

Electronic Supplementary Information

Synthesis and biological evaluation of 4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxamides and their zinc(II) complexes as candidate antidiabetic agents

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A general procedure for synthesizing 1-arylmethyl-4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxamides (**5a–e**)

Under argon atmosphere, to a solution of benzylamine (1.00 ml, 9.14 mmol) in dry ethanol (3 ml) was added slowly acrylamide (0.85 g, 11.9 mmol) at 0 °C, and then the mixture was stirred at room temperature for 1–7 days. After evaporation of the solvent, the obtained solid was purified by column chromatography on silica gel (46-50 mm) with chloroform/methanol mixed solvent system as an eluent to afford the product. All the products are known, and therefore the identification of these compounds were carried out only by means of ¹H NMR without further purification.

3-(Benzylamino)propanamide (**5a**)¹ [CAS ID: 16490-80-5]

Yield 82%. ¹H NMR (400 MHz, CDCl₃) δ/ppm 7.46 (s, 1H), 7.34–7.22 (m, 6H), 6.23 (s, 1H), 3.77 (s, 2H), 2.88 (t, *J* = 6.0 Hz, 2H), 2.37 (t, *J* = 6.0 Hz, 2H).

3-[(4-Methylphenyl)methyl]amino]propanamide (**5b**) [CAS ID: 99981-59-6]

Yield 77%. ¹H NMR (400 MHz, CDCl₃) δ/ppm 7.61 (br. s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.32 (br. s, 1H), 3.76 (s, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.39 (t, *J* = 5.9 Hz, 2H), 2.34 (s, 3H).

3-[(4-Fluorophenyl)methyl]amino]propanamide (**5c**) [CAS ID: 1094453-44-7]

Yield 79%. ¹H NMR (400 MHz, CDCl₃) δ/ppm 7.38–7.19 (m, 3H), 7.02 (t, *J* = 8.6 Hz, 2H), 5.45 (br. s, 1H), 3.77 (s, 2H), 2.91 (t, *J* = 5.8 Hz, 2H), 2.41 (t, *J* = 5.8 Hz, 2H).

3-[(4-Chlorophenyl)methyl]amino]propanamide (**5d**) [CAS ID: 807277-73-2]

Yield 71%. ¹H NMR (400 MHz, CDCl₃) δ/ppm 7.33–7.11 (m, 5H), 5.34 (br. s, 1H), 3.78 (s, 2H), 2.90 (t, *J* = 5.9 Hz, 2H), 2.41 (t, *J* = 5.9 Hz, 2H).

[3,5-bis(trifluoromethyl)phenylmethyl]amino]propanamide (**5e**) [CAS ID: 1527625-53-1]

Yield 86%. ¹H NMR (400 MHz, CDCl₃) δ/ppm 7.80 (s, 2H), 7.78 (s, 1H), 6.49 (br. s, 1H), 5.59 (br. s, 1H), 3.94 (s, 2H), 2.93 (t, *J* = 5.9 Hz, 2H), 2.45 (t, *J* = 5.9 Hz, 2H).

A general procedure for the reactions of **5a–e** with diethyl oxalate

Under argon atmosphere, to a mixture of **5** (5.74 mmol) and diethyl oxalate (0.85 ml, 6.27 mmol) was added ethanolic sodium ethoxide, prepared by dissolving sodium (203 mg, 8.84 mmol) in dry ethanol (4 mL), and the mixture was refluxed for 1.5 hours. After cooling to room temperature, the resulting colorless precipitate was collected and then dissolved in water. The aqueous solution was acidified with 10% HCl to pH = 3. The resulting precipitate was collected and dried *in vacuo* to afford the mixture of **1** and **6** as colorless solids. For the reaction of **5a**, the yields of **1a** and **6a** were determined by means of ¹H NMR. For **5b–e**, the formation of **6b–e**² was confirmed only by TLC analysis, and the resulting mixed products were purified by column chromatography on silica gel (46-50 mm, 50 g) with chloroform/methanol mixture (CHCl₃/MeOH = 30/1) as eluent to obtain **1b–e**.

Reference

1. A. Salaun, A. Favre, B. Le Grel, M. Potel and P. Le Grel, *J. Org. Chem.*, 2006, **71**, 150-158.
2. H. Kawarada, Y. Yoshikawa, H. Yasui, S. Kuwahara, Y. Habata and R. Saito, *Metallomics*, 2011, **3**, 675-679.

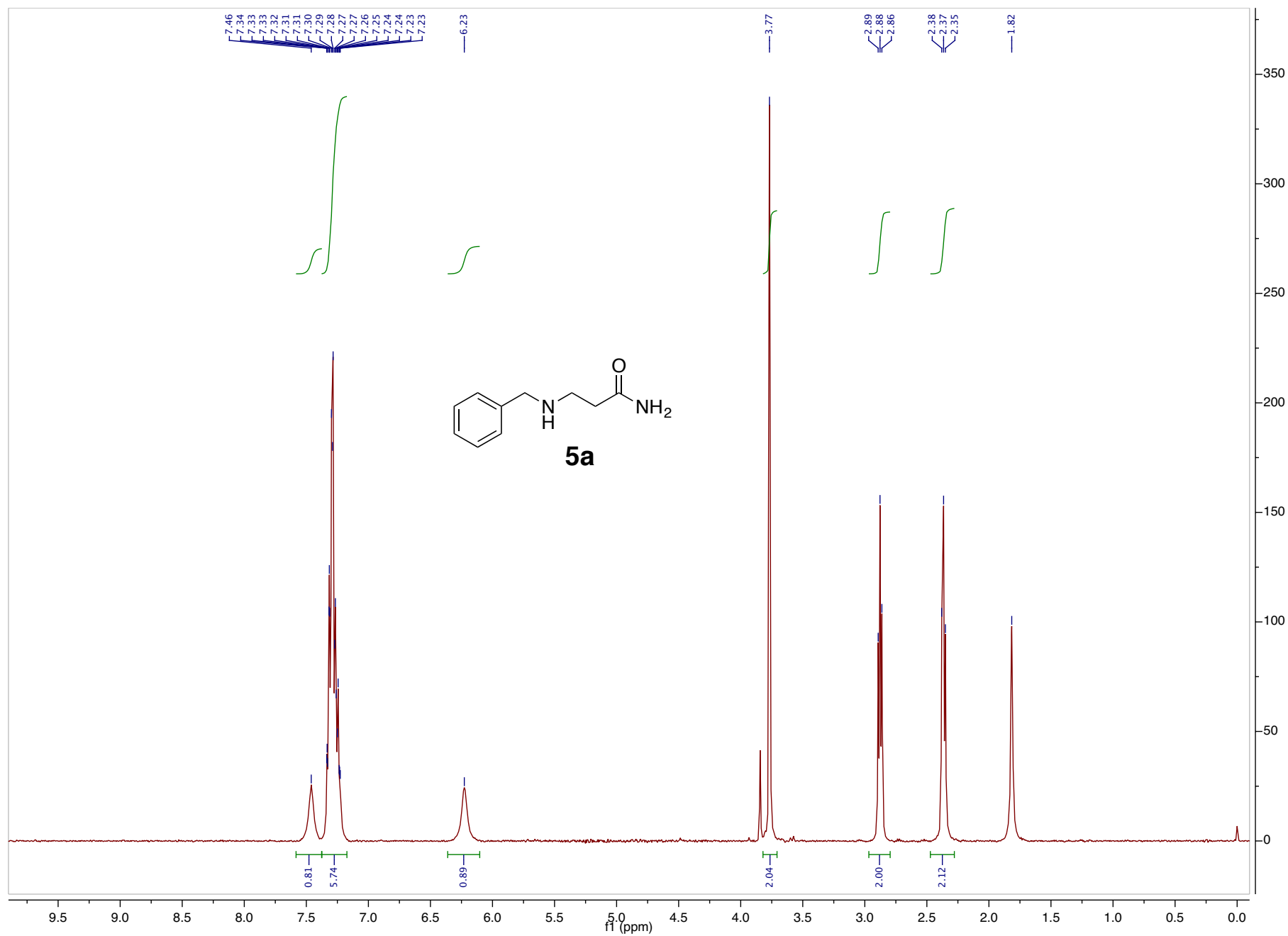


Fig. S1. ¹H NMR spectrum of **5a** (400 MHz, CDCl₃)

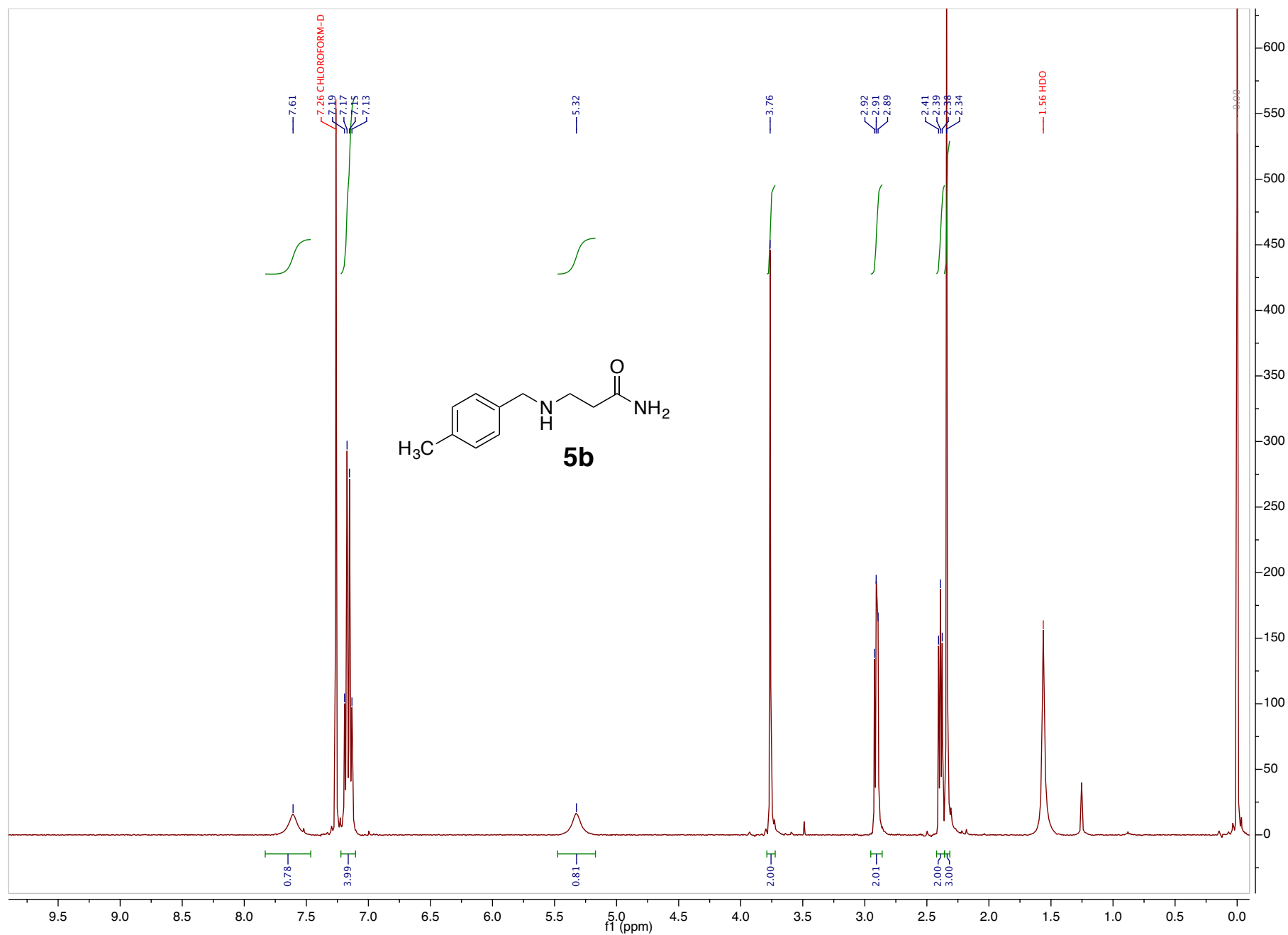


Fig. S2. ^1H NMR spectrum of **5b** (400 MHz, CDCl_3)

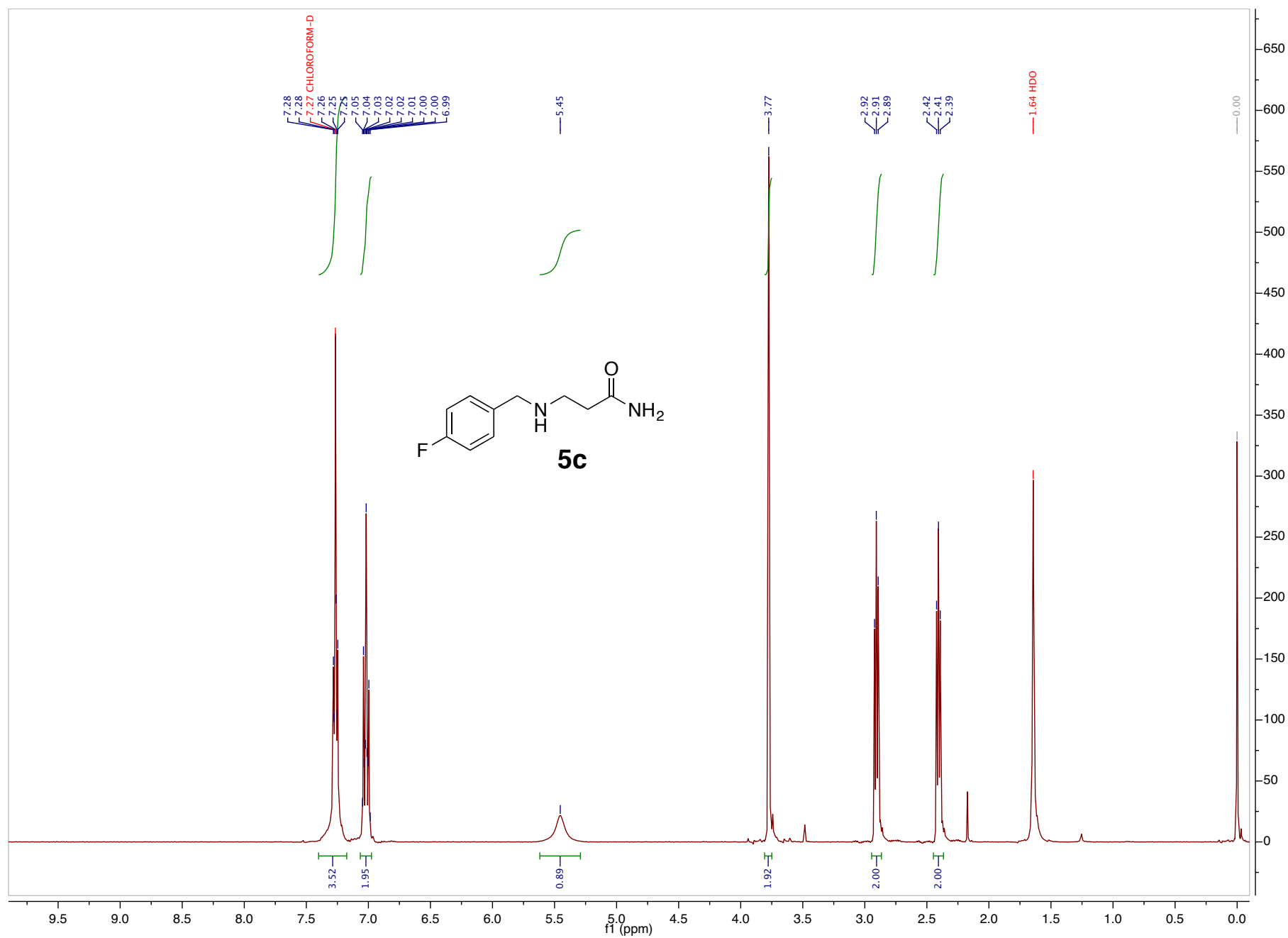


Fig. S3. ¹H NMR spectrum of **5c** (400 MHz, CDCl₃)

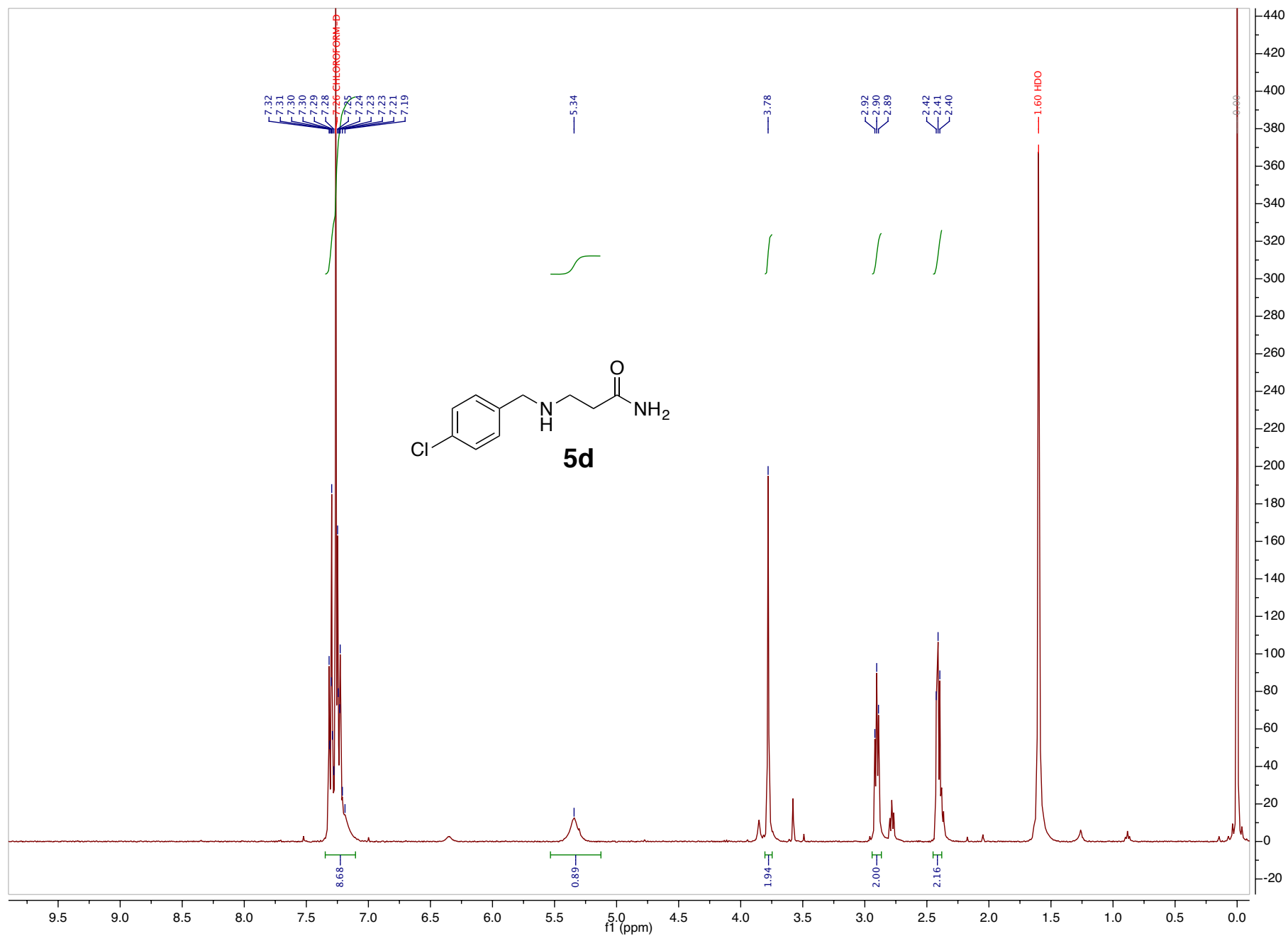


Fig. S4. ¹H NMR spectrum of **5d** (400 MHz, CDCl₃)

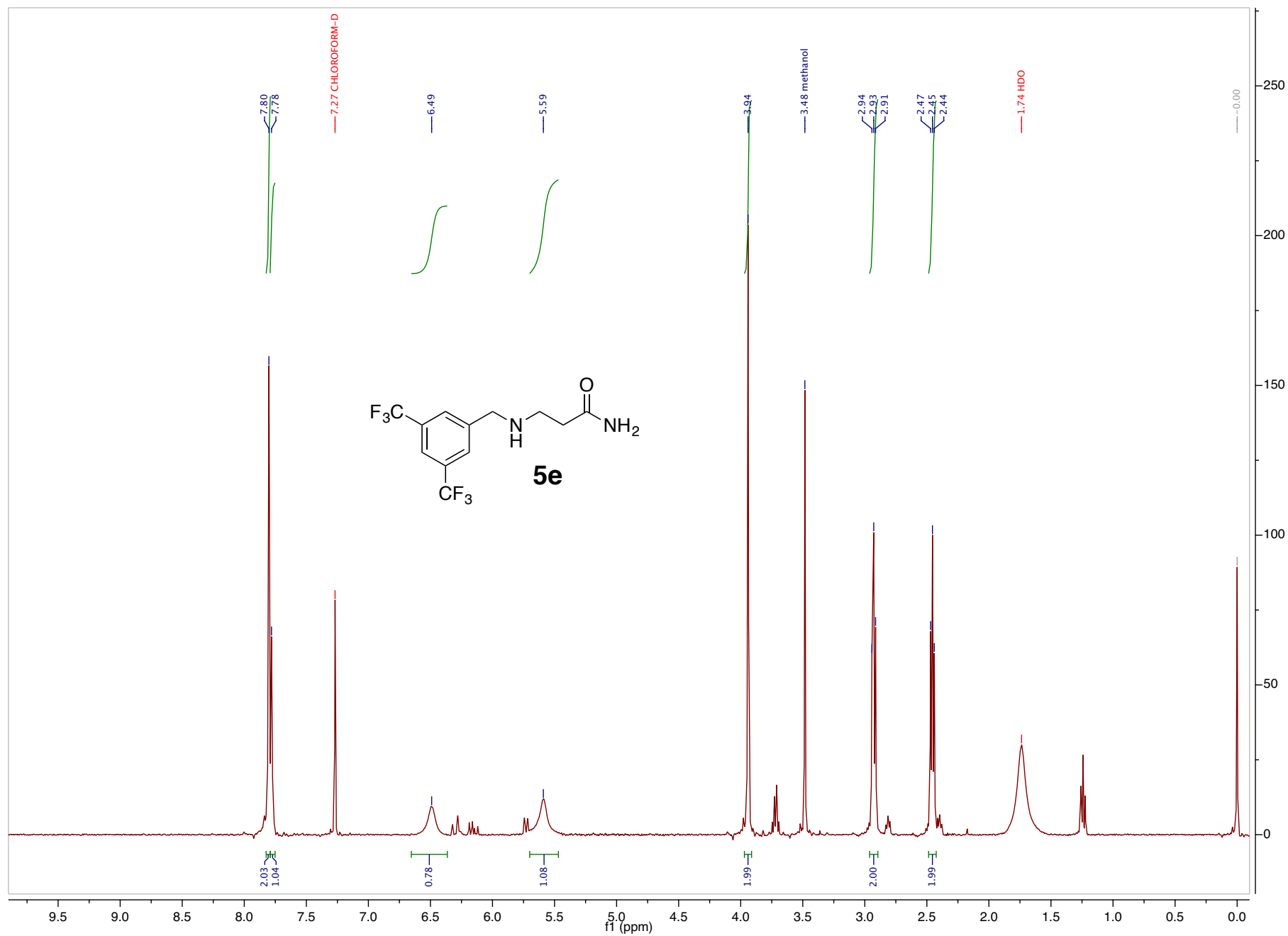


Fig. S5. ¹H NMR spectrum of **5e** (400 MHz, CDCl₃)

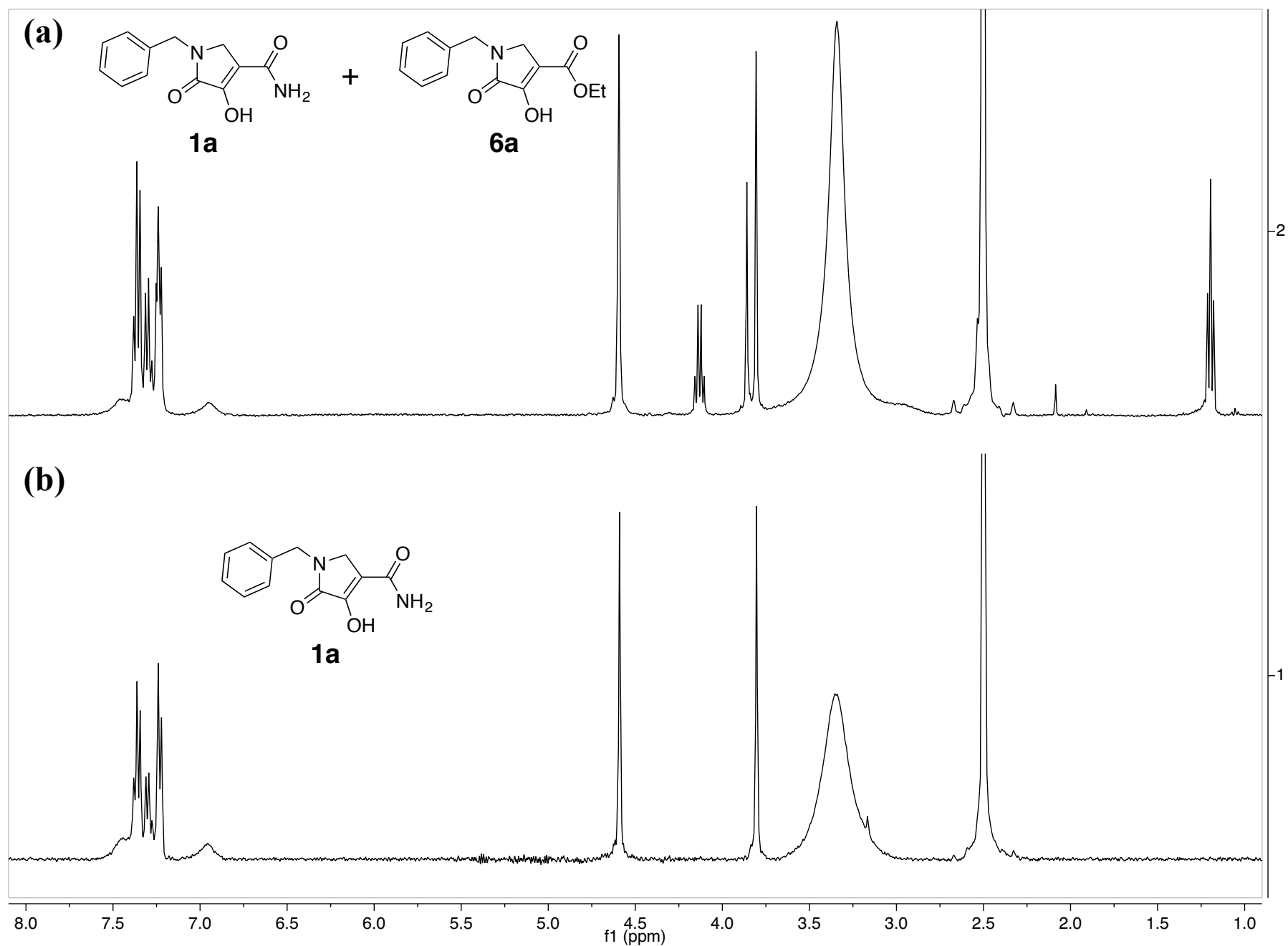


Fig. S6. ^1H NMR spectra of (a) the products obtained in the reaction of **5a** with diethyl oxalate and (b) **1a** (400 MHz, $\text{DMSO}-d_6$)

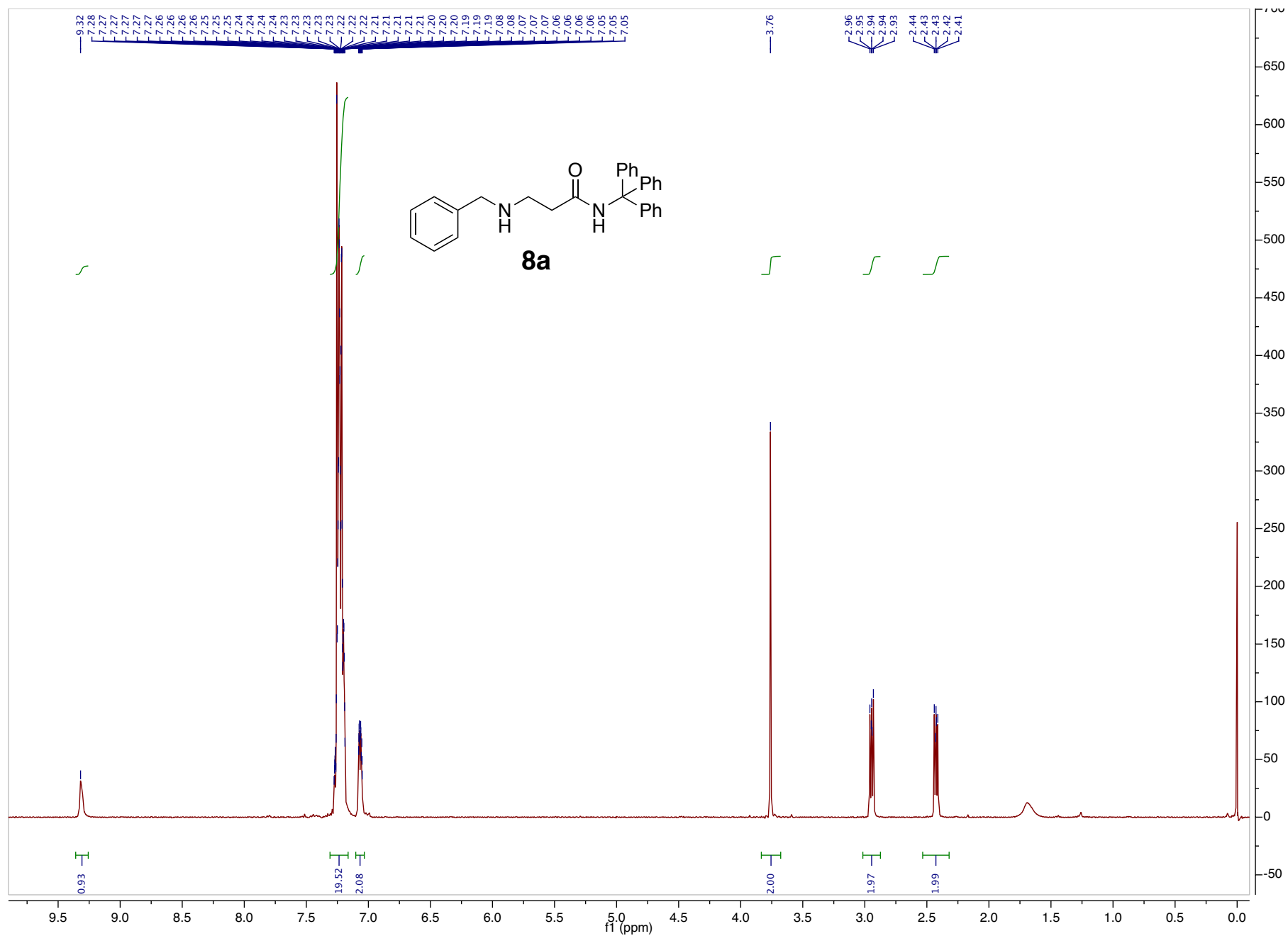


Fig. S7. ^1H NMR spectrum of **8a** (400 MHz, CDCl_3)

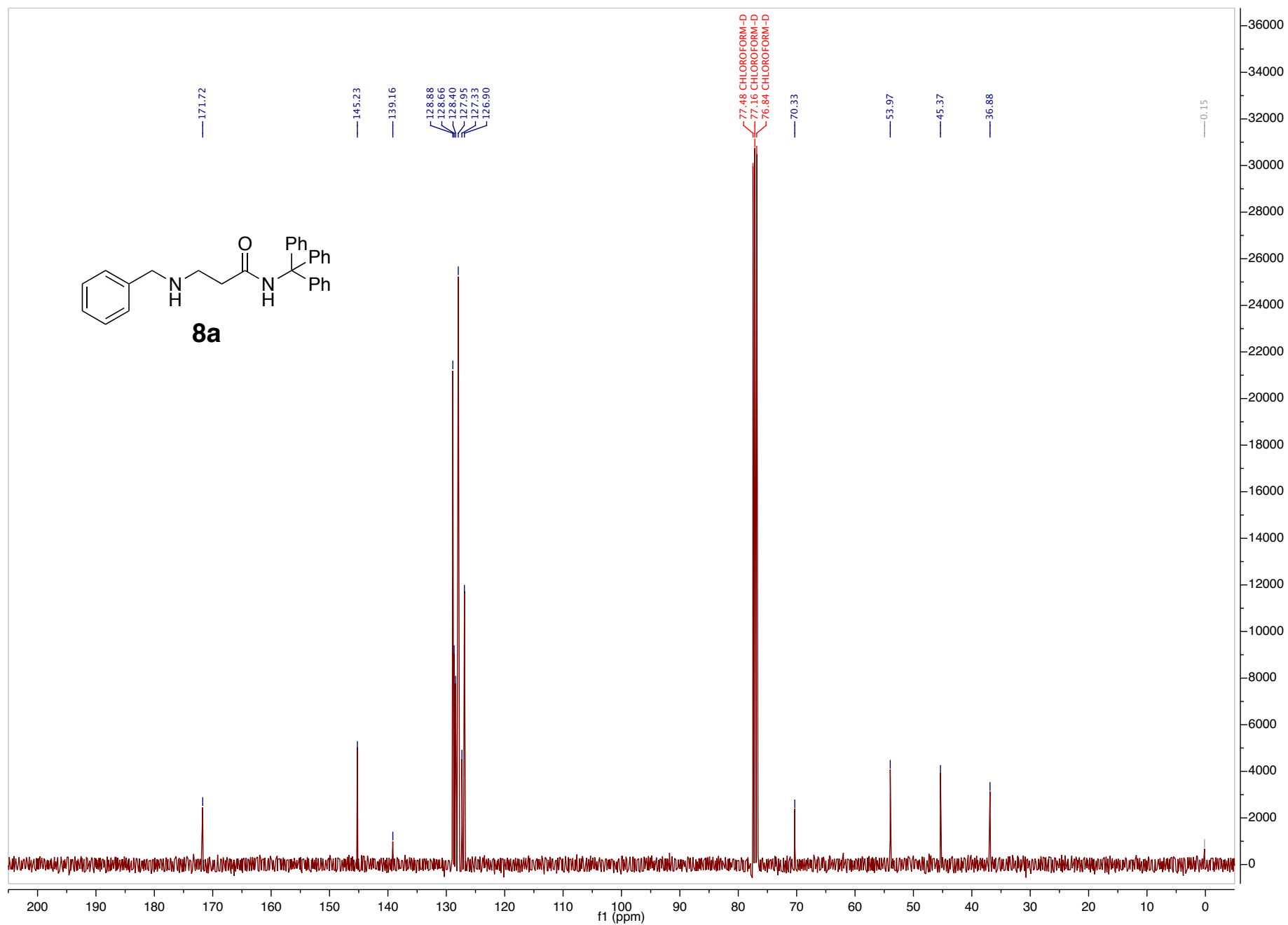


Fig. S8. ^{13}C NMR spectrum of **8a** (100 MHz, CDCl_3)

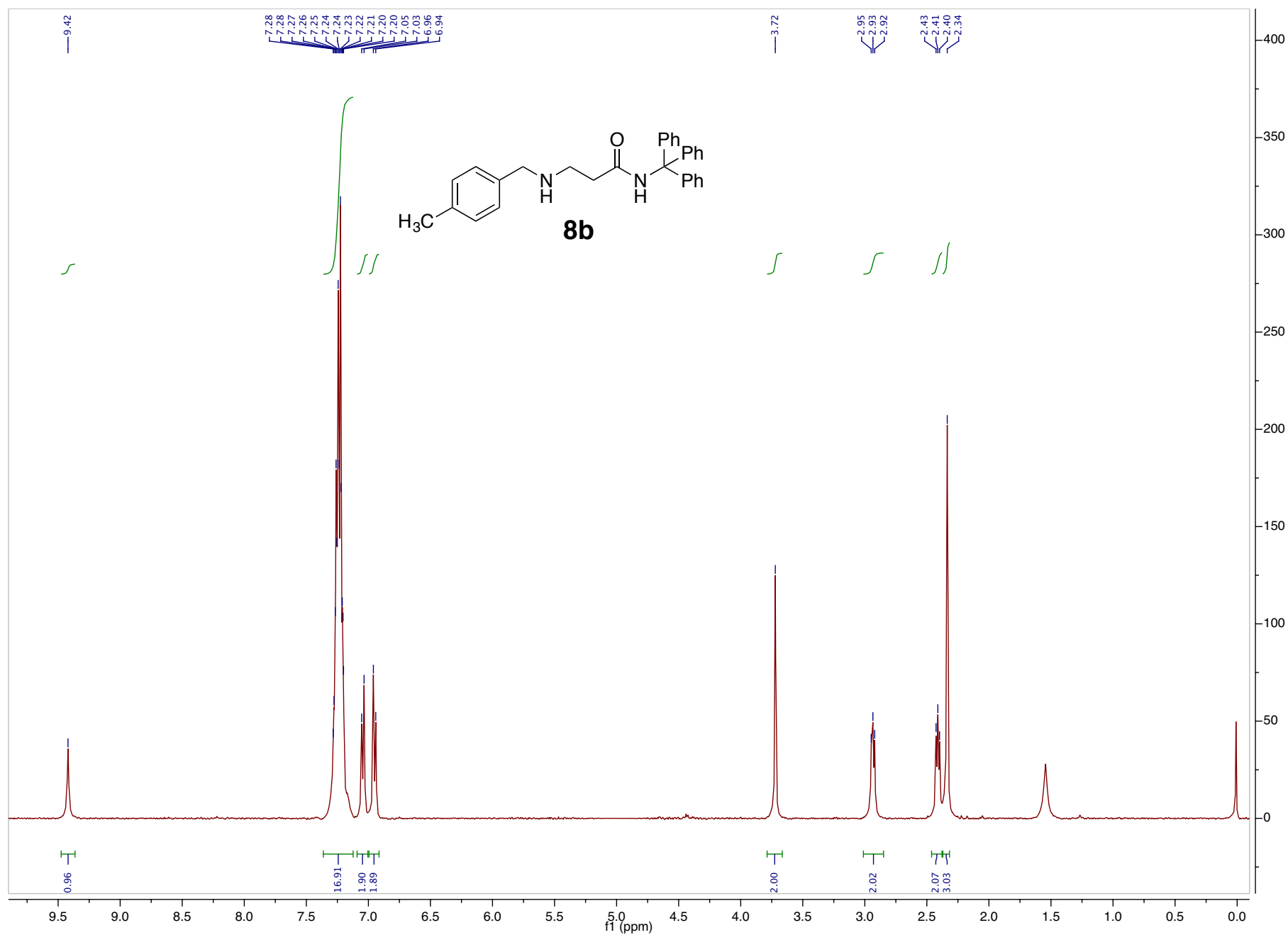


Fig. S9. ^1H NMR spectrum of **8b** (400 MHz, CDCl_3)

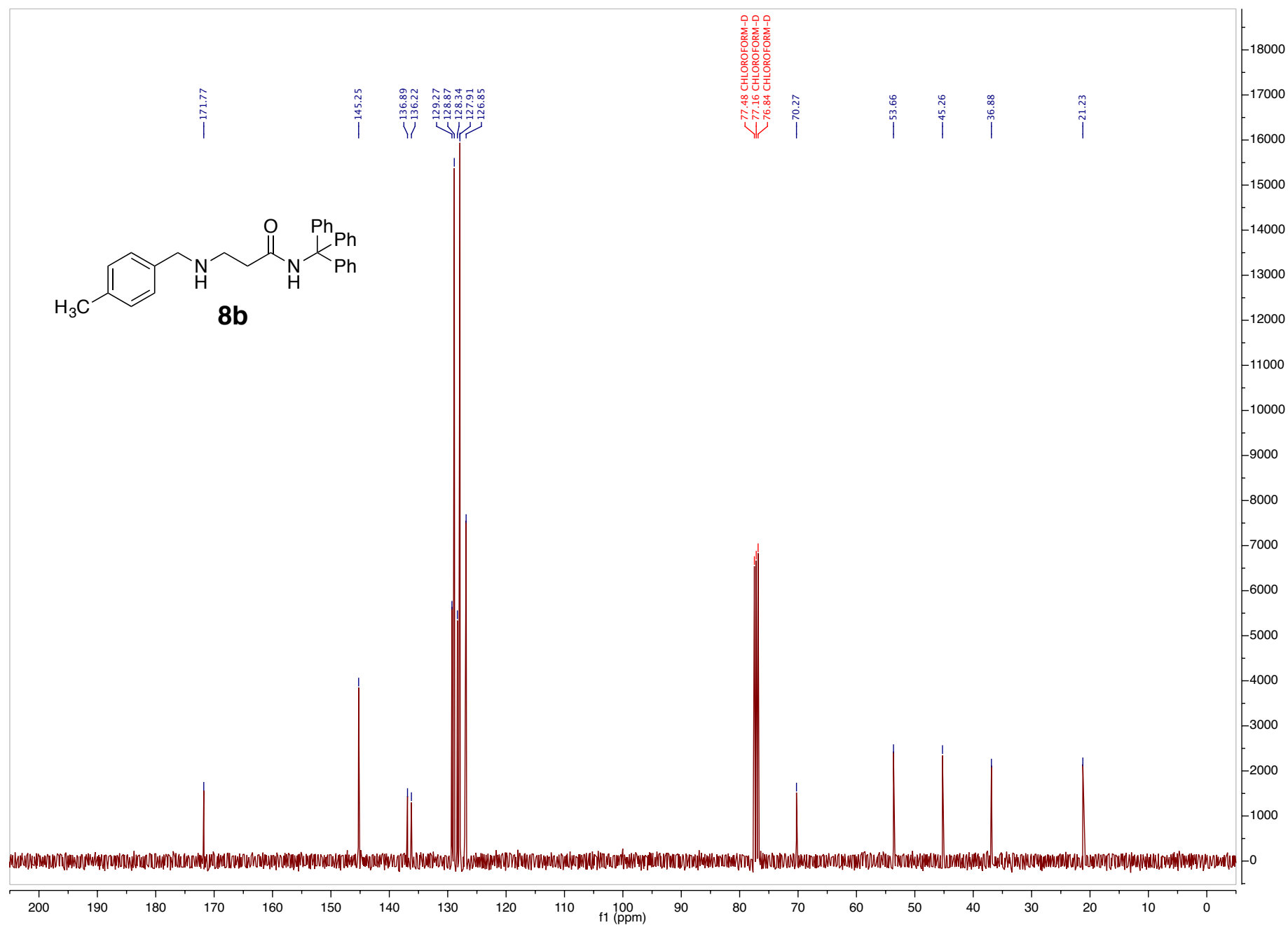


Fig. S10. ^{13}C NMR spectrum of **8b** (100 MHz, CDCl_3)

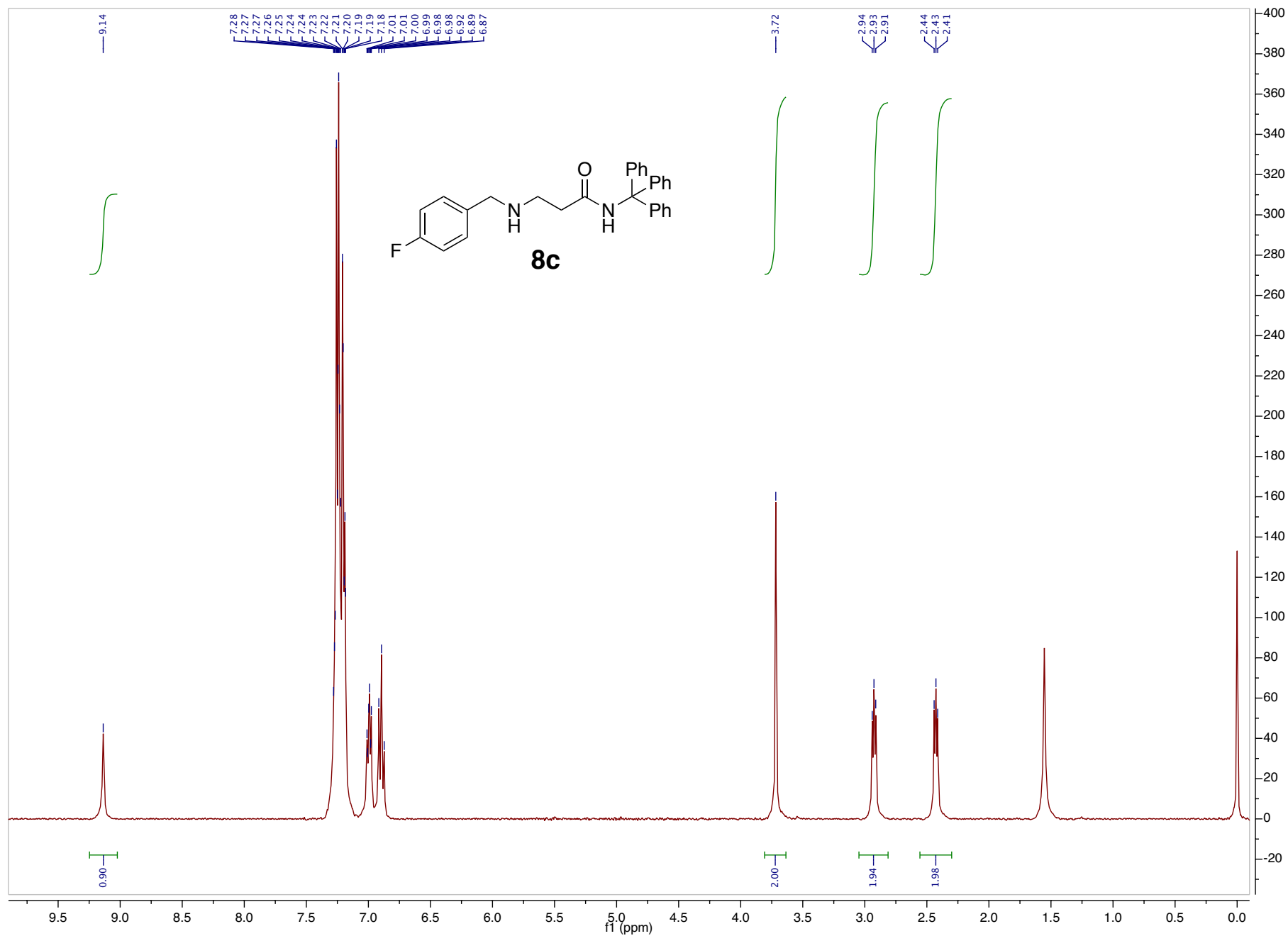


Fig. S11. ¹H NMR spectrum of **8c** (400 MHz, CDCl₃)

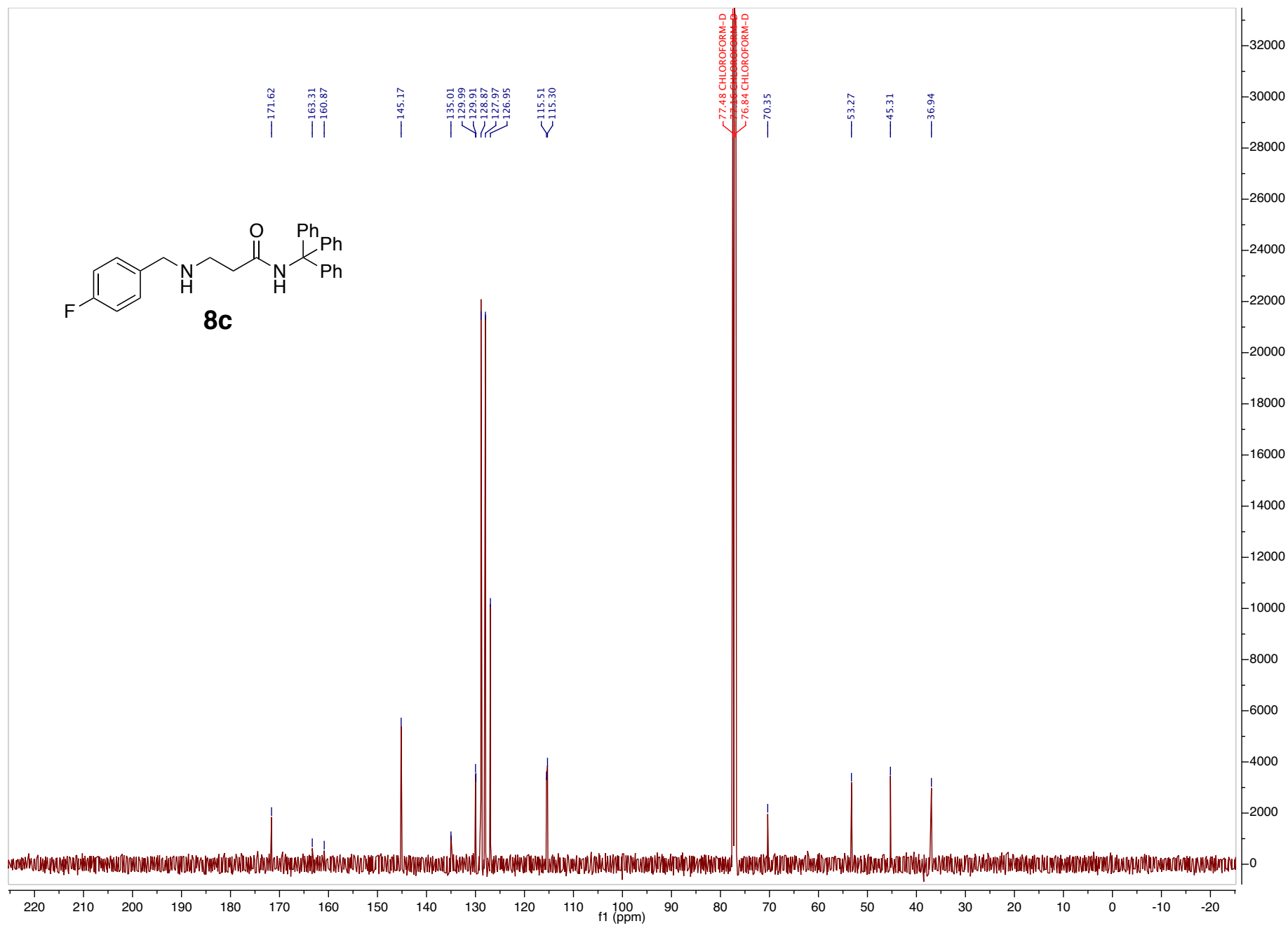


Fig. S12. ¹³C NMR spectrum of **8c** (100 MHz, CDCl₃)

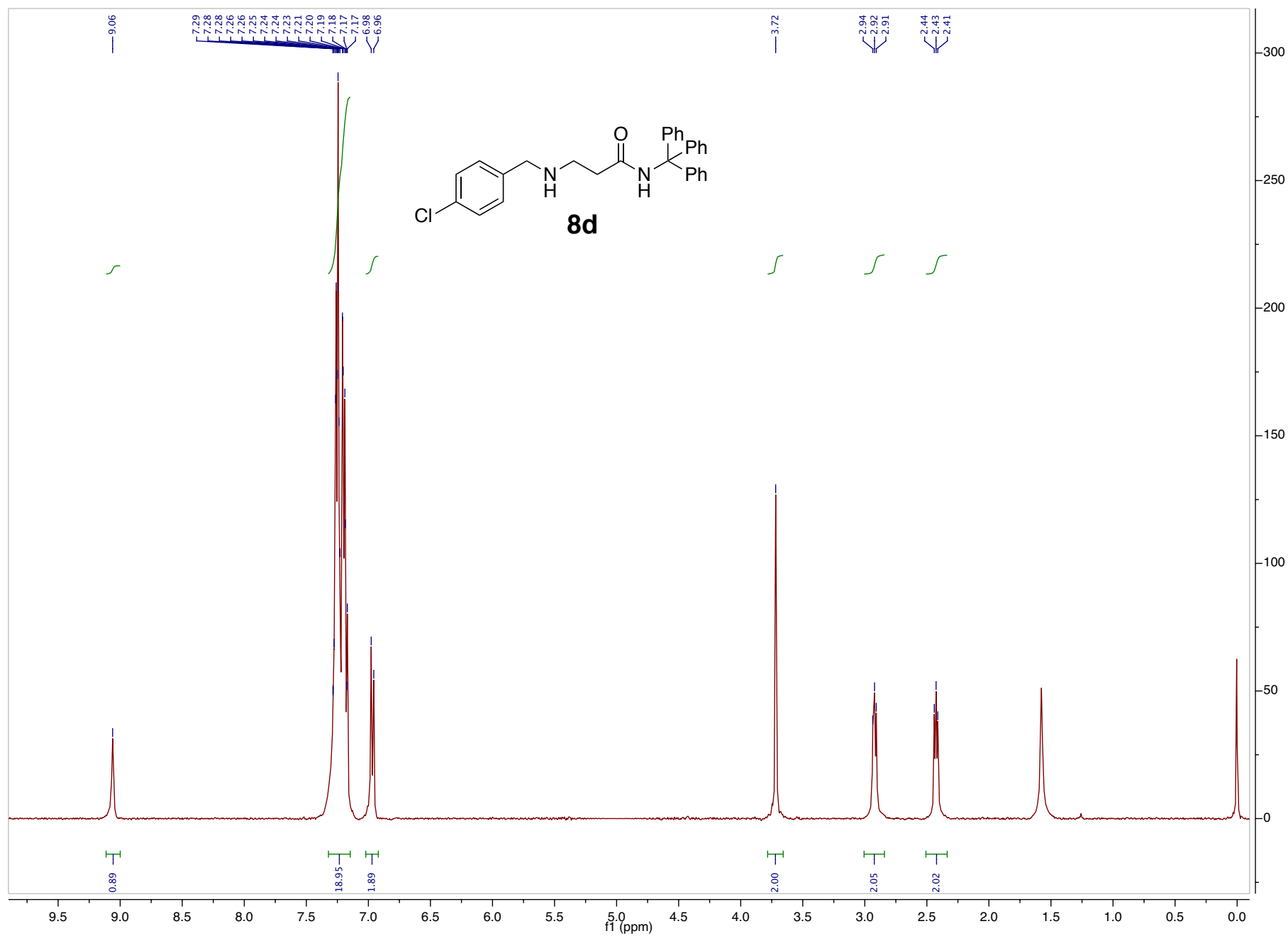


Fig. S13. ^1H NMR spectrum of **8d** (400 MHz, CDCl_3)

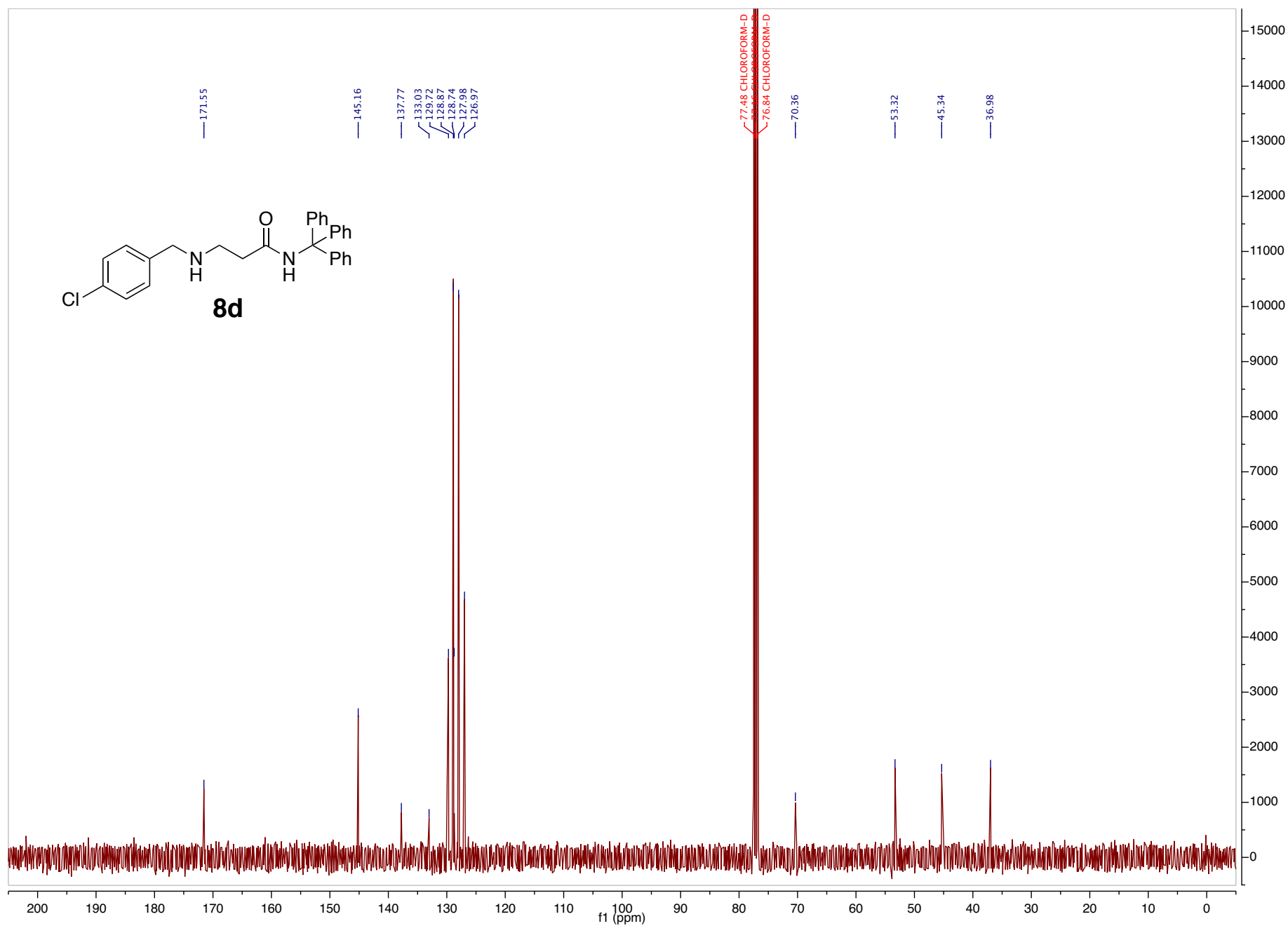


Fig. S14. ¹³C NMR spectrum of **8d** (100 MHz, CDCl₃)

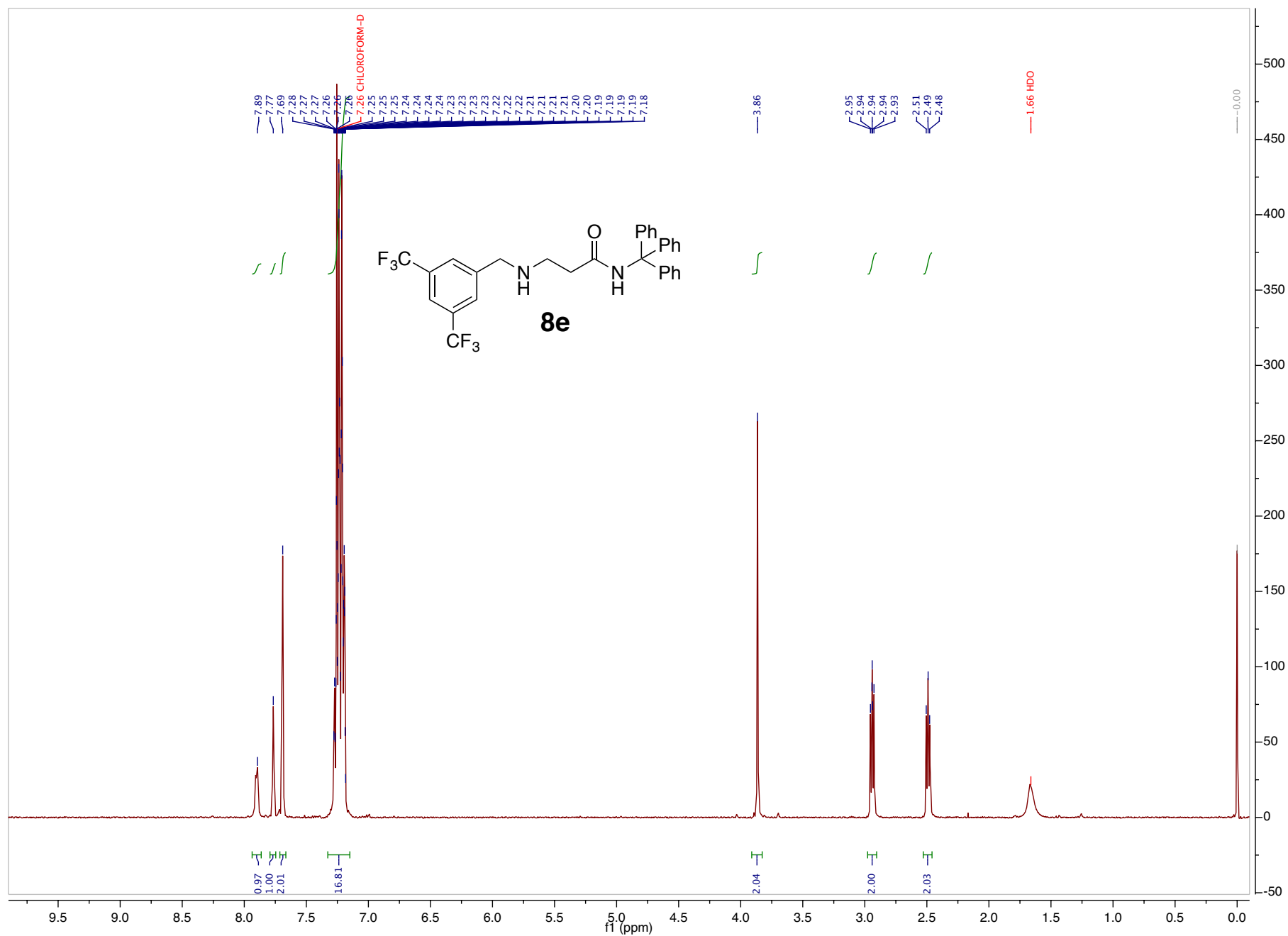


Fig. S15. ^1H NMR spectrum of **8e** (400 MHz, CDCl_3)

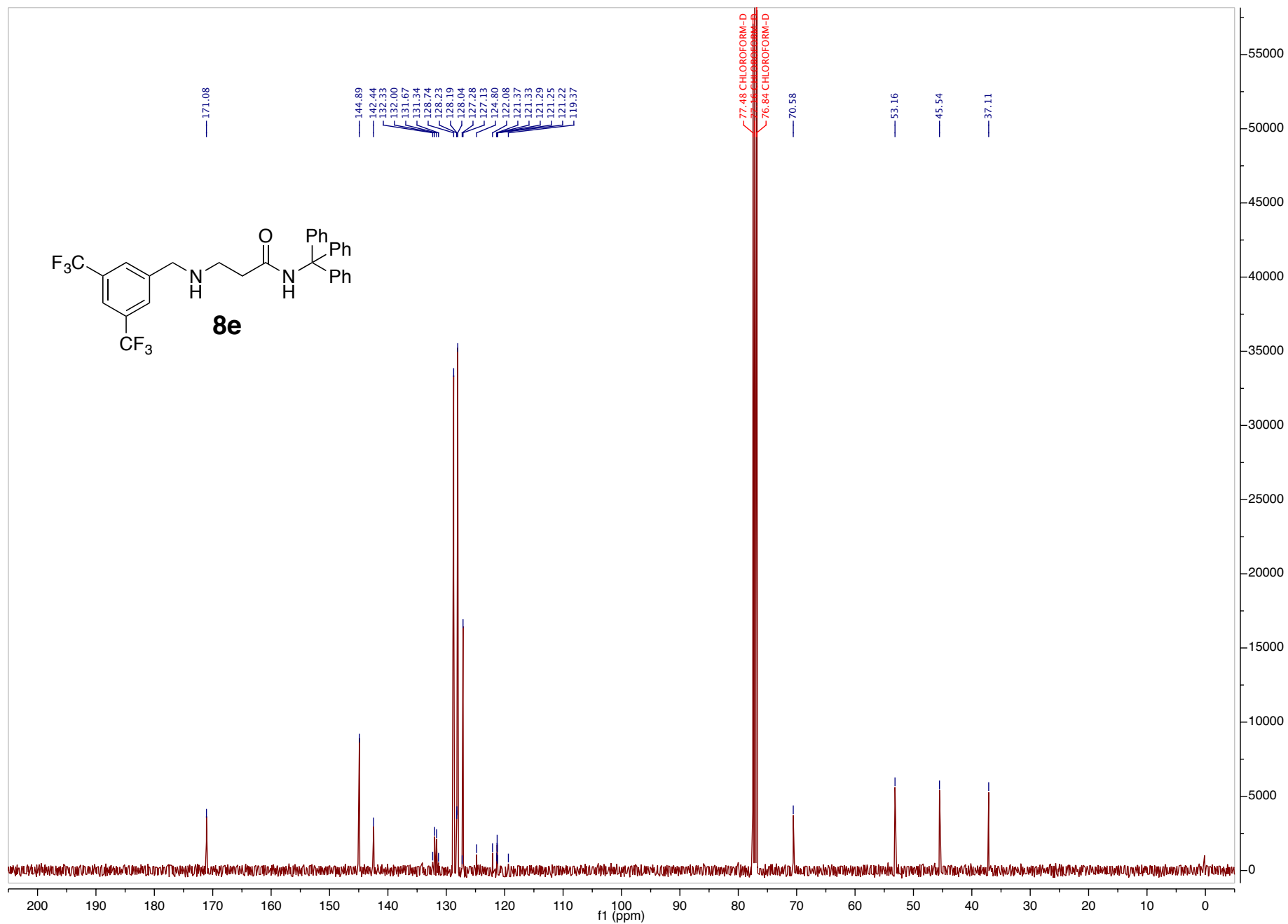


Fig. S16. ¹³C NMR spectrum of **8e** (100 MHz, CDCl₃)

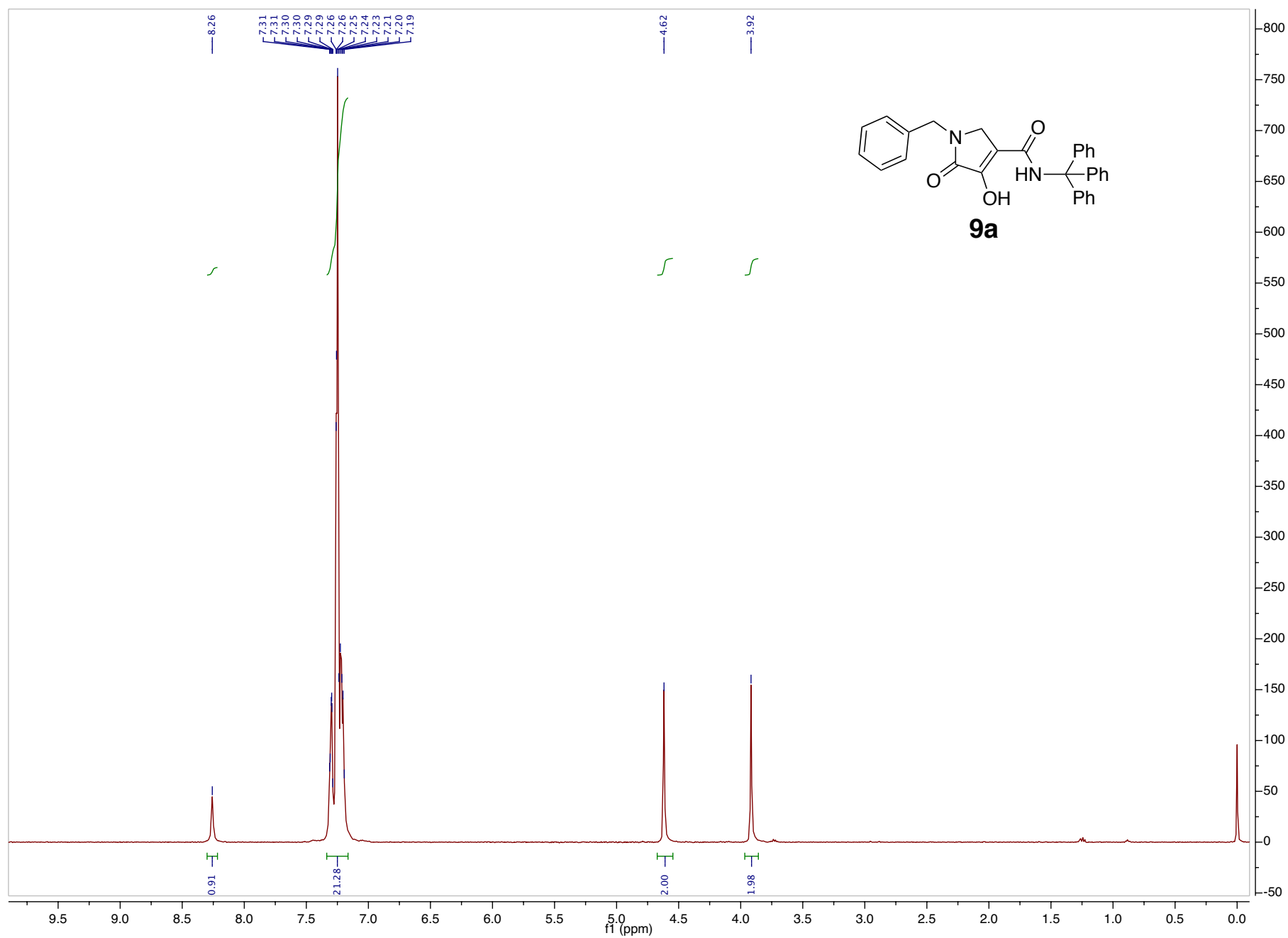


Fig. S17. ^1H NMR spectrum of **9a** (400 MHz, CDCl_3)

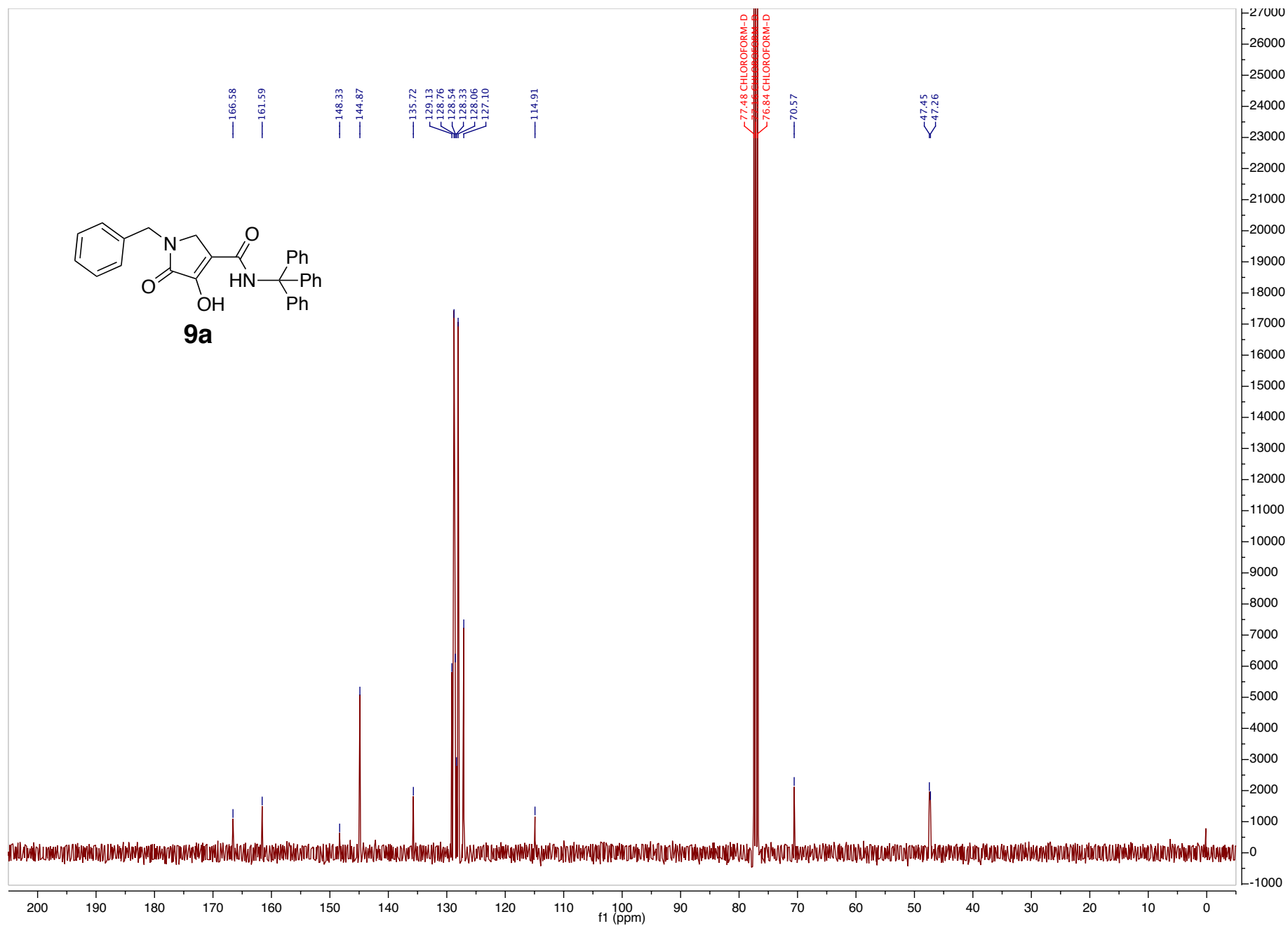


Fig. S18. ^{13}C NMR spectrum of **9a** (100 MHz, CDCl_3)

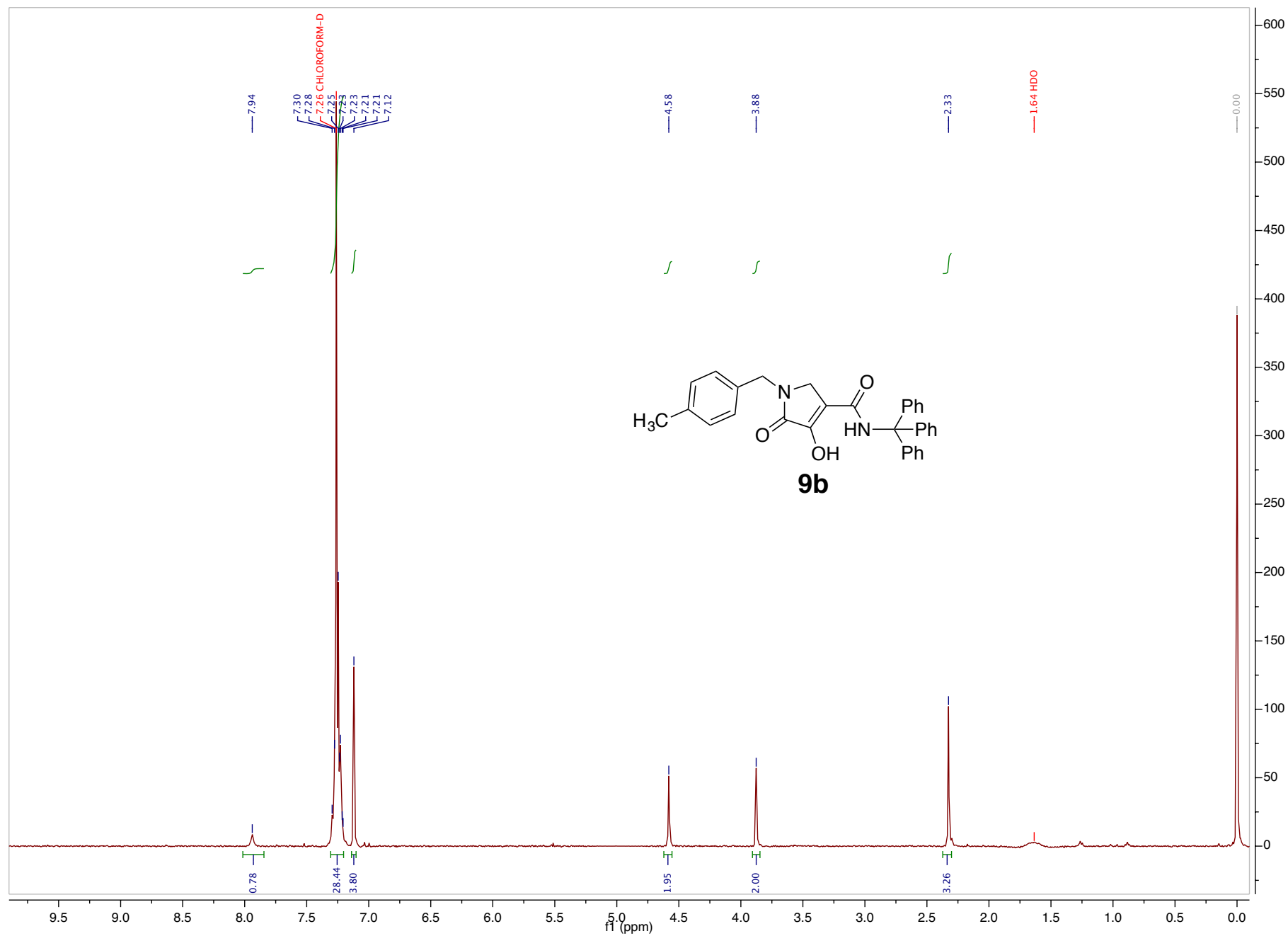


Fig. S19. ¹H NMR spectrum of **9b** (400 MHz, CDCl₃)

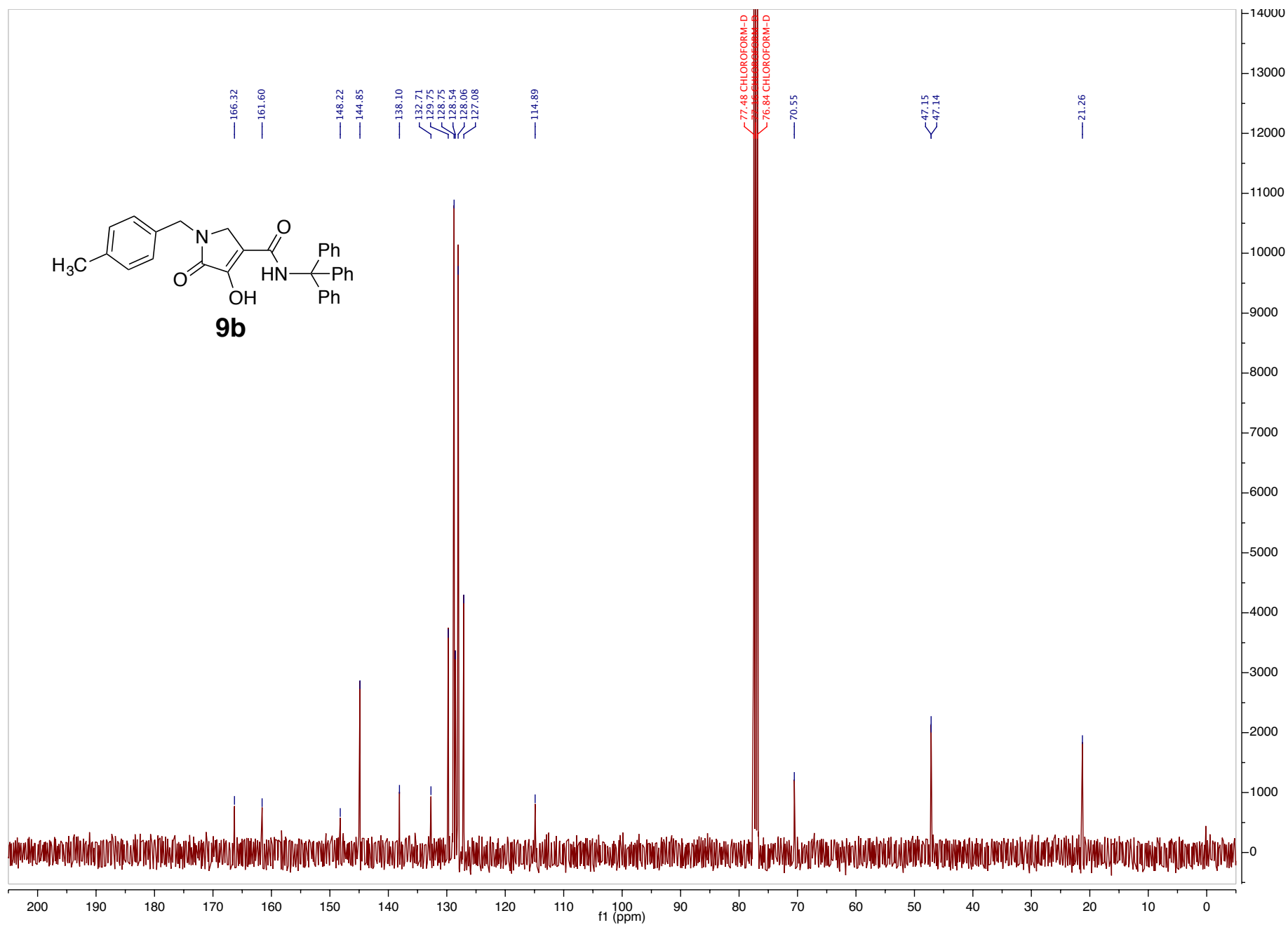


Fig. S20. ^{13}C NMR spectrum of **9b** (100 MHz, CDCl_3)

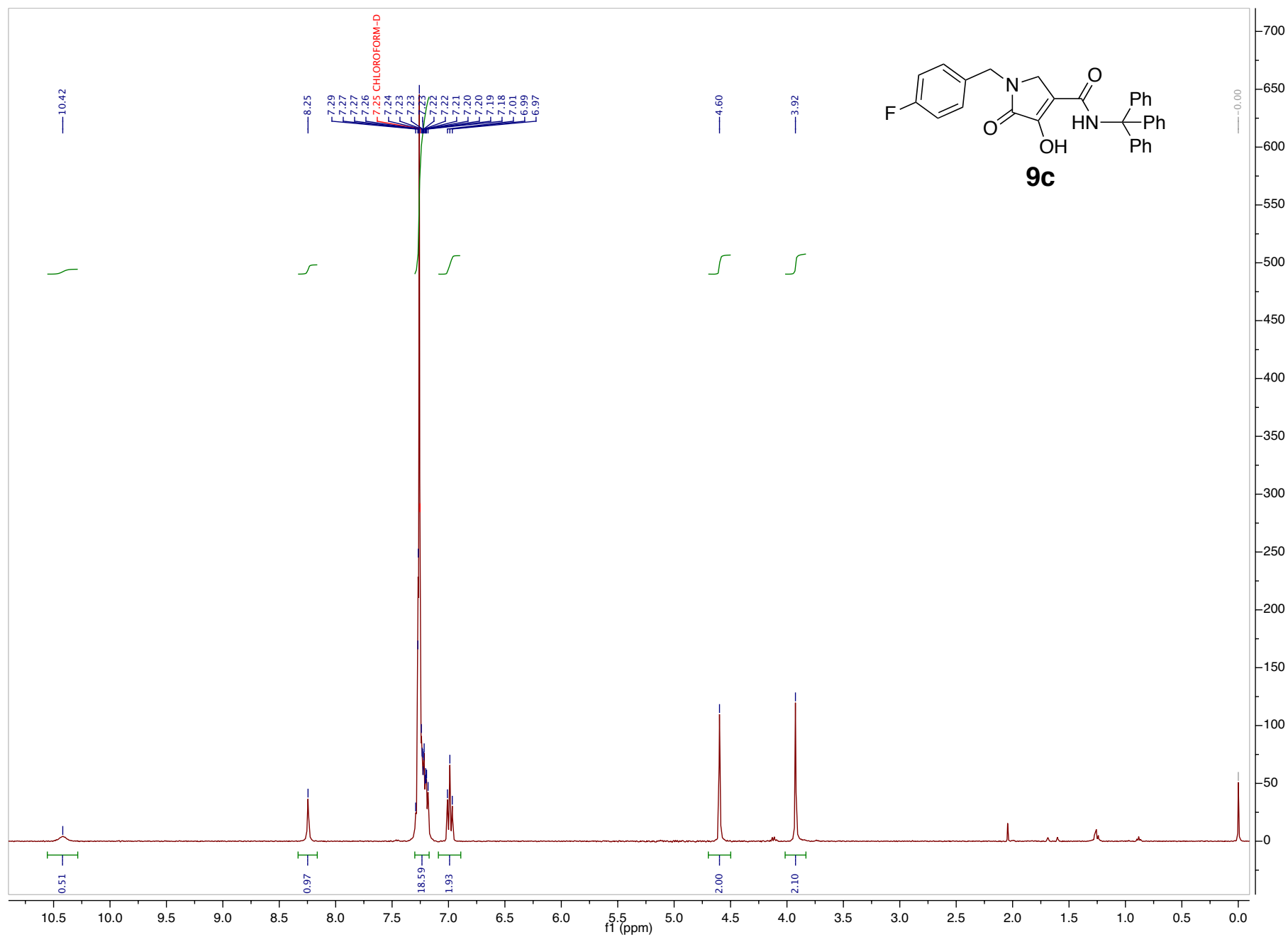


Fig. S21. ¹H NMR spectrum of **9c** (400 MHz, CDCl₃)

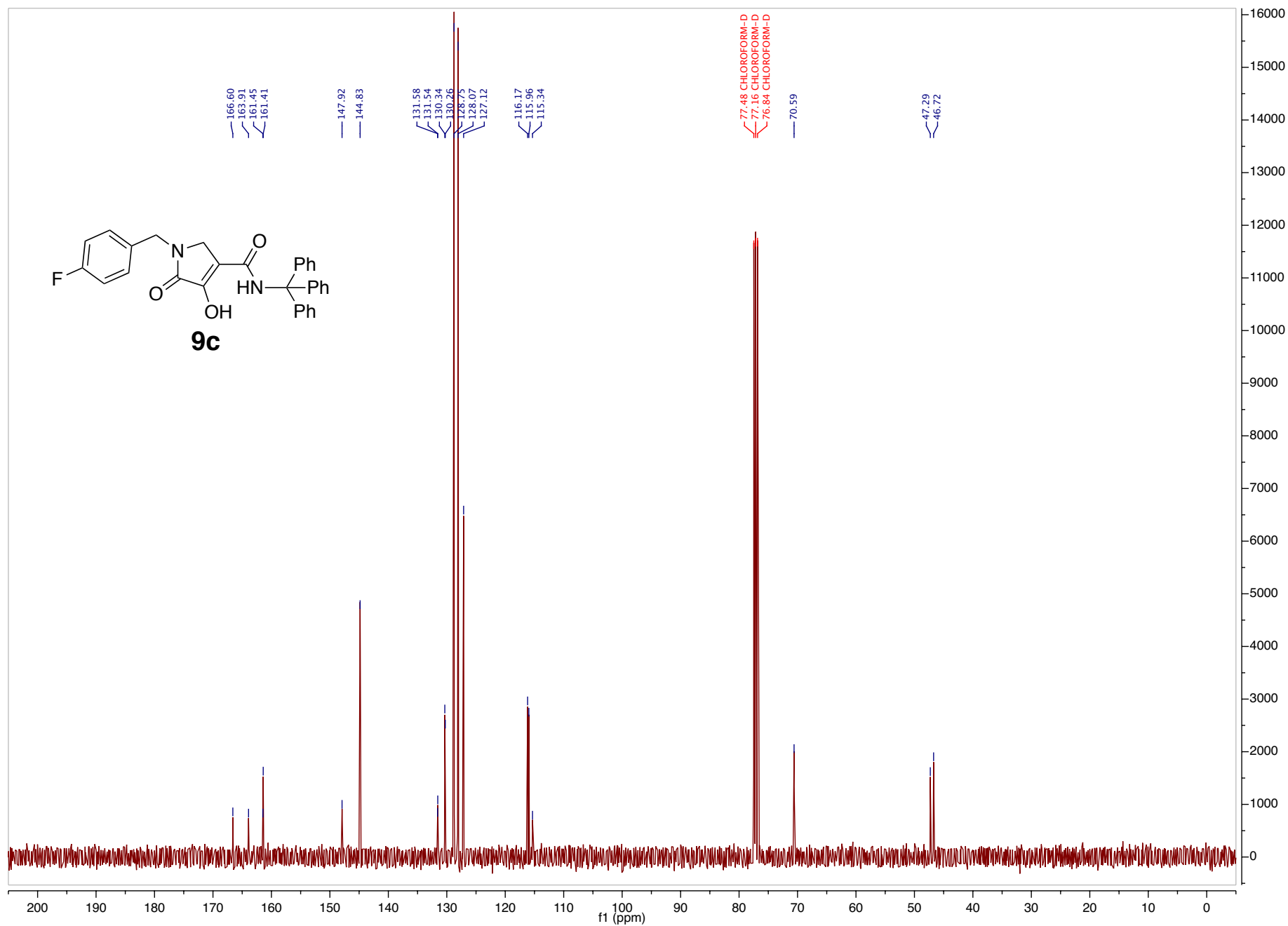


Fig. S22. ¹³C NMR spectrum of **9c** (100 MHz, CDCl₃)

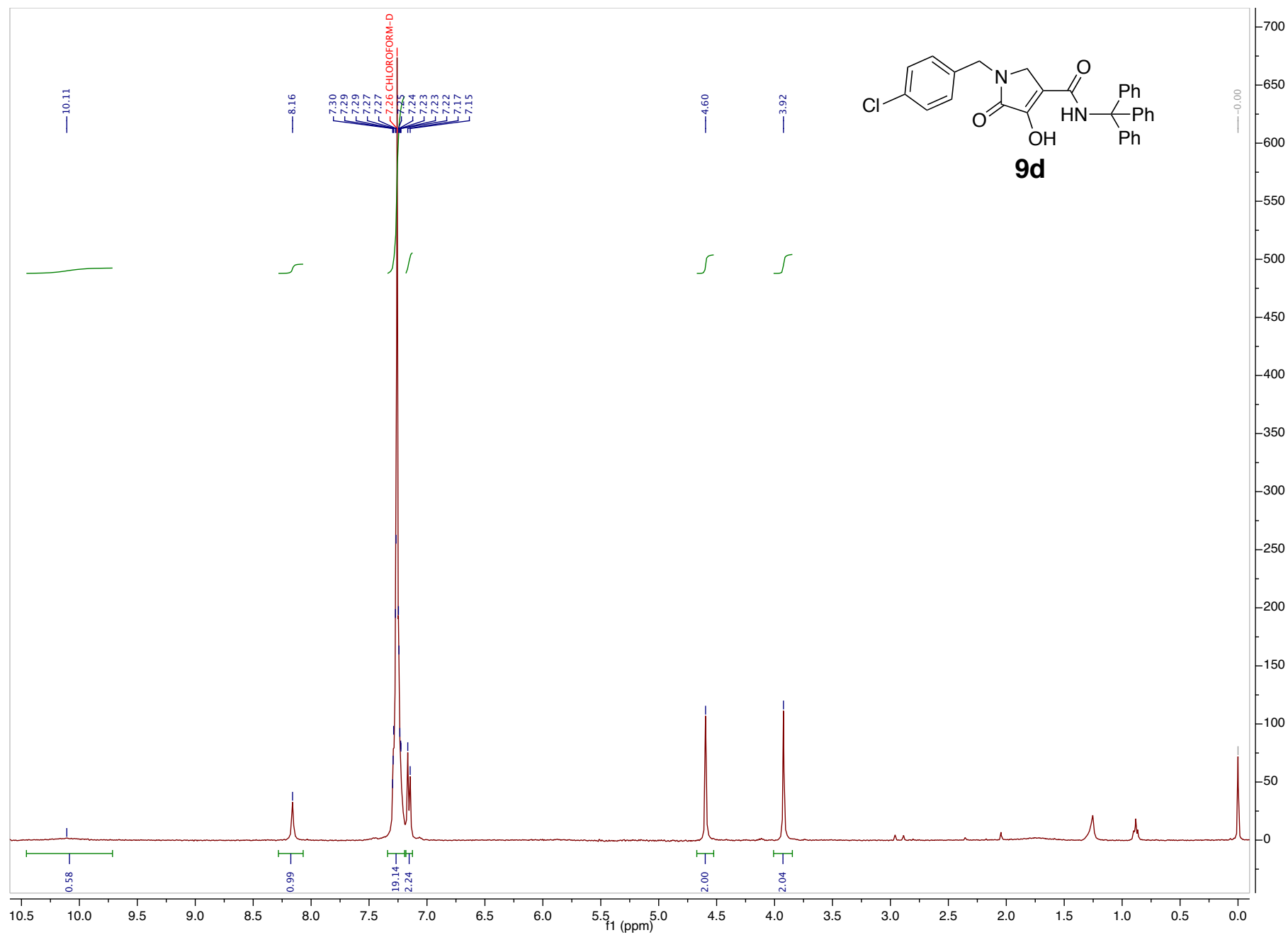


Fig. S23. ^1H NMR spectrum of **9d** (400 MHz, CDCl_3)

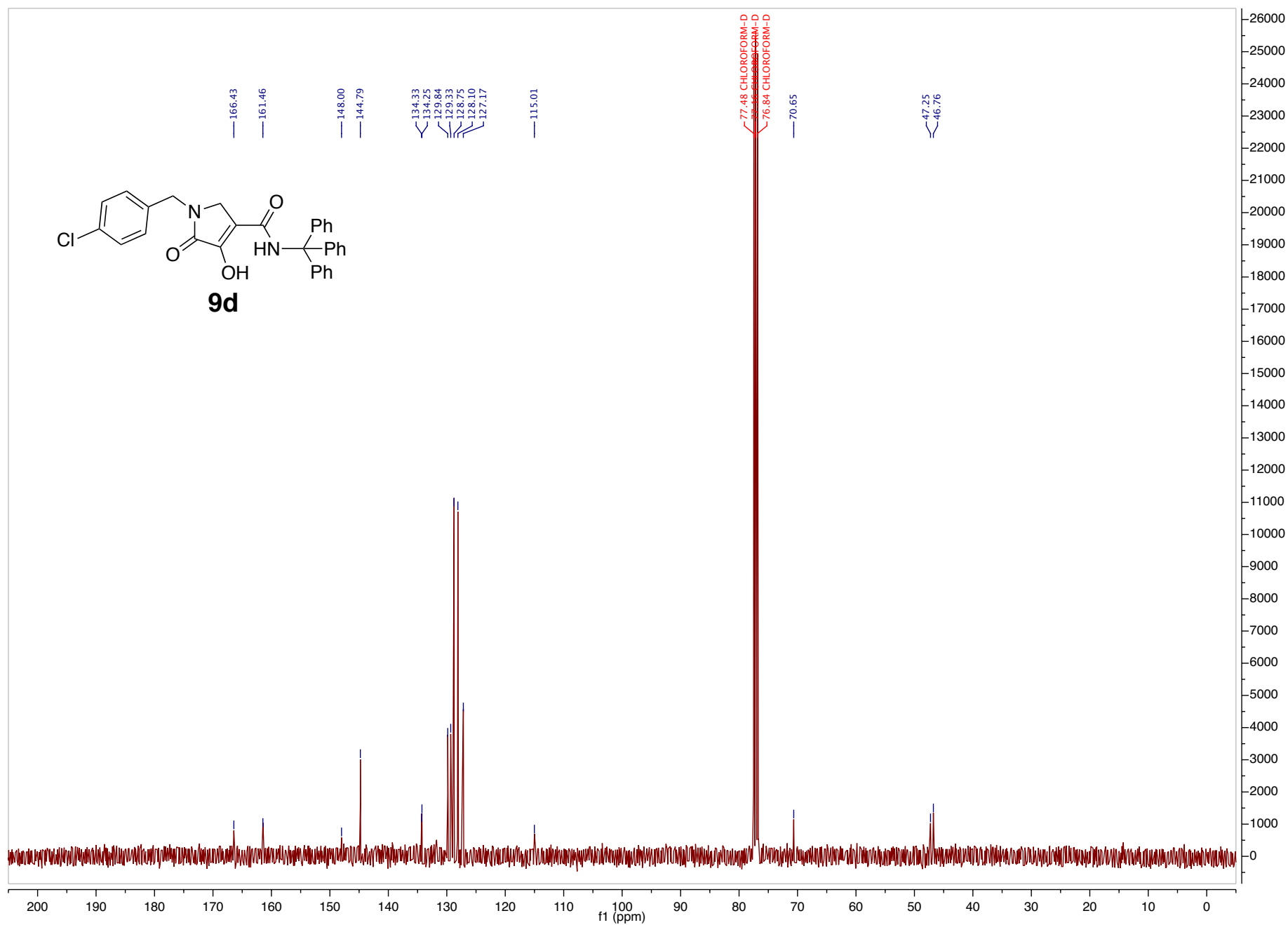


Fig. S24. ^{13}C NMR spectrum of **9d** (100 MHz, CDCl_3)

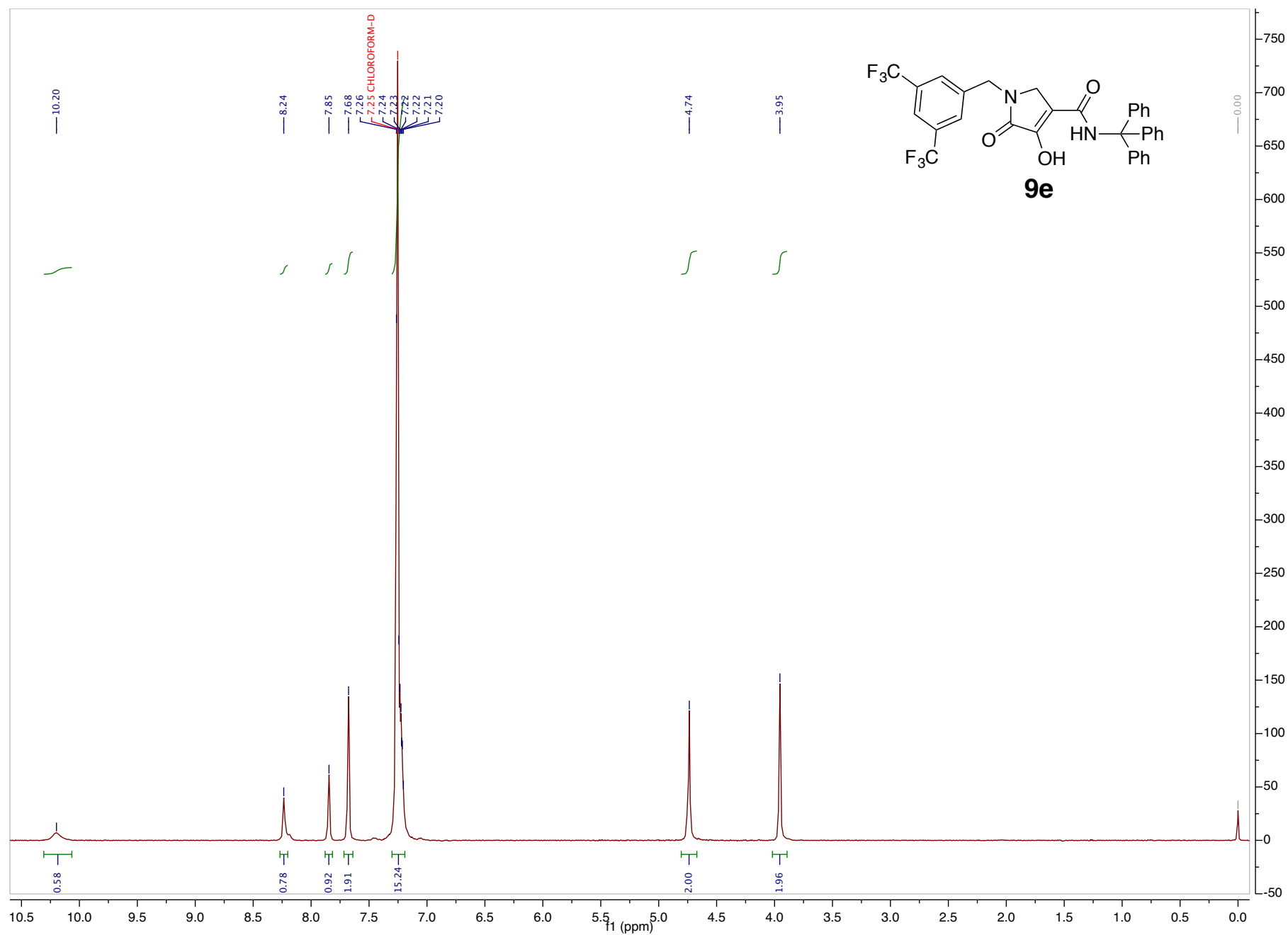


Fig. S25. ^1H NMR spectrum of **9e** (400 MHz, CDCl_3)

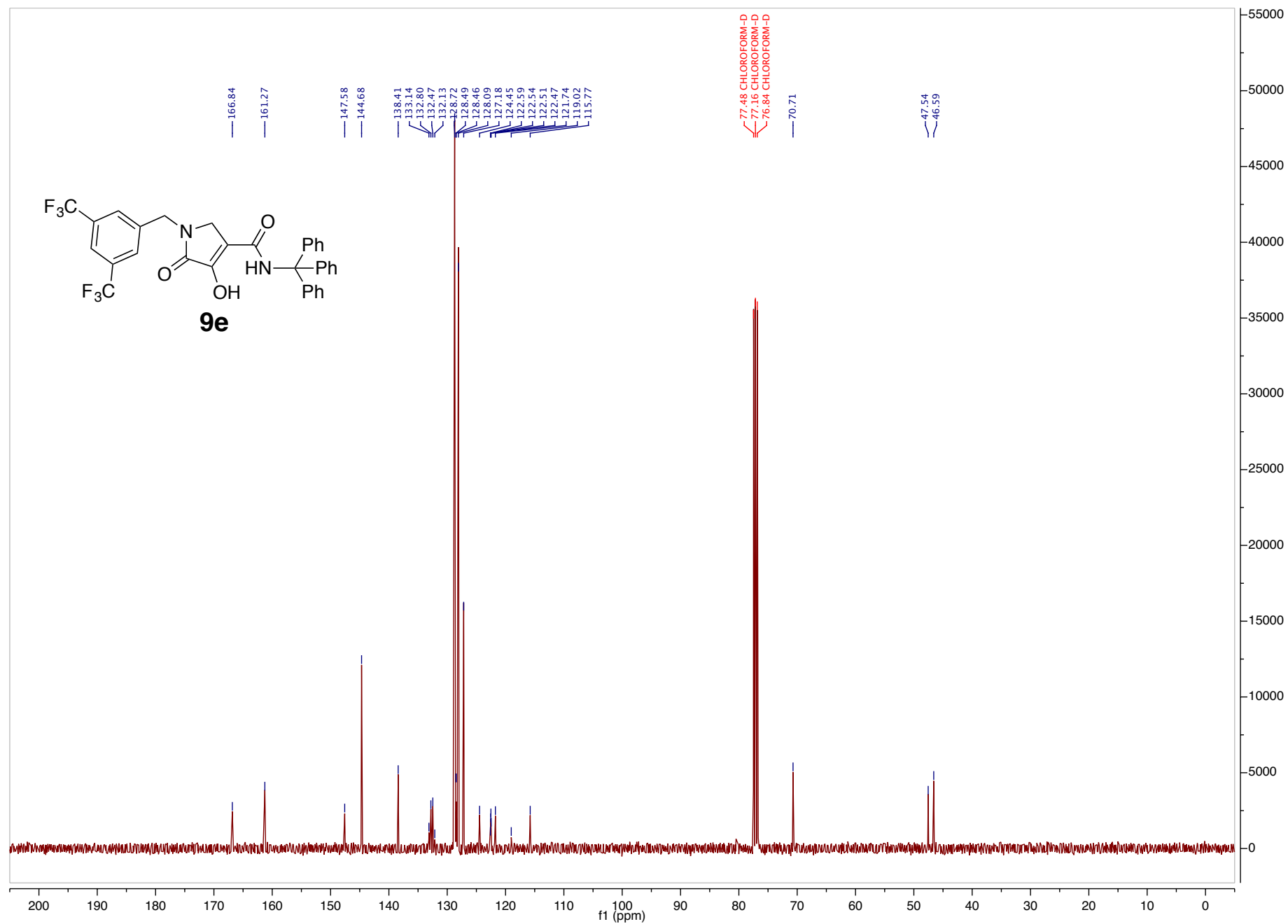


Fig. S26. ^{13}C NMR spectrum of **9e** (100 MHz, CDCl_3)

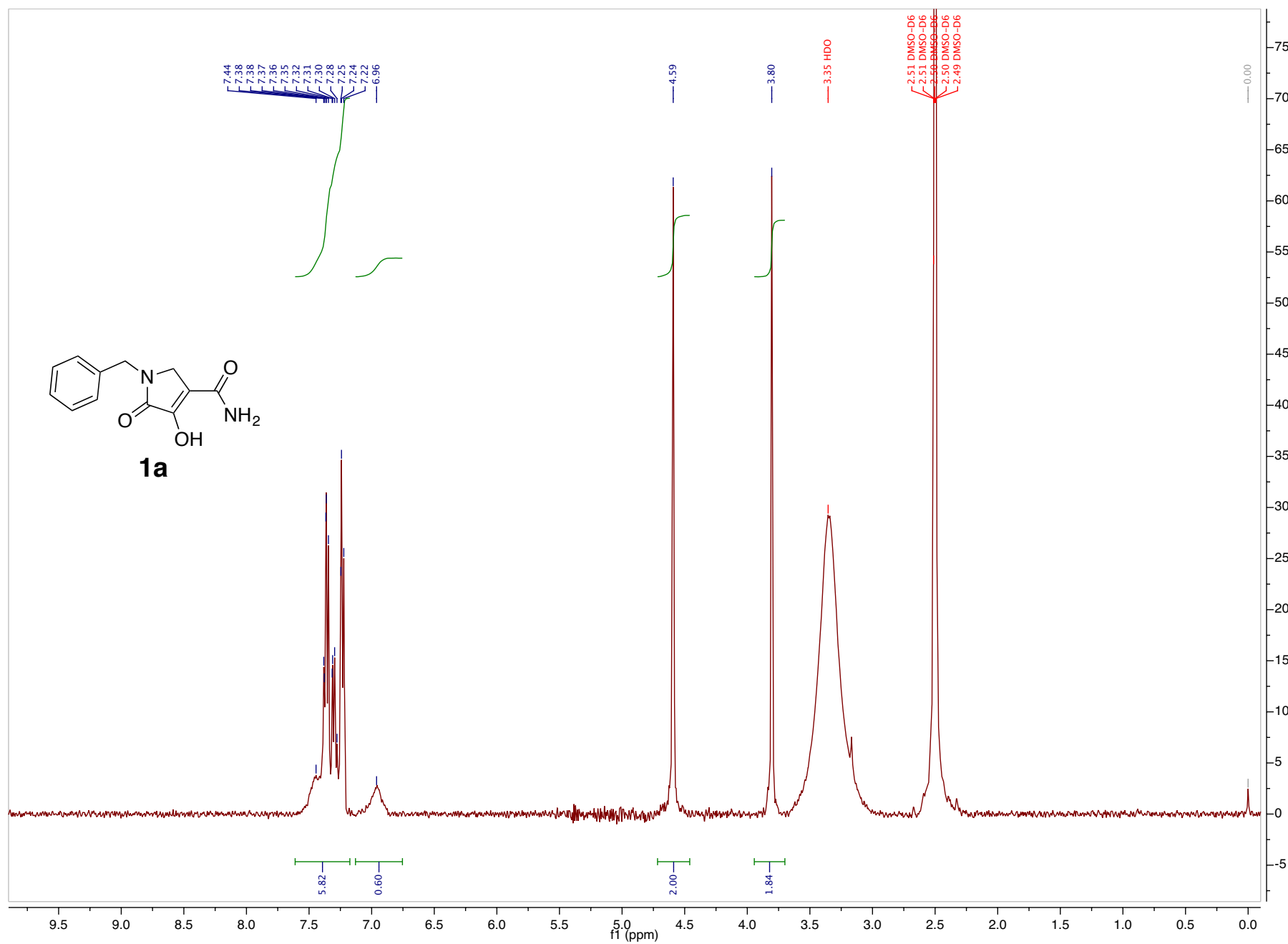


Fig. S27. ¹H NMR spectrum of **1a** (400 MHz, CDCl₃)

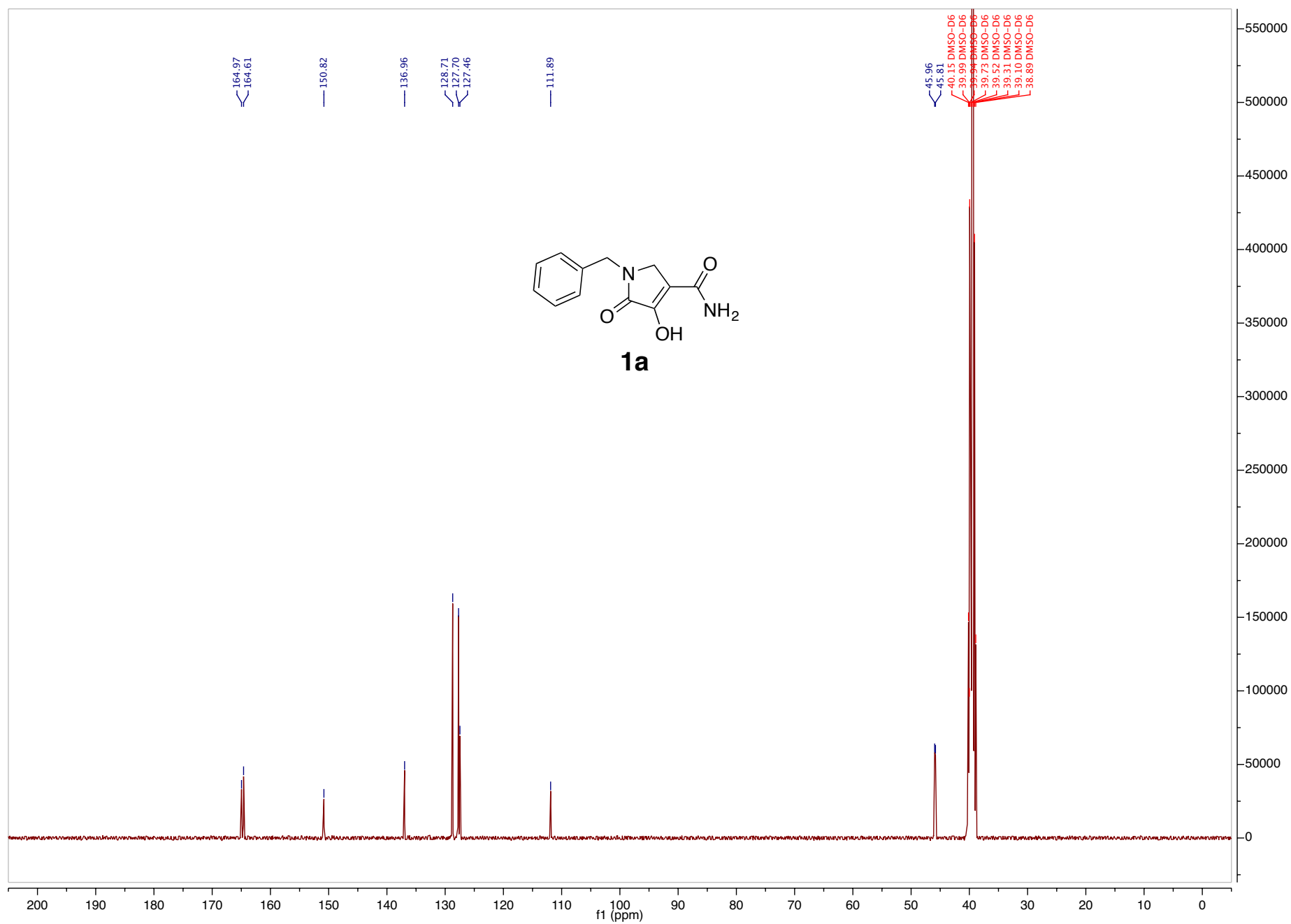


Fig. S28. ¹³C NMR spectrum of **1a** (100 MHz, CDCl₃)

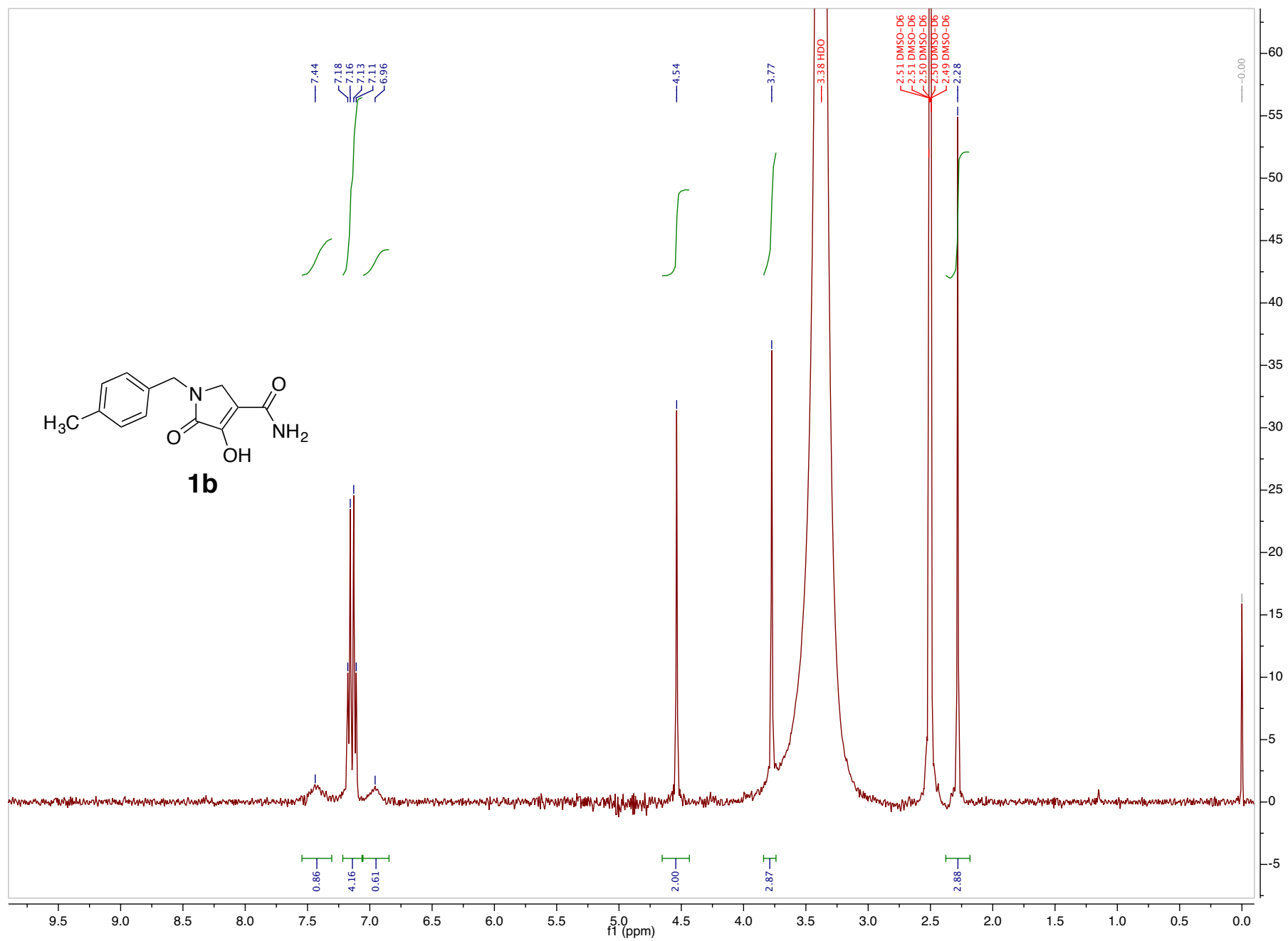


Fig. S29. ¹H NMR spectrum of **1b** (400 MHz, CDCl₃)

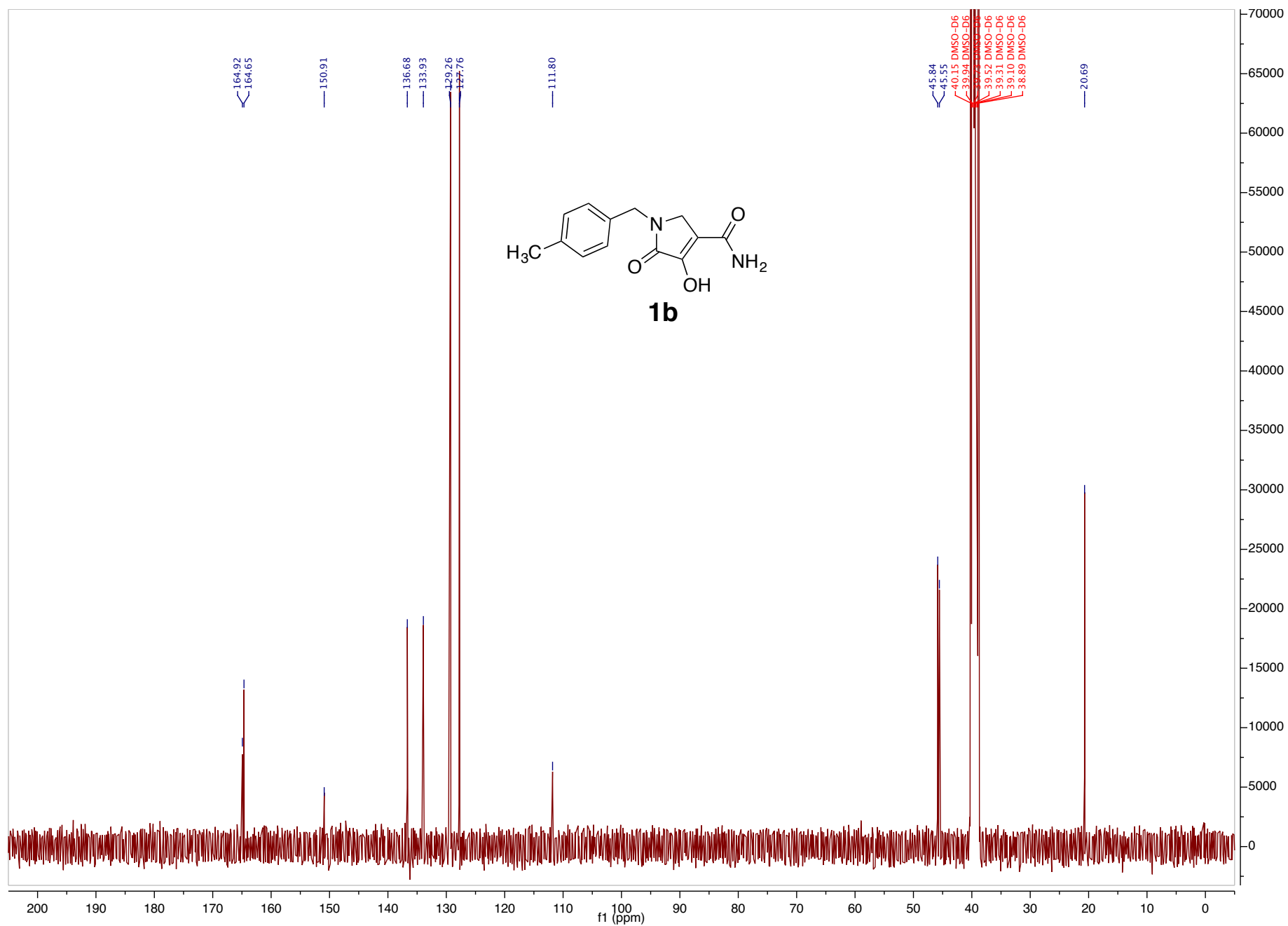


Fig. S30. ^{13}C NMR spectrum of **1b** (100 MHz, CDCl_3)

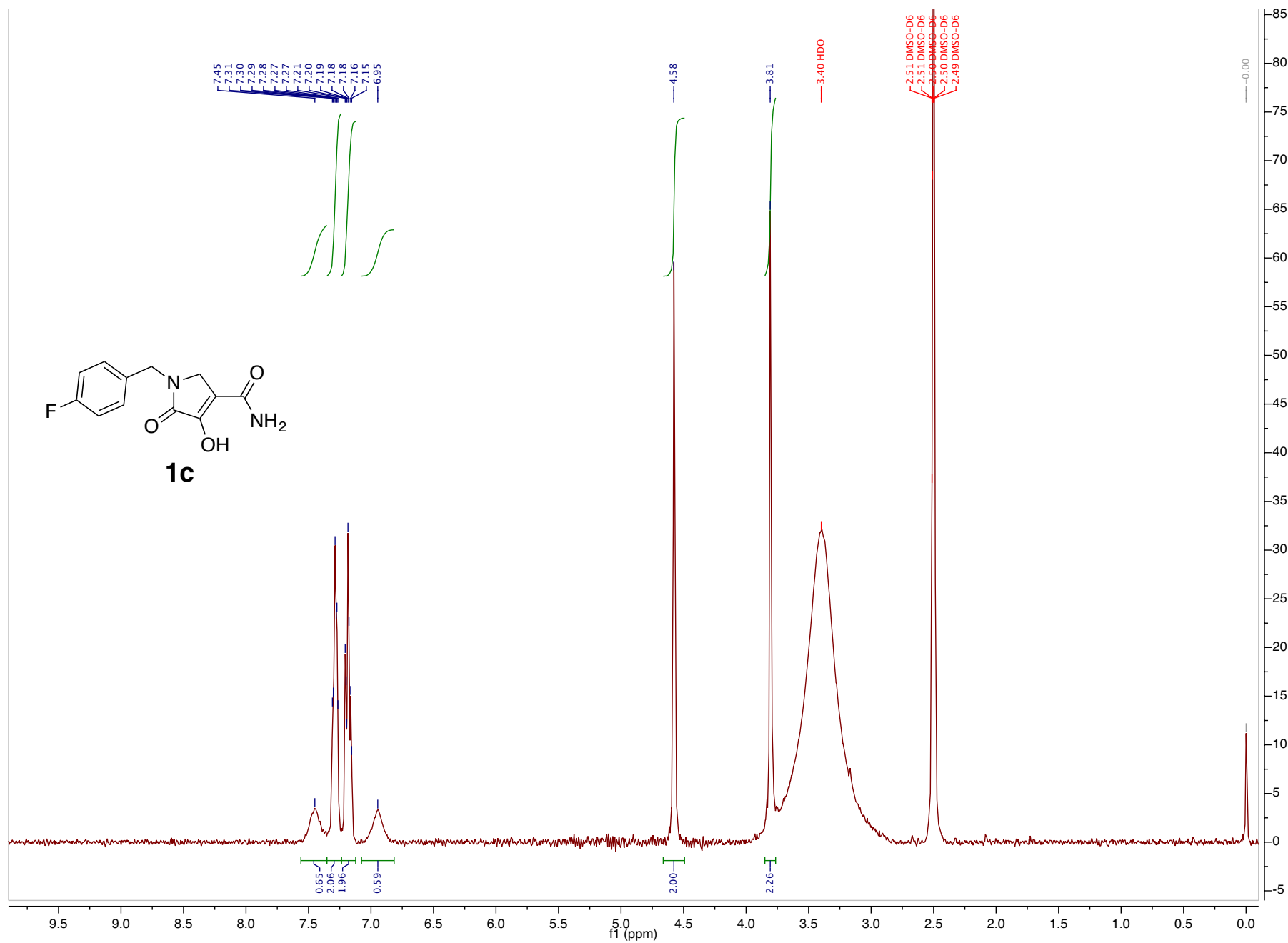


Fig. S31. ¹H NMR spectrum of **1c** (400 MHz, CDCl₃)

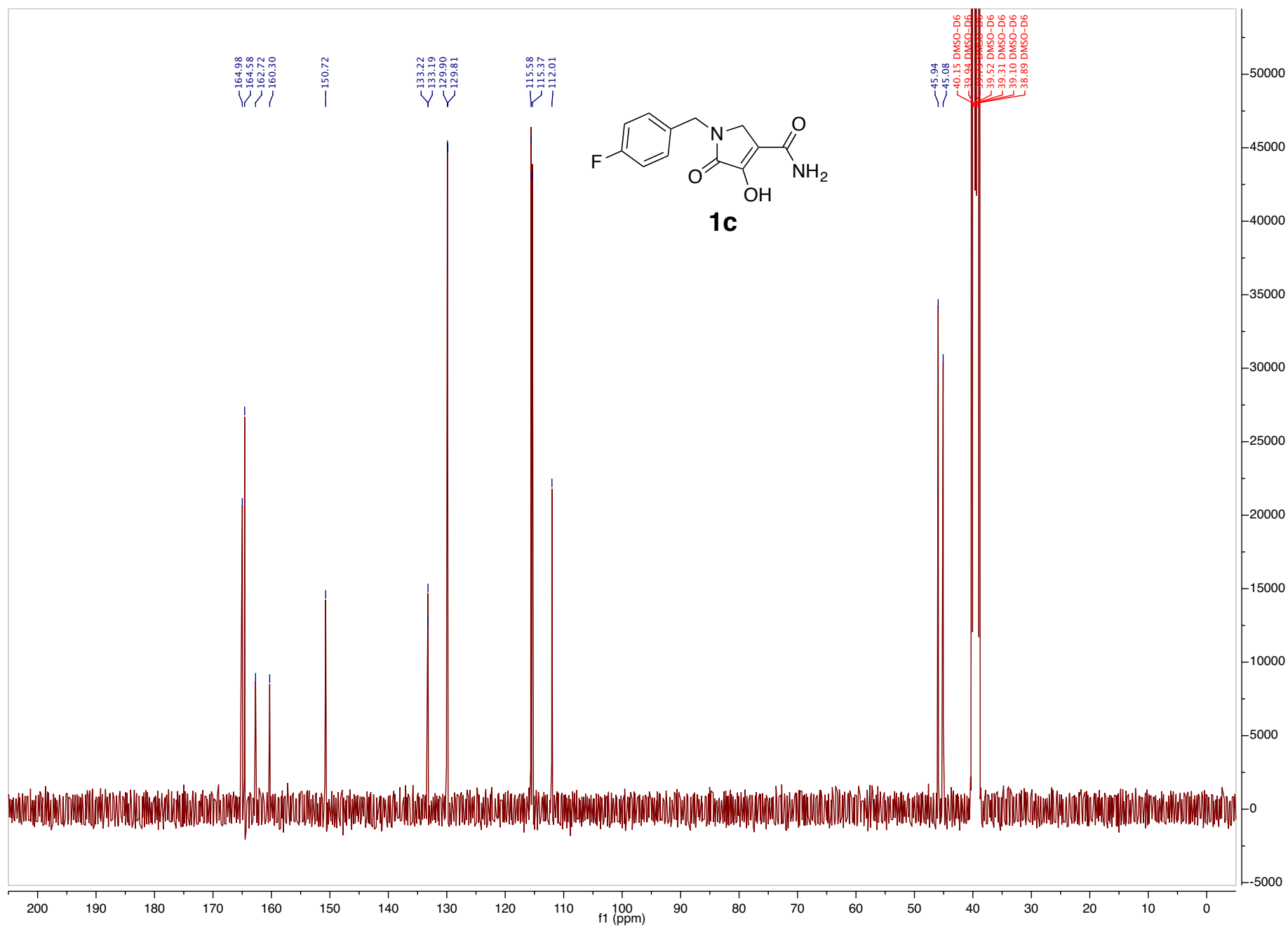


Fig. S32. ^{13}C NMR spectrum of **1c** (100 MHz, CDCl_3)

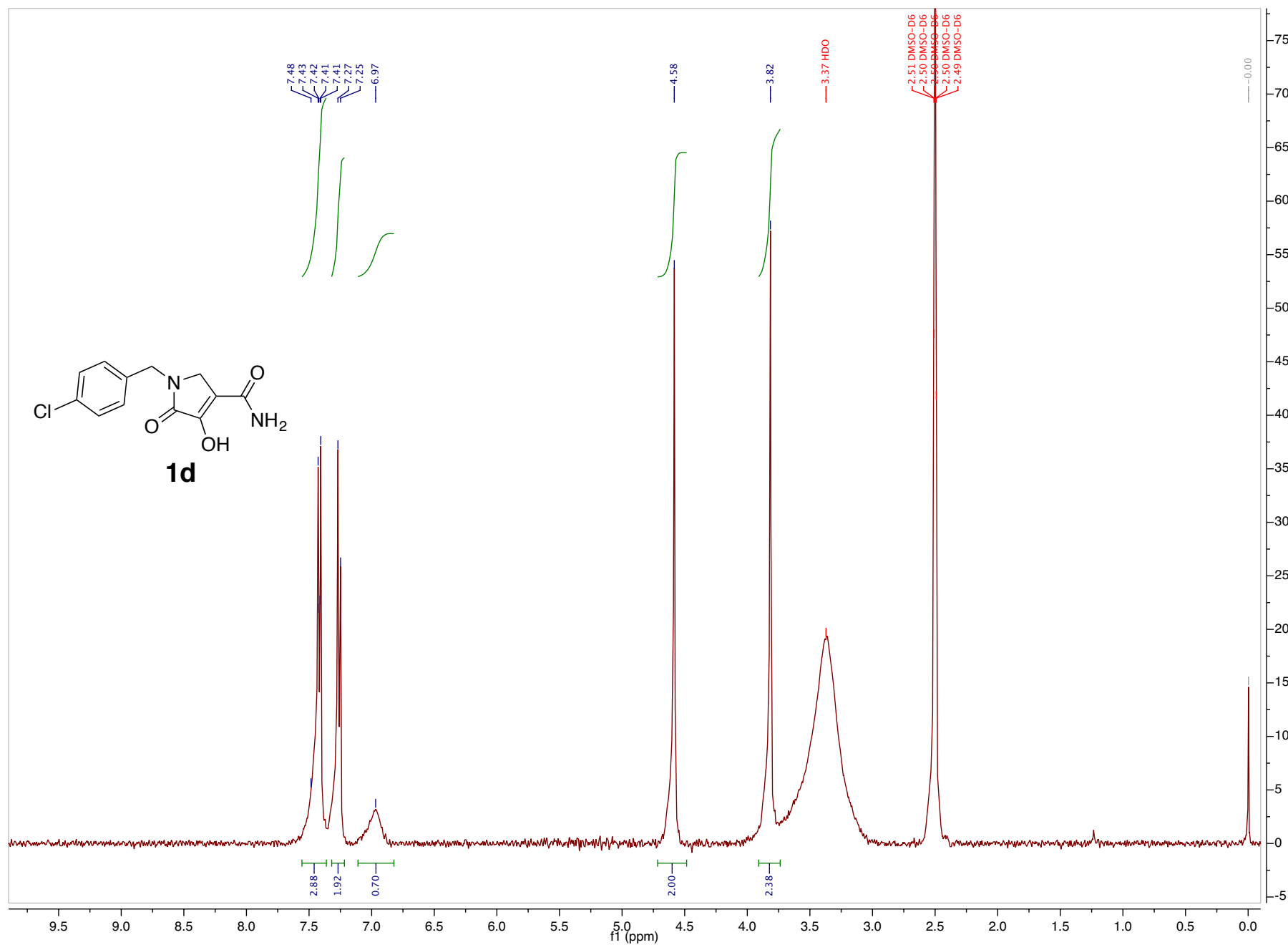


Fig. S33. ¹H NMR spectrum of **1d** (400 MHz, CDCl₃)

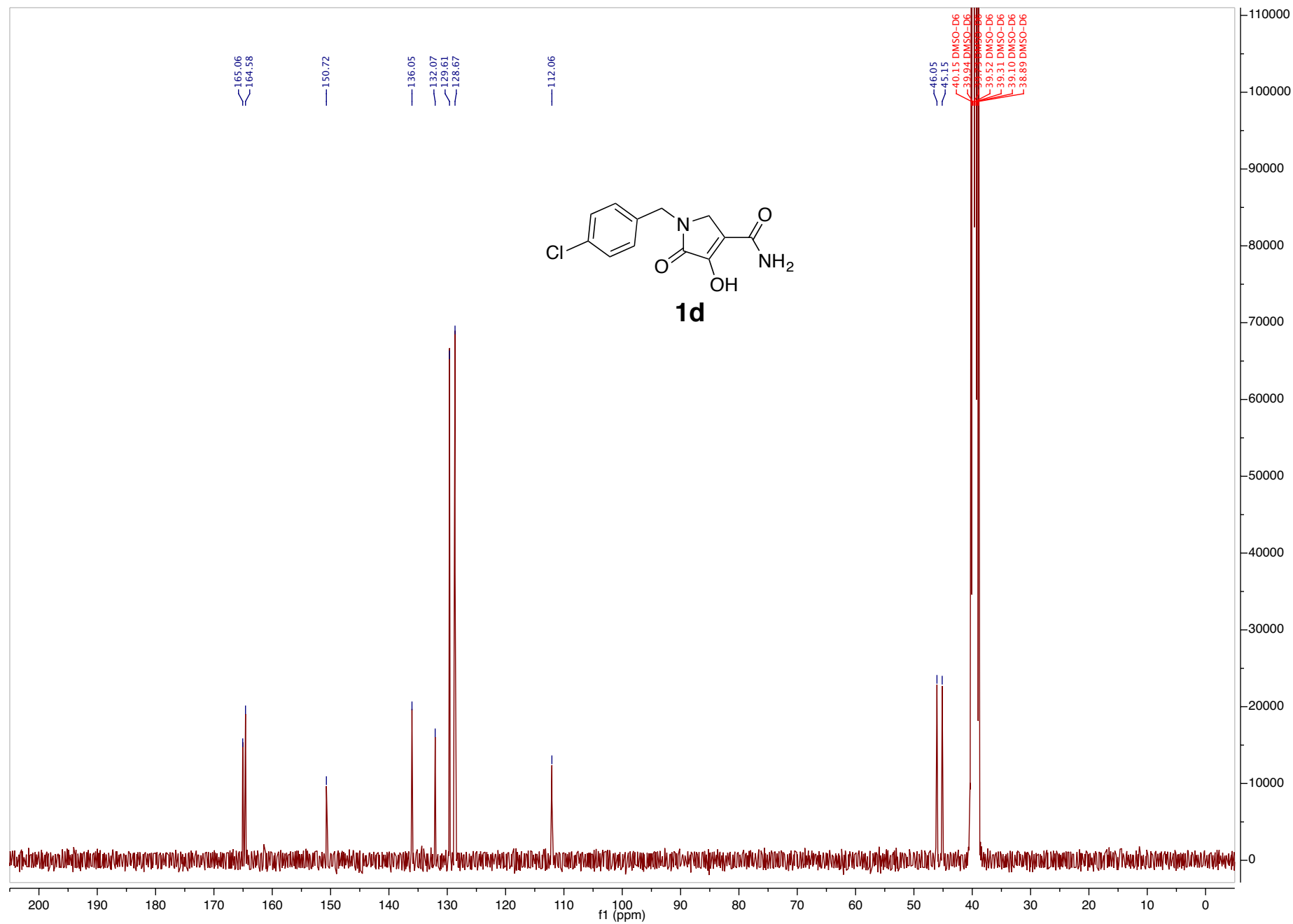


Fig. S34. ¹³C NMR spectrum of **1d** (100 MHz, CDCl₃)

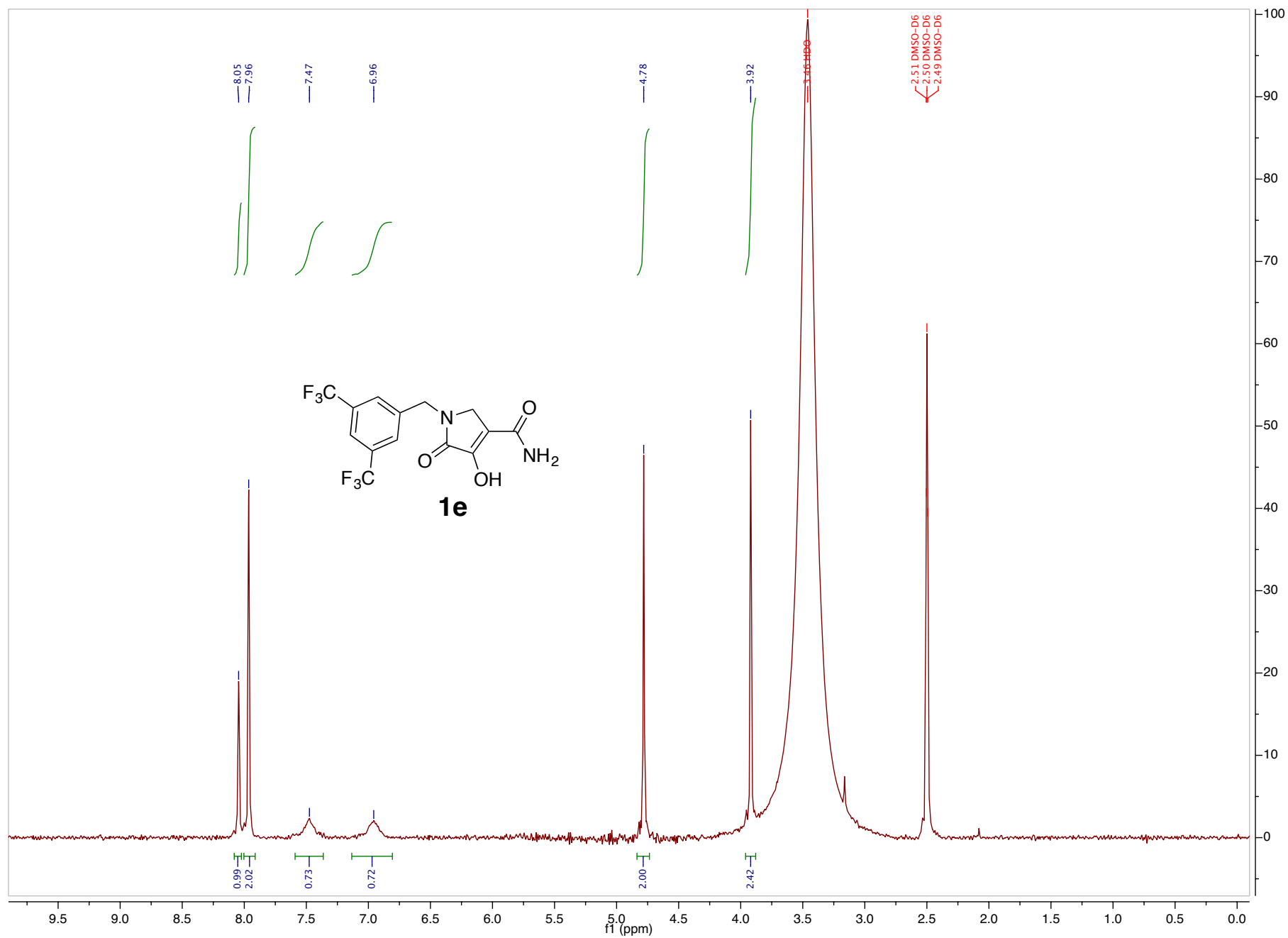


Fig. S35. ¹H NMR spectrum of **1e** (400 MHz, CDCl₃)

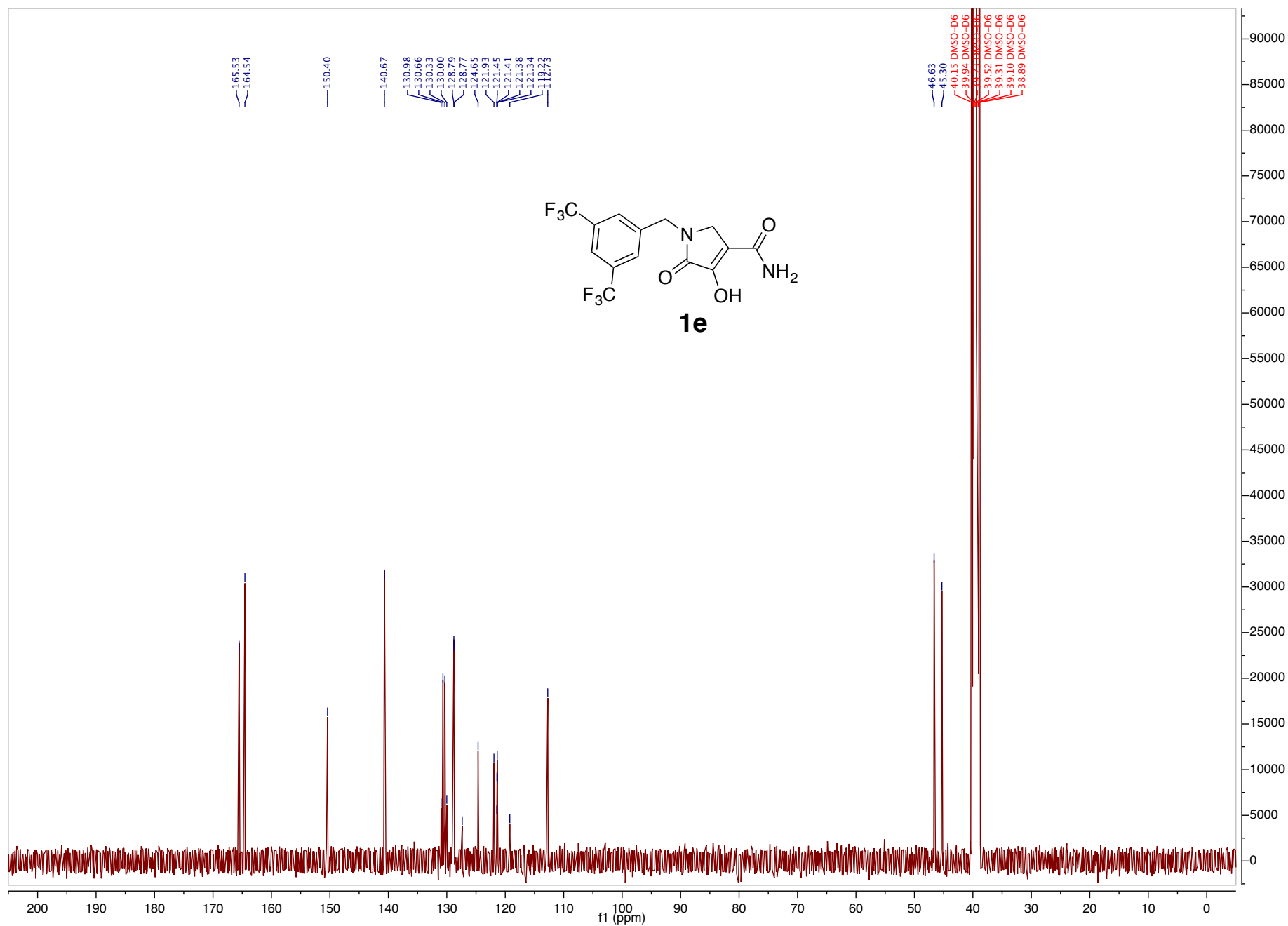


Fig. S36. ^{13}C NMR spectrum of **1e** (100 MHz, CDCl_3)

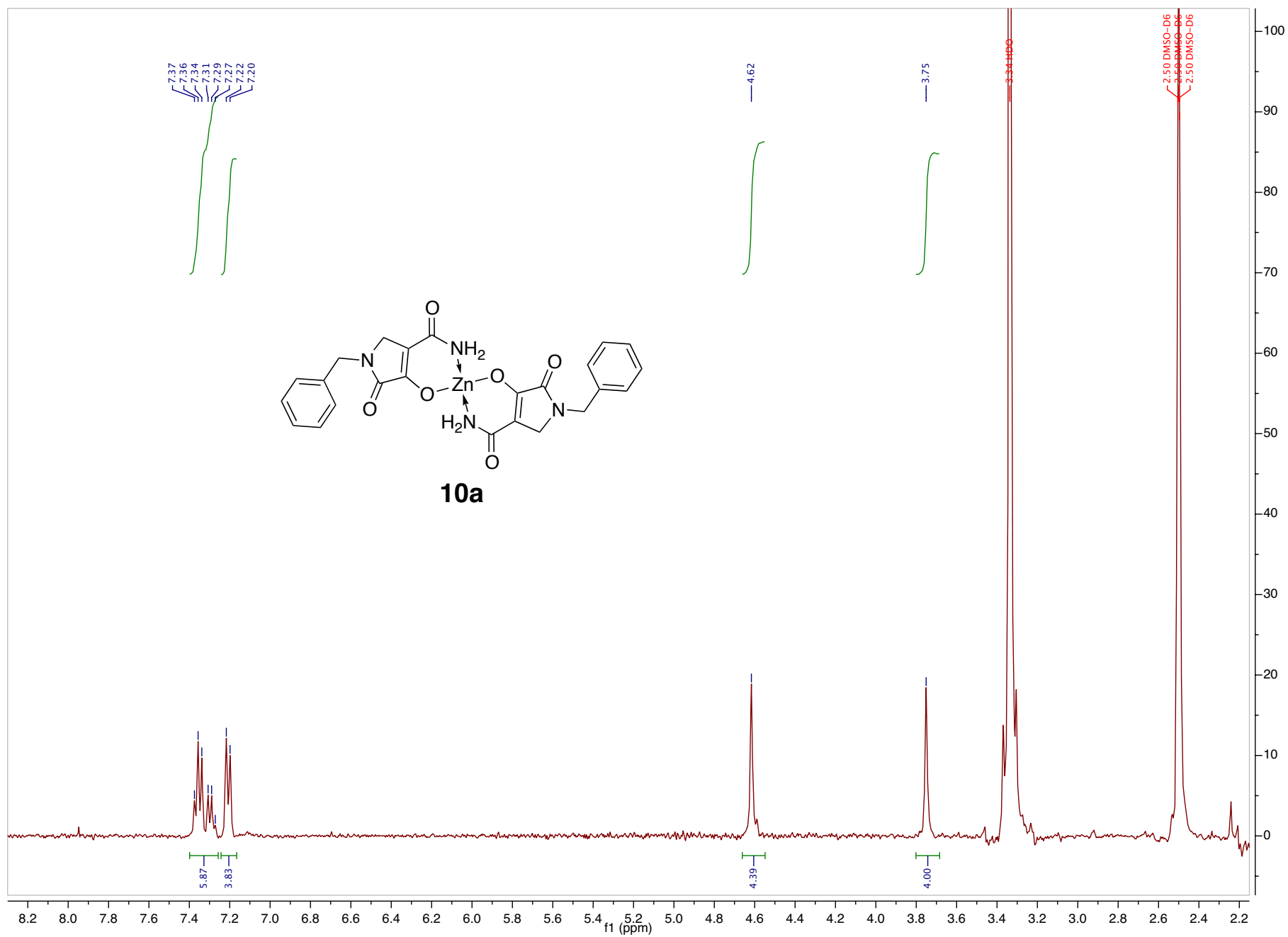


Fig. S37. ^1H NMR spectrum of **10a** (400 MHz, $\text{DMSO}-d_6$)

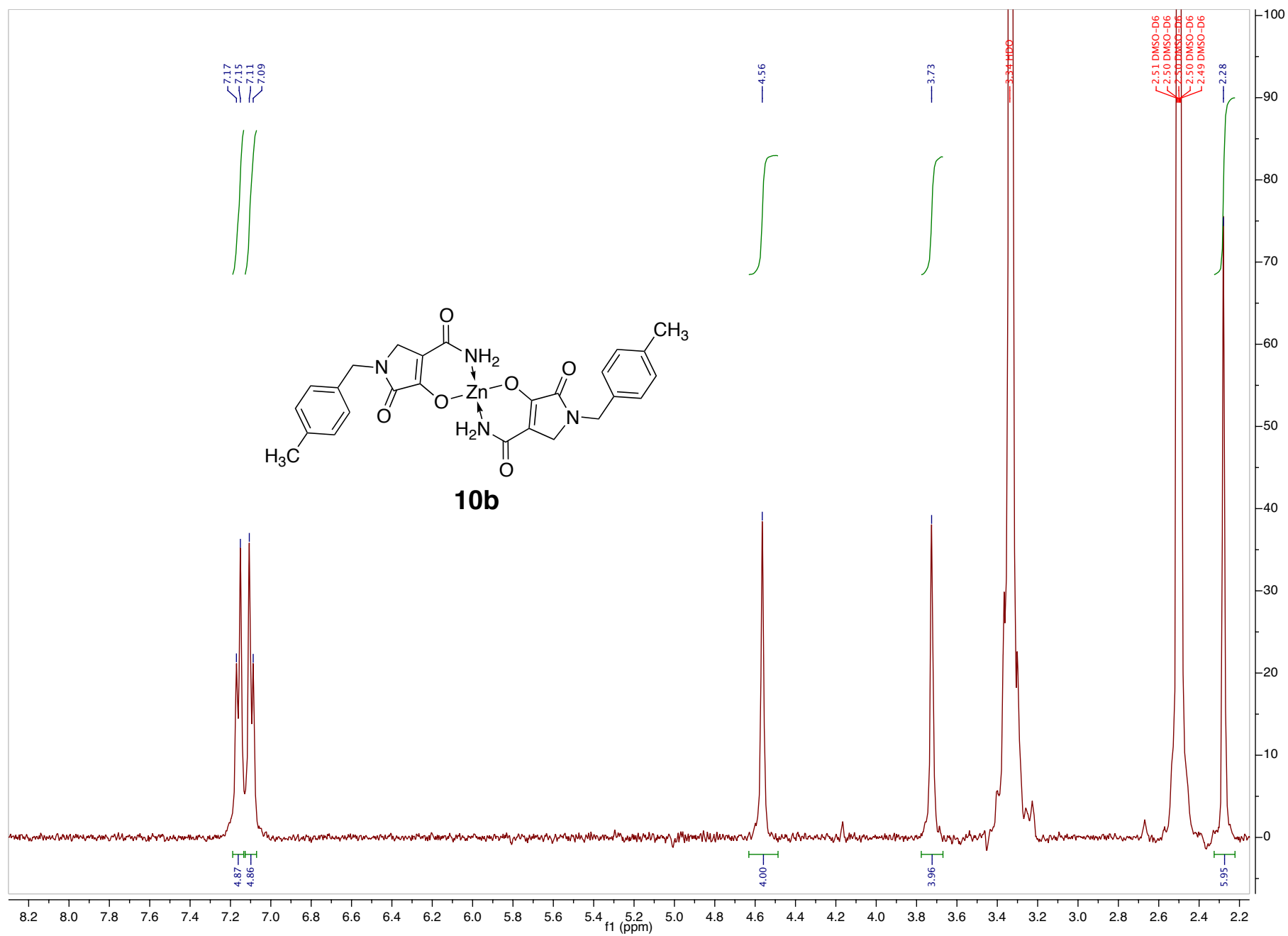


Fig. S38. ¹H NMR spectrum of **10b** (400 MHz, DMSO-*d*₆)

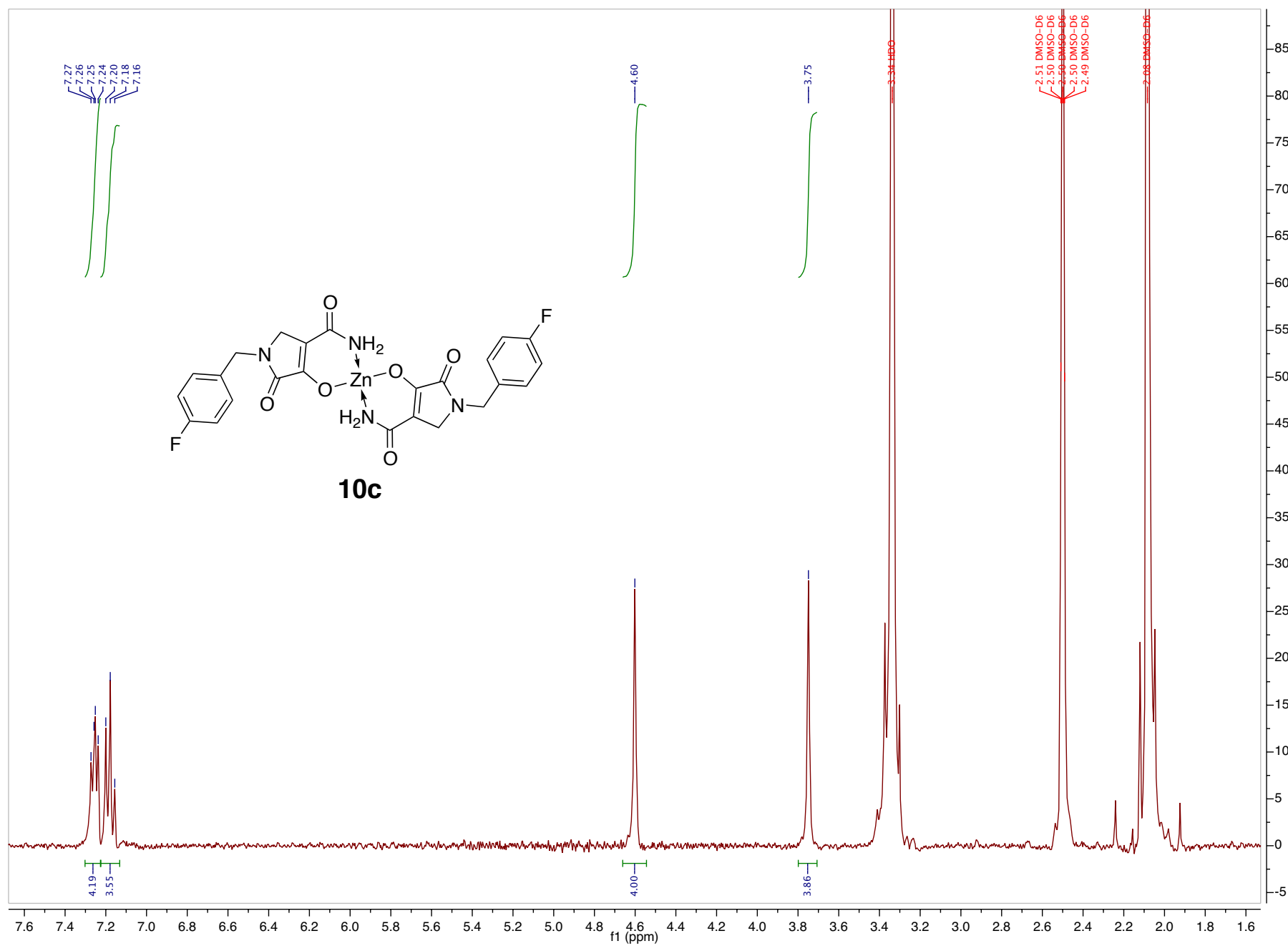


Fig. S39. ^1H NMR spectrum of **10c** (400 MHz, $\text{DMSO}-d_6$)

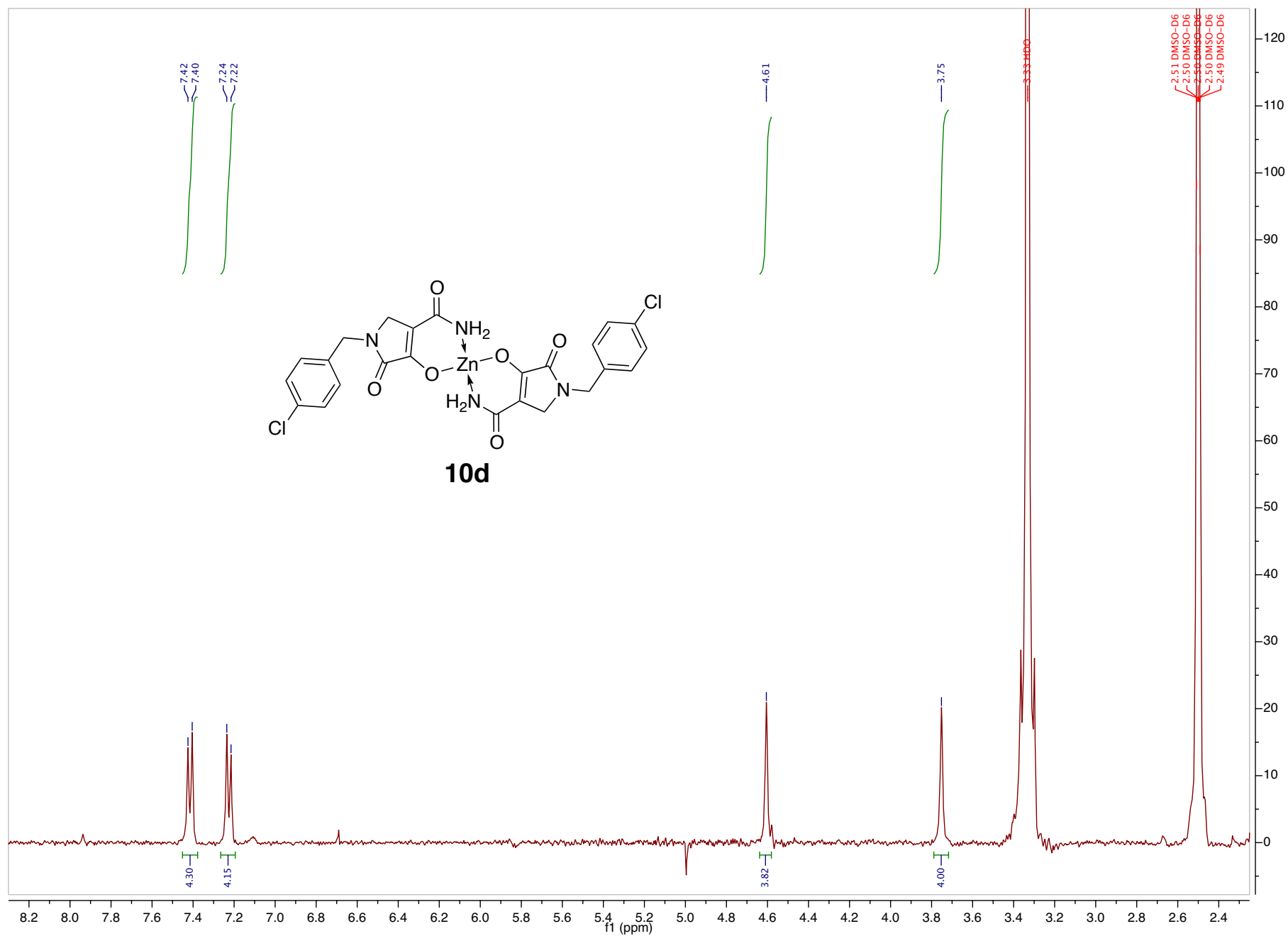


Fig. S40. ¹H NMR spectrum of **10d** (400 MHz, DMSO-*d*₆)

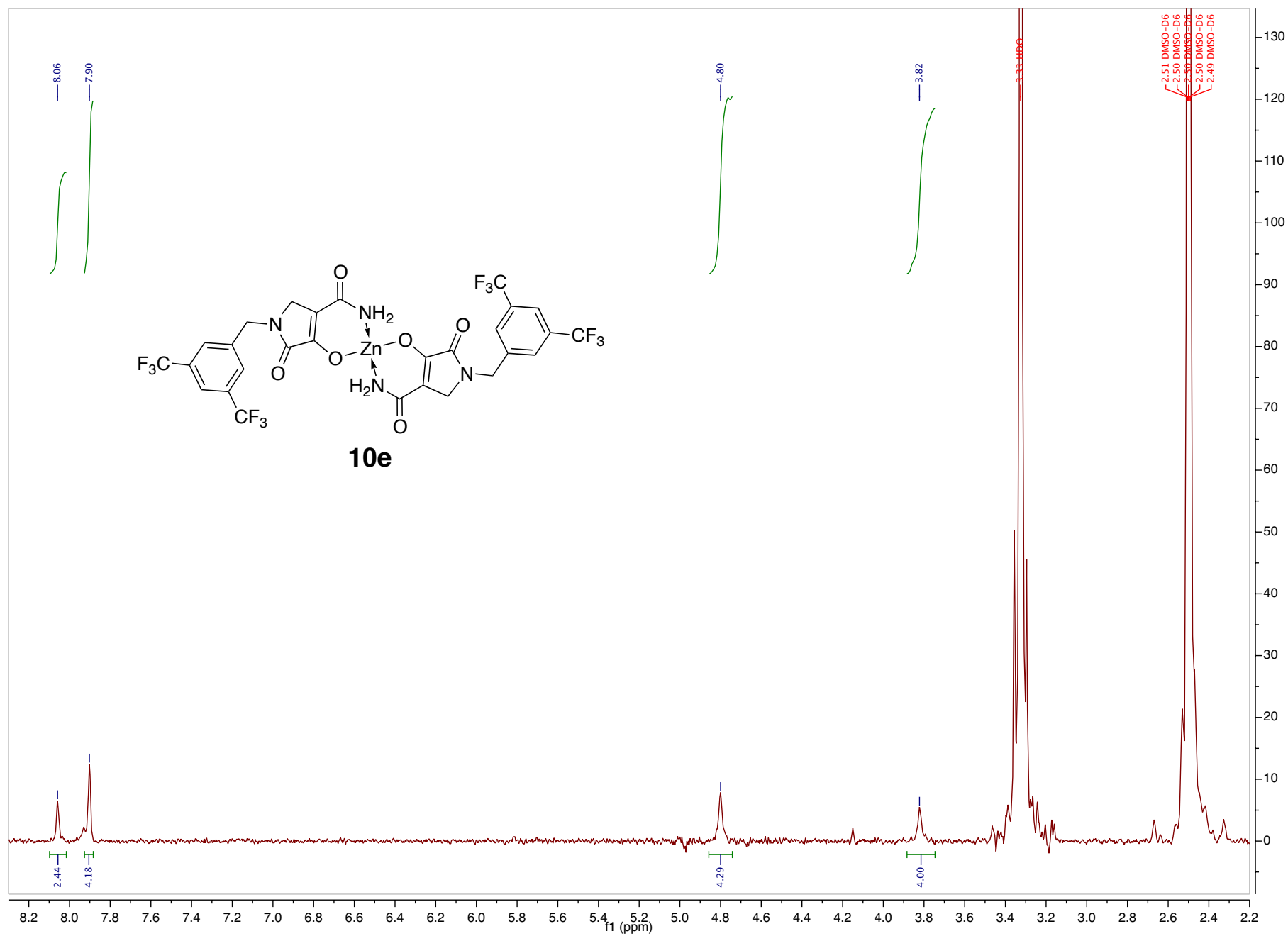


Fig. S41. ^1H NMR spectrum of **10e** (400 MHz, $\text{DMSO}-d_6$)