Electronic Supporting Information

New Thienobenzo/Naphtho-Triazoles as Butyrylcholinesterase Inhibitors. Design, Synthesis and Computational Study

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† These authors contributed equally to this work.

Content:

1. ^{1}H and ^{13}C NMR spectra of synthesized compounds

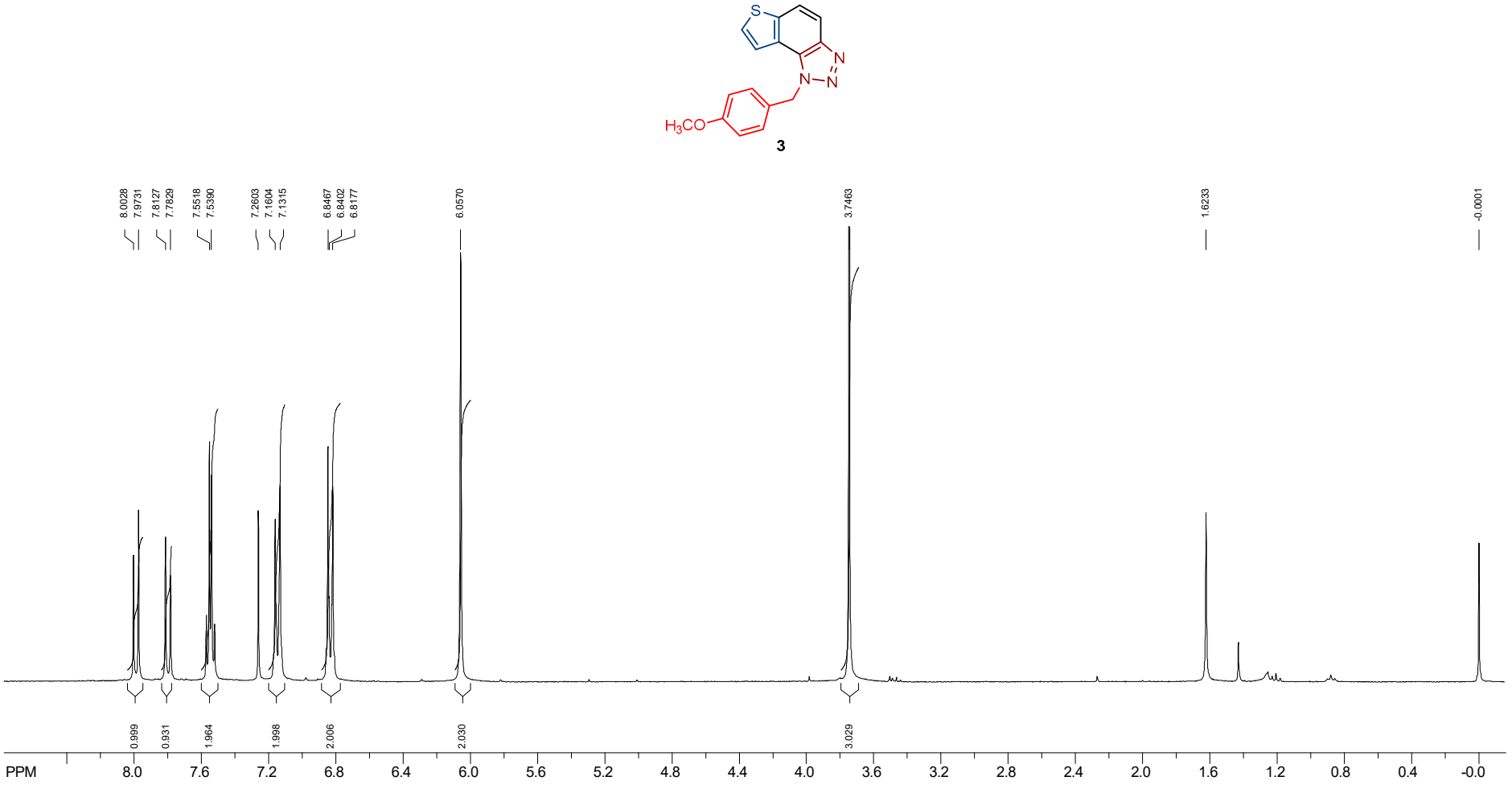

Figure S1. ^{1}H NMR spectrum ($CDCl_3$) of compound **3**.

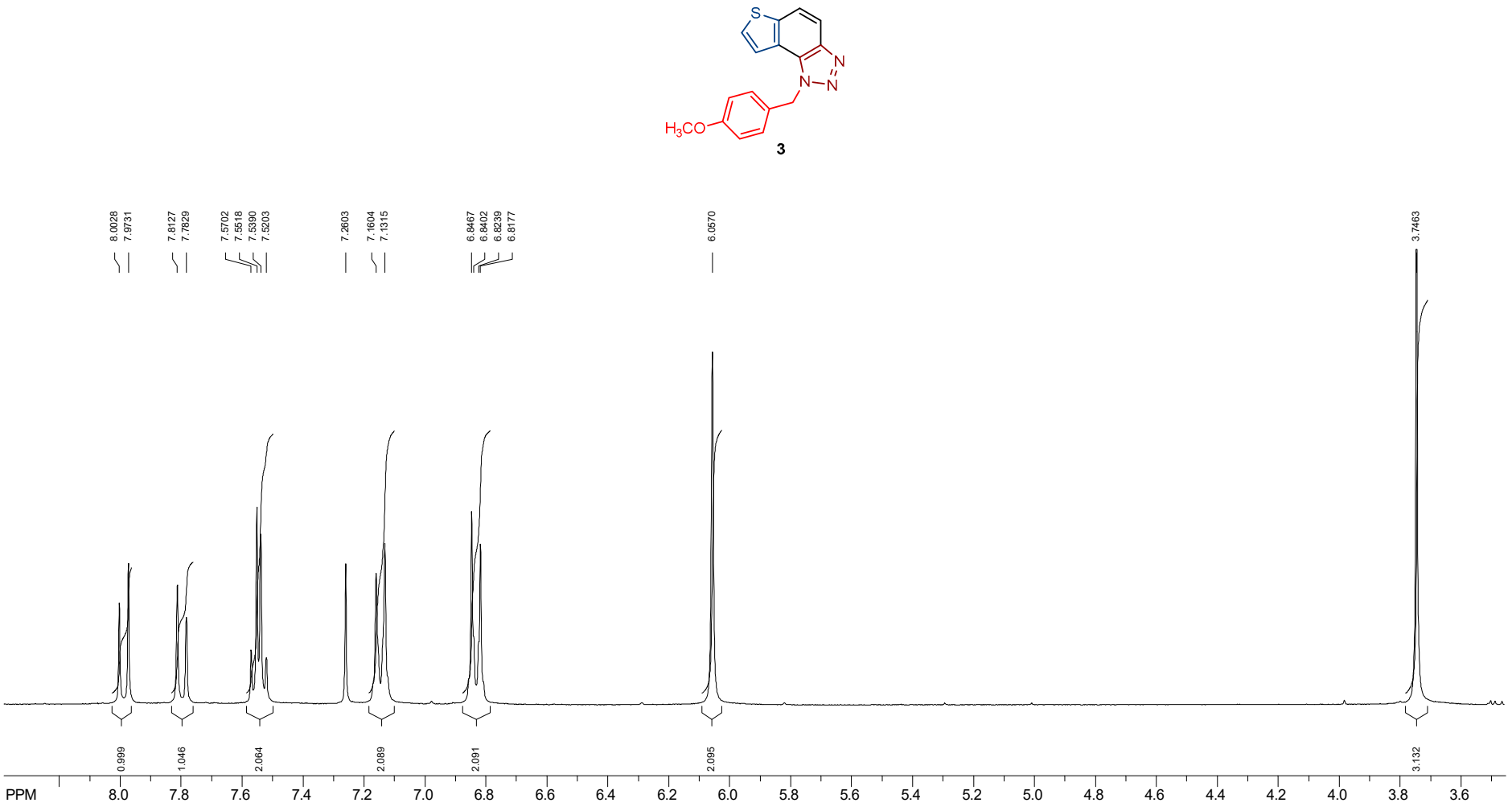

Figure S2. Part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **3**.

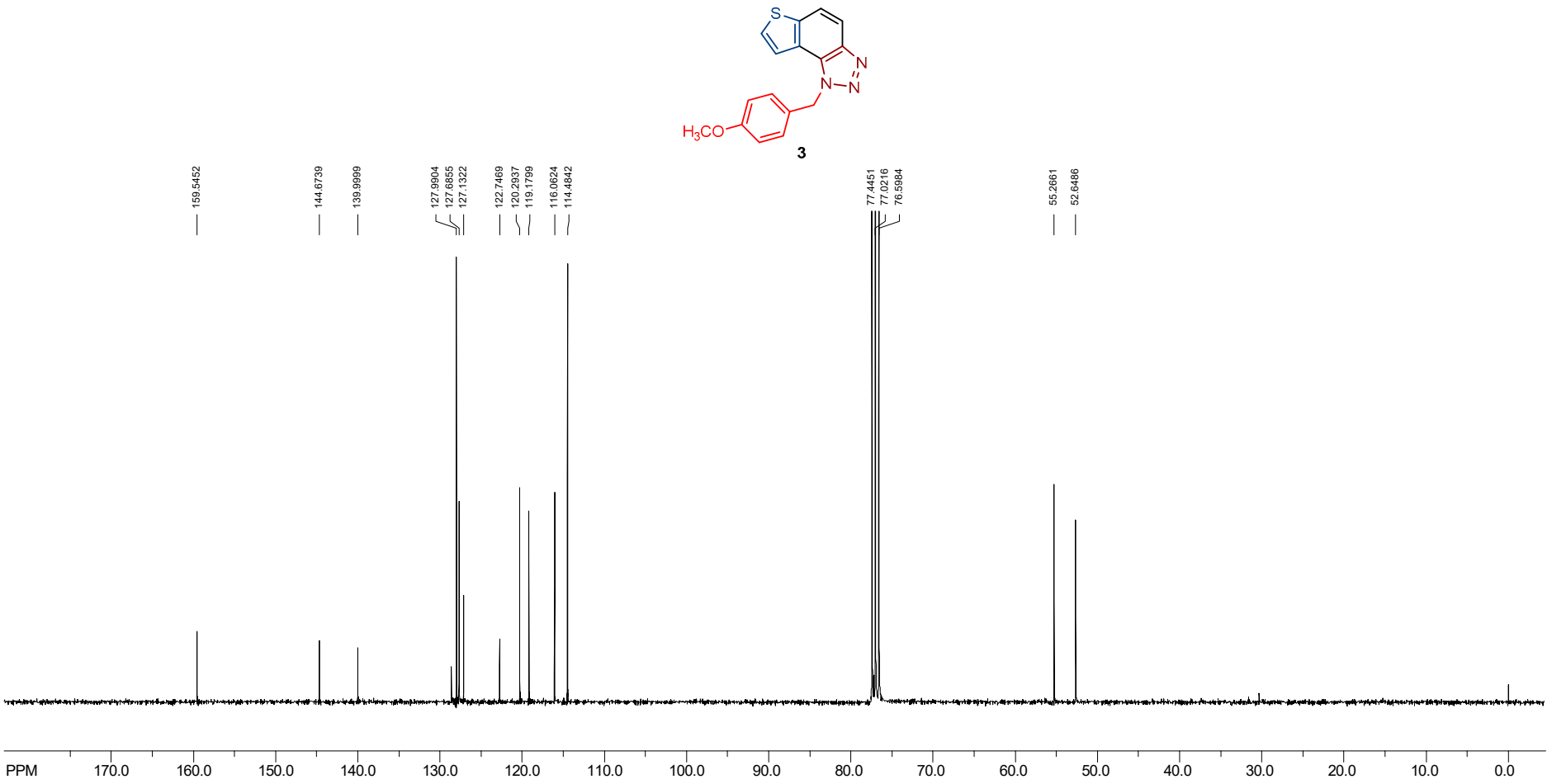

Figure S3. ^{1}H NMR spectrum ($CDCl_3$) of compound **3**.

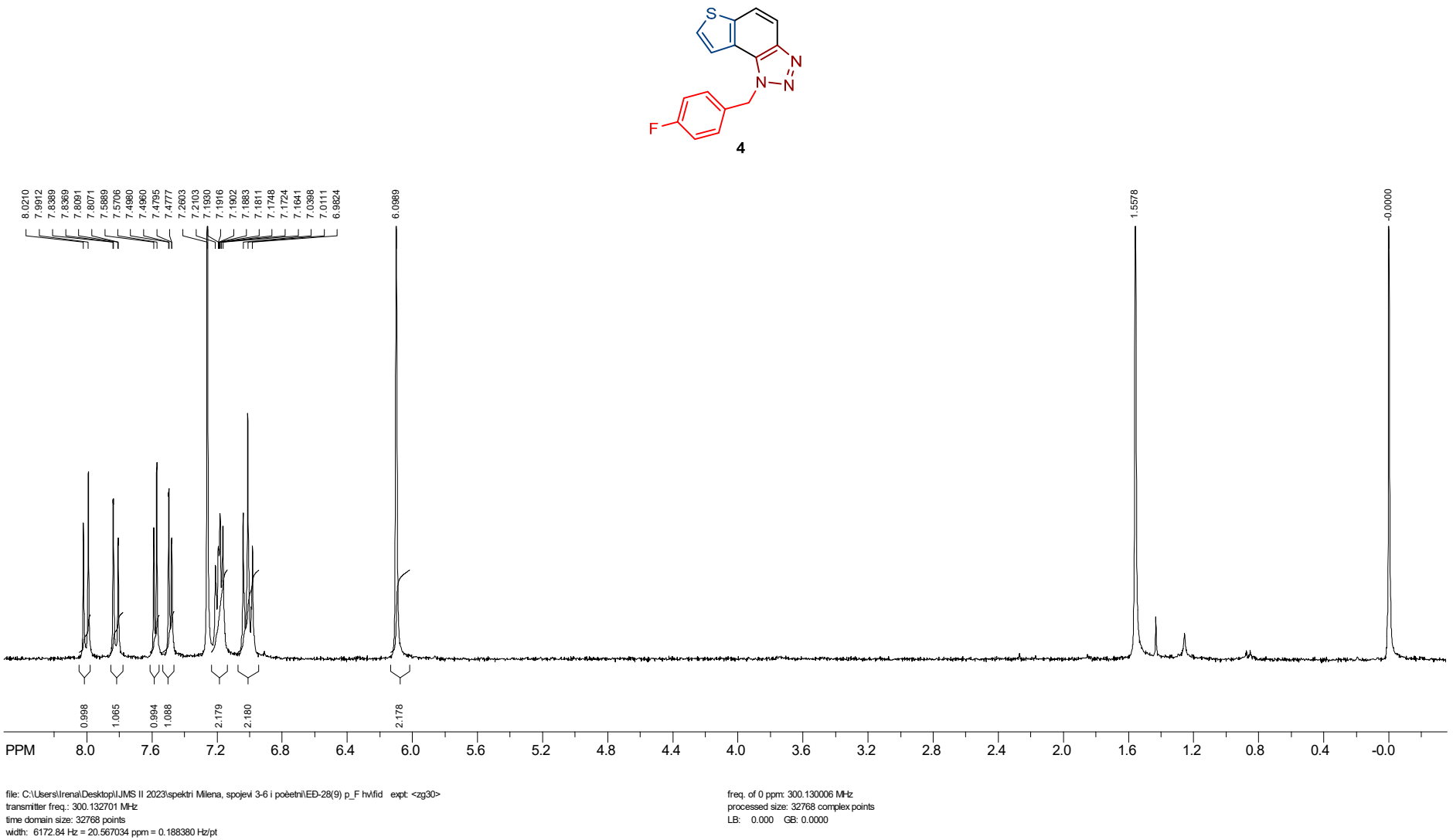

Figure S4. ^{1}H NMR spectrum ($CDCl_3$) of compound **4**.

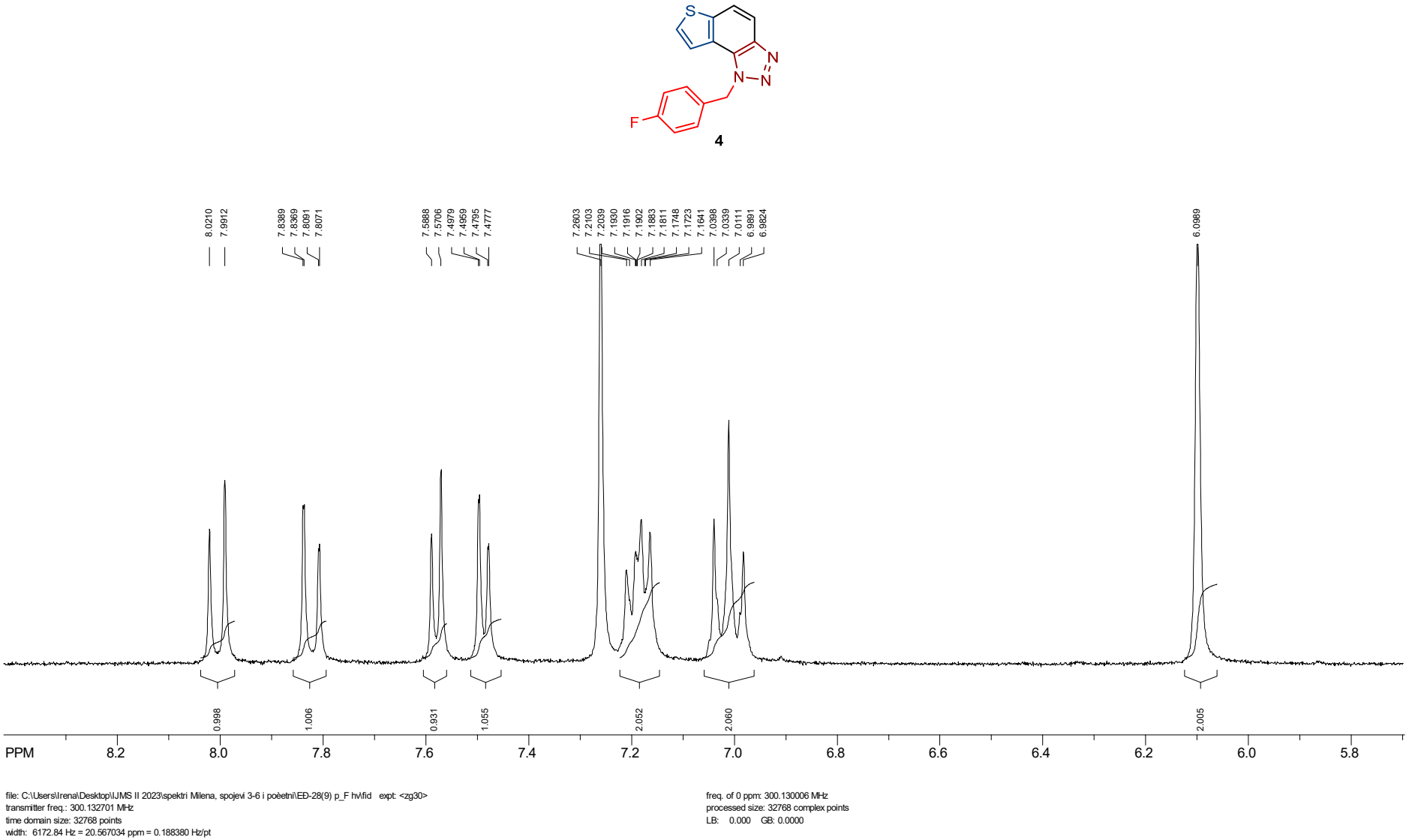

Figure S5. Part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **4**.

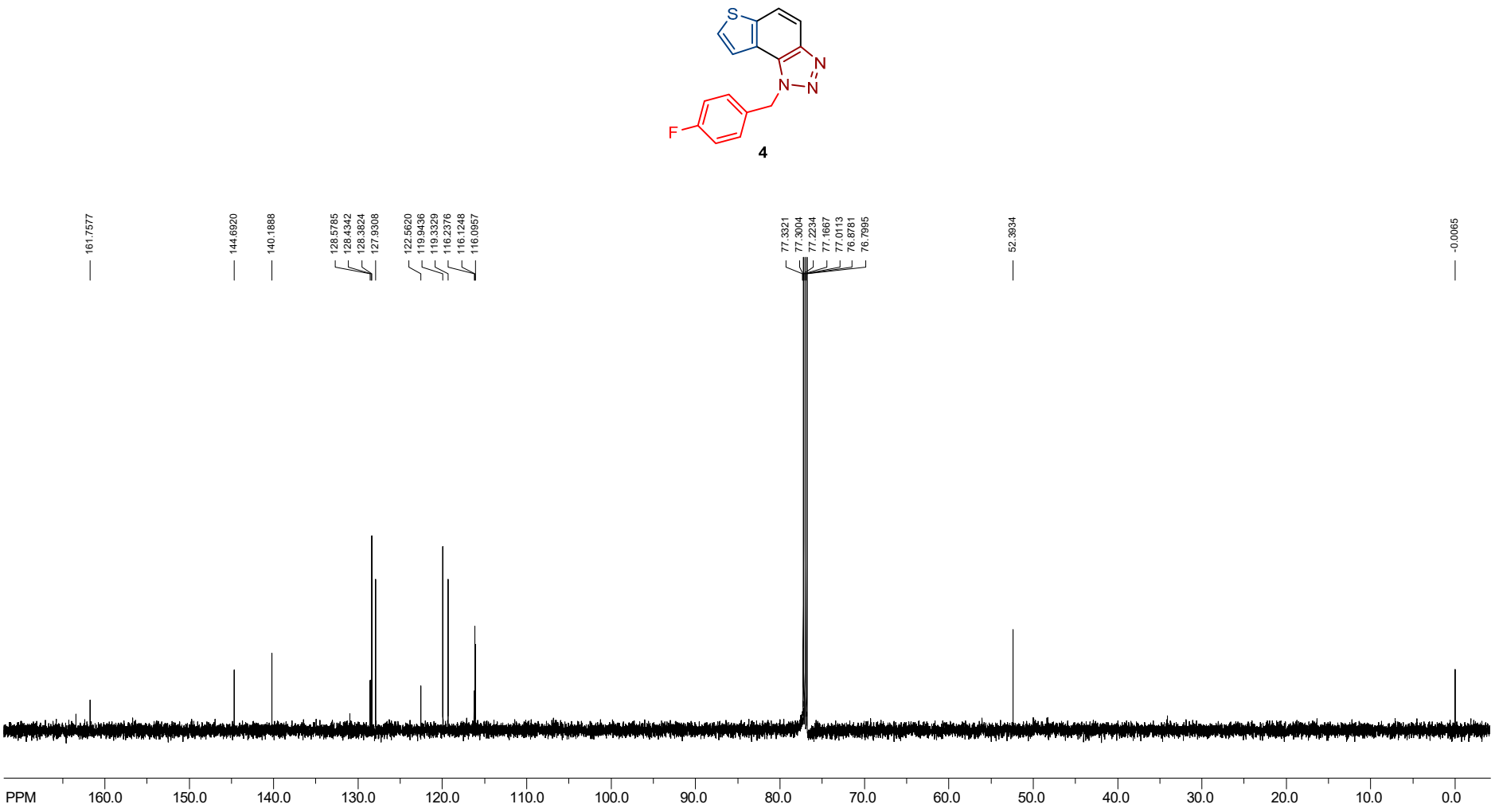

Figure S6. ^{13}C NMR spectrum ($CDCl_3$) of compound **4**.

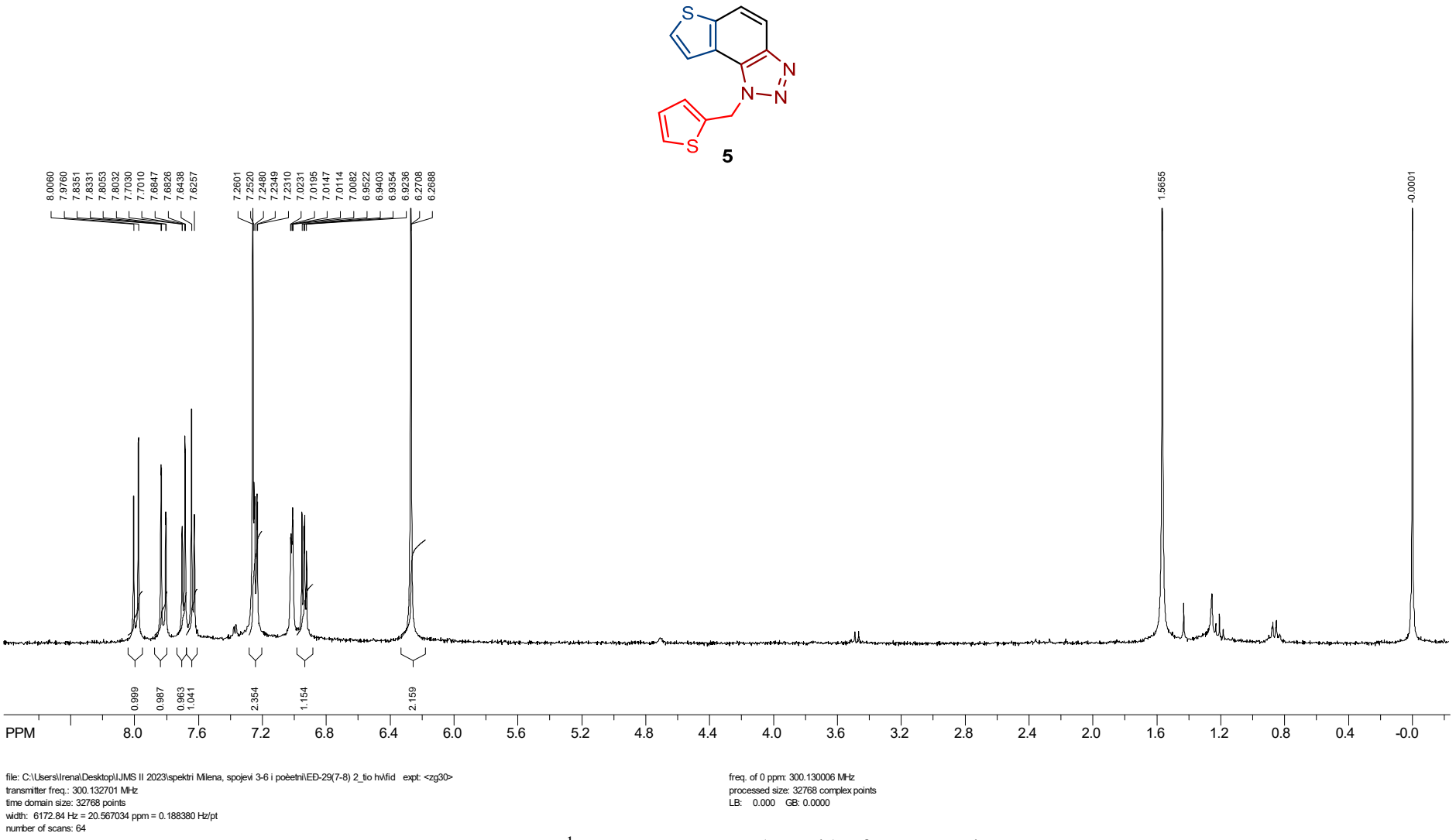

Figure S7. ^{1}H NMR spectrum ($CDCl_3$) of compound **5**.

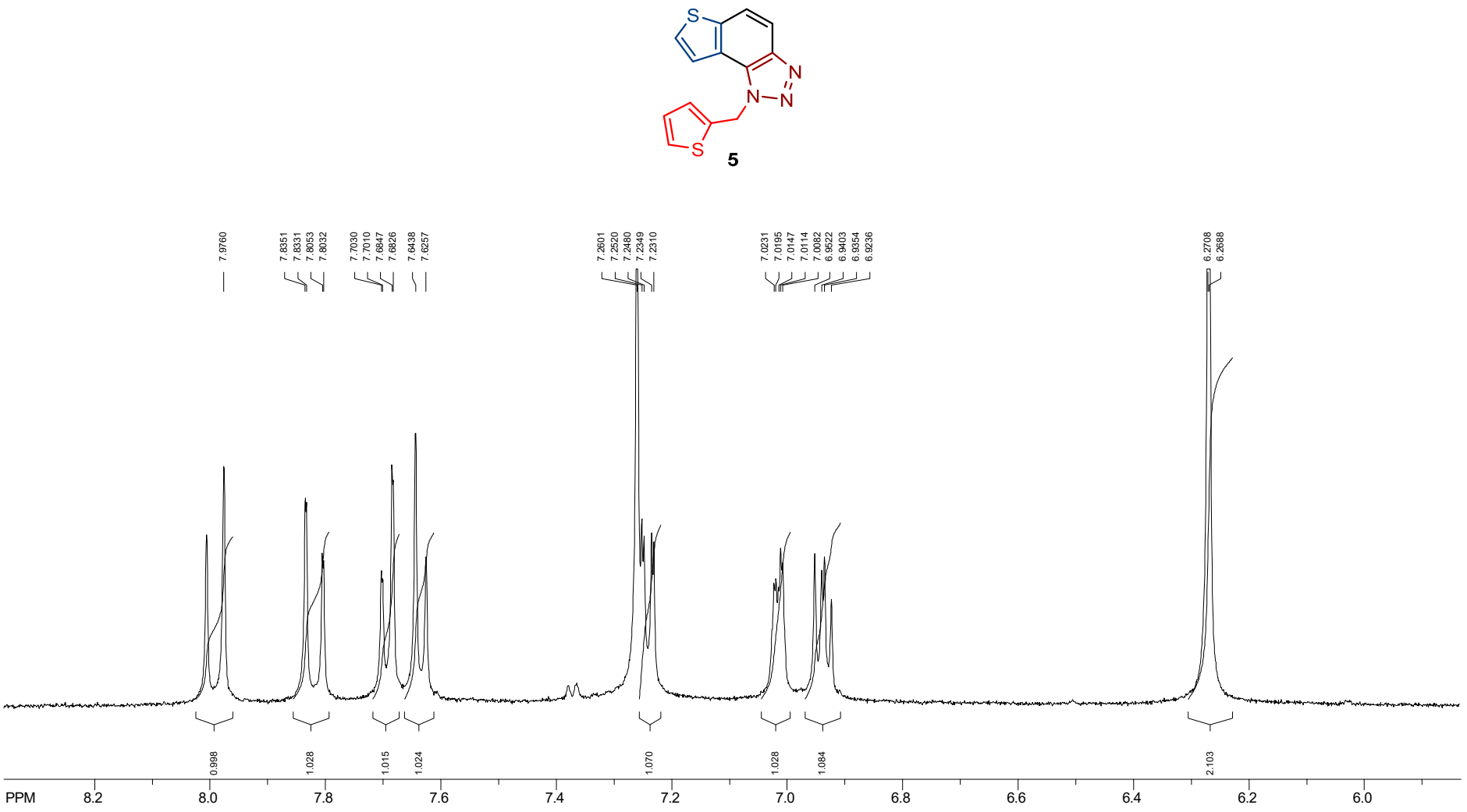

Figure S8. Part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **5**.

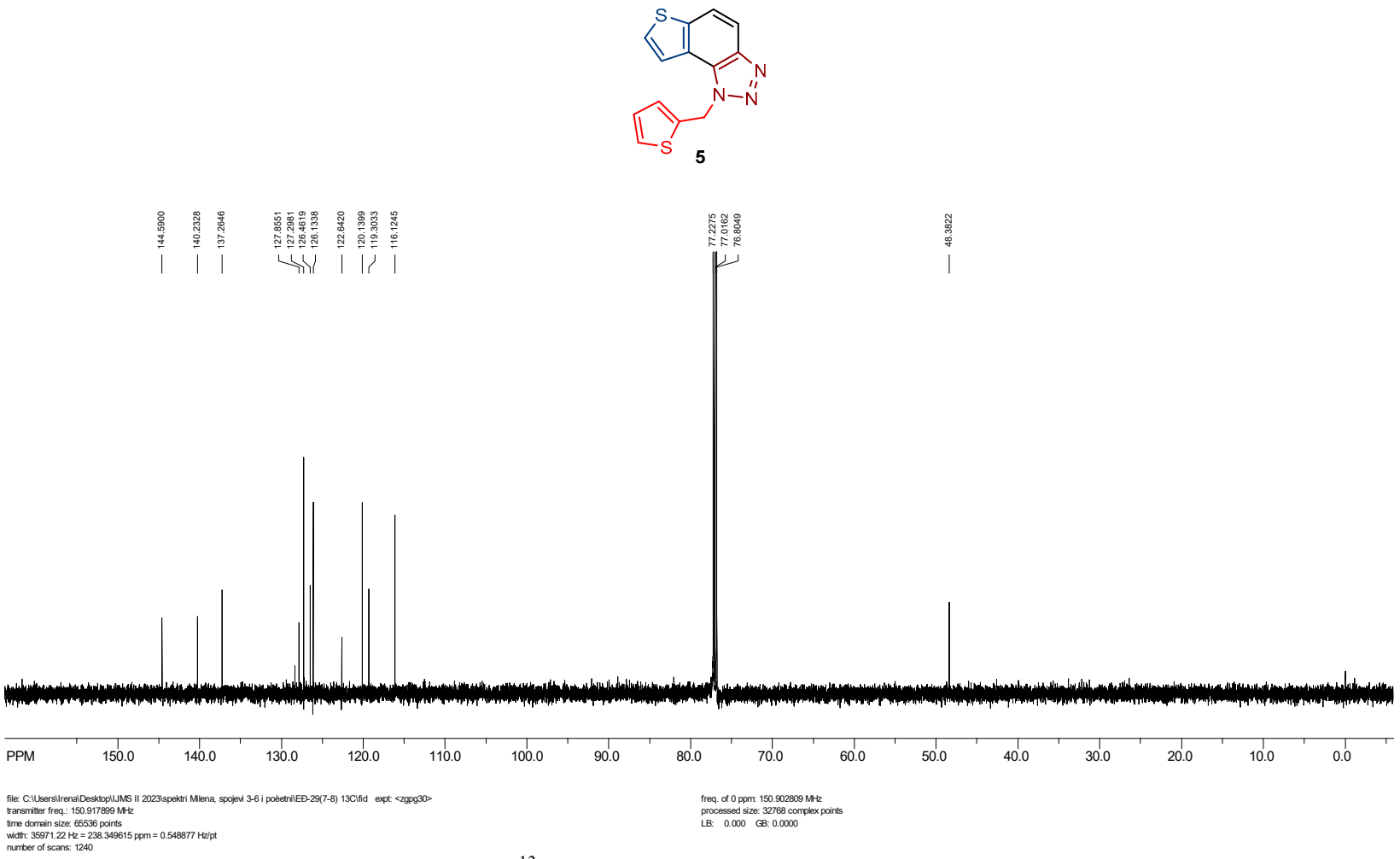

Figure S9. ^{13}C NMR spectrum ($CDCl_3$) of compound **5**.

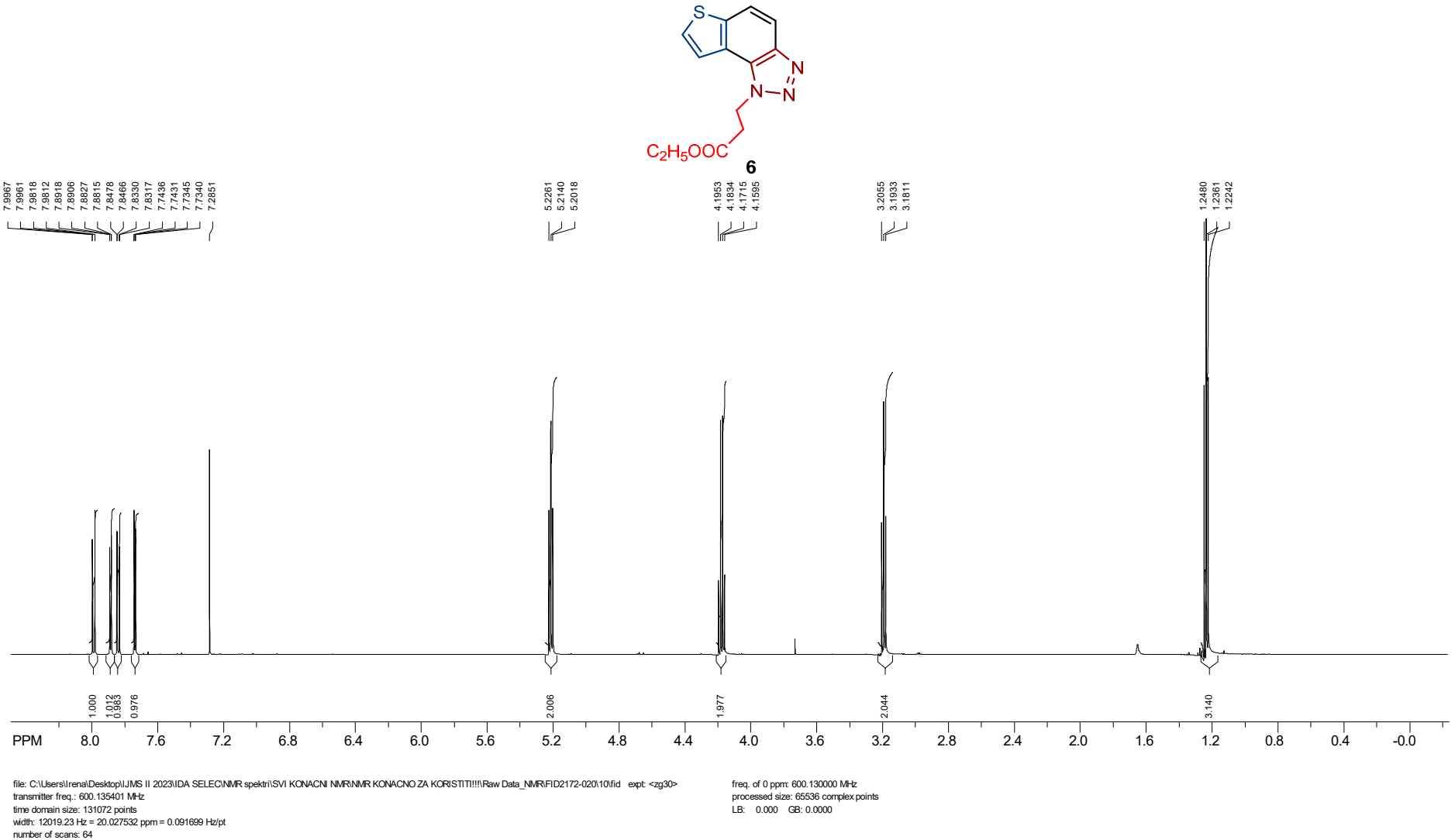

Figure S10. ^{1}H NMR spectrum ($CDCl_3$) of compound **6**.

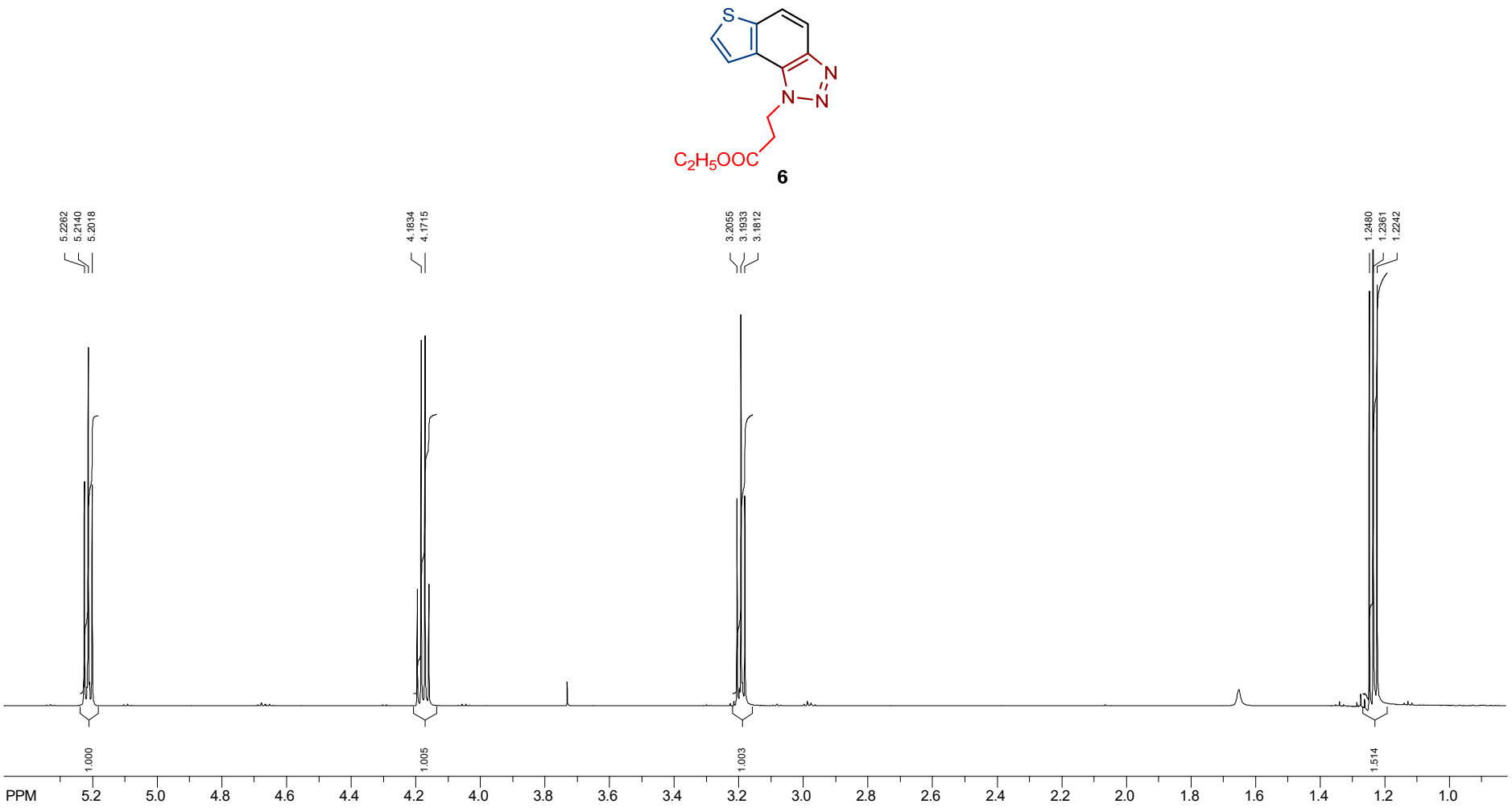

Figure S11. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **6**.

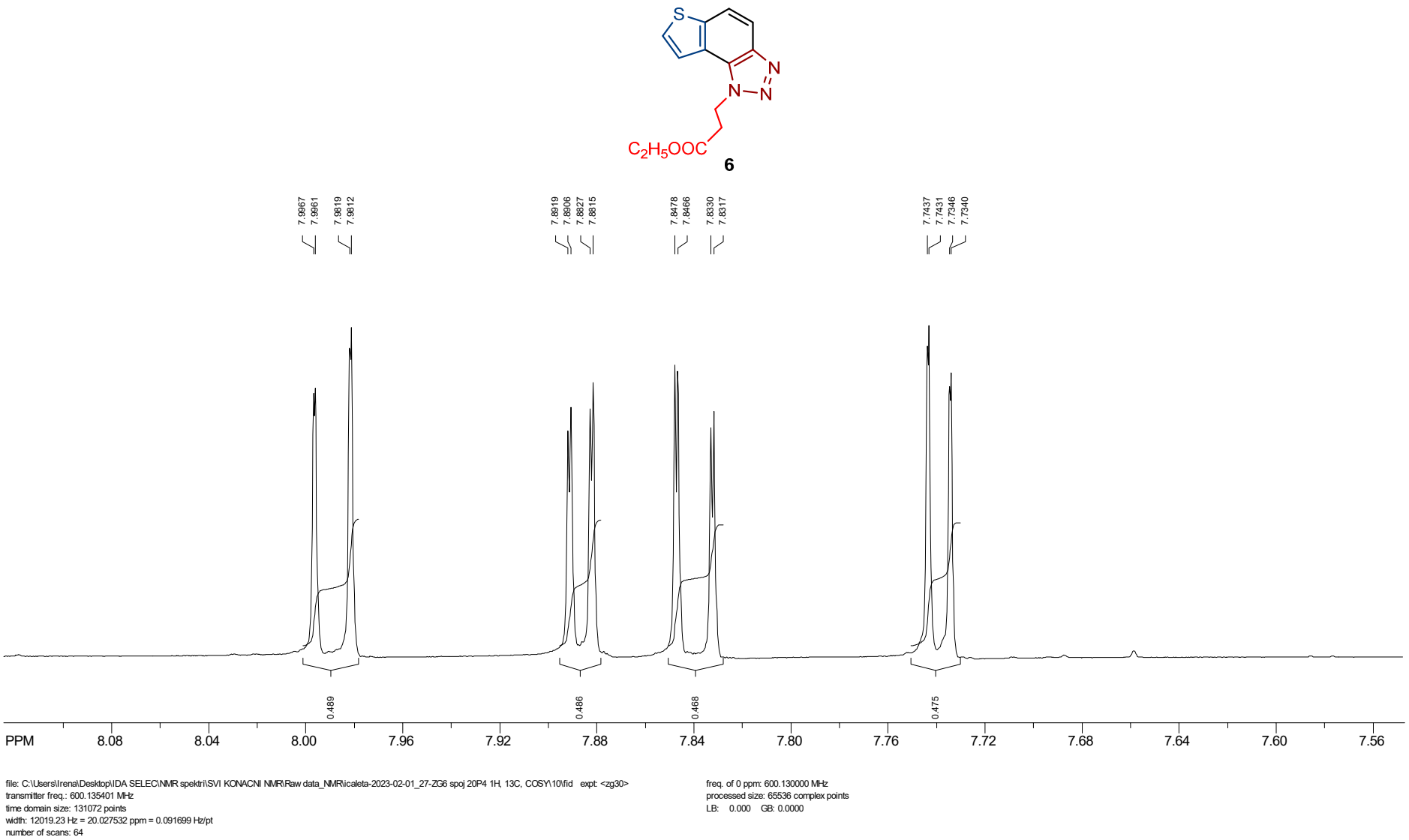

Figure S12. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **6**.

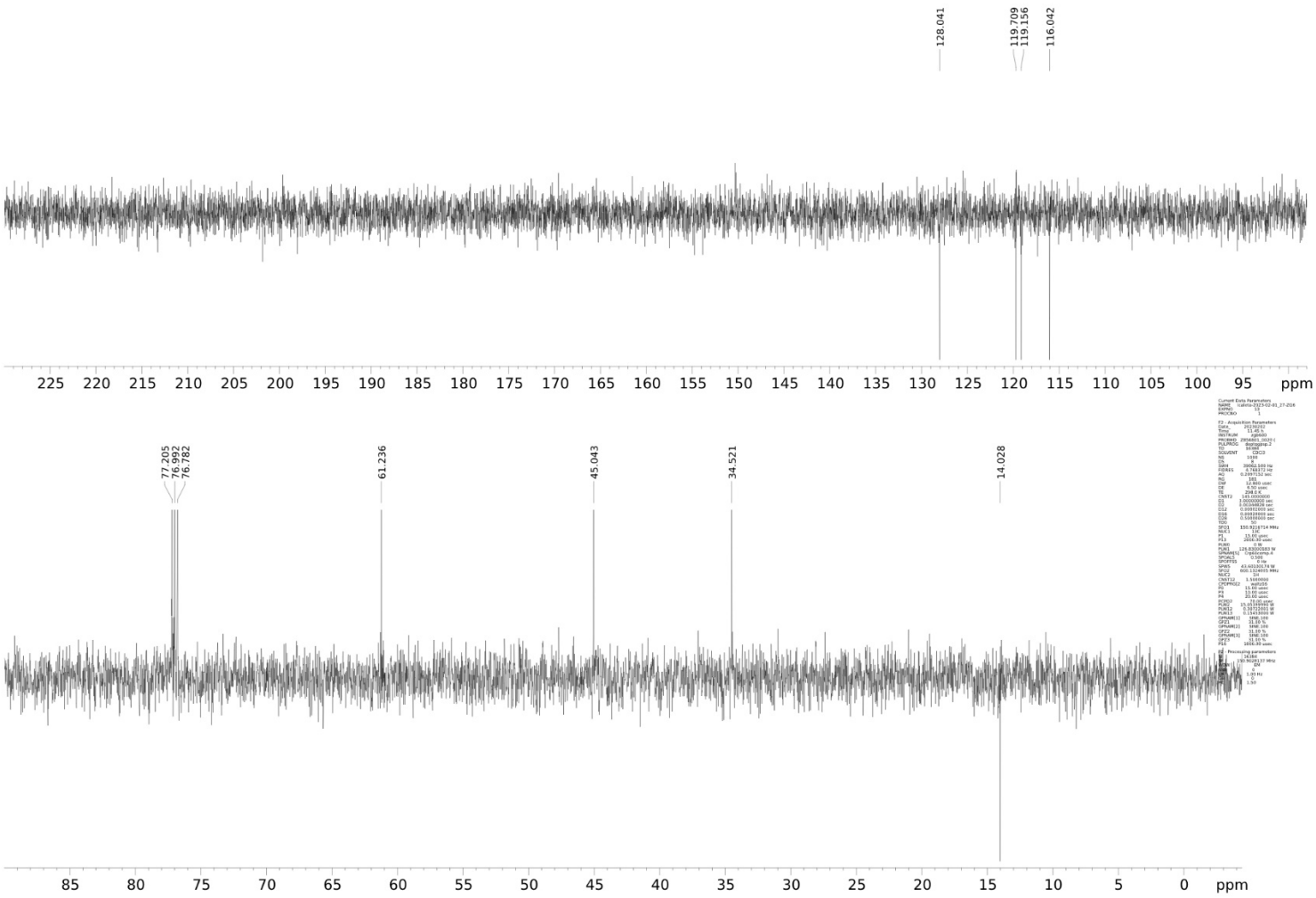

Figure S13. ^{13}C NMR spectrum ($CDCl_3$) of compound **6**.

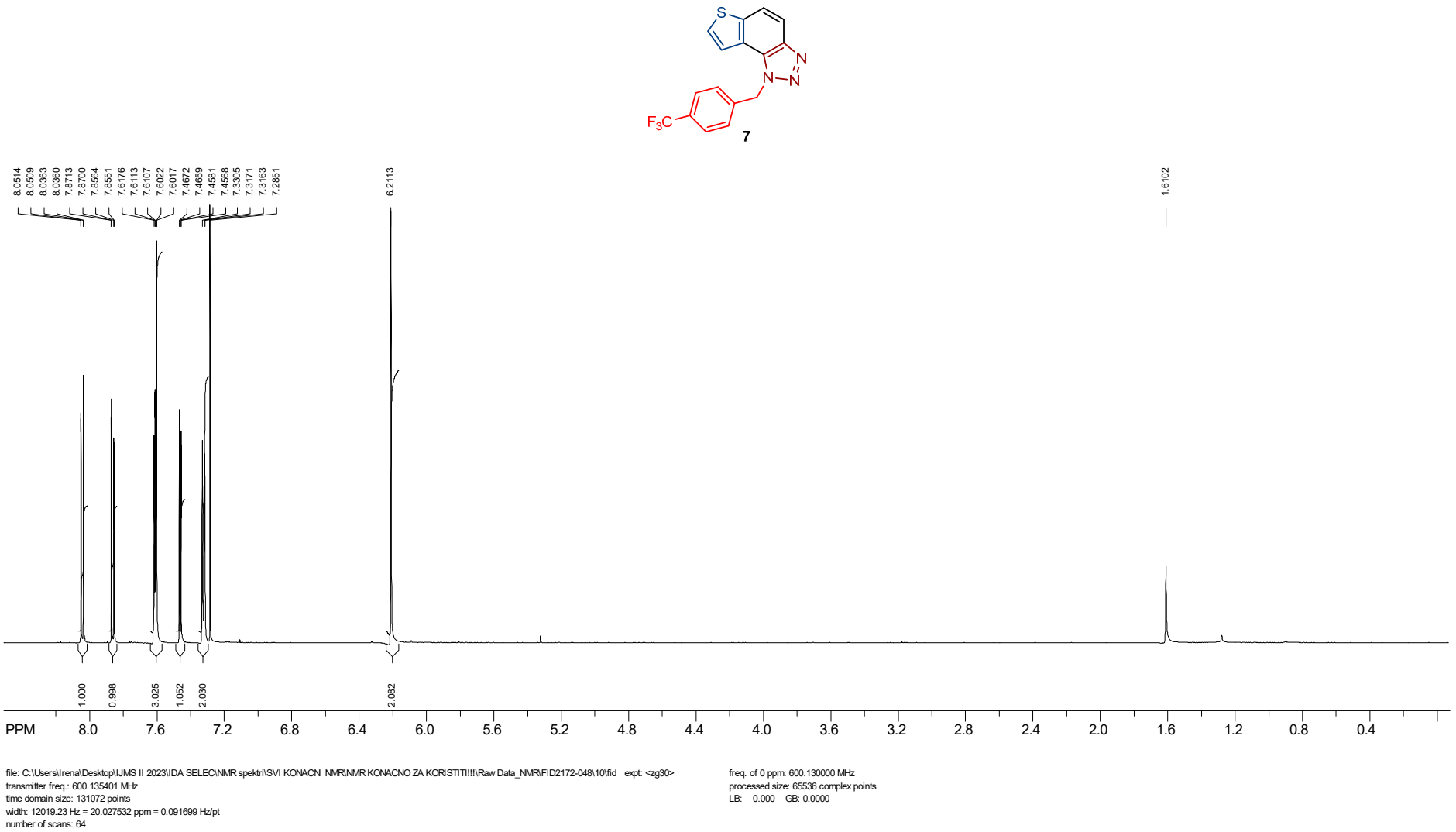

Figure S14. ^{1}H NMR spectrum ($CDCl_3$) of compound **7**.

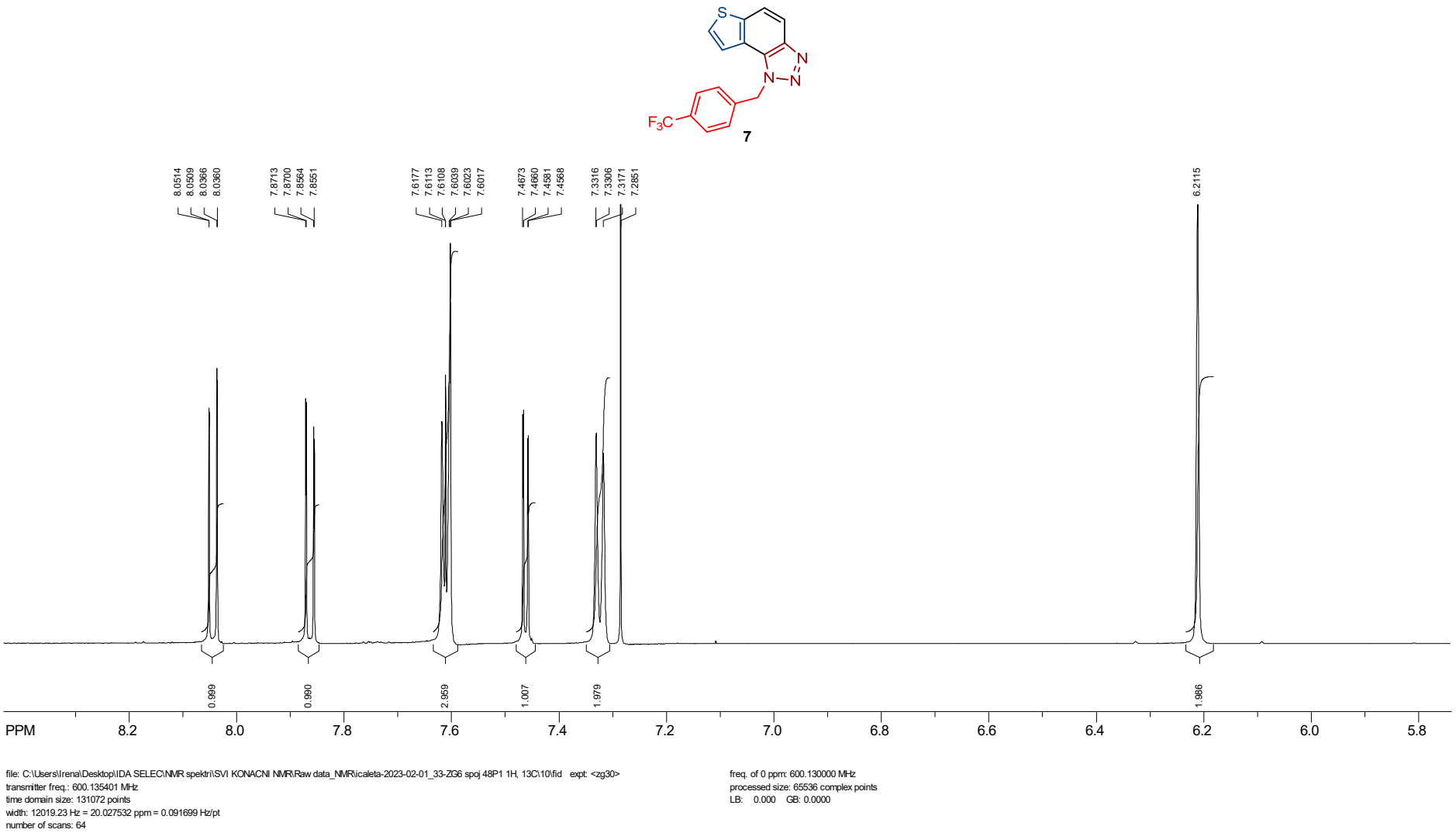

Figure S15. Part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **7**.

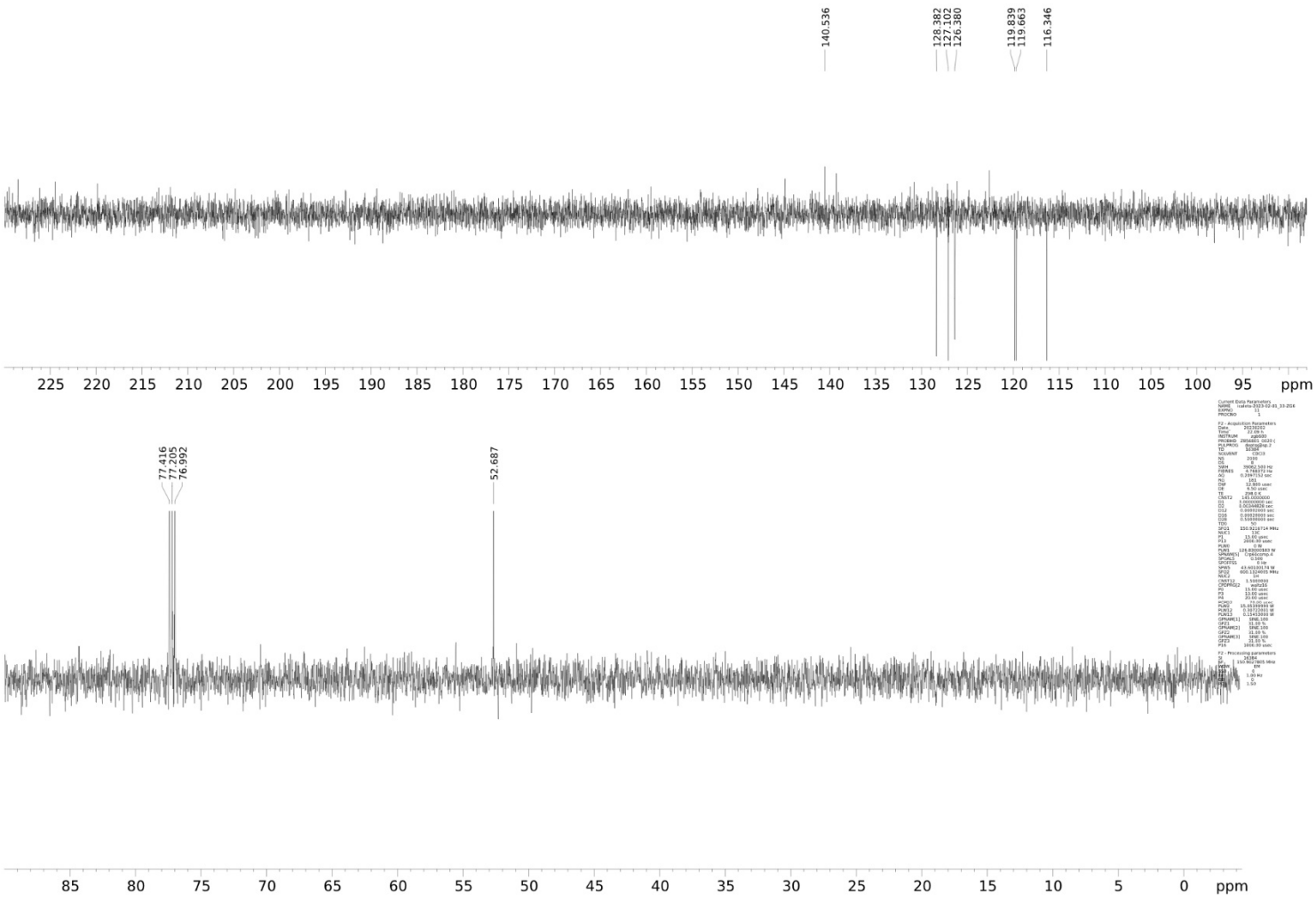

Figure S16. ^{13}C NMR spectrum ($CDCl_3$) of compound **7**.

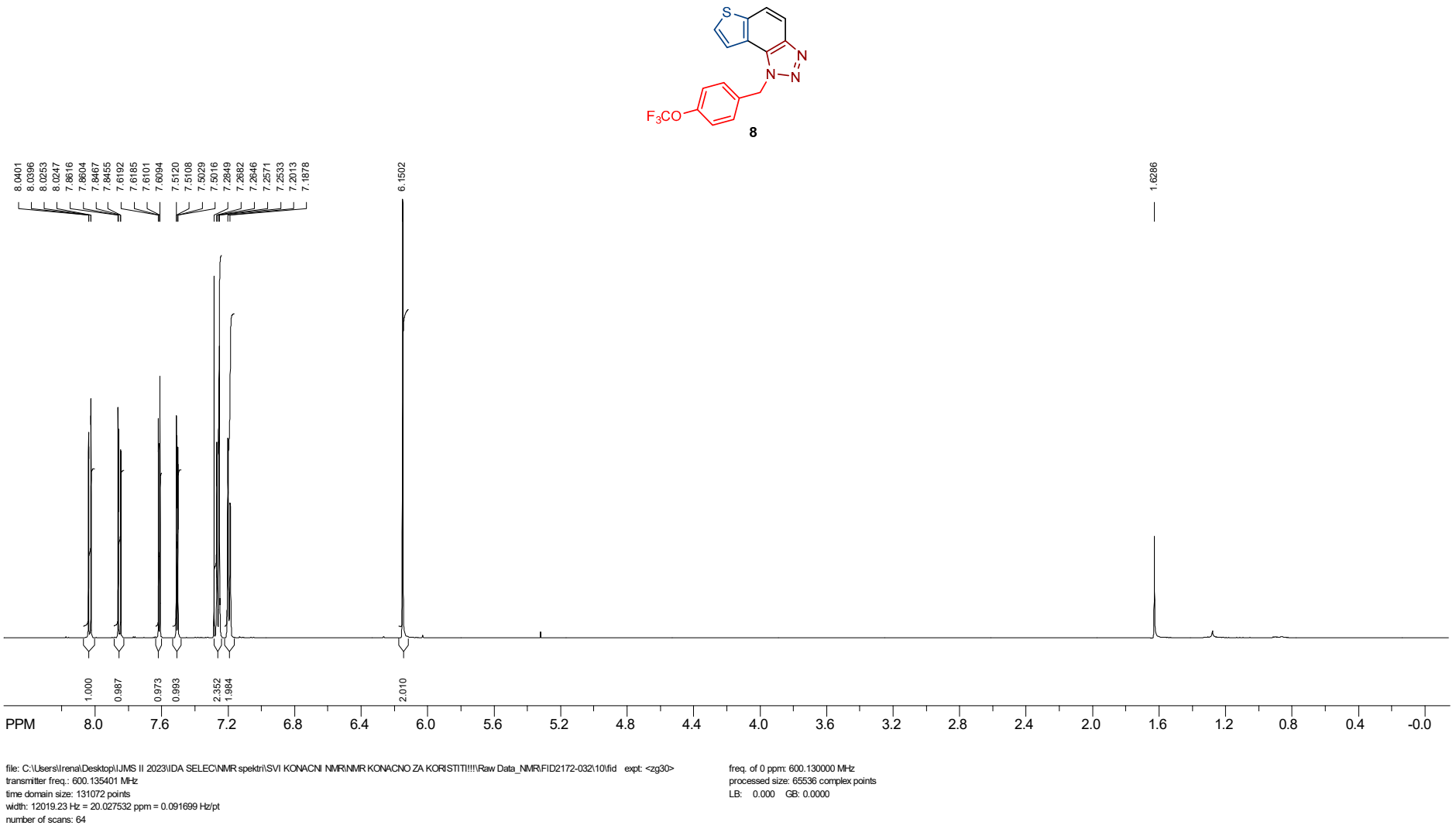

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Figure S17. ^{1}H NMR spectrum ($CDCl_3$) of compound **8**.

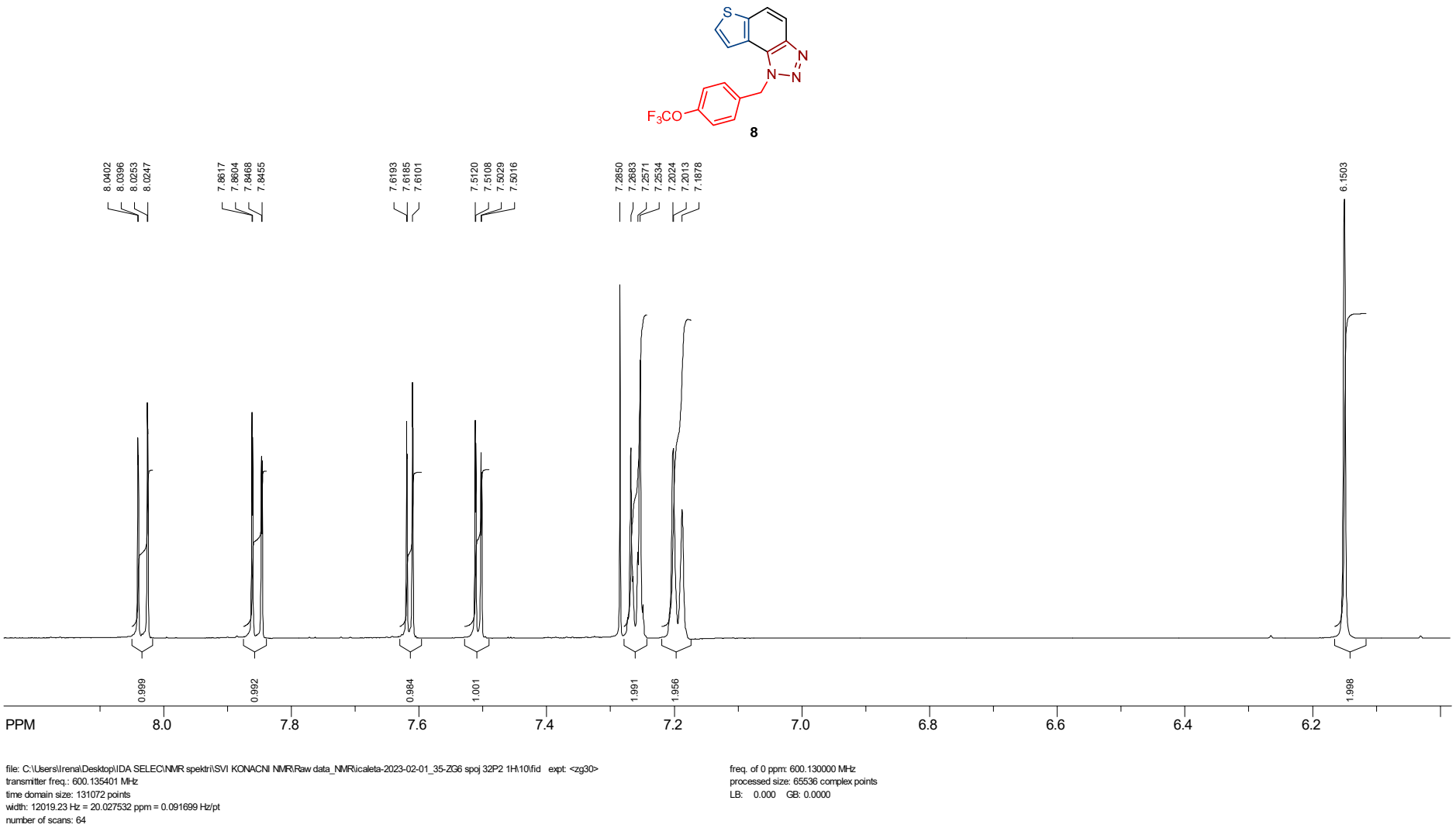
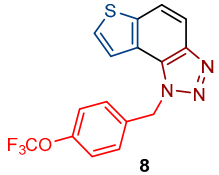


Figure S18. Part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **8**.



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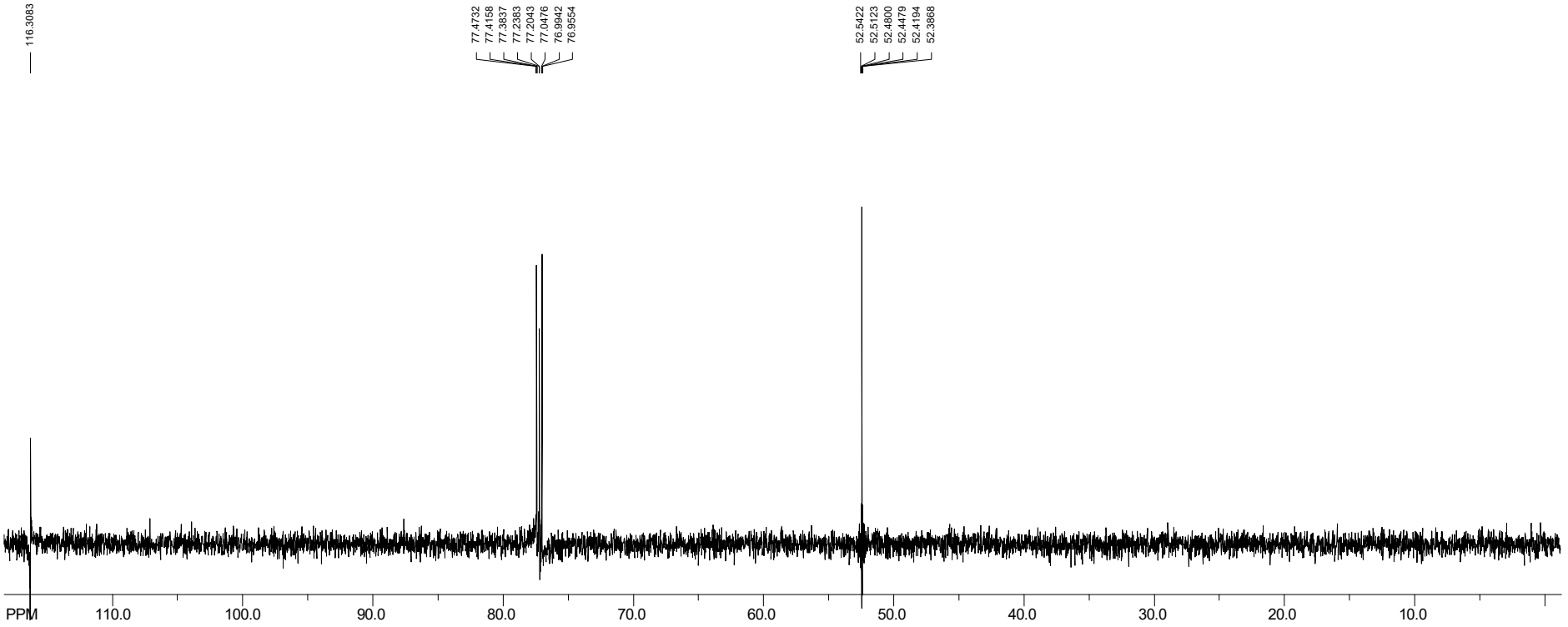

file: C:\Users\Irena\Desktop\IJMS II 2023\IDA SELEC\NMR spektri\SVI KONACNI NMR\NMR KONACNO ZA KORISTITI!!!\Raw Data_NMR\FID2172-032\11\fid expt: <deptqgpsp.2>
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width: 39062.50 Hz = 258.826315 ppm = 2.384186 Hz/pt
number of scans: 1000

freq. of 0 ppm: 150.902782 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

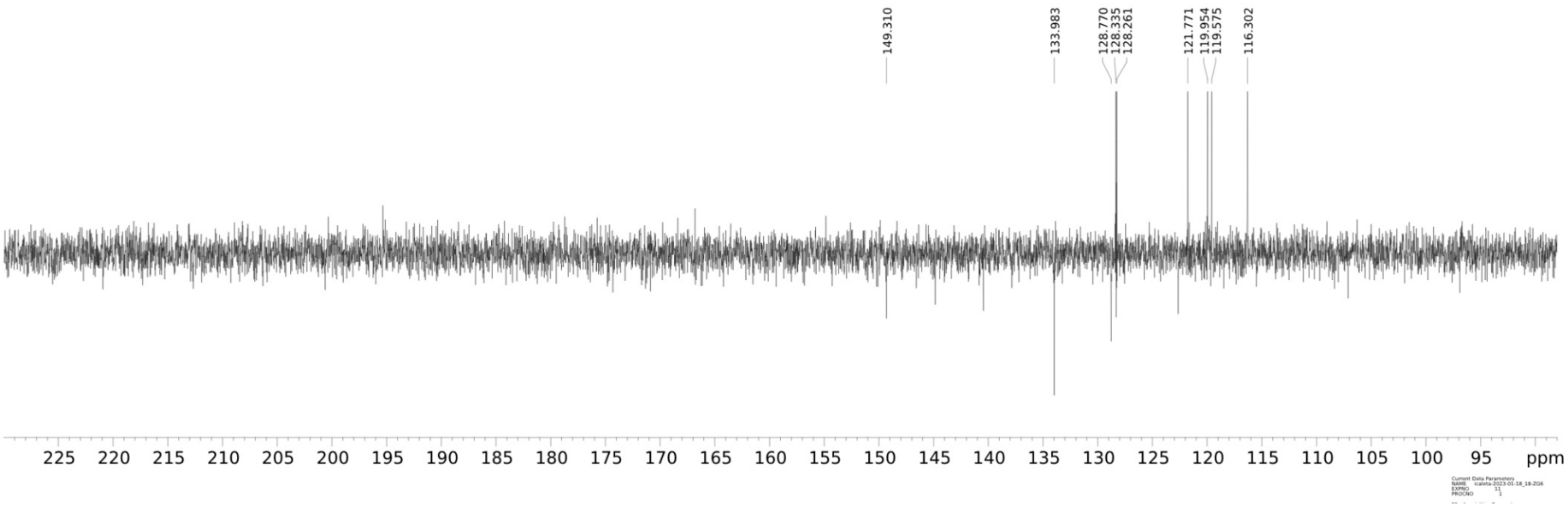


Figure S19. ^{13}C NMR spectrum ($CDCl_3$) of compound **8**.

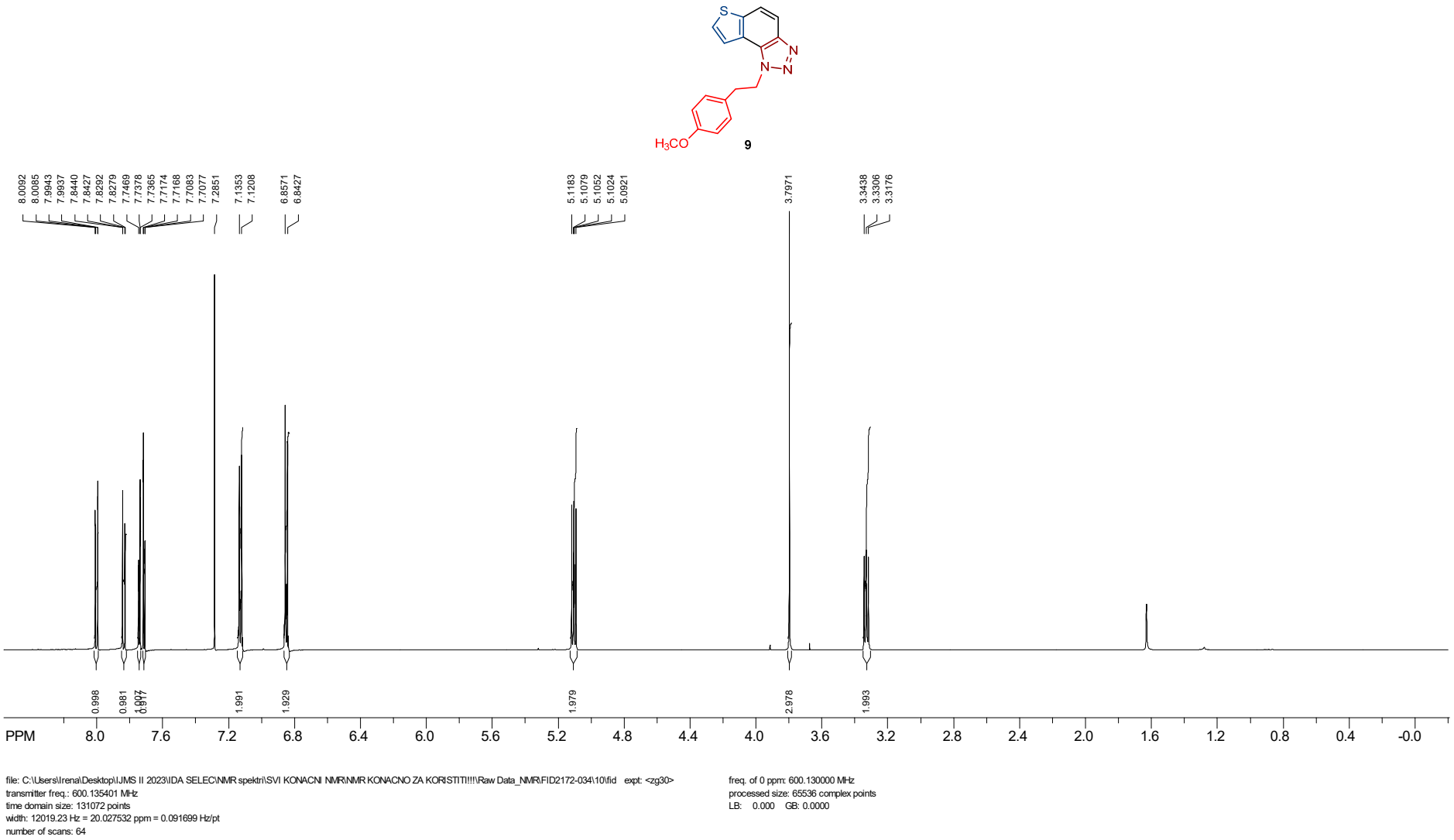


Figure S20. ^{1}H NMR spectrum ($CDCl_3$) of compound **9**.

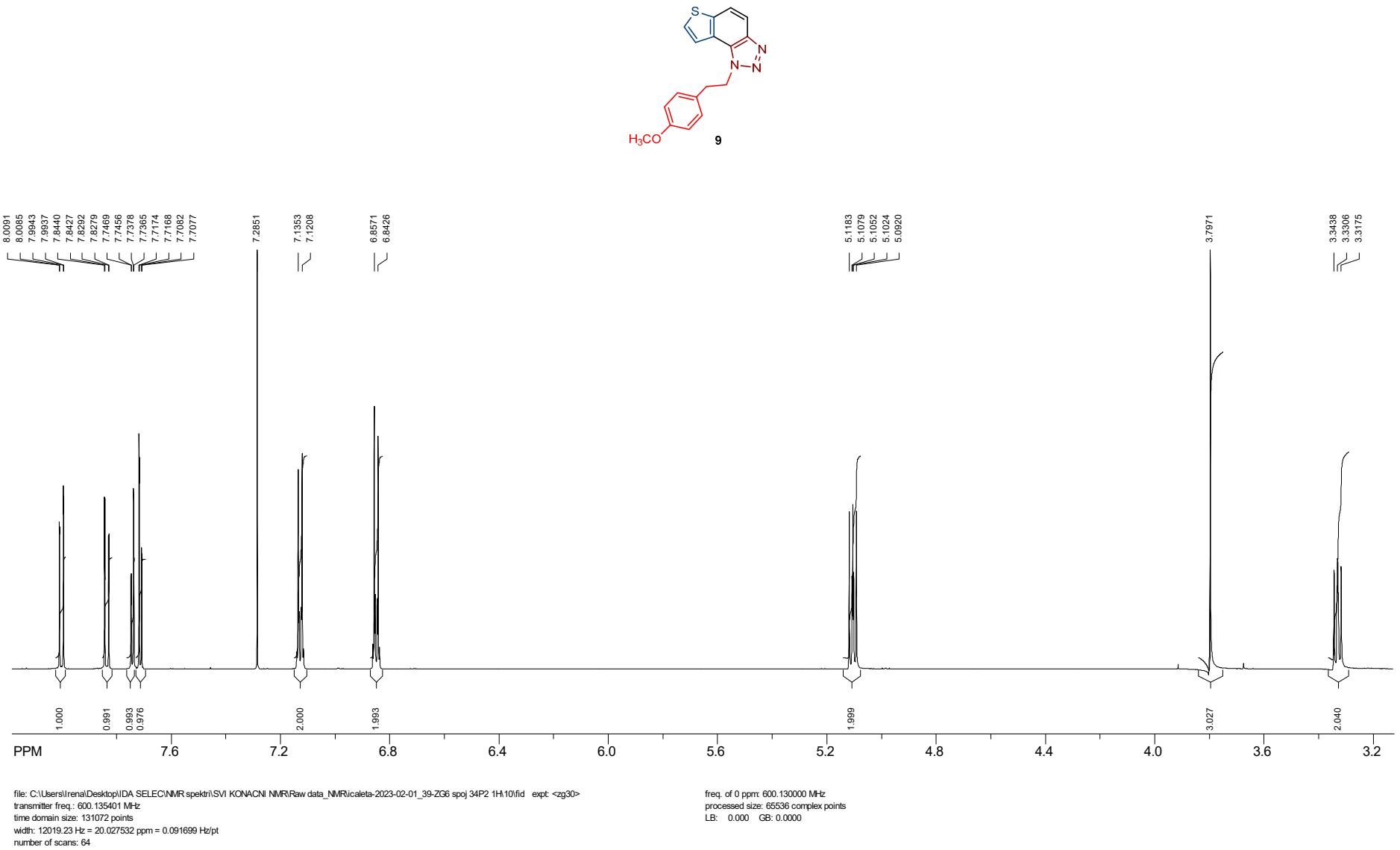


Figure S21. Part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **9**.

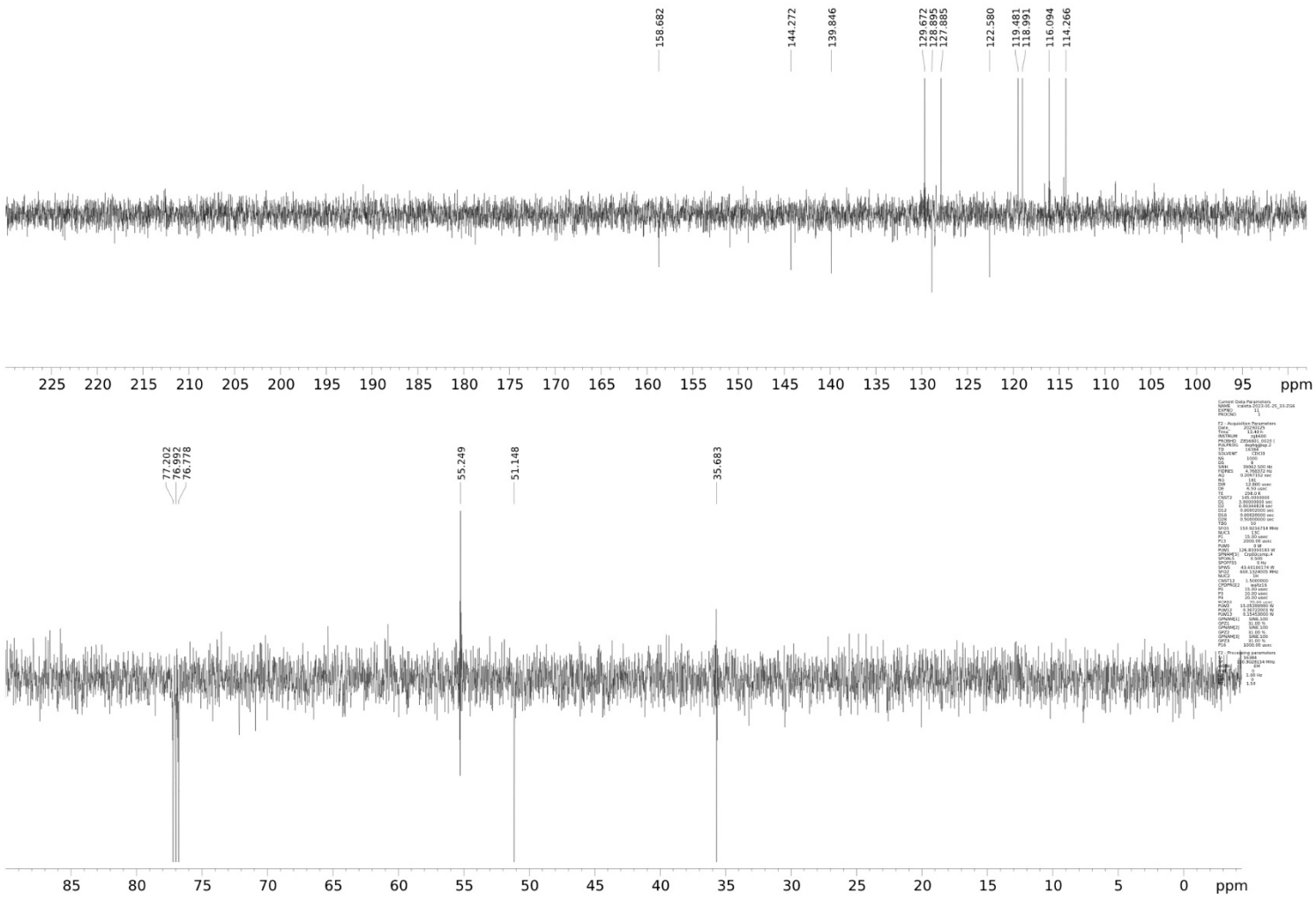


Figure S22. ^{13}C NMR spectrum ($CDCl_3$) of compound **9**.

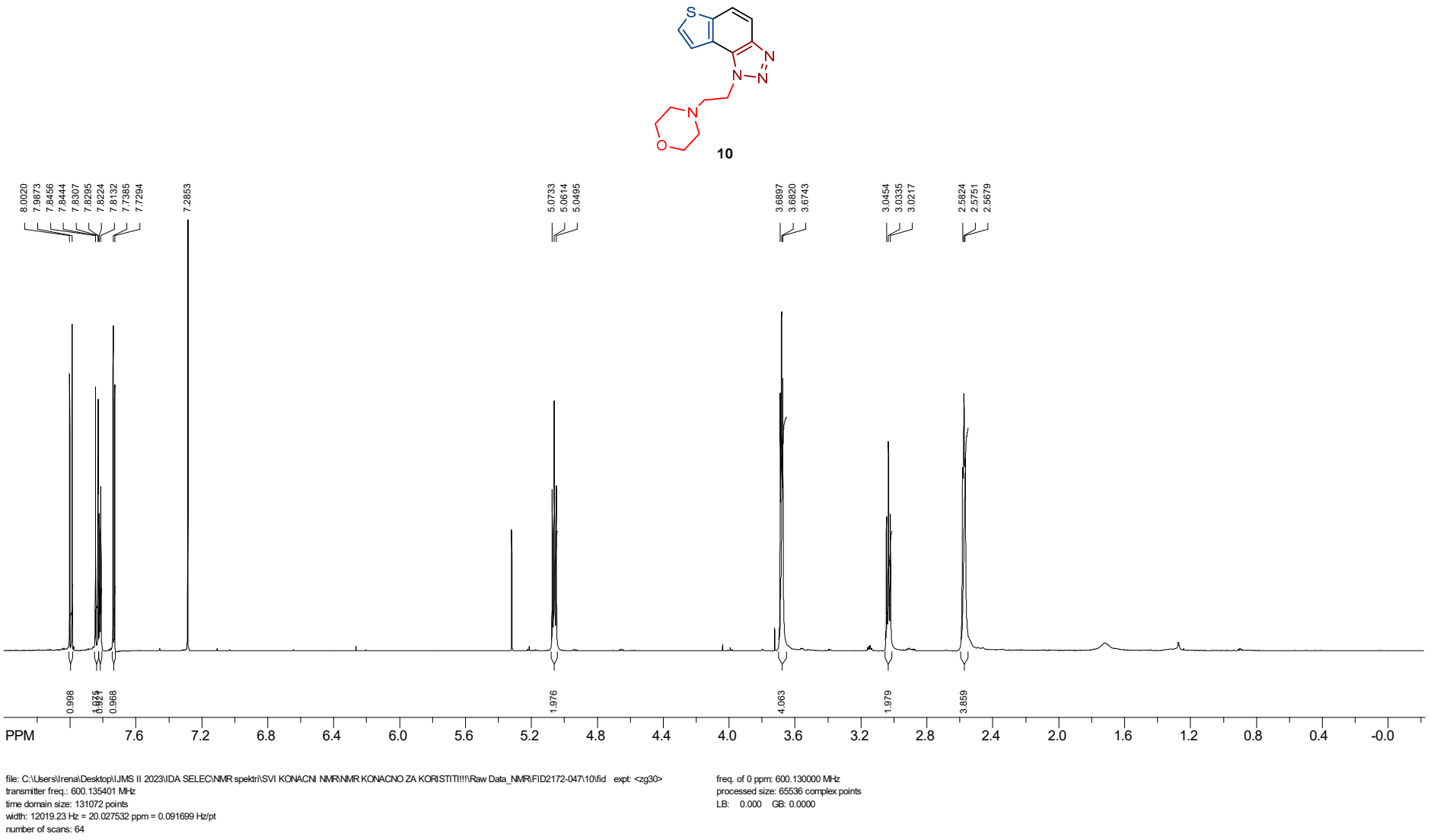


Figure S23. ^{1}H NMR spectrum ($CDCl_3$) of compound **10**.

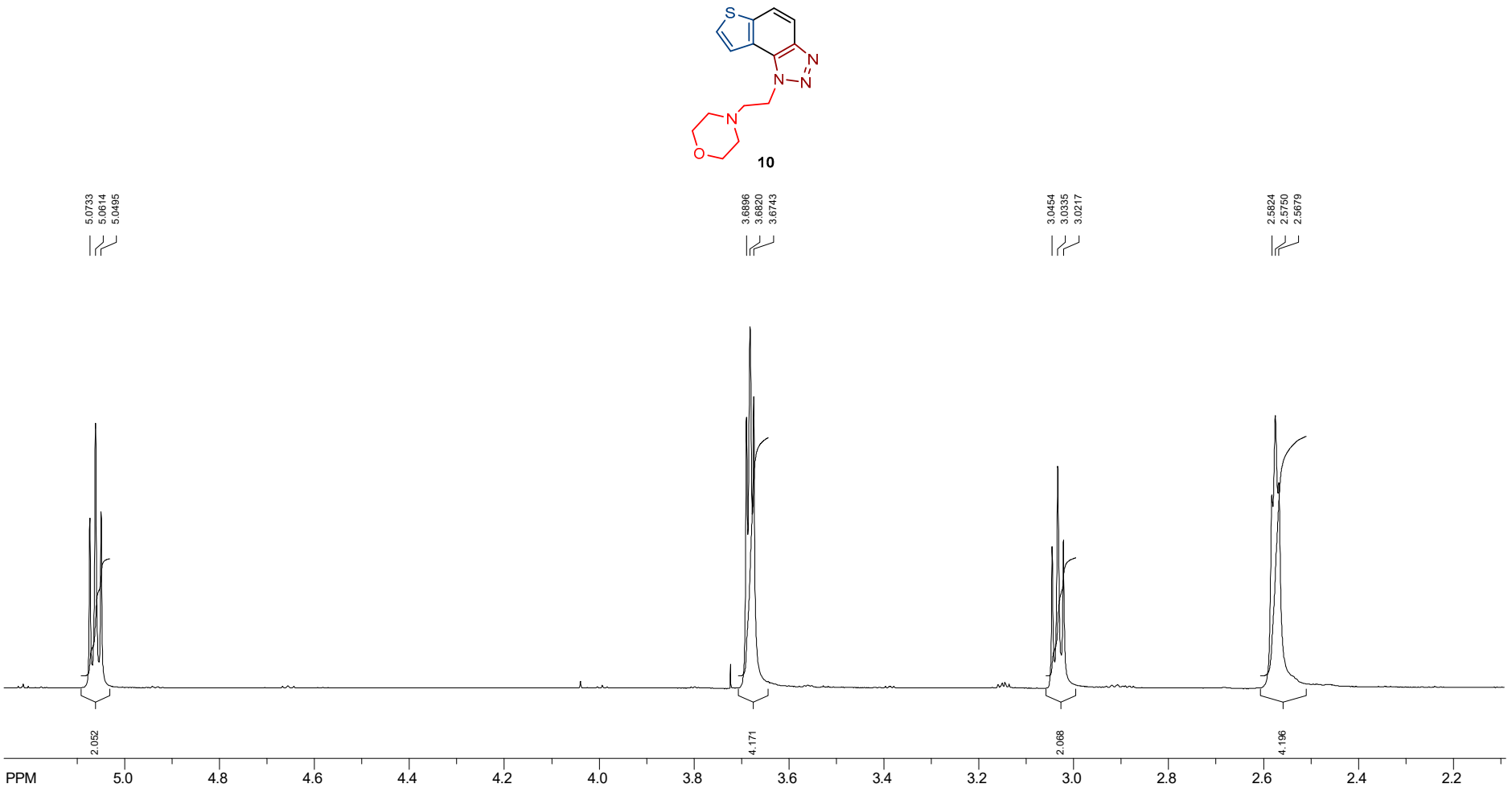


Figure S24. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **10**.

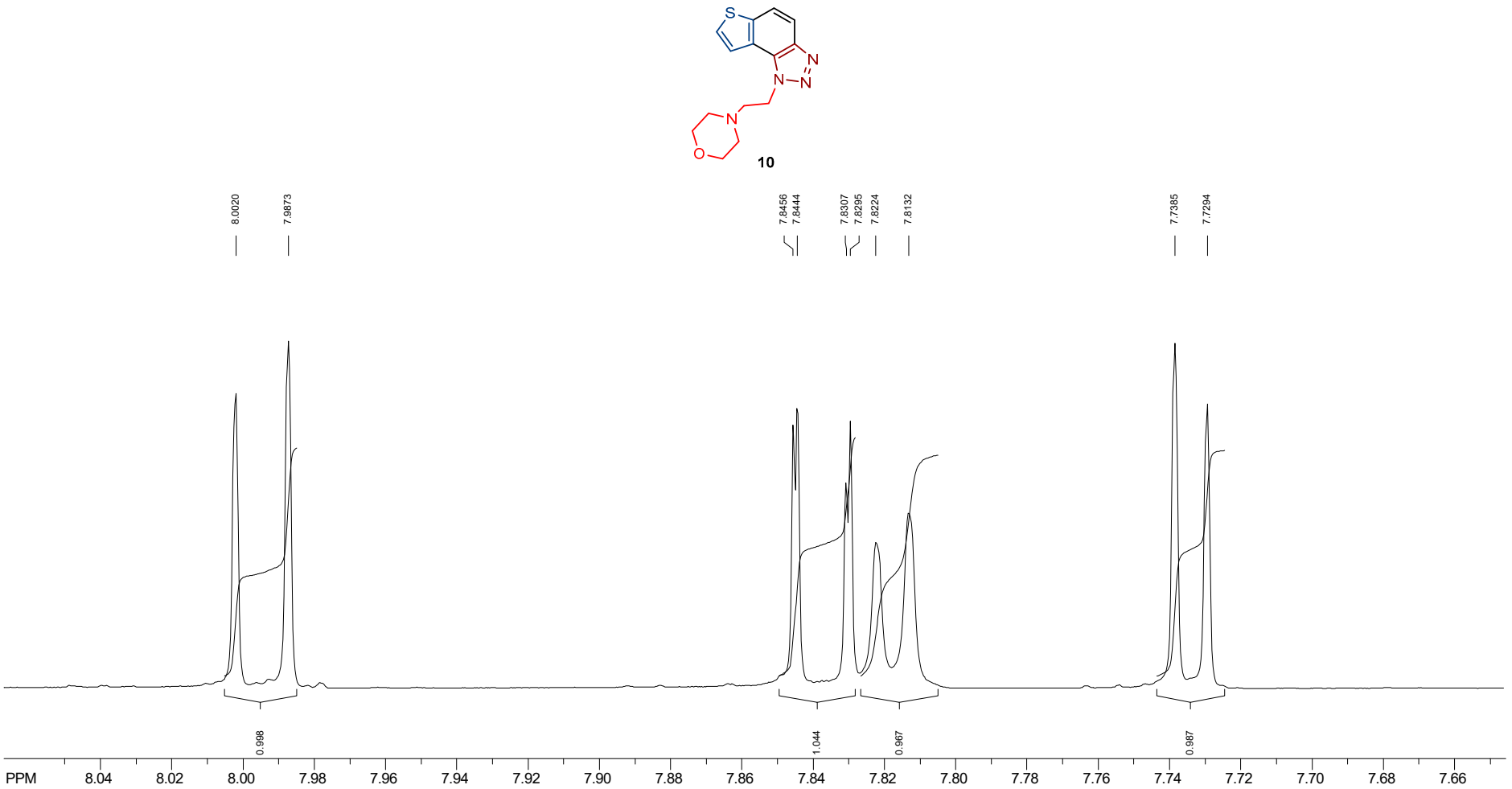


Figure S25. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **10**.

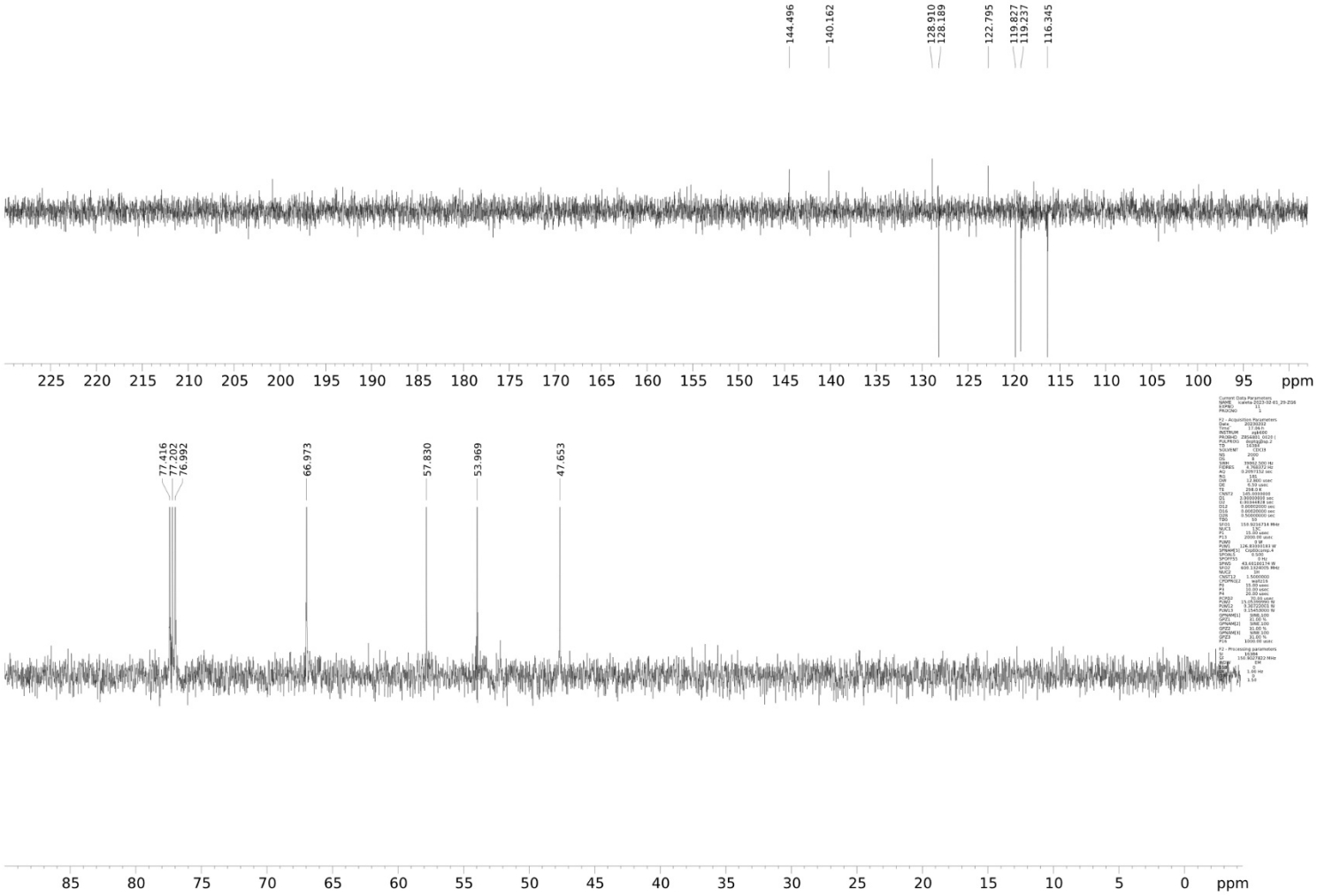


Figure S26. ^{13}C NMR spectrum ($CDCl_3$) of compound **10**.

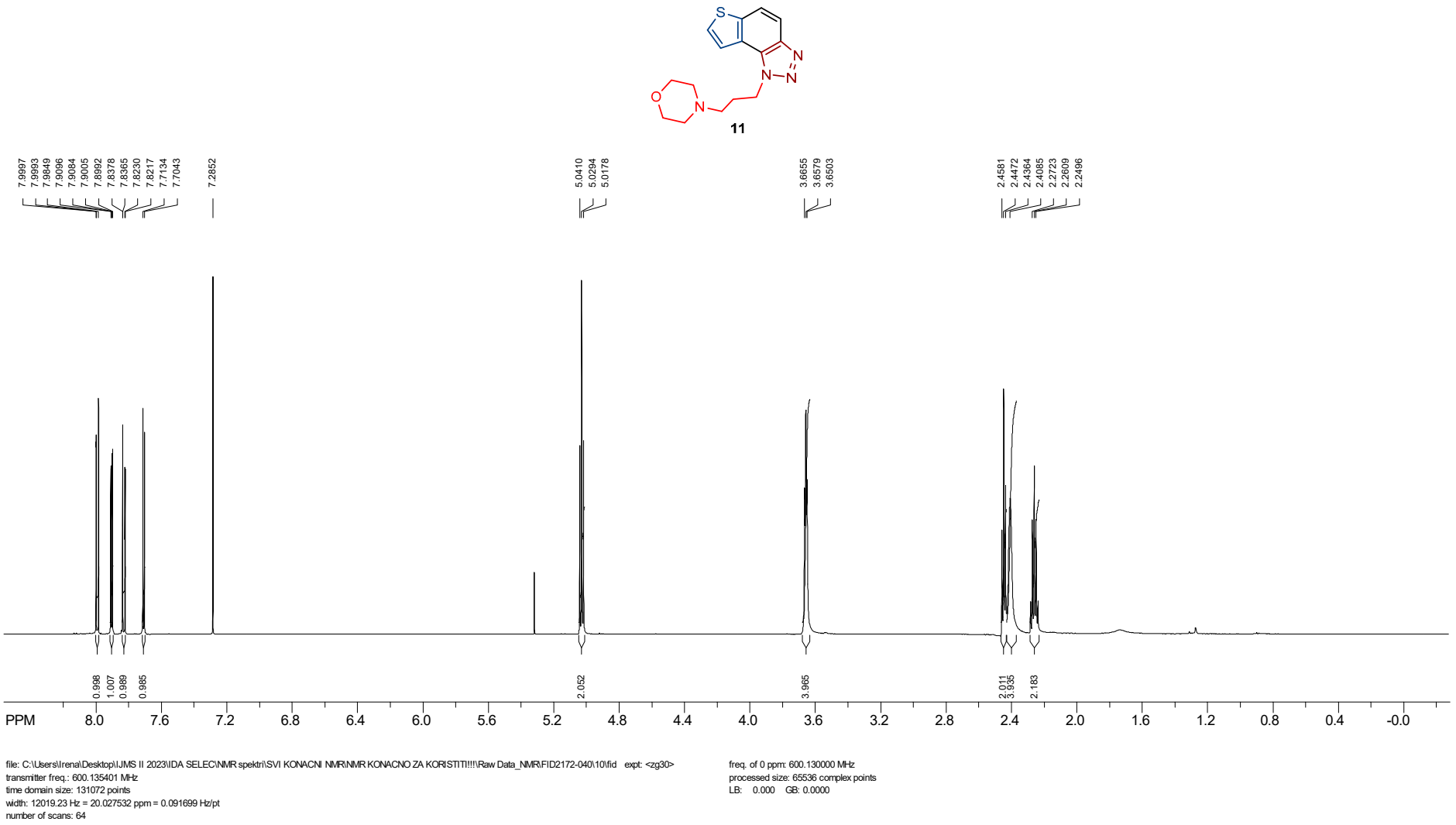


Figure S27. ^{1}H NMR spectrum ($CDCl_3$) of compound **11**.

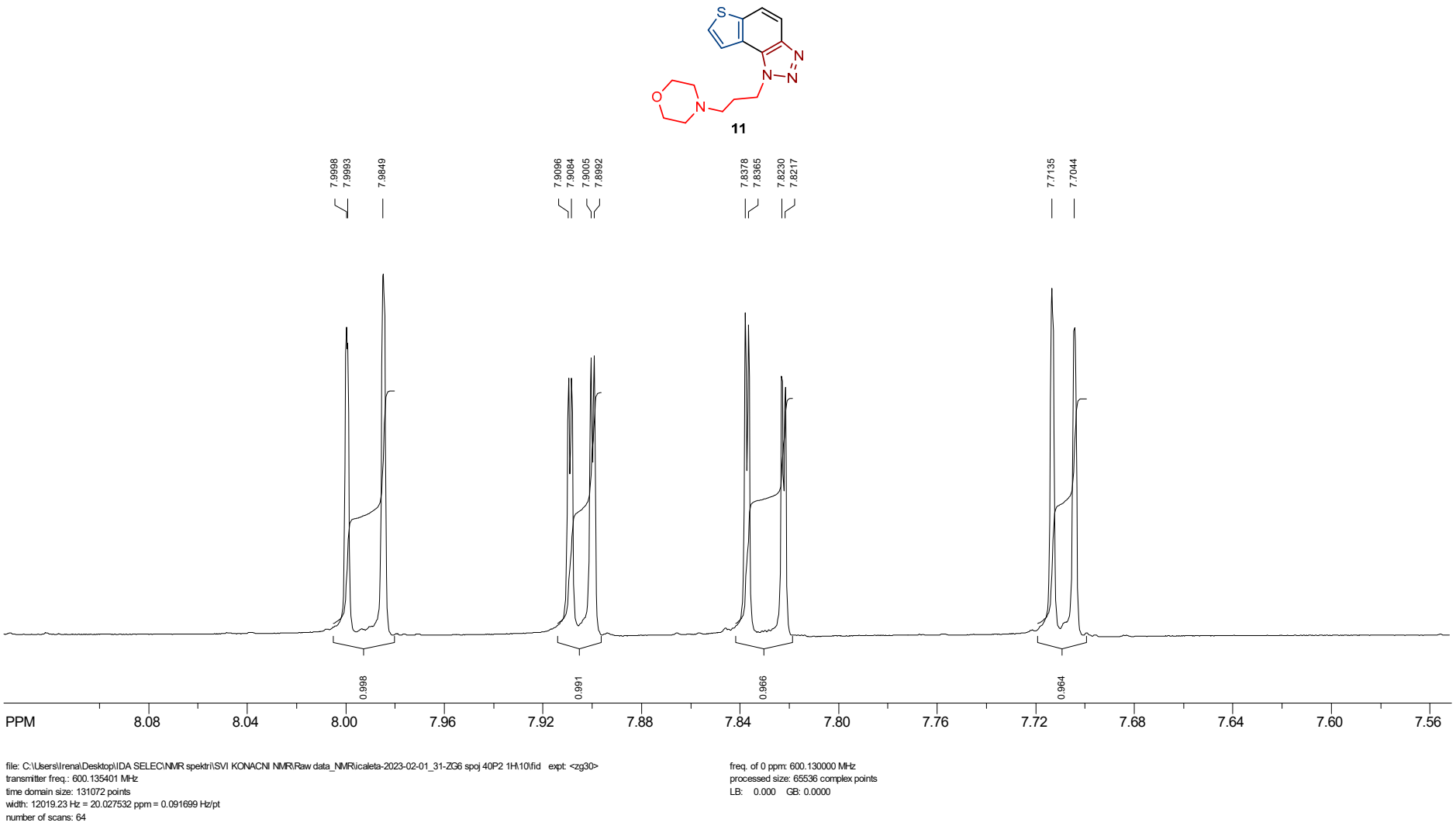


Figure S28. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **11**.

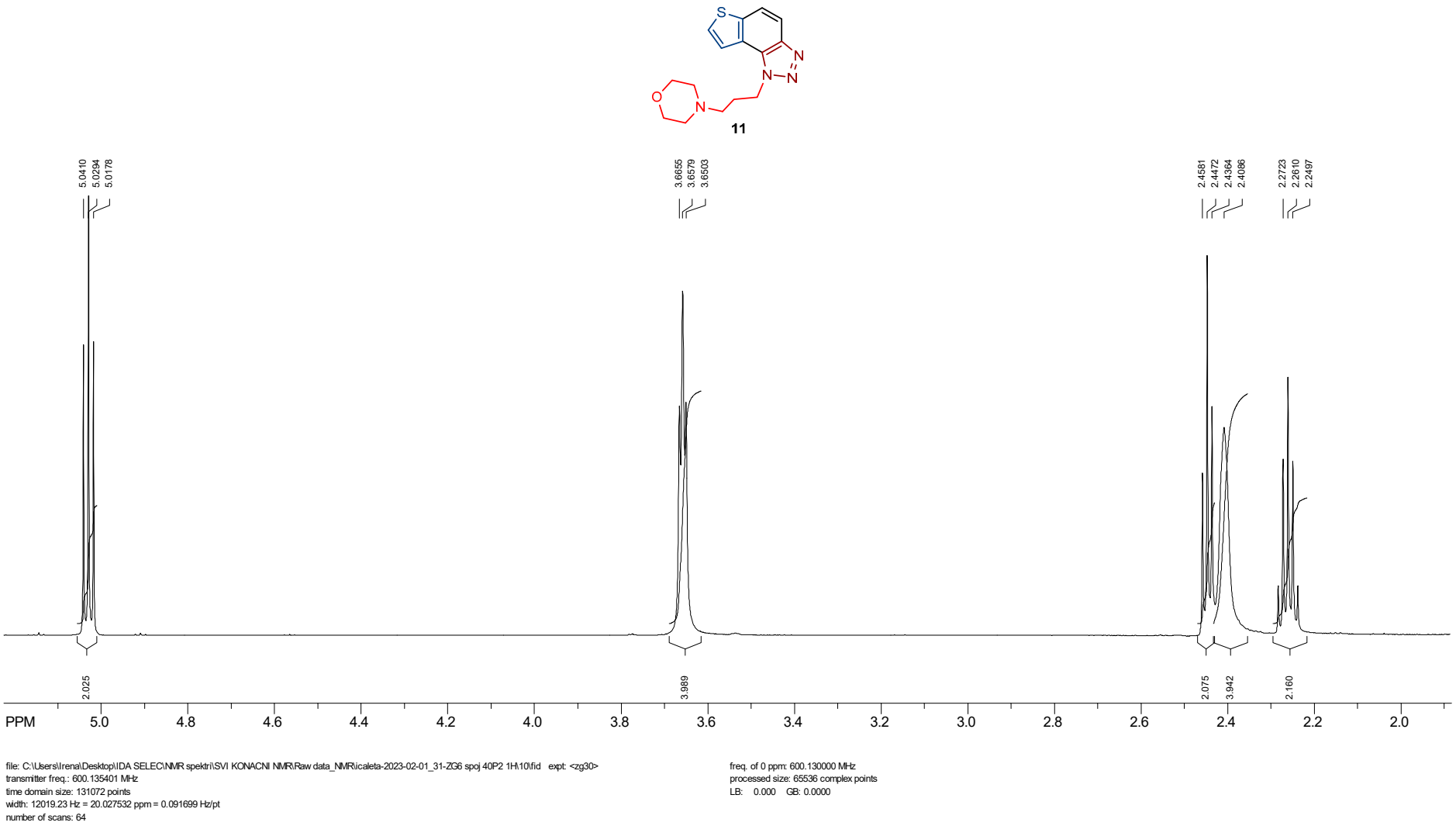


Figure S29. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **11**.

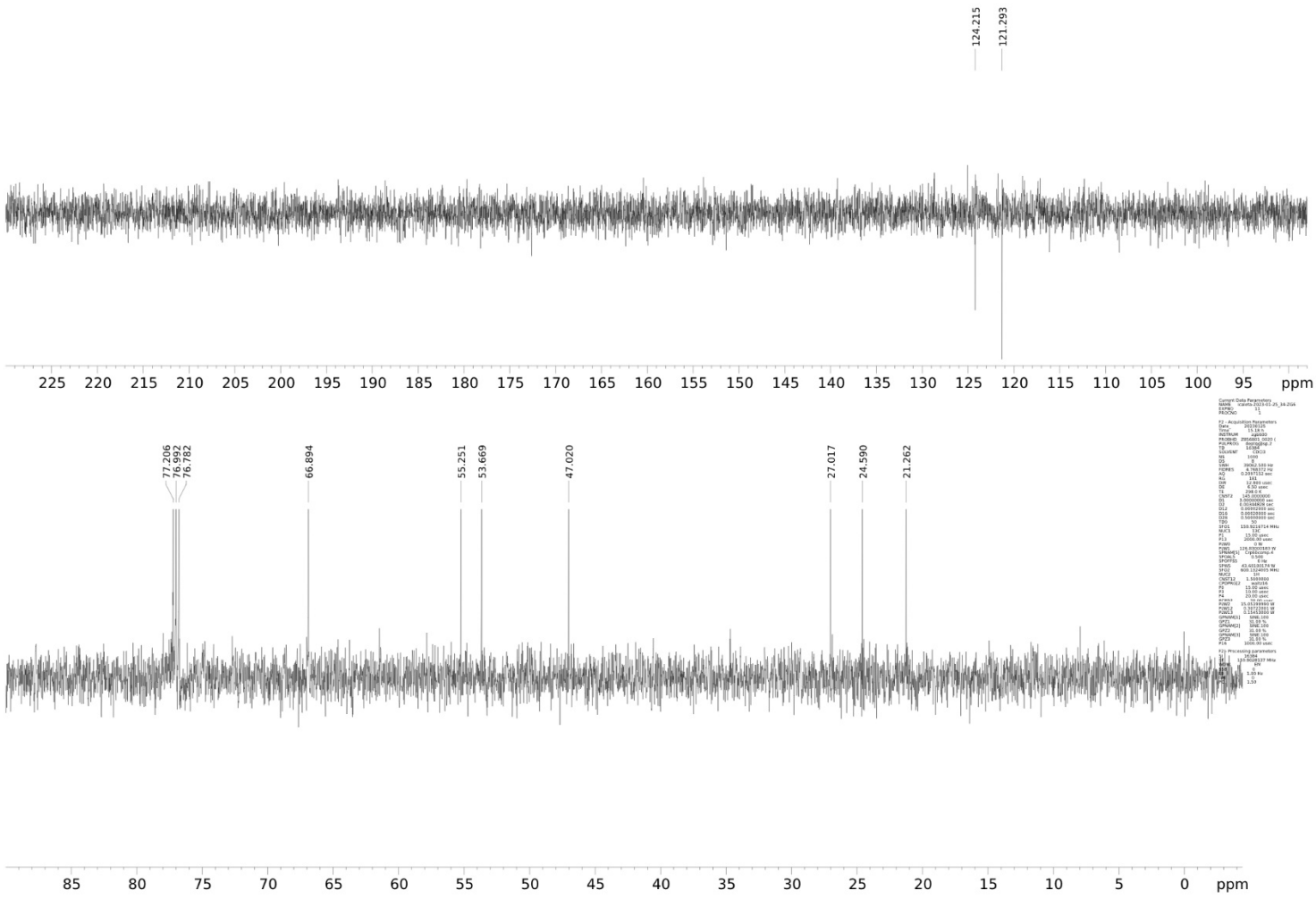


Figure S30. ^{13}C NMR spectrum ($CDCl_3$) of compound **11**.

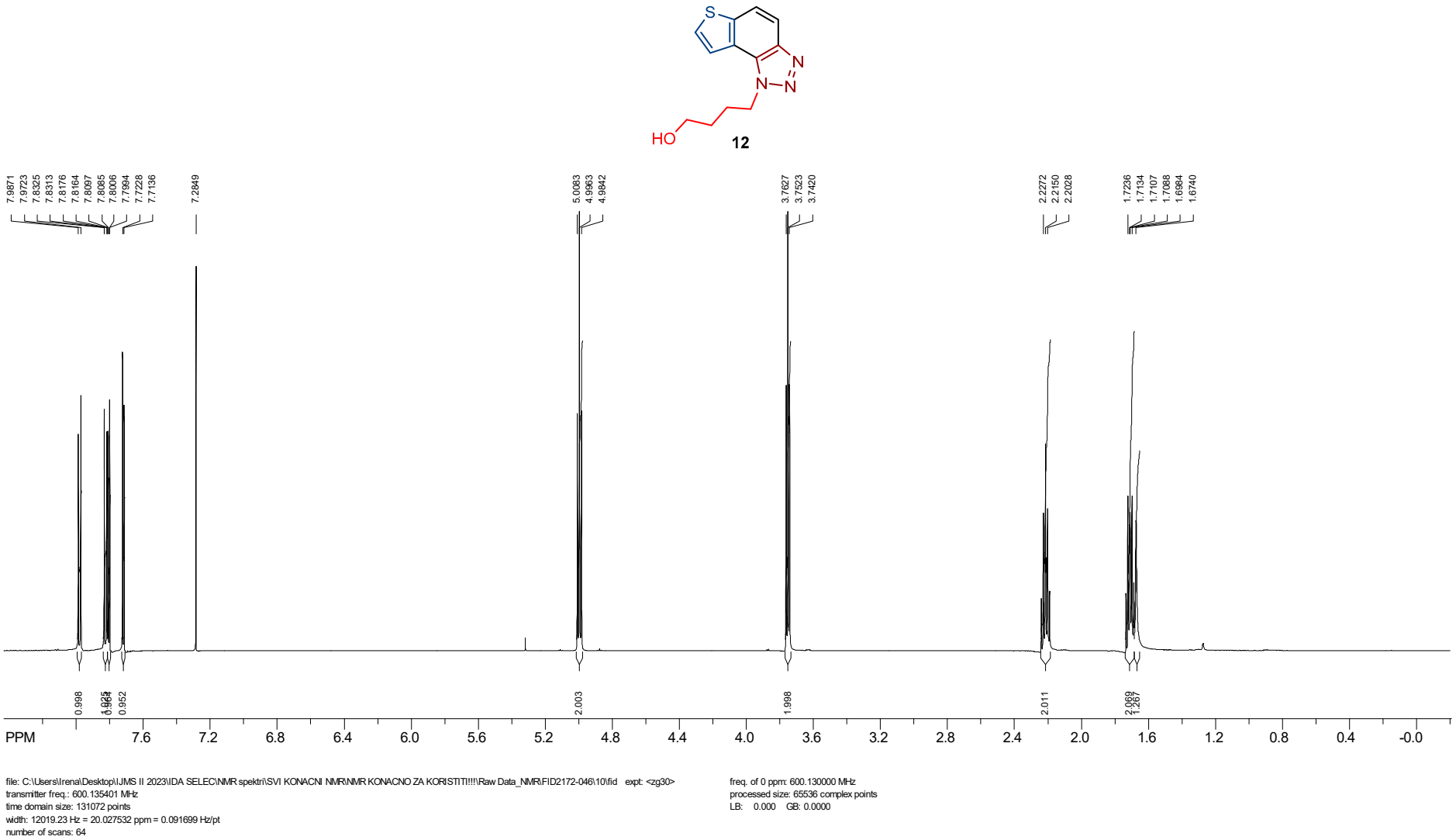


Figure S31. ^{1}H NMR spectrum ($CDCl_3$) of compound **12**.

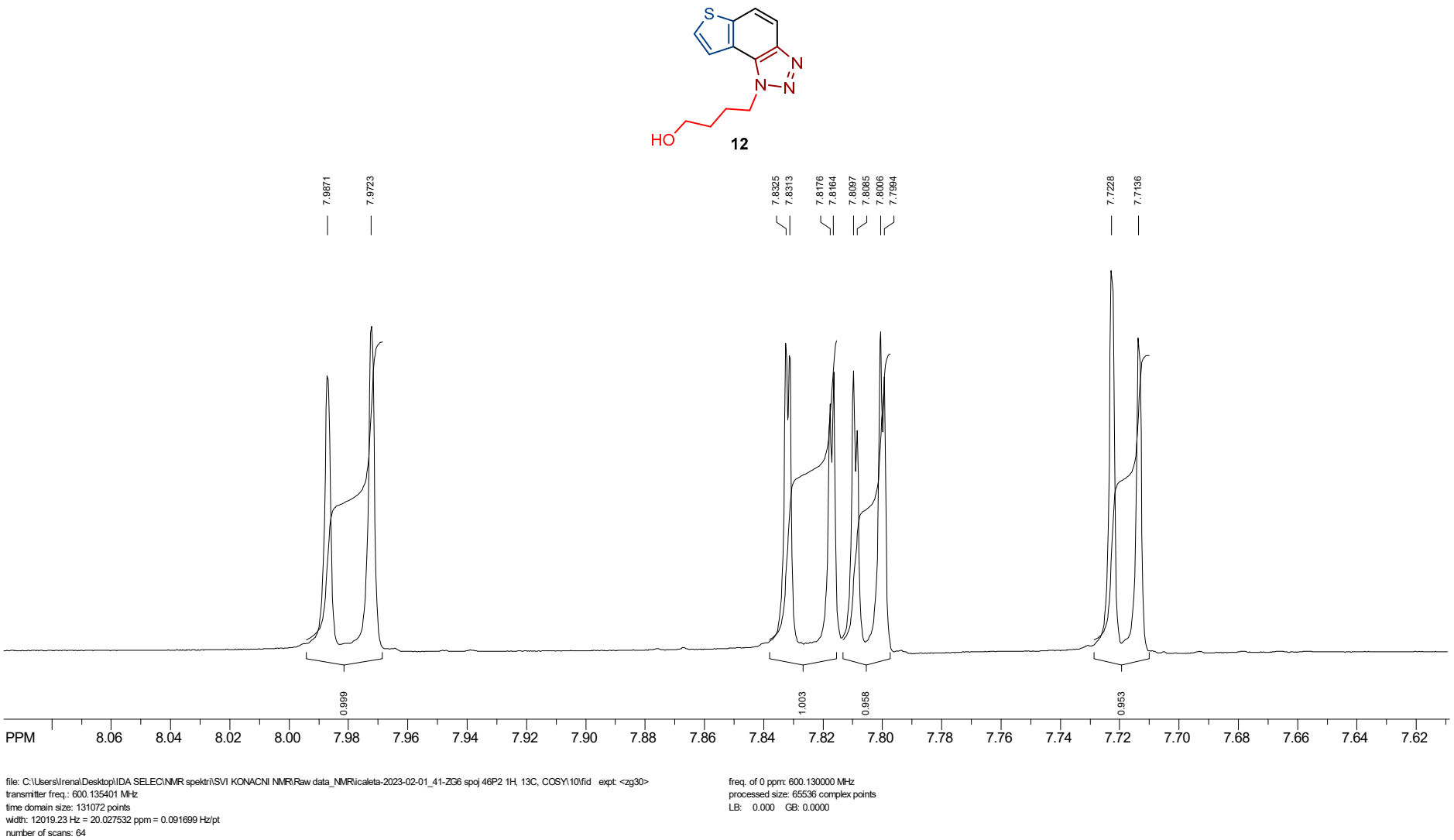


Figure S32. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **12**.

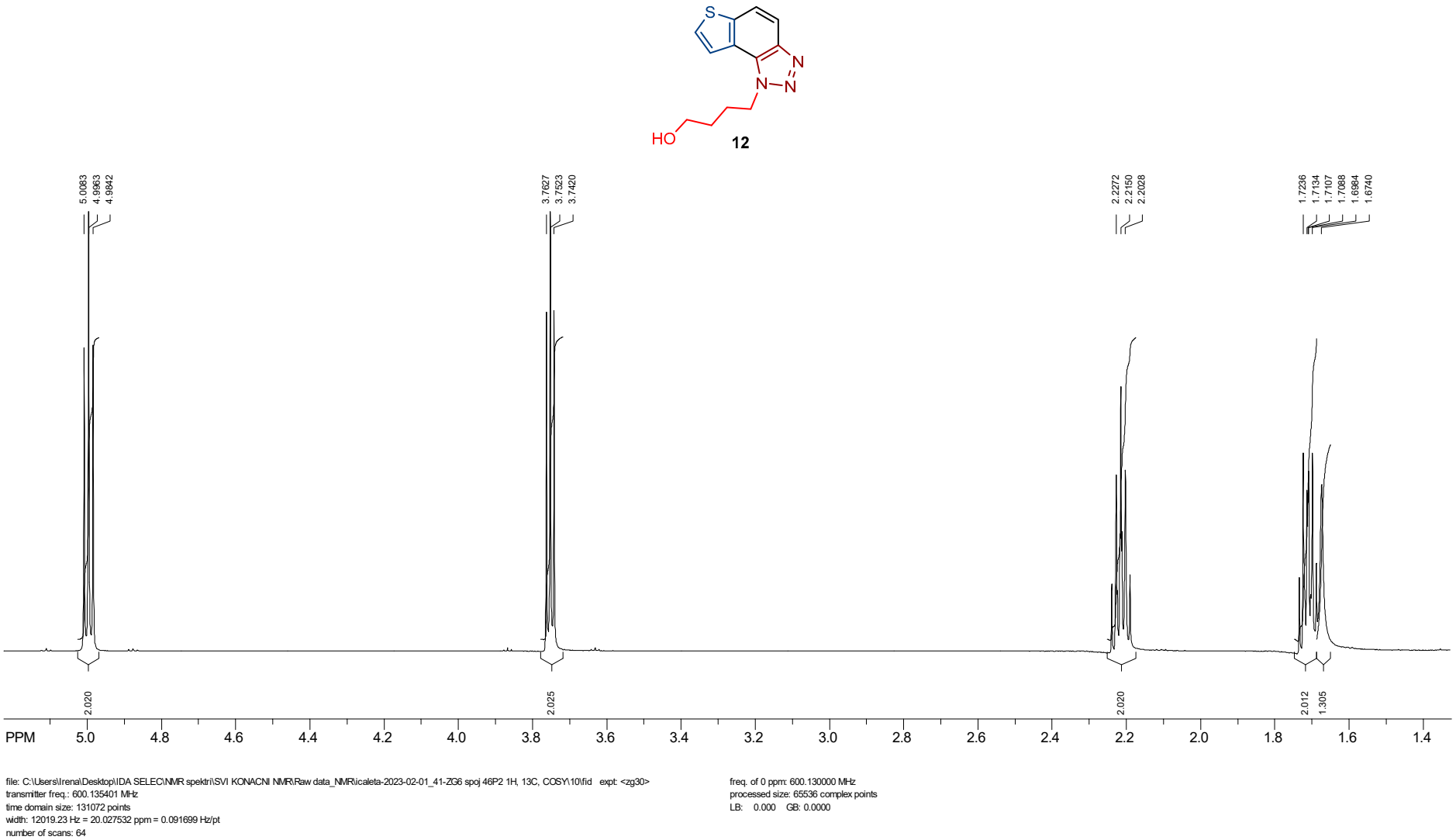


Figure S33. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **12**.

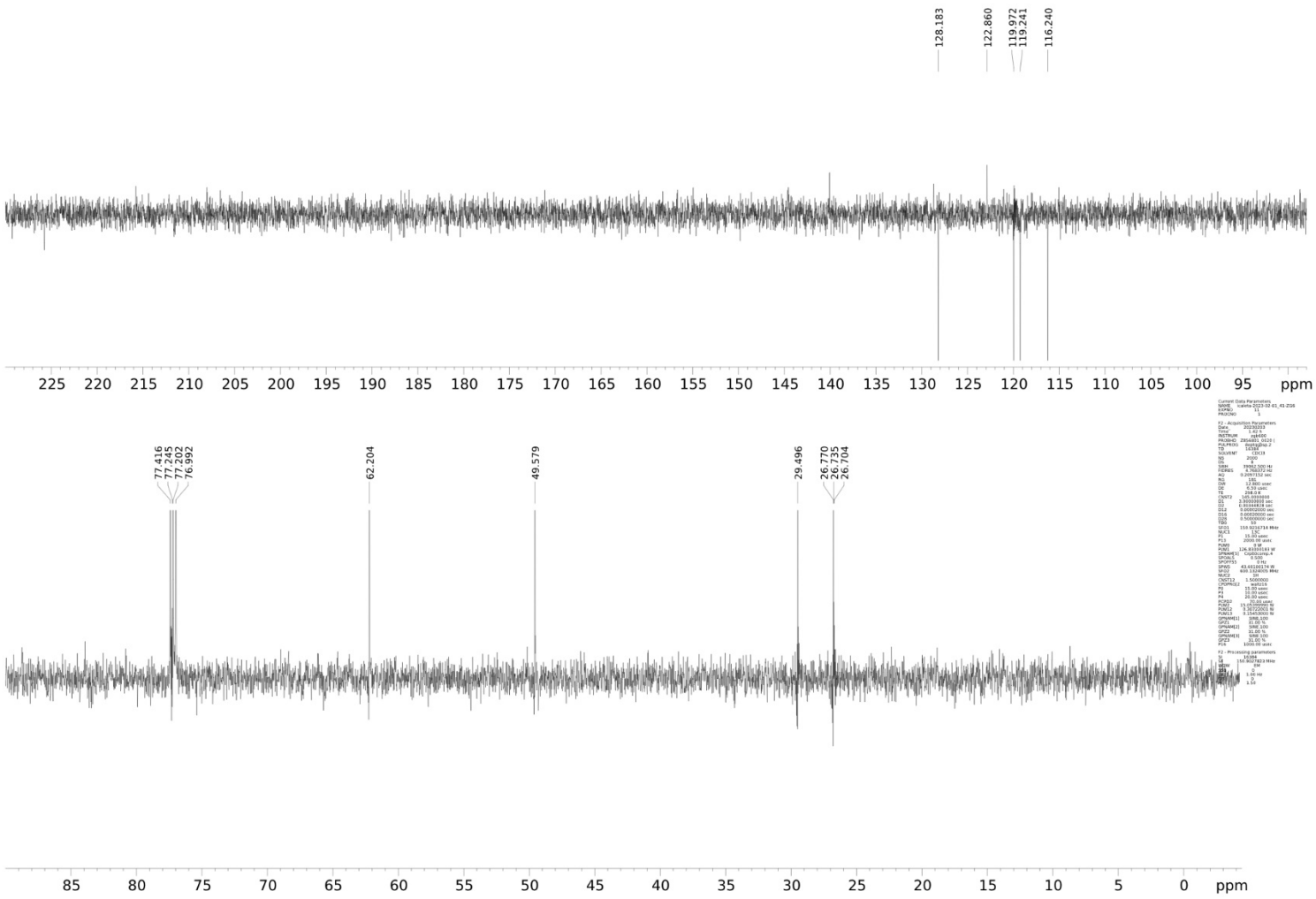


Figure S34. ^{13}C NMR spectrum ($CDCl_3$) of compound **12**.

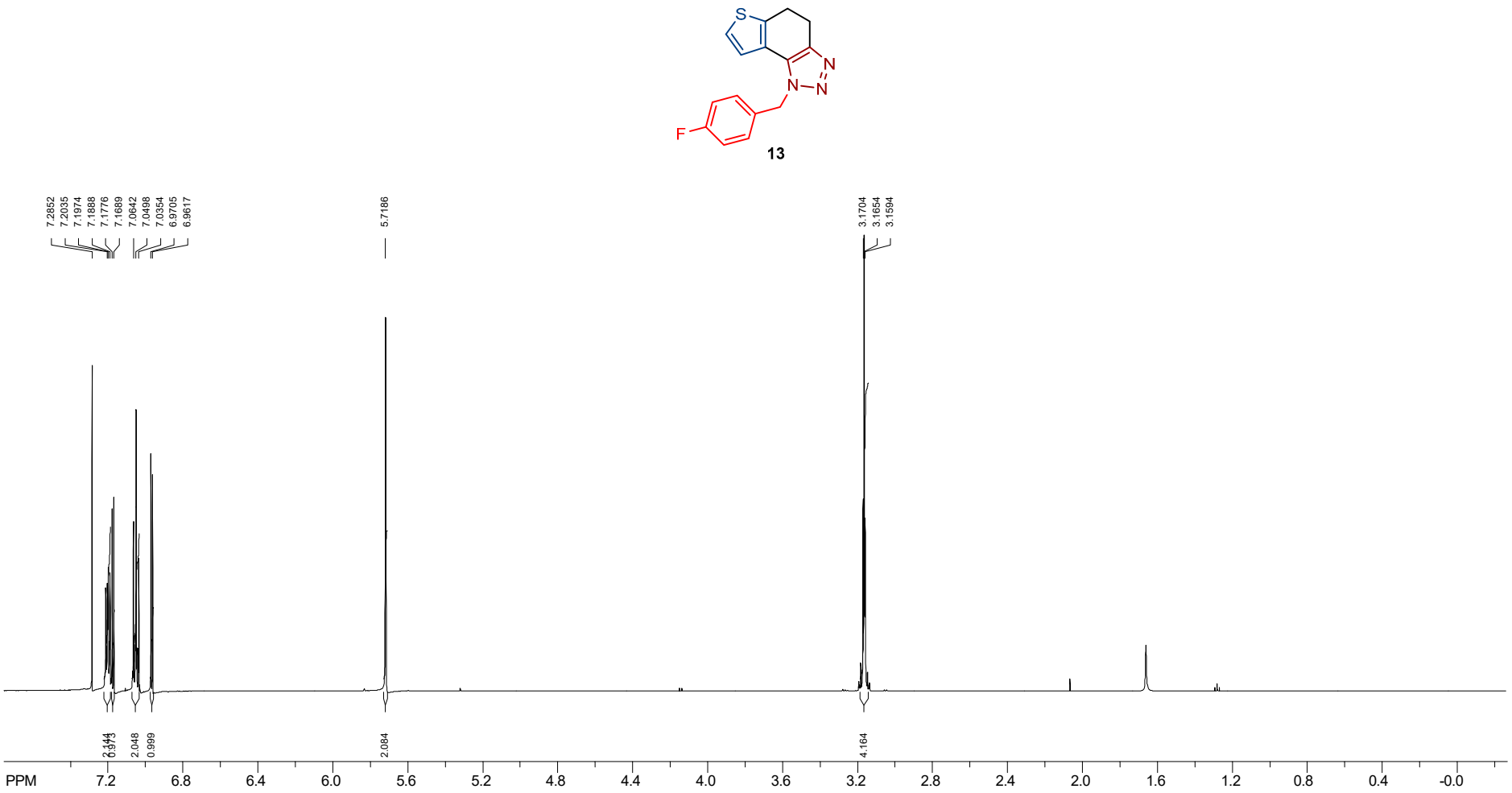


Figure S35. ^{1}H NMR spectrum ($CDCl_3$) of compound **13**.

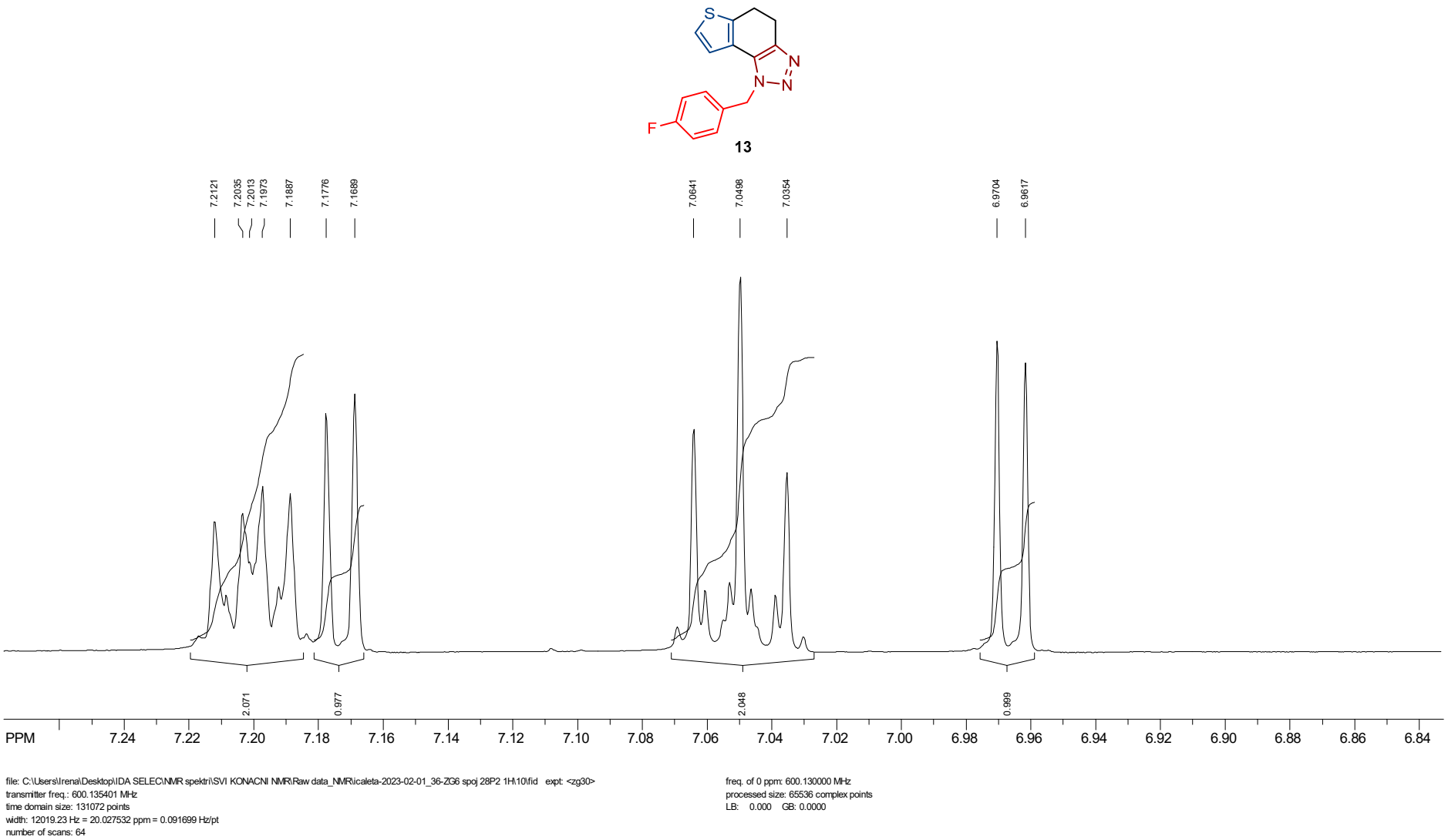


Figure S36. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **13**.

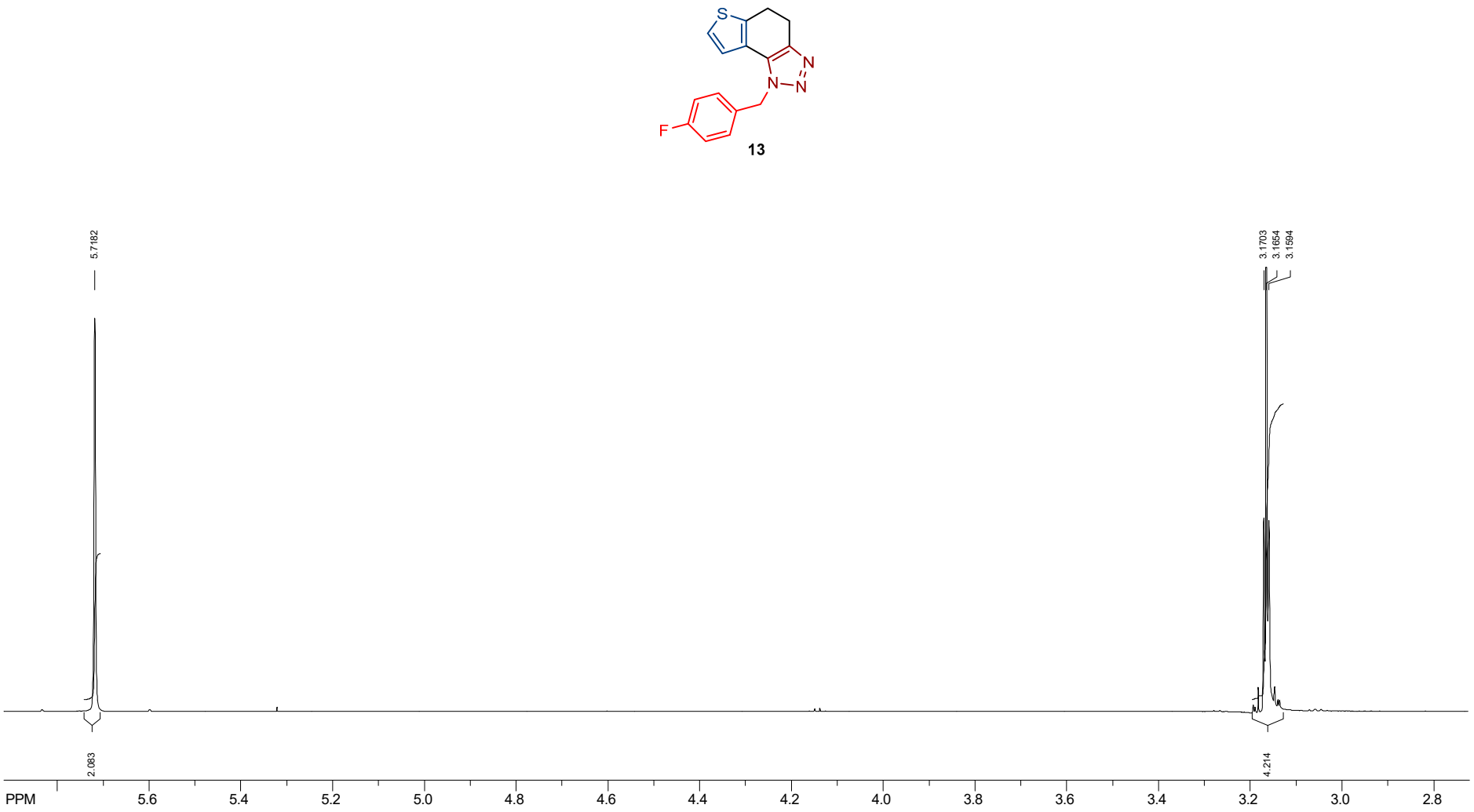


Figure S37. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **13**.

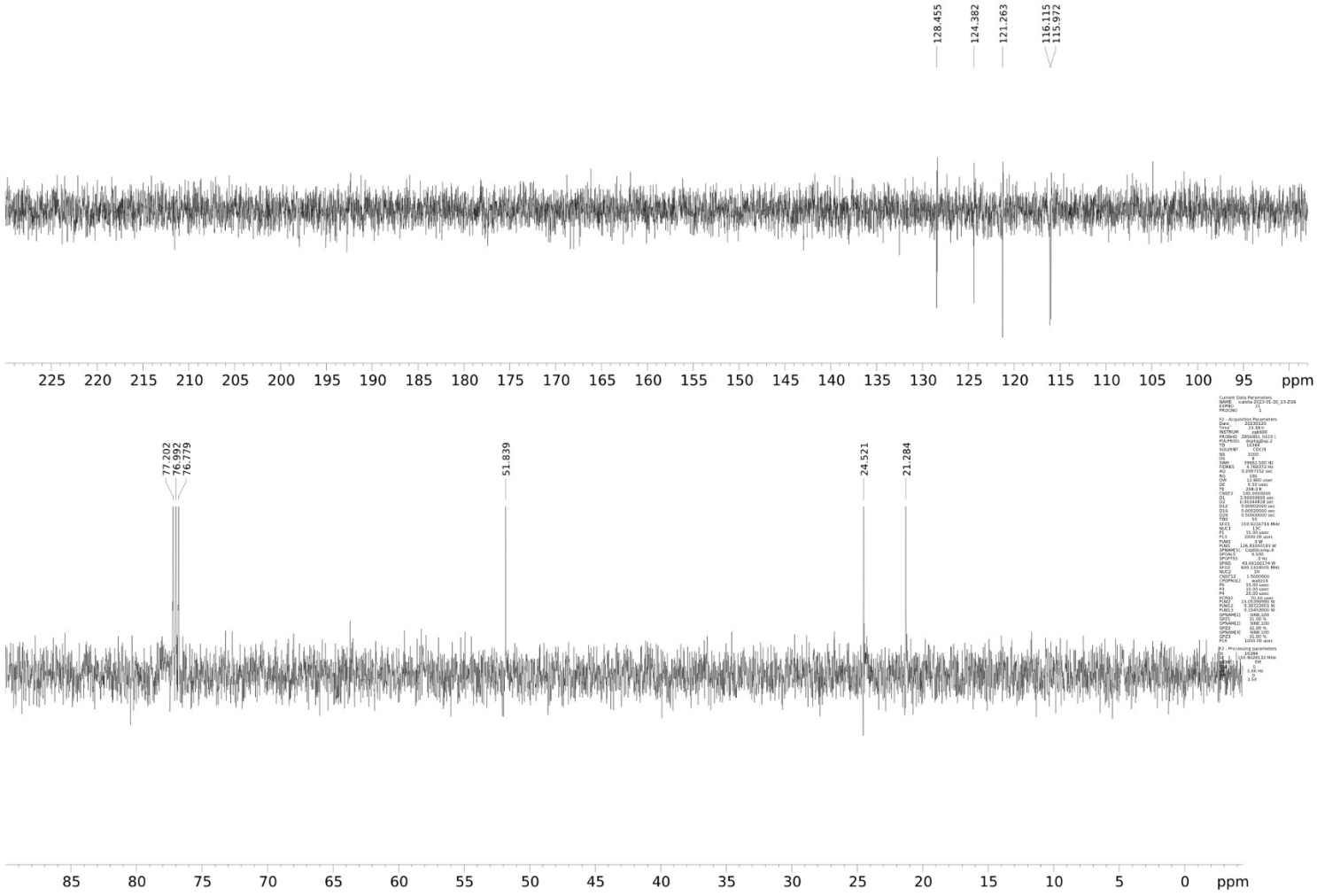


Figure S38. ^{13}C NMR spectrum ($CDCl_3$) of compound **13**.

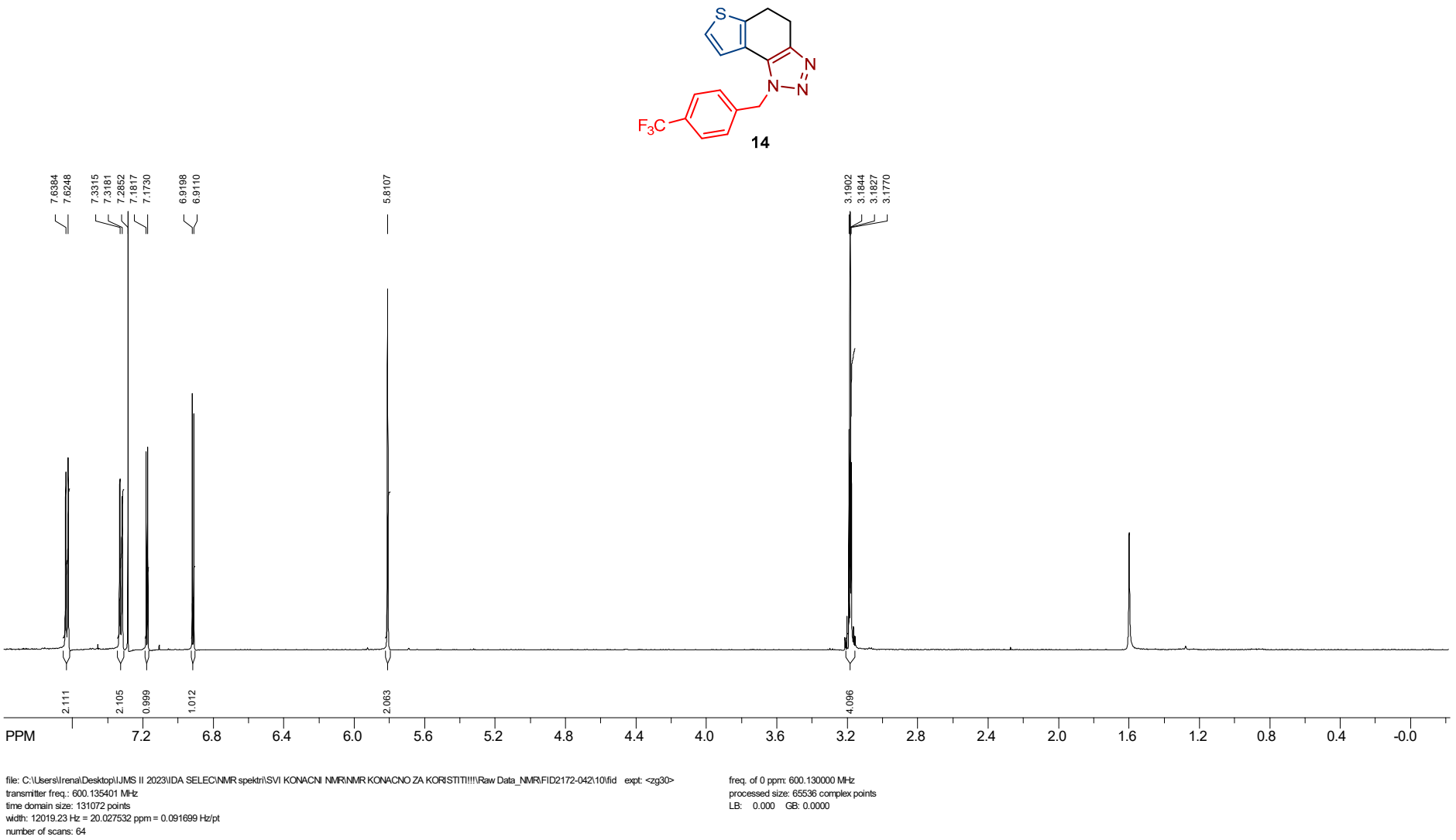


Figure S39. ^{1}H NMR spectrum ($CDCl_3$) of compound **14**.

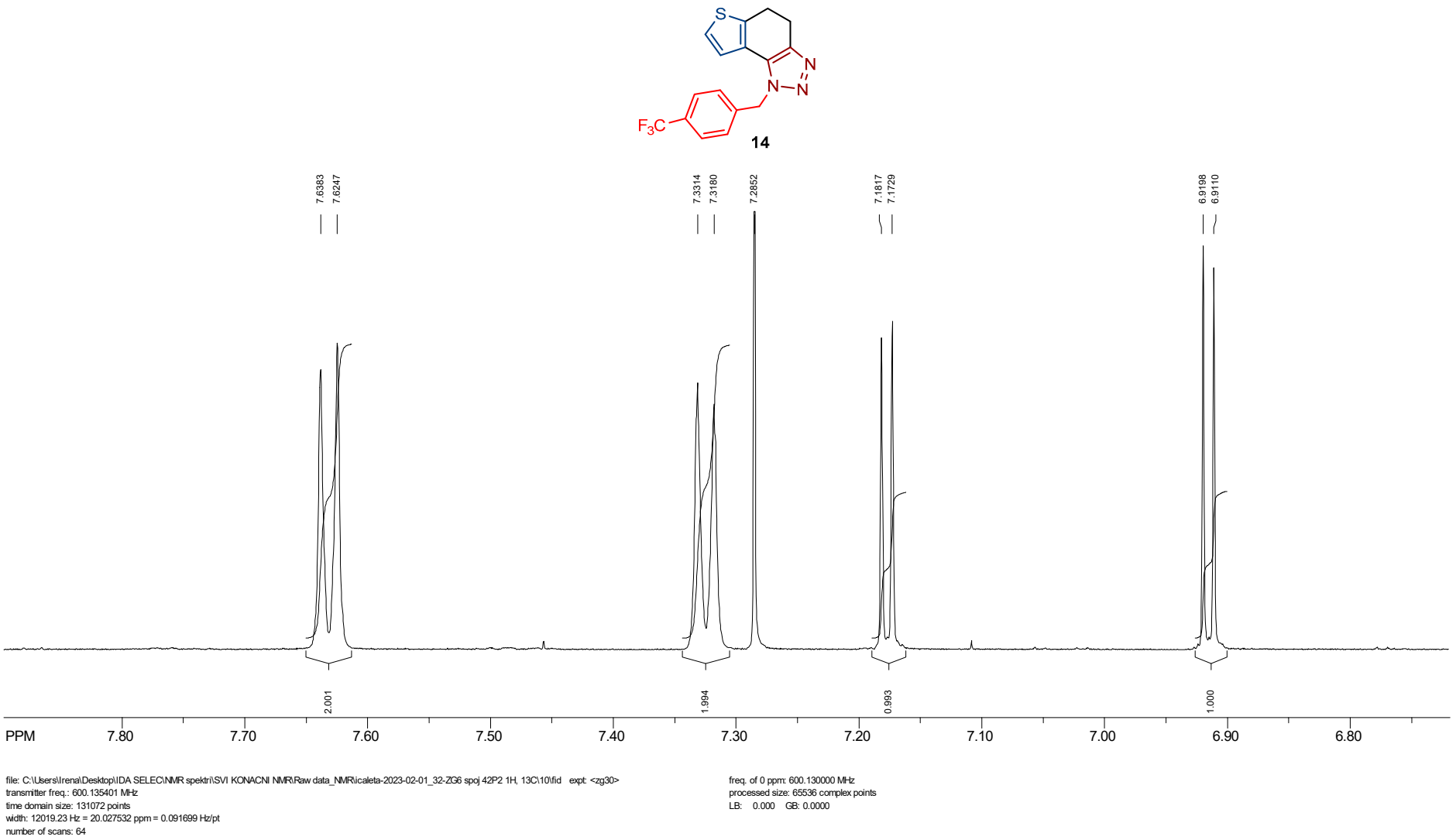


Figure S40. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **14**.

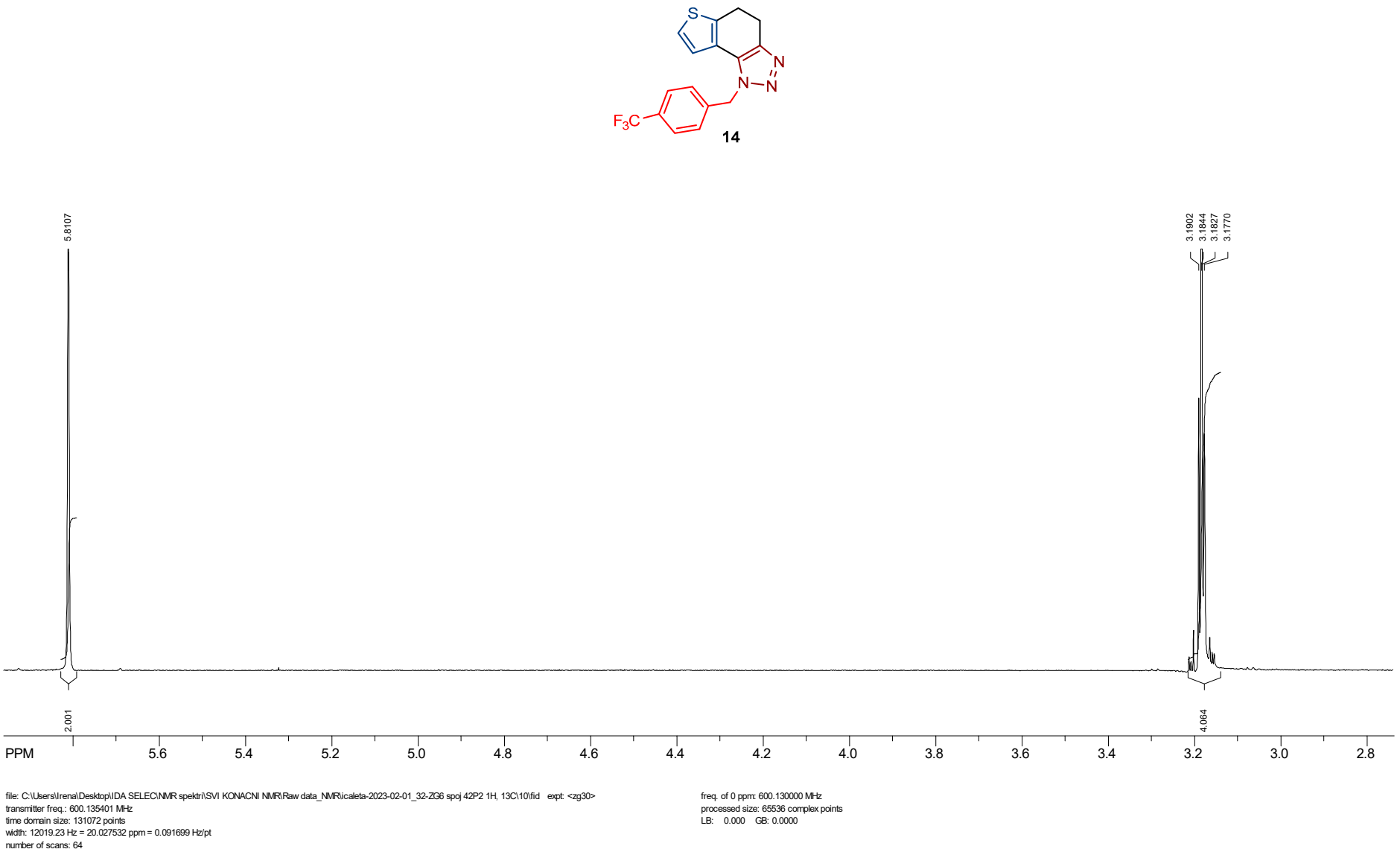


Figure S41. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **14**.

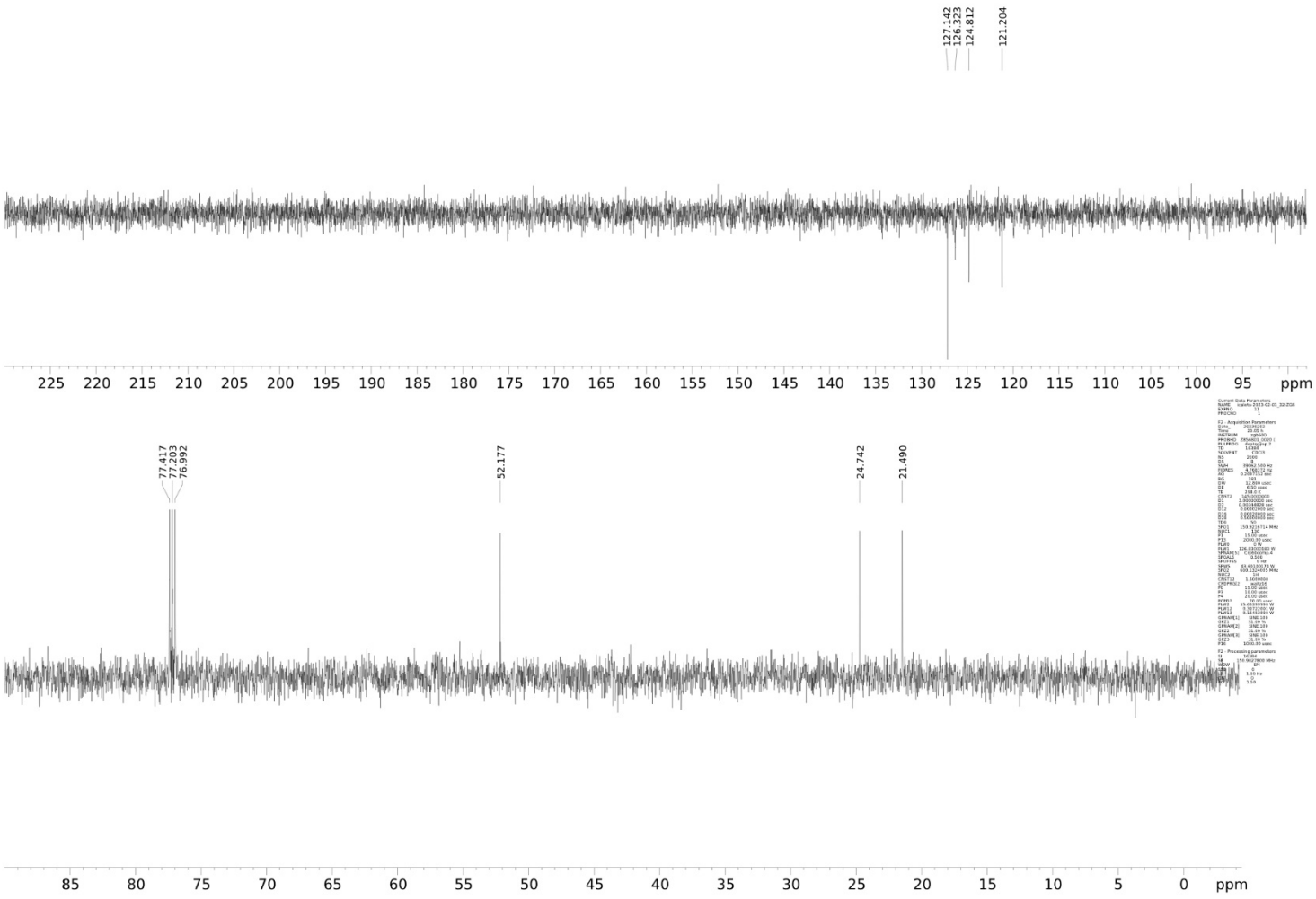


Figure S42. ^{13}C NMR spectrum ($CDCl_3$) of compound **14**.

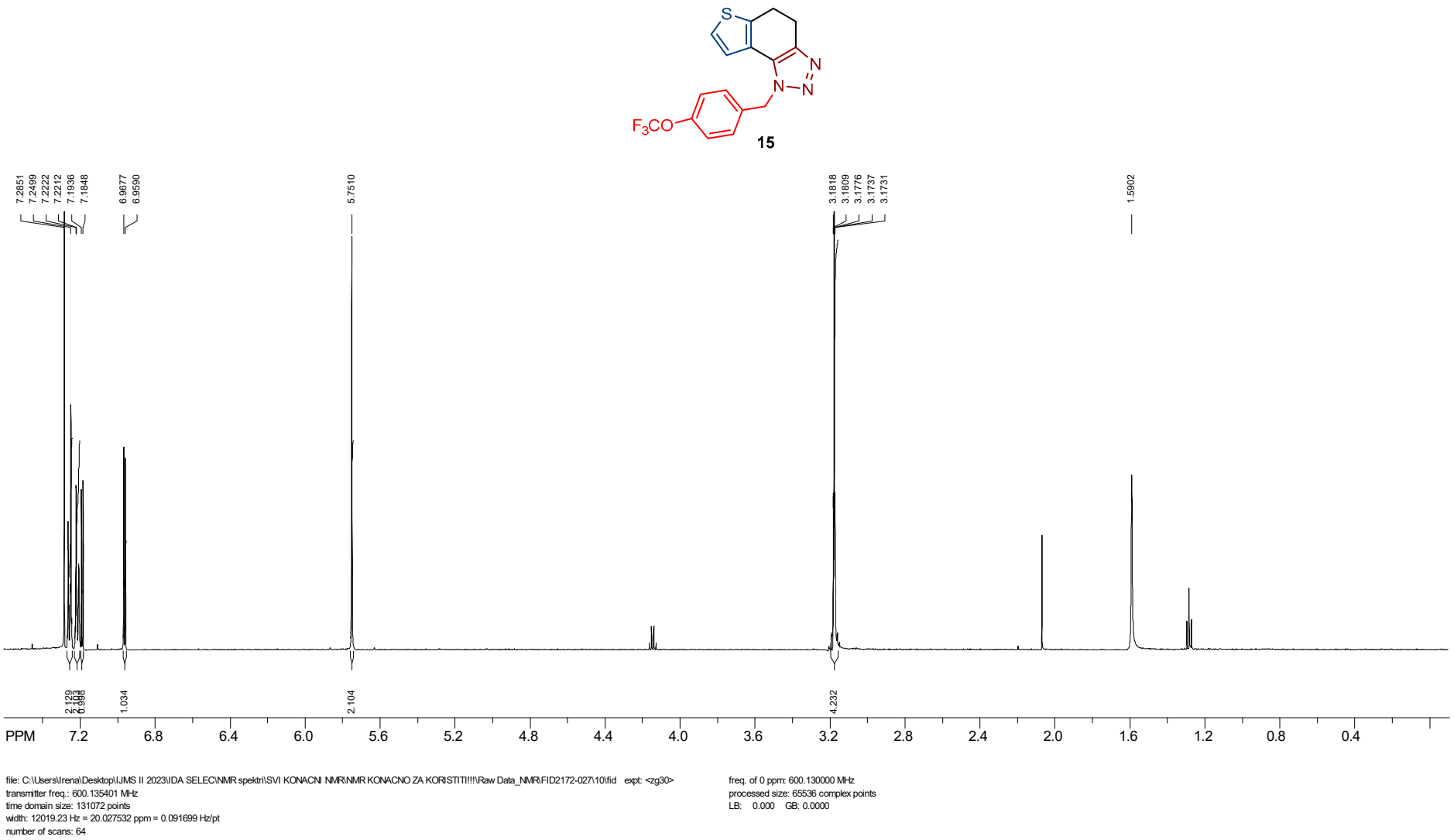


Figure S43. ^{1}H NMR spectrum ($CDCl_3$) of compound **15**.

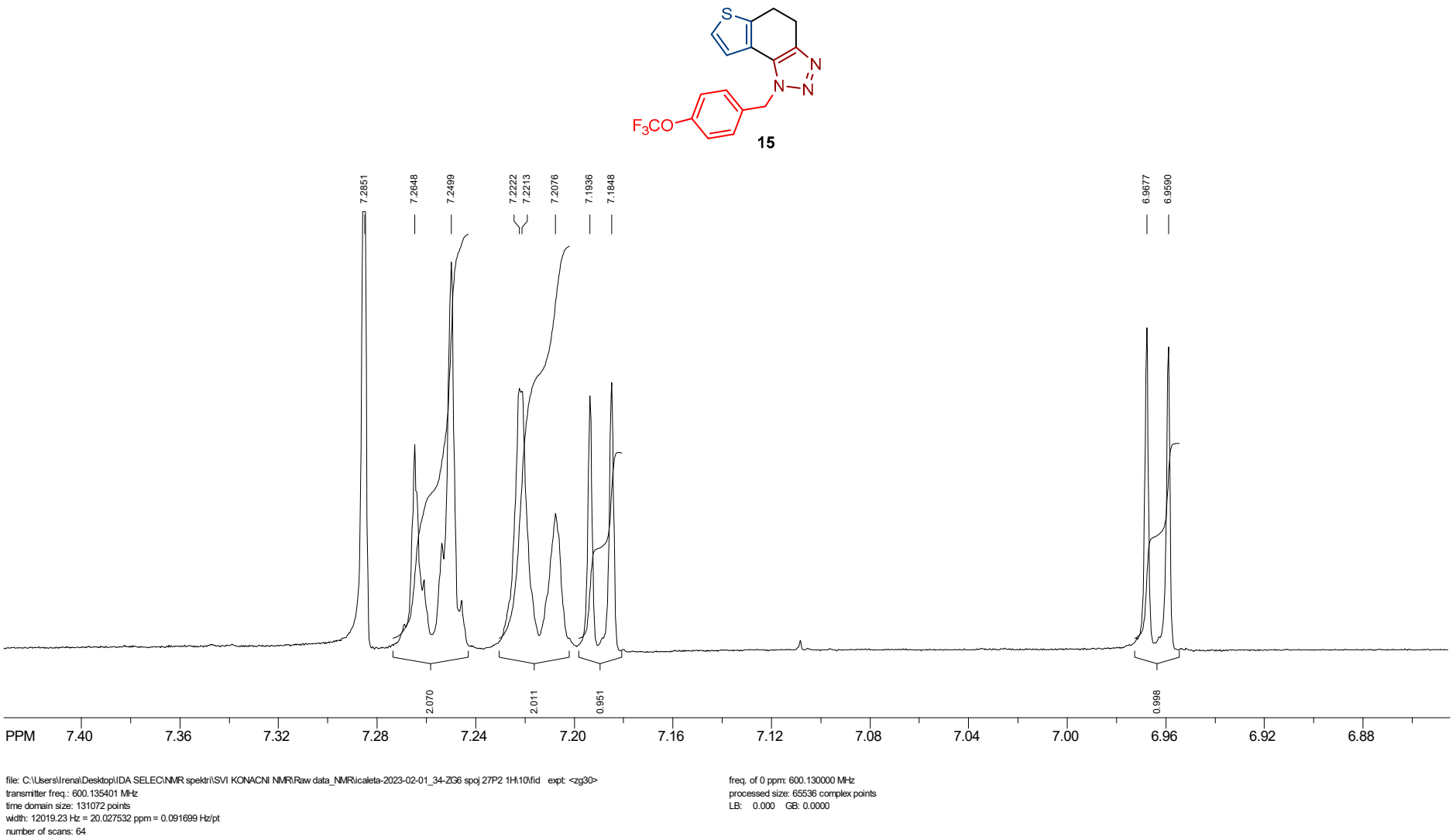


Figure S44. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **15**.

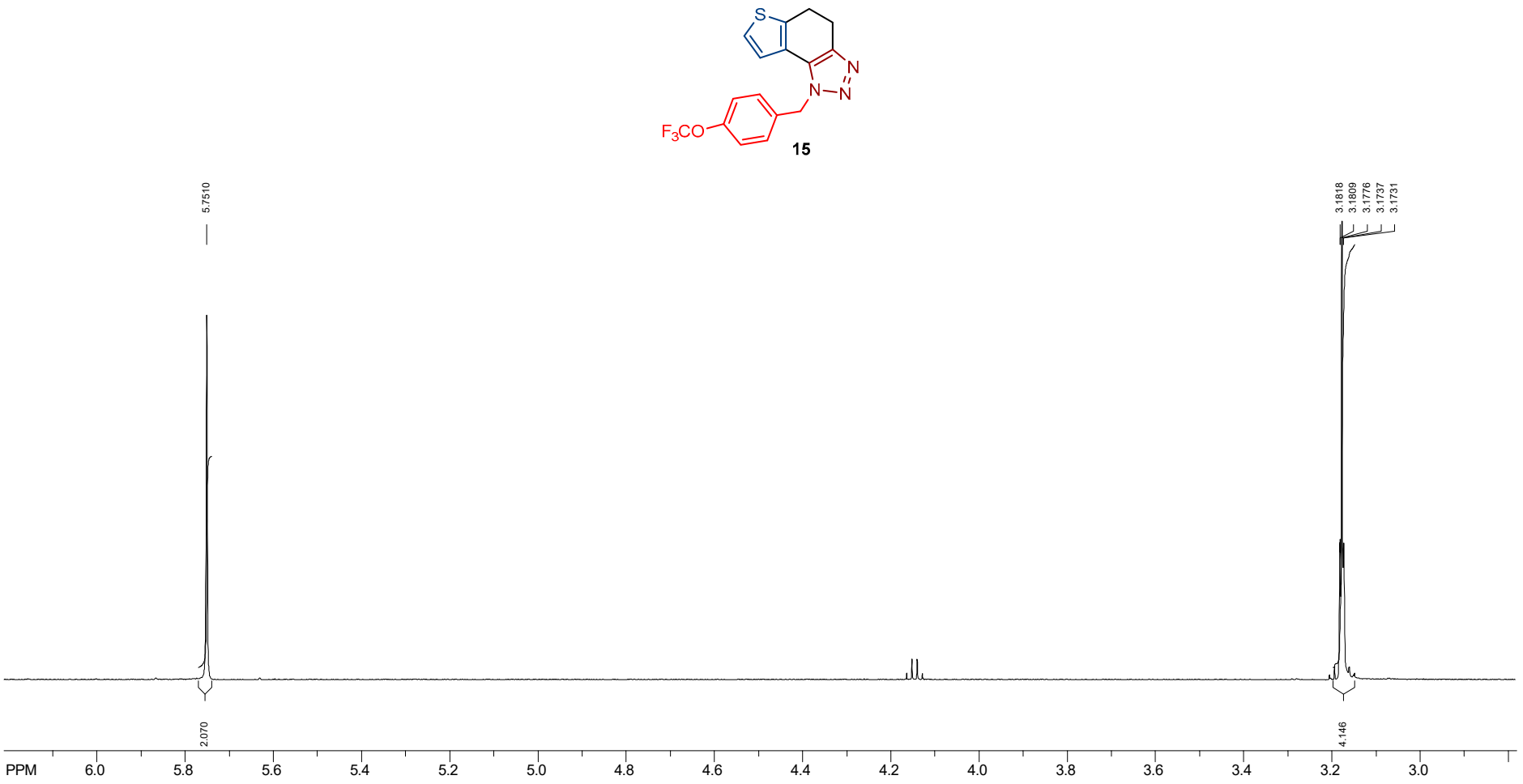


Figure S45. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **15**.

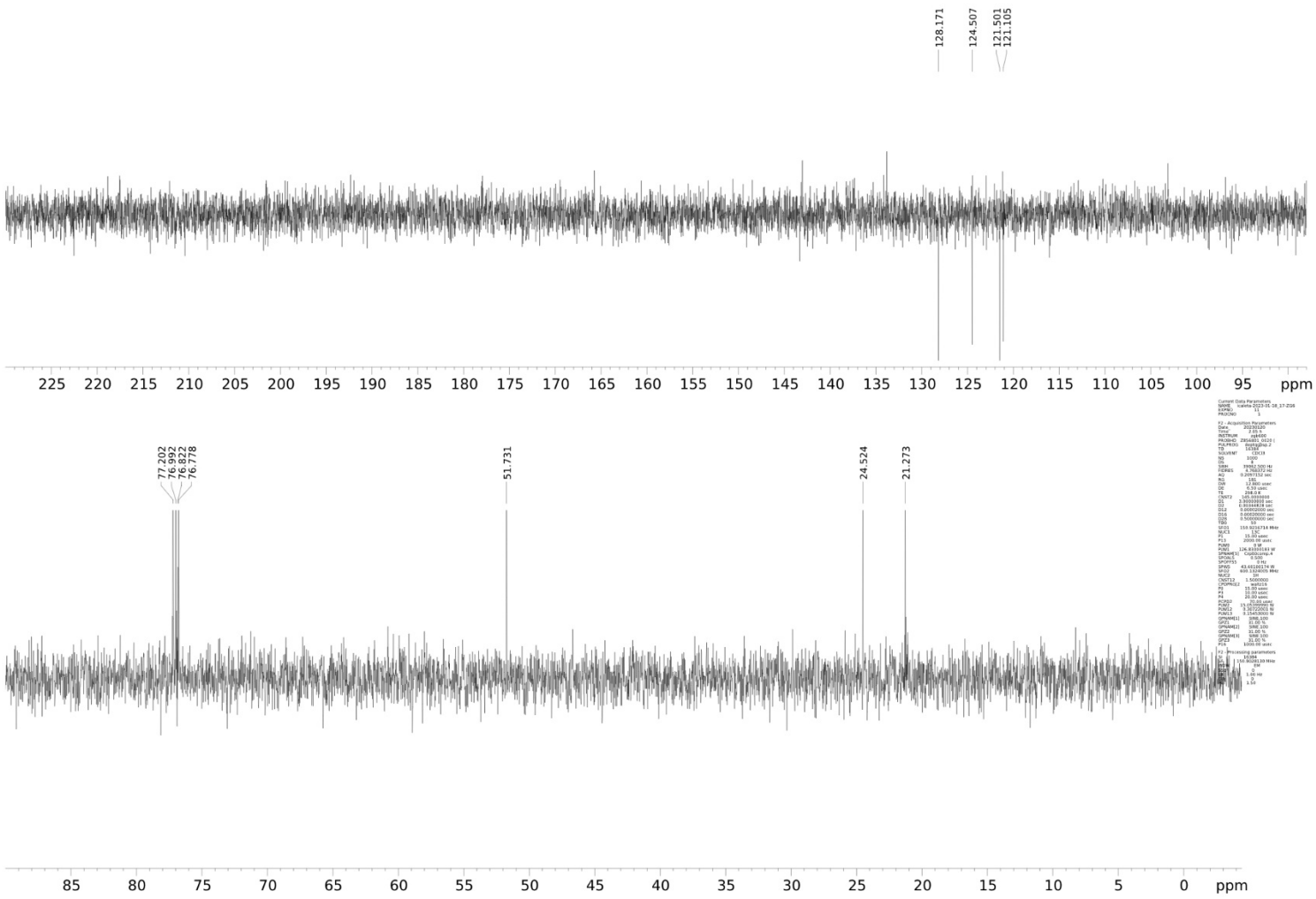


Figure S46. ^{13}C NMR spectrum ($CDCl_3$) of compound **15**.

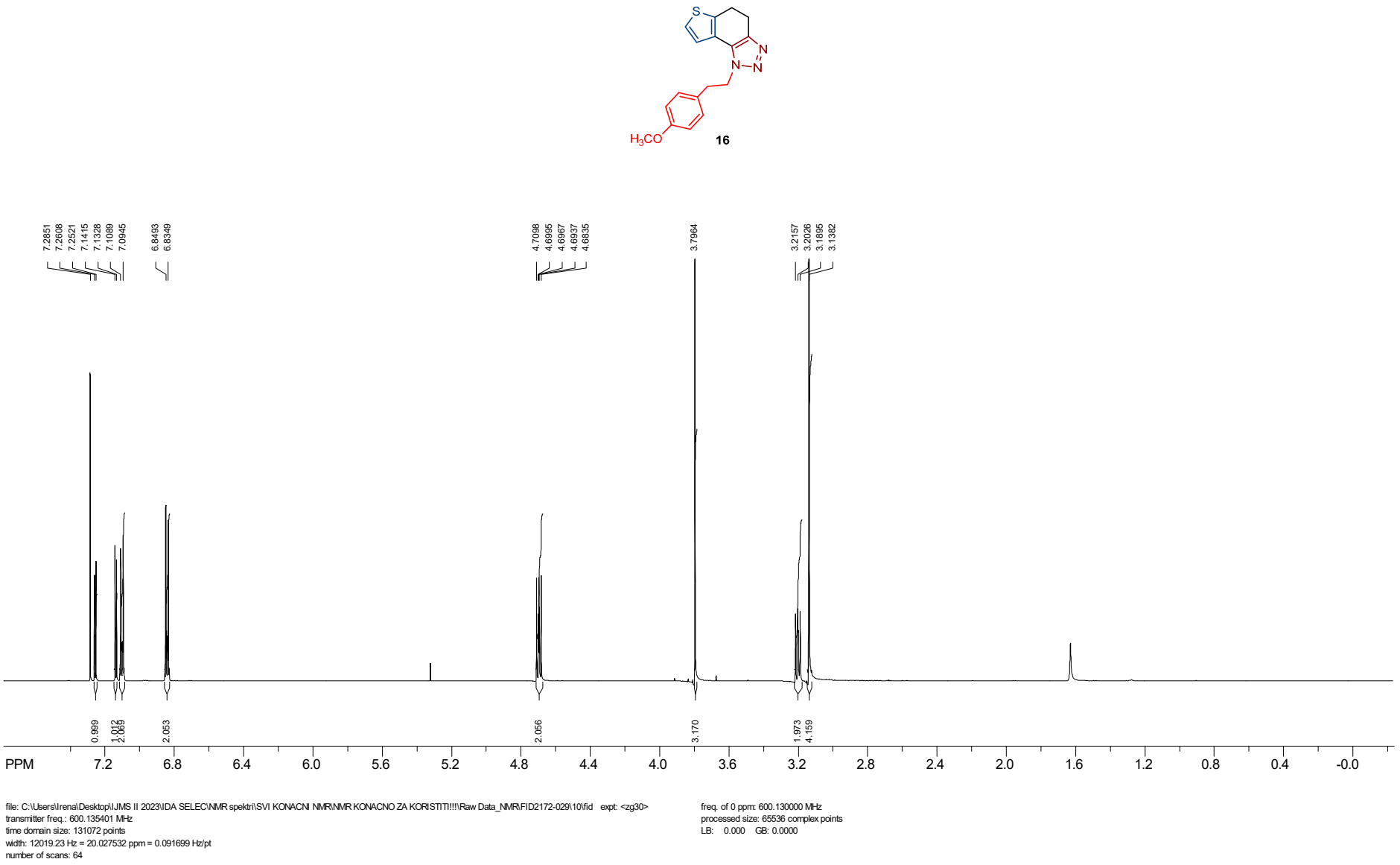


Figure S47. ^{1}H NMR spectrum ($CDCl_3$) of compound **16**.

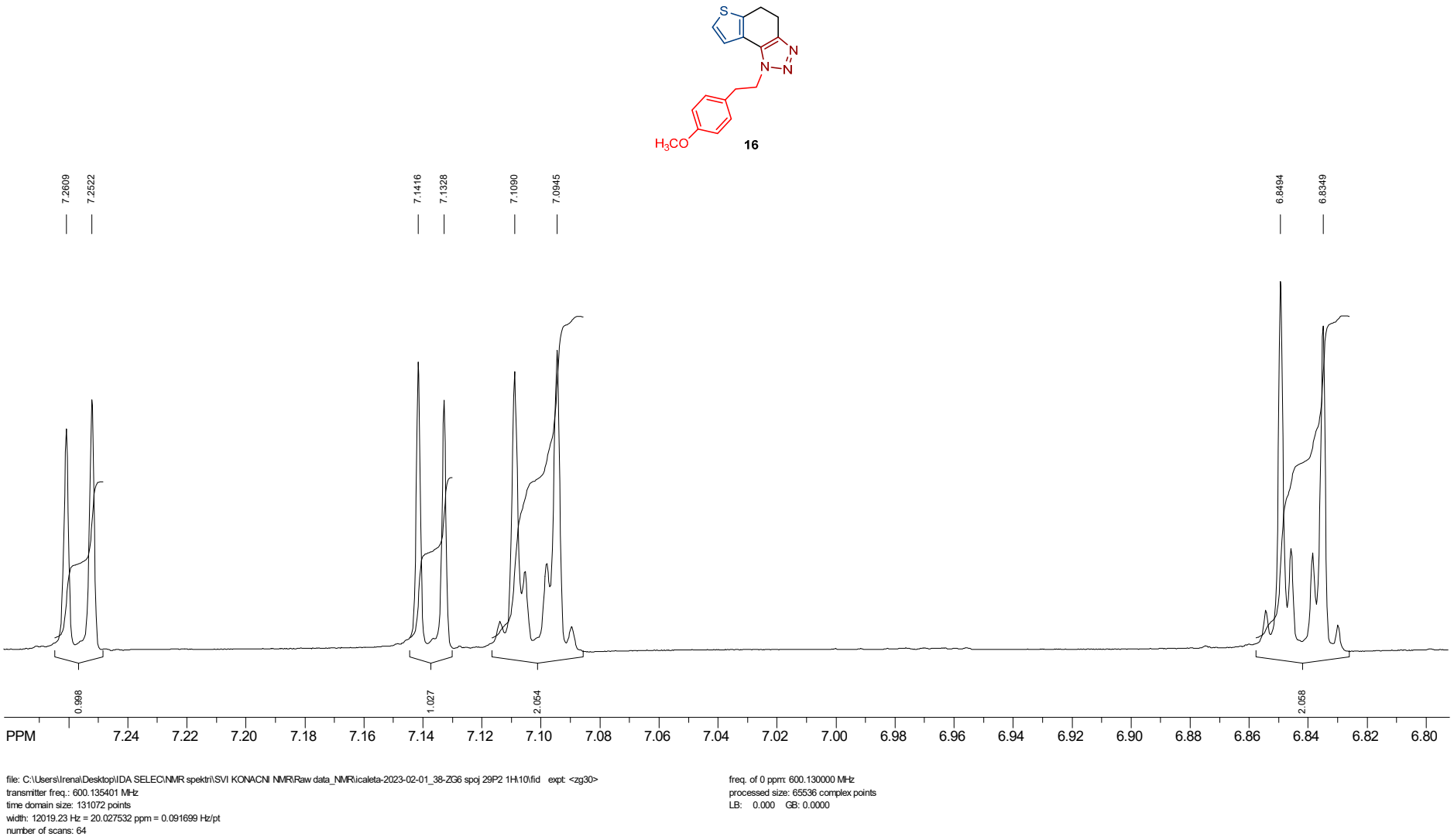


Figure S48. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **16**.

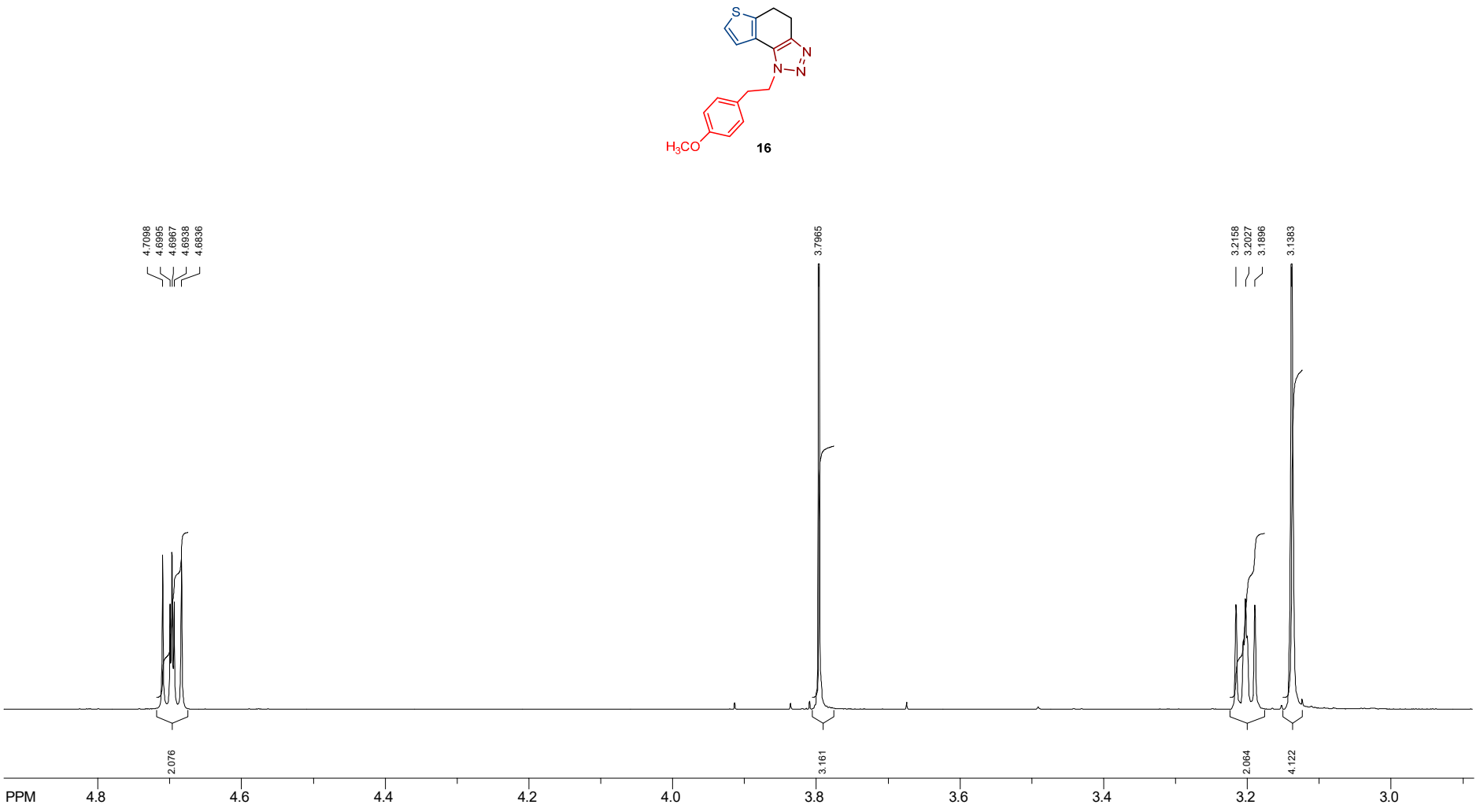


Figure S49. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **16**.

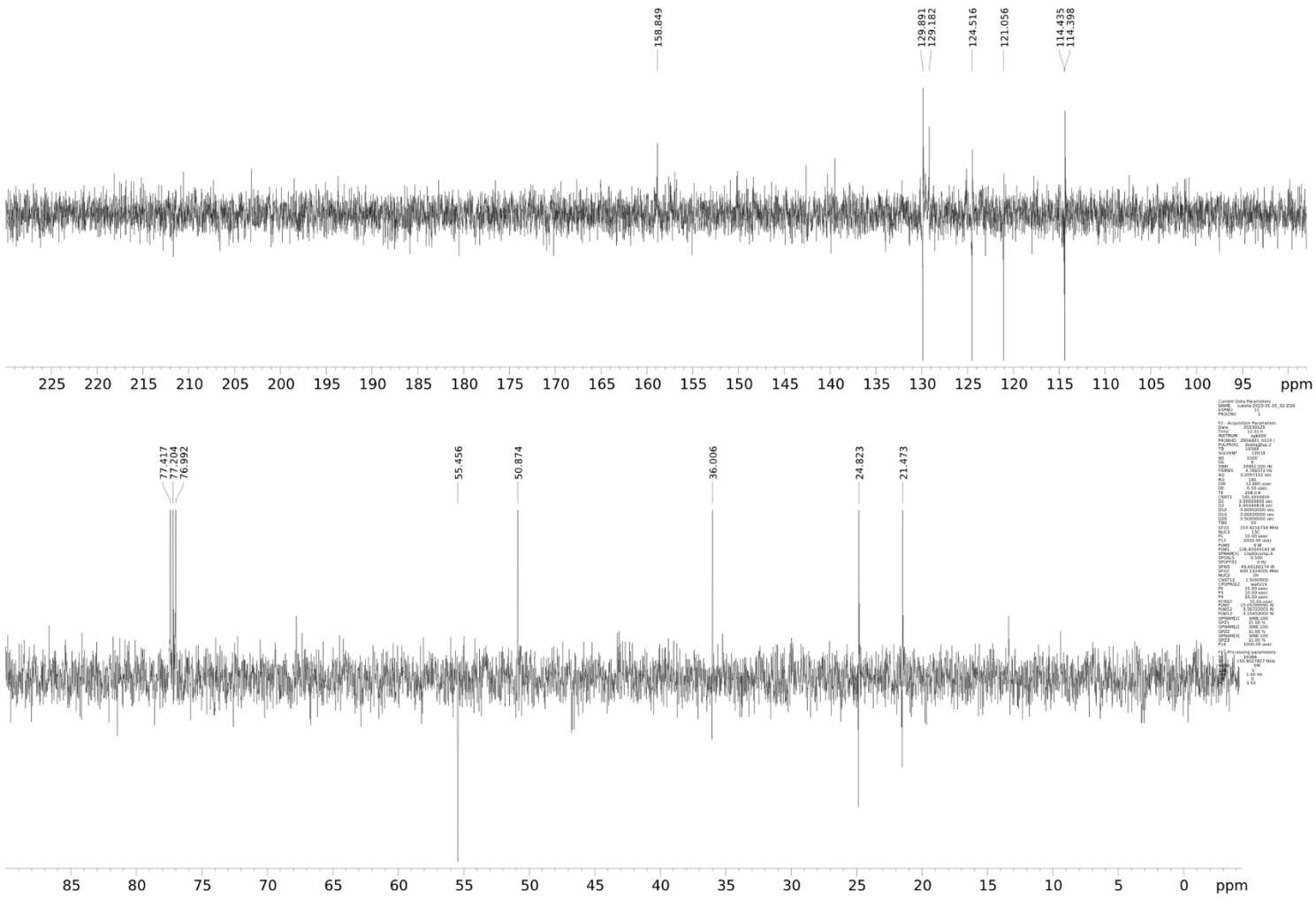


Figure S50. ^{13}C NMR spectrum ($CDCl_3$) of compound **16**.

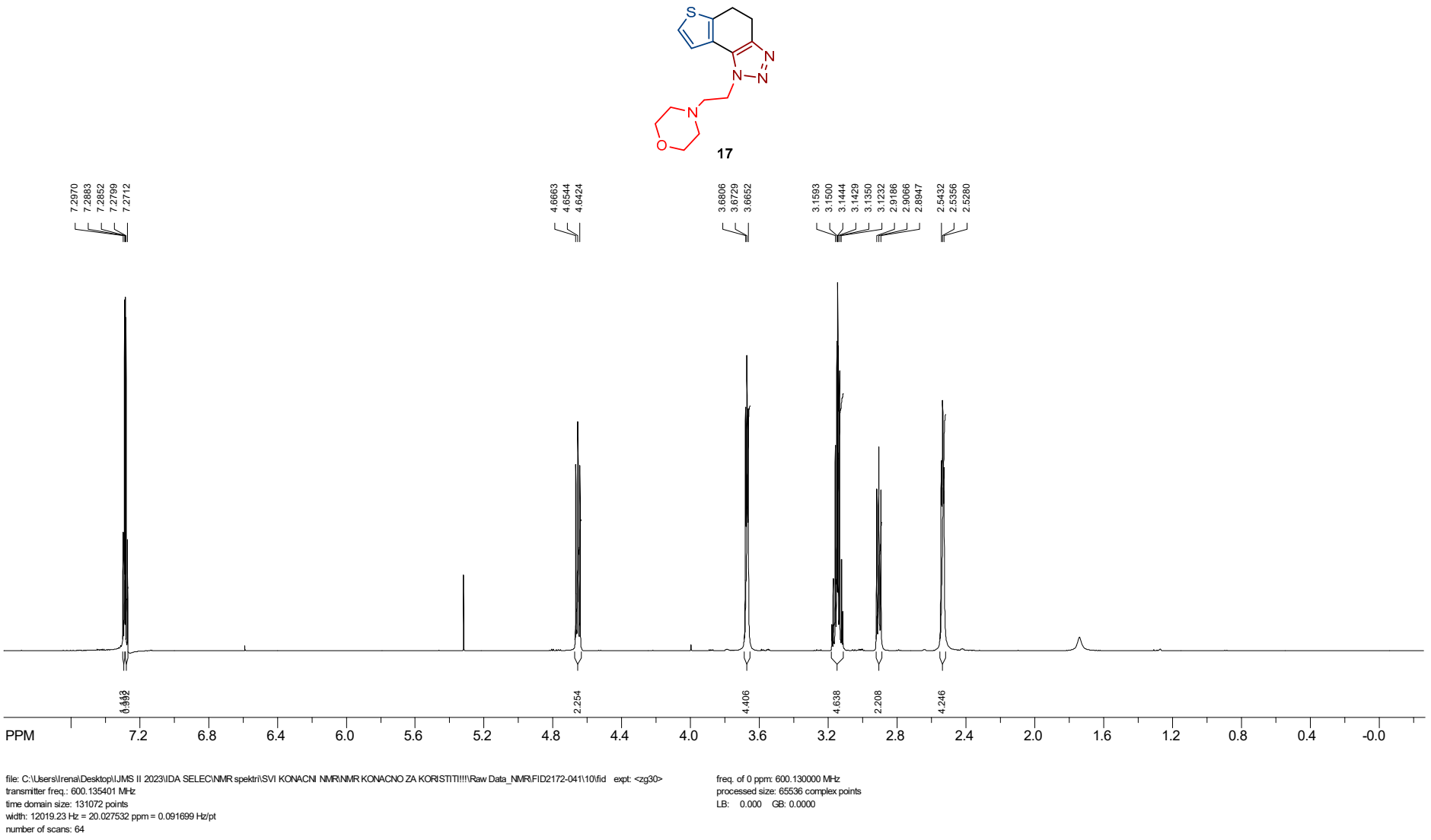


Figure S51. ^{1}H NMR spectrum ($CDCl_3$) of compound **17**.

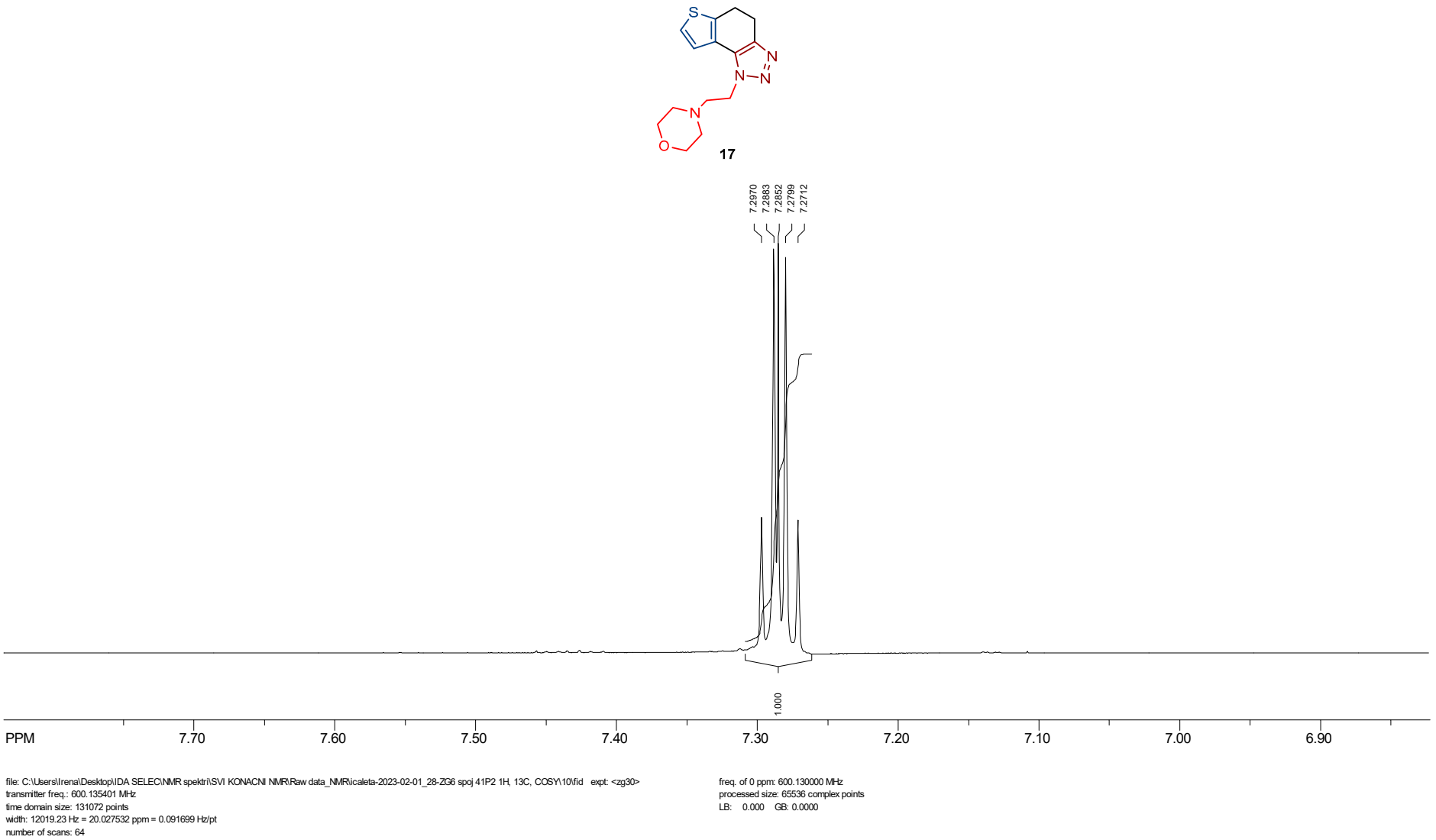


Figure S52. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **17**.

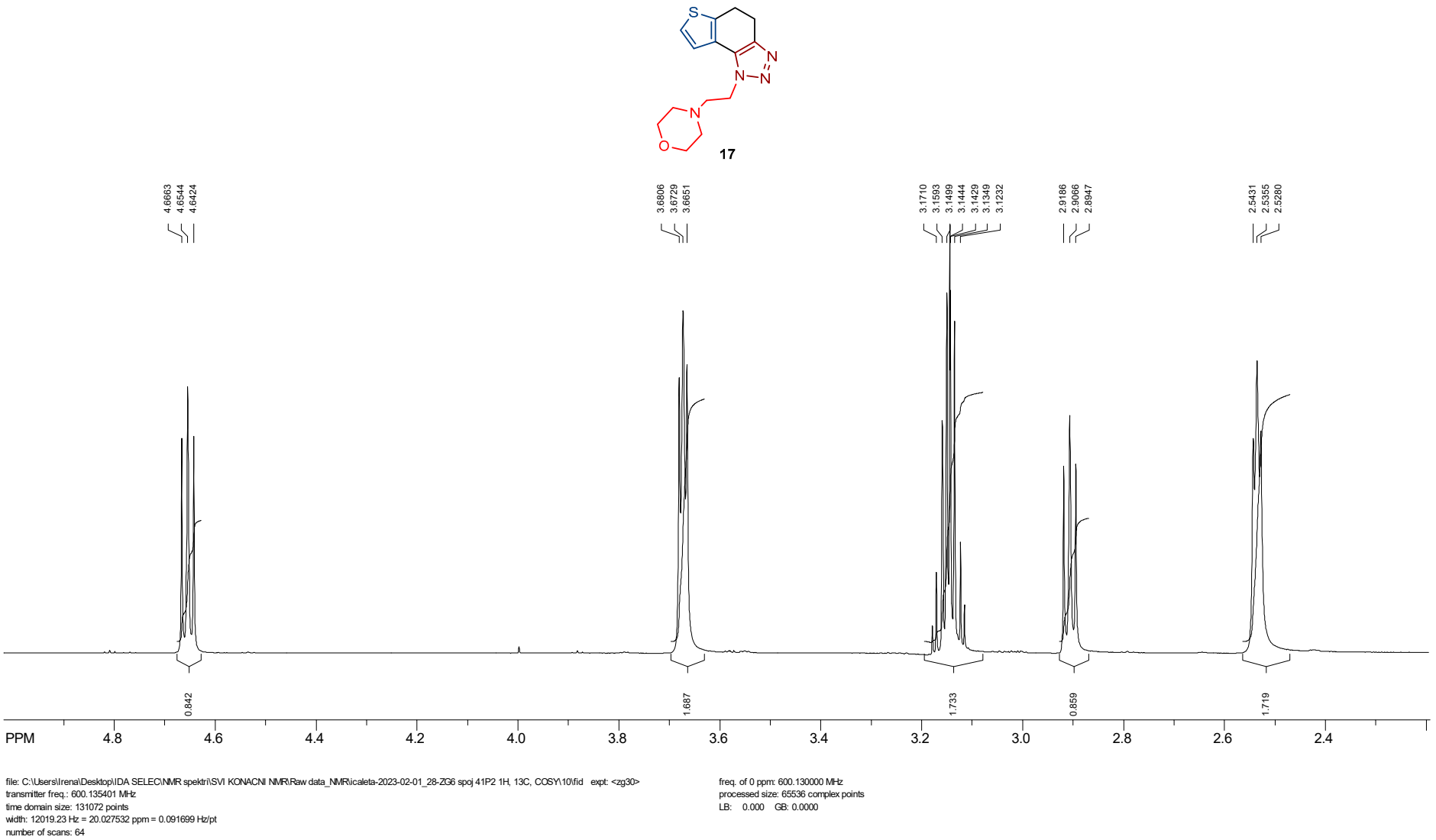


Figure S53. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **17**.

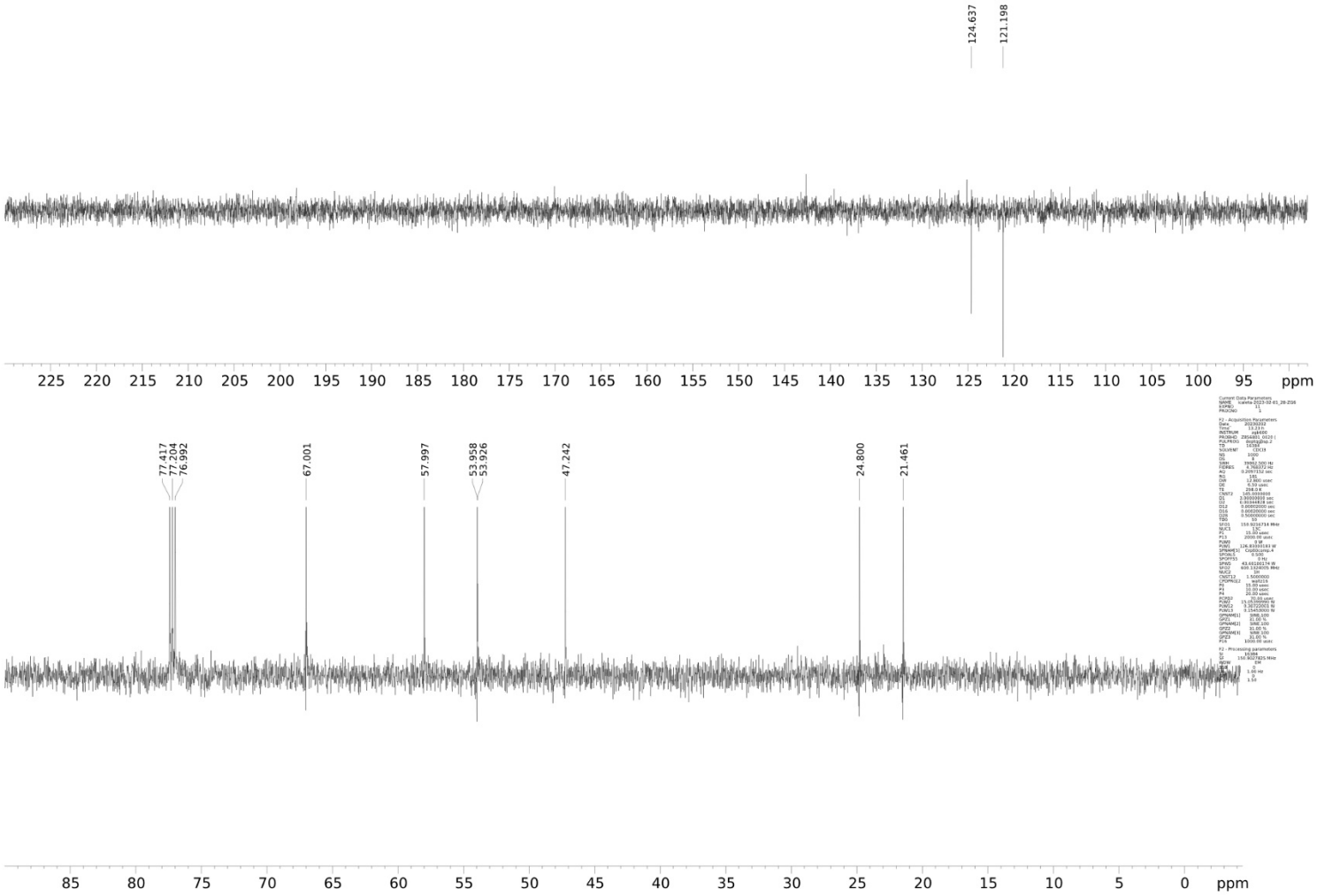


Figure S54. ^{13}C NMR spectrum ($CDCl_3$) of compound **17**.

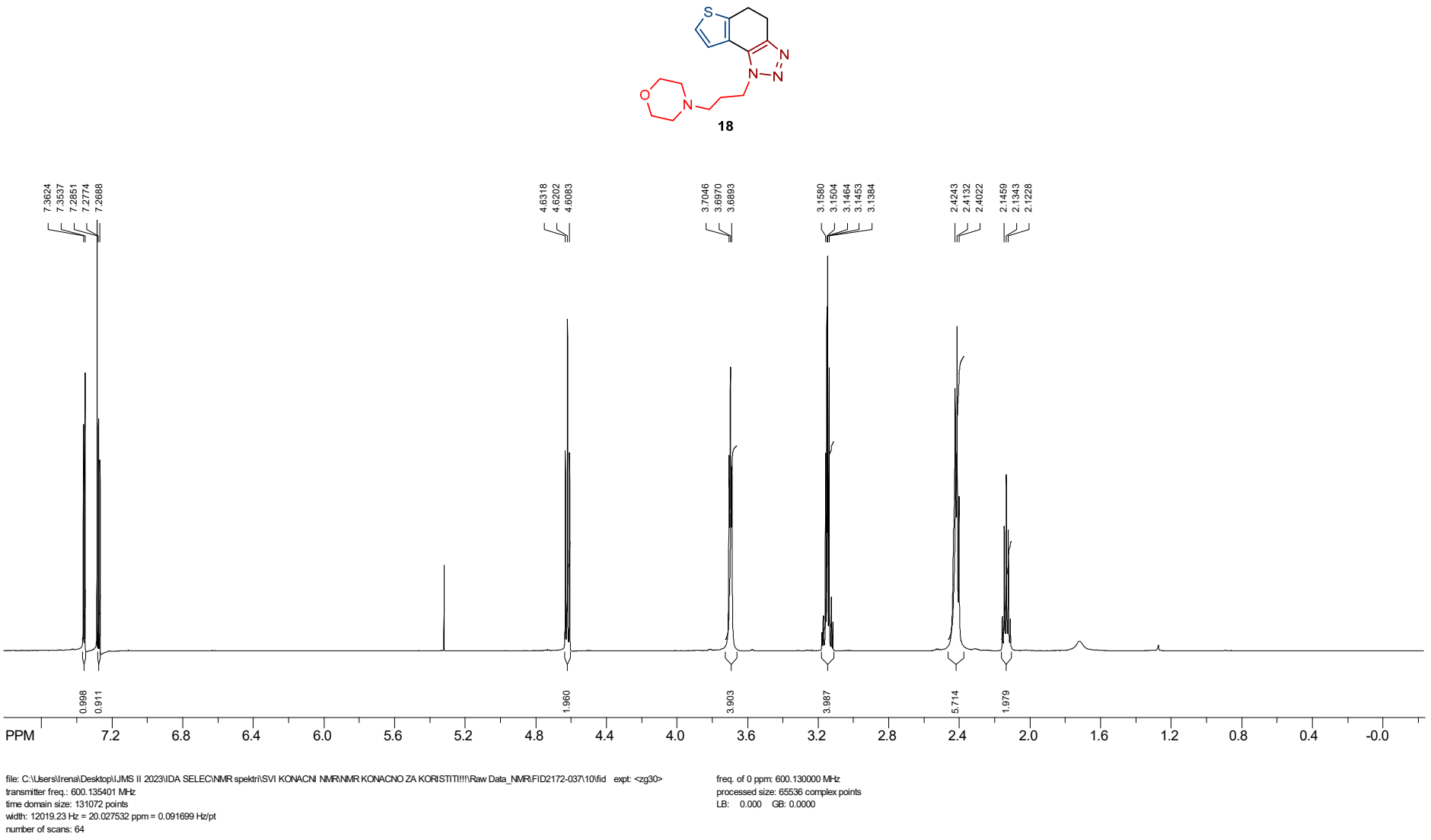


Figure S55. ^{1}H NMR spectrum ($CDCl_3$) of compound **18**.

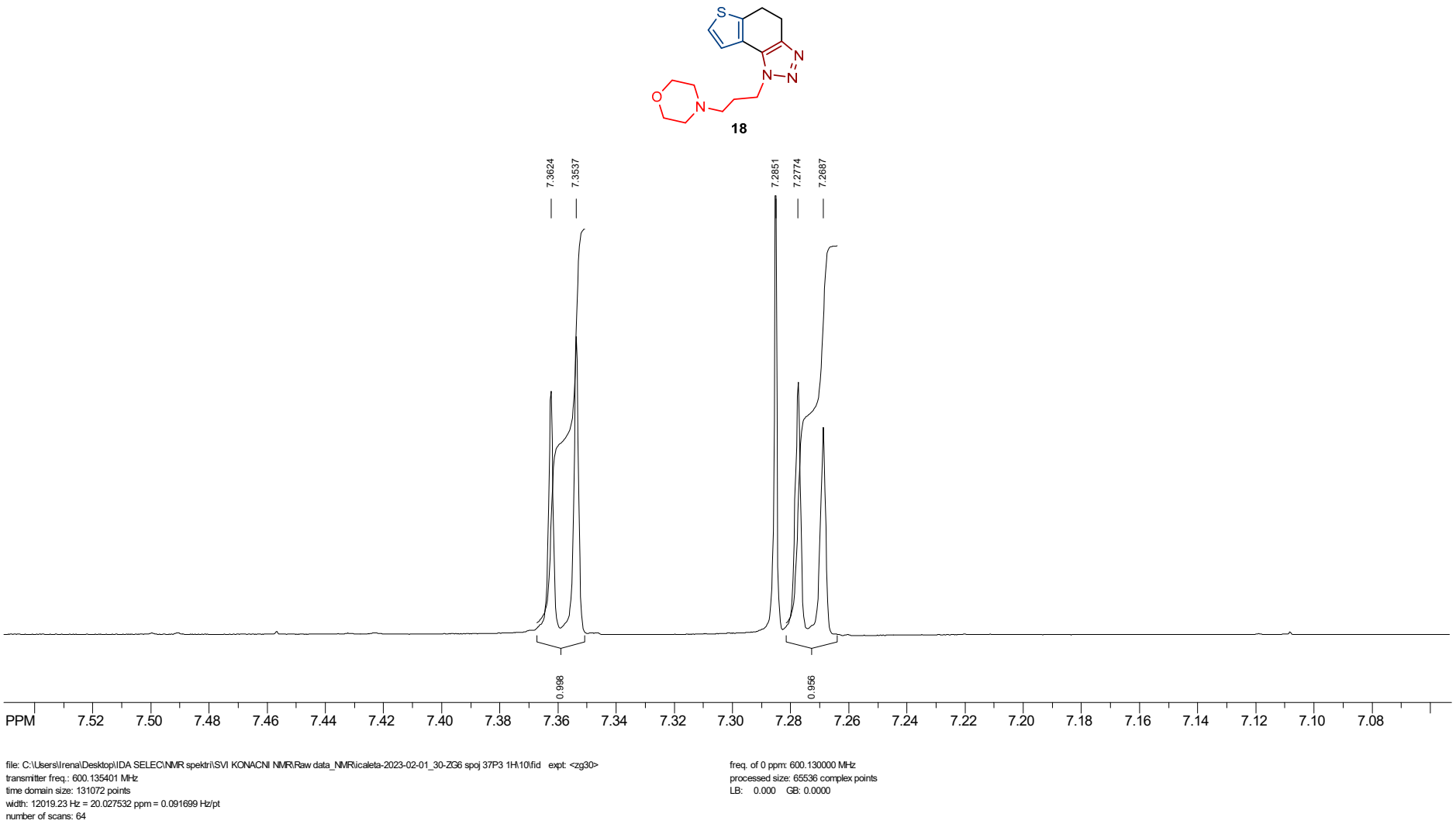


Figure S56. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **18**.

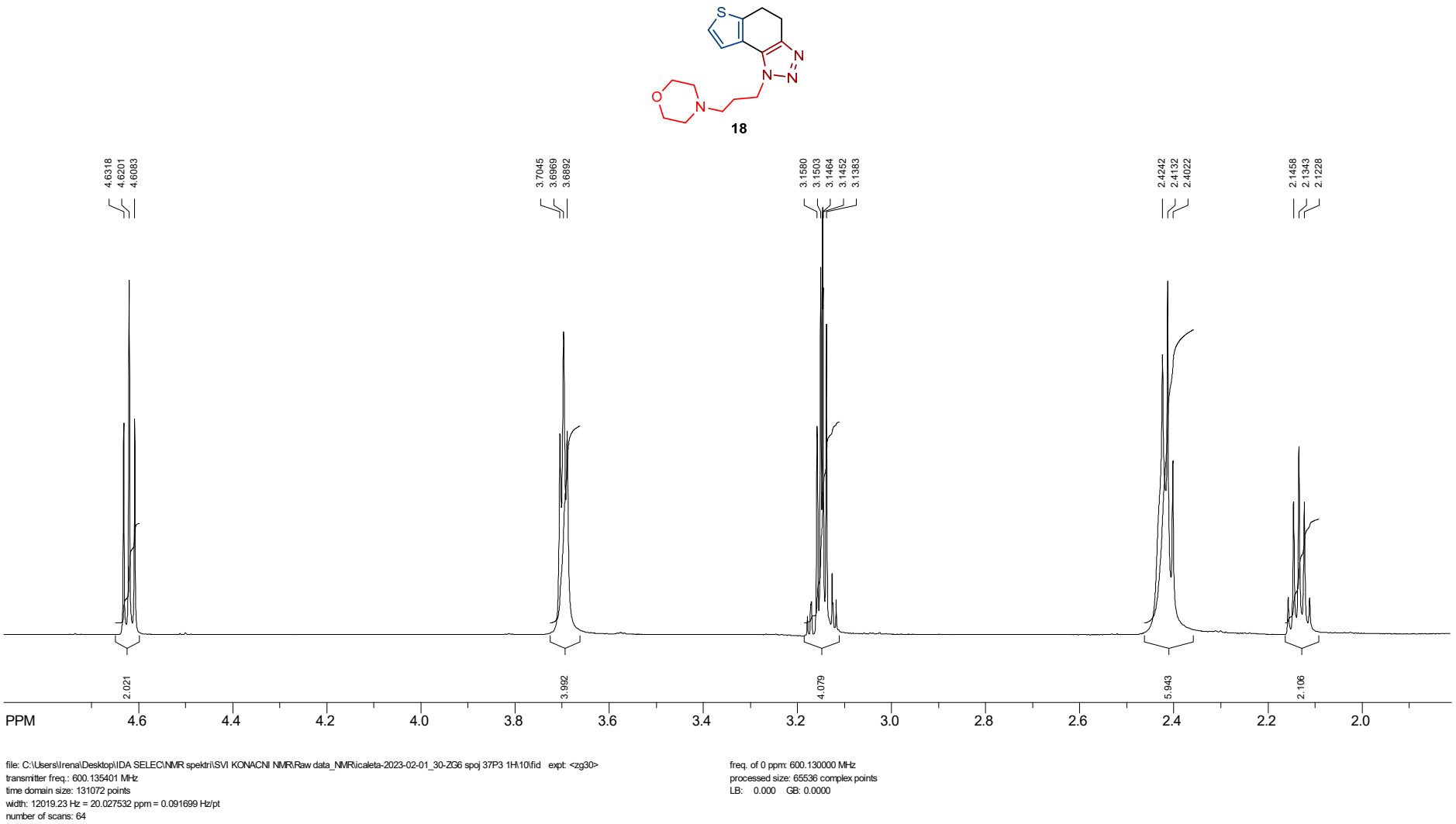


Figure S57. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **18**.

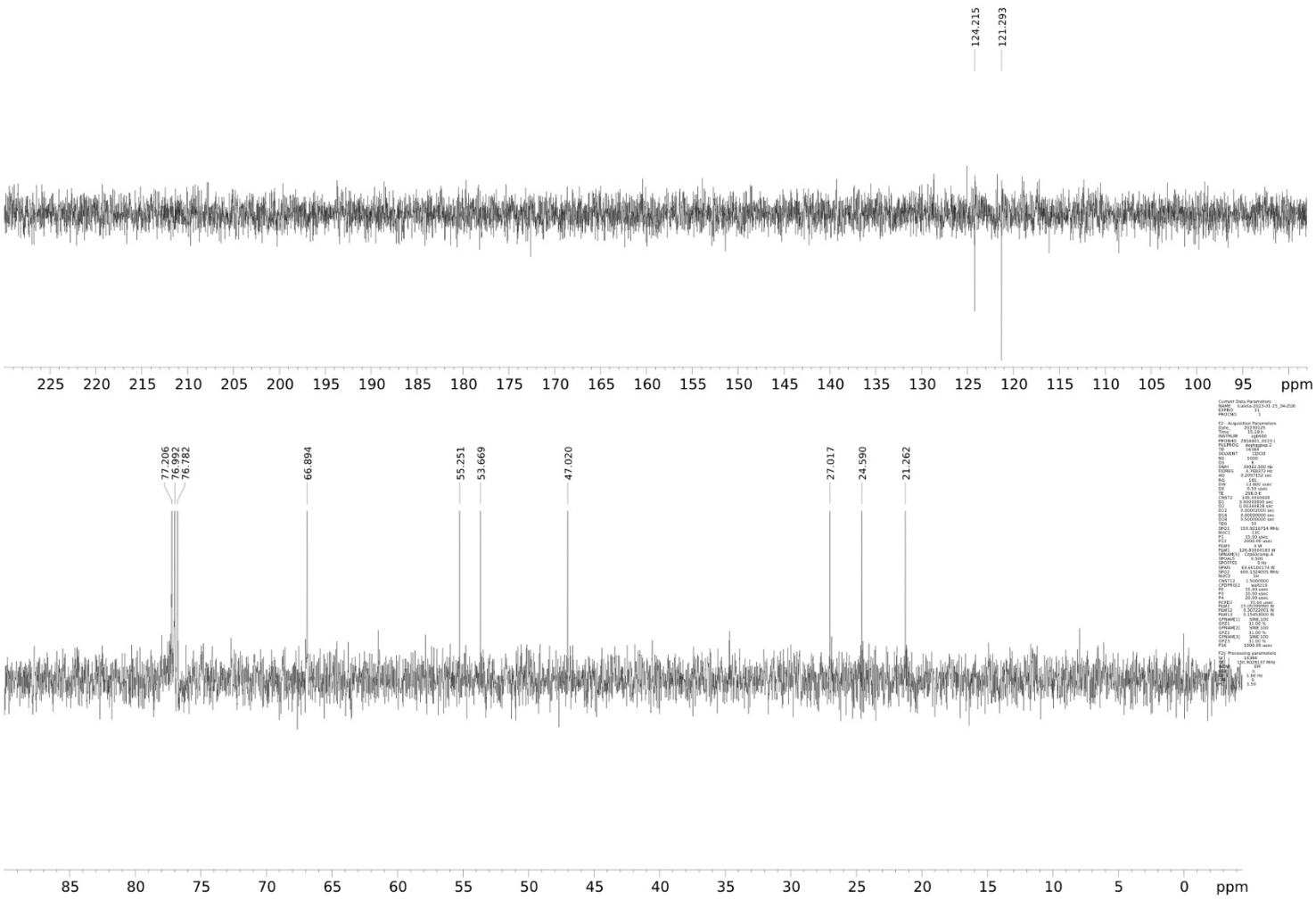


Figure S58. ^{13}C NMR spectrum ($CDCl_3$) of compound **18**.

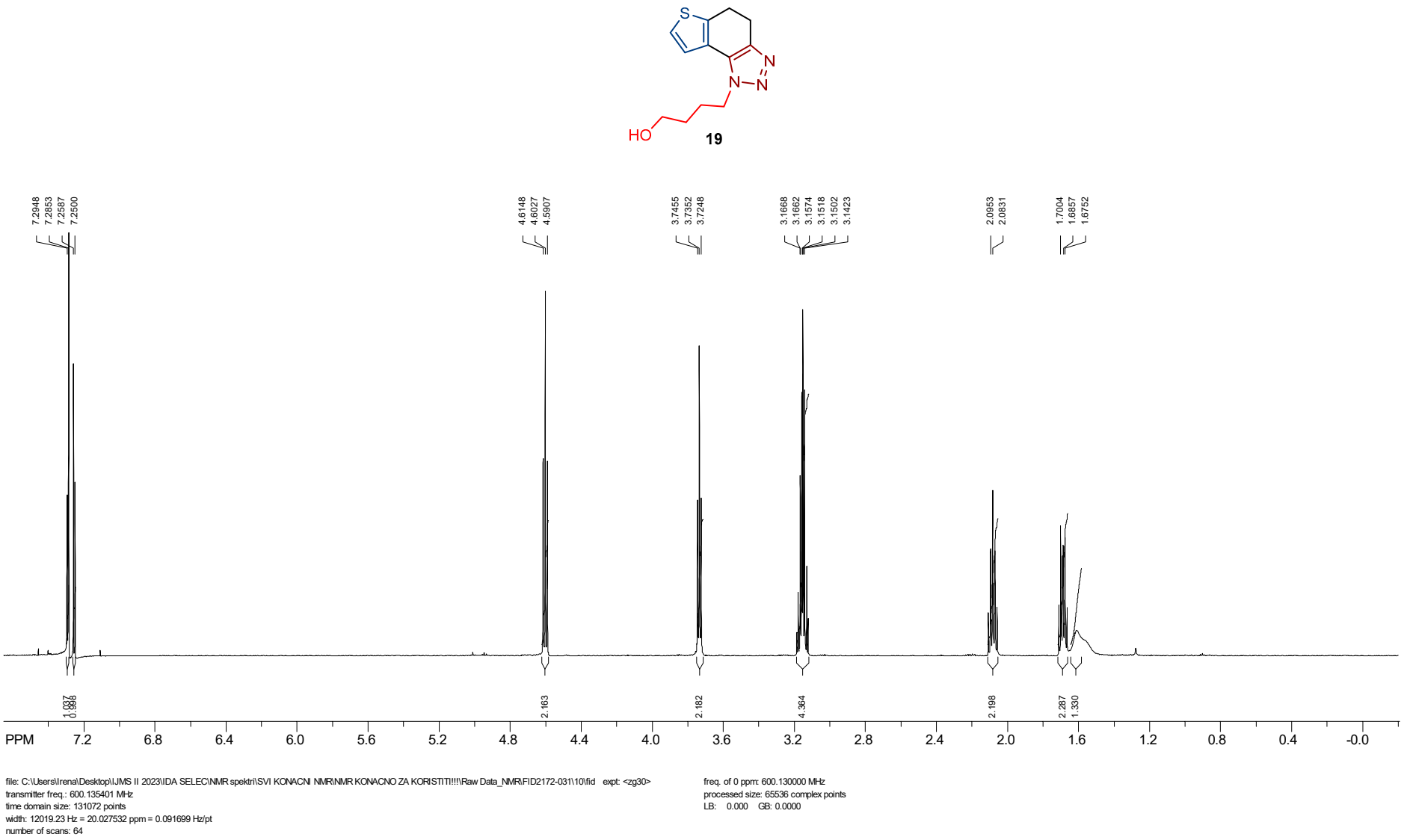


Figure S59. ^{1}H NMR spectrum ($CDCl_3$) of compound **19**.

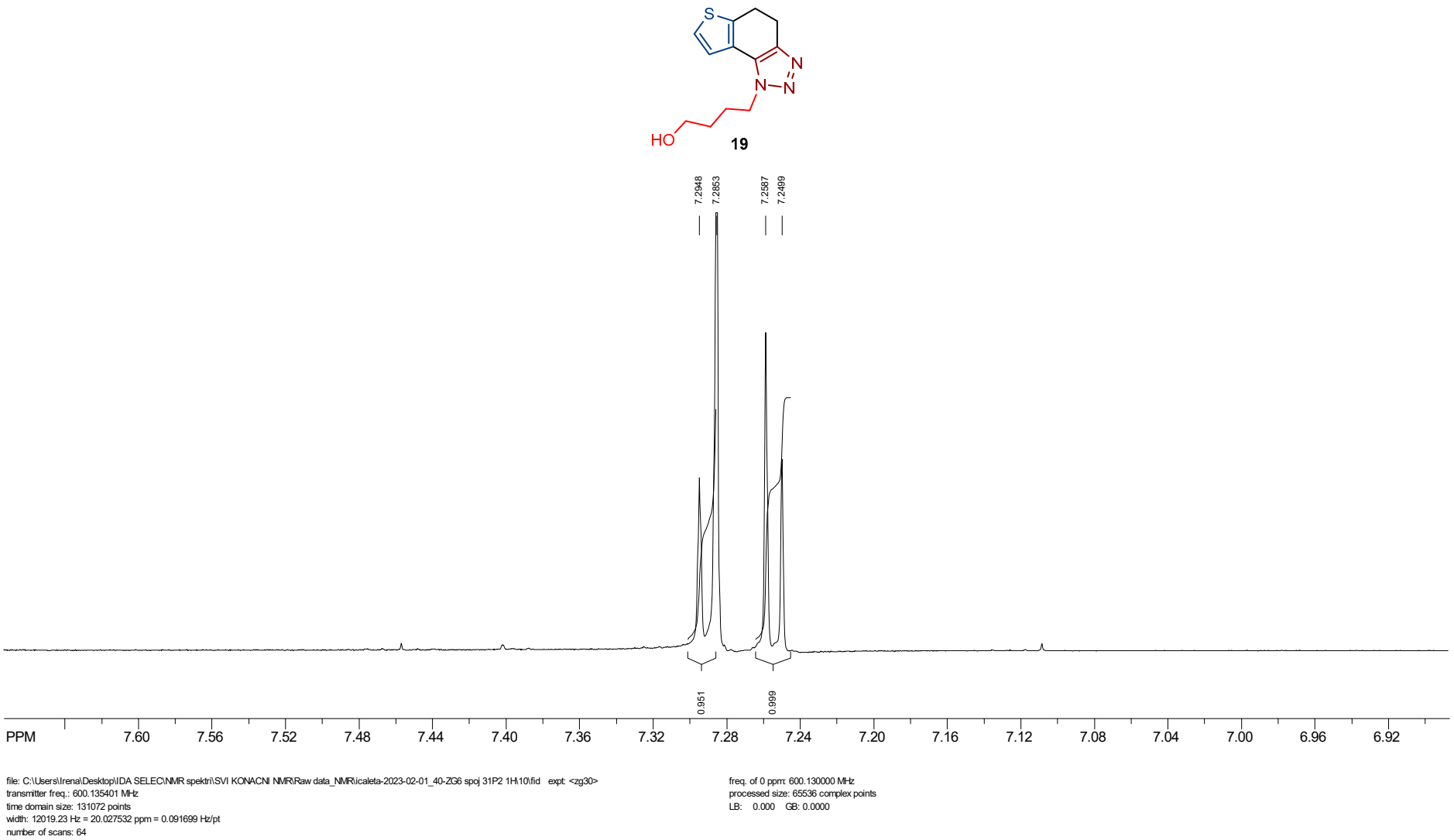


Figure S60. Aromatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **19**.

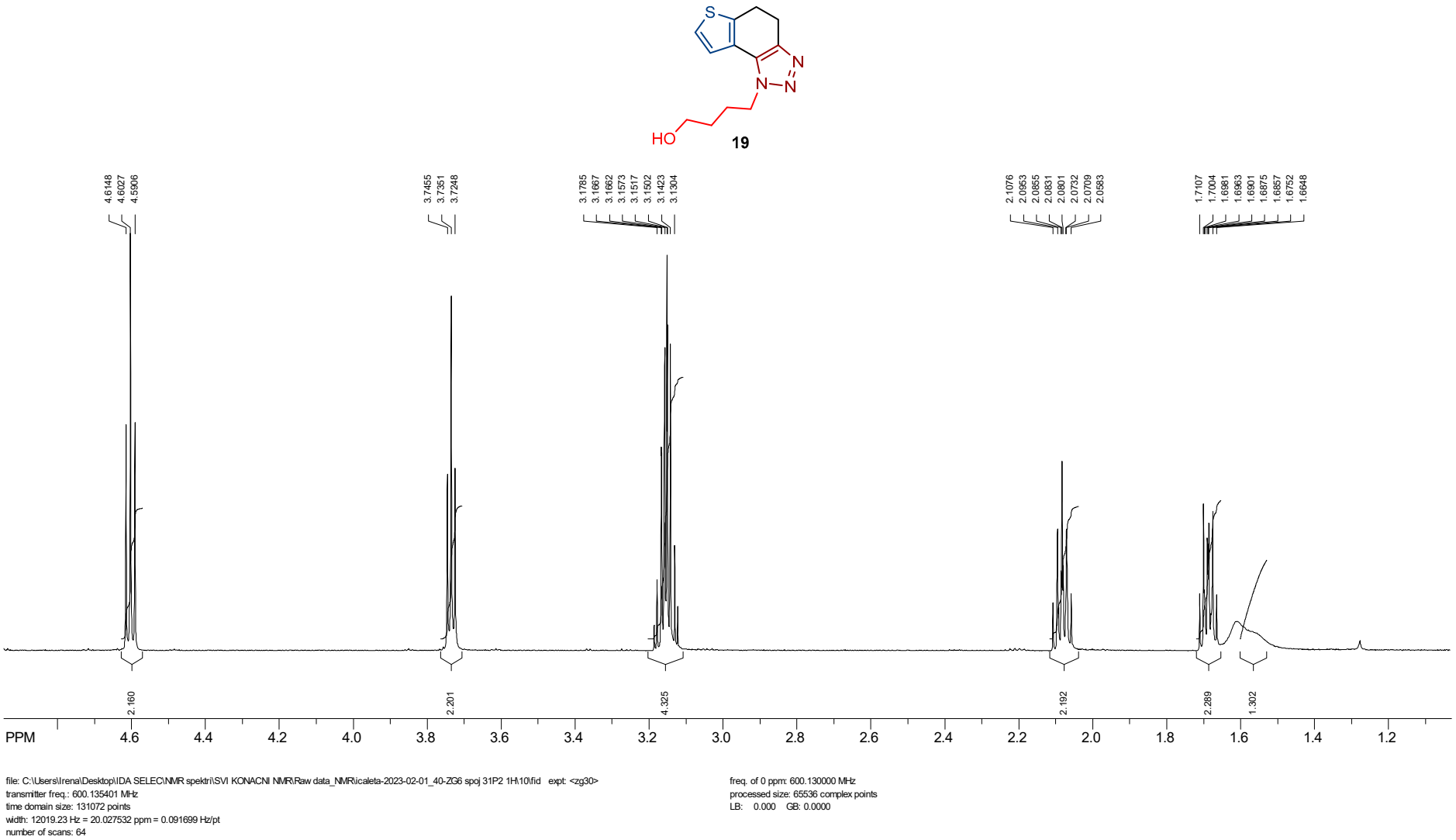


Figure S61. Aliphatic part of the ^{1}H NMR spectrum ($CDCl_3$) of compound **19**.

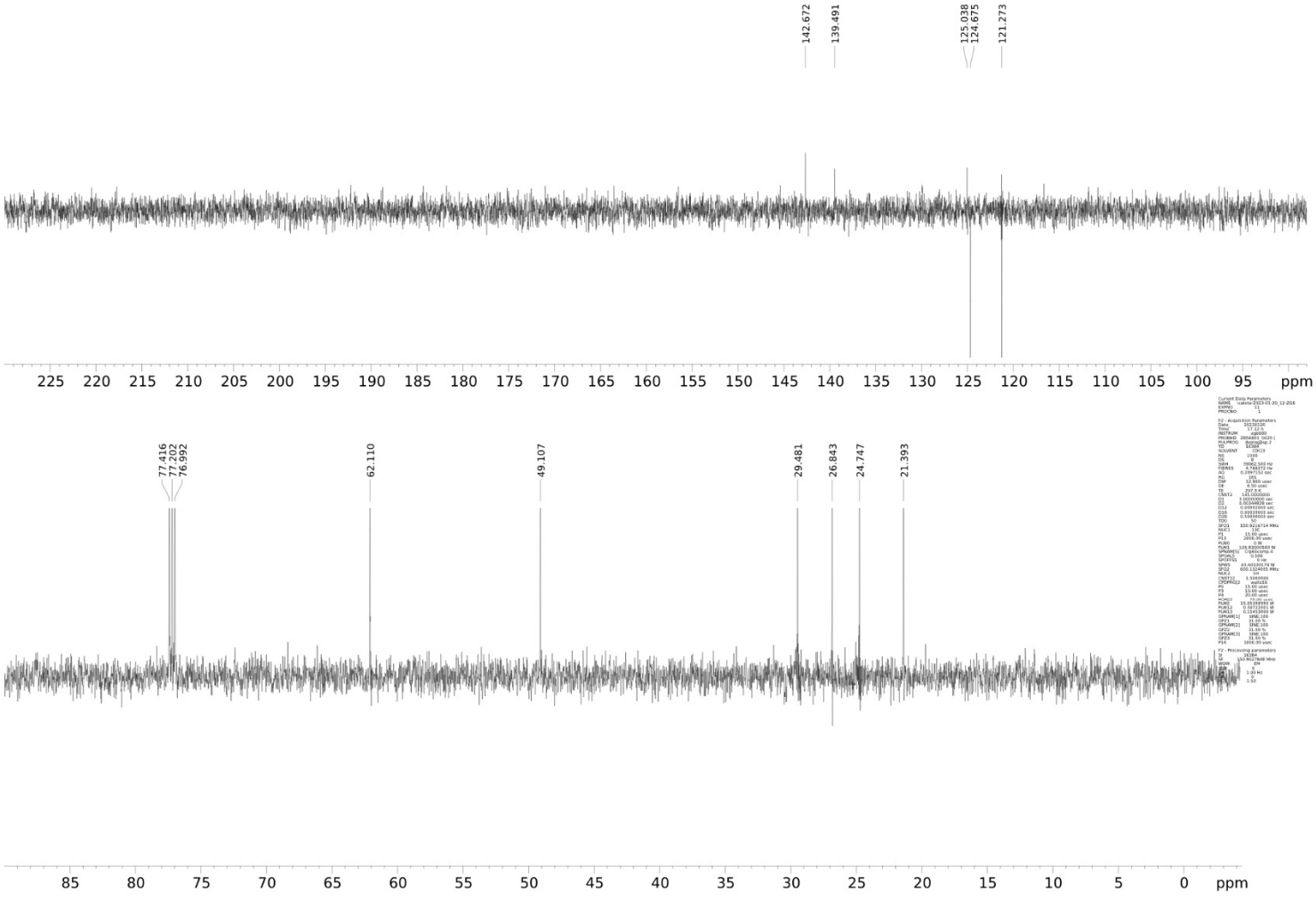
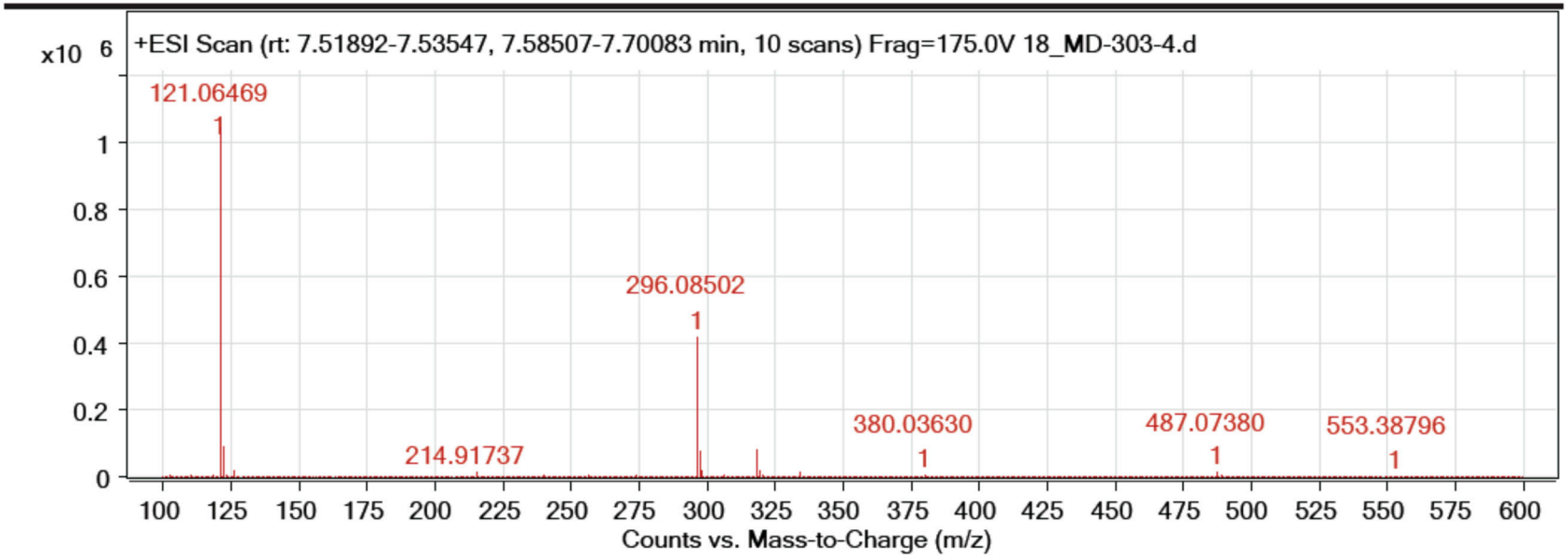


Figure S62. ^{13}C NMR spectrum ($CDCl_3$) of compound **19**.

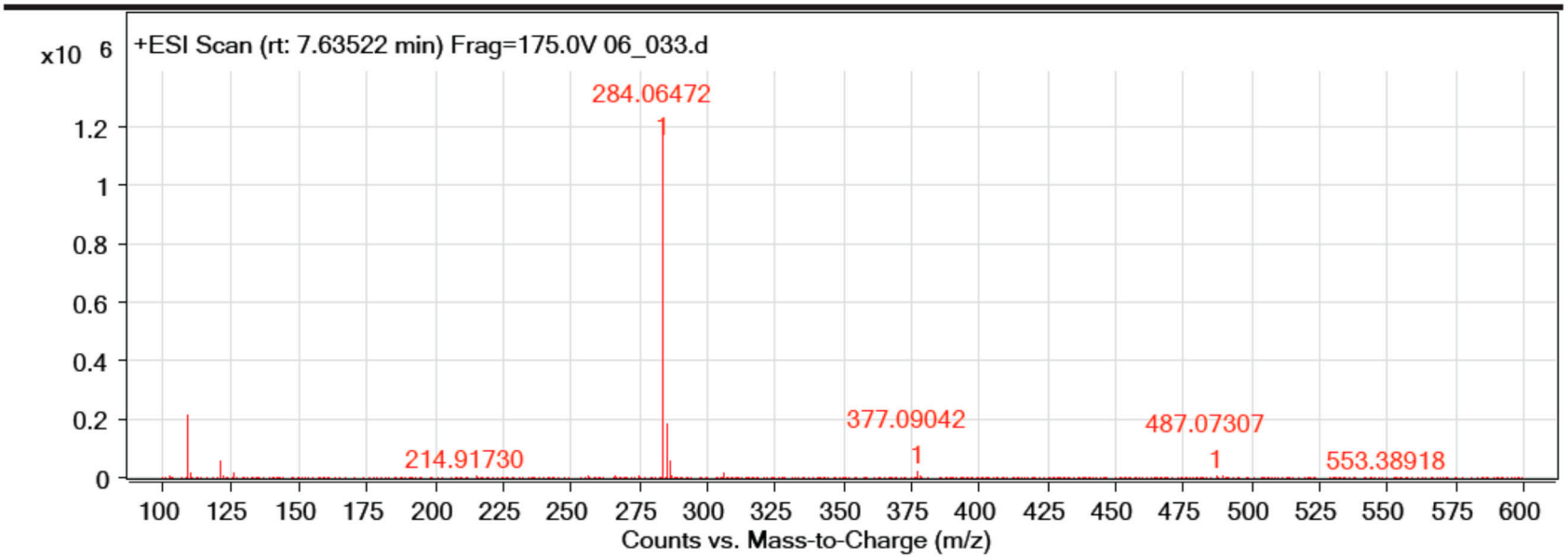
2. MS spectra and HRMS analyses of synthesized compounds



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C16 H13 N3 O S	True	295.07774	295.07793	0.66	C16 H14 N3 O S	98.78

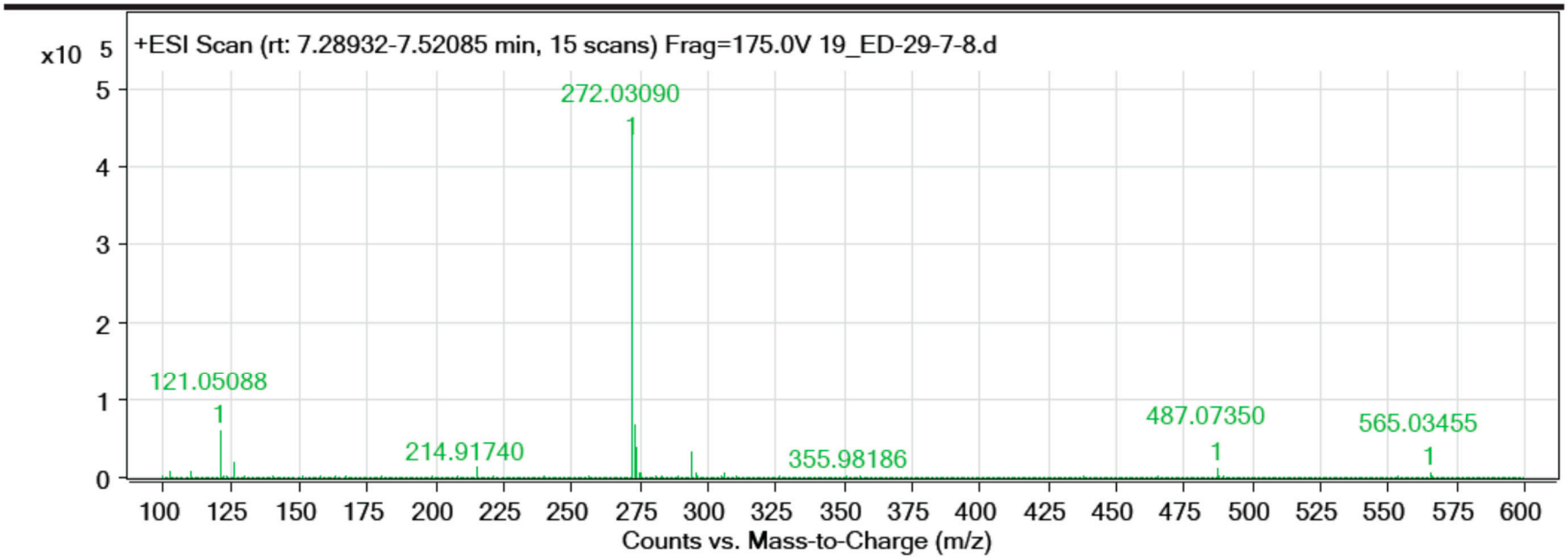
Figure S63. Mass spectrum and the result of the HRMS analysis for compound **3**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H10 F N3 S	True	283.05749	283.05795	1.6	C15 H11 F N3 S	97.27

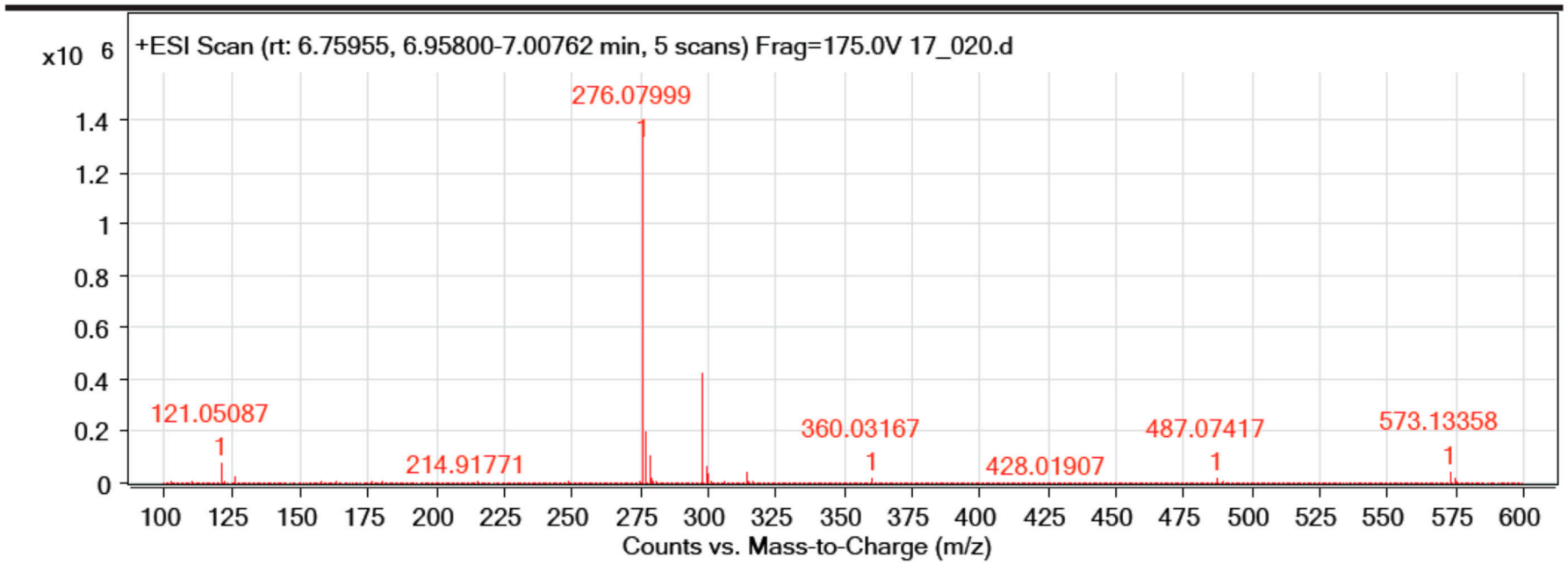
Figure S64. Mass spectrum and the result of the HRMS analysis for compound **4**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C13 H9 N3 S2	True	271.02361	271.02379	0.66	C13 H10 N3 S2	97.99

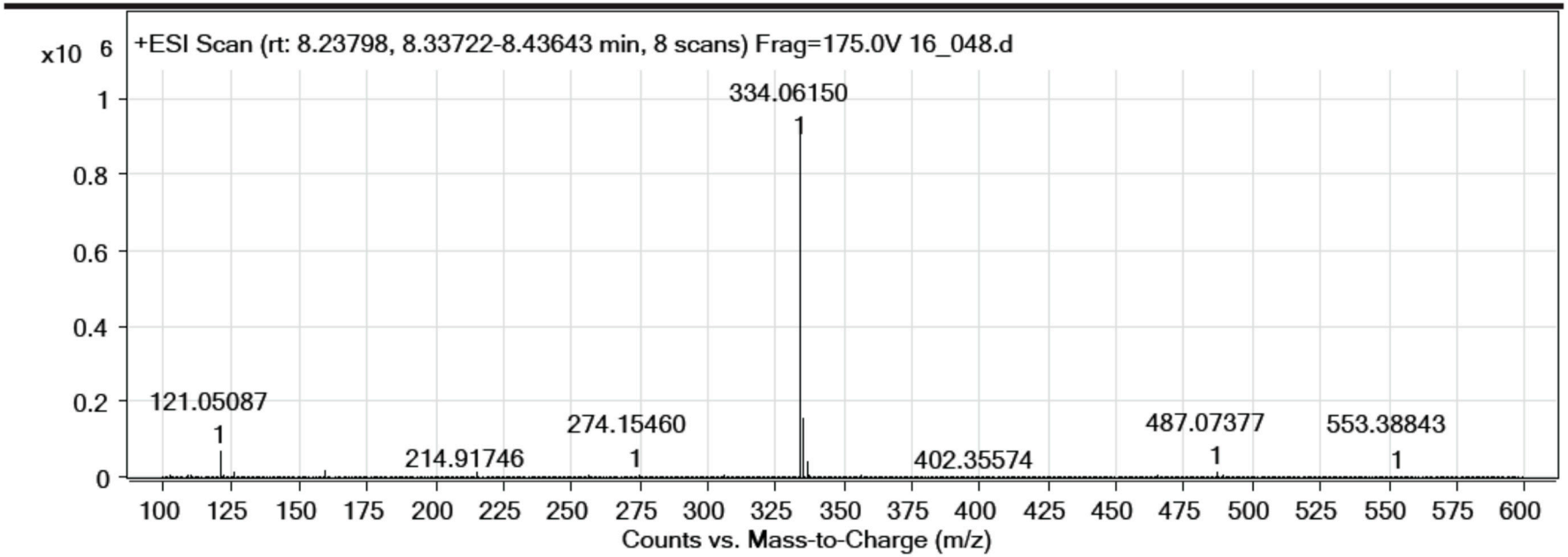
Figure S65. Mass spectrum and the result of the HRMS analysis for compound **5**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C13 H13 N3 O2 S	True	275.07275	275.07285	0.35	C13 H14 N3 O2 S	92.17

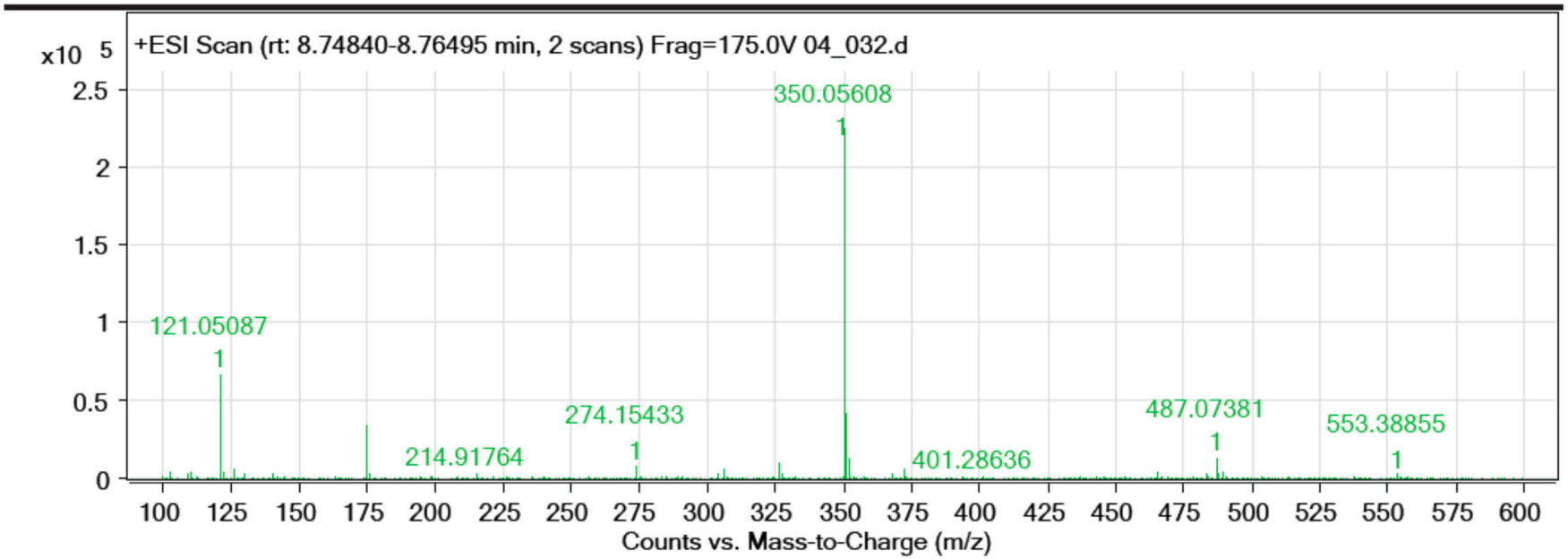
Figure S66. Mass spectrum and the result of the HRMS analysis for compound **6**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C16 H10 F3 N3 S	True	333.05423	333.05475	1.57	C16 H11 F3 N3 S	96.49

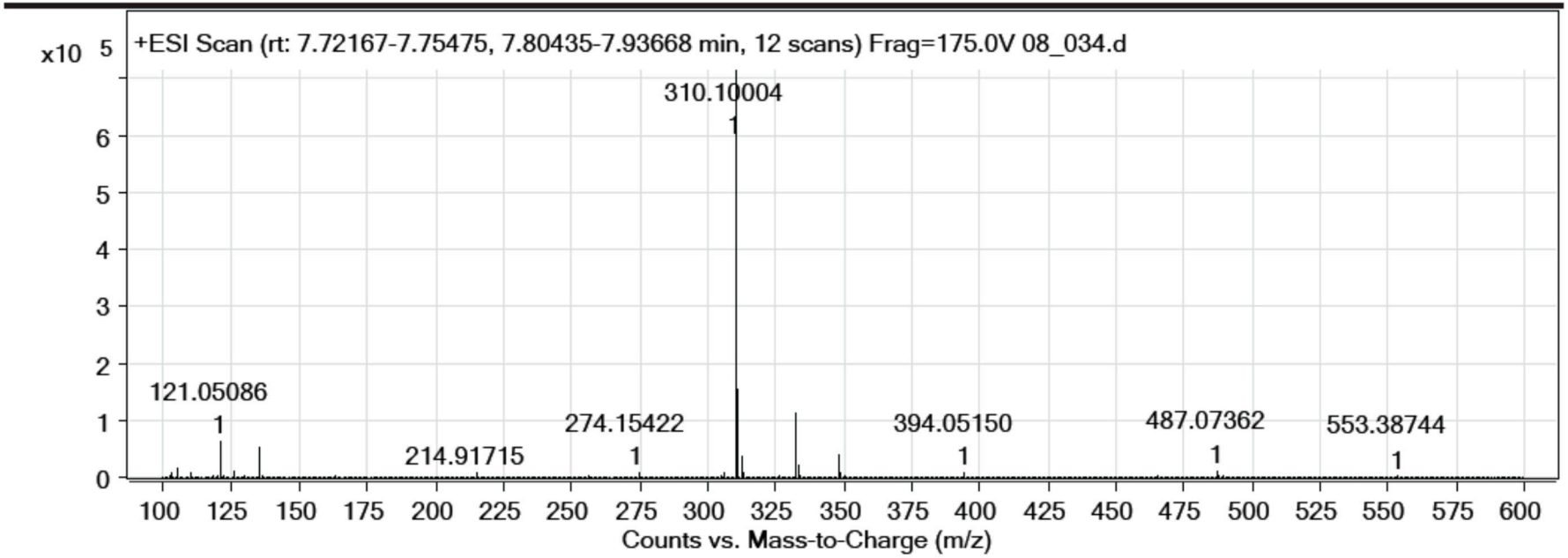
Figure S67. Mass spectrum and the result of the HRMS analysis for compound **7**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C16 H10 F3 N3 O S	True	349.04885	349.04967	2.33	C16 H11 F3 N3 O S	97.62

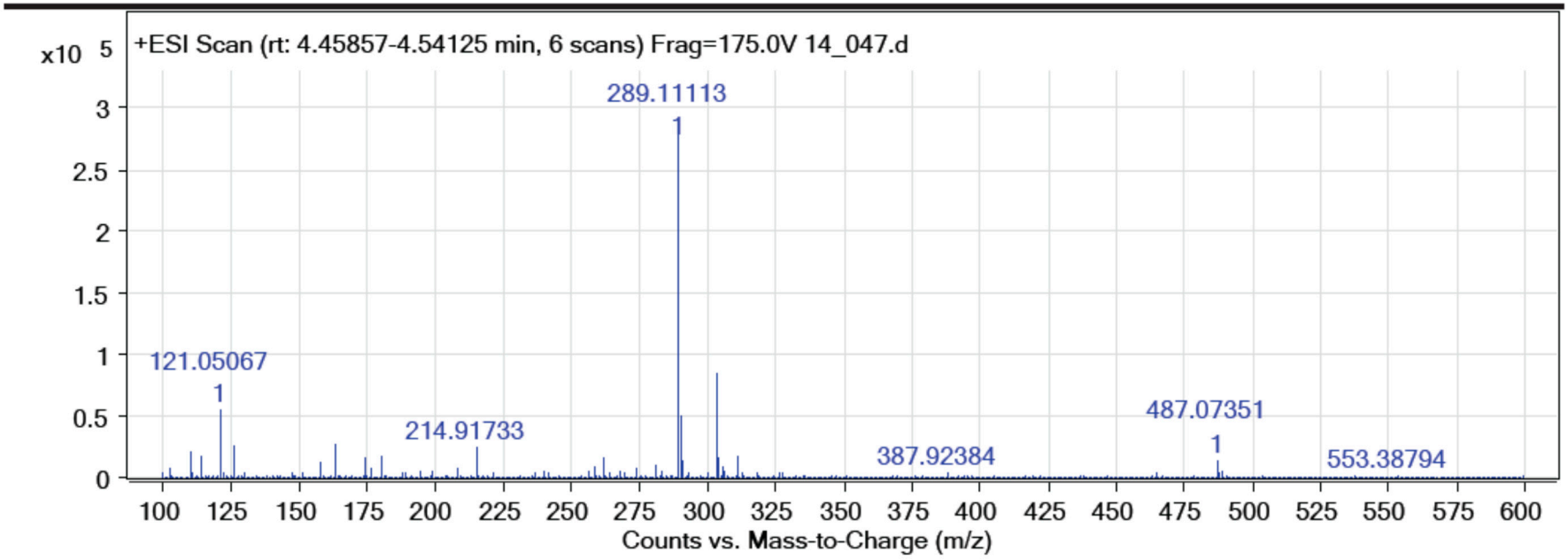
Figure S68. Mass spectrum and the result of the HRMS analysis for compound **8**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C17 H15 N3 O S	True	309.0928	309.09358	2.53	C17 H16 N3 O S	95.06

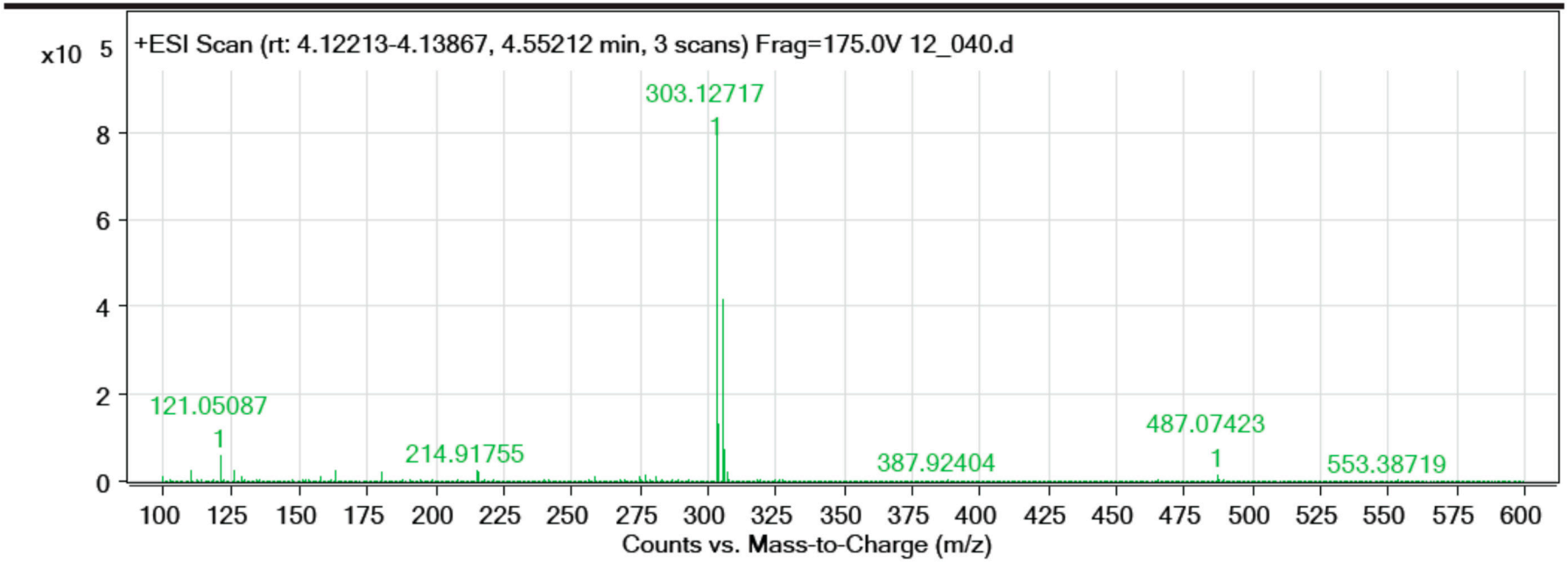
Figure S69. Mass spectrum and the result of the HRMS analysis for compound **9**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C14 H16 N4 O S	True	288.10402	288.10448	1.62	C14 H17 N4 O S	96.71

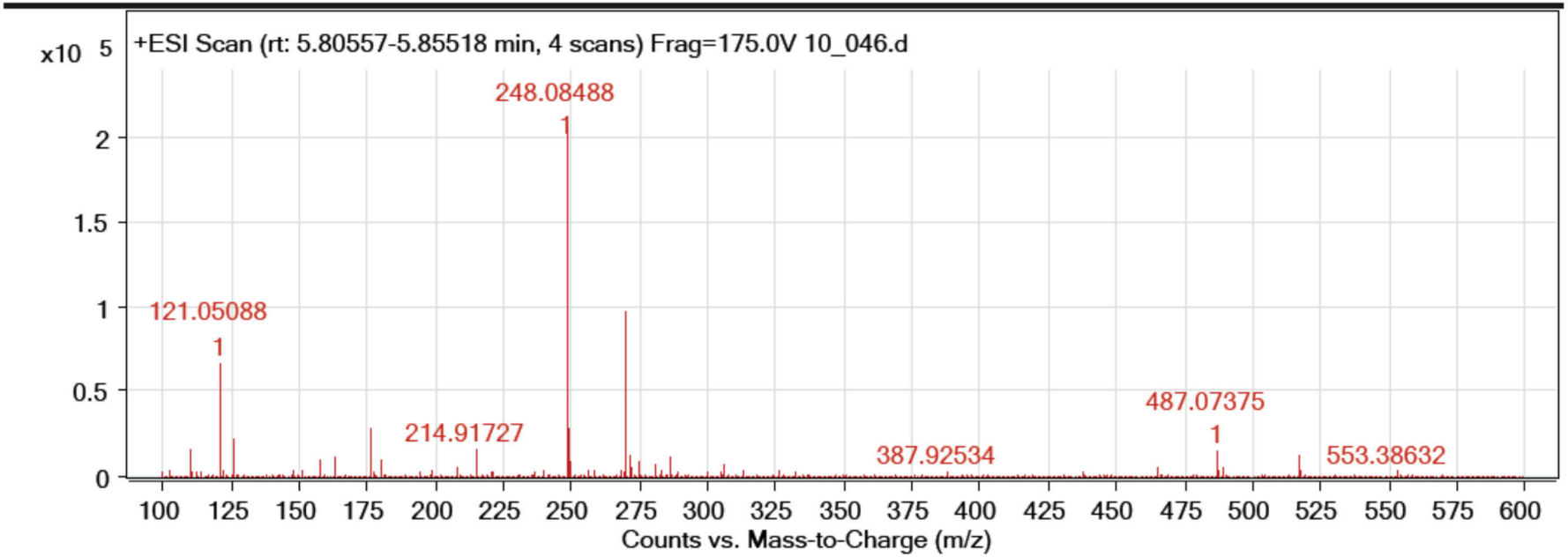
Figure S70. Mass spectrum and the result of the HRMS analysis for compound **10**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H18 N4 O S	True	302.11994	302.12013	0.62	C15 H19 N4 O S	95.53

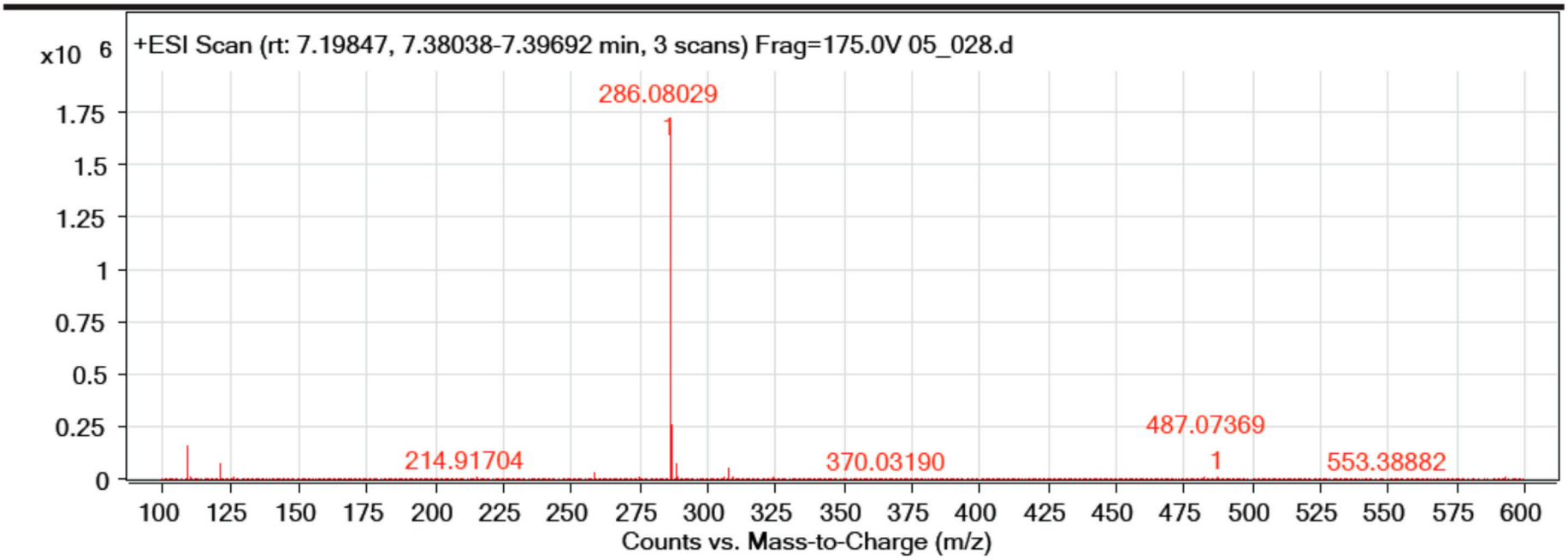
Figure S71. Mass spectrum and the result of the HRMS analysis for compound **11**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C12 H13 N3 O S	True	247.07759	247.07793	1.38	C12 H14 N3 O S	98.63

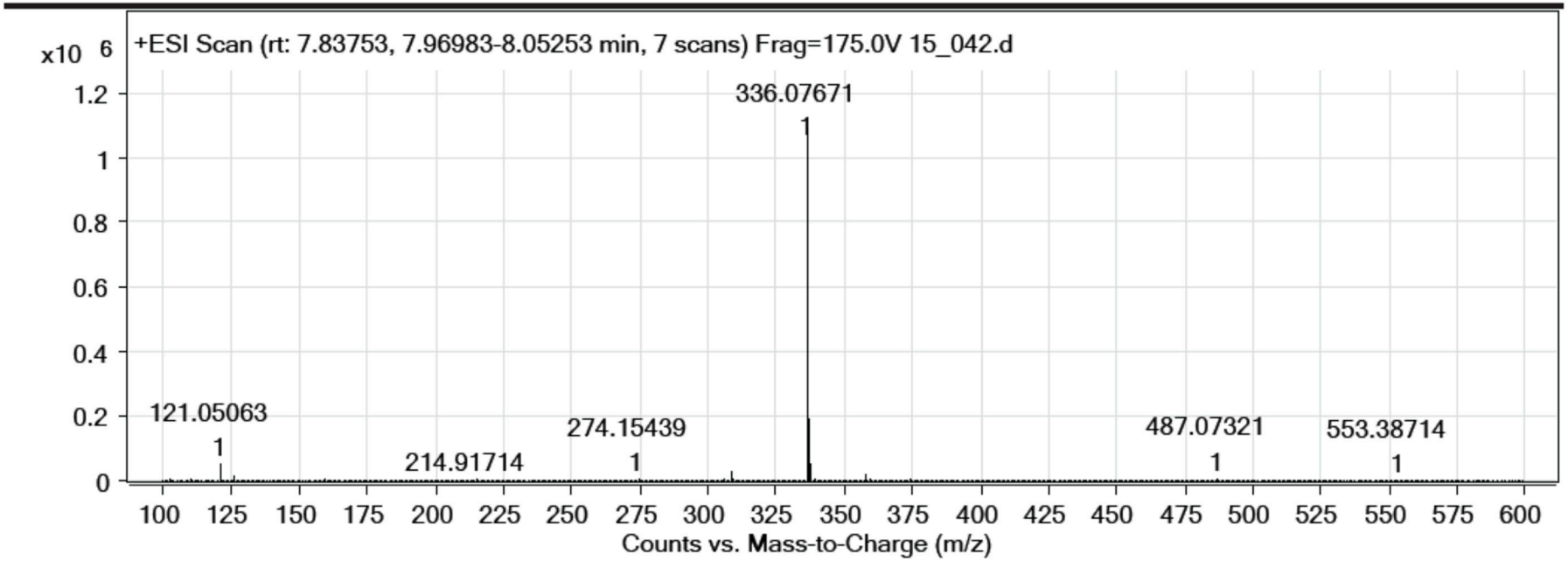
Figure S72. Mass spectrum and the result of the HRMS analysis for compound **12**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H12 F N3 S	True	285.07306	285.0736	1.88	C15 H13 F N3 S	96.38

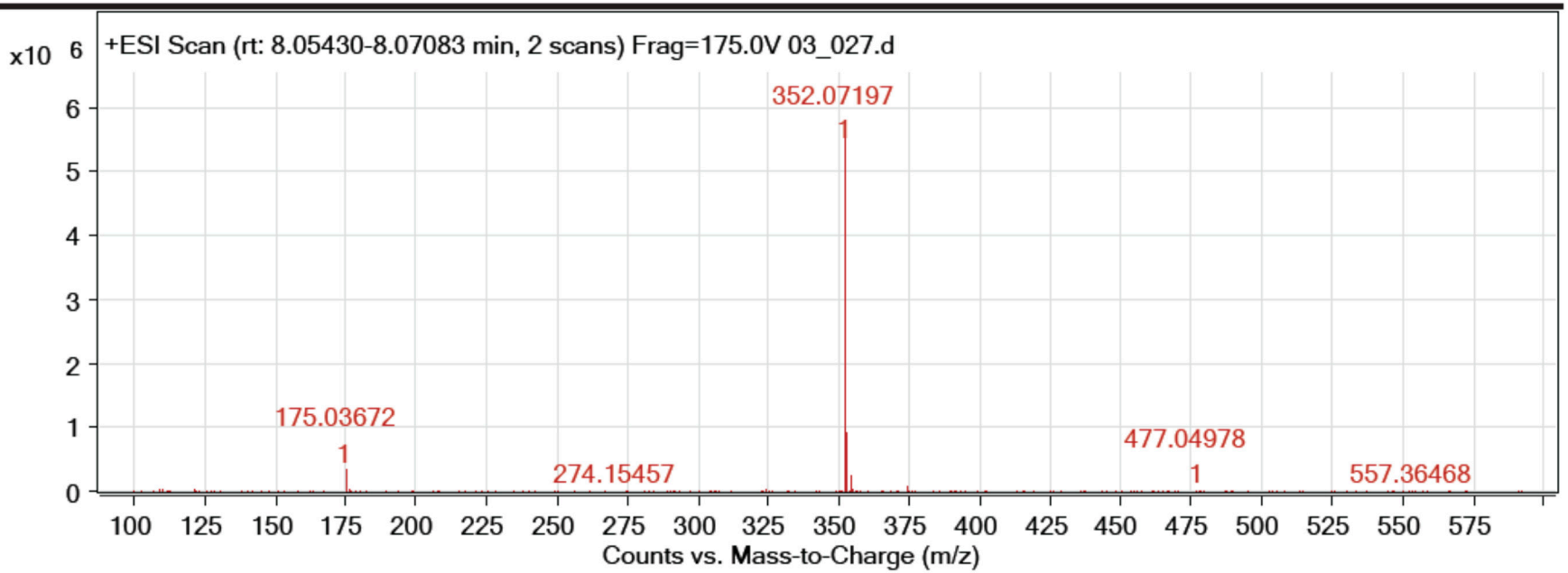
Figure S73. Mass spectrum and the result of the HRMS analysis for compound **13**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C16 H12 F3 N3 S	True	335.06947	335.0704	2.78	C16 H13 F3 N3 S	95.91

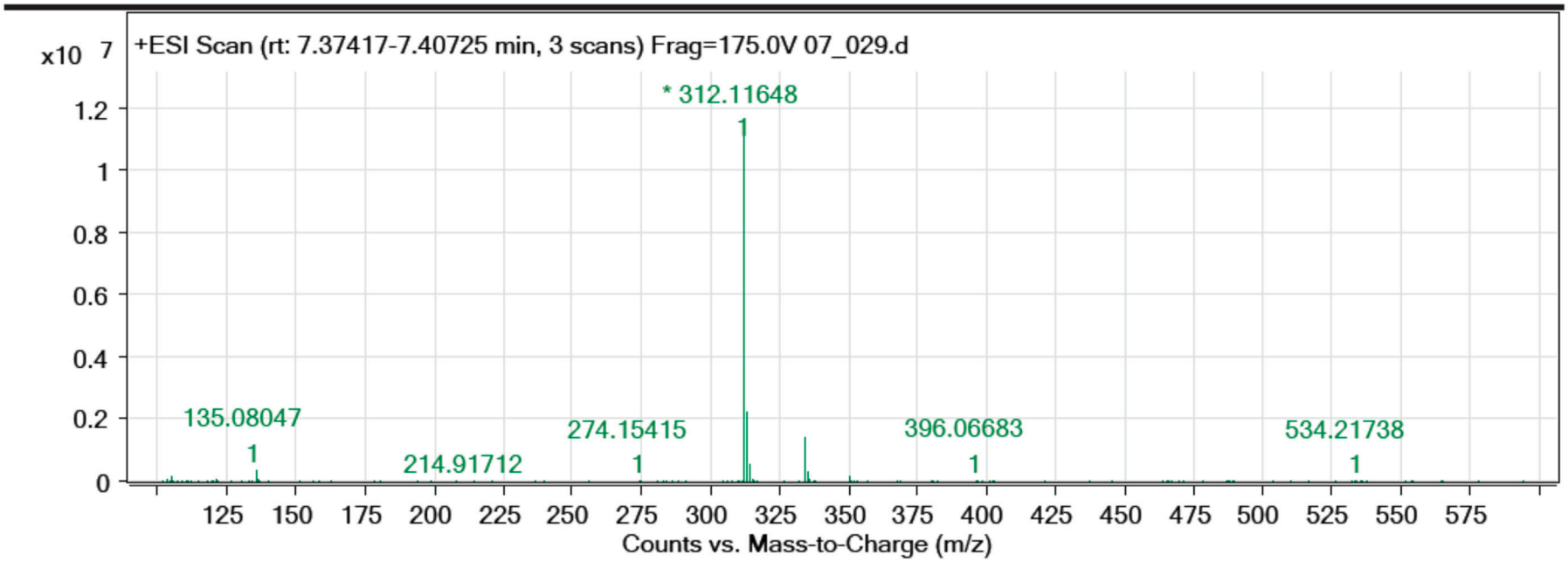
Figure S74. Mass spectrum and the result of the HRMS analysis for compound **14**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C16 H11 F3 N3 O S	True	350.05555	350.05749	5.54	C16 H12 F3 N3 O S	37.49
C16 H12 F3 N3 O S	True	351.06471	351.06532	1.73	C16 H13 F3 N3 O S	95.48

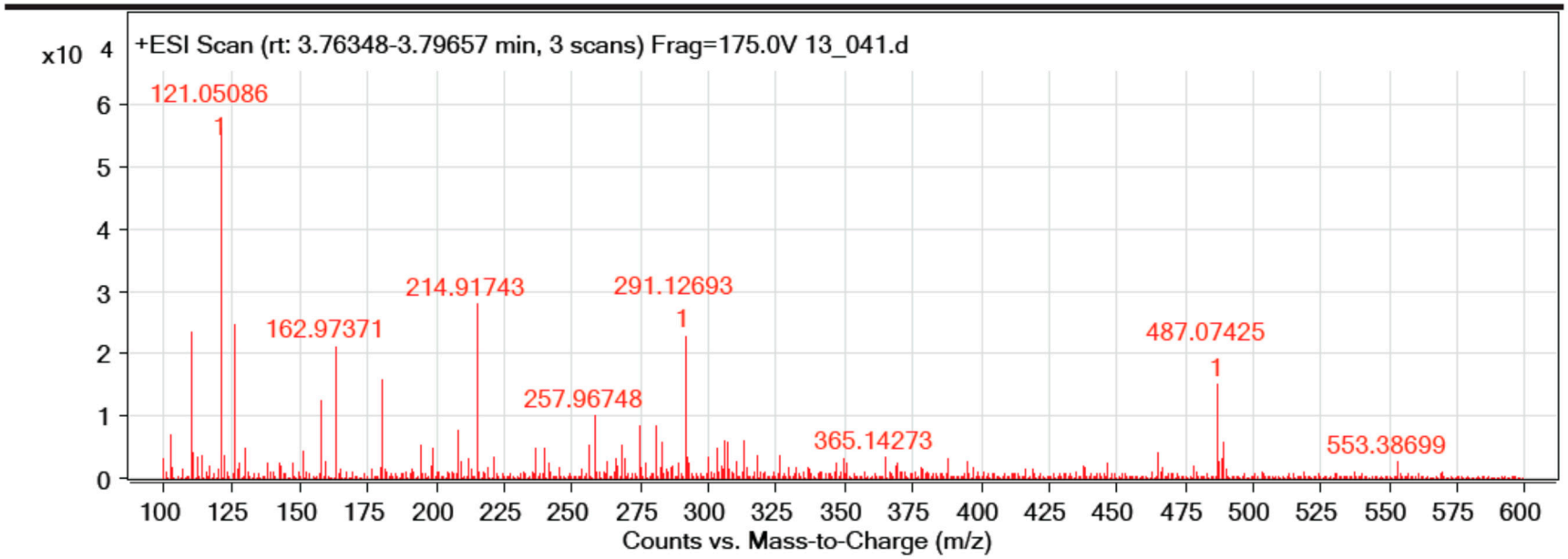
Figure S75. Mass spectrum and the result of the HRMS analysis for compound **15**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C17 H17 N3 O S	True	311.10905	311.10923	0.6	C17 H18 N3 O S	97.23

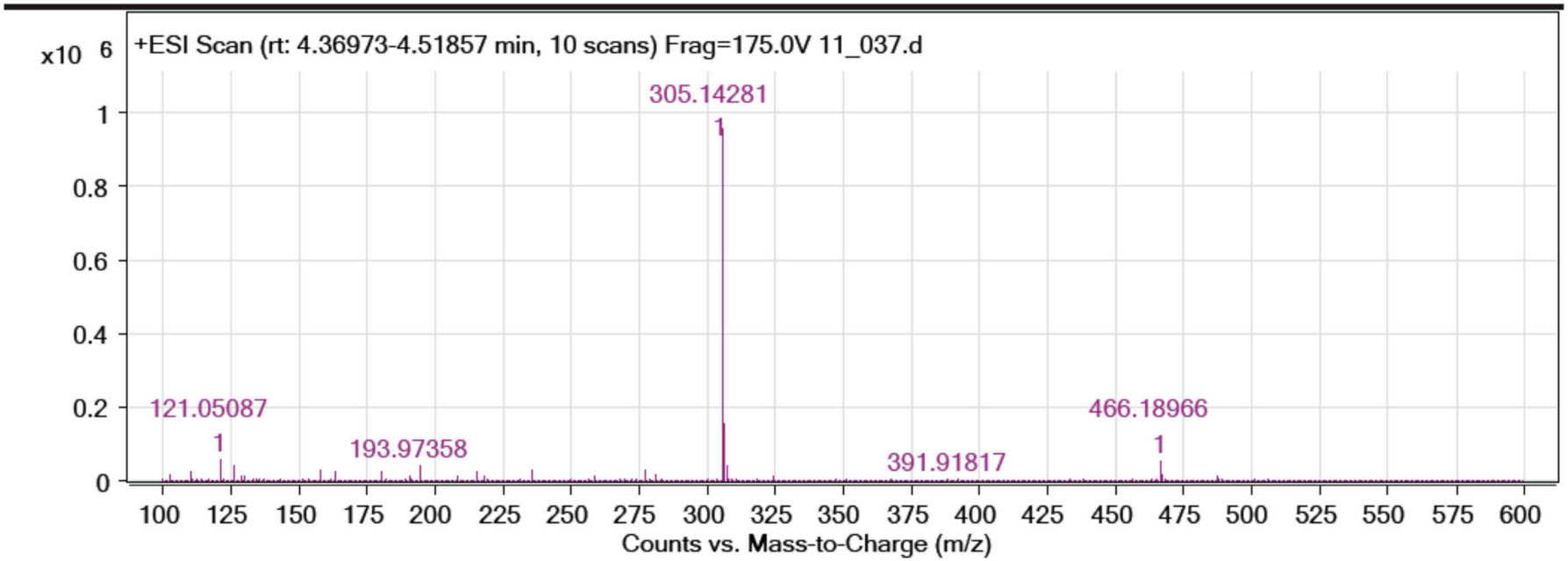
Figure S76. Mass spectrum and the result of the HRMS analysis for compound **16**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C14 H18 N4 O S	True	290.11972	290.12013	1.4	C14 H19 N4 O S	95.24

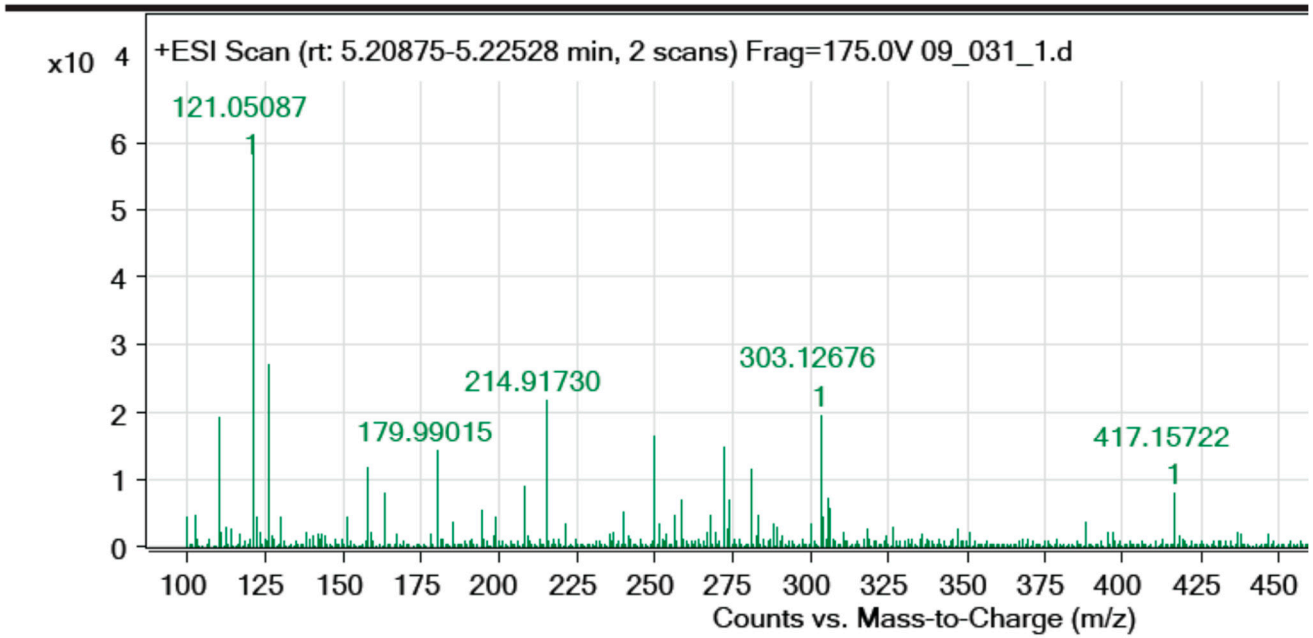
Figure S77. Mass spectrum and the result of the HRMS analysis for compound **17**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C15 H20 N4 O S	True	304.13556	304.13578	0.72	C15 H21 N4 O S	97.77

Figure S78. Mass spectrum and the result of the HRMS analysis for compound **18**.



Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C12 H15 N3 O S	True	249.09357	249.09358	0.04	C12 H16 N3 O S	95.5

Figure S79. Mass spectrum and the result of the HRMS analysis for compound **19**.

3. Cartesian coordinates of ligands docked into AChE and BChE

Molecule 1 docked into AChE

N	0.578	28.912	35.616
C	1.905	28.793	35.904
C	2.488	28.580	34.656
N	1.507	28.569	33.706
N	0.378	28.761	34.294
C	2.683	28.851	37.107
C	4.089	28.691	36.924
C	4.659	28.481	35.619
H	5.752	28.364	35.525
C	3.891	28.422	34.499
H	4.340	28.258	33.505
C	4.925	28.740	38.061
H	6.014	28.620	37.932
C	4.419	28.933	39.324
H	5.091	28.970	40.198
C	3.031	29.082	39.482
C	2.171	29.044	38.409
H	1.086	29.164	38.565
Cl	2.388	29.317	41.085
C	-0.572	29.066	36.515
H	-0.217	28.923	37.562
C	-1.609	27.986	36.211
H	-2.483	28.103	36.894
H	-1.174	26.960	36.257
H	-1.912	27.984	35.138
C	-1.157	30.469	36.399
H	-2.031	30.586	37.082
H	-1.418	30.723	35.345
H	-0.386	31.255	36.574

Molecule 4 docked into AChE

C	-2.482	28.098	35.517
H	-3.478	27.893	35.944
C	-2.134	27.555	34.279
C	-0.872	27.818	33.747
H	-0.592	27.387	32.771
C	0.038	28.617	34.431
H	1.034	28.829	34.007
C	-0.337	29.141	35.659
C	-1.583	28.895	36.216
H	-1.855	29.324	37.195
F	0.535	29.905	36.331
C	-3.121	26.710	33.499
H	-3.334	25.753	34.029
H	-4.140	27.161	33.524
N	-2.696	26.465	32.138
N	-2.517	25.195	31.706
N	-2.103	25.213	30.492
C	-1.992	26.522	30.090
C	-1.588	27.057	28.845
H	-1.298	26.397	28.010
C	-2.365	27.345	31.156
C	-1.567	28.422	28.707
H	-1.263	28.877	27.749
C	-1.938	29.247	29.802
C	-2.342	28.755	31.054
S	-1.952	30.986	29.796
C	-2.647	29.802	31.988
H	-2.977	29.625	33.026
C	-2.482	31.033	31.445
H	-2.666	31.970	31.997

Molecule 17 docked into AChE

S	3.274	28.938	39.542
C	2.961	28.674	37.870
C	1.712	29.137	37.525
C	1.008	29.724	38.624

```
H     -0.002  30.160  38.547
C      1.733  29.680  39.777
H      1.378  30.072  40.745
C      3.884  27.947  36.923
H      3.734  26.843  36.973
H      4.943  27.993  37.270
C      3.739  28.472  35.479
H      4.259  27.821  34.738
H      4.325  29.405  35.308
C      2.287  28.647  35.159
C      1.361  28.978  36.124
N      1.660  28.568  33.964
N      0.397  28.824  34.137
N      0.197  29.071  35.444
C     -1.128  29.392  35.954
H     -1.225  29.126  37.032
H     -1.902  28.707  35.536
C     -1.486  30.856  35.706
H     -2.589  31.017  35.682
H     -1.251  31.172  34.663
N     -0.833  31.705  36.692
C     -0.370  32.965  36.115
H     -1.194  33.524  35.613
H      0.282  32.804  35.225
C      0.318  33.799  37.186
H      0.743  34.740  36.764
H      1.266  33.324  37.531
O     -0.555  34.060  38.264
C     -1.006  32.851  38.838
H     -1.638  33.034  39.738
H     -0.174  32.292  39.326
C     -1.729  31.996  37.809
H     -2.154  31.068  38.258
H     -2.683  32.463  37.471


Molecule 1 docked into BChE
```

```
N      131.042 112.533  41.066
C      131.022 113.642  41.858
C      130.332 113.215  42.992
N      129.969 111.910  42.823
N      130.392 111.521  41.672
C      131.530 114.977  41.735
C      131.288 115.821  42.859
C      130.578 115.345  44.018
H      130.416 116.032  44.865
C      130.102 114.075  44.100
H      129.558 113.725  44.993
C      131.762 117.150  42.816
H      131.584 117.811  43.681
C      132.438 117.643  41.727
H      132.800 118.685  41.716
C      132.660 116.797  40.627
C      132.222 115.493  40.617
H      132.411 114.853  39.739
Cl     133.509 117.424  39.241
C      131.552 112.358  39.701
H      131.912 113.348  39.335
C      130.420 111.895  38.786
H      130.807 111.762  37.749
H      129.543 112.582  38.822
H      129.919 110.975  39.169
C      132.729 111.390  39.690
H      133.116 111.257  38.653
H      132.468 110.415  40.163
H      133.533 111.707  40.395

Molecule 4 docked into BChE

C     132.970 115.489  37.287
H     132.973 114.391  37.388
C     133.288 116.286  38.388
C     133.283 117.674  38.251
H     133.531 118.307  39.119
C     132.970 118.270  37.034
```

```
H     132.971 119.368  36.926
C     132.657 117.450  35.960
C     132.650 116.067  36.064
H     132.396 115.439  35.194
F     132.346 118.014  34.784
C     133.666 115.659  39.714
H     134.743 115.833  39.946
H     133.674 114.546  39.642
N     132.822 116.102  40.804
N     132.905 117.378  41.246
N     132.105 117.538  42.236
C     131.468 116.345  42.478
C     130.494 116.017  43.449
H     130.130 116.772  44.166
C     131.935 115.401  41.559
C     130.015 114.733  43.473
H     129.251 114.441  44.213
C     130.506 113.780  42.541
C     131.473 114.064  41.563
S     130.015 112.114  42.447
C     131.803 112.921  40.761
H     132.543 112.935  39.943
C     131.098 111.822  41.126
H     131.203 110.841  40.632

Molecule 9 docked into BChE

C    131.765 114.410  41.555
H    132.310 114.534  40.604
C    131.414 115.540  42.288
C    130.727 115.354  43.494
H    130.440 116.233  44.095
C    130.401 114.086  43.946
H    129.858 113.963  44.898
C    130.760 112.961  43.195
C    131.446 113.124  41.992
H    131.734 112.245  41.392
C    131.806 116.922  41.826
```

```
H    131.848 117.651  42.669
H    131.000 117.411  41.231
C    133.125 116.851  41.059
H    133.430 115.793  40.882
H    133.978 117.179  41.697
N    133.086 117.601  39.811
C    133.043 117.118  38.543
C    133.025 115.819  37.979
C    133.015 118.266  37.748
C    133.043 114.507  38.563
H    133.078 114.316  39.649
C    132.978 115.787  36.577
C    133.012 113.530  37.623
H    133.020 112.454  37.864
S    132.959 114.145  36.004
C    132.951 116.947  35.758
H    132.916 116.848  34.660
C    132.969 118.191  36.337
H    132.948 119.105  35.720
N    133.042 119.362  38.574
N    133.083 118.951  39.792
O    130.394 111.762  43.717
C    130.707 111.520  45.071
H    130.406 110.536  45.500
H    130.287 112.340  45.699
H    131.800 111.674 45.230
```

4. Estimated free energies of binding obtained by molecular docking

Table S1. Free energies of binding, ΔG_{bind} obtained by molecular docking of listed molecules into the active site of BChE, along with the number of conformational clusters and distribution of conformations.

Compound	ΔG_{bind}/kcal mol^{-1}		Number of distinctive conformational clusters	Distribution of conformations within clusters with $n > 1$ (n = cluster population)
	lowest	highest		
1	−5.92	−5.71	1	25
3	−6.13	−5.85	4	7, 11, 6
4	−5.96	−5.61	5	12, 8, 2, 2
5	−5.91	−5.52	5	2, 15, 5, 2
6	−5.85	−4.82	10	5, 4, 6, 2, 3
9	−6.37	−5.45	10	4, 3, 5, 4, 3, 2, 3
13	−6.11	−5.70	6	5, 8, 9
Galantamine	−6.26	−6.17	1	25

5. Crystallographic details and crystal structure of compound 5

Table S2. Crystallographic, data collection and refinement data.

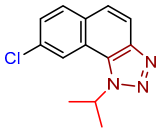
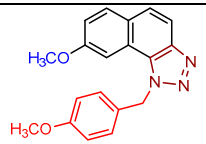
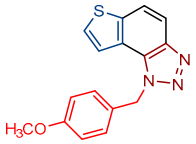
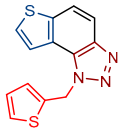
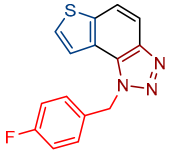
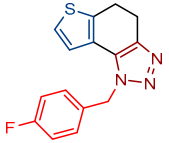
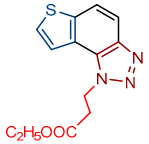
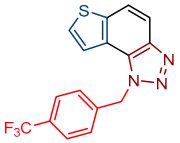
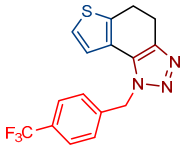
Compound	**5**
Empirical formula	$C_{26}H_{18}N_6S_4$
Formula wt. / g mol^{-1}	542.70

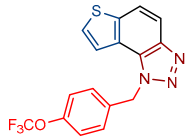
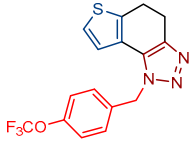
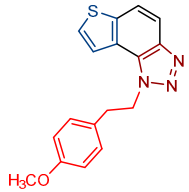
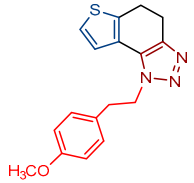
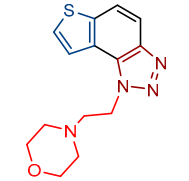
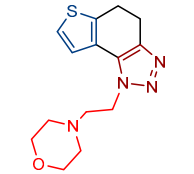
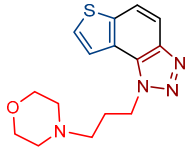
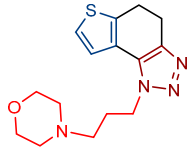
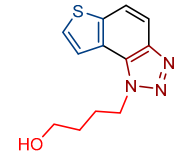
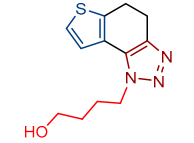
Colour	yellow
Crystal dimensions / mm	0.22 x 0.09 x 0.02
Space group	$P\,2_1/n$
a / Å	9.98930(10)
b / Å	13.47420(10)
c / Å	18.3819(3)
α / °	90
β / °	97.2340(10)
γ / °	90
Z	2
V / Å^3	2454.47(5)
D_{calc} / g cm^{-3}	1.469
λ / Å	1.54179 (Cu$K\alpha$)
μ / mm^{-1}	3.792
Θ range / °	4.08 – 79.73
T / K	293(2)
Diffractometer type	Synergy S
Range of h, k, l	$-11 < h < 12$; $-17 < k < 17$; $-23 < l < 23$
Reflections collected	38715
Independent reflections	5301
Observed reflections ($I \geq 2\sigma$)	4621
Absorption correction	Multi-scan

T_{min}, T_{max}	0.5661; 1.0000
R_{int}	0.0658
R (F)	0.0519
R_w (F^2)	0.1647
Goodness of fit	0.810
H atom treatment	Constrained
No. of parameters	325
No. of restraints	0
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.454; -0.495

6. Reorganized experimental results on the inhibitory activity of 1-19 (Table S2)

Table S3. Calculated IC_{50} values for compounds **1-19**.

Compound	Structure	IC_{50} (μM) AChE	IC_{50} (μM) BChE	Compound	Structure	IC_{50} (μM) AChE	IC_{50} (μM) BChE
1		59.9	39.6	**2**		-	-
3		116.0	25.5	**5**		118.6	23.4
4		97.0	37.5	**13**		-	58.0
6		-	39.6	**Galantamine**		0.15	7.9
7		139.6	> 150	**14**		117.6	> 150

8		68.0	213.5	**15**		88.7	-
9		-	18.6	**16**		145.3	119.4
10		-	-	**17**		45.6	-
11		-	-	**18**		-	-
12		-	106.7	**19**		-	74.1