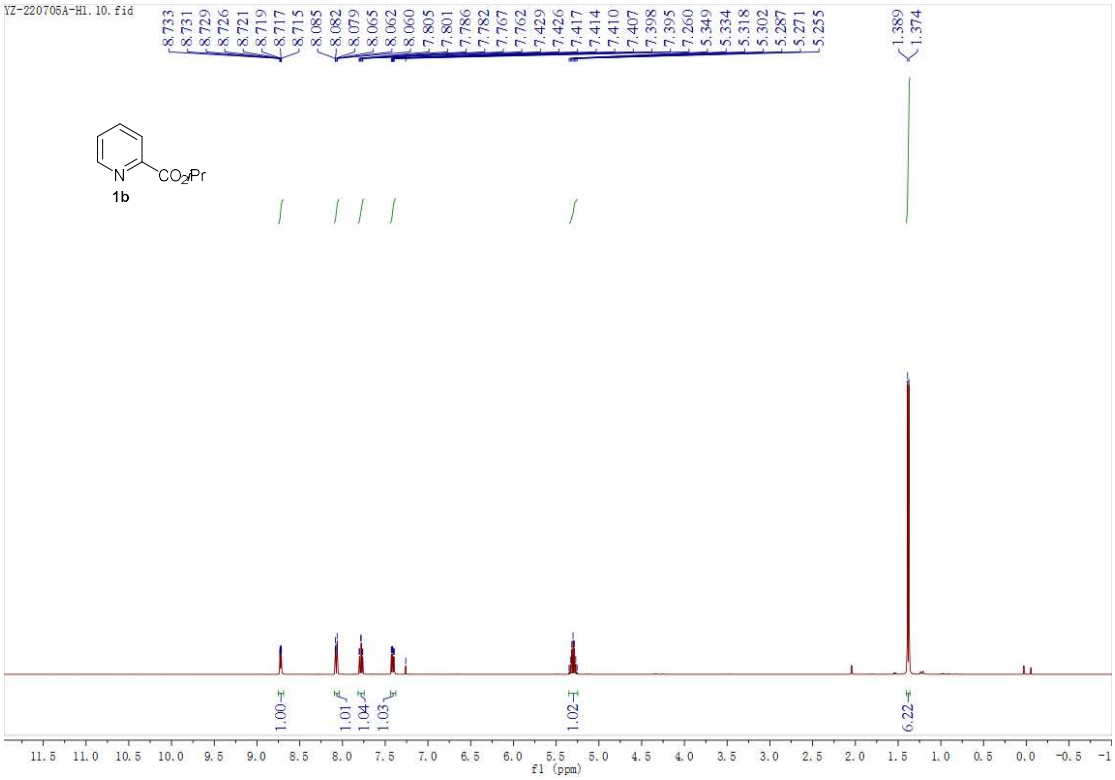
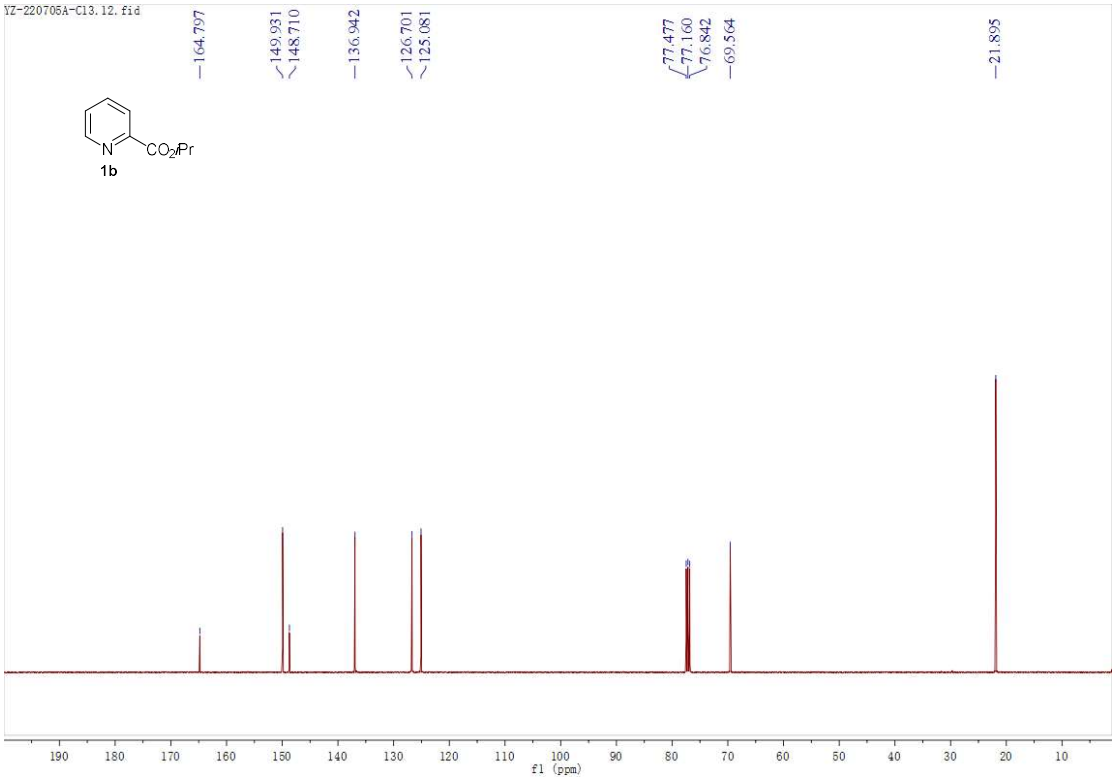
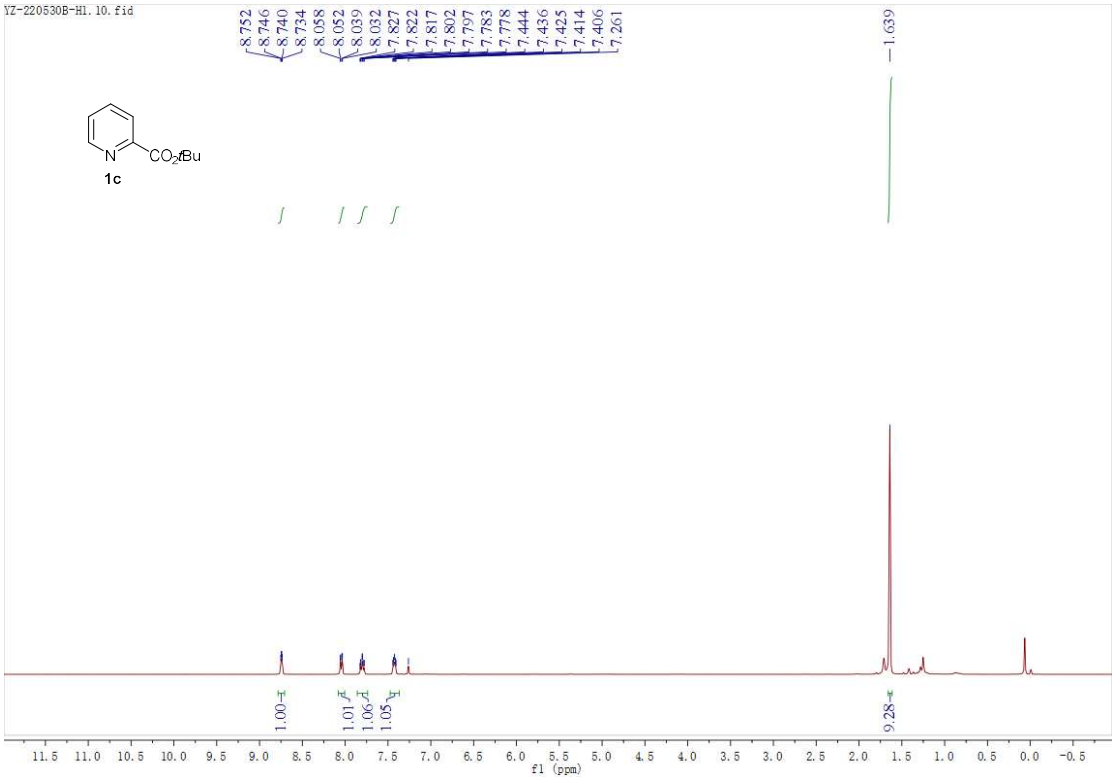
4. NMR Spectra



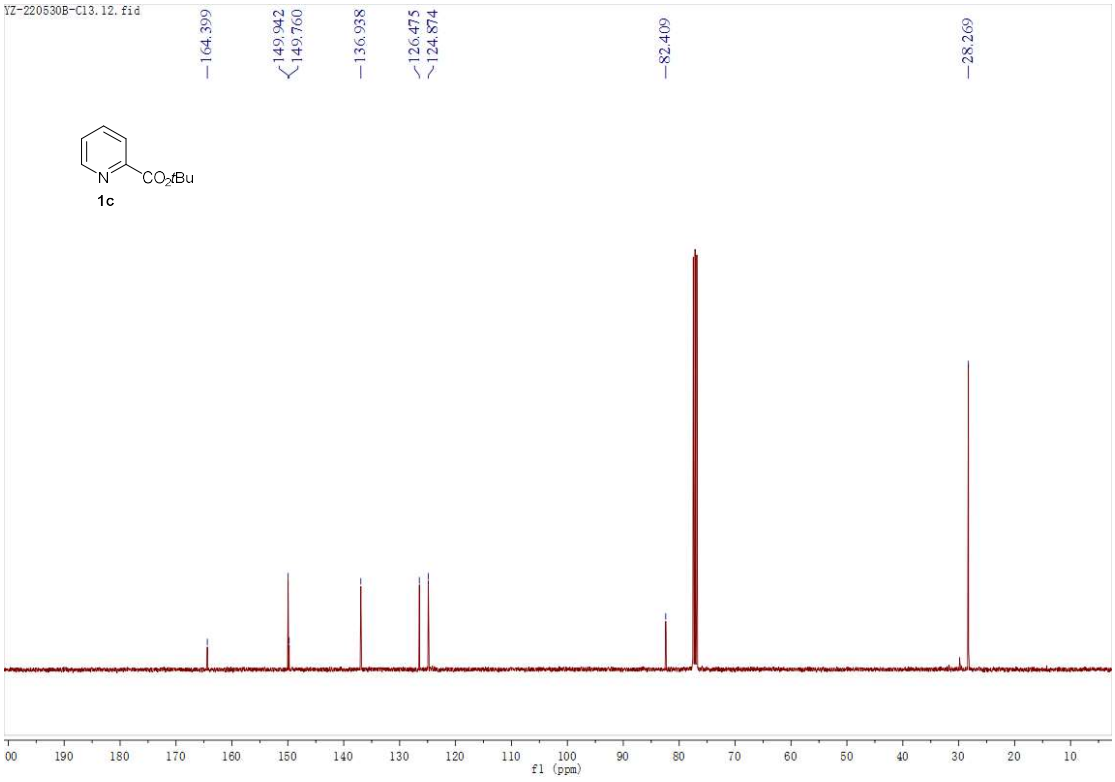
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1b



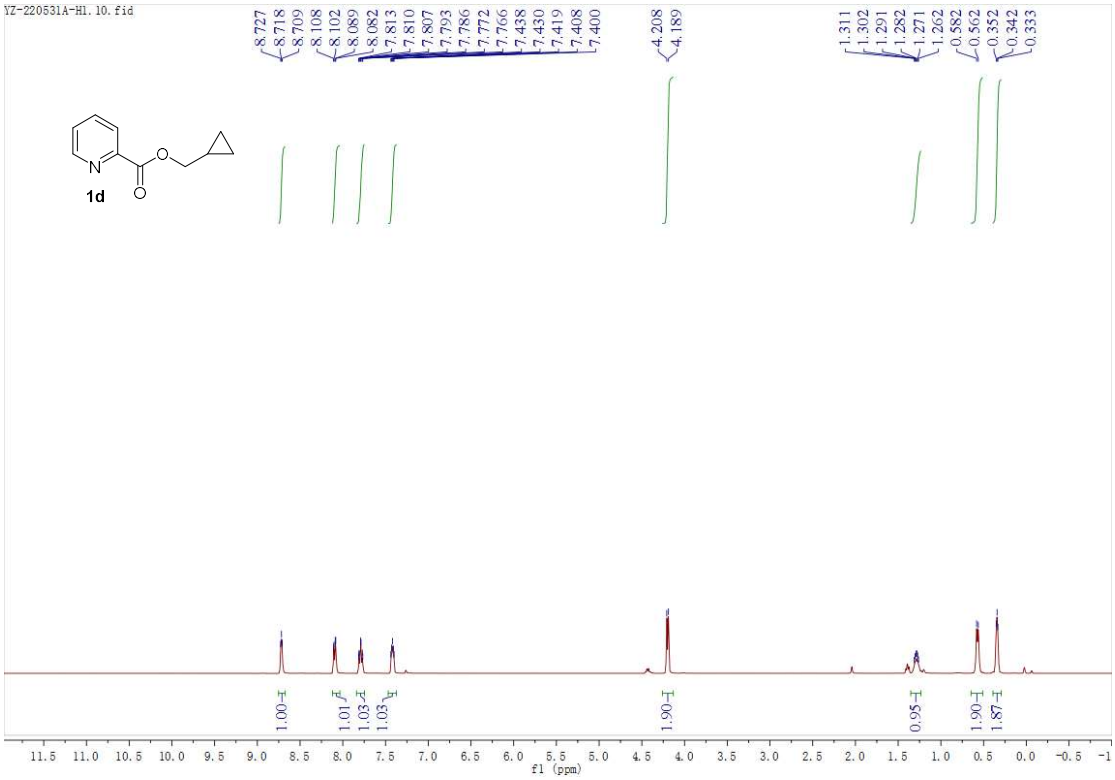
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1b



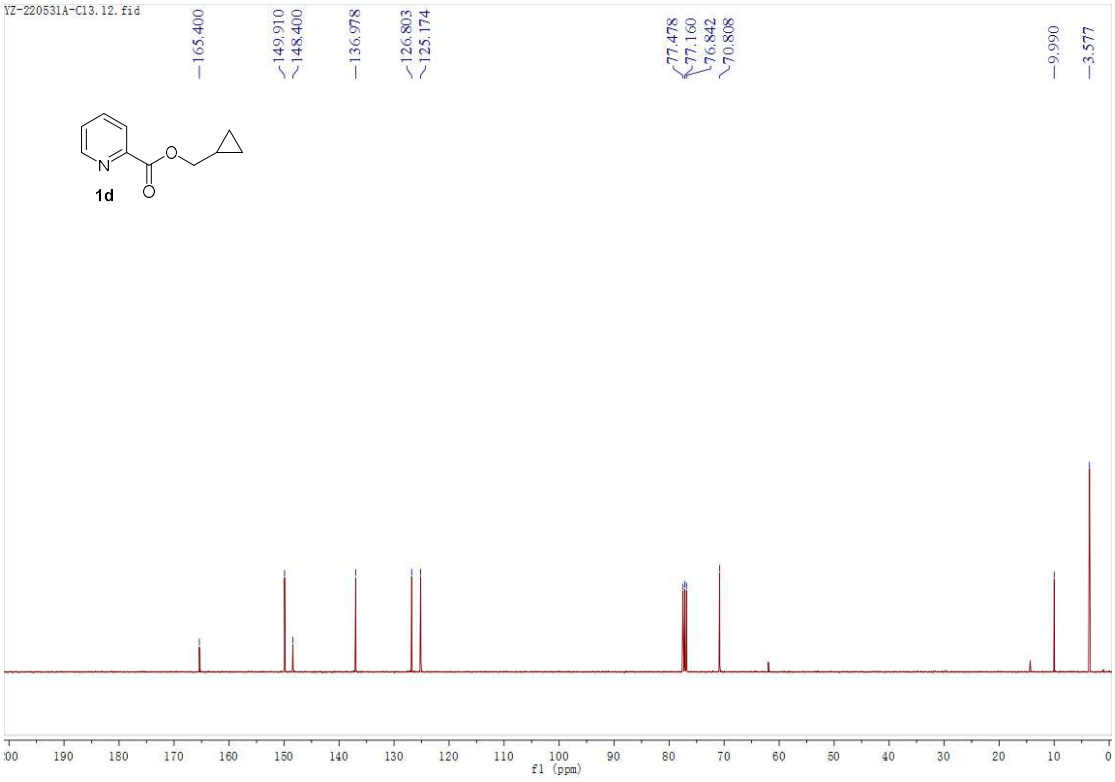
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1c



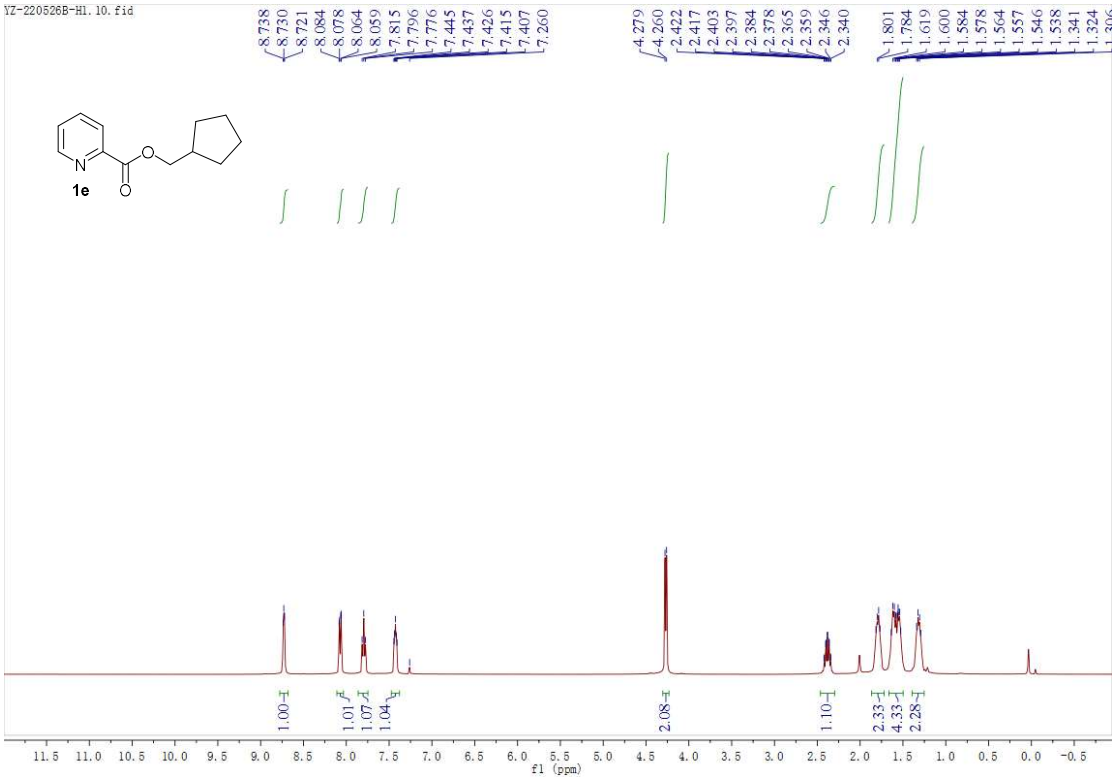
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1c



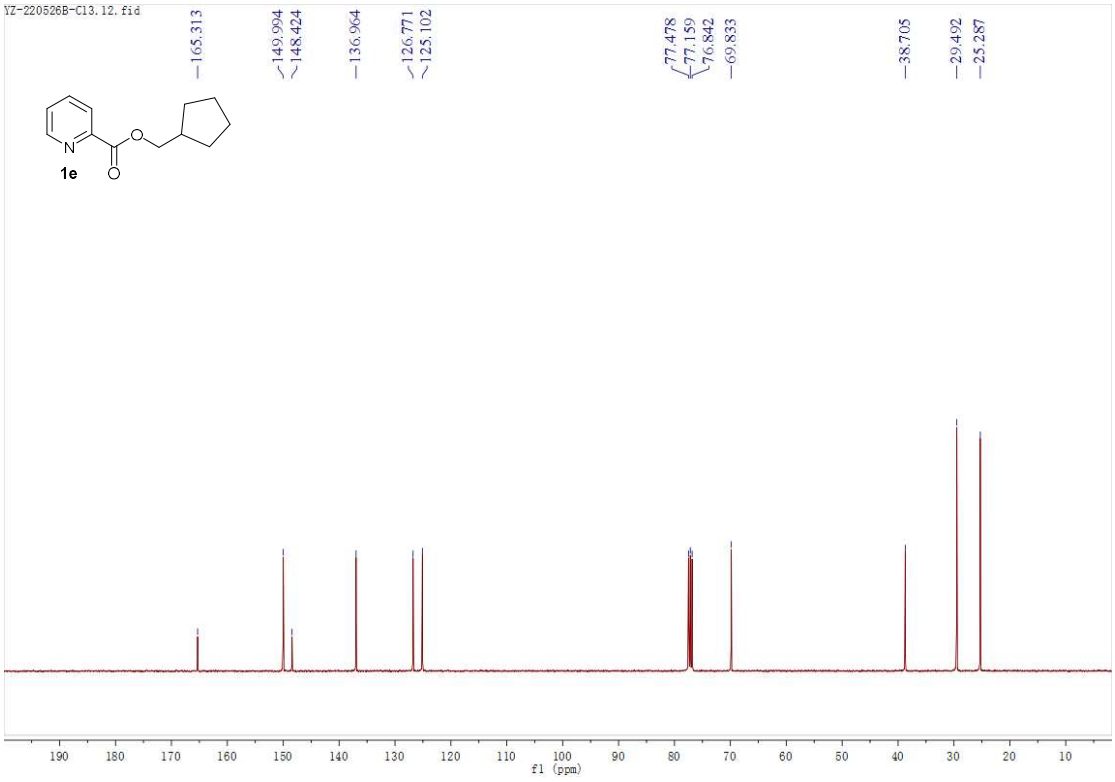
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1d



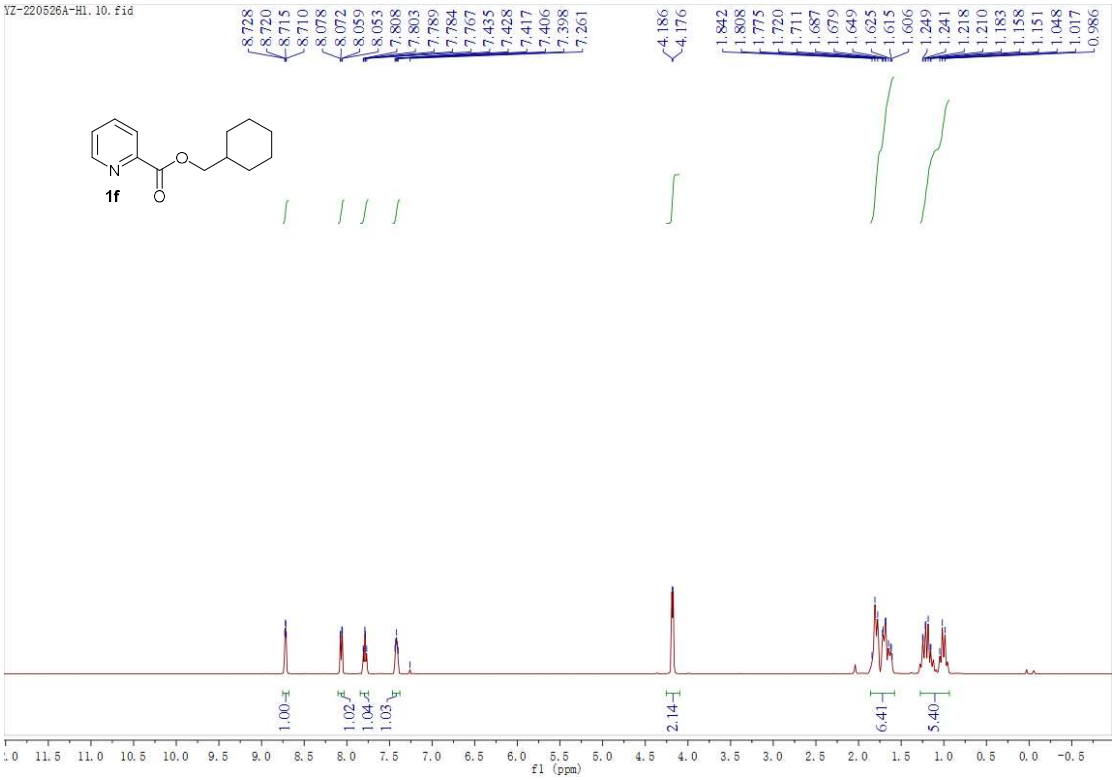
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1d



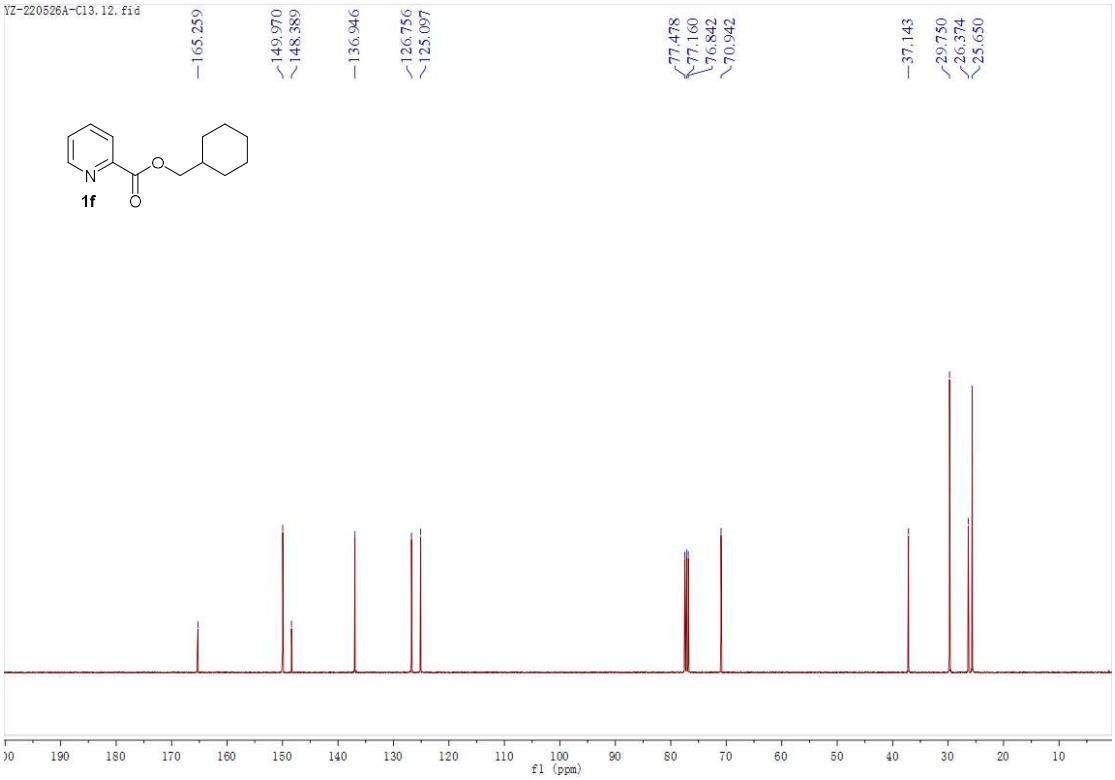
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1e



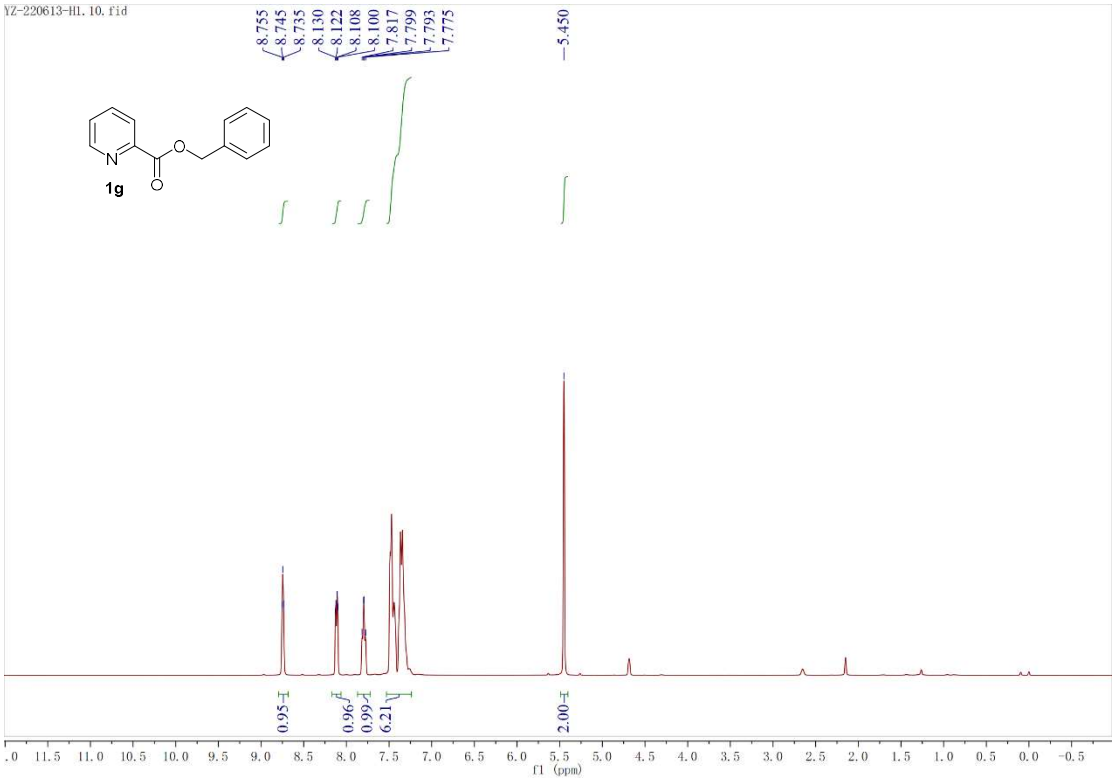
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1e



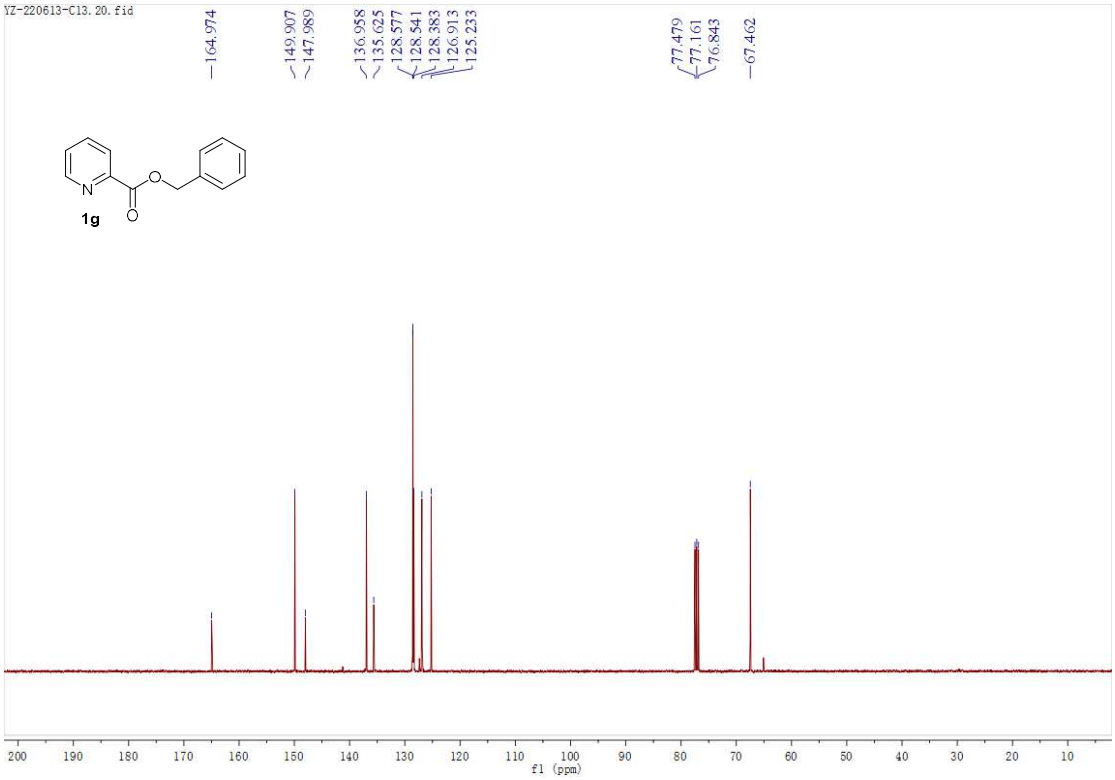
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1f



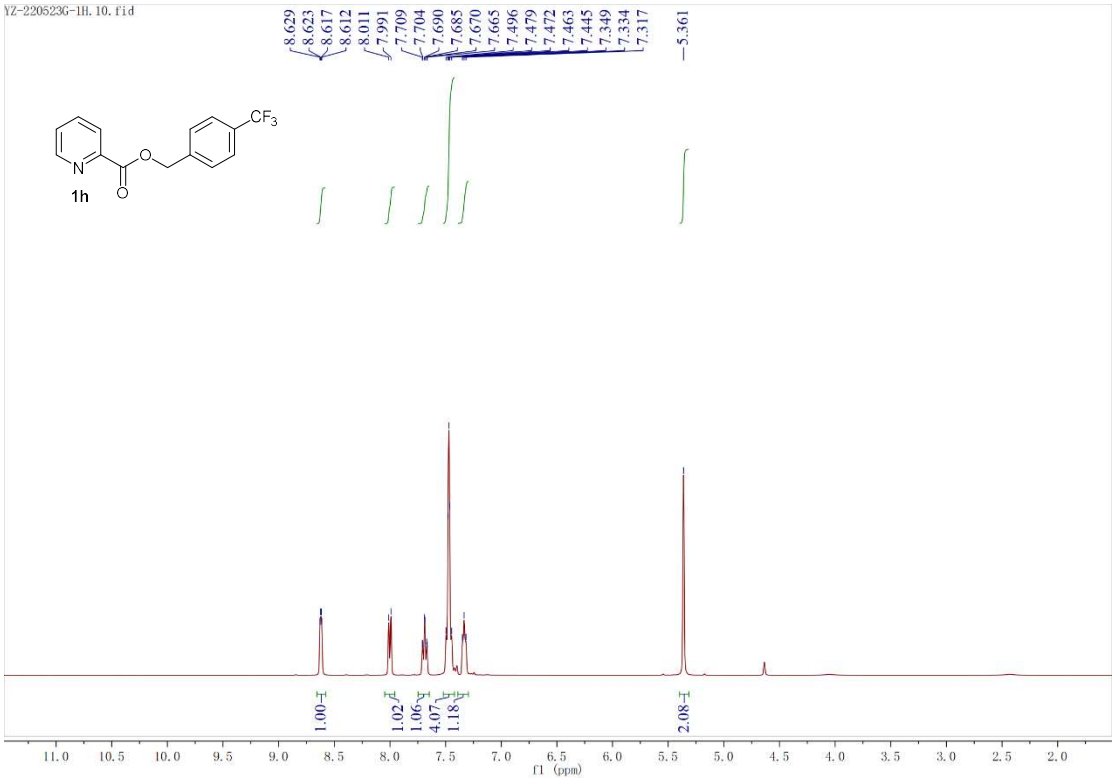
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1f



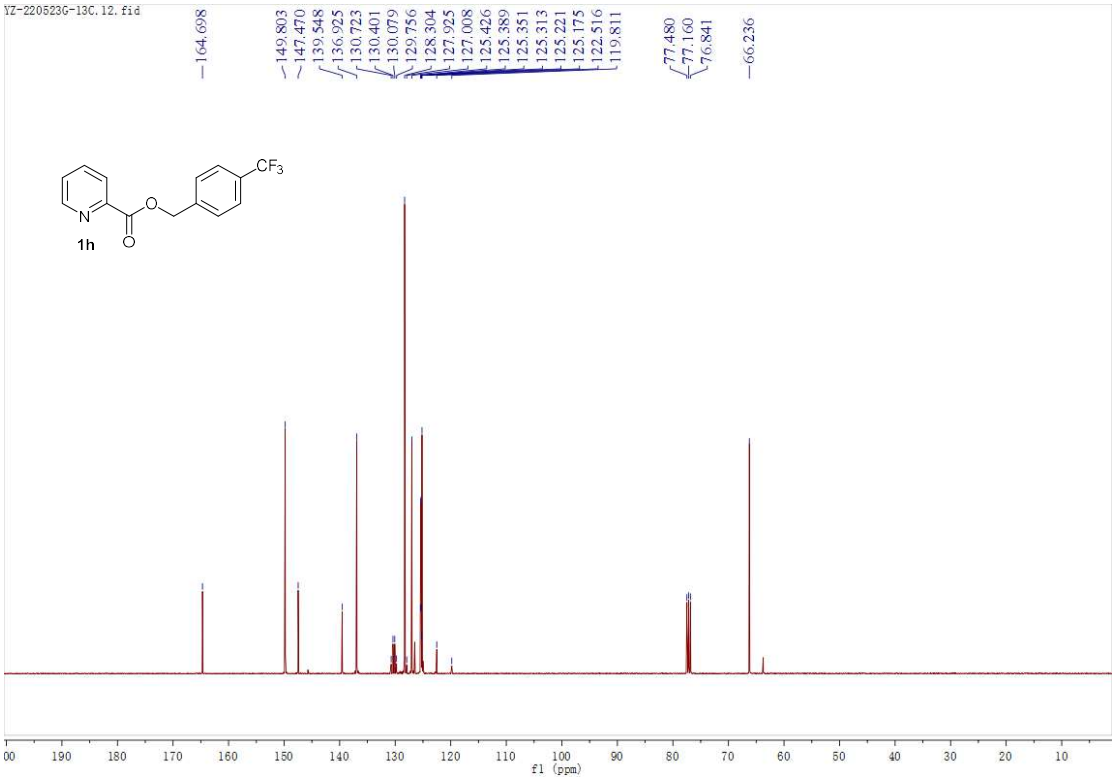
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1g



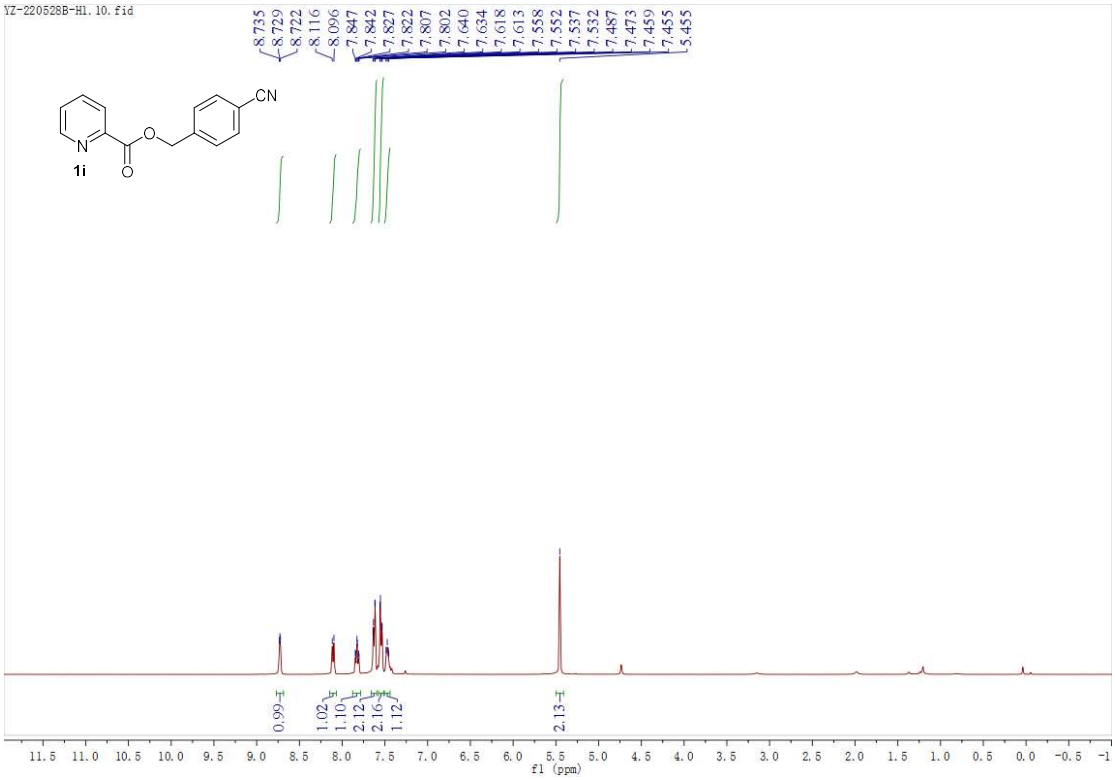
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1g



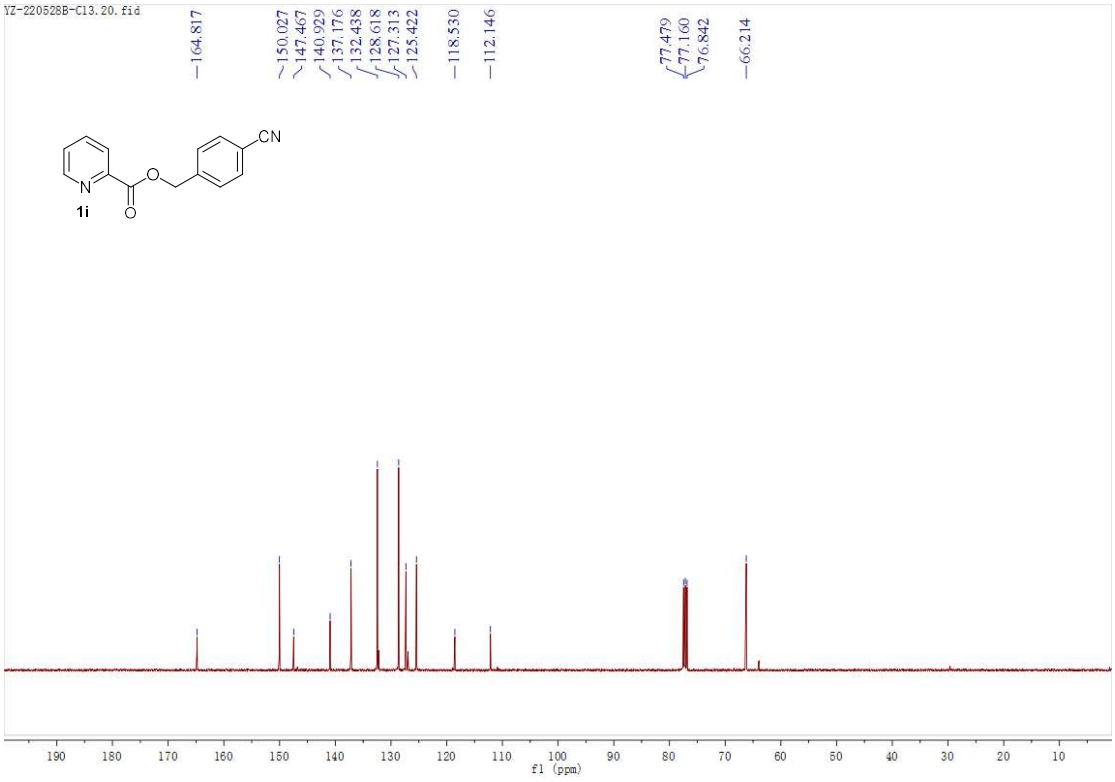
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1h



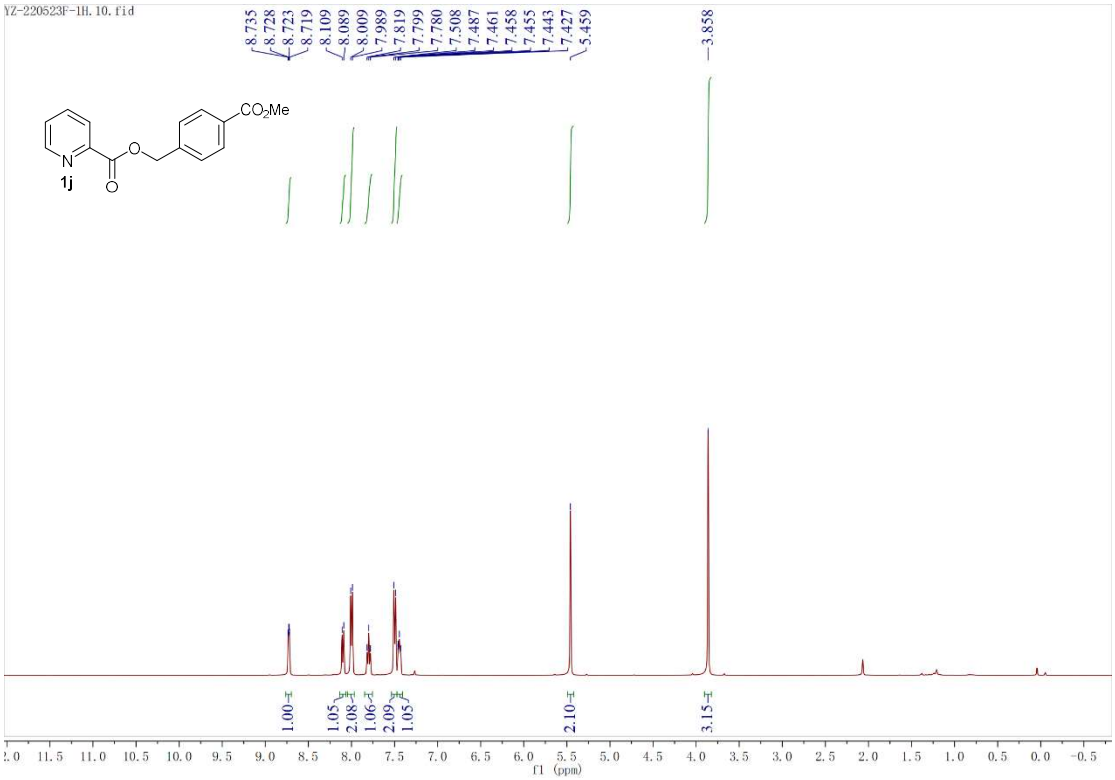
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1h



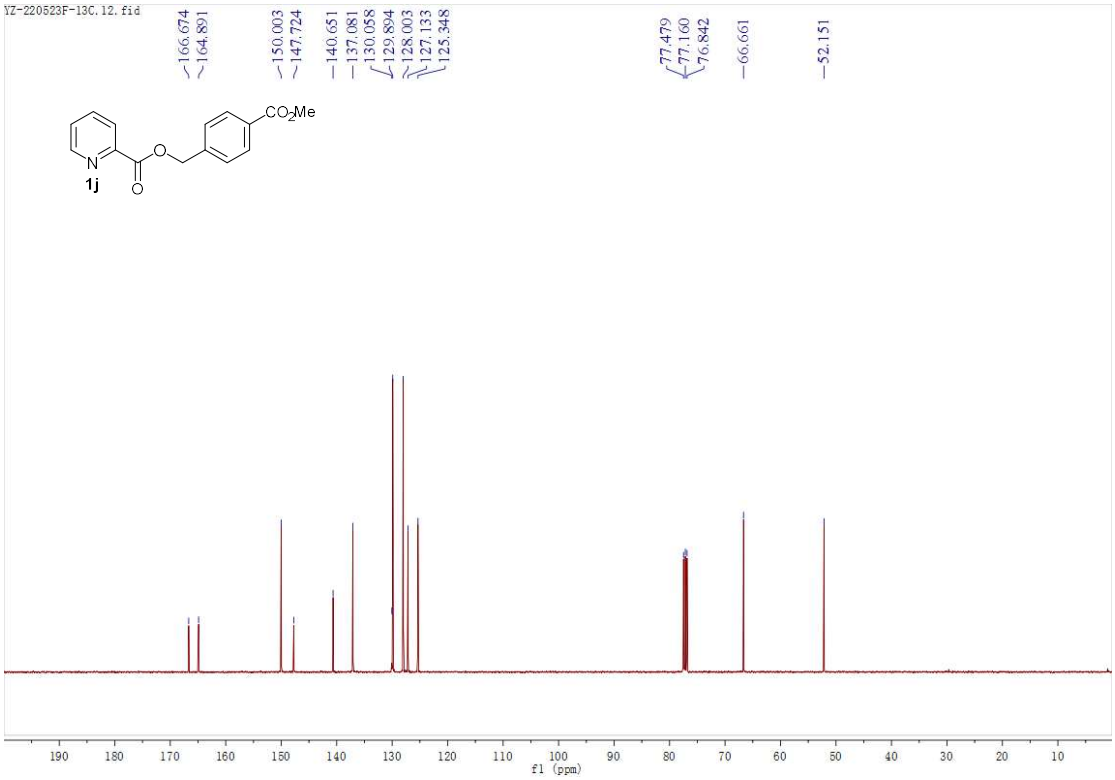
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 2i



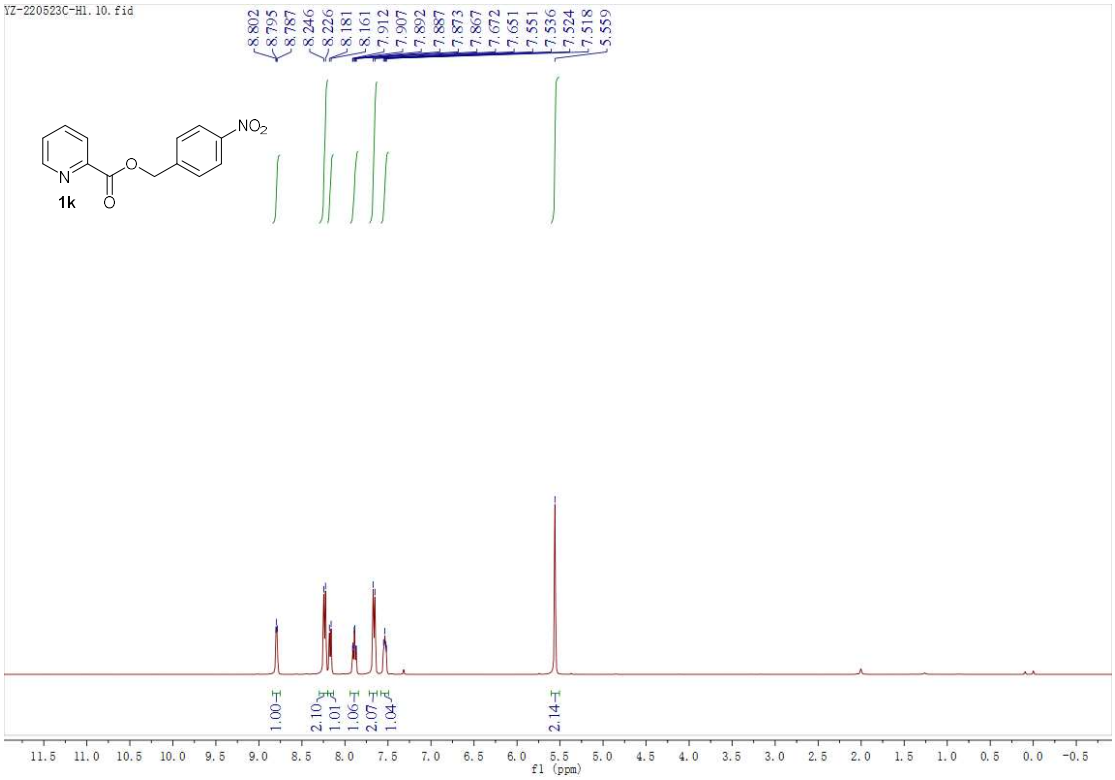
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 2i



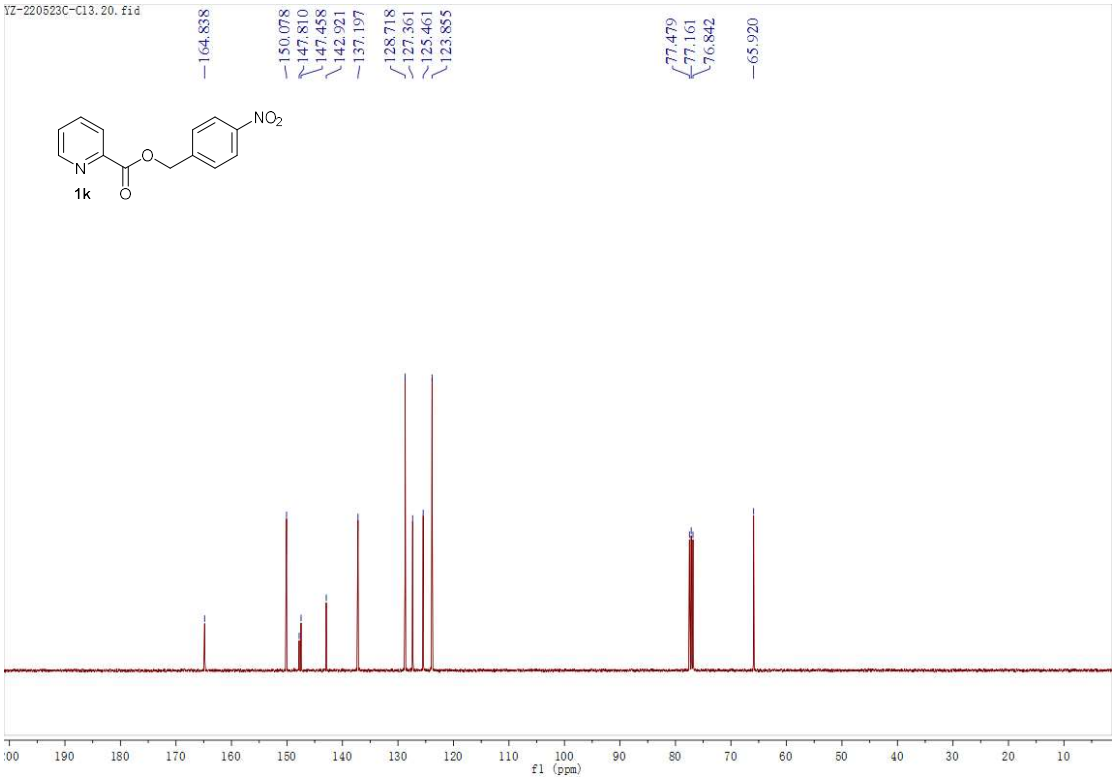
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1j



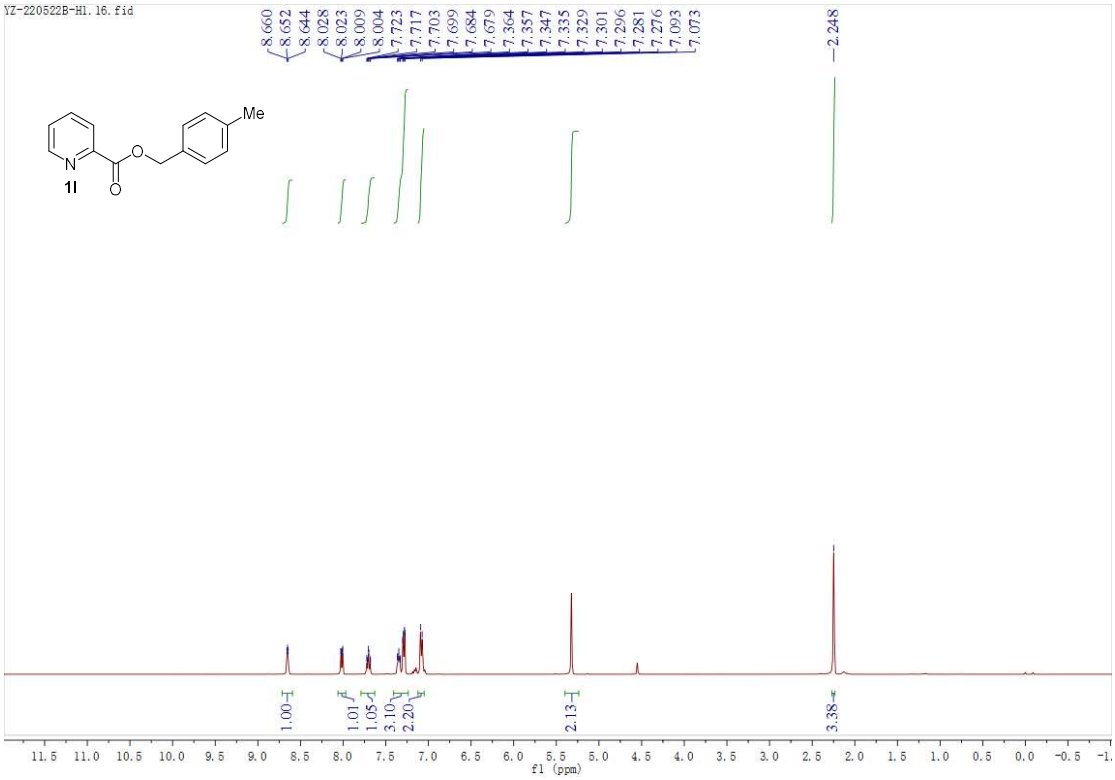
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1j



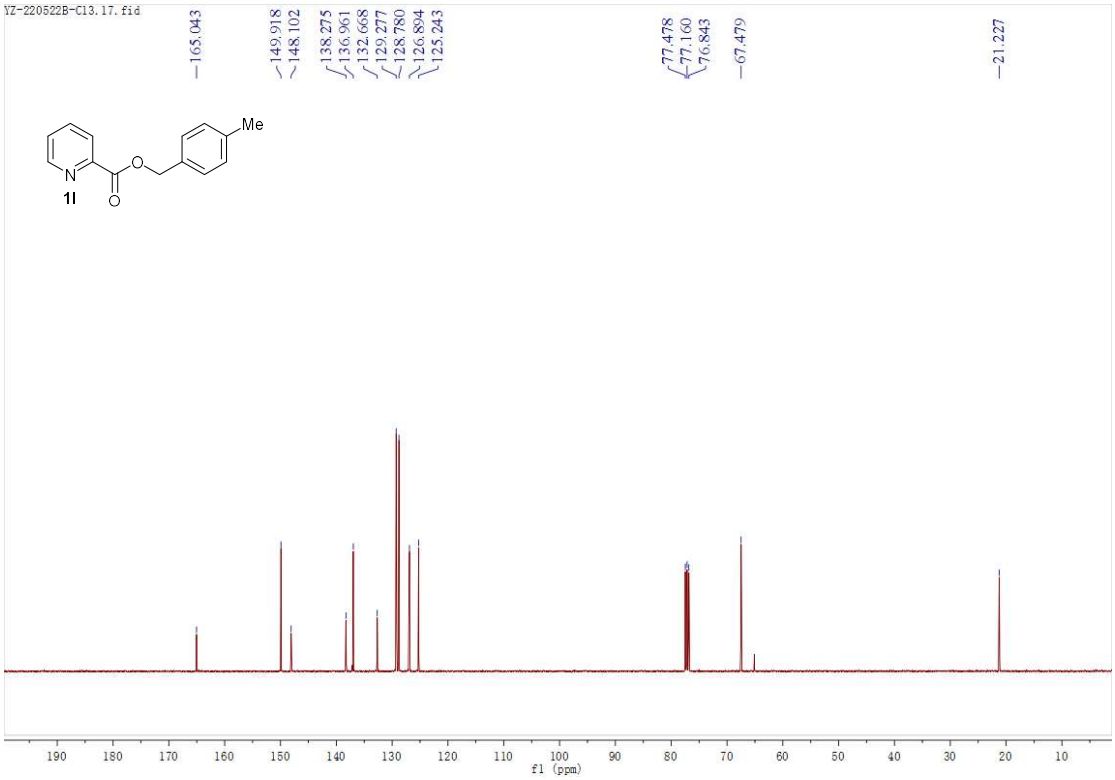
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1k



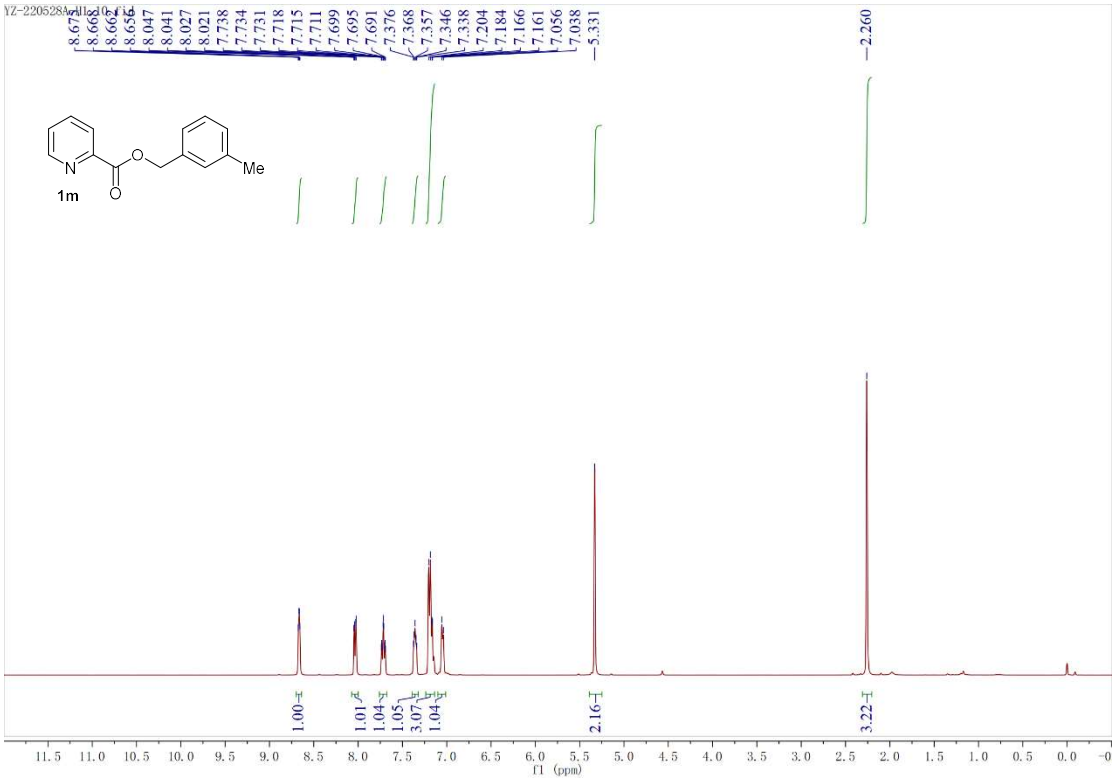
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1k



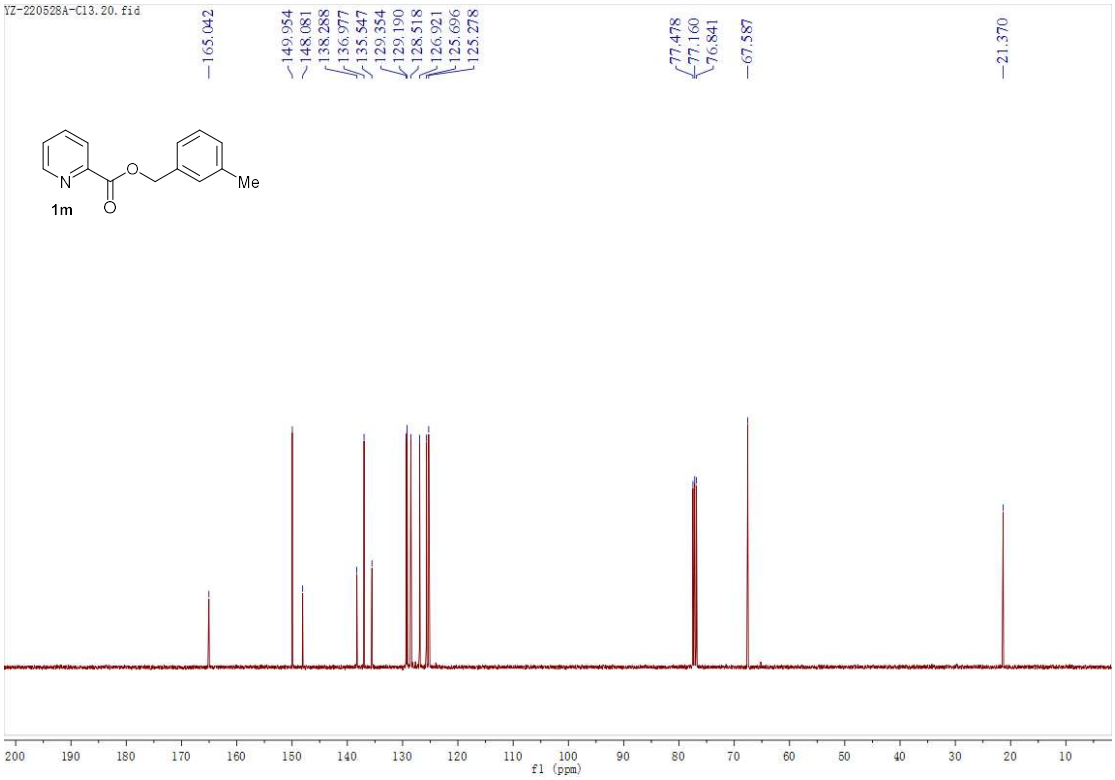
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1l



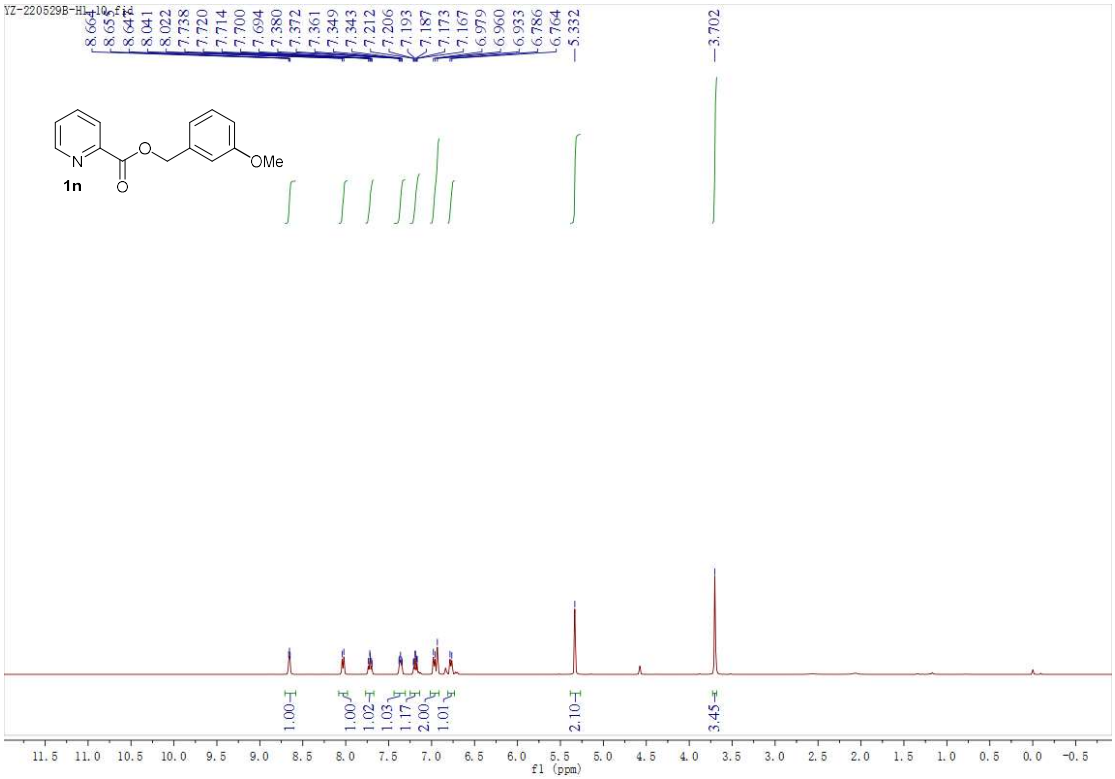
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1l



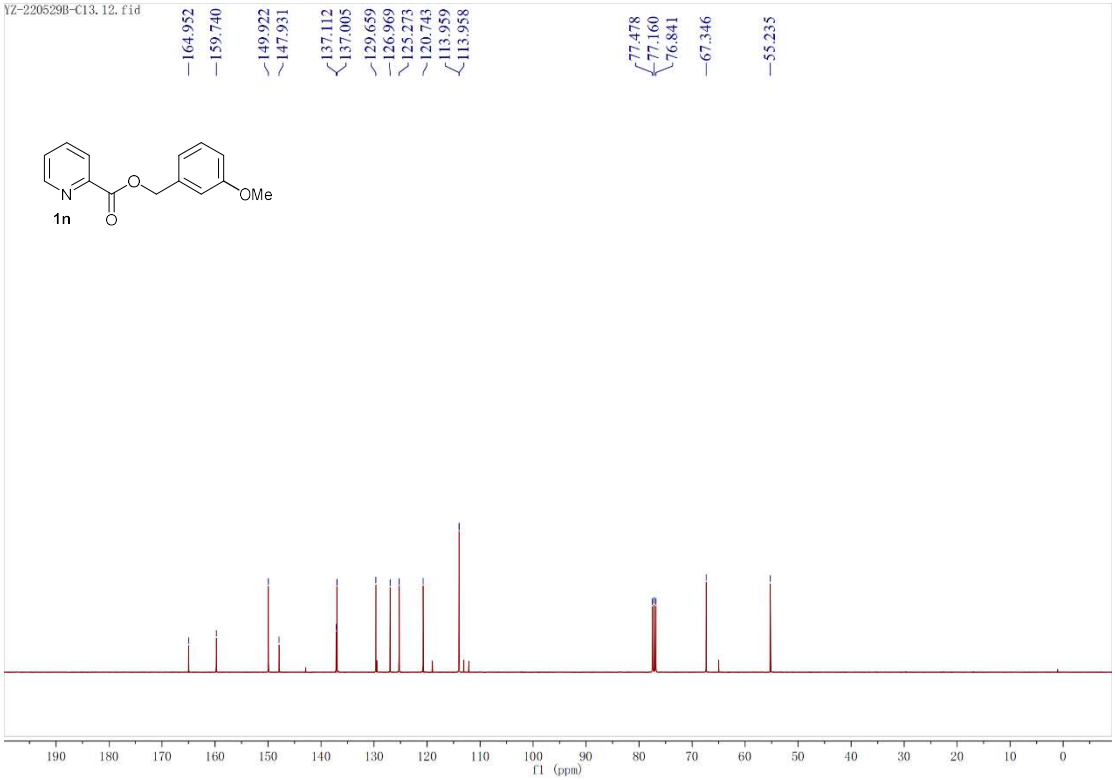
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1m



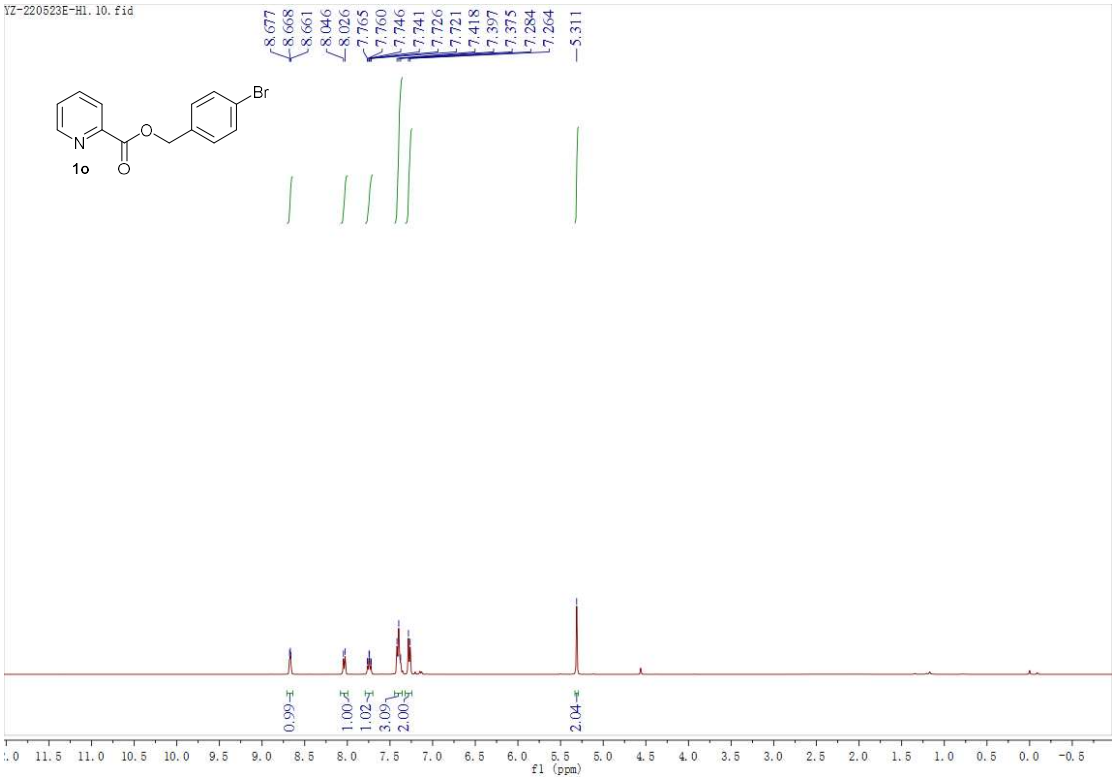
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1m



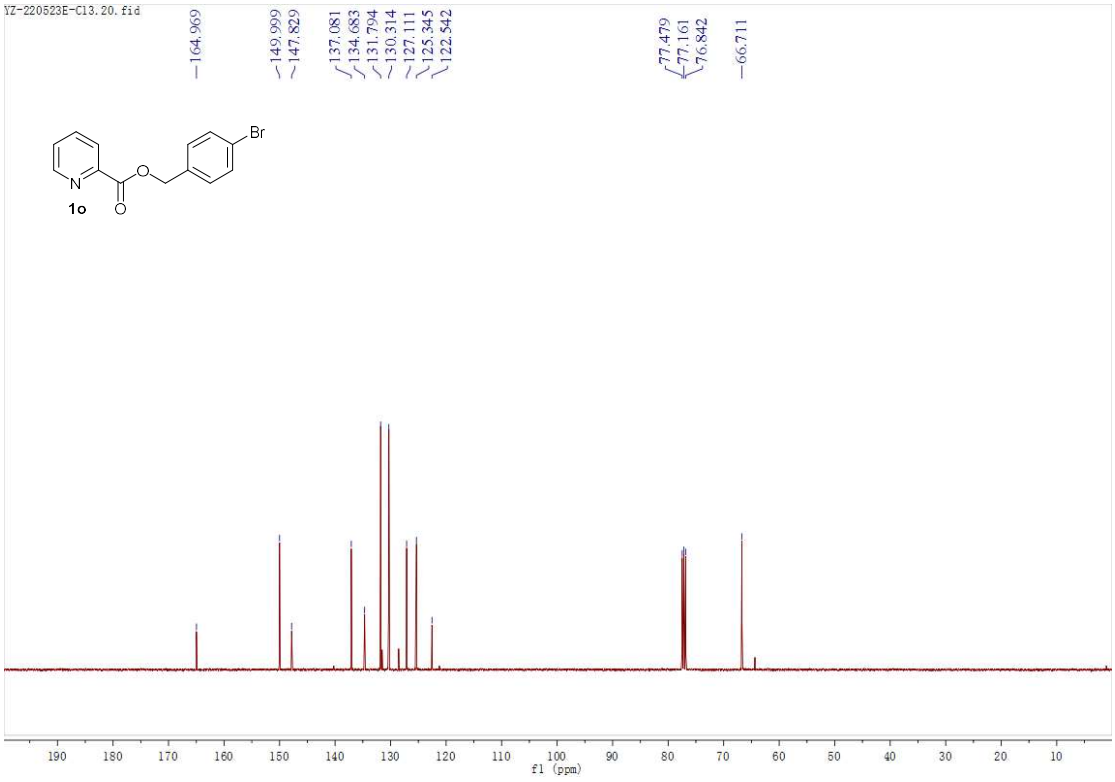
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1n



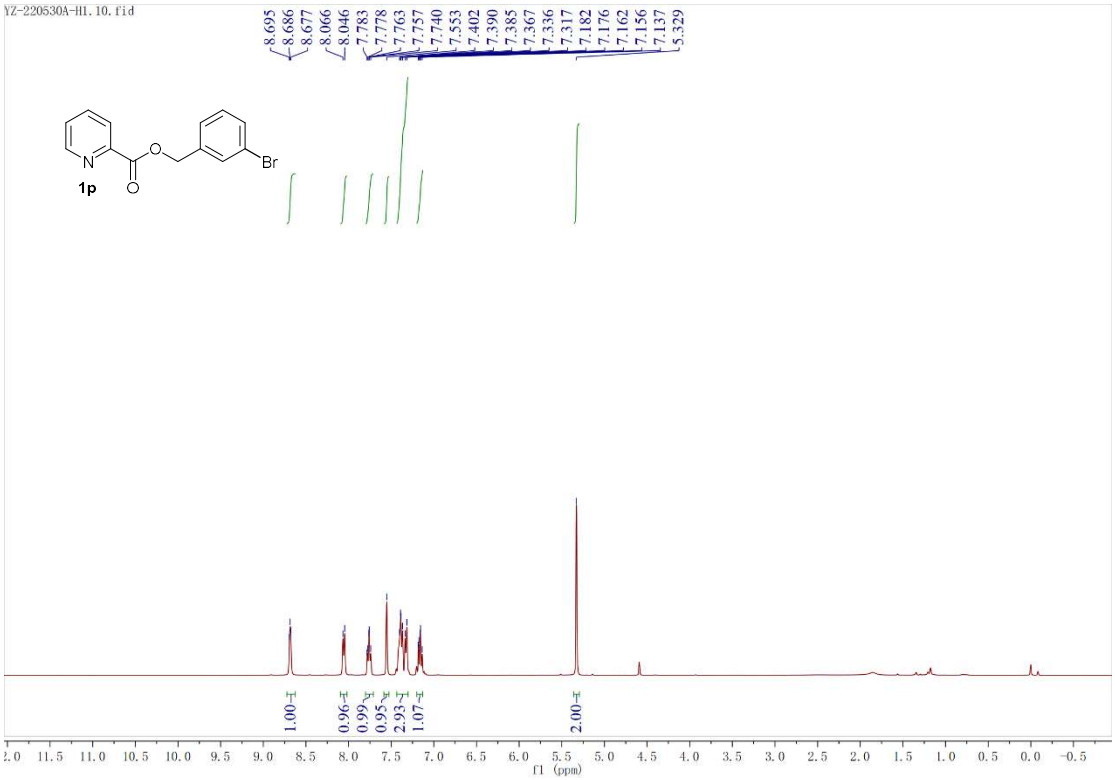
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1n



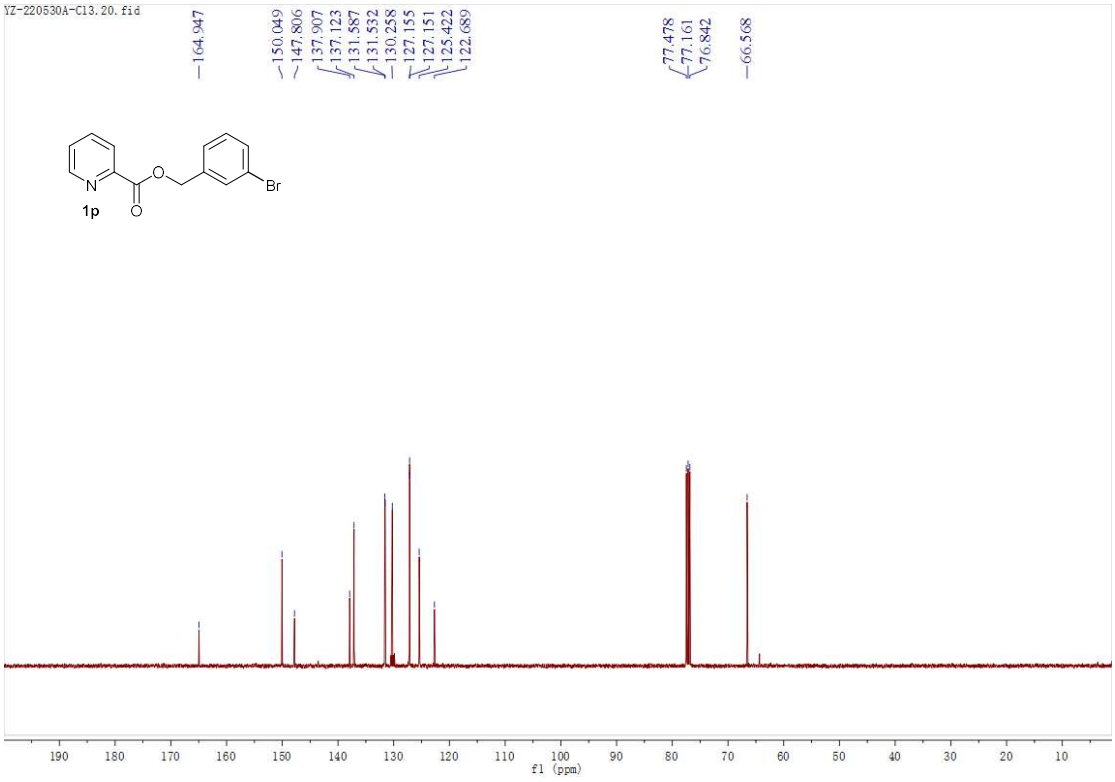
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1o



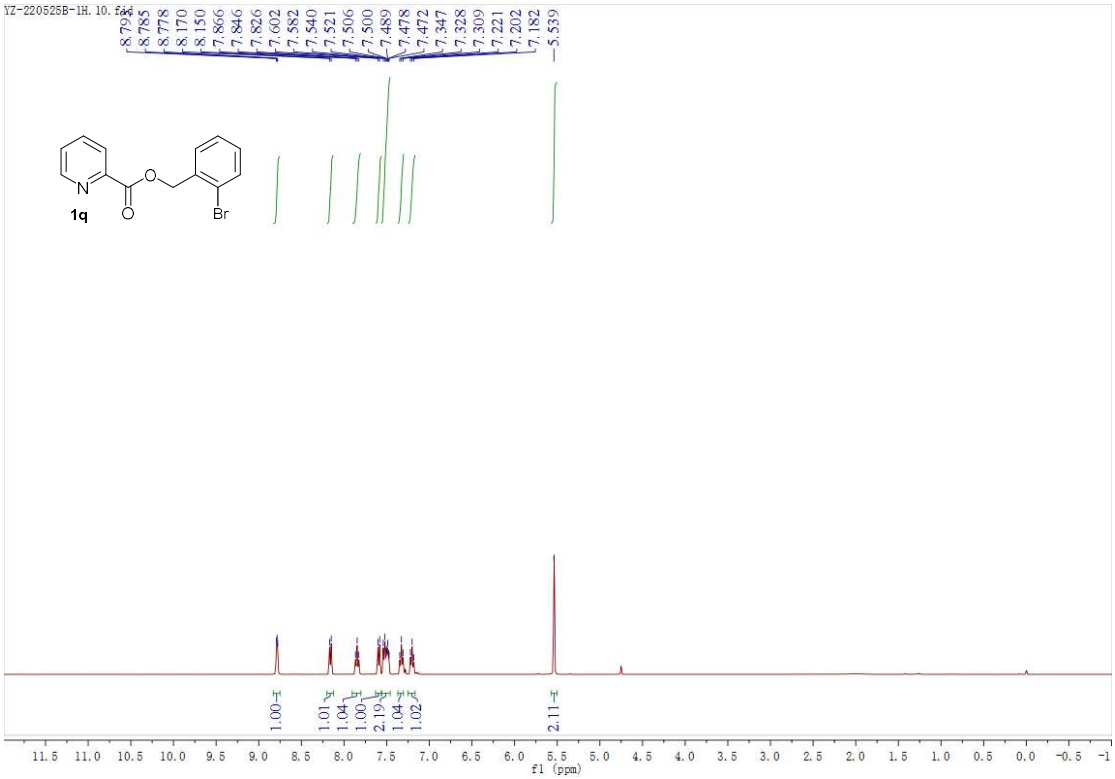
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1o



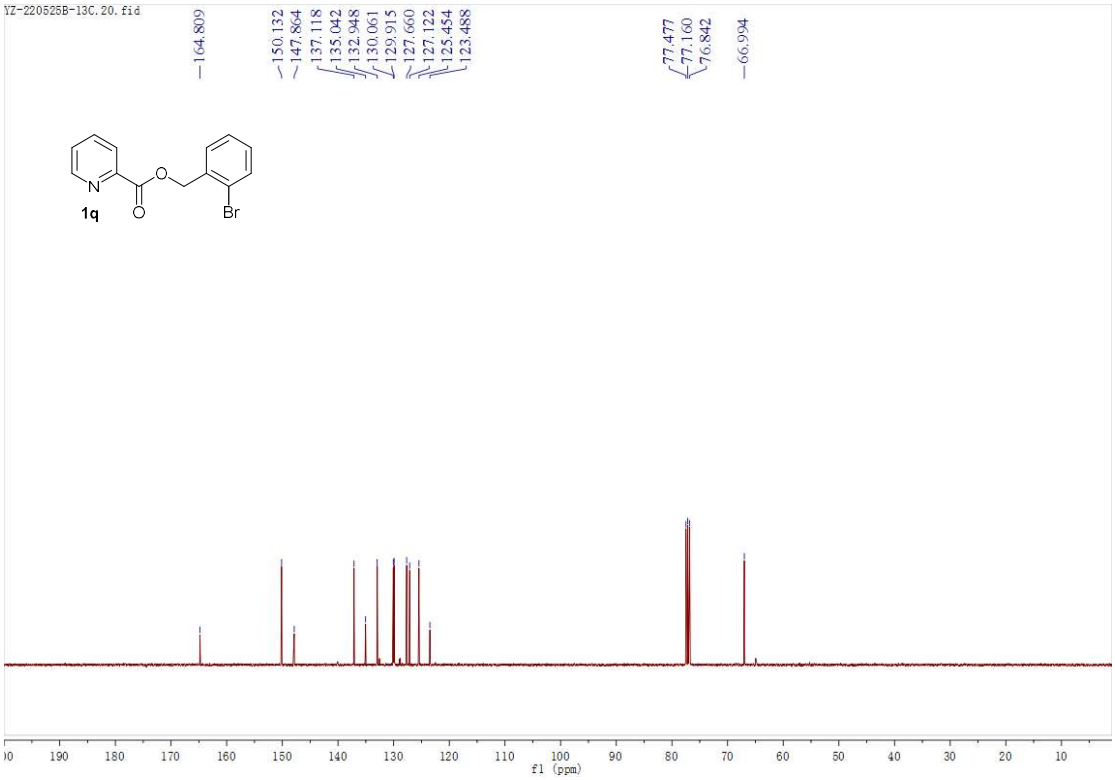
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1p



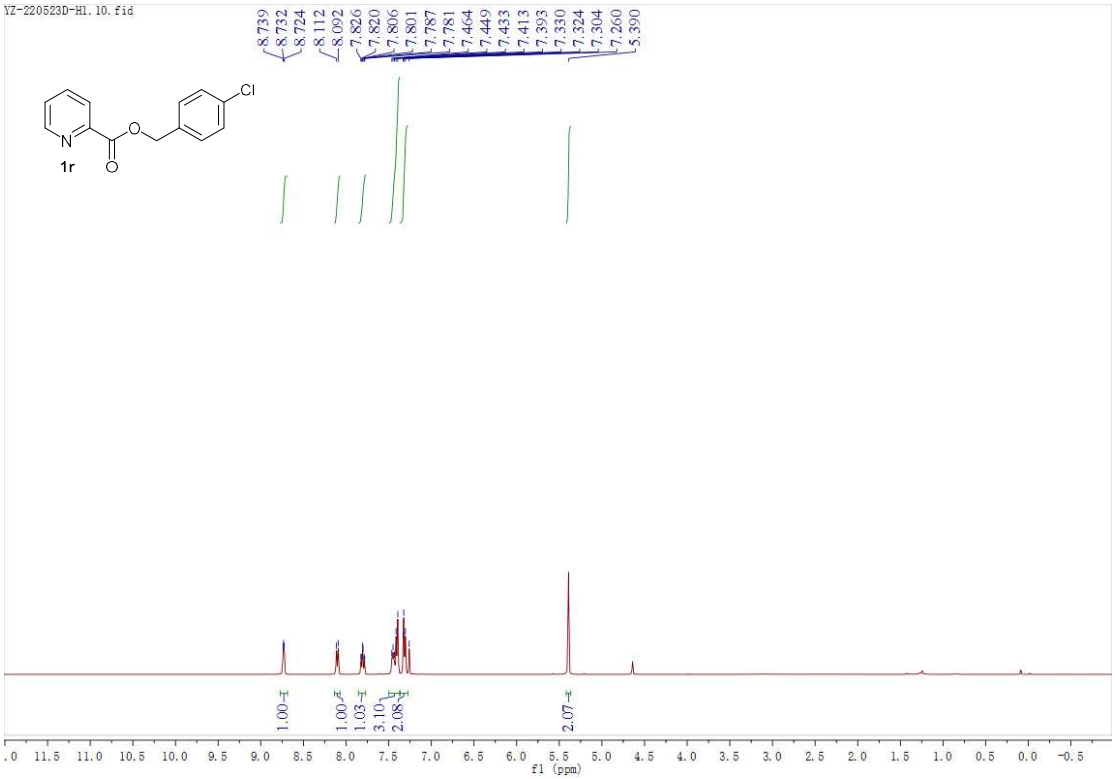
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1p



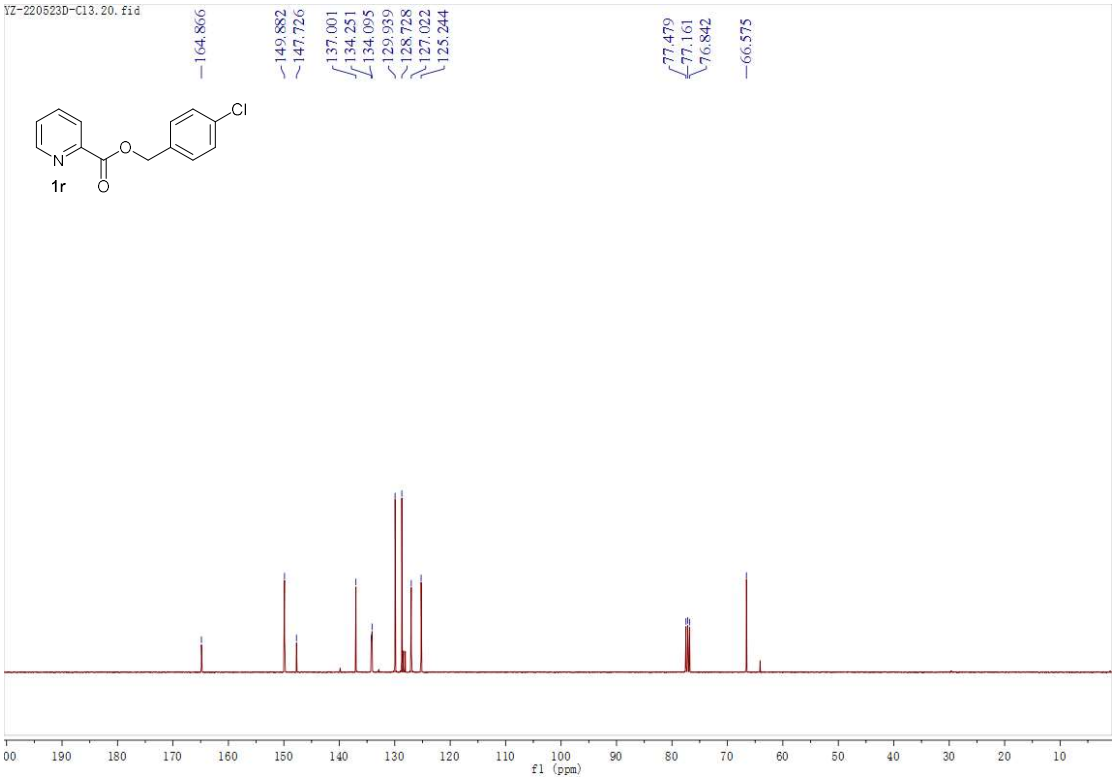
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1q



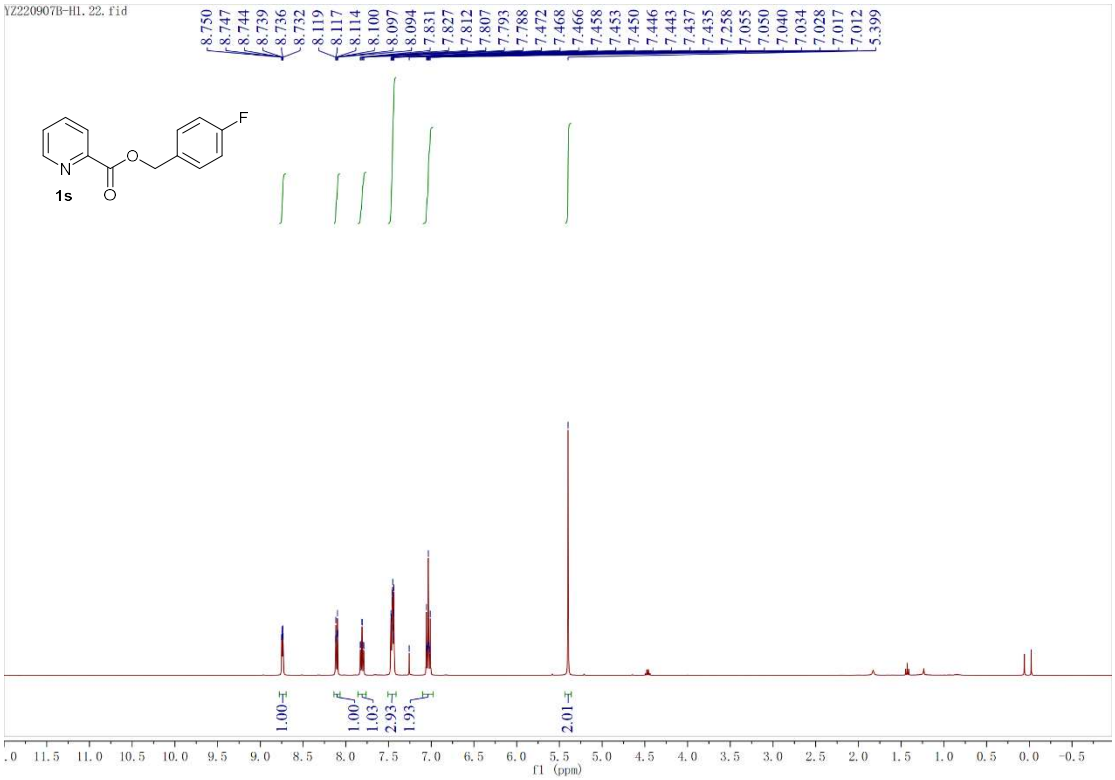
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1q



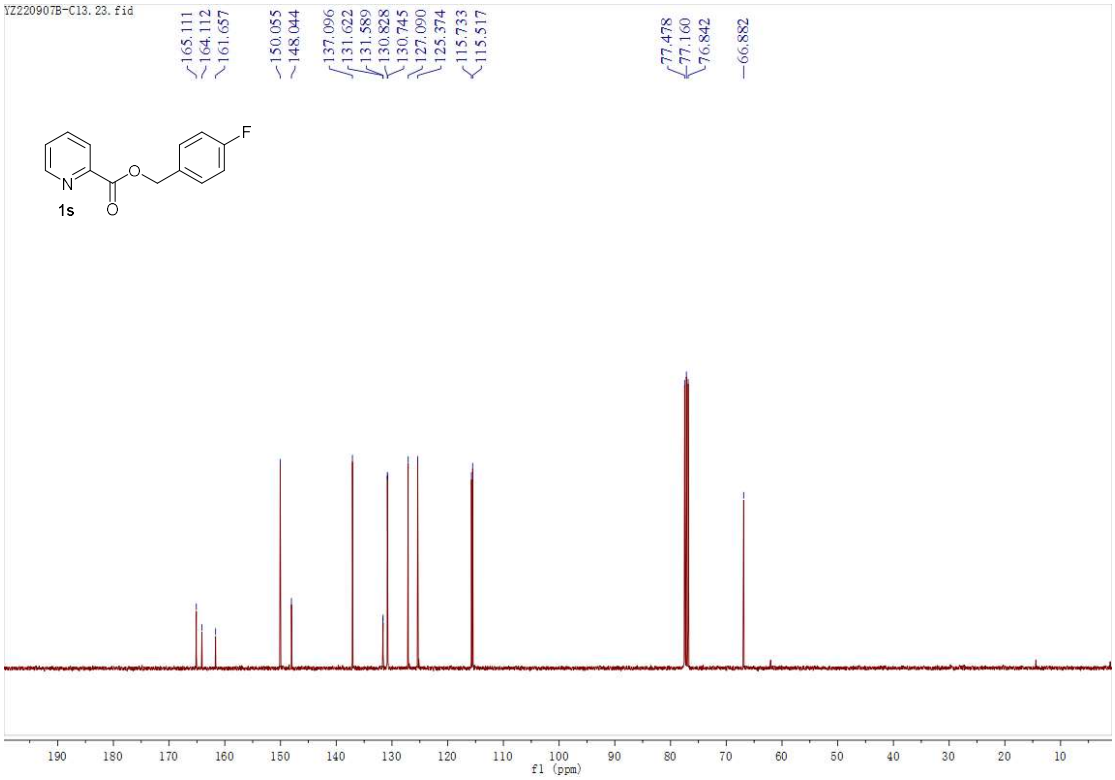
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1r



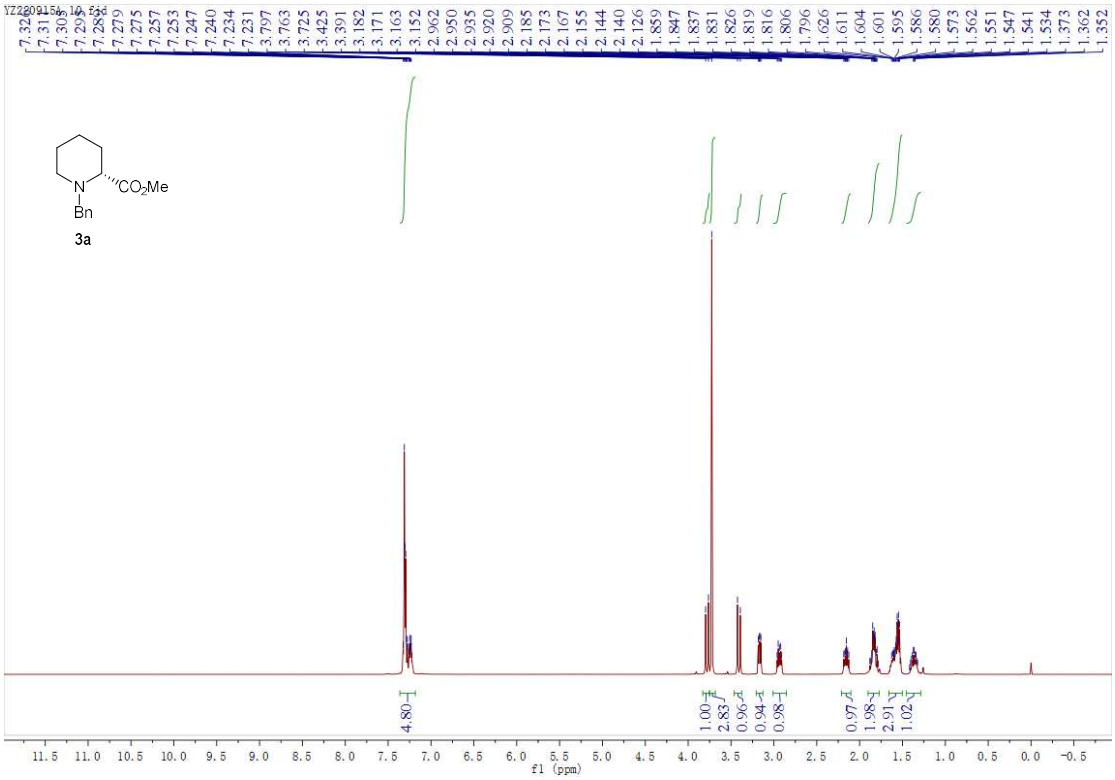
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1r



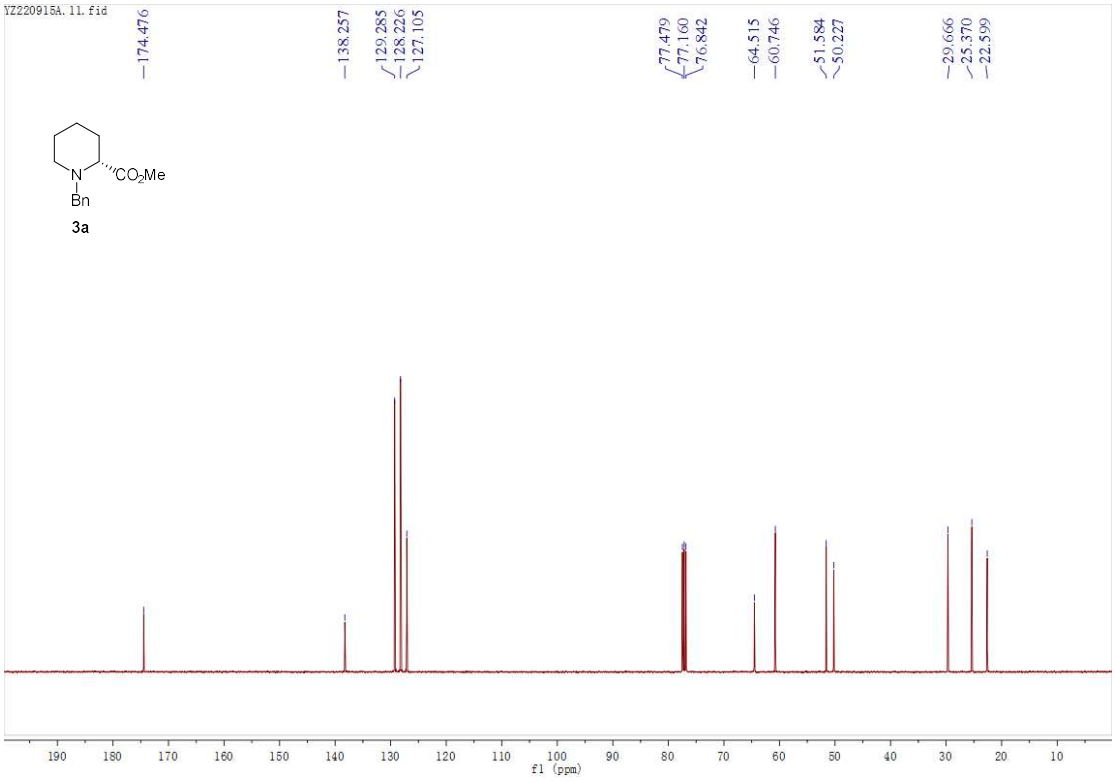
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 1s



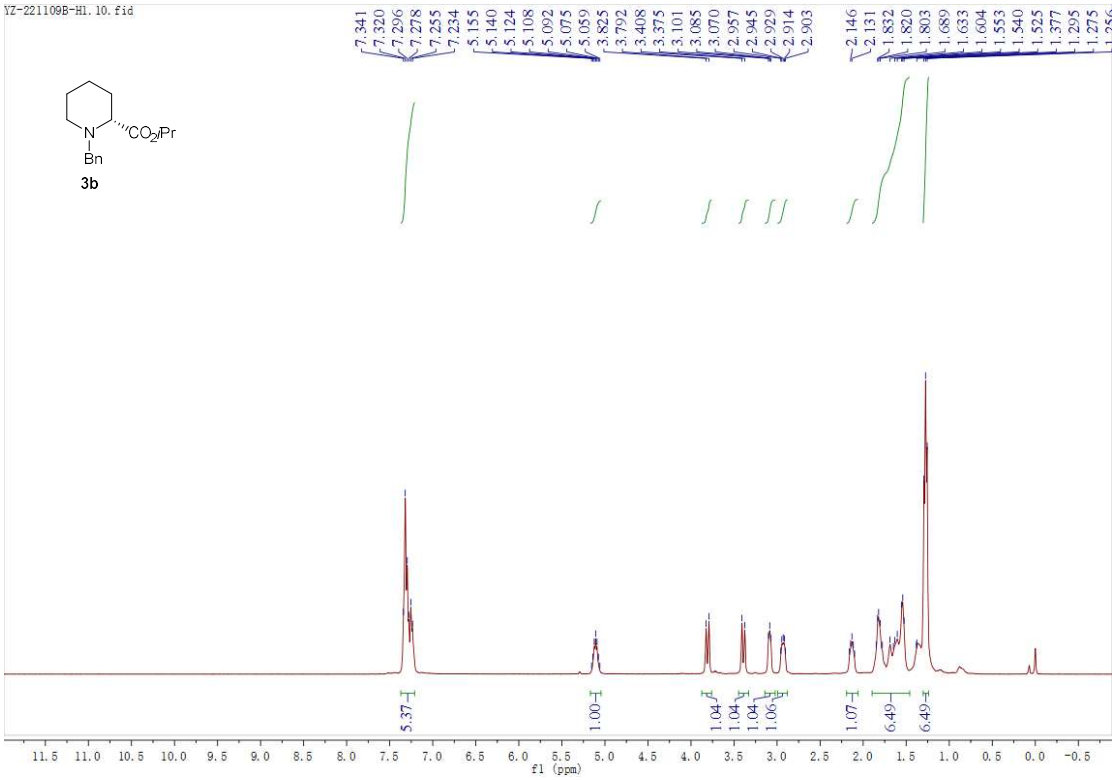
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 1s



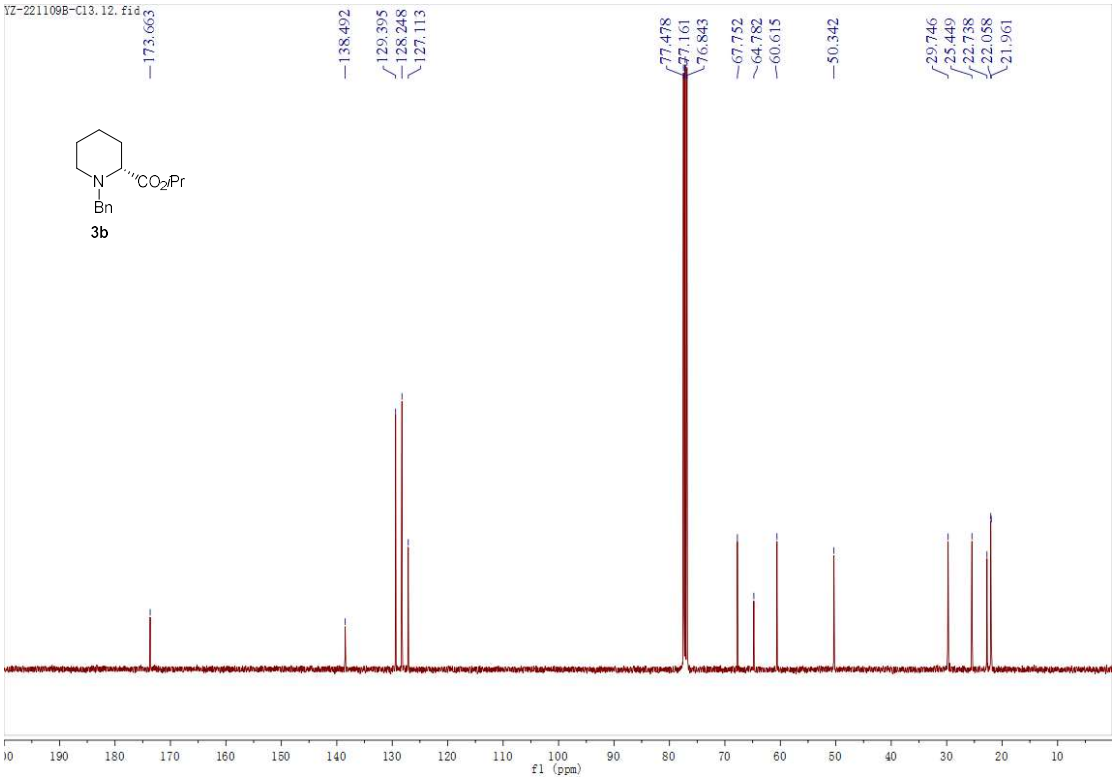
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3a



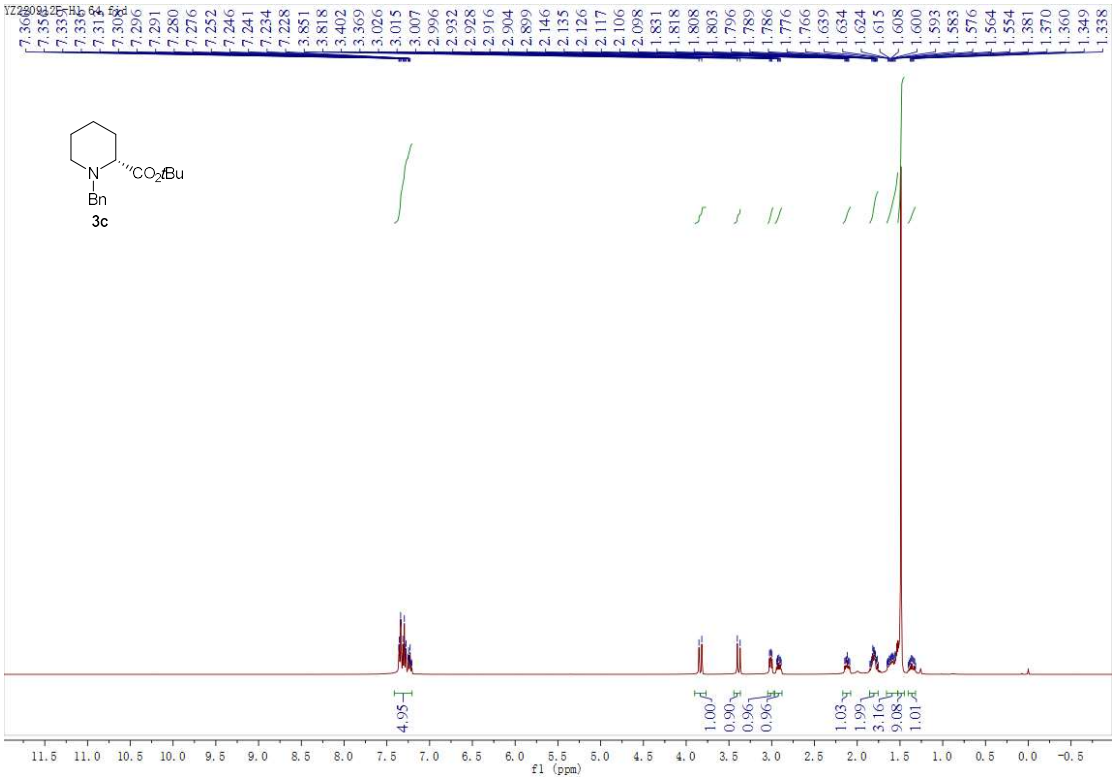
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3a



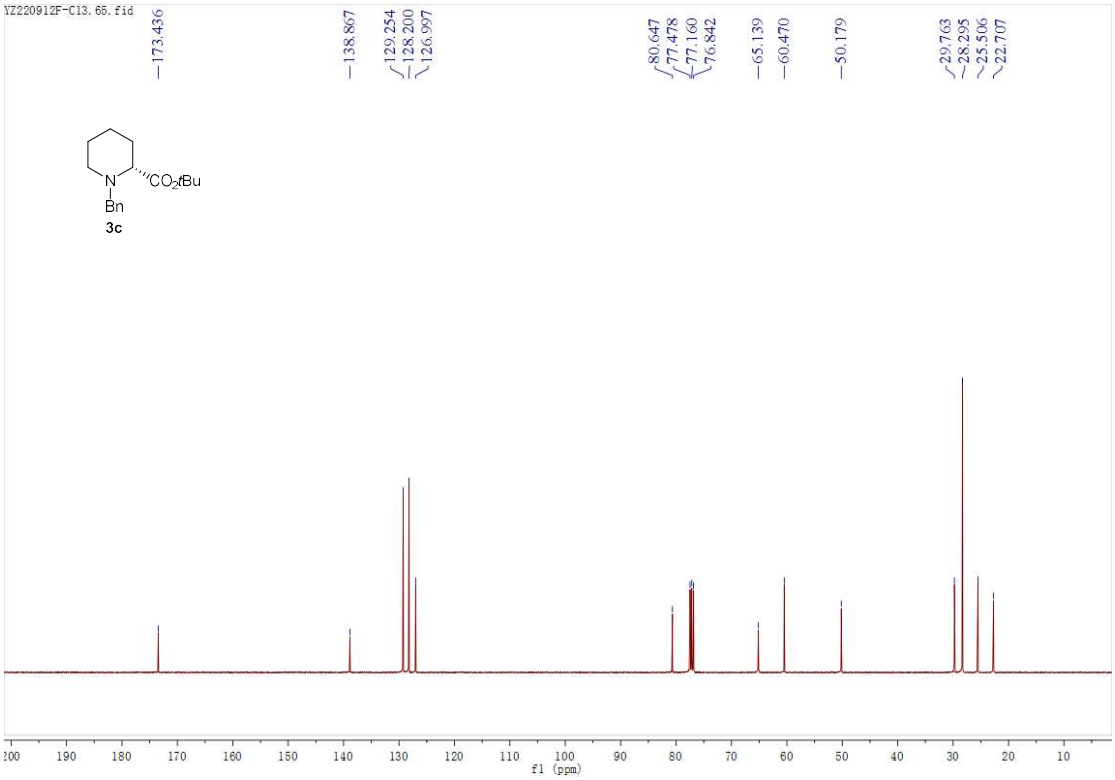
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3b



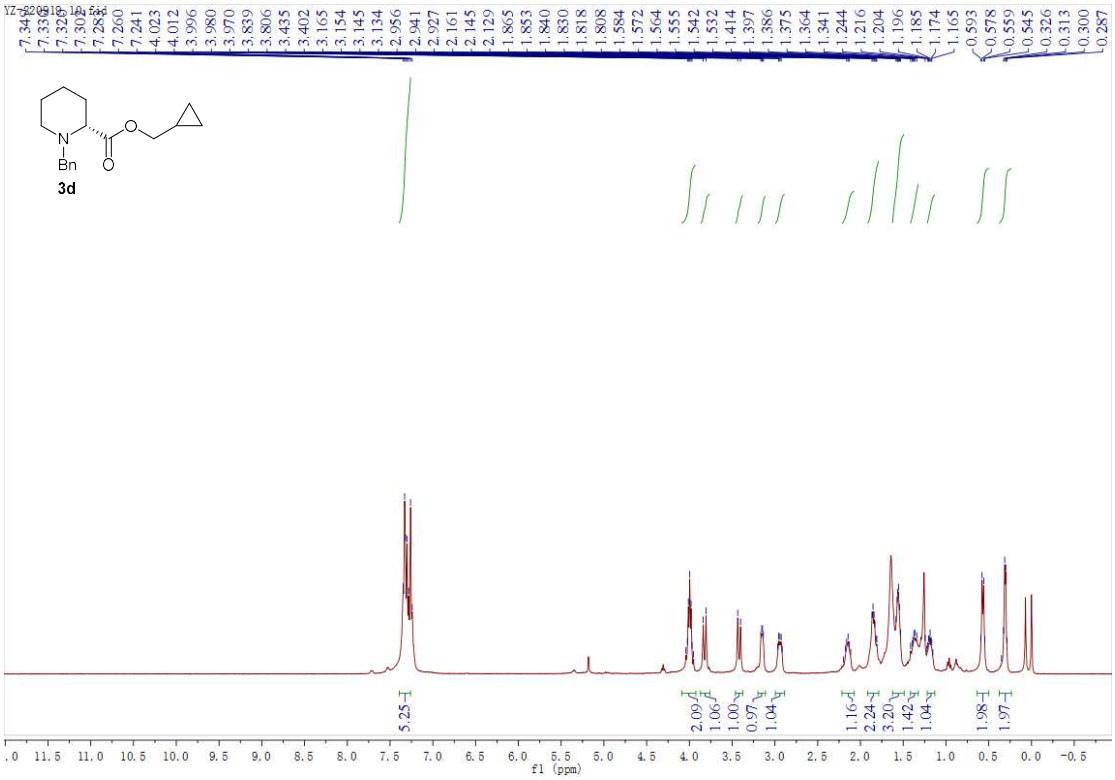
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3b



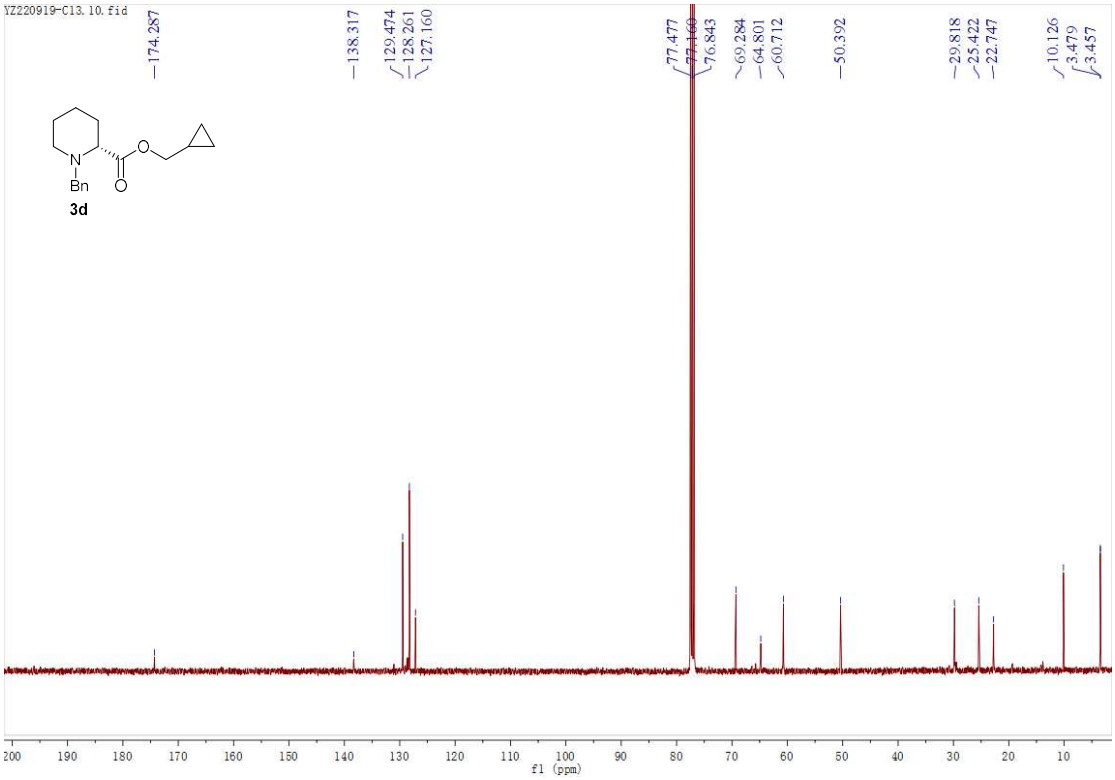
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3c



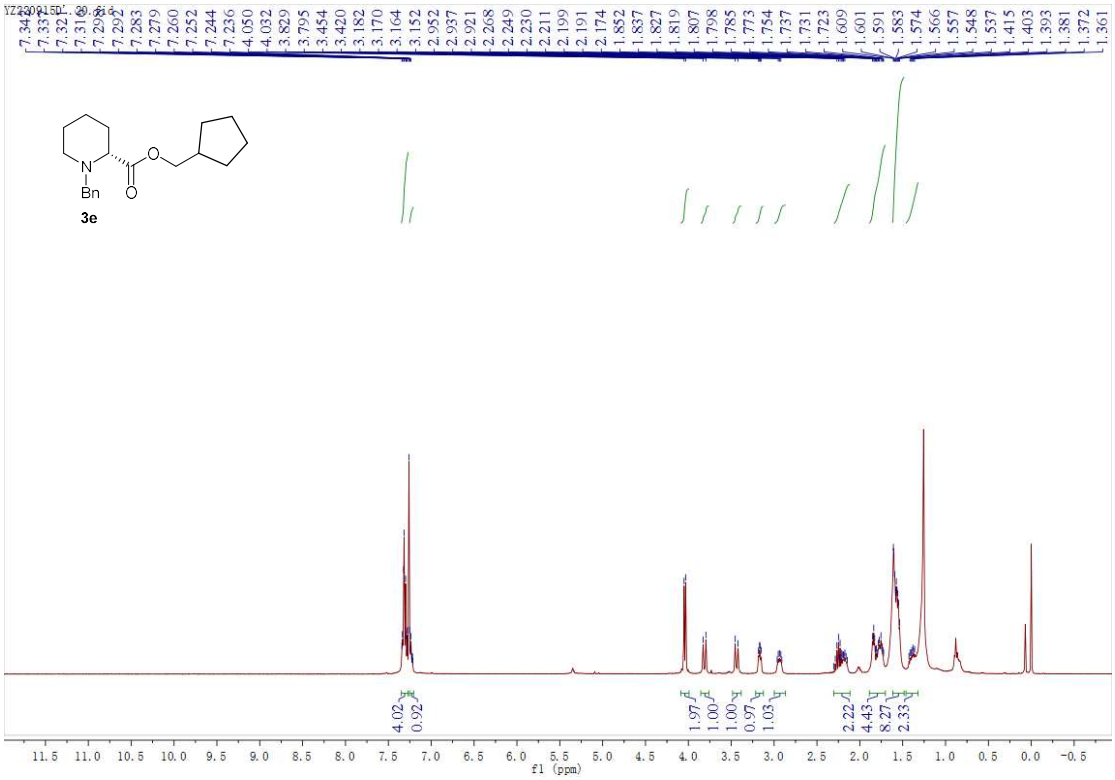
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3c



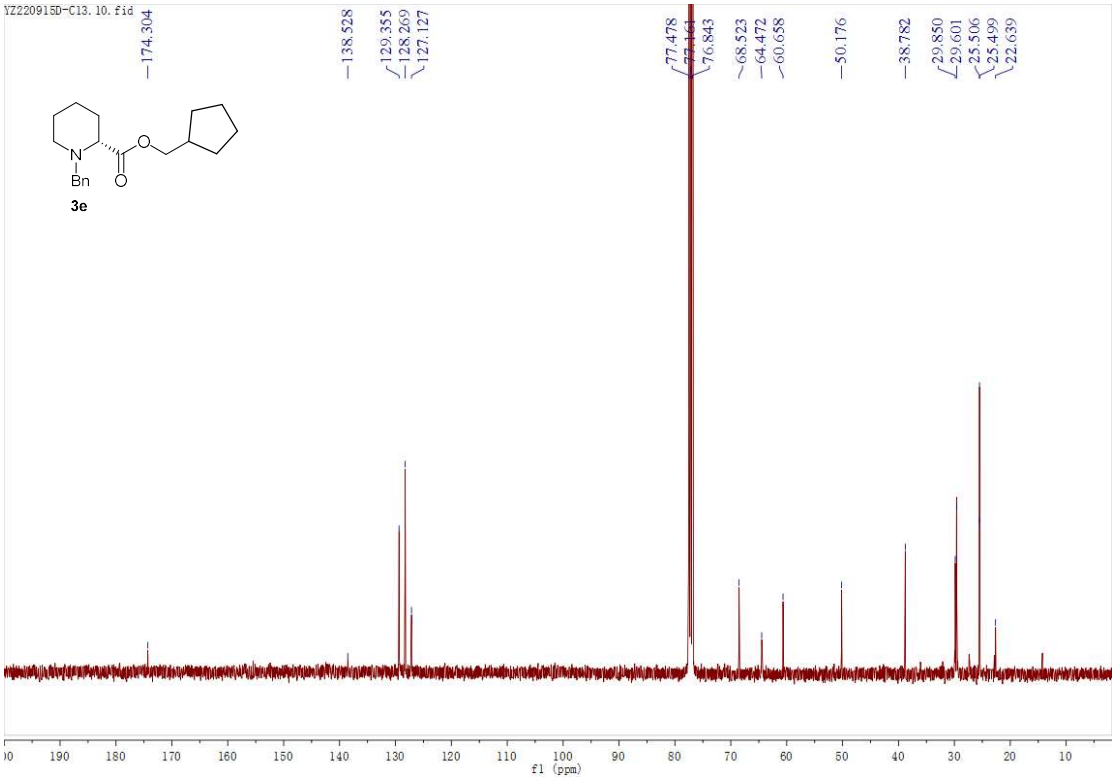
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3d



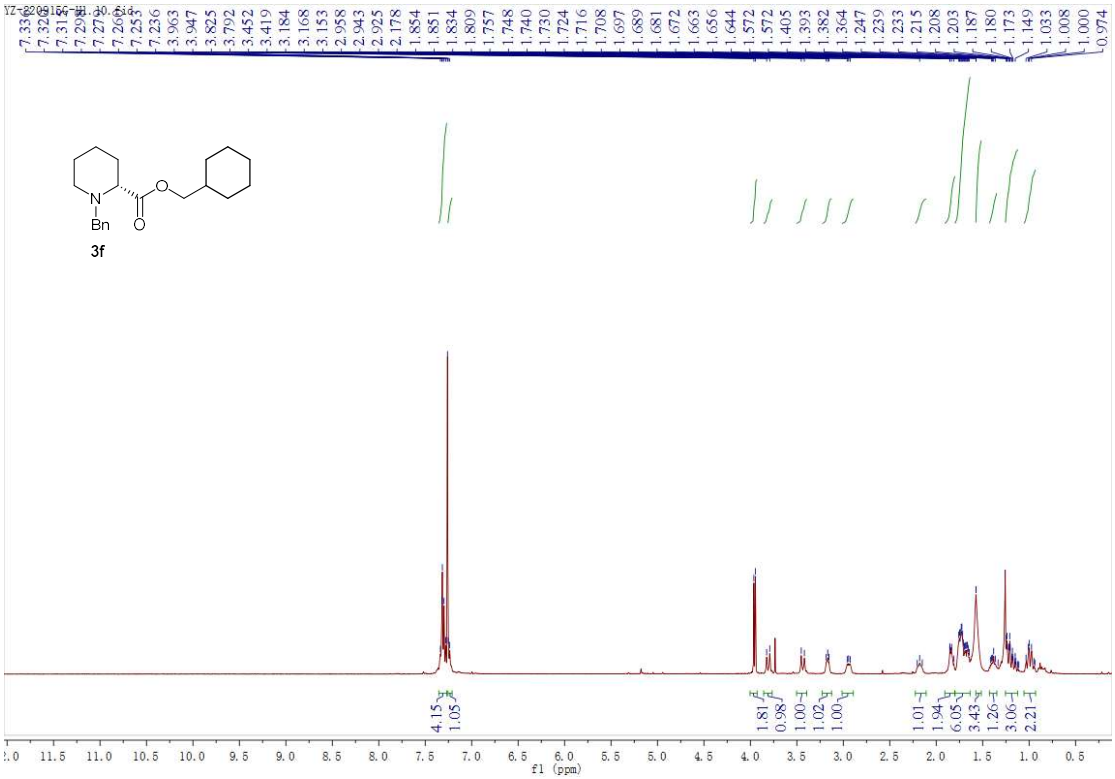
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3d



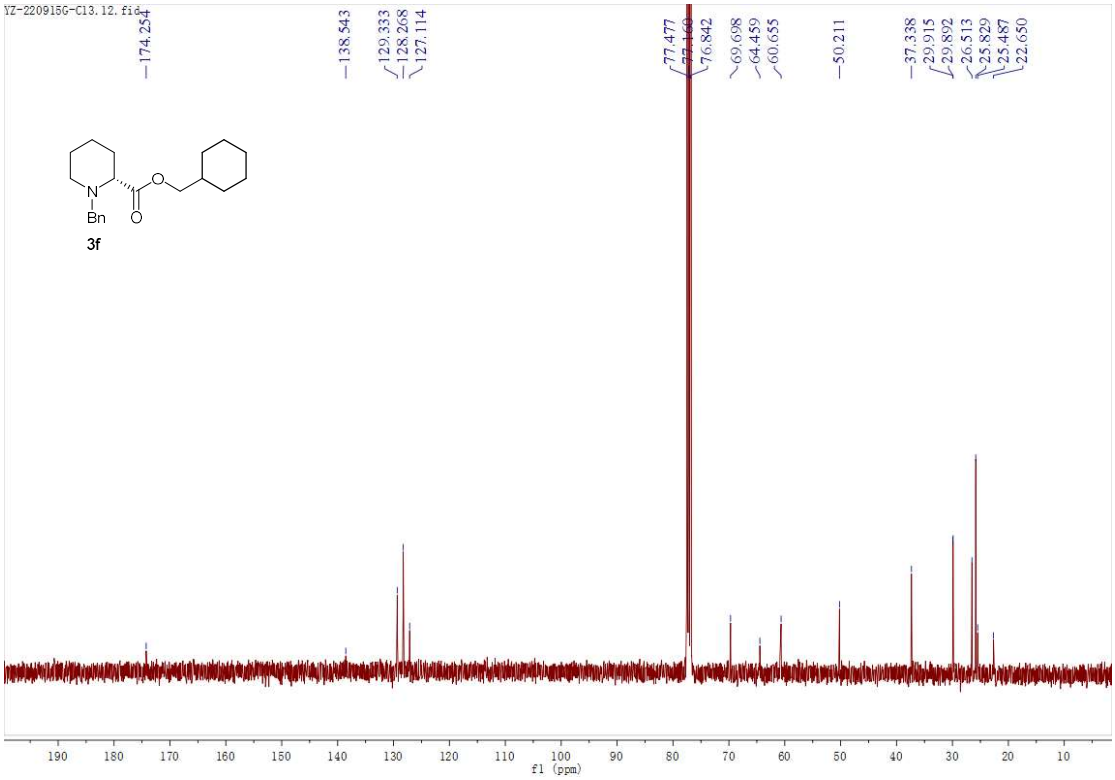
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3e



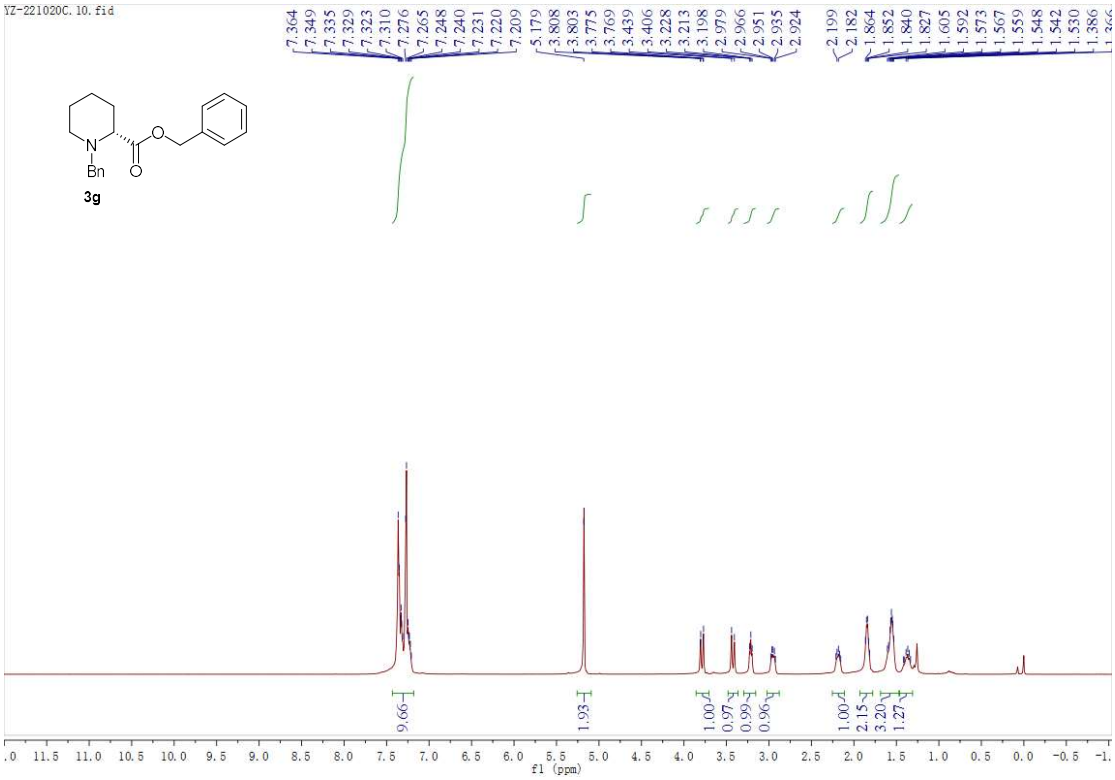
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3e



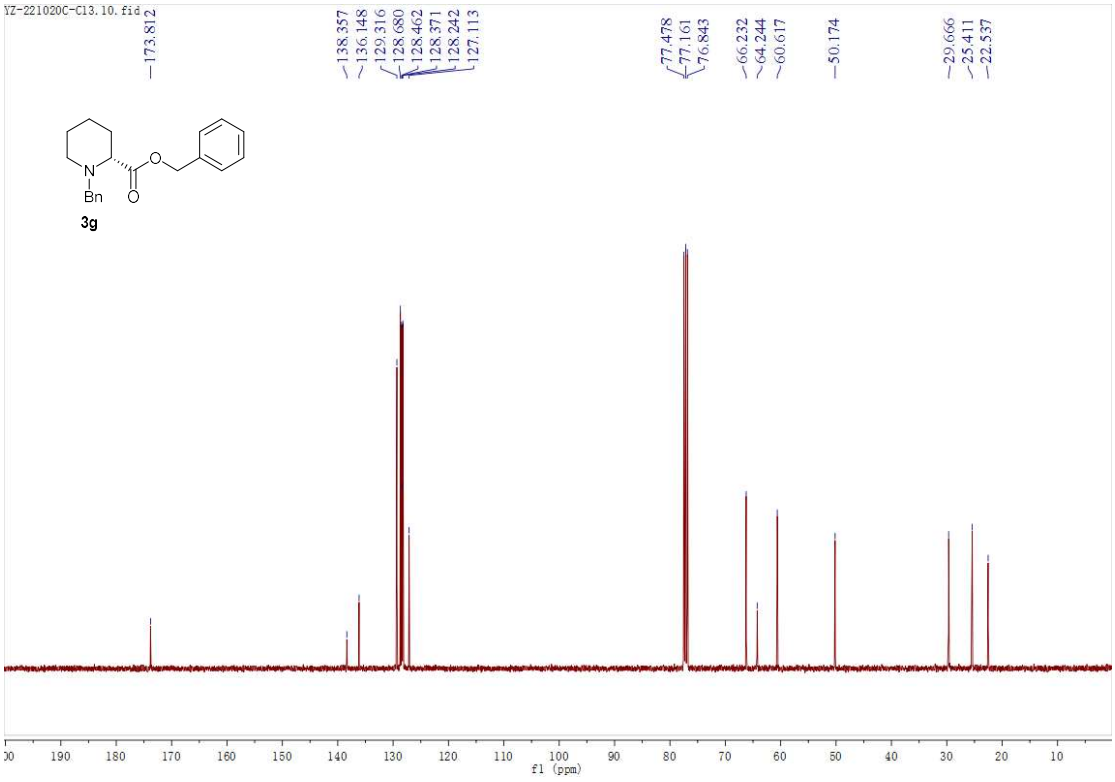
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3f



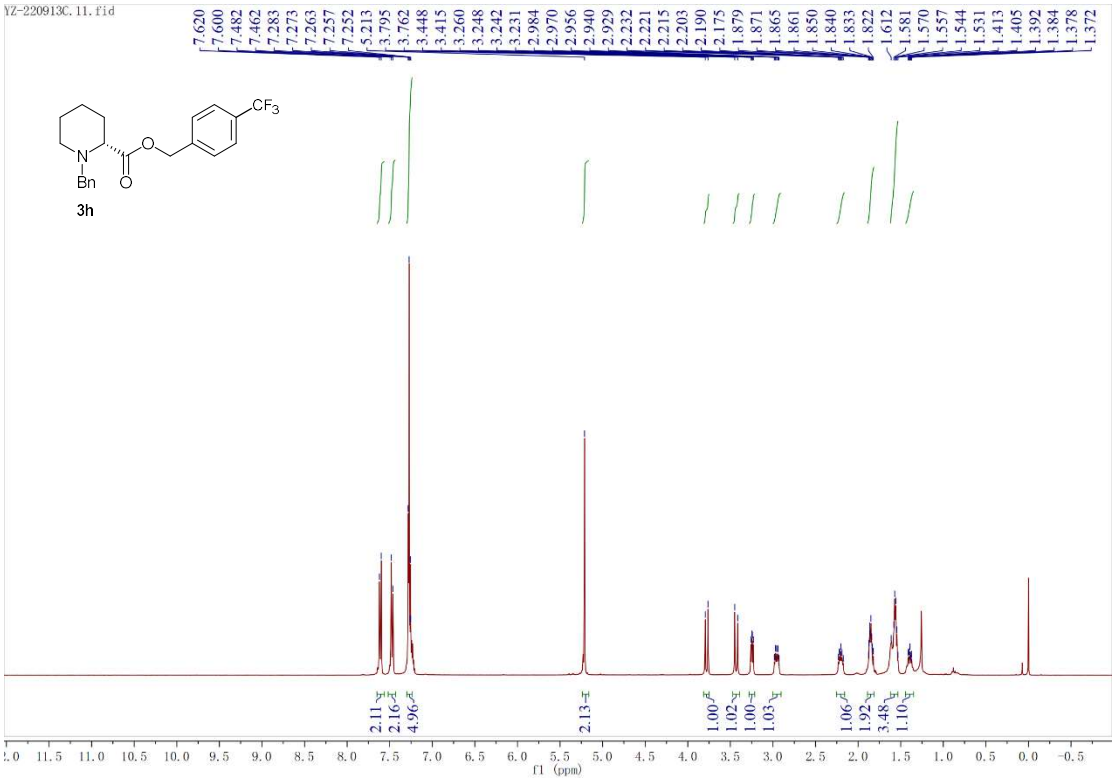
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3f



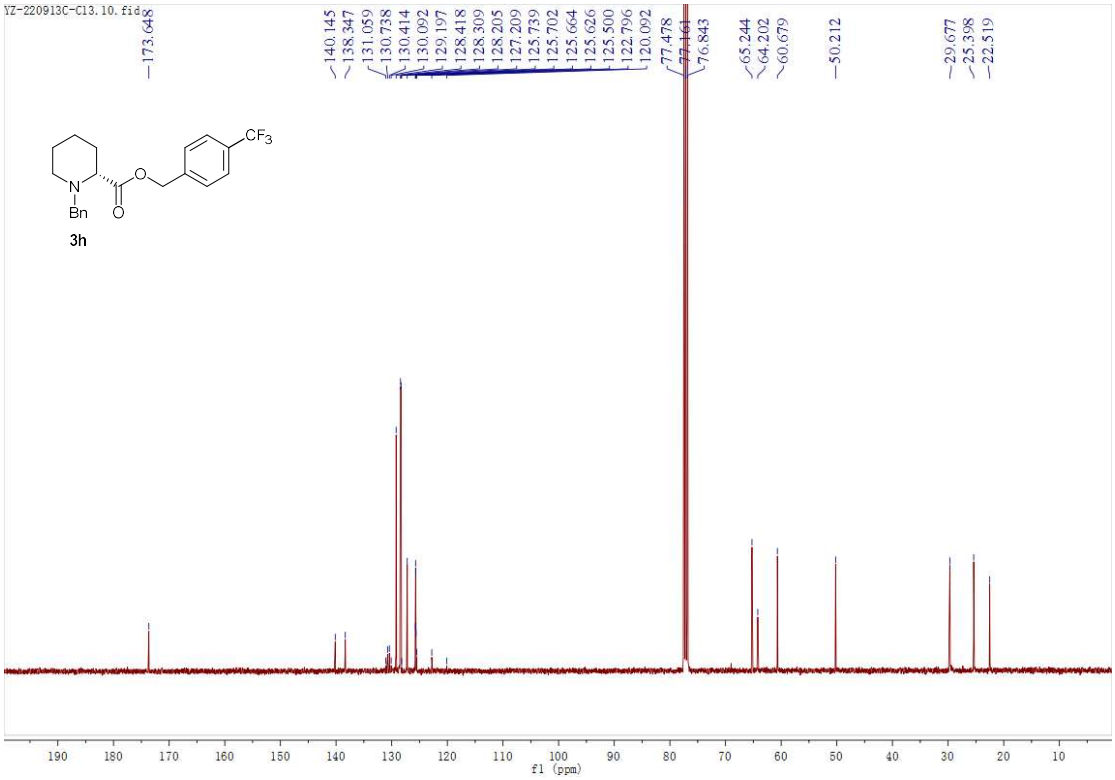
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3g



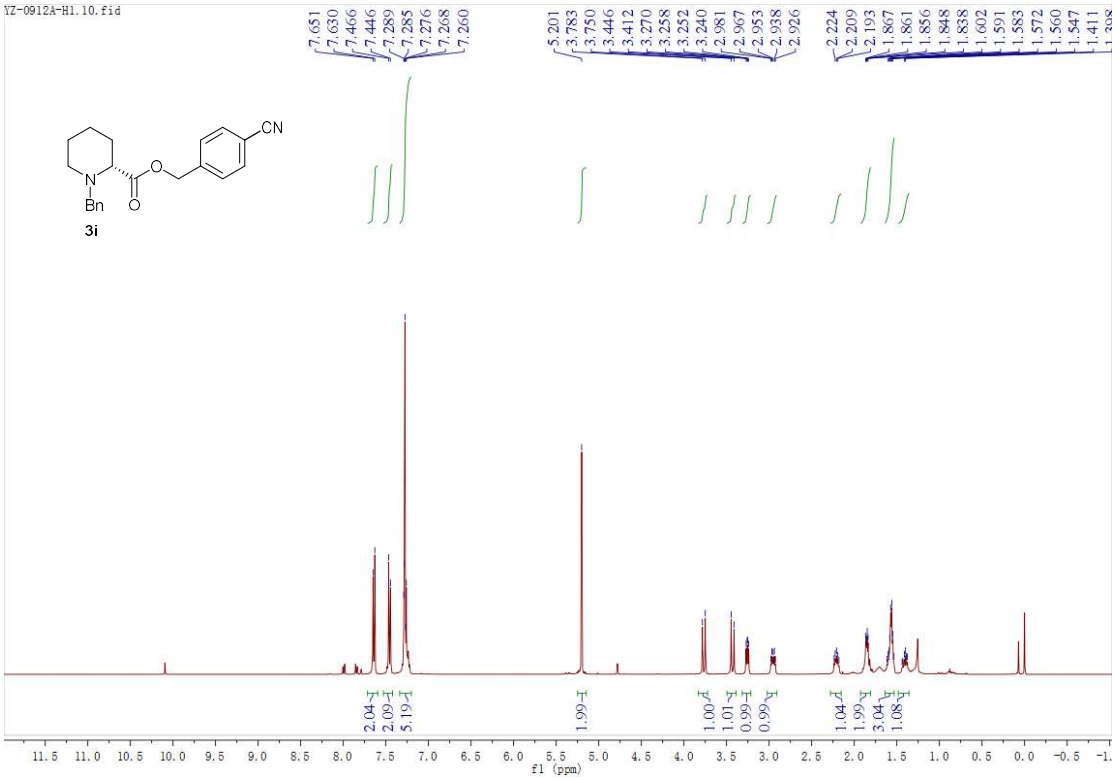
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3g



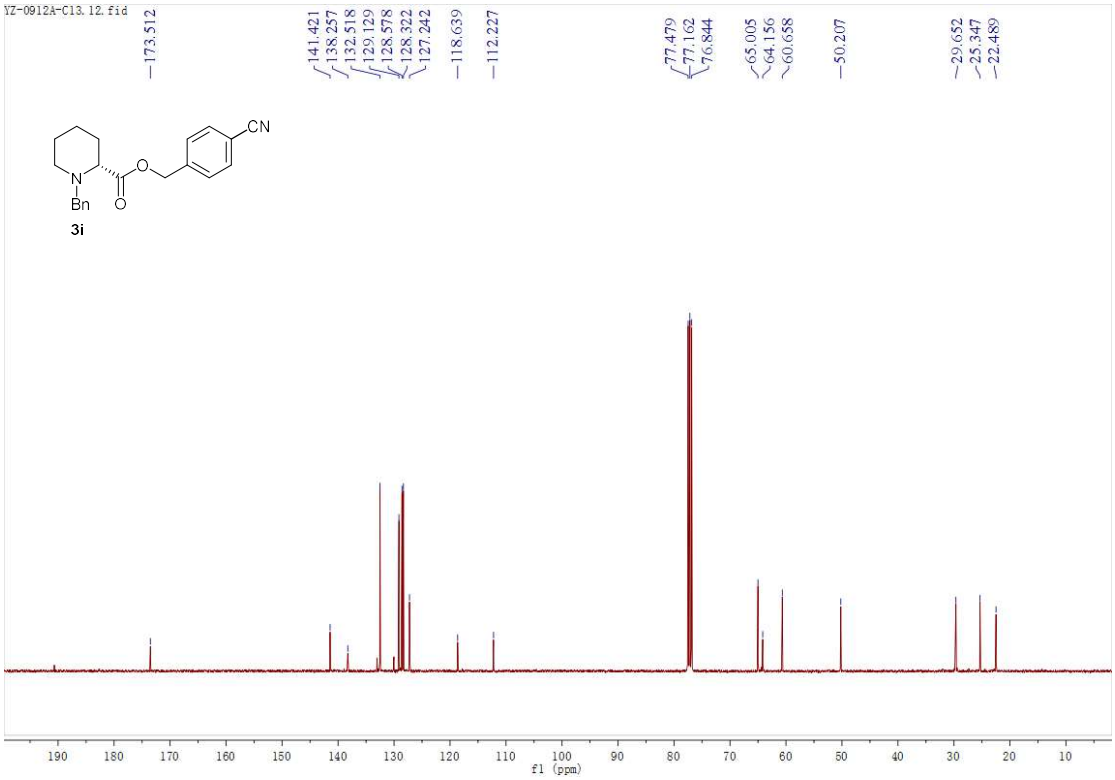
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3h



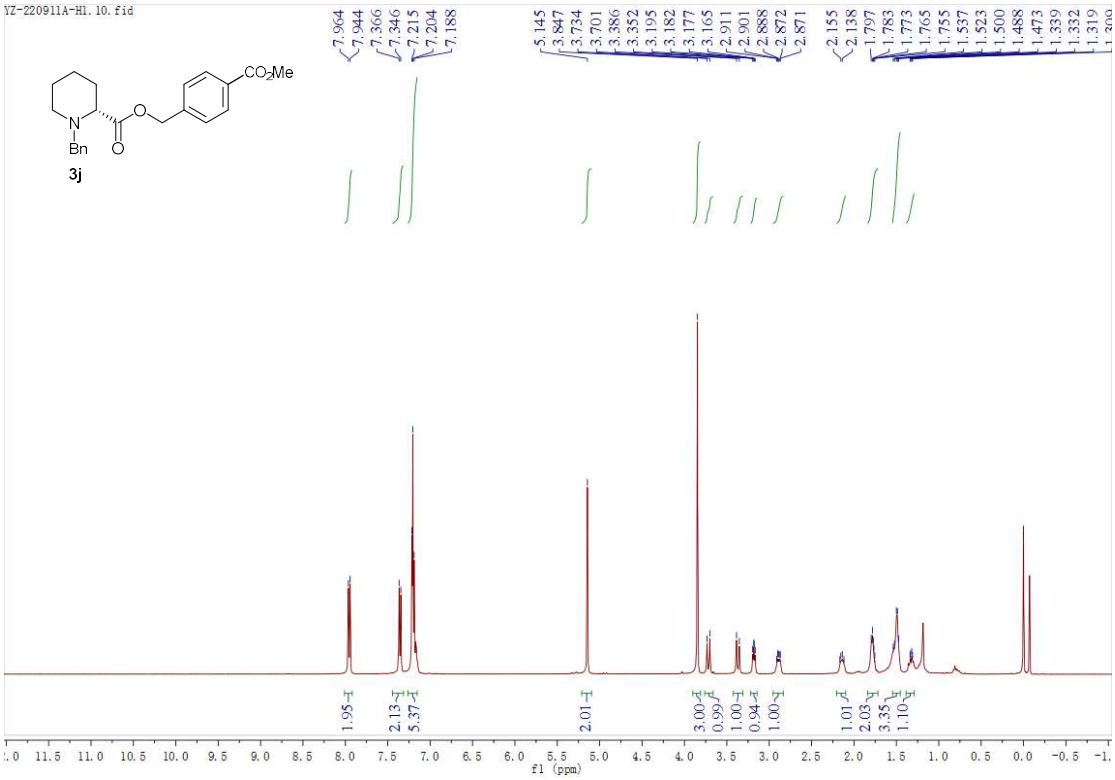
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3h



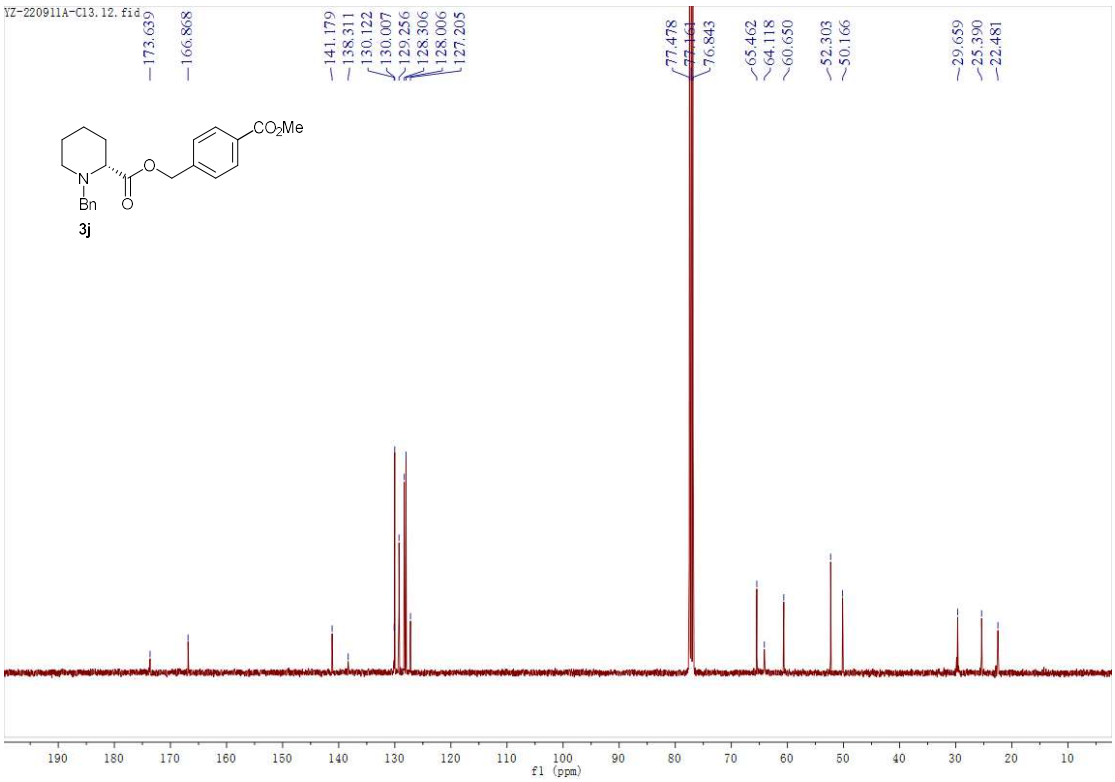
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3i



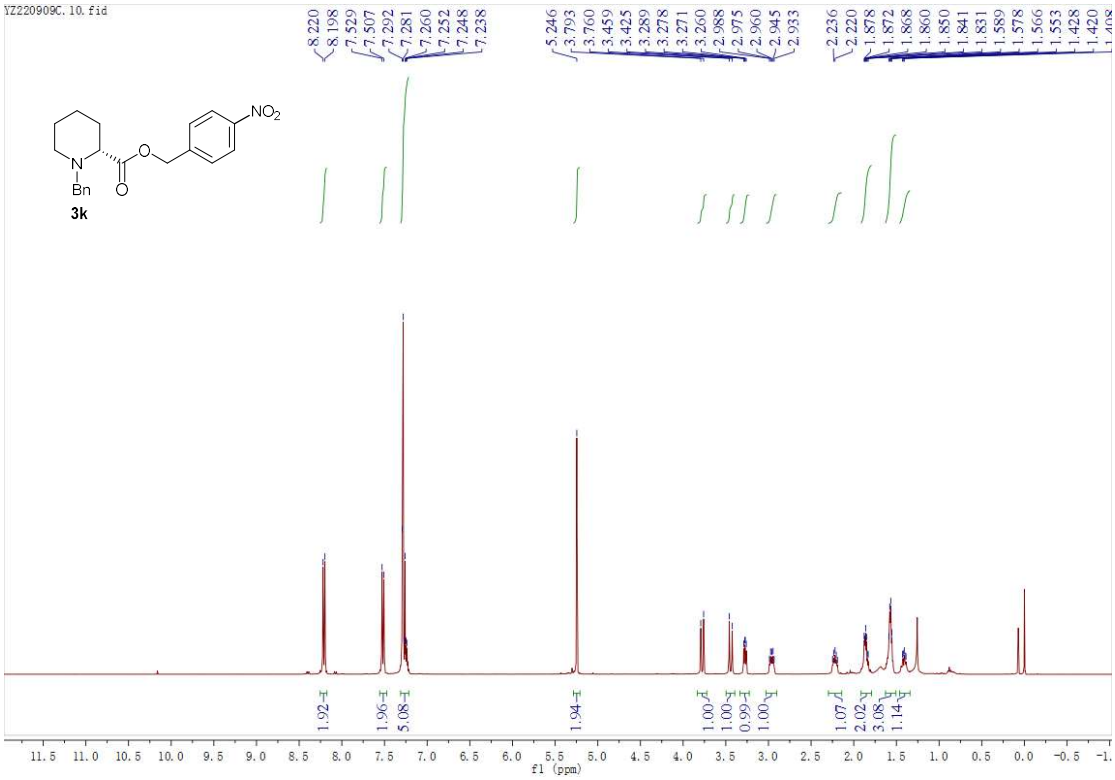
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3i



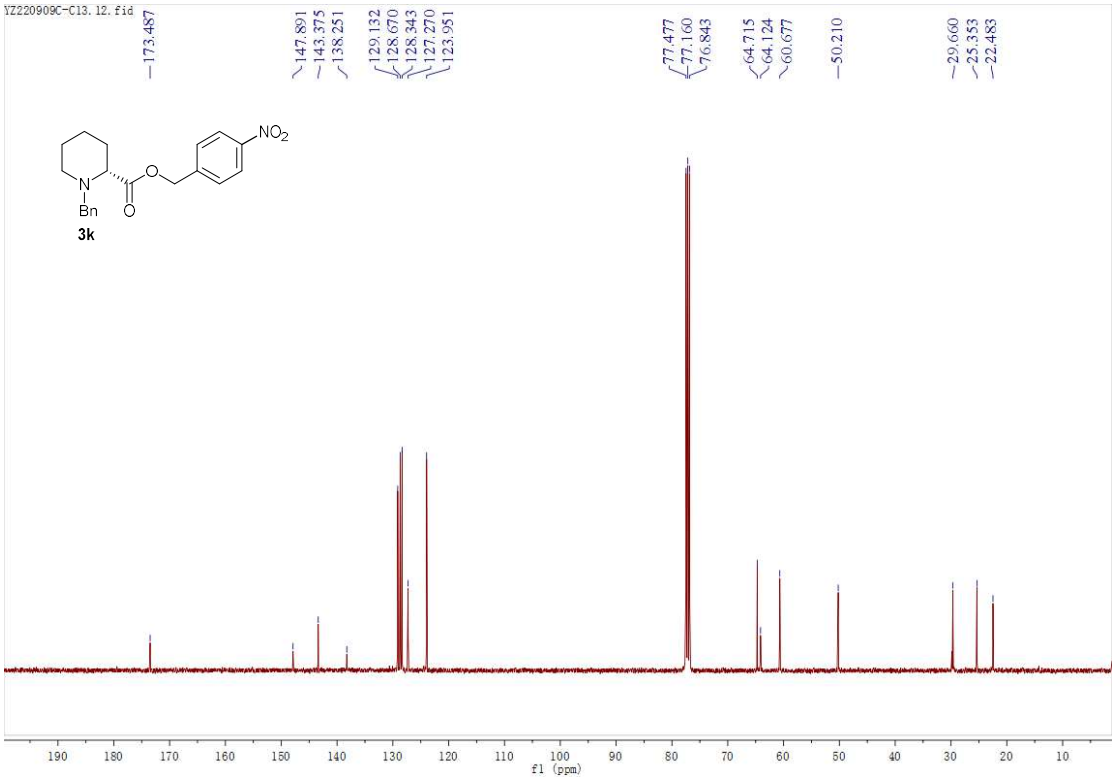
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3j



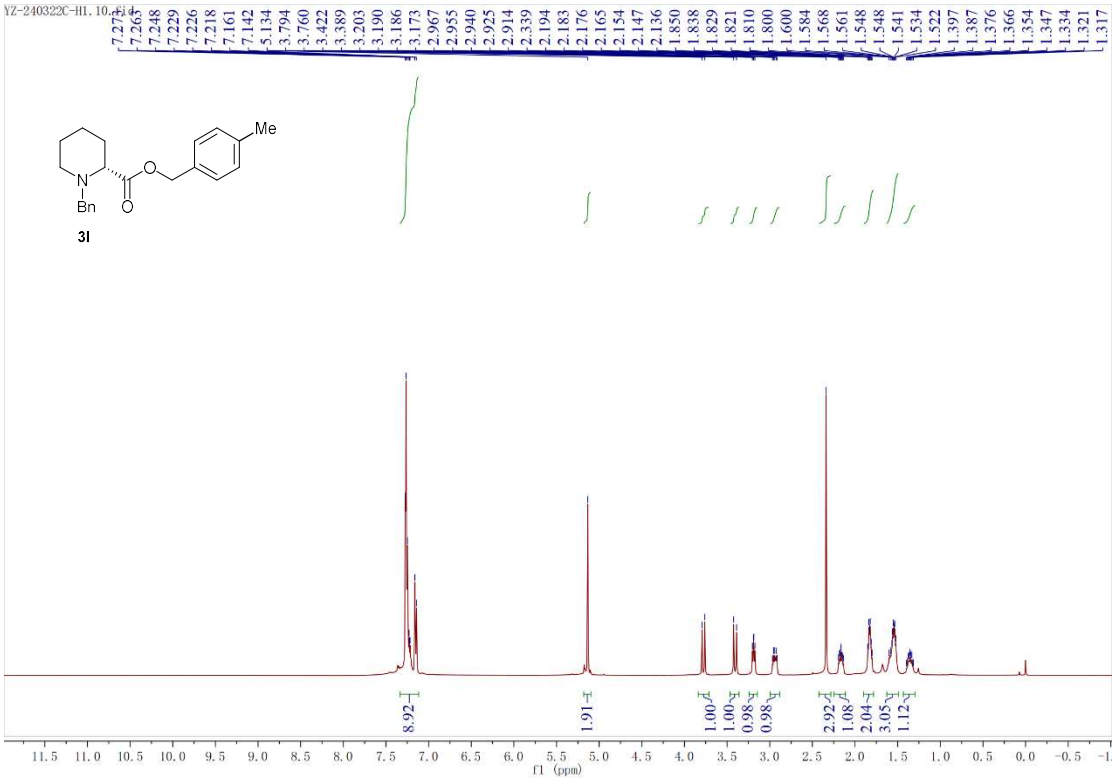
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3j



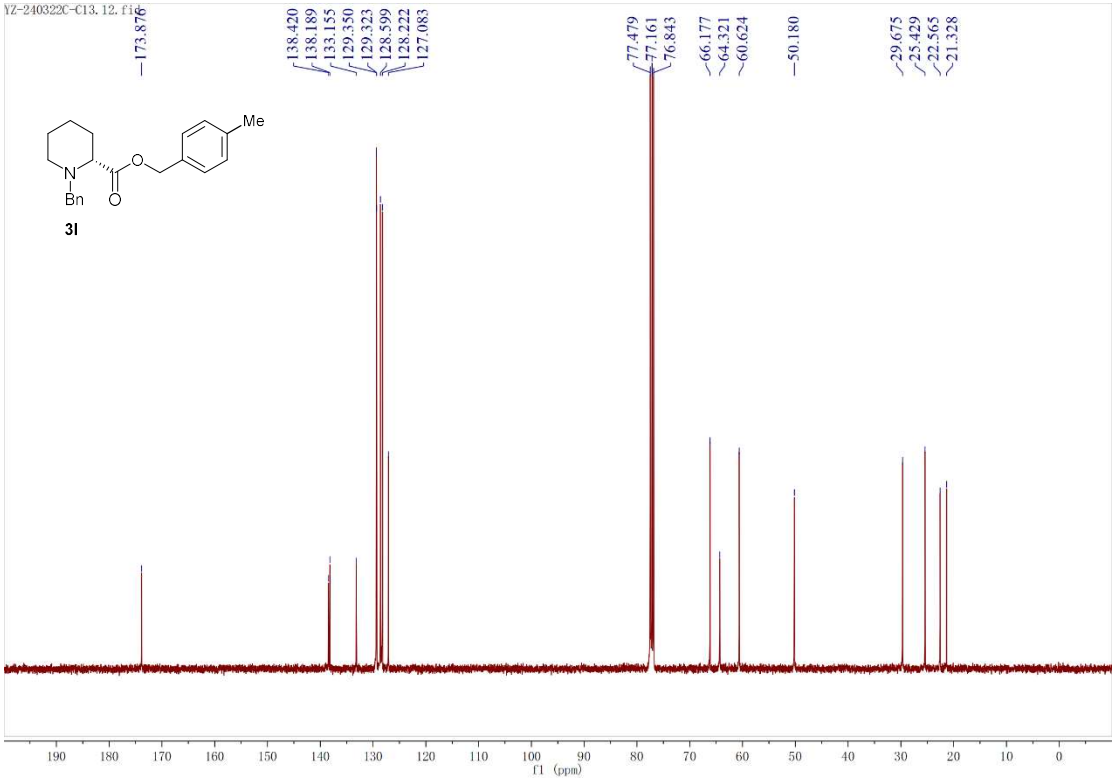
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3k



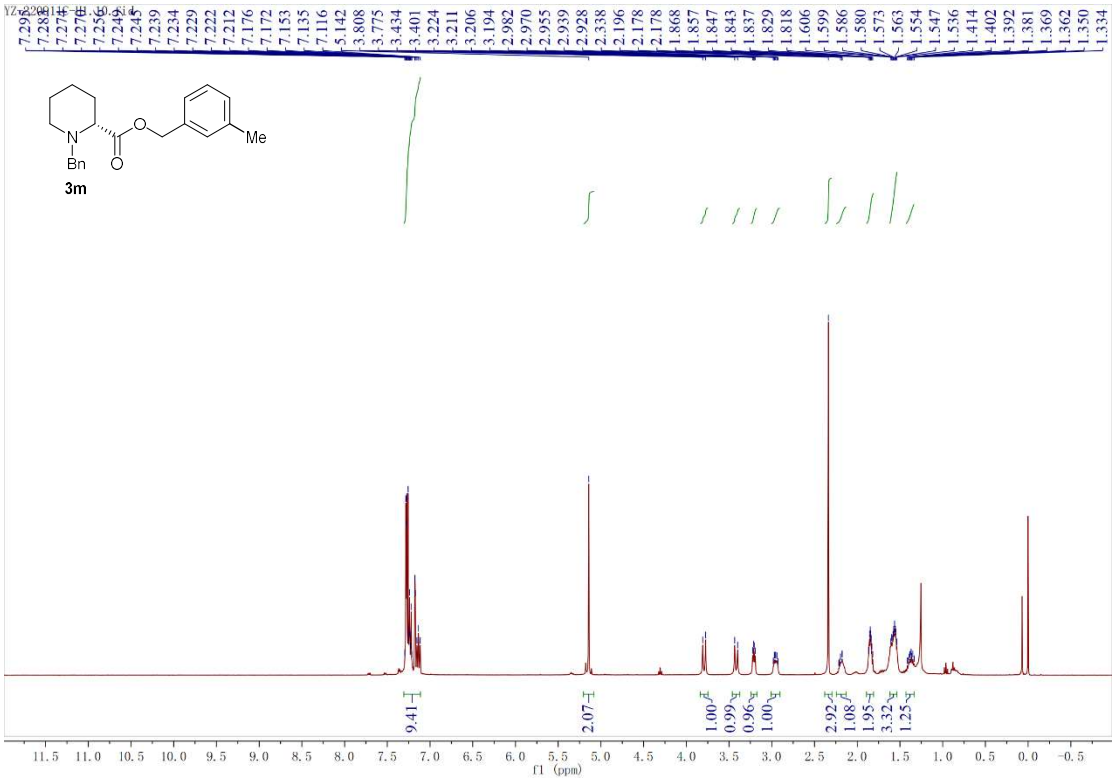
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3k



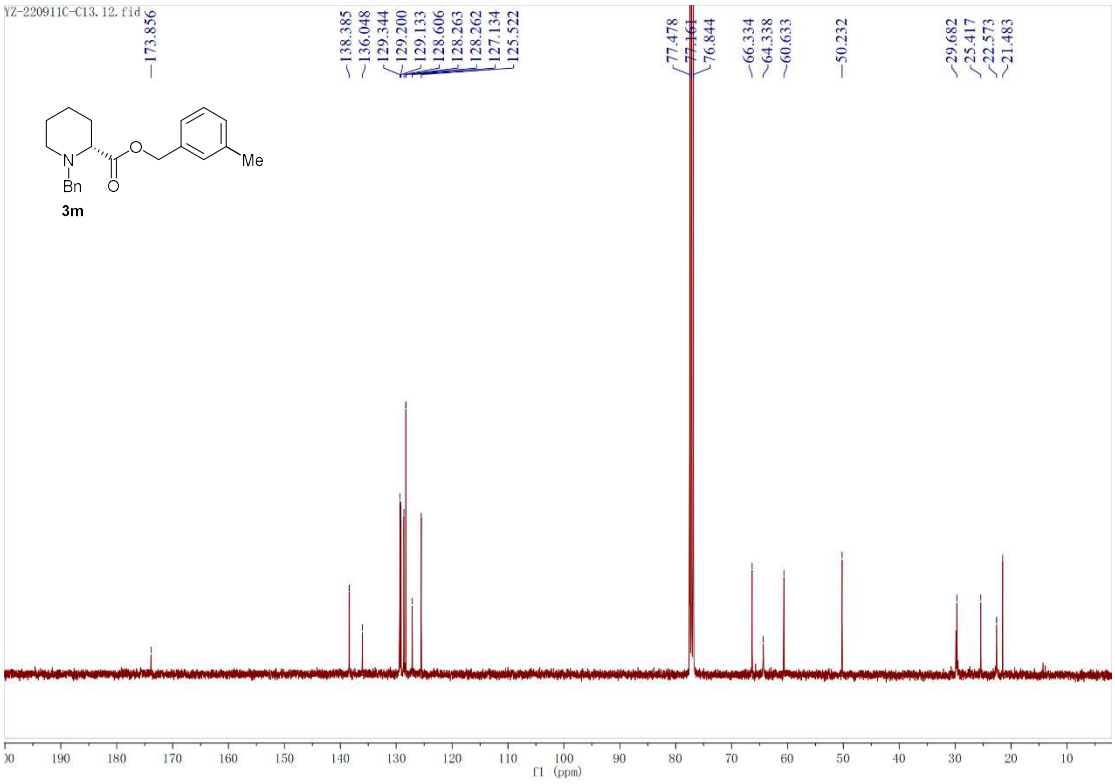
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3l



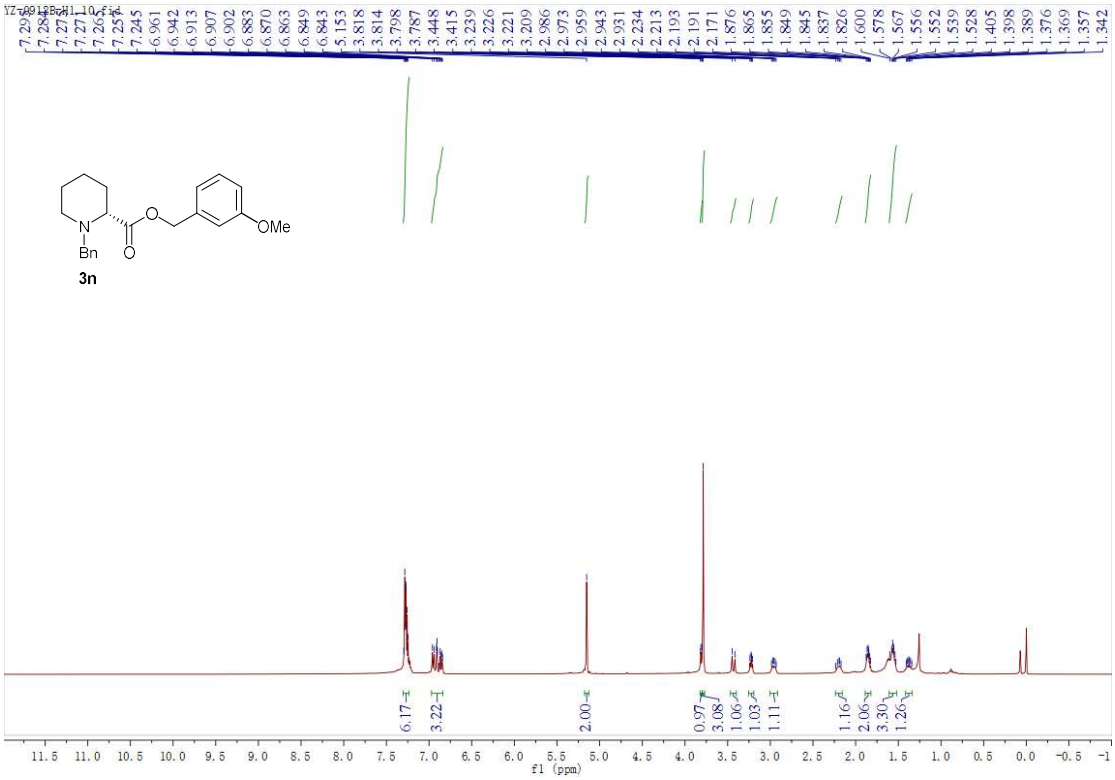
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3l



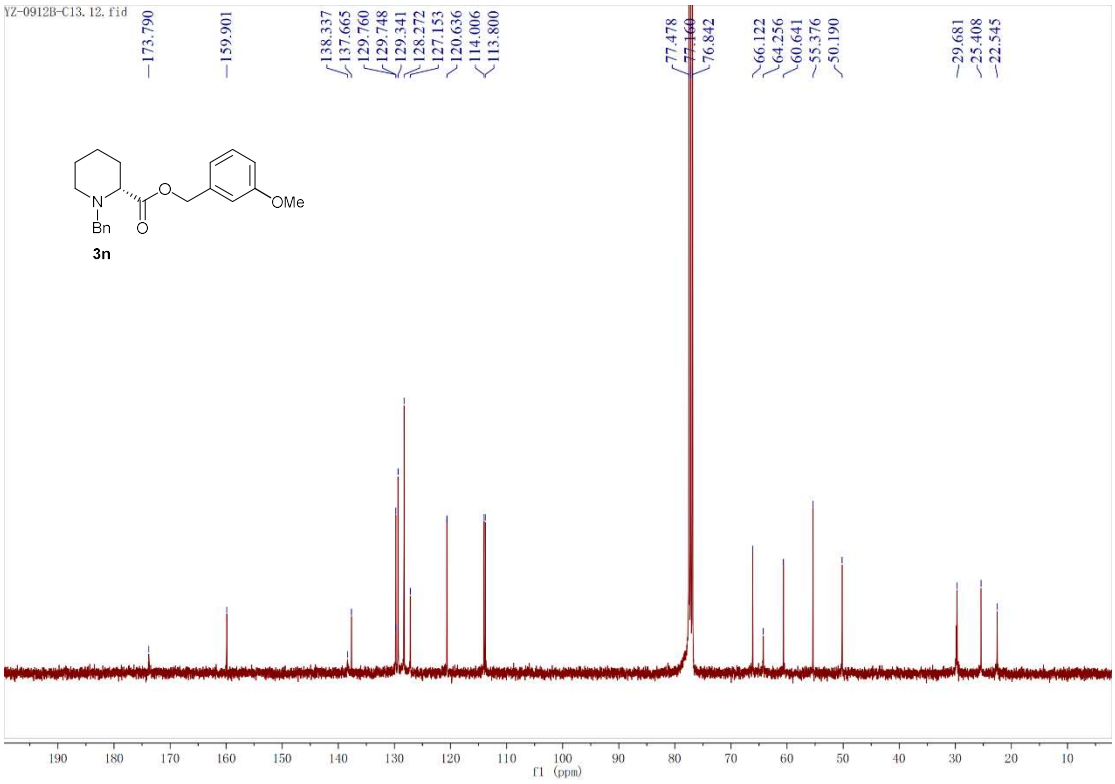
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3m



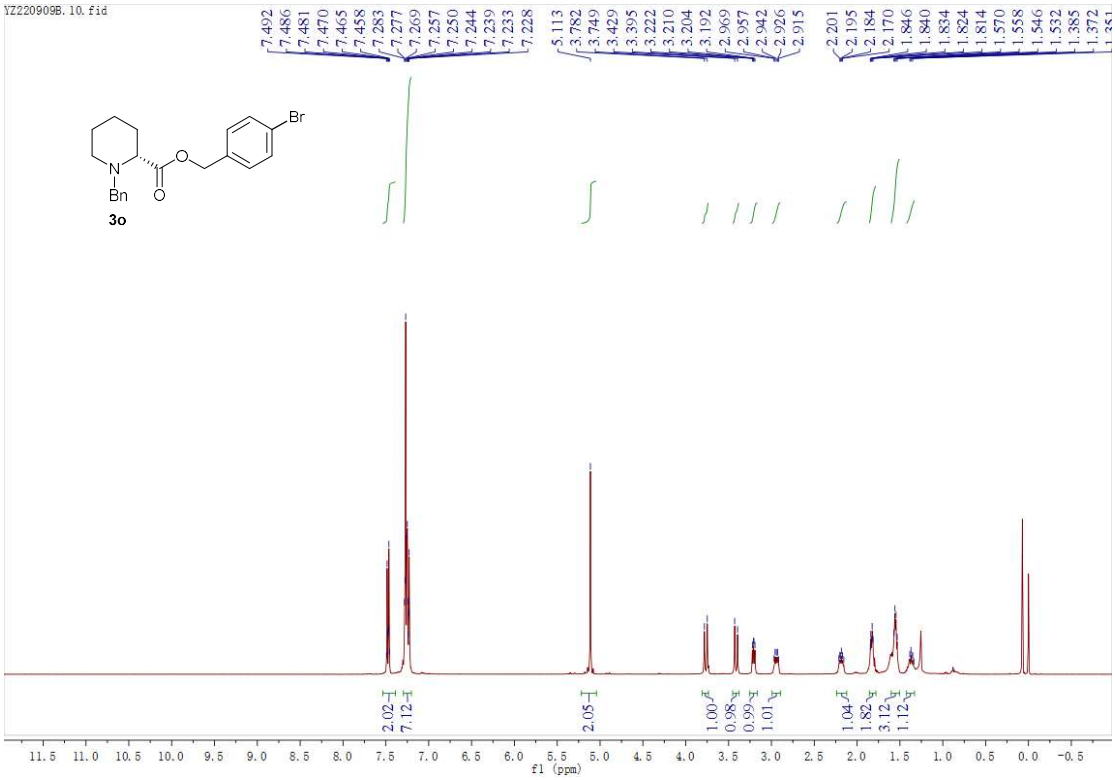
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3m



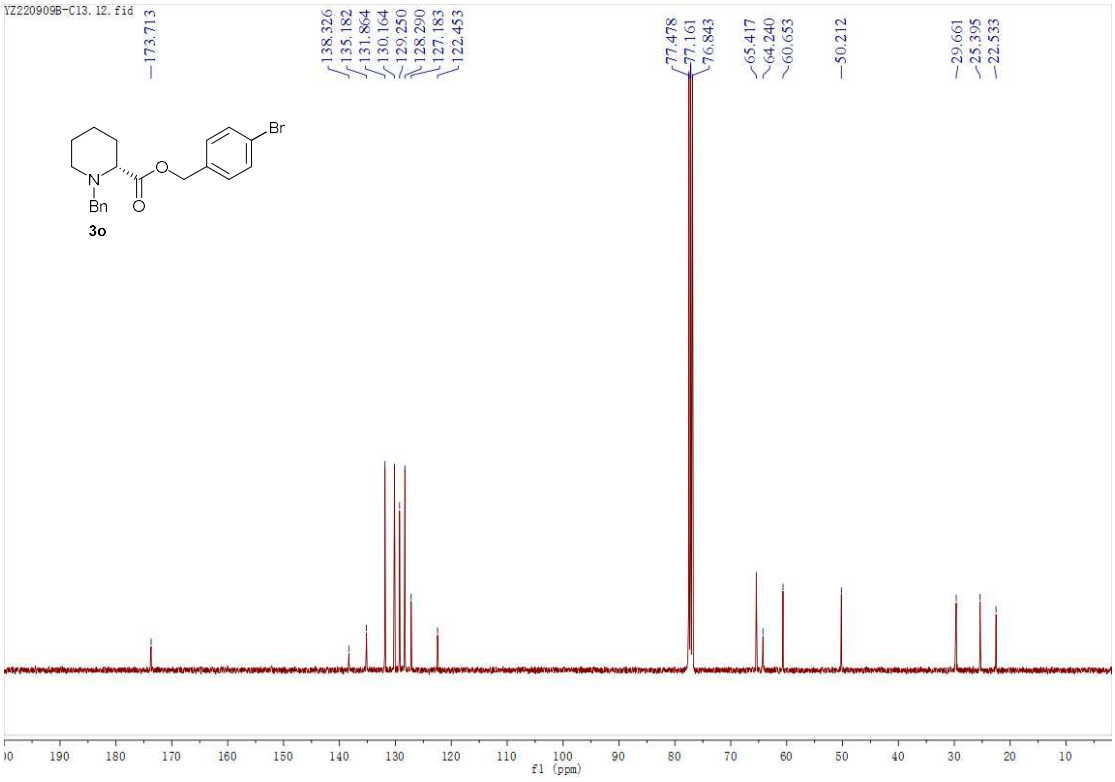
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3n



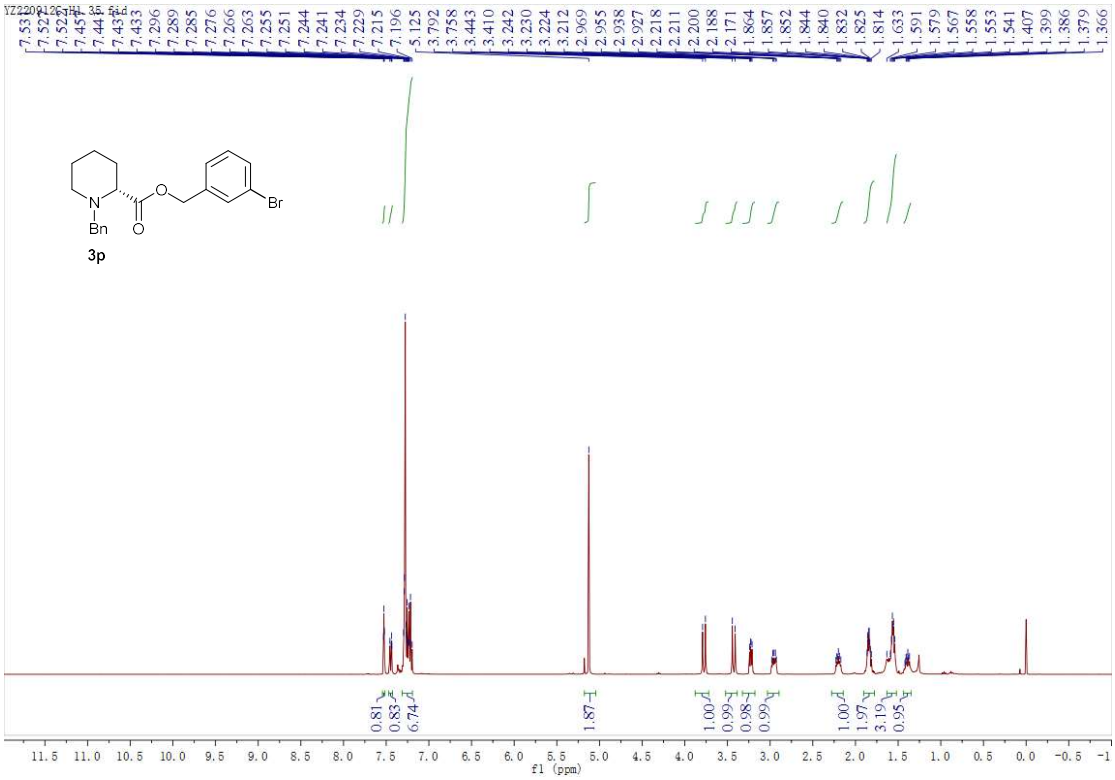
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3n



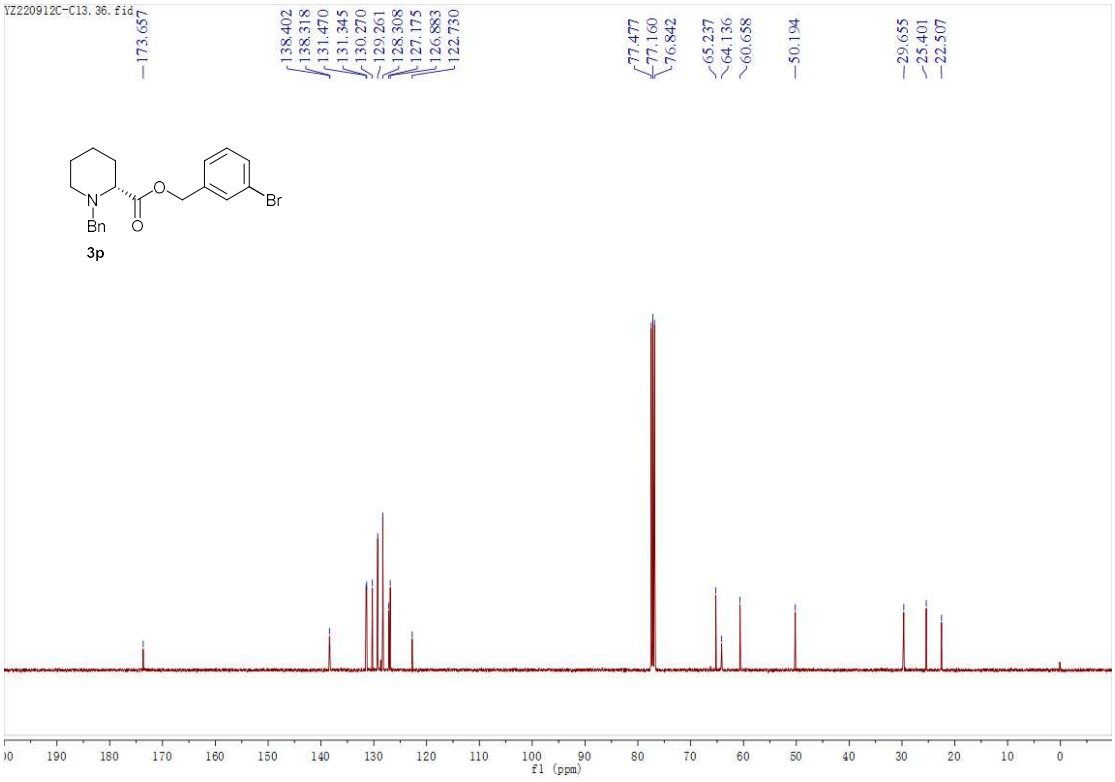
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3o



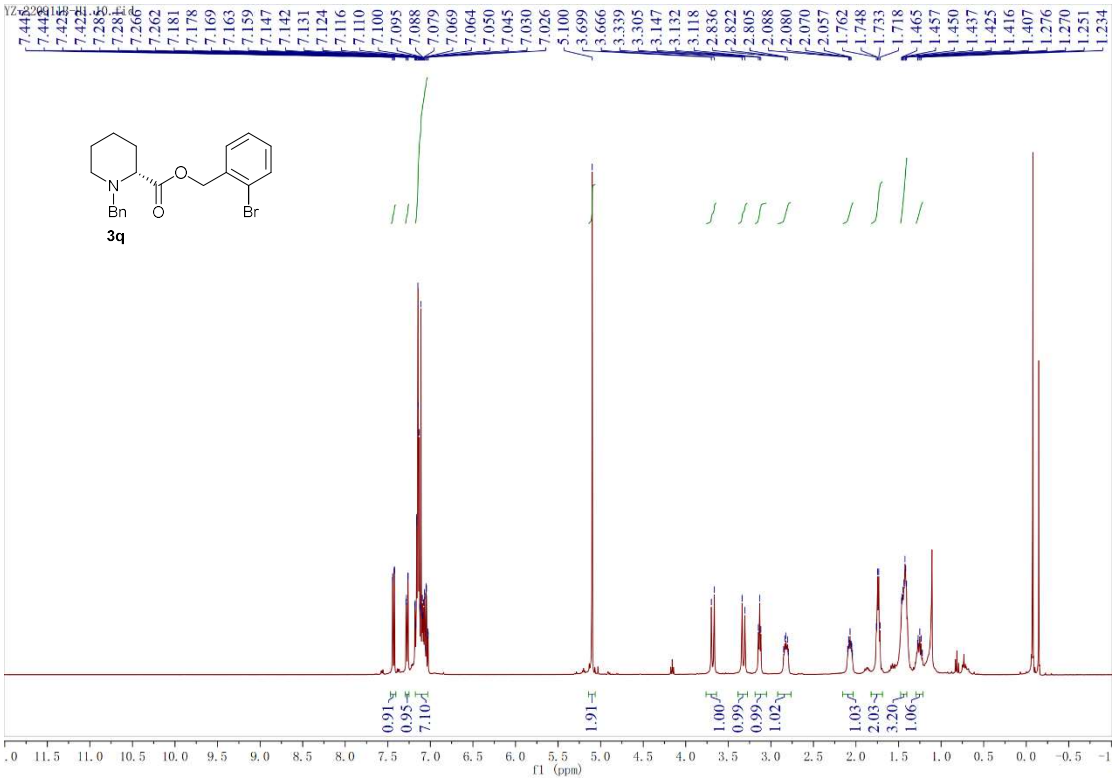
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3o



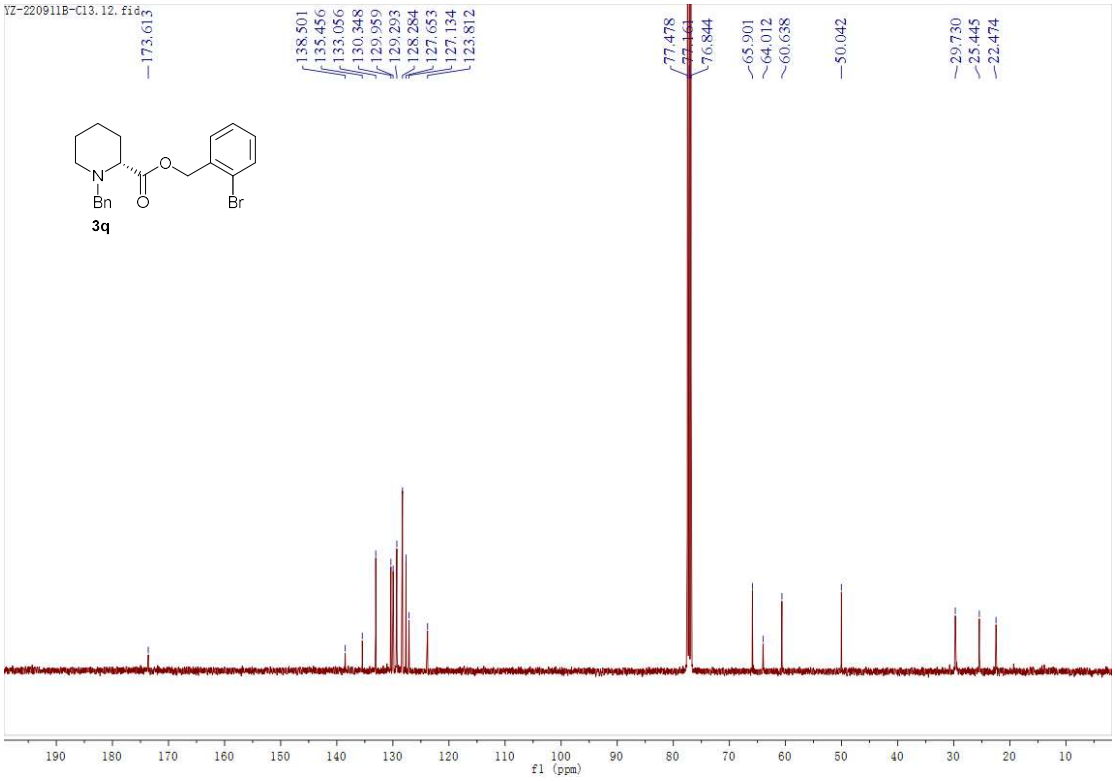
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3p



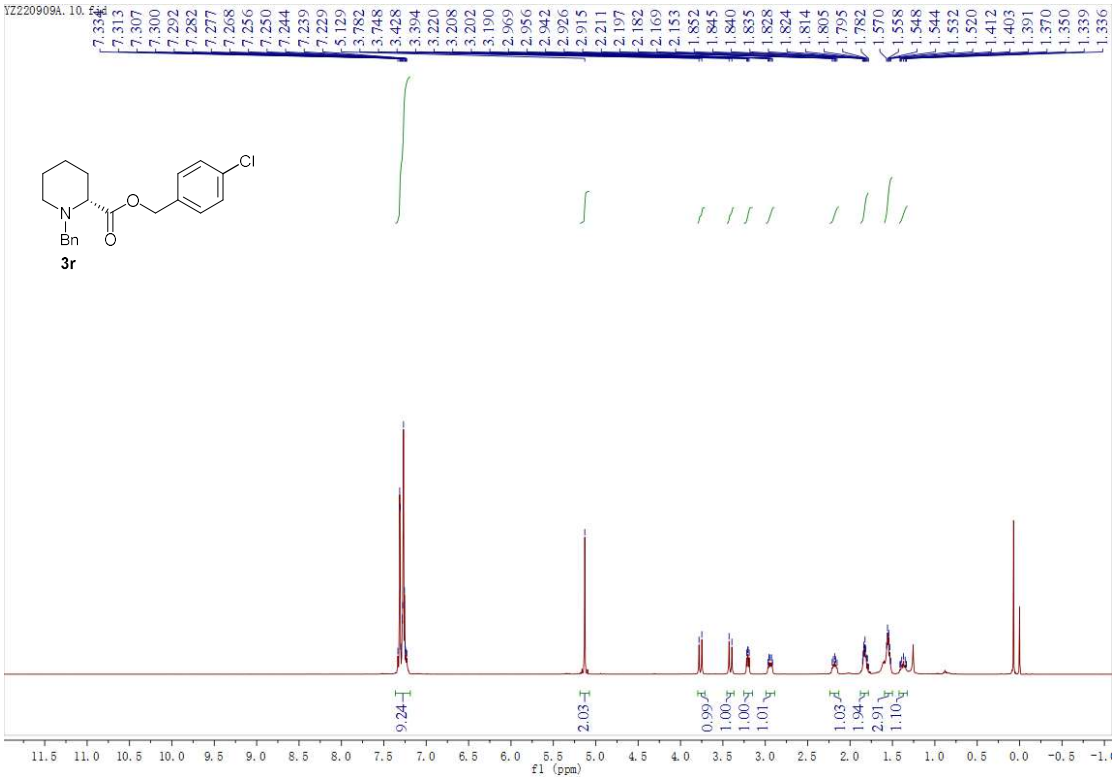
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3p



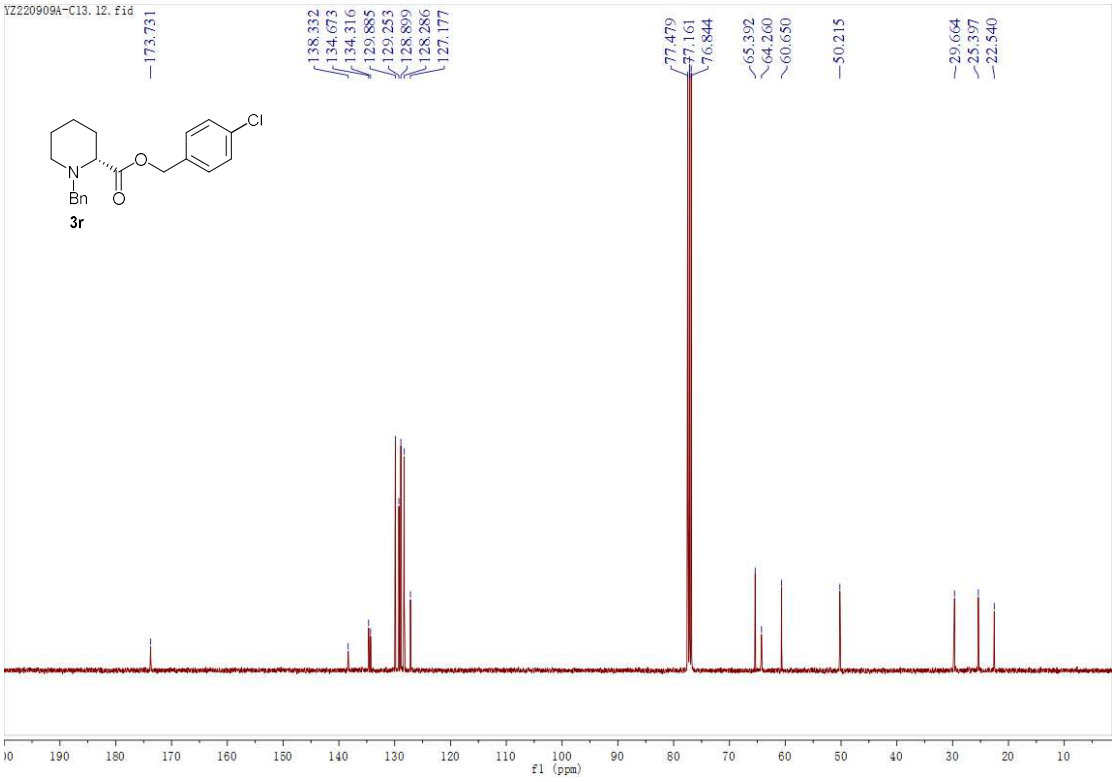
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3q



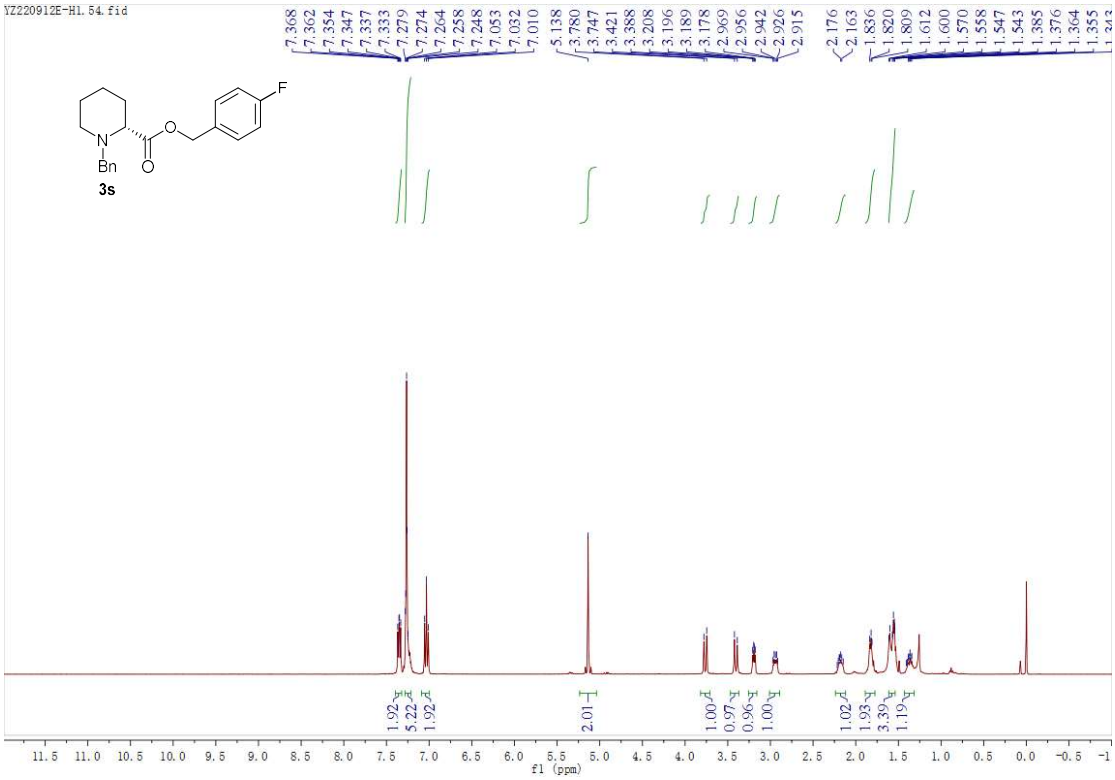
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3q



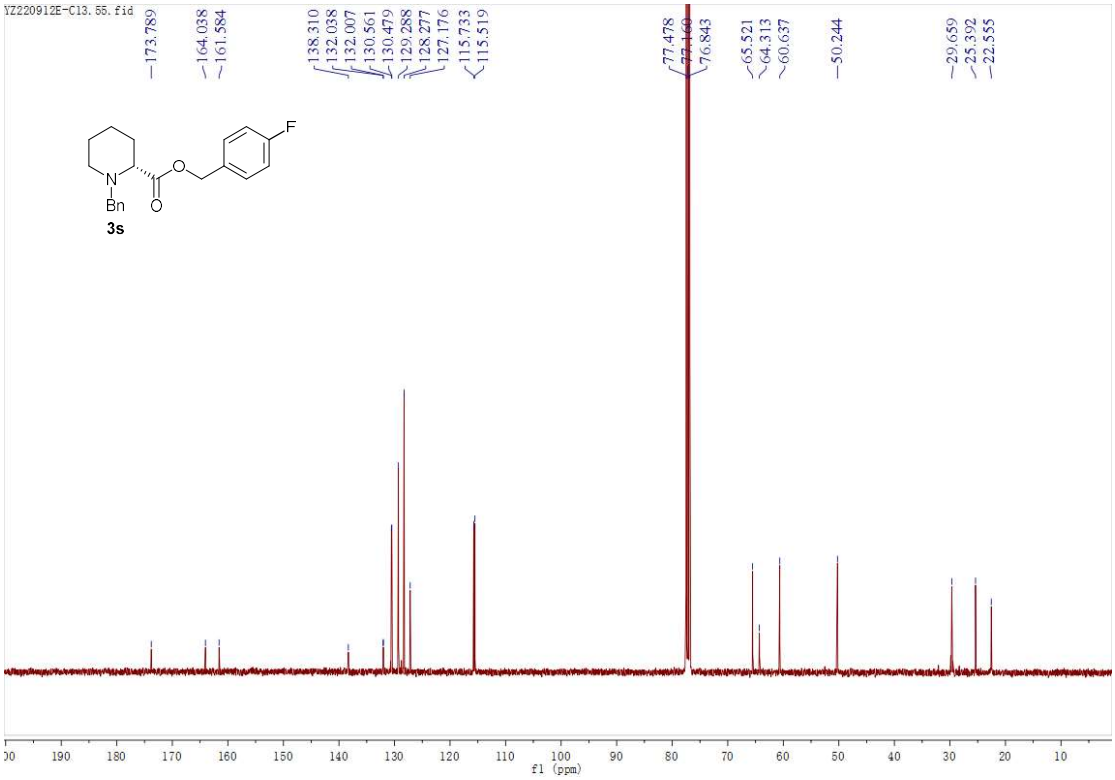
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3r



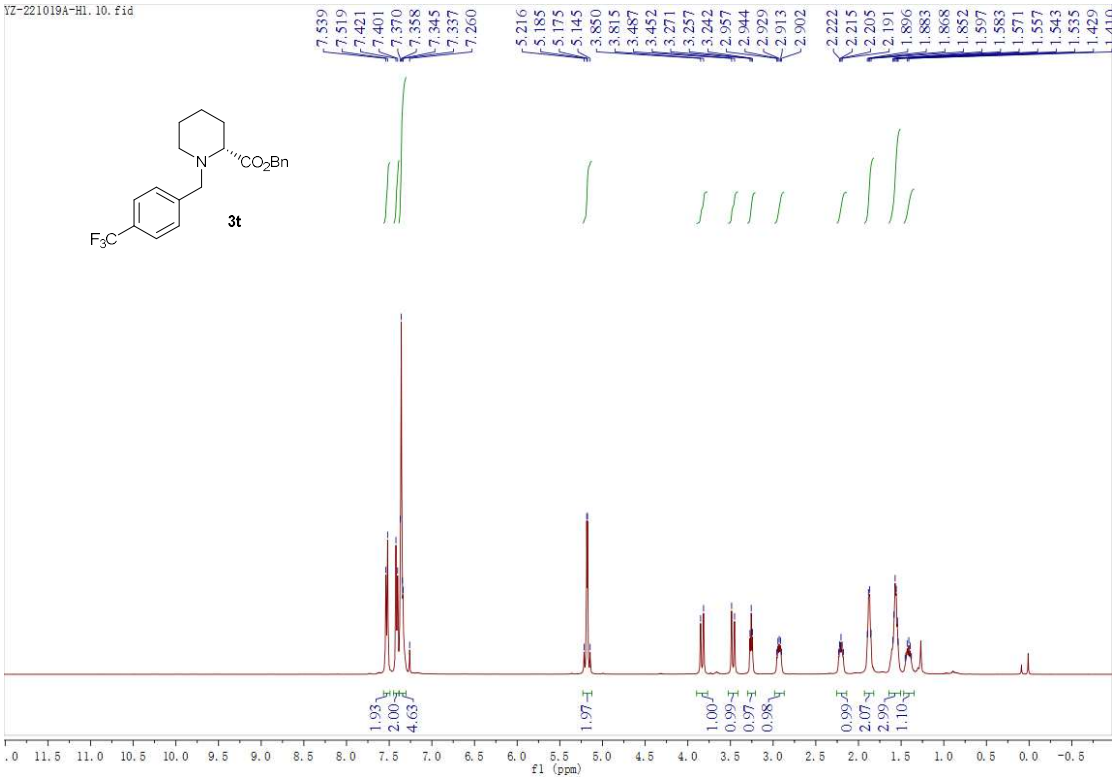
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3r



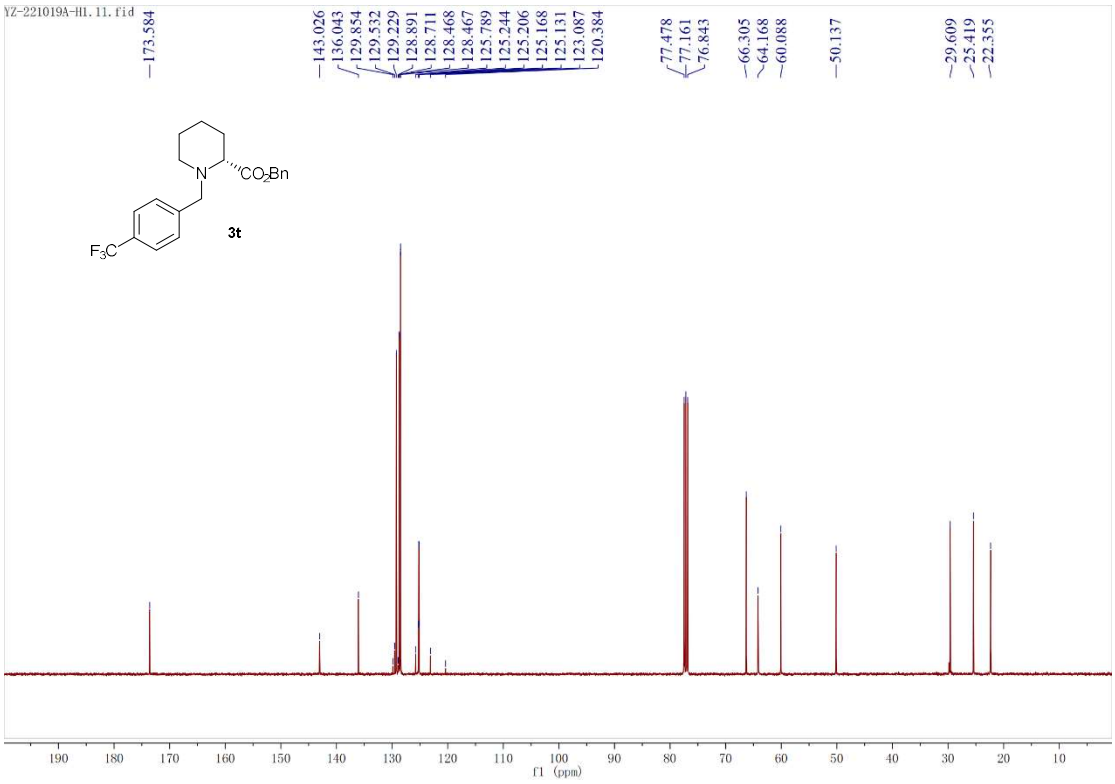
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3s



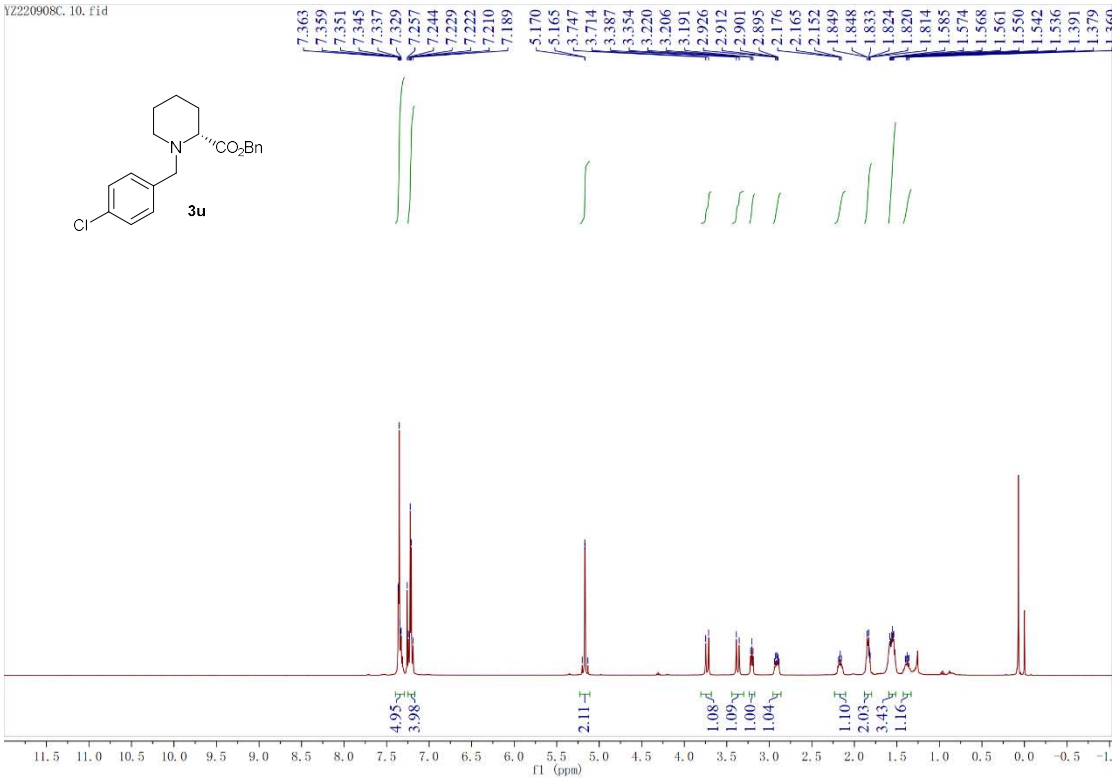
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3s



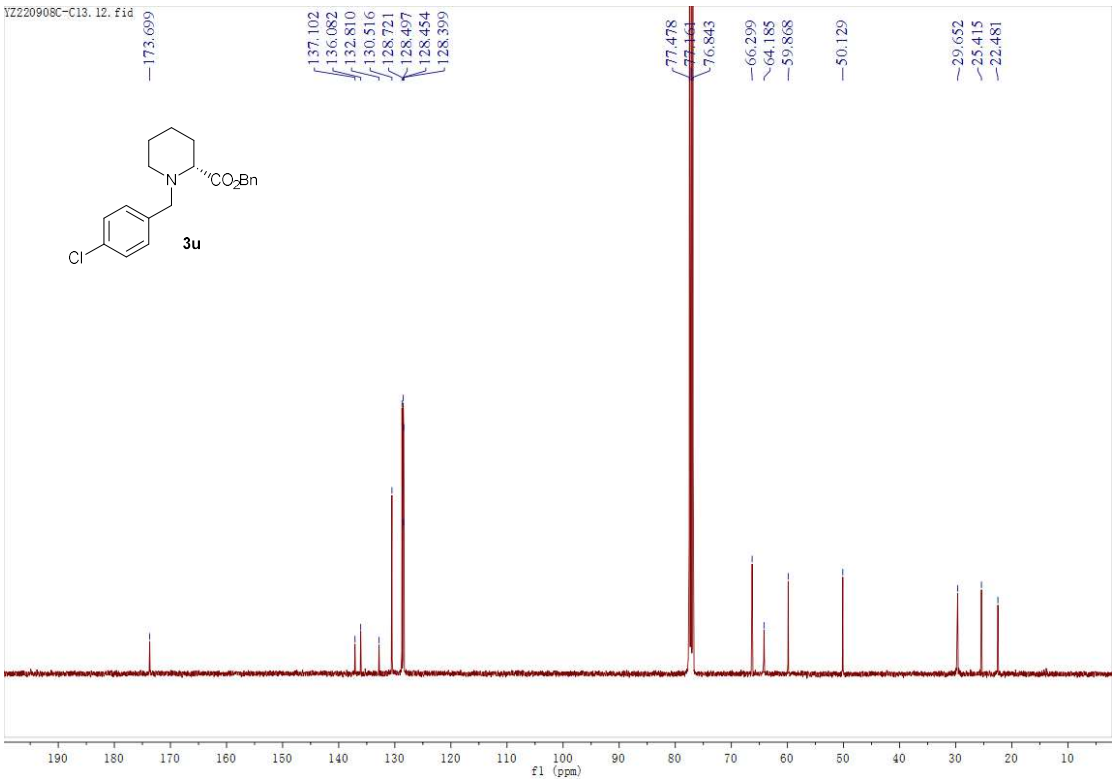
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3t



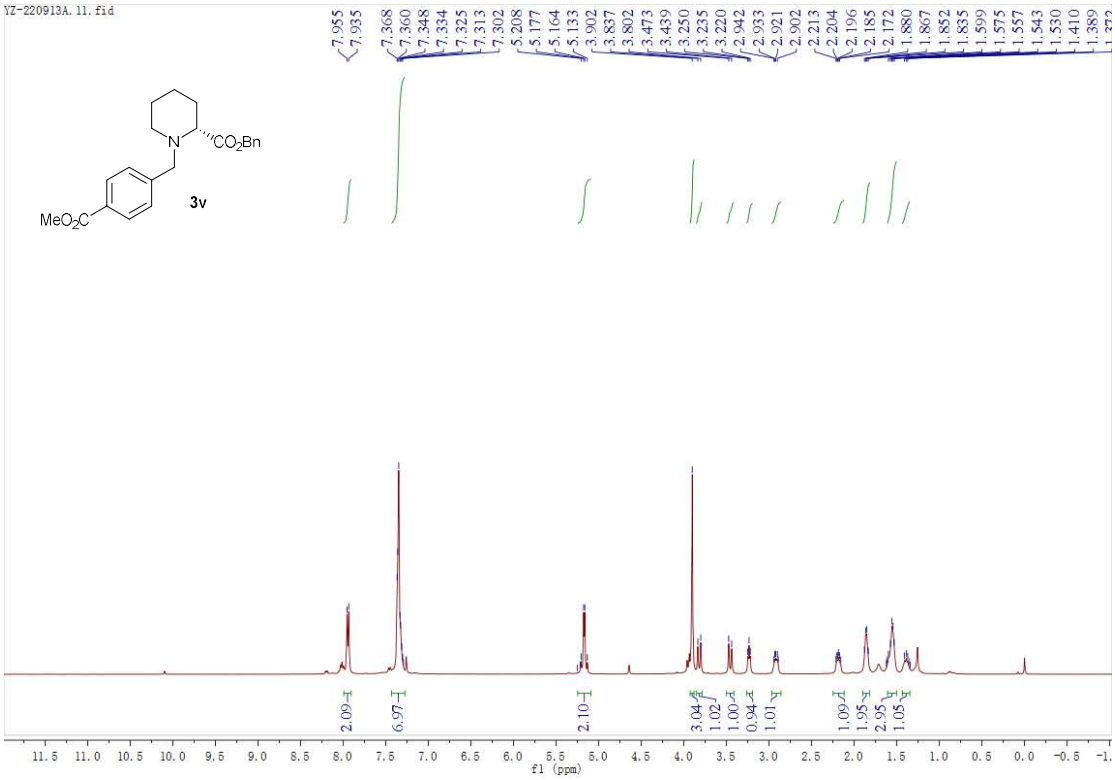
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3t



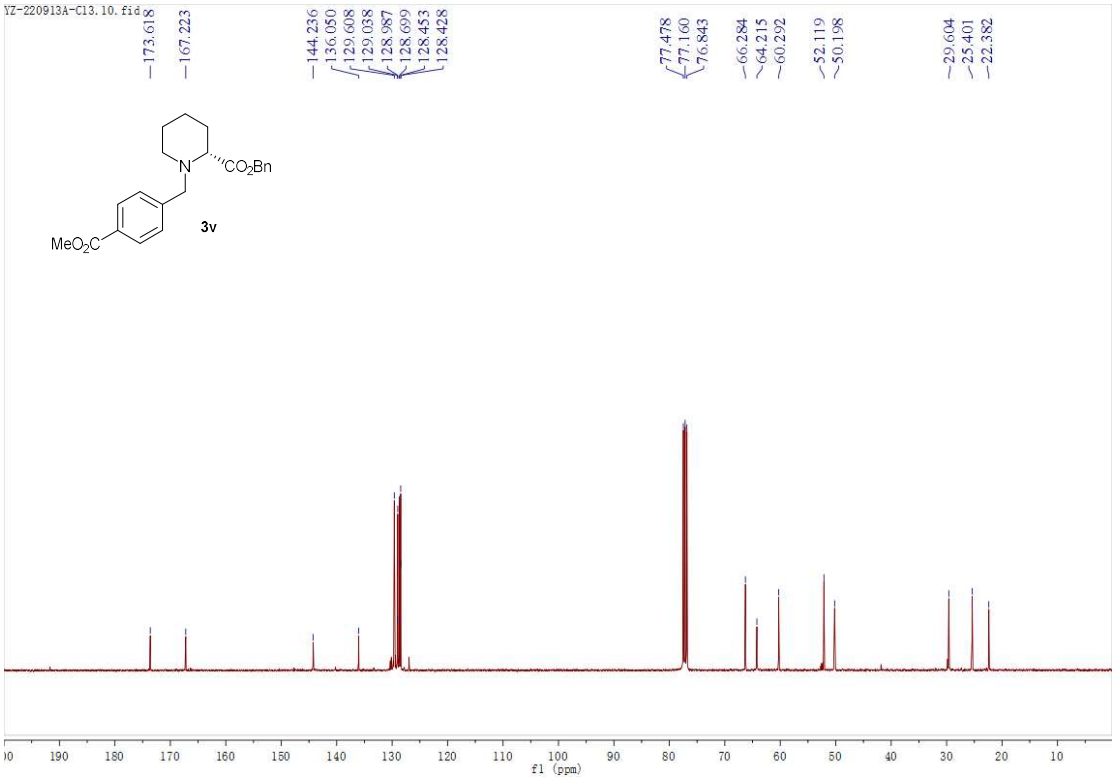
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3u



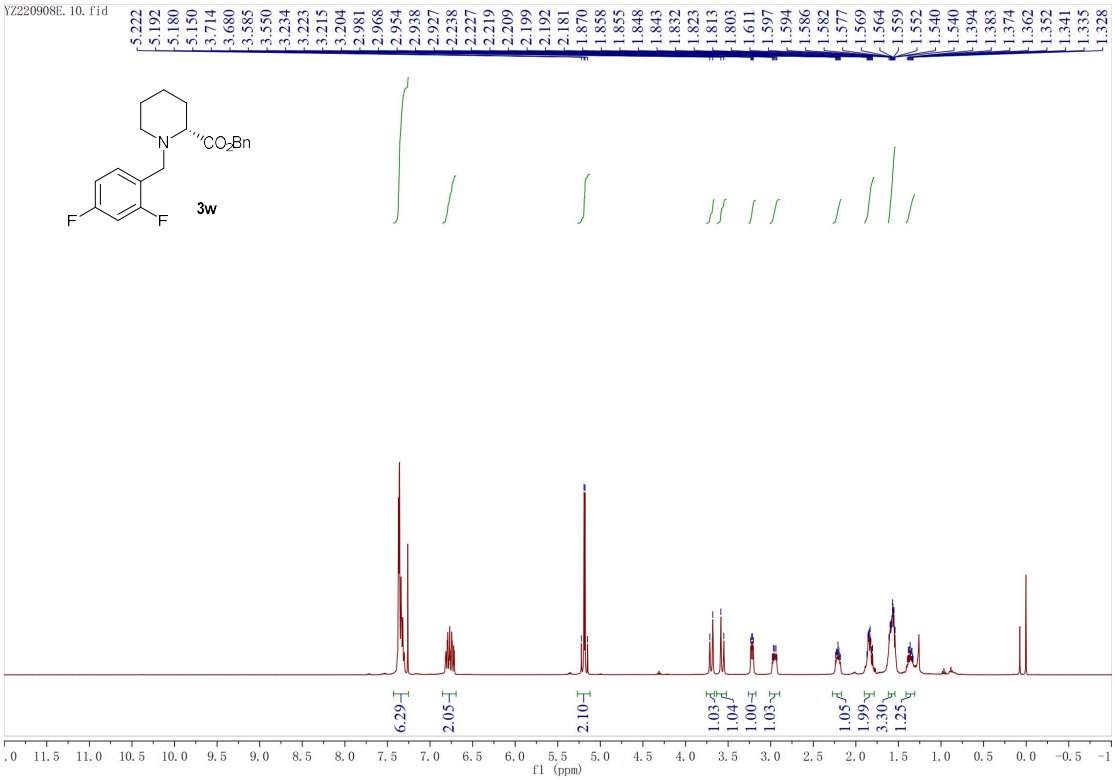
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3u



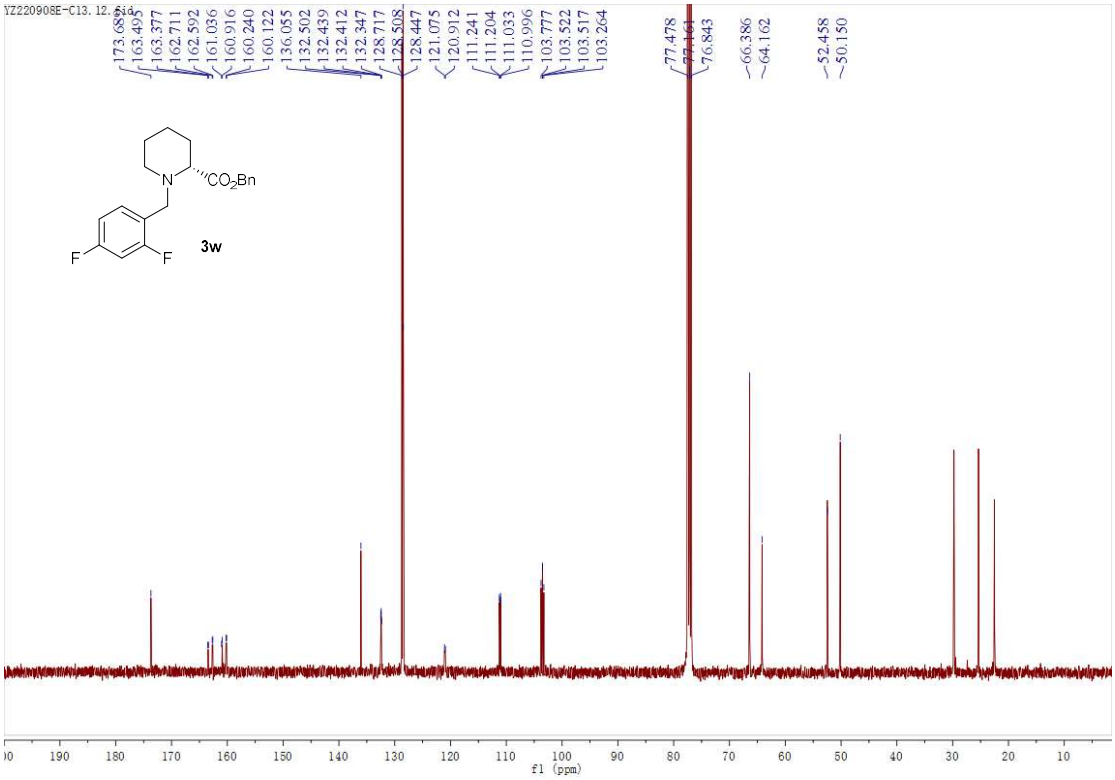
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3v



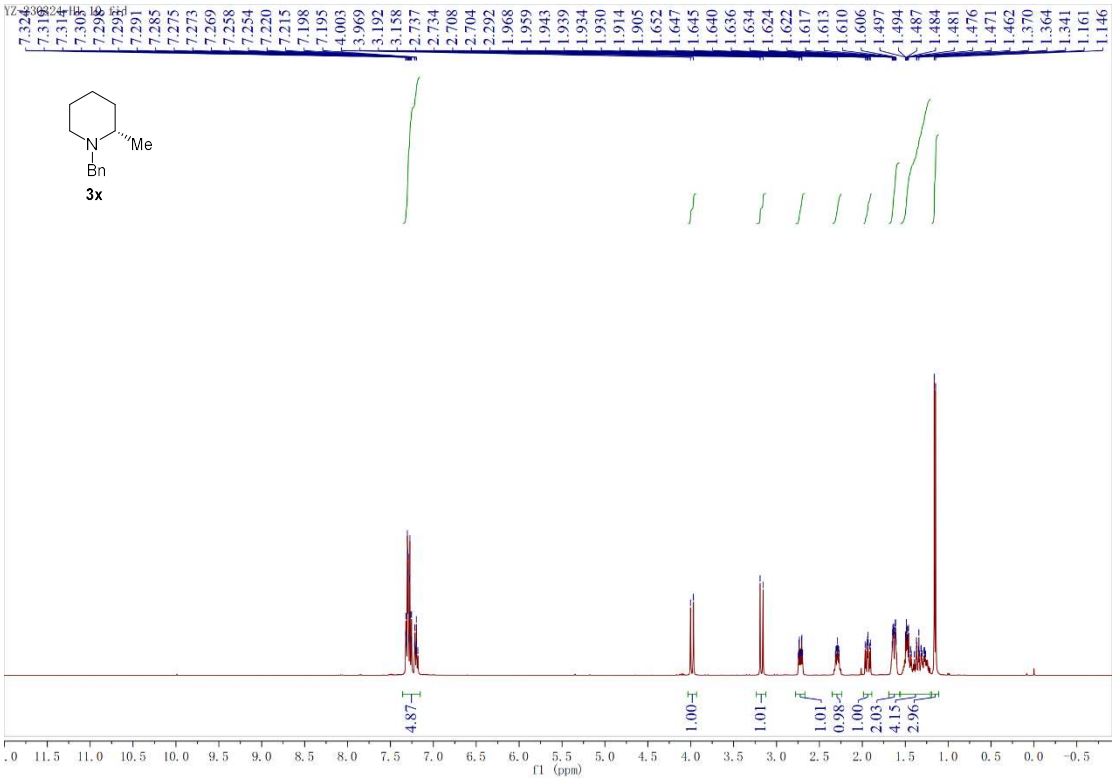
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3v



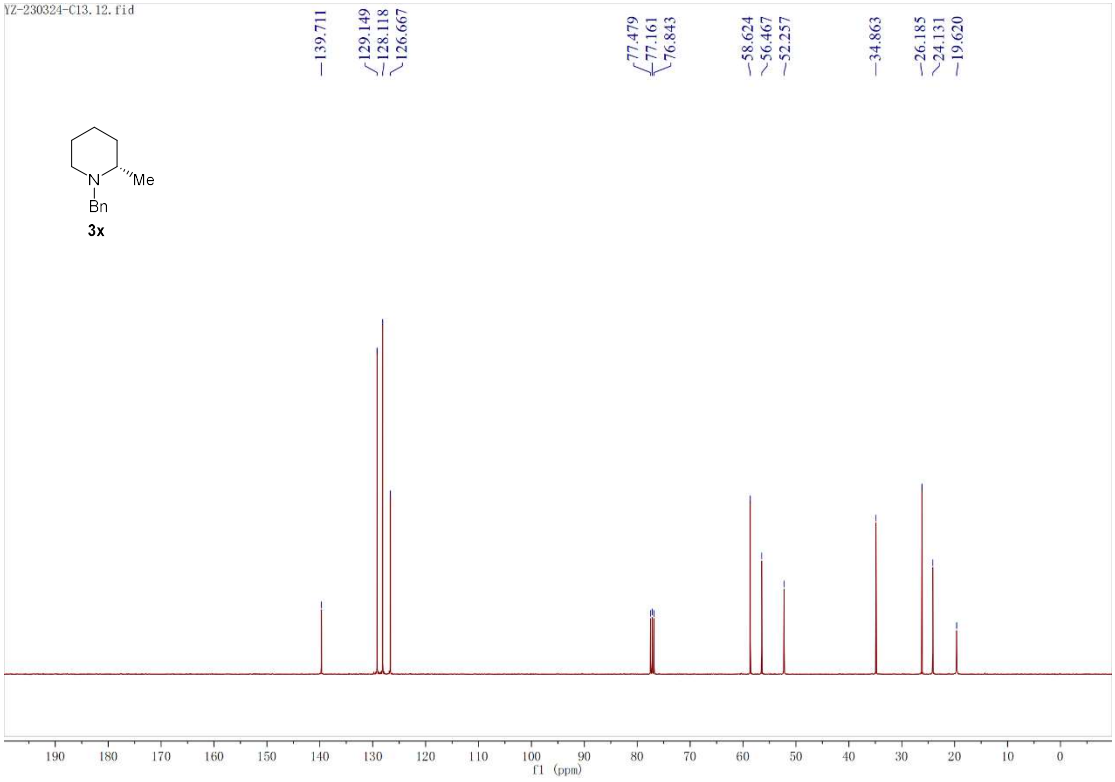
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3w



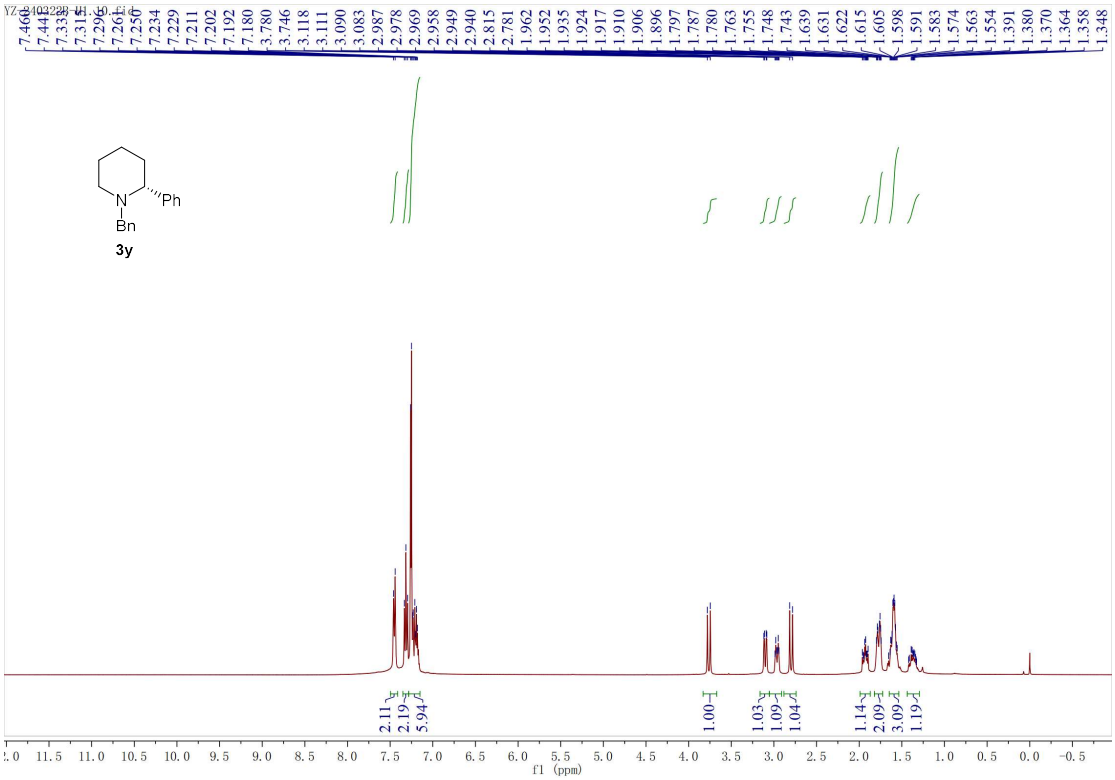
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3w



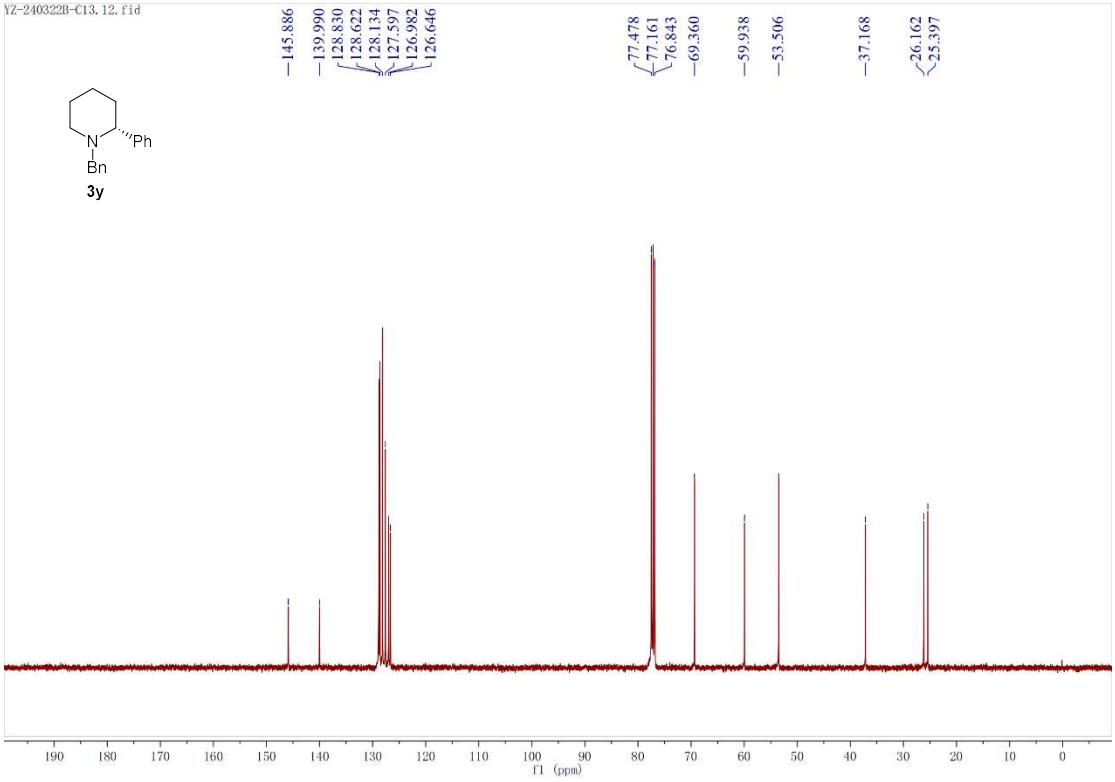
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3x



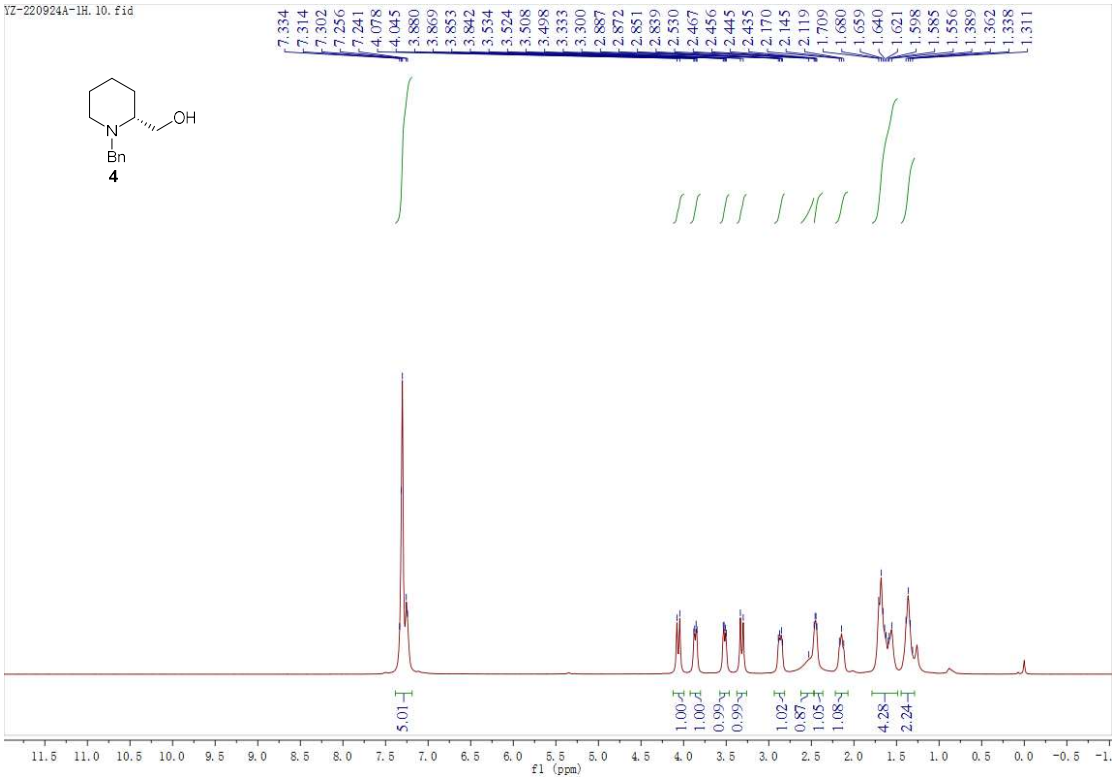
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3x



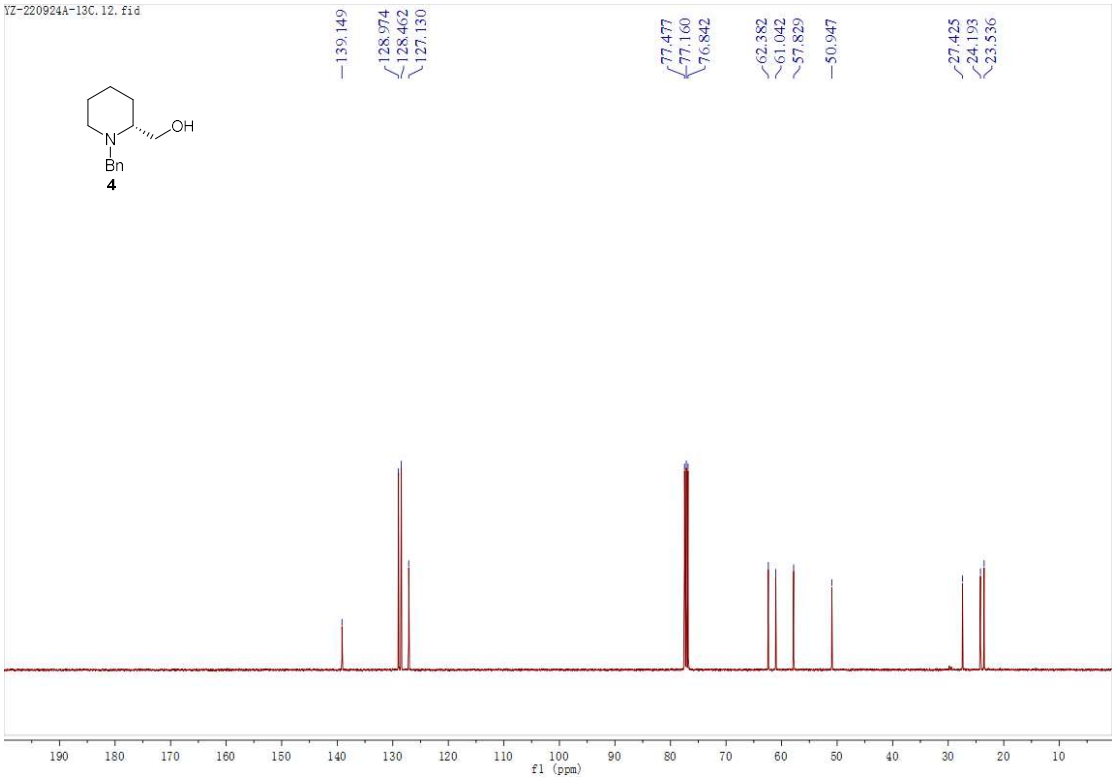
[1]H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 3y



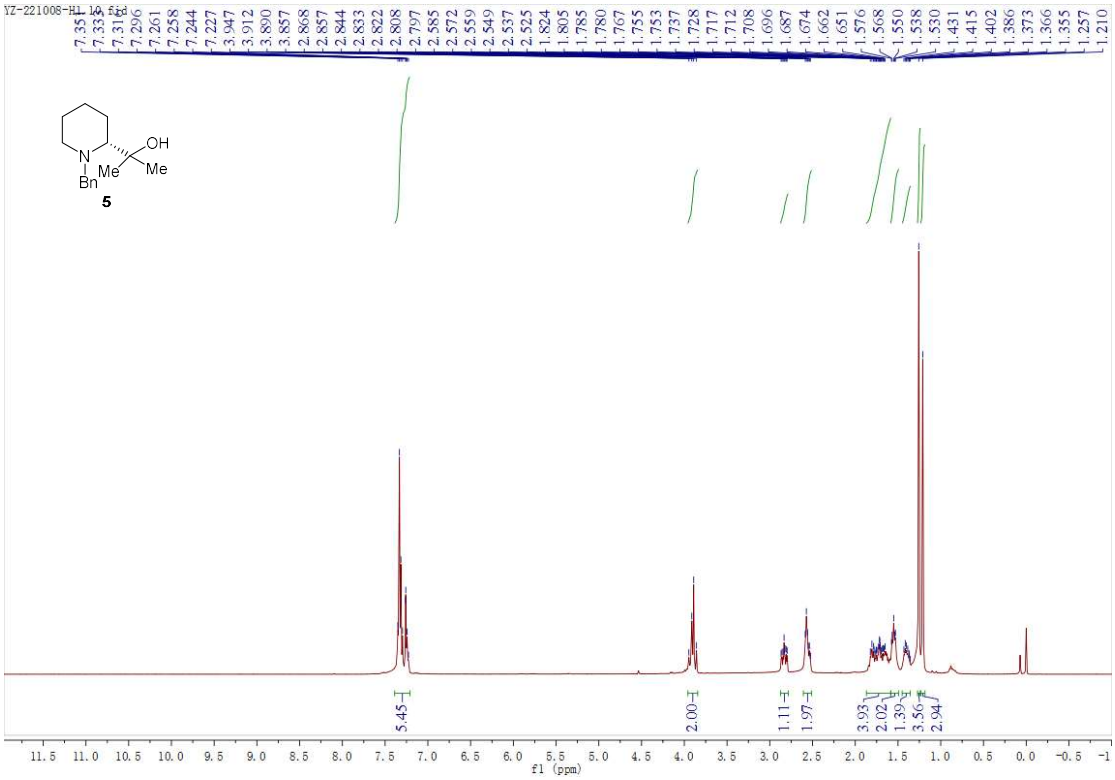
[13]C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 3y



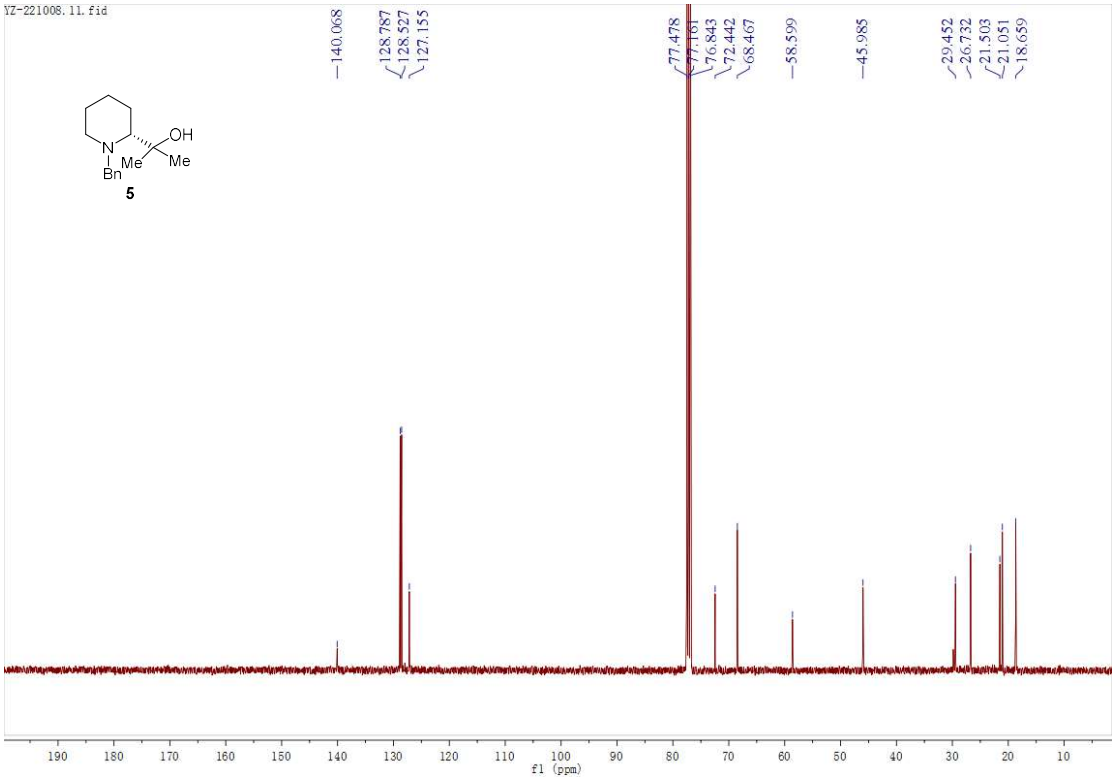
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 4



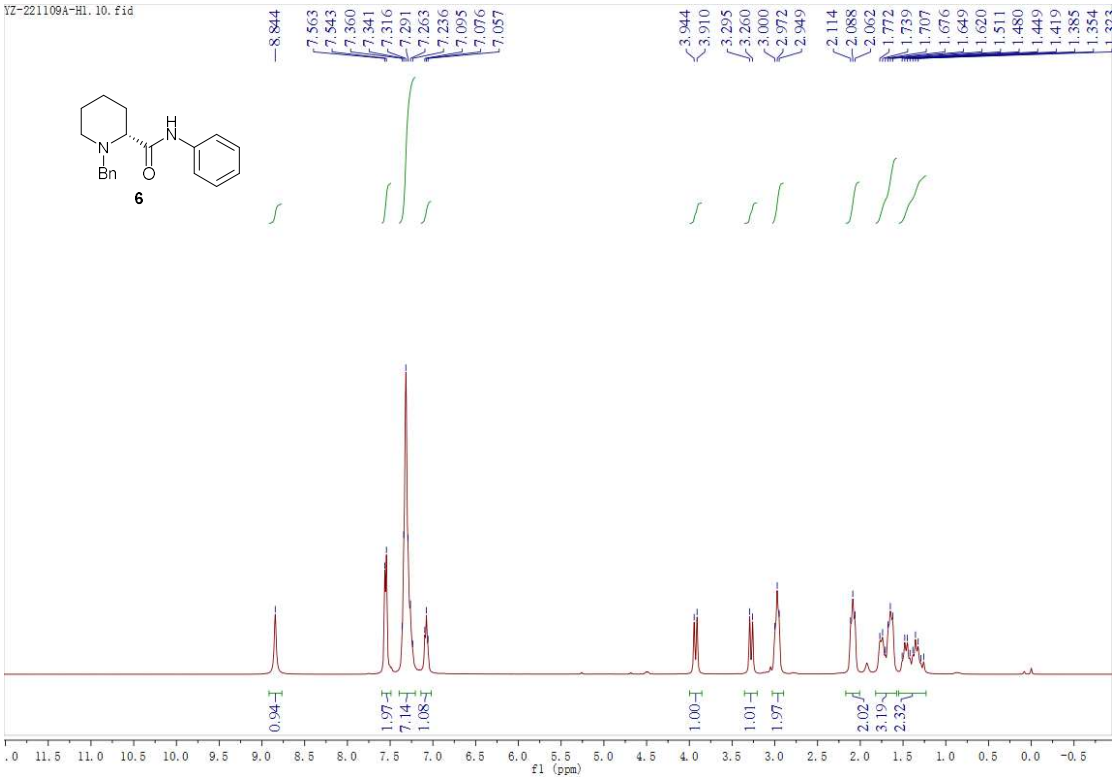
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 4



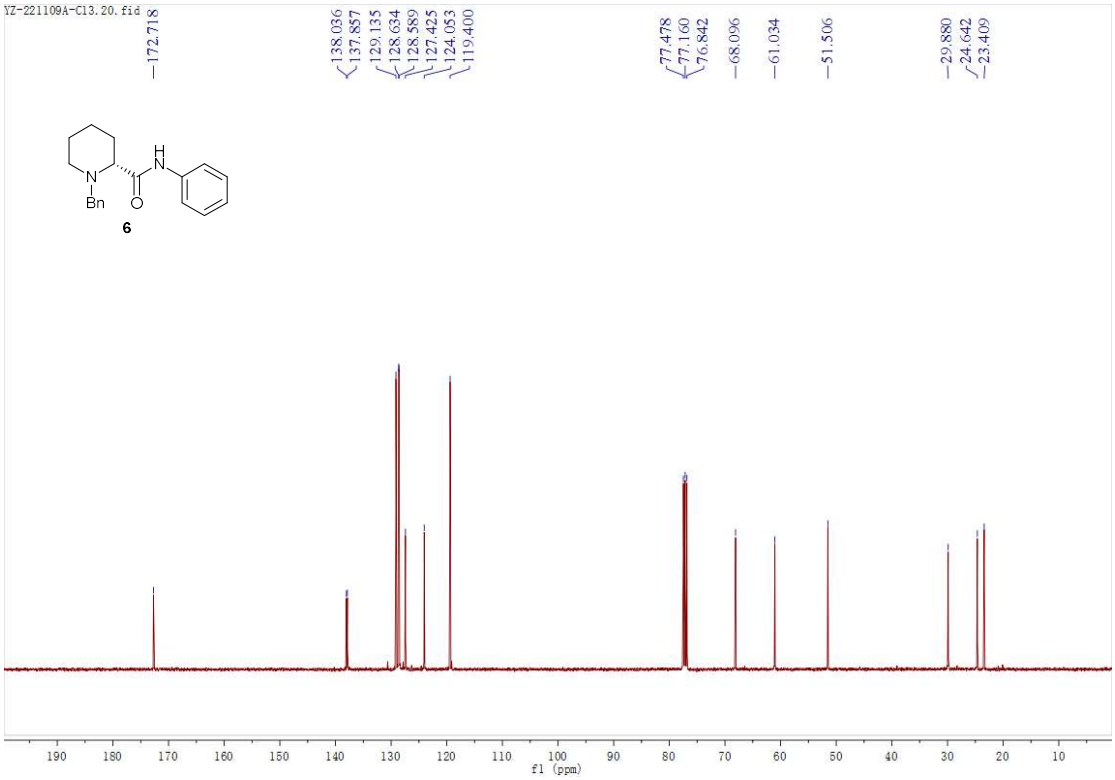
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 5



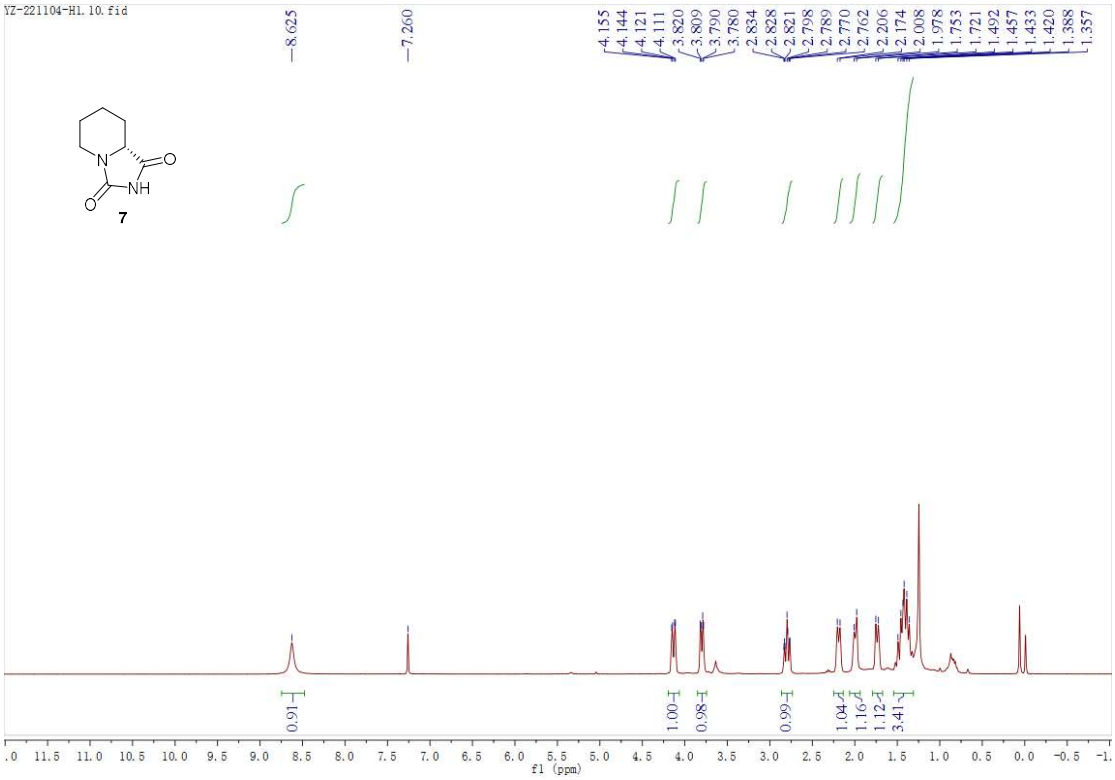
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 5



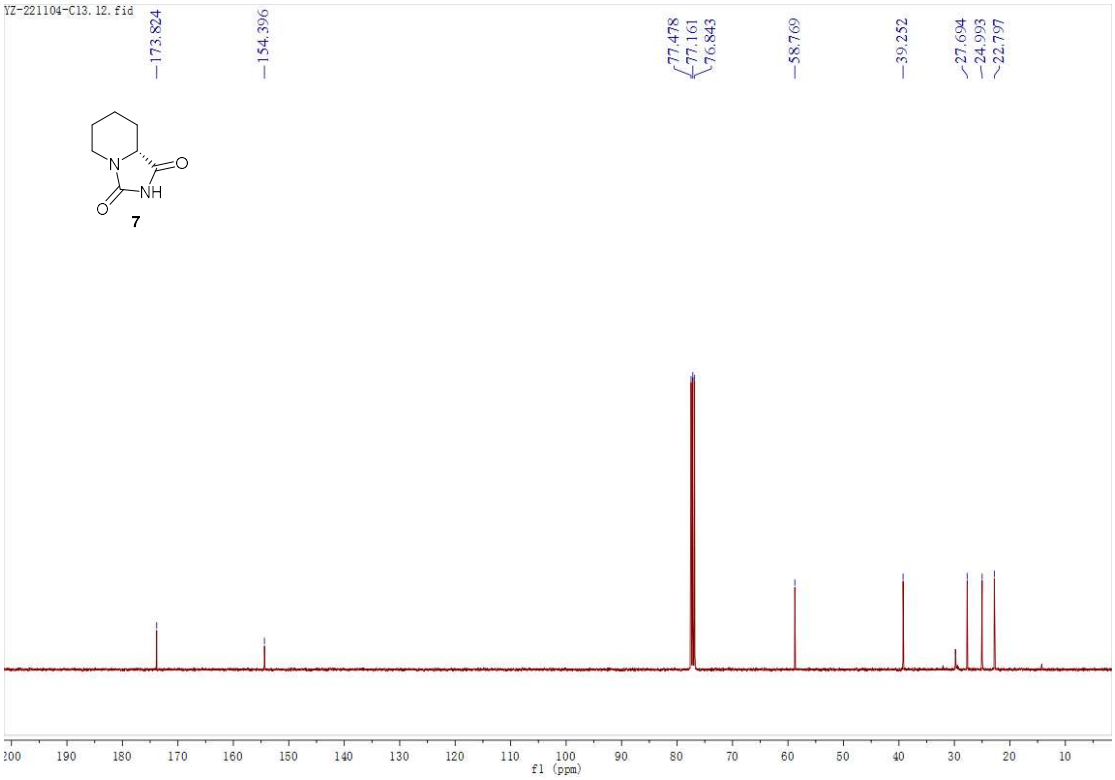
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 6



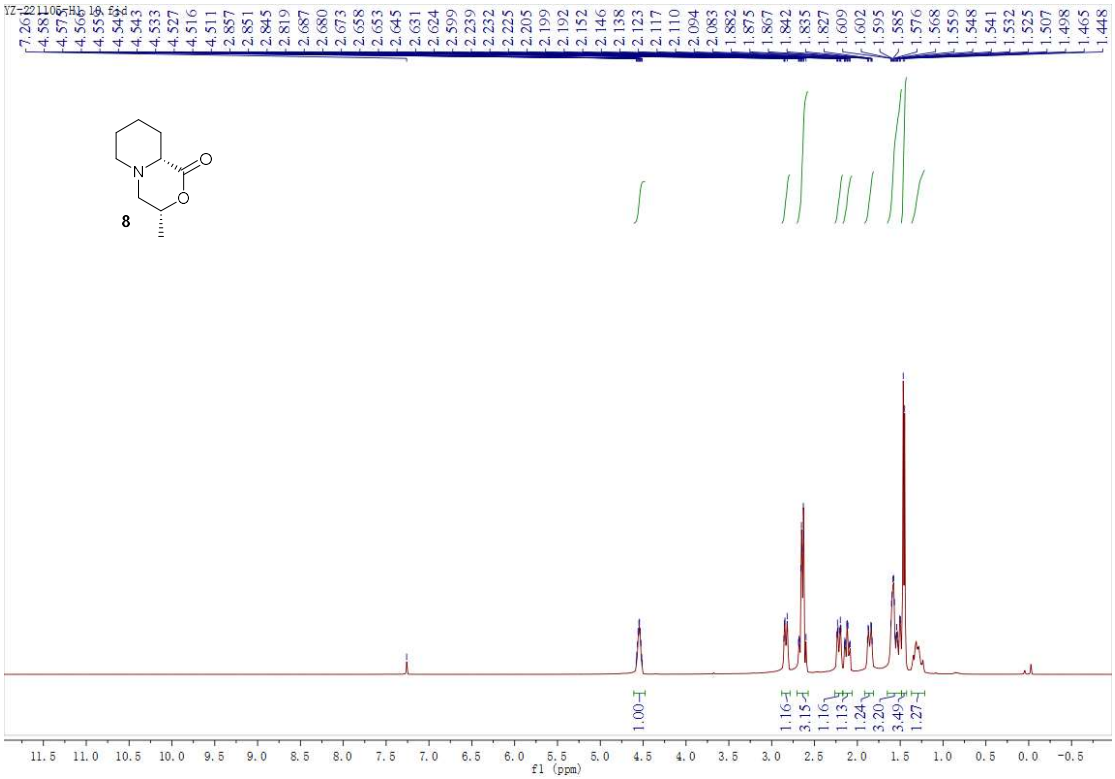
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 6



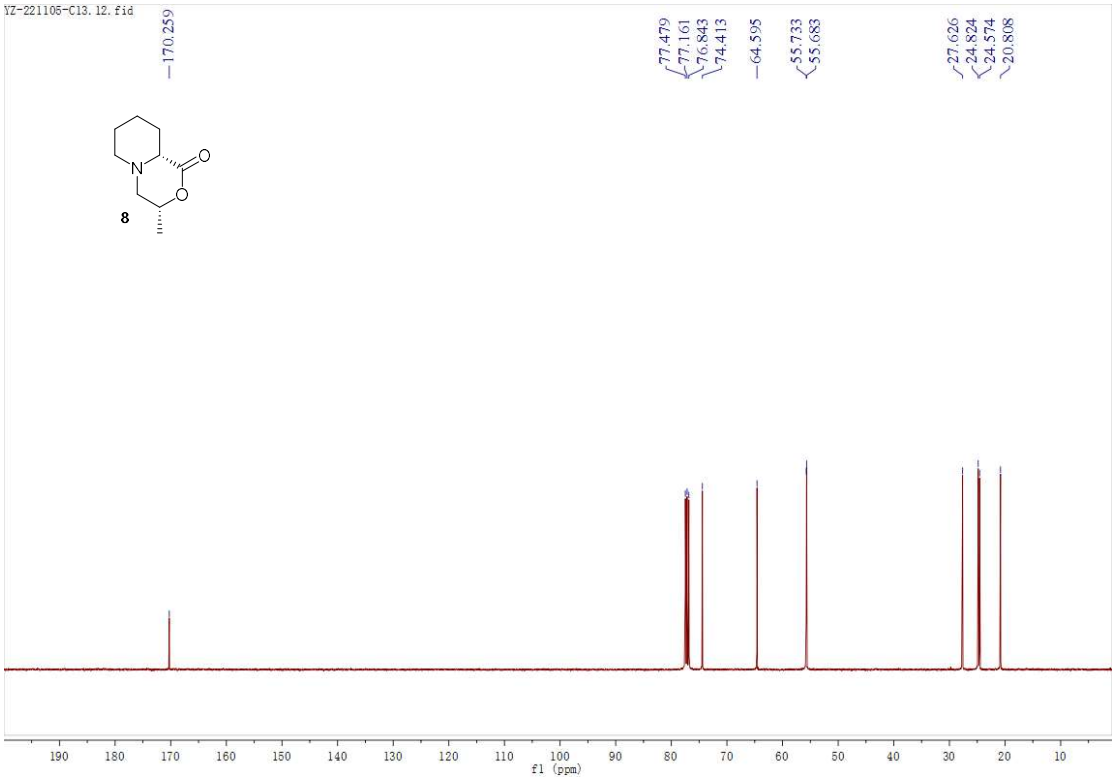
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 7



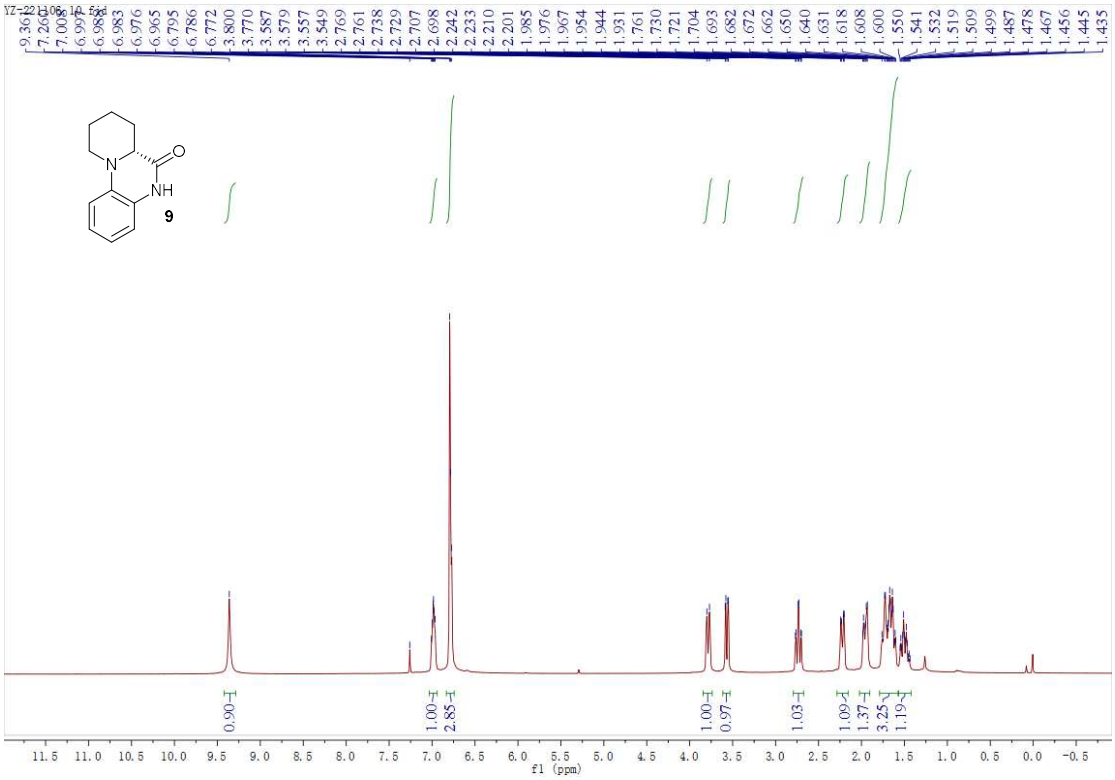
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 7



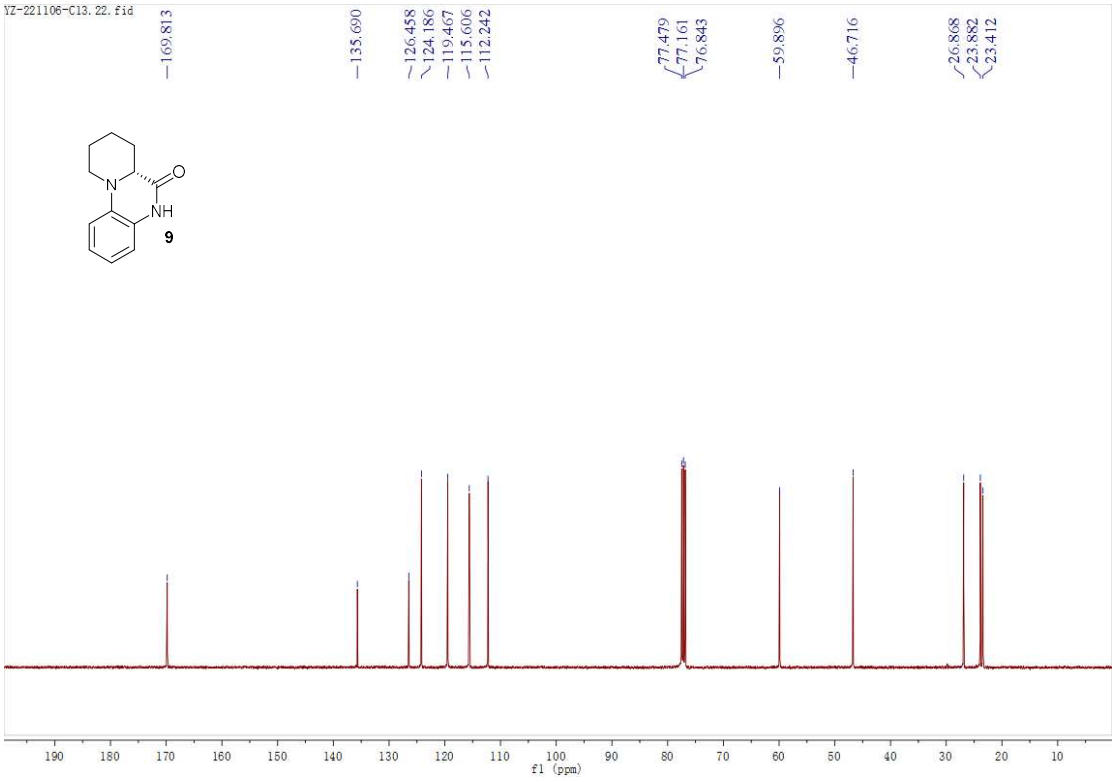
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 8



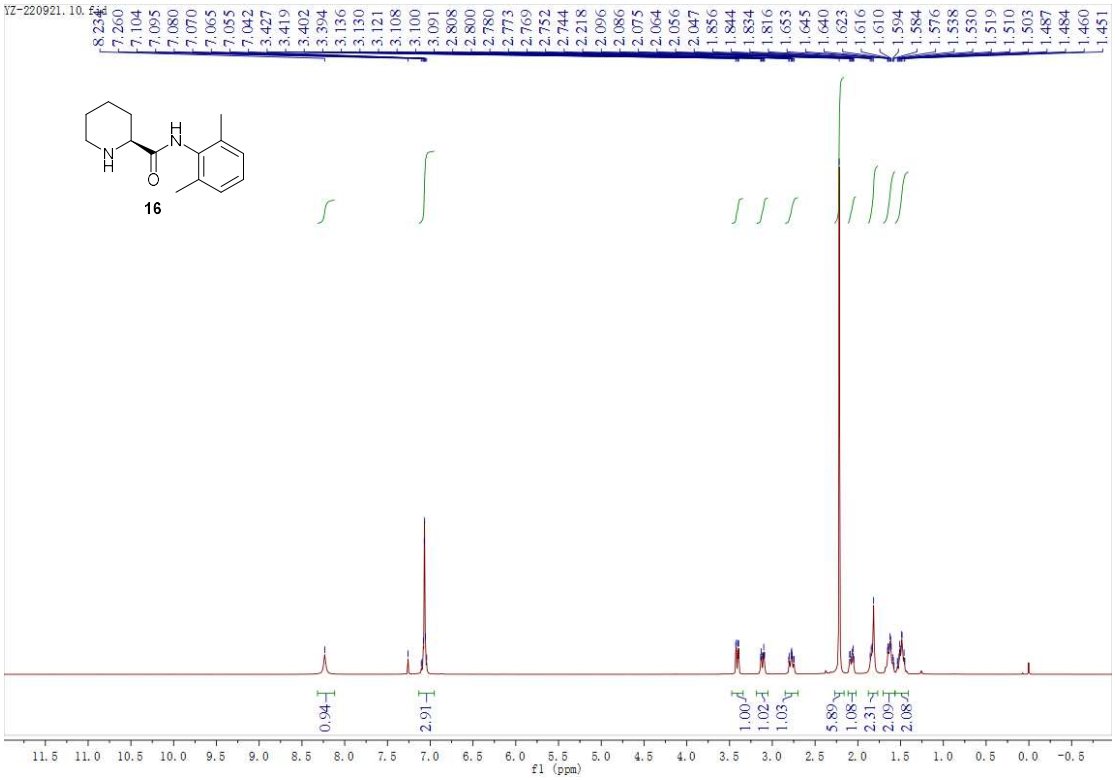
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 8



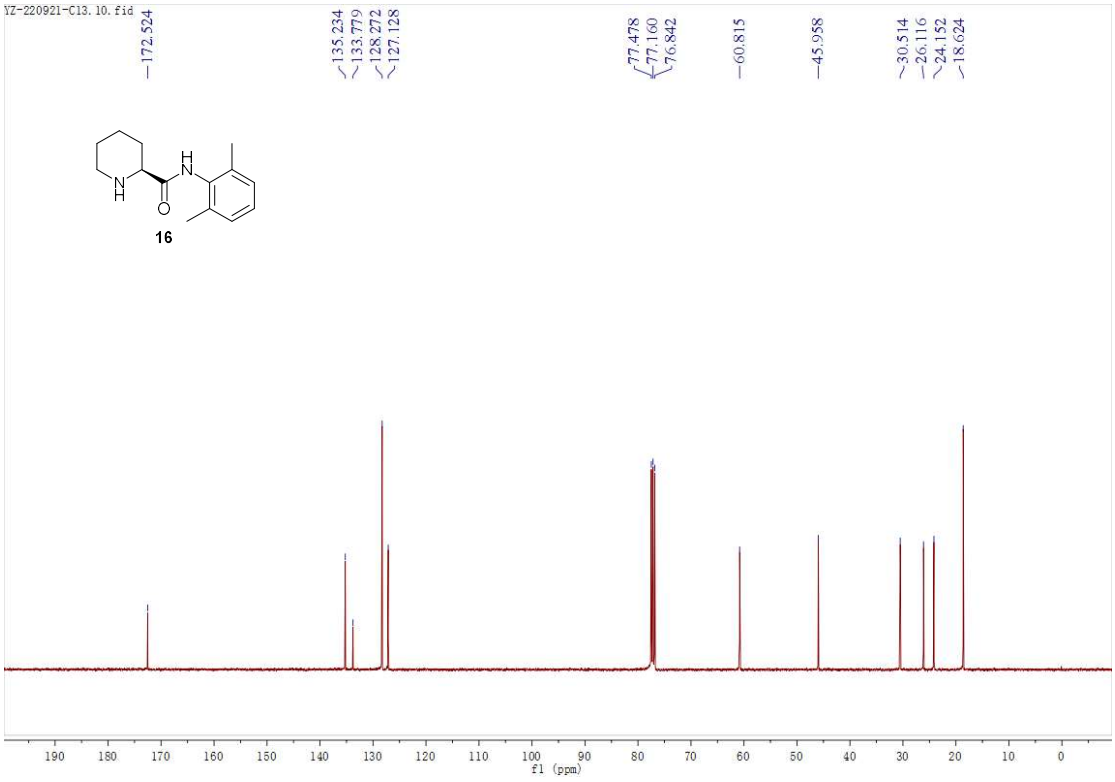
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 9



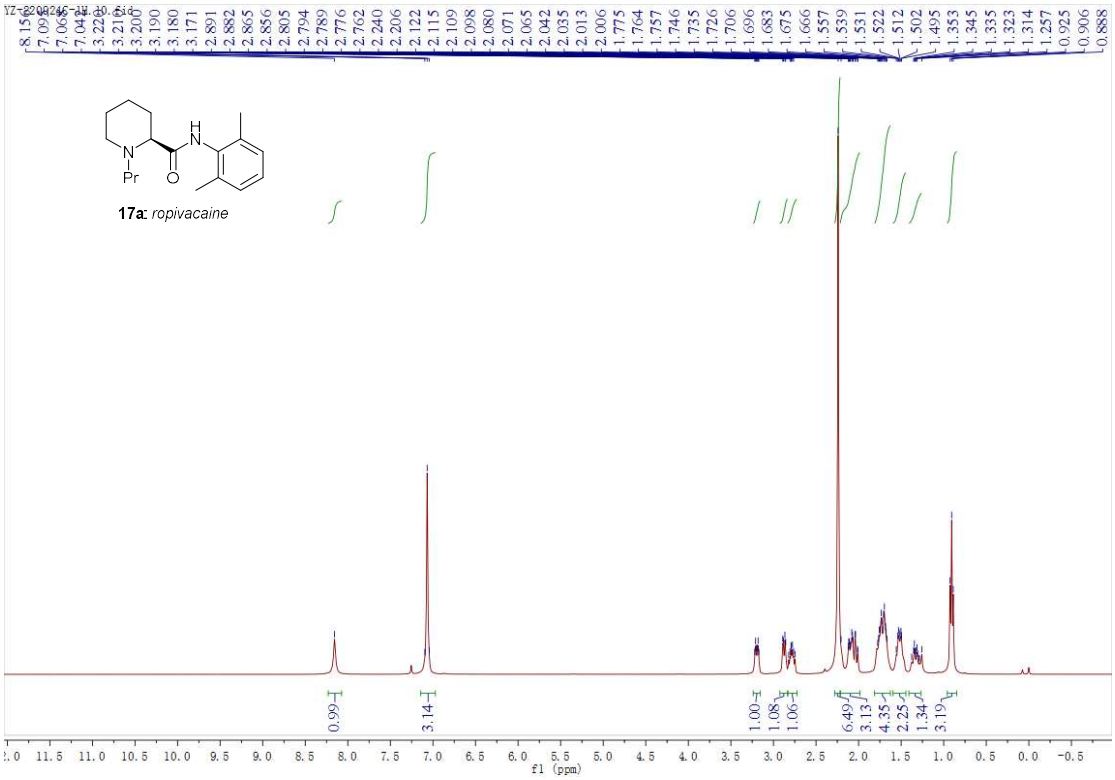
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 9



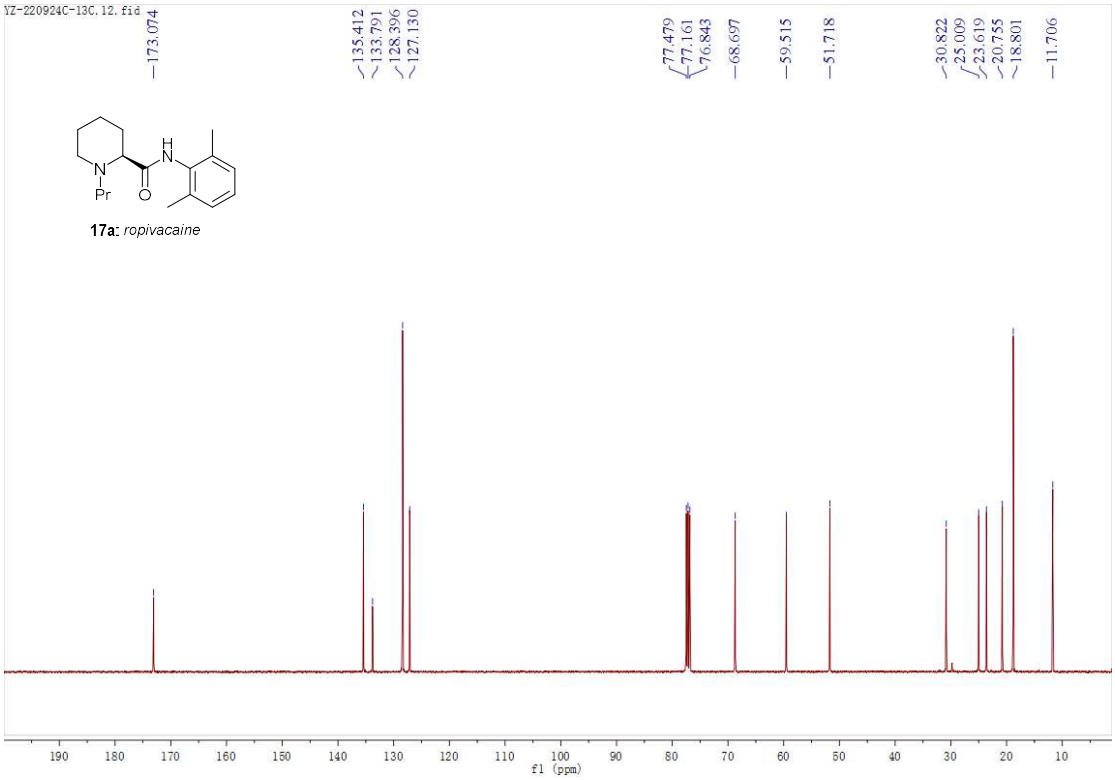
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 16



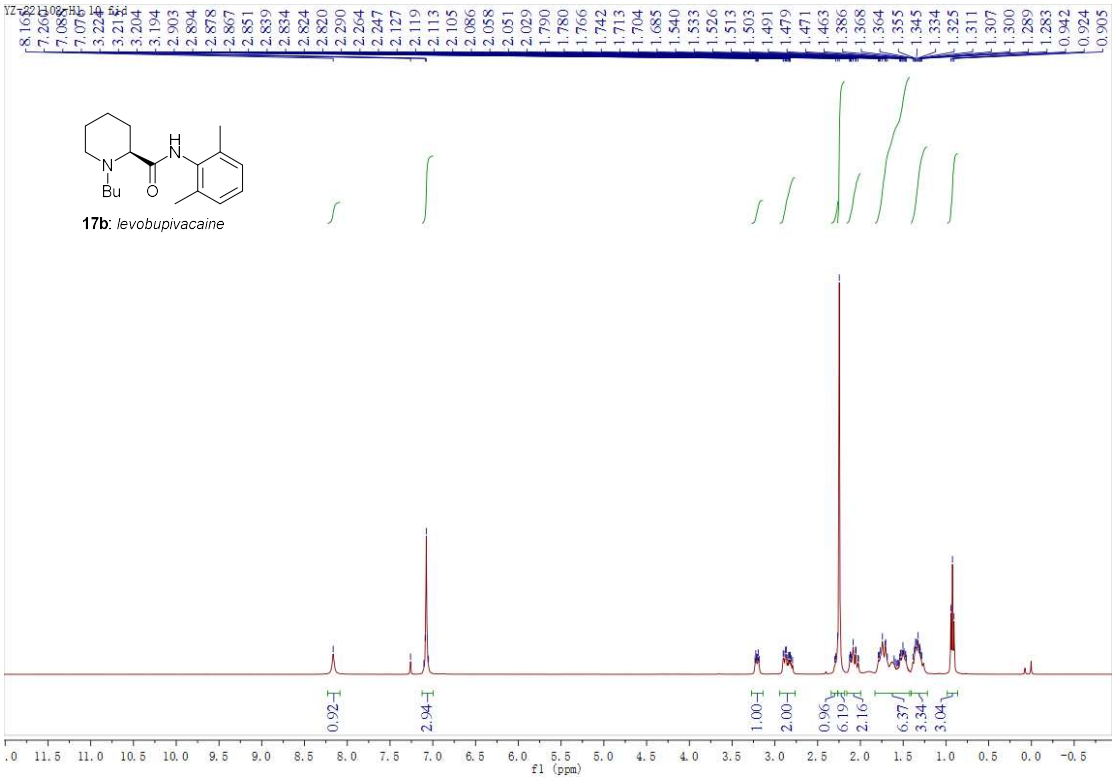
^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 16



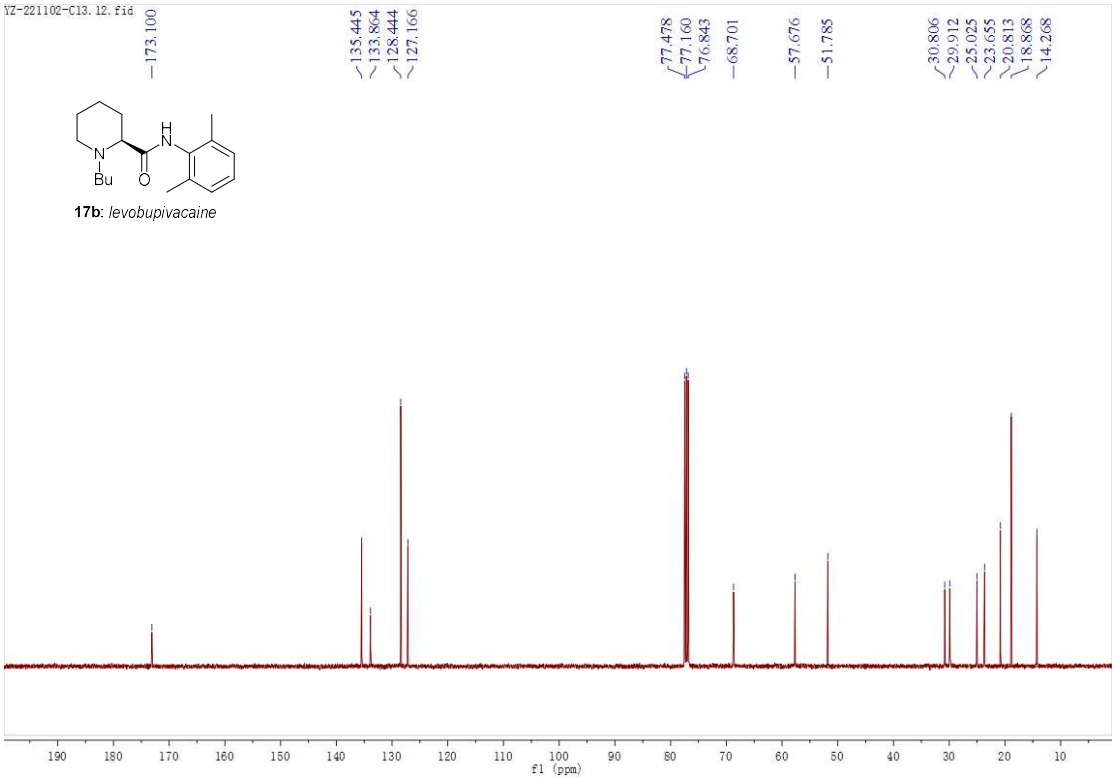
^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 17a



^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 17a

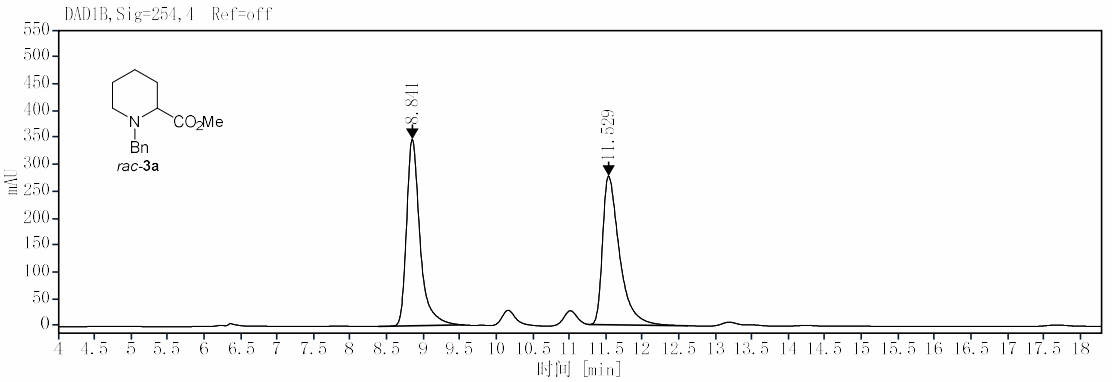


^{1}H-NMR Spectrum (400 MHz, Chloroform-*d*) of Compound 17b



^{13}C-NMR Spectrum (100 MHz, Chloroform-*d*) of Compound 17b

5. HPLC Spectra



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
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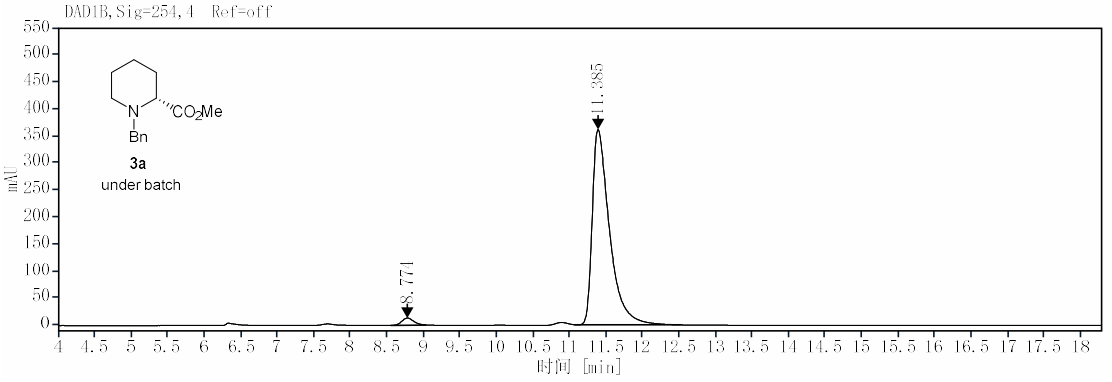
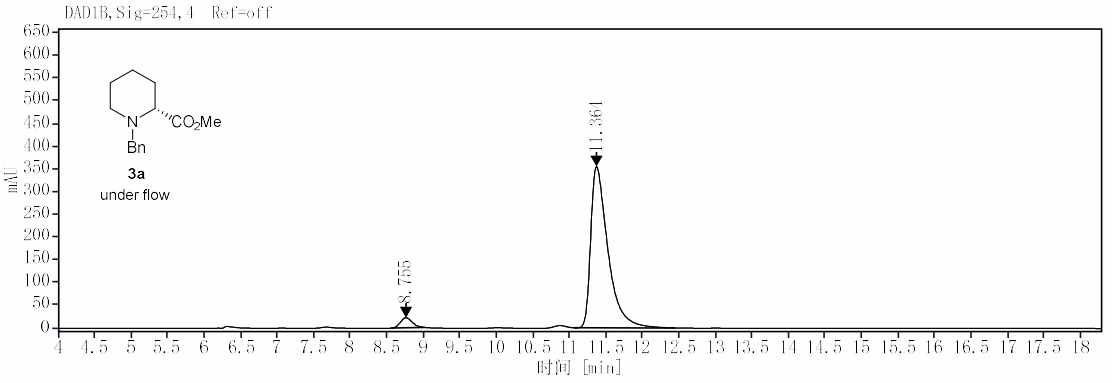
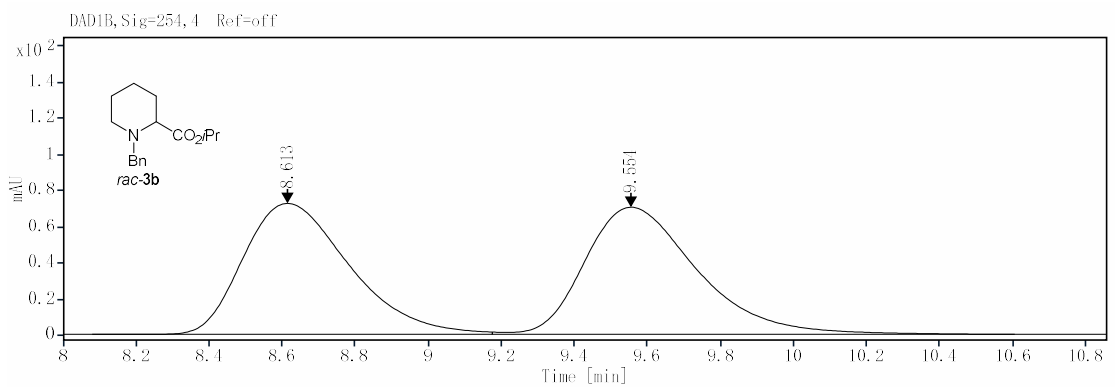
11.529	MM m	0.24	4443.38	276.29	50.06



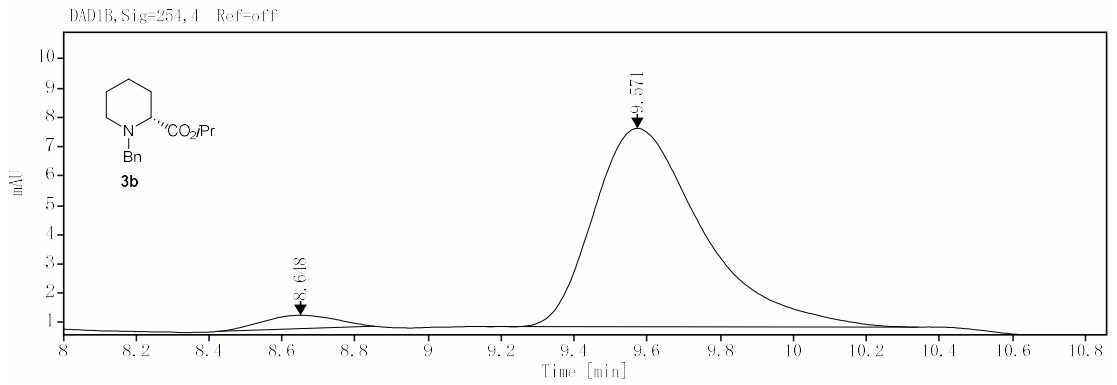
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.774	MM m	0.18	148.54	13.19	2.44
11.385	MM m	0.25	5938.85	361.54	97.56



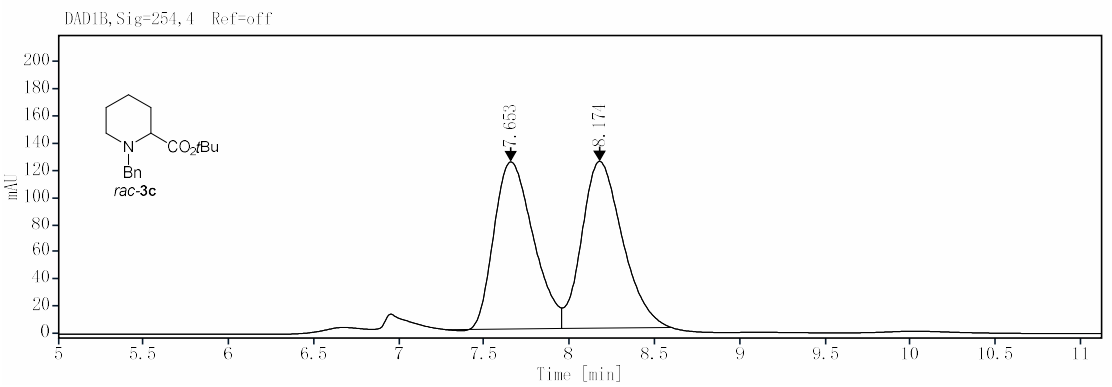
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.755	MM m	0.17	252.11	22.46	4.15
11.364	MM m	0.24	5815.70	355.56	95.85



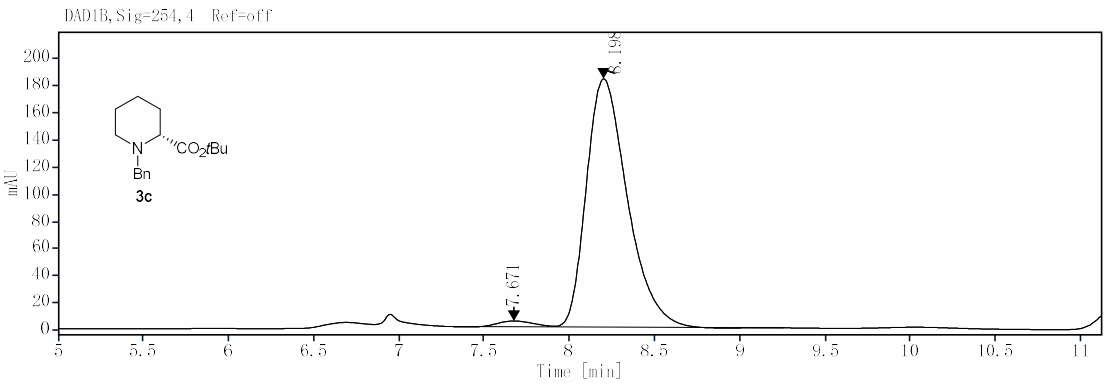
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.613	MM m	0.31	1662.06	72.32	49.28
9.554	MM m	0.33	1504.80	70.24	50.72



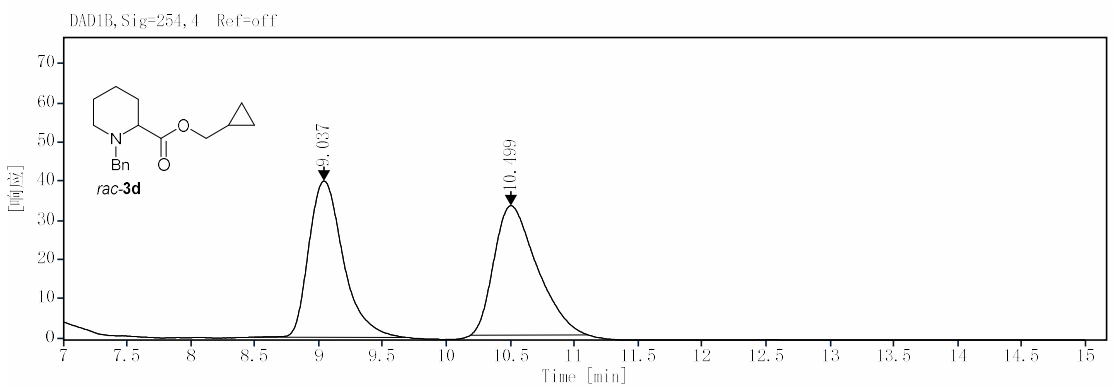
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.648	MM m	0.21	6.38	0.46	4.37
9.571	MM m	0.31	139.58	6.76	95.63



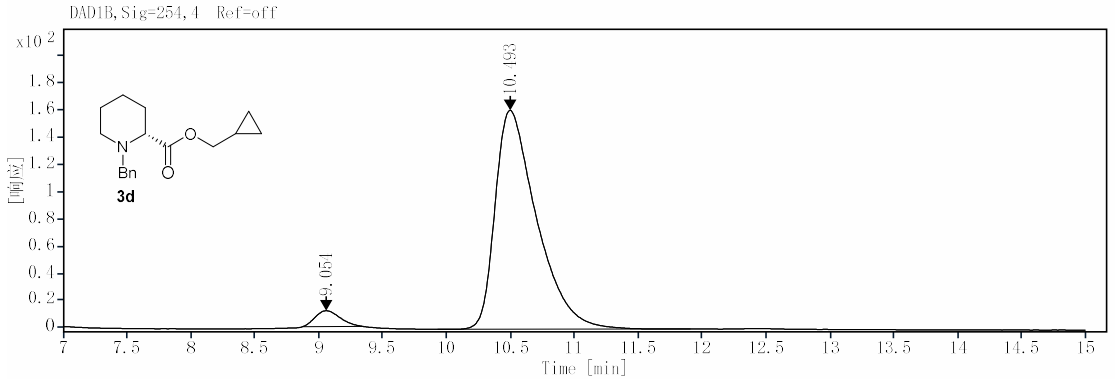
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
7.653	MM m	0.25	1975.95	123.26	49.14
8.174	MM m	0.26	2045.27	123.07	50.86



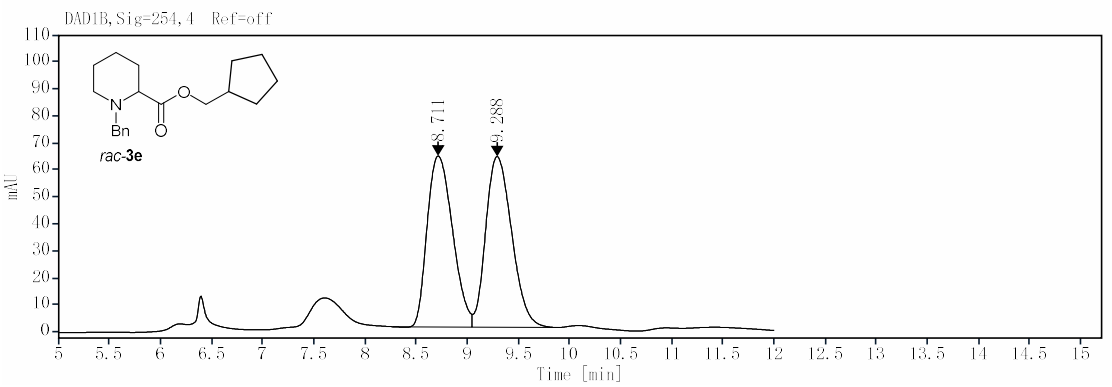
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
7.671	MM m	0.22	57.37	4.25	1.84
8.198	MM m	0.26	3058.02	182.98	98.16



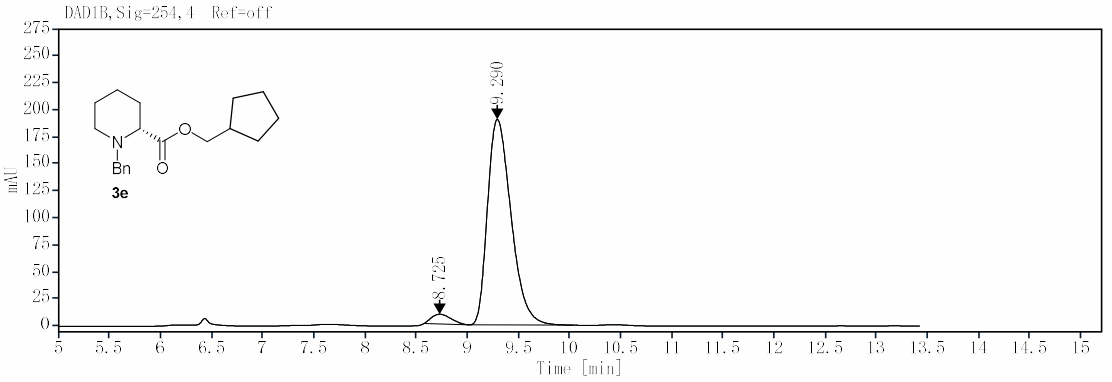
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
9.037	MM m	0.29	749.07	39.95	49.21
10.499	MM m	0.35	773.22	33.09	50.79



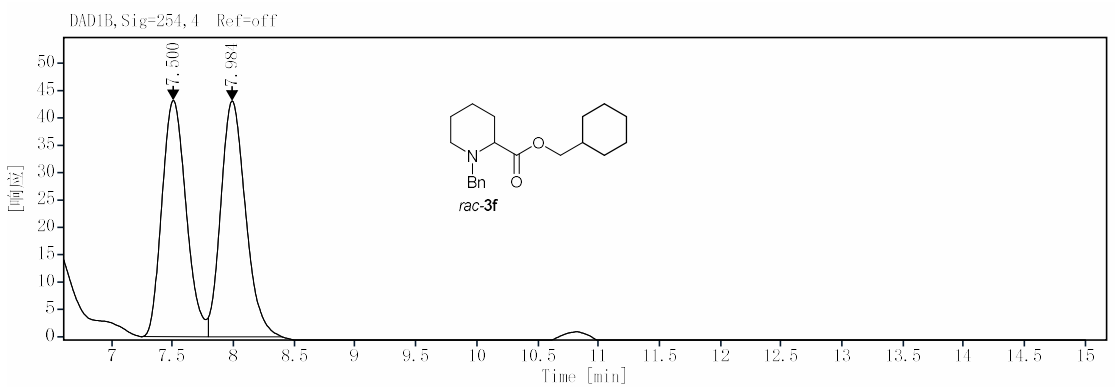
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
9.054	MM m	0.22	158.86	11.69	4.19
10.493	MM m	0.34	3634.00	160.99	95.81



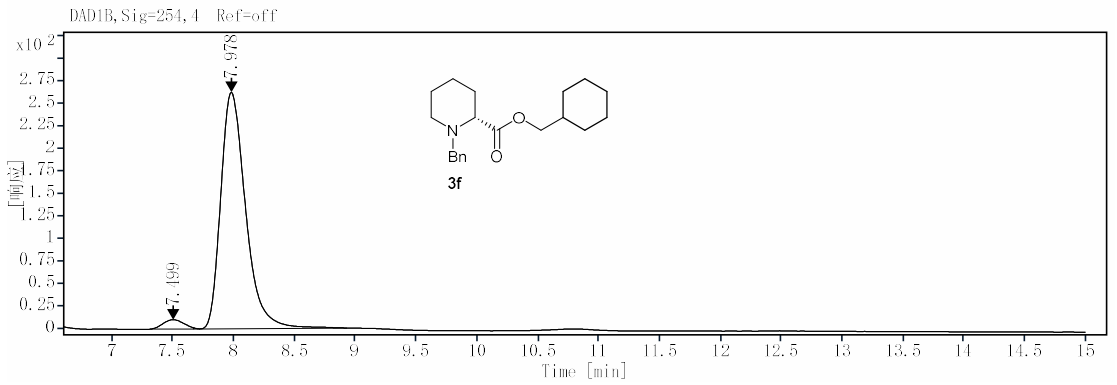
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.711	MM m	0.28	1092.12	63.33	49.42
9.288	MM m	0.28	1117.94	63.20	50.58



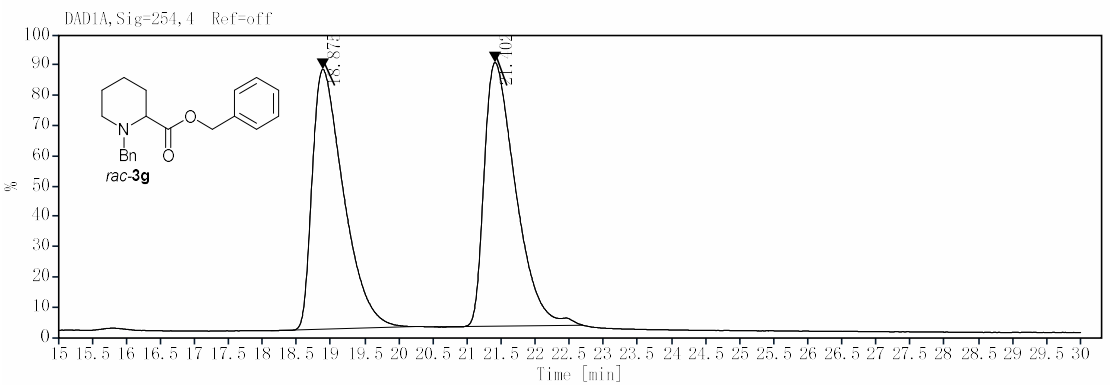
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.725	MM m	0.22	119.38	9.01	3.77
9.290	MM m	0.25	3048.64	190.33	96.23



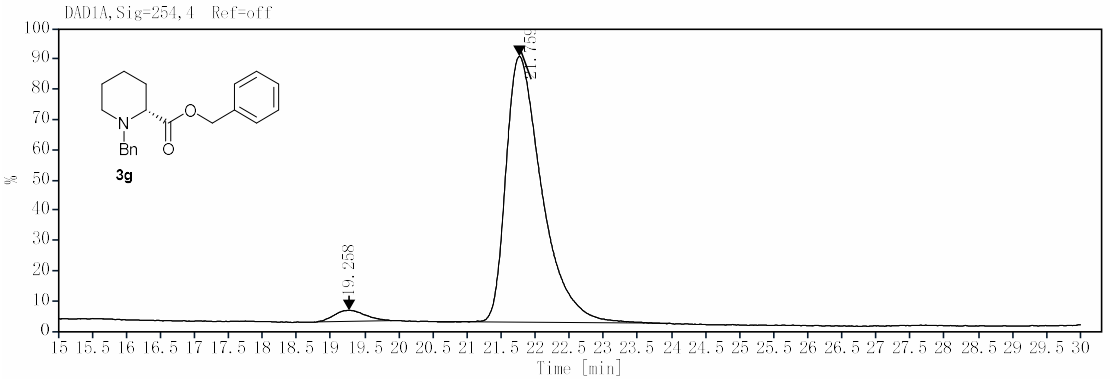
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
7.500	MM m	0.22	599.79	43.31	49.49
7.984	MM m	0.22	612.27	43.25	50.51



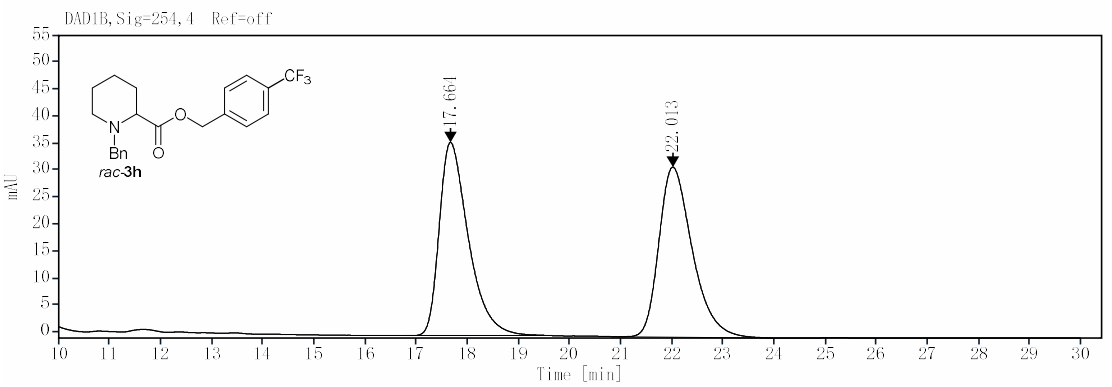
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
7.499	MM m	0.19	121.25	10.33	3.16
7.978	MM m	0.22	3715.43	262.17	96.84



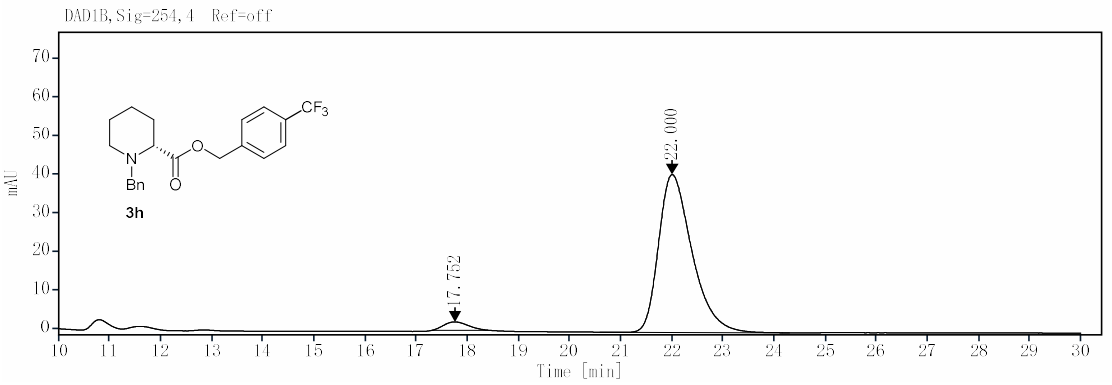
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
18.875	MM m	0.48	2574.91	80.44	49.53
21.402	MM m	0.49	2624.25	81.63	50.47



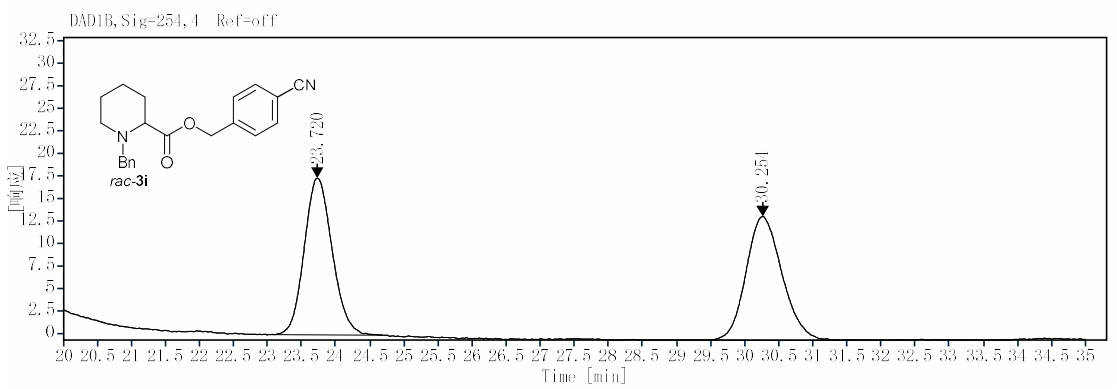
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
19.258	MM m	0.37	42.25	1.35	3.40
21.759	MM m	0.54	1202.00	32.71	96.60



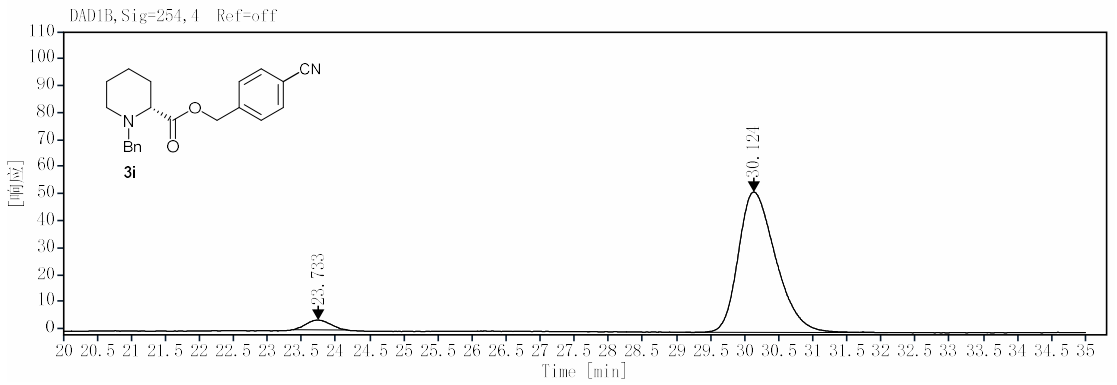
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
17.664	MM m	0.60	1415.18	35.75	49.72
22.013	MM m	0.69	1430.97	31.50	50.28



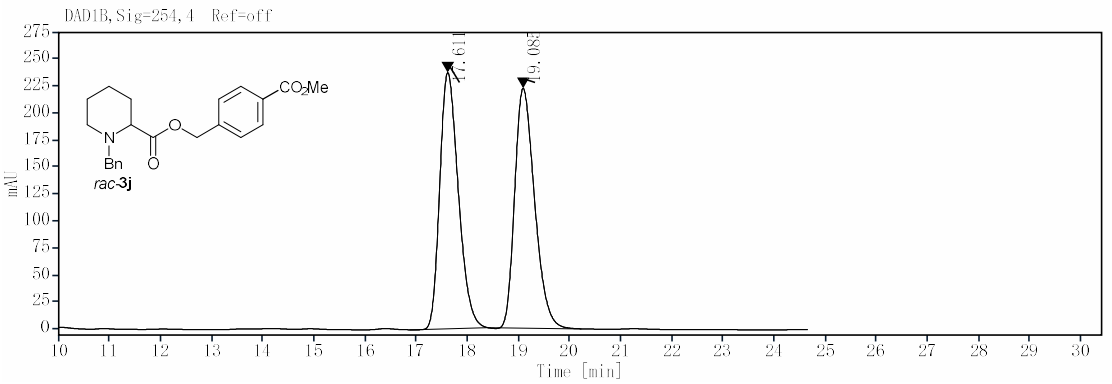
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
17.752	MM m	0.42	72.20	2.18	3.74
22.000	MM m	0.69	1857.23	40.91	96.26



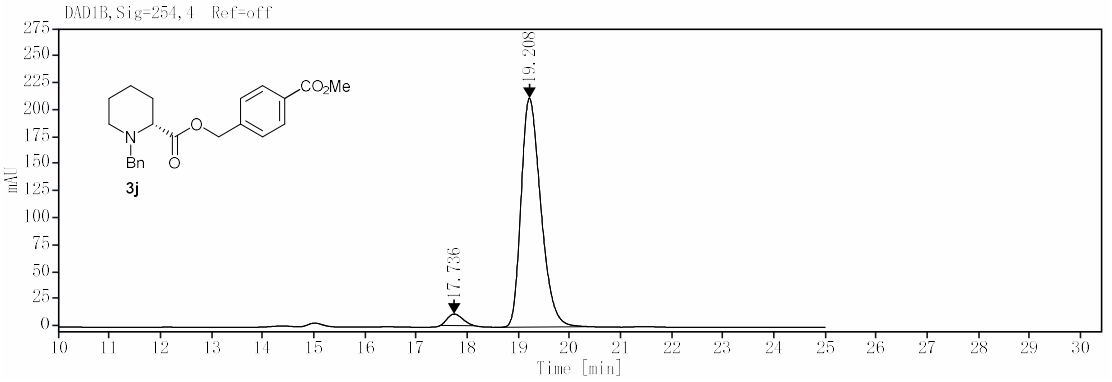
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
23.720	MM m	0.43	496.25	17.40	49.46
30.254	MM m	0.49	507.16	13.75	50.54



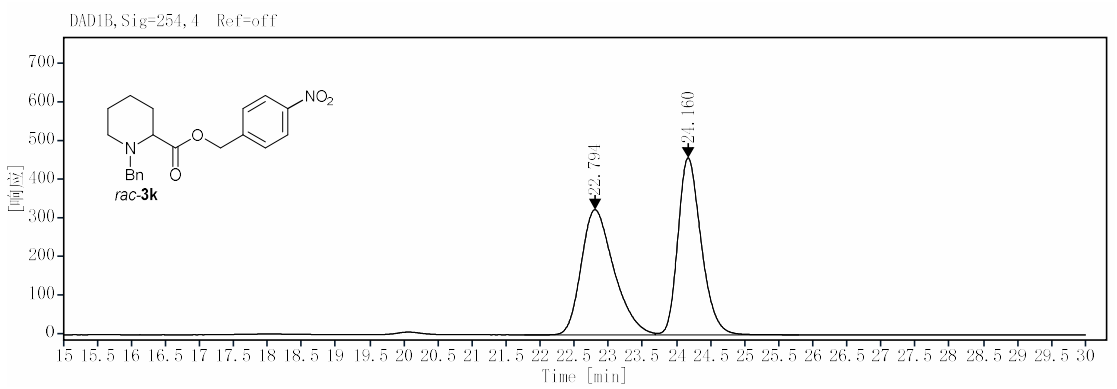
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
23.733	MM m	0.30	86.98	3.59	4.20
30.124	MM m	0.58	1981.53	51.99	95.80



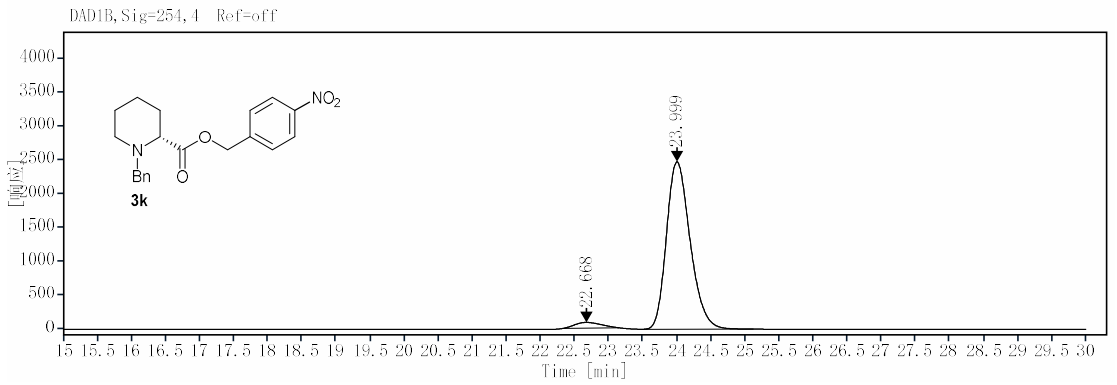
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
17.611	MM m	0.39	5980.10	237.07	49.93
19.085	MM m	0.42	5997.87	222.03	50.07



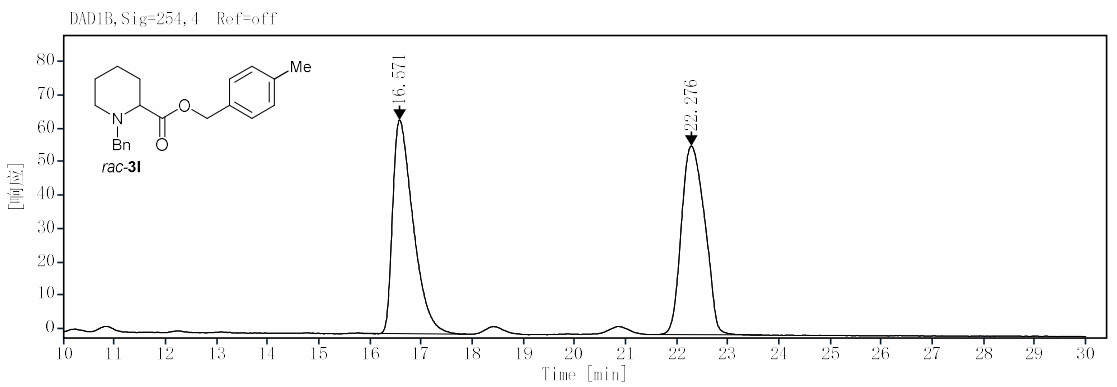
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
17.736	MM m	0.33	225.87	10.77	3.83
19.208	MM m	0.41	5678.34	211.89	96.17



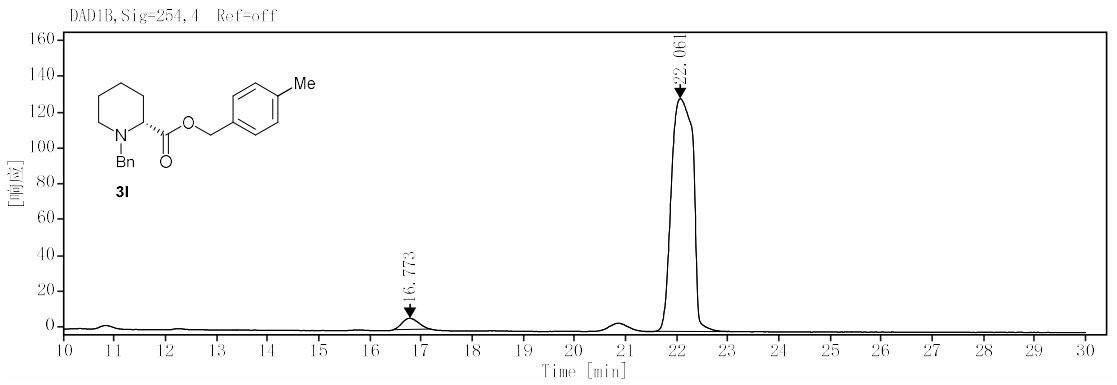
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
22.794	MM m	0.51	10816.27	324.47	49.84
24.160	MM m	0.36	10886.89	458.81	50.16



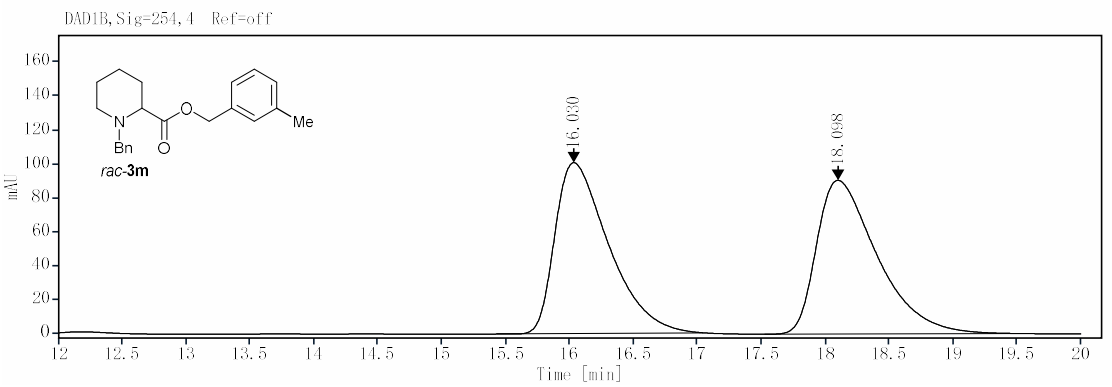
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
22.668	MM m	0.43	2342.90	86.39	3.76
23.999	MM m	0.37	59896.30	2481.70	96.24



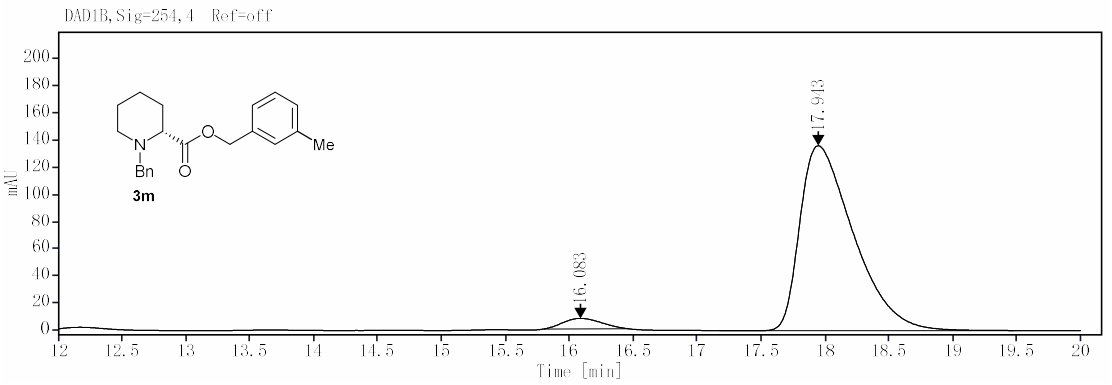
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.571	MM m	0.42	1787.49	64.09	49.82
22.276	MM m	0.55	1800.34	56.60	50.18



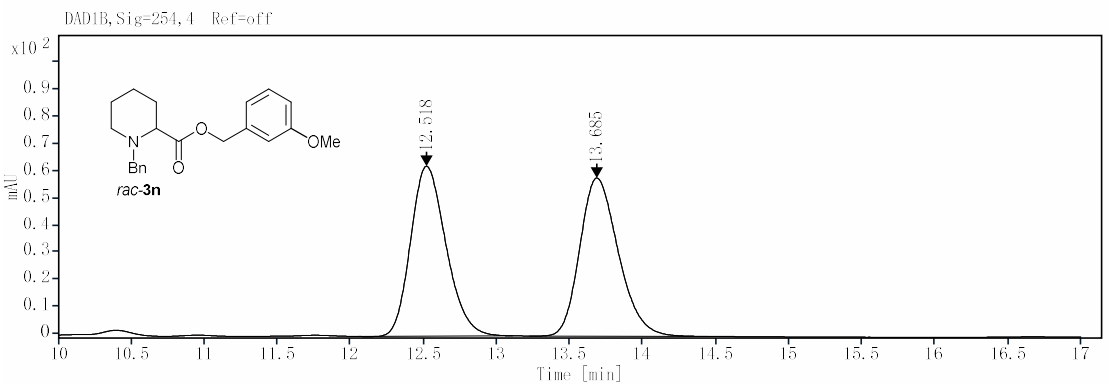
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.773	MM m	0.32	137.70	6.23	3.47
22.016	MM m	0.44	3831.11	130.18	96.53



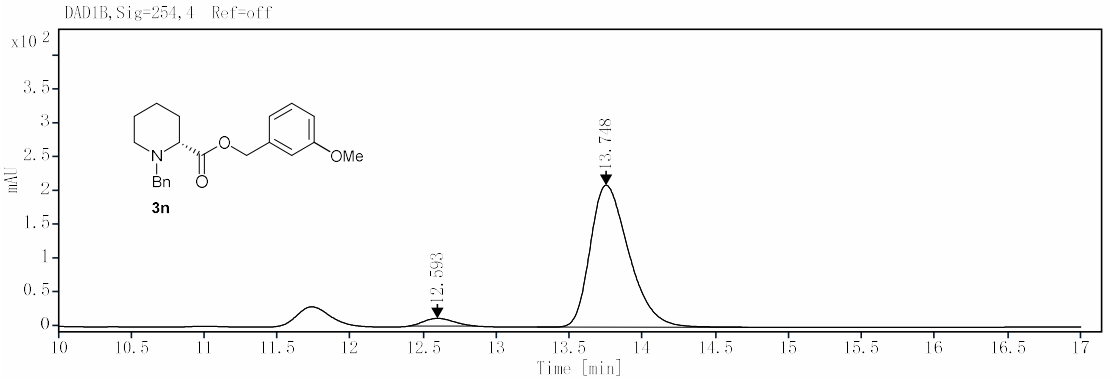
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.030	MM m	0.44	2940.59	100.62	49.67
18.098	MM m	0.50	2979.57	90.51	50.33



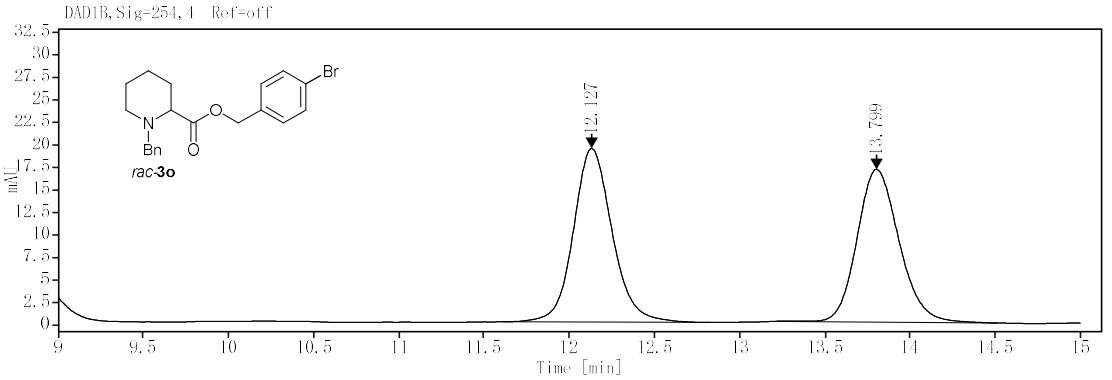
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
16.083	MM m	0.34	162.49	7.76	3.94
17.943	MM m	0.44	3961.75	136.21	96.06



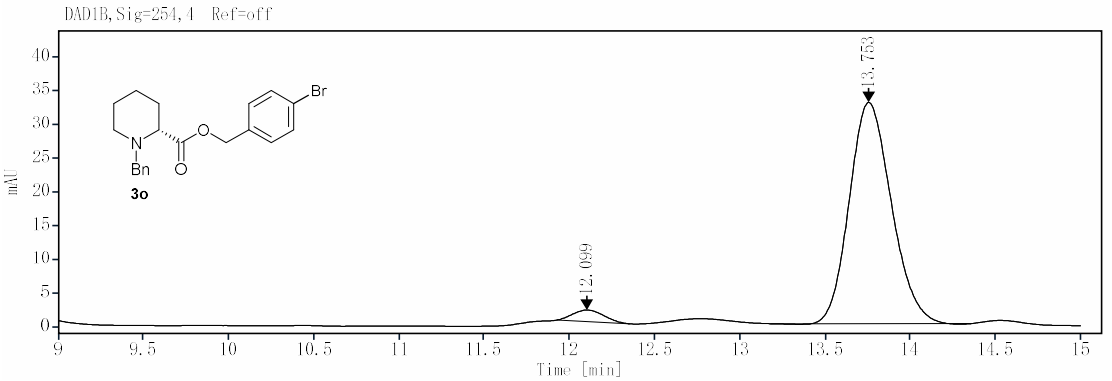
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.518	MM m	0.26	1058.62	62.67	49.74
13.685	MM m	0.28	1069.80	58.31	50.26



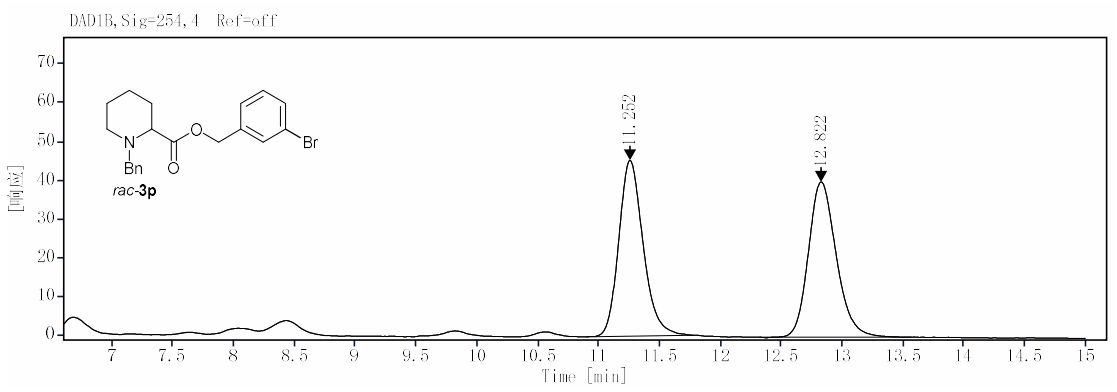
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.593	MM m	0.23	159.38	11.31	3.97
13.748	MM m	0.28	3856.64	209.94	96.03



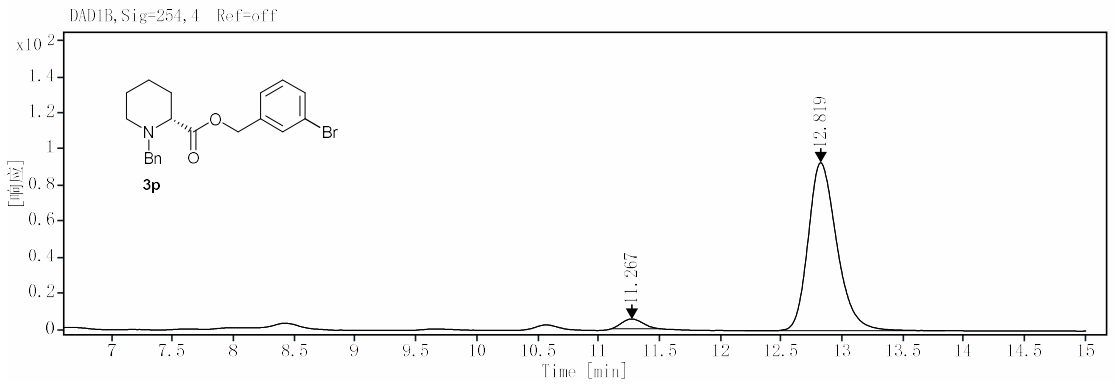
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.127	MM m	0.24	305.06	19.30	51.12
13.799	MM m	0.26	291.72	16.98	48.88



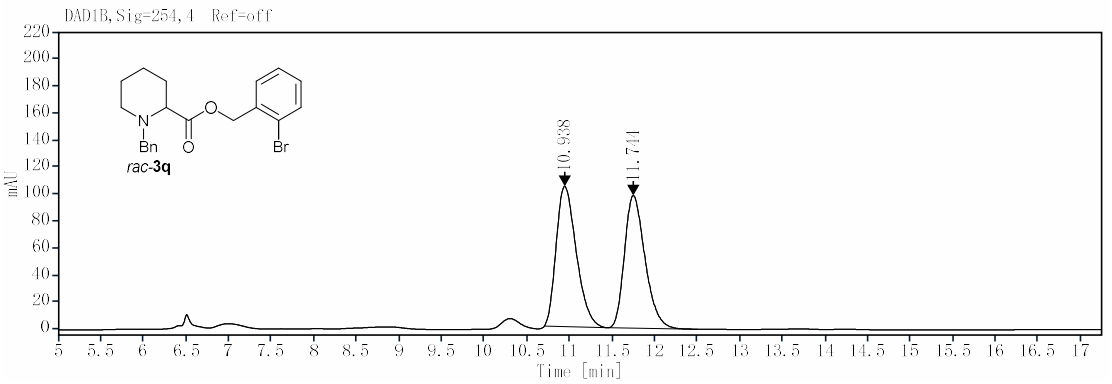
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.099	MM m	0.21	21.75	1.71	3.73
13.753	MM m	0.27	561.53	32.76	96.27



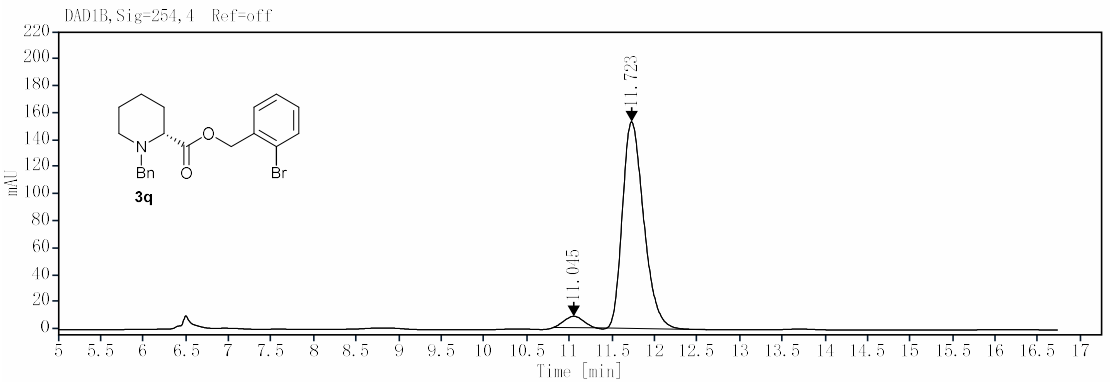
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
11.252	MM m	0.22	632.82	45.29	49.97
12.822	MM m	0.24	633.63	39.99	50.03



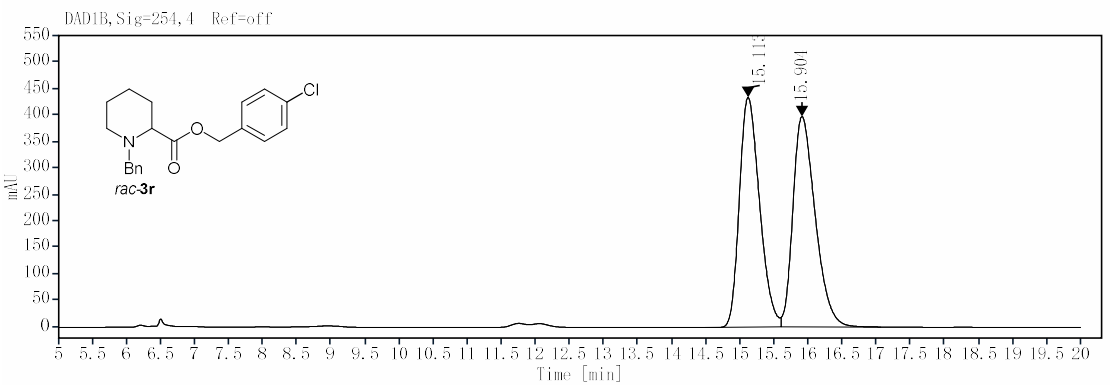
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
11.267	MM m	0.19	65.24	5.38	4.11
12.819	MM m	0.25	1520.59	92.96	95.89



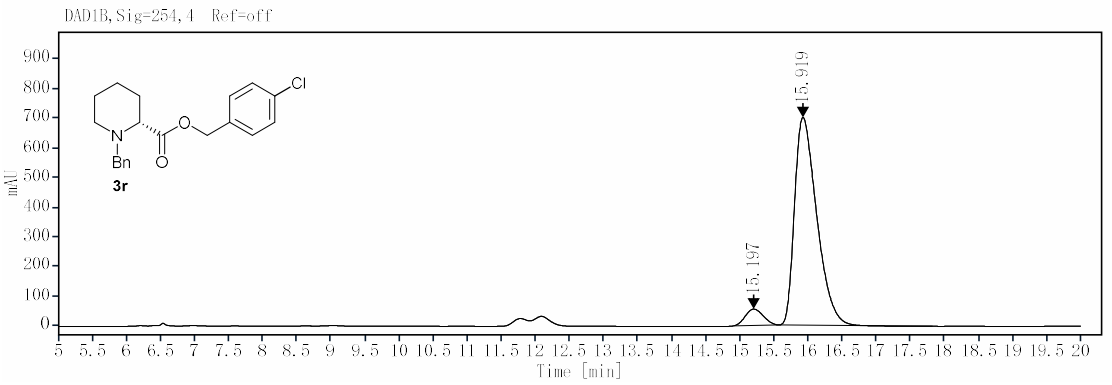
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.938	MM m	0.25	1706.39	103.97	50.83
11.744	MM m	0.26	1650.62	98.25	49.17



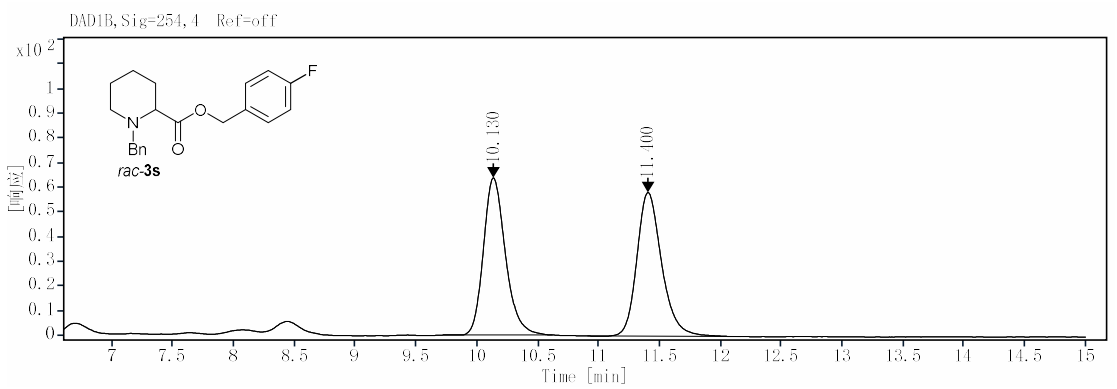
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
11.045	MM m	0.26	132.91	8.42	4.76
11.723	MM m	0.27	2660.07	153.11	95.24



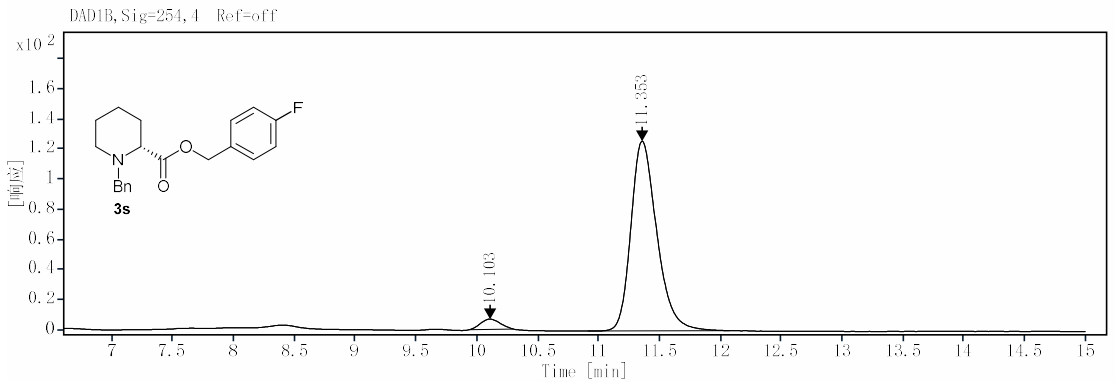
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
15.113	MM m	0.32	8925.84	433.81	49.69
15.904	MM m	0.35	9036.70	397.26	50.31



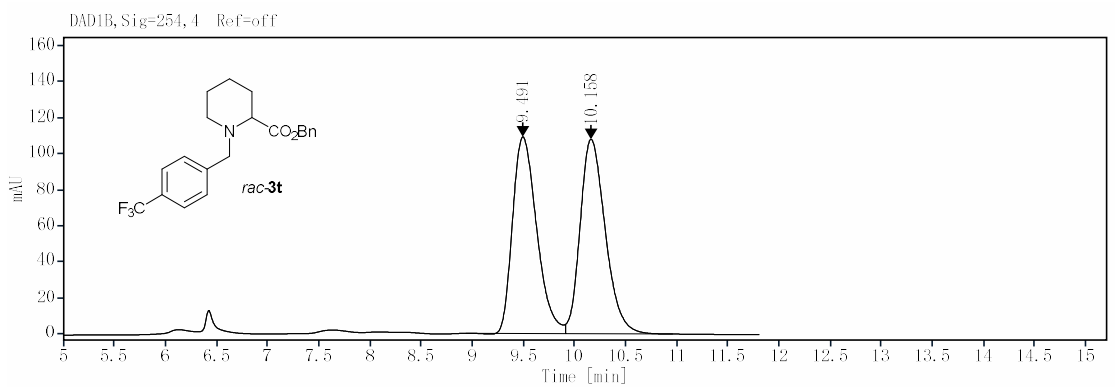
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
15.197	MM m	0.29	1005.41	55.23	5.96
15.919	MM m	0.35	9036.70	700.34	94.04



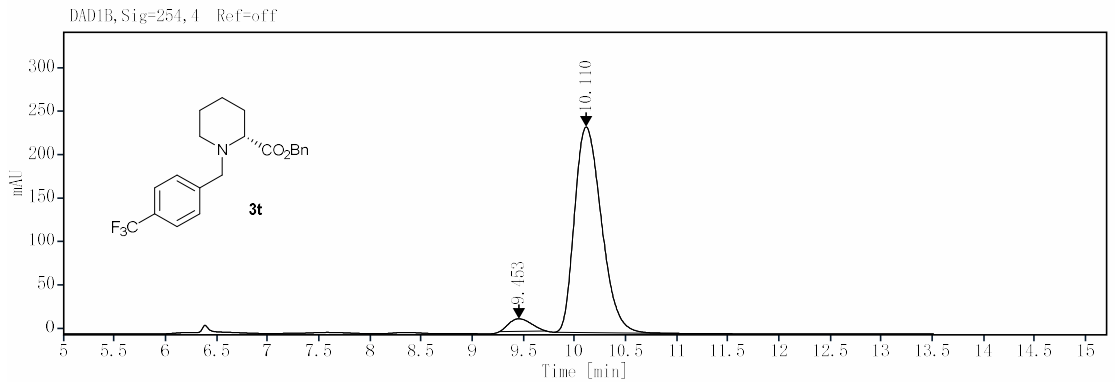
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.130	MM m	0.19	803.56	63.79	49.34
11.400	MM m	0.22	825.02	58.31	50.66



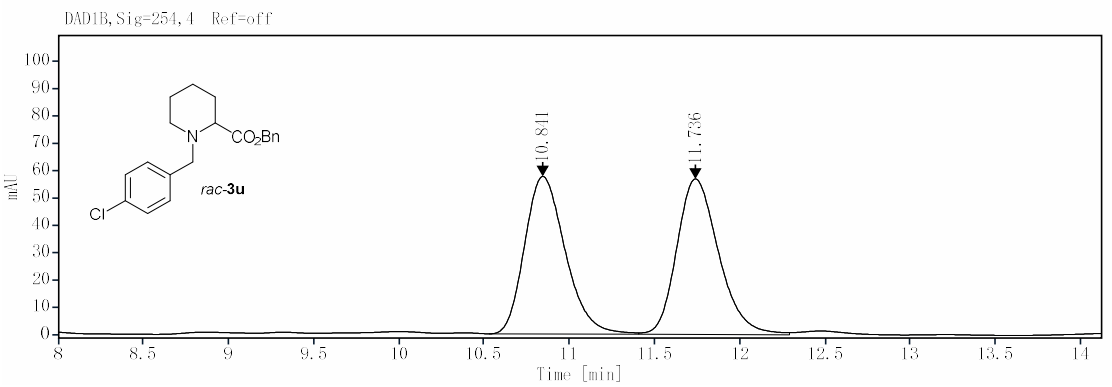
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.103	MM m	0.18	74.85	6.78	3.84
11.353	MM m	0.23	1873.68	126.19	96.16



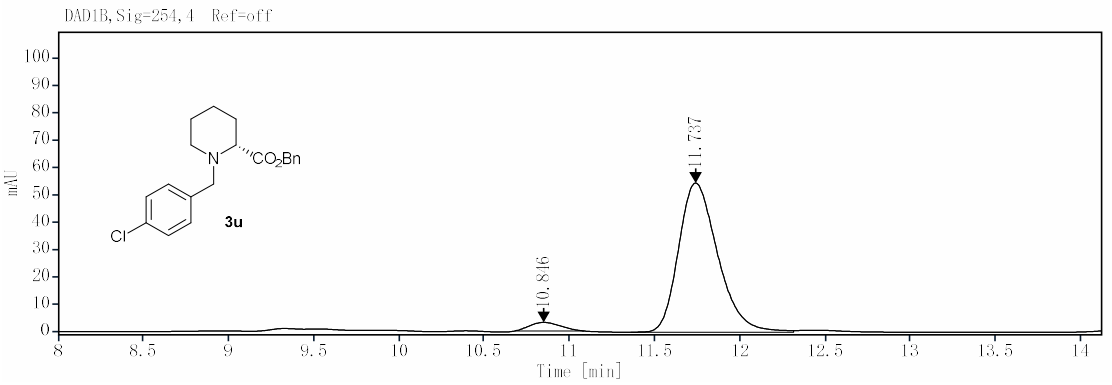
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
9.491	MM m	0.26	1795.86	109.18	49.27
10.158	MM m	0.27	1849.41	108.03	50.73



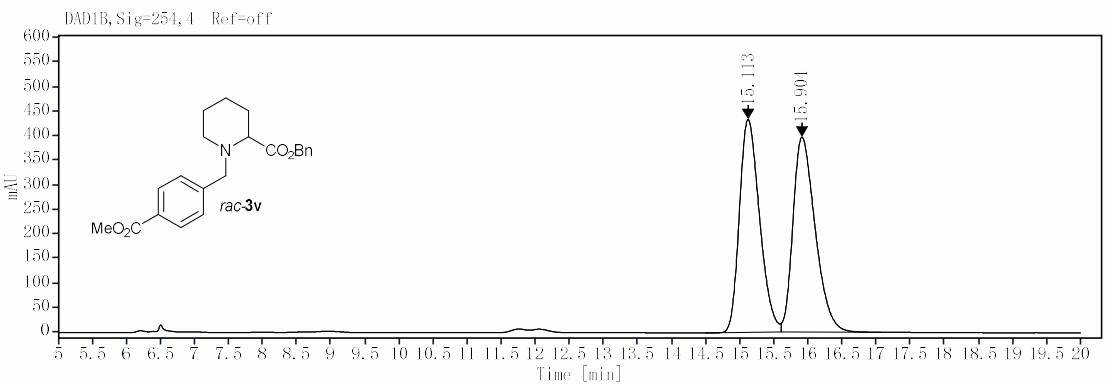
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
9.453	MM m	0.25	221.98	14.52	4.89
10.110	MM m	0.29	4316.69	236.03	95.11



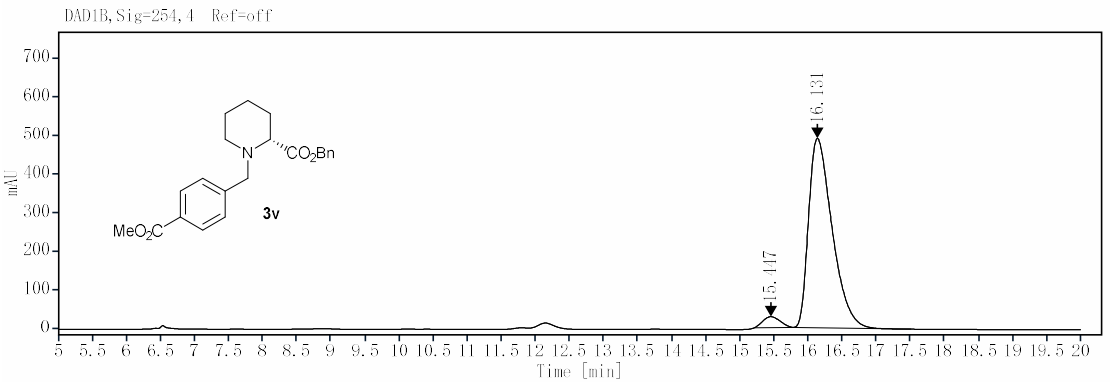
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.841	MM m	0.88	959.49	57.76	49.64
11.736	MM m	0.88	973.57	57.01	50.36



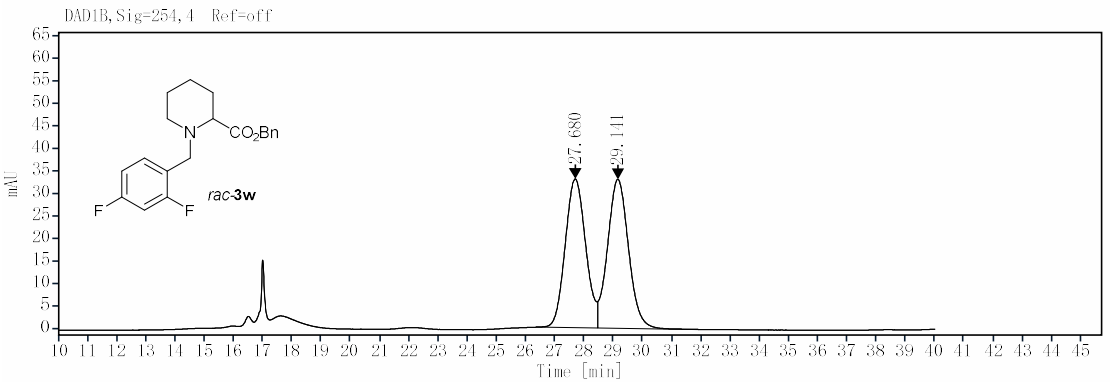
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.846	MM m	0.20	39.31	3.12	4.30
11.737	MM m	0.96	874.92	54.71	95.70



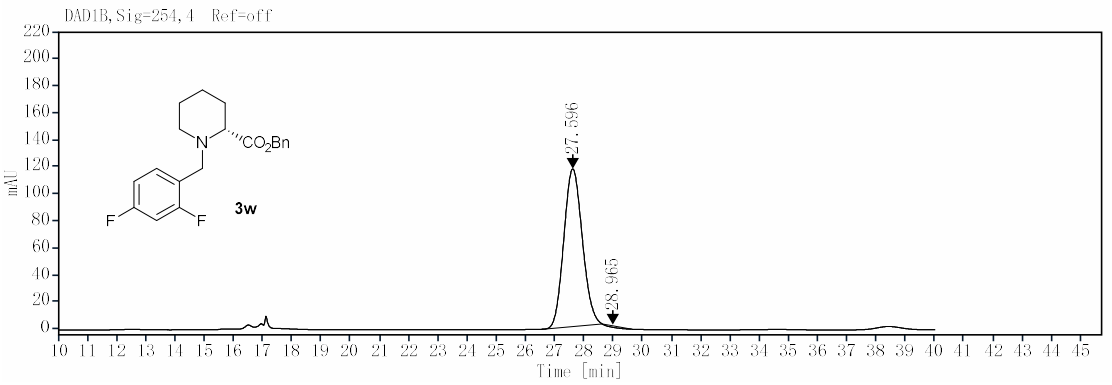
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
15.447	MM m	0.28	491.91	28.19	4.00
16.131	MM m	0.37	11797.57	491.05	96.00



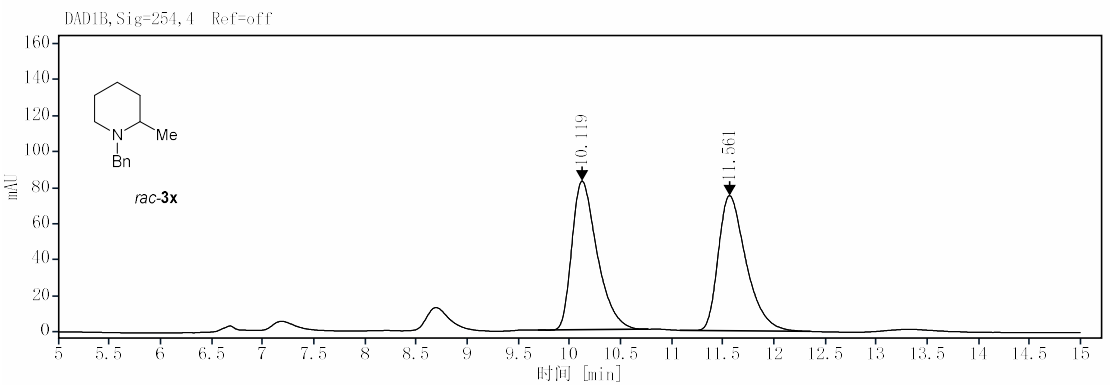
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
15.447	MM m	0.28	491.91	28.19	4.00
16.131	MM m	0.37	11797.57	491.05	96.00



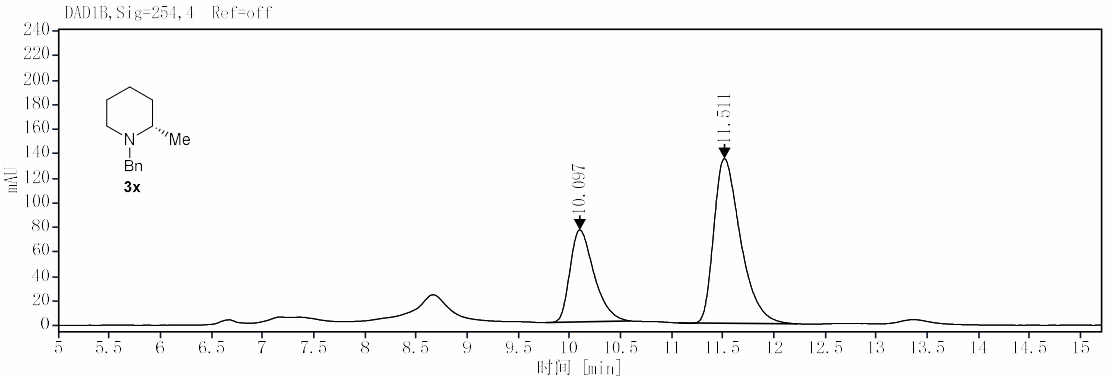
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
27.680	MM m	0.76	1612.43	33.07	49.40
29.141	MM m	0.77	1651.90	33.11	50.60



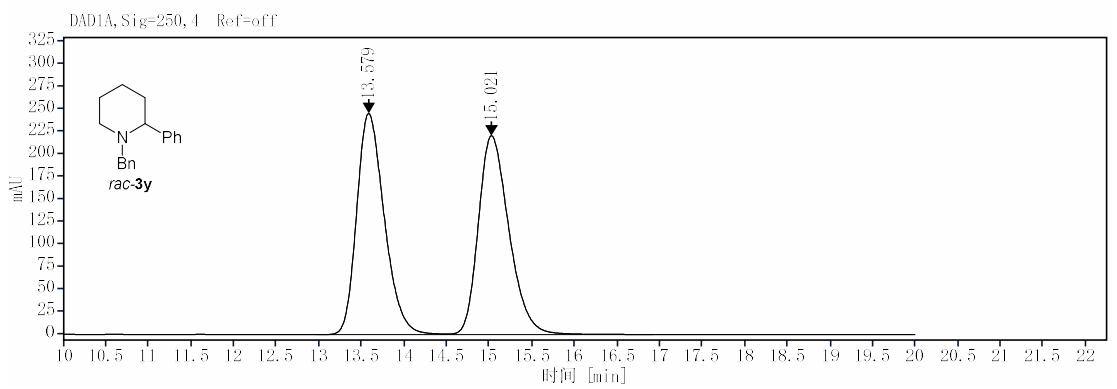
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
27.596	MM m	0.69	5145.46	1116.83	99.20
28.965	MM m	066	41.24	1.05	0.80



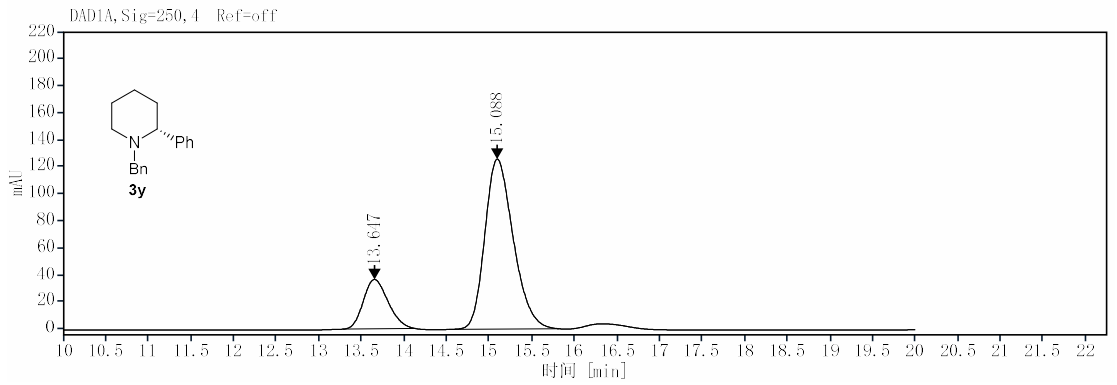
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.119	MM m	0.26	1419.16	82.64	49.91
11.561	MM m	0.29	1424.55	75.11	50.09



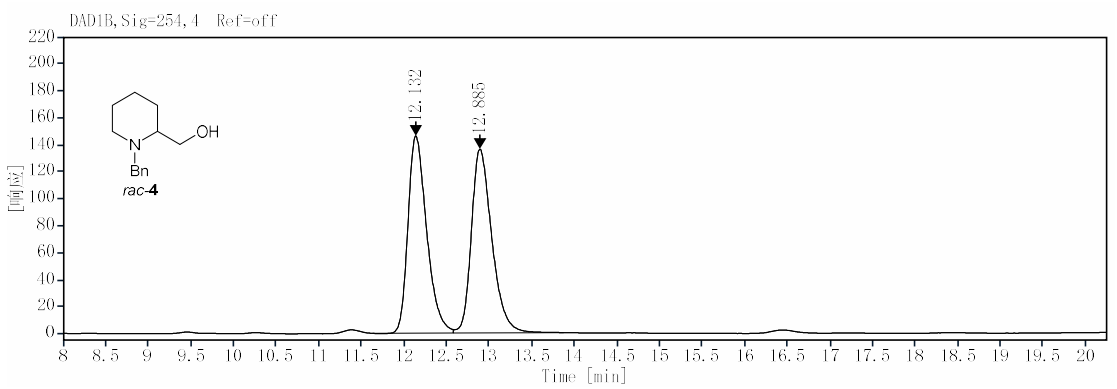
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.097	MM m	0.25	1224.26	74.95	33.43
11.511	MM m	0.28	2437.88	134.22	66.57



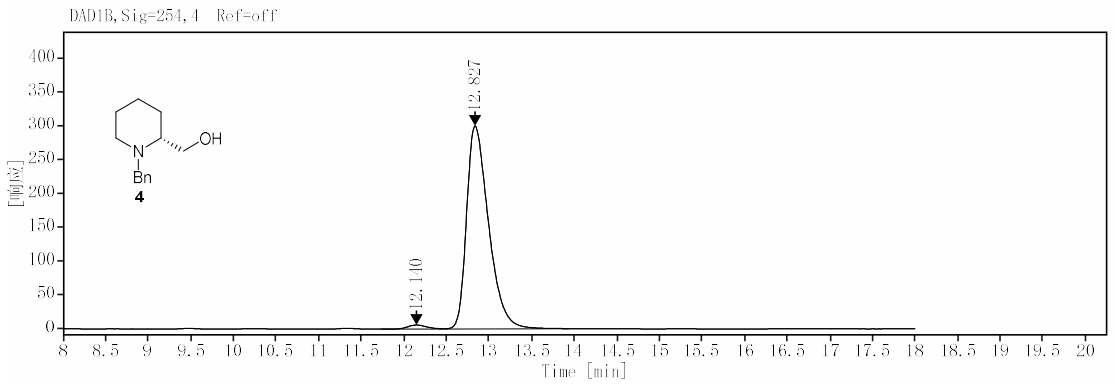
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
13.579	BV	1.53	5546.16	245.68	50.11
15.021	VB	2.41	5521.33	220.96	49.89



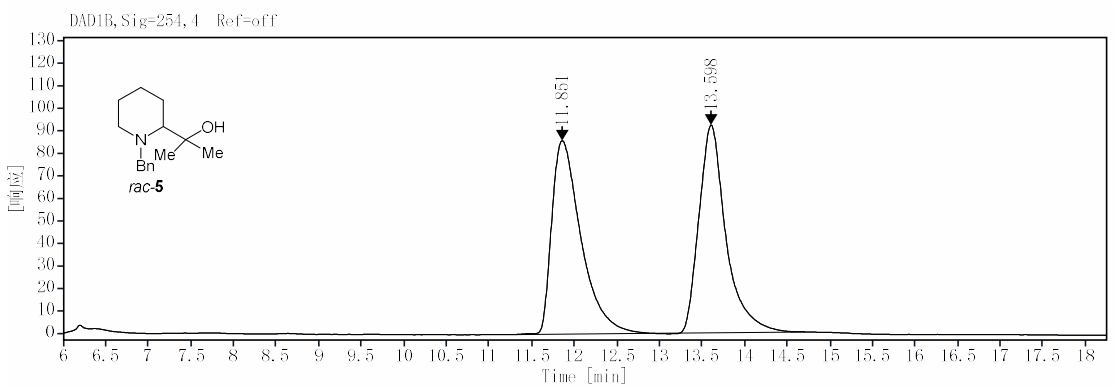
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
13.647	MM m	0.31	743.22	36.65	20.25
15.088	MM m	0.36	2926.78	125.99	79.75



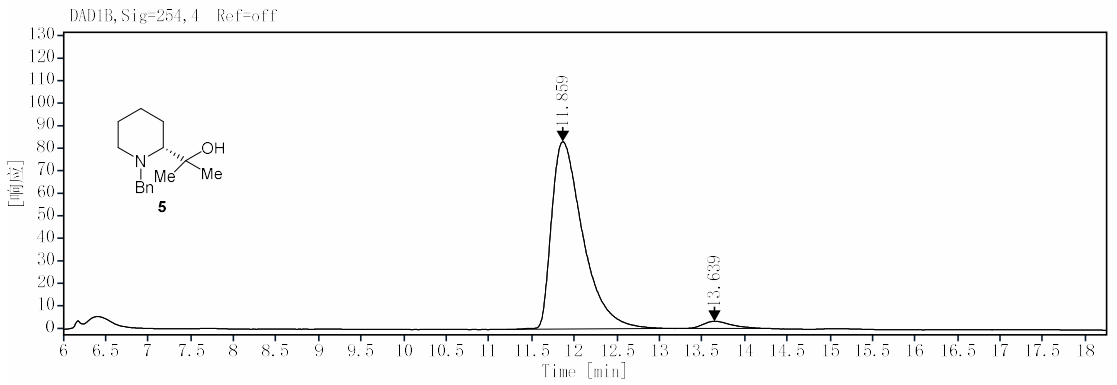
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.132	MM m	0.23	2230.01	146.11	49.51
12.885	MM m	0.25	2274.07	136.15	50.49



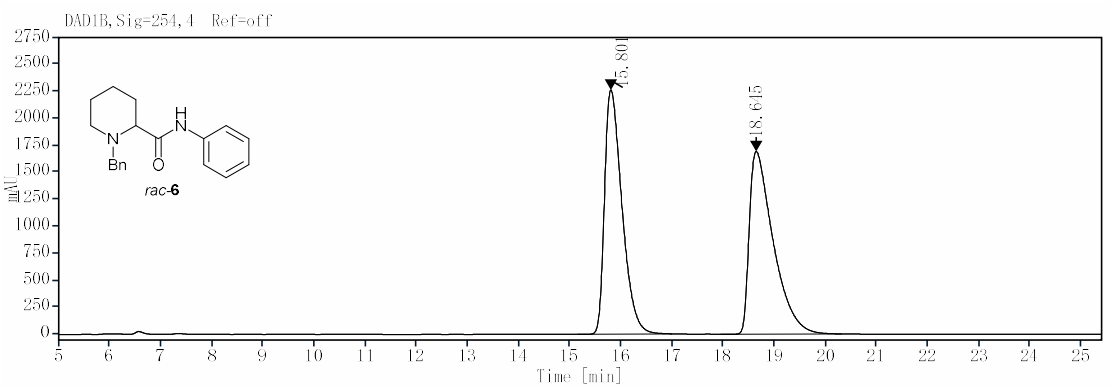
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.140	MM m	0.24	91.36	5.94	1.66
12.827	MM m	0.27	5398.82	300.73	98.34



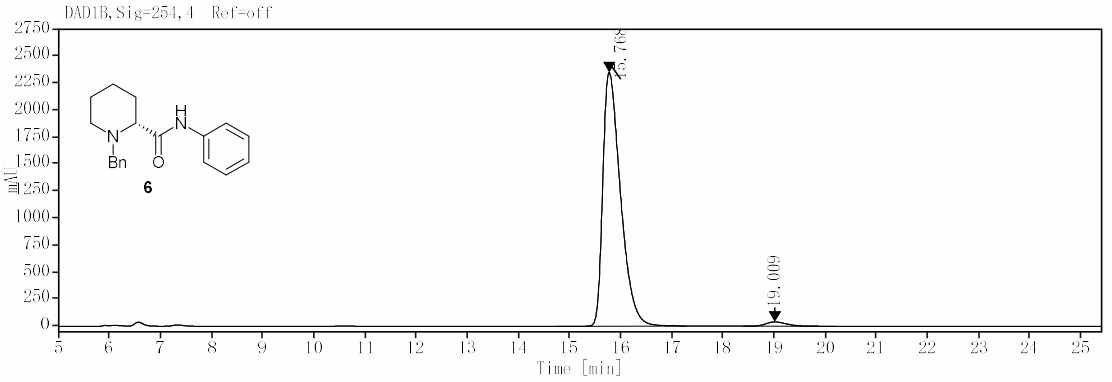
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
11.851	MM m	0.36	2046.07	85.97	50.21
13.598	MM m	0.34	2028.71	92.33	49.79



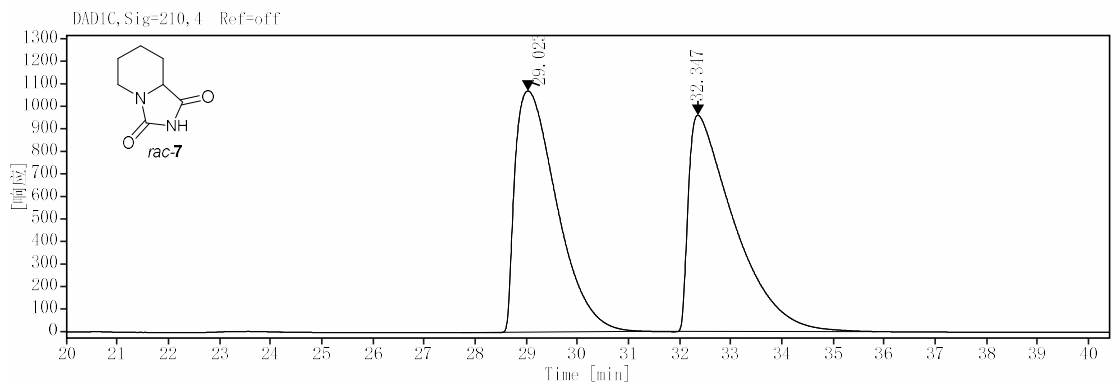
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
11.859	MM m	0.39	2122.89	83.25	96.71
13.639	MM m	0.28	72.21	3.18	3.29



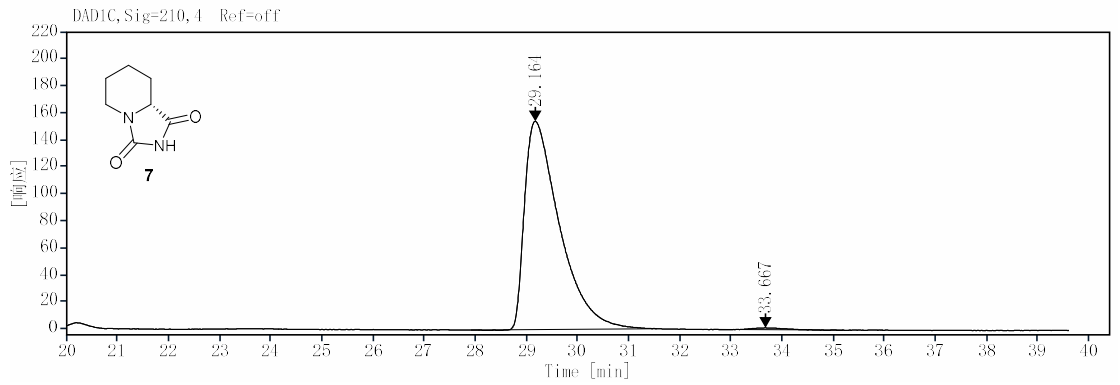
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
15.801	MM m	0.36	53746.55	2260.99	49.45
18.645	MM m	0.48	54944.28	1691.45	50.55



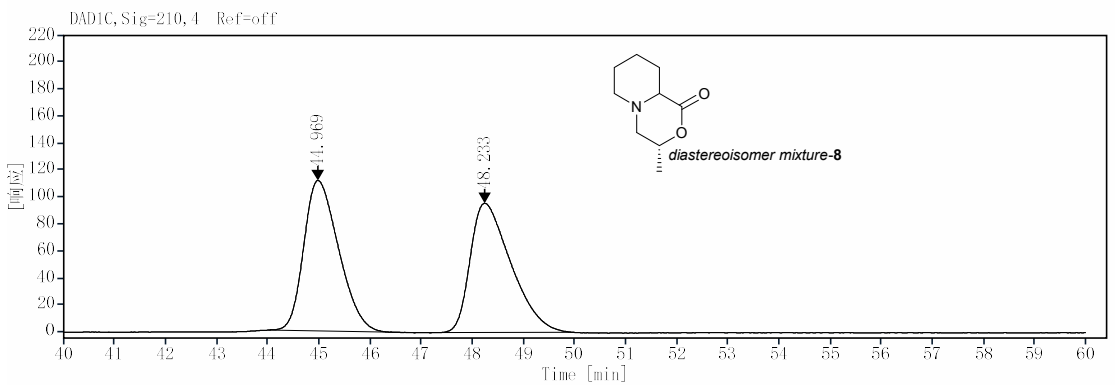
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
15.768	MM m	0.37	56494.79	2348.72	98.07
19.009	MM m	0.43	1114.60	39.84	1.93



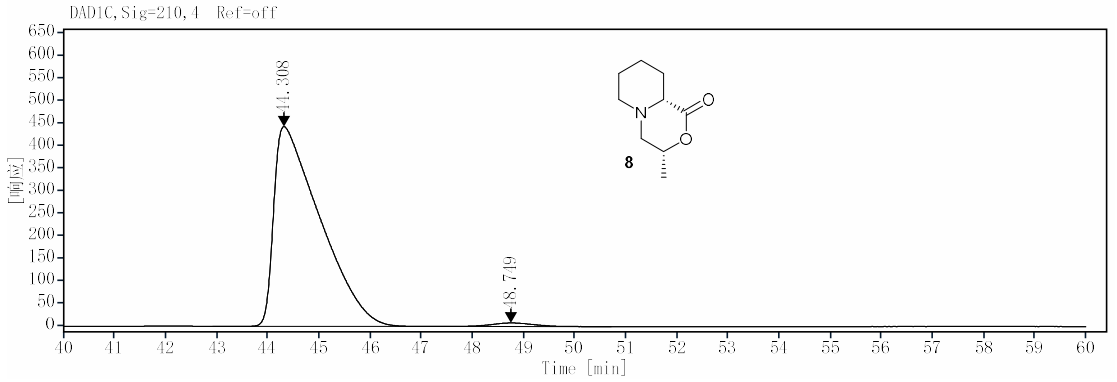
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
29.023	MM m	0.85	60720.56	1071.12	50.48
32.347	MM m	0.85	59562.98	959.52	49.52



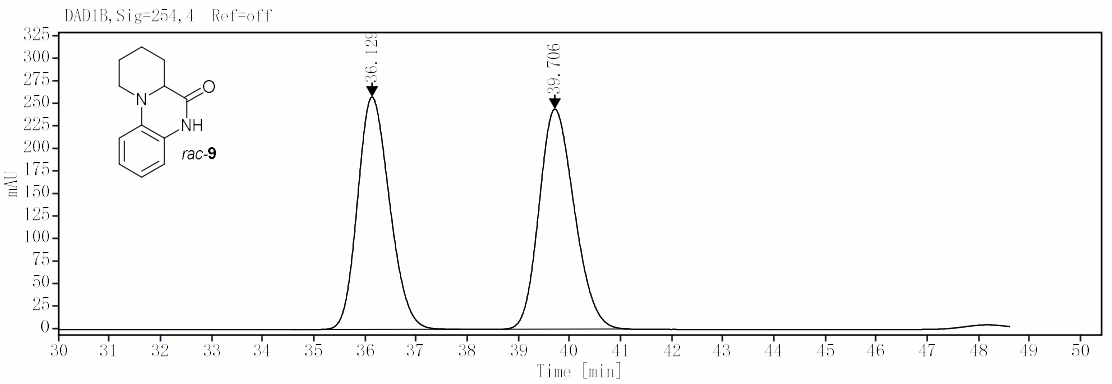
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
29.164	MM m	0.70	7338.03	154.32	99.19
33.667	MM m	0.51	60.02	1.40	0.81



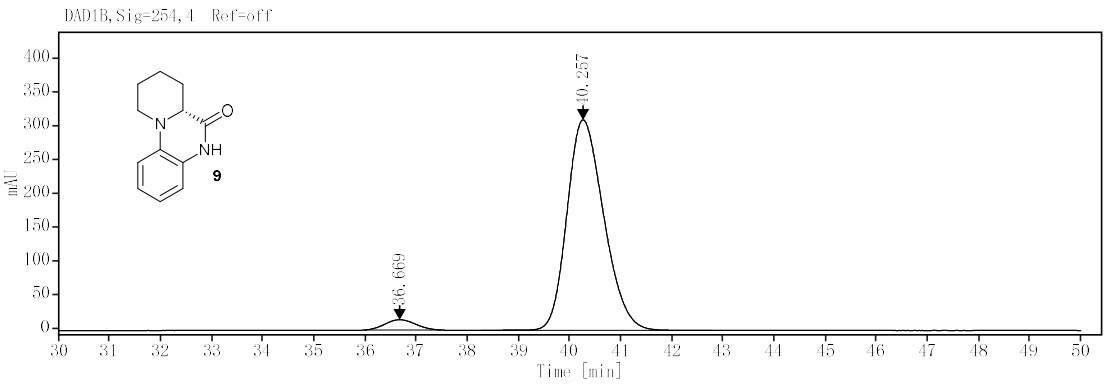
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
44.969	MM m	0.70	5290.55	111.46	49.92
48.233	MM m	0.79	5308.45	95.72	50.08



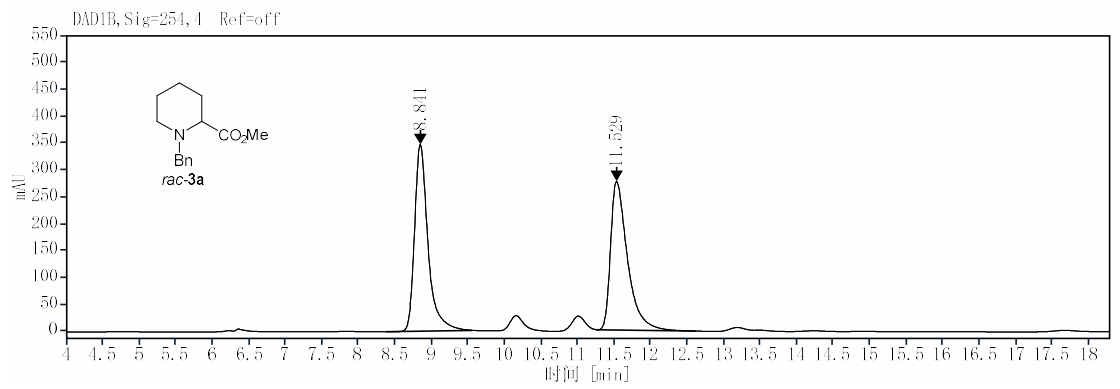
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
44.308	MM m	0.85	27939.52	444.11	98.43
48.749	MM m	0.66	445.47	7.99	1.57



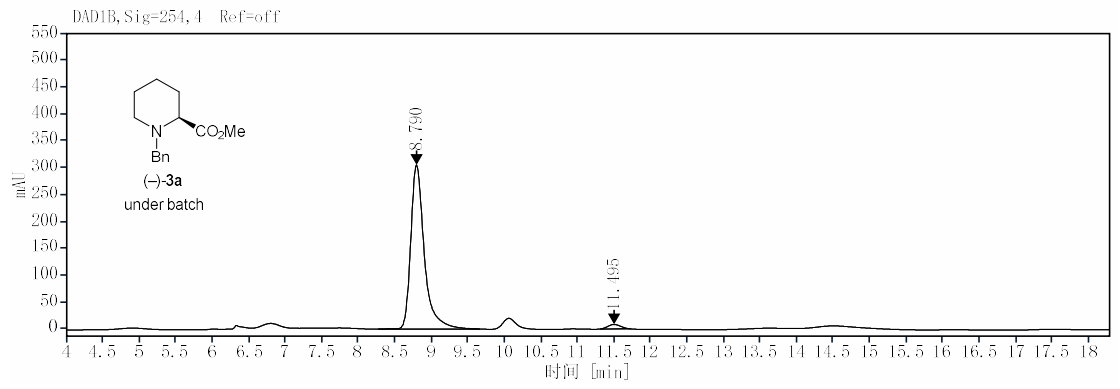
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
36.129	MM m	0.68	11247.51	258.17	48.97
39.706	MM m	0.75	11719.47	244.45	51.03



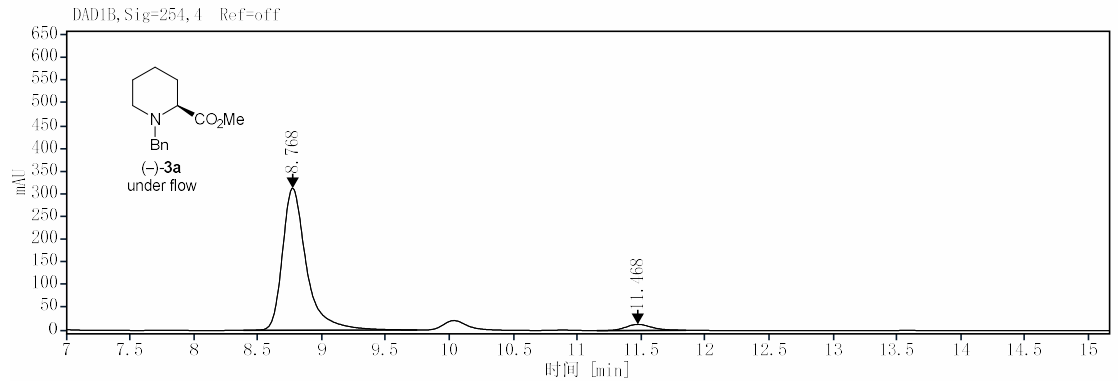
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
36.669	MM m	0.64	636.13	15.34	3.92
40.257	MM m	0.78	15601.95	311.78	96.08



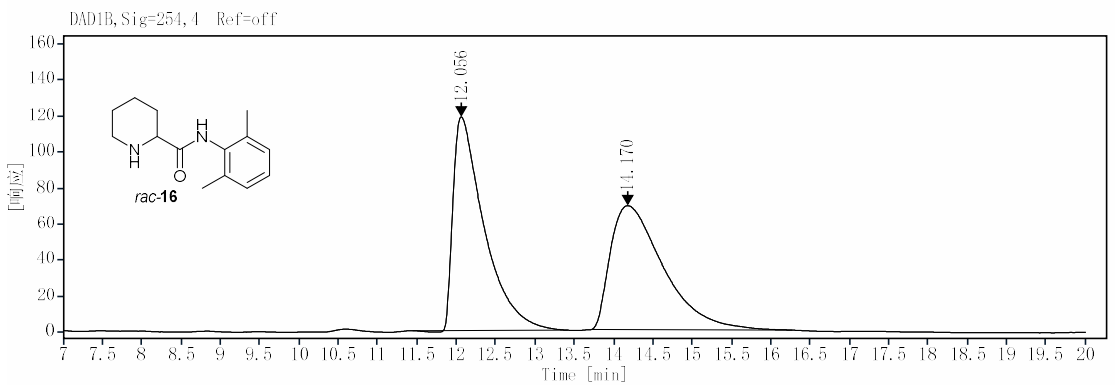
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.841	MM m	0.19	4432.49	347.17	49.94
11.529	MM m	0.24	4443.38	276.29	50.06



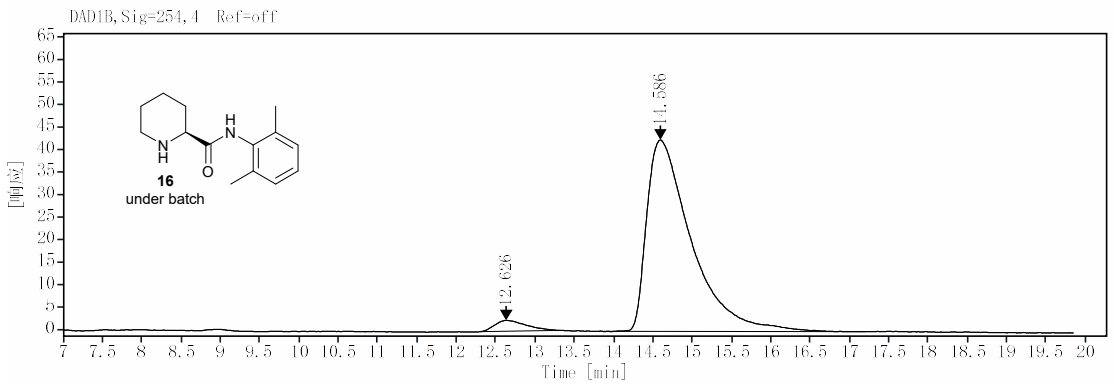
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.790	MM m	0.19	3939.38	305.18	97.47
11.495	MM m	0.19	102.37	8.37	2.53



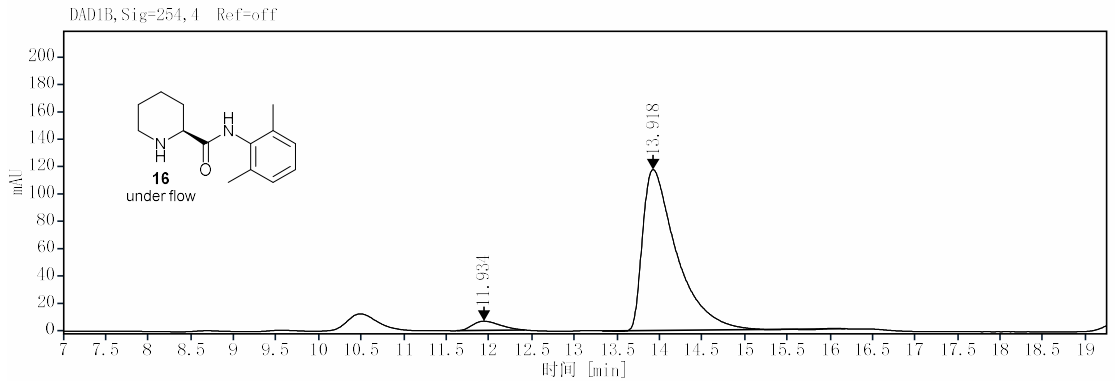
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
8.768	MM m	0.20	4073.16	312.77	95.56
11.468	MM m	0.22	189.35	13.41	4.44



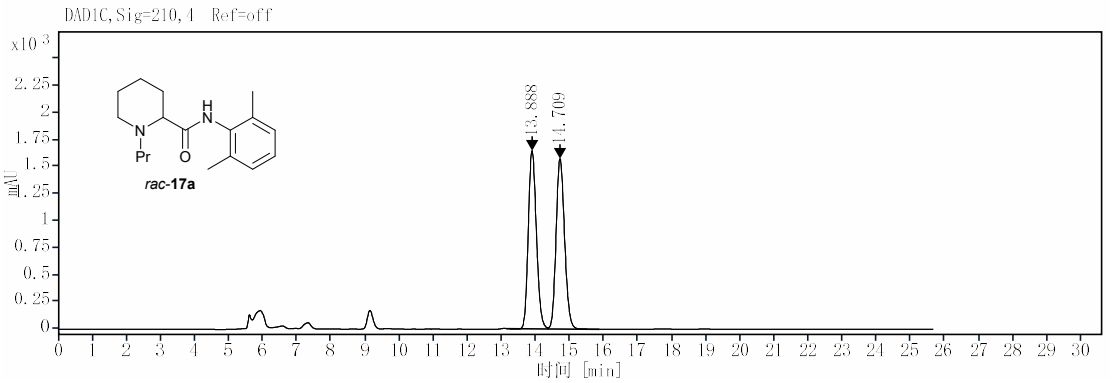
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.056	MM m	0.40	3249.94	118.71	50.11
14.170	MM m	0.70	3235.15	68.85	49.89



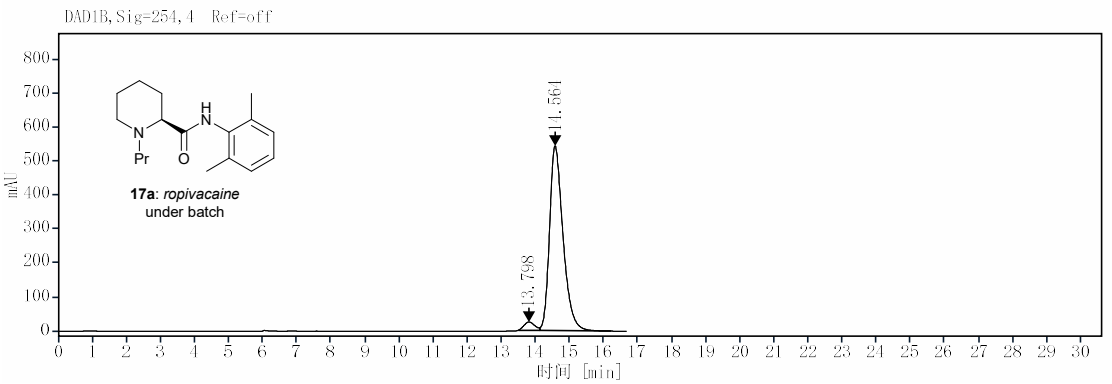
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
12.626	MM m	0.34	66.52	2.42	3.82
14.586	MM m	0.56	1674.33	42.54	96.18



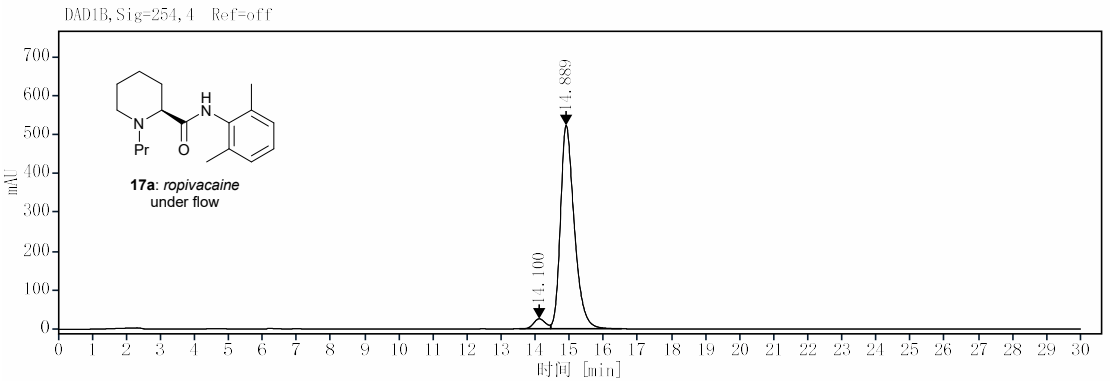
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
11.934	MM m	0.34	153.33	6.80	4.48
13.918	MM m	0.41	3272.86	117.97	95.52



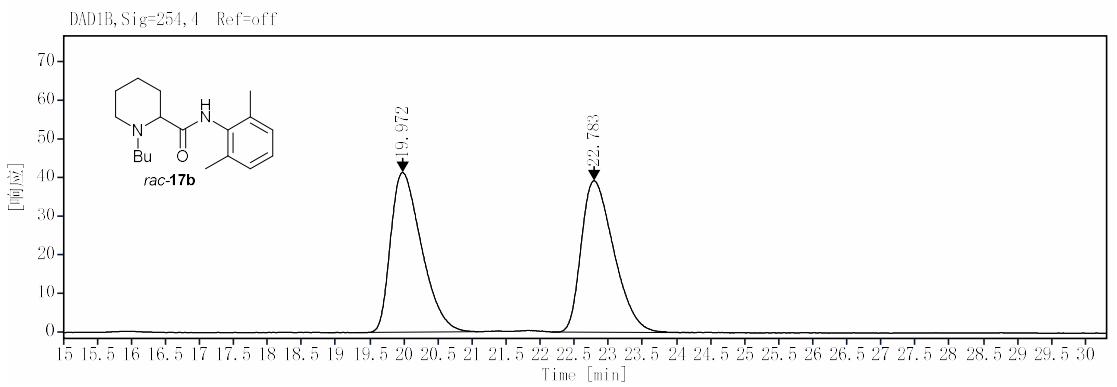
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
13.888	MM m	0.26	27128.86	1647.57	49.78
14.709	MM m	0.27	27374.08	1575.79	50.22



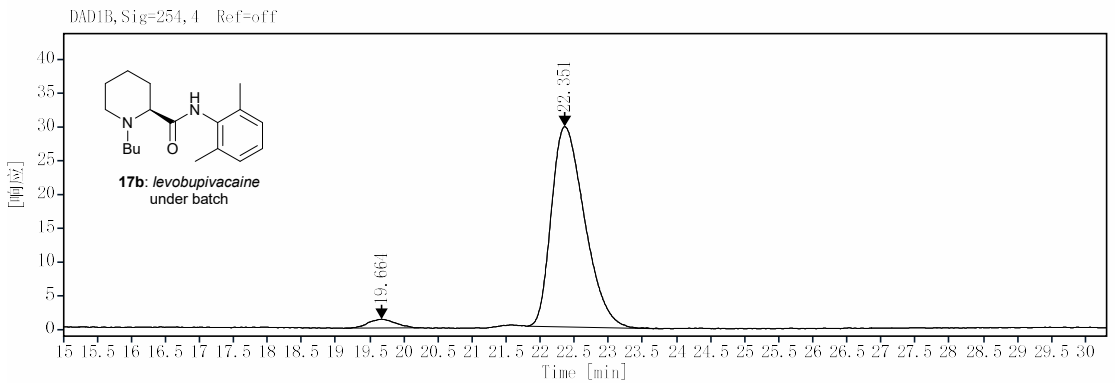
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
13.798	MM m	0.34	544.43	24.70	3.50
14.564	MM m	0.42	15025.39	545.62	96.50



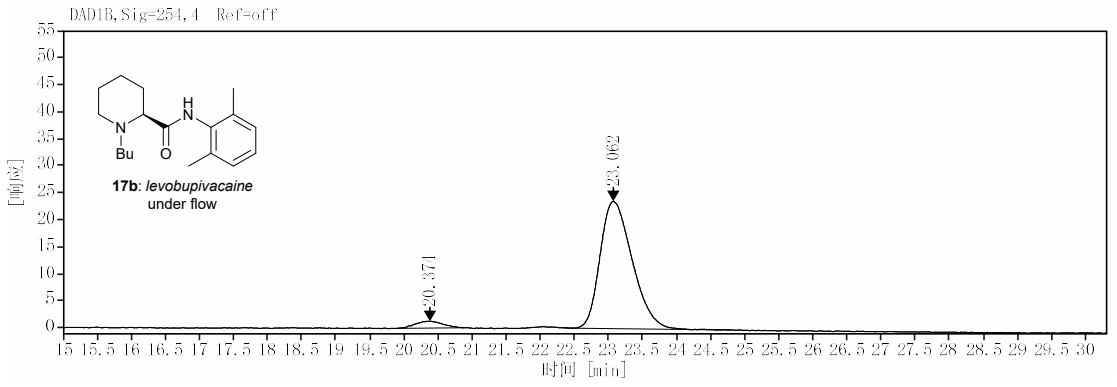
Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
14.100	MM m	0.37	623.63	25.80	4.03
14.889	MM m	0.43	14838.67	525.72	95.97



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
19.972	MM m	0.48	1303.95	41.42	50.01
22.783	MM m	0.50	1303.39	39.27	49.99



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
19.664	MM m	0.33	35.27	1.28	3.38
22.351	MM m	0.51	1007.21	29.67	96.62



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
20.374	MM m	0.34	35.03	1.24	4.35
23.062	MM m	0.45	770.97	23.55	95.65

6. Crystallographic Data

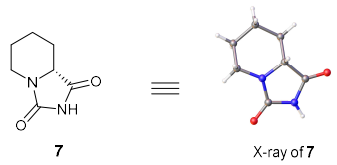


Figure 1. ORTEP of the molecular structure of **7.**

Diffraction-quality crystal of compound **7** was obtained in ethyl acetate and petroleum ether.

CCDC 2221385 contains the supplementary crystallographic data for compound **7**.

Empirical formula	$C_7H_{10}N_2O_2$
Formula weight	154.17
Temperature/K	302.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.3586(2)
b/Å	6.1328(3)
c/Å	11.1471(5)
α/°	90
β/°	98.5290(10)
γ/°	90
Volume/Å^3	362.28(3)
Z	2
ρ_{calc}g/cm^3	1.413
μ/mm^{-1}	0.878
F(000)	164.0
Crystal size/mm^3	0.5 × 0.26 × 0.22
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	17.458 to 136.312
Index ranges	$-6 \le h \le 6$, $-7 \le k \le 7$, $-13 \le l \le 13$
Reflections collected	5724
Independent reflections	1310 [R_{int} = 0.0405, R_{sigma} = 0.0332]
Data/restraints/parameters	1310/1/100
Goodness-of-fit on F^2	1.099
Final R indexes [I>=2σ (I)]	R_1 = 0.0317, wR_2 = 0.0831
Final R indexes [all data]	R_1 = 0.0318, wR_2 = 0.0832
Largest diff. peak/hole / e Å^{-3}	0.17/-0.16
Flack parameter	-0.04(7)