

**Electronic Supplementary Information for**  
**Optimization of the anti-cancer activity of phosphatidylinositol-3**  
**kinase pathway inhibitor PITENIN-1: switching a thiourea with**  
**1,2,3-triazole**

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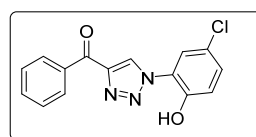
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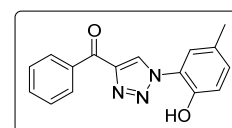
**General information:** Reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. <sup>1</sup>H NMR spectra were recorded on JEOL AL-400 (400 MHz), Bruker AC 200 MHz, Bruker DRX 400 MHz and Bruker DRX 500 MHz spectrometers, and TMS was used as an internal standard of spectrometers. The chemical shifts were reported in parts per million ( $\delta$ ) relative to internal standard TMS (0 ppm), for CDCl<sub>3</sub> (7.27 ppm), MeOH (*D*<sub>4</sub>) (3.35 ppm) and DMSO (*D*<sub>6</sub>) (2.50 ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). <sup>13</sup>C NMR spectra were obtained by JEOL AL-400 (100 MHz), (125 MHz), (100 MHz) and (50 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in CDCl<sub>3</sub>, 48.0 ppm in MeOH (*D*<sub>4</sub>) and 39.5 ppm in DMSO (*D*<sub>6</sub>)). CDCl<sub>3</sub>, DMSO (*D*<sub>6</sub>) and MeOH (*D*<sub>4</sub>) were used as a NMR solvents. Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump, and IR spectra were recorded on FT-IR PerkinElmer spectrometer by neat for oil sample and a CH<sub>3</sub>Cl solution for solid samples. Column chromatography was performed over silica gel 100-200 mesh. All reagents were weighed and handled in air and backfilled under argon at room temperature. Unless otherwise noted, all reactions were performed under an argon atmosphere. All reagents were purchased from Aldrich and Alfa Easer and used without further purification.

**General experimental procedure:** To a solution of azide **4** (1.0 eq.) and alkyne **3** (1.1 eq.) in <sup>t</sup>BuOH:H<sub>2</sub>O (3:1) at rt, sodium ascorbate (0.2 eq.) and CuSO<sub>4</sub>·5H<sub>2</sub>O (0.2 eq.) were added and the resulting brick reddish mixture was stirred vigorously for 10 min. The reaction mixture was diluted and extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvents were evaporated under reduced pressure. The product was purified by column chromatography.

**(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1aa):** Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> = 0.2). The title compound was determined as colourless solid (87%). mp: 210–211 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)): δ 7.04 (d, *J* = 8.8 Hz, 1H), 7.18 (dd, *J* = 2.3, 8.7 Hz, 1H), 7.42–7.58 (m, 3H), 7.79 (s, 1H), 8.29 (d, *J* = 6.4 Hz, 2H), 8.96 (s, 1H), 10.49 (br s, 1H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)): δ 117.9 (d), 123.0 (d), 123.4 (s), 123.7 (s), 127.6 (d, 2C), 129.1 (d), 129.3 (d), 129.5 (d, 2C), 132.4 (d), 135.9 (s), 146.4 (s), 147.1 (s), 184.7 (s) ppm.; IR(cm<sup>-1</sup>):ν 3070, 3010, 2774, 1622, 1596, 1425, 1222, 1095, 902, 721, 681; HRMS(ESI) calcd for C<sub>15</sub>H<sub>10</sub>O<sub>2</sub>N<sub>3</sub>ClNa [M+Na]<sup>+</sup>: 322.0354; found: 322.0357.

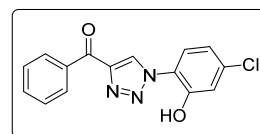


**(1-(2-Hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1ab):** Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> = 0.3). The title compound was determined as colourless solid (91%). Mp: 200–202 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)) δ 2.27 (s, 3H), 6.90 (d, *J* = 8.3, 1H), 7.05 (dd, *J* = 1.6, 8.3, 1H), 7.42–7.61 (m, 4H), 8.28–8.32 (m, 2H), 8.90 (s, 1H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)) δ 19.6 (q), 116.5 (d), 123.1 (s), 124.0 (d), 128.0 (d), 129.3 (s, 2C), 129.9 (d), 130.7 (d, 4C), 133.0 (d), 136.4 (s), 146.3 (s), 173.1 (s) ppm; IR(cm<sup>-1</sup>):ν 3176, 3148, 2956, 2921, 1649, 1521, 1448, 1225, 1180, 1050, 907, 816, 722, 685; calcd for C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>N<sub>3</sub> (M + Na<sup>+</sup>): 302.0900; found: 302.0889.

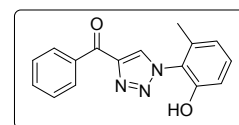


**(1-(4-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1ac):** Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> = 0.2). The title compound was determined as colourless solid (87%). Mp: 238–239 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)): δ 7.55 (d, *J* = 8.6 Hz, 1H), 7.13 (s, 1H), 7.54–7.59 (m, 2H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.81 (d, *J* = 7.5 Hz,

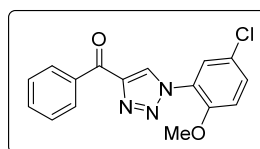
1H), 8.33 (d,  $J = 7.3$  Hz, 2H), 9.01 (s, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ ):  $\delta$  116.7 (d), 119.7 (d), 122.5 (s), 124.9 (d), 128.0 (d, 3C), 129.8 (d, 2C), 133.0 (d), 135.3 (s), 136.3 (s), 146.4 (s), 149.5 (s), 186.1 (s) ppm; IR ( $\text{cm}^{-1}$ ):  $\nu$  2954, 2913, 2846, 1510, 1453, 1419, 1243, 1160, 890, 854, 725, 682; HRMS(ESI) calcd for  $\text{C}_{15}\text{H}_{10}\text{O}_2\text{N}_3\text{ClNa}$  ( $\text{M}^+ + \text{Na}$ ): 322.0354; found: 322.0355.



**(1-(2-Hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1ae):** Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f = 0.3$ ). The title compound was determined as colourless solid (84%). Mp: 182–184 °C;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ ):  $\delta$  2.35 (s, 3H), 6.83 (dd,  $J = 1.1$ , 8.2 Hz, 1H), 6.90 (s, 1H), 7.50–7.62 (m, 3H), 7.67 (d,  $J = 8.2$  Hz, 1H), 8.31–8.37 (m, 2H), 8.97 (s, 1H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ )  $\delta$  20.6 (q), 117.2 (d), 120.5 (d), 121.2 (s), 123.5 (d), 128.1 (d, 2C), 129.8 (d), 129.9 (d, 2C), 133.0 (d), 136.4 (s), 140.8 (s), 146.3 (s), 148.5 (s), 186.3 (s) ppm; IR ( $\text{cm}^{-1}$ ):  $\nu$  2993, 2415, 1601, 1569, 1515, 1421, 1260, 1158, 981, 897, 723, 683; HRMS(ESI) calcd for  $\text{C}_{16}\text{H}_{13}\text{O}_2\text{N}_3\text{Na}$  ( $\text{M}^+ + \text{Na}$ ): 302.0900; found: 302.0896.

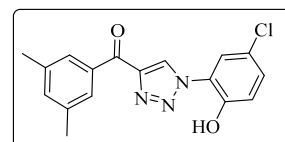


**(1-(5-Chloro-2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1af):** Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f = 0.2$ ). The title compound was determined as colourless solid (43%). Mp: 135–137 °C;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.94 (s, 3H), 7.04 (d,  $J = 9.0$  Hz, 1H), 7.44 (dd,  $J = 2.7$ , 9.0 Hz, 1H), 7.51–7.64 (m, 3H), 7.95 (d,  $J = 2.7$  Hz, 1H), 8.43–8.48 (m, 2H), 8.87 (bs, 1H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  56.4 (q), 113.5 (d), 125.1 (d), 126.4 (s, 2C), 128.4 (d, 2C), 130.3 (d), 130.6 (d, 3C), 133.3 (d), 149.5 (s, 2C), 175.7 (s), 197.8 (s) ppm; IR ( $\text{cm}^{-1}$ ):  $\nu$  3020, 1647, 1498, 1239, 1132, 1014, 986, 894, 813, 719, 640; HRMS(ESI) calcd for  $\text{C}_{16}\text{H}_{12}\text{O}_2\text{N}_3\text{ClNa}$  ( $\text{M}^+ + \text{Na}$ ): 336.0510; found: 336.0510.



**(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(3,5-dimethylphenyl)methanone**

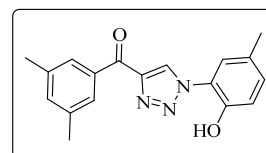
**(1ba):** Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f = 0.2$ ). The title compound was determined as colourless solid (83%). Mp: 232–234 °C;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3 + \text{DMSO} (\text{D}_6)$ ):  $\delta$  2.40 (s, 6H), 7.01 (d,  $J = 8.7$  Hz, 1H), 7.22–7.29 (m, 2H), 7.84 (d,  $J = 2.5$  Hz, 1H), 7.95 (s, 2H), 8.97 (s, 1H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3 + \text{DMSO} (\text{D}_6)$ ):  $\delta$  21.2 (q, 2C), 118.7 (d), 123.2 (d, 2C), 128.16



(d, 3C), 129.20 (s), 130.02 (d), 135.20 (s, 2C), 138.07 (s, 2C), 147.50 (s), 151.82 (s), 175.3 (s) ppm; IR( $\text{cm}^{-1}$ ): $\nu$  3174, 2958, 2918, 2114, 1623, 1589, 1496, 1295, 1258, 1212, 1021, 801, 731, 651; HRMS(ESI) calcd for  $\text{C}_{17}\text{H}_{15}\text{O}_2\text{N}_3\text{Cl}$  ( $\text{M}^+\text{H}$ ): 328.0847; found: 328.0847.

**(3,5-Dimethylphenyl)(1-(2-hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-yl)methanone**

**(1bb):** Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f$  = 0.3). The title compound was determined as colourless solid (85%). Mp: 188–190 °C;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$  + MeOH ( $\text{D}_4$ ) + DMSO ( $\text{D}_6$ ))  $\delta$



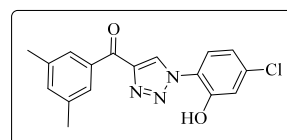
2.34 (s, 3H), 2.40 (s, 6H), 6.99 (d,  $J$  = 8.34 Hz, 1H), 7.09–7.20 (m, 1H), 7.29 (s, 1H), 7.56–7.63 (m, 1H), 7.88 (s, 2H), 8.94 (s, 1H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$  + MeOH ( $\text{D}_4$ ) + DMSO ( $\text{D}_6$ )):  $\delta$  18.7 (q), 19.6 (q, 2C), 115.9 (d), 122.6 (s), 123.6 (d), 126.8 (d, 2C), 128.5 (s), 129.3 (d), 130.0 (d), 133.8 (d), 136.0 (s), 137.1 (s, 2C), 145.7 (s), 145.9 (s), 185.4 (s) ppm; IR( $\text{cm}^{-1}$ ): $\nu$  3182, 2956, 2921, 2859, 1616, 1593, 1521, 1298, 1253, 1208, 1151, 1019, 805, 767, 696; HRMS(ESI) calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_3$  ( $\text{M}^+\text{H}$ ): 308.1394; found: 308.1387.

**(1-(4-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(3,5-dimethylphenyl)methanone (1bc):**

Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f$  = 0.2).

The title compound was determined as colourless solid (91%). Mp:

149–151 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  + DMSO ( $\text{D}_6$ ))  $\delta$  2.35 (s, 6H), 6.95 (dd,  $J$  = 2.0, 8.6 Hz, 1H), 7.12 (d,  $J$  = 2.0 Hz, 1H), 7.22 (bs, 1H), 7.70 (d,  $J$  = 8.6 Hz, 1H), 7.85 (s, 2H), 8.91 (s, 1H) 11.0 (bs, 1H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  + DMSO ( $\text{D}_6$ ))  $\delta$  19.7 (q, 2C), 115.8 (d), 118.2 (d), 121.4 (s), 124.03 (d), 126.3 (d, 2C), 128.6 (d), 133.2 (d), 133.4 (s), 135.3 (s), 136.2 (s, 2C), 145.4 (s), 148.8 (s), 184.0 (s) ppm; IR( $\text{cm}^{-1}$ ): $\nu$  3067, 2950, 2400, 1587, 1499, 1424, 1297, 1228, 1022, 854, 797, 765; HRMS(ESI) calcd for  $\text{C}_{17}\text{H}_{15}\text{O}_2\text{N}_3\text{Cl}$  ( $\text{M}^+\text{H}$ ): 328.0847; found: 328.0833.

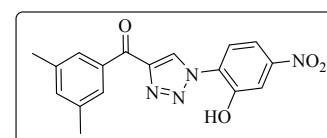


**(3,5-Dimethylphenyl)(1-(2-hydroxy-4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methanone (1bd):**

Isolated by column chromatography (pet.ether/AcOEt = 7:3,  $R_f$  =

0.2). The title compound was determined as yellow solid (86%). Mp:

237–239 °C;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$  + MeOH ( $\text{D}_4$ ) + DMSO ( $\text{D}_6$ )):  $\delta$  2.38 (s, 6H), 6.21 (d,  $J$  = 8.1 Hz, 1H), 7.18 (s, 1H), 7.28 (d,  $J$  = 8.8 Hz, 1H), 7.55 (s, 2H), 7.65 (d,  $J$  = 8.0 Hz, 1H), 7.73–7.88 (m, 2H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$  + MeOH



(D<sub>4</sub>) + DMSO (D<sub>6</sub>):  $\delta$  20.3 (q, 2C), 109.3 (d), 110.9 (d), 115.9 (d), 124.6 (d, 2C), 133.0 (d), 134.6 (s), 137.4 (s, 2C), 138.2 (s), 141.1 (d), 141.2 (s), 141.7 (s), 145.0 (s), 191.4 (s) ppm; IR(cm<sup>-1</sup>): $\nu$  3377, 3311, 3091, 2885, 2198, 1929, 1627, 1594, 1521, 1428, 1262, 1182, 1081, 948, 870, 742, 643.

**(3,5-Dimethylphenyl)(1-(2-hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-yl)methanone**

**(1be)**: Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> =

0.3). The title compound was determined as colourless solid (91%). Mp:

188–190 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)):  $\delta$  2.37 (s, 3H),

2.42 (s, 6H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.91 (s, 1H), 7.31 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.88 (s,

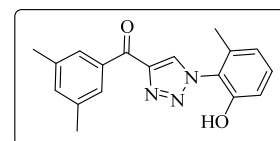
2H), 8.92 (s, 1H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)):  $\delta$  19.6 (q, 3C), 116.3 (d),

119.7 (d), 120.7 (s), 123.3 (d), 126.8 (d, 2C), 129.3 (d), 133.8 (d), 136.0 (s), 137.1 (s, 2C), 140.1

(s), 145.7 (s), 148.1 (s), 185.4 (s) ppm; IR(cm<sup>-1</sup>): $\nu$  3402, 2918, 2254, 2128, 1626, 1595, 1521,

1430, 1234, 1022, 996, 824, 761; HRMS(ESI) calcd for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>N<sub>3</sub> (M<sup>+</sup>+H): 308.1394; found:

308.1381.



**(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(4-isopropylphenyl)methanone (1ca)**:

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> = 0.2).

The title compound was determined as colourless solid (86%). Mp:

187–189 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO

(D<sub>6</sub>)):  $\delta$  1.23 (d, *J* = 6.9 Hz, 6H), 2.95 (spt, *J* = 6.9 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J*

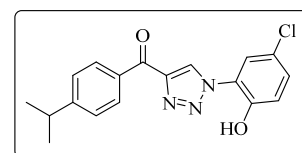
= 2.5, 8.8 Hz, 1H), 7.36 (d, *J* = 8.31 Hz, 2H), 7.75 (d, *J* = 2.7 Hz, 1H), 8.20 (d, *J* = 8.1 Hz, 2H),

8.97 (s, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)):  $\delta$  21.9 (q, 2C),

33.0 (d), 117.2 (d), 122.9 (s), 123.0 (d), 123.5 (s), 125.3 (d, 2C), 129.0 (d), 129.2 (d), 129.3 (d,

2C), 133.4 (s), 145.8 (s), 147.2 (s), 153.8 (s), 184.1 (s) ppm; IR(cm<sup>-1</sup>): $\nu$  3459, 2989, 1621, 1575,

1515, 1286, 1250, 1196, 1027, 785, 762.



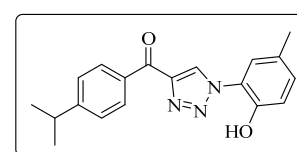
**(1-(2-Hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-yl)(4-isopropylphenyl)methanone (1cb)**:

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> = 0.3). The title compound was

determined as colourless solid (83%). Mp: 131–133 °C; <sup>1</sup>H NMR (500

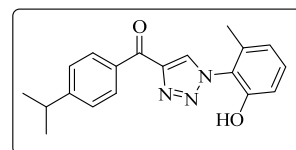
MHz, MeOH (D<sub>4</sub>)):  $\delta$  1.48 (d, *J* = 6.8 Hz, 6H), 2.52 (s, 3H), 3.20 (spt, *J*

= 6.9 Hz, 1H), 7.20–7.35 (m, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.78 (s,

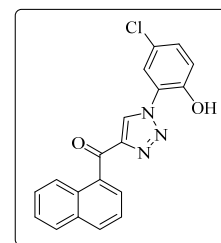


1H), 8.50 (d,  $J = 8.3$  Hz, 2H), 9.18 (s, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz, MeOH ( $D_4$ )):  $\delta$  20.6 (q), 24.2 (q, 2C), 35.7 (d), 118.1 (d), 125.1 (s), 126.0 (d), 127.8 (d, 2C), 131.0 (s), 131.7 (d), 131.8 (d, 2C), 132.4 (d), 136.1 (s), 148.1 (s), 148.5 (s), 156.5 (s), 187.1 (s) ppm; IR( $\text{cm}^{-1}$ ): $\nu$  3177, 2961, 2925, 2869, 1622, 1600, 1523, 1416, 1348, 1274, 1187, 1047, 907, 814, 773; HRMS(ESI) calcd for  $\text{C}_{19}\text{H}_{20}\text{O}_2\text{N}_3$  ( $\text{M}^+\text{+H}$ ): 322.1550; found: 322.1548.

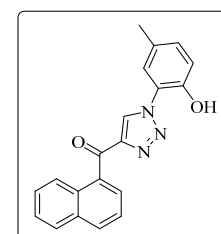
**(1-(2-Hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-yl)(4-isopropylphenyl)methanone (1c):** Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f = 0.3$ ). The title compound was determined as colourless solid (82%). Mp: 172–174 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3 + \text{MeOH} (D_4) + \text{DMSO} (D_6)$ ):  $\delta$  1.26 (s, 3H), 1.27 (s, 3H), 2.33 (s, 3H), 2.98 (spt,  $J = 6.87$  Hz, 1H), 6.83 (d,  $J = 7.3$  Hz, 1H), 6.99 (s, 1H), 7.44 (d,  $J = 8.2$  Hz, 2H), 7.60 (d,  $J = 8.2$  Hz, 1H), 8.29 (d,  $J = 8.2$  Hz, 2H), 9.01 (s, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{MeOH} (D_4) + \text{DMSO} (D_6)$ ):  $\delta$  21.3 (q), 23.9 (q, 2C), 34.5 (d), 118.1 (d), 121.1 (d, 2C), 122.4 (s), 125.3 (d), 127.1 (d, 2C), 131.1 (d, 2C), 135.2 (s), 141.6 (s), 147.4 (s), 150.1 (s), 155.2 (s), 185.5 (s) ppm; IR( $\text{cm}^{-1}$ ): $\nu$  3176, 2960, 1629, 1604, 1520, 1504, 1425, 1267, 1159, 1049, 907, 820, 770; HRMS(ESI) calcd for  $\text{C}_{19}\text{H}_{20}\text{O}_2\text{N}_3$  ( $\text{M}^+\text{+H}$ ): 322.1550; found: 322.1550.



**(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-1-yl)methanone (1da):** Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f = 0.2$ ). The title compound was determined as colourless solid (87%). Mp: 255–257 °C;  $^1\text{H}$  NMR (500 MHz, MeOH ( $D_4$ ) + DMSO ( $D_6$ )):  $\delta$  7.12 (d,  $J = 8.9$  Hz, 1H), 7.38 (dd,  $J = 2.4, 8.5$  Hz, 1H), 7.56 (dd,  $J = 3.4, 6.4$  Hz, 2H), 7.61 (t,  $J = 7.9$  Hz, 1H), 7.74 (d,  $J = 2.4$  Hz, 1H), 8.01 (d,  $J = 7.3$  Hz, 2H), 8.13 (d,  $J = 8.2$  Hz, 1H), 7.54 (dd,  $J = 3.1, 5.8$  Hz, 1H), 9.07 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz, MeOH ( $D_4$ ) + DMSO ( $D_6$ )):  $\delta$  119.2 (d), 123.9 (s), 125.2 (d), 125.3 (s), 125.4 (d), 125.7 (d), 127.1 (d), 128.2 (d), 129.2 (d), 130.1 (d), 130.9 (s), 131.1 (d), 131.6 (d), 132.8 (d), 134.3 (s), 135.5 (s), 148.1 (s), 149.5 (s), 188.8 (s) ppm; IR( $\text{cm}^{-1}$ ): $\nu$  3067, 2950, 1942, 1736, 1645, 1598, 1437, 1303, 1233, 1158, 880, 748, 624; HRMS(ESI) calcd for  $\text{C}_{19}\text{H}_{12}\text{O}_2\text{N}_3\text{ClNa}$  ( $\text{M}^+\text{+Na}$ ): 372.0510; found: 372.0507.



**(1-(2-Hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-1-yl)methanone (1db):** Isolated by column chromatography (pet.ether/AcOEt = 8:2,  $R_f = 0.3$ ). The

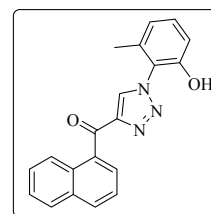


title compound was determined as colourless solid (91%). Mp: 222–223 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)): δ 2.36 (s, 3H), 6.98 (d, *J* = 8.3 Hz, 1H), 7.14–7.16 (m, 1H), 7.56–7.65 (m, 5H), 7.96–7.98 (m, 1H), 8.04 (dd, *J* = 1.0, 7.1 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 8.35–8.41 (m, 1H), 8.96 (s, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)): δ 19.5 (q), 116.4 (d), 123.0 (s), 123.9 (d), 124.0 (d), 124.7 (d), 126.0 (d), 127.1 (d), 128.0 (d), 129.0 (d), 129.2 (s), 130.0 (d), 130.2 (s), 130.7 (d), 132.2 (d), 133.5 (s), 134.3 (s), 146.3 (s), 146.9 (s), 188.6 (s) ppm; IR(cm<sup>-1</sup>): ν 3070, 2920, 1627, 1522, 1457, 1368, 1286, 1256, 1164, 1031, 903, 786; HRMS(ESI) calcd for C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>N<sub>3</sub> (M<sup>+</sup>+H): 330.1237; found: 330.1243.

**(1-(2-Hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-1-yl)methanone (1de):**

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> = 0.3). The title compound was determined as colourless solid (84%). Mp: 221–223 °C;

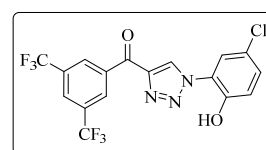
<sup>1</sup>H NMR (500 MHz, DMSO (D<sub>6</sub>)): δ 2.27 (s, 3H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.87 (s, 1H), 7.47–7.51 (m, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.86–7.88 (m, 1H), 7.99 (t, *J* = 7.5 Hz, 2H), 8.27–8.29 (m, 1H), 8.85 (s,



1H), 10.21 (bs, 1H) ppm; <sup>13</sup>C NMR (125 MHz, DMSO (D<sub>6</sub>)): δ 20.3 (q), 116.8 (d), 119.7 (d), 120.7 (s), 123.0 (d), 123.5 (d), 124.3 (d), 125.5 (d), 126.5 (d), 127.5 (d), 128.5 (d), 129.1 (d), 129.6 (s), 131.3 (d), 132.7 (s), 133.9 (s), 139.7 (s), 146.5 (s), 147.9 (s), 187.5 (s) ppm; IR(cm<sup>-1</sup>): ν 3161, 2921, 1628, 1608, 1522, 1436, 1283, 1254, 1032, 902, 786, 764; HRMS(ESI) calcd for C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>N<sub>3</sub> (M<sup>+</sup>+H): 330.1237; found: 330.1221.

**(3,5-Bis(trifluoromethyl)phenyl)(1-(5-chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)methanone (1ea):**

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R<sub>f</sub> = 0.2). The title compound was determined as colourless solid (82%). Mp: 210–212 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ

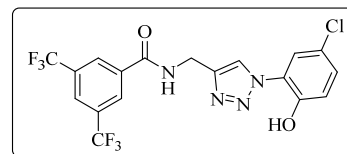


7.08 (d, *J* = 8.9 Hz, 1H), 7.32 (dd, *J* = 2.4, 8.9 Hz, 1H), 7.94 (d, *J* = 2.4 Hz, 1H), 8.17 (bs, 1H), 8.99 (bs, 2H), 9.22 (s, 1H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 118.0 (d), 121.6 (s), 123.6 (d, 2C), 123.8 (s), 124.0 (s), 124.4 (s), 126.0 (d, t, *J* = 3.6 Hz), 130.1 (d), 130.4 (d, *J* = 2.7 Hz), 130.5 (d), 131.4 (s, d, *J* = 33.6 Hz), 131.9 (s, d, *J* = 34.5 Hz), 137.8 (s), 146.1 (s), 147.5 (s), 182.5 (s) ppm; IR(cm<sup>-1</sup>): ν 3187, 2959, 1640, 1527, 1419, 1280, 1134, 910, 819, 768; HRMS(ESI) calcd for C<sub>17</sub>H<sub>9</sub>O<sub>2</sub>N<sub>3</sub>ClF<sub>6</sub> (M<sup>+</sup>+H): 436.0282; found: 436.0289..



***N*-((1-(5-chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3,5-**

**bis(trifluoromethyl)benzamide (1fa):** Isolated by column chromatography (pet.ether/AcOEt = 9:1,  $R_f$  = 0.5). The title compound was determined as colourless solid (85%). Mp: 204–206



°C;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.43 (s, 2H), 6.69 (d,  $J$  = 8.8 Hz, 1H), 6.93 (dd,  $J$  = 2.7, 8.7 Hz, 1H), 7.40 (d,  $J$  = 8.6 Hz, 1H), 7.71 (bs, 1H), 8.12 (s, 1H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  34.6 (t), 117.6 (d), 119.8 (d), 123.4 (d), 123.8 (s), 124.3 (d), 124.5 (d), 125.2 (s), 127.4 (d,  $J$  = 2.9 Hz), 129.1 (d), 130.6 (s), 130.7 (s, d,  $J$  = 33.7 Hz), 131.6 (s, d,  $J$  = 34.0 Hz), 135.6 (s), 143.5 (s), 147.4 (s, 2C), 164.8 (s) ppm; IR( $\text{cm}^{-1}$ ):  $\nu$  3085, 2926, 1645, 1597, 1460, 1376, 1280, 1176, 1132, 906, 773, 689; HRMS(ESI) calcd for  $\text{C}_{18}\text{H}_{12}\text{O}_2\text{N}_4\text{ClF}_6$  ( $\text{M}^+$ +H): 465.0547; found: 465.0533.

## Biology

**Cells.** Human ovarian carcinoma A2780, malignant glioblastoma U87MG and breast carcinoma T47D cells were obtained from ATCC. Cells were maintained in DMEM media (Fisher) supplemented with 10% fetal bovine serum (Sigma) and 1% antibiotic-antimycotic mix (Invitrogen).

**Lipid overlay assay.** Assay was performed using 1 µg/ml recombinant Akt PH domain protein as described previously.<sup>1</sup>

**Cell viability.** Cells were seeded into white clear bottom tissue culture treated 96 well plates at the density of  $10 \times 10^3$  cells per well. After 24 hr, cells were treated with the inhibitors in DMSO (final DMSO concentration was maintained at 0.5% in all wells). Cell viability relative to the control, DMSO treated wells was determined using CellTiter-Glo viability assay (Promega).

**Western blotting.** Cells were treated with indicated concentrations of compounds in 6 well plates ( $6 \times 10^5$  cells per well) for 7 hr. Cells were lysed in 1XRIPA buffer (Cell Signaling). Protein concentrations were normalized using 660 nm protein assay reagent (Pierce). Equal amounts of protein were loaded on SDS-PAGE. Western blotting was performed using standard protocols using S6 and phospho-Ser235/236-S6 antibodies (Cell Signaling).

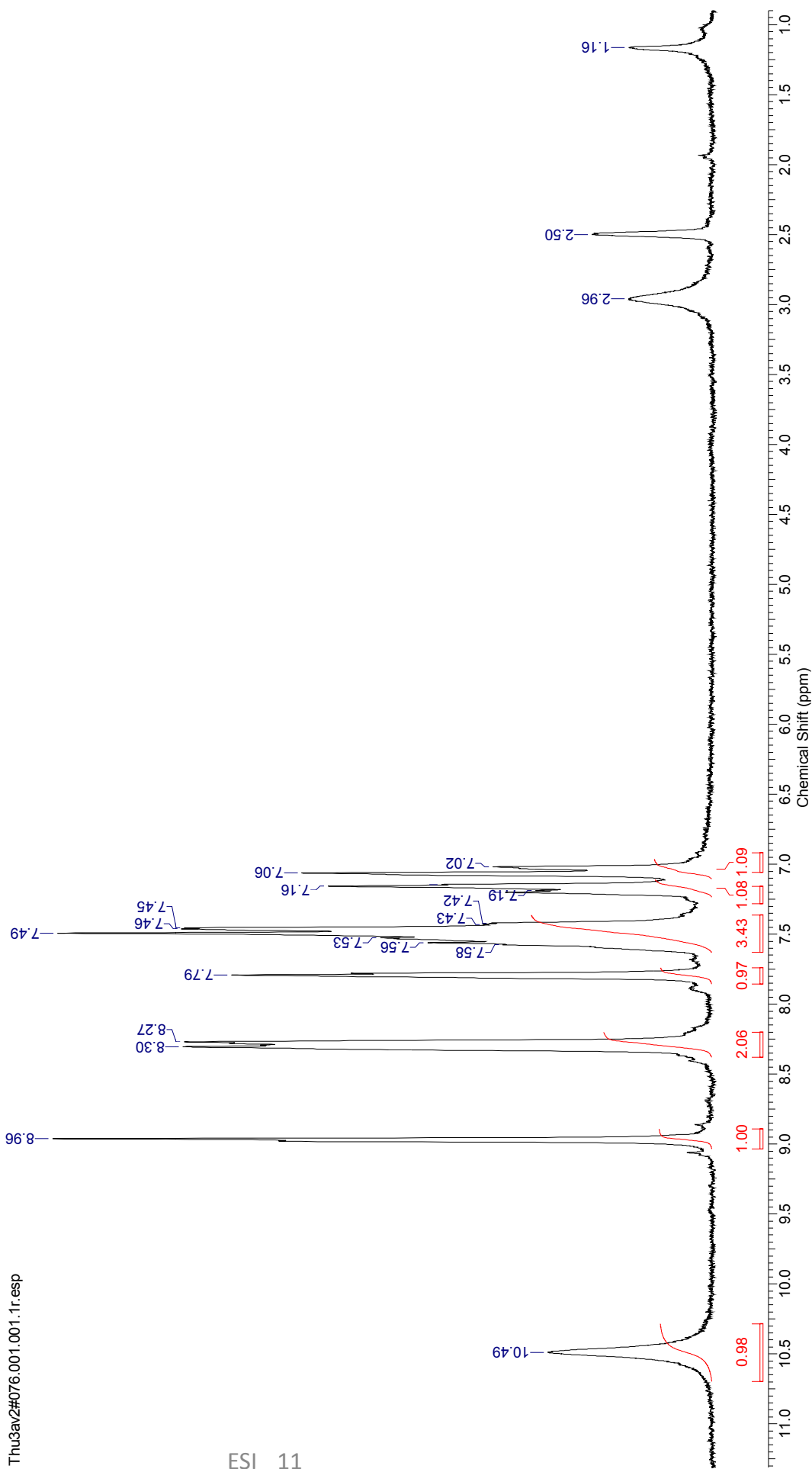
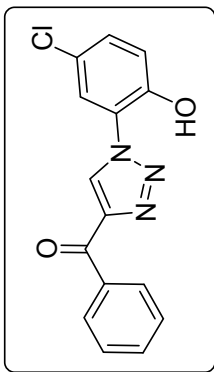
**Wounds healing assay.** Assay was performed using monolayers of A2780 cells as previously described.<sup>2</sup>

**Metabolic stability measurements.** Mouse microsomal stability assays were performed by Cypotex. Pharmacokinetics analysis was performed by PharmaLegacy.

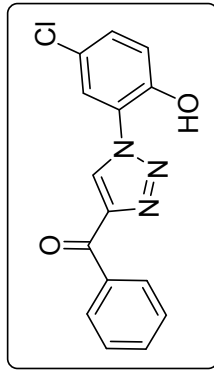
## References:

1. B. C. Miao, I. Skidan, J. S. Yang, A. Lugovskoy, M. Reibarkh, K. Long, T. Brazell, K. A. Durugkar, J. Maki, C. V. Ramana, B. Schaffhausen, G. Wagner, V. Torchilin, J. Y. Yuan and A. Degterev, *Proc. Natl. Acad. Sci. U.S.A.*, 2010, **107**, 20126-20131.
2. B. Miao, I. Skidan, J. Yang, Z. You, X. Fu, M. Famulok, B. Schaffhausen, V. Torchilin, J. Yuan and A. Degterev, *Oncogene*, 2012, **31**, 4317-4332.

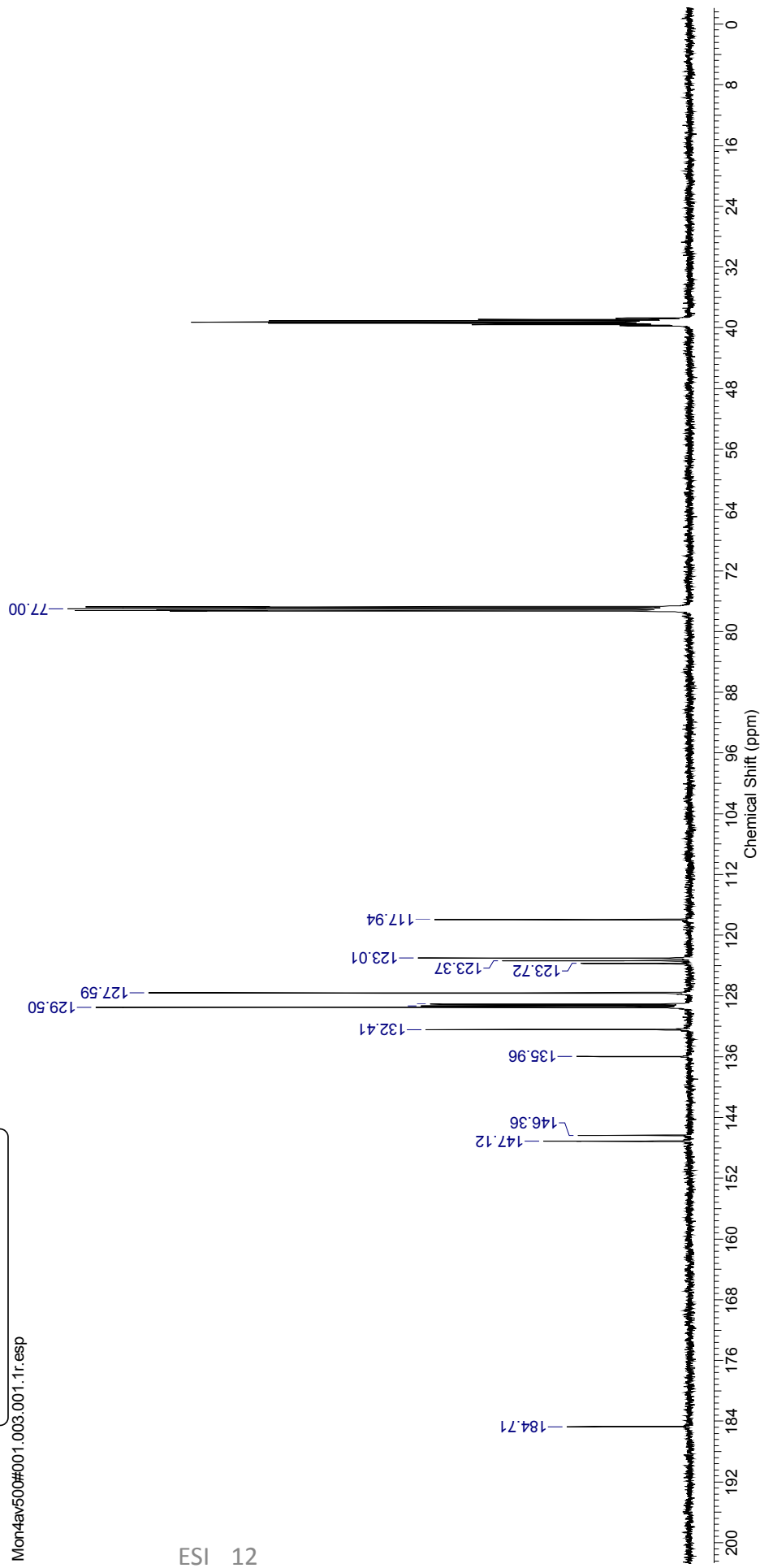
# 1aa, 200 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)



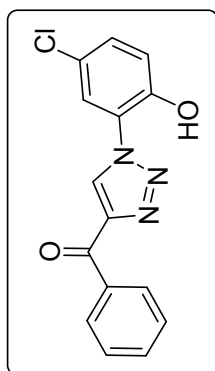
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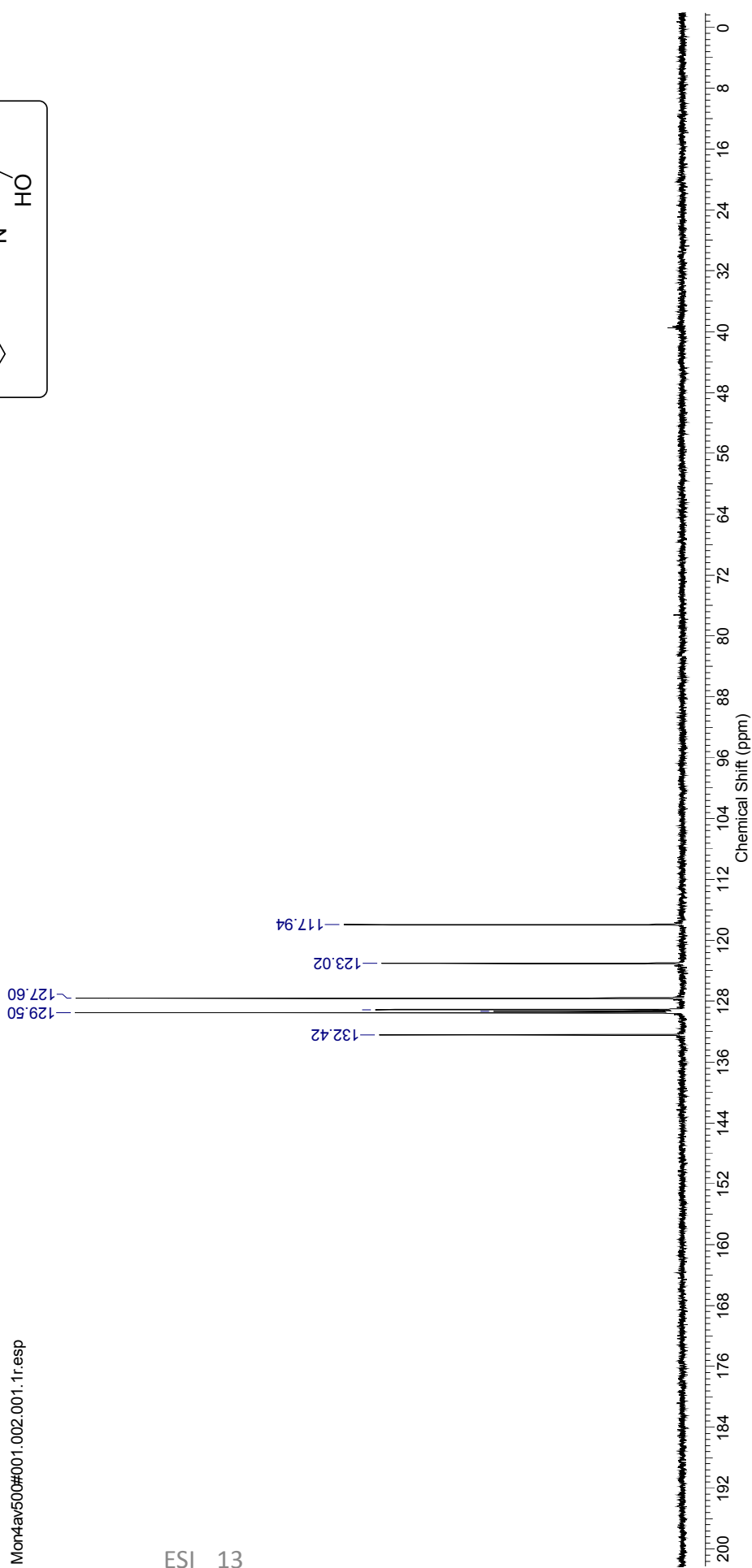
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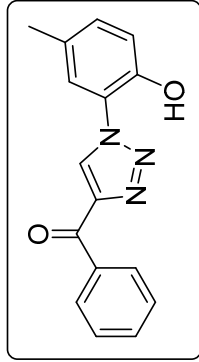
# 1aa, 125 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)



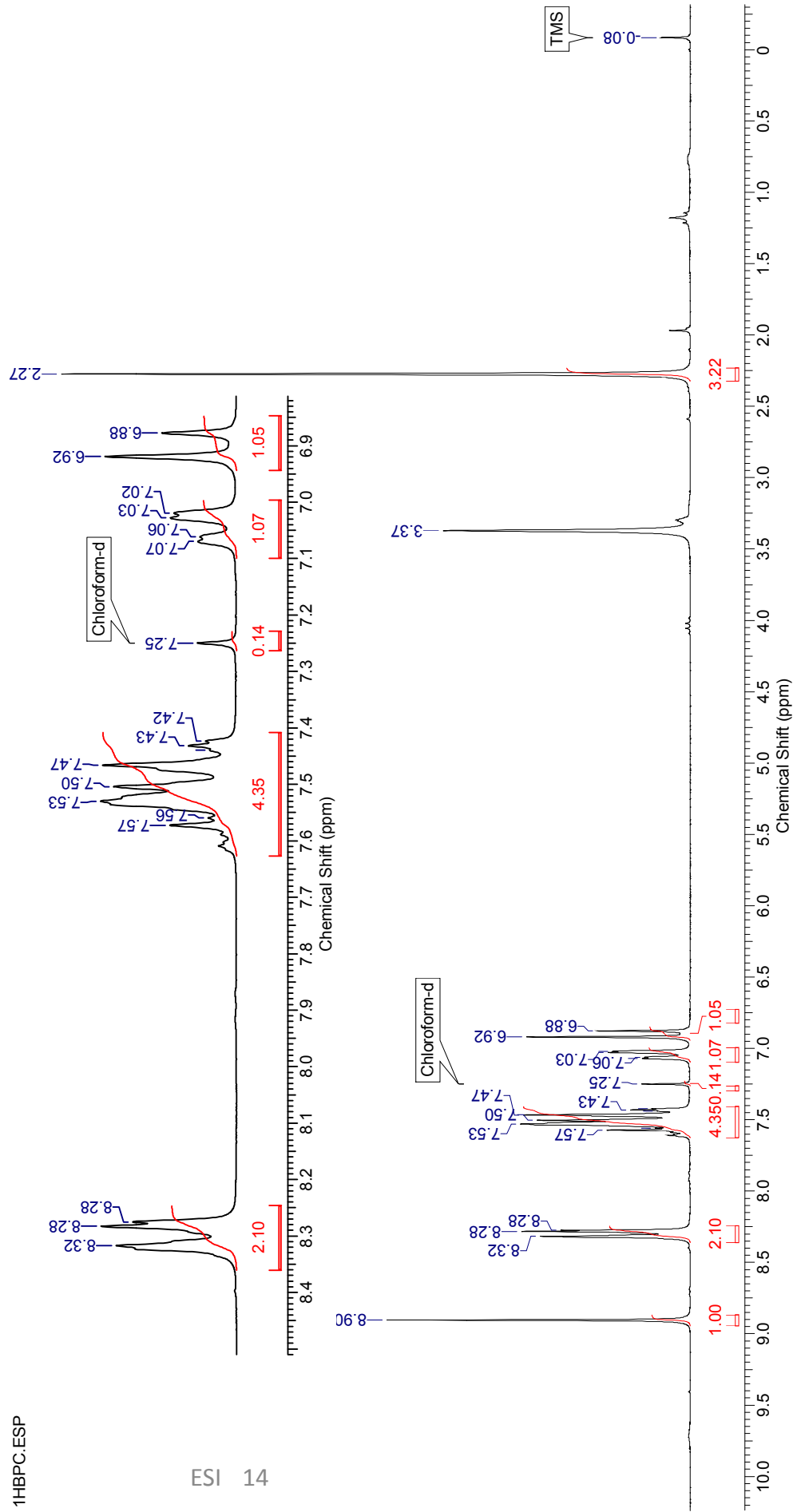
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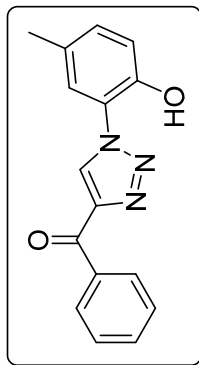
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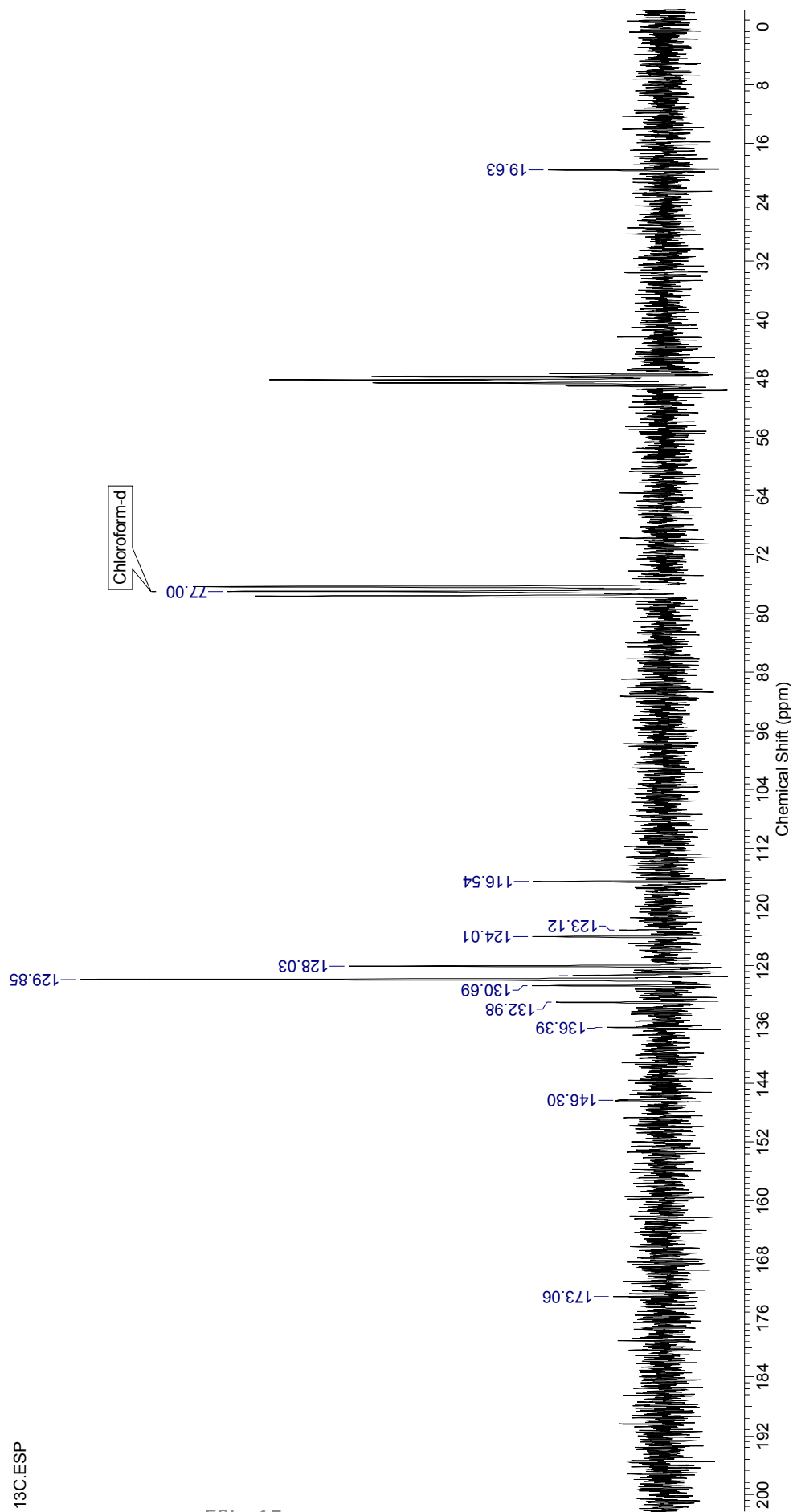
1HBPQ.ESP



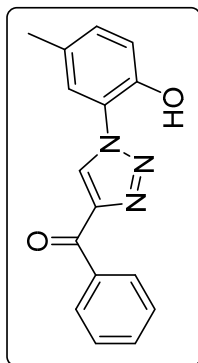
# 1ab, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



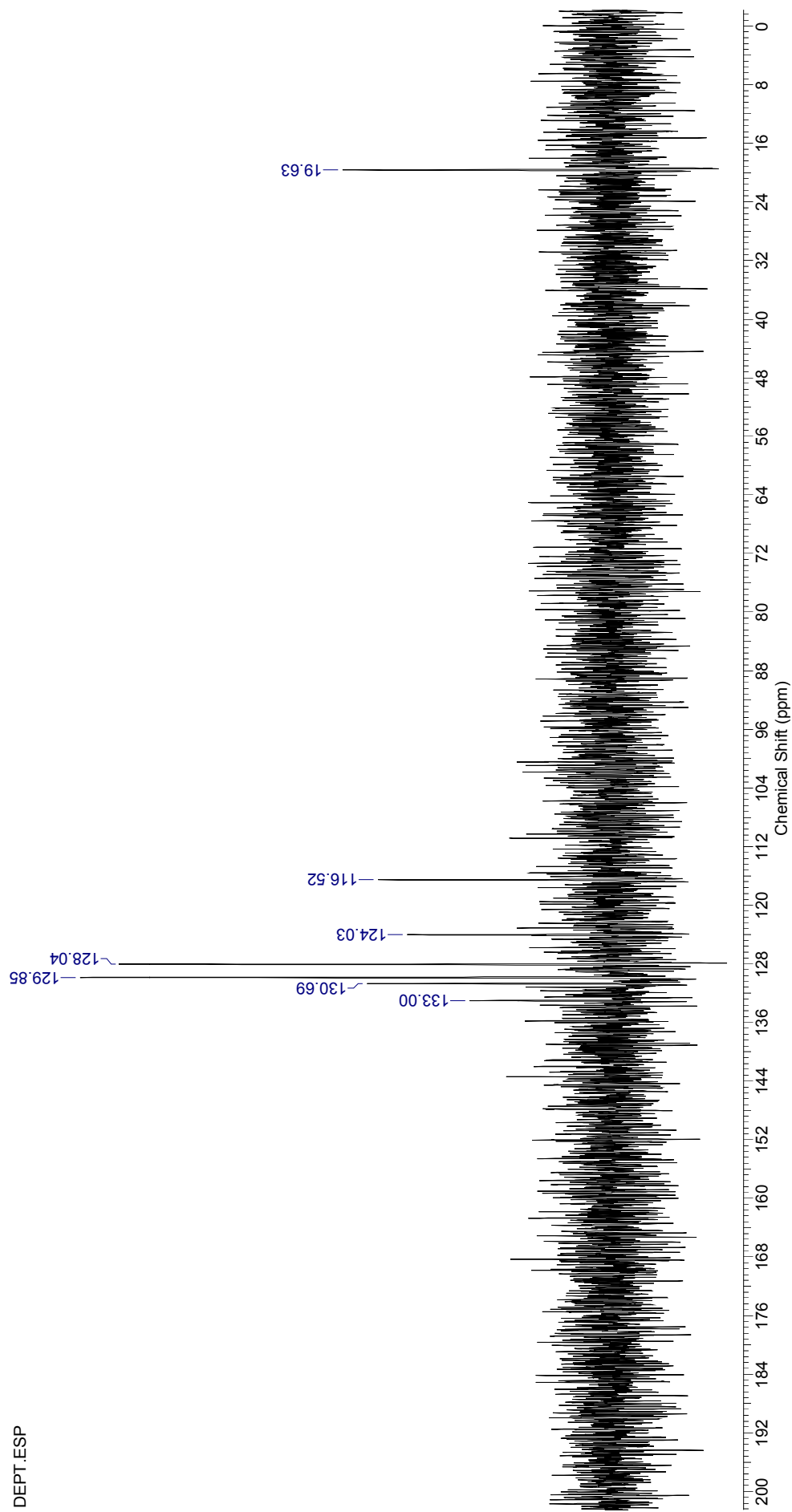
13C.ESP



# 1ab, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

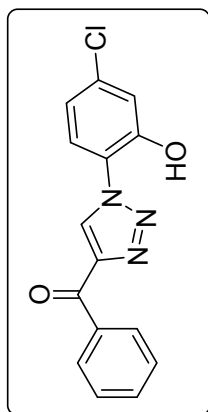


DEPT.ESP



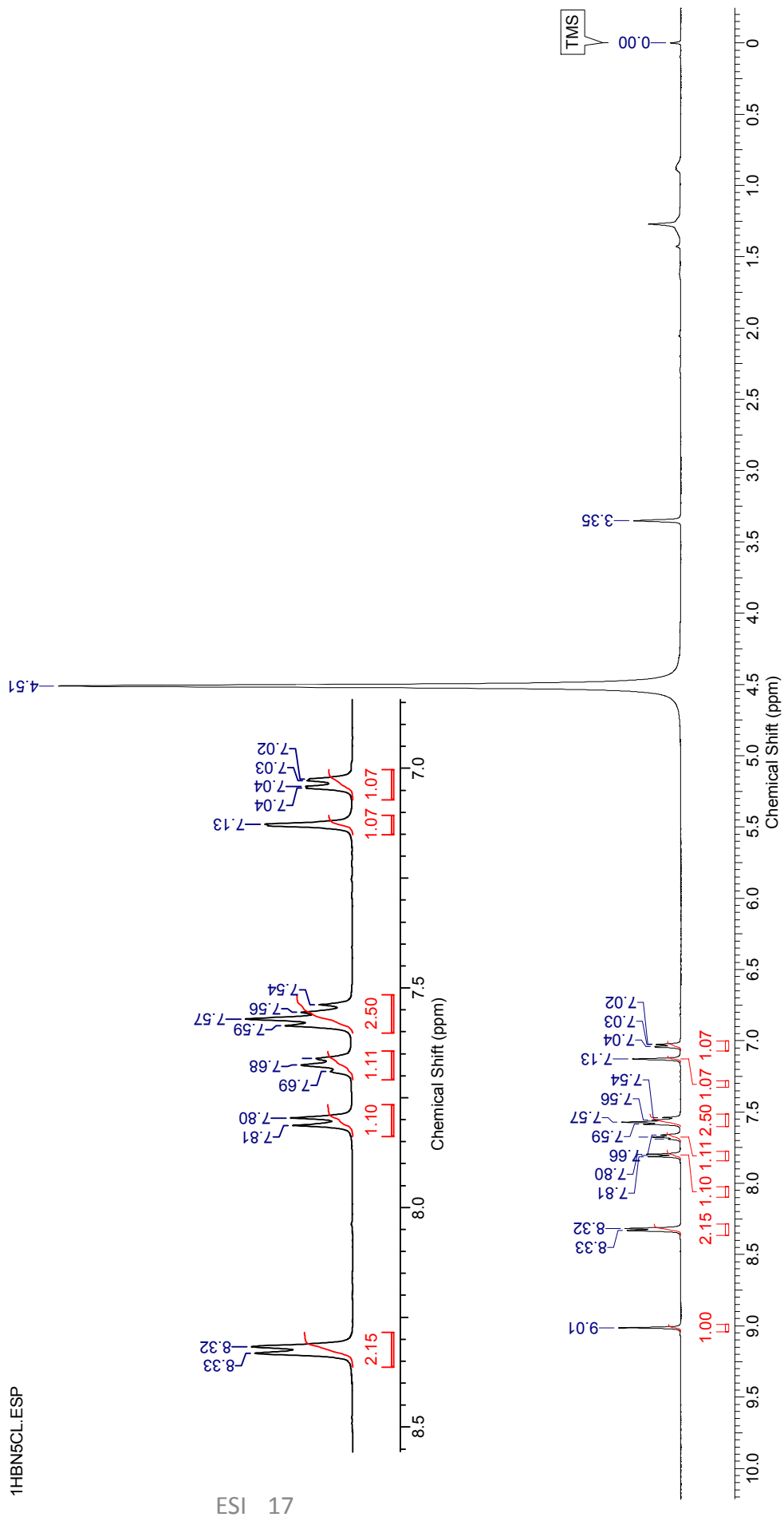


# 1ac, 500 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

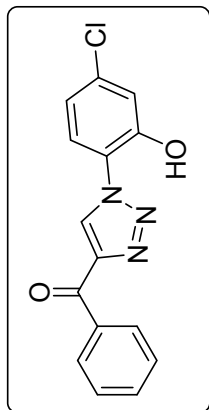


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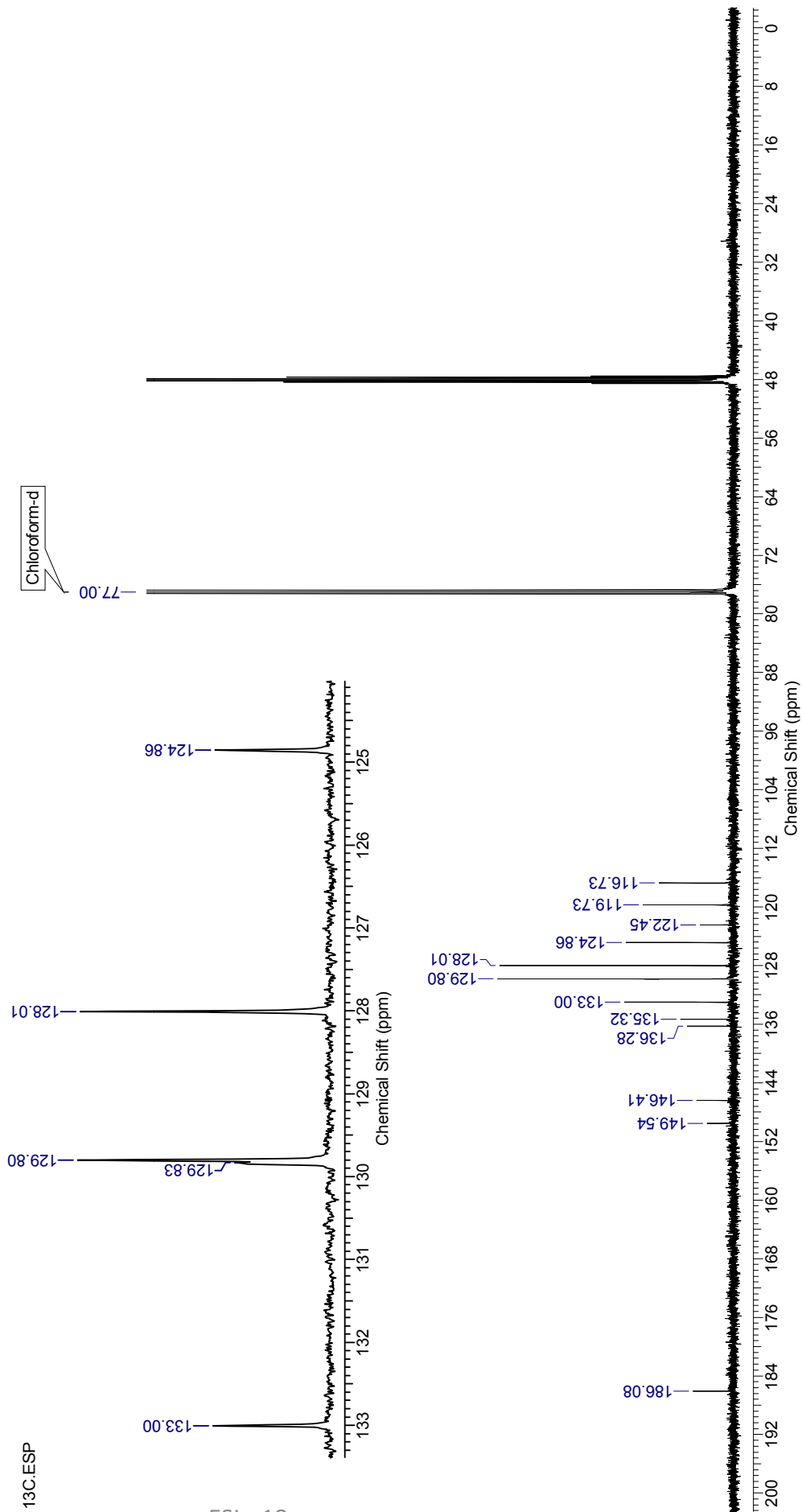
1HBN5CL.ESP



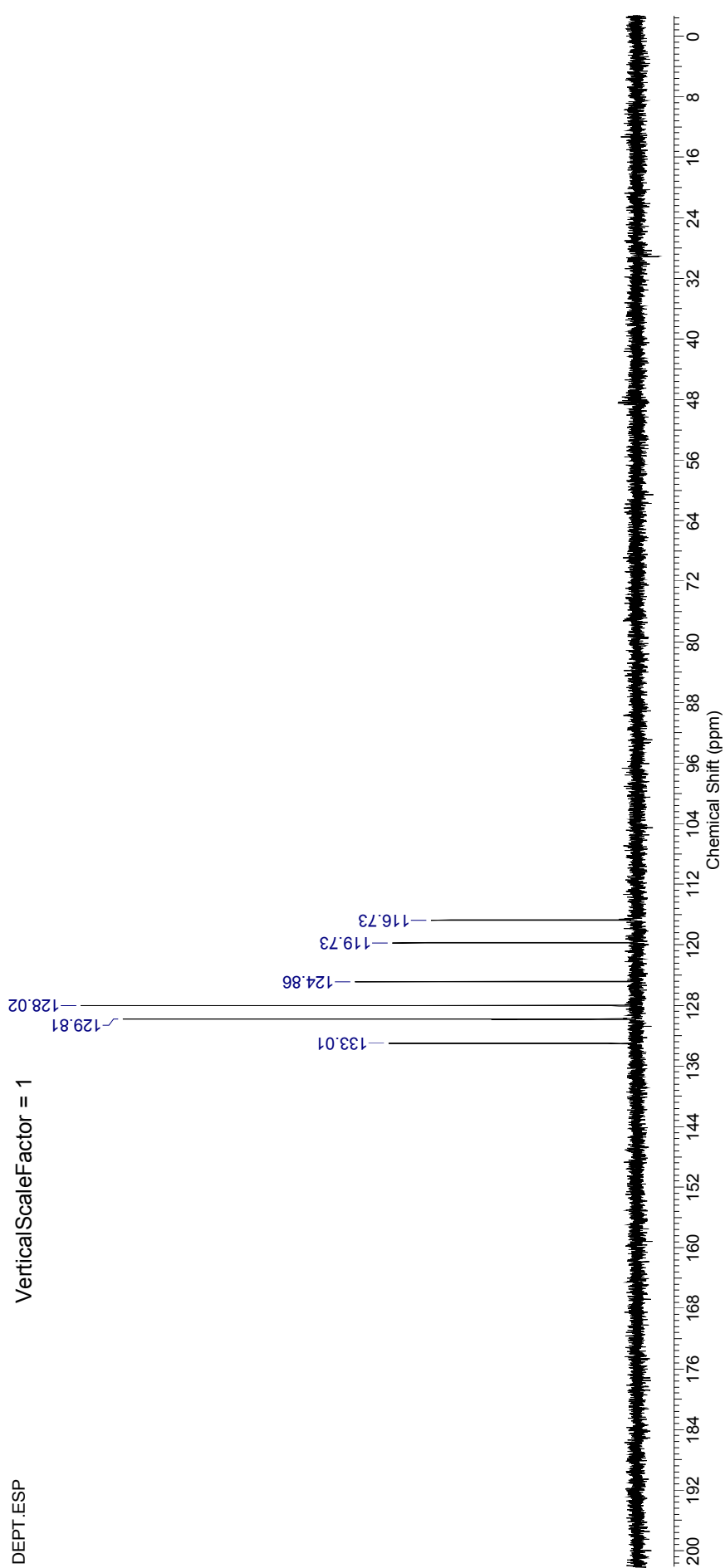
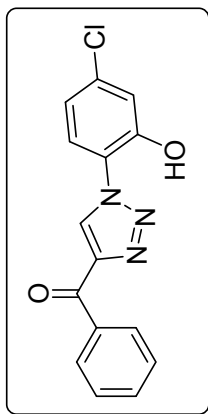
# 1ac, 125 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



13C.ESP

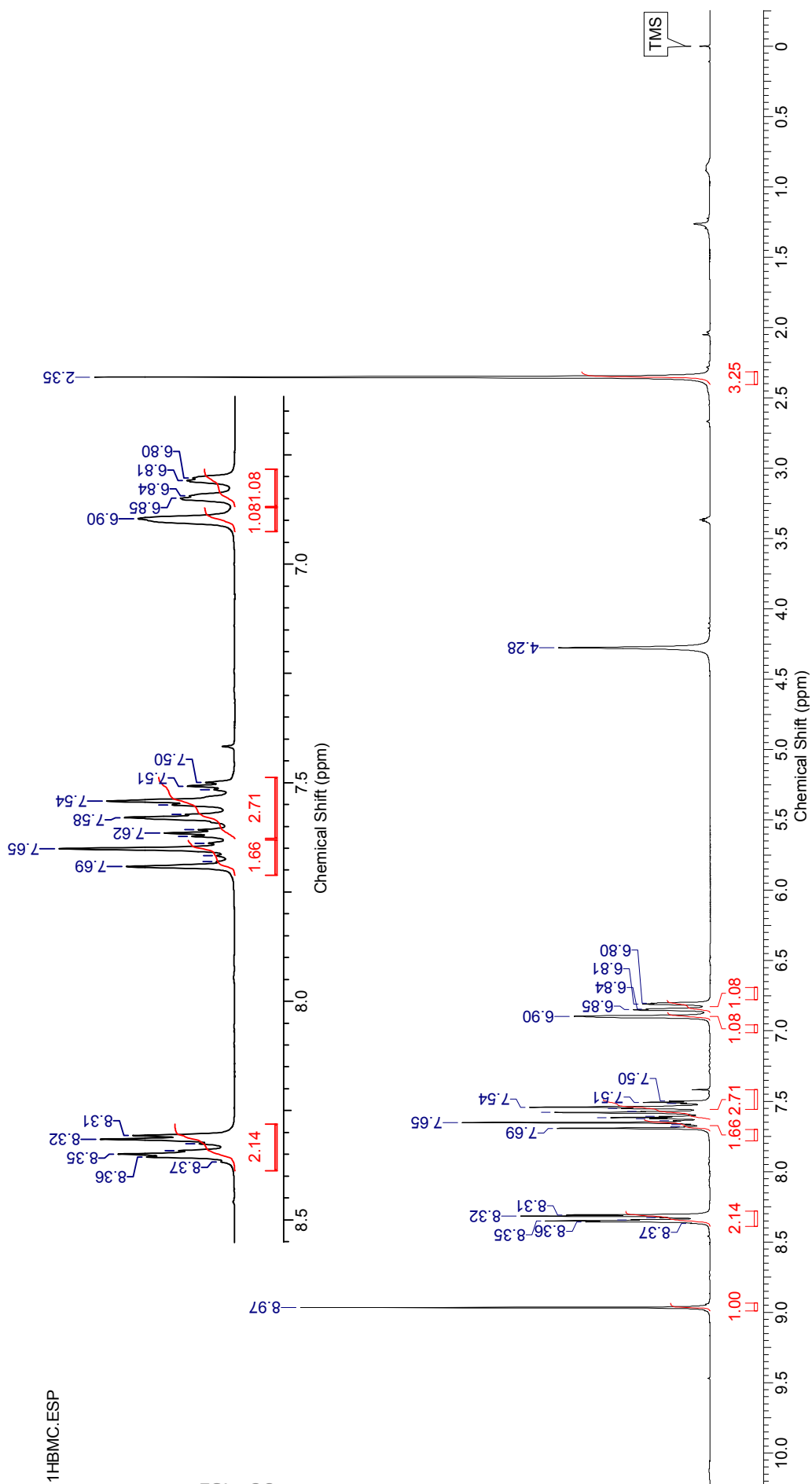
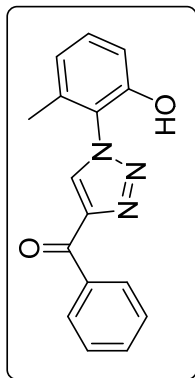


**1ac**, 125 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



# 1ae, 200 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

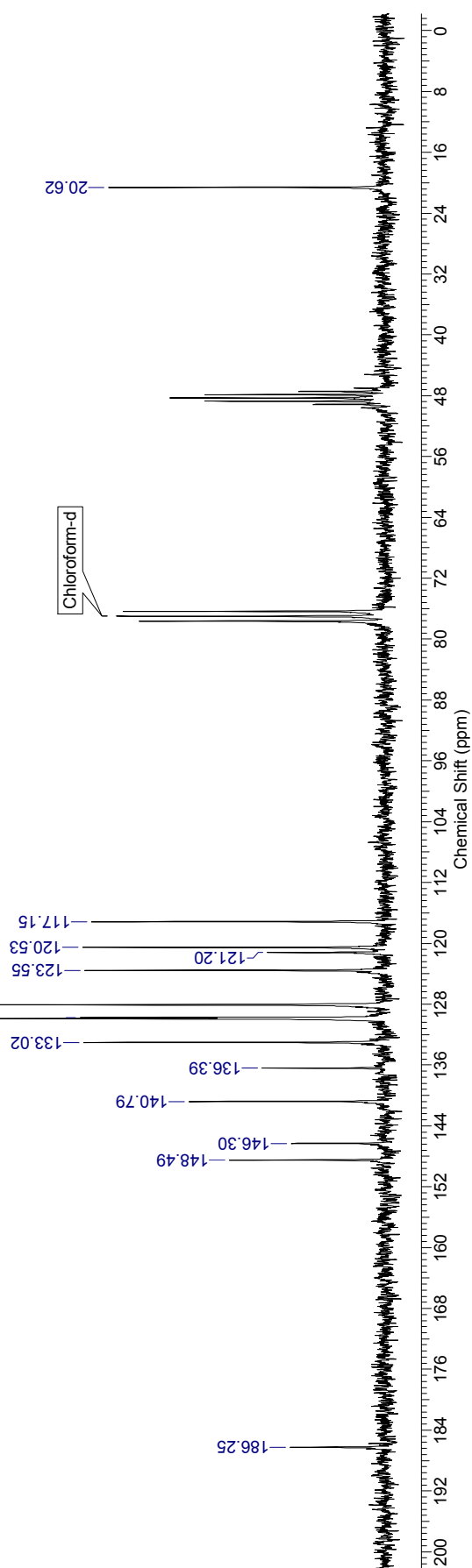
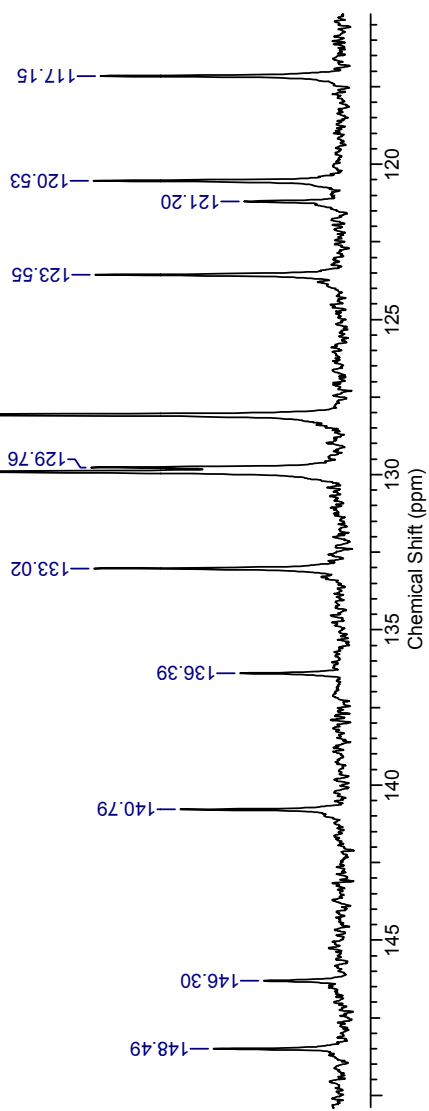
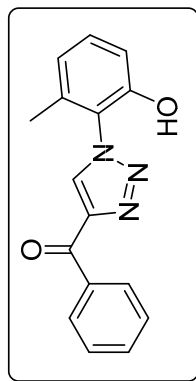
<sup>1</sup>HBMG.ESP



<sup>1</sup>HBMG.ESP

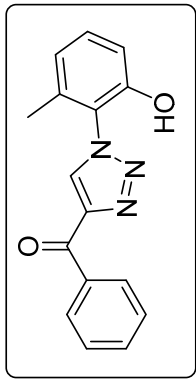
# 1ae, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

<sup>13</sup>C.ESP

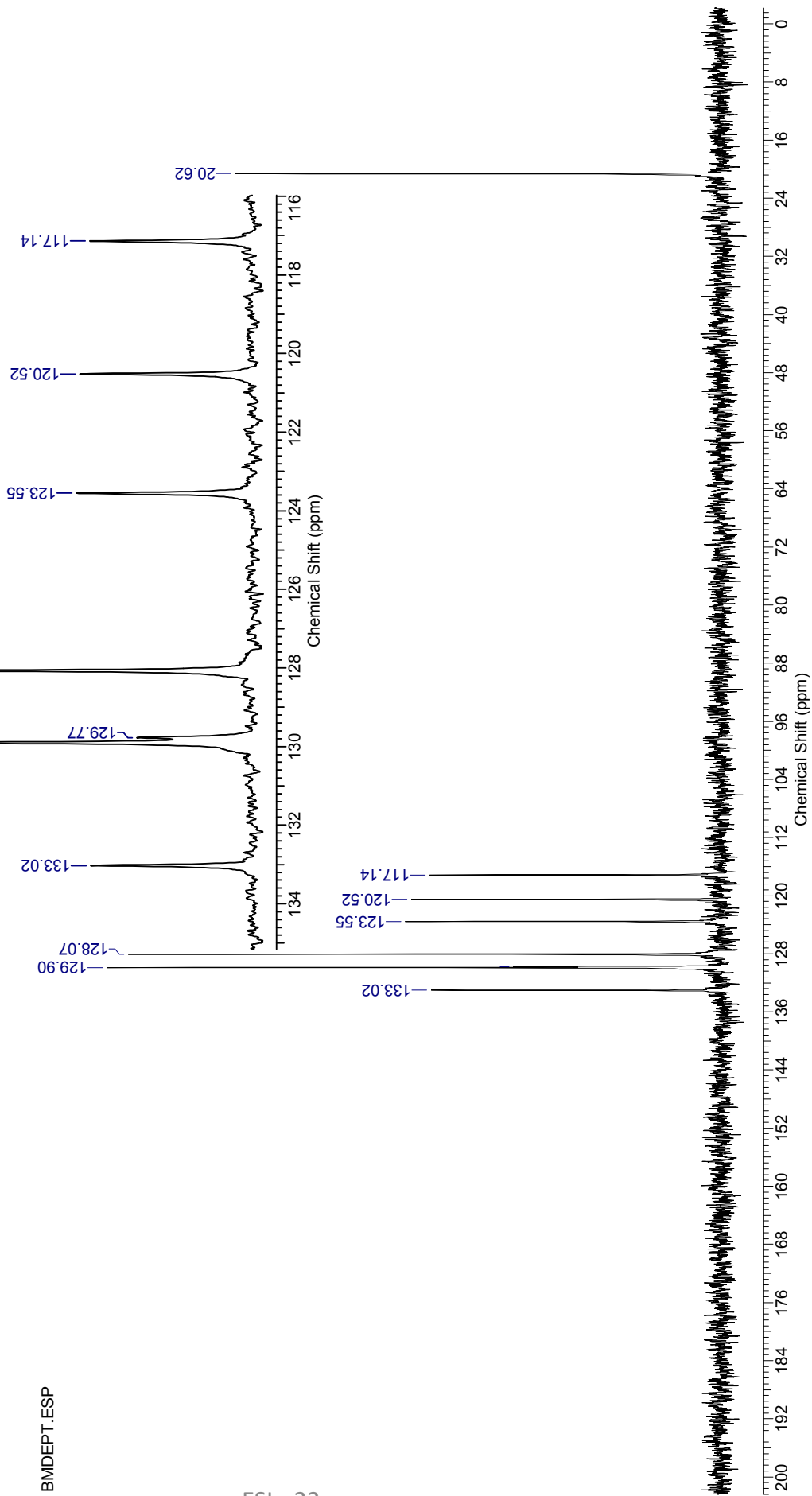


13C.ESP

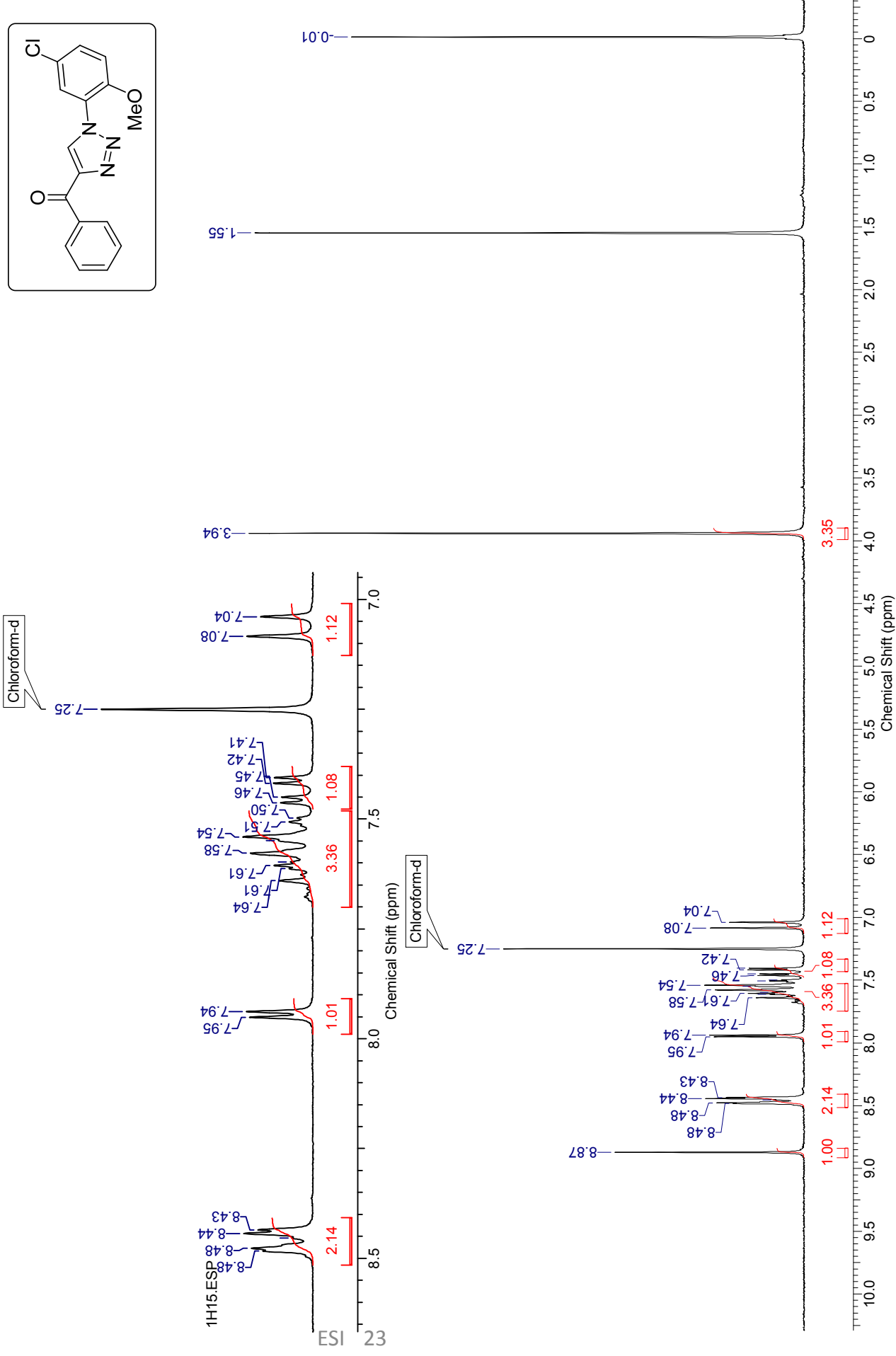
# 1ae, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



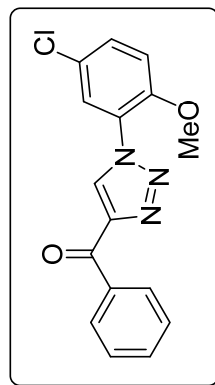
BMDEPT.ESP



BMDEPT.ESP

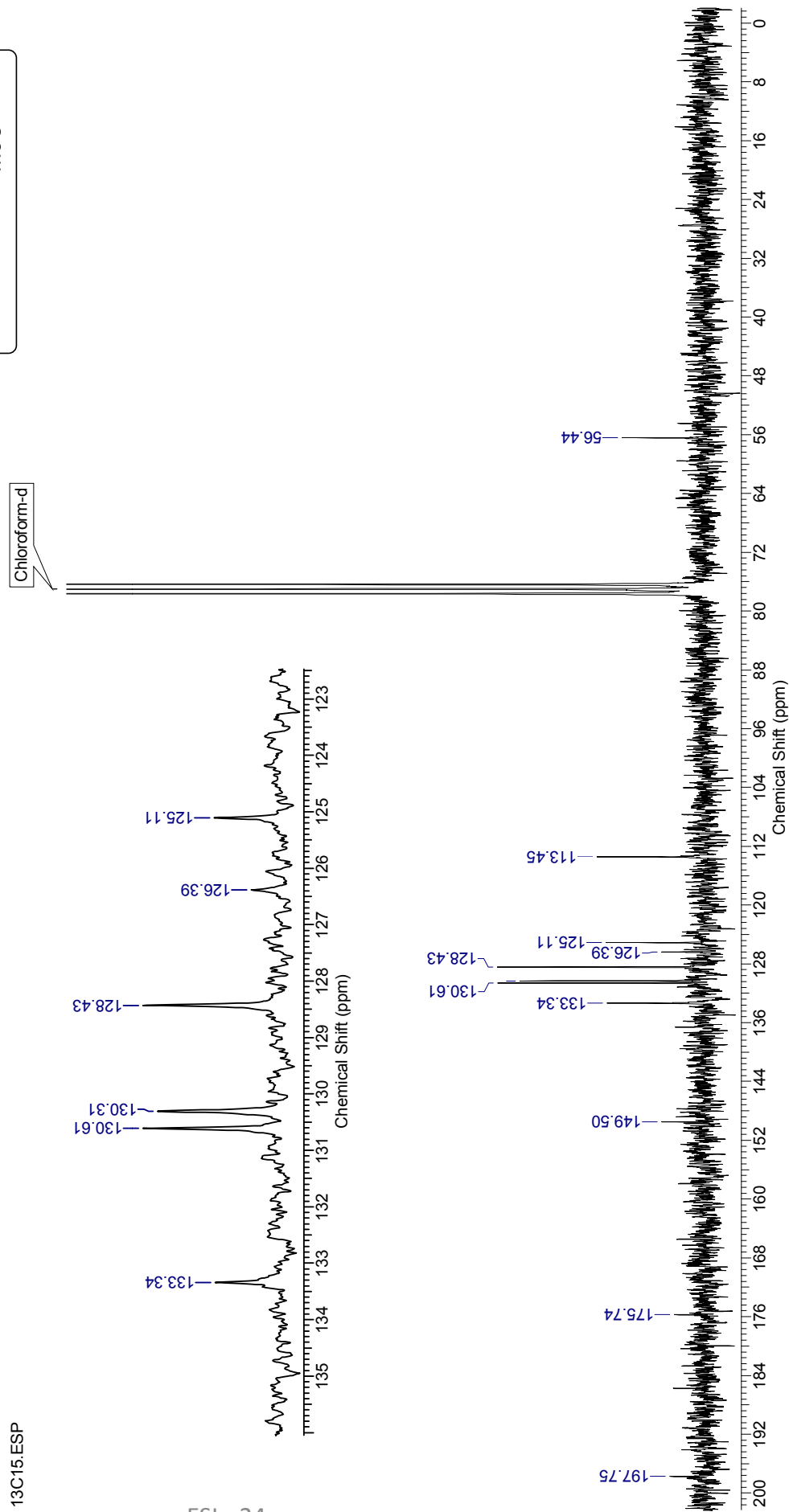
**1af, 200 MHz, CDCl<sub>3</sub>**

# 1af, 50 MHz, CDCl<sub>3</sub>



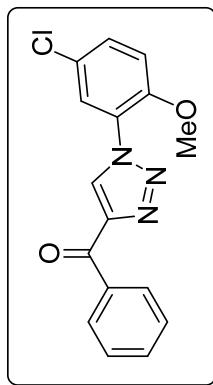
13C15.ESP

13C15.ESP

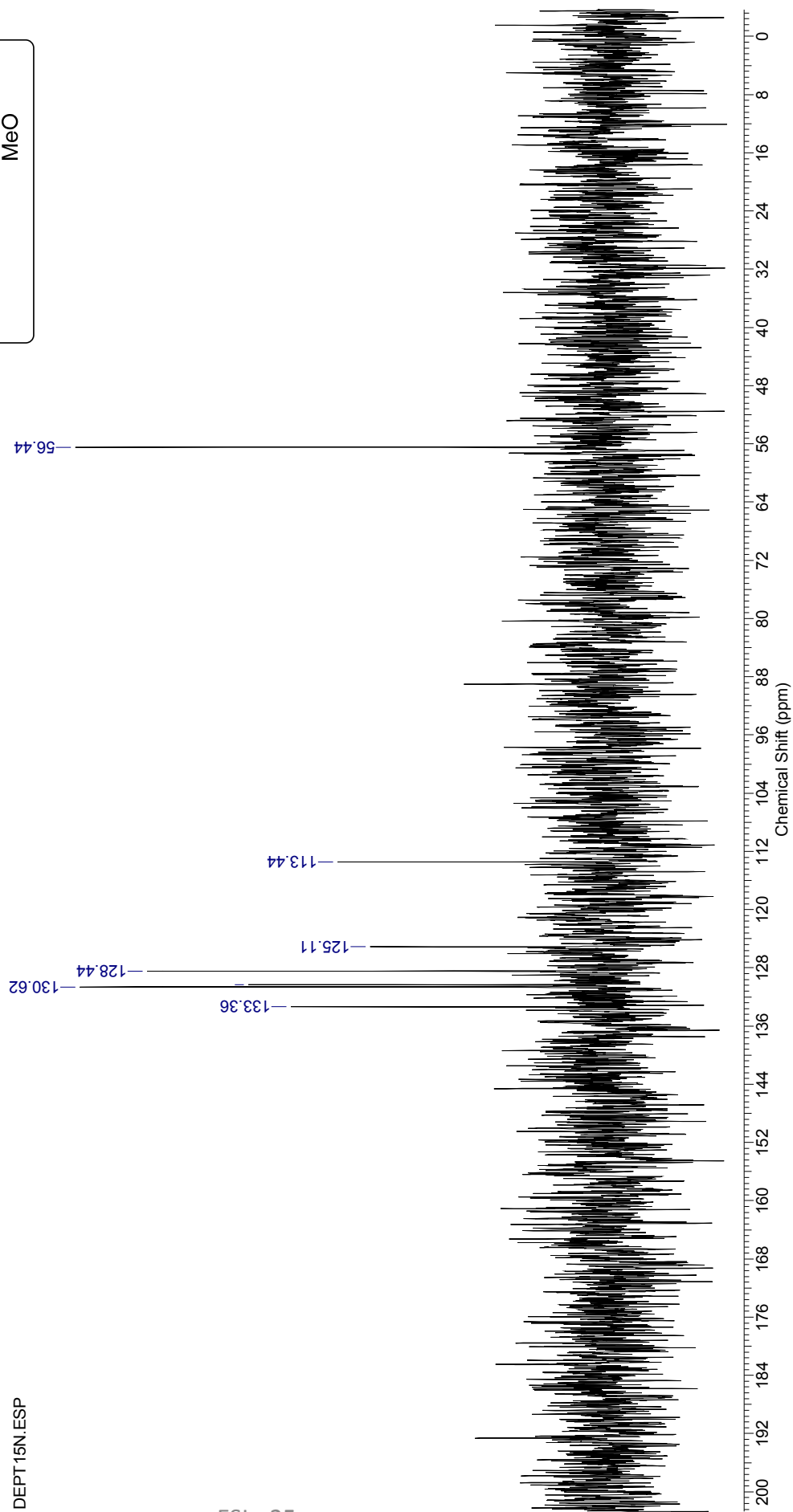




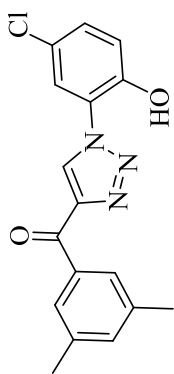
# 1af, 50 MHz, CDCl<sub>3</sub>



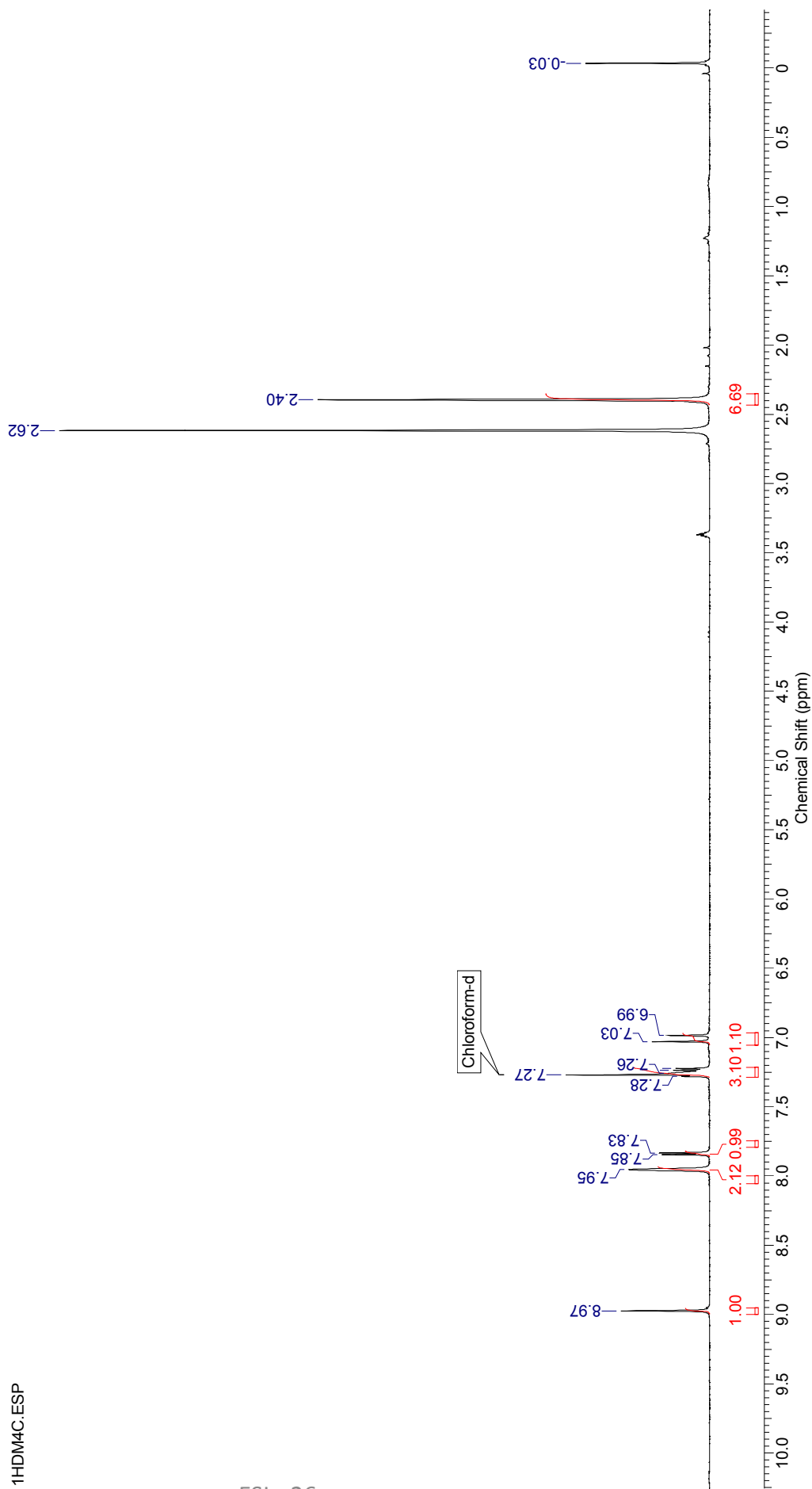
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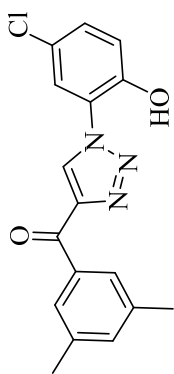
# 1ba, 200 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)



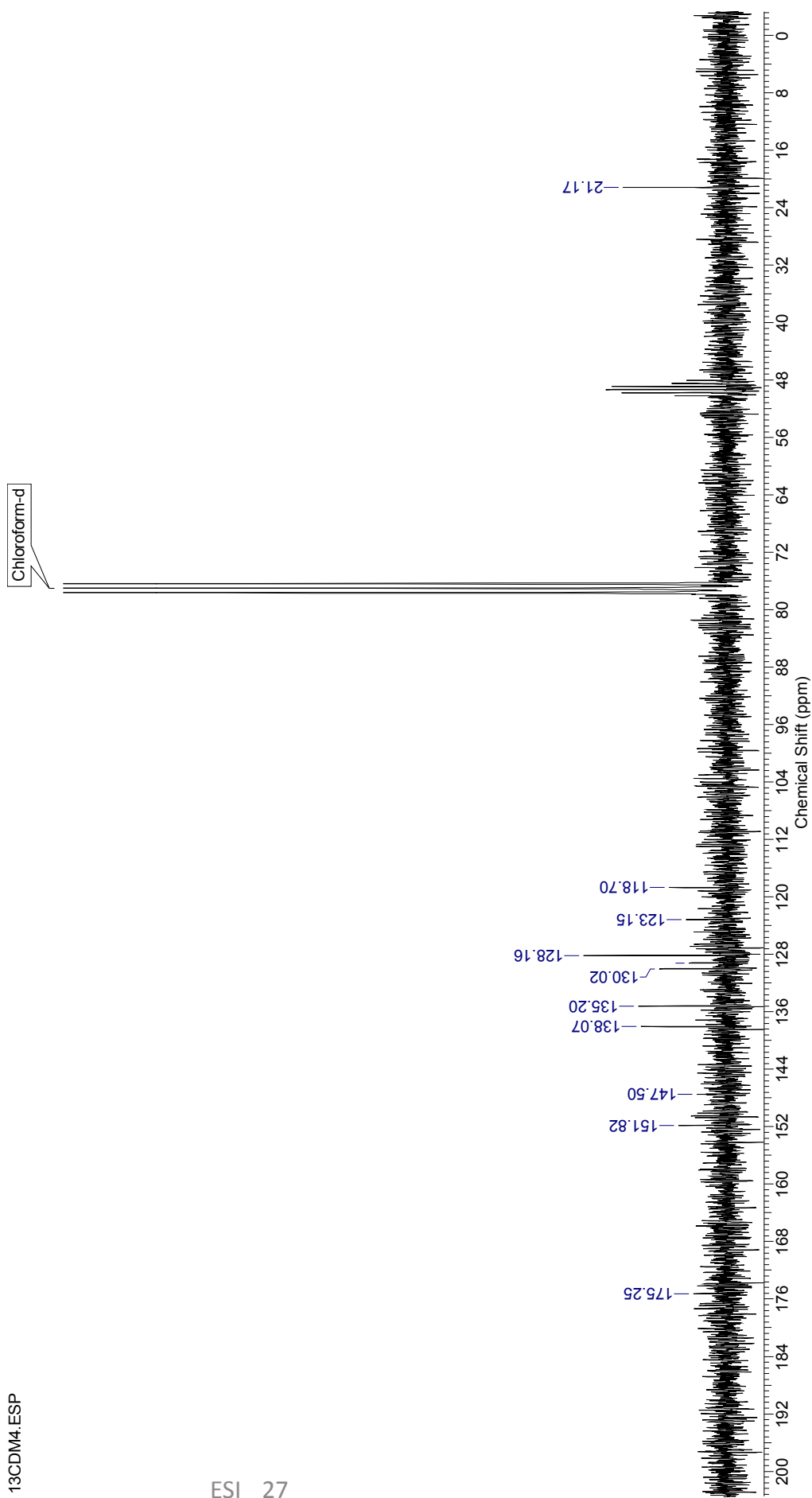
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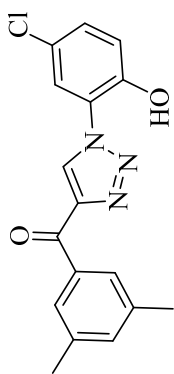
# 1ba, 50 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)



13CDM4.ESP

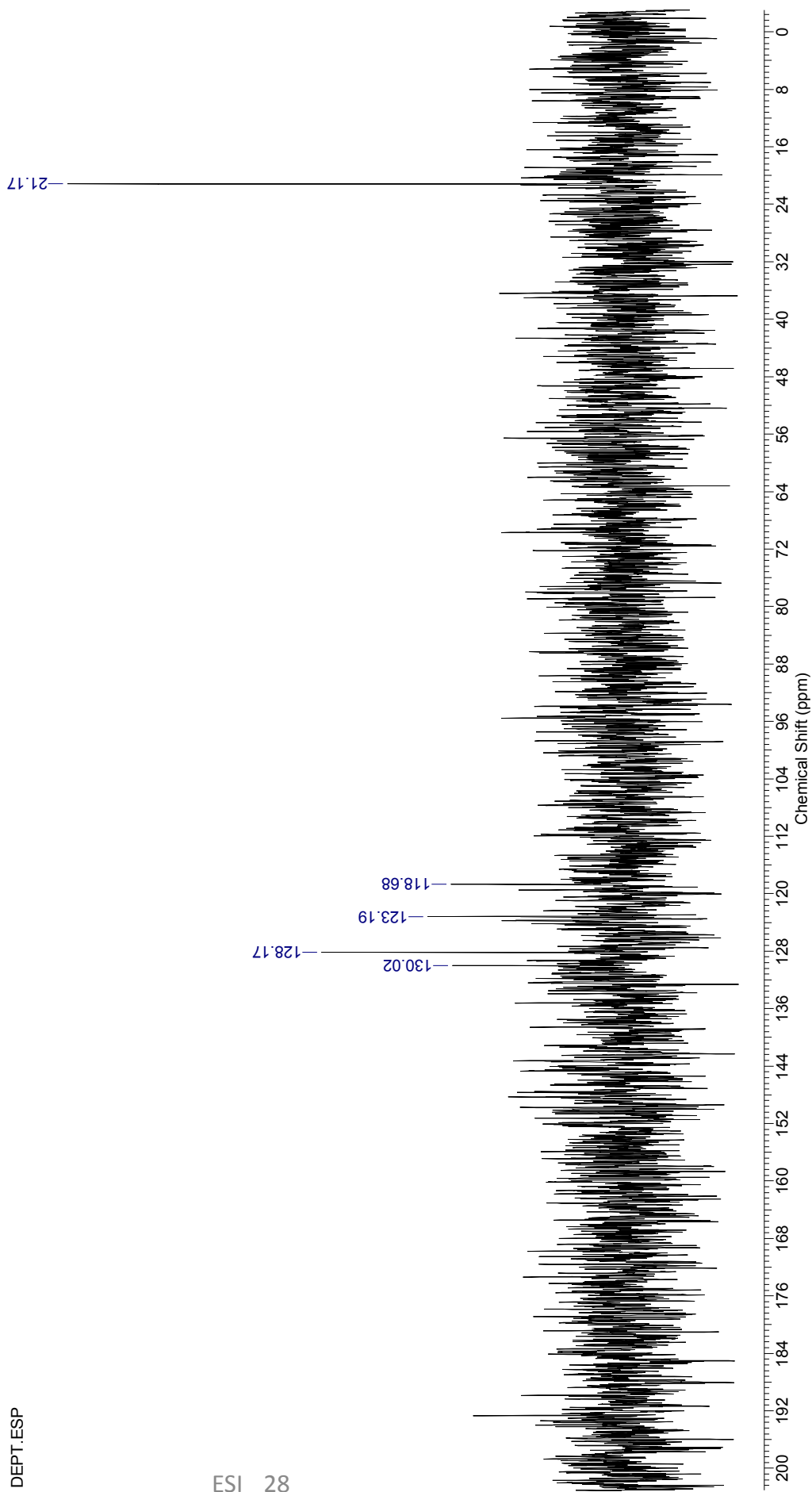


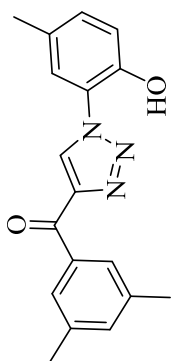
# 1ba, 50 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)



DEPT.ESP

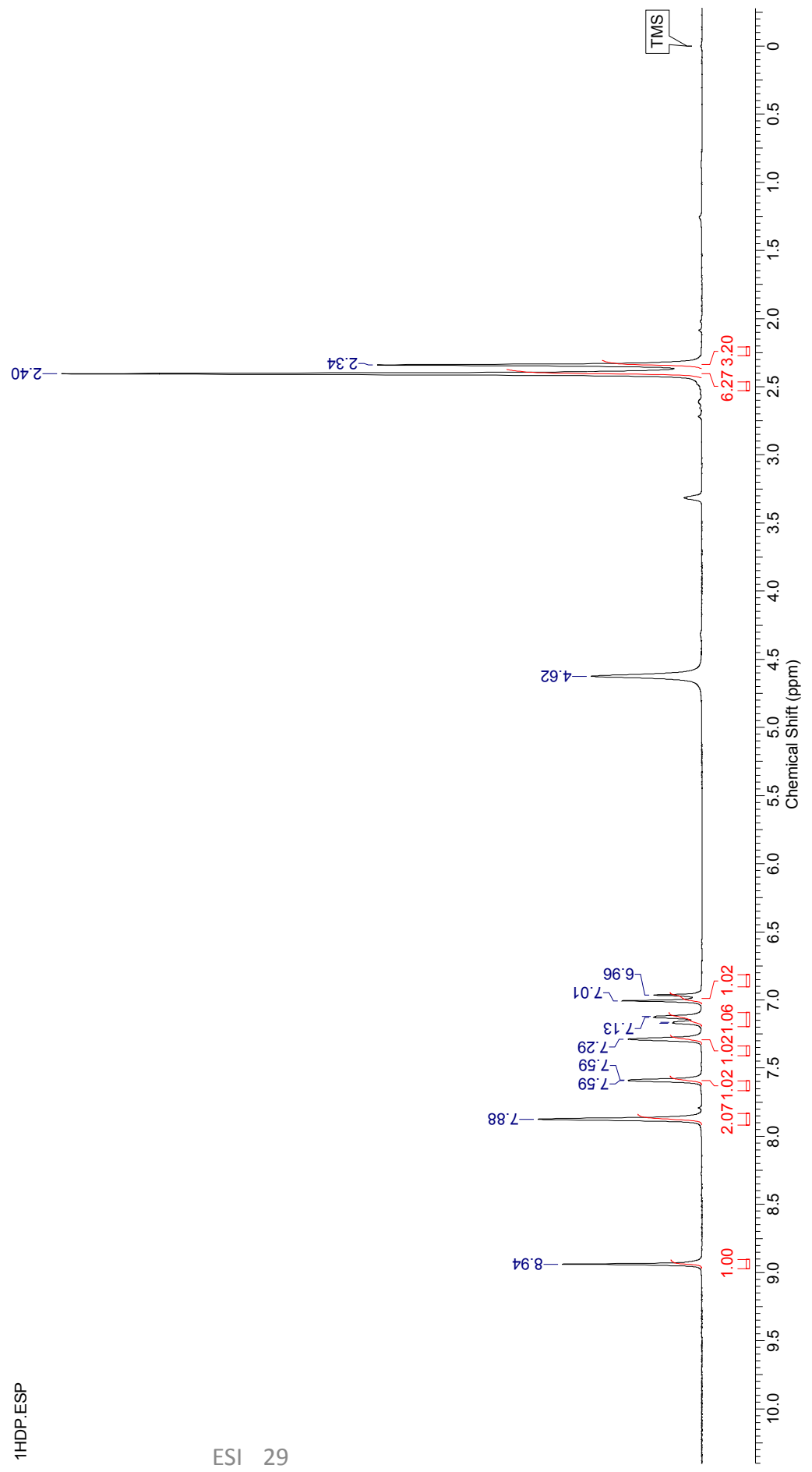
ESI 28

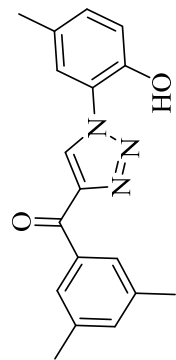




**1bb**, 200 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)

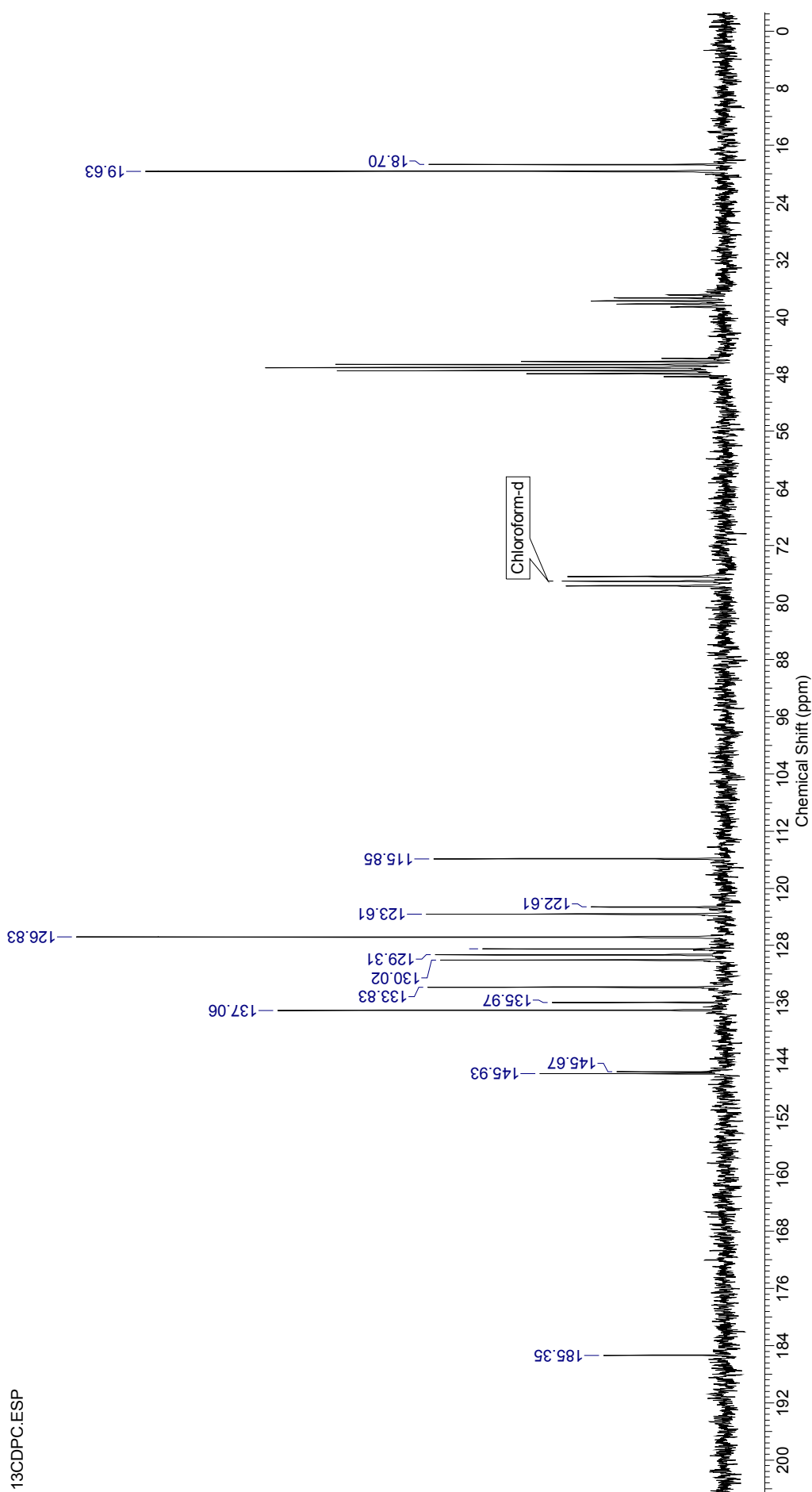
1HDP.ESP

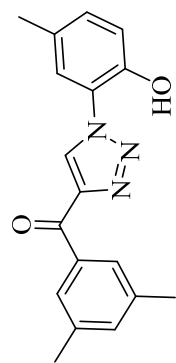




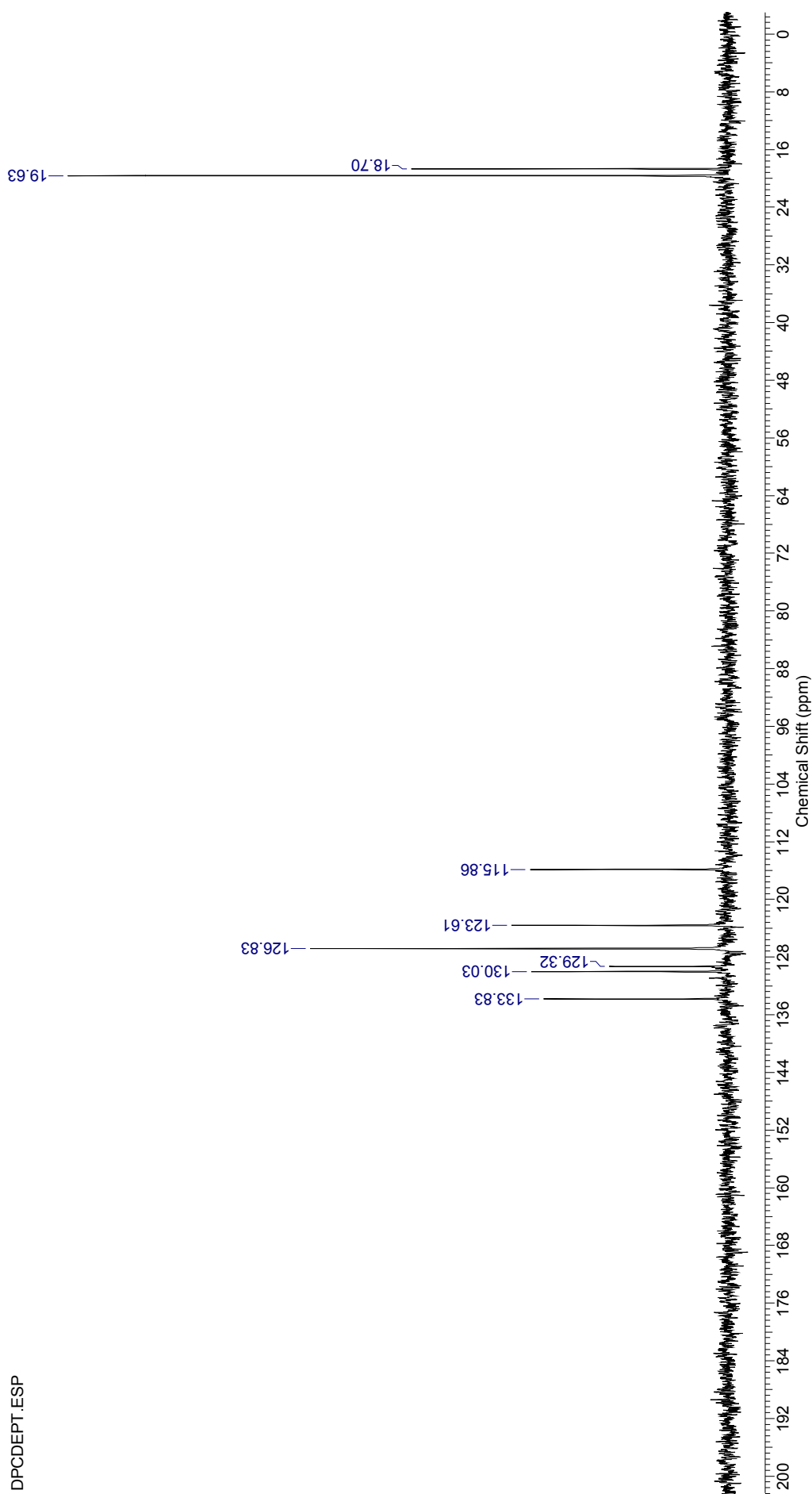
**1bb**, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)

13CDPC.ESP



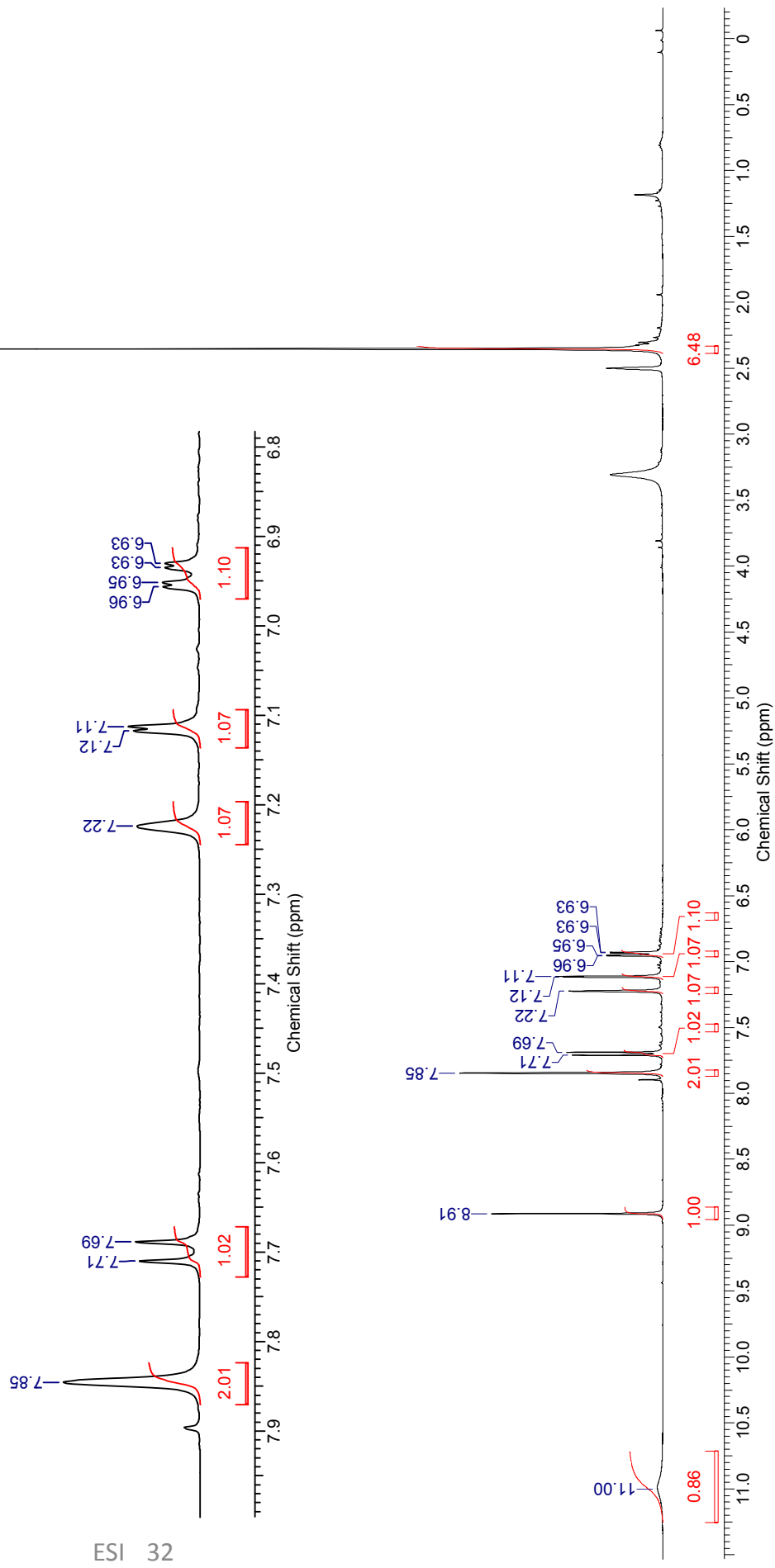
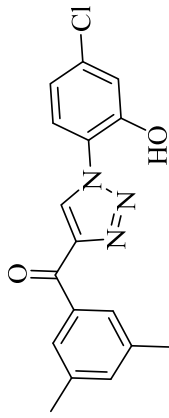


**1bb**, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)



# 1bc, 400 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)

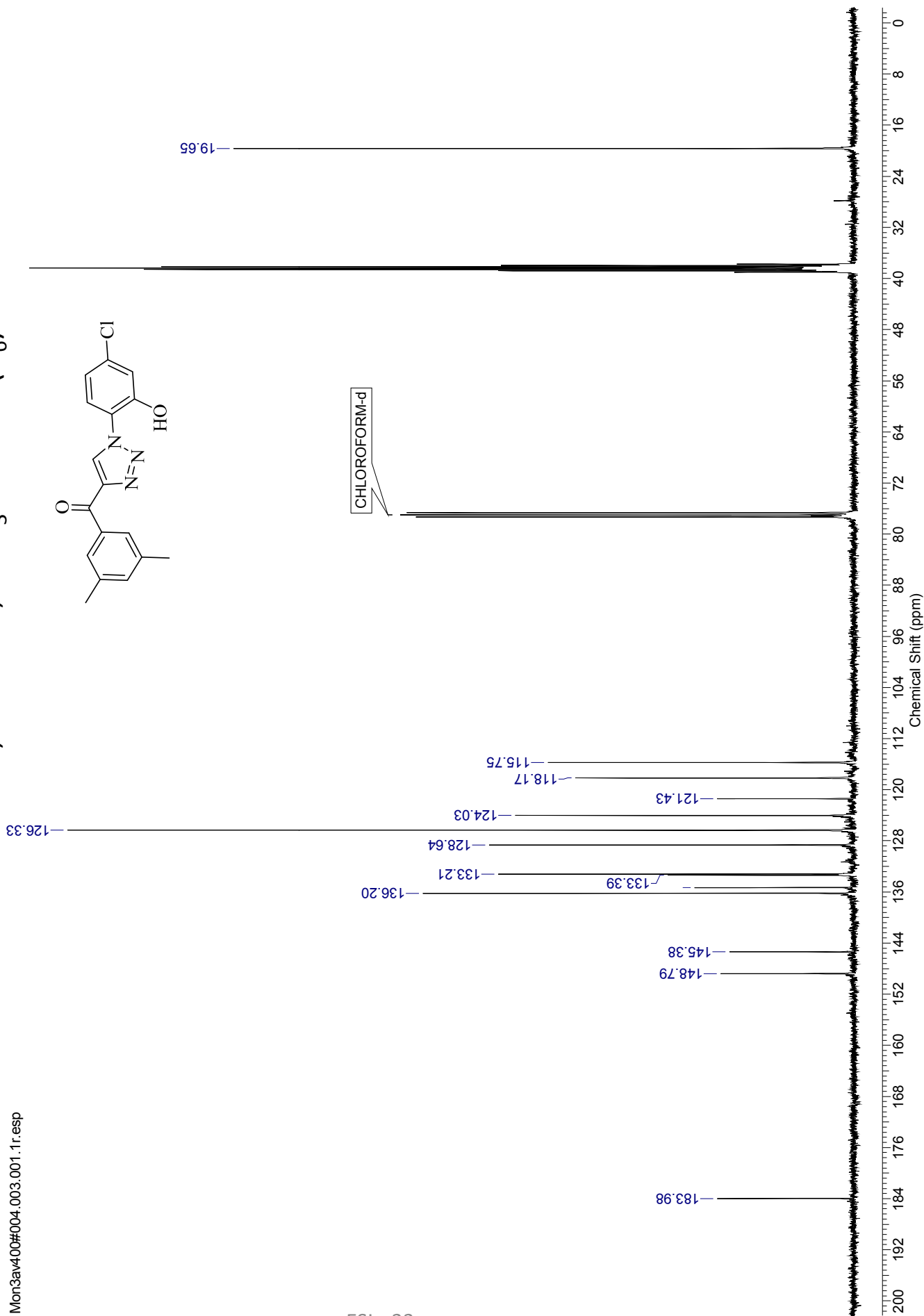
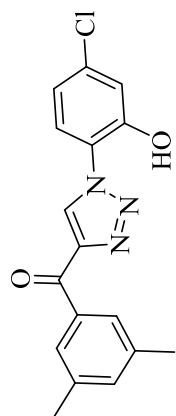
DMSO-d6  
-2.35





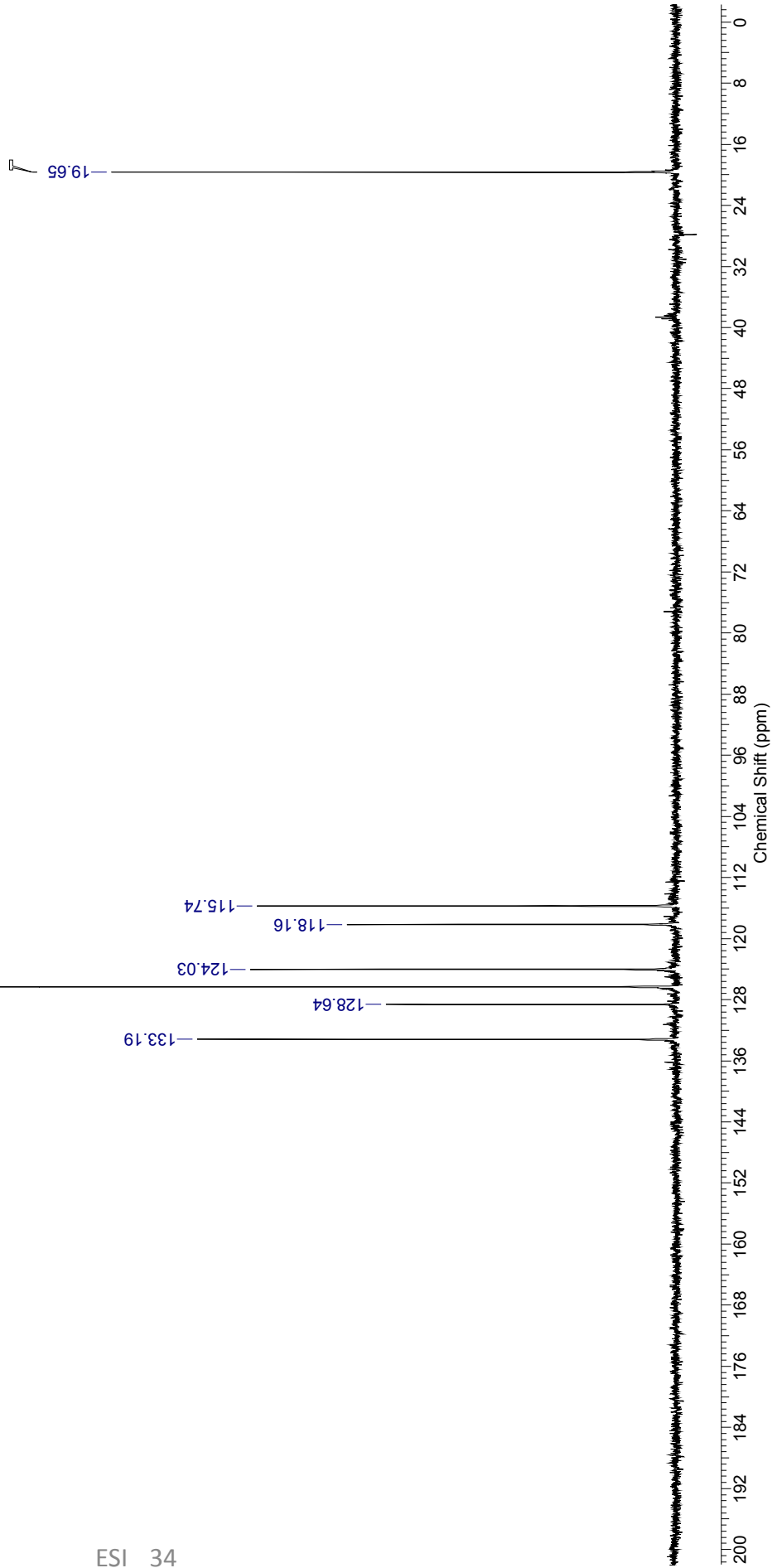
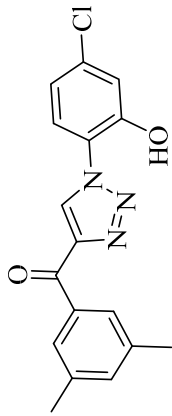
# 1bc, 100 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)

Mon3av400#004.003.001.1r.esp

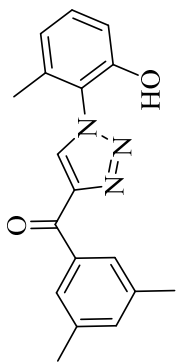


# 1bc, 100 MHz, CDCl<sub>3</sub> + DMSO (D<sub>6</sub>)

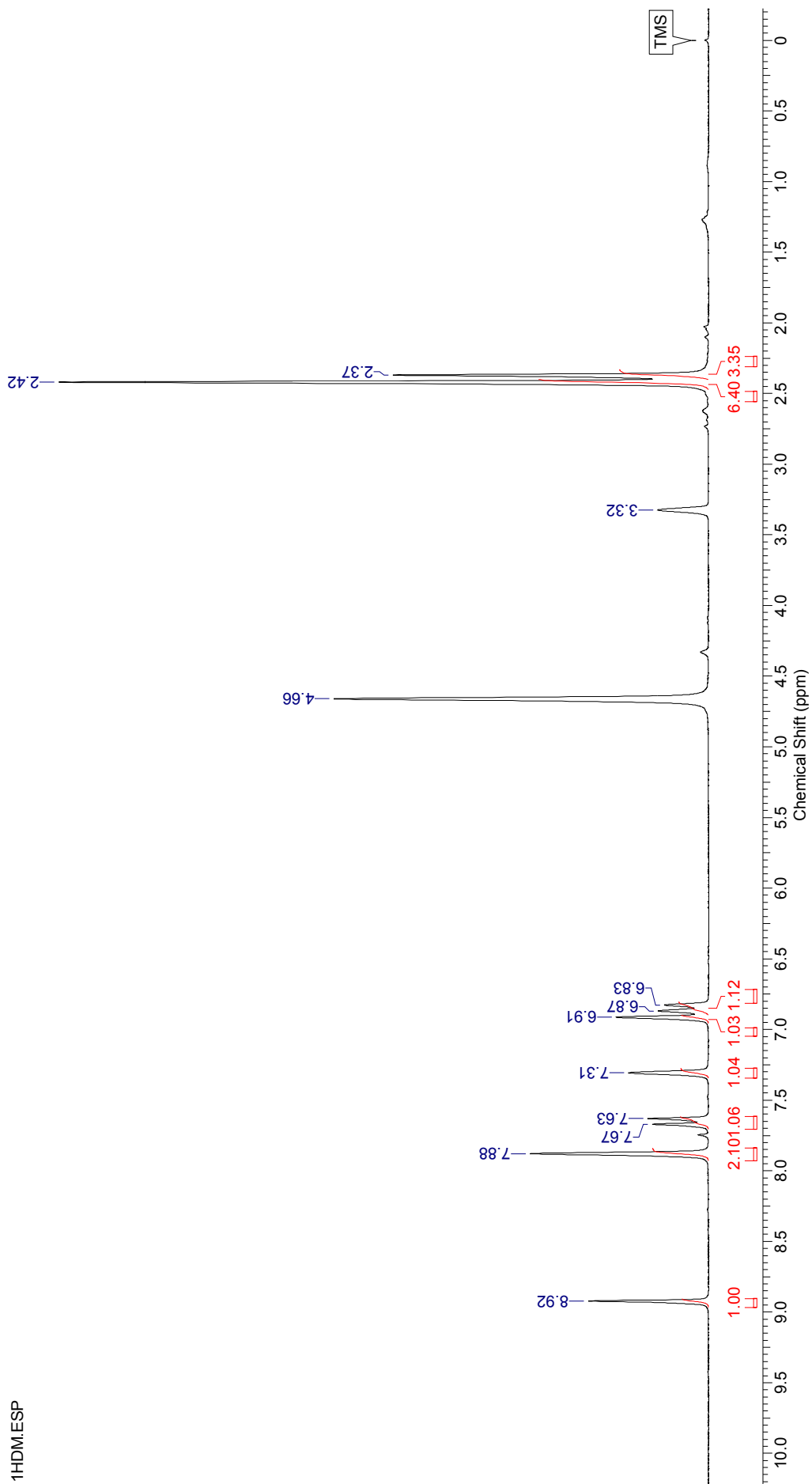
Mon3av400#004.002.001.1r.esp



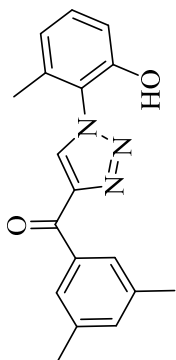
# 1be, 200 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



1HDM.ESP

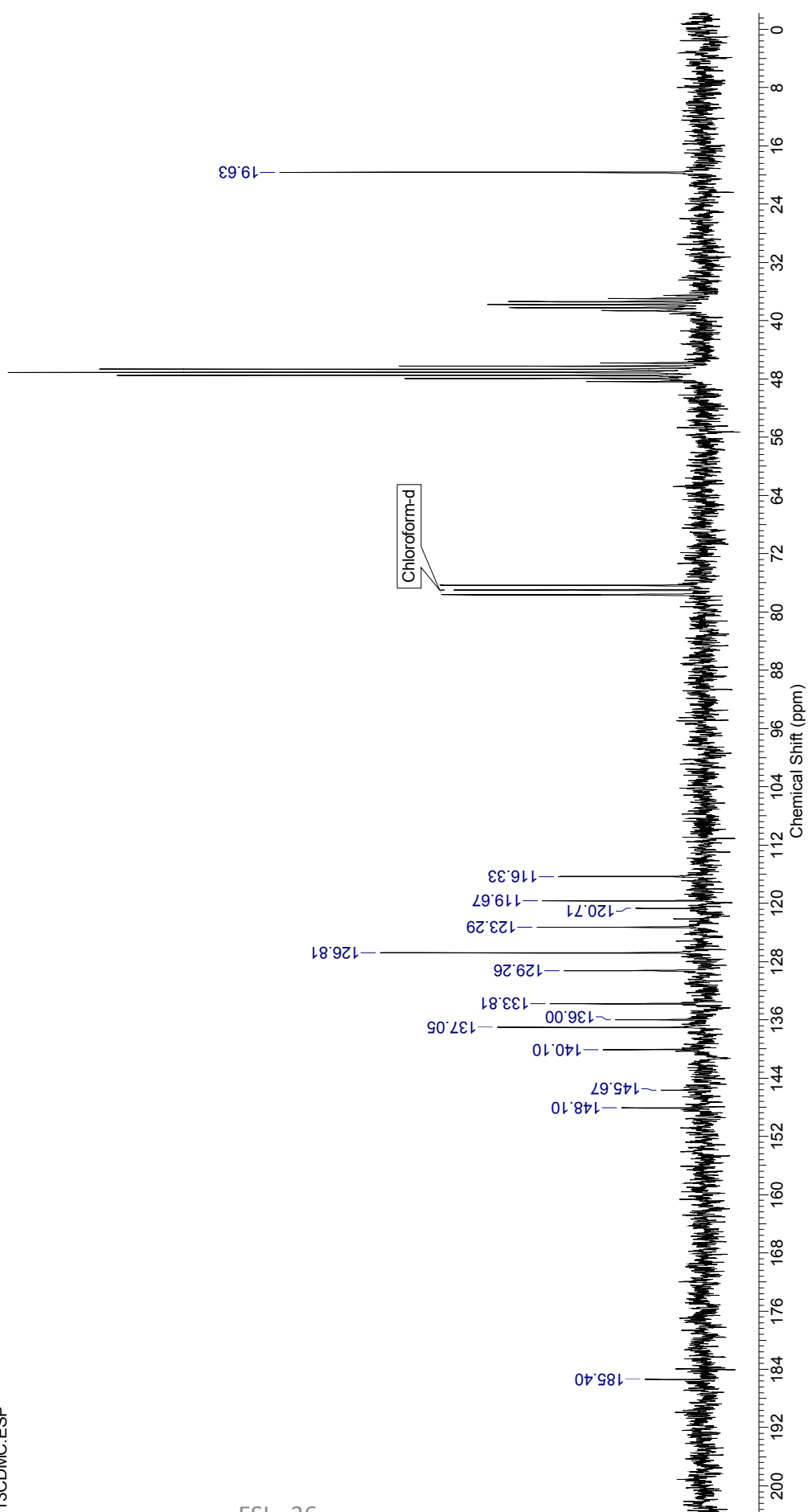


# 1be, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

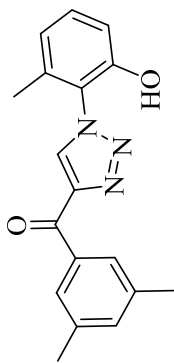


13CDMC.ESP

ESI 36

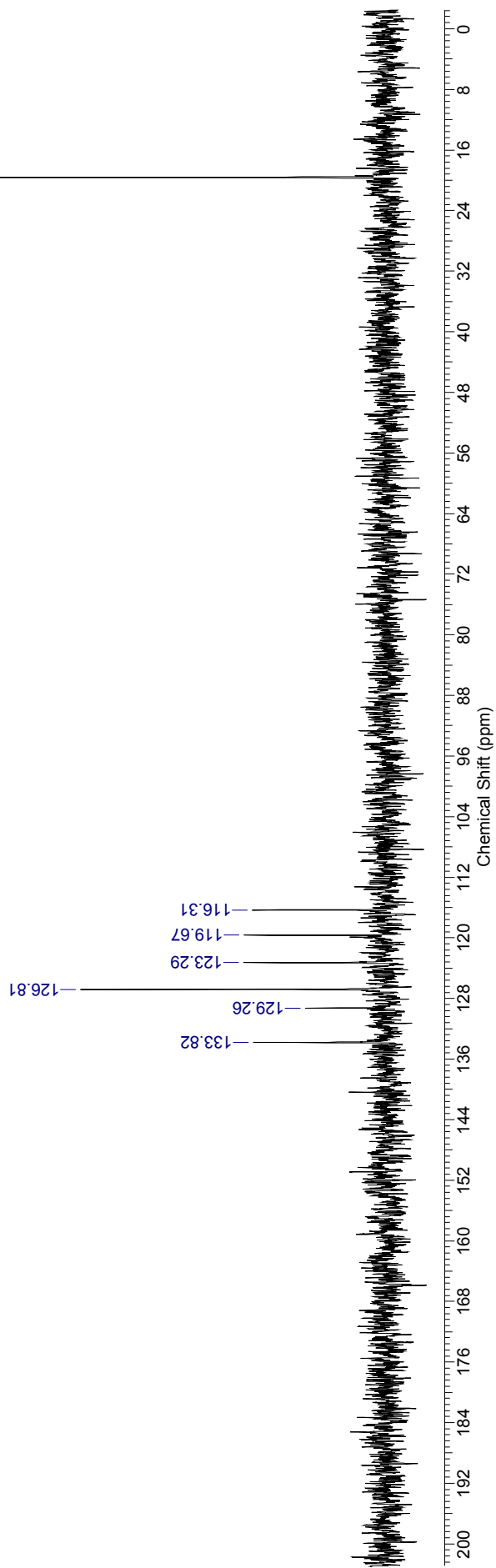


# 1be, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

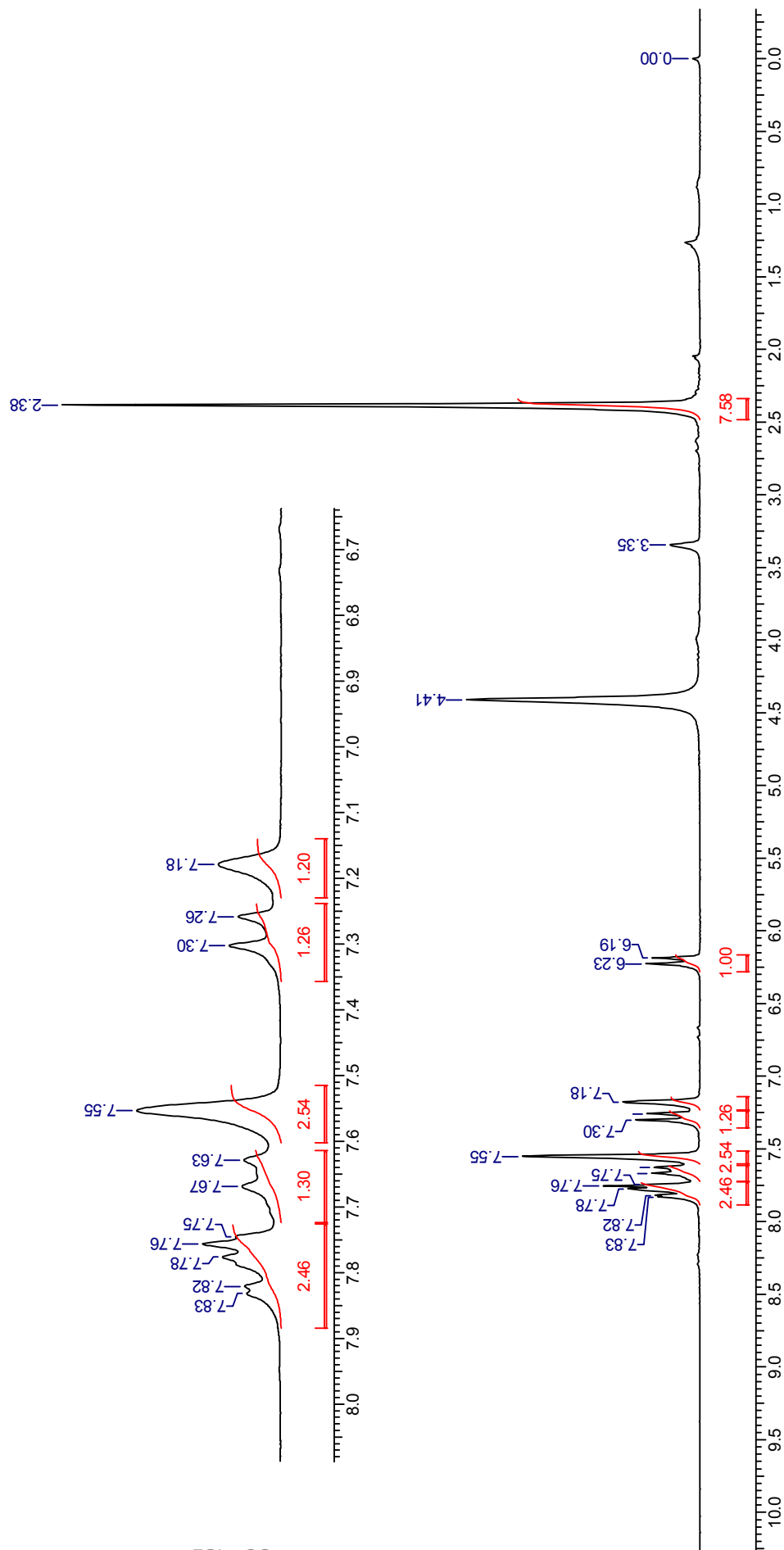
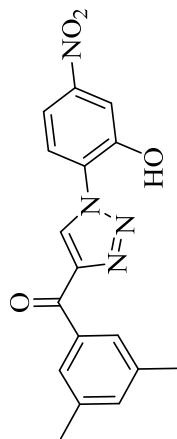


DMCDEPT.ESP

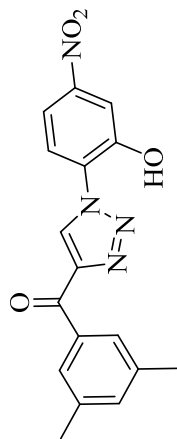
ESI 37



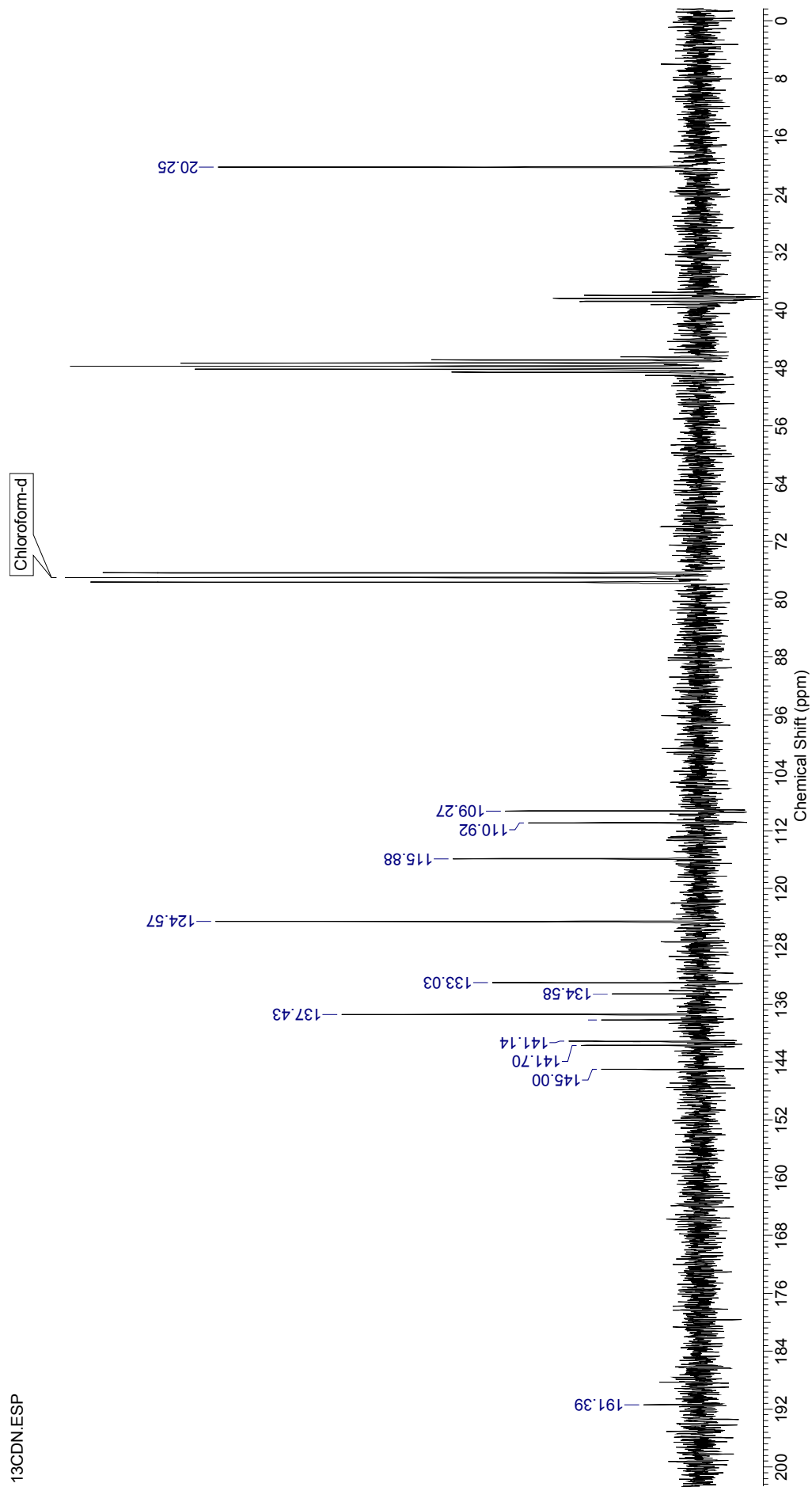
# 1bd, 200 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)



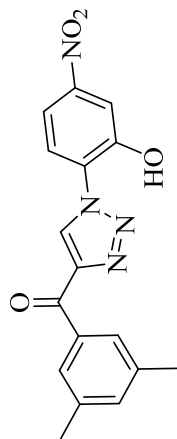
# 1bd, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)



<sup>13</sup>CDN.ESP

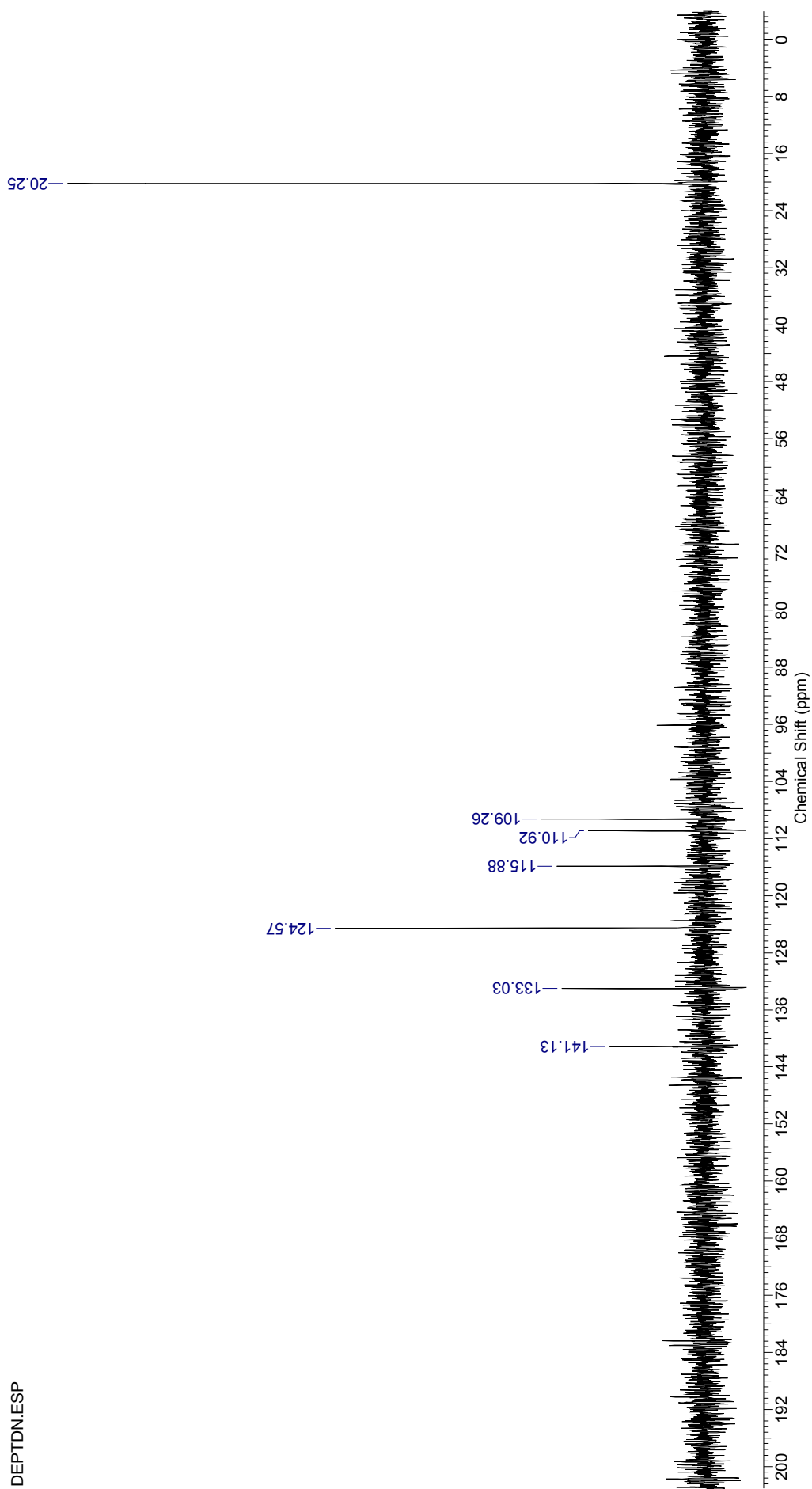


**1bd, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)**



DEPTDN.ESP

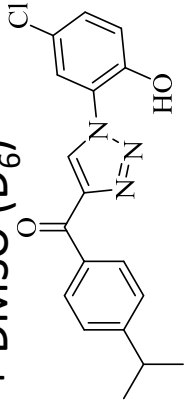
ESI 40



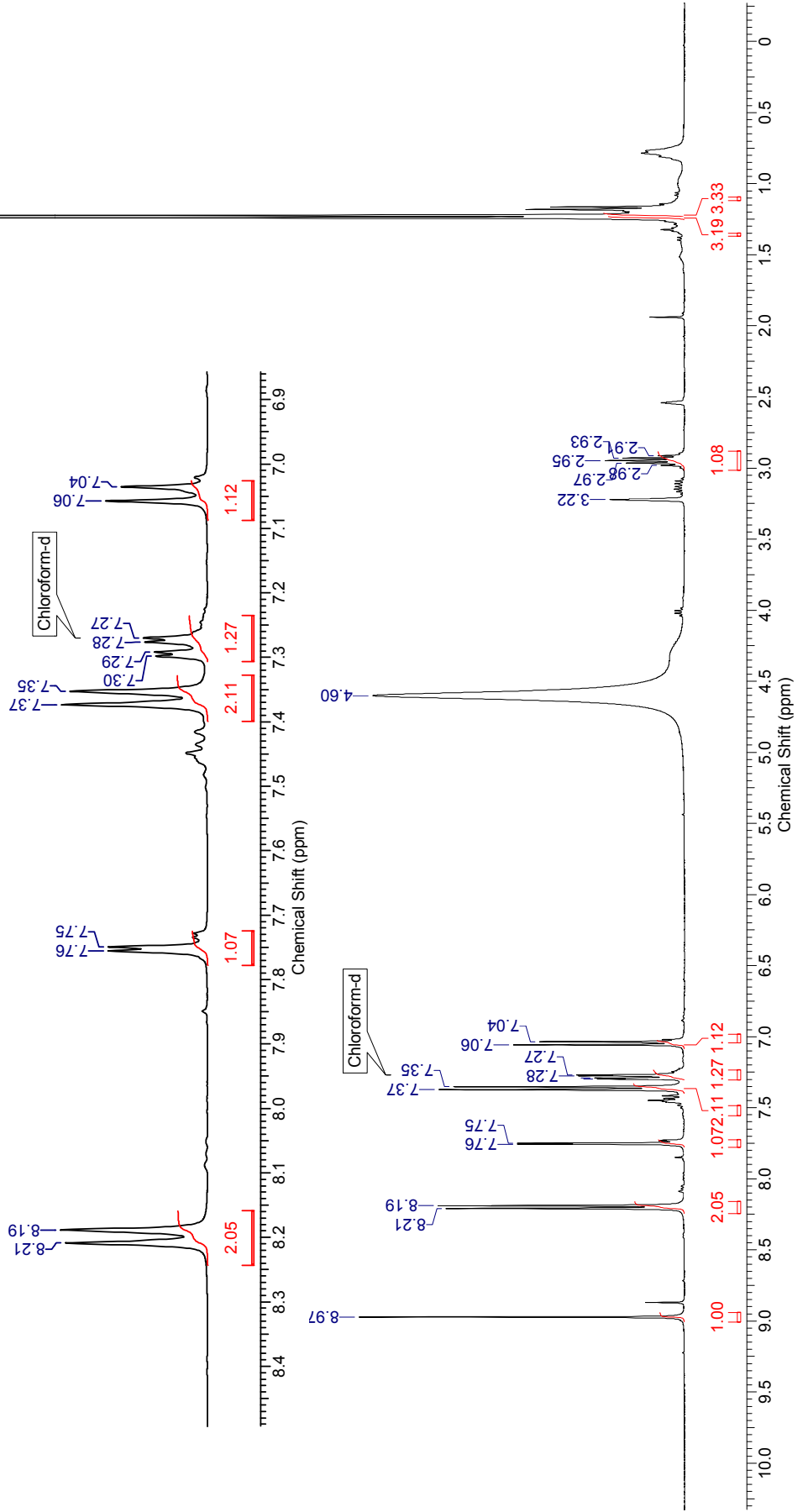


<sup>1</sup>H NMR.ESP

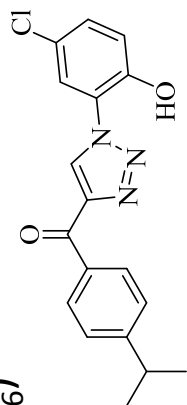
# 1ca, 400 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)



<sup>1</sup>H NMR.ESP

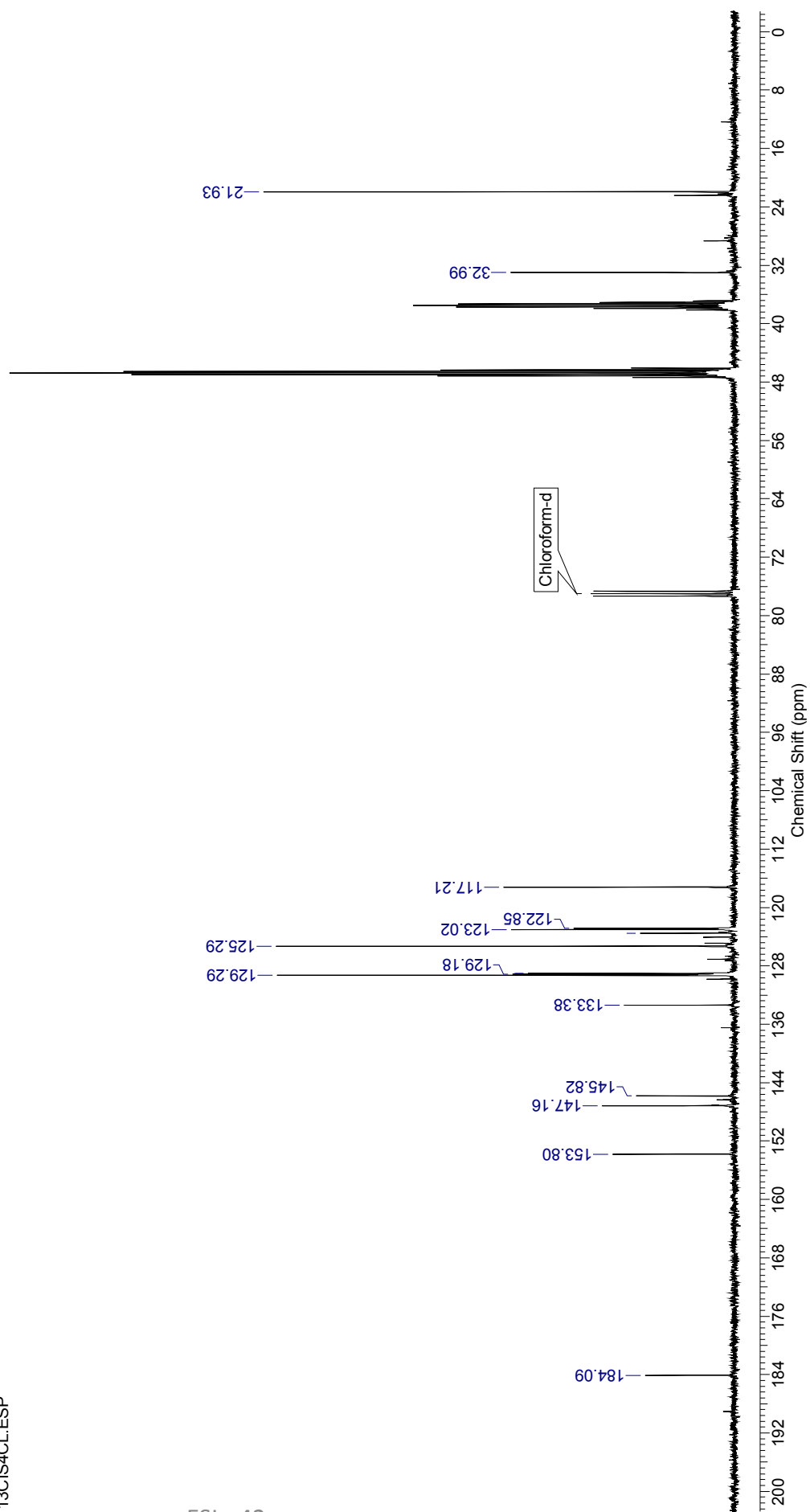


# 1ca, 100 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)

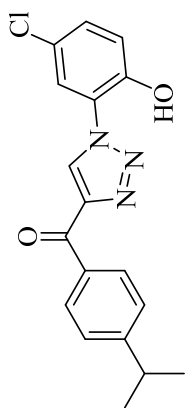


13CIS4CL.ESP

ESI 42

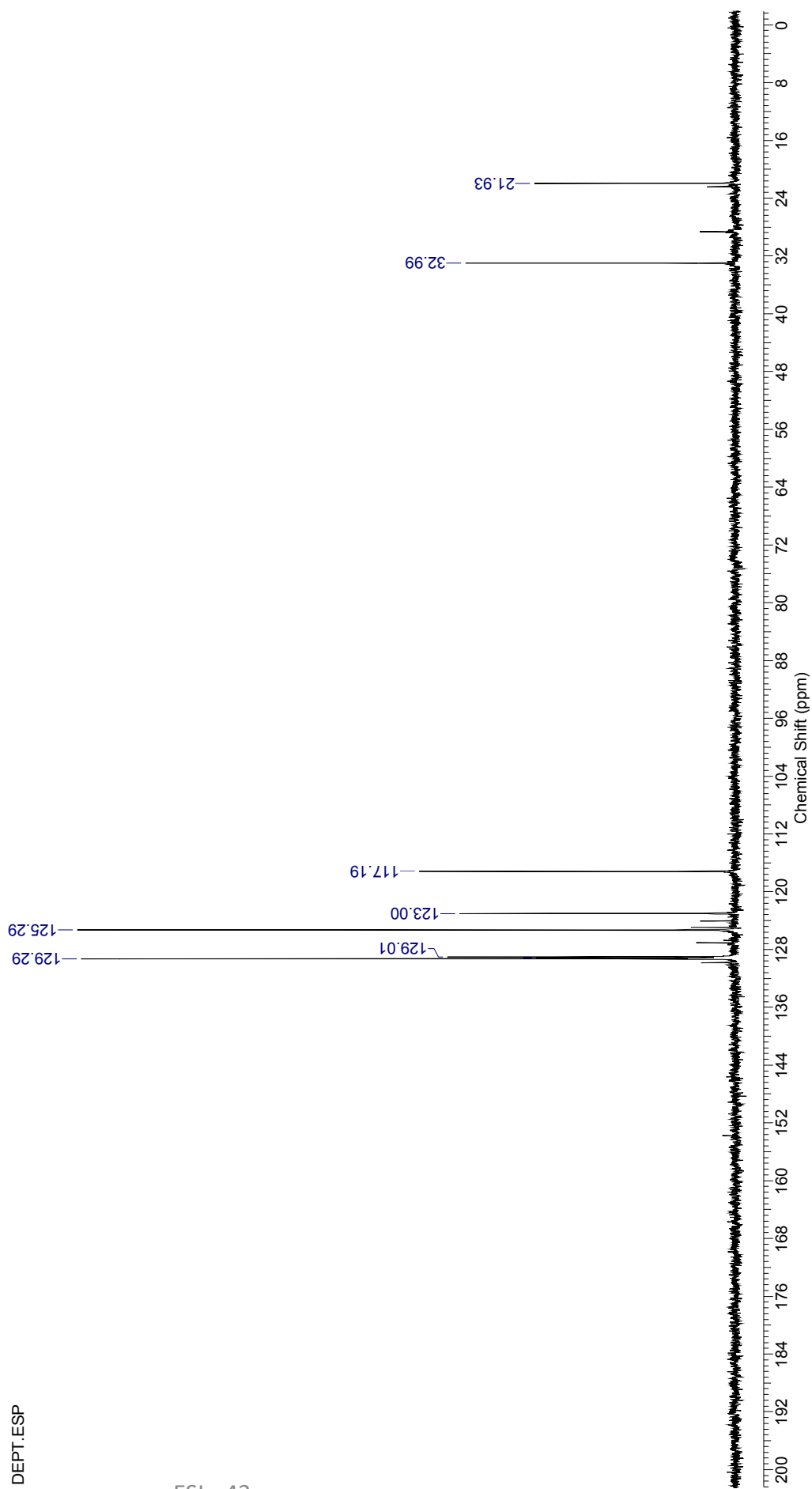


# 1ca, 100 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)

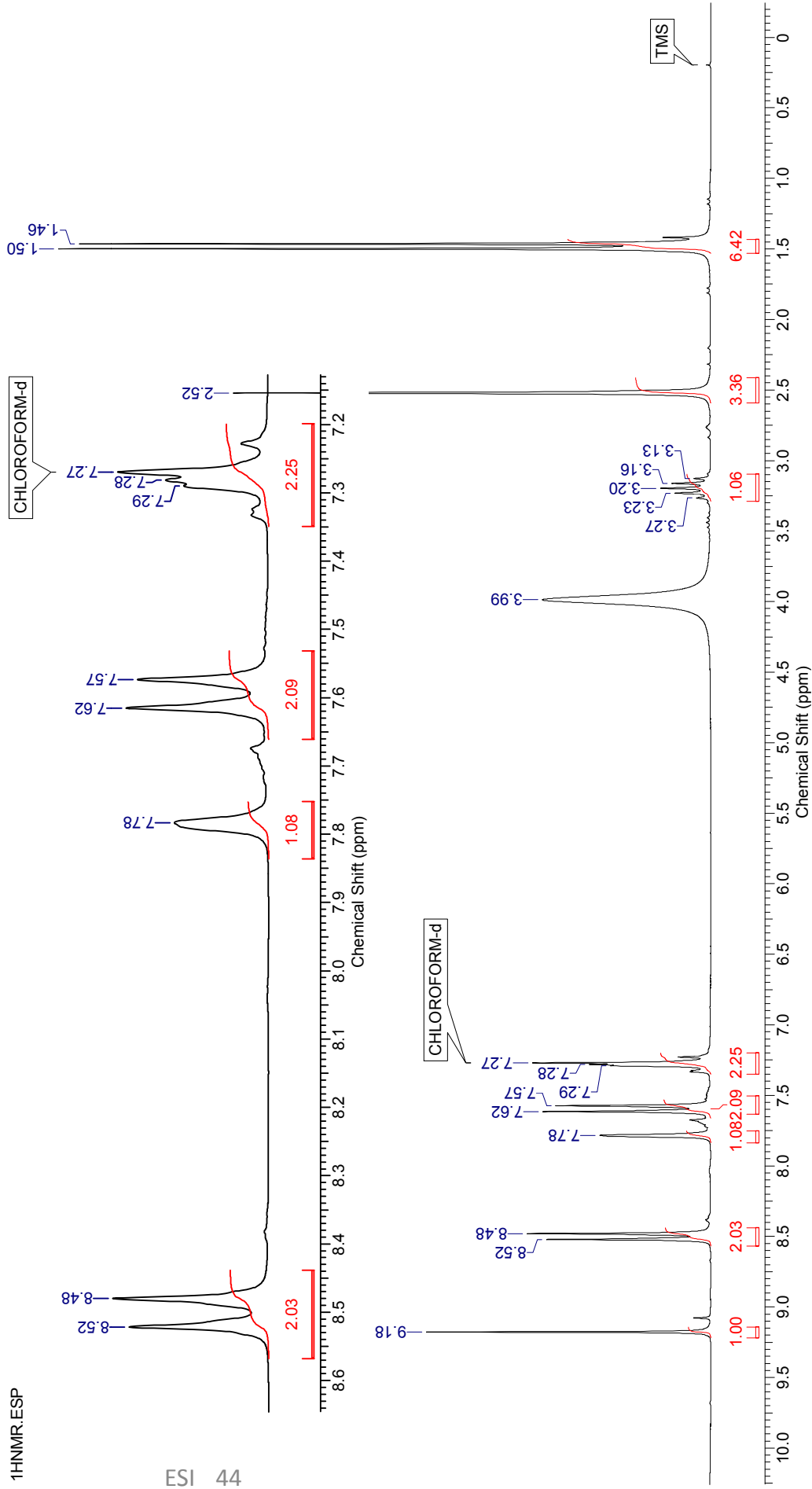
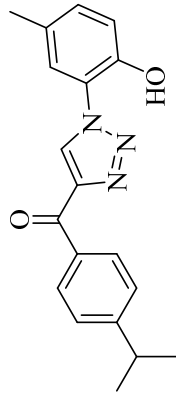


DEPT.ESP

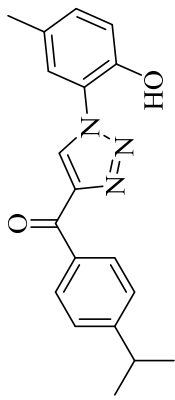
ESI 43



# 1cb, 500 MHz, MeOH (D<sub>4</sub>)

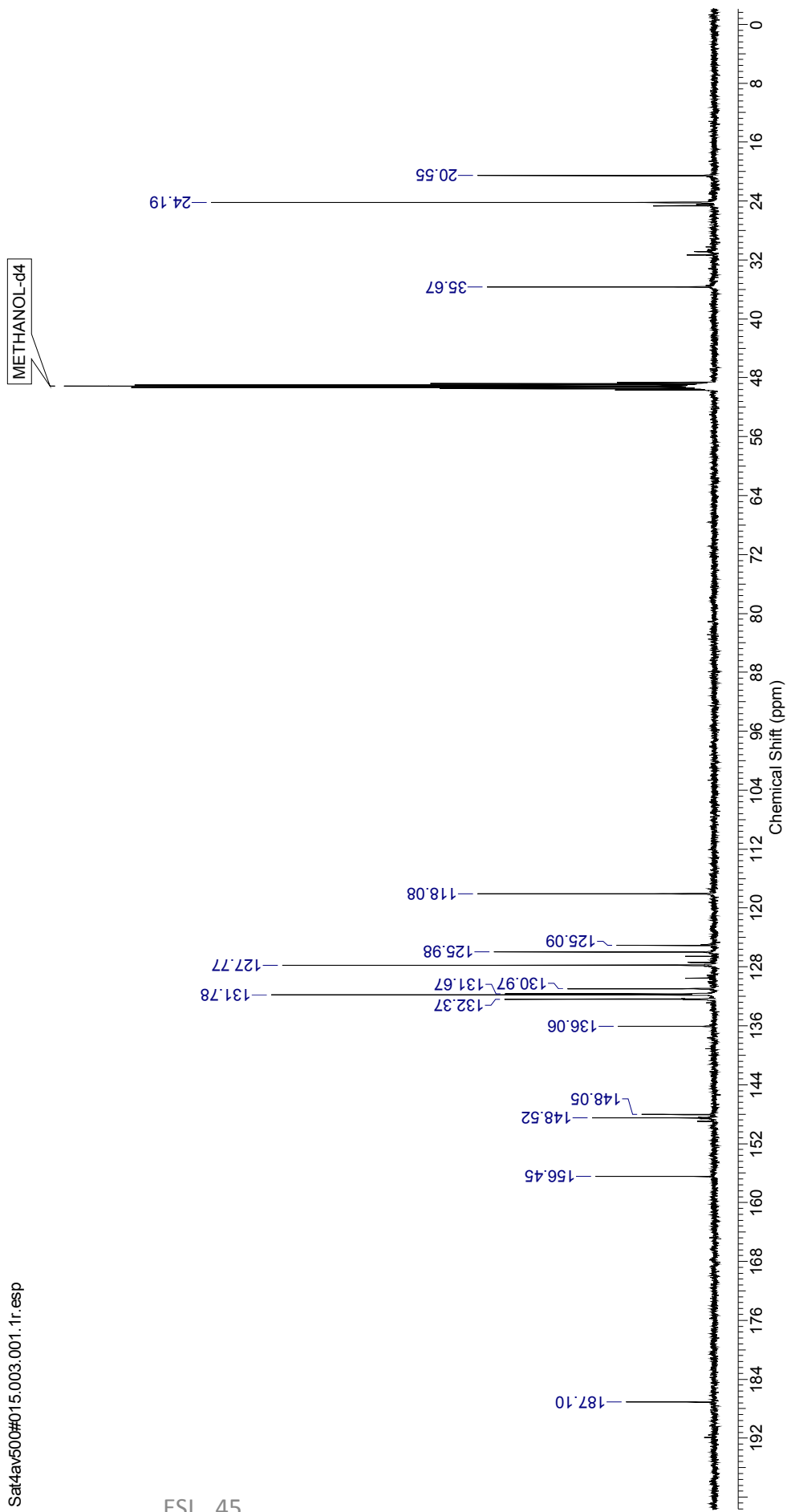


# 1cb, 125 MHz, MeOH (D<sub>4</sub>)

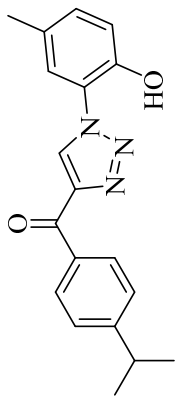


Sat4av500#015.003.001.1r.esp

ESI 45

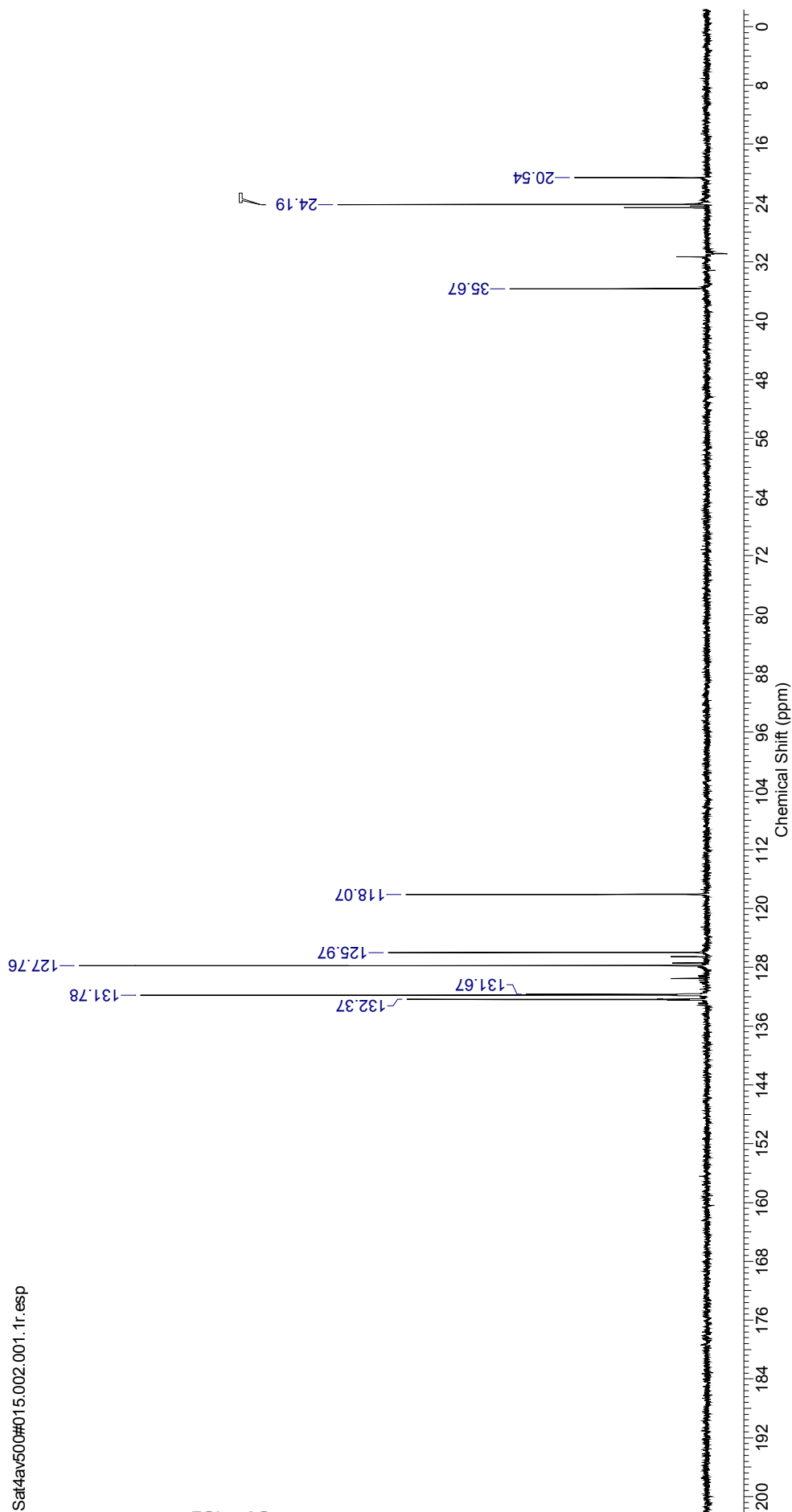


# 1cb, 125 MHz, MeOH (D<sub>4</sub>)

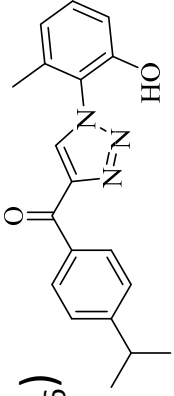


Sat4av500#015.002.001.1r.esp

ESI 46

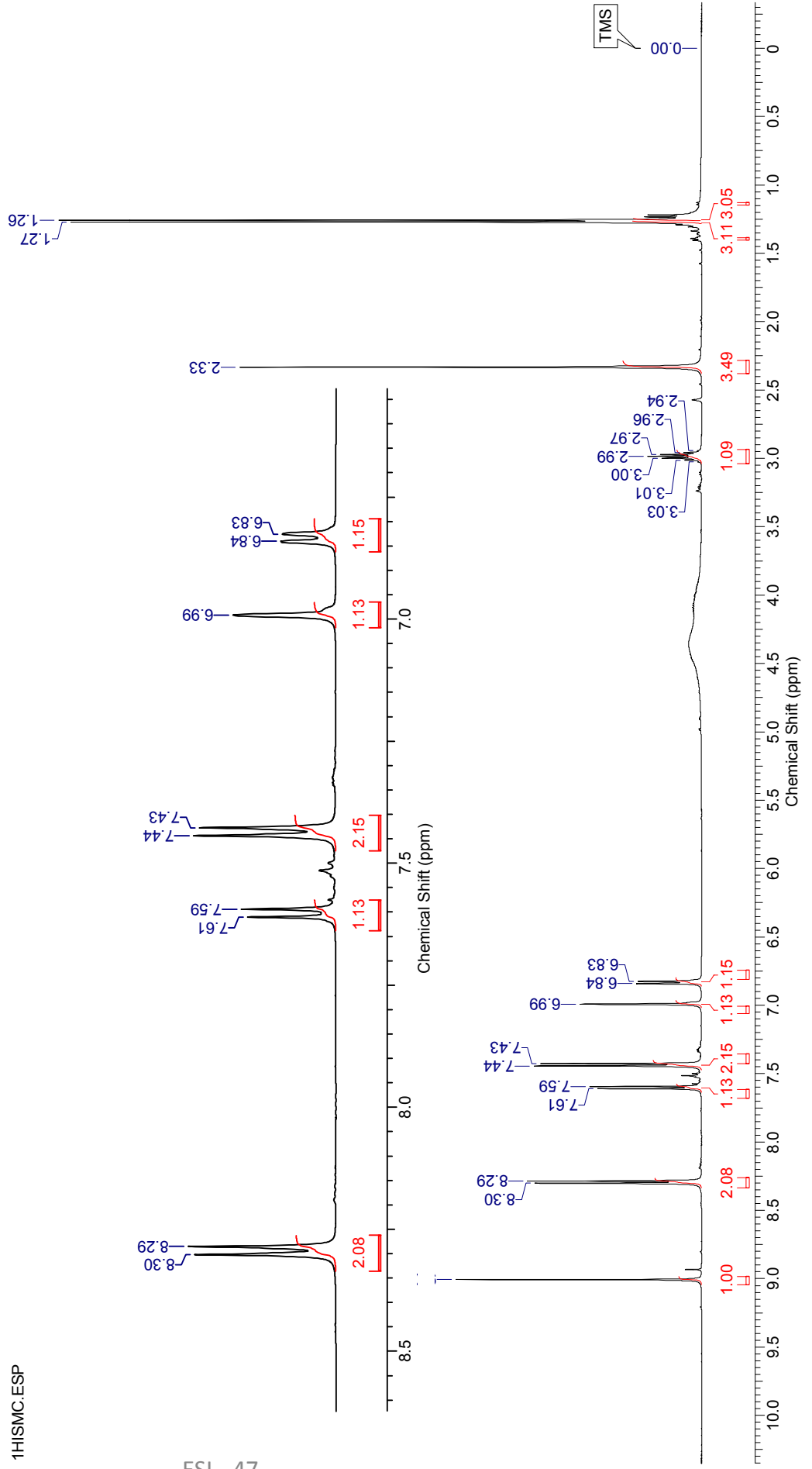


# 1ce, 500 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)

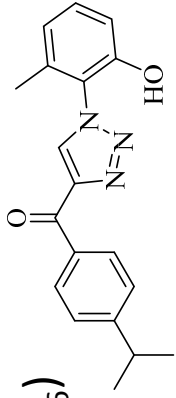


1H1SMC.ESP

1H1SMC.ESP

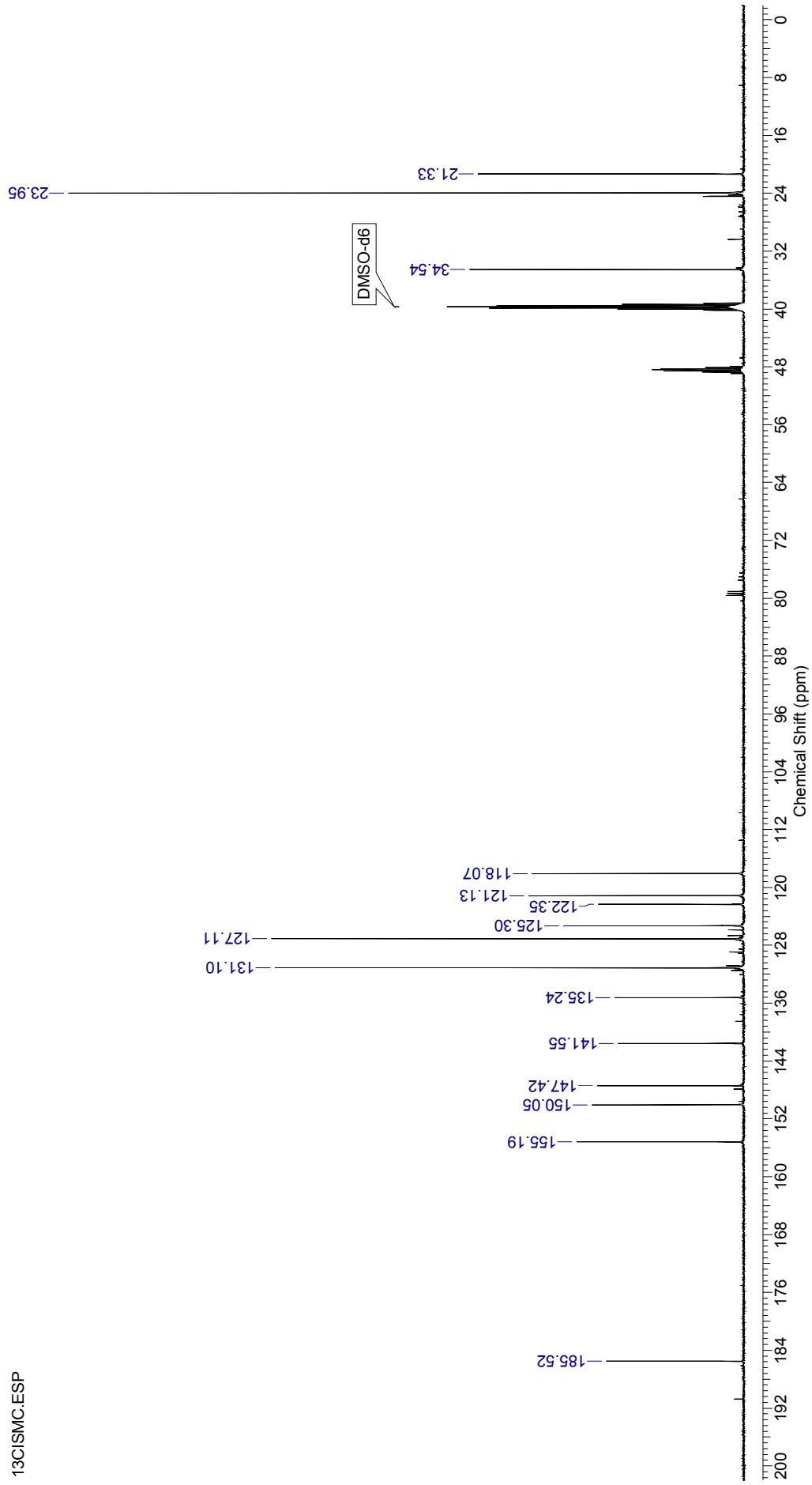


**1ce, 125 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)**



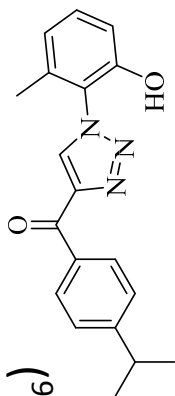
13CISMC.ESP

ESI 48



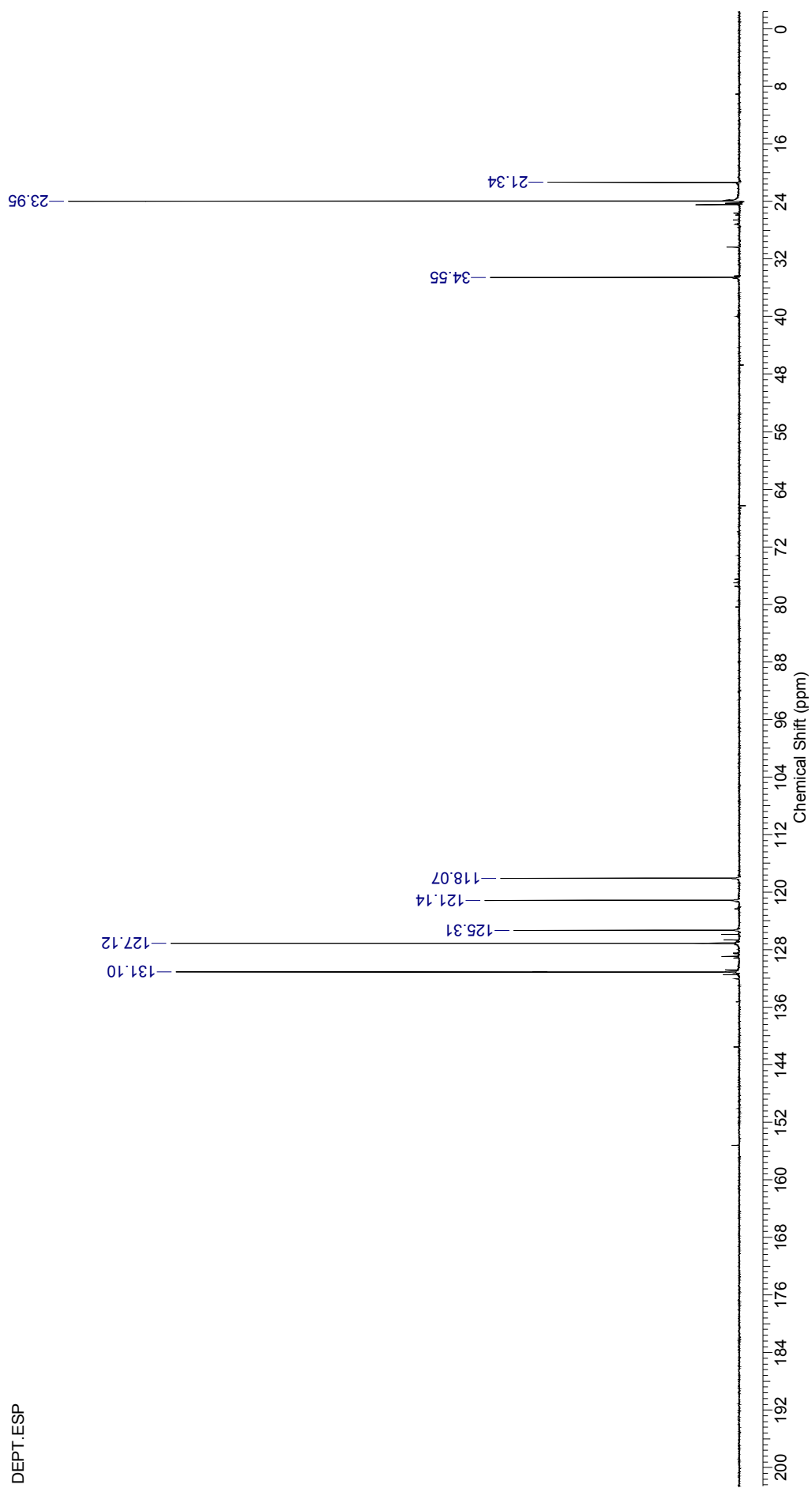


**1ce**, 125 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)



DEPT.ESP

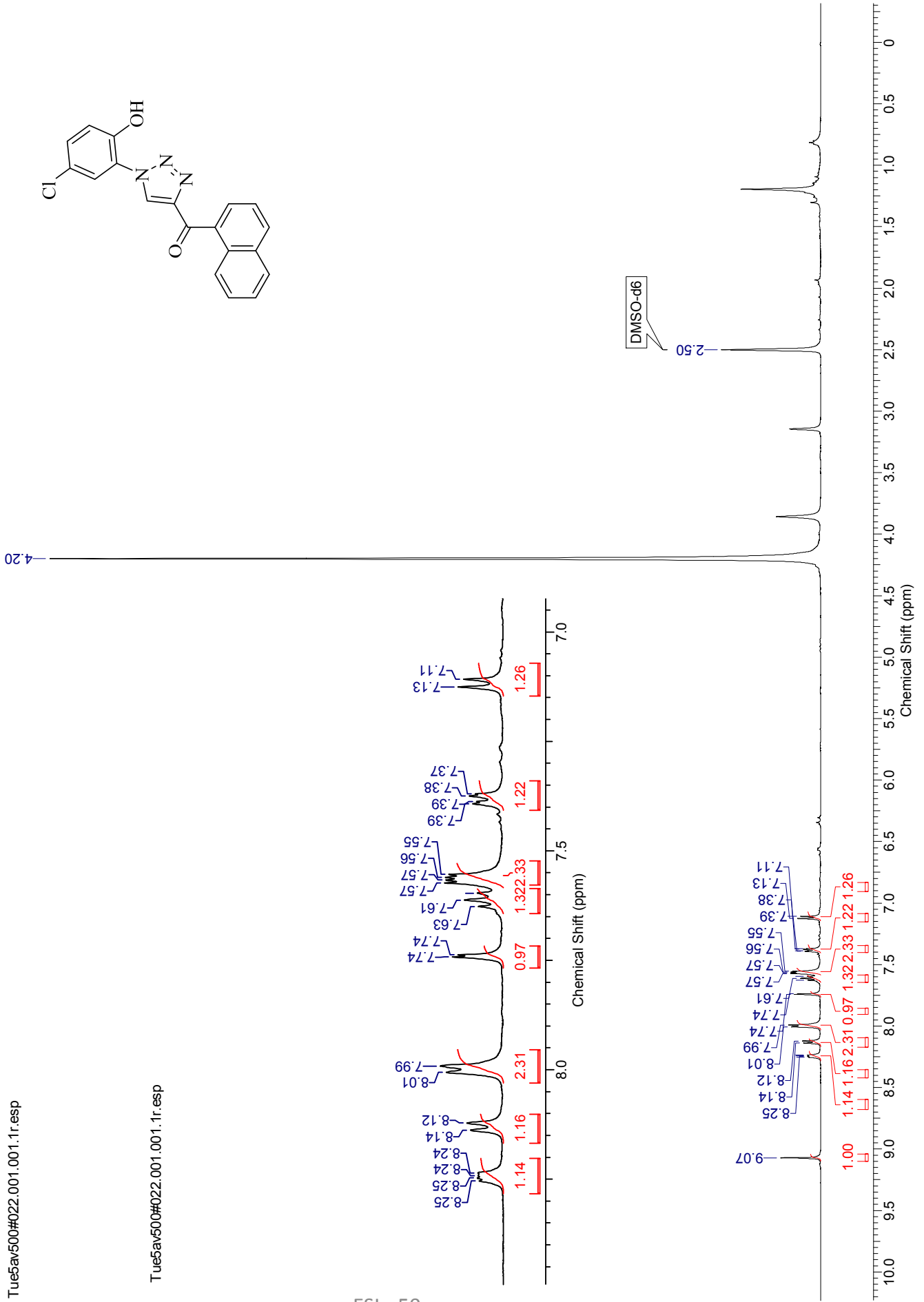
ESI 49



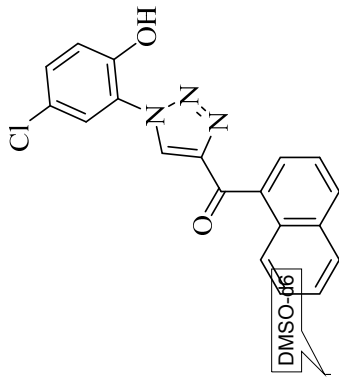
# 1da, 500 MHz, MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)

Tue5av500#022.001.001.1r.esp

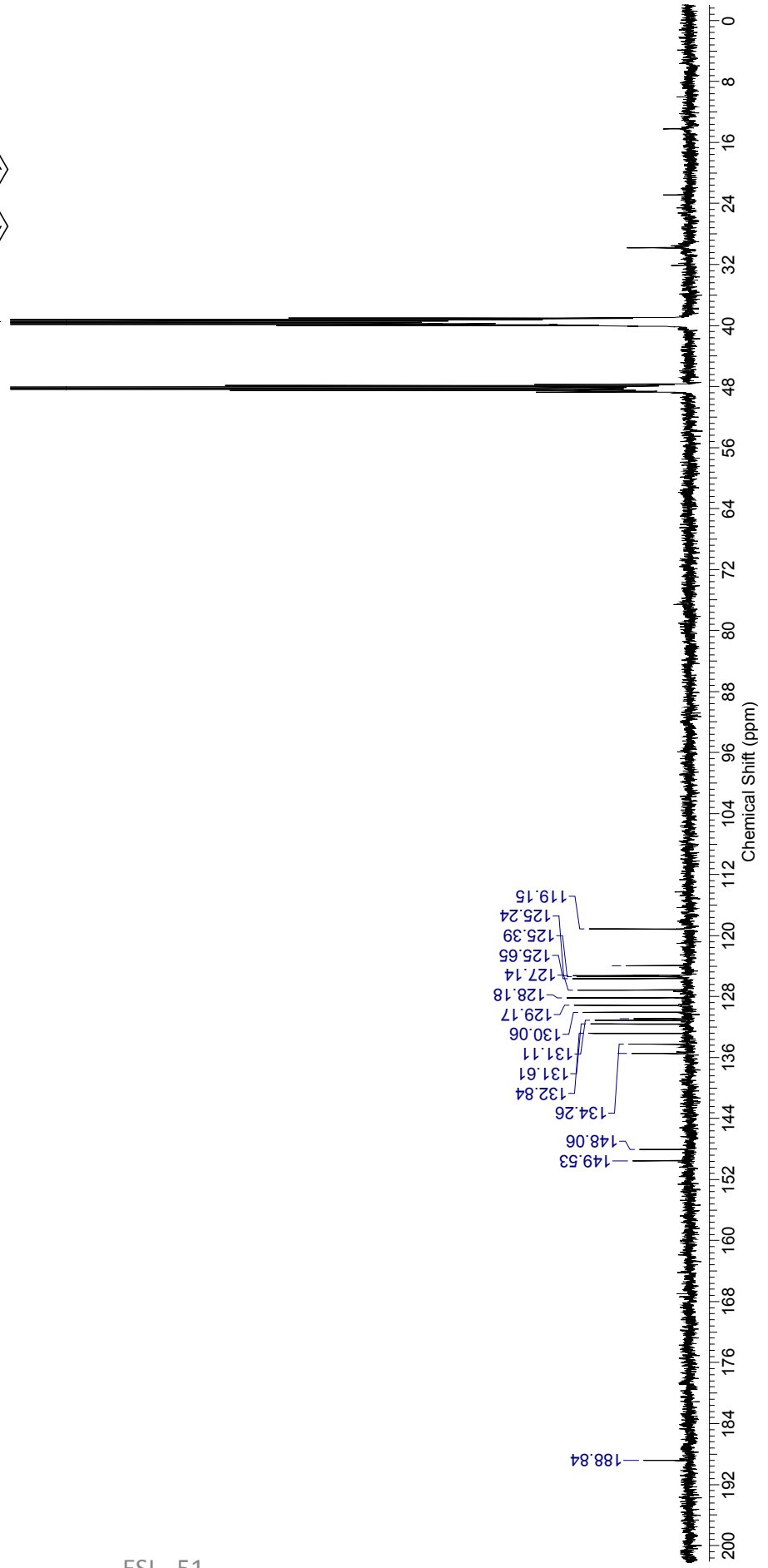
Tue5av500#022.001.001.1r.esp



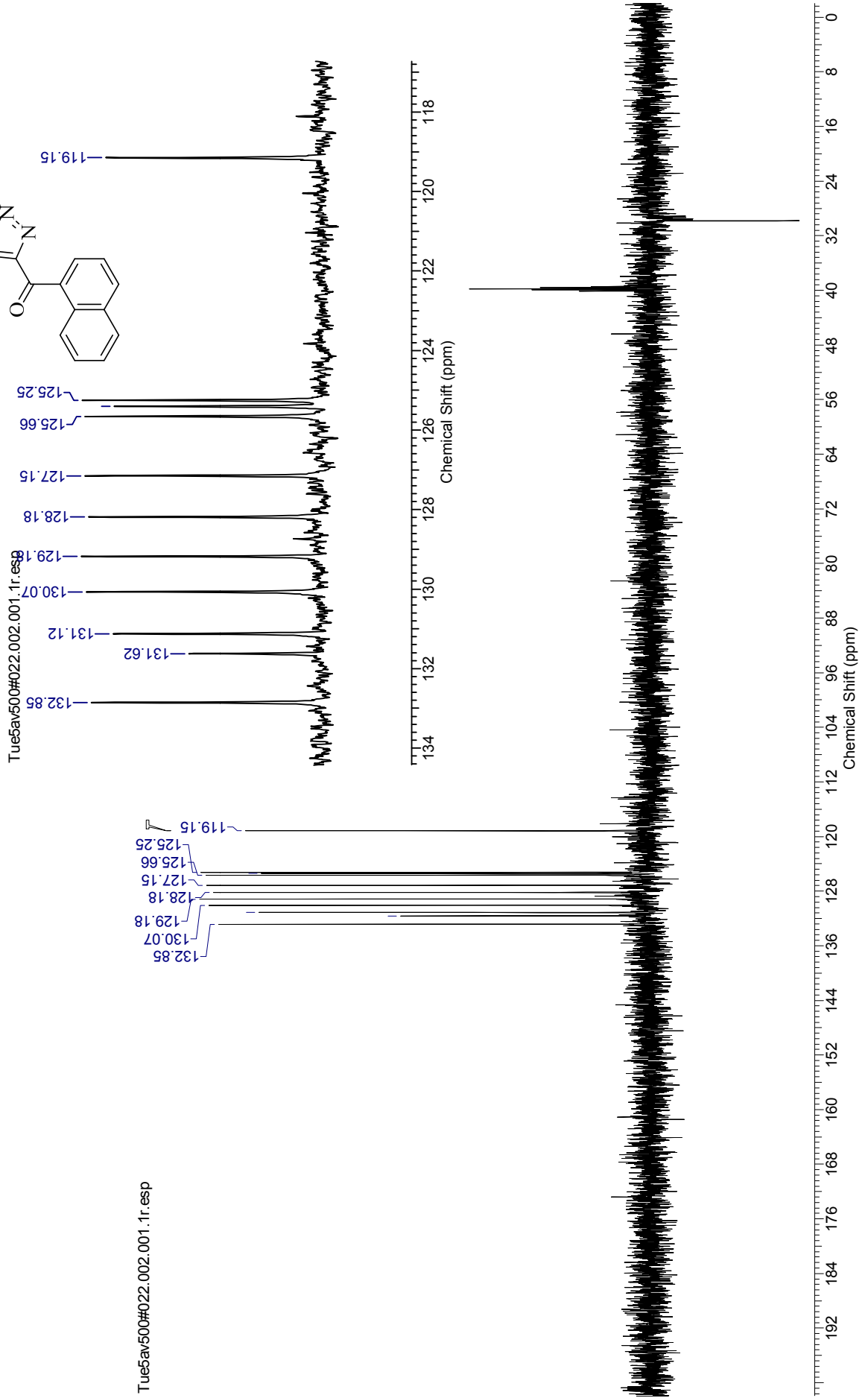
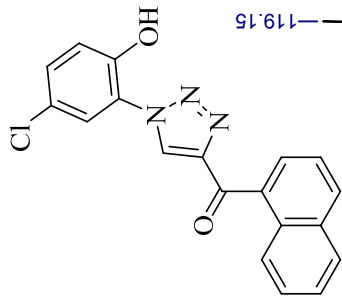
# 1da, 125 MHz, MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)



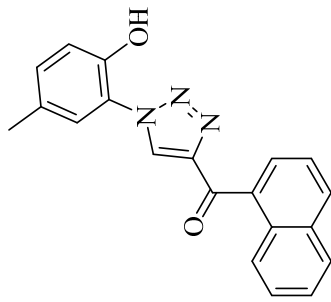
Tue5av500#022.003.001.1r.esp



# 1da, 125 MHz, MeOH (D<sub>4</sub>) + DMSO (D<sub>6</sub>)

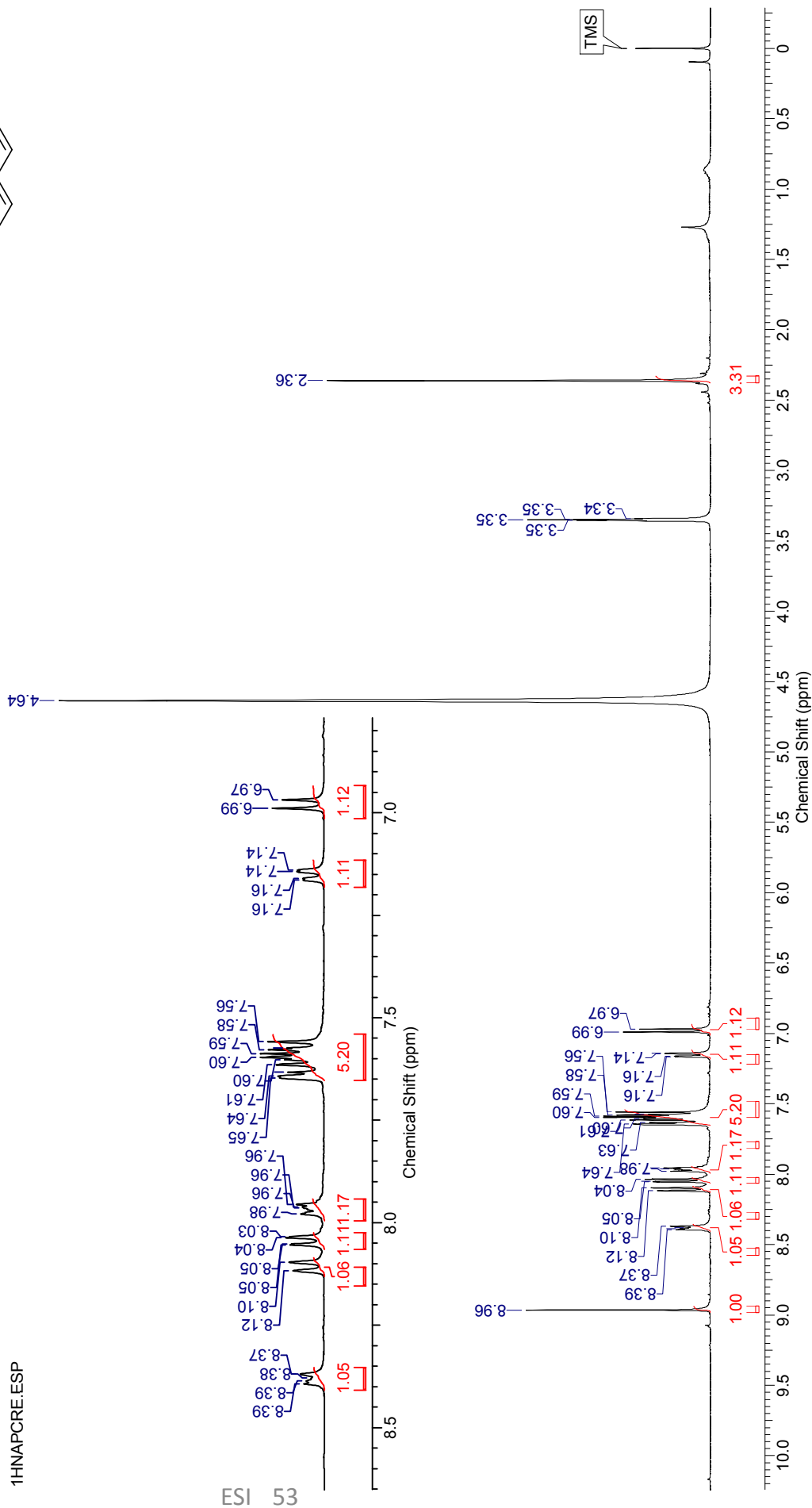


# 1db, 400 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



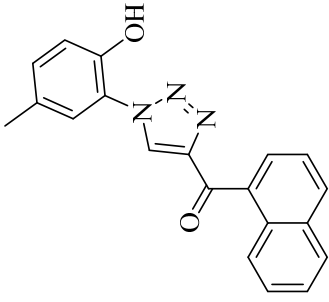
1HNAPCRE.ESP

1HNAPCRE.ESP

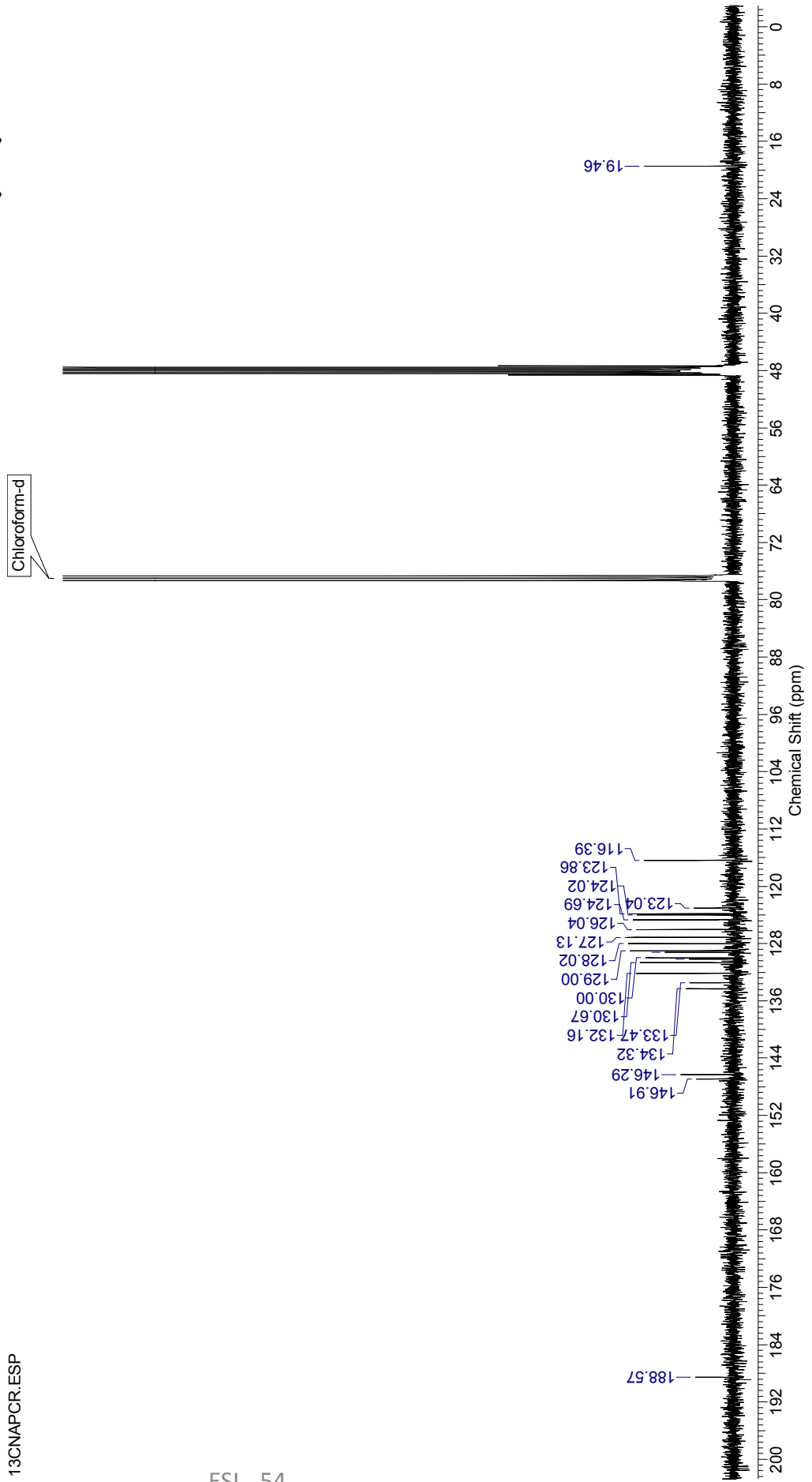


ESI 53

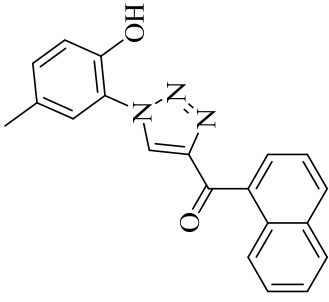
# 1db, 100 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



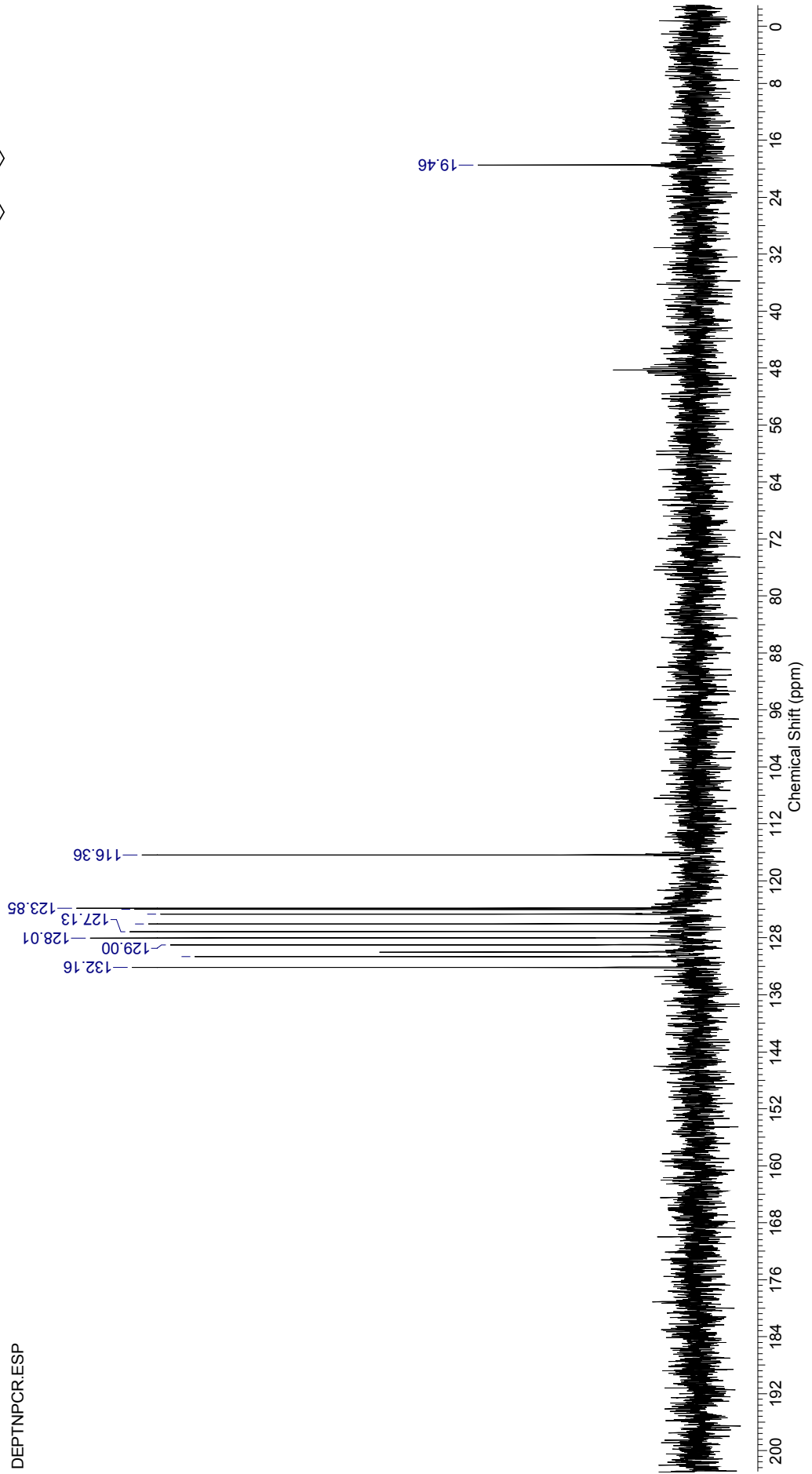
13CNAPCR.ESP



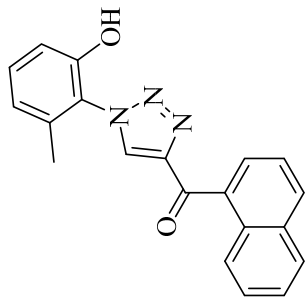
**1db, 100 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)**



DEPTNPCR.ESP

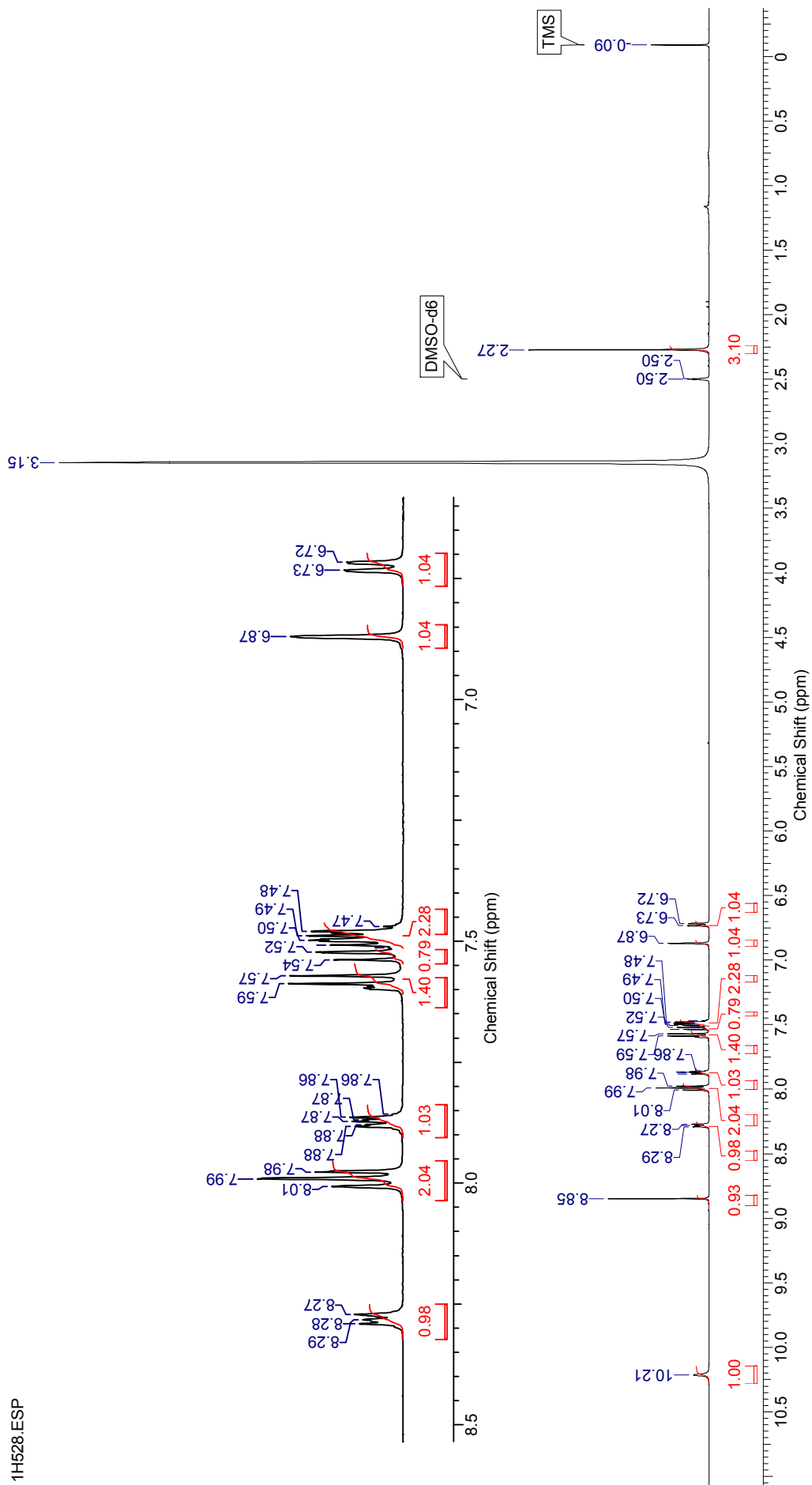


# 1de, 500 MHz, DMSO (D<sub>6</sub>)



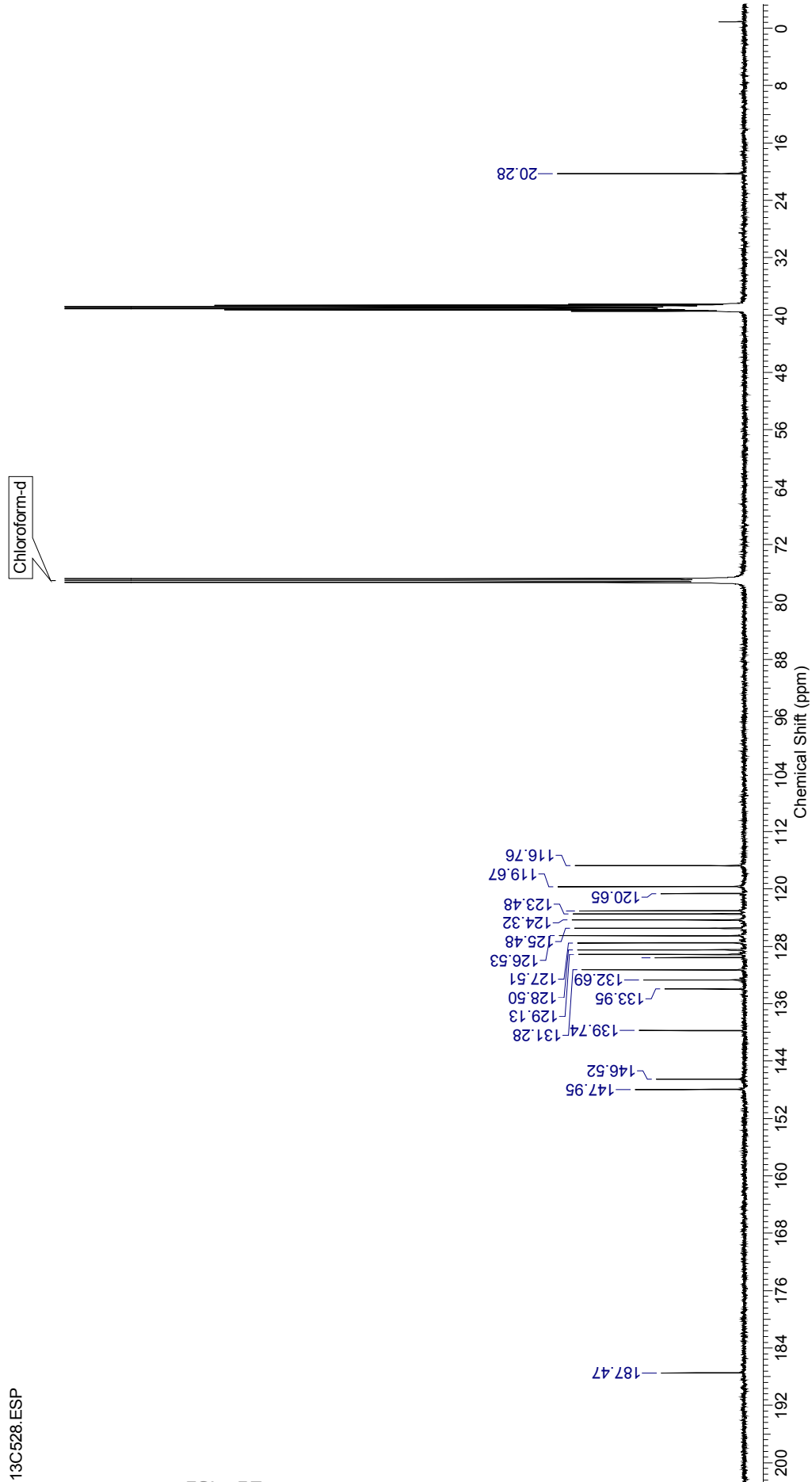
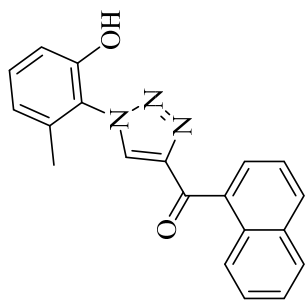
1H528.ESP

1H528.ESP

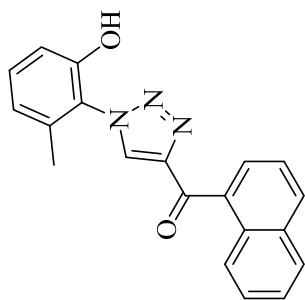




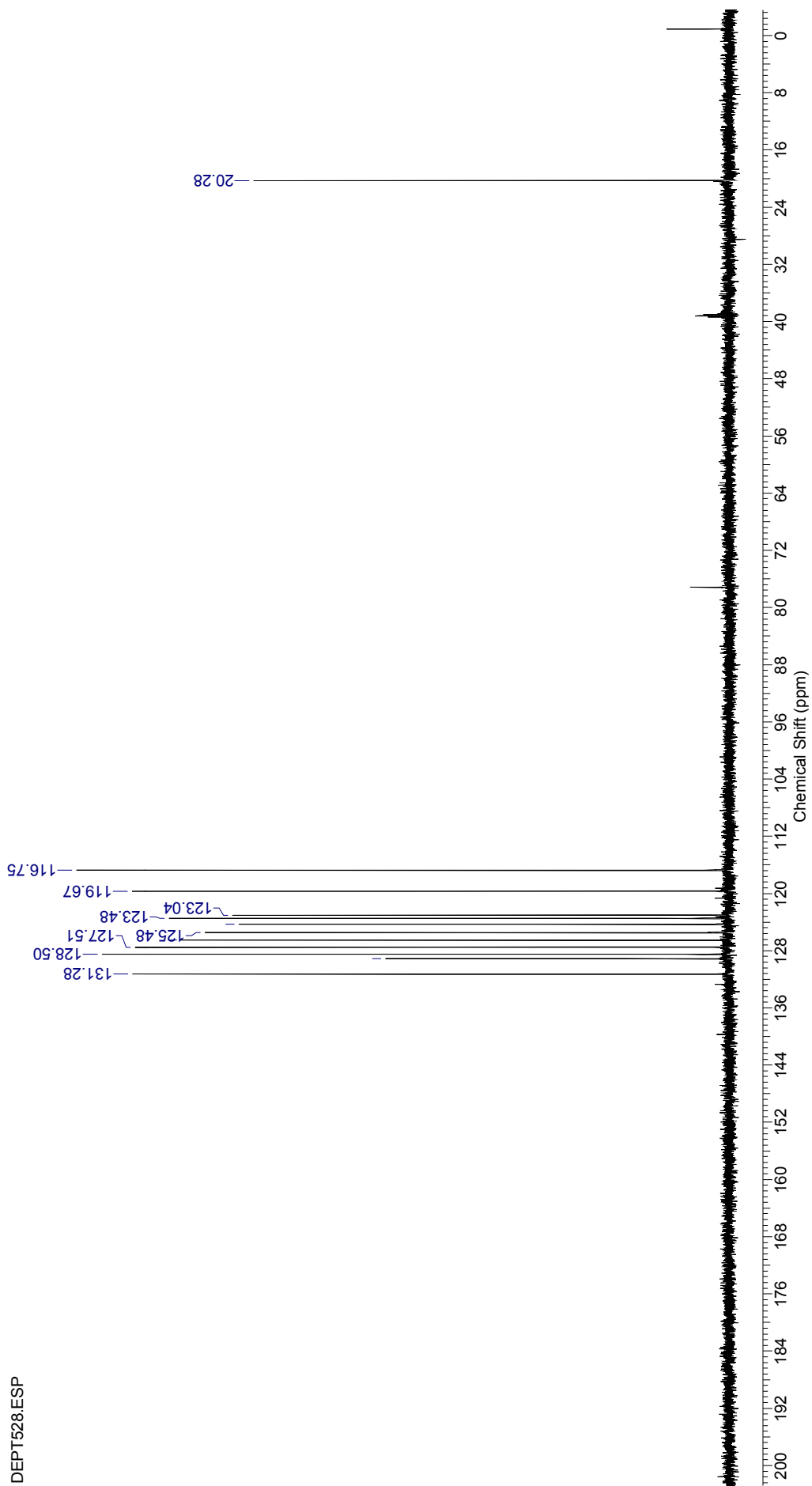
# 1de, 125 MHz, DMSO (D<sub>6</sub>)



# 1de, 125 MHz, DMSO (D<sub>6</sub>)

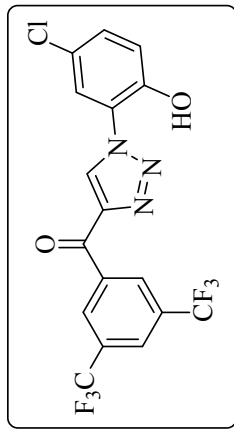


DEPT528.ESP

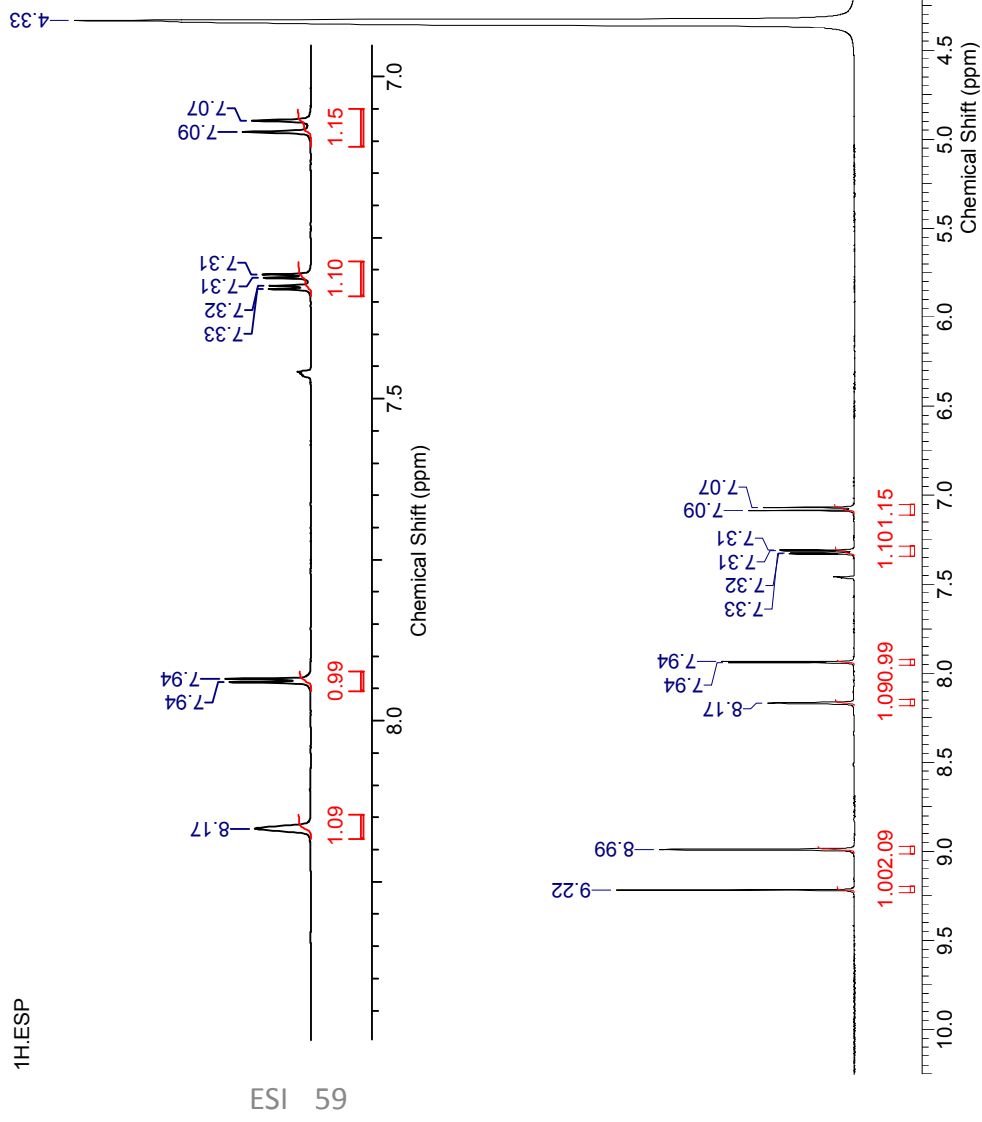


# 1ea, 500 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

1H.ESP



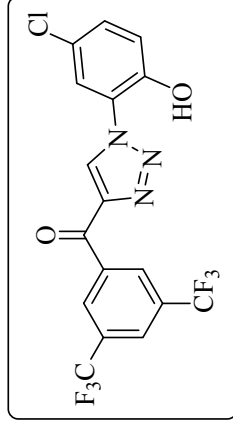
1H.ESP



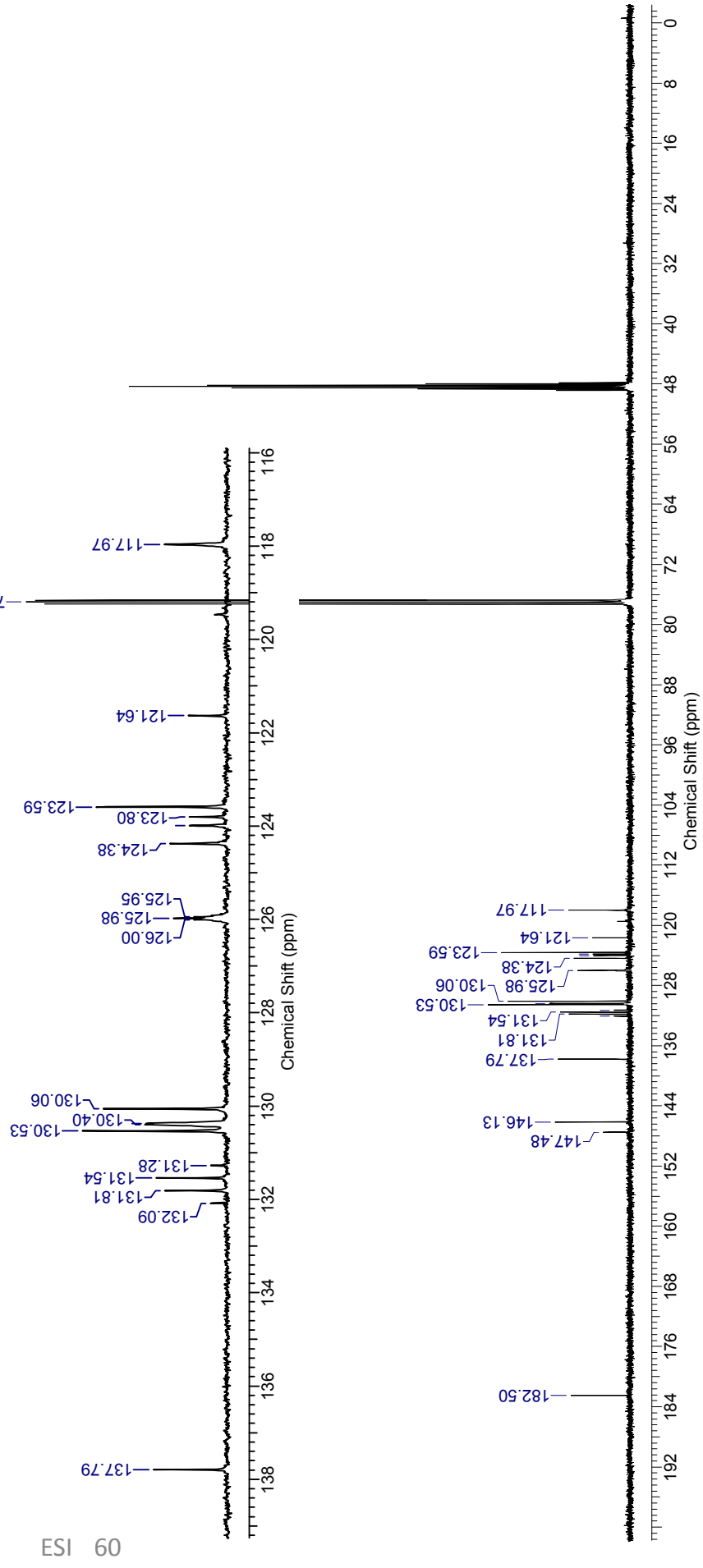
ESI 59

# 1ea, 125 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)

<sup>13</sup>C.ESP

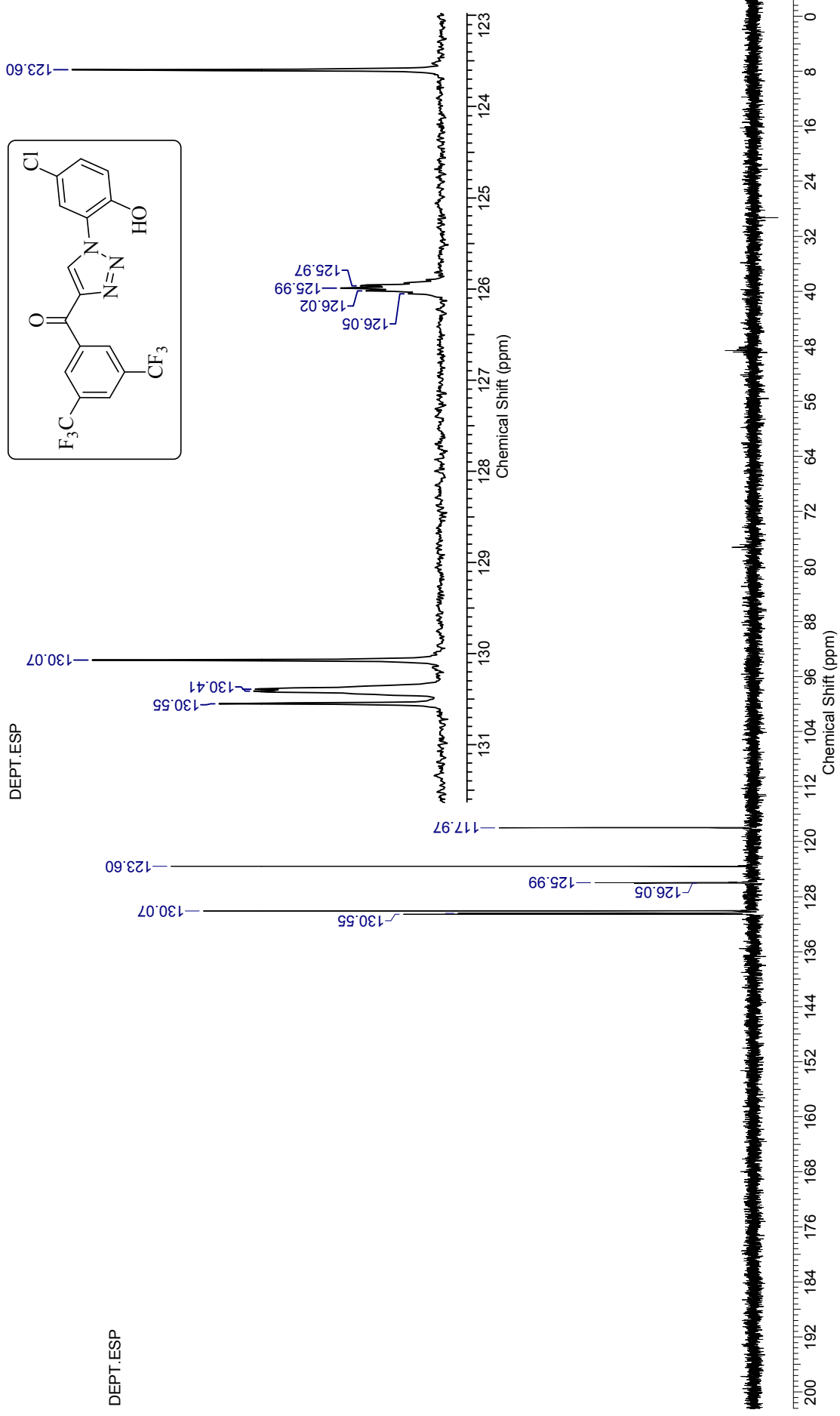


<sup>13</sup>C.ESP

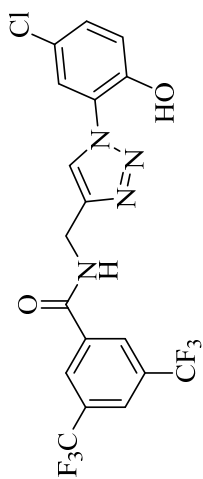


09 ISI

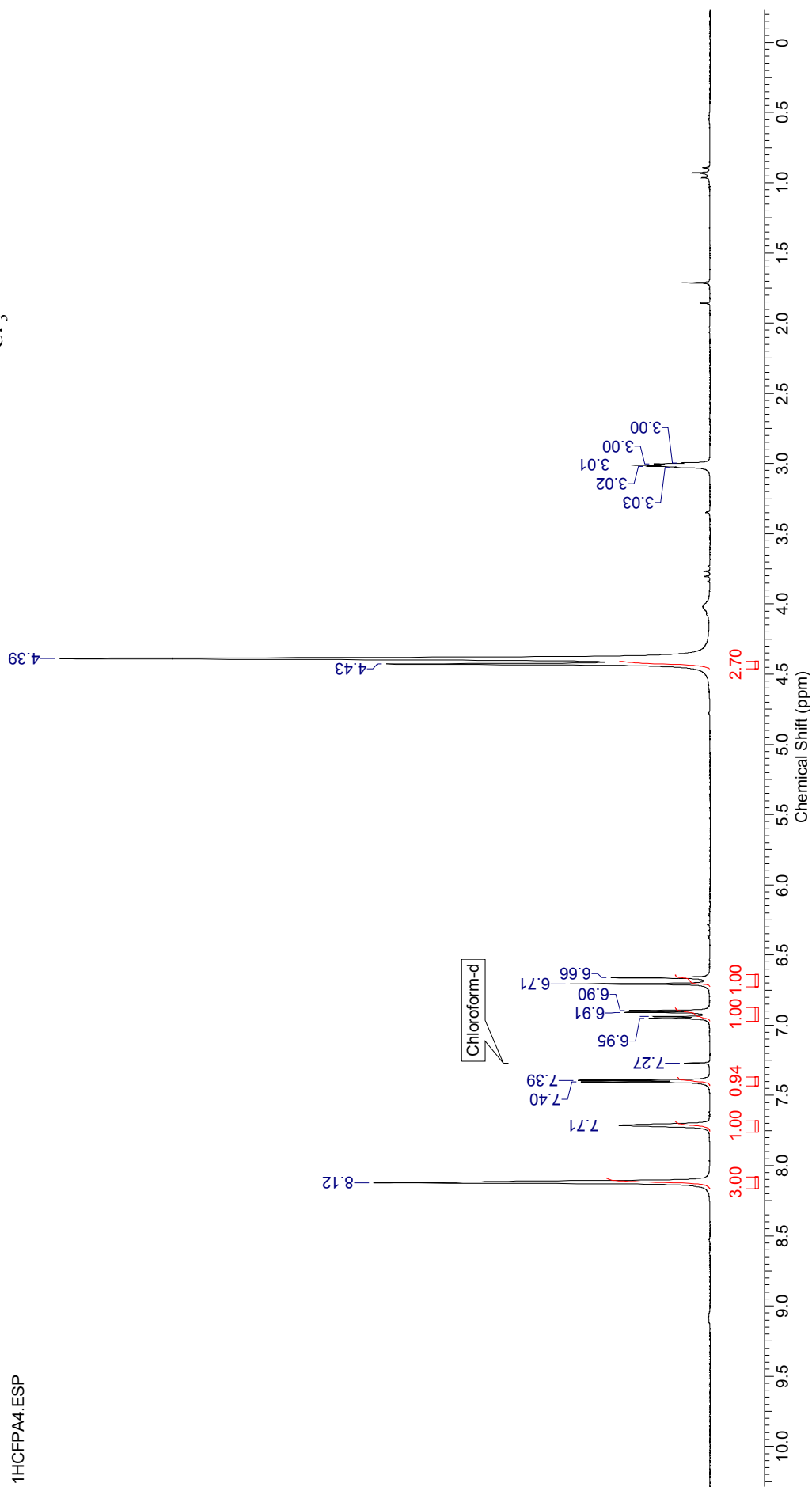
# 1ea, 125 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



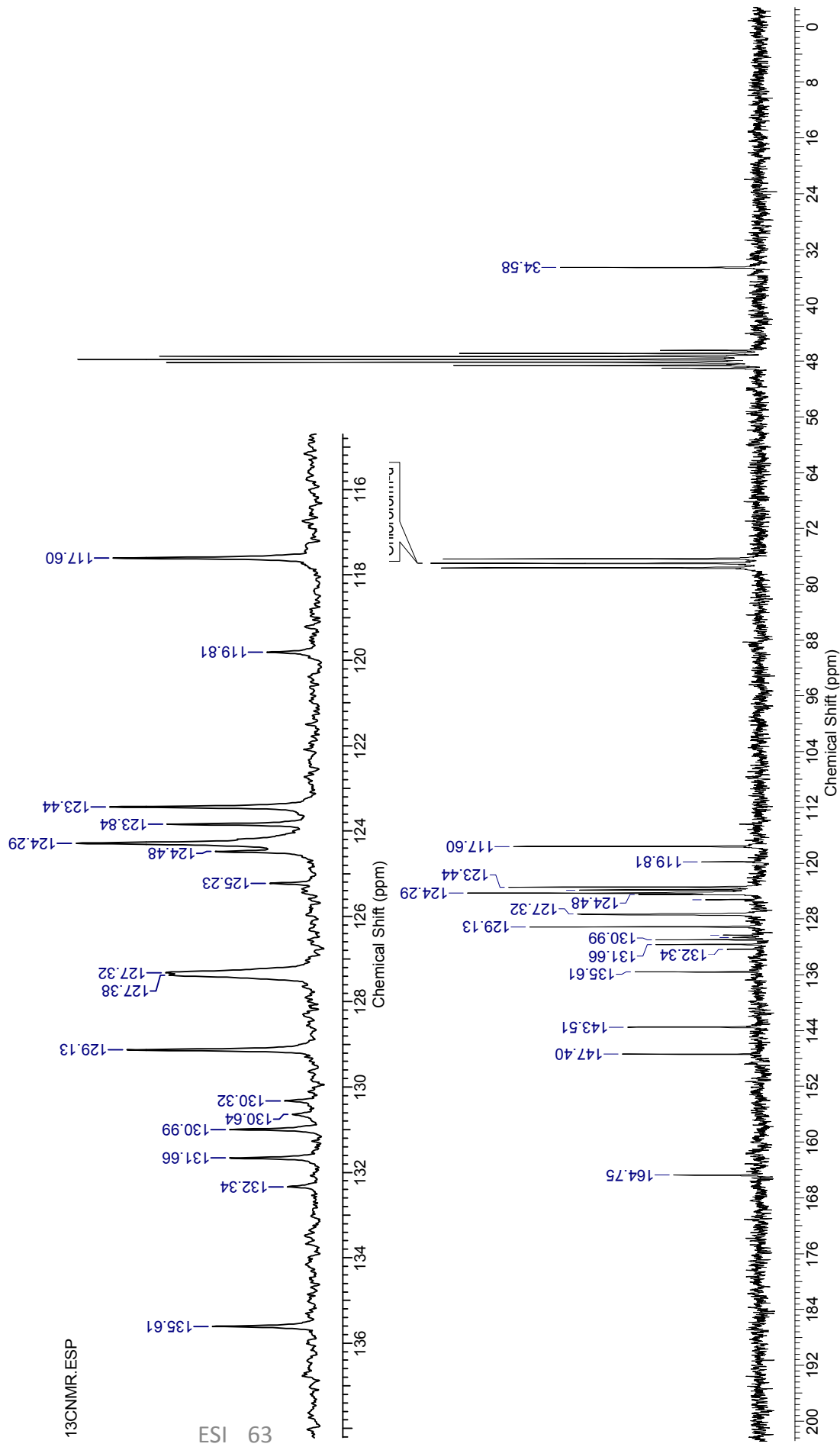
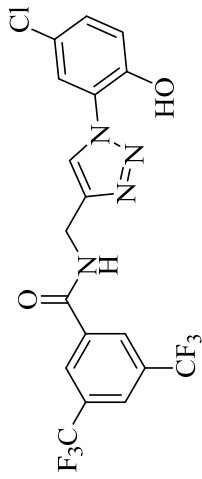
# 1fa, 200 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



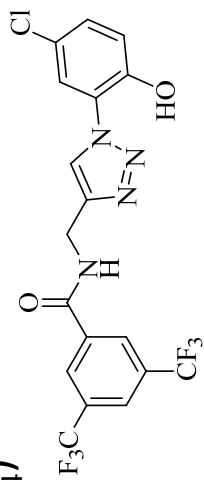
1HCFPA4.ESP



# 1fa, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



# 1fa, 50 MHz, CDCl<sub>3</sub> + MeOH (D<sub>4</sub>)



DEPT.ESP

