Electronic Supplementary Material (ESI) for ChemComm.

Palladium catalysed C3-arylation of 4-hydroxy-2-pyridones

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Supporting Information

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I. General Information

All reactions were carried out in dried glass reaction tube equipped with a magnetic stir bar under argon atmosphere with dry solvents under anhydrous conditions. Dry 1,4-dioxane was distilled from sodium (Na) and benzophenone, dry acetonitrile from P_2O_5 whereas dry toluene, dry dimethylsolfoxide (DMSO) and dry dimethylformamide (DMF) were distilled from CaH_2. The solvents were kept under argon using molecular sieves 4Å in their bottles. Reagents were purchased at the highest commercial quality and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and seebach as developing agent. E. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Brüker 300 AM and Agilent 500 spectrometer using CD_3COCD_3 as solvent and calibrated using TMS as an internal reference. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, oct = octet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF (time of flight) mass spectrometer at a 4000 V emitter voltage. Melting points were obtained by Stuart Melting Point Apparatus SMP3, Bibby Scientific. Microanalyses were performed on a Perkin-Elmer 2400-II element analyzer.

II. NMR Kinetic Experiments

Experiment 1

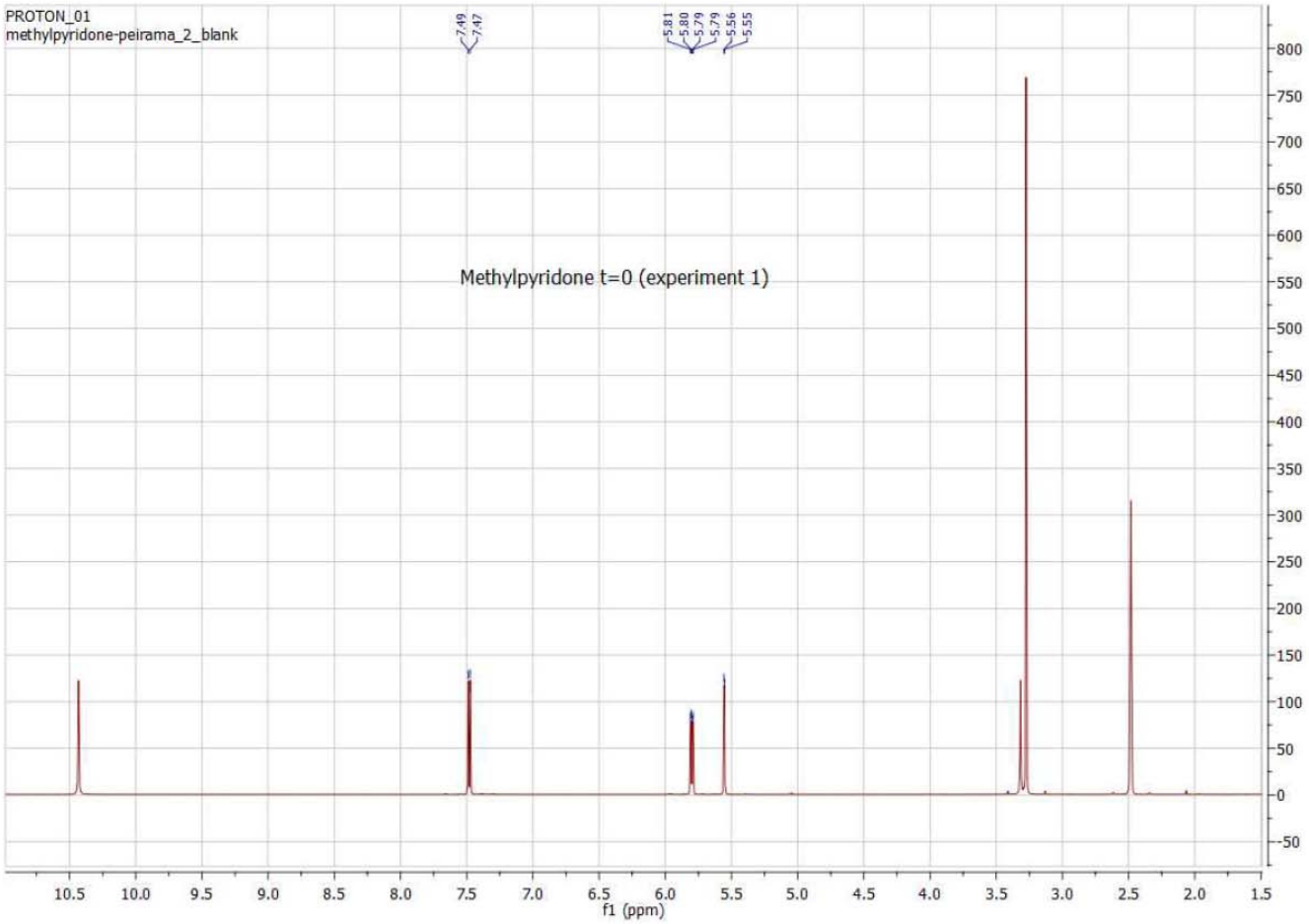
10mg of N-methyl-4-hydroxy-2-pyridone were dissolved in DMSO-d6 in an NMR tube. Palladium acetate (1 equiv) was added and directly the NMR tube was introduced in an 500 MHz Agilent AVANCE NMR spectrometer. ^{1}H-NMR's were obtained in the time and temperatures indicated in each spectra.

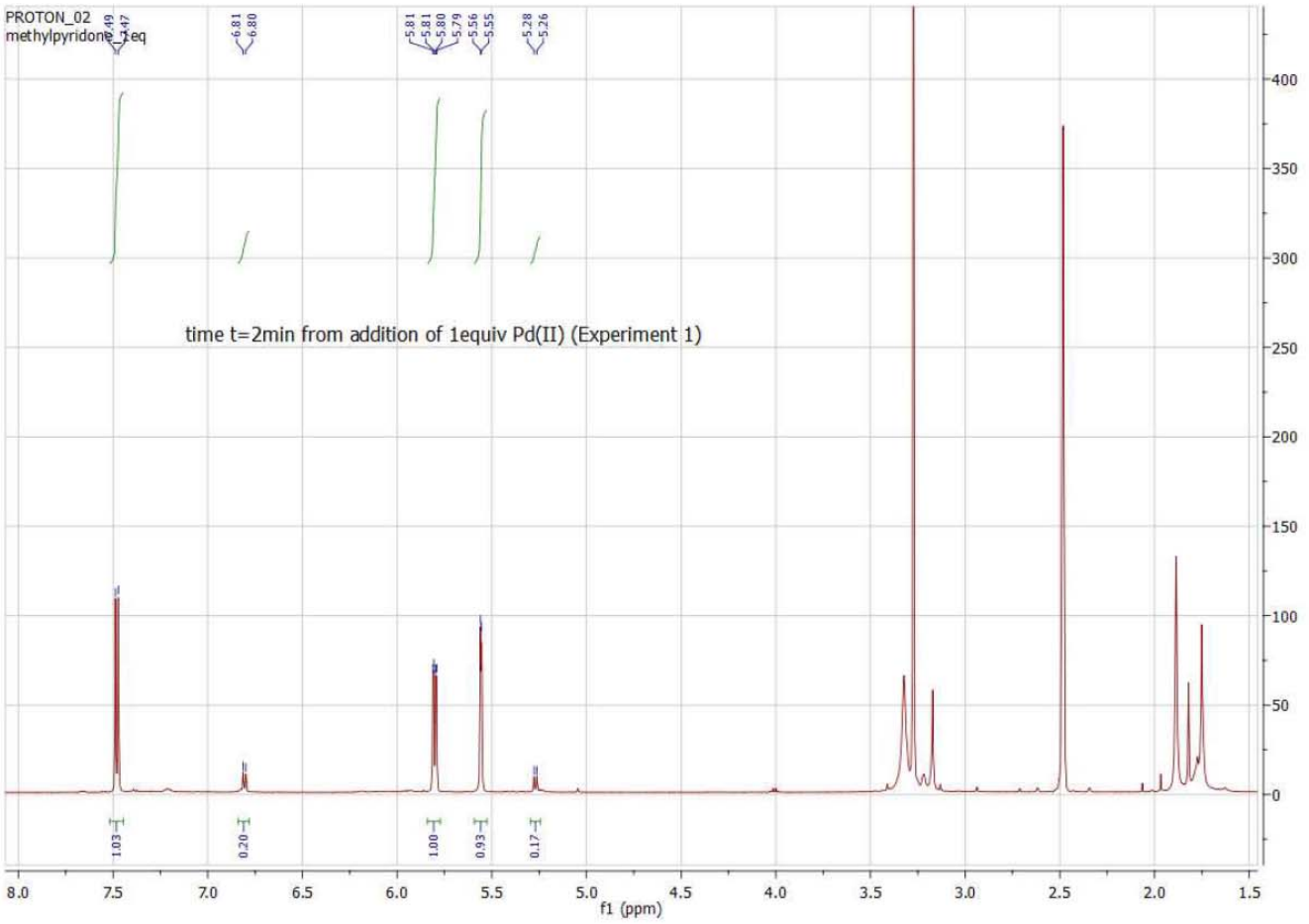
Experiment 2

10mg of N-methyl-4-hydroxy-2-pyridone were dissolved in DMSO-d6 in an NMR tube followed by 1 equiv. of pottasium carbonate. After the first ^{1}H-NMR spectra was obtained palladium acetate 10 mol% was introduced in the NMR tube and ^{1}H-NMR's were obtained in the time and temperatures indicated in each spectra.

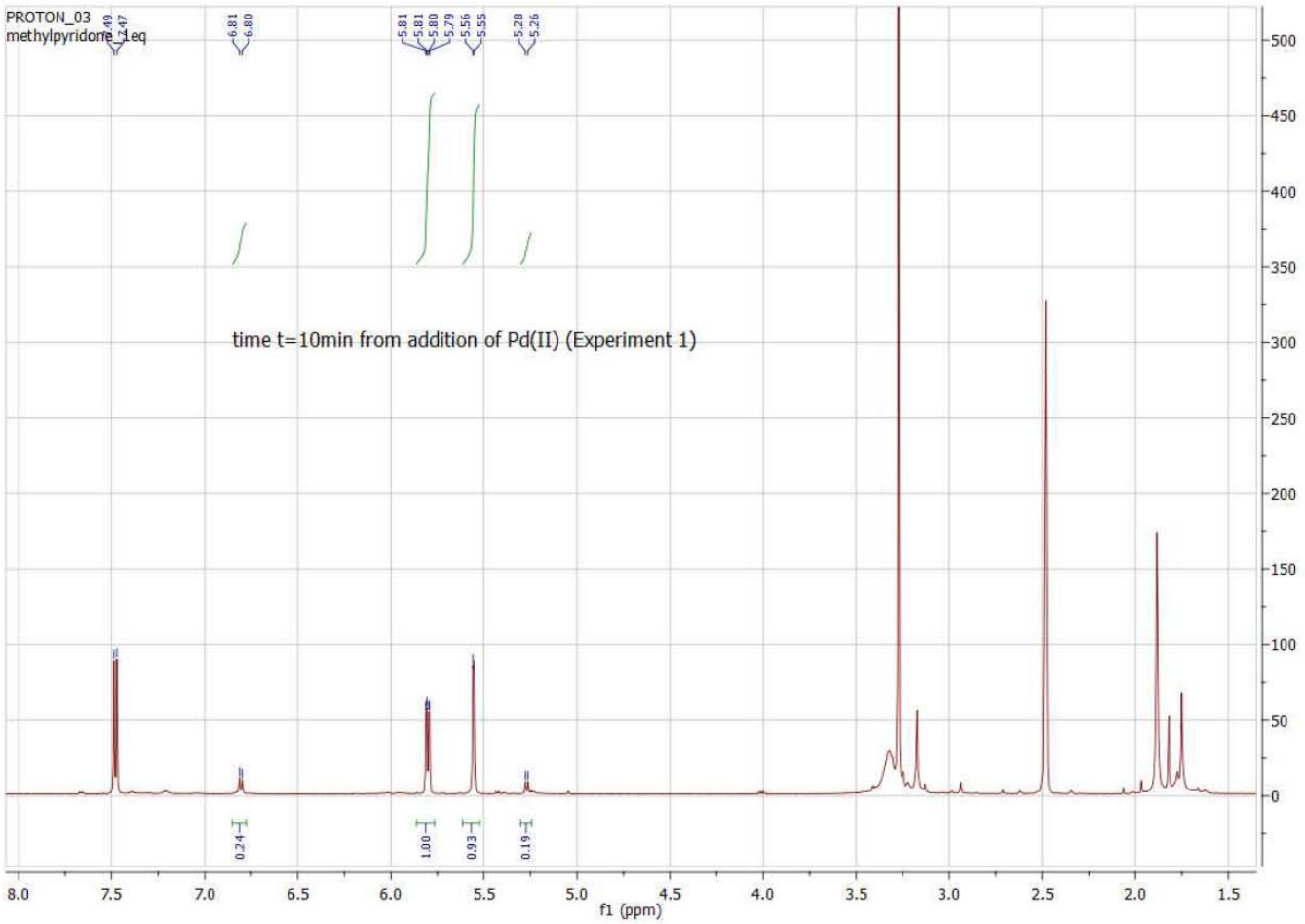
Experiment 3

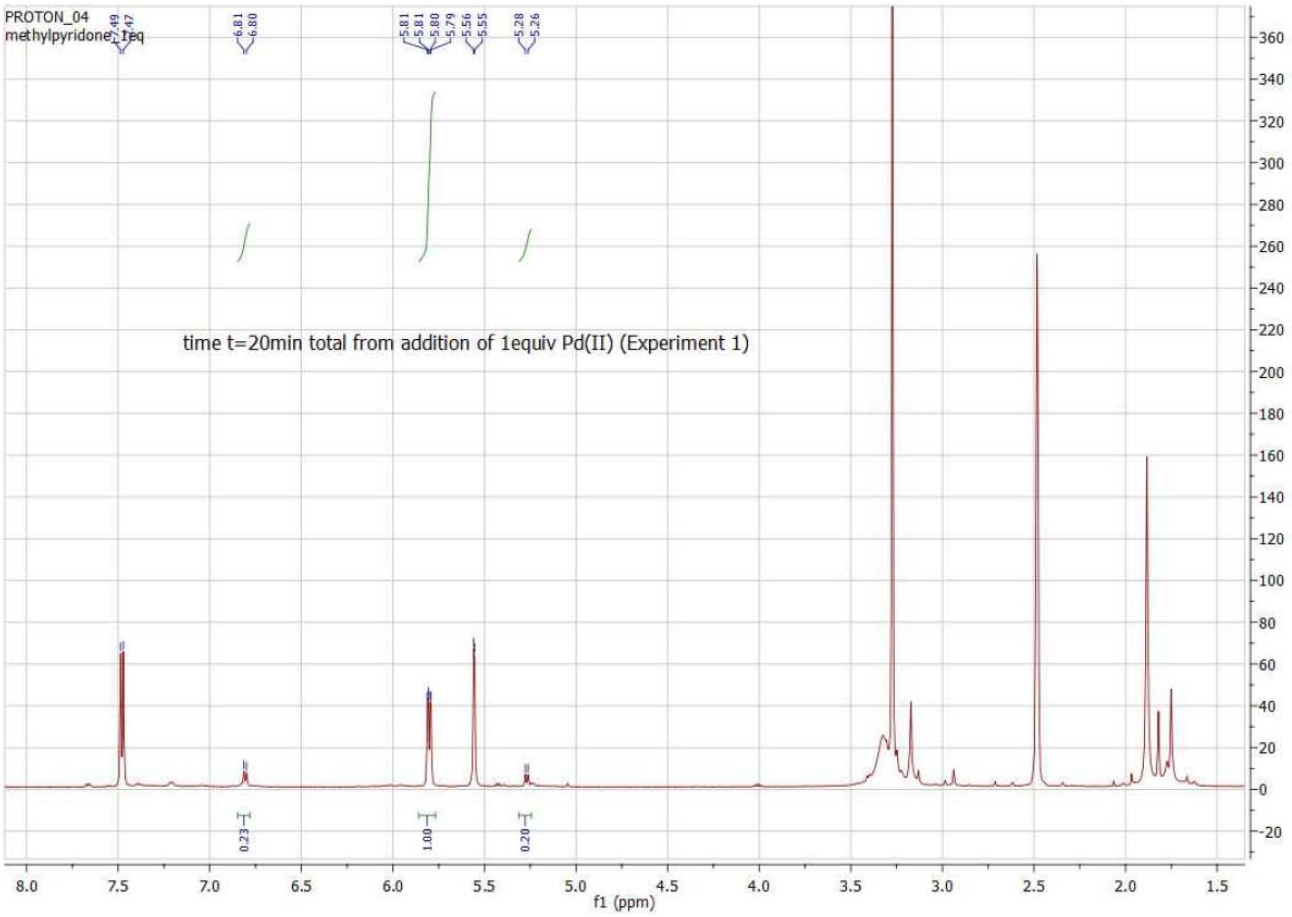
10mg of N-methyl-4-hydroxy-2-pyridone were dissolved in DMSO-d6 in an NMR tube followed by 10 mol% palladium acetate. The sample was allowed to stand for 20min at rt before potassium carbonate (0.5 equiv) was introduced in the tube. ^{1}H-NMR's were obtained in the time and temperatures indicated in each spectra.



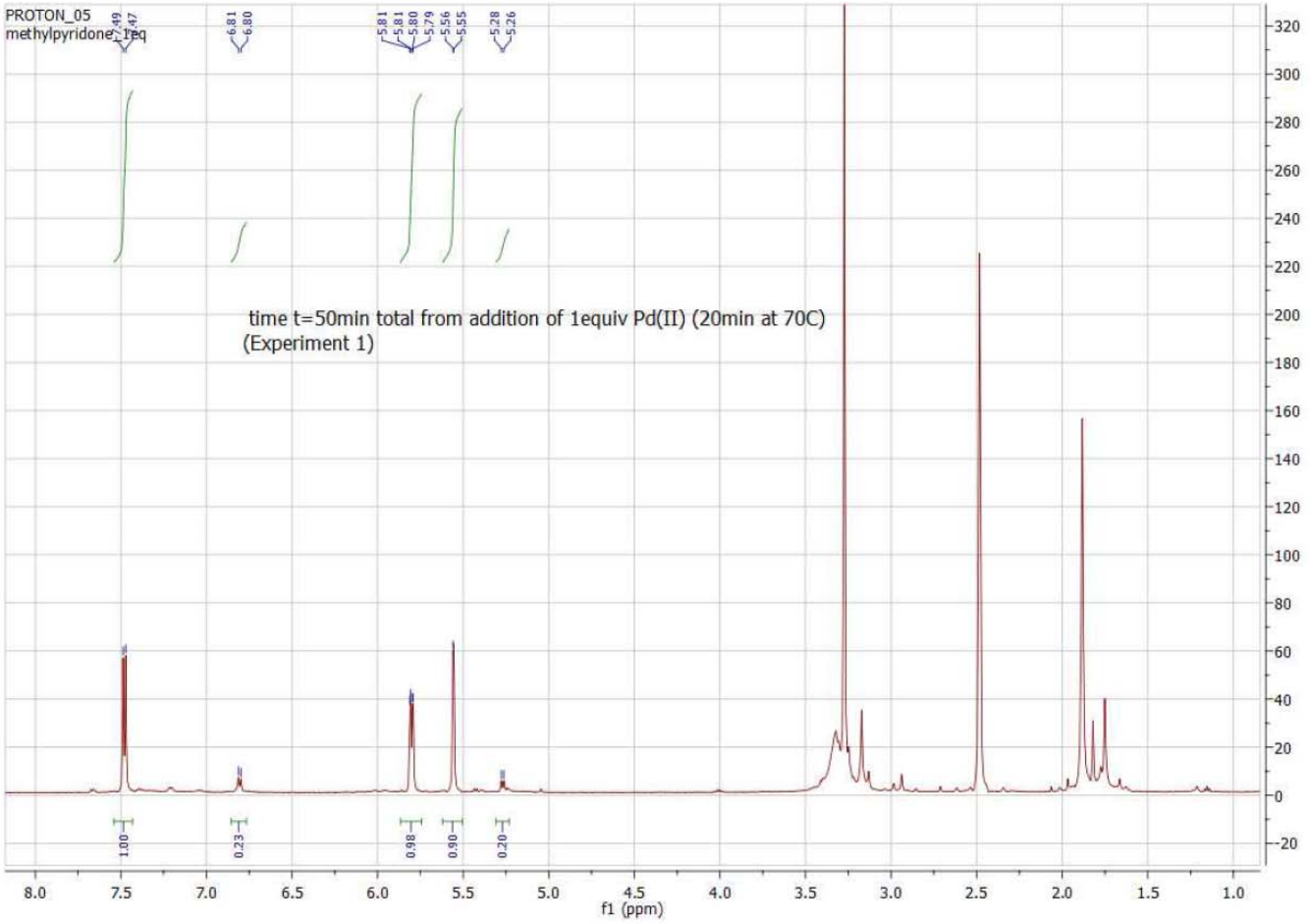


Experiment 1- DMSO-d6 500MHz

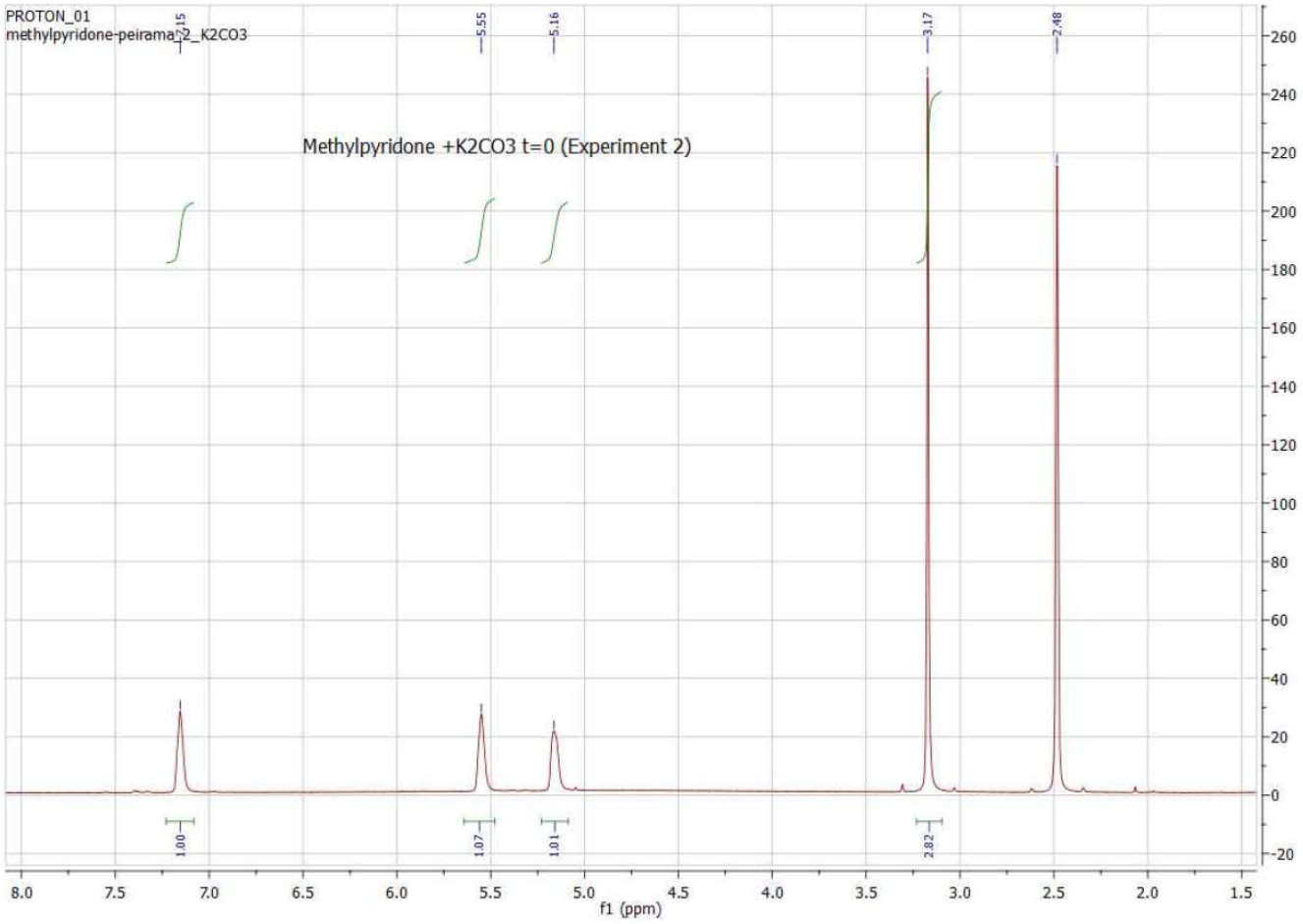


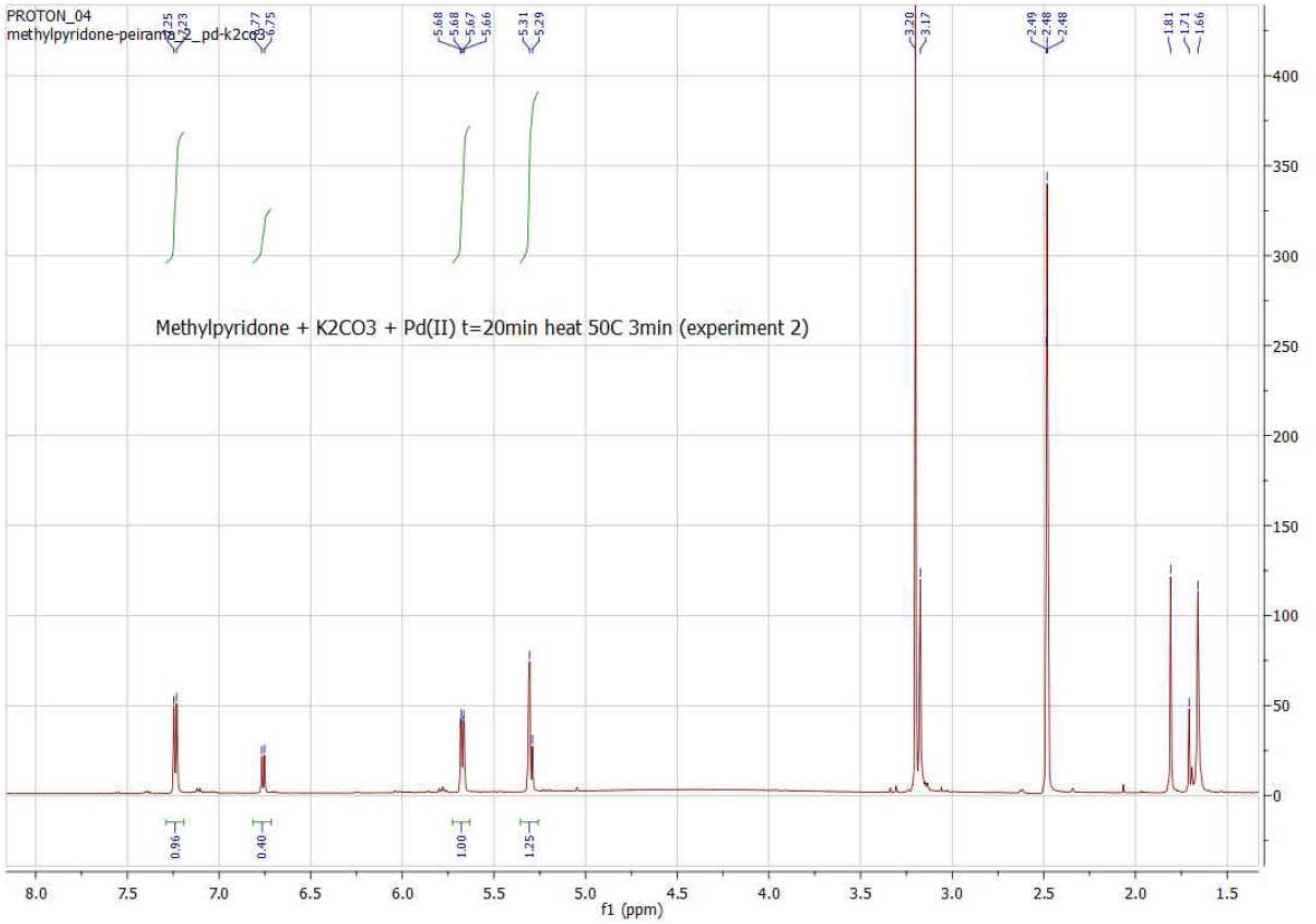


Experiment 1- DMSO-d6 500MHz

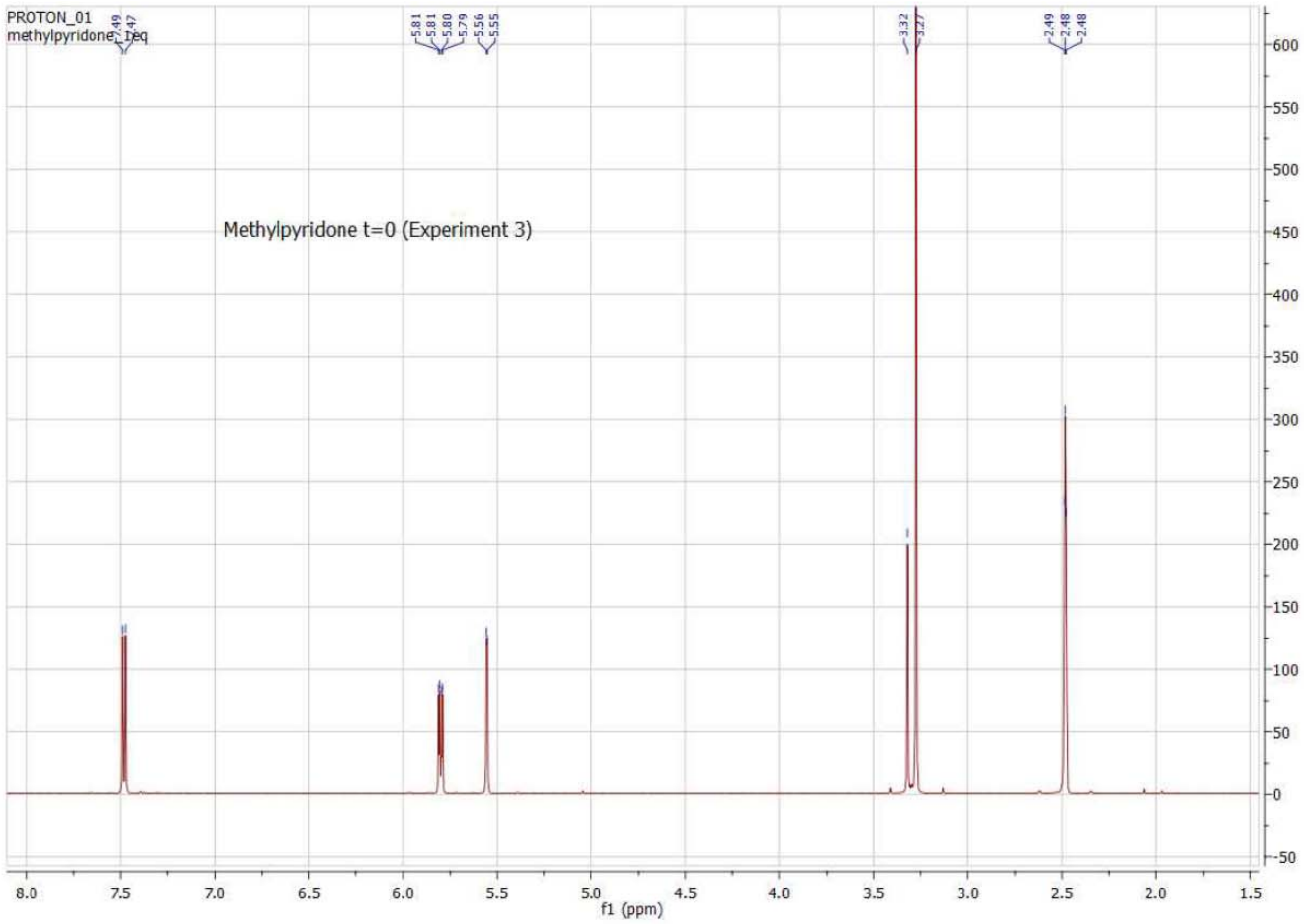


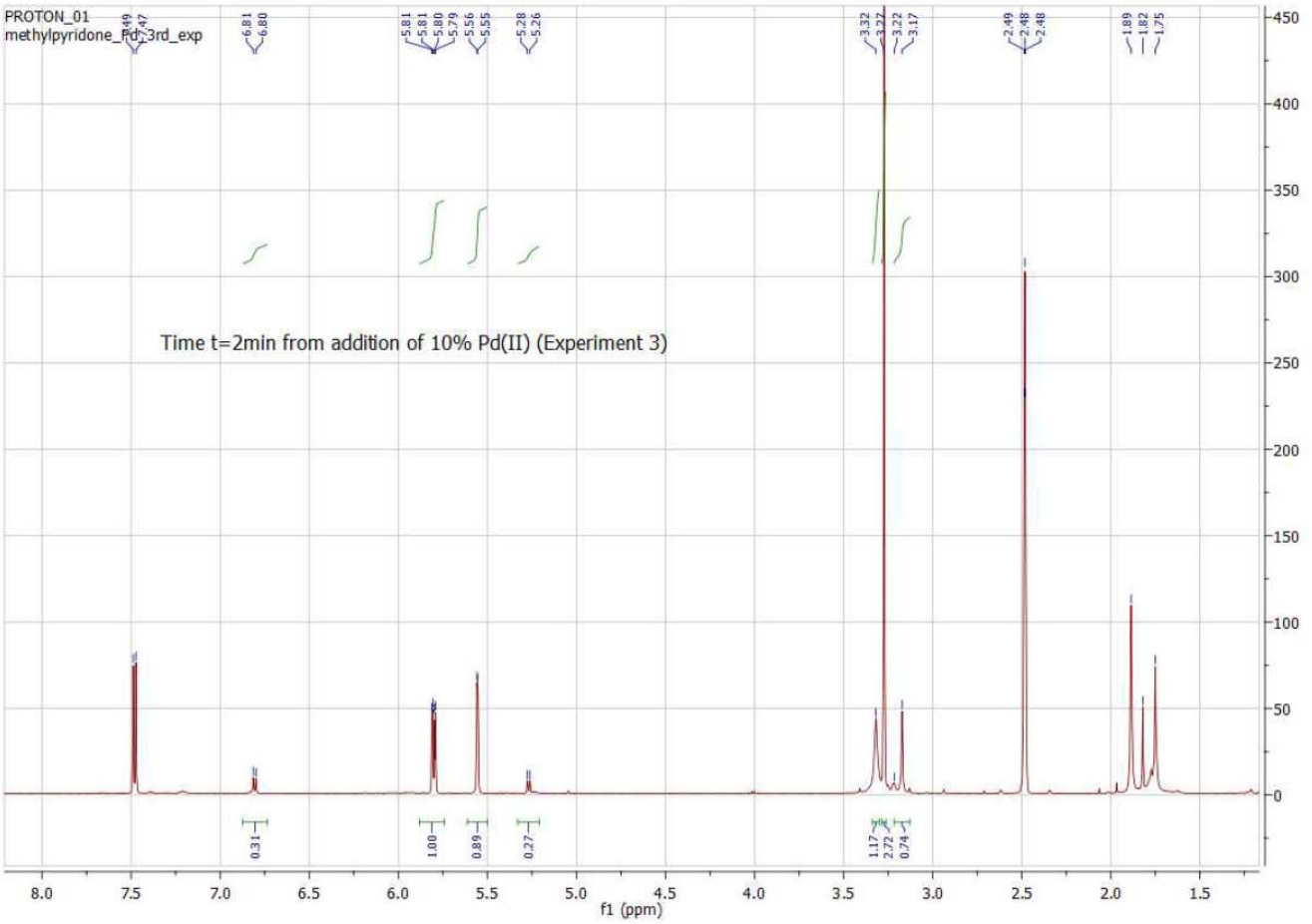
Experiment 1- DMSO-d6 500MHz



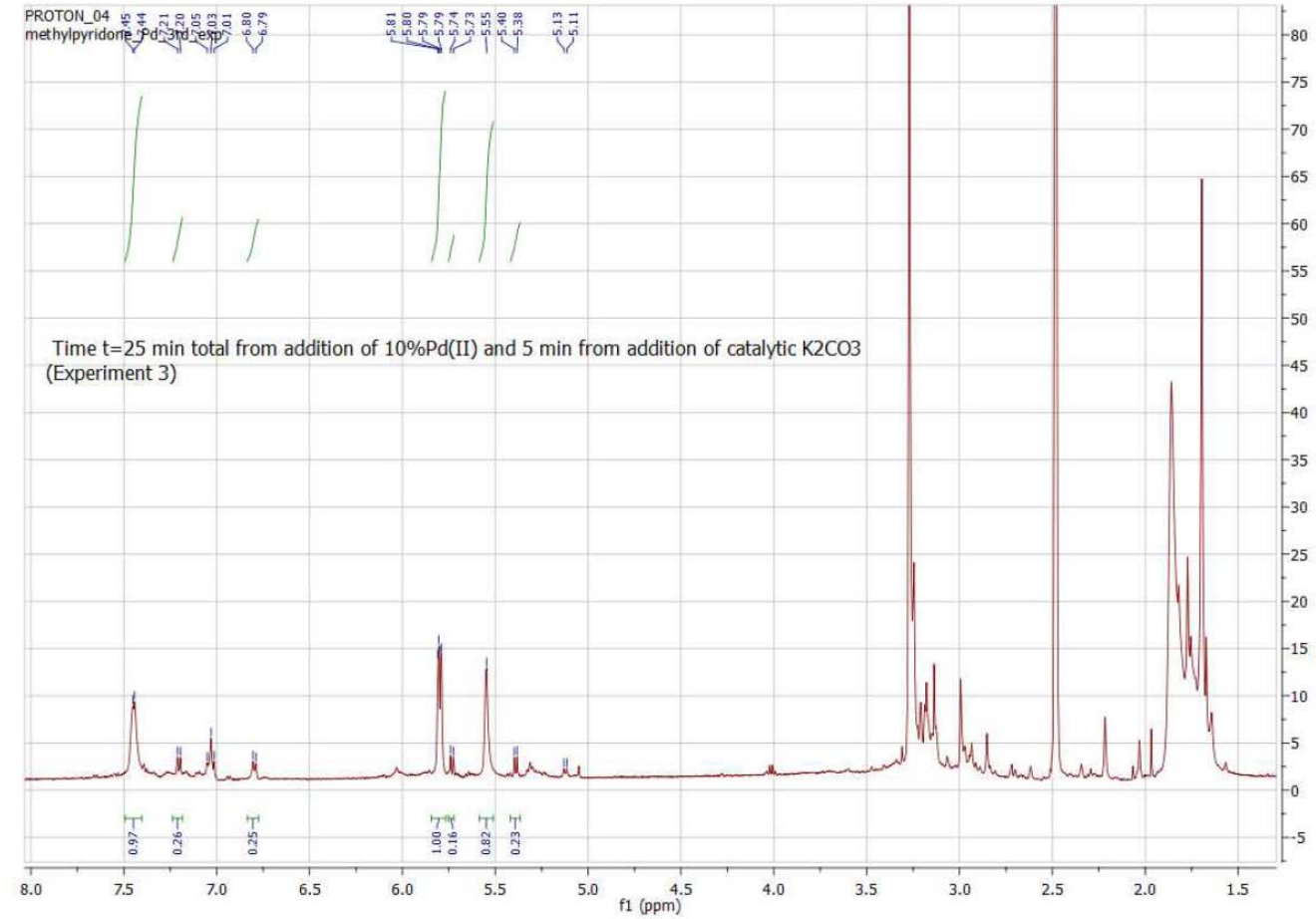


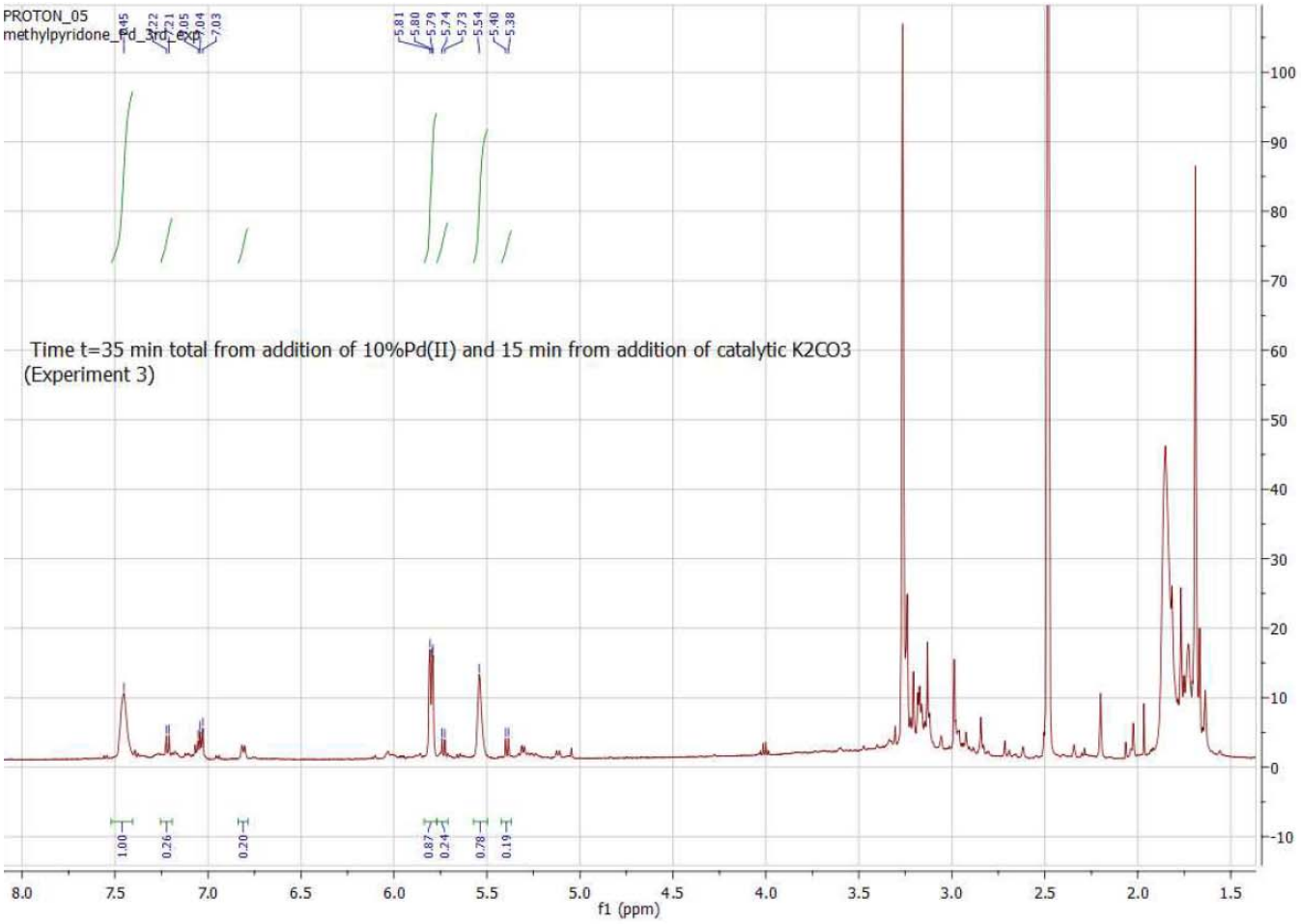
Experiment 2- DMSO-d6 500MHz



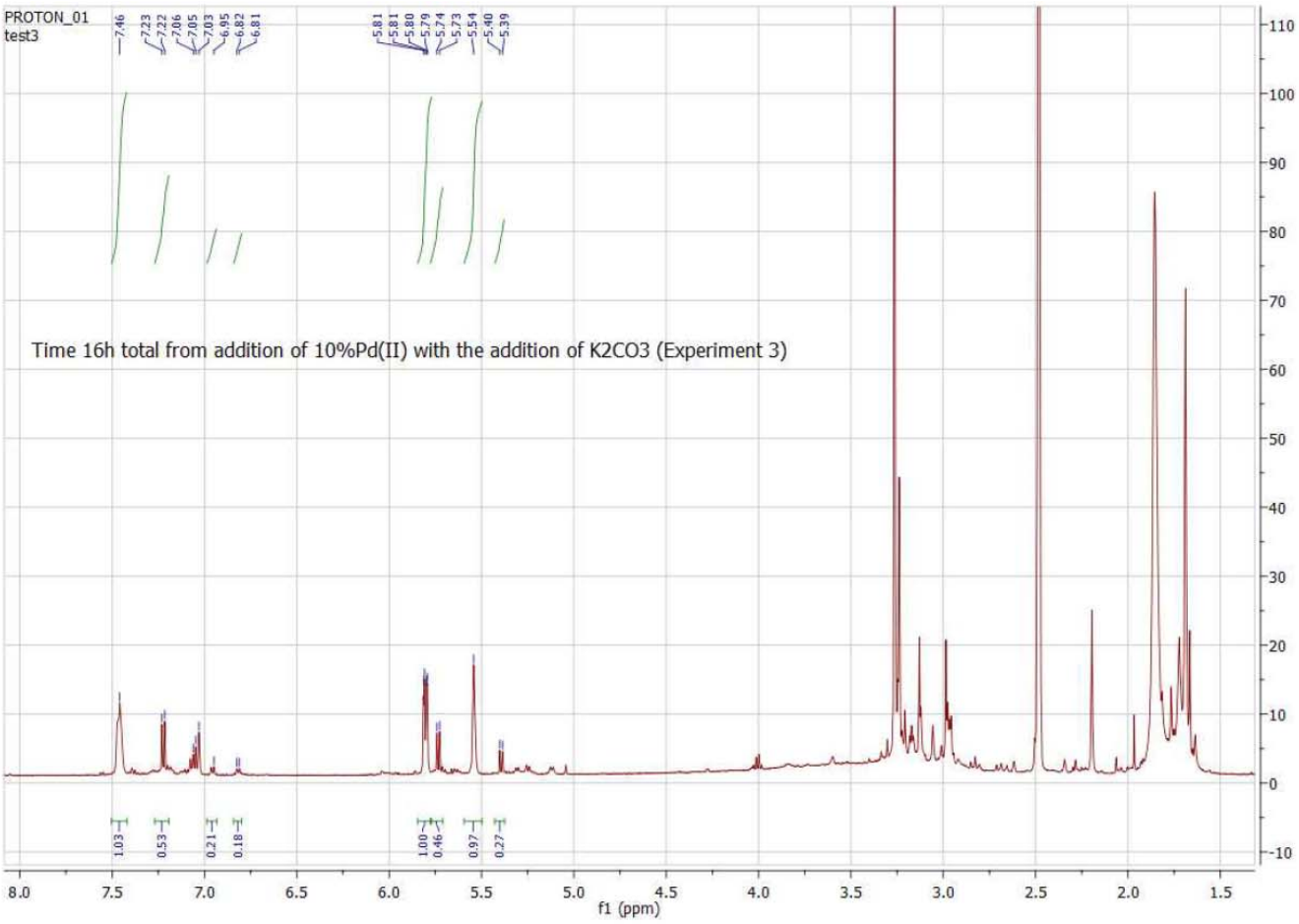


Experiment 3- DMSO-d6 500MHz





Experiment 3- DMSO-d6 500MHz

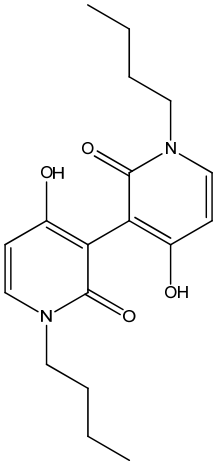


Experiment 3- DMSO-d6 500MHz

III. General experimental procedure

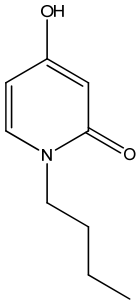
A dried screw glass vial equipped with a magnetic stirring bar was charged with 4-hydroxy-1-alkyl-pyridin-2(1H)-one (**1**) (0.24 mmol), $Cu(OAc)_2$ (87mg, 0.48mmol, 2 equiv), $ArB(OH)_2$ (0.72 mmol, 3 equiv), $Pd(OAc)_2$ (2.7mg, 0.012 mmol, 5 mol%) successively followed by 1,4-dioxane (2ml). After the reaction mixture was charged with argon gas was refluxed overnight at 90°C. Then, the reaction mixture was quenched by the addition of 1.5 ml of saturated aqueous ammonium chloride, stirred for 15 min and the reaction mixture was extracted with EtOAc (3 X 2 ml). The combined organic extracts are dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel flash column chromatography (DCM:AcOEt = 100:0 to 0:100) to give the desired arylated compounds.

IV. Physical properties of compounds



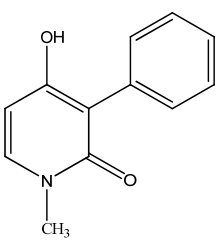
1,1'-dibutyl-4,4'-dihydroxy-[3,3'-bipyridine]-2,2'(1H,1'H)-dione (12)

oily colourless residue. R_f = 0.52 (CH_2Cl_2 : EtOAc, 9 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.84 (d, *J* = 5Hz, 1H), 6.30 (d, *J* = 5Hz, 1H), 4.15 (t, *J* = 7Hz, 2H), 1.77 (quin, *J* = 7Hz, 2H), 1.38 (sex, *J* = 7Hz, 2H), 0.95 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 169.1, 163.8, 138.0, 109.1, 105.5, 50.0, 31.3, 19.5, 13.0; HRMS (ESI) calcd for $C_{18}H_{25}N_2O_4^+$ $[M + H]^+$: 333.1814, found 333.1823.



1-butyl-4-hydroxypyridin-2(1H)-one (13)

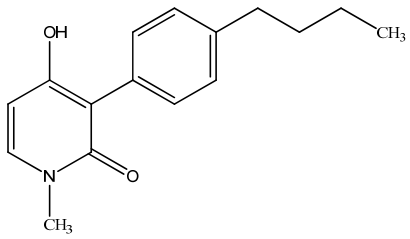
Following the procedure from patent WO2009/33703 A1; white solid. mp. 153-156 °C. R_f = 0.48 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (brs, 1H), 6.44 (brs, 2H), 3.96 (brs, 2H), 1.70 (brs, 2H), 1.33 (brs, 2H), 0.91 (brs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 163.7, 138.9, 105.5, 99.0, 50.5, 31.5, 19.7, 13.6; HRMS (ESI) calcd for $C_9H_{14}NO_2^+$ $[M + H]^+$: 168.1024, found 168.1021.



4-hydroxy-1-methyl-3-phenylpyridin-2(1H)-one (7)

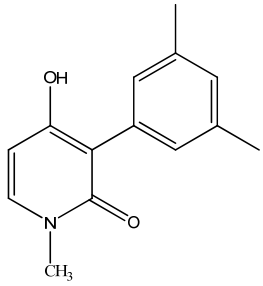
yield = 40mg (85%) white solid. mp. 182-185 °C. R_f = 0.23 (EtOAc). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.46 – 7.44 (m, 3H), 7.31 (dd, *J* = 10Hz, 2H), 7.21 (dd, *J* = 10Hz 1H), 6.08 (d, *J* = 5Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 163.5, 162.6, 138.7, 134.9, 131.8, 128.1, 127.1, 112.6, 100.1, 36.2; HRMS (ESI) calcd for $C_{12}H_{12}NO_2^+$ $[M + H]^+$: 202.0868, found 202.0881; Anal. calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96%. Found: C, 71.32; H, 5.26; N, 7.24%.

3-(4-butylphenyl)-4-hydroxy-1-methylpyridin-2(1H)-one (2a)



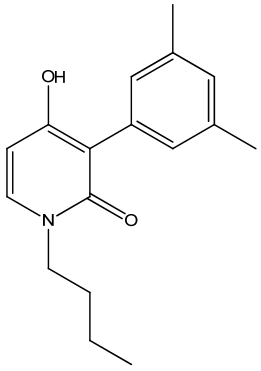
yield = 54mg (89%) white solid. mp. 148-149 °C. R_f = 0.34 (CH_2Cl_2 : CH_3COCH_3, 4 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.43 (d, *J* = 5Hz, 1H), 7.36 (d, *J* = 5Hz, 2H), 7.15 (d, *J* = 5Hz, 2H), 6.06 (d, *J* = 5Hz, 1H), 3.43 (s, 3H), 2.61 (t, *J* = 5Hz, 2H), 1.63 – 1.59 (m, 2H), 1.40 – 1.36 (m, 2H), 0.93 (t, *J* = 5Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 163.6, 162.6, 141.5, 138.4, 132.1, 131.7, 128.2, 112.6, 100.2, 37.1, 36.0, 34.5, 23.0, 14.2; HRMS (ESI) calcd for $C_{16}H_{20}NO_2^+$ $[M + H]^+$: 258.1494, found 258.1492; Anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44%. Found: C, 74.72; H, 7.50; N, 5.38%.

3-(3,5-dimethylphenyl)-4-hydroxy-1-methylpyridin-2(1H)-one (2b)



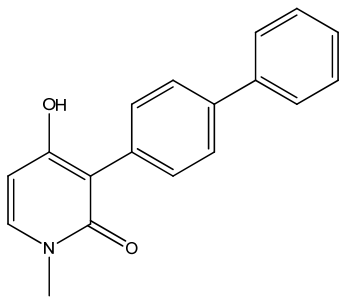
yield = 39mg (71%) white solid. mp. 151-154 °C. R_f = 0.33 (CH_2Cl_2 : CH_3COCH_3, 4 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.45 (d, *J* = 5Hz, 1H), 7.00 (s, 2H), 6.86 (s, 1H), 6.04 (d, *J* = 10Hz, 1H), 3.43 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 163.4, 162.2, 138.6, 137.3, 134.6, 129.5, 128.9, 113.0, 99.8, 37.0, 21.3; HRMS (ESI) calcd for $C_{14}H_{16}NO_2^+$ $[M + H]^+$: 230.1181, found 230.1180.

1-butyl-3-(3,5-dimethylphenyl)-4-hydroxypyridin-2(1H)-one (2c)



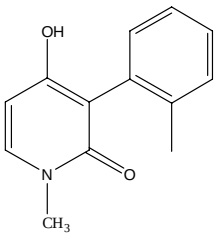
yield = 38mg (80%) white solid. mp. 137-139 °C. R_f = 0.33 (CH_2Cl_2 : EtOAc, 9 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.44 (d, *J* = 8Hz, 1H), 7.00 (brs, 2H), 6.86 (brs, 1H), 6.05 (d, *J* = 8Hz, 1H), 3.90 (t, *J* = 7Hz, 2H), 1.67 (quin, *J* = 7Hz, 2H), 1.34 (sex, *J* = 7Hz, 2H), 0.92 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 162.1, 161.3, 137.1, 136.4, 133.8, 128.7, 127.9, 112.3, 99.1, 48.5, 31.4, 20.5, 19.6, 13.1; HRMS (ESI) calcd for $C_{17}H_{22}NO_2^+$ $[M + H]^+$: 272.1650, found 272.1654; Anal. calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16%. Found: C, 75.20; H, 7.88; N, 5.19%.

3-(biphenyl-4-yl)-4-hydroxy-1-methylpyridin-2(1H)-one (2d)



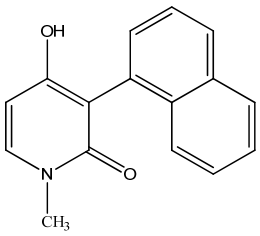
yield = 21mg (33%) white solid. R_f = 0.33 (CH_2Cl_2 : CH_3COCH_3, 3 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.63 (d, *J* = 8Hz, 2H), 7.59 (d, *J* = 8Hz, 2H),7.49 (d, *J* = 8Hz, 2H), 7.42 (t, *J* = 8Hz, 2H), 7.35 (d, *J* = 8Hz, 1H), 7.29 (d, *J* = 8Hz, 1H), 6.08 (d, *J* = 8Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 168.8, 168.6, 141.4, 139,2, 138.5, 136.7, 131.4, 128.3, 126.5, 126.4, 125.7, 101.3, 97.2, 36.1; HRMS (ESI) calcd for $C_{18}H_{16}NO_2^+$ $[M + H]^+$: 278.1181, found 278.1170; Anal. calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05%. Found: C, 77.63; H, 5.69; N, 5.29%.

4-hydroxy-1-methyl-3-o-tolylpyridin-2(1H)-one (2e)



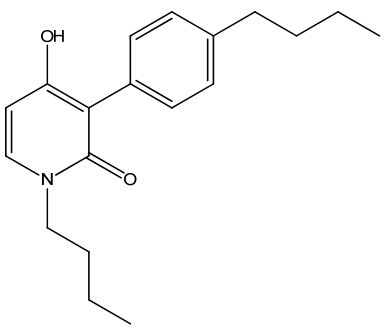
yield = 34mg (67%) white solid. mp. 135-138 ^{o}C. R_f = 0.21 (CH_2Cl_2 : CH_3COCH_3, 3 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.49 (d, *J* = 10Hz, 1H), 7.20-7.10 (m, 4H), 6.04 (d, *J* = 10Hz, 1H), 3.44 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 162.2, 161.8, 138.1, 138.0, 133.7, 131.3, 129.4, 127.1, 125.1, 111.9, 98.4, 36.1, 19.0; HRMS (ESI) calcd for $C_{13}H_{14}NO_2^+$ $[M + H]^+$: 216.1024, found 216.1042; Anal. calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51%. Found: C, 72.59; H, 5.99; N, 6.38%.

4-hydroxy-1-methyl-3-(naphthalen-1-yl)pyridin-2(1H)-one (2f)



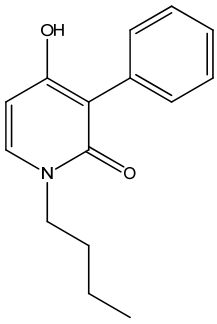
yield = 32mg (54%) yellowish solid. mp. 178-180 ^{o}C. R_f = 0.38 (CH_2Cl_2 : CH_3COCH_3, 3 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.90 (d, *J* = 5Hz, 1H), 7.84 (d, *J* = 10Hz, 1H), 7.65 (d, *J* = 10Hz, 1H), 7.60 (d, *J* = 10Hz, 1H), 7.51-7.44 (m, 2H), 7.40-7.36 (m, 2H), 6.12 (d, *J* = 10Hz, 1H), 3.47 (s, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 162.6, 162.5, 138.6, 133.9, 132.9, 132.1, 128.9, 128.0, 127.5, 125.9, 125.5, 125.3, 125.3, 110.5, 98.8, 36.1; HRMS (ESI) calcd for $C_{16}H_{14}NO_2^+$ $[M + H]^+$: 252.1024, found 252.1038.

1-butyl-3-(4-butylphenyl)-4-hydroxypyridin-2(1H)-one (2g)

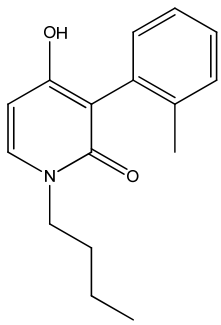


yield = 46mg (86%) oily residue. R_f = 0.30 (CH_2Cl_2 EtOAc, 9 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.44 (d, *J* = 8Hz, 1H), 7.37 (d, *J* = 8Hz, 2H), 7.15 (d, *J* = 8Hz, 2H), 6.06 (d, *J* = 8Hz, 1H), 3.90 (t, *J* = 7Hz, 2H), 2.61 (t, *J* = 7Hz, 2H), 1.68 (quin, *J* = 7Hz, 2H), 1.61 (quin, *J* = 7Hz, 2H), 1.36 (oct, *J* = 7Hz, 4H), 0.94 (dt, *J* = 7Hz, *J* = 2Hz, 6H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 162.1, 161.2, 140.6, 137.0, 131.3, 130.9, 127.3, 111.9, 99.1, 48.5, 35.1, 33.6, 31.4, 22.1, 19.6, 13.3, 13.1; HRMS (ESI) calcd for $C_{19}H_{26}NO_2^+$ $[M + H]^+$: 300.1964, found 300.1933. Anal. calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68%. Found: C, 76.25; H, 8.44; N, 4.71%.

1-butyl-4-hydroxy-3-phenylpyridin-2(1H)-one (2h)

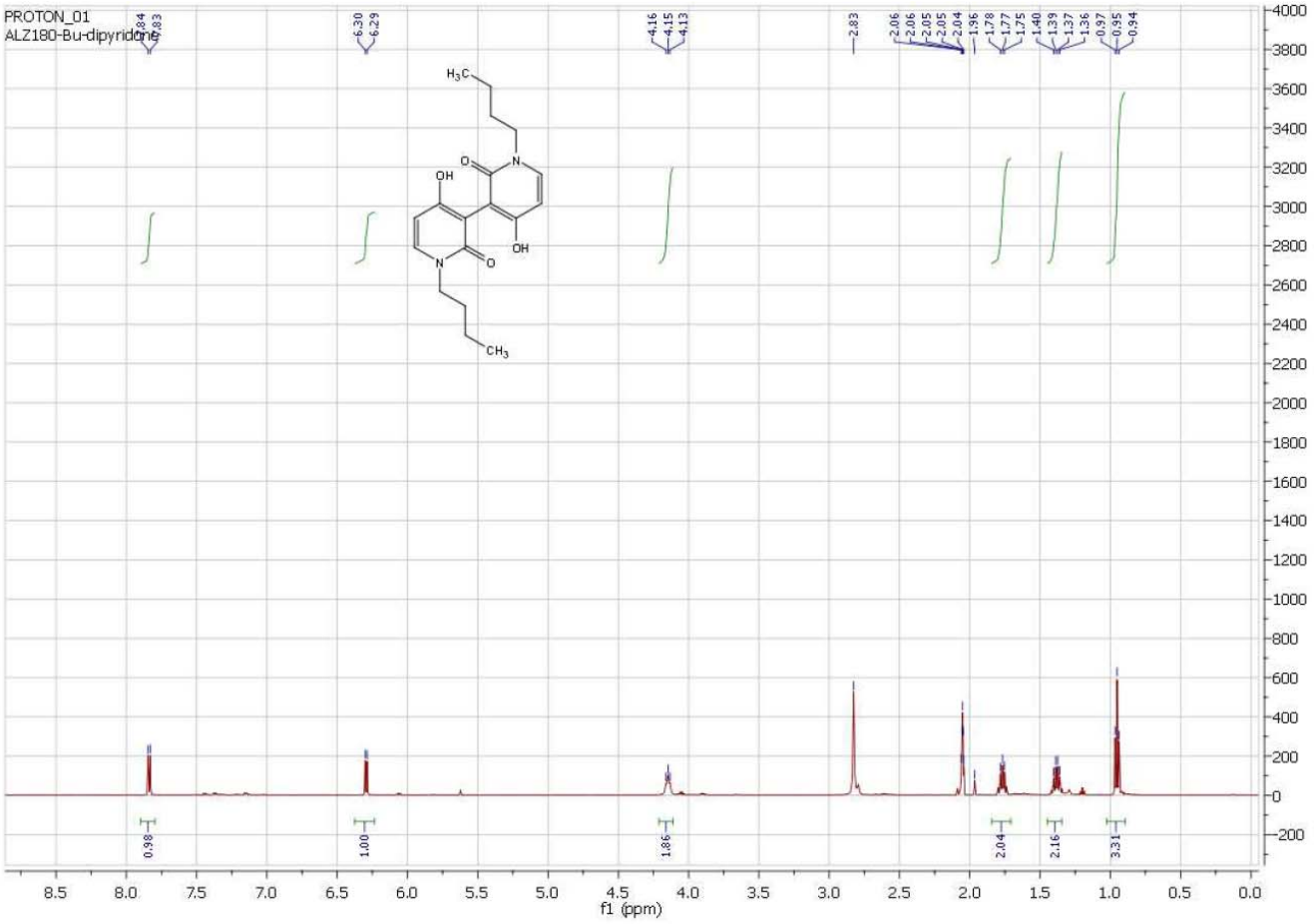


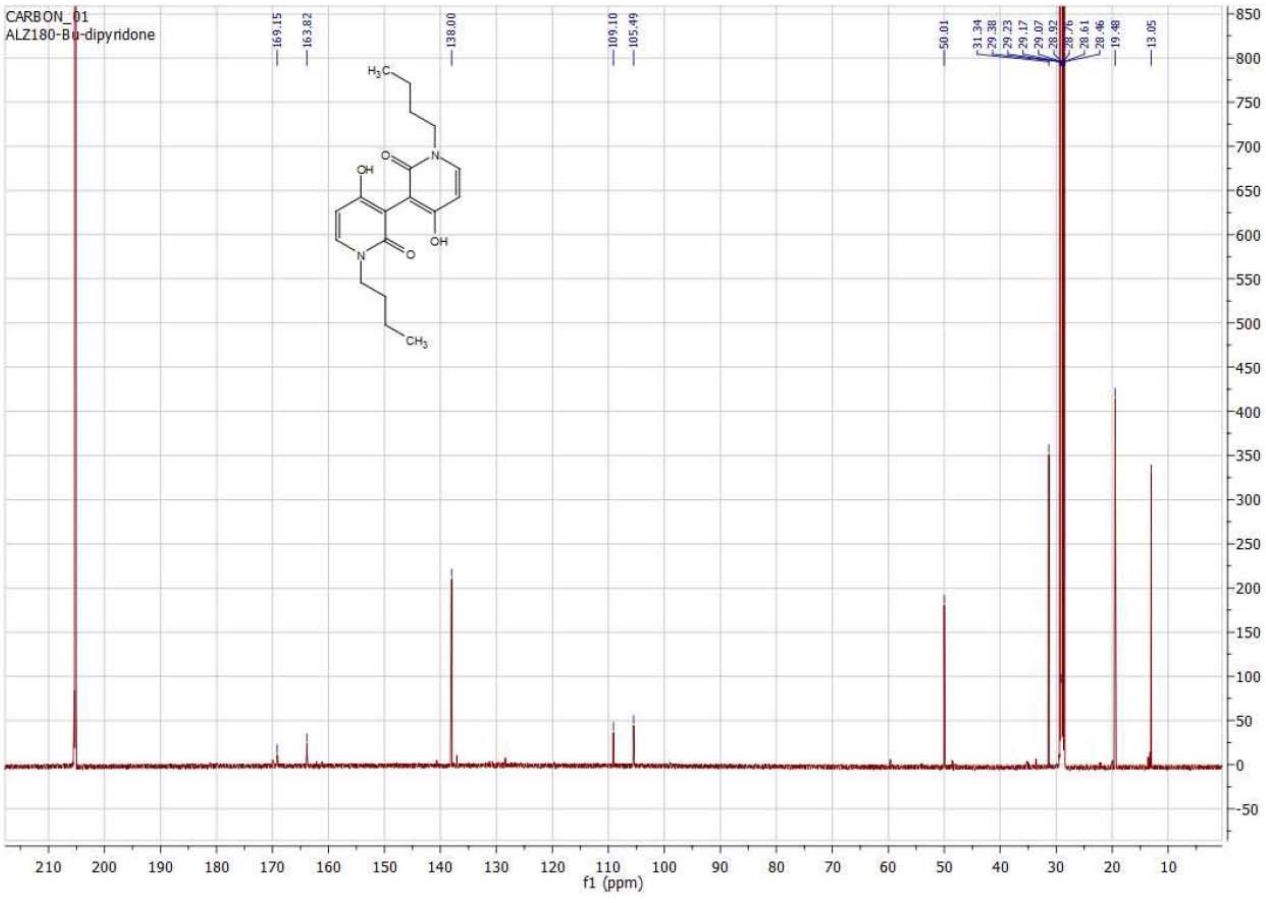
yield = 35mg (82%) orange solid. mp. 106-110 ^{o}C. R_f = 0.23 (CH_2Cl_2 : EtOAc, 9 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.45 (brd, *J* = 5Hz, 3H), 7.31 (t, *J* = 7Hz, 2H), 7.21 (d, *J* = 7Hz, 1H), 6.08 (d, *J* = 5Hz, 1H), 3.91 (t, *J* = 7Hz, 2H), 1.68 (quin, *J* = 7Hz, 2H), 1.35 (sex, *J* = 7Hz, 2H), 0.92 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 162.1, 161.5, 137.2, 134.1, 131.0, 127.2, 126.2, 111.9, 99.2, 48.6, 31.4, 19.6, 13.1; HRMS (ESI) calcd for $C_{15}H_{18}NO_2^+$ $[M + H]^+$: 244.1338, found 244.1342.



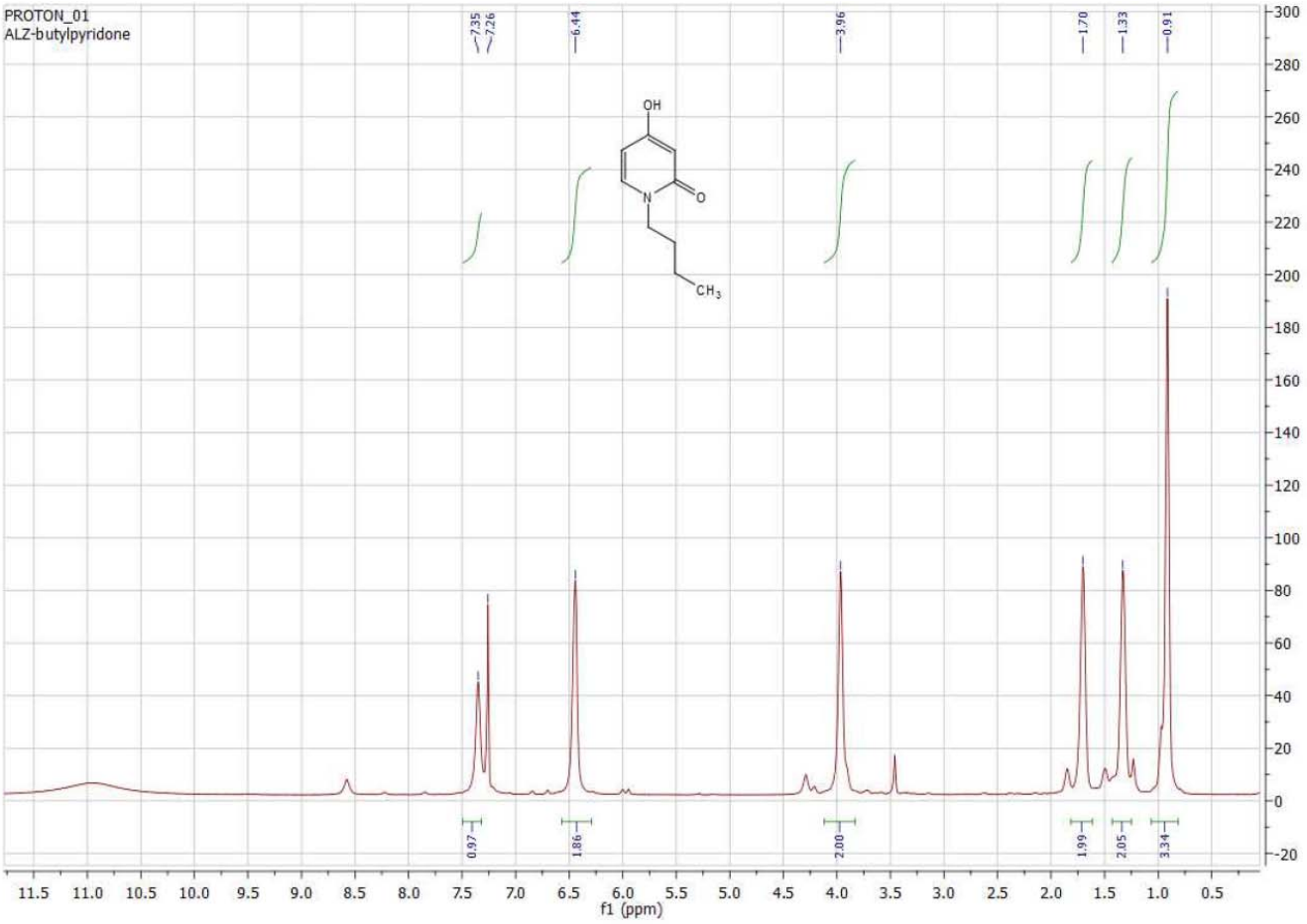
1-butyl-4-hydroxy-3-o-tolylpyridin-2(1H)-one (2i)

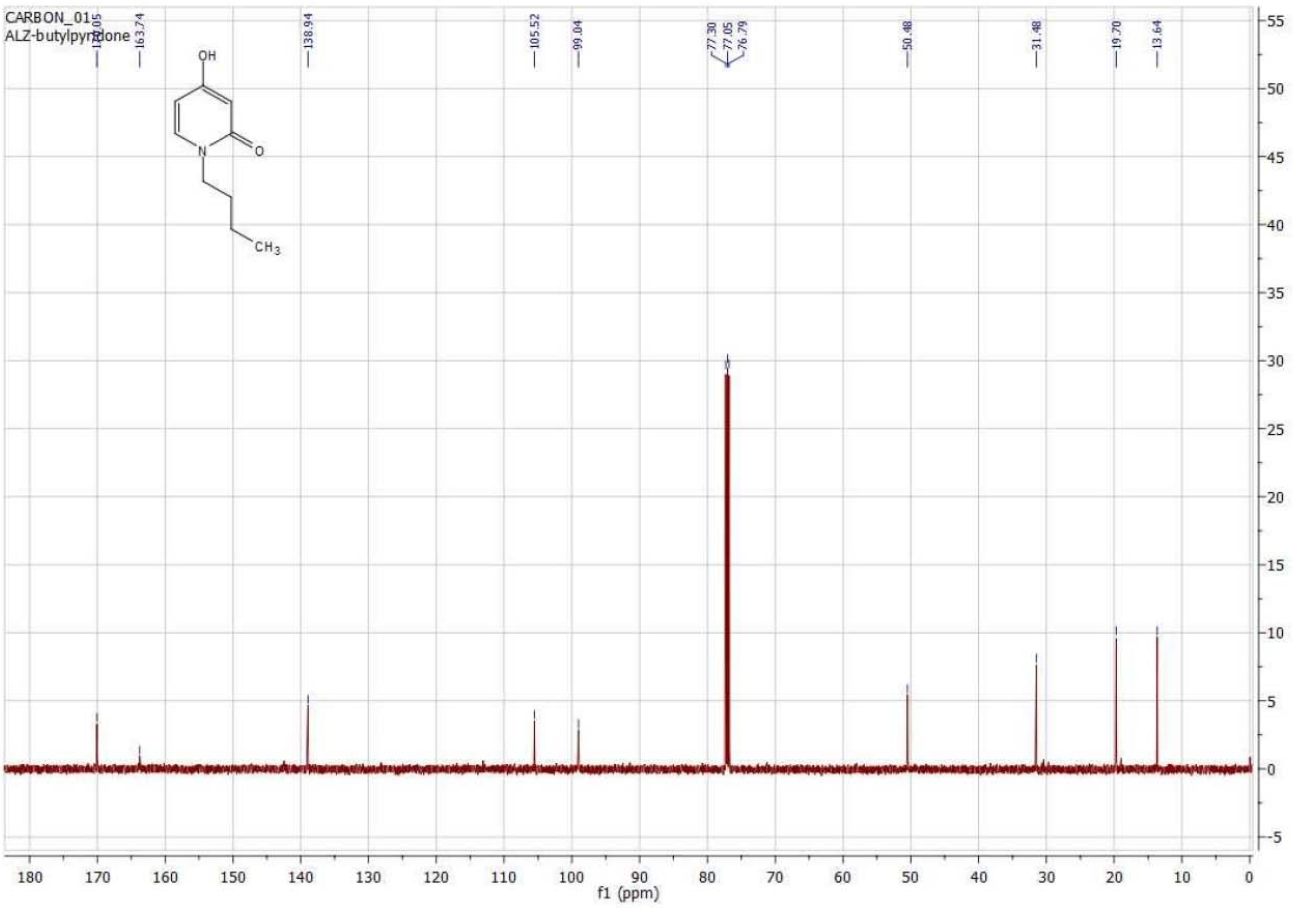
yield = 28mg (62%) white solid. R_f = 0.25 (CH_2Cl_2 : EtOAc, 9 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.50 (d, *J* = 8Hz, 1H), 7.22 – 7.09 (m, 4H) 6.06 (d, *J* = 8Hz, 1H), 3.91 (t, *J* = 7Hz, 2H), 1.68 (quin, *J* = 7Hz, 2H), 1.35 (sex, *J* = 7Hz, 2H), 0.92 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 161.6, 161.4, 138.1, 137.4, 133.8, 131.3, 129.4, 127.0, 125.1, 112.1, 98.7, 48.3, 31.4, 19.5, 18.9, 13.1; HRMS (ESI) calcd for $C_{16}H_{20}NO_2^+$ $[M + H]^+$: 258.1494, found 258.1474; Anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44%. Found: C, 74.88; H, 7.20; N, 5.72%.



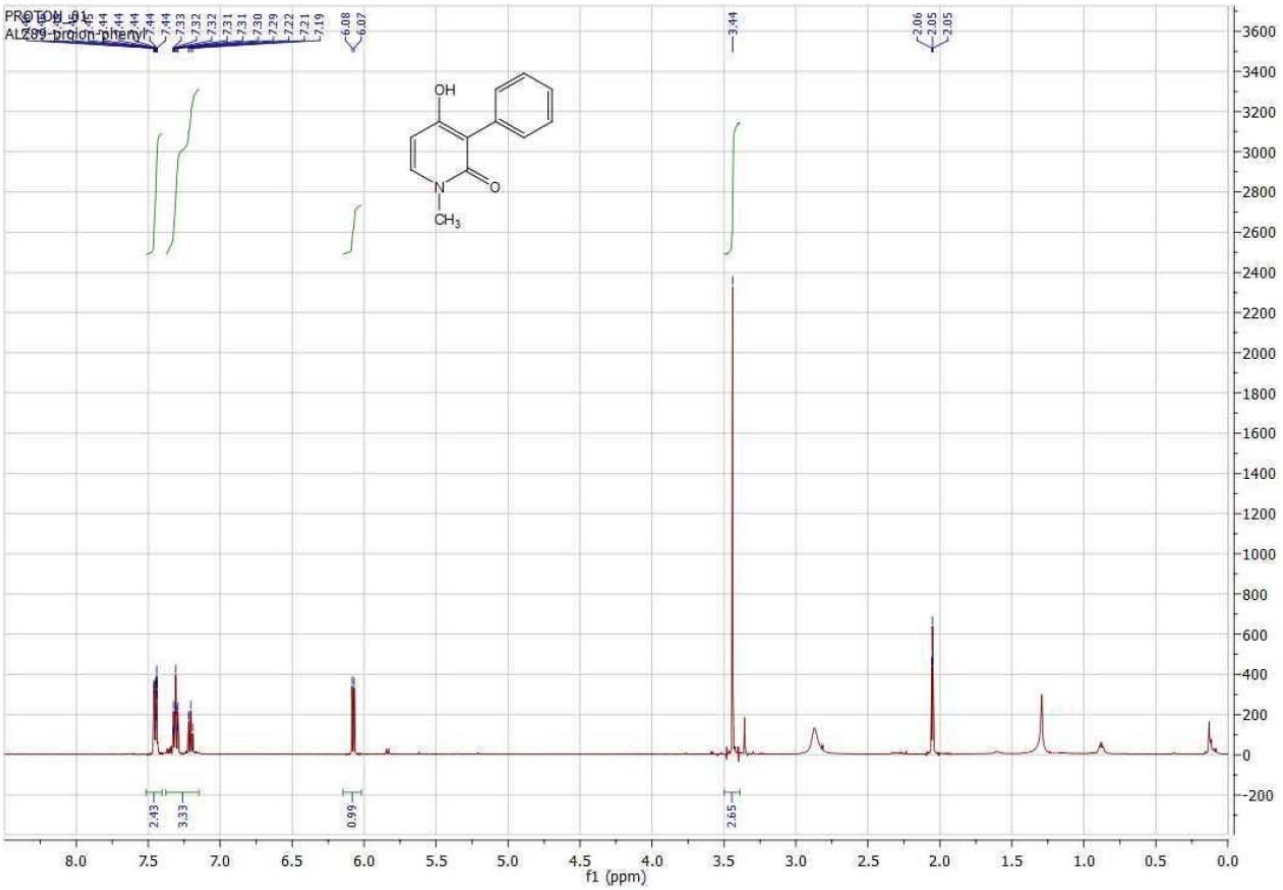


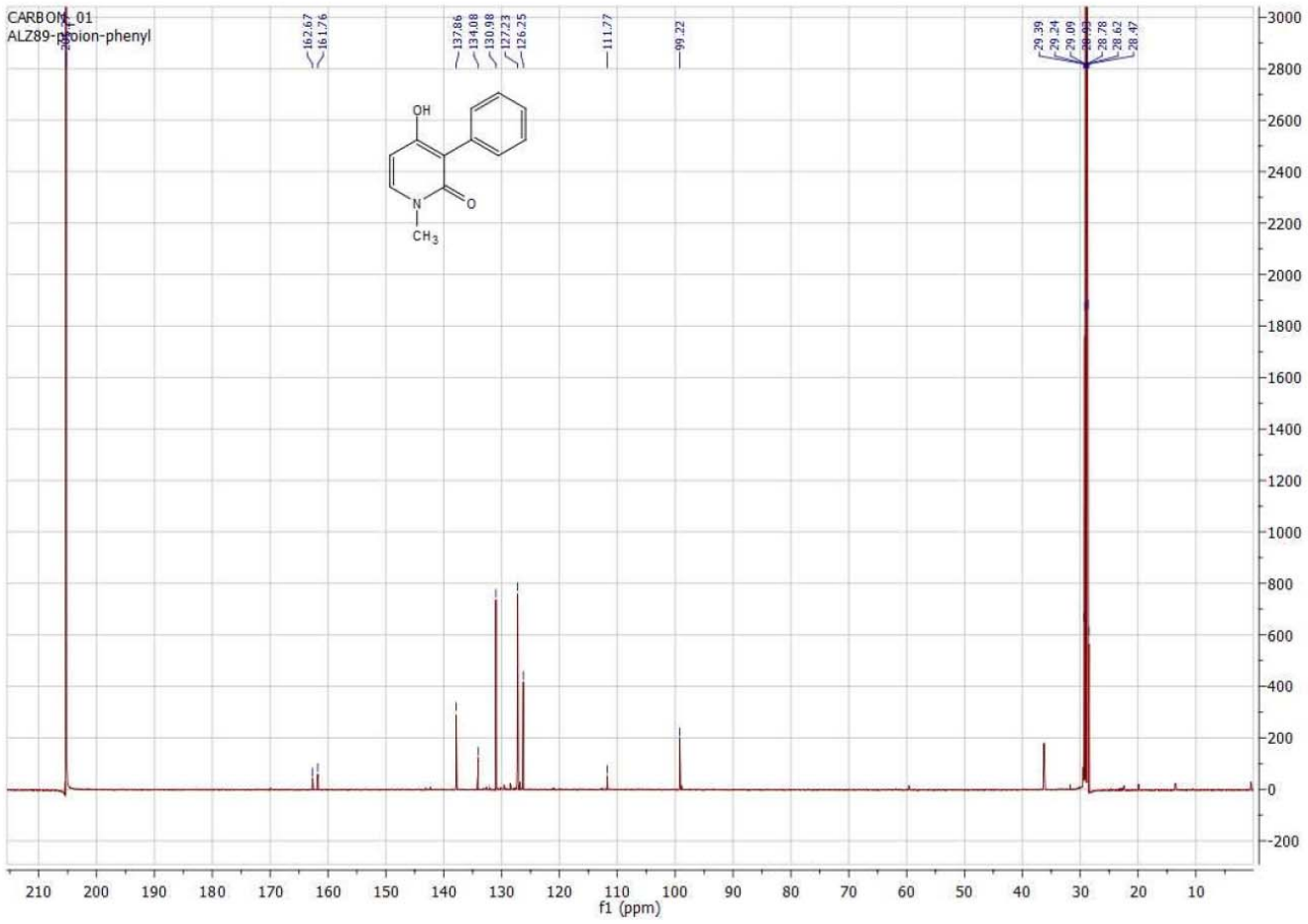
Compound **12** in CD_6CO 500MHz



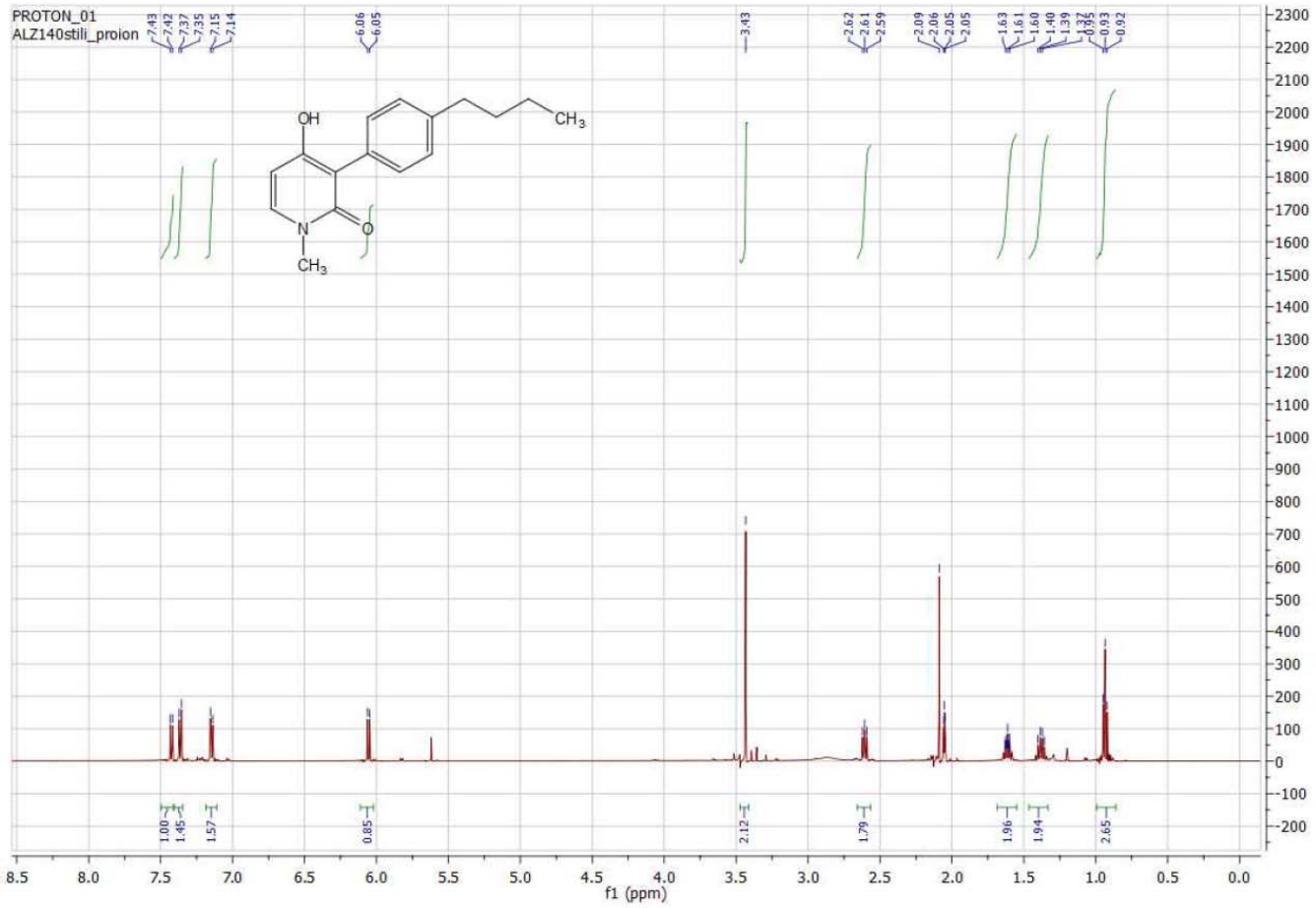


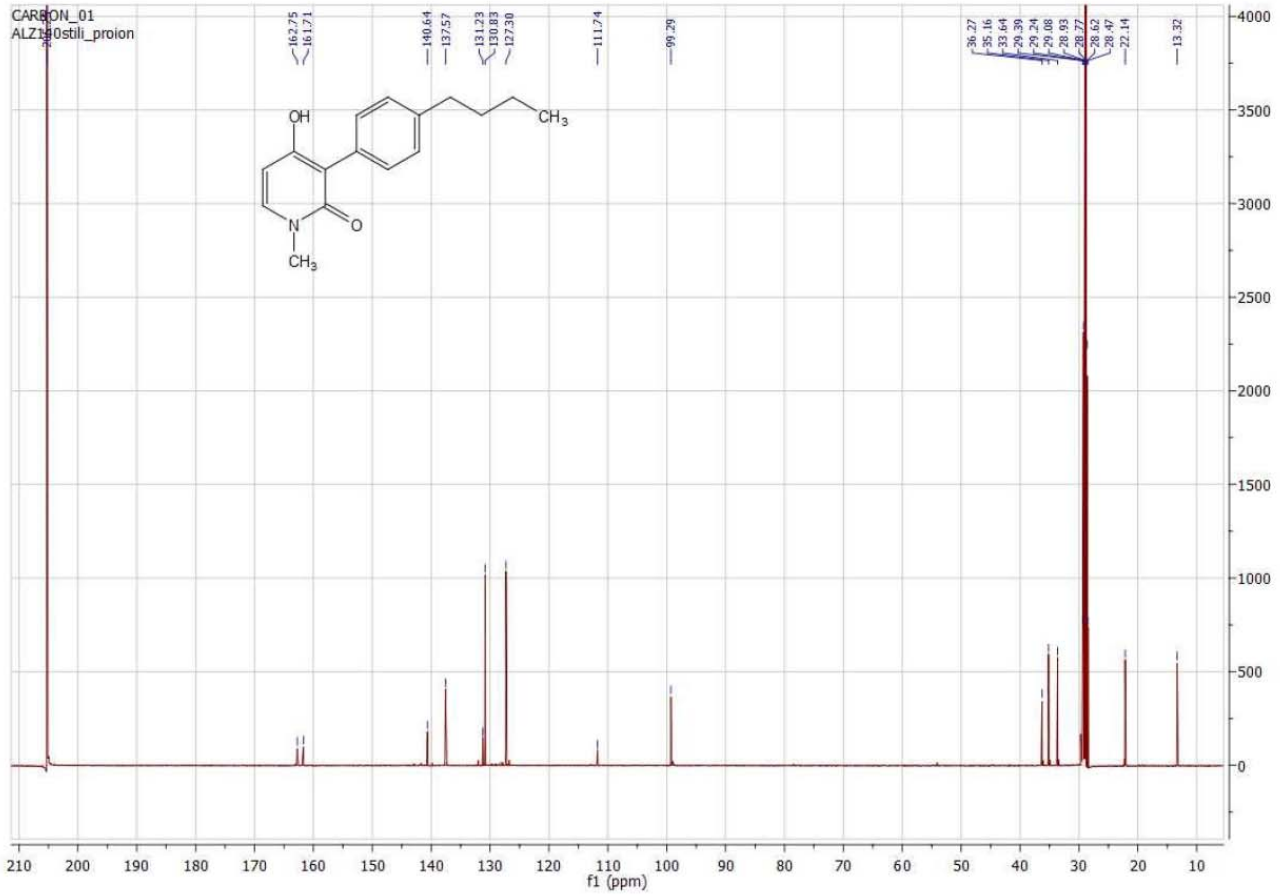
Compound **13** in $CDCl_3$ 500MHz



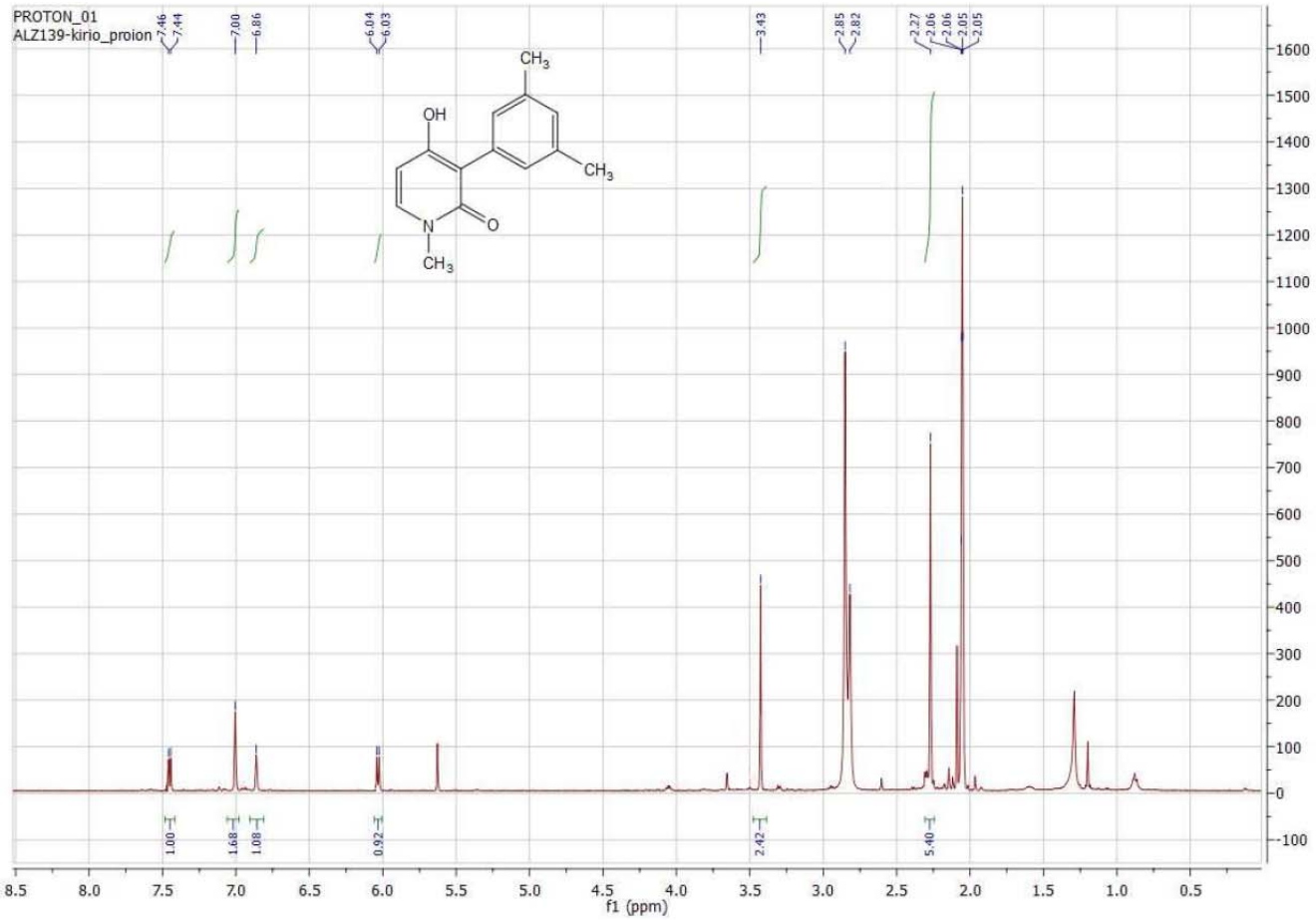


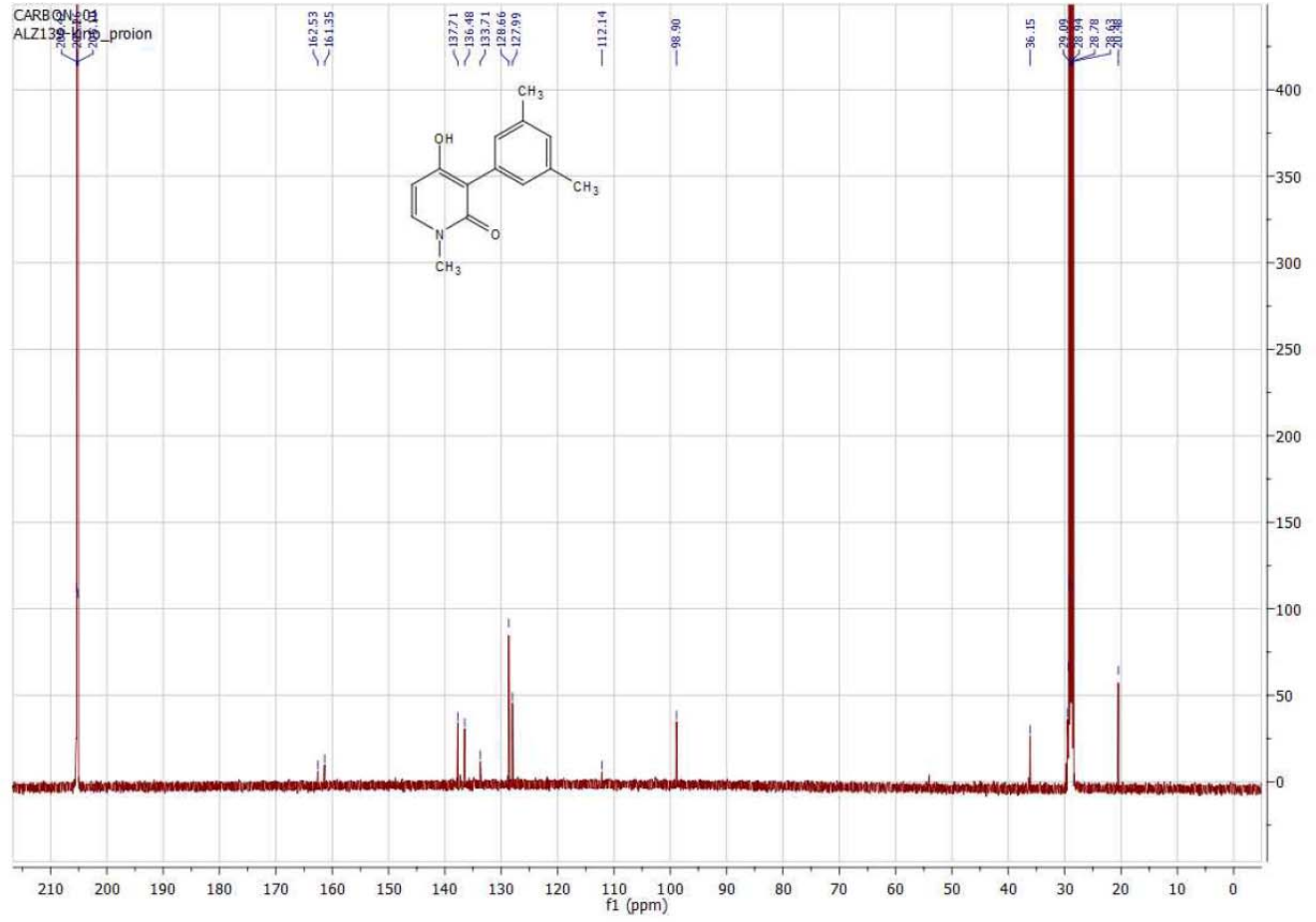
Compound **7** in CD_6CO 500MHz



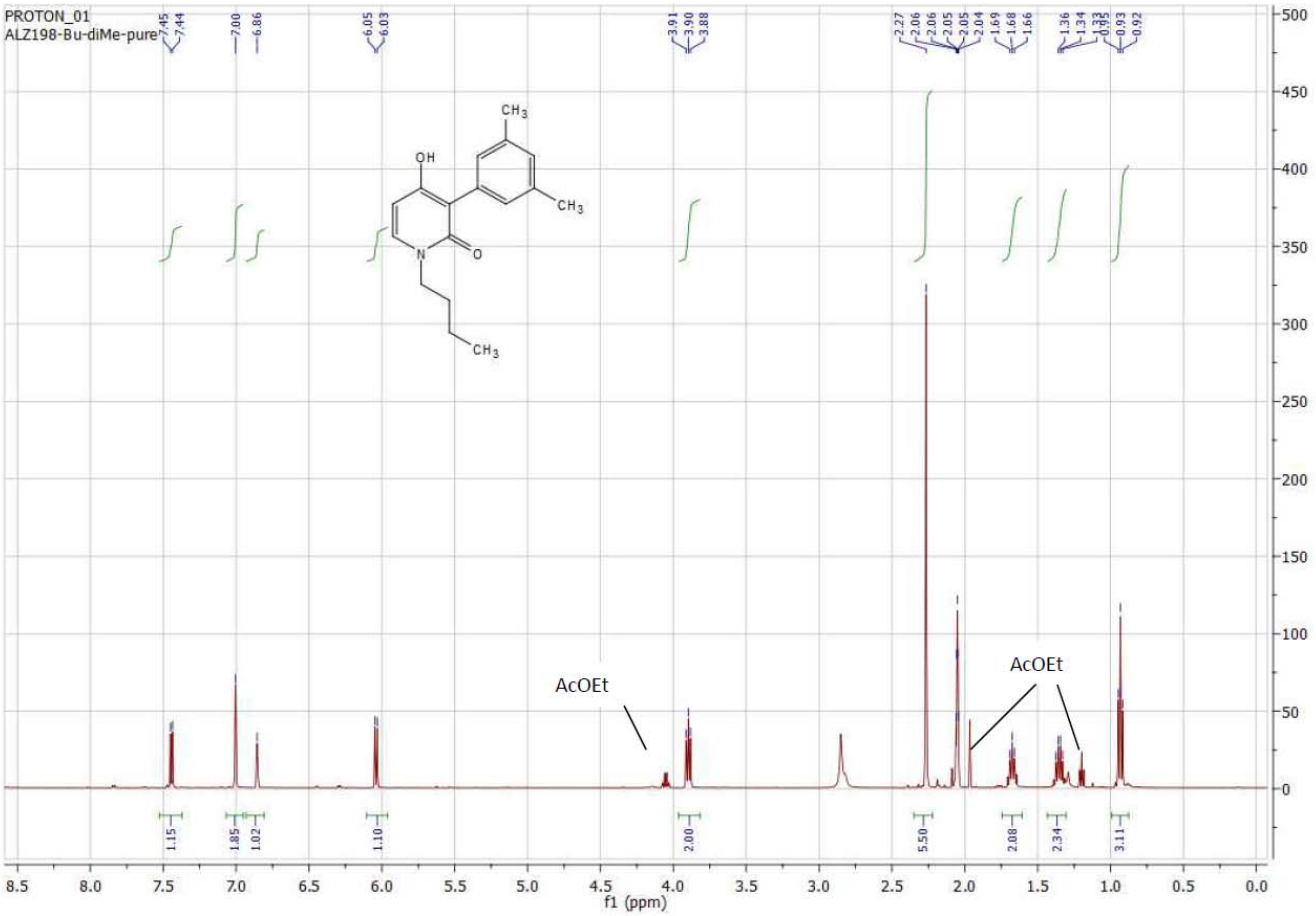


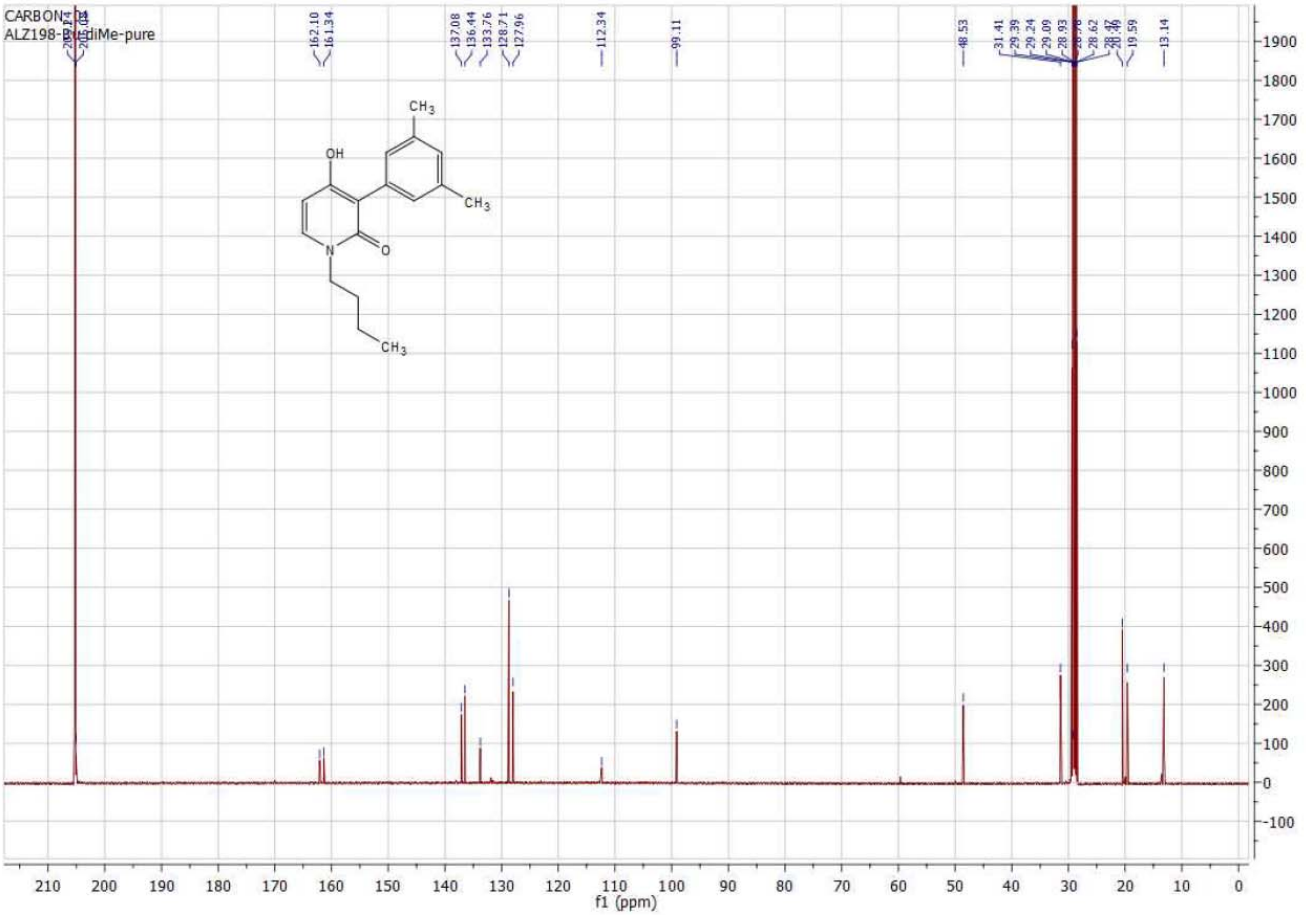
Compound **2a** in CD_6CO 500MHz



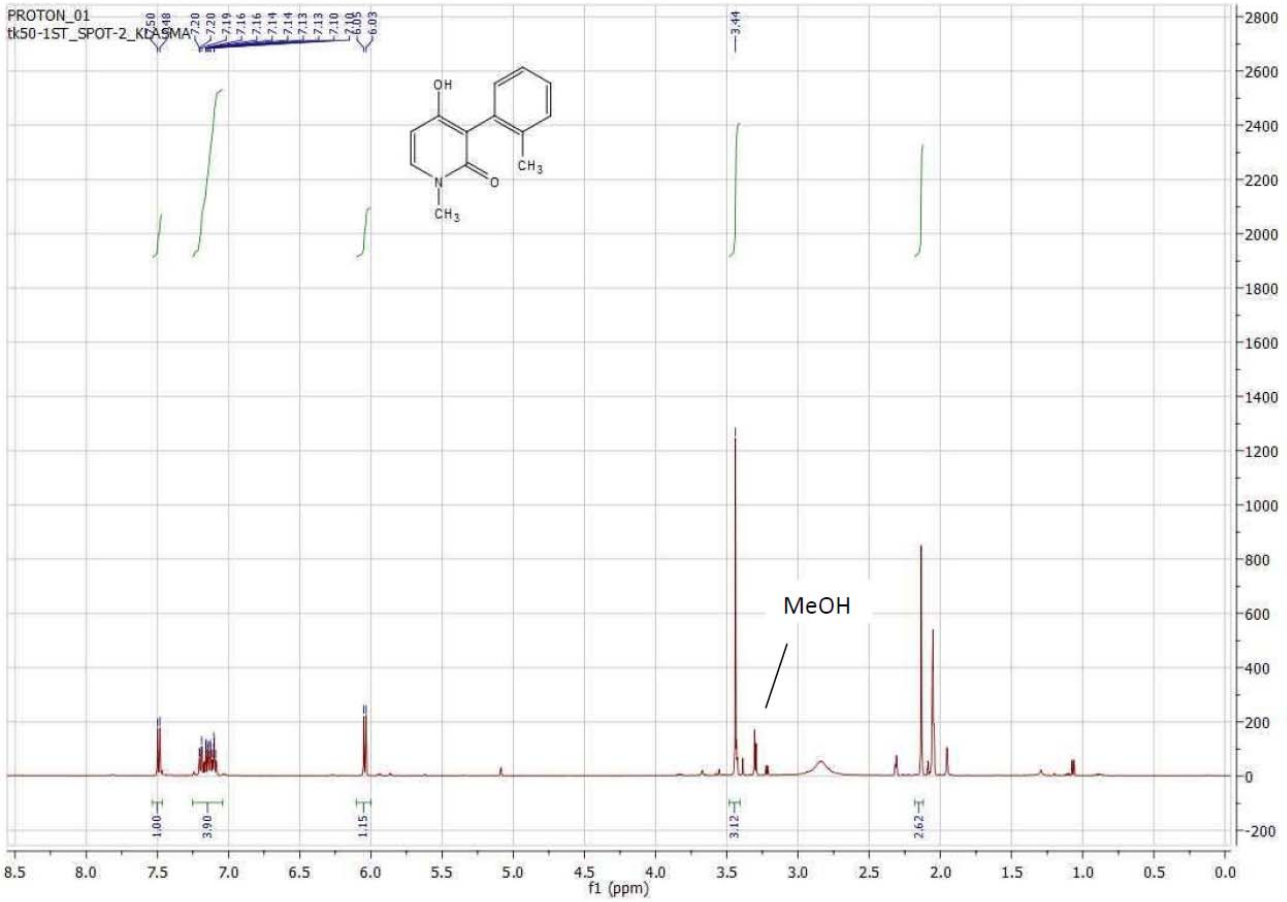


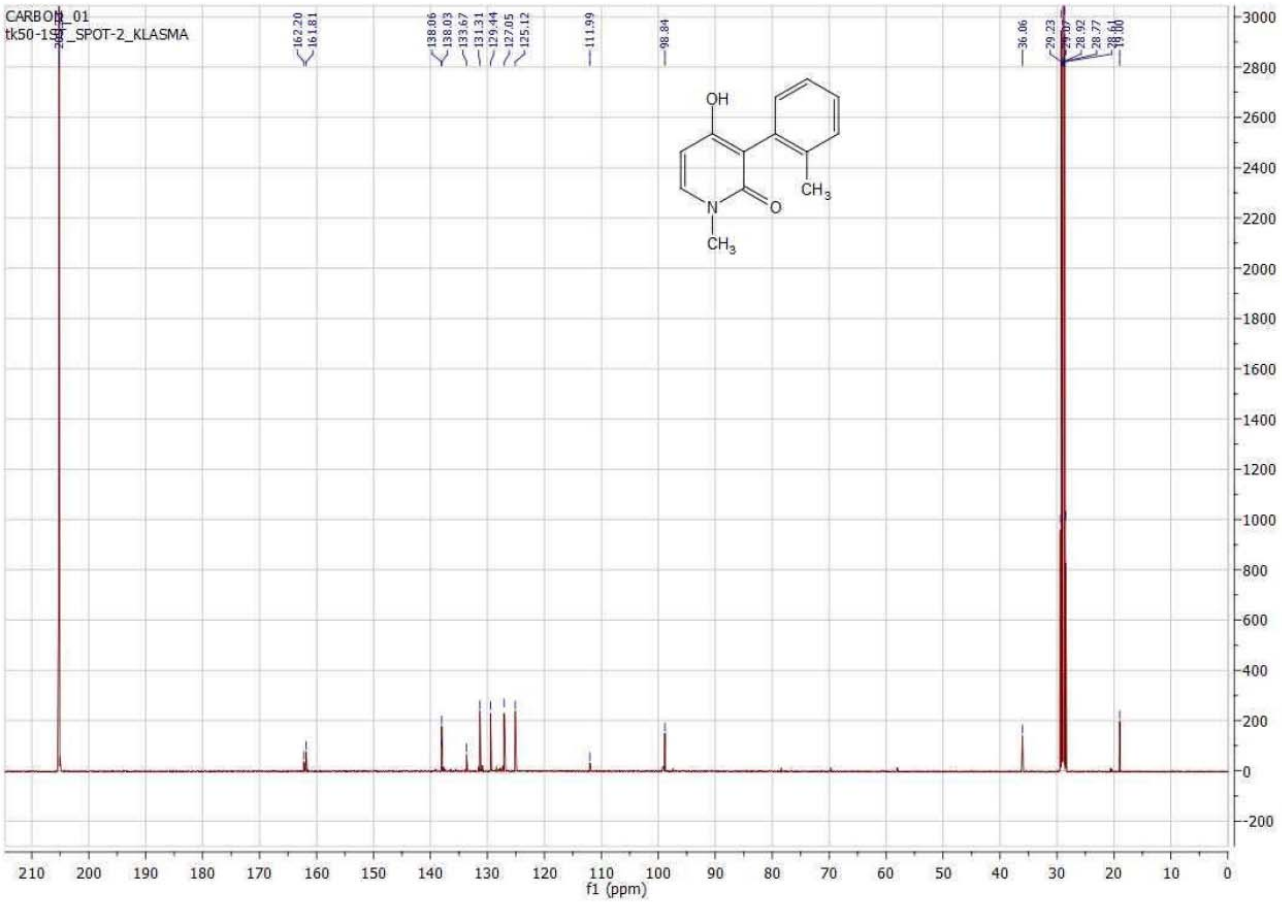
Compound **2b** in CD_6CO 500MHz



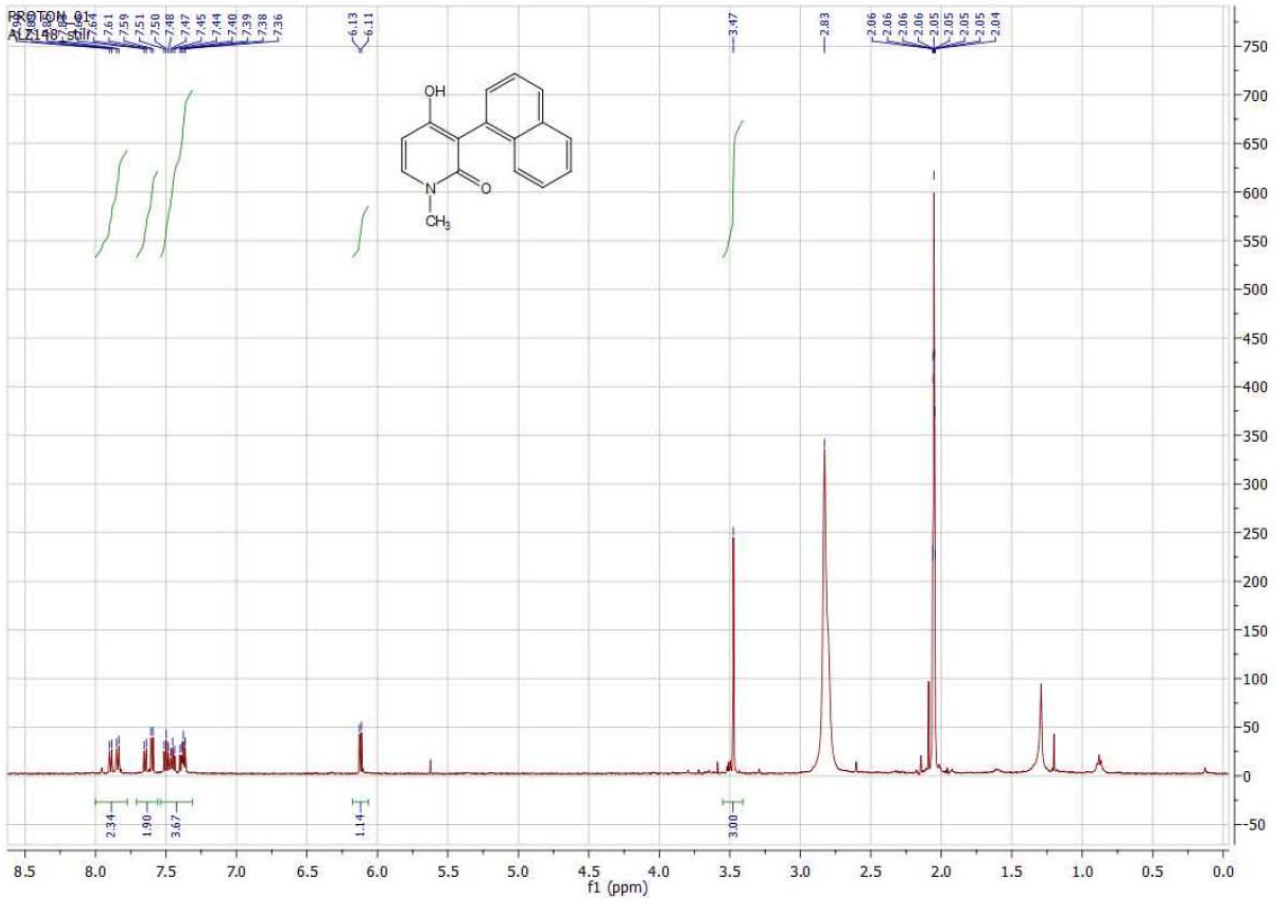


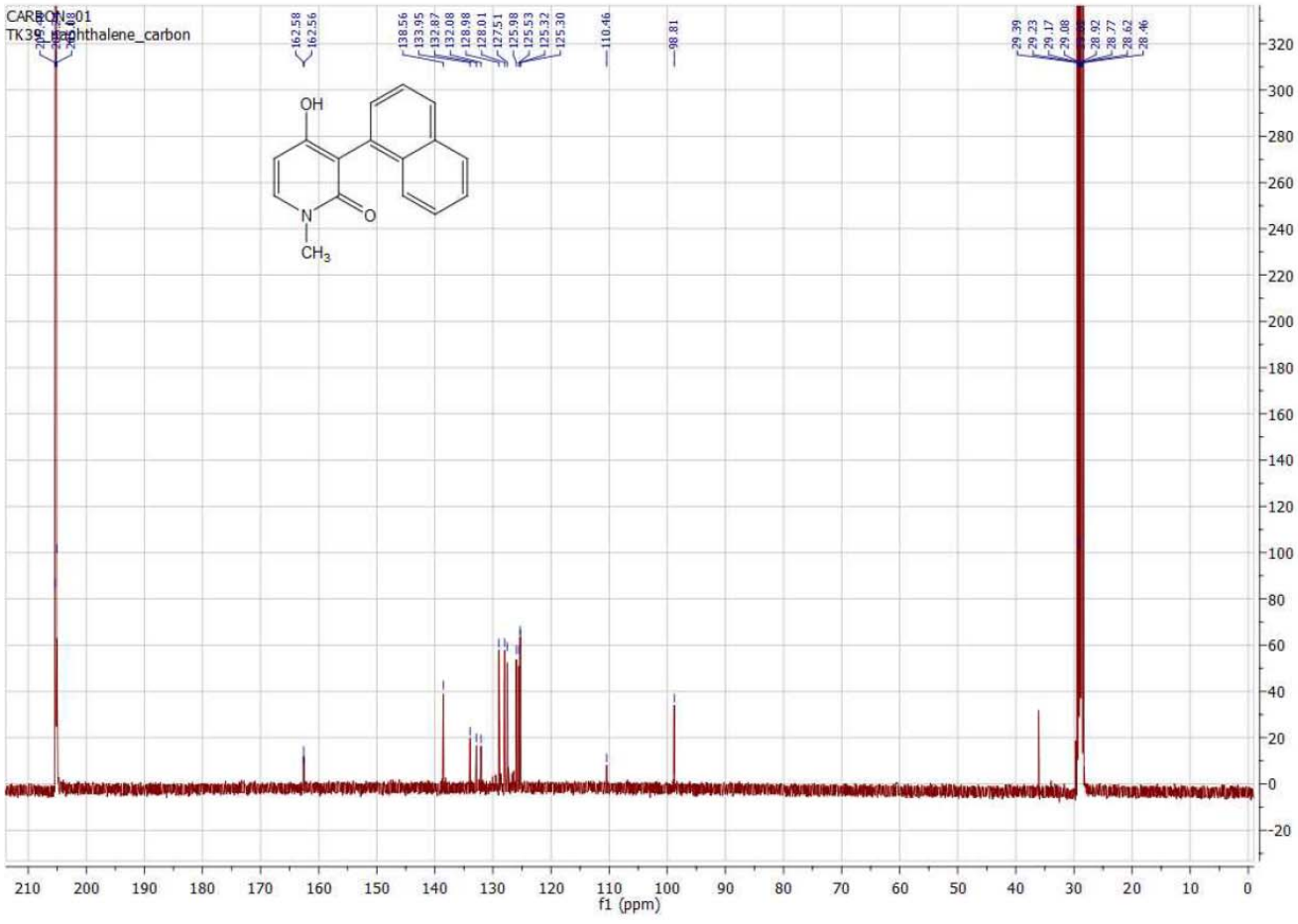
Compound **2c** in CD_6CO 500MHz



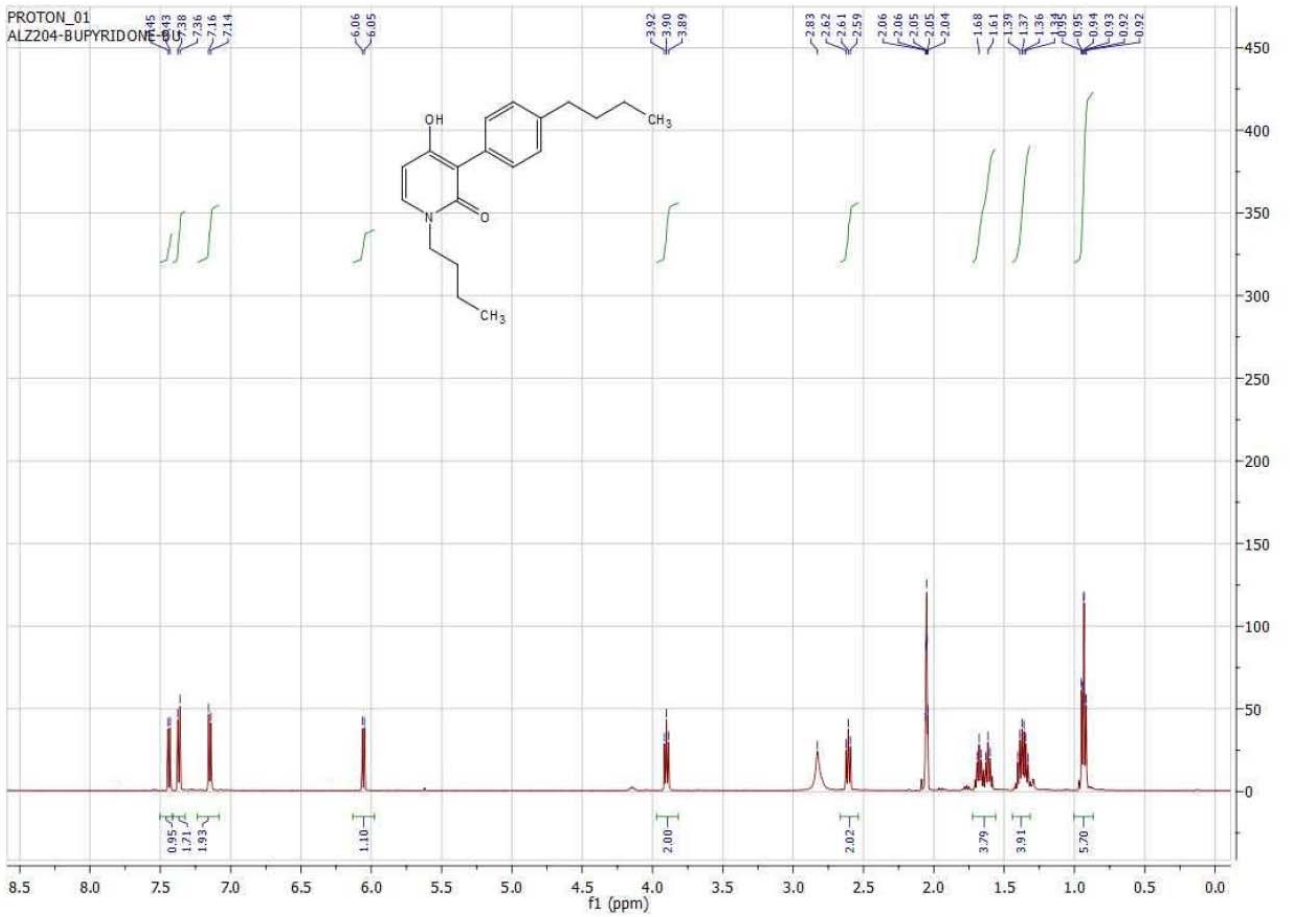


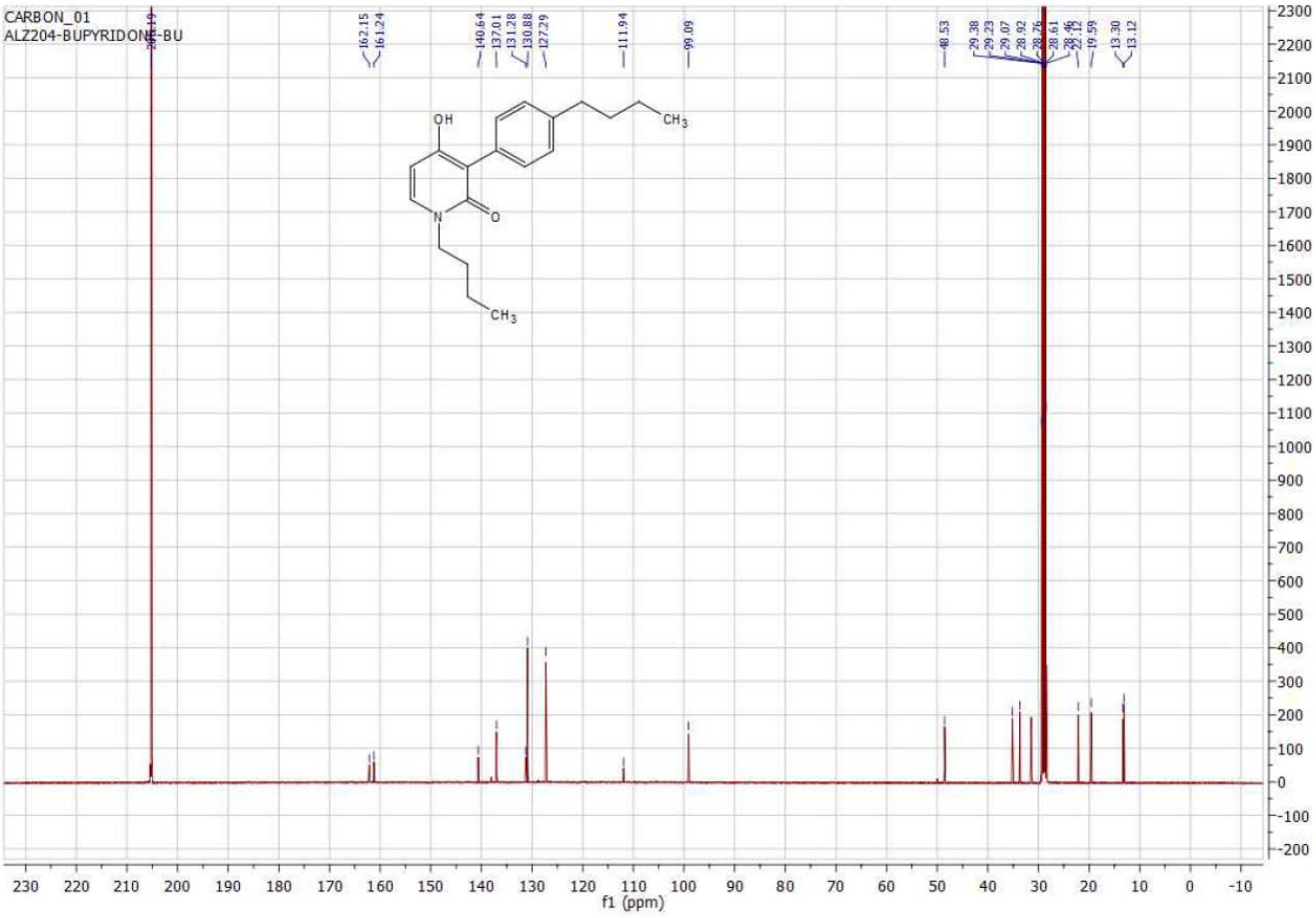
Compound **2e** in CD_6CO 500MHz



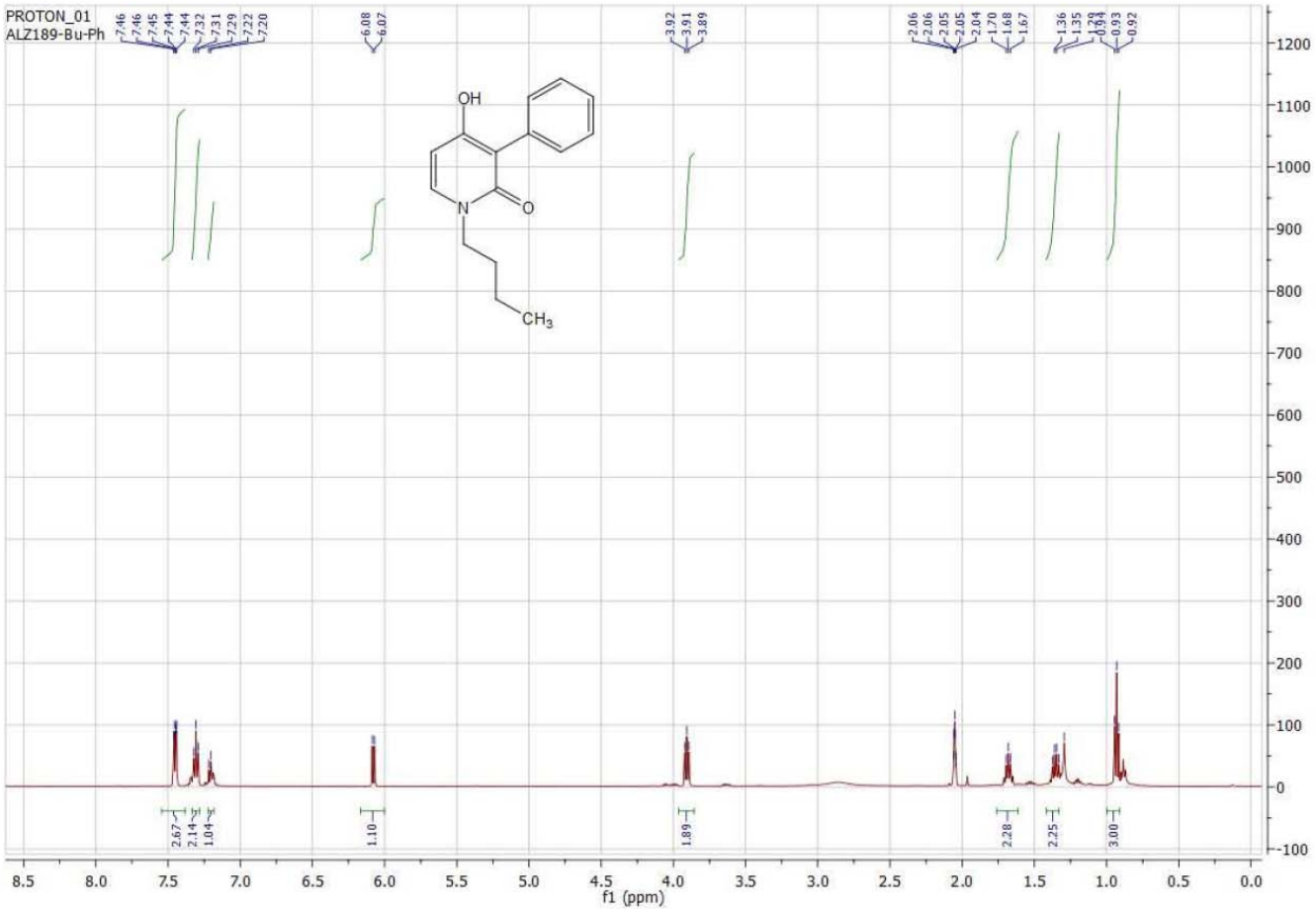


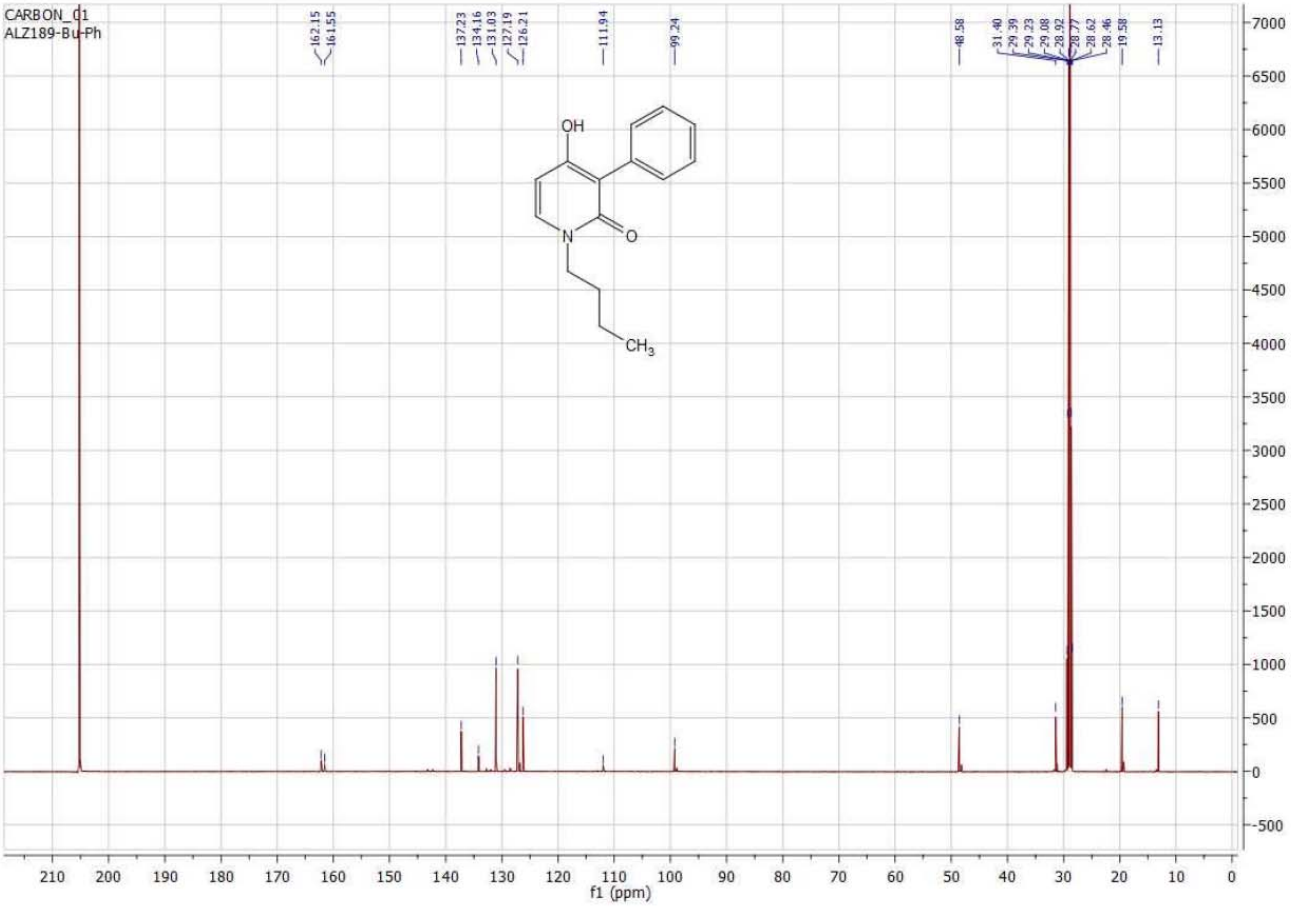
Compound **2f** in CD_6CO 500MHz



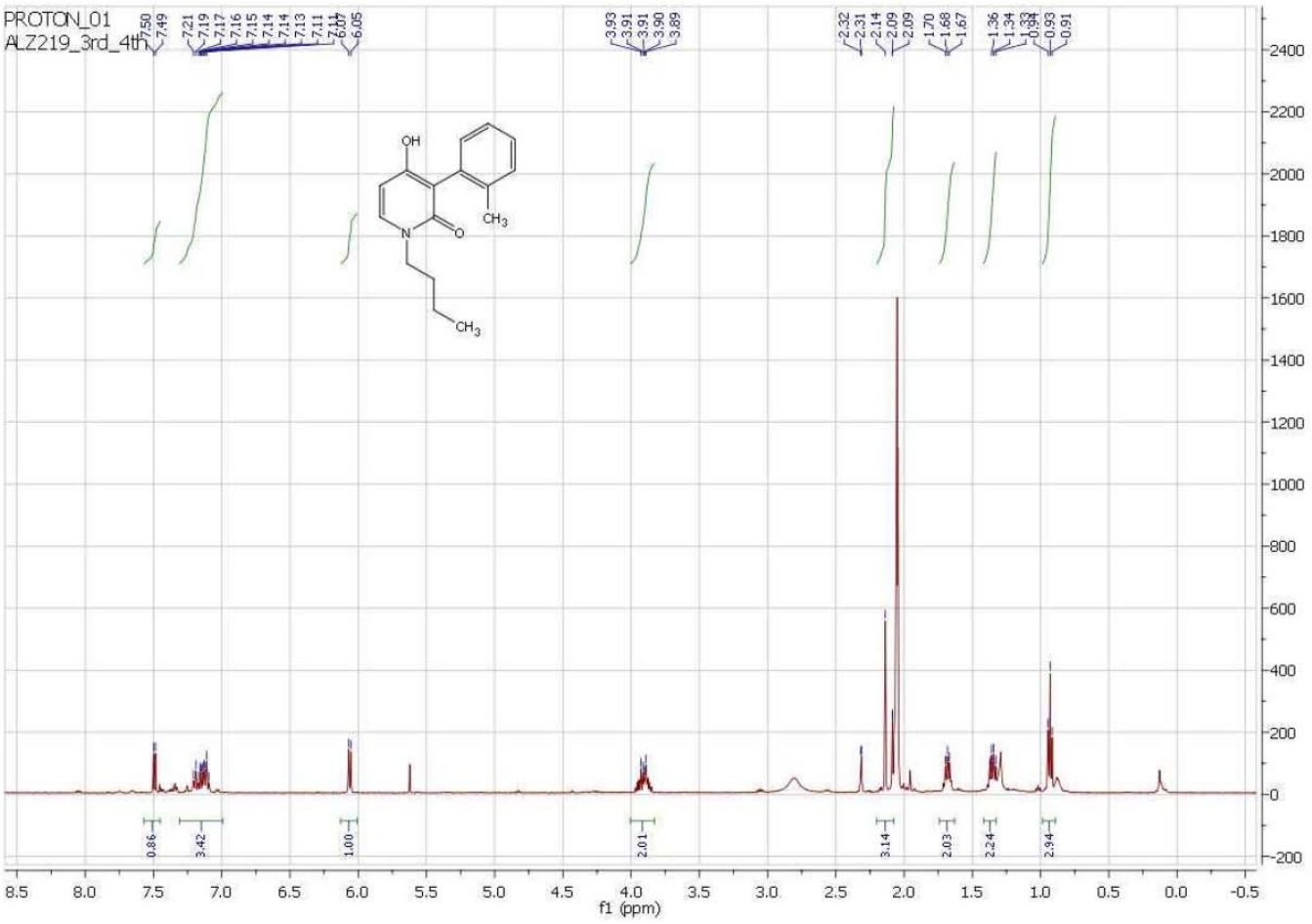


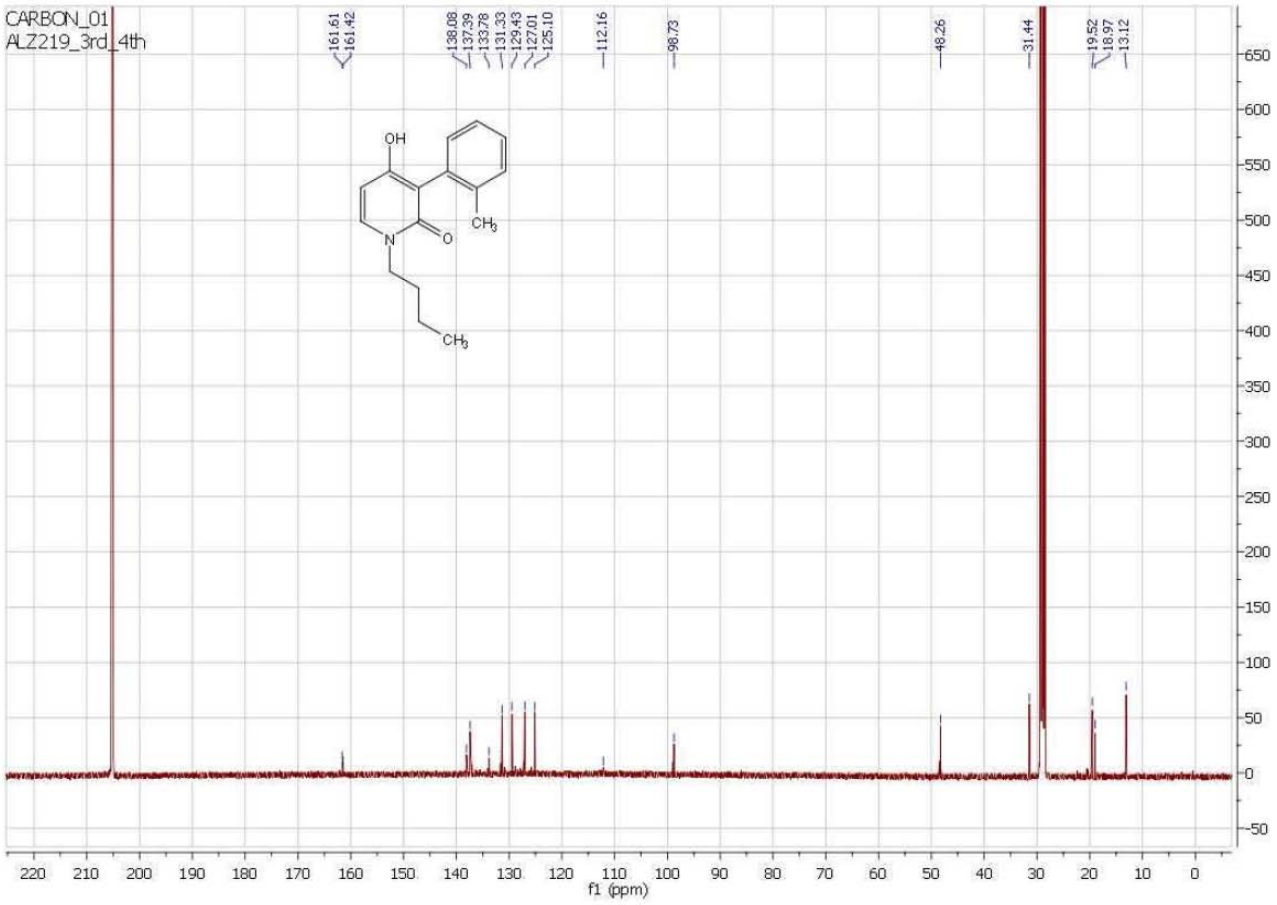
Compound **2g** in CD_6CO 500MHz





Compound **2h** in CD_6CO 500MHz





Compound **2i** in CD_6CO 500MHz