Supporting Information

Efficient and chemoselective alkylation of amines/amino acids using alcohols as alkylating reagents under mild conditions

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Contents (60 pages):

General Methods

Melting points were uncorrected. Optical rotations were measured with Perkin-Elmer 341 automatic polarimeter. Infrared spectra were measured using KBr pellet techniques. ^{1}H-NMR spectra were acquired at 400 or 500 MHz and ^{13}C were acquired at 100 or 125 MHz. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography-mass spectrum (direct injection). Silica gel (300-400 mesh) was used for flash column chromatography. The alcohols used are analytically pure grade.

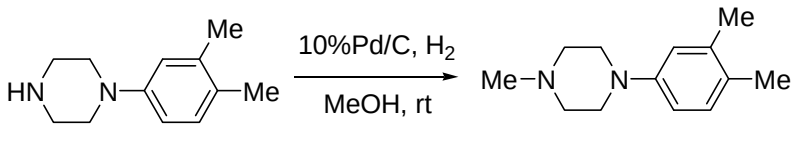
General procedure for the alkylation of amines with alcohol.

After vacuume to remove air from the reaction tube, the stirred mixture of the amines/amino acids (0.1 mmol), 10% Pd/C (100 mg, 0.094 mmol) or 20% $Pd(OH)_2/C$ (80 mg, 0.114 mmol) in an alcohol (5 mL) was hydrogenated under 1 atm of hydrogen (balloon) at room temperature. The reaction was vigorously stirred. When the reaction was judged to be complete by TLC monitoring, the mixture was filtered using a filter paper under a reduced pressure, and the filtrate was washed with the corresponding alcohol (5 mL) and the filtrate was concentrated under reduced pressure (about 80% of the solvent could be recovered by dstillation). The crude product was purified by flash column chromatography on silica gel, if necessary. Yield and time are indicated in Table 1 and Table 2.

Procedure for the recovery and recycle of 10%Pd/C.

The catalyst (10%Pd/C) was recovered by filtration through a filter paper under reduced pressue, and reused following the general procedure. This procedure was repeated four times with the results indicated in Table 3. **Caution:** upon washing of 10%Pd/C, this catalyst might burned spontaneously when expose to air, and precautions should be taken (avoiding the excessively dryness of Pd/C during the vacuum filtration).

Table 1. *N*-Alkylation reaction of amine with recycled catalyst or solvent.



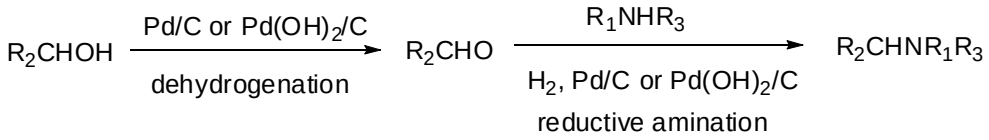
25 **26**

Entry	Cycle	T (h)	Yield (%)[c]
1[a]	1	14	73
2[a]	2	19	86
3[a]	3	21	71
4[a]	4	24	79
5[b]	1	16	70

[a] Reaction with recycled catalyst.

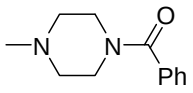
[b] Reaction with recycled solvent.

[c] Isolated yield.



Scheme 1. A plausible mechanism for the *N*-alkylation of an amine with an alcohol.

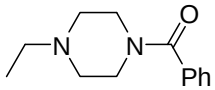
(4-Methylpiperazin-1-yl)(phenyl)methanone (2a)



Following the general procedure, the reaction of *N*-benzoylpiperazine (**1**) (0.1 mmol, 19 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **2a**[3] as a colorless oil (17.3 mg, 85%).

By using 20%$Pd(OH)_2$/C (80 mg) as the catalyst, 12.6 mg of **2a** was obtained (yield: 62%). IR (film) ν_{max}: 2936, 2850, 2786, 1632, 1424, 1296, 1271, 1168, 1141, 1128, 1019, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.35 (br s, 2H), 2.48 (br s, 2H), 3.44 (br s, 2H), 3.79 (br s, 2H), 7.28-7.42 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.0, 46.0, 47.5, 55.0(2C), 127.0, 128.4, 129.6, 135.8, 170.3; MS (ESI): *m/z* 205.1 ($M+H^+$, 100).

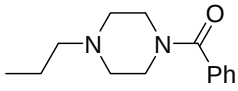
(4-Ethylpiperazin-1-yl)(phenyl)methanone (2b)



Following the general procedure, the reaction of *N*-benzoylpiperazine (**1**) (0.1 mmol, 19 mg) in EtOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **2b**[4] as a colorless oil (19.4 mg, 89%).

By using 20%$Pd(OH)_2$/C (80 mg) as the catalyst, 16.1 mg of **2b** was obtained (yield: 74%). IR (film) ν_{max}: 2970, 2924, 2805, 1632, 1577, 1427, 1290, 1260, 1165, 1119, 1013, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.08 (t, J = 7.2 Hz, 3H), 2.38 (br s, 2H), 2.43 (q, J = 7.2 Hz, 2H), 2.50 (br s, 2H), 3.43 (br s, 2H), 3.79 (br s, 2H), 7.36-7.40 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.8, 42.2, 47.7, 52.2, 52.4, 53.0, 127.0, 128.4, 129.6, 135.8, 170.2; MS (ESI): *m/z* 219.1 ($M+H^+$, 100).

Phenyl(4-propylpiperazin-1-yl)methanone (2c)

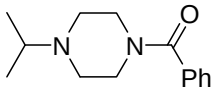


Following the general procedure, the reaction of *N*-benzoylpiperazine (**1**) (0.1 mmol, 19 mg) in *n*-PrOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **2c**[5] as a

colorless oil (17.6 mg, 76%).

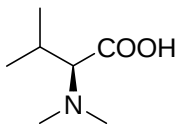
By using 20%$Pd(OH)_2/C$ (80 mg) as the catalyst, 21.3 mg of **2c** was obtained (yield: 92%). IR (film) ν_{max}: 2964, 2921, 2866, 2805, 2765, 1632, 1427, 1372, 1293, 1278, 1159, 1015, 1001 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.91 (t, *J* = 7.4 Hz, 3H), 1.51 (tq apparent sextet, *J* = 7.7 ,7.4 Hz, 2H), 2.33 (t, *J* = 7.7 Hz, 2H), 2.38 (br s, 2H), 2.52 (br s, 2H), 3.44 (br s, 2H), 3.50 (br s, 2H), 7.39 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8, 19.9, 42.2, 47.7, 52.9, 53.4, 60.5, 127.0, 128.4, 129.6, 136.0, 170.2; MS (ESI): *m/z* 233.1 ($M+H^+$, 100).

(4-Isopropylpiperazin-1-yl)(phenyl)methanone (2d)



Following the general procedure, the reaction was performed starting from *N*-benzoylpiperazine (**1**) (0.1 mmol, 19 mg), *i*-PrOH (5 mL) and 10% Pd/C (100 mg). The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2–CH_3OH (60:1), gave **2d**[6] as a colorless oil (14.8 mg, 64%). IR (film) ν_{max}: 2969, 2924, 2853, 2811, 1631, 1576, 1424, 1283, 1262, 1177, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04 (d, *J* = 6.6 Hz, 6H), 2.45 (br s, 2H), 2.58 (br s, 2H), 2.72 (h, *J* = 6.6 Hz, 1H), 3.42 (br s, 2H), 3.79 (br s, 2H), 7.38 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.3, 42.3, 48.0, 48.3, 49.0, 54.6, 127.0, 128.4, 129.5, 135.9, 170.1; MS (ESI): *m/z* 233.1 ($M+H^+$, 100).

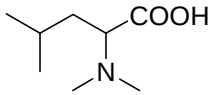
(*S*)-2-(Dimethylamino)-3-methylbutanoic acid (Dov, 3)



Following the general procedure, the reaction of L-valine (**15**) (0.1 mmol, 11.7 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **3** as a white solid (13.5 mg, 93%). $[\alpha]_D^{20}$ +45.4 (*c* 0.80, H_2O) {lit.[13] $[\alpha]_D^{14}$ +40.6 (*c* 2, H_2O)}; M.p. 154-156 °C (EtOH/CH_3COCH_3) (lit.[13] 154 °C). IR (KBr) ν_{max}: 3436, 2961, 2765, 1604, 1461, 1421, 1372, 1351 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 0.96 (d, *J* = 6.8 Hz,

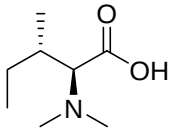
3H), 1.09 (d, *J* = 6.8 Hz, 3H), 2.29-2.42 (m, 1H), 2.89 (d, *J* = 7.4 Hz, 6H), 3.43 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 15.8, 19.3, 26.0, 40.0, 43.0, 76.1, 171.6; MS (ESI): *m/z* 146.0 ($M+H^+$, 100).

(*R*/*S*)-2-(Dimethylamino)-4-methylpentanoic acid (4)



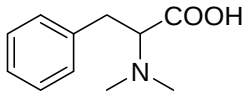
Following the general procedure, the reaction of (±)-leucine (**13**) (0.1 mmol, 13.1 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **4** as a white solid (13.6 mg, 94%). M.p. 192-194 °C (EtOH) (lit.[12] 194 °C). IR (KBr) ν_{max}: 3436, 2960, 2869, 1625, 1472, 1378, 1341, 1323, 1146, 1119 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ: 0.95-1.01 (t, 6H), 1.60-1.80 (m, 3H), 2.90 (br s, 6H), 3.58 (dd, *J* = 9.7, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 20.7, 22.7, 25.1, 36.8, 40.1, 42.3, 70.3, 173.5; MS (ESI): *m/z* 160.1 ($M+H^+$, 100).

(2*S*,3*S*)-2-(Dimethylamino)-3-methylpentanoic acid (2*S*,3*S*)-*N*,*N*-diMe-Ile) (**5**)



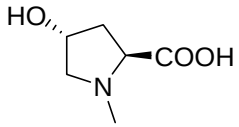
Following the general procedure, the reaction of L-isoleucine (**16**) (0.1 mmol, 13.1 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **5** as a white solid (14.5 mg, 91%). $[\alpha]_D^{20}$ +53.3 (*c* 1.13, H_2O) {lit. [14] $[\alpha]_D^{20}$ +48 (*c* 1, H_2O)}; M.p. 174-175 °C (CH_3COCH_3) (lit.[14] 173-174 °C). IR (KBr) ν_{max}: 3433, 2970, 2869, 1622, 1470, 1385, 1311, 1144, 1064 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ: 0.93-1.02 (m, 6H), 1.28-1.41 (m, 1H), 1.48-1.61 (m, 1H), 2.03-2.14 (m, 1H), 2.88 (s, 3H), 2.91 (s, 3H), 3.52 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 11.2, 13.1, 26.6, 32.7, 39.7, 43.5, 74.9, 171.7; MS (ESI): *m/z* 160.0 ($M+H^+$, 100).

(*R*/*S*)-2-(Dimethylamino)-3-phenylpropanoic acid (6)



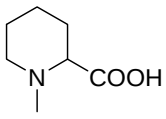
Following the general procedure, the reaction of (±)-phenylalanine (**14**) (0.1 mmol, 16.5 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **6** as a white solid (17.8 mg, 92%). M.p. 229-230 °C (MeOH) (lit.[13] 228 °C). IR (KBr) ν_{max}: 3430, 3031, 2921, 1616, 1418, 1378, 1348, 1335, 1287, 1177, 1144, 1089, 1025 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 2.94 (br s, 6H), 3.13 (dd, *J* = 13.7, 9.2 Hz, 1H), 3.35 (dd, *J* = 13.7, 5.7 Hz, 1H), 3.85 (dd, *J* = 9.2, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 34.0, 41.5, 42.4, 72.2, 127.5, 129.0, 129.2, 135.4, 172.2; MS (ESI): *m/z* 194.0 ($M+H^+$, 100).

(2*S*,4*R*)-4-Hydroxy-1-methylpyrrolidine-2-carboxylic acid (7)



Following the general procedure, the reaction of (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (**11**) (0.1 mmol, 13.1 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **7** as a white solid (12.6 mg, 87%). $[\alpha]_D^{20}$ –90.0 (*c* 0.13, CH_3OH) {lit.[15] $[\alpha]_D^{20}$ –95.0 (*c* 0.1, CH_3OH)}; M.p. 238-240 °C (MeOH) (lit.[16] 237-241 °C). IR (KBr) ν_{max}: 3418, 1625, 1403, 1339, 1208, 1071 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 2.20-2.31 (m, 1H), 2.44-2.55 (m, 1H), 3.06 (s, 3H), 3.21 (d, *J* = 13.0 Hz, 1H), 3.97 (dd, *J* = 13.0, 4.6 Hz, 1H), 4.21 (dd, *J* = 11.0, 7.5 Hz, 1H), 4.62-4.67 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 38.3, 43.2, 62.7, 69.5, 70.1, 172.9; MS (ESI): *m/z* 145.9 ($M+H^+$, 100).

(*R*/*S*)-1-Methylpiperidine-2-carboxylic acid (8)

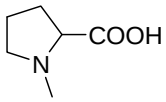


Following the general procedure, the reaction of (±)-piperidine-2-carboxylic acid (**12**) (0.1 mmol, 12.9 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **8** as a white solid (12.9 mg, 90%).

By using 20%$Pd(OH)_2$/C (80 mg) as the catalyst, 13.4 mg of **8** was obtained (yield: 94%). M.p. 208-209 °C (EtOH) (lit.[10] 208-210 °C). IR (KBr) ν_{max}: 3401, 3026, 2959,

2933, 2860, 1614, 1393, 1354, 1322, 1284, 1114 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 1.53-1.66 (m, 1H), 1.70-1.84 (m, 2H), 1.87-2.03 (m, 2H), 2.22-2.31 (m, 1H), 2.91 (s, 3H), 3.04-3.13 (m, 1H), 3.50-3.58 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ: 16.9, 21.0, 22.6, 28.0, 42.4, 54.5, 69.0, 174.1; MS (ESI): *m/z* 144.1 ($M+H^+$, 100).

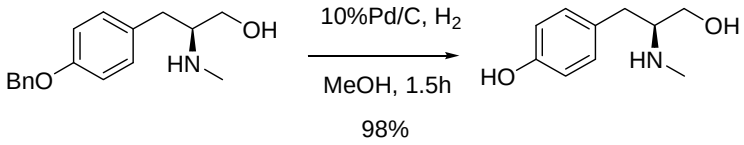
(*R*/*S*)-1-Methylpyrrolidine-2-carboxylic acid (10)



Following the general procedure, the reaction of (±)-proline (**9**) (0.1 mmol, 11.5 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **10** as a white solid (11.5 mg, 89%).

By using 20%$Pd(OH)_2$/C (80 mg) as the catalyst, 10.7 mg of **10** was obtained (yield: 83%). M.p. 168-169 °C (EtOH) (lit.[8] 168-170 °C). IR (KBr) ν_{max}: 3430, 3064, 2857, 1628, 1473, 1455, 1400, 1321 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 2.00-2.11 (m, 1H), 2.11-2.29 (m, 2H), 2.52-2.65 (m, 1H), 3.00 (s, 3H), 3.18-3.28 (m, 1H), 3.77-3.85 (m, 1H), 3.97-4.04 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 22.8, 28.8, 40.8, 56.5, 70.5, 173.3; MS (ESI): *m/z* 152.0 ($M+Na^+$, 100).

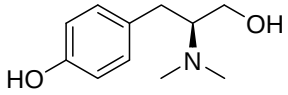
(*S*)-4-(3-Hydroxy-2-(methylamino)propyl)phenol (17)



To a mixture of (*S*)-3-(4-(benzyloxy)phenyl)-2-(methylamino)propan-1-ol[17] (68 mg, 0.25 mmol) and 10% Pd/C (20 mg) was added MeOH (5 mL). The mixture was stirred at room temperature under an atmosphere of H_2 for 1.5 hours. The mixture was filtered and concentrated under reduced pressure to give **17** (44.5 mg, 98%) as a white solid. $[\alpha]_D^{20}$ +11.2 (*c* 0.5, MeOH); M.p. 152-153 °C (MeOH). IR (KBr) ν_{max}: 3430, 3305, 3143, 2912, 1616, 1592, 1519, 1467, 1443, 1363, 1269, 1238, 1107, 1065, 1031 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 2.35 (s, 3H), 2.51 (dd, *J* = 15.1, 9.7 Hz, 1H), 2.59-2.67 (m, 2H), 3.34 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.47 (dd, *J* = 11.2, 4.0 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ:

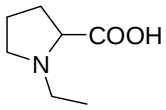
33.8, 36.9, 63.0, 64.1, 116.4, 130.5, 131.2, 157.1; MS (ESI): *m/z* 182.0 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.62; H, 8.58; N, 7.38.

(*S*)-4-(2-(Dimethylamino)-3-hydroxypropyl)phenol (18)



Following the general procedure, the reaction of (*S*)-4-(3-hydroxy-2-(methylamino)propyl)phenol (**17**) (0.1 mmol, 18.1 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **18** as a white solid (14 mg, 72%). $[\alpha]_D^{20}$ +7.3 (*c* 0.55, MeOH); M.p. 153-155 ^oC (MeOH). IR (KBr) ν_{max}: 3168, 2933, 2869, 2835, 2799, 1613, 1589, 1516, 1461, 1384, 1275, 1247, 1235, 1165, 1061, 1037, 1010 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 2.37 (s, 6H), 2.43 (dd, *J* = 13.2, 9.3 Hz, 1H), 2.68-2.82 (m, 2H), 3.49 (d, *J* = 5.6 Hz, 2H), 6.68-6.74 (m, 2H), 6.99-7.04 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ: 32.1, 41.4, 61.2, 68.9, 116.3, 131.0, 131.8, 156.8; MS (ESI): *m/z* 196.0 ($M+H^+$, 100).

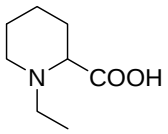
1-Ethylpyrrolidine-2-carboxylic acid (19)



Following the general procedure, the reaction of (±)-proline (**9**) (0.1 mmol, 11.5 mg) in EtOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **19** as a white solid (12.2 mg, 85%).

By using 20%$Pd(OH)_2$/C (80 mg) as the catalyst, 10.7 mg of **19** was obtained (yield: 75%). M.p. 168-169 ^oC ($CHCl_3$) (lit.[9] 170 ^oC). IR (KBr) ν_{max}: 3433, 3055, 2985, 2881, 1628, 1461, 1400, 1327, 1235, 1171, 1043 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 1.34 (t, *J* = 7.2 Hz, 3H), 1.88-2.02 (m, 1H), 2.04-2.19 (m, 2H), 2.38-2.50 (m, 1H), 3.05-3.14 (m, 1H), 3.15-3.26 (m, 1H), 3.27-3.38 (m, 1H), 3.69-3.78 (m, 1H), 3.83-3.90 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ: 11.3, 24.4, 30.3, 51.6, 55.5, 70.1, 173.3; MS (ESI): *m/z* 144.1 ($M+H^+$, 100).

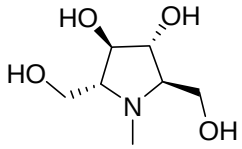
1-Ethylpiperidine-2-carboxylic acid (20)



Following the general procedure, the reaction of (±)-piperidine-2-carboxylic acid (**12**) (0.1 mmol, 12.9 mg) in EtOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **20**[11] as a white solid (13.5 mg, 86%).

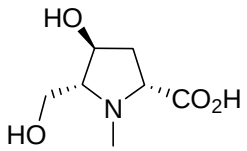
By using 20%$Pd(OH)_2$/C (80 mg) as the catalyst, 15.1 mg of **20** was obtained (yield: 96%). M.p. 200-201 ^oC (EtOH). IR (KBr) ν_{max}: 3427, 2975, 2940, 2927, 2863, 1617, 1457, 1377, 1322, 1274, 1175, 1085, 1018 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 1.34 (t, *J* = 7.4 Hz, 3H), 1.50-1.63 (m, 1H), 1.63-1.82 (m, 2H), 1.82-1.91 (m, 1H), 1.91-2.00 (m, 1H), 2.16-2.26 (m, 1H), 2.90-3.01 (m, 1H), 3.06-3.18 (m, 1H), 3.26-3.37 (m, 1H), 3.51-3.58 (m, 1H), 3.59-3.67 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 8.6, 21.1, 22.3, 27.9, 50.6, 51.3, 67.6, 174.4; MS (ESI): *m/z* 180.1 ($M+Na^+$, 100).

(2*R*,3*R*,4*R*,5*R*)-2,5-Bis(hydroxymethyl)-1-methylpyrrolidine-3,4-diol (22)



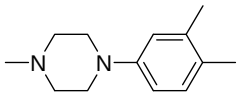
To 4.2 mg of 10% Pd/C was added a solution of compound (2*R*,3*R*,4*R*,5*R*)-**21** (14.0 mg, 0.032 mmol) in 2 mL of dry methanol. The mixture was stirred under 1 atm of hydrogen for two days at rt and then filtered through filter paper under reduced pressure. After concentration under reduced pressure, the resulting residue afforded compound **22** (5.0 mg, 89%). $[\alpha]_D^{20}$ –8.0 (*c* 0.4, H_2O) [lit.[19] $[\alpha]_D^{20}$ –8.5 (*c* 1.0, H_2O)]; IR (film): ν_{max} : 3350, 2922, 1423, 1252, 1120 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ : 2.59 (s, 3H), 3.03~3.10 (m, 2H), 3.85 (dd, *J* = 1.4, 4.6 Hz, 4H), 4.00 (td, *J* = 2.8, 4.6 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ : 37.8, 61.6, 72.5, 80.0; MS (ESI) *m/z* 178 ($M+H^+$, 100).

(2*R*,4*S*,5*R*)-1-Methyl-4-hydroxy-5-hydroxymethyl pyrrolidine-2-carboxylic acid (24)

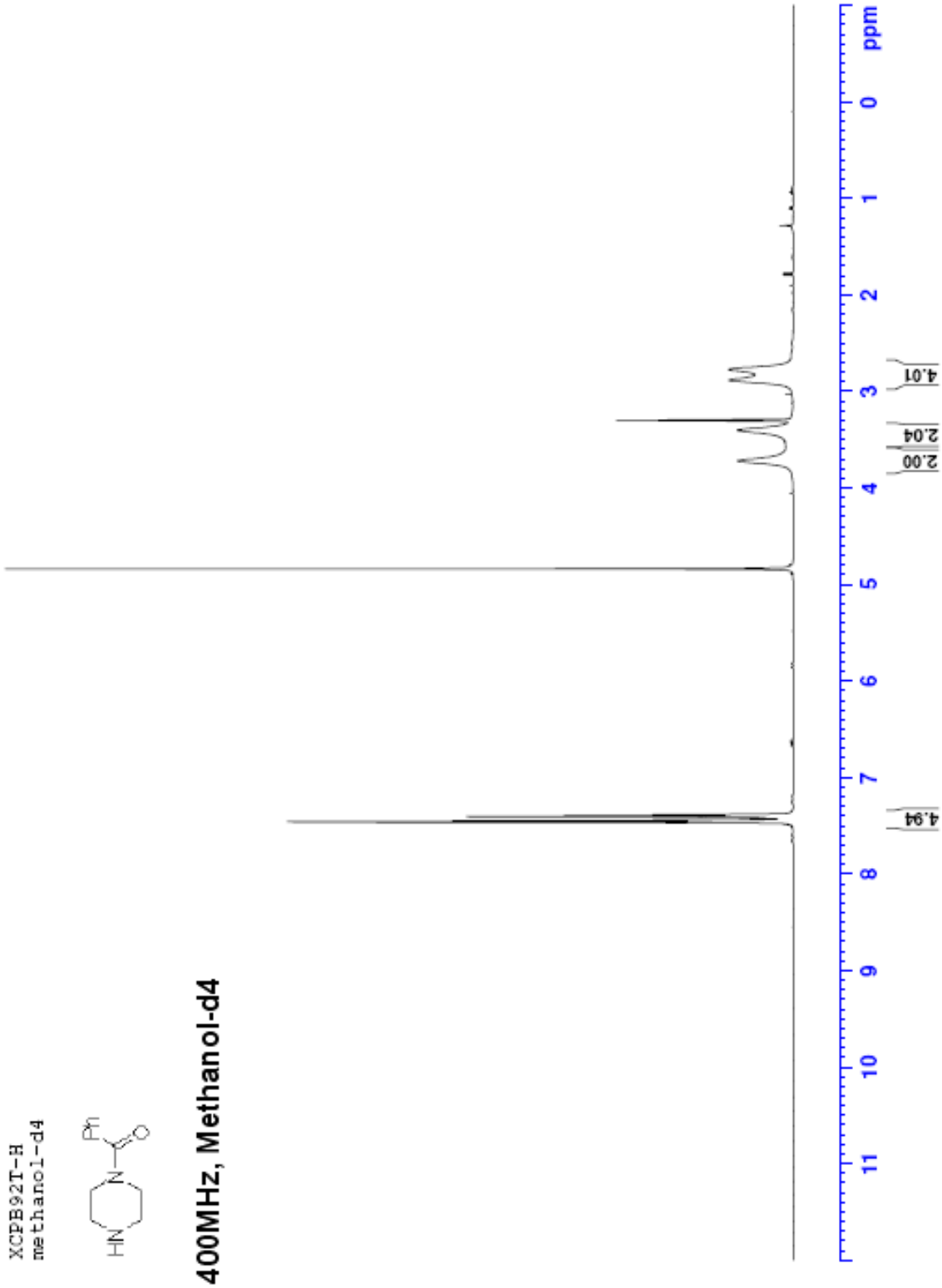


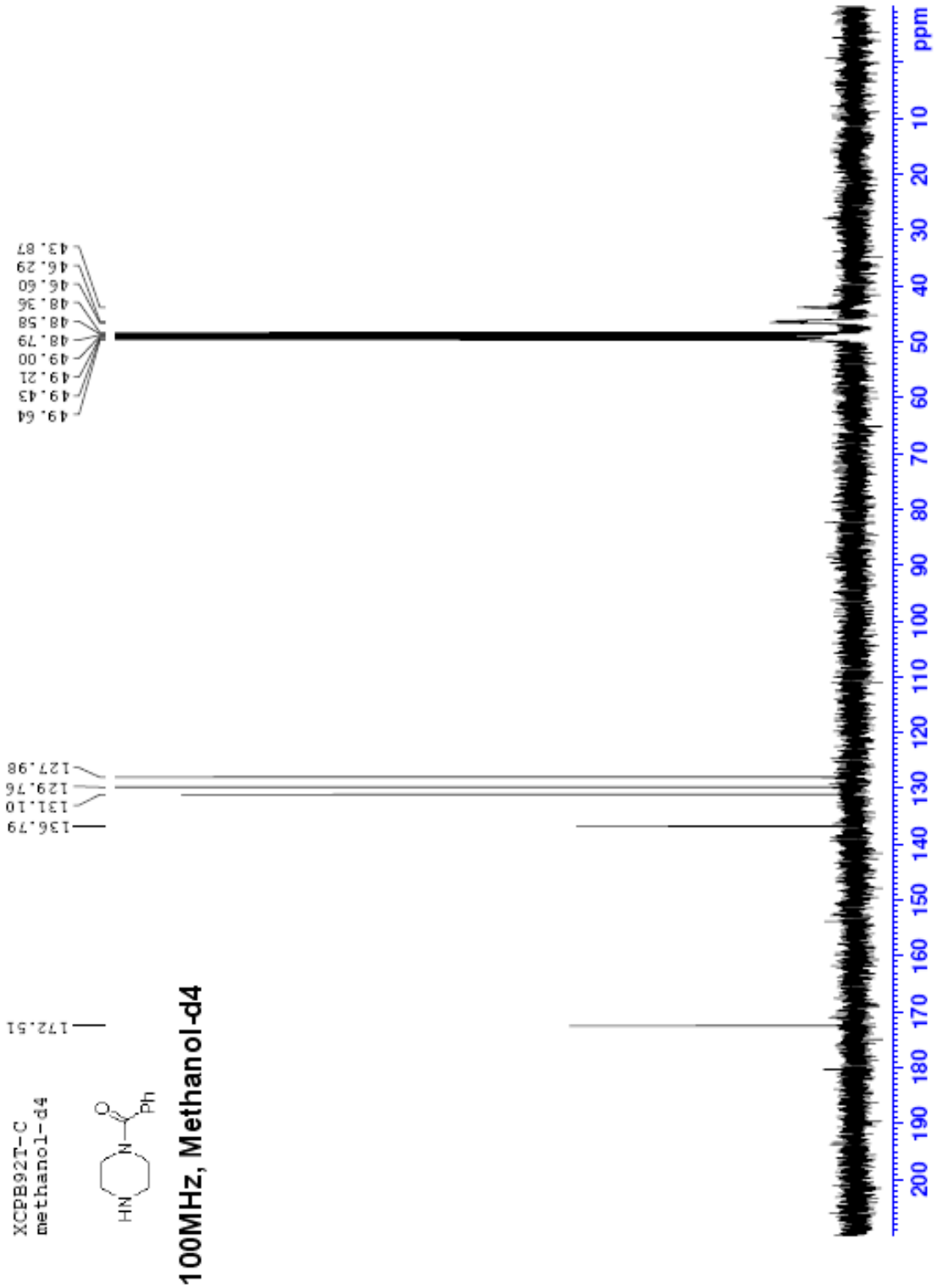
To 50 mg of 20% $Pd(OH)_2/C$ was added a solution of compound (2*R*,4*S*,5*R*)-**23** (16 mg, 0.047 mmol) in 5 mL of MeOH. The mixture was hydrogenated under 1 atm hydrogen pressure and stirred at room temperature for 15 h. The mixture was filtered through celite and the filtrate was evaporated in *vacuo* to afford **24** (8.1 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ +55.2 (*c* 0.63, MeOH), IR (film): 1024, 1093, 1334, 1383, 1629, 3317 cm^{-1}; ^{1}H-NMR (400 MHz, D_2O) δ 2.40 (ddd, *J* = 5.4, 8.5, 13.9 Hz, 1H), 2.49 (ddd, *J* = 5.4, 8.5, 13.9 Hz, 1H), 3.13 (s, 3H), 3.55 (dd, *J* = 4.6, 9.2 Hz, 1H), 3.92 (dd, *J* = 4.6, 12.9 Hz, 1H), 4.03 (dd, *J* = 4.6, 12.9 Hz, 1H), 4.25 (t, *J* = 8.5 Hz, 1H), 4.39 (dd, *J* = 5.4, 9.2 Hz, 1H); ^{13}C-NMR (100 MHz, D_2O) δ 36.5, 42.4, 56.7, 69.9, 70.2, 76.3, 172.7; MS (ESI): 198 *m/z* ($M+Na^+$, 100). ESI-HRMS: calcd for [$C_7H_{13}NO_4$ + H^+]: 176.0923; found: 176.0937.

1-(3,4-Dimethylphenyl)-4-methylpiperazine (26)



Following the general procedure, the reaction of 1-(3,4-dimethylphenyl)piperazine (**25**) (0.1 mmol, 19 mg) in MeOH (5 mL) and in the presence of 10% Pd/C (100 mg) gave **26** as a yellow oil (14.9 mg, 73%). IR (film) ν_{max}: 2967, 2936, 2793, 1622, 1507, 1449, 1375, 1293, 1244, 1153, 1000 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, 3H), 2.23 (s, 3H), 2.36 (s, 3H), 2.59 (t, *J* = 5.0 Hz, 4H), 3.17 (t, *J* = 5.0 Hz, 4H), 6.69 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7, 20.1, 46.1, 49.7, 55.2, 113.8, 118.1, 128.0, 130.2, 137.1, 149.6; MS (ESI): *m/z* 205.1 ($M+H^+$, 100). ESI-HRMS: calcd for [$C_{13}H_{20}N_2+H^+$]: 205.1705; found: 205.1696.


XCPB92T-H
methanol-d4
400MHz, Methanol-d4
Ph
N
O
HN
4.94
2.00
2.04
4.01
ppm
0
1
2
3
4
5
6
7
8
9
10
11


XCPB92T-C
methanol-d4
100MHz, Methanol-d4
172.51
136.79
131.10
129.76
127.98
49.64
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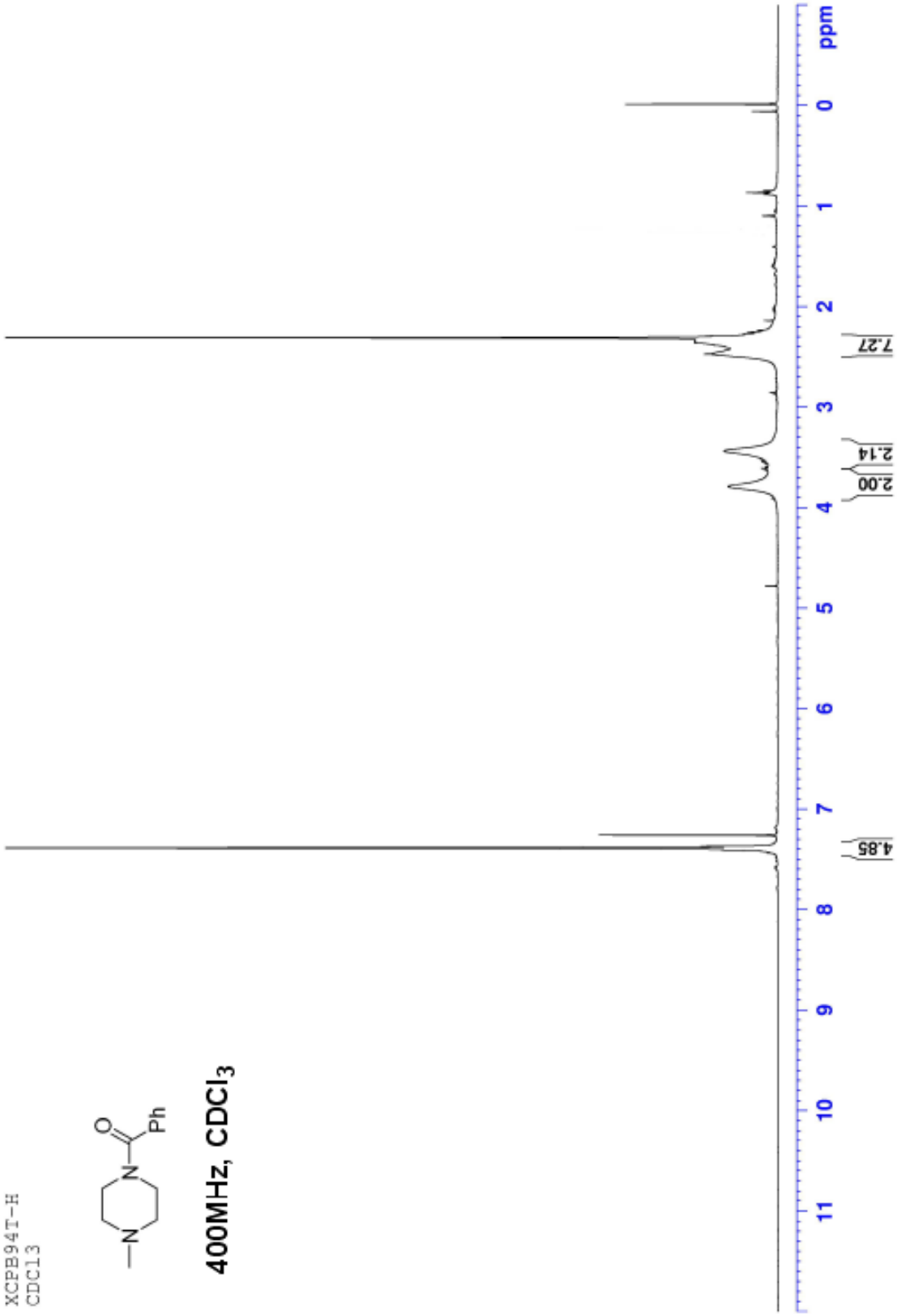
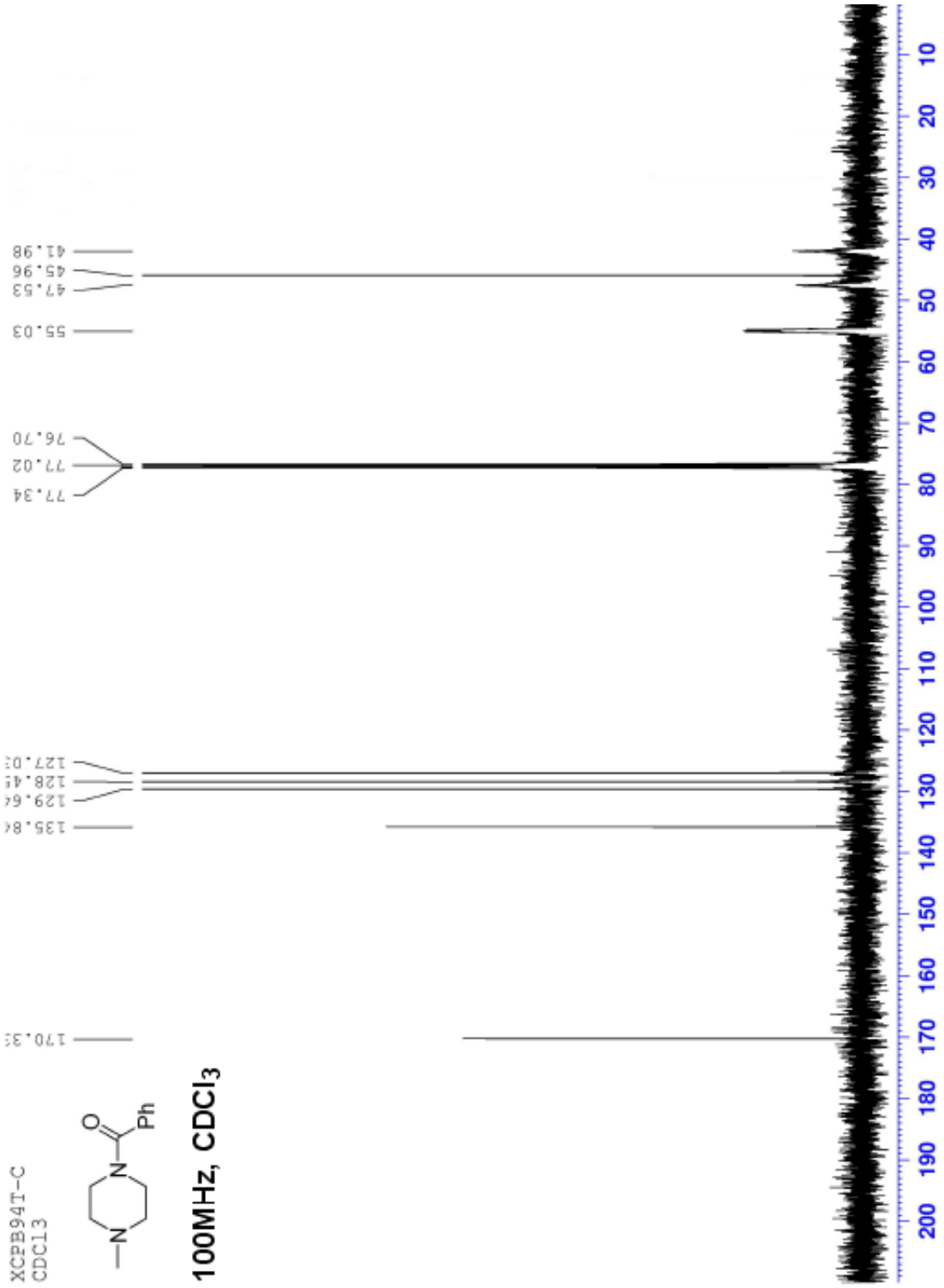
48.58
48.36
46.60
46.29
43.87
ppm


XCPB94T-H
CDCl3
400MHz, CDCl3
O
Ph
N
N
ppm
0
1
2
3
4
5
6
7
8
9
10
11
7.27
2.14
2.00
4.85


XCPB94T-C
CDCl3
100MHz, CDCl3
O
Ph
N
N
41.98
45.96
47.53
55.03
76.70
77.02
77.34
127.03
128.41
129.64
135.84
170.33
10
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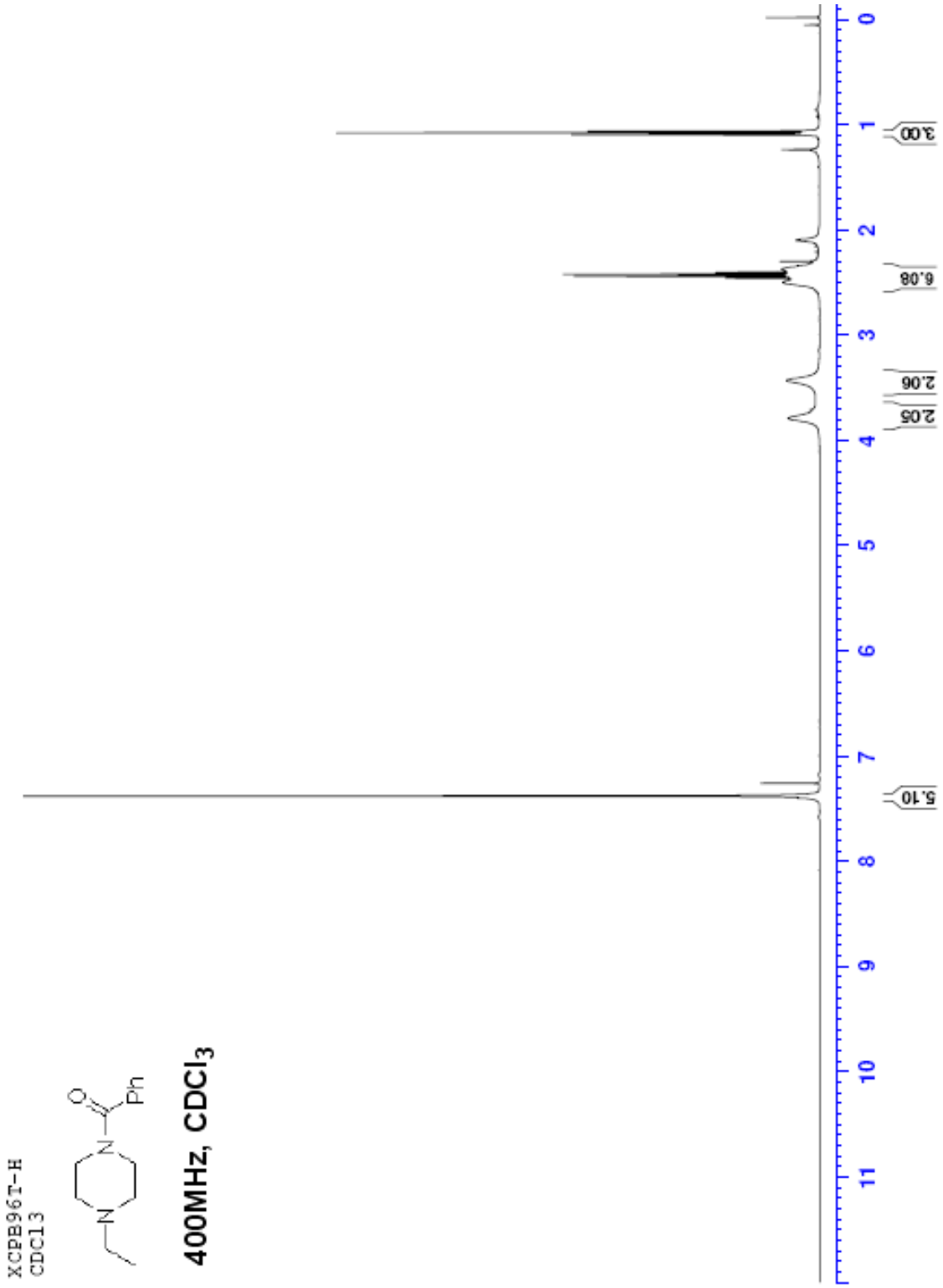
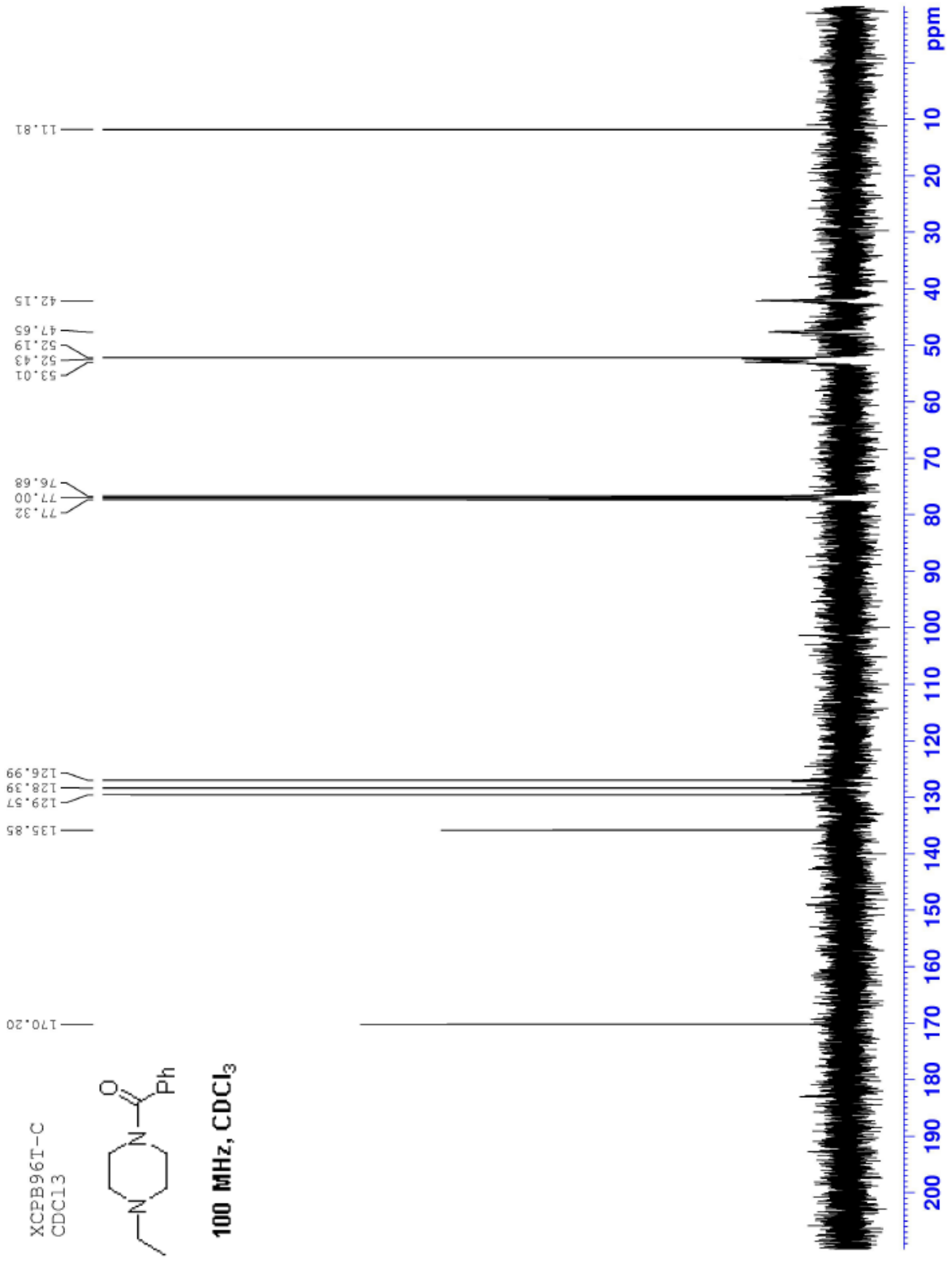
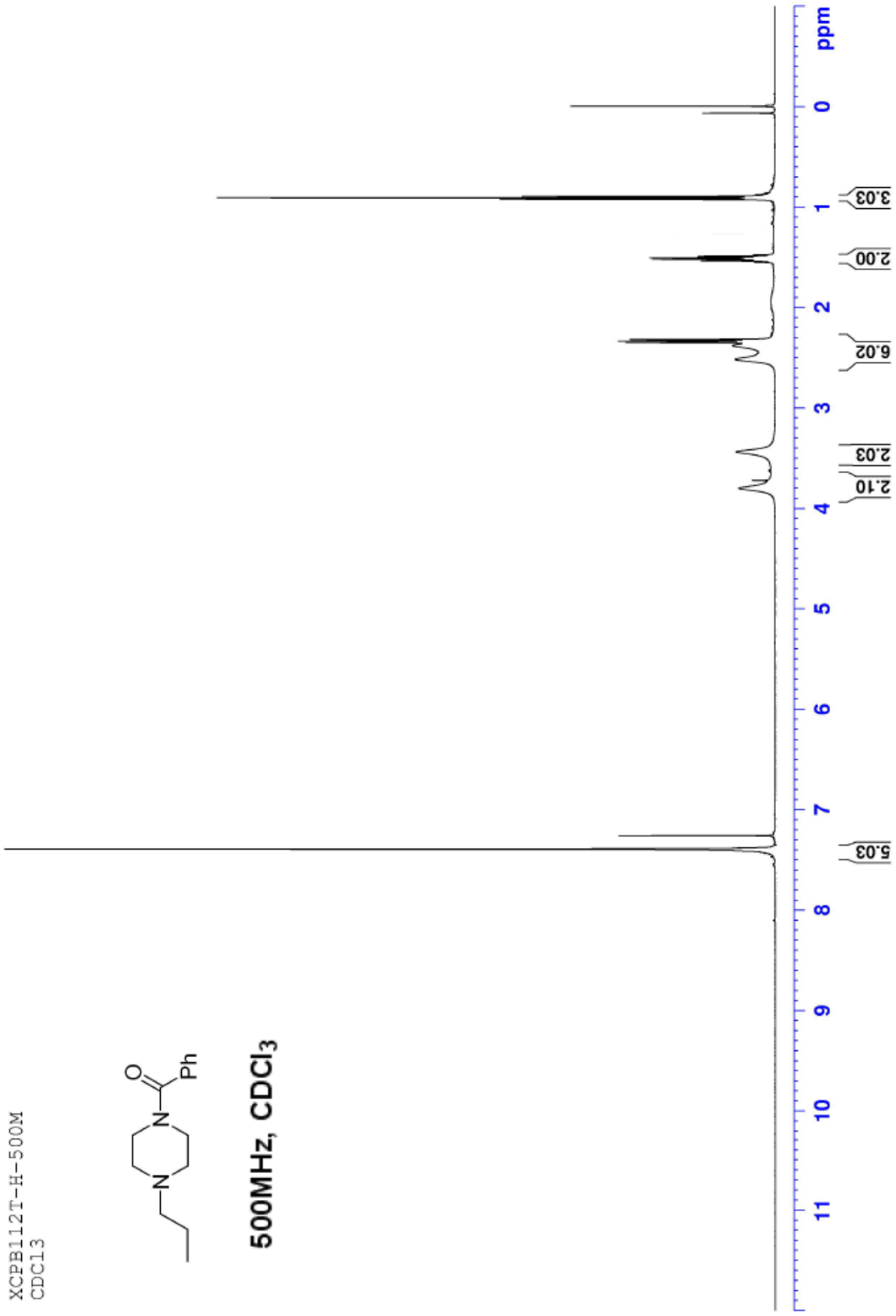
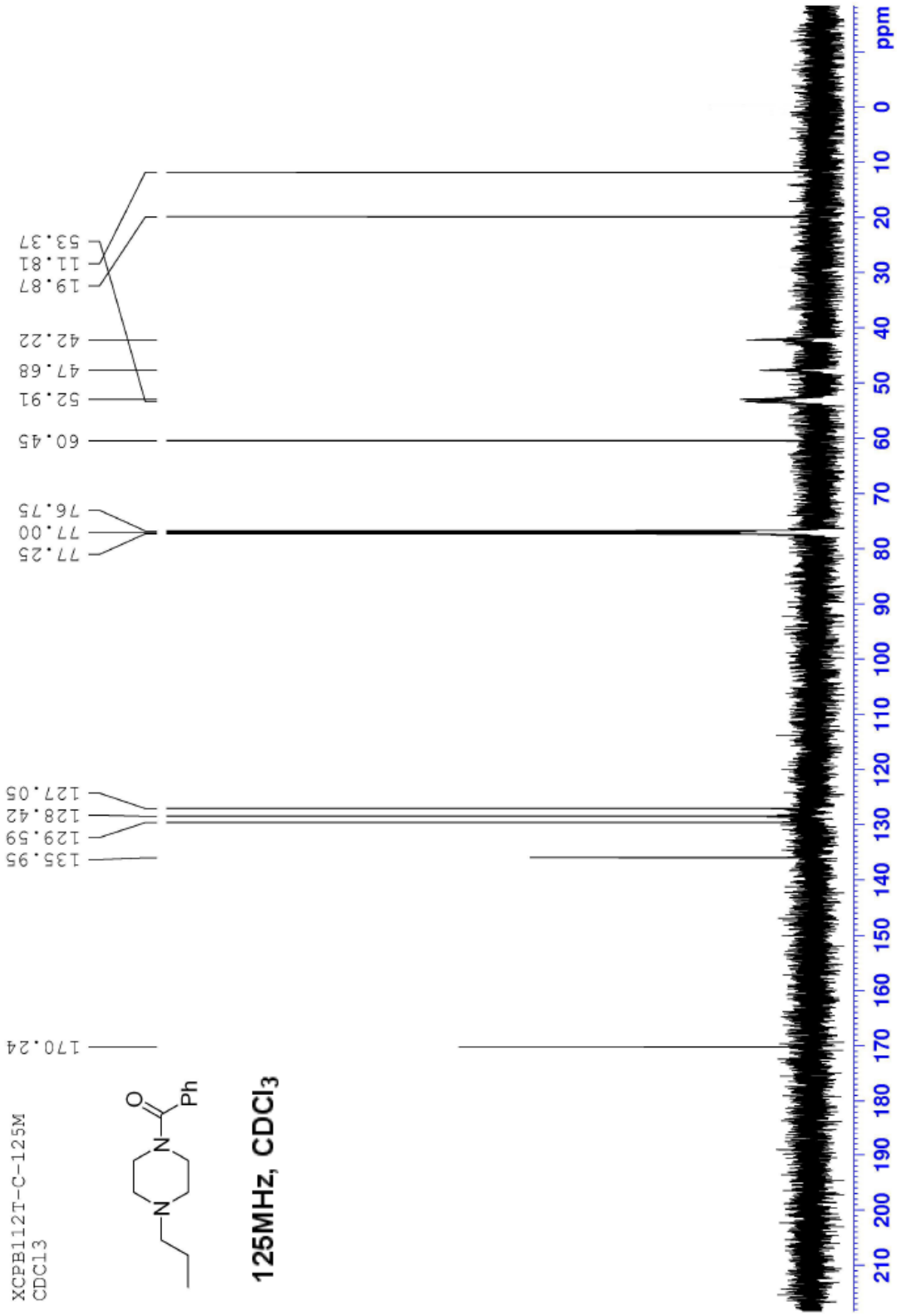
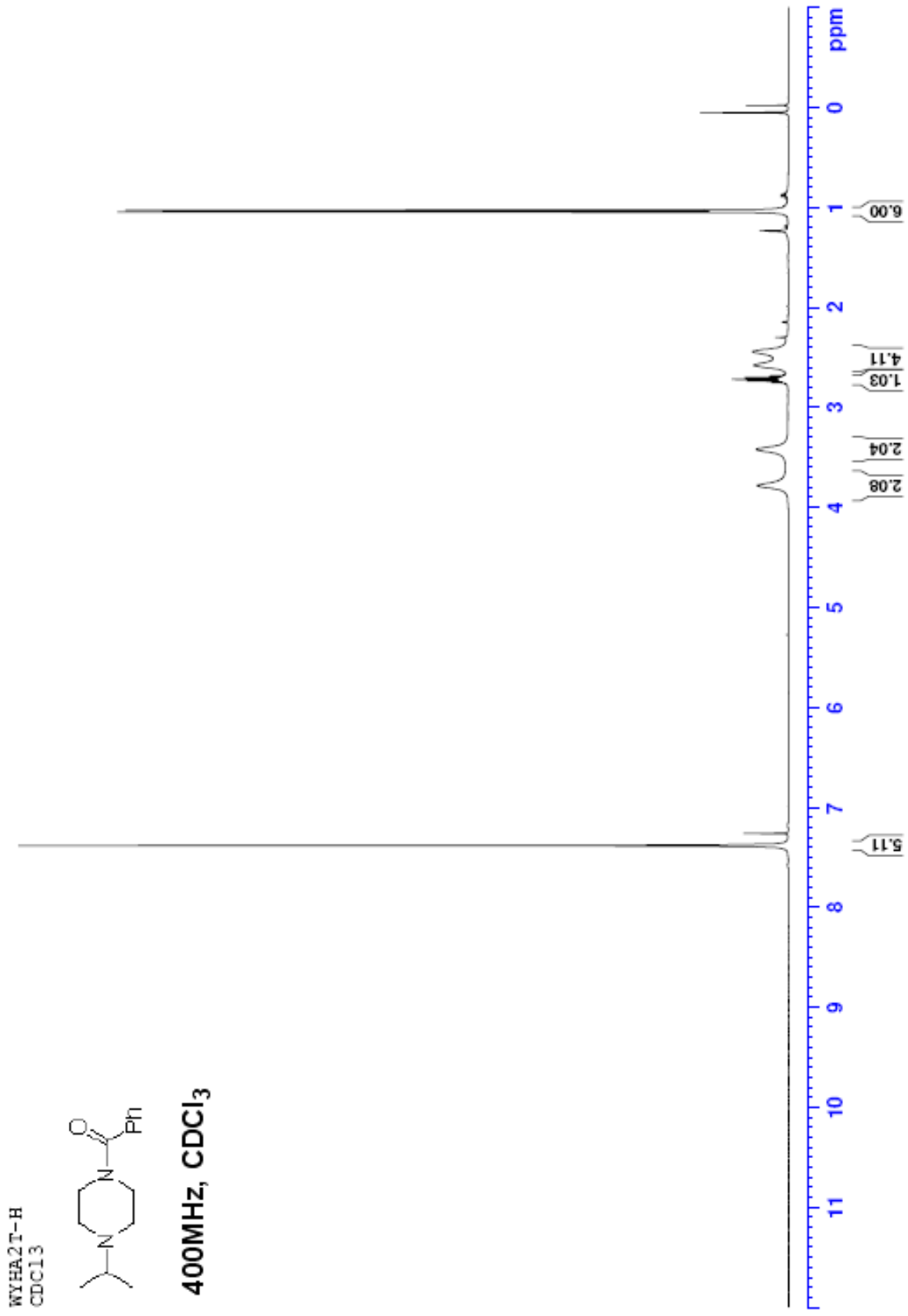
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

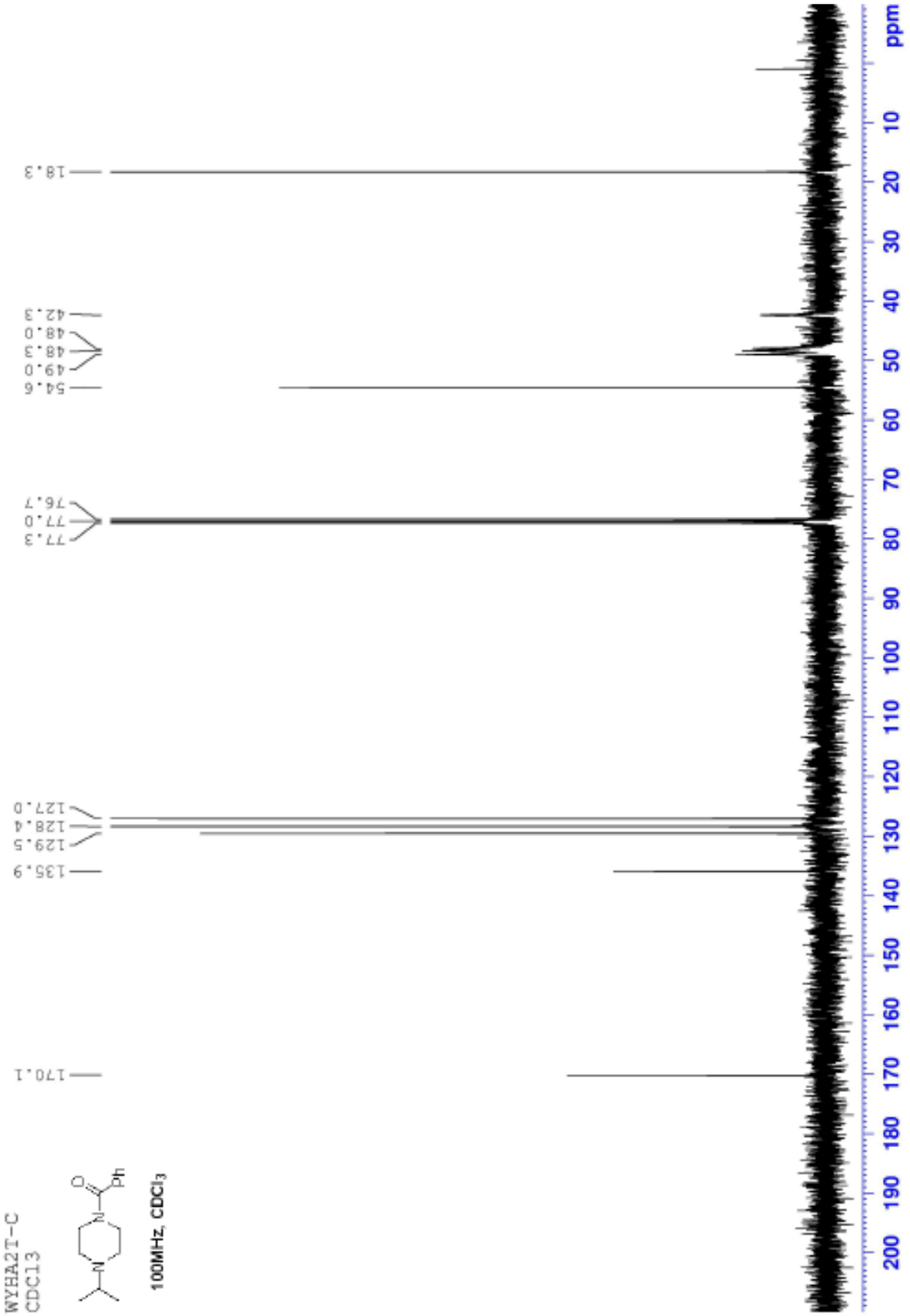

XCPB96T-H
CDCl3
400MHz, CDCl3
Ph
O
N
N
5.10
3.00
6.08
2.06
2.05
0
1
2
3
4
5
6
7
8
9
10
11

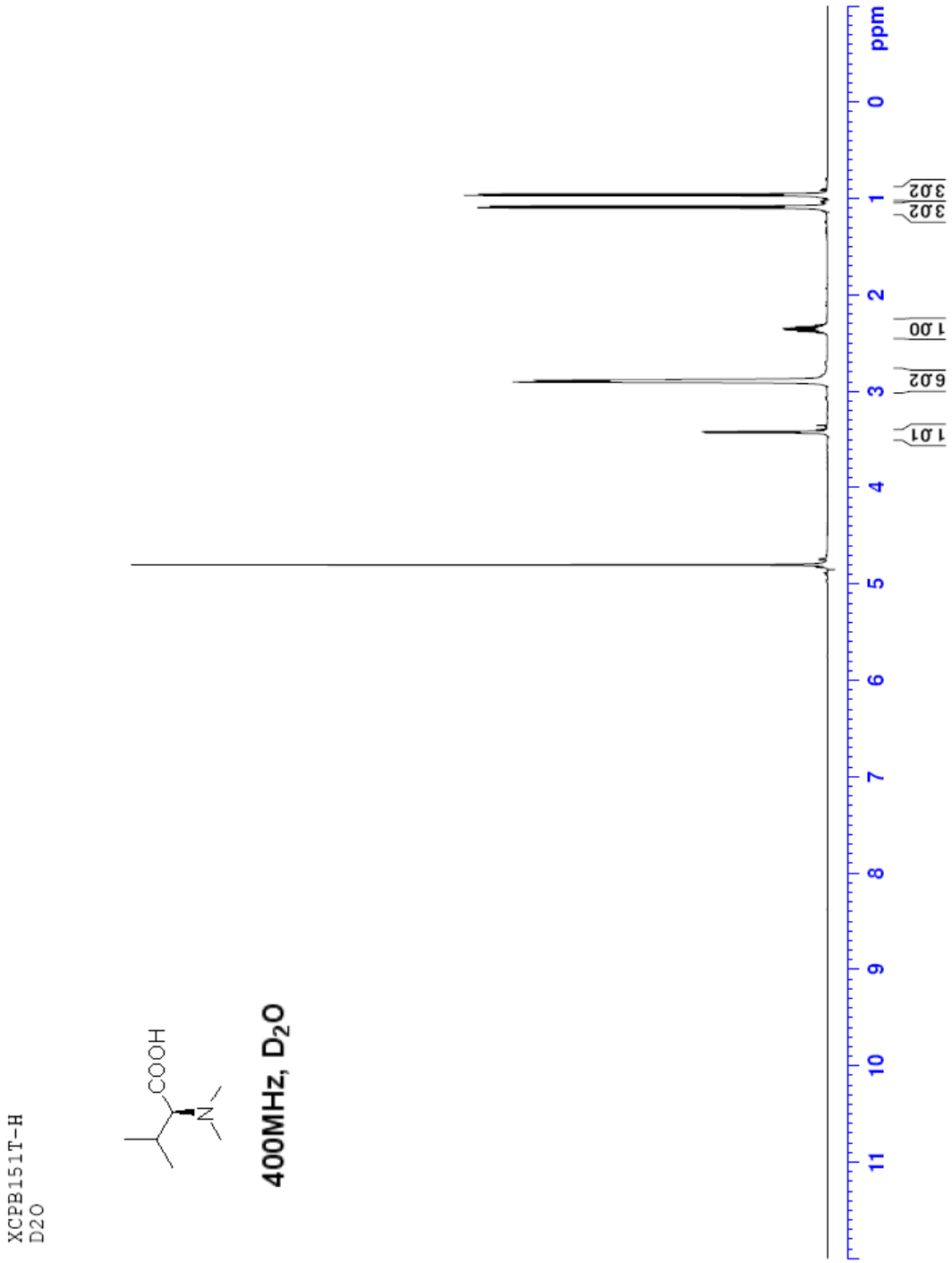

XCPB96T-C
CDCl3
100 MHz, CDCl3
O
N
Ph
N
170.20
135.85
129.57
128.39
126.99
77.32
77.00
76.68
53.01
52.43
52.19
47.65
42.15
11.81
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200


XCPB112T-H-500M
CDCl3
500MHz, CDCl3
O
N
N
Ph
ppm
0
1
2
3
4
5
6
7
8
9
10
11
3.03
2.00
6.02
2.03
2.10
5.03


XCPB112T-C-125M
CDCl3
125MHz, CDCl3
O
N
N
Ph
170.24
135.95
129.59
128.42
127.05
77.25
77.00
76.75
60.45
52.91
47.68
42.22
19.87
11.81
53.37
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


WYHA2T-H
CDCl3
400MHz, CDCl3
O
Ph
N
N
ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.00
4.11
1.03
2.04
2.08
5.11


WYHA2T-C
CDCl3
100MHz, CDCl3
O
Ph
N
N
18.3
42.3
48.0
48.3
49.0
54.6
76.7
77.0
77.3
127.0
128.4
129.5
135.9
170.1
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200


XCPB151T-H
D2O
COOH
N
400MHz, D2O
ppm
0
1
2
3
4
5
6
7
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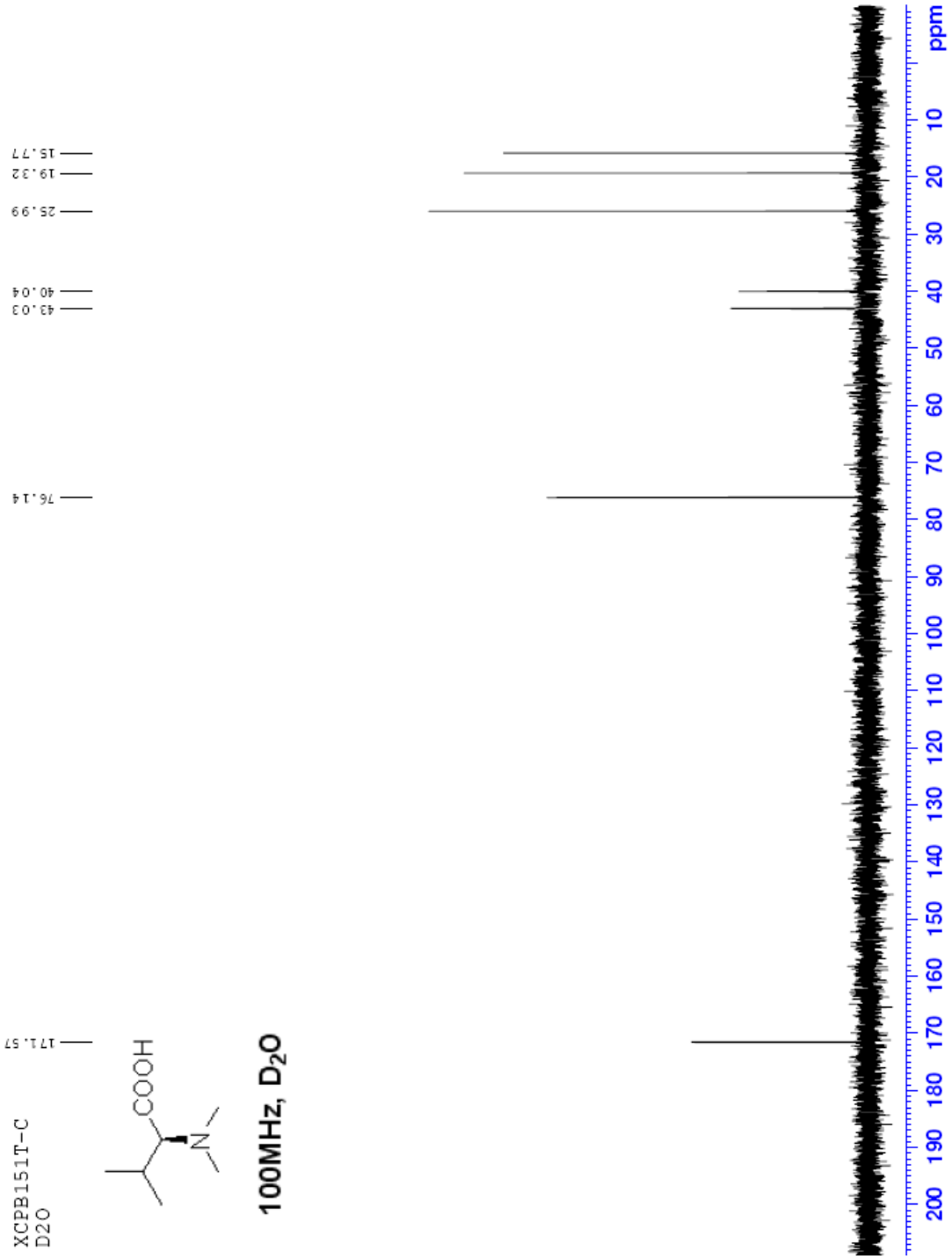
11
3.02
3.02
1.00
6.02
1.01


XCPB151T-C
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COOH
N
100MHz, D2O
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25.99
40.04
43.03
76.14
171.57
ppm
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20
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50
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110
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130
140
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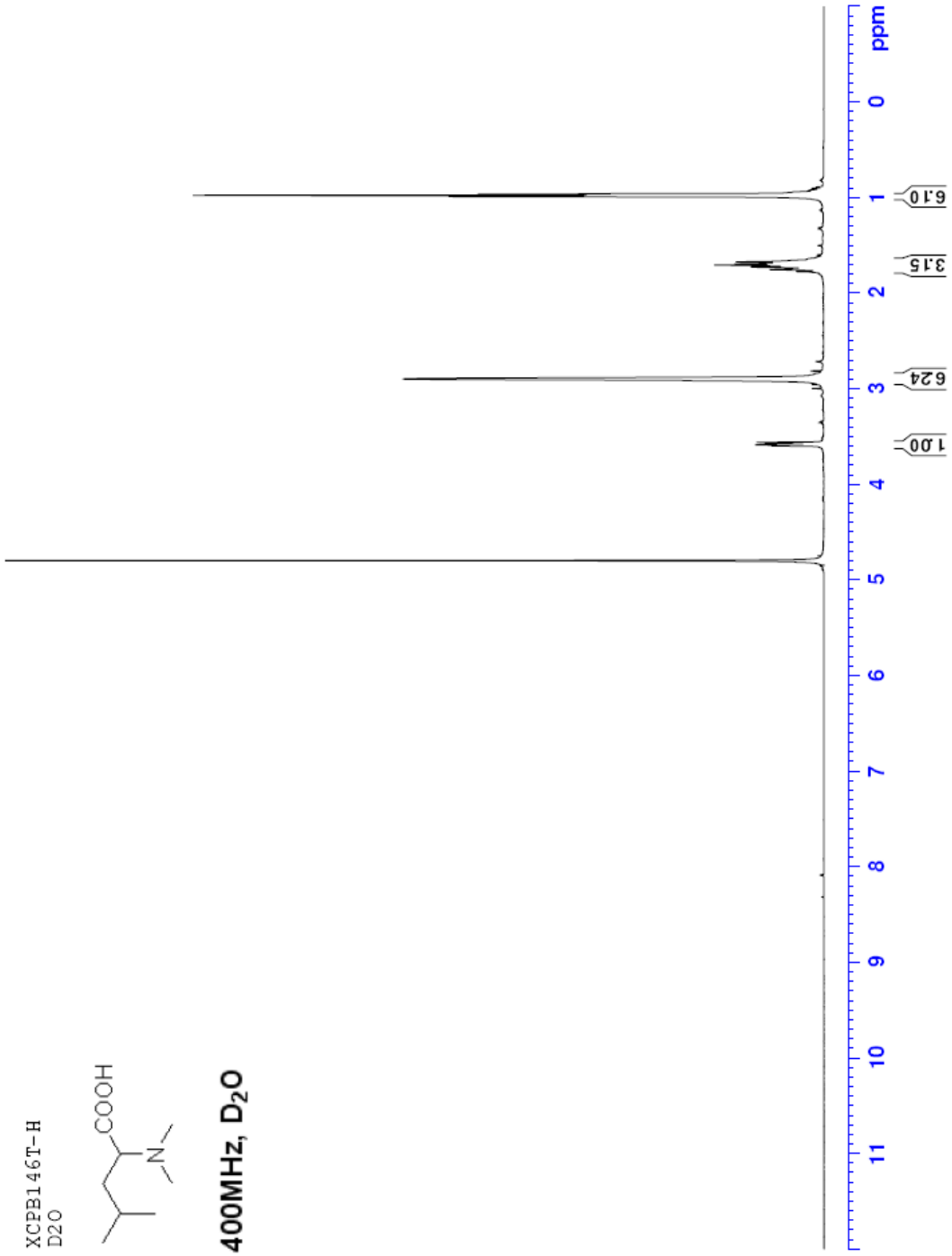
170
180
190
200


XCPB146T-H
D2O
COOH
N
400MHz, D2O
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3.15
6.24
1.00
ppm
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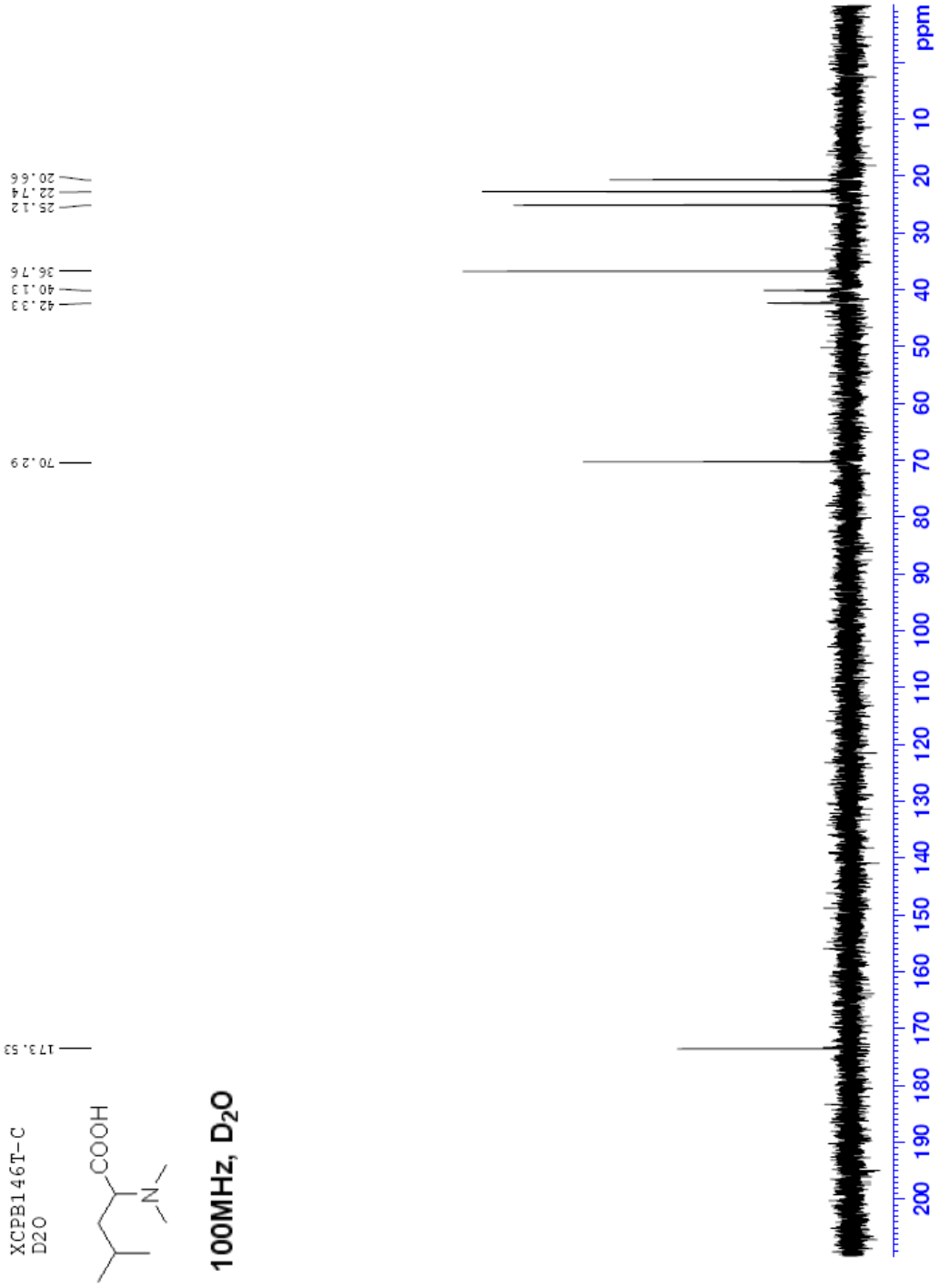
1
2
3
4
5
6
7
8
9
10
11


XCPB146T-C
D2O
COOH
N
100MHz, D2O
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70.29
42.33
40.13
36.76
25.12
22.74
20.66
ppm
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20
30
40
50
60
70
80
90
100
110
120
130
140
150
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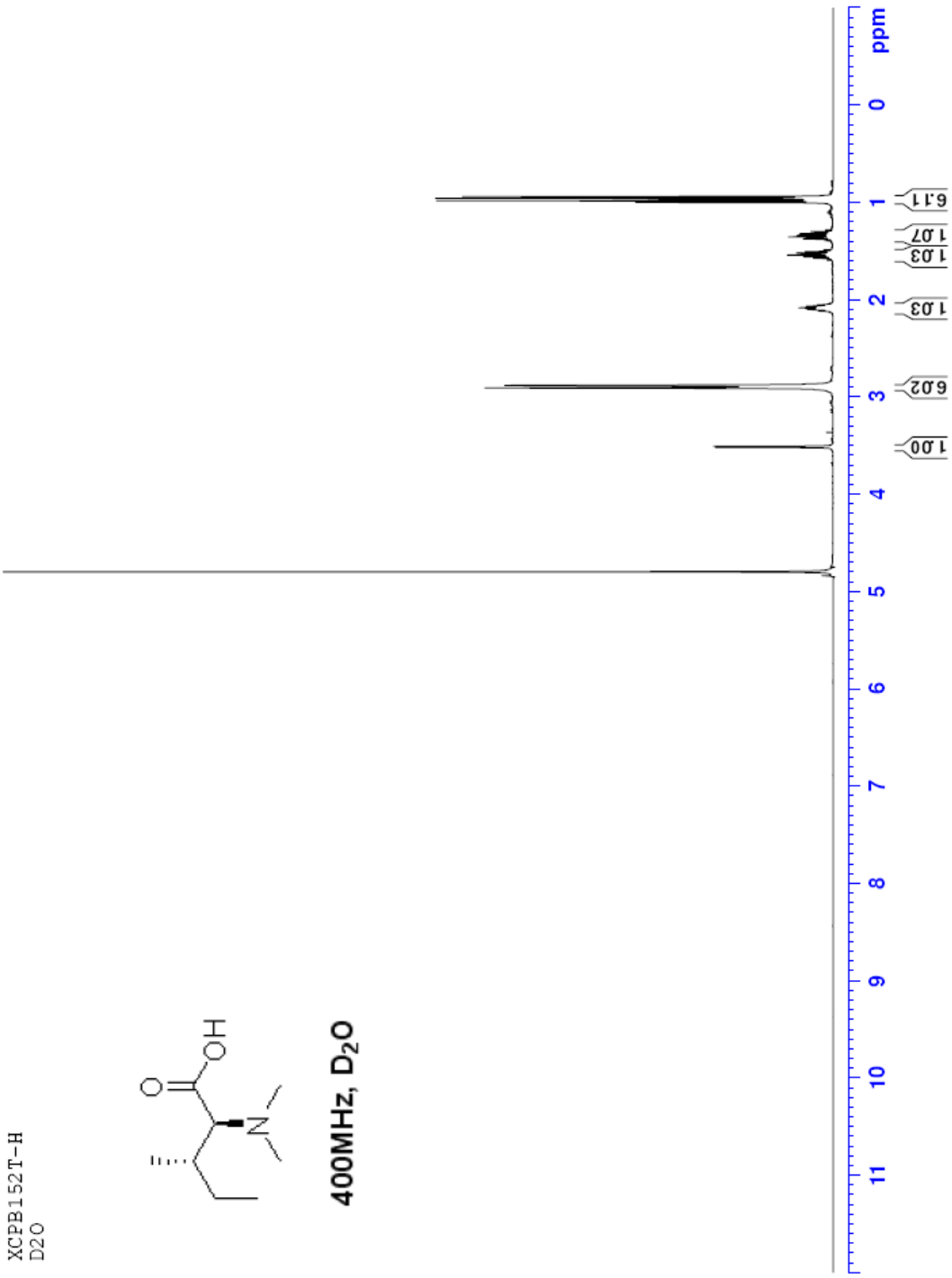
170
180
190
200


XCPB152T-H
D2O
400MHz, D2O
ppm
0
1
2
3
4
5
6
7
8
9
10
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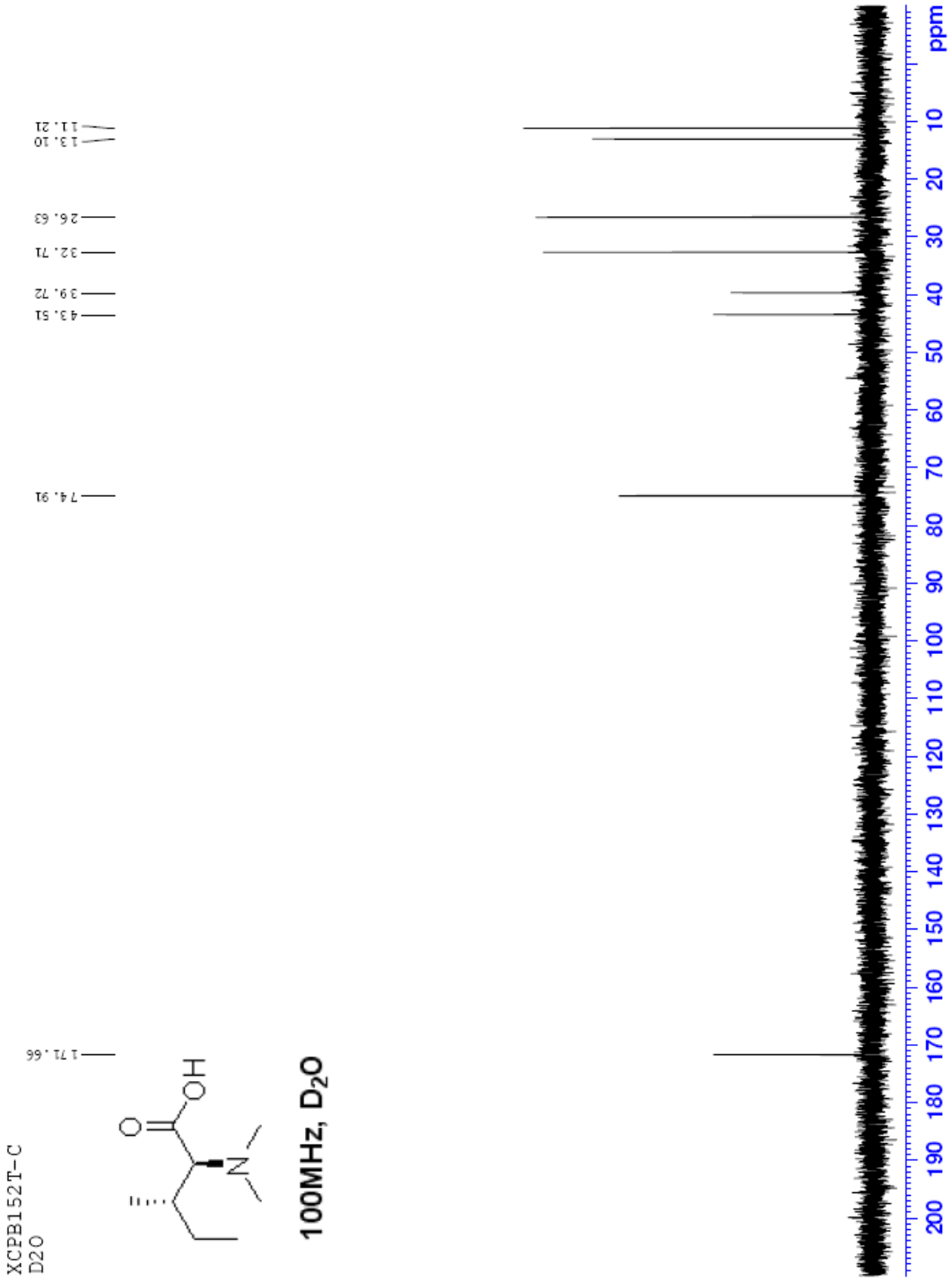
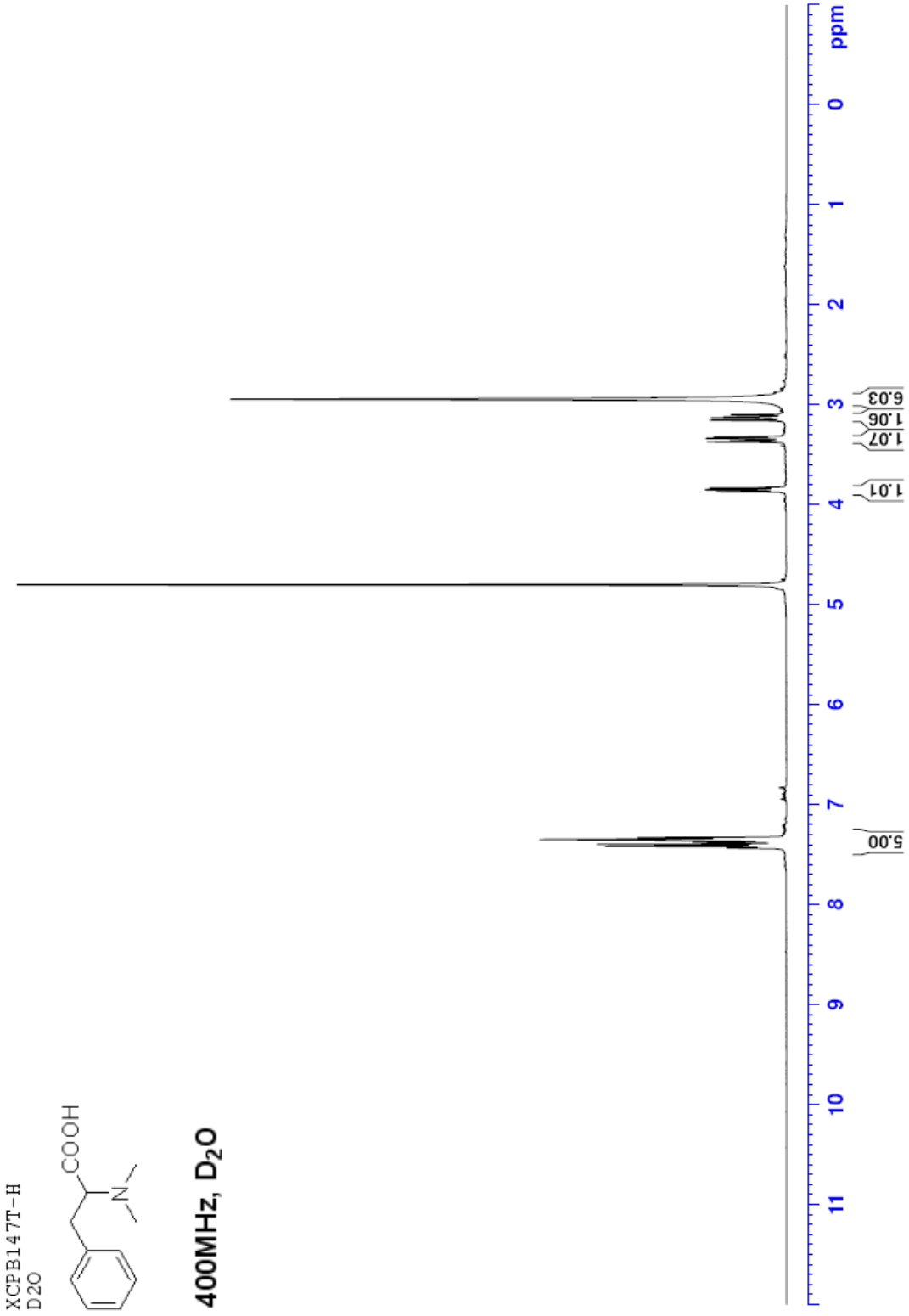
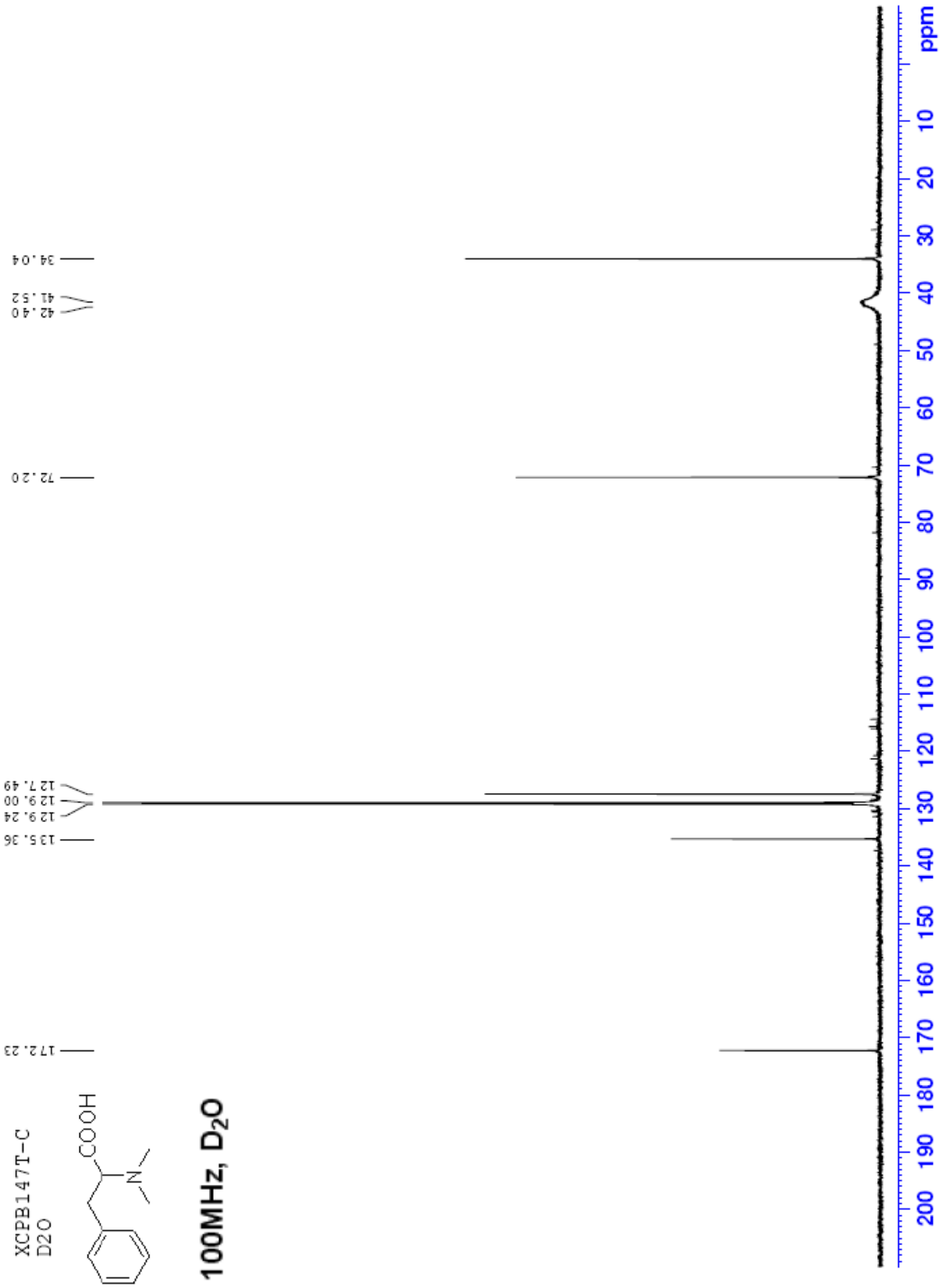
6.11
1.07
1.03
1.03
6.02
1.00


XCPB152T-C
D2O
100MHz, D2O
11.21
13.10
26.63
32.71
39.72
43.51
74.91
173.66
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200


XCPB147T-H
D2O
COOH
N
400MHz, D2O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.03
1.06
1.07
1.01
5.00


XCPB147T-C
D2O
COOH
N
100MHz, D2O
172.23
135.36
129.24
129.00
127.49
72.20
42.40
41.52
34.04
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
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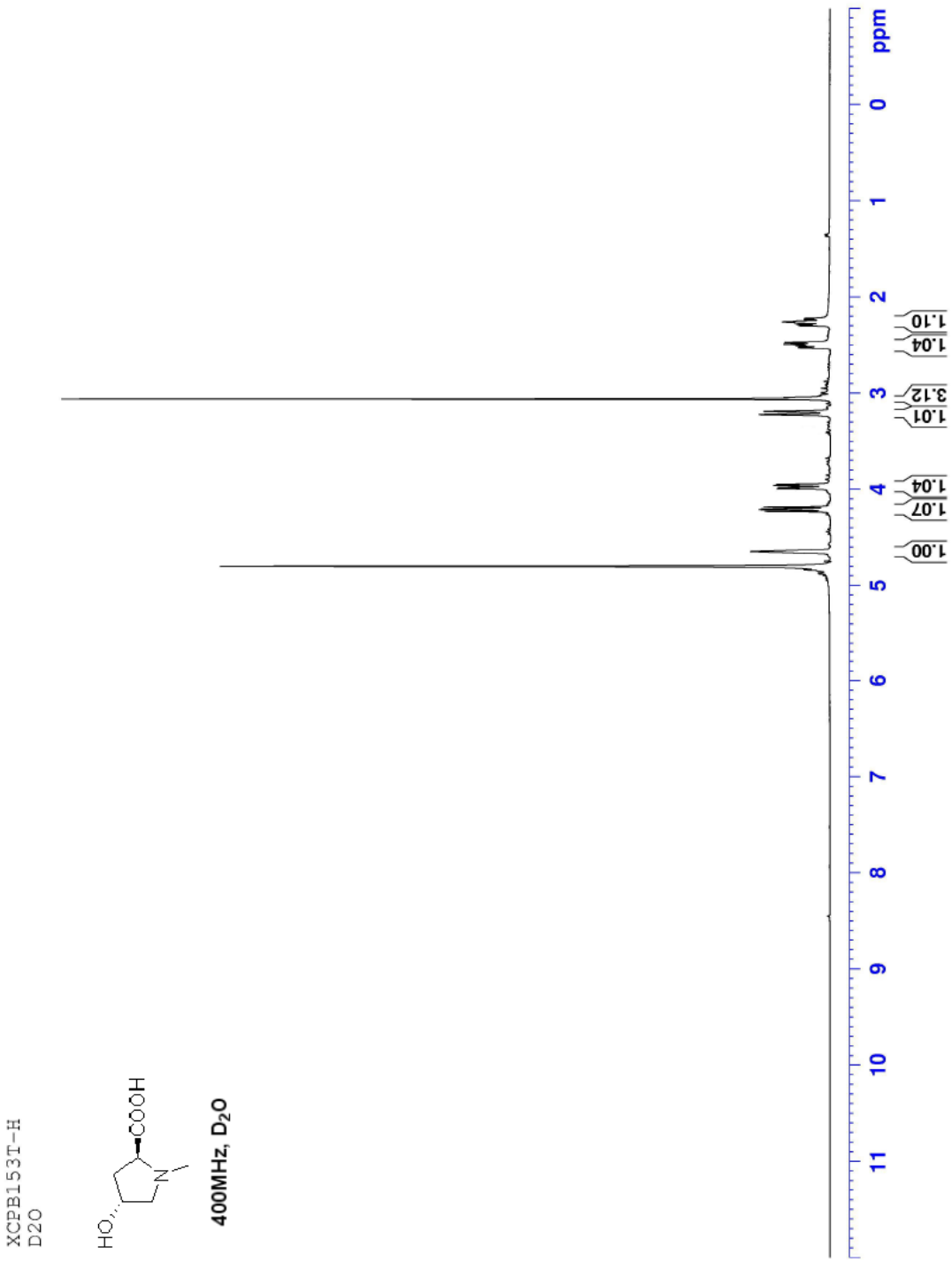
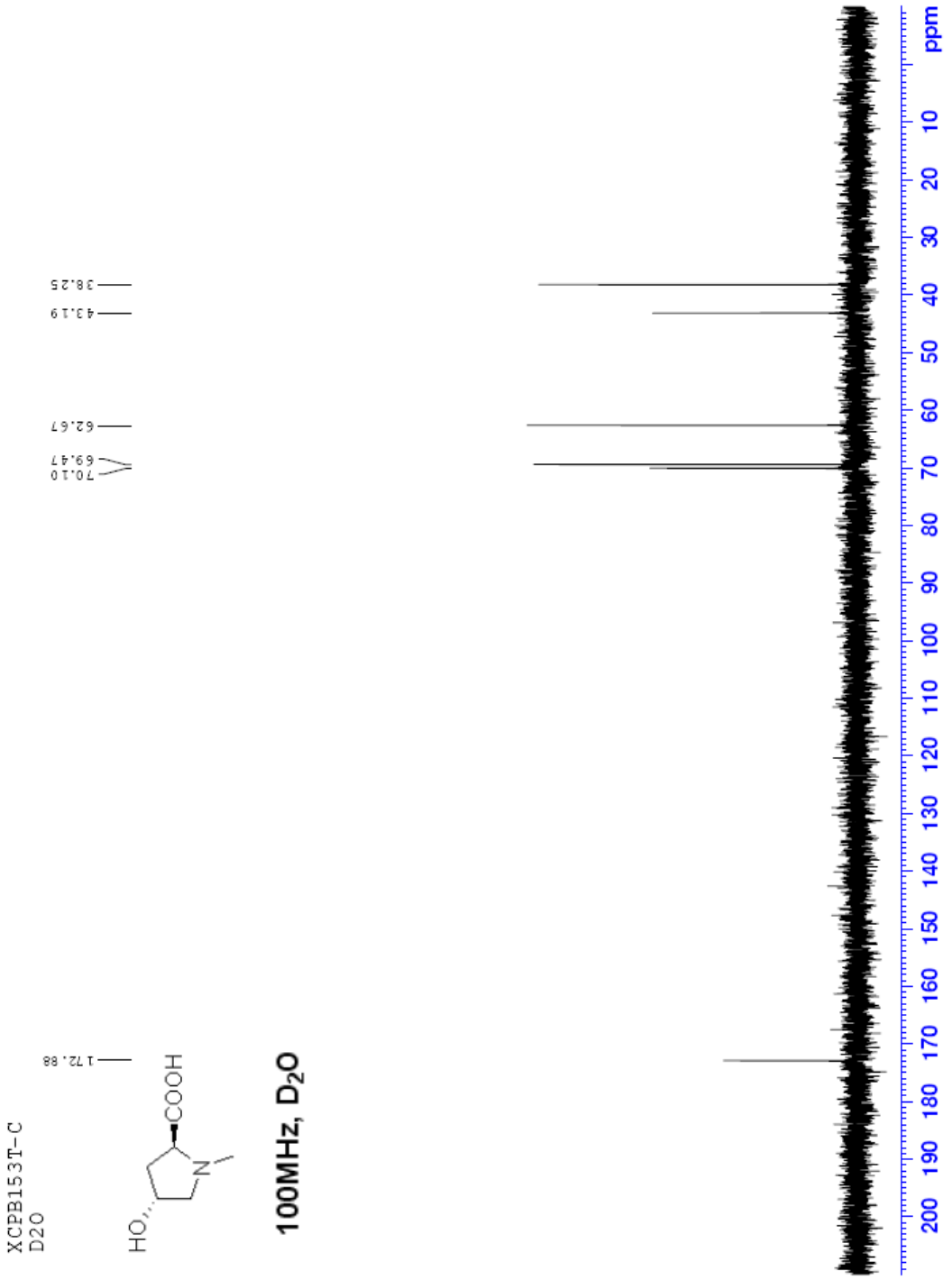
160
170
180
190
200


XCPB153T-H
D2O
400MHz, D2O
HO
COOH
N
ppm
0
1
2
3
4
5
6
7
8
9
10
11
1.00
1.07
1.04
3.12
1.01
1.04
1.10


XCPB153T-C
D2O
100MHz, D2O
HO
COOH
N
172.88
70.10
69.47
62.67
43.19
38.25
ppm
10
20
30
40
50
60
70
80
90
100
110
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130
140
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160
170
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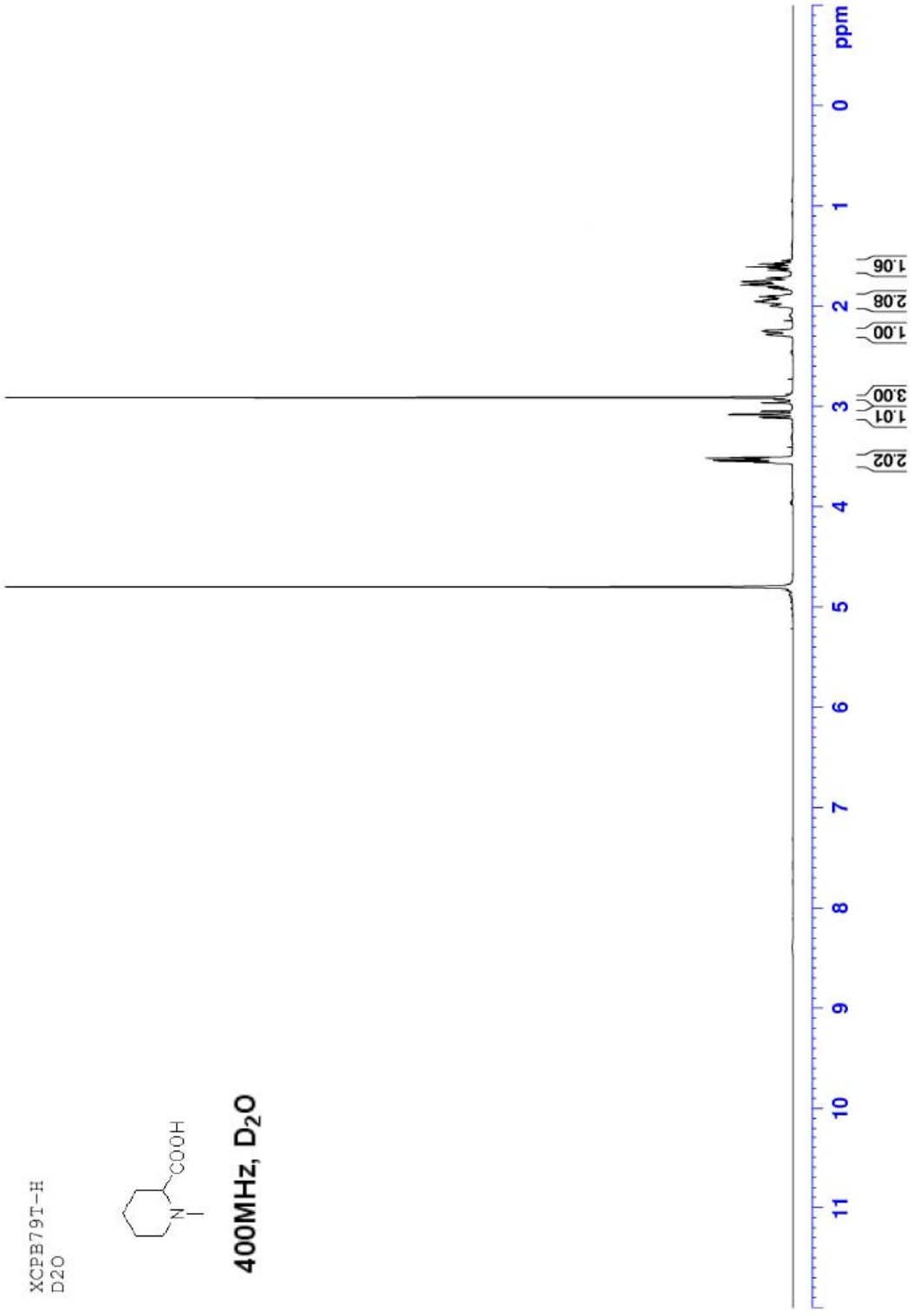
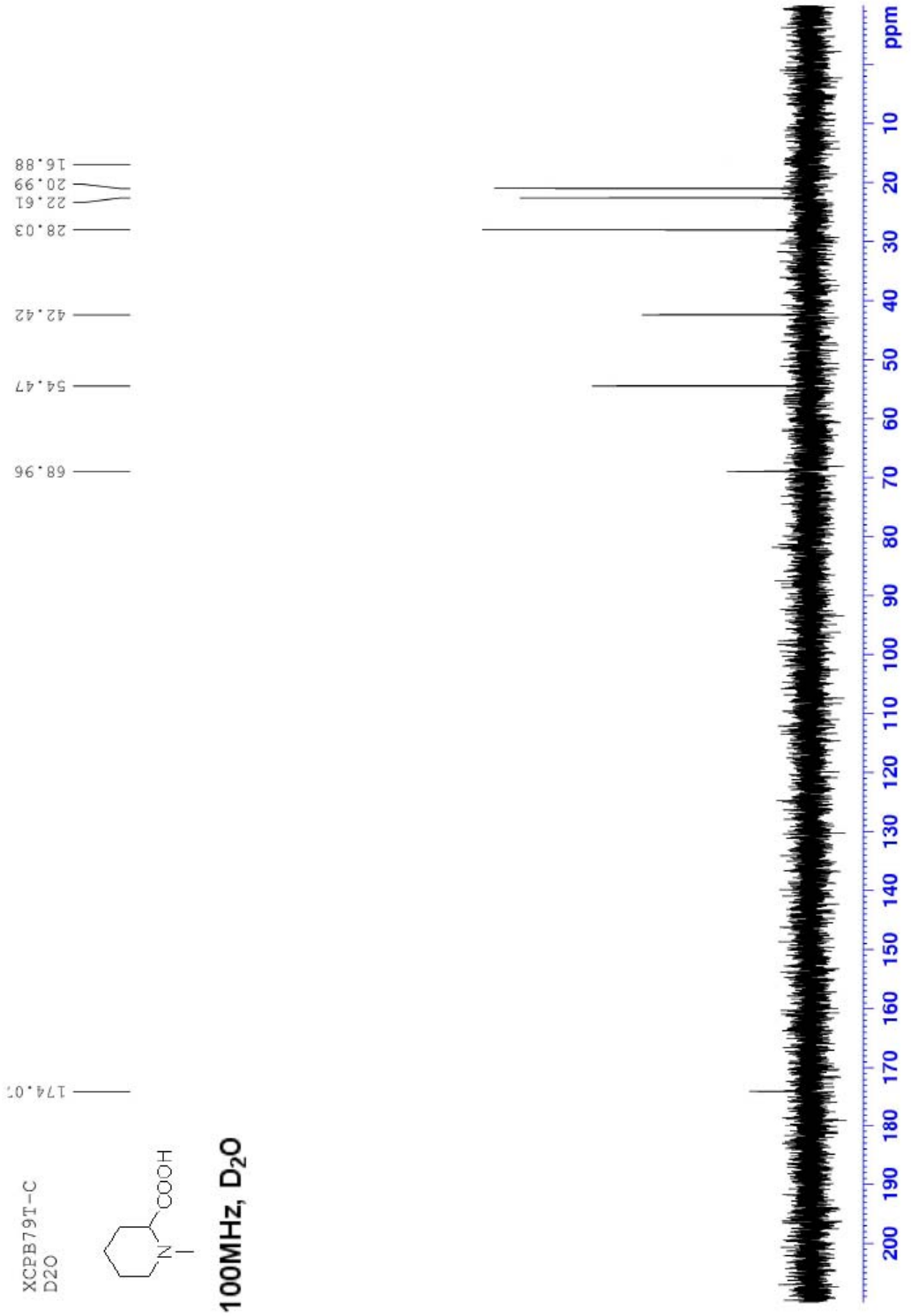
190
200


XCPB79T-H
D2O
COOH
N
H
400MHz, D2O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
1.06
2.08
1.00
3.00
1.01
2.02


XCPB79T-C
D2O
100MHz, D2O
COOH
N
174.01
68.96
54.47
42.42
28.03
22.61
20.99
16.88
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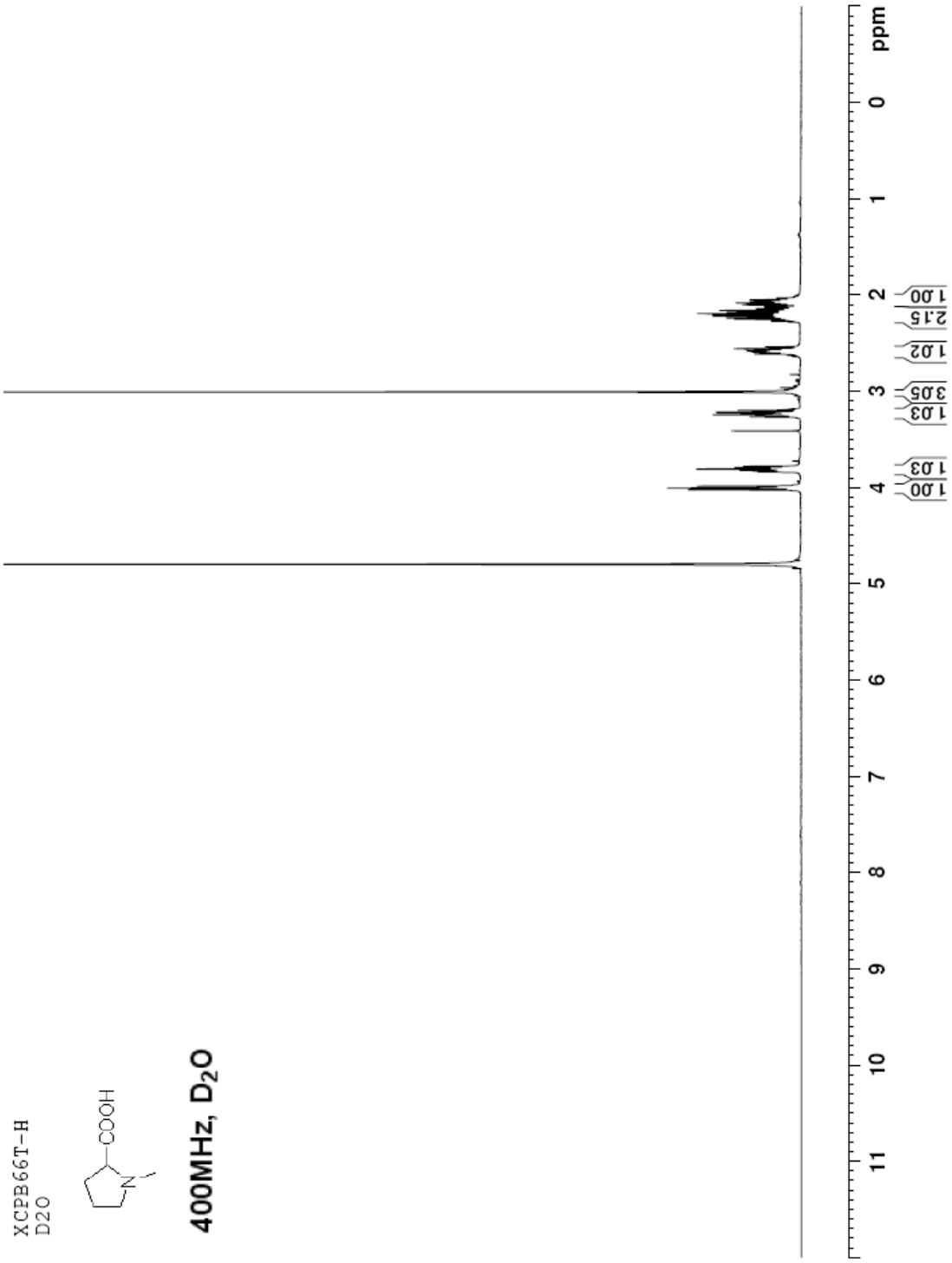
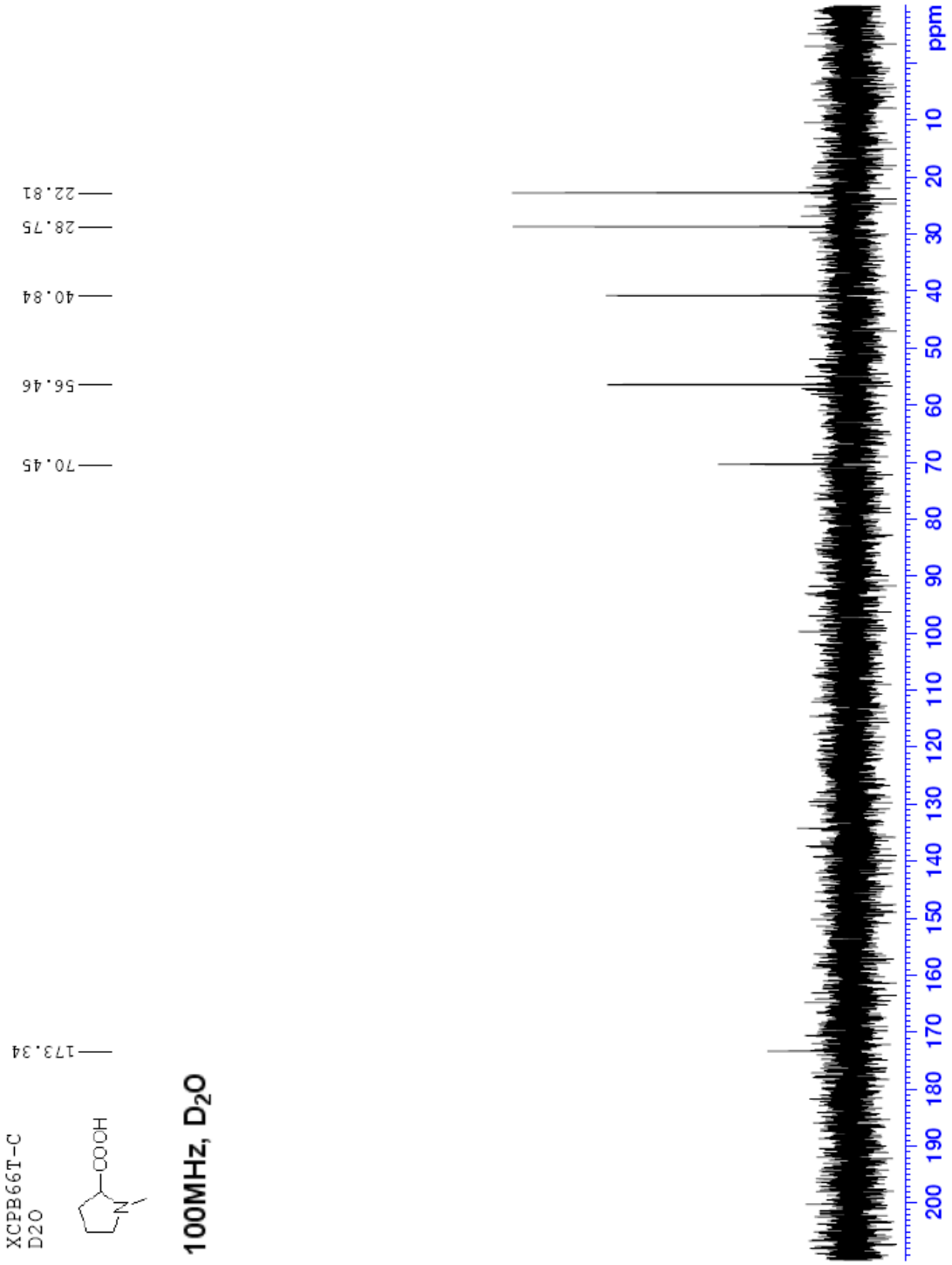
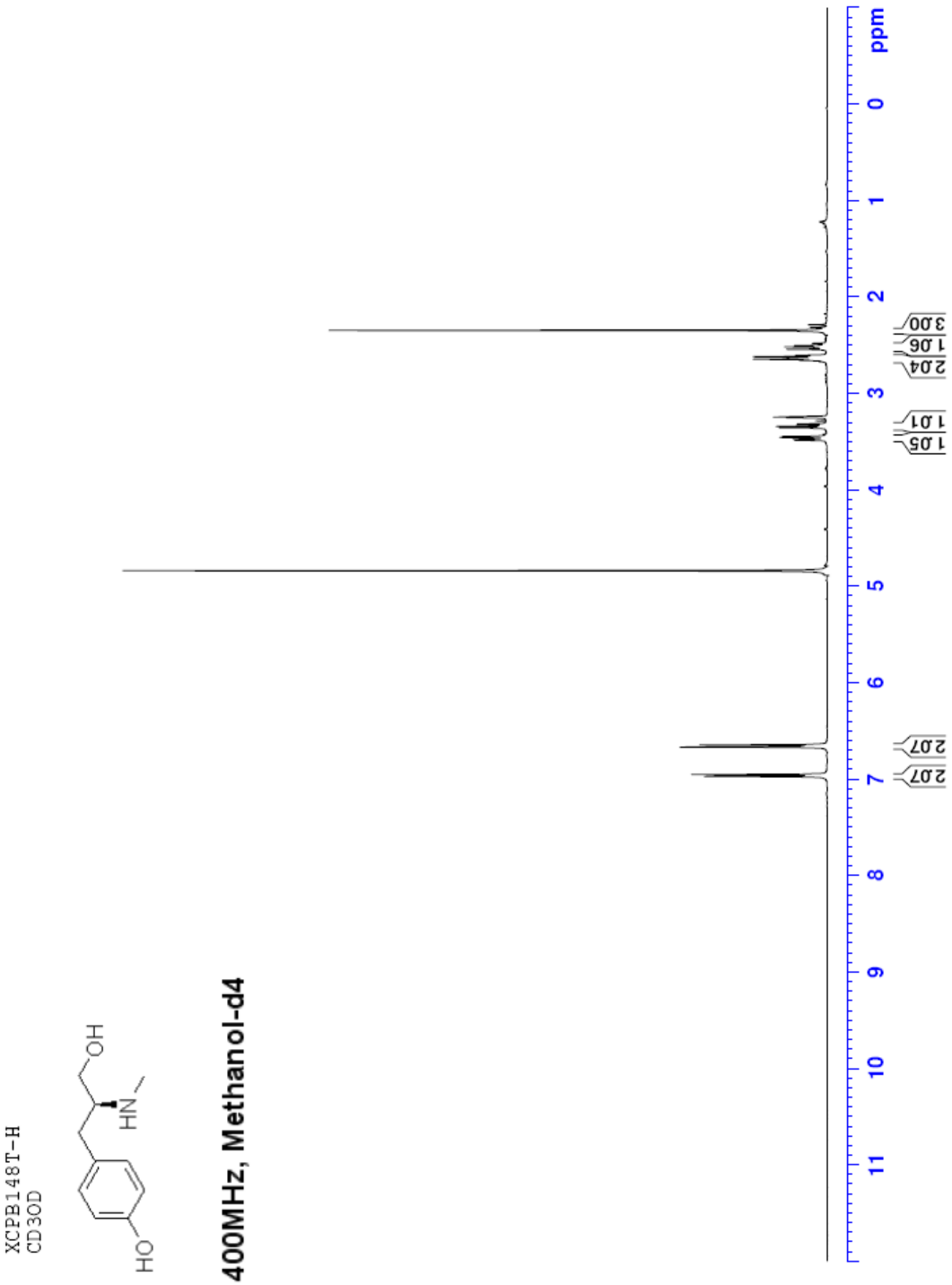
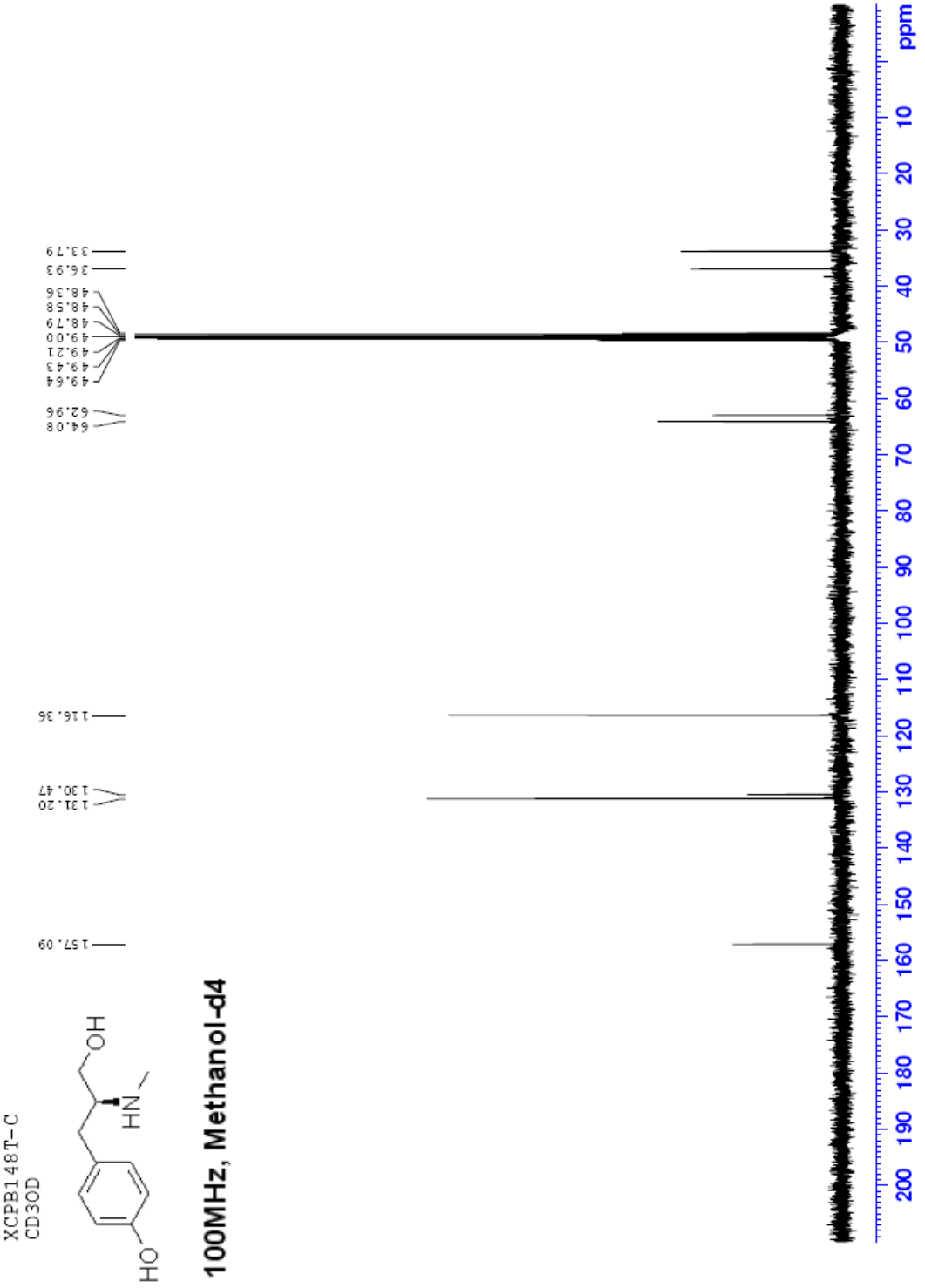
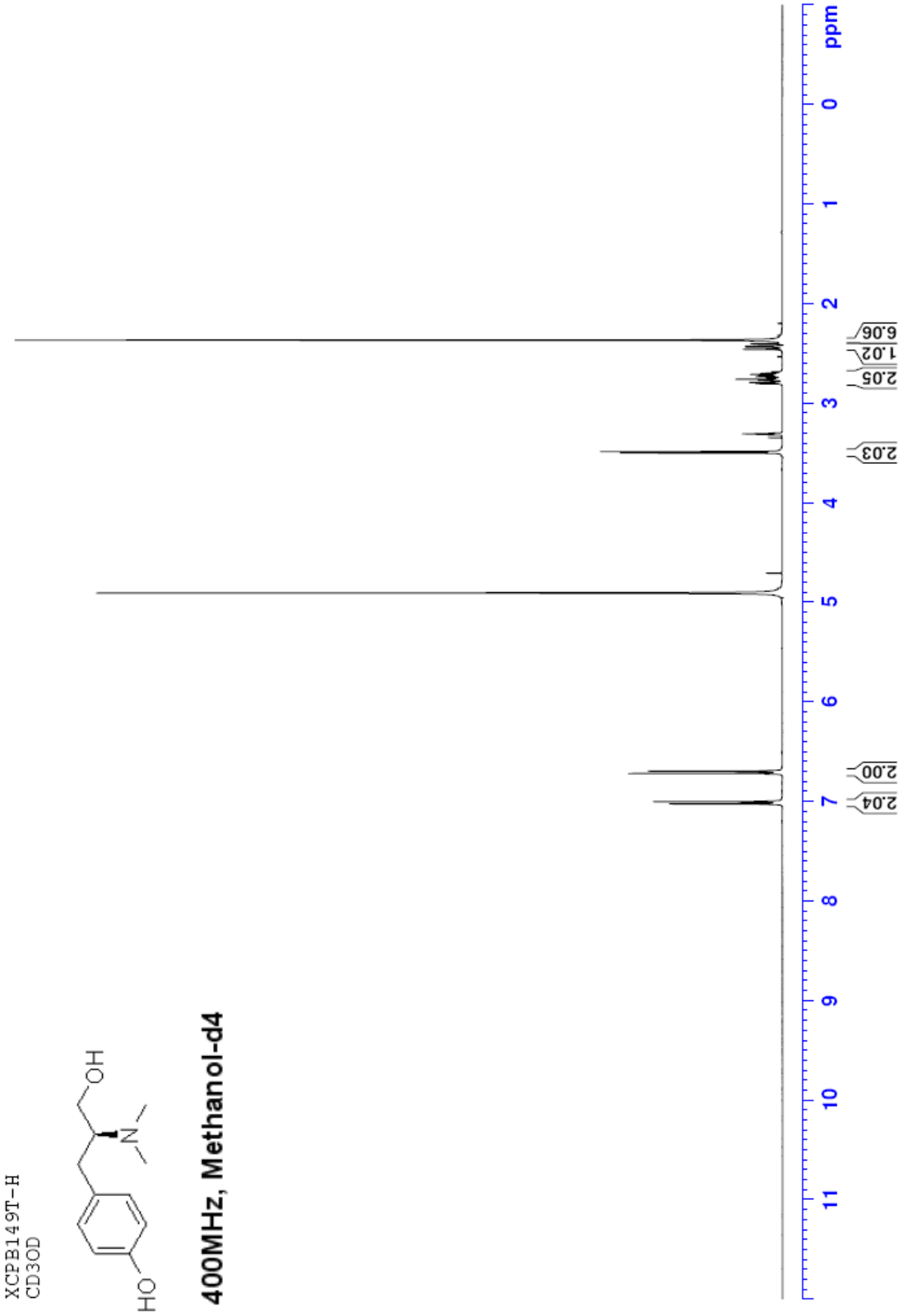
110
120
130
140
150
160
170
180
190
200

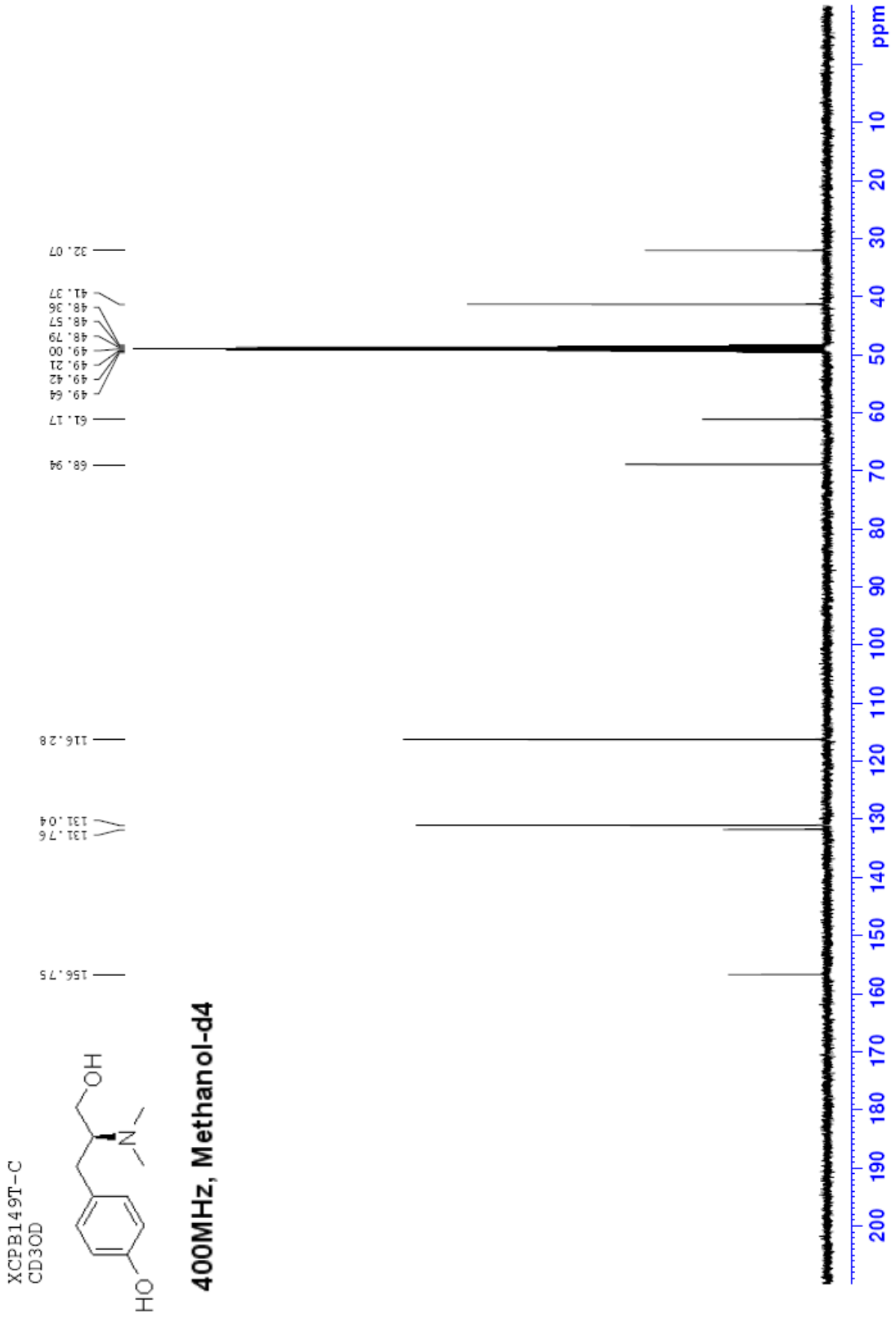

XCPB66T-H
D2O
COOH
400MHz, D2O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
1.00
1.03
3.05
1.03
2.15
1.00

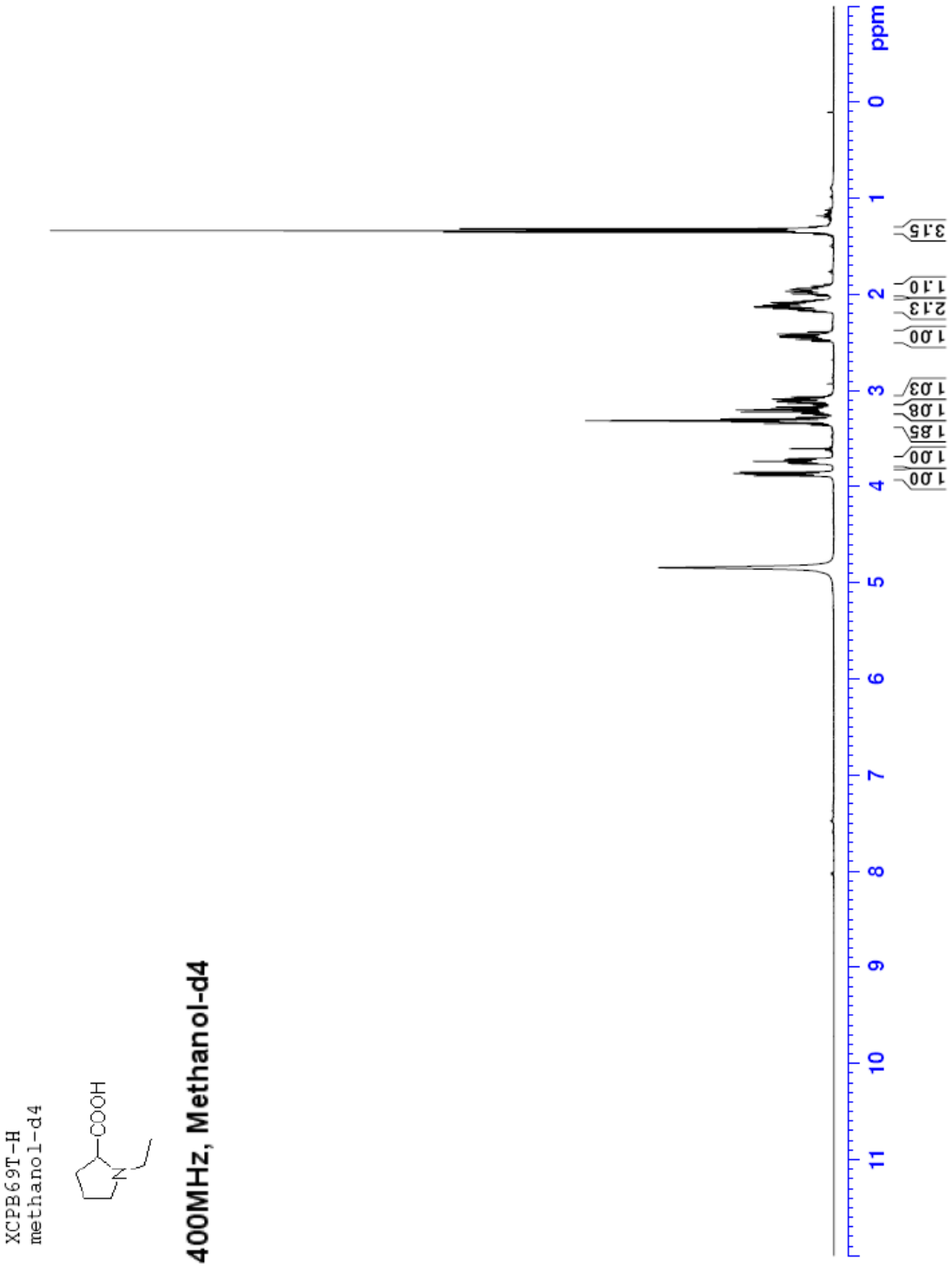

XCPB66T-C
D2O
COOH
N
100MHz, D2O
173.34
70.45
56.46
40.84
28.75
22.81
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

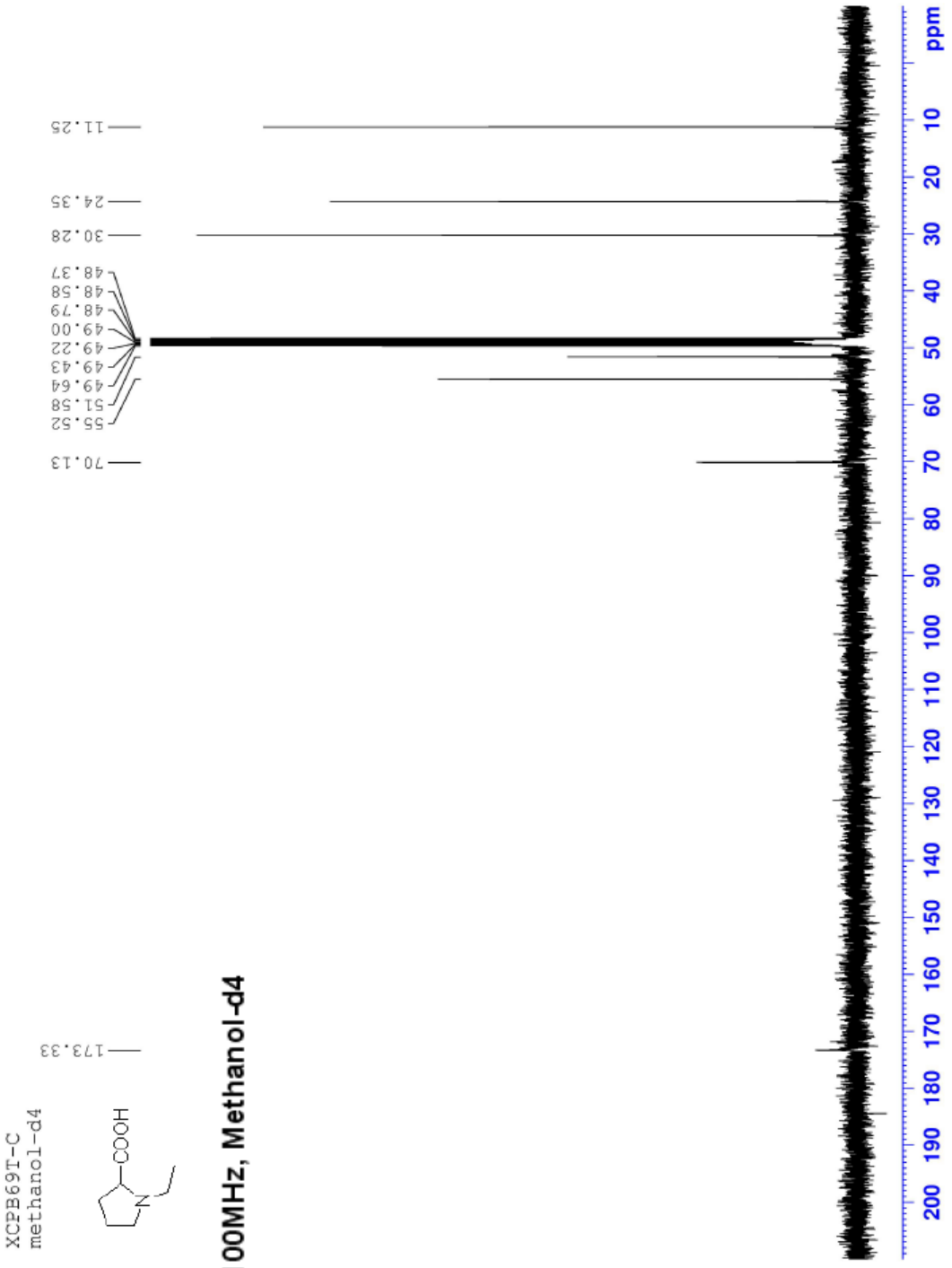

XCPB148T-H
CD3OD
400MHz, Methanol-d4
OH
HN
HO
ppm
0
1
2
3
4
5
6
7
8
9
10
11
2.07
2.07
1.05
1.01
2.04
1.06
3.00

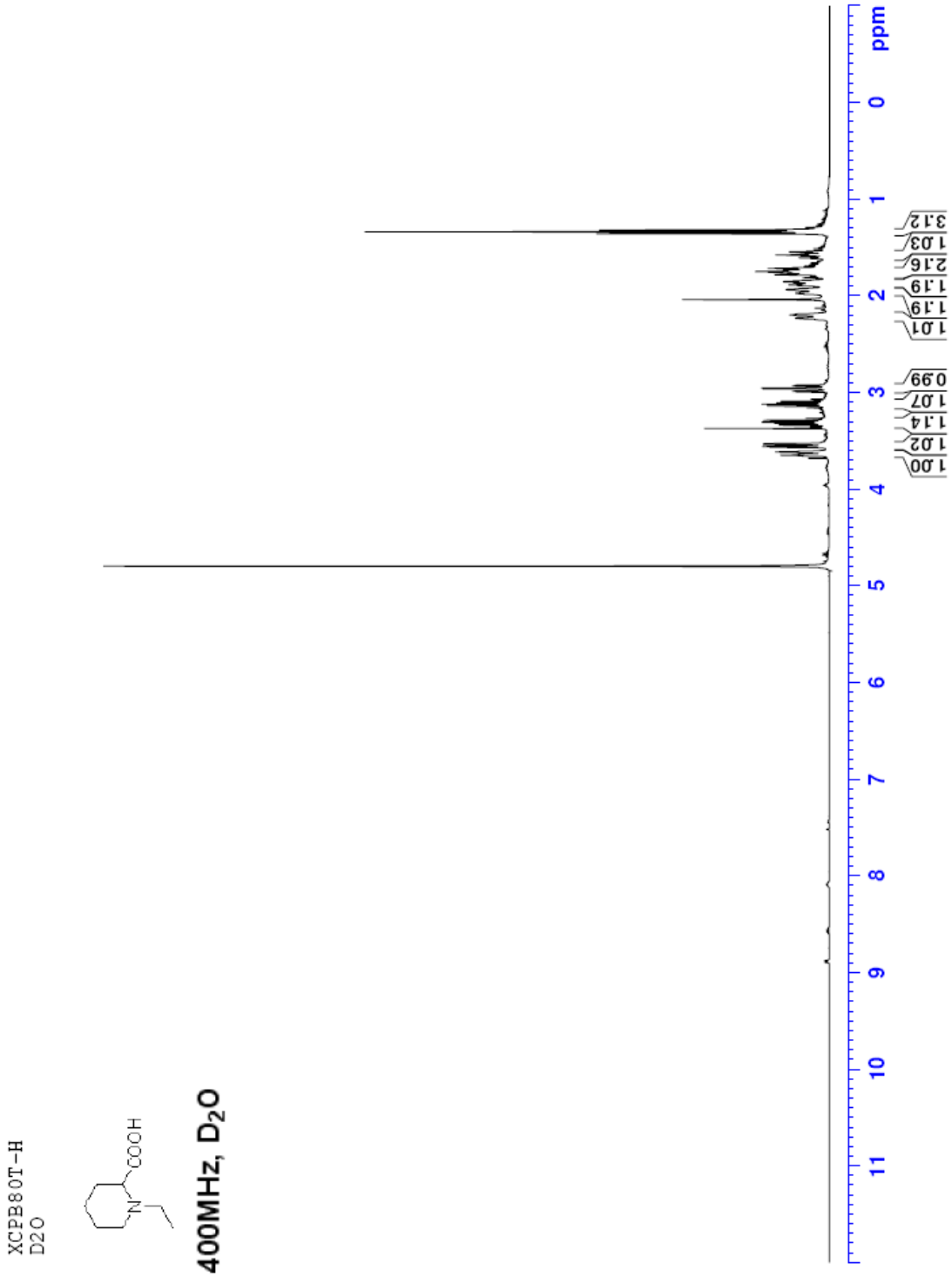

XCPB148T-C
CD3OD
100MHz, Methanol-d4
HO
HN
OH
157.09
131.20
130.47
116.36
64.08
62.96
49.64
49.43
49.21
49.00
48.79
48.58
48.36
36.93
33.79
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

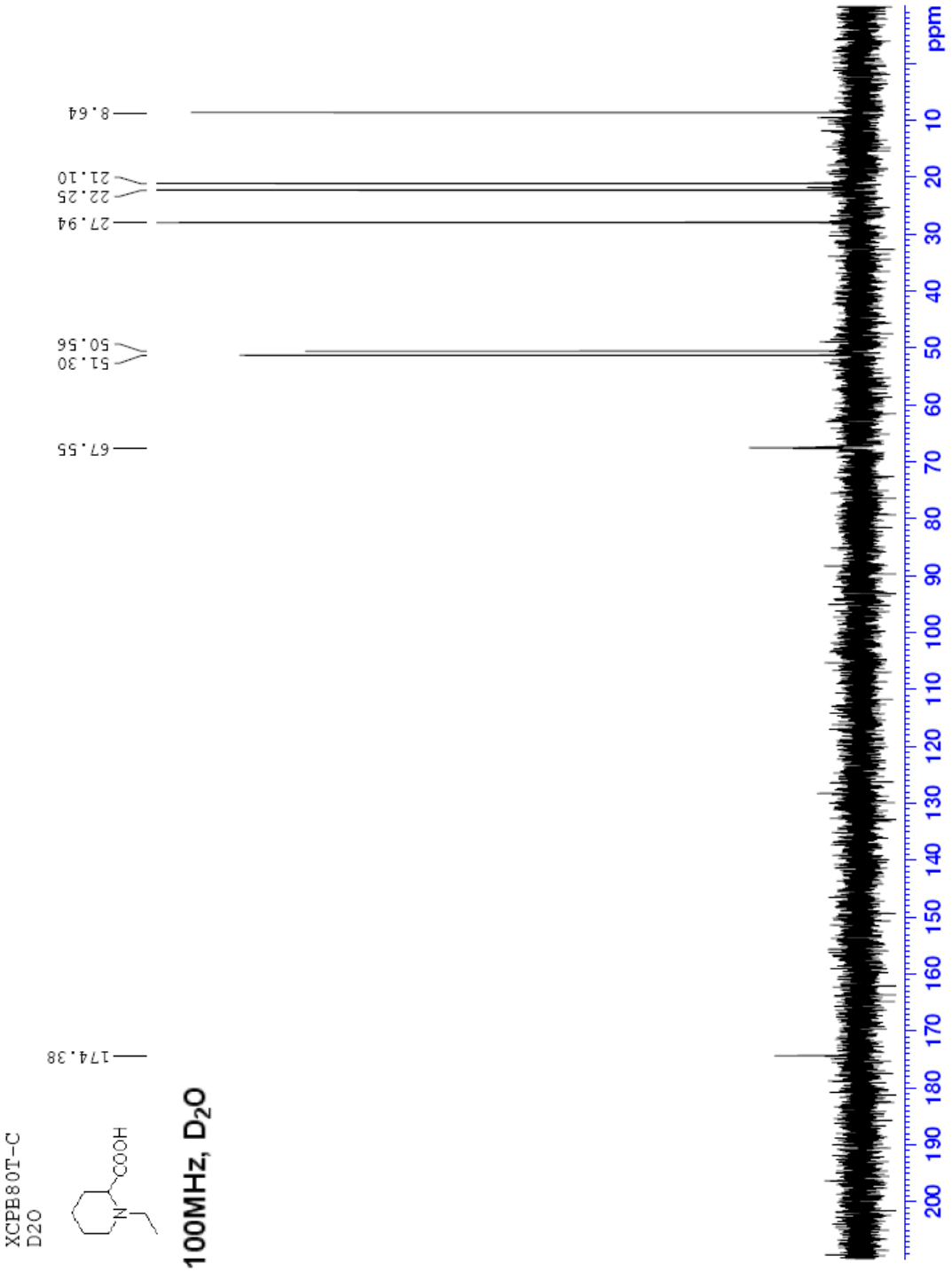

XCPB149T-H
CD3OD
400MHz, Methanol-d4
OH
N
HO
ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.06
1.02
2.05
2.03
2.00
2.04

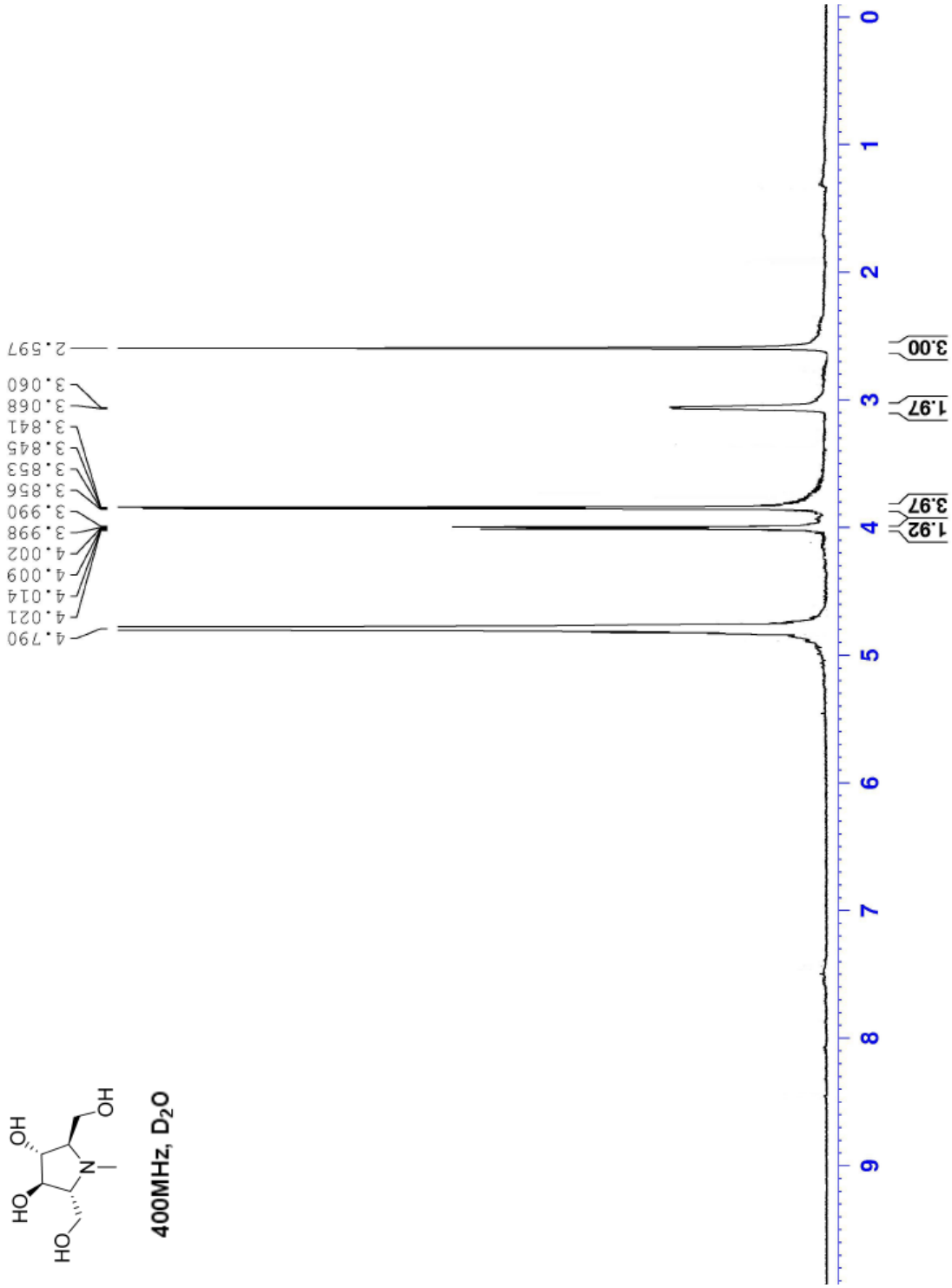

XCPB149T-C
CD3OD
400MHz, Methanol-d4
156.75
131.76
131.04
116.28
68.94
61.17
49.64
49.42
49.21
49.00
48.79
48.57
48.36
41.37
32.07
ppm

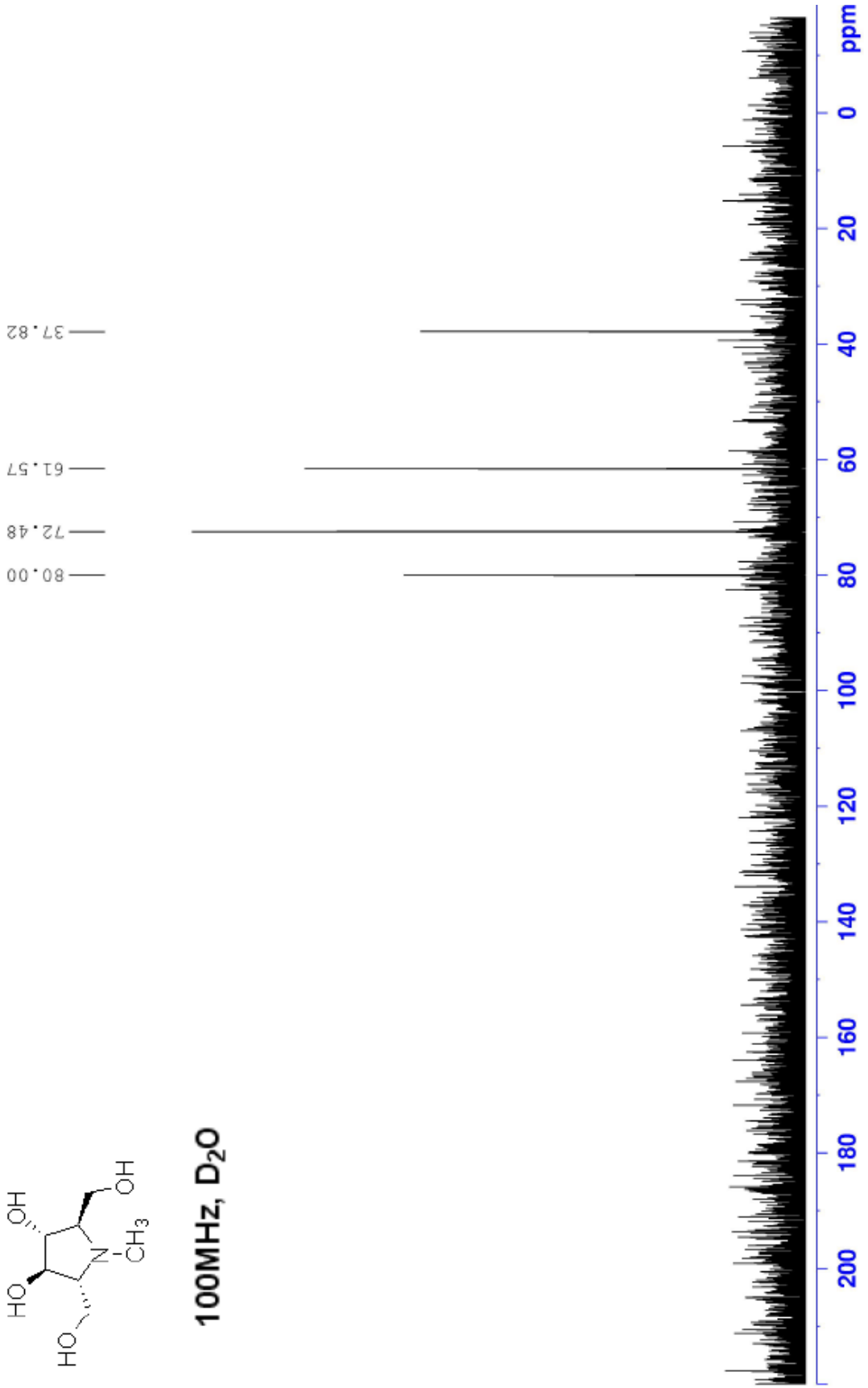

XCPB69T-H
methanol-d4
COOH
N
400MHz, Methanol-d4
ppm
0
1
2
3
4
5
6
7
8
9
10
11
3.15
1.10
2.13
1.00
1.03
1.08
1.85
1.00
1.00

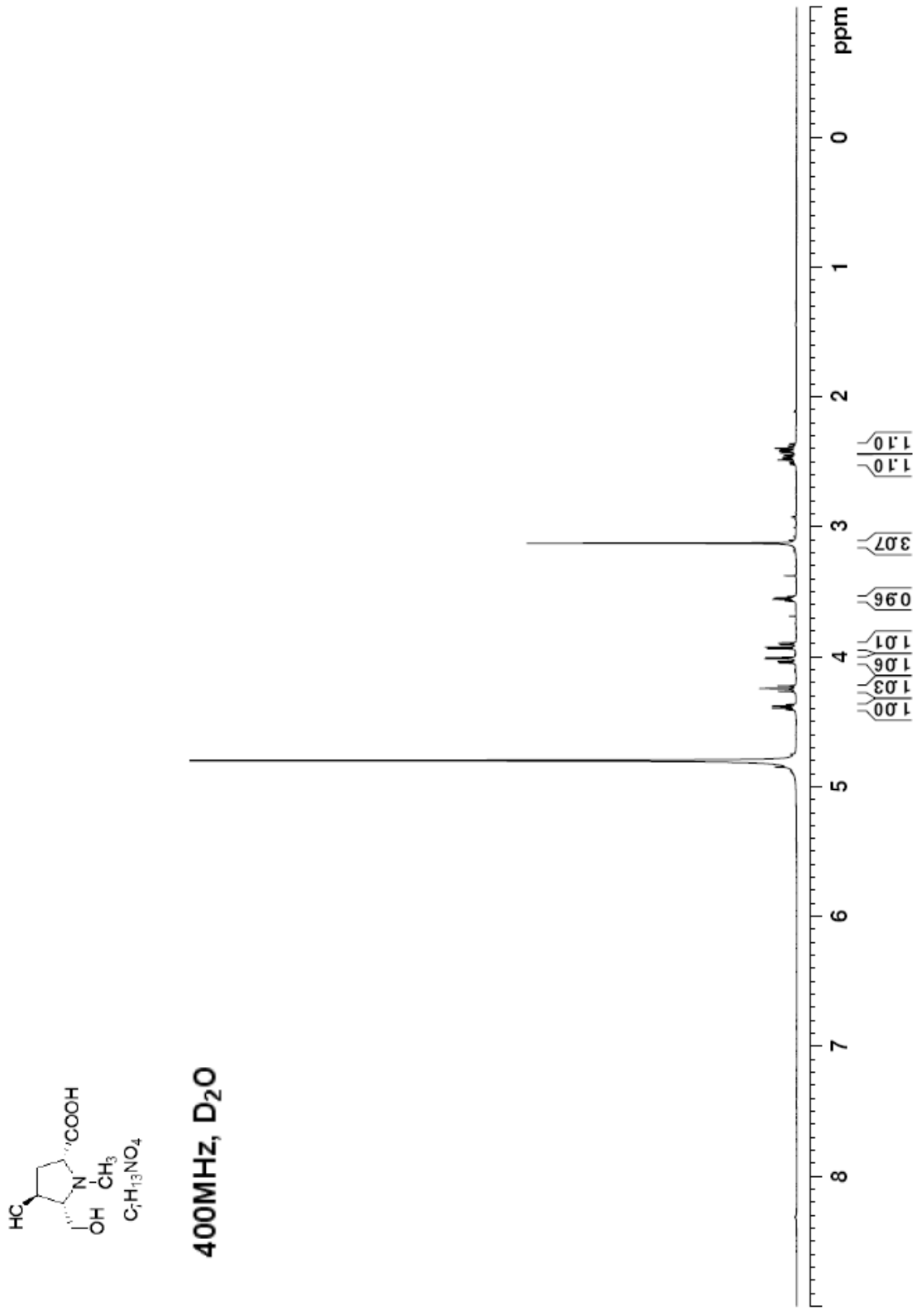

XCPB69T-C
methanol-d4
100MHz, Methanol-d4
COOH
N
173.33
70.13
55.52
51.58
49.64
49.43
49.22
49.00
48.79
48.58
48.37
30.28
24.35
11.25
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

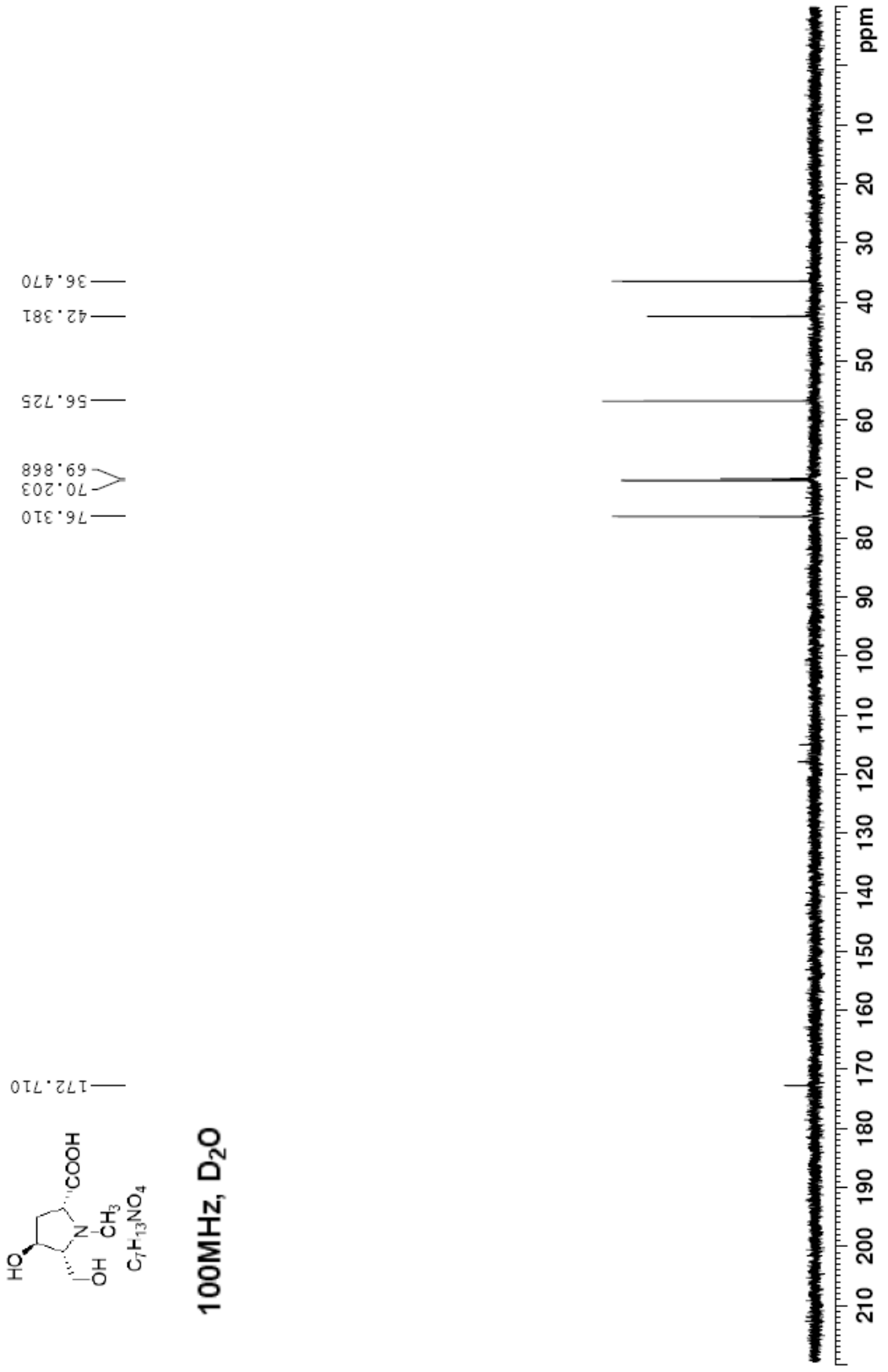

XCPB80T-H
D2O
COOH
N
400MHz, D2O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
1.00
1.02
1.14
1.07
0.99
1.01
1.19
1.19
2.16
1.03
3.12

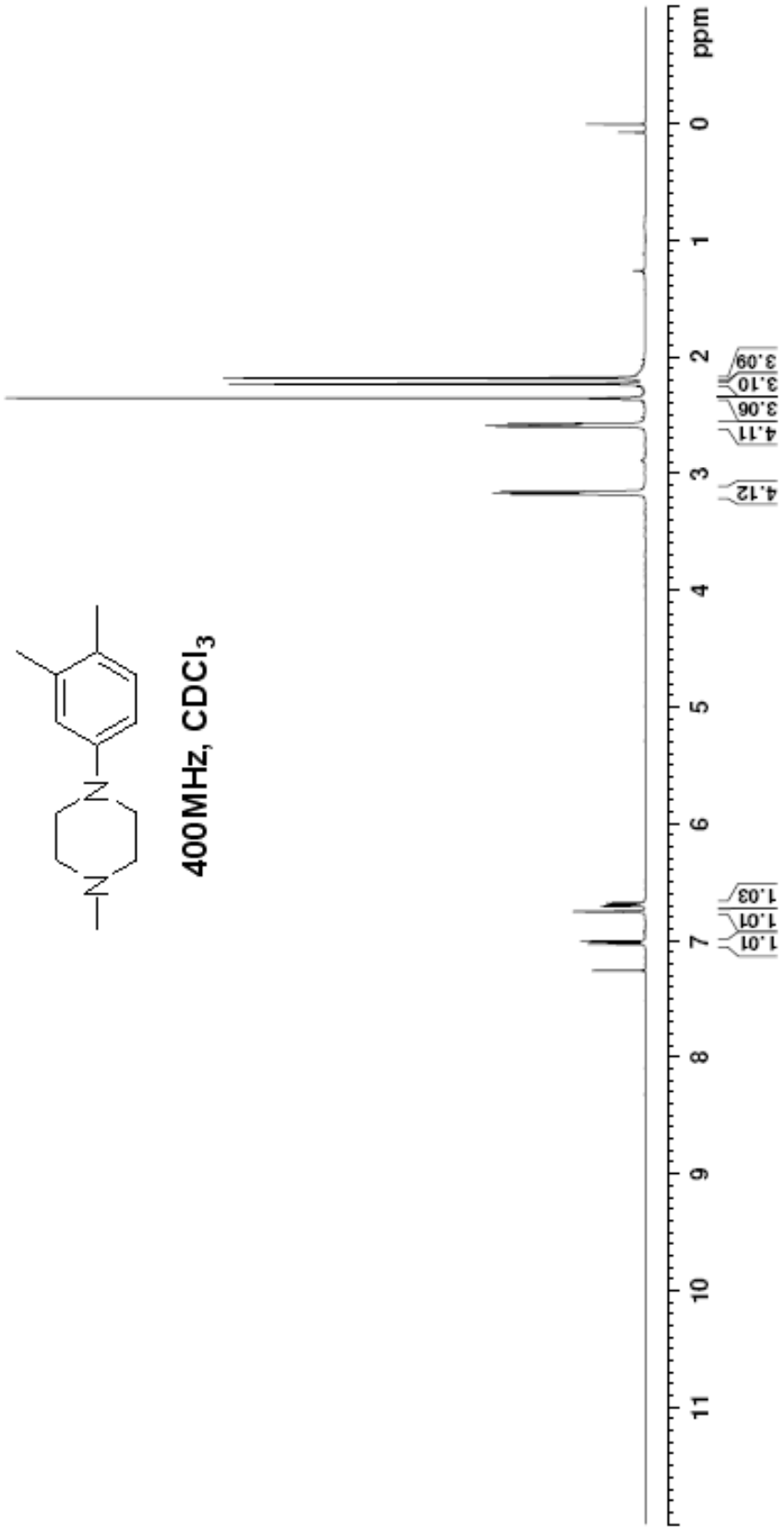

XCPB80T-C
D2O
COOH
N
100MHz, D2O
174.38
67.55
51.30
50.56
27.94
22.25
21.10
8.64
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200


2.597
3.060
3.068
3.841
3.845
3.853
3.856
3.990
3.998
4.002
4.009
4.014
4.021
4.790
3.00
1.97
3.97
1.92
0
1
2
3
4
5
6
7
8
9
OH
HO
N
OH
HO
400MHz, D2O


37.82
61.57
72.48
80.00
ppm
0
20
40
60
80
100
120
140
160
180
200
100MHz, D2O
OH
OH
N
CH3
HO
HO


400MHz, D2O
C7H13NO4
HC
COOH
N
CH3
OH
ppm
0
1
2
3
4
5
6
7
8
1.10
1.10
3.07
0.96
1.01
1.06
1.03
1.00


100MHz, D2O
C7H13NO4
172.710
76.310
70.203
69.868
56.725
42.381
36.470
ppm


400MHz, CDCl3
ppm
0
1
2
3
4
5
6
7
8
9
10
11
3.09
3.10
3.06
4.11
4.12
1.03
1.01
1.01


XCPB75T-C
CDC13
18.71
20.15
46.09
49.65
55.22
76.70
77.02
77.33
113.82
118.07
128.01
130.16
137.06
149.61
100MHz, CDCl3
ppm

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