Supporting Information

Regioselective Copper-Catalyzed Dearomative Alkynylation of N-Alkyl Nicotinate and Isoquinoline Salts

Jun-Ju Mai, Fei Li, Xiasen Dong, Mingyuan Shi, Xiao-Jing Li, Hua-Dong Xu, Mei-Hua Shen* and Chi-Fan Zhu*

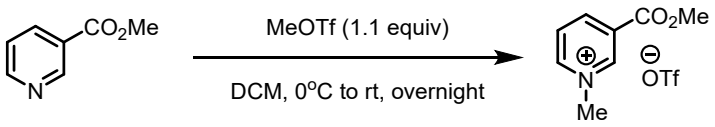
School of Pharmacy, Changzhou University, Changzhou, Jiangsu Province 213164, China. E-mail: shenmh@cczu.edu.cn, chifanzhu@cczu.edu.cn.

Table of Contents

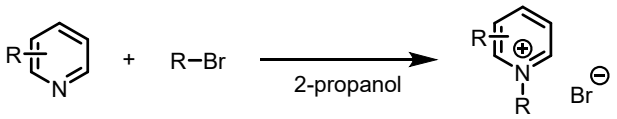
1. General Information and Materials

NMR spectra were recorded using Bruker AV-300 / AV-400/ AV-500 spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets), coupling constants (Hz) and integration. High resolution mass spectra were acquired on an agilent 6230 spectrometer and were obtained by peak matching. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator and/or by exposure to phosphormolybdic acid/cerium (IV) sulfate/ninhydrine followed by brief heating with a heat gun. Liquid chromatography (flash chromatography) was performed on 60Å (40-60 μm) mesh silica gel (SiO2). All reactions were carried out under nitrogen with anhydrous solvents in oven-dried glassware, unless otherwise noted. All reagents were commercially obtained and, where appropriate, purified prior to use

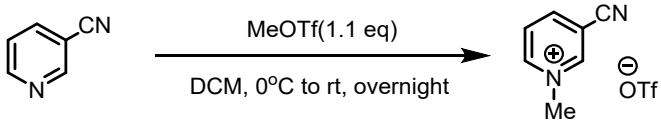
2.Synthesis of Pyridinium Salt:



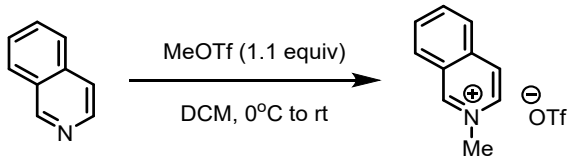
In a Schlenk flask, the specified nicotinic ester (1.0 equiv.) was dissolved in CH_2Cl_2 (0.1M) and cooled to 0 ℃ in an ice water bath. MeOTf (1.1 equiv.) was added slowly via syringe and the reaction mixture was stirred overnight allowing it to warm to ambient temperature. 1/3 of the CH_2Cl_2 was removed under reduced pressure and obtained oil was slowly added to a beaker containing rapidly stirring Et_2O (50 mL). Stirring was continued for additional 30 min at which point, the initial thick oil solidified. This solid was filtered and washed with Et_2O (50 mL) to give pyridinium salt [1].



Specified nicotinic ester (1.0 equiv) was dissolved in 2-propanol (48 mL). Bromo compound (1.0 equiv) was added over 5 min and the reaction mixture was stirred for 18h at room temperature. diethyl ether (200 mL) was added to the slurry and the suspension was filtered, washed 5 times with diethyl ether and dried on frit under nitrogen flow for 18 h to afford 1-benzyl-3-(methoxycarbonyl) pyridinium bromide as a white solid[2] 。



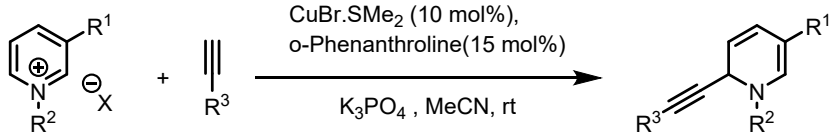
In a Schlenk flask, the specified 3-Cyanopyridine (1.0 equiv.) was dissolved in CH_2Cl_2 (0.1M) and cooled to 0 ℃ in an ice water bath. MeOTf (1.1 equiv.) was added slowly via syringe and the reaction mixture was stirred overnight allowing it to warm to ambient temperature. 1/3 of the CH_2Cl_2 was removed under reduced pressure and obtained oil was slowly added to a beaker containing rapidly stirring Et_2O (50 mL). Stirring was continued for additional 30 min at which point, the initial thick oil solidified. This solid was filtered and washed with Et_2O (50 mL) to give pyridinium salt[1].



To a flame dried 50 ml round-bottom flask under argon atmosphere, isoquinoline (2.0 mmol, 1.0 equiv) was taken followed by dry DCM (10 ml). The solution was cooled to 0 ° C, and methyl trifluoromethanesulfonate (3.0 mmol, 1.5 equiv) was added dropwise via syringe. The reaction mixture was 3 slowly warmed to room temperature with TLC monitoring. Upon consumption of starting material, DCM was removed under reduced pressure, and the residue was washed with diethyl ether (3-5 times) to remove low polar impurities to obtain pure salt. In few cases, the ether wash was not sufficient, and the salts were purified by flash column chromatography using 5-10% methanol in DCM as the eluting solvent[3].

3 Preparation and Characterization of the products

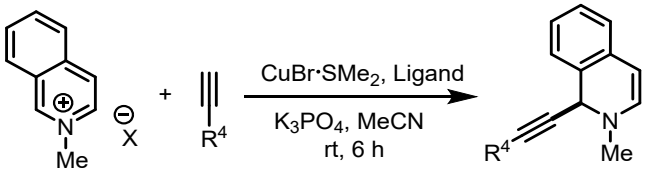
General procedure for synthesis of 3a-r



1 **2** **3a-3r**

A 10 mL Schlenk tube containing a stirring bar was charged with $CuBr.SMe_2$ (0.1 equiv., 0.03 mmol), *o*-Phenanthroline (0.15 equiv., 0.045 mmol), substituted Pyridinium salt **1** (0.3 mmol), K_3PO_4 (2.0 equiv., 0.6 mmol). The tube was then evacuated and back-filled with argon three times. Then substituted Phenylacetylene **2** (0.6 mmol in 1mL anhydrous MeCN) was added to the tube under nitrogen atmosphere, and stirred at room temperature for 10 h. After the reaction was completed (monitored by TLC), the reaction mixture was filtered with diatomite and purified by column chromatography on silica gel (PE : EA = 20:1) to give the desired product.

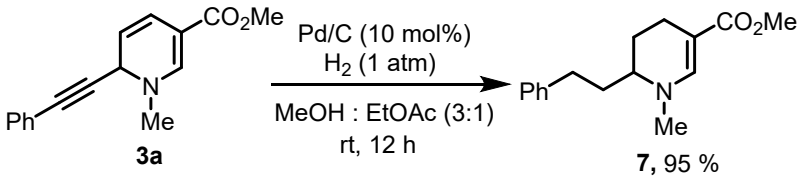
General procedure for synthesis of 6a-j



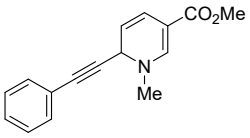
4 **5** **6a-6j**

A 10 mL Schlenk tube containing a stirring bar was charged with $CuBr.SMe_2$ (0.1 equiv., 0.03 mmol), *o*-Phenanthroline (0.15 equiv., 0.045 mmol), substituted Isoquinolinium salt **4** (0.3 mmol), K_3PO_4 (2.0 equiv., 0.6 mmol). The tube was then evacuated and back-filled with argon three times. Then substituted Phenylacetylene **5** (0.6 mmol in 1mL anhydrous MeCN) was added to the tube under nitrogen atmosphere, and stirred at room temperature for 10 h. After the reaction was completed (monitored by TLC), the reaction mixture was filtered with diatomite and purified by column chromatography on silica gel (PE : EA = 50:1) to give the desired product.

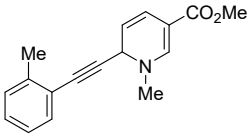
General procedure for synthesis of sismethyl 1-methyl-6-phenethyl-1,4,5,6-tetrahydropyridine-3-carboxylate



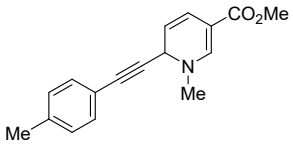
A sealed vial (20 mL) with a magnetic stirbar was charged with **3a** (253 mg, 0.998 mmol, 1.0 equiv.), 10% Pd/C (106 mg, 0.099 mmol, 0.1 equiv.), and 3:1 MeOH : EtOAc (1.5 mL : 0.5 mL). The reaction was stirred under H_2 at room temperature for Overnight and filtered over celite. The solids were rinsed with EtOAc (10 mL) and the resulting filtrate was concentrated under reduced pressure and purified via flash column chromatography to afford **7** as an yellowish oil.



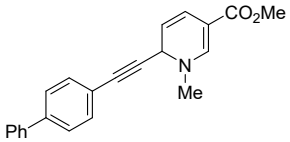
methyl 1-methyl-6-(phenylethynyl)-1,6-dihydropyridine-3-carboxylate(3a): yellowish oil; 63.0 mg, 83 %, 3a:3a' = 25:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3a) δ 7.43–7.39 (m, 2H), 7.34–7.28 (m, 3H), 7.26 (s, 1H), 6.46 (d, J = 9.2 Hz, 1H), 5.18–5.09 (m, 2H), 3.69 (s, 3H), 3.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 146.8, 131.8, 128.6, 128.3, 122.3, 122.0, 109.8, 96.8, 51.4, 50.8, 41.6. HRMS (EI^+): calcd. for $[C_{16}H_{16}NO_2]^+$: 254.1176, found: 254.1177.



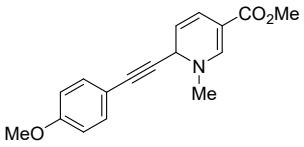
methyl 1-methyl-6-(o-tolylethynyl)-1,6-dihydropyridine-3-carboxylate(3b): yellowish oil; 56.9 mg, 71 %, 3b:3b' = 26:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3b) δ 7.37 (d, J = 7.6 Hz, 1H), 7.28–7.26 (m, 1H), 7.24–7.16 (m, 2H), 7.14–7.09 (m, 1H), 6.49–6.43 (m, 1H), 5.22–5.11 (m, 2H), 3.69 (s, 3H), 3.10 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 146.7, 140.3, 132.0, 129.4, 128.6, 125.5, 122.1, 121.9, 110.0, 96.8, 90.2, 83.8, 51.5, 50.8, 41.6, 20.7. HRMS (EI^+): calcd. for $[C_{17}H_{18}NO_2]^+$: 268.1332, found: 268.1339



methyl 1-methyl-6-(p-tolylethynyl)-1,6-dihydropyridine-3-carboxylate(3c): yellowish oil; 60.9 mg, 76 %, 3c:3c' = 25:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3b) δ 7.30 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 7.10 (d, J = 7.6 Hz, 2H), 6.45 (d, J = 8.8 Hz, 1H), 5.15–5.09 (m, 2H), 3.68 (s, 3H), 3.08 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 146.7, 138.7, 131.7, 129.1, 121.9, 119.2, 109.9, 96.7, 85.6, 84.9, 51.4, 50.7, 41.6, 21.5. HRMS (EI^+): calcd. for $[C_{17}H_{18}NO_2]^+$: 268.1332, found: 268.1335.

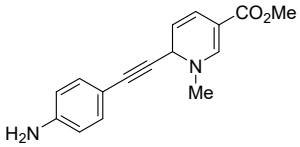


methyl 6-([1,1'-biphenyl]-4-ylethynyl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3d): yellowish oil; 71.1 mg, 72 %, 3e:3e' = 34:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3e) δ 7.57–7.51 (m, 4H), 7.48–7.40 (m, 4H), 7.36–7.31 (m, 1H), 7.26 (s, 1H), 6.47 (d, J = 9.2 Hz, 1H), 5.18–5.11 (m, 2H), 3.69 (s, 3H), 3.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 146.8, 141.3, 140.2, 132.3, 128.9, 127.7, 127.0(2), 126.9(7), 122.1, 121.2, 109.8, 96.8, 86.9, 84.7, 51.4, 50.8, 41.6. HRMS (EI^+): calcd. for $[C_{22}H_{20}NO_2]^+$: 330.1489, found: 330.1488.

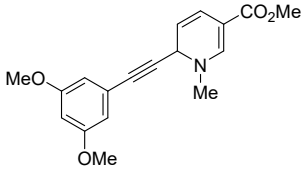


methyl 6-((4-methoxyphenyl)ethynyl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3e): yellowish oil; 55.2 mg, 65 %, 3d:3d' = 22:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3d) δ 7.37–7.32 (m, 2H), 7.25

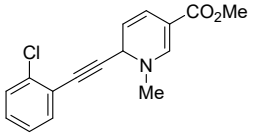
(s, 1H), 6.84–6.79 (m, 2H), 6.47–6.42 (m, 1H), 5.15–5.09 (m, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 159.8, 146.8, 133.3, 121.8, 114.3, 113.9, 109.9, 96.6, 84.9, 84.7, 55.3, 51.4, 50.8, 41.6. HRMS (EI$^+$): calcd. for $[C_{17}H_{18}NO_3]^+$: 284.1281, found: 284.1293.



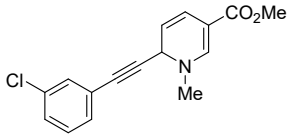
methyl 6-((4-aminophenyl)ethynyl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3f): yellowish oil; 54.7 mg, 68 %, 3g:3g' = 21:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3g) δ 7.24 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.56 (d, *J* = 8.4 Hz, 2H), 6.45–6.40 (m, 1H), 5.13–5.08 (m, 2H), 3.85 (s, 2H), 3.68 (s, 3H), 3.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 147.0, 146.8, 133.2, 121.7, 114.6, 111.4, 110.2, 96.5, 85.4, 84.1, 51.4, 50.7, 41.6. HRMS (EI$^+$): calcd. for $[C_{16}H_{17}N_2O_2]^+$: 269.1285, found: 269.1284.



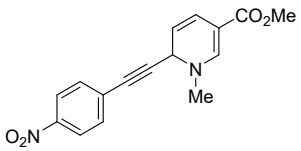
methyl 6-((3,5-dimethoxyphenyl)ethynyl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3g): yellowish oil; 53.5 mg, 57 %, 3f:3f' = 20:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3f) δ 7.24 (s, 1H), 6.55 (d, *J* = 2.4 Hz, 2H), 6.48–6.39 (m, 2H), 5.15–5.08 (m, 2H), 3.75 (s, 6H), 3.68 (s, 3H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 160.5, 146.7, 123.6, 122.1, 109.6, 109.5, 102.1, 96.8, 85.8, 84.7, 55.4, 51.3, 50.8, 41.6. HRMS (EI$^+$): calcd. for $[C_{18}H_{20}NO_4]^+$: 314.1387, found: 314.1388.



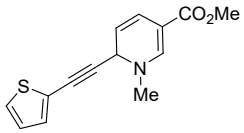
methyl 6-((2-chlorophenyl)ethynyl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3h): yellowish oil; 56.8 mg, 66 %,3h:3h' = 33:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3h) δ 7.44–7.40 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 7.23–7.12 (m, 2H), 6.45 (d, *J* = 9.6 Hz, 1H), 5.19 (d, *J* = 4.4 Hz, 1H), 5.15–5.10 (m, 1H), 3.67 (s, 3H), 3.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 146.7, 136.0, 133.4, 129.6, 129.2, 126.5, 122.3, 109.4, 96.8, 91.5, 81.6, 51.5, 50.7, 41.6. HRMS (EI$^+$): calcd. for $[C_{16}H_{15}ClNO_2]^+$: 288.0786, found: 288.0785.



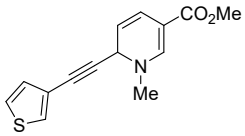
methyl 6-((3-chlorophenyl)ethynyl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3i): yellowish oil; 52.5 mg, 61 %, 3i:3i' = 21:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3i) δ 7.41 (t, *J* = 1.8 Hz, 1H), 7.31–7.28 (m, 2H), 7.26–7.23 (m, 2H), 6.49–6.45 (m, 1H), 5.15–5.10 (m, 2H), 3.70 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 146.6, 134.1, 131.7, 129.9, 129.6, 128.9, 124.0, 122.3, 109.4, 97.0, 87.4, 83.4, 51.3, 50.8, 41.6. HRMS (EI$^+$): calcd. for $[C_{16}H_{15}ClNO_2]^+$: 288.0786, found: 288.0788.



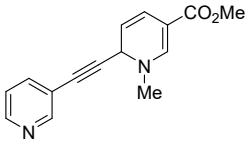
methyl 1-methyl-6-((4-nitrophenyl)ethynyl)-1,6-dihydropyridine-3-carboxylate(3j): yellowish oil; 41.1 mg, 46 % , 3j:3j' = 16:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3j) δ 8.21–8.15 (m, 2H), 7.60–7.52 (m, 2H), 7.27 (s, 1H), 6.56–6.45 (m, 1H), 5.22–5.09 (m, 2H), 3.70 (s, 3H), 3.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 132.6, 129.2, 123.6, 122.7, 108.9, 97.4, 91.4, 51.3, 50.9, 41.7. HRMS (EI$^+$): calcd. for $[C_{16}H_{15}N_2O_4]^+$: 299.1026, found: 299.1025.



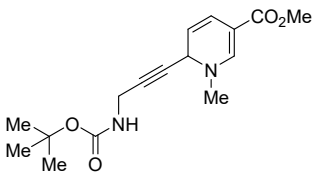
methyl 1-methyl-6-(thiophen-2-ylethynyl)-1,6-dihydropyridine-3-carboxylate(3k): yellowish oil; 59.1mg, 76 %, 3k:3k' = 16:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3k) δ 7.26–7.23 (m, 2H), 7.19 (d, *J* = 3.6 Hz, 1H), 6.97–6.93 (m, 1H), 6.45 (d, *J* = 8.8 Hz, 1H), 5.15 (d, *J* = 4.4 Hz, 1H), 5.12–5.08 (m, 1H), 3.68 (s, 3H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 146.7, 132.6, 127.6, 127.0, 122.2(1), 122.1(6), 109.4, 96.9, 90.1, 78.1, 51.5, 50.8, 41.6. HRMS (EI$^+$): calcd. for $[C_{14}H_{14}NO_2S]^+$: 260.0740, found: 260.0741.



methyl 1-methyl-6-(thiophen-3-ylethynyl)-1,6-dihydropyridine-3-carboxylate(3l): yellow oil, 64.5 mg, 83 %, 3x:3x' = 21:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3x) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.36 (m, 1H), 7.25 – 7.23 (m, 2H), 7.09 – 7.06 (m, 1H), 6.48 – 6.42 (m, 1H), 5.12 – 5.08 (m, 2H), 3.68 (s, 3H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 146.7, 129.9, 129.4, 125.4, 122.0, 121.3, 109.7, 96.8, 85.9, 79.9, 51.3, 50.8, 41.6.

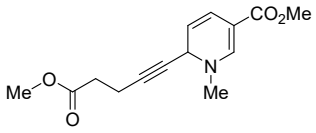


methyl 1-methyl-6-(pyridin-3-ylethynyl)-1,6-dihydropyridine-3-carboxylate(3m): yellow oil, 63.2 mg, 83 %, 3s:3s' = 8.0:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3s) δ 8.64–8.58 (m, 1H), 8.51–8.48 (m, 1H), 7.69–7.65 (m, 1H), 7.24–7.18 (m, 2H), 6.46–6.42 (m, 1H), 5.14–5.08 (m, 2H), 3.65 (s, 3H), 3.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 152.4, 148.9, 146.6, 138.7, 123.0, 122.4, 119.5, 109.2, 97.1, 89.6, 81.4, 51.3, 50.8, 41.6.

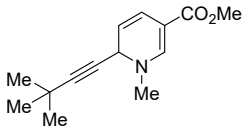


methyl 6-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-1-methyl-1,6-dihydropyridine-3-carboxylate (3n): yellow oil, 38.6 mg, 42 %, 3l:3l' = 19:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3l) δ

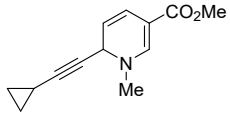
7.20 (s, 1H), 6.40 (d, *J* = 10.0 Hz, 1H), 5.03–4.99 (m, 1H), 4.91–4.88 (m, 1H), 4.72 (s, 1H), 3.92 (s, 2H), 3.67 (s, 3H), 3.01 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 155.3, 146.7, 122.0, 109.6, 96.8, 81.1, 50.8, 50.7, 41.5, 28.3. HRMS (EI^+): calcd. for $[C_{16}H_{23}N_2O_4]^+$: 307.1652, found: 307.1655.



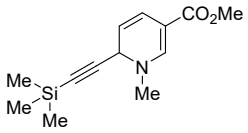
methyl 6-(5-methoxy-5-oxopent-1-yn-1-yl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3o): yellow oil, 33.9 mg, 43 %, 3u:3u' = 28:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3u) δ 6.37 (d, *J* = 11.2 Hz, 1H), 5.04 – 4.95 (m, 1H), 4.87 (d, *J* = 4.0 Hz, 1H), 3.66 (d, *J* = 6.0 Hz, 6H), 2.99 (s, 3H), 2.50 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 166.7, 146.7, 121.6, 110.1, 96.5, 83.4, 78.4, 51.8, 50.8, 50.7, 41.4, 33.2, 14.7.



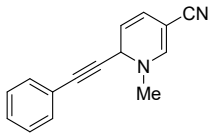
methyl 6-(3,3-dimethylbut-1-yn-1-yl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3p): yellow oil, 39.1 mg, 56 %, 3v:3v' = 24:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3v) δ 7.20 (s, 1H), 6.38–6.32 (m, 1H), 5.04–4.98 (m, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 3.67 (s, 3H), 3.00 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 146.8, 121.2, 110.8, 96.0, 93.7, 77.2, 75.9, 51.0, 50.7, 41.3, 30.9, 27.4.



methyl 6-(cyclopropylethynyl)-1-methyl-1,6-dihydropyridine-3-carboxylate(3q): yellow oil, 32.6 mg, 50 %, 3t:3t' = 16:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3t) δ 6.38–6.33 (m, 1H), 5.05–4.96 (m, 1H), 4.87–4.83 (m, 1H), 3.66 (s, 3H), 2.99 (s, 3H), 1.27–1.18 (m, 1H), 0.78–0.73 (m, 2H), 0.67–0.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 147.3, 122.0, 111.0, 96.9, 89.2, 73.4, 51.5, 51.3, 42.0, 8.9(4), 8.8(7).

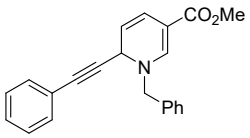


methyl 1-methyl-6-((trimethylsilyl)ethynyl)-1,6-dihydropyridine-3-carboxylate(3r): yellow oil, 33.6 mg, 45 %, 3w:3w' = 25:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3w) δ 7.20 (s, 1H), 6.38 (d, *J* = 10.0 Hz, 1H), 5.07–4.97 (m, 1H), 4.93 (d, *J* = 4.4 Hz, 1H), 3.67 (s, 3H), 3.01 (s, 3H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 146.9, 122.0, 110.0, 102.3, 96.6, 89.7, 51.7, 50.9, 41.6.

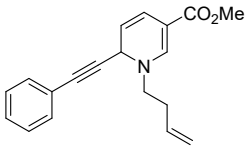


methyl-6-(phenylethynyl)-1,6-dihydropyridine-3-carbonitrile(3s): yellowish oil; 29.7 mg, 45 %, 3m:3m' = 76:1. ^{1}H NMR (400 MHz, $CDCl_3$, for major 3m) δ 7.45–7.41 (m, 2H), 7.36–7.30 (m, 3H), 6.74 (s, 1H), 6.00–5.92 (m, 1H), 5.21–5.12 (m, 2H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6,

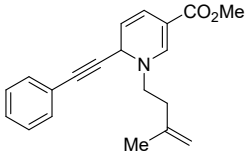
131.8(4), 131.8(0), 128.8, 122.0, 121.4, 120.9, 111.3, 85.4, 85.4, 50.7, 41.5. HRMS (EI^+): calcd. for $[C_{15}H_{13}N_2]^+$: 221.1073, found: 221.1074.



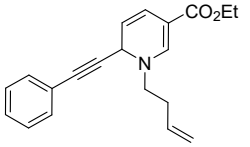
methyl 1-benzyl-6-(phenylethynyl)-1,6-dihydropyridine-3-carboxylate(3t): yellowish oil; 70.1 mg, 71 %, 3n:3n' = 21:1. ^1H NMR (400 MHz, $CDCl_3$, for major 3n) δ 7.47–7.29 (m, 11H), 6.48 (d, *J* = 9.6 Hz, 1H), 5.18–5.04 (m, 2H), 4.65 (d, *J* = 14.8 Hz, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 146.4, 135.0, 131.9, 129.0, 128.6, 128.3(7), 128.3(2), 128.2, 122.4, 122.1, 110.3, 97.5, 86.4, 84.9, 57.9, 50.9, 48.5. HRMS (EI^+): calcd. for $[C_{22}H_{20}NO_2]^+$: 330.1489, found: 330.1496.



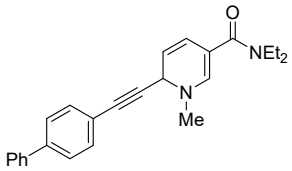
methyl 1-(but-3-en-1-yl)-6-(phenylethynyl)-1,6-dihydropyridine-3-carboxylate(3u): yellowish oil; 58.0 mg, 66 %, 3o:3o' = 14:1. ^1H NMR (400 MHz, $CDCl_3$, for major 3o) δ 7.43–7.39 (m, 2H), 7.34–7.26 (m, 4H), 6.49–6.43 (m, 1H), 5.85–5.74 (m, 1H), 5.23 (d, *J* = 4.8 Hz, 1H), 5.18–5.10 (m, 3H), 3.69 (s, 3H), 3.63–3.52 (m, 1H), 3.25 (s, 1H), 2.50–2.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 146.1, 134.0, 131.8, 128.6, 128.3, 128.0, 122.3(3), 122.3(1), 118.0, 109.7, 97.1, 87.0, 84.4, 53.9, 50.8, 49.3, 32.4. HRMS (EI^+): calcd. for $[C_{19}H_{22}NO_2]^+$: 294.1489, found: 294.1492.



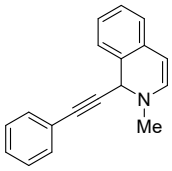
methyl 1-(3-methylbut-3-en-1-yl)-6-(phenylethynyl)-1,6-dihydropyridine-3-carboxylate(3v): yellowish oil; 70.0mg, 76 %, 3p:3p' = 15:1. ^1H NMR (400 MHz, $CDCl_3$, for major 3p) δ 7.43–7.39 (m, 2H), 7.34–7.27 (m, 4H), 6.56–6.34 (m, 1H), 5.26 (d, *J* = 4.8 Hz, 1H), 5.15–5.08 (m, 1H), 4.86–4.77 (m, 2H), 3.69 (s, 3H), 3.66–3.57 (m, 1H), 3.35–3.28 (m, 1H), 2.41 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 146.0, 141.7, 131.8, 128.6, 128.3, 122.4, 122.3, 113.0, 109.7, 97.1, 86.9, 84.4, 52.7, 50.8, 49.3, 36.1, 22.5. HRMS (EI^+): calcd. for $[C_{20}H_{22}NO_2]^+$: 308.1645, found: 308.1645.



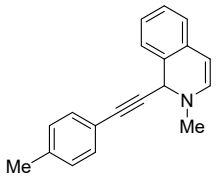
ethyl 1-(but-3-en-1-yl)-6-(phenylethynyl)-1,6-dihydropyridine-3-carboxylate(3w): yellowish oil; 58.0 mg, 63 %,3q:3q' = 12:1. ^1H NMR (400 MHz, $CDCl_3$, for major 3q) δ 7.47–7.36 (m, 2H), 7.33–7.22 (m, 4H), 6.48 (d, *J* = 9.6 Hz, 1H), 5.91–5.71 (m, 1H), 5.23 (d, *J* = 4.4 Hz, 1H), 5.19–5.09 (m, 3H), 4.20–4.10 (m, 2H), 3.64–3.49 (m, 1H), 3.29–3.21 (m, 1H), 2.52–2.39 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 146.0, 134.1, 131.8, 128.6, 128.3, 122.4, 117.9, 109.6, 97.5, 87.0, 84.4, 59.3, 53.8, 49.3, 32.4, 14.6. HRMS (EI+): calcd. for $[C_{20}H_{20}NO_2]$+: 308.1645, found: 308.1656.



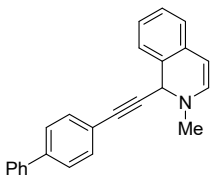
6-([1,1'-biphenyl]-4-ylethynyl)-N,N-diethyl-1-methyl-1,6-dihydropyridine-3-carboxamide(3x): yellow oil, 53.3 mg, 48 %, 3r:3r'=66:1.^{1}H NMR (400 MHz, $CDCl_3$, for major 3r) δ 7.59–7.53 (m, 4H), 7.49–7.42 (m, 4H), 7.38–7.33 (m, 1H), 6.84 (s, 1H), 6.15 (d, *J* = 9.6 Hz, 1H), 5.18–5.10 (m, 1H), 5.06 (d, *J* = 5.2 Hz, 1H), 3.43–3.37 (m, 4H), 3.05 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 143.3, 141.2, 140.2, 132.2, 128.9, 127.7, 127.0(2), 126.9(7), 123.8, 121.5, 108.5, 102.8, 87.5, 83.9, 50.8, 41.4, 41.1, 13.6.



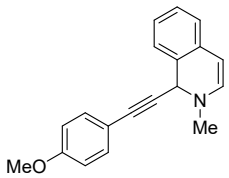
2-methyl-1-(phenylethynyl)-1,2-dihydroisoquinoline(6a): yellowish oil; 51.5 mg,70 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.23 (m, 2H), 7.18–7.13 (m, 3H), 7.08–7.02 (m, 1H), 6.90–6.85 (m, 1H), 6.65–6.60 (m, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 9.2 Hz, 1H), 5.77–5.70 (m, 1H), 4.94 (d, *J* = 5.6 Hz, 1H), 2.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 131.8, 129.3, 128.2(0), 128.1(7), 127.1, 126.5, 122.8, 121.9, 121.7, 118.0, 111.5, 86.2, 84.4, 52.3, 36.2. HRMS (EI^+): calcd. for $[C_{18}H_{16}N]^+$: 246.1277, found: 246.1288.



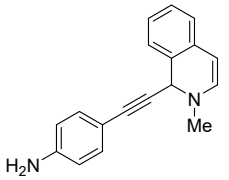
2-methyl-1-(p-tolylethynyl)-1,2-dihydroisoquinoline (6b): yellow oil,47.4 mg, 61 %.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 7.17–7.13 (m, 1H), 7.08–7.04 (m, 2H), 7.00–6.94 (m, 1H), 6.75–6.68 (m, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 9.6 Hz, 1H), 5.87–5.80 (m, 1H), 5.03 (d, *J* = 5.2 Hz, 1H), 2.96 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 138.3, 131.7, 129.3, 128.9, 127.1, 126.4, 121.9, 121.9, 119.7, 118.0, 111.5, 85.6, 84.6, 52.3, 36.2, 21.5. HRMS (EI^+): calcd. for $[C_{19}H_{18}N]^+$: 260.1434, found: 260.1436.



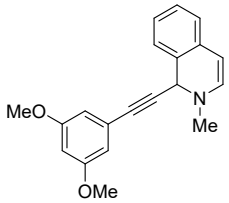
1-([1,1'-biphenyl]-4-ylethynyl)-2-methyl-1,2-dihydroisoquinoline(6d): yellowish oil; 64.5 mg, 67 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.56 (m, 2H), 7.55–7.50 (m, 2H), 7.50–7.42 (m, 4H), 7.41–7.35 (m, 1H), 7.23–7.16 (m, 1H), 7.05–7.00 (m, 1H), 6.80–6.74 (m, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 9.2 Hz, 1H), 5.92–5.84 (m, 1H), 5.09 (d, *J* = 5.6 Hz, 1H), 3.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 140.9, 140.4, 132.3, 129.4, 128.9, 127.7, 127.1, 127.0, 126.9, 126.6, 122.0, 121.8, 121.7, 118.1, 111.5, 87.0, 84.4, 52.4, 36.3. HRMS (EI^+): calcd. for $[C_{24}H_{20}N]^+$: 322.1590, found: 322.1594.



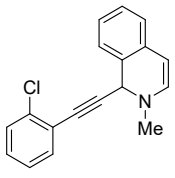
1-((4-methoxyphenyl)ethynyl)-2-methyl-1,2-dihydroisoquinoline(6c): yellow oil, 46.2 mg, 56 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.18–7.12 (m, 1H), 7.00–6.95 (m, 1H), 6.81–6.75 (m, 2H), 6.75–6.69 (m, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 9.6 Hz, 1H), 5.86–5.80 (m, 1H), 5.03 (d, *J* = 5.6 Hz, 1H), 3.78 (s, 3H), 2.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 144.3, 133.3, 129.2, 127.0, 126.3, 121.9(5), 121.9(1), 117.9, 114.9, 113.8, 111.4, 84.8, 84.3, 55.3, 52.3, 36.2. HRMS (EI^+): calcd. for $[C_{19}H_{18}NO]^+$: 276.1383, found: 276.1381.



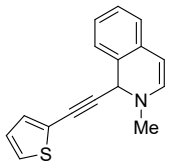
4-((2-methyl-1,2-dihydroisoquinolin-1-yl)ethynyl)aniline(6e): yellowish oil ; 35.9 mg, 46 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.11 (m, 3H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.55–6.49 (m, 2H), 6.47 (d, *J* = 9.6 Hz, 1H), 5.86–5.80 (m, 1H), 5.03 (d, *J* = 5.2 Hz, 1H), 3.71 (s, 2H), 2.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 144.4, 133.1, 129.2, 127.0, 126.2, 122.2, 122.0, 117.8, 114.6, 112.1, 111.4, 85.0, 84.0, 52.3, 36.2. HRMS (EI^+): calcd. for $[C_{18}H_{17}N_2]^+$: 261.1386, found: 261.1397.



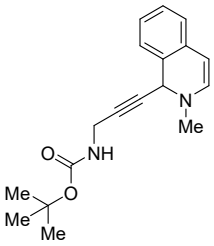
1-((3,5-dimethoxyphenyl)ethynyl)-2-methyl-1,2-dihydroisoquinoline (6f): yellow oil, 75.9mg, 83 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.15 (m, 1H), 7.03–6.97 (m, 1H), 6.78–6.71 (m, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.56–6.48 (m, 3H), 6.42 (t, *J* = 2.4 Hz, 1H), 5.88–5.81 (m, 1H), 5.06 (d, *J* = 5.6 Hz, 1H), 3.75 (s, 6H), 2.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 144.2, 129.4, 127.1, 126.6, 124.1, 121.9, 121.6, 118.0, 111.59, 109.6, 101.7, 85.9, 84.4, 55.4, 52.3, 36.3. HRMS (EI^+): calcd. for $[C_{20}H_{20}NO_2]^+$: 306.1489, found: 306.1487.



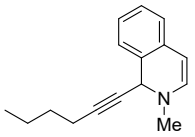
1-((2-chlorophenyl)ethynyl)-2-methyl-1,2-dihydroisoquinoline (6g): yellow oil, 61.1 mg, 73 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.33 (m, 2H), 7.24–7.12 (m, 3H), 7.03–6.99 (m, 1H), 6.81–6.71 (m, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 9.6 Hz, 1H), 5.93–5.83 (m, 1H), 5.09 (d, *J* = 5.6 Hz, 1H), 3.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 136.0, 133.4, 129.4, 129.3, 129.2, 127.1, 126.9, 126.3, 122.8, 122.0, 121.5, 118.2, 111.7, 91.8, 81.3, 52.4, 36.4. HRMS (EI^+): calcd. for $[C_{18}H_{15}ClN]^+$: 280.0888, found: 280.0894.



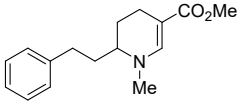
2-methyl-1-(thiophen-2-ylethynyl)-1,2-dihydroisoquinoline (6h): yellow oil, 51.2 mg, 68 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.11 (m, 3H), 7.01–6.97 (m, 1H), 6.94–6.90 (m, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 9.2 Hz, 1H), 5.85–5.78 (m, 1H), 5.07 (d, *J* = 5.2 Hz, 1H), 2.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 132.2, 129.4, 127.1(4), 127.0(5), 126.9, 126.7, 122.7, 121.8, 121.3, 118.1, 111.5, 90.3, 52.5, 36.3. HRMS (EI$^+$): calcd. for $[C_{16}H_{14}NS]^+$: 252.0841, found: 252.0844.



tert-butyl (3-(2-methyl-1,2-dihydroisoquinolin-1-yl)prop-2-yn-1-yl)carbamate (6i): yellow oil, 45.6 mg, 51 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.09 (m, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.73–6.67 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 5.74–5.68 (m, 1H), 4.76 (d, *J* = 5.6 Hz, 2H), 3.91–3.83 (m, 2H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 144.1, 129.3, 127.1, 126.4, 121.8, 121.7, 118.1, 111.5, 80.6, 80.2, 79.8, 71.2, 51.5, 36.1, 30.6, 28.4. HRMS (EI$^+$): calcd. for $[C_{18}H_{23}N_2O_2]^+$: 299.1754, found: 299.1764.



1-(hex-1-yn-1-yl)-2-methyl-1,2-dihydroisoquinoline (6j): yellow oil, 35.8 mg, 53 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.10 (m, 1H), 6.98–6.92 (m, 1H), 6.74–6.68 (m, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 9.2 Hz, 1H), 5.80–5.72 (m, 1H), 4.79–4.75 (m, 1H), 2.89 (s, 3H), 2.17–2.10 (m, 2H), 1.45–1.30 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 129.1, 126.9, 125.9, 122.7, 122.0, 117.8, 111.4, 85.1, 51.8, 36.1, 30.8, 21.9, 18.4, 13.6. HRMS (EI$^+$): calcd. for $[C_{16}H_{20}N]^+$: 226.1590, found:226.1587.



methyl 1-methyl-6-phenethylpiperidine-3-carboxylate (7): yellow oil, 245 mg, 95 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 3H), 7.29–7.17 (m, 3H), 3.72 (s, 3H), 3.19–3.12 (m, 1H), 2.99 (s, 3H), 2.80–2.70 (m, 1H), 2.66–2.54 (m, 1H), 2.50–2.41 (m, 1H), 2.28–2.14 (m, 1H), 2.02–1.86 (m, 2H), 1.79–1.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 145.8, 141.4, 128.5, 128.3, 128.3, 126.0, 93.2, 77.4, 55.8, 50.5, 41.7, 32.4, 32.0, 23.4, 16.2. HRMS (EI$^+$): calcd. for $[C_{16}H_{22}NO_2]^+$: 260.1646, found:260.1644.

4.References

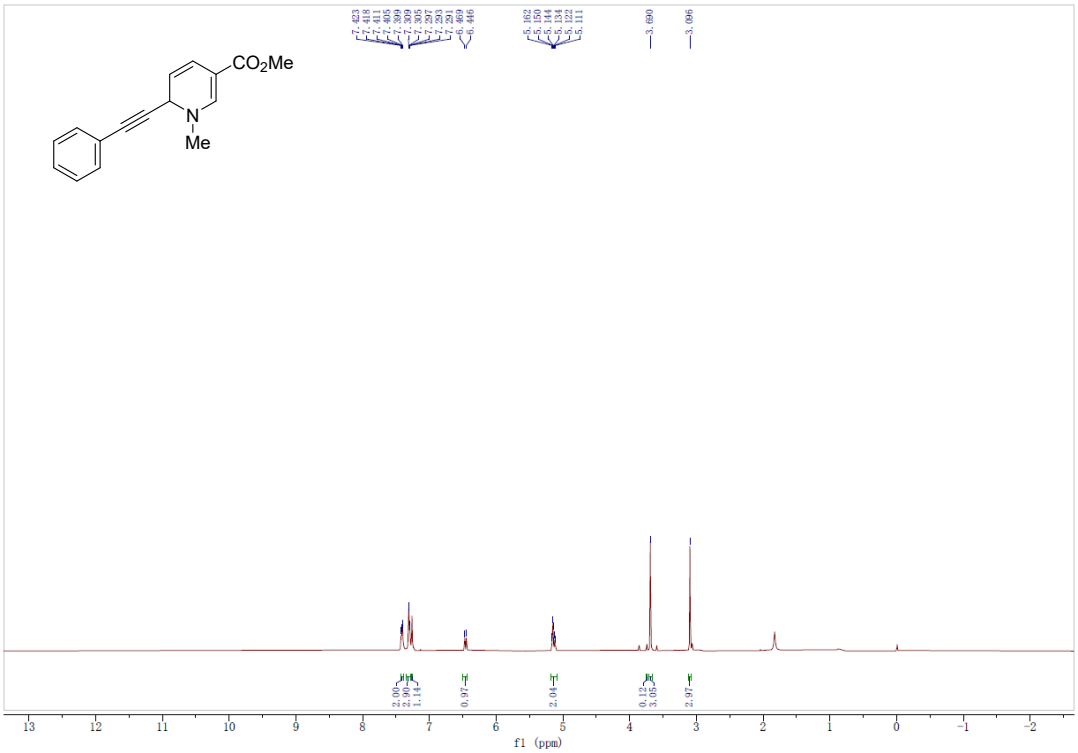
[1]. D. J. Robinson, K. G. Ortiz, N. P. O'Hare, R. R. Karimov, Dearomatization of Heteroarenium Salts with ArBpin Reagents. Application to the Total Synthesis of a Nuphar Alkaloid, *Org. Lett.,* 2022, **24**, 19, 3445–3449.

[2]. C. Baumert, M. Günthel, S. Krawczyk, M. Hemmer, T. Wersig, A. Langner, J. Molnár, H. Lage, A. Hilgeroth, Development of small-molecule P-gp inhibitors of the N-benzyl 1,4-dihydropyridine type: Novel aspects in SAR and bioanalytical evaluation of multidrug resistance (MDR) reversal properties, *Bioorganic & Medicinal Chemistry.,*2013*,* **1***,* 166-177.

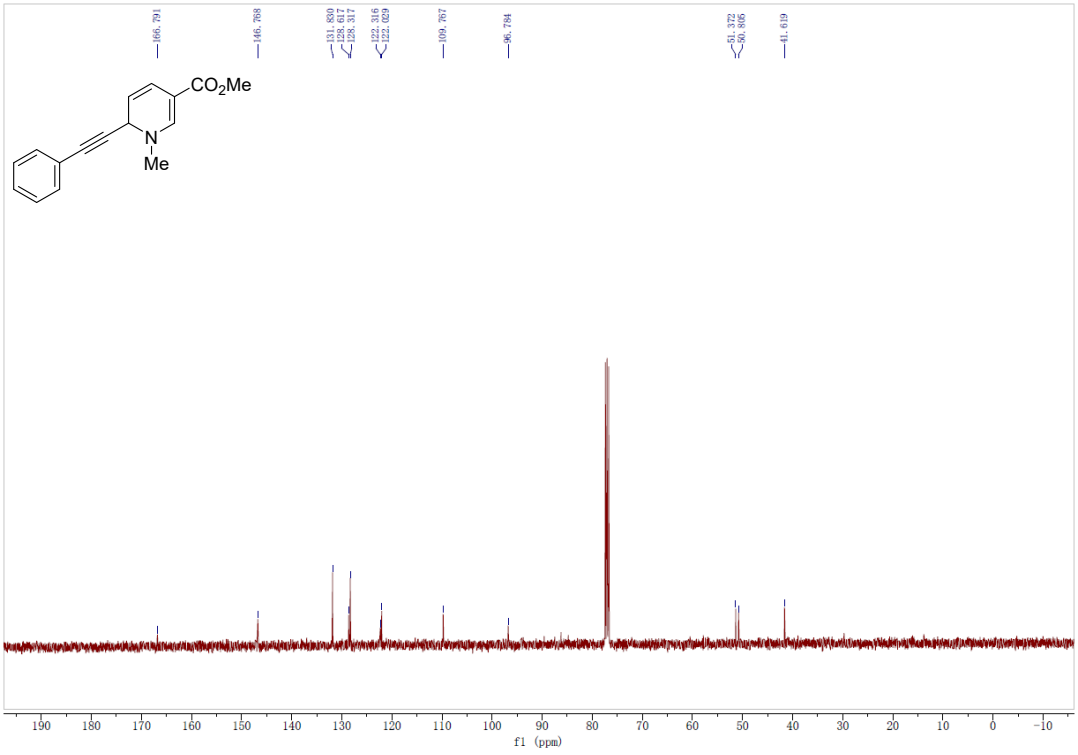
[3]. Y. Huang, Z. Qi, X. Li, Rhodium-Catalyzed Enantioselective Addition of Heteroarenium Salts Enabled by Nucleophilic Cyclization of 2-Alkynylanilines, *Org. Lett.* 2023, **25,** 47, 8439–8444.

5.Copies of ^{1}H and ^{13}C NMR spectra

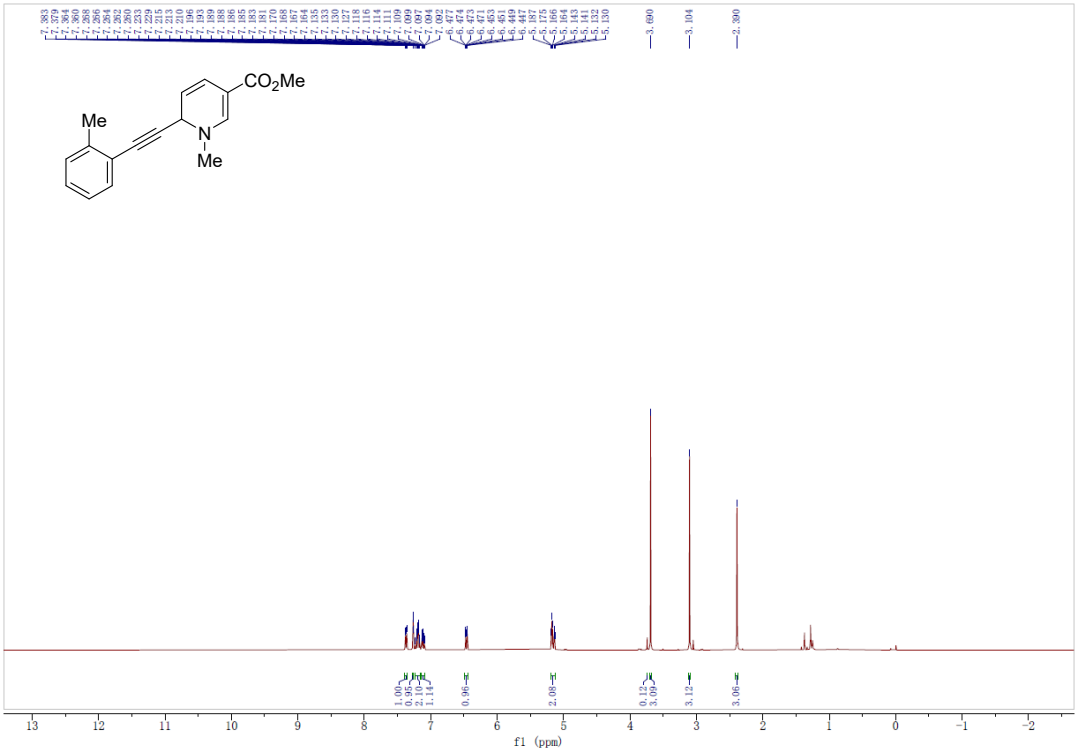
^{1}H NMR of 3a



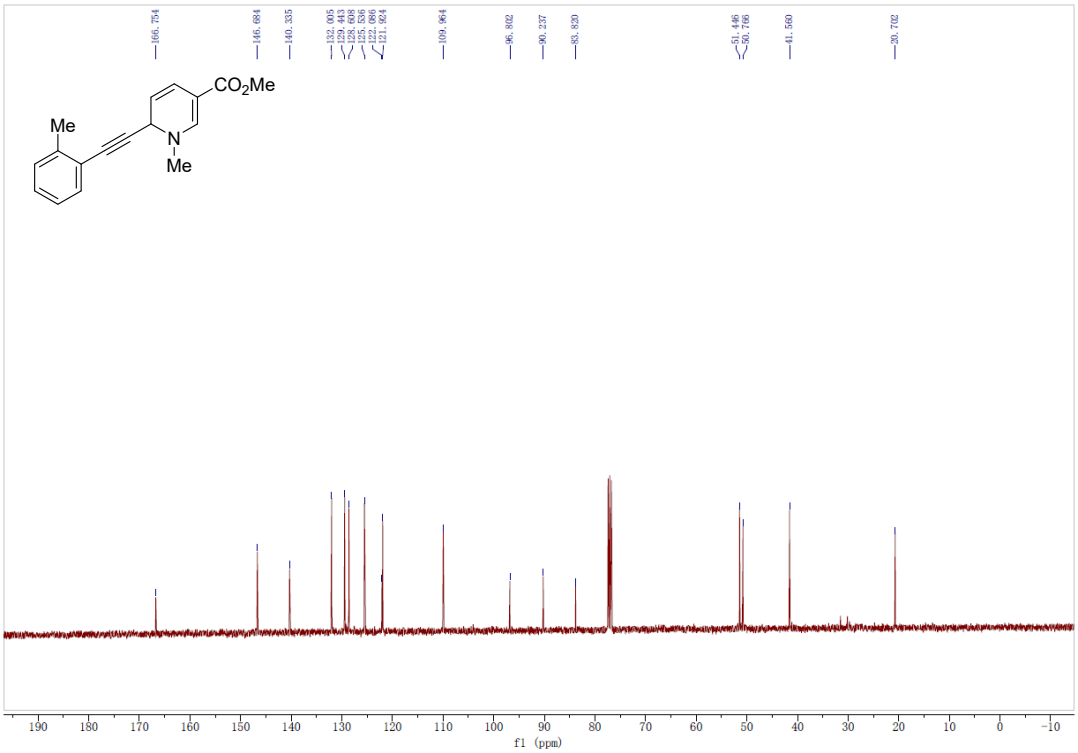
^{13}C NMR of 3a



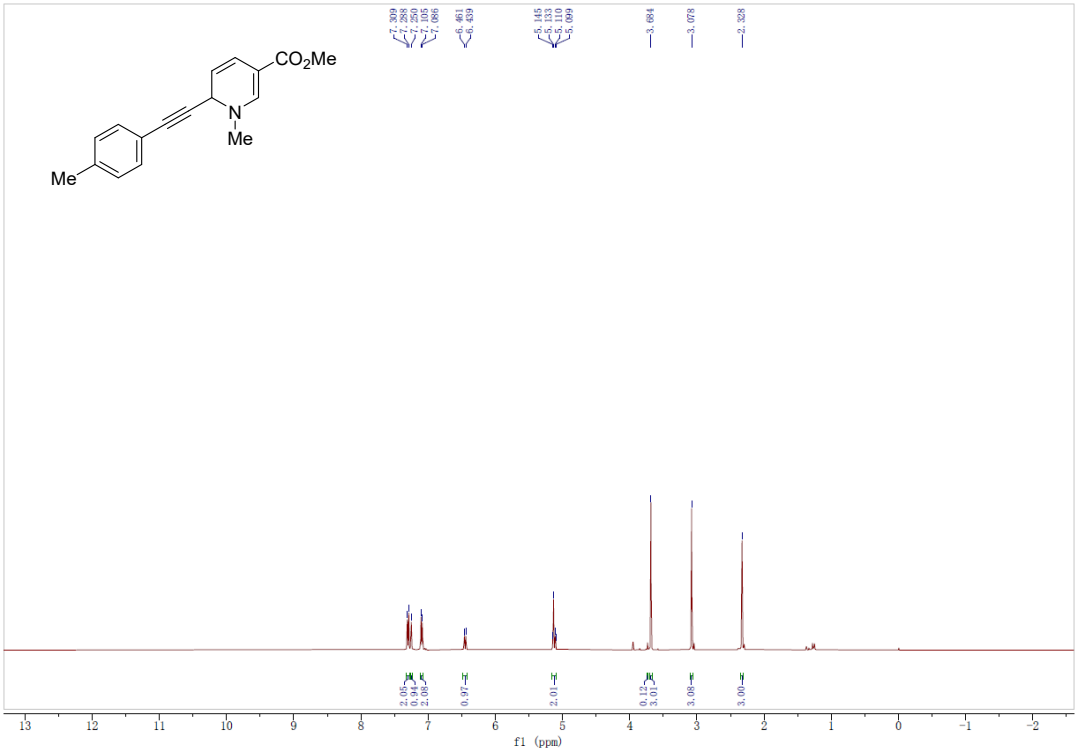
^{1}H NMR of 3b



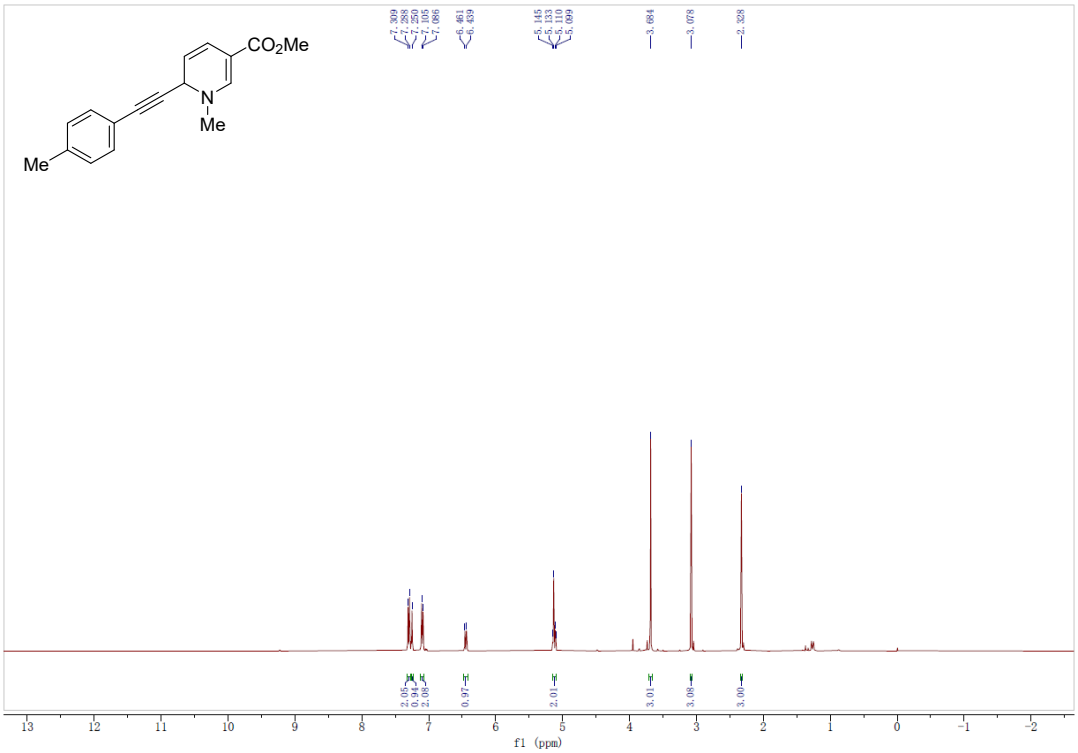
^{13}C NMR of 3b



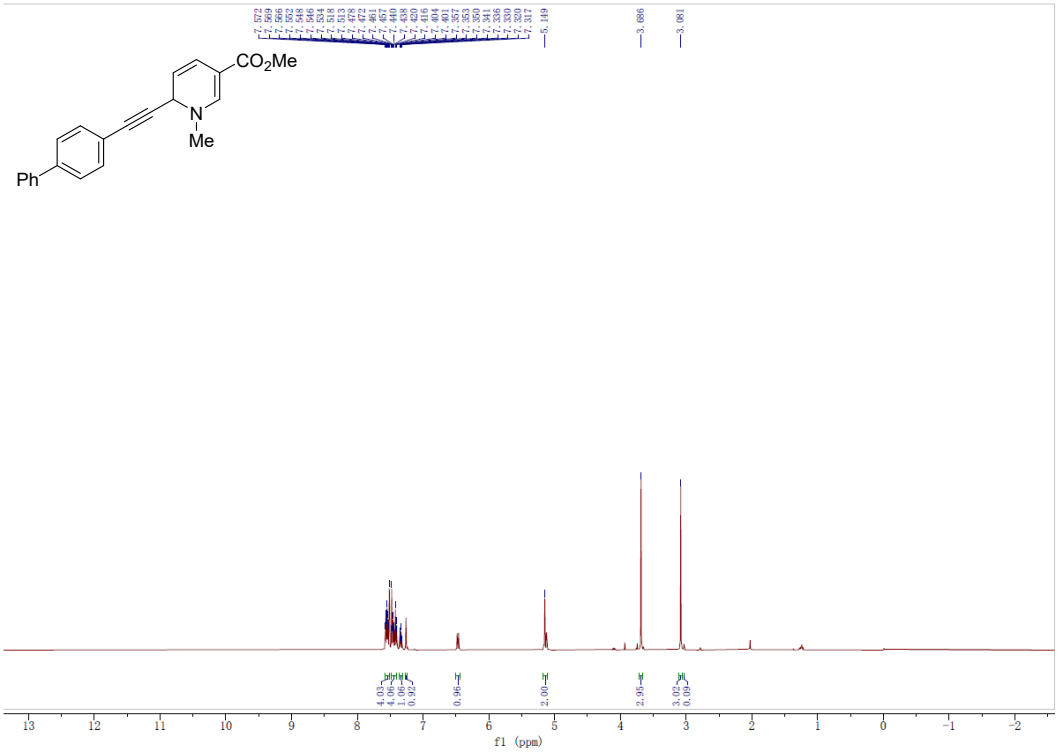
^{1}H NMR of 3c



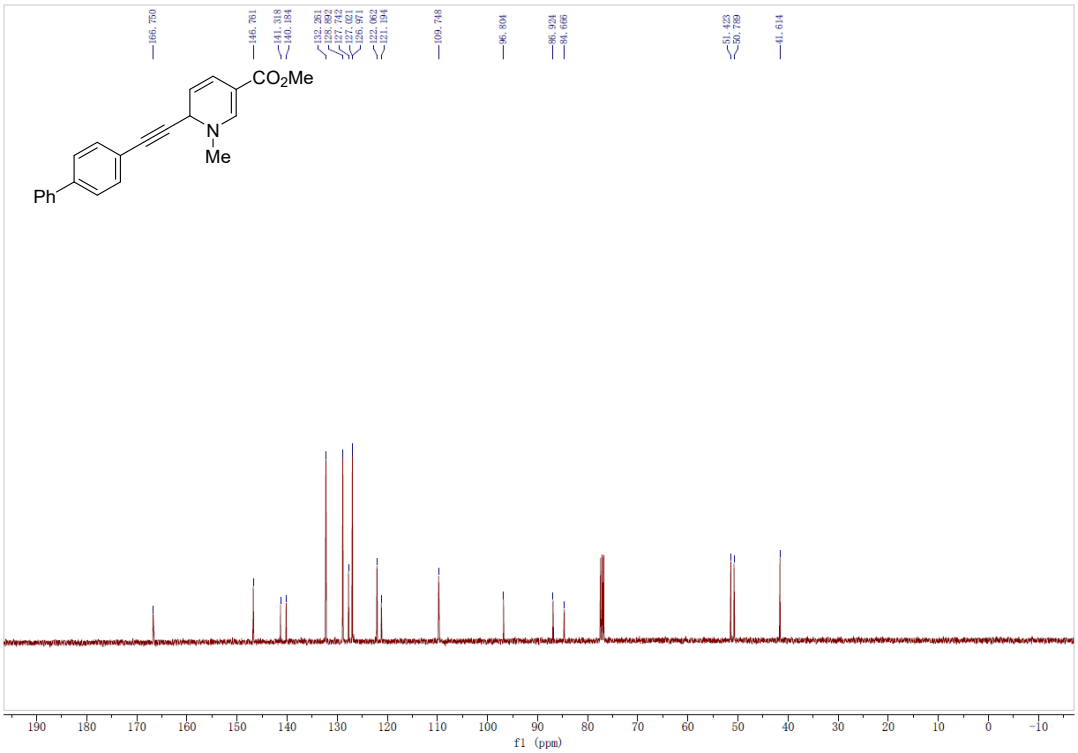
^{13}C NMR of 3c



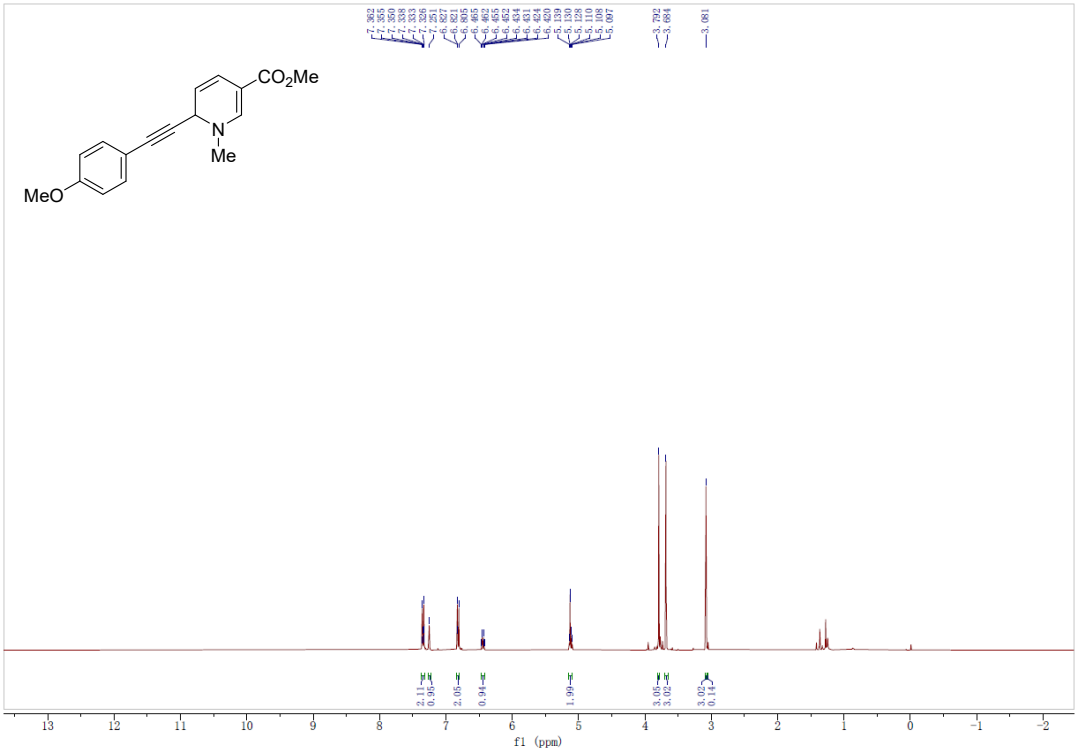
^{1}H NMR of 3d



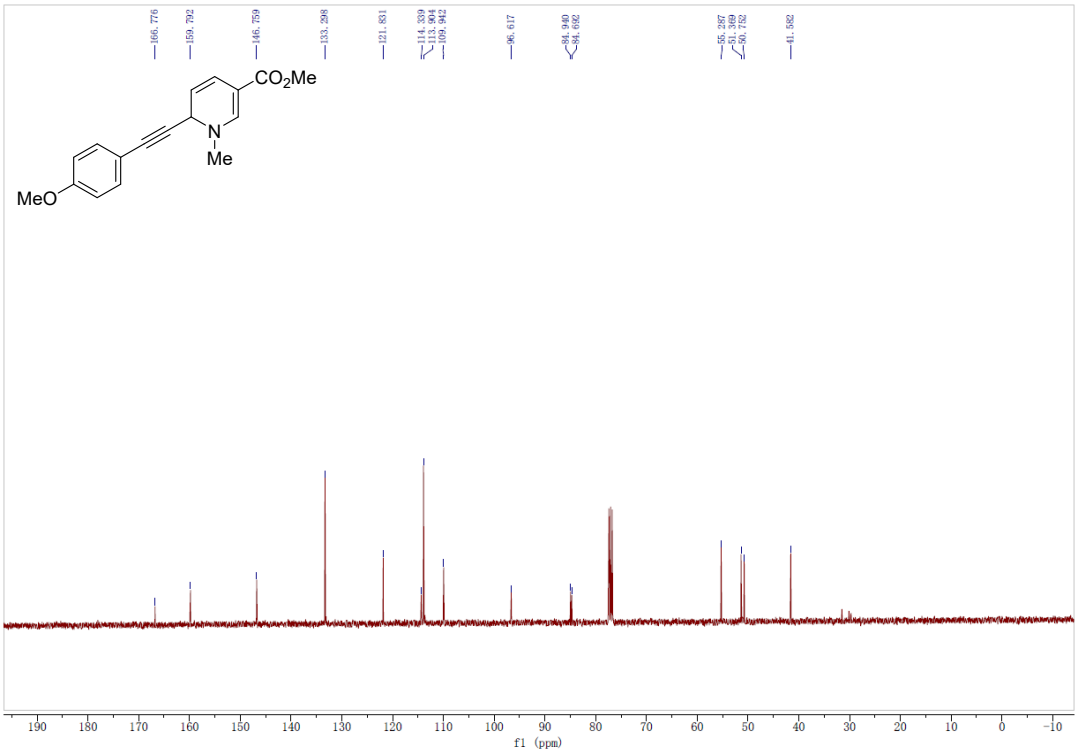
^{13}C NMR of 3d



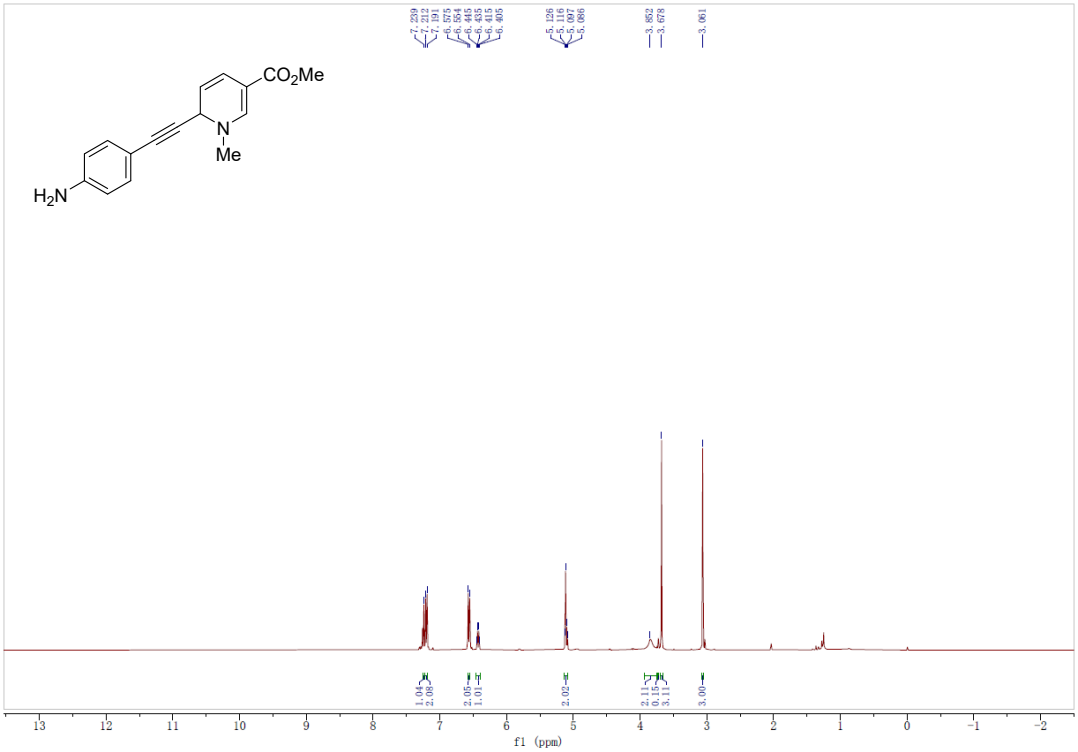
^{1}H NMR of 3e



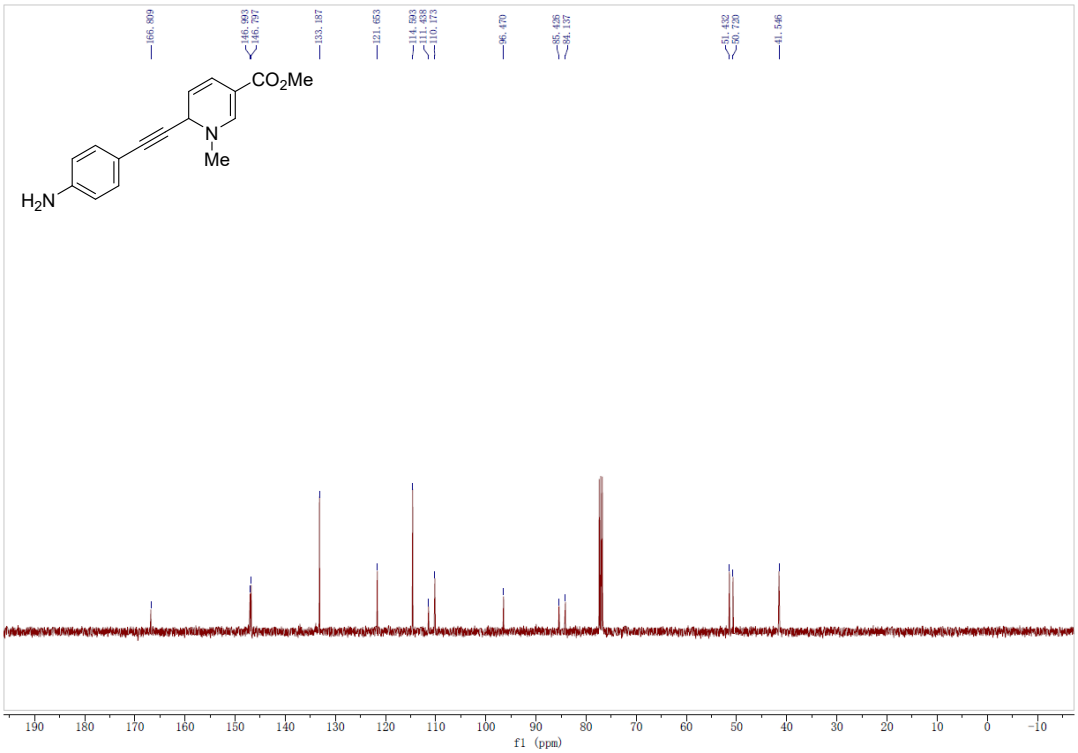
^{13}C NMR of 3e



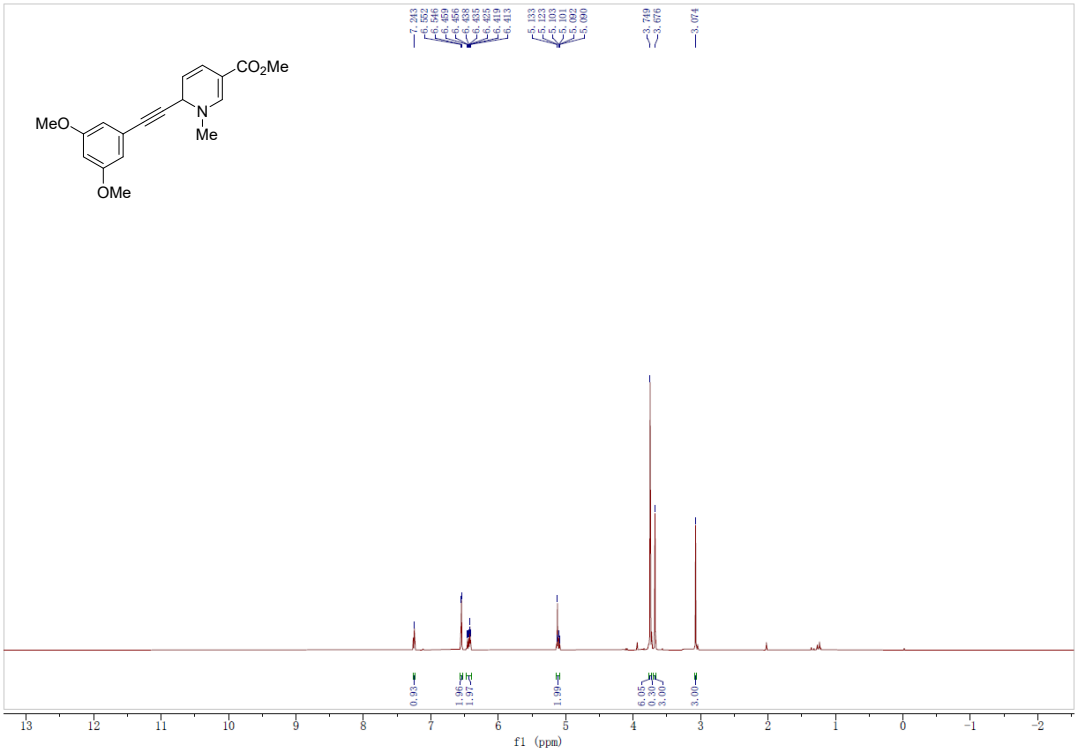
^{1}H NMR of 3f



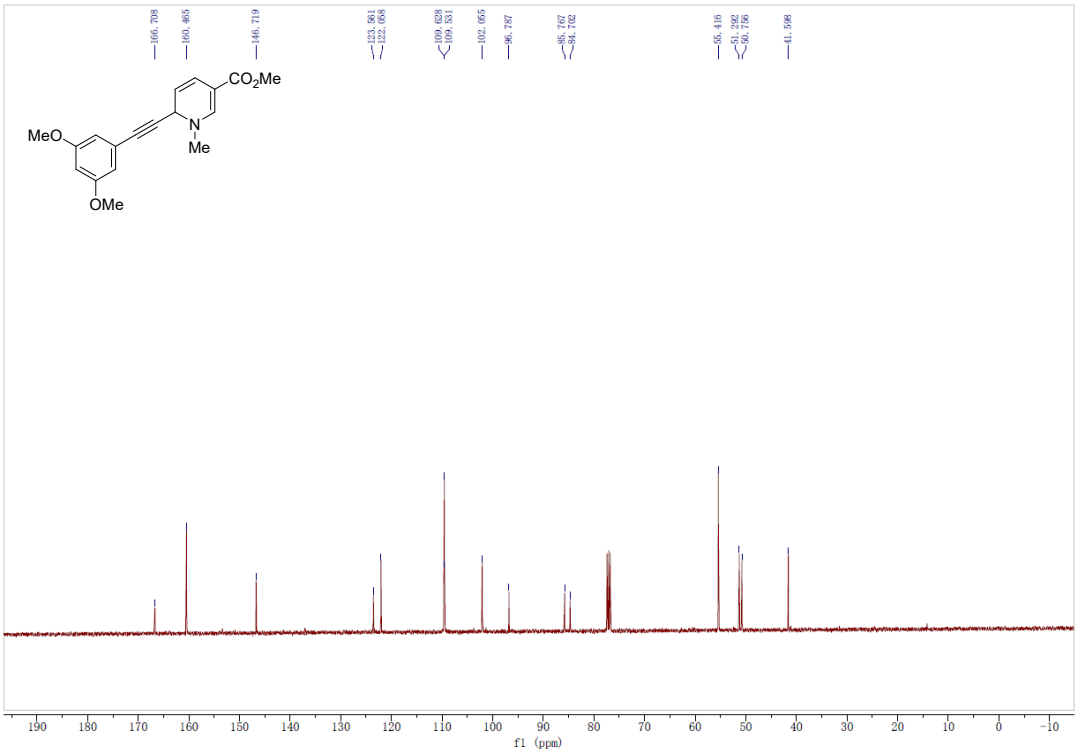
^{13}C NMR of 3f



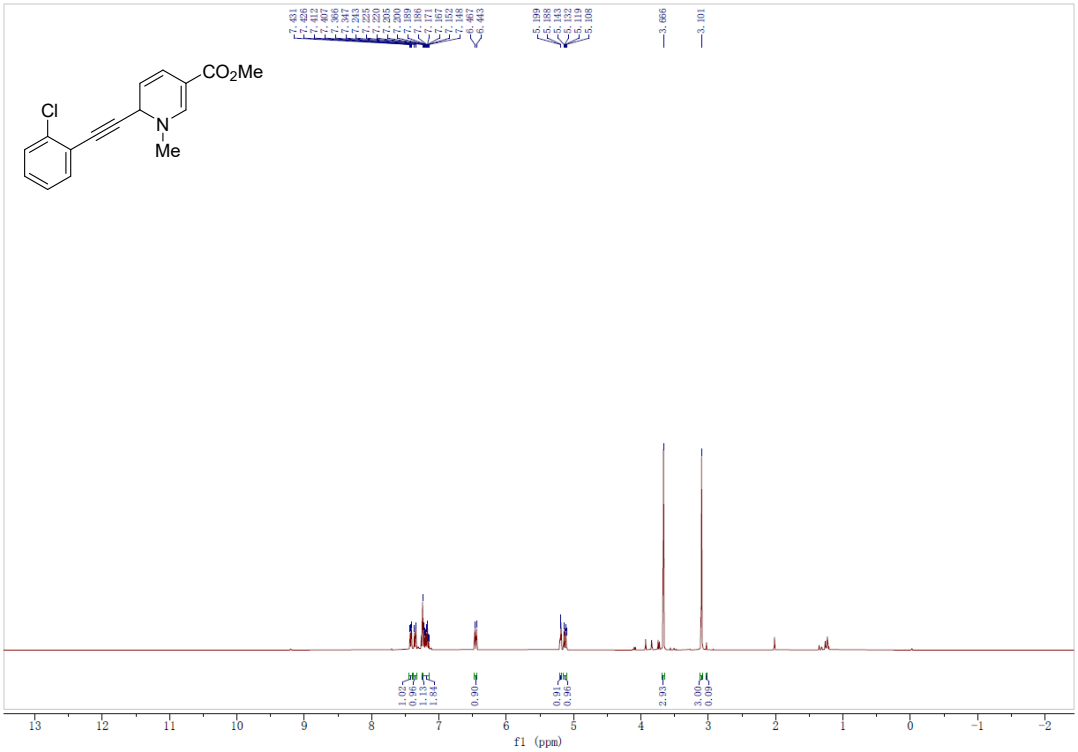
^{1}H NMR of 3g



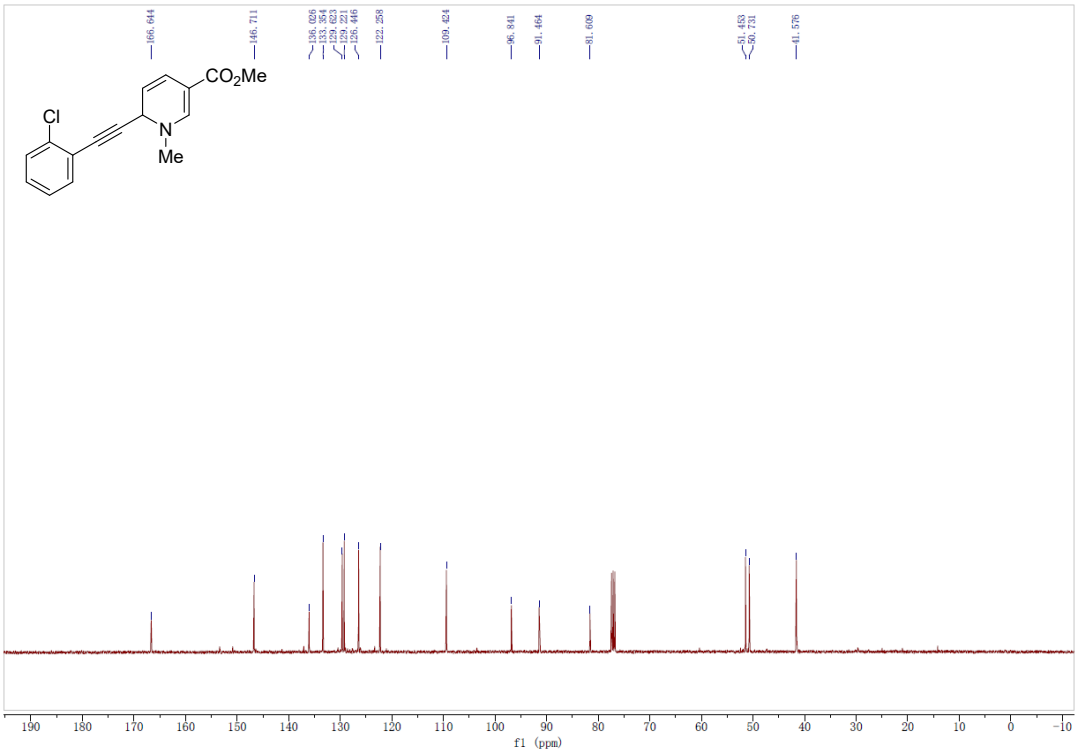
^{13}C NMR of 3g



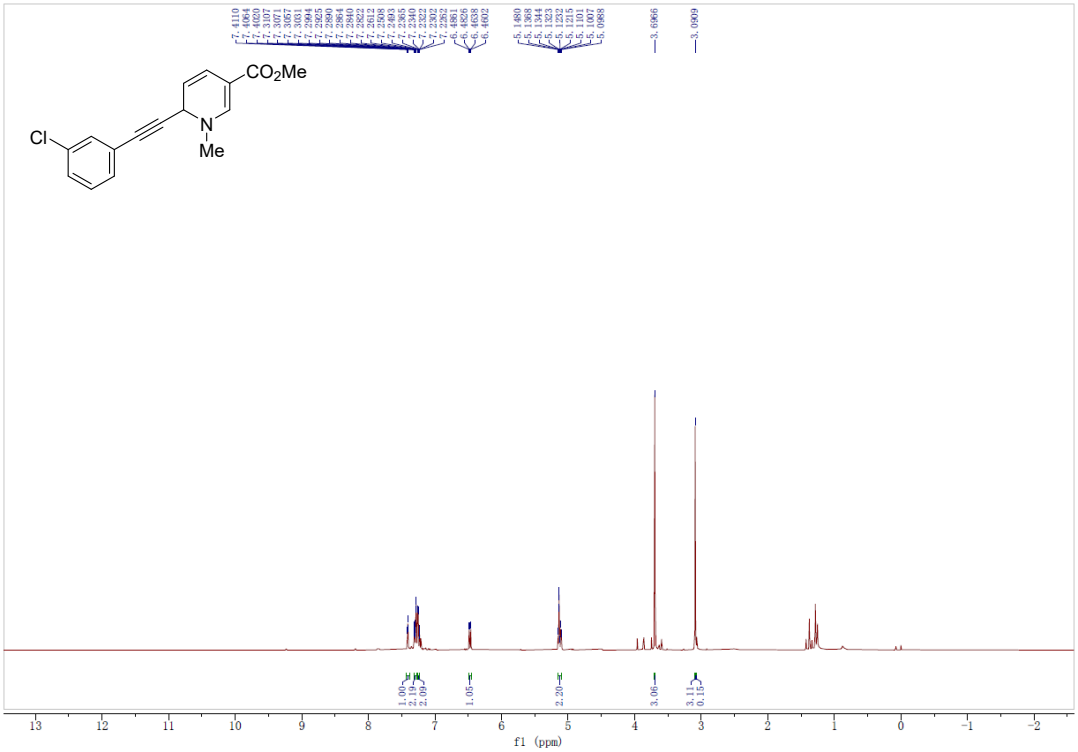
^{1}H NMR of 3h



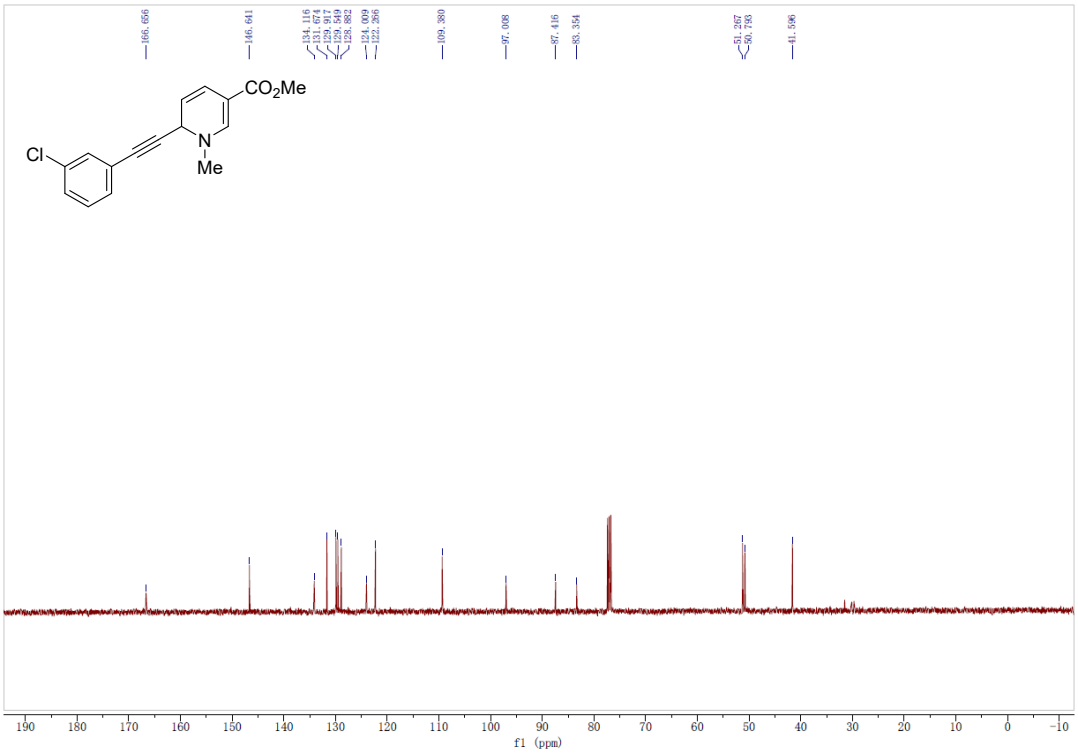
^{13}C NMR of 3h



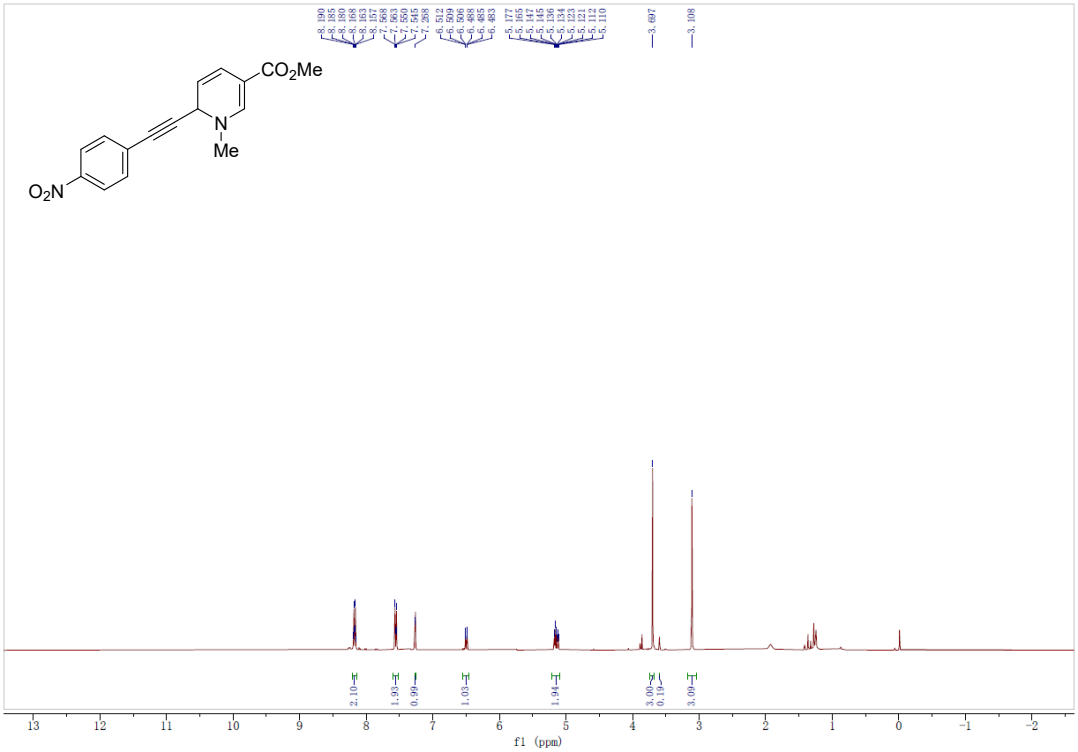
^{1}H NMR of 3i



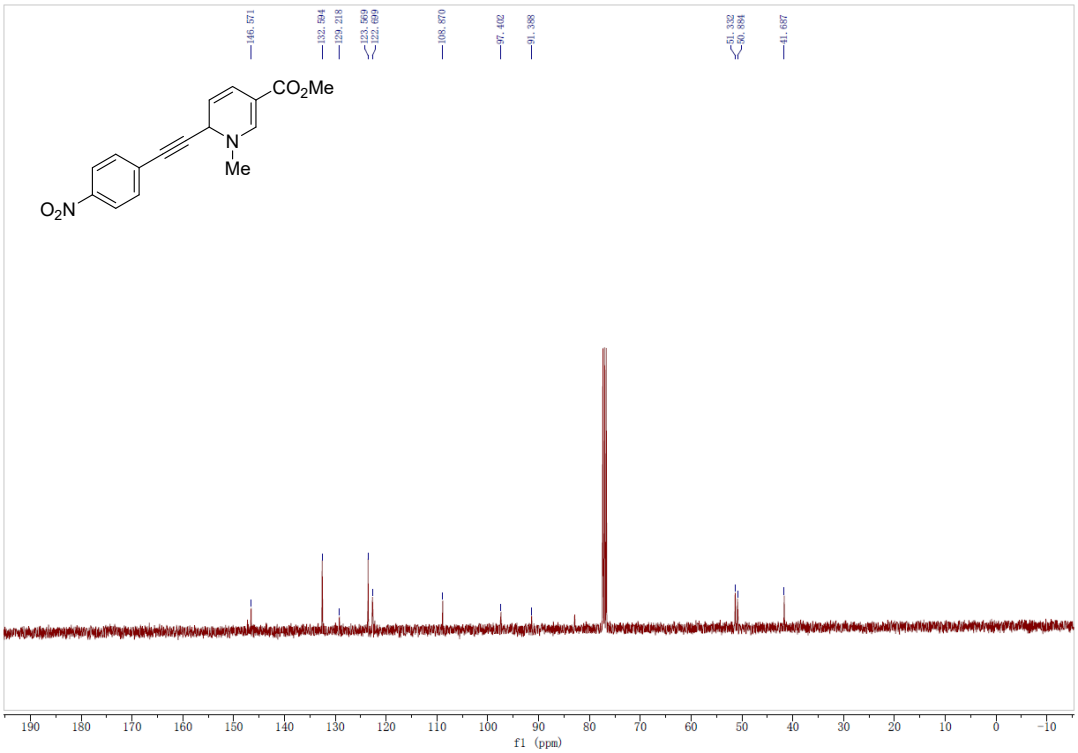
^{13}C NMR of 3i



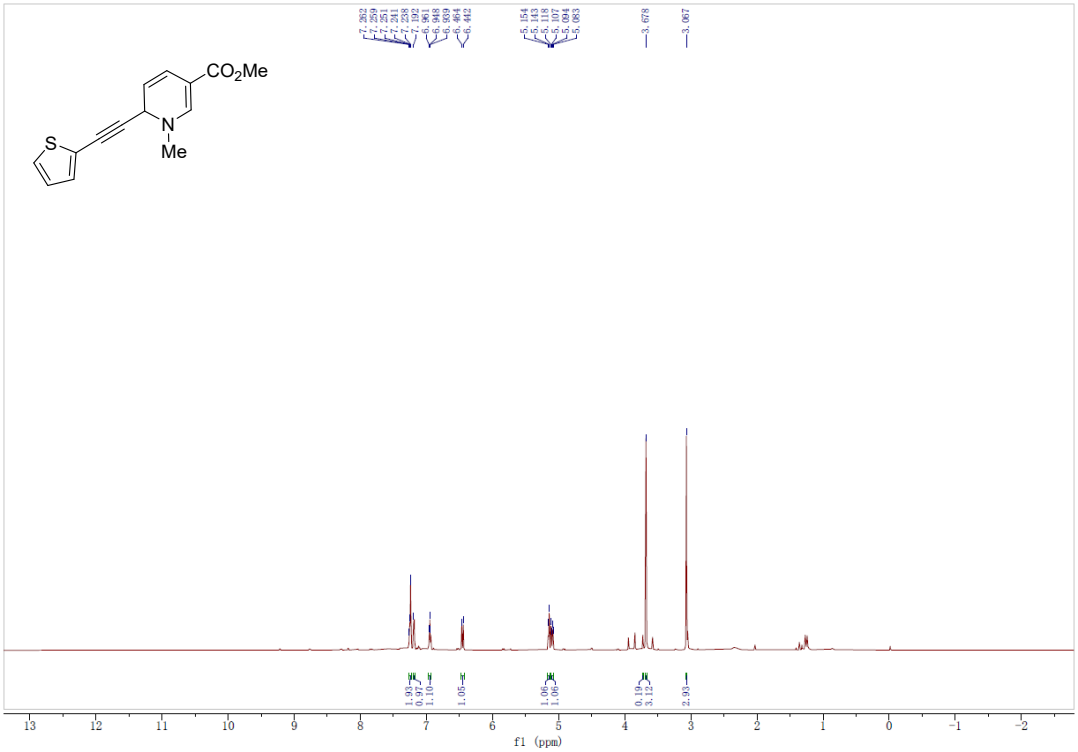
^{1}H NMR of 3j



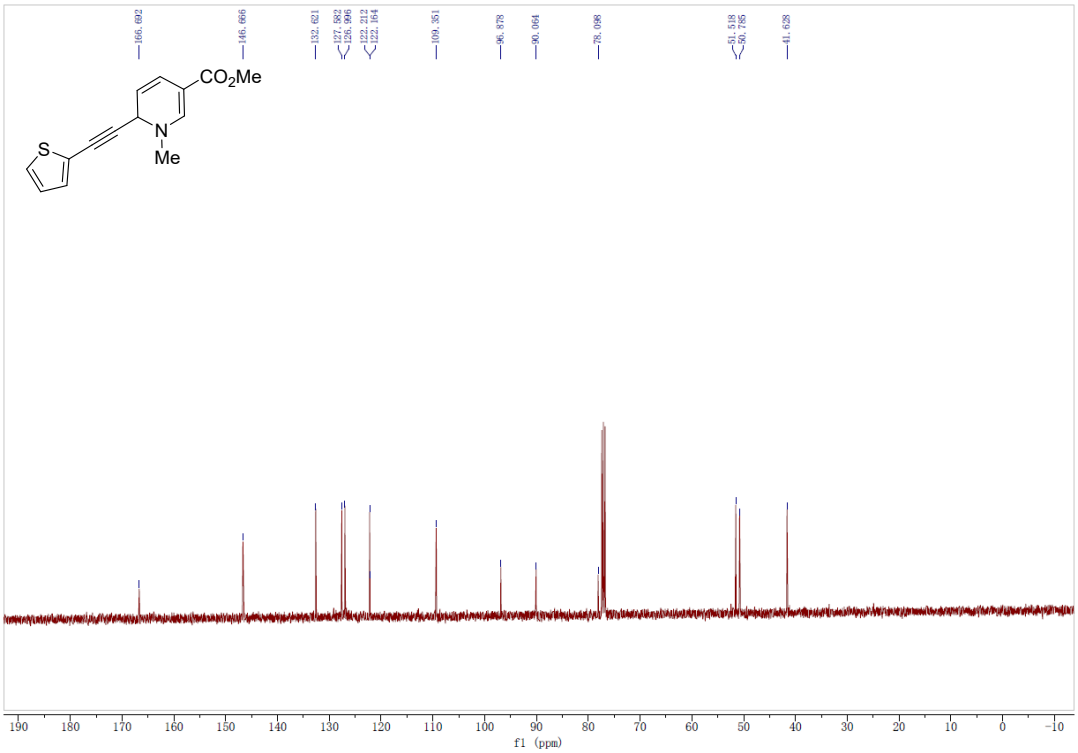
^{13}C NMR of 3j



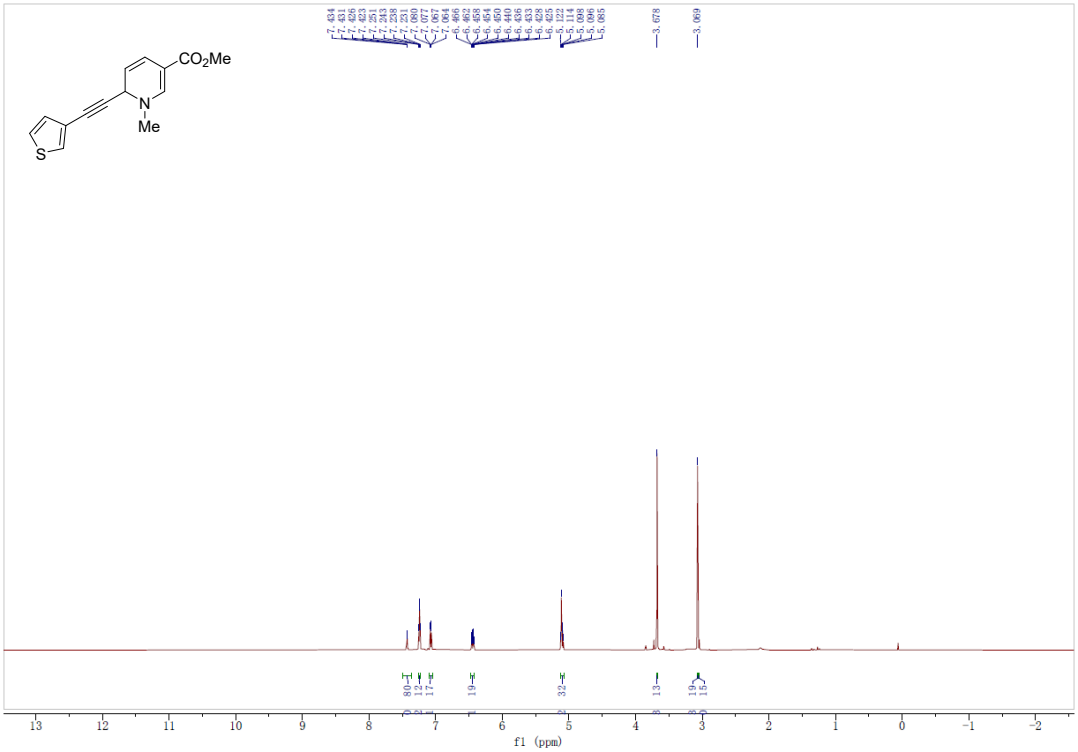
^{1}H NMR of 3k



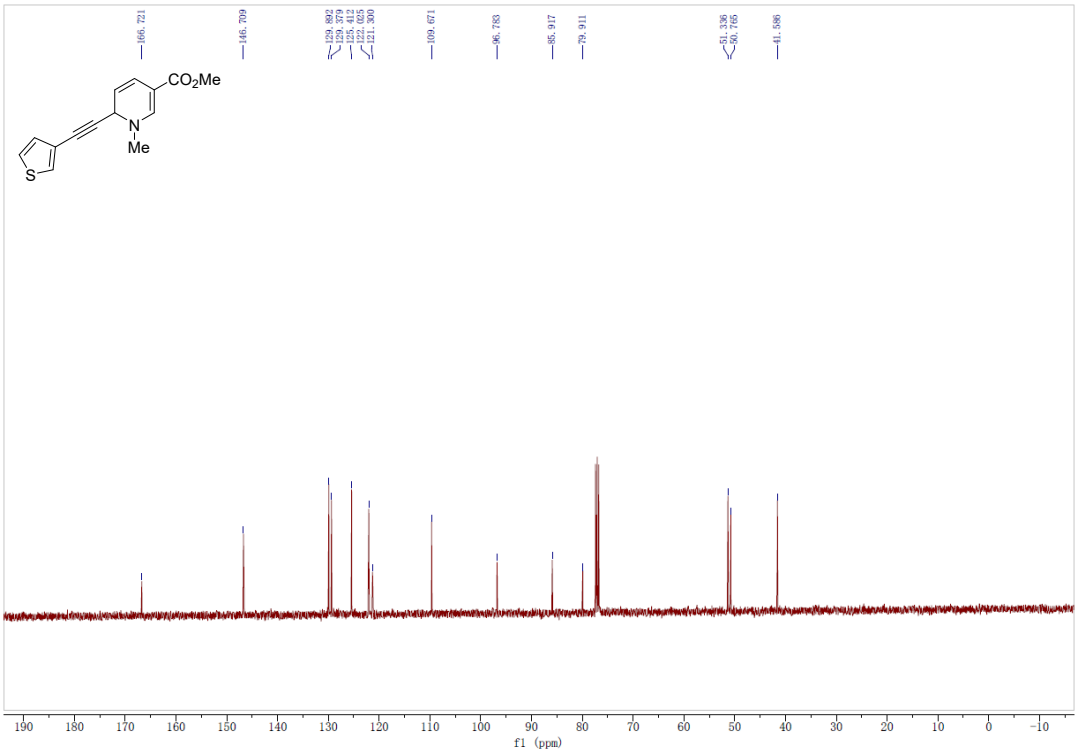
^{13}C NMR of 3k



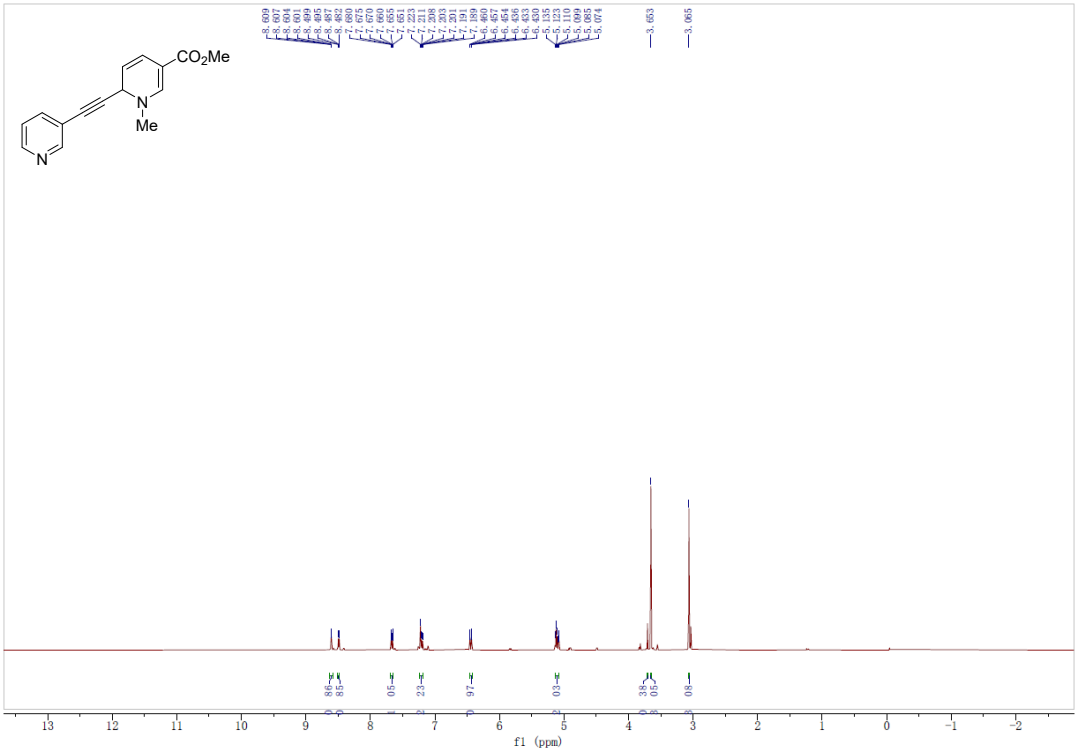
^{1}H NMR of 3l



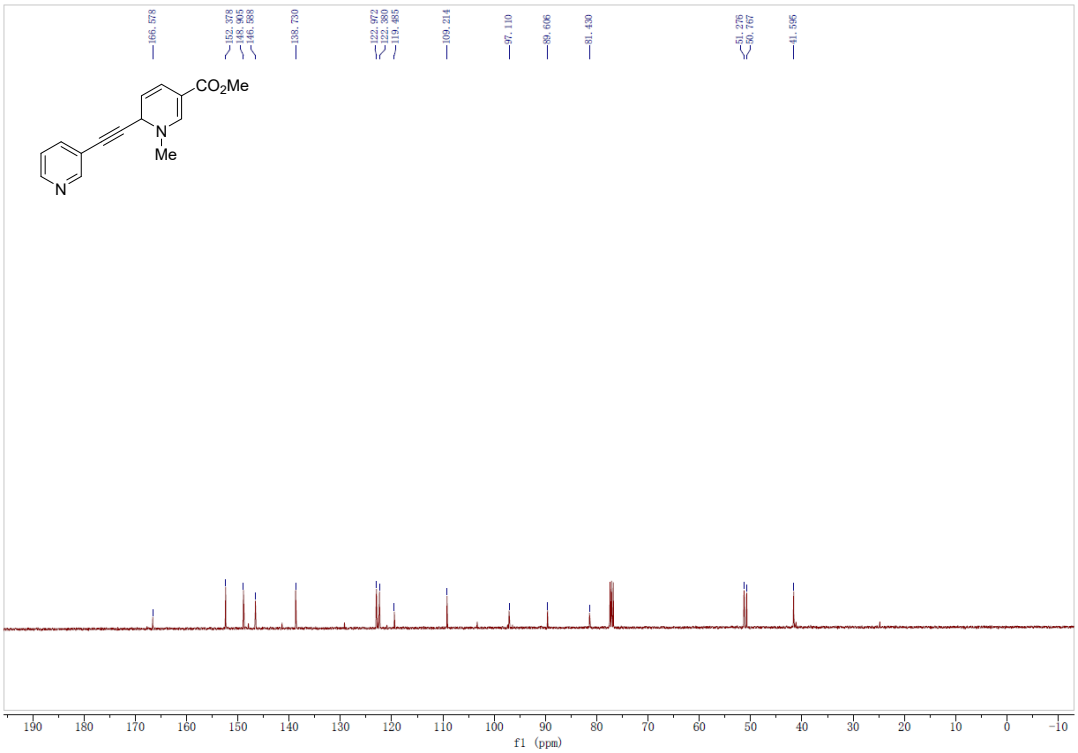
^{13}C NMR of 3l



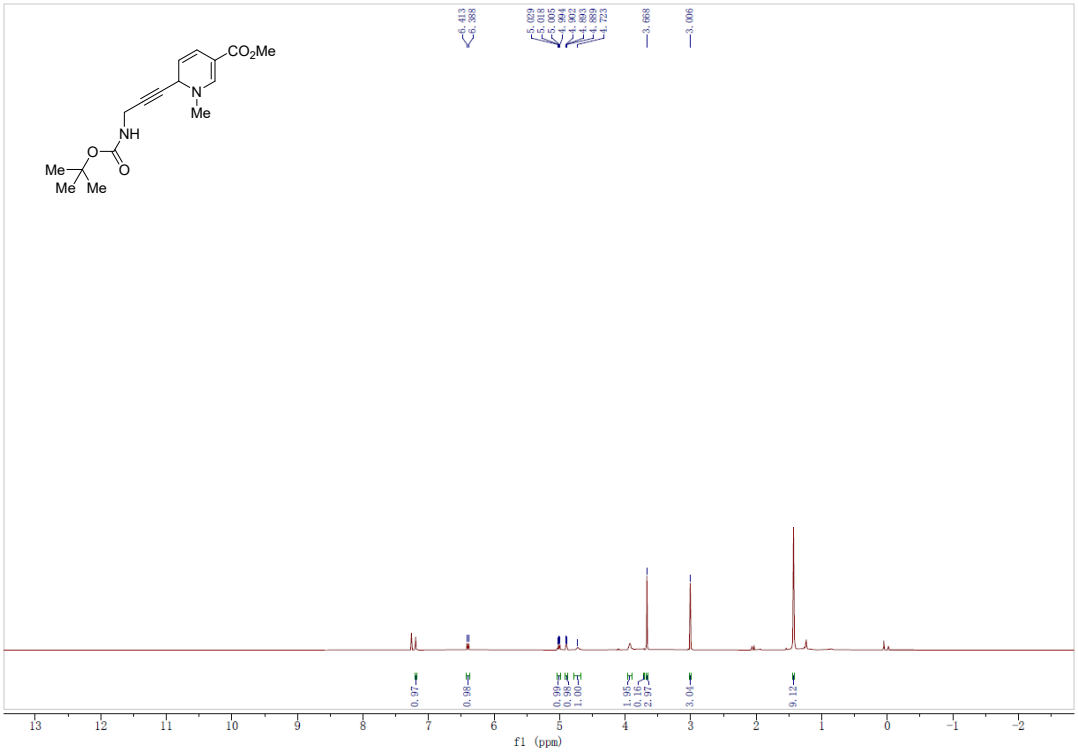
^{1}H NMR of 3m



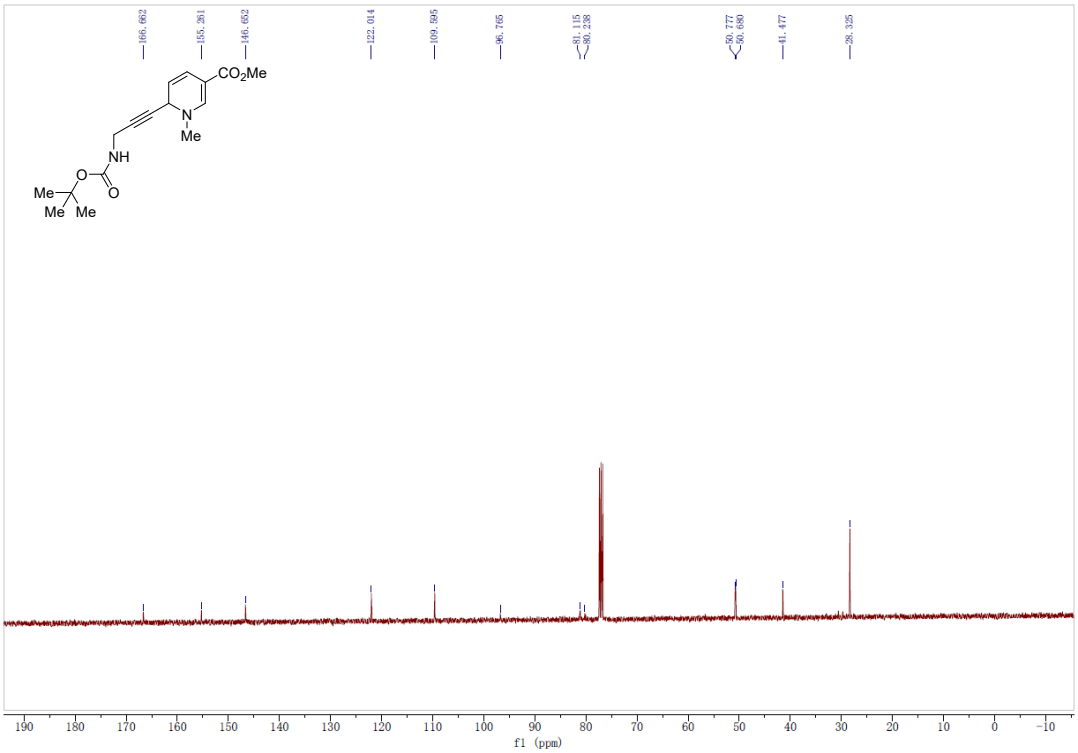
^{13}C NMR of 3m



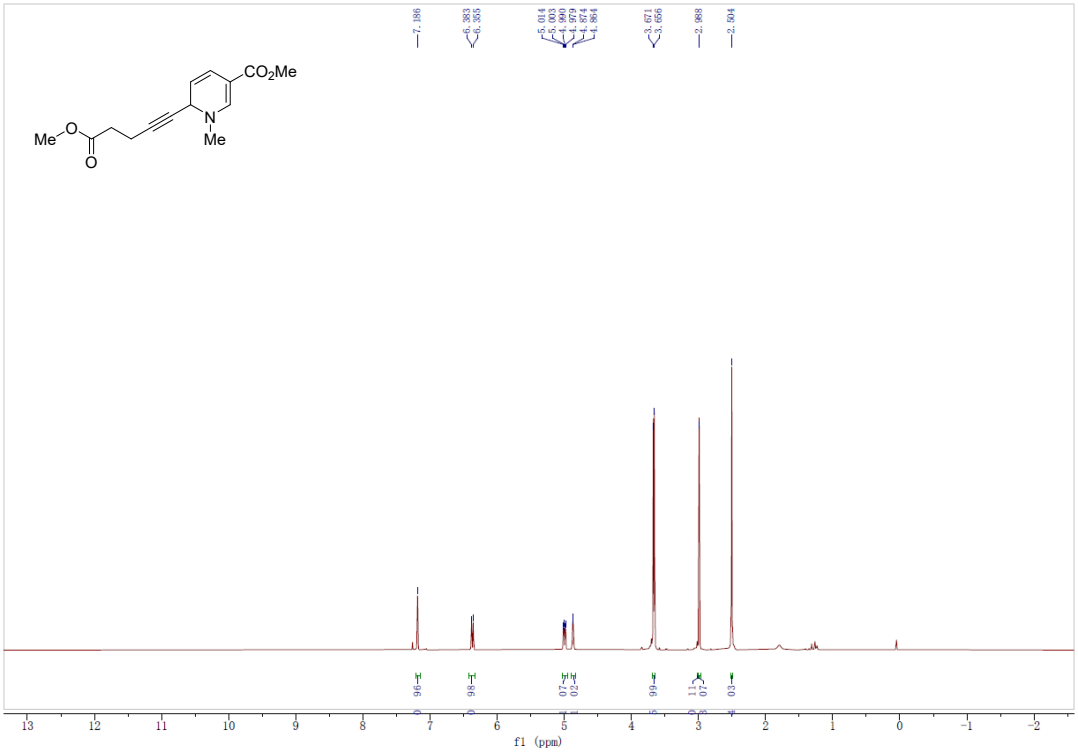
^{1}H NMR of 3n



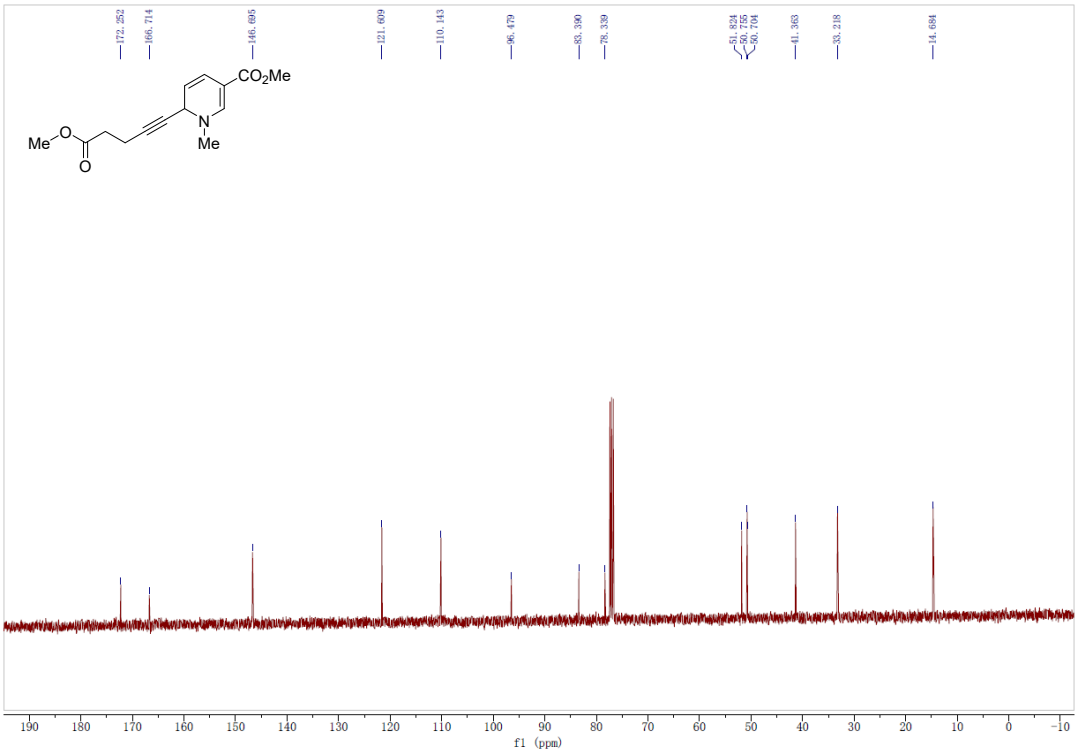
^{13}C NMR of 3n



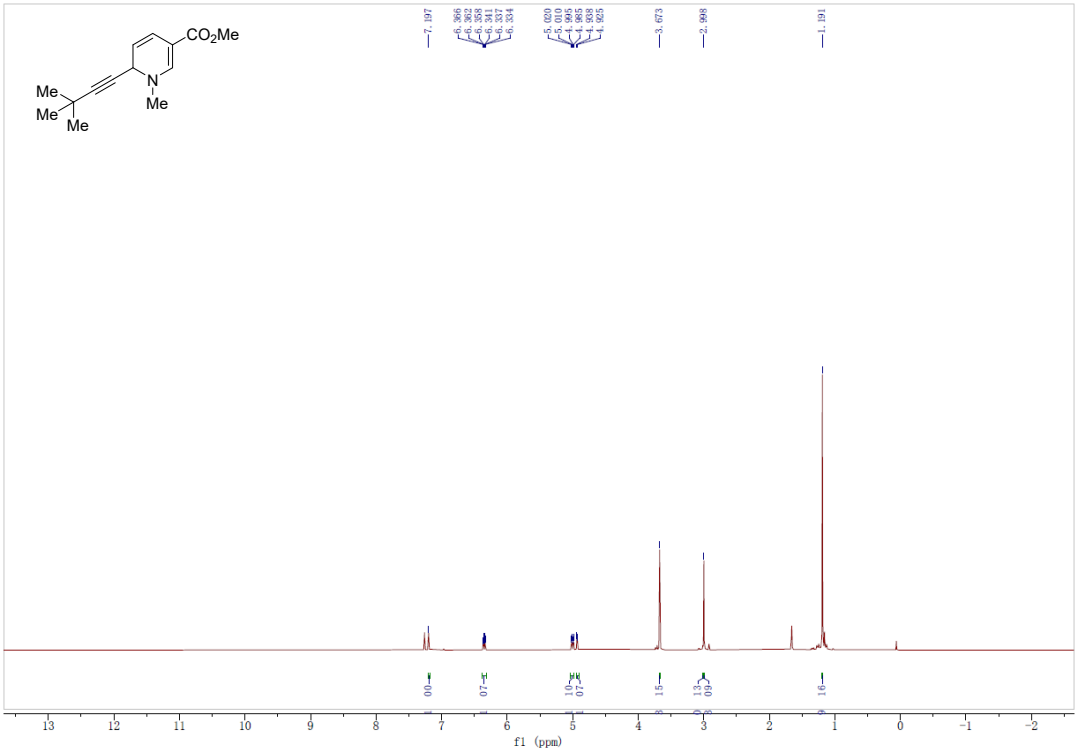
^{1}H NMR of 3o



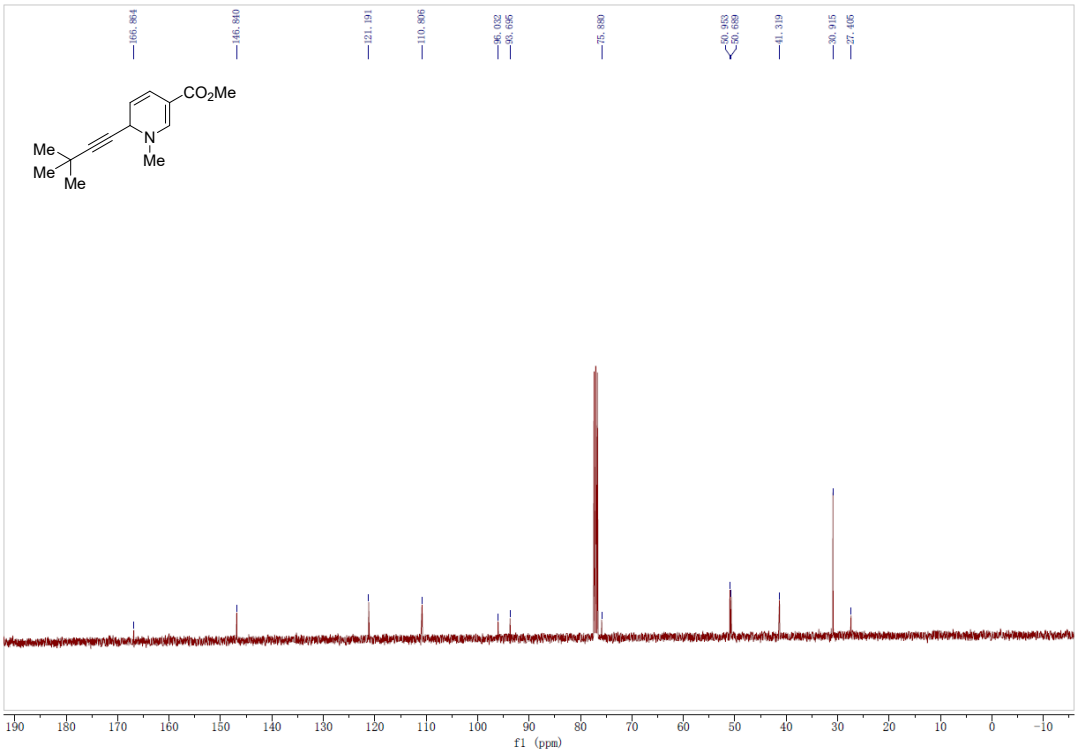
^{13}C NMR of 3o



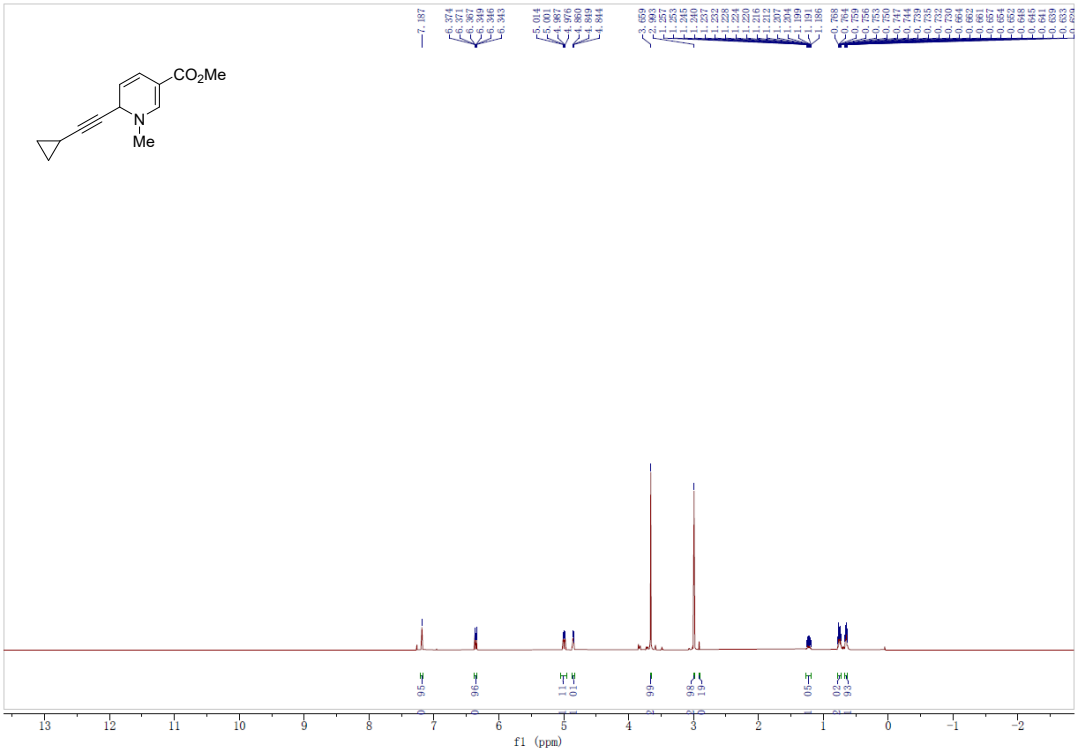
^{1}H NMR of 3p



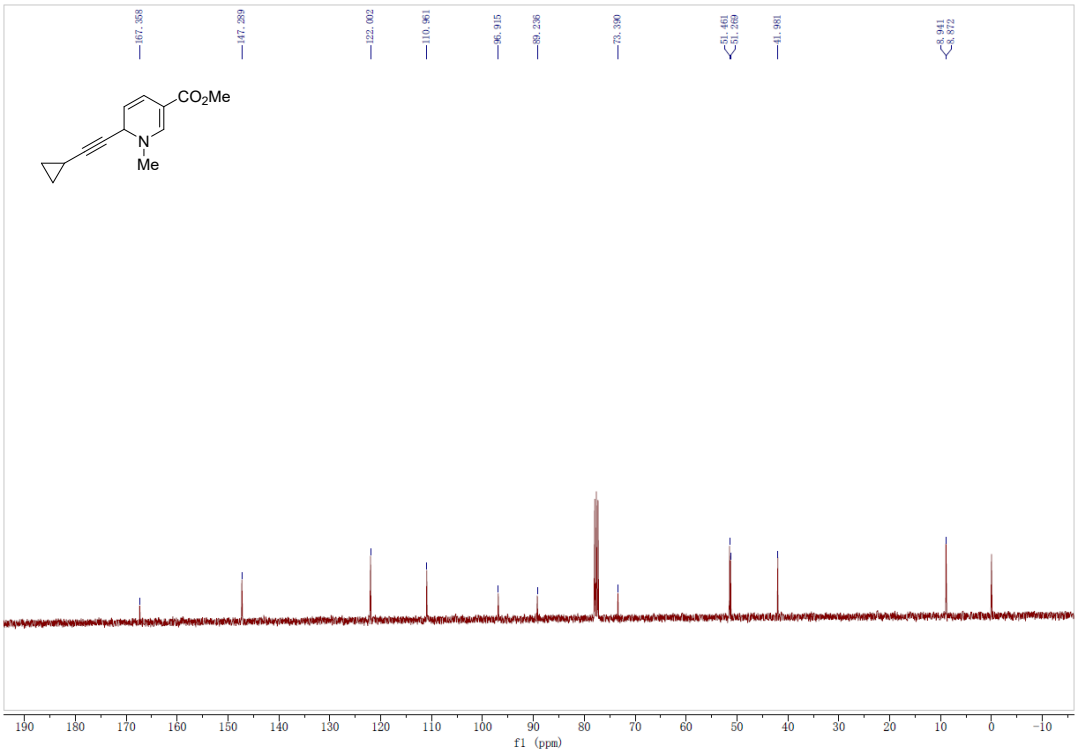
^{13}C NMR of 3p



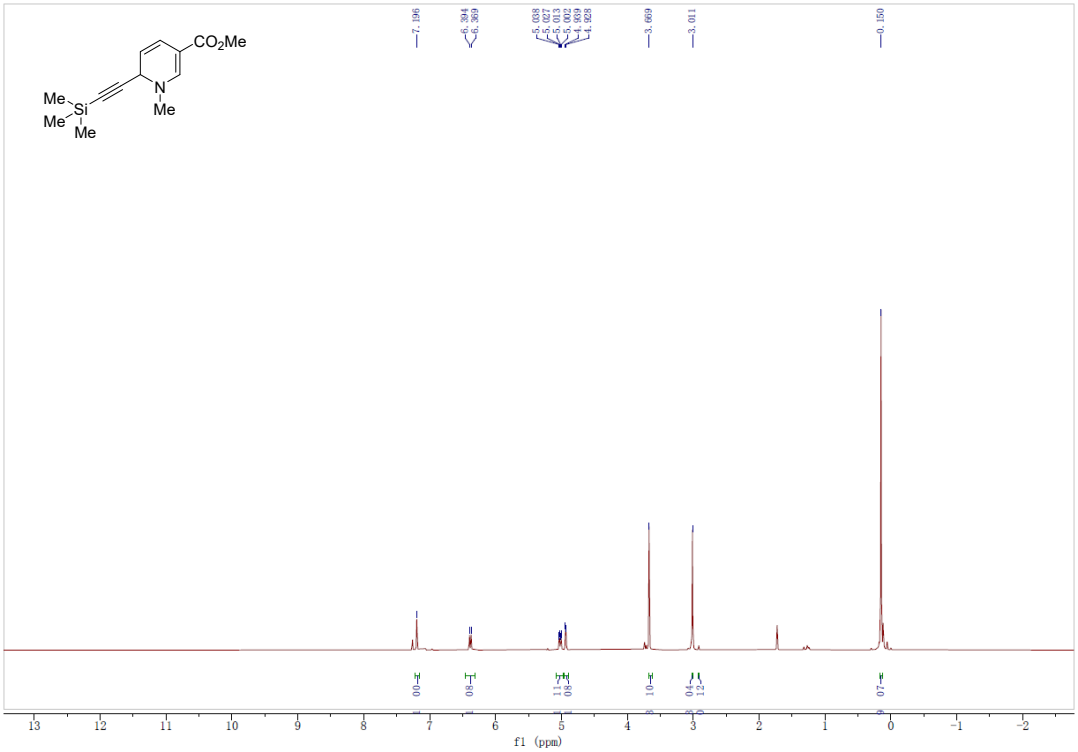
^{1}H NMR of 3q



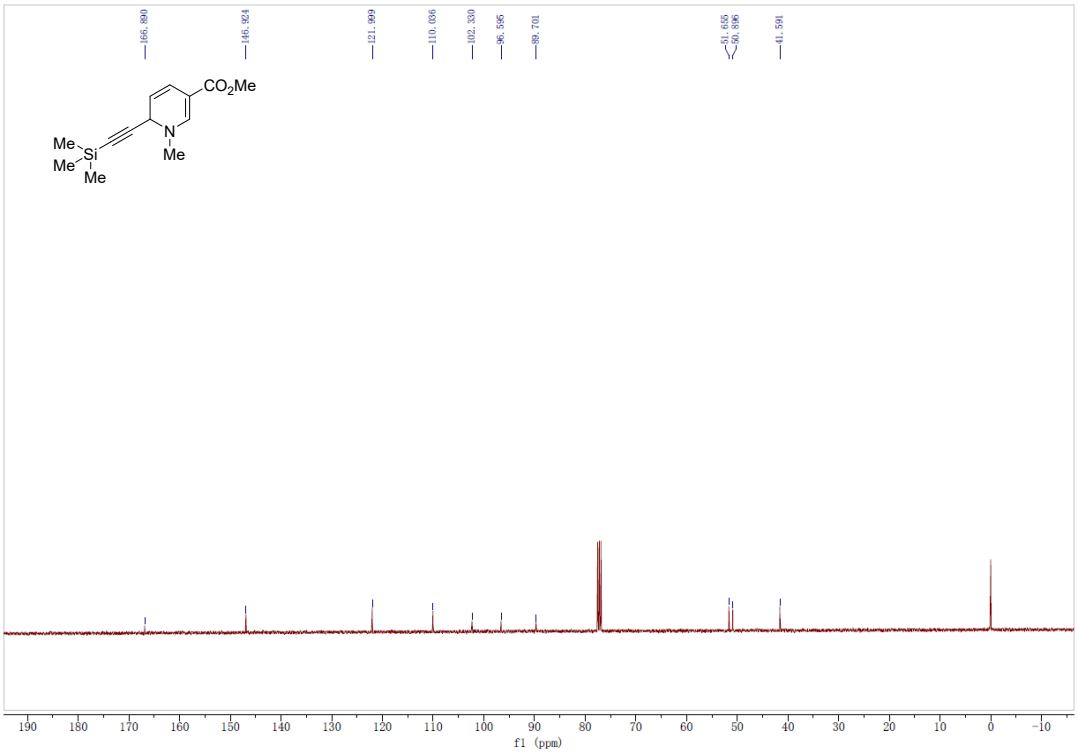
^{13}C NMR of 3q



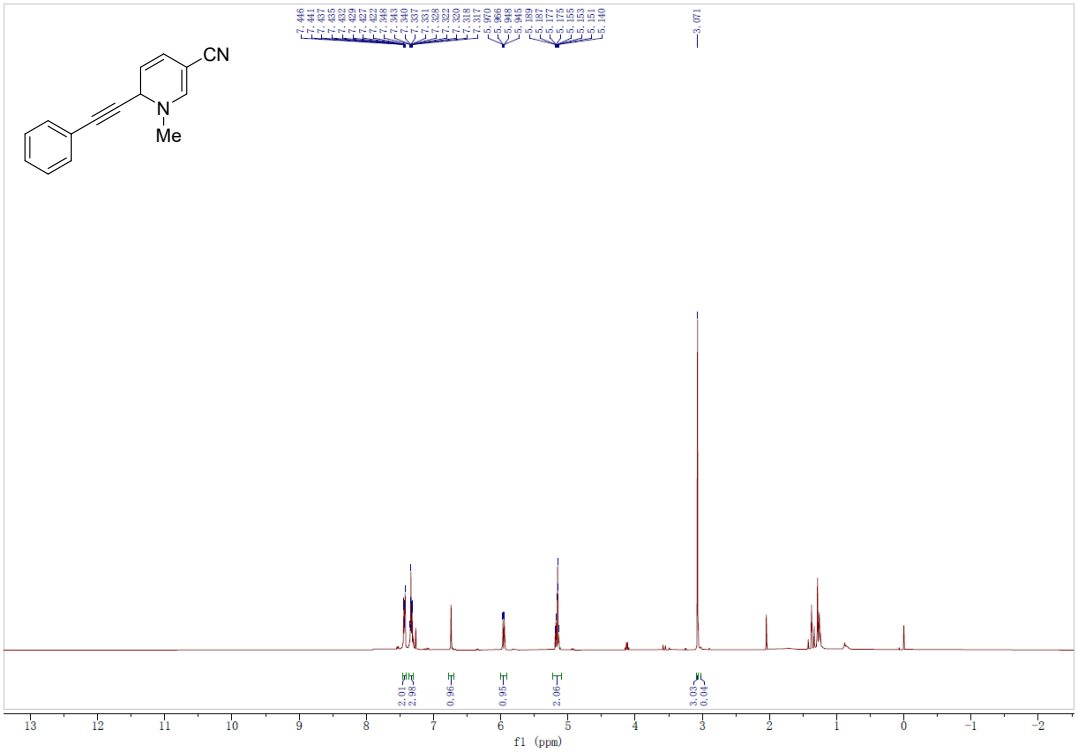
^{1}H NMR of 3r



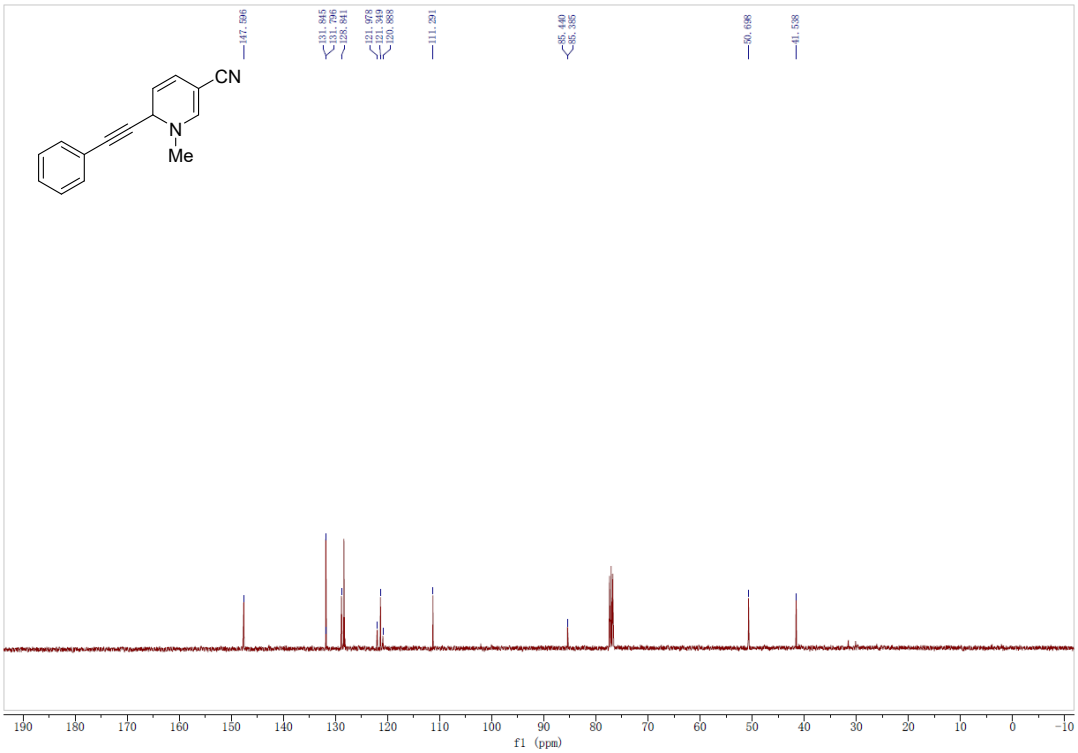
^{13}C NMR of 3r



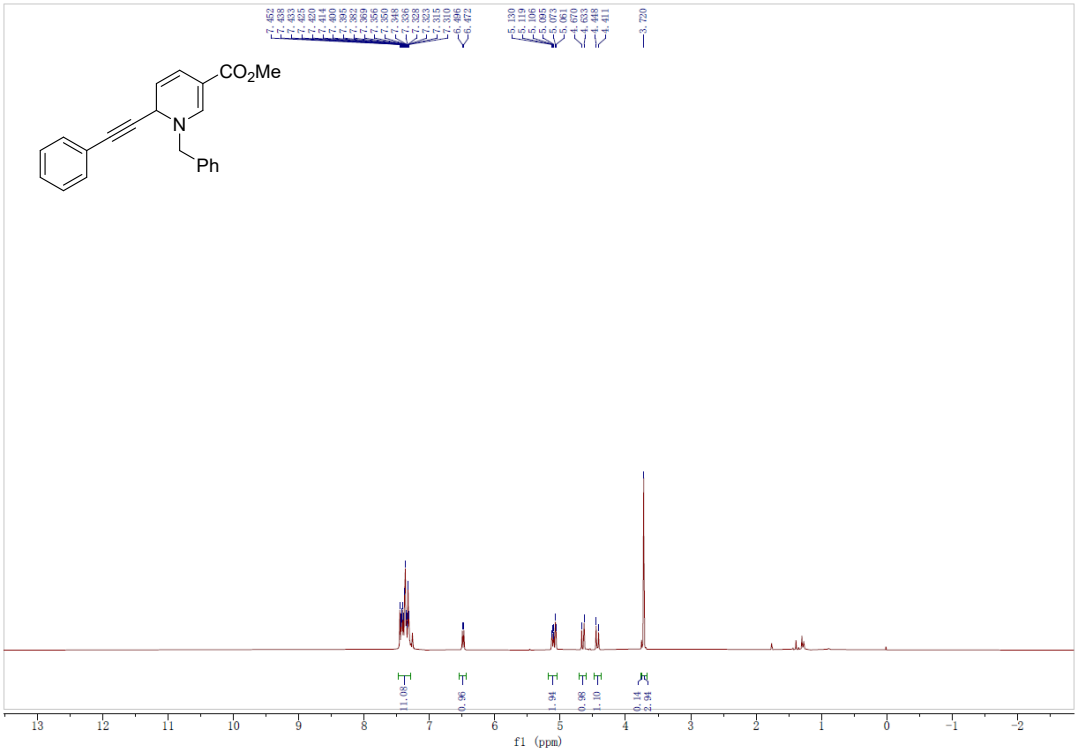
^{1}H NMR of 3s



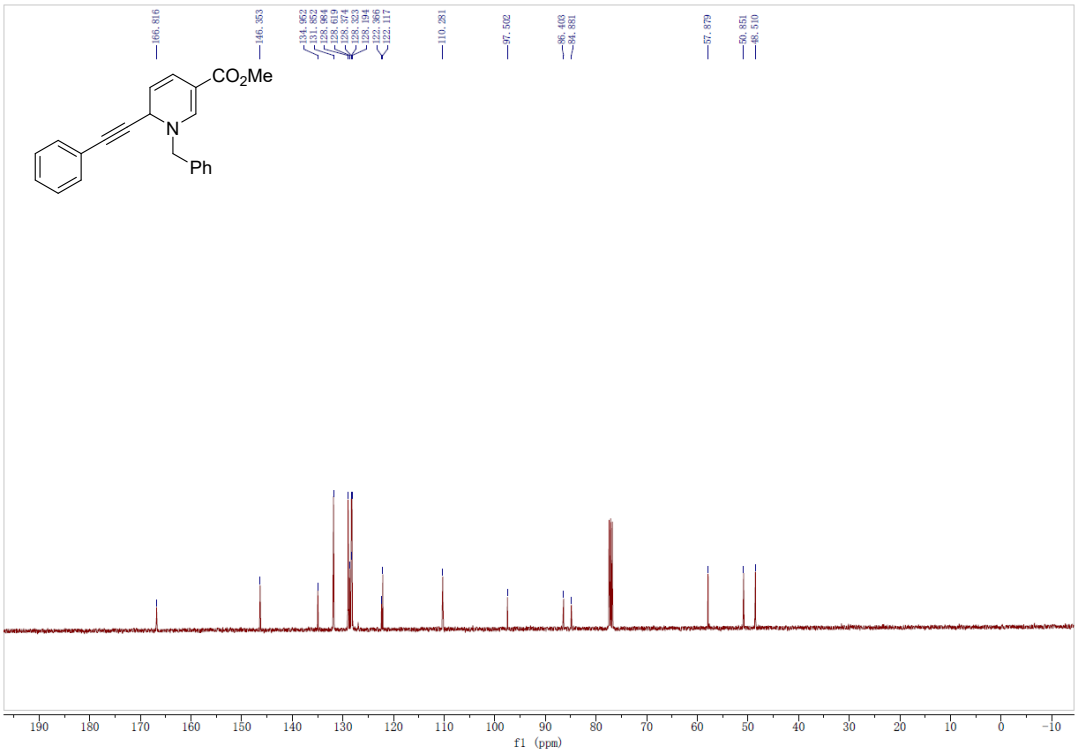
^{13}C NMR of 3s



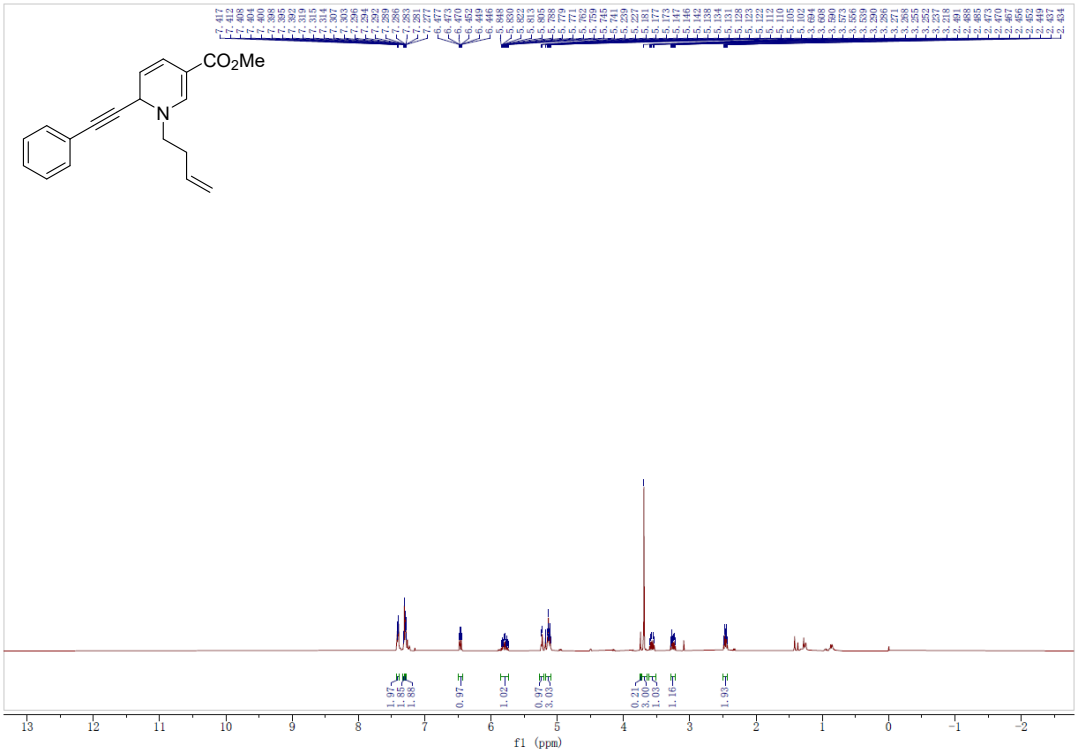
^{1}H NMR of 3t



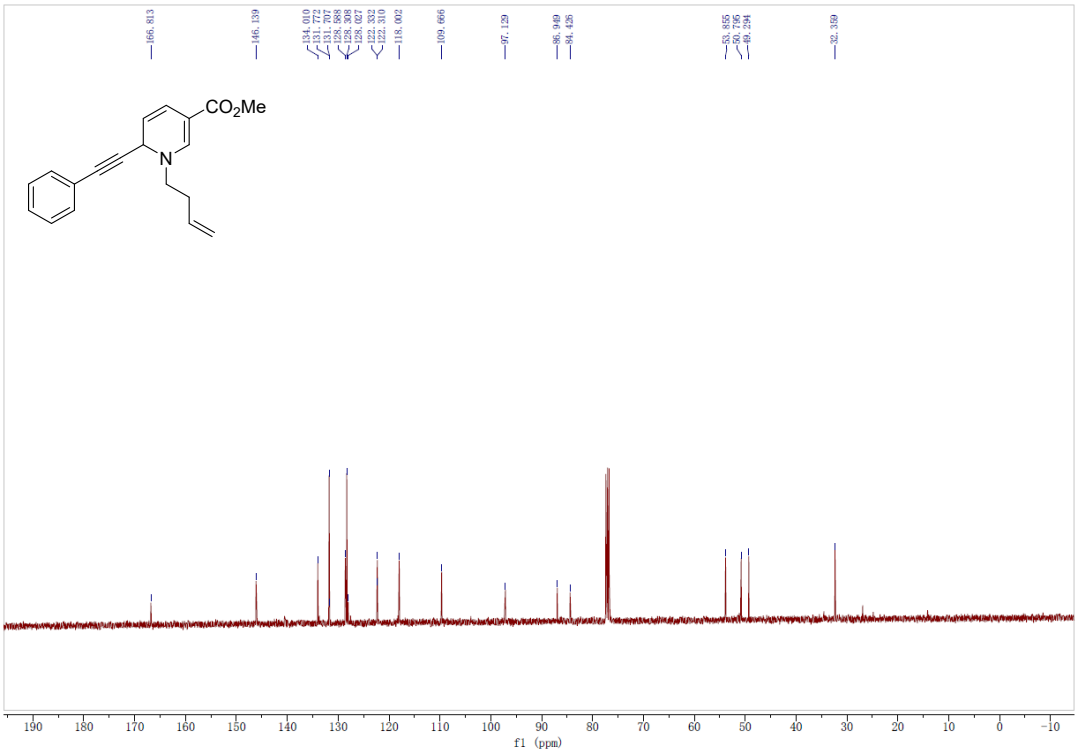
^{13}C NMR of 3t



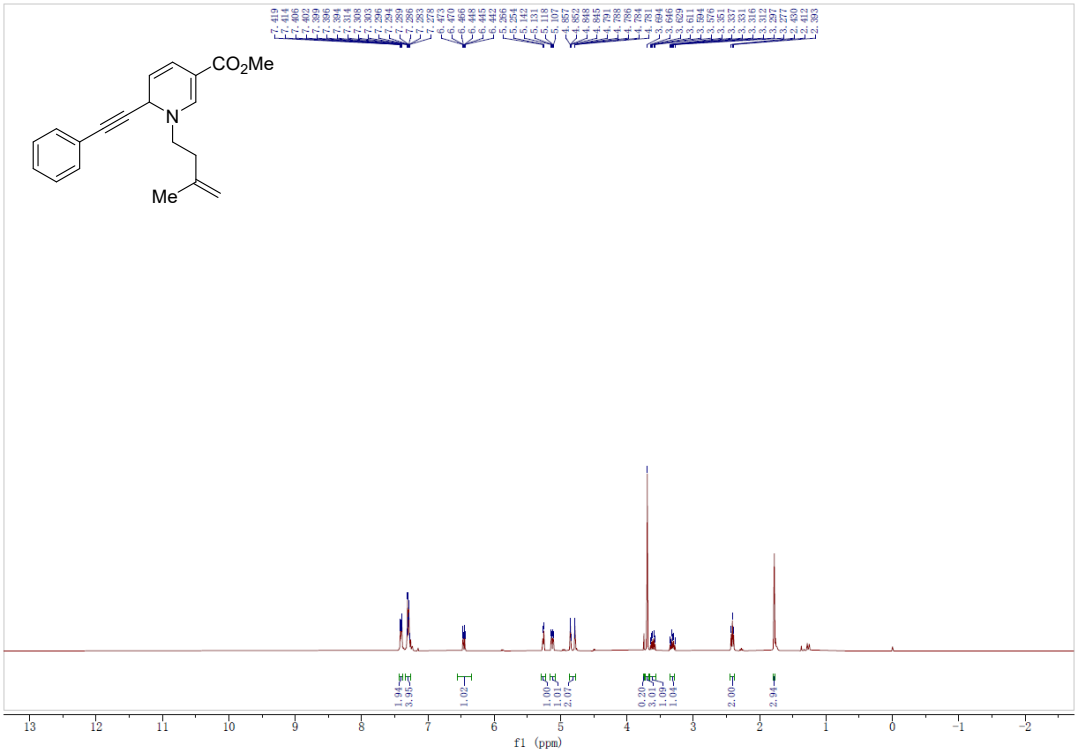
^{1}H NMR of 3u



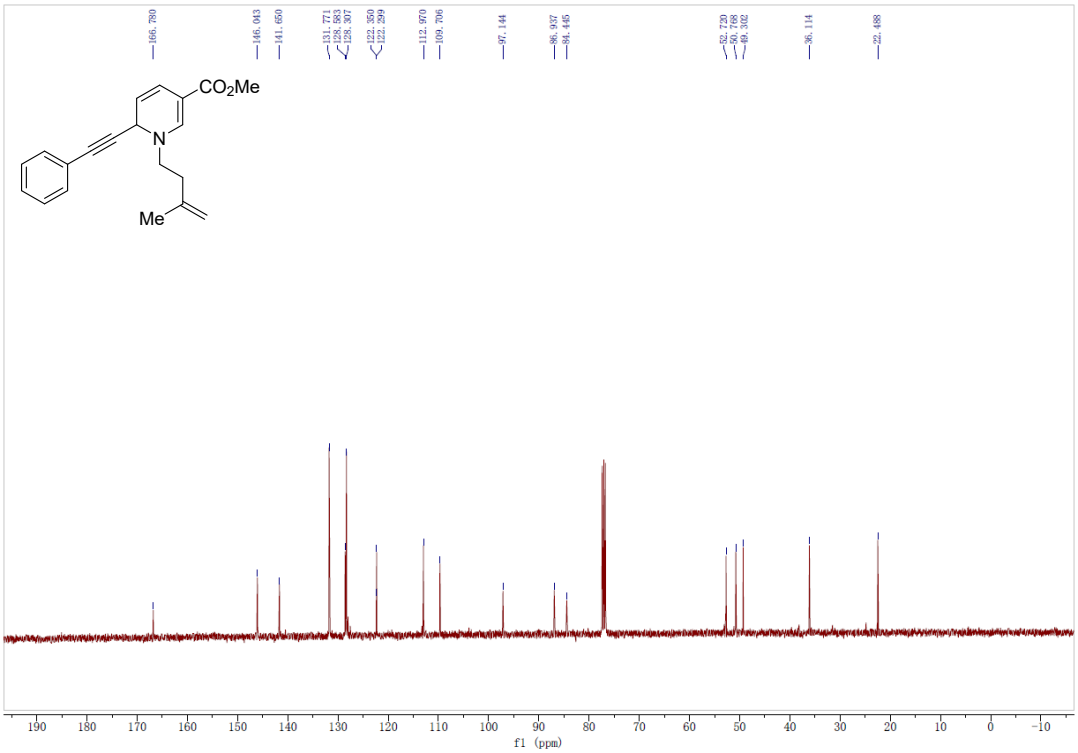
^{13}C NMR of 3u



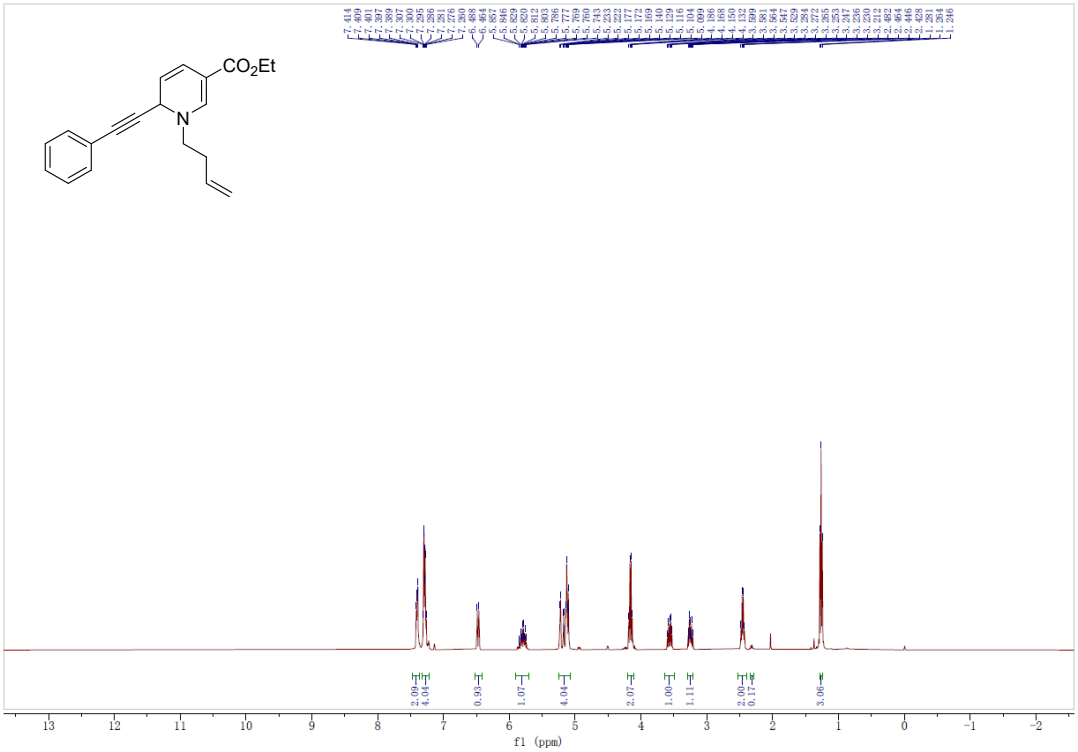
^{1}H NMR of 3v



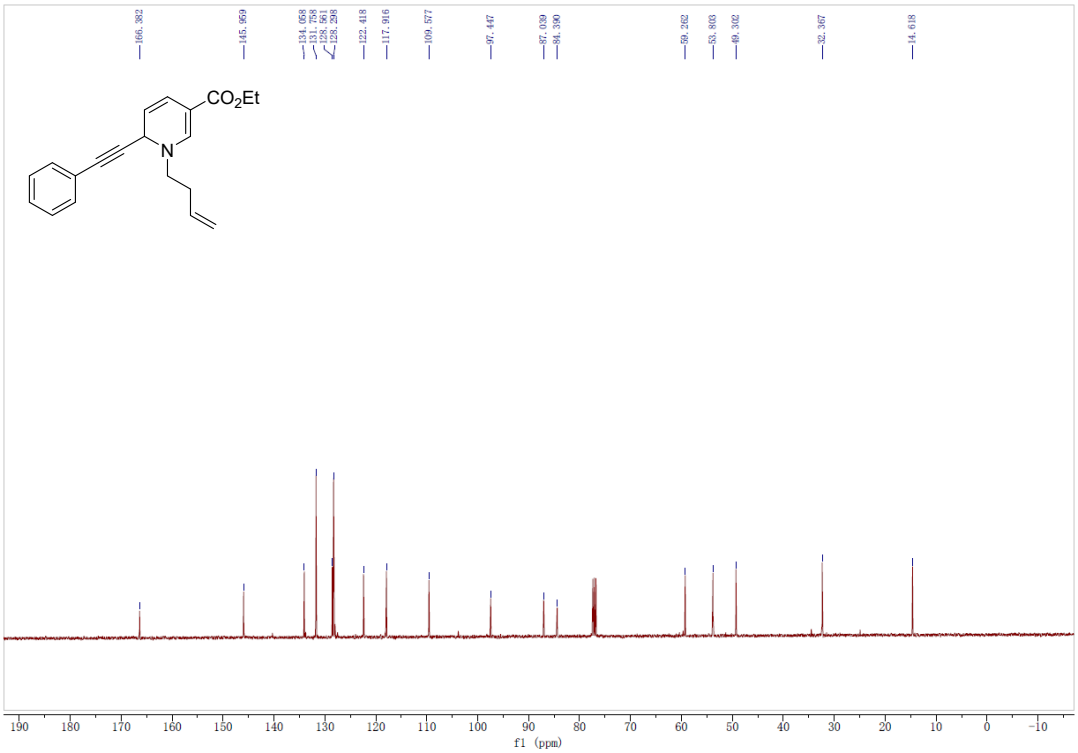
^{13}C NMR of 3v



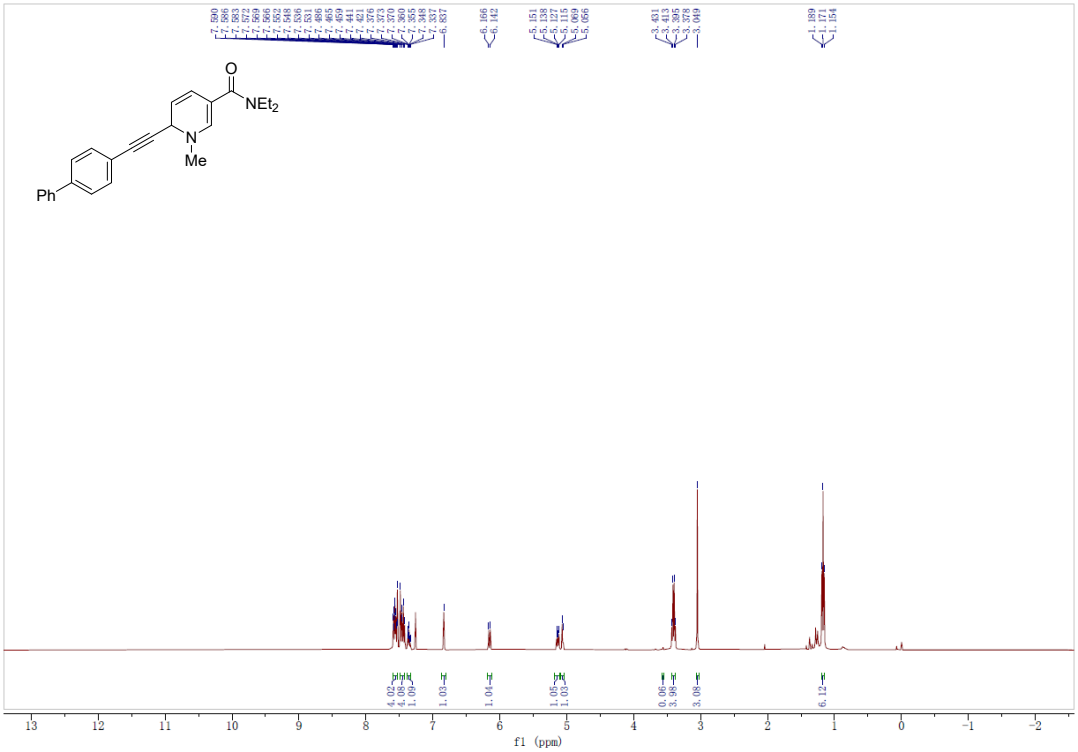
^{1}H NMR of 3w



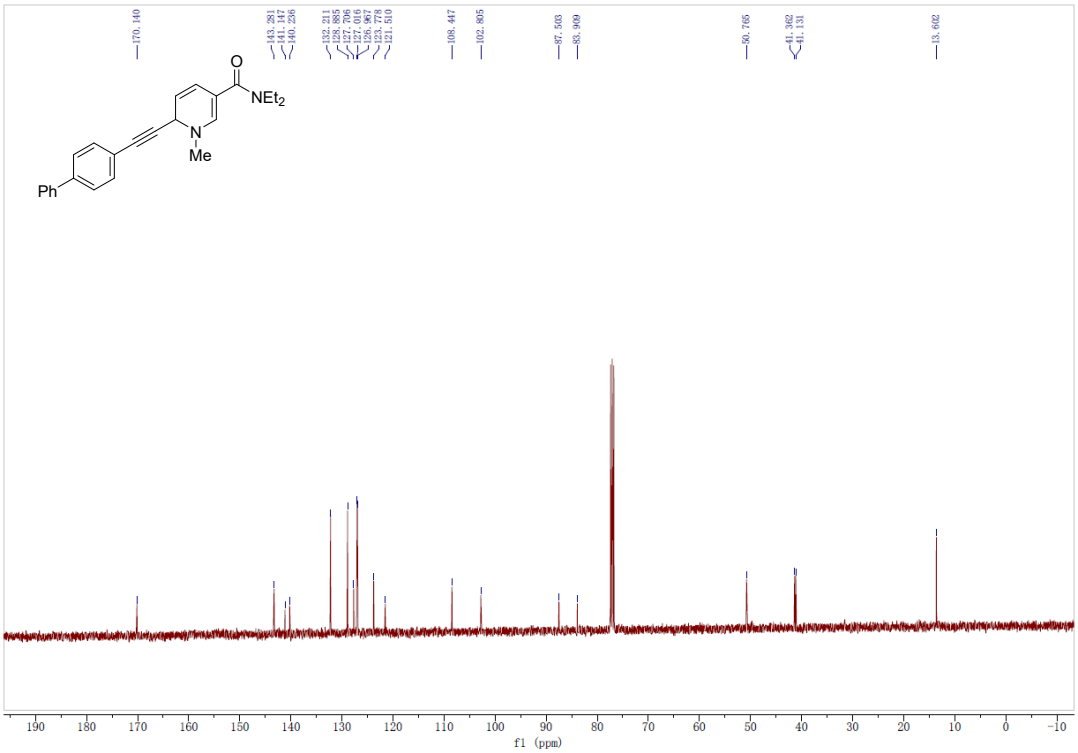
^{13}C NMR of 3w



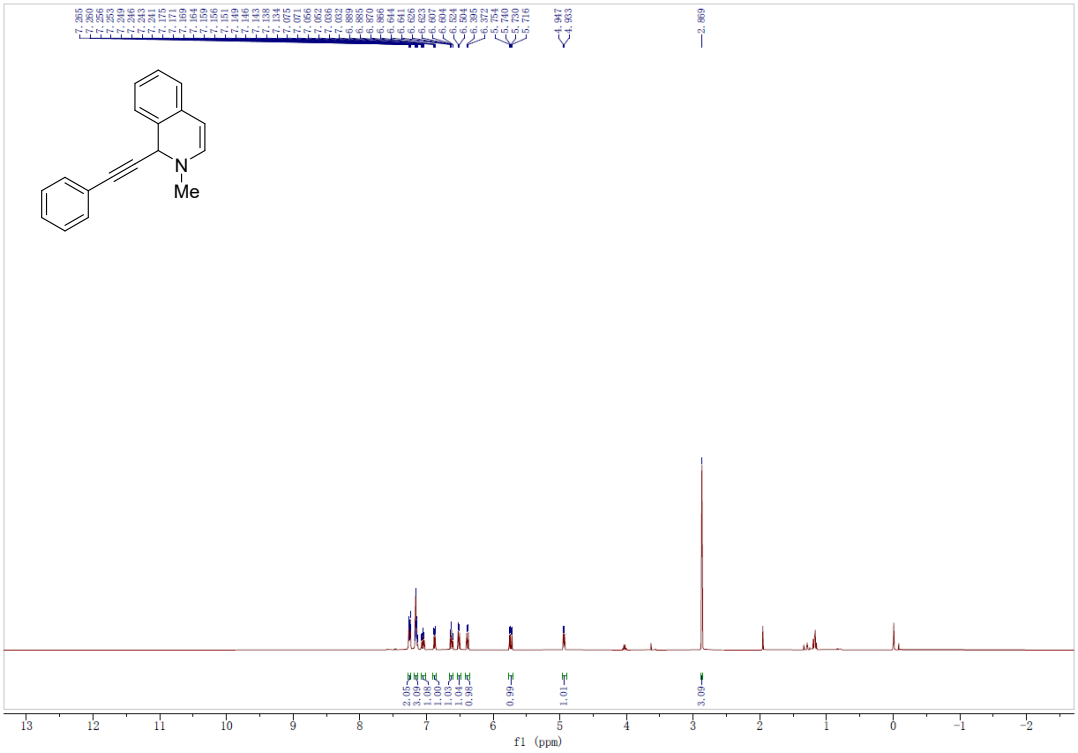
^{1}H NMR of 3x



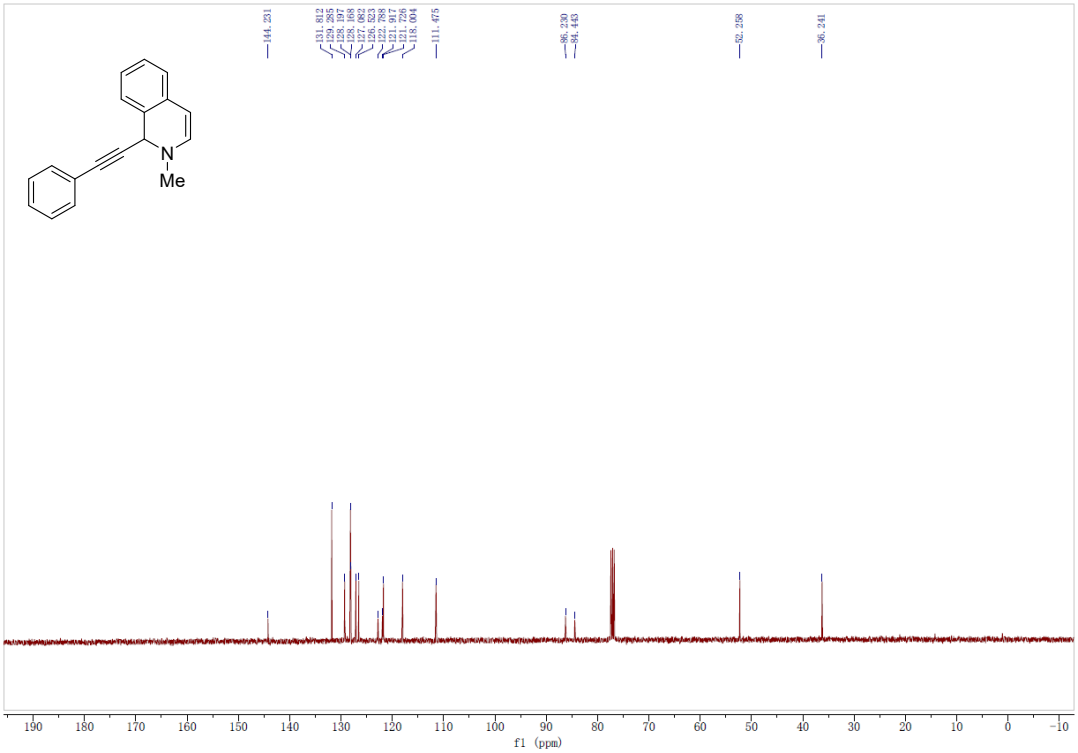
^{13}C NMR of 3x



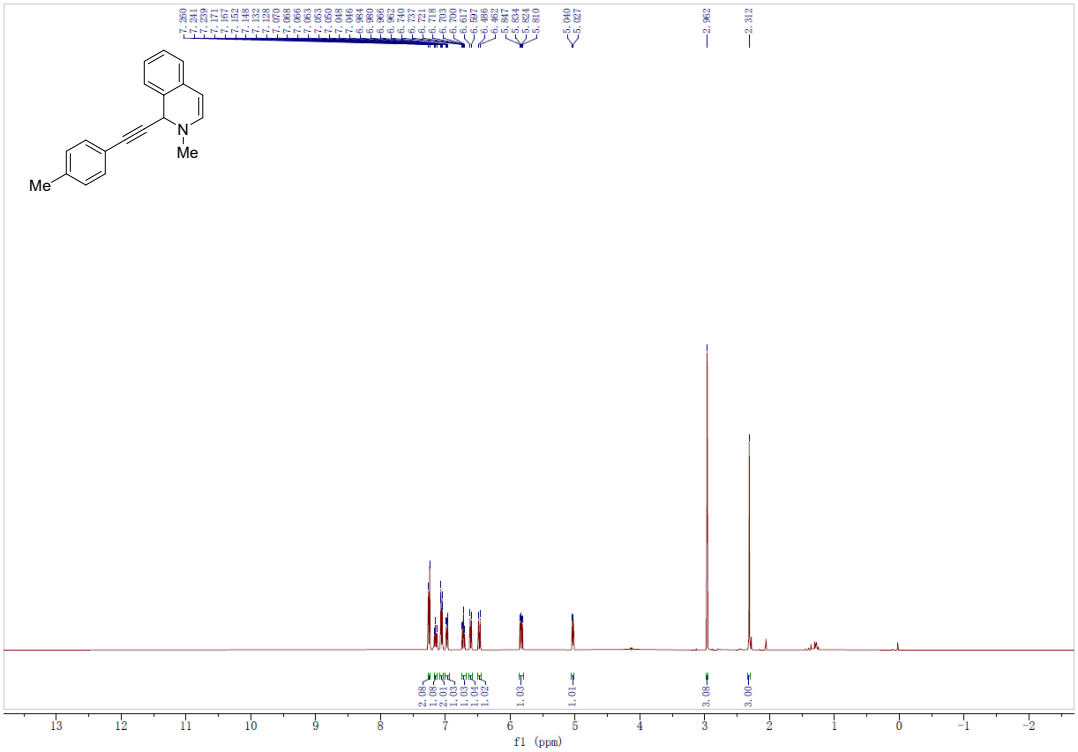
^{1}H NMR of 6a



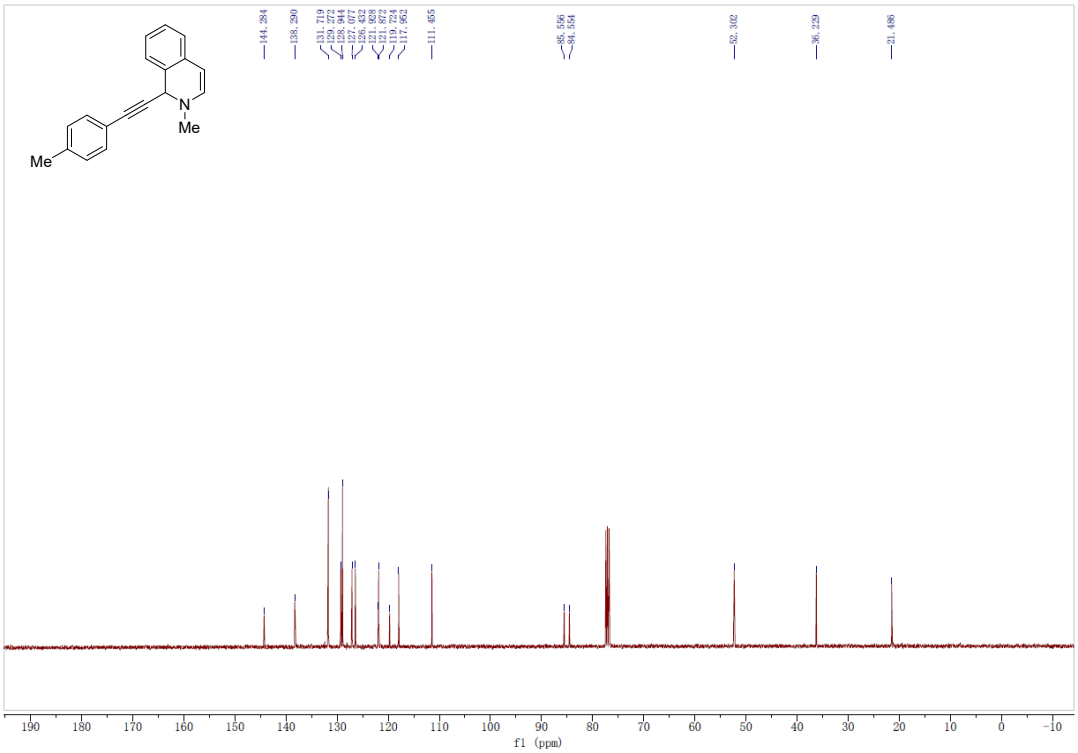
^{13}C NMR of 6a



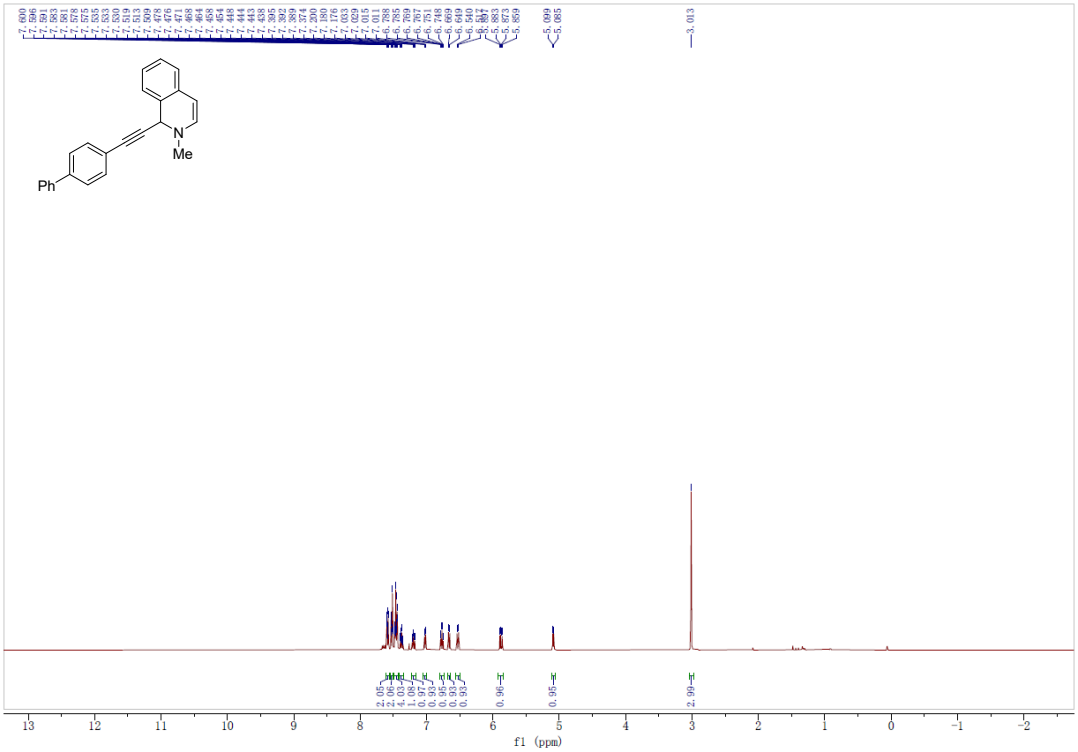
^{1}H NMR of 6b



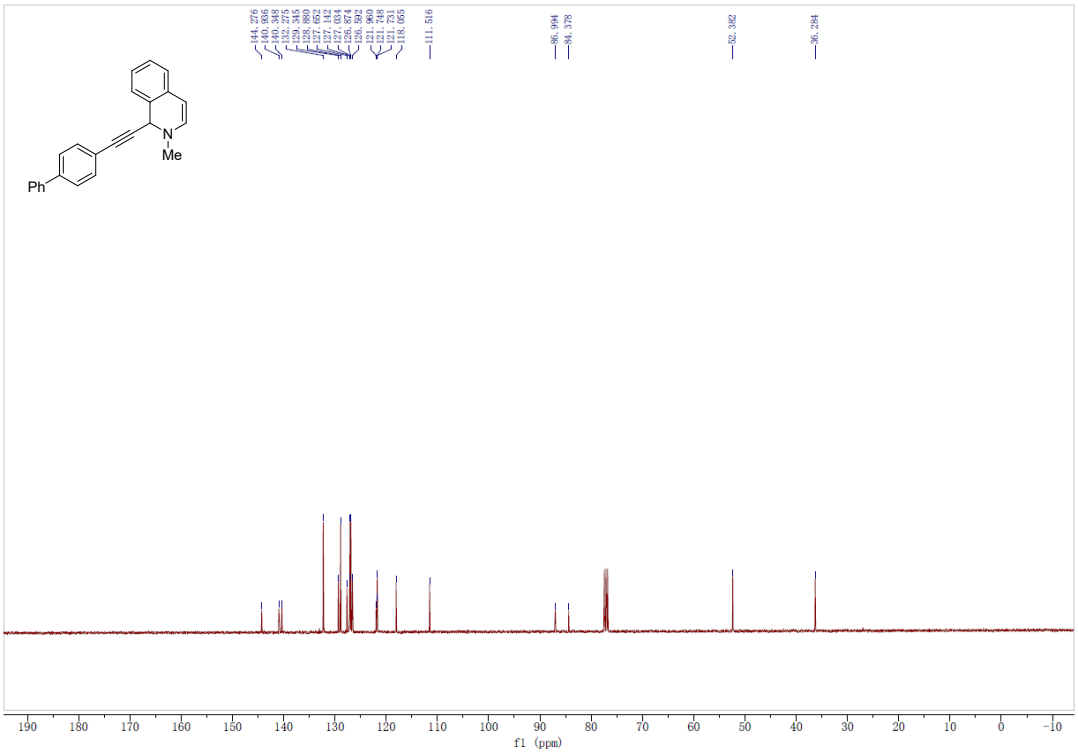
^{13}C NMR of 6b



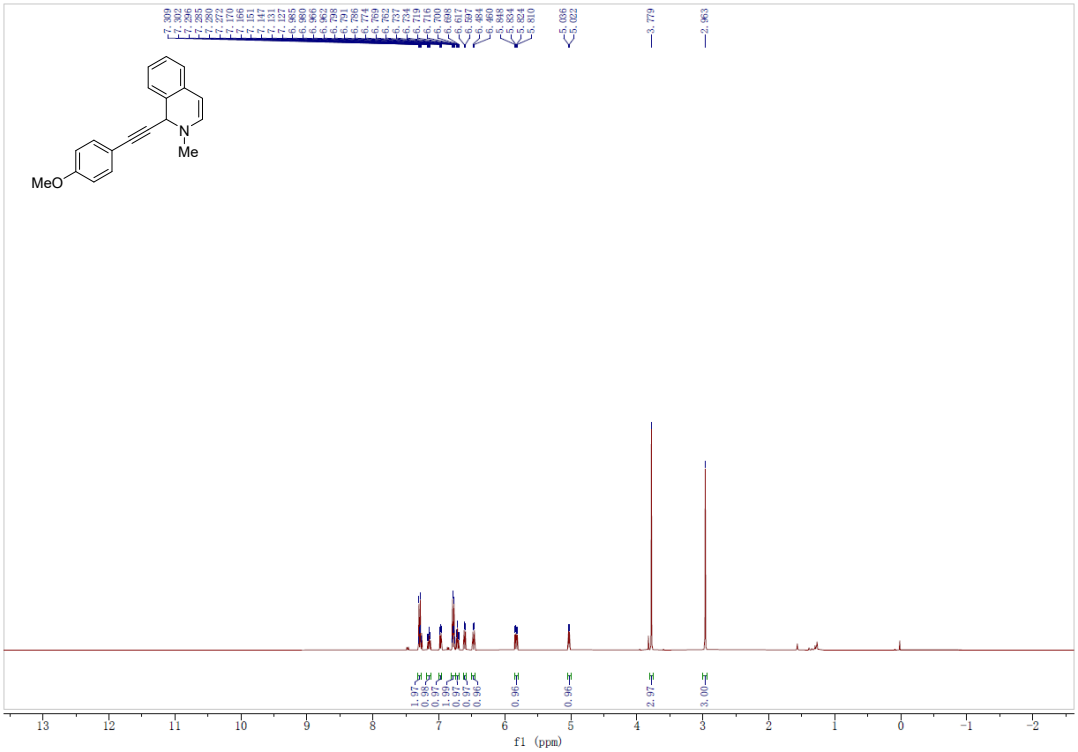
^{1}H NMR of 6c



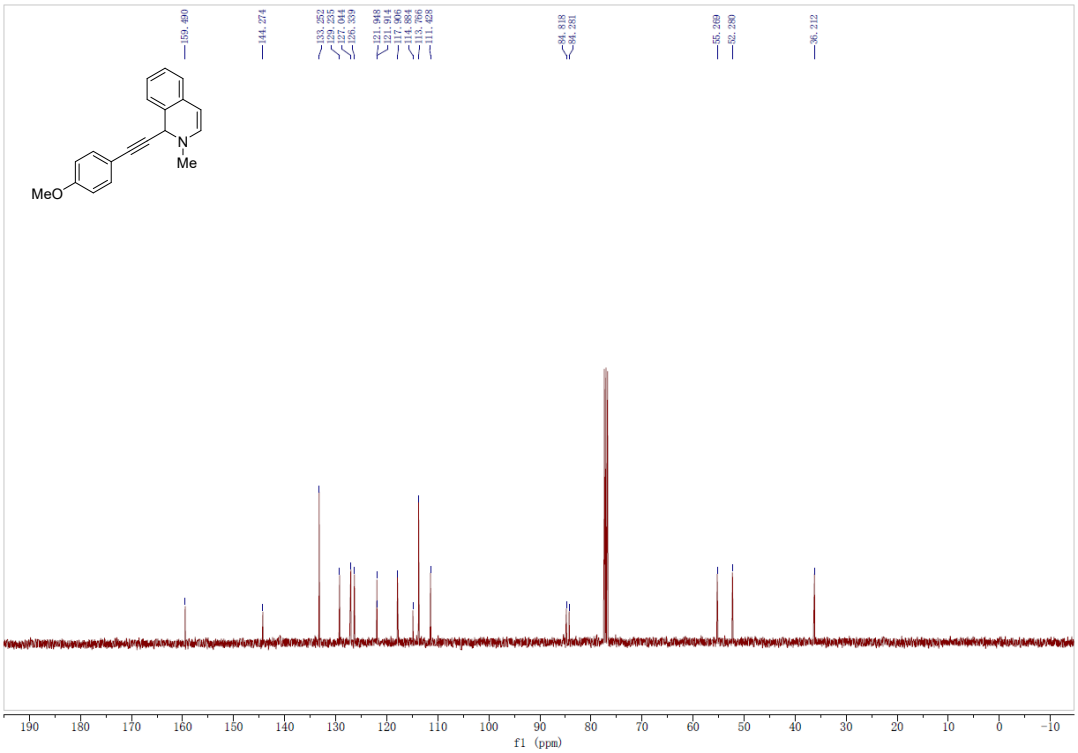
^{13}C NMR of 6c



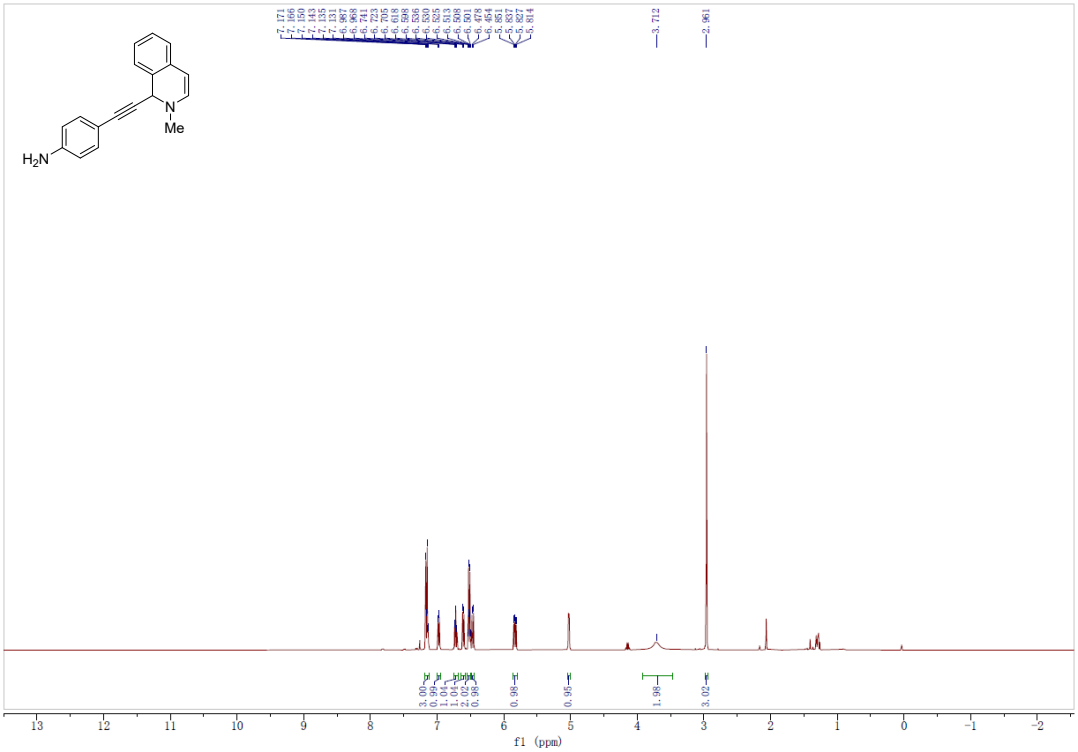
^{1}H NMR of 6d



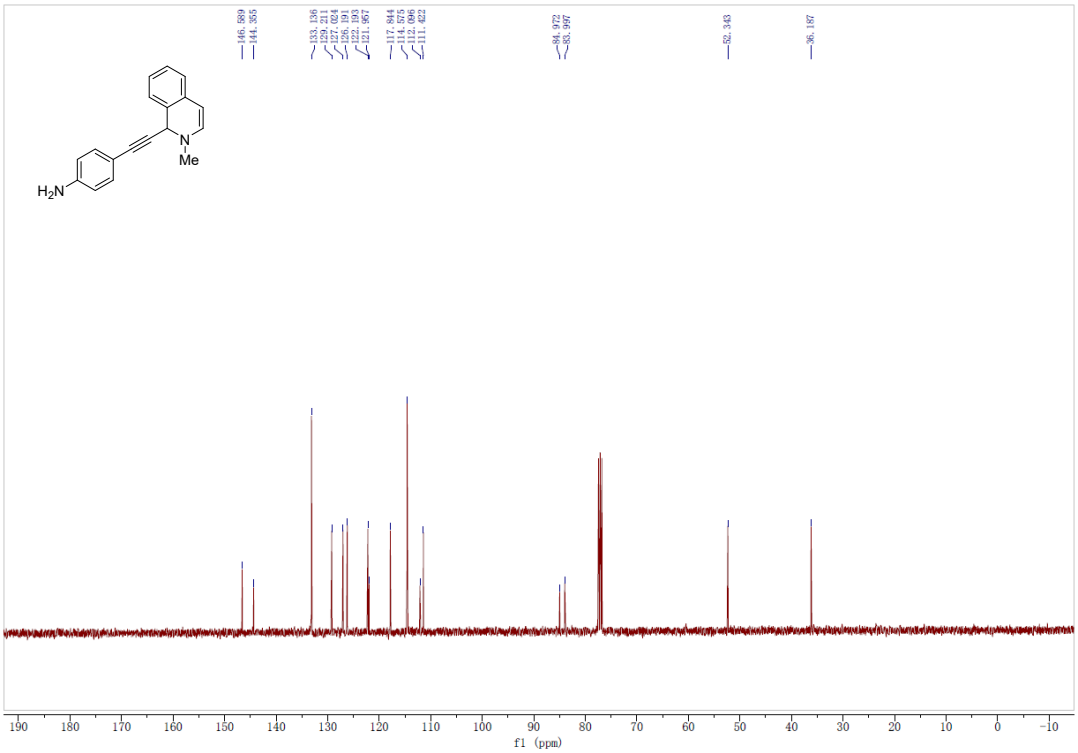
^{13}C NMR of 6d



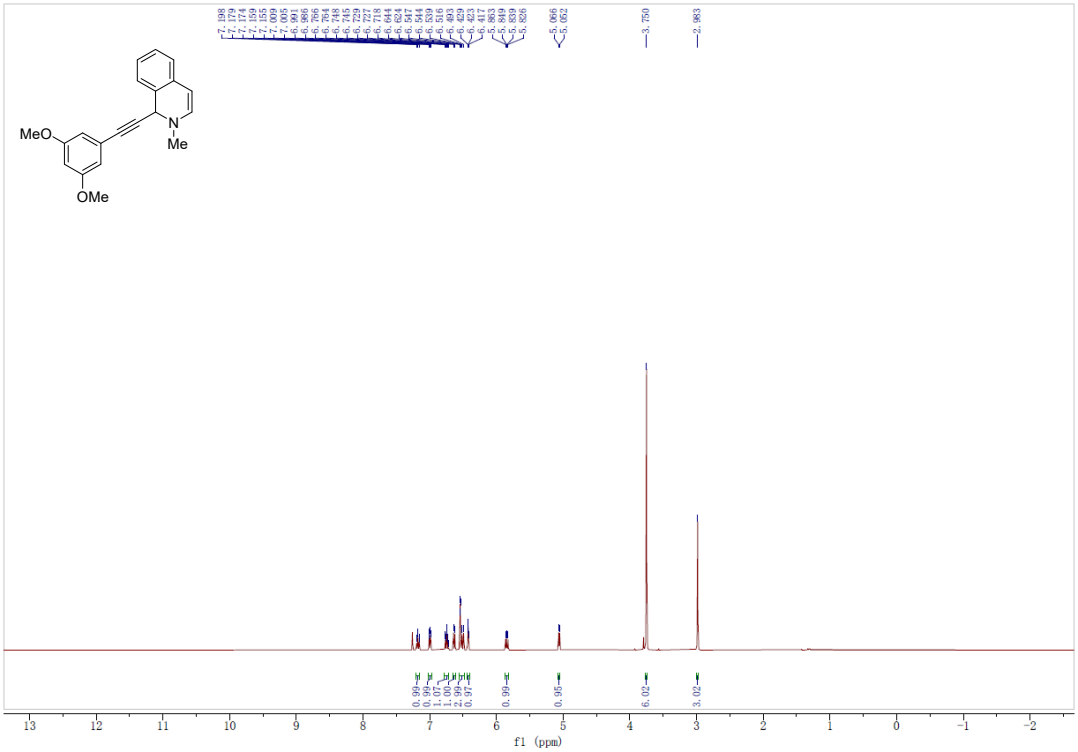
^{1}H NMR of 6e



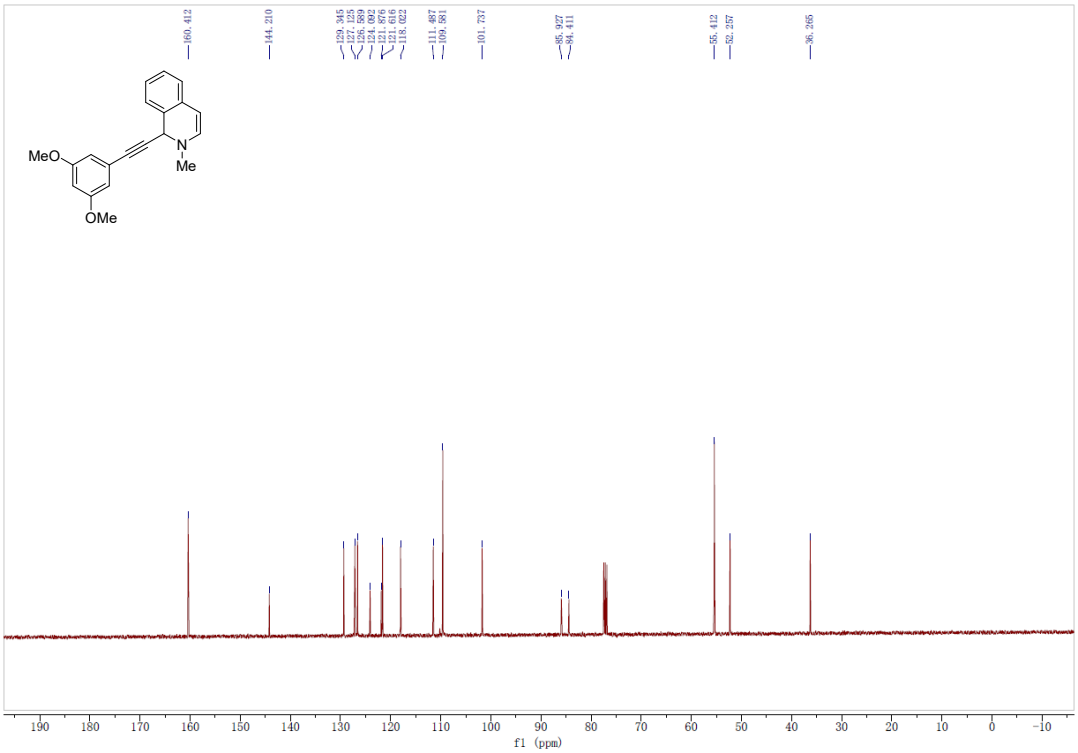
^{13}C NMR of 6e



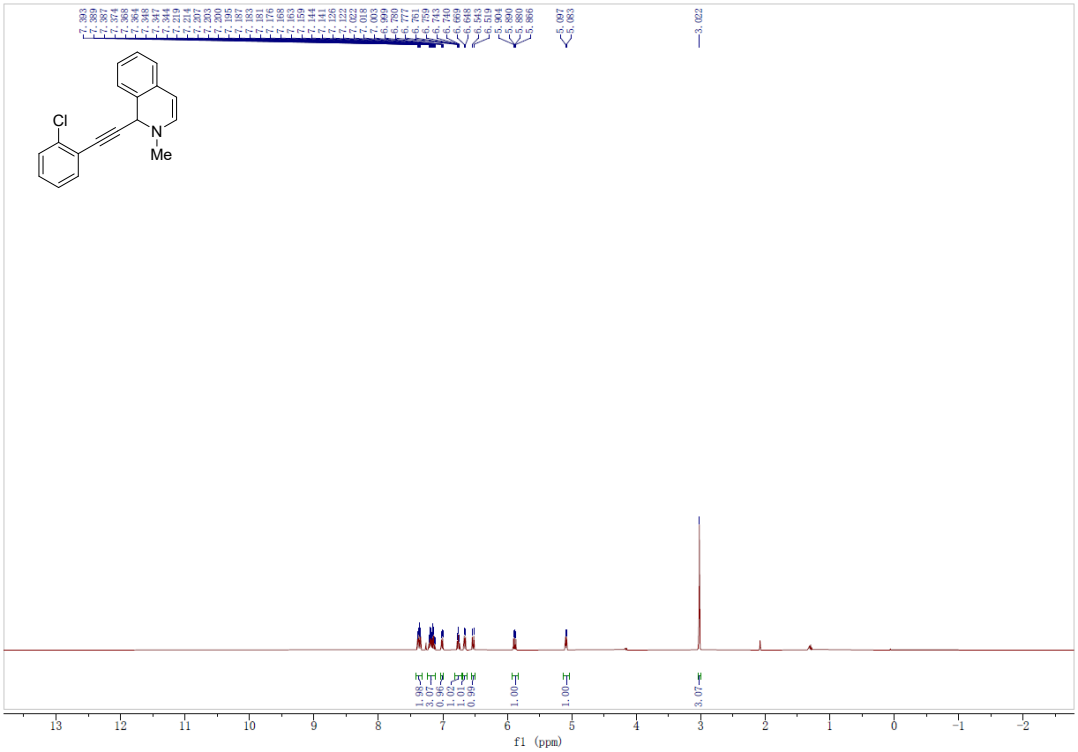
^{1}H NMR of 6f



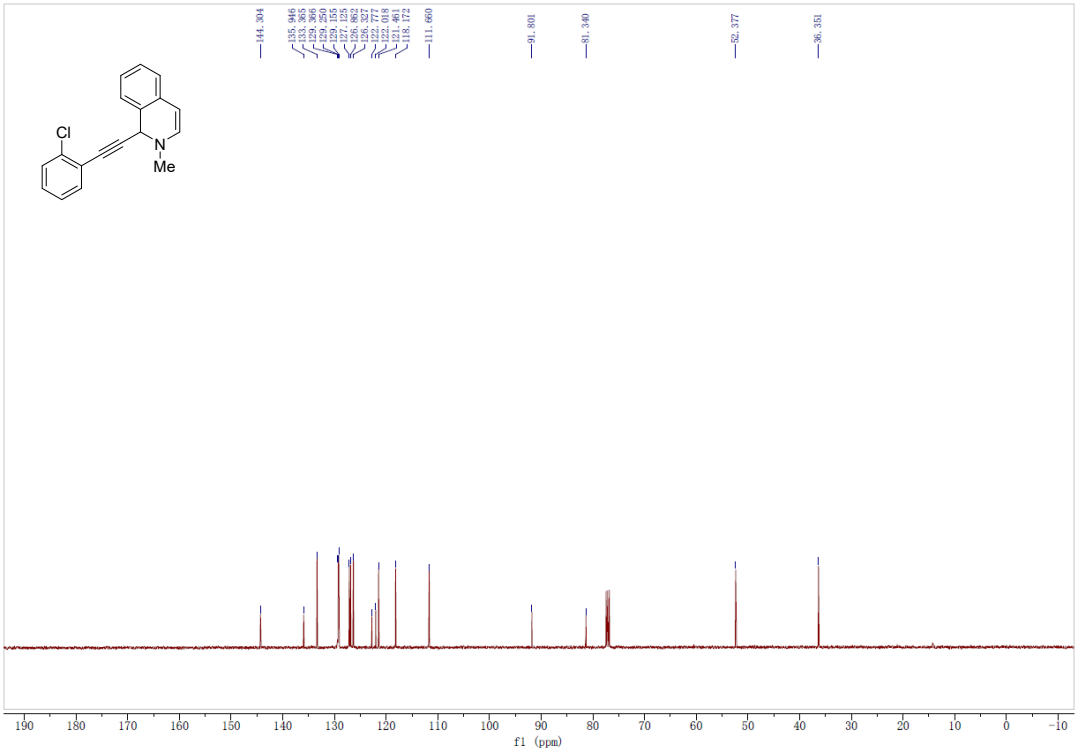
^{13}C NMR of 6f



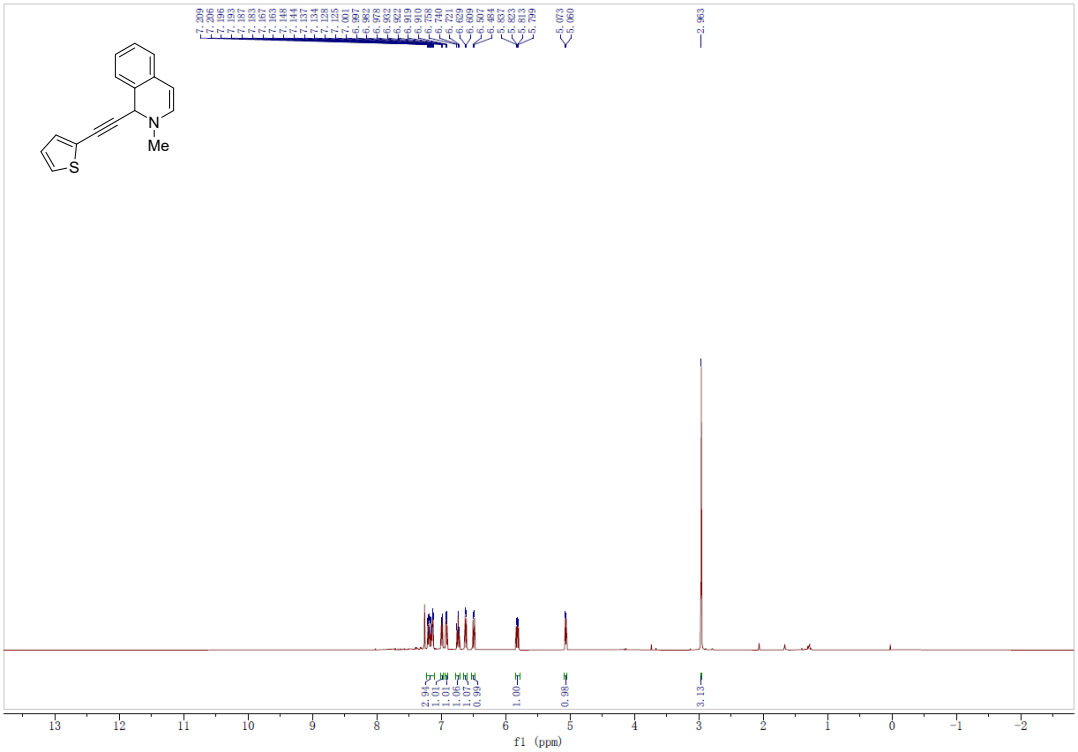
^{1}H NMR of 6g



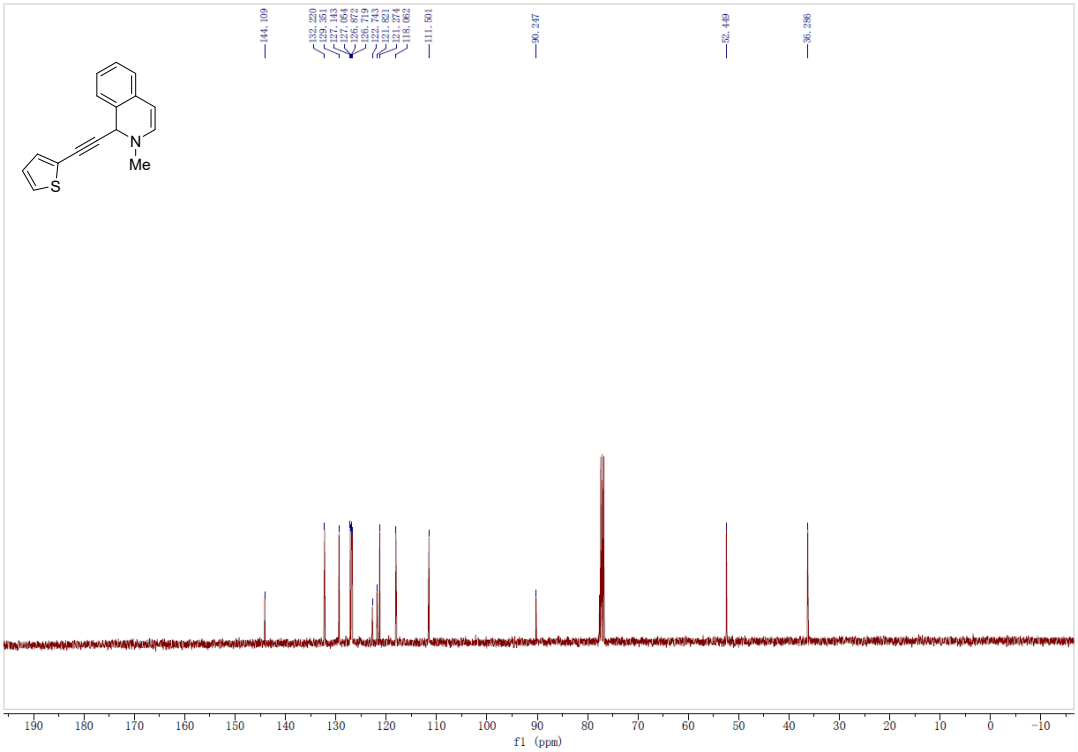
^{13}C NMR of 6g



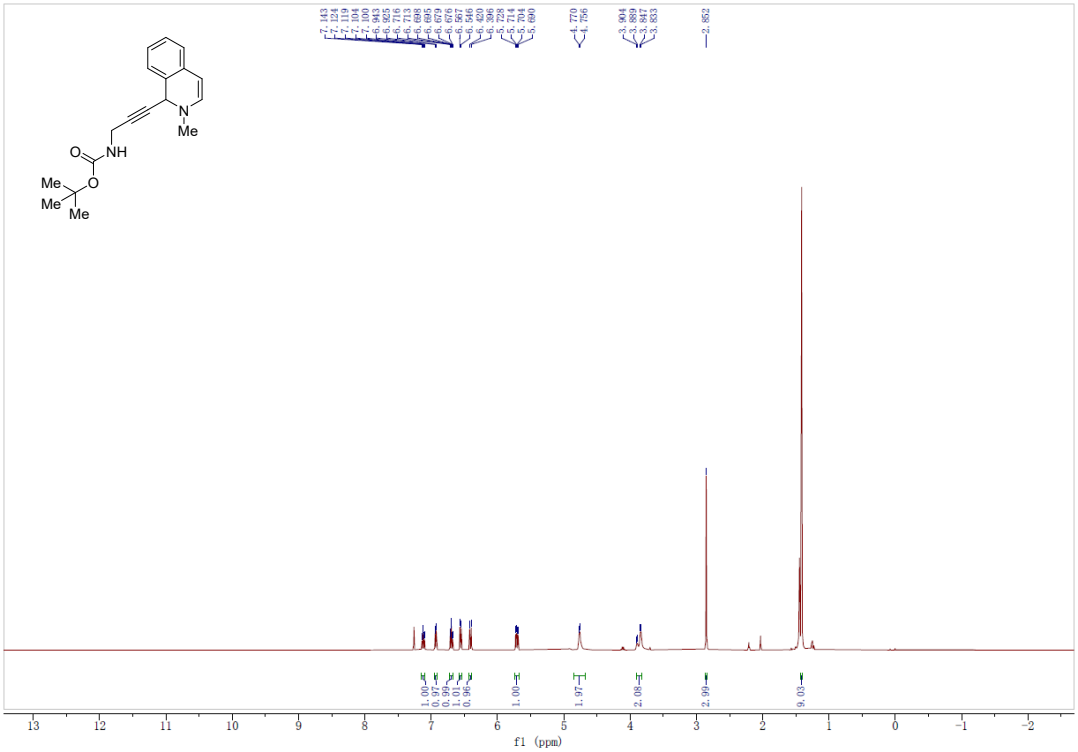
^{1}H NMR of 6h



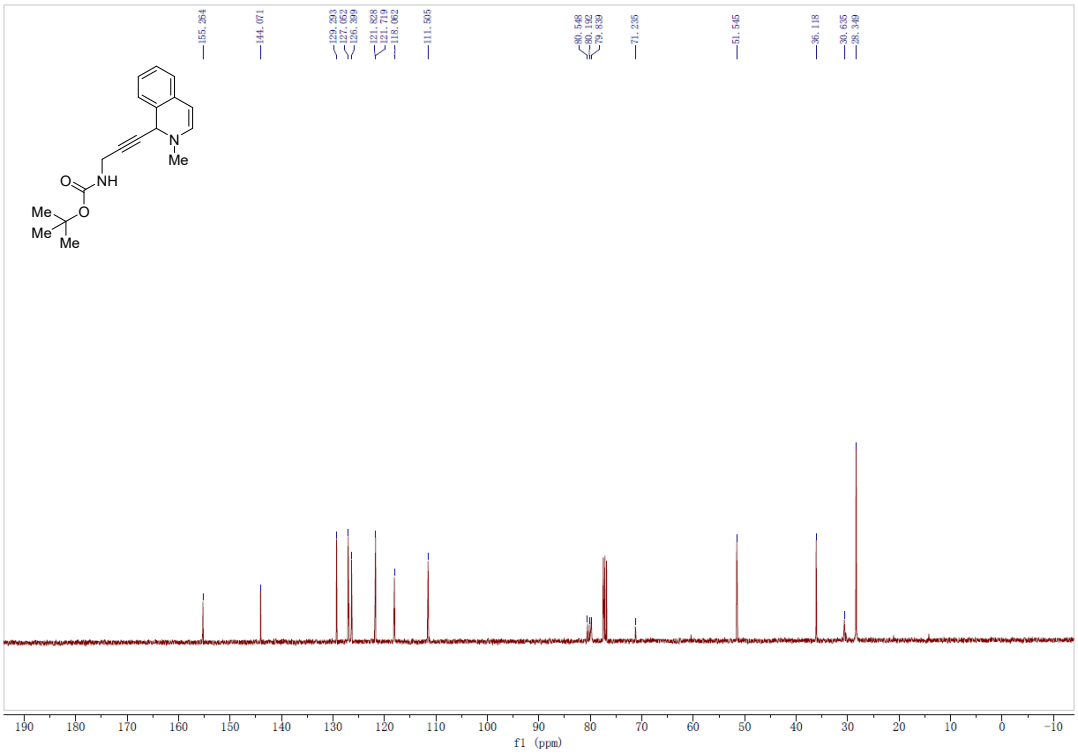
^{13}C NMR of 6h



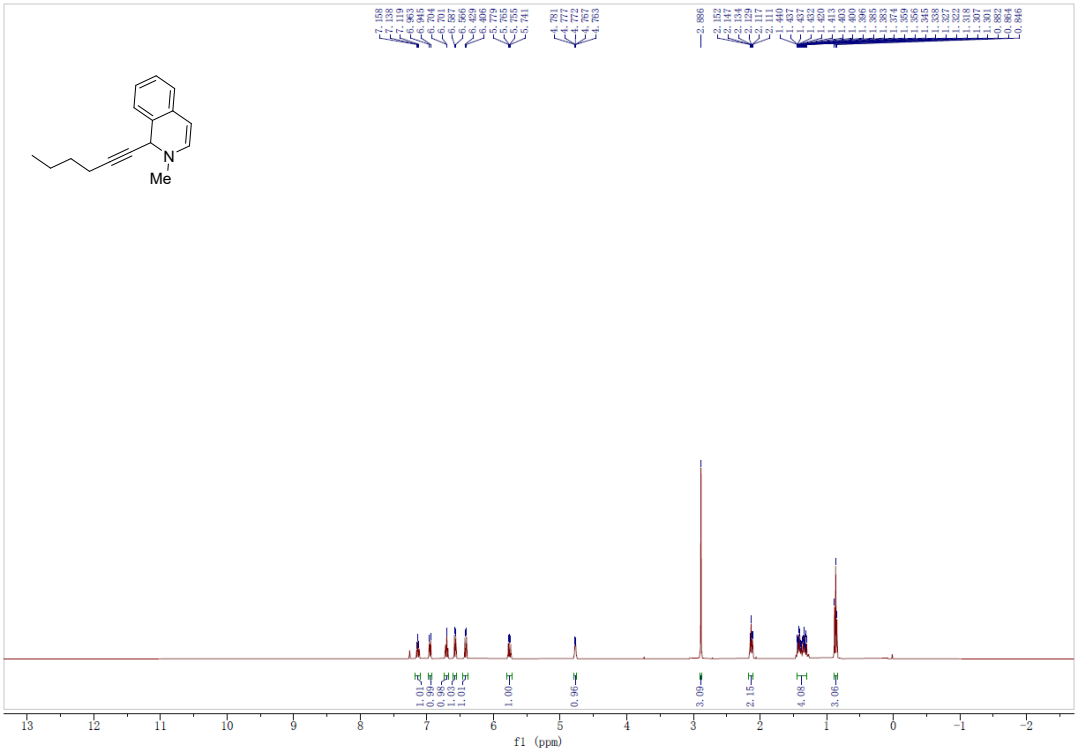
^{1}H NMR of 6i



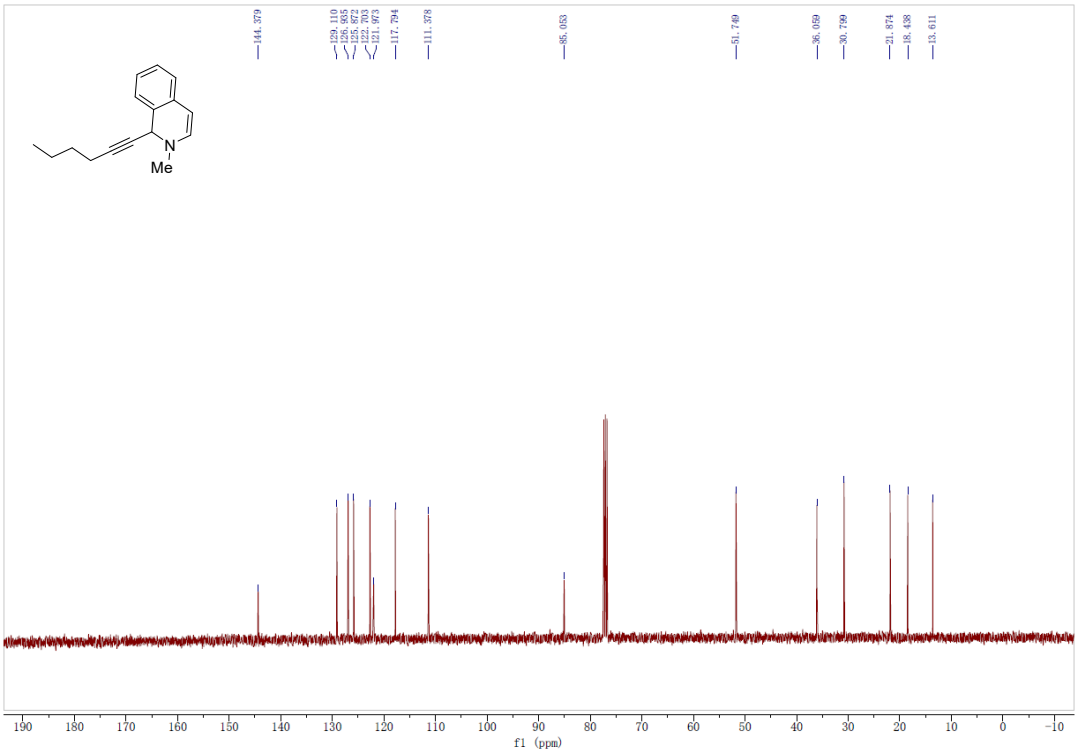
^{13}C NMR of 6i



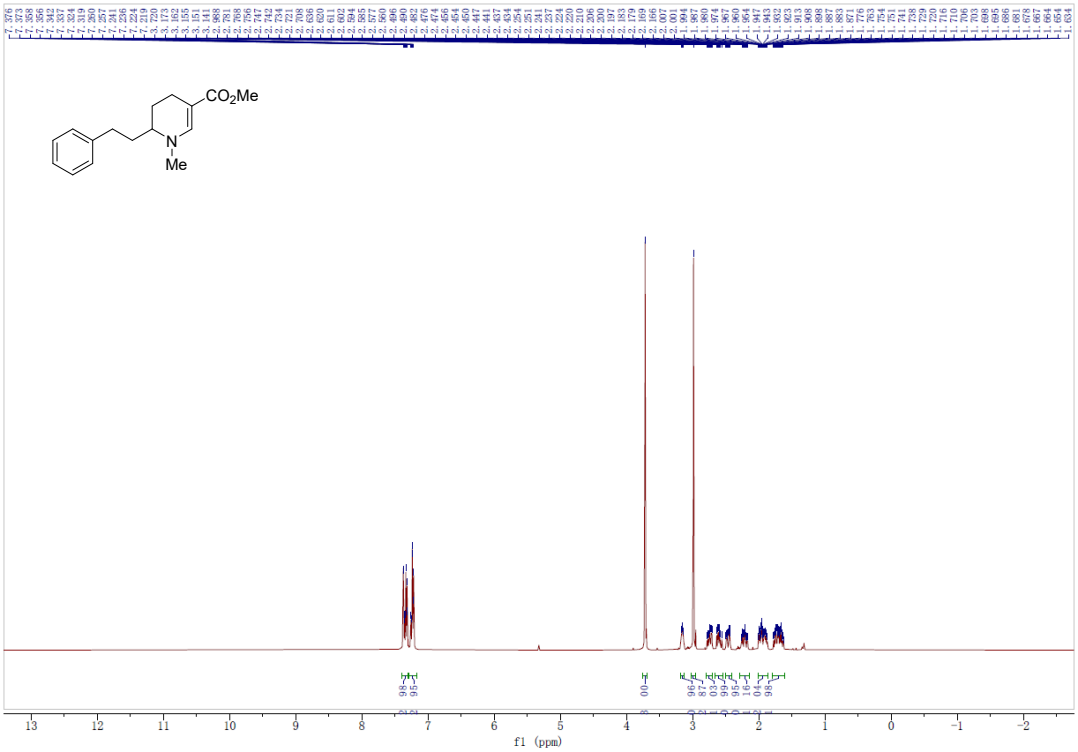
^{1}H NMR of 6j



^{13}C NMR of 6j



^{1}H NMR of 7



^{13}C NMR of 7