Electronic Supporting Information

Article

New charged cholinesterase inhibitors; Design, synthesis and characterization

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Content:

1. NMR spectra

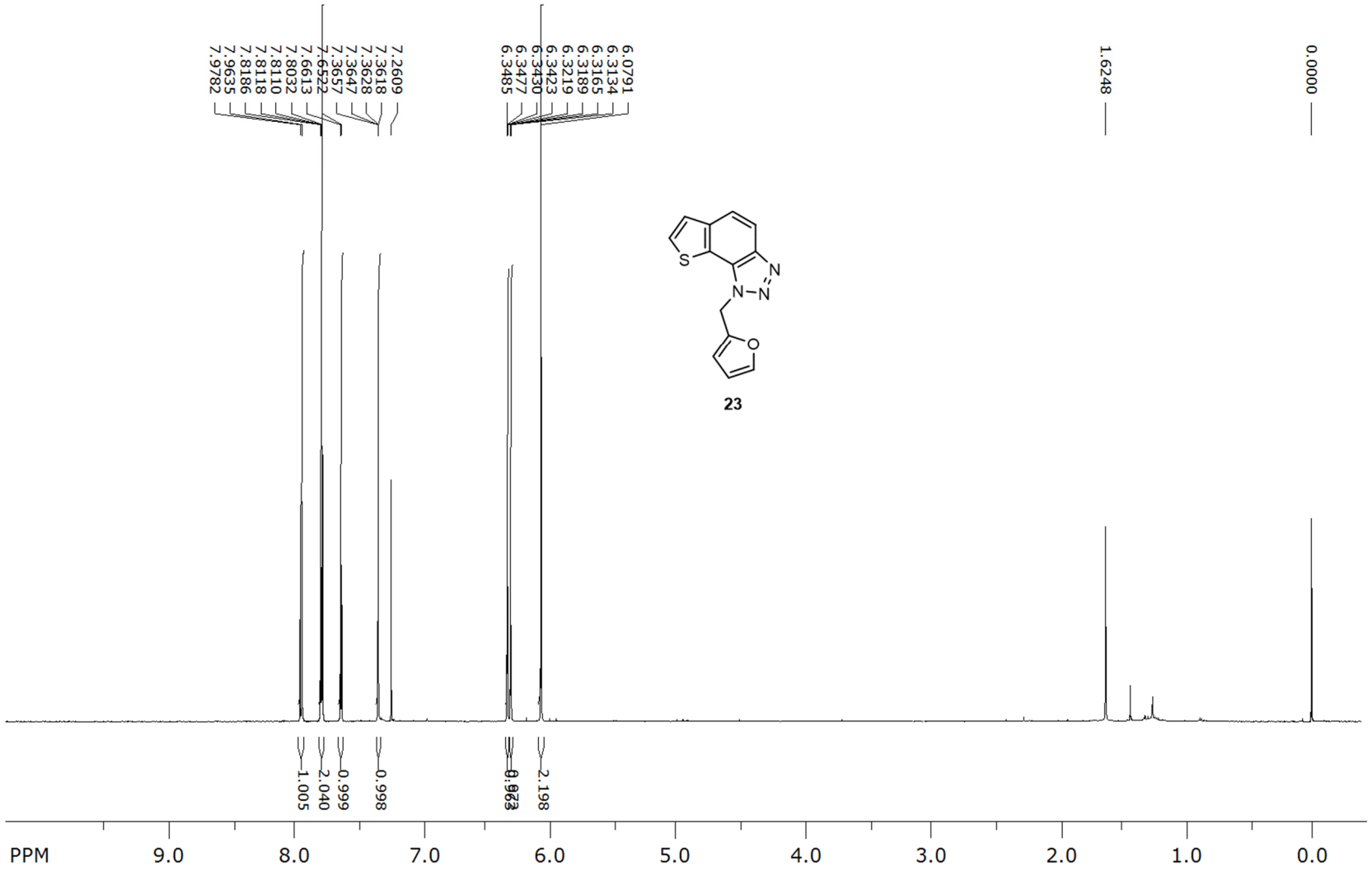


Figure S1. ^{1}H NMR ($CDCl_3$) spectrum of **23**.

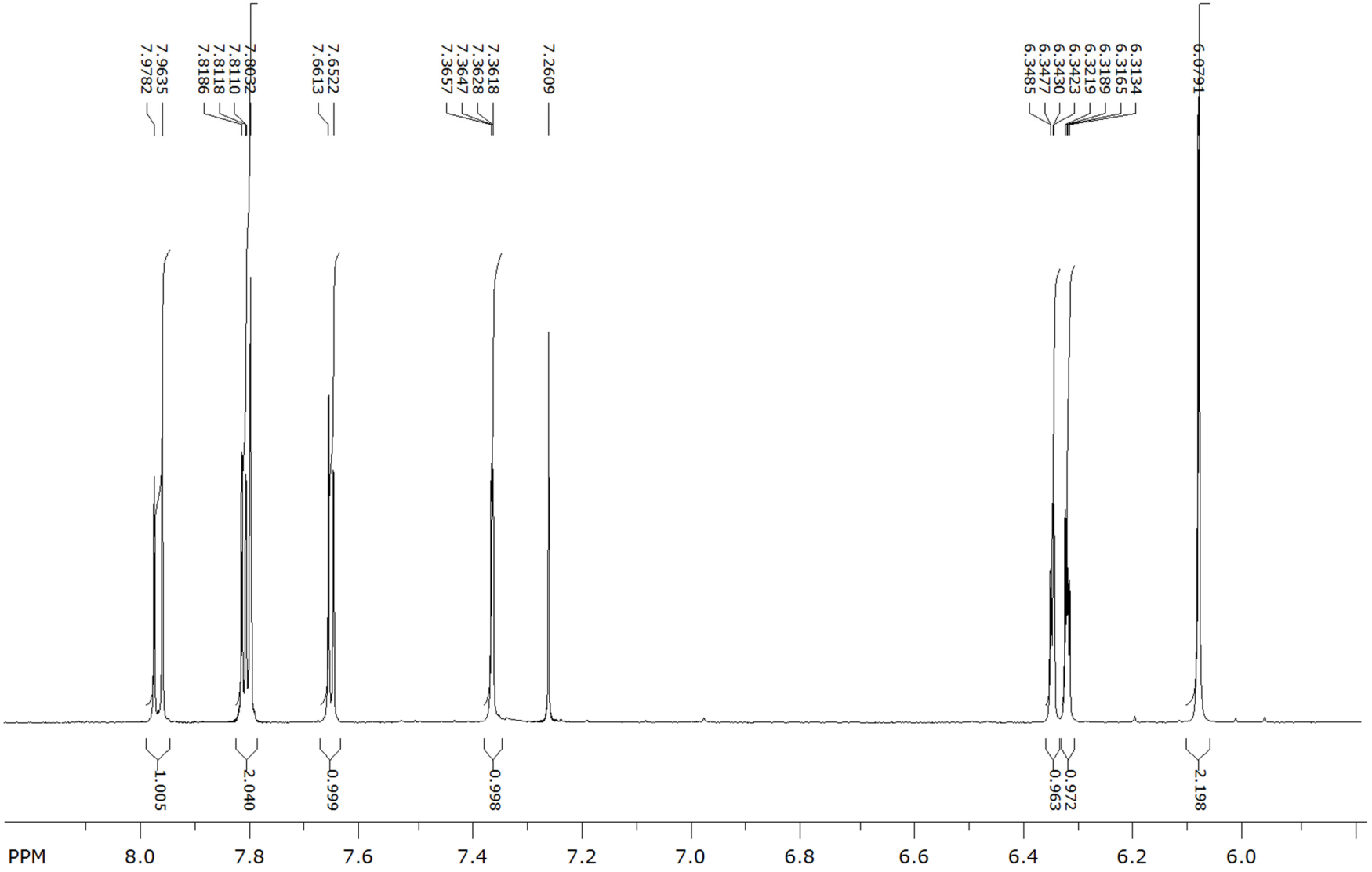


Figure S2. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **23**.

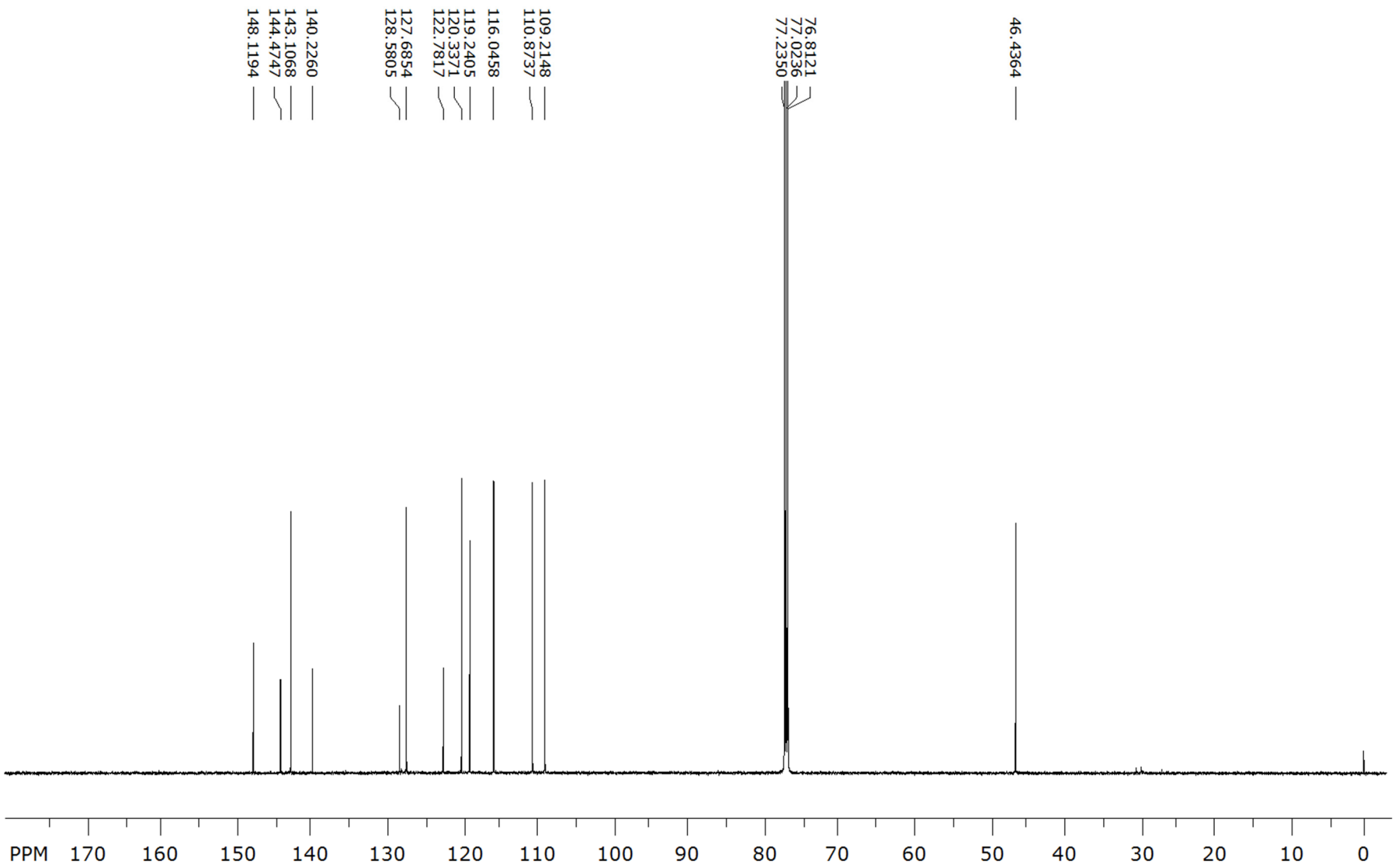


Figure S3. ^{13}C NMR ($CDCl_3$) spectrum of **23**.

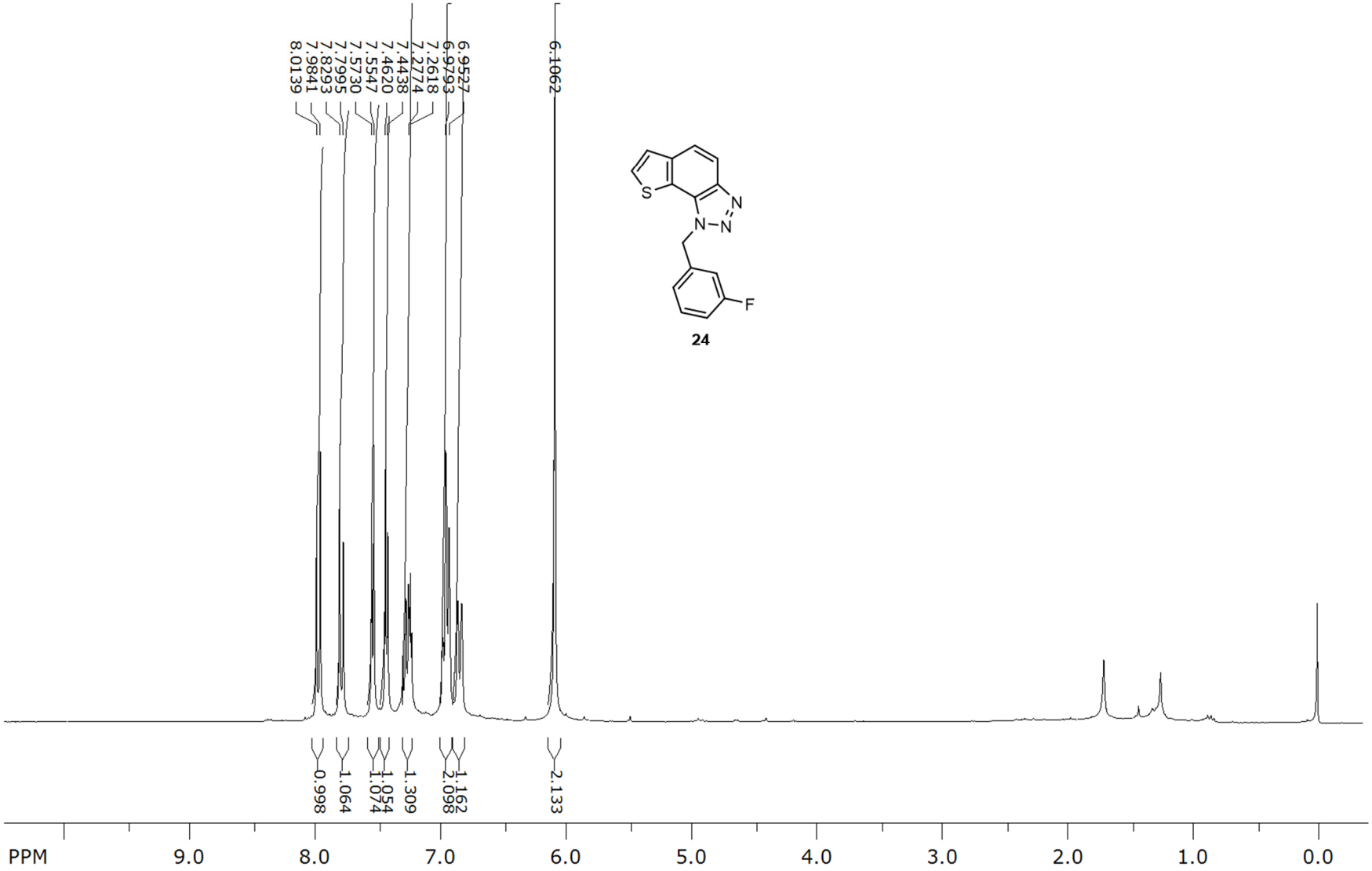


Figure S4. ^{1}H NMR ($CDCl_3$) spectrum of **24**.

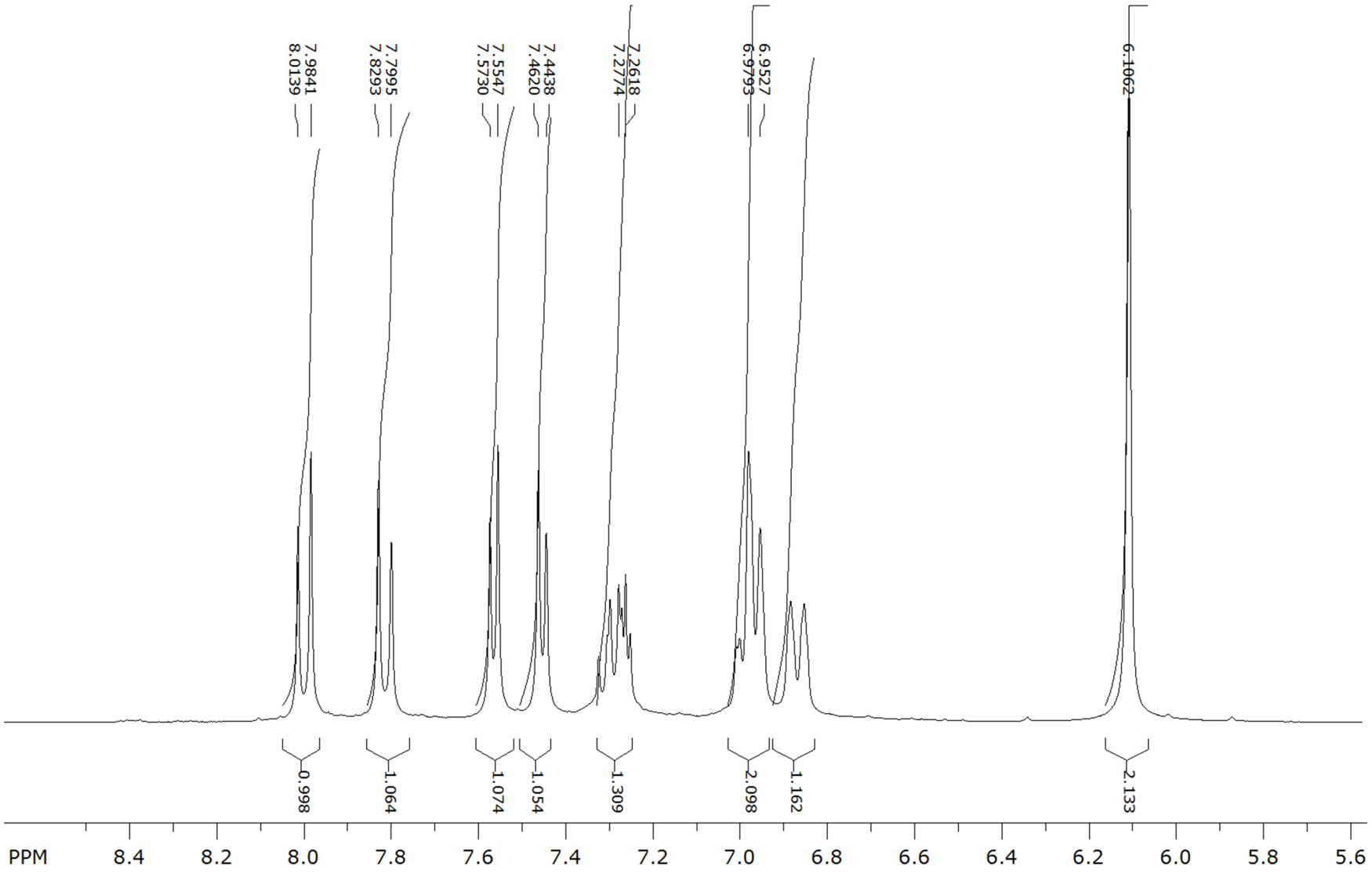


Figure S5. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **24**.

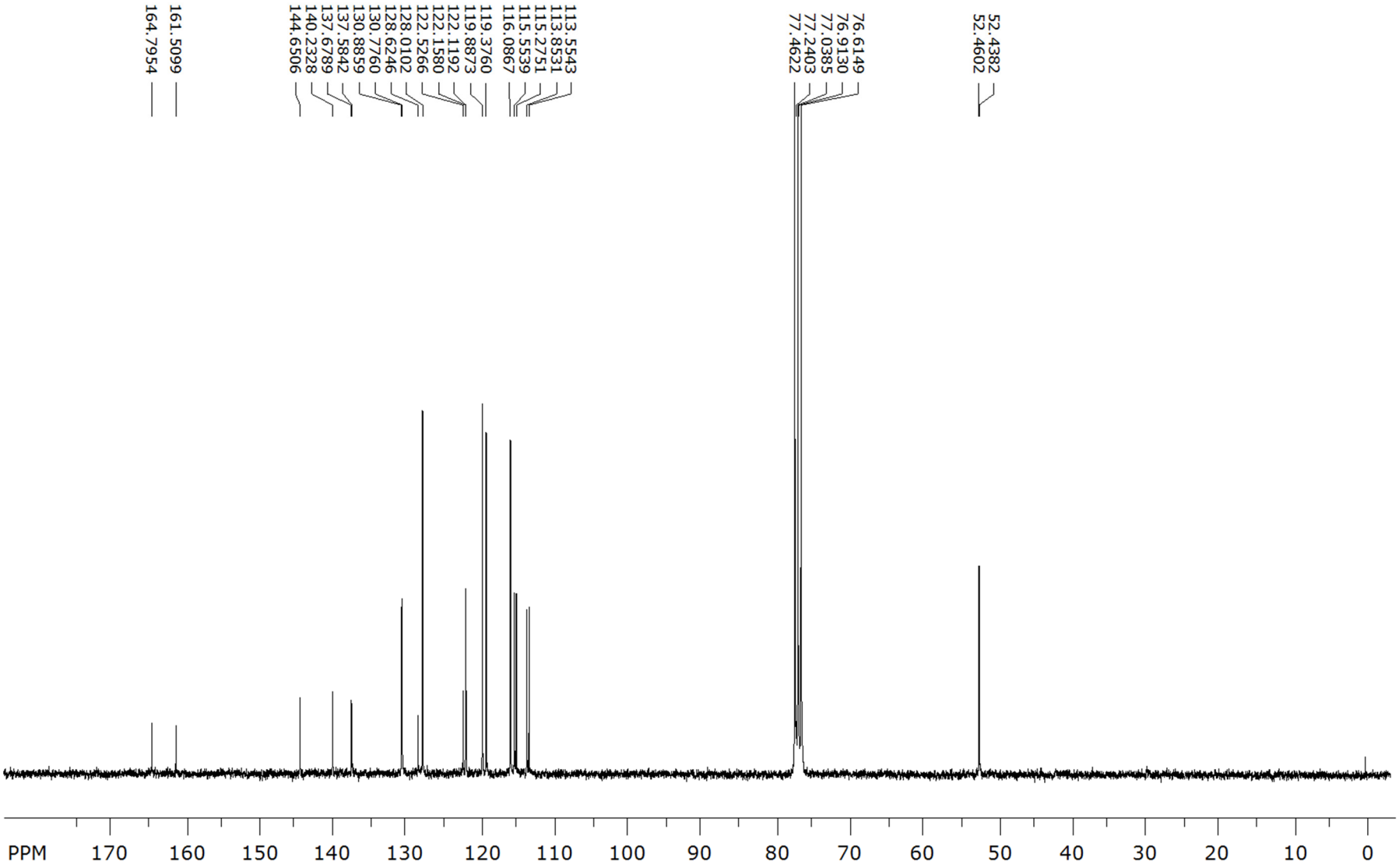


Figure S6. ^{13}C NMR ($CDCl_3$) spectrum of **24**.

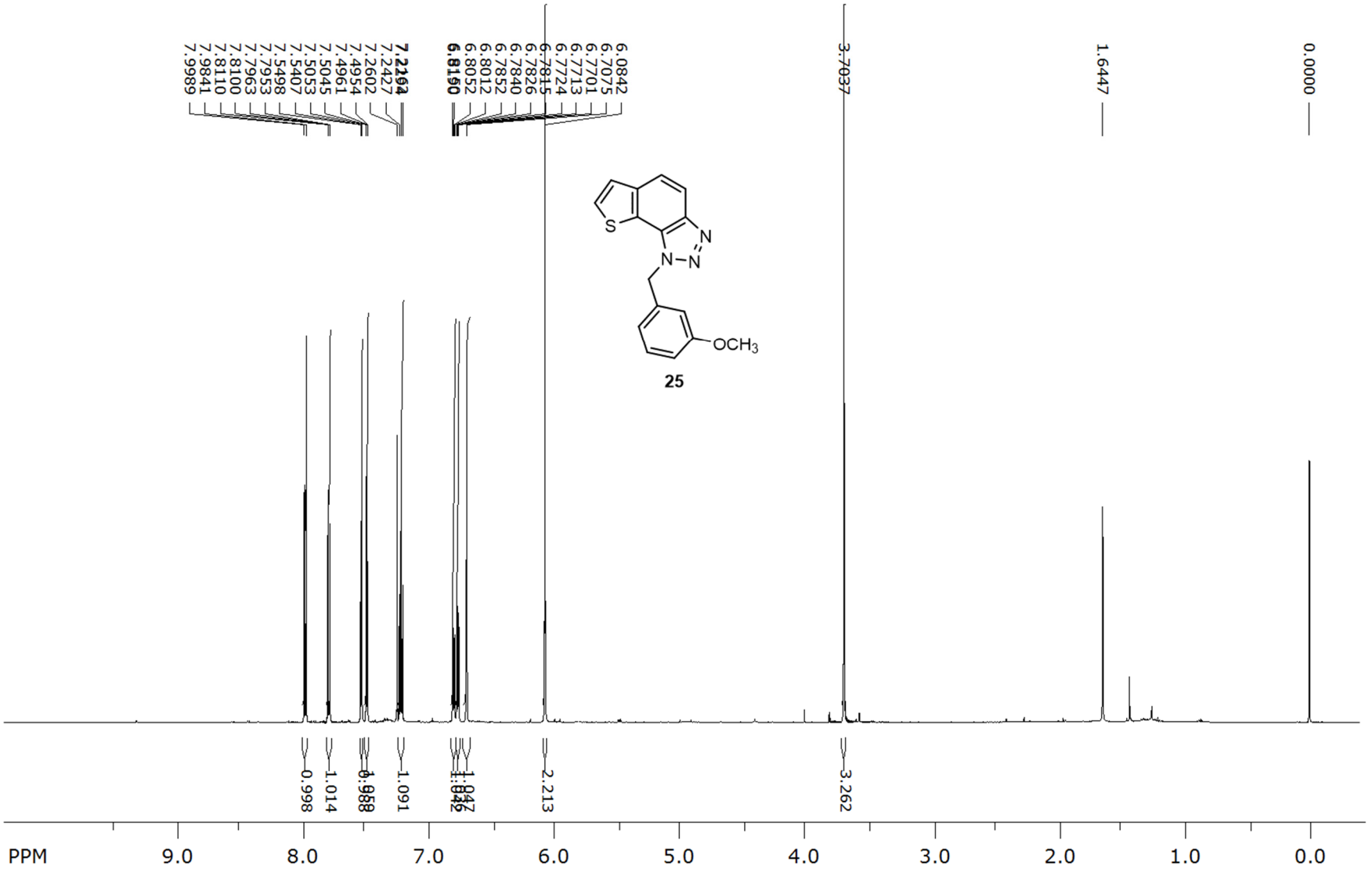


Figure S7. ^{1}H NMR ($CDCl_3$) spectrum of **25**.

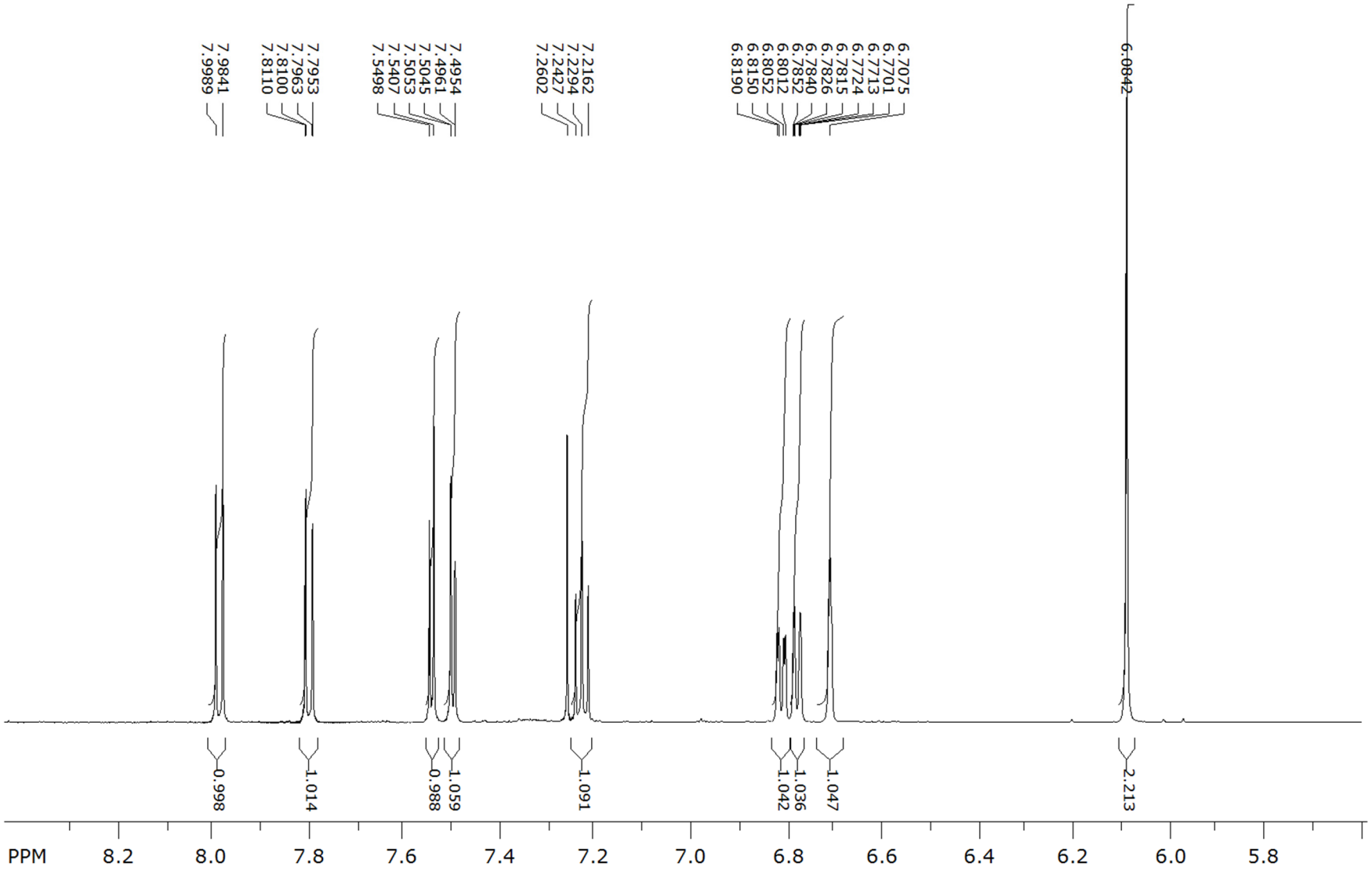


Figure S8. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **25**.

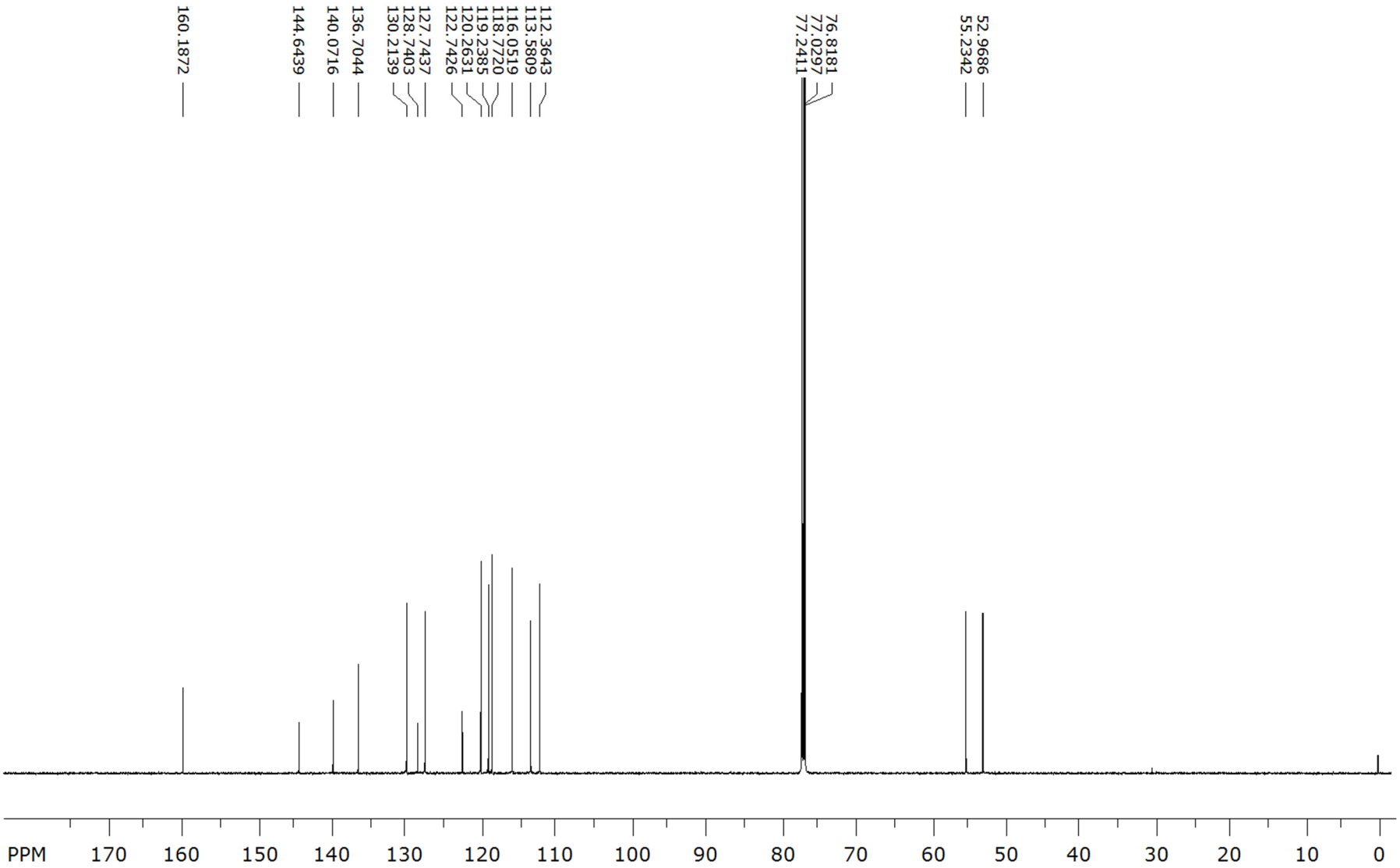


Figure S9. ^{13}C NMR ($CDCl_3$) spectrum of **25**.

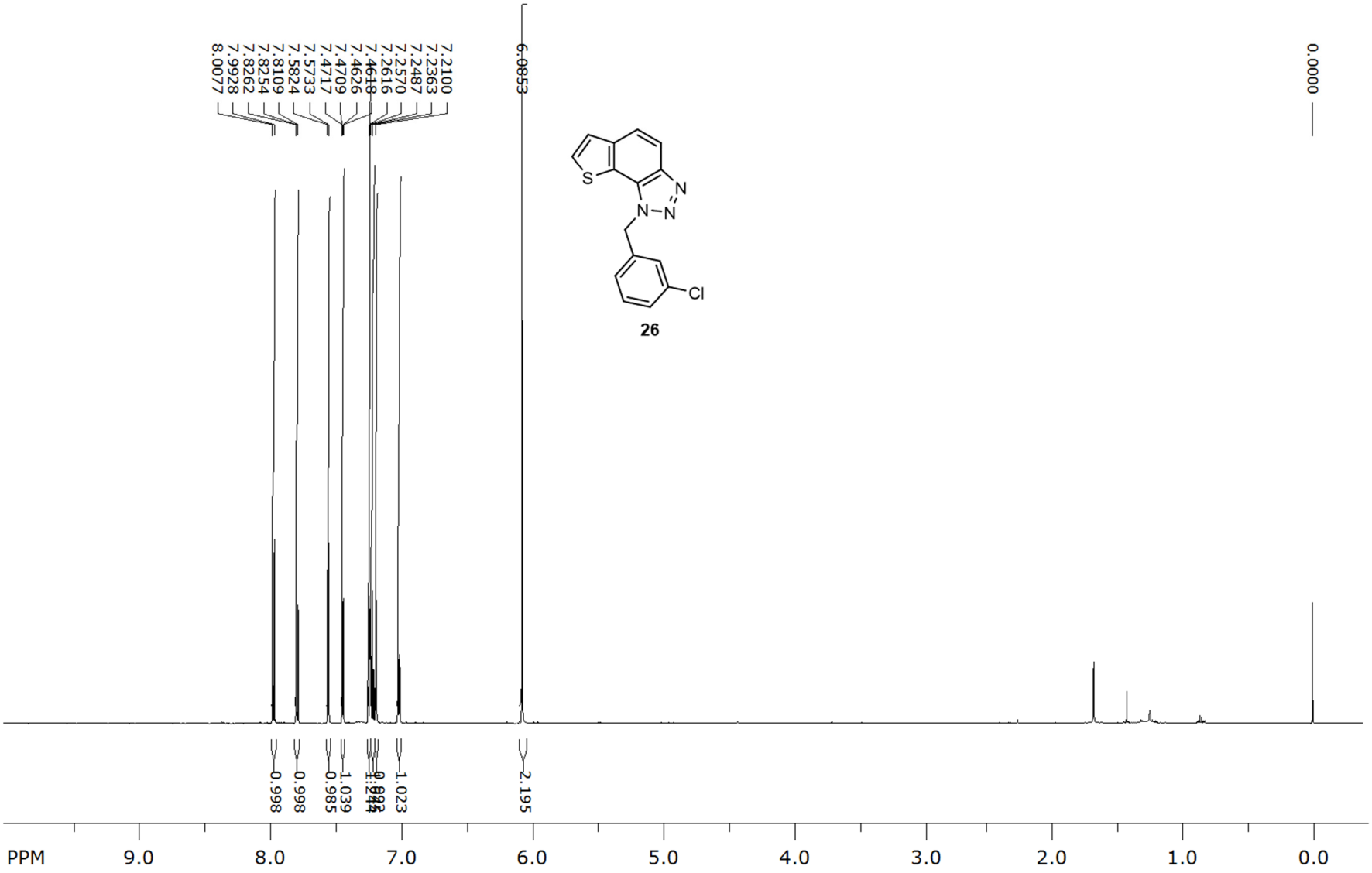


Figure S10. ^{1}H NMR ($CDCl_3$) spectrum of **26**.

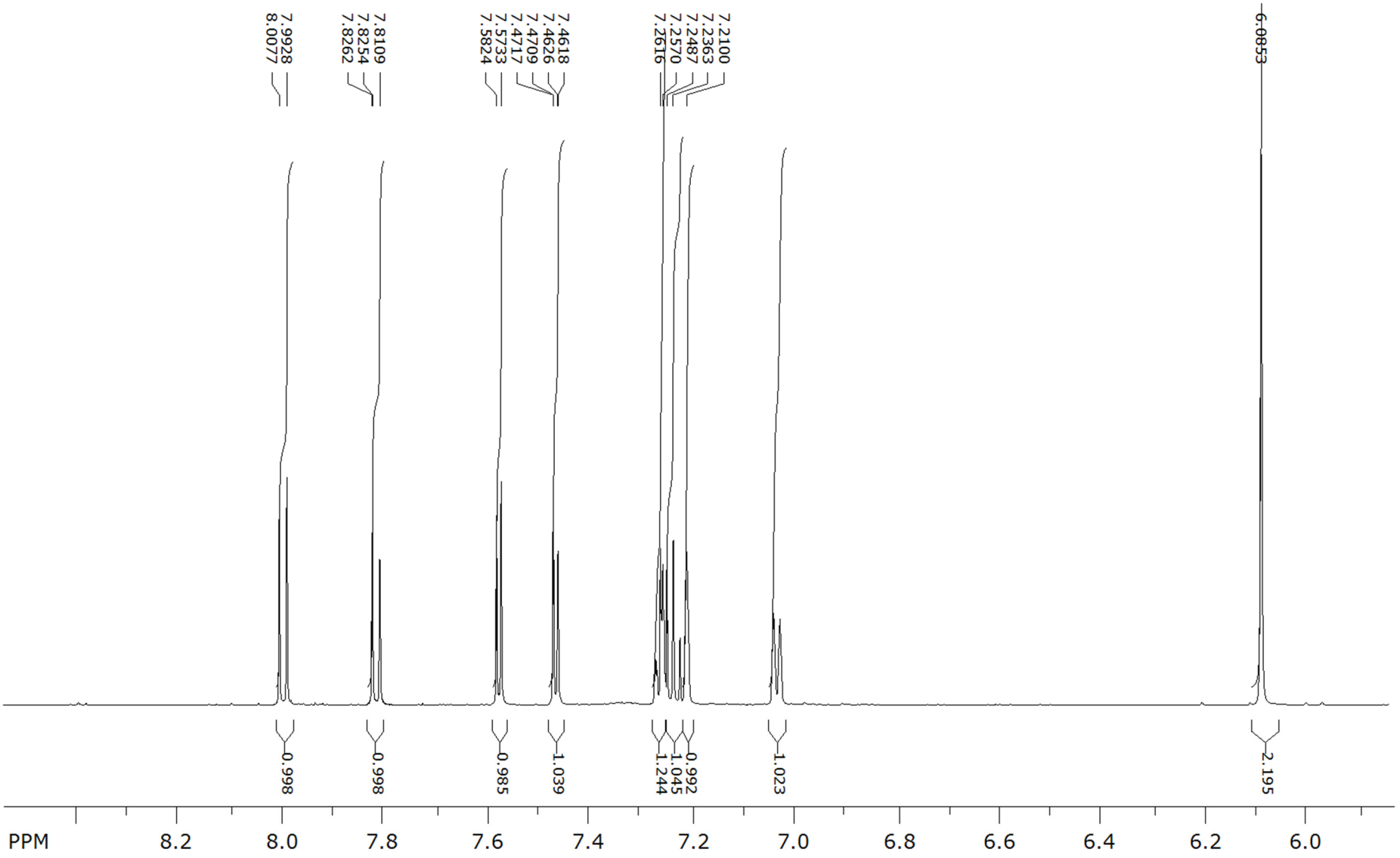


Figure S11. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **26**.

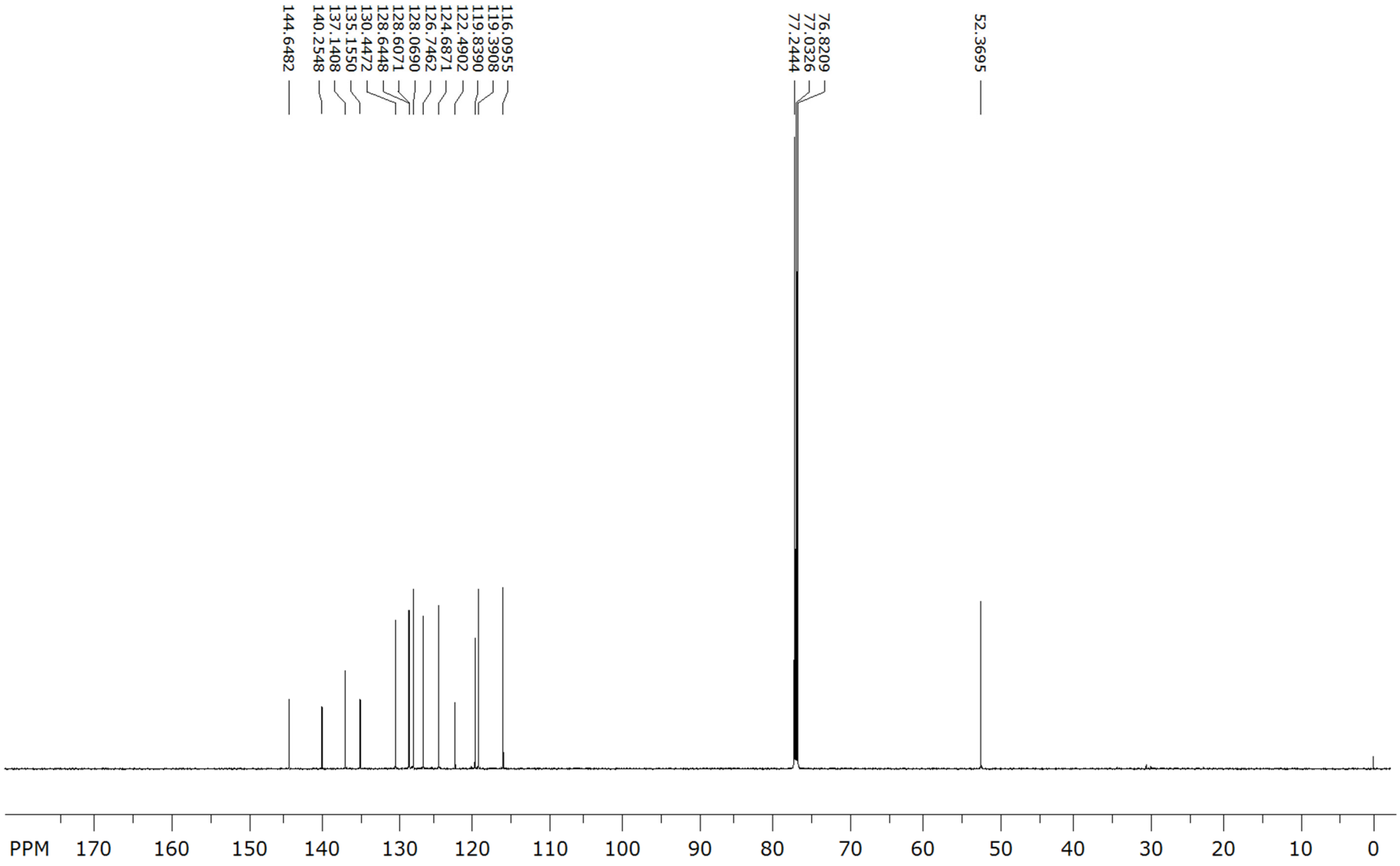


Figure S12. ^{13}C NMR ($CDCl_3$) spectrum of **26**.

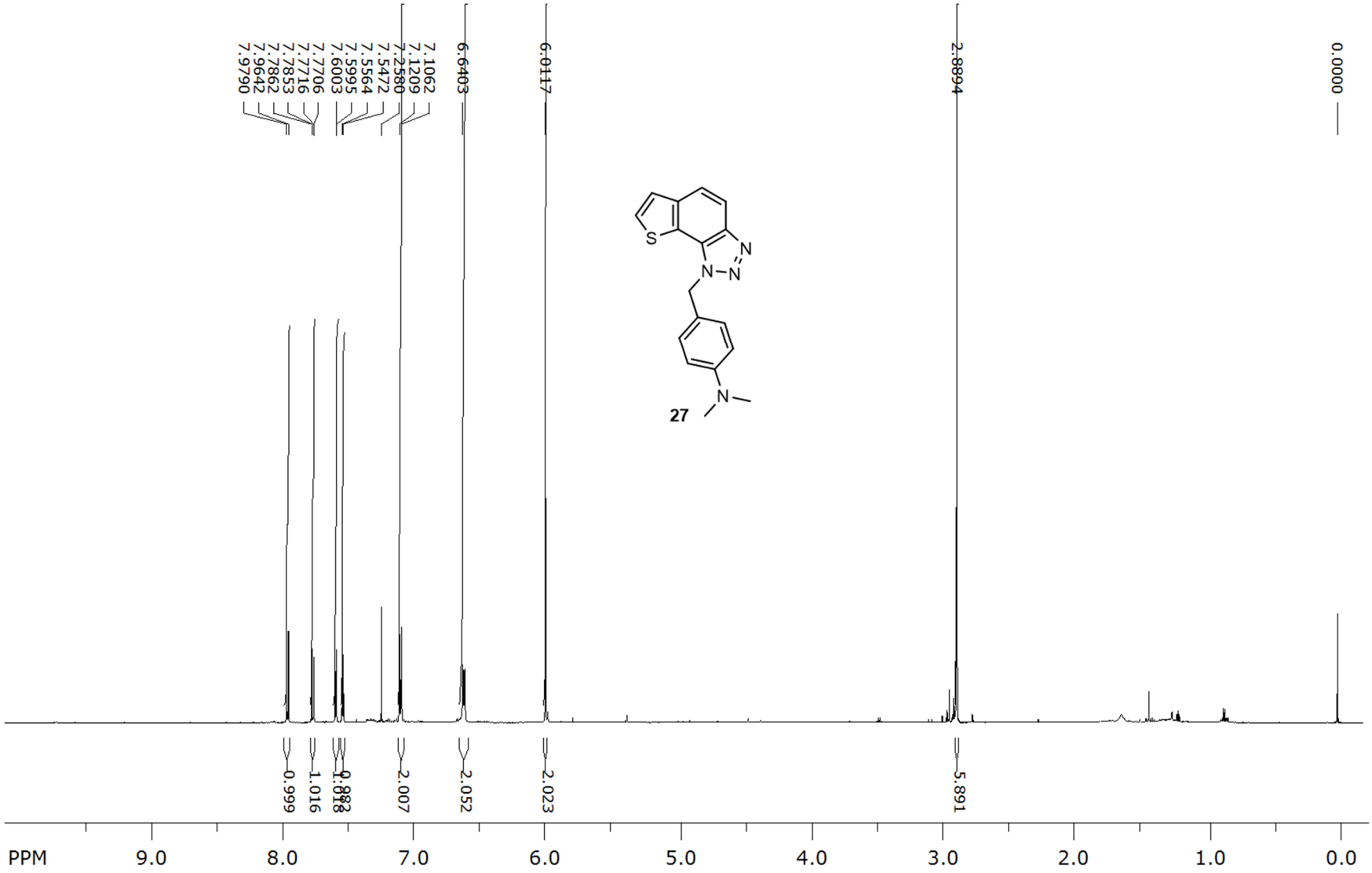


Figure S13. ^{1}H NMR ($CDCl_3$) spectrum of **27**.

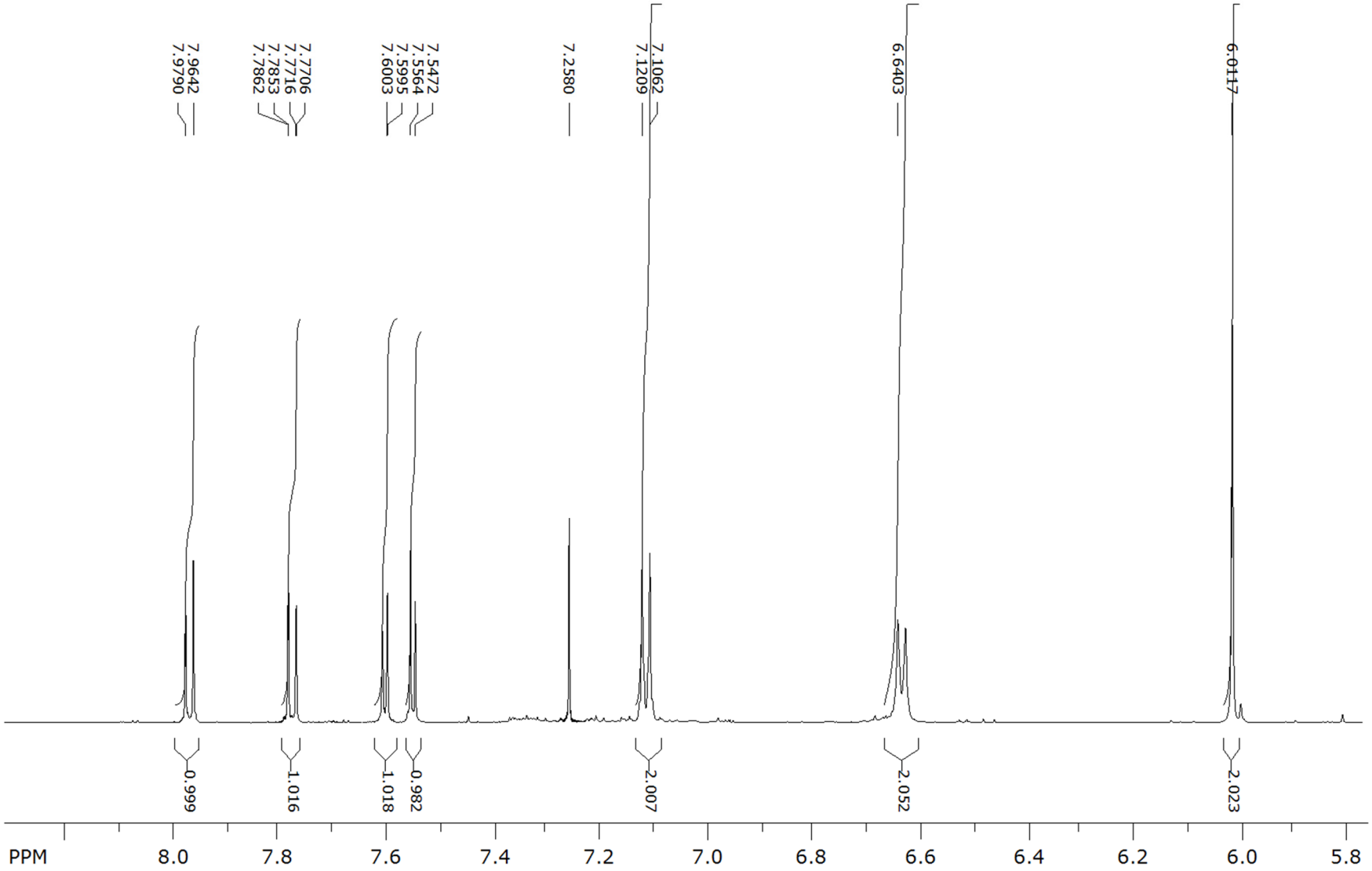


Figure S14. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **27**.

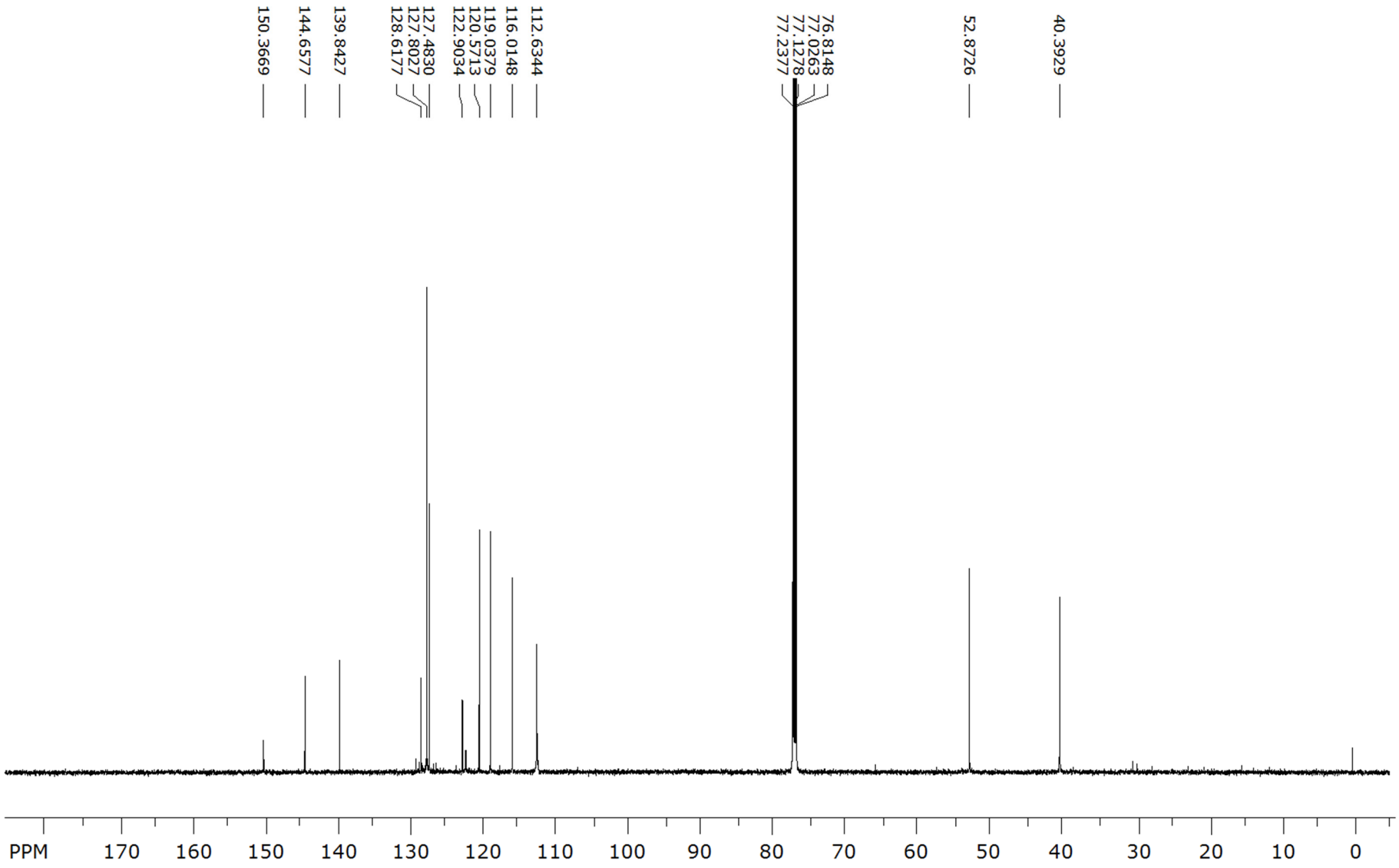


Figure S15. ^{13}C NMR ($CDCl_3$) spectrum of **27**.

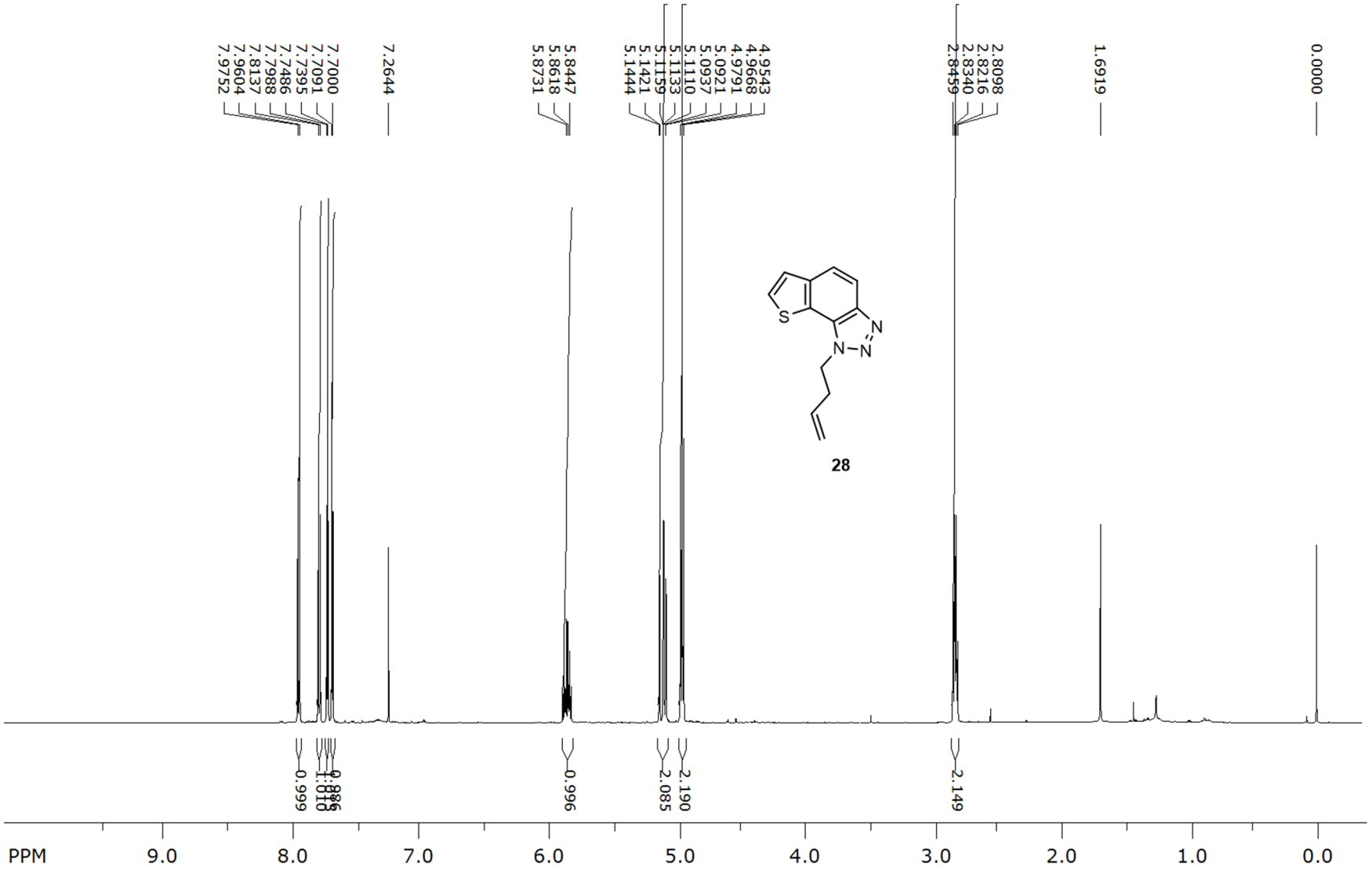


Figure S16. ^{1}H NMR ($CDCl_3$) spectrum of **28**.

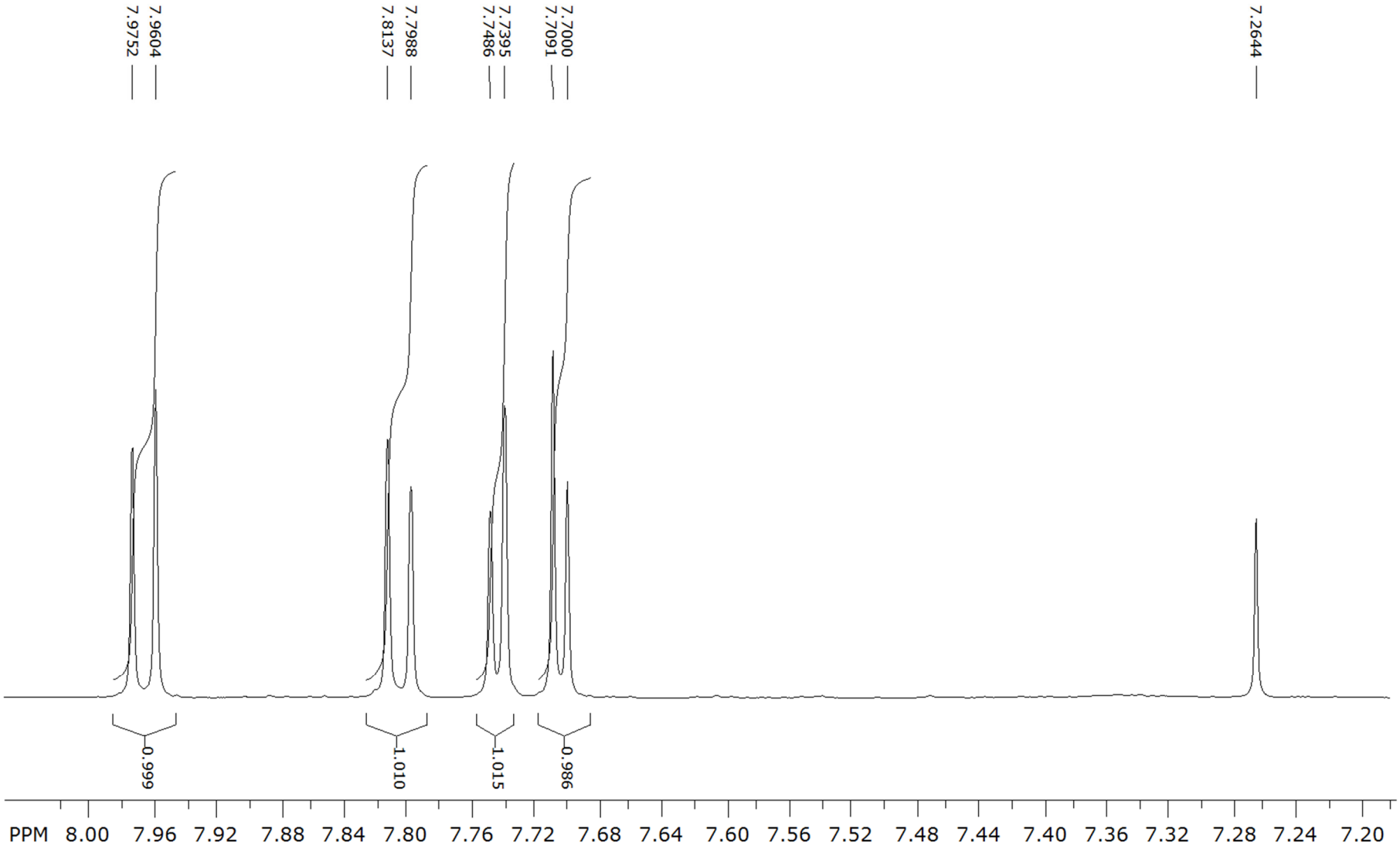


Figure S17. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **28**.

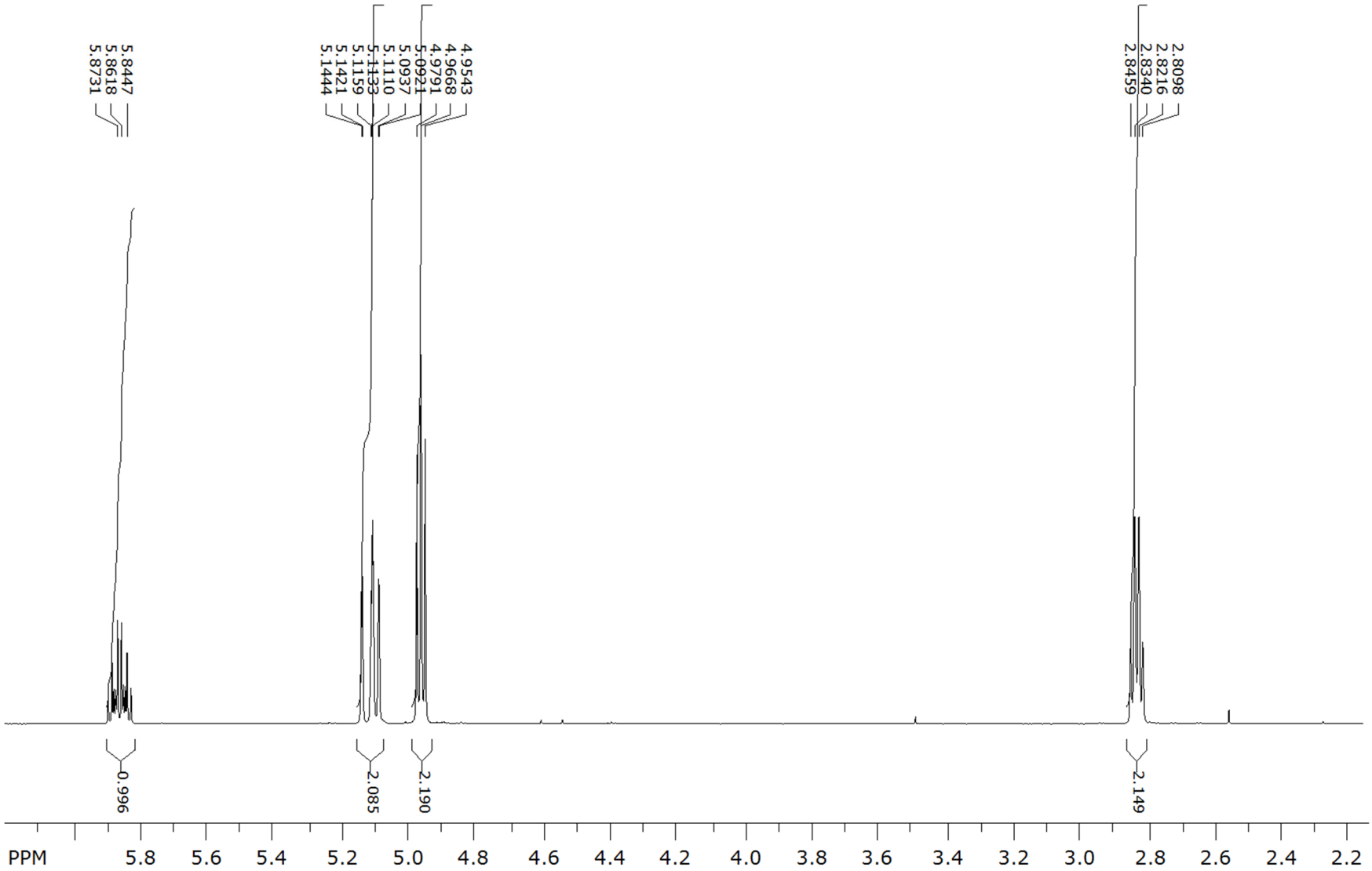


Figure S18. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **28**.

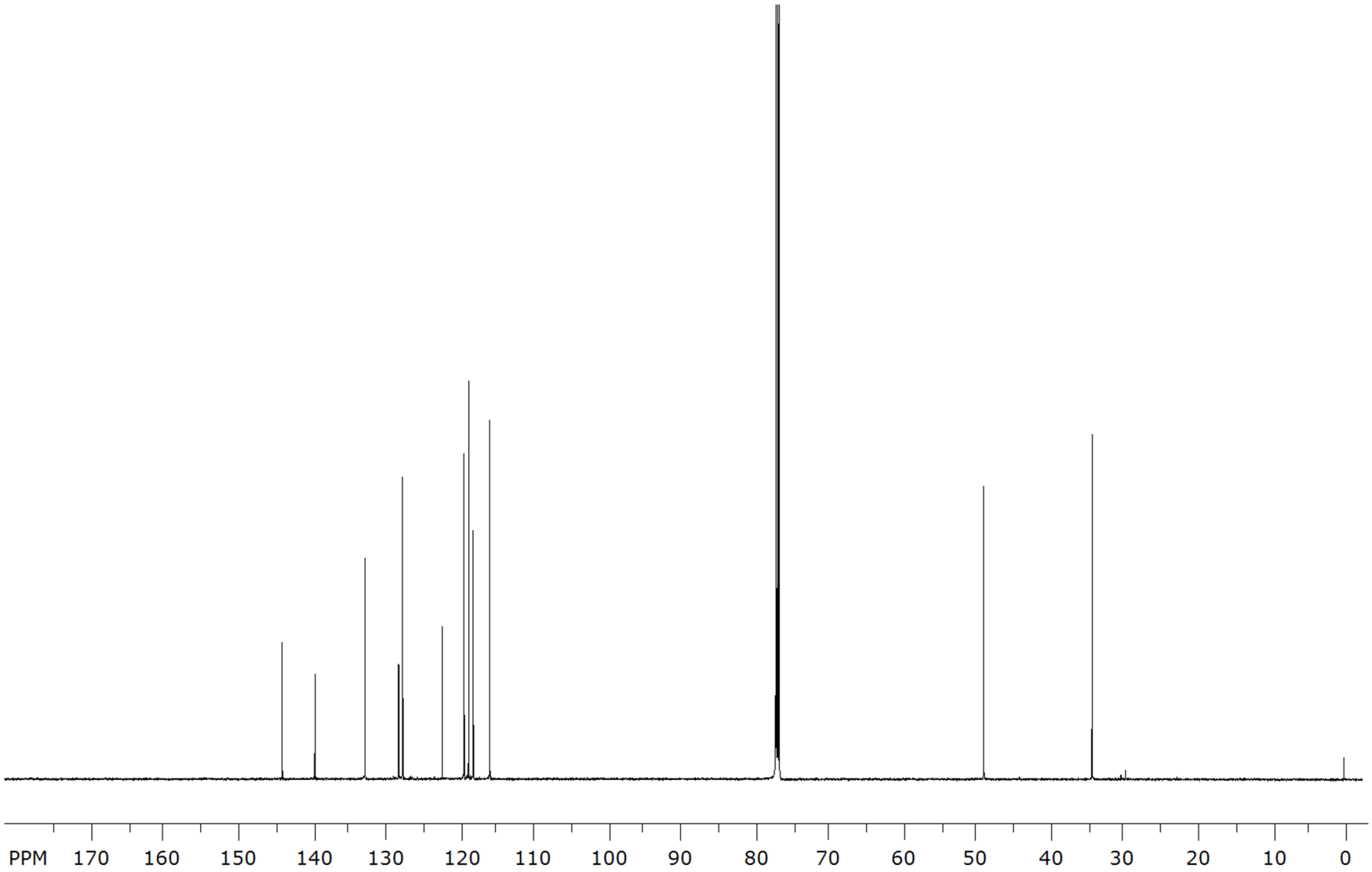


Figure S19. ^{13}C NMR ($CDCl_3$) spectrum of **28** (*Spin Works 3.0*).

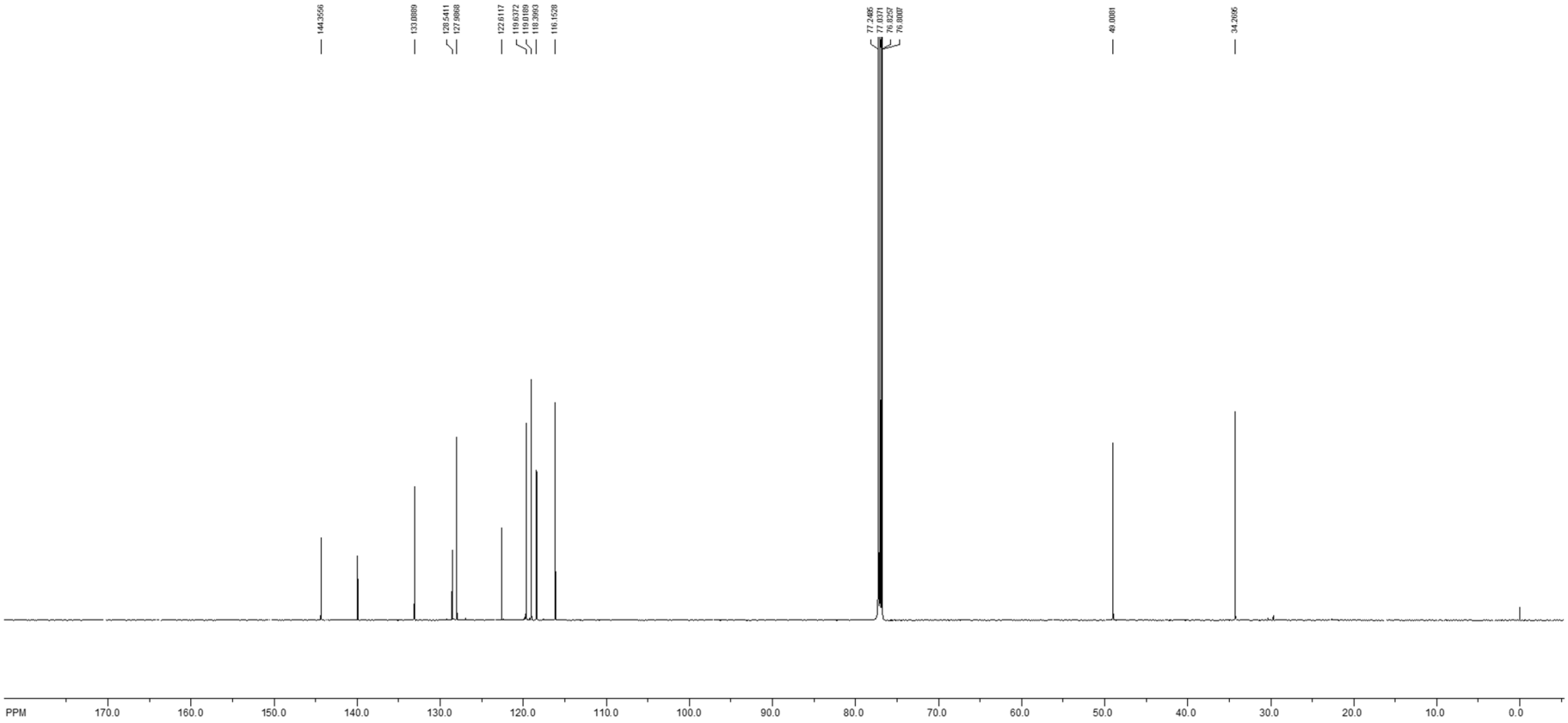


Figure S20. ^{13}C NMR ($CDCl_3$) spectrum of **28** (*Spin Works 2.5.5.*).

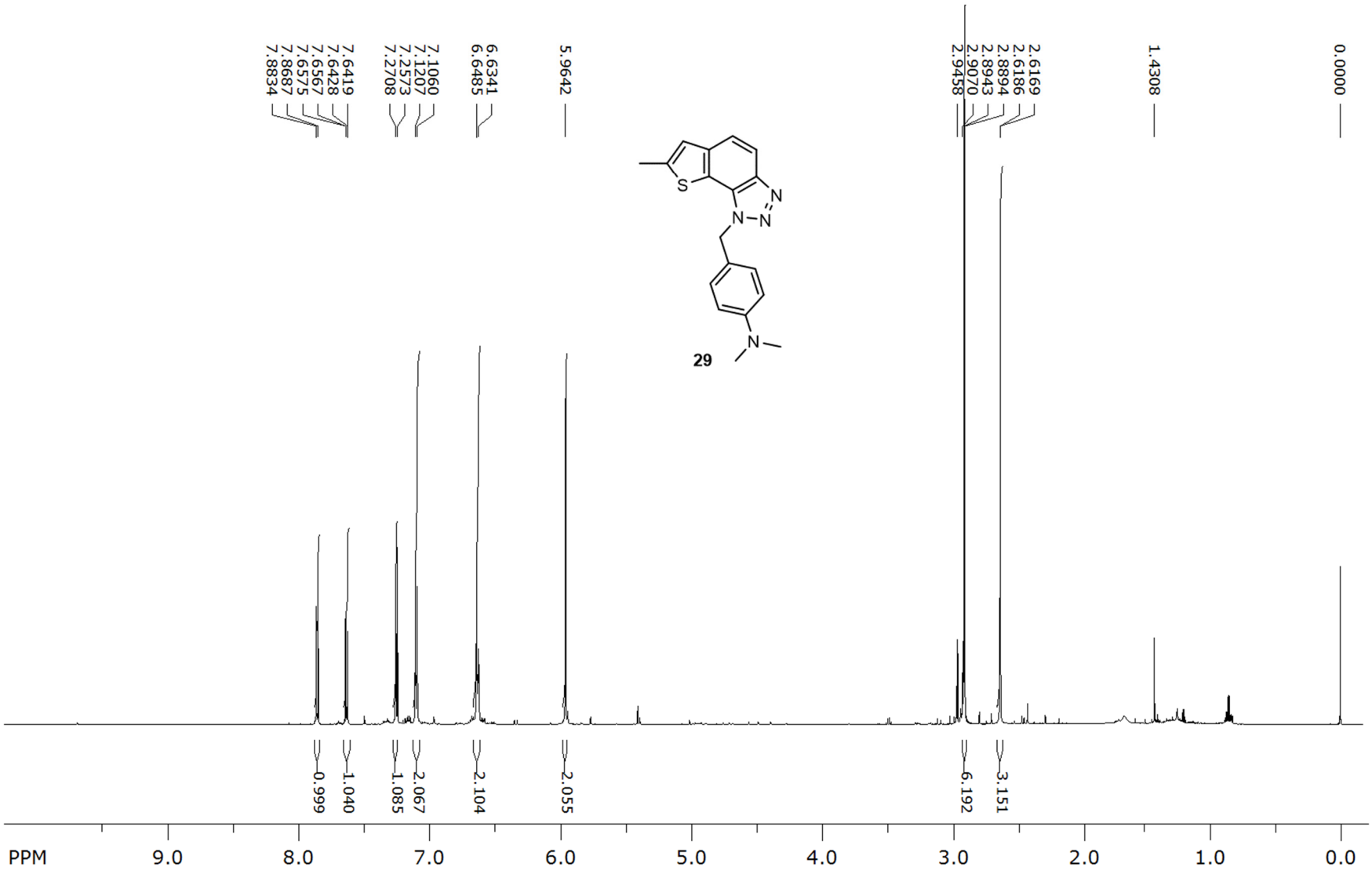


Figure S21. ^{1}H NMR ($CDCl_3$) spectrum of **29**.

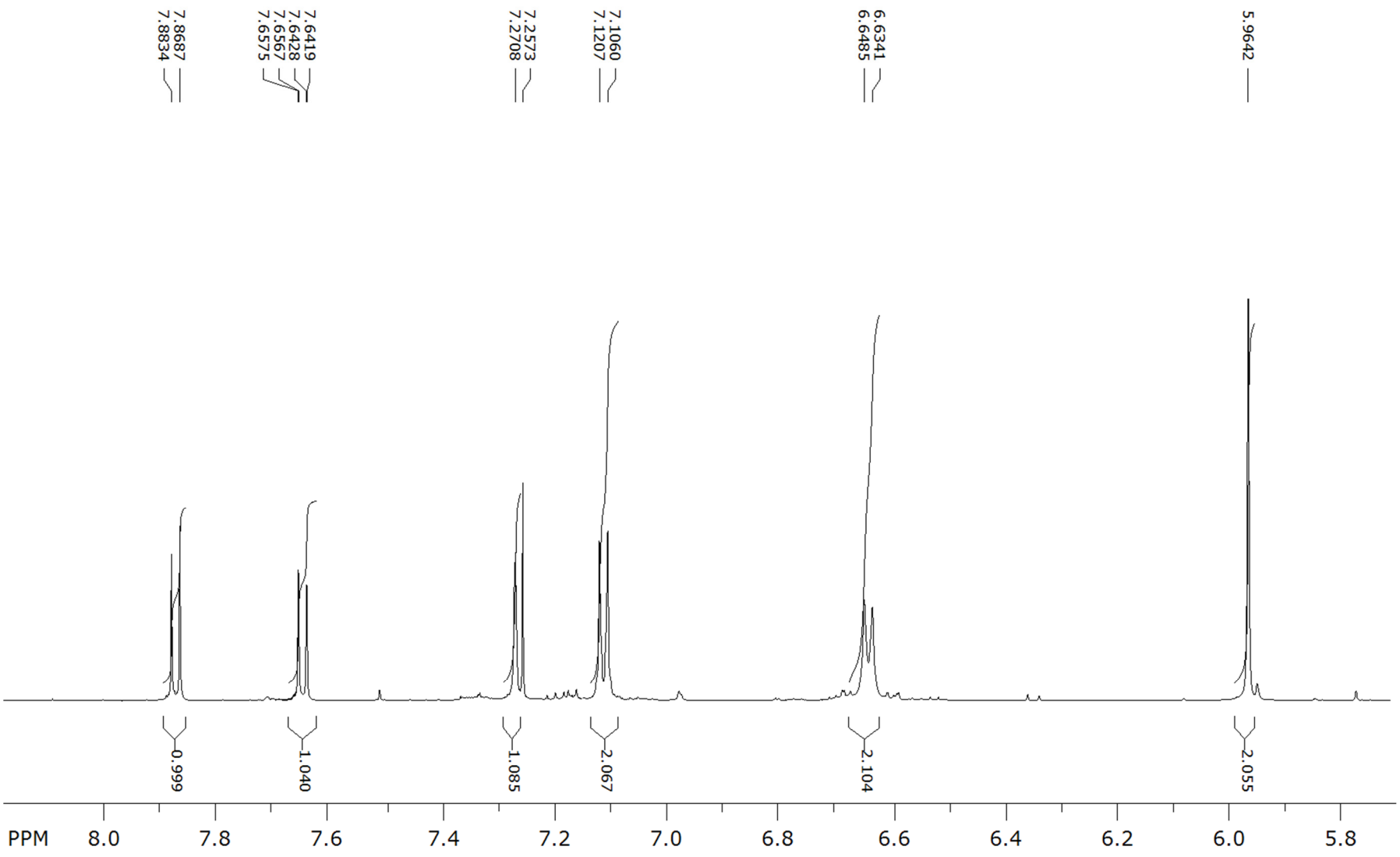


Figure S22. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **29**.

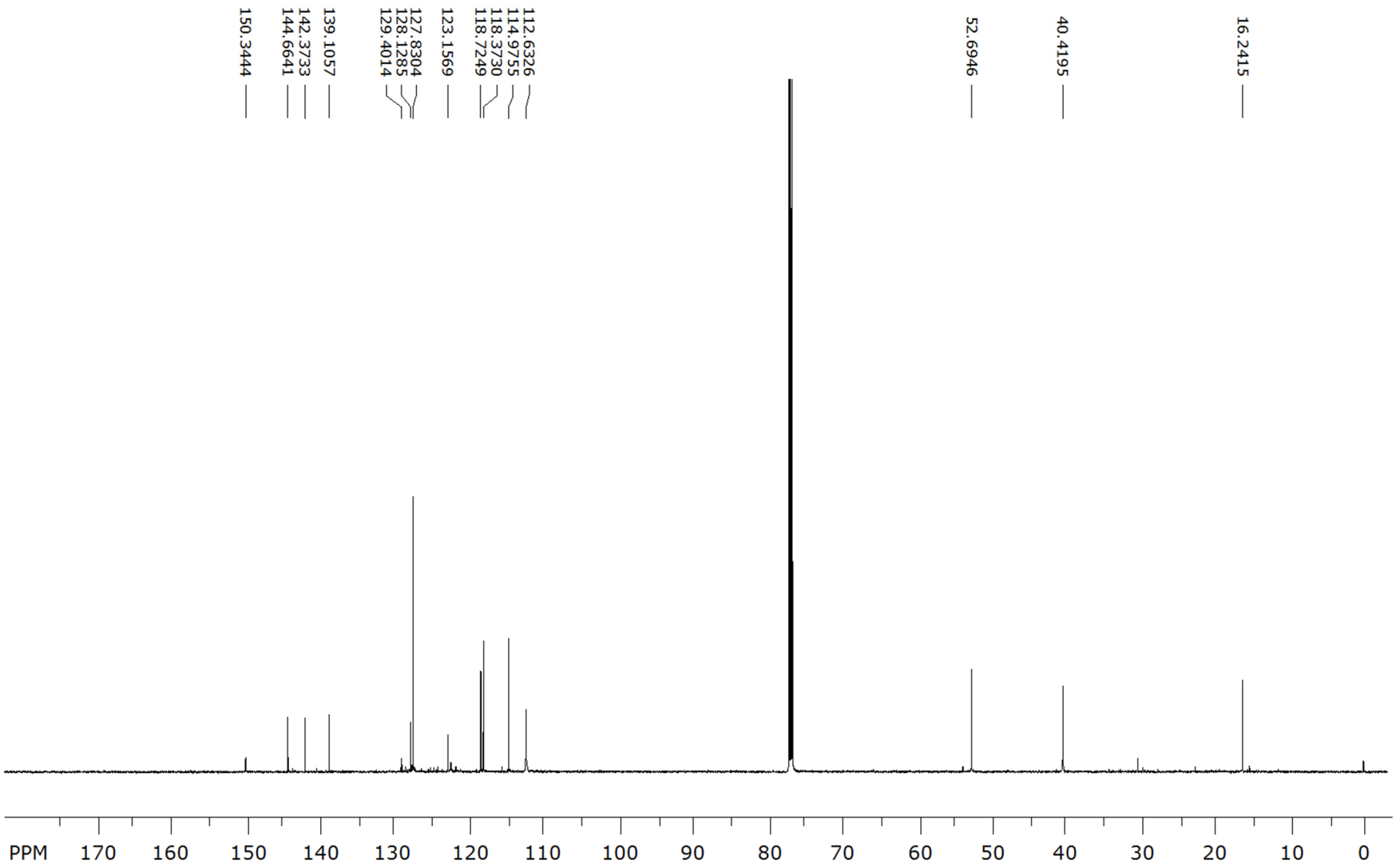


Figure S23. ^{13}C NMR ($CDCl_3$) spectrum of **29**.

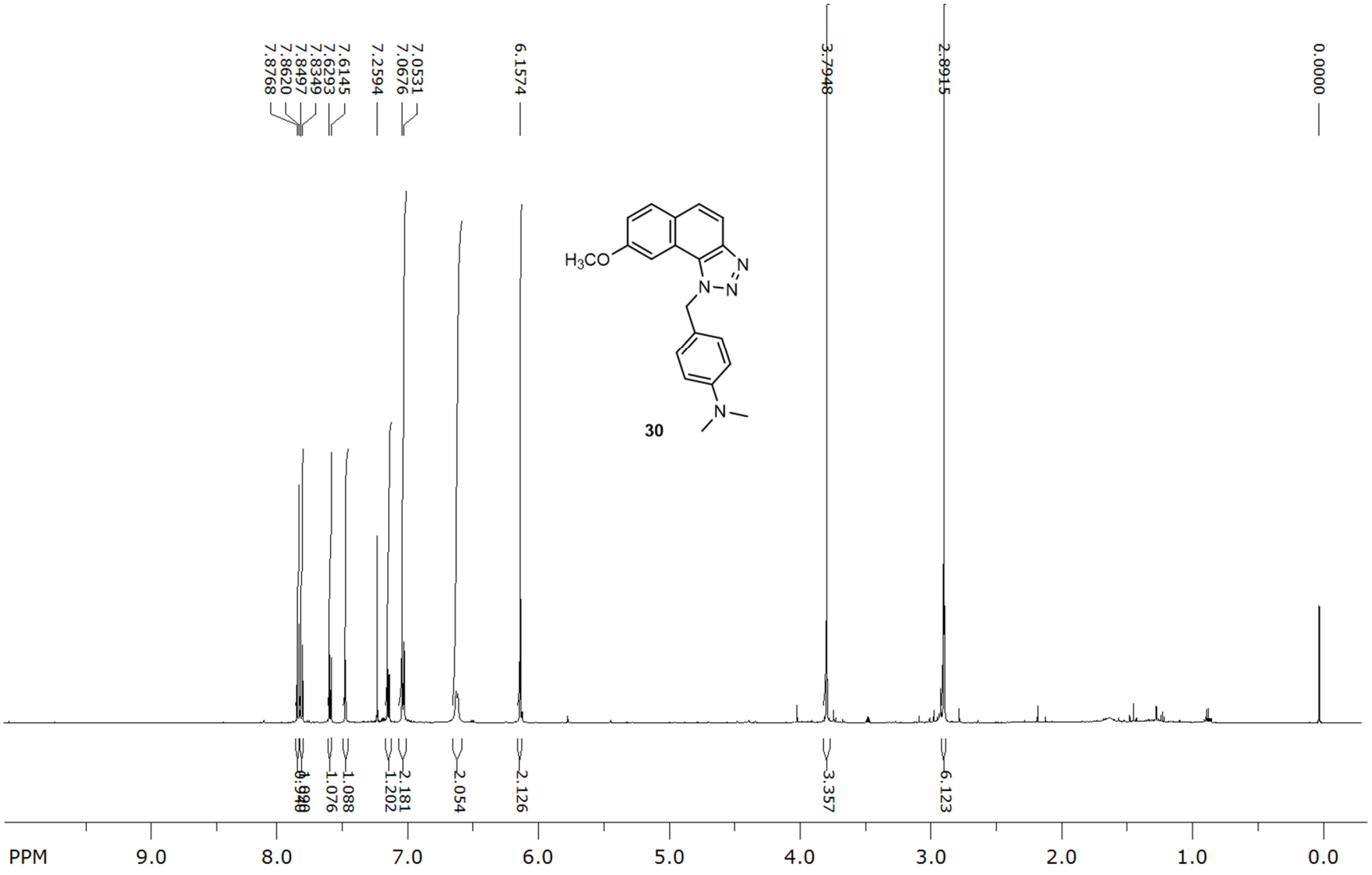


Figure S24. ^{1}H NMR ($CDCl_3$) spectrum of **30**.

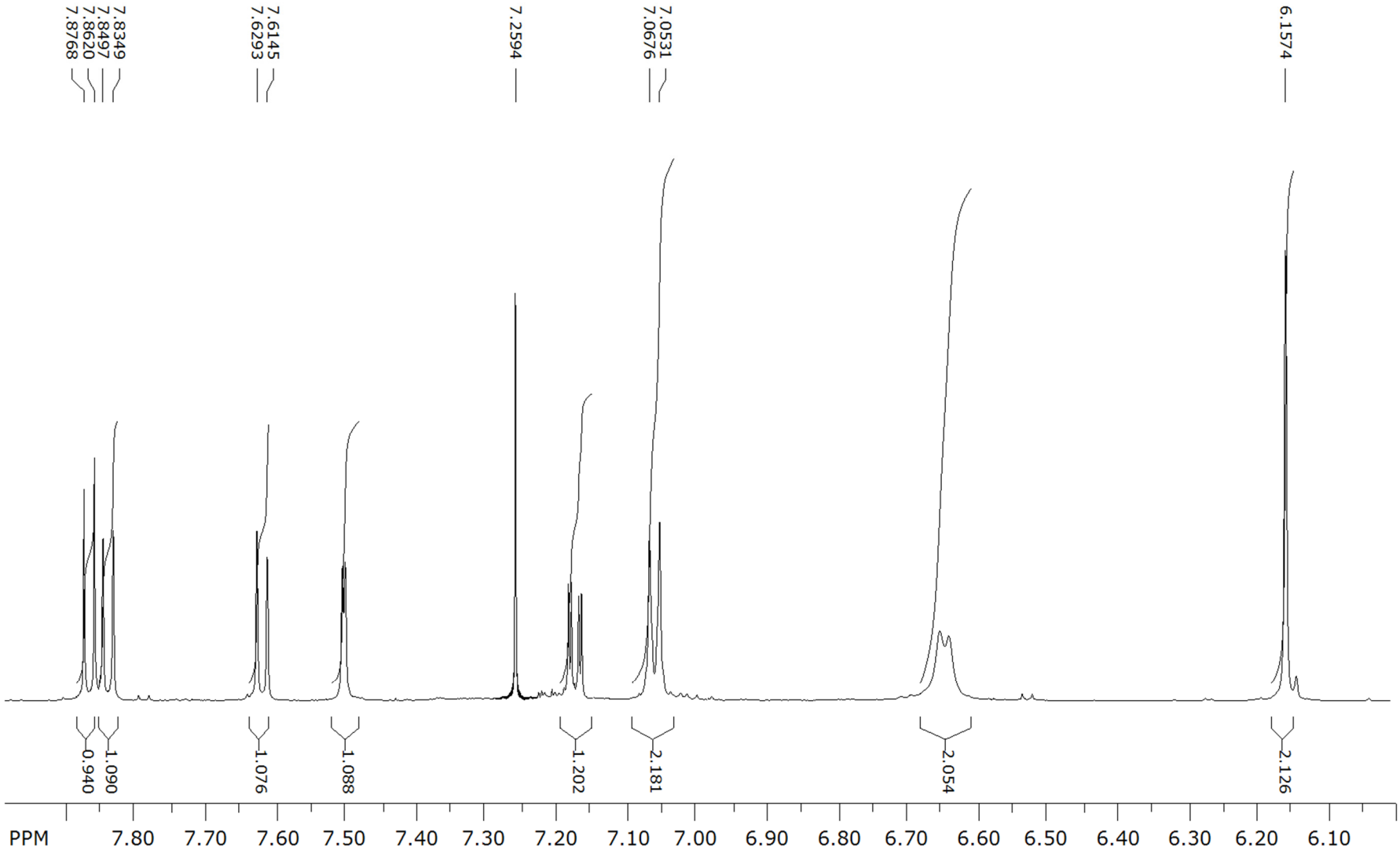


Figure S25. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **30**.

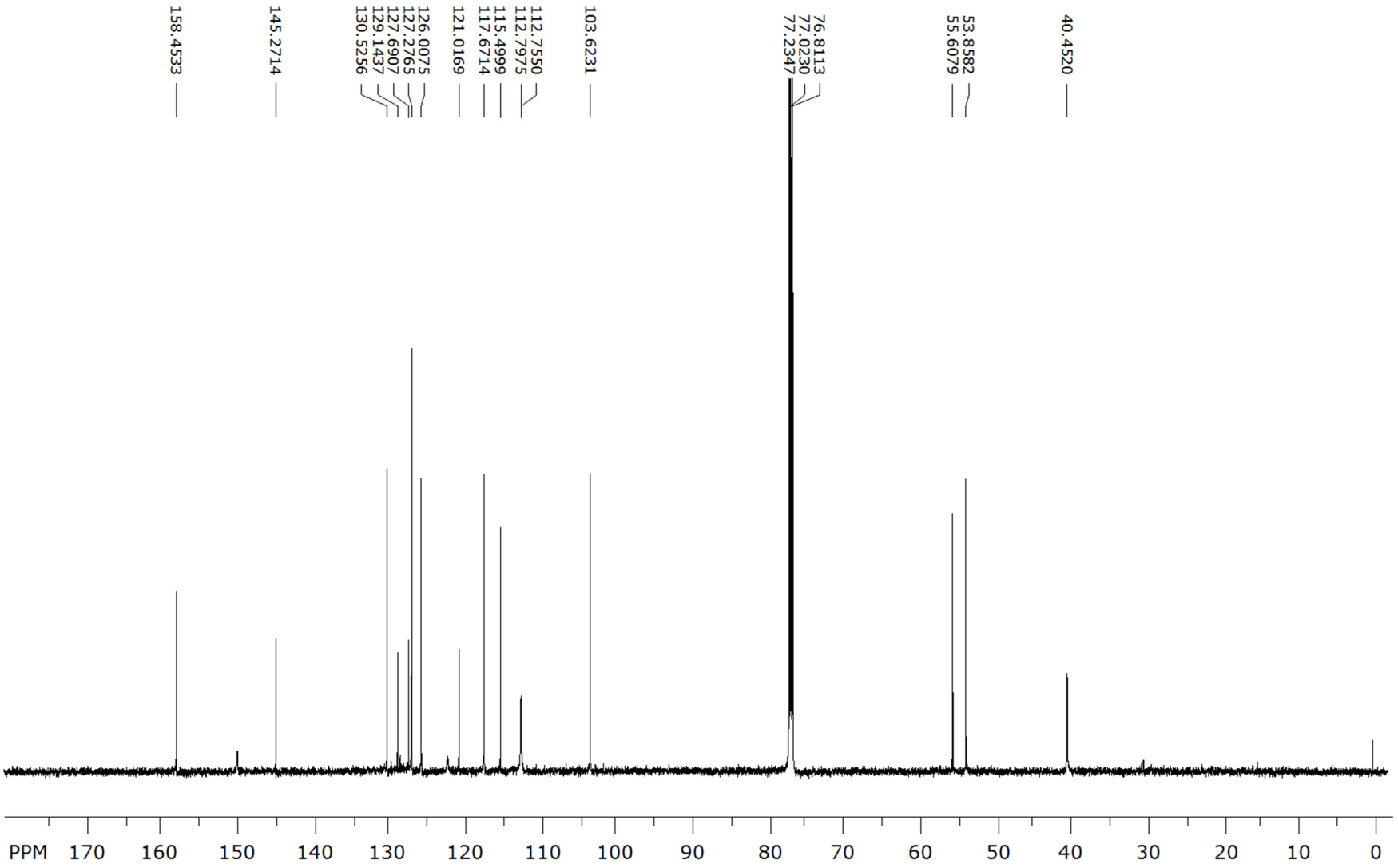


Figure S26. ^{13}C NMR ($CDCl_3$) spectrum of **30**.

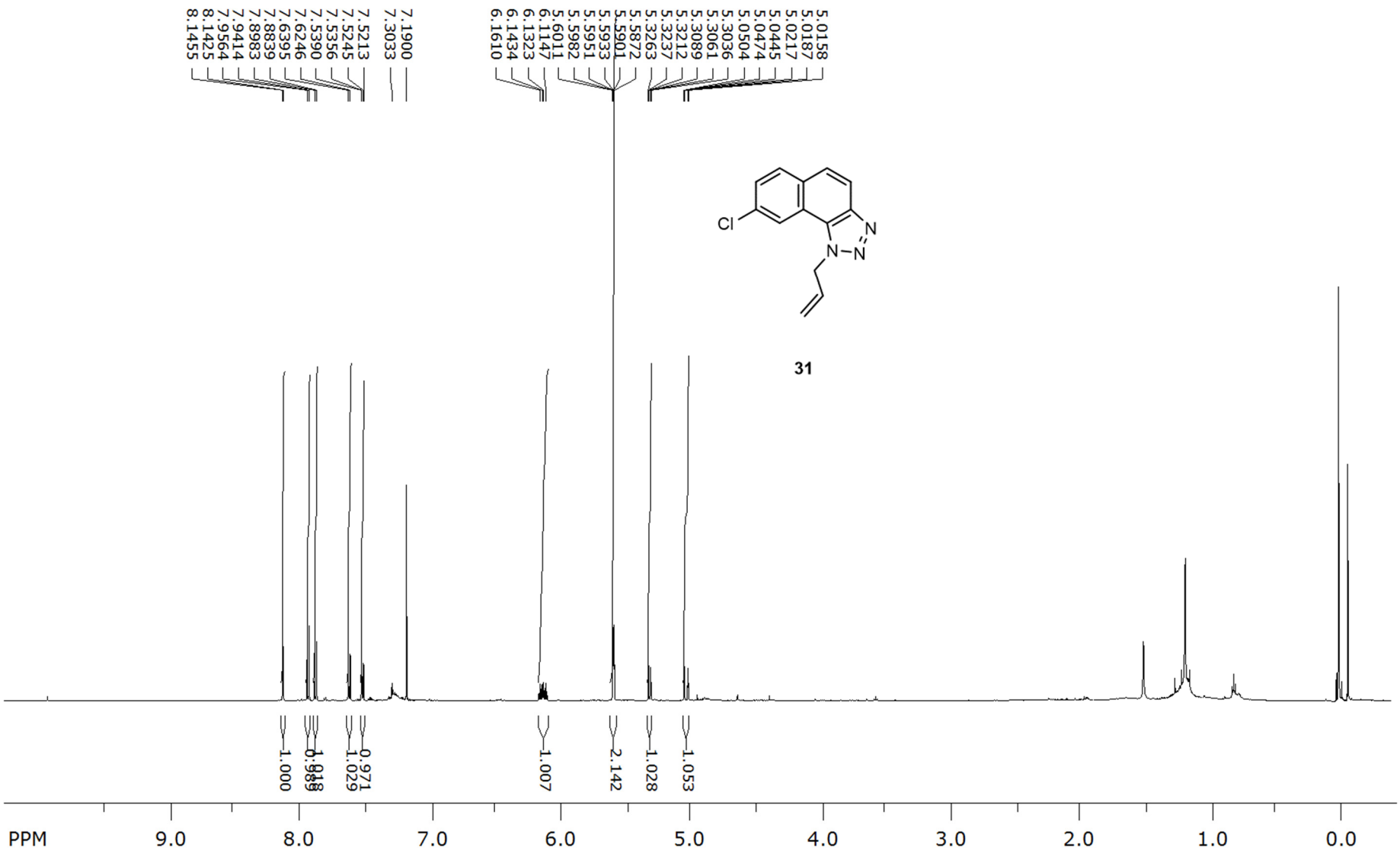


Figure S27. ^{1}H NMR ($CDCl_3$) spectrum of **31**.

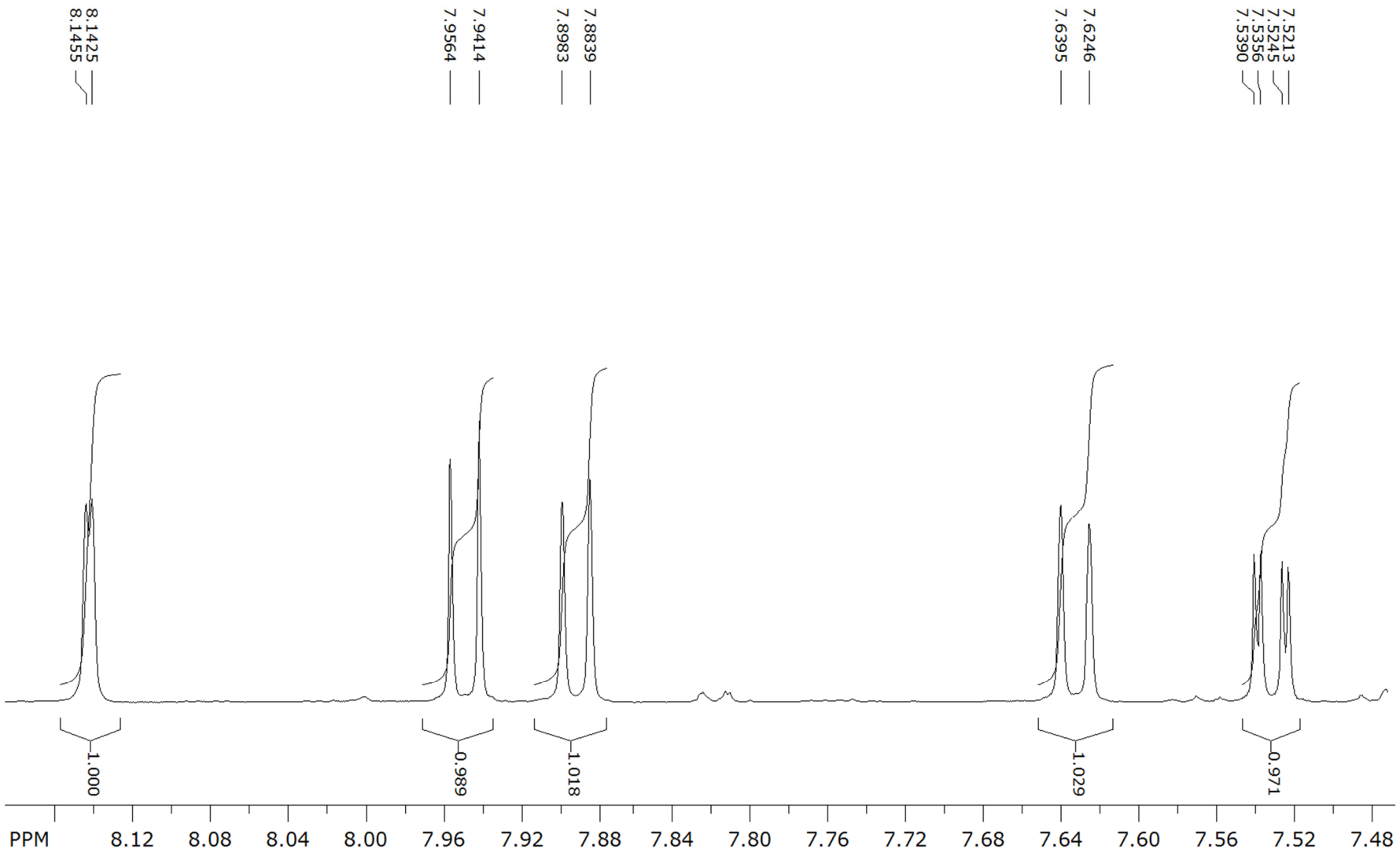


Figure S28. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **31**.

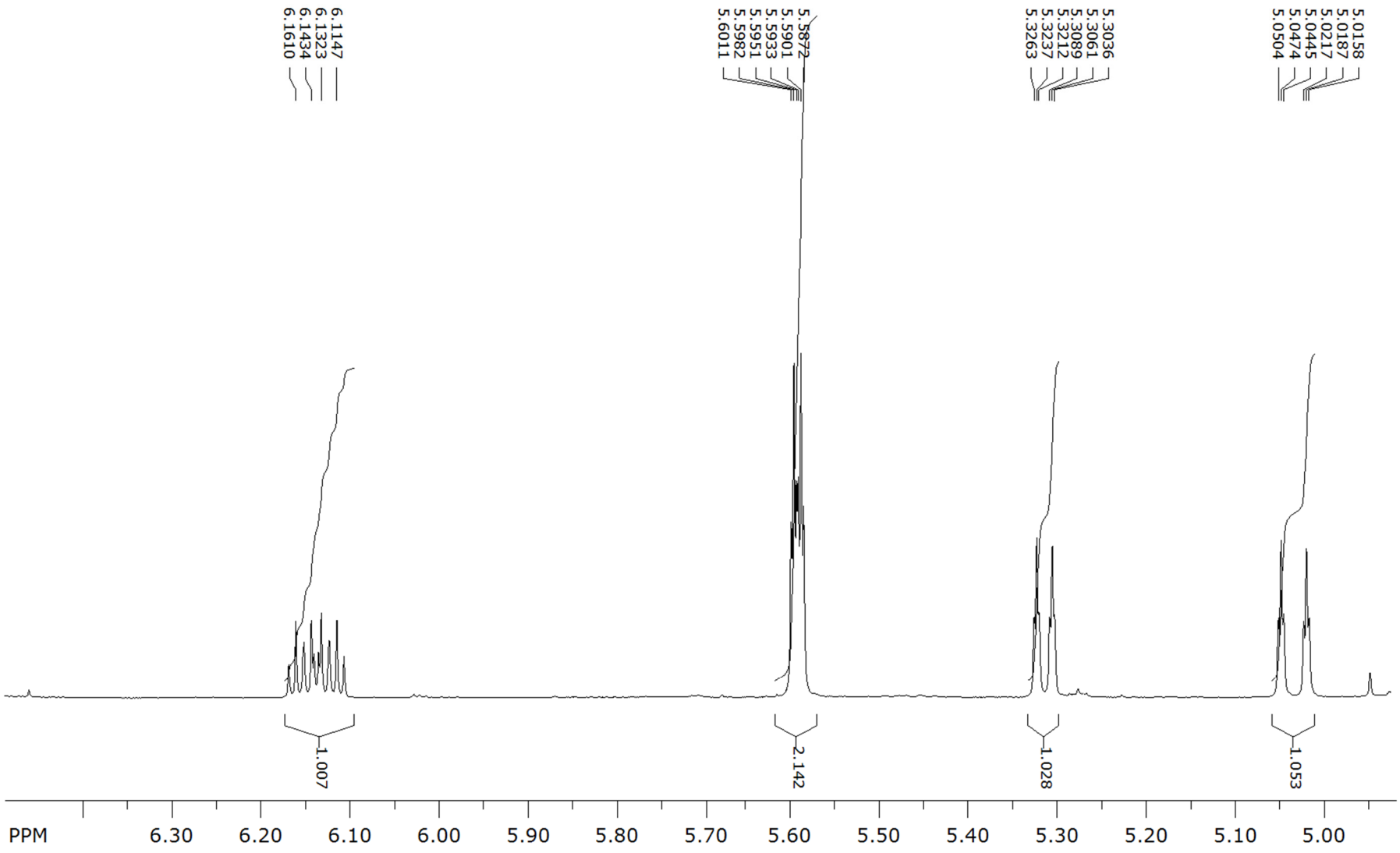


Figure S29. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **31**.

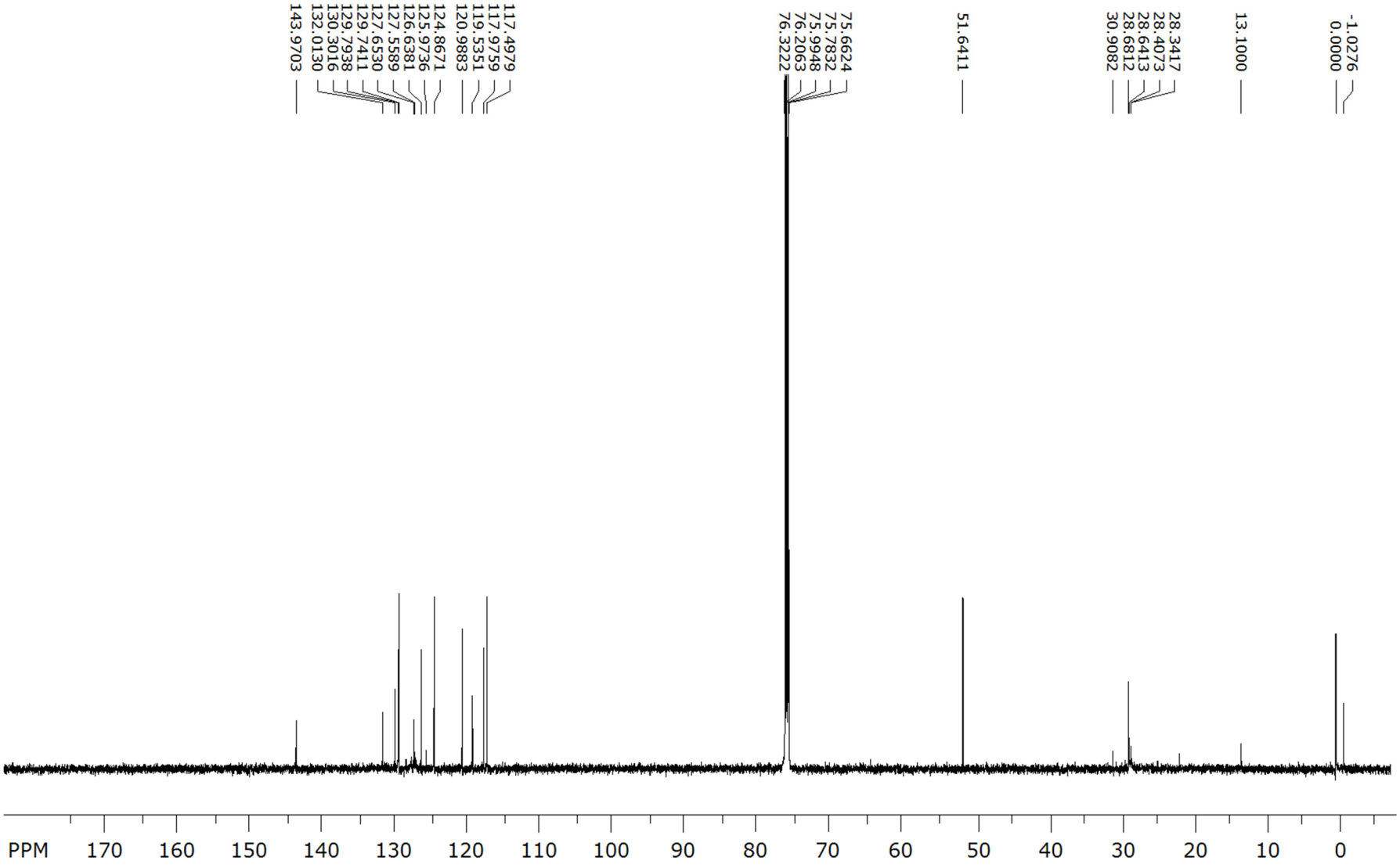


Figure S30. ^{13}C NMR ($CDCl_3$) spectrum of **31**.

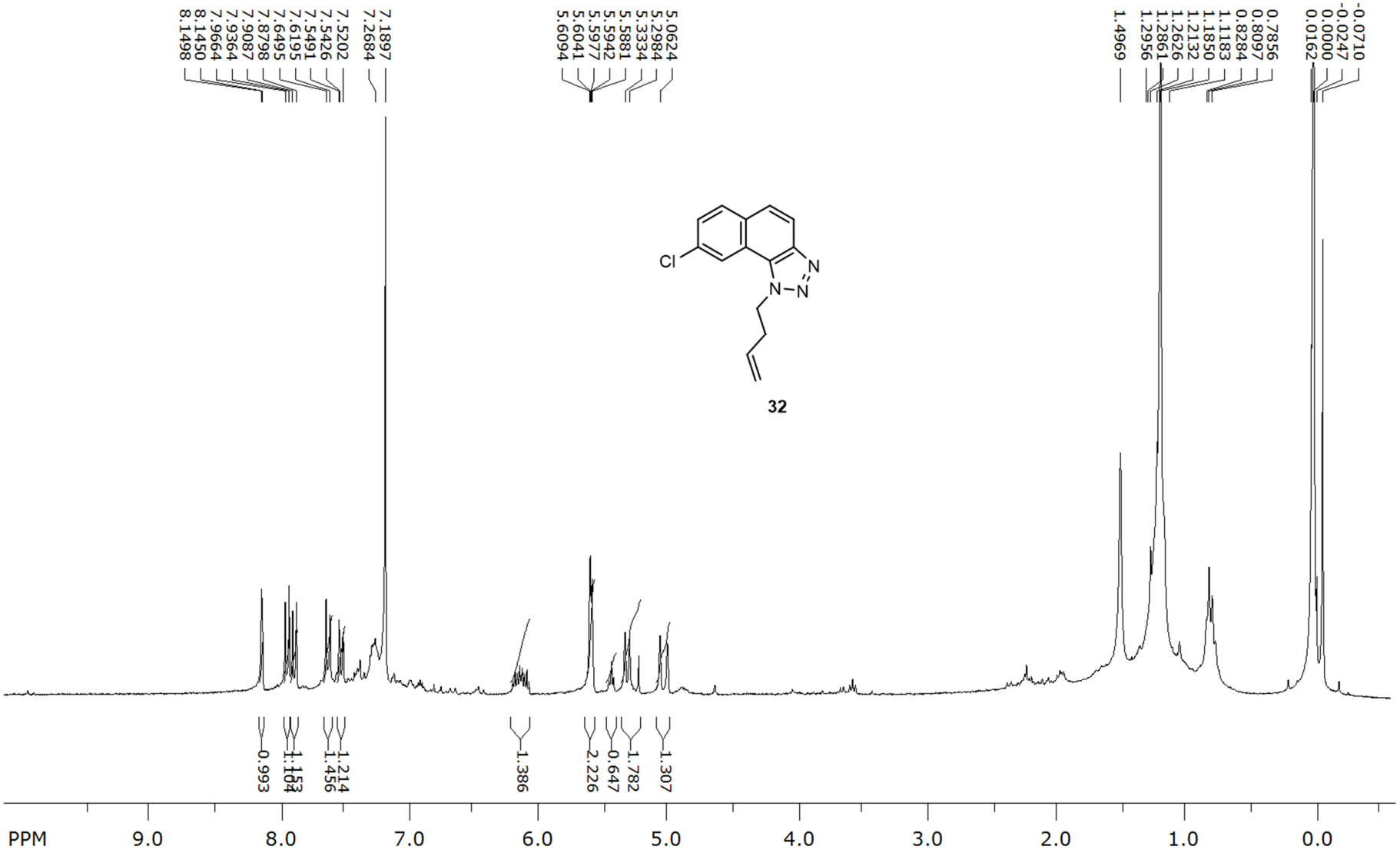


Figure S31. ^{1}H NMR ($CDCl_3$) spectrum of **32**.

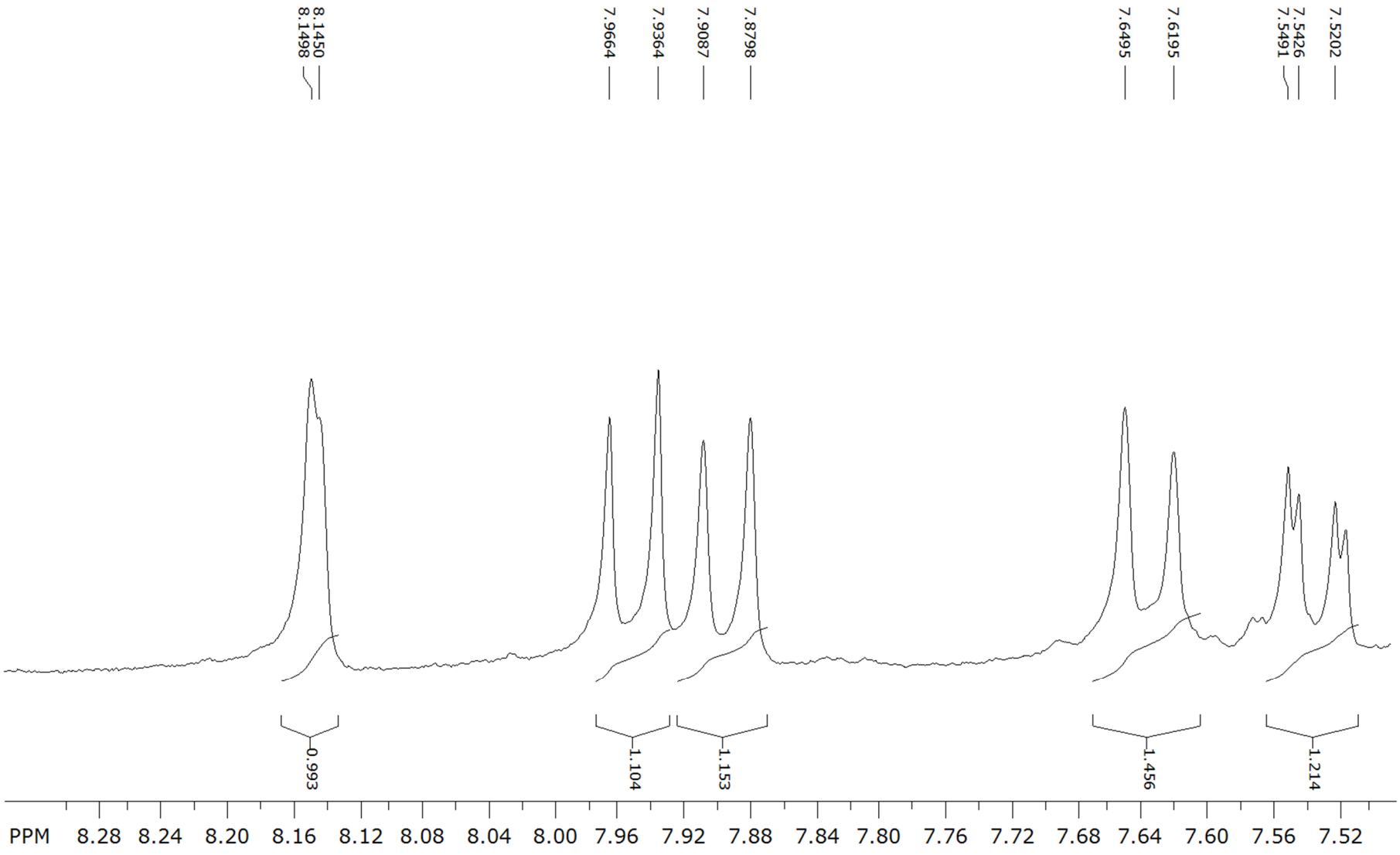


Figure S32. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **32**.

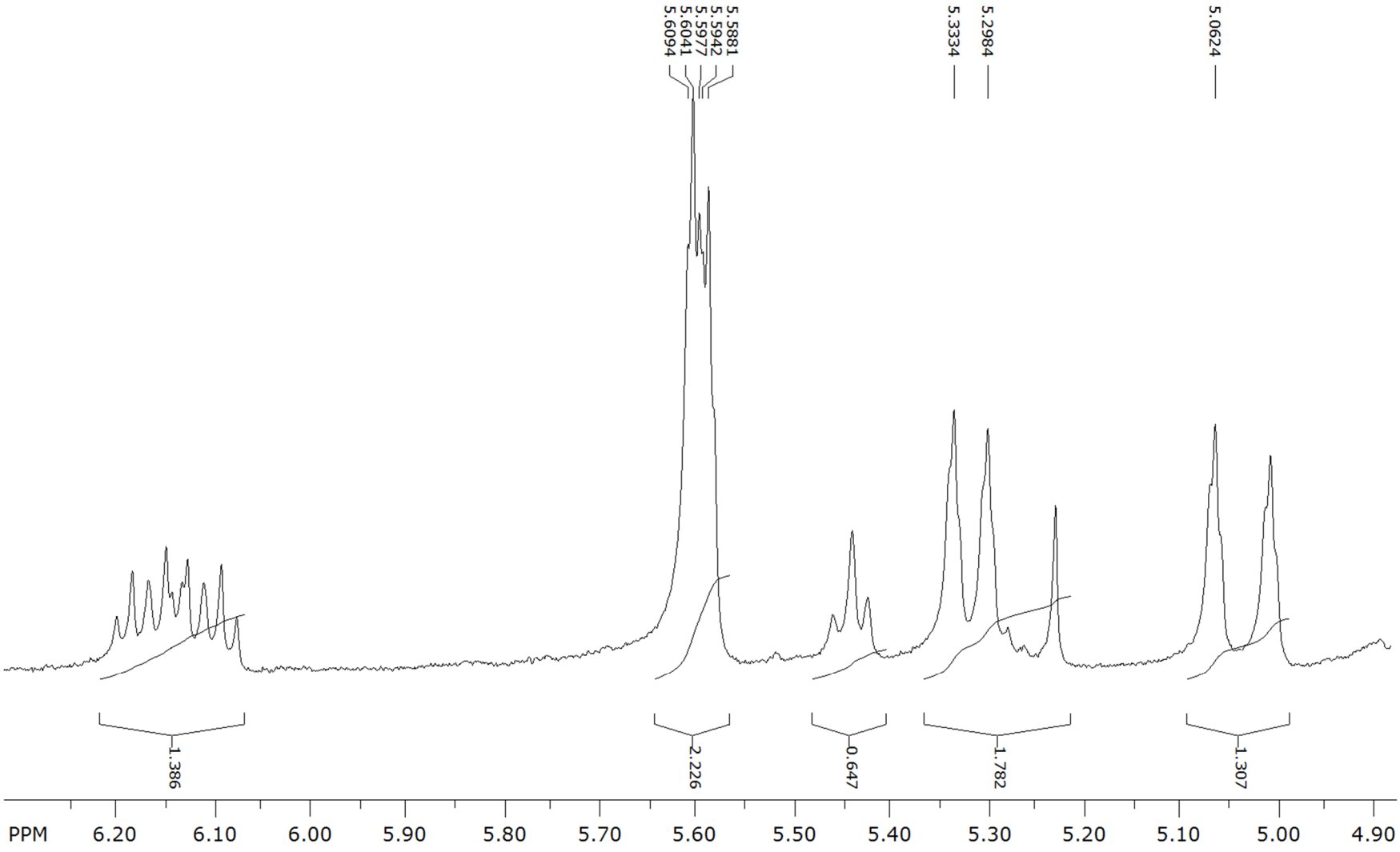


Figure S33. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **32**.

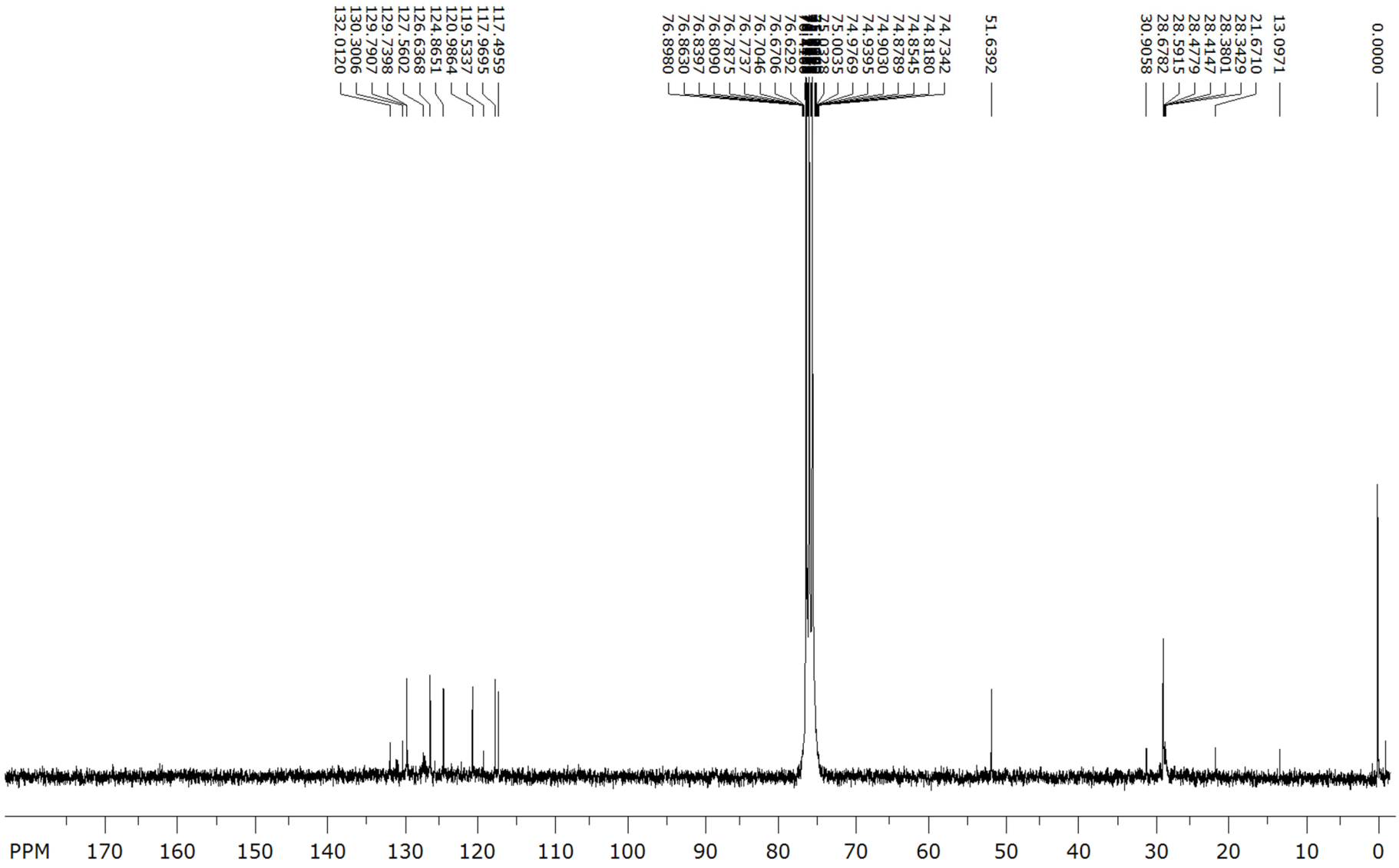


Figure S34. ^{13}C NMR ($CDCl_3$) spectrum of **32**.

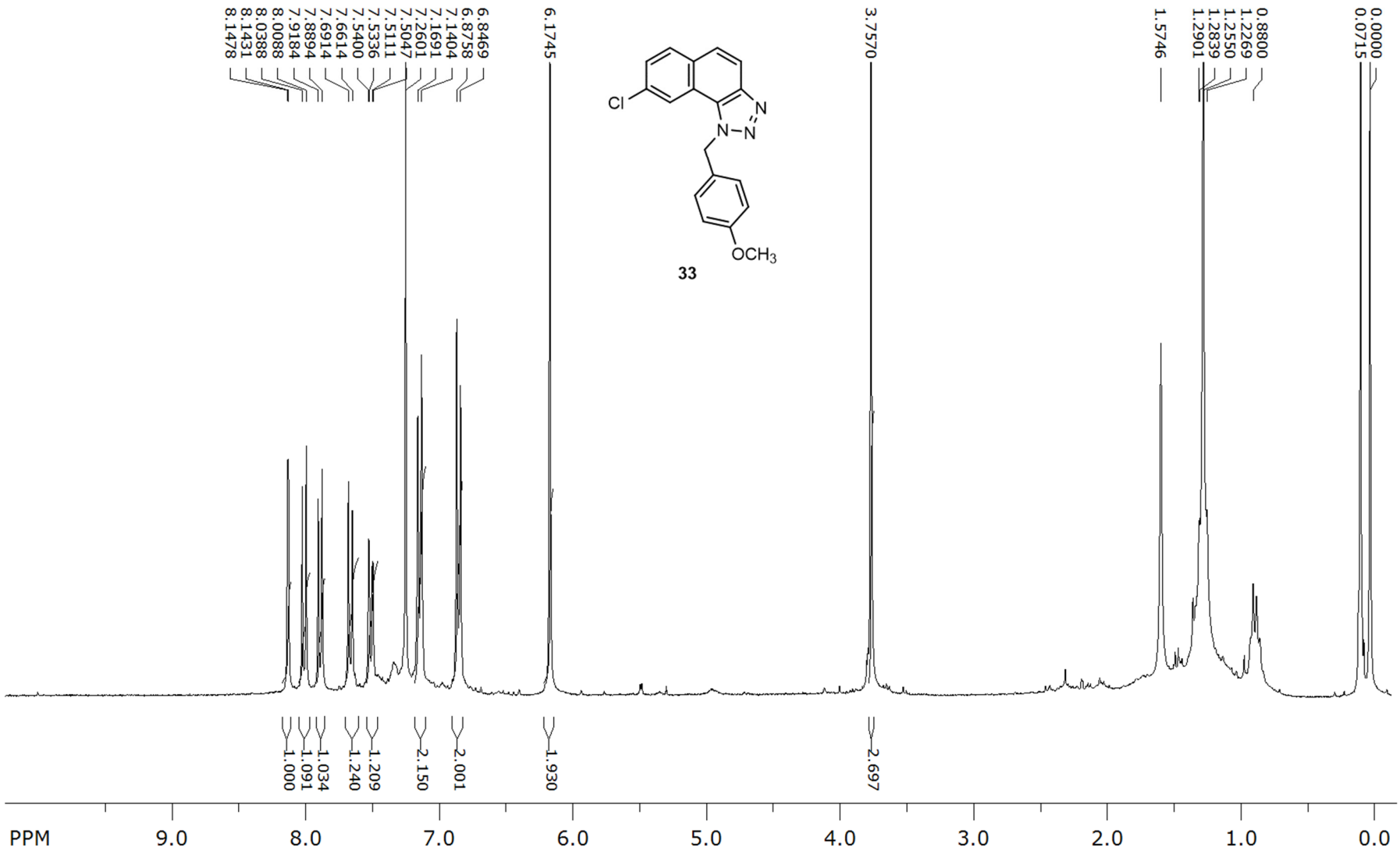


Figure S35. ^{1}H NMR ($CDCl_3$) spectrum of **33**.

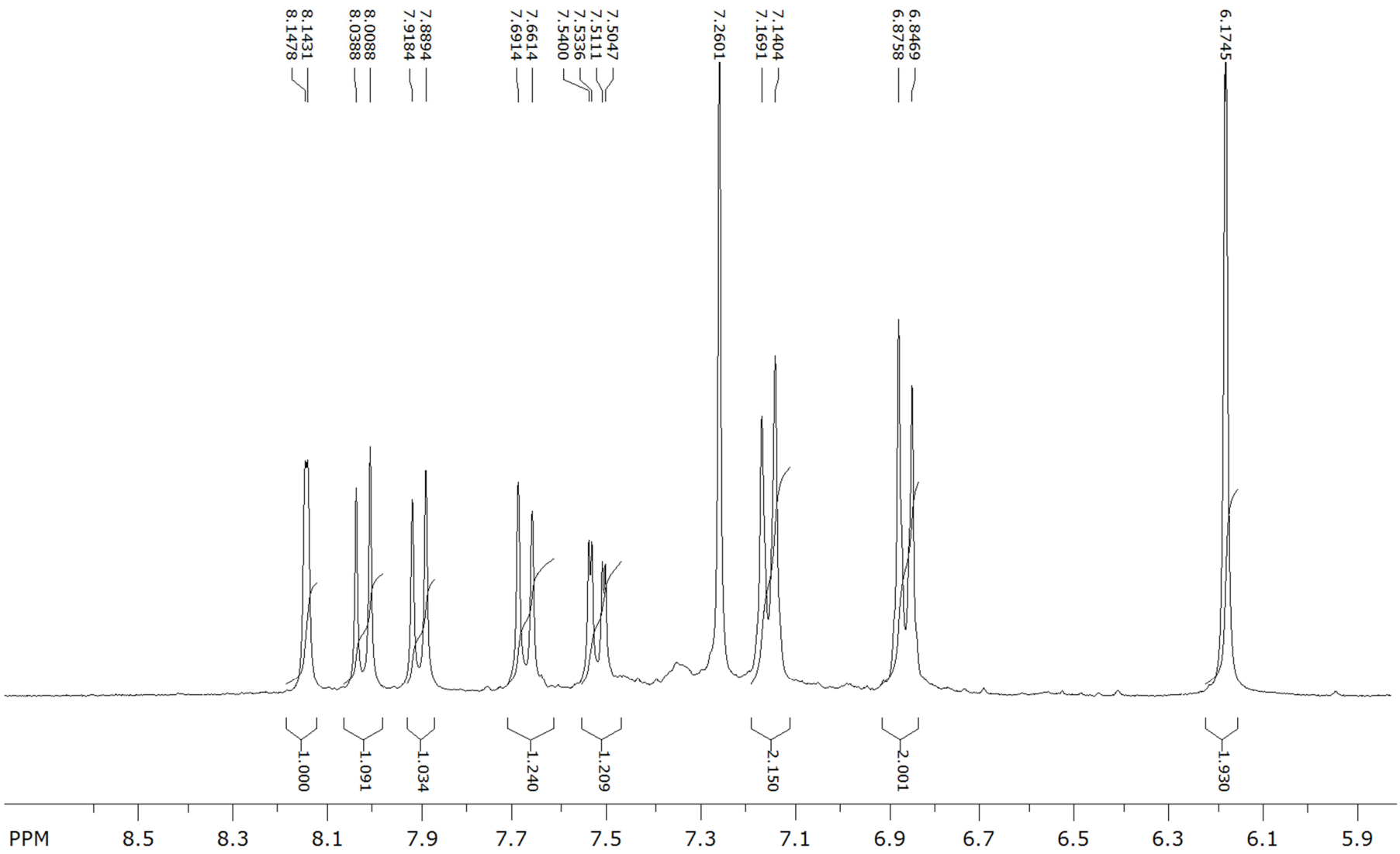


Figure S36. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **33**.

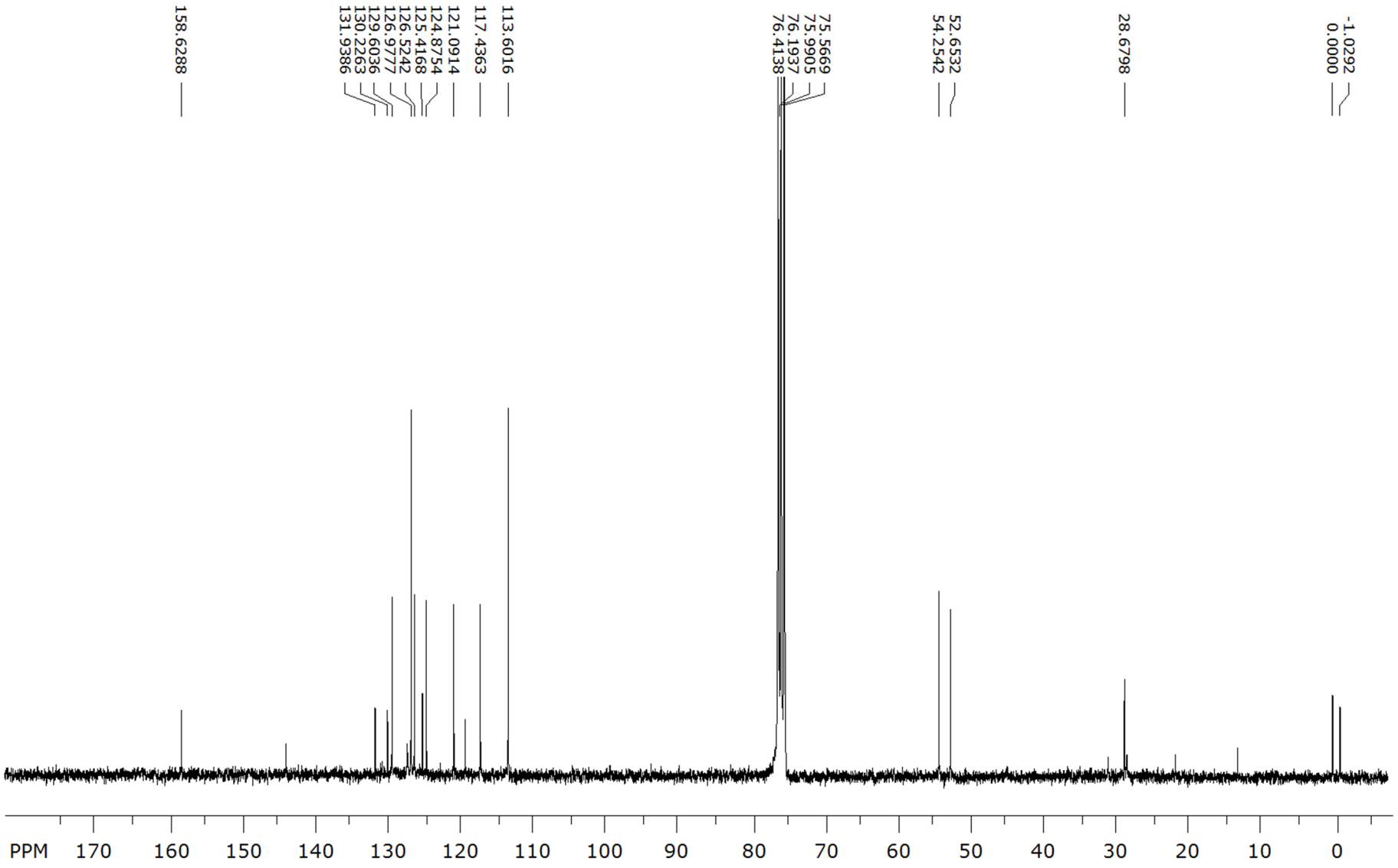


Figure S37. ^{13}C NMR ($CDCl_3$) spectrum of **33**.

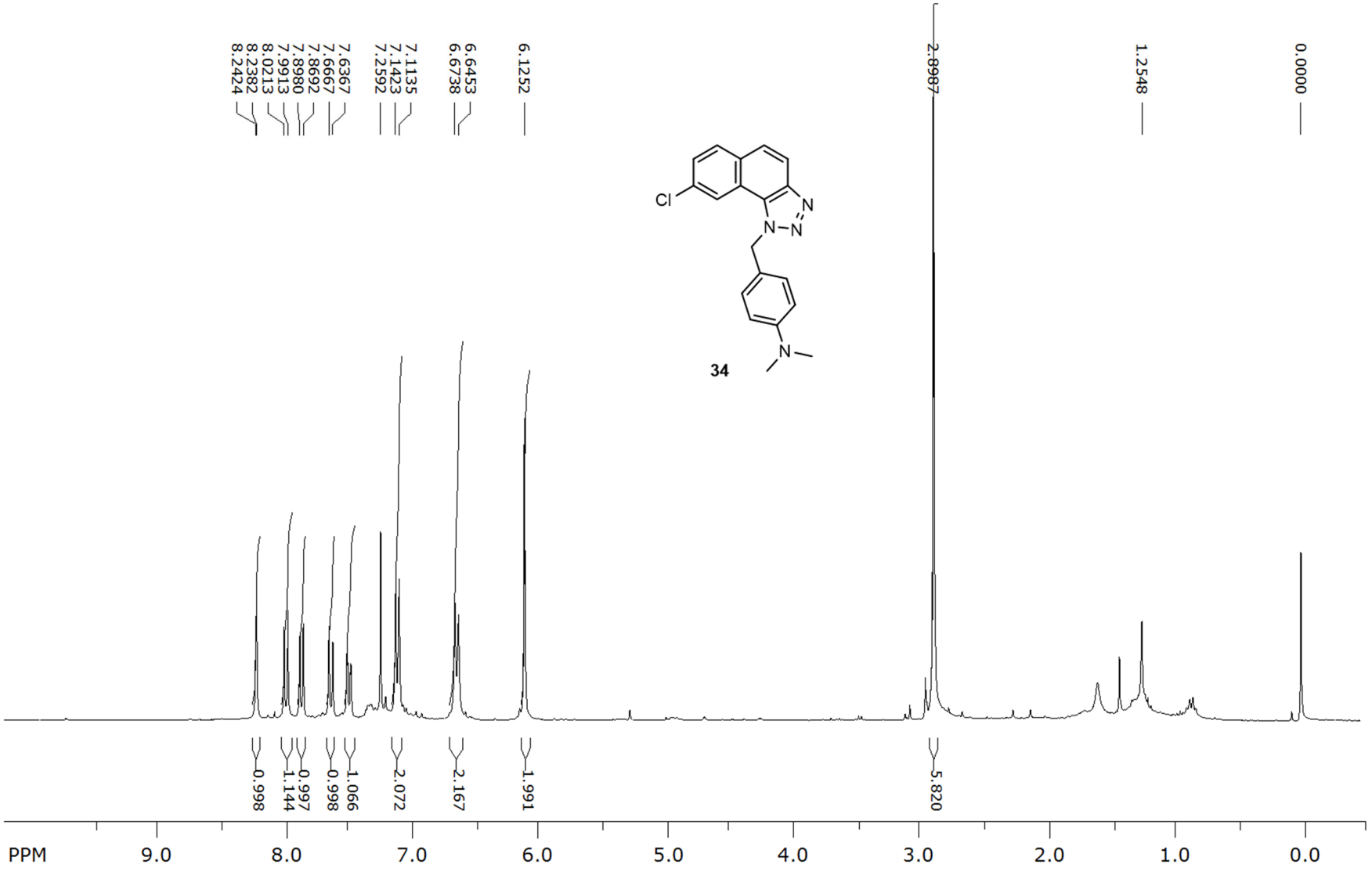


Figure S38. ^{1}H NMR ($CDCl_3$) spectrum of **34**.

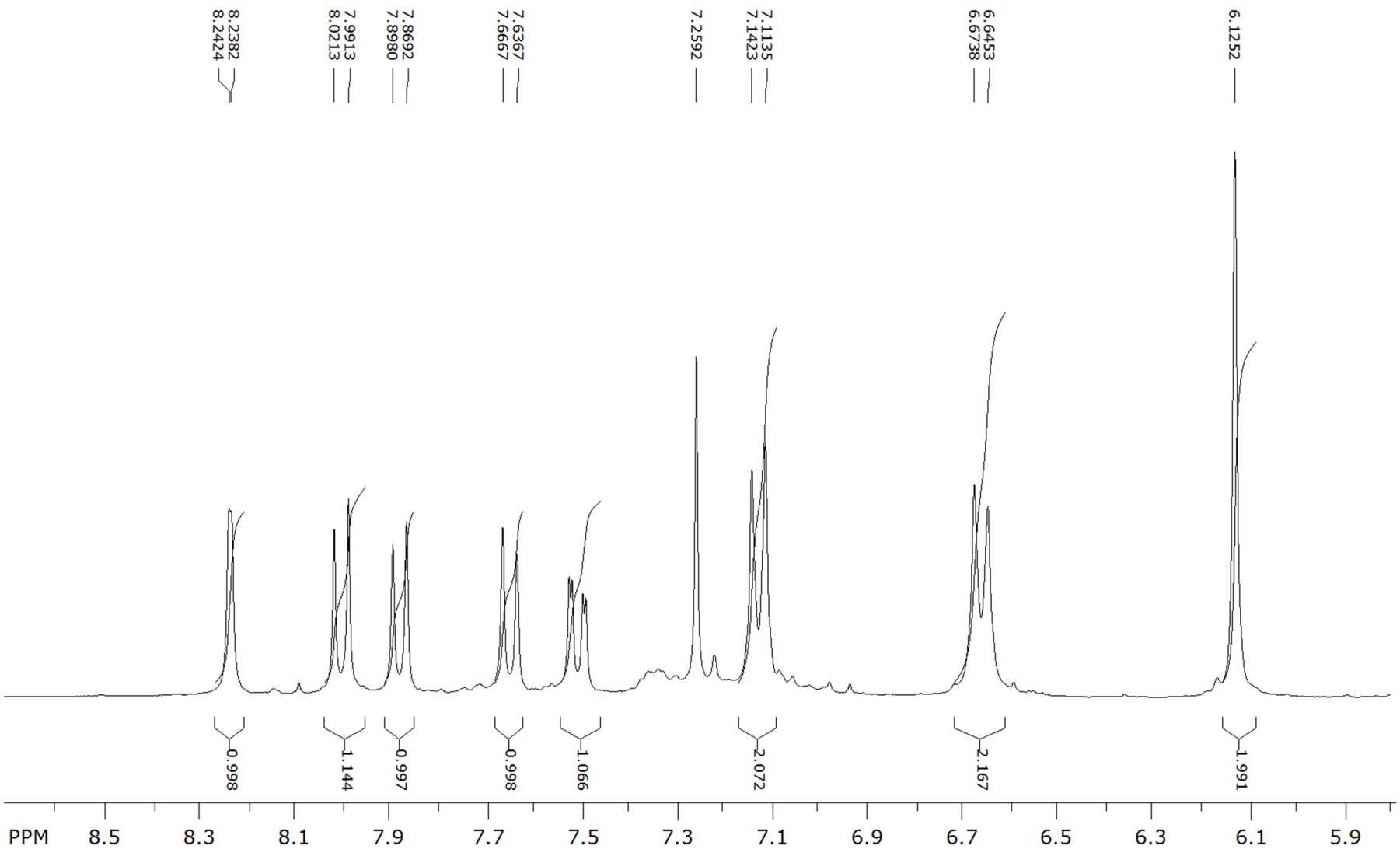


Figure S39. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **34**.

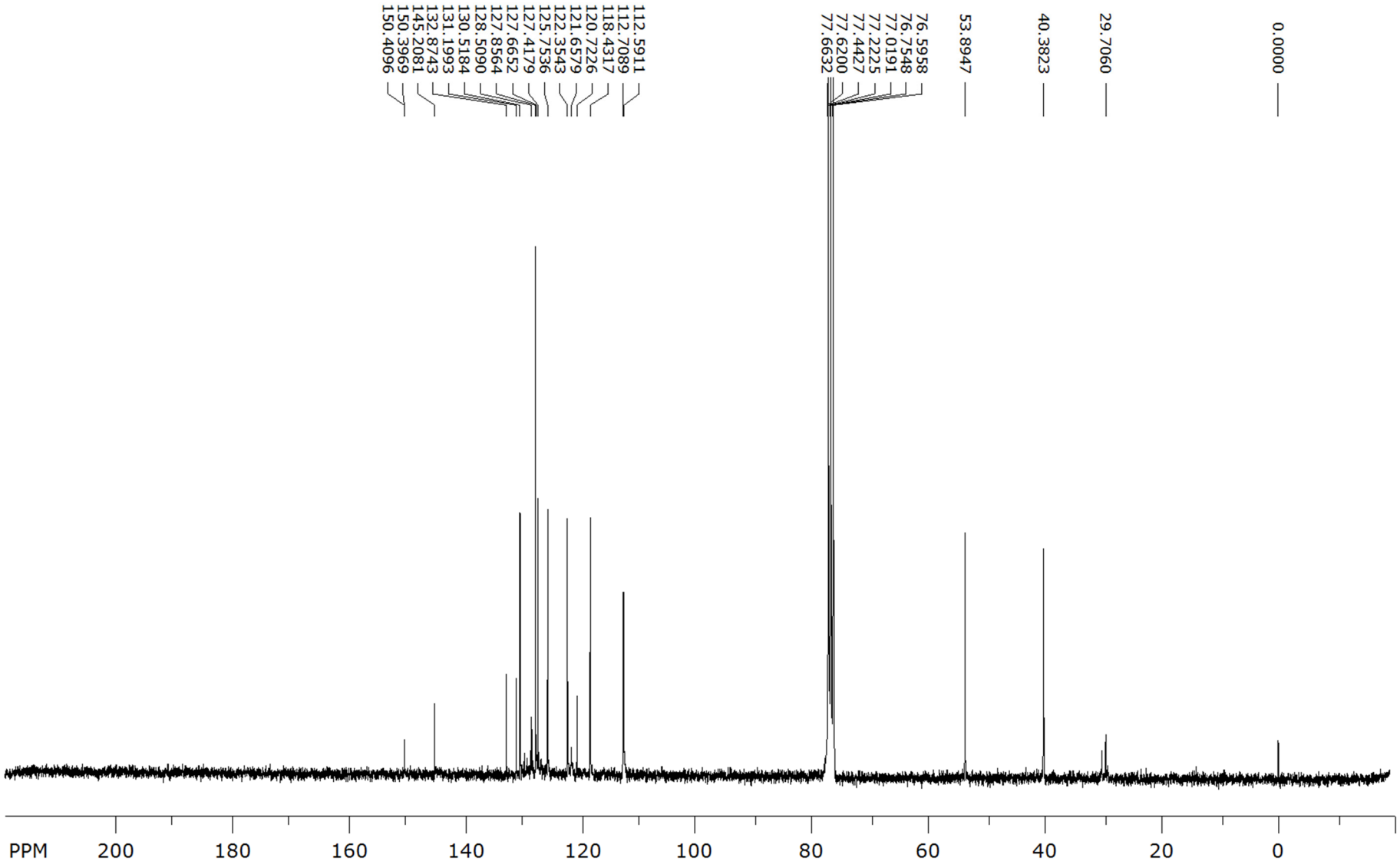


Figure S40. ^{13}C NMR ($CDCl_3$) spectrum of **34**.

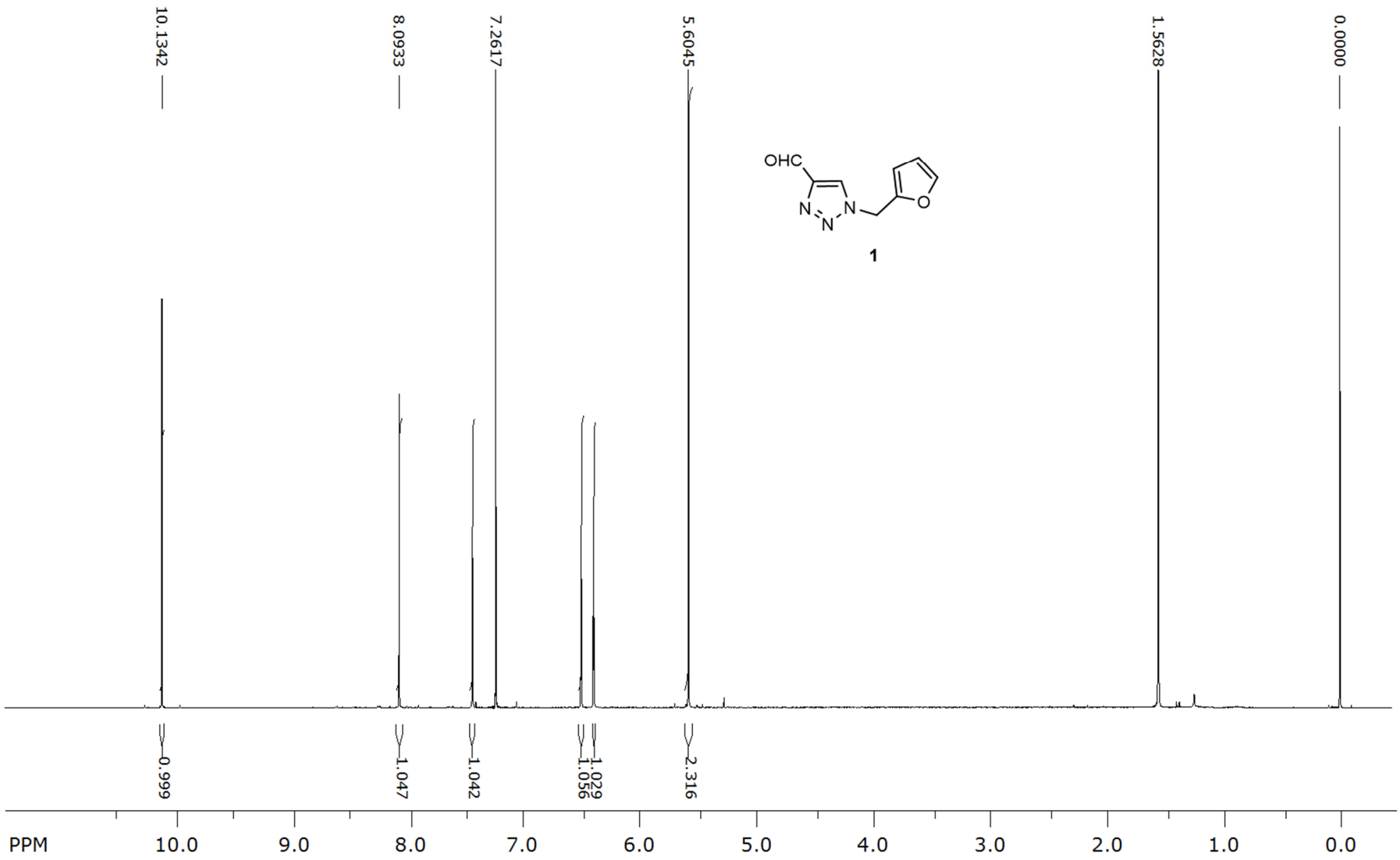


Figure S41. ^{1}H NMR ($CDCl_3$) spectrum of **1**.

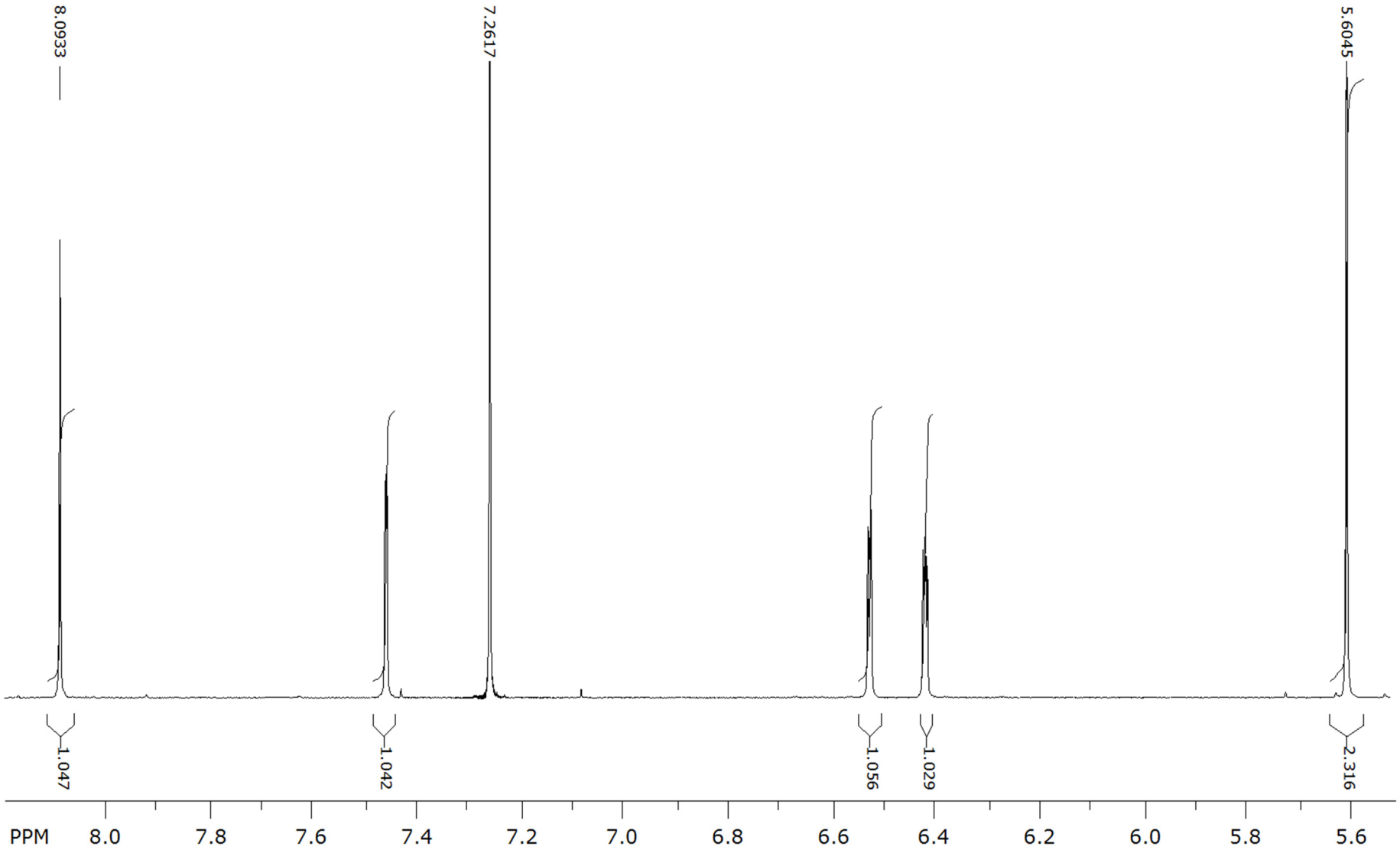


Figure S42. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **1**.

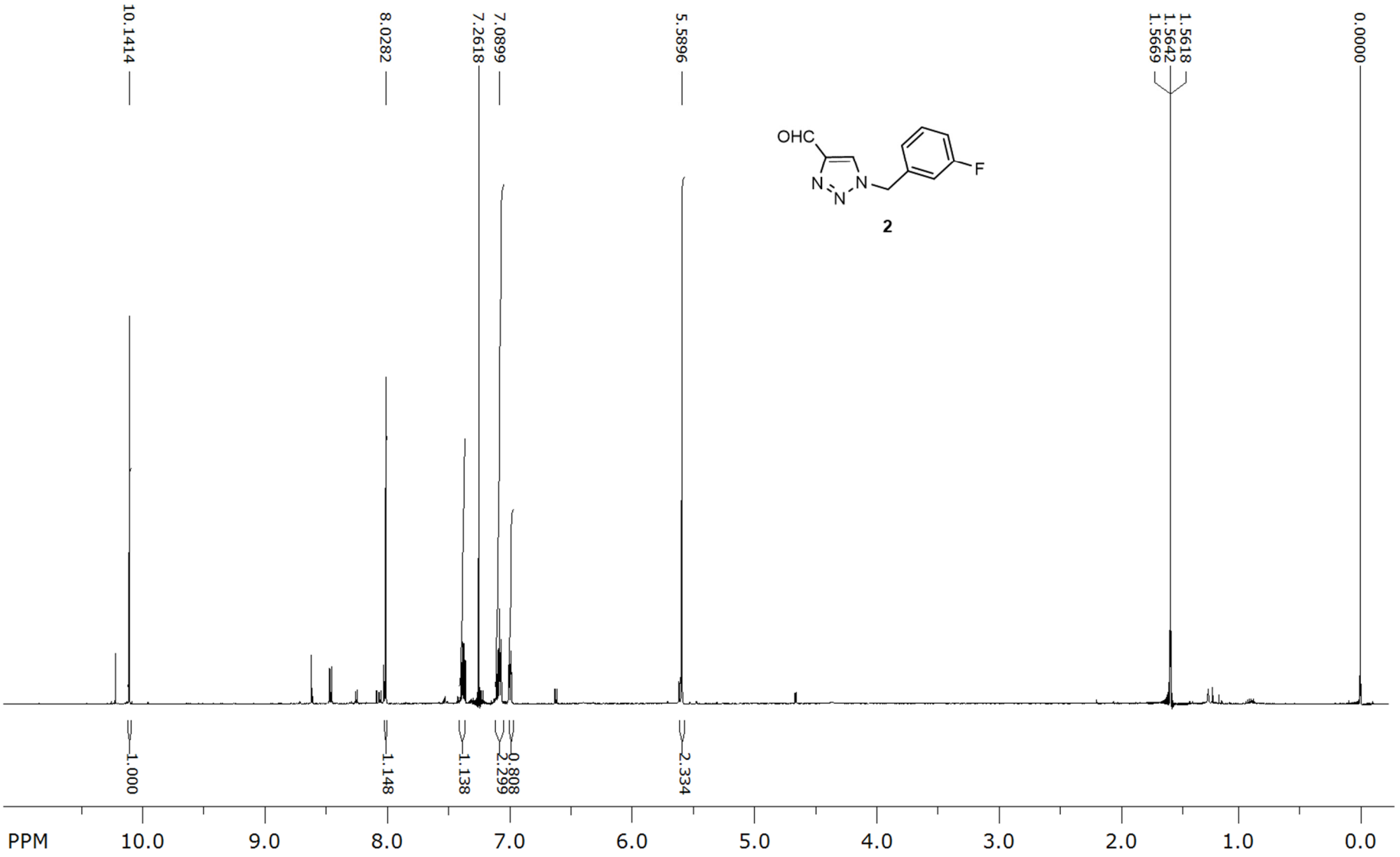


Figure S43. ^{1}H NMR ($CDCl_3$) spectrum of **2**.

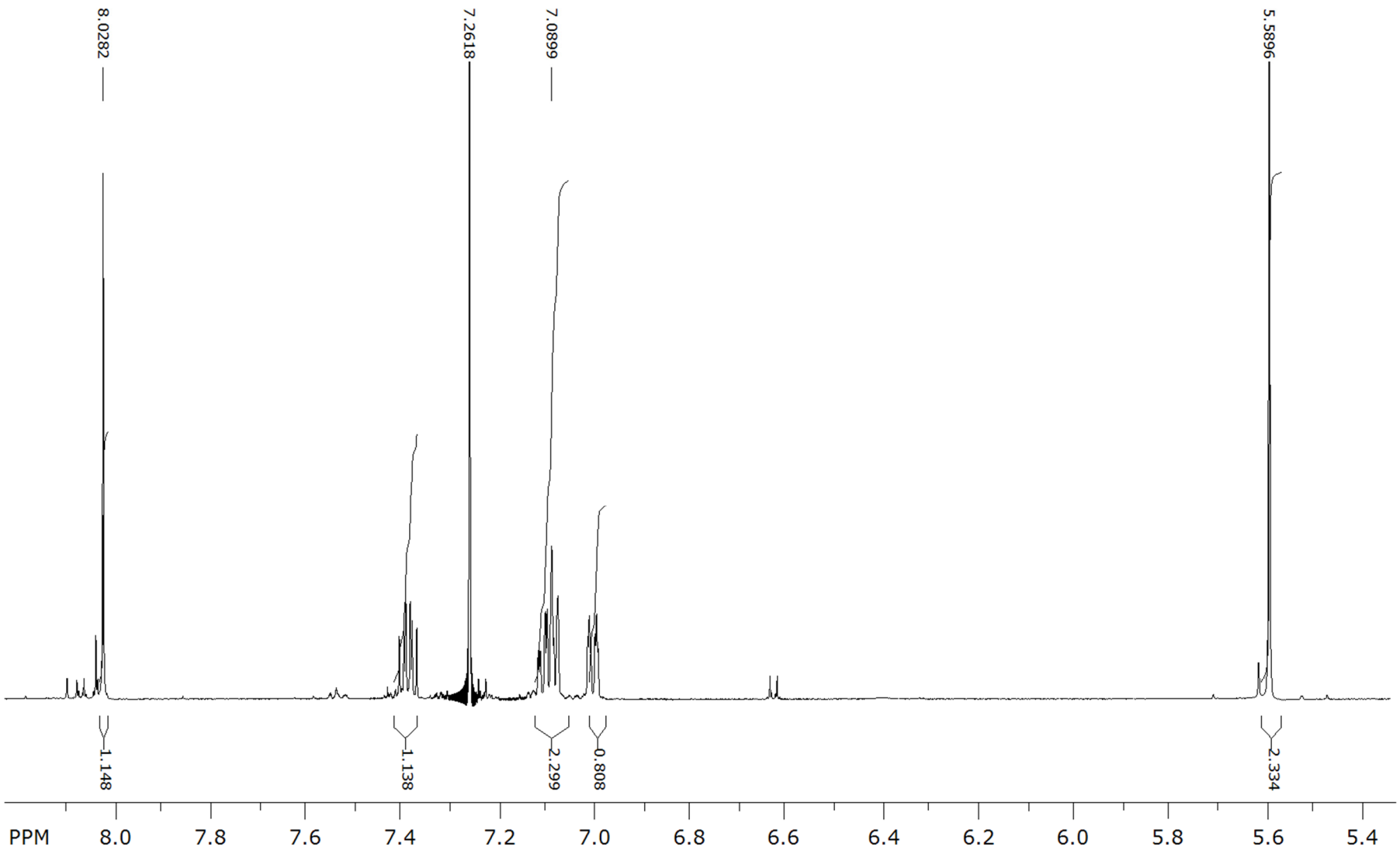


Figure S44. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **2**.

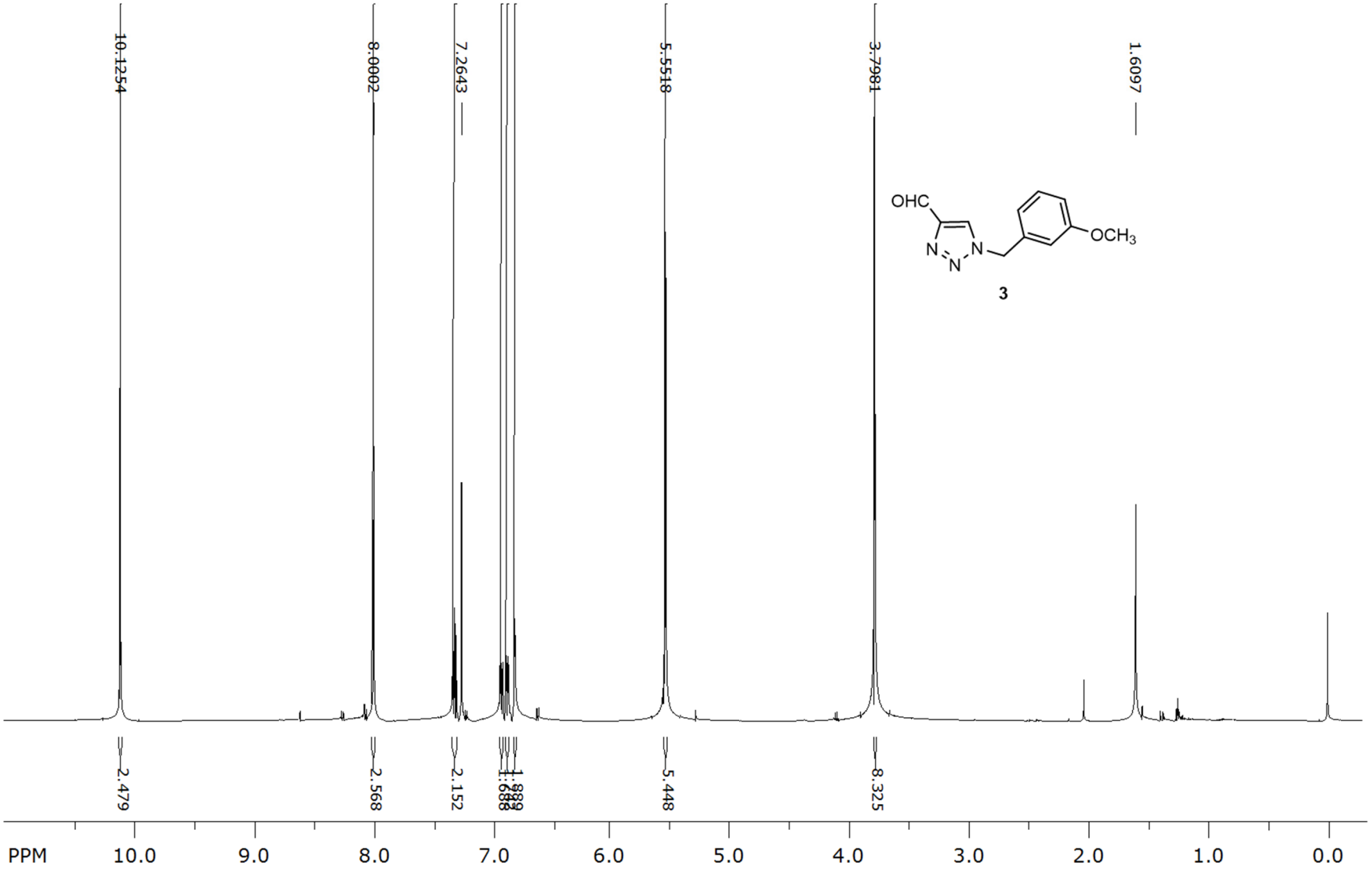


Figure S45. ^{1}H NMR ($CDCl_3$) spectrum of **3**.

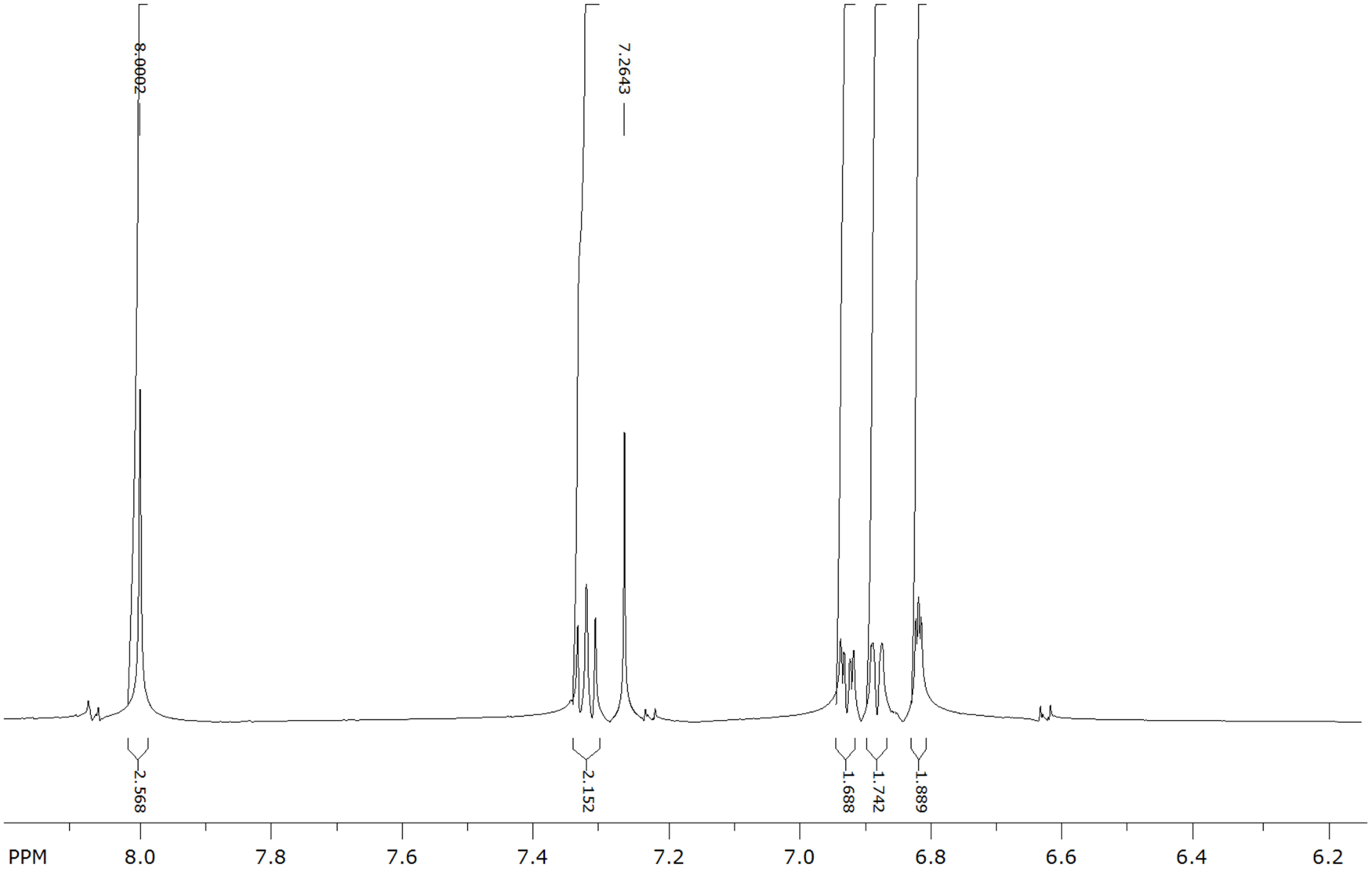


Figure S46. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **3**.

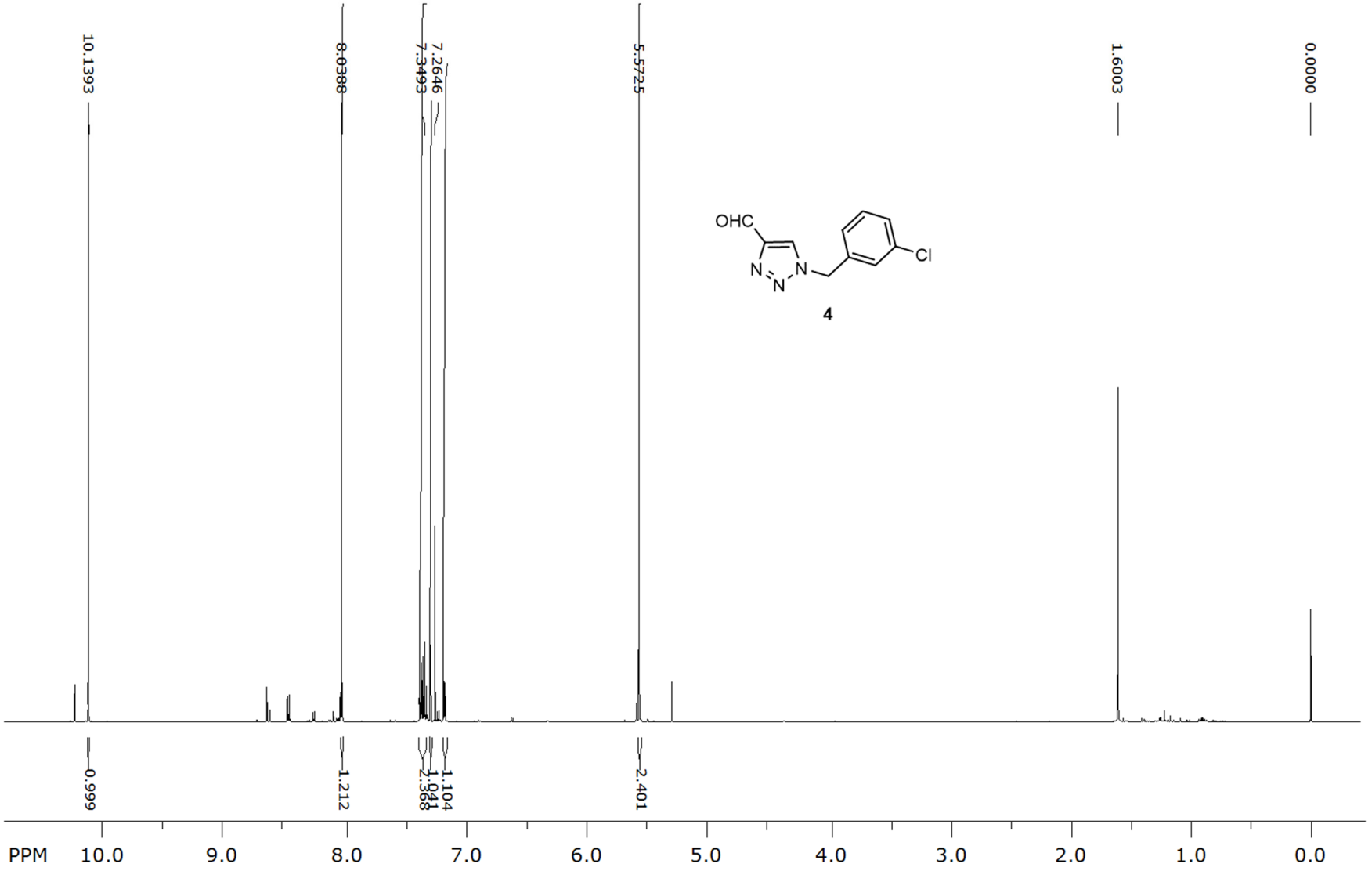


Figure S47. ^{1}H NMR ($CDCl_3$) spectrum of **4**.

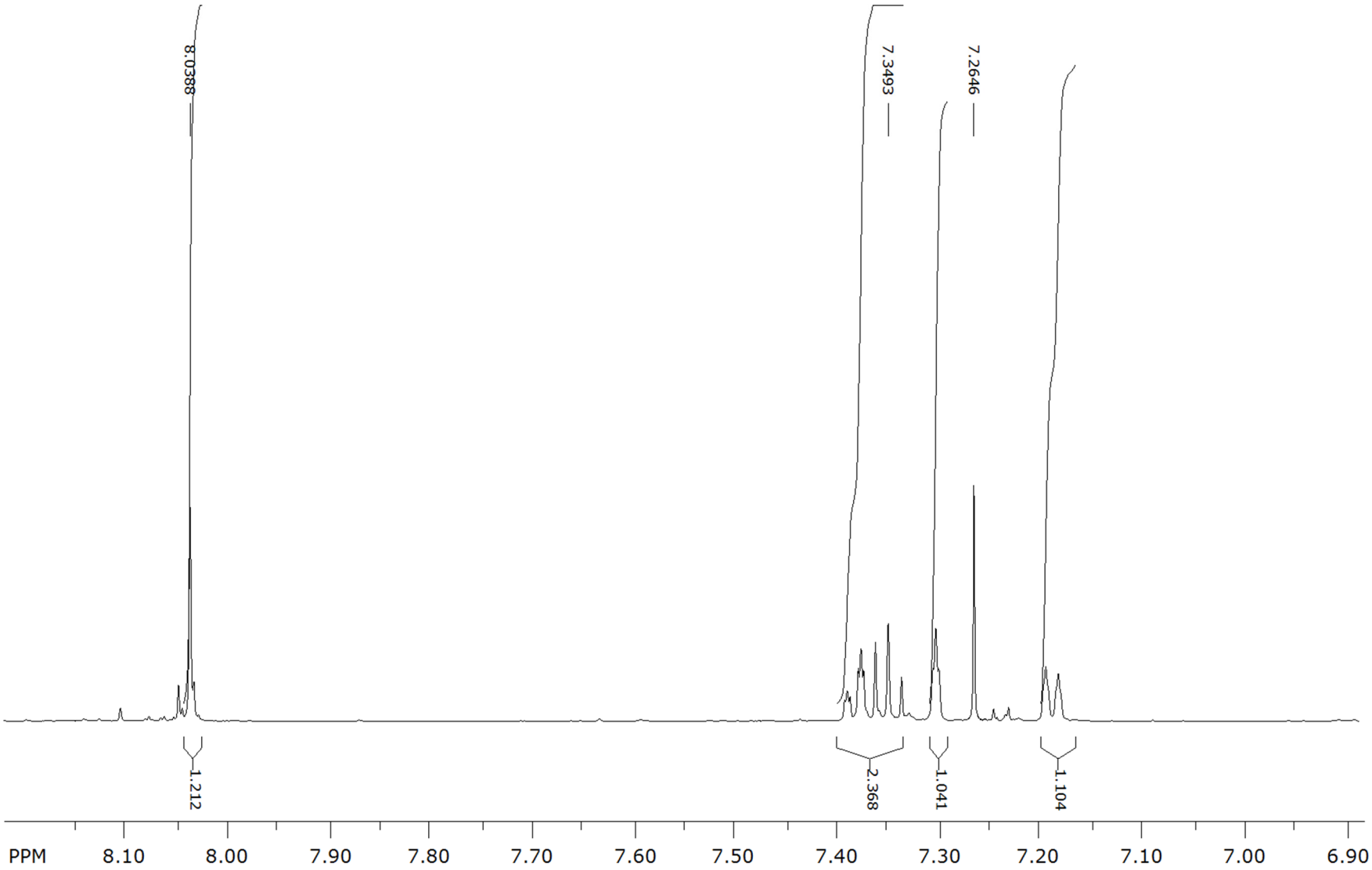


Figure S48. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **4**.

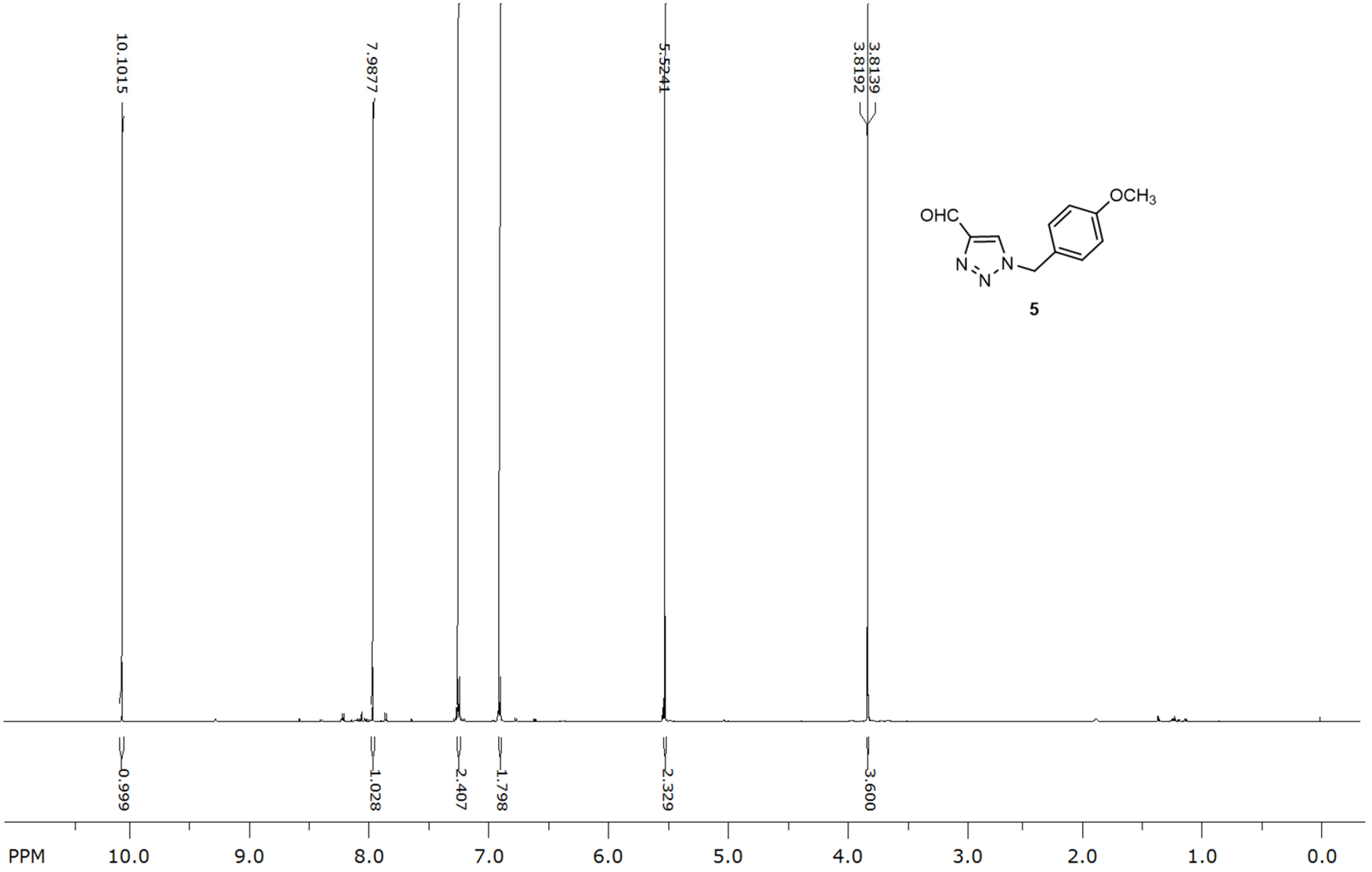


Figure S49. ^{1}H NMR ($CDCl_3$) spectrum of **5**.

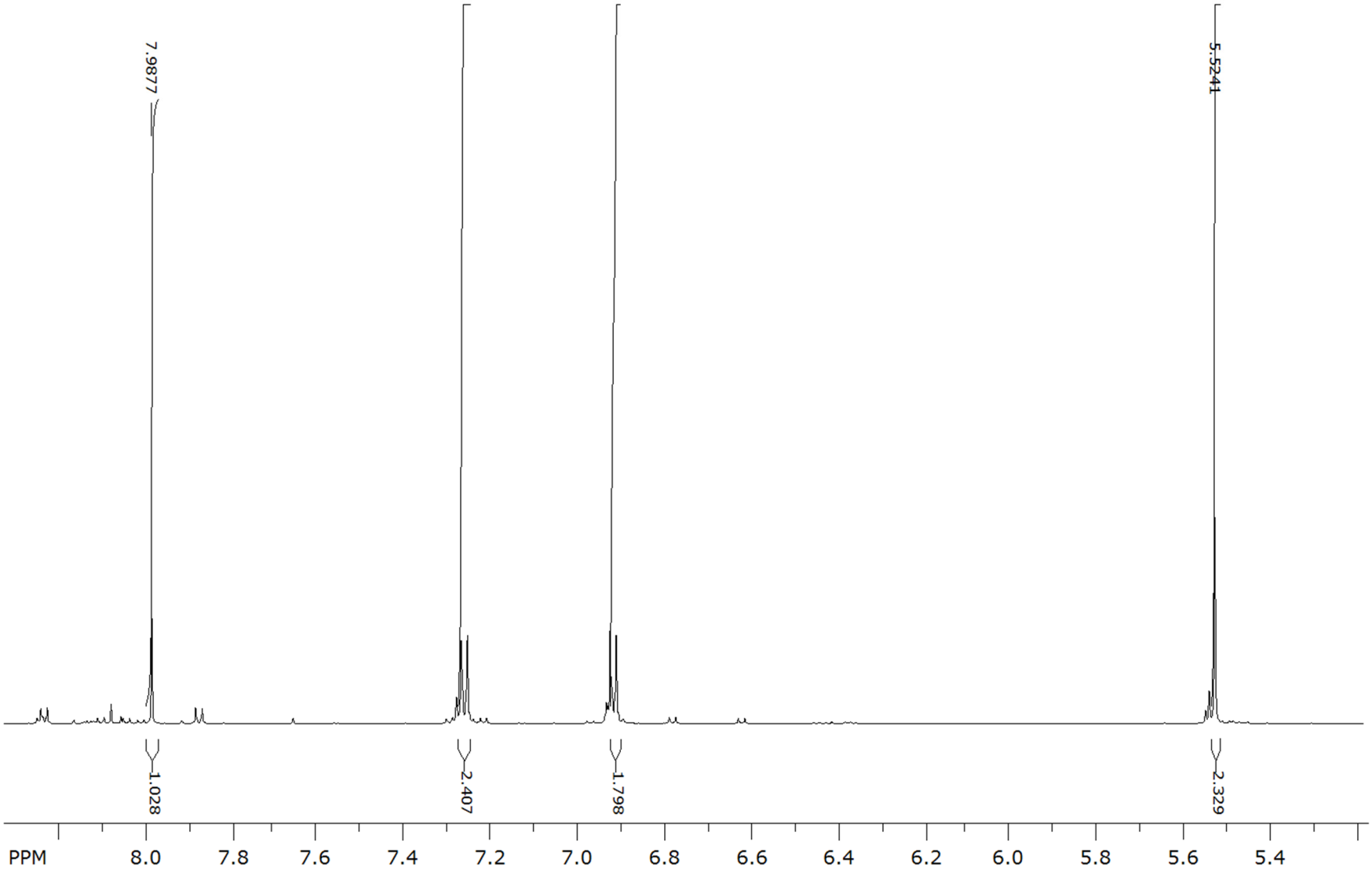


Figure S50. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **5**.

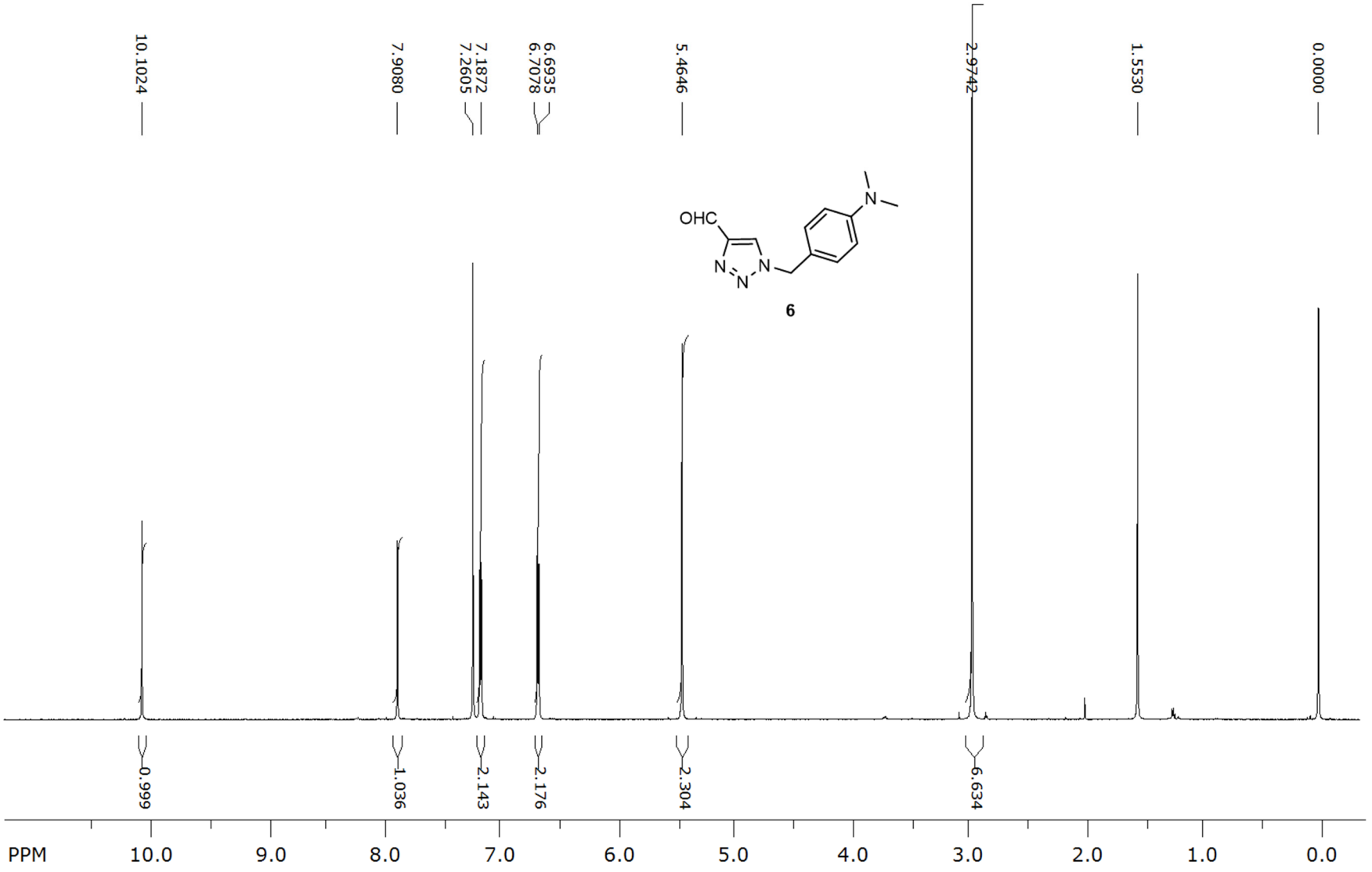


Figure S51. ^{1}H NMR ($CDCl_3$) spectrum of **6**.

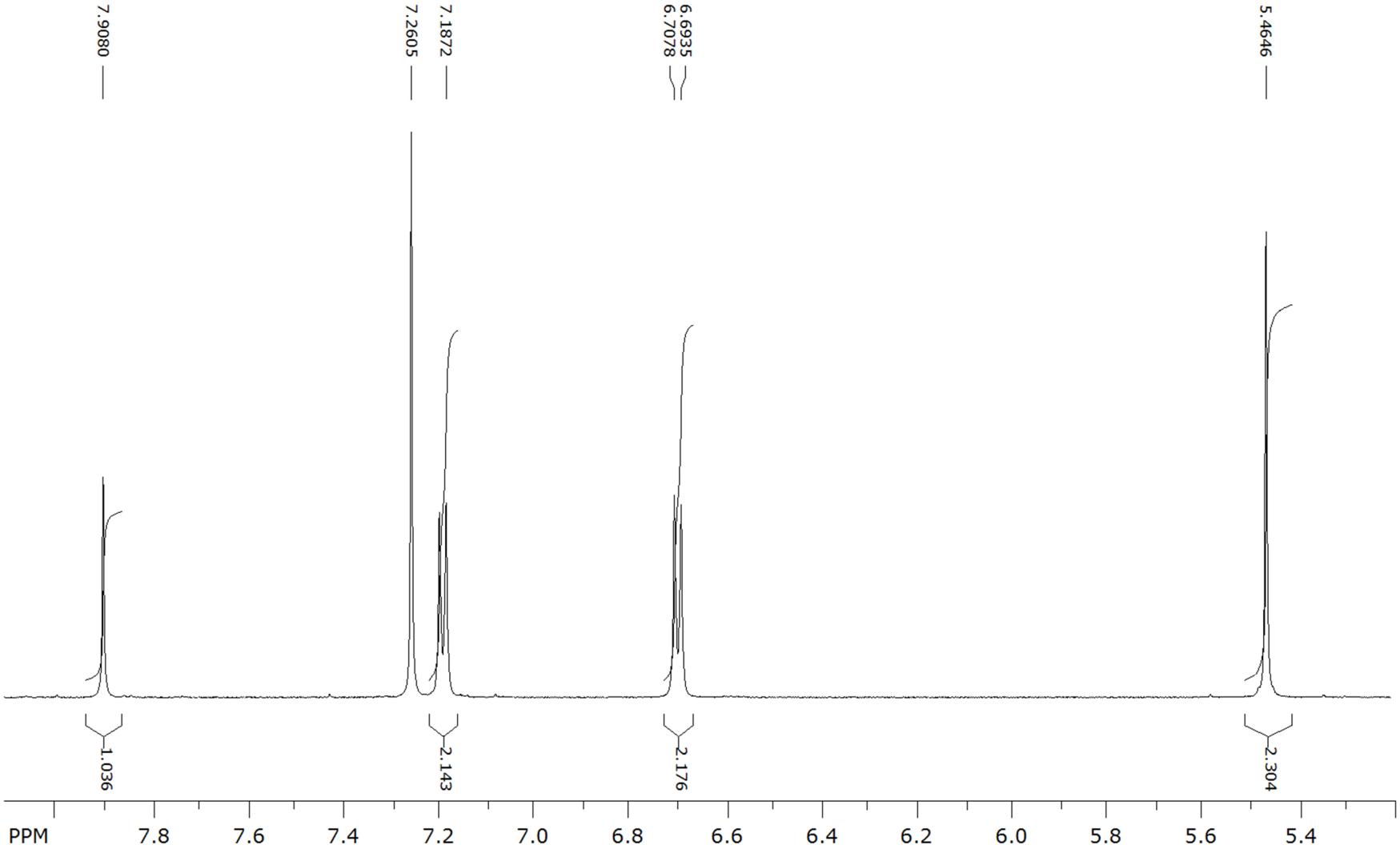


Figure S52. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **6**.

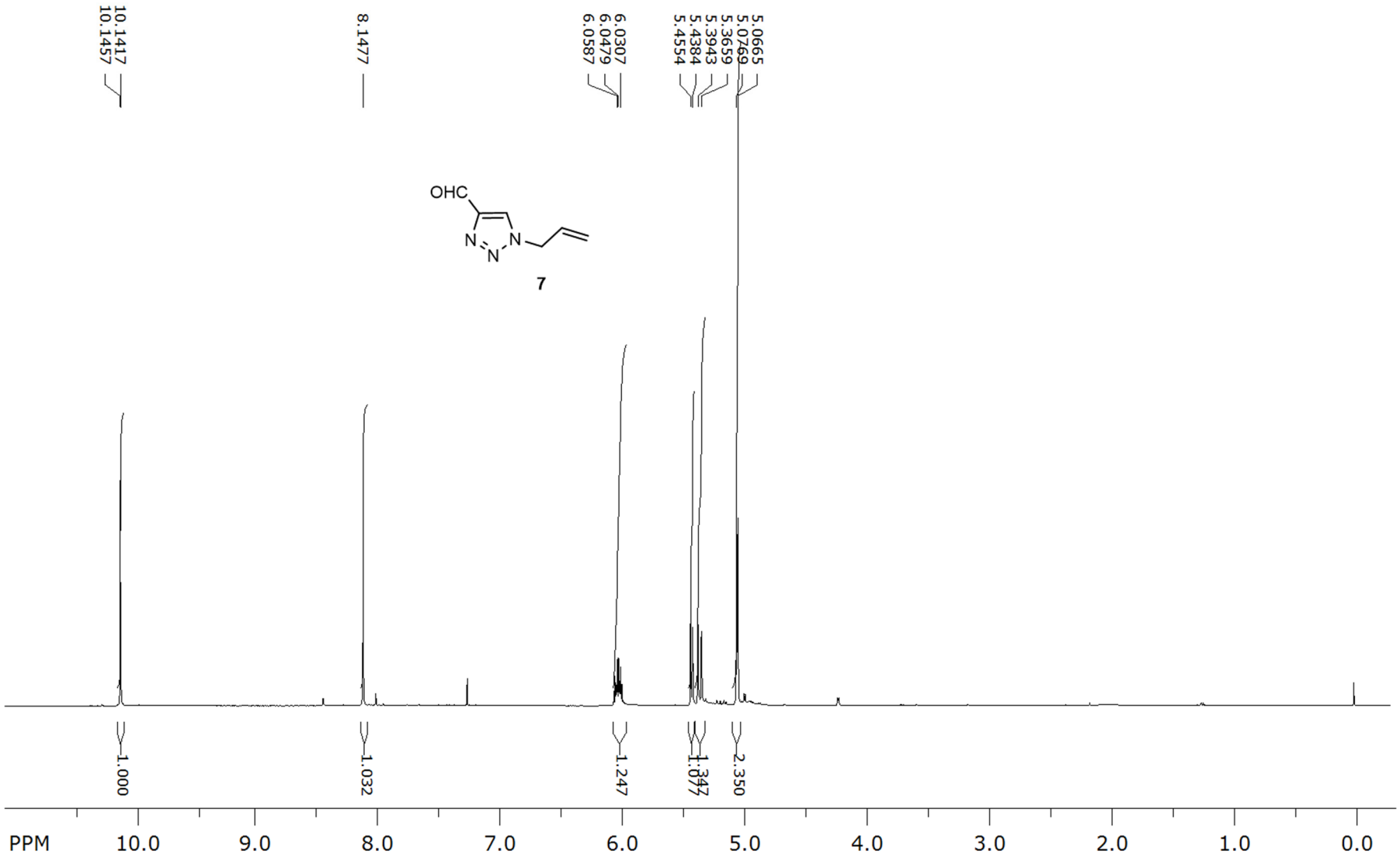


Figure S53. ^{1}H NMR ($CDCl_3$) spectrum of **7**.

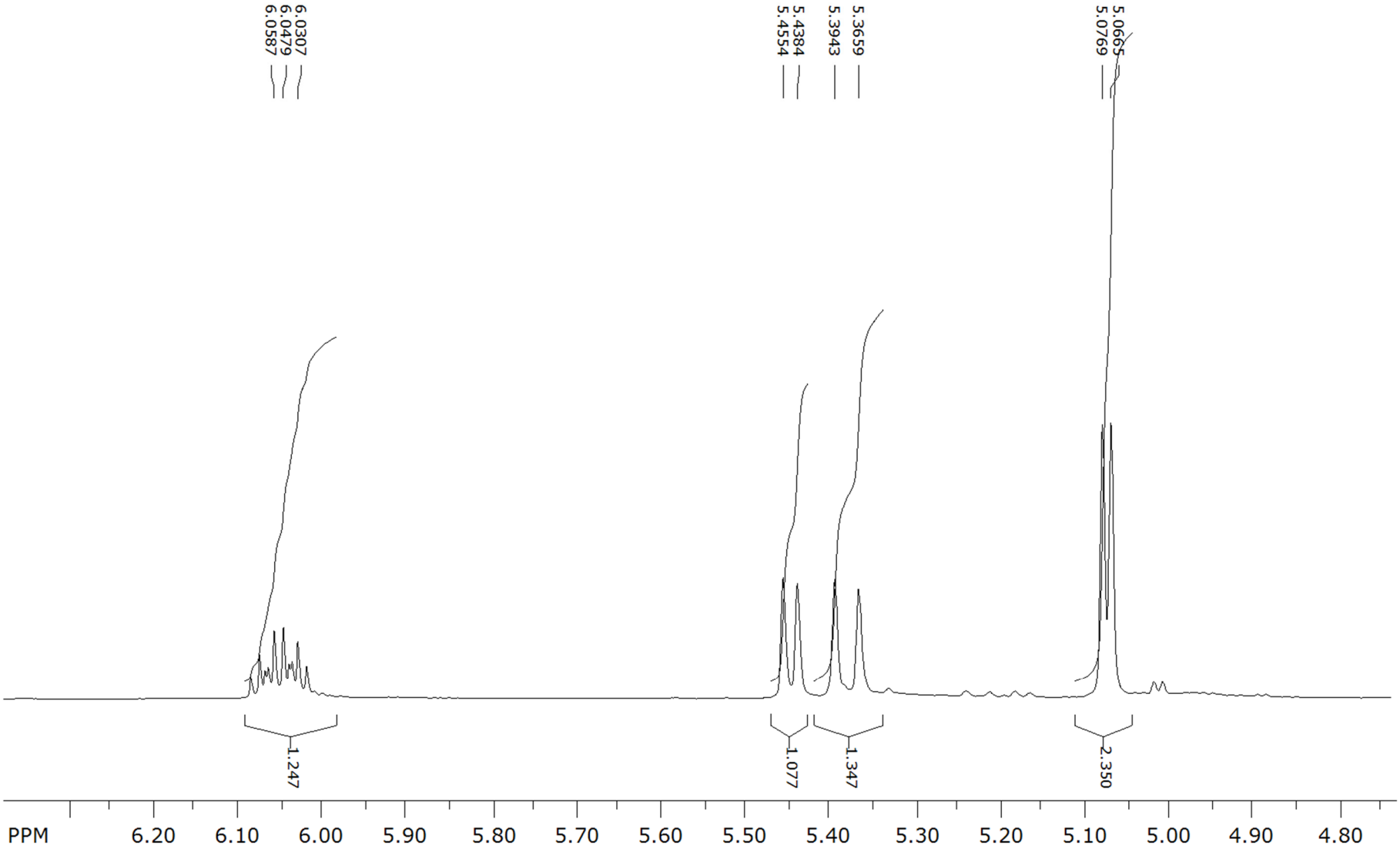


Figure S54. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **7**.

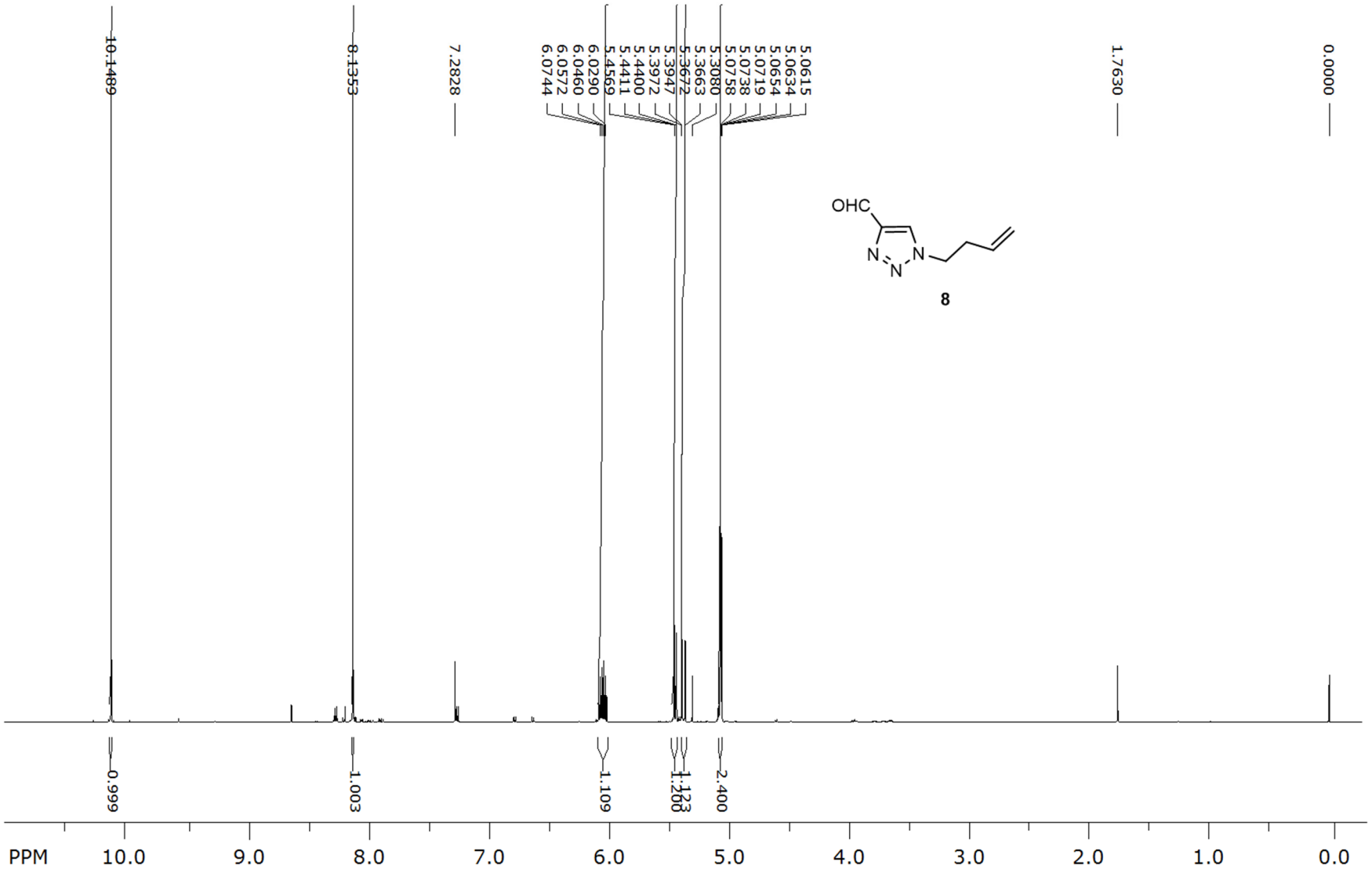


Figure S55. ^{1}H NMR ($CDCl_3$) spectrum of **8**.

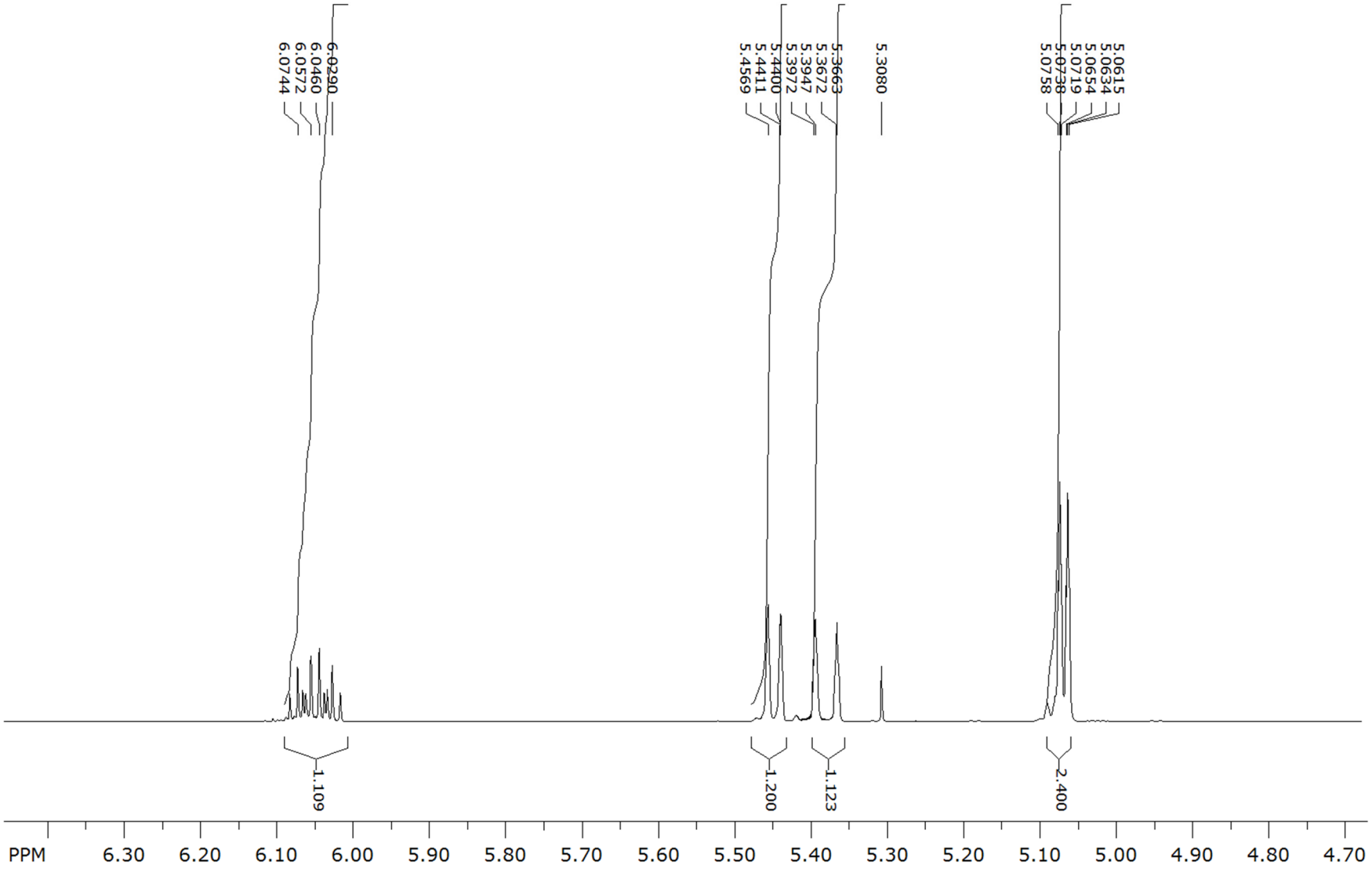


Figure S56. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **8**.

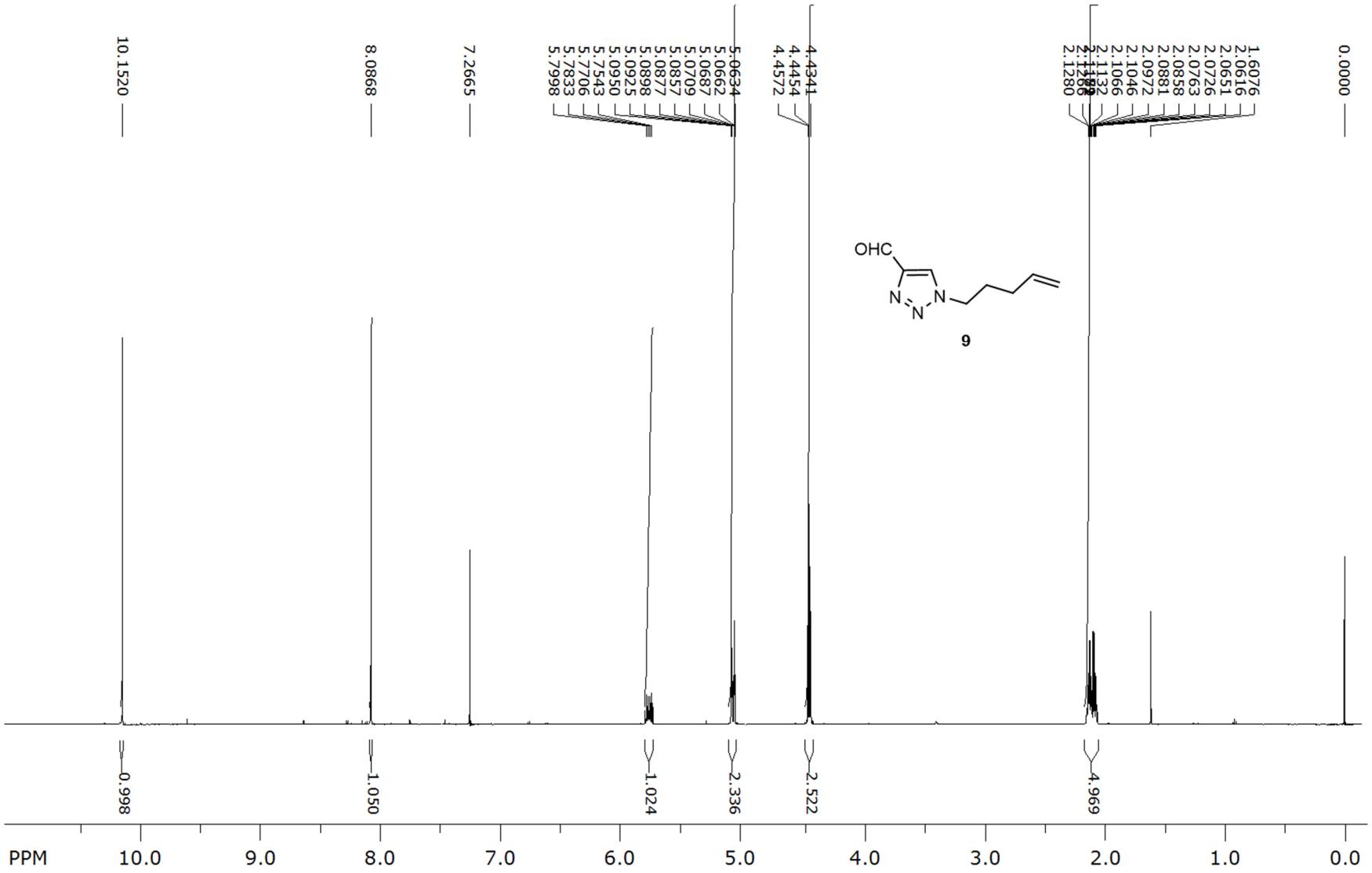


Figure S57. ^{1}H NMR ($CDCl_3$) spectrum of **9**.

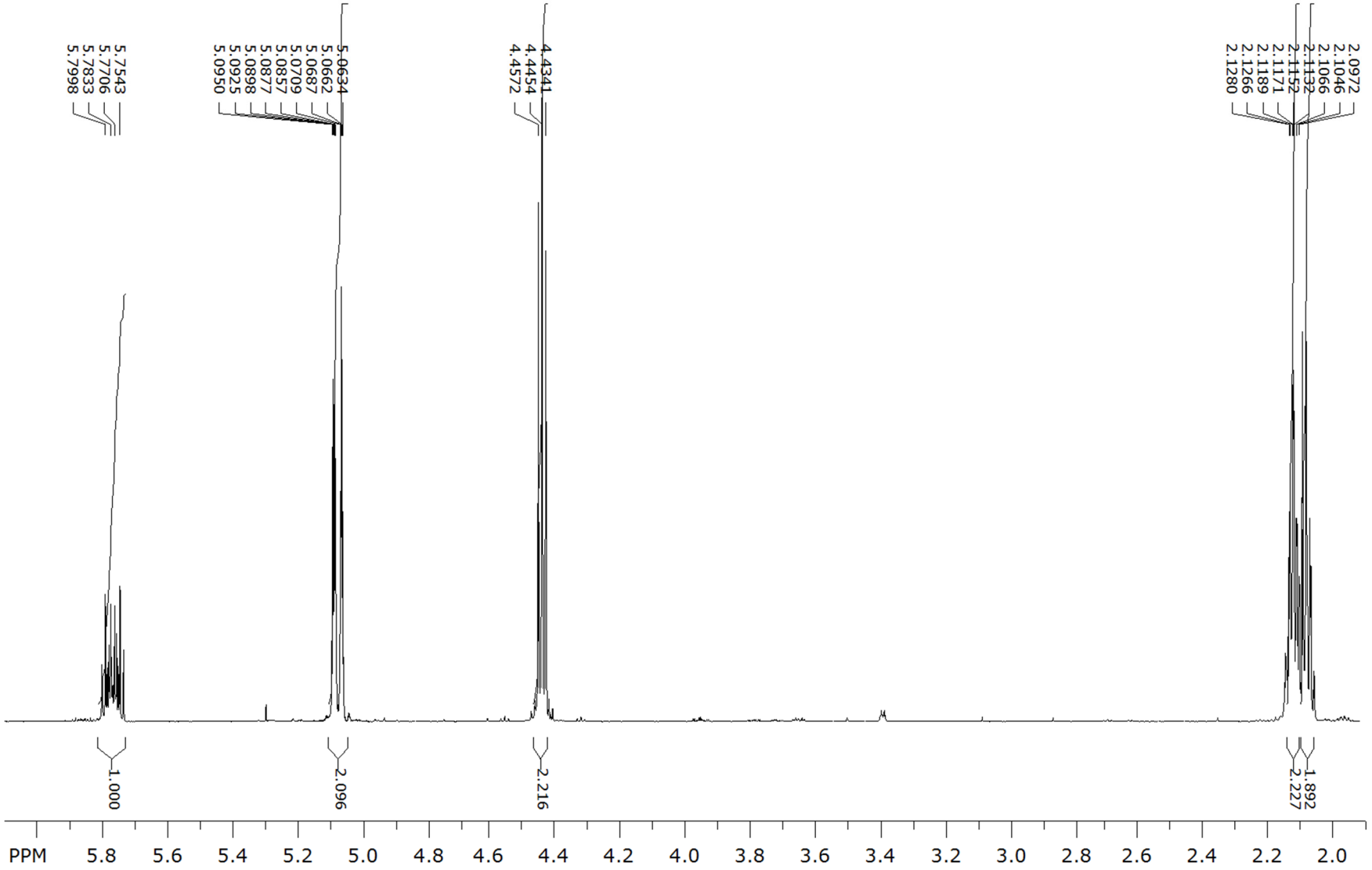


Figure S58. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **9**.

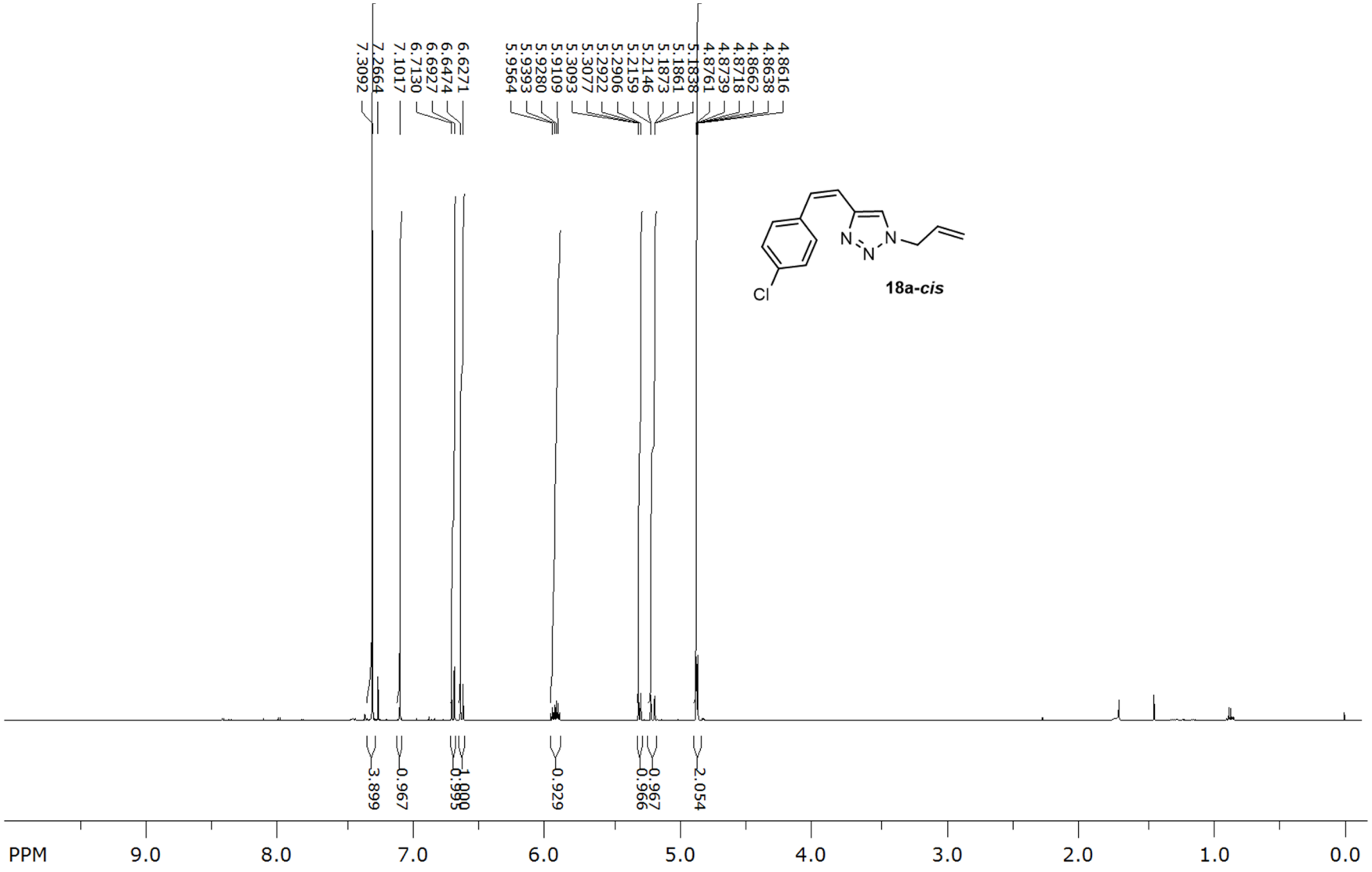


Figure S59. ^{1}H NMR ($CDCl_3$) spectrum of ***cis*-18**.

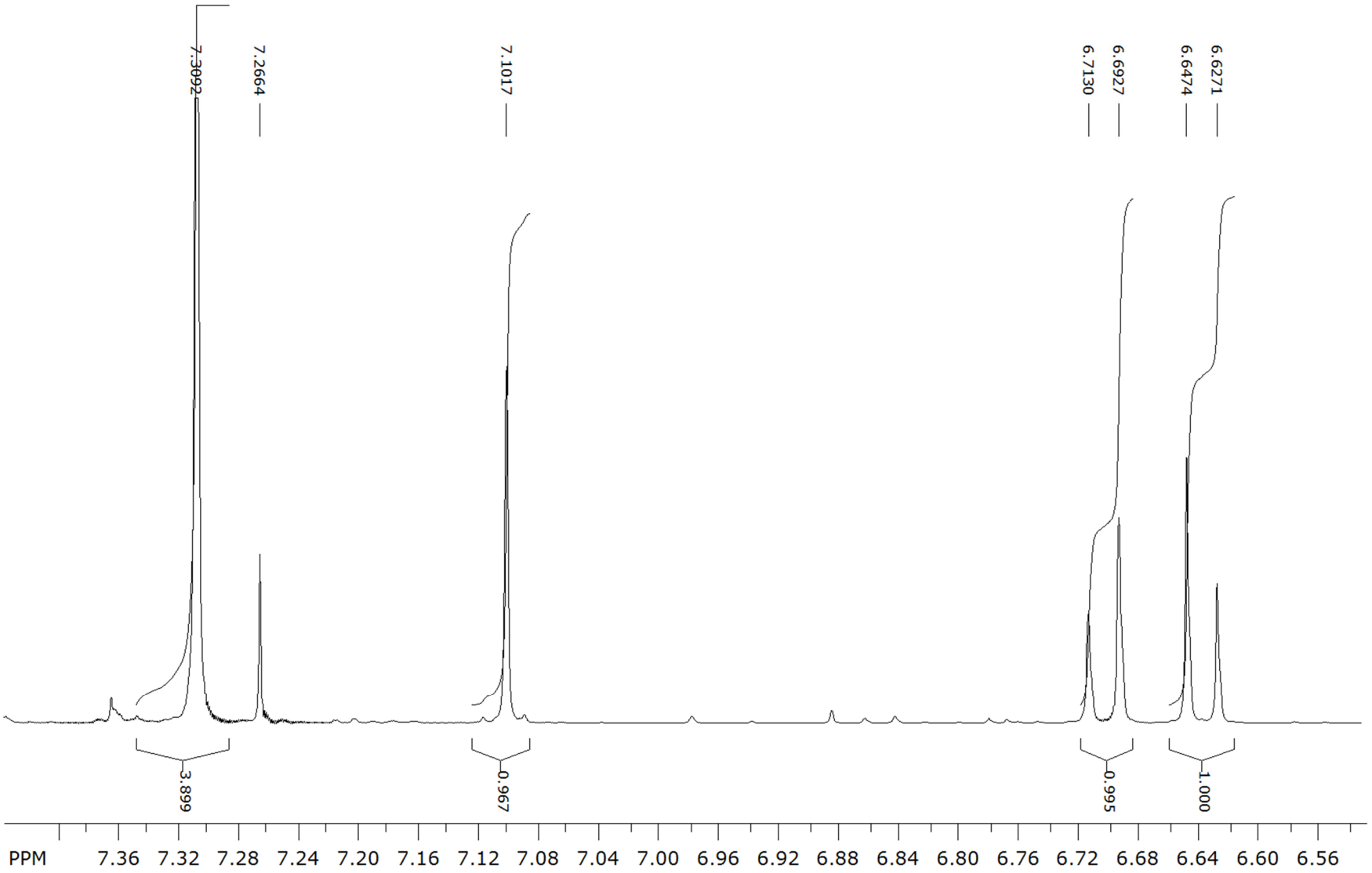


Figure S60. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of ***cis*-18**.

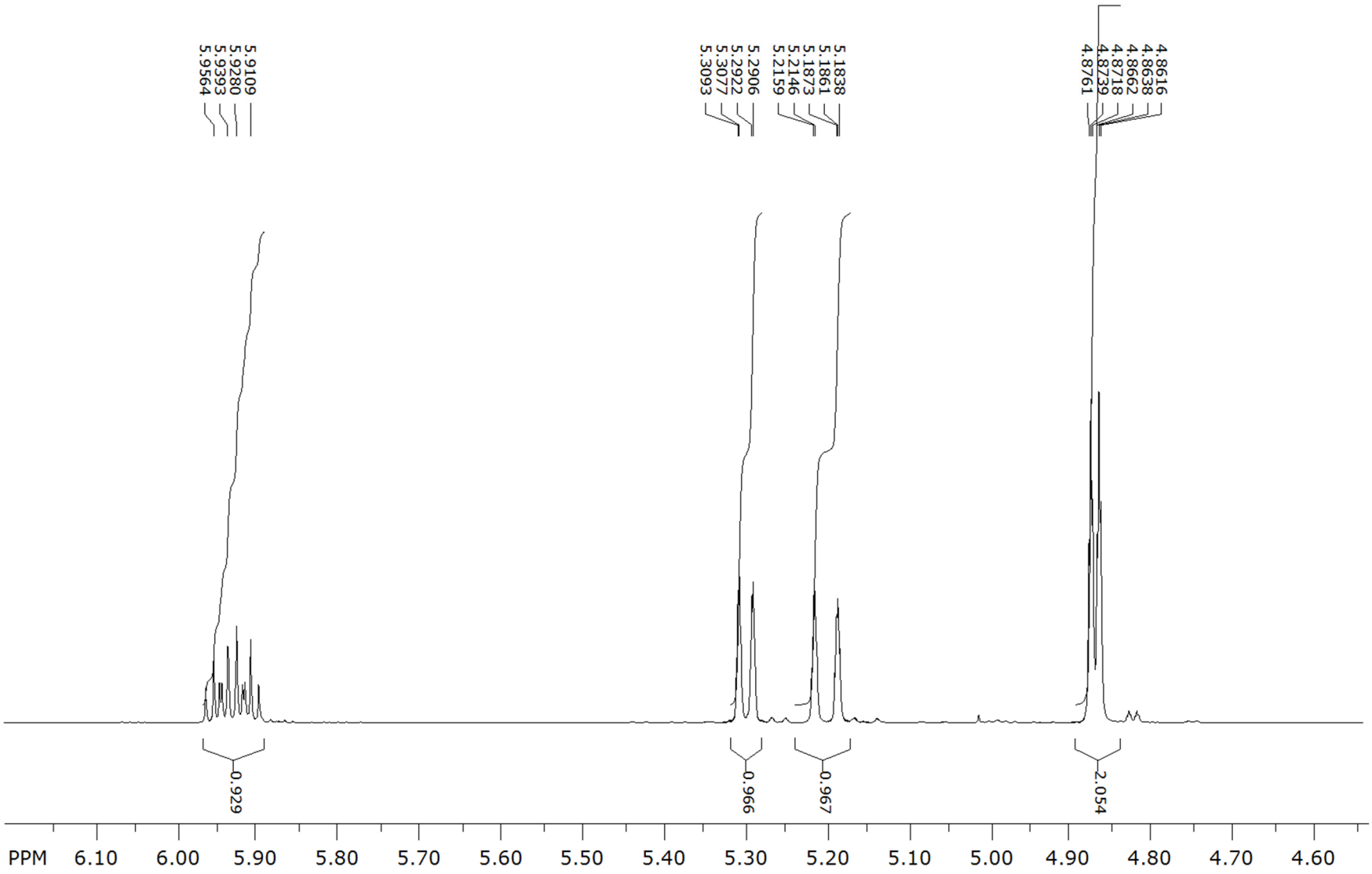


Figure S61. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of ***cis*-18**.

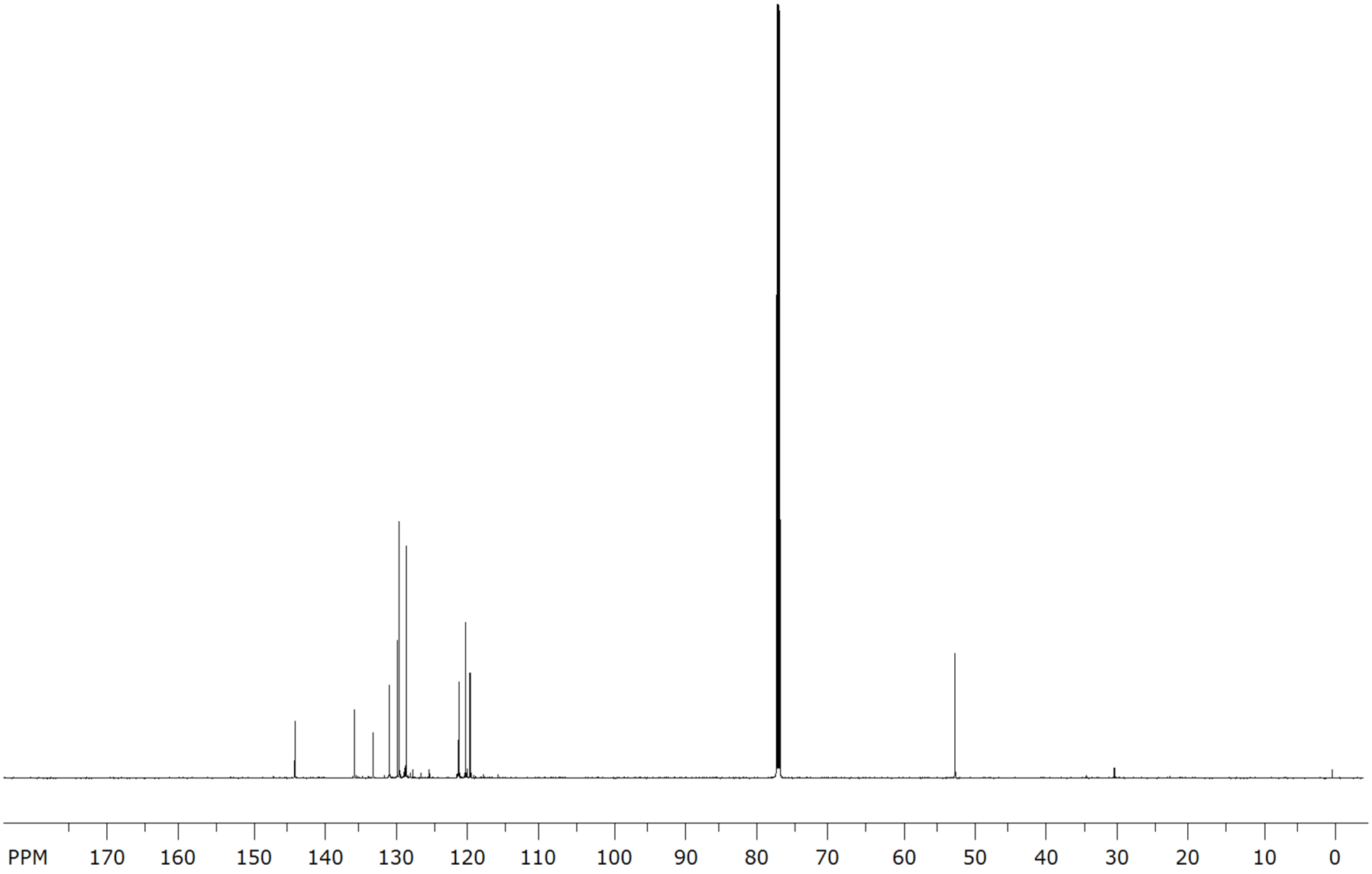


Figure S62. ^{13}C NMR ($CDCl_3$) spectrum of ***cis*-18** (*Spin Works 3.0*).

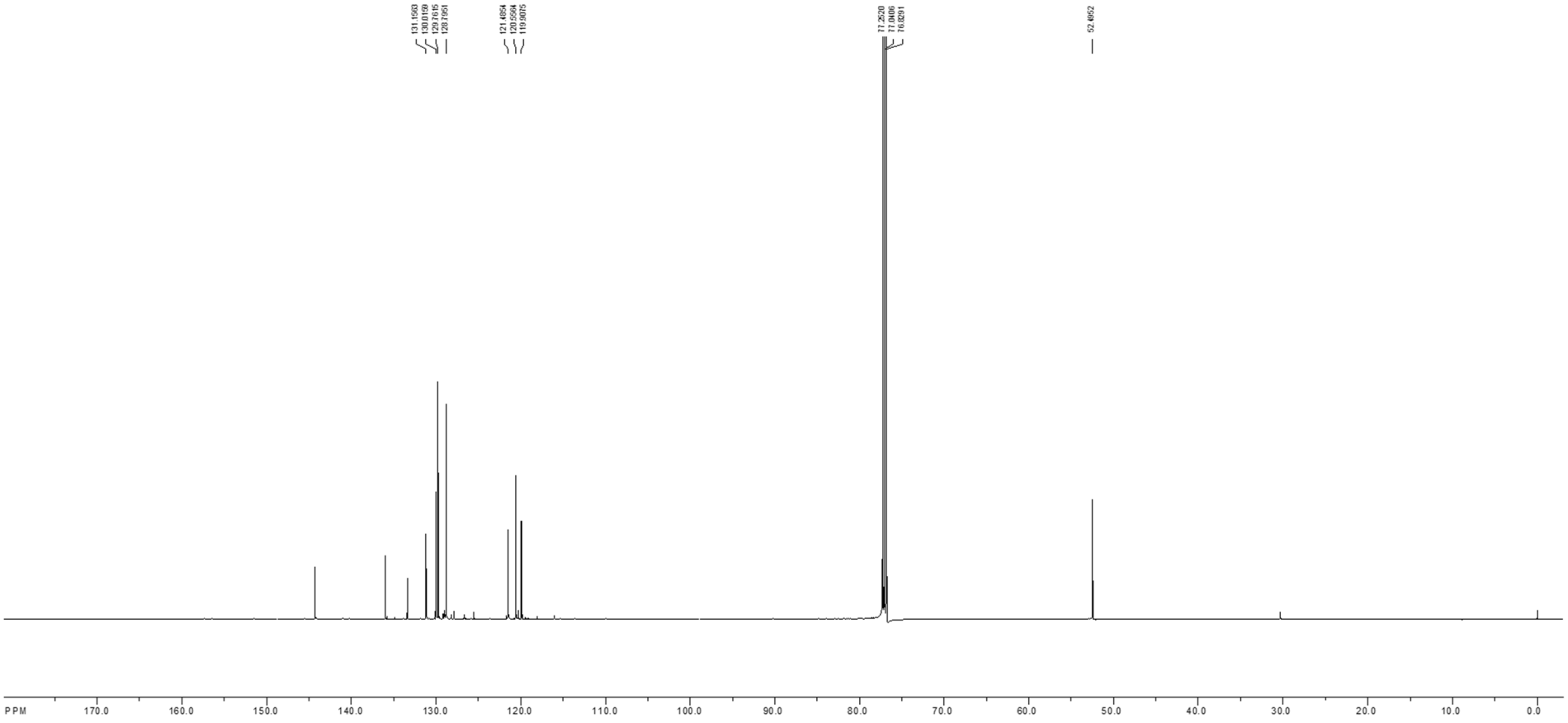


Figure S63. ^{13}C NMR ($CDCl_3$) spectrum of ***cis*-18** (*Spin Works 2.5.5.*).

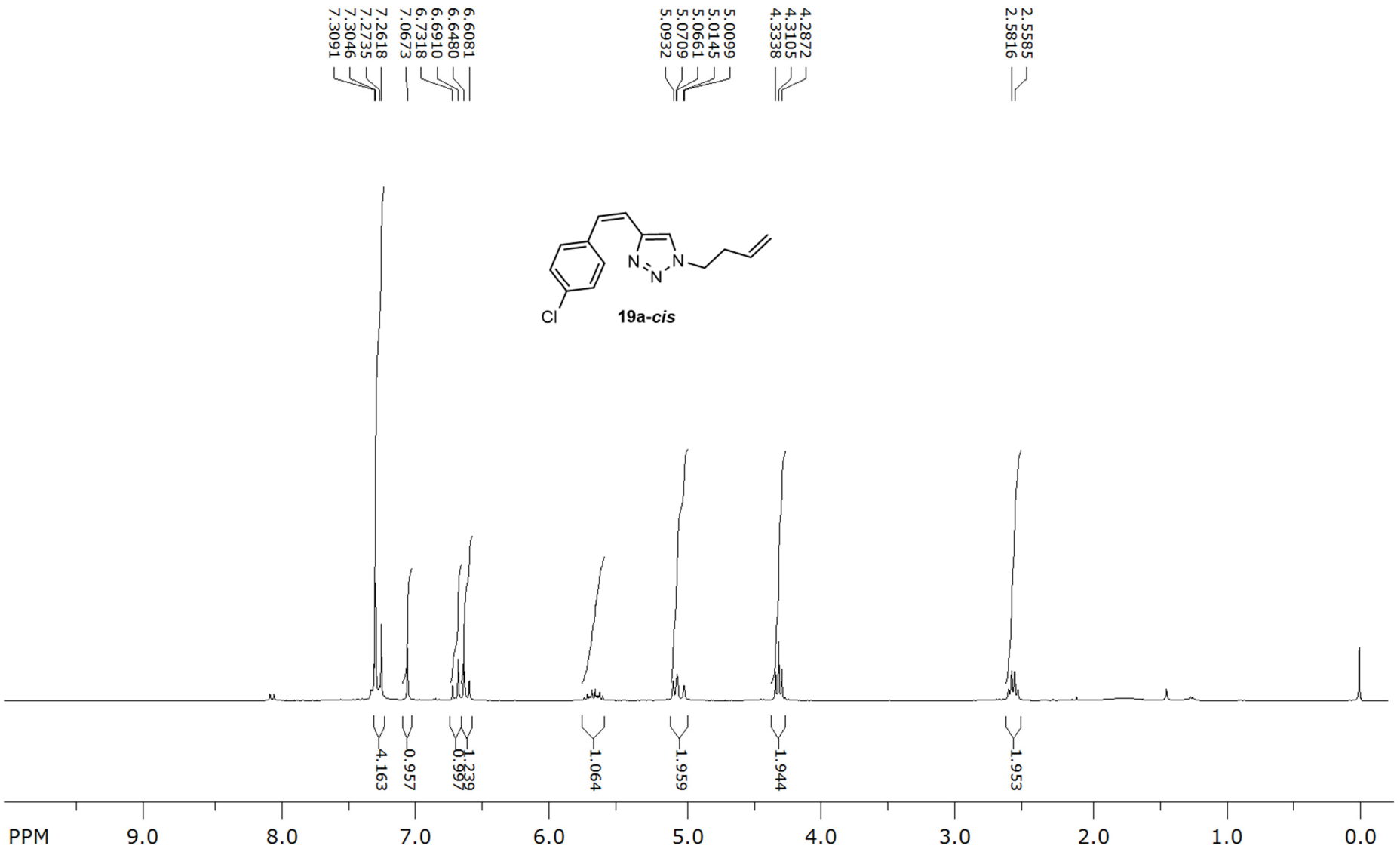


Figure S64. ^{1}H NMR ($CDCl_3$) spectrum of *cis*-**19**.

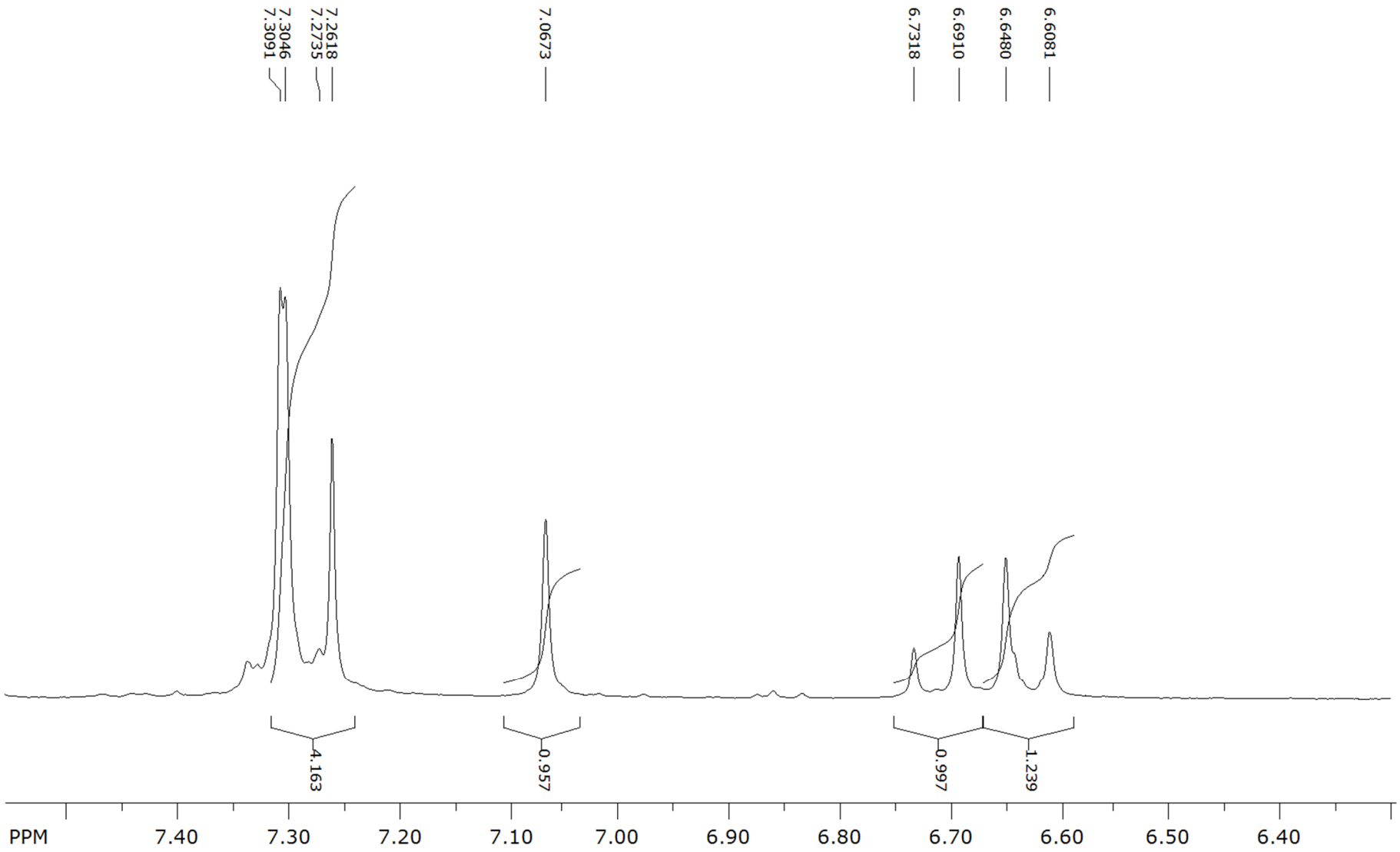


Figure S65. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of *cis*-**19**.

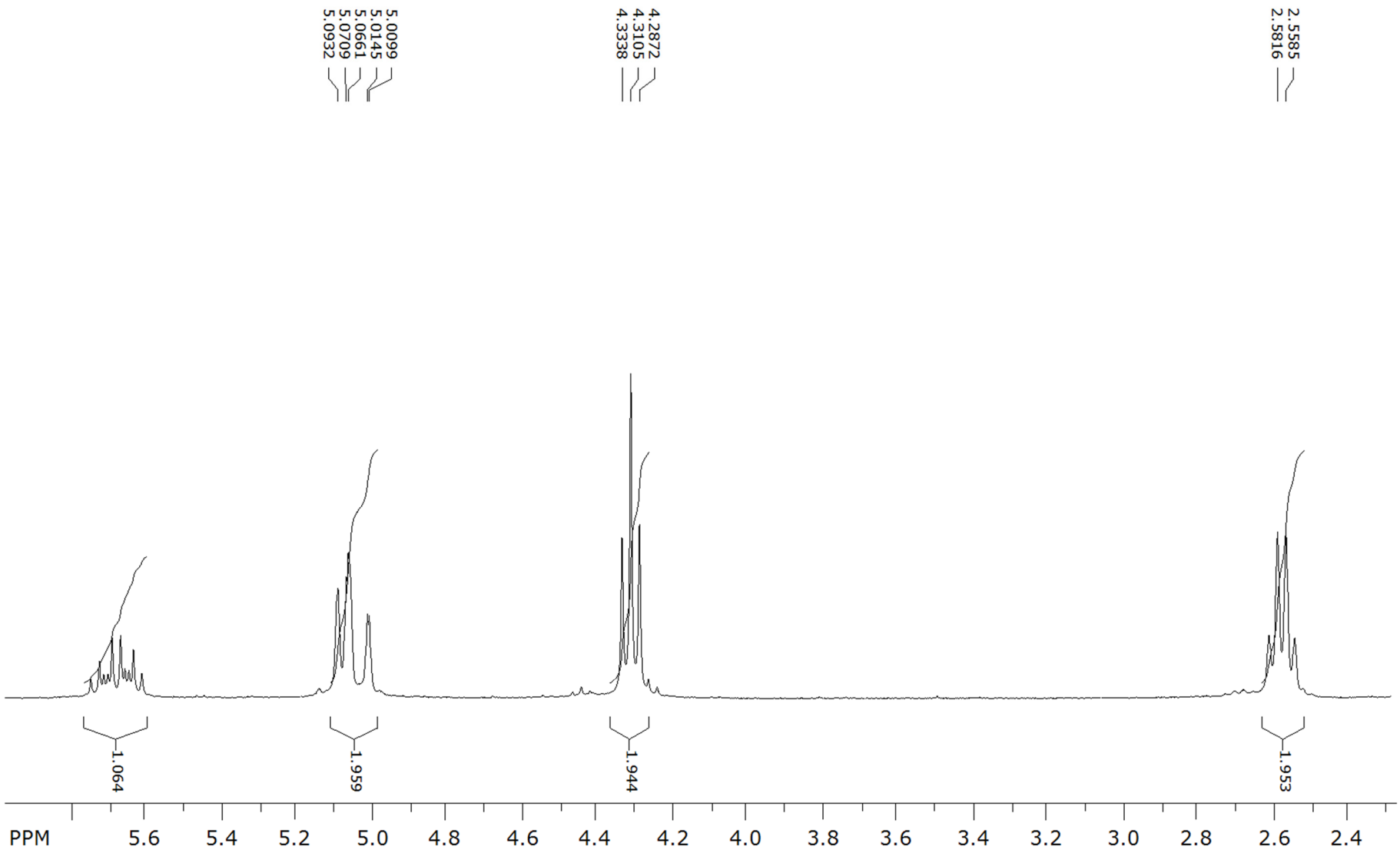


Figure S66. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of *cis*-**19**.

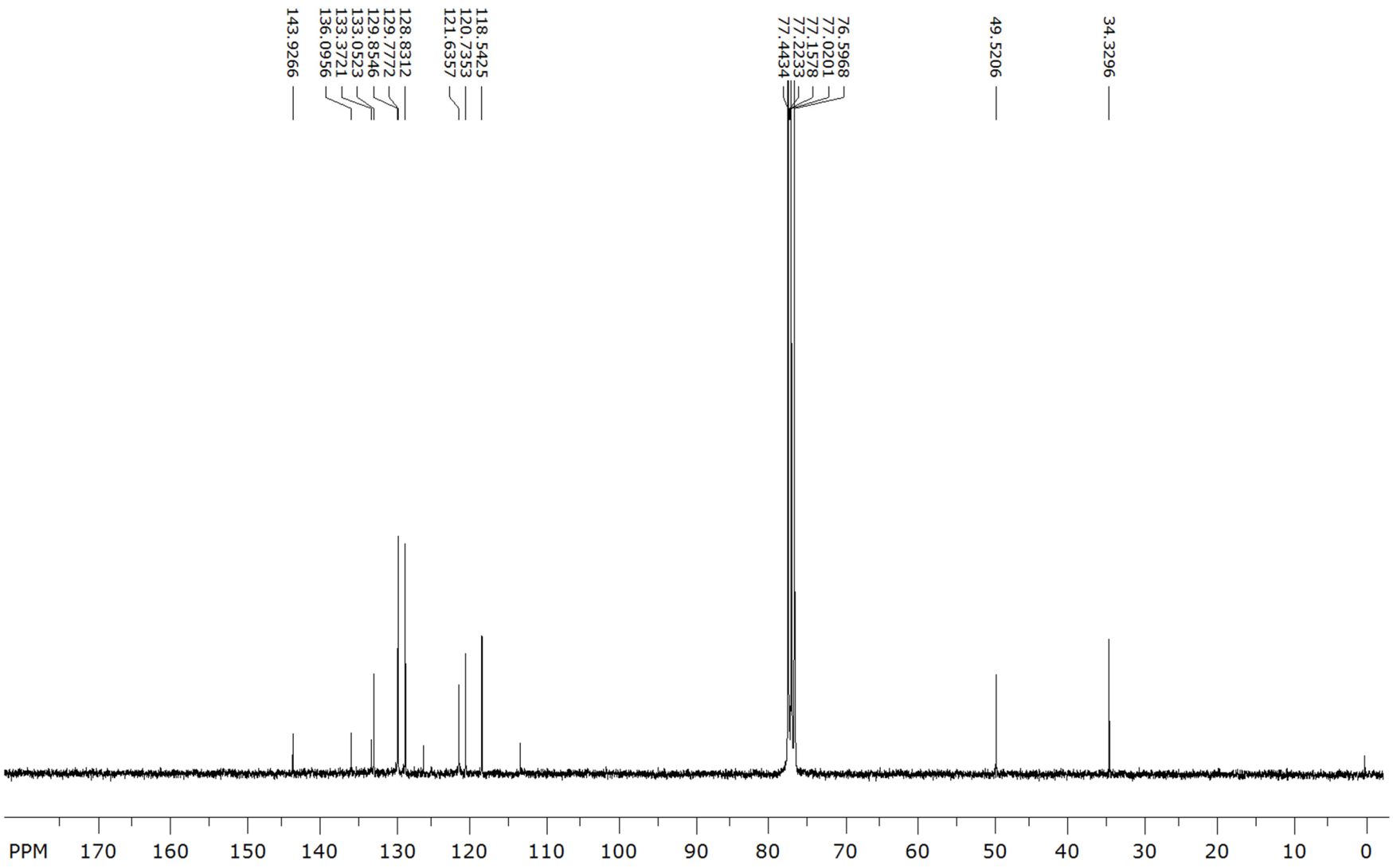


Figure S67. ^{13}C NMR ($CDCl_3$) spectrum of *cis*-**19**.

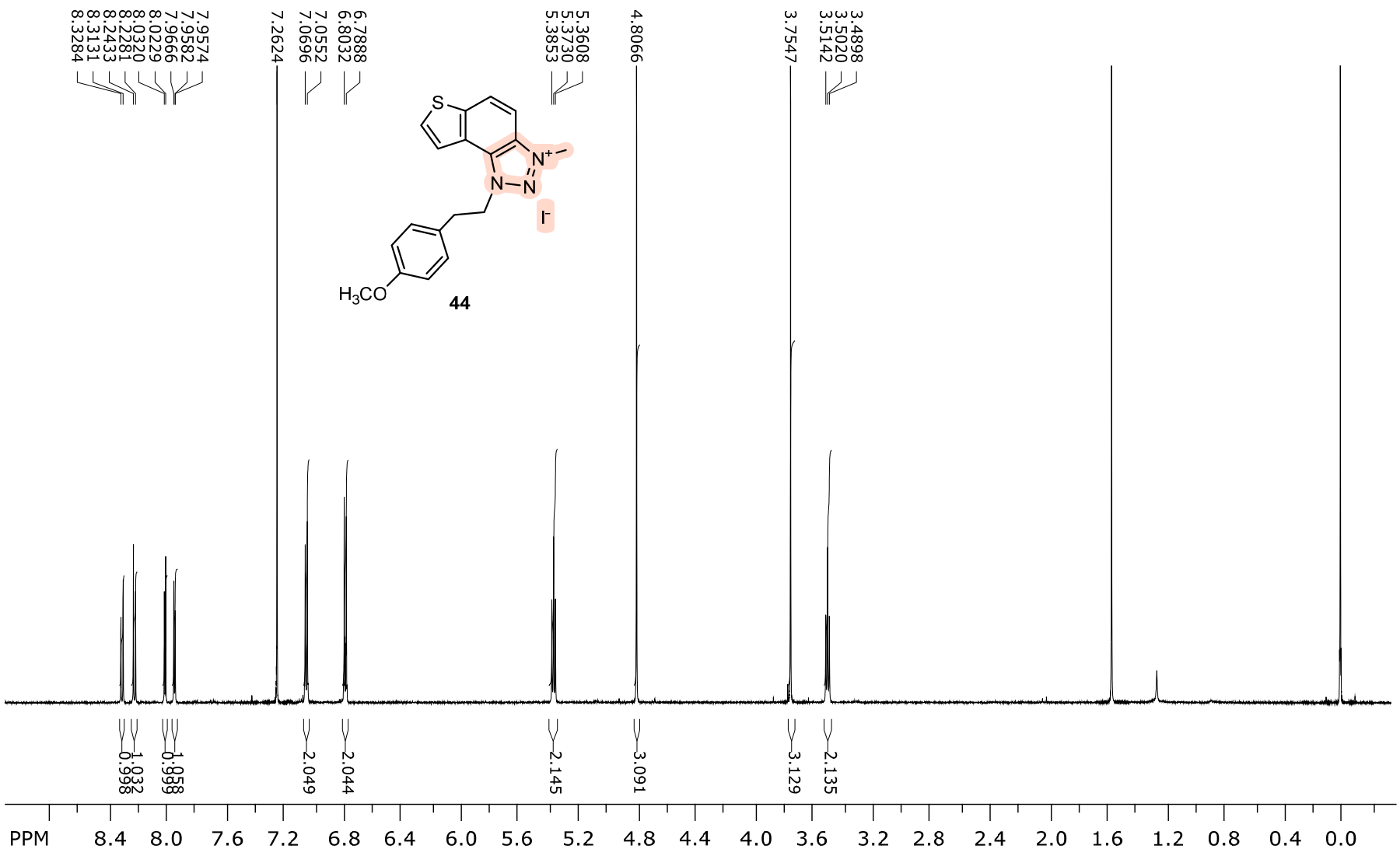


Figure S68. ^{1}H NMR ($CDCl_3$) spectrum of **44**.

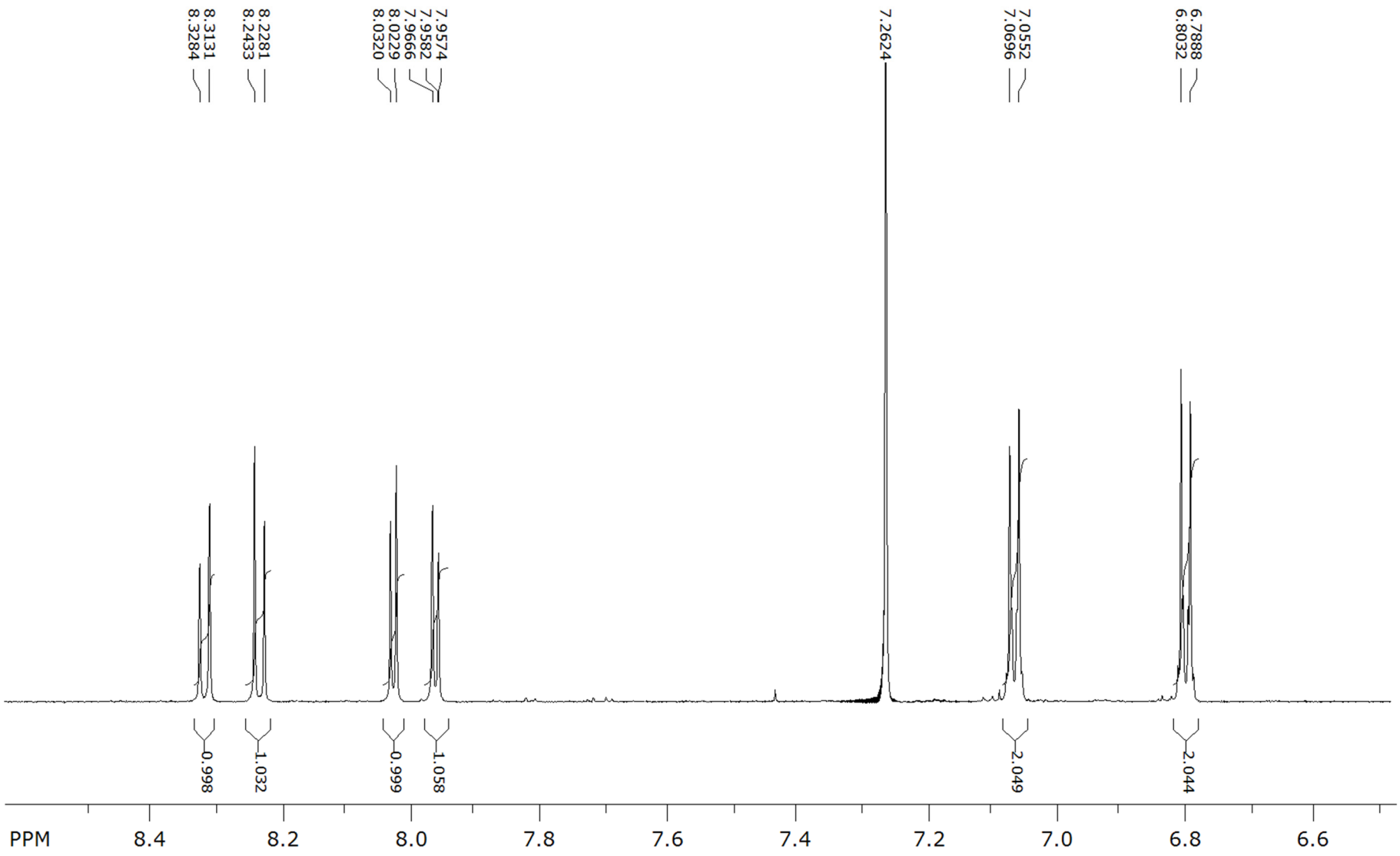


Figure S69. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **44**.

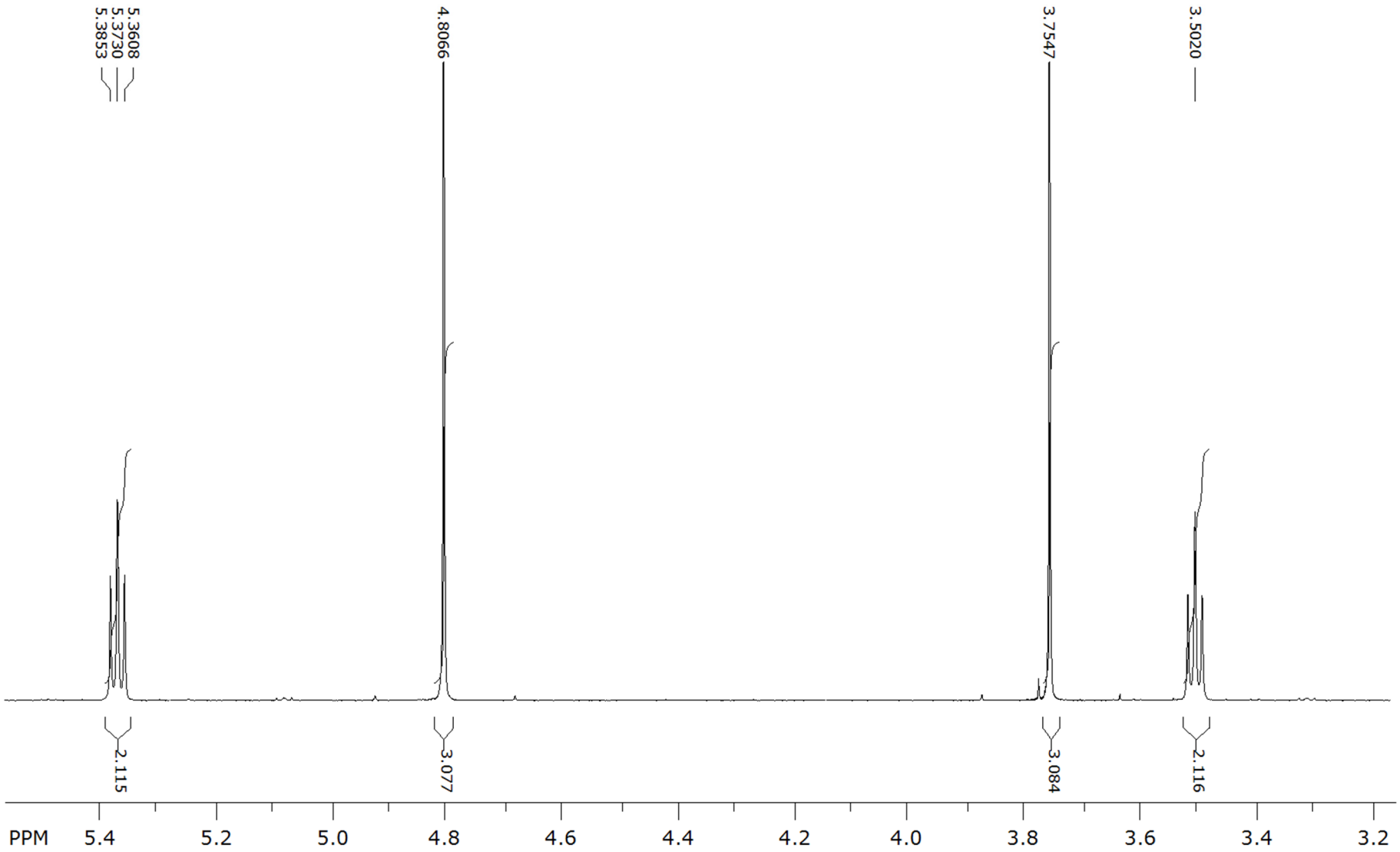


Figure S70. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **44**.

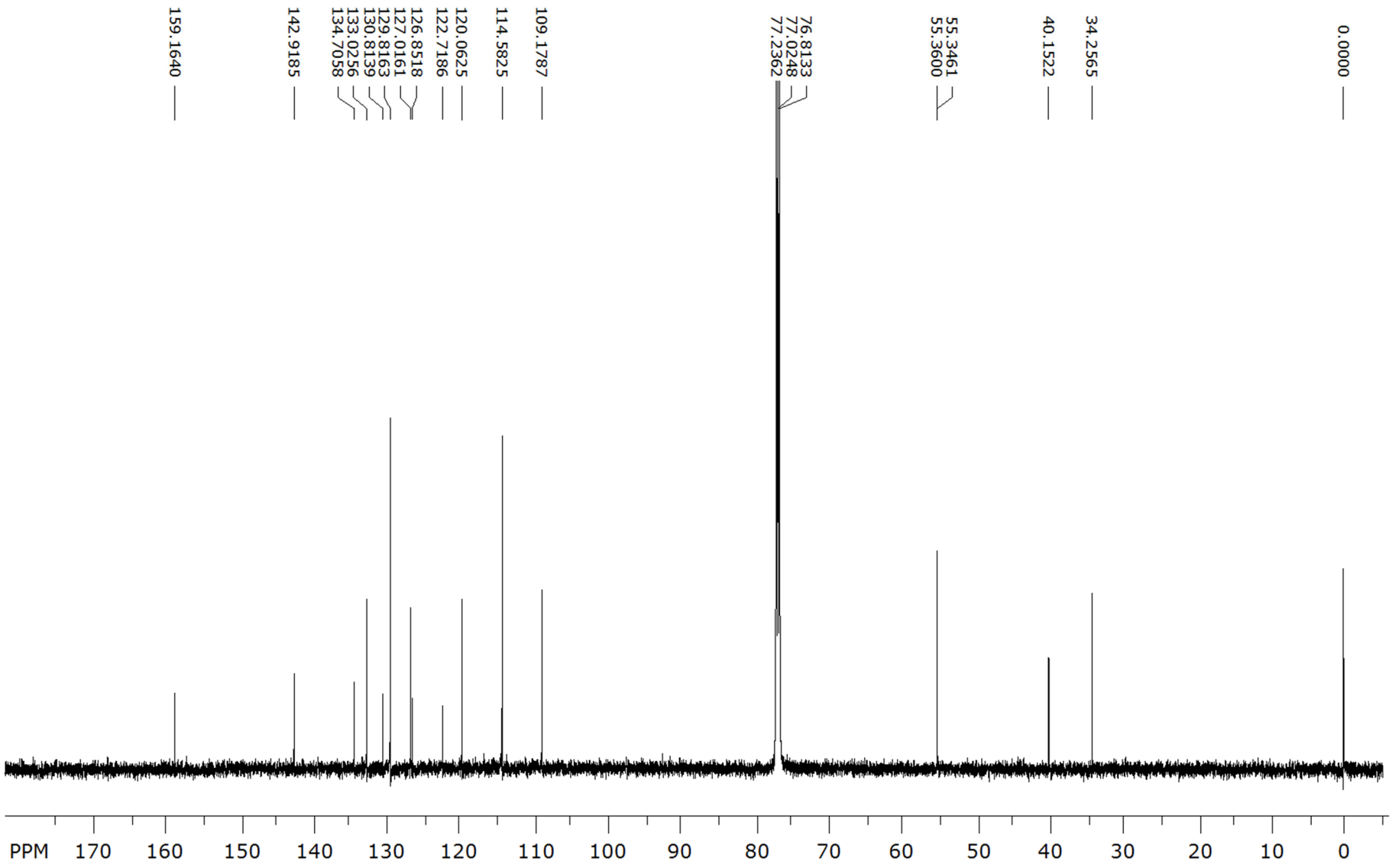


Figure S71. ^{13}C NMR ($CDCl_3$) spectrum of **44**.

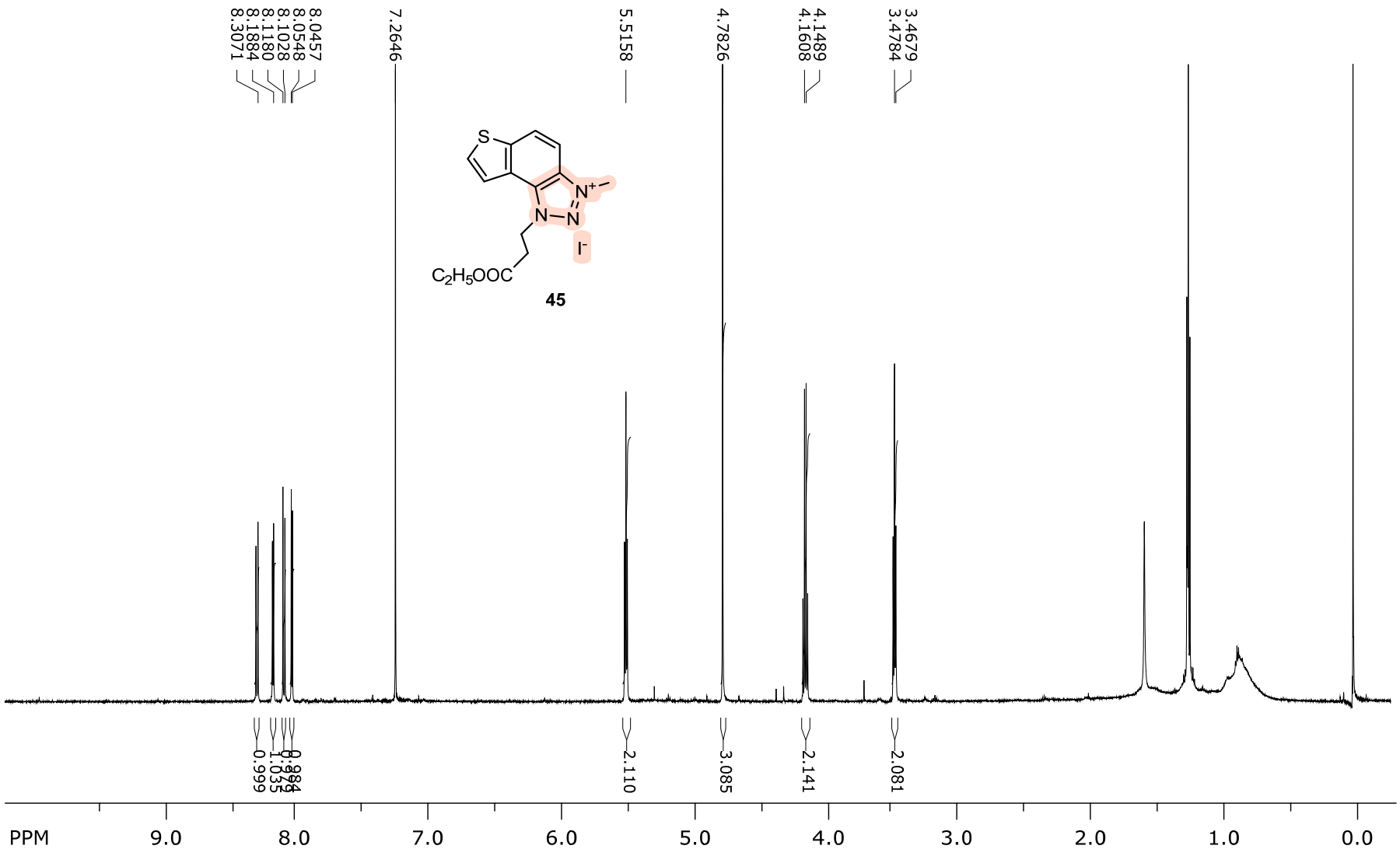


Figure S72. ^{1}H NMR ($CDCl_3$) spectrum of **45**.

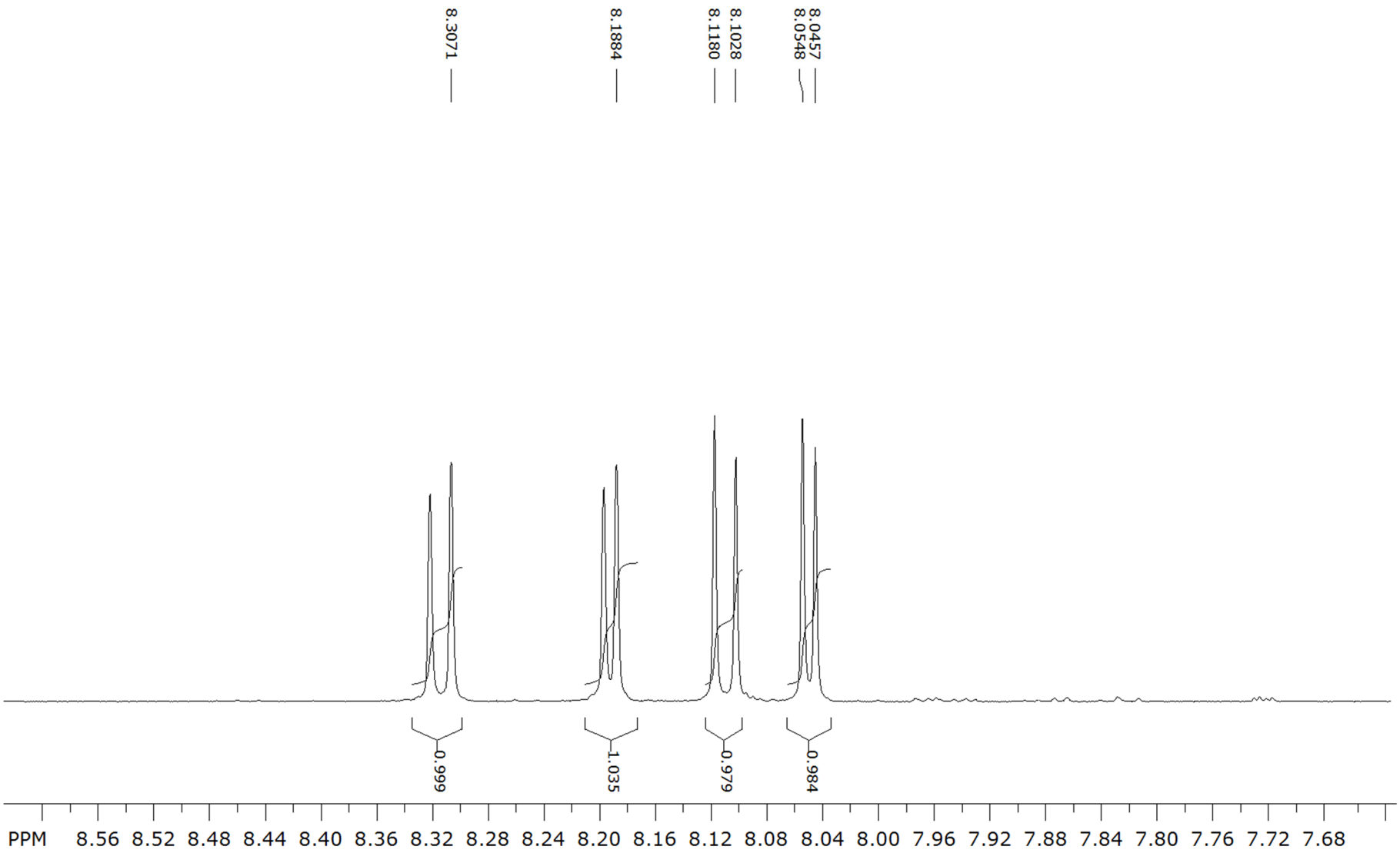


Figure S73. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **45**.

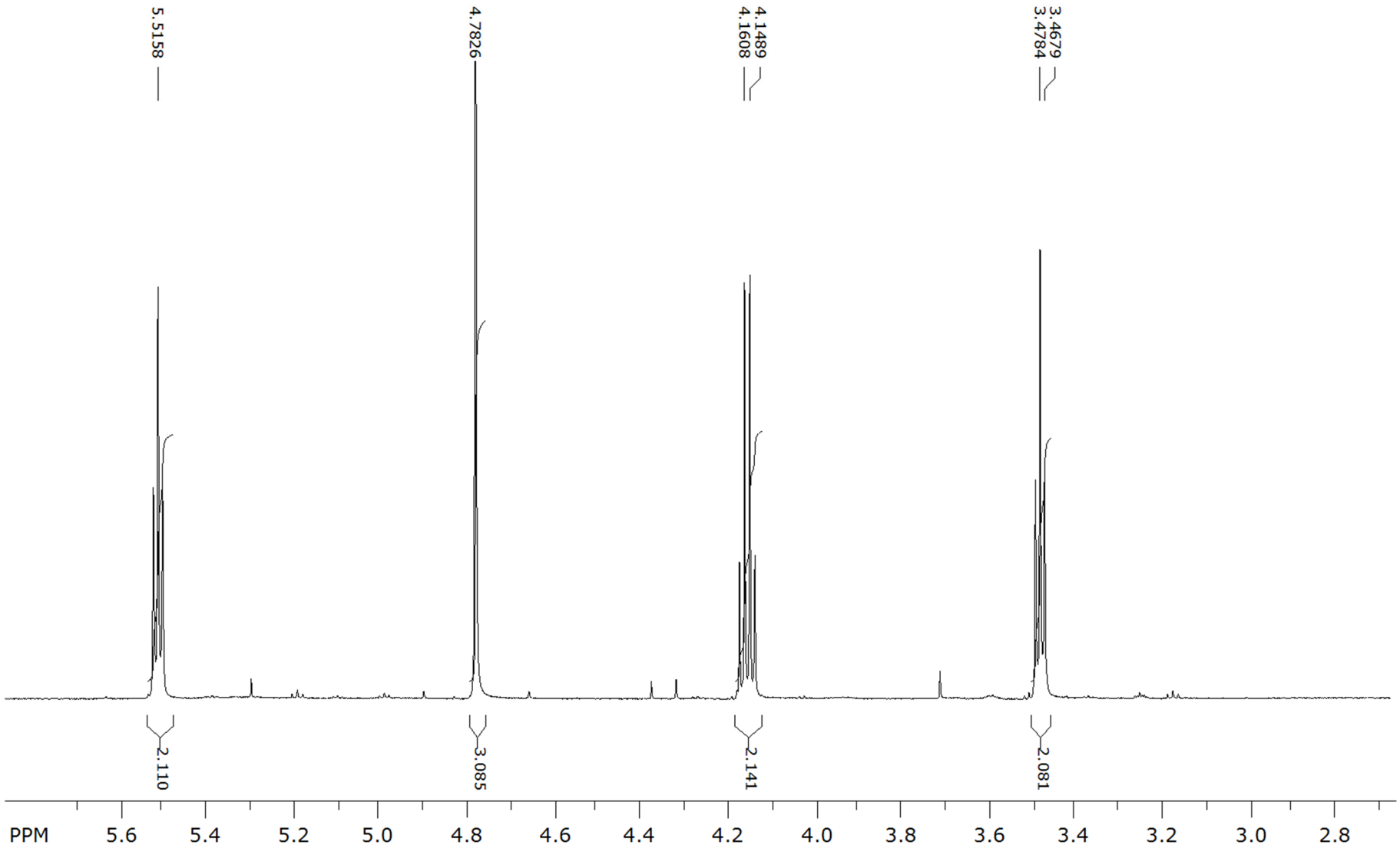


Figure S74. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **45**.

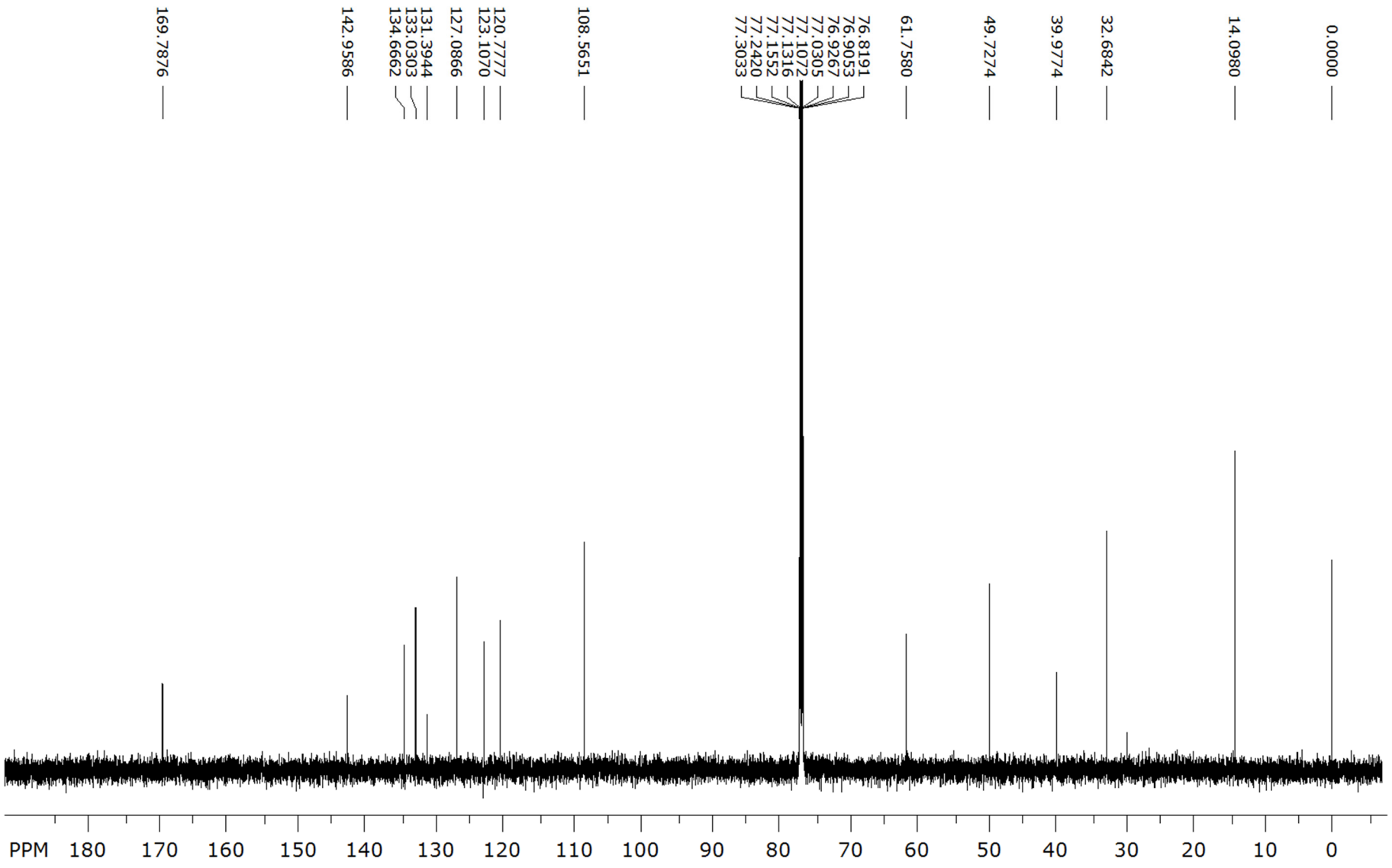


Figure S75. ^{13}C NMR ($CDCl_3$) spectrum of **45**.

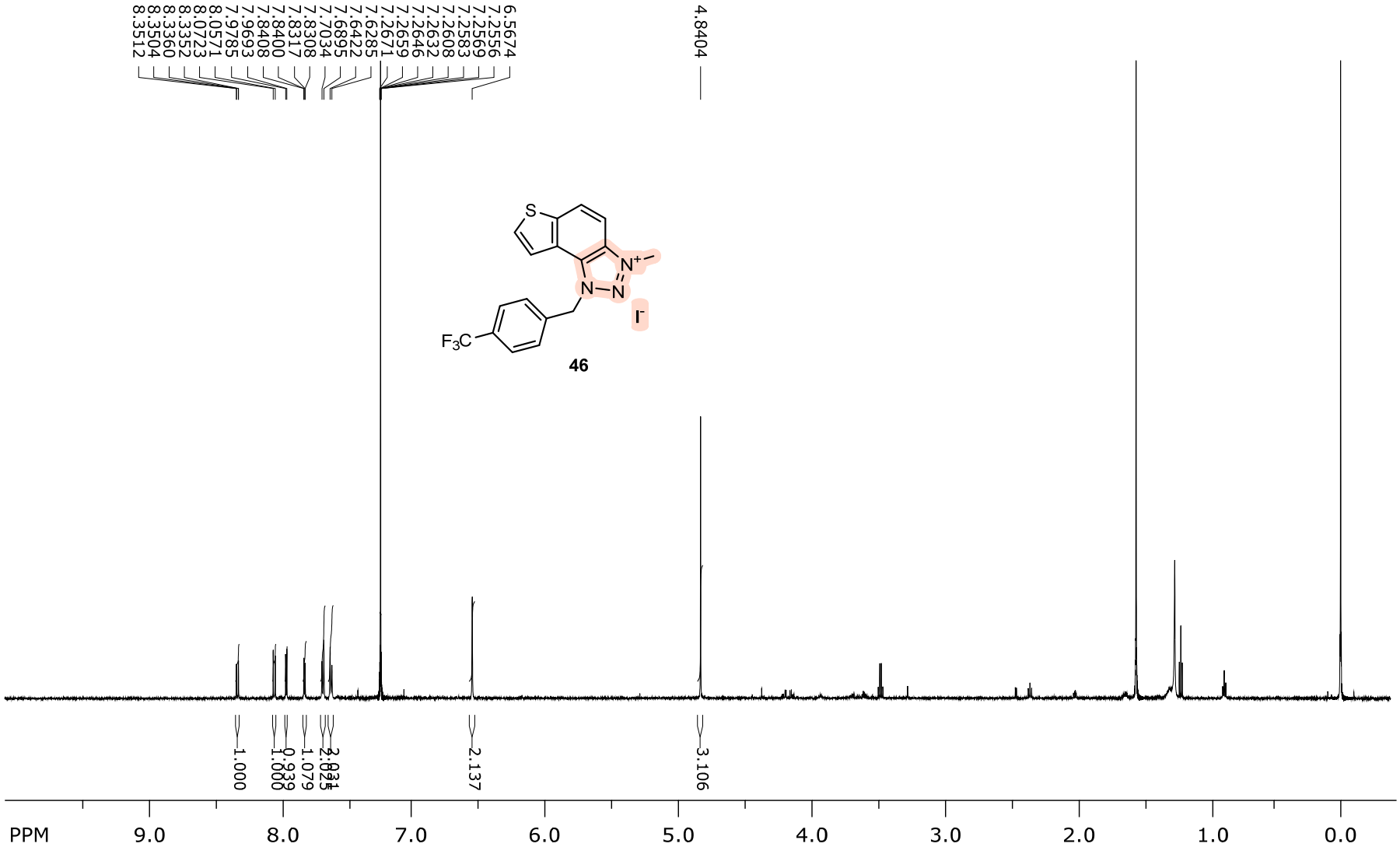


Figure S76. ^{1}H NMR ($CDCl_3$) spectrum of **46**.

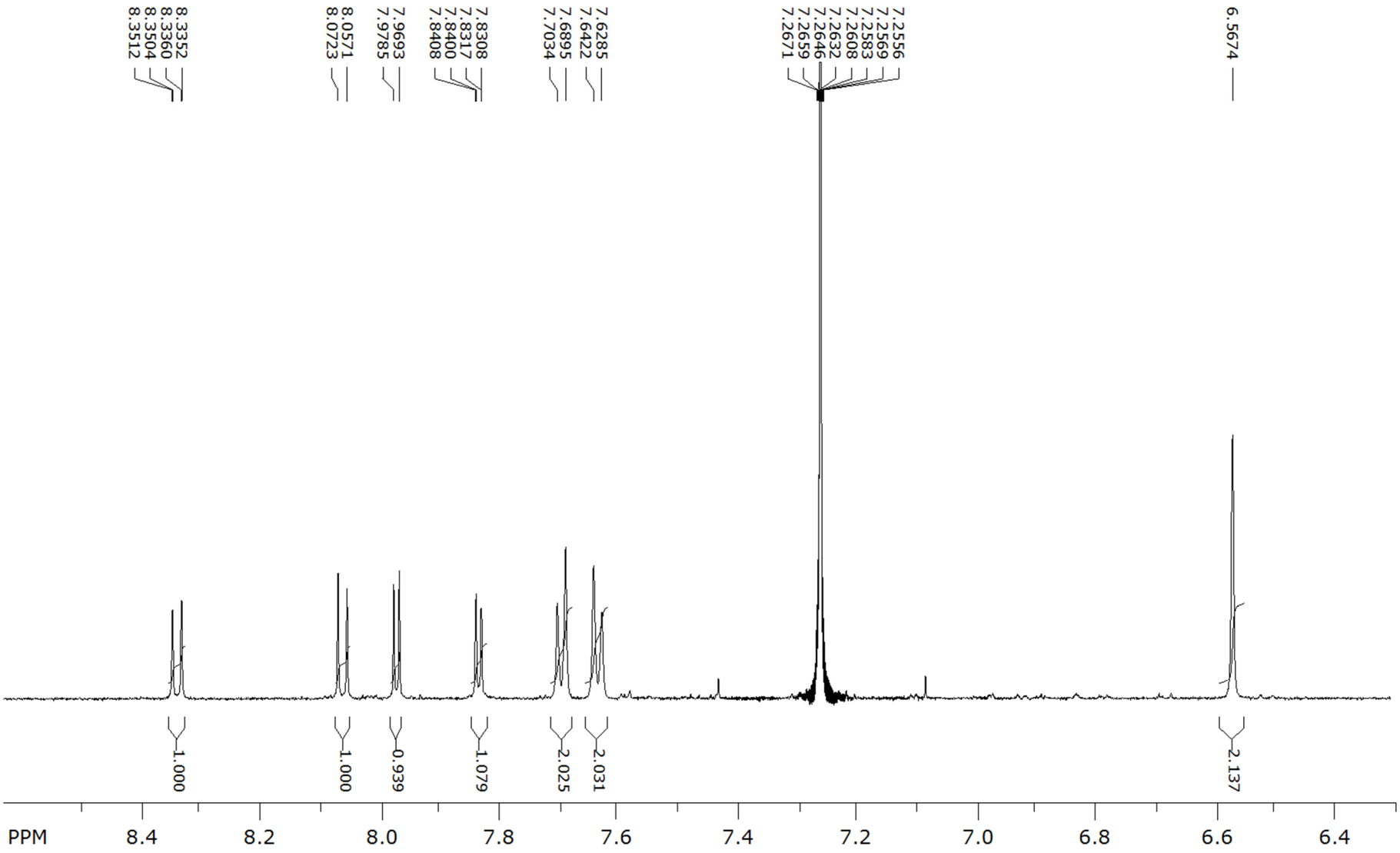


Figure S77. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **46**.

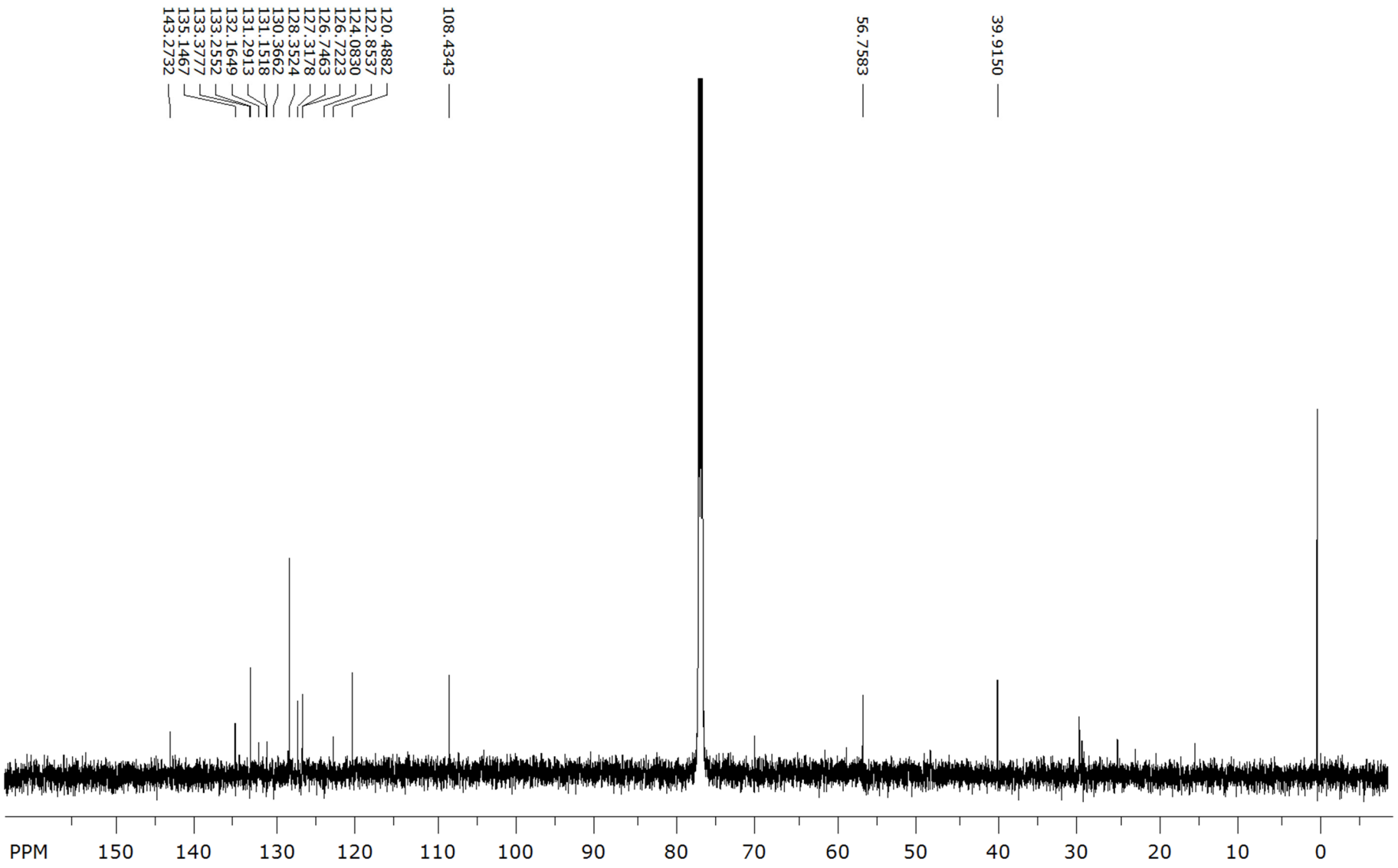
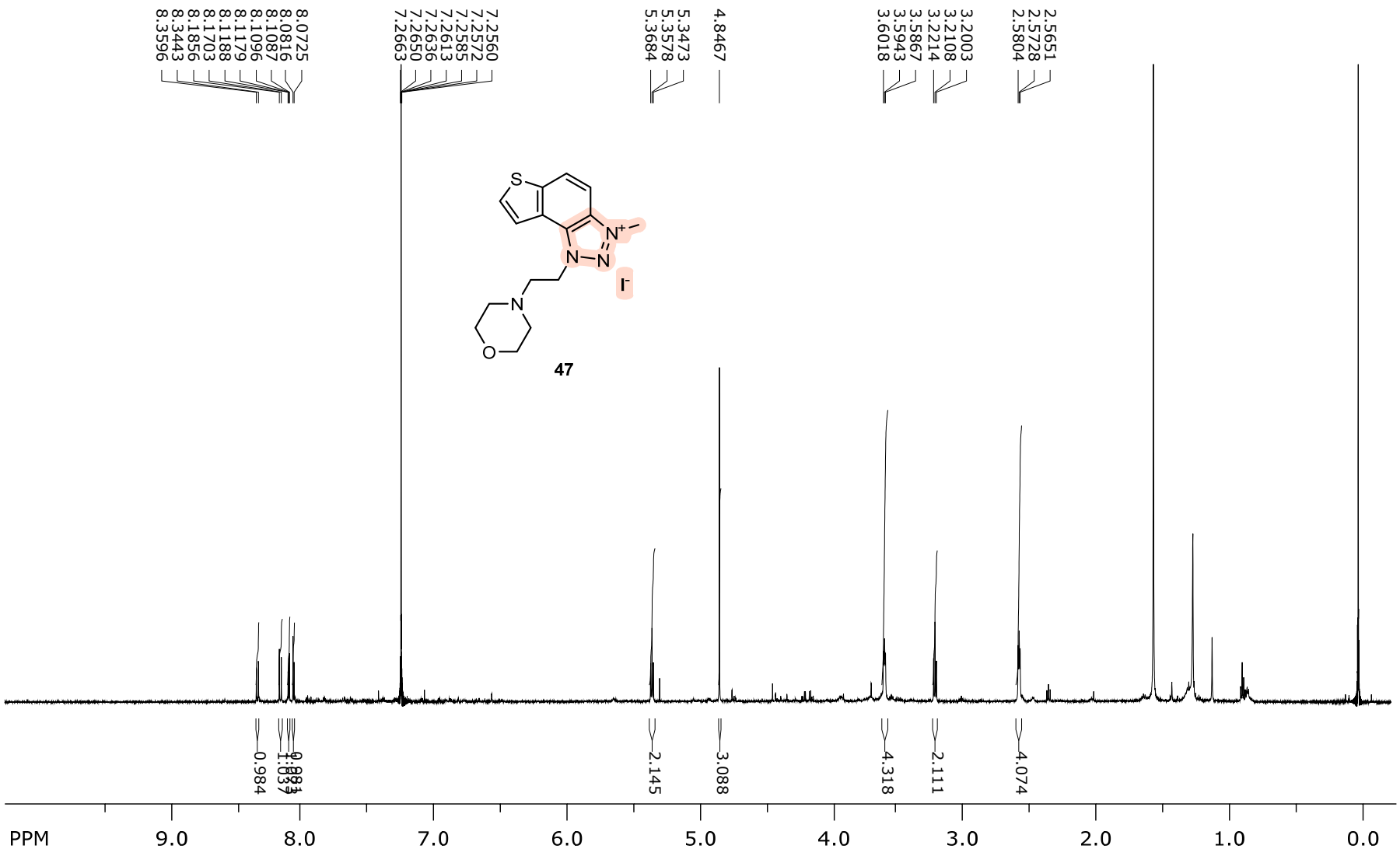


Figure S78. ^{13}C NMR ($CDCl_3$) spectrum of **46**.



47

Figure S79. ^{1}H NMR ($CDCl_3$) spectrum of **47**.

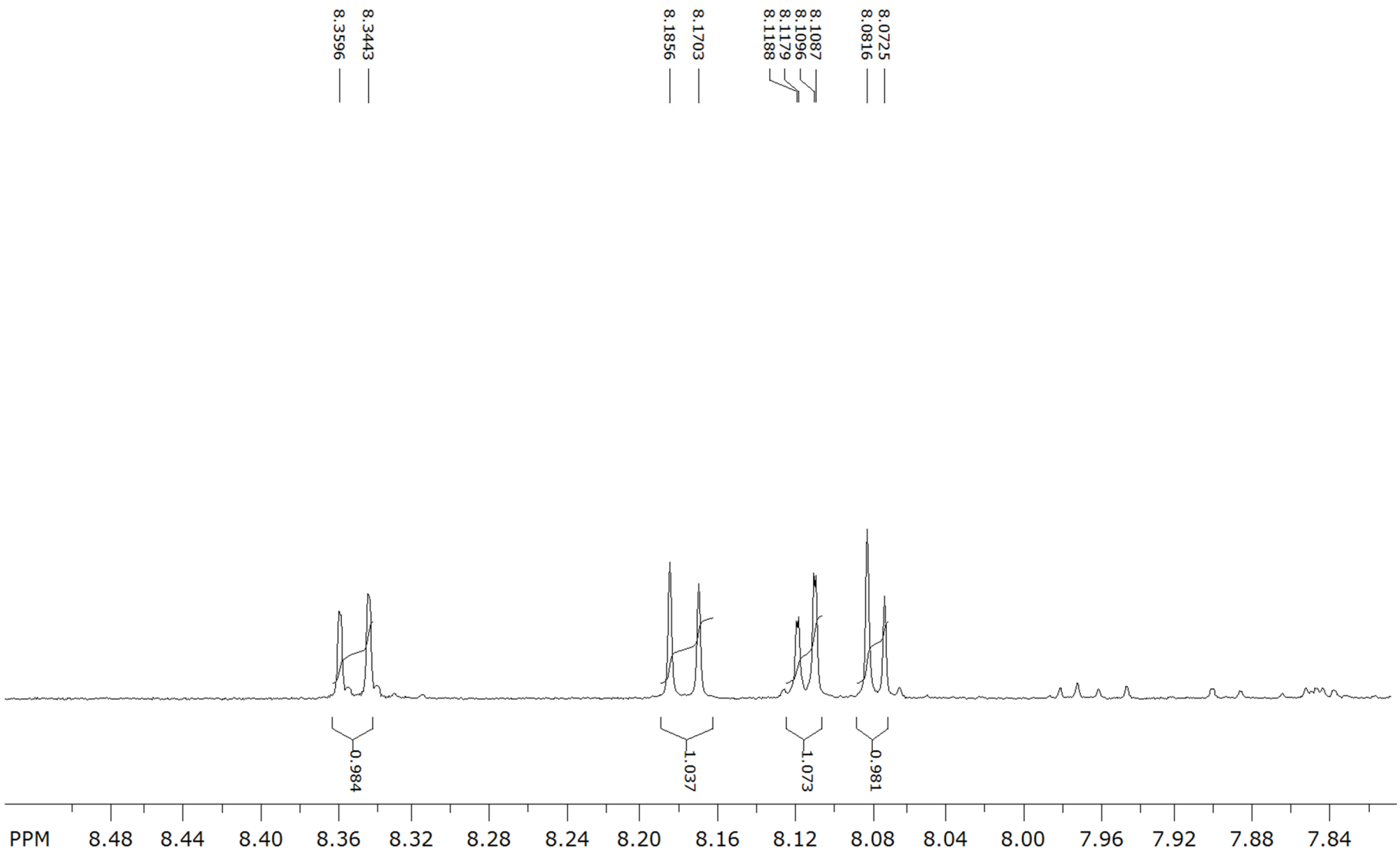


Figure S80. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **47**.

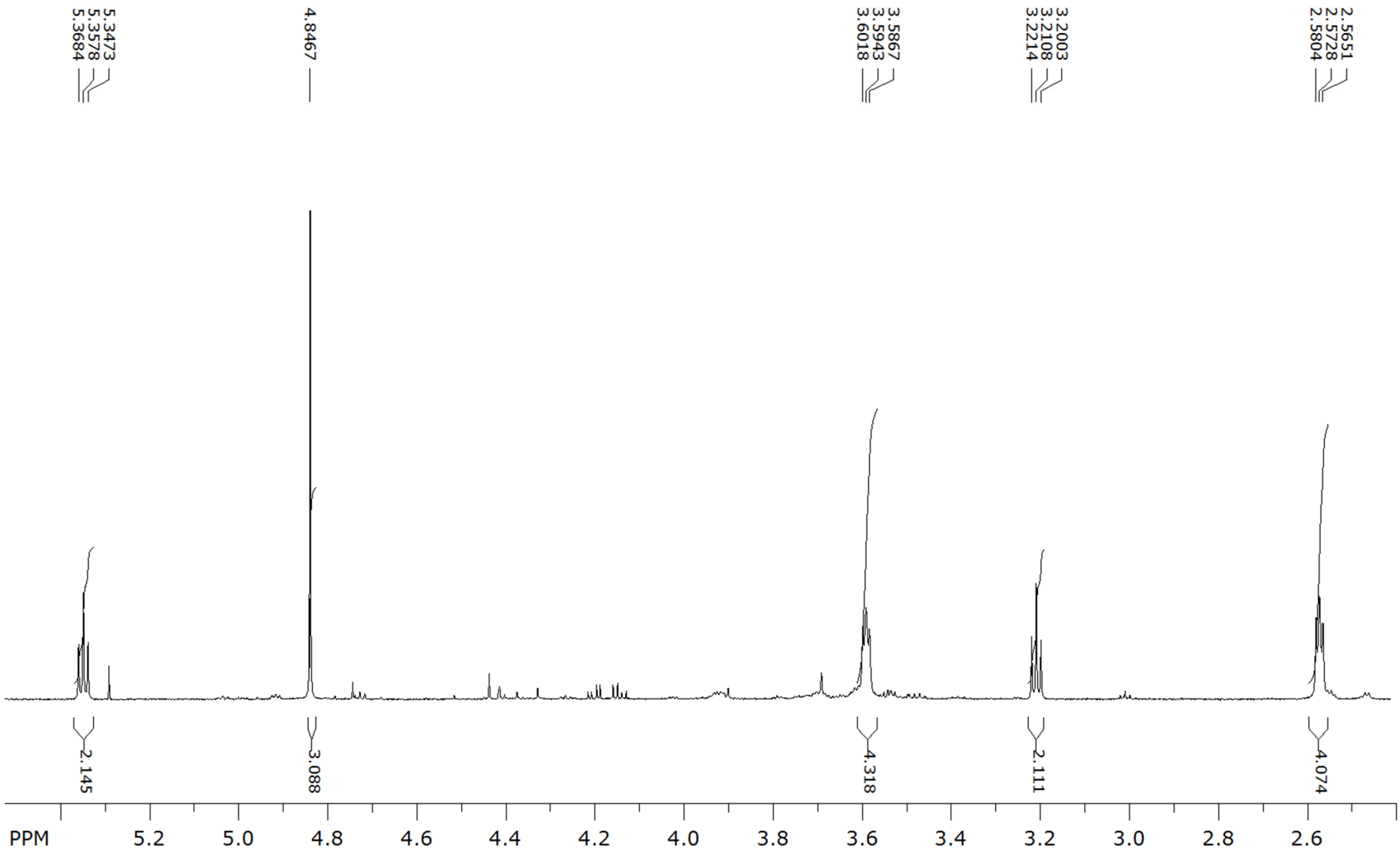


Figure S81. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **47**.

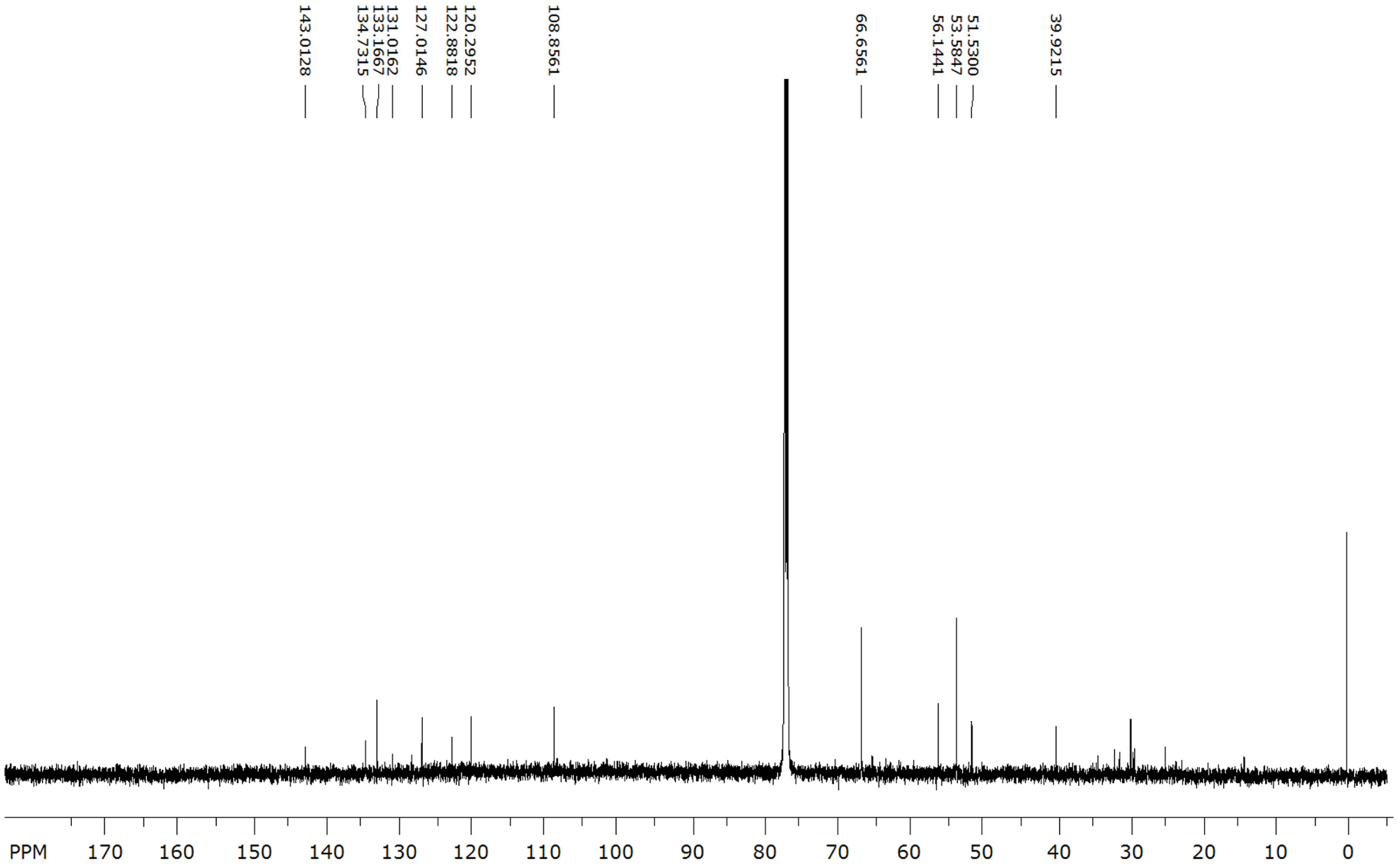


Figure S82. ^{13}C NMR ($CDCl_3$) spectrum of **47**.

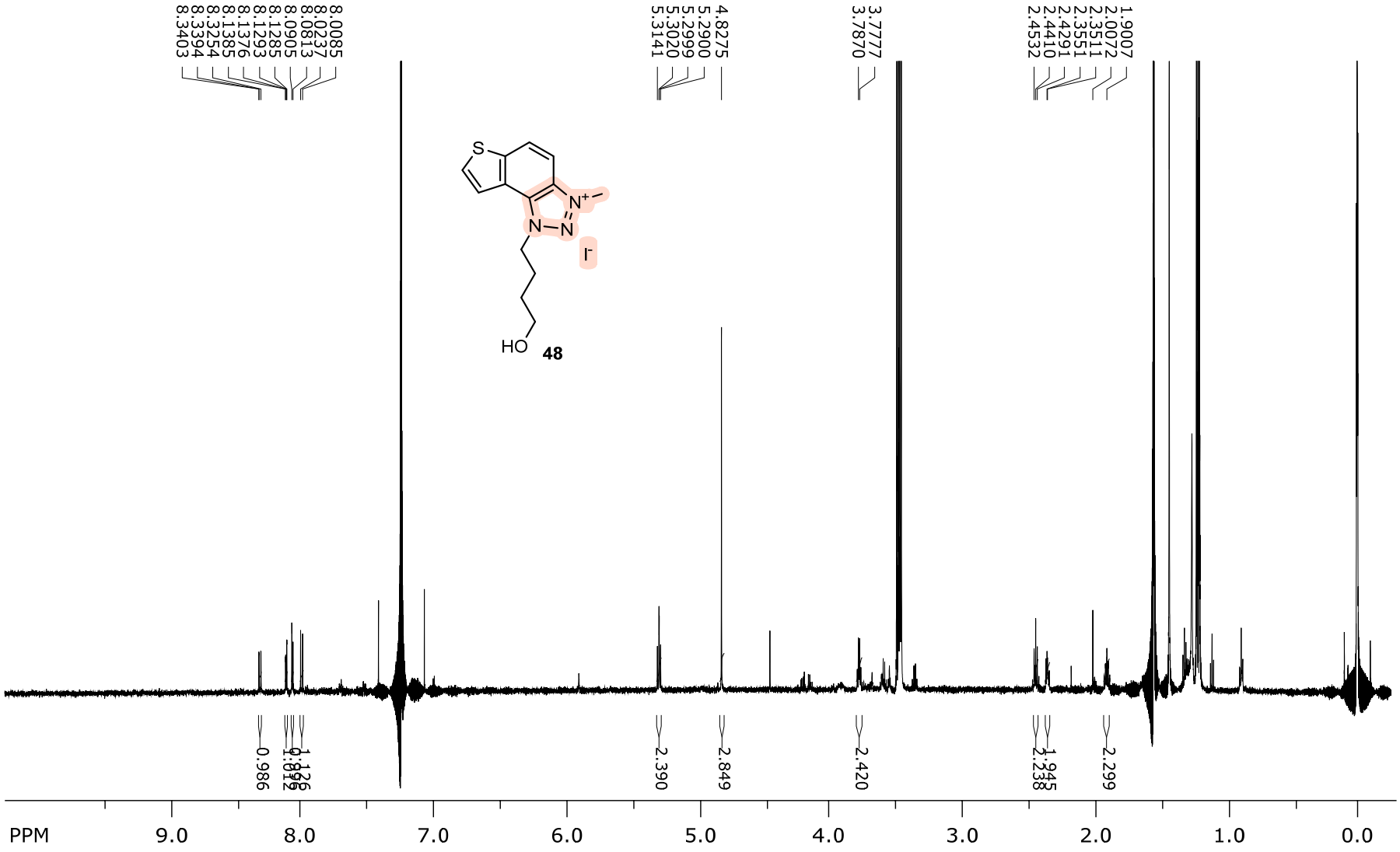


Figure S83. ^{1}H NMR ($CDCl_3$) spectrum of **48**.

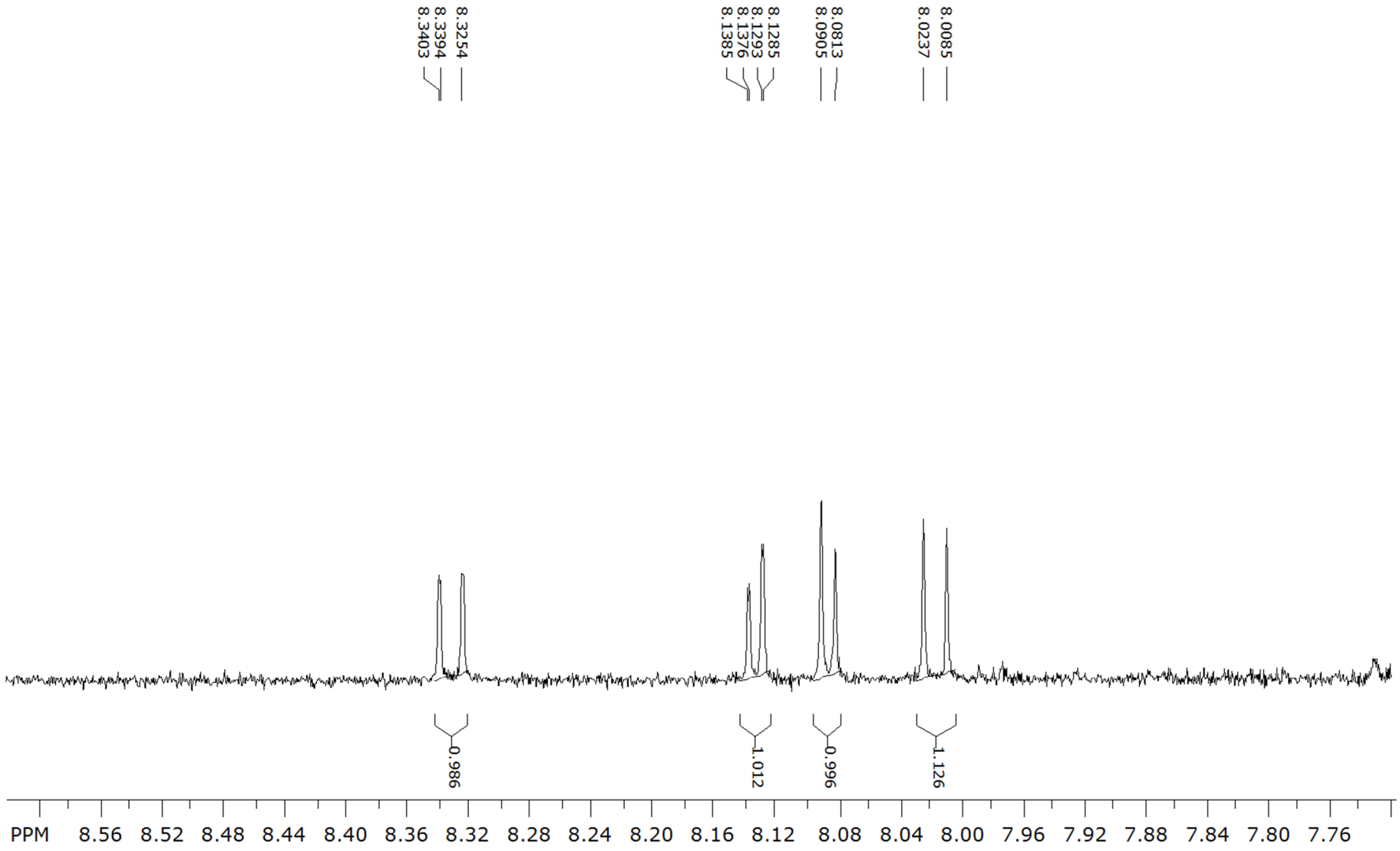


Figure S84. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **48**.

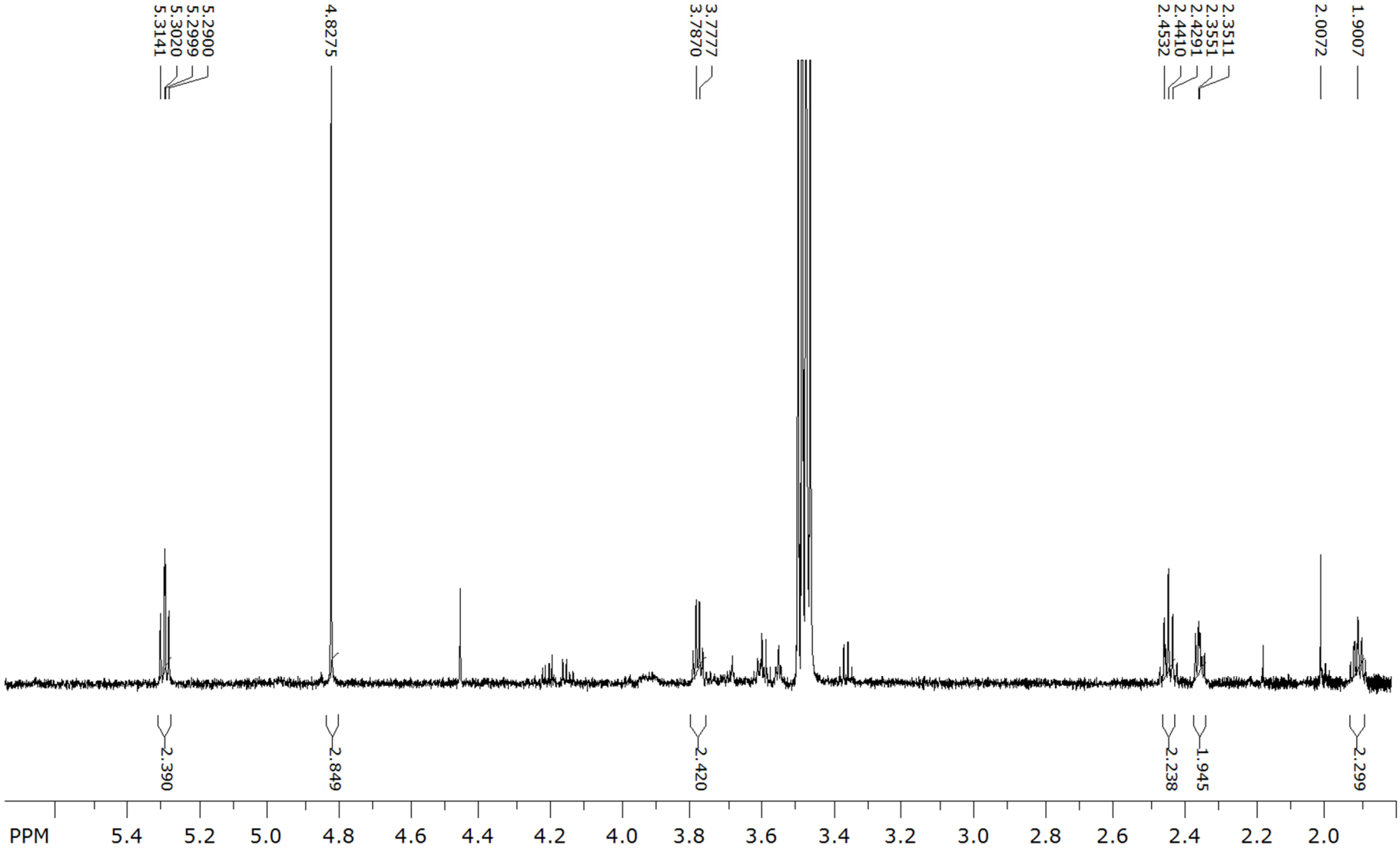


Figure S85. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **48**.

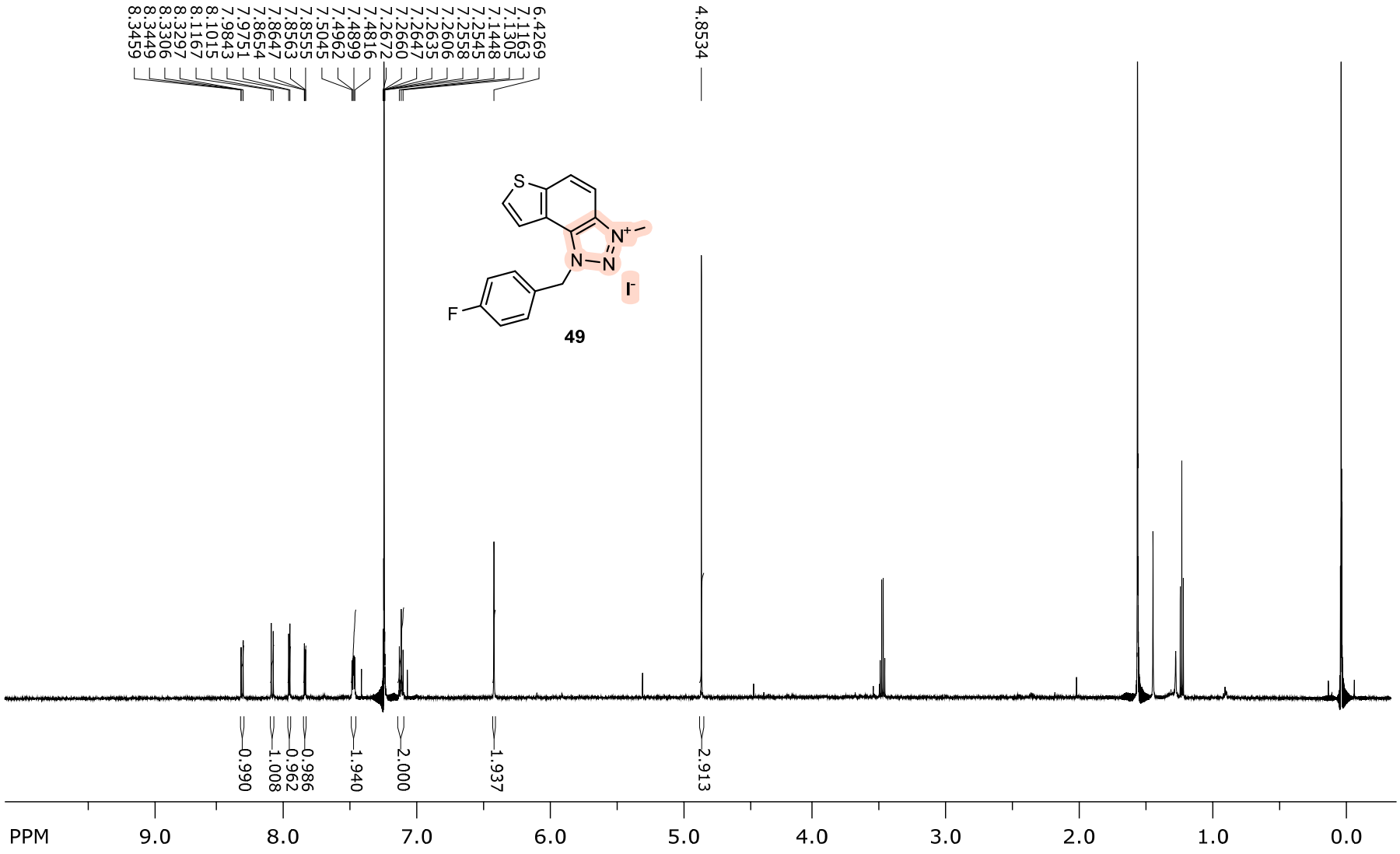


Figure S86. ^{1}H NMR ($CDCl_3$) spectrum of **49**.

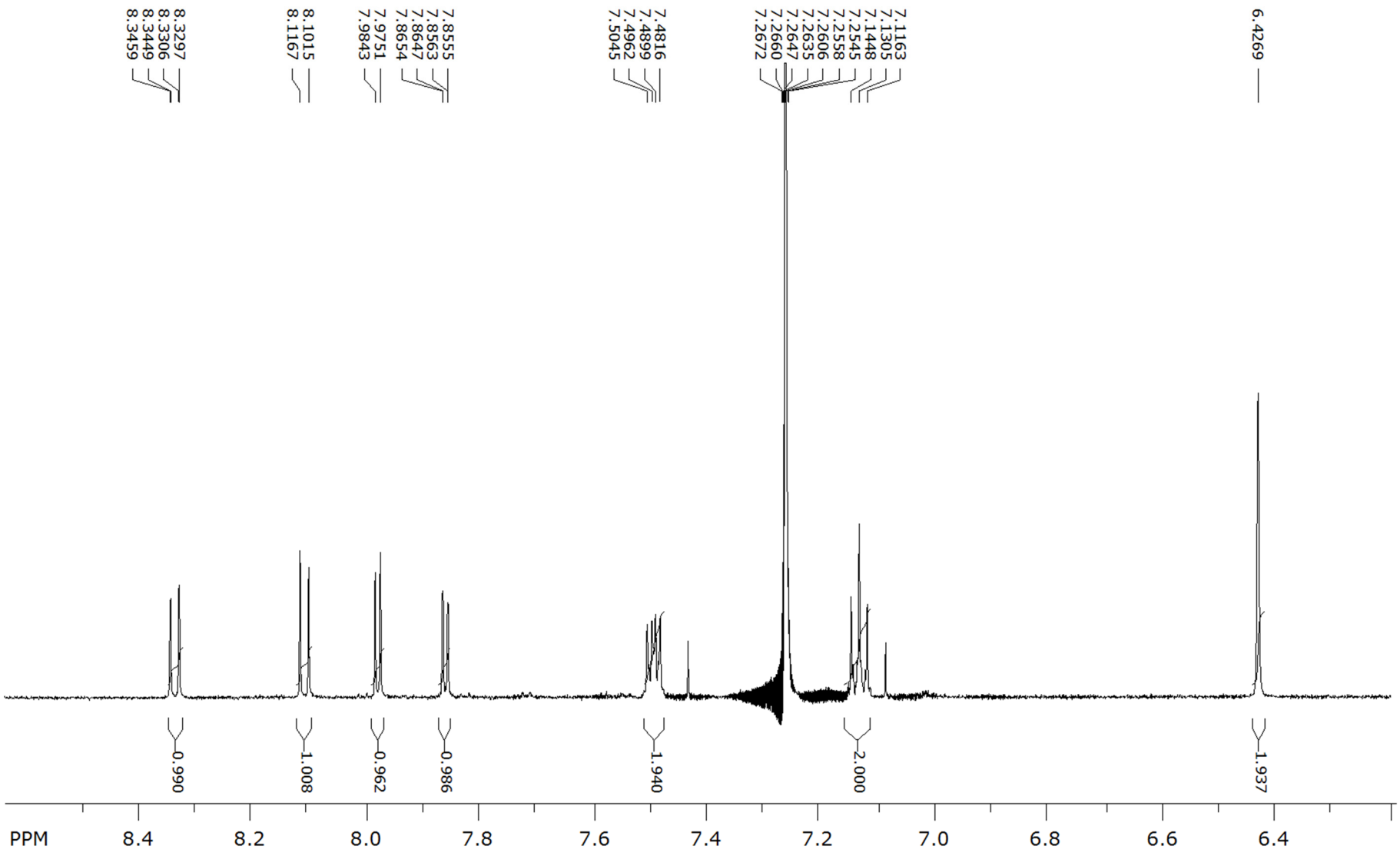


Figure S87. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **49**.

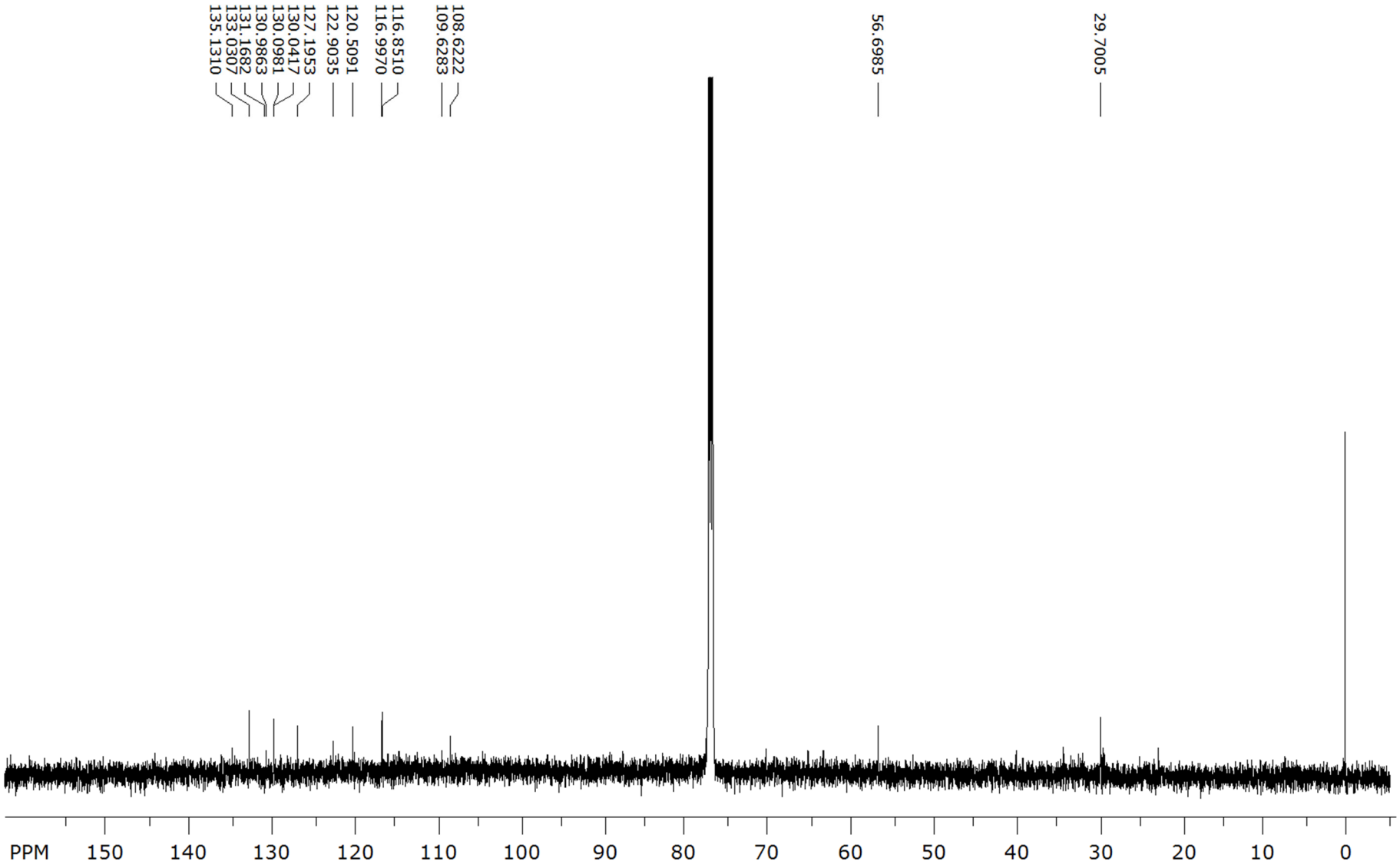


Figure S88. ^{13}C NMR ($CDCl_3$) spectrum of **49**.

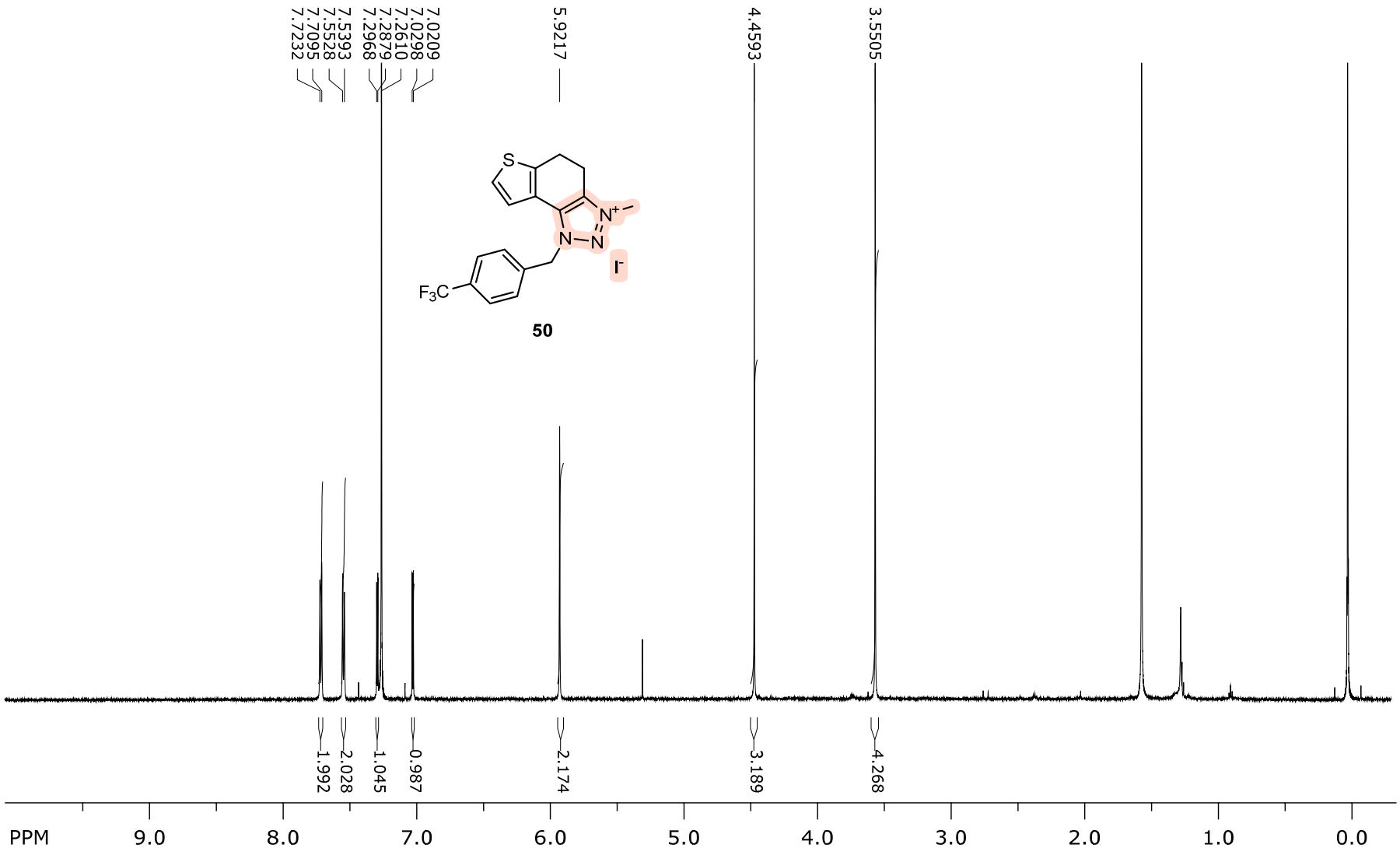


Figure S89. ^{1}H NMR ($CDCl_3$) spectrum of **50**.

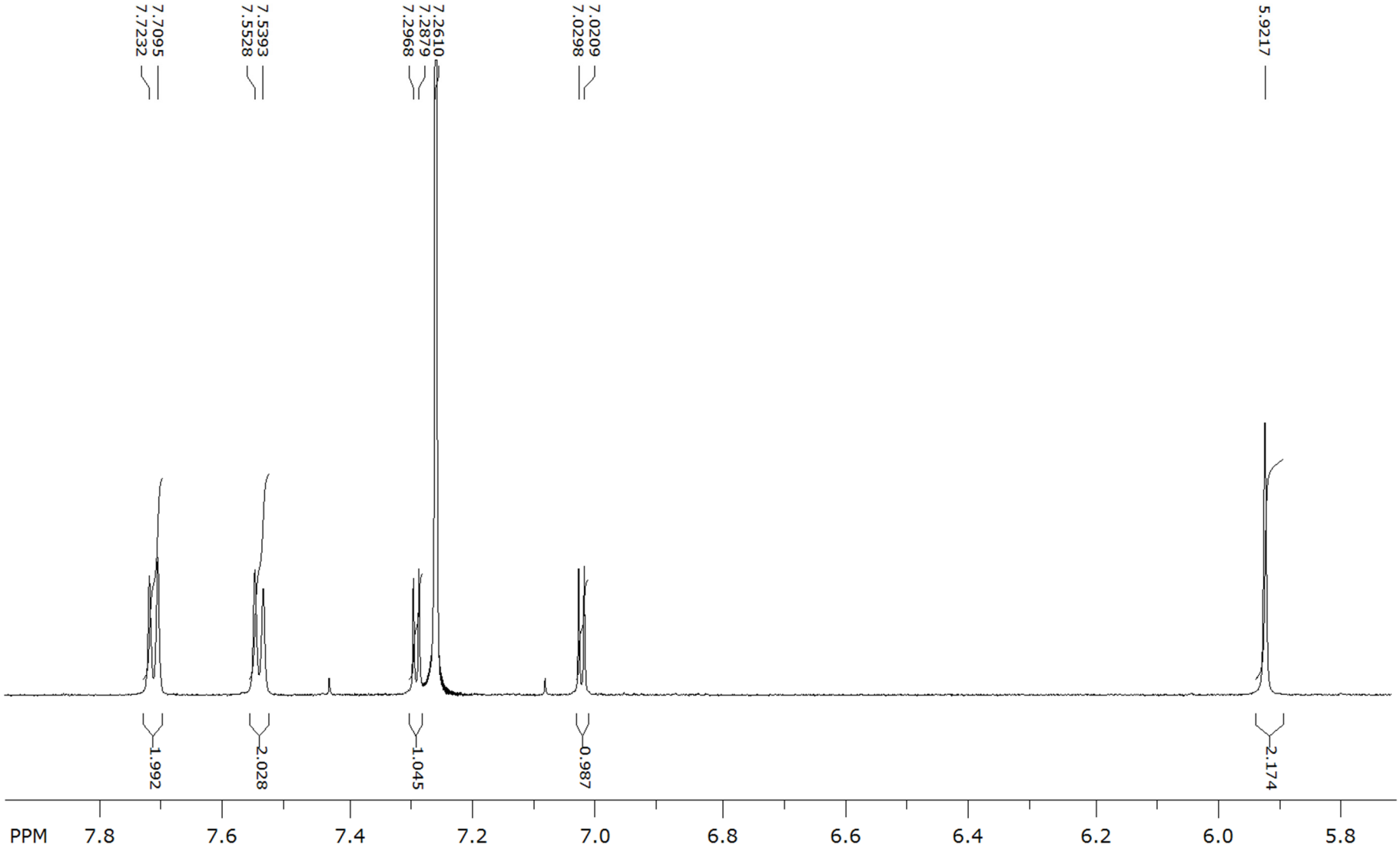


Figure S90. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **50**.

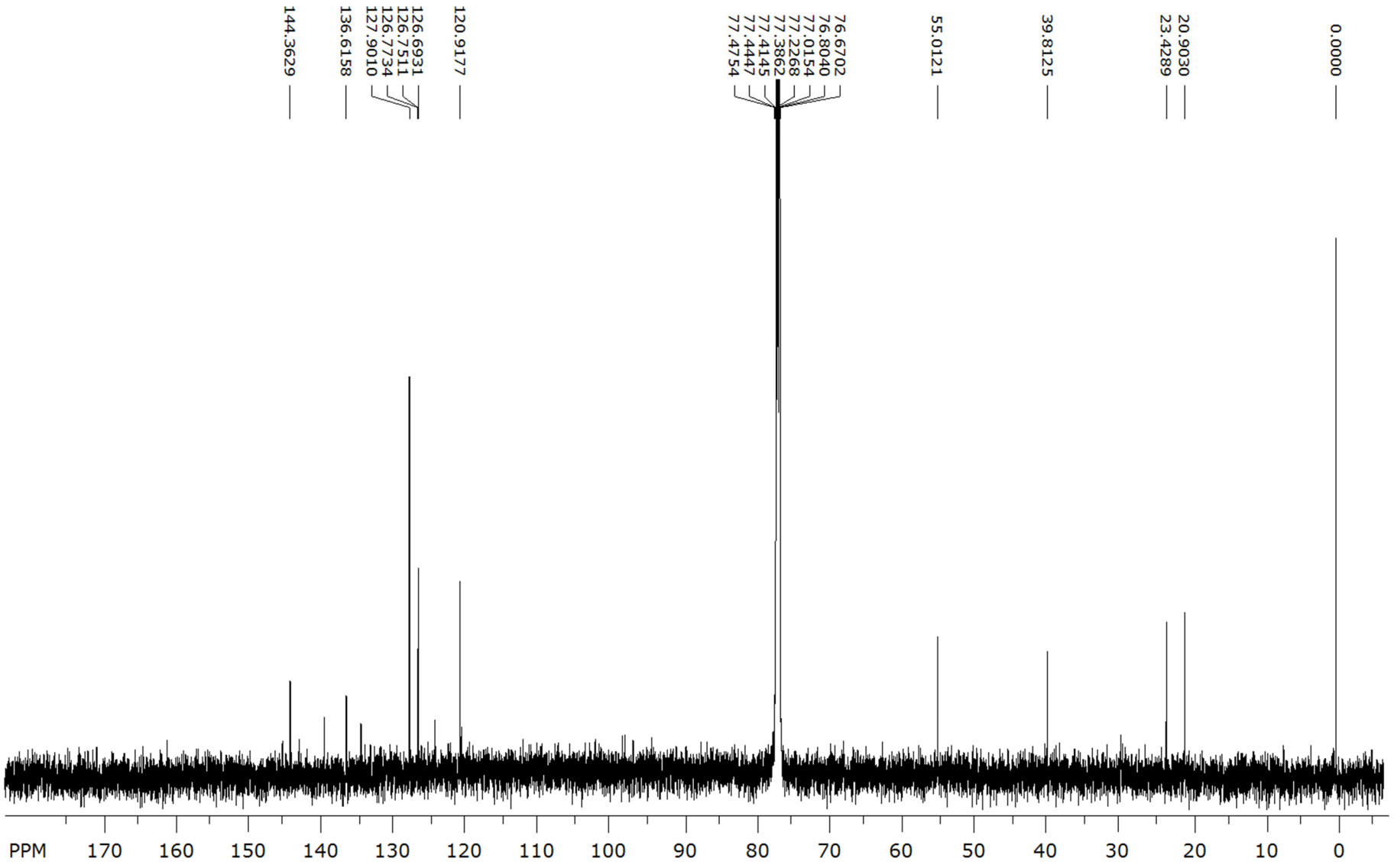


Figure S91. ^{13}C NMR ($CDCl_3$) spectrum of **50**.

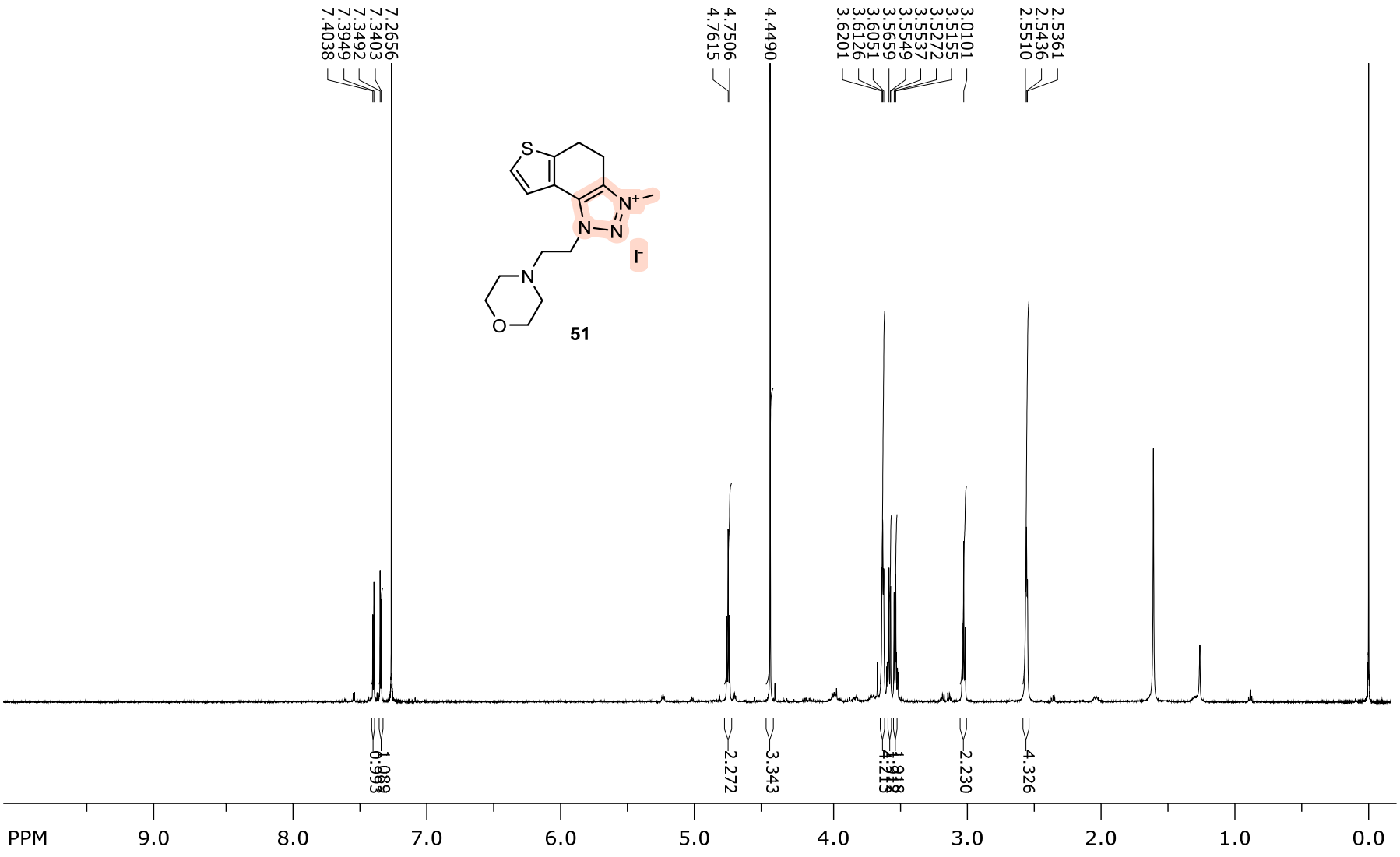


Figure S92. ^{1}H NMR ($CDCl_3$) spectrum of **51**.

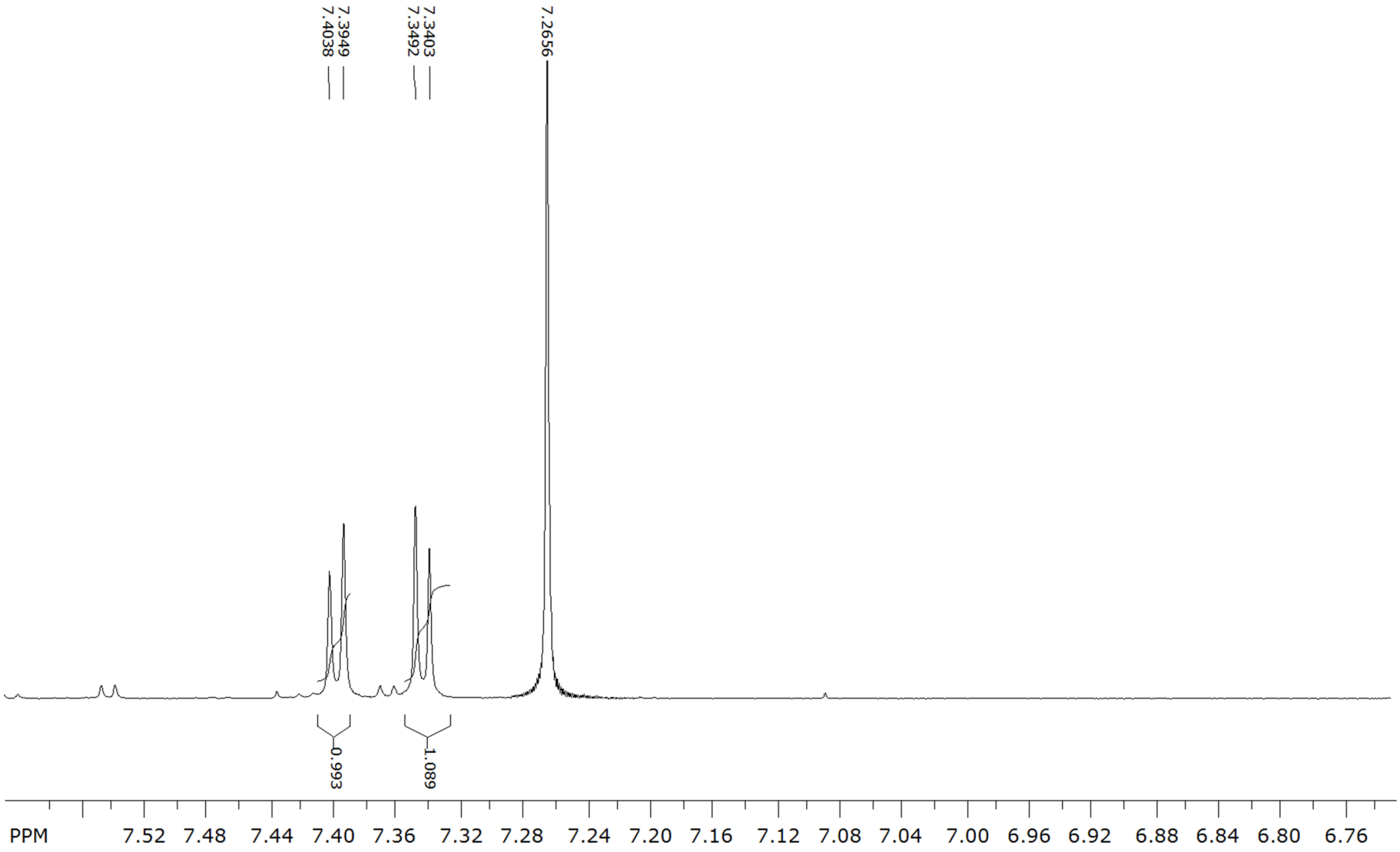


Figure S93. ^{1}H NMR ($CDCl_3$) spectrum of aromatic part of **51**.

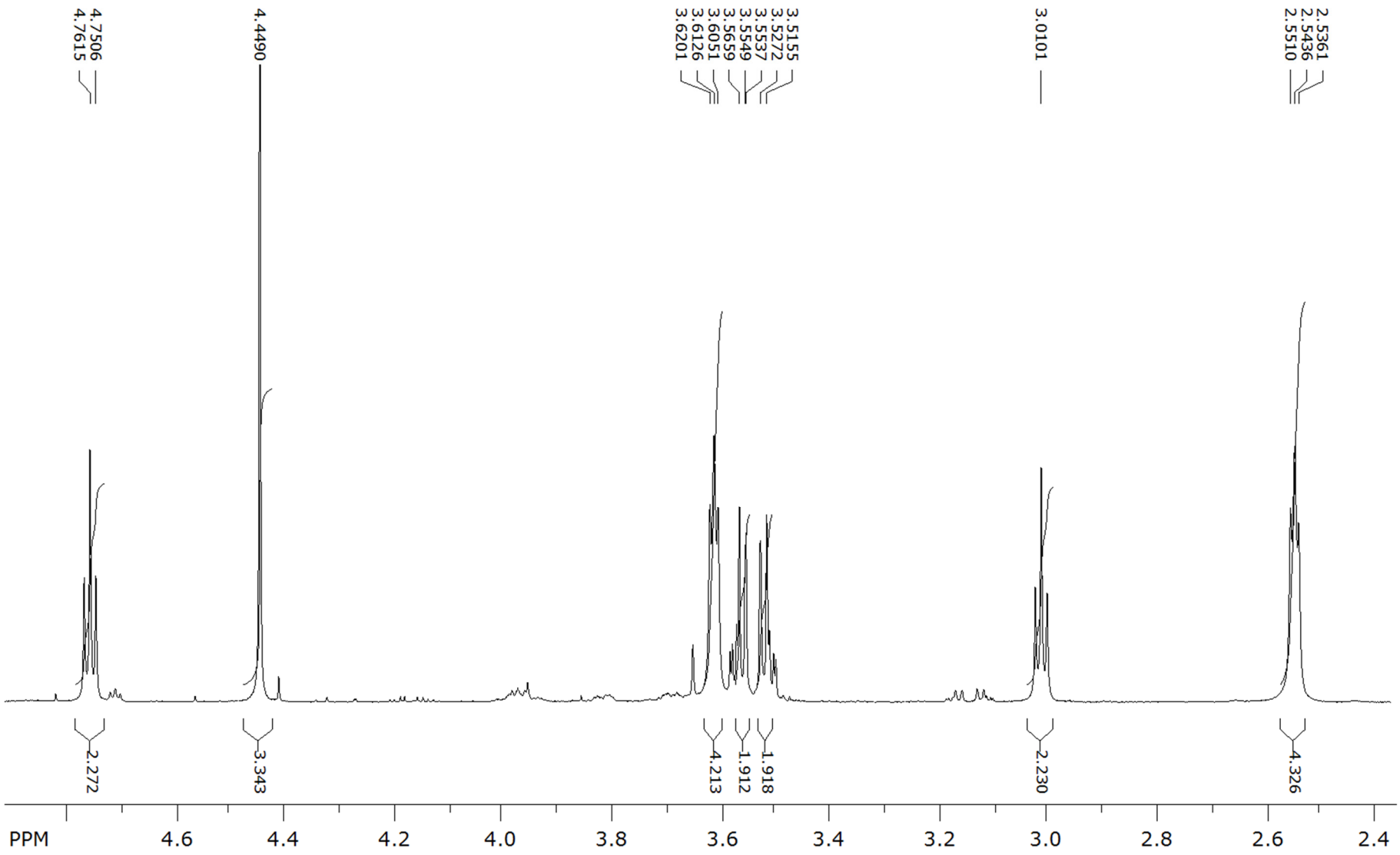


Figure S94. ^{1}H NMR ($CDCl_3$) spectrum of aliphatic part of **51**.

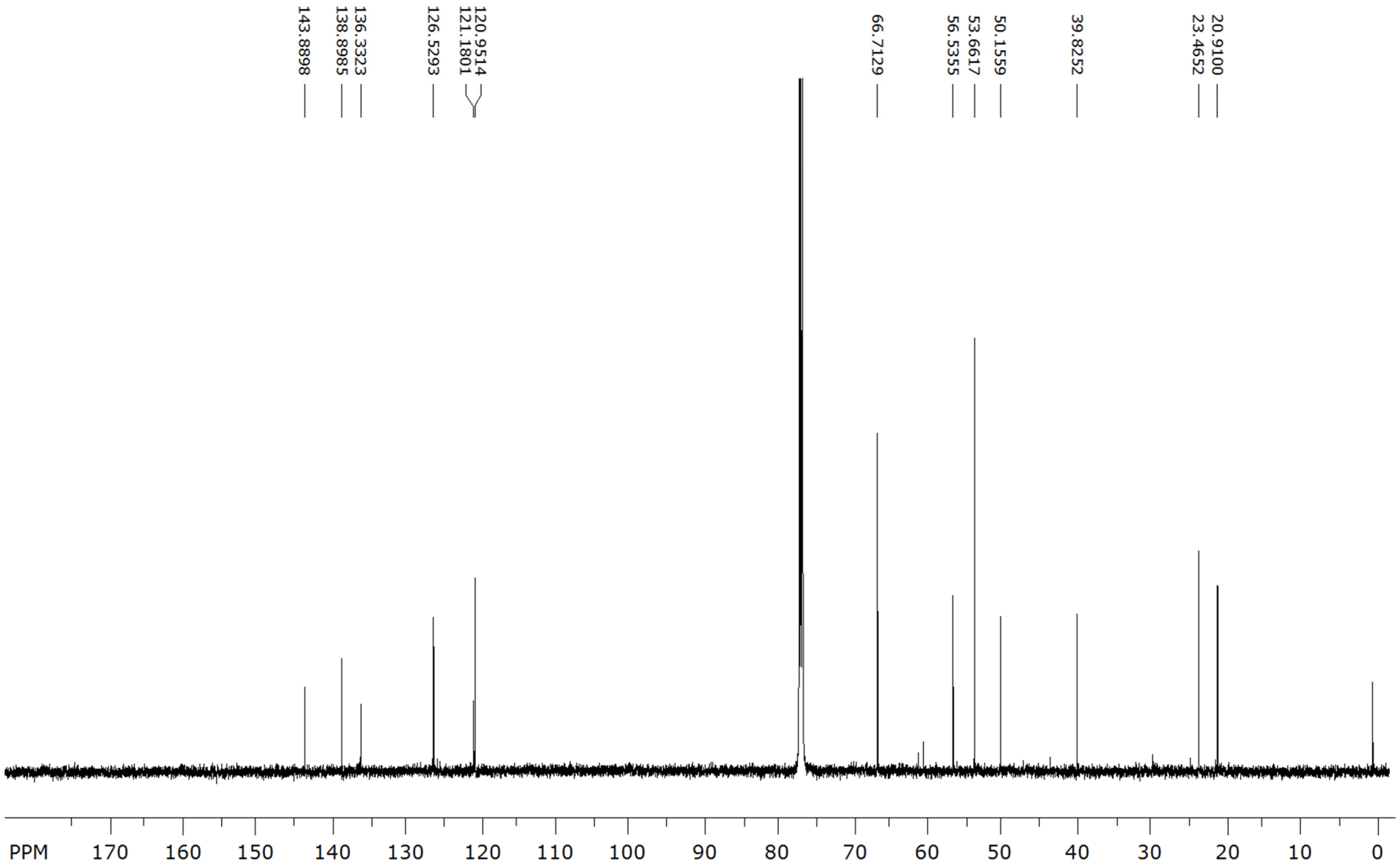
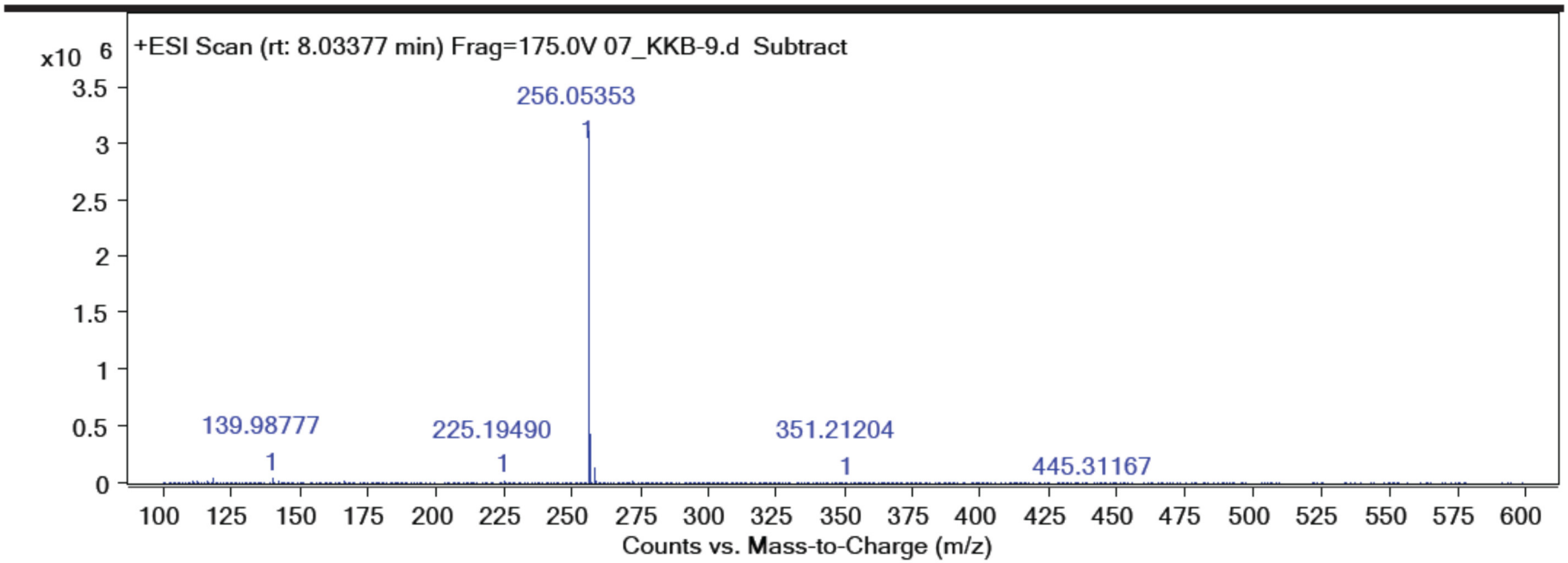


Figure S95. ^{13}C NMR ($CDCl_3$) spectrum of **51**.

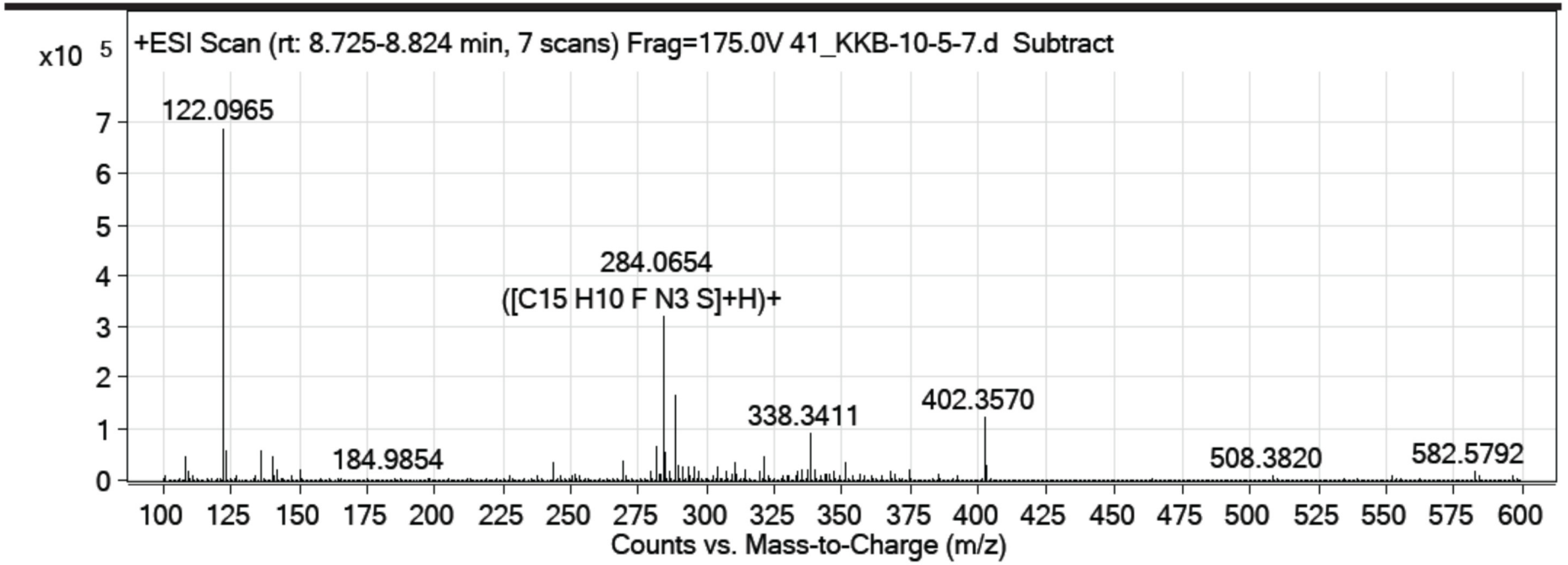
2. Mass spectra and HRMS analyses



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C13 H9 N3 O S	True	255.04633	255.04663	1.2	C13 H10 N3 O S	96.98

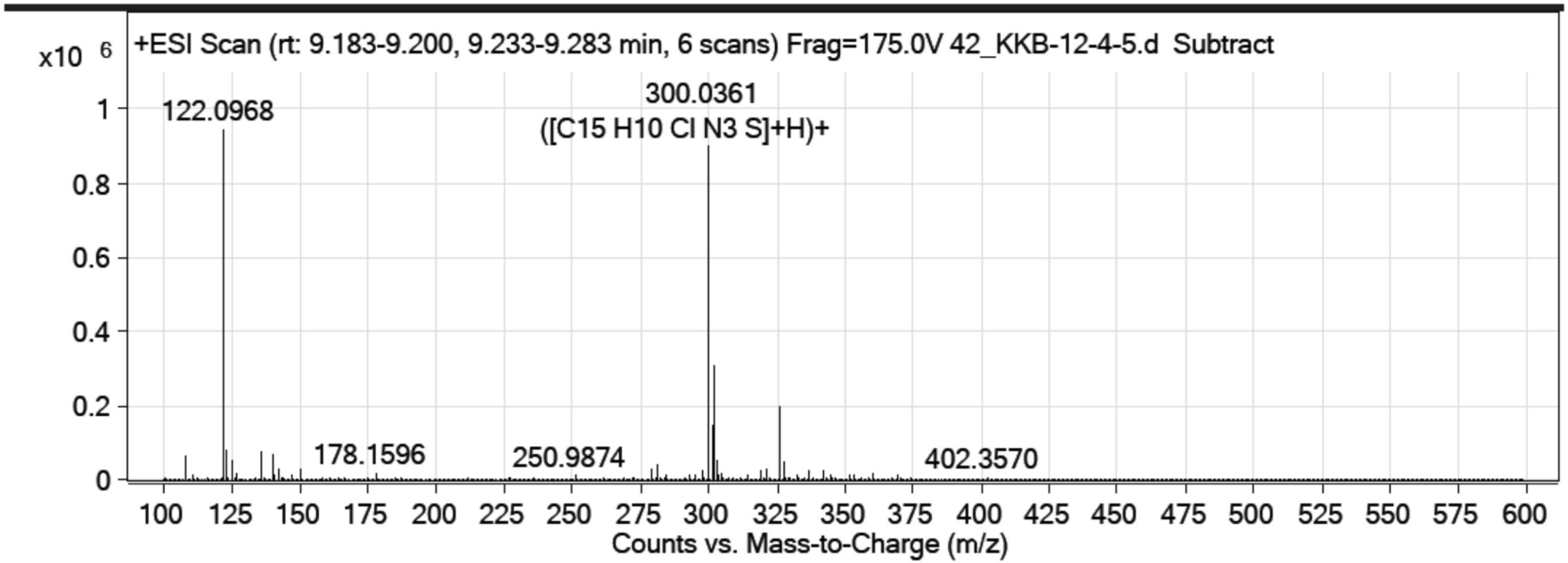
Figure S96. Mass spectrum and HRMS analysis of compound **23**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H10 F N3 S	True	283.0581	283.0579	-0.53	C15 H11 F N3 S	98.47

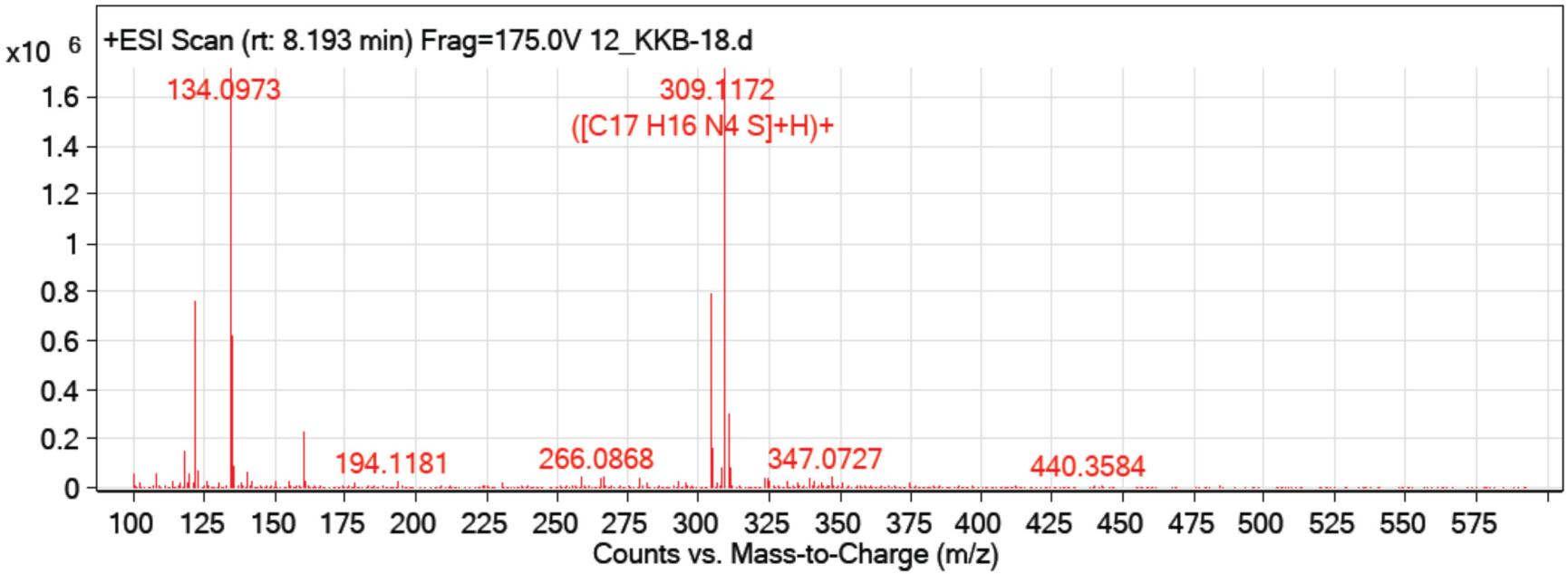
Figure S97. Mass spectrum and HRMS analysis of compound **24**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H10 Cl N3 S	True	299.0288	299.0284	-1.5	C15 H11 Cl N3 S	97.66

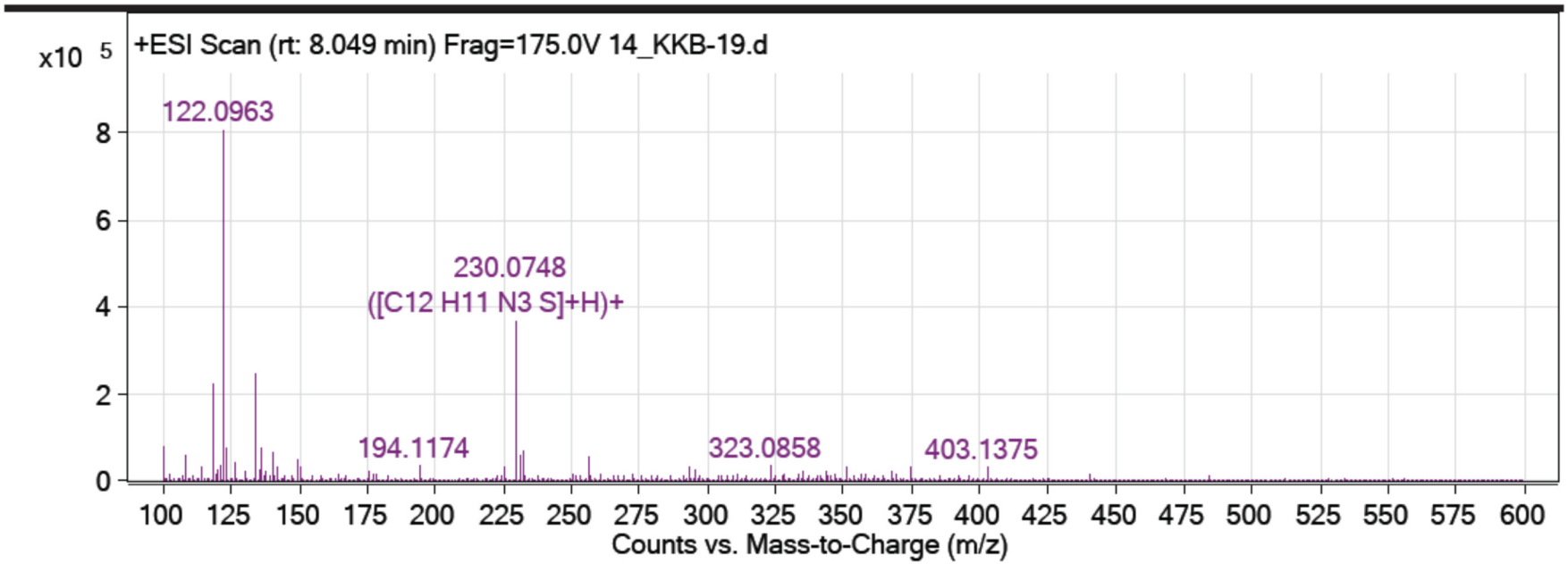
Figure S98. Mass spectrum and HRMS analysis of compound **26**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C17 H16 N4 S	True	308.11	308.1096	-1.44	C17 H17 N4 S	96.35

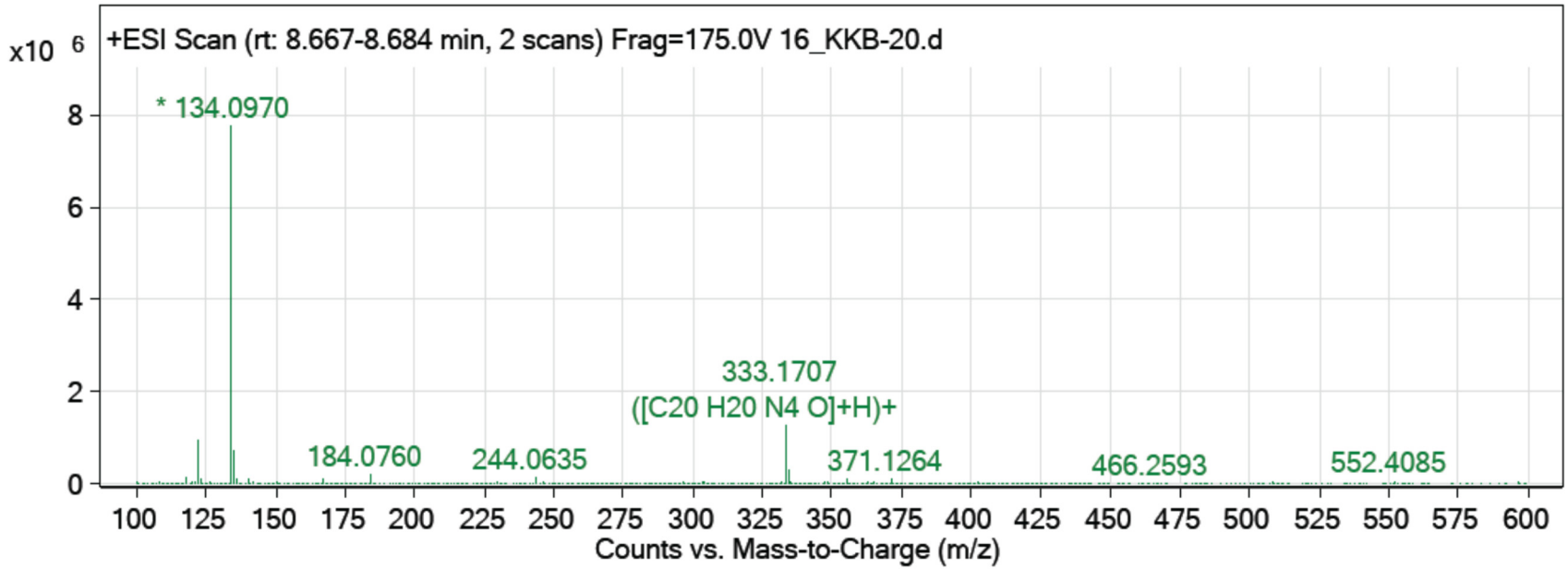
Figure S99. Mass spectrum and HRMS analysis of compound **27**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C12 H11 N3 S	True	229.0676	229.0674	-0.87	C12 H12 N3 S	47.44

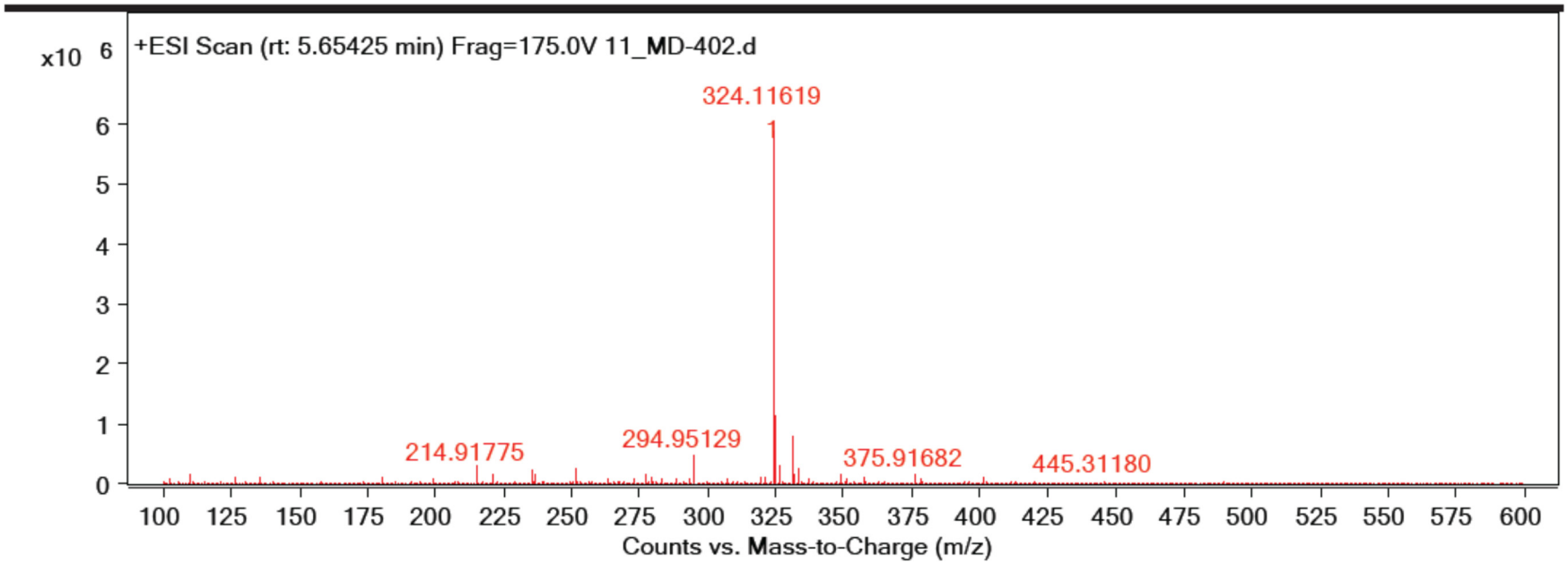
Figure S100. Mass spectrum and HRMS analysis of compound **28**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C20 H20 N4 O	True	332.1635	332.1637	0.64	C20 H21 N4 O	98.1

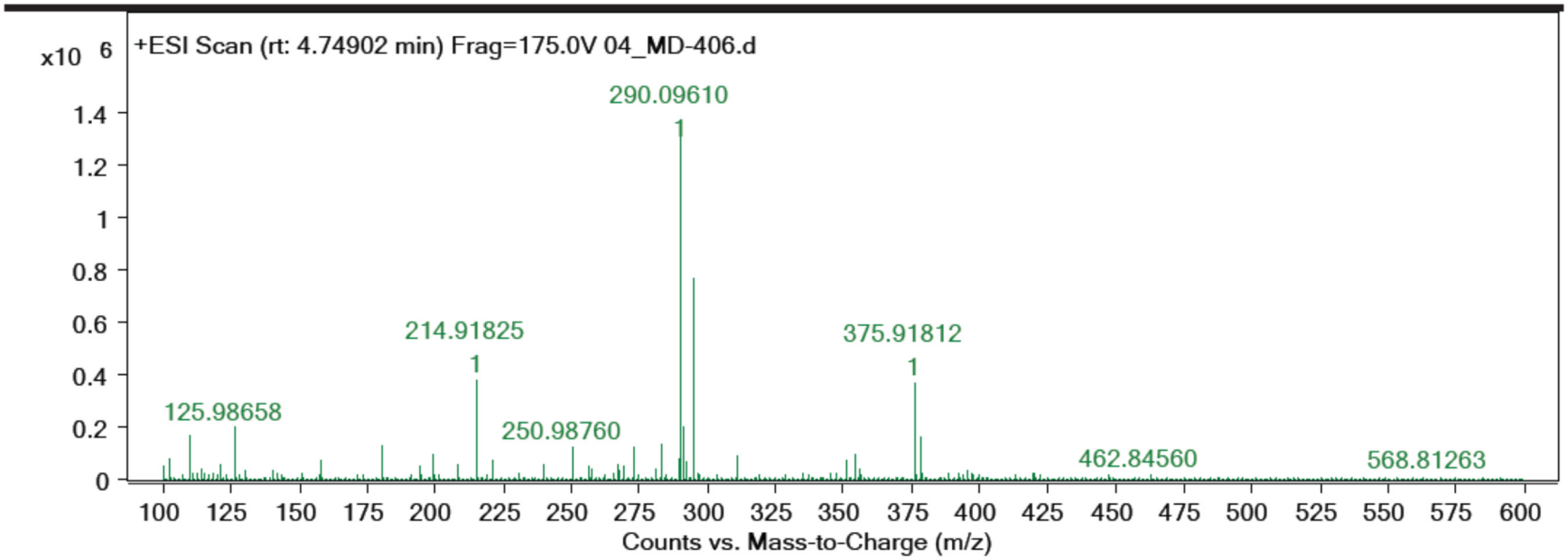
Figure S101. Mass spectrum and HRMS analysis of compound **30**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C18 H17 N3 O S	True	323.10892	323.10923	0.97	C18 H18 N3 O S	97.78

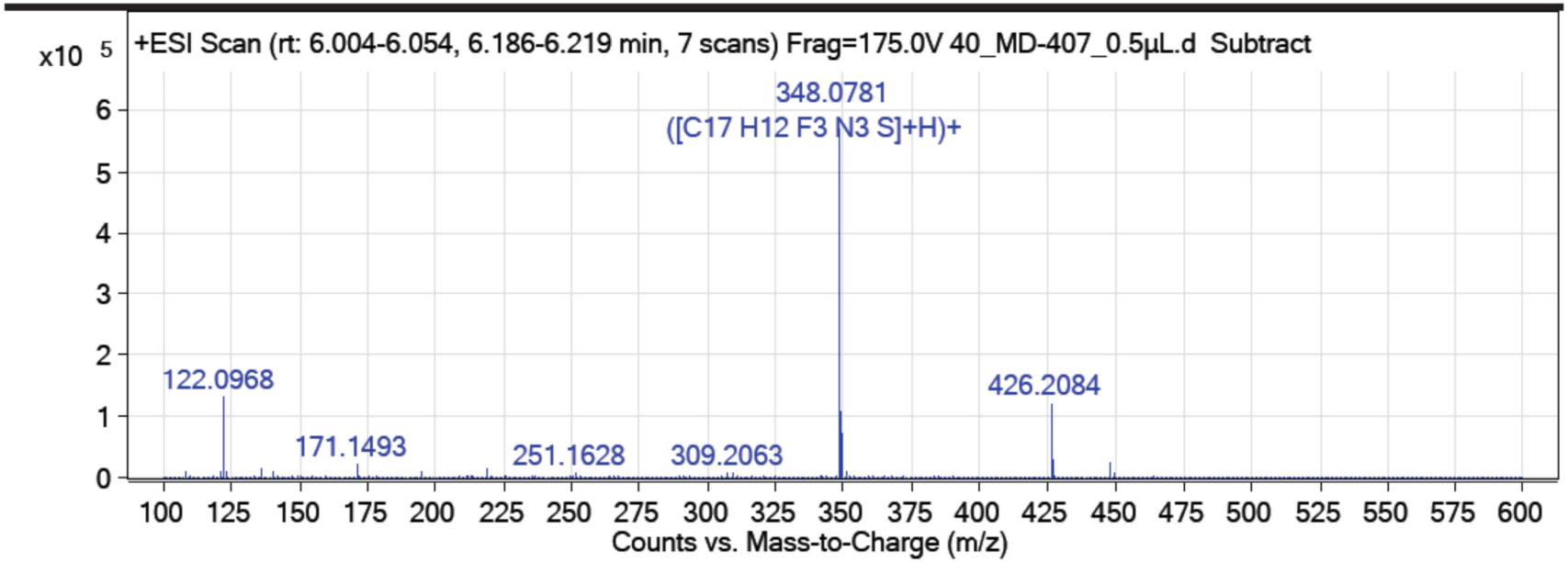
Figure S102. Mass spectrum and HRMS analysis of compound **44**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C14 H15 N3 O2 S	True	289.08892	289.0885	-1.46	C14 H16 N3 O2 S	96.73

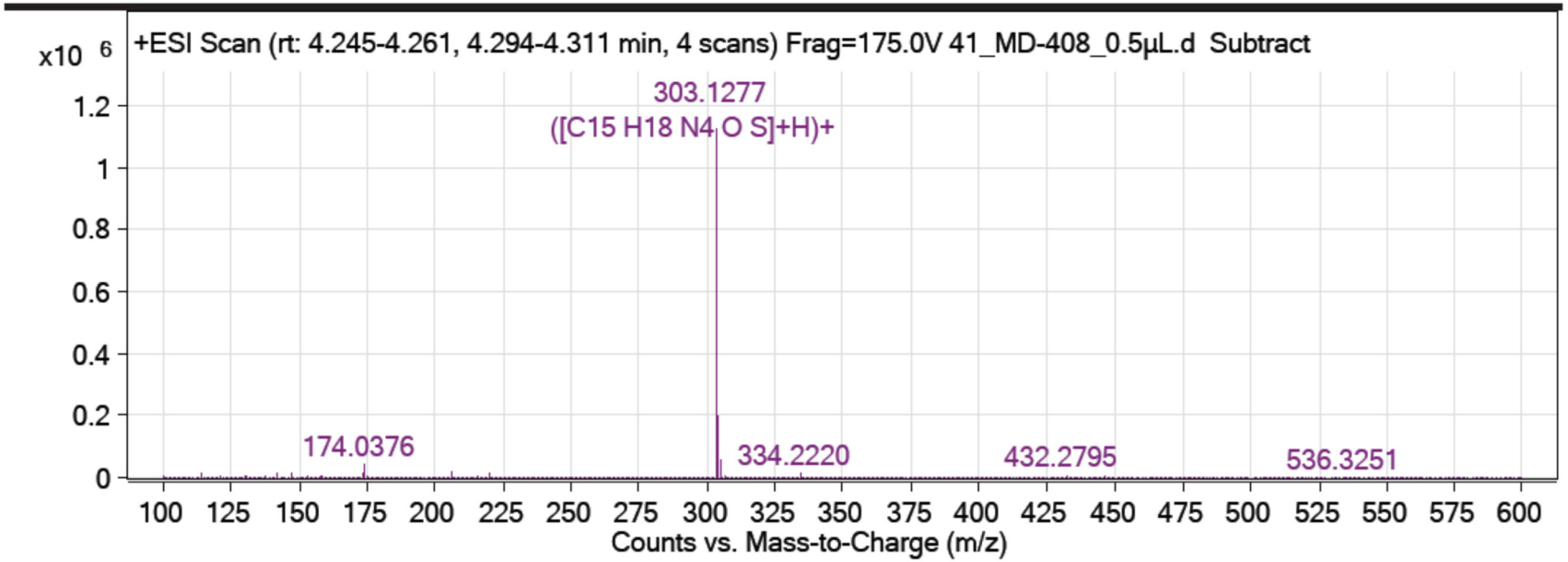
Figure S103. Mass spectrum and HRMS analysis of compound **45**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C17 H12 F3 N3 S	True	347.0708	347.0704	-1.08	C17 H13 F3 N3 S	47.19

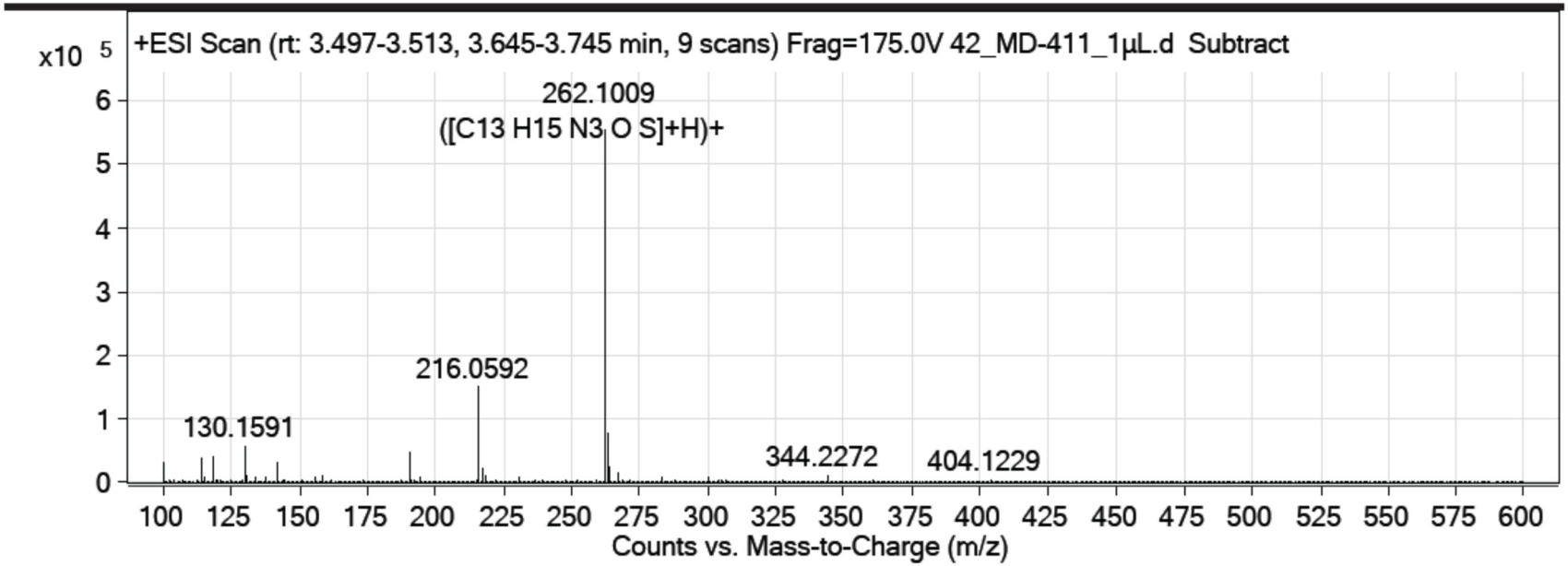
Figure S104. Mass spectrum and HRMS analysis of compound **46**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H18 N4 O S	True	302.1205	302.1201	-1.16	C15 H19 N4 O S	98

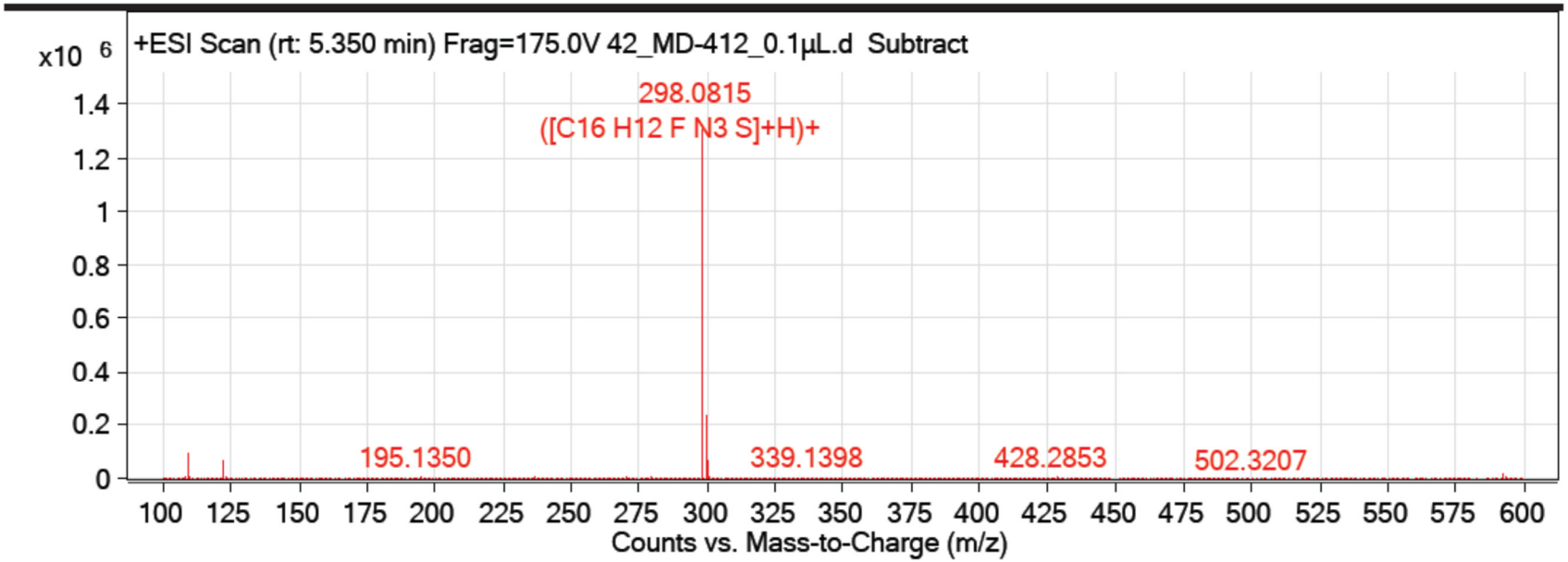
Figure S105. Mass spectrum and HRMS analysis of compound **47**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C13 H15 N3 O S	True	261.0937	261.0936	-0.47	C13 H16 N3 O S	98.04

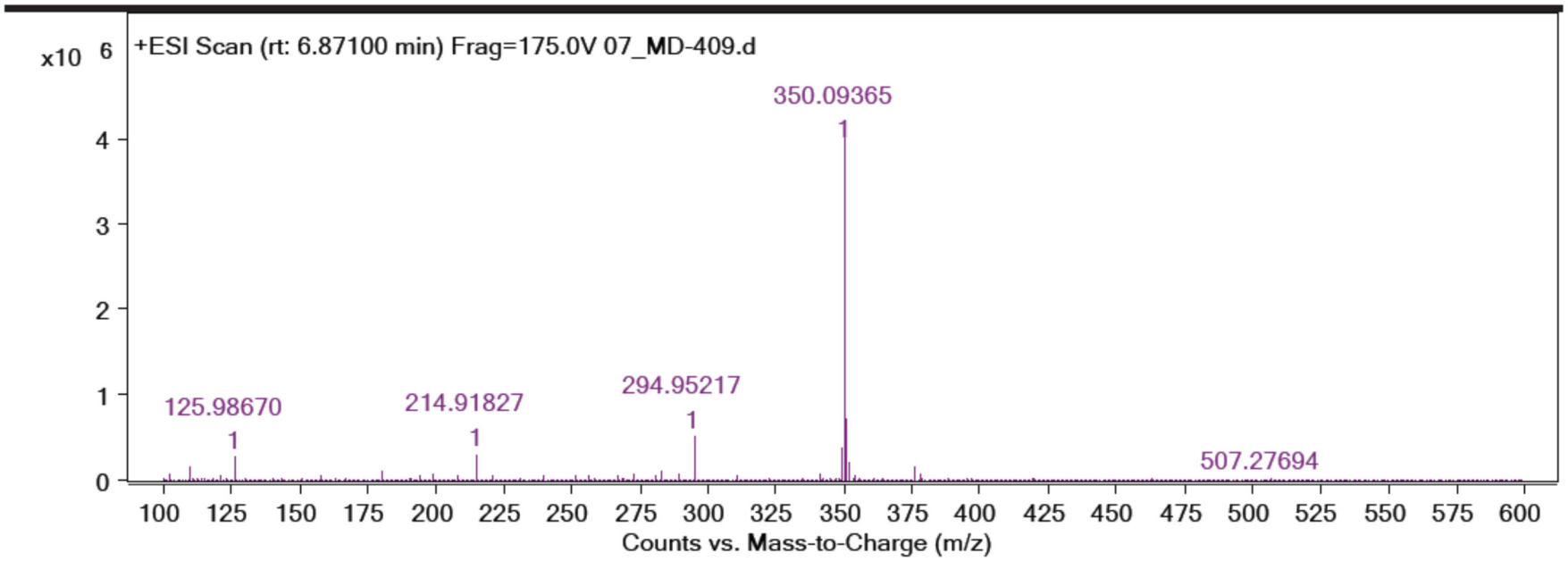
Figure S106. Mass spectrum and HRMS analysis of compound **48**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C16 H12 F N3 S	True	297.0742	297.0736	-2.14	C16 H13 F N3 S	97.4

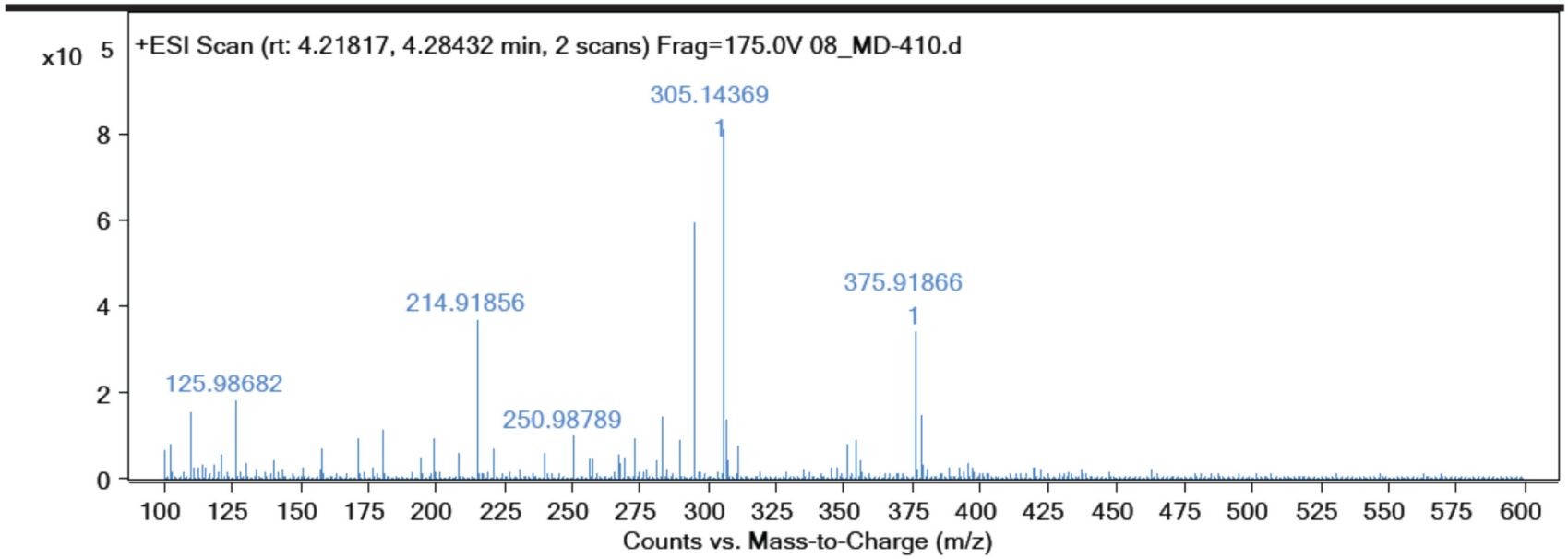
Figure S107. Mass spectrum and HRMS analysis of compound **49**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C17 H14 F3 N3 S	True	349.08642	349.08605	-1.07	C17 H15 F3 N3 S	97.2

Figure S108. Mass spectrum and HRMS analysis of compound **50**.

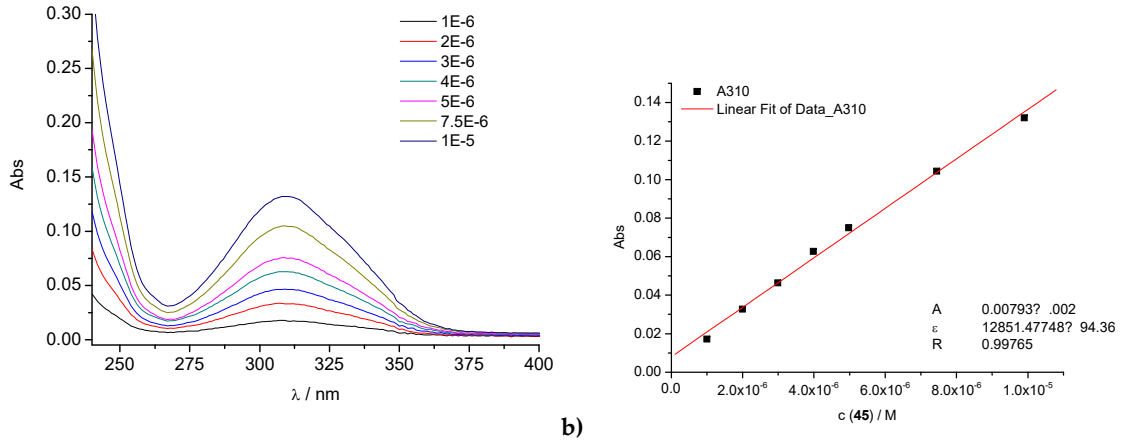


Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H20 N4 O S	True	304.13644	304.13578	-2.16	C15 H21 N4 O S	96.94

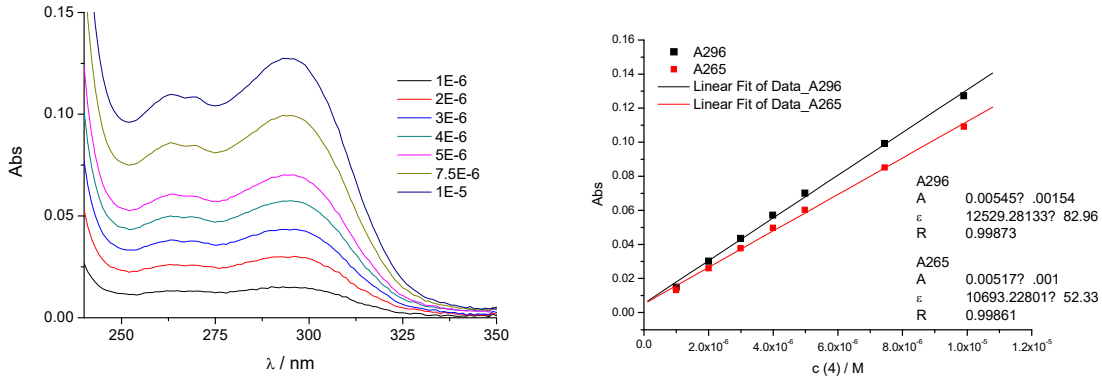
Figure S109. Mass spectrum and HRMS analysis of compound **51**.

3. Spectrophotometric data and DNA binding



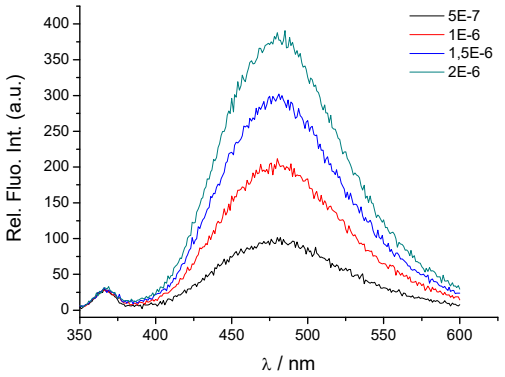
a) **b)**

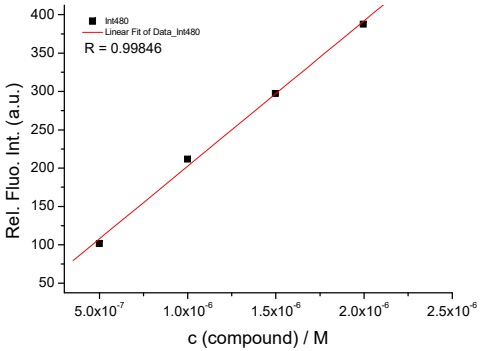
Figure S110. a) The UV/vis spectra dependence of **3** on concentration, b) dependence of absorption at 310 nm on *c*(**45**) at 310 nm. Molar extinction coefficient (ε at 310 nm) is 12851.5 M^{-1} cm^{-1}.



a) **b)**

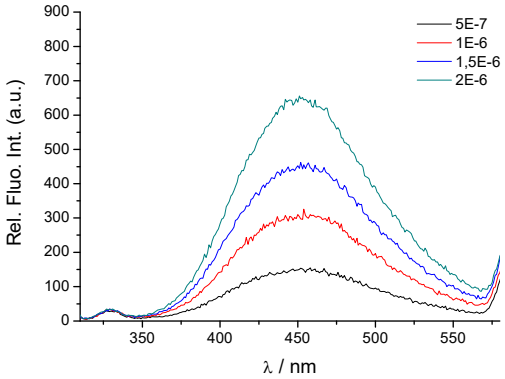
Figure S111. a) The UV/vis spectra dependence of **4** on concentration. The sample shows two absorbance peaks, at 296 nm and at 265 nm, b) dependence of absorption at 296 nm on c(**50**) (black) and 265 nm (red). Molar extinction coefficient (ε) is 12529.3 M^{-1} cm^{-1} at 296 nm and 10693.2 M^{-1} cm^{-1} at 265 nm.

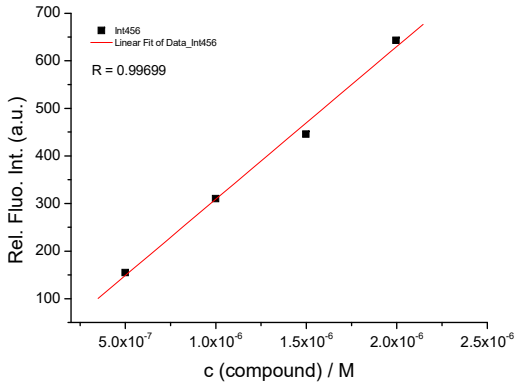




a) b)

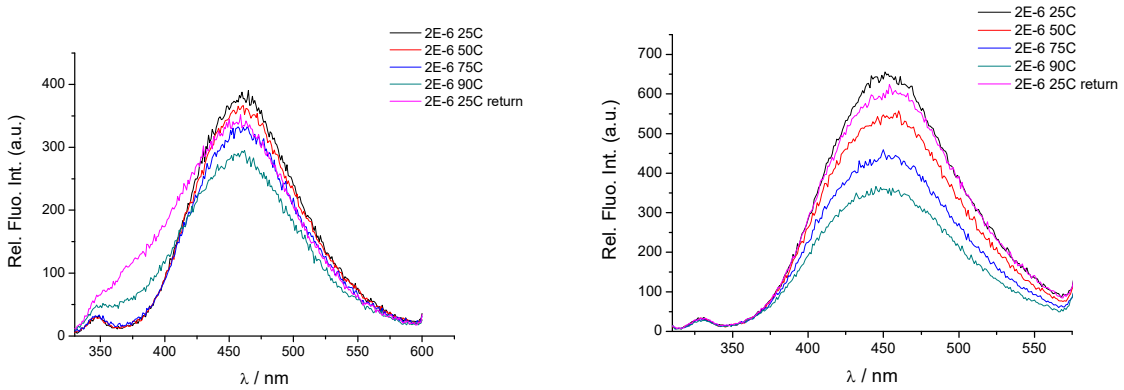
Figure S112. a) fluorescence intensity dependence of **45** on concentration. The sample shows a fluorescence maximum at 480 nm, b) dependence of emission at 480 nm on c(**45**).





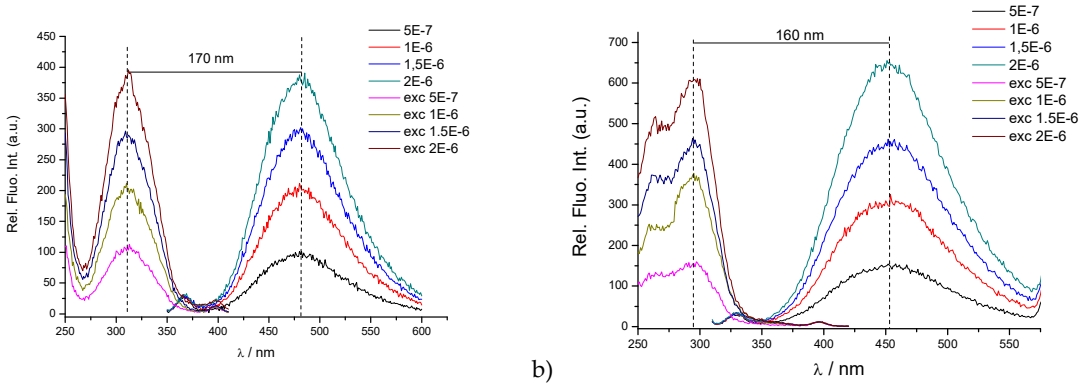
a) b)

Figure S113. a) fluorescence intensity dependence of **50** on concentration. The sample shows a fluorescence maximum at 456 nm, b) dependence of emission at 456 nm on c(**50**).



a) b)

Figure 114. a) temperature stability of **3** at 2×10^{-6} M. Decrease of fluorescence intensity upon heating and cooling is visible, along with broadening of the peak, b) temperature stability of **4** at 2×10^{-6} M. The sample shows a slight decrease in fluorescence intensity after heating.



a) b)

Figure S115. a) emission and excitation (exc) spectra of **45** at increasing concentrations displaying Stokes shift of 170 nm, b) emission and excitation (exc) spectra of **50** at increasing concentrations displaying Stokes shift of 160 nm.

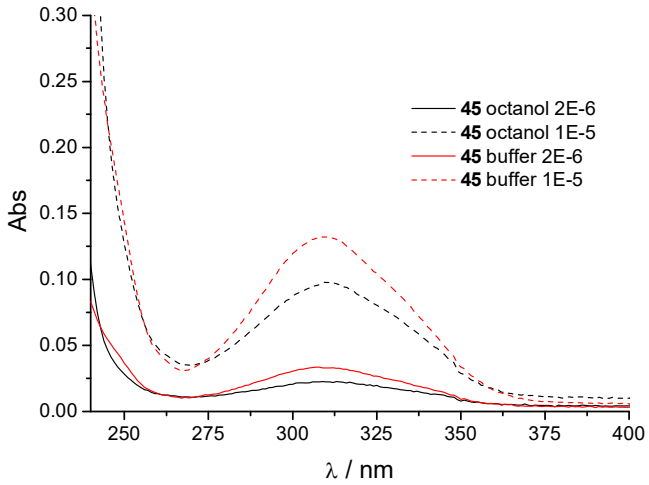


Figure S116. Comparison of UV/vis spectra of **45** at two concentrations (solid lines – c = 2×10^{-6} M, dashed lines – c = 1×10^{-5} M) in 1-octanol (black) and aqueous solution (red).

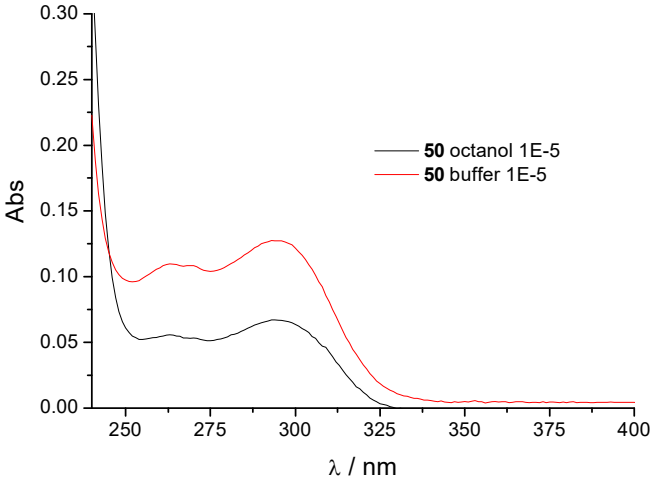
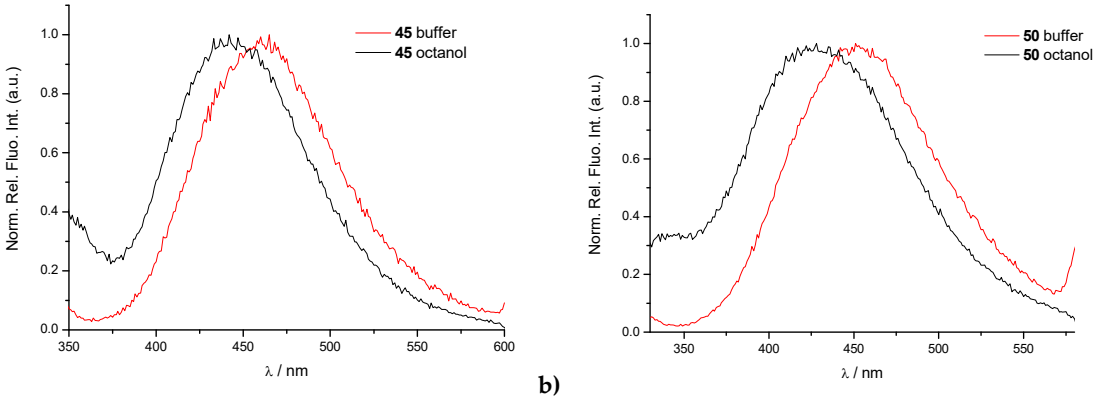


Figure S117. Comparison of UV/vis spectra of **50** at concentration *c* = 10 μM in 1-octanol (black) and aqueous solution (red).



a) b)

Figure S118. a) Comparison of normalised fluorescence spectra of **45** **50** in 1-octanol (black) and aqueous solution (red), b) comparison of normalised fluorescence spectra of **50** in 1-octanol (black) and aqueous solution (red).

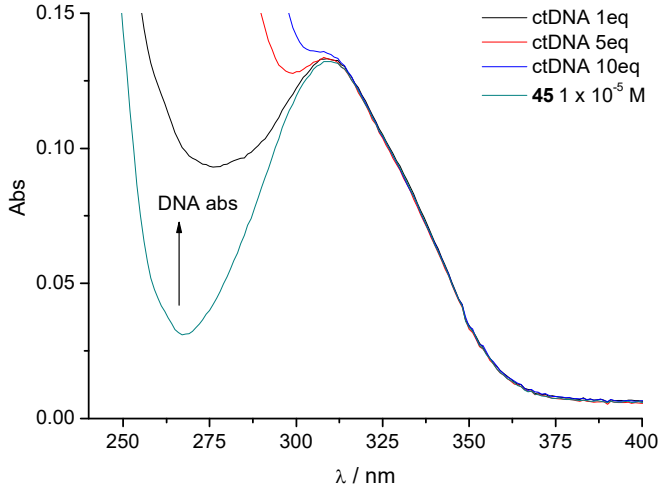


Figure S119. Difference in absorption for **45** (c = 1×10^{-5} M) before and after the addition of ctDNA (1eq = 1 × 10^{-5} M; 5eq = 5 × 10^{-5} M; 10eq = 1 × 10^{-4} M).

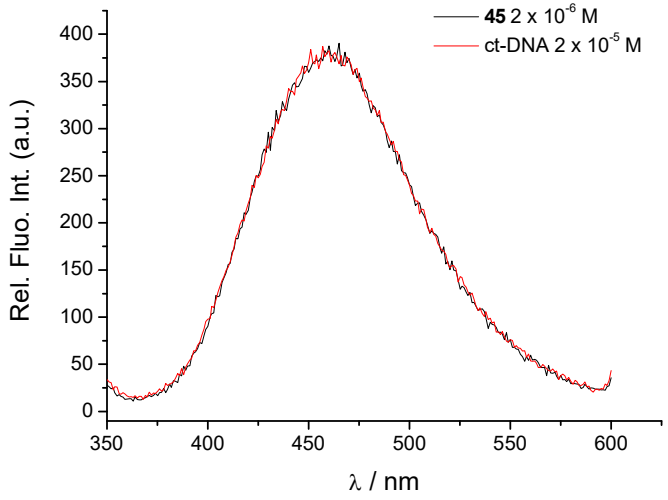


Figure S120. Impact of 10-fold *ct*-DNA addition on the fluorescence spectra for **45** (c = 2×10^{-6} M, λ_{exc} = 310 nm).

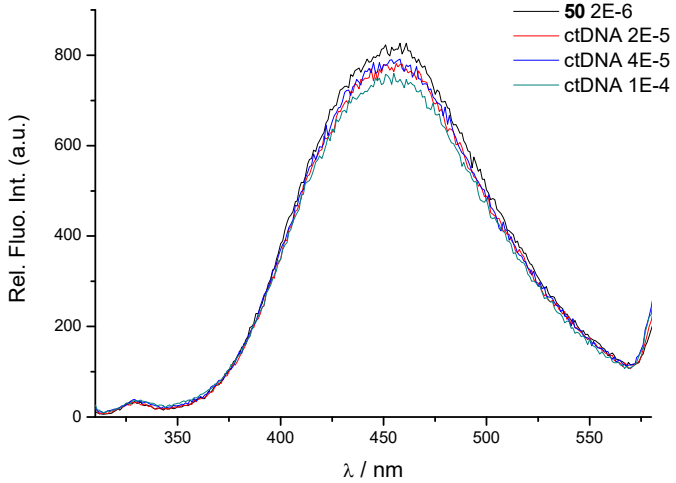


Figure S121. Impact of 10-, 20- and 50-fold *ct*-DNA addition on the fluorescence spectra for **50** (c = 2×10^{-6} M, λ_{exc} = 296 nm).

4. Cartesian coordinates of ligands docked into AChE and BChE

Table S1.
Ligand **44** docked into AChE

C	-10.331	-42.895	27.272
H	-10.996	-42.937	26.393
C	-10.570	-43.603	28.493
C	-9.562	-43.376	29.463
S	-8.345	-42.294	28.842
C	-9.182	-42.162	27.326
H	-8.819	-41.545	26.487
C	-9.562	-43.957	30.756
H	-8.740	-43.730	31.456
C	-10.578	-44.803	31.149
H	-10.595	-45.265	32.150
C	-11.594	-45.045	30.202
C	-11.603	-44.474	28.917
N	-12.730	-45.815	30.248
N	-13.415	-45.761	29.122
N	-12.743	-44.960	28.321
C	-13.224	-46.639	31.353
H	-12.645	-46.685	32.305
H	-13.379	-47.678	30.980
H	-14.270	-46.331	31.587
C	-13.245	-44.675	26.952
H	-12.525	-44.028	26.398
H	-13.199	-45.592	26.320
C	-14.653	-44.067	26.917
H	-15.445	-44.825	27.119
H	-14.846	-43.399	27.789
C	-14.862	-43.358	25.595
C	-14.490	-42.013	25.433
H	-14.019	-41.476	26.273
C	-14.705	-41.348	24.234
H	-14.405	-40.292	24.129
C	-15.304	-42.017	23.153

```
C    -15.679 -43.359  23.296
H    -16.146 -43.898  22.454
C    -15.457 -44.011  24.512
H    -15.759 -45.066  24.620
O    -15.466 -41.281  22.026
C    -16.719 -40.643  21.801
H    -16.852 -40.038  20.874
H    -16.965 -40.009  22.685
H    -17.528 -41.408  21.852
```

Ligand **45** docked into AChE

```
N   -12.903 -44.401  27.744
C   -11.701 -44.215  28.385
C   -11.759 -45.054  29.512
N   -12.988 -45.660  29.432
N   -13.671 -45.267  28.374
C   -10.565 -43.413  28.121
C    -9.526 -43.540  29.078
C    -9.593 -44.390  30.211
H    -8.741 -44.433  30.911
C   -10.710 -45.163  30.449
H   -10.779 -45.830  31.324
S    -8.180 -42.516  28.661
C    -9.004 -41.943  27.245
H    -8.568 -41.207  26.549
C   -10.244 -42.490  27.075
H   -10.916 -42.250  26.234
C   -13.580 -46.636  30.350
H   -13.003 -46.968  31.244
H   -13.881 -47.537  29.766
H   -14.570 -46.251  30.688
C   -13.355 -43.750  26.498
H   -12.484 -43.397  25.898
H   -13.838 -42.769  26.717
C   -14.272 -44.627  25.654
H   -13.955 -45.696  25.643
```

H -15.275 -44.772 26.118
C -14.353 -44.023 24.255
O -14.701 -44.654 23.278
O -13.996 -42.740 24.268
C -15.081 -41.762 24.279
H -15.949 -42.082 24.901
H -14.827 -40.838 24.848
C -15.457 -41.484 22.838
H -16.285 -40.737 22.846
H -15.711 -42.408 22.269
H -14.589 -41.164 22.216

Ligand **44** docked into BCh**E**
C 3.806 -8.577 -9.248
H 4.682 -8.527 -8.579
C 2.805 -7.558 -9.334
C 1.787 -7.869 -10.271
S 2.094 -9.412 -11.021
C 3.547 -9.617 -10.092
H 4.198 -10.503 -10.176
C 0.680 -7.029 -10.545
H -0.071 -7.343 -11.290
C 0.530 -5.824 -9.892
H -0.325 -5.157 -10.092
C 1.529 -5.490 -8.954
C 2.632 -6.316 -8.676
N 1.700 -4.397 -8.141
N 2.792 -4.488 -7.406
N 3.354 -5.635 -7.723
C 0.845 -3.215 -8.018
H 0.984 -2.327 -7.358
H -0.174 -3.604 -7.788
H 0.745 -2.808 -9.051
C 4.620 -6.057 -7.070
H 5.134 -6.837 -7.679

H	4.408	-6.648	-6.149
C	5.577	-4.898	-6.759
H	5.301	-4.363	-5.821
H	5.454	-4.047	-7.469
C	7.000	-5.416	-6.726
C	8.066	-4.571	-6.372
H	7.858	-3.524	-6.094
C	9.375	-5.030	-6.366
H	10.196	-4.349	-6.085
C	9.658	-6.361	-6.717
C	8.608	-7.218	-7.071
H	8.815	-8.266	-7.346
C	7.296	-6.737	-7.073
H	6.474	-7.416	-7.355
O	10.967	-6.712	-6.677
C	11.879	-5.870	-5.980
H	12.955	-6.159	-5.947
H	11.512	-5.725	-4.937
H	11.795	-4.834	-6.384

Ligand **45** docked into BCh**E**

N	2.259	-7.245	-8.798
C	2.765	-6.082	-8.266
C	4.083	-6.399	-7.894
N	4.235	-7.719	-8.241
N	3.142	-8.222	-8.781
C	2.232	-4.787	-8.062
C	3.136	-3.873	-7.463
C	4.465	-4.201	-7.092
H	5.108	-3.432	-6.632
C	4.963	-5.470	-7.300
H	5.993	-5.744	-7.017
S	2.385	-2.314	-7.257
C	0.905	-2.892	-7.956
H	0.009	-2.261	-8.081
C	0.955	-4.202	-8.336

```
H      0.113  -4.744  -8.798
C      5.417  -8.569  -8.080
H      6.341  -8.144  -7.623
H      5.679  -9.006  -9.072
H      5.125  -9.480  -7.508
C      0.902  -7.456  -9.342
H      0.154  -6.842  -8.788
H      0.529  -8.475  -9.088
C      0.804  -7.203 -10.842
H      1.387  -6.310 -11.167
H     -0.205  -6.845 -11.153
C      1.226  -8.477 -11.567
O      2.030  -8.490 -12.478
O      0.599  -9.541 -11.067
C      1.417 -10.728 -10.830
H      0.973 -11.656 -11.261
H      2.362 -10.730 -11.422
C      1.654 -10.825  -9.336
H      2.278 -11.731  -9.155
H      0.709 -10.823  -8.744
H      2.098  -9.897  -8.905
```

Table S2. Free energies of binding, ΔG_{bind} obtained by molecular docking of ligands **44** and **45** into the active site of AChE (4EY7.pdb), along with the number of conformational clusters and distribution of conformations.

Ligand	ΔG_{bind}/kcal mol^{-1}		Number of distinctive conformational clusters	Distribution of conformations within clusters with $n > 1$ (n = cluster population)
	lowest	highest		
44	−9.47	−8.41	9	8, 2, 7, 3
45	−8.23	−7.11	11	3, 2, 2, 6, 2, 4, 2,
Galantamine	−10.10	−10.10	1	25

Table S3. Free energies of binding, ΔG_{bind} obtained by molecular docking of ligands **44** and **45** into the active site of BChE (3DJY.pdb), along with the number of conformational clusters and distribution of conformations.

Ligand	ΔG_{bind}/kcal mol^{-1}		Number of distinctive conformational clusters	Distribution of conformations within clusters with $n > 1$ (n = cluster population)
	lowest	highest		
44	−8.57	−8.38	3	15, 6, 4
45	−6.89	−6.06	10	10, 2, 6
Galantamine	−7.31	−7.28	1	25