Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Photoredox-Catalysed Regioselective Synthesis of C-4-Alkylated Pyridines with *N* -(Acyloxy)phthalimides

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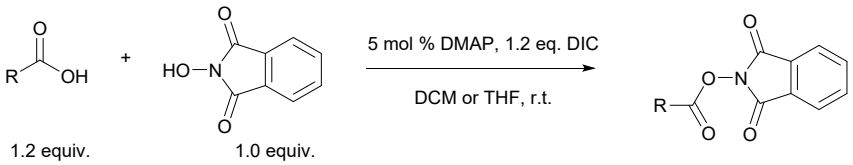
1. General information

Unless otherwise noted, all solvents and other reagents were commercially available and used without further purification. All reagents were weighed and handled under air at room temperature. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was purchased from Bidepharm. The all commercial reagents were purchased from TCI, Sigma-Aldrich, Adamas-beta chemistry and Energy Chemical of the highest purity grade. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. The LED blue light, Kessil (PR160-440nm) was purchased from Kessil, NMR spectra were recorded on a Varian-MERCURY Plus-400 NMR spectrometer, a Brucker AVANCE III 500 NMR spectrometer, or a Brucker AVANCE III 600 NMR spectrometer and mass spectra (HRMS) were recorded on Micromass Ultra Q-TOF (ESI). The peaks were internally referenced to TMS (0.00 ppm) or residual undeuterated solvent signal. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Pyridinium salts and NHPI esters were prepared according to the previous literatures.

1.1 General procedure for the synthesis of NHPI esters

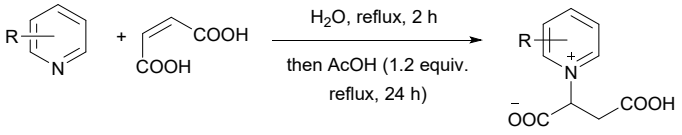


According to the reported literature[1], the redox active esters can be synthesized by condensation of corresponding carboxylic acids with *N*-hydroxyphthalimide. The corresponding alkyl carboxylic acid (12 mmol, 1.2 equiv.), *N*-hydroxyphthalimide (1.63 g, 10 mmol, 1.0 equiv.), and 4-dimethylaminopyridine (DMAP) (61mg, 0.5 mmol, 5 mol %) were mixed in a flask with a magnetic stirring bar. THF or DCM (40 mL) (according to the solubility of the carboxylic acids) was added. Then (Diisopropylcarbodiimide) DIC (1.51 g, 12 mmol, 1.2 equiv.) was added slowly at room temperature. The reaction mixture was stirred at room temperature for 6 h. After *N*-hydroxyphthalimide was completely converted, the white precipitate was filtered off and the solution was concentrated under vacuum. Corresponding redox active esters were purified by column chromatography on silica gel (DCM/MeOH or PE/EA as eluent) or further recrystallization with (PE /EA).

All the redox active esters are reported and their spectral data are consistent with the literature data. [2-14]

1.2 General procedure for the synthesis of pyridinium salts

General procedure A



According to the reported literature[15] , a solution of maleic acid (1.16 g, 10 mmol) and substituted pyridine (1 equiv., 10 mmol) in H_2O (5 mL) was stirred at 90 °C for 2 h. After a crystalline solid appeared in reaction mixture, acetic acid (686 µL, 1.2 equiv. 12 mmol) was added. The solution was kept in suspension with stirring at the same temperature for 24 h. The crude reaction mixture was cooled down to room temperature, filtered, washed with small amount of MeOH and EtOAc. The resulting white solid was dried under reduced pressure by rotary evaporator and high vacuum for overnight. The product was obtained and used for next step without further purification.

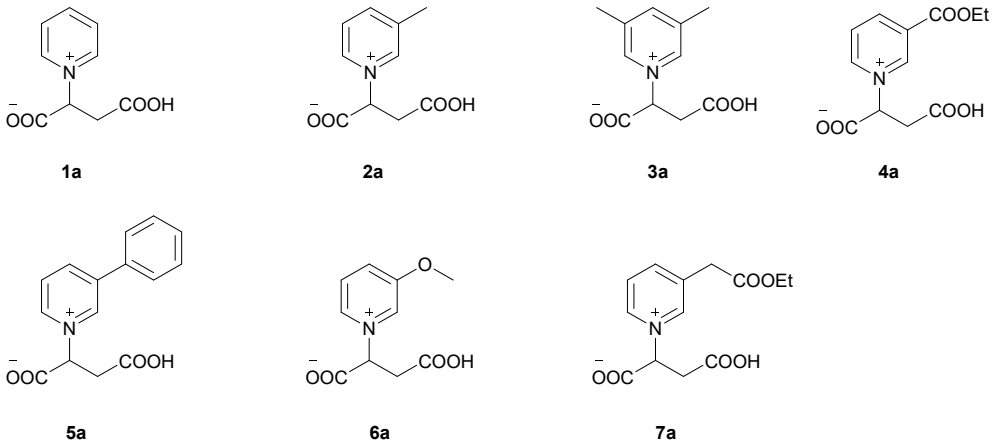


Figure S1. Synthesized pyridinium salts followed by general procedure A

General Procedure B

According to the reported literature[15], a solution of pyridinium carboxylate salt (2.5 mmol, 1 equiv.) in EtOH (12.5 mL, 0.2 M) with concentrated sulfuric acid (2 equiv., 5 mmol, 260 µL) was stirred at 90 °C for 18 h. Upon completion, the solvent (EtOH) was evaporated under reduced pressure. The concentrated crude mixture was diluted in dichloromethane (15 mL) and H_2O (2 mL) and extracted by dichloromethane monitoring by TLC both aqueous and organic phase until no desired product in the aqueous phase was observed. The combined organic phase was dried by Na_2SO_4, filtered, concentrated under reduced pressure. The resulting colorless liquid was used for next step without further purification.

All the pyridinium salts are reported and their spectral data are consistent with the literature data[15].

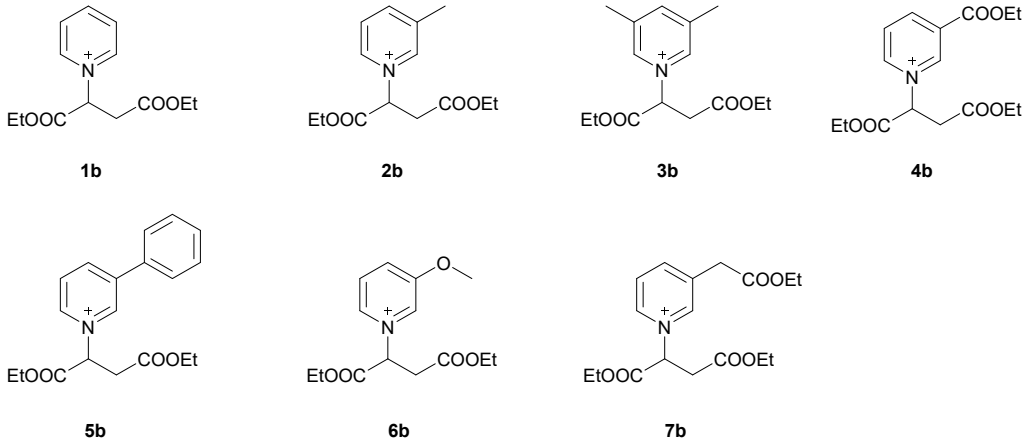
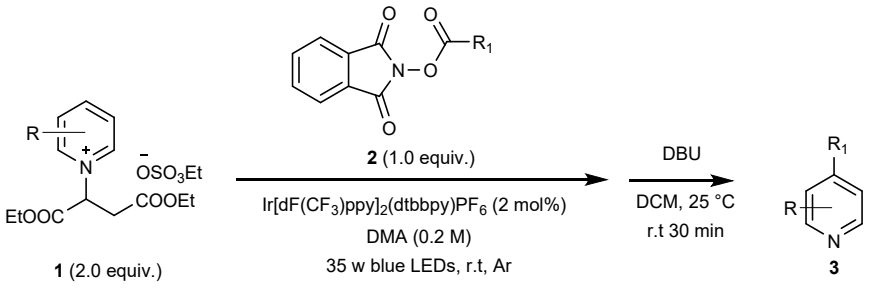


Figure S2. Synthesized pyridinium salts according to the general procedure B, Counter-anion = ethyl sulfate ($EtOSO3^-$).

1.3 General procedure for the photoredox-catalysed C-4 alkylation and deprotection reactions.



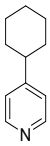
Pyridinium salts (2.0 equiv., 0.8 mmol), redox active ester (1.0 equiv., 0.4 mmol), $Ir[dF(CF_3)ppy]_{2(}dtbbpy)PF_6$ (2.0 mol %, 8.8 mg), DMA (2 mL) were placed in a screwed vial equipped with a stirring bar. The vial was evacuated and backfilled with Ar for three times. The mixture was then irradiated by 36 W blue LEDs for 10 h. After 10 h, reaction mixture was diluted with DCM (3 mL) and the aqueous phase was extracted with DCM (3 x 3 mL) and the combined organic layers was added DBU (6.0 equiv., 358 µL), after stirred at room temperature for 30 min, the reaction mixture was transferred to a separatory funnel and washed with 1 *N* NaOH for 3 times [Note: In case of base sensitive substrate, aq. NaOH could be changed by 1 *N* Na_2CO_3]. The organic phase was washed with brine for 3 times. The resulting organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude material was purified by silica gel chromatography to yield the desired product. (DCM/MeOH or PE/EA as eluent).

1.4 General procedure for gram-scale

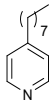
Pyridinium salts (2.0 equiv., 8 mmol), redox active ester (1.0 equiv., 4 mmol), $Ir[dF(CF_3)ppy]_{2(}dtbbpy)PF_6$ (2.0 mol %, 88 mg), DMA (20 mL) were placed in a 50 mL two-necked flask equipped with a stirring bar. The flask was evacuated and backfilled with Ar for three times. The mixture was then irradiated by 36 W blue LEDs for 10 h. After 10 h, the reaction mixture was diluted with DCM (20 mL) and the aqueous phase was extracted with DCM (10 x 3 mL) and the combined organic layers was added DBU (6.0 equiv., 3580 µL) then stirred at room temperature for 30 min. The reaction mixture was transferred to a separatory funnel and washed with 1 *N* NaOH for 3 times. The organic phase was washed with brine for 3 times. And the resulting organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude material was purified by silica gel chromatography to yield the desired product. (PE/EA as eluent).

2. Characterization data of the products

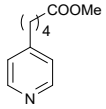
Spectral Data



4-cyclohexylpyridine (3a1) orange liquid, **78% (50 mg) ^{1}H NMR** (500 MHz, Chloroform-d) δ 8.46 (d, *J* = 6.0 Hz, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 2.51 – 2.42 (m, 1H), 1.89 – 1.79 (m, 4H), 1.78 – 1.71 (m, 1H), 1.43 – 1.32 (m, 4H), 1.28 – 1.20 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.69, 149.74, 122.45, 43.92, 33.61, 26.63, 26.04; **HRMS** (ESI) m/z: calcd for $C_{11}H_{16}N^+$ $(M+H)^+$ 162.1277, found 162.1275. Characterization data matched that reported in the literature[15].

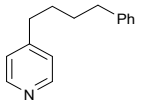


4-octylpyridine (3b) colourless oil, 71% (54 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.46 (d, *J* = 5.2 Hz, 2H), 7.09 (d, *J* = 5.8 Hz, 2H), 2.61 – 2.54 (t, *J* = 6.0 Hz, 2H), 1.60 (p, *J* = 7.2 Hz, 2H), 1.40 – 1.10 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.34, 149.05, 123.42, 34.74, 31.32, 28.85, 28.67, 22.13, 13.57; **HRMS** (ESI) m/z: calcd for $C_{13}H_{22}N^+$ $(M+H)^+$ 192.1747, found 192.1742. Characterization data matched that reported in the literature[16].

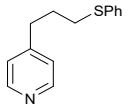


Methyl 5-(pyridin-4-yl)pentanoate (3c) colourless oil, 63% (49 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.48 (d, *J* = 5.9 Hz, 2H), 7.11 (d, *J* = 5.9 Hz, 2H), 3.65 (s, 3H), 2.73 – 2.51 (m, 2H), 2.40 – 2.20 (m, 2H), 1.82 – 1.54 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.91, 151.40, 149.73, 124.07, 51.68, 35.00, 33.85, 29.74,

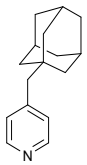
24.54; **HRMS** (ESI) m/z: calcd for $C_{11}H_{16}NO_2^+$ $(M+H)^+$ 194.1176, found 194.1173. Characterization data matched that reported in the literature[15].



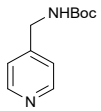
4-(4-phenylbutyl)pyridine (3d) colourless oil, 83% (70 mg) ^{1}H NMR (600 MHz, Chloroform-d) δ 8.50 (d, *J* = 5.9 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.20 – 7.14 (m, 3H), 7.12 (d, *J* = 5.8 Hz, 2H), 2.66 – 2.61 (m, 4H), 1.66 (m, 3.8 Hz, 4H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.47, 149.45, 142.15, 128.43, 125.91, 124.30, 35.73, 35.21, 30.98, 29.83; **HRMS** (ESI) m/z: calcd for $C_{15}H_{18}N^+$ $(M+H)^+$ 212.1434, found 212.1440.



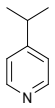
4-(3-(phenylthio)propyl)pyridine (3e) yellow oil, 50% (46 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.49 (d, *J* = 4.9 Hz, 2H), 7.34 – 7.23 (m, 4H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 5.7 Hz, 2H), 2.91 (t, *J* = 7.1 Hz, 2H), 2.80 – 2.68 (t, *J* = 7.1 Hz, 2H), 1.96 (p, *J* = 7.2 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.45, 149.84, 136.10, 129.58, 129.05, 126.27, 124.05, 33.92, 33.07, 29.56; **HRMS** (ESI) m/z: calcd for $C_{14}H_{16}NS^+$ $(M+H)^+$ 230.0998, found 230.0999.



4-((adamantan-1-yl)methyl)pyridine (3f) orange solid, 44% (40 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.47 (d, *J* = 5.0 Hz, 2H), 7.00 (d, *J* = 5.4 Hz, 2H), 2.35 (s, 2H), 1.94 (t, *J* = 3.2 Hz, 3H), 1.71 – 1.60 (m, 3H), 1.60 – 1.50 (m, 3H), 1.47 (d, *J* = 2.8 Hz, 6H).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.09, 147.38, 126.13, 50.73, 42.45, 36.95, 33.67, 28.74; **HRMS** (ESI) m/z: calcd for $C_{16}H_{22}N^+$ $(M+H)^+$ 228.1747, found 228.1744.

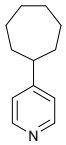


Tert-butyl (pyridin-4-ylmethyl)carbamate (3g) pale yellow oil, 89% (74 mg) ^{1}H NMR (600 MHz, Chloroform-d) δ 8.47 (d, *J* = 5.2 Hz, 2H), 7.15 (d, *J* = 5.4 Hz, 2H), 5.41 (t, *J* = 6.6 Hz, 1H), 4.27 (d, *J* = 6.4 Hz, 2H), 1.42 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.10, 149.87, 148.39, 122.01, 79.93, 43.49, 28.42; **HRMS** (ESI) m/z: calcd for $C_{11}H_{17}N_2O_2^+$ $(M+H)^+$ 209.1285, found 209.1280. Characterization data matched that reported in the literature[17].

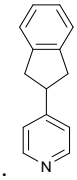


4-isopropylpyridine (3h) colourless oil, 60% (29 mg) ^{1}H NMR (600 MHz, Chloroform-d) δ 8.47 (d, *J* = 6.2 Hz, 2H), 7.11 (d, *J* = 6.2 Hz, 2H), 2.85 (hept, *J* = 6.9 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (151 MHz,

$CDCl_3$) δ 157.58, 149.80, 122.06, 33.62, 23.17; **HRMS** (ESI) m/z: calcd for $C_8H_{12}N^+$ $(M+H)^+$ 122.0964, found 122.0963. Characterization data matched that reported in the literature[15].



4-cycloheptylpyridine (3i) colourless oil, 83% (58 mg) ^{1}H NMR (600 MHz, Chloroform-d) δ 8.45 (d, *J* = 5.1 Hz, 2H), 7.08 (d, *J* = 5.3 Hz, 2H), 2.63 (tt, *J* = 10.5, 3.7 Hz, 1H), 1.87 (m, 2H), 1.78 (m, 2H), 1.68 (m, 2H), 1.65 – 1.47 (m, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.51, 149.79, 122.36, 46.35, 36.01, 27.95, 27.17; **HRMS** (ESI) m/z: calcd for $C_{12}H_{18}N^+$ $(M+H)^+$ 176.1434, found 176.1434. Characterization data matched that reported in the literature[18].



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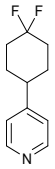
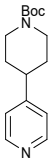
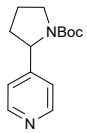
4-(2,3-dihydro-1*H*-inden-2-yl)pyridine (3j) brown solid, 73% (57 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.51 (d, *J* = 5.1 Hz, 2H), 7.30 – 7.16 (m, 6H), 3.66 (p, *J* = 8.2 Hz, 1H), 3.38 (dd, *J* = 15.6, 8.2 Hz, 2H), 3.06 (dd, *J* = 15.6, 8.2 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.57, 149.83, 142.14, 126.77, 124.40, 122.47, 44.46, 40.13; **HRMS** (ESI) m/z: calcd for $C_{14}H_{14}N^+$ $(M+H)^+$ 196.1121, found 196.1124.



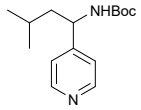
4-(4,4-difluorocyclohexyl)pyridine (3k) colourless oil, 65% (51 mg) ^{1}H NMR (600 MHz, Chloroform-d) δ 8.59 (s, 2H), 7.16 (s, 2H), 2.59 (tt, *J* = 12.1, 3.4 Hz, 1H), 2.22 (m, 2H), 2.02 – 1.75 (m, 6H); **^{13}C NMR** (126 MHz, Chloroform-d) δ 153.92, 150.02, 122.84 (dd, *J* = 242.7, 239.4 Hz), 122.48, 41.90, 33.89 (dd, *J* = 25.6, 23.1 Hz), 29.55 (d, *J* = 10.1 Hz); **HRMS** (ESI) m/z: calcd for $C_{11}H_{14}F_2N^+$ $(M+H)^+$ 198.1089, found 198.1083. Characterization data matched that reported in the literature[15].



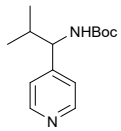
Tert-butyl 4-(pyridin-4-yl)piperidine-1-carboxylate (3l) white solid, 81% (84 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.49 (d, *J* = 4.7 Hz, 2H), 7.10 (d, *J* = 5.0 Hz, 2), 4.31 – 4.14 (m, 2H), 2.82 – 2.73 (m, 2H), 2.62 (tt, *J* = 12.2, 3.7 Hz, 1H), 1.80 (d, *J* = 12.8 Hz, 2H), 1.63 – 1.52 (m, 2H), 1.45 – 1.44 (m, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.80, 154.67, 149.94, 122.37, 79.72, 44.16, 42.05, 32.32, 28.53; **HRMS** (ESI) m/z: calcd for $C_{15}H_{23}N_2O_2^+$ $(M+H)^+$ 263.1754, found 263.1754.



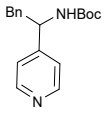
Tert-butyl 2-(pyridin-4-yl)pyrrolidine-1-carboxylate (d.r) (3m) colorless oil, 88% (87 mg) owing to the presence of rotamers around the tertiary amide,the product gives two sets of NMR signals. **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.48 (d, *J* = 5.2 Hz, 2H), 7.06 (d, *J* = 6.0 Hz, 2H), 4.90 –4.65 (m, 1H), 3.63 – 3.44 (m, 2H), 2.39 – 2.20 (m, 1H), 1.95 – 1.63 (m, 3H), 1.41 (s, 3H), 1.15 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.52, 154.26, 153.27, 149.74, 120.80, 79.81, 60.54, 60.00, 47.39, 47.16, 35.55, 34.35, 28.50, 28.17, 23.66, 23.27; **HRMS** (ESI) m/z: calcd for $C_{14}H_{21}N_2O_2^+$ $(M+H)^+$ 249.1598, found 249.1594. Characterization data matched that reported in the literature[19].



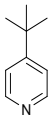
Tert-butyl (3-methyl-1-(pyridin-4-yl)butyl)carbamate (d.r) (3n) colorless oil, 85% (90 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.53 (d, *J* = 5.1 Hz, 2H), 7.18 (d, *J* = 5.0 Hz, 2H), 4.99 (s, 1H), 4.70 – 4.62 (m, 1H), 1.65 – 1.25 (m, 12H), 0.97 – 0.90 (m, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 155.30, 152.94, 150.02, 121.45, 79.91, 52.42, 45.87, 28.45, 25.03, 22.93, 22.19; **HRMS** (ESI) m/z: calcd for $C_{15}H_{25}N_2O_2^+$ $(M+H)^+$ 265.1911, found 265.1909.



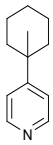
Tert-butyl (2-methyl-1-(pyridin-4-yl)propyl)carbamate (d.r) (3o) colorless oil, 85% (85 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.54 (d, *J* = 6.0 Hz, 2H), 7.16 (d, *J* = 5.7 Hz, 2H), 5.26 – 5.03 (m, 1H), 4.49 – 4.38 (m, 1H), 2.04 – 1.87 (m, 1H), 1.46 – 1.21 (m, 9H), 0.92 – 0.81 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.55, 151.83, 149.68, 122.24, 79.94, 59.68, 33.21, 28.43, 19.70, 18.04; **HRMS** (ESI) m/z: calcd for $C_{14}H_{23}N_2O_2^+$ $(M+H)^+$ 251.1754, found 251.1758. Characterization data matched that reported in the literature[20].



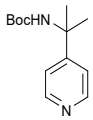
Tert-butyl (2-phenyl-1-(pyridin-4-yl)ethyl)carbamate (d.r) (3p) colorless oil, 80% (95 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.52 (d, *J* = 6.0 Hz, 2H), 7.30 – 7.20 (m, 3H), 7.12 (d, *J* = 6.0 Hz, 2H), 7.02 (dd, *J* = 7.3, 2.0 Hz, 2H), 5.09 – 5.01 (m, 1H), 4.94 (s, 1H), 3.02 (d, *J* = 6.8 Hz, 2H), 1.37 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.12, 151.68, 149.91, 136.34, 129.41, 128.69, 127.09, 121.68, 80.19, 55.10, 42.67, 28.37; **HRMS** (ESI) m/z: calcd for $C_{18}H_{23}$ $N_2O_2^+$ $(M+H)^+$ 299.1754, found 299.1755. Characterization data matched that reported in the literature[20].



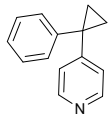
4-(tert-butyl)pyridine (3q) colorless oil, 71% (38 mg) ^{1}H NMR (600 MHz, Chloroform-d) δ 8.48 (d, *J* = 6.2 Hz, 2H), 7.24 (d, *J* = 6.3 Hz, 2H), 1.28 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.97, 149.71, 120.78, 34.70, 30.57; **HRMS** (ESI) m/z: calcd for $C_9H_{14}N^+$ $(M+H)^+$ 136.1121 found 136.1123. Characterization data matched that reported in the literature[15].



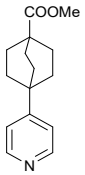
4-(1-methylcyclohexyl)pyridine (3r) colorless oil, 94% (66 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.52 (d, *J* = 6.2 Hz, 2H), 7.27 (d, *J* = 6.3 Hz, 2H), 2.05 – 1.87 (m, 2H), 1.64 – 1.48 (m, 4H), 1.47 – 1.29 (m, 4H), 1.17– 1.13 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.85, 149.69, 121.73, 38.26, 37.24, 30.02, 26.18, 22.56; **HRMS** (ESI) m/z: calcd for $C_{12}H_{18}N^+$ $(M+H)^+$ 176.1434 found 176.1434. Characterization data matched that reported in the literature[15].



Tert-butyl (2-(pyridin-4-yl)propan-2-yl)carbamate (3s) colorless oil, 62% (58 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.53 (d, *J* = 6.2 Hz, 2H), 7.28 (d, *J* = 5.9 Hz, 2H), 5.11 (s, 1H), 1.73 – 1.14 (m, 15H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.71, 154.13, 149.85, 120.25, 79.48, 54.53, 29.27, 28.39; **HRMS** (ESI) m/z: calcd for $C_{13}H_{21}N_2O_2^+$ $(M+H)^+$ 237.1598 found 237.1601.

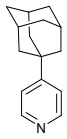


4-(1-phenylcyclopropyl)pyridine (3t) pale brown liquid, 77% (60 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.43 (d, *J* = 6.2 Hz, 2H), 7.37 – 7.23 (m, 5H), 6.94 (d, *J* = 6.3 Hz, 2H), 1.46 – 1.42 (m, 2H), 1.37 – 1.33 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.31, 149.36, 142.88, 129.92, 128.76, 127.13, 122.00, 29.28, 17.98; **HRMS** (ESI) m/z: calcd for $C_{14}H_{14}N^+$ $(M+H)^+$ 196.1121 found 196.1120. Characterization data matched that reported in the literature[15].

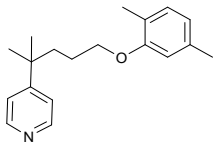


Methyl 4-(pyridin-4-yl)bicyclo[2.2.2]octane-1-carboxylate (3u) orange liquid, 83% (81 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.50 (d, *J* = 6.2 Hz, 2H), 7.20 (d, *J* = 6.3 Hz, 2H), 3.66 (s, 3H), 1.96 – 1.88 (m, 6H), 1.86 – 1.76 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.00, 158.56, 149.66, 121.19, 51.88, 39.12, 34.90,

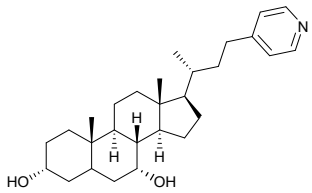
31.17, 28.53; **HRMS** (ESI) m/z: calcd for $C_{15}H_{20}NO_2^+$ $(M+H)^+$ 246.1489 found 246.1489. Characterization data matched that reported in the literature[15].



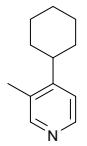
4-(adamantan-1-yl)pyridine (3v) yellow solid, 94% (80 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.49 (d, *J* = 6.3 Hz, 2H), 7.22 (d, *J* = 6.3 Hz, 2H), 2.12 – 2.04 (m, 3H), 1.86 (d, *J* = 3.0 Hz, 6H), 1.81 – 1.69 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.91, 149.76, 120.41, 42.43, 36.65, 36.29, 28.71; **HRMS** (ESI) m/z: calcd for $C_{15}H_{20}N^+$ $(M+H)^+$ 214.1590, found 214.1593. Characterization data matched that reported in the literature[15].



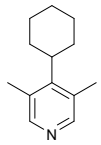
4-(5-(2,5-dimethylphenoxy)-2-methylpentan-2-yl)pyridine (3w) white solid, 74% (84 mg) ^{1}H NMR (600 MHz, Chloroform-d) δ 8.57 (d, *J* = 5.8 Hz, 2H), 7.33 (d, *J* = 6.2 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.56 (s, 1H), 3.85 (t, *J* = 6.2 Hz, 2H), 2.29 (s, 3H), 2.17 (s, 3H), 1.87 – 1.81 (m, 2H), 1.59 – 1.52 (m, 2H), 1.35 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.58, 156.87, 149.43, 136.53, 130.37, 123.44, 121.80, 120.79, 111.88, 67.78, 39.95, 37.83, 28.29, 24.91, 21.47, 15.89; **HRMS** (ESI) m/z: calcd for $C_{19}H_{26}NO^+$ $(M+H)^+$ 284.2009, found 284.2010.



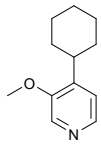
(3R,7R,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R)-4-(pyridin-4-yl)butan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthrene-3,7-diol (3x) white solid, 42% (71 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.46 (d, *J* = 4.9 Hz, 2H), 7.09 (d, *J* = 5.8 Hz, 2H), 5.29 (s, 1H), 3.87 – 3.80 (m, 1H), 3.63 (s, 1H), 3.46 (tt, *J* = 11.1, 4.4 Hz, 1H), 2.66 (ddd, *J* = 13.7, 11.0, 4.8 Hz, 1H), 2.46 (ddd, *J* = 13.7, 10.7, 6.1 Hz, 1H), 2.20 (td, *J* = 13.1, 11.2 Hz, 1H), 2.04 – 1.93 (m, 2H), 1.92 – 1.78 (m, 5H), 1.77 – 1.58 (m, 5H), 1.56 – 1.43 (m, 4H), 1.44 – 1.32 (m, 4H), 1.32 – 1.16 (m, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 3H), 0.64 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.49, 149.65, 124.06, 72.09, 68.62, 55.88, 50.62, 42.85, 41.62, 40.02, 39.80, 39.56, 36.99, 35.66, 35.47, 35.19, 34.81, 32.99, 31.99, 30.81, 28.38, 23.83, 22.91, 20.72, 18.70, 11.91; **HRMS** (ESI) m/z: calcd for $C_{28}H_{44}NO_2^+$ $(M+H)^+$ 426.3367, found 426.3368.



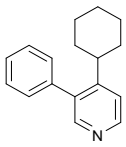
4-cyclohexyl-3-methylpyridine (4a) yellow liquid, 84% (59 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.42 (d, *J* = 5.4 Hz, 1H), 8.39 (s, 1H), 7.18 (d, *J* = 5.3 Hz, 1H), 2.69 (tt, *J* = 11.4, 3.2 Hz, 1H), 2.34 – 2.28 (s, 3H), 1.96 – 1.69 (m, 5H), 1.46 – 1.26 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.83, 149.96, 147.26, 131.96, 121.26, 40.06, 32.73, 26.76, 26.10, 16.22; **HRMS** (ESI) m/z: calcd for $C_{12}H_{18}N^+$ $(M+H)^+$ 176.1434, found 176.1430. Characterization data matched that reported in the literature[15].



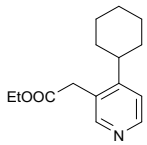
4-cyclohexyl-3,5-dimethylpyridine (4b) yellowish liquid, 82% (62 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.11 (s, 2H), 2.90 (tt, *J* = 12.2, 3.5 Hz, 1H), 2.32 (s, 6H), 1.88 – 1.72 (m, 5H), 1.66 – 1.59 (m, 2H), 1.40 – 1.23 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.40, 149.98, 130.74, 41.58, 29.72, 27.27, 26.19, 18.23; **HRMS** (ESI) m/z: calcd for $C_{13}H_{20}N^+$ $(M+H)^+$ 190.1590, found 190.1591. Characterization data matched that reported in the literature[15].



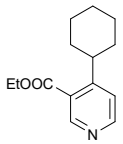
4-cyclohexyl-3-methoxypyridine (4c) yellowish liquid, 83% (63 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.21 (s, 1H), 8.19 (d, *J* = 5.0 Hz, 1H), 7.11 (d, *J* = 4.9 Hz, 1H), 3.91 (s, 3H), 2.93 (tt, *J* = 11.6, 3.2 Hz, 1H), 1.91 – 1.63 (m, 5H), 1.52 – 1.15 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.55, 145.42, 142.84, 132.73, 121.55, 56.17, 36.60, 32.41, 26.81, 26.29; **HRMS** (ESI) m/z: calcd for $C_{12}H_{18}NO^+$ $(M+H)^+$ 192.1383, found 192.1384. Characterization data matched that reported in the literature[15].



4-cyclohexyl-3-phenylpyridine (4d) colorless liquid, 65% (62 mg) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.52 (d, *J* = 5.3 Hz, 1H), 8.41 (s, 1H), 7.49 – 7.37 (m, 3H), 7.33 – 7.22 (m, 3H), 2.68 (tt, *J* = 12.0, 3.1 Hz, 1H), 1.86 – 1.61 (m, 5H), 1.53 – 1.33 (m, 2H), 1.36 – 1.05 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.37, 150.29, 148.63, 137.95, 137.19, 129.47, 128.42, 127.63, 121.43, 39.73, 33.82, 26.44, 25.97; **HRMS** (ESI) m/z: calcd for $C_{17}H_{20}N^+$ $(M+H)^+$ 238.1590, found 238.1592. Characterization data matched that reported in the literature[15].



Ethyl 2-(4-cyclohexylpyridin-3-yl)acetate (4e) yellowish liquid, 75% (74 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.43 (d, *J* = 5.2 Hz, 1H), 8.38 (s, 1H), 7.17 (d, *J* = 5.2 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 2H), 2.74 – 2.61 (m, 1H), 1.92 – 1.72 (m, 5H), 1.49 – 1.28 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, CDCl3) δ 171.07, 155.25, 151.40, 149.04, 127.79, 121.33, 61.25, 40.01, 36.26, 33.39, 26.77, 26.10, 14.26; **HRMS** (ESI) m/z: calcd for $C_{15}H_{22}NO_2^+$ $(M+H)^+$ 248.1645, found 248.1644. Characterization data matched that reported in the literature[15].



Ethyl 4-cyclohexylnicotinate (4f) yellowish liquid, 46% (43 mg) ^{1}H NMR (500 MHz, Chloroform-d) δ 8.92 (s, 1H), 8.58 (d, *J* = 5.3 Hz, 1H), 7.28 (d, *J* = 5.3 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.39 (tt, *J* = 11.4, 3.0 Hz, 1H), 1.89 – 1.81 (m, 4H), 1.80 – 1.74 (m, 1H), 1.44 – 1.24 (m, 8H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.80, 157.67, 152.25, 151.21, 126.26, 121.68, 61.42, 39.91, 33.67, 26.76, 26.18, 14.38; **HRMS** (ESI) m/z: calcd for $C_{14}H_{20}NO_2^+$ $(M+H)^+$ 234.1489, found 234.1483. Characterization data matched that reported in the literature[15].

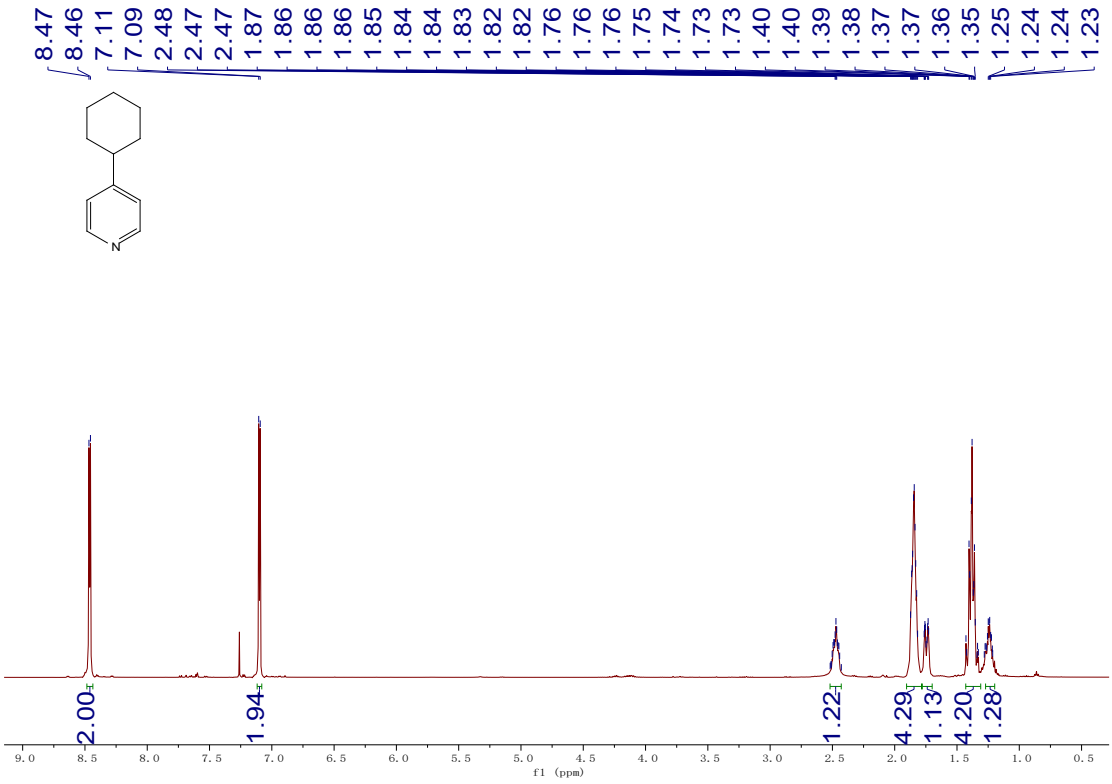
3. Reference

1. W. Kong, C. Yu, H. An and Q. Song, Photoredox-Catalyzed Decarboxylative Alkylation of Silyl Enol Ethers To Synthesize Functionalized Aryl Alkyl Ketones, *Org. Lett.*, 2018, **20**, 349-352.
2. A. Tortajada, Y. Duan, B. Sahoo, F. Cong, G. Toupalas, A. Sallustrau, O. Loreau, D. Audisio and R. Martin, Catalytic Decarboxylation/Carboxylation Platform for Accessing Isotopically Labeled Carboxylic Acids, *Acs Catal*, 2019, **9**, 5897-5901.
3. J. Yang, J. Zhang, L. Qi, C. Hu and Y. Chen, Visible-light-induced chemoselective reductive decarboxylative alkynylation under biomolecule-compatible conditions, *Chem. Commun.*, 2015, **51**, 5275-5278.
4. X. Lu, B. Xiao, L. Liu and Y. Fu, Formation of C(sp(3))-C(sp(3)) Bonds through Nickel-Catalyzed Decarboxylative Olefin Hydroalkylation Reactions, *Chem. – Eur. J.*, 2016, **22**, 11161-11164.
5. J. Schwarz and B. König, Metal-free, visible-light-mediated, decarboxylative alkylation of biomass-derived compounds, *Green Chem.*, 2016, **18**, 4743-4749.
6. J. T. M. Correia, G. Piva da Silva, C. M. Kisukuri, E. Andre, B. Pires, P. S. Carneiro and M. W. Paixao, Metal-Free Photoinduced Hydroalkylation Cascade Enabled by an Electron-Donor-Acceptor Complex, *J. Org. Chem.*, 2020, **85**, 9820-9834.
7. N. Papaioannou, M. J. Fray, A. Rennhack, T. J. Sanderson and J. E. Stokes, Regioselective Amidomethylation of 4-Chloro-3-fluoropyridine by Metalation and Minisci-Type Reactions, *J. Org. Chem.*, 2020, **85**, 12067-12079.
8. G. Pratsch, G. L. Lackner and L. E. Overman, Constructing Quaternary Carbons from N-(Acyloxy)phthalimide Precursors of Tertiary Radicals Using Visible-Light Photocatalysis, *J. Org. Chem.*, 2015, **80**, 6025-6036.
9. J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C. M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate and P. S. Baran, Practical Ni-Catalyzed Aryl-Alkyl Cross-Coupling of Secondary Redox-Active Esters, *J. Am. Chem. Soc.*, 2016, **138**, 2174-2177.
10. K. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. Ackerman and D. J. Weix, Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides, *J. Am. Chem. Soc.*, 2016, **138**, 5016-5019.
11. F. Toriyama, J. Cornella, L. Wimmer, T. G. Chen, D. D. Dixon, G. Creech and P. S. Baran, Redox-Active Esters in Fe-Catalyzed C-C Coupling, *J. Am. Chem. Soc.*, 2016, **138**, 11132-11135.
12. Z. P. Yang, D. J. Freas and G. C. Fu, The Asymmetric Synthesis of Amines via Nickel-Catalyzed Enantioconvergent Substitution Reactions, *J. Am. Chem. Soc.*, 2021, **143**, 2930-2937.
13. A. Tlahuext-Aca, R. A. Garza-Sanchez, M. Schafer and F. Glorius, Visible-Light-Mediated Synthesis of Ketones by the Oxidative Alkylation of Styrenes, *Org. Lett.*, 2018, **20**, 1546-1549.
14. J. Y. He, G. L. Chen, B. X. Zhang, Y. Li, J. R. Chen, W. J. Xiao, F. Liu and C. Z. Li, Catalytic Decarboxylative Radical Sulfonylation, *Chem.-Us.*, 2020, **6**, 1149-1159.
15. J. Choi, G. Laudadio, E. Godineau and P. S. Baran, Practical and Regioselective Synthesis of C-4-Alkylated Pyridines, *J. Am. Chem. Soc.*, 2021, **143**, 11927-11933.
16. A. I. M. C. Lobo Ferreira, A. S. M. C. Rodrigues, M. Villas, E. Tojo, L. P. N. Rebelo and L. M. N. B. F. Santos, Crystallization and Glass-Forming Ability of Ionic Liquids: Novel Insights into Their Thermal Behavior, *ACS Sustain. Chem. Eng.*, 2019, **7**, 2989-2997.

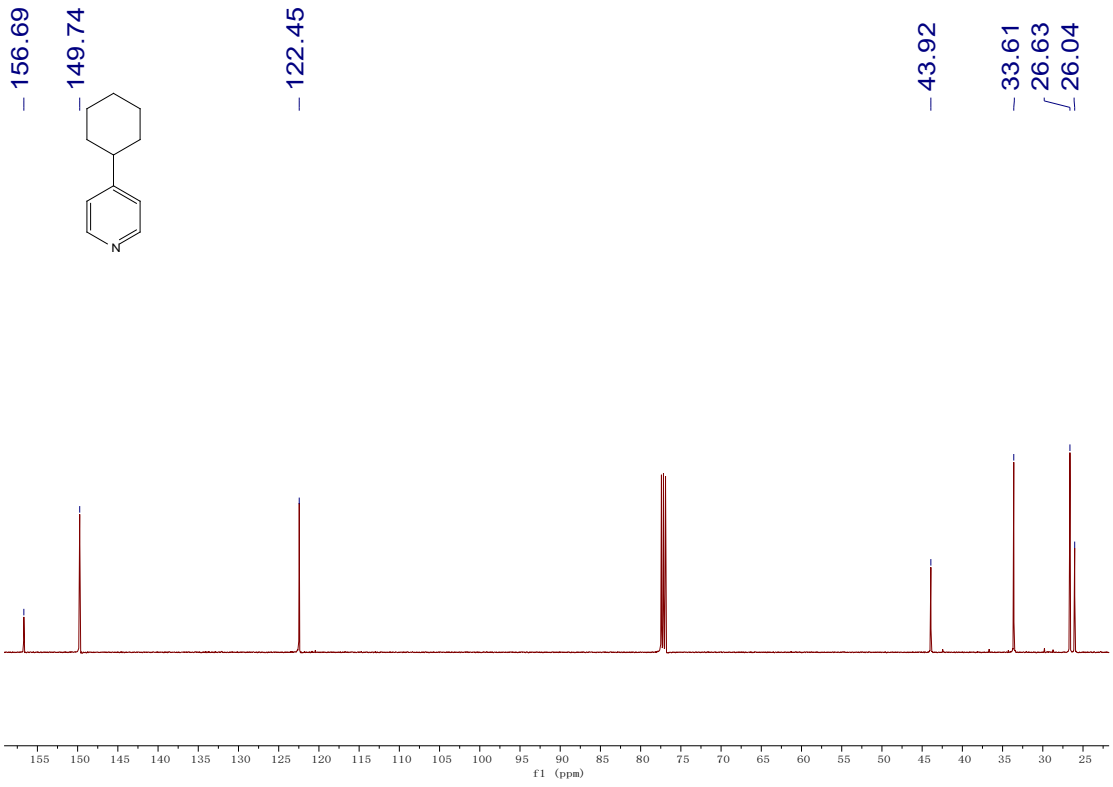
17. M. F. Braña, J. M. Castellano, M. L. L. Rodriguez, M. Gálvez, M. R. Amil and E. Rubio, Synthesis of 1,2-di-(4-pyridyl)ethylenediamine and related compounds, *J. Heterocycl. Chem.*, 1987, **24**, 369-371.
18. G. A. Molander, O. A. Argintaru, I. Aron and S. D. Dreher, Nickel-Catalyzed Cross-Coupling of Potassium Aryl- and Heteroaryltrifluoroborates with Unactivated Alkyl Halides, *Org. Lett.*, 2010, **12**, 5783-5785.
19. Z. Zuo and D. W. C. MacMillan, Decarboxylative Arylation of α-Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore, *J. Am. Chem. Soc.*, 2014, **136**, 5257-5260.
20. B. Lipp, A. M. Nauth and T. Opatz, Transition-Metal-Free Decarboxylative Photoredox Coupling of Carboxylic Acids and Alcohols with Aromatic Nitriles, *J. Org. Chem.*, 2016, **81**, 6875-6882.

Copies of 1H and 13C NMR Spectra

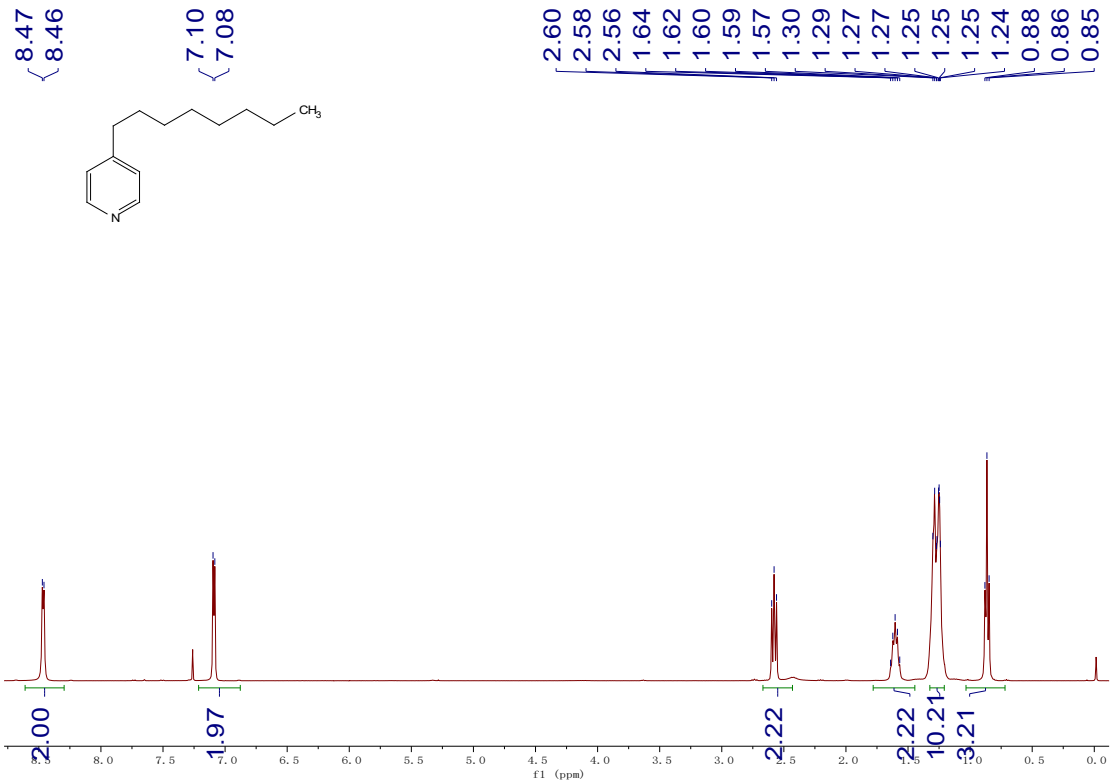
^{1}H NMR of compound **3a1**



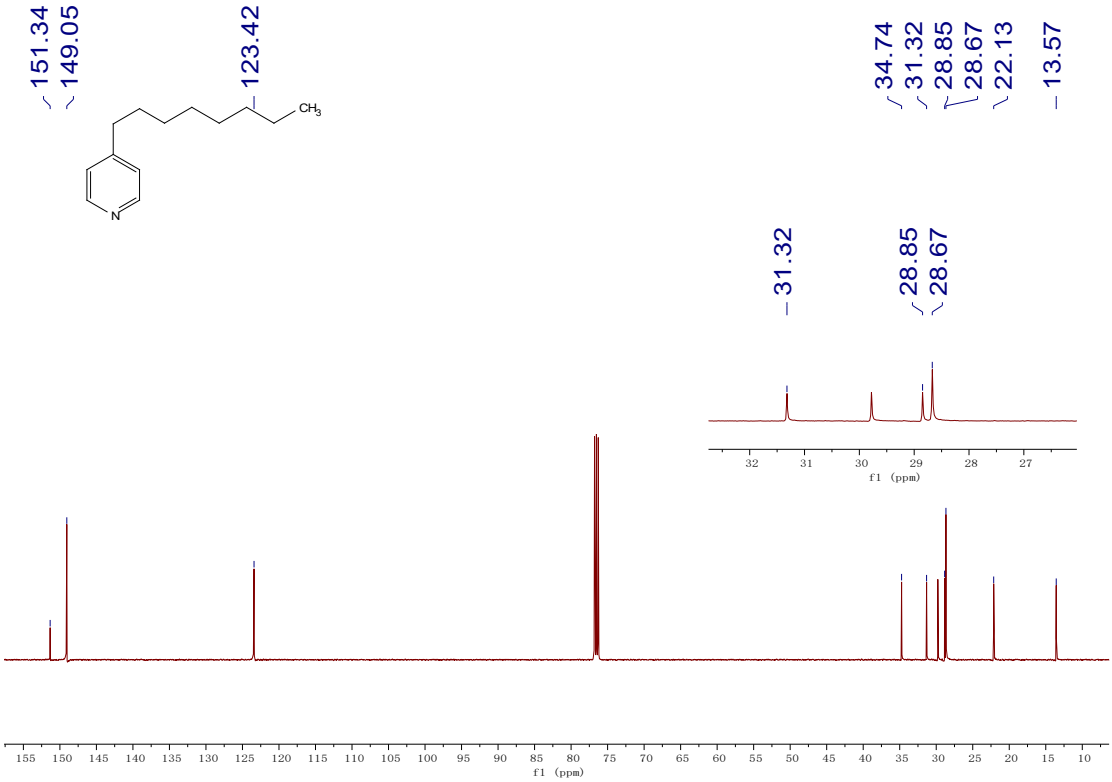
^{13}C NMR of compound **3a1**



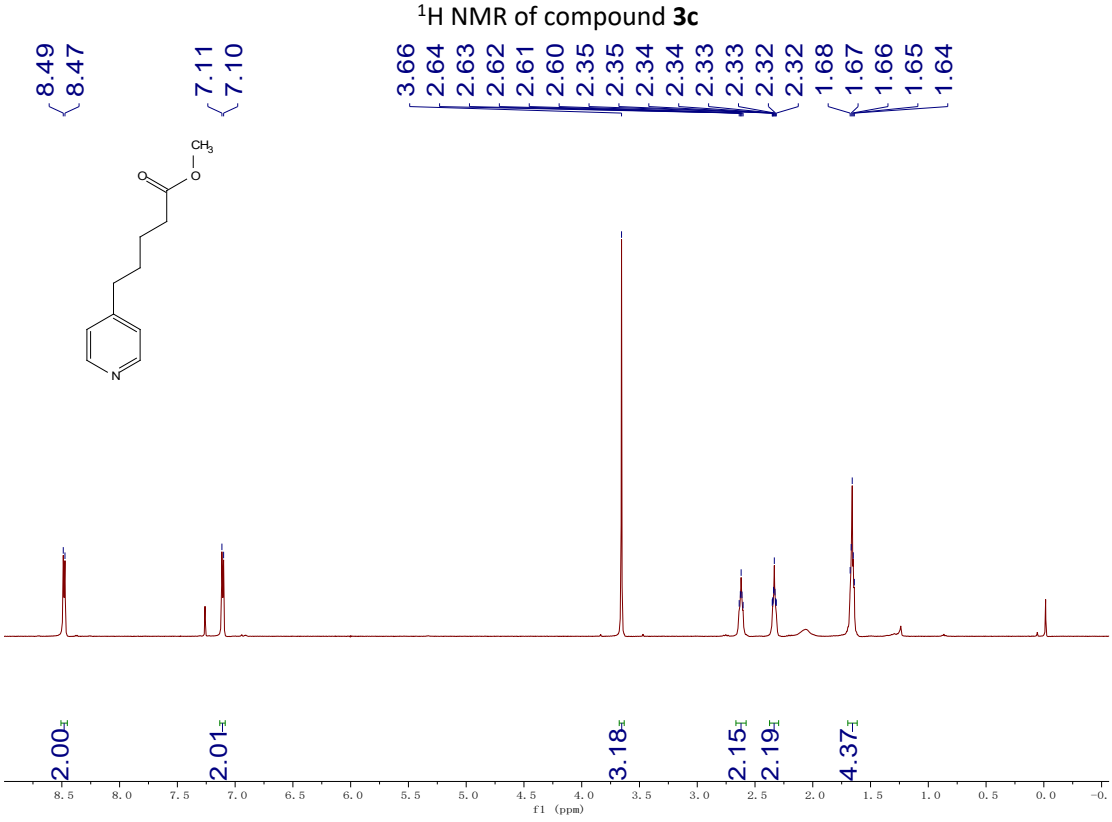
^{1}H NMR of compound **3b**



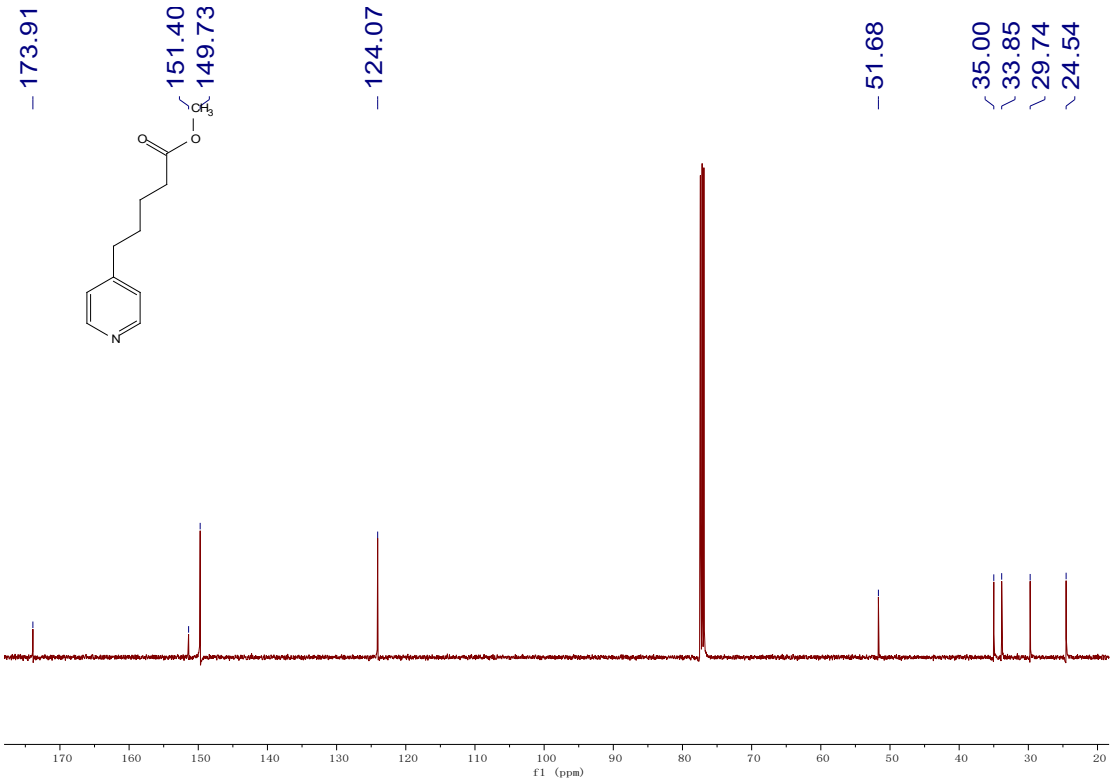
^{13}C NMR of compound **3b**



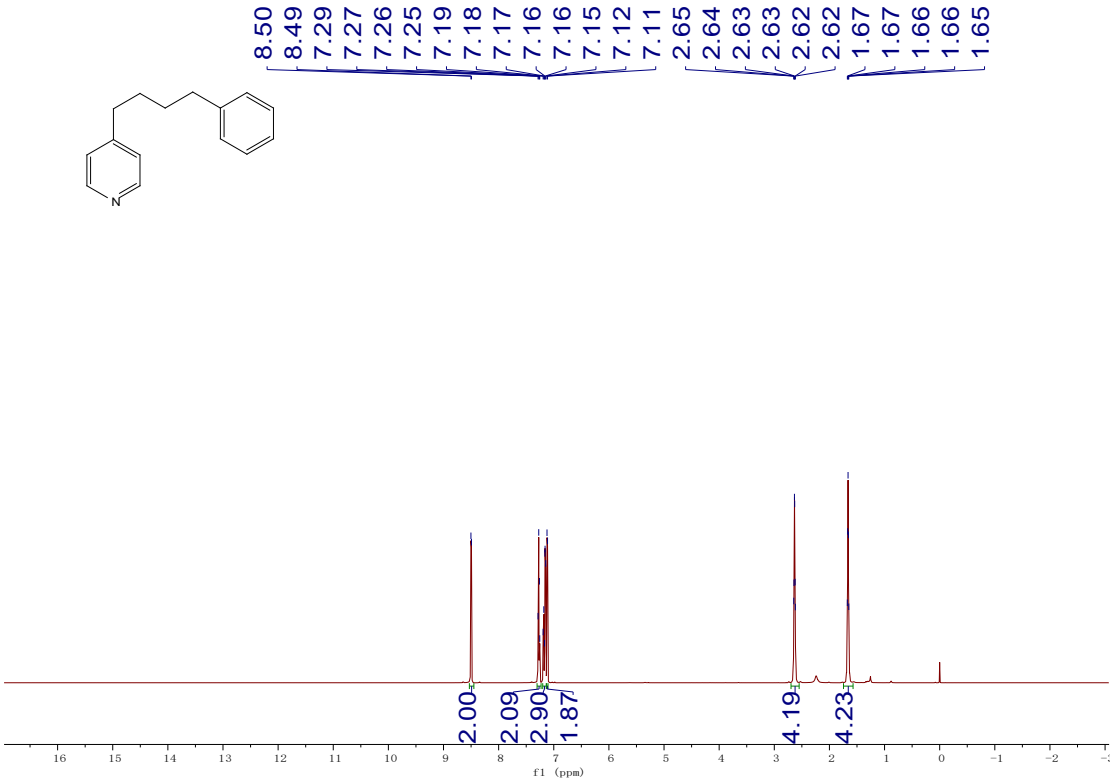
^{1}H NMR of compound **3c**



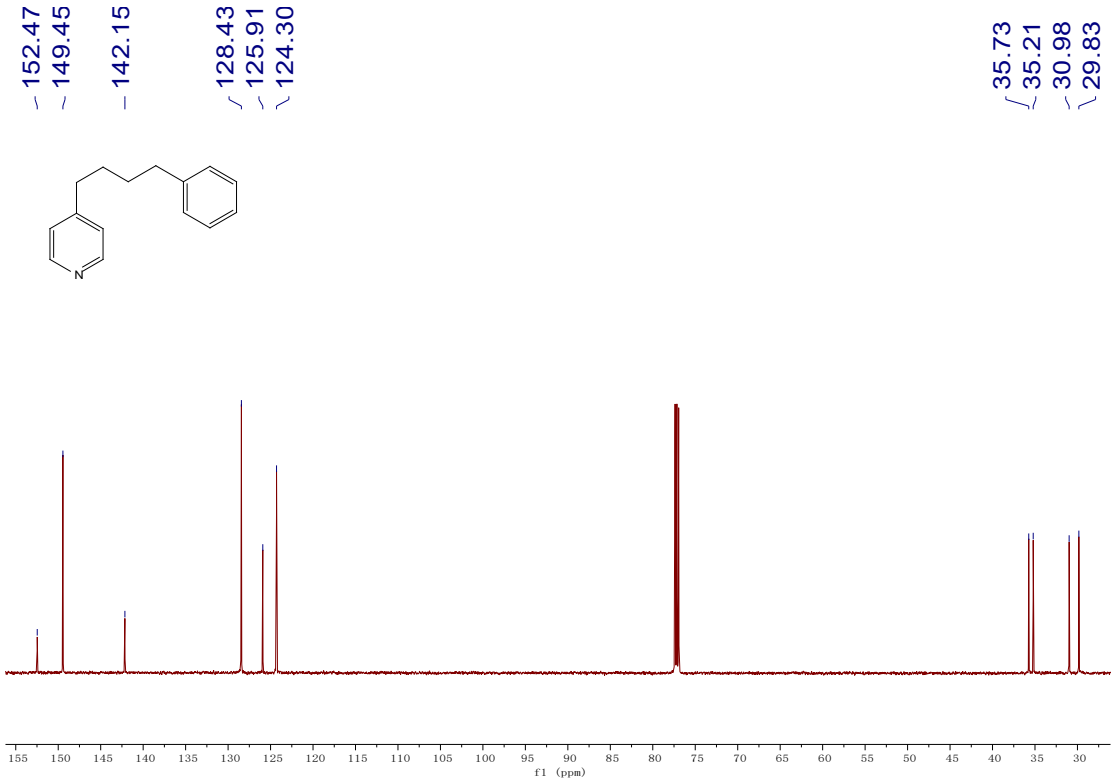
^{13}C NMR of compound **3c**



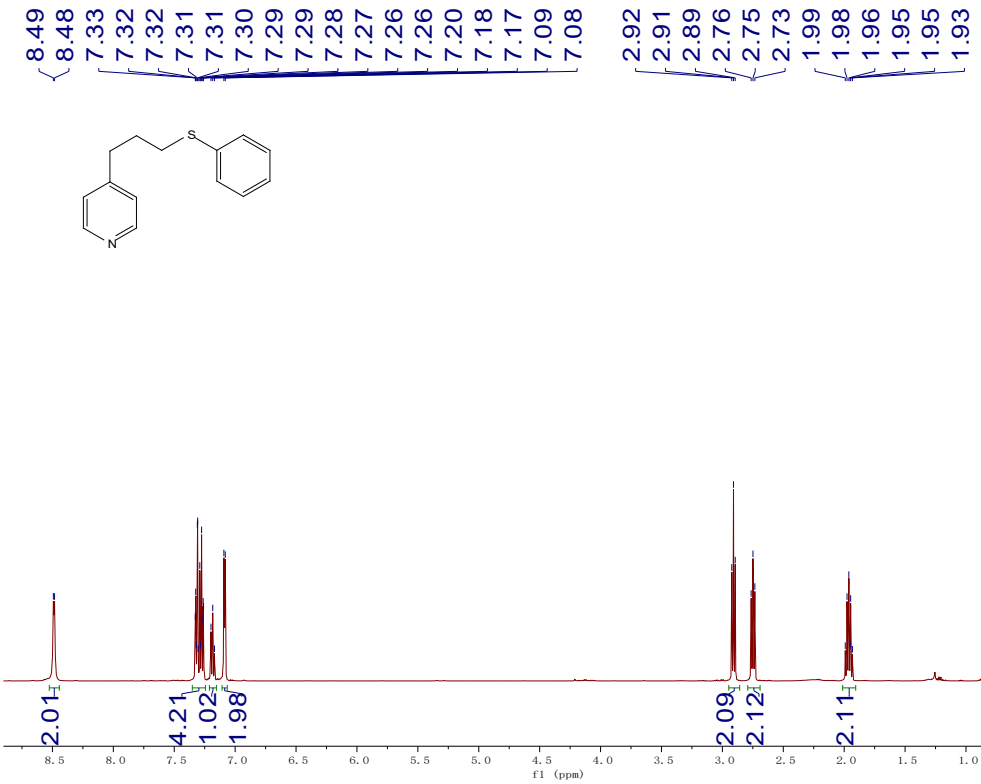
^{1}H NMR of compound **3d**



^{13}C NMR of compound **3d**



^{1}H NMR of compound **3e**



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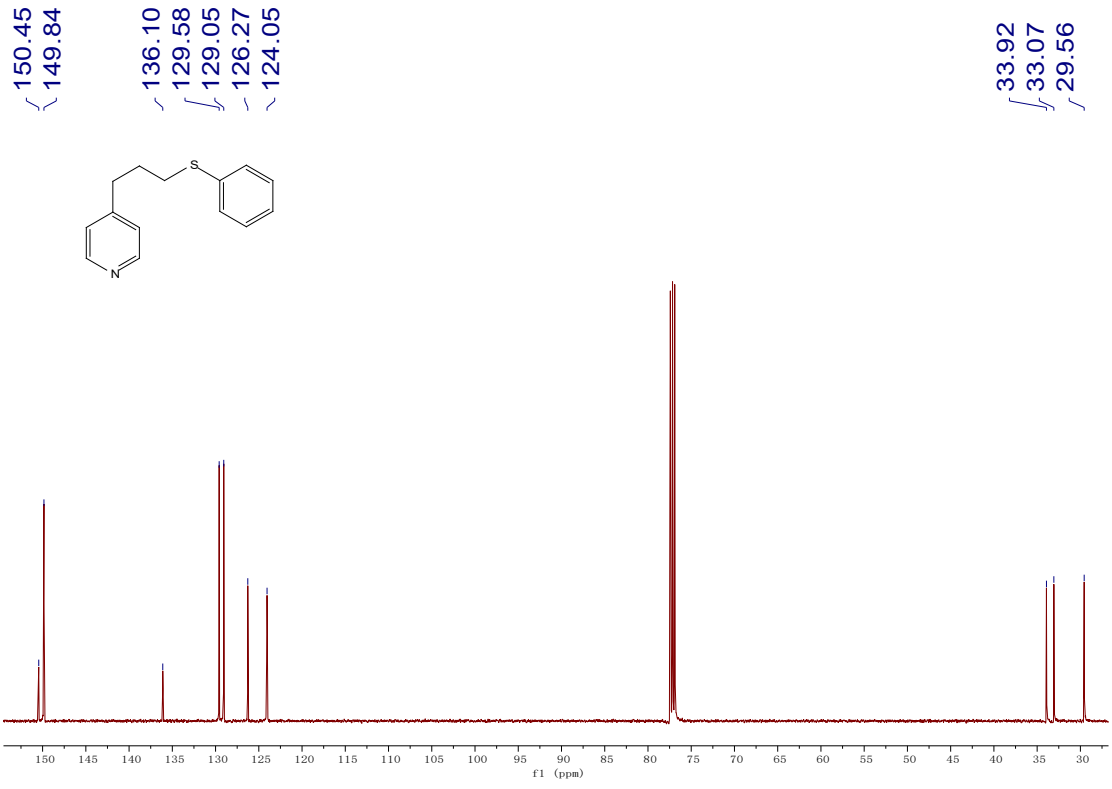
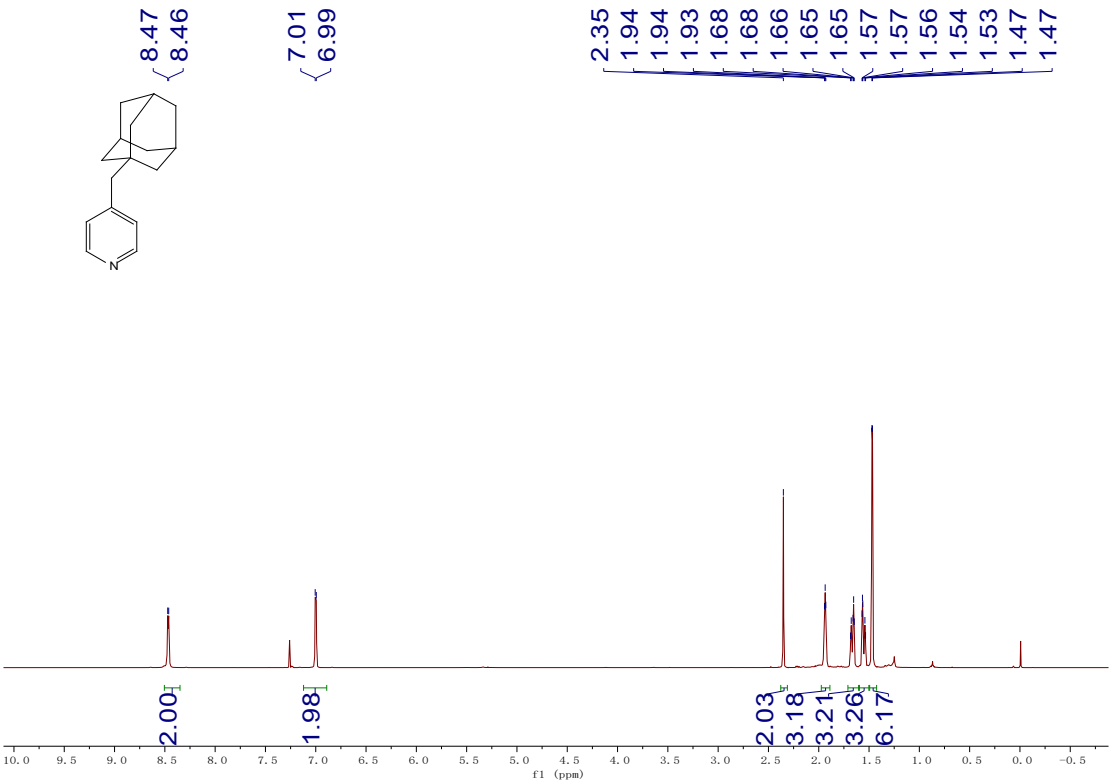
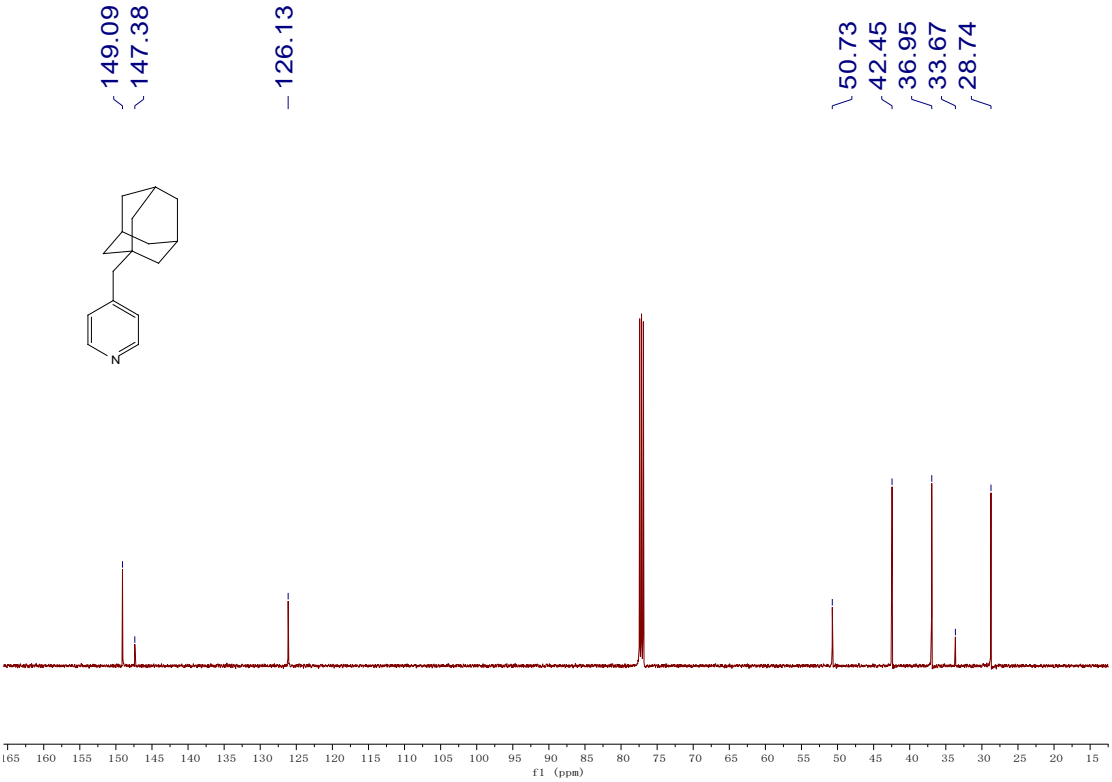


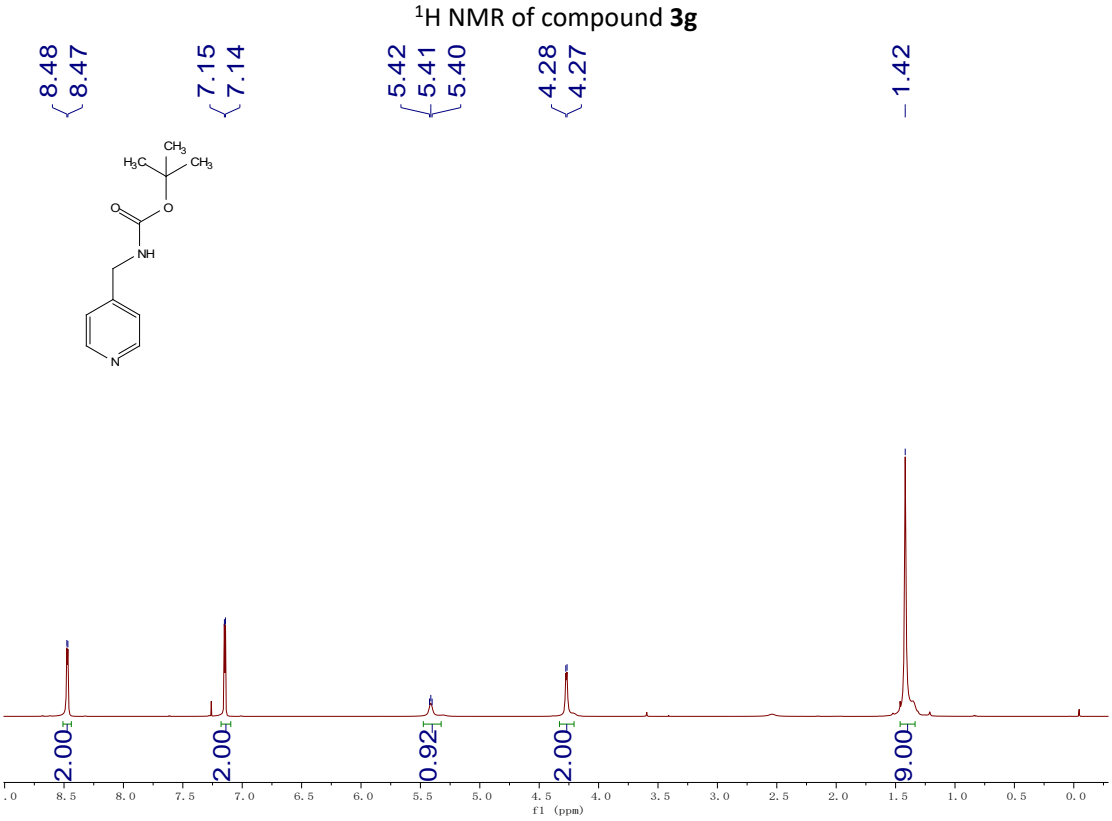
^{1}H NMR of compound **3f**



^{13}C NMR of compound **3f**



^{1}H NMR of compound **3g**



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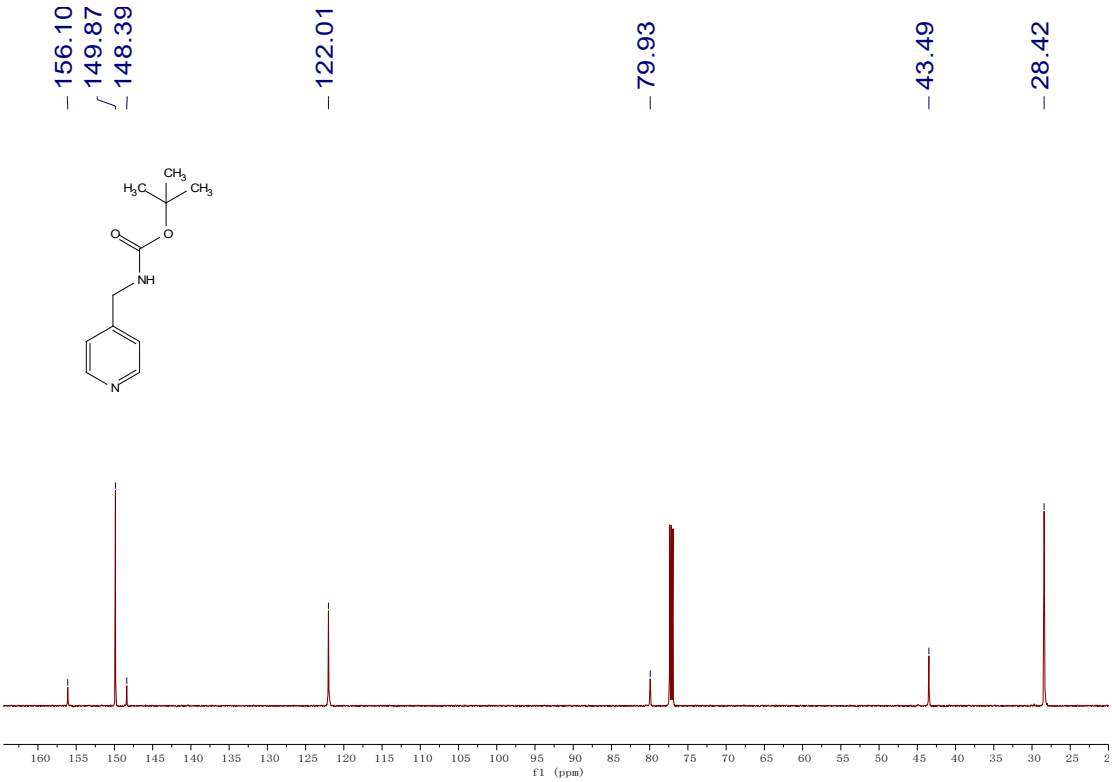
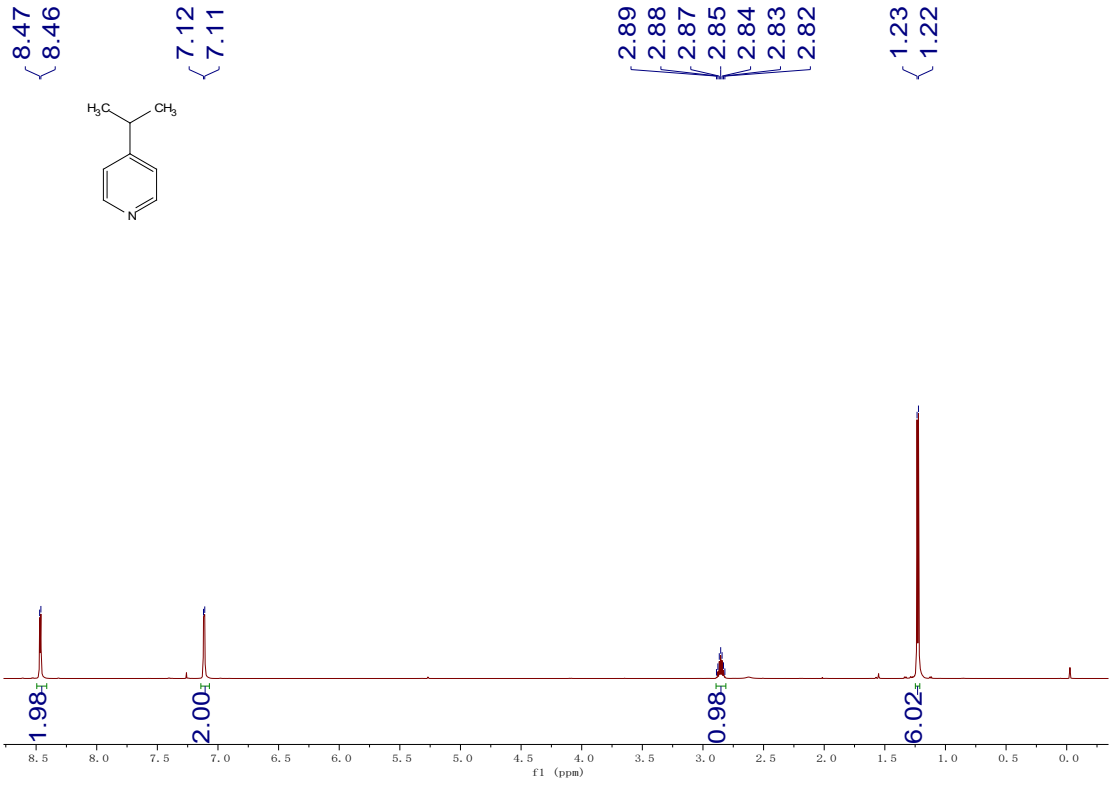
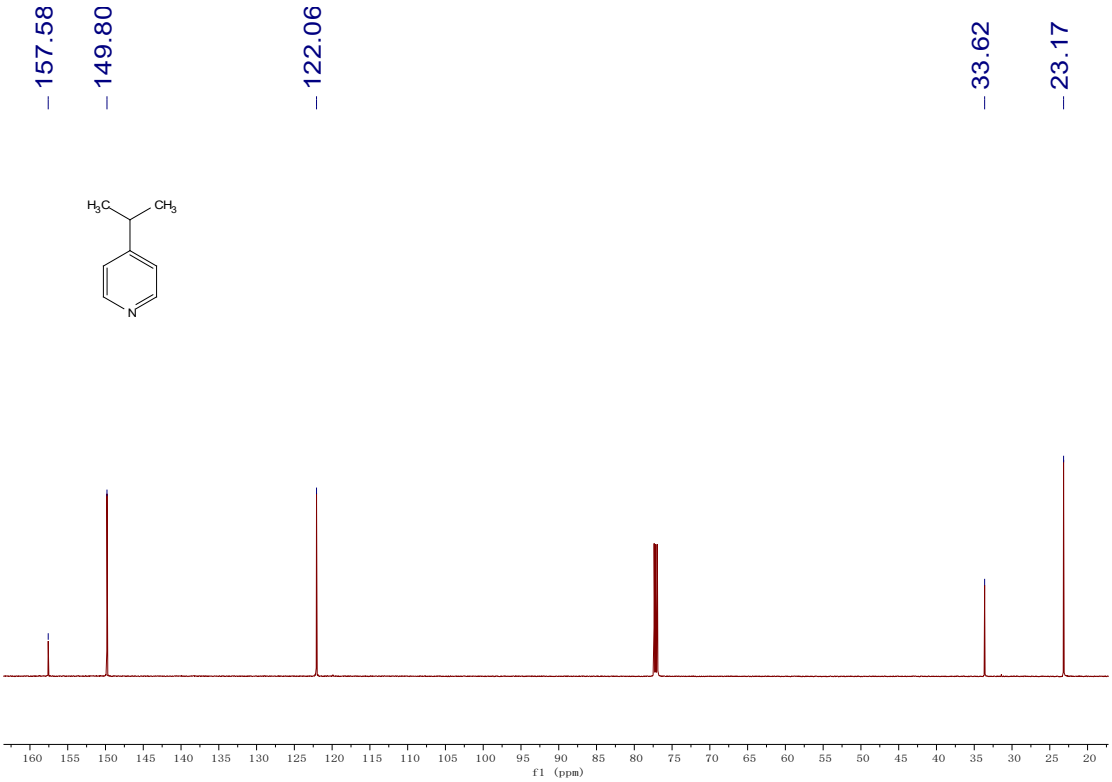


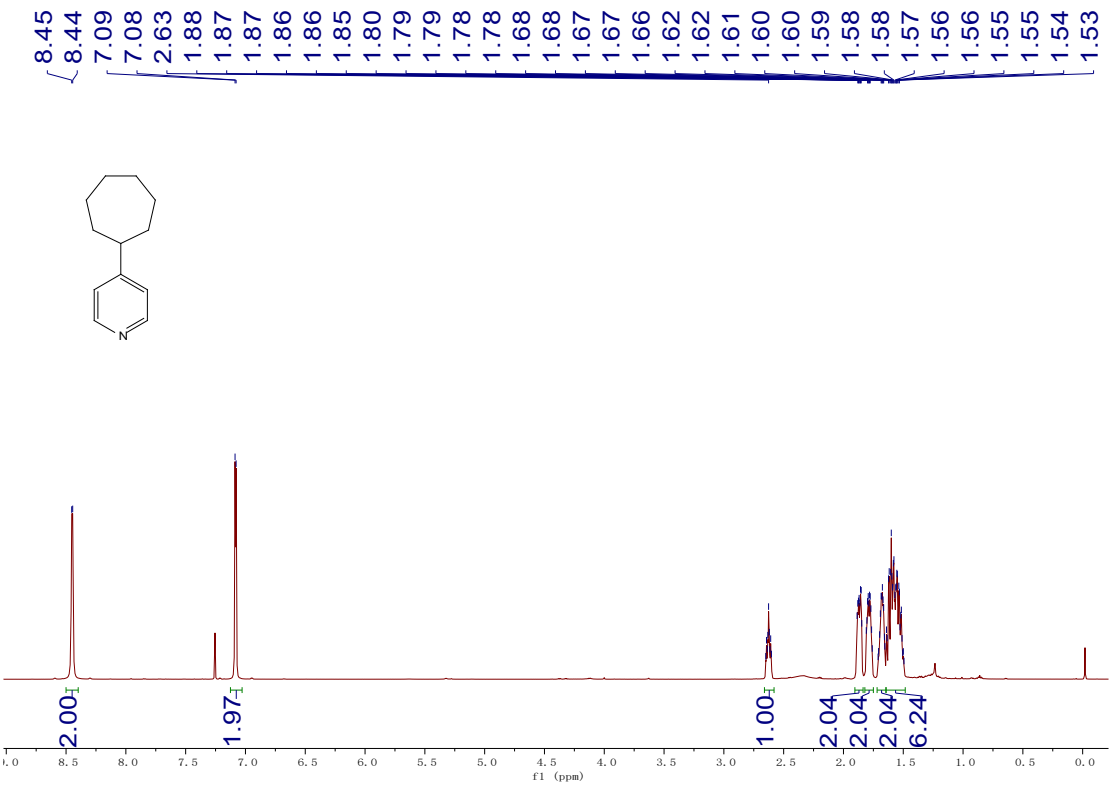
^{1}H NMR of compound **3h**



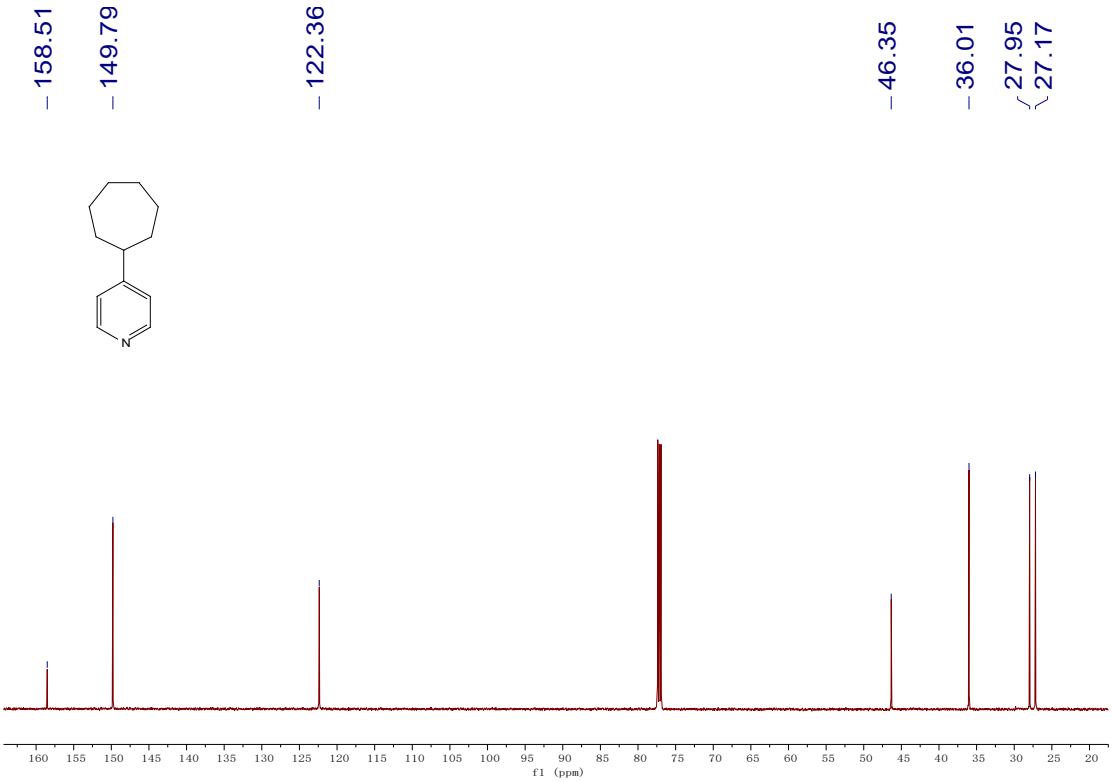
^{13}C NMR of compound **3h**



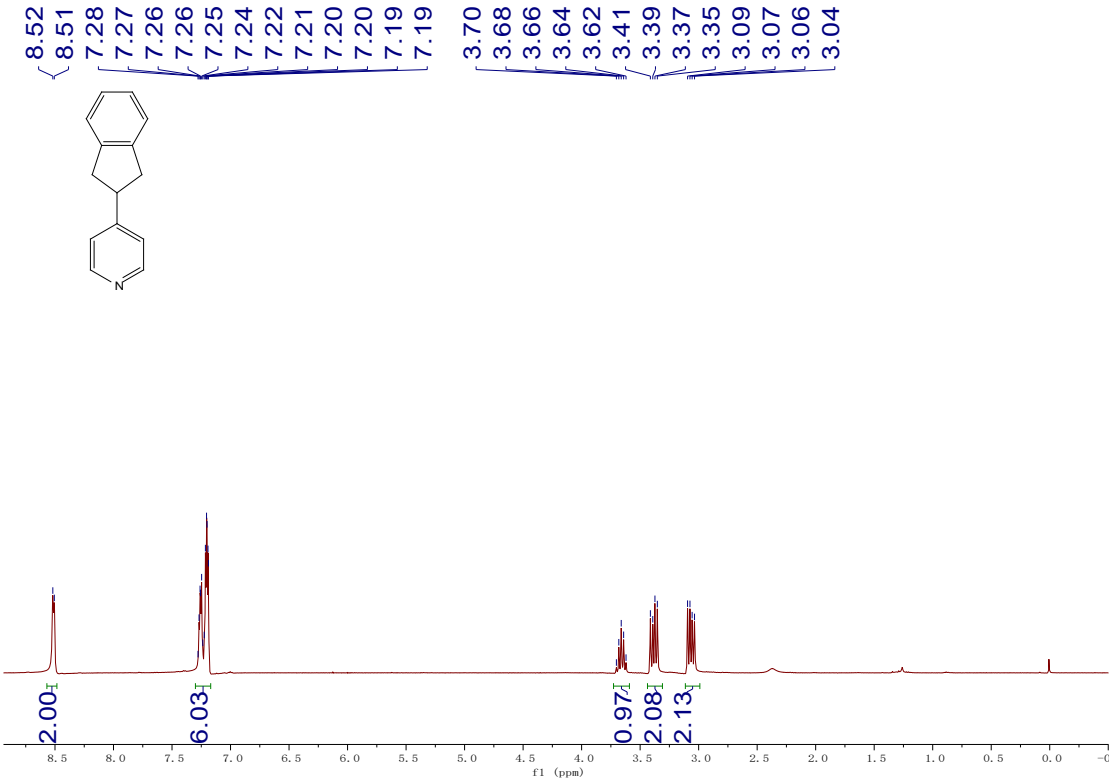
^{1}H NMR of compound **3i**



^{13}C NMR of compound **3i**



^{1}H NMR of compound **3j**



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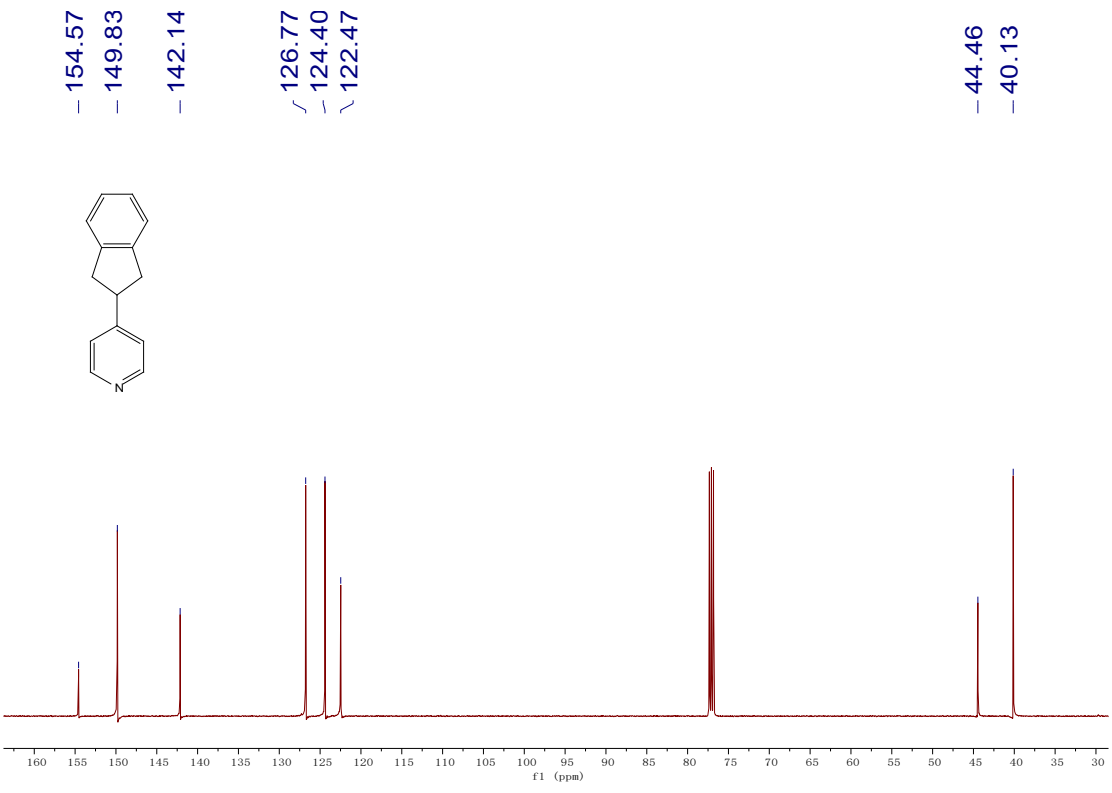

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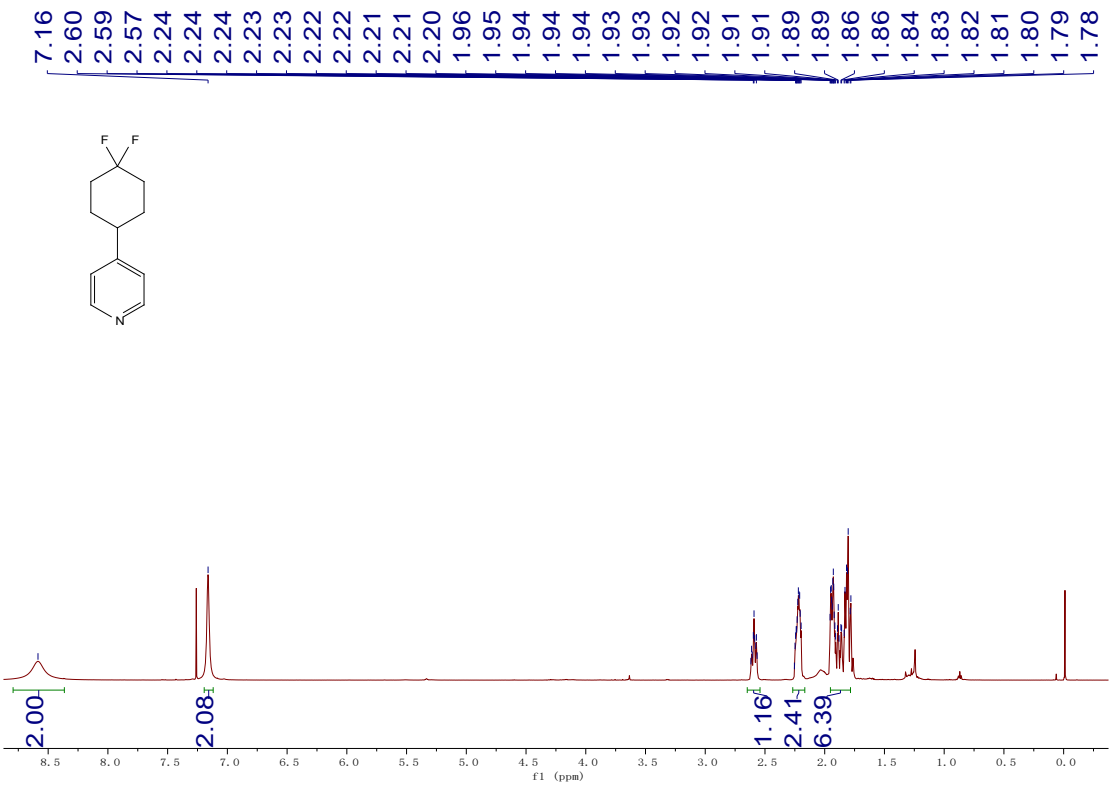

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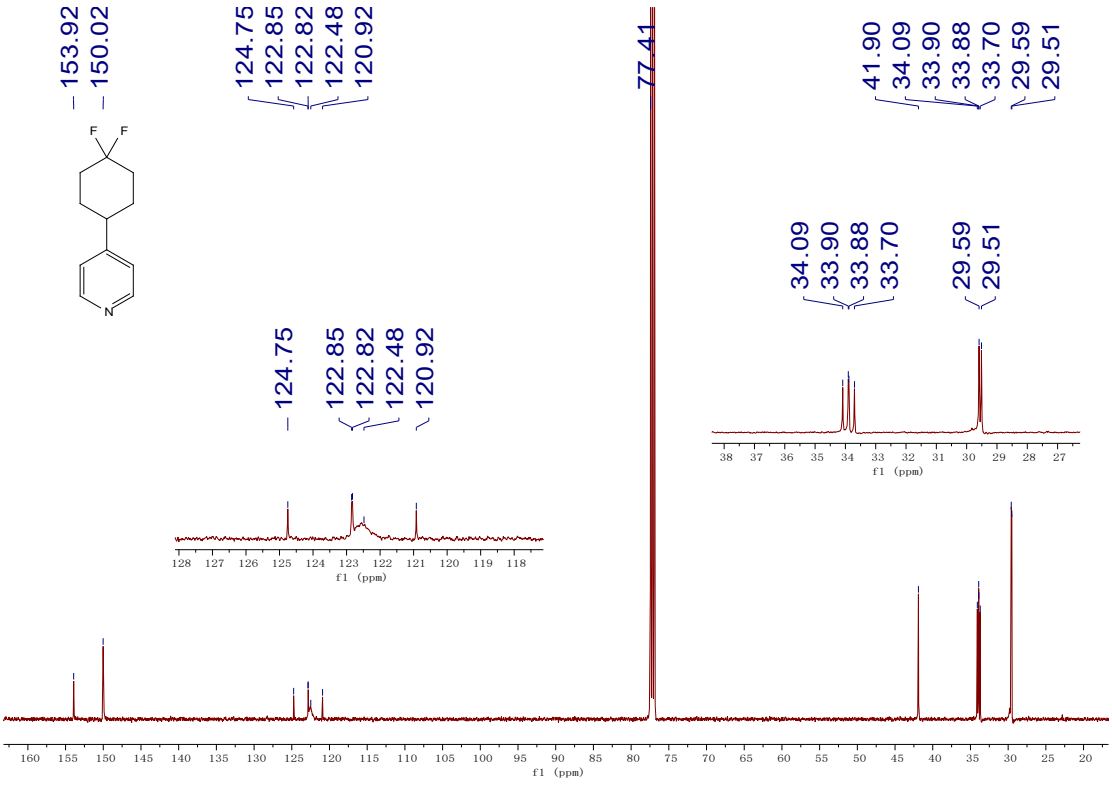
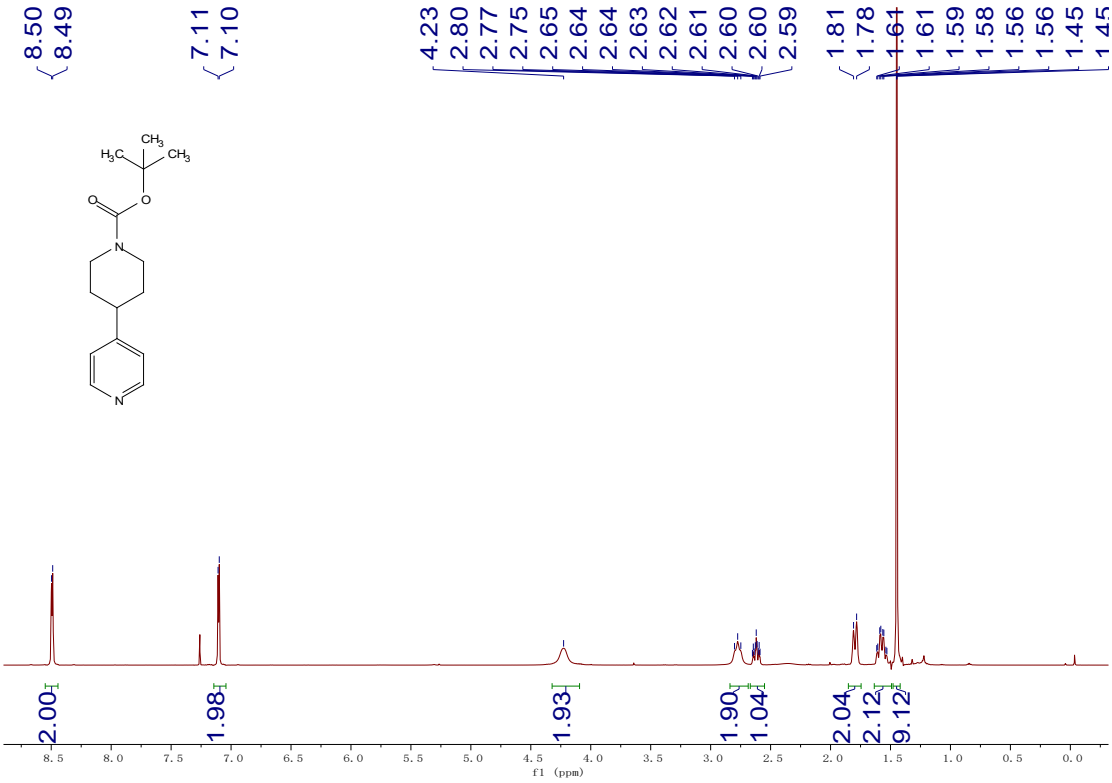


^{1}H NMR of compound **3l**



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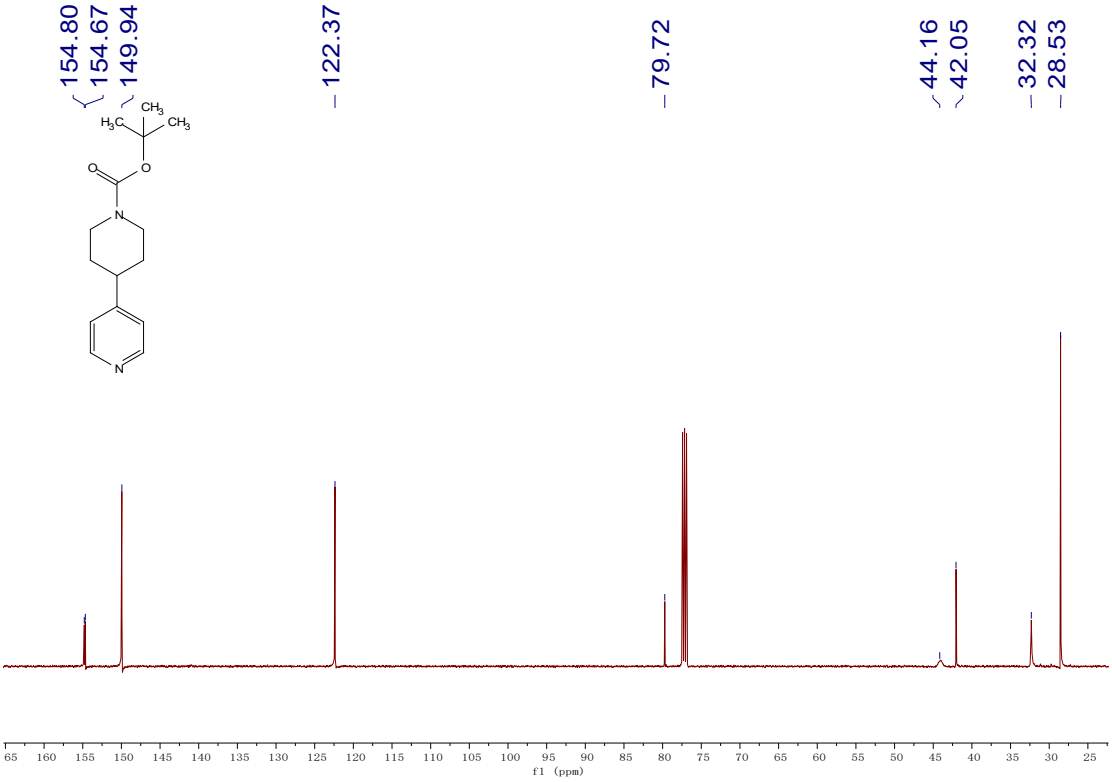
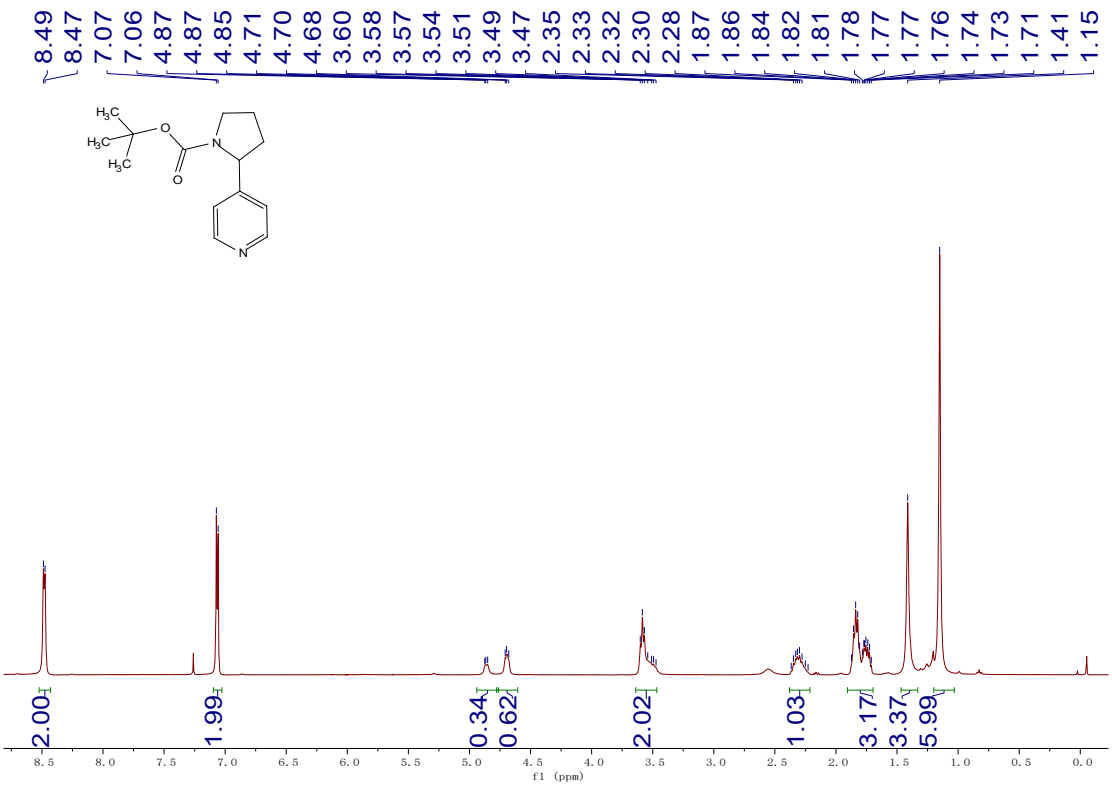
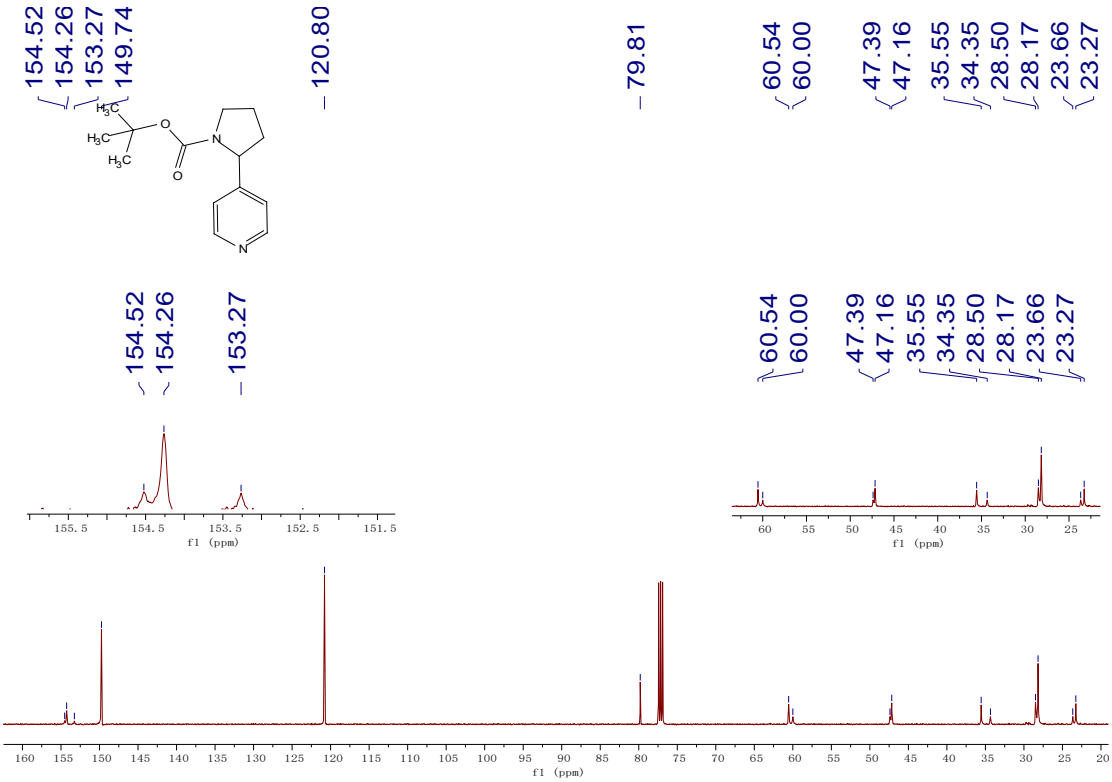


^{1}H NMR of compound **3m**



^{13}C NMR of compound **3m**



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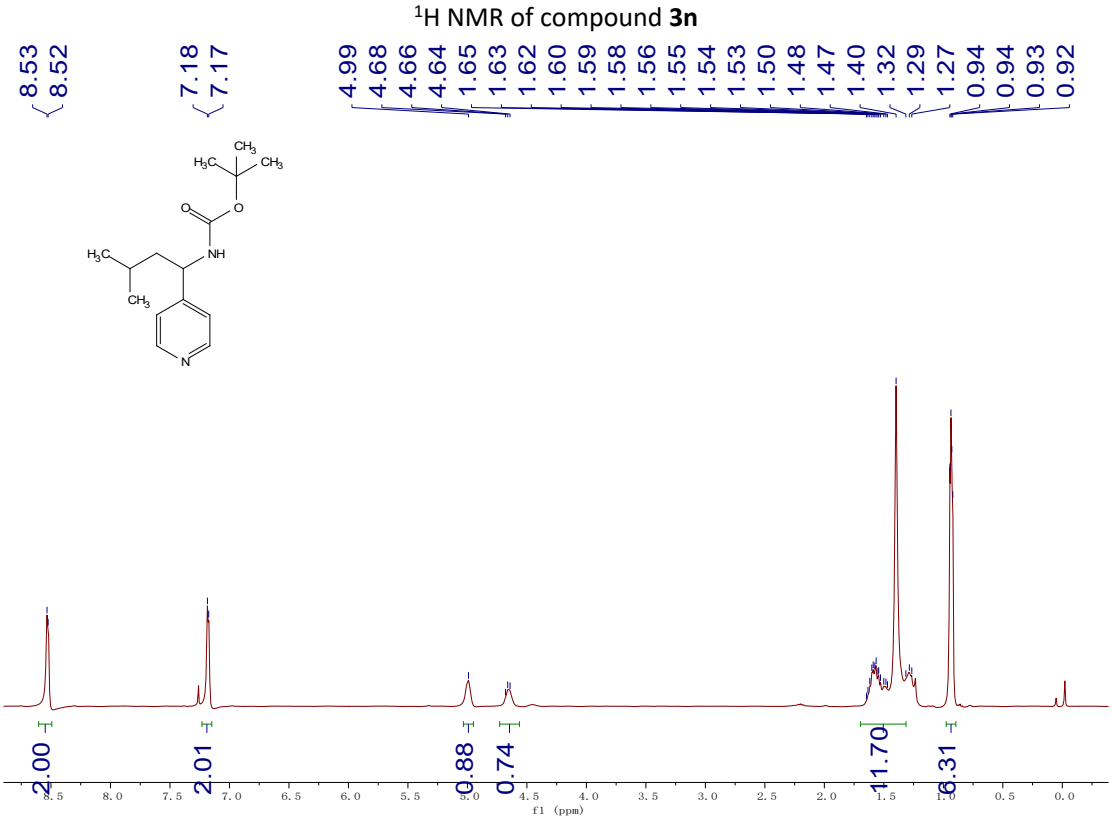

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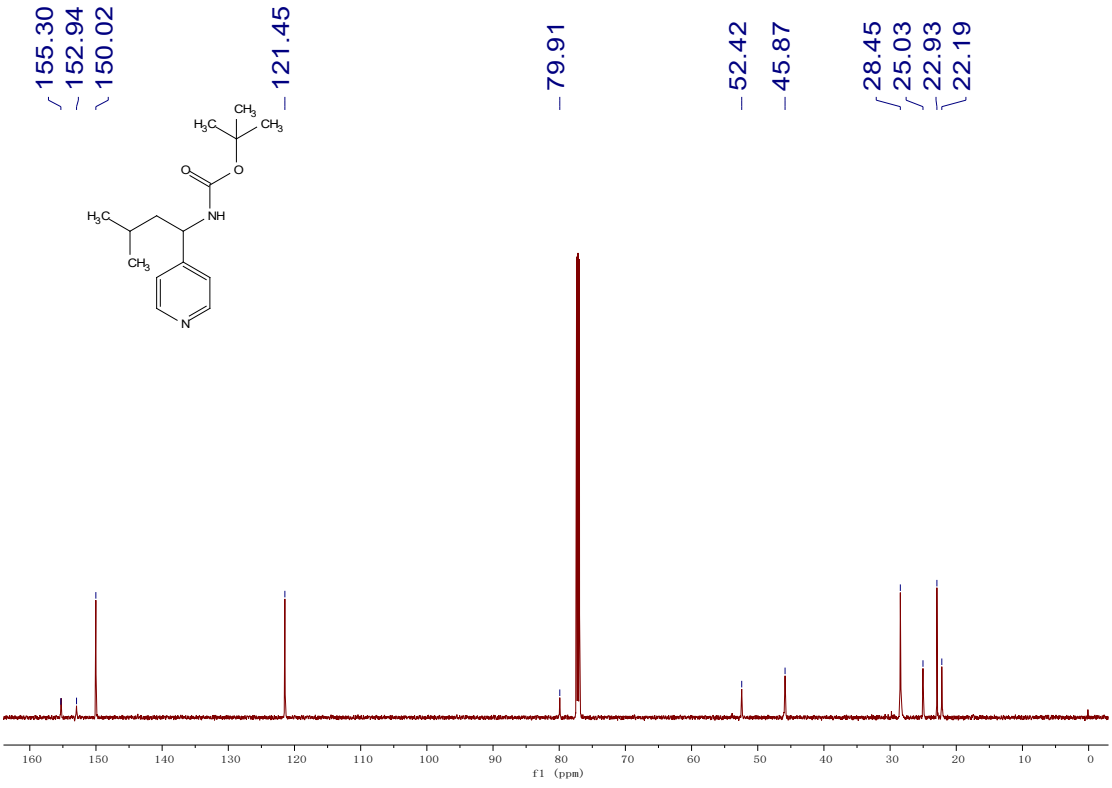

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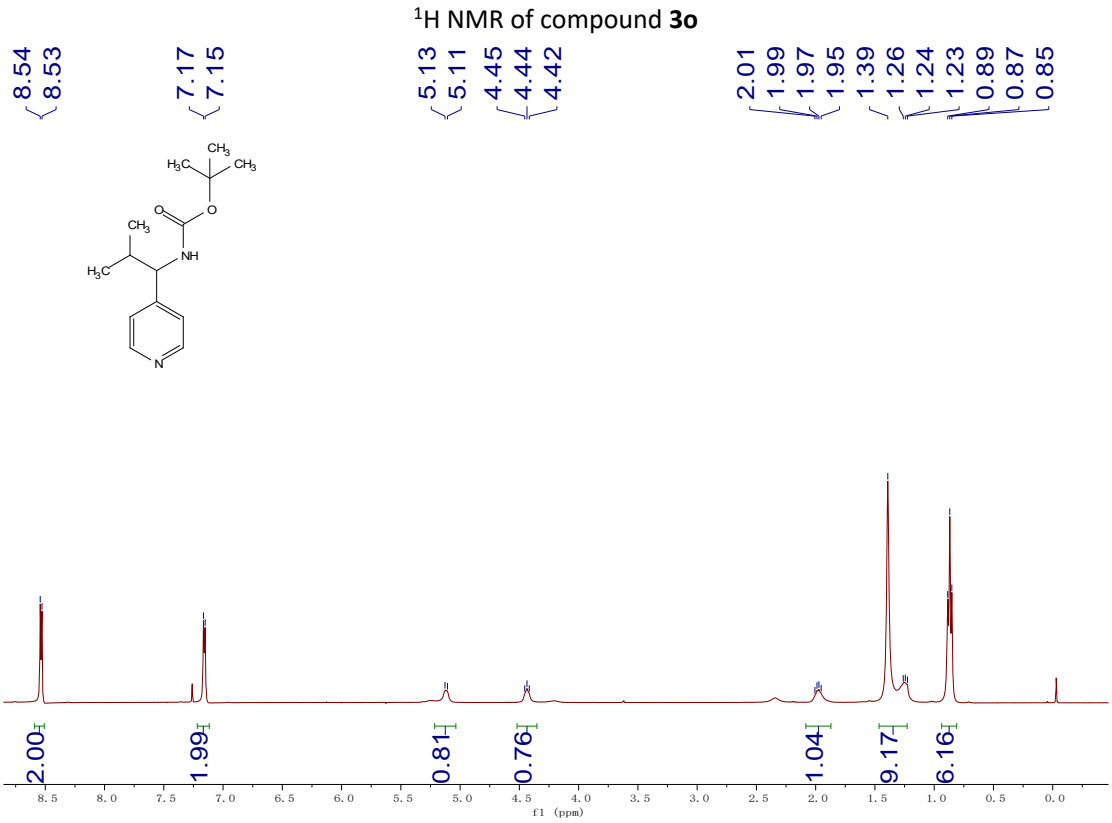
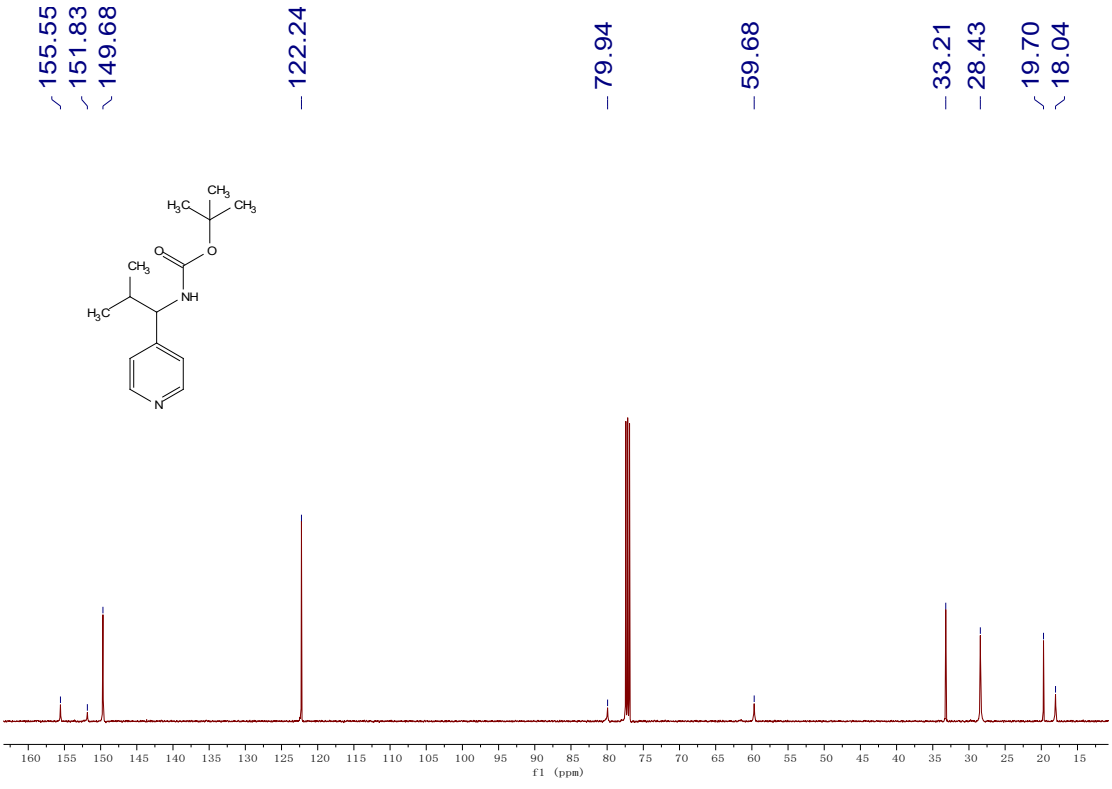
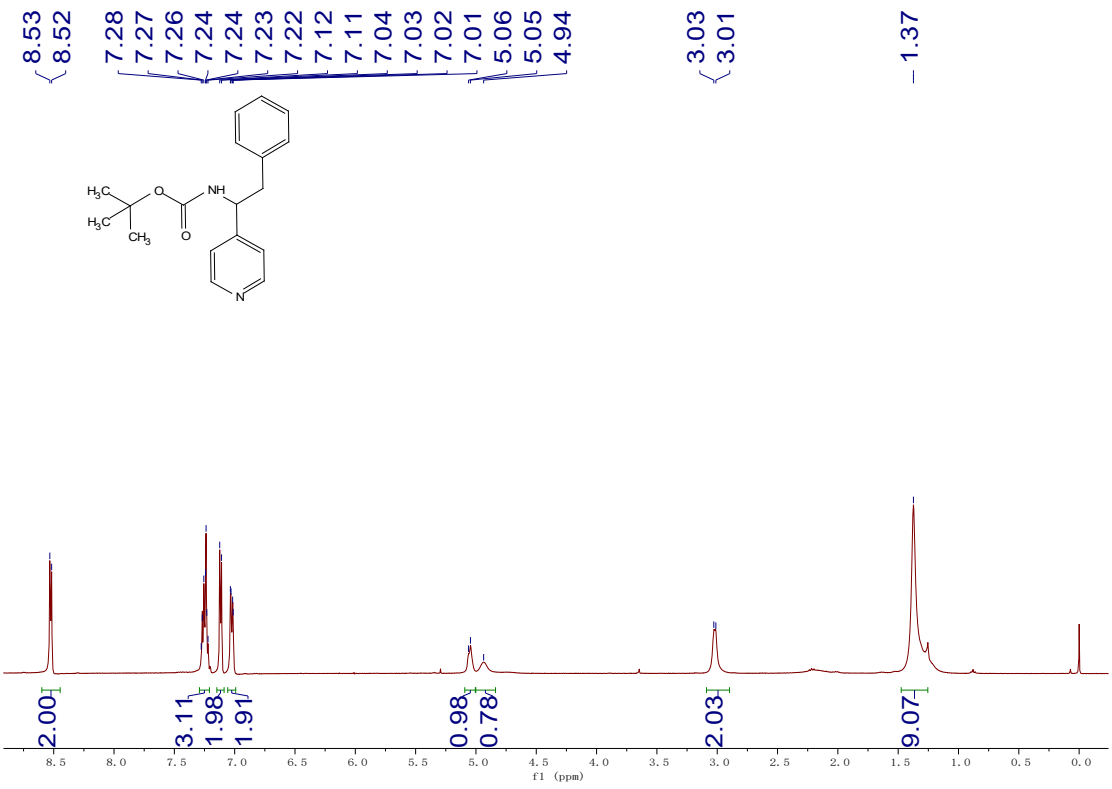


^{13}C NMR of compound **3o**



^{1}H NMR of compound **3p**



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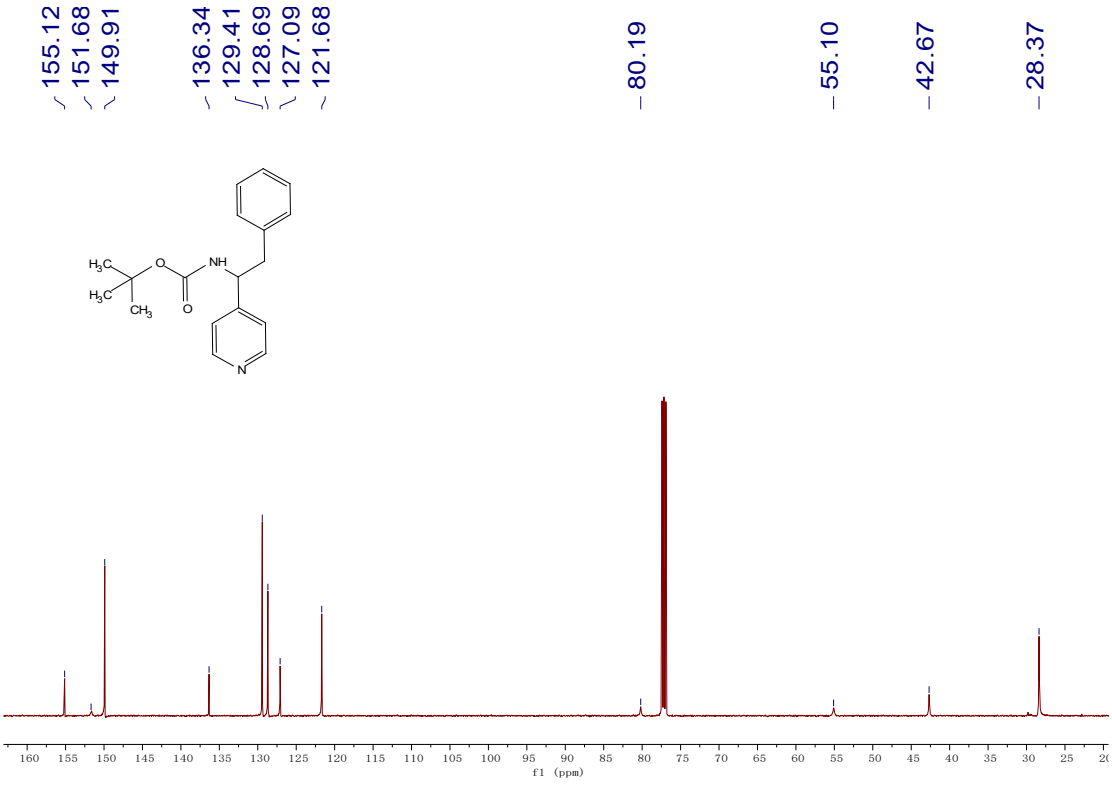
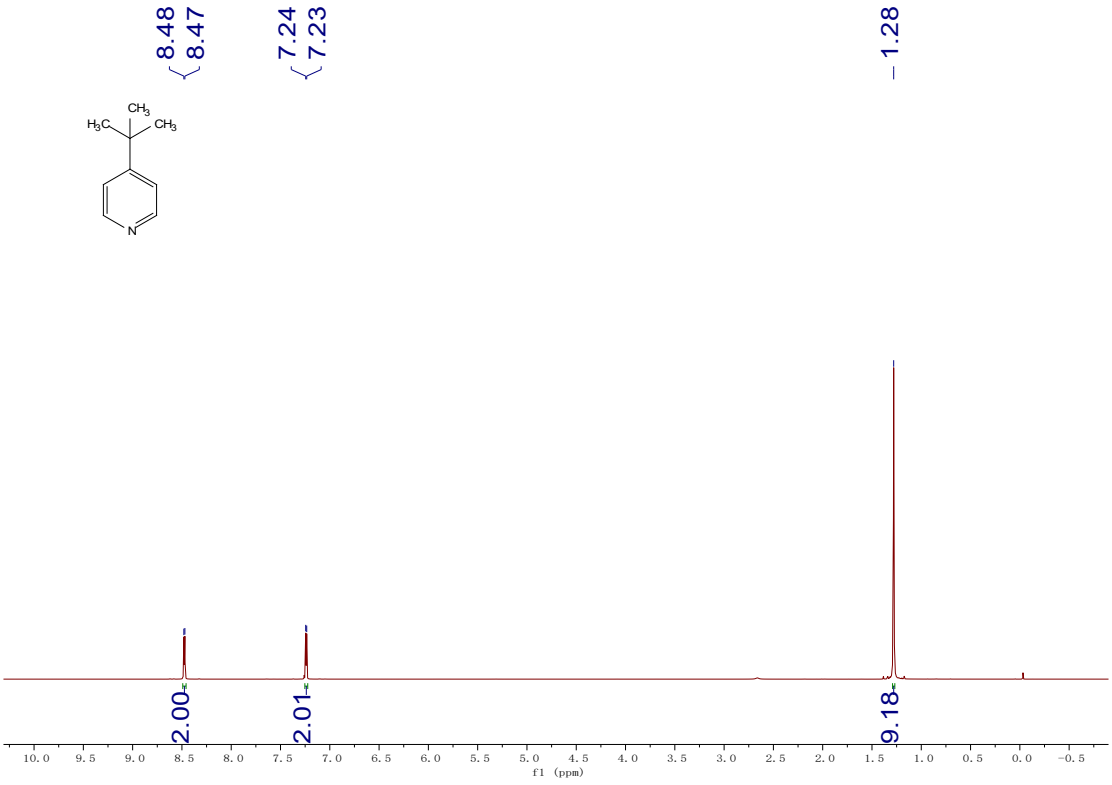


^{1}H NMR of compound **3q**



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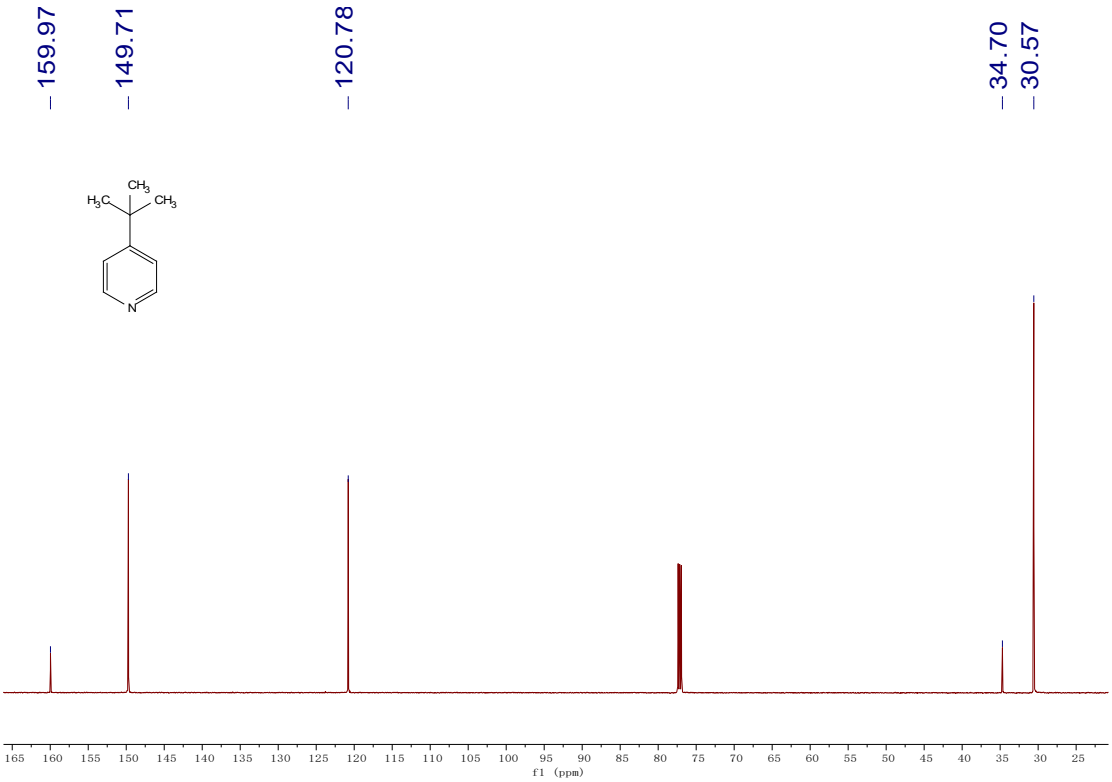
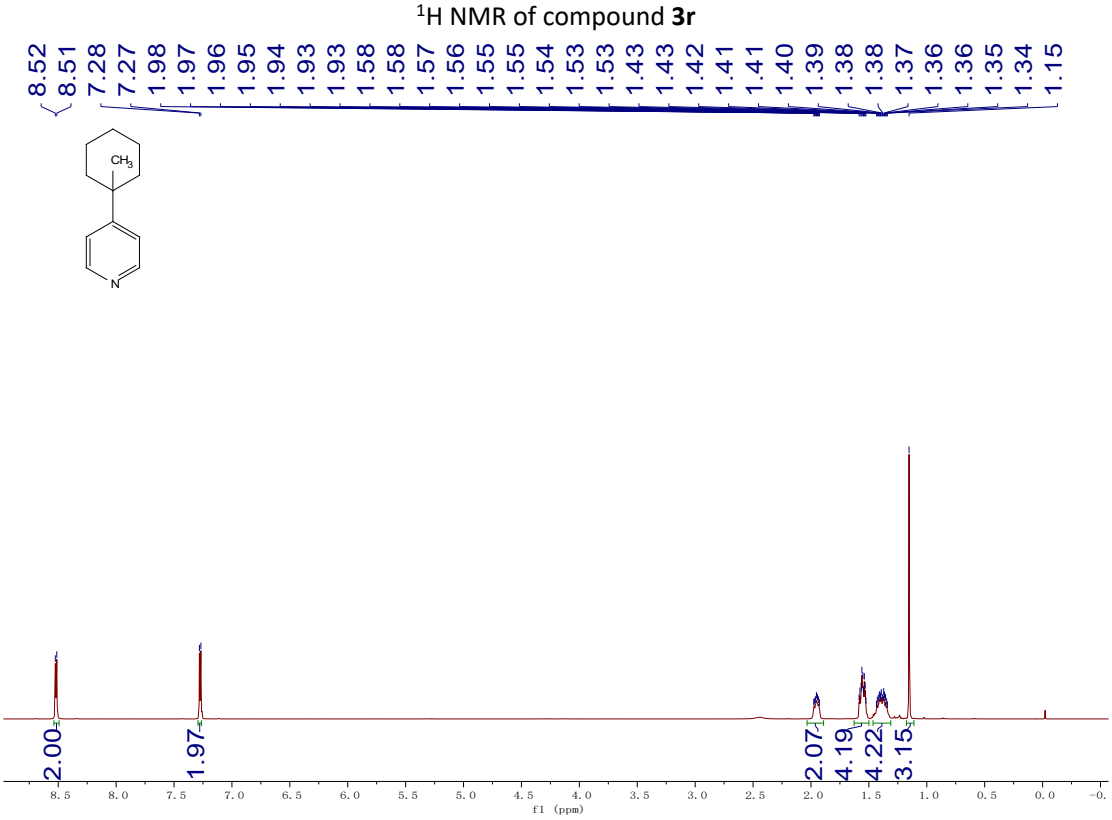


^{1}H NMR of compound **3r**



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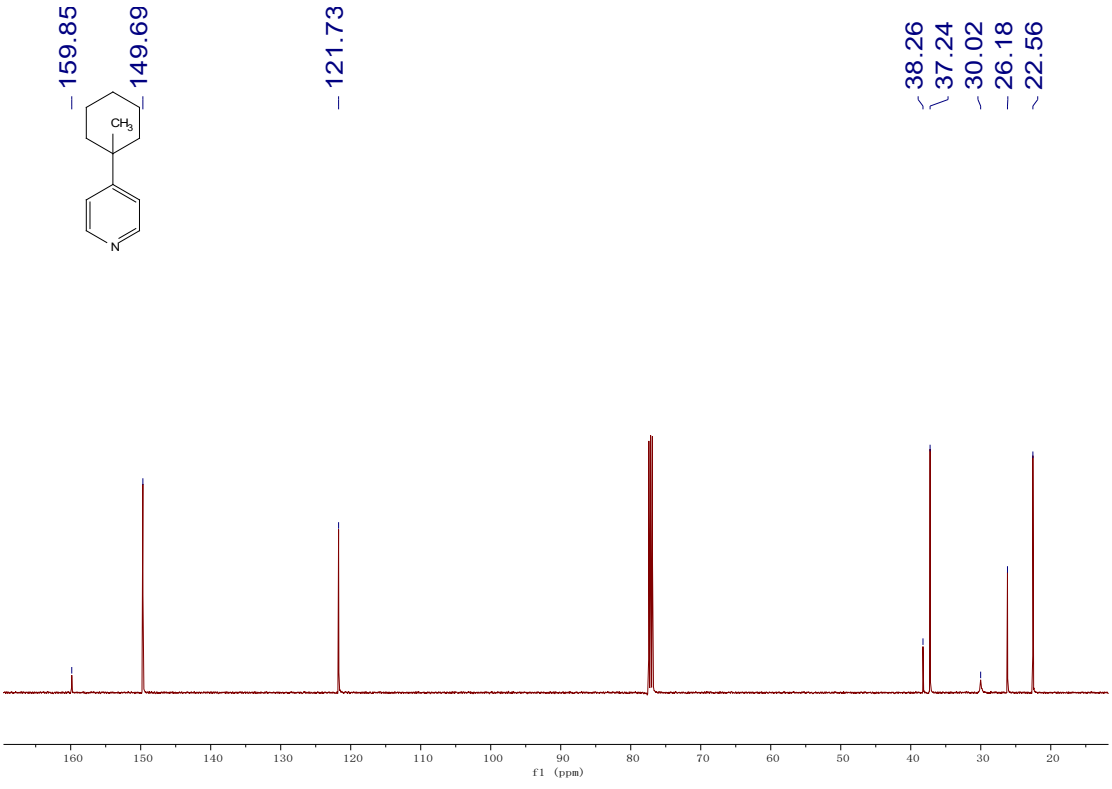

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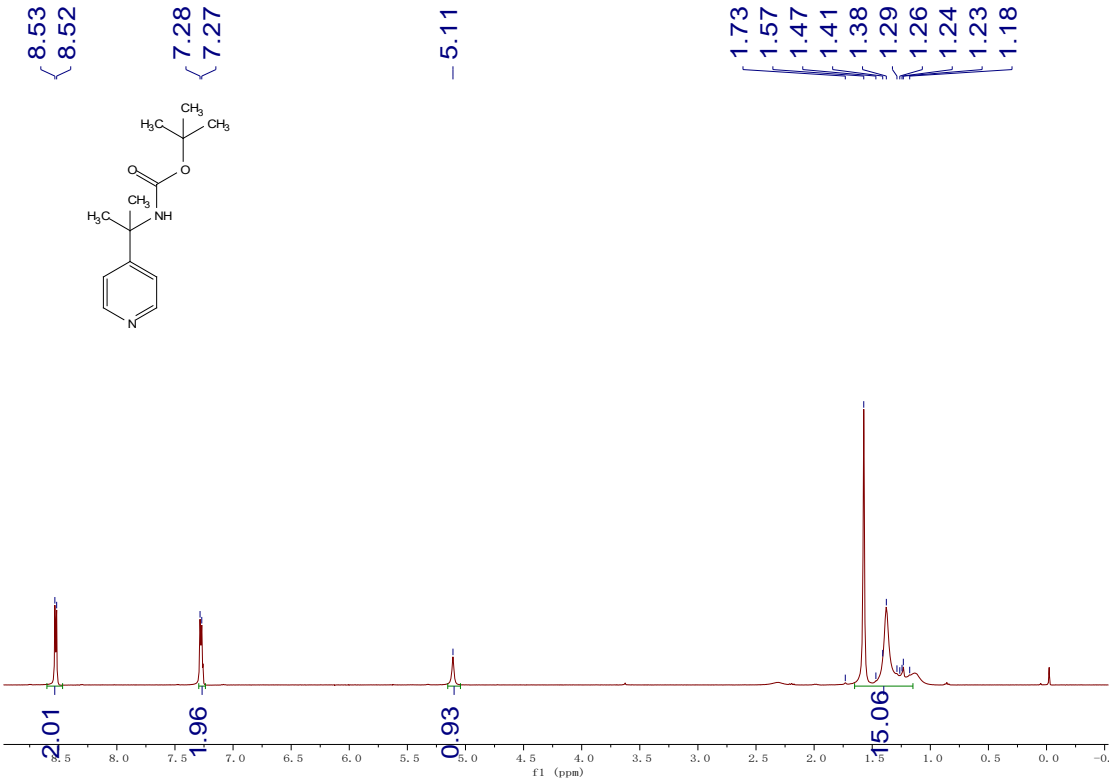

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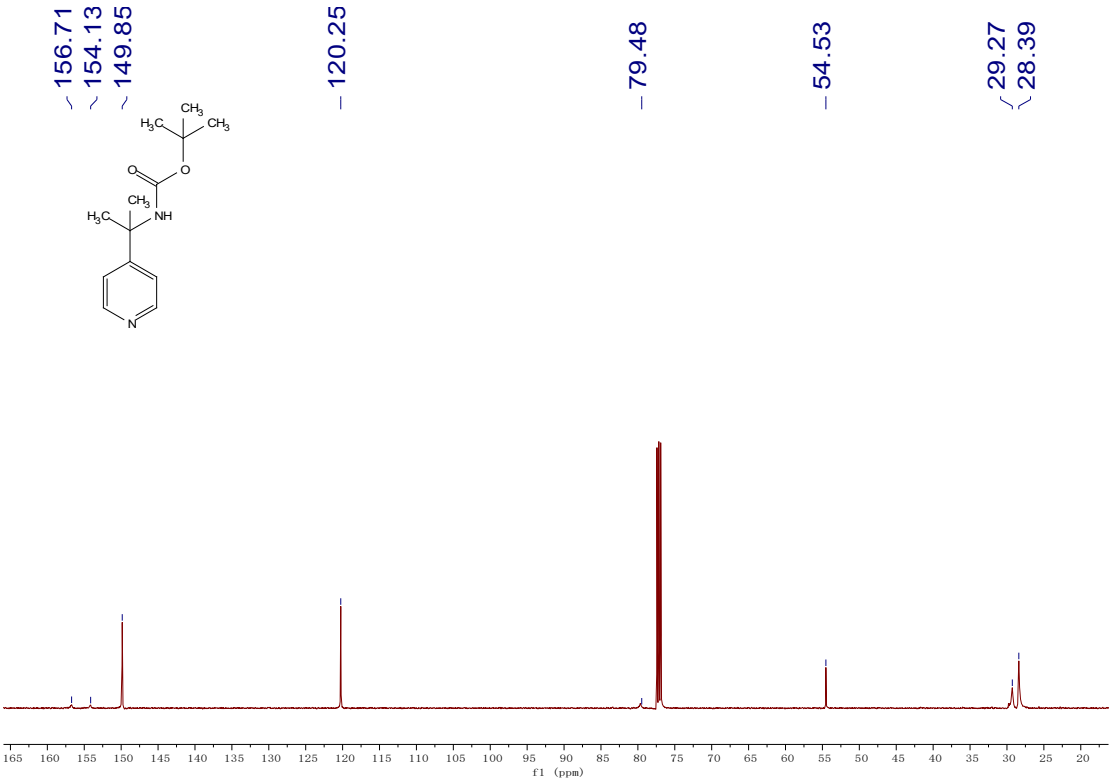
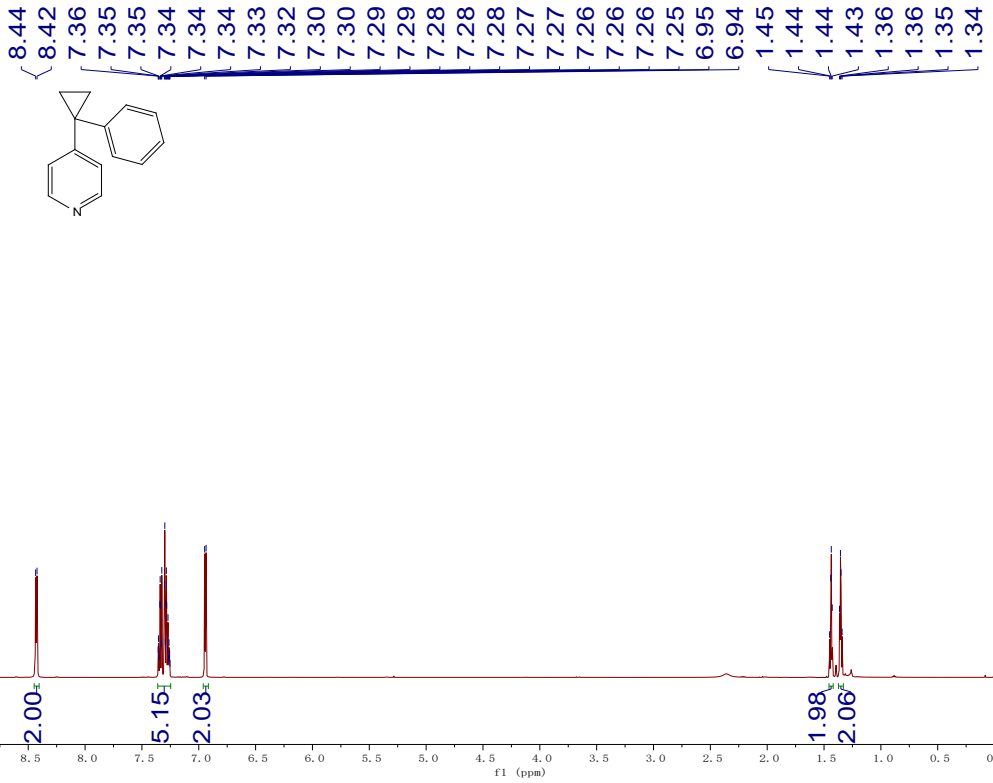


^{1}H NMR of compound **3t**



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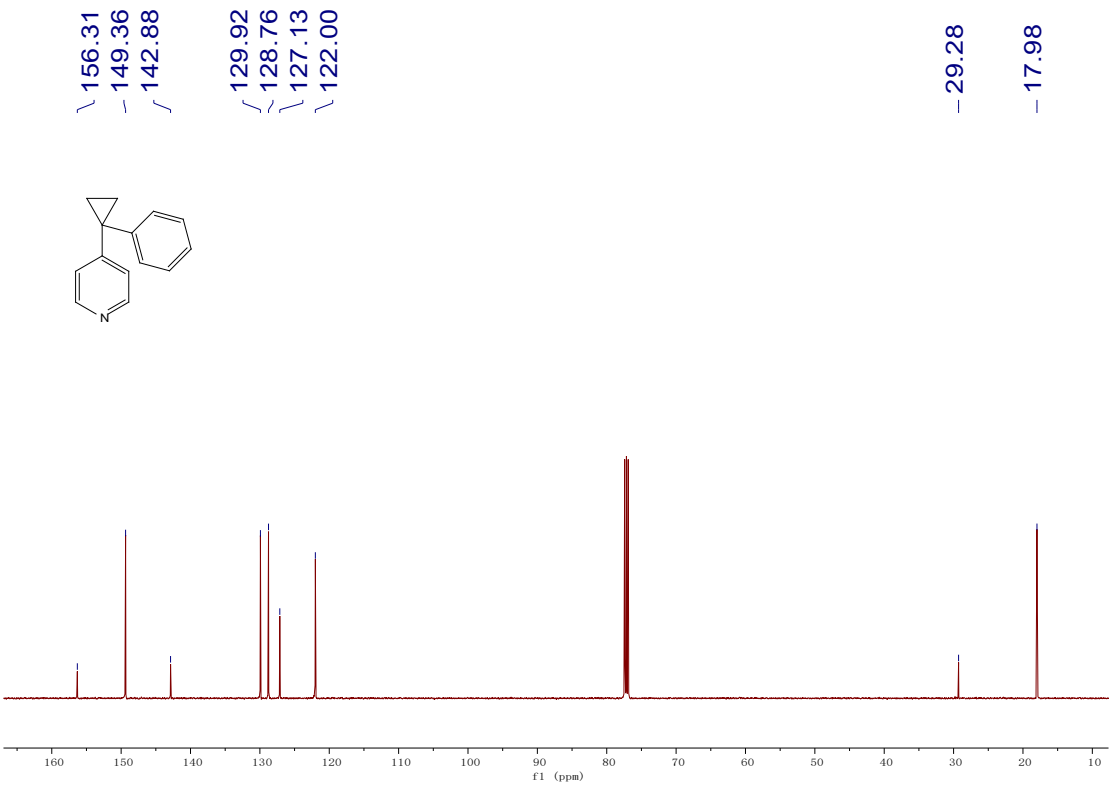
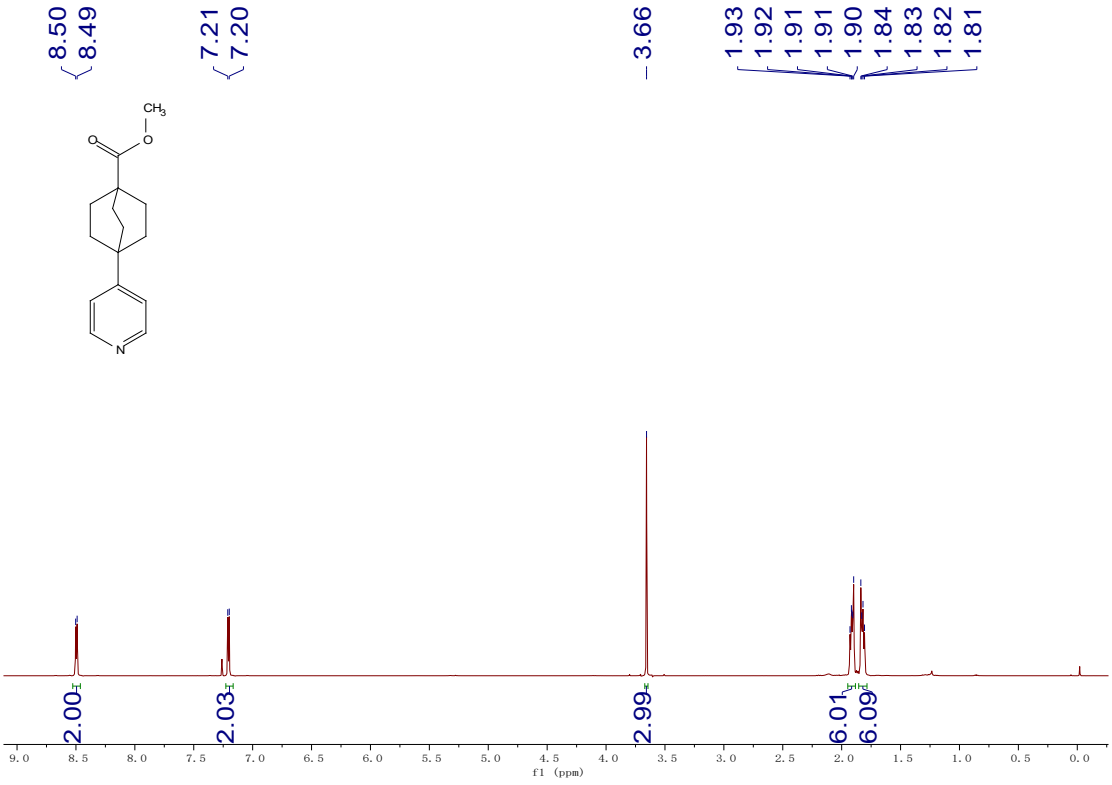


^{1}H NMR of compound **3u**



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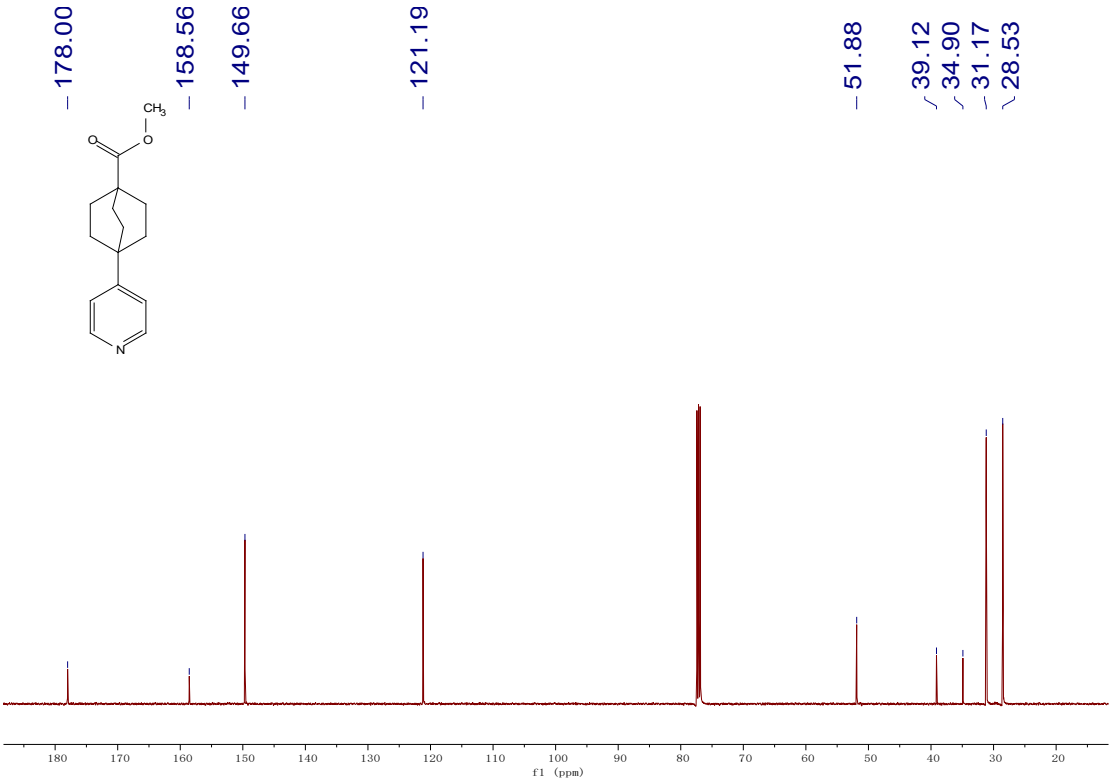

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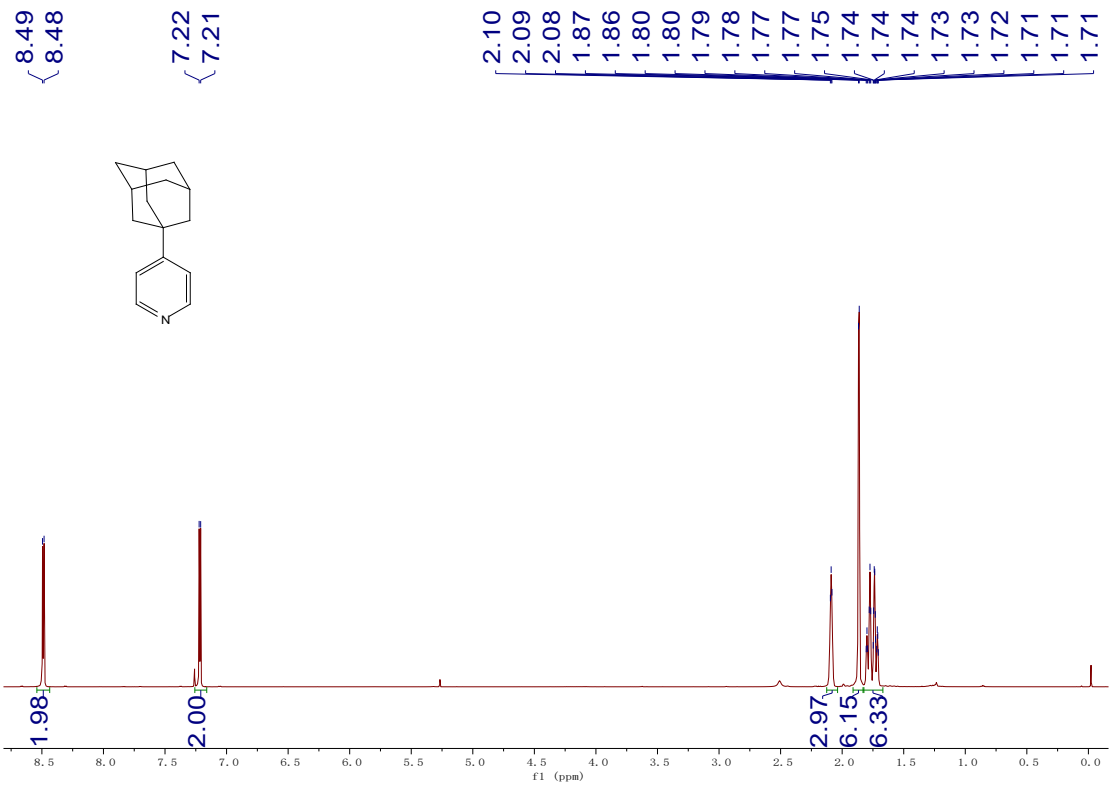

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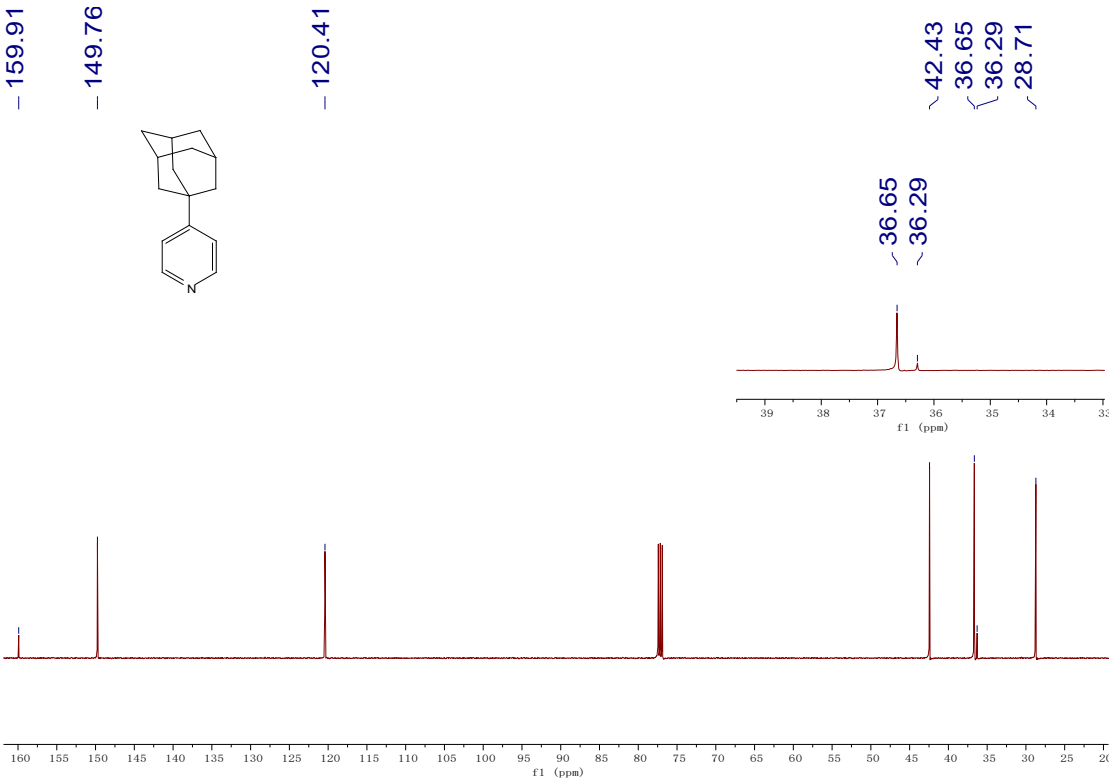

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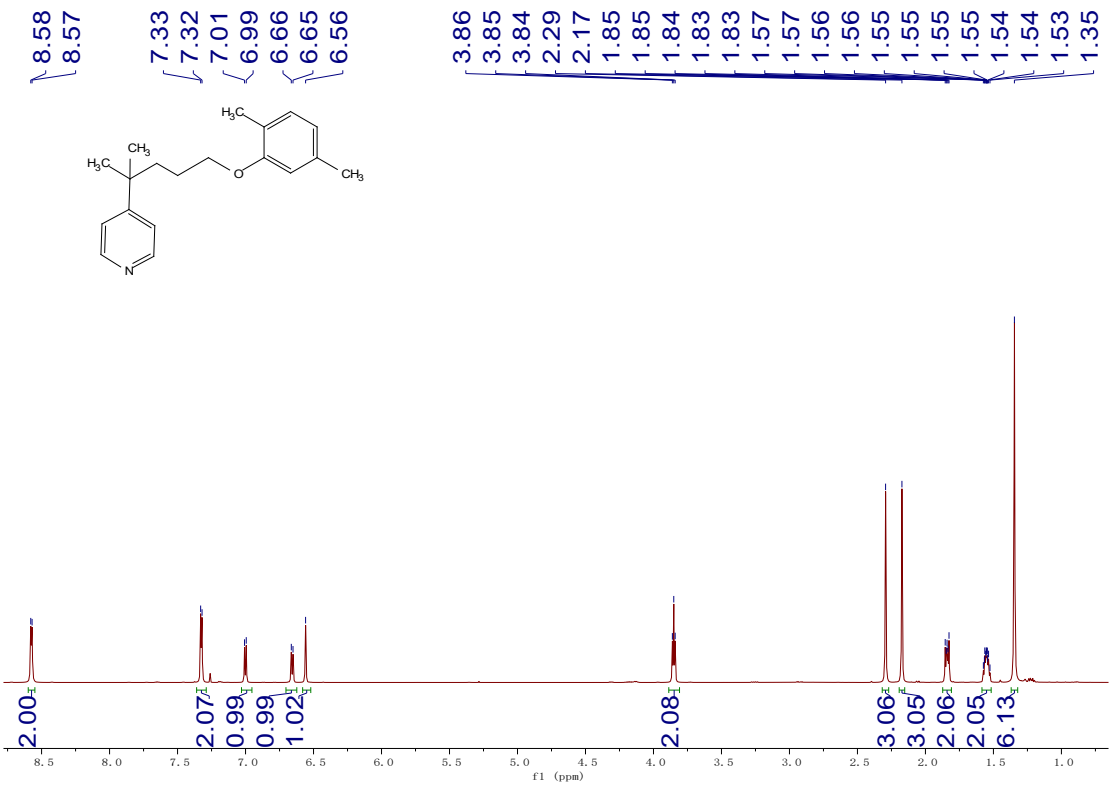

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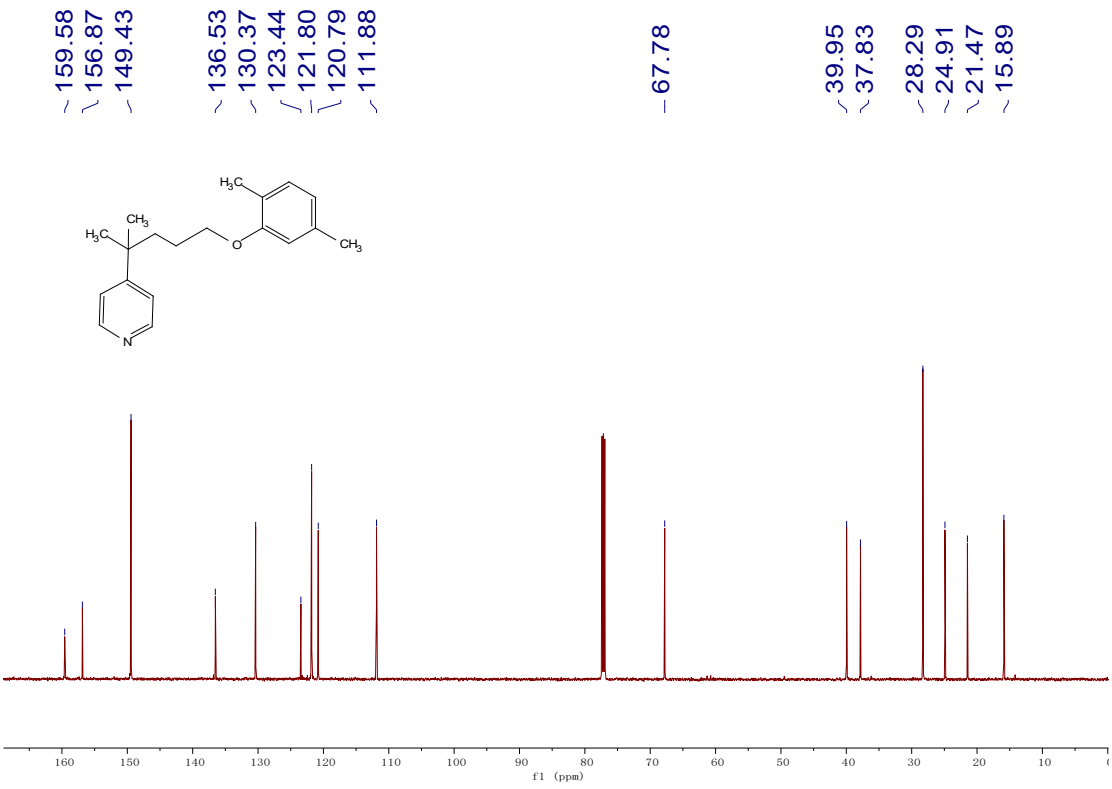
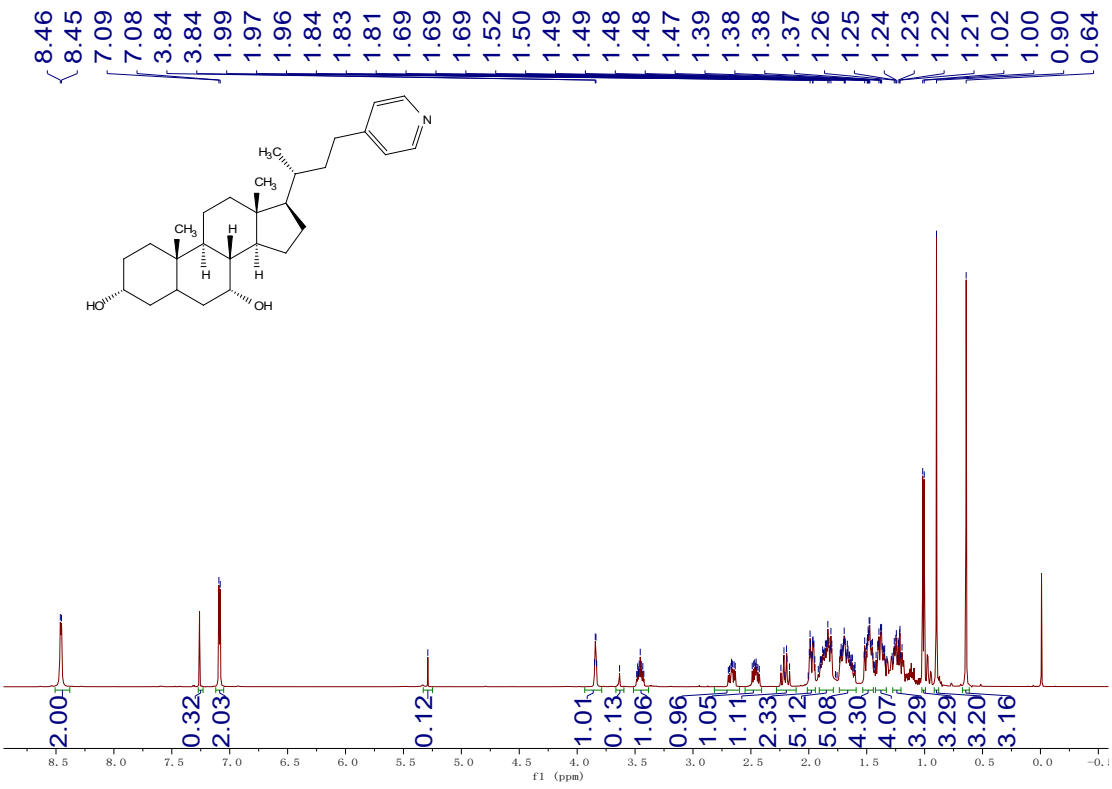
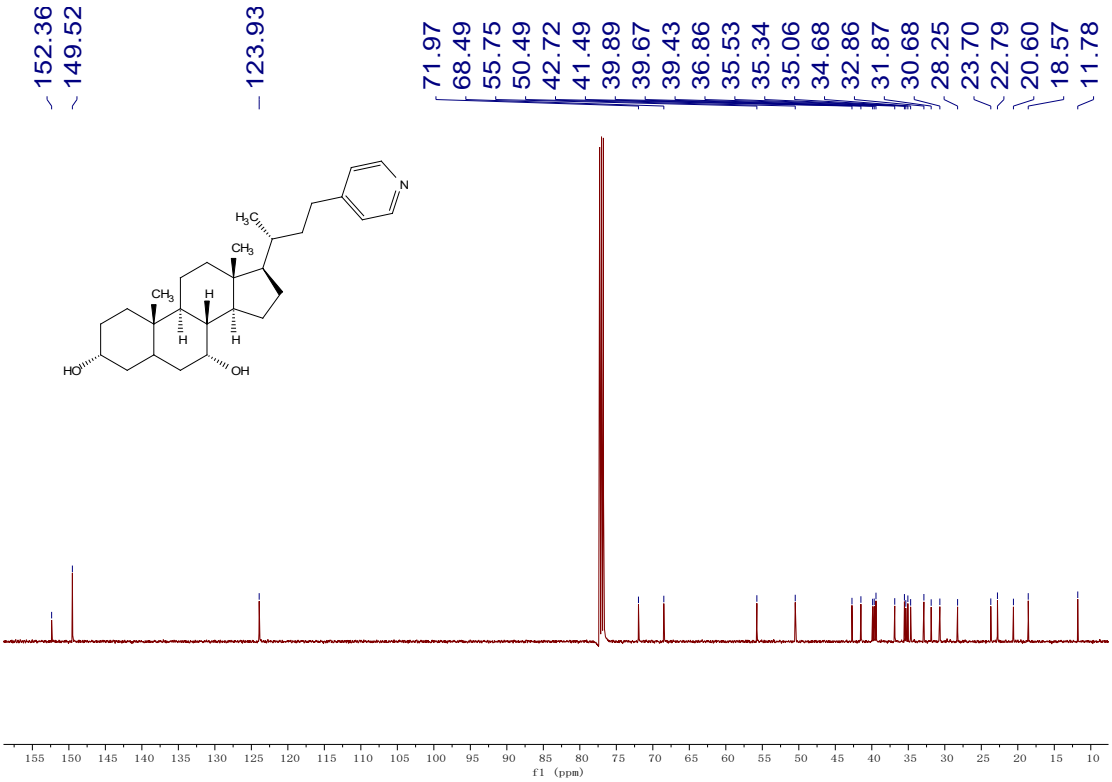


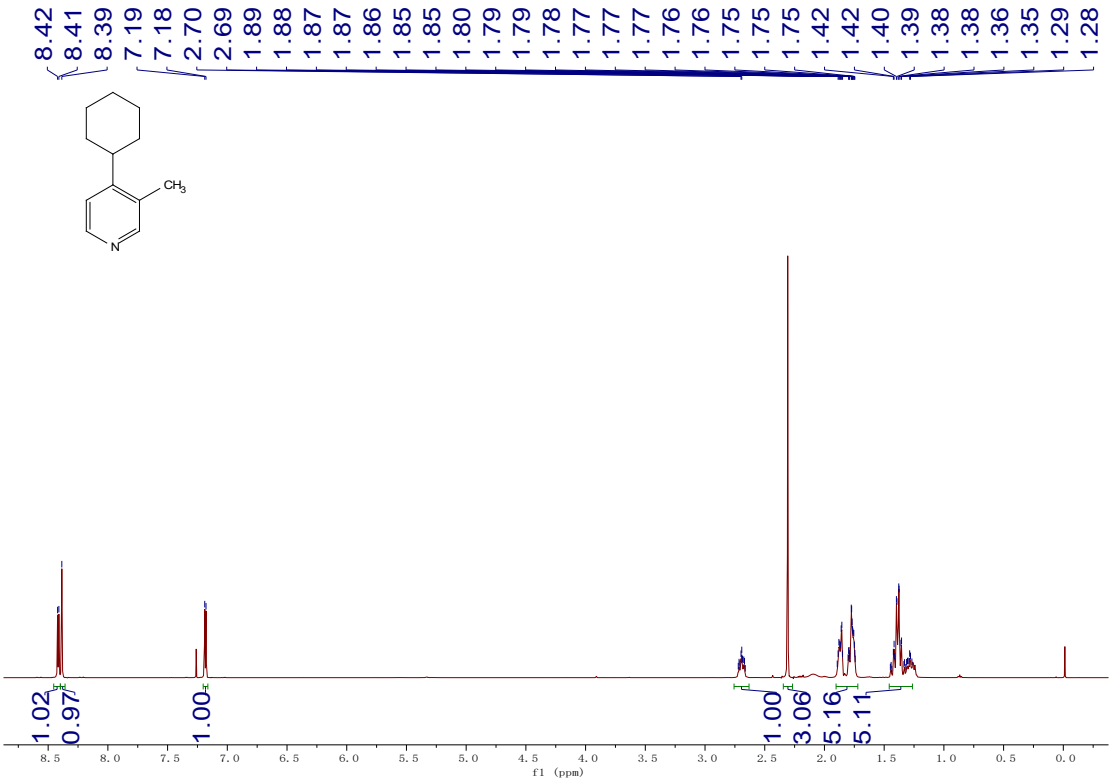
^{1}H NMR of compound **3x**



^{13}C NMR of compound **3x**



^{1}H NMR of compound **4a**



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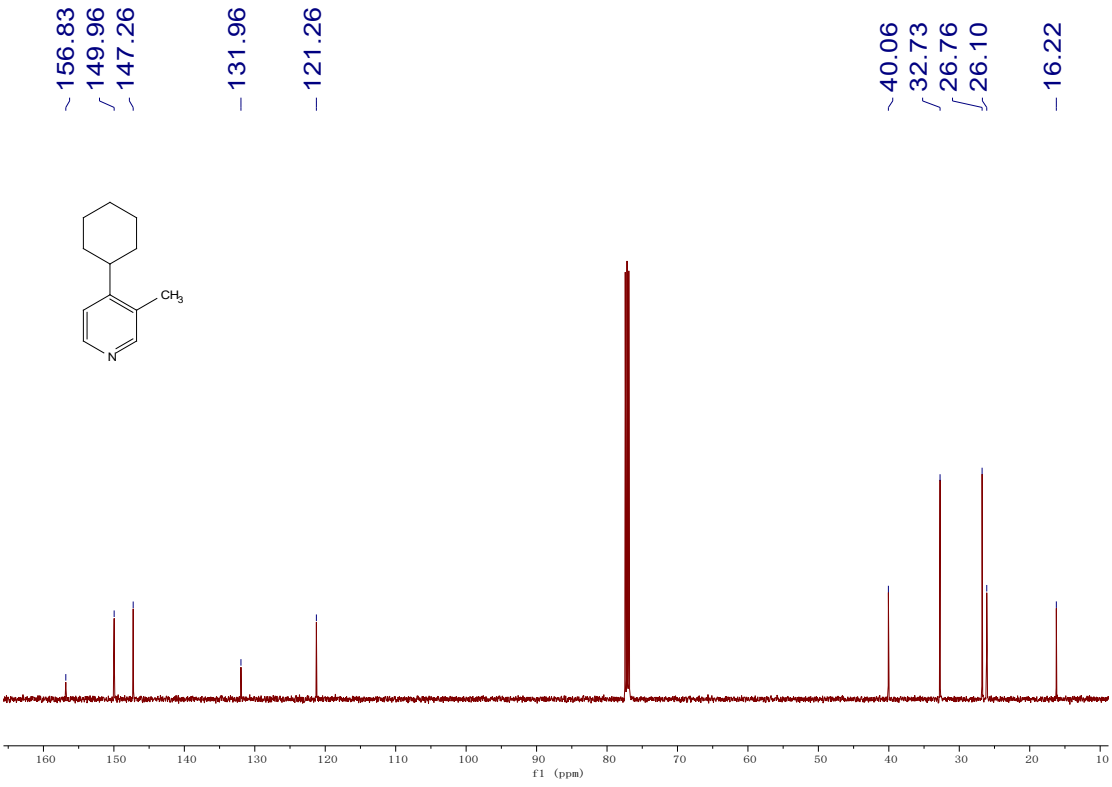
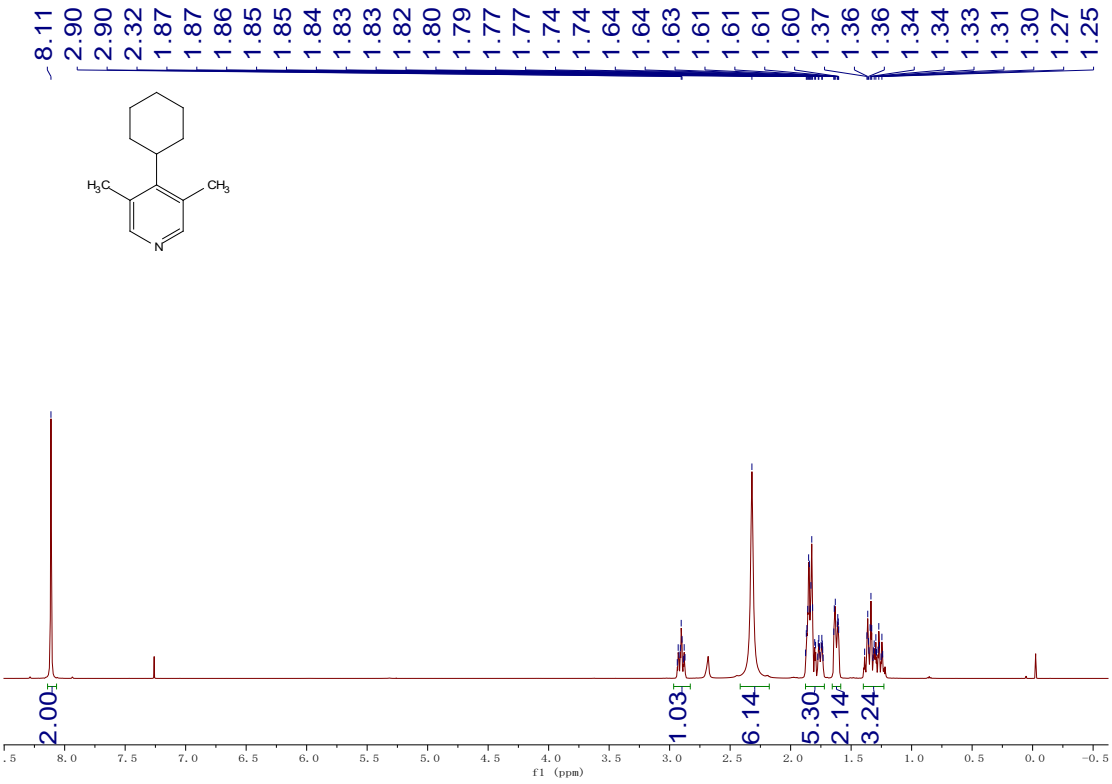


^{1}H NMR of compound **4b**



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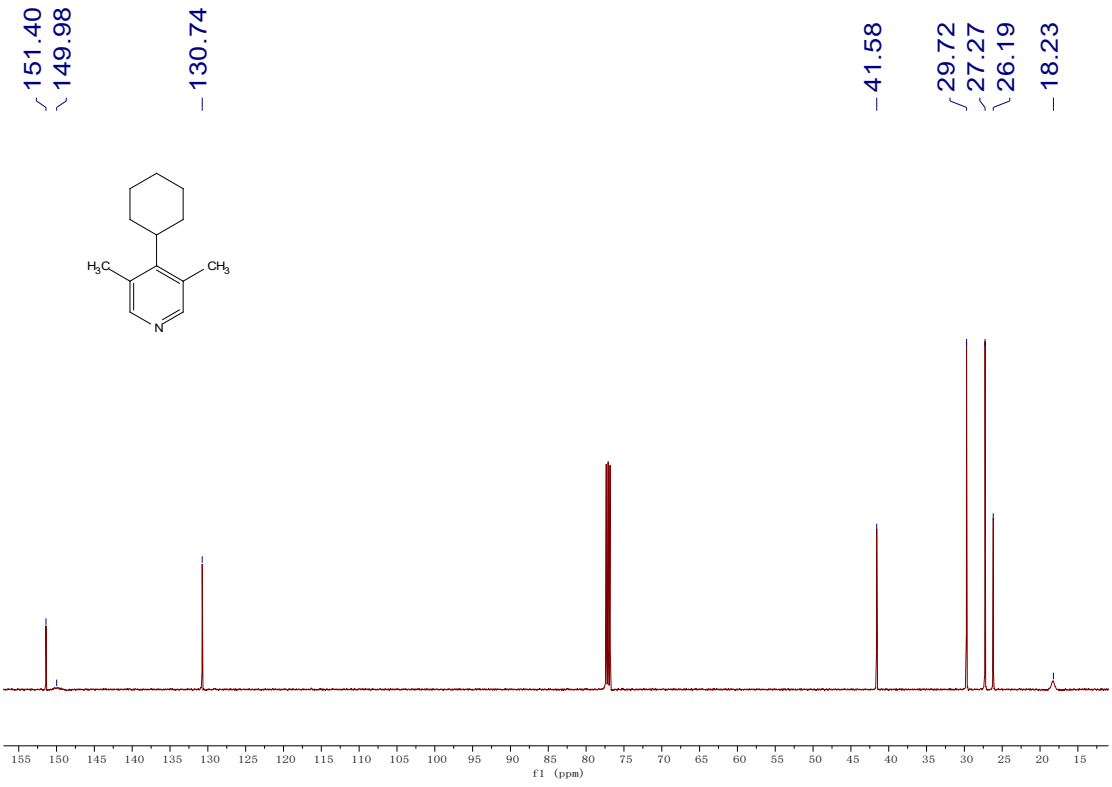
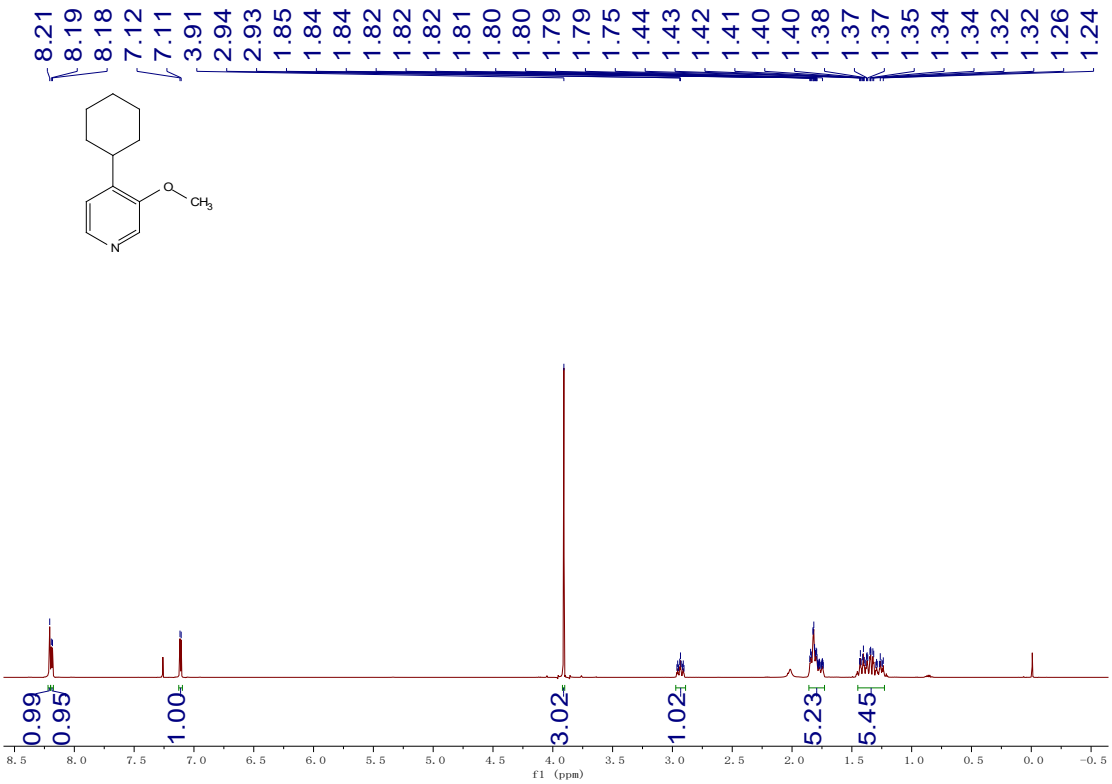


^{1}H NMR of compound **4c**



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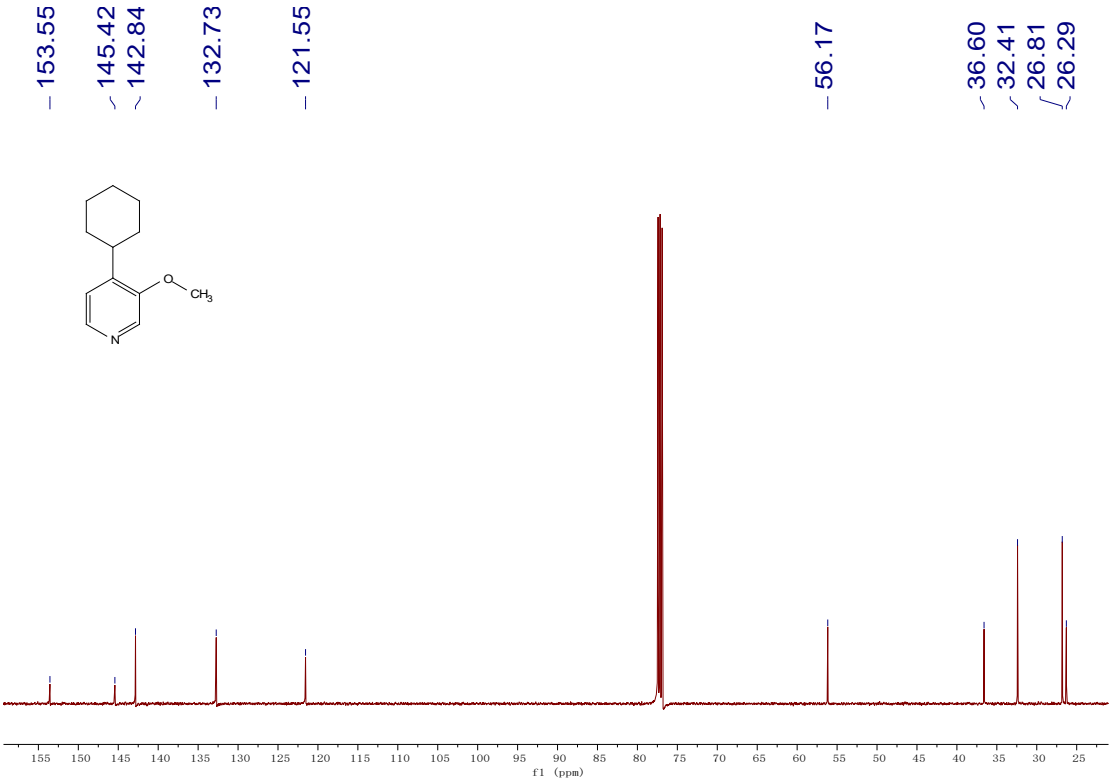
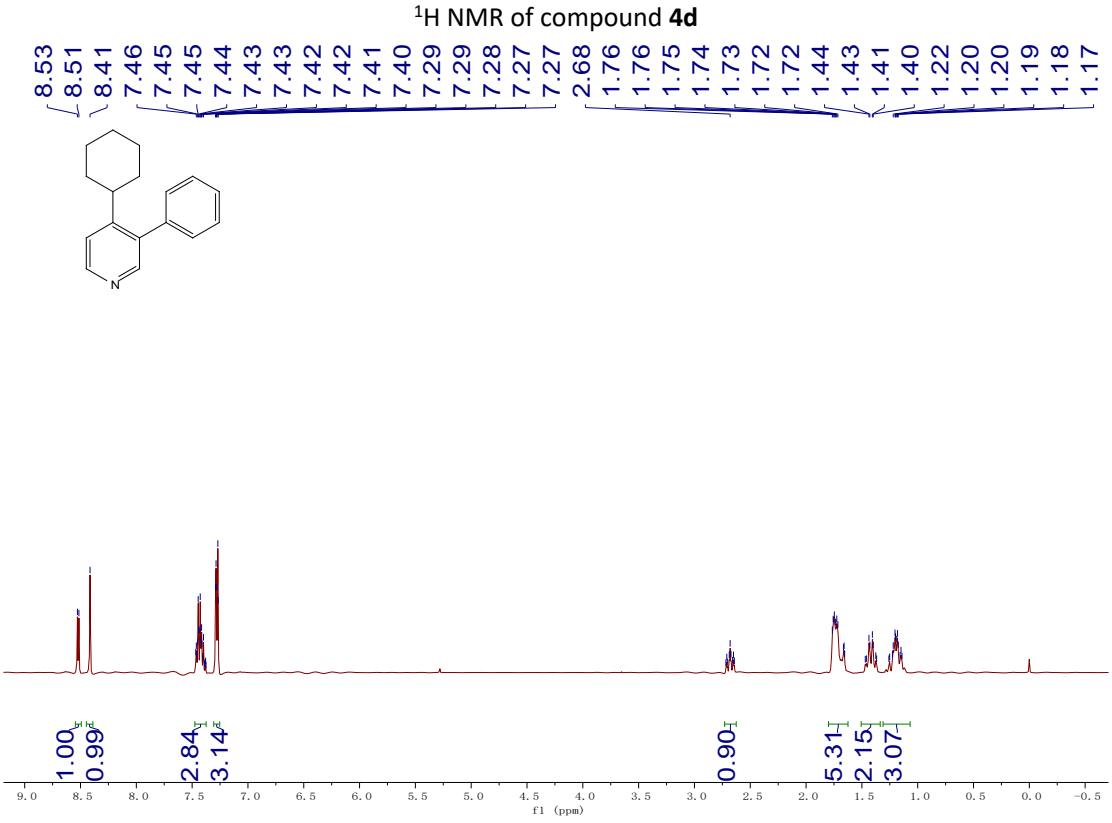
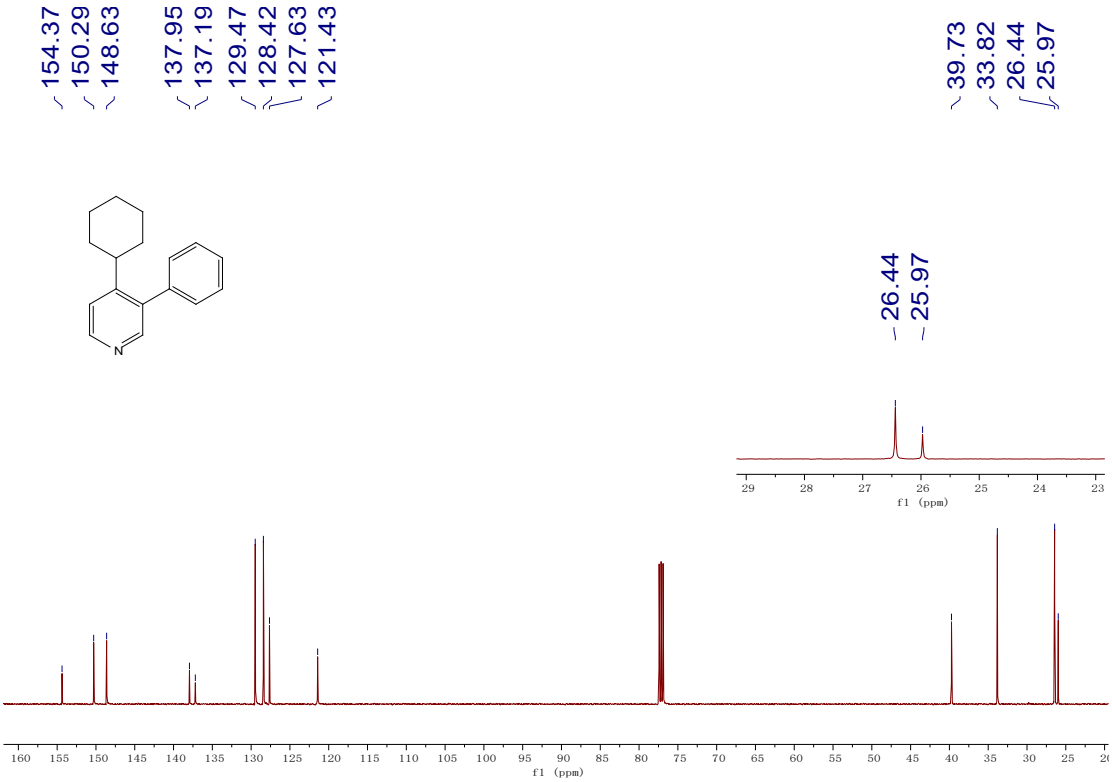


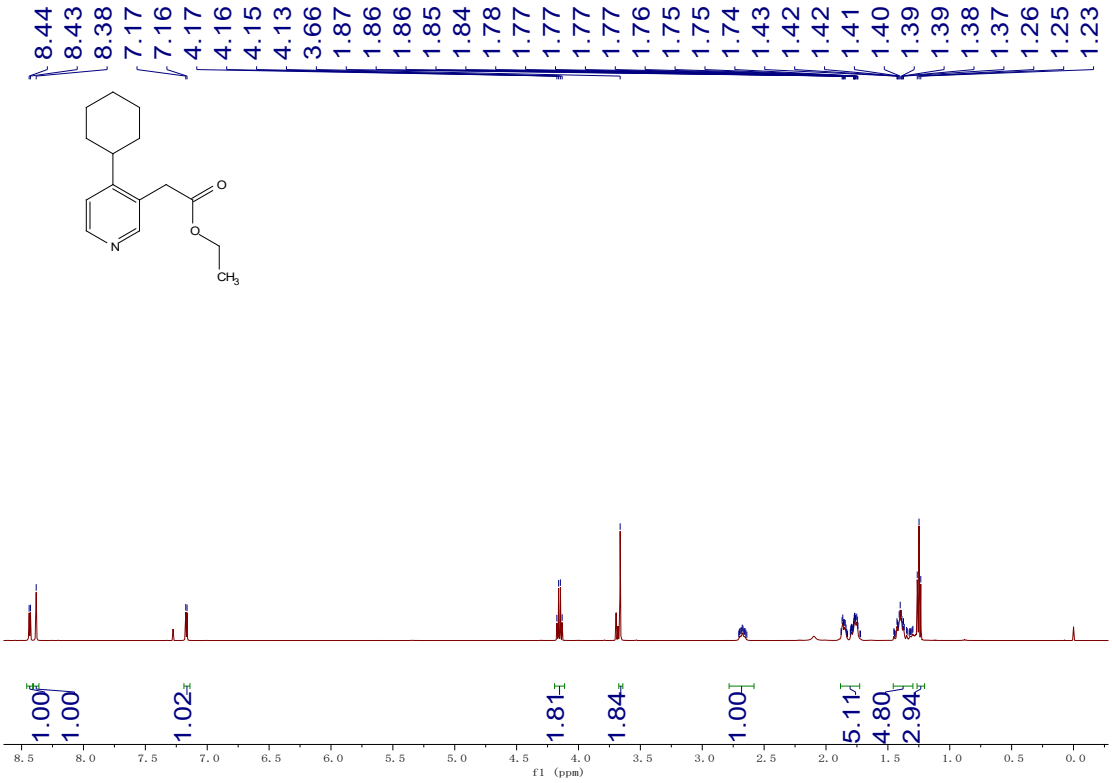
^{1}H NMR of compound **4d**



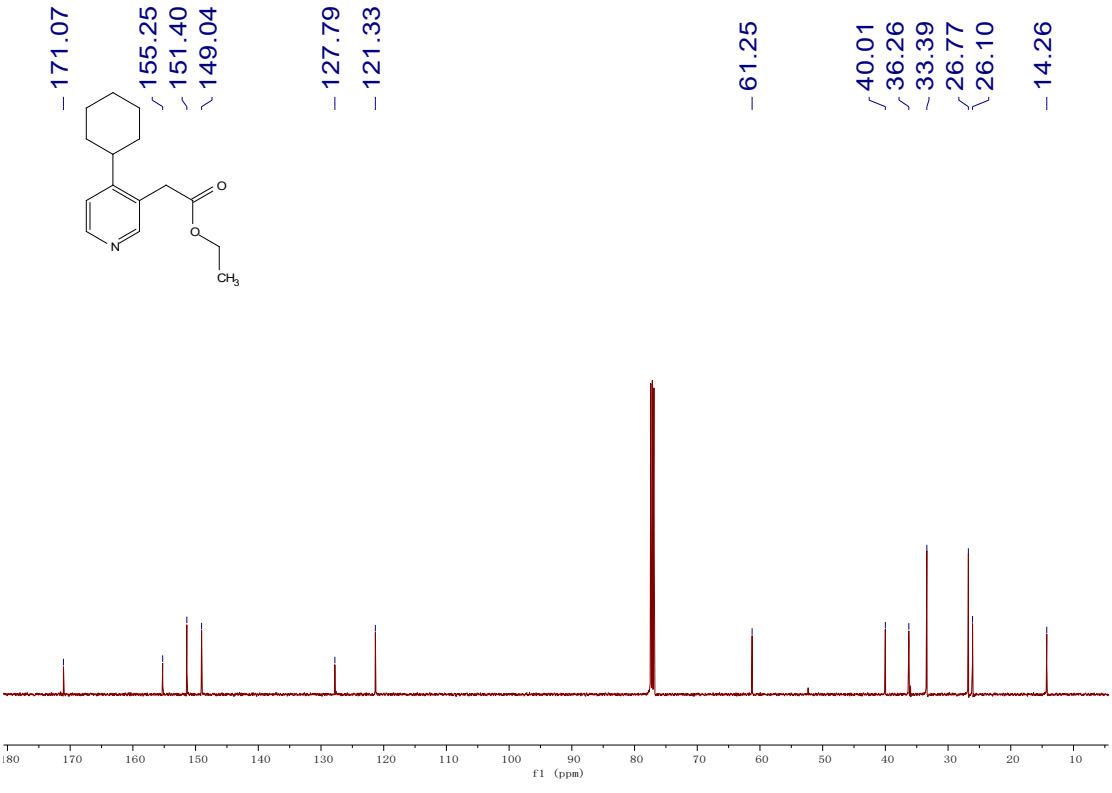
^{13}C NMR of compound **4d**



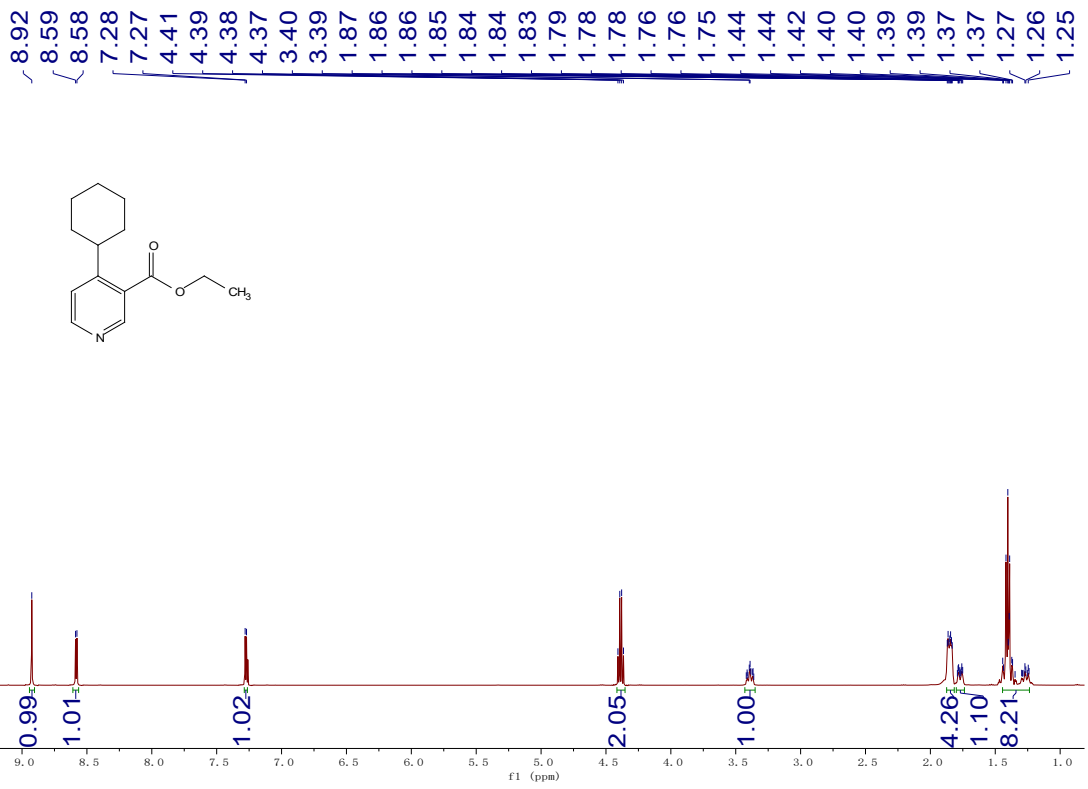
^{1}H NMR of compound **4e**



^{13}C NMR of compound **4e**



^{1}H NMR of compound **4f**



^{13}C NMR of compound **4f**