

# Elagolix Sodium Salt and Its Synthetic Intermediates: A Spec-troscopic, Crystallographic, and Conformational Study

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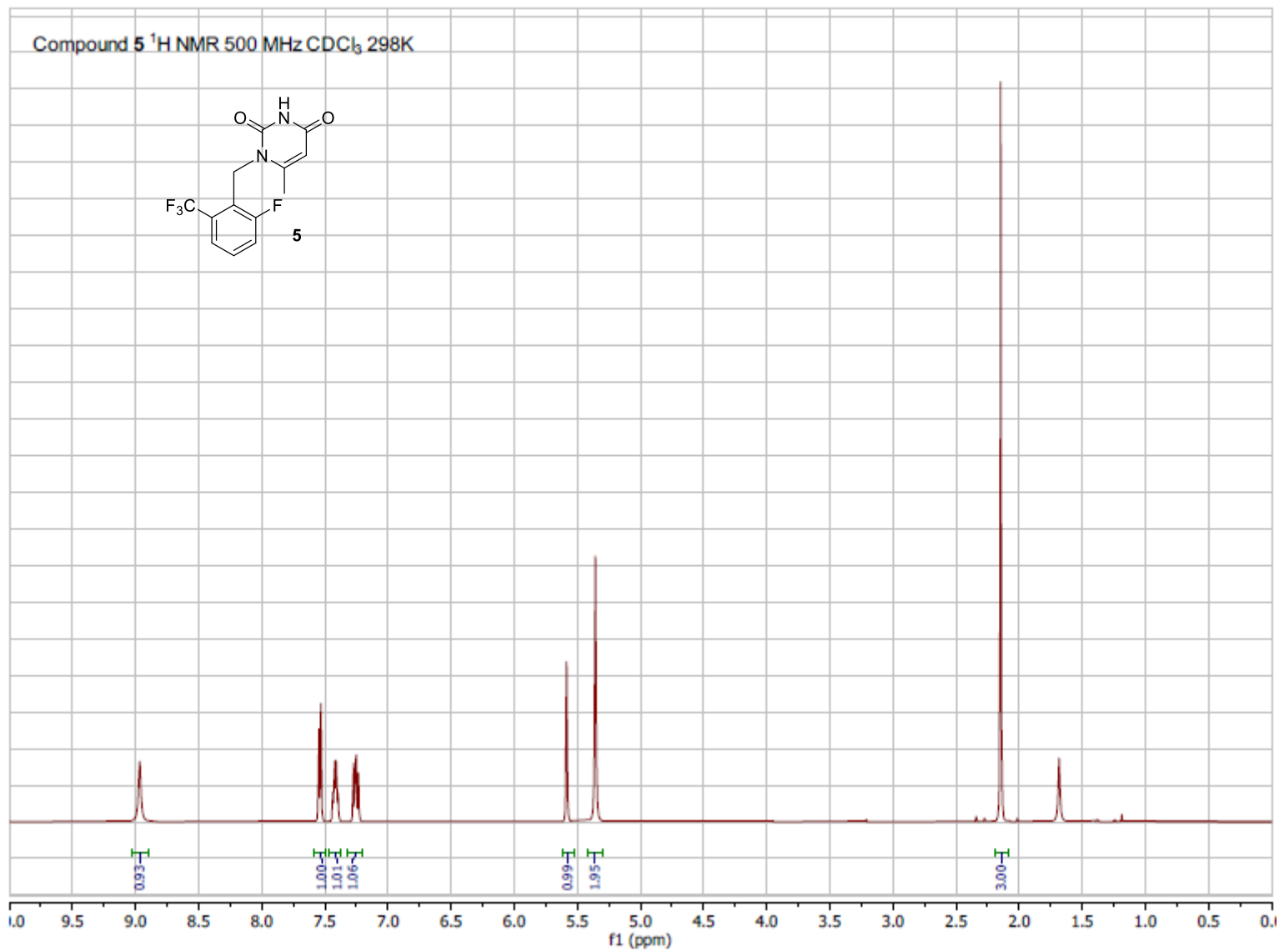


Figure S1.  $^1\text{H}$  NMR of compound **5**

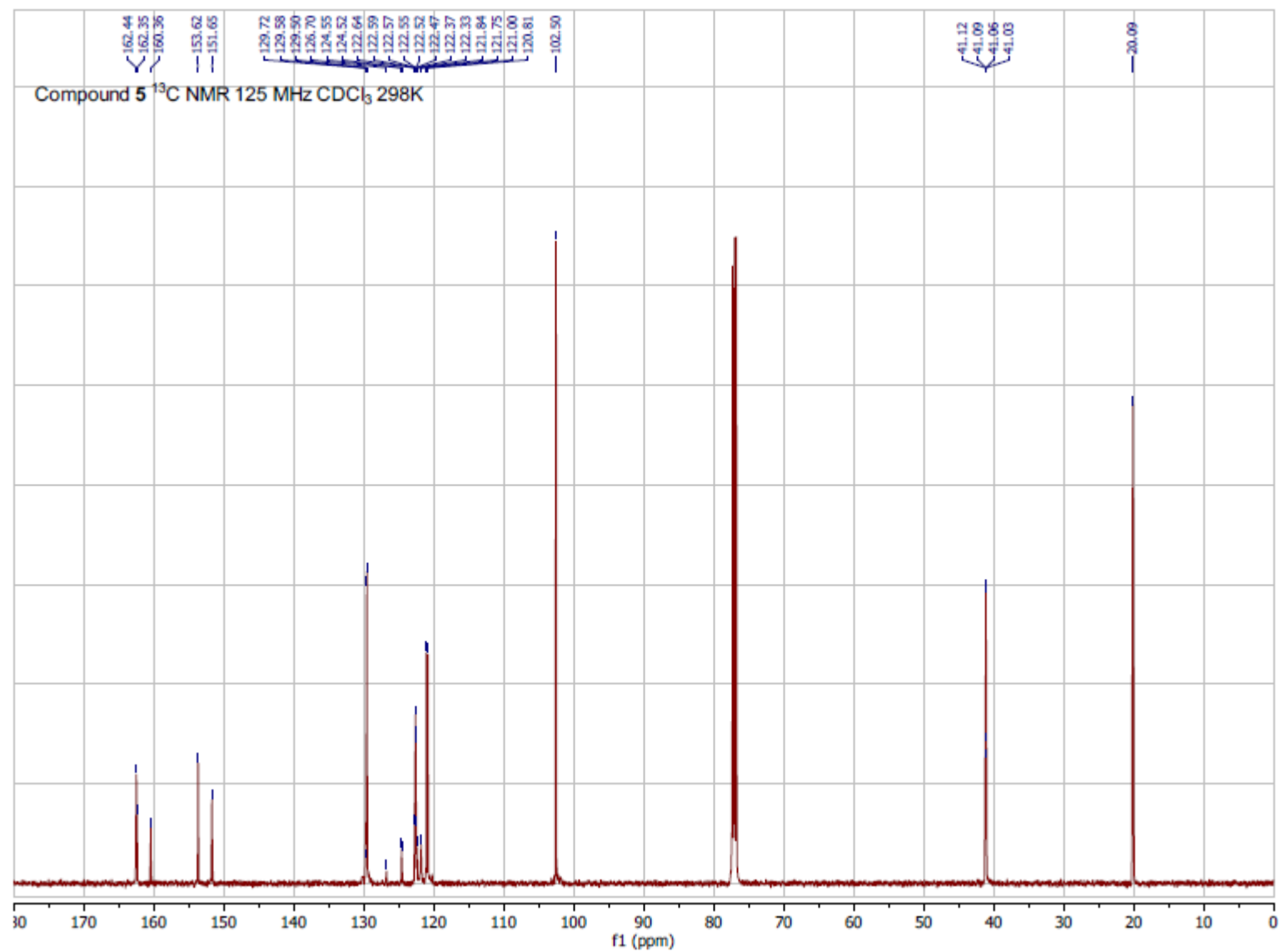
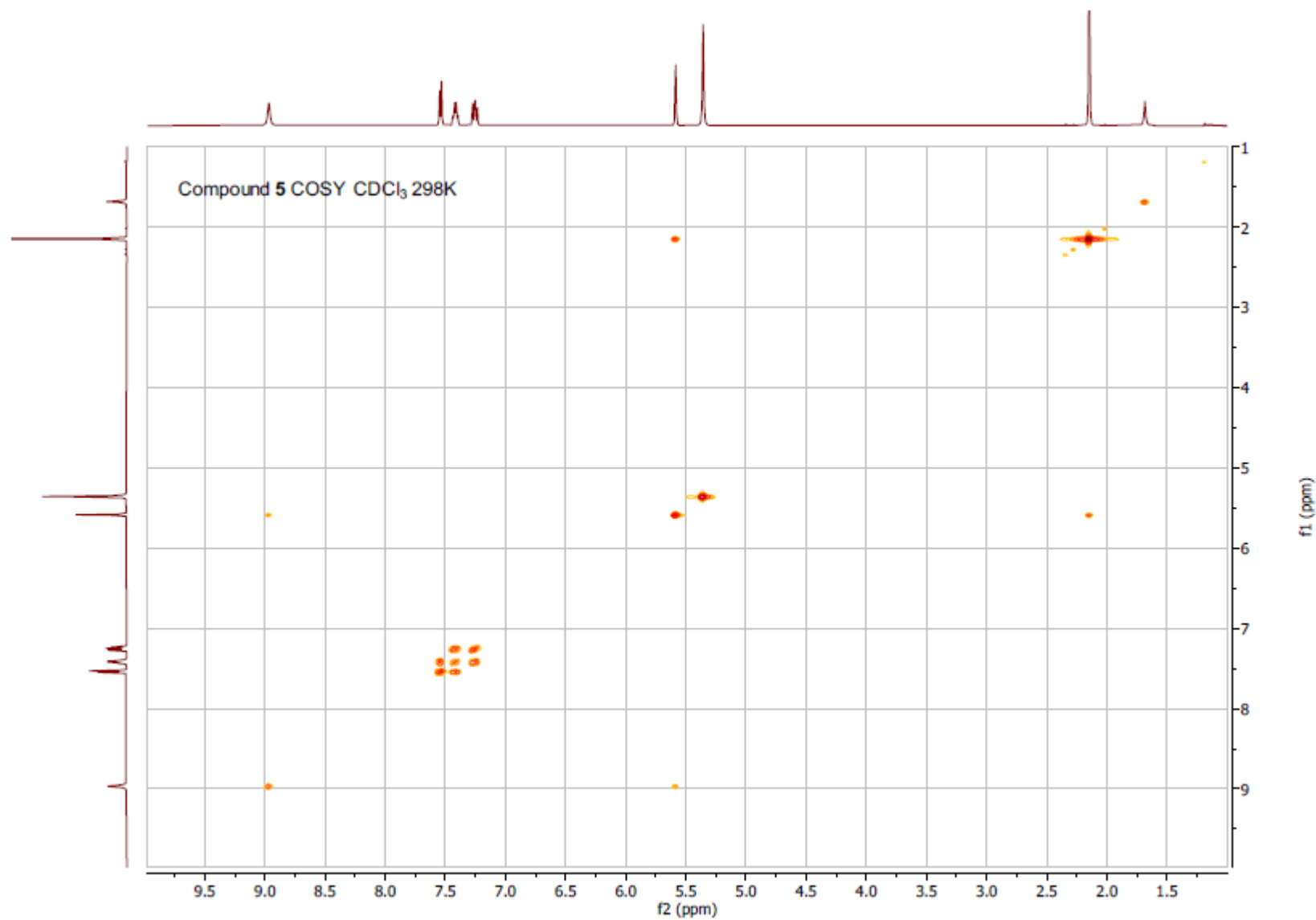
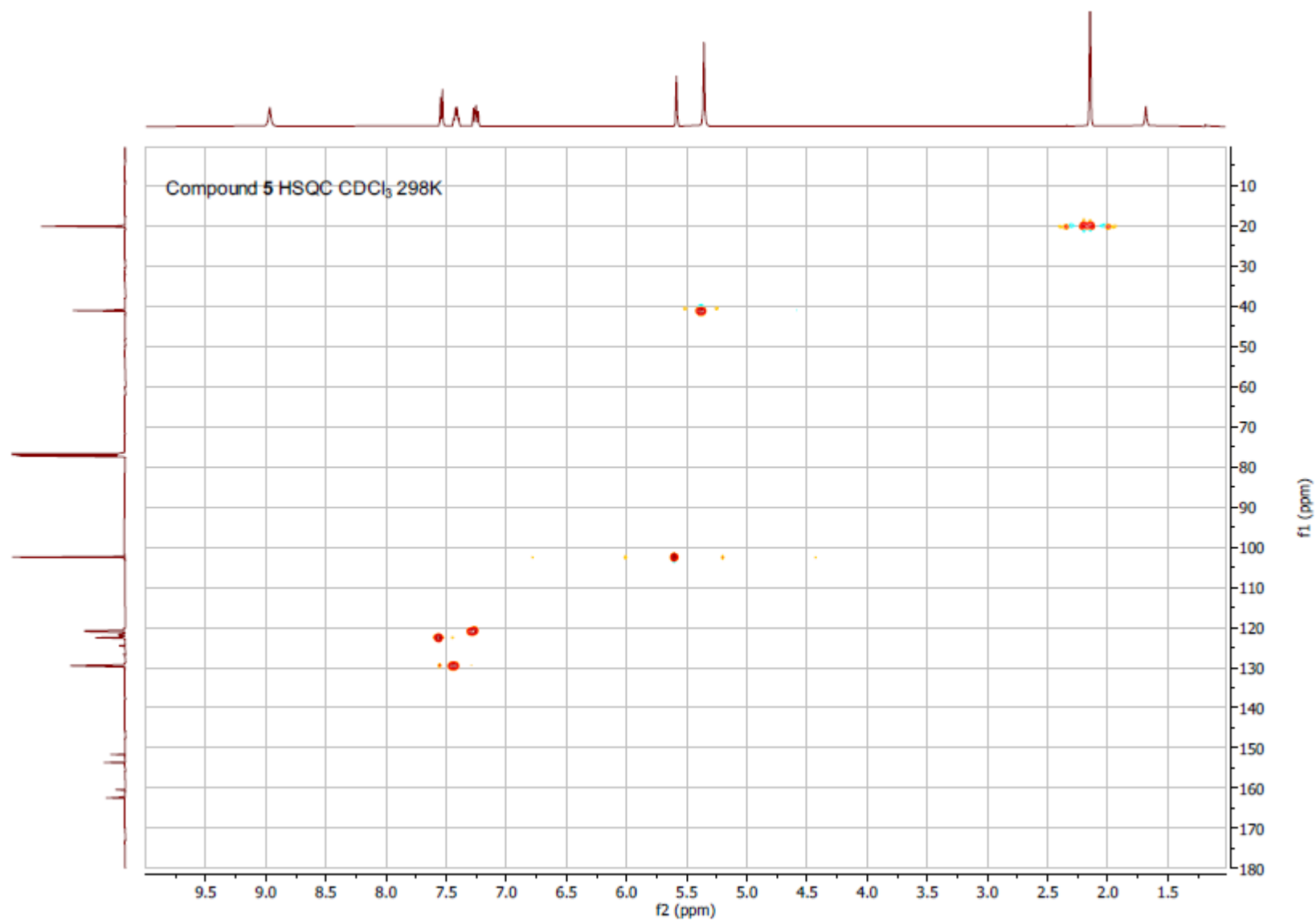


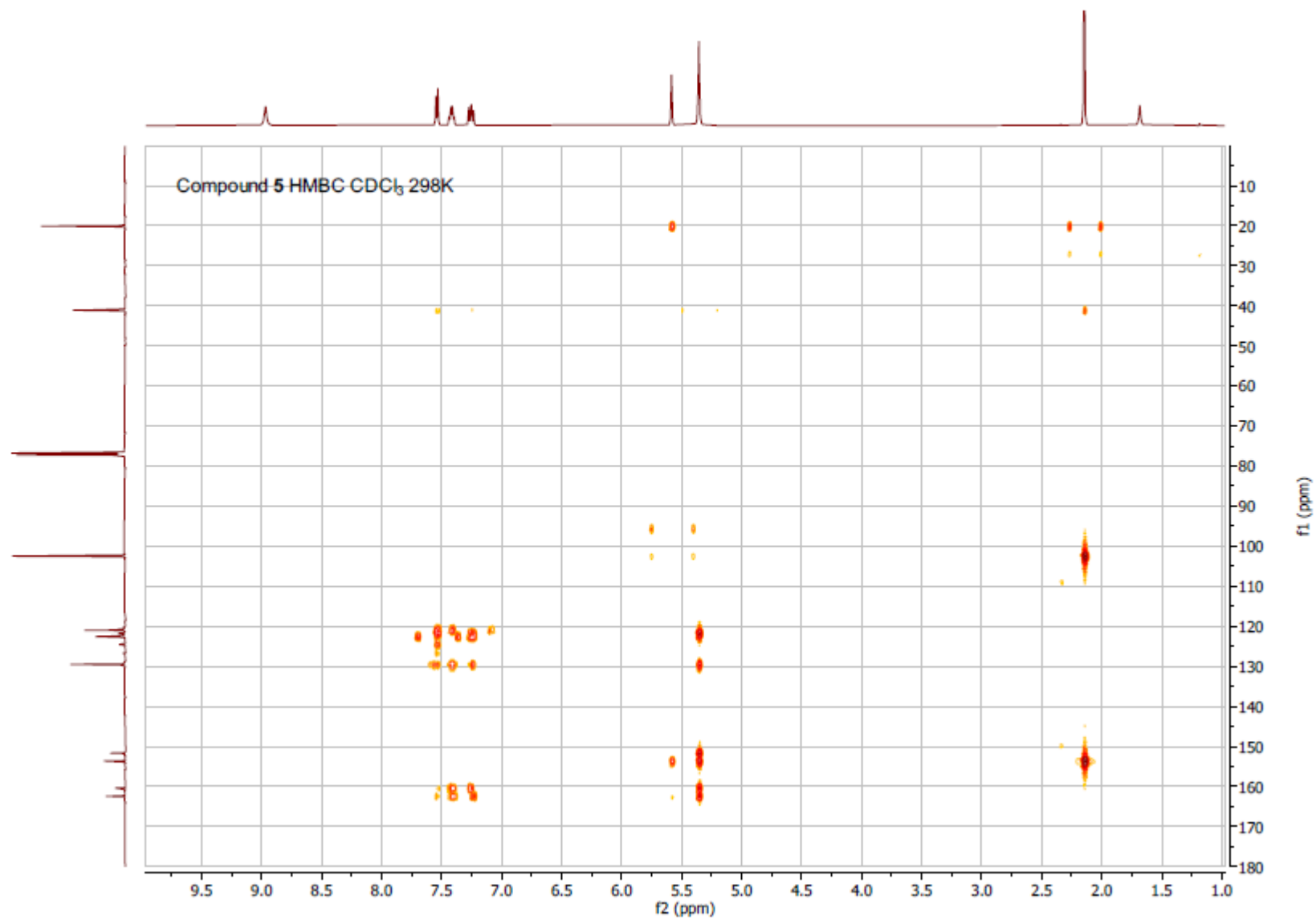
Figure S2.  $^{13}\text{C}$  NMR of compound 5



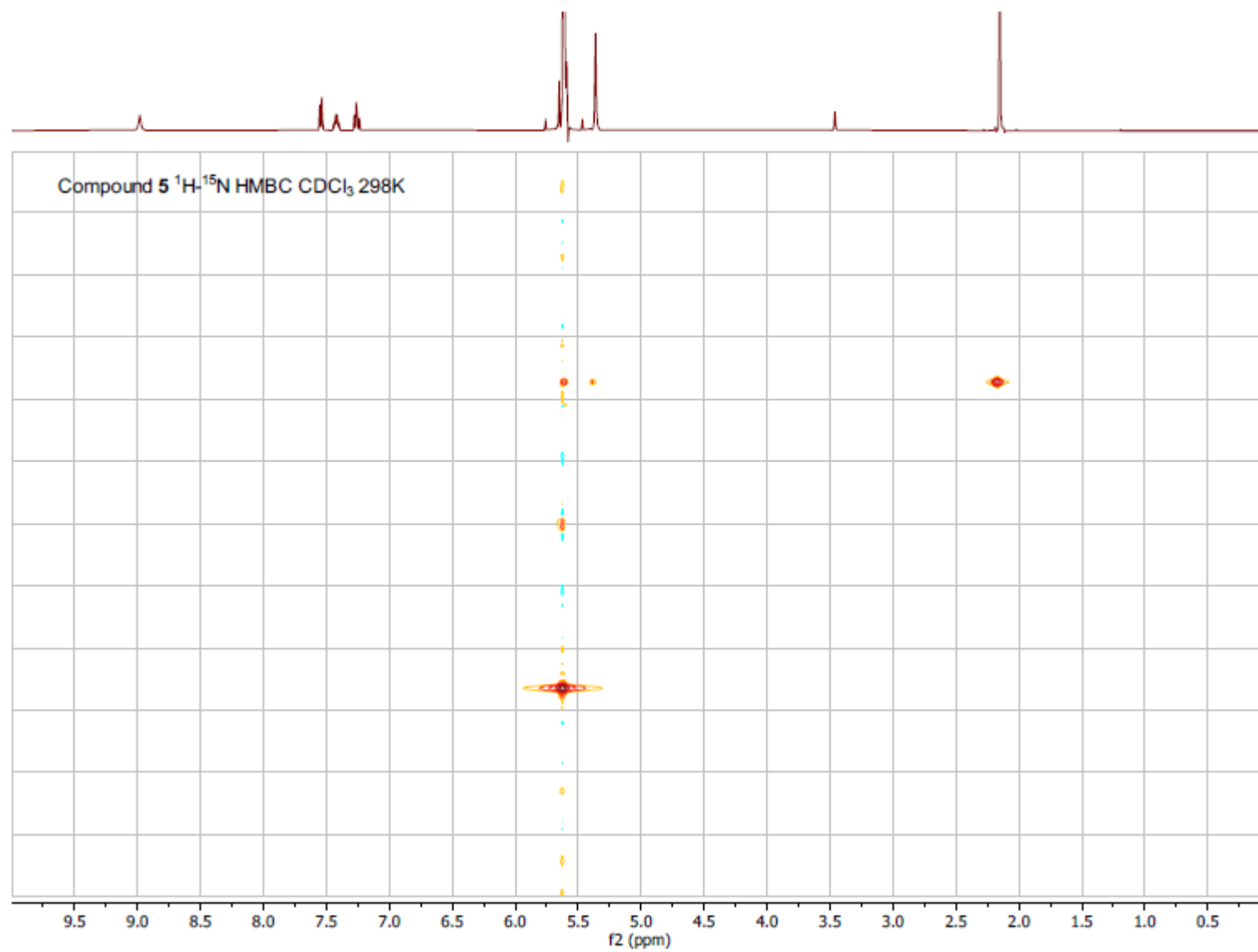
**Figure S3.** COSY of compound 5



**Figure S4.**  $^1\text{H}$ - $^{13}\text{C}$  HSQC of compound 5

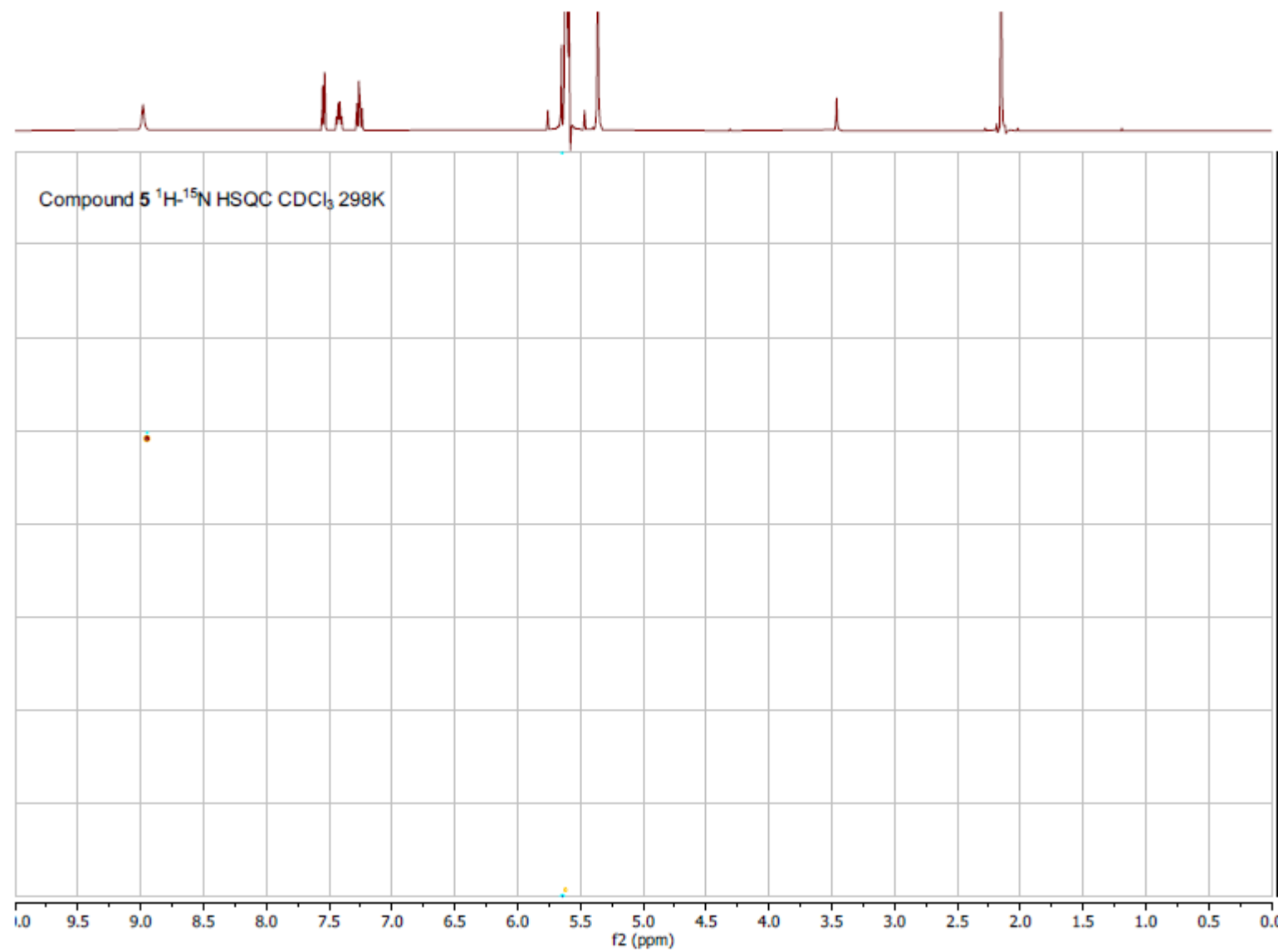


**Figure S5.**  $^1\text{H}$ - $^{13}\text{C}$  HMBC of compound 5



**Figure S6.**  $^1\text{H}$ - $^{15}\text{N}$  HMBC of compound 5





**Figure S7.**  $^1\text{H}$ - $^{15}\text{N}$  HSQC of compound 5

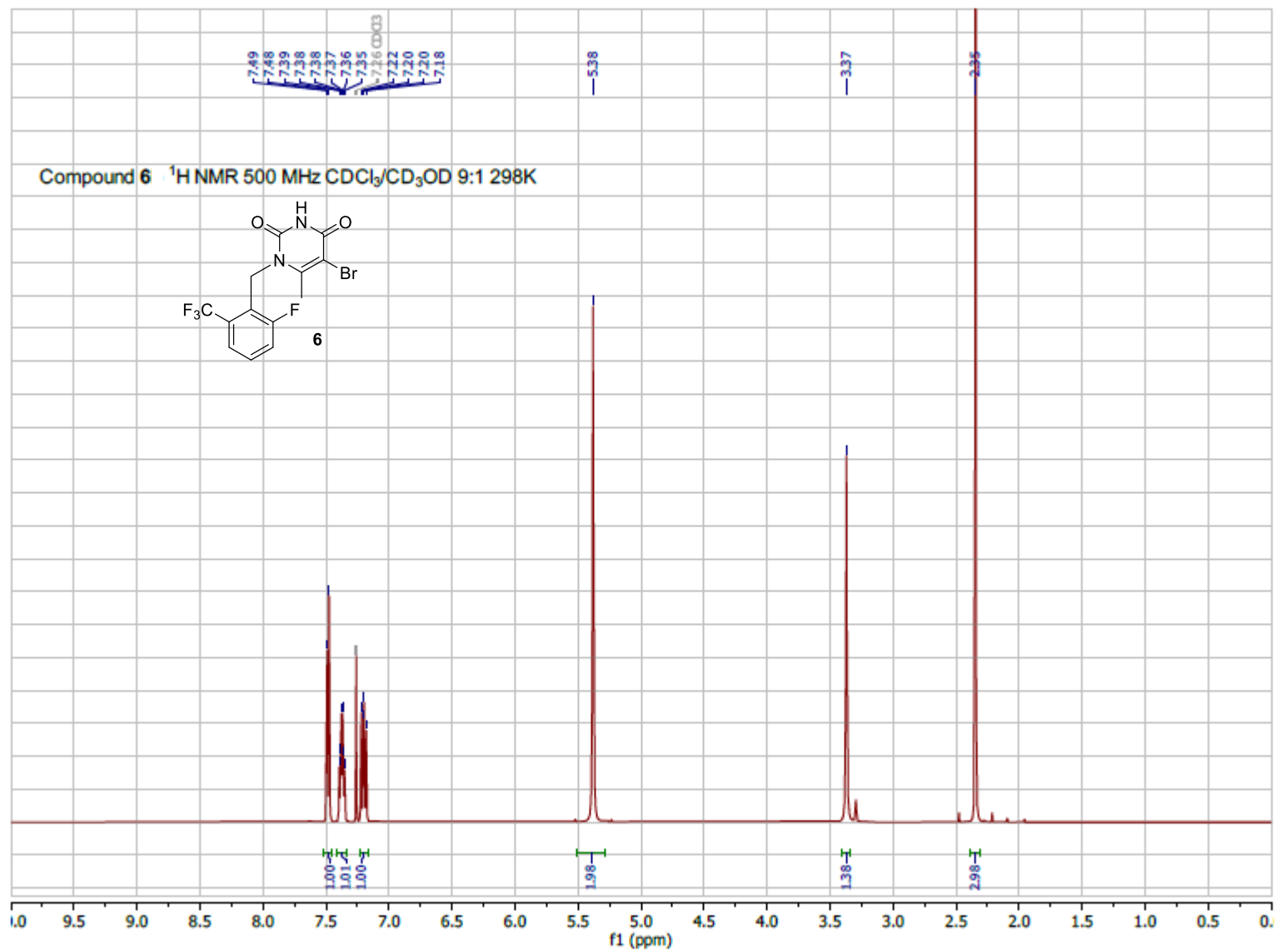


Figure S8.  $^1\text{H}$  NMR of compound **6**

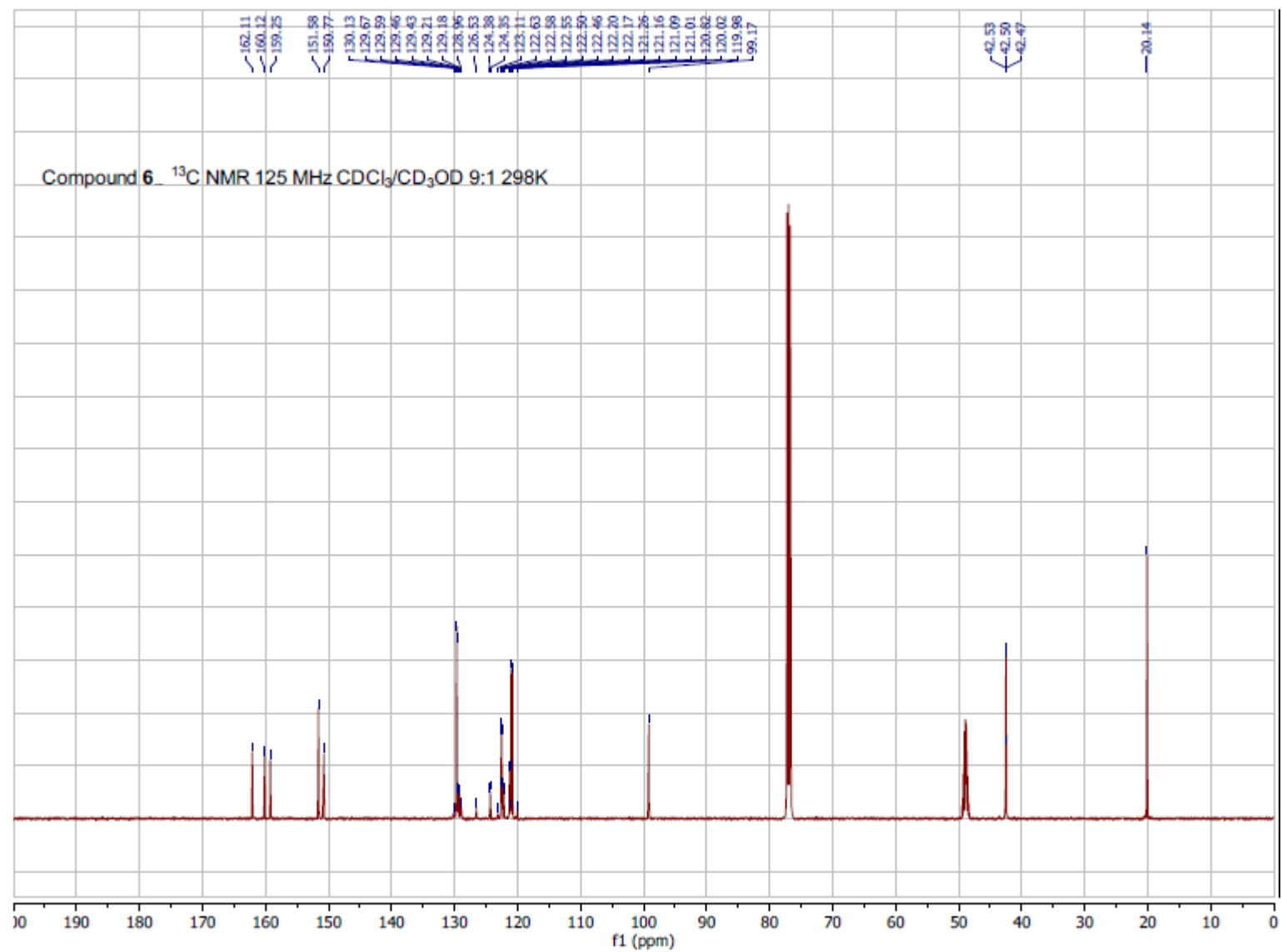


Figure S9.  $^{13}\text{C}$  NMR of compound 6

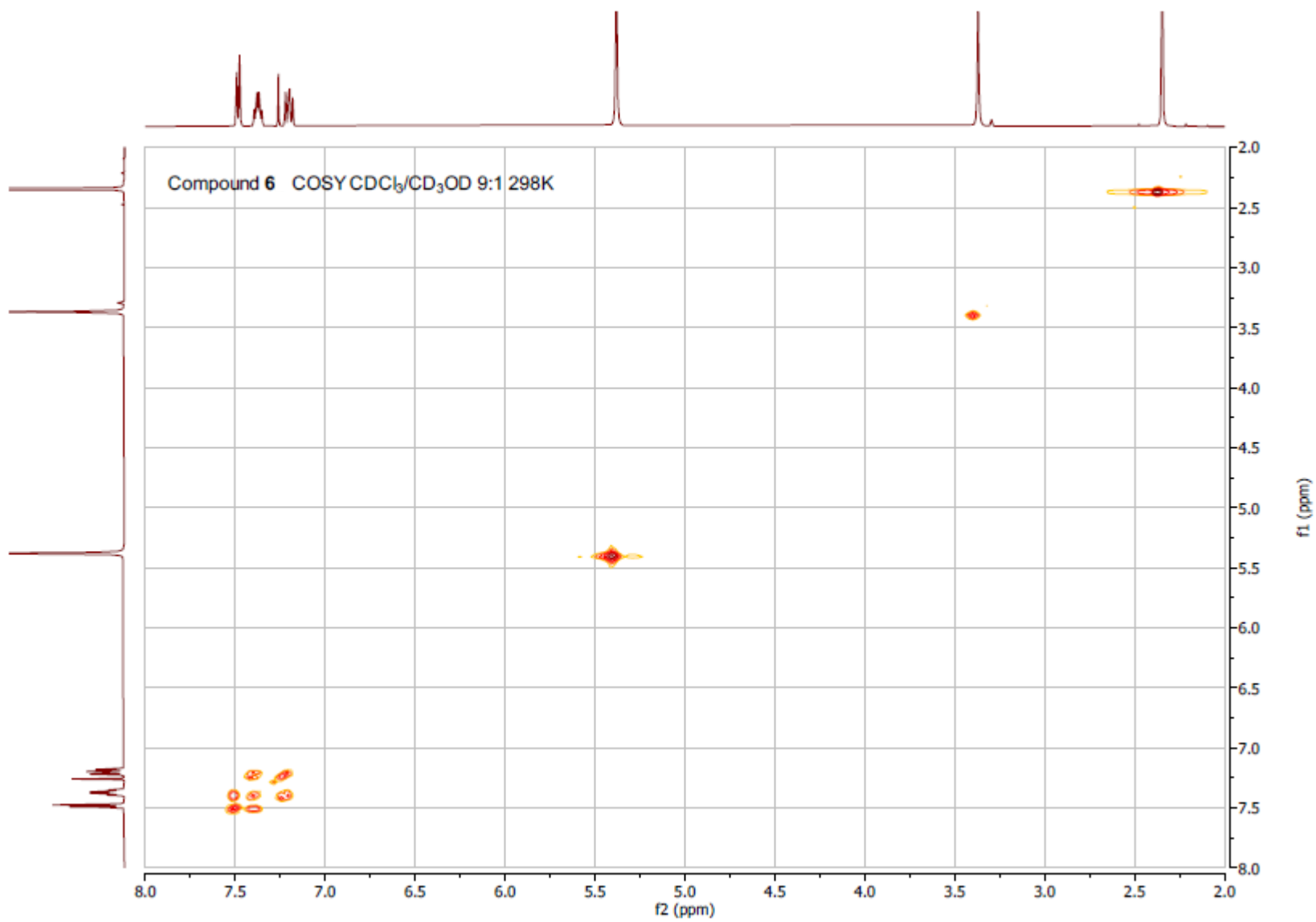
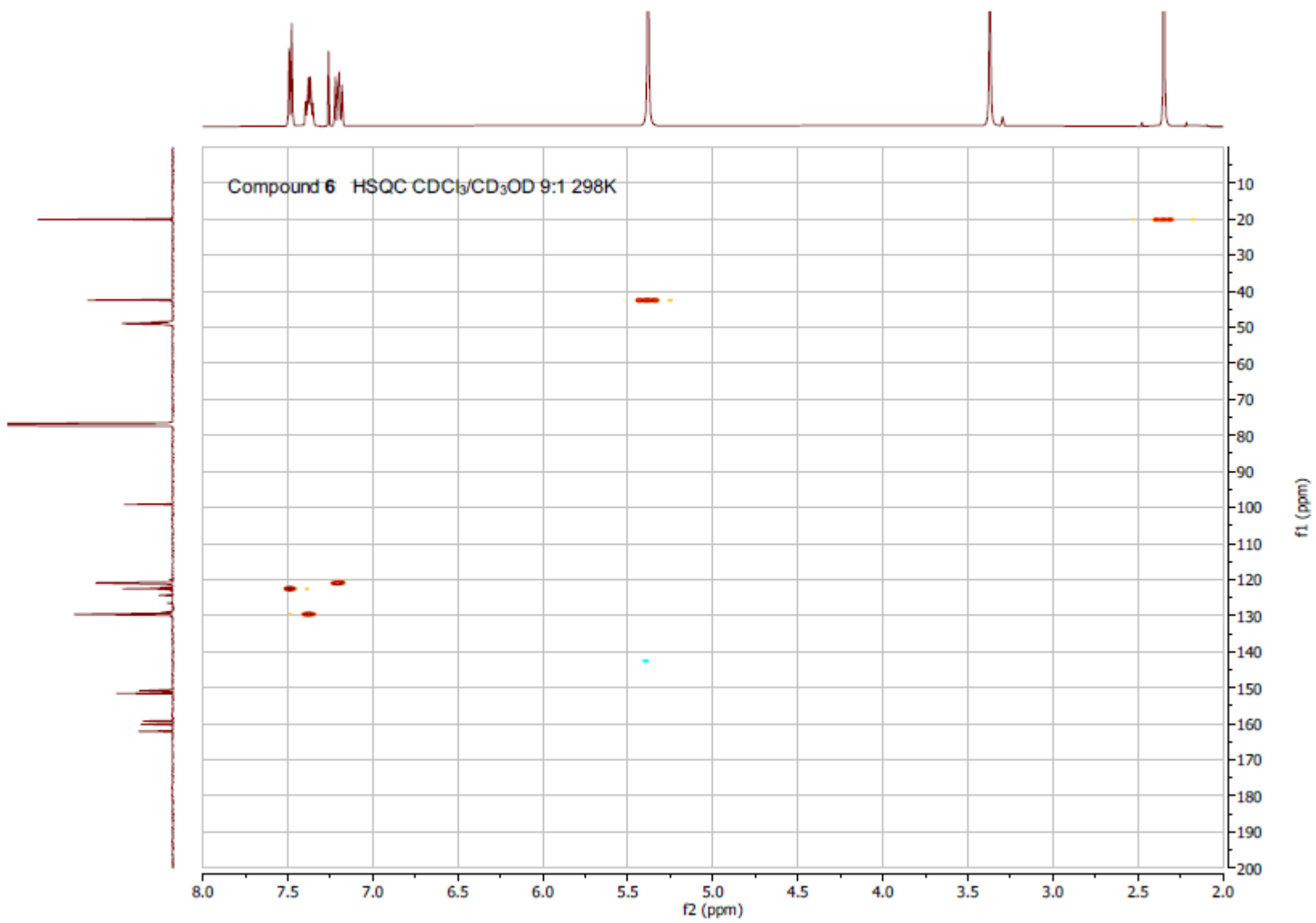


Figure S10. COSY of compound 6



**Figure S11.**  $^1\text{H}$ - $^{13}\text{C}$  HSQC of compound 6

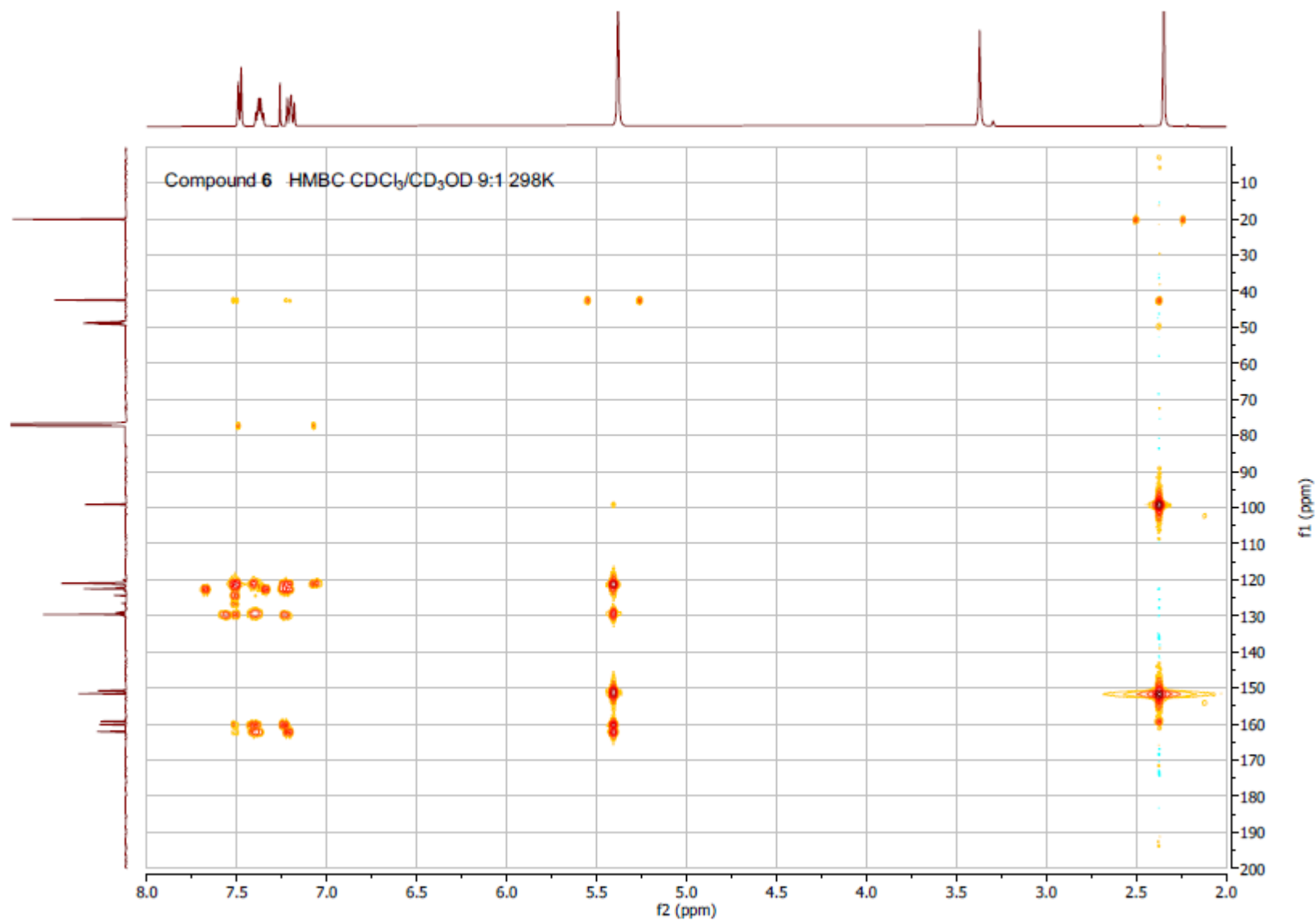


Figure S12.  $^1\text{H}$ - $^{13}\text{C}$  HMBC of compound 6

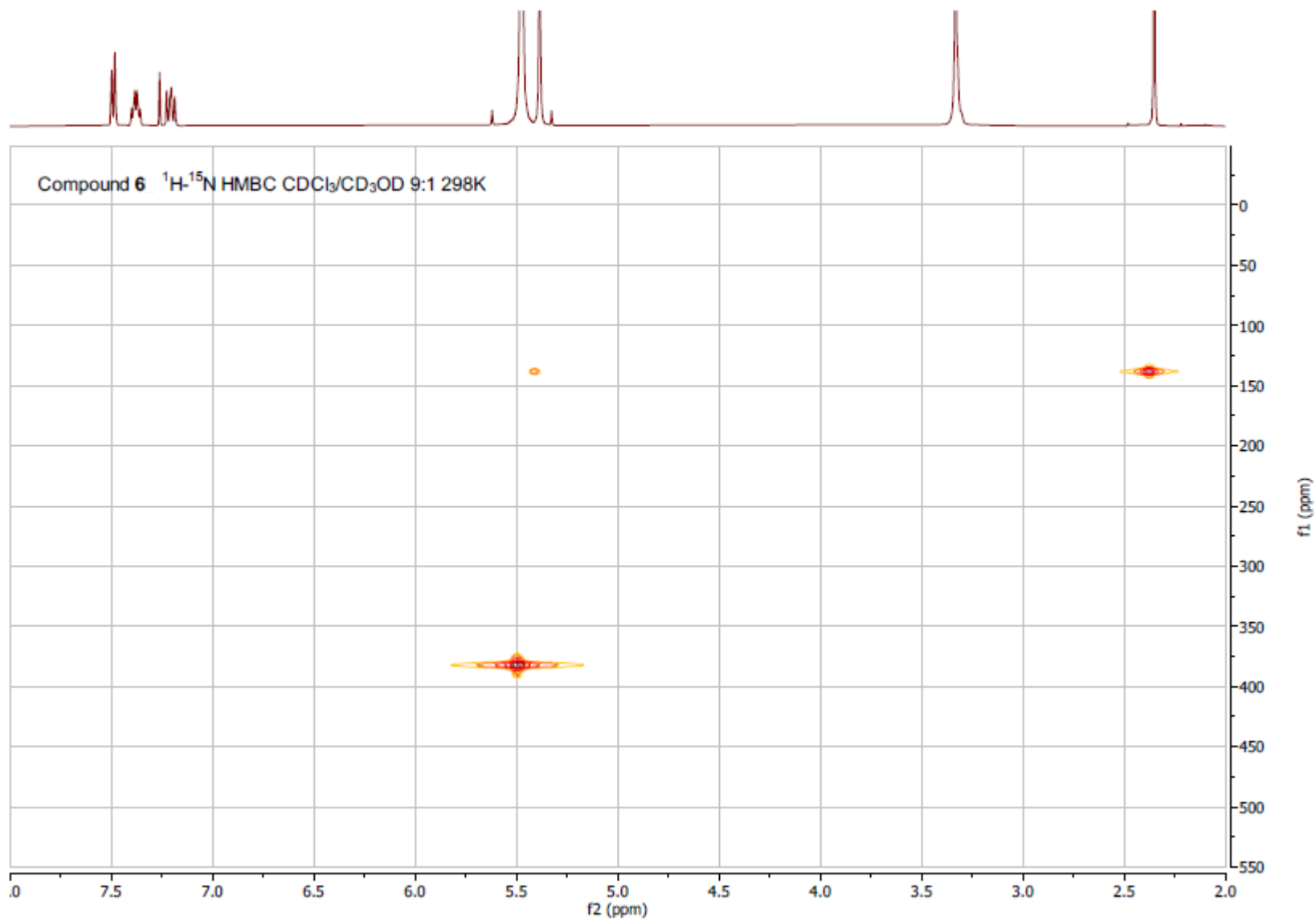


Figure S13.  $^1\text{H}$ - $^{15}\text{N}$  HMBC of compound 6

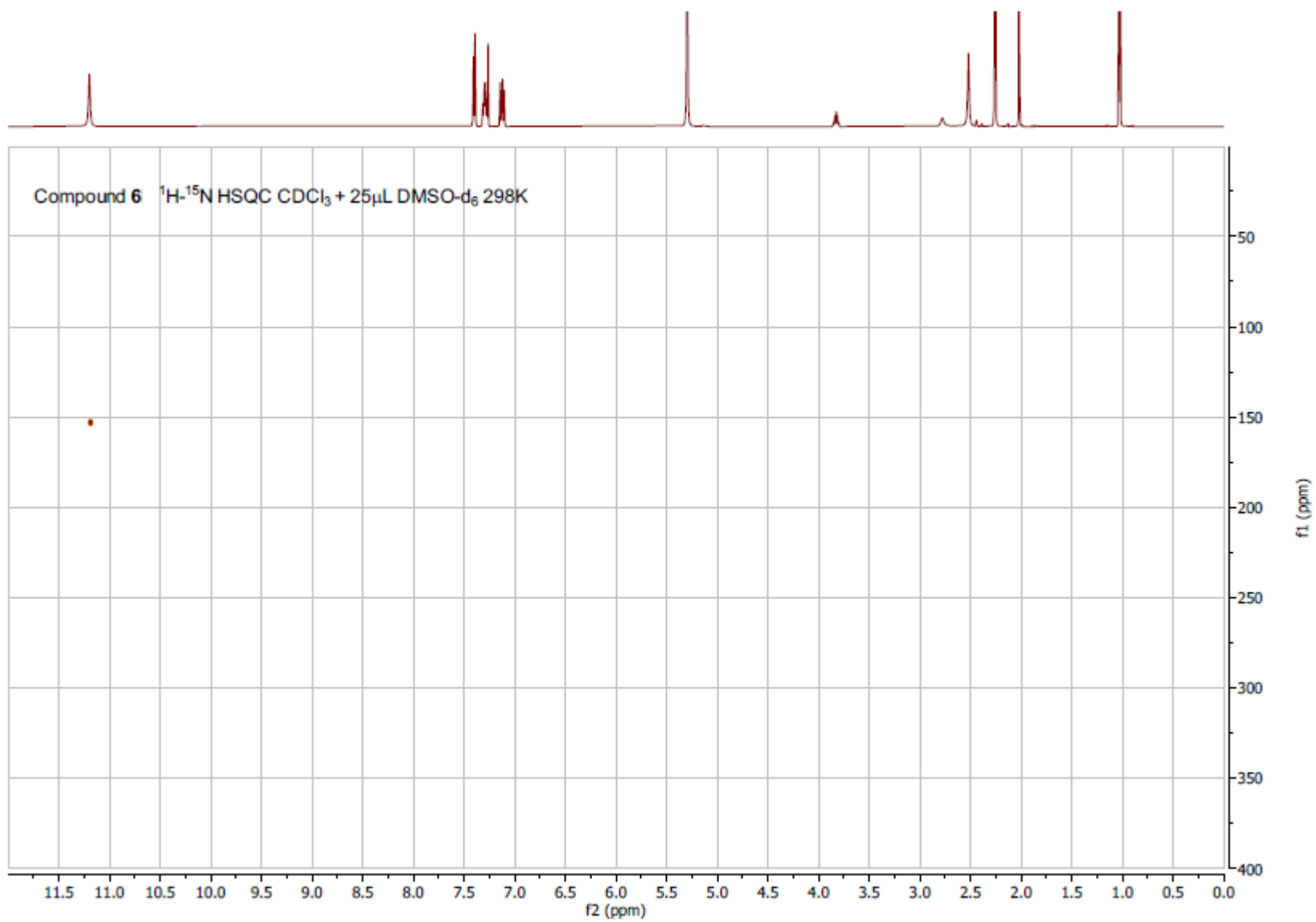


Figure S14.  $^1\text{H}$ - $^{15}\text{N}$  HSQC of compound 6



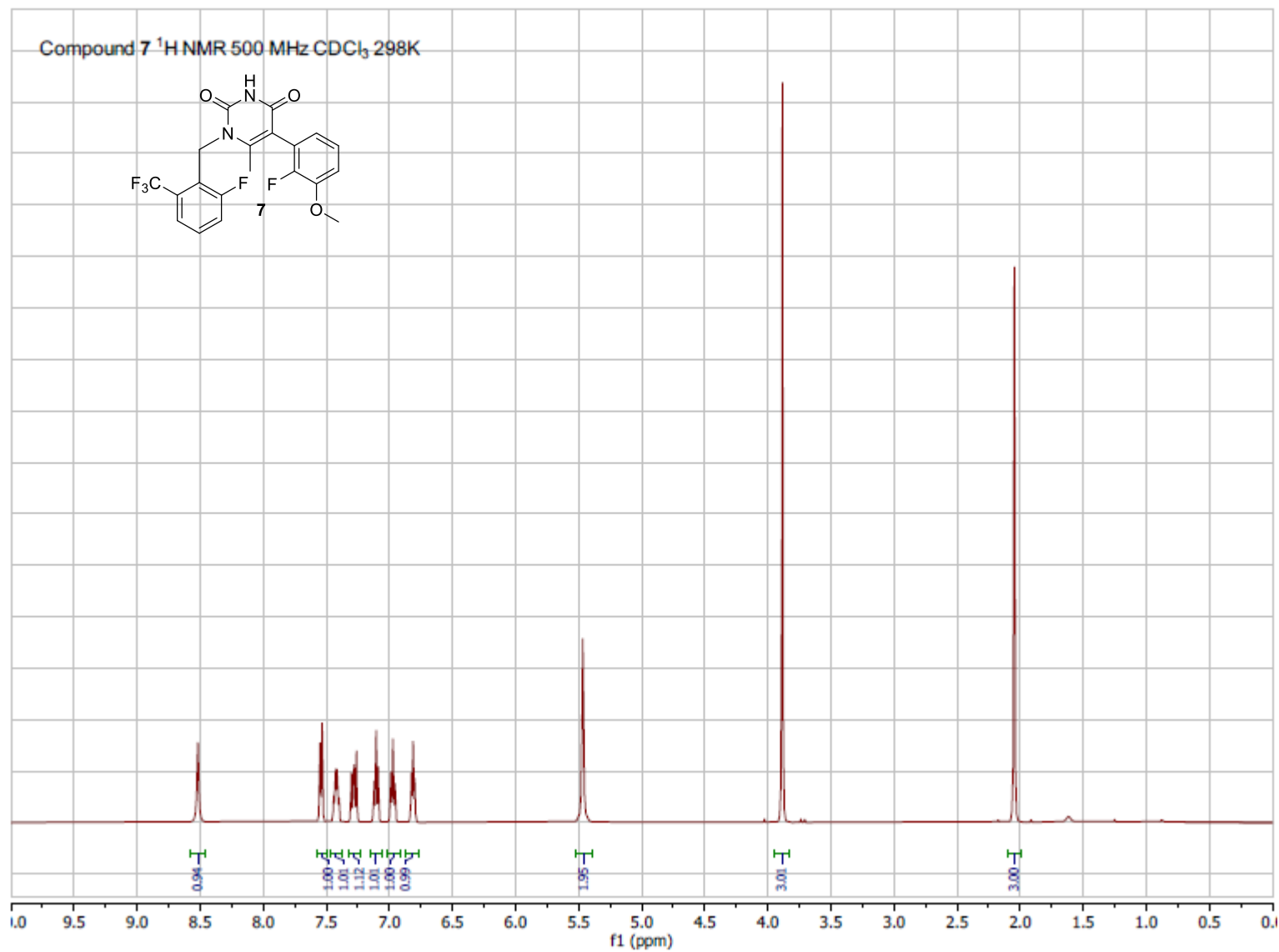


Figure S15.  $^1\text{H}$  NMR of compound **7**

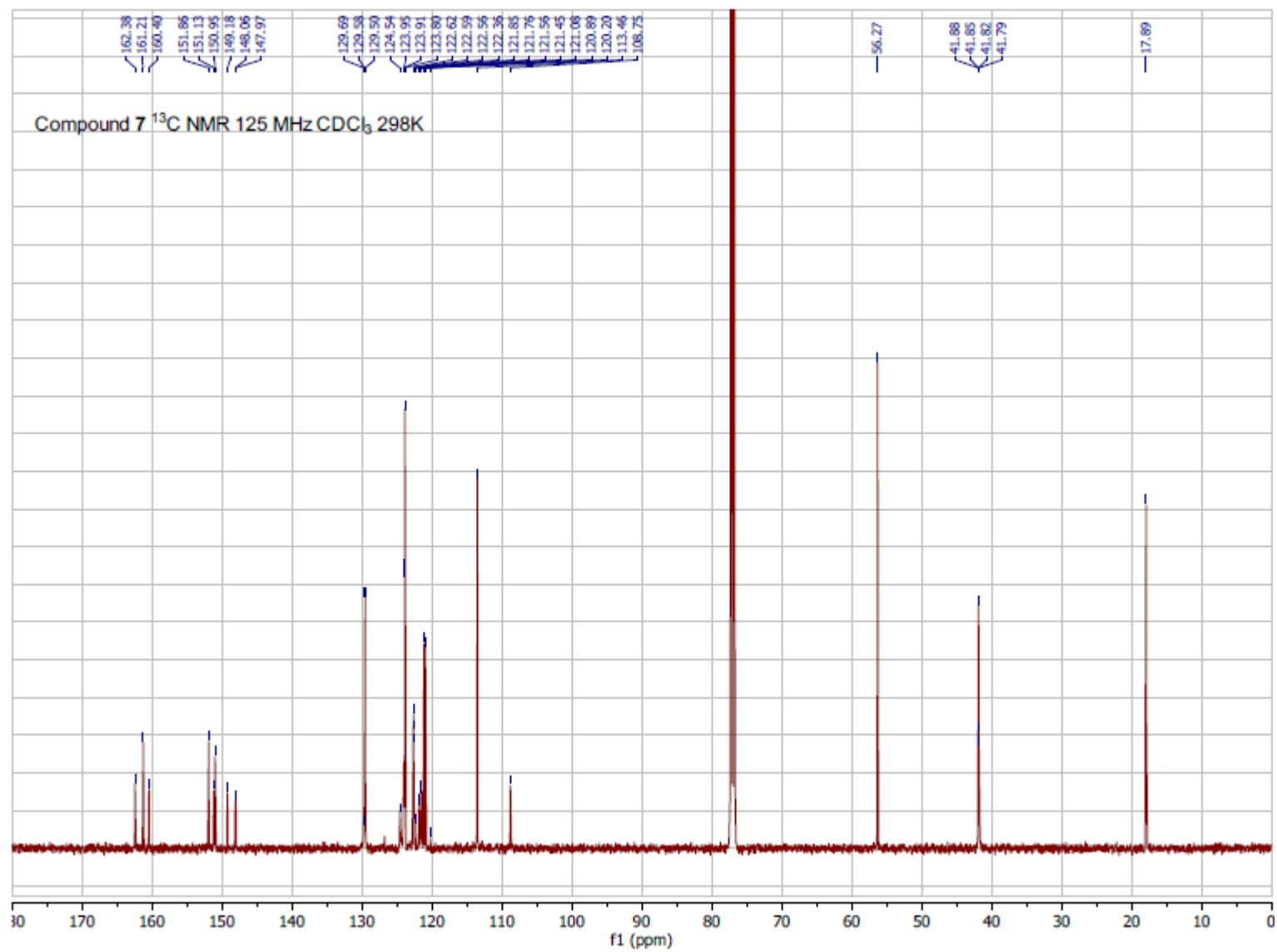


Figure S16.  $^{13}\text{C}$  NMR of compound 7

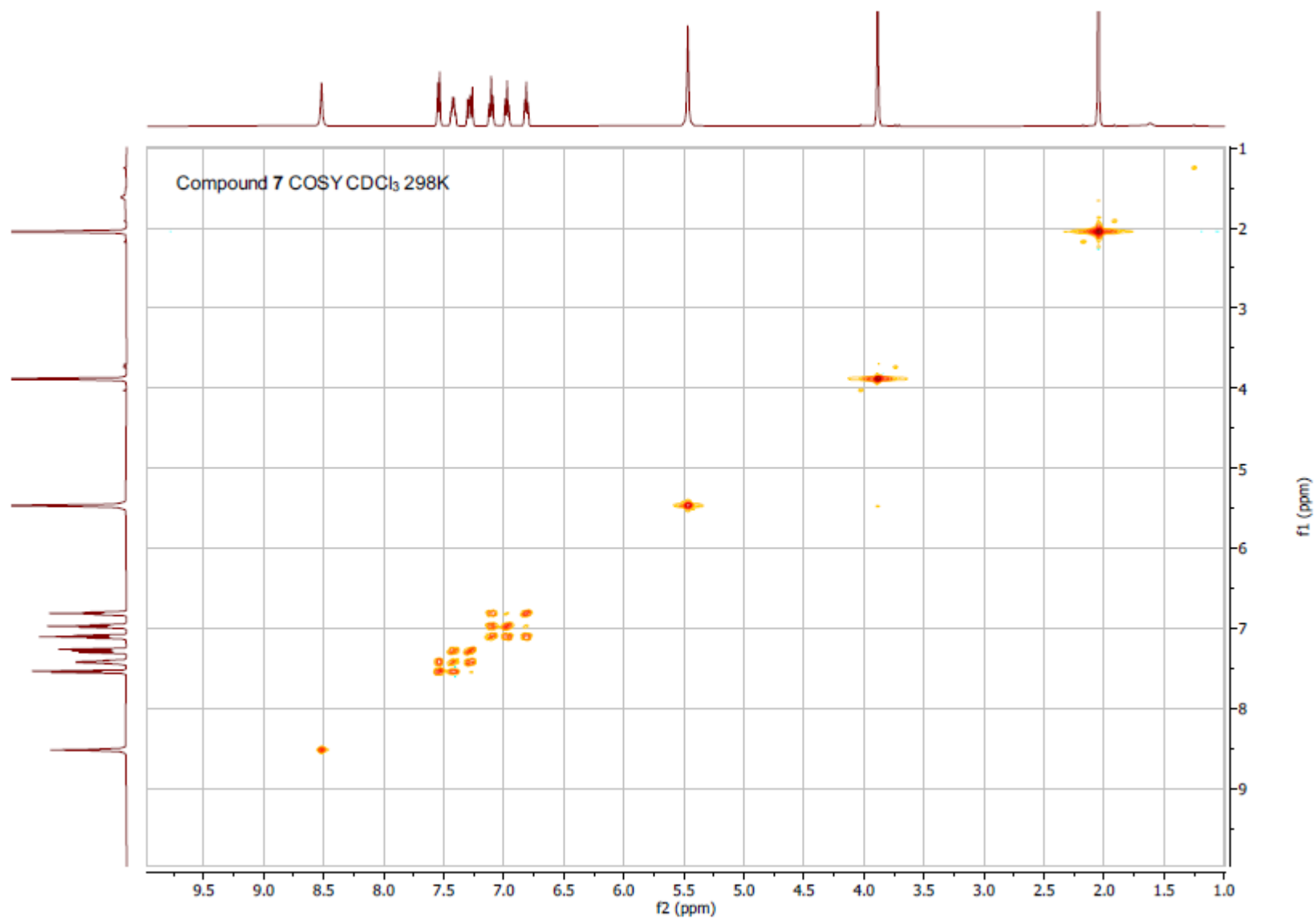
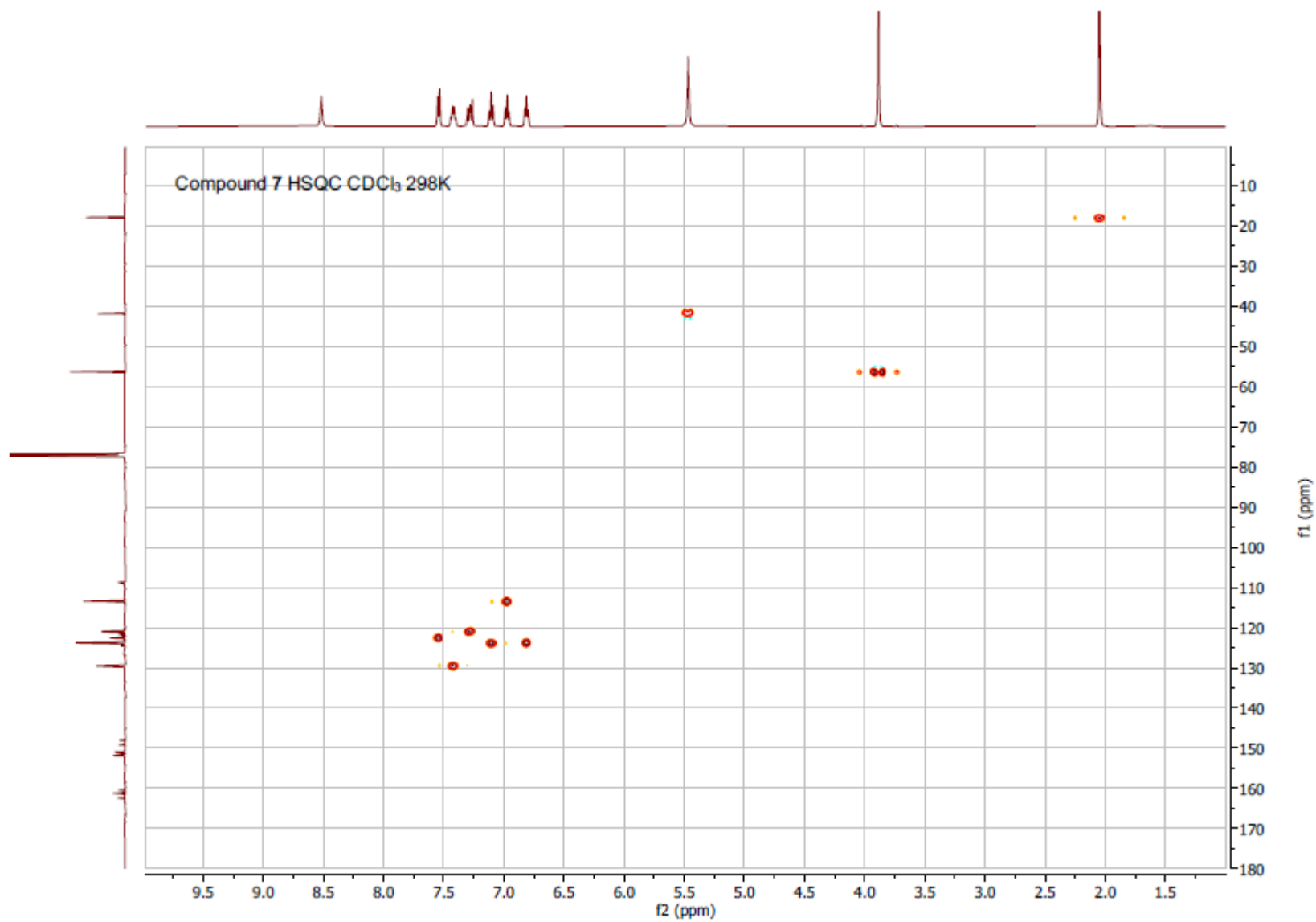
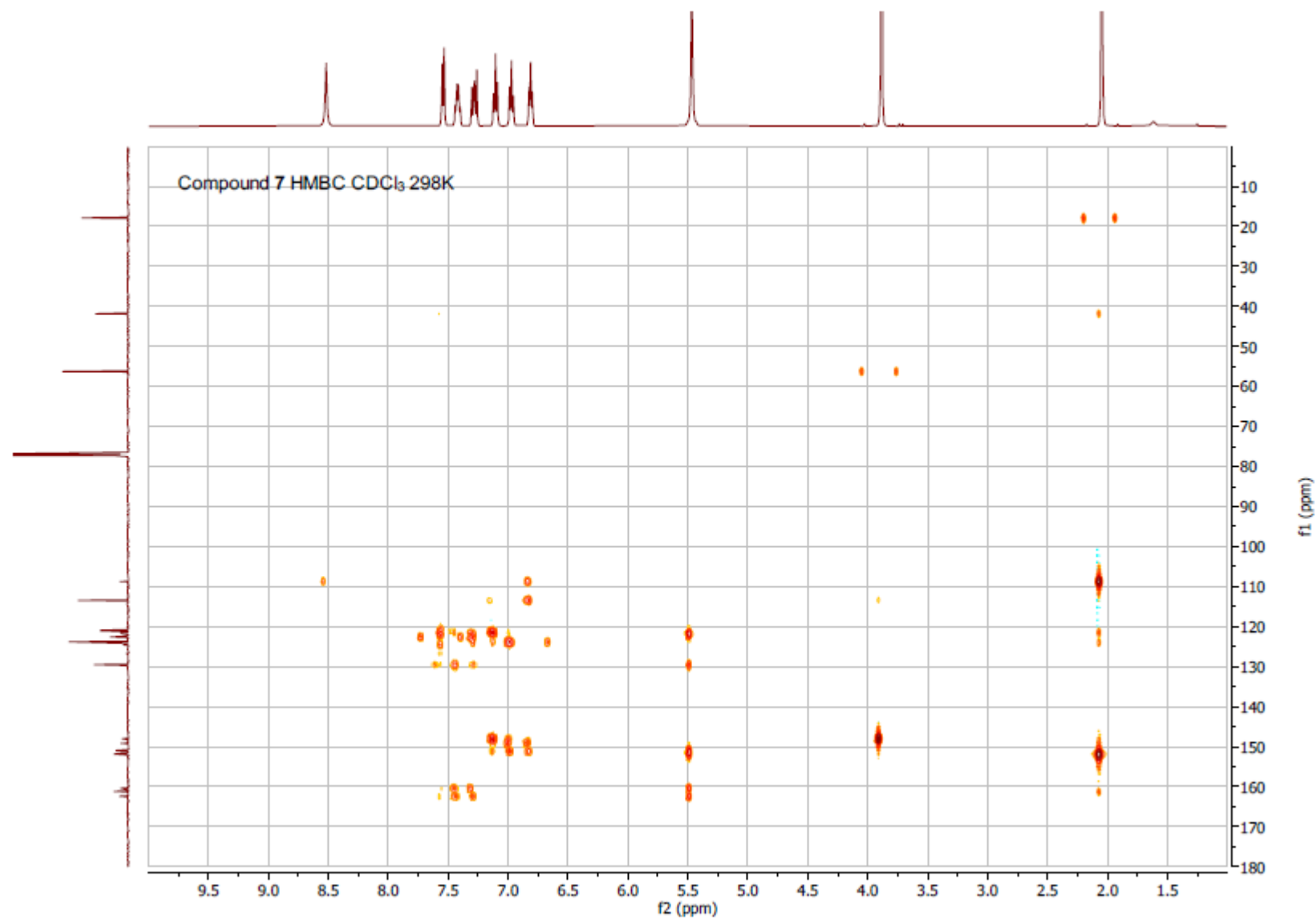


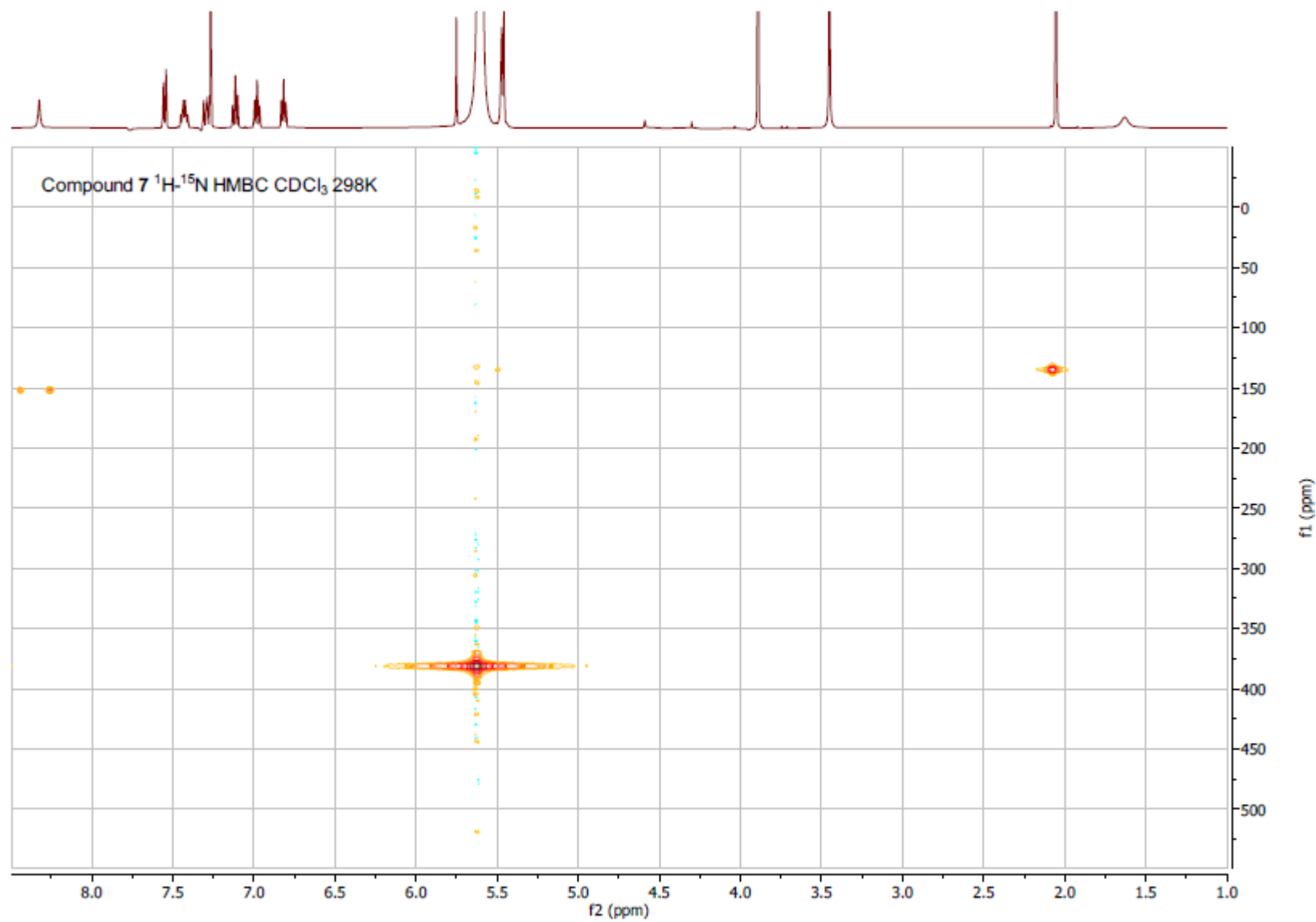
Figure S17. COSY of compound 7



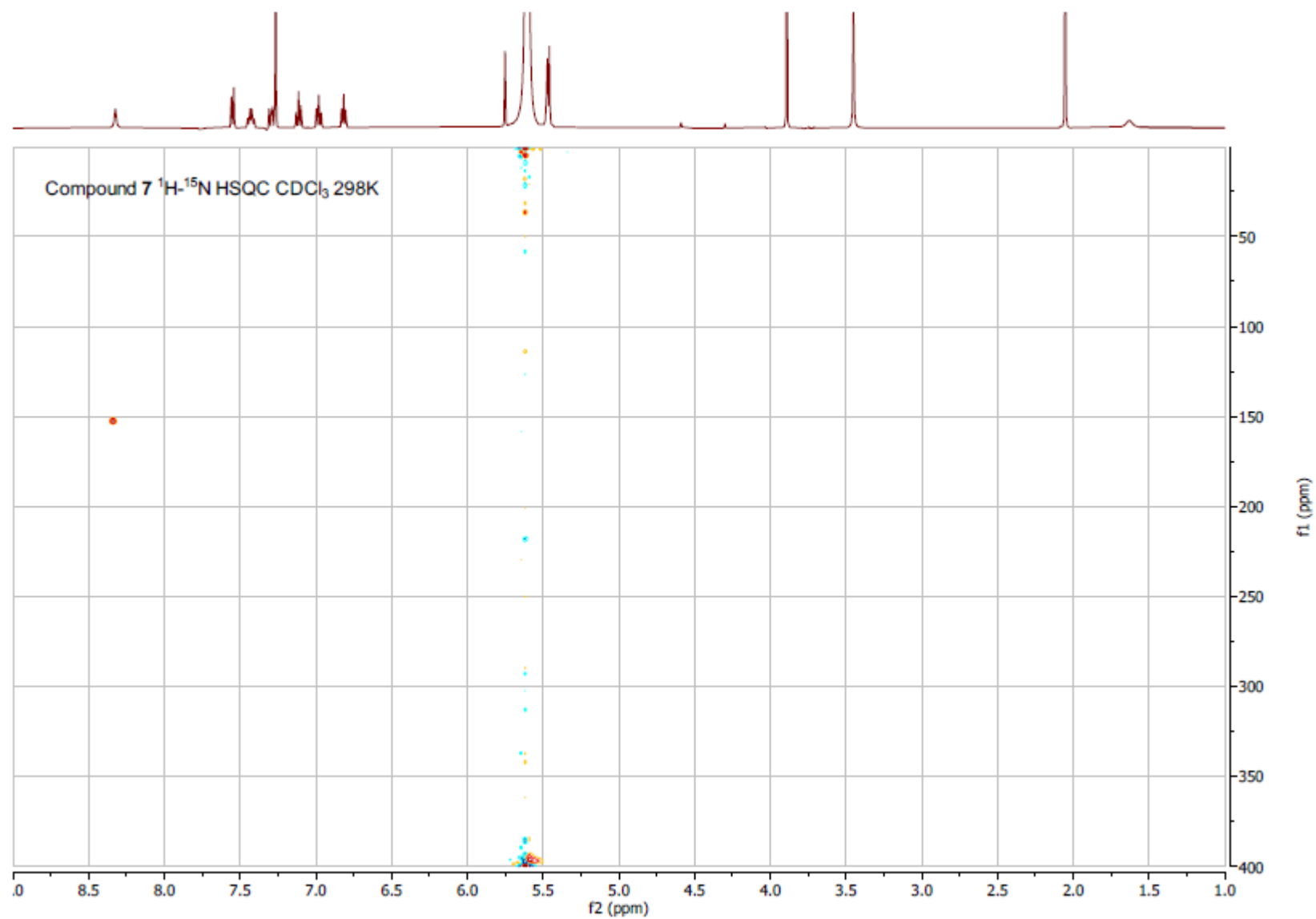
**Figure S18.**  $^1\text{H}$ - $^{13}\text{C}$  HSQC of compound 7



**Figure S19.** <sup>1</sup>H-<sup>13</sup>C HMBC of compound 7



**Figure S20.**  $^1\text{H}$ - $^{15}\text{N}$  HMBC of compound 7



**Figure S21.**  $^1\text{H}$ - $^{15}\text{N}$  HSQC of compound 7

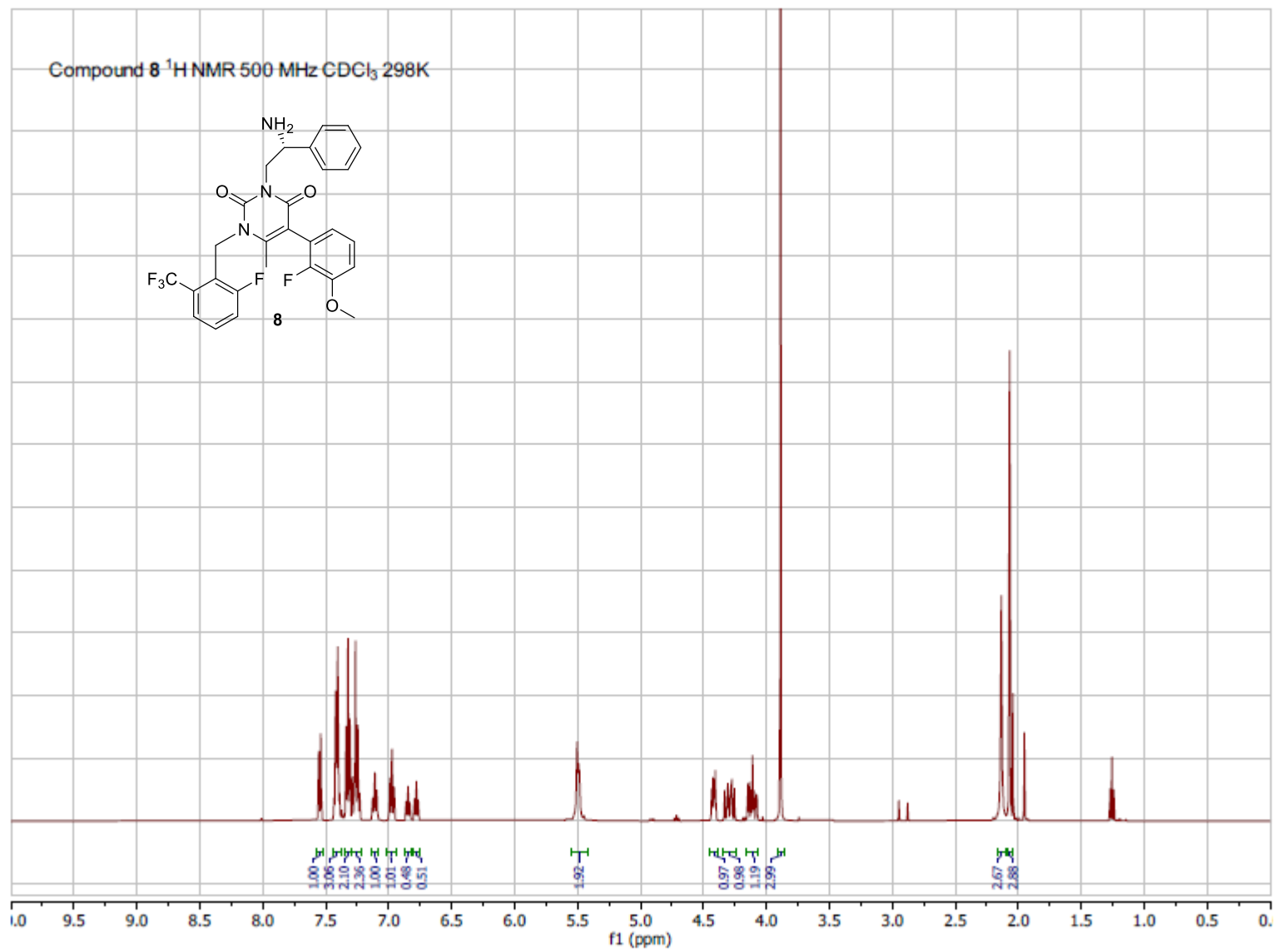


Figure S22.  $^1\text{H}$  NMR of compound **8**



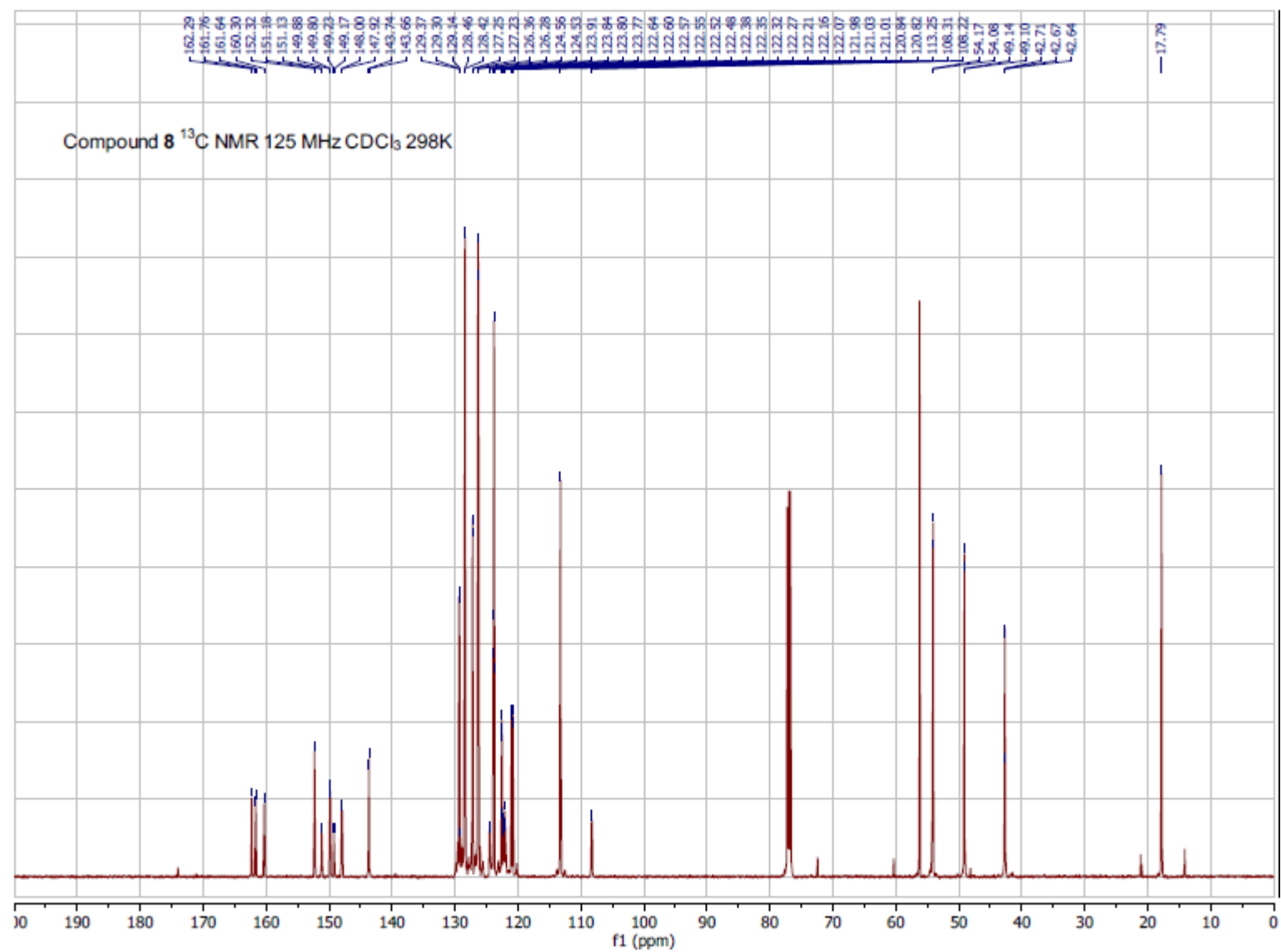


Figure S23.  $^{13}\text{C}$  NMR of compound 8

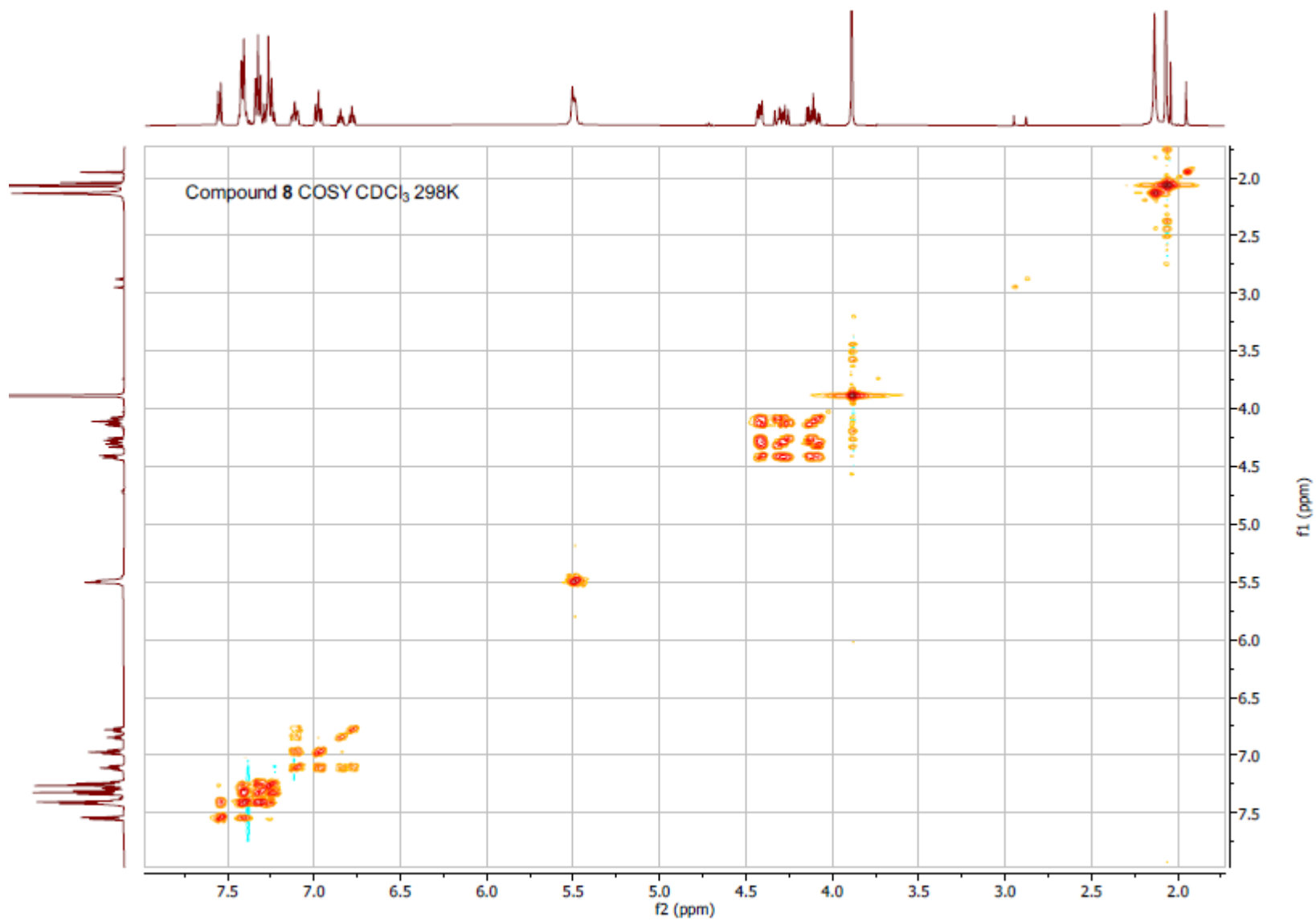
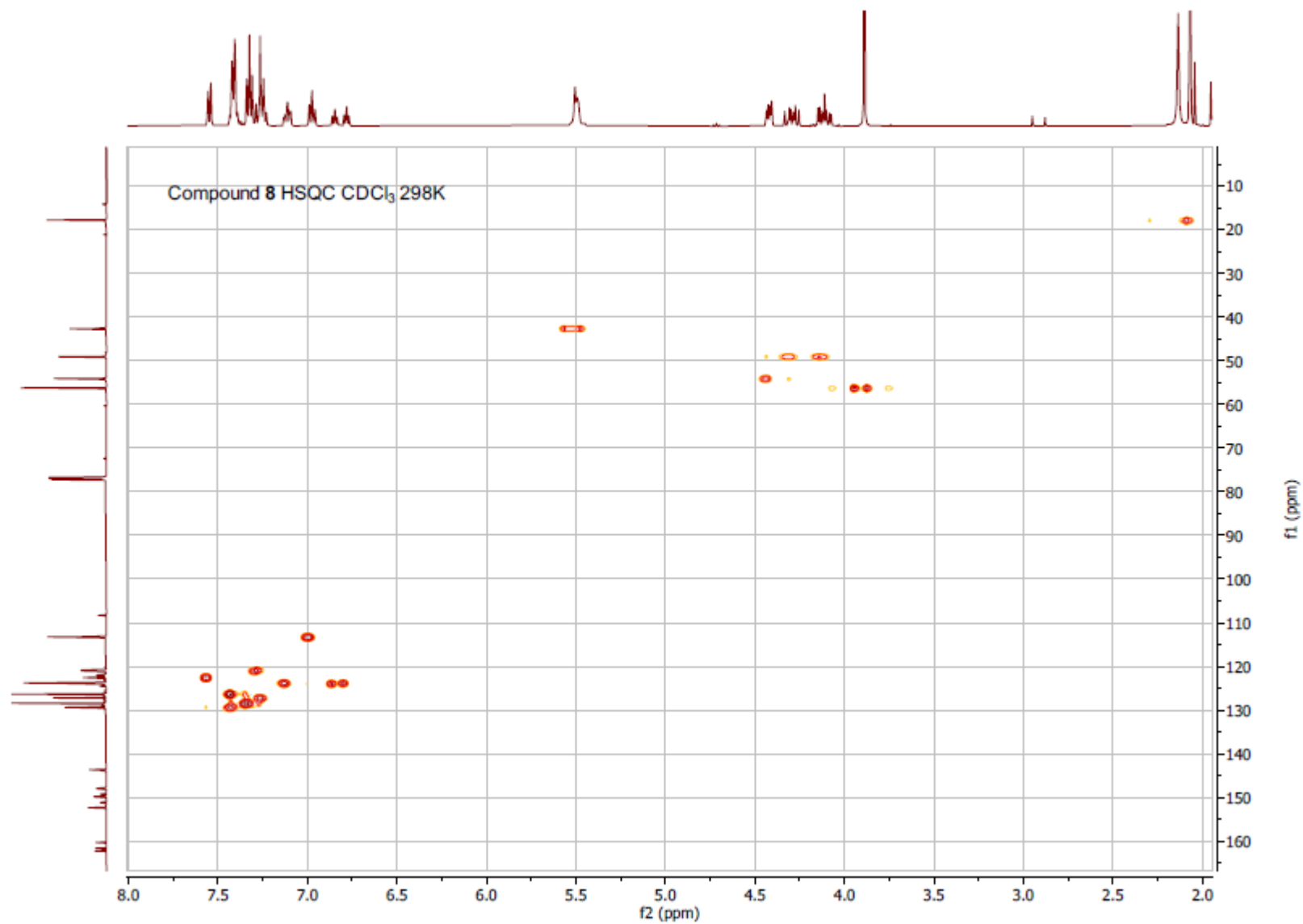
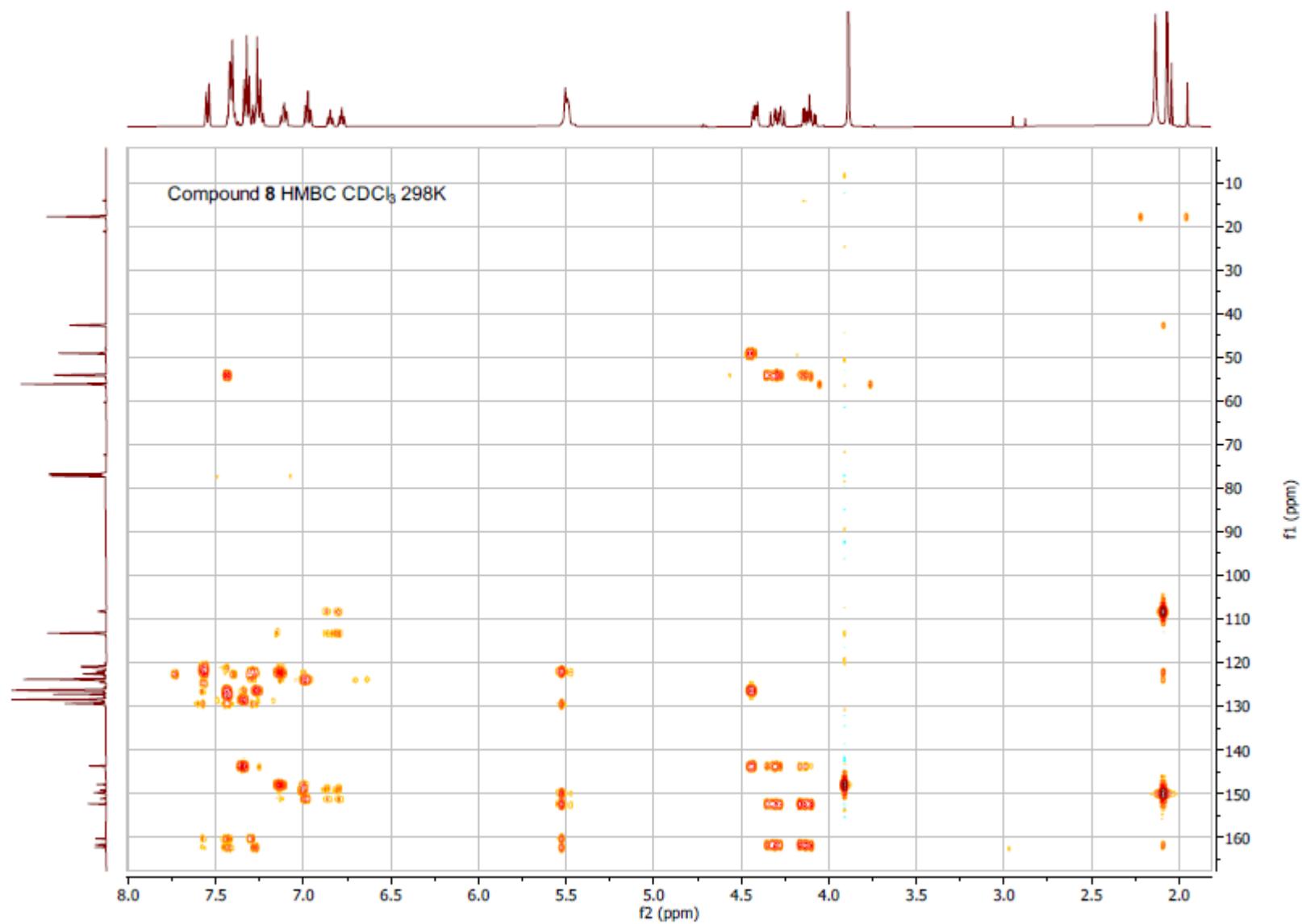


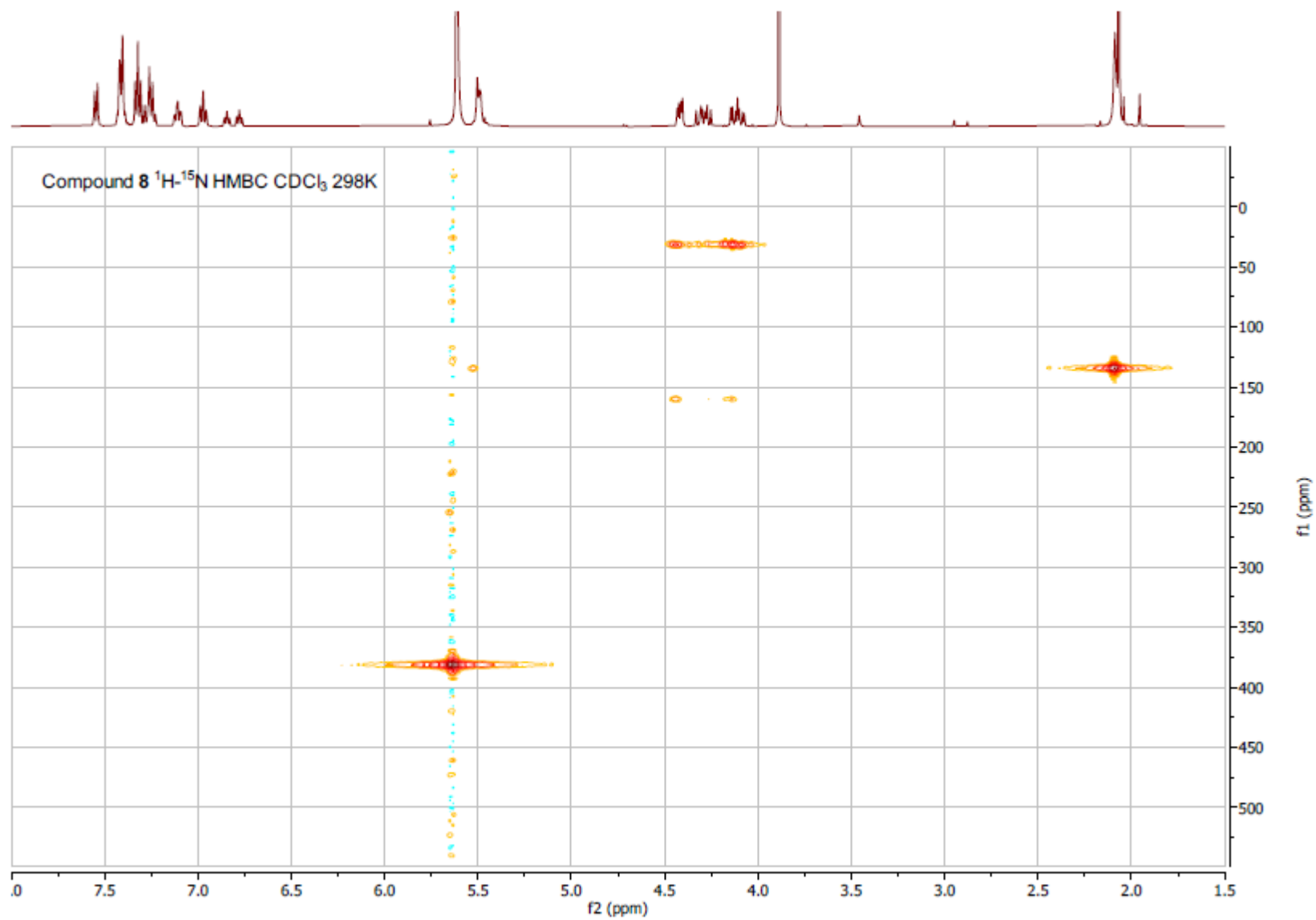
Figure S24. COSY of compound 8



**Figure S25.** <sup>1</sup>H-<sup>13</sup>C HSQC of compound 8



**Figure S26.** <sup>1</sup>H-<sup>13</sup>C HMBC of compound 8



**Figure S27.**  $^1\text{H}$ - $^{15}\text{N}$  HMBC of compound 8

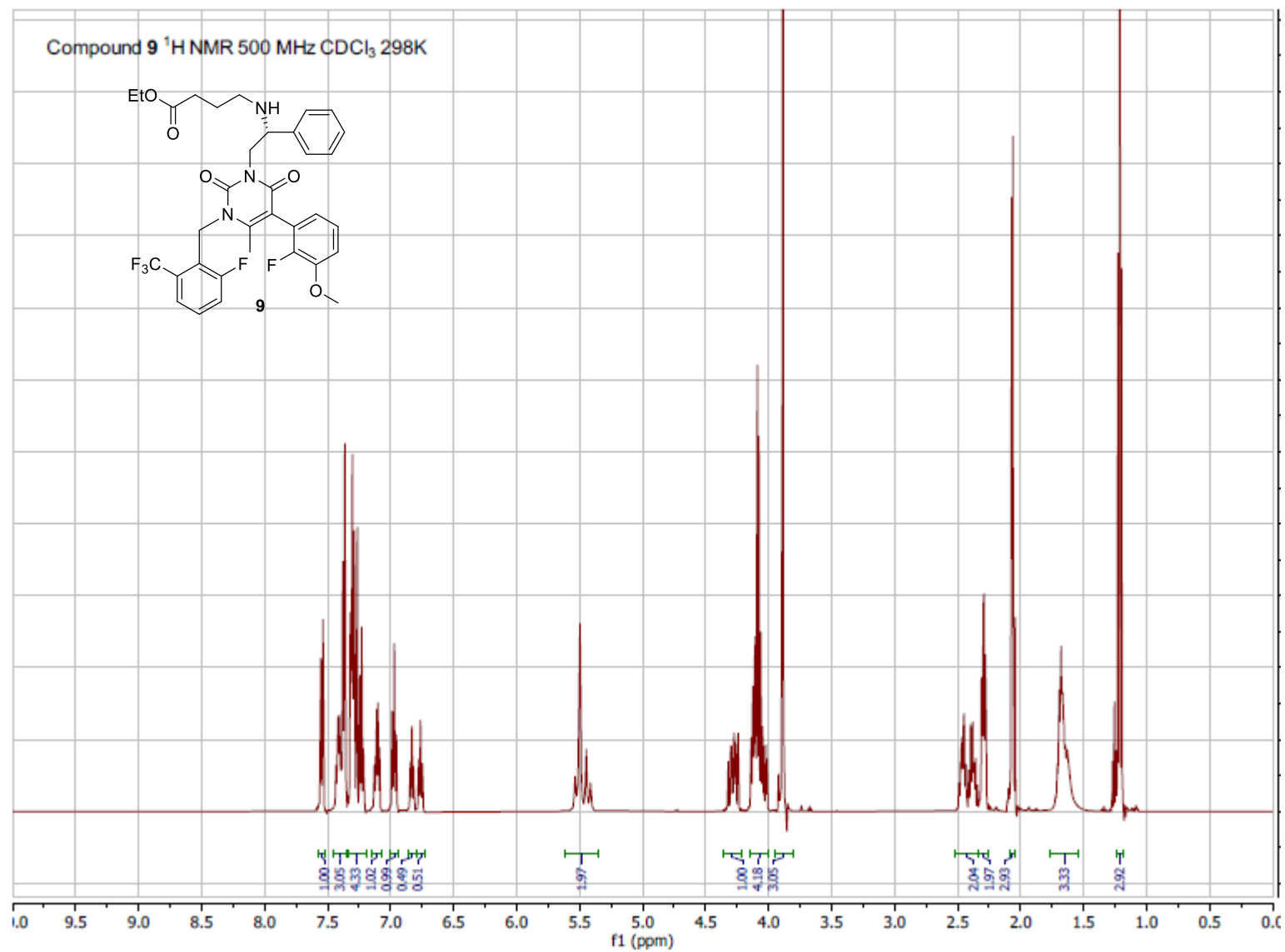


Figure S28.  $^1\text{H}$  NMR of compound **9**

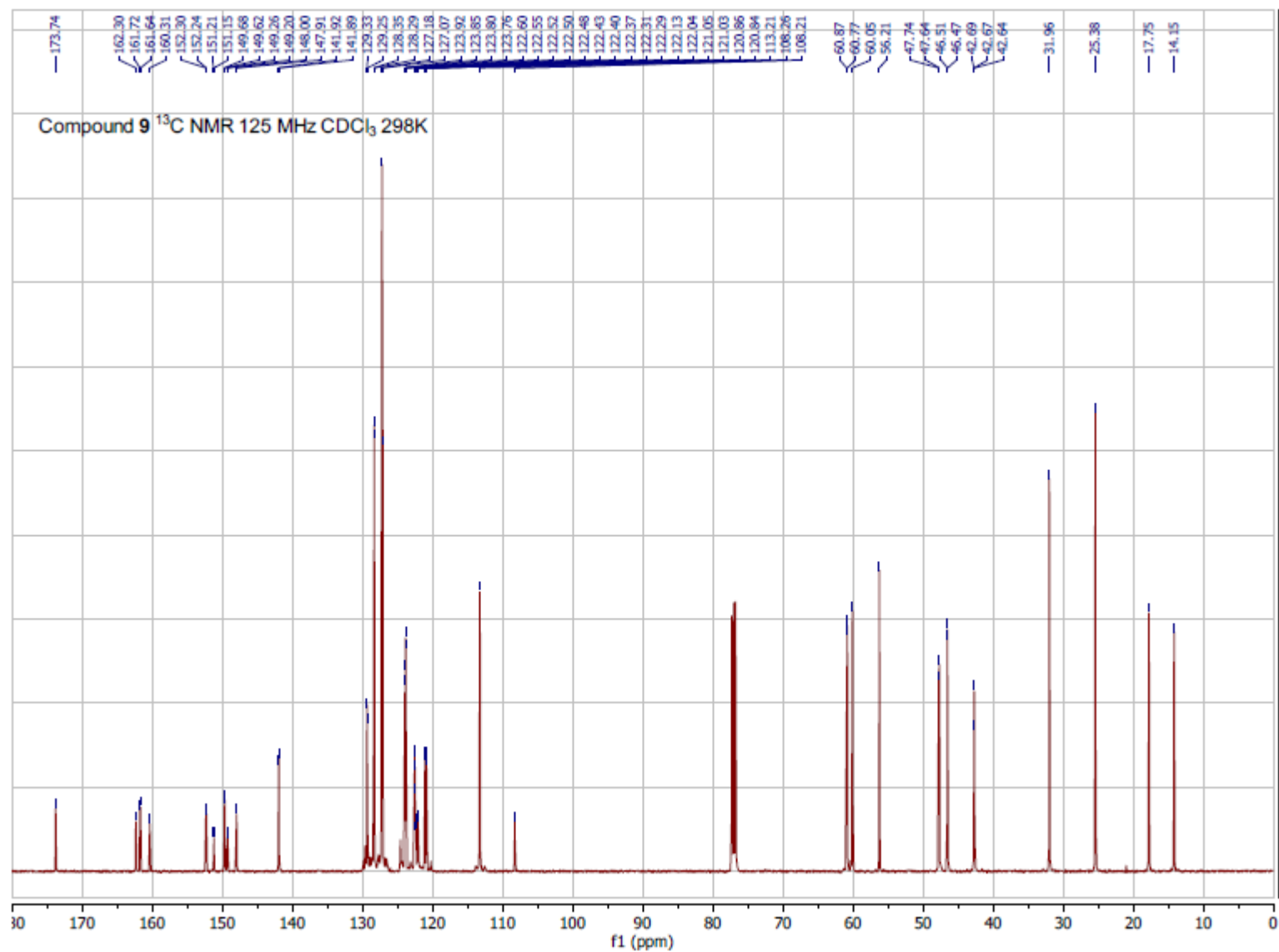


Figure S29.  $^{13}\text{C}$  NMR of compound 9

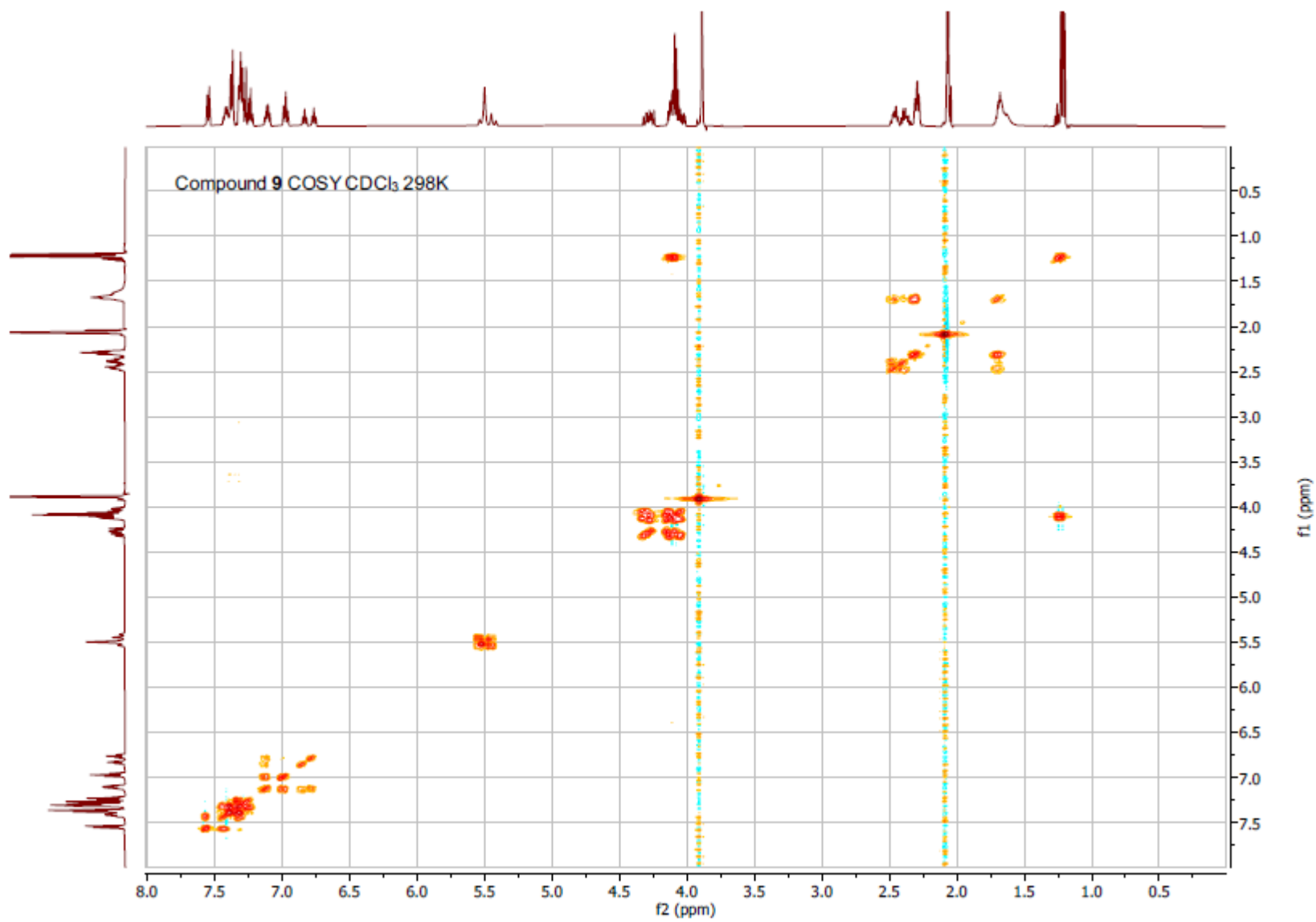


Figure S30. COSY of compound 9



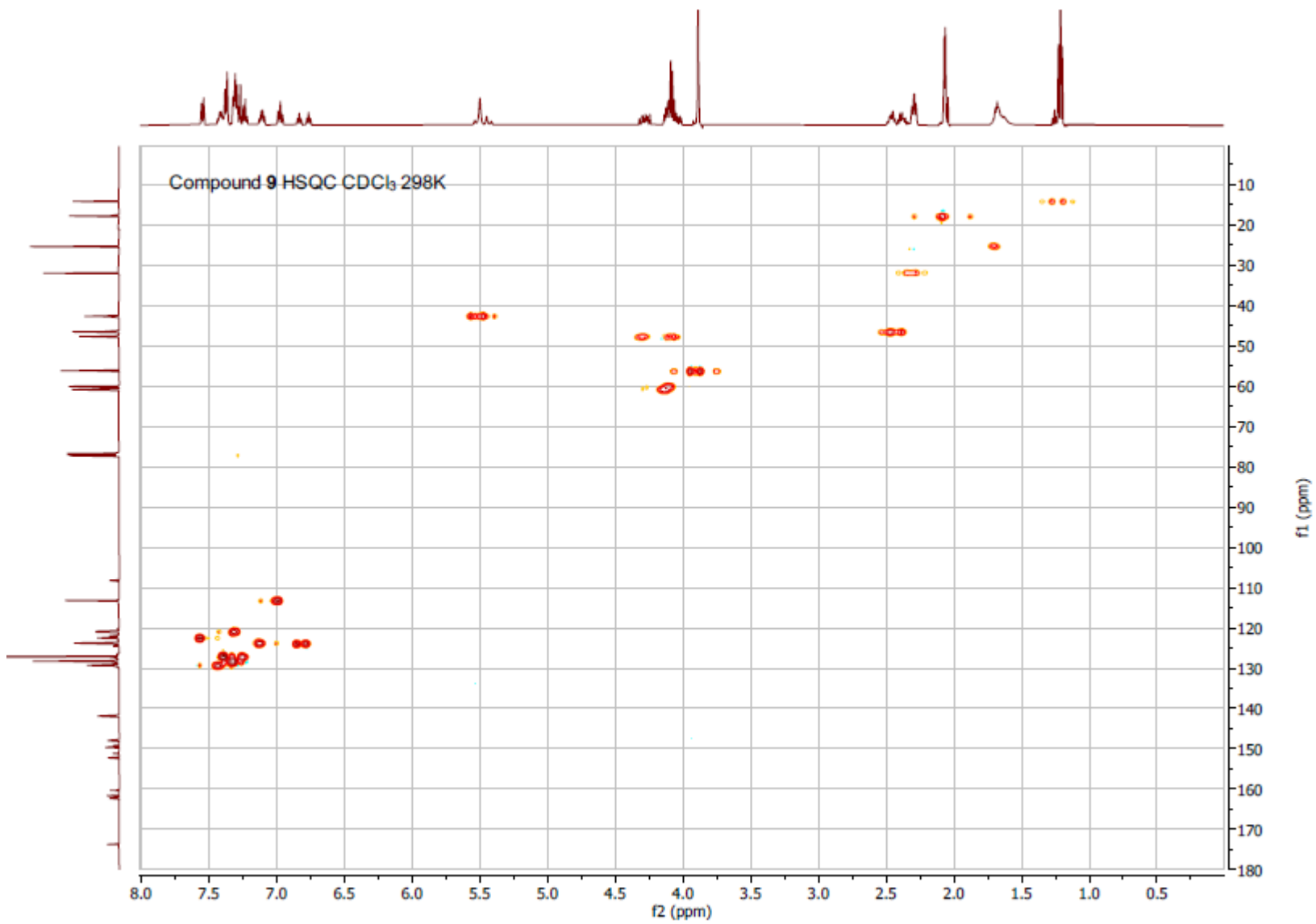


Figure S31.  $^1\text{H}$ - $^{13}\text{C}$  HSQC of compound 9

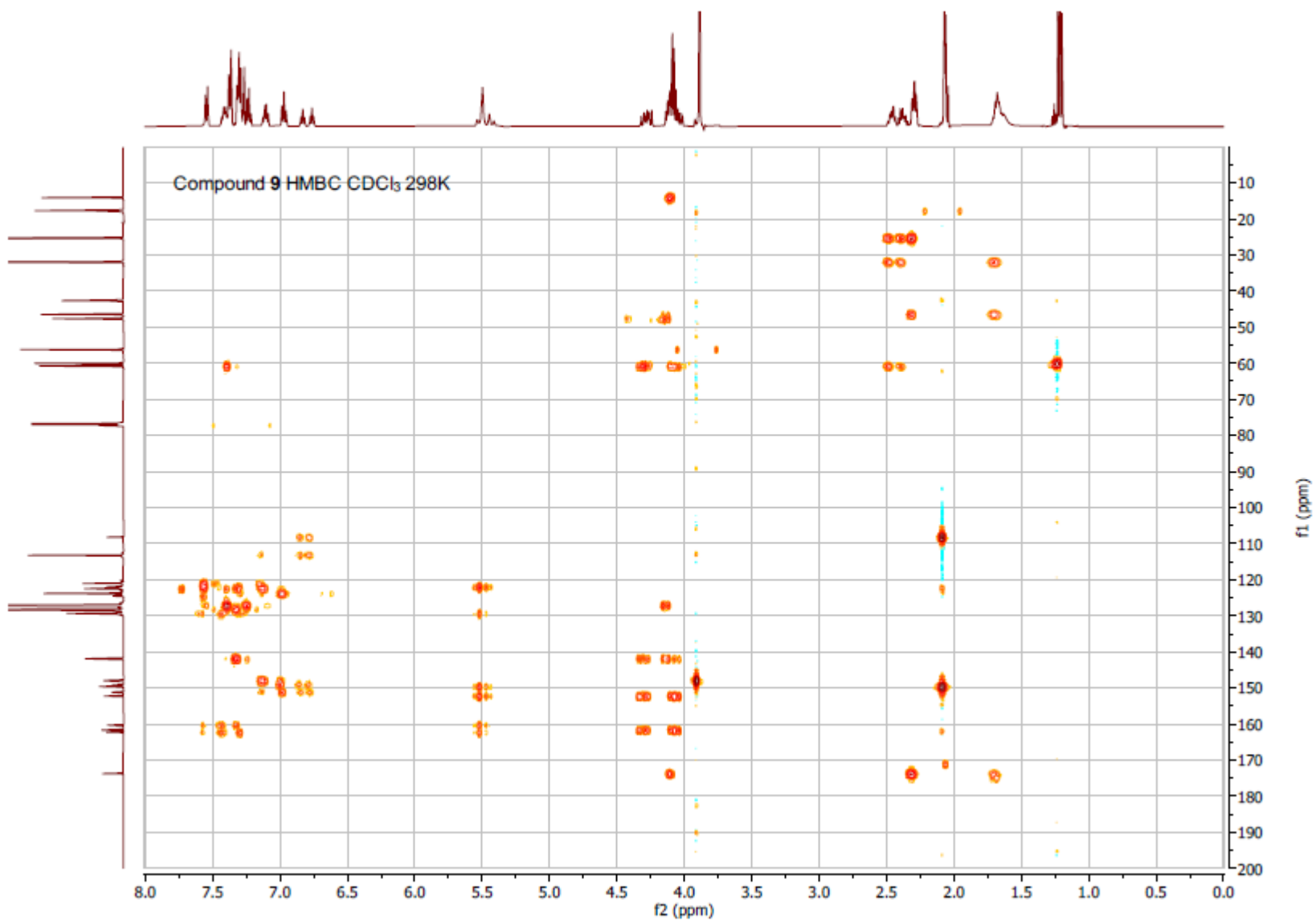
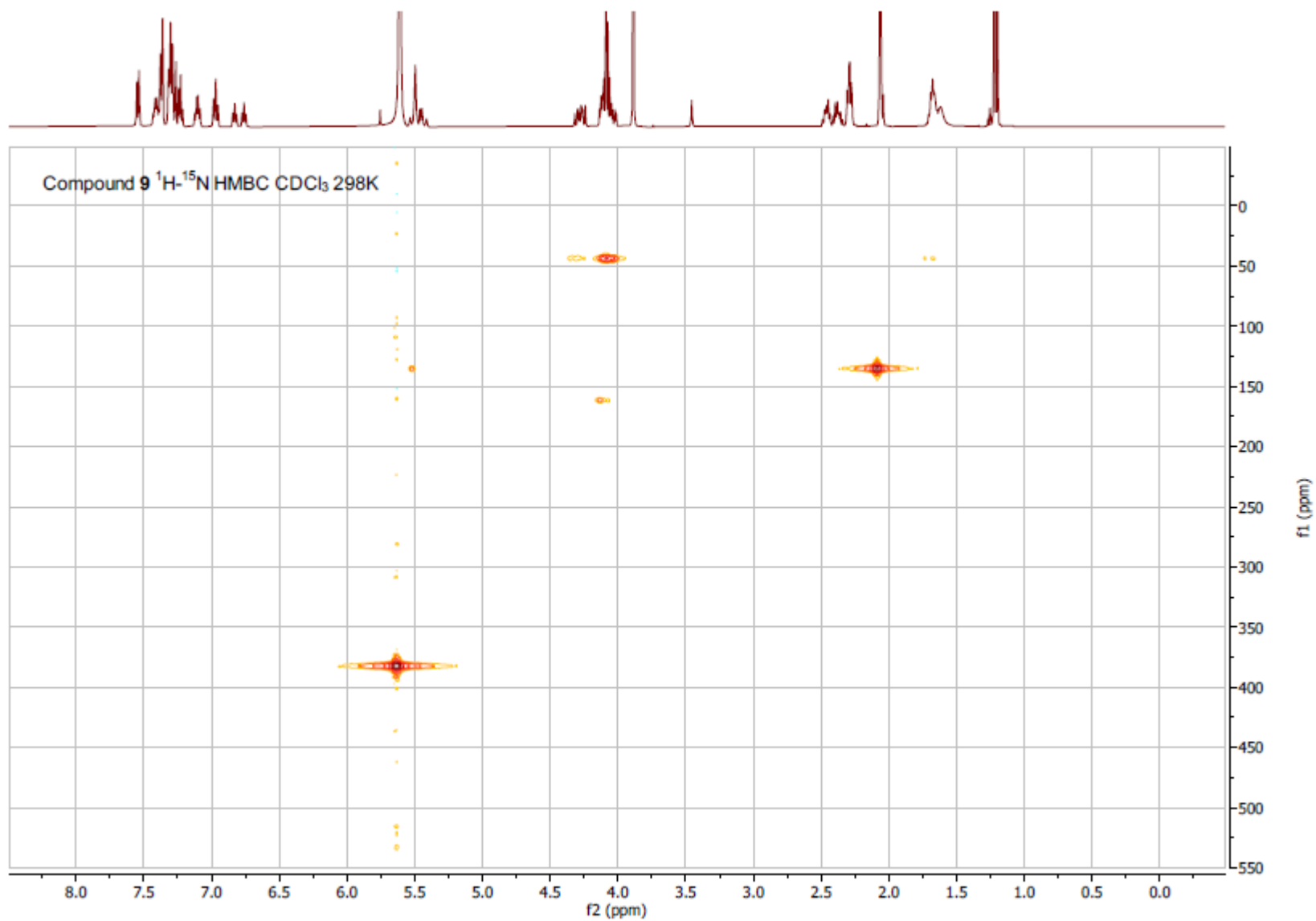


Figure S32. <sup>1</sup>H-<sup>13</sup>C HMBC of compound 9



**Figure S33.**  $^1\text{H}$ - $^{15}\text{N}$  HMBC of compound 9

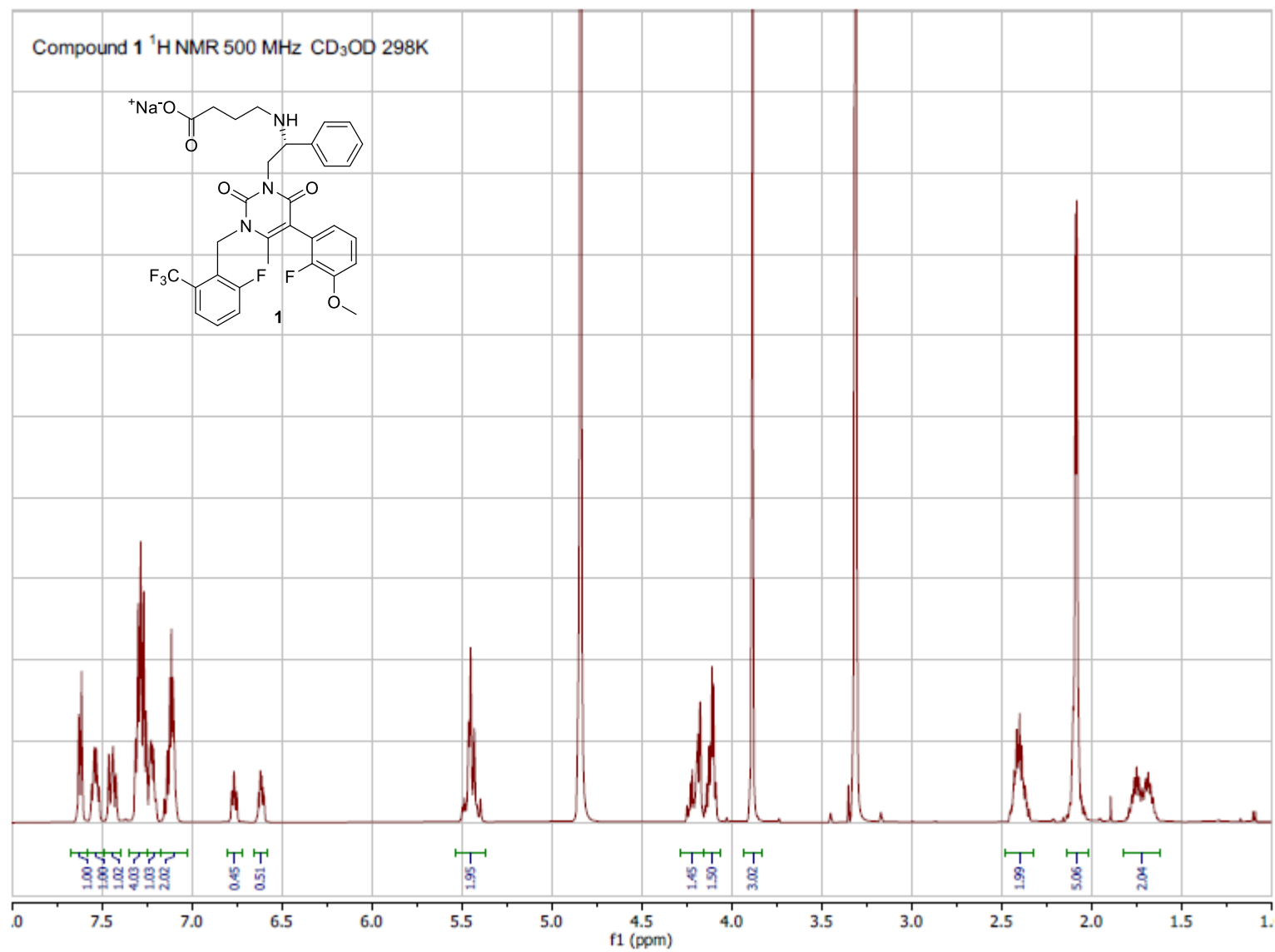


Figure S34.  $^1\text{H}$  NMR of compound 1

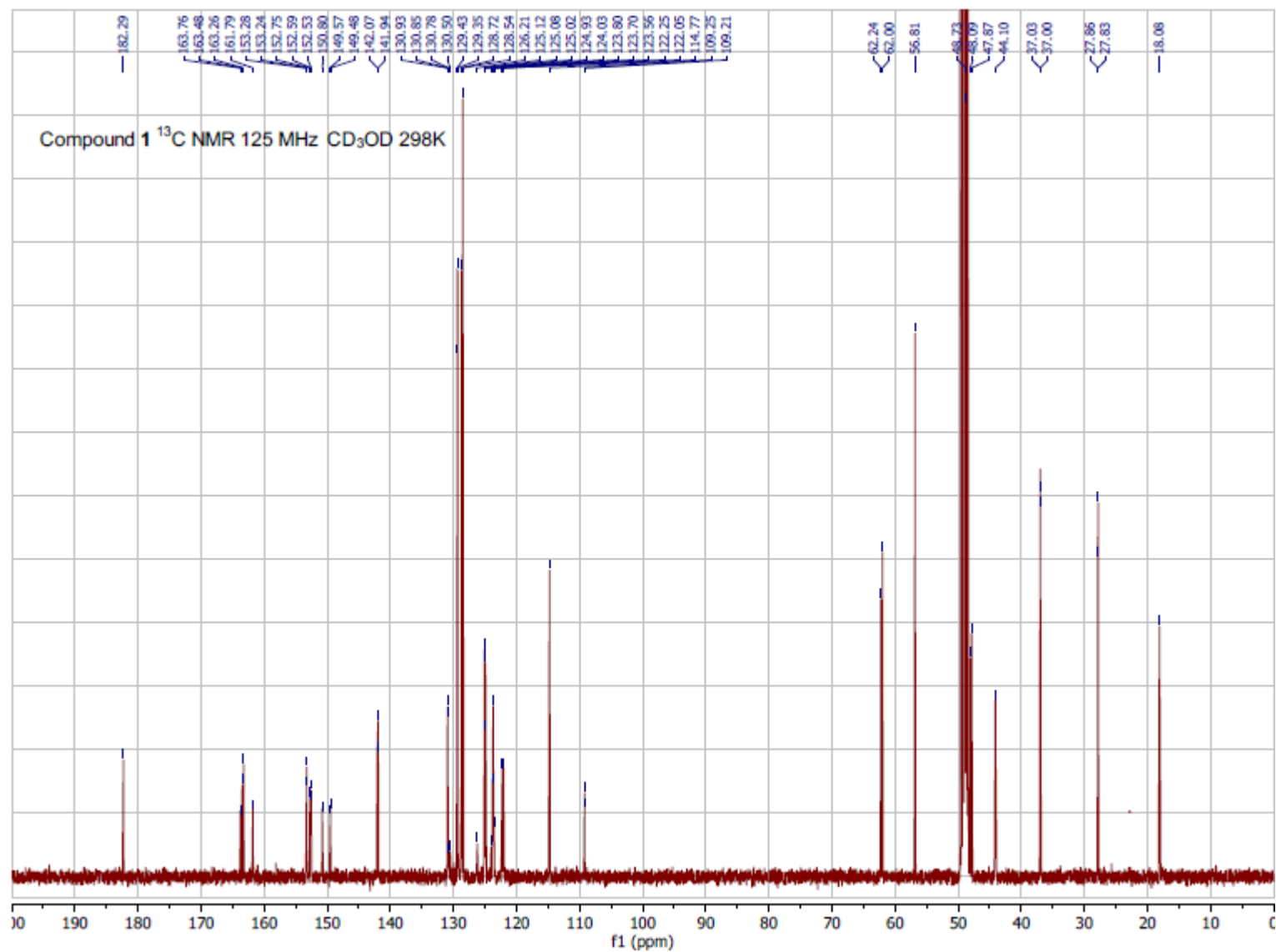


Figure S35.  $^{13}\text{C}$  NMR of compound **1**

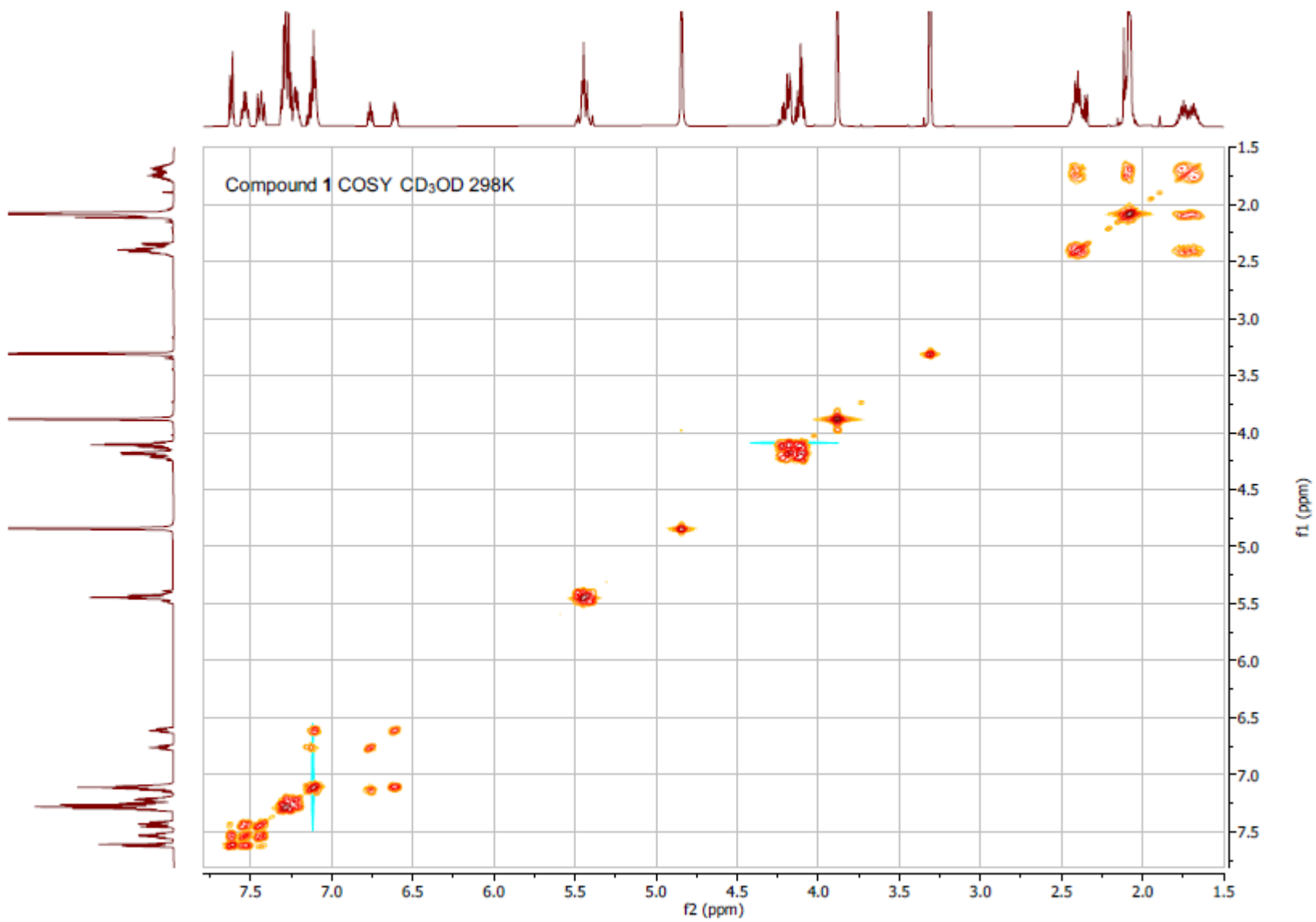
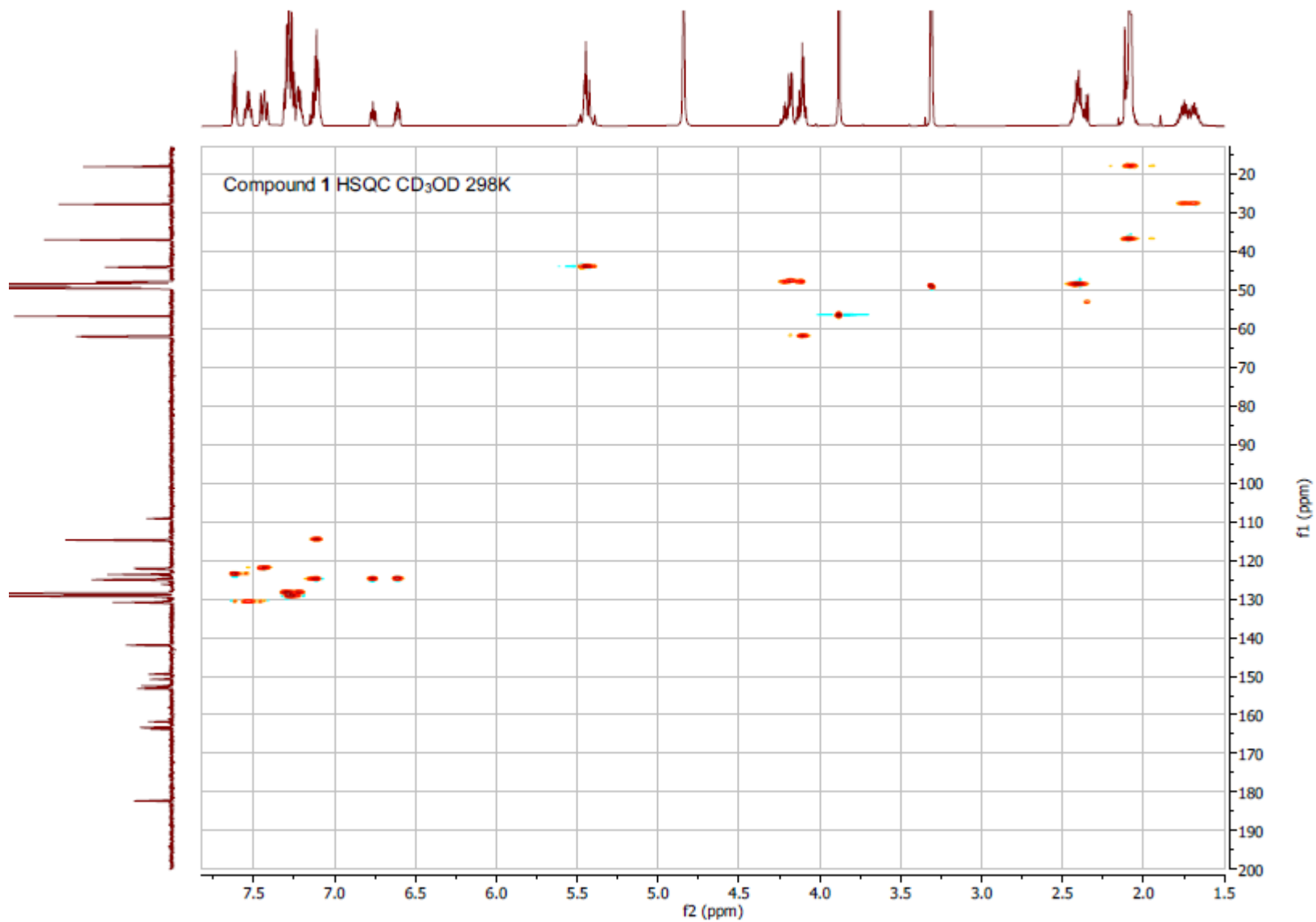
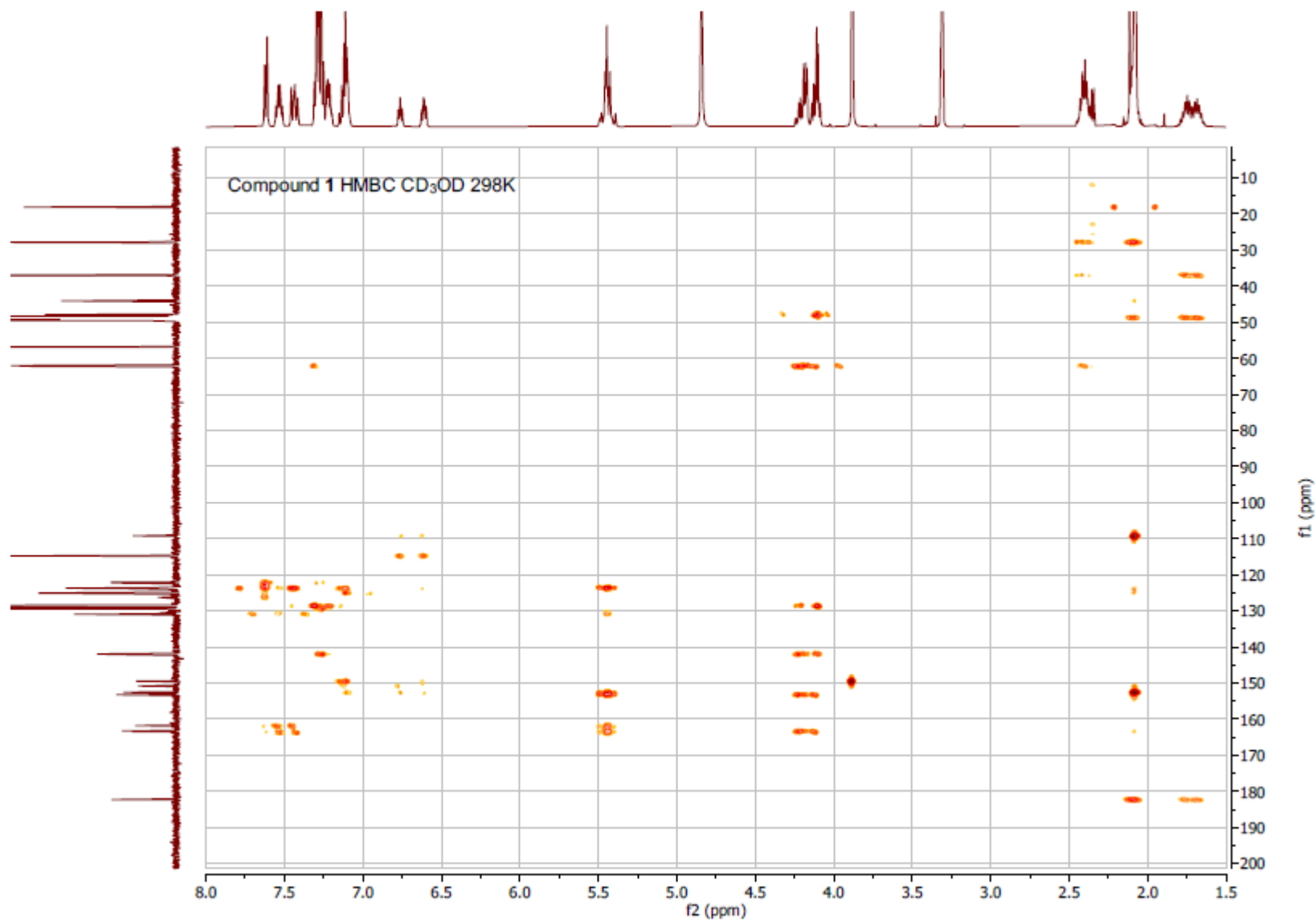


Figure S36. COSY of compound 1



**Figure S37.**  $^1\text{H}$ - $^{13}\text{C}$  HSQC of compound 1



**Figure S38.** <sup>1</sup>H-<sup>13</sup>C HMBC of compound 1



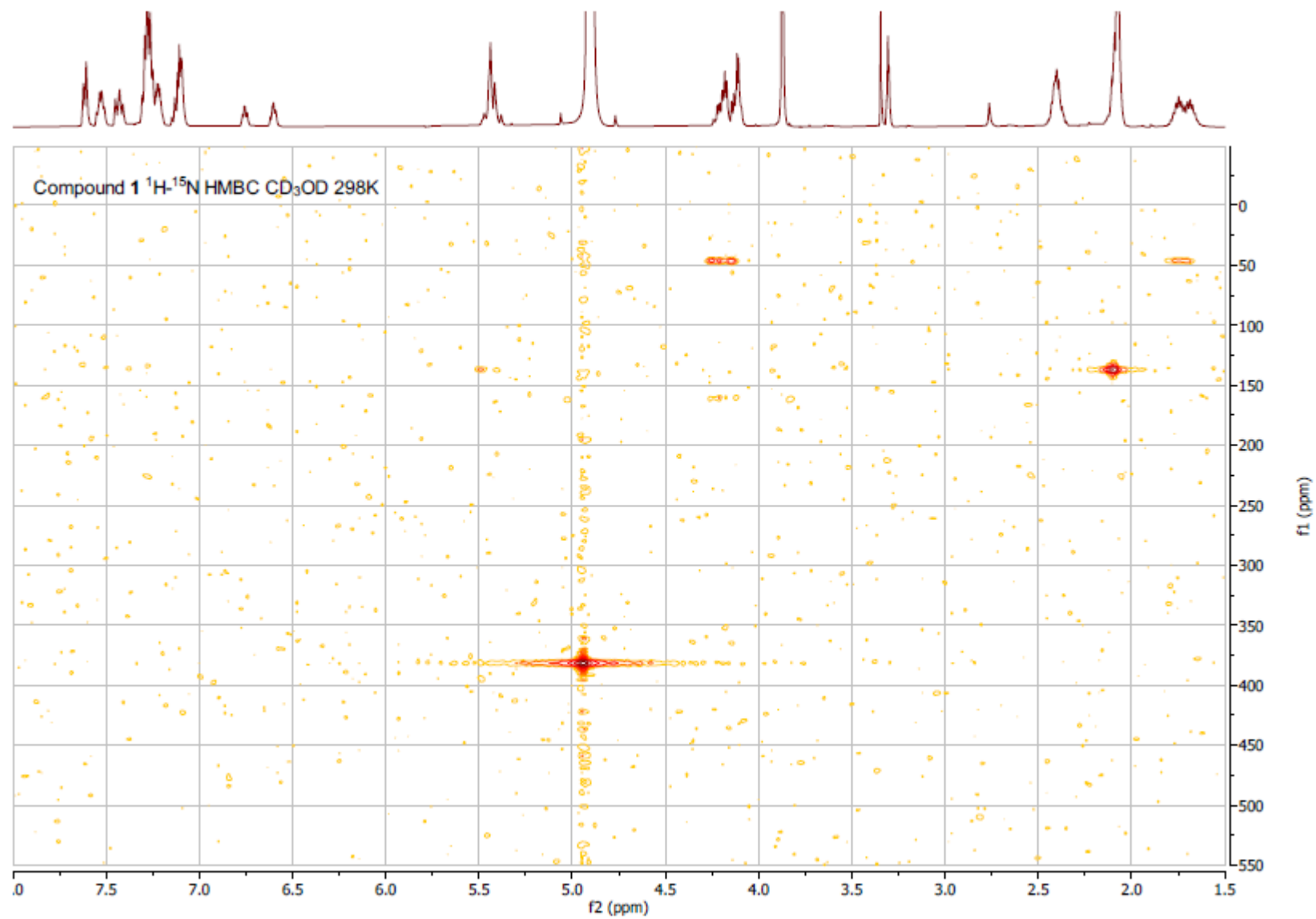


Figure S39.  $^1\text{H}$ - $^{15}\text{N}$  HMBC of compound 1

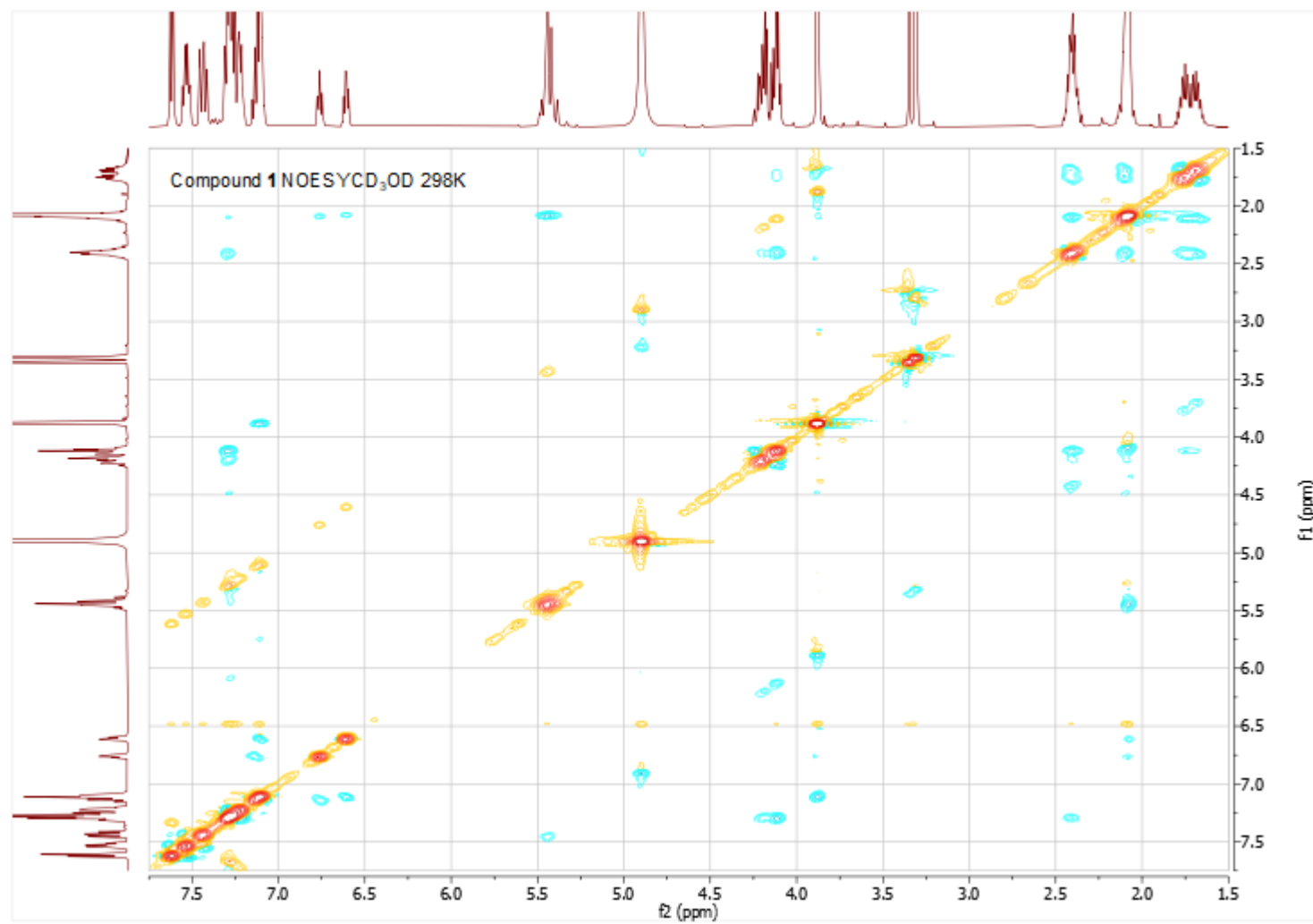
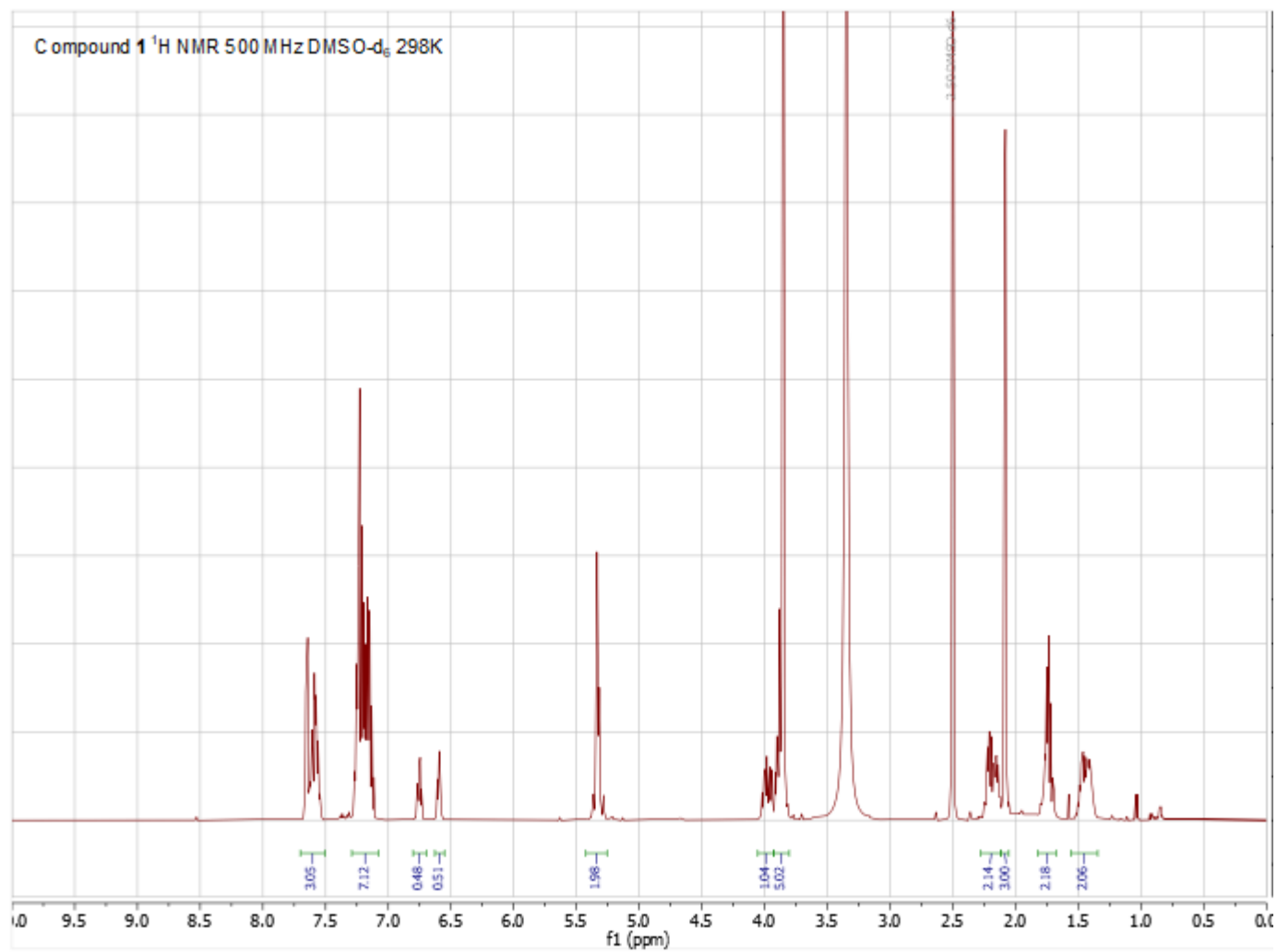
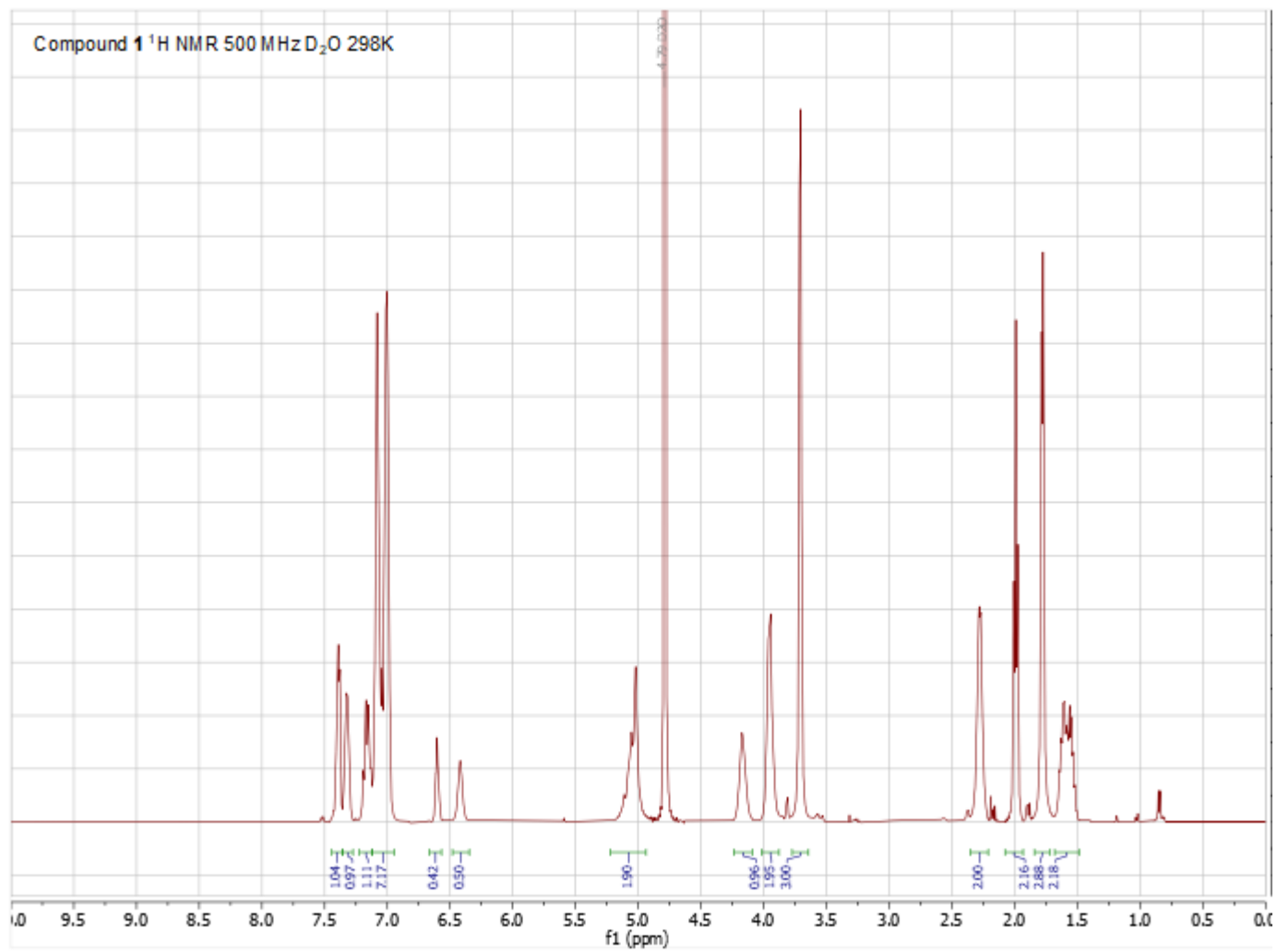


Figure S40. NOESY of compound 1



**Figure S41.**  $^1\text{H}$  NMR of compound **1** in DMSO- $\text{d}_6$



**Figure S42.**  $^1\text{H}$  NMR of compound **1** in  $\text{D}_2\text{O}$

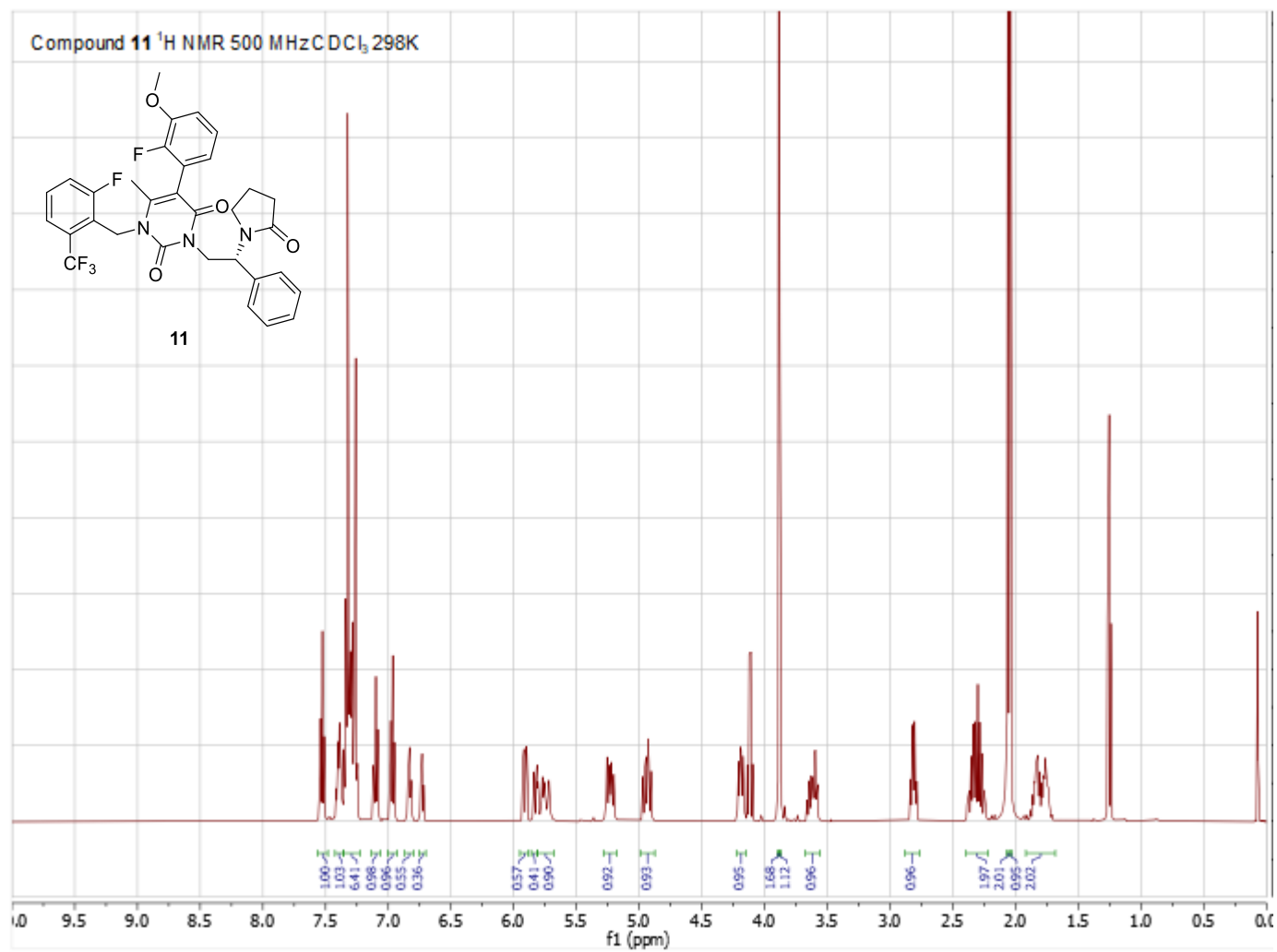


Figure S43.  $^1\text{H}$  NMR of compound **11**

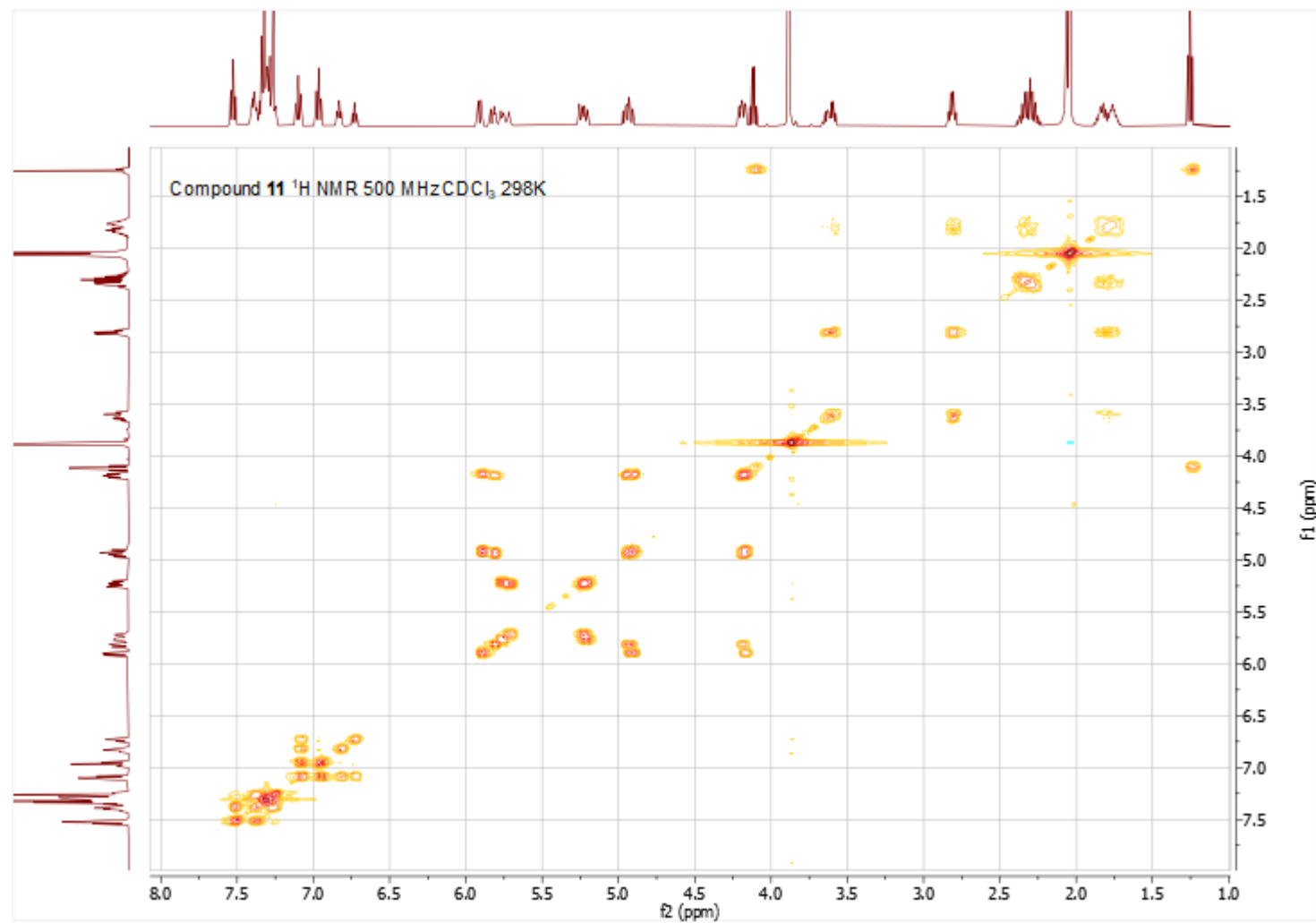


Figure S44. COSY of compound **11**

Conformers	Water $\Delta E$ (kcal/mol)	Water (%)	Methanol $\Delta E$ (kcal/mol)	Methanol (%)
<b>1A</b>	4.65	0.0	4.68	0.0
<b>1C</b>	0.84	18.4	0.73	21.2
<b>1D</b>	4.74	0.0	4.72	0.0
<b>1E</b>	7.88	0.0	n.c.	n.c.
<b>1H</b>	2.54	1.0	2.52	1.0
<b>1I</b>	2.66	0.9	2.64	0.8
<b>1J</b>	5.68	0.0	n.c.	n.c.
<b>1K</b>	5.42	0.0	n.c.	n.c.
<b>1L</b>	4.61	0.0	4.58	0.0
<b>1M</b>	0.00	75.6	0.00	73.0
<b>1O</b>	4.22	0.1	4.20	0.1
<b>1Q</b>	4.45	0.0	4.43	0.0
<b>1S</b>	1.93	2.9	1.92	2.9
<b>1T</b>	4.30	0.1	4.28	0.1
<b>1U</b>	4.59	0.0	4.58	0.0
<b>1V</b>	4.27	0.1	4.32	0.0
<b>1W</b>	2.75	0.7	2.74	0.7

<sup>1</sup>n.c. = not calculated.

**Table S1.** Relative energies and equilibrium percentages of the optimized conformations endowed with  $\Delta E < 5$  kcal/mol in the gas phase, in water and methanol solvent models.

Internuclear H-21/H-15 distance estimated by 2D NOESY				Internuclear distances of each H-15 proton from H-21 estimated by conformational analyses <sup>3</sup>
Atropisomer	H-21/H-15 cross peak intensity <sup>1</sup>	H-21/H-20 cross peak intensity	H-21/H15 distance <sup>2</sup>	
1-aR	-174489.7	-2699647.4	3.9 Å	3.89 Å - 4.90 Å - 5.30 Å (Average value = 4.70 Å)
1-aS	-161152.2	-2364674.9	3.9 Å	3.95 Å - 5.33 Å - 4.91 Å (Average value = 4.73 Å)

<sup>1</sup> One-third of the intensity of the cross peak; <sup>2</sup> The following general formula for quantitative distance information by measurement of the cross-peak intensities, within the initial rate approximation, was used:  $r_{H-21/H-20}/r_{H-21/H-15} = (a_{H-21/H-15}/a_{H-21/H-20})^{1/6}$ ;  $r$  = internuclear distance,  $a$  = intensity (volume). The internuclear distance between the aromatic protons H-21 and H-20 was fixed to 2.47 Å as reported in *Journal of Molecular Liquids* **2022**, 367,120481. <sup>3</sup> see experimental section of the manuscript.

**Table S2.** Internuclear H-15/H-21 distance estimated by 2D NOESY experiment.