Supporting Information

Modular Synthesis of Di- and Trisubstituted Imidazoles from Ketones and Aldehydes: A Route to Kinase Inhibitors

Ian de Toledo[1], Thiago A. Grigolo[1], James M. Bennett[2], Jonathan M. Elkins[2,3], Ronaldo A. Pilli[1]*.

[1] *Department of Organic Chemistry, Institute of Chemistry, University of Campinas, UNICAMP, Campinas, CEP 13083-970 (Brazil)*

[2] *Structural Genomics Consortium, Nuffield Department of Medicine, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford, OX3 7DQ, UK*

[3] *Structural Genomics Consortium, Departamento de Genética e Evolução, Instituto de Biologia, UNICAMP, Campinas, SP, 13083-886, Brazil*

**e-mail: pilli@iqm.unicamp.br*

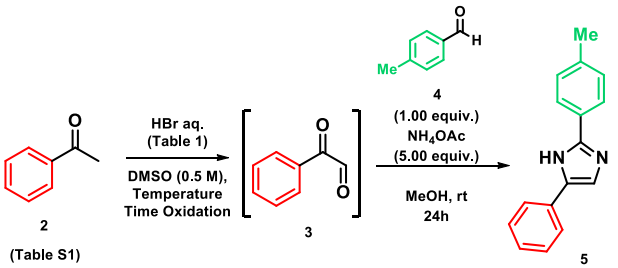
Table Of Contents

1. Optimization Data

Optimization of the reaction conditions. *5-phenyl-2-(p-tolyl)-1H-imidazole (**5**)*. A 6 mL vial was charged with acetophenone **2** (46 mg, 0.375 mmol, 1.25 equiv.), DMSO (0.75 mL, 0.5 M), concentrated aqueous HBr (48% w/w, 8.9 M) (4.24 μL, 0.03 mmol, 10 mol%), deionized water (71 μL) and a magnetic stirrer bar under air. The reaction mixture was stirred in a pre-heated aluminum block at 85 ºC and was followed by TLC analysis (30% AcOEt/Hex, p-ASD). After consumption of starting material, the reaction mixture was cooled to room temperature and diluted with MeOH (1.25 mL, 0.19 M, final concentration relative to acetophenone 2**,** 2:8 mixture of DMSO:MeOH). This stock DMSO:MeOH solution was added dropwise over 30 minutes via syringe to a 6 mL vial containing *p*-tolualdehyde **4** (37 mg, 0.30 mmol, 1.00 equiv.), NH_4OAc (116 mg, 1.50

mmol, 5.00 equiv.) and MeOH (1.5 mL, 0.2 M in relation to **4**). The reaction mixture was stirred at room temperature for 18h and then poured directly into a separatory funnel containing a mixture of satd. $NaHCO_3$ and satd. $Na_2S_2O_3$ (1:1, 1x 20 mL) and AcOEt (10 mL). The phases were separated and the aqueous phase was extracted with AcOEt (5x 5 mL). The organic phases were combined, washed with satd. NaCl solution (1x 5 mL), dried over Na_2SO_4, filtered and concentrated in the rotaevaporator. The residue was diluted with AcOEt (5 mL) and a 1 mL aliquot was taken and concentrated in vacuo. To this, 1,3,5-trimethoxybenzene (10.2 mg, 0.06 mmol) and acetone-d_6 (0.6 mL) was added and the sample was analyzed by ^{1}H NMR. The crude mixtures were combined and purification of the residue by silica gel chromatography, eluting with AcOEt in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **5** as a white solid (69% yield, 48 mg, 0.21 mmol).

Table S1. Optimization of the reaction conditions for the synthesis of the disubstituted imidazole **5**

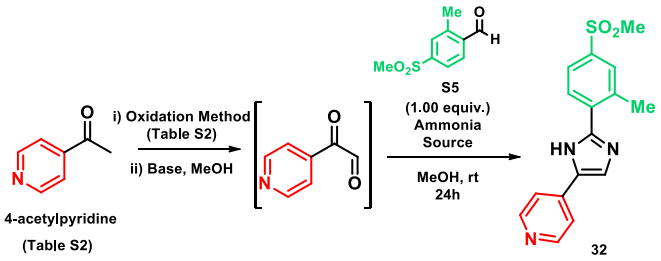


Entry	HBr loading (mol%)	Temperature (°C)	Time Oxidation (h)	Solvent	Acetophenone (equiv.)	Yield[b] (%)
1	200	60	24	MeOH:DMSO (8:2)	1.00	48
2	100	60	48	MeOH:DMSO (8:2)	1.00	54
3	50	60	72	MeOH:DMSO (8:2)	1.00	57
4	50	85	12	MeOH:DMSO (8:2)	1.00	55
5	30	85	18	MeOH:DMSO (8:2)	1.00	60
6	10	85	18	MeOH:DMSO (8:2)	1.00	61
7	10	85	18	EtOH:DMSO (8:2)	1.00	49
8	10	85	18	*n*-PrOH:DMSO (8:2)	1.00	56
9	10	85	18	*i*-PrOH:DMSO (8:2)	1.00	44
10	10	85	18	MeOH:DMSO:MeCN (5:2:3)	1.00	45
11	10	85	18	MeOH:DMSO:DCM (5:2:3)	1.00	44
12	10	85	18	MeOH:DMSO:DMF (5:2:3)	1.00	45
13	10	85	18	MeOH:DMSO:PhMe (5:2:3)	1.00	47
14	10	85	18	MeOH:DMSO:THF (5:2:3)	1.00	44
15	10	85	18	MeOH:DMSO:AcOEt (5:2:3)	1.00	43
16	10	85	18	MeOH:DMSO (3:7)	1.00	45
17	10	85	18	**MeOH:DMSO (8:2)**	**1.25**	**69 (69)**
18	**10**	**85**	**18**	MeOH:DMSO (8:2)	1.50	66
19	10	85	18	MeOH:DMSO (8:2)	1.75	73
20	10	85	18	MeOH:DMSO (8:2)	2.00	67
21[c]	10	85	18	**DMSO then MeOH**	**1.25**	**(52)**

[a]Oxidation step performed using acetophenone **2** (**Table 1**), aqueous HBr (48% w/w, 8.9 M) (**Table 1**) and DMSO (0.50 M). Condensation step performed by slow addition (30 min) of glyoxal **3** solution in MeOH:DMSO (8:2, 0.19 M relative to acetophenone **2**) to a mixture of tolualdehyde **4** (0.3 mmol) and NH_4OAc (1.5 mmol) in MeOH (1 mL, 0.20 M) [b]Yield after work-up as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard. Isolated yield given in parentheses. [c] **Performed under stepwise procedure. Oxidation step:** Acetophenone **2** (**Table S1**), aqueous HBr (48% w/w, 8.9 M) (**Table S1**) and DMSO (0.50 M) (66% isolated yield). Condensation step performed by slow addition (30 min) of glyoxal **3** (1.25 equiv.) solution in MeOH (0.19 M relative to glyoxal **3**) to a mixture of tolualdehyde **4** (0.168 mmol) and NH_4OAc (5.00 equiv.) in MeOH (0.20 M) (79% isolated yield)

Optimization of the reaction conditions. *4-(2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**32**).* A 10 mL round-bottom flask was charged with 4-acetylpiridine (219 mg, 1.70 mmol, 1.70 equiv.), magnetic stirrer bar and DMSO (3.5 mL, 0.5 M) under air and concentrated HBr aqueous (48% w/w, 8.9 M) (595 mL, 5.25 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was stirred in pre-heated oil bath at 60 ºC for 8h. After consumption of the starting material, indicated by TLC analysis (AcOEt, *p*-ASD*)*, the reaction mixture was left to reach room temperature and MeOH (5.7 mL, 0.19 M) was added. This reaction mixture was added dropwise over 30 minutes via syringe to a solution of **S5** (198 mg, 1.00 mmol, 1.00 equiv.) and NH_4OAc (771 mg, 10.0 mmol, 10.0 equiv.) in MeOH (5 mL, 0.2 M in relation to **S5**) at room temperature. The reaction mixture was stirred at room temperature for 18h and the solvent was removed in the rotaevaporator, the residue was diluted with 10% MeOH/DCM (10 mL) and poured into separatory funnel containing satd. $NaHCO_3$ (1x 40 mL) and 10% MeOH/DCM (1x 15 mL). The phases were separated, and the aqueous phase was extracted with 10% MeOH/DCM (7x 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in the rotaevaporator. Purification by silica gel chromatography, eluting with MeOH in DCM (gradient elution 5% → 9%) yielded **32** as a pale yellow solid (67% yield, 210 mg, 0.67 mmol).

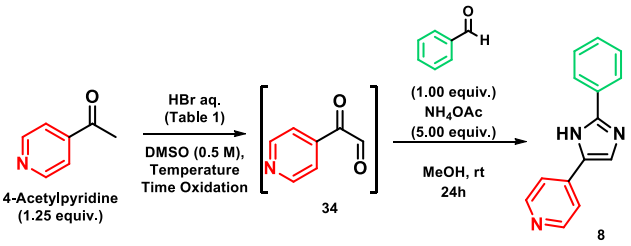
Table S2. Optimization of the reaction conditions for the synthesis of the disubstituted imidazole **32**



Entry	Oxidation Method	Base	Time Oxidation	Ammonia Source	4-acetylpyridine (equiv.)	Yield[a] (%)
1[b]	DMSO/48% HBr aq.	Na_2CO_3	12h	NH_4OAc (10 equiv.)	1.00	45
2c	DMSO/NaBr/H_2SO_4	Na_2CO_3	10 min	NH_4OAc (10 equiv.)	1.00	19
3d	DMSO/I_2	Na_2CO_3	8h	NH_4OAc (10 equiv.)	1.00	-
4[b]	DMSO/48% HBr aq.	K_2CO_3	8h	NH_4OAc (10 equiv.)	1.50	57
5[b]	DMSO/48% HBr aq.	Et_3N	8h	NH_4OAc (10 equiv.)	1.50	54
6[b]	DMSO/48% HBr aq.	Et_3N	24h	NH_4OAc (10 equiv.)	1.50	48
7[e]	DMSO/48% HBr aq.	Et_3N	8h	NH_4OAc (10 equiv.)	1.50	53
8[b]	DMSO/48% HBr aq.	$(NH_4)_2CO_3$	8h	$(NH_4)_2CO_3$ (10 equiv.)	1.50	51
9[b]	DMSO/48% HBr aq.	-	8h	NH_4OAc (10 equiv.)	1.50	66
10[b]	DMSO/48% HBr aq.	-	8h	NH_4OAc (10 equiv.)	1.75	67
11[b]	DMSO/48% HBr aq.	-	8h	NH_4OAc (10 equiv.)		

[a]Oxidation step performed using 4-acetylpyrydine (**Table S2**), aqueous HBr (48% w/w, 8.9 M) (**300 mol%**) and DMSO (0.50 M). Condensation step performed by slow addition (30 min) of glyoxal solution in MeOH:DMSO (8:2, 0.19 M relative to 4-acetylpyridine) to a mixture of aldehyde (1.0 mmol) and NH_4OAc (10 mmol) in MeOH (3.3 mL, 0.30 M). [a]Isolated yield after column cromatography [b]300 mol% of HBr aq. was employed and the reaction was stirred at 60 ºC [c] Oxidation step performed according conditions reported by Karpov and colaborators[1] [d] Oxidation step performed according conditions reported by Zhu and colaborators[2] [e]Performed under reduced pressure (~60 mmHg)

Table S3. Optimization of the reaction conditions for the synthesis of the disubstituted imidazole **8**



Entry	HBr loading (mol%)	Temperature (°C)	Time Oxidation (h)	Solvent	Yield[b] (%)
1	10	85	24	MeOH:DMSO (8:2)	0
2	110	85	4	MeOH:DMSO (8:2)	29
3	200	85	4	MeOH:DMSO (8:2)	49
4	300	60	8	MeOH:DMSO (8:2)	56

[a]Oxidation step performed using 4-acetylpyridine (**1.25 equiv.**), aqueous HBr (48% w/w, 8.9 M) (**Table S3**) and DMSO (0.50 M). Condensation step performed by slow addition (30 min) of glyoxal **3** solution in MeOH:DMSO (8:2, 0.19 M relative t o4-acetylpyridine) to a mixture of benzaldehyde (0.3 mmol) and NH_4OAc (1.5 mmol) in MeOH (1.5 mL, 0.20 M) [b] **Isolated yield.**

2. NMR Considerations

It was noted during the course of this project that addition of TFA and D_2O to the sample in DMSO-d_6 for NMR characterization provided enhancement in resolution due to conversion of both tautomers present in the mixture to the corresponding protonated TFA salt. For substrates that did not provided a clear NMR spectrum, such as the three substituted imidazoles and some disubstituted imidazoles, the mixture of 0.5 mL of DMSO-d_6, 0.1 mL of D_2O and 8 μL of TFA was the solvent of choice for carrying NMR analysis when the substrate was not acid labile. The improvement in the spectra resolution can be seen in **Figures 1-4** for the trisubstituted imidazole **59** in both ^1H and ^{13}C NMR. When this mixture of solvents was used, a broad signal corresponding to peak of HOD at 4.20 – 4.00 ppm appears in the ^1H NMR spectra and two quartets at δ 159.5 (q, J_{CF} = 36.8 Hz) e 116.4 (q, J_{CF} = 290.8 Hz), corresponding to two carbons present in the TFA, are seen in the ^{13}C NMR spectra.

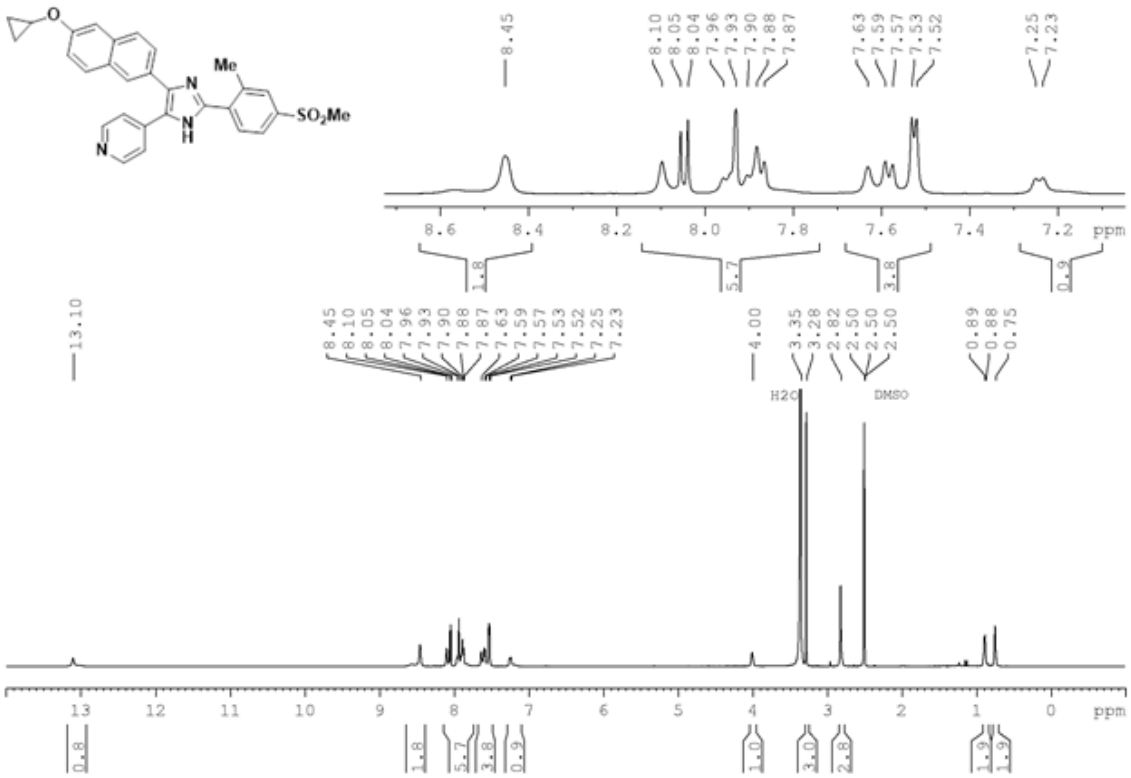


Figure S1. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **59**

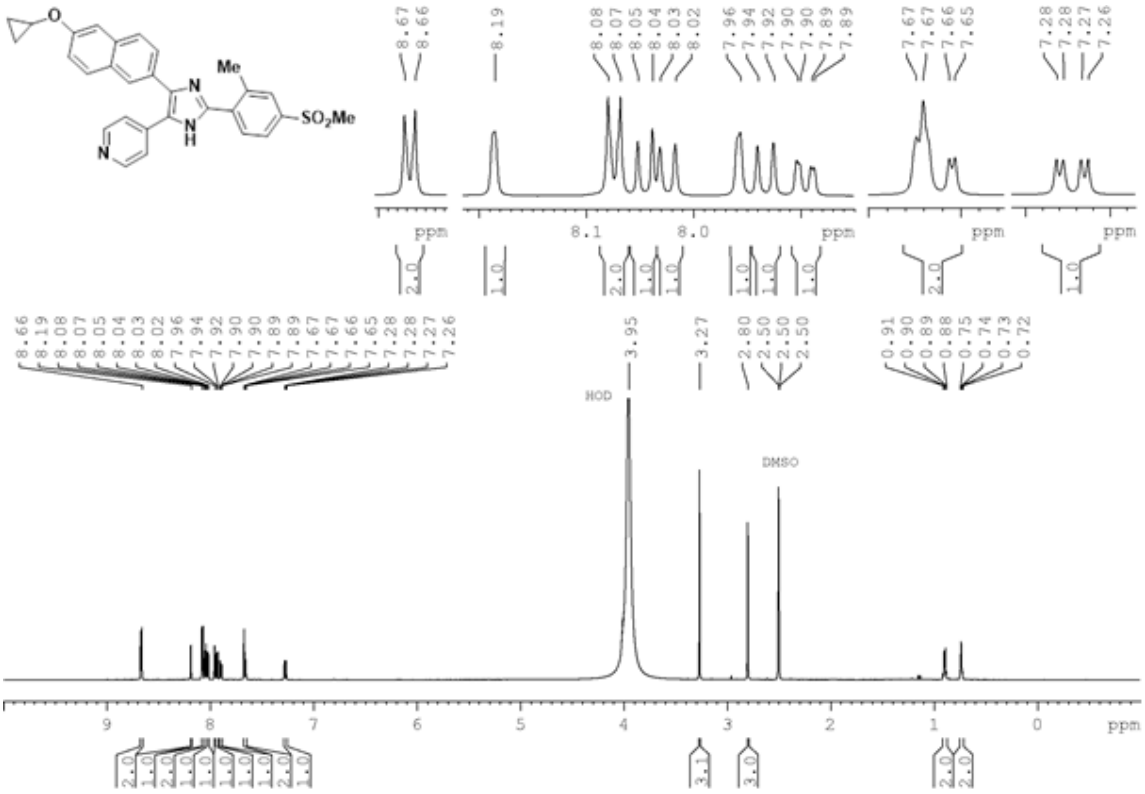


Figure S2. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 600 MHz) of **59**

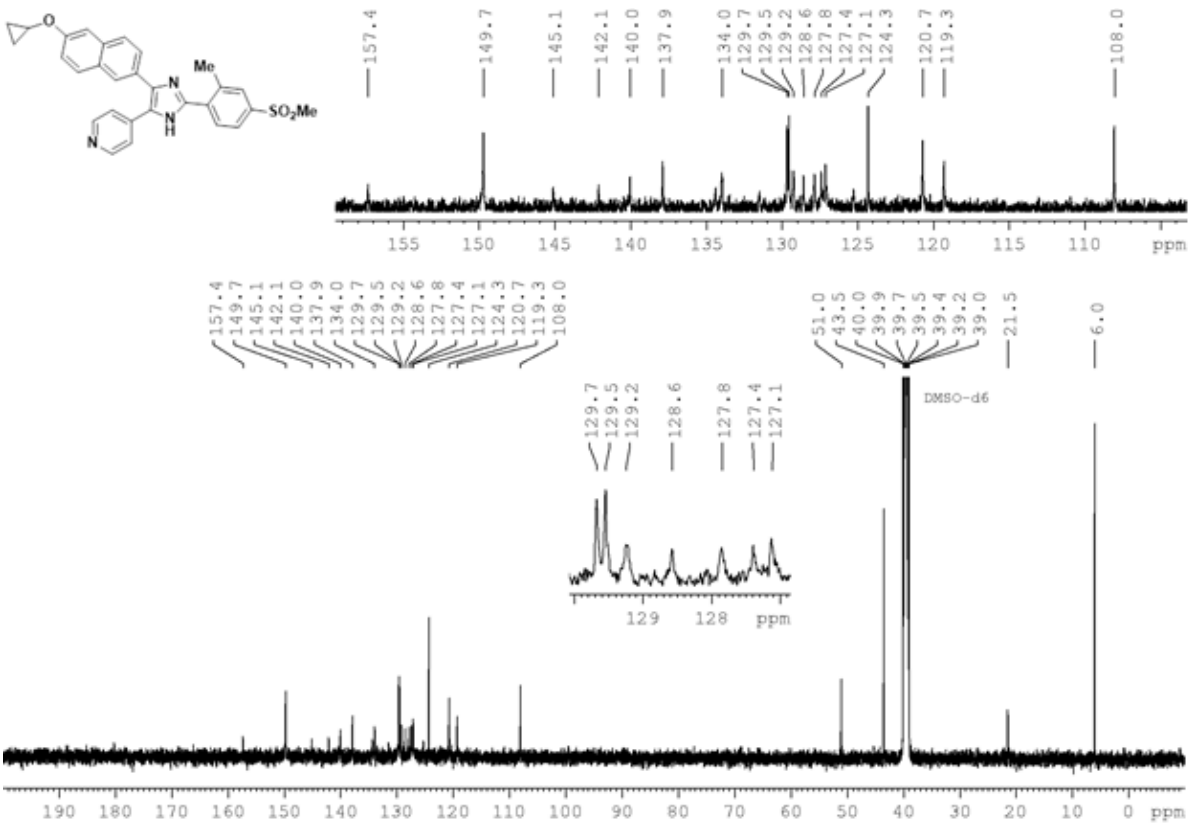


Figure S3. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **59**

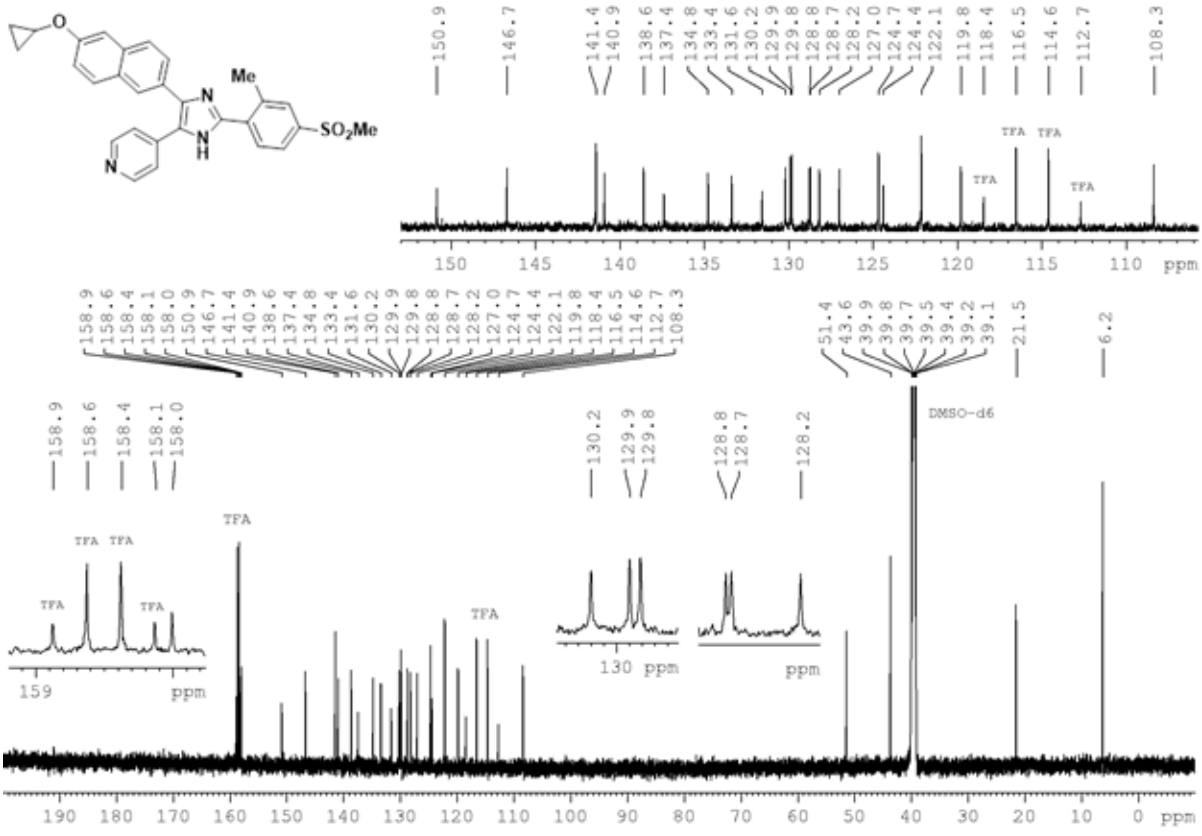
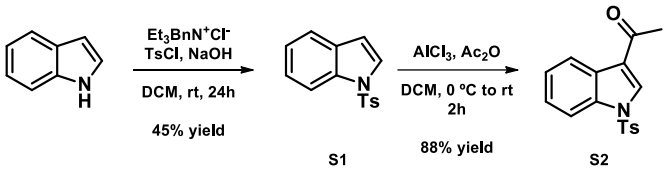
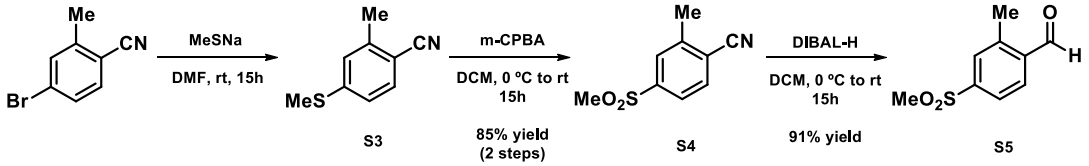


Figure S4. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 151 MHz) of **59**

3. Synthesis of compounds S1-S16



1-Tosyl-1H-indole (**S1**) and 1-(1-tosyl-1H-indol-3-yl)ethenone (**S2**) were prepared according to literature procedure[1]



*2-Methyl-4-(methylthio)benzonitrile (***S3***)*. Following a modified literature procedure[2,3]. A 250 mL round-bottom flask was charged with 4-bromo-2-methylbenzonitrile (3.03 g, 15.0 mmol, 1.00 equiv.), a magnetic stirrer bar and dry DMF (30 mL, 0.5 M) under inert atmosphere. Then, sodium thiomethoxide (1.22 g, 16.5 mmol, 1.10 equiv.) was added in portions by briefly removing the Suba seal and the reaction mixture was stirred for 15h at room temperature. After consumption of the starting material, indicated by TLC analysis (20% AcOEt/Hex), water (1x 150 mL) was added and the aqueous phase was extracted with Et_2O (3x 90 mL). The organic phases were combined, washed with a mixture of satd. NaCl:H_2O (1:1, v/v) (3x 75 mL), dried over $MgSO_4$, filtered and concentrated in the rotaevaporator to afford a pale yellow solid (quantitative yield, 2.45 g, 15.0 mmol). The crude solid was used in the next step without further purification. A small amount (~20 mg) was purified by column flash chromatography (0 → 20% AcOEt/Hex) for further characterization. $\mathbf{R_f}$ = 0.52 (20% AcOEt/Hex, UV, KMnO4, I_2/SiO_2); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.46 (d, *J* = 8.2 Hz, 3H), 7.10 (s, 1H), 7.06 (dd, *J* = 8.1, 2.0 Hz, 1H), 2.50 (s, 3H), 2.49 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$) δ** 145.8, 142.2, 132.6, 126.5, 122.9, 118.4, 108.4, 20.6, 14.8 ; **ν_{max} (cm^{-1}, thin film, ATR):** 2920 (w), 2900 (w), 2217 (m), 1595 (s), 1584 (w), 1486 (w), 1440 (w), 1397 (w), 1380 (w), 1220 (m), 1206 (w), 1189 (w), 1083 (m), 966 (w), 888 (m), 872 (w), 813 (m), 806 (s); **mp:** 60.0 – 62.0 °C (AcOEt). Spectroscopic data are in accordance with the literature[2]

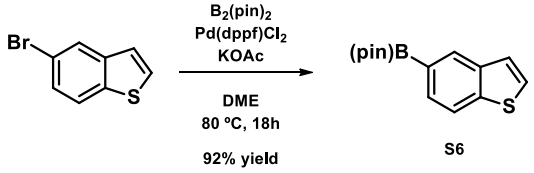
*2-Methyl-4-(methylsulfonyl)benzonitrile (***S4***)* A 100 mL round-bottom flask was

charged with the crude product (2.45 g, 15.0 mmol, 1.00 equiv.), a large magnetic stirrer bar (2 cm x 1 cm) and DCM (55 mL, 0.27 M) under air. The solution was cooled to 0 ºC in ice/water bath and solid *m*-CPBA (77% peracid, 8.07 g, 36.0 mmol, 2.40 equiv.) was added in small portions over 10 minutes, under vigorous stirring. After the addition, the mixture was stirred at 0 ºC for 20 minutes and then for 15h at room temperature. After consumption of the starting material, indicated by TLC analysis (20% AcOEt/Hex), the reaction mixture was poured in a separation funnel containing Et_2O (350 mL) and NaOH 2M aqueous (75 mL) and the phases were separated. The organic phase was washed with a mixture of satd. $NaHCO_3$ and satd. $Na_2S_2O_3$ (1:1, v/v) (3x 75 mL), followed by washing with satd. NaCl (1x 75 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in the rotaevaporator. The residue was purified by recrystallization with AcOEt and hexanes to afford **S4** (85% for two steps, 2.49 g, 12.7 mmol) as colorless needles. **R_f** = 0.54 (50% AcOEt/Hex, $KMnO_4$, Dragendorff); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.92 (d, *J* = 0.5 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H), 2.67 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 144.3, 144.0, 133.7, 129.1, 125.3, 118.2, 116.5, 44.4, 20.8; **ν_{max} (cm^{-1}, thin film, ATR):** 3010 (w), 2932 (w), 2231 (w), 1400 (w), 1389 (w), 1322 (w), 1303 (s), 1287 (s), 1178 (w), 1144 (m), 1120 (s), 1089 (m), 968 (s), 898 (w), 888 (w), 832 (m), 763 (s); **mp:** 147.9 – 148.9 °C (AcOEt/Hex).

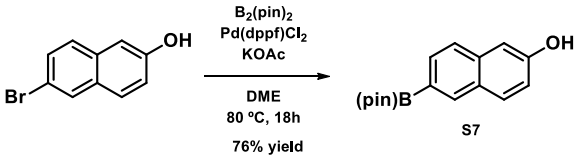
2-Methyl-4-(methylsulfonyl)benzaldehyde (**S5**) A 250 mL round-bottom flask was charged with 2-methyl-4-(methylsulfonyl)benzonitrile (2.48 g, 12.7 mmol, 1.00 equiv.), a magnetic stirrer bar and dry DCM (51 mL, 0.25 M) under inert atmosphere. The mixture was stirred and cooled to -15 ºC in an ice/brine bath for 15 minutes and then DIBAL-H (99%, 2.9 mL, 15.2 mmol, 1.20 equiv.) in dry DCM (15.2 mL) was added dropwise along the flask wall over 30 minutes using syringe pump. The reaction mixture was left stirring at -15 ºC for 1h, and then, at 0 ºC for 3h. After consumption of the starting material, indicated by TLC analysis (50% AcOEt/Hex, Dragendorff stain), MeOH (1x 10 mL) and HCl 1 M aqueous (1x 10 mL) were added at 0 ºC, the ice/water bath was removed, and the reaction mixture was left to reach room temperature. Then, HCl 1 M aqueous (1x 100 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (5x 100 mL) and the organic phases were combined, washed with satd. NaCl solution (1x 75 mL), dried over $MgSO_4$, filtered and concentrated in the rotaevaporator to afford **S5** as a white solid (91% yield, 2.13 g, 10.7 mmol) which was used without

further purification. **R_f** = 0.52 (50% AcOEt/Hex, UV, $KMnO_4$); **^{1}H NMR (400 MHz, $CDCl_3$) δ** 10.36 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.0 , 1.3 Hz, 1H), 7.85 (s, 1H), 3.07 (s, 3H), 2.75 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 191.4, 144.4, 142.1, 137.6, 132.4, 130.6, 125.3, 44.3, 19.6; **ν_{max} (cm^{-1}, thin film, ATR):** 3010 (w), 2952 (w), 2862 (w), 1694 (m), 1599 (w), 1457 (w), 1394 (w), 1310 (s), 1292 (s), 1184 (w), 1147 (s), 1112 (w), 1089 (w), 965 (m), 826 (w), 796 (w), 759 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ calcd. for $C_9H_{11}O_3S$ 199.0423; Found 199.0418; **mp:** 118.2 – 120.9 °C (AcOEt). Spectroscopic data are in accordance with the literature[4]

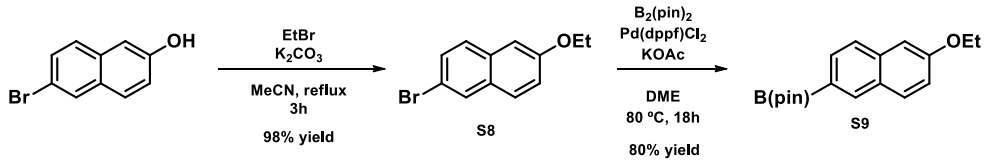
Miyaura Borylation: General Procedure A. A sealed tube was charged with the corresponding bromide (1.00 equiv.), $B_2(pin)_2$ (1.05 – 1.50 equiv.), Pd(dppf)Cl_2•DCM (5 mol%) and KOAc (3.00 equiv.) and a magnetic stirrer bar under inert atmosphere. Then, degassed DME (0.4 M) was added and the tube glass tube was sealed. The reaction mixture was stirred in a pre-heated oil bath at 80 ºC for 14-18h. After consumption of the starting material, indicated by TLC analysis, the reaction mixture was allowed to reach room temperature and it was diluted with DCM, filtered in pad silica gel (3 cm) which was washed with DCM until all product was eluted and the filtrate was concentrated under in the reduced pressure. The crude product was purified by silica gel column chromatography.



*2-(Benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (***S6***)*. The title compound was prepared according to general procedure A, using 5-bromobenzo[b]thiophene (330 mg, 1.5 mmol, 1.00 equiv.), $B_2(pin)_2$ (589 mg, 2.25 mmol, 1.50 equiv.), Pd(dppf)Cl_2•DCM (56 mg, 5 mol%) and KOAc (442 mg, 4.50 mmol, 3.00 equiv.). Purification by silica gel chromatography, eluting with Et_2O in hexanes (21 cm x 20 mm, gradient elution, 0% → 10%, 1% increases, 50 mL runs, 15 mL fractions) yielded **S6** as white solid (92% yield, 359 mg, 1.38 mmol). **R_f** = 0.20 (5% Et_2O/Hex, UV, Curcumin). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.32 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 5.3 Hz, 1H), 7.35 (d, *J* = 5.5 Hz, 1H), 1.38 (s, 12H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 142.8, 139.3, 130.9, 129.9, 126.1, 124.3, 122.0, 84.0, 25.1. Spectroscopic data are in accordance with the literature[5].



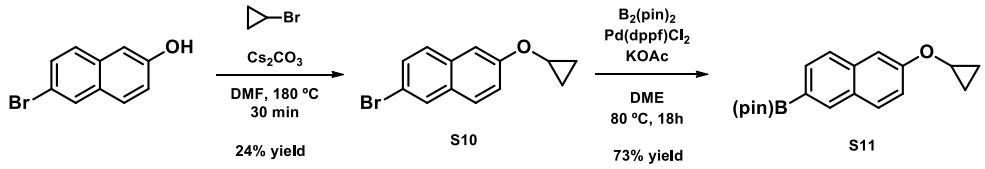
*6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (***S7***).* The title compound was prepared according to general procedure A, using 6-bromo-2-naphthol (341 mg, 1.50 mmol, 1.00 equiv.), $B_2(pin)_2$ (589 mg, 2.25 mmol, 1.50 equiv.), $Pd(dppf)Cl_2$•DCM (56 mg, 5 mol%) and KOAc (442 mg, 4.50 mmol, 3.00 equiv.). Purification by silica gel chromatography, eluting with acetone in hexanes (20 cm x 20 mm, gradient elution, 0% → 20%, 2% increases, 50 mL runs, 15 mL fractions) yielded **S7** as a white solid (76% yield, 310 mg, 1.15 mmol). $\mathbf{R_f}$ = 0.15 (10% Acetone/Hex, UV, $KMnO_4$, Curcumin stain). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.30 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.82 – 7.75 (m, 2H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.42 (s, 1H), 1.39 (s, 12H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 154.6, 136.6, 136.3, 131.3, 130.9, 128.5, 125.7, 117.9, 109.5, 84.1, 25.0. **ν_{max} (cm^{-1}, thin film, ATR):** 3288 (br), 2980 (w), 1624 (m), 1485 (s), 1426 (w), 1389 (m), 1377 (m), 1354 (m), 1330 (s), 1298 (m), 1273 (w), 1201 (s), 1169 (w),1137 (s), 1078 (m), 962 (w), 926 (w), 912 (w), 858 (s), 839 (m), 818 (w), 705 (w), 691 (s). **HRMS (ESI+/TOF) m/z:** peak not found in HRMS analysis. **mp:** 158.3 – 160.1 °C (acetone/hexanes).



2-Bromo-6-ethoxynaphthalene (**S8**) was prepared according to literature procedure[6].

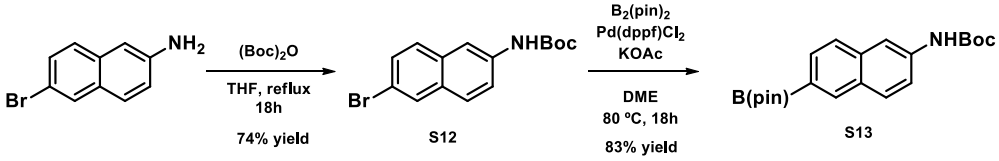
*2-(6-ethoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (***S9***).* The title compound was prepared according to general procedure A, using **S8** (126 mg, 0.5 mmol, 1.00 equiv.), $B_2(pin)_2$ (196 mg, 0.75 mmol, 1.50 equiv.), $Pd(dppf)Cl_2$•DCM (19 mg, 5 mol%) and KOAc (147 mg, 1.50 mmol, 3.00 equiv.). Purification by silica gel chromatography, eluting with AcOEt in Hexanes (20 cm x 20 mm, gradient elution, 0% → 10%, 1% increases, 50 mL runs, 15 mL fractions) yielded **S9** as a white solid (80% yield, 119 mg, 0.04 mmol). $\mathbf{R_f}$ = 0.37 (5% AcOEt/Hexanes, Curcumin Stain). **^{1}H NMR**

(500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.80 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.13 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H), 1.39 (s, 12H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.0, 136.6, 136.1, 131.2, 130.3, 128.5, 126.0, 119.1, 106.5, 83.9, 63.6, 25.1, 14.9. **ν_{max} (cm^{-1}, thin film, ATR):** 2979 (w), 2922 (w), 1625 (m), 1477 (m), 1380 (m), 1342 (m), 1293 (w), 1271 (w), 1206 (s), 1168 (w), 1140 (m), 1111 (w), 1079 (m), 962 (w), 939 (w), 910 (w), 861 (m), 834 (w), 824 (m), 709 (w), 694 (m). **HRMS (ESI+/TOF) m/z:** peak not found in HRMS analysis. **mp:** 88.8 – 91.2 °C (AcOEt)**.**



2-Bromo-6-cyclopropoxynaphthalene (**S10**) was prepared according to literature procedure[7].

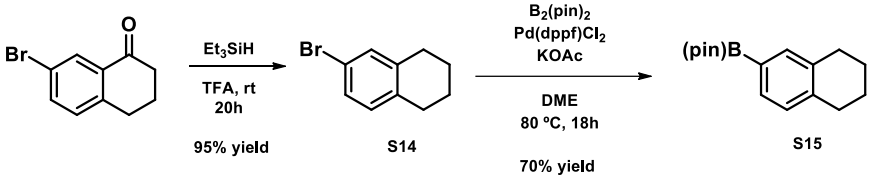
*2-(6-cyclopropoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (***S11***).* The title compound was prepared according to general procedure A, using **S10** (105 mg, 0.4 mmol, 1.00 equiv.), $B_2(pin)_2$ (110 mg, 0.42 mmol, 1.05 equiv.), Pd(dppf)Cl_2•DCM (15 mg, 5 mol%) and KOAc (118 mg, 1.2 mmol, 3.00 equiv.). Purification by silica gel chromatography, eluting with AcOEt in hexanes (10 cm x 20 mm, gradient elution, 0% → 10%, 1% increases, 30 mL runs, 10 mL fractions) yielded **S11** as a white solid (73% yield, 91 mg, 0.29 mmol). **R_f** = 0.28 (5% AcOEt/Hex, UV, Curcumin Stain). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.29 (s, 1H), 7.81 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 2.6, 8.8 Hz, 1H), 3.89 – 3.84 (m, 1H), 1.39 (s, 12H), 0.87 – 0.81 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.0, 136.5, 136.1, 131.2, 130.3, 128.7, 126.1, 118.7, 108.1, 83.9, 51.1, 25.1, 6.4. Spectroscopic data are in accordance with the literature[7].



*Tert-butyl (6-bromonaphthalen-2-yl)carbamate (***S12***).* Following a modified literature procedure[8]. In 10 mL round-bottom flask, 3-amino-2-naphthol (680 mg, 3.00

mmol, 1.00 equiv.) and a magnetic stir bar was added under N_2 atmosphere. Anhydrous THF (6 mL, 0.5 M) was added via syringe followed by $(Boc)_2O$ (0.88 mL, 3.75 mmol, 1.25 equiv). The reaction mixture was then refluxed with stirring and monitored via TLC. After consumption of the starting material, the reaction mixture was cooled and THF was removed under reduced pressure and the residue was directly purified through flash column chromatography (0% -> 15% EtOAc/Hex, 4% increase until 12%, 12% (2x runs), 3% increase until 15%, 12% (2x runs), 100 mL runs). A pinkish solid was obtained which was triturated with hexanes (5-6 x 30 mL) to afford **S12** as a white solid (74% yield, 714 mg, 2.22 mmol). $\mathbf{R_f}$ = 0.60 (20% AcOEt/Hex, UV, *p*-ASD). **^{1}H NMR (500 MHz, DMSO) δ** 9.64 (s, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.47 (m, 2H), 1.50 (s, 9H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ** 152.8, 137.8, 132.2, 130.3, 129.3, 129.3, 129.2, 127.6, 120.6, 116.8, 113.3, 79.4, 28.1. Spectroscopic data are in accordance with the literature[9].

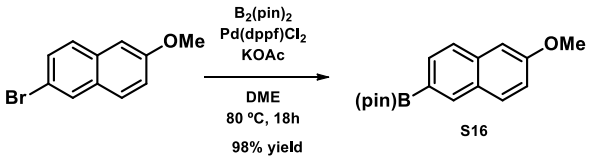
*Tert-butyl (6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)carbamate (***S13***)*. The title compound was prepared according to general procedure A, using **S12** (488 mg, 1.50 mmol, 1.00 equiv.), $B_2(pin)_2$ (589 mg, 2.25 mmol, 1.50 equiv.), $Pd(dppf)Cl_2$•DCM (56 mg, 5 mol%) and KOAc (442 mg, 4.5 mmol, 3.00 equiv.). Purification by silica gel chromatography, eluting with AcOEt in hexanes (18 cm x 30 mm, gradient elution, 0% → 20%, 1% increases until 10% then 2% increases until 20%, 100 mL runs, 20 mL fractions) yielded a white solid which was triturated (1x 10 mL) and washed with hexanes (4x 10 mL) to afford **S13** as a white solid (83% yield, 461 mg, 1.25 mmol). $\mathbf{R_f}$ = 0.32 (10% AcOEt/Hex, UV, Curcumin Stain). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.28 (s, 1H), 7.99 (s, 1H), 7.80 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.68 (s, 1H), 1.55 (s, 9H), 1.38 (s, 12H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 152.8, 137.0, 136.0, 135.9, 131.2, 129.7, 129.5, 126.6, 119.1, 114.3, 84.0, 80.9, 28.5, 25.1. Spectroscopic data are in accordance with the literature[9].



*6-Bromo-1,2,3,4-tetrahydronaphthalene (***S14***)*. Following a modified literature procedure[10]. To a stirred solution of the 7-bromotetralone (1150 mg, 5.00 mmol, 1.00

equiv.) in trifluoroacetic acid (3.1 mL, 40.0 mmol, 8.00 equiv.) at room temperature was added the Et_3SiH (1.8 mL, 11.0 mmol, 2.20 equiv) dropwise. After addition of Et_3SiH, reaction mixture became slightly warm and, after 30 min, the solution turned cloudy. After 1h40, starting material was not totally consumed. Then, Et_3SiH (0.8 mL, 5 mmol, 1 equiv.) was added and the reaction mixture was left to stir for 12h. After consumption of the starting material, indicated by TLC analysis, the reaction mixture was added dropwise to a cooled sat. $NaHCO_3$ solution (60 mL). After neutralization, the aqueous layer was extracted with ether (3x 40 mL). The organic layers were combined, washed with brine and dried over $MgSO_4$. Purification by silica gel chromatography, eluting with hexanes (22 cm x 30 mm, isocratic elution, 400 mL run, 20 mL fractions) yielded **S14** as a translucent oil (95% yield, 1.00 g, 4.74 mmol). $\mathbf{R_f}$ **=** 0.48 (Hexanes, $KMnO_4$ stain). **^{1}H NMR (250 MHz, $CDCl_3$) δ** 7.23 – 7.15 (m, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 2.79 – 2.64 (m, 4H), 1.85 – 1.70 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 139.5, 136.2, 131.9, 130.9, 128.5, 119.0, 29.3, 29.0, 23.1, 22.9. Spectroscopic data are in accordance with the literature[11].

*4,4,5,5-Tetramethyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3,2-dioxaborolane (***S15***)*. The title compound was prepared according to general procedure A, using **S14** (317 mg, 1.05 mmol, 1.00 equiv.), $B_2(pin)_2$ (412 mg, 2.25 mmol, 1.50 equiv.), $Pd(dppf)Cl_2$•DCM (56 mg, 5 mol%) and KOAc (442 mg, 4.5 mmol, 3.00 equiv.). Purification by silica gel chromatography, eluting with DCM in hexanes (20 cm x 20 mm, isocratic elution, 25% DCM/Hex, 300 mL run, 12 mL fractions) yielded **S15** as a white solid (70% yield, 273 mg, 1.06 mmol). $\mathbf{R_f}$ **=** 0.37 (25% DCM/Hex, UV, Curcumin Stain, $KMnO_4$ stain). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.55 – 7.51 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 2.82 – 2.75 (m, 4H), 1.83 – 1.76 (m, 4H) 1.34 (s, 12H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 140.9, 136.7, 135.8, 131.9, 128.8, 83.7, 29.8, 29.3, 25.0, 23.4, 23.2. Spectroscopic data are in accordance with the literature[11]



2-(6-methoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**S16**). The title compound was prepared according to general procedure A, using 2-bromo-6-methoxynaphthalene (367 mg, 1.50 mmol, 1.00 equiv.), $B_2(pin)_2$ (412 mg, 1.58 mmol,

1.05 equiv.), Pd(dppf)Cl_2•DCM (56 mg, 5 mol%) and KOAc (442 mg, 4.50 mmol, 3.00 equiv.). Purification by silica gel chromatography, eluting with AcOEt in Hexanes (15 cm x 15 mm, isocratic elution, 10% AcOEt/Hex, 250 mL run, 20 mL fractions) yielded **S16** as a white solid (98% yield, 415 mg, 1.46 mmol). $\mathbf{R_f}$ = 0.37 (5% AcOEt/Hexanes, Curcumin Stain). Spectroscopic data are in accordance with the literature[12]

4. TR-FRET binding displacement assay

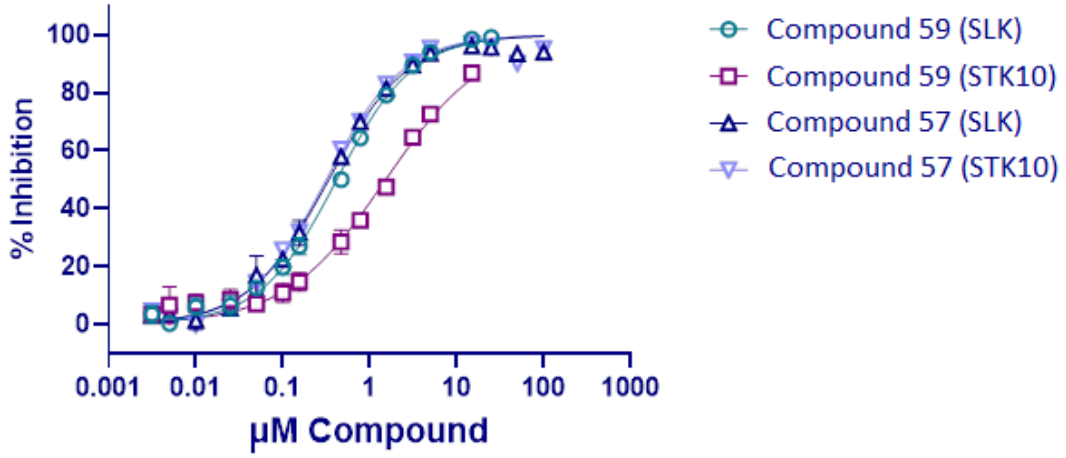


Figure S5. Percentage inhibition for compounds 57 and 59 against STK10 and SLK as measured in a TR-FRET binding–displacement assay. Each measurement was measured in duplicate.

5. References

(1) Gharpure, S. J.; Anuradha, D.; Prasad, J. V. K.; Srinivasa Rao, P. Stereoselective Synthesis of *Cis* -2,6-Disubstituted Morpholines and 1,4-Oxathianes by Intramolecular Reductive Etherification of 1,5-Diketones. *Eur. J. Org. Chem.* **2015**, *2015* (1), 86–90.

(2) Bruce, I.; Culshaw, A. J.; Devereux, N. J.; Gessier, F.; MC, K. J.; Neef, J.; Oakman, H. E.; McKenna, J. Organic Compounds. US2010035874 (A1), 2010.

(3) Creary, X.; Sky, A. F.; Phillips, G.; Alonso, D. E. Reaction of Arylhalodiazirines with Thiophenoxide: A Redox Process. *J. Am. Chem. Soc.* **1993**, *115* (17), 7584–7592.

(4) Sandham, D. A.; Barker, L.; Brown, L.; Brown, Z.; Budd, D.; Charlton, S. J.; Chatterjee, D.; Cox, B.; Dubois, G.; Duggan, N.; et al. Discovery of Fevipiprant (NVP-QAW039), a Potent and Selective DP 2 Receptor Antagonist for Treatment of Asthma. *ACS Med. Chem. Lett.* **2017**, *8* (5), 582–586.

(5) Taylor, N. J.; Emer, E.; Preshlock, S.; Schedler, M.; Tredwell, M.; Verhoog, S.; Mercier, J.; Genicot, C.; Gouverneur, V. Derisking the Cu-Mediated 18F-Fluorination of Heterocyclic Positron Emission Tomography Radioligands. *J. Am. Chem. Soc.* **2017**, *139* (24), 8267–8276.

(6) Arakawa, Y.; Nakajima, S.; Kang, S.; Shigeta, M.; Konishi, G.; Watanabe, J. Design of an Extremely High Birefringence Nematic Liquid Crystal Based on a Dinaphthyl-

Diacetylene Mesogen. *J. Mater. Chem.* **2012**, *22* (28), 13908.

(7) Vidadala, R. S. R.; Rivas, K. L.; Ojo, K. K.; Hulverson, M. A.; Zambriski, J. A.; Bruzual, I.; Schultz, T. L.; Huang, W.; Zhang, Z.; Scheele, S.; et al. Development of an Orally Available and Central Nervous System (CNS) Penetrant Toxoplasma Gondii Calcium-Dependent Protein Kinase 1 (TgCDPK1) Inhibitor with Minimal Human Ether-a-Go-Go-Related Gene (HERG) Activity for the Treatment of Toxoplasmosis. *J. Med. Chem.* **2016**, *59* (13), 6531–6546.

(8) Kumar, S.; Hernandez, D.; Hoa, B.; Lee, Y.; Yang, J. S.; McCurdy, A. Synthesis, Photochromic Properties, and Light-Controlled Metal Complexation of a Naphthopyran Derivative. *Org. Lett.* **2008**, *10* (17), 3761–3764.

(9) Naumiec, G. R.; Cai, L.; Lu, S.; Pike, V. W. Quinuclidine and DABCO Enhance the Radiofluorination of 5-Substituted 2-Halopyridines. *European J. Org. Chem.* **2017**, *2017* (45), 6593–6603.

(10) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. Silane Reductions in Acidic Media. II. Reductions of Aryl Aldehydes and Ketones by Trialkylsilanes in Trifluoroacetic Acid. Selective Method for Converting the Carbonyl Group to Methylene. *J. Org. Chem.* **1973**, *38* (15), 2675–2681.

(11) Sakai, N.; Kobayashi, T.; Ogiwara, Y. One-Pot Synthesis of Tetralin Derivatives from 3-Benzoylpropionic Acids: Indium-Catalyzed Hydrosilylation of Ketones and Carboxylic Acids and Intramolecular Cyclization. *Chem. Lett.* **2015**, *44* (11), 1503–1505.

(12) Liu, C.; Ji, C.-L.; Hong, X.; Szostak, M. Palladium-Catalyzed Decarbonylative Borylation of Carboxylic Acids: Tuning Reaction Selectivity by Computation. *Angew. Chemie Int. Ed.* **2018**, *57* (51), 16721–16726.

6. NMR Spectra

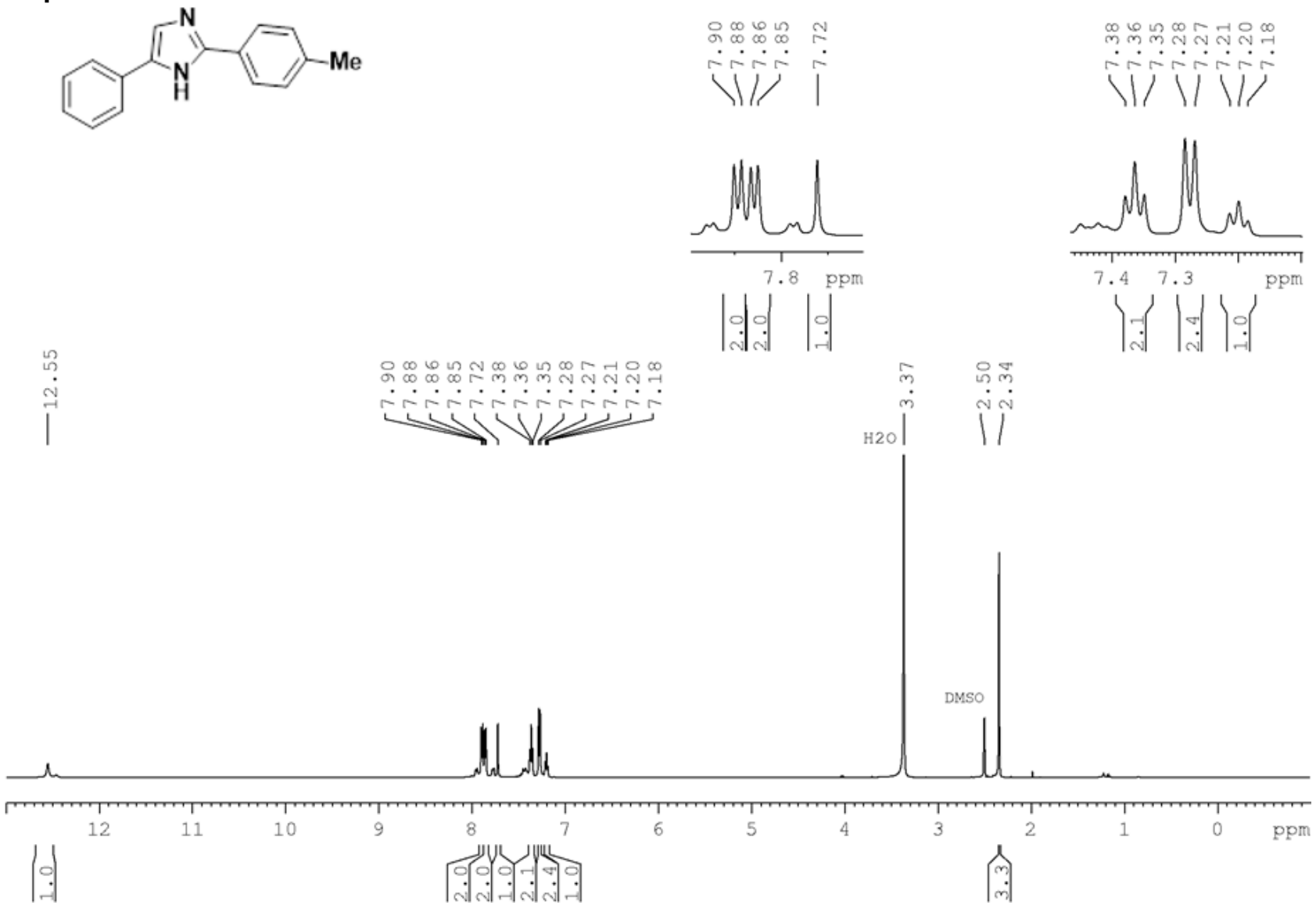


Figure S6. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **5**

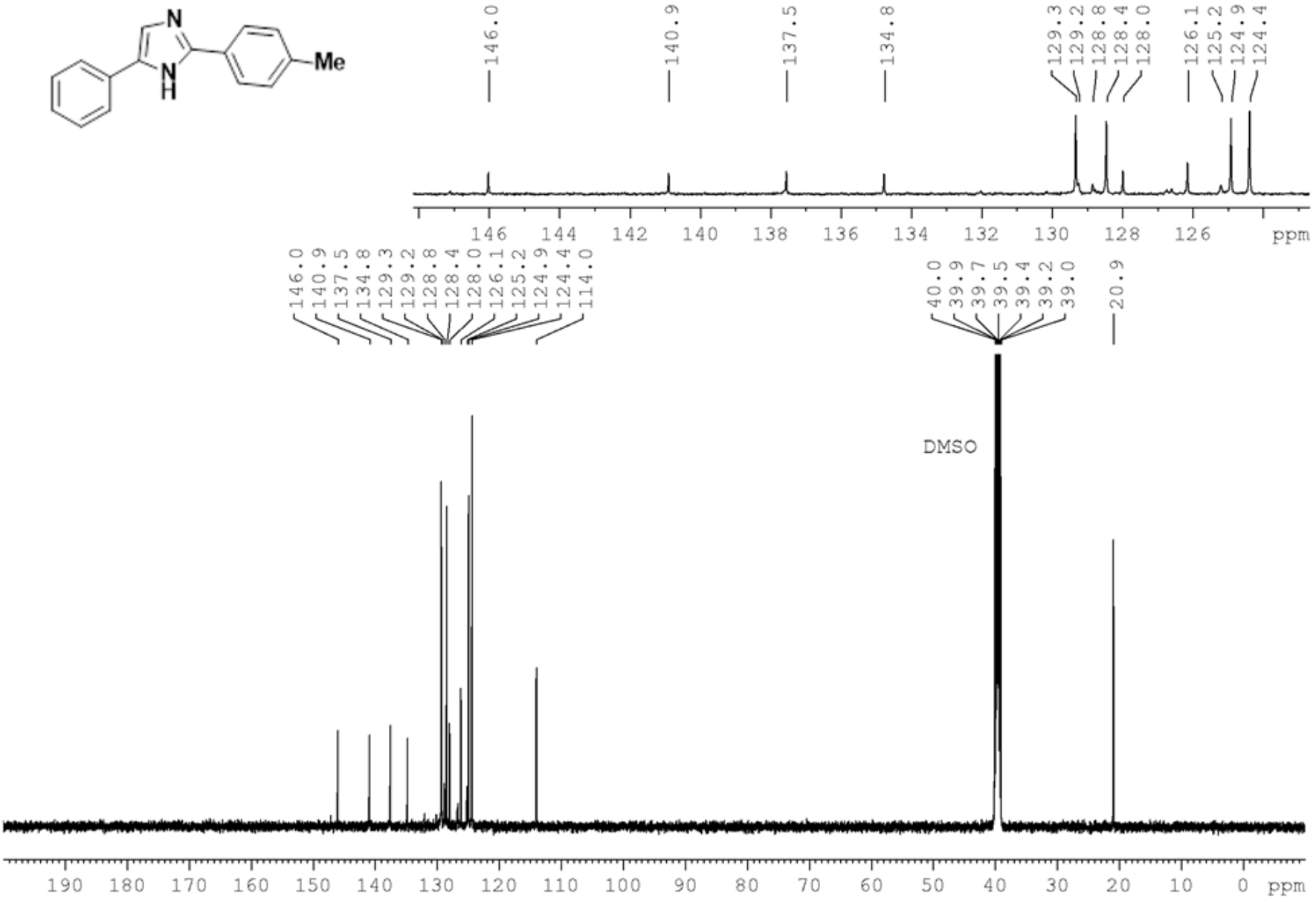


Figure S7. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **5**

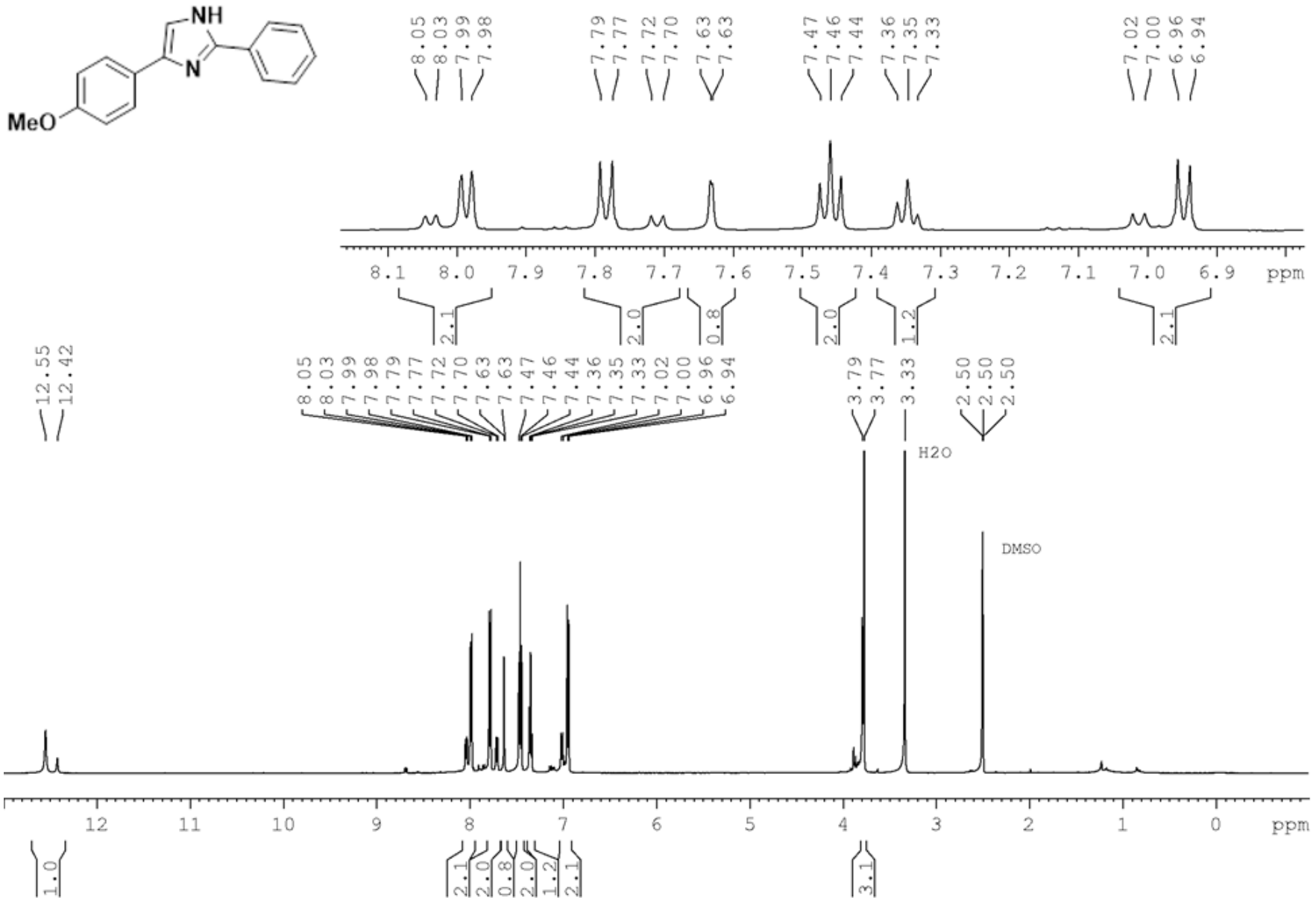


Figure S8. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **6**

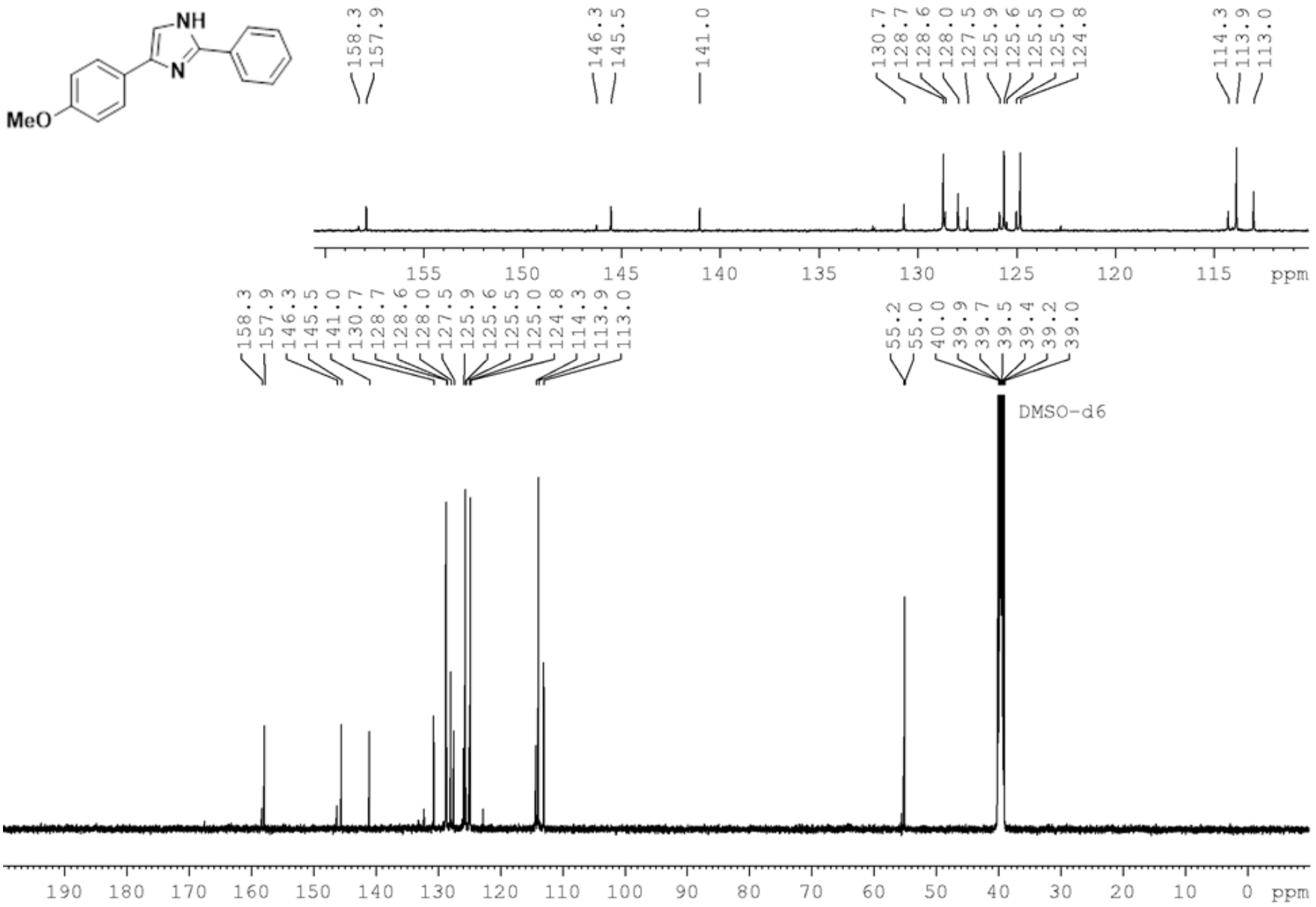


Figure S9. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **6**

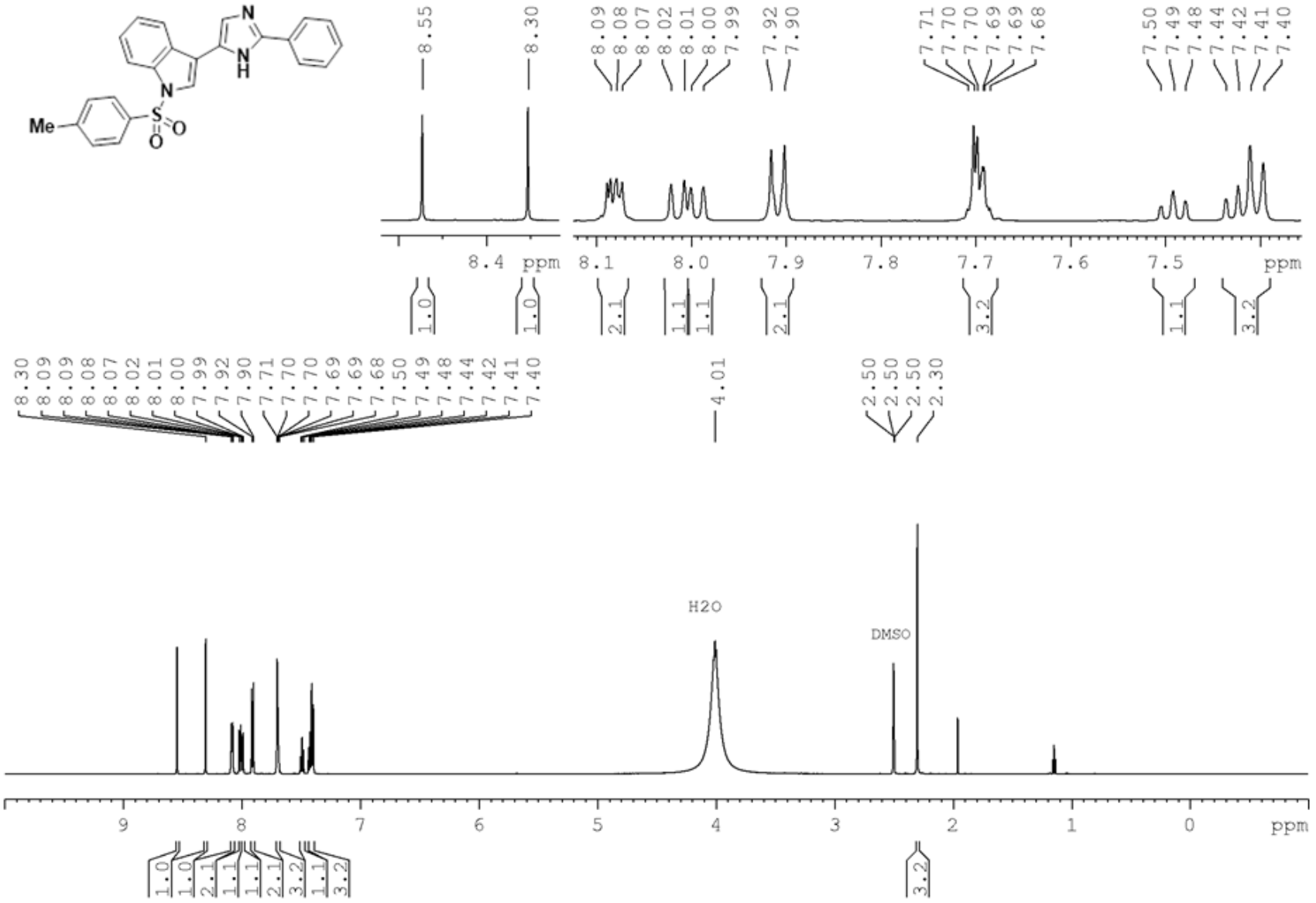


Figure S10. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 600 MHz) of **7**

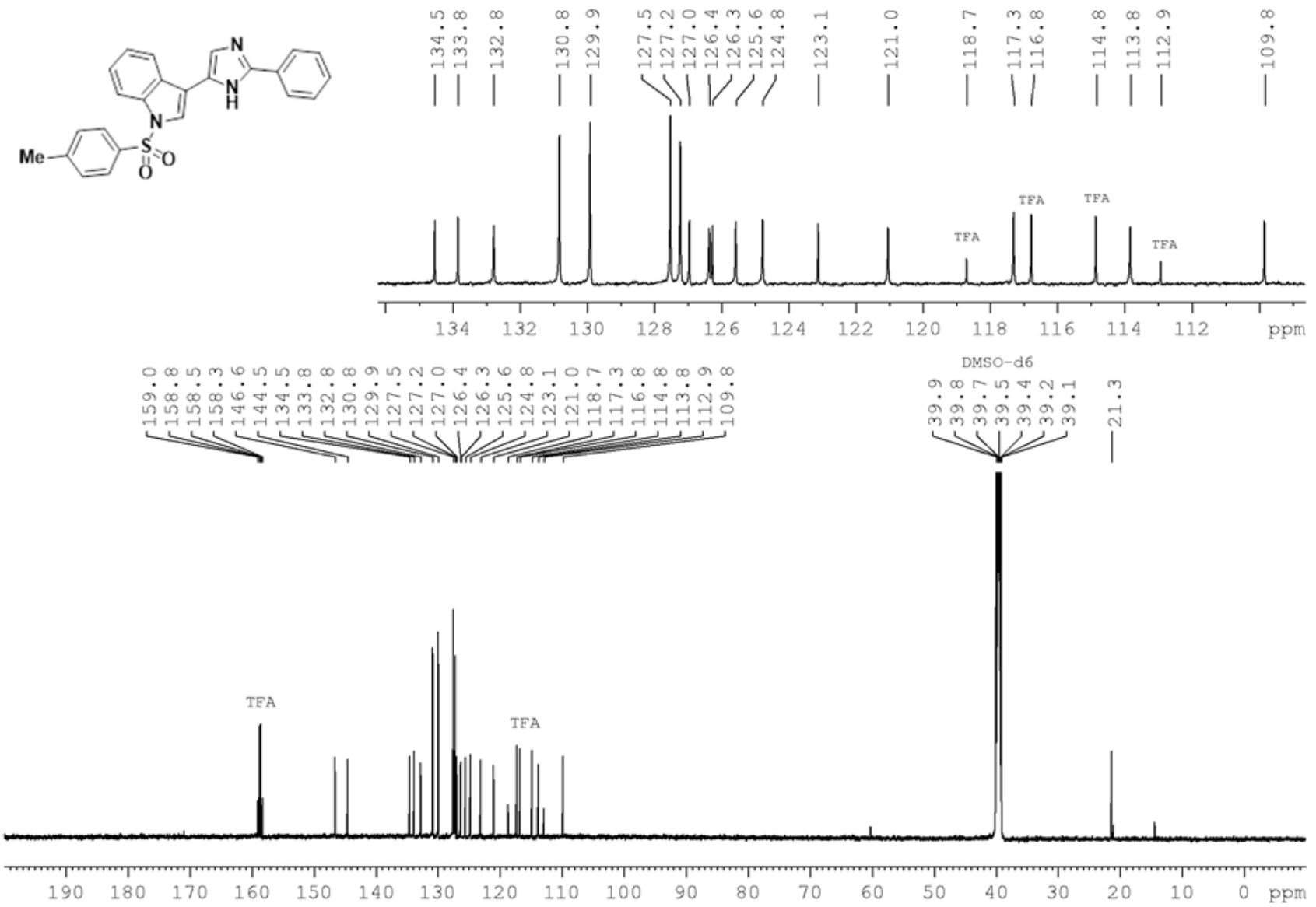


Figure S11. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 151 MHz) of **7**

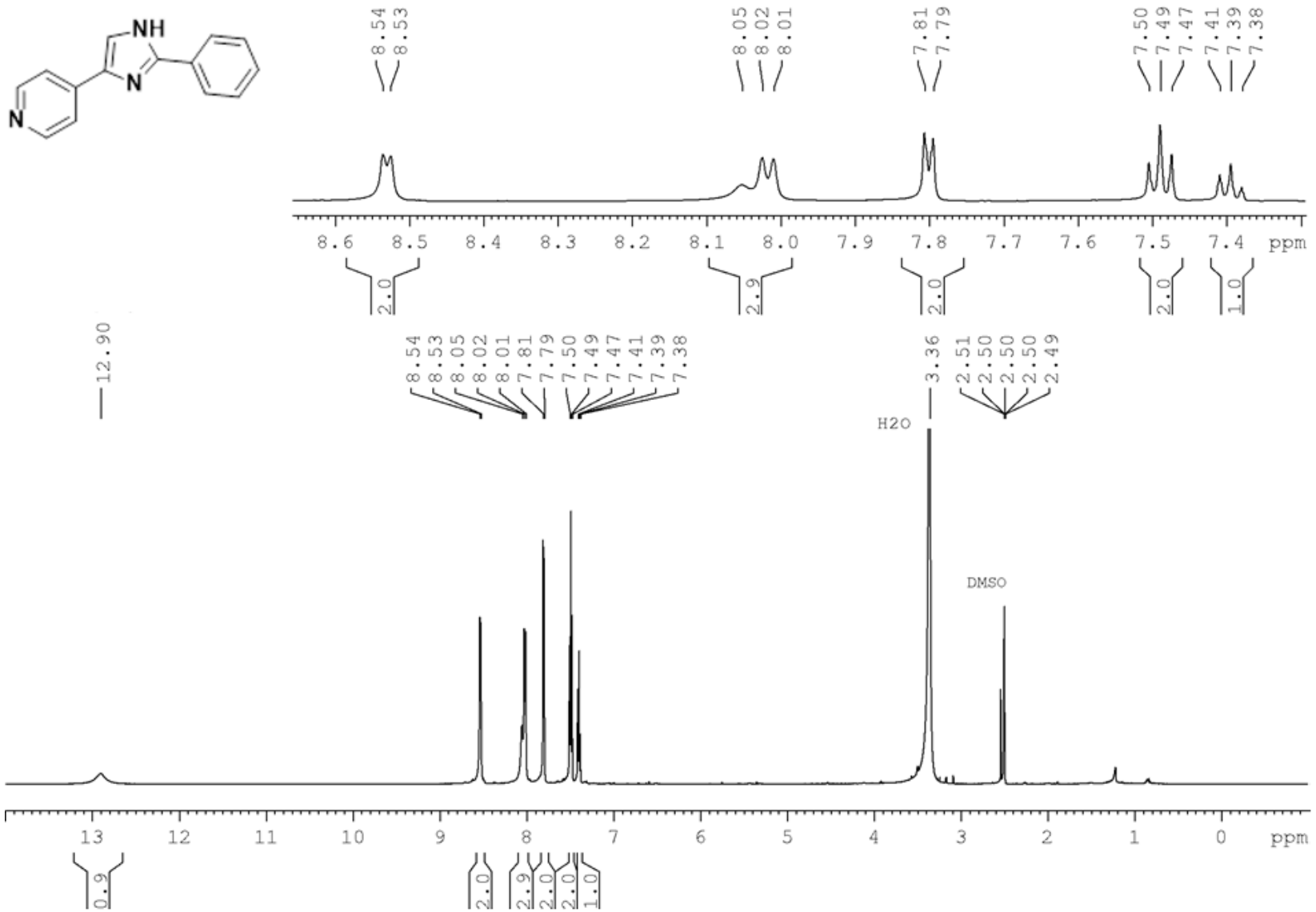


Figure S12. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **8**

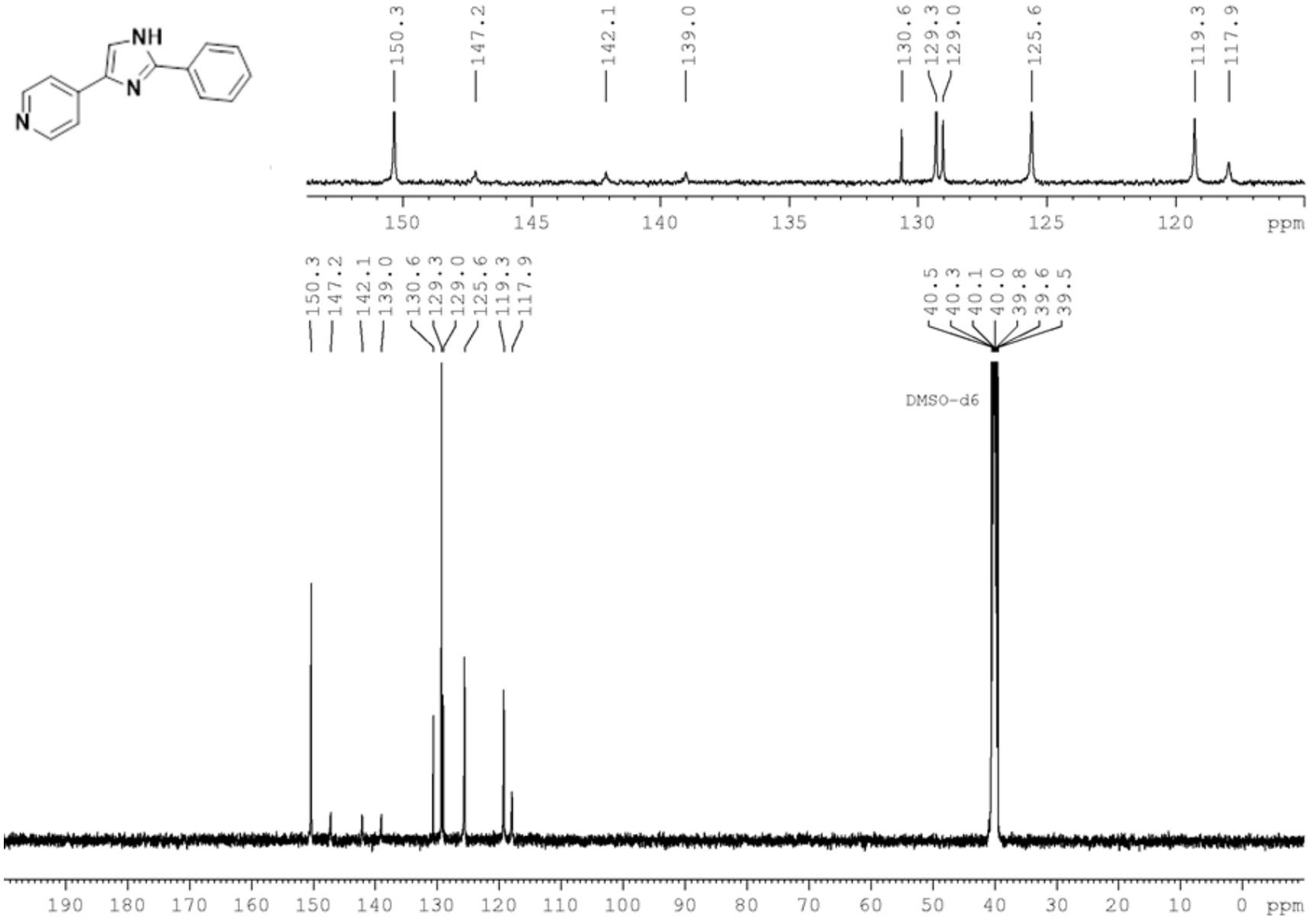


Figure S13. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **8**

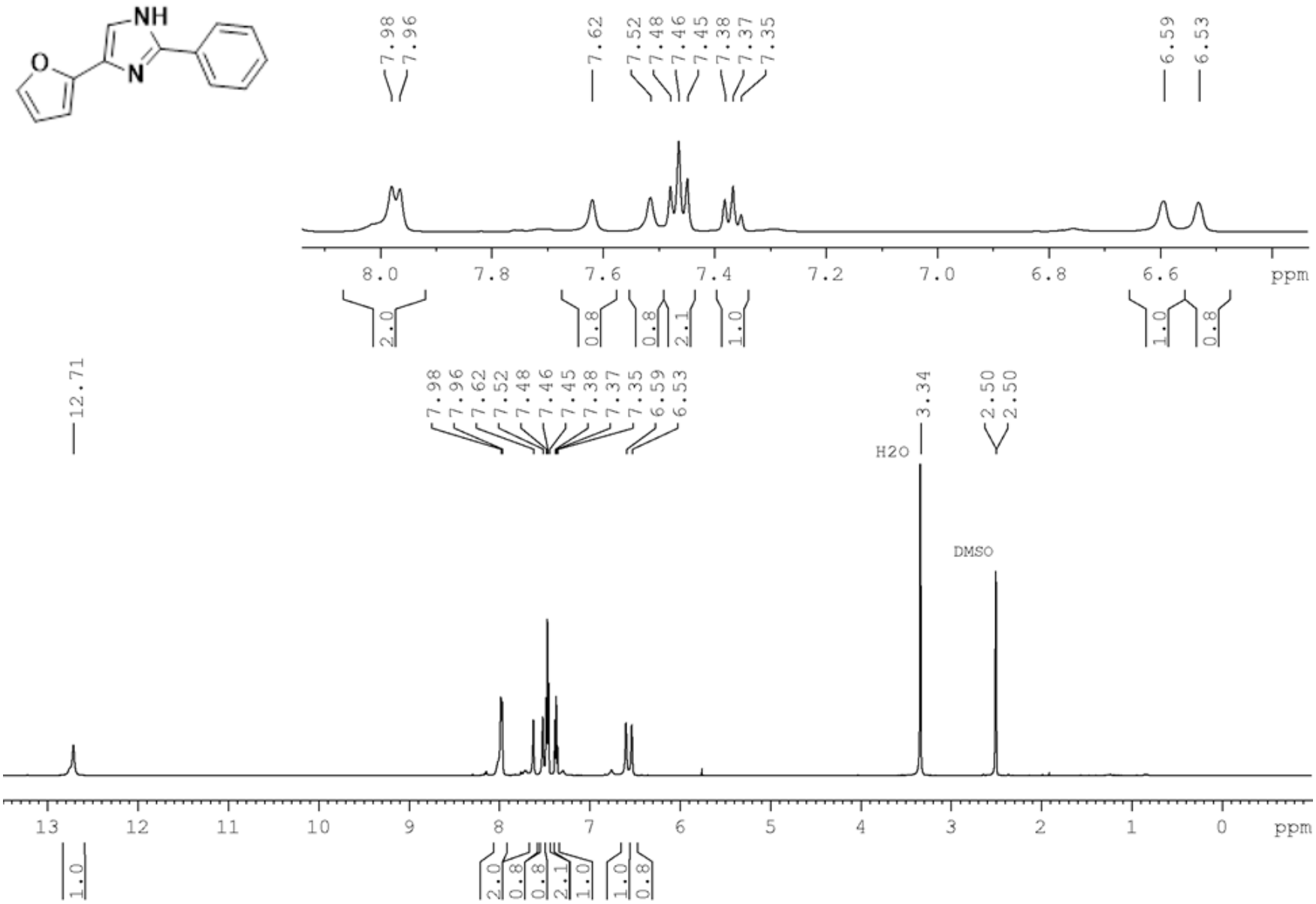


Figure S14. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **9**

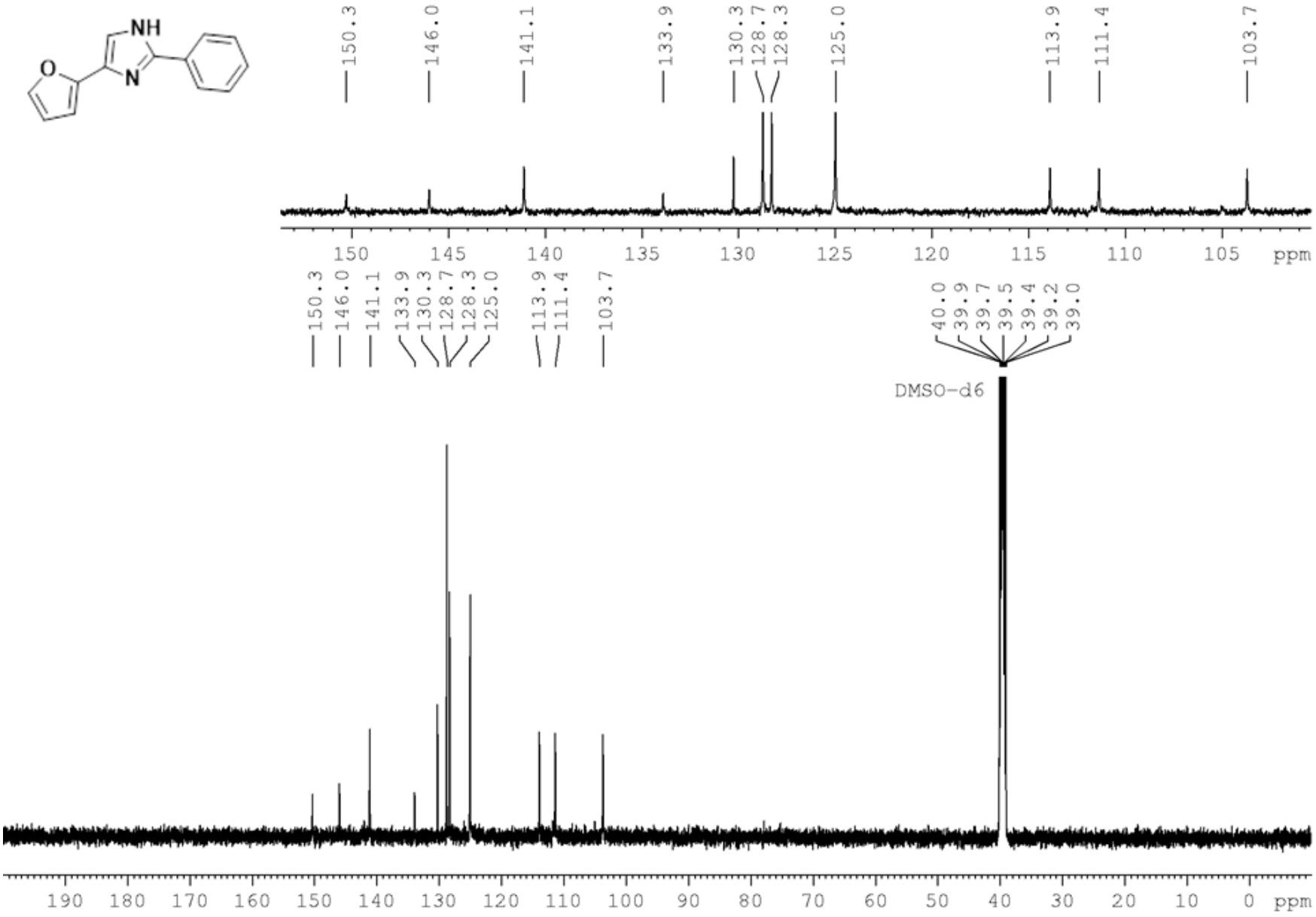


Figure S15. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **9**

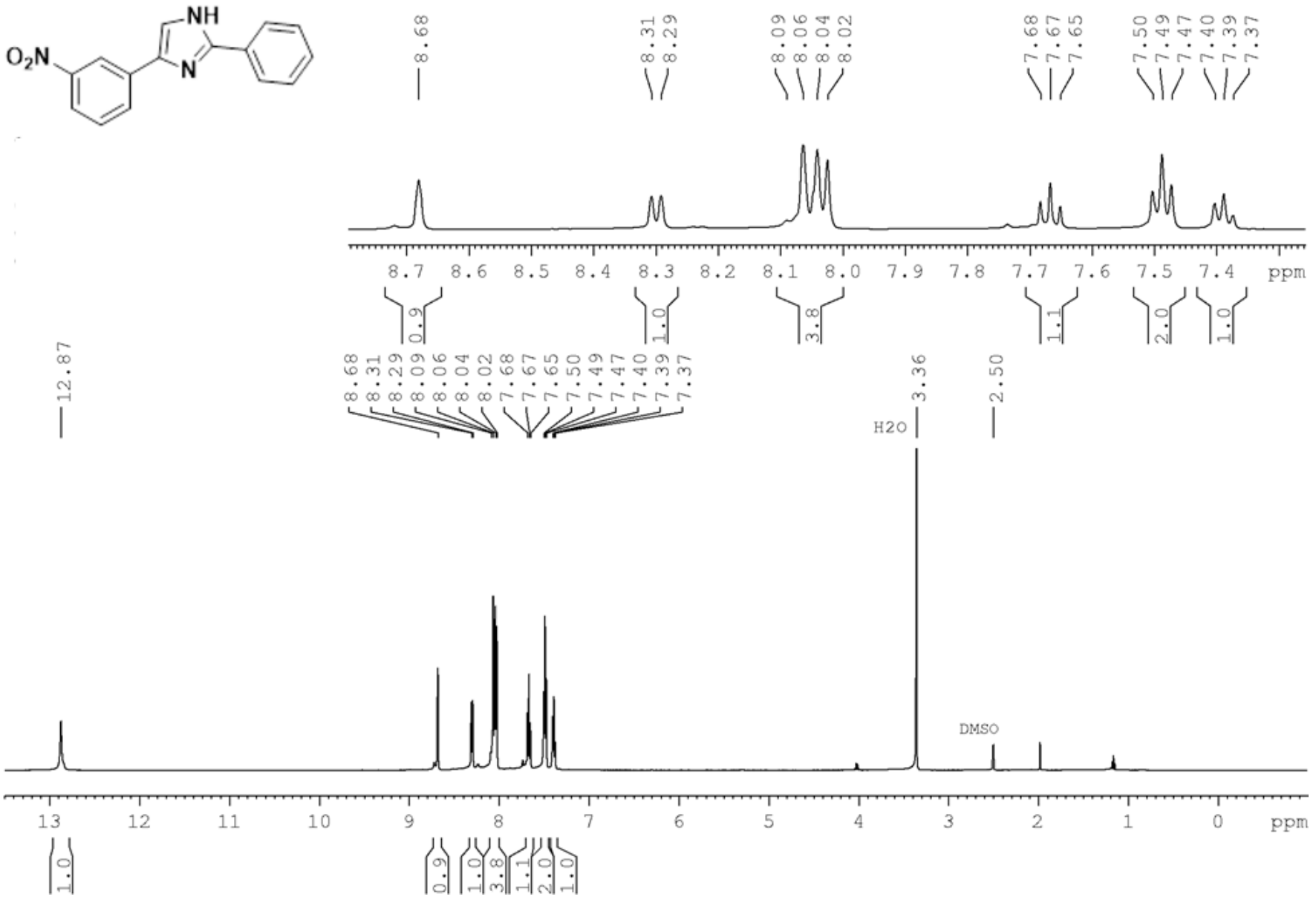


Figure S16. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **10**

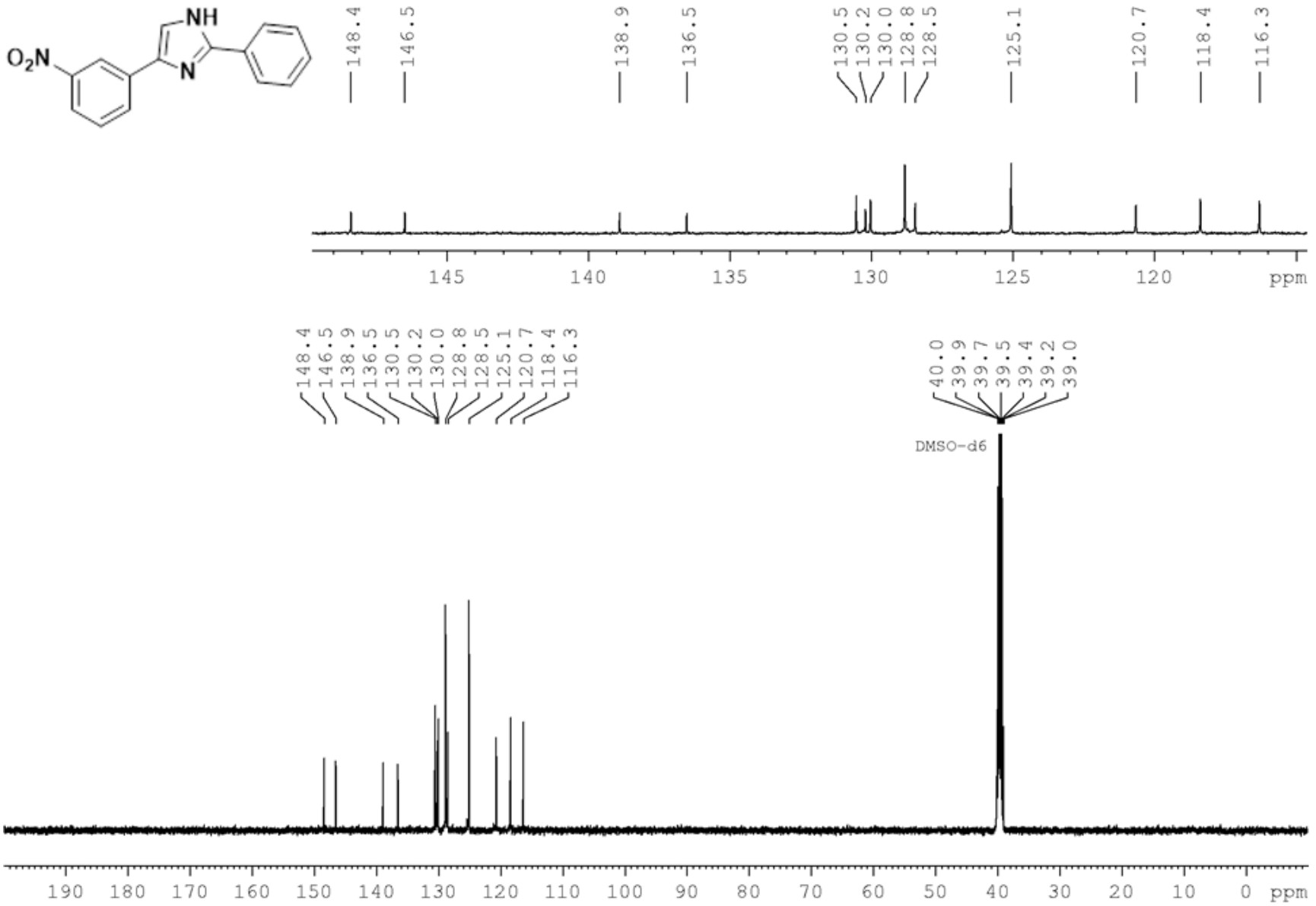


Figure S17. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **10**

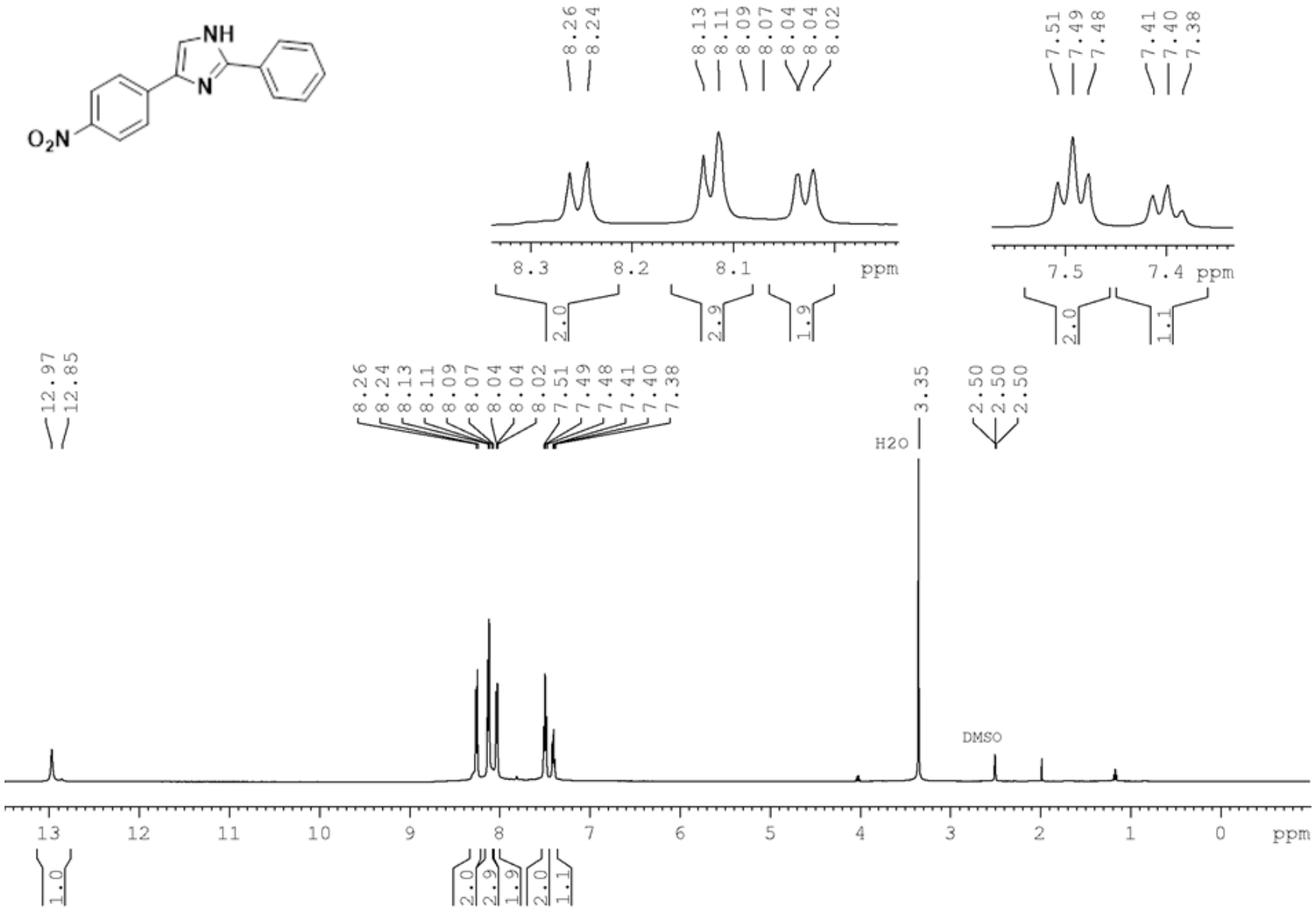


Figure S18. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **11**

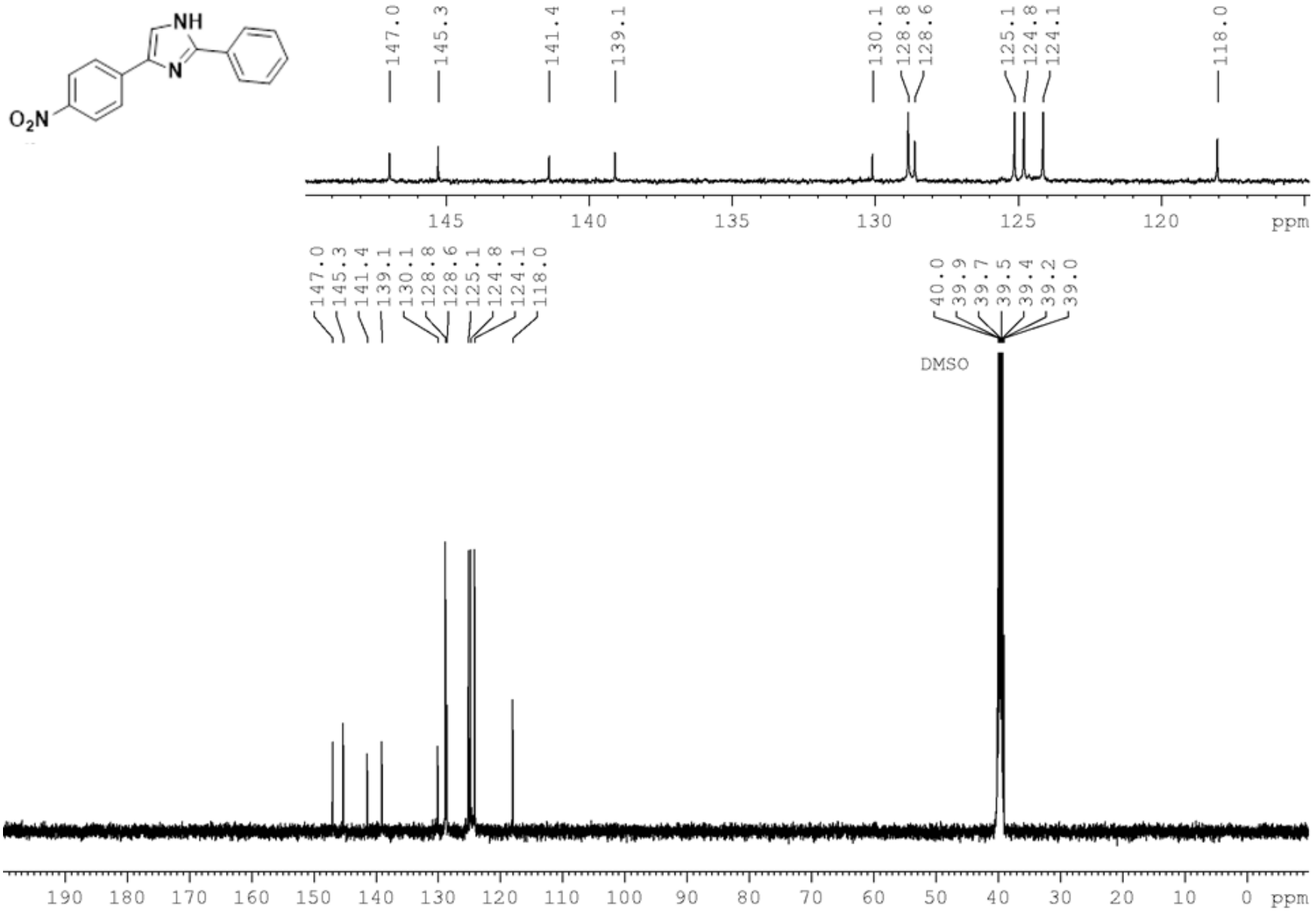


Figure S19. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **11**

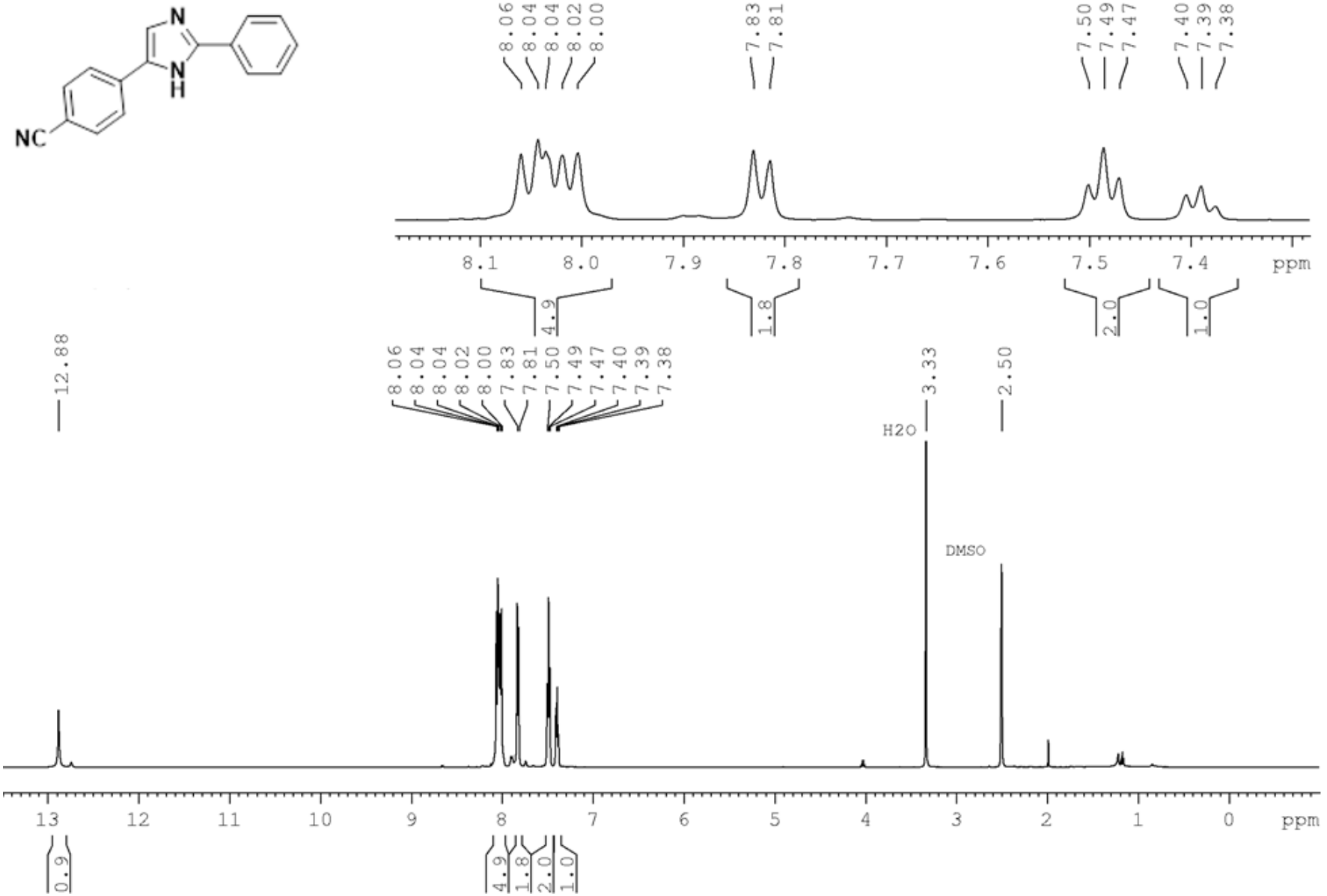


Figure S20. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **12**

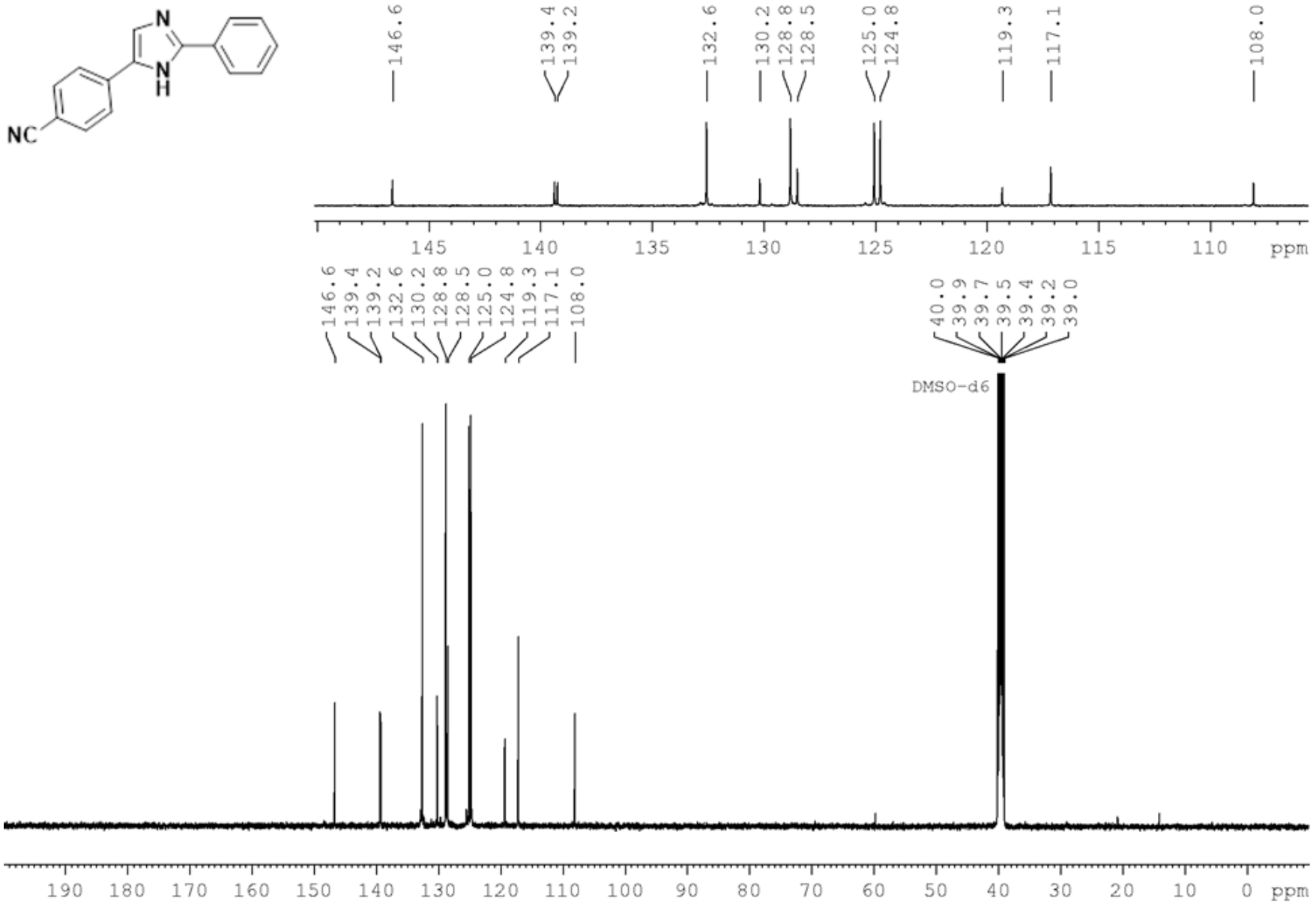


Figure S21. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **12**

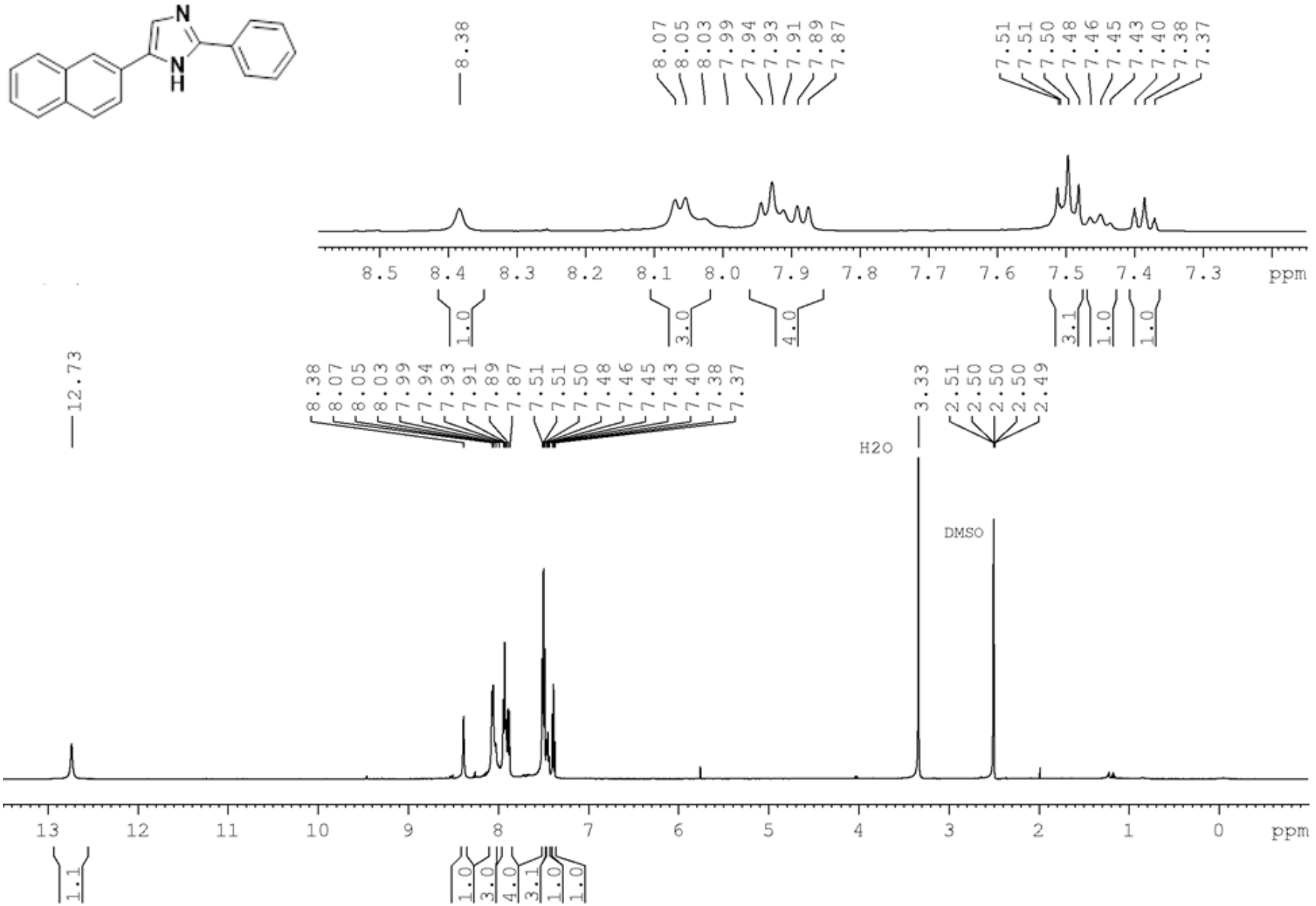


Figure S22. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **13**

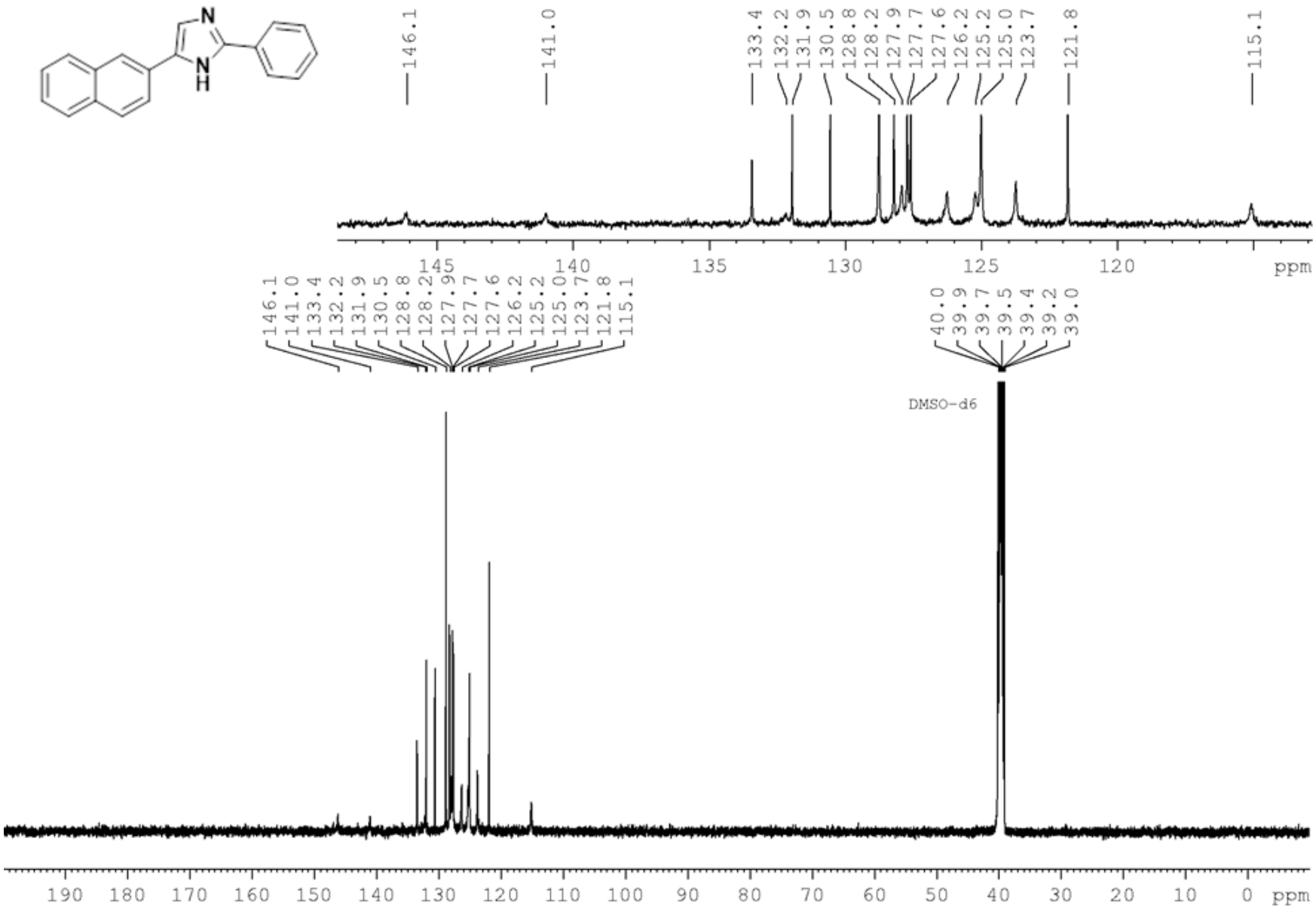


Figure S23. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **13**

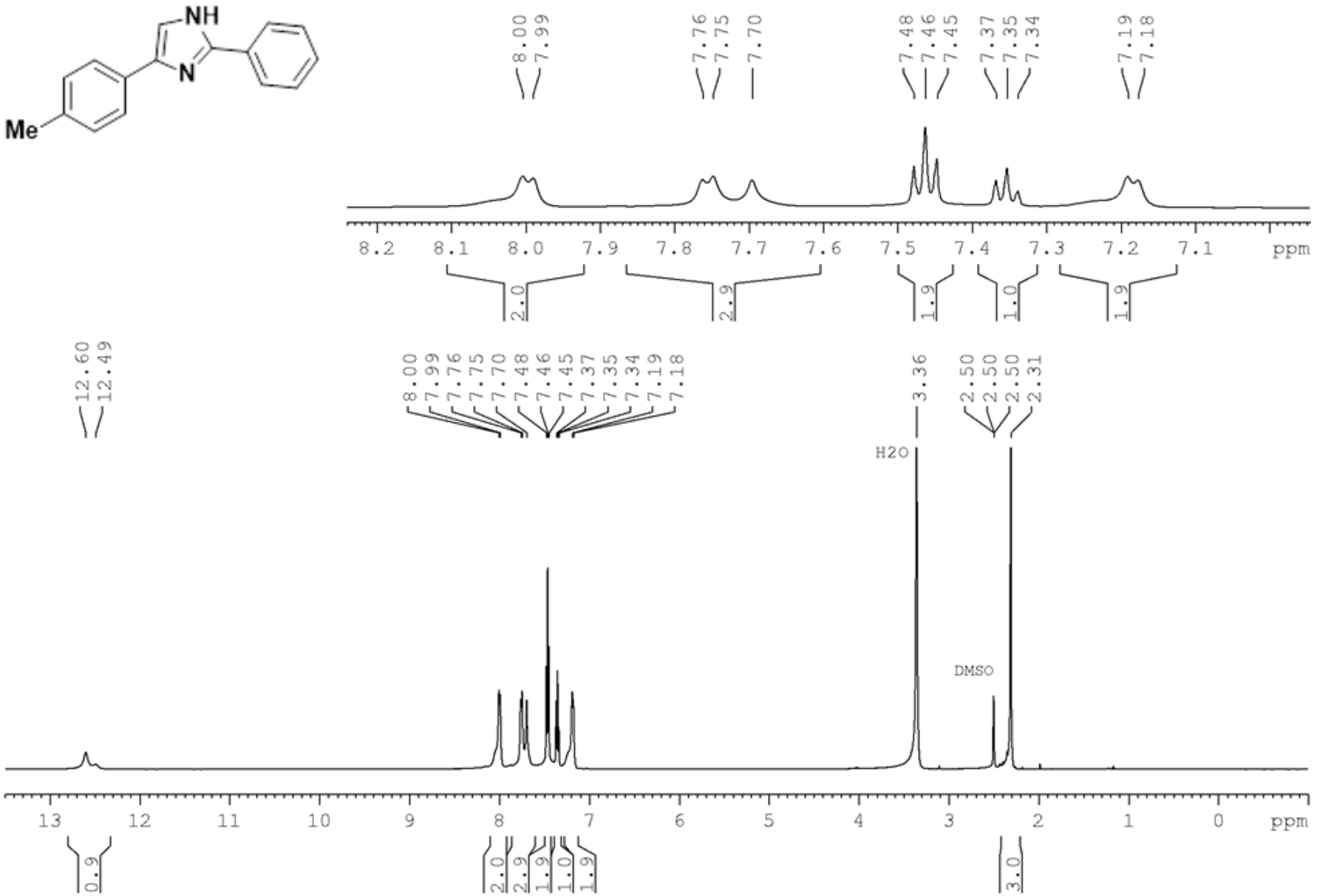


Figure S24. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **14**

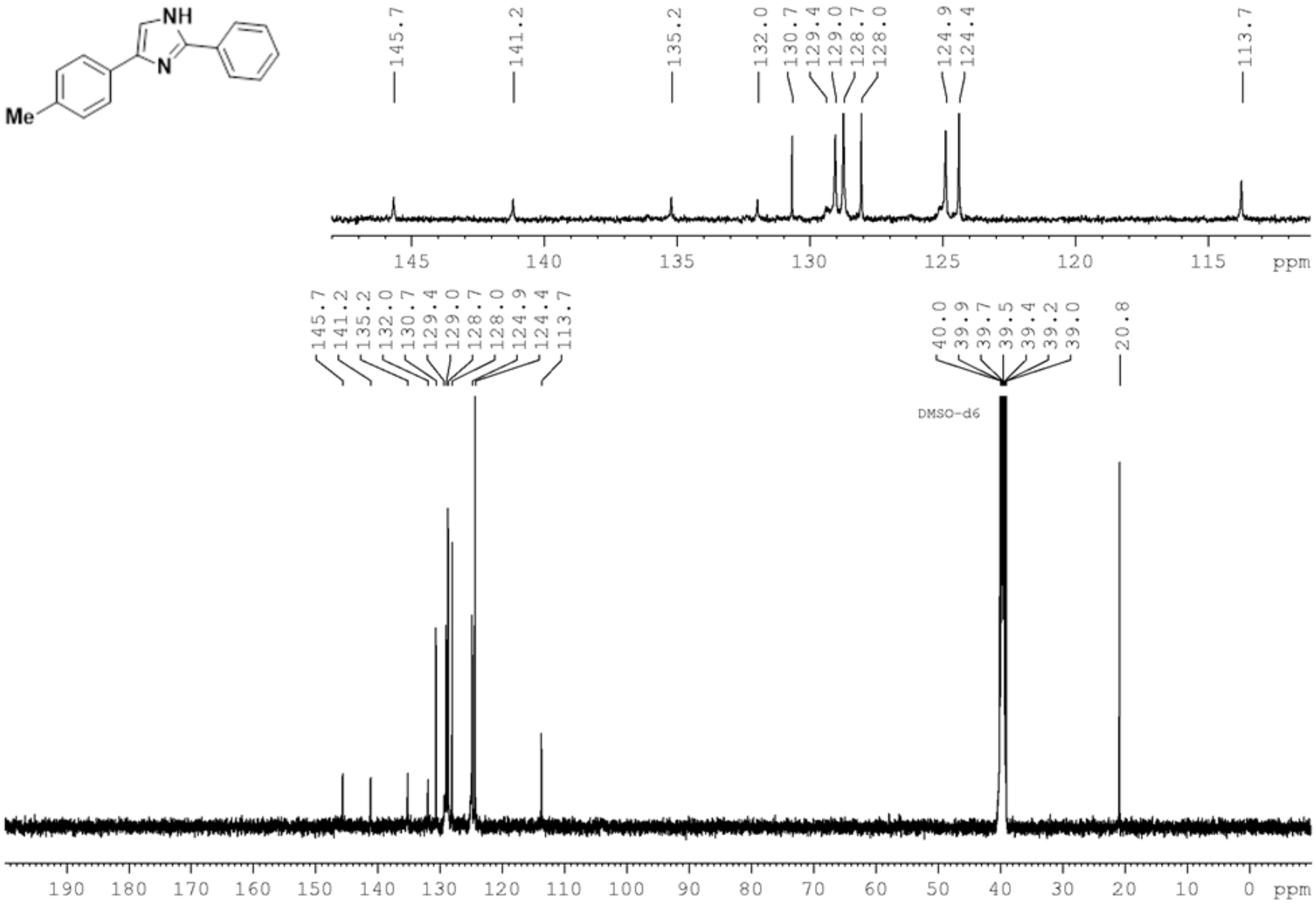


Figure S25. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **14**

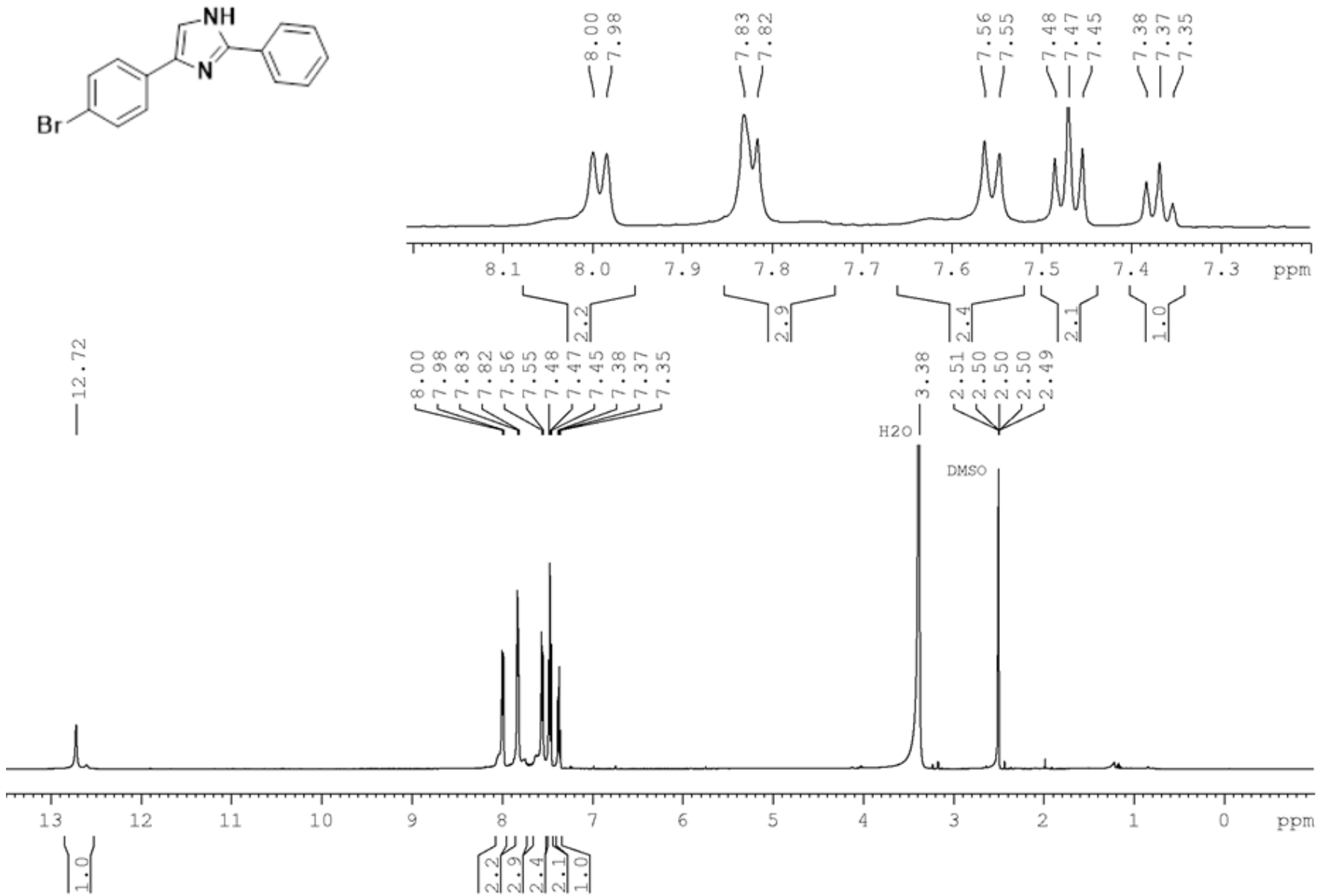


Figure S26. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **15**

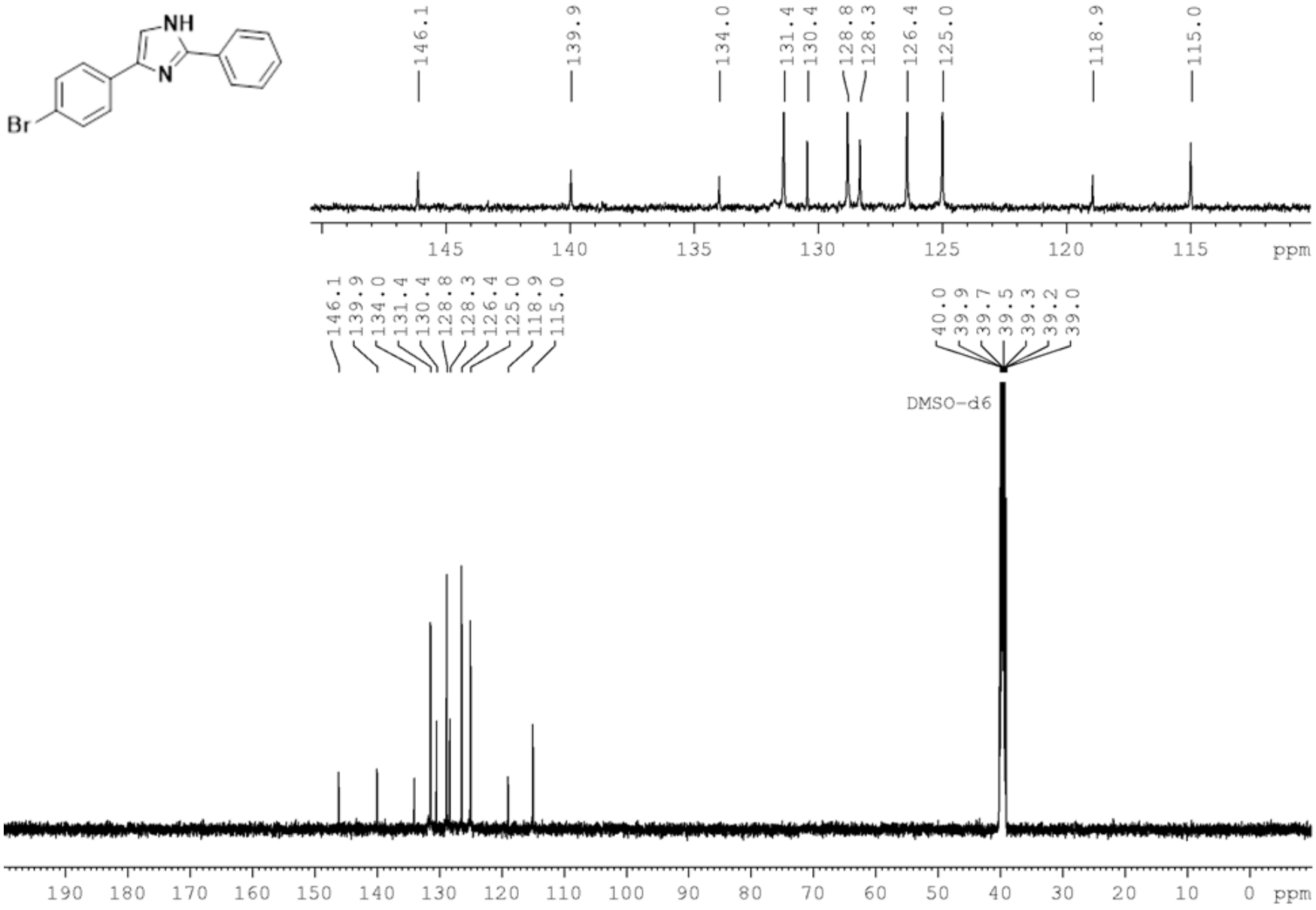


Figure S27. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **15**

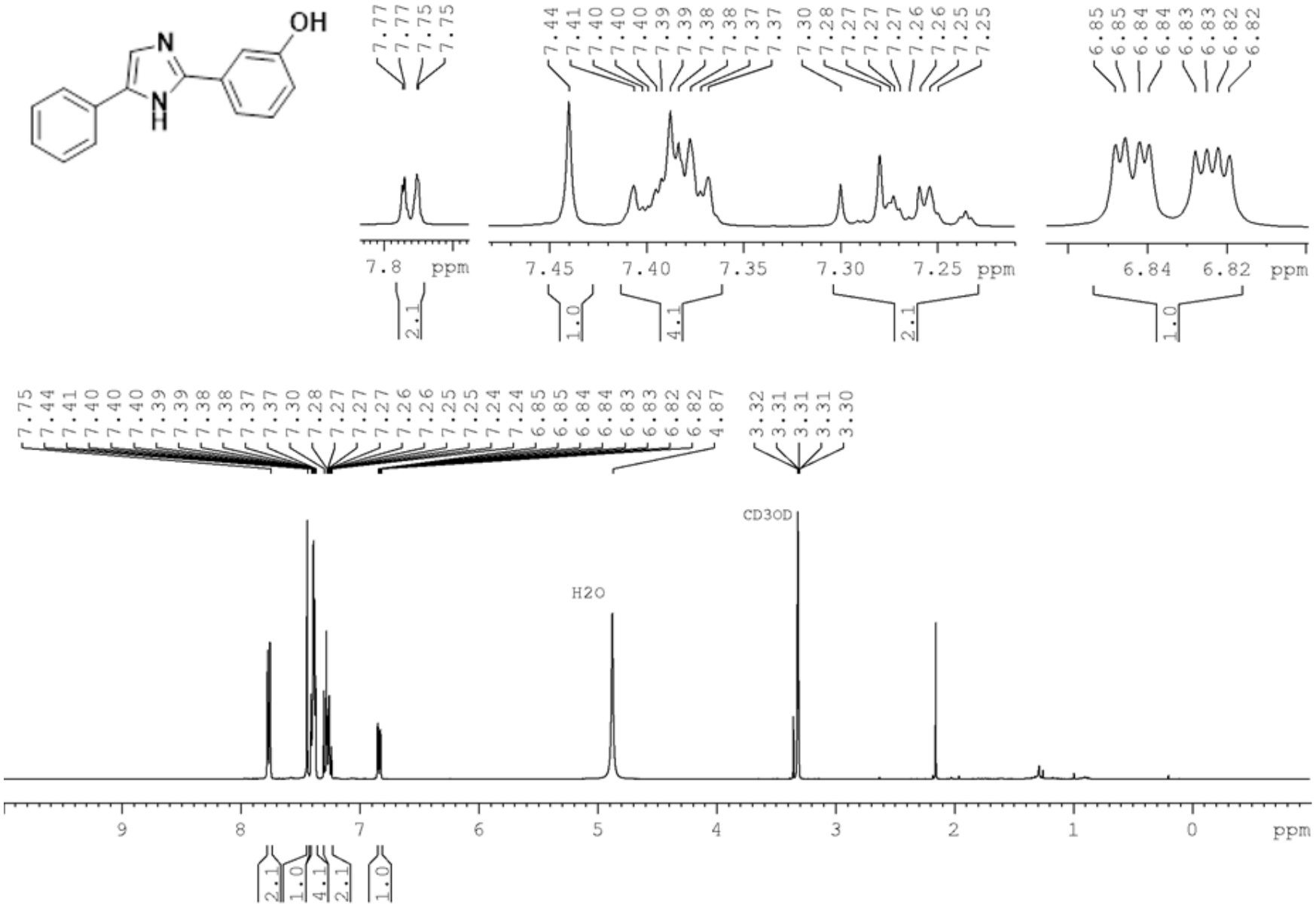


Figure S28. ^{1}H NMR Spectra (MeOD-d_4, 400 MHz) of **16**

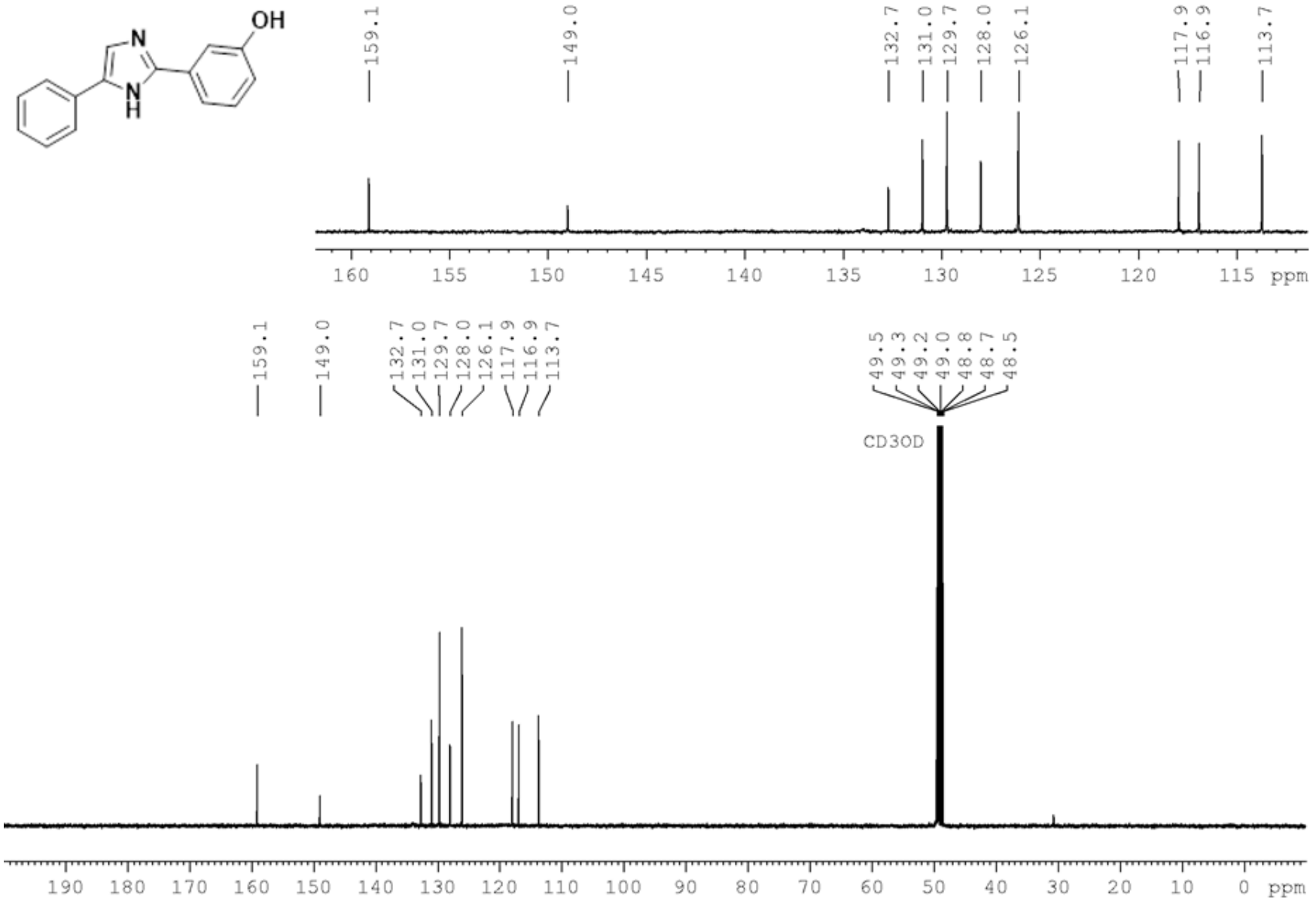


Figure S29. $^{13}C\{^{1}H\}$ NMR Spectra (MeOD-d_4, 126 MHz) of **16**

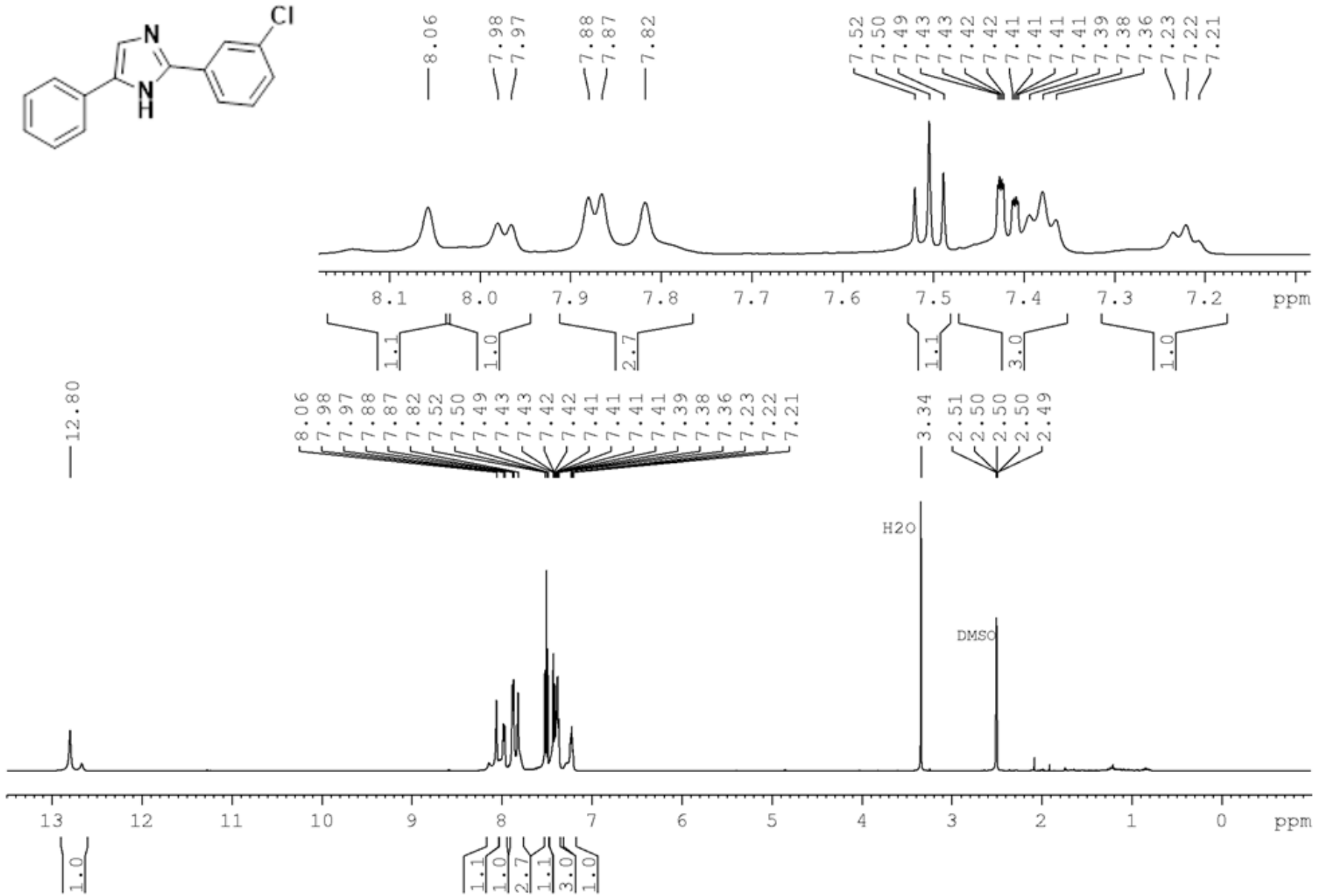


Figure S30. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **17**

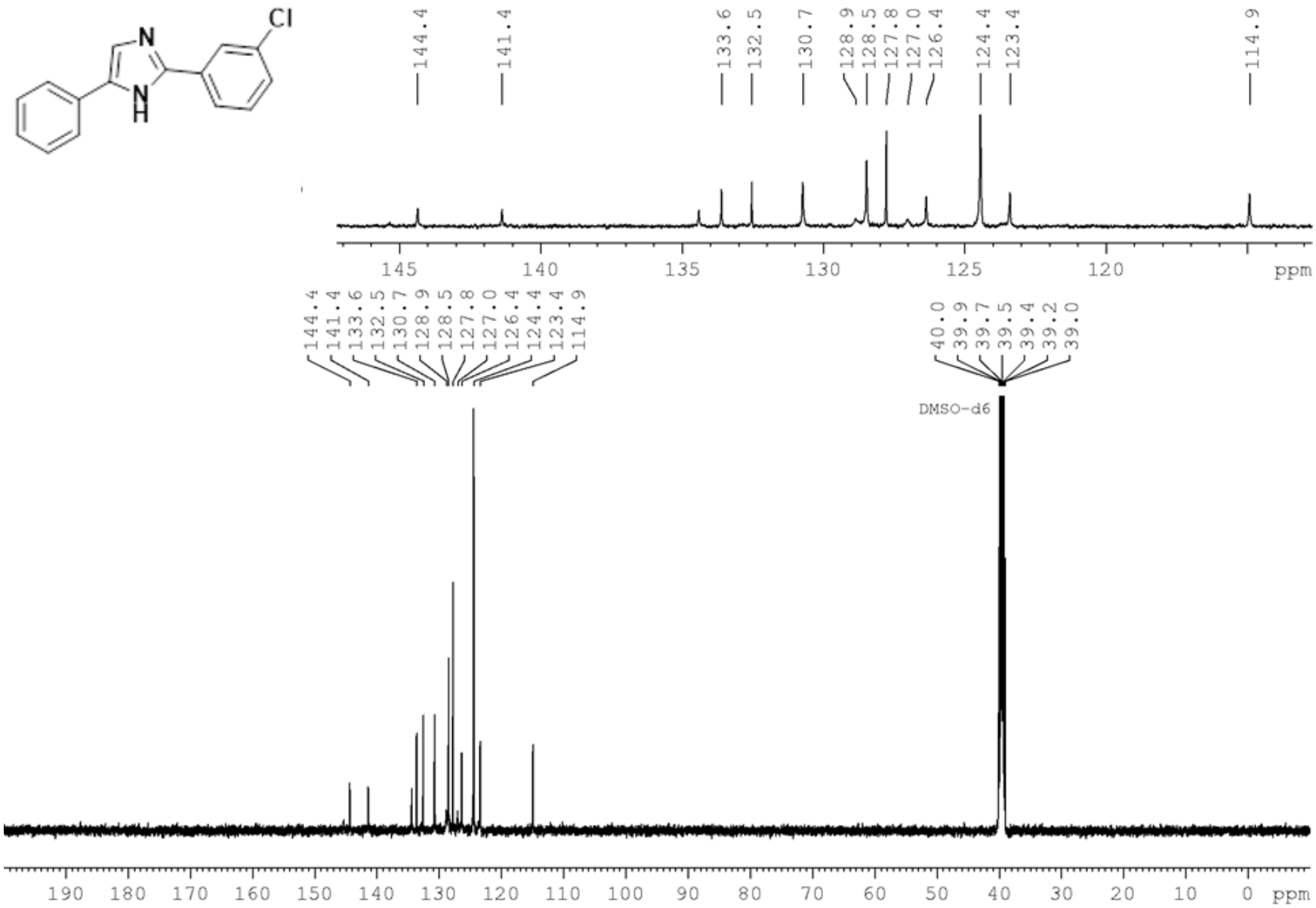


Figure S31. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **17**

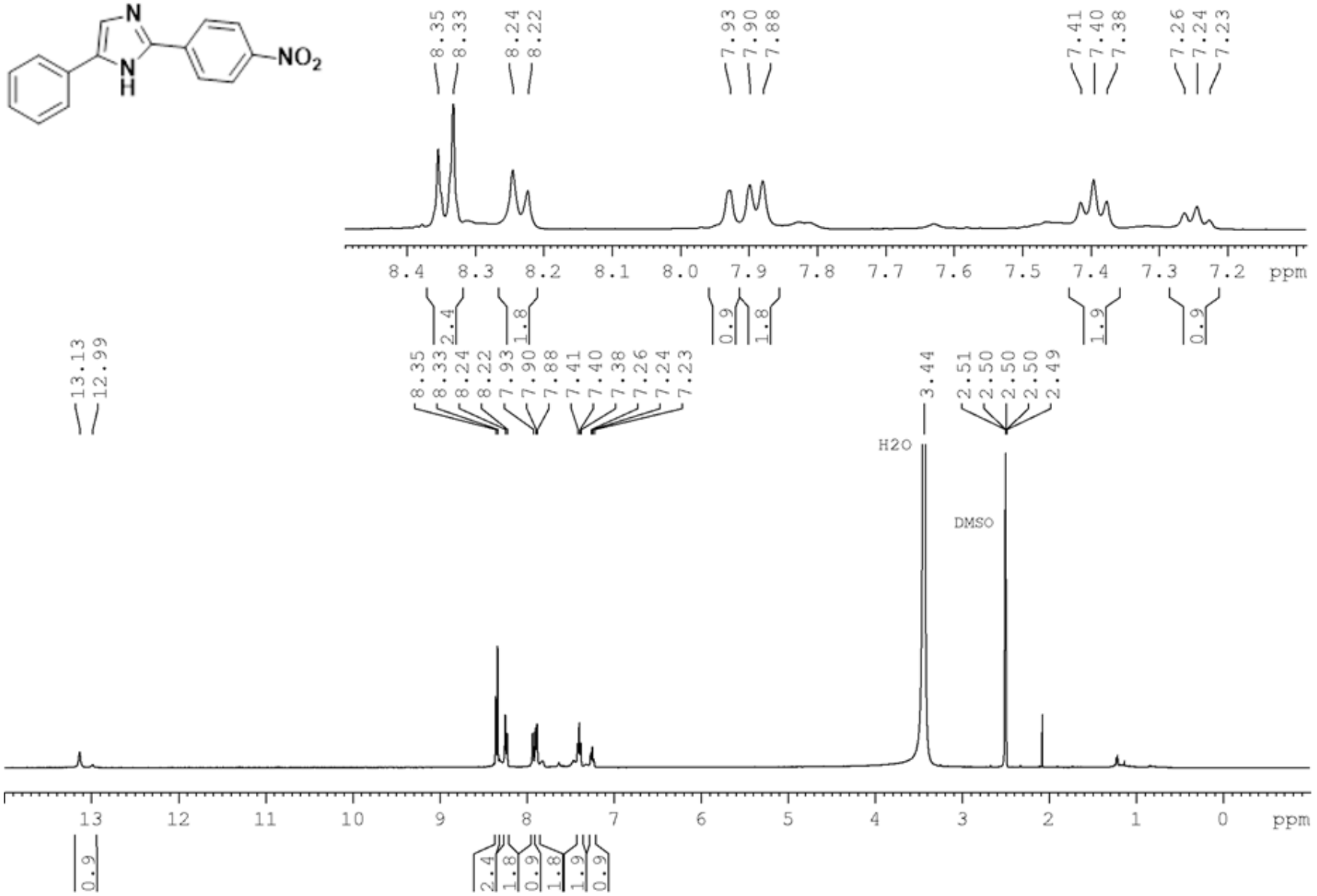


Figure S32. ^{1}H NMR Spectra (DMSO-d_6, 400 MHz) of **18**

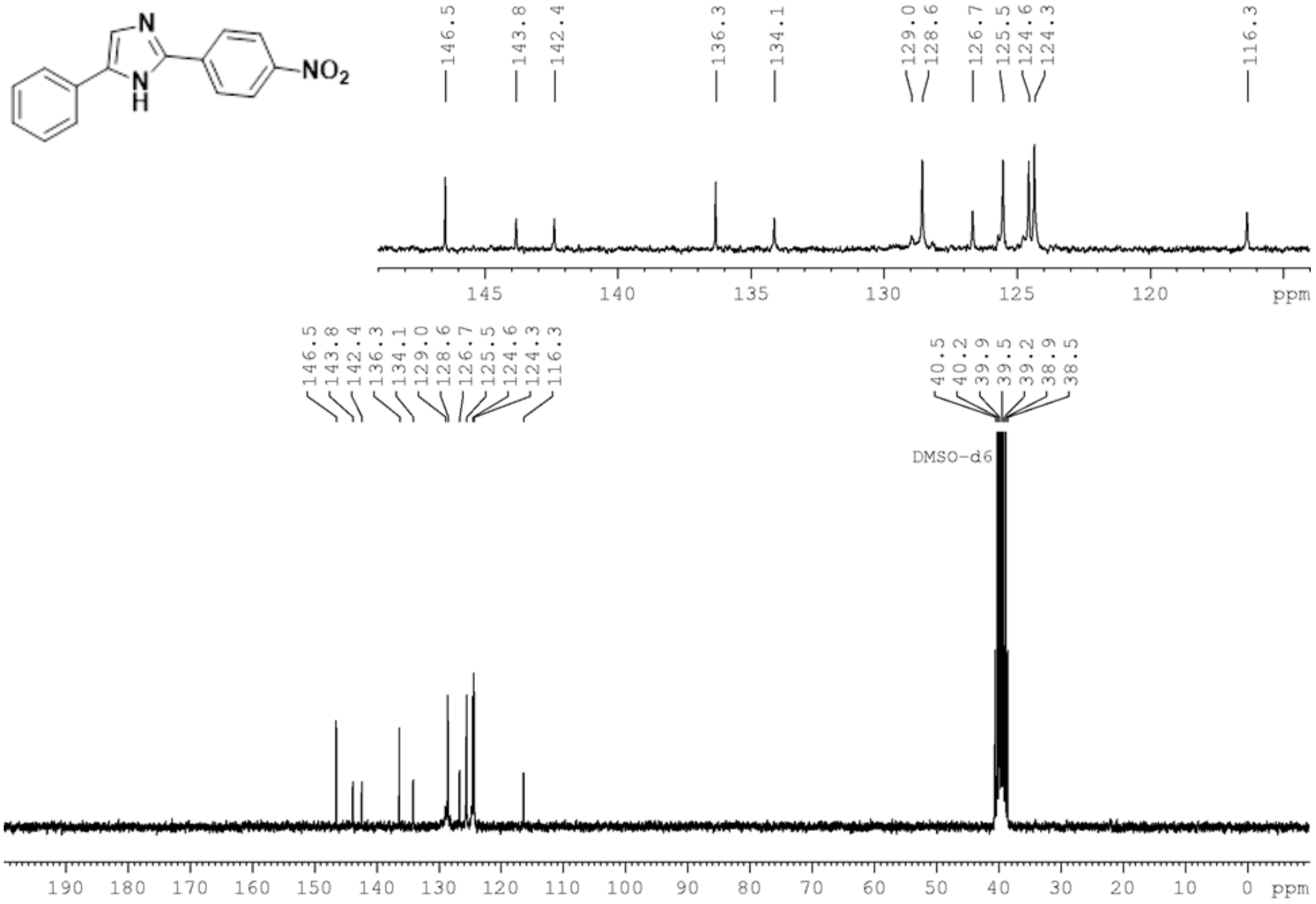


Figure S33. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 63 MHz) of **18**

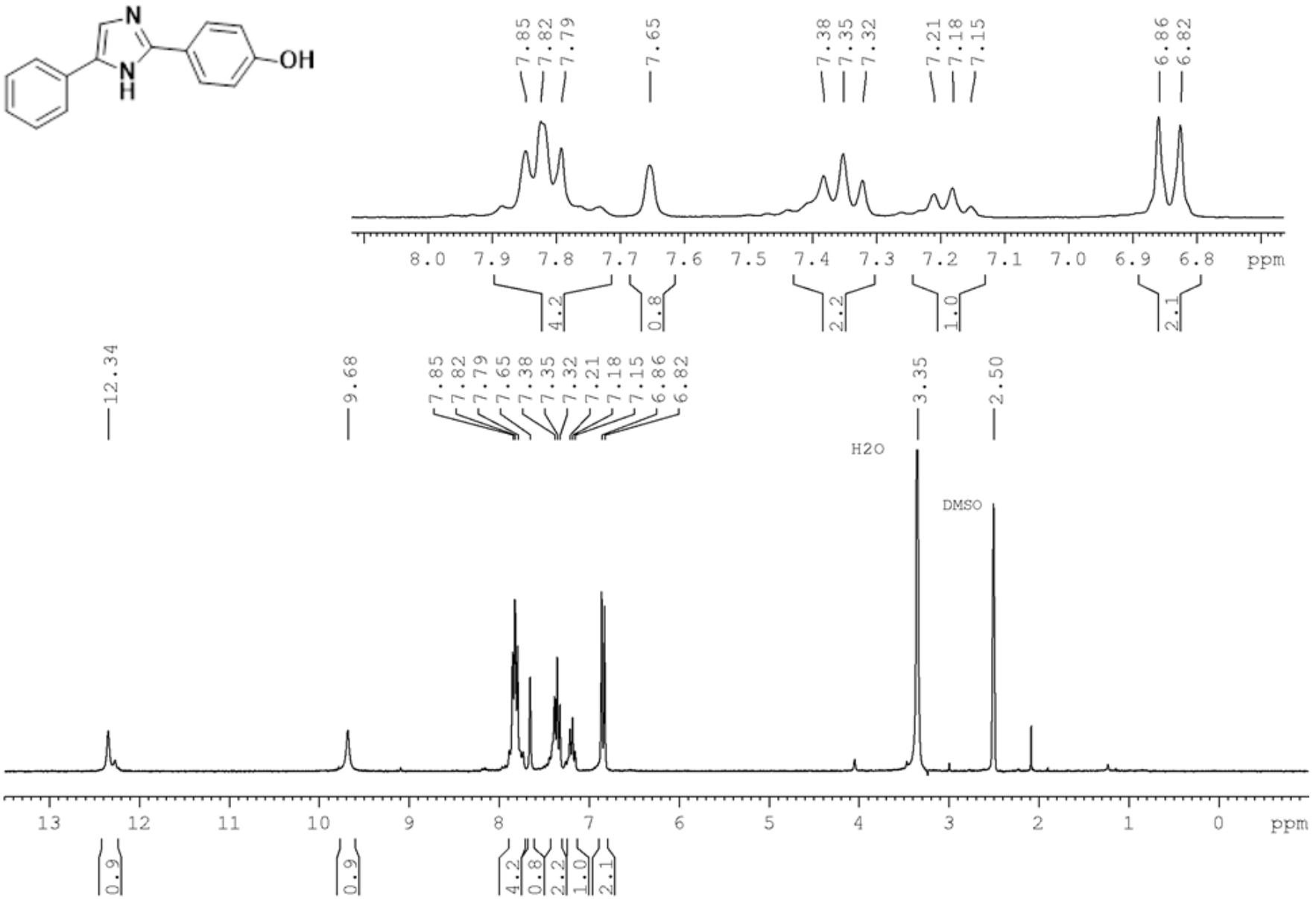


Figure S34. ^{1}H NMR Spectra (DMSO-d_6, 250 MHz) of **19**

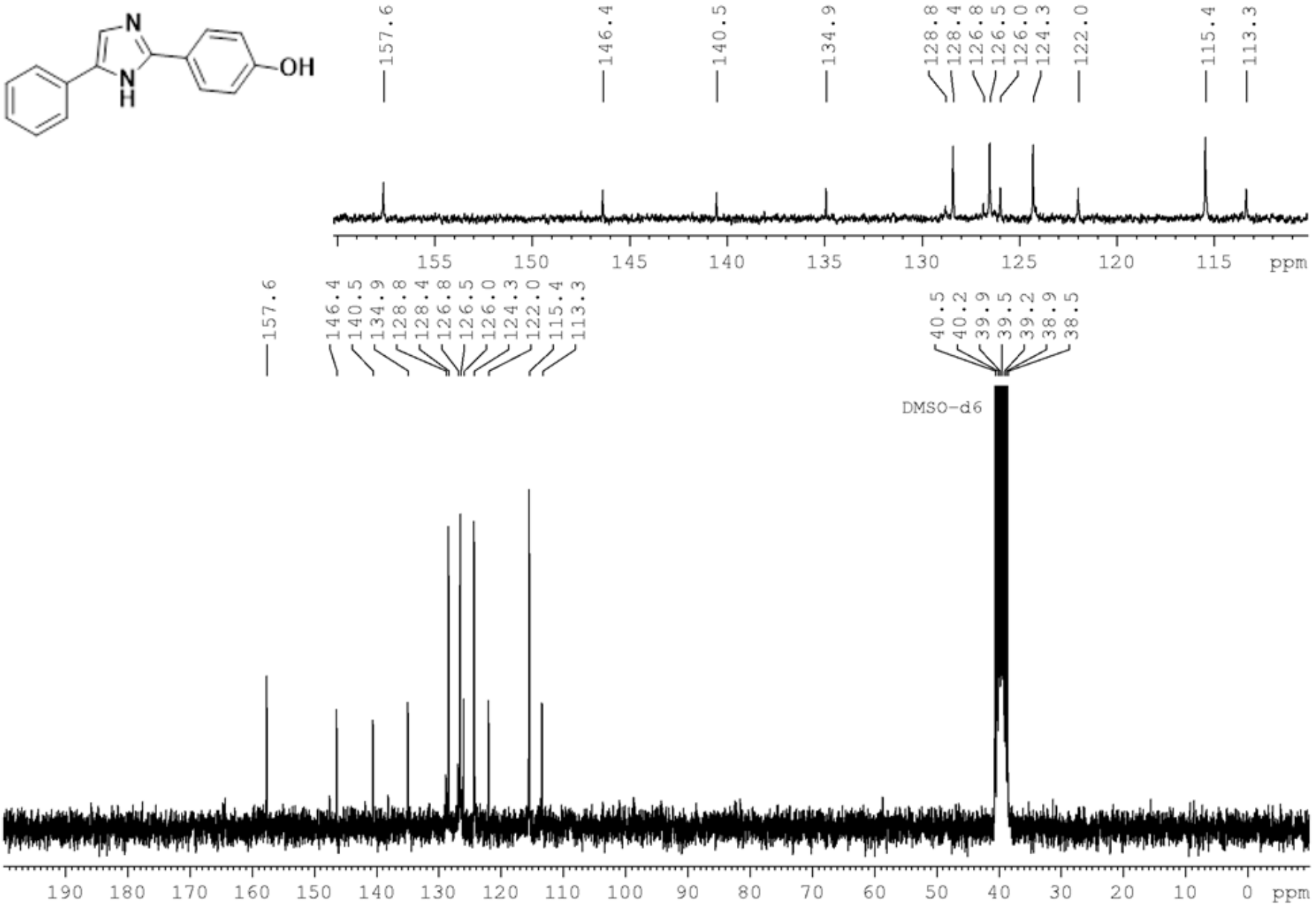


Figure S35. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 63 MHz) of **19**

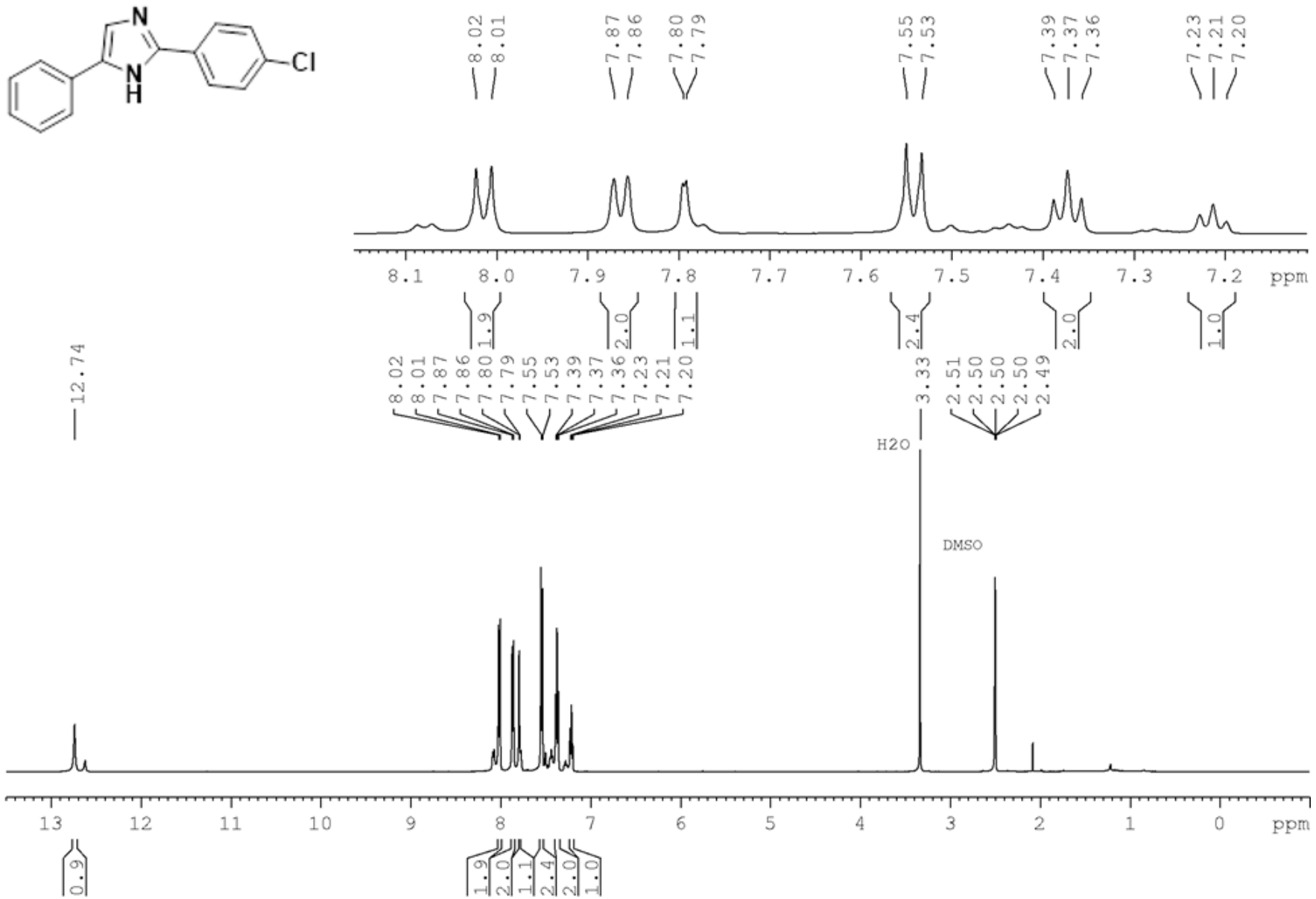


Figure S36. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **20**

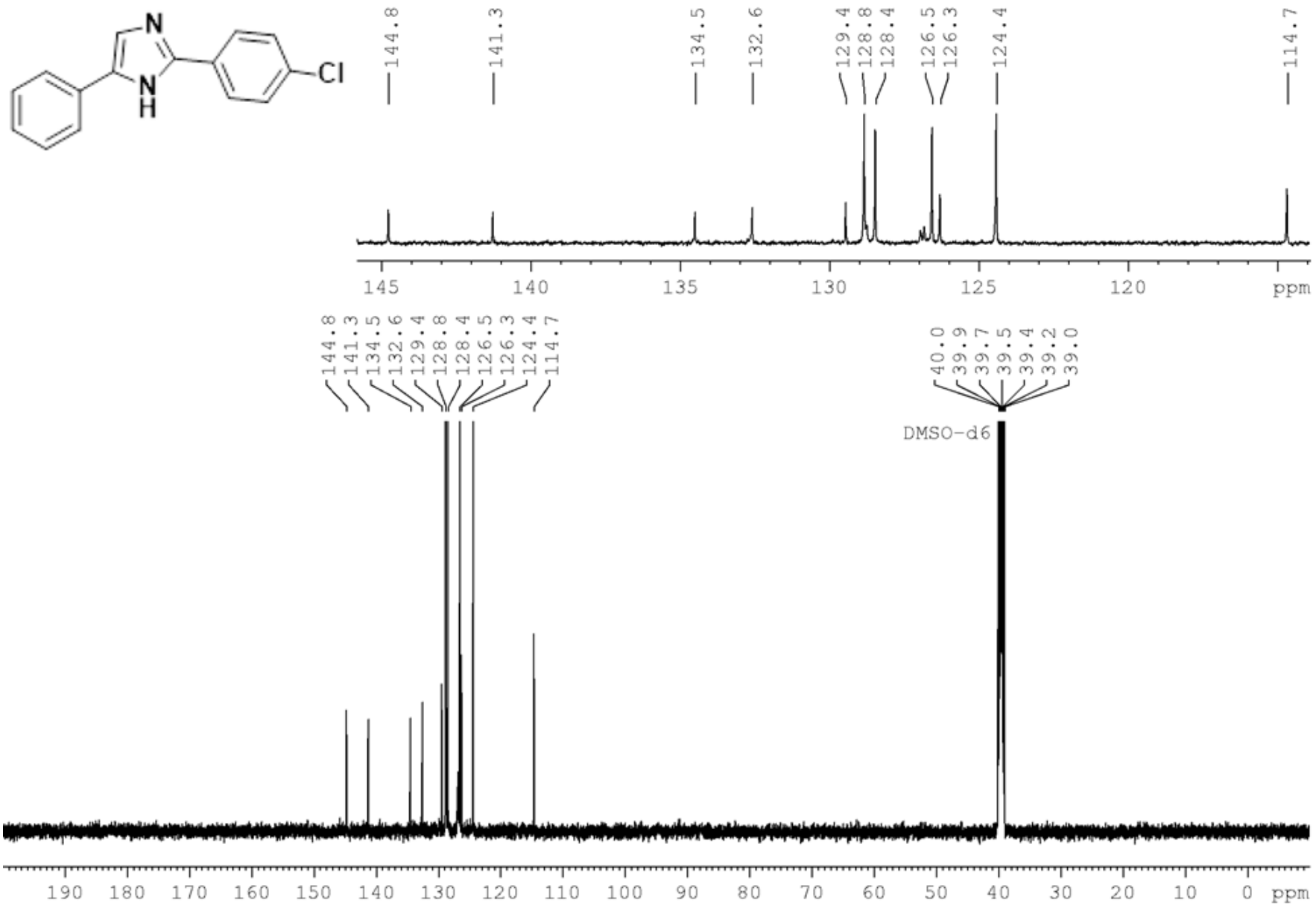


Figure S37. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **20**

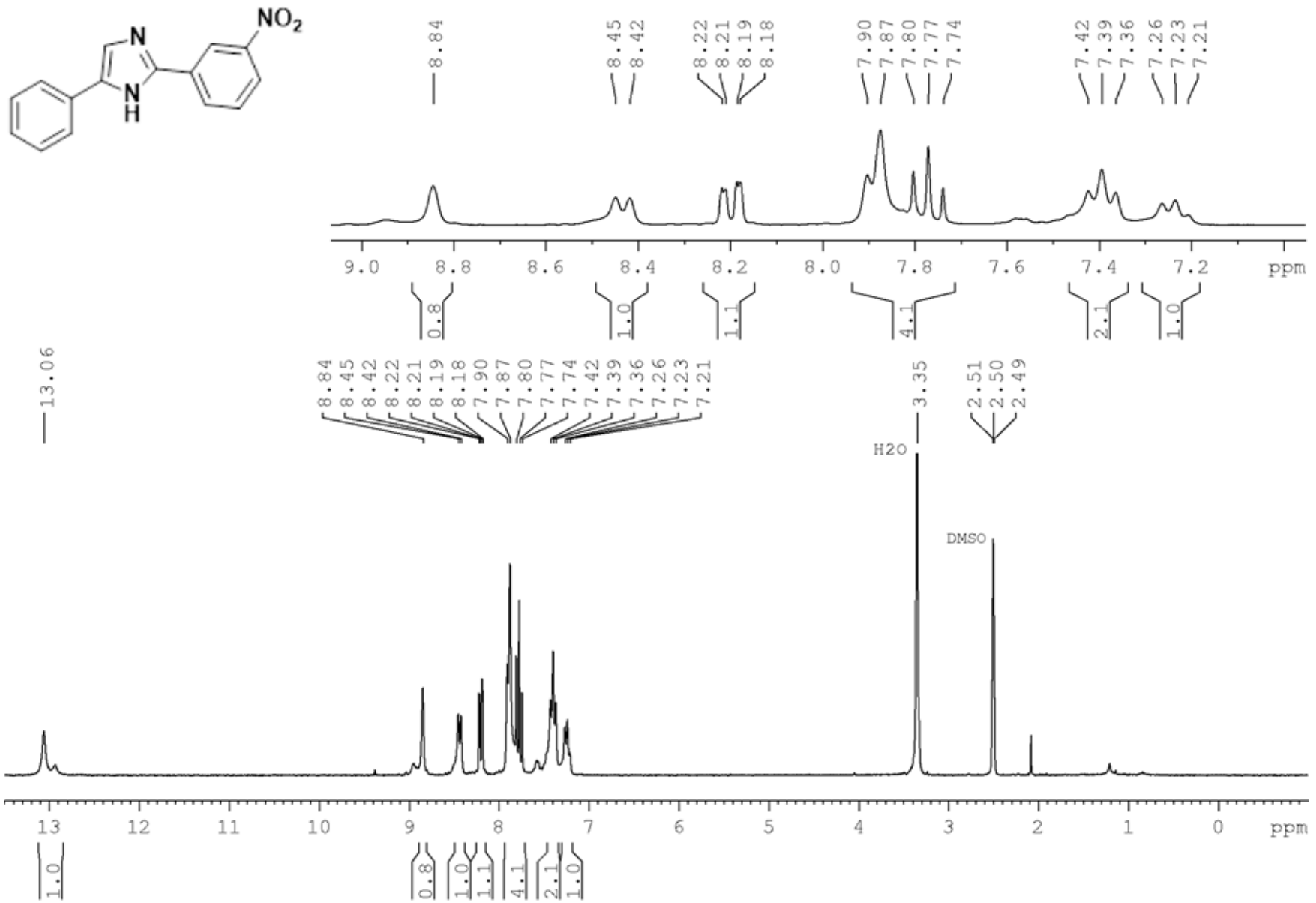


Figure S38. ^{1}H NMR Spectra (DMSO-d_6, 250 MHz) of **21**

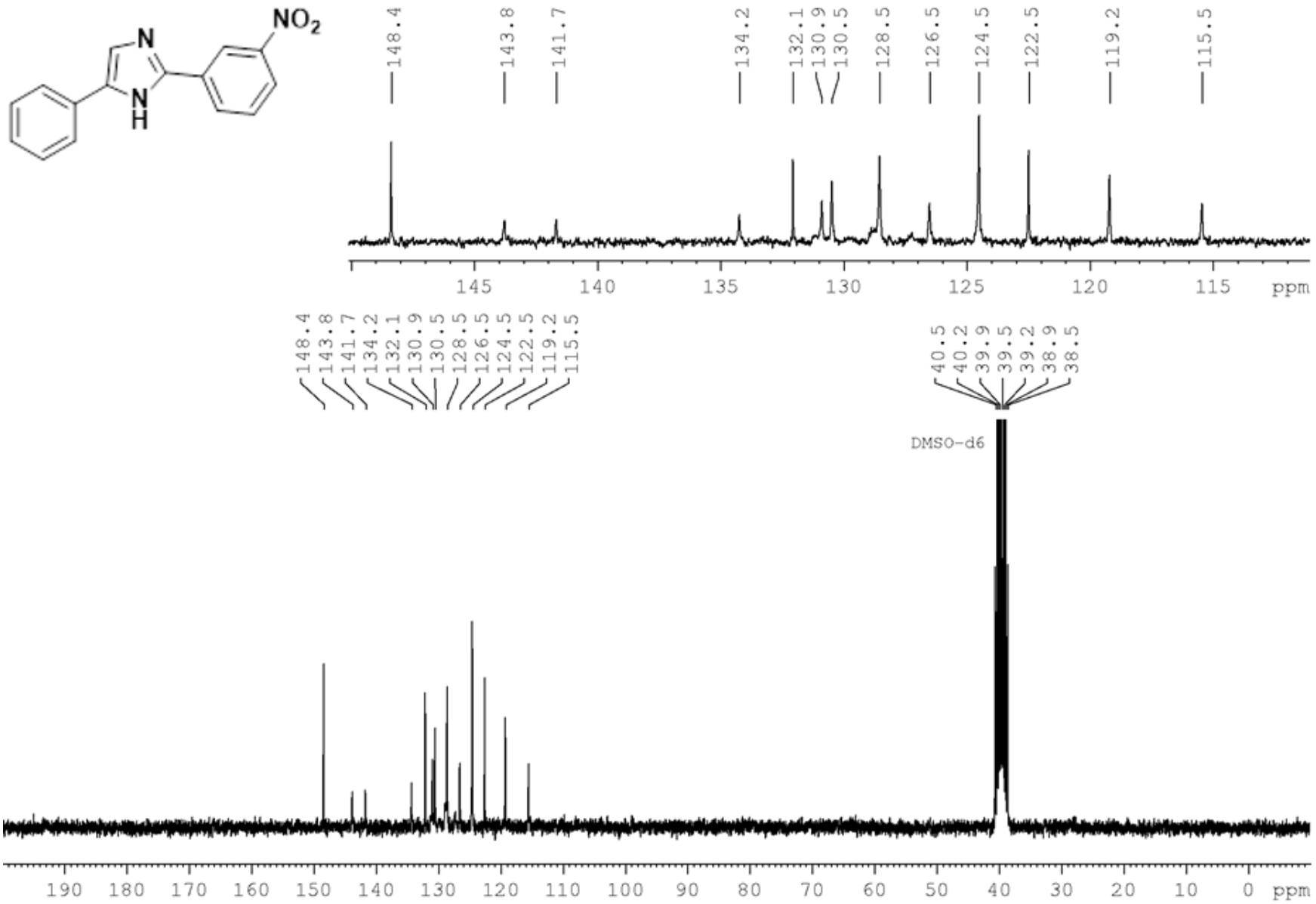


Figure S39. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 63 MHz) of **21**

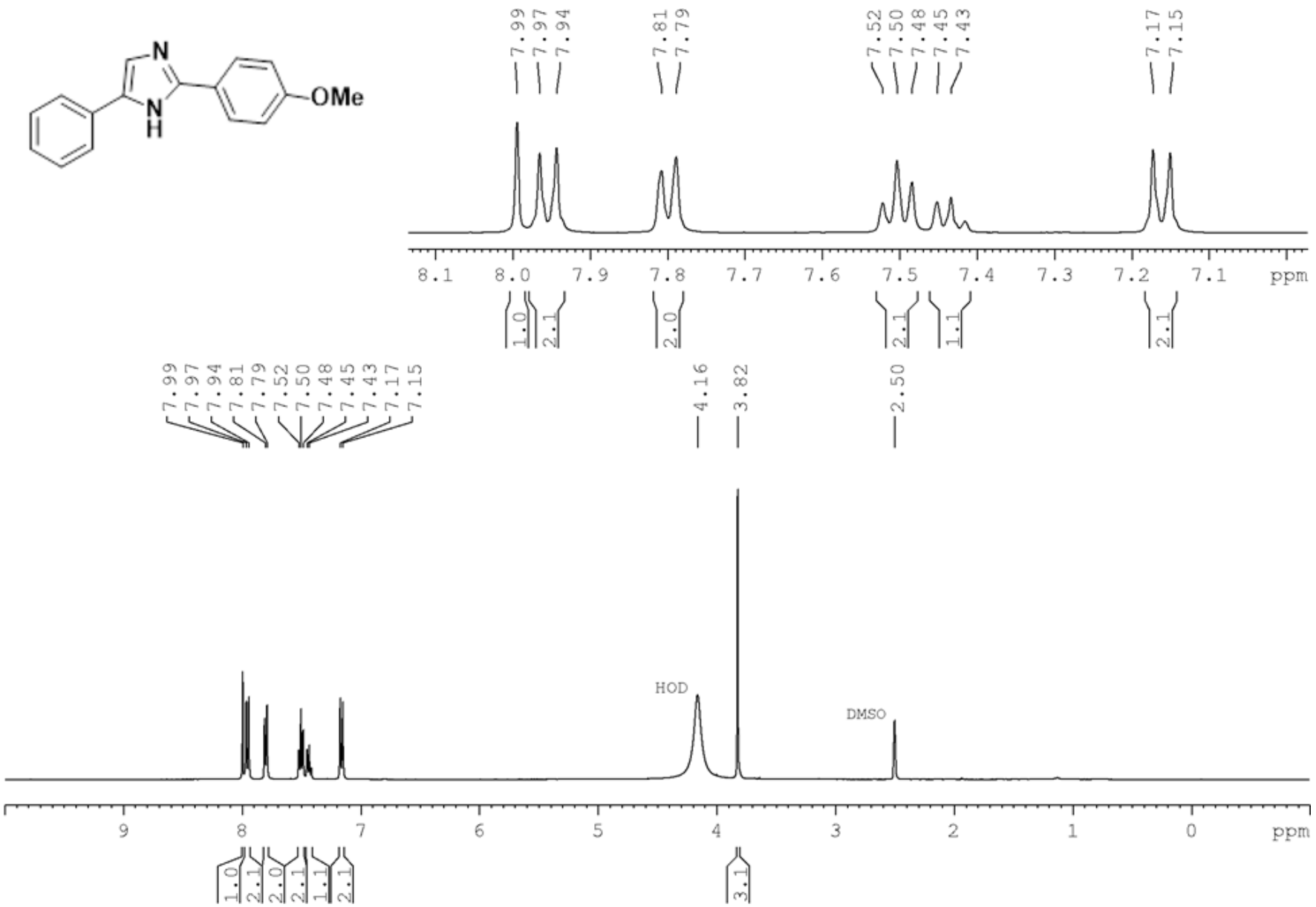


Figure S40. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 400 MHz) of **22**

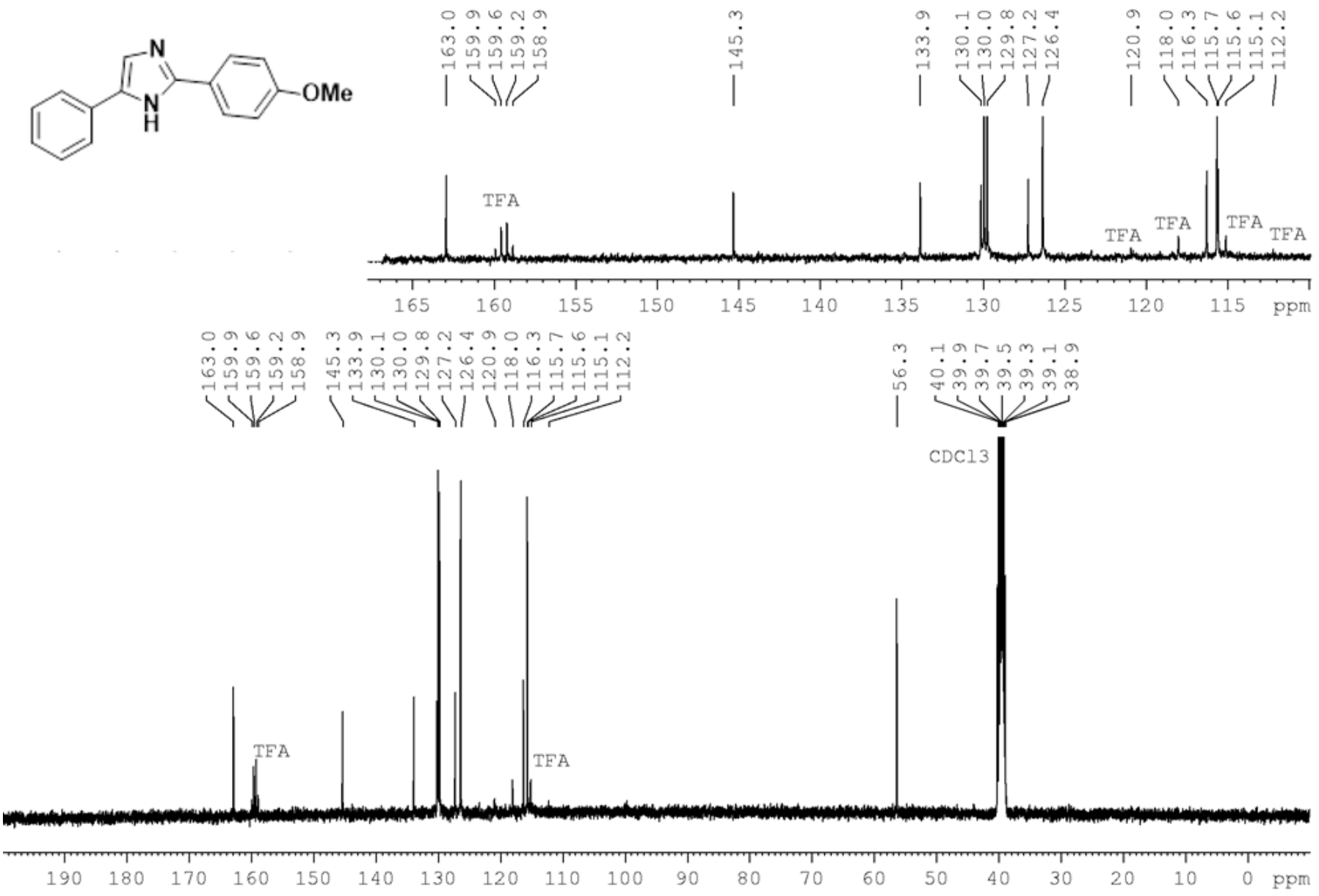


Figure S41. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 101 MHz) of **22**

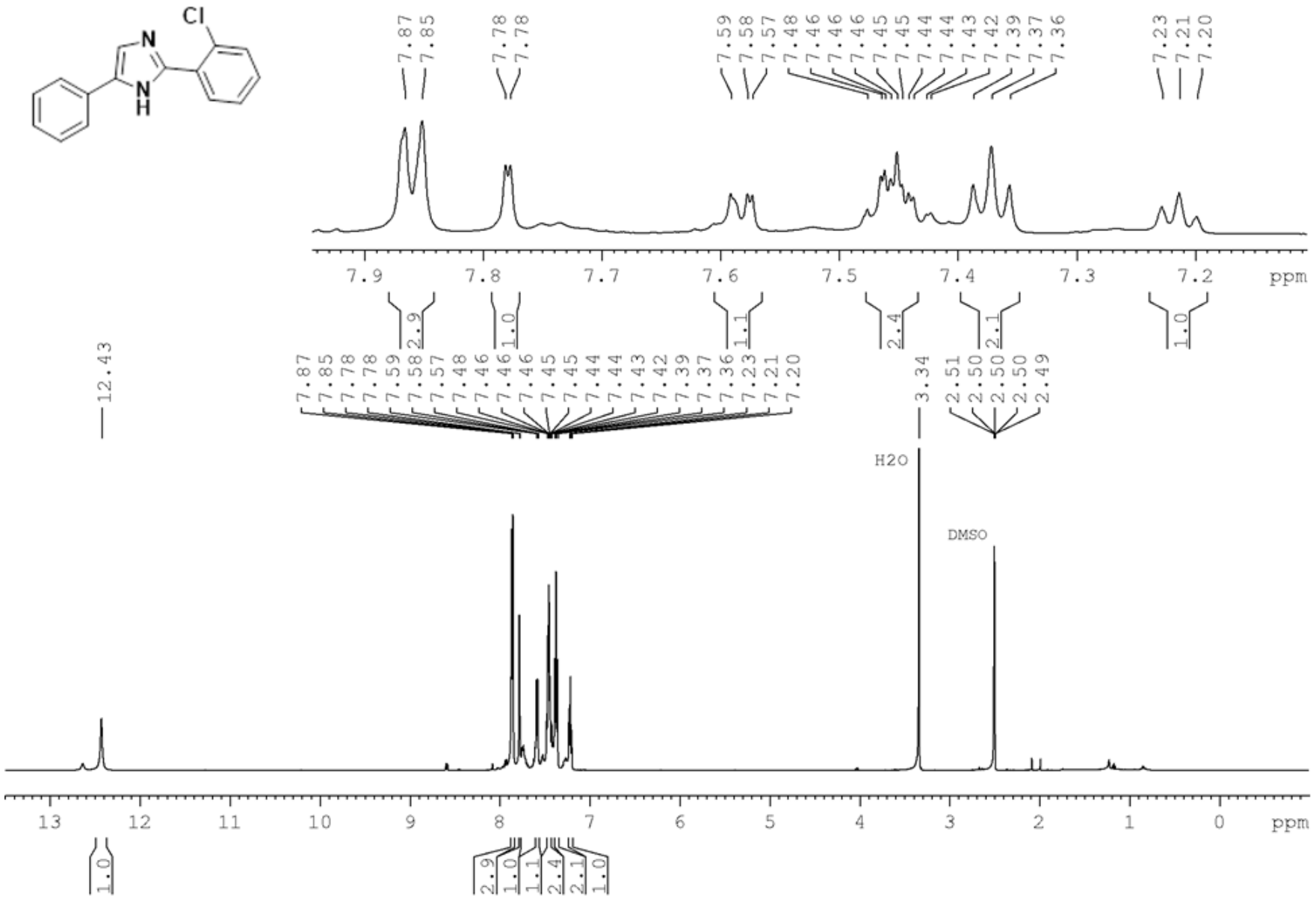


Figure S42. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **23**

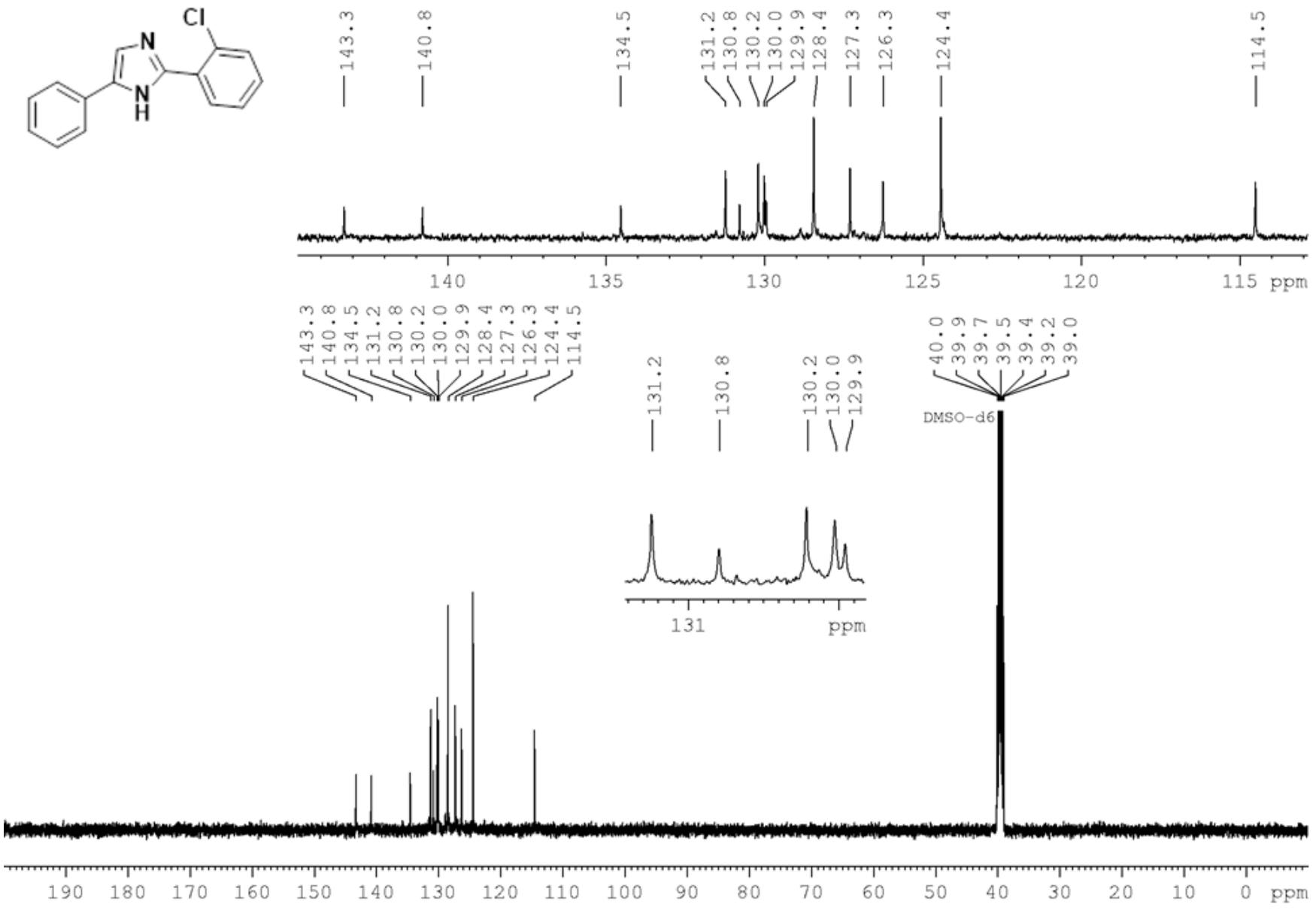


Figure S43. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **23**

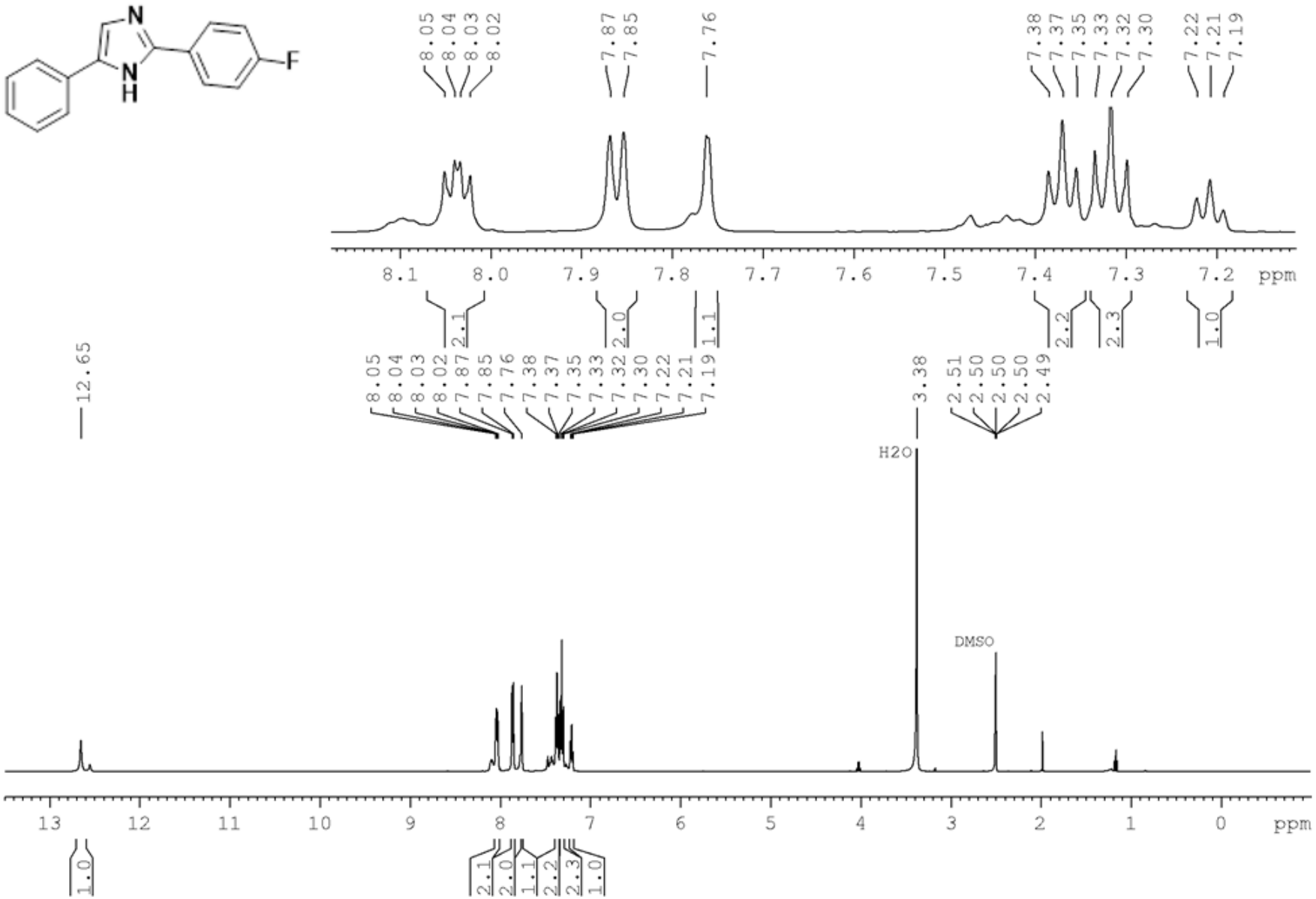


Figure S44. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **24**

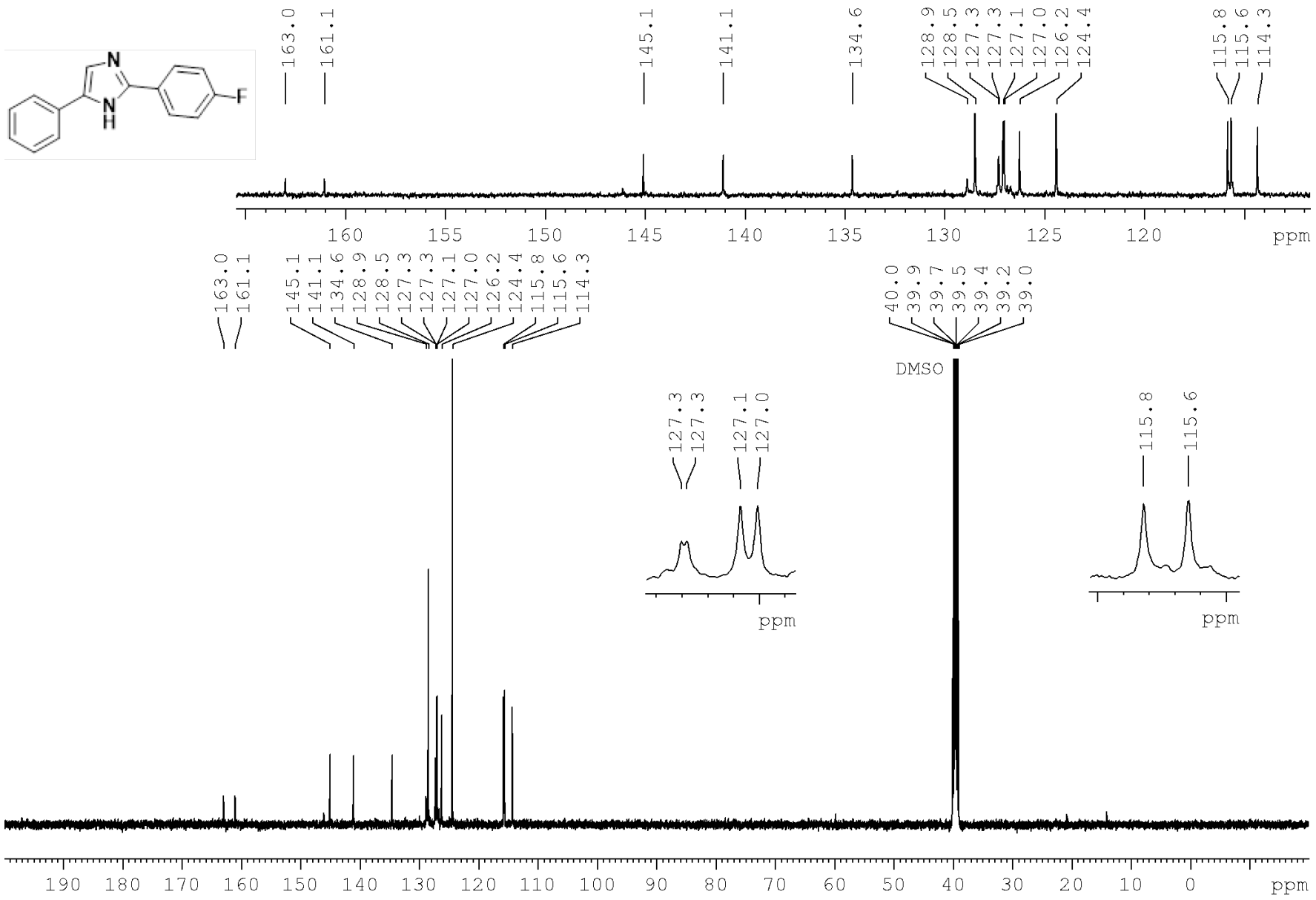


Figure S45. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **24**

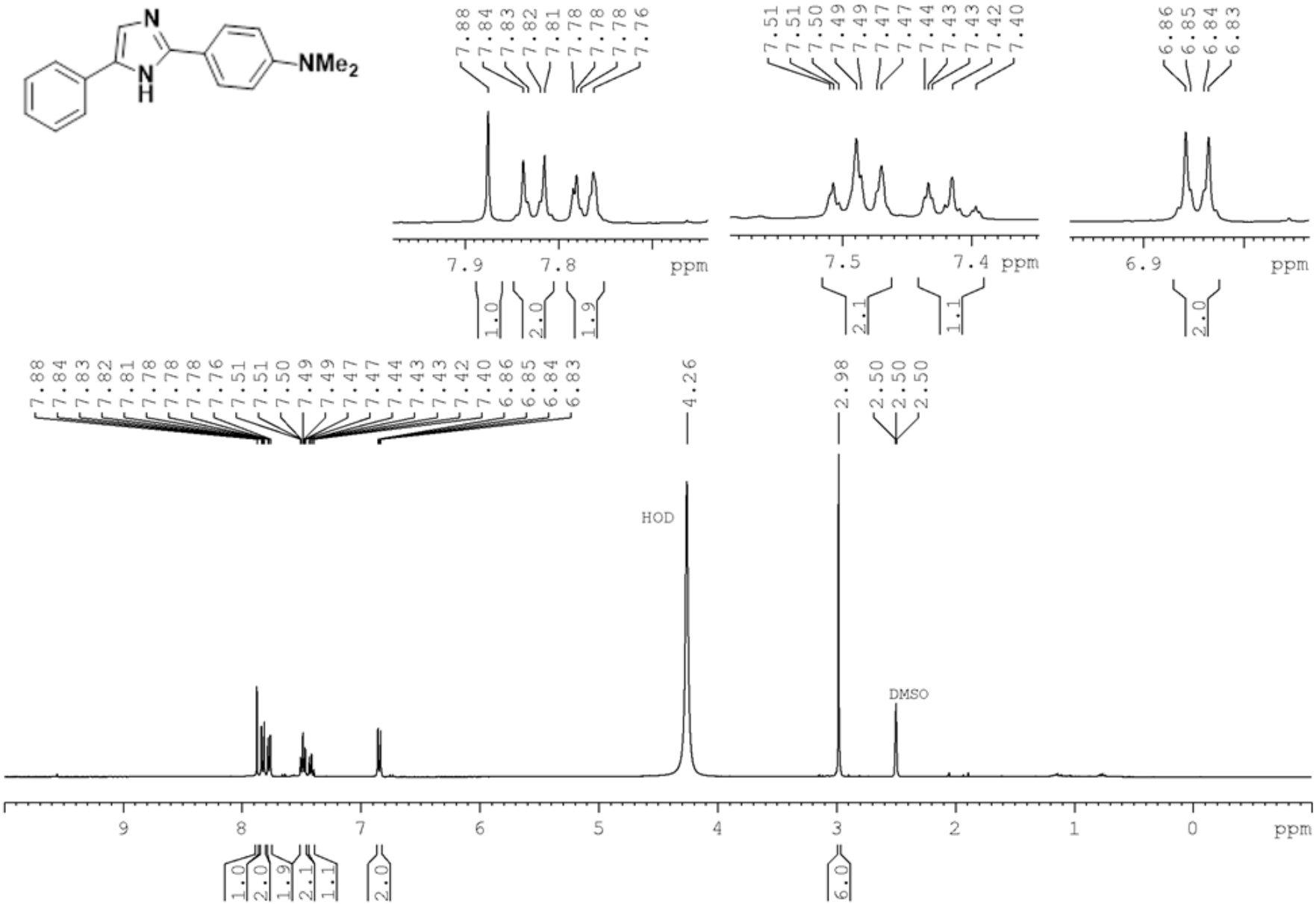


Figure S46. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 400 MHz) of **25**

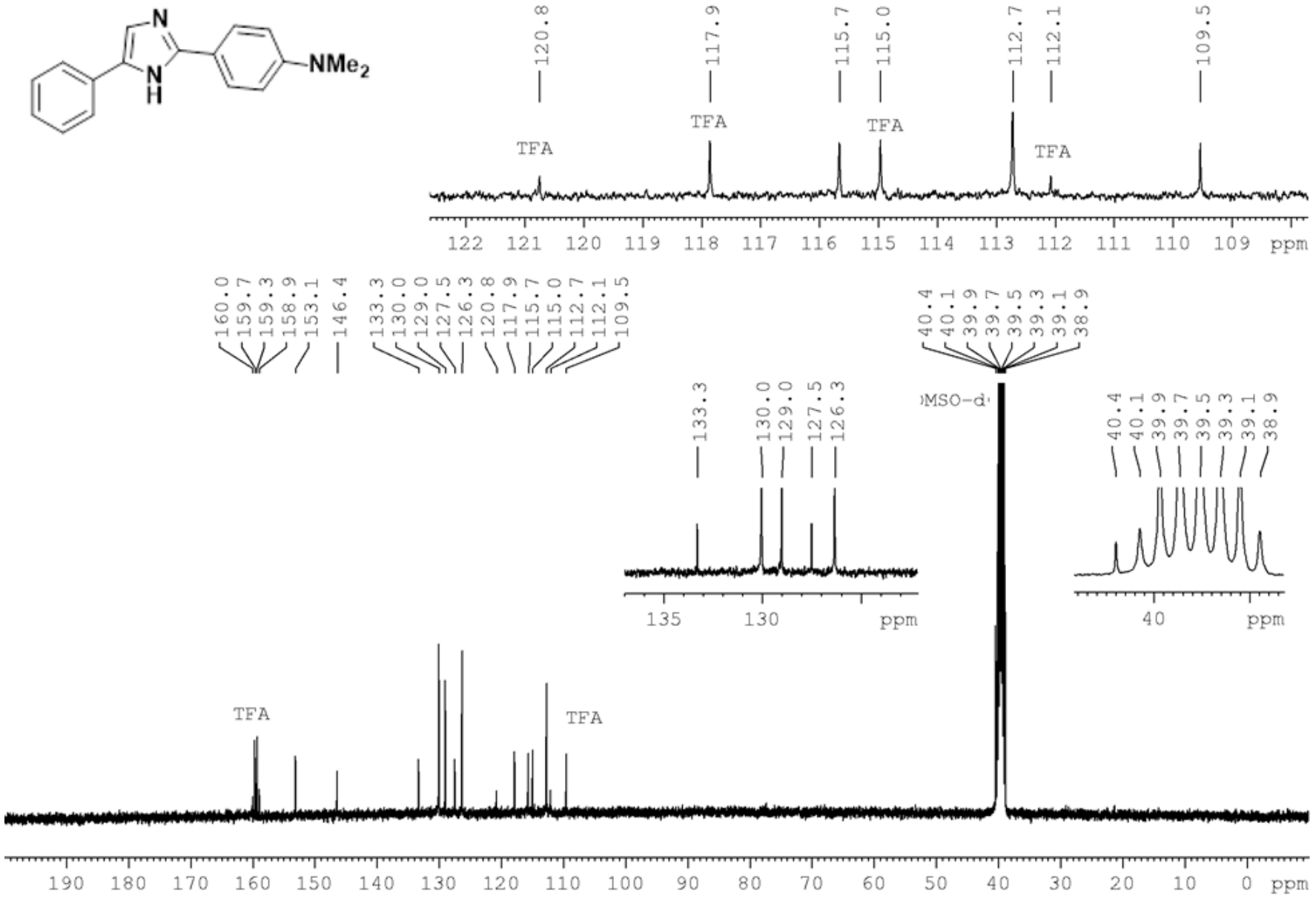


Figure S47. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 101 MHz) of **25**

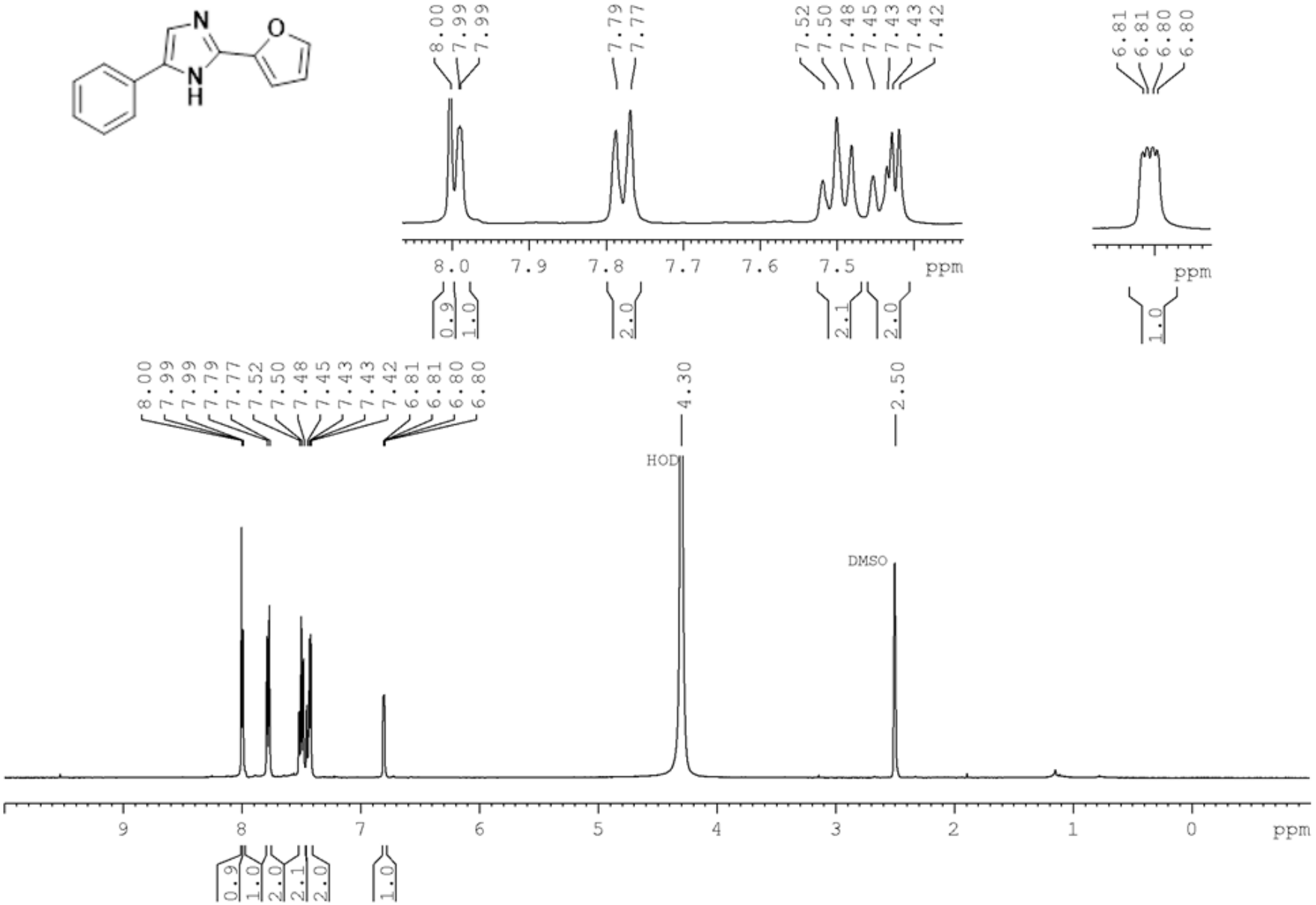


Figure S48. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 400 MHz) of **26**

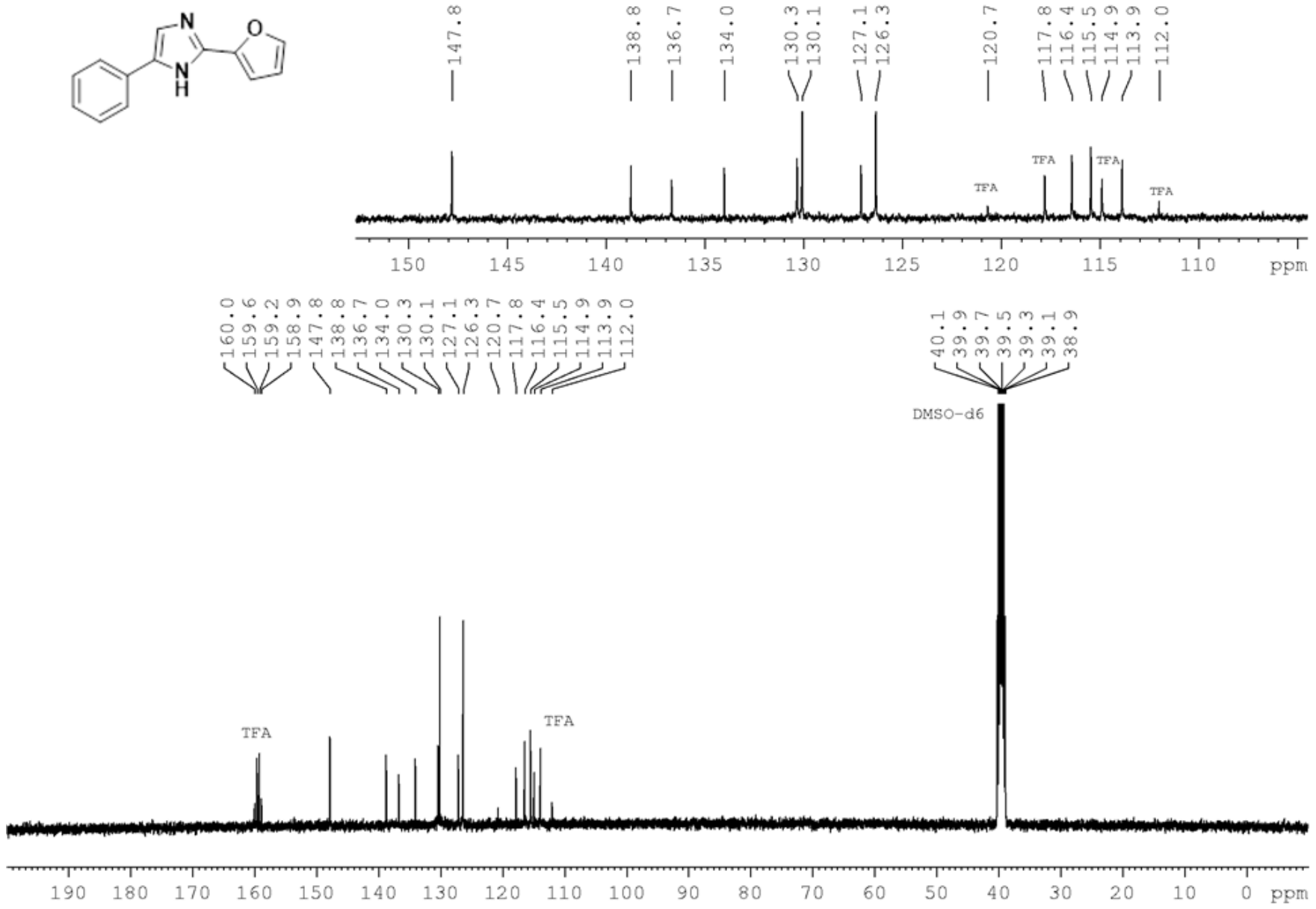


Figure S49. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 101 MHz) of **26**

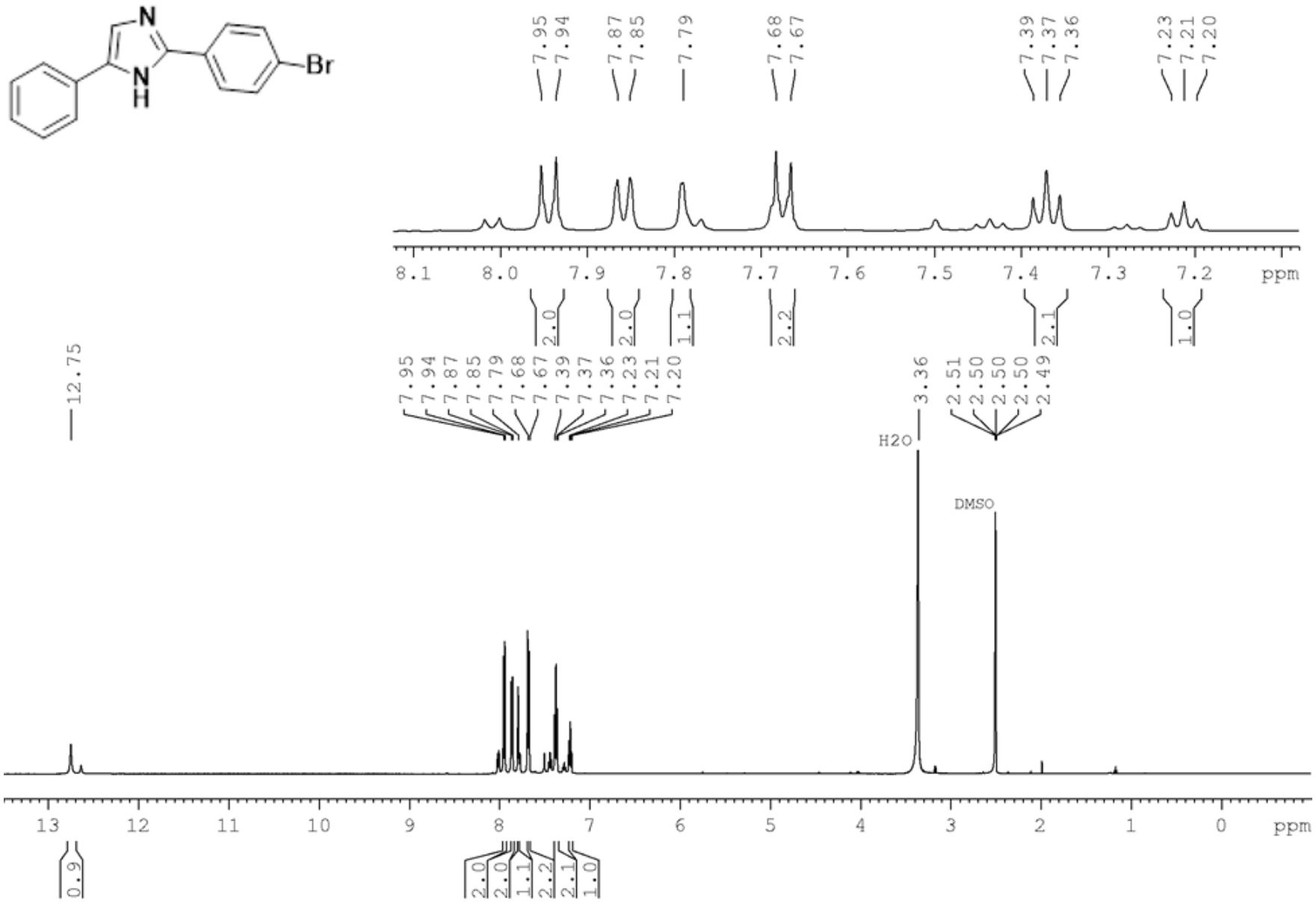


Figure S50. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **27**

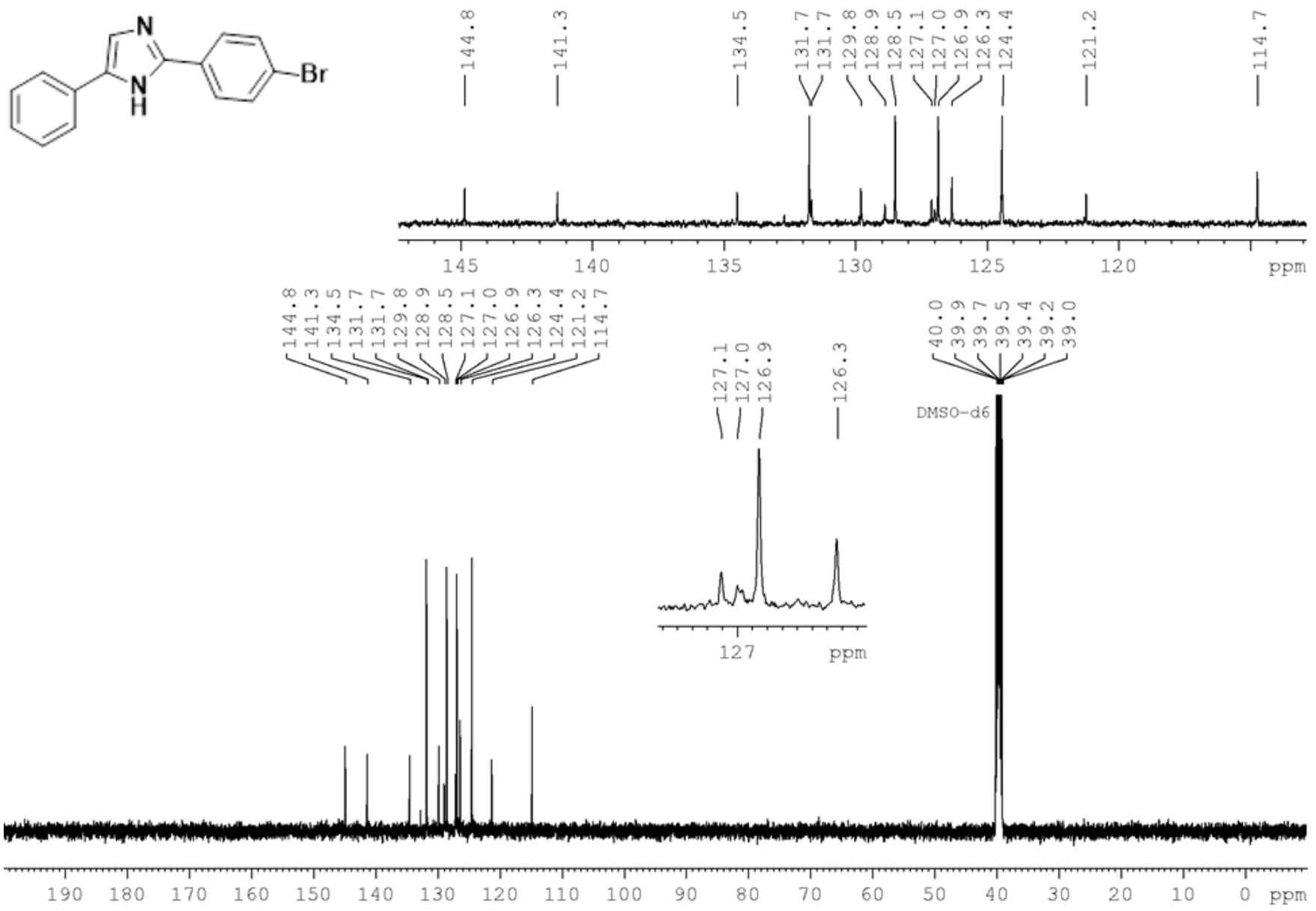


Figure S51. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **27**

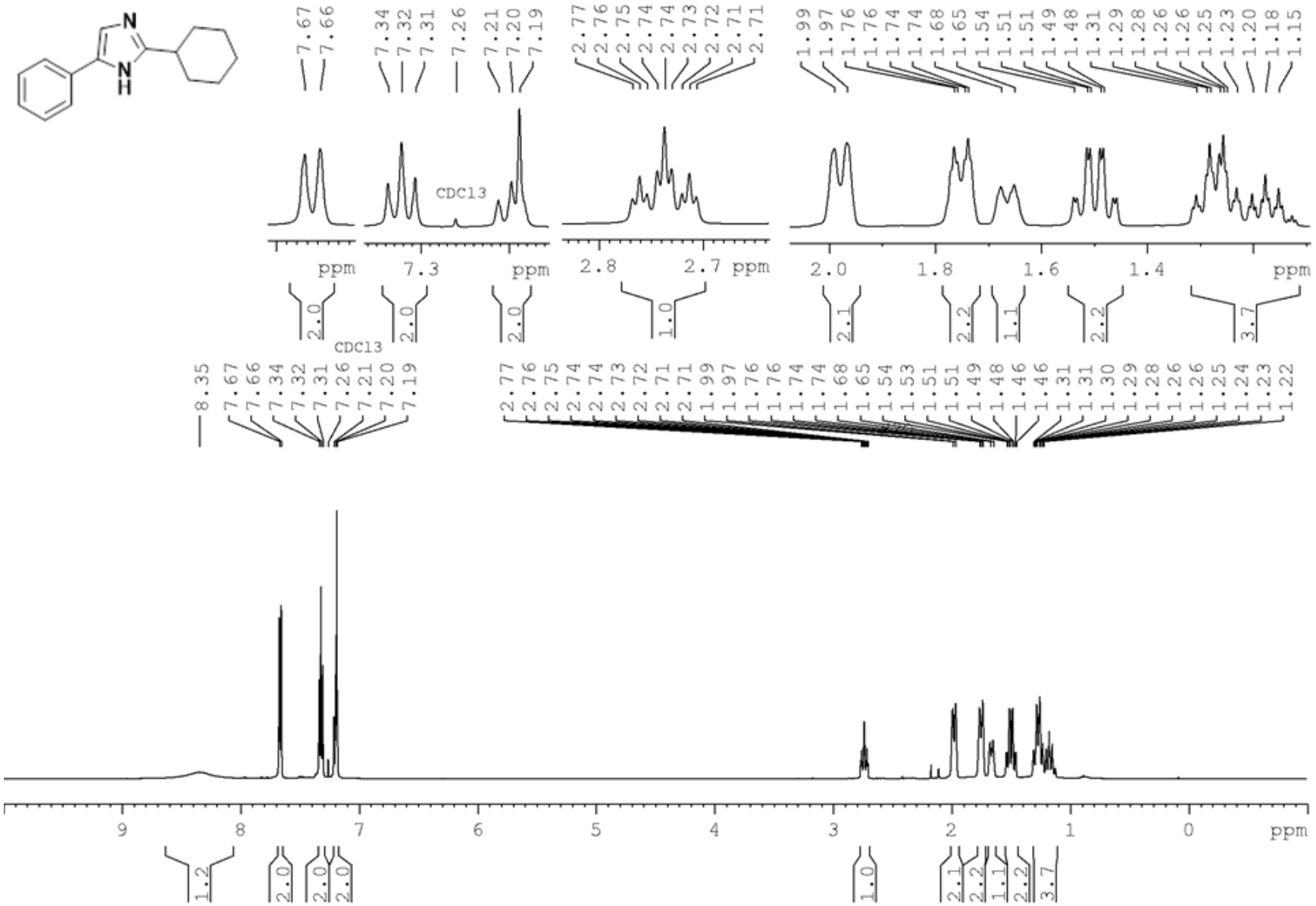


Figure S52. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **28**

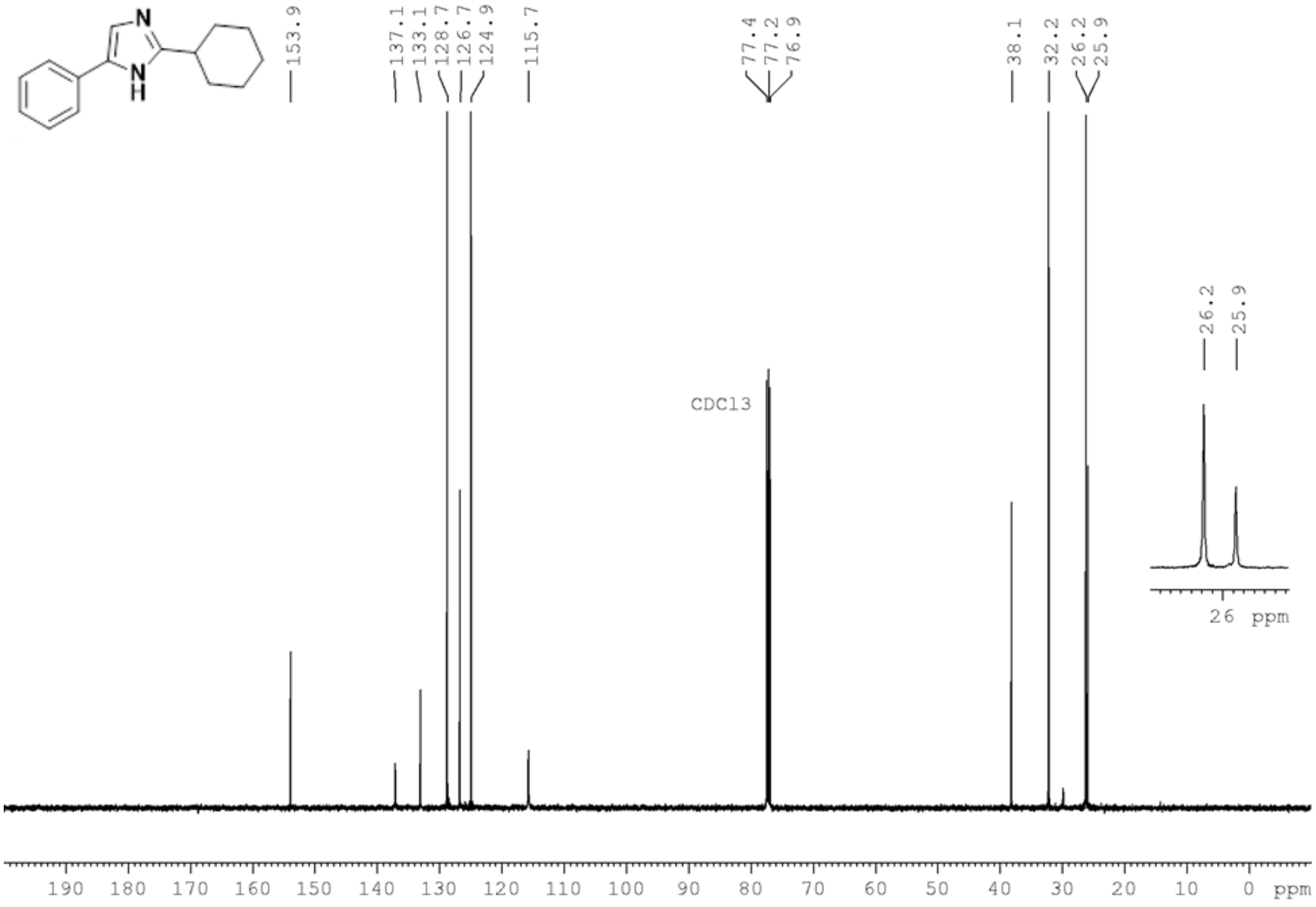


Figure S53. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **28**

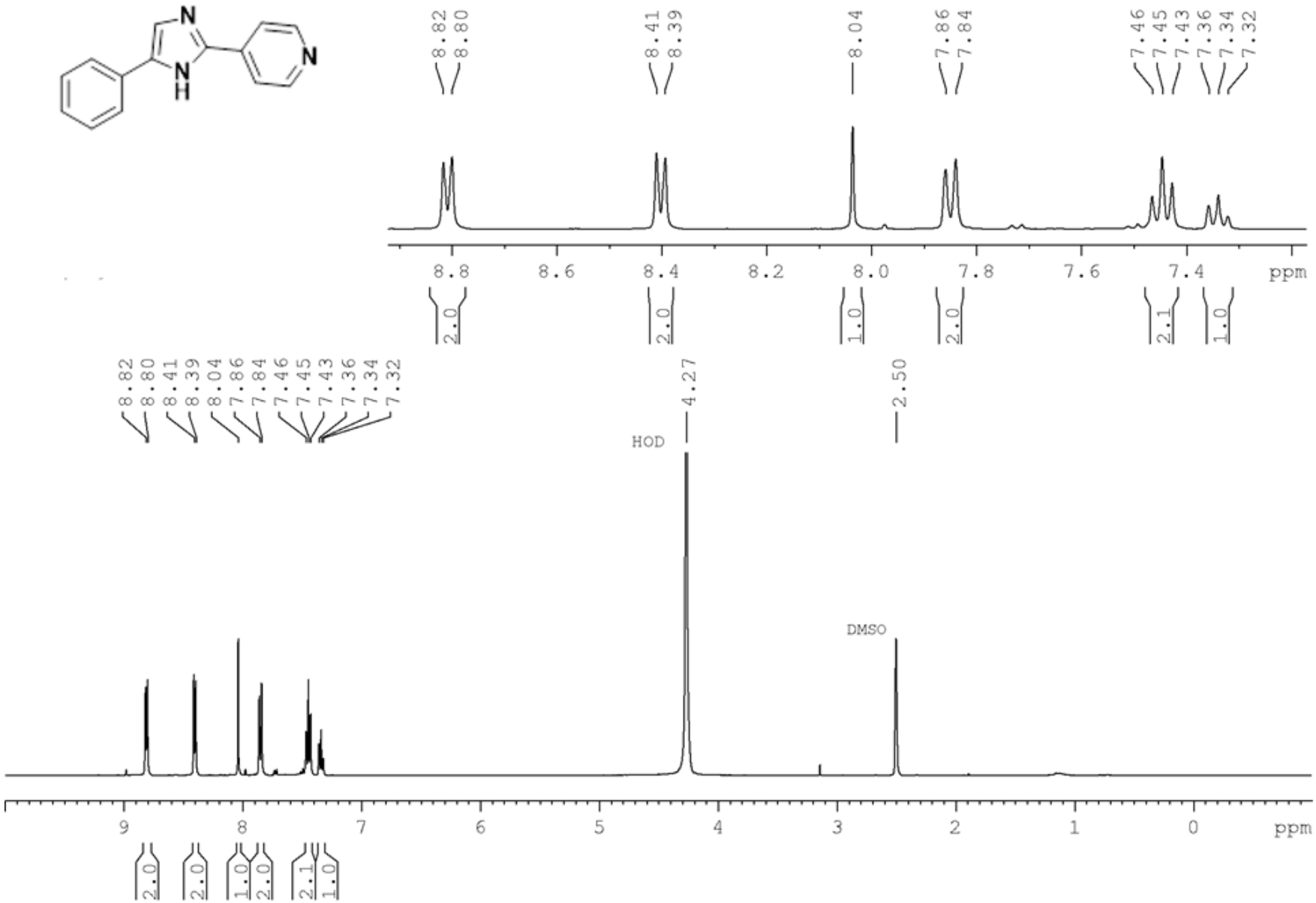


Figure S54. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 400 MHz) of **29**

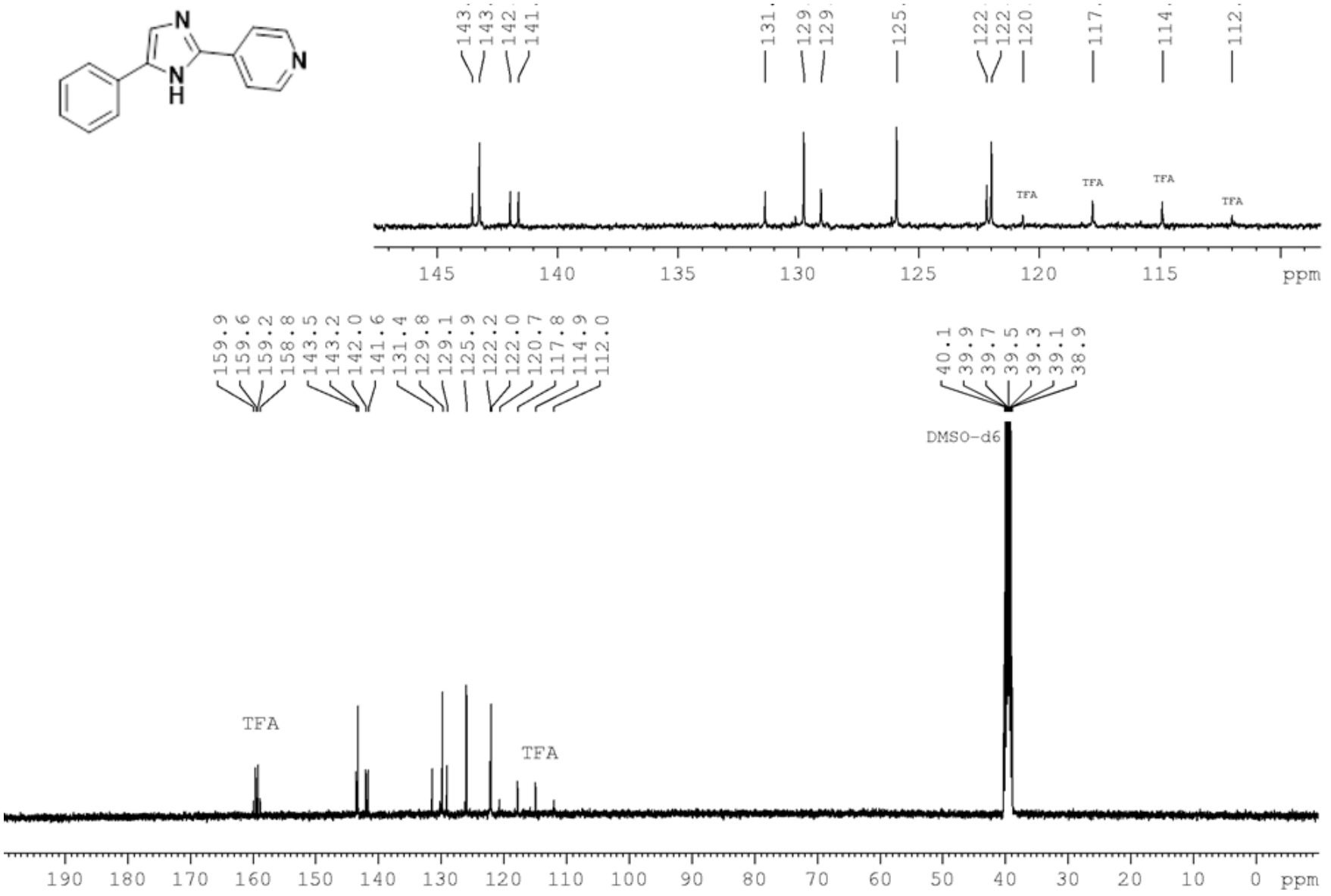


Figure S55. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 101 MHz) of **29**

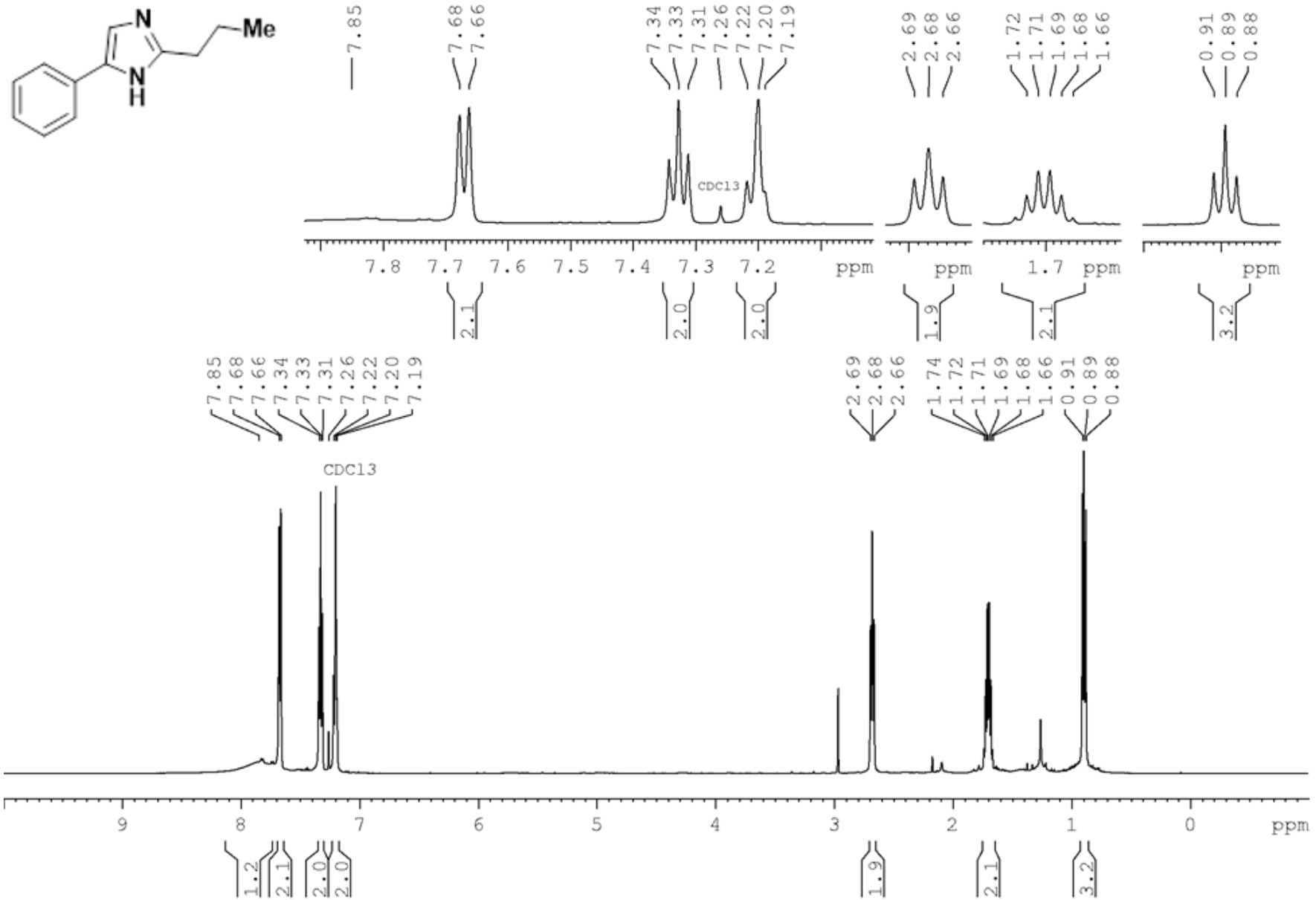


Figure S56. ^{1}H NMR Spectra ($CDCL_3$, 500 MHz) of **30**

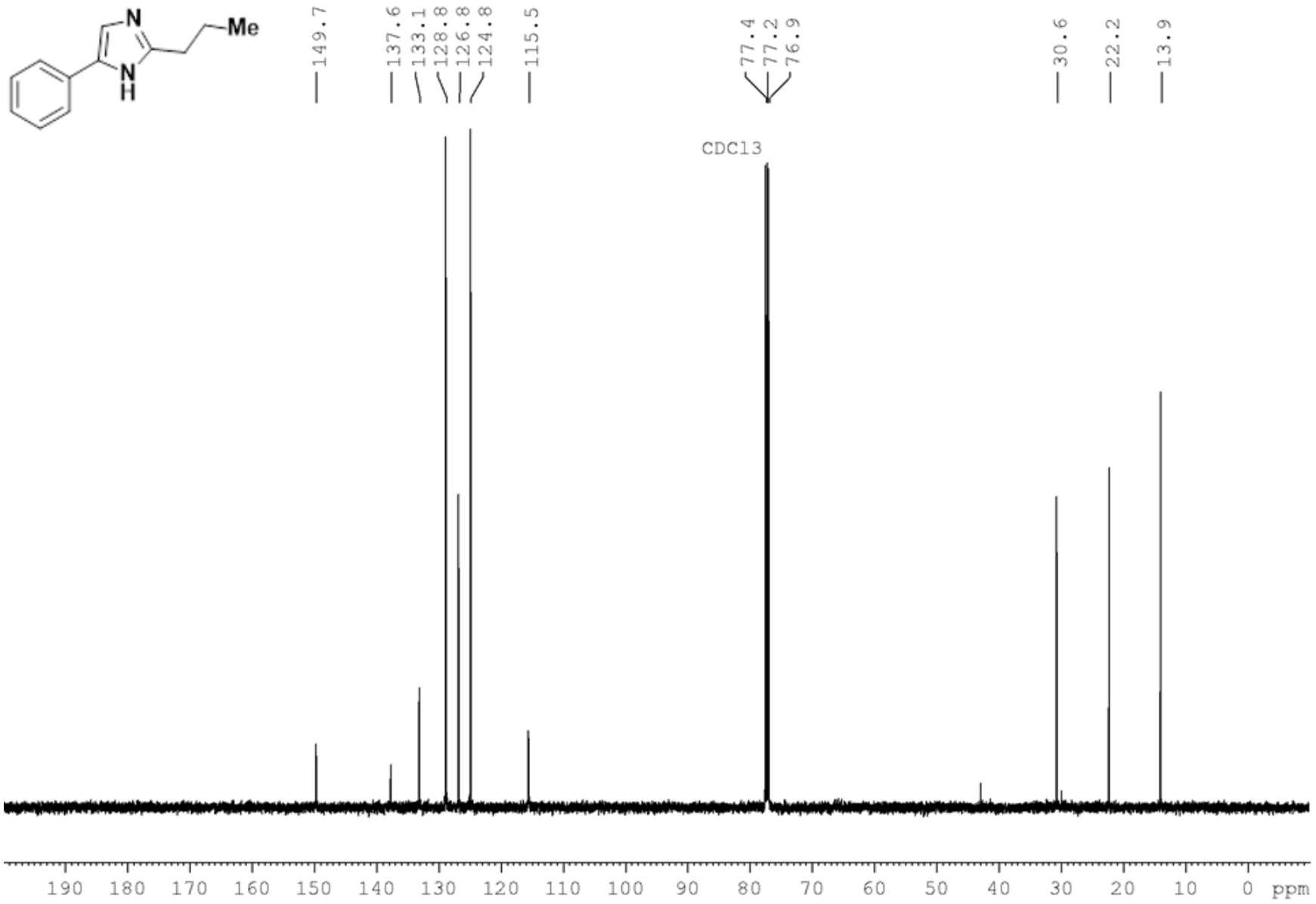


Figure S57. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **30**

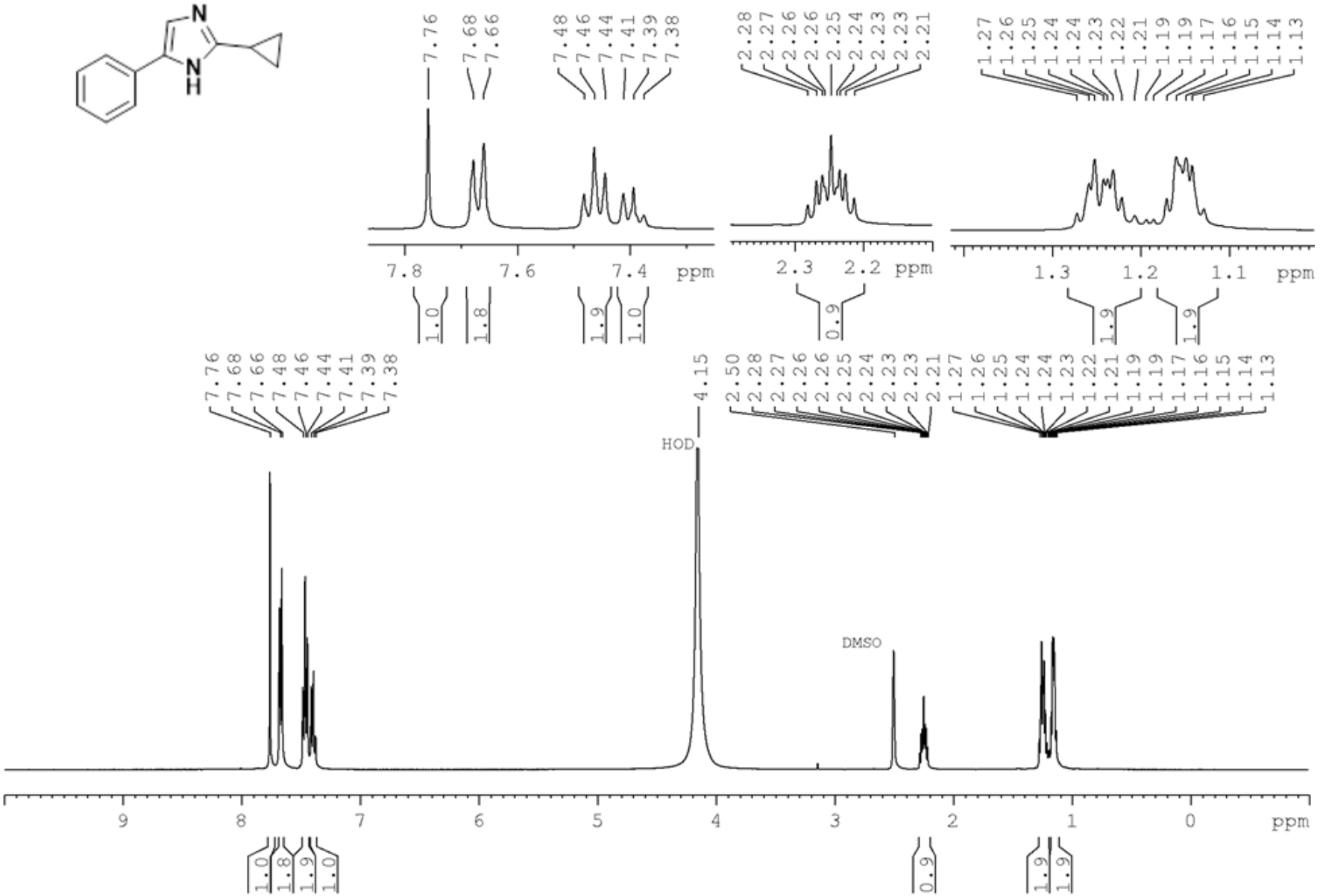


Figure S58. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 400 MHz) of **31**

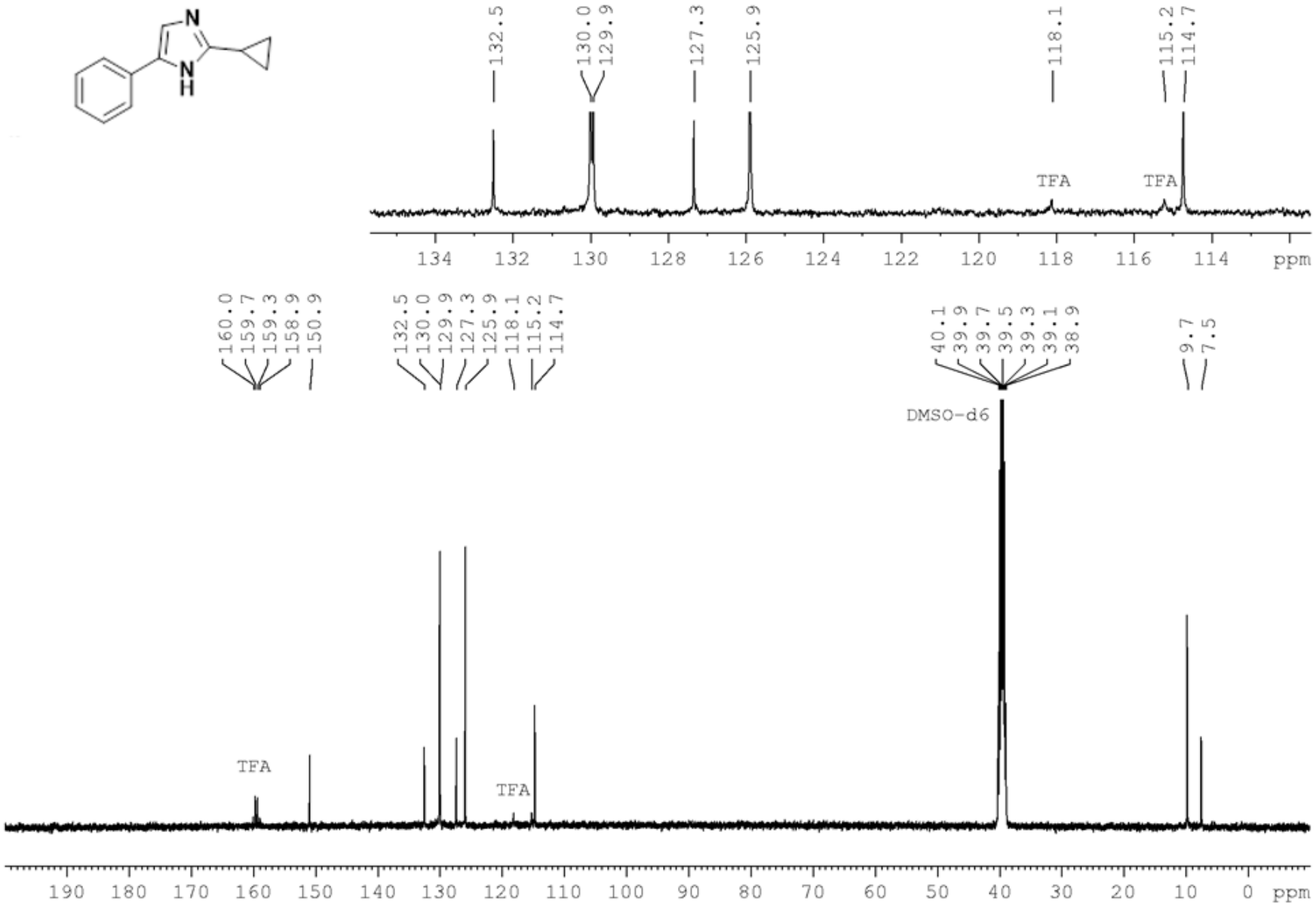


Figure S59. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 101 MHz) of **31**

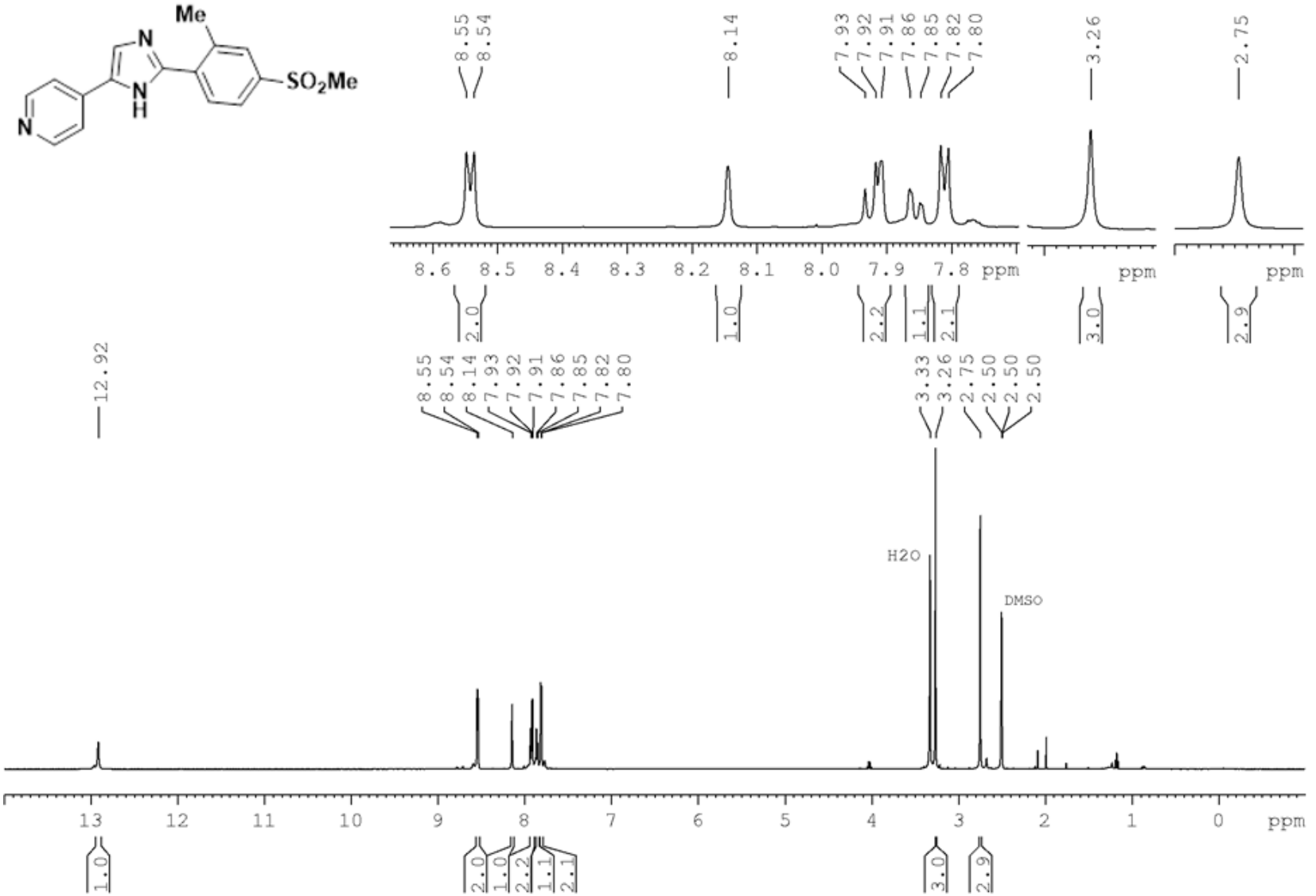


Figure S60. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **32**

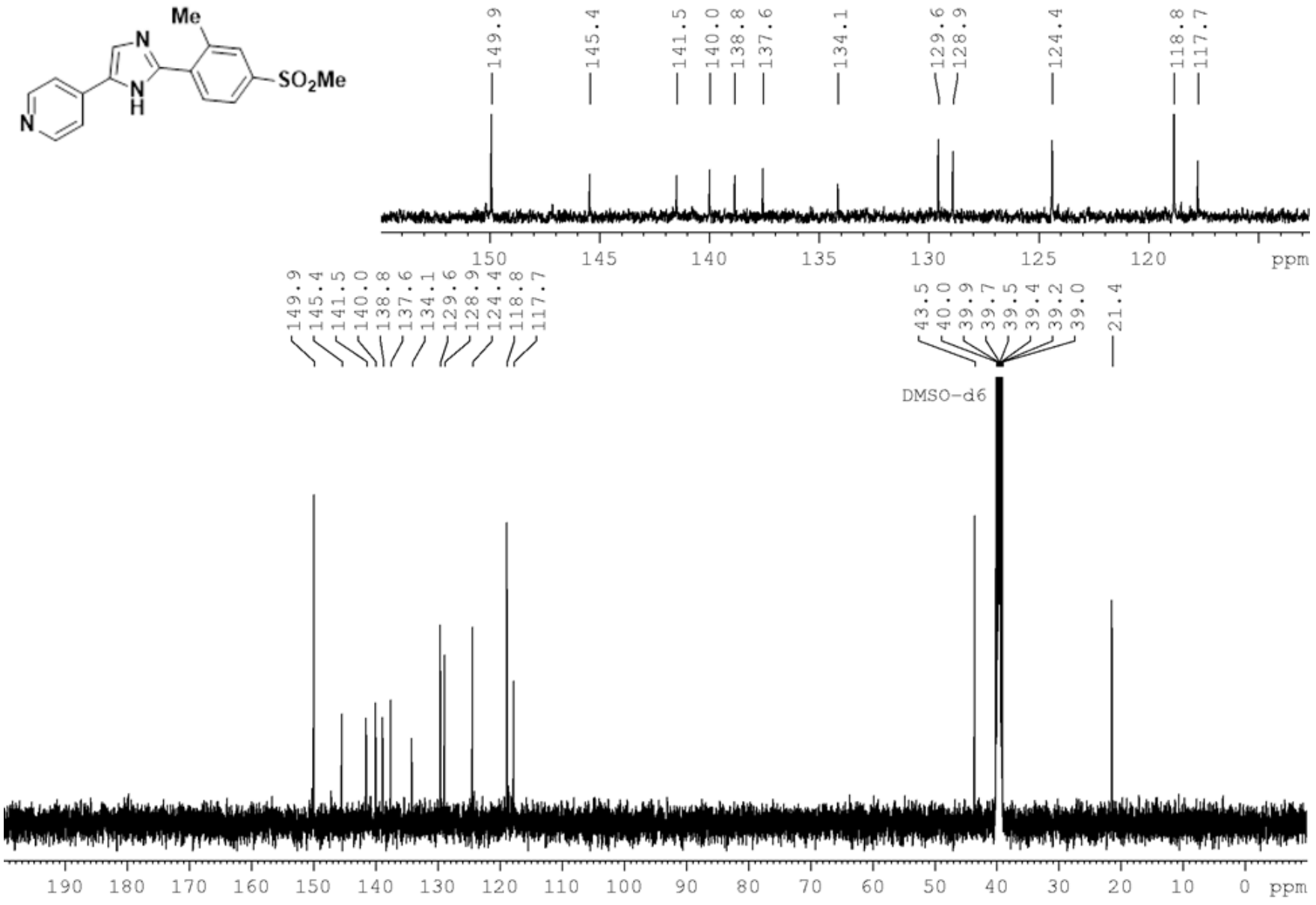


Figure S61. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **32**

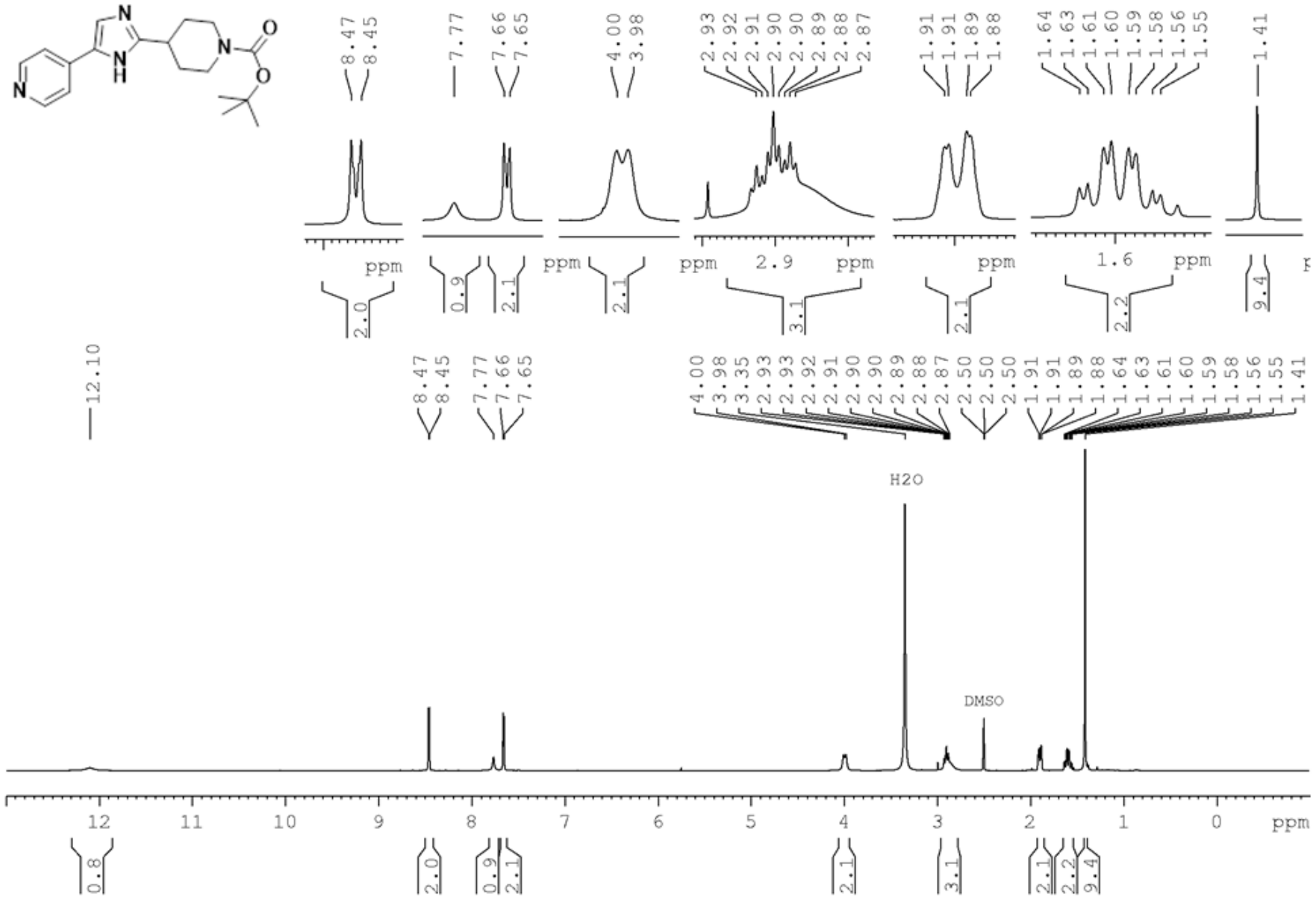


Figure S62. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **36**

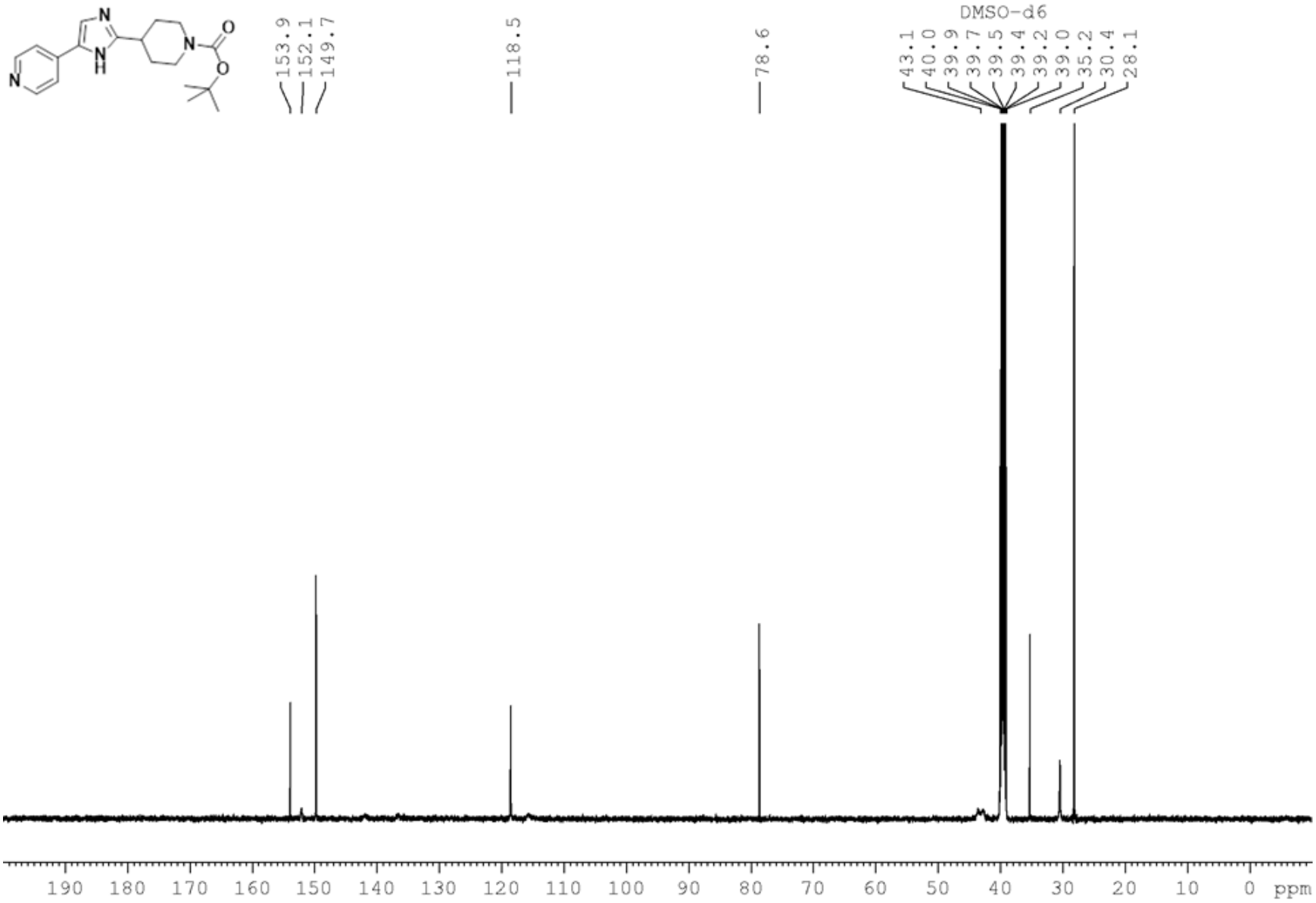


Figure S63. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **36**

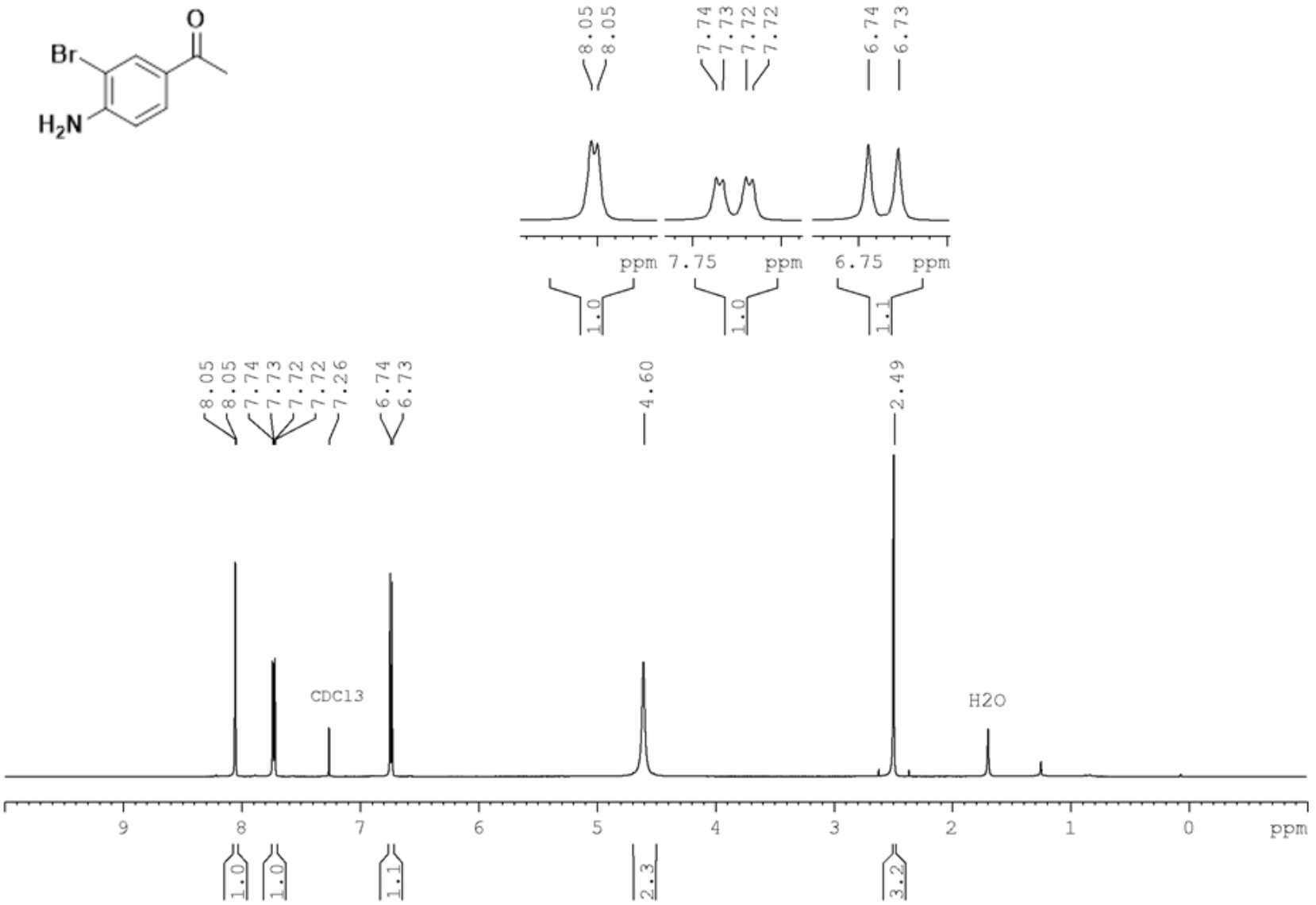


Figure S64. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **43**

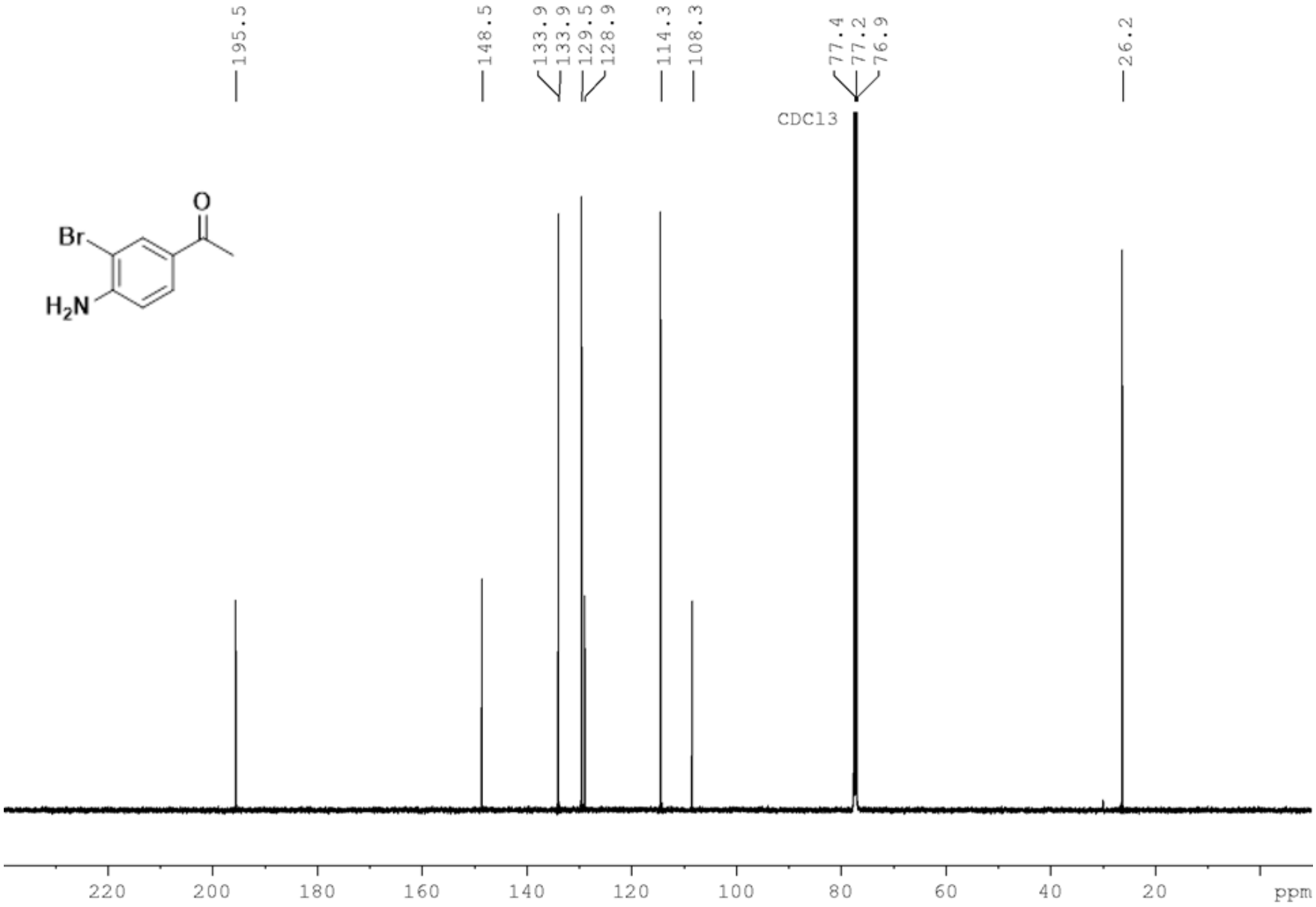


Figure S65. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **43**

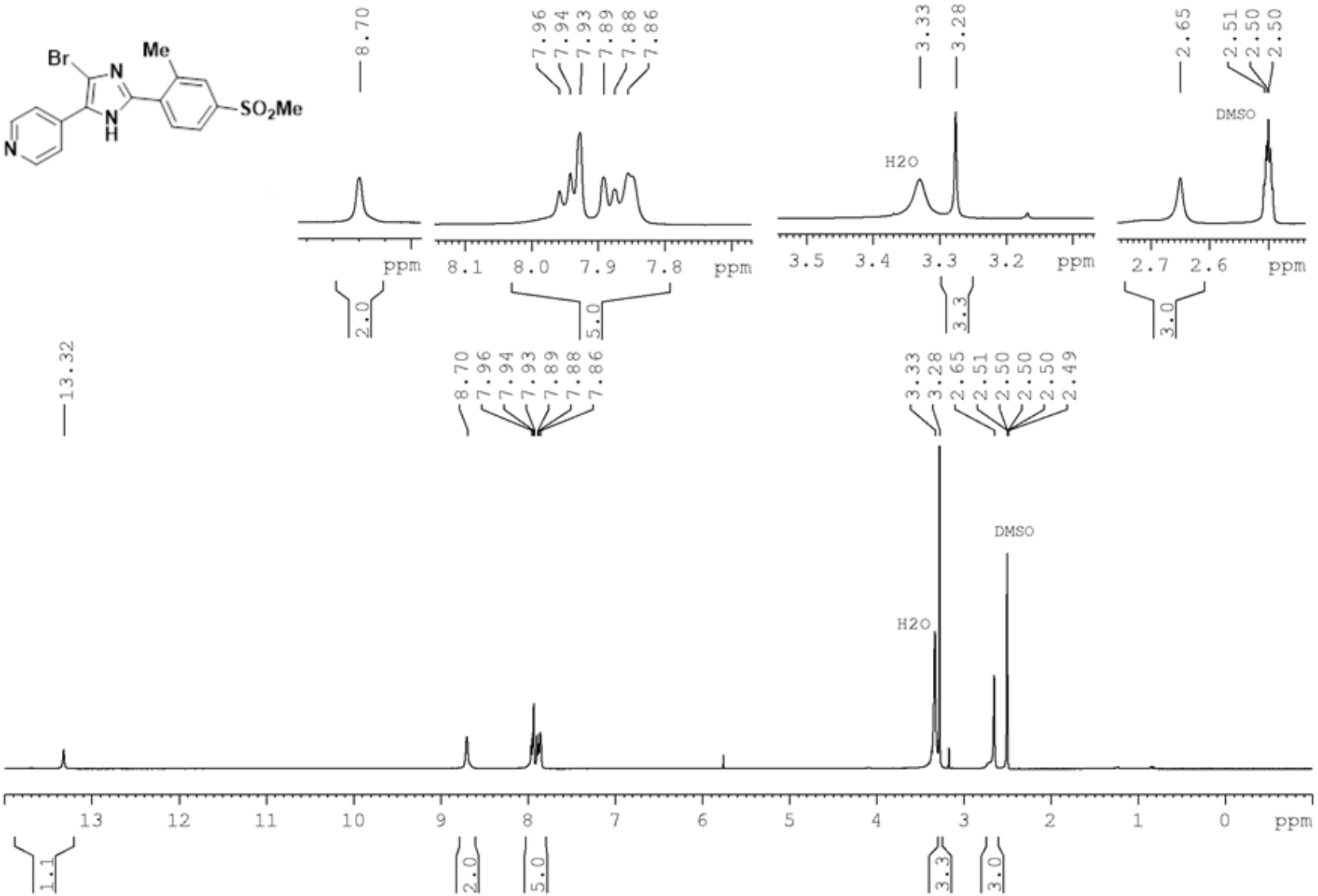


Figure S66. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **44**

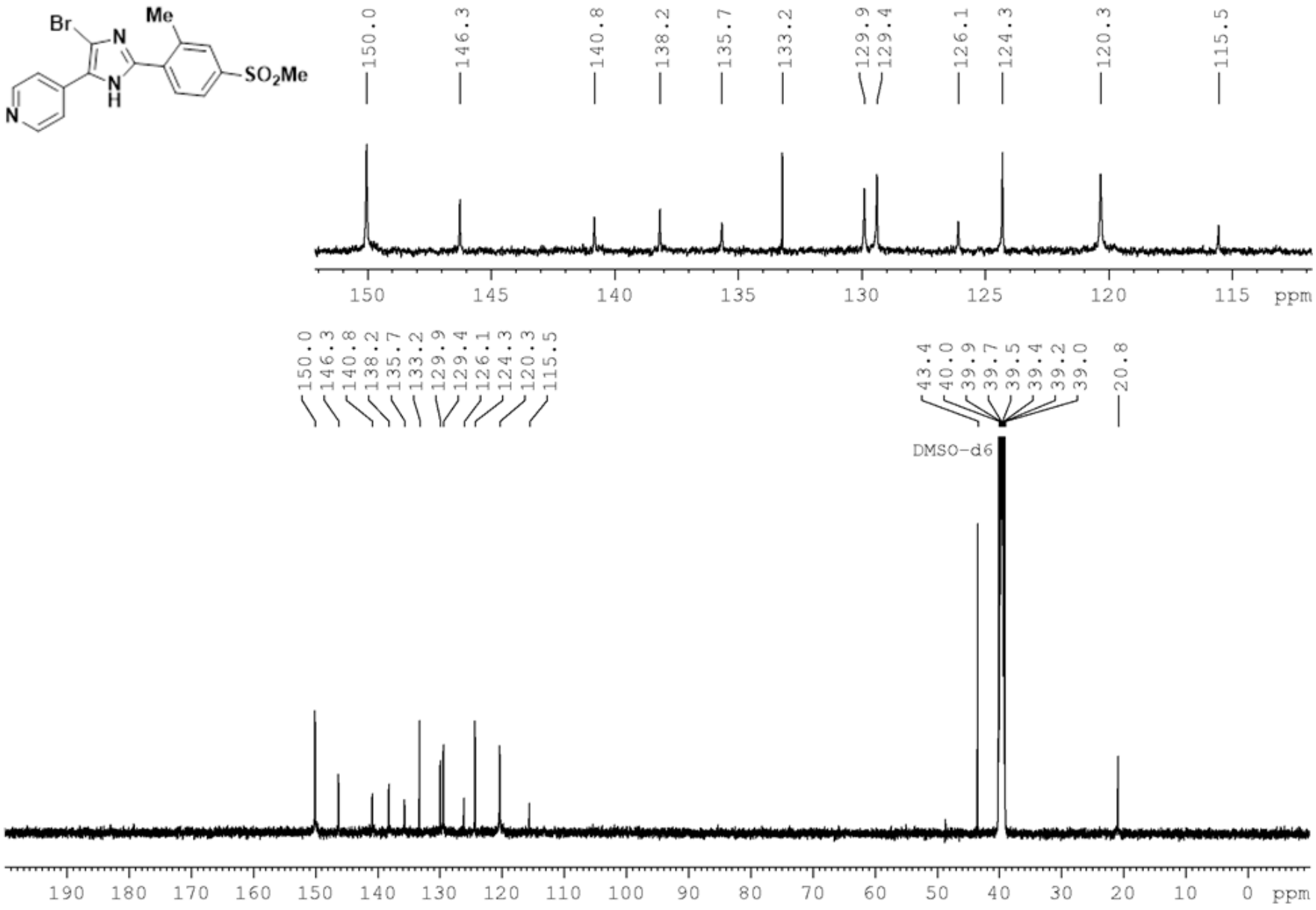


Figure S67. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **44**

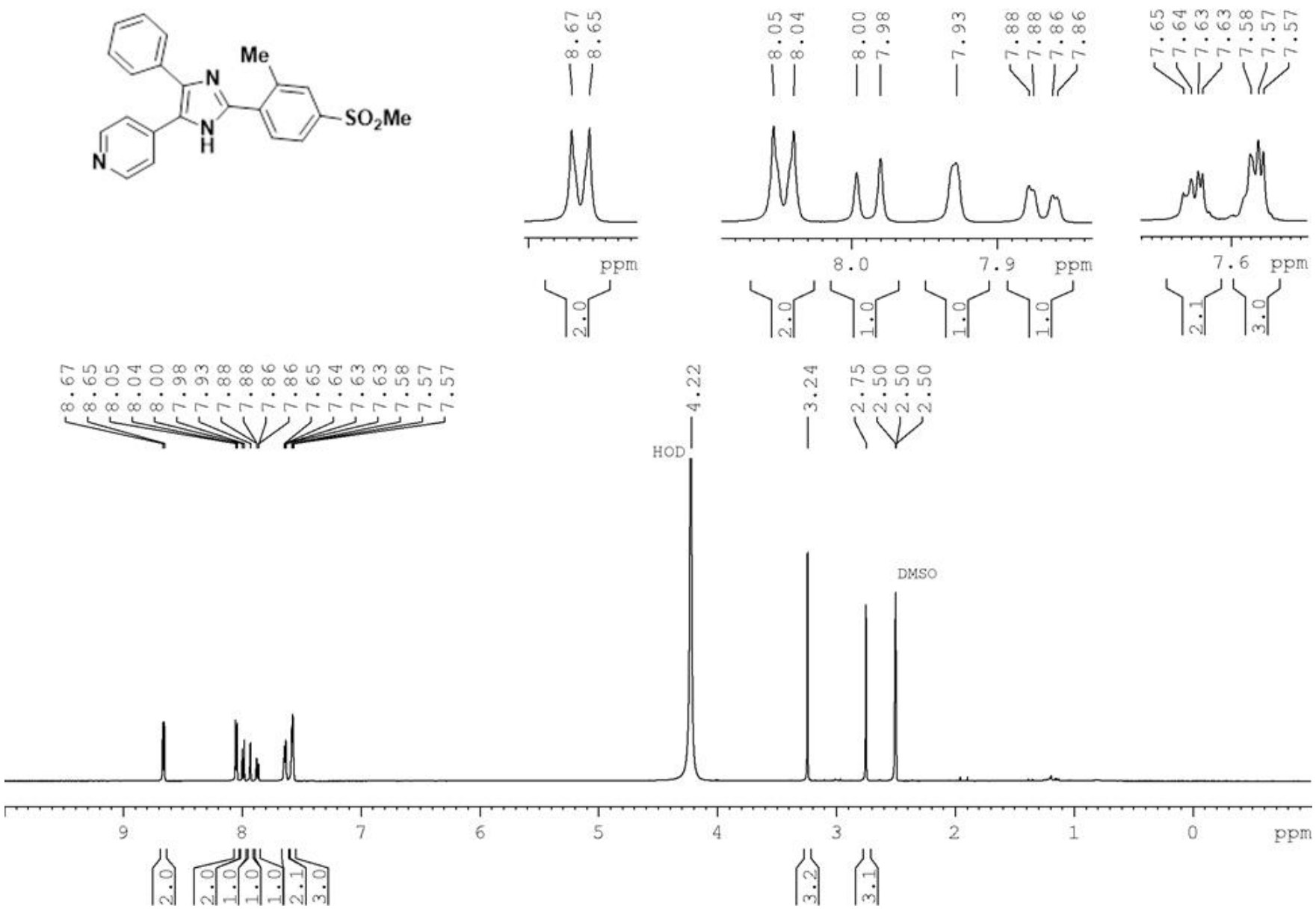


Figure S68. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **46**

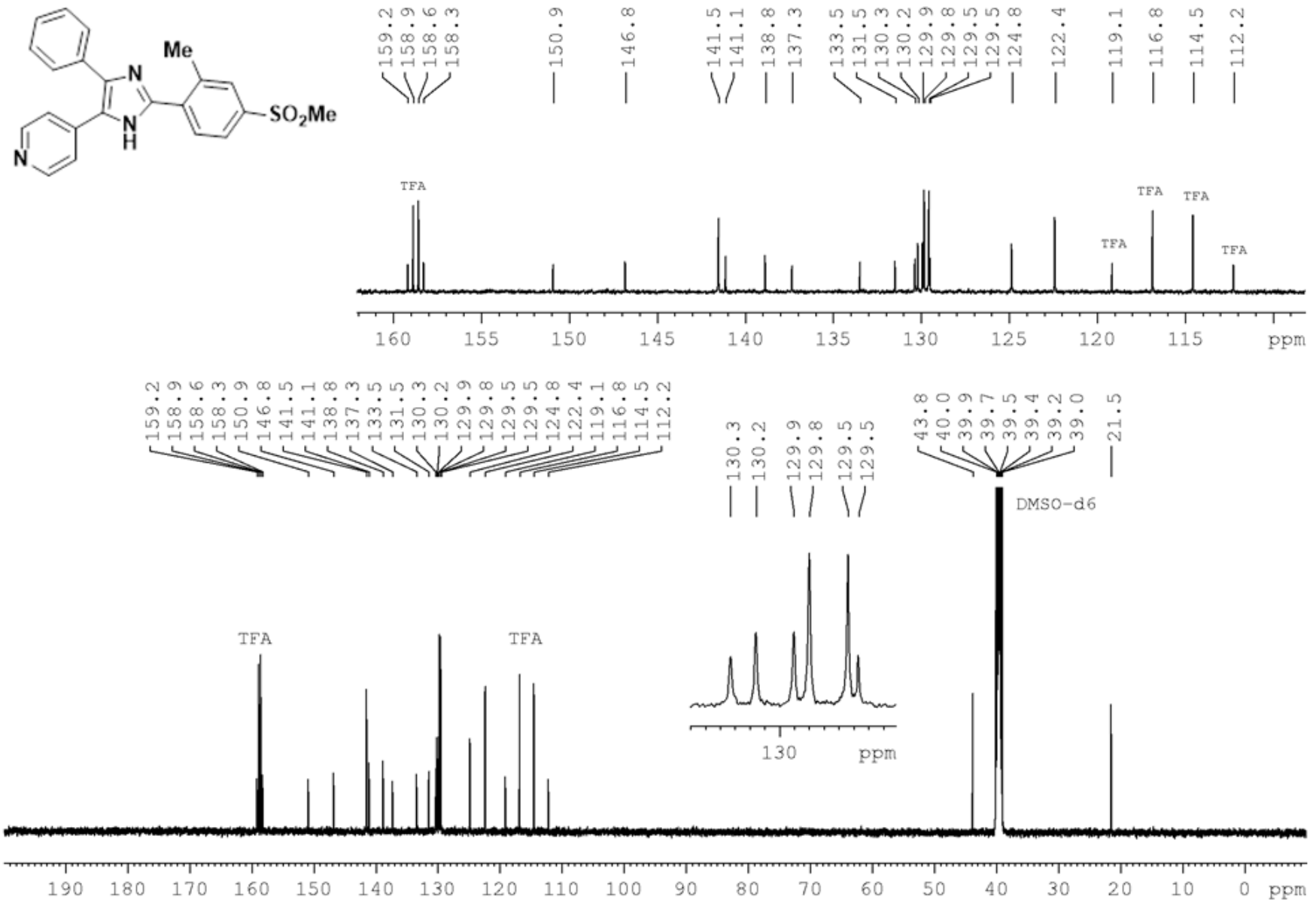


Figure S69. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **46**

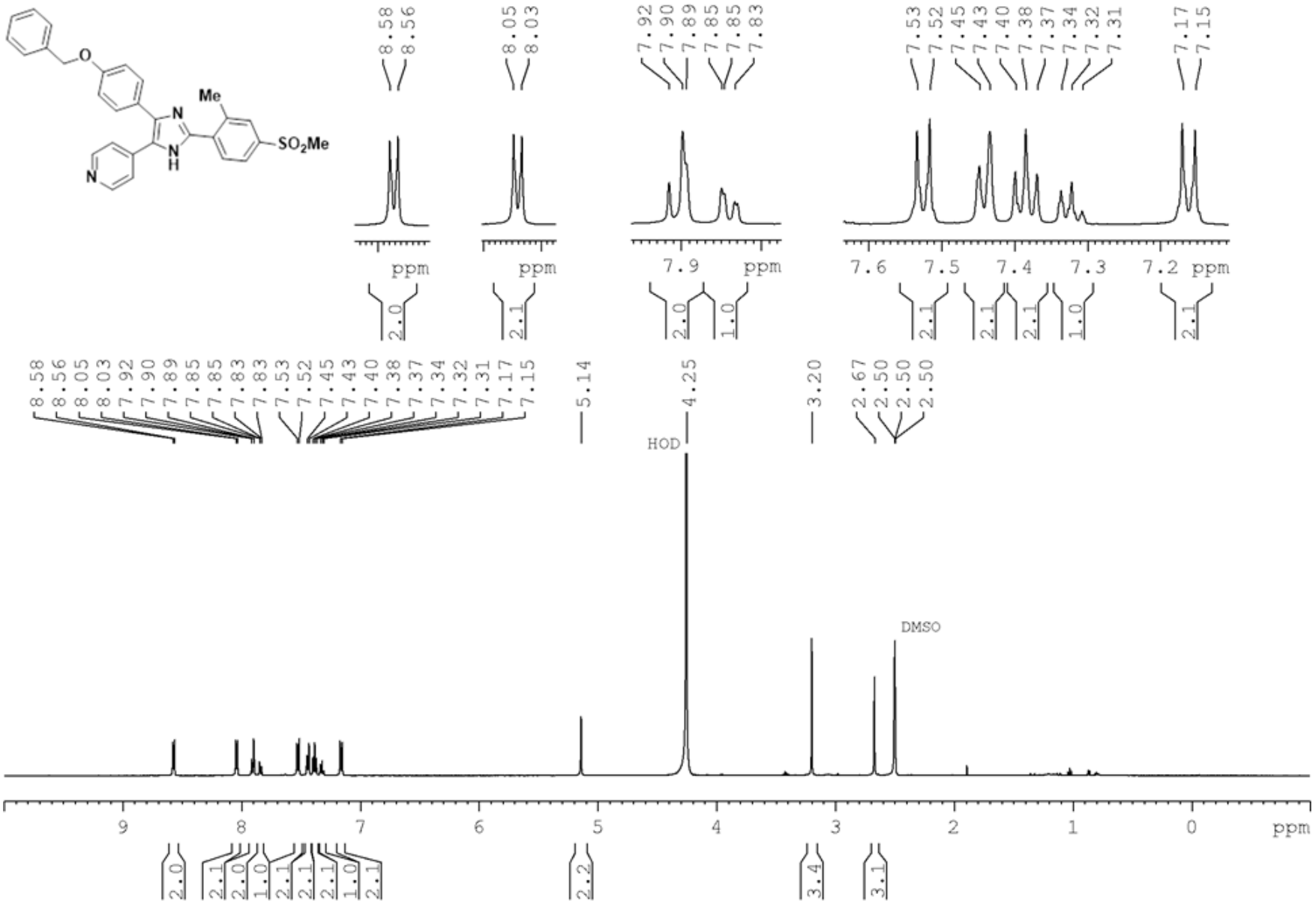


Figure S70. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **47**

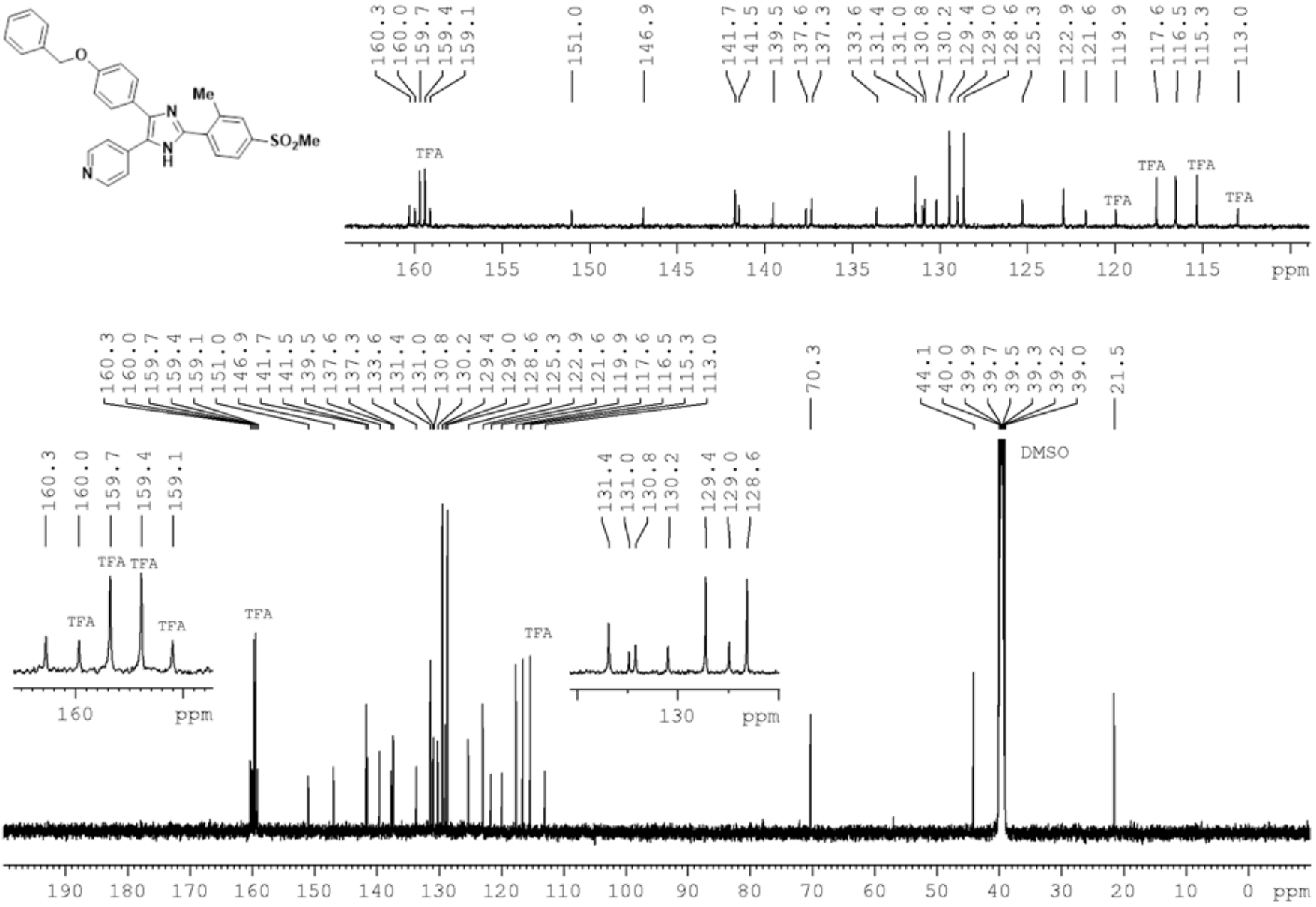


Figure S71. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **47**

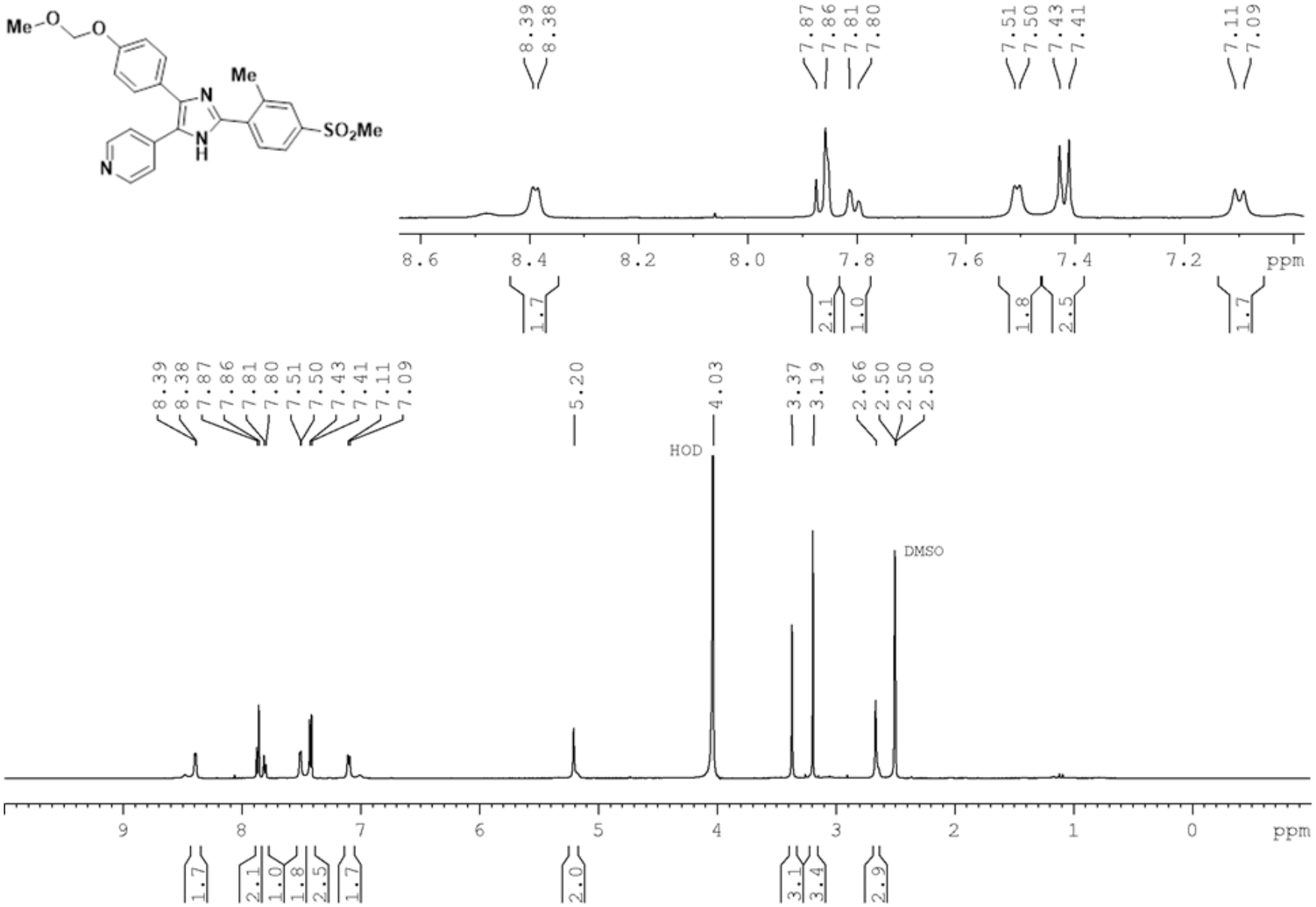


Figure S72. ^{1}H NMR Spectra (DMSO-d_6/D_2O, 500 MHz) of **48**

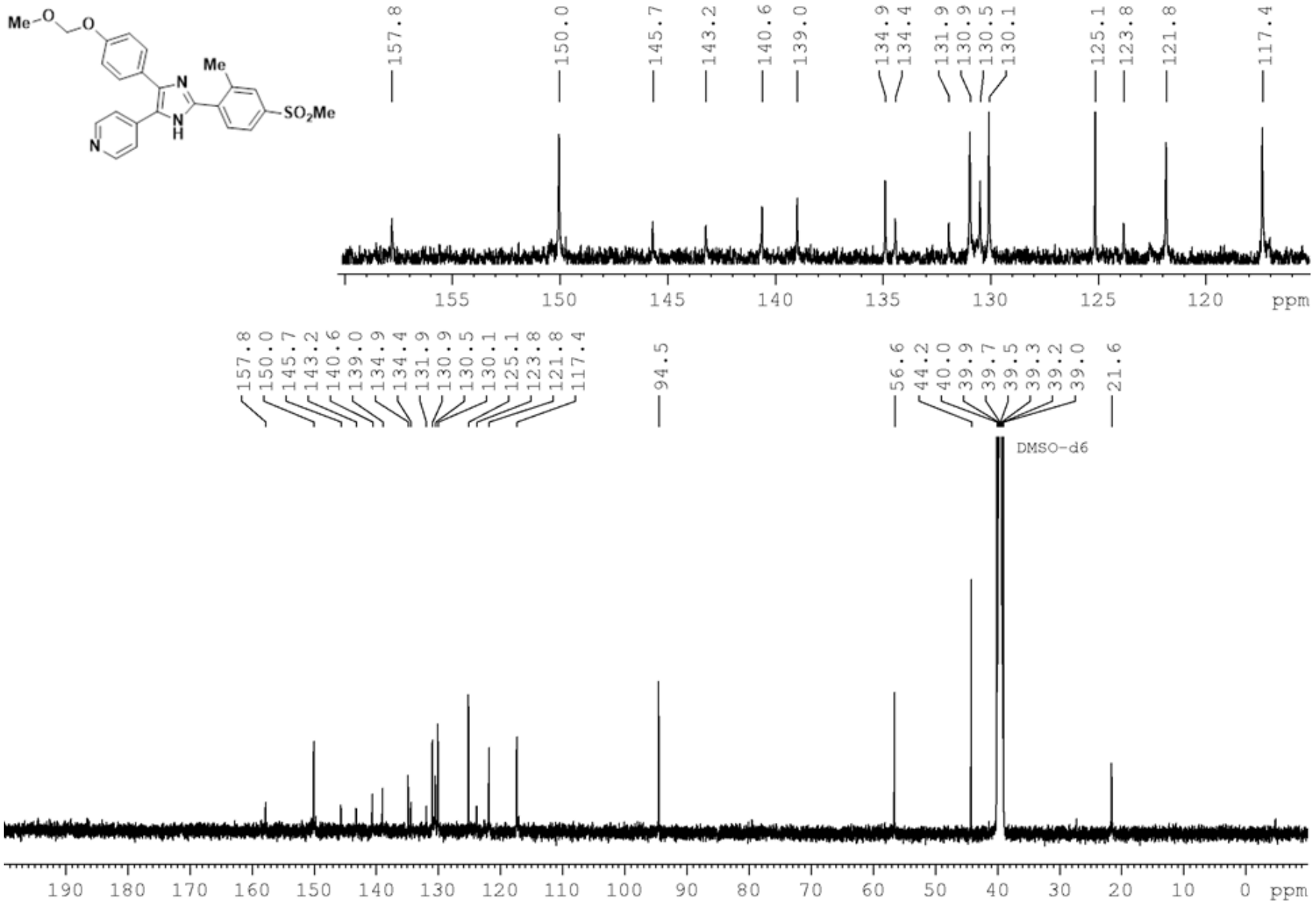


Figure S73. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O, 126 MHz) of **48**

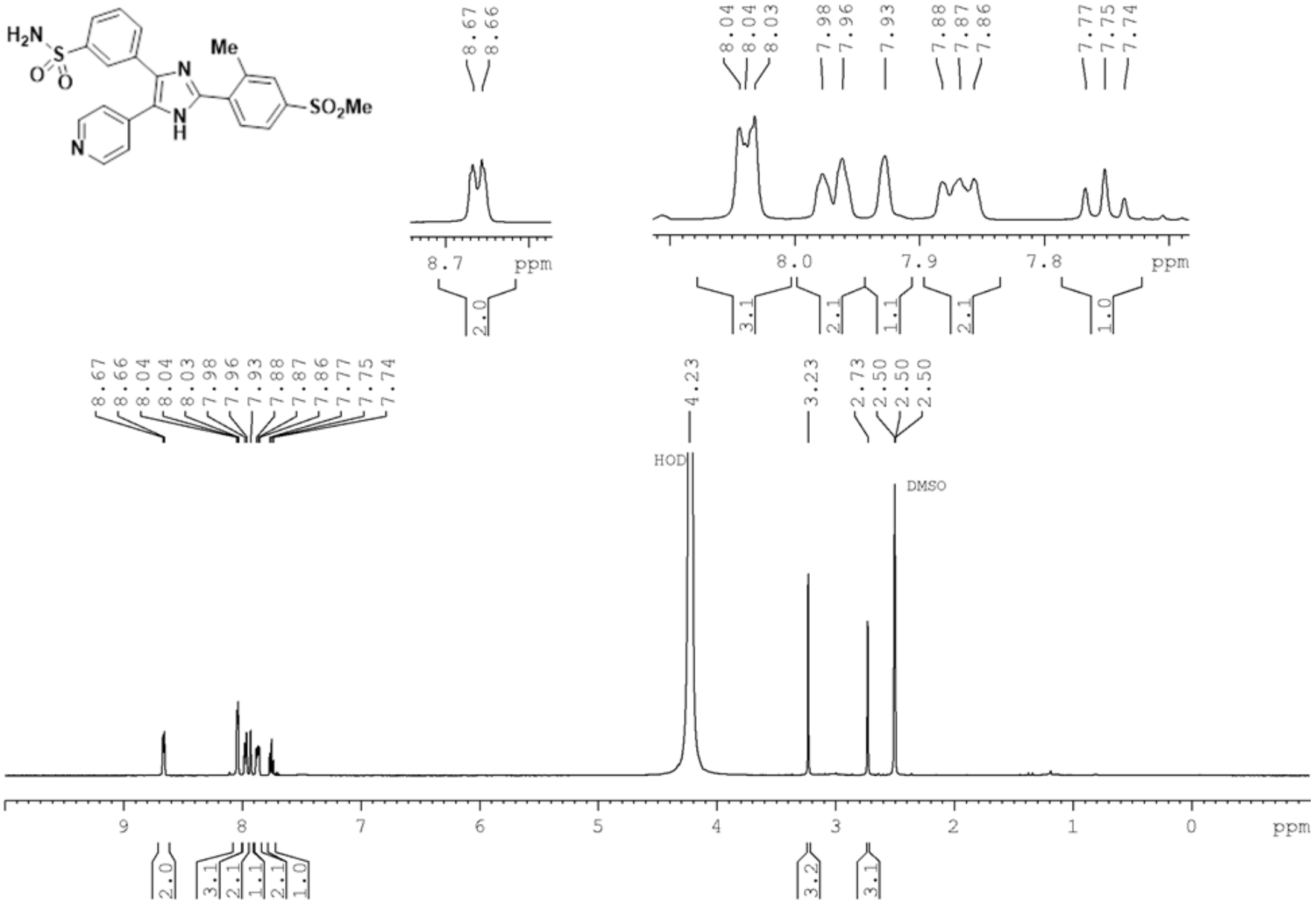


Figure S74. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **49**

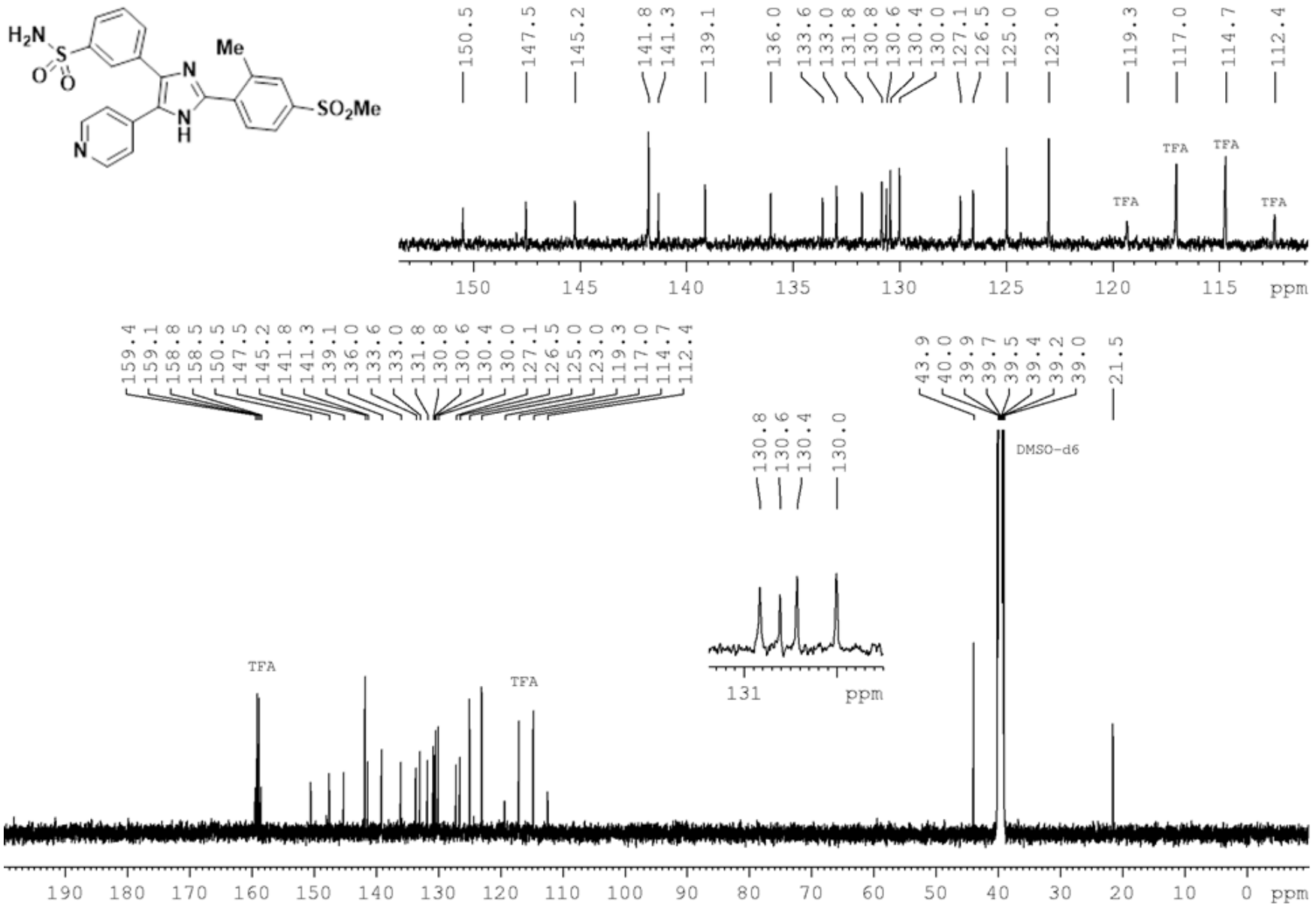


Figure S75. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **49**

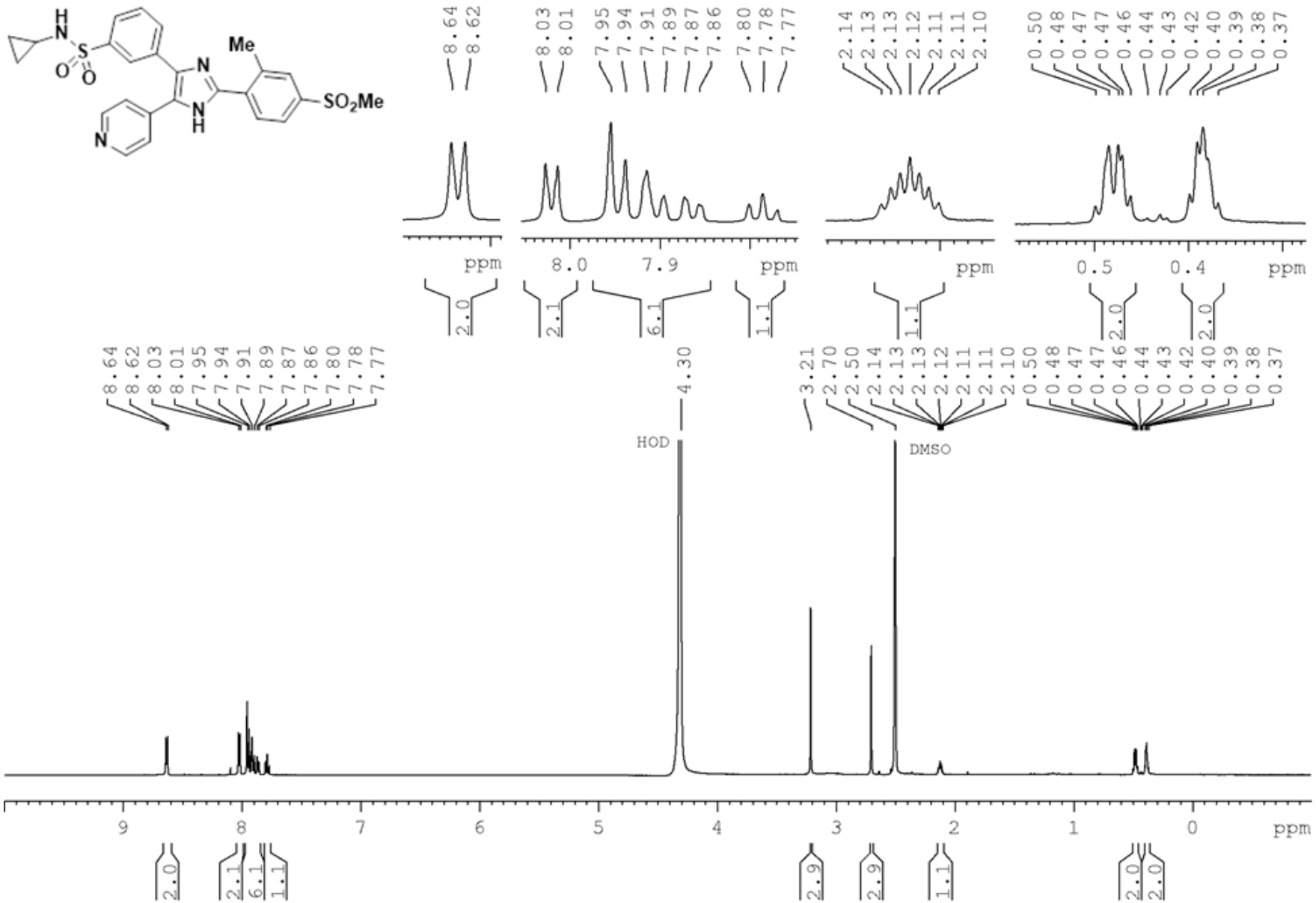


Figure S76. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **50**

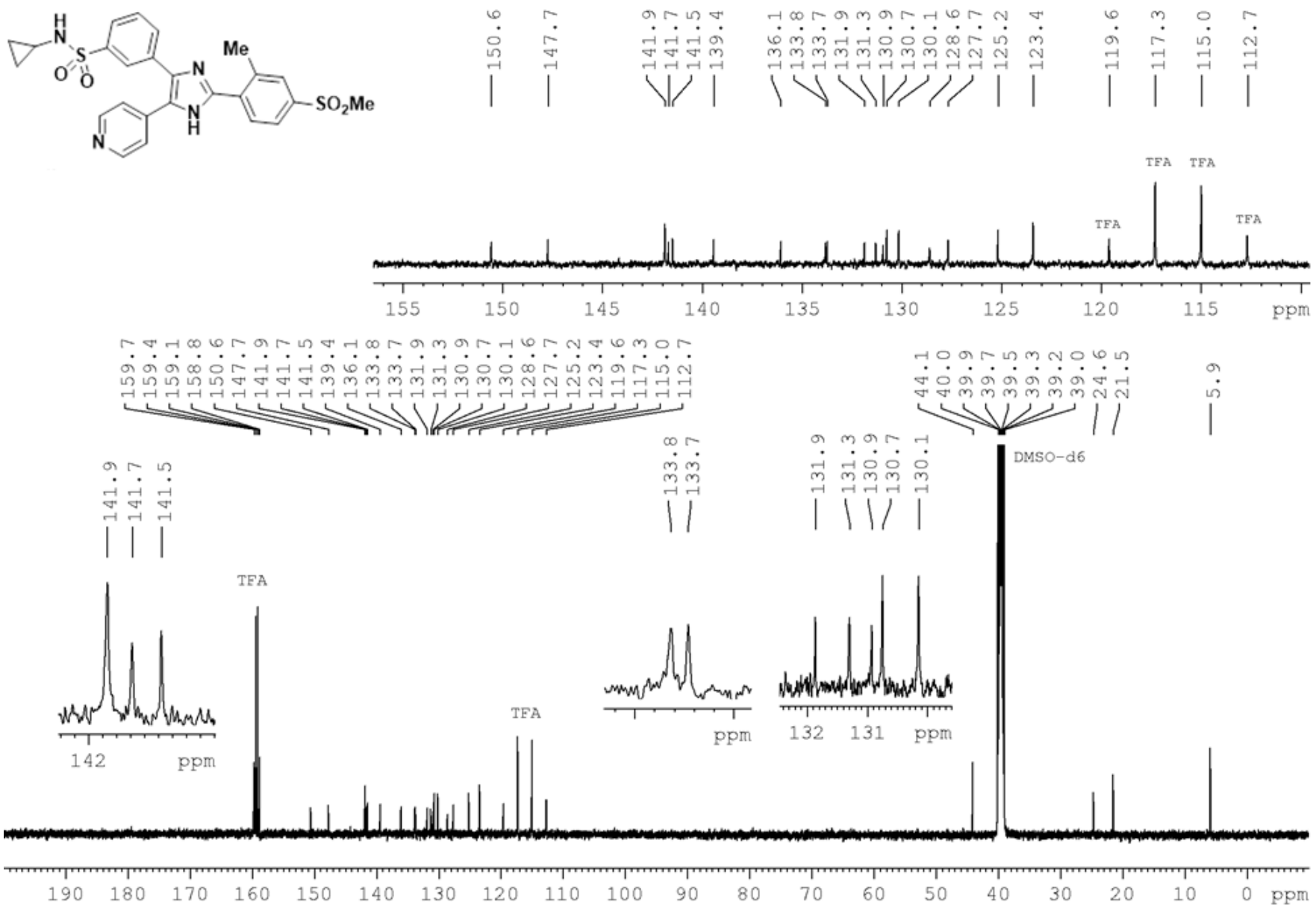


Figure S77. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **50**

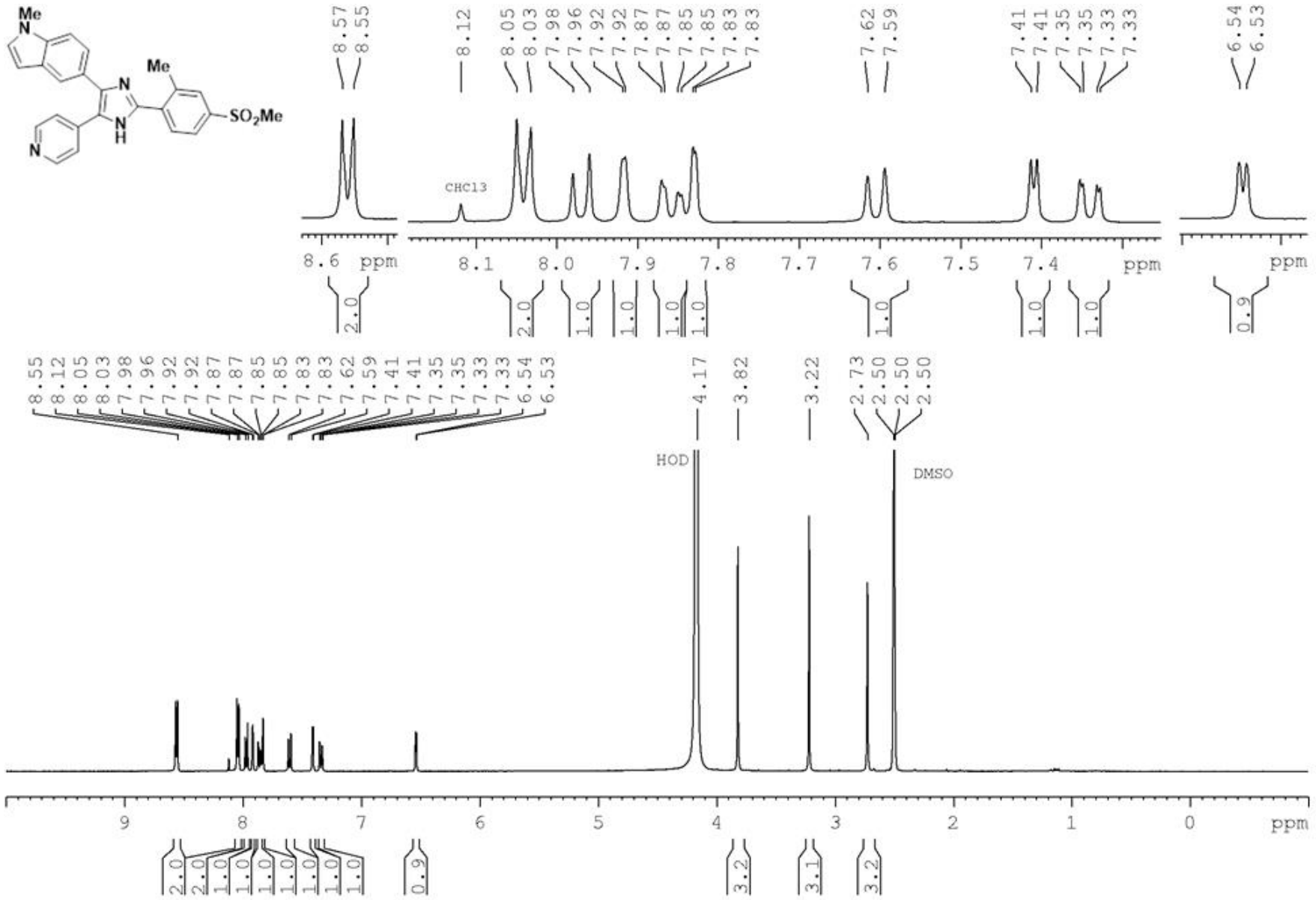


Figure S78. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 400 MHz) of **51**

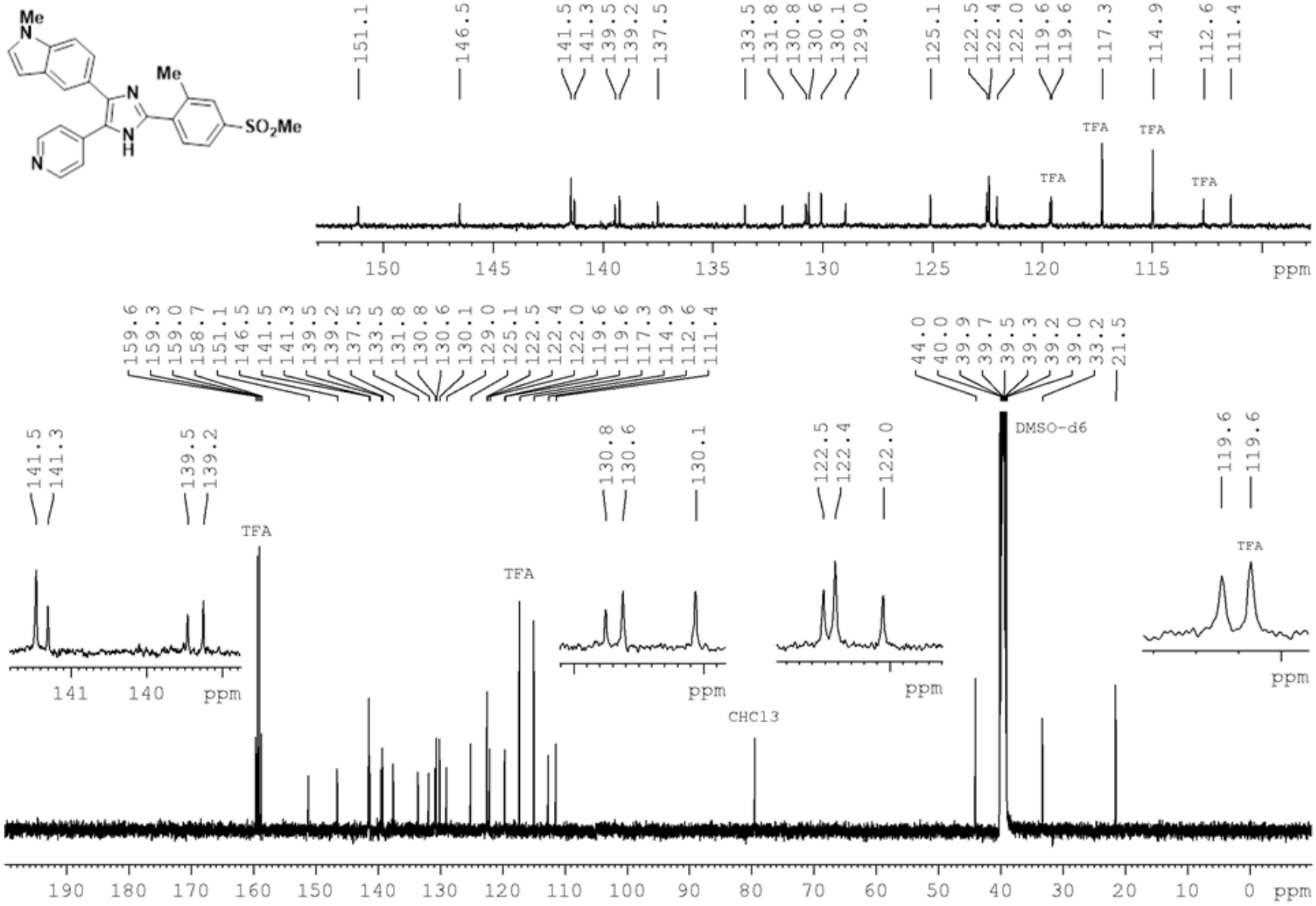


Figure S79. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **51**

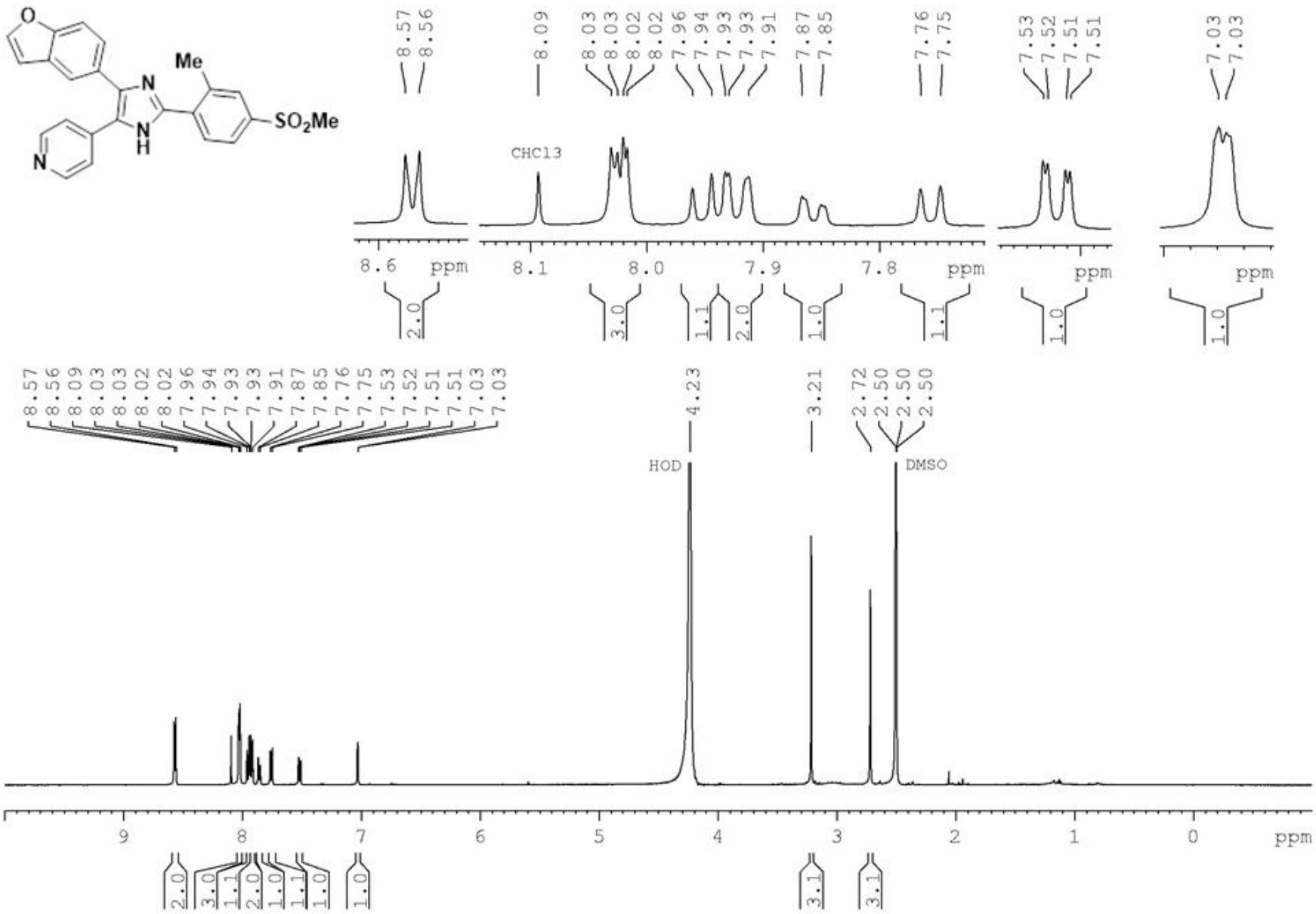


Figure S80. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **52**

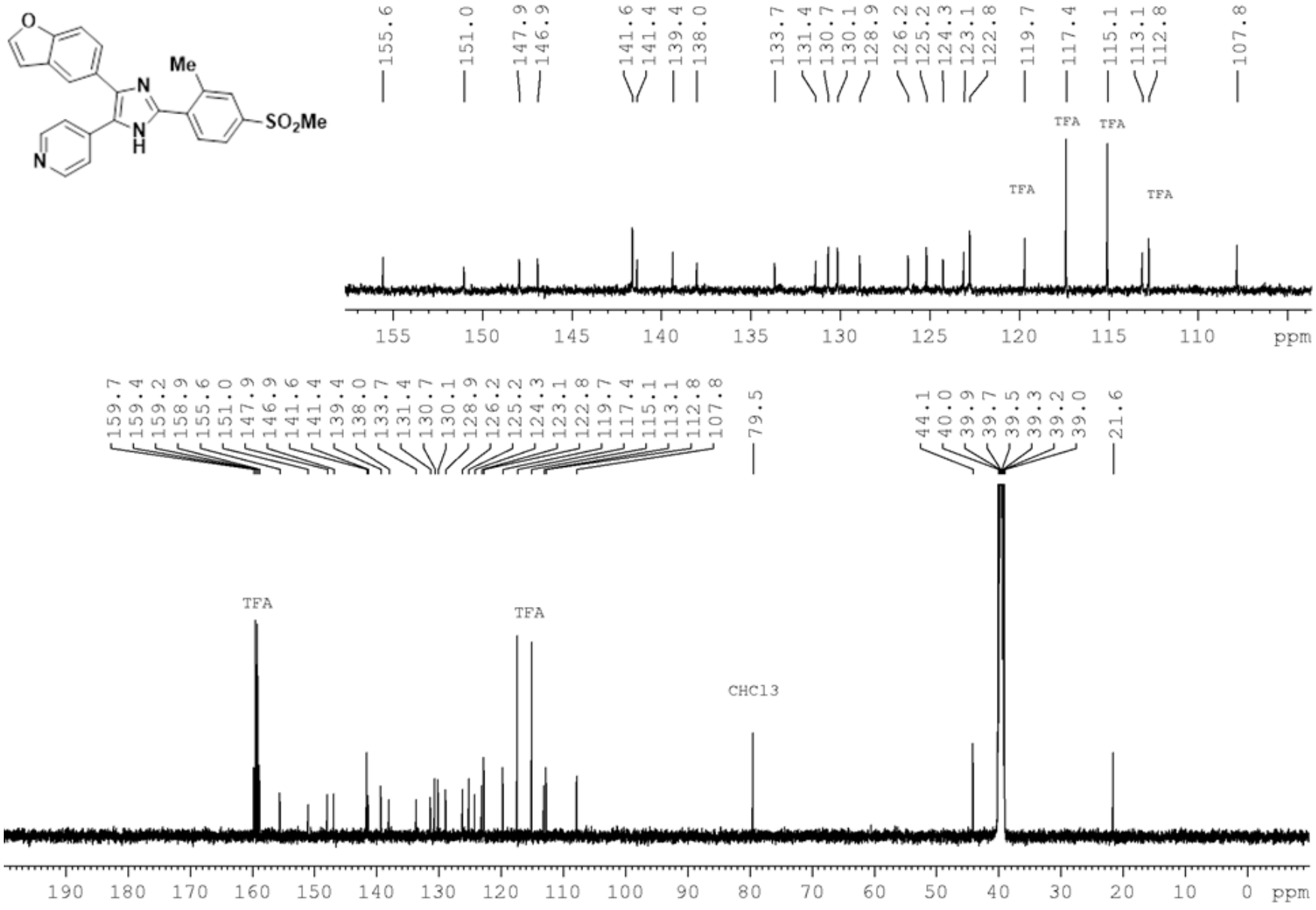


Figure S81. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **52**

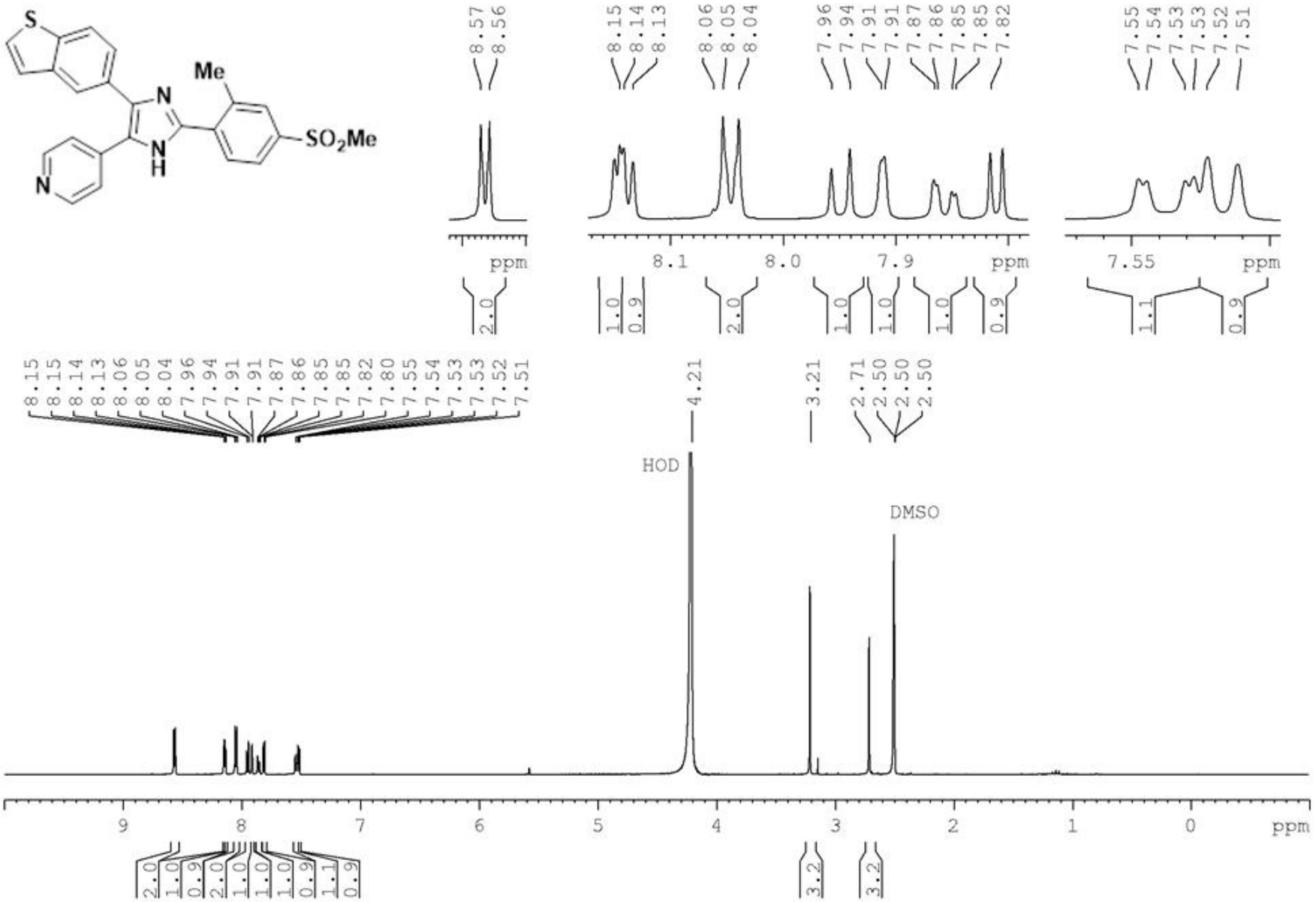


Figure S82. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **53**

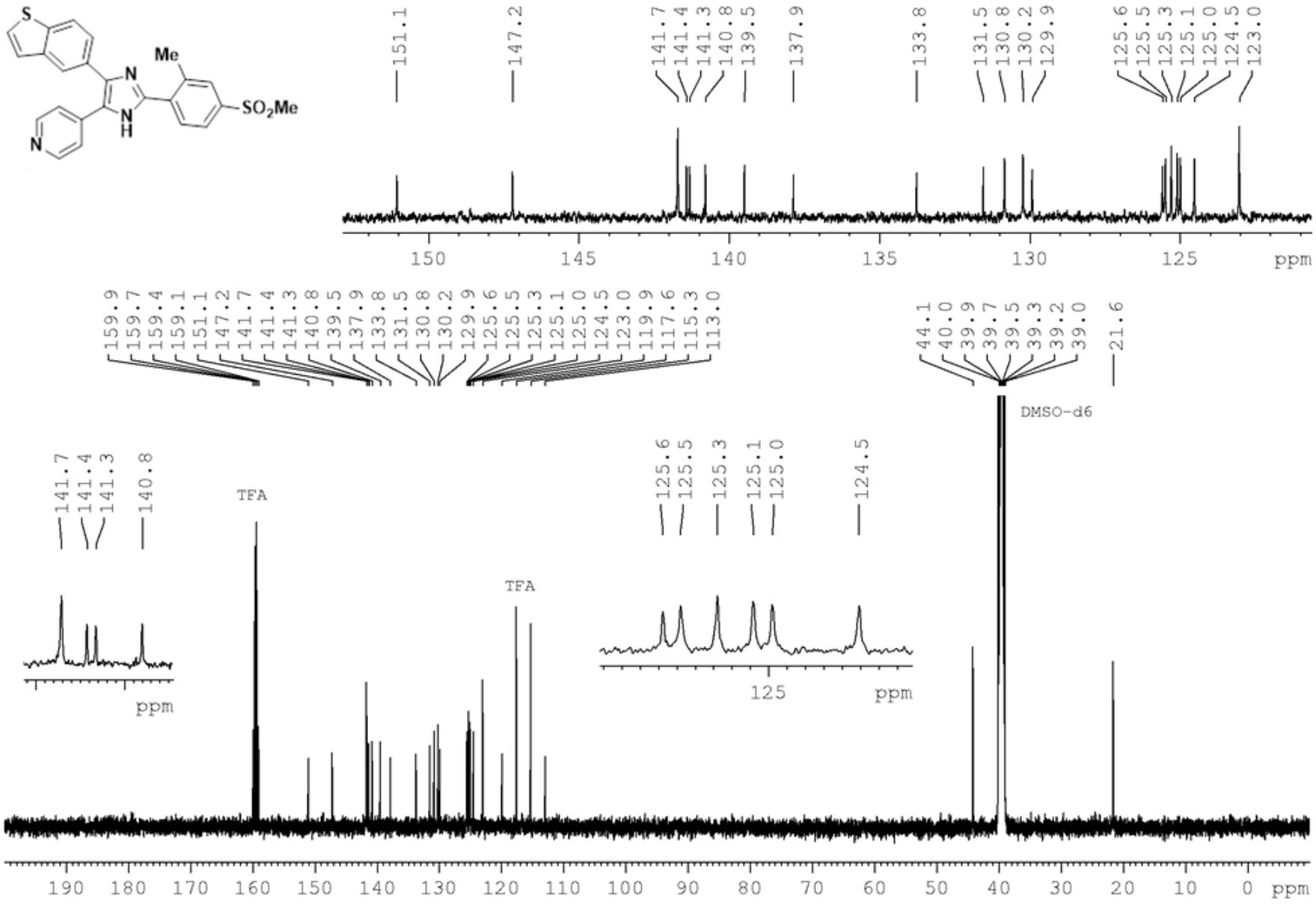


Figure S83. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **53**

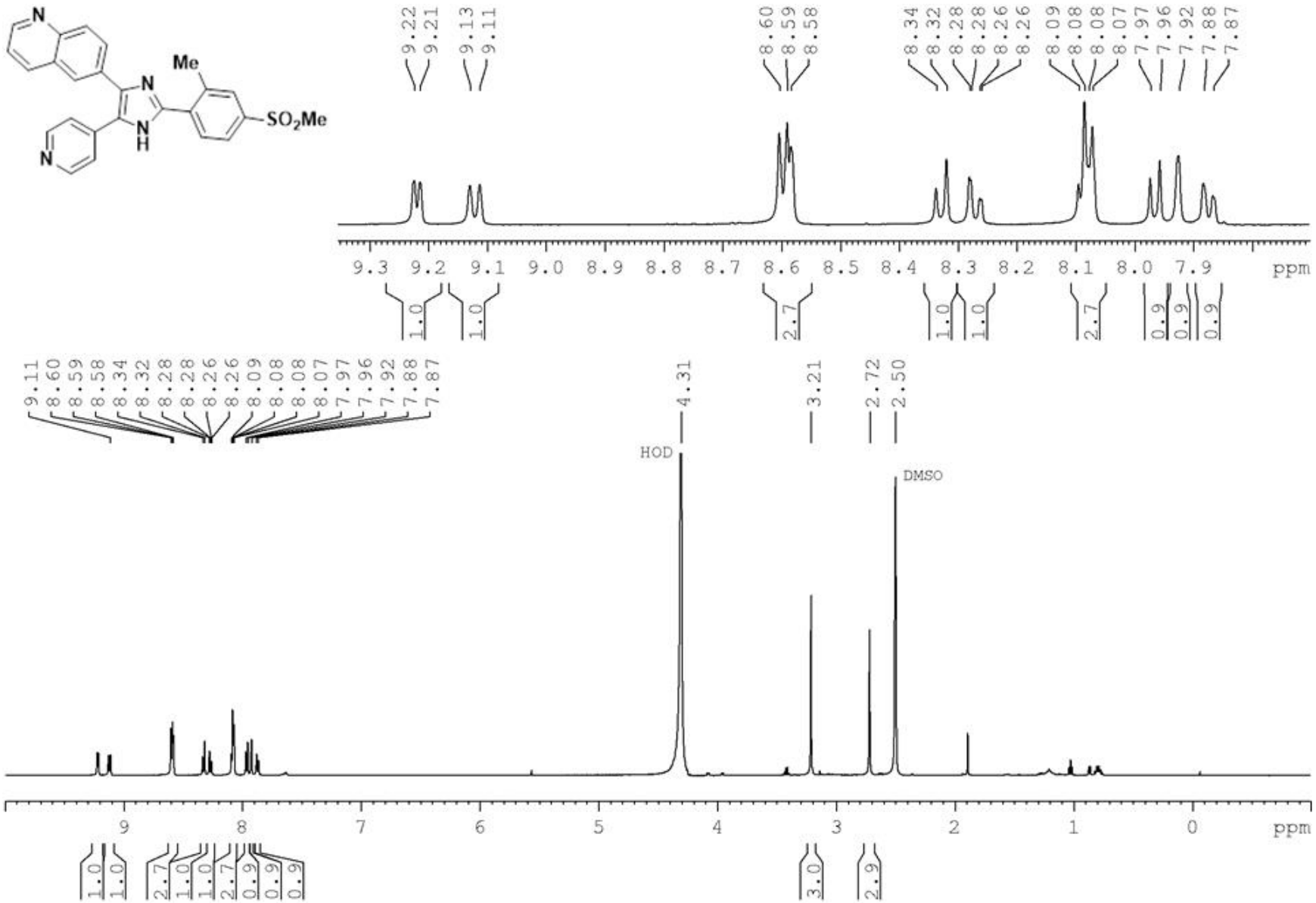


Figure S84. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **54**

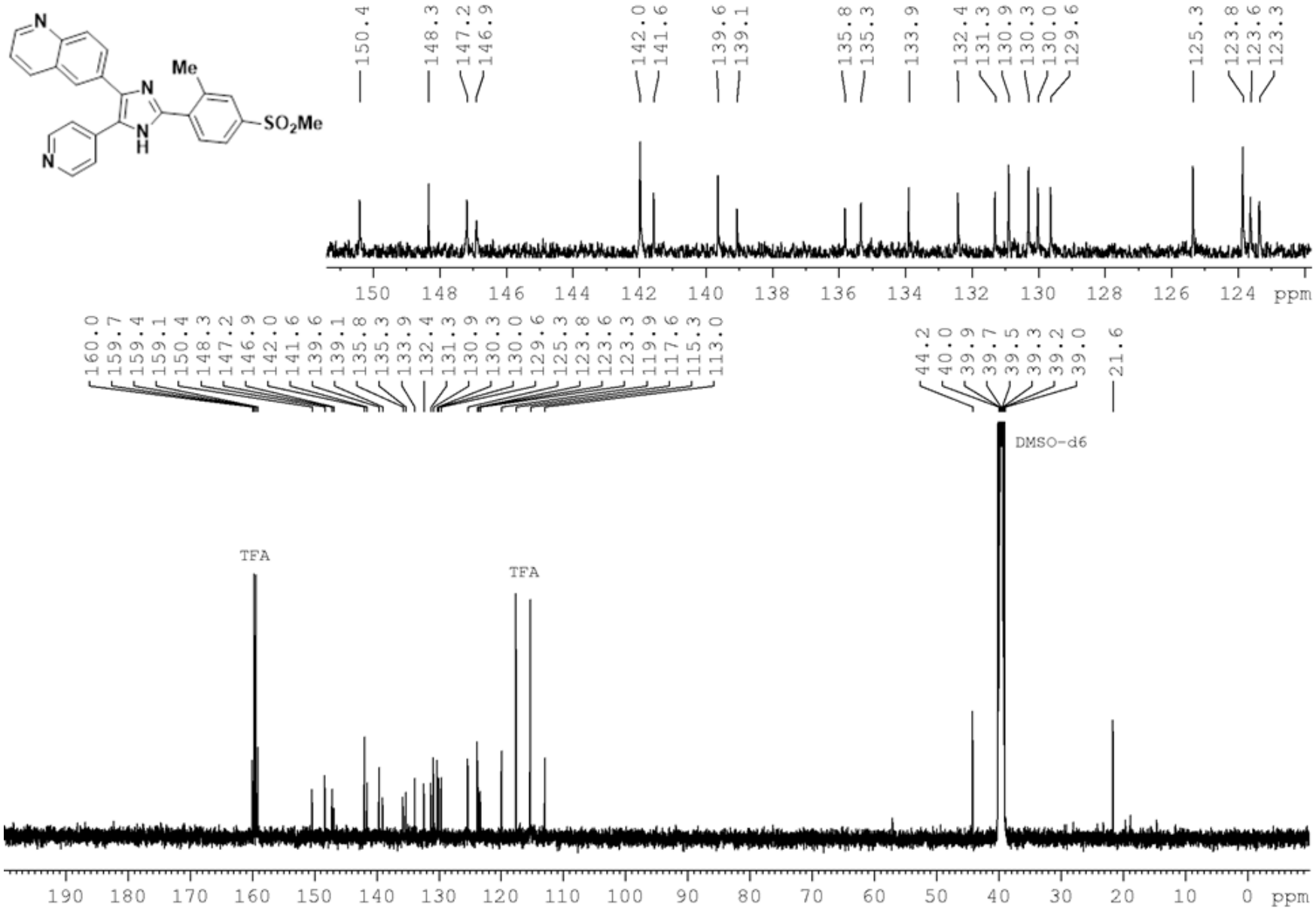


Figure S85. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **54**

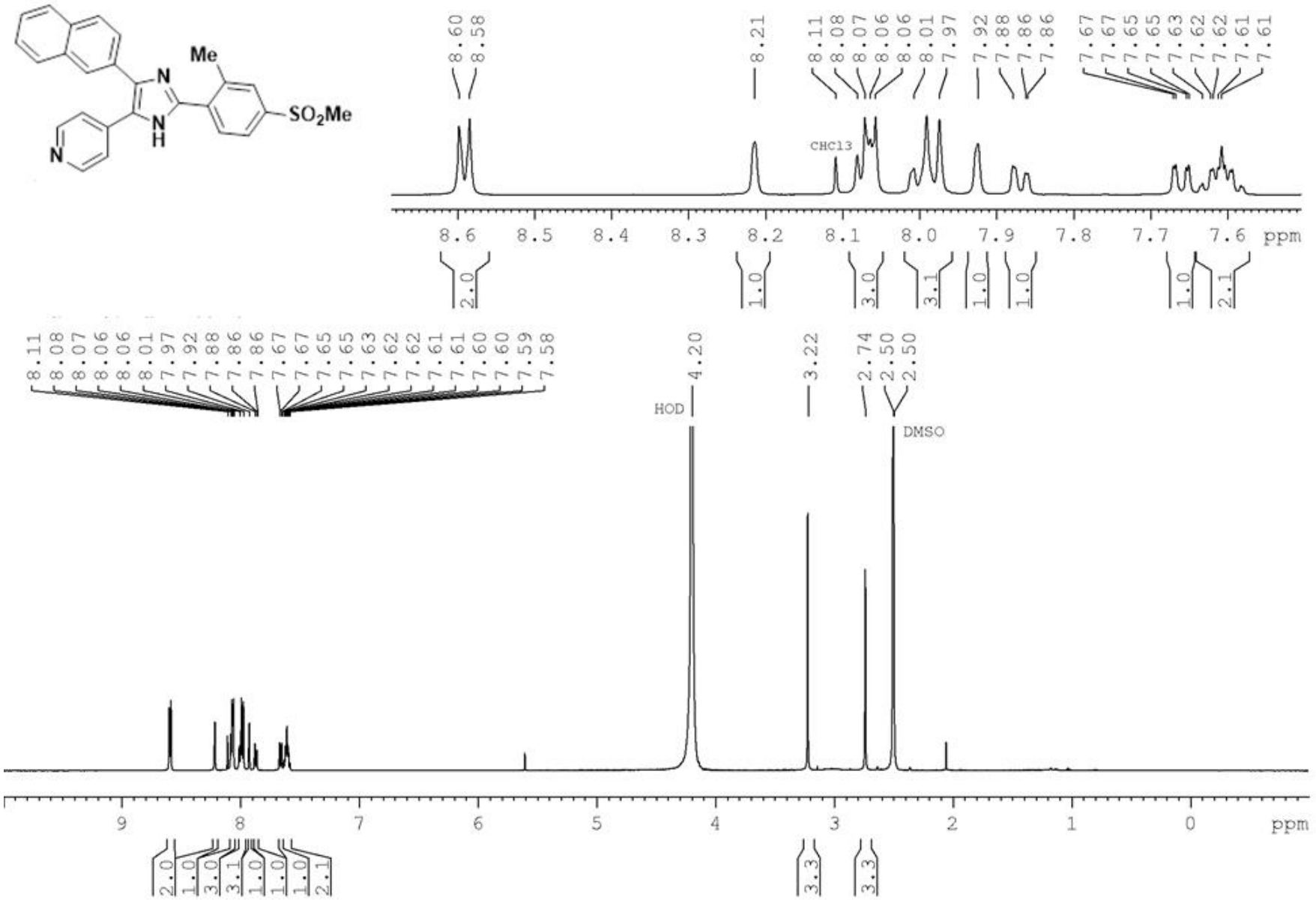


Figure S86. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **55**

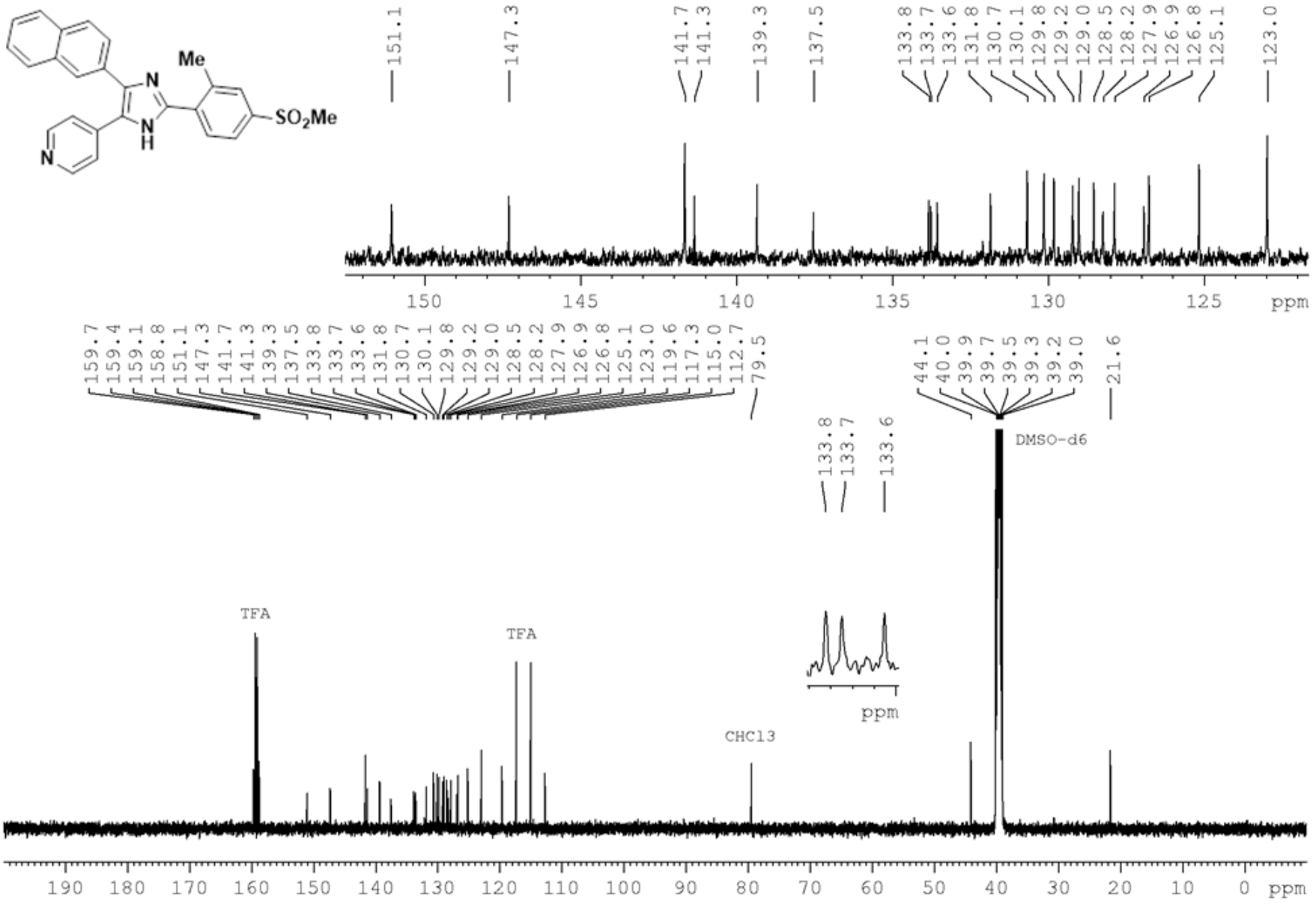


Figure S87. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **55**

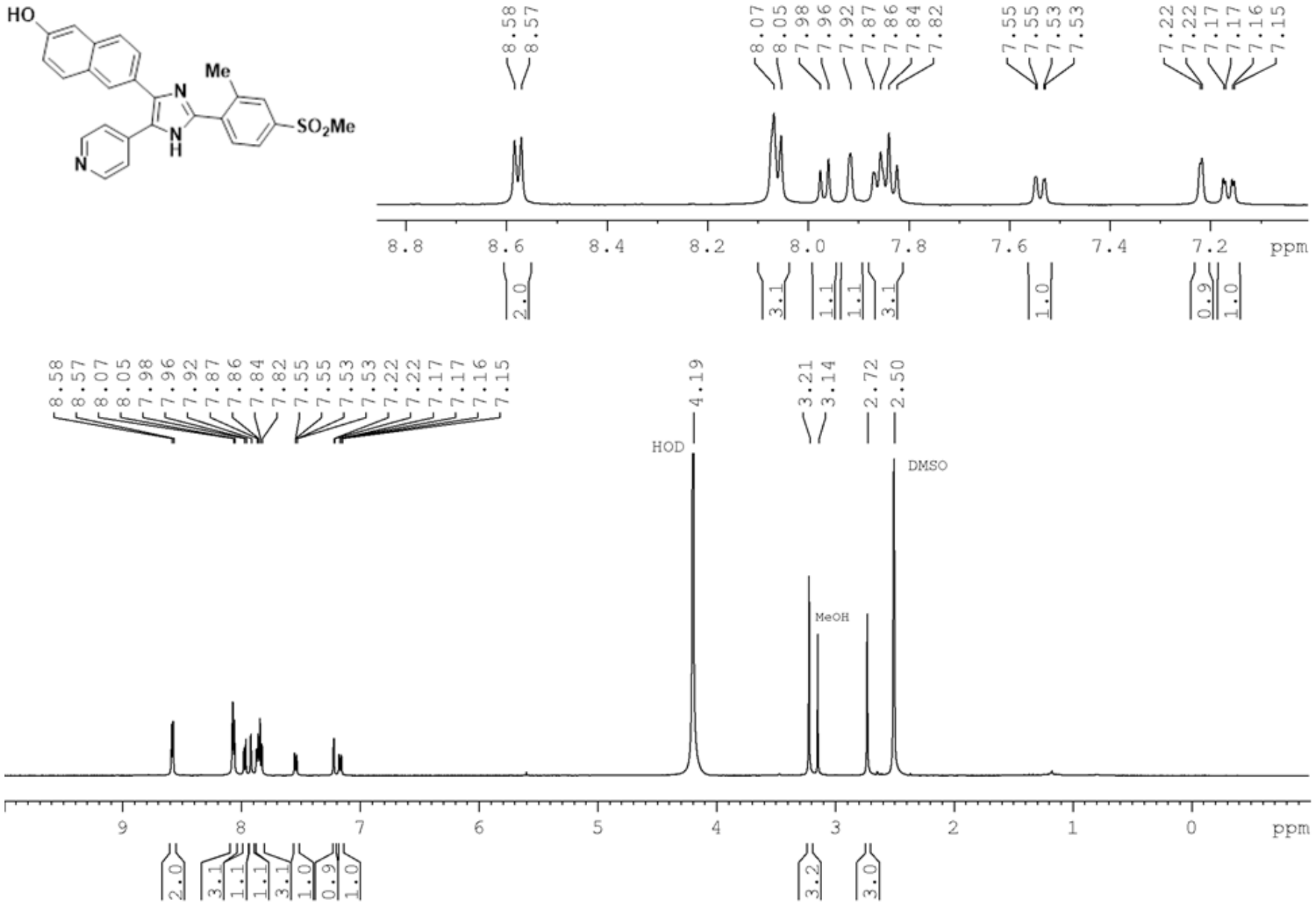


Figure S88. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **56**

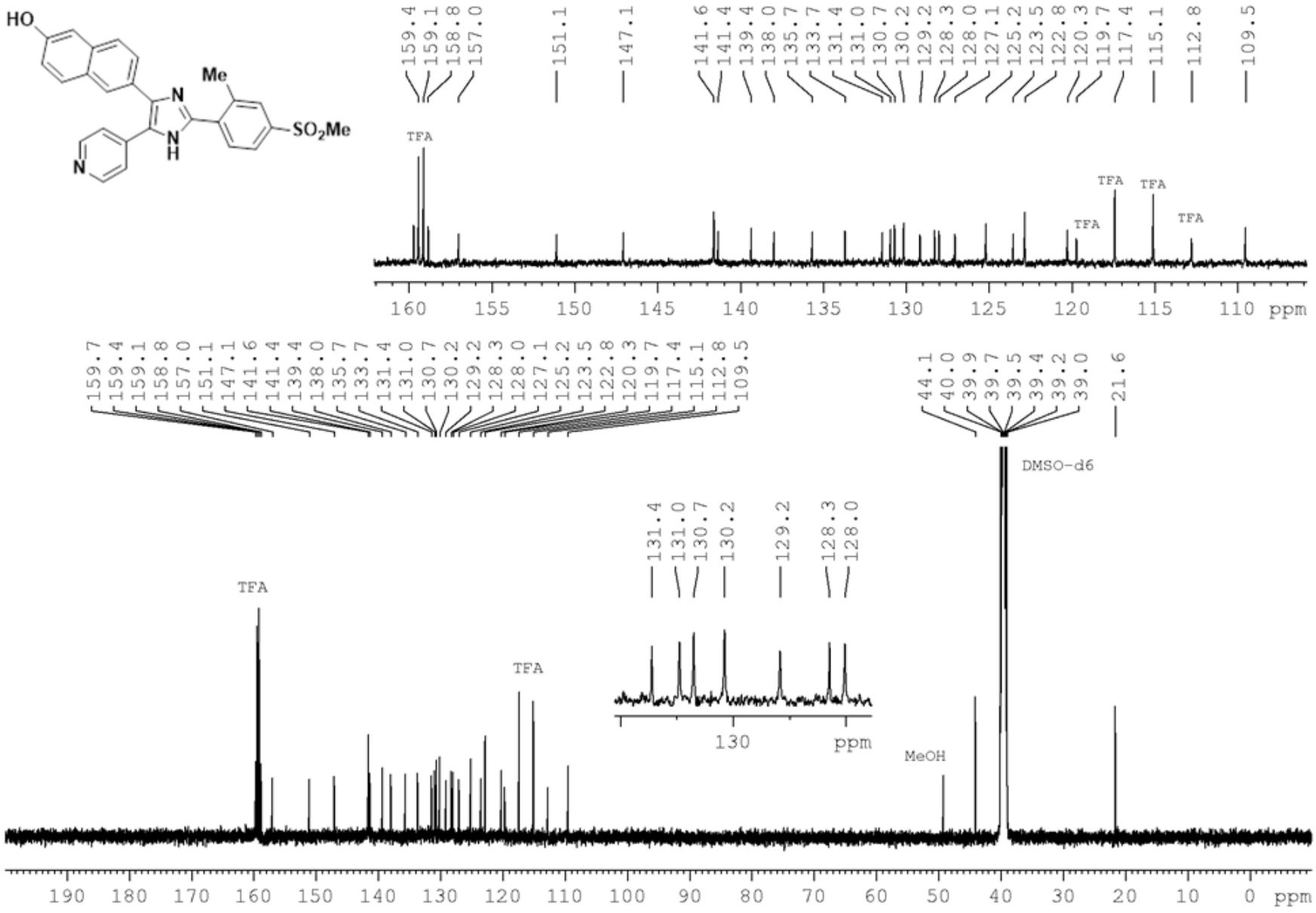


Figure S89. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **56**

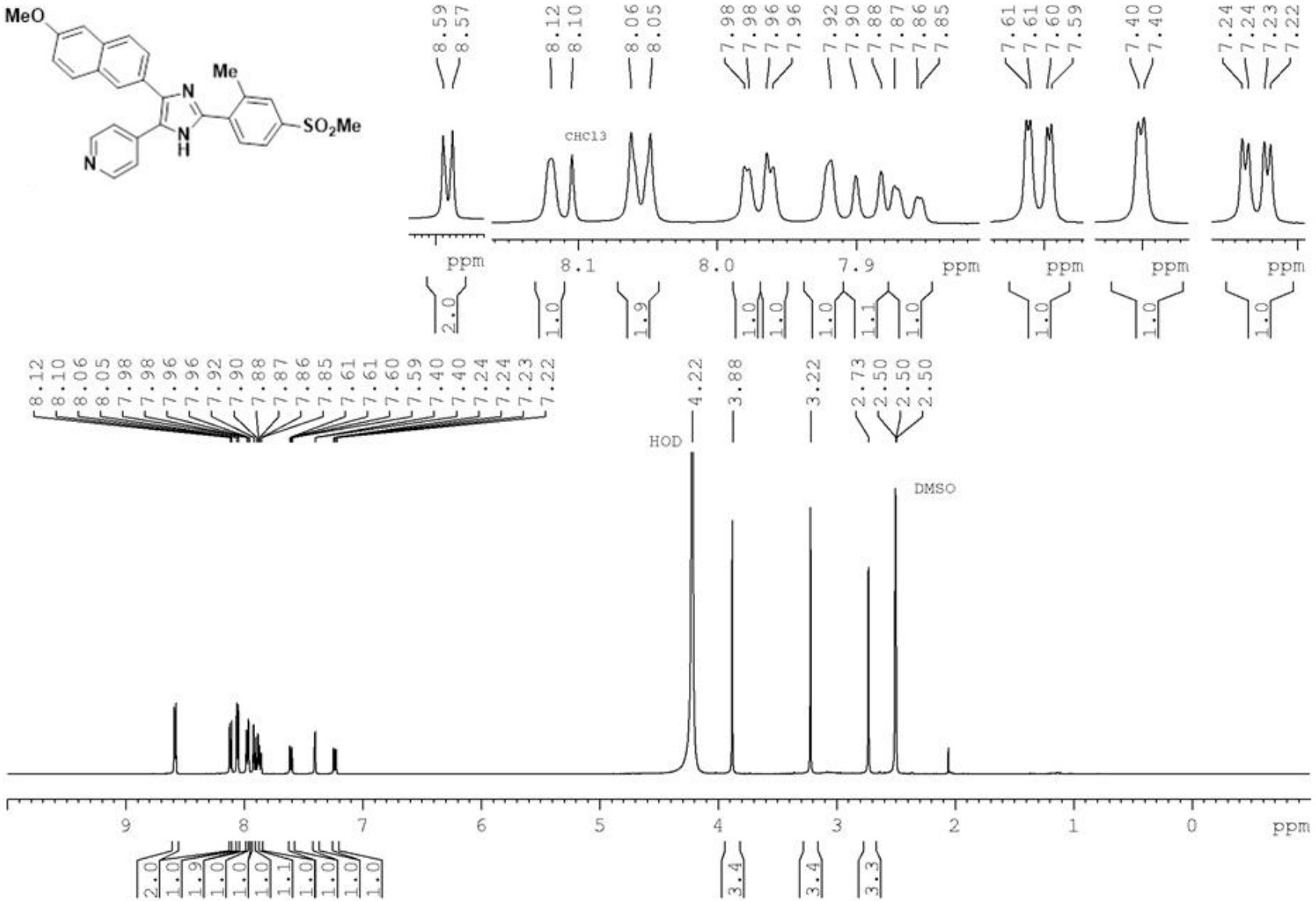


Figure S90. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **57**

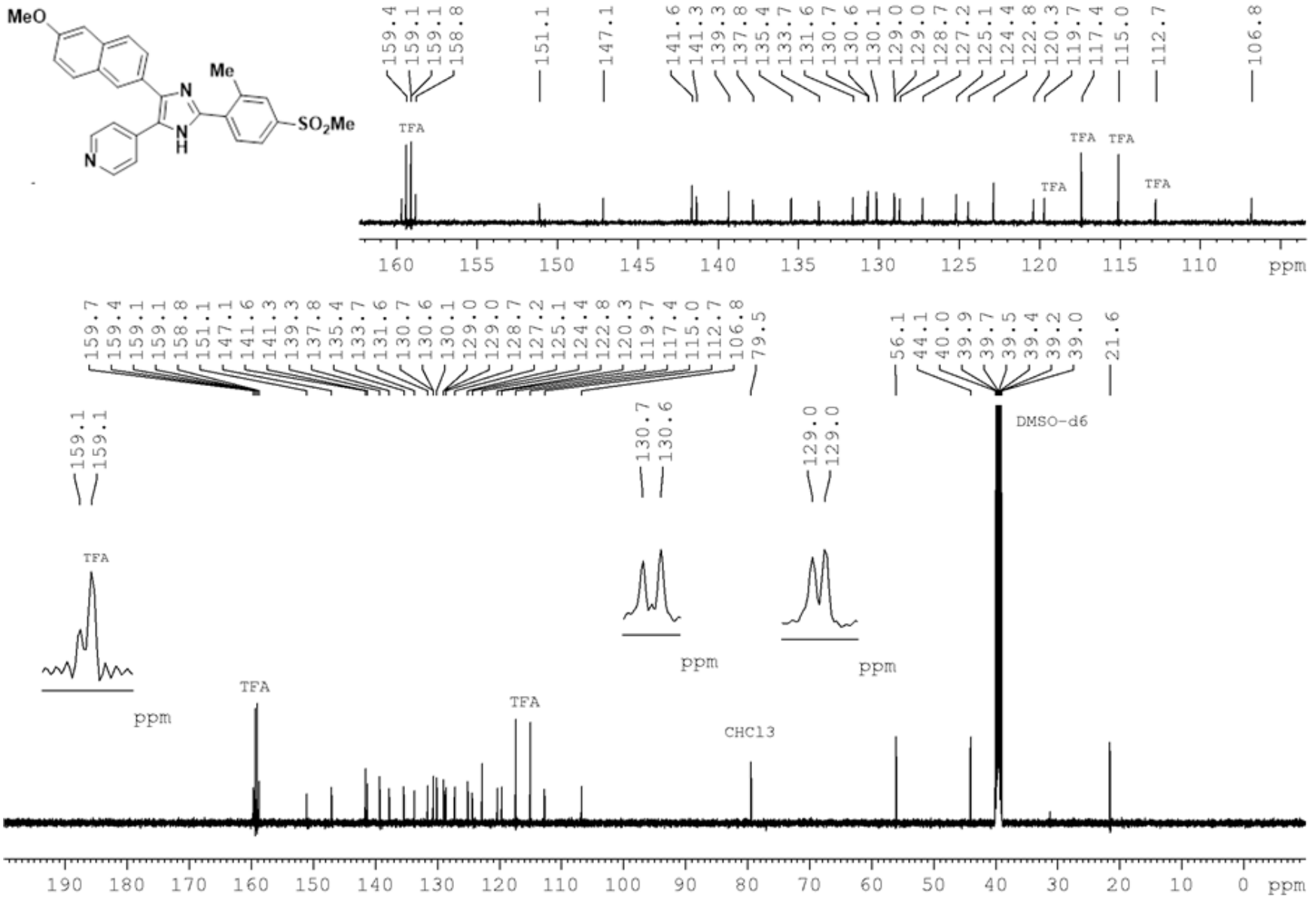


Figure S91. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **57**

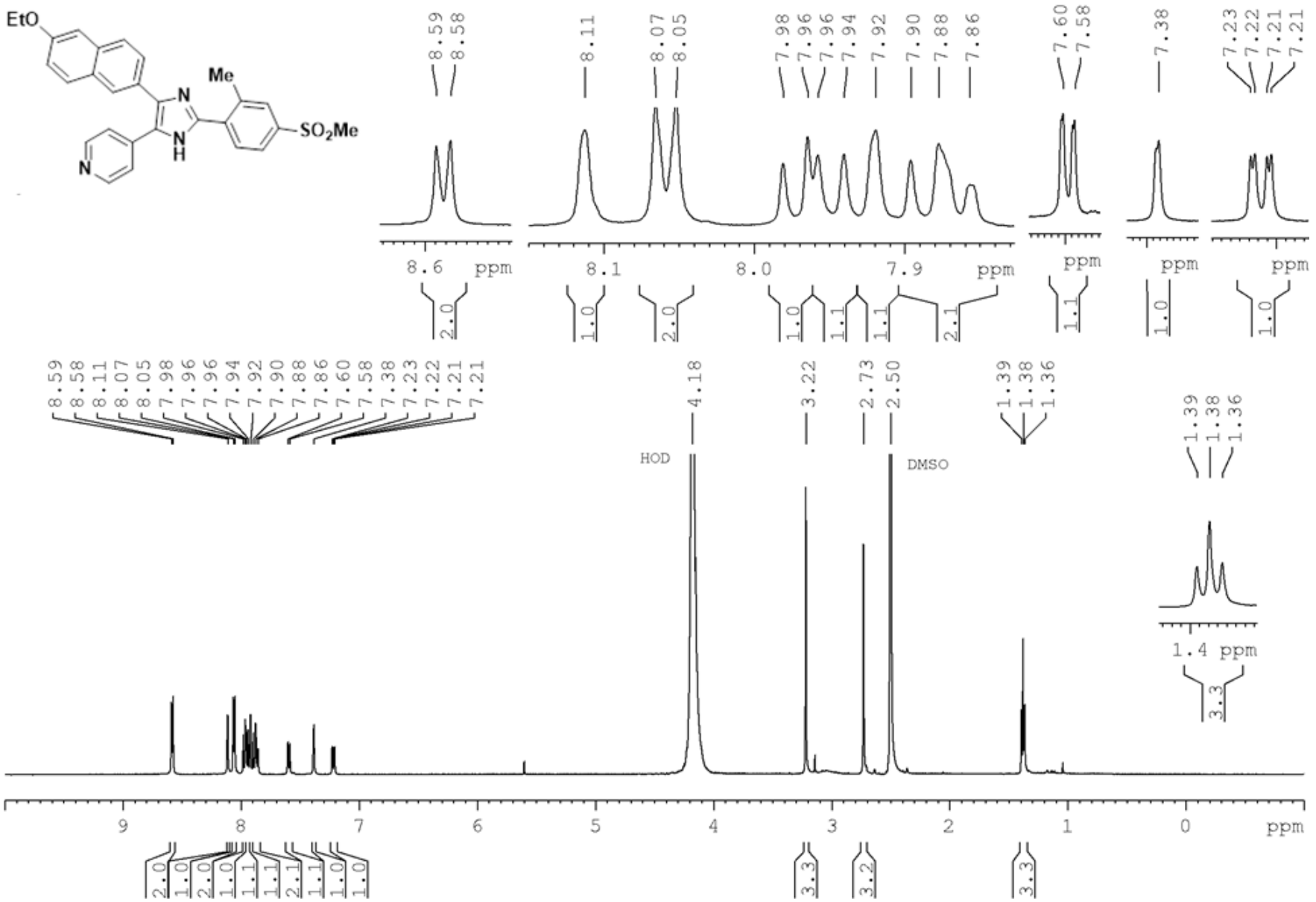


Figure S92. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **58**

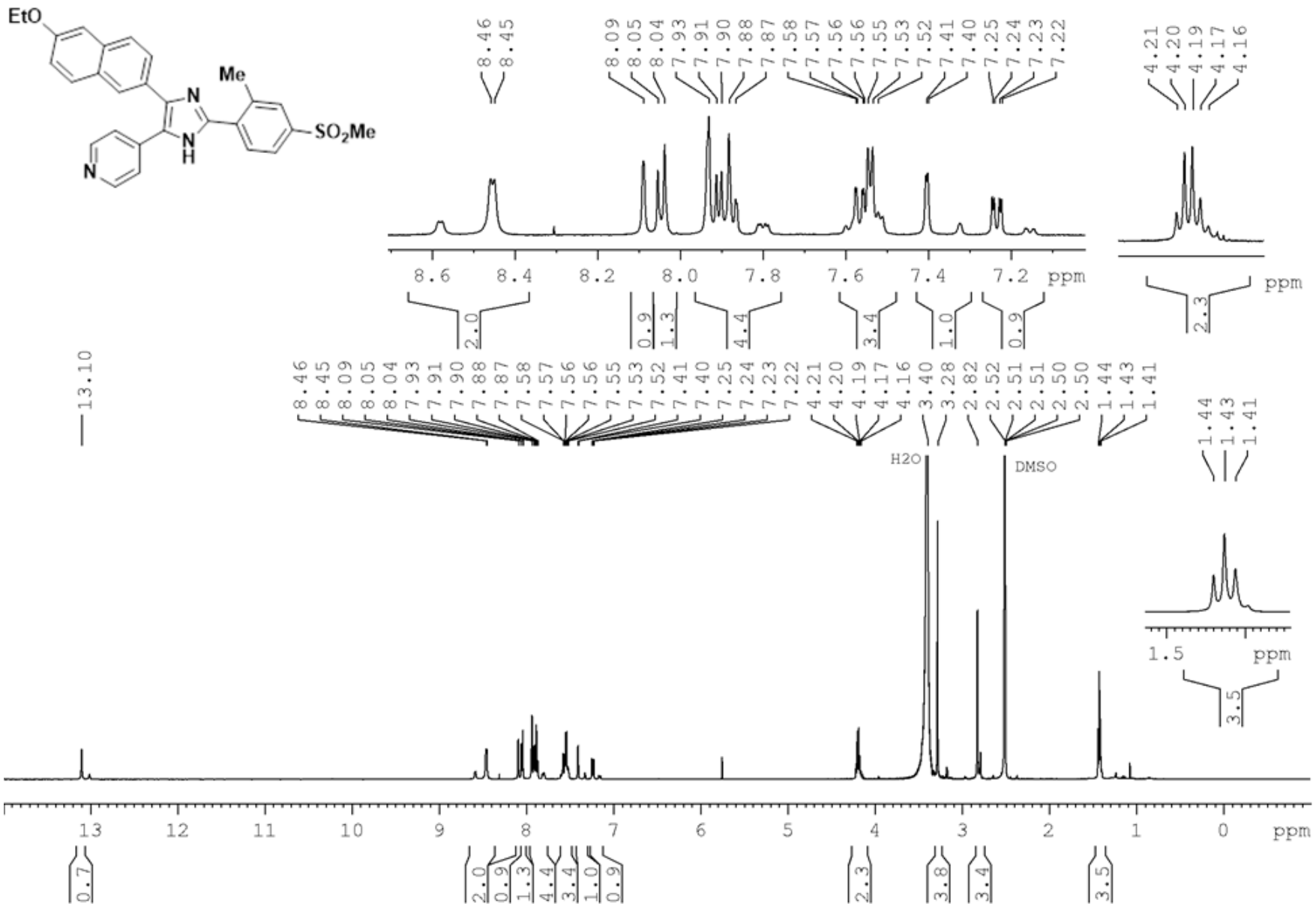


Figure S93. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **58**

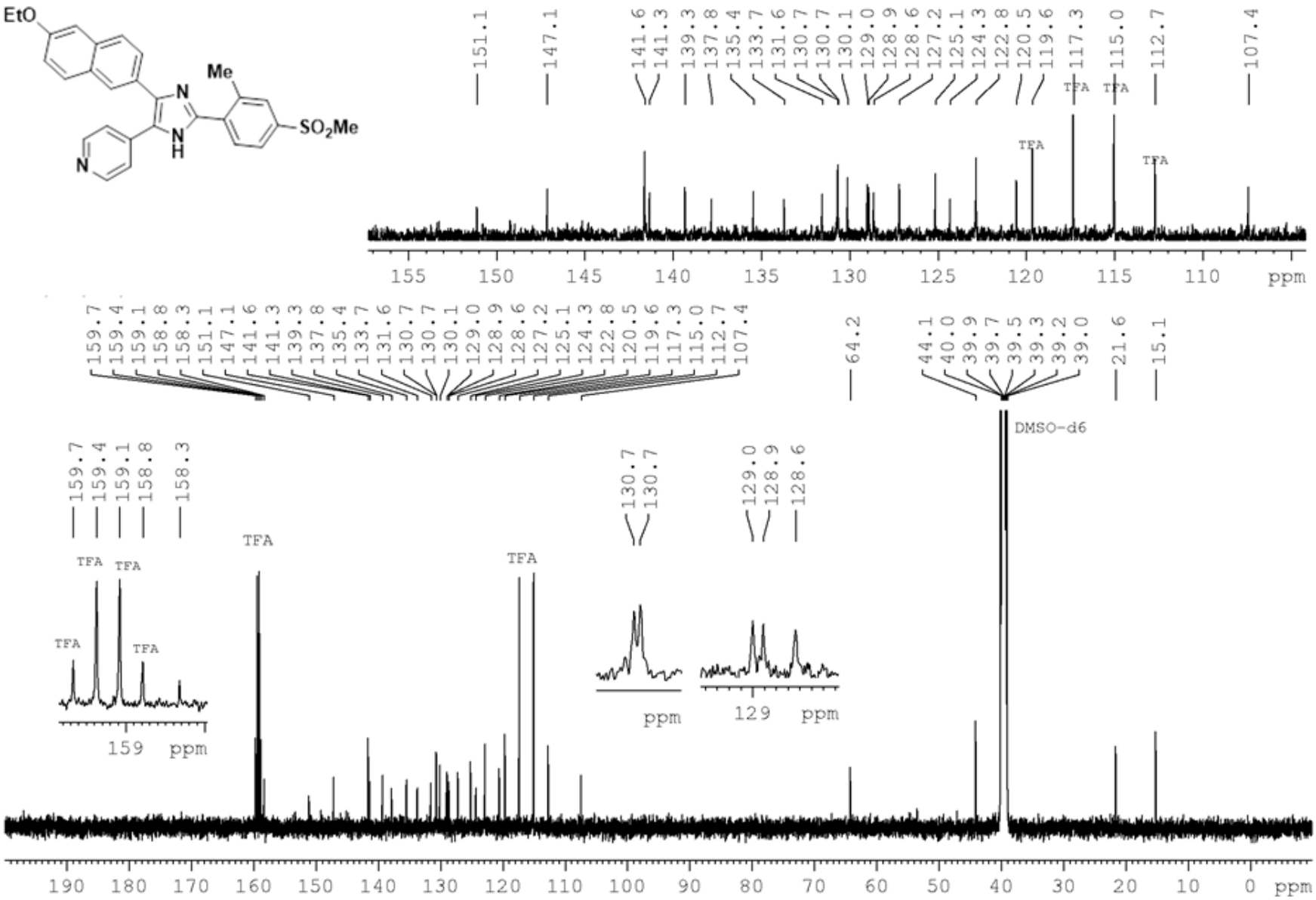


Figure S94. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **58**

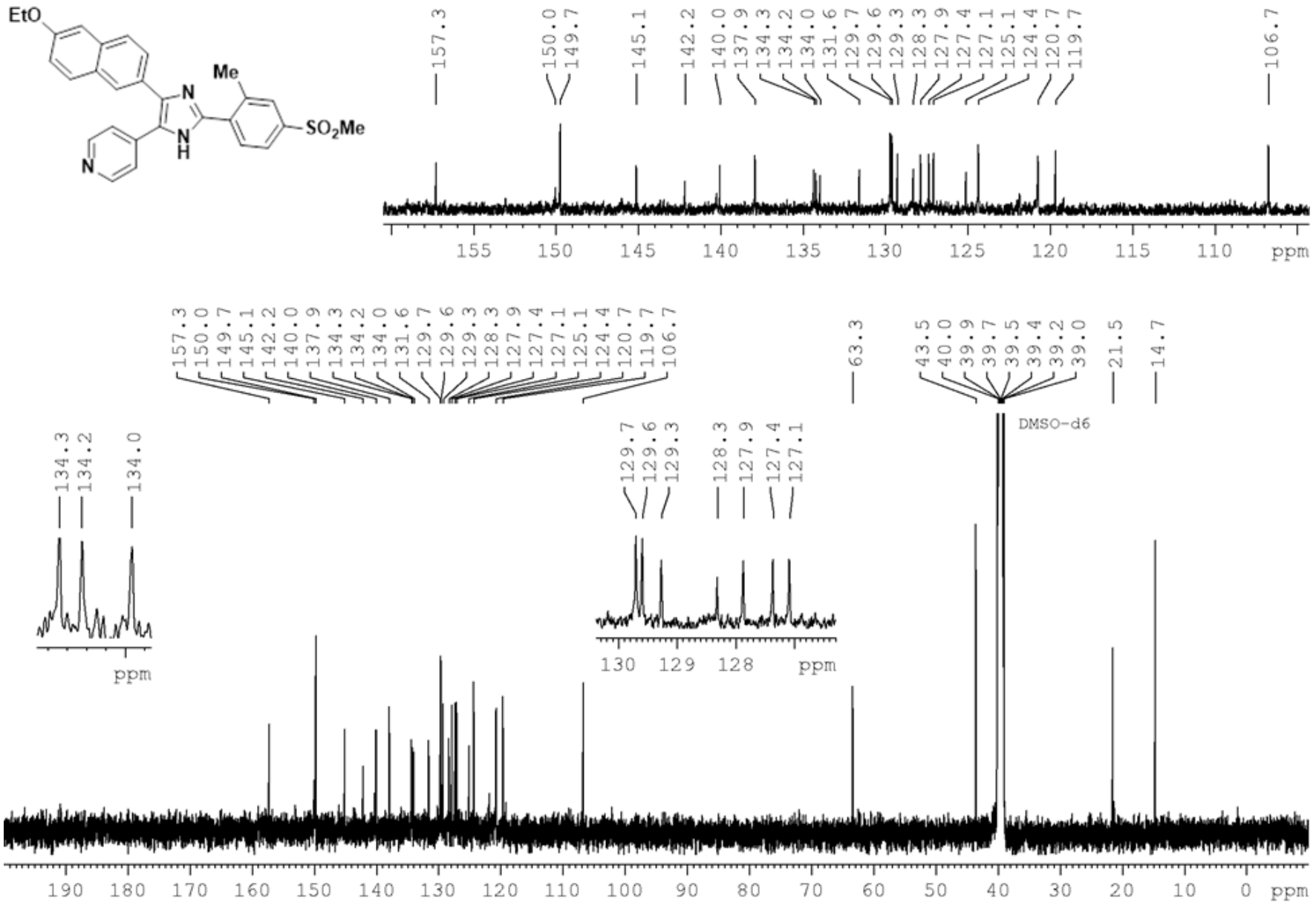


Figure S95. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **58**

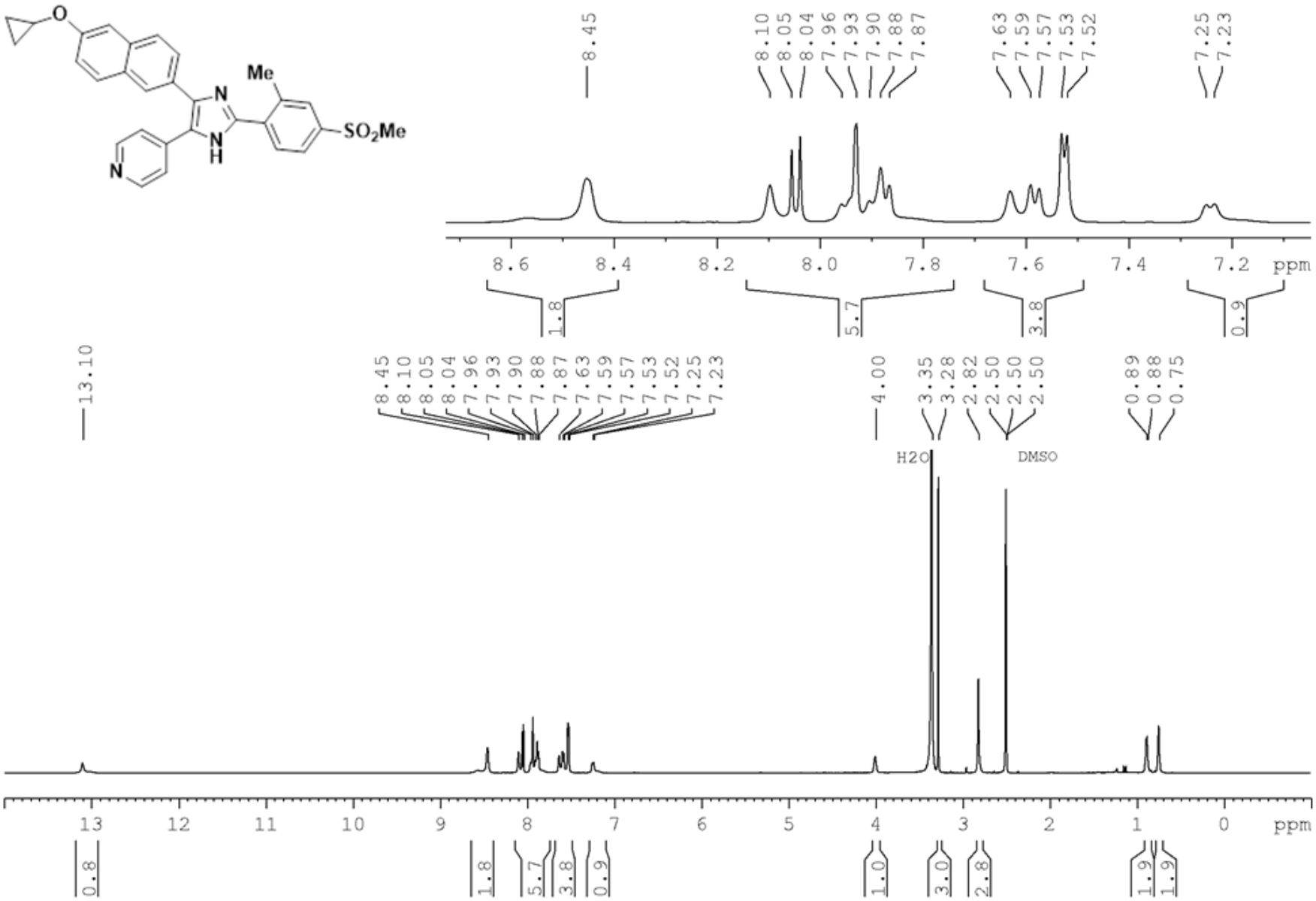


Figure S96. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **59**

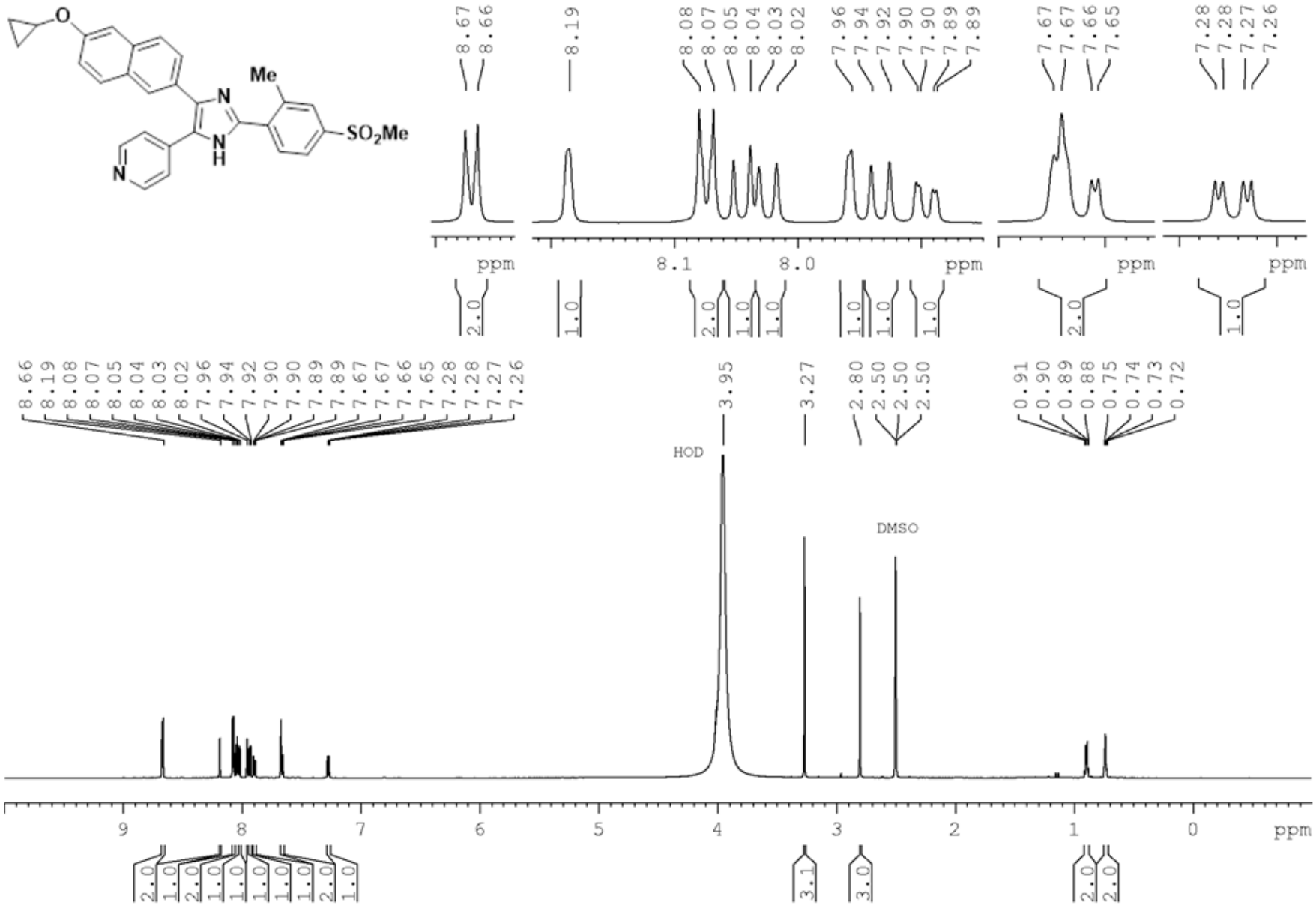


Figure S97. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 600 MHz) of **59**

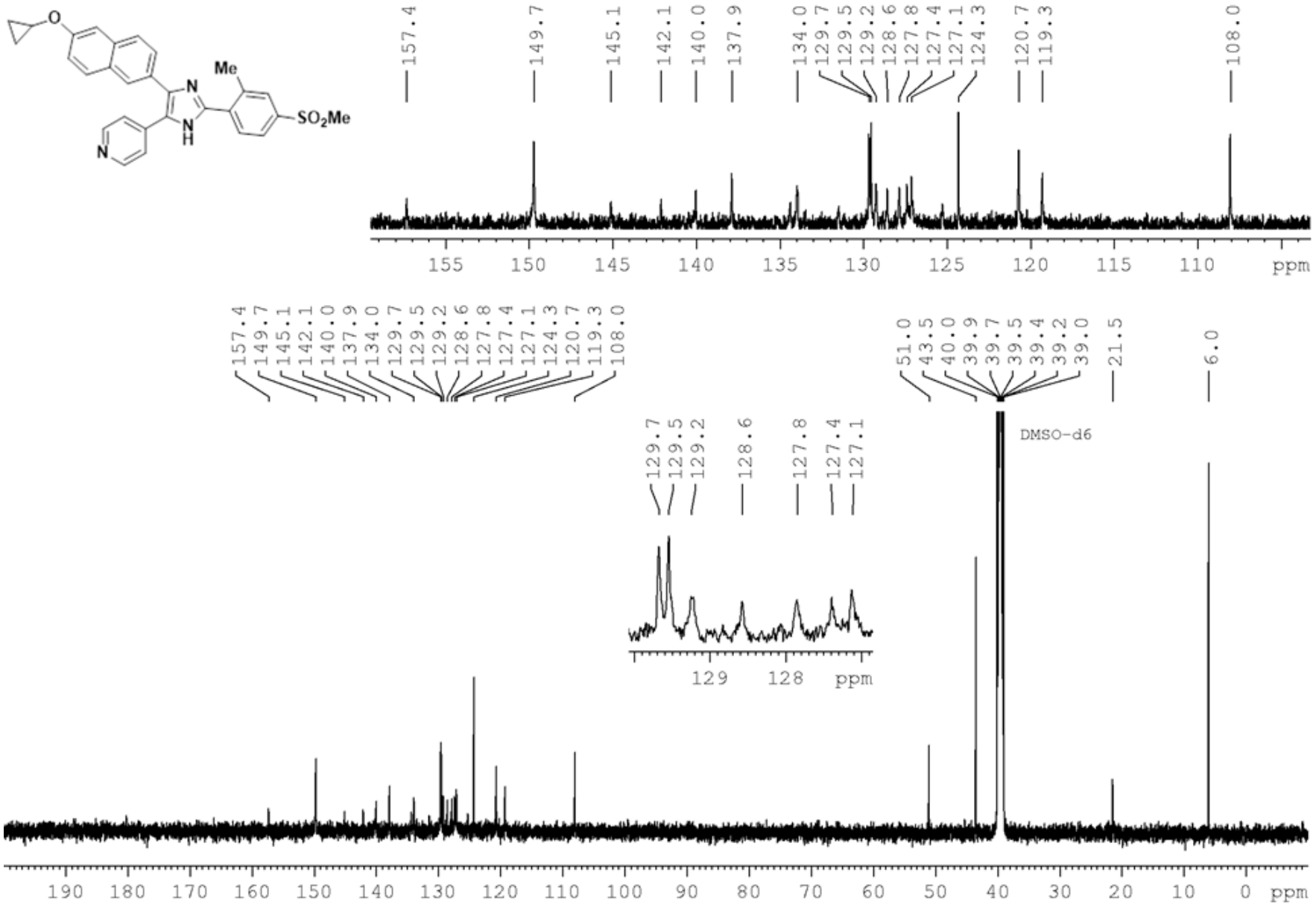


Figure S98. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **59**

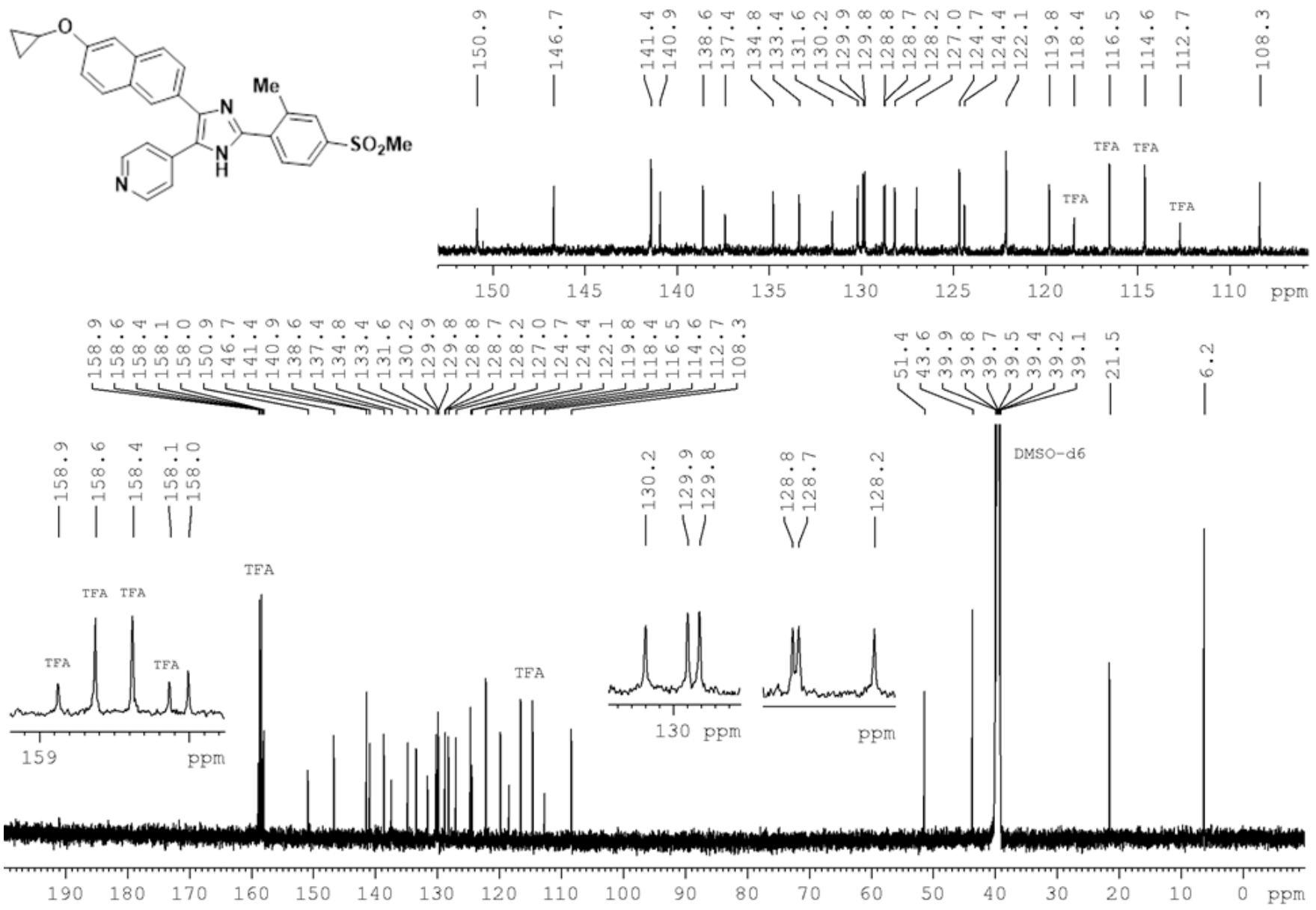


Figure S99. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 151 MHz) of **59**

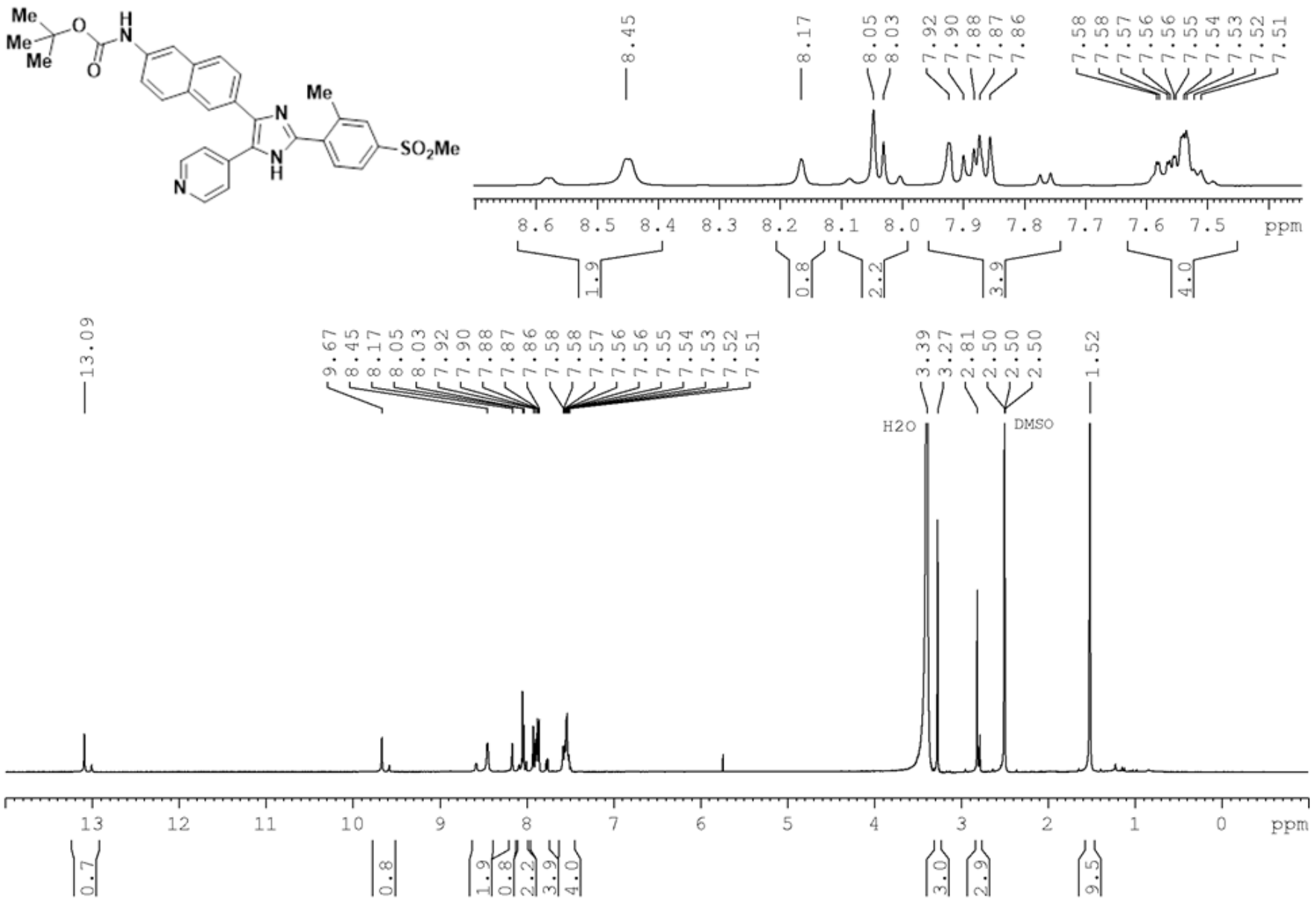


Figure S100. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **60**

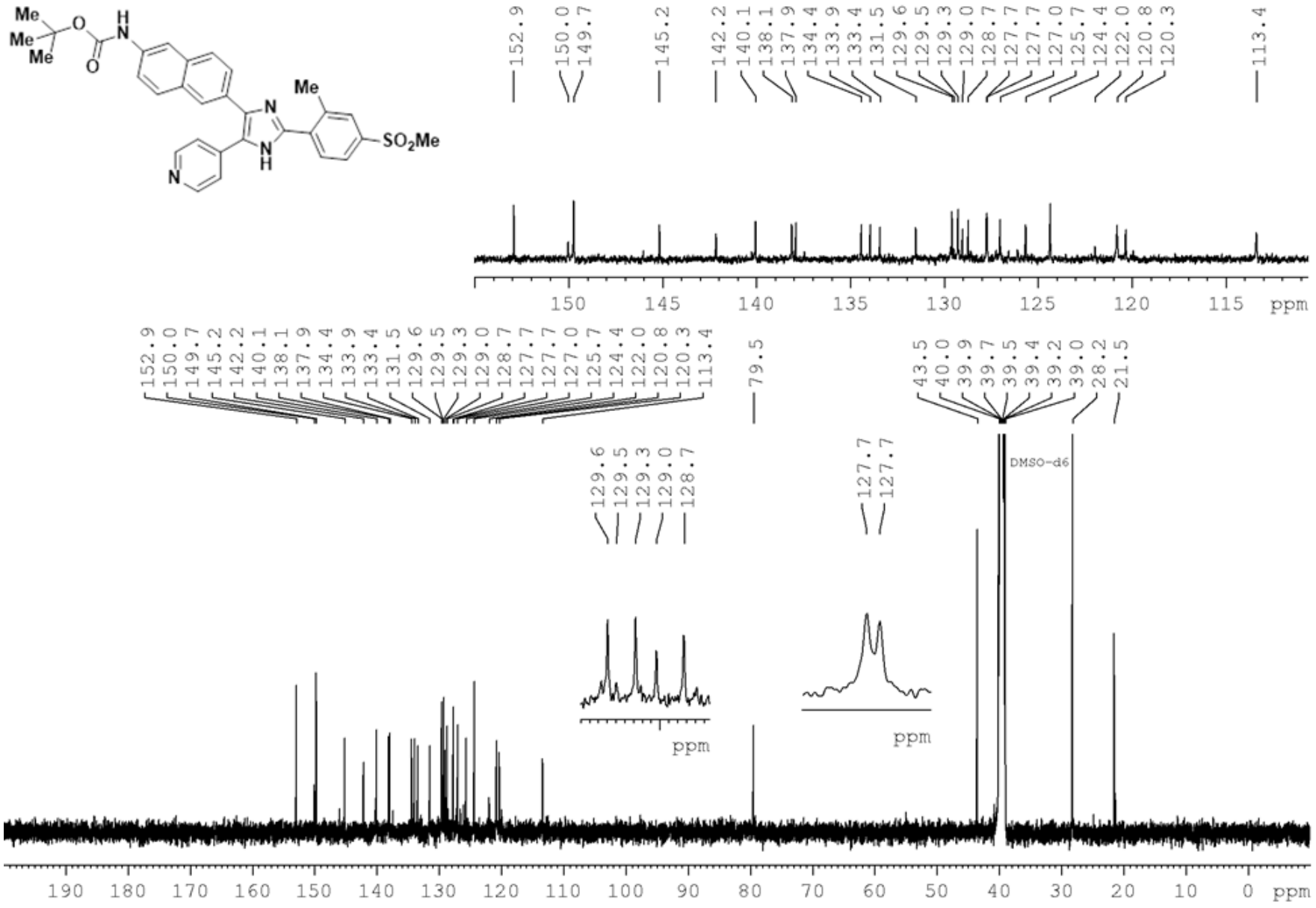


Figure S101. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **60**

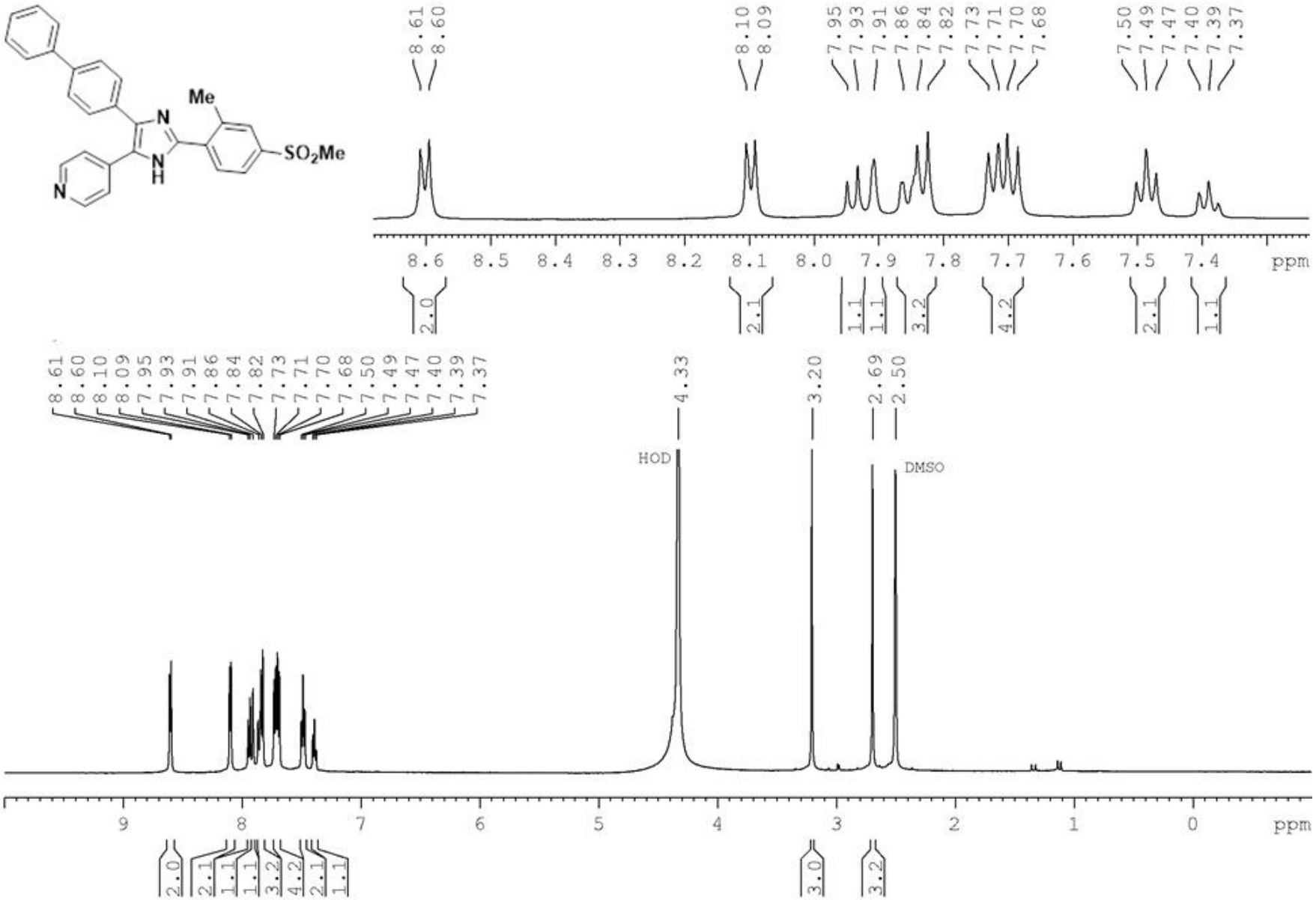


Figure S102. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **61**

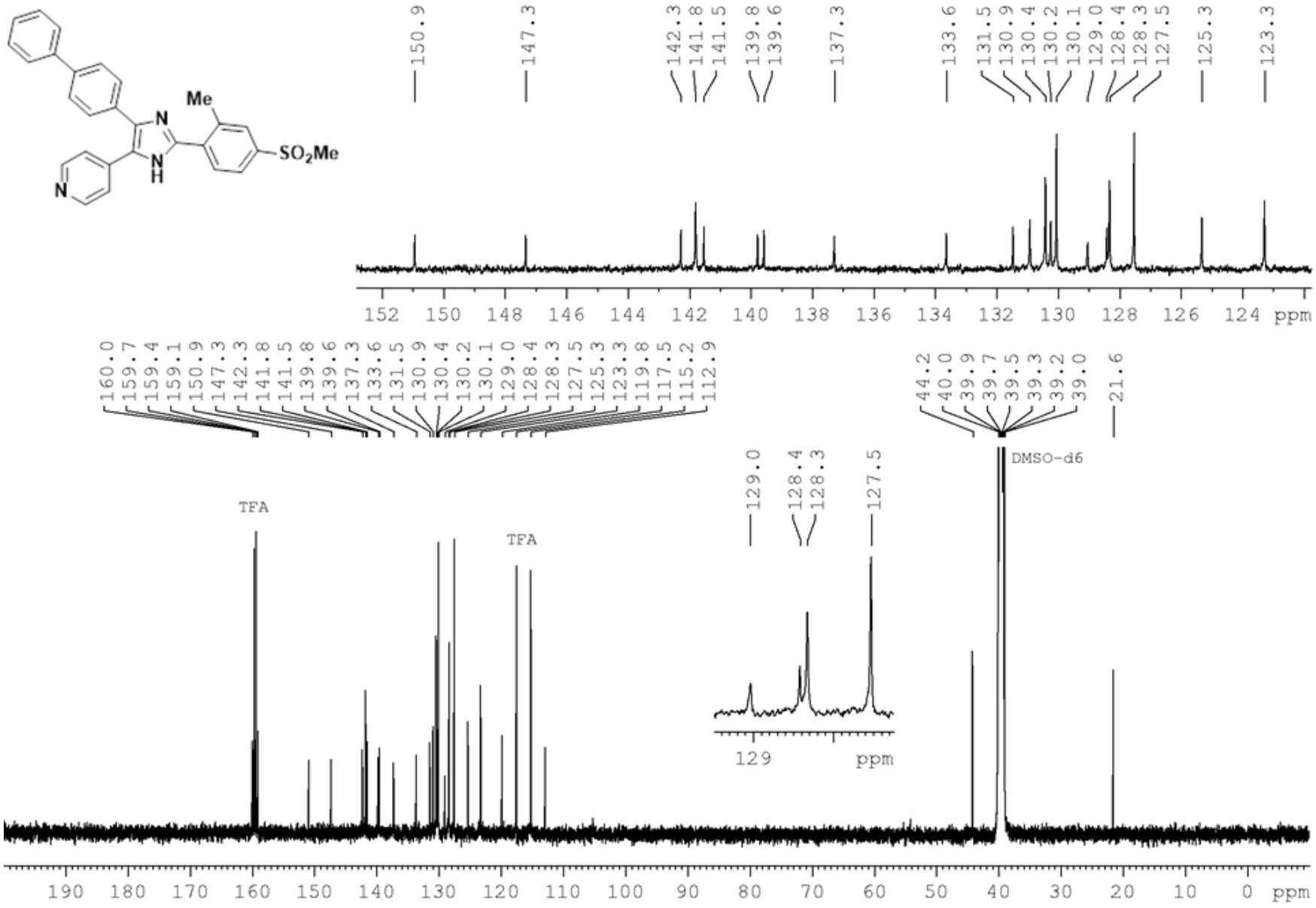


Figure S103. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **61**

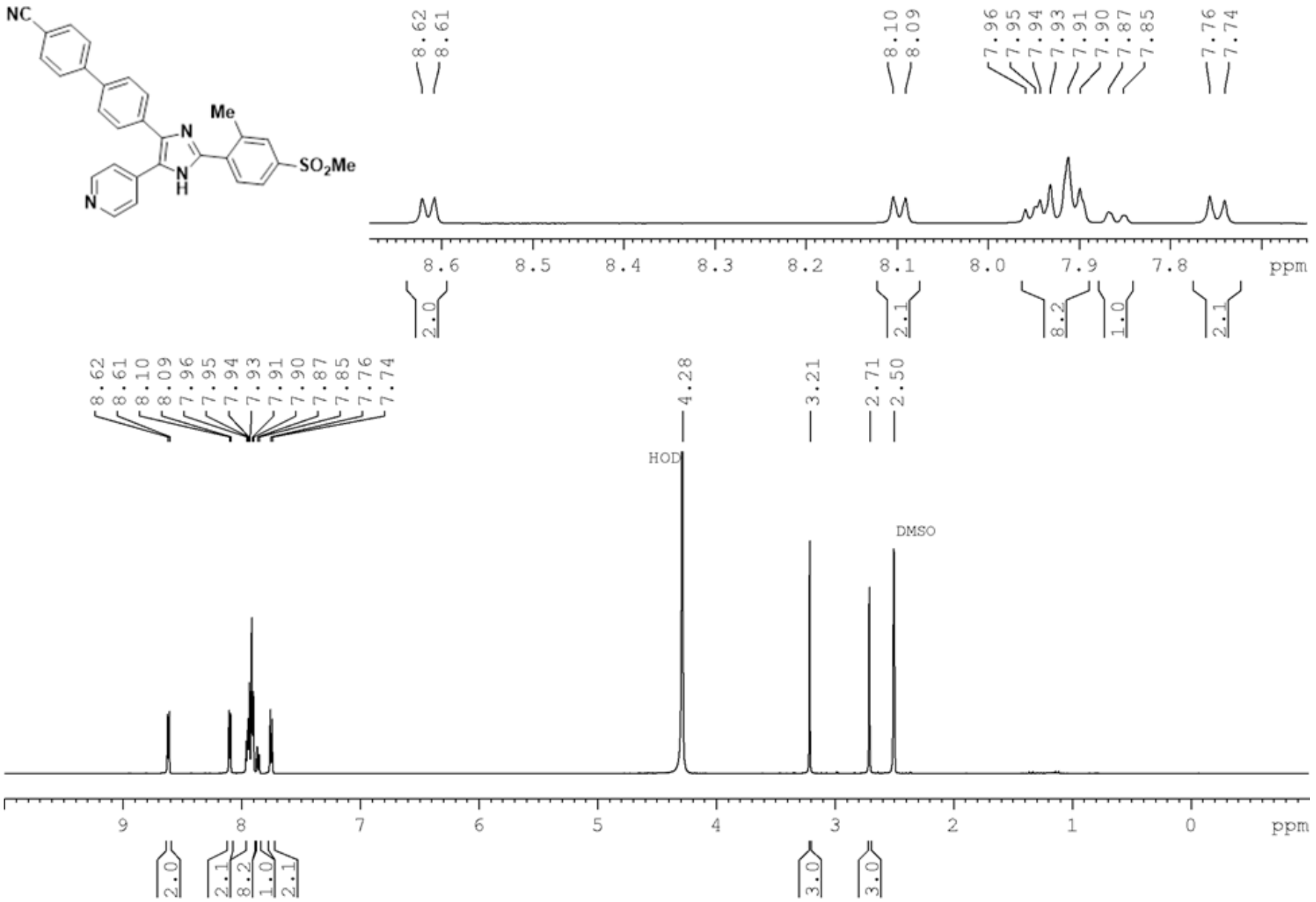


Figure S104. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **62**

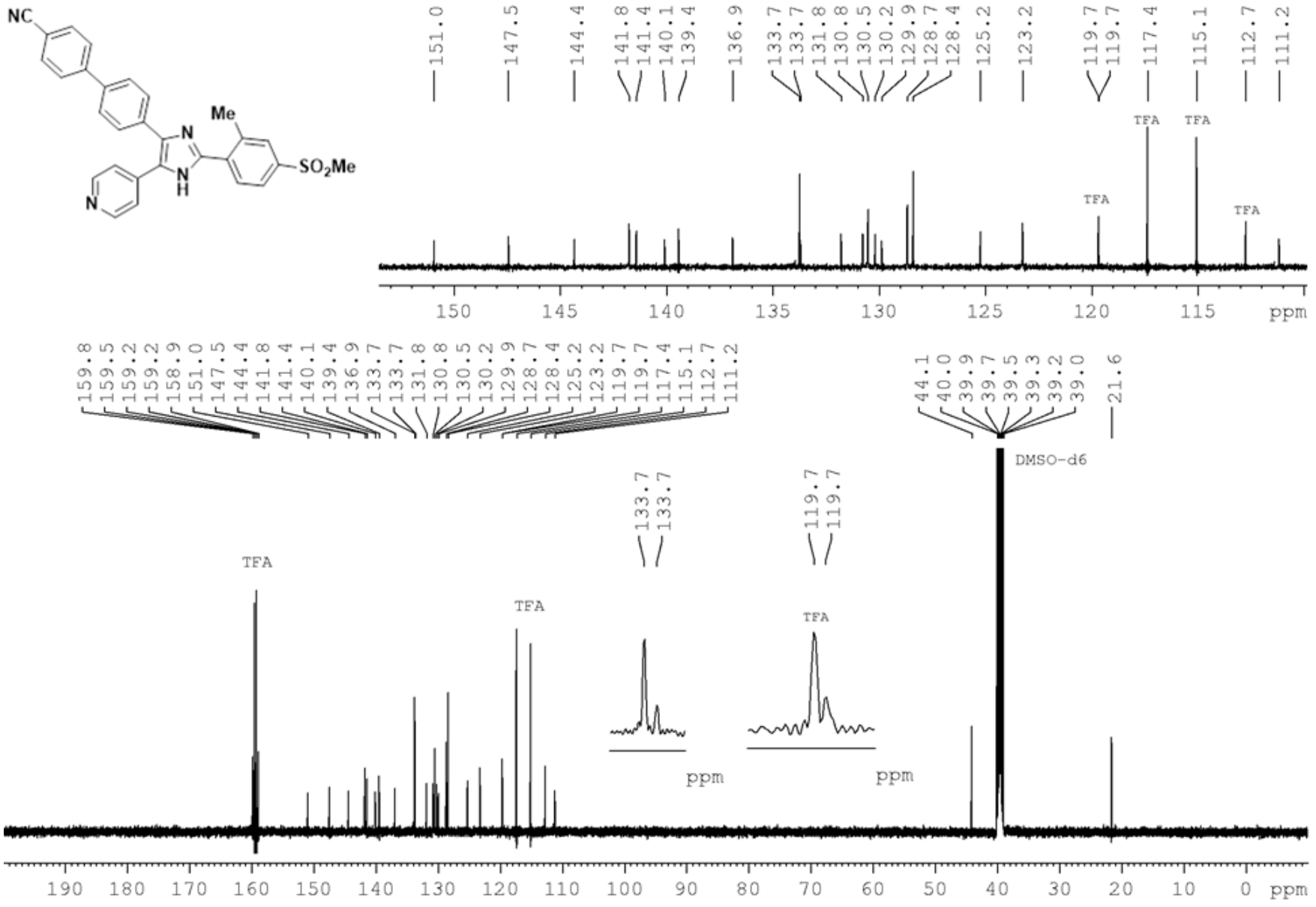


Figure S105. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **62**

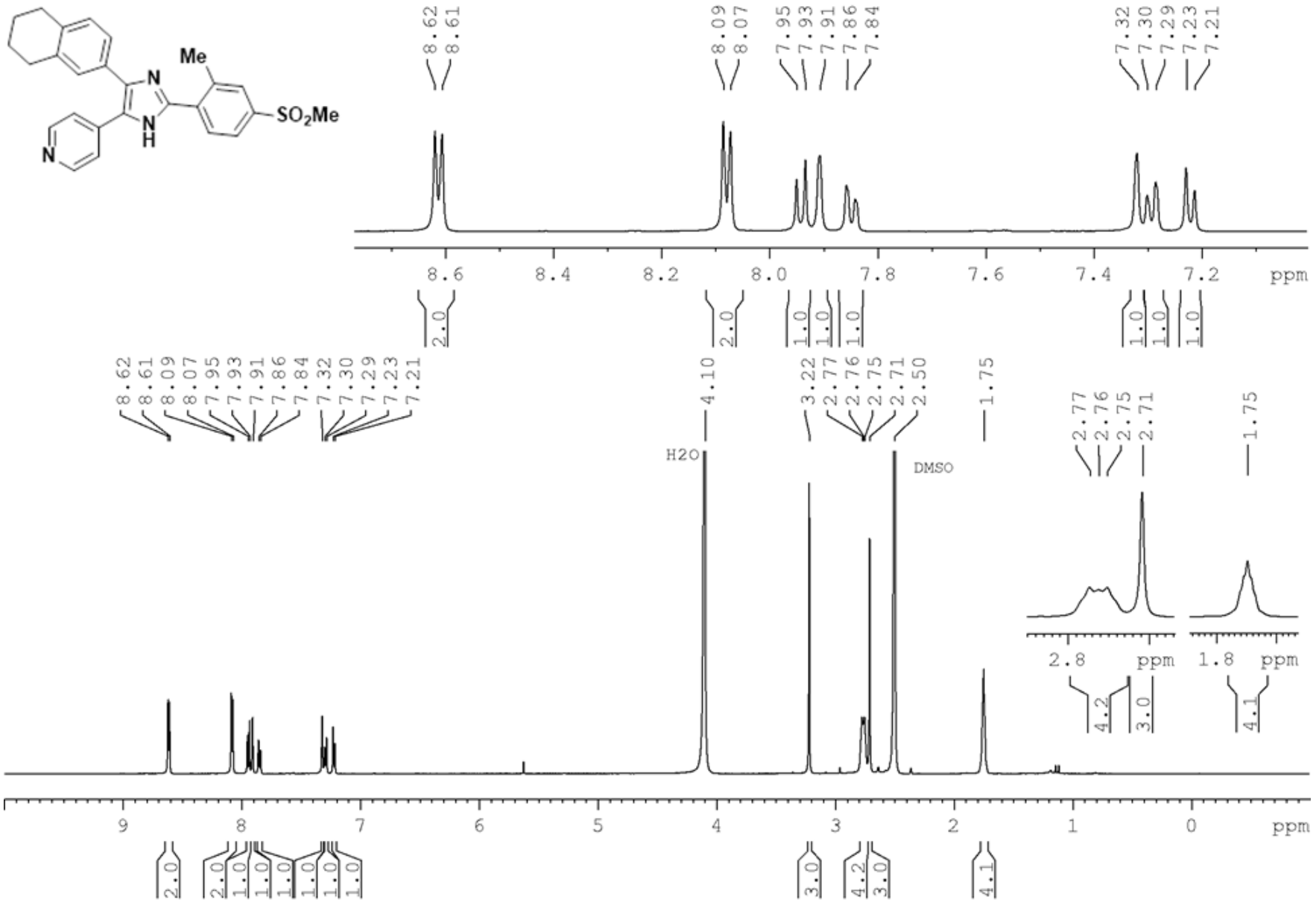


Figure S106. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **63**

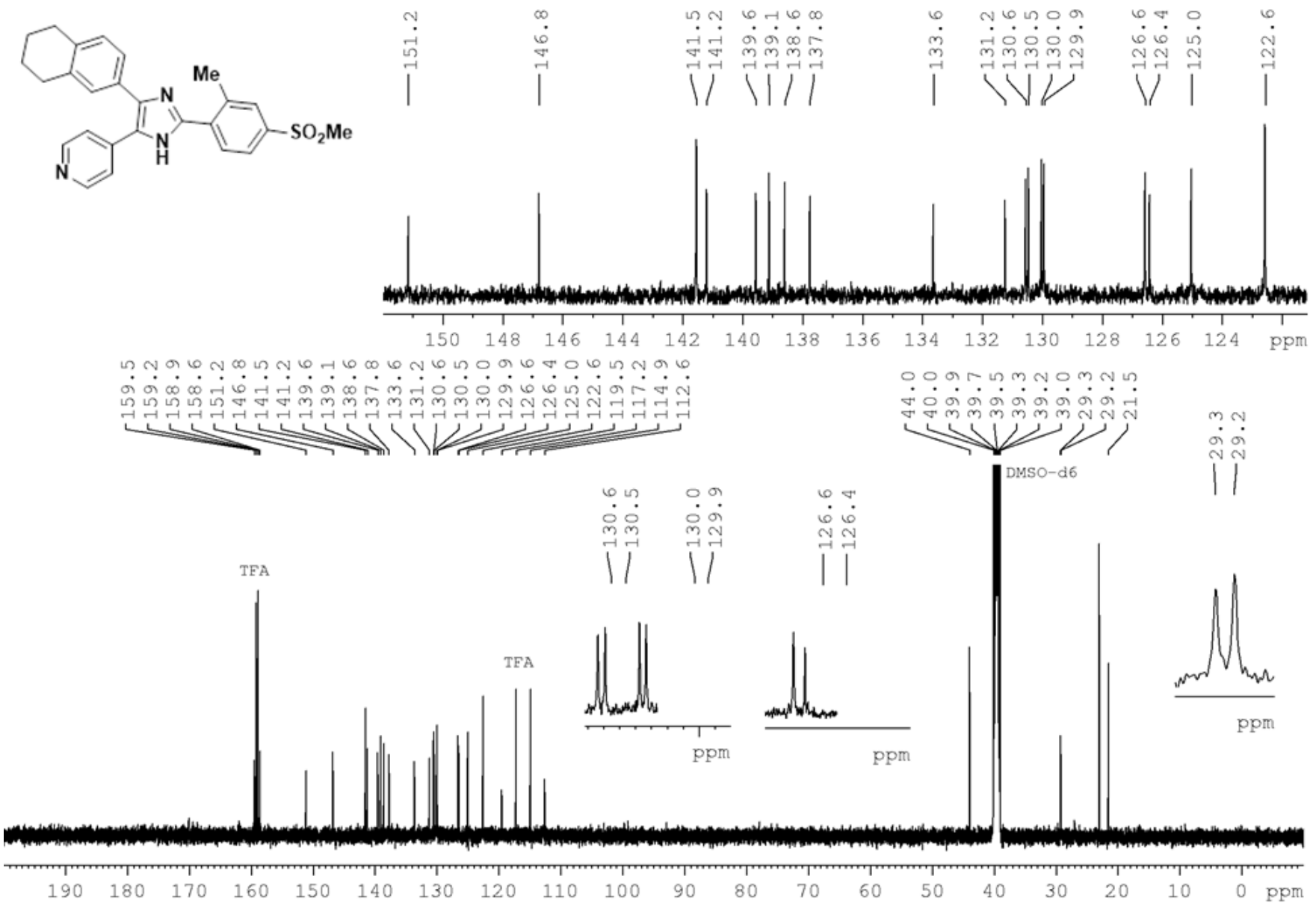


Figure S107. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **63**

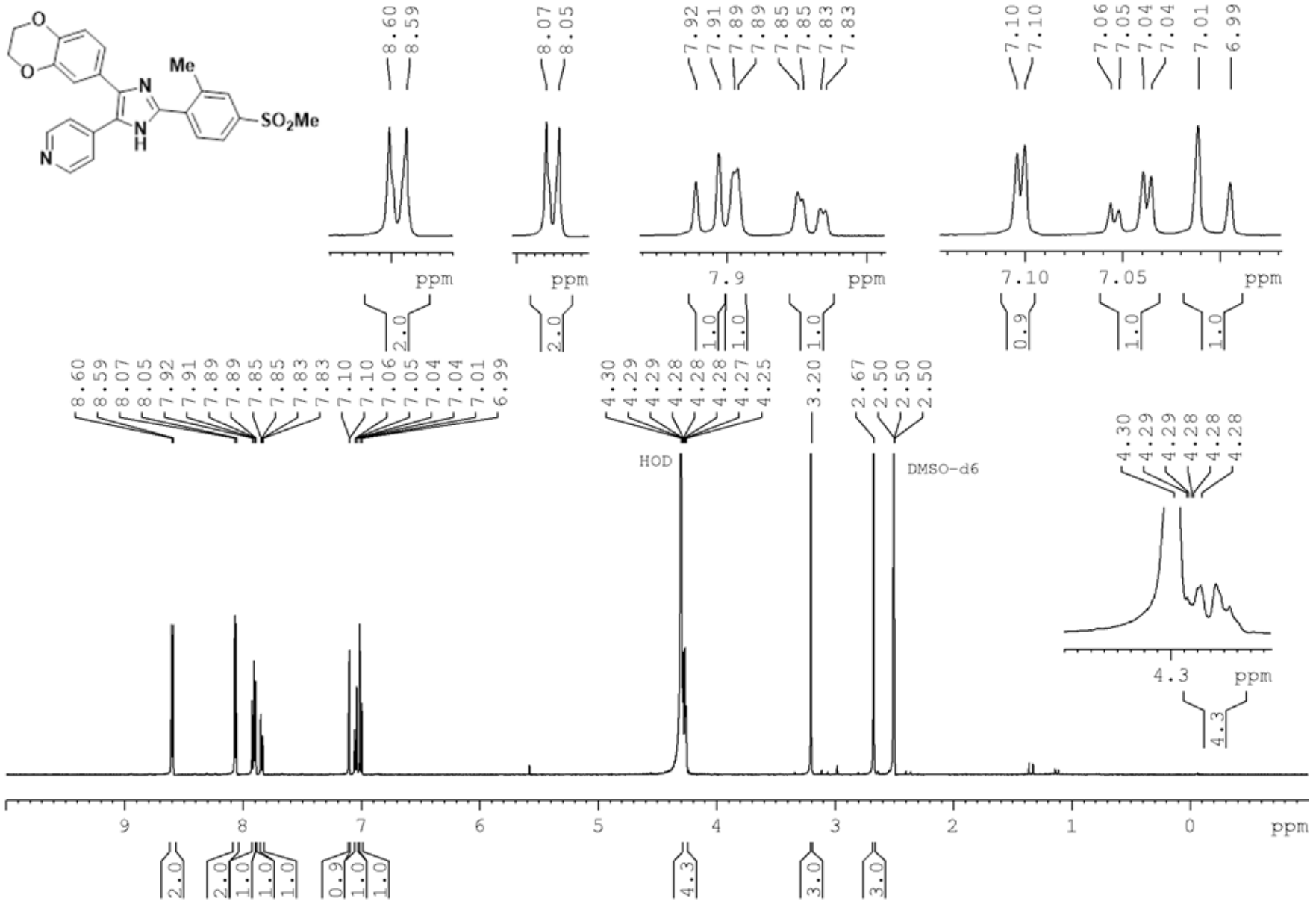


Figure S108. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **64**

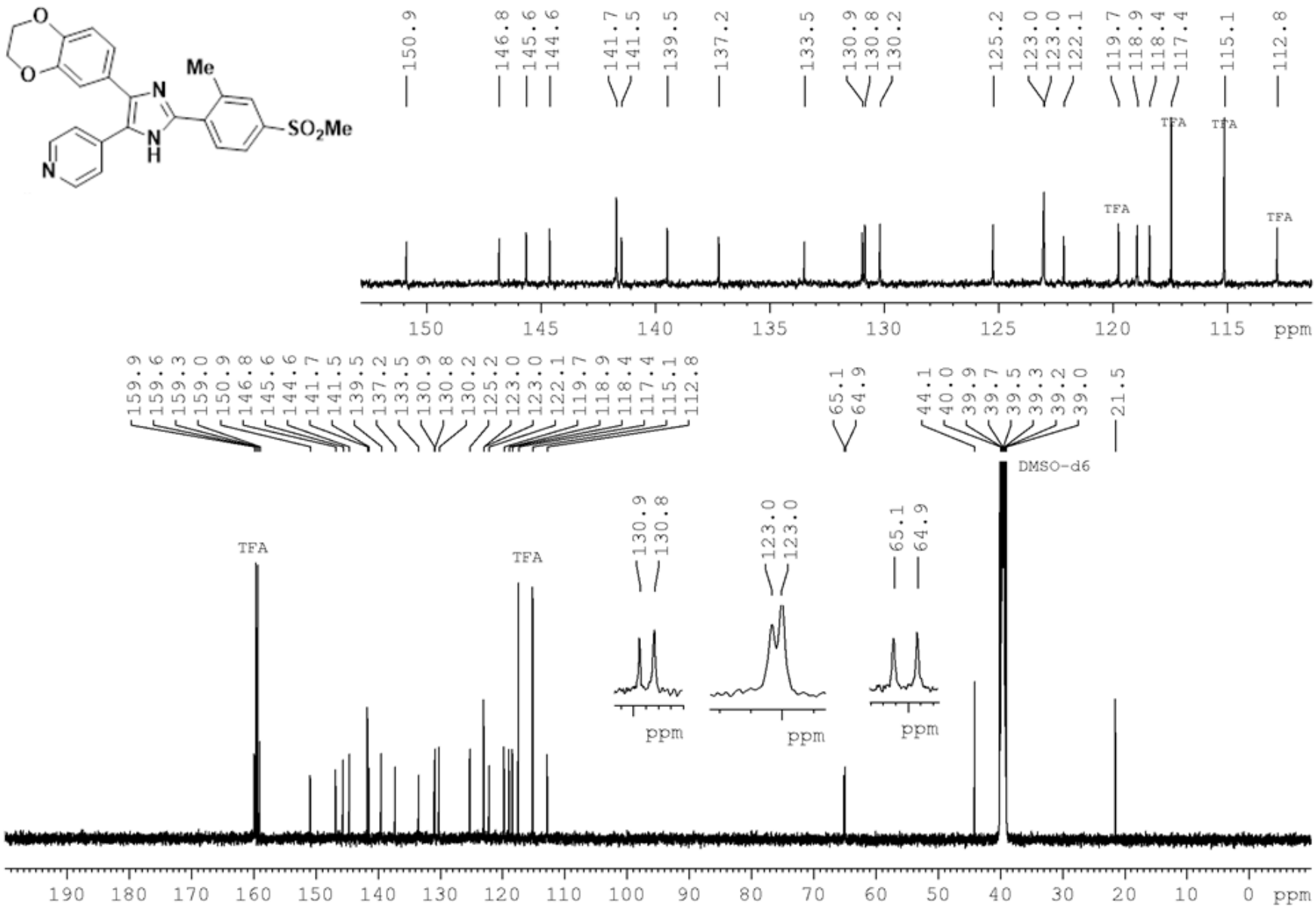


Figure S109. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **64**

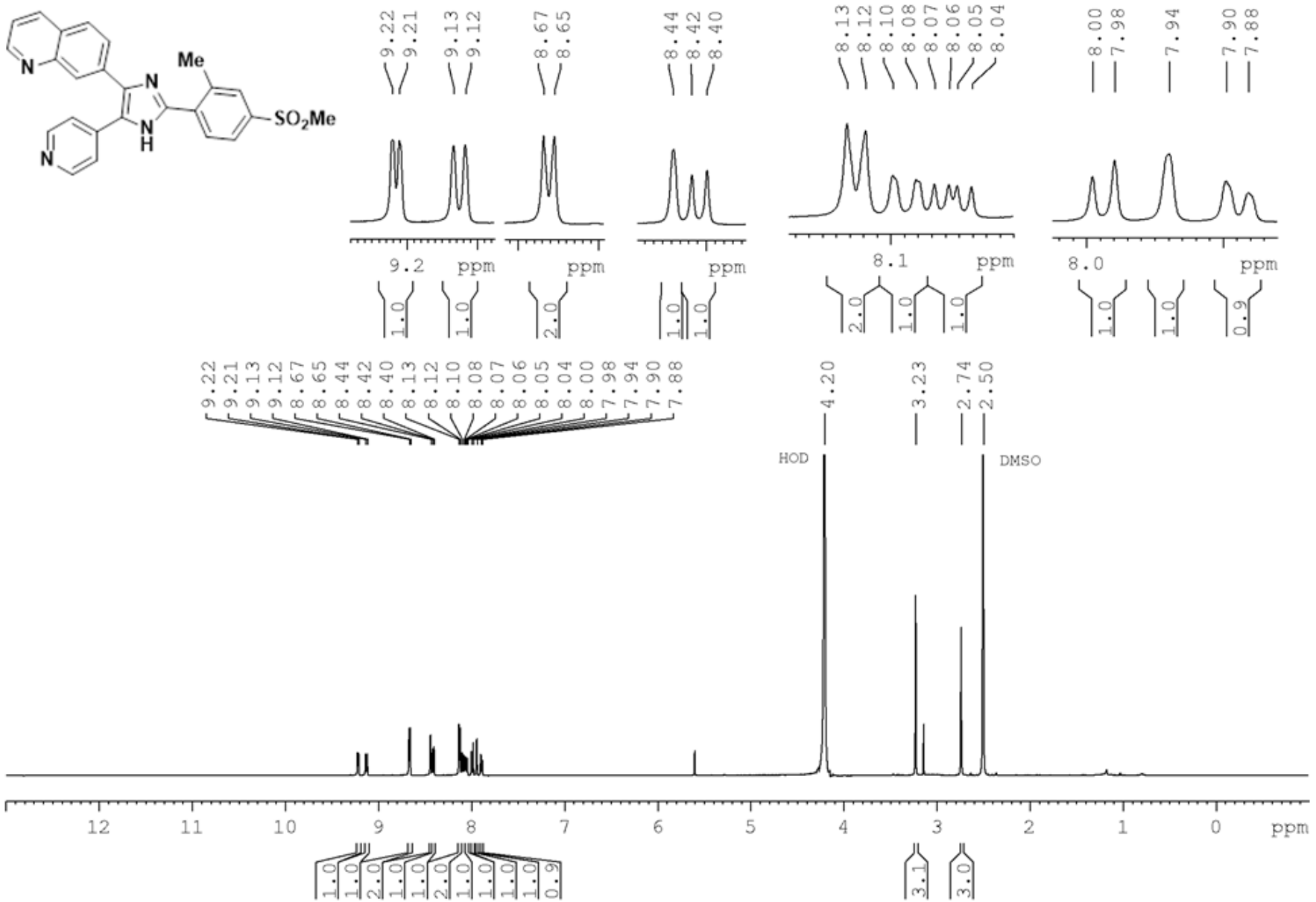


Figure S110. ^{1}H NMR Spectra (DMSO-d_6/D_2O/TFA, 500 MHz) of **67**

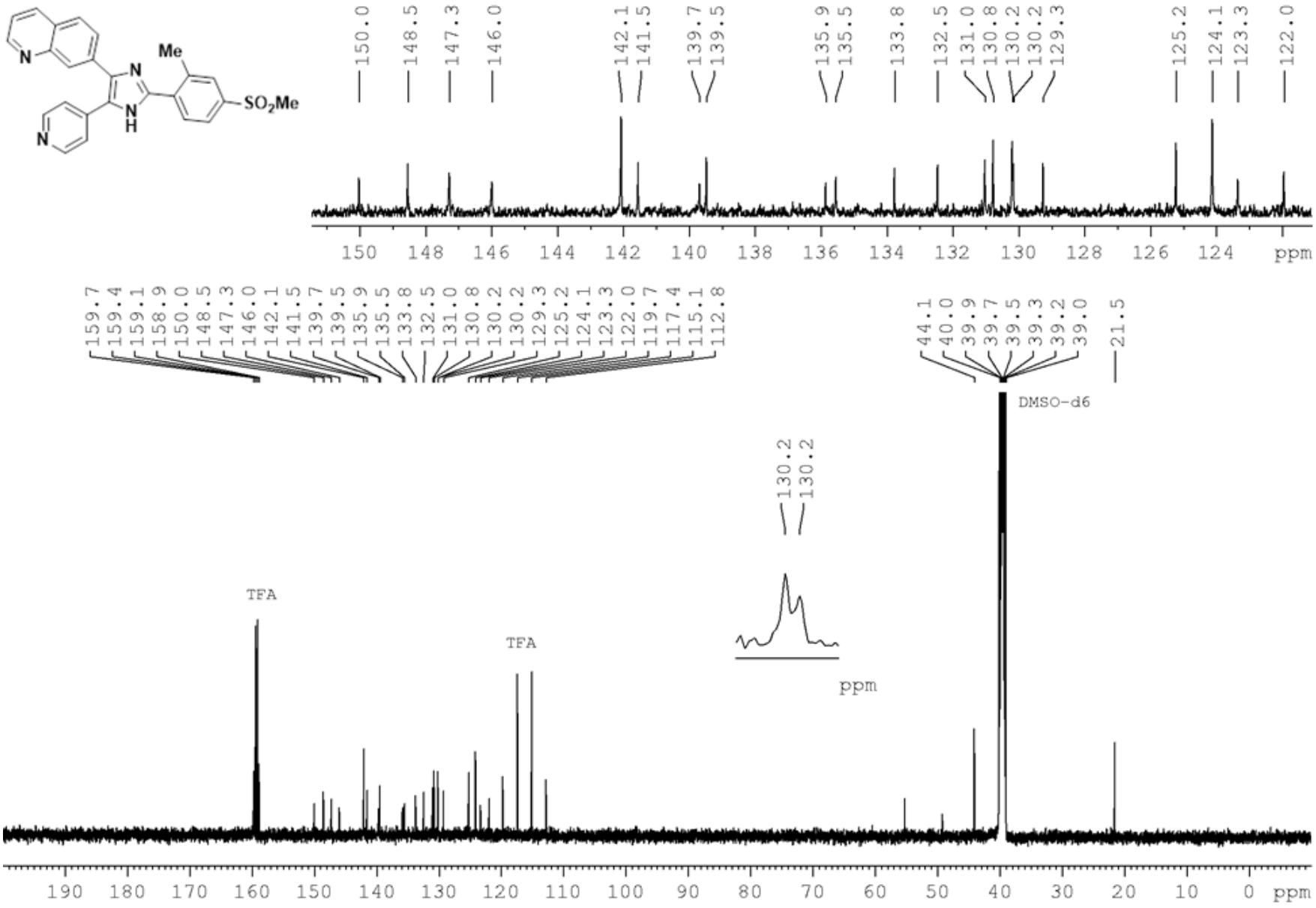


Figure S111. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6/D_2O/TFA, 126 MHz) of **67**

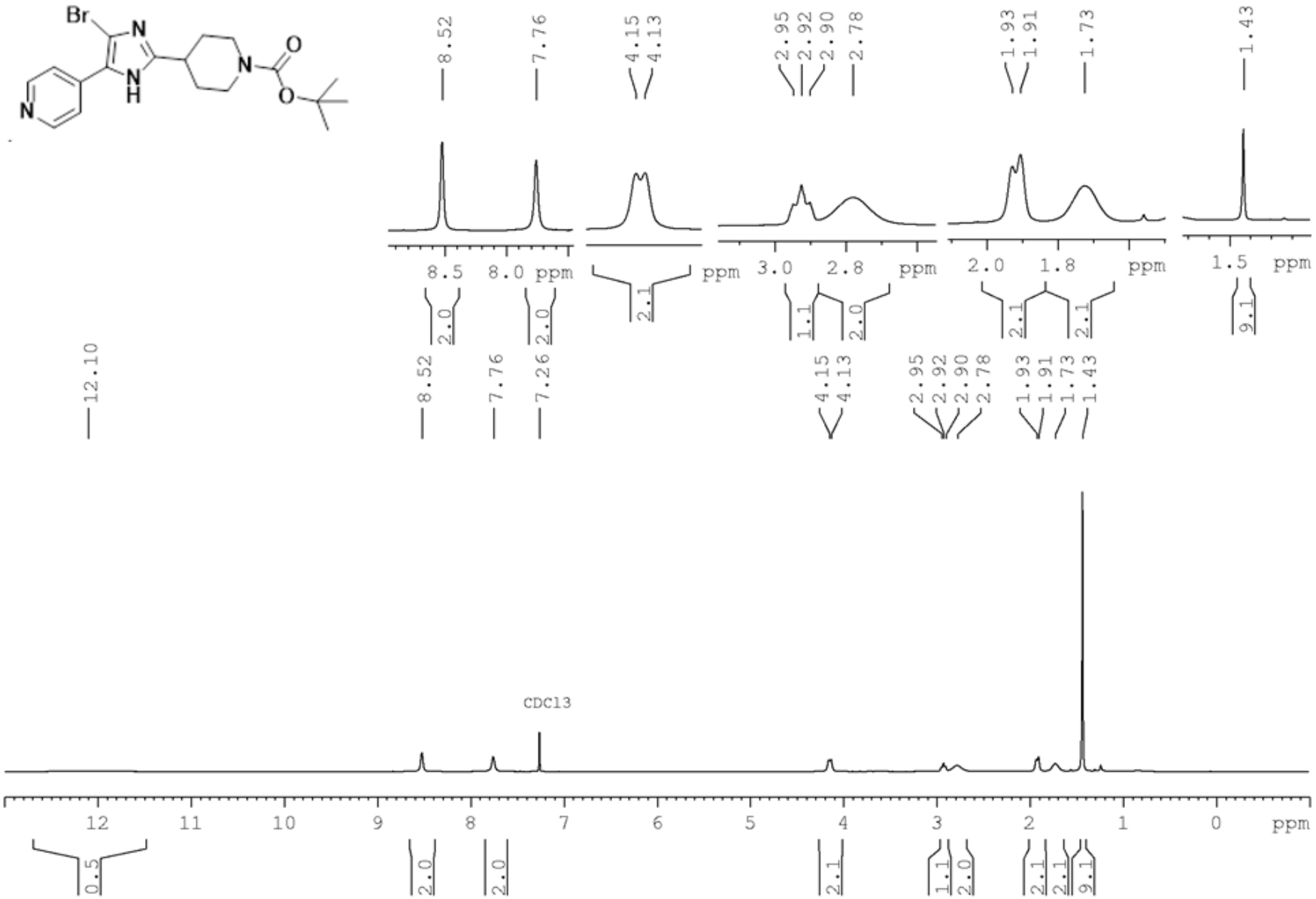


Figure S112. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **69**

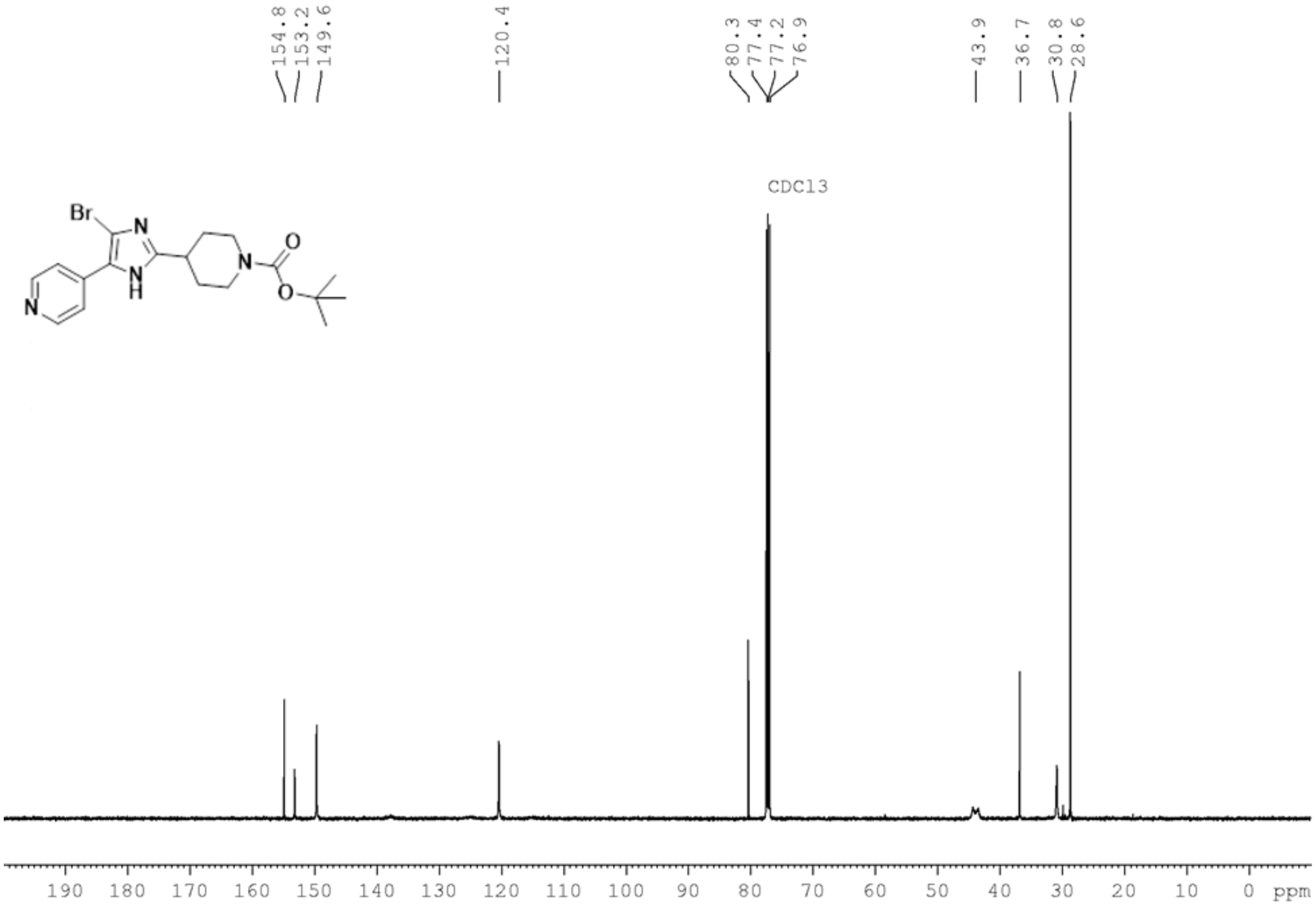


Figure S113. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **69**

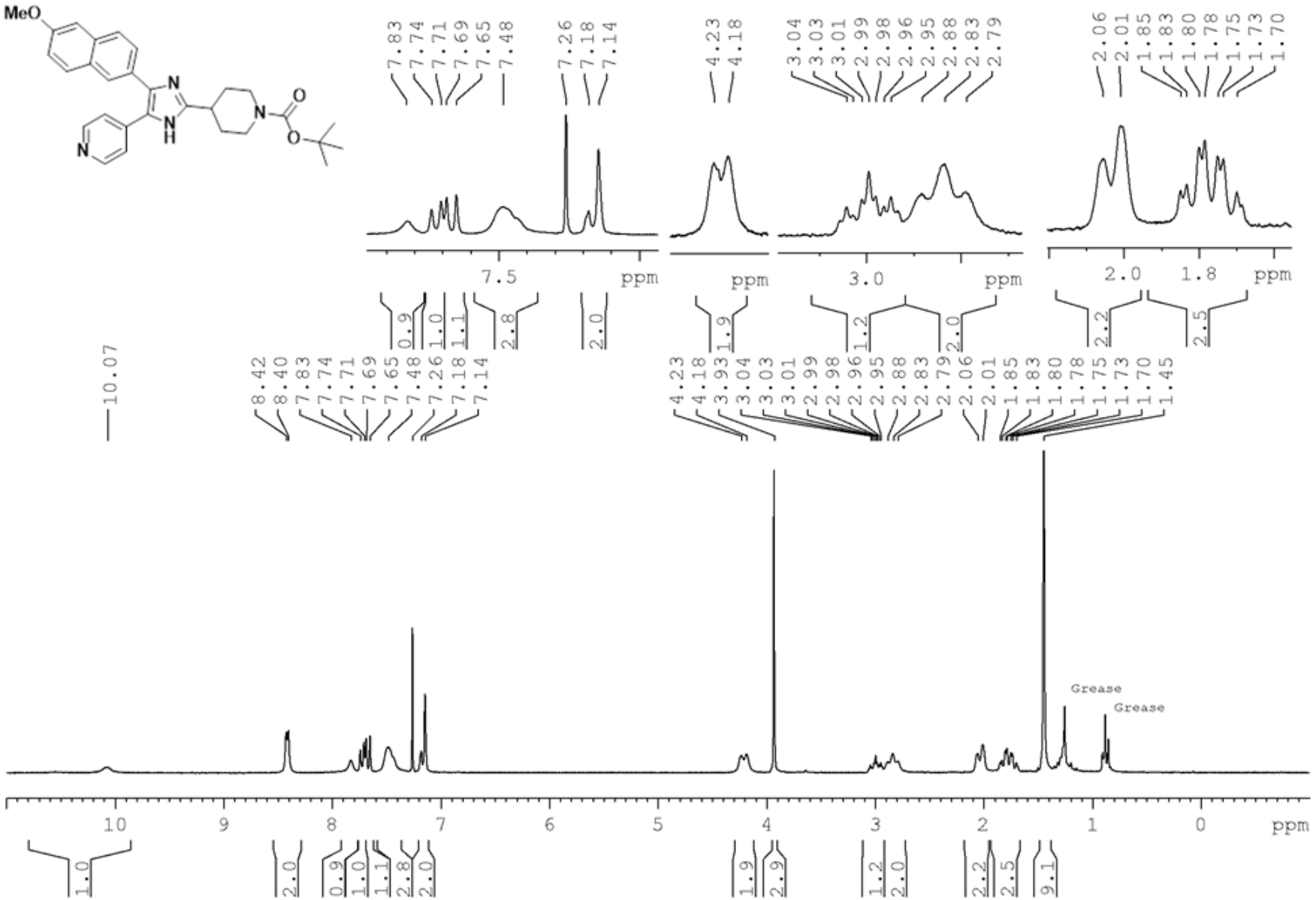


Figure S114. ^{1}H NMR Spectra ($CDCl_3$, 250 MHz) of **71**

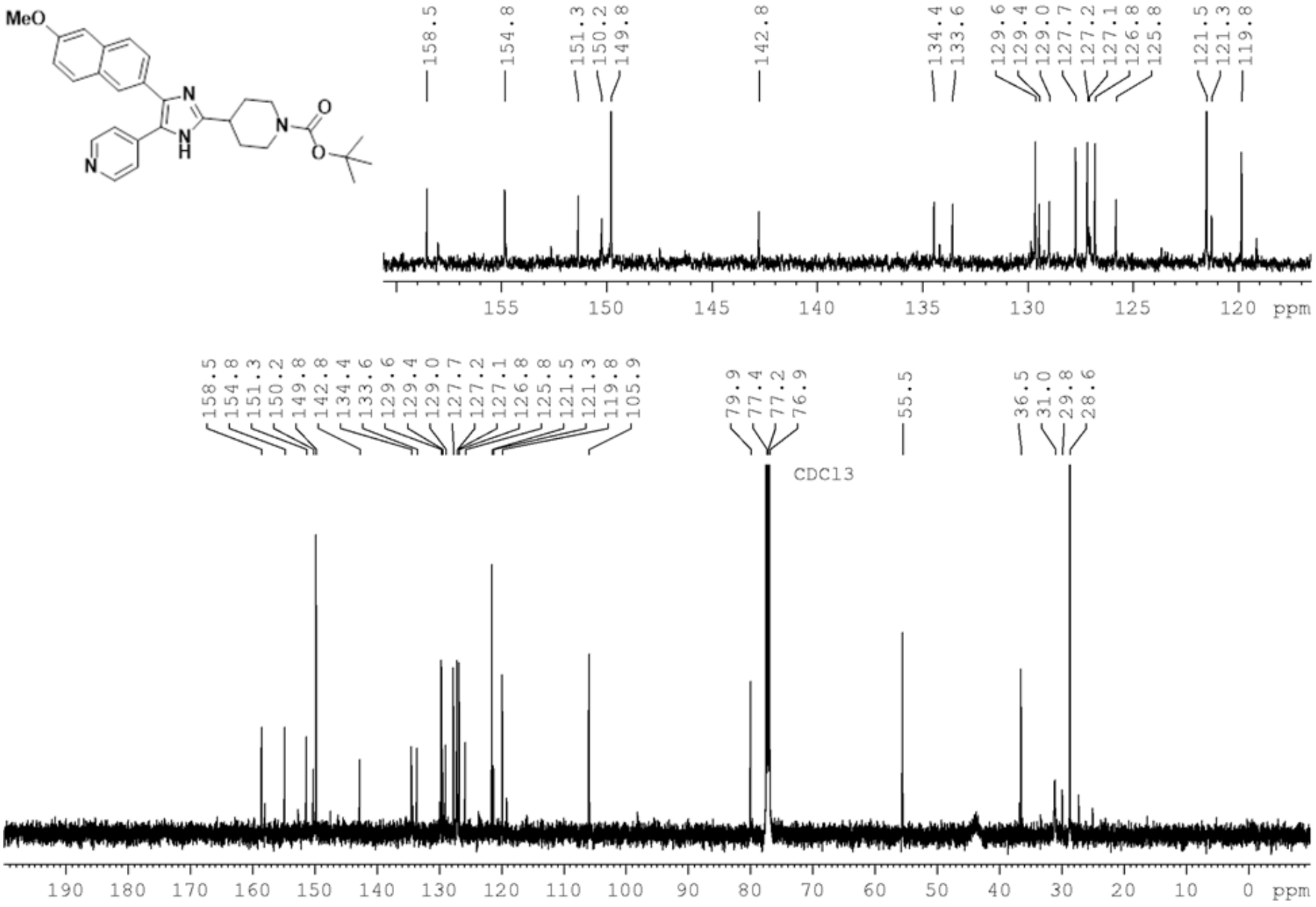


Figure S115. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **71**

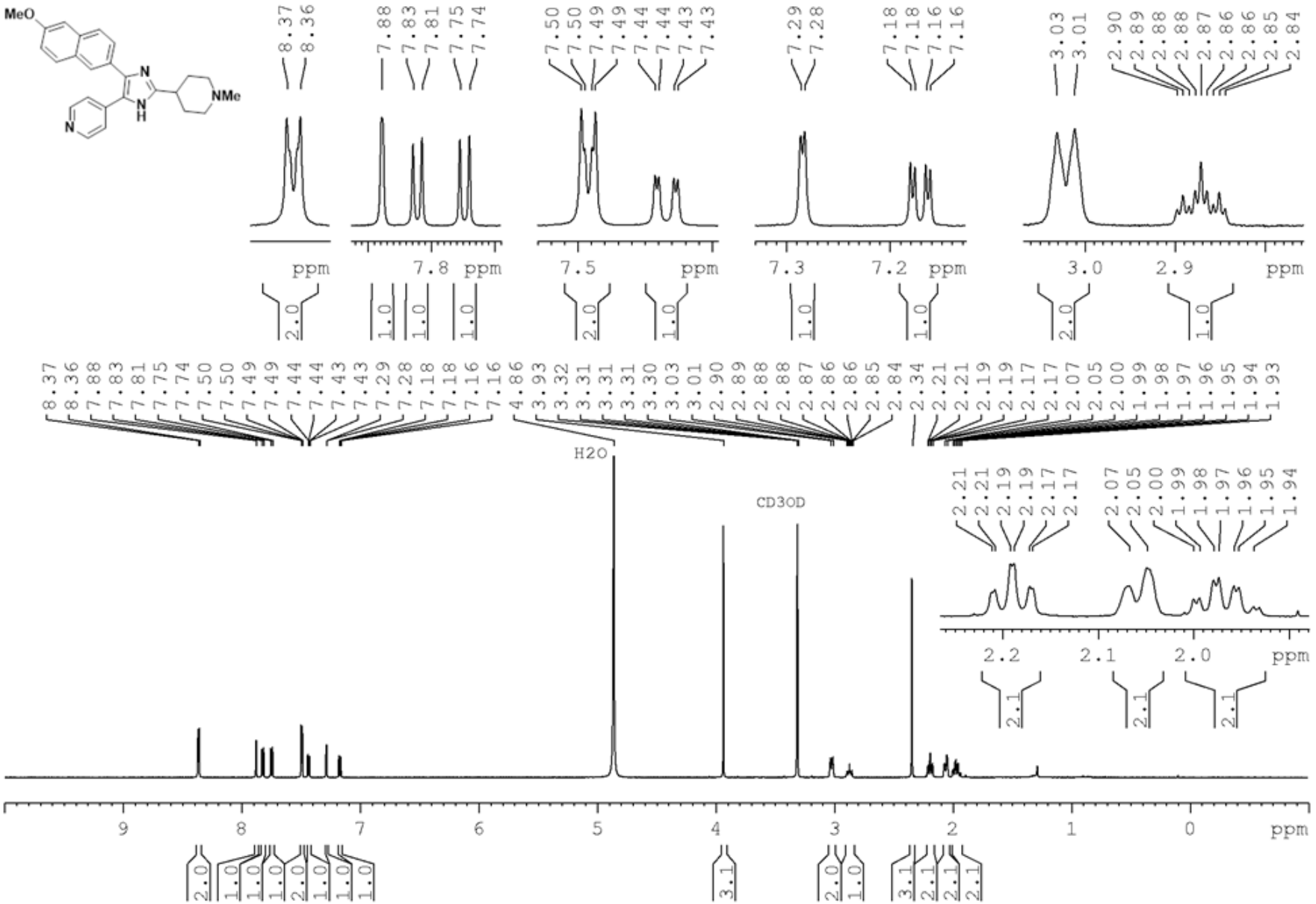


Figure S116. ^{1}H NMR Spectra (CD_3OD, 600 MHz) of **72**

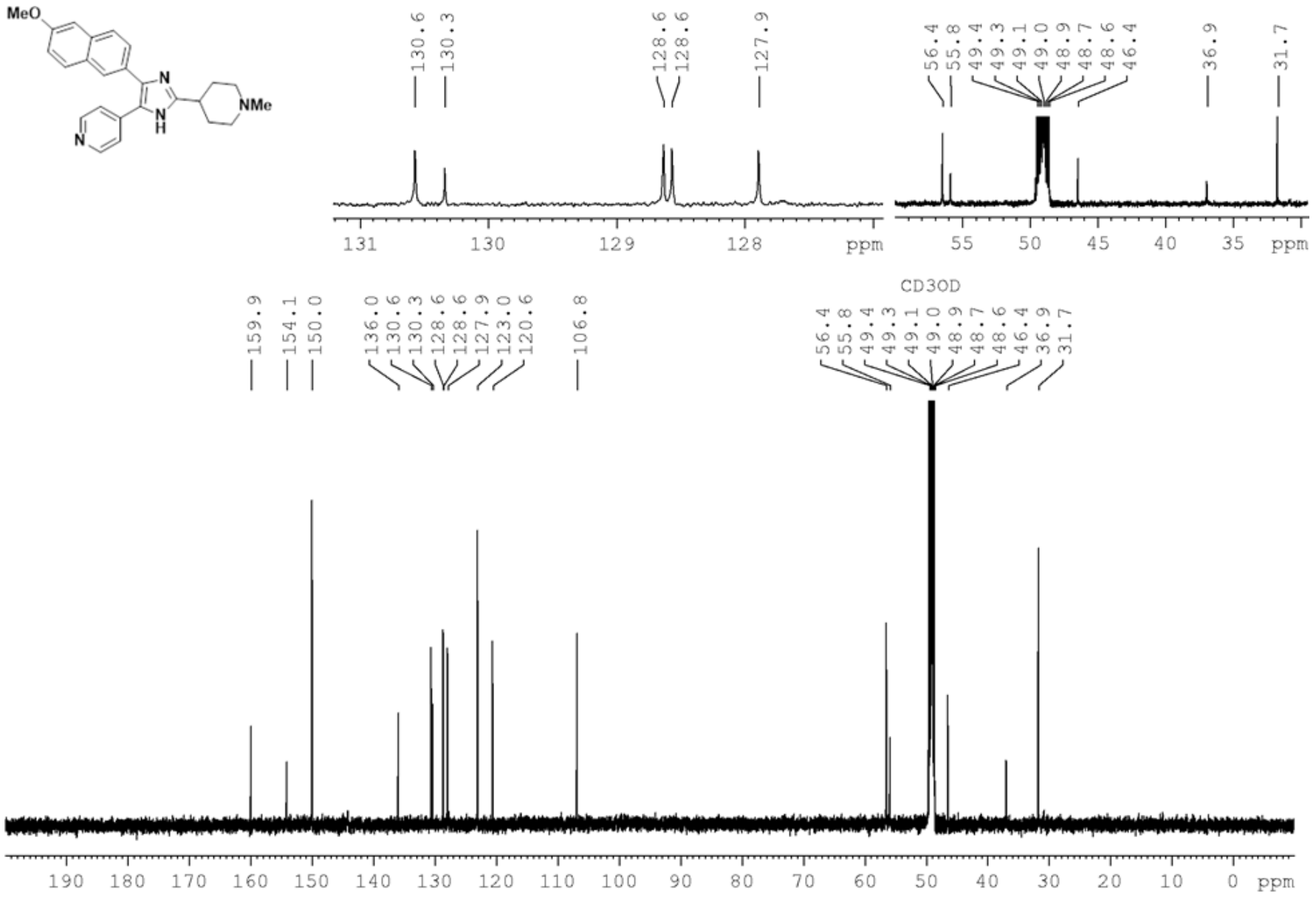


Figure S117. $^{13}C\{^{1}H\}$ NMR Spectra (CD_3OD, 151 MHz) of **72**

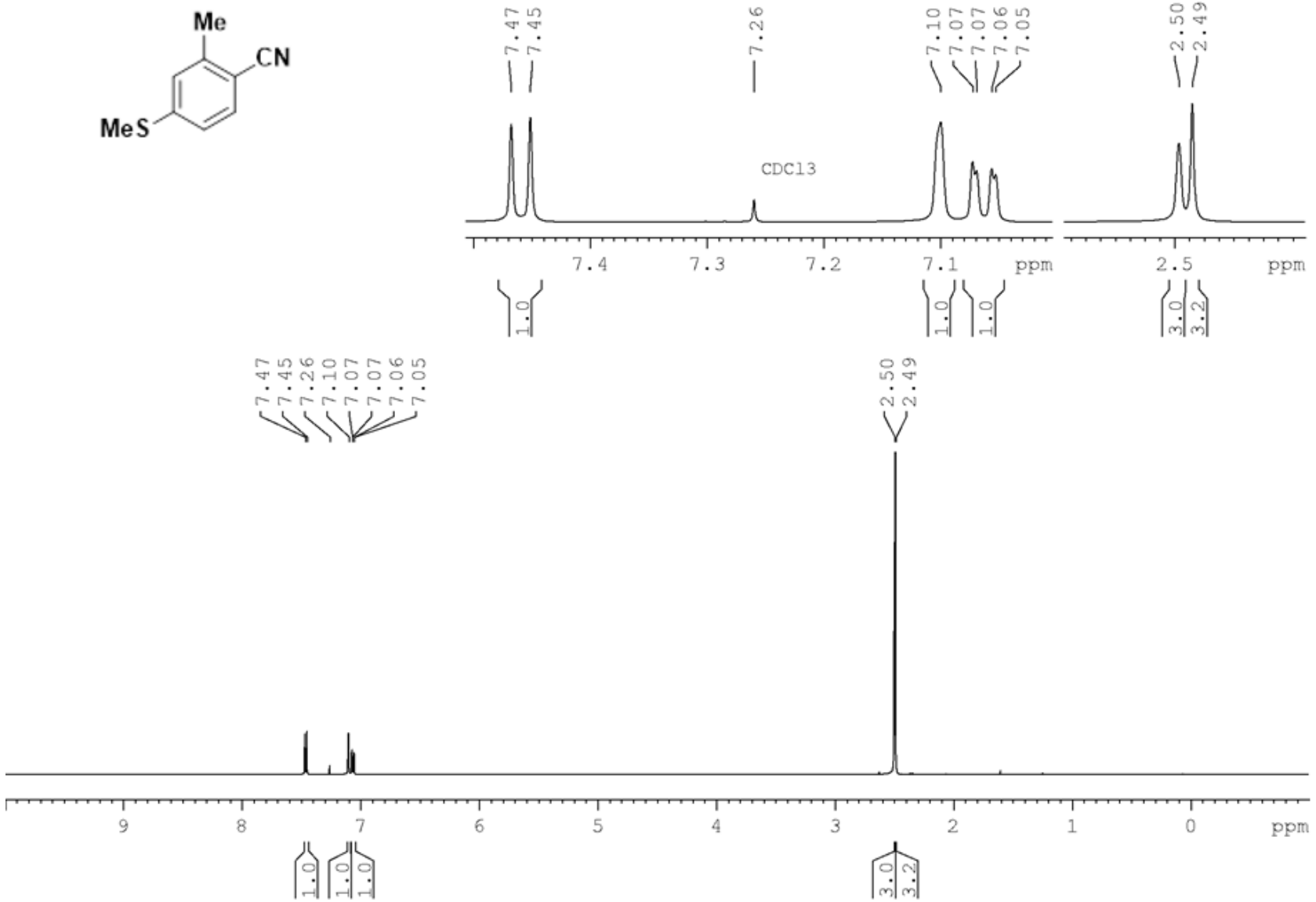


Figure S118. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S3**

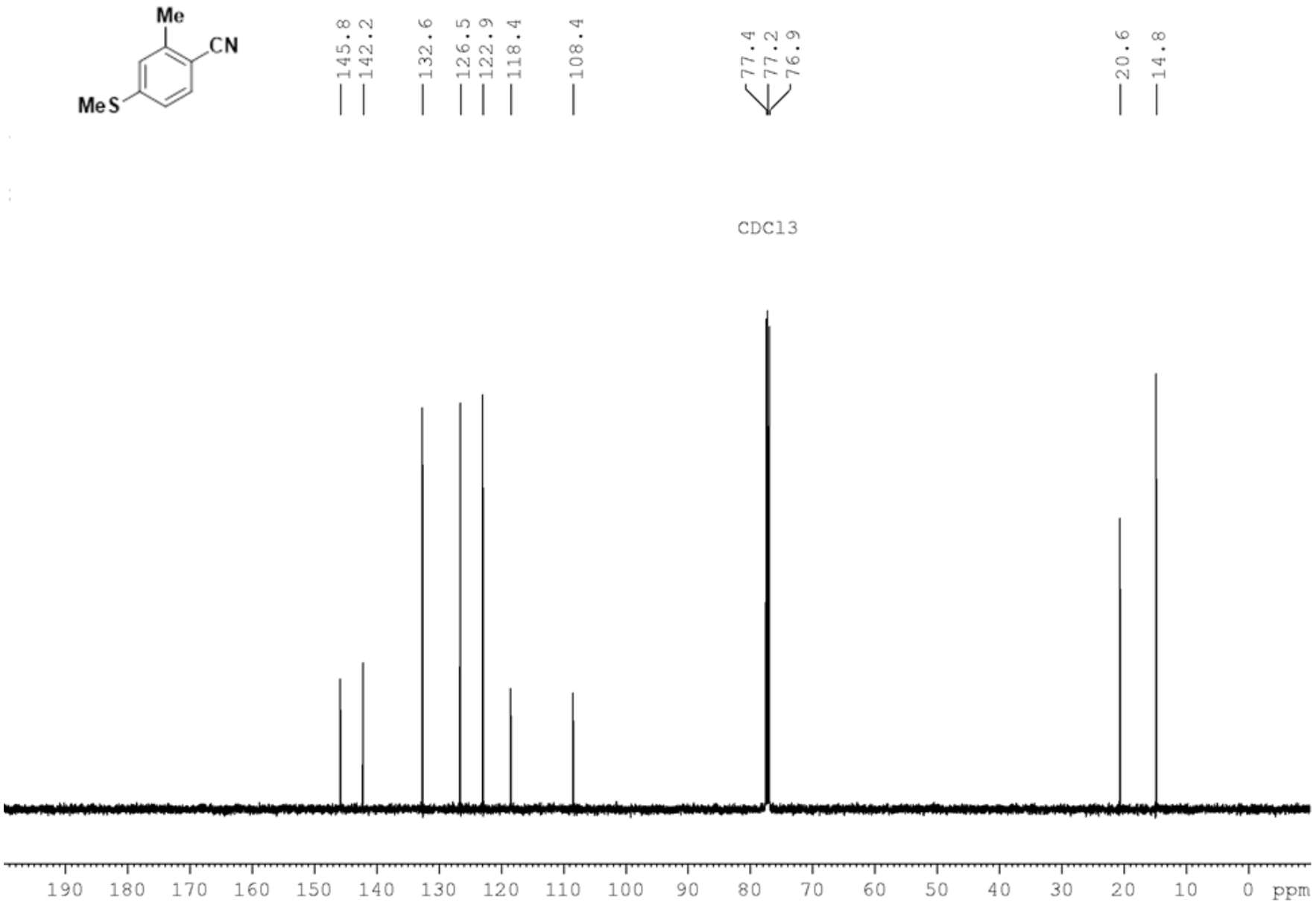


Figure S119. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S3**

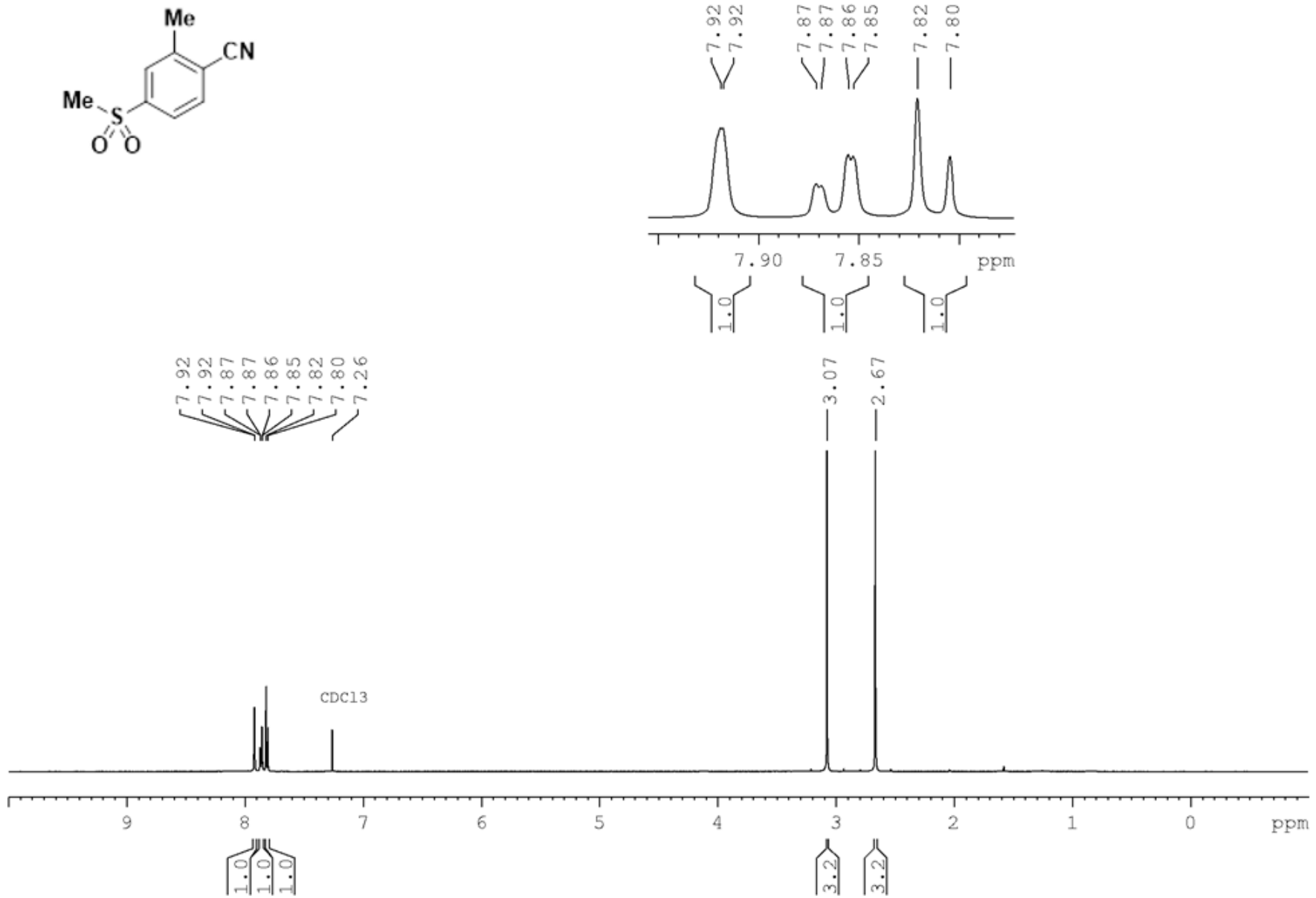


Figure S120. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S4**

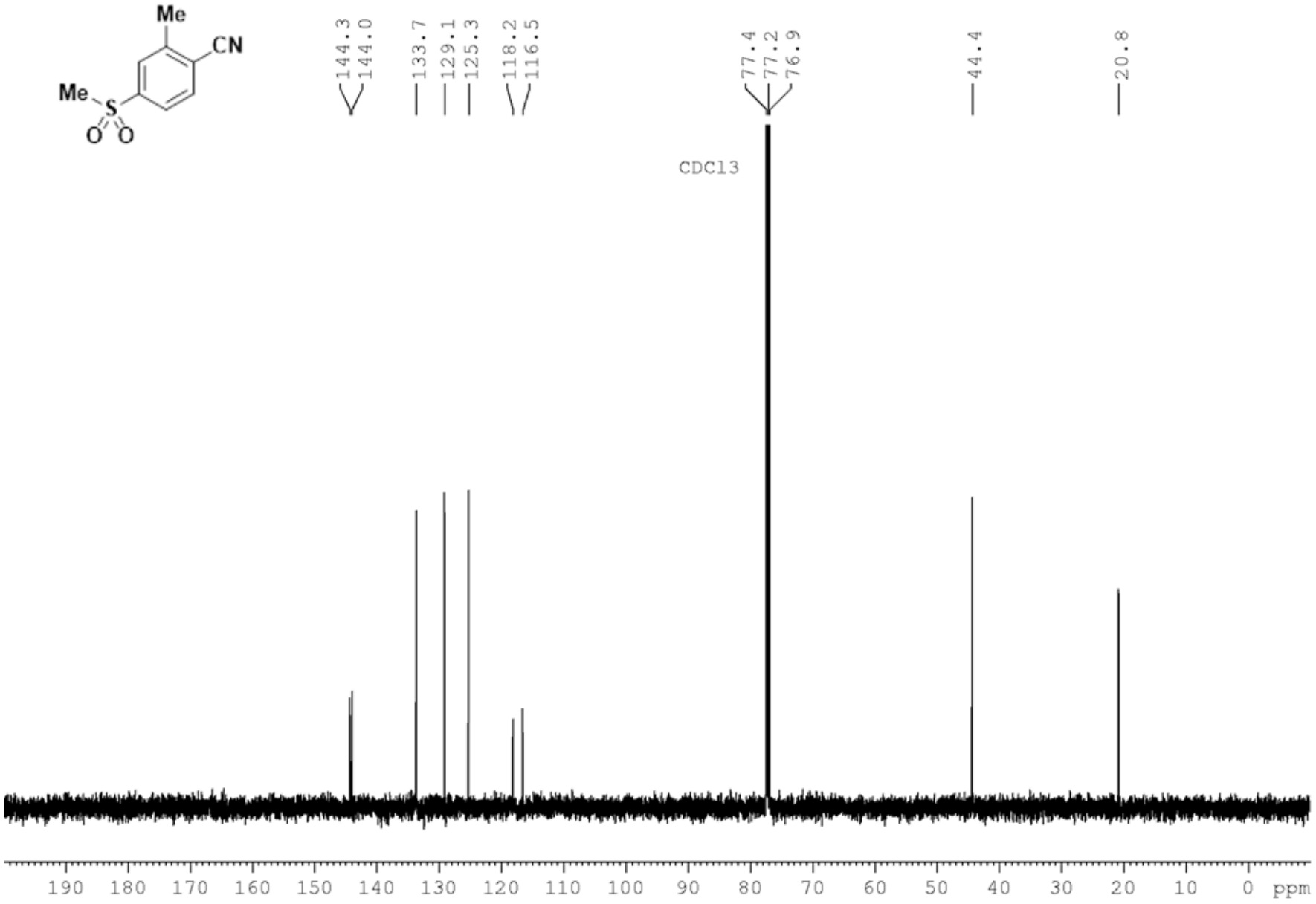


Figure S121. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S4**

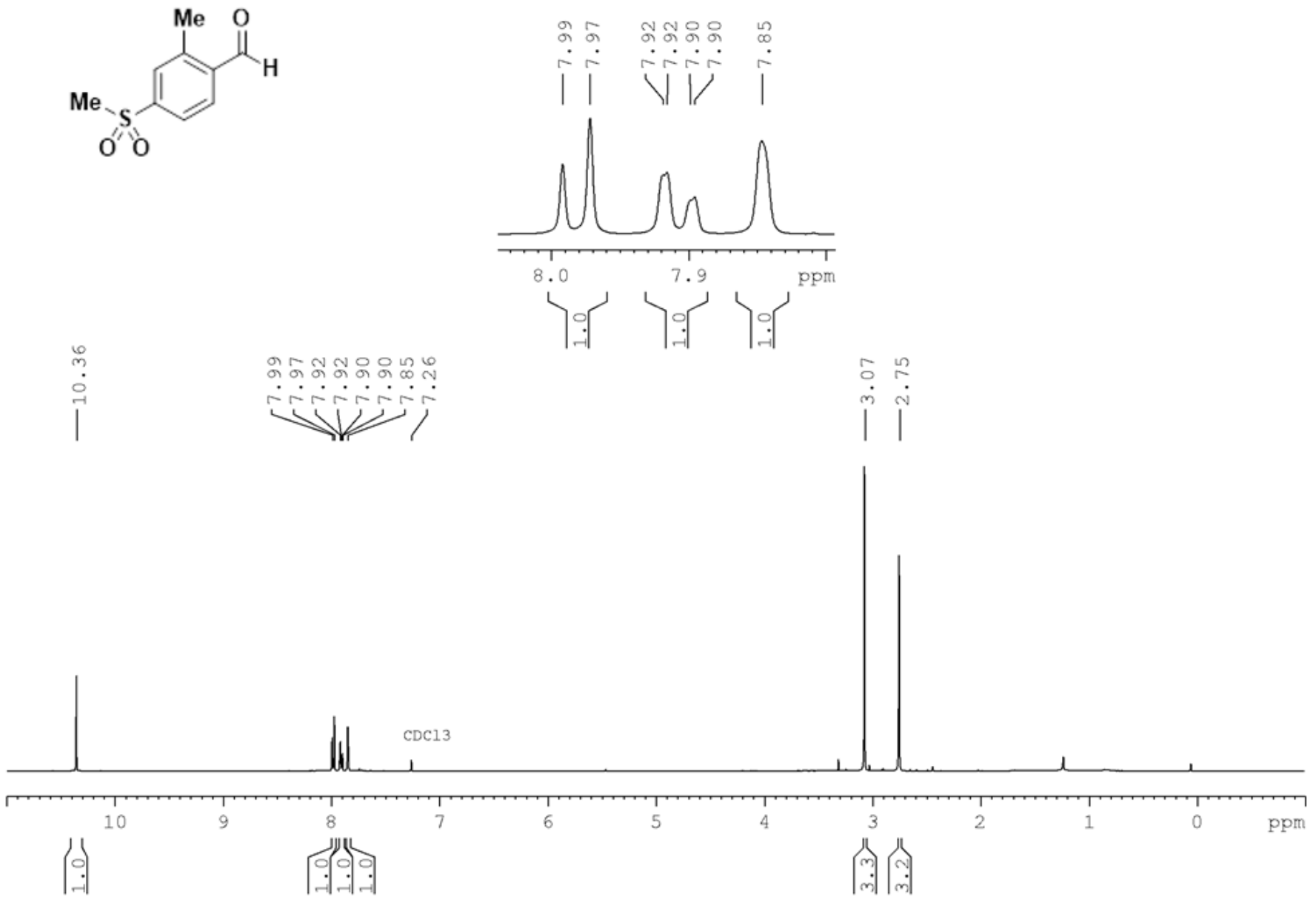


Figure S122. ^{1}H NMR Spectra ($CDCl_3$, 400 MHz) of **S5**

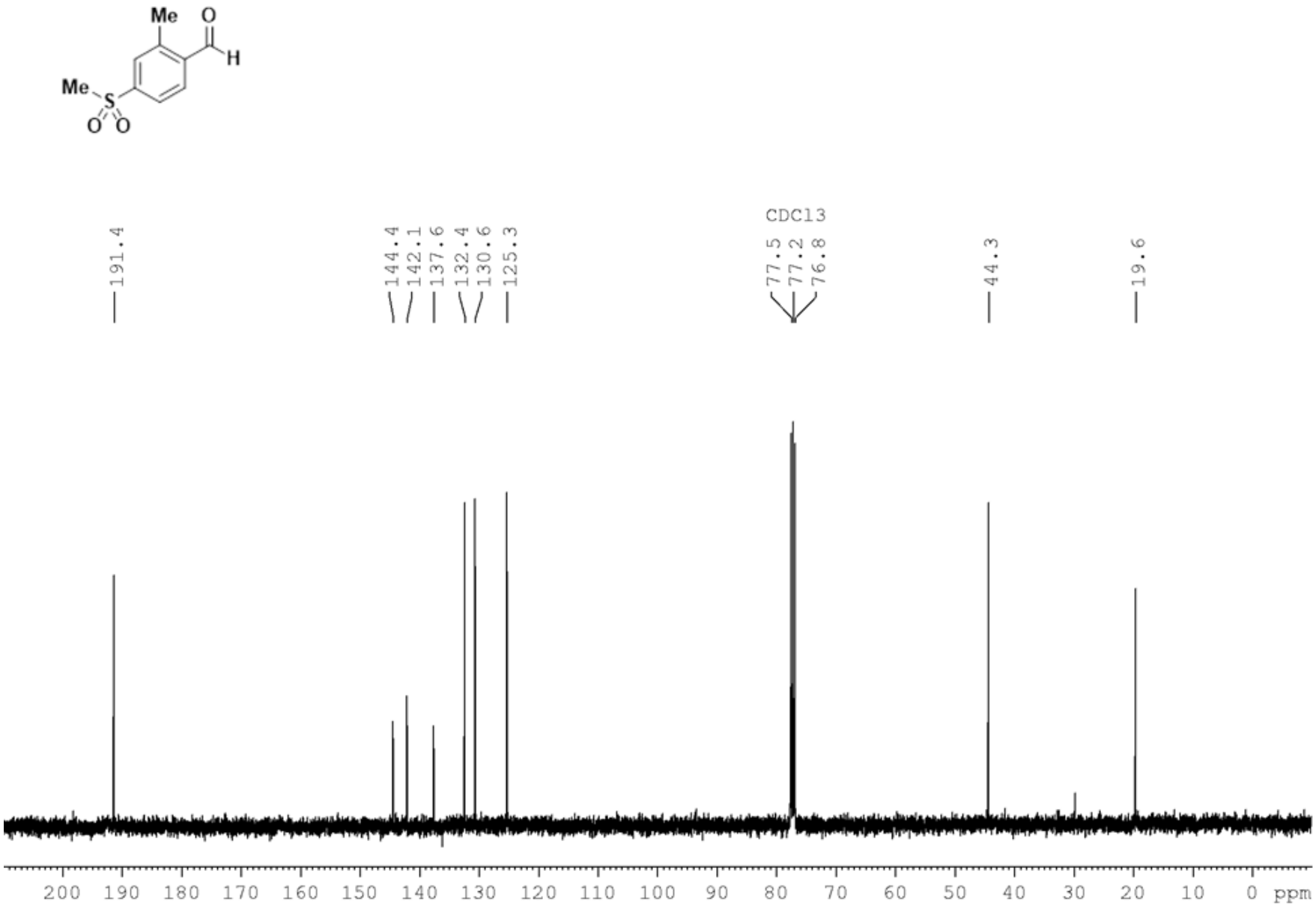


Figure S123. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 101 MHz) of **S5**

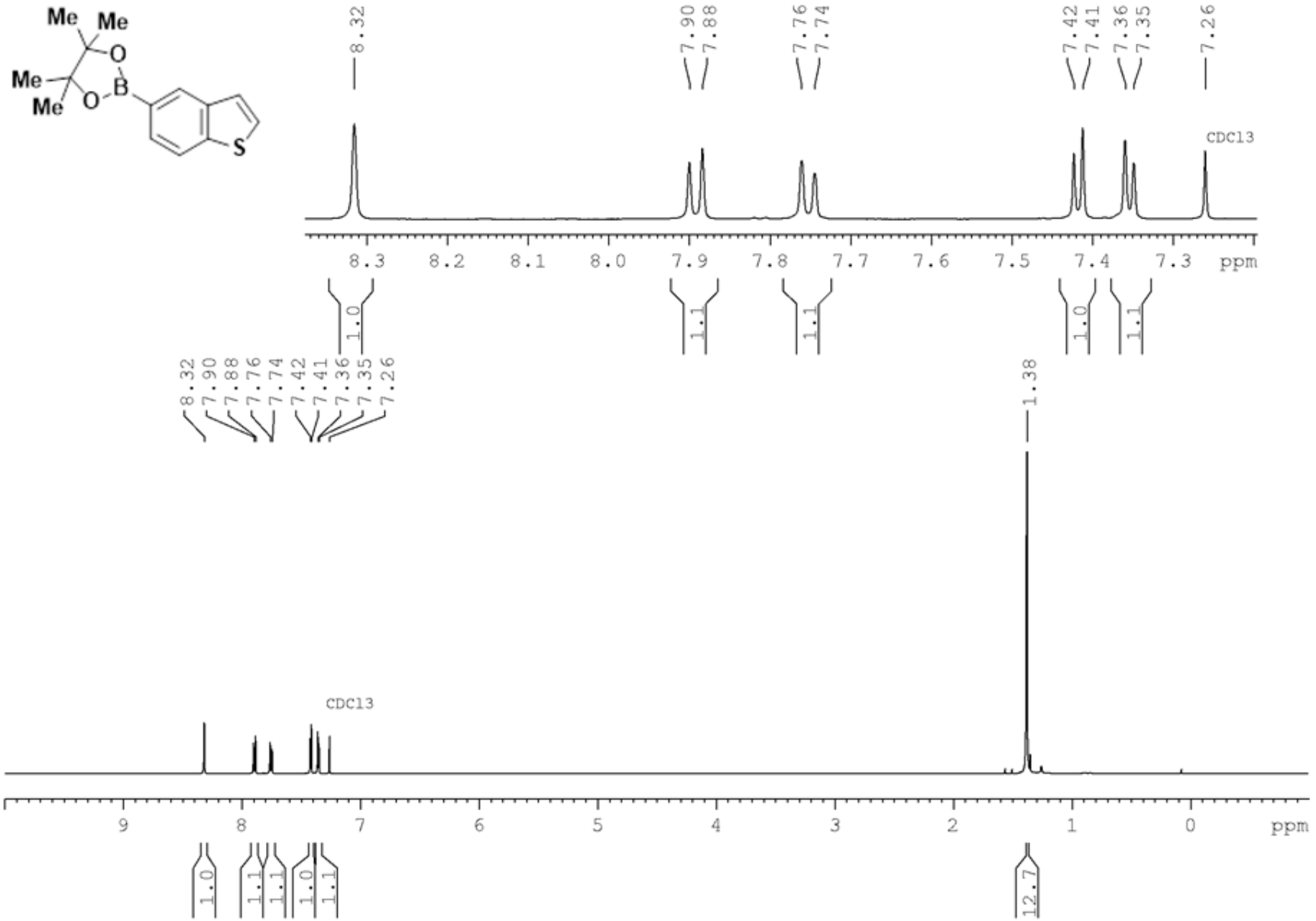


Figure S124. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S6**

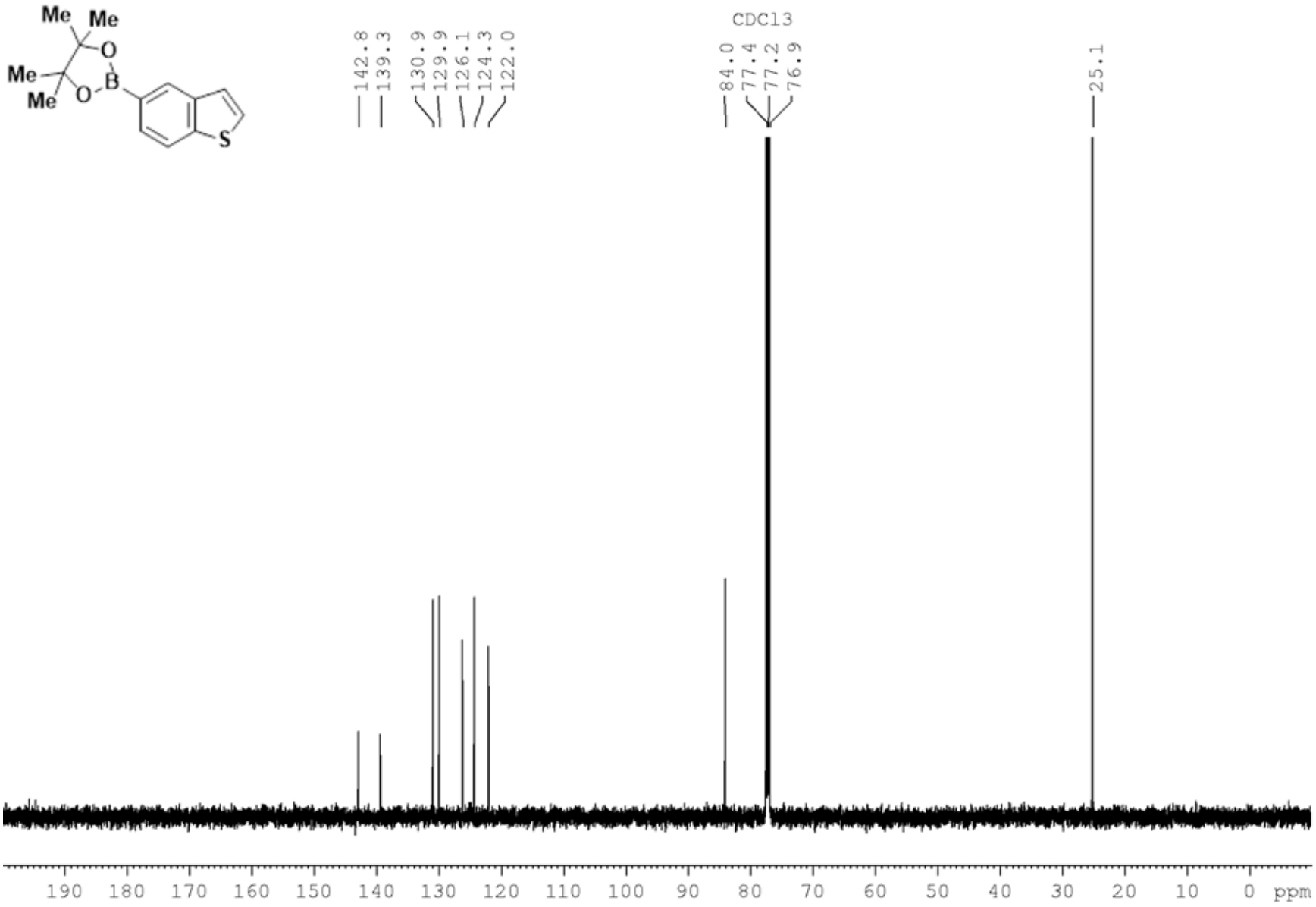


Figure S125. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S6**

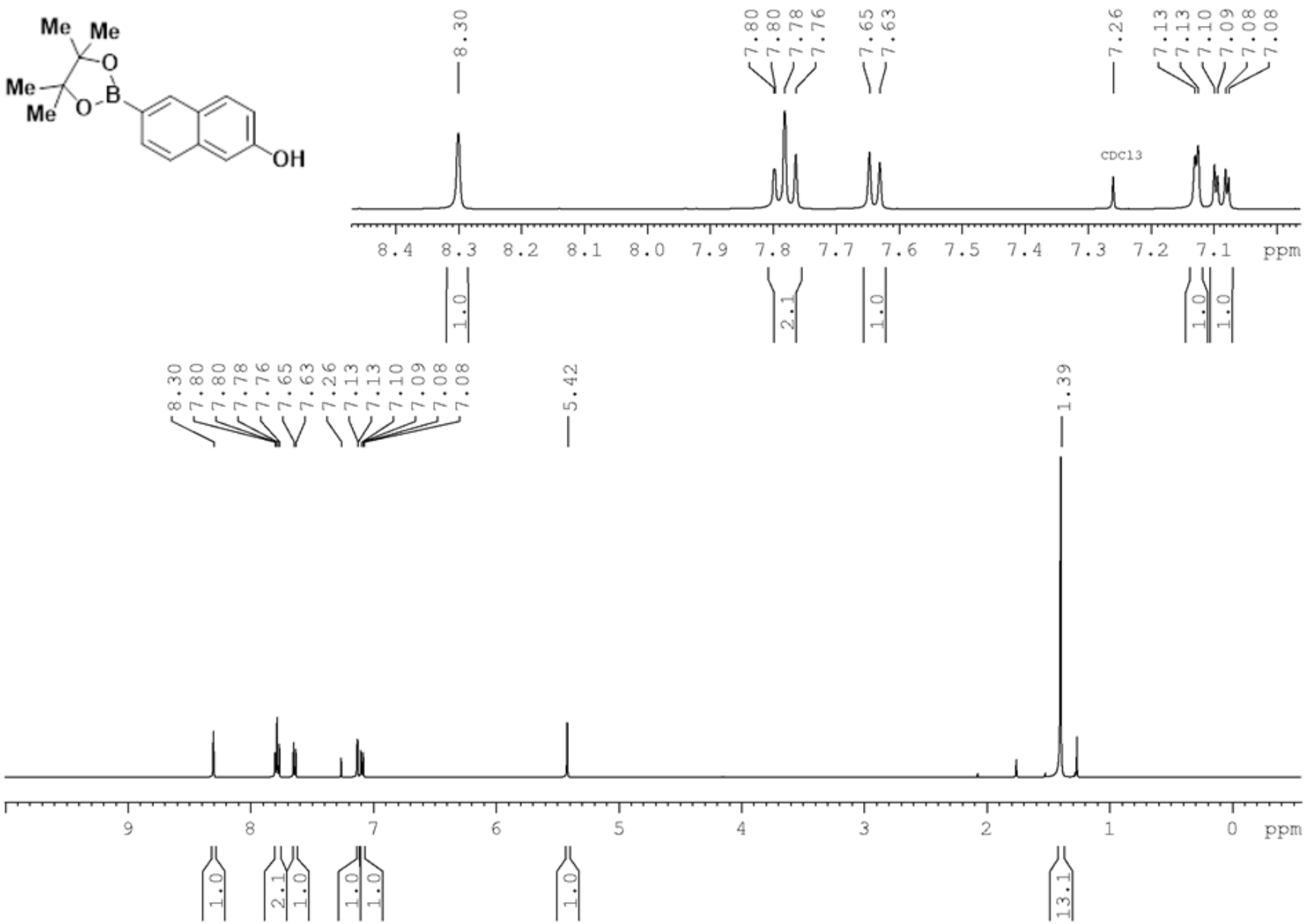


Figure S126. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S7**

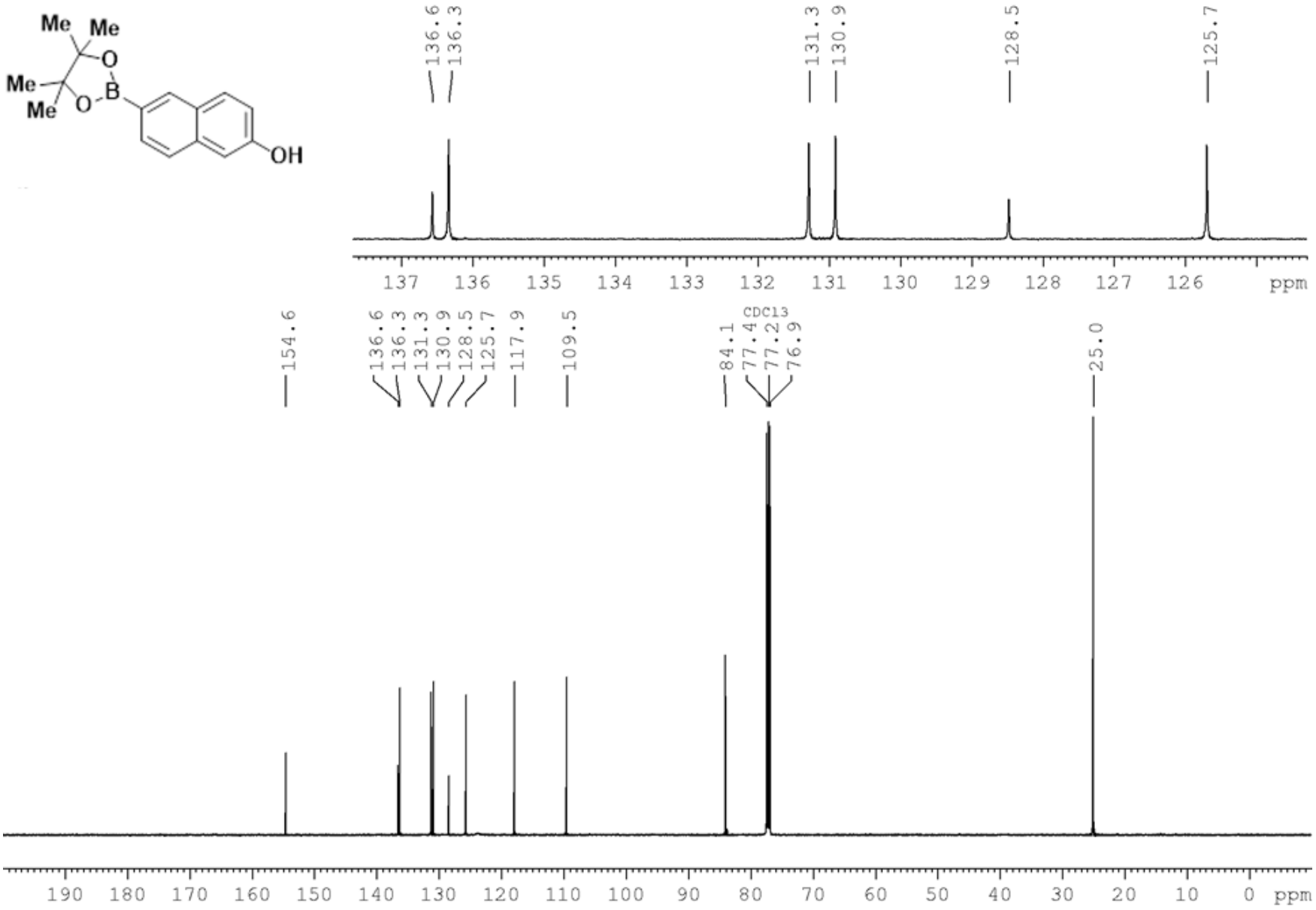


Figure S127. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S7**

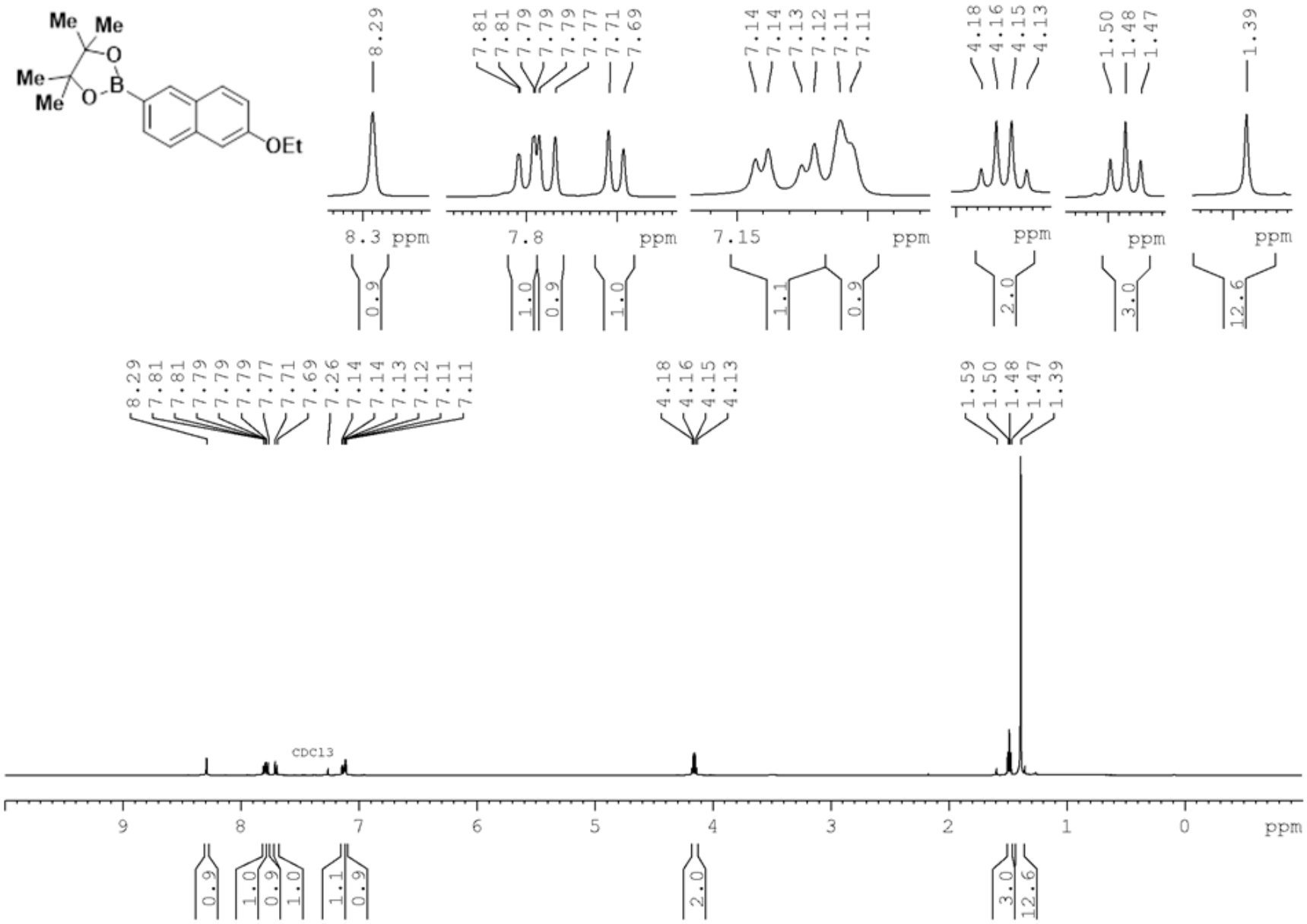


Figure S128. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S9**

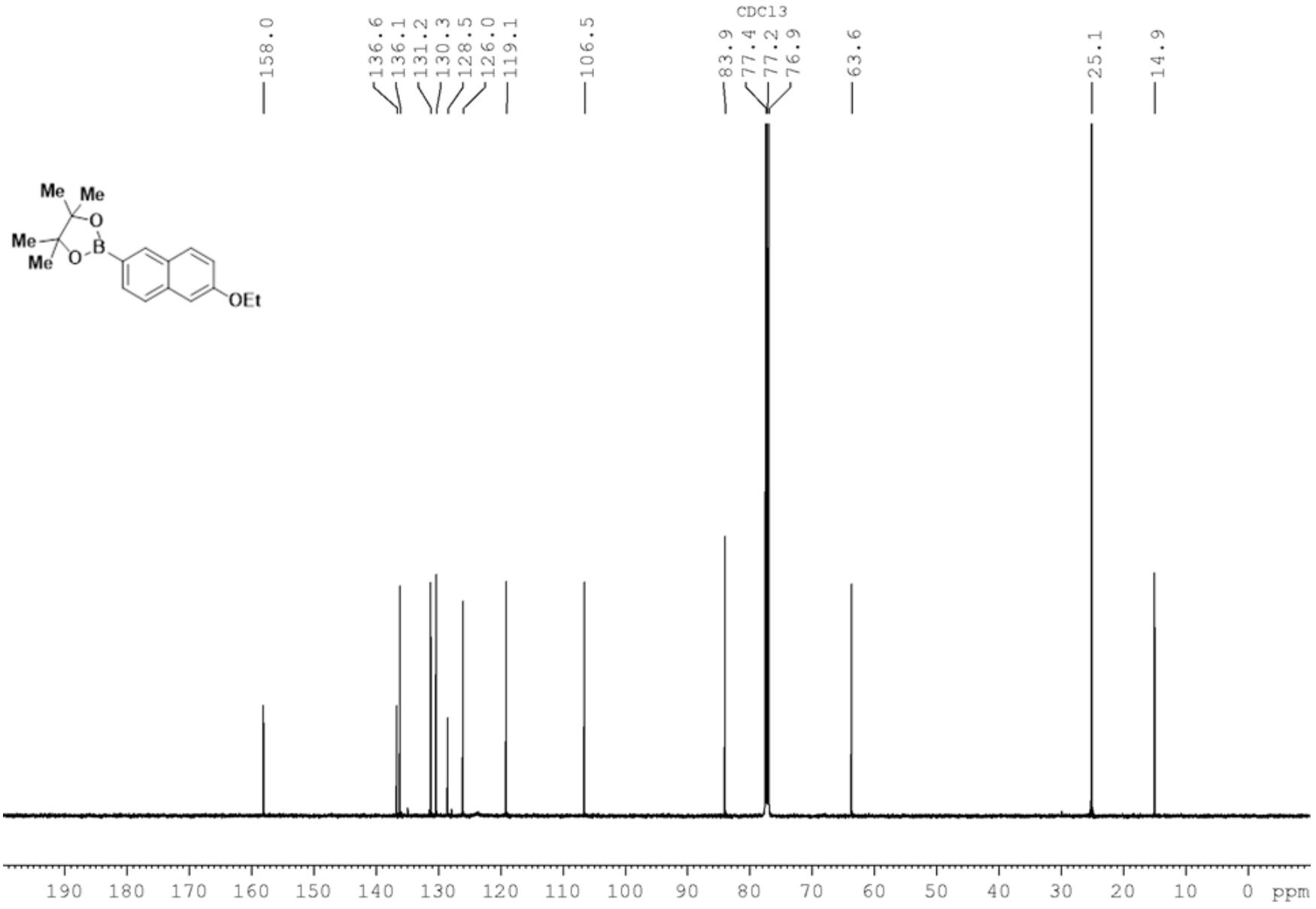


Figure S129. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S9**

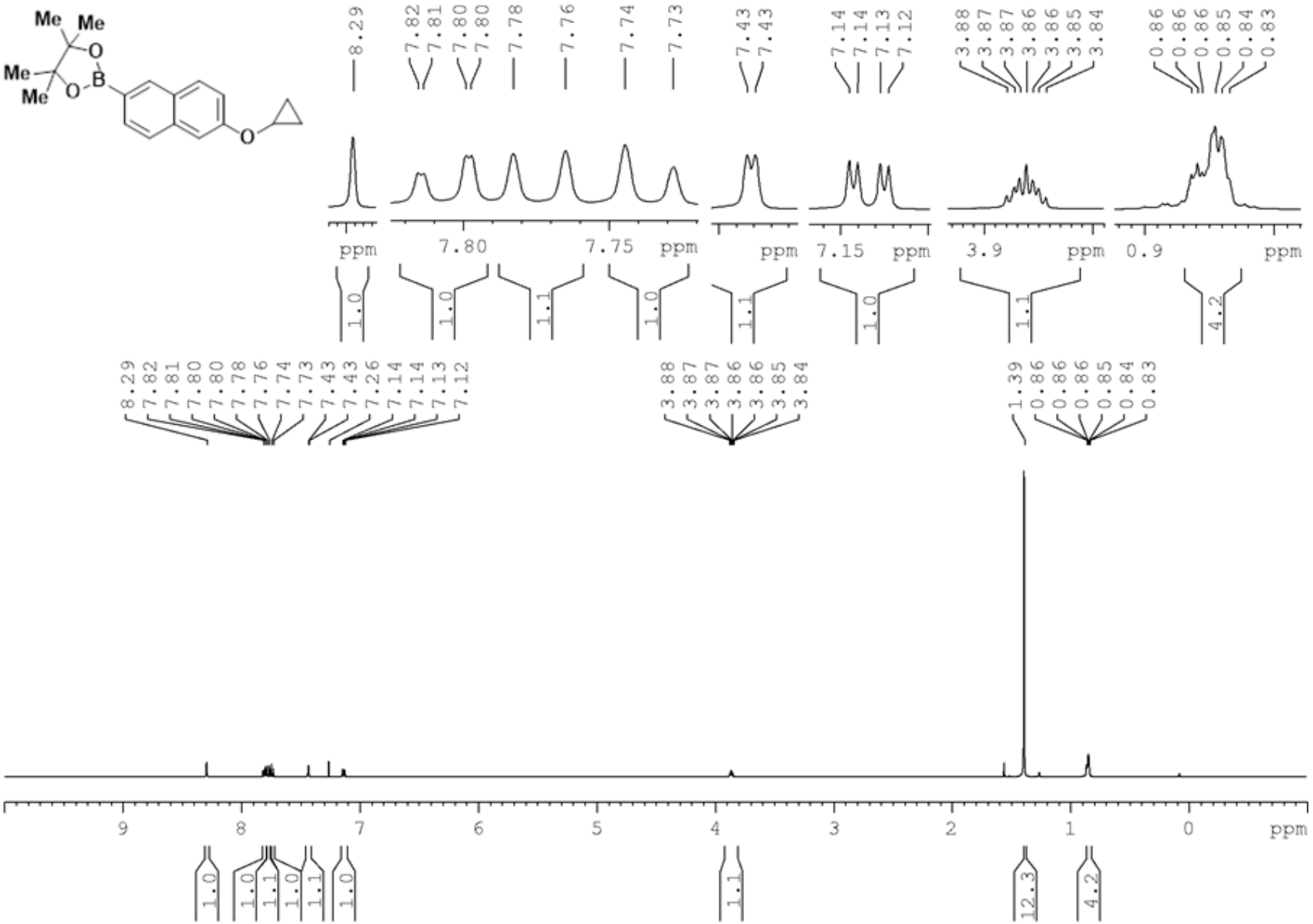


Figure S130. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S11**

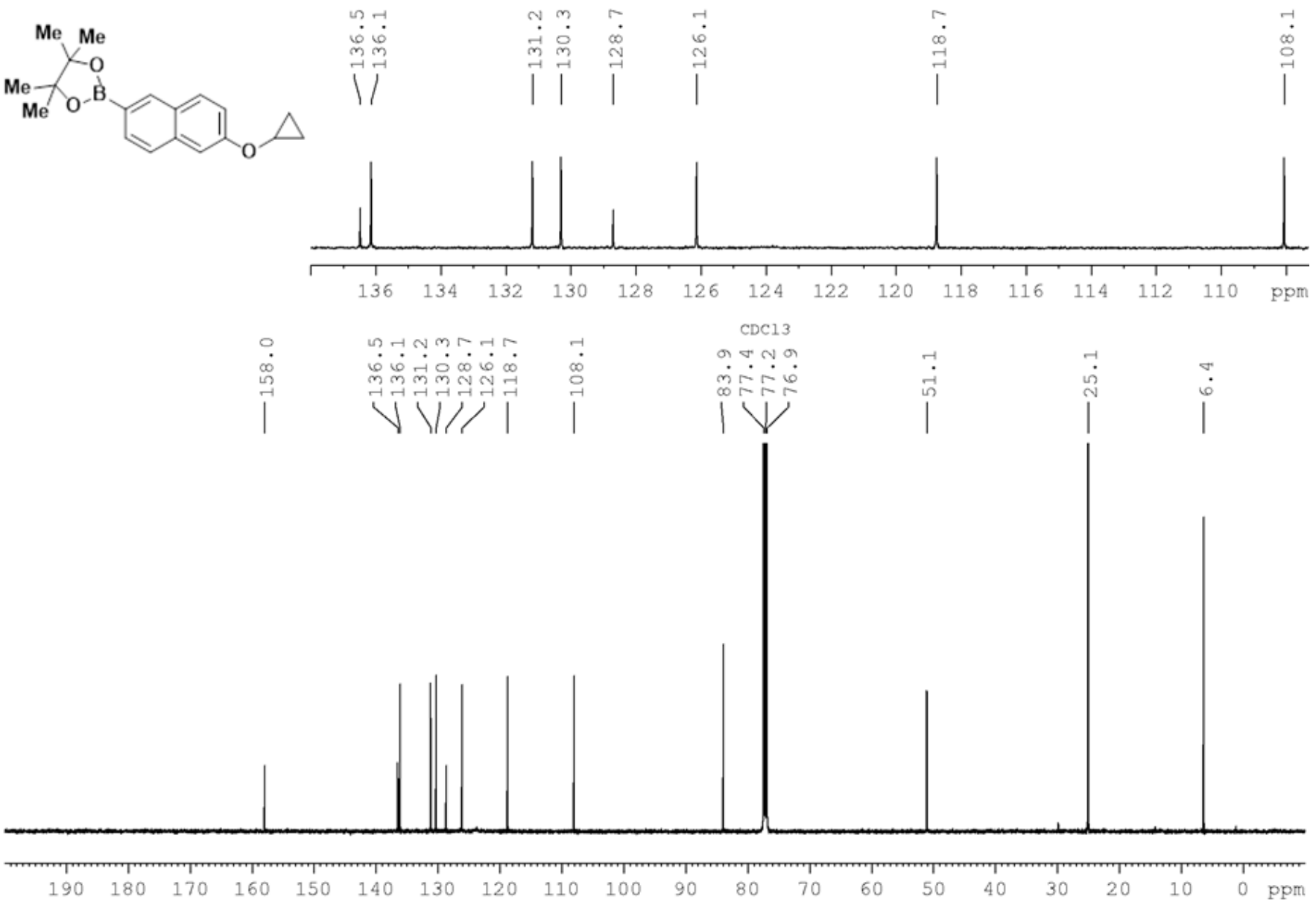


Figure S131. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S11**

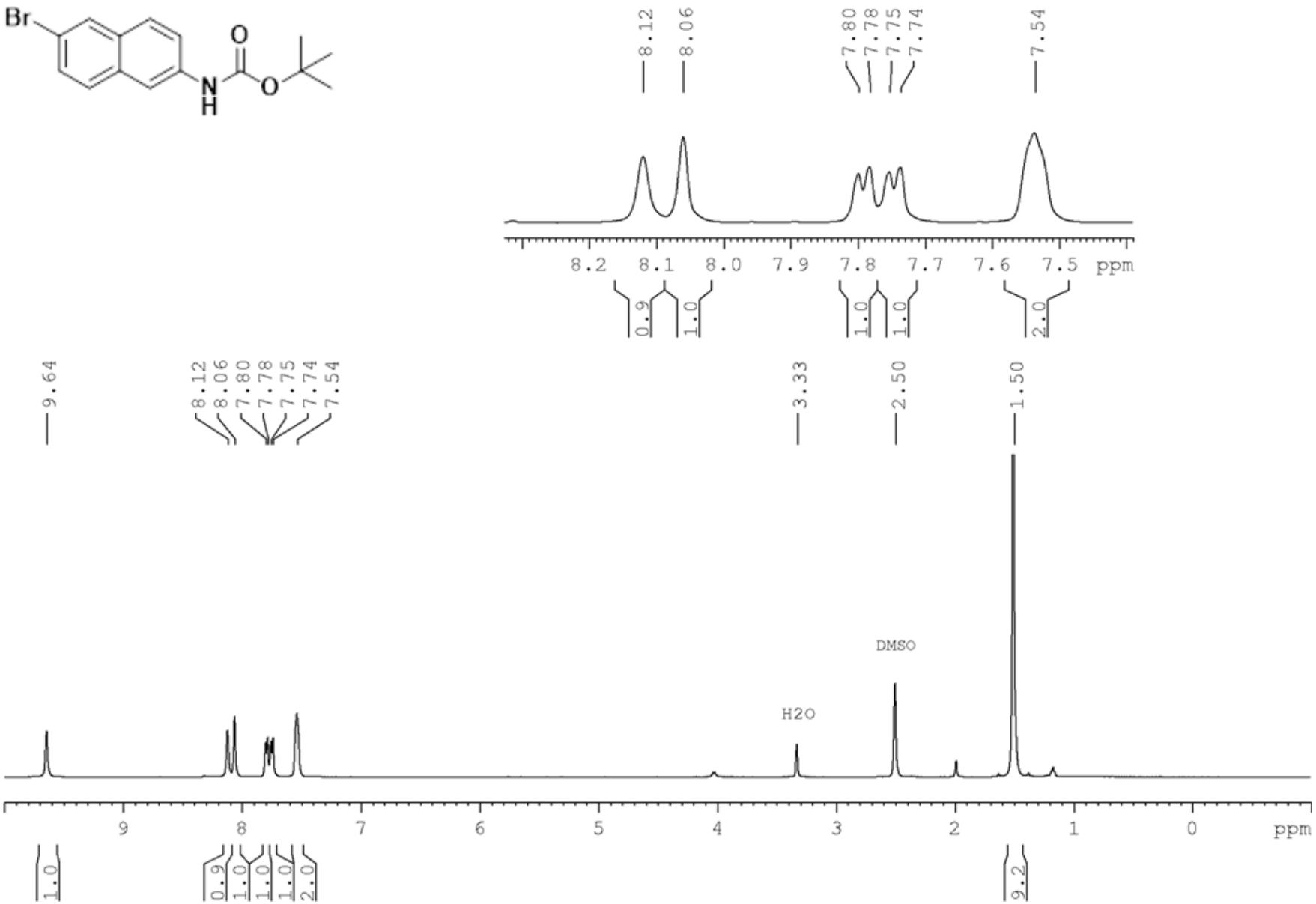


Figure S132. ^{1}H NMR Spectra (DMSO-d_6, 500 MHz) of **S12**

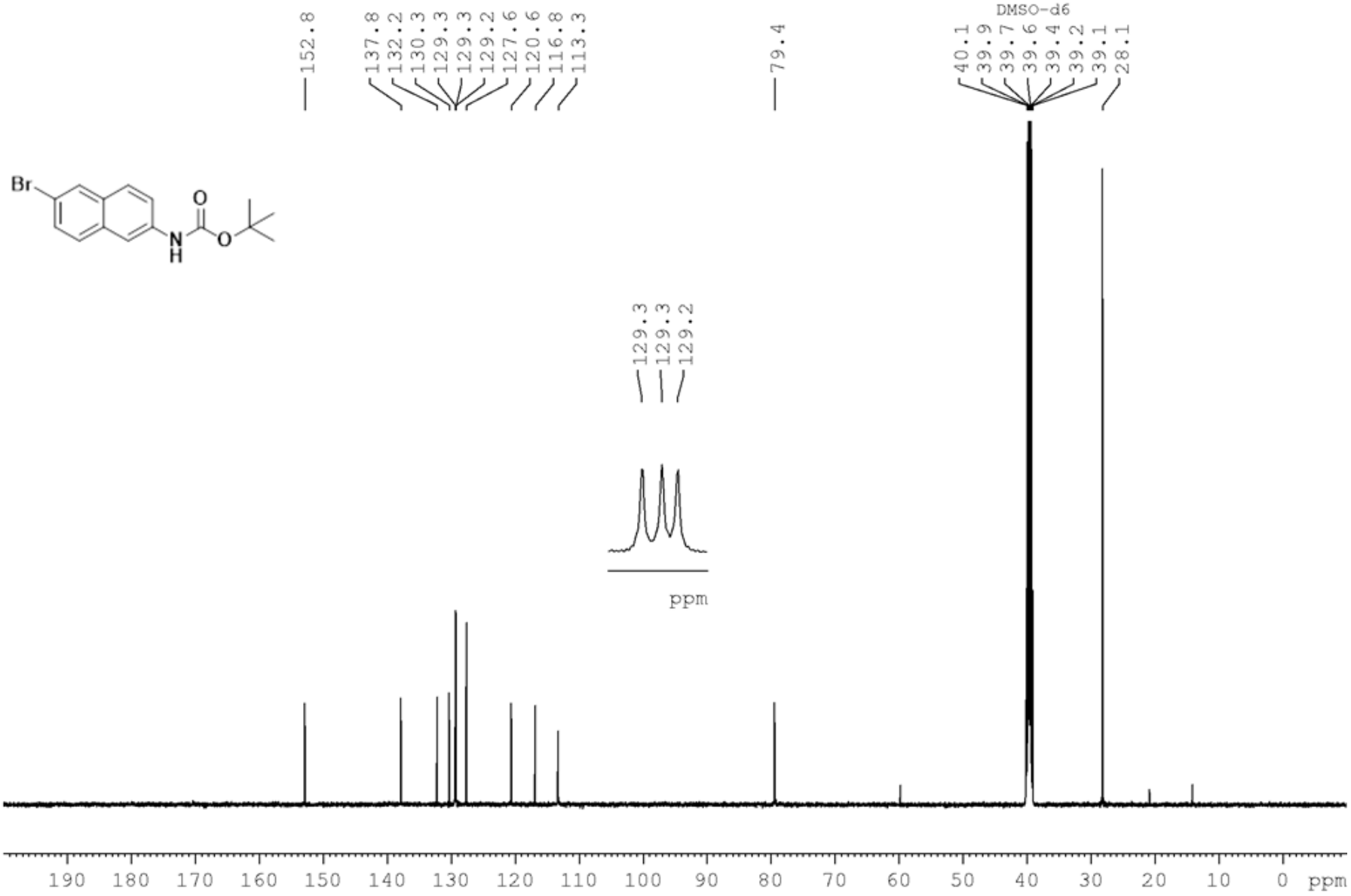


Figure S133. $^{13}C\{^{1}H\}$ NMR Spectra (DMSO-d_6, 126 MHz) of **S12**

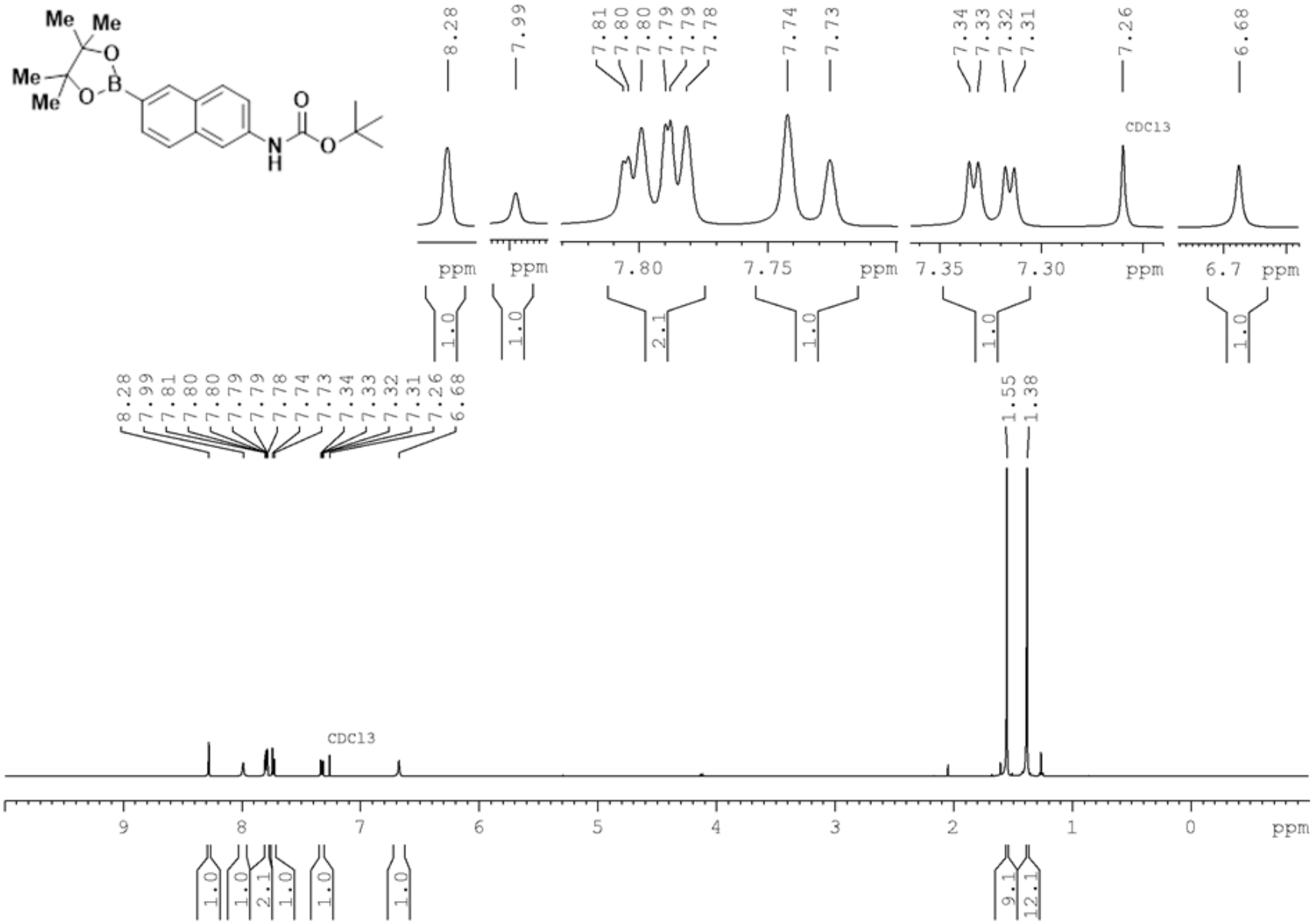


Figure S134. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S13**

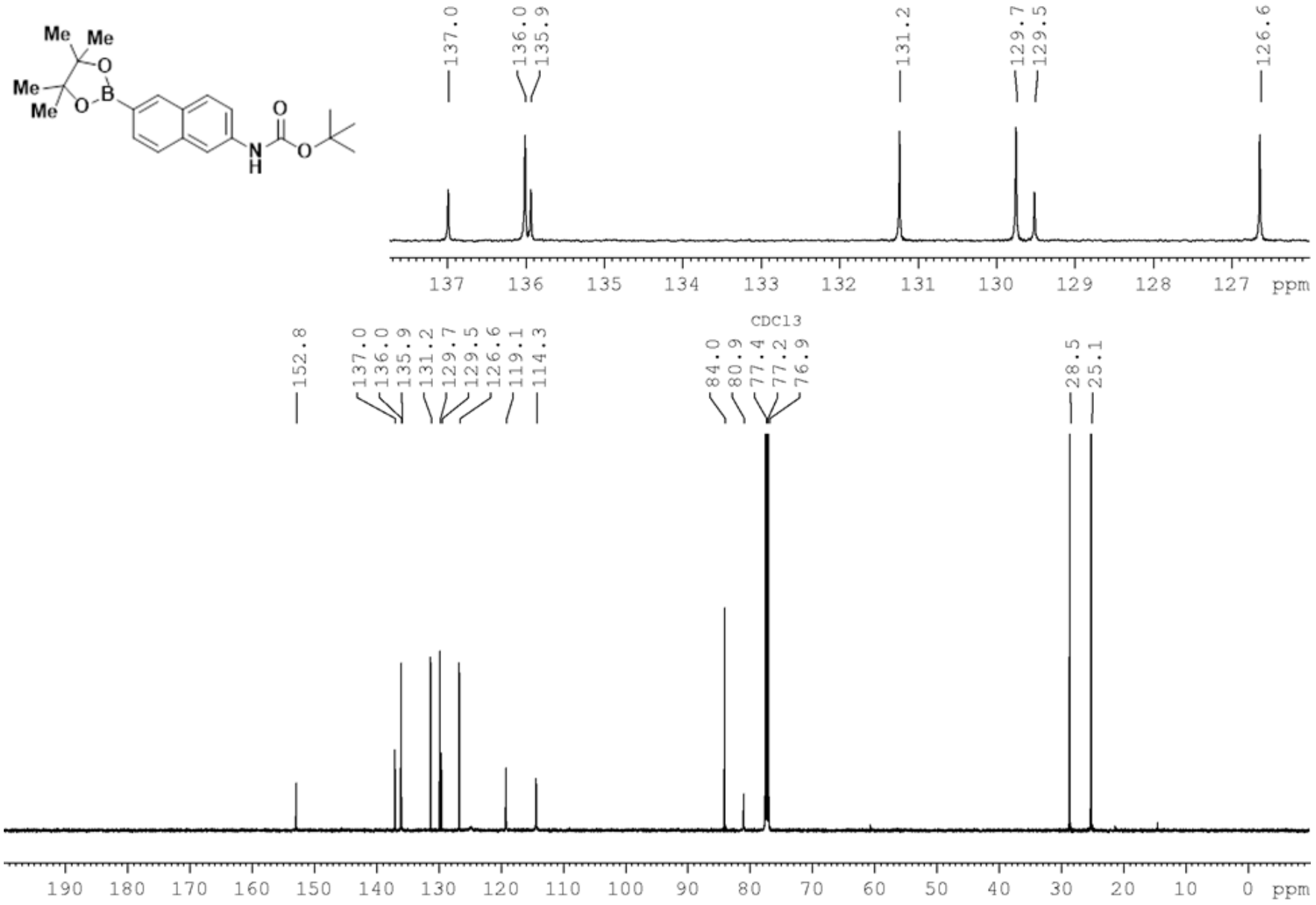


Figure S135. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S13**

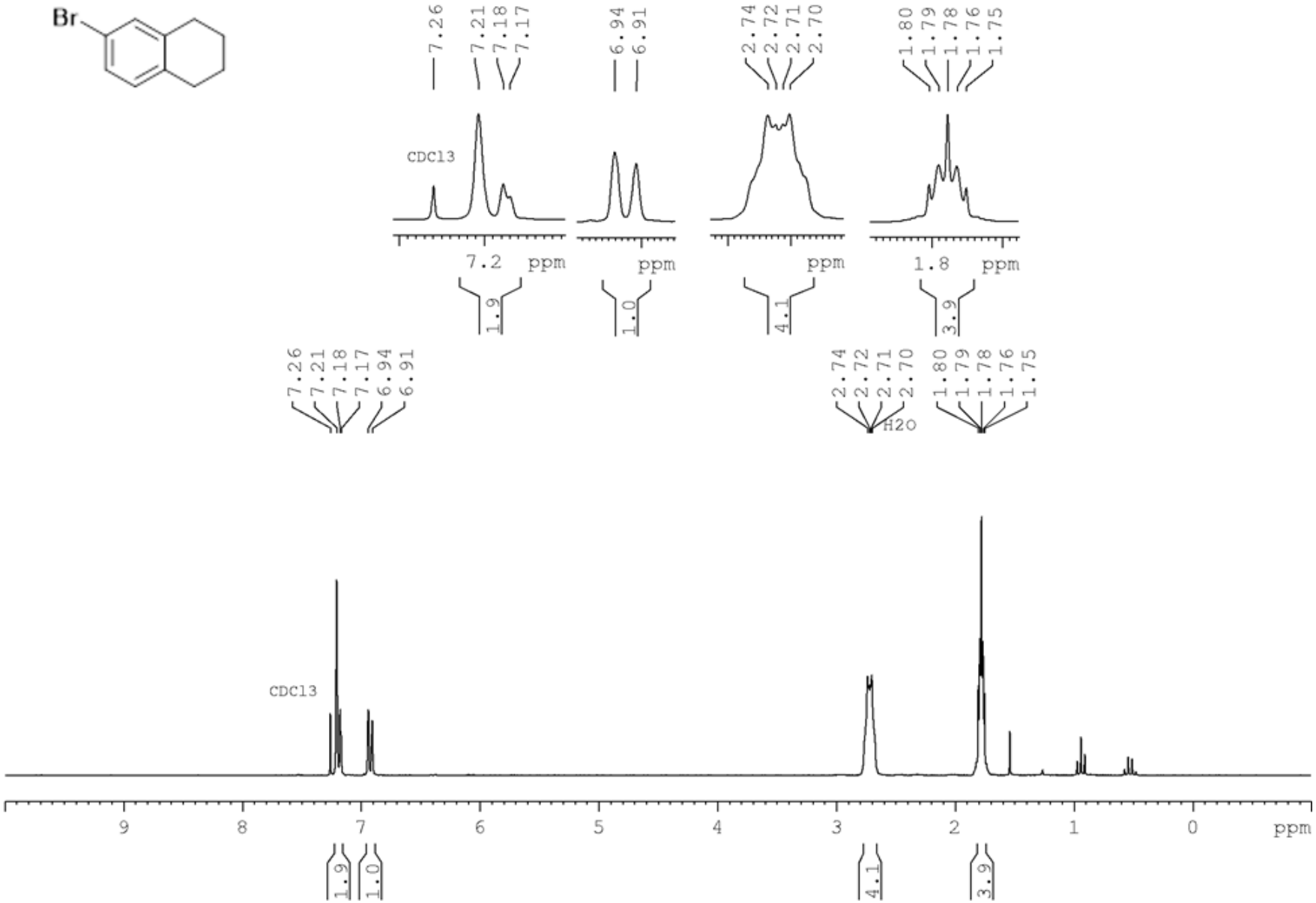


Figure S136. ^{1}H NMR Spectra ($CDCl_3$, 250 MHz) of **S14**

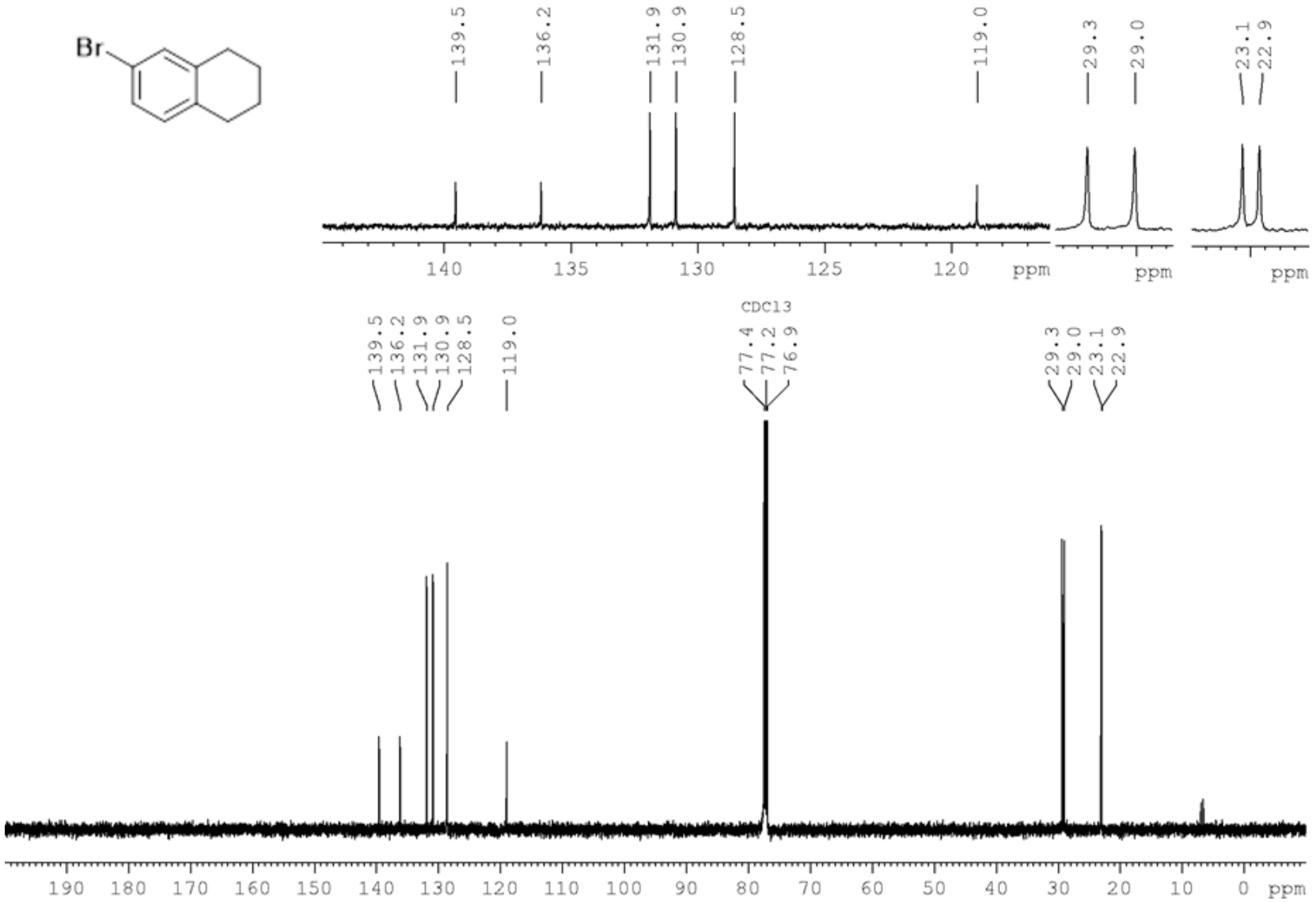


Figure S137. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S14**

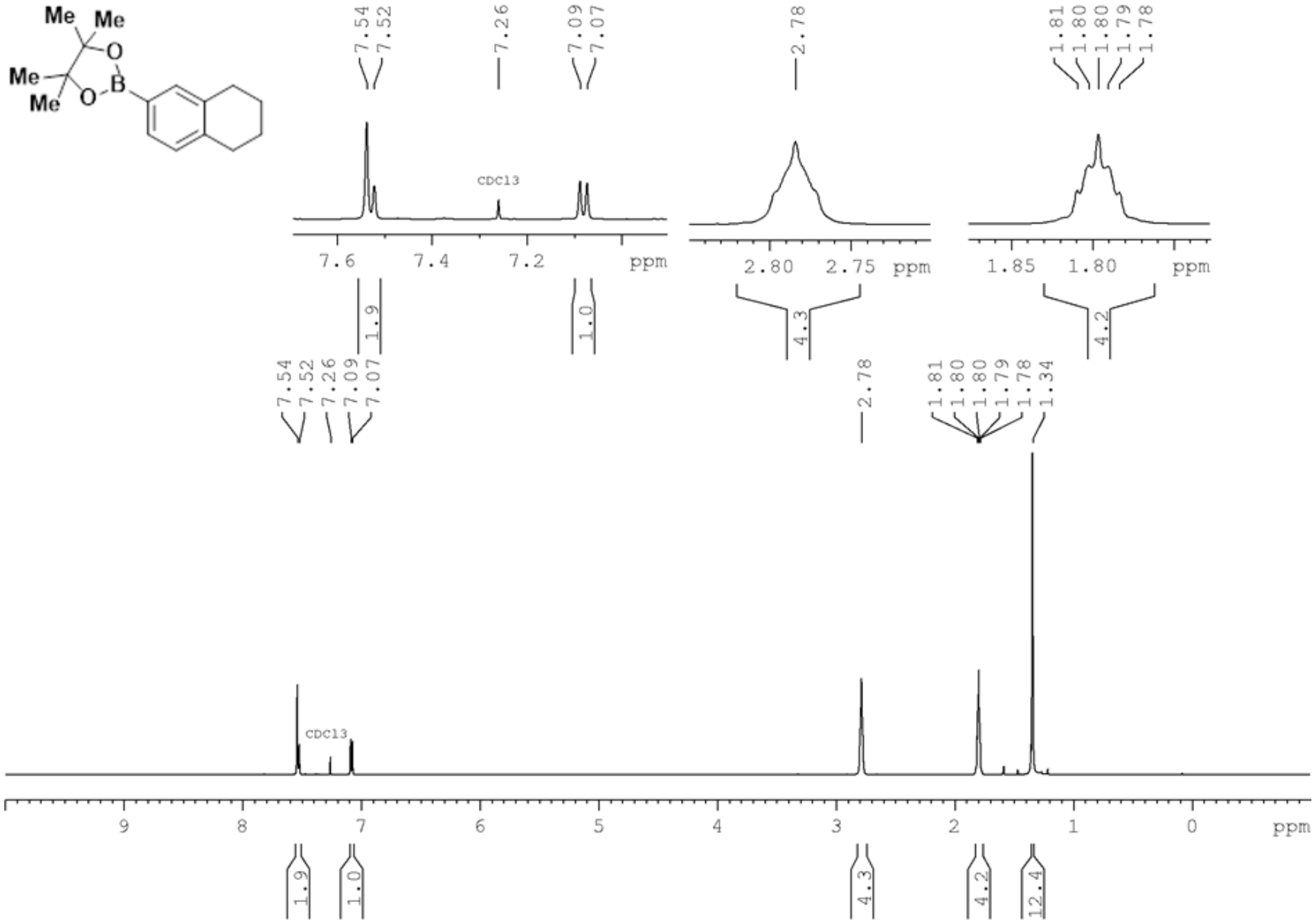


Figure S138. ^{1}H NMR Spectra ($CDCl_3$, 500 MHz) of **S15**

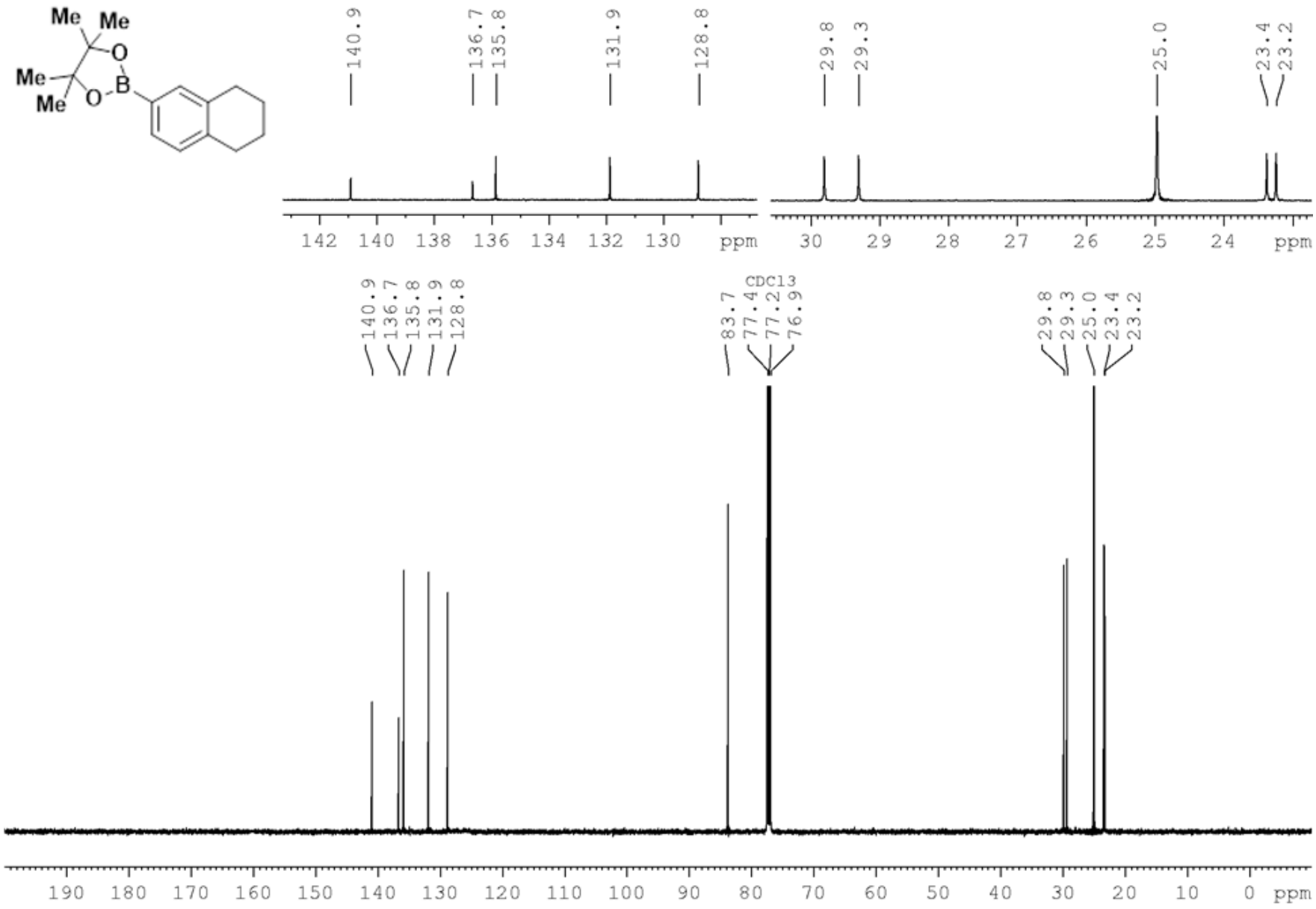


Figure S139. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 126 MHz) of **S15**

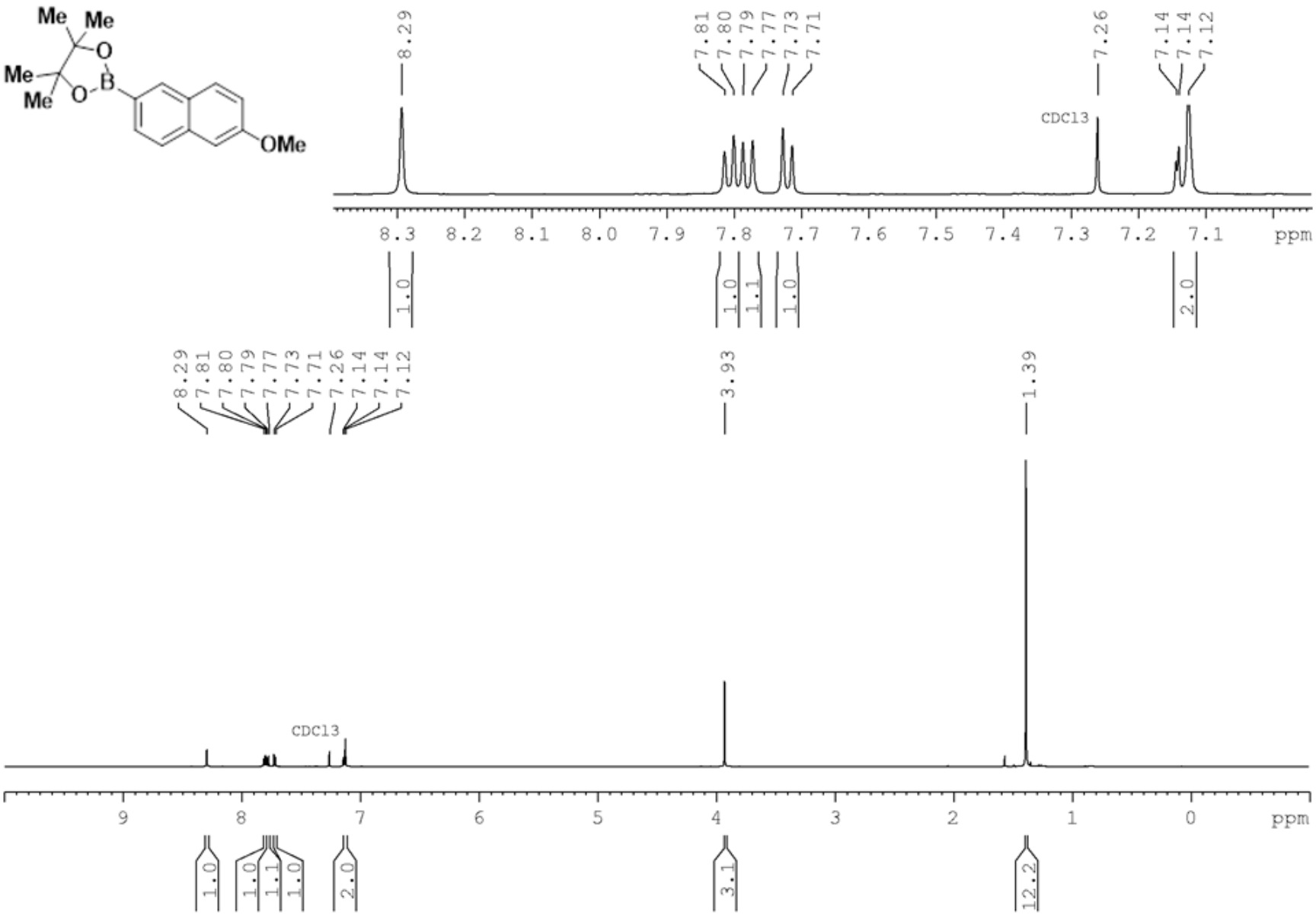


Figure S140. ^{1}H NMR Spectra ($CDCl_3$, 600 MHz) of **S16**

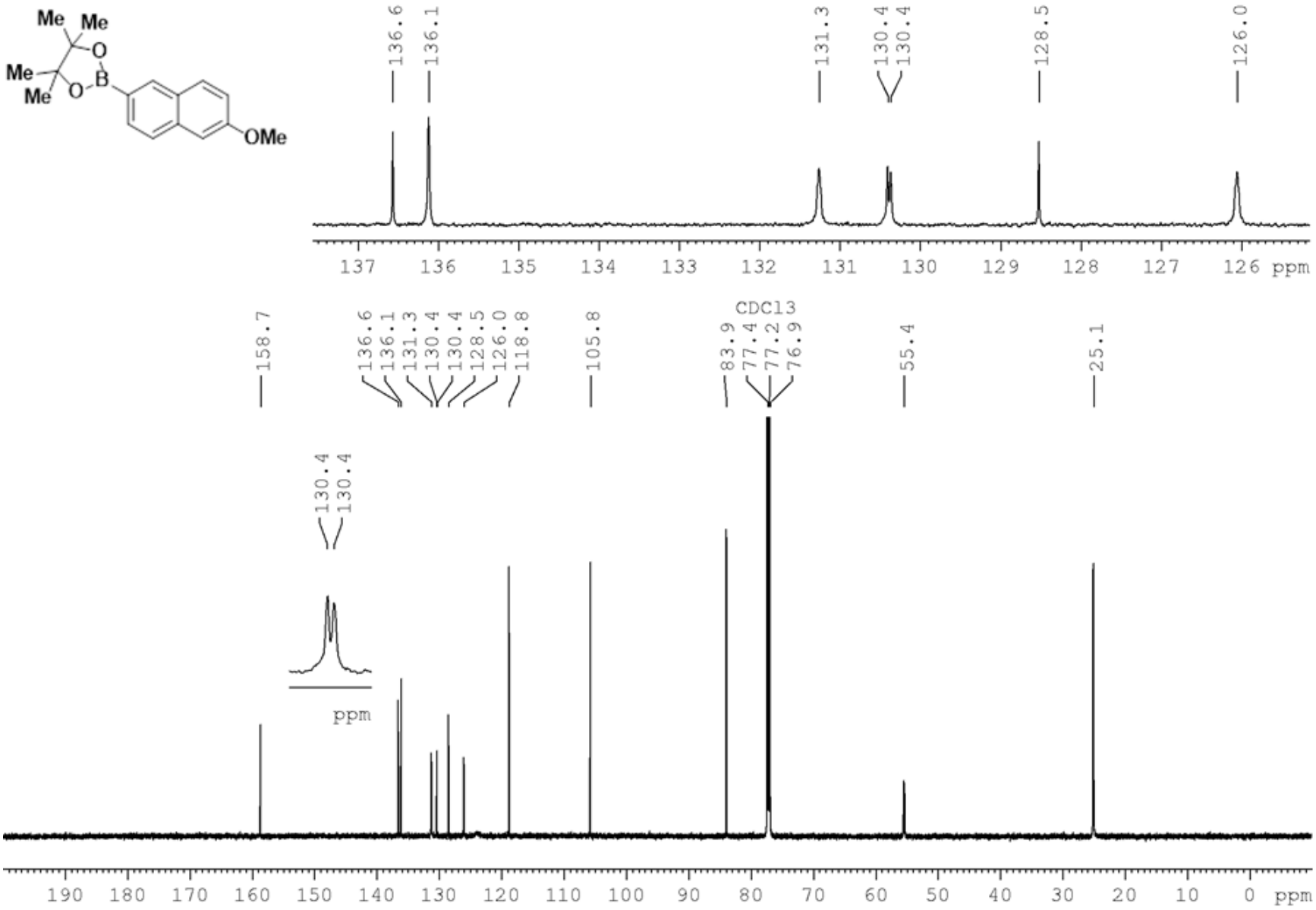


Figure S141. $^{13}C\{^{1}H\}$ NMR Spectra ($CDCl_3$, 151 MHz) of **S16**