Supplementary data

Lamellarin-inspired potent topoisomerase I inhibitors with the unprecedented benzo[*g*][1]benzopyrano[4,3-*b*]indol-6(13*H*)-one scaffold

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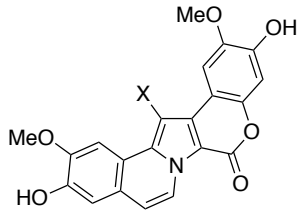
Table S1. Antiproliferative activity of F-ring defected lamellarin D analogues **6a**–**6g** against selected human cancer cell lines.



6a: X = H
6b: X = Me
6c: X = CH_2NMe_2
6d: X = CHO
6e: X = Br
6f: X = Cl
6g: X = F

Human cancer cell line		Antiproliferative activity (GI_{50} in nM)[a]								
		6a[e]	**6b**[g]	**6c**[e]	**6d**[e]	**6e**[g]	**6f**[e]	**6g**[e]	SN-38 (**4**)[f]	lamellarin D (**5**)[e]
Breast	MCF-7	76	110	55	37	41	13	110	3.0	<10
CNS	U251	27	9.1	100	29	29	<10	71	2.8	<10
Colon	HCT-116	33	33	310	78	67	37	120	23	<10
Lung	NCI-H522	<10	4.7	82	21	14	<10	<10	3.7	<10
Melanoma	LOX-IMVI	20	5.5	180	35	25	<10	24	5.3	<10
Ovarian	SK-OV-3	83	38	1600	230	500	250	470	23	38
Renal	ACHN	14	3.8	44	26	15	<10	28	5.9	<10
Stomach	MKN28	84	64	2300	230	560	130	360	110	50
Prostate	DU-145	20	4.7	110	28	28	<10	24	4.3	<10
MG-MID[b]		100	47.9	794	182	363	129	224	40.7	41.7
Delta[c]		1	1.09	1.26	1.26	1.42	1.11	1.35	1.26	0.62
Range[d]		2.72	2.42	2.46	3.46	3.58	4	2.59	2.91	2.30

[a] Concentration for 50% inhibition of cell growth relative to control. Cell growth was determined according to sulforhodamine B assay.
[b] Mean GI_{50} value in all cell lines tested.
[c] Difference in log GI_{50} value between the most sensitive cells and the MG-MID value.
[d] Difference in log GI_{50} value between the most and least sensitive cells.
[e] The GI_{50} value was obtained from the dose-response curve in the test range between 10^{-4} and 10^{-8} M.
[f] The GI_{50} value was obtained from the dose-response curve in the test range between 10^{-5} and 10^{-9} M.
[g] The GI_{50} value was obtained from the dose-response curve in the test range between 10^{-6} and 10^{-10} M.

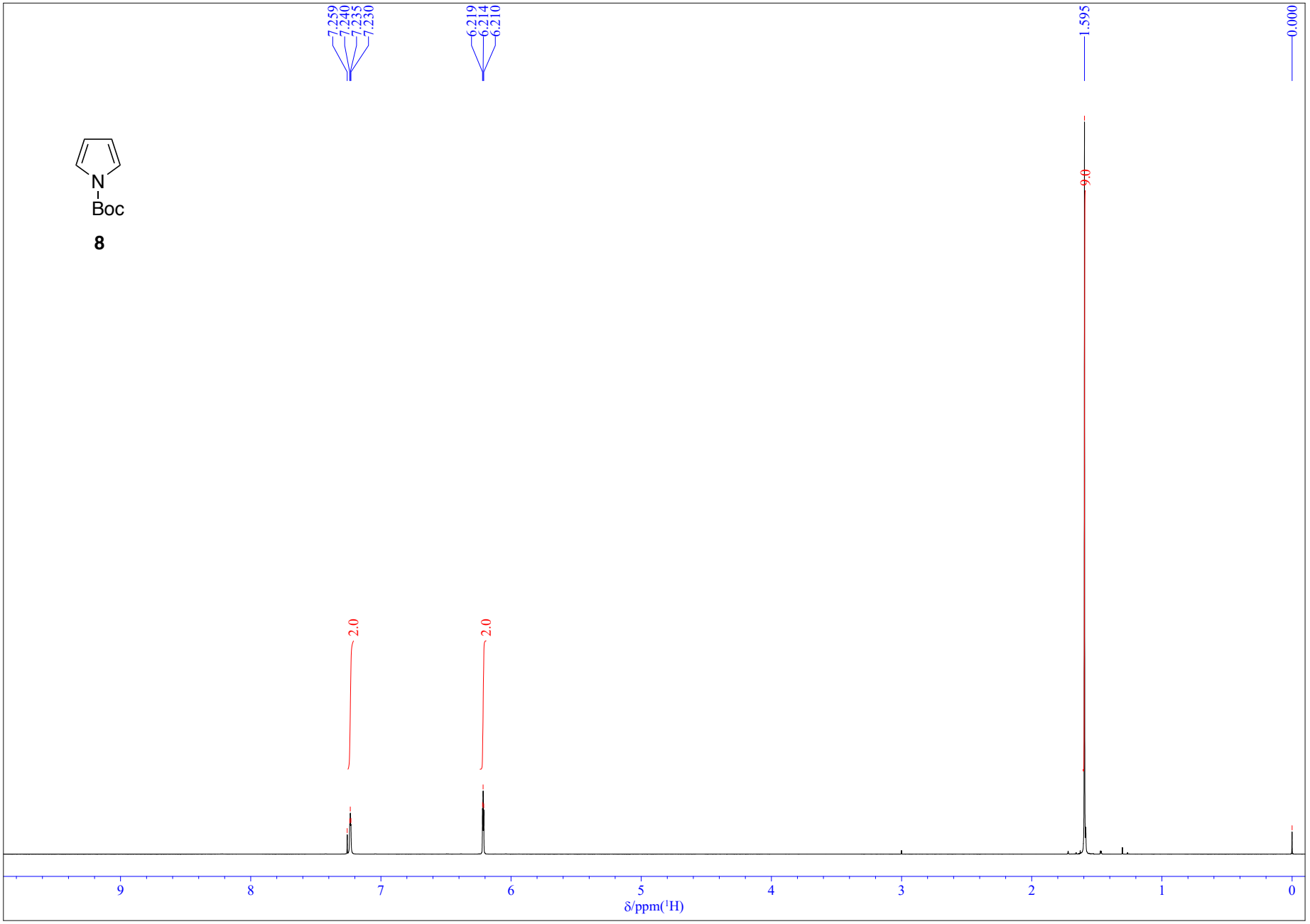


Figure S1. ^{1}H NMR spectrum of compound **8** (500 MHz, $CDCl_3$).

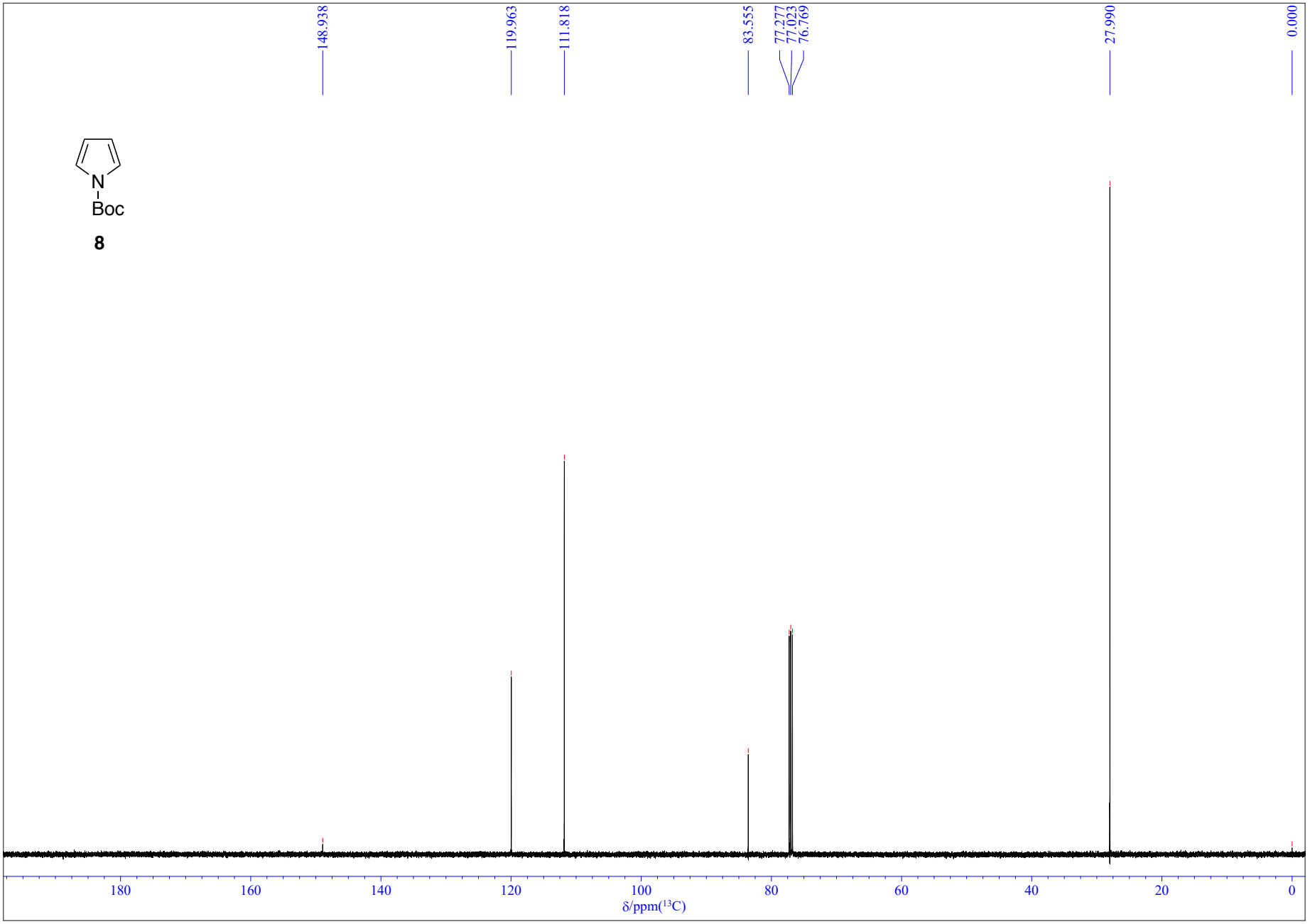


Figure S2. ^{13}C NMR spectrum of compound **8** (126 MHz, $CDCl_3$).

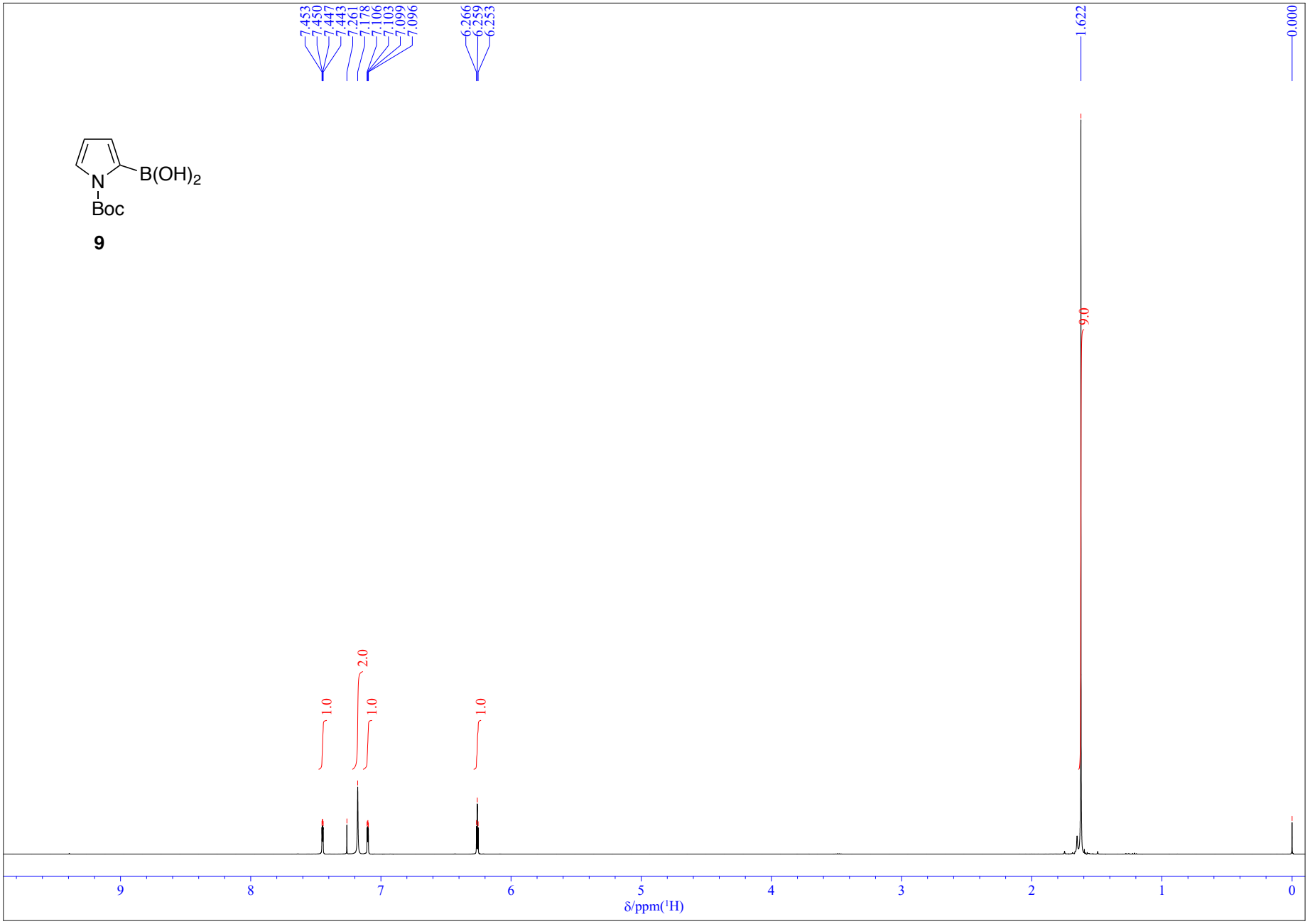


Figure S3. ^{1}H NMR spectrum of compound **9** (500 MHz, $CDCl_3$).

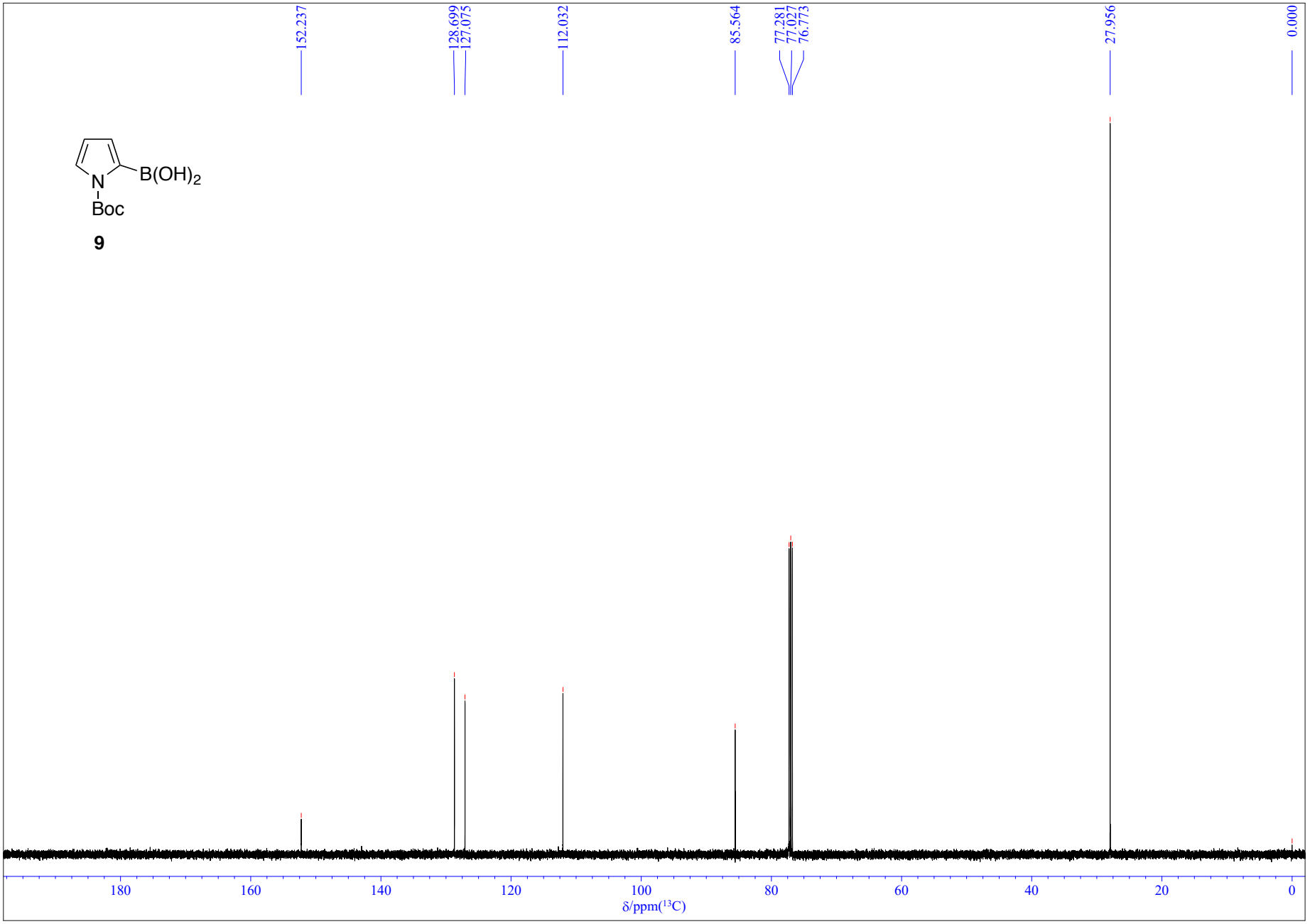


Figure S4. ^{13}C NMR spectrum of compound **9** (126 MHz, $CDCl_3$).

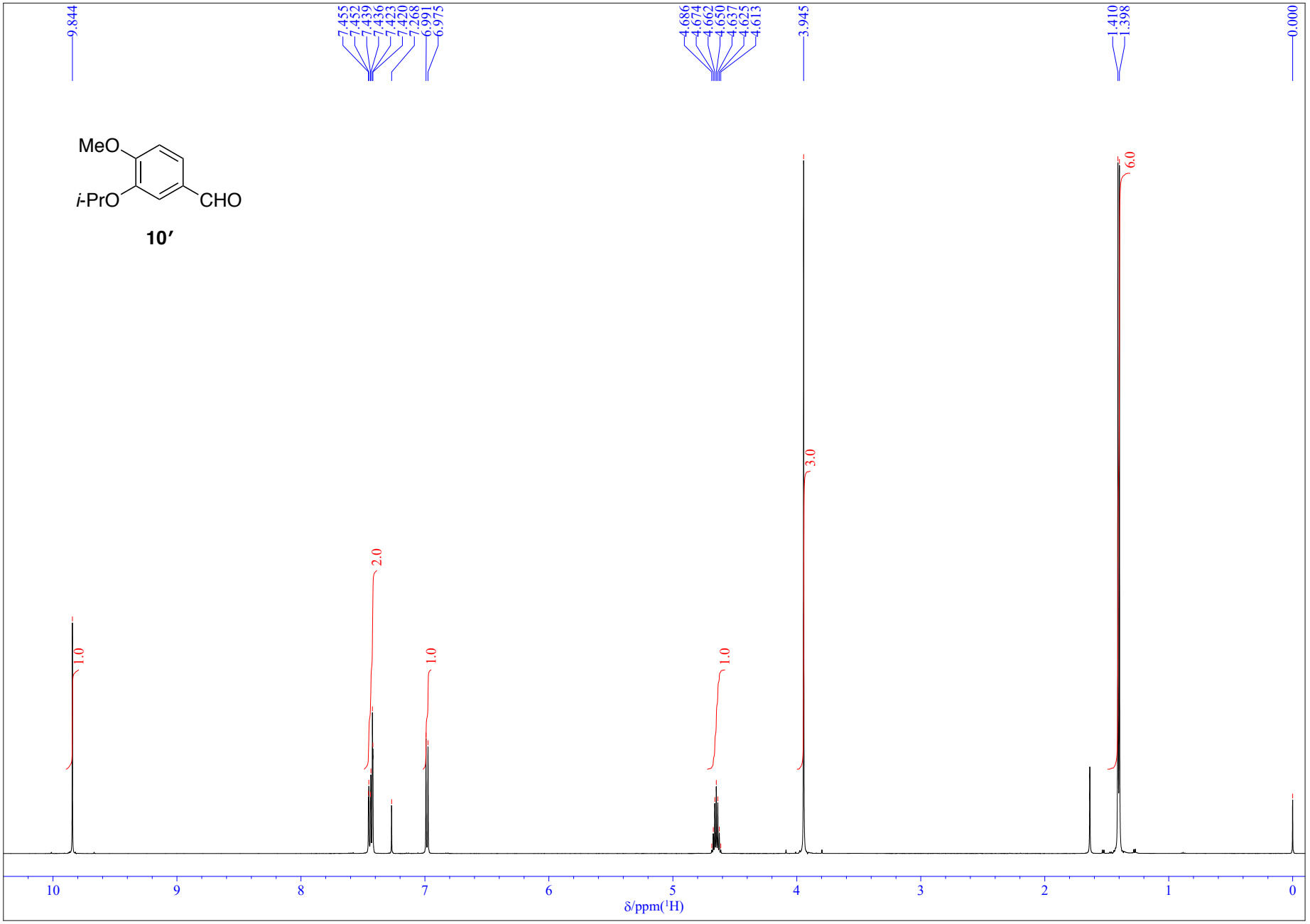


Figure S5. ^{1}H NMR spectrum of compound **10′** (500 MHz, $CDCl_3$).

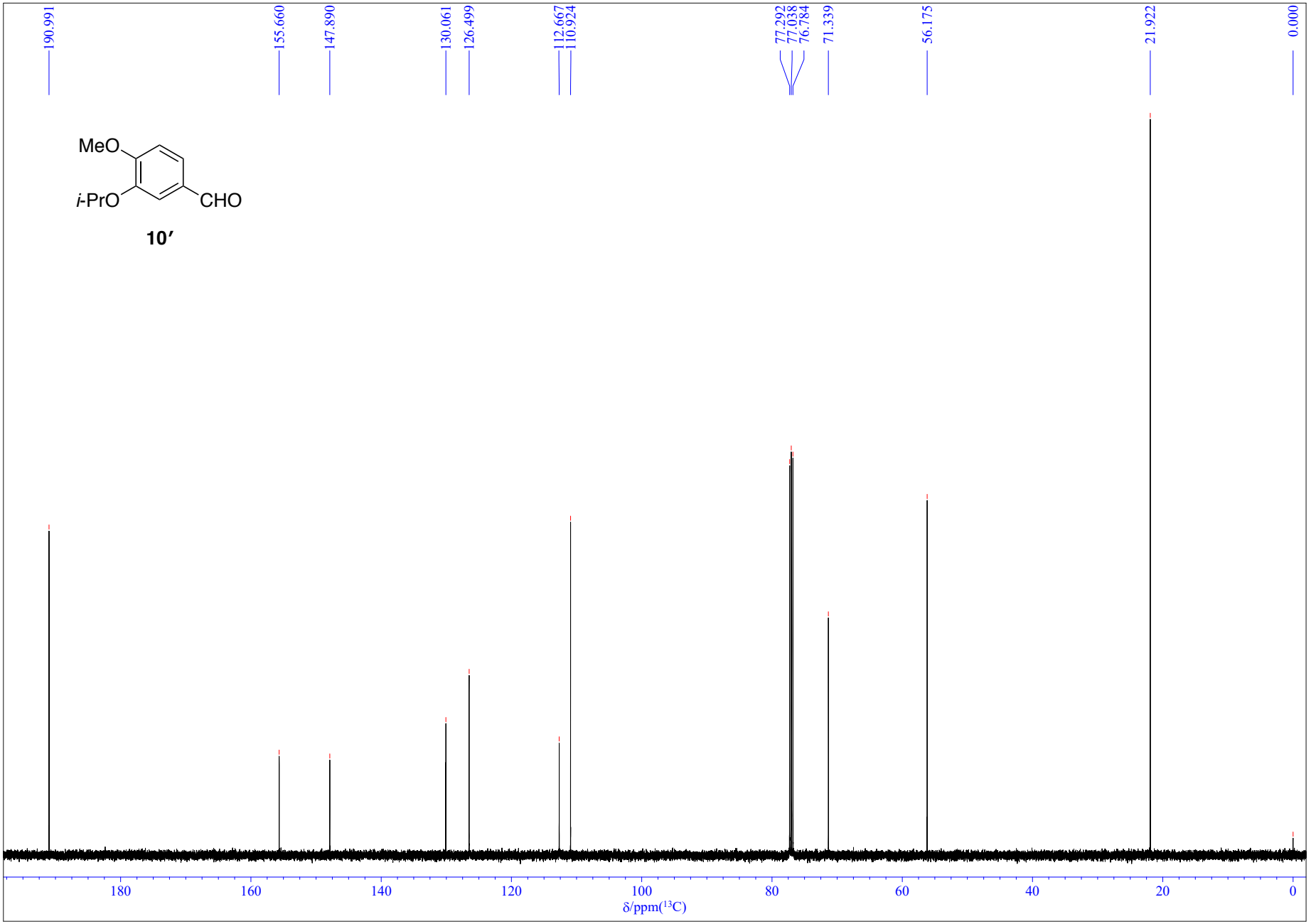


Figure S6. ^{13}C NMR spectrum of compound **10′** (126 MHz, $CDCl_3$).

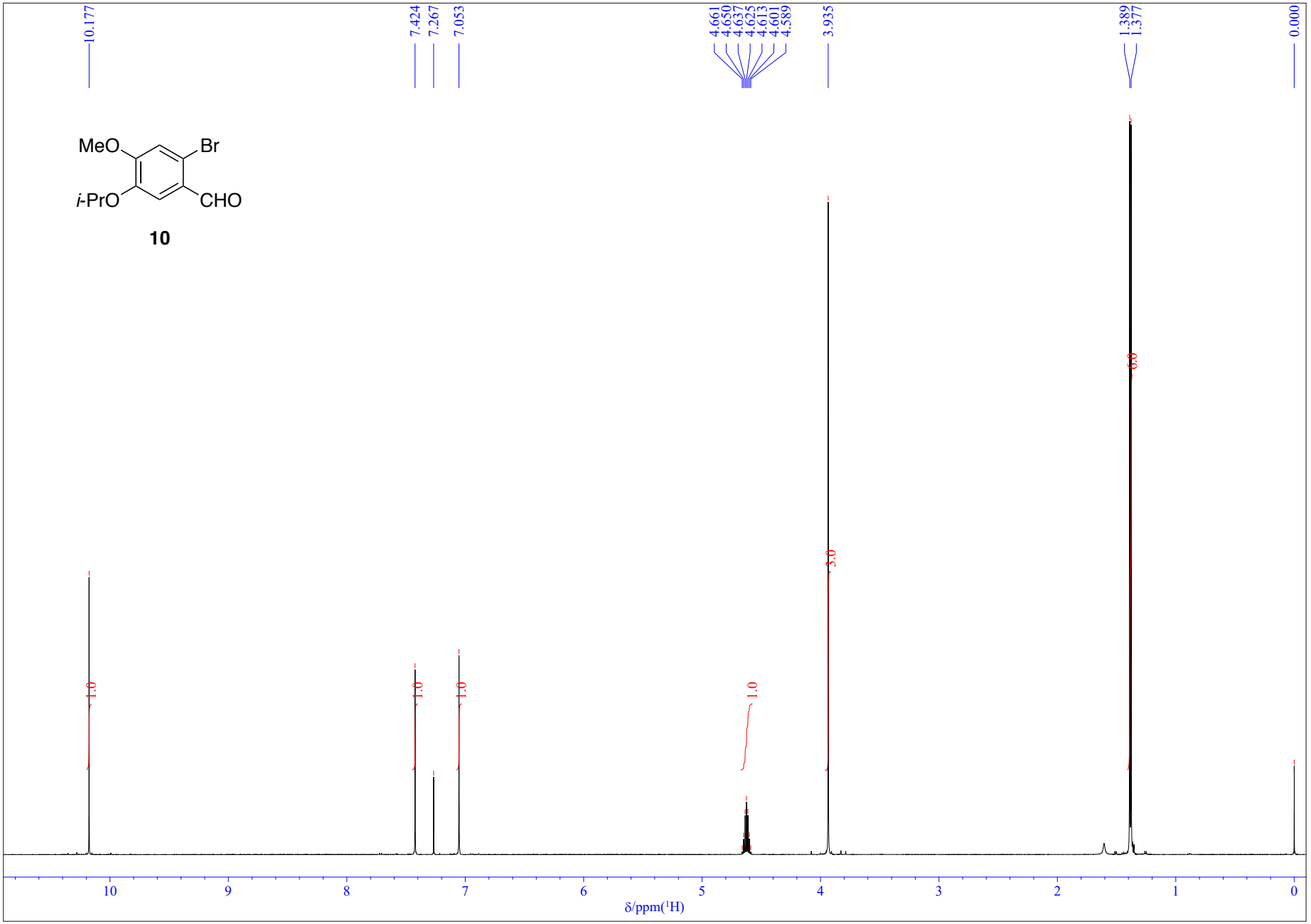


Figure S7. ^{1}H NMR spectrum of compound **10** (500 MHz, $CDCl_3$).

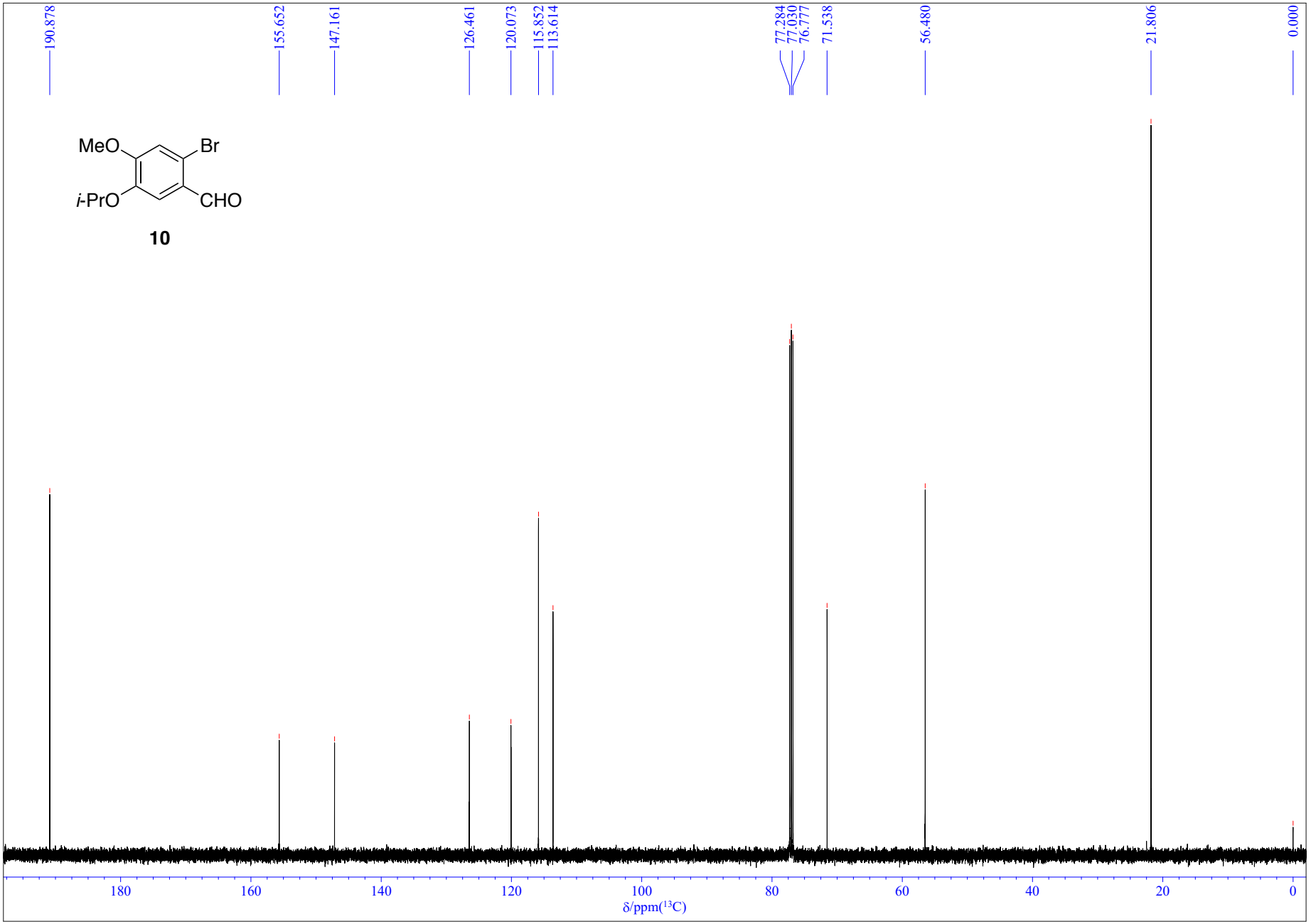


Figure S8. ^{13}C NMR spectrum of compound **10** (126 MHz, $CDCl_3$).

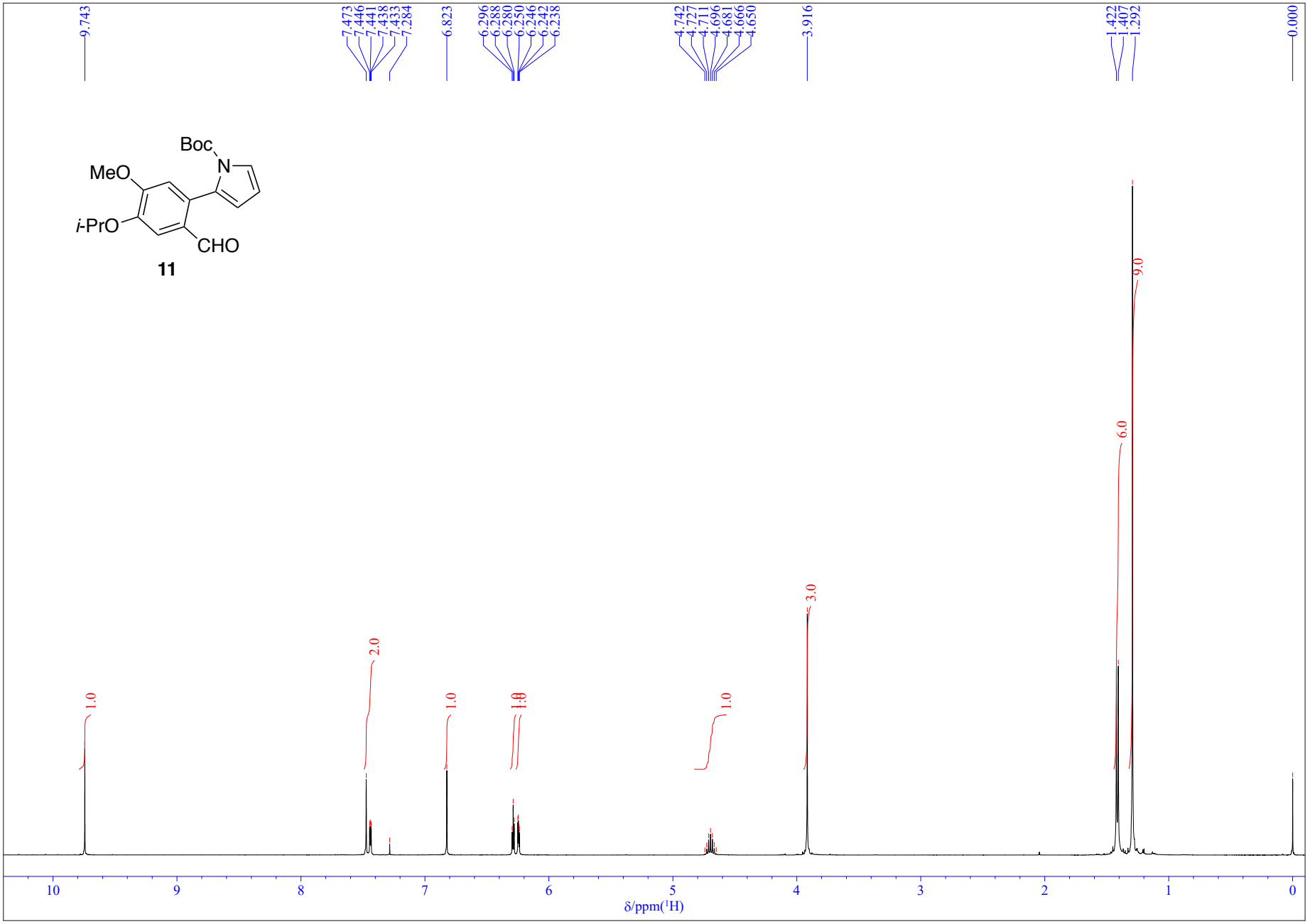


Figure S9. ^{1}H NMR spectrum of compound **11** (400 MHz, $CDCl_3$).

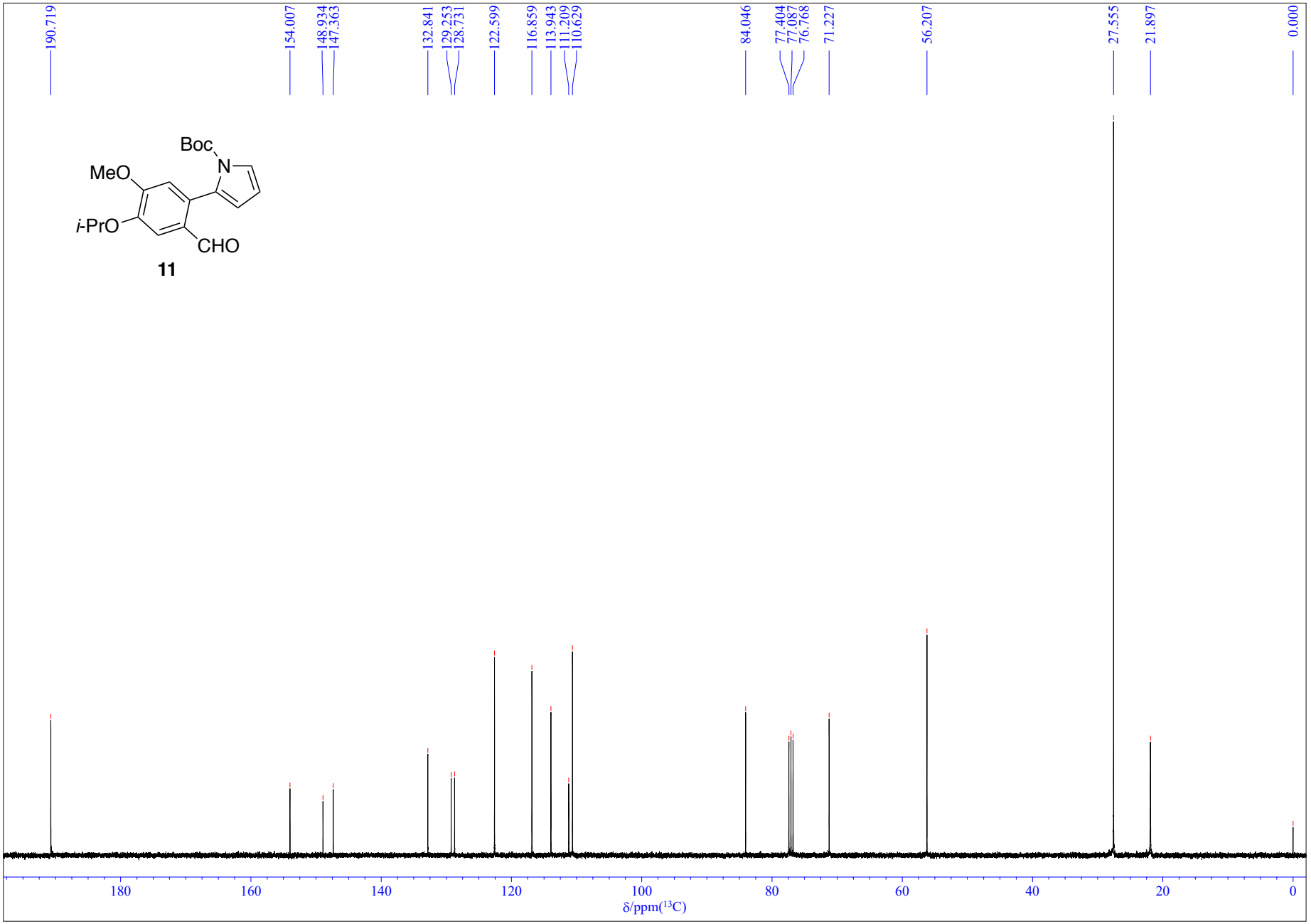


Figure S10. ^{13}C NMR spectrum of compound **11** (100 MHz, $CDCl_3$).

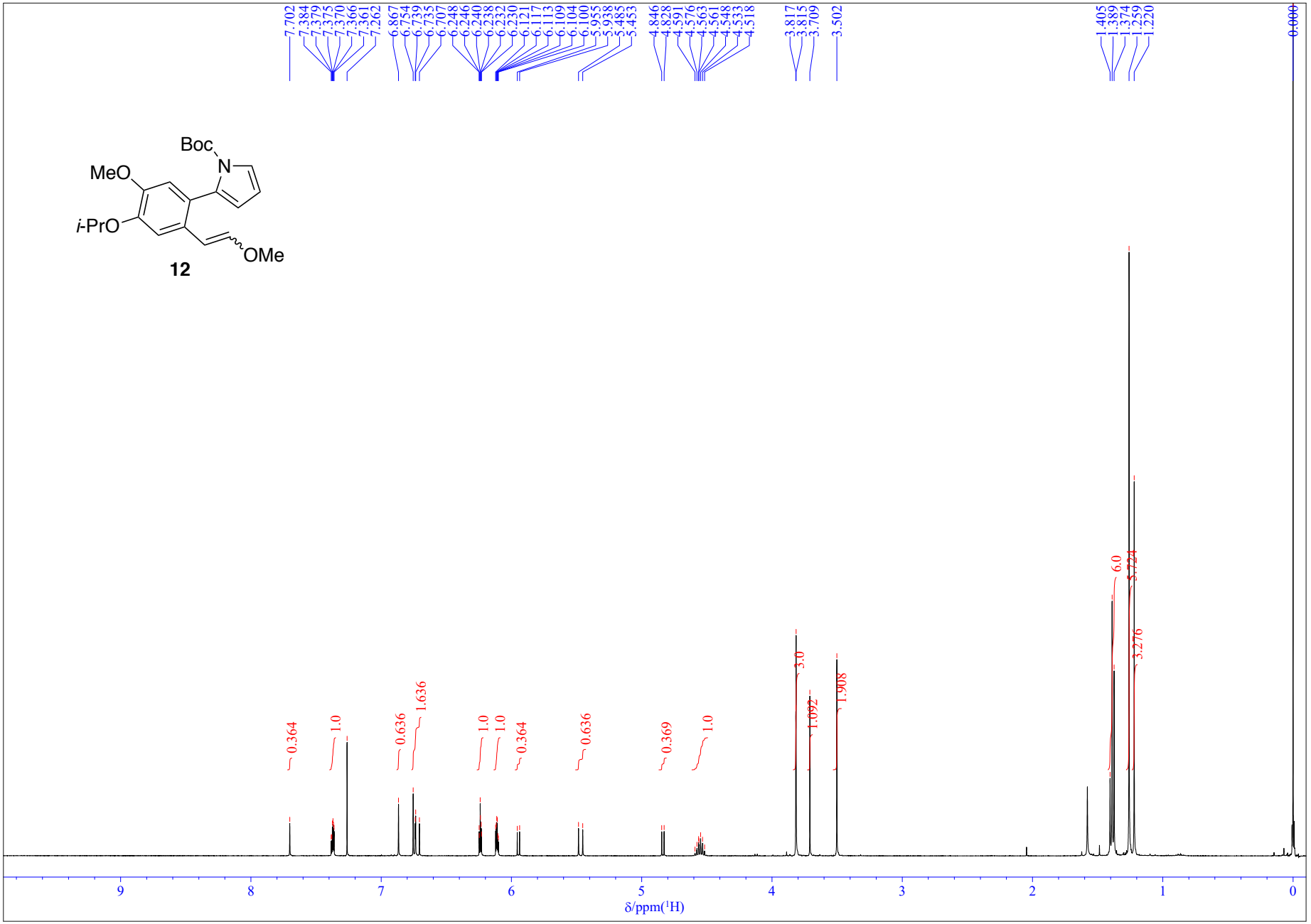


Figure S11. ^{1}H NMR spectrum of compound **12** (400 MHz, $CDCl_3$).

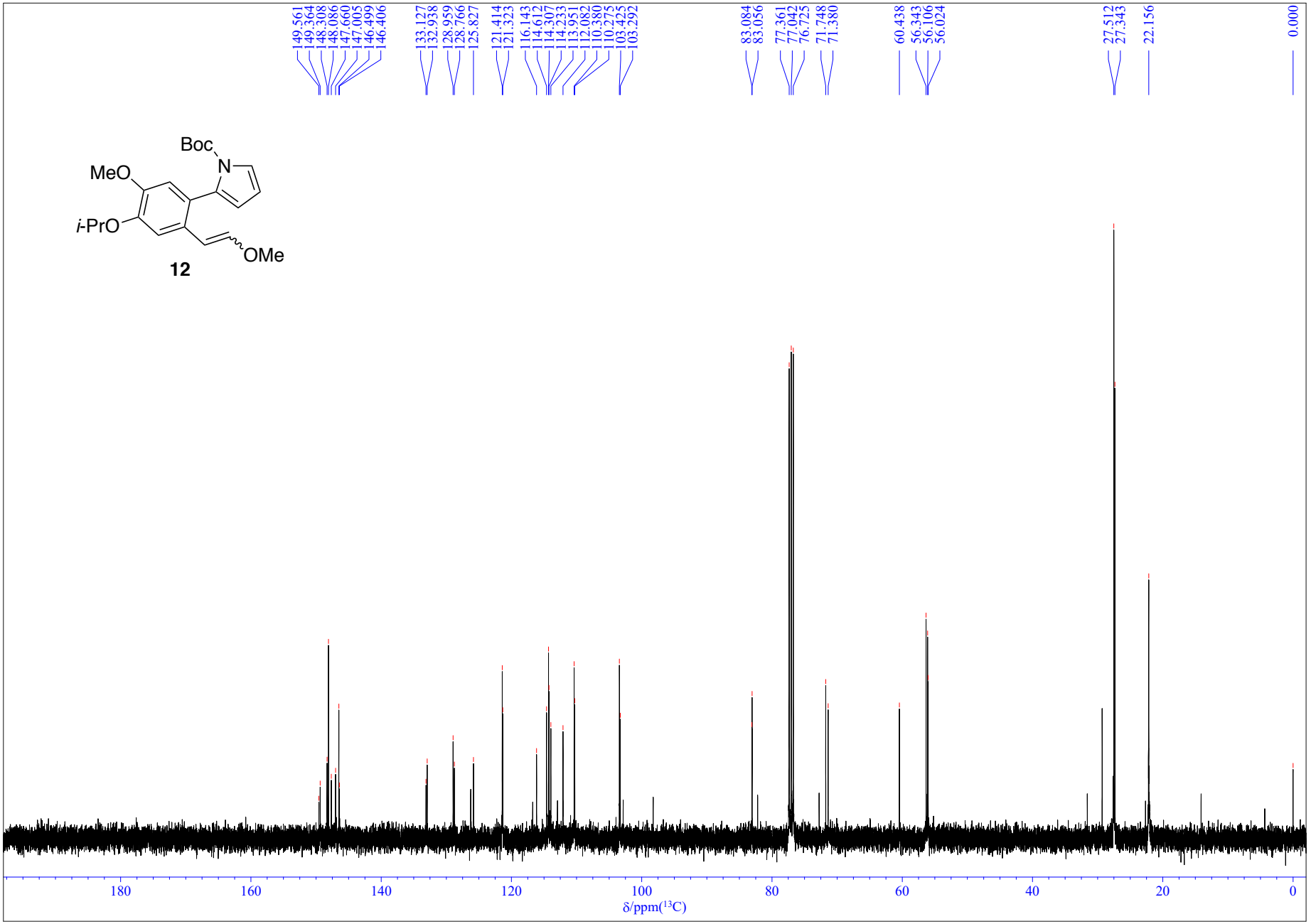


Figure S12. ^{13}C NMR spectrum of compound **12** (100 MHz, $CDCl_3$).

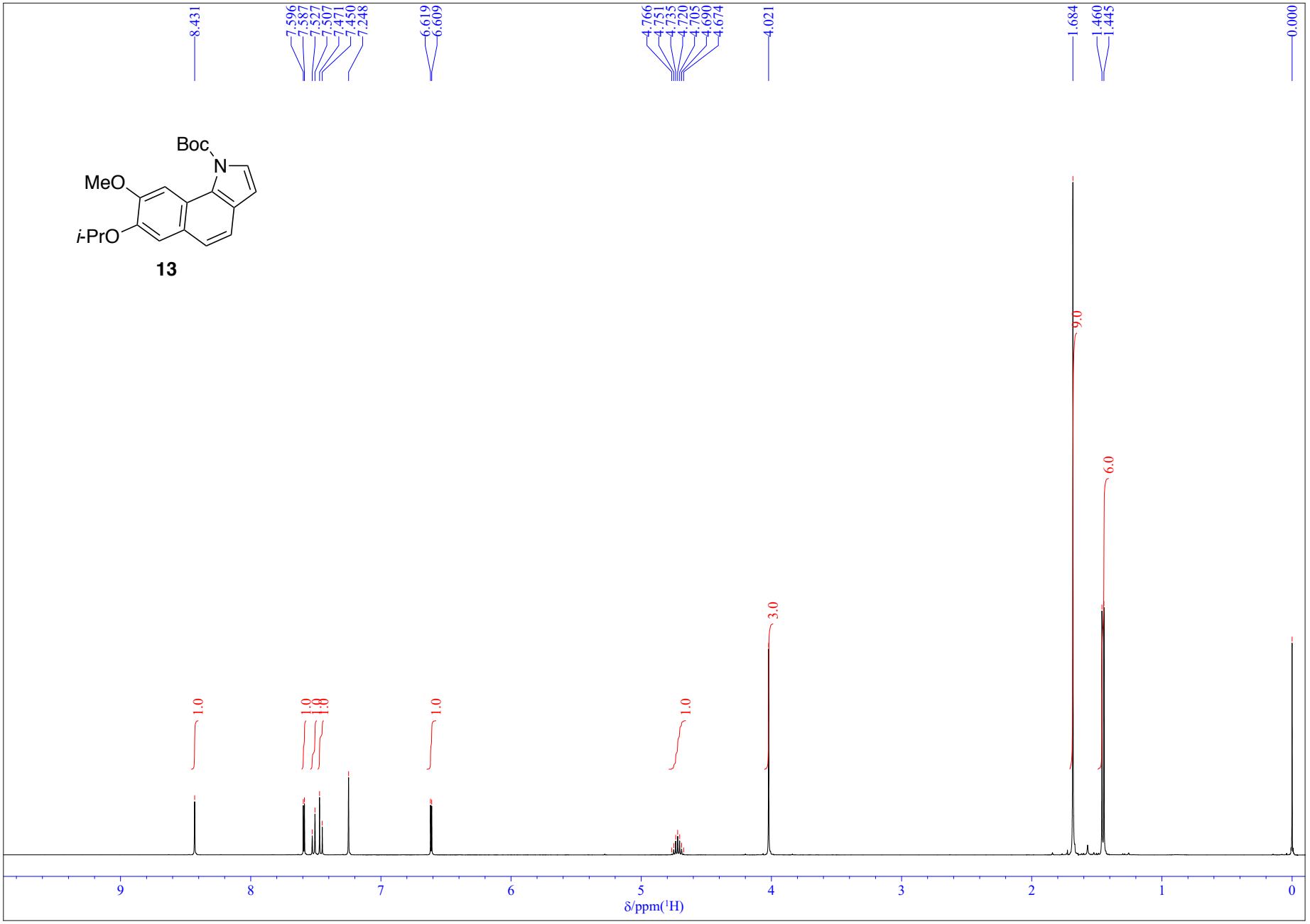


Figure S13. ^{1}H NMR spectrum of compound **13** (400 MHz, $CDCl_3$).

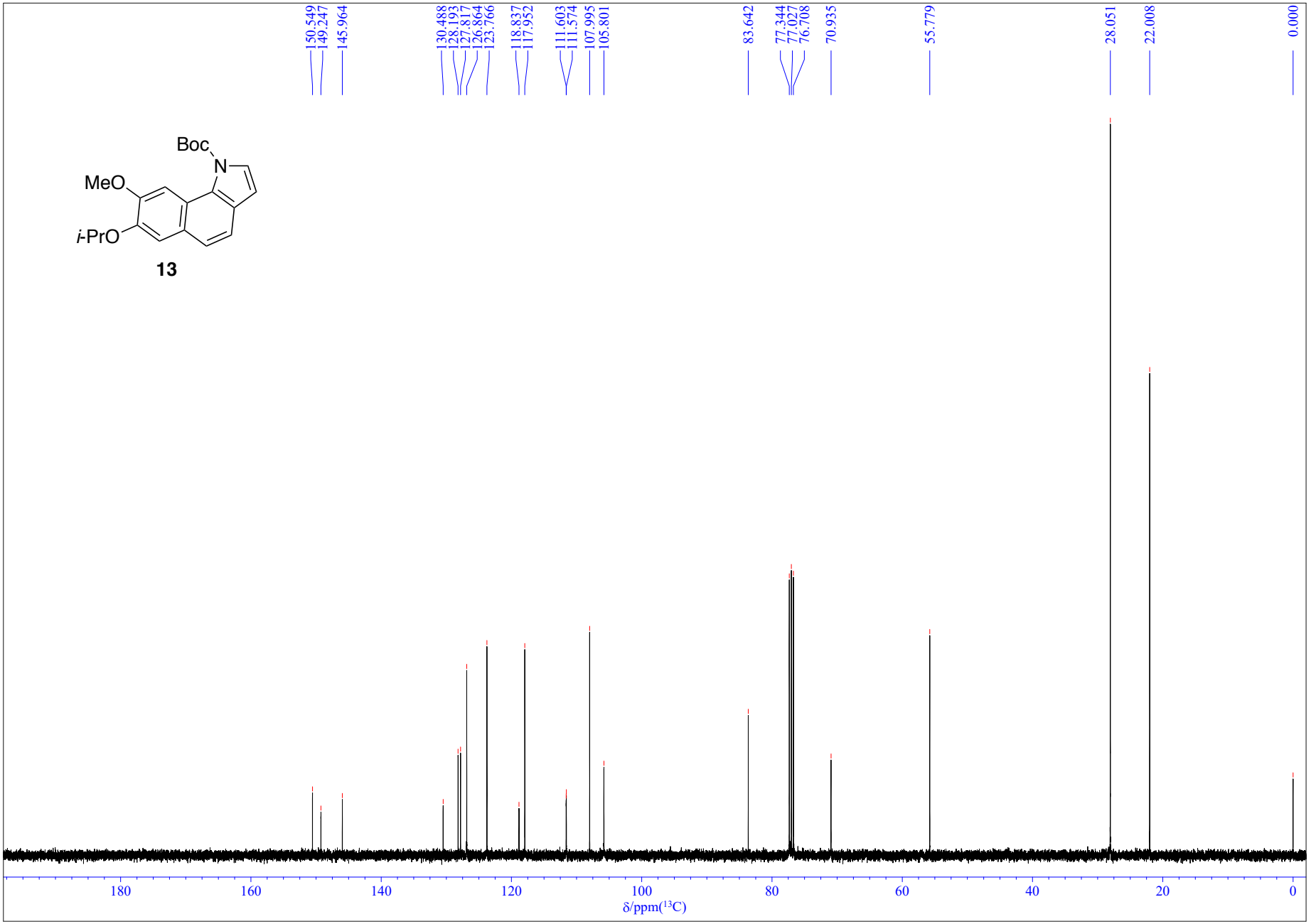


Figure S14. ^{13}C NMR spectrum of compound **13** (100 MHz, $CDCl_3$).

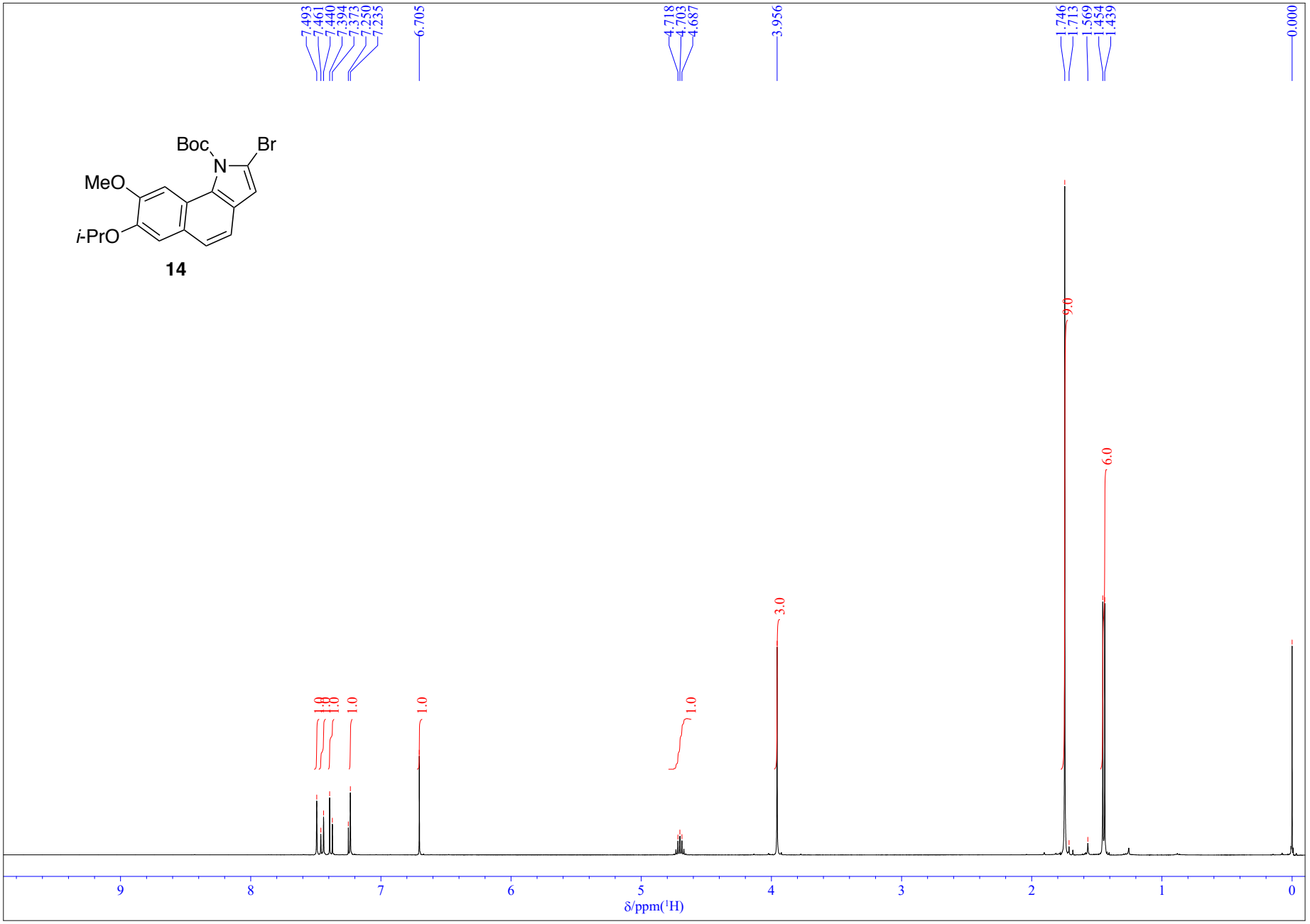


Figure S15. ^{1}H NMR spectrum of compound **14** (400 MHz, $CDCl_3$).

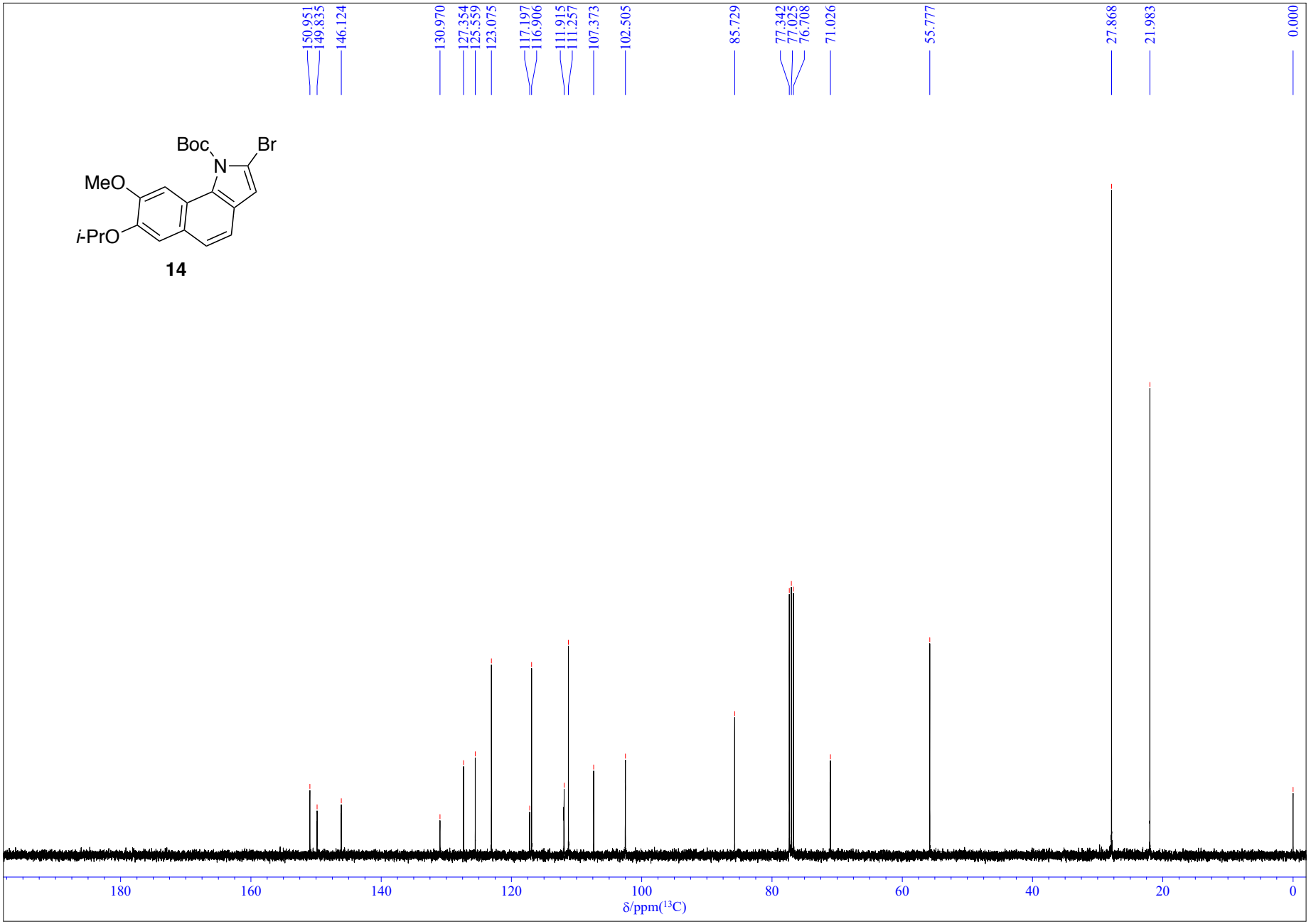


Figure S16. ^{13}C NMR spectrum of compound **14** (100 MHz, $CDCl_3$).

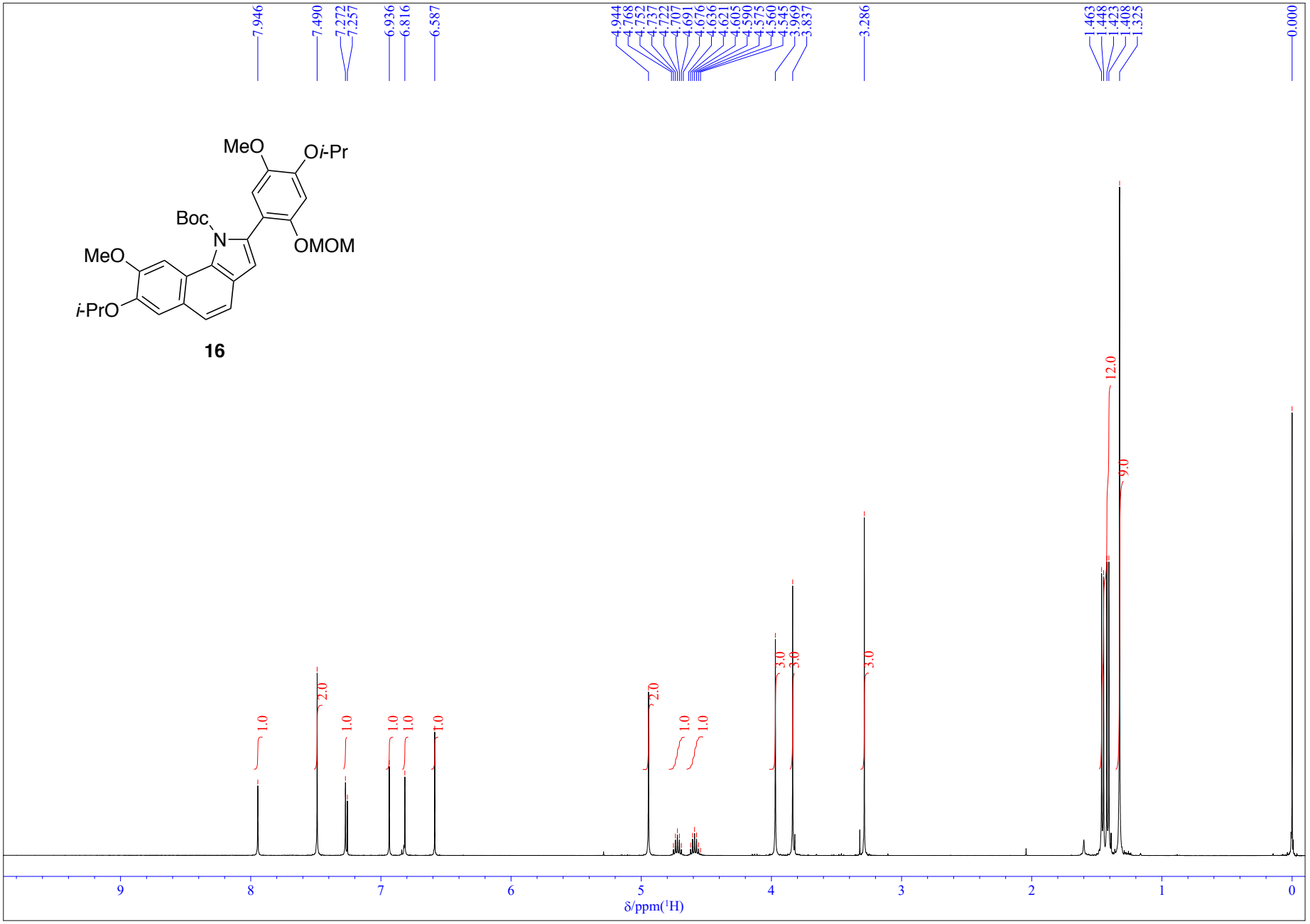


Figure S17. ^{1}H NMR spectrum of compound **16** (400 MHz, $CDCl_3$).

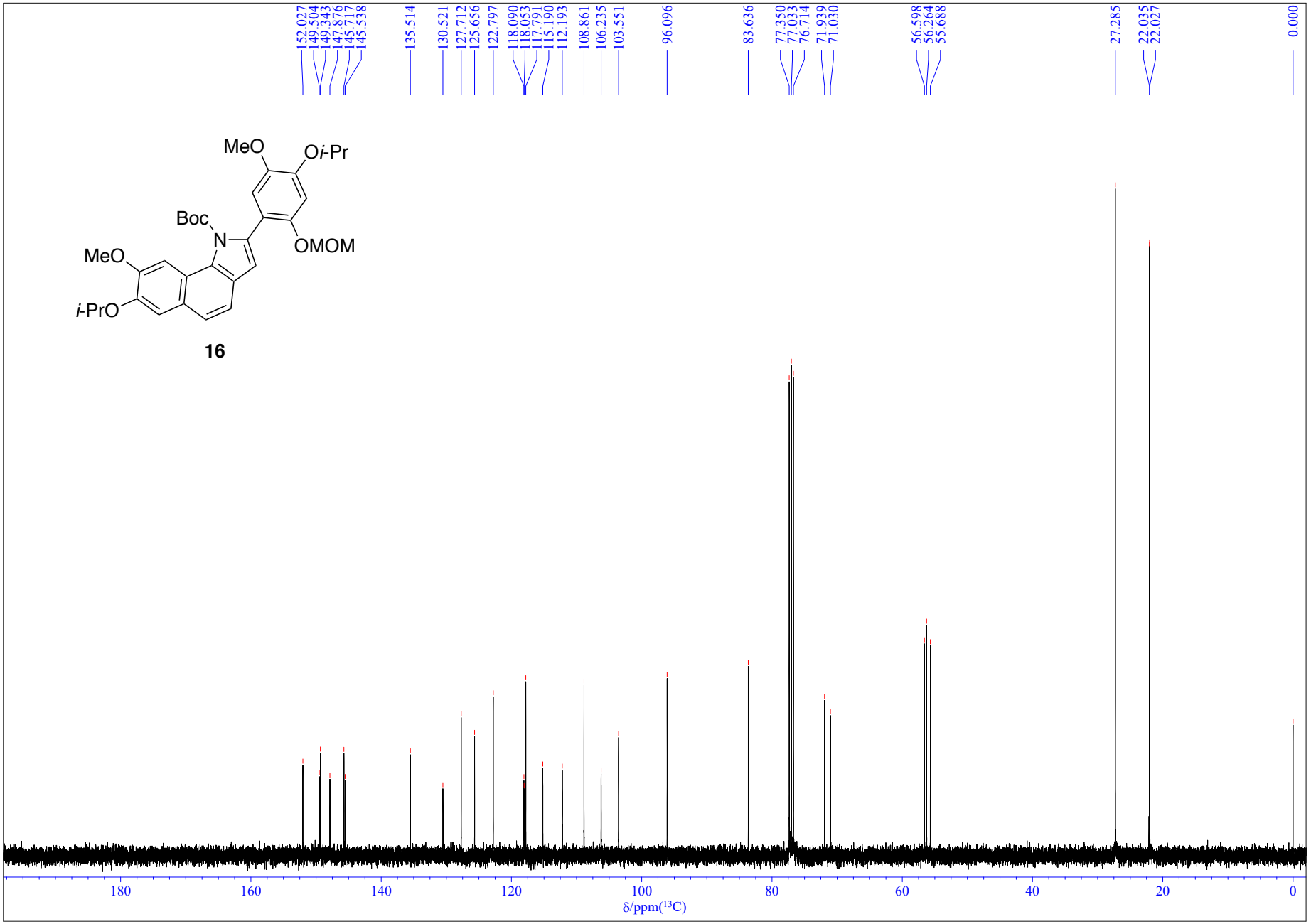


Figure S18. ^{13}C NMR spectrum of compound **16** (100 MHz, $CDCl_3$).

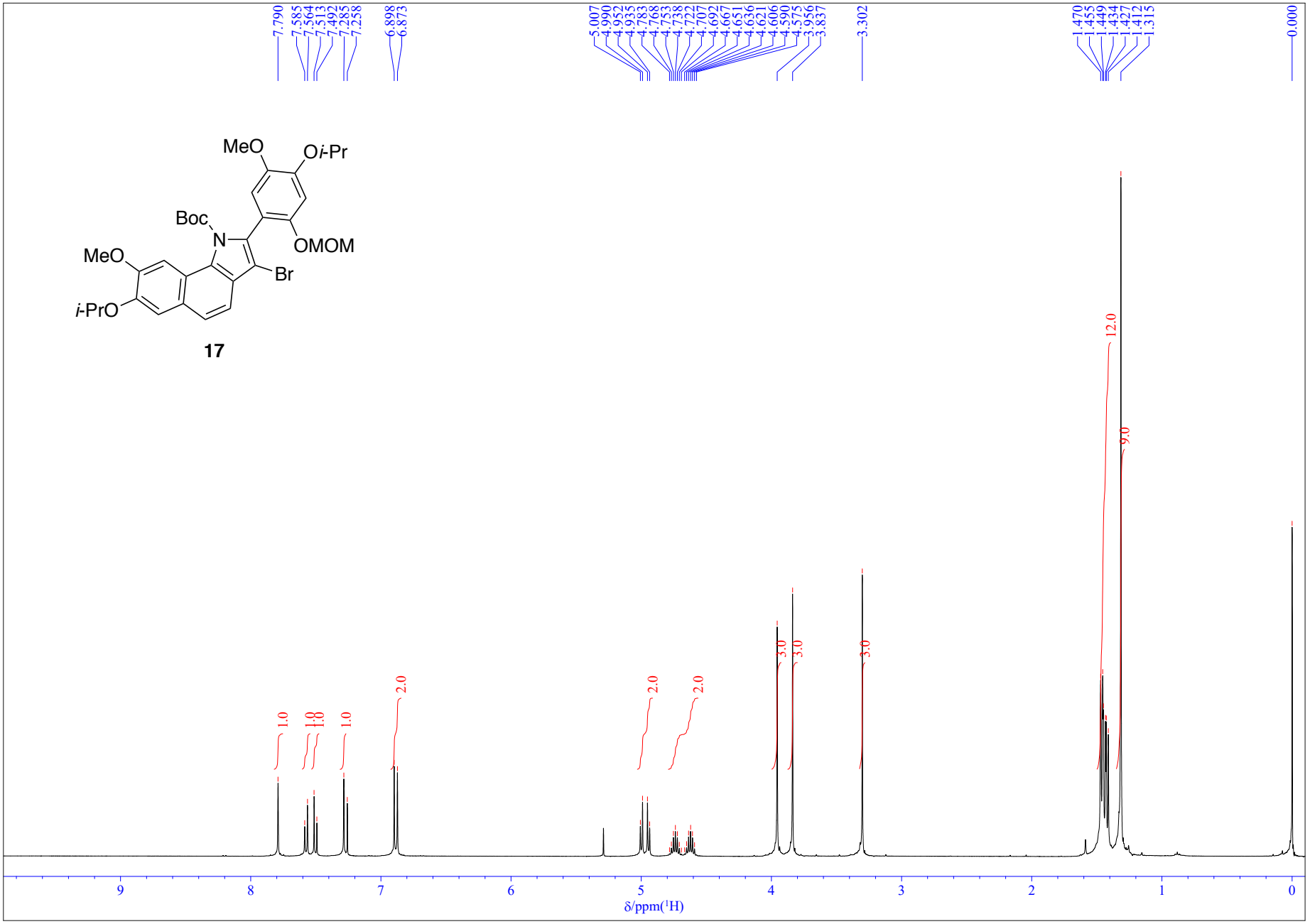


Figure S19. ^{1}H NMR spectrum of compound **17** (400 MHz, $CDCl_3$).

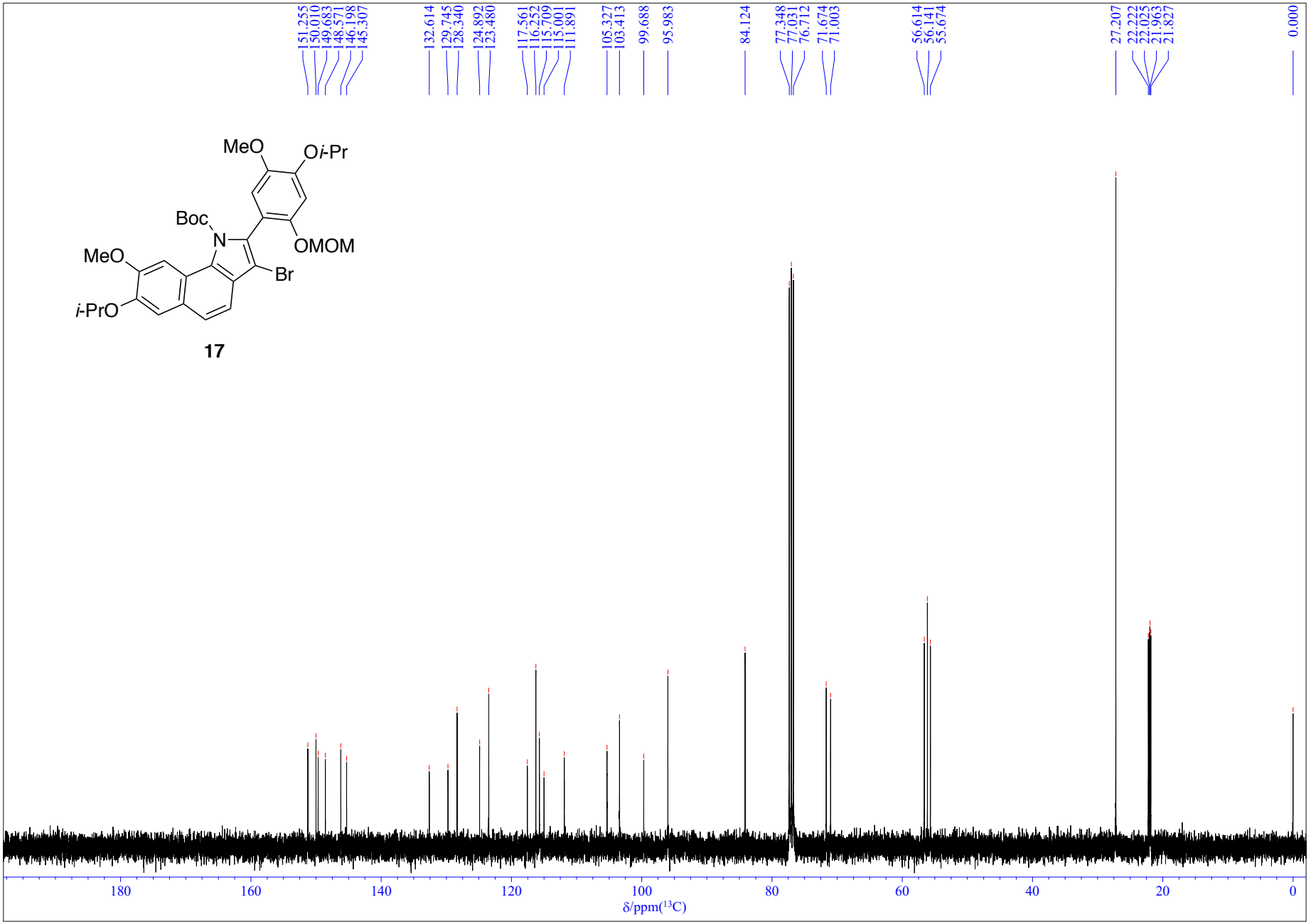


Figure S20. ^{13}C NMR spectrum of compound **17** (100 MHz, $CDCl_3$).

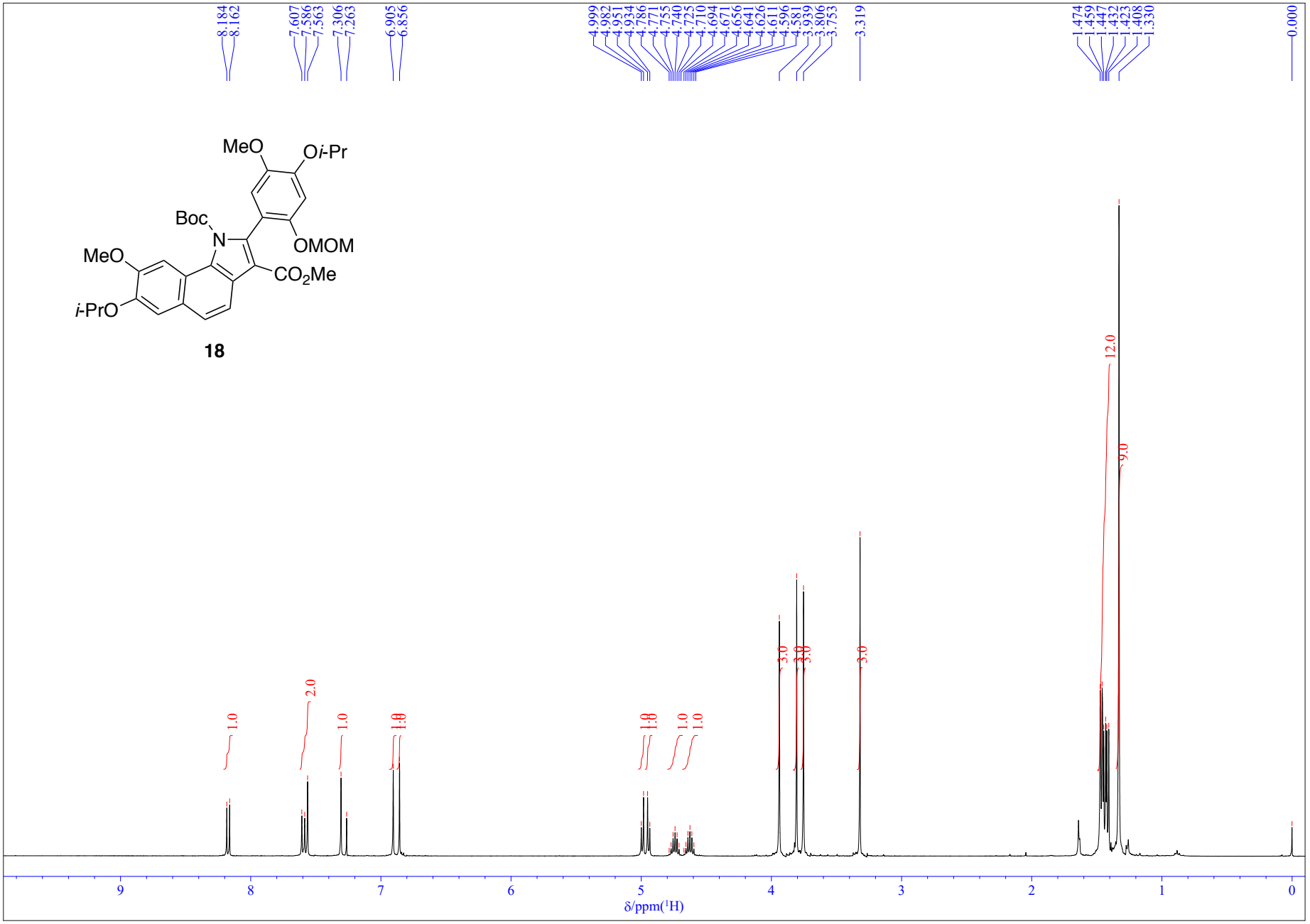


Figure S21. ^{1}H NMR spectrum of compound **18** (400 MHz, $CDCl_3$).

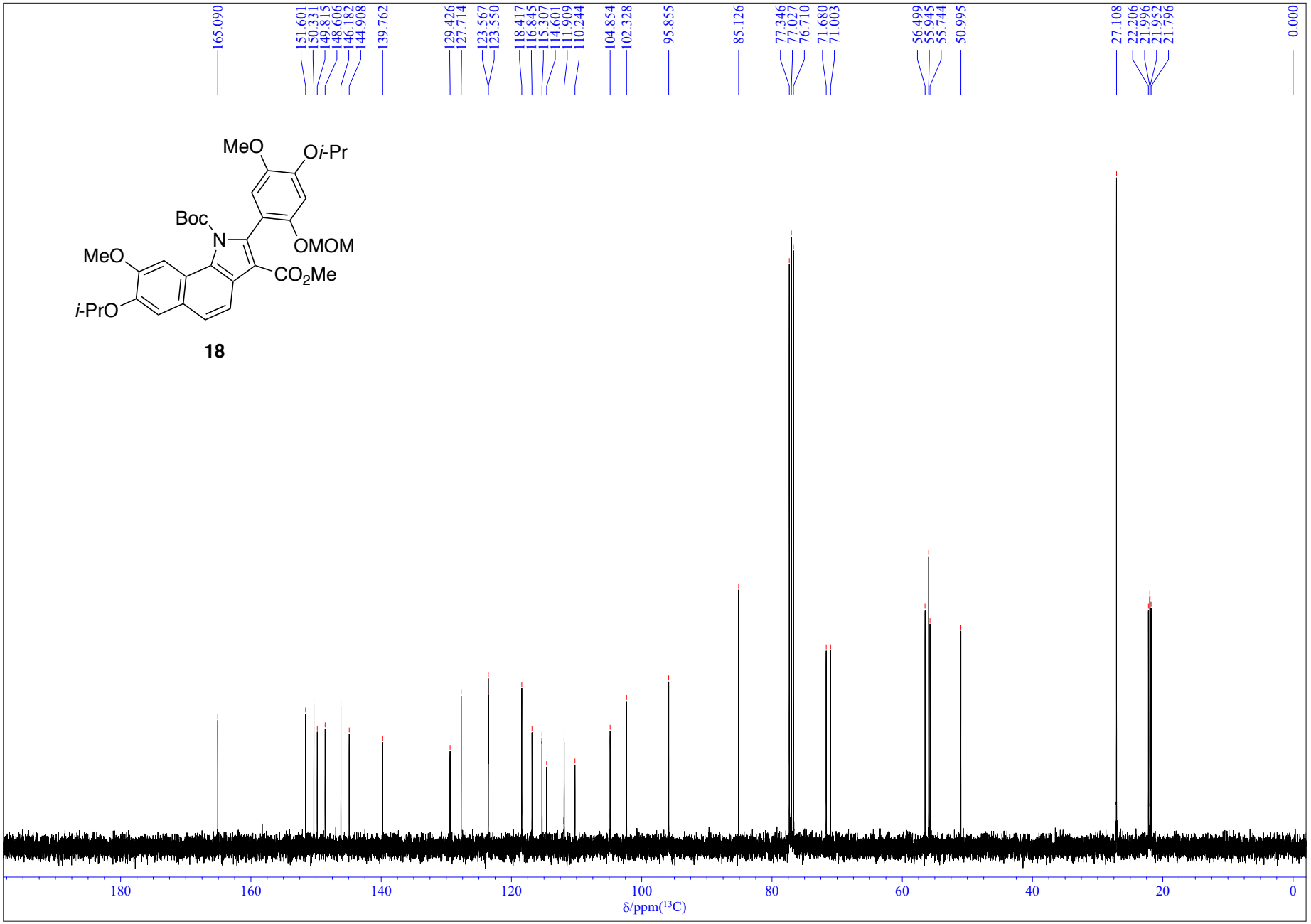


Figure S22. ^{13}C NMR spectrum of compound **18** (100 MHz, $CDCl_3$).

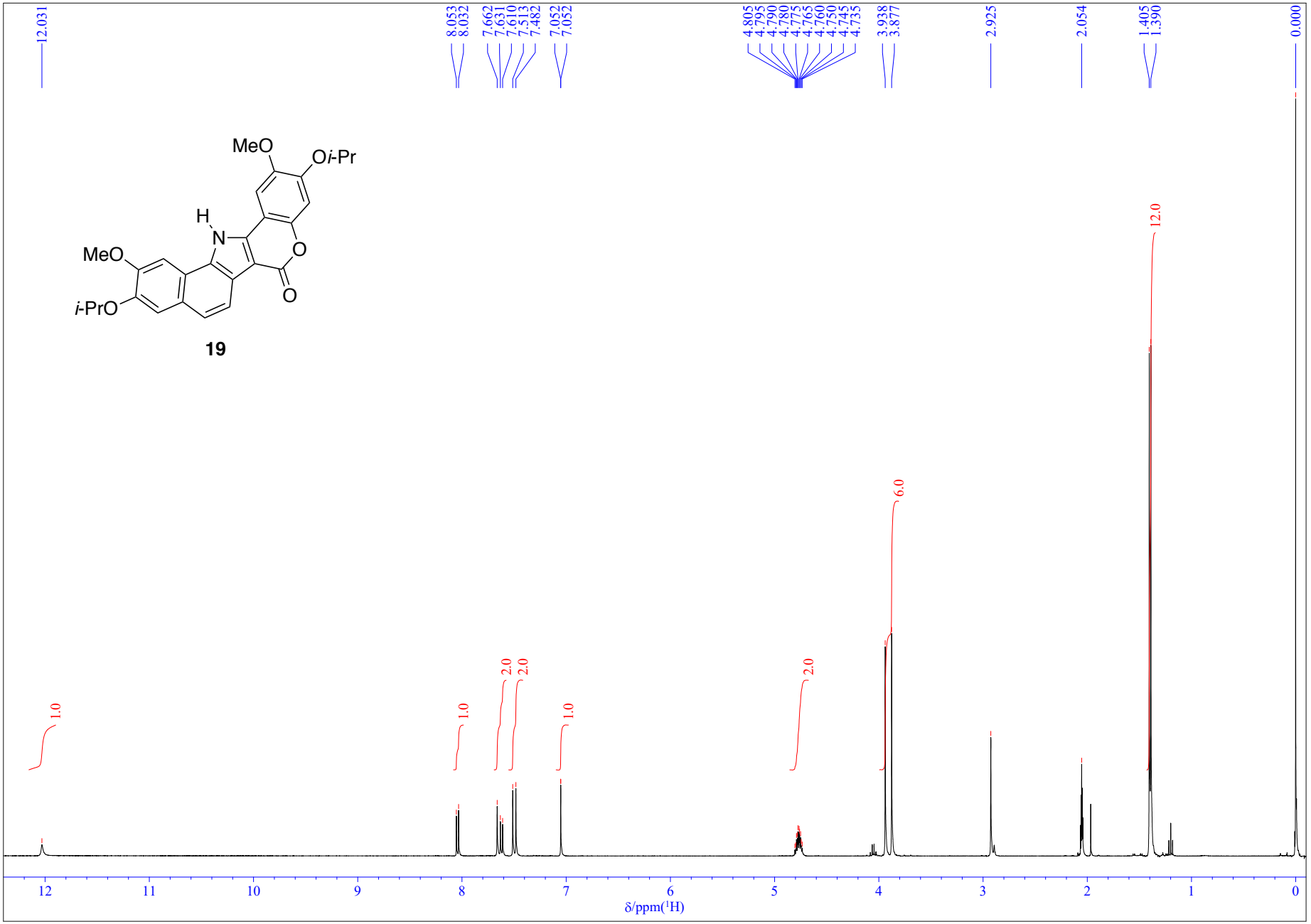


Figure S23. ^{1}H NMR spectrum of compound **19** (400 MHz, acetone-d_6).

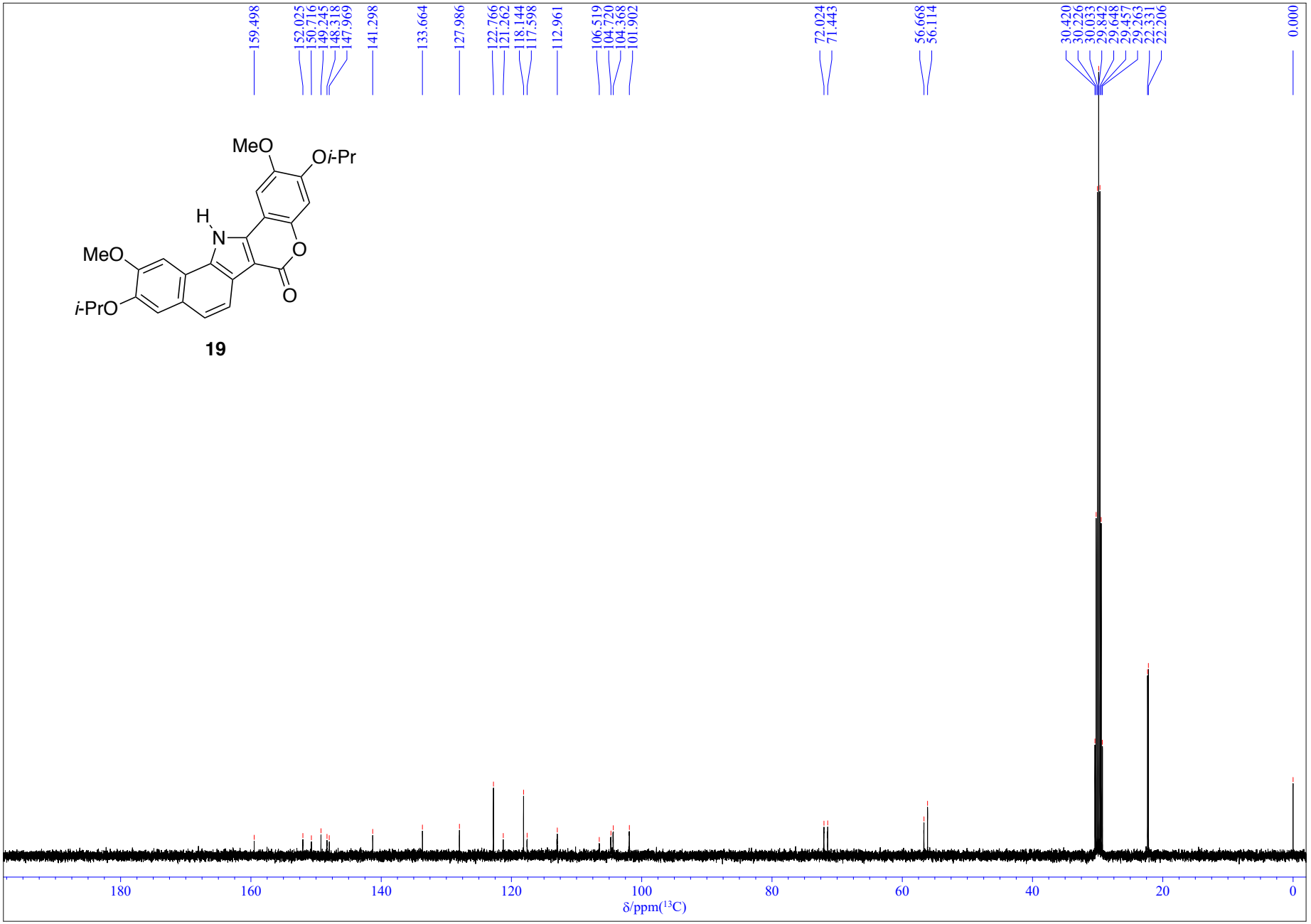


Figure S24. ^{13}C NMR spectrum of compound **19** (100 MHz, acetone-d_6).

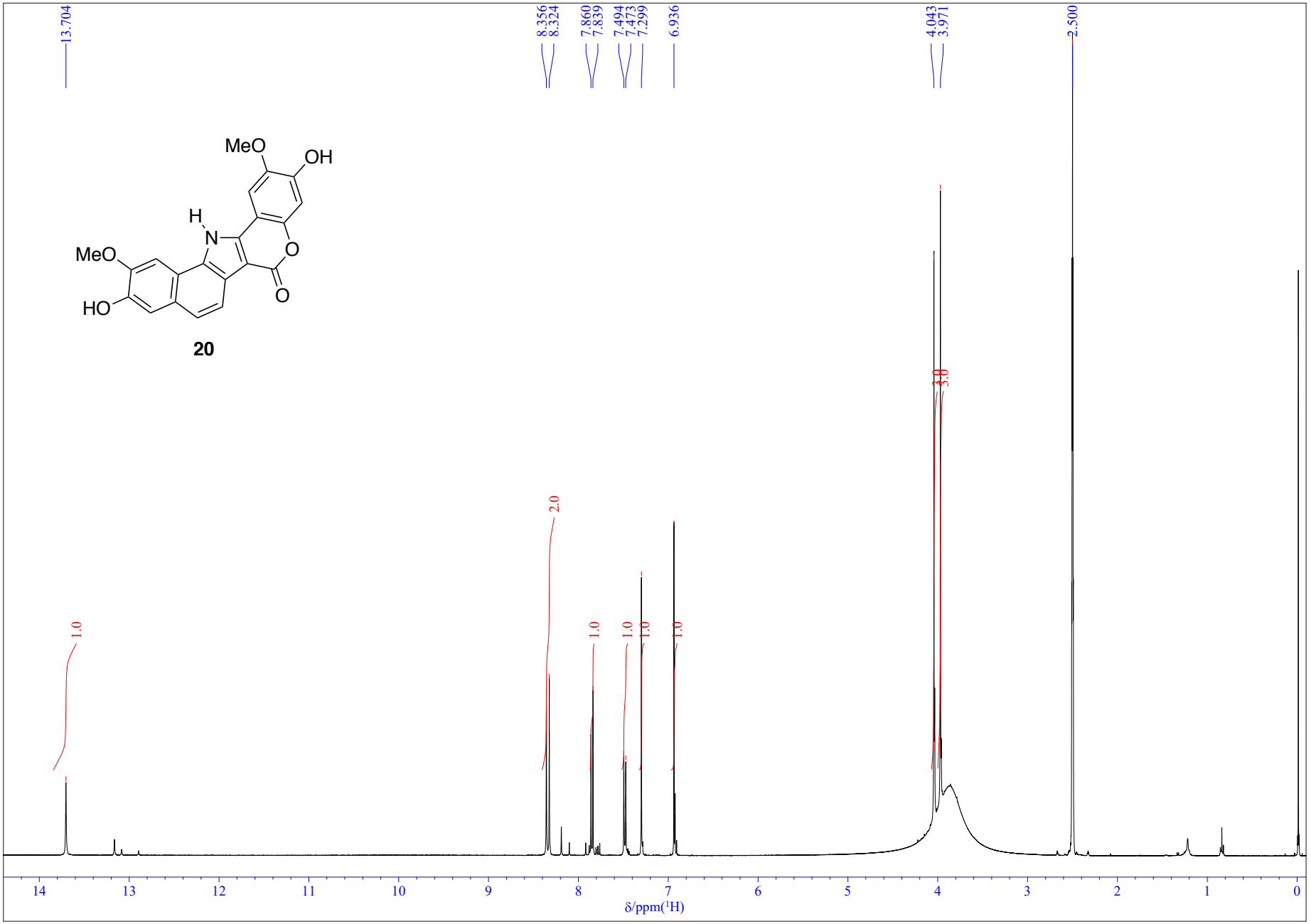


Figure S25. ^{1}H NMR spectrum of compound **20** (400 MHz, DMSO-d_6).

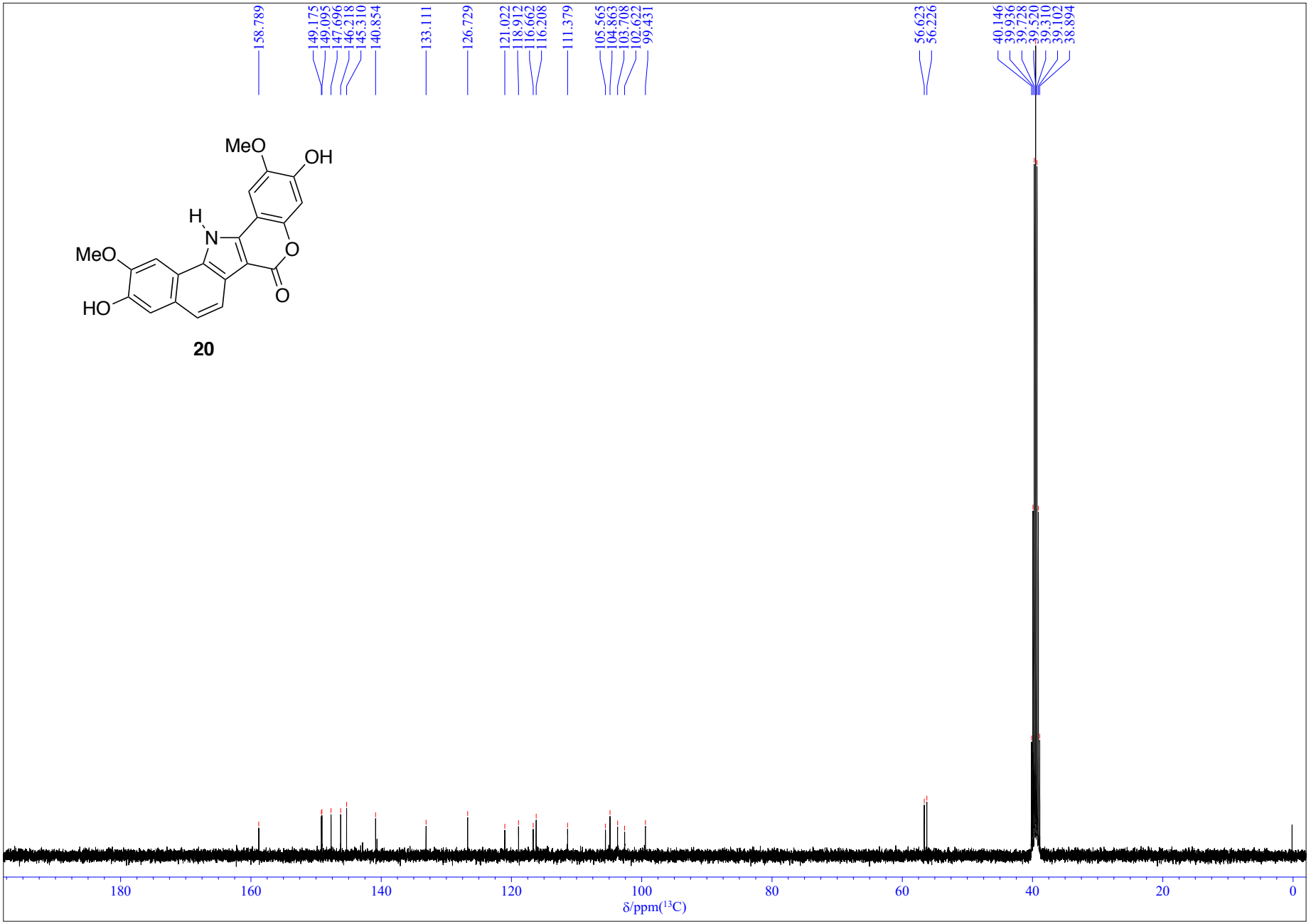


Figure S26. ^{13}C NMR spectrum of compound **20** (100 MHz, DMSO-d_6).

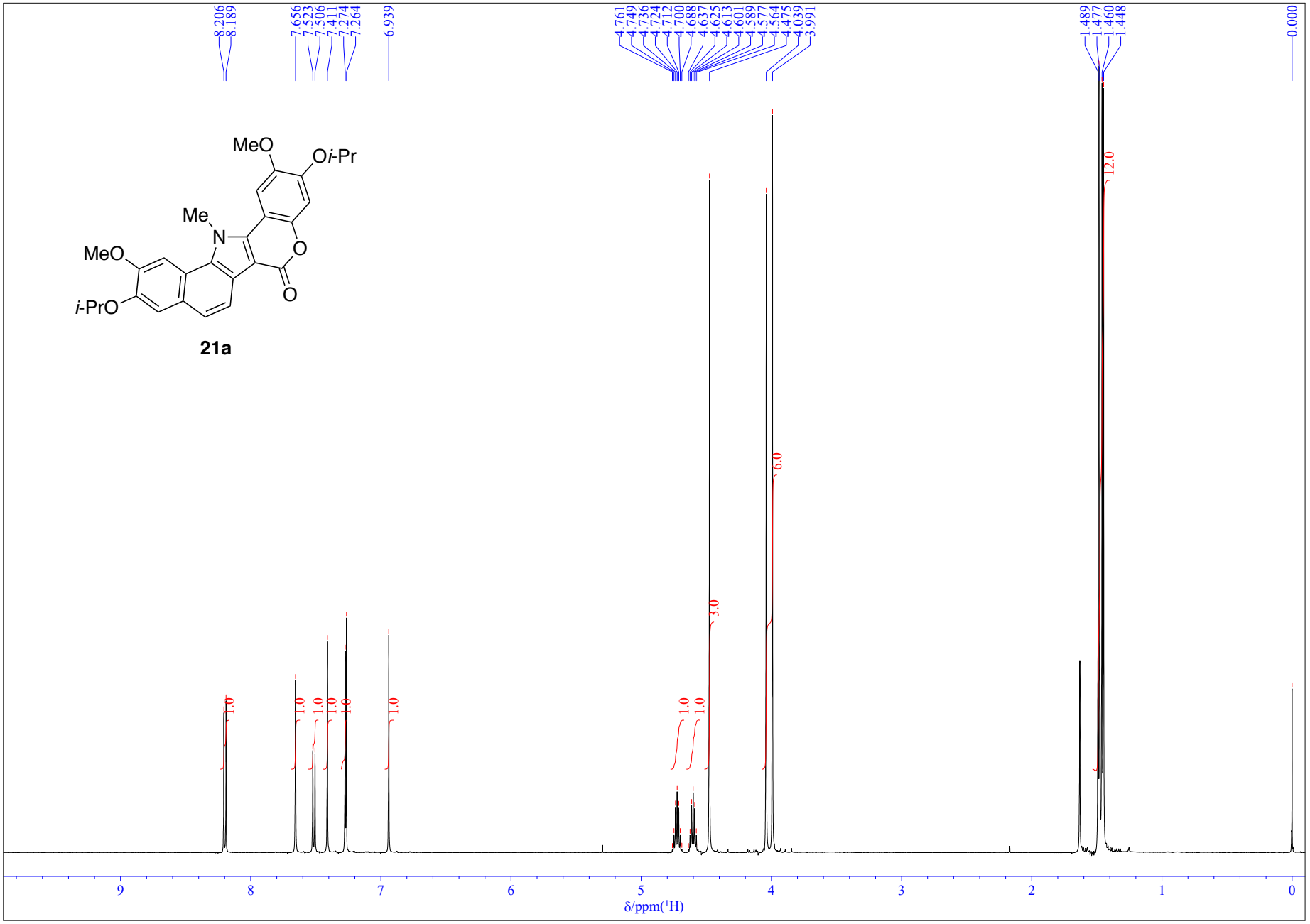


Figure S27. ^{1}H NMR spectrum of compound **21a** (500 MHz, $CDCl_3$).

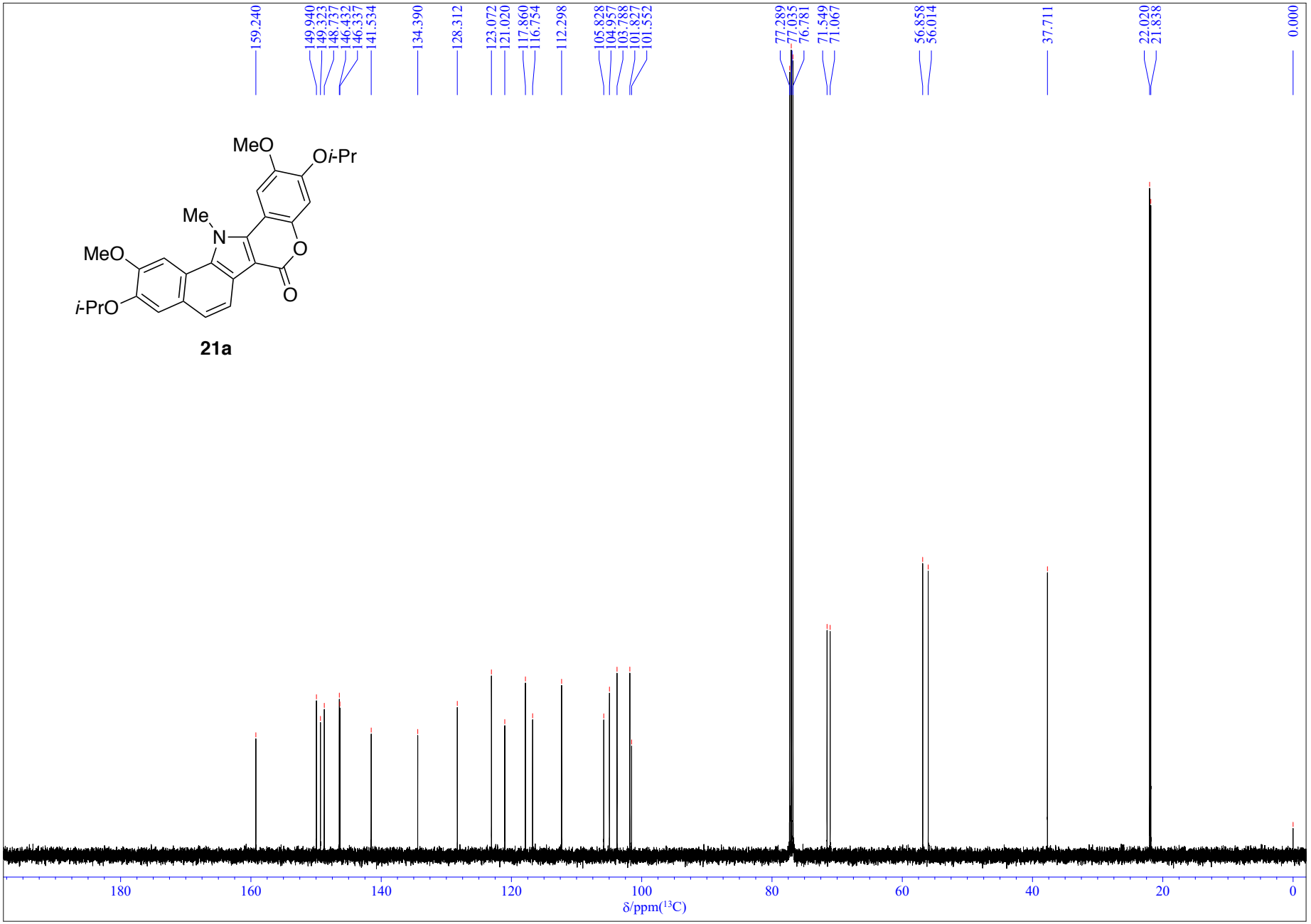


Figure S28. ^{13}C NMR spectrum of compound **21a** (126 MHz, $CDCl_3$).

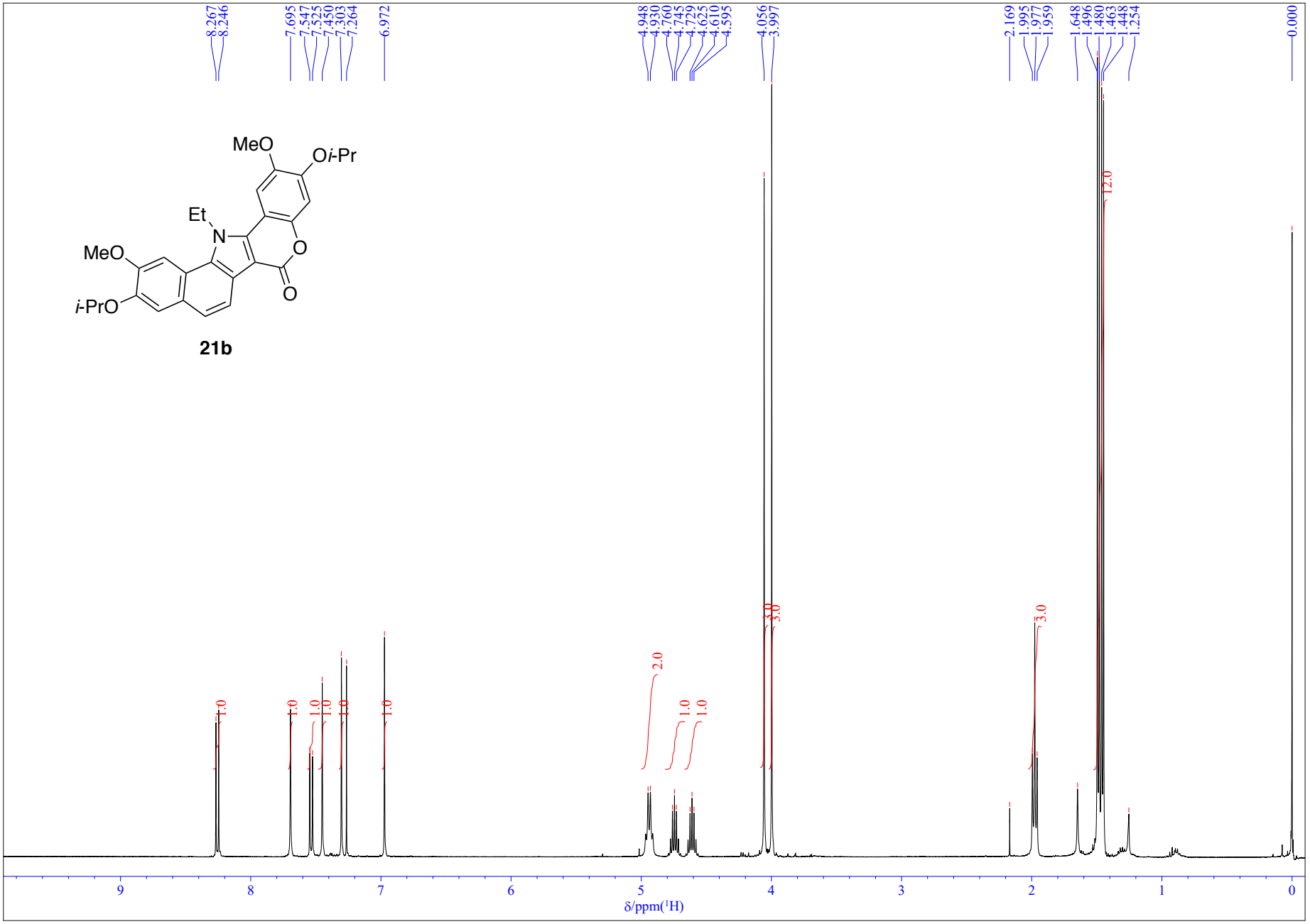


Figure S29. ^{1}H NMR spectrum of compound **21b** (400 MHz, $CDCl_3$).

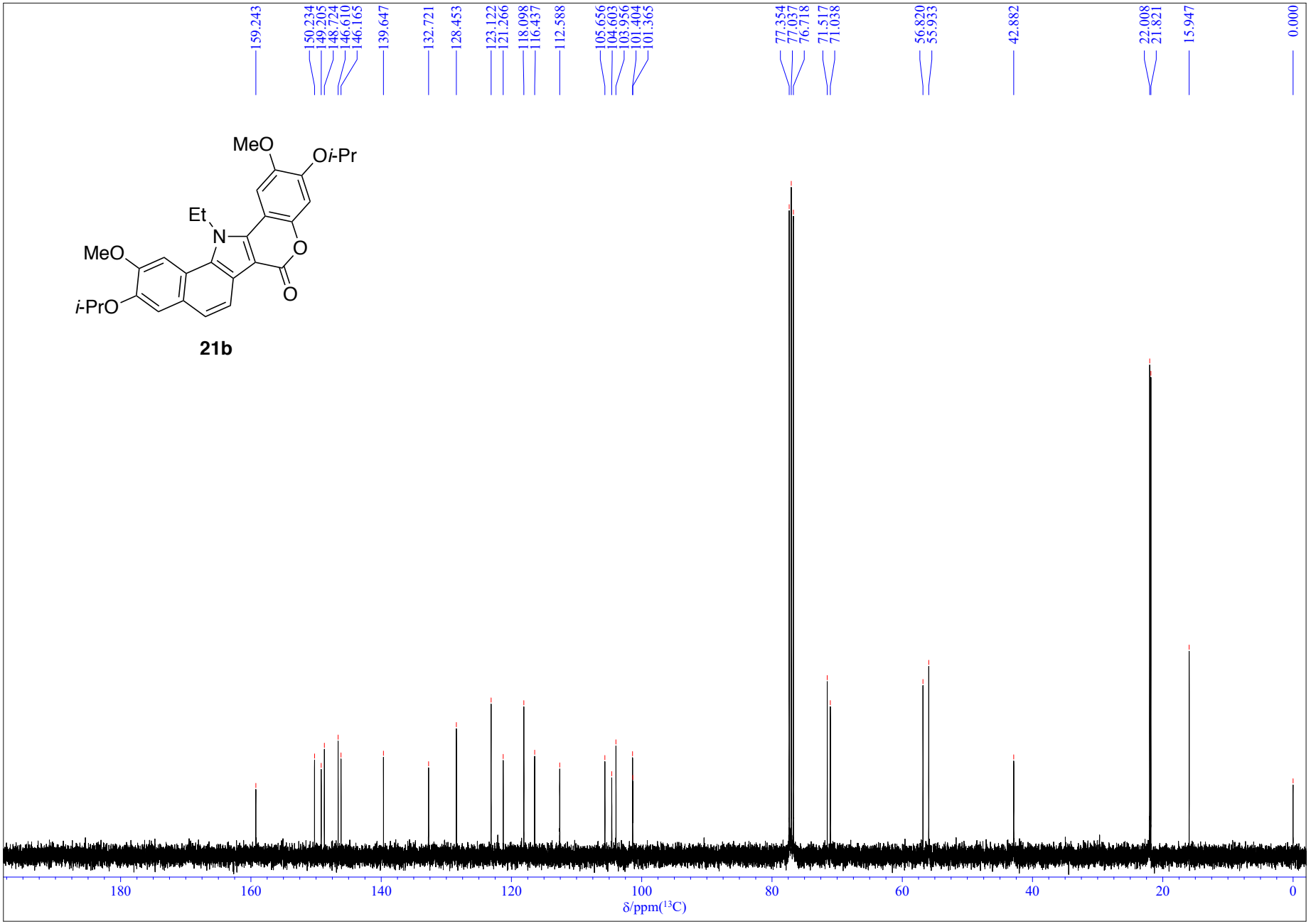


Figure S30. ^{13}C NMR spectrum of compound **21b** (100 MHz, $CDCl_3$).

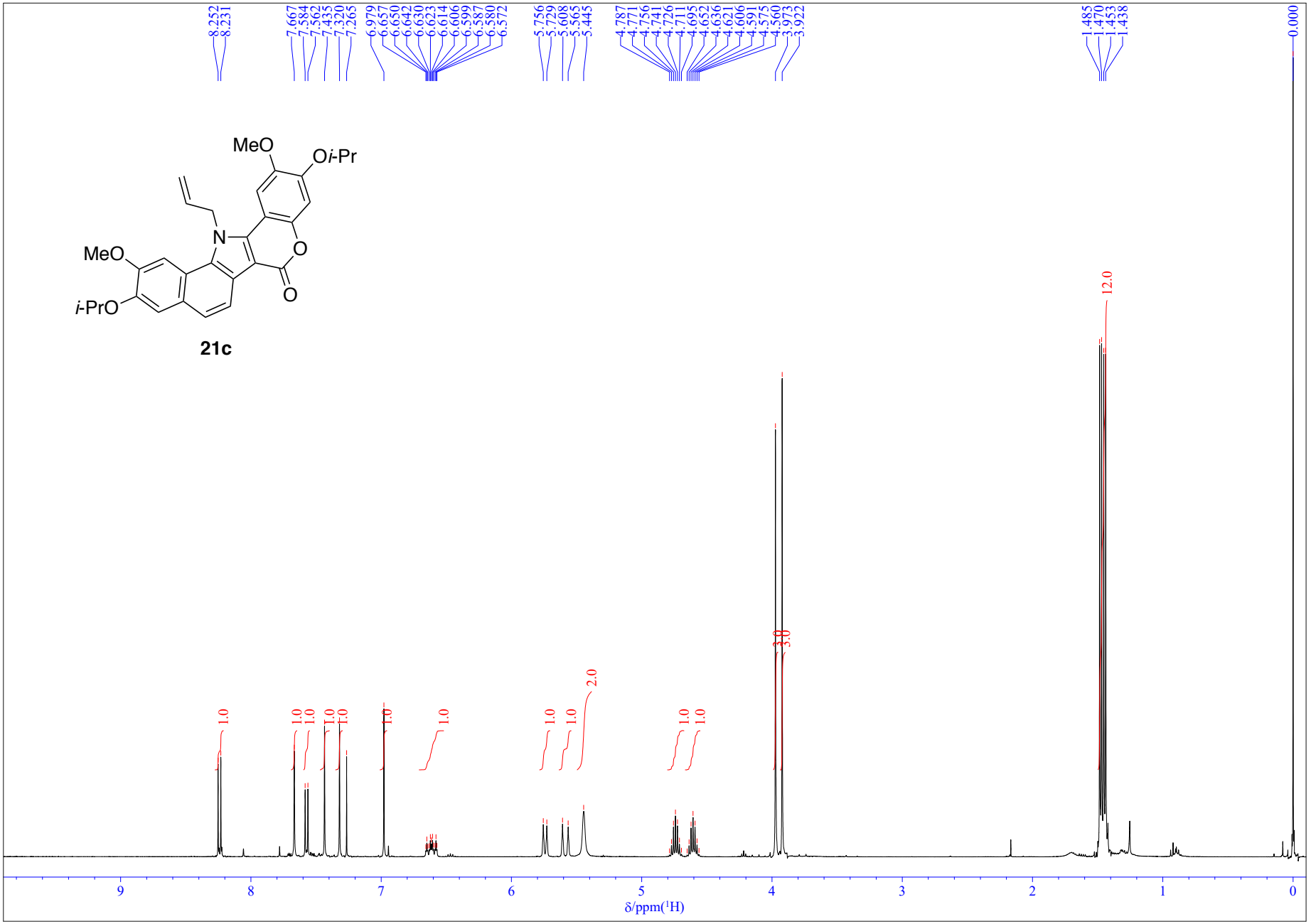
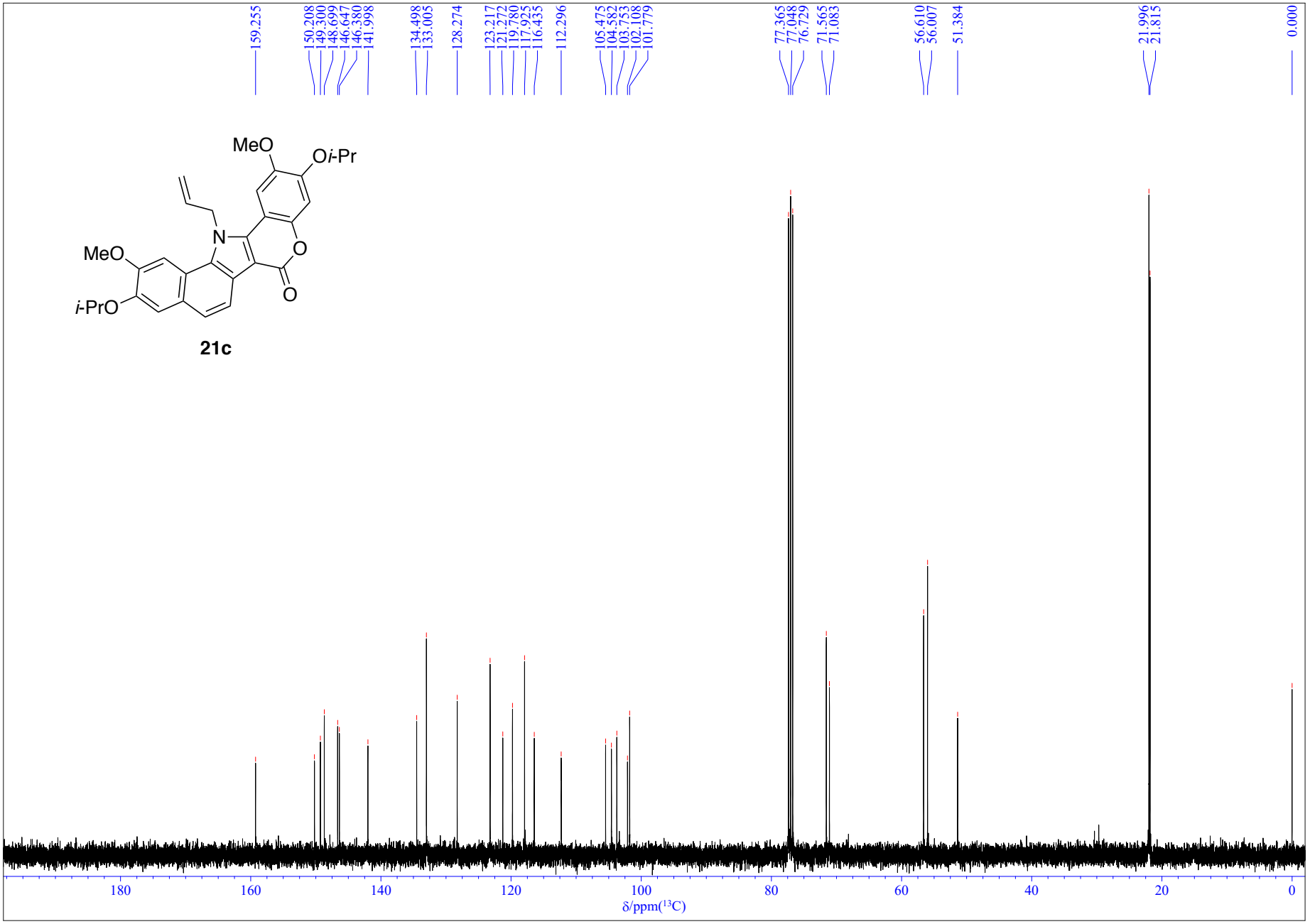


Figure S31. ^{1}H NMR spectrum of compound **21c** (400 MHz, $CDCl_3$).



21c

Figure S32. ^{13}C NMR spectrum of compound **21c** (100 MHz, $CDCl_3$).

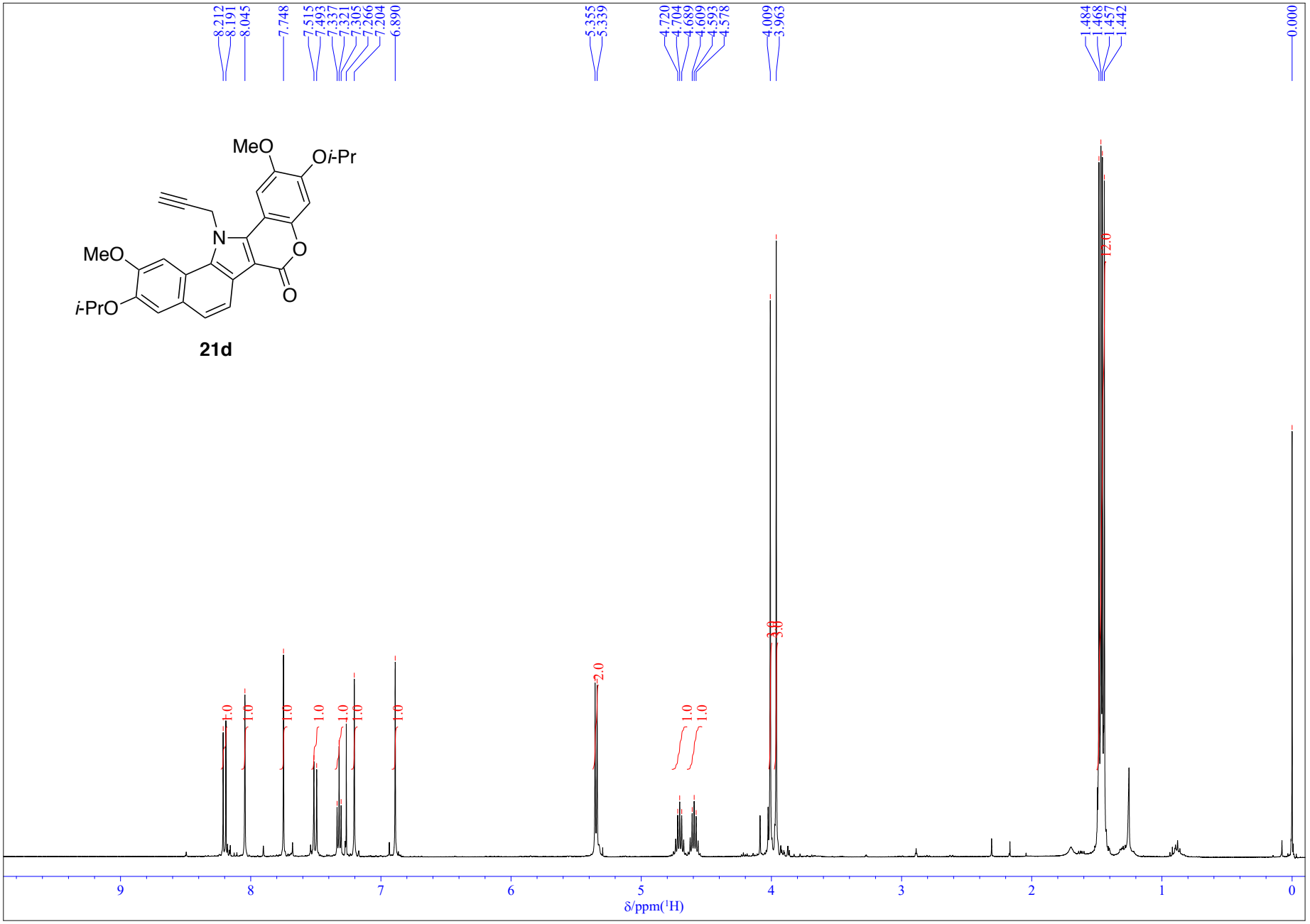


Figure S33. ^{1}H NMR spectrum of compound **21d** (400 MHz, $CDCl_3$).

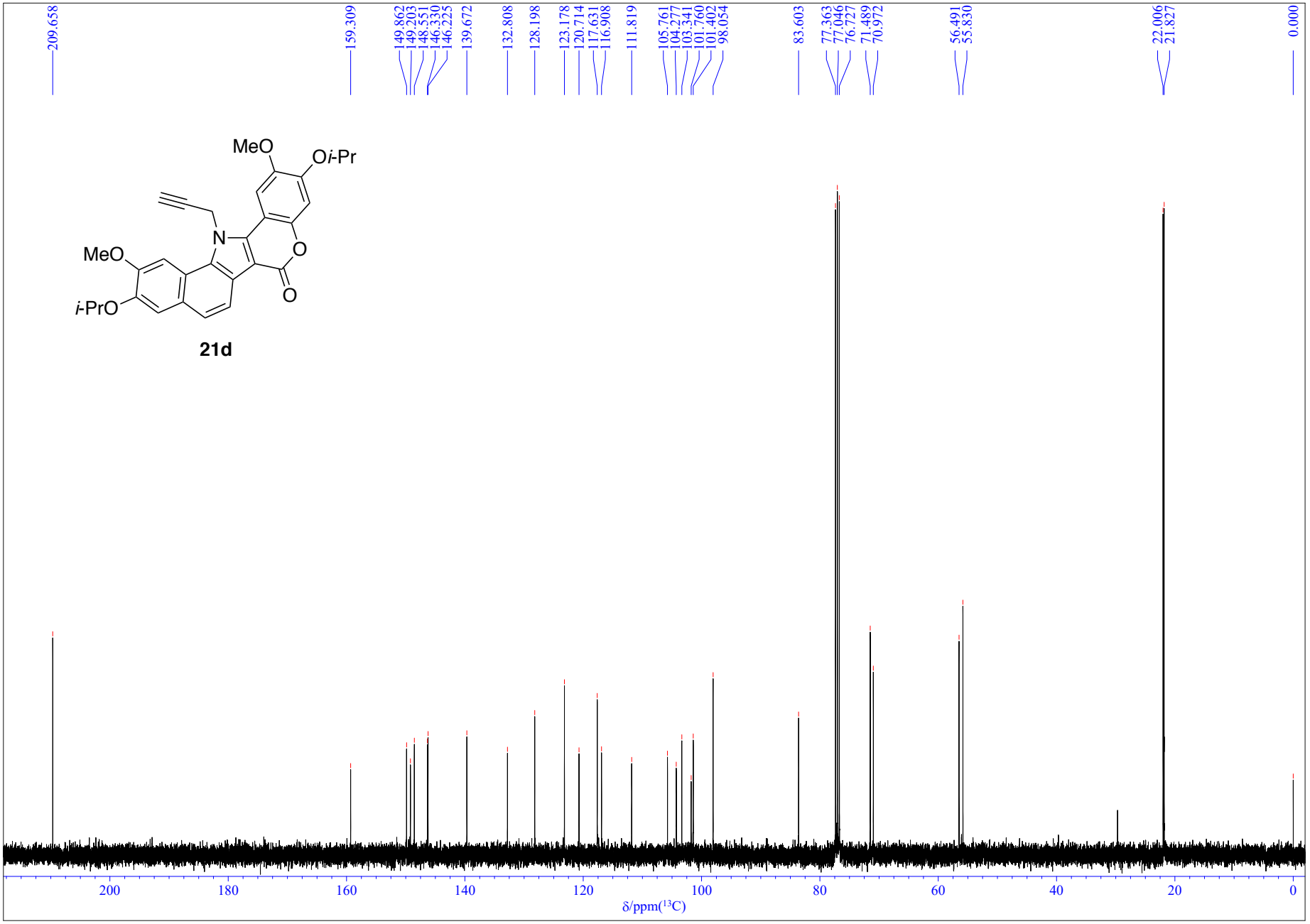


Figure S34. ^{13}C NMR spectrum of compound **21d** (100 MHz, $CDCl_3$).

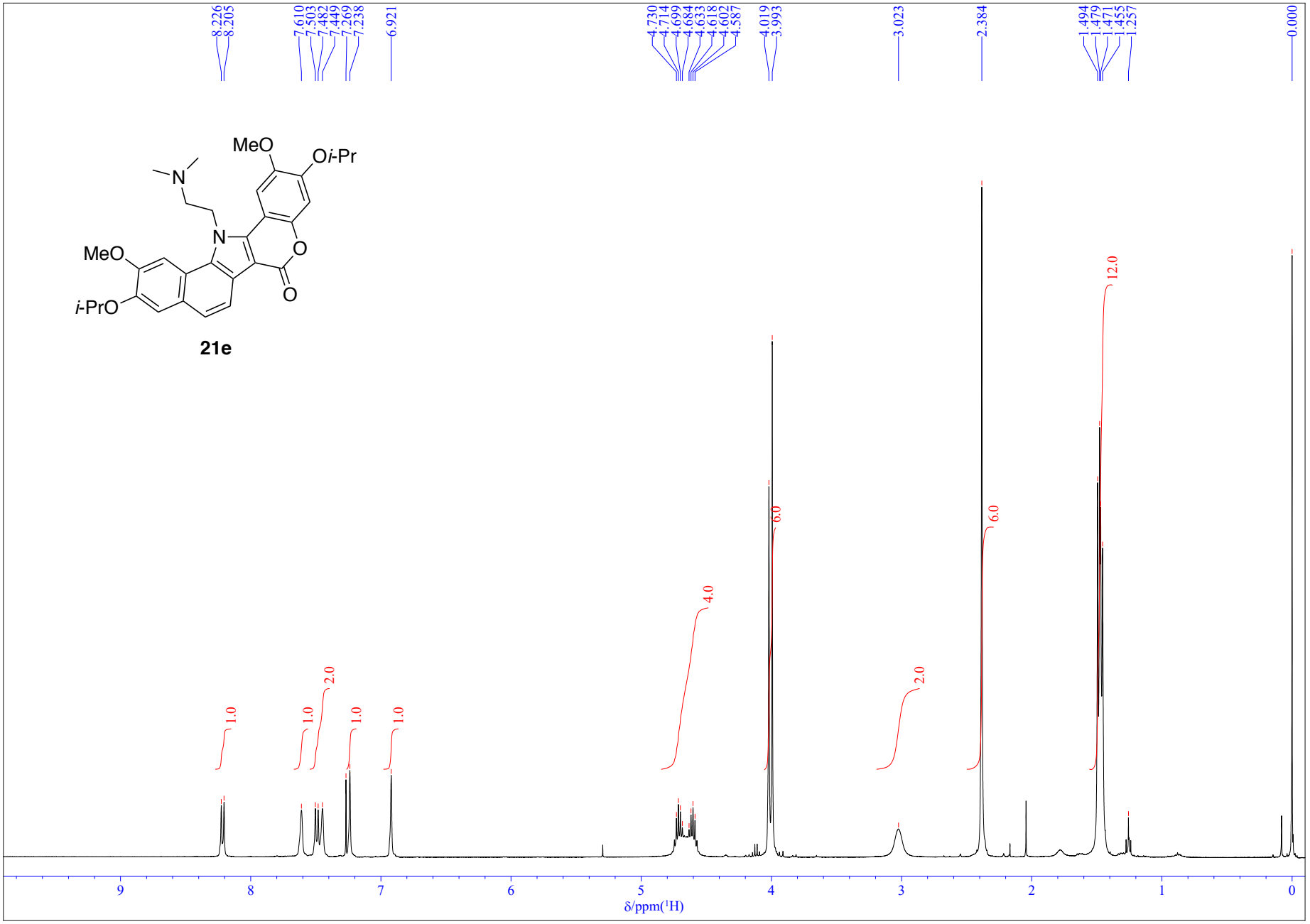


Figure S35. ^{1}H NMR spectrum of compound **21e** (400 MHz, $CDCl_3$).

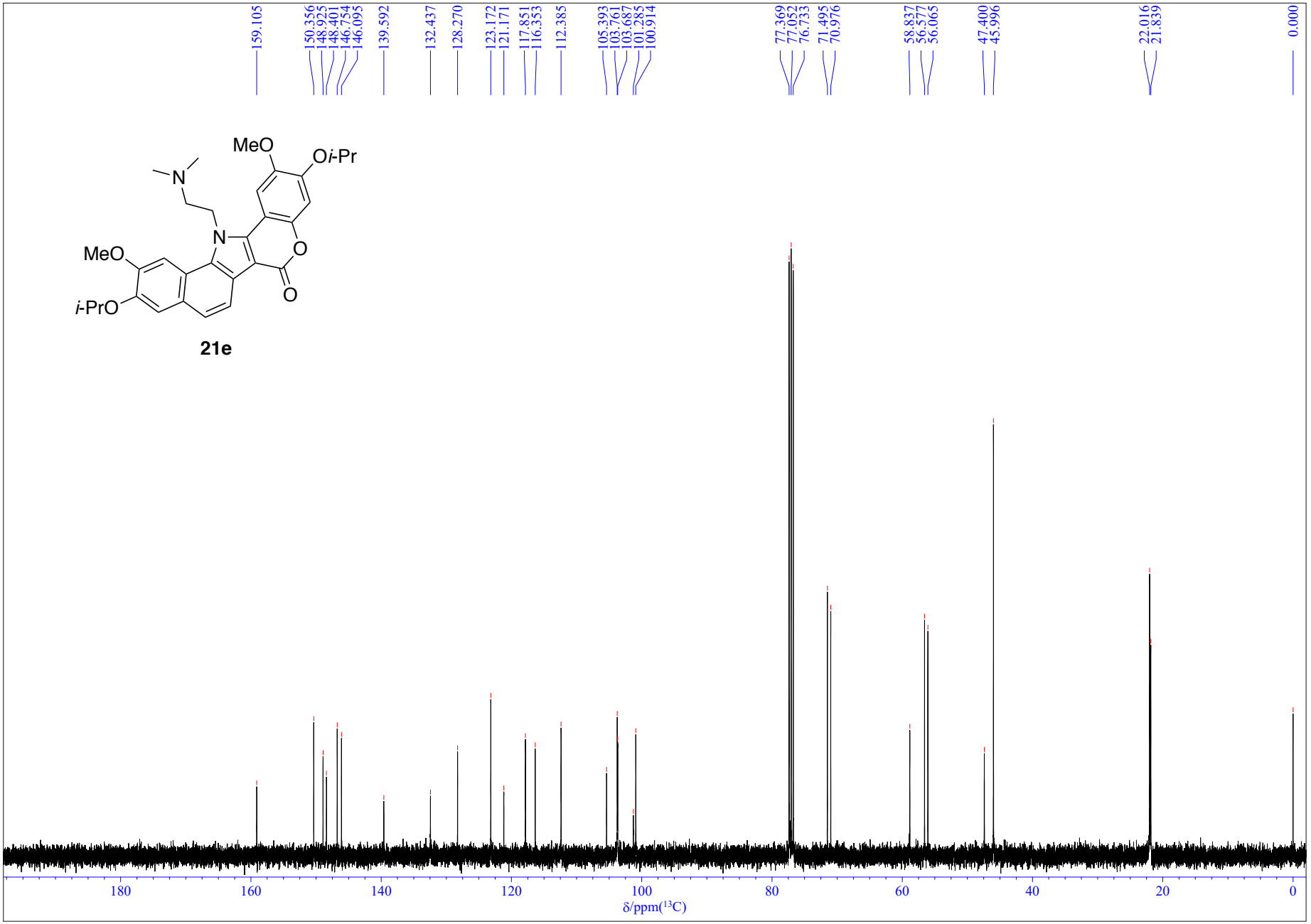


Figure S36. ^{13}C NMR spectrum of compound **21e** (100 MHz, $CDCl_3$).

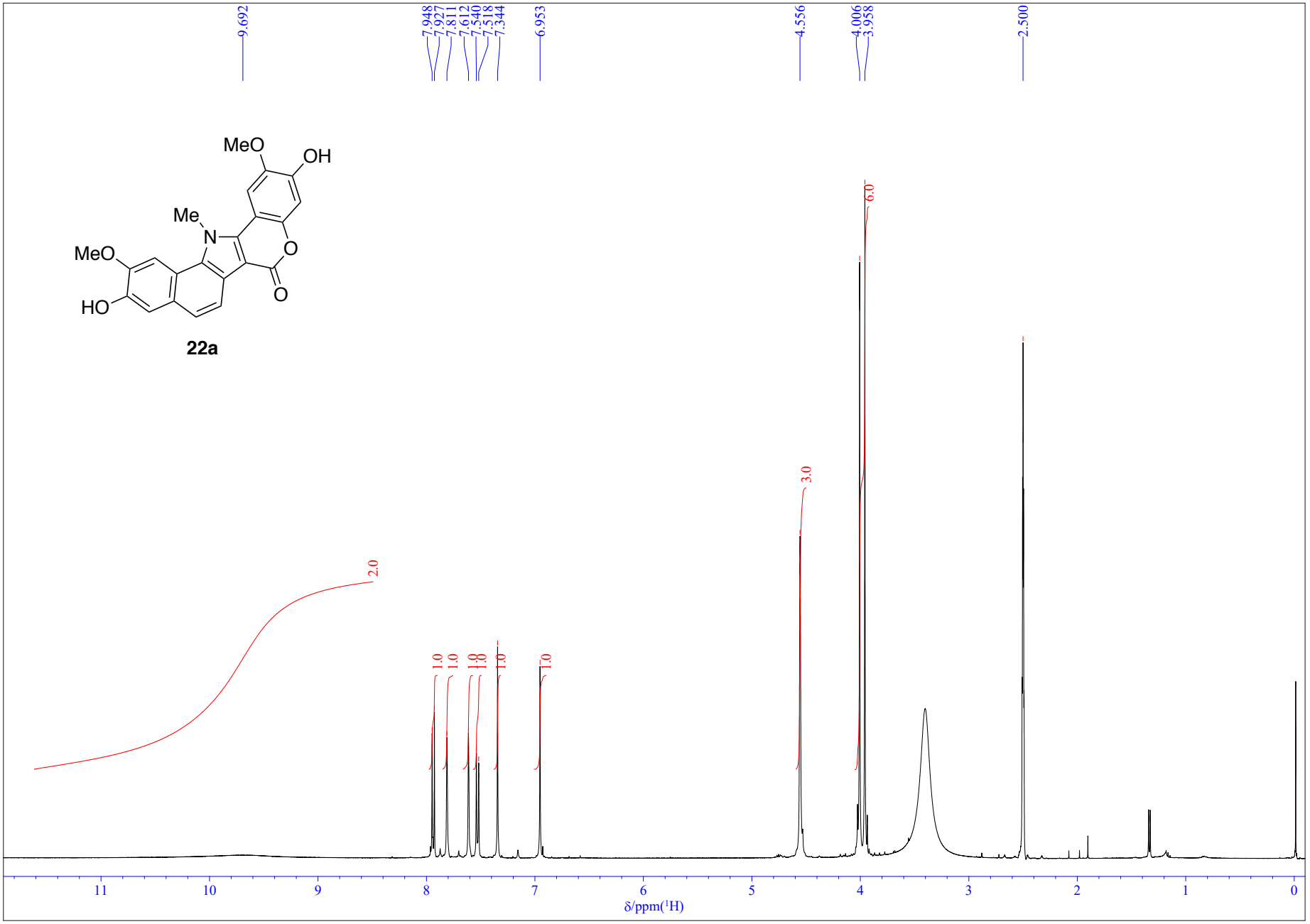


Figure S37. ^{1}H NMR spectrum of compound **22a** (400 MHz, DMSO-d_6).

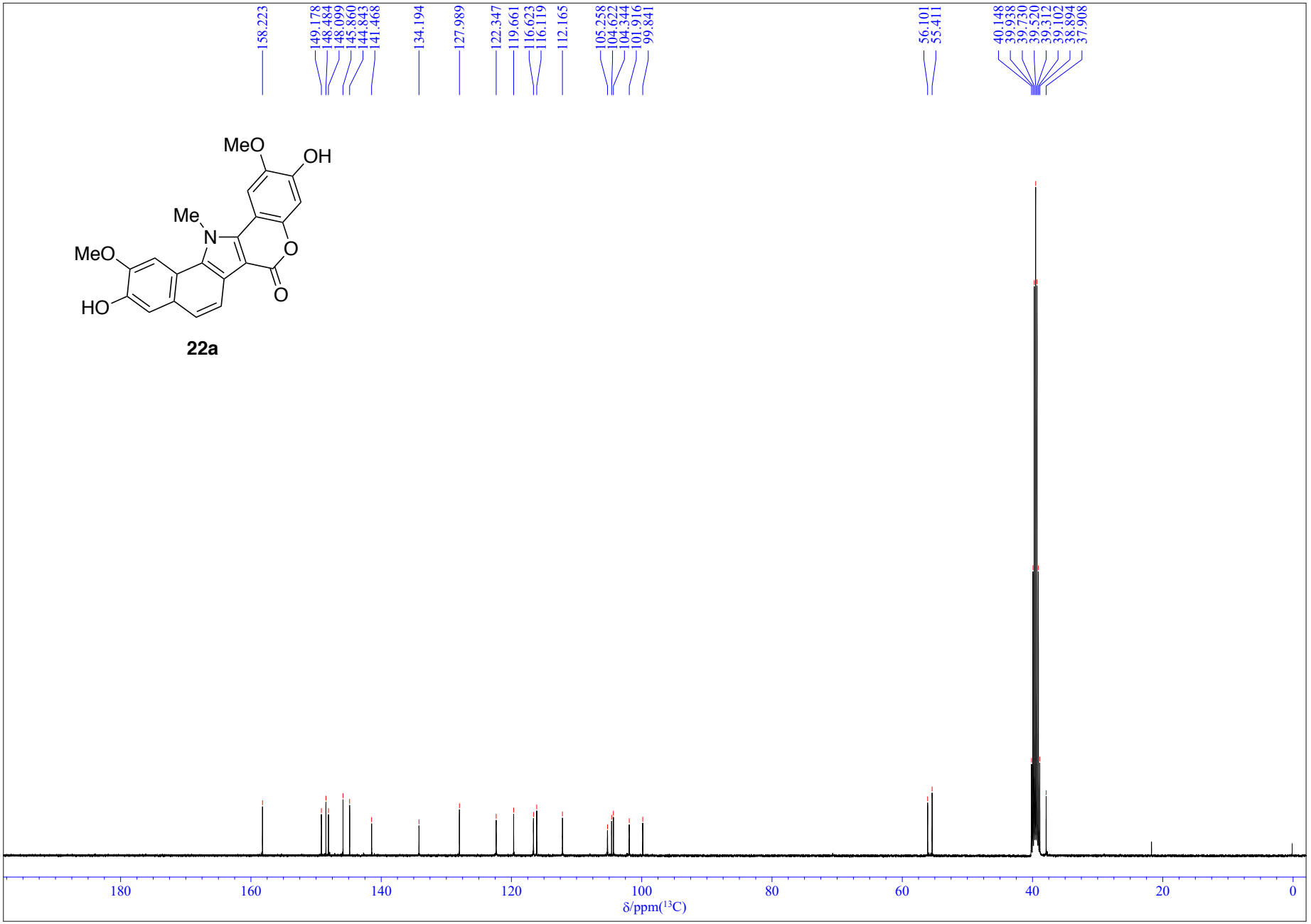


Figure S38. ^{13}C NMR spectrum of compound **22a** (100 MHz, DMSO-d_6).

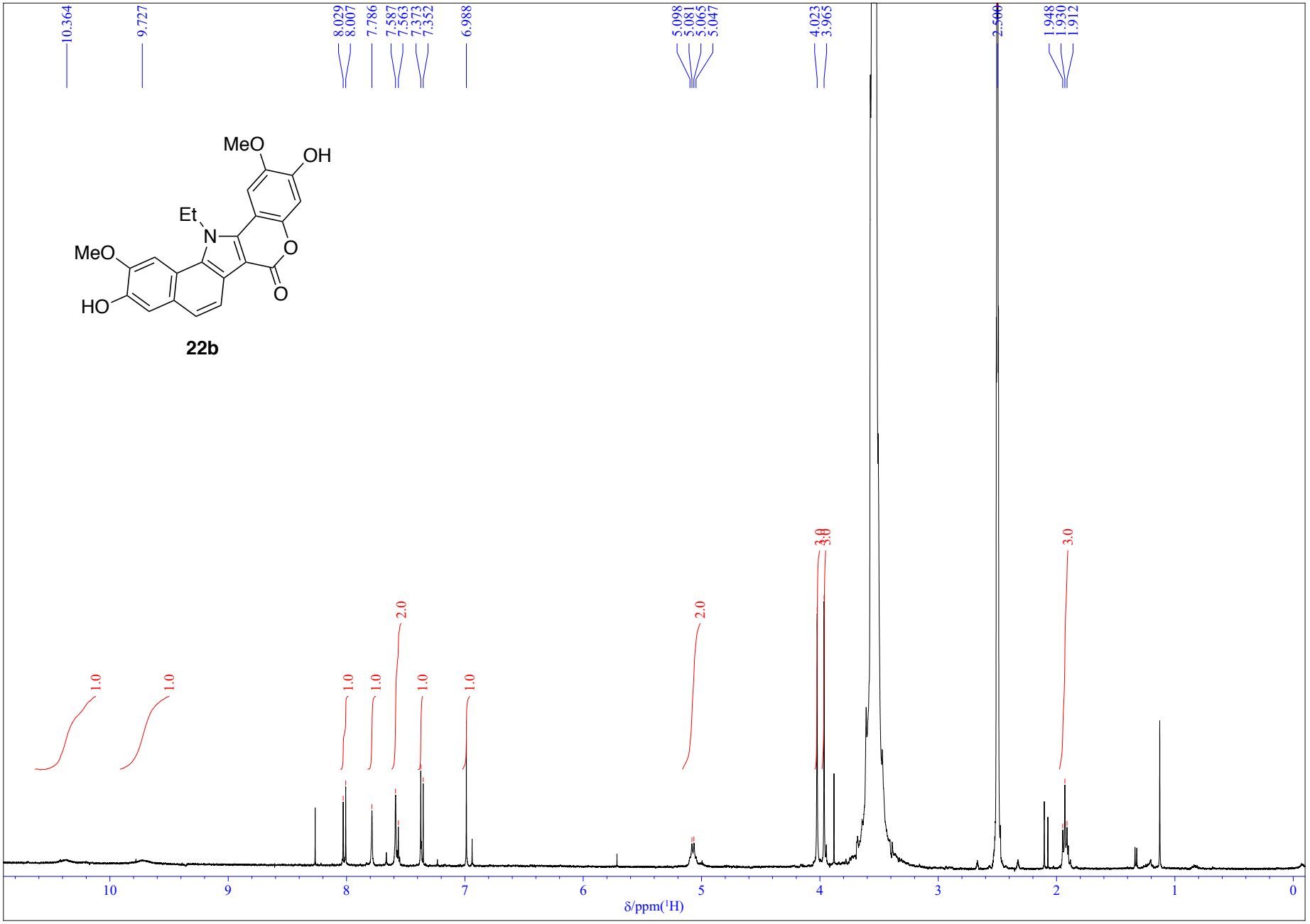


Figure S39. ^{1}H NMR spectrum of compound **22b** (400 MHz, DMSO-d_6).

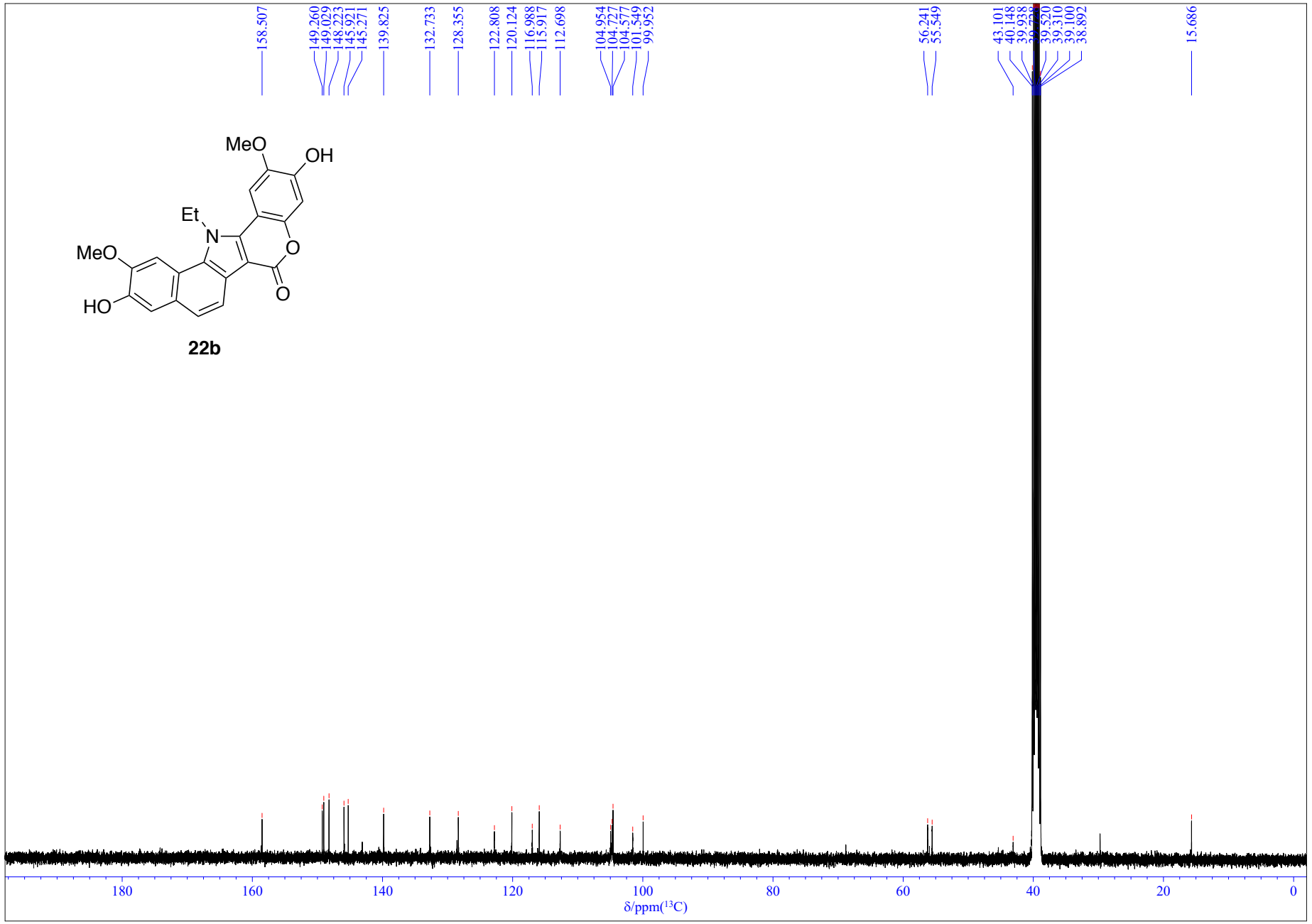


Figure S40. ^{13}C NMR spectrum of compound **22b** (100 MHz, DMSO-d_6).

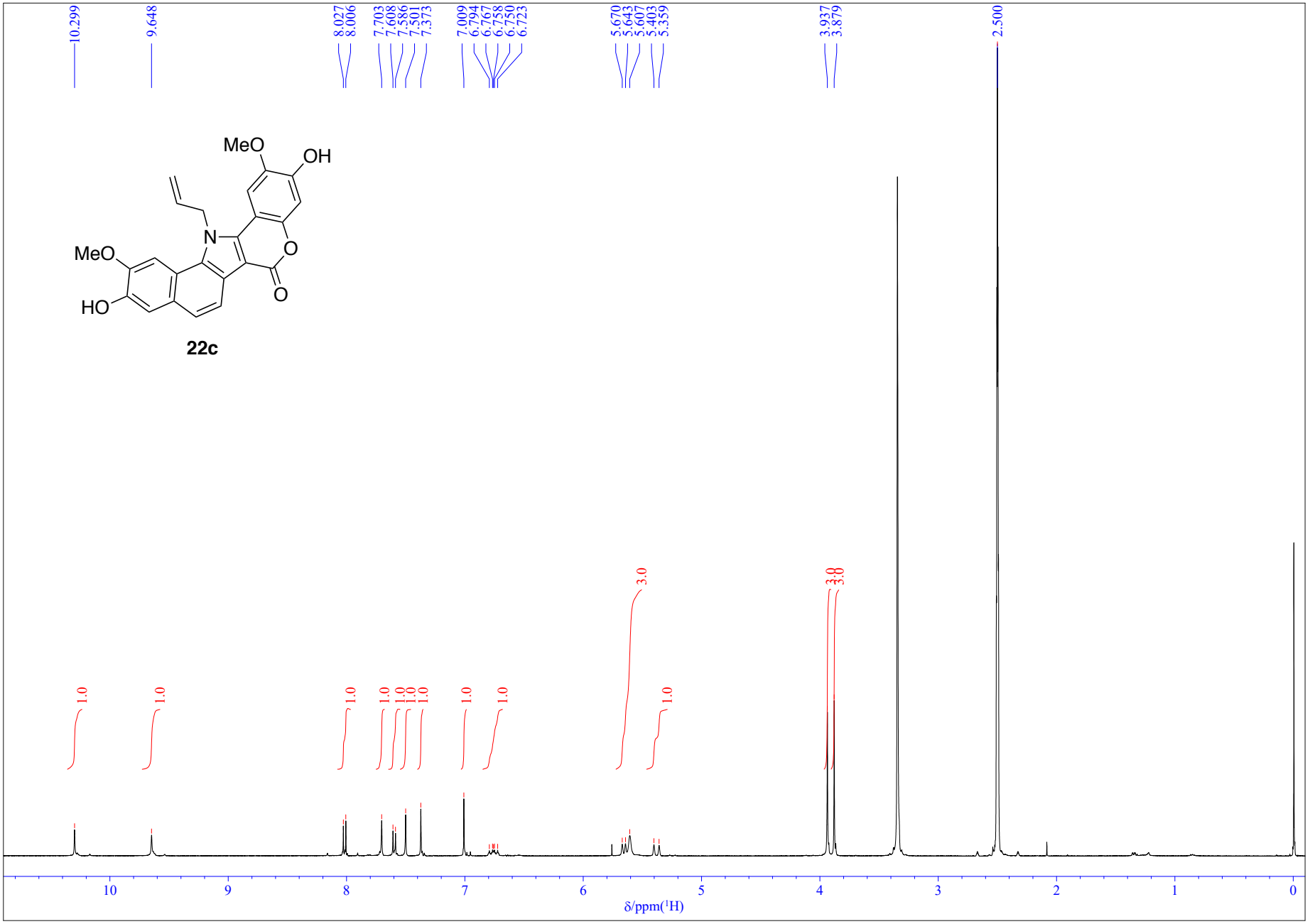


Figure S41. ^{1}H NMR spectrum of compound **22c** (400 MHz, DMSO-d_6).

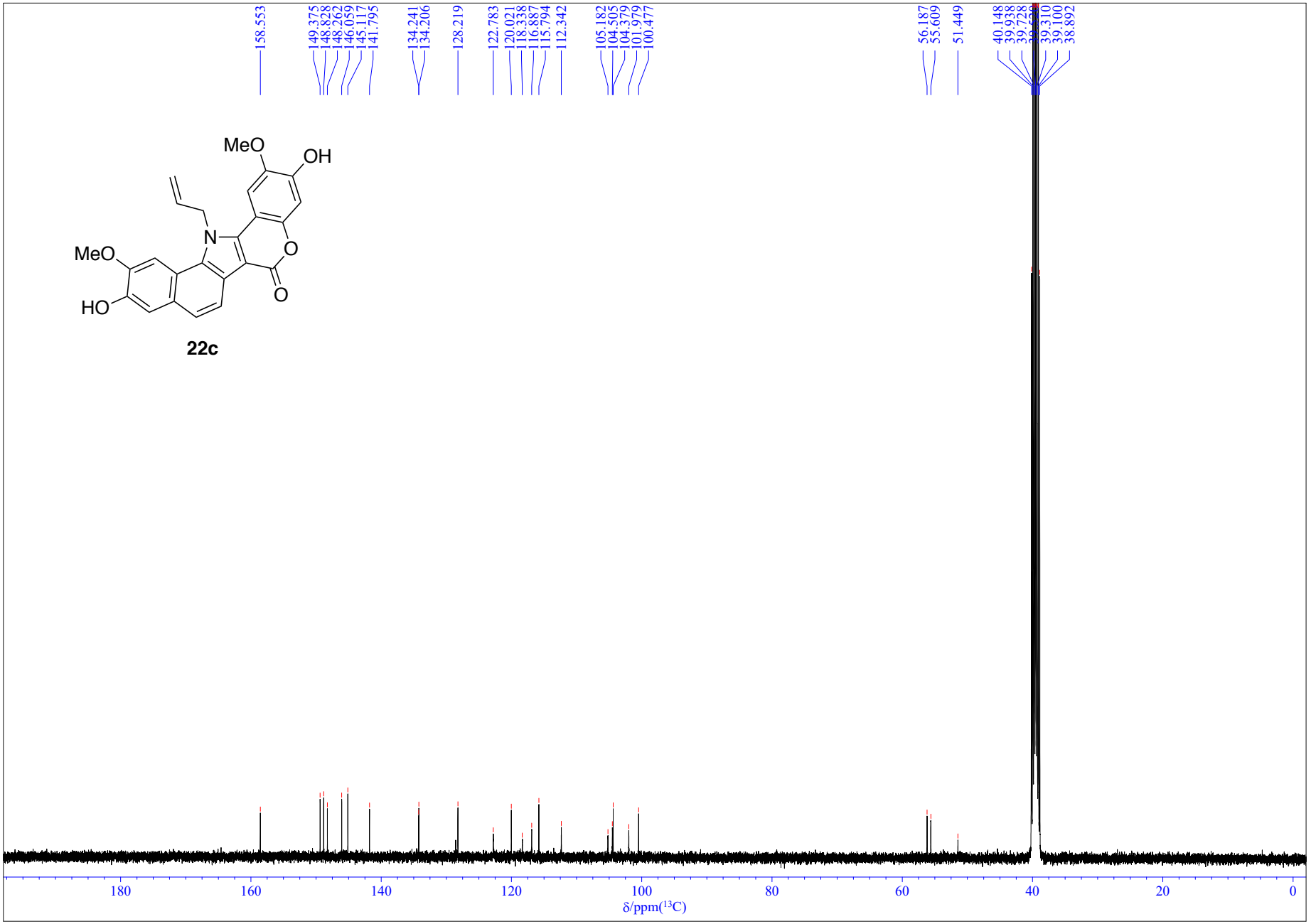


Figure S42. ^{13}C NMR spectrum of compound **22c** (100 MHz, DMSO-d_6).

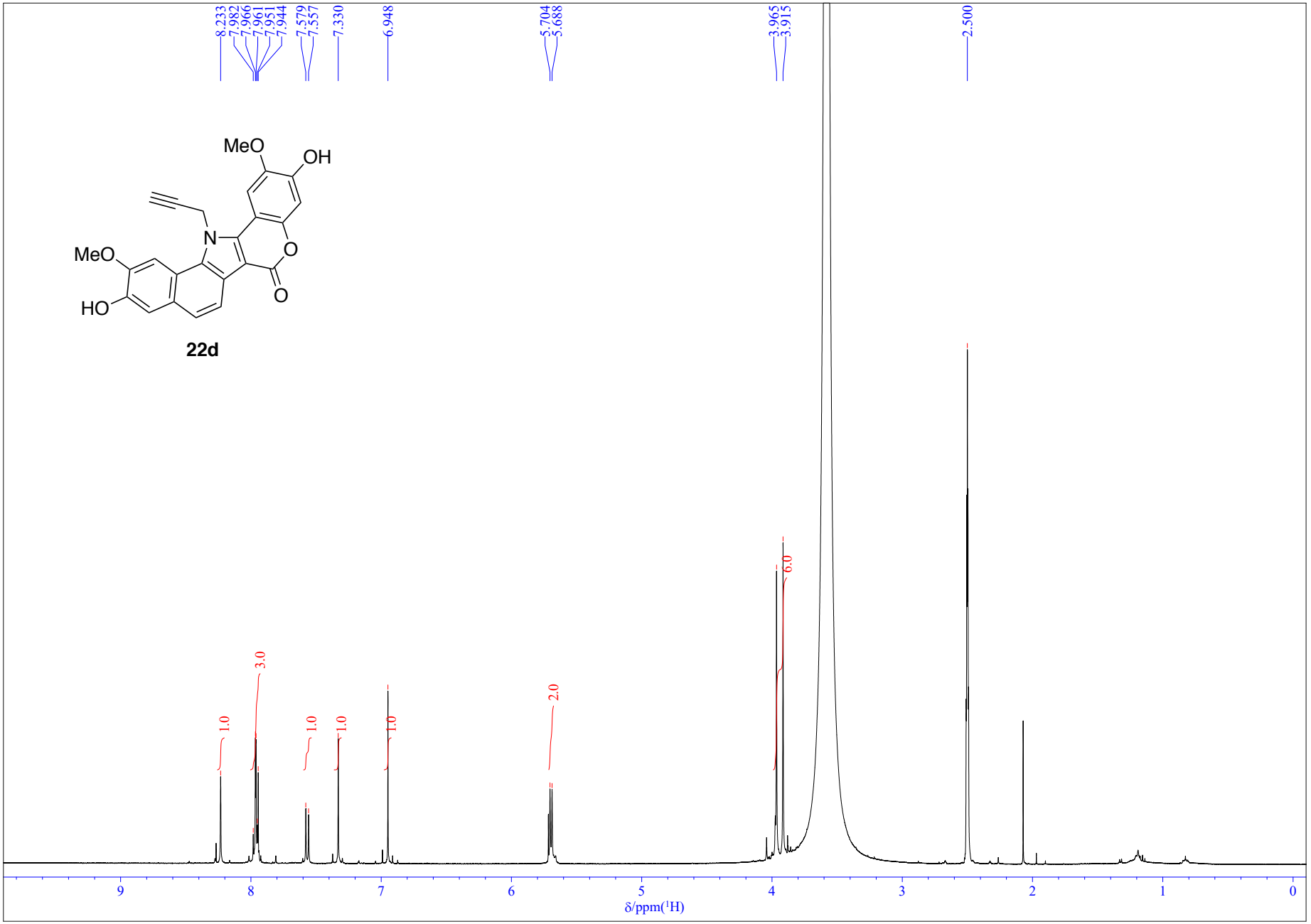


Figure S43. ^{1}H NMR spectrum of compound **22d** (400 MHz, DMSO-d_6).

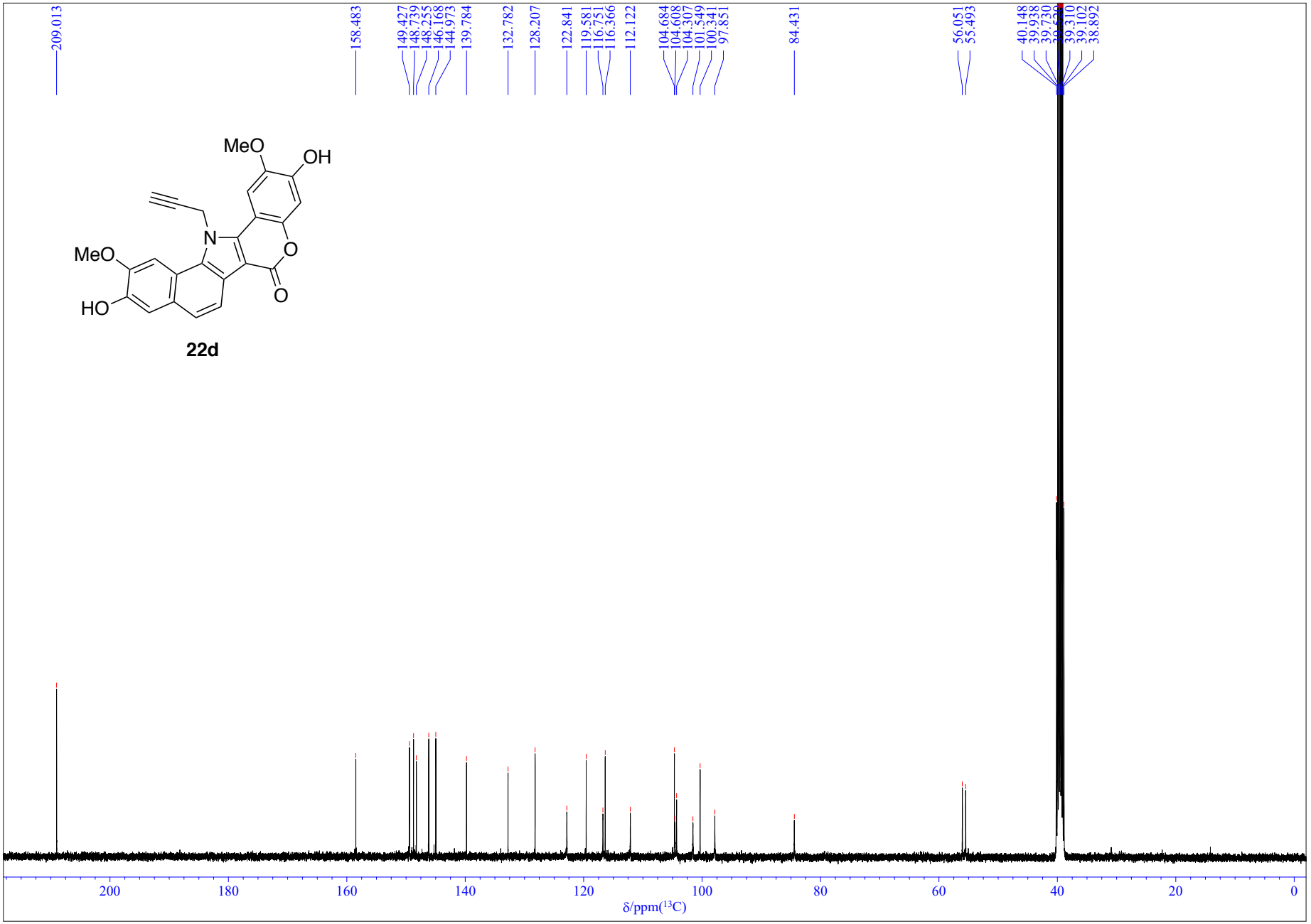


Figure S44. ^{13}C NMR spectrum of compound **22d** (100 MHz, DMSO-d_6).

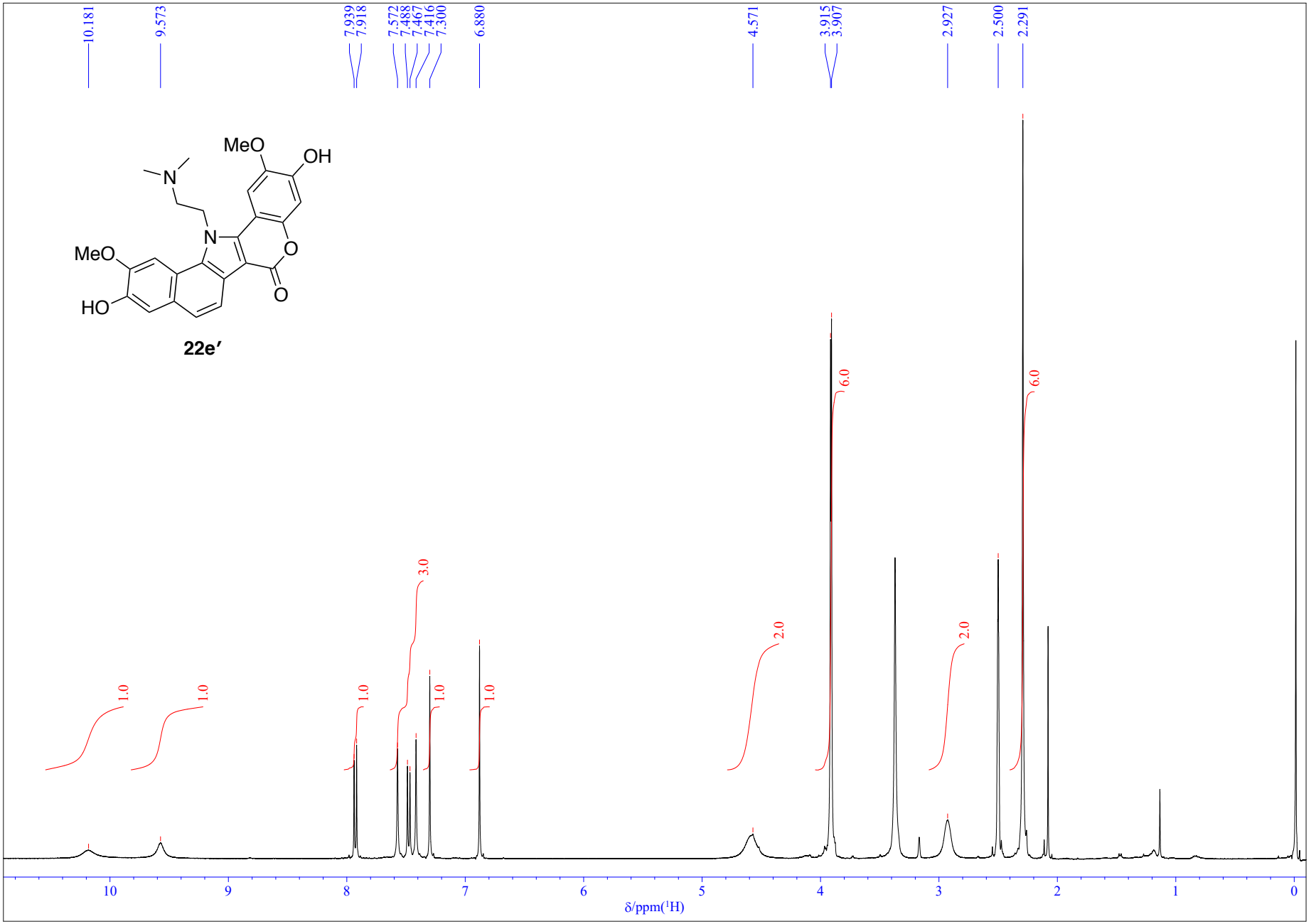


Figure S45. ^{1}H NMR spectrum of compound **22e′** (400 MHz, DMSO-d_6).

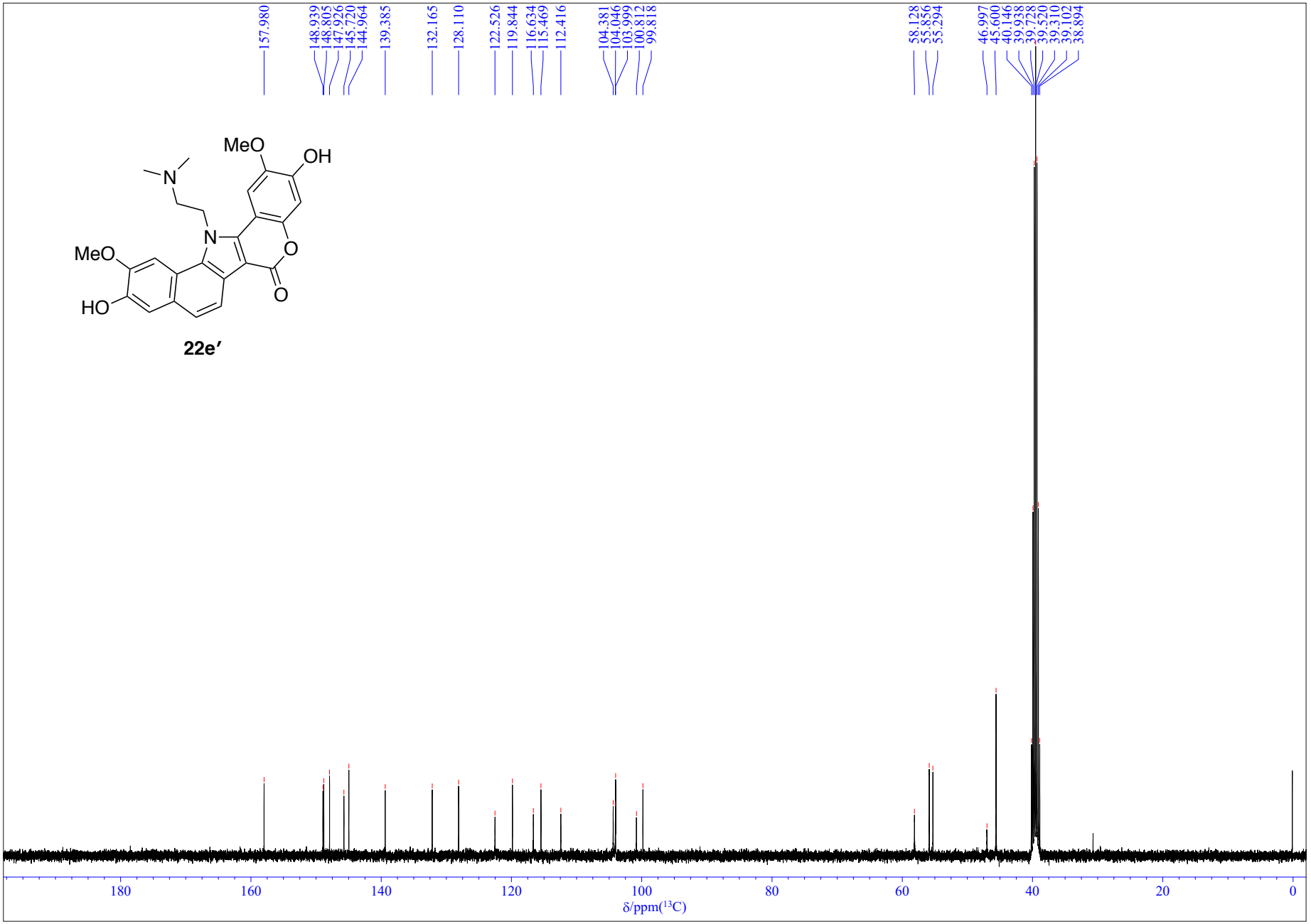


Figure S46. ^{13}C NMR spectrum of compound **22e′** (100 MHz, DMSO-d_6).

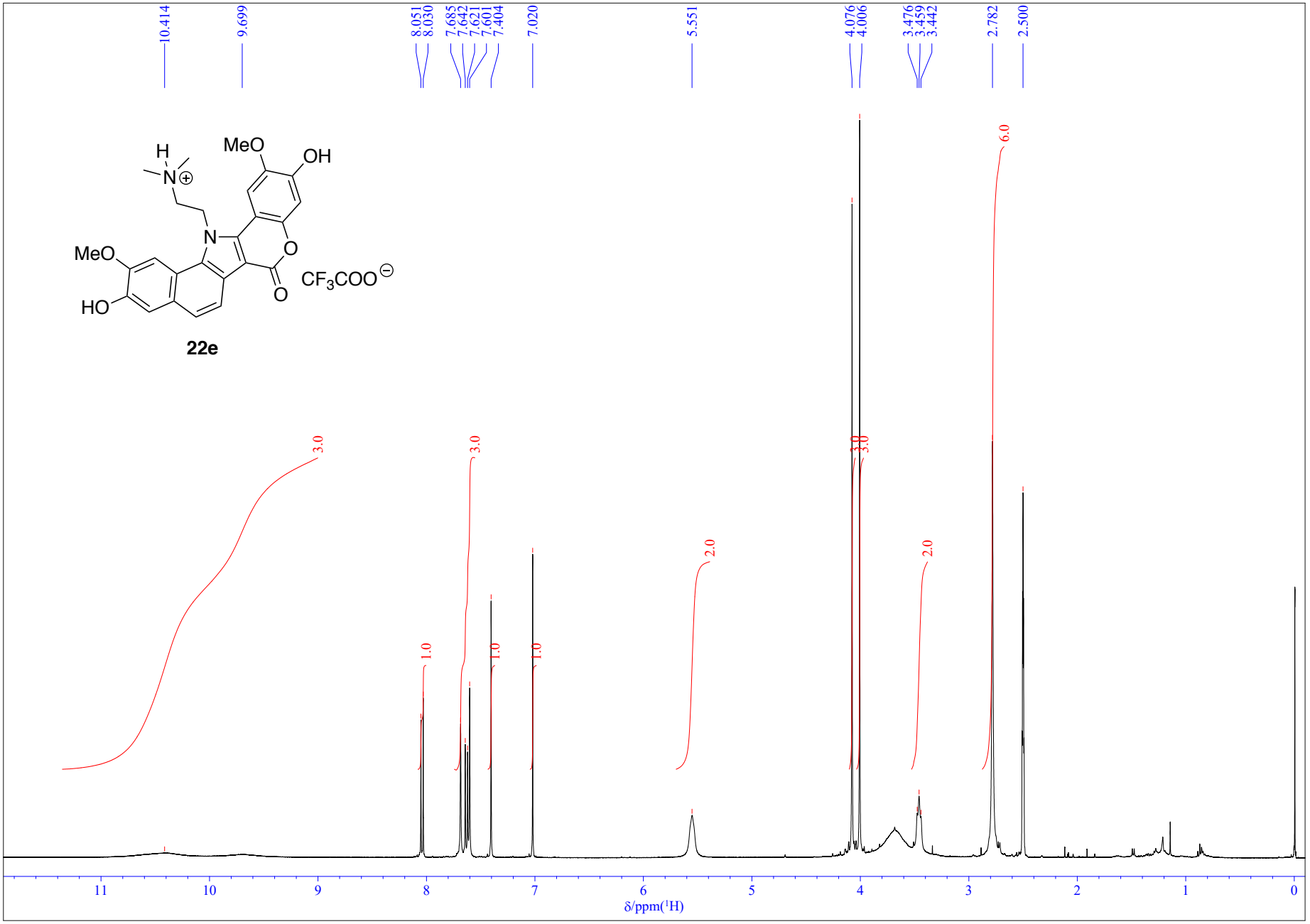


Figure S47. ^{1}H NMR spectrum of compound **22e** (400 MHz, DMSO-d_6).

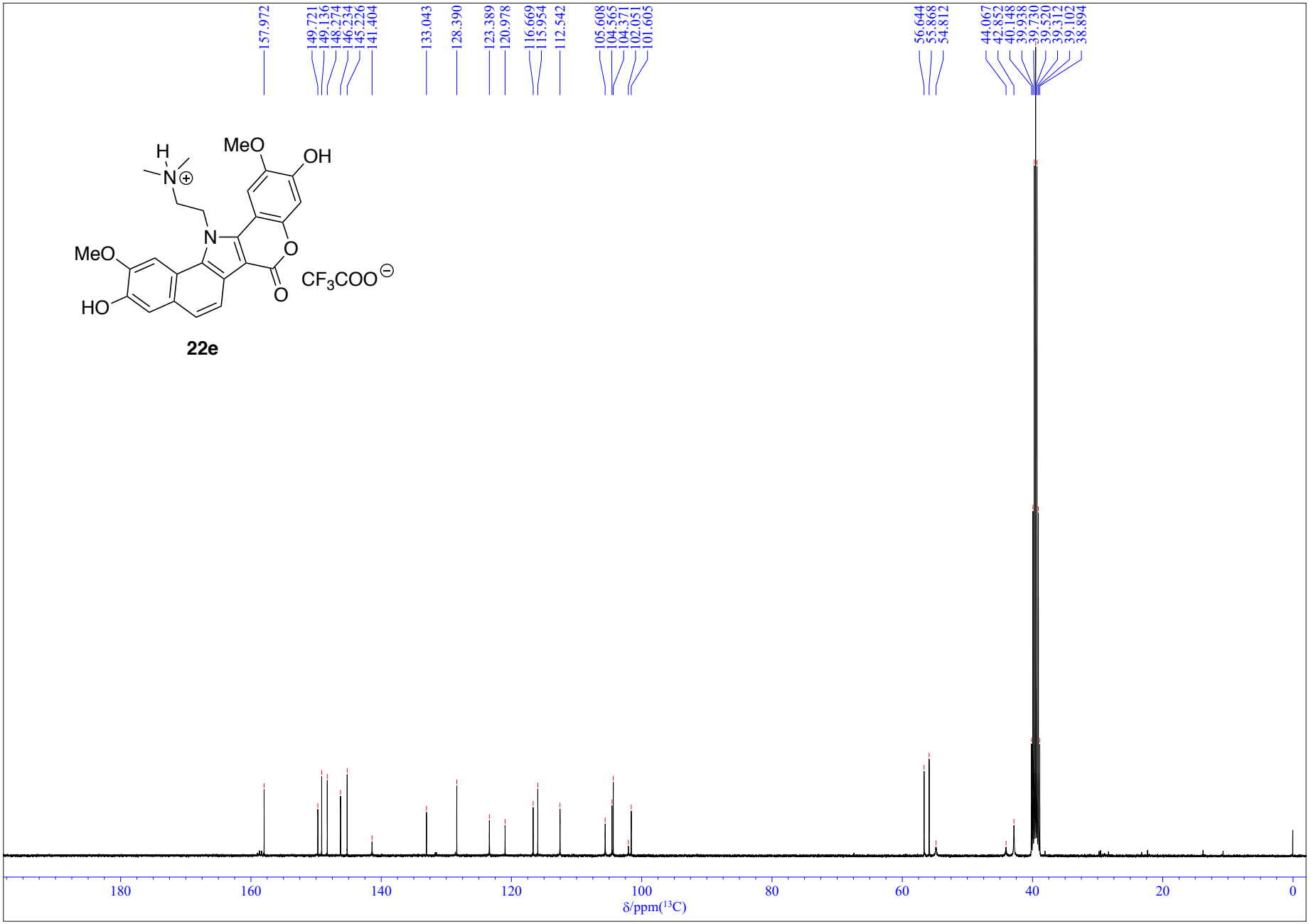


Figure S48. ^{13}C NMR spectrum of compound **22e** (100 MHz, DMSO-d_6).

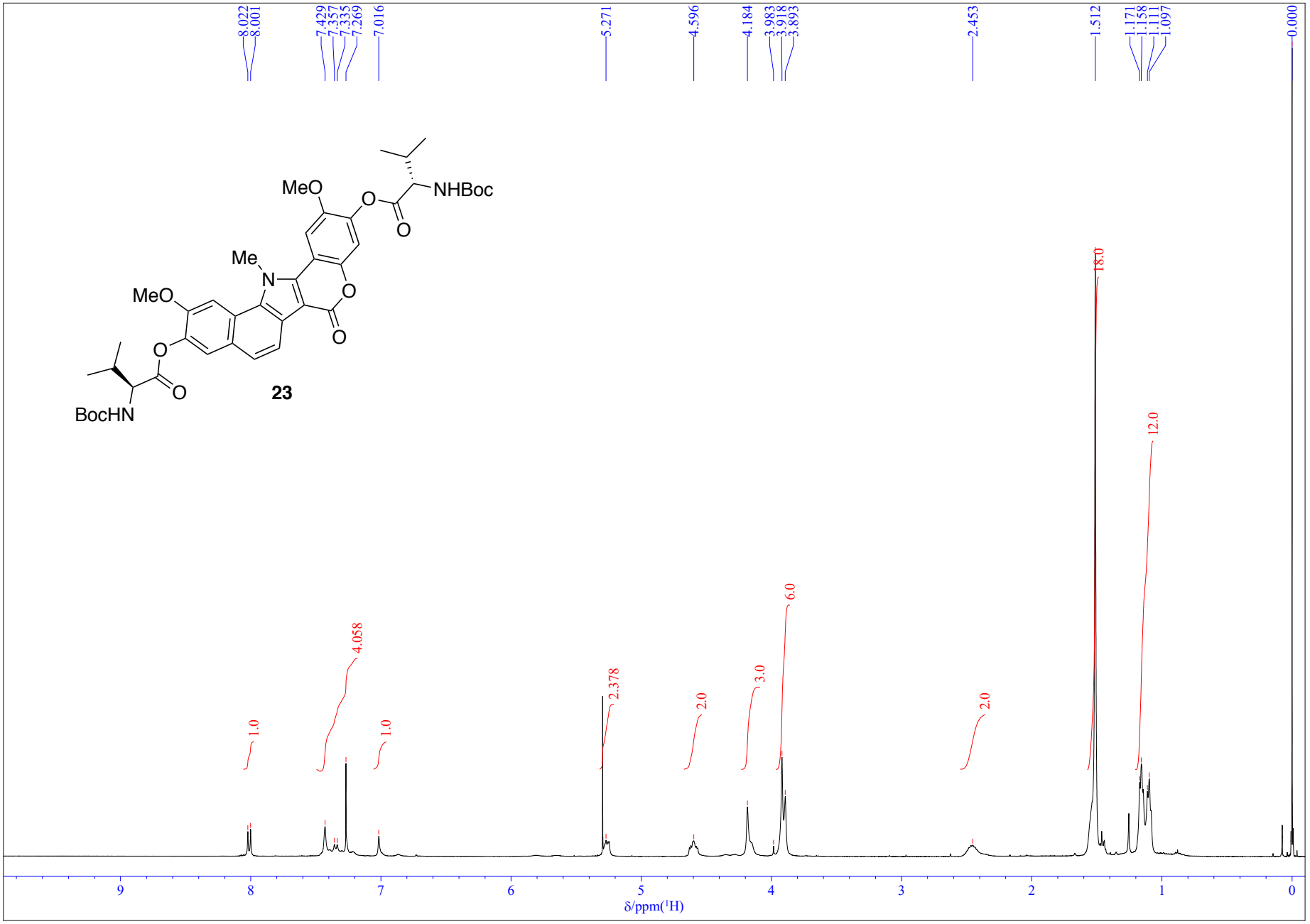


Figure S49. ^{1}H NMR spectrum of compound **23** (400 MHz, $CDCl_3$).

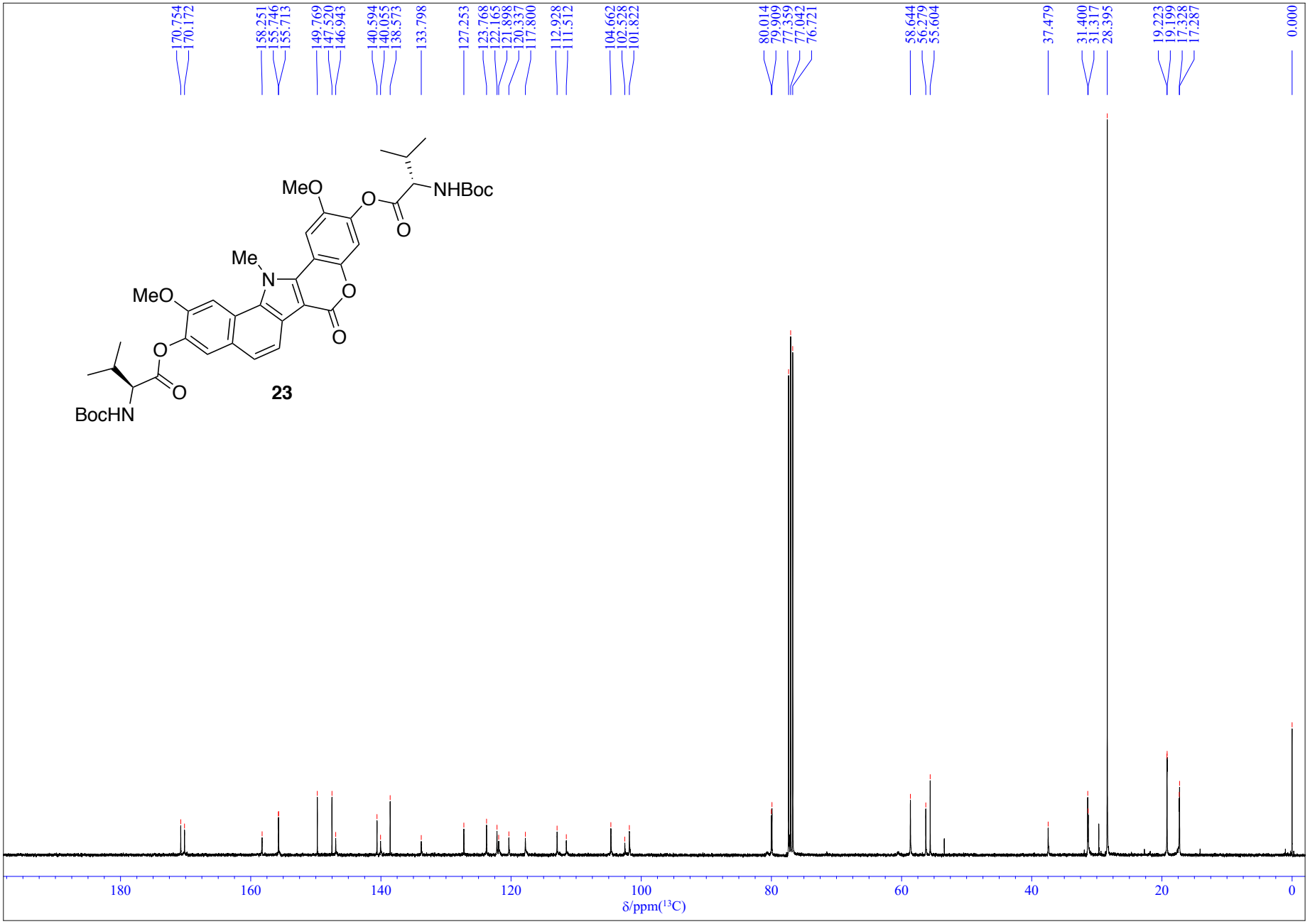


Figure S50. ^{13}C NMR spectrum of compound **23** (100 MHz, $CDCl_3$).

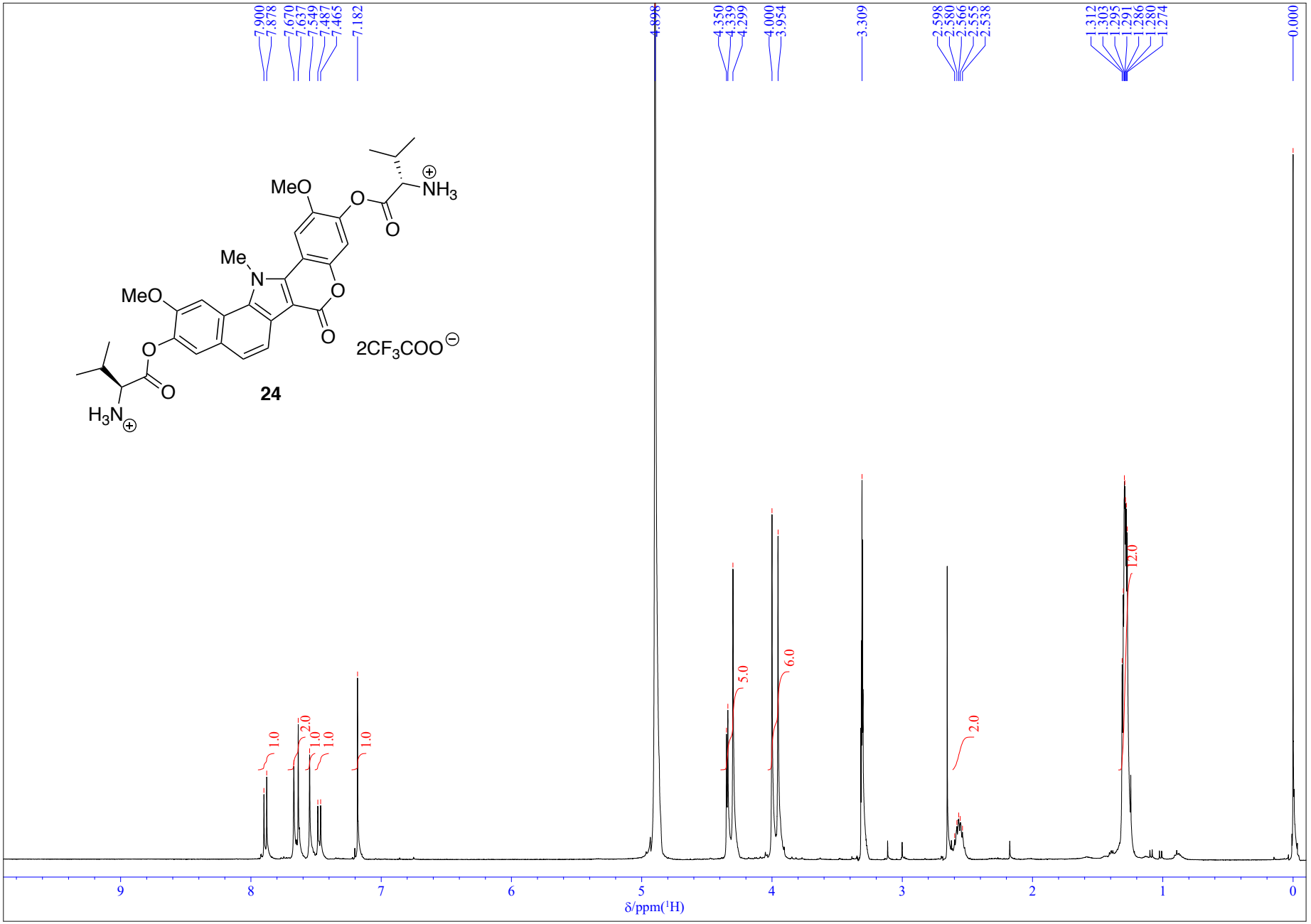


Figure S51. ^{1}H NMR spectrum of compound **24** (400 MHz, methanol-d_4).

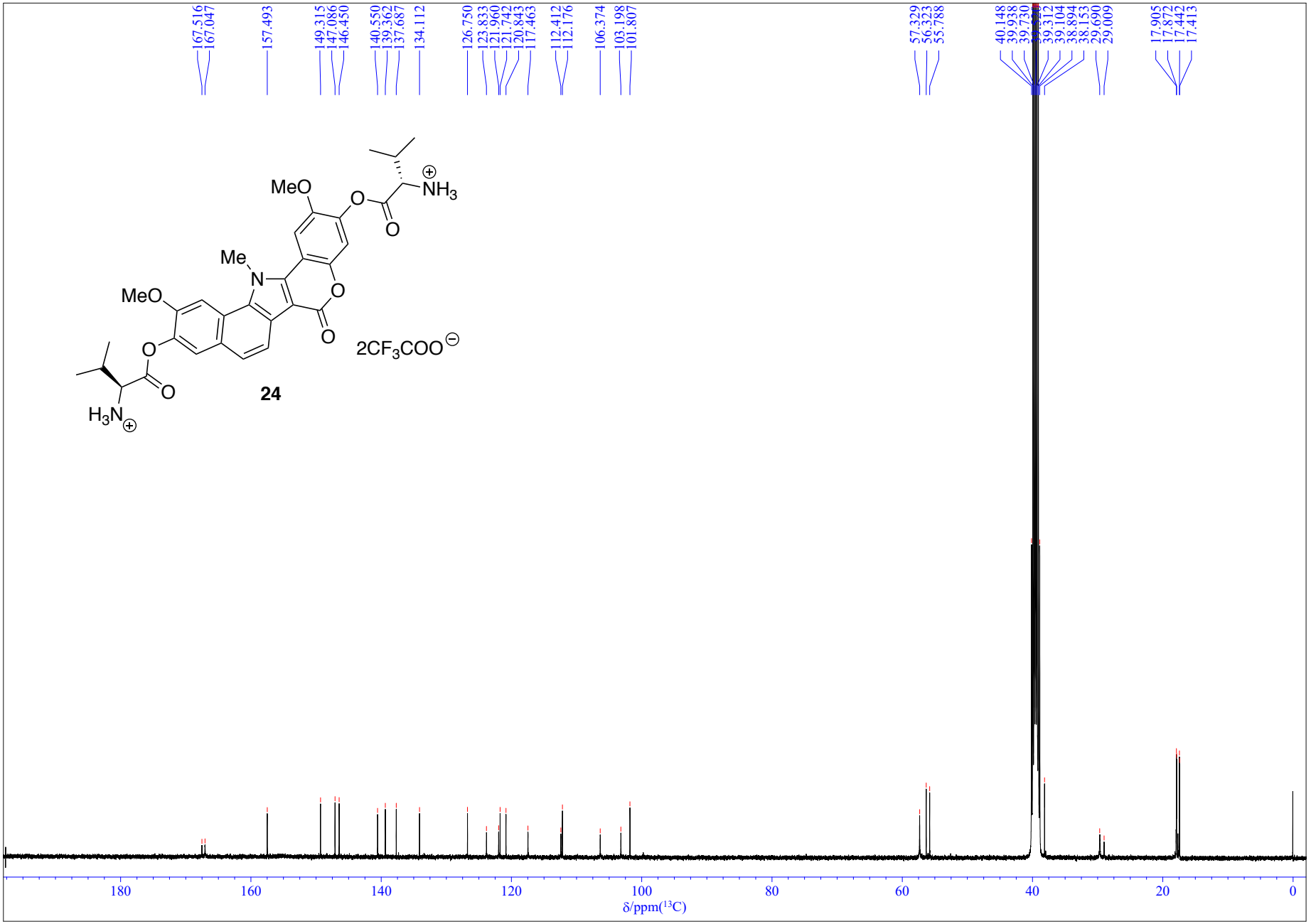
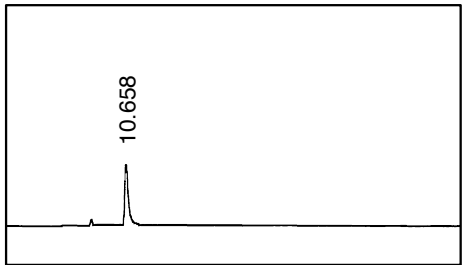
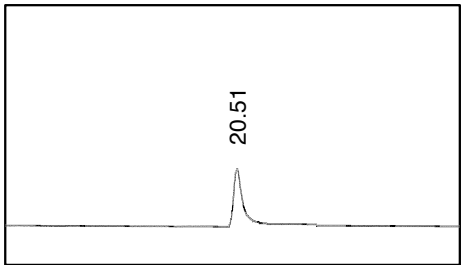


Figure S52. ^{13}C NMR spectrum of compound **24** (100 MHz, DMSO-d_6).

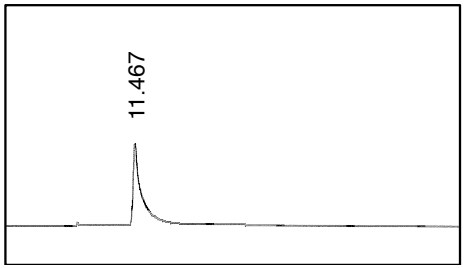
lamellarin D (**5**)
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: EtOAc–MeOH (19:1)
Flow rate: 0.5 mL/min



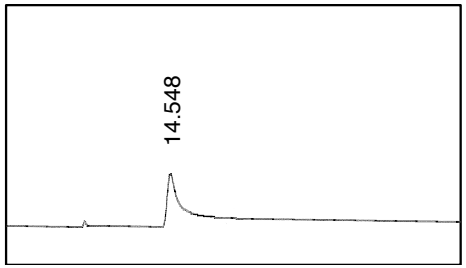
BBPI **20**
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: EtOAc–MeOH (19:1)
Flow rate: 0.5 mL/min



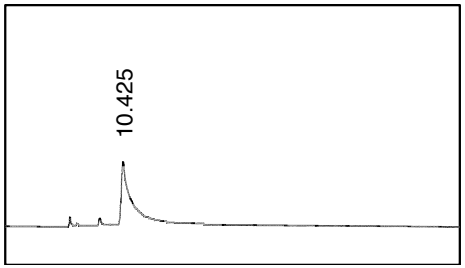
BBPI **21a**
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: EtOAc–MeOH (19:1)
Flow rate: 0.5 mL/min



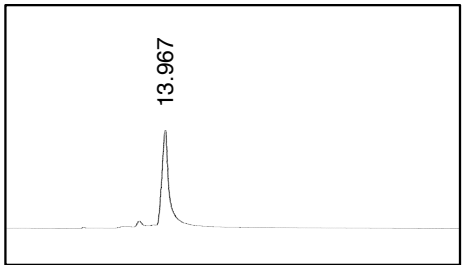
BBPI **21b**
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: EtOAc
Flow rate: 0.5 mL/min



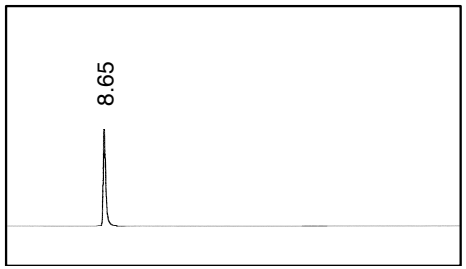
BBPI **21c**
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: EtOAc–MeOH (19:1)
Flow rate: 0.5 mL/min



BBPI **21d**
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: EtOAc
Flow rate: 0.5 mL/min



BBPI **21e**
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: MeOH
Flow rate: 0.4 mL/min



BBPI **24**
Inertsil diol column (4.6 mm i.d. × 250 mm)
Eluent: MeOH
Flow rate: 1.0 mL/min

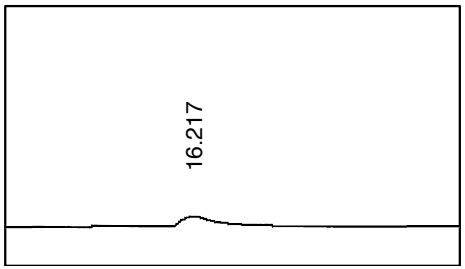


Figure S53. HPLC profiles of lamellarin D (**5**) and BBPIs **20**, **22a**–**e**, and **24**.

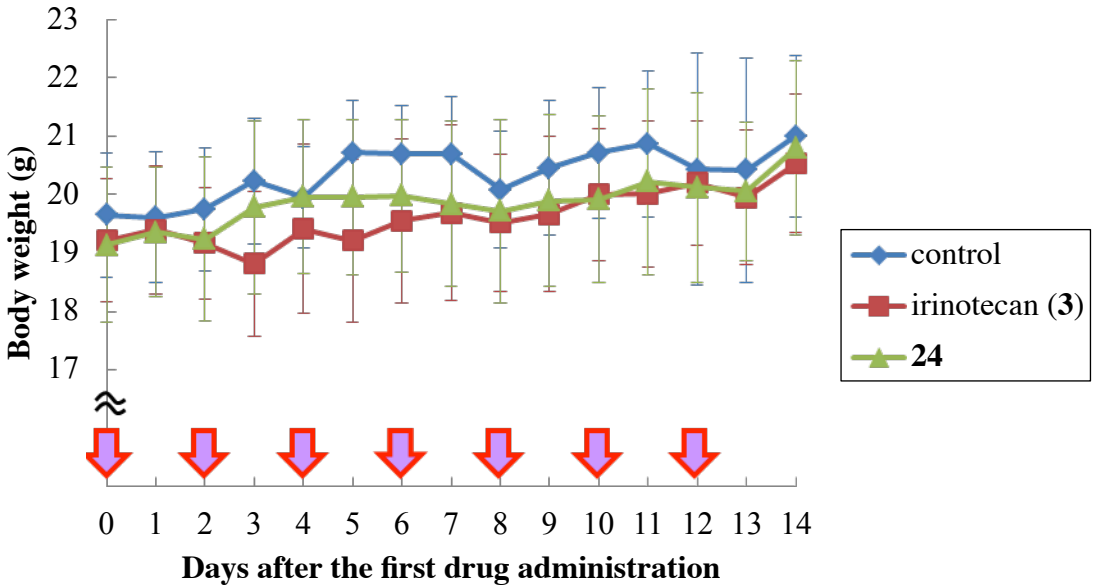


Figure S54. Changes in body weight of BALB/c mice treated with irinotecan (**3**) or **24**.