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Palladium-Catalyzed Direct Alkenylation of 4-hydroxy-2-pyridones.

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Supporting Information

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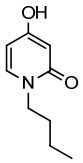
I. General Information

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 the indicated deuteriorated solvents and calibrated using residual peaks 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. All 4-hydroxy-2-pyridone spectra are presenting small amounts of rotamers which has been taken care to be reduced by the appropriate choice of deuteriorated solvents. 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.

II Preparation of N-Substituted 4-Hydroxy-2-pyridones

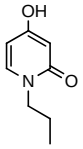


N-Butyl-4-hydroxy-2-pyridone (3a)

A round bottom flask equipped with a condenser was charged with 4-benzyloxy-2-hydroxy-pyridine (0.250 g; 1.24 mmoles) and 1-iodobutane (0.212 ml; 1.86 mmoles) and dissolved in DMF (3 ml). Potassium carbonate (0.258 g; 1.86 mmoles) was added in one portion and the mixture was heated to 80 ^{o}C for 48 h. The resulting was evaporated to dryness under reduced pressure and chromatographed with silica gel (petroleum ether : EtOAc 2:1) to provide *N*-butyl-4-benzyloxy-2-pyridone (0.170 g; 53% yield). R_f = 0.66 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.32 (m, *5*H), 7.10 (d, *J* = 10Hz, 1H), 5.96 (d, *J* = 2.5Hz, 1H), 5.92 (dd, *J* = 10Hz *J* = 2.5Hz, 1H), 4.95 (s, 2H), 3.84 (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, $CDCl_3$): δ = 166.8, 163.9, 137.5, 135.3, 128.6, 128.4, 127.6, 100.6, 98.4, 70.0, 48.7, 31.4, 19.8, 13.7.

The resulting *N*-butyl-4-benzyloxy-2-pyridone (0.170 g) was added in a 25 mL sealed tube and was dissolved in **4** mL of methanol. After charging it with 0.017 g of 10% Pd/C, hydrogen gas was bubbled in

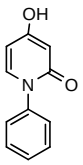
for 15 min before the tube is sealed and stirred at room temperature for **12** h. Filtration through Celite and concentration gave N-butyl-4-hydroxy-2-pyridone (0.117 g, 90% yield) as a white solid which was used without further purification. R_f = 0.69 (CH_2Cl_2 : CH_3COCH_3, 1 : 2). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.44 (d, *J* = 7Hz, 1H), 5.88 (d, *J* = 7Hz, 1H), 5.70 (s, 1H), 3.84 (t, *J* = 7.5Hz, 2H), 1.64 (q, *J* = 7Hz, 2H), 1.32 (six, *J* = 7Hz, 2H), 0.92 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 170.1, 163.7, 138.9, 106.5, 99.0, 50.5, 31.5, 19.7, 13.6.



_N_-Propyl-4-hydroxy-2-pyridone (3b)

A round bottom flask equipped with a condenser was charged with 4-benzyloxy-2-hydroxy-pyridine (0.200 g; 0.99 mmoles) and allylbromide (0.130 ml; 1.5 mmoles) and dissolved in DMF (2 ml). Potassium carbonate (0.206 g; 1.5 mmoles) was added in one portion and the mixture was heated to 80 ^{o}C for 12 h. The resulting was evaporated to dryness under reduced pressure and chromatographed with silica gel (CH_2Cl_2 100%) to provide *N*-allyl-4-benzyloxy-2-pyridone (0.216 g; 90% yield). R_f = 0.68 (Petroleum ether : EtOAc, 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40-7.34 (m, 5H), 7.11 (d, *J* = 7.5Hz, 1H), 6.0 (d, *J* =2.5Hz, 1H), 5.98 (dd, *J* =7.5Hz *J* = 2.5Hz, 1H), 5.96-5.89 (m, 1H), 5.24 (d, *J* = 10Hz, 1H), 5.17 (d, *J* = 17Hz, 1H), 5.00 (s, 2H), 4.51 (d, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 163.7, 136.9, 135.3, 132.8, 128.7, 128.4, 127.7, 118.1, 101.2, 98.4, 70.2, 50.1.

The resulting *N*-allyl-4-benzyloxy-2-pyridone (0.216 g) was added in a 25 mL sealed tube and was dissolved in 5 mL of methanol. After charging it with 0.021 g of 10% Pd/C, hydrogen gas was bubbled in for 15 min before the tube is sealed and stirred at room temperature for 12 h. Filtration through Celite and concentration gave *N*-propyl-4-hydroxy-2-pyridone (0.116 g, 85% yield) as a white solid which was used without further purification. R_f = 0.60 (CH_2Cl_2 : CH_3COCH_3, 1 : 2). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.46 (d, *J* = 7Hz, 1H), 5.95 (d, *J* = 7Hz, 1H), 5.79 (br s, 1H), 3.83 (t, *J* = 6.5Hz, 2H), 1.69 (six, *J* = 6.5Hz, 2H), 0.89 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 167.2, 163.7, 138.9, 100.1, 98.7, 49.8, 22.5, 10.3.



_N_-Phenyl-4-hydroxy-2-pyridone (3c)

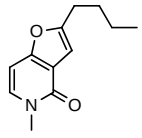
A mixture of 4-benzyloxy-2-pyridone (0.260 g; 1.3 mmoles), bromobenzene (0.179 ml, 1.7 mmol), CuI (0.762 g, 0.4 mmol), potassium carbonate (0.387 g, 2.8 mmol), in DMF (5 ml) was heated to 150 ^{o}C for 72

h. After being stirred for 72h, cold water (10mL) was added, and the white solid was filtered and washed with CH_2Cl_2. The mixture was extracted with brine (3 x 10 mL). The organic fraction was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was a white solid which was used without further purification to give compound *N*-phenyl-4-benzyloxy-2-pyridone (0.195 mg, 54% yield) . R_f =0.88 (CH_2Cl_2 : CH_3COCH_3, 1 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.54-7.35 (m, 10H), 6.07 (dd, *J* = 8Hz *J* = 2.5Hz, 1H), 5.94 (d, *J* = 2.5Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 167.2, 162.6, 141.2, 138.5, 136.2, 128.8, 128.5, 128.2, 127.8, 127.7, 126.8, 100.2, 98.0, 69.9.

The resulting *N*-phenyl-4-benzyloxy-2-pyridone (0.195 g) was added in a 25 ml sealed tube and was dissolved in 5 mL of methanol. After charging it with 0.019 g of 10% Pd/C, hydrogen gas was bubbled in for 15 min before the tube is sealed and stirred at room temperature for 12 h. Filtration through Celite and concentration gave N-phenyl-4-hydroxy-2-pyridone (0.209 g, 92% yield) as a white solid which was used without further purification. R_f = 0.53 (CH_2Cl_2 : : CH_3COCH_3, 1 : 1). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.80 (brs, 1H), 7.52-7.27 (m, 6H), 5.94 (dd, *J* = 7.5Hz, *J* = 2.5Hz, 1H), 5.63 (d, *J* = 2.5Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.4, 163.0, 141.2, 139.8, 129.3, 128.1, 127.3, 100.8, 99.0.

III General Experimental Procedure for the 3-Alkenylation of 4-Hydroxy-2-pyridones (3-3c)

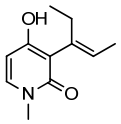
A dried screw glass vial equipped with a magnetic stirring bar was charged with the *N*-substituted-4-hydroxy-2-pyridinone (**3-3c**) (0.24 to 0.16 mmoles), $Cu(OAc)_2$ (1 equiv), dry acetonitrile (3 ml), the desired alkene (3 equiv), and formic acid (2 equiv) successively, followed by $Pd(OAc)_2$ (5 mol%). The vial is tightly closed with its screw cap. The reaction is immediately emerged at 40 ^{o}C oil bath and is vigorously stirred for the indicated time. Then, the reaction mixture is quenched by the addition of 4 ml of saturated sodium bicarbonate solution, stirred for 5 min and the reaction mixture is extracted with EtOAc (4 X 5 ml). The combined organic extracts are dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel flash column chromatography is followed to give the desired alkylated compounds.



2-Butyl-5-methyl-furo[3,2-*c*]pyridin-4-*(5H)*-one (5)

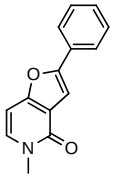
Following the general procedure described above *N*-methyl-4-hydroxypyridone-2 (**3**)[1] (30 mg, 0.24 mmoles) was reacted with 1-hexene (42 µL, 0.72 mmoles) for 3h to give 39 mg, 80% yield of **5** as a white solid, m.p. 199-204 ^{o}C, after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 25:1) ; R_f = 0.39 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 7.5Hz, 1H), 6.56 (s, 1H), 6.44 (d, *J* = 7.5Hz, 1H),

3.60 (s, 3H), 2.72 (t, *J* = 7.3Hz, 2H), 1.69 (quin, *J* = 7.3Hz, 2H, 1.40 (six, *J* = 7.3Hz, 2H), 0.94 (t, *J* = 7.3Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCD_3$): δ = 159.6, 158.6, 158.4, 133.3, 117.3, 102.2, 95.8, 37.0, 29.7, 27.8, 22.1, 13.7; HRMS: calcd for $C_{12}H_{16}NO_2^+$ [M + H^+]: 206.1181, found 206.1179.



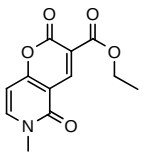
_N_-Methyl-4-hydroxy-3-(pent-2-en-3-yl)pyridin-2(*1H*)-one (17)

Following the general procedure described above *N*-methyl-4-hydroxypyridone-2 (**3**)[1] (30 mg, 0.24 mmoles) was reacted with 2-pentene (77.7 µL, 0.72 mmoles) for 4.5h to give 26 mg, 57% yield of **17** as a yellow viscus oil after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 25:1); R_f = 0.36 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.41 (d, *J* = 7.6Hz, 1H), 5.95 (d, *J* = 7.6Hz, 1H), 5.57 (q, *J* = 6.0Hz, 1H), 3.40 (s, 3H), 2.37 (m, 1H), 2.25 (m, 1H), 1.44 (d, *J* = 6.7Hz, 3H), 0.91 (t, *J* = 7.3Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6): δ = 161.8, 160.9, 137.6, 135.3, 122.8, 110.1, 98.3, 35.8, 28.5, 13.9, 11.9; HRMS: calcd for $C_{11}H_{16}NO_2^+$ [M + H^+]: 194.1181, found 194.1183; Anal. calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%. Found: C, 68.43; H, 7.85; N, 7.20%.



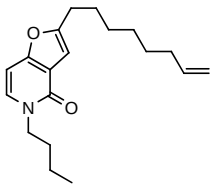
2-Phenyl-5-methyl-furo[3,2-*c*]pyridin-4-*(5H)*-one (18)

Following the general procedure described above *N*-methyl-4-hydroxypyridone-2 (**3**)[1] (30 mg, 0.24 mmoles) was reacted with styrene (82.3 µL, 0.72 mmoles) for 3h to give 47 mg, 87% yield of **18** as a yellow solid, m.p.166-168^{o}C, after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 8:1); R_f = 0.52 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.2Hz, 2H), 7.46-7.31 (m, 3H), 7.21 (s, 1H), 7.20 (d, *J* = 7.0Hz, 1H), 6.57 (d, *J* = 7.0Hz, 1H), 3.6 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 159.0, 154.9, 134.3, 129.7, 128.8, 128.4, 124.4, 118.2, 101.8, 95.6, 37.0; HRMS: calcd for $C_{14}H_{12}NO_2^+$ [M + H^+]: 226.0868, found 226.0863; Anal. calcd for $C_{11}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.72; H, 4.97; N, 6.16%.



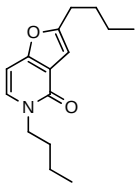
Ethyl-6-methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]pyridine-3-carboxylate (19)[3]

Following the general procedure described above N-methyl-4-hydroxypyridone-2 (**3**)[1] (30 mg, 0.24 mmoles) was reacted with diethyl-2-methylene malonate[2] (124 mg, 0.72 mmoles) for 2h to give 53 mg, 89% yield of **27** as a yelow solid; Mp 152-155 ^{o}C; ^{1}H NMR and ^{13}C NMR are identical to the reported.[3]



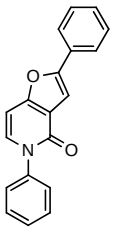
2-(1-octene)-5-butyl-furo[3,2-*c*]pyridin-4-*(5H)*-one (20)

Following the general procedure described above N-butyl-4-hydroxypyridone-2 (**3a**) (30 mg, 0.18 mmoles) was reacted with 1,9-decadiene (99.5 µL, 0.54 mmoles) for 3h to give 49 mg, 68% yield of **19** as a yellow oil after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 45:1); R_f = 0.68 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 7.45 (d, *J* = 7.5Hz, 1H), 6.52 (d, *J* = 7.5Hz, 1H), 6.51 (s, 1H), 5.81 (m, 1H), 4.99 (d, *J* = 17.5Hz, 1H), 4.91 (d, *J* = 9.9Hz, 1H), 4.00 (t, *J* = 6.5Hz, 2H), 2.74 (t, *J* = 7.2Hz, 2H), 1.75-1.65 (m, 4H), 1.46-1.31 (m, 10H), 0.93 (t, *J* = 7.6Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 158.5, 158.1, 157.7, 138.8, 133.9, 116.8, 113.8, 102.1, 94.3, 48.0, 33.5, 31.7, 31.6, 28.3, 27.6, 27.5, 22.4, 19.5, 13.1; HRMS: calcd for $C_{19}H_{28}NO_2^+$ [M + H^+]: 302.2120, found 302.2121.



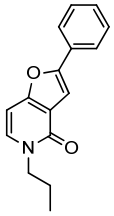
2-Butyl-5-butyl-furo[3,2-*c*]pyridin-4-*(5H)*-one (21)

Following the general procedure described above *N*-butyl-4-hydroxypyridone-2 (**3a**) (30 mg, 0.18 mmoles) was reacted with 1-hexene (30.6 µL, 0.54 mmoles) for 3h to give 27.6 mg, 62% yield of **23** as a brown oil after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 45:1); R_f = 0.62 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$): 7.12 (d, *J* = 7.5Hz, 1H), 6.66 (s, 1H), 6.51 (d, *J* = 7.5Hz, 1H), 4.02 (t, *J* = 7.1Hz, 2H), 2.72 (t, *J* = 6.9Hz, 2H), 1.79-1.63 (m, 4H), 1.45-1.31 (m, 4H), 0.98-0.90 (m, 6H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 163.6, 163.4, 163.0, 139.1, 121.9, 107.3, 99.5, 53.2, 36.8, 34.9, 32.5, 27.1, 24.7, 18.3, 18.2; HRMS: calcd for $C_{15}H_{22}NO_2^+$ [M + H^+]: 248.1650, found 248.1645; Anal. calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66%. Found: C, 72.80; H, 8.55; N, 5.60%.



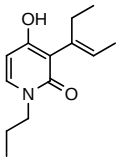
2-Phenyl-5-phenyl-furo[3,2-*c*]pyridin-4-*(5H)*-one (22)

Following the general procedure described above *N*-phenyl-4-hydroxypyridone-2 (**3c**) (30 mg, 0.16 mmoles) was reacted with styrene (55 µL, 0.48 mmoles) for 4.5h to give 43 mg, 74% yield of **22** as a yellow viscous oil after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 45:1); R_f = 0.69 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.8Hz, 2H), 7.56-7.32 (m, 9H), 7.29 (d, *J* = 7.5Hz, 1H), 6.67 (d, *J* = 7.5Hz, 1H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 159.1, 159.0, 155.3, 141.0, 134.5, 129.7, 129.3, 128.9, 128.5, 128.4, 127.0, 124.4, 118.5, 102.2, 96.0; HRMS: calcd for $C_{19}H_{14}NO_2^+$ [M + H^+]: 288.1024, found 288.1019.



2-Phenyl-5-propyl-furo[3,2-*c*]pyridin-4-*(5H)*-one (23)

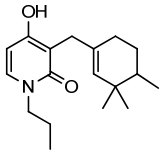
Following the general procedure described above *N*-propyl-4-hydroxypyridone-2 (**3b**) (20 mg, 0.13 mmoles) was reacted with styrene (44.7 µL, 0.39 mmoles) for 3h to give 29 mg, 89% yield of **20** as a viscus oil after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 45:1); R_f = 0.70 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85-7.33 (m, 5H), 7.24 (s, 1H), 7.20 (d, *J* = 7.1Hz, 1H), 6.59 (d, *J* = 7.1Hz, 1H), 4.04 (t, *J* = 7.5Hz, 2H), 1.85 (six, *J* = 7.5Hz, 2H), 1.02 (t, *J* = 7.5Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 158.7, 154.8, 133.6, 129.7, 128.7, 128.2, 124.3, 118.2, 101.9, 95.2, 50.6, 22.7, 10.9; HRMS: calcd for $C_{16}H_{16}NO_2^+$ [M + H^+]: 254.1181, found 254.1175; Anal. calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%. Found: C, 75.91; H, 5.94; N, 5.56%.



***N*-propyl-4-hydroxy-3-(pent-2-en-3-yl)pyridin-2(*1H*)-one (24)**

Following the general procedure described above *N*-propyl-4-hydroxypyridone-2 (**3b**) (30 mg, 0.196 mmoles) was reacted with 2-pentene (63.5 µL, 0.588 mmoles) for 6h to give 26.5 mg, 61% yield of **24** as a

yellow oil after chromatographic purification (CH_2Cl_2 : $(C_2H_5)_2O$ 40:1); R_f = 0.45 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 7.5Hz, 1H), 6.08 (d, *J* = 7.5Hz, 1H), 5.89 (q, *J* = 6.7Hz, 1H), 3.90 (m, 2H), 2.43 (m, 2H), 1.78 (six, *J* = 7.2Hz, 2H), 1.57 (d, *J* = 6.4Hz, 3H), 0.99 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4, 159.9, 136.7, 135.4, 125.7, 110.7, 98.4, 50.9, 28.5, 22.7, 14.6, 12.9, 11.1; HRMS: calcd for $C_{13}H_{20}NO_2^+$ [M + H^+]: 222.1494, found 222.1495.



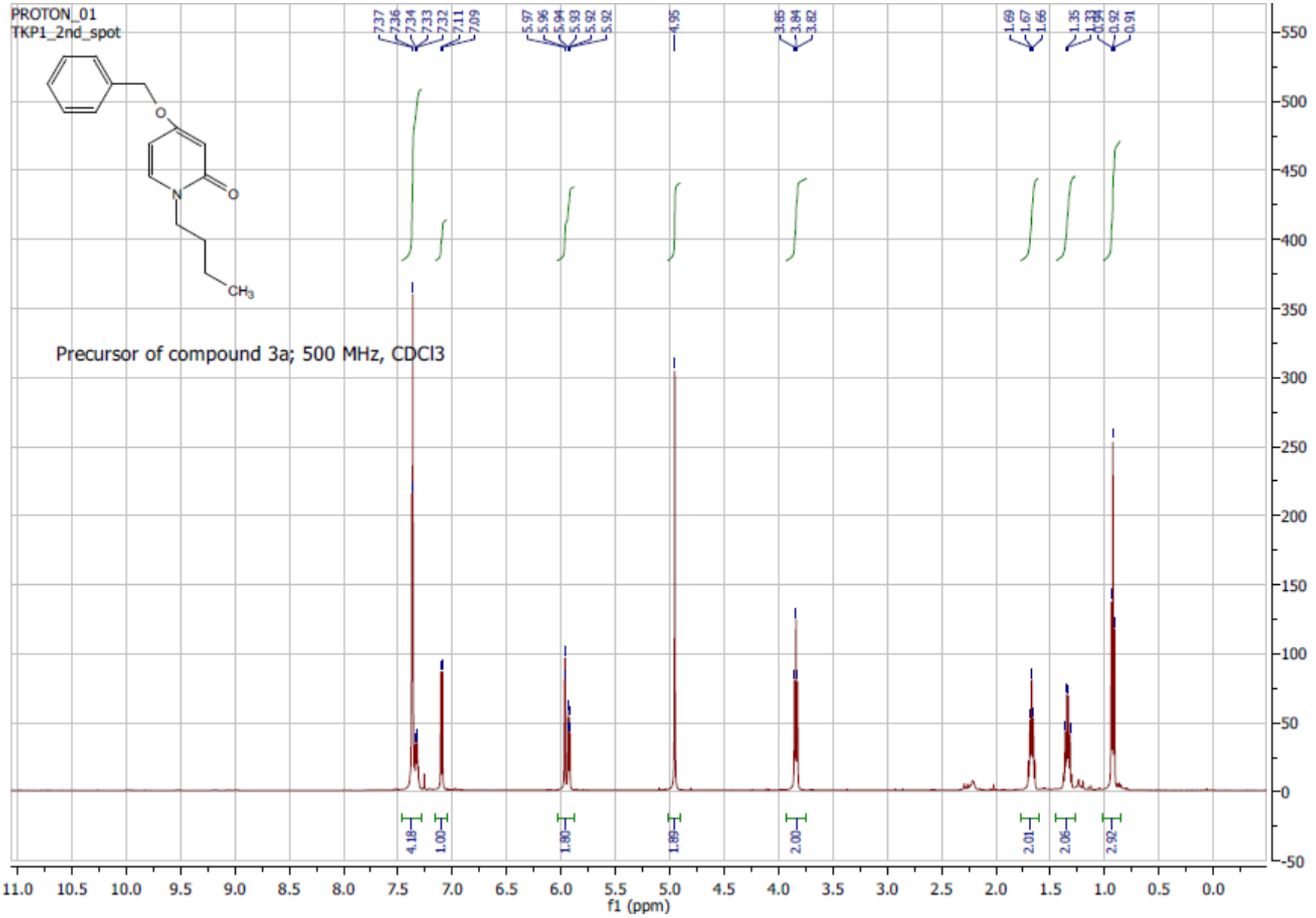
4-Hydroxy-1-propyl-3-((3,3,4-trimethylcyclohex-1-ene-1-yl)methyl)pyridin-2(1*H*)-one (25)

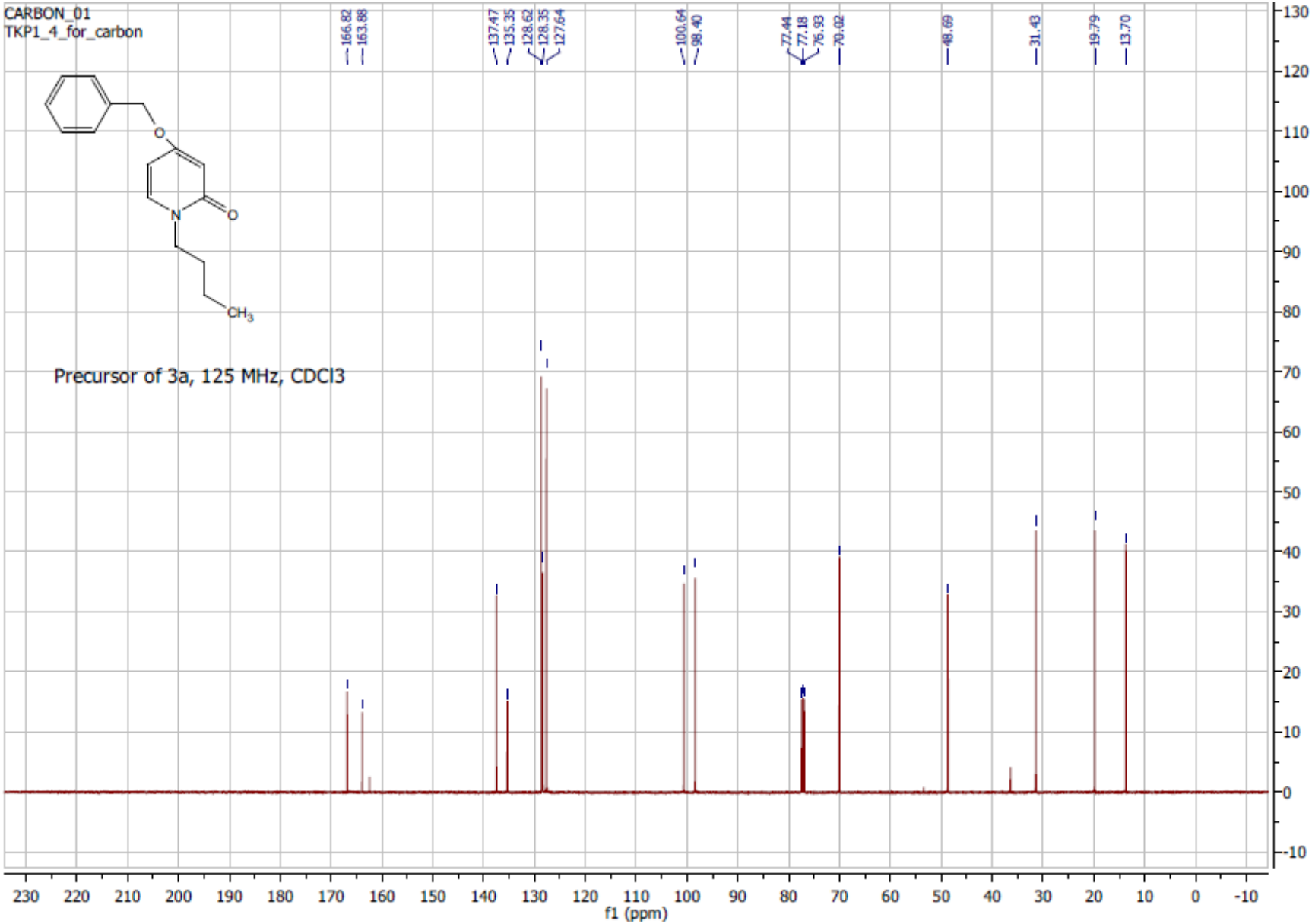
Following the general procedure described above N-propyl-4-hydroxypyridone-2 (**3b**) (10 mg, 0.065 mmoles) was reacted with β-pinene (30.7 µL, 0.195 mmoles) for 3h to give 13.9 mg, 74% yield of **25** as a white solid,m.p. 117-125 ^oC, after chromatographic pyrification (CH_2Cl_2 : $(C_2H_5)_2O$ 40:1); R_f = 0.48 (CH_2Cl_2 : $(C_2H_5)_2O$, 1 : 1). ^1H 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: calcd for $C_{18}H_{28}NO_2^+$ [M + H^+]: 290.2120, found 290.2115

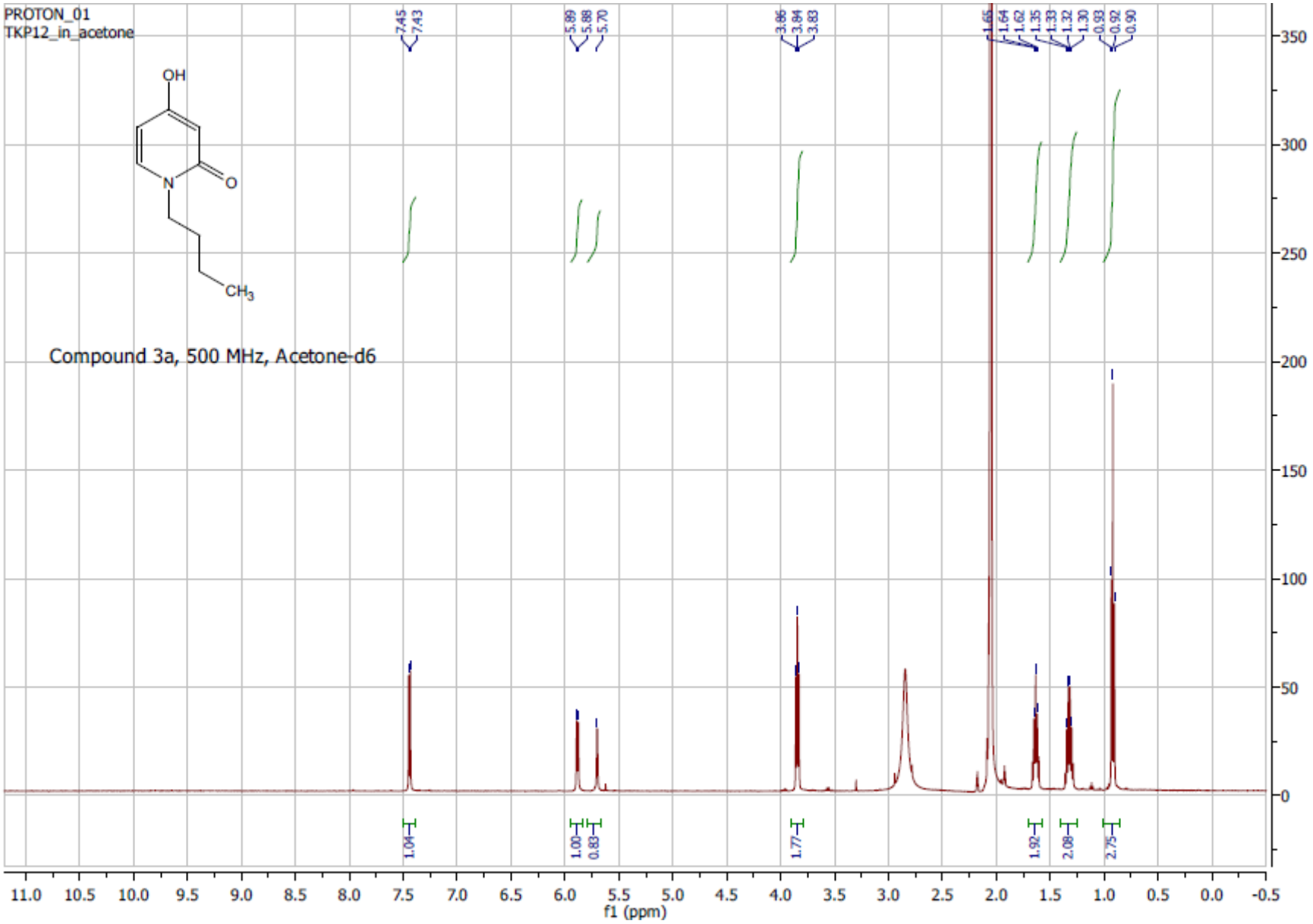
REFERENCES

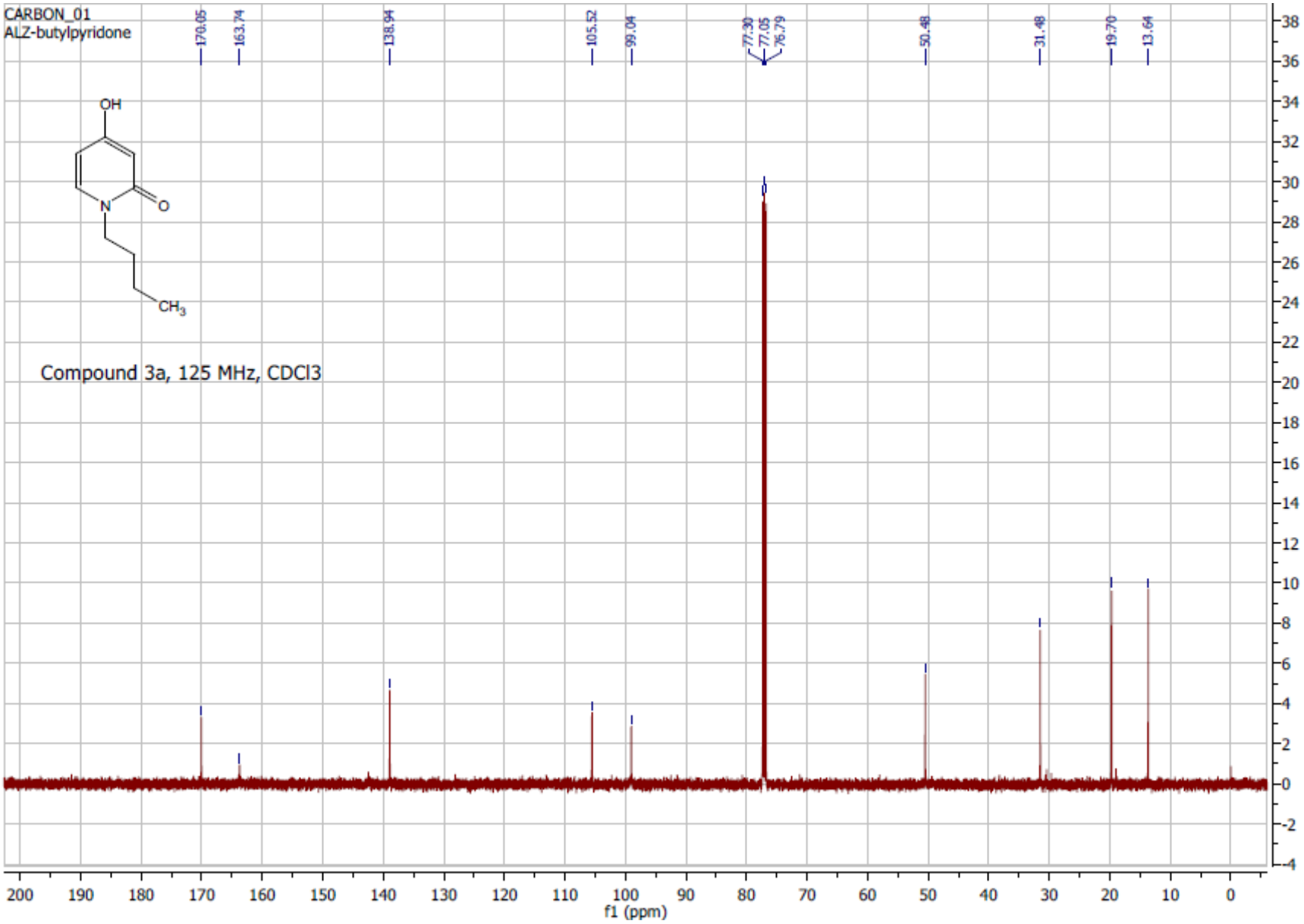
1. P. S. Charifson, A.-L. Grillot, T. H. Grossman, J. D. Parsons, M. Badia, S. Bellon, D. D. Dainiger, J. E. Drumm, C. H. Gross, A. LeTiran, Y. Liao, N. Mani, D. P. Nicolau, E. Perola, et al. *J. Med. Chem* **2008**, *51*, 5243.
2. M. Matziari, M. Nasopoulou, A. Yiotakis, *Org. Lett.* **2006**, *8*, 2317.
3. S. Strah, J. Svete, B. Stanovnik, *Journal of Heterocyclic Chemistry* **1996**, *33*, 751.

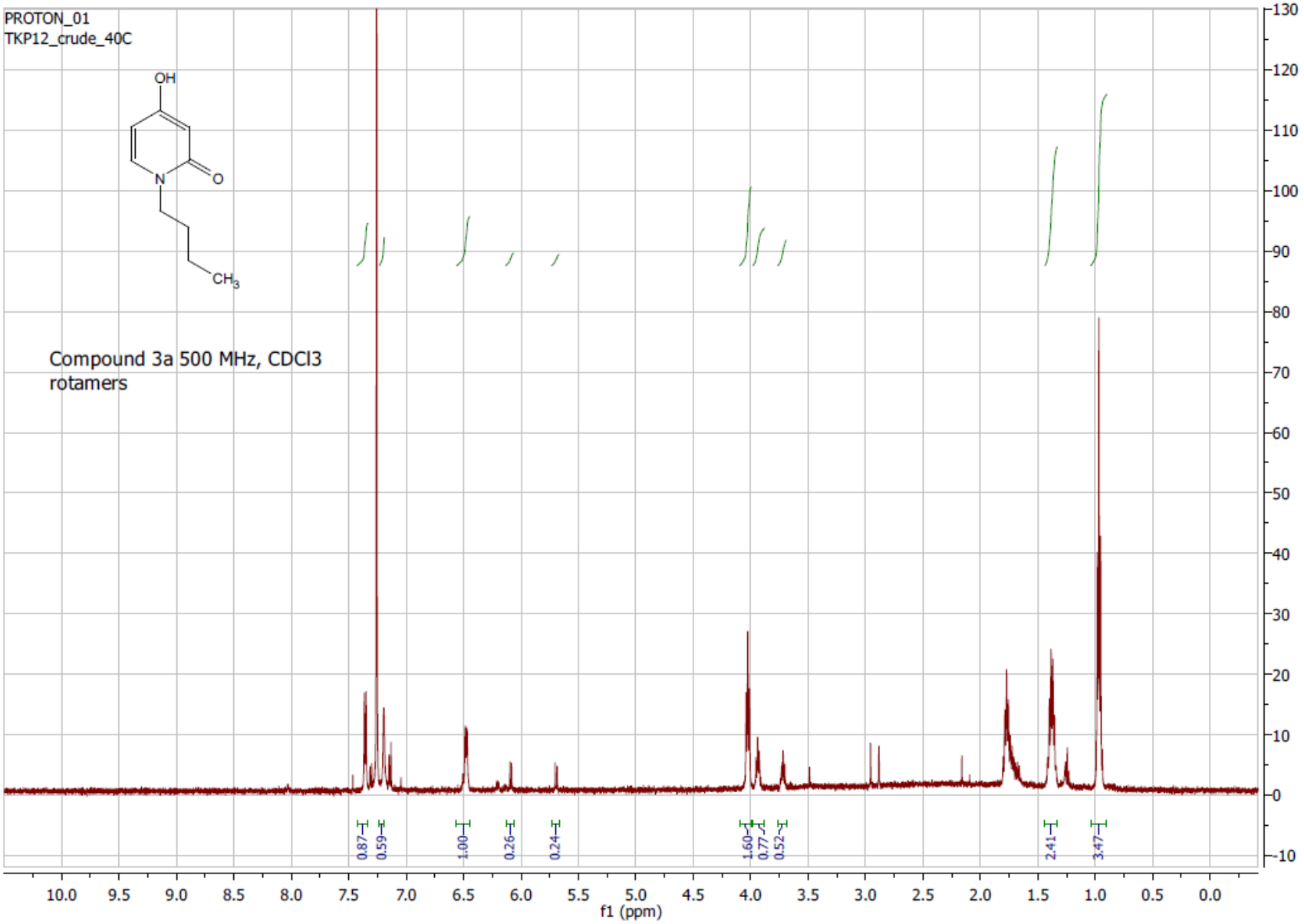
NMR Spectra of compounds

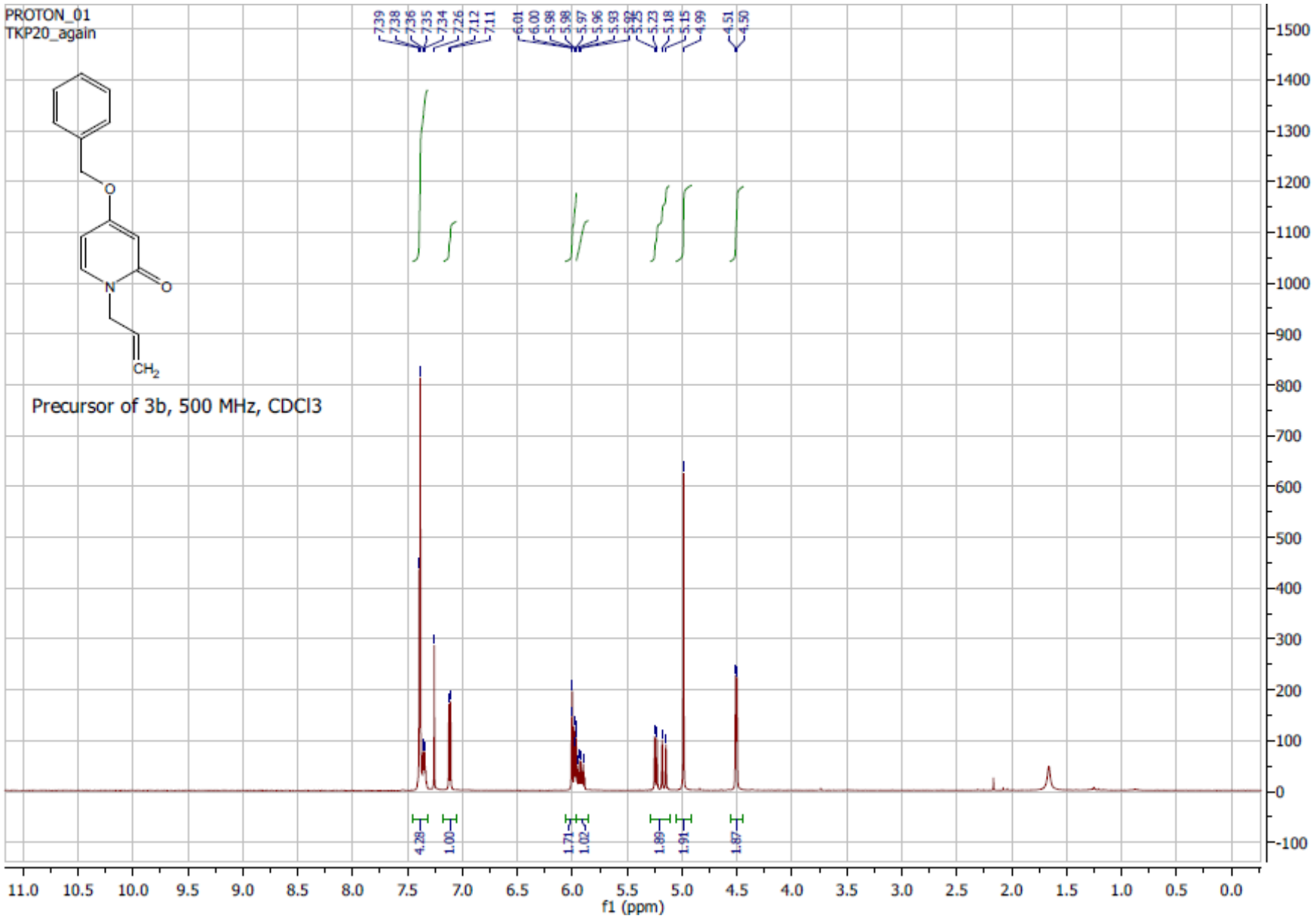

PROTON_01
TKP1_2nd_spot
Precursor of compound 3a; 500 MHz, CDCl3
7.37
7.36
7.34
7.33
7.32
7.11
7.09
5.97
5.96
5.94
5.93
5.92
5.92
4.95
3.85
3.84
3.82
1.69
1.67
1.66
1.35
0.92
0.91
4.18
1.00
1.80
1.89
2.00
2.01
2.06
2.92
f1 (ppm)

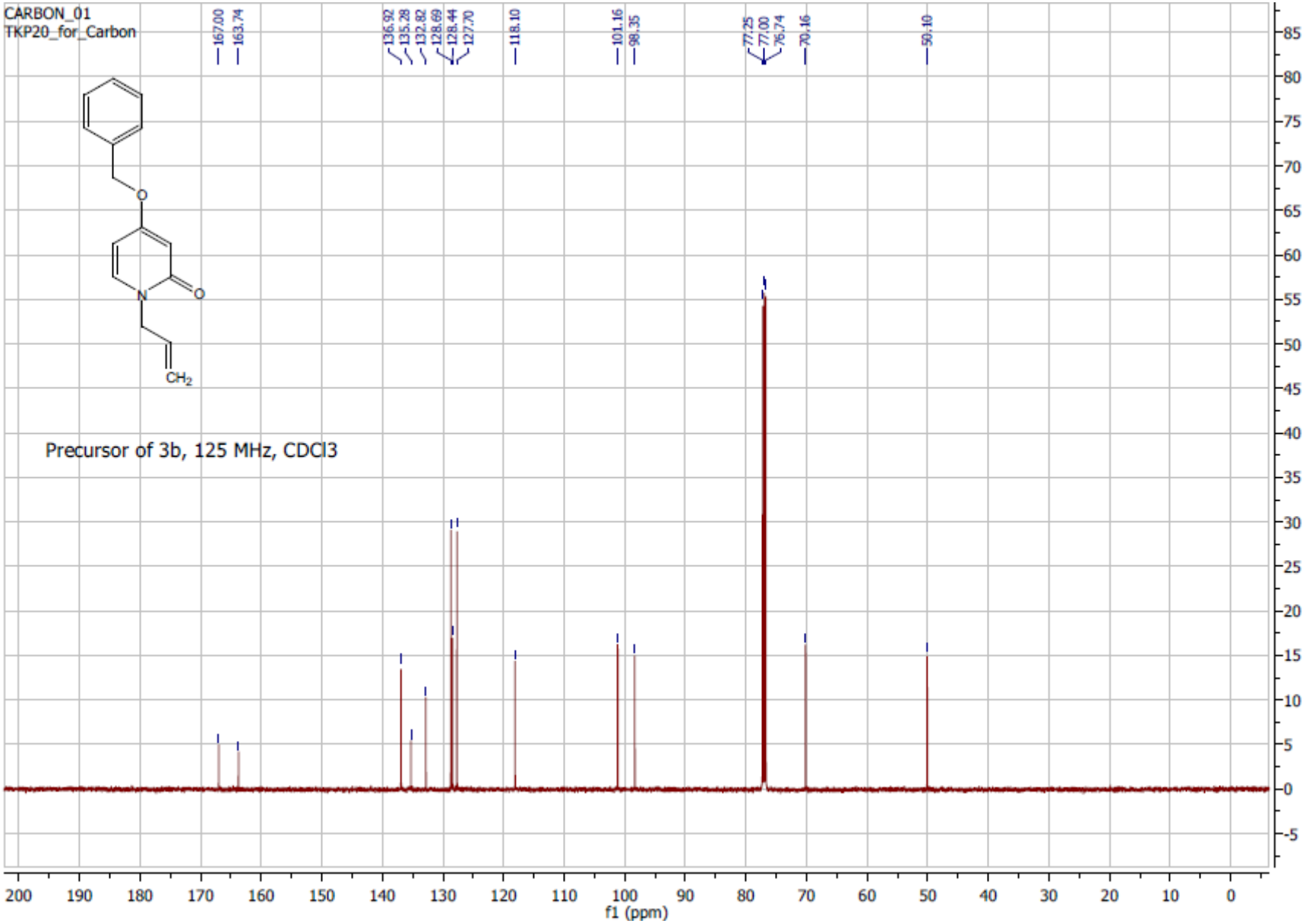

CARBON_01
TKP1_4_for_carbon
166.82
163.88
137.47
135.35
128.62
128.35
127.64
100.64
98.40
77.44
77.18
76.93
70.02
48.69
31.43
19.79
13.70
O
N
O
CH3
Precursor of 3a, 125 MHz, CDCl3
f1 (ppm)

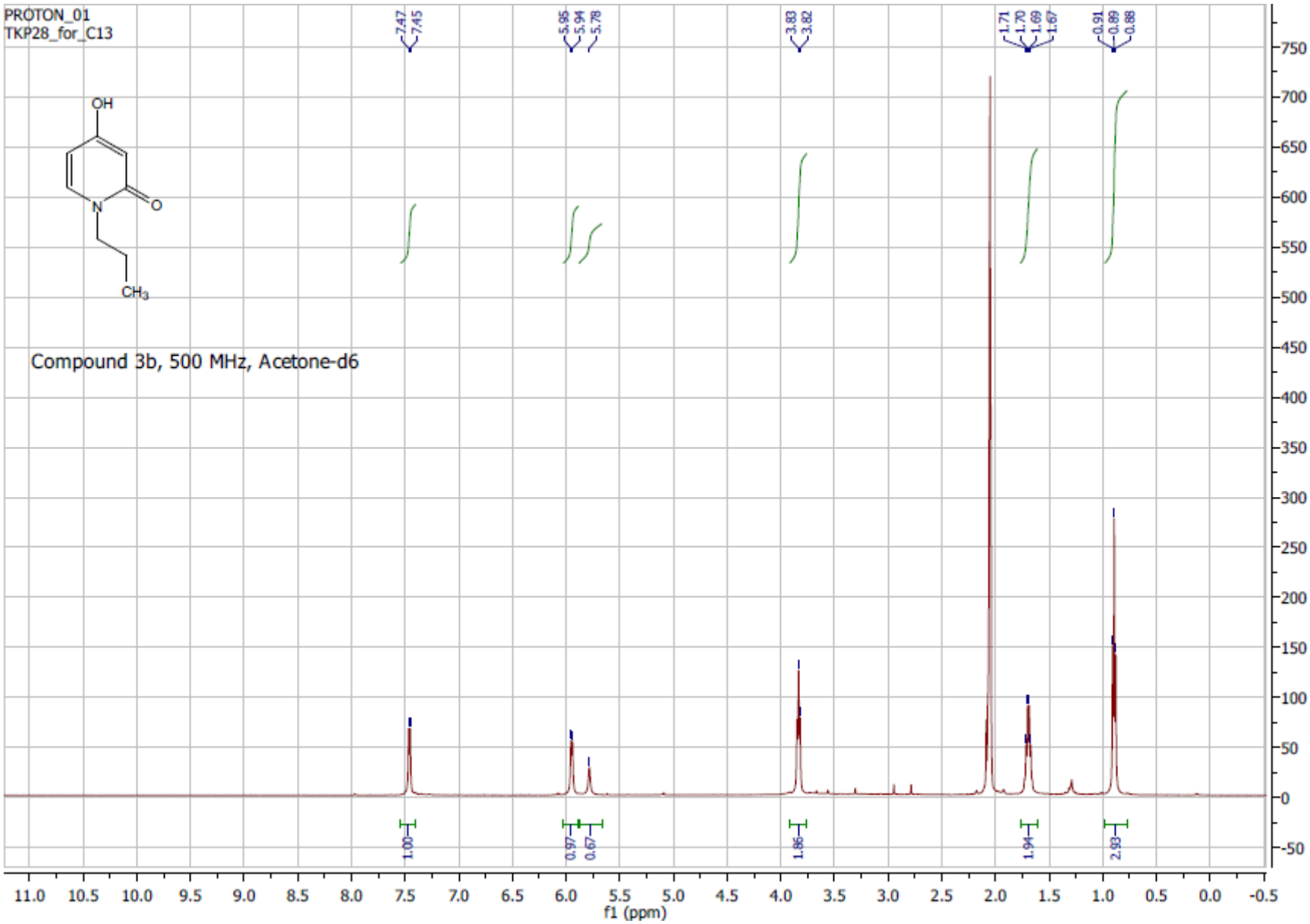

PROTON_01
TKP12_in_acetone
OH
N
O
CH3
Compound 3a, 500 MHz, Acetone-d6
7.45
7.43
5.89
5.88
5.70
3.86
3.84
3.83
1.65
1.64
1.62
1.35
1.33
1.32
1.30
0.93
0.92
0.90
1.04
1.00
0.83
1.77
1.92
2.08
2.75
f1 (ppm)

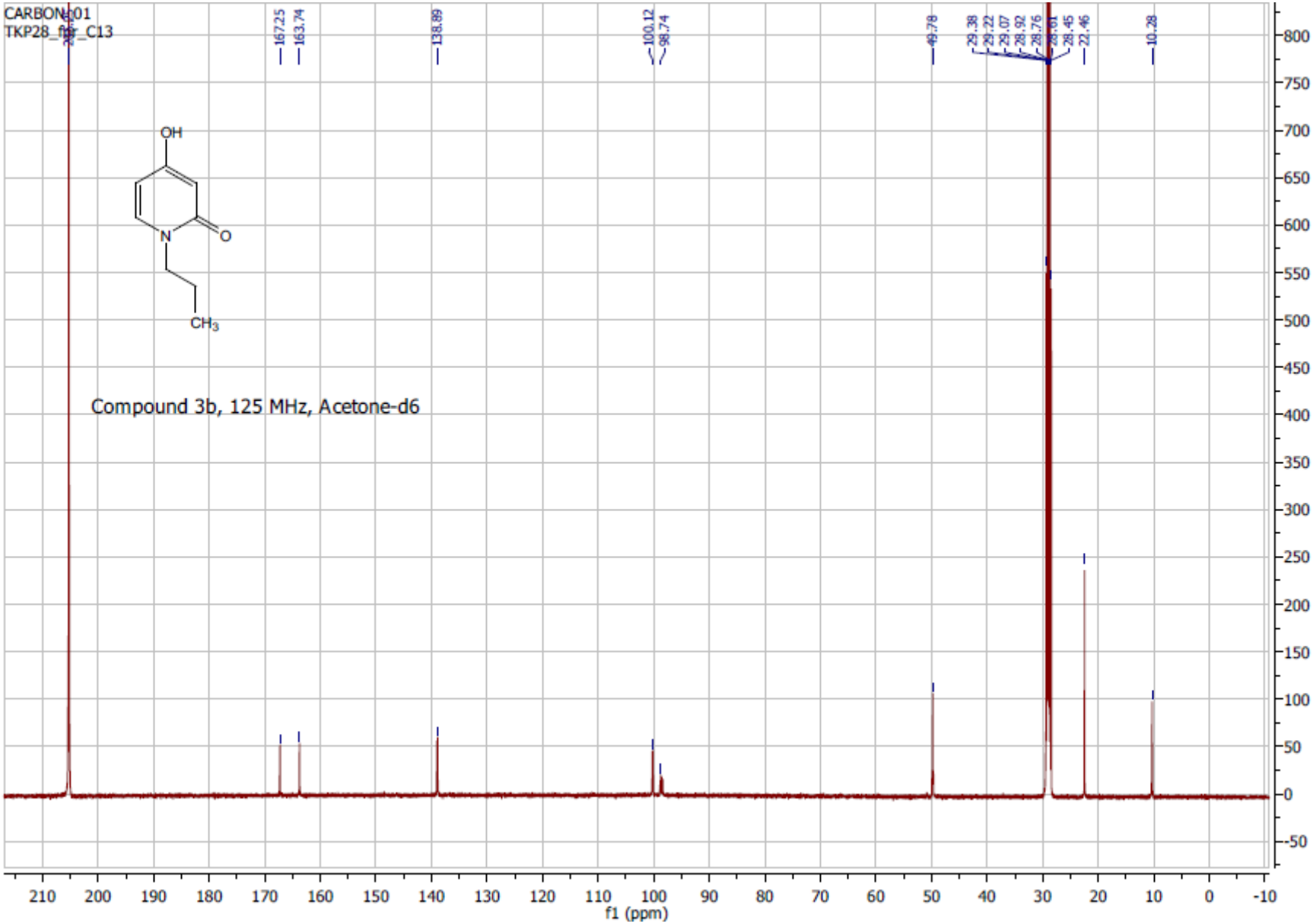

CARBON_01
ALZ-butylpyridone
170.05
163.74
138.94
105.52
99.04
77.30
77.05
76.79
50.48
31.48
19.70
13.64
OH
N
O
CH3
Compound 3a, 125 MHz, CDCl3
f1 (ppm)

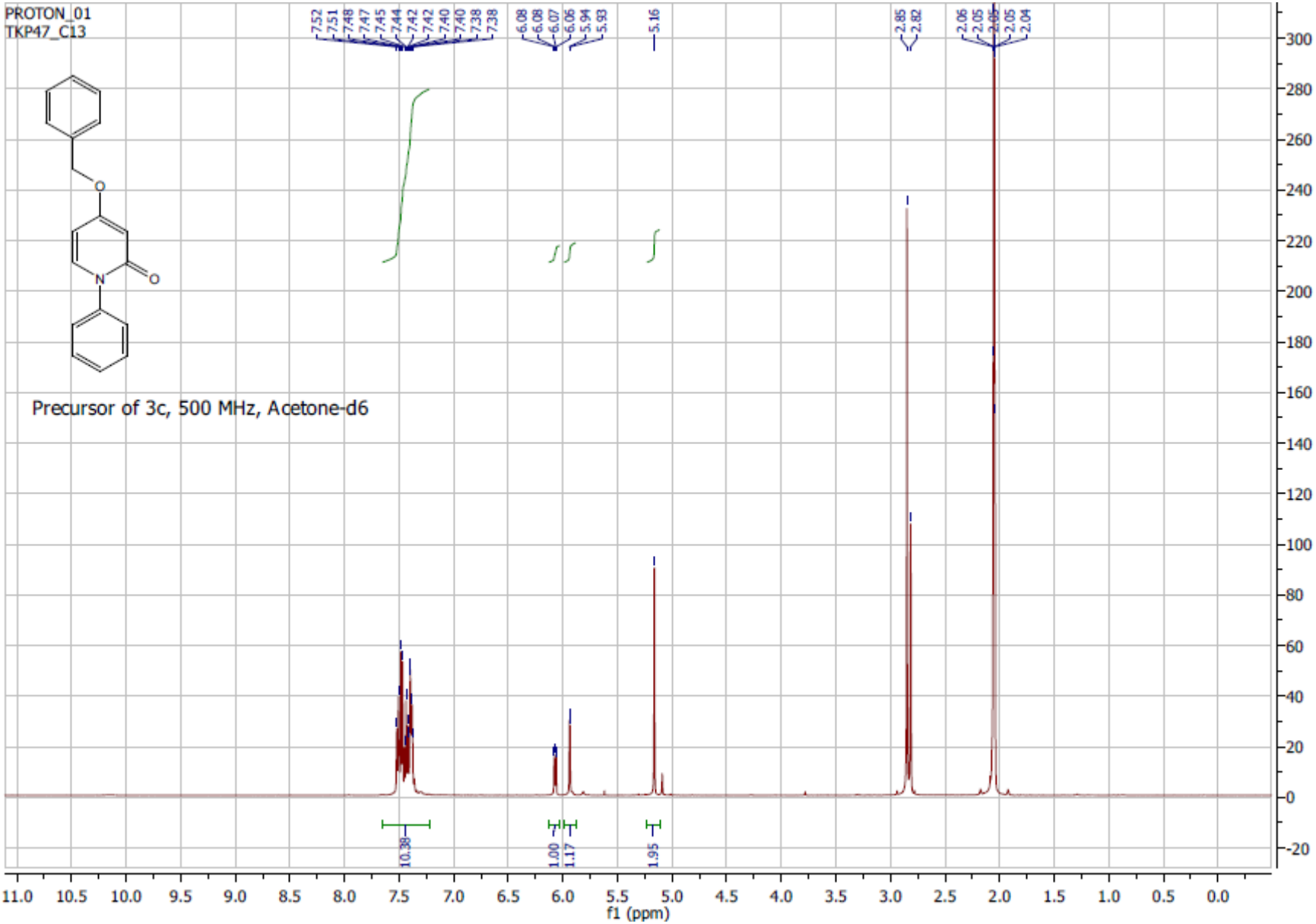

PROTON_01
TKP12_crude_40C
OH
N
O
CH3
Compound 3a 500 MHz, CDCl3
rotamers
0.87
0.59
1.00
0.26
0.24
1.60
0.77
0.52
2.41
3.47
f1 (ppm)


PROTON_01
TKP20_again
Precursor of 3b, 500 MHz, CDCl3
f1 (ppm)


CARBON_01
TKP20_for_Carbon
167.00
163.74
136.92
135.28
132.82
128.69
128.44
127.70
118.10
101.16
98.35
77.25
77.00
76.74
70.16
50.10
O
N
O
CH2
Precursor of 3b, 125 MHz, CDCl3
f1 (ppm)


PROTON_01
TKP28_for_C13
OH
N
O
CH3
Compound 3b, 500 MHz, Acetone-d6
7.47
7.45
5.95
5.94
5.78
3.83
3.82
1.71
1.70
1.69
1.67
0.91
0.89
0.88
1.00
0.97
0.67
1.86
1.94
2.93
f1 (ppm)


CARBON-01
TKP28_fid_C13
167.25
163.74
138.89
100.12
98.74
49.78
29.38
29.22
29.07
28.92
28.76
28.61
28.45
22.46
10.28
OH
N
O
CH3
Compound 3b, 125 MHz, Acetone-d6
f1 (ppm)


PROTON_01
TKP47_C13
Precursor of 3c, 500 MHz, Acetone-d6
7.52
7.51
7.48
7.47
7.45
7.44
7.42
7.42
7.40
7.40
7.38
7.38
6.08
6.08
6.07
6.06
5.94
5.93
5.16
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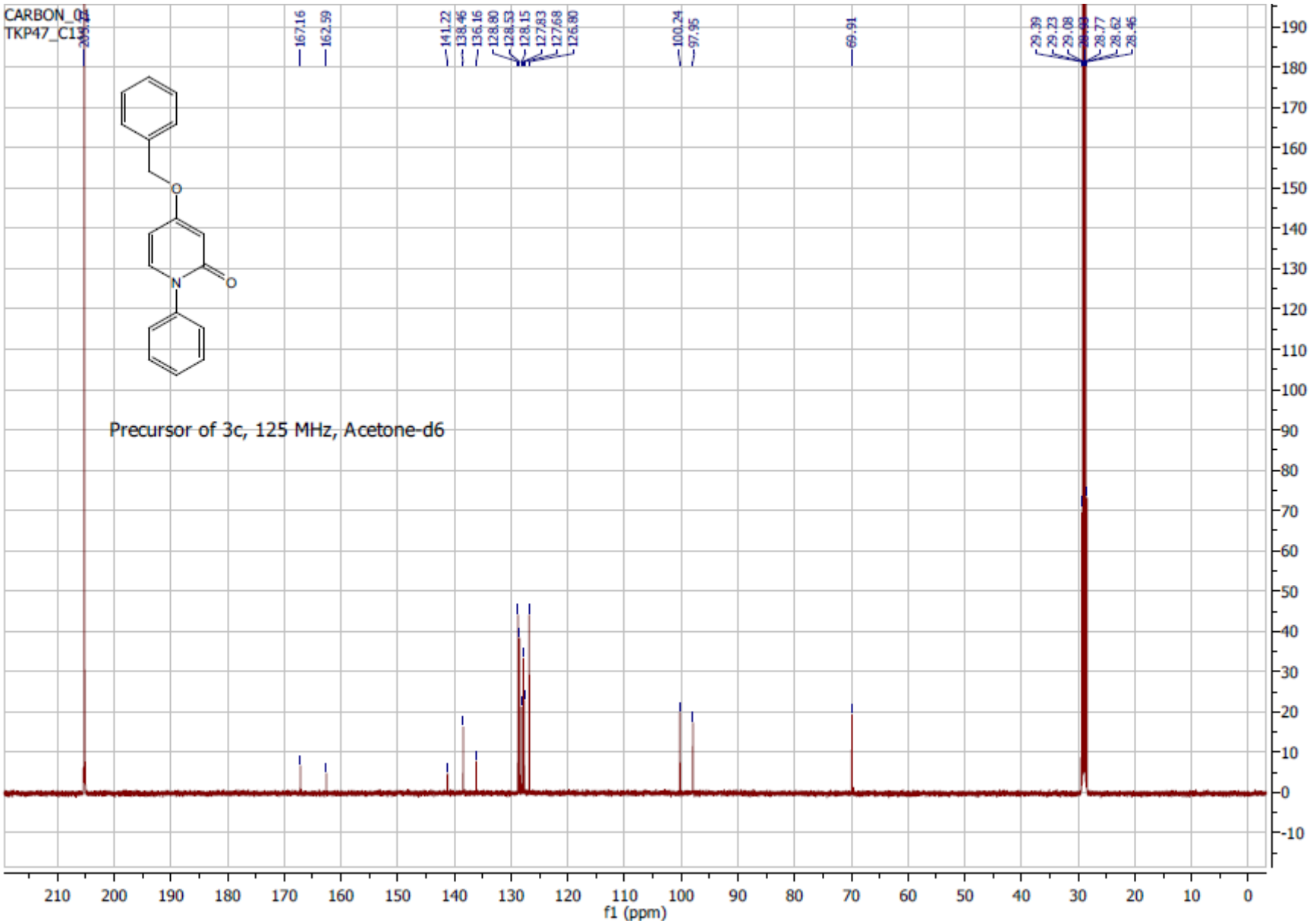
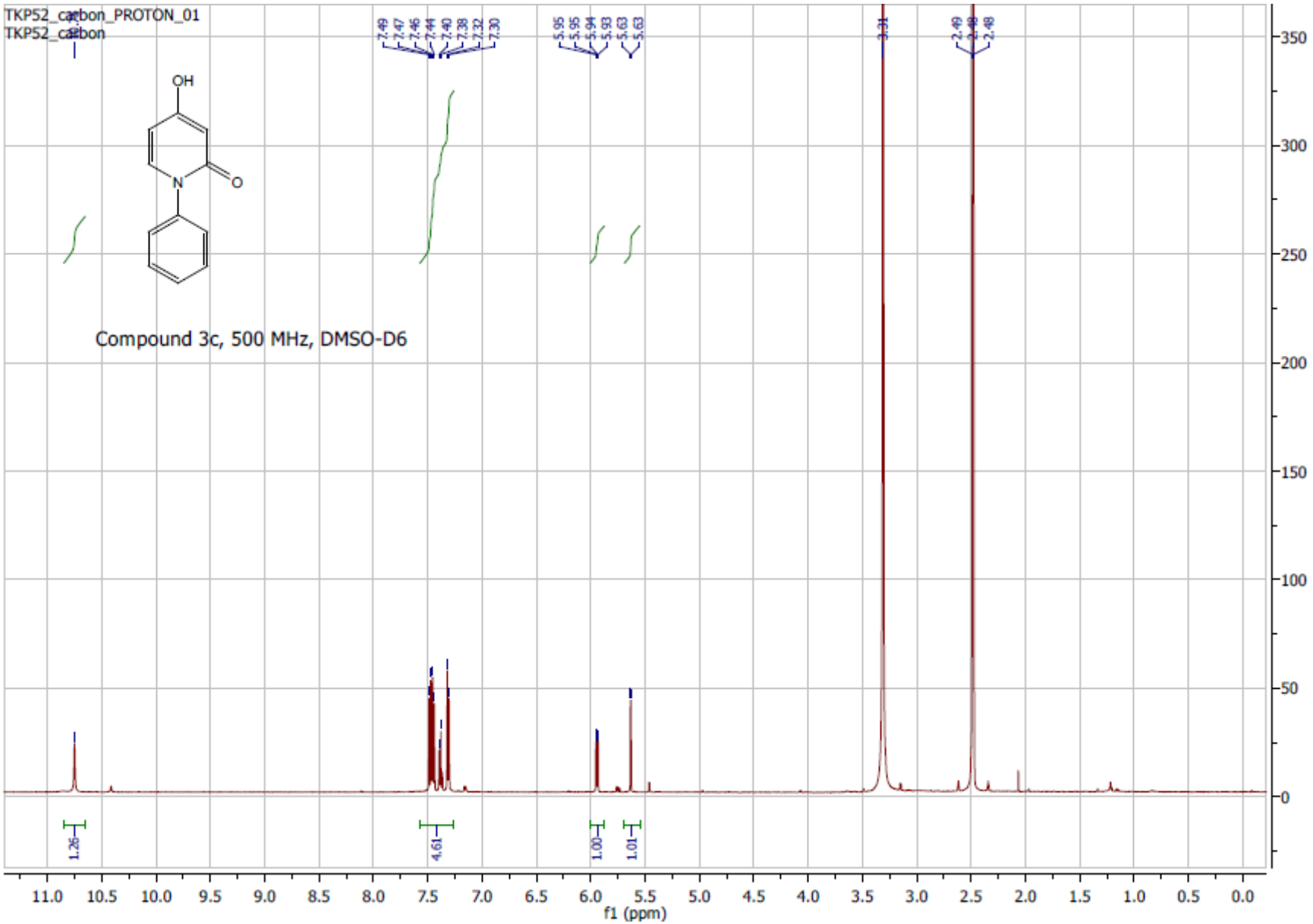
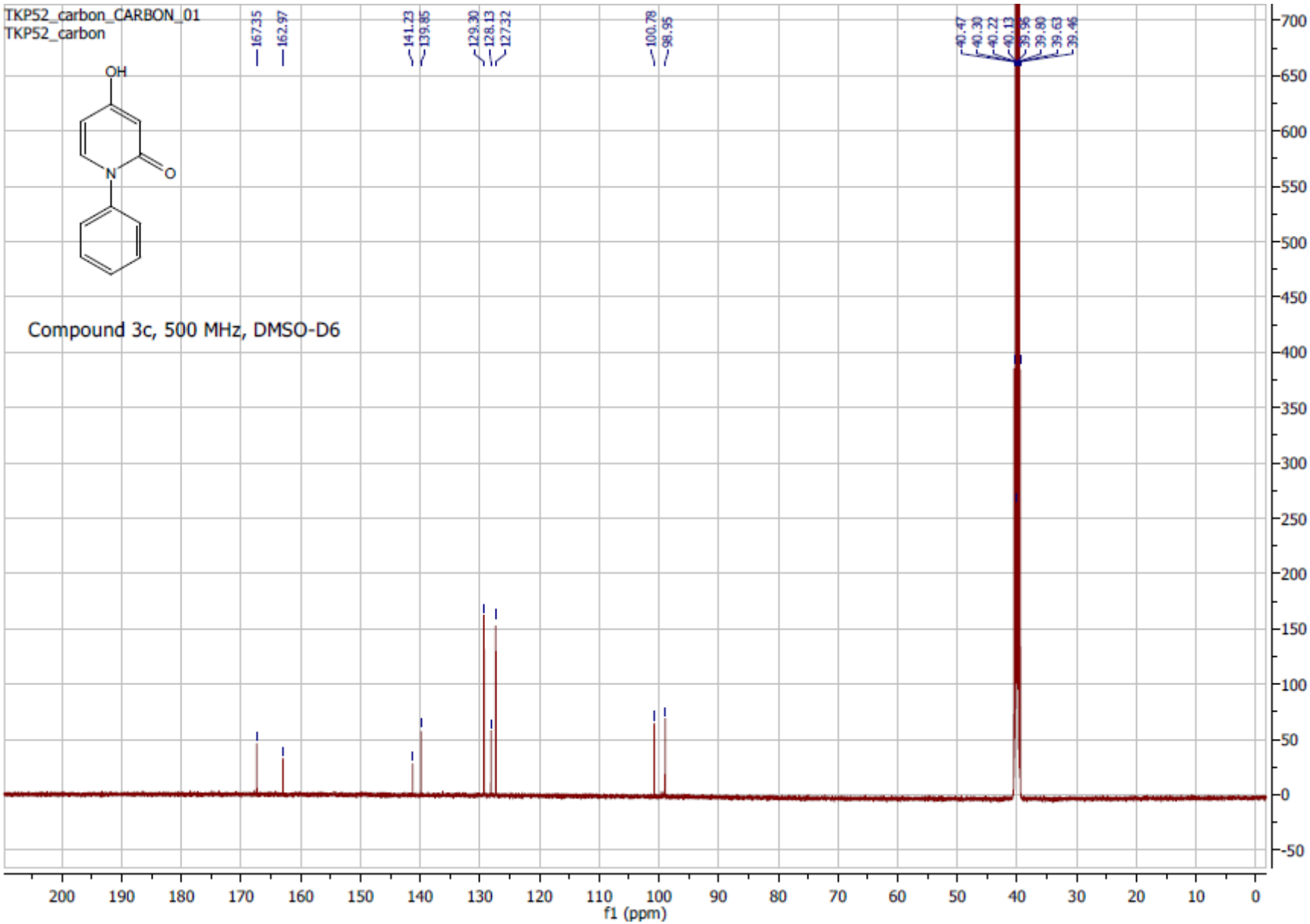
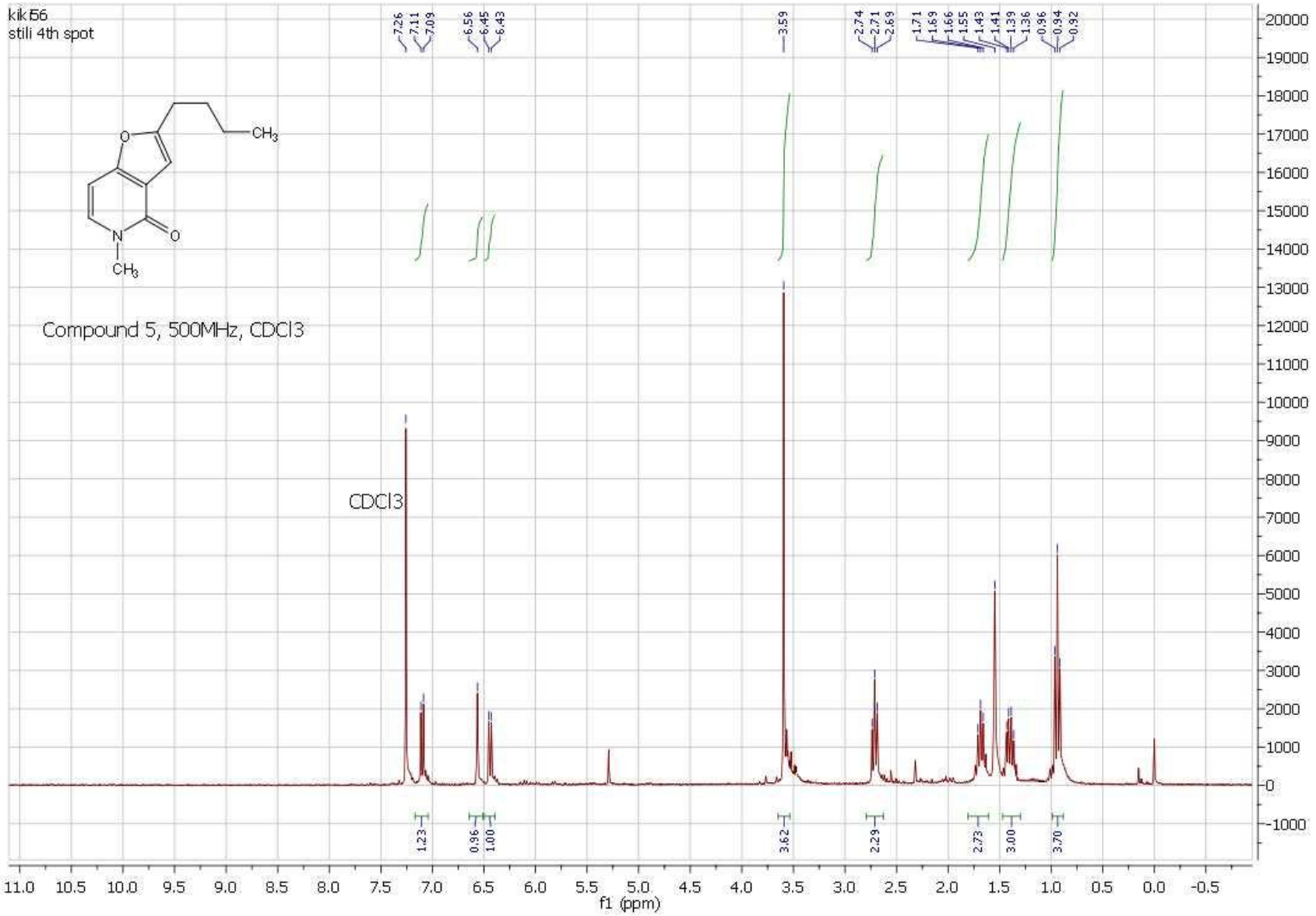
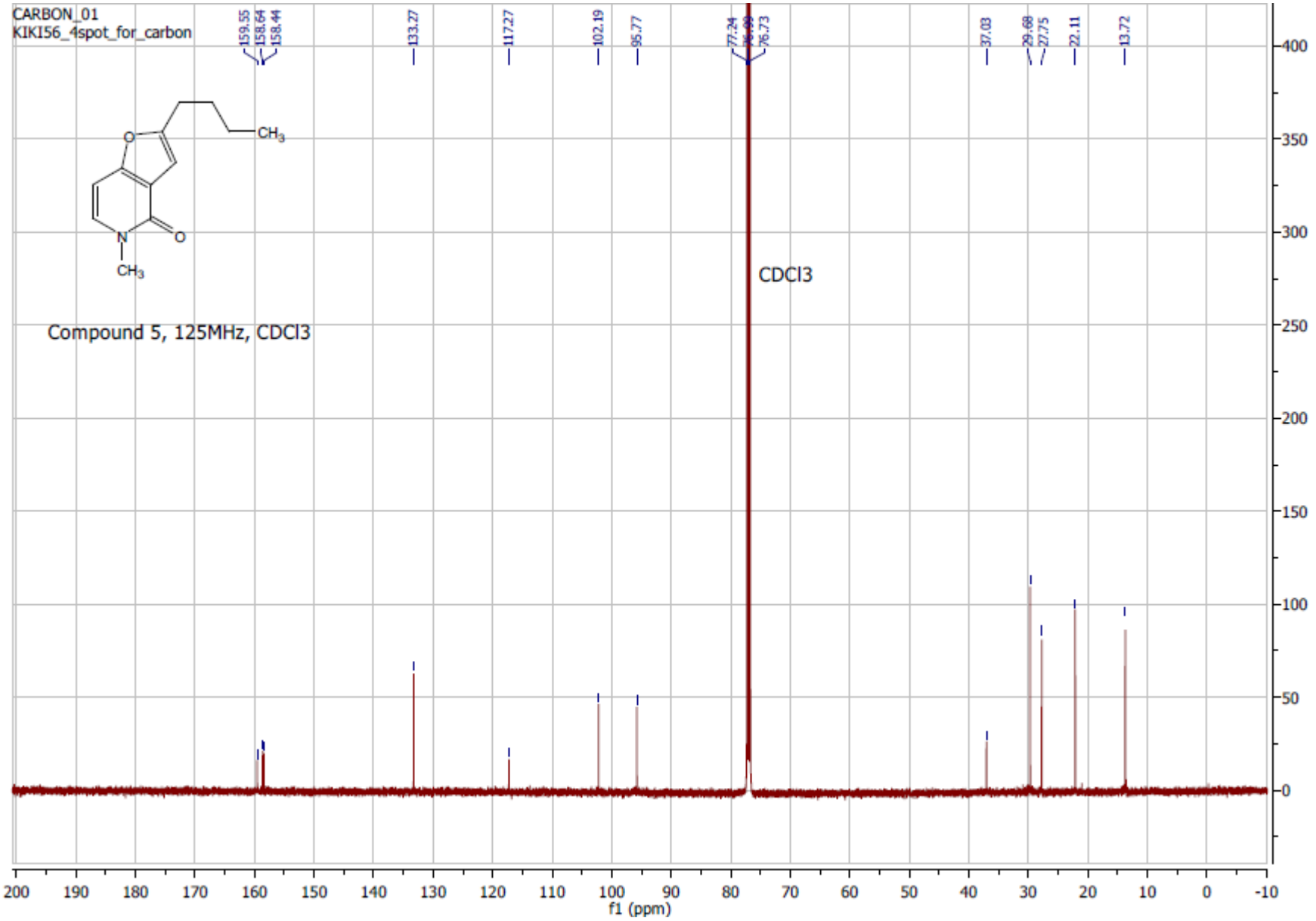
10.38
1.00
1.17
1.95
f1 (ppm)

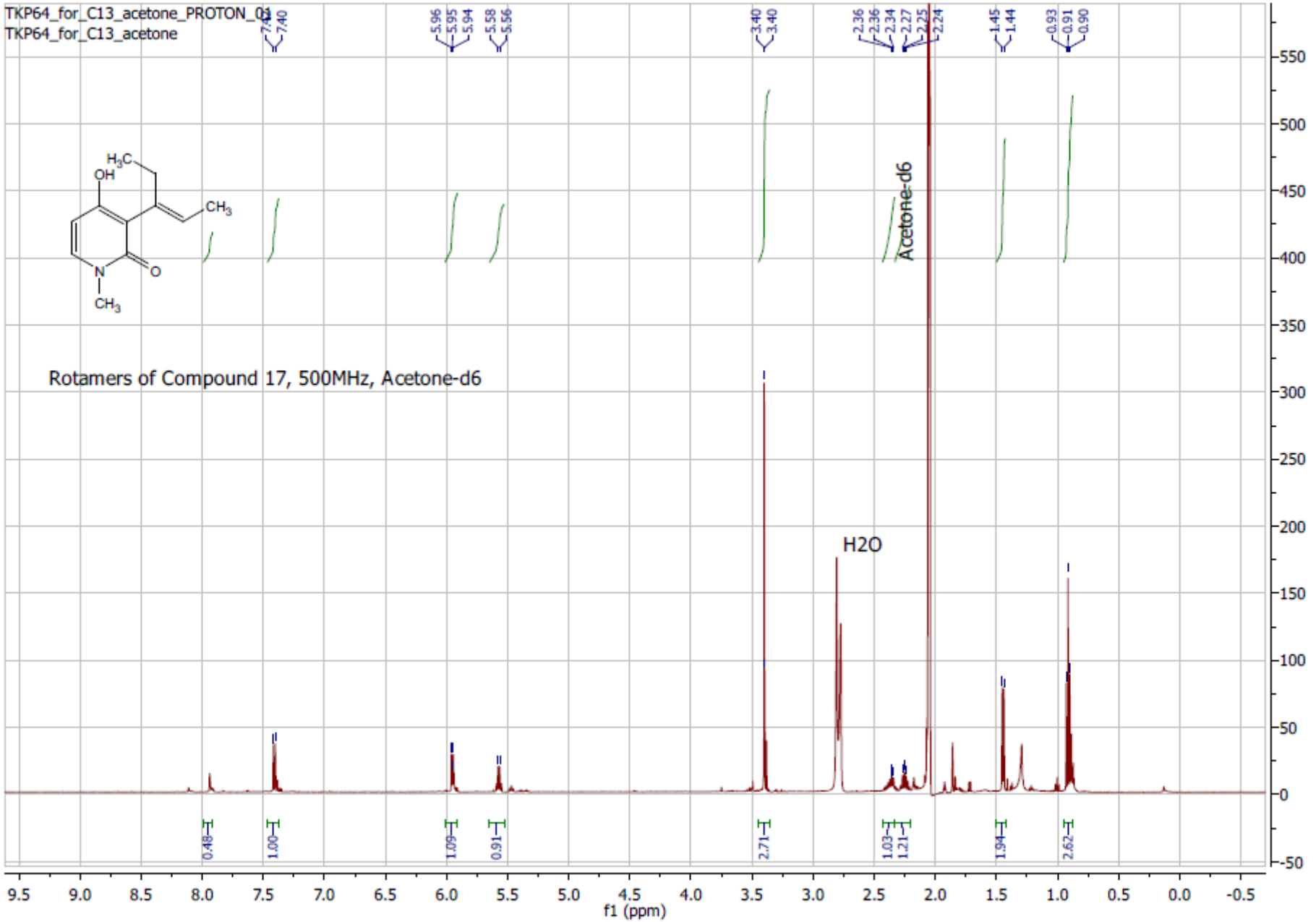

CARBON_01
TKP47_C13
167.16
162.99
141.22
138.46
136.16
128.80
128.53
128.15
127.83
127.68
126.80
100.24
97.95
69.91
29.39
29.23
29.08
28.77
28.62
28.46
O
N
O
Precursor of 3c, 125 MHz, Acetone-d6
f1 (ppm)

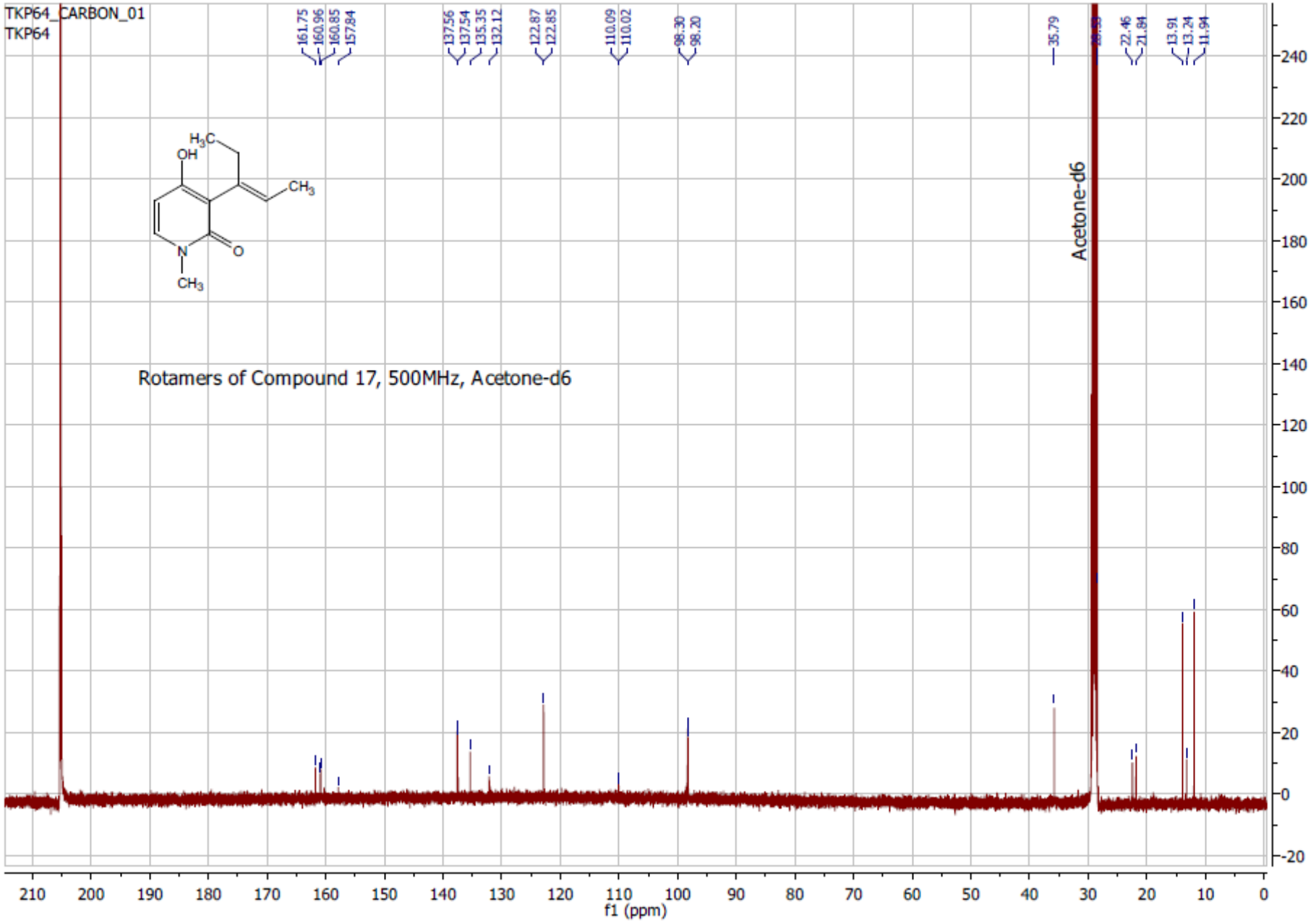

TKP52_carbon_PROTON_01
TKP52_carbon
OH
N
O
Compound 3c, 500 MHz, DMSO-D6
7.49
7.47
7.46
7.44
7.40
7.38
7.32
7.30
5.95
5.95
5.94
5.93
5.63
5.63
3.31
2.49
2.48
2.48
1.26
4.61
1.00
1.01
f1 (ppm)

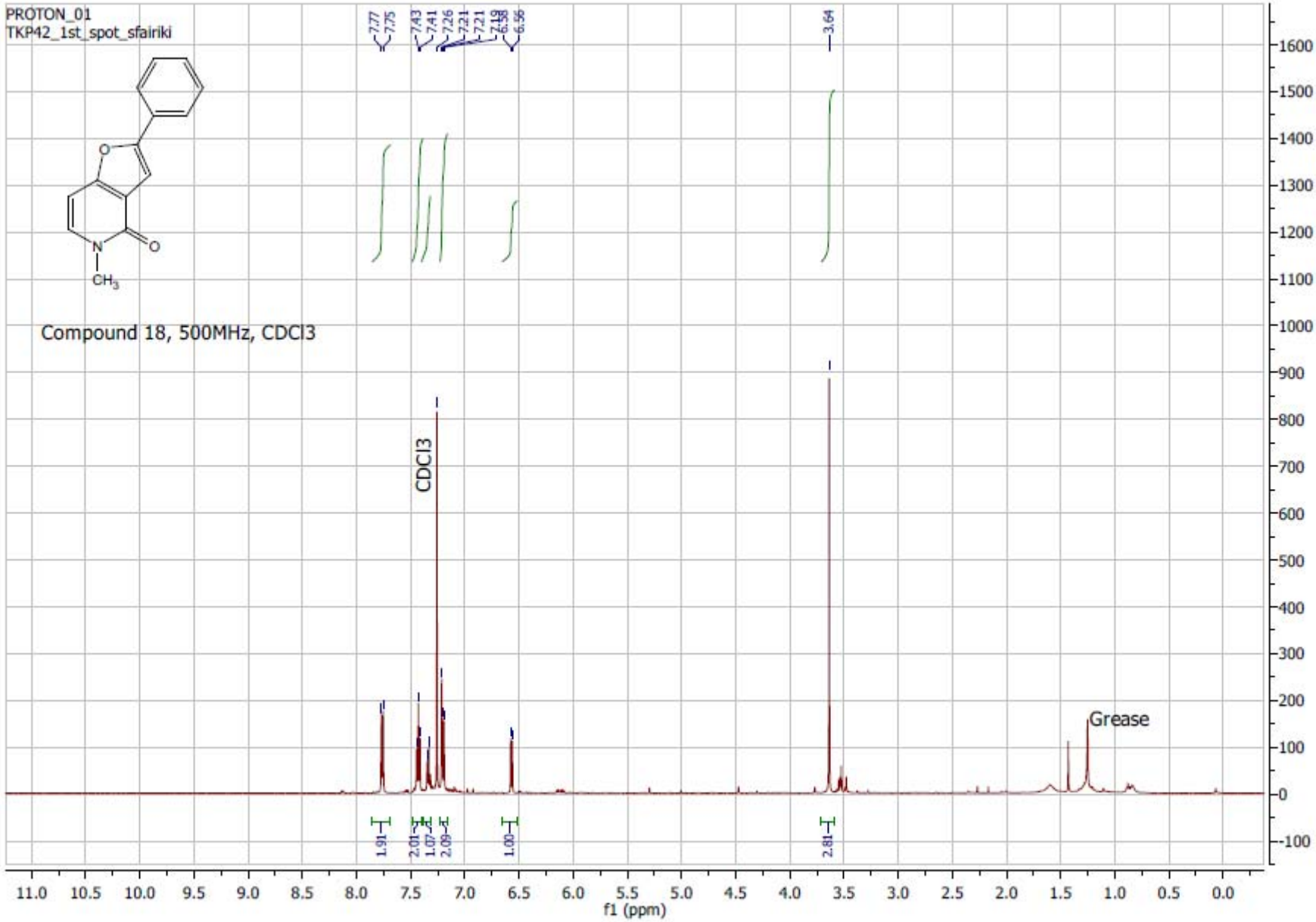

TKP52_carbon_CARBON_01
TKP52_carbon
OH
N
O
167.35
162.97
141.23
139.85
129.30
128.13
127.32
100.78
98.95
40.47
40.30
40.22
40.13
39.96
39.80
39.63
39.46
Compound 3c, 500 MHz, DMSO-D6
f1 (ppm)

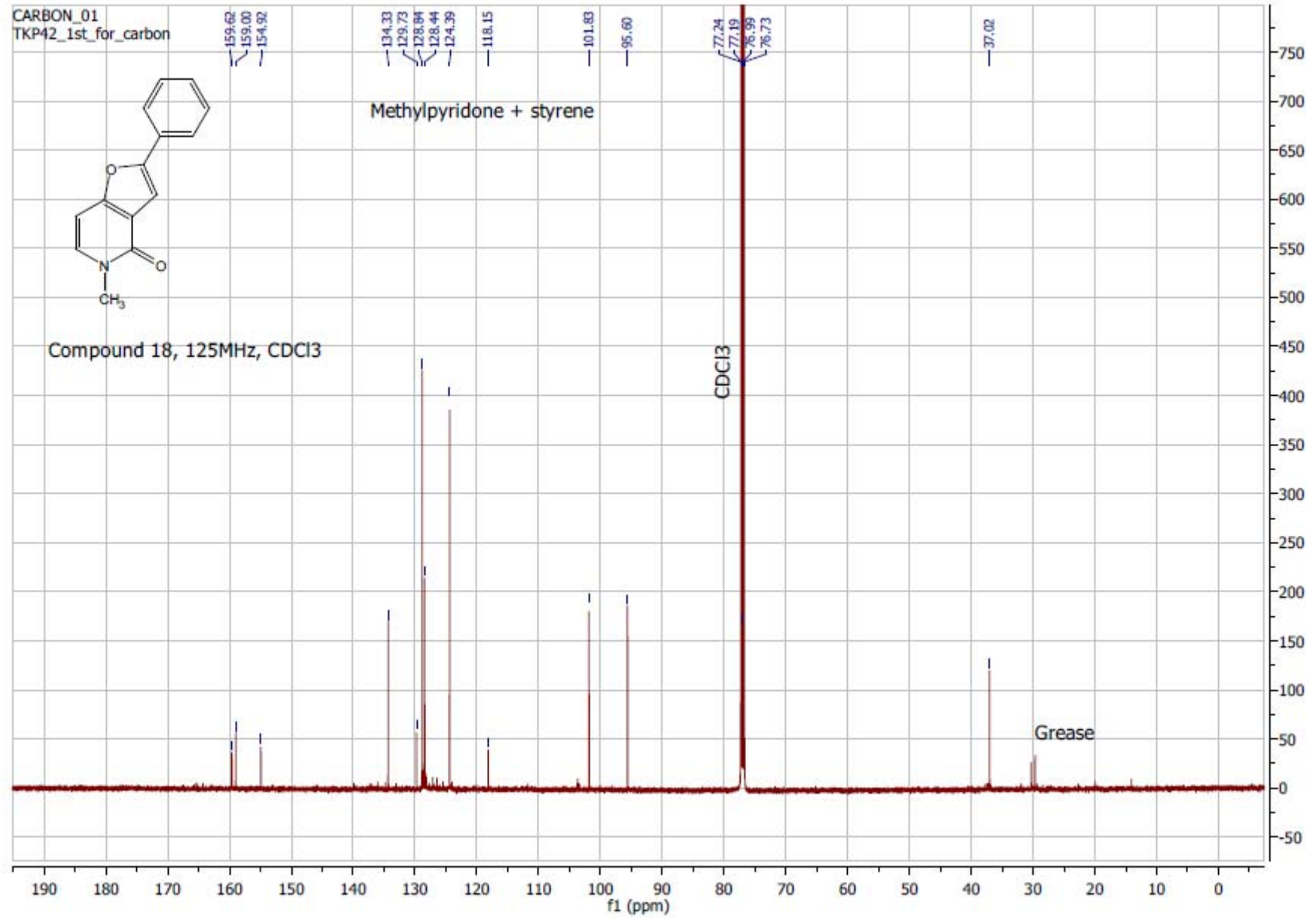

kik56
stili 4th spot
Compound 5, 500MHz, CDCl3
CDCl3
f1 (ppm)

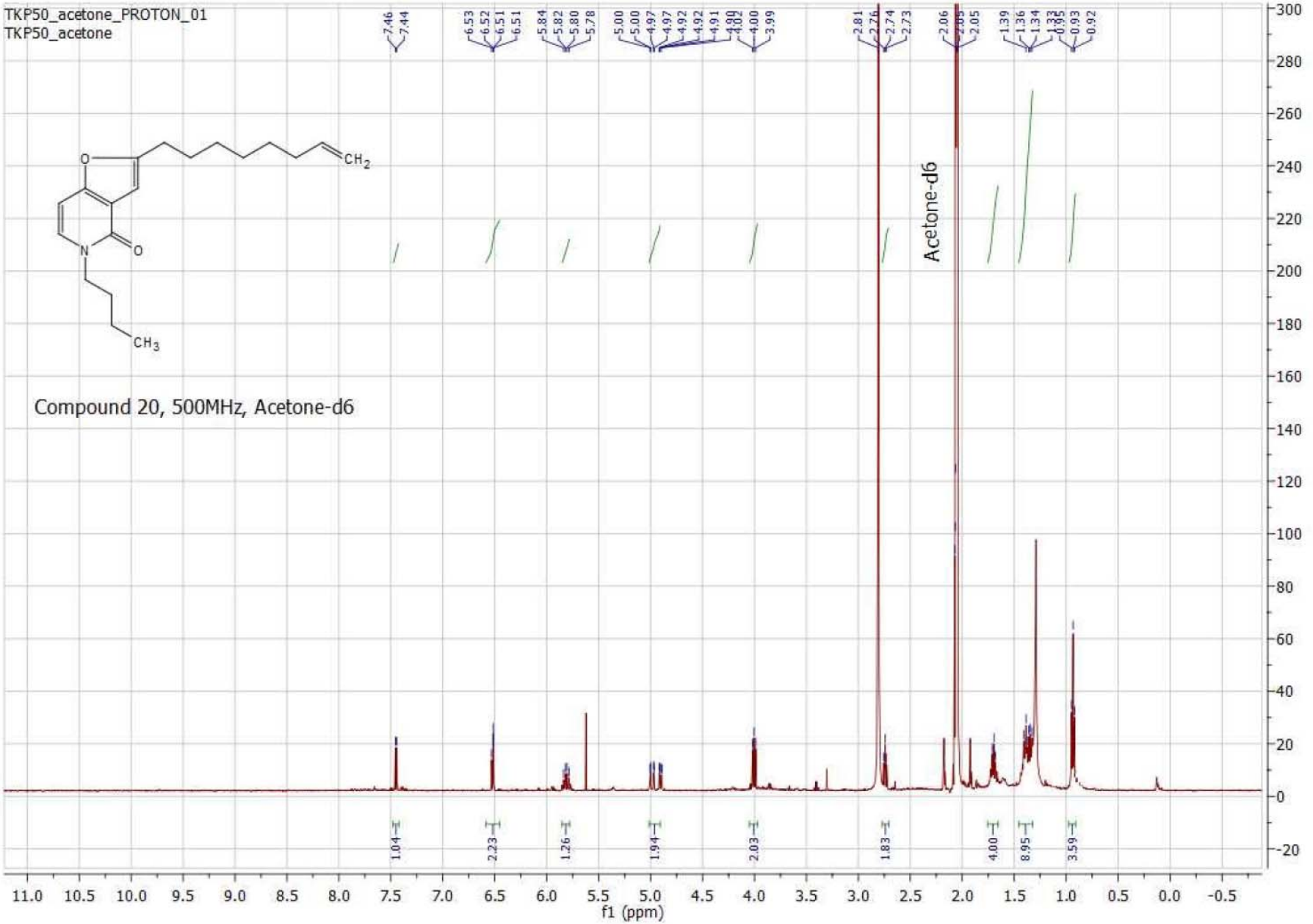

CARBON_01
KIKI56_4spot_for_carbon
159.55
158.64
158.44
133.27
117.27
102.19
95.77
77.24
76.73
37.03
29.68
27.75
22.11
13.72
CDCl3
Compound 5, 125MHz, CDCl3
f1 (ppm)

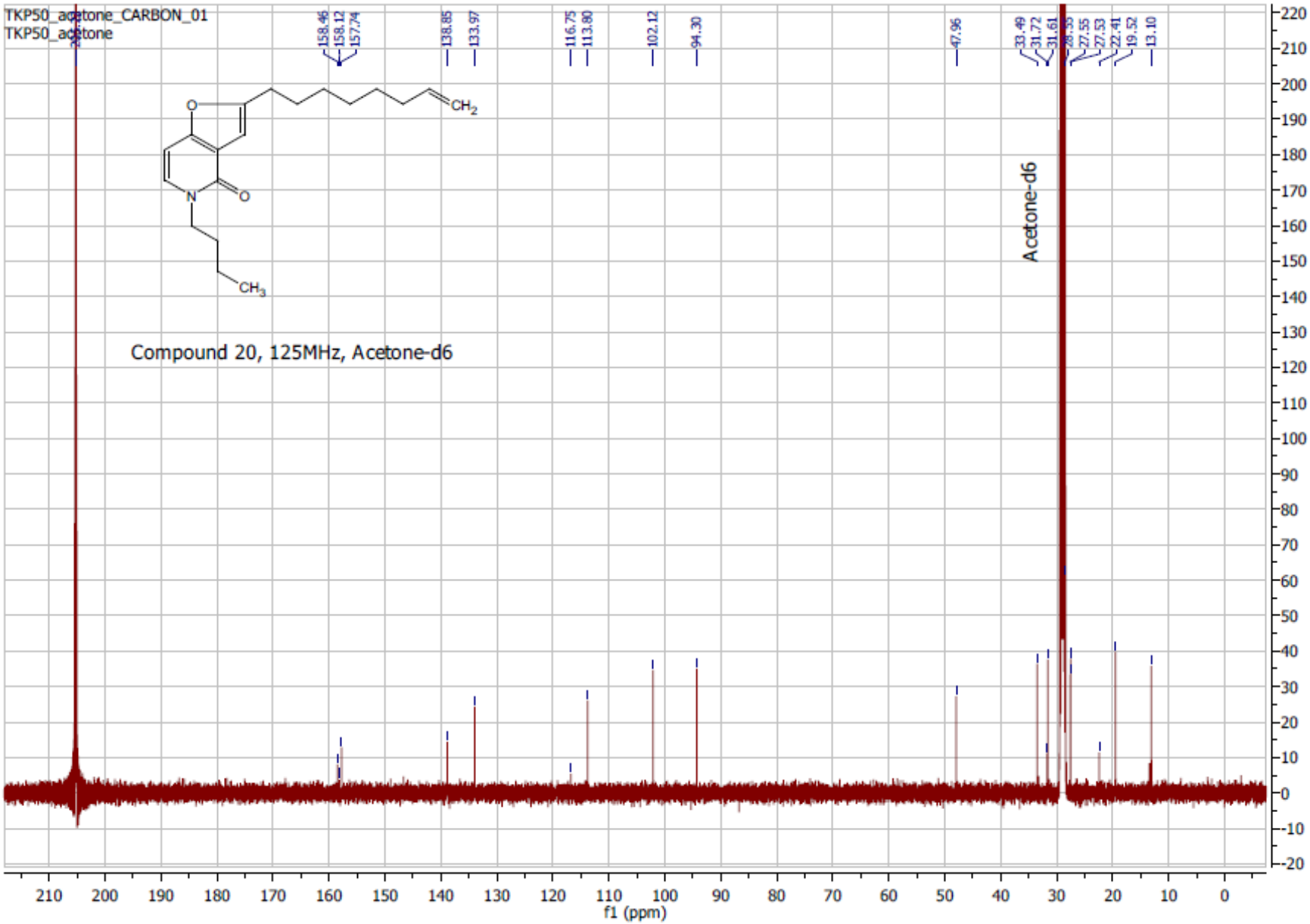

TKP64_for_C13_acetone_PROTON_01
TKP64_for_C13_acetone
Rotamers of Compound 17, 500MHz, Acetone-d6
Acetone-d6
H2O
f1 (ppm)

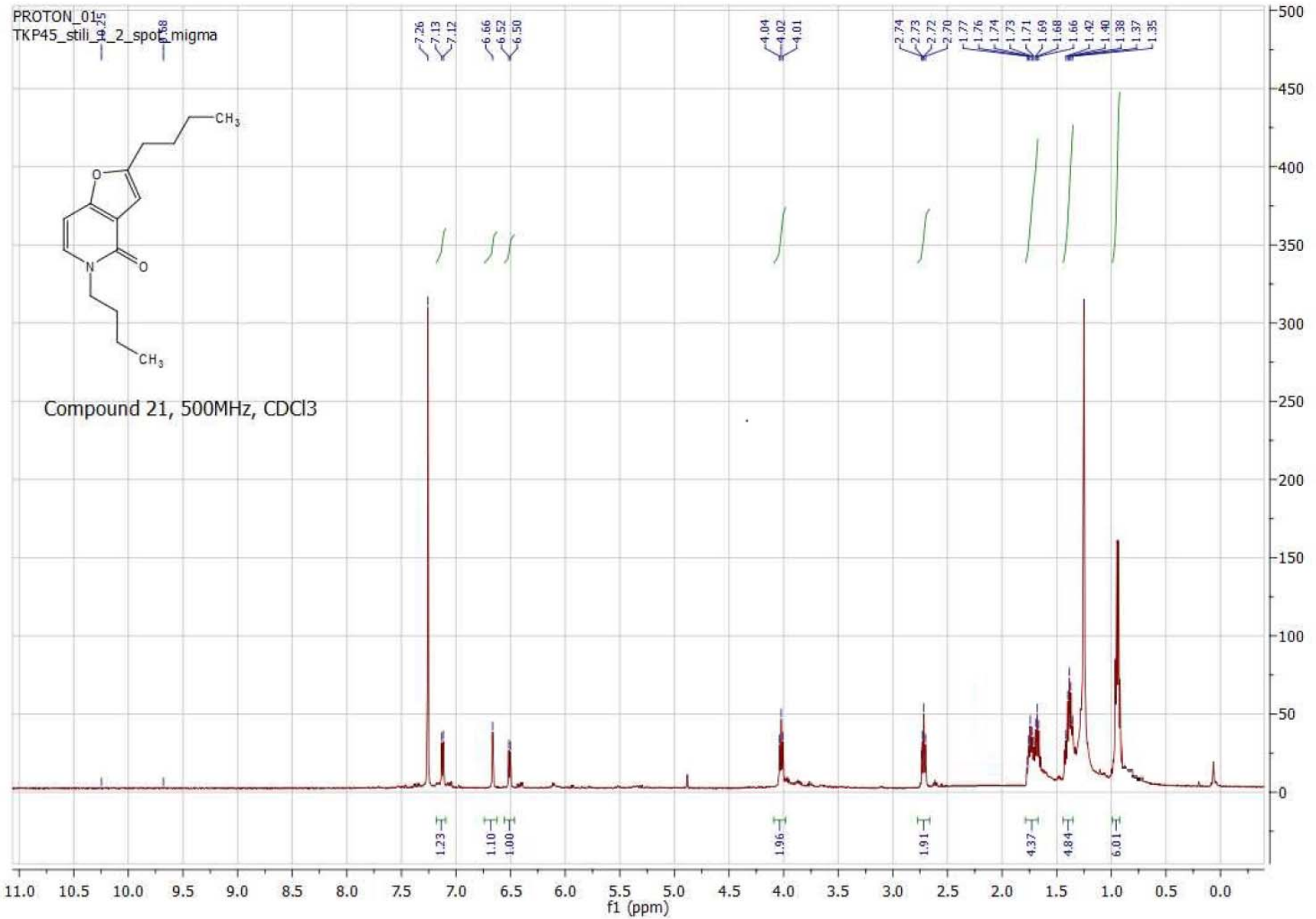

TKP64_CARBON_01
TKP64
161.75
160.96
160.85
157.84
137.56
137.54
135.35
132.12
122.87
122.85
110.09
110.02
98.30
98.20
35.79
29.53
22.46
21.84
13.91
13.24
11.94
Acetone-d6
H3C
OH
CH3
N
O
CH3
Rotamers of Compound 17, 500MHz, Acetone-d6
f1 (ppm)

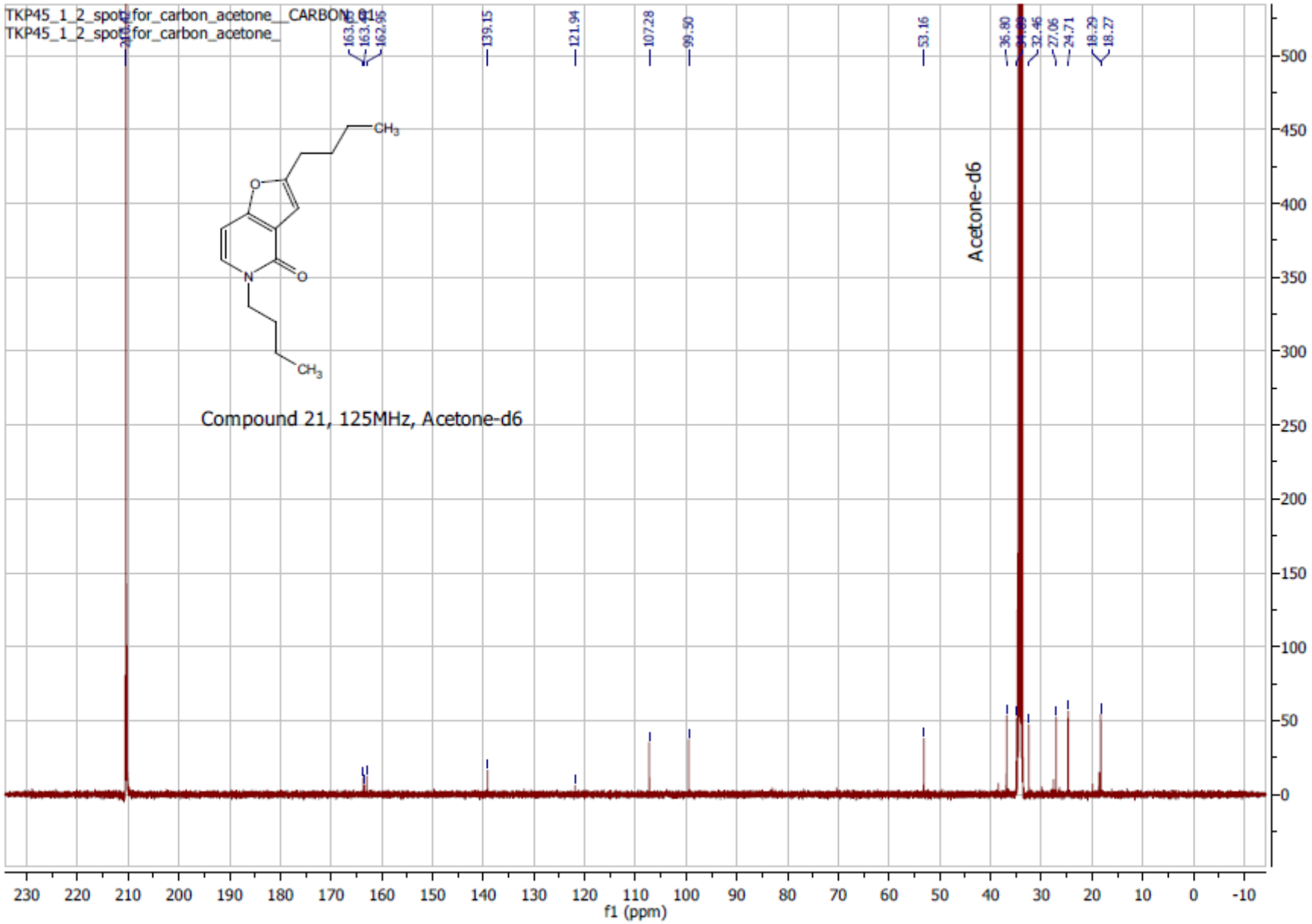

PROTON_01
TKP42_1st_spot_sfairiki
Compound 18, 500MHz, CDCl3
CDCl3
Grease
f1 (ppm)

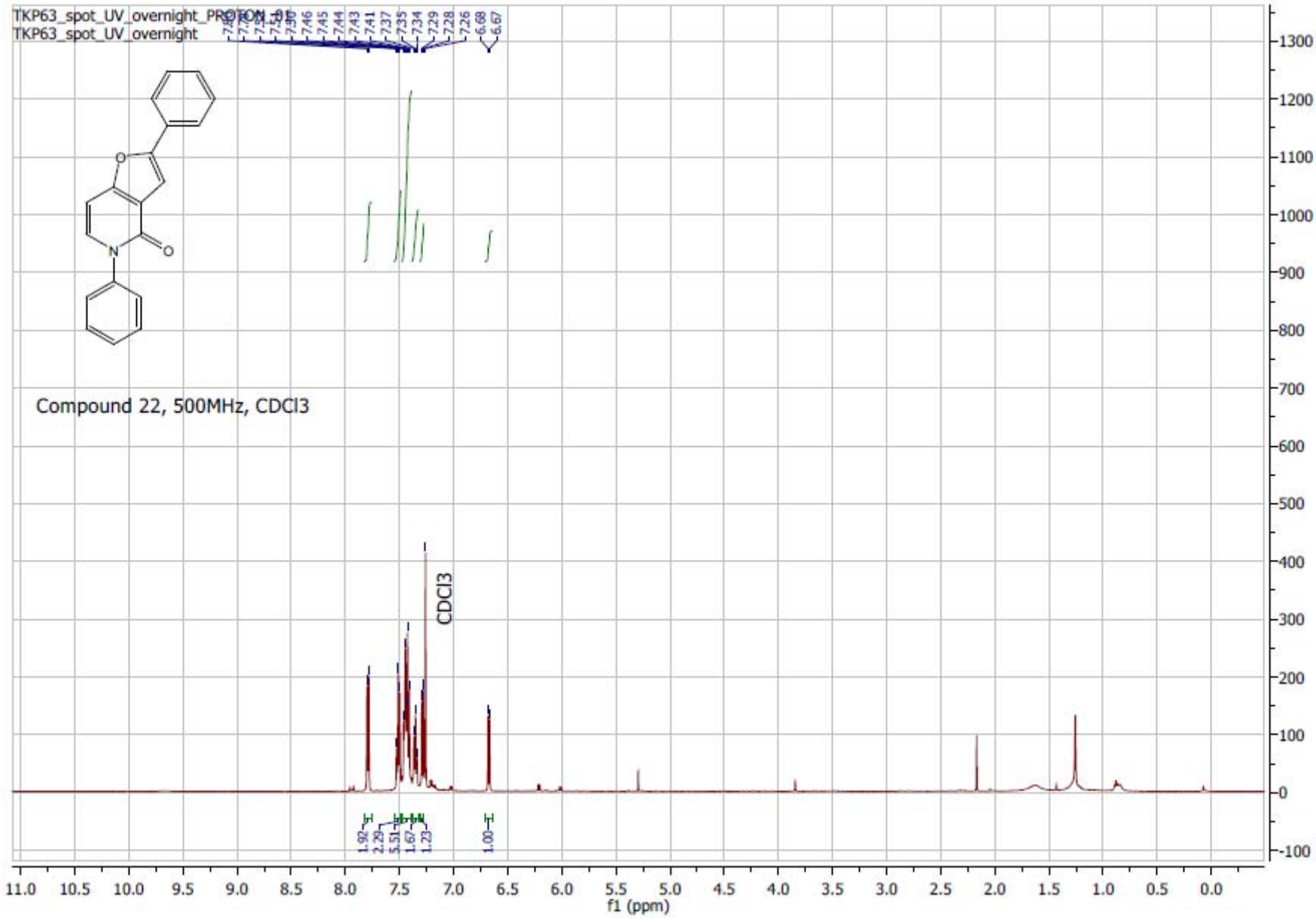

CARBON_01
TKP42_1st_for_carbon
159.62
159.00
154.92
134.33
129.73
128.84
128.44
124.39
118.15
101.83
95.60
77.24
77.19
76.99
76.73
37.02
Methylpyridone + styrene
Compound 18, 125MHz, CDCl3
CDCl3
Grease
f1 (ppm)

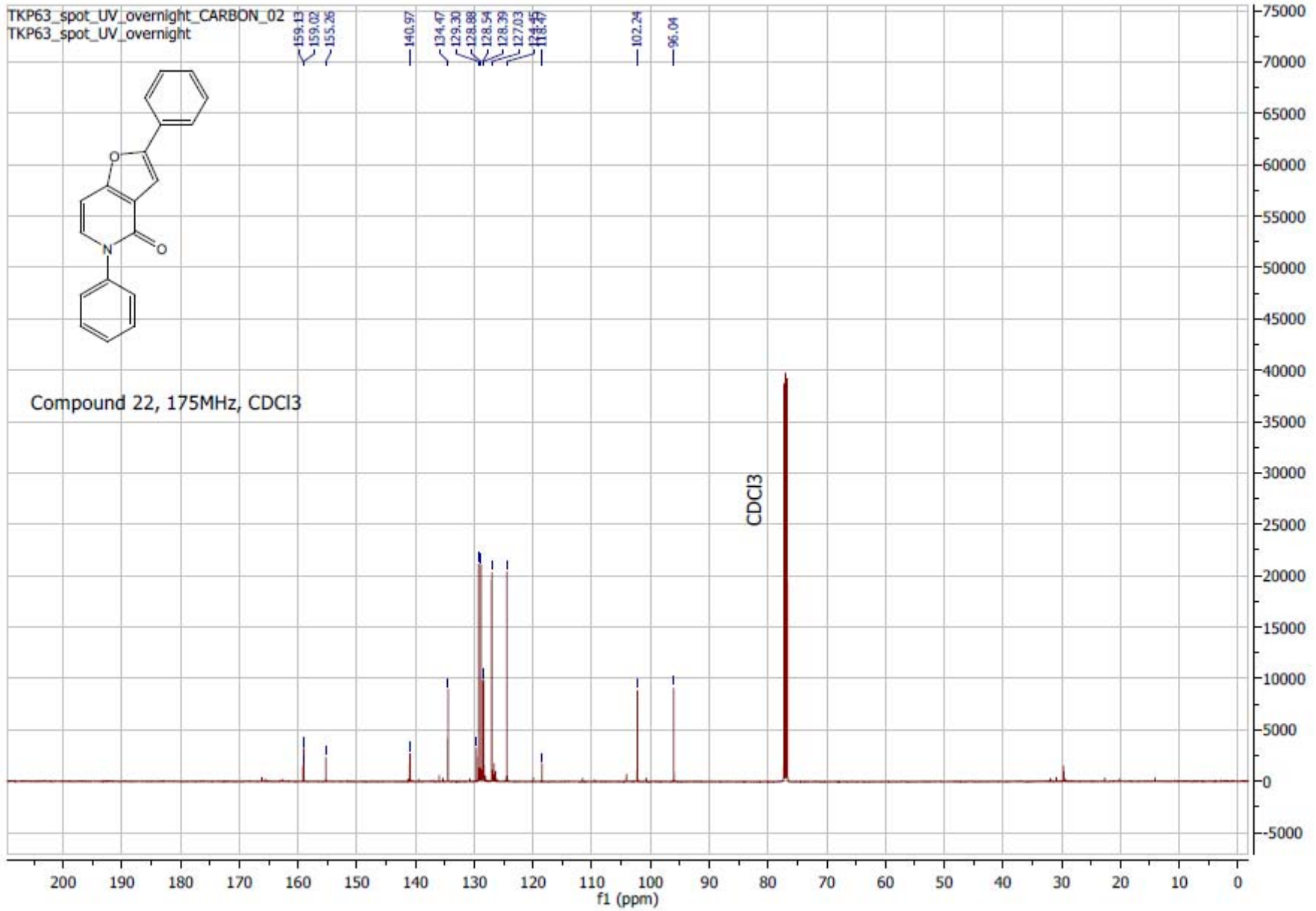

TKP50_acetone_PROTON_01
TKP50_acetone
Acetone-d6
Compound 20, 500MHz, Acetone-d6
f1 (ppm)

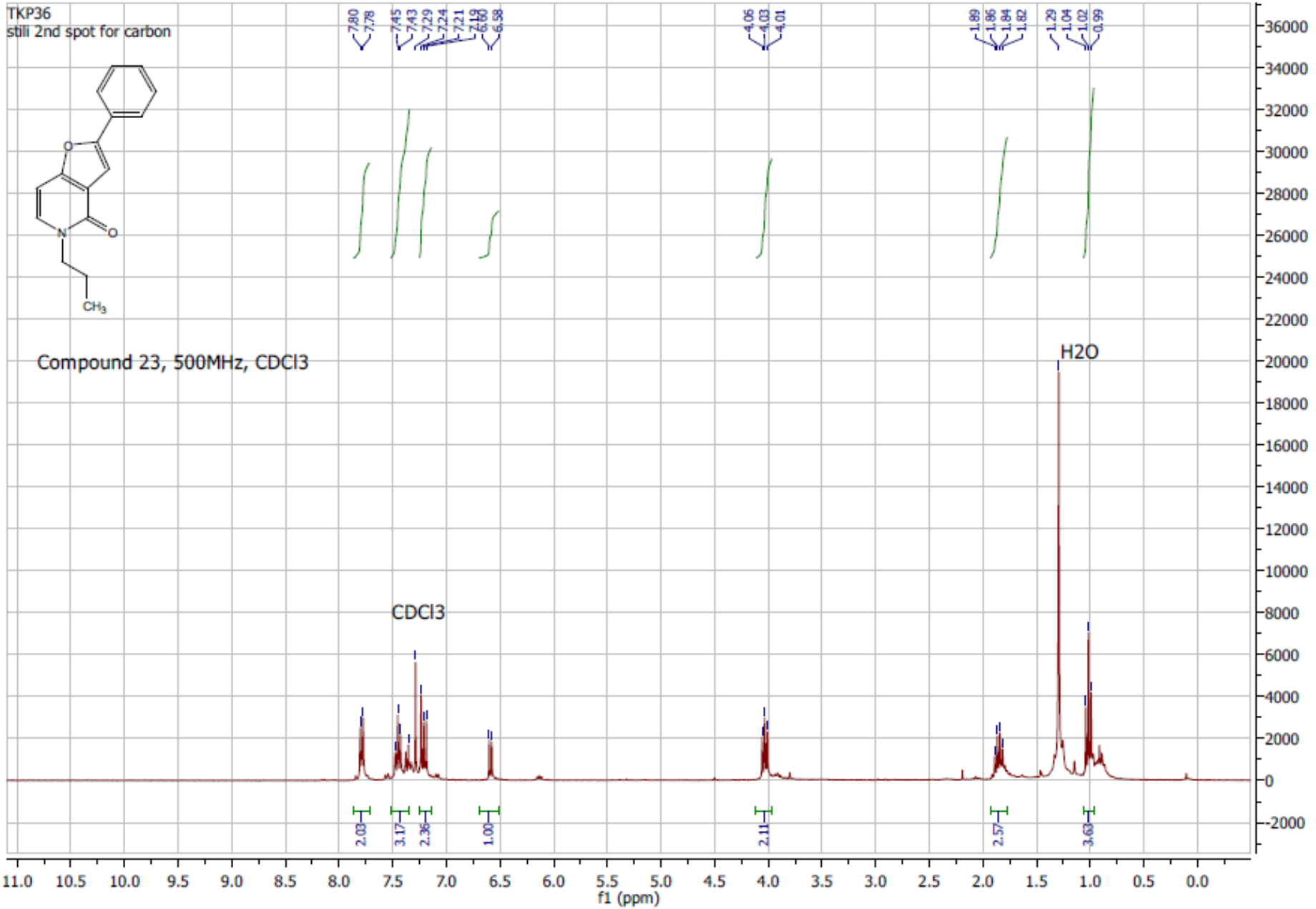

TKP50_acetone_CARBON_01
TKP50_acetone
158.46
158.12
157.74
138.85
133.97
116.75
113.80
102.12
94.30
47.96
33.49
31.72
31.61
28.55
27.55
27.53
22.41
19.52
13.10
Acetone-d6
Compound 20, 125MHz, Acetone-d6
f1 (ppm)

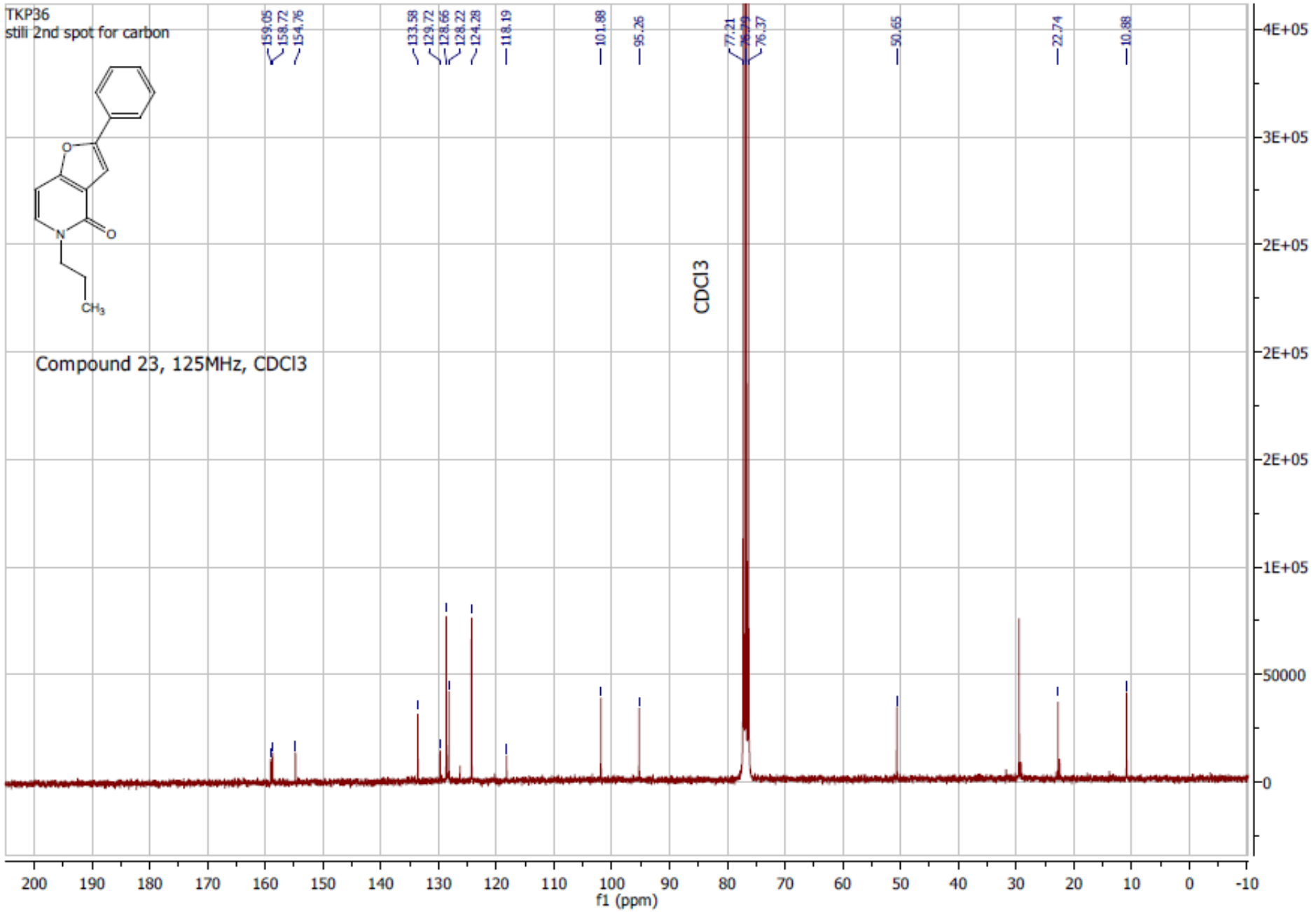

PROTON_01
TKP45_stili_1_2_spot_migma
Compound 21, 500MHz, CDCl3
f1 (ppm)

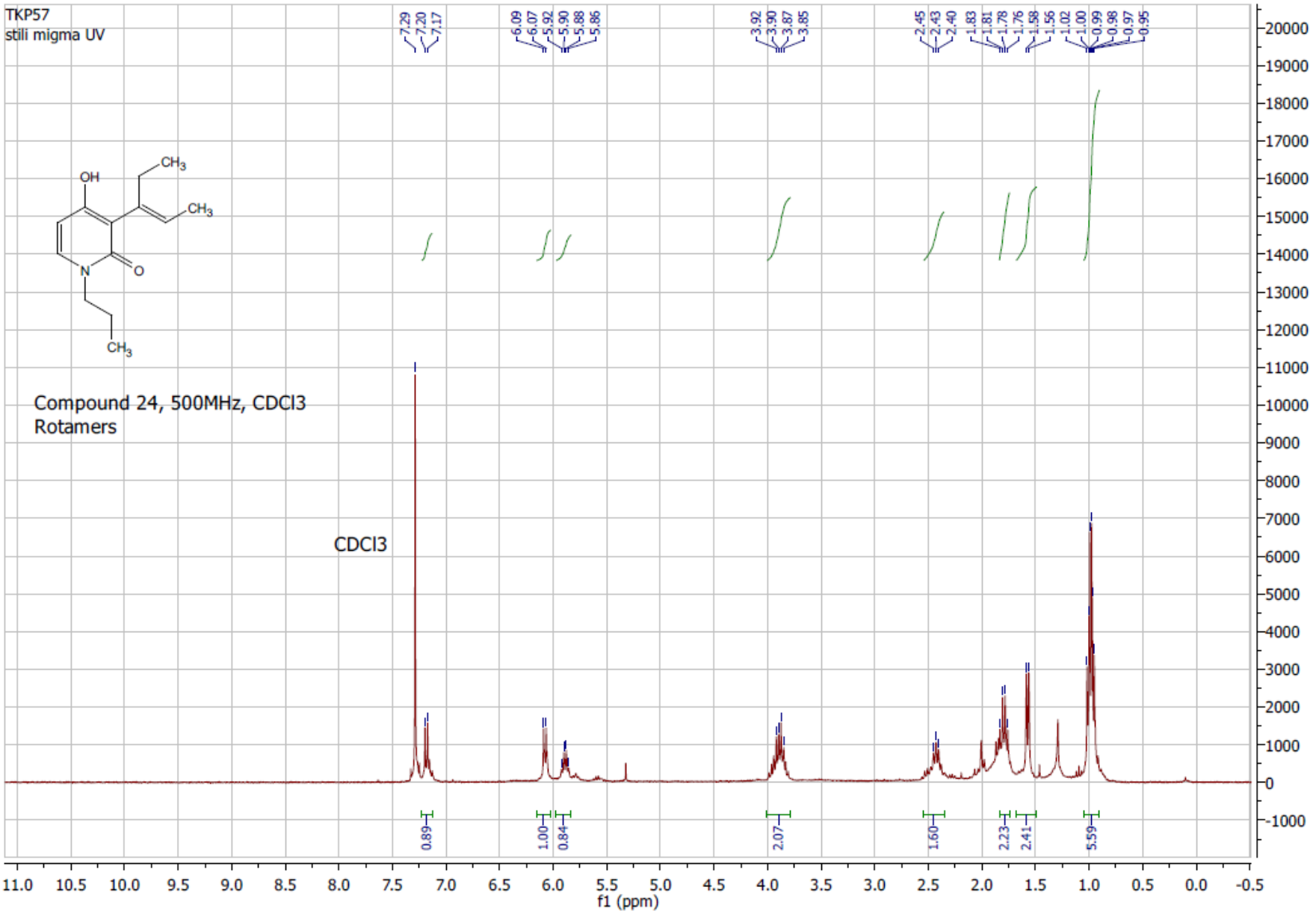

TKP45_1_2_spot2_for_carbon_acetone__CARBON_01
TKP45_1_2_spot2_for_carbon_acetone_
163.41
163.11
162.95
139.15
121.94
107.28
99.50
53.16
36.80
34.69
32.46
27.06
24.71
18.29
18.27
Acetone-d6
CH3
O
N
O
CH3
Compound 21, 125MHz, Acetone-d6
f1 (ppm)

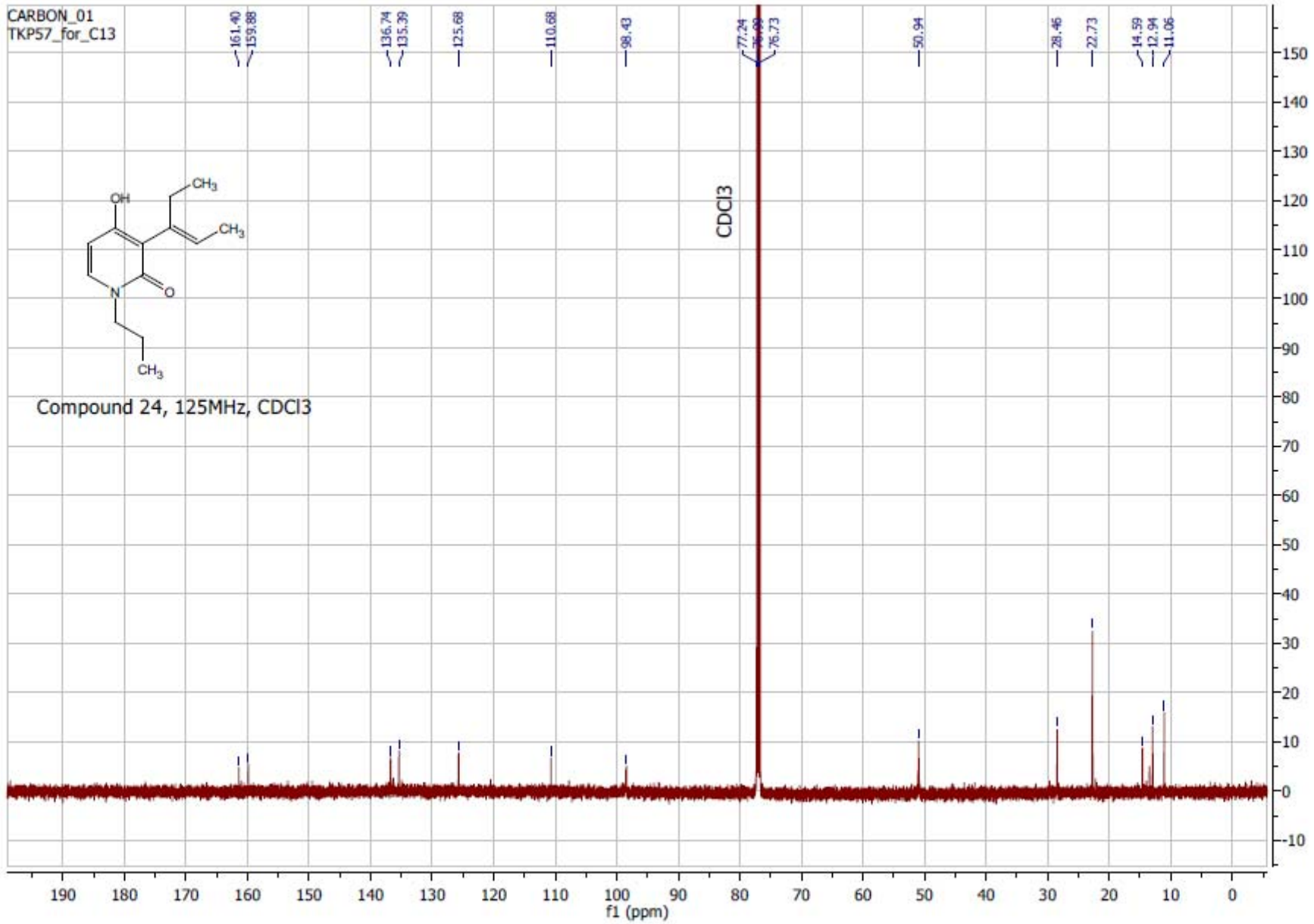

TKP63_spot_UV_overnight_PROTON_01
TKP63_spot_UV_overnight
Compound 22, 500MHz, CDCl3
CDCl3
f1 (ppm)

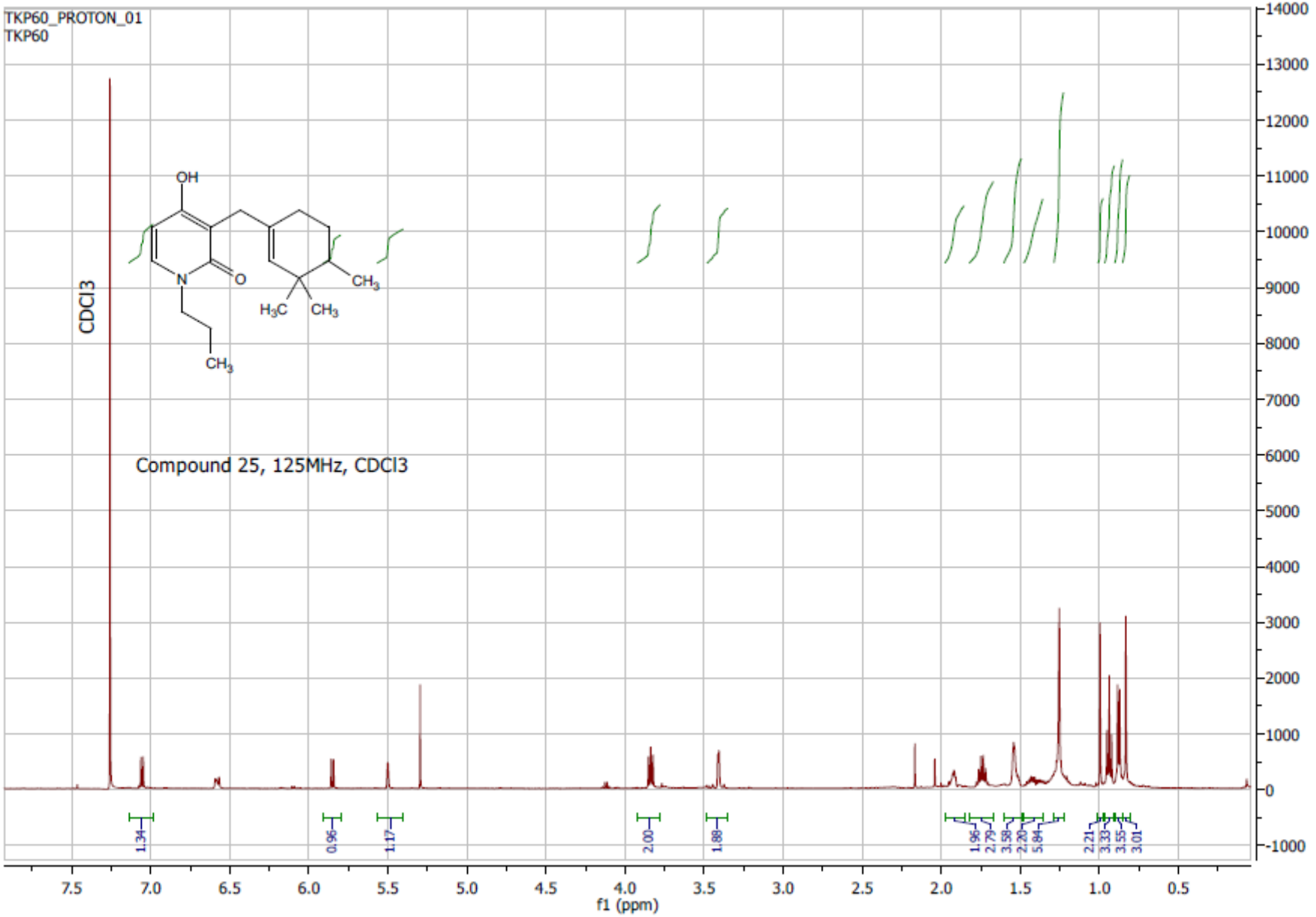

TKP63_spot_UV_overnight_CARBON_02
TKP63_spot_UV_overnight
159.13
159.02
155.26
140.97
134.47
129.30
128.88
128.54
128.39
127.03
102.24
96.04
Compound 22, 175MHz, CDCl3
CDCl3
f1 (ppm)

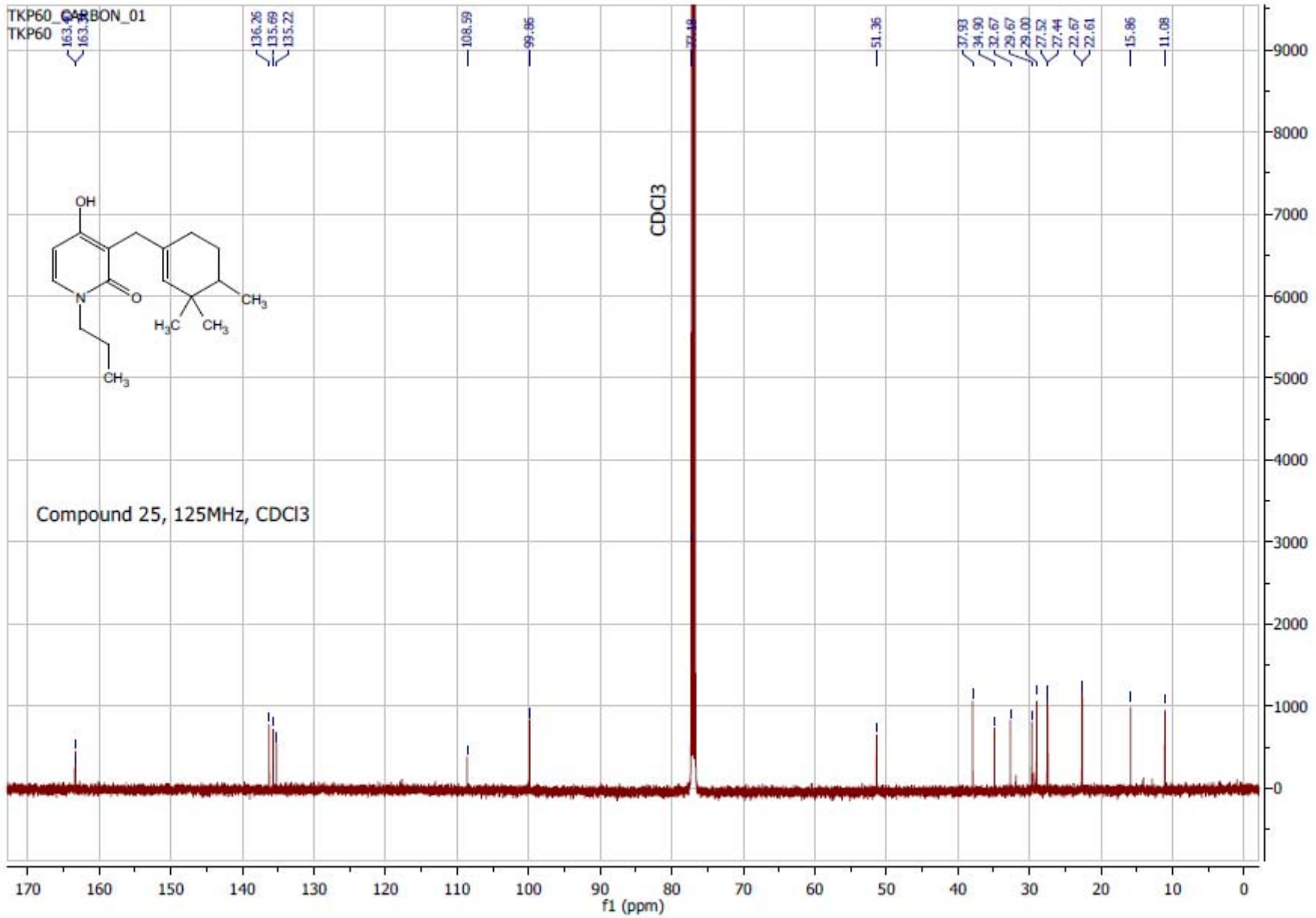

TKP36
stili 2nd spot for carbon
Compound 23, 500MHz, CDCl3
CDCl3
H2O
f1 (ppm)


TKP36
stili 2nd spot for carbon
159.05
158.72
154.76
133.58
129.72
128.66
128.22
124.28
118.19
101.88
95.26
77.21
76.79
76.37
50.65
22.74
10.88
CDCl3
Compound 23, 125MHz, CDCl3
O
N
O
CH3
4E+05
3E+05
2E+05
2E+05
2E+05
1E+05
50000
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


TKP57
stili migma UV
7.29
7.20
7.17
6.09
6.07
5.92
5.90
5.88
5.86
3.92
3.90
3.87
3.85
2.45
2.43
2.40
1.83
1.81
1.78
1.76
1.58
1.56
1.02
1.00
0.99
0.98
0.97
0.95
OH
CH3
CH3
N
O
CH3
Compound 24, 500MHz, CDCl3
Rotamers
CDCl3
0.89
1.00
0.84
2.07
1.60
2.23
2.41
5.59
f1 (ppm)


CARBON_01
TKP57_for_C13
161.40
159.88
136.74
135.39
125.68
110.68
98.43
77.24
76.90
76.73
50.94
28.46
22.73
14.59
12.94
11.06
CDCl3
OH
CH3
CH3
N
O
CH3
Compound 24, 125MHz, CDCl3
f1 (ppm)


TKP60_PROTON_01
TKP60
CDCl3
OH
N
O
CH3
H3C
CH3
CH3
Compound 25, 125MHz, CDCl3
1.34
0.96
1.17
2.00
1.88
1.96
2.79
3.58
2.20
5.84
2.21
3.33
3.55
3.01
f1 (ppm)


TKP60_CARBON_01
TKP60
163.47
163.36
136.26
135.69
135.22
108.59
99.86
77.48
51.36
37.93
34.90
32.67
29.67
29.00
27.52
27.44
22.67
22.61
15.86
11.08
CDCl3
OH
O
N
CH3
H3C
CH3
CH3
Compound 25, 125MHz, CDCl3
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)