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New pyridine dithiaazacrown ether derivatives: synthesis, structural characterization, *in silico* and *in vitro* biological studies

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1. Chemicals and solvents

All reagents including aryl aldehydes, ammonium acetate, acetic acid were purchased from Sigma Aldrich, Merck and used without any additional purification. Solvents for reaction, extraction and column chromatography as well as for crystallization such as acetonitrile, ethanol, methanol, dichloromethane, *n*-hexane, and ethyl acetate wer were purchased from Macron Fine Chemicals™, Merck and DEAJUNG, Korea.

2. Instrument

Melting points were recorded in open capillary tubes on a digital Stuart SMP3 apparatus. TLC analysis was performed in small TLC chamber by using commercially prepared silica gel plates (Merck, F254) and visualized by either UV lamp (λ = 254 nm). Column chromatography was packed manually using Silica gel with particle size from 0.063 to 0.2 mm) bought from Merck. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 500 Spectrometer (500 and 125 MHz, respectively) and Avance NEO 600MHz in $CDCl_3$ at 25 ^{0}C with TMS used as internal standard. Liquid chromatography- high resolution mass spectrometry (LC-HRMS) were recorded on Thermo Scientific LTQ Orbitrap XL using electrospray ionization source at positive mode. IR spectra were recorded as KBr pellets on FTIR Affinity – 1S SHIMADZU instrument in the range of 400 and 4000 cm^{-1}. The X-ray data for the single crystals of **4d** was collected on a Bruker D8 QUEST instrument at 100 K with Mo-Kα radiation (λ = 0.71073 Å) using a TRIUMPH monochromator. Structure solution and refinement were performed with the SHELXT and SHELXL 2014/7 programs.

3. Reference compounds studied in the past.

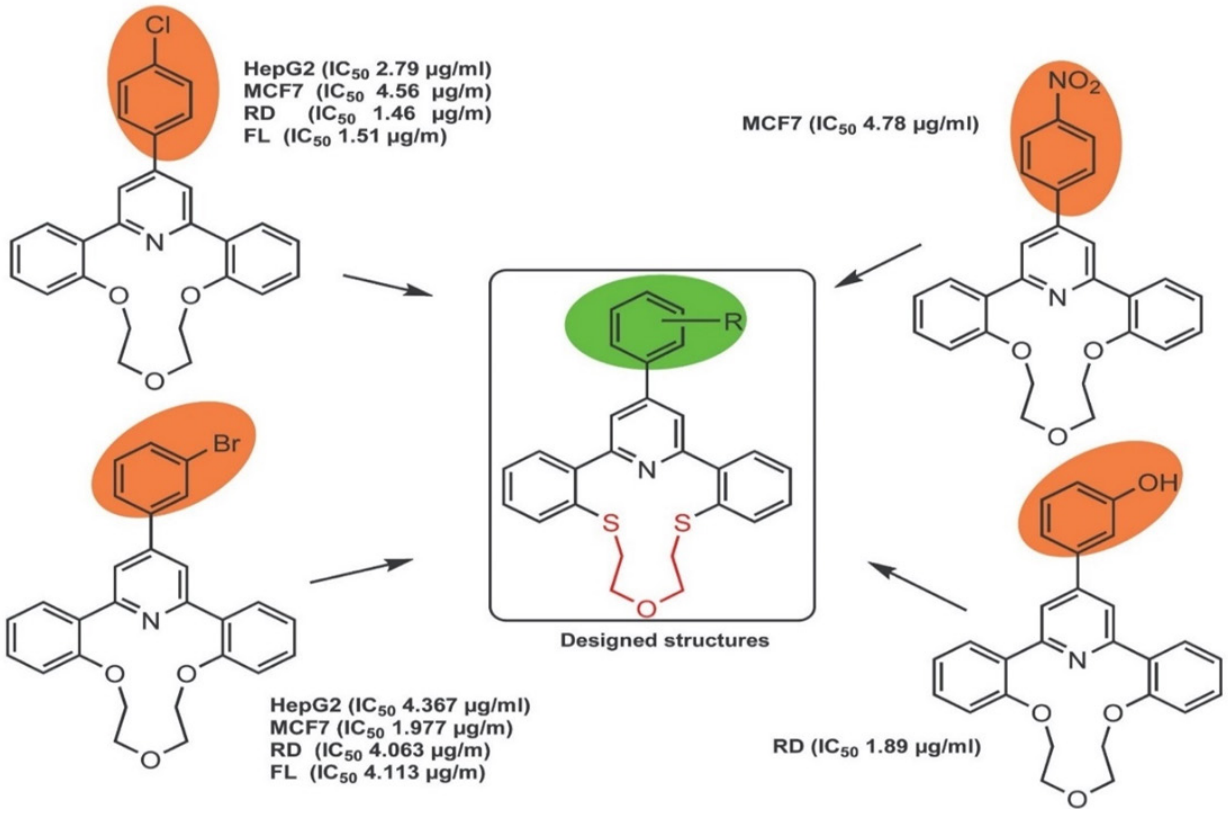


Figure S1. The cytotoxic activity of (γ-arylpyridino)dibenzoaza-14-crown-4 ether derivatives and the design of the novel (γ-arylpyridino) analogous.

4. General process for the synthesis of dithiacrown ether 2a-h

In round bottom flask were placed 1,5-bis(2-acetylphenylsulfanyl)-3-oxapentane **1** (374 mg, 1.0 mmol, 1.0 equiv), aromatic aldehyde derivative (1.1 mmol, 1.1 equiv) and NH_4OAc (770 mg, 10.0 mmol, 10 equiv) in AcOH (10 mL), and the reaction mixture heated under reflux for 36 h. After cooling down to ambient temperature, the reaction was neutralized by the addition of saturated aqueous K_2CO_3 solution followed by xtraction with CH_2Cl_2 (3×30 mL). The organic phases were combined, washed with redistilled water and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography with an elution of *n*-hexane in combined with EtOAc affording the products as colorless solids.

5. Characterization of synthetic compounds 2a-h

5.1. The physical parameters of the synthesized compounds 2a-h

Table S1. The physical parameters of the synthesized compounds **2a-h**

Entry	Yield (%)	R_f	Mp (°C)
2a	31	0.59	190 – 191
2b	38	0.55	185 – 186
2c	35	0.5	182 – 184
2d	30	0.65	188 – 189
2e	30	0.6	221–222[a]
2f	43	0.65	176-177[a]
2g	26	0.6	205 – 206
2h	32	0.36	214-216

Note: [a] reference 19 in the manuscript.

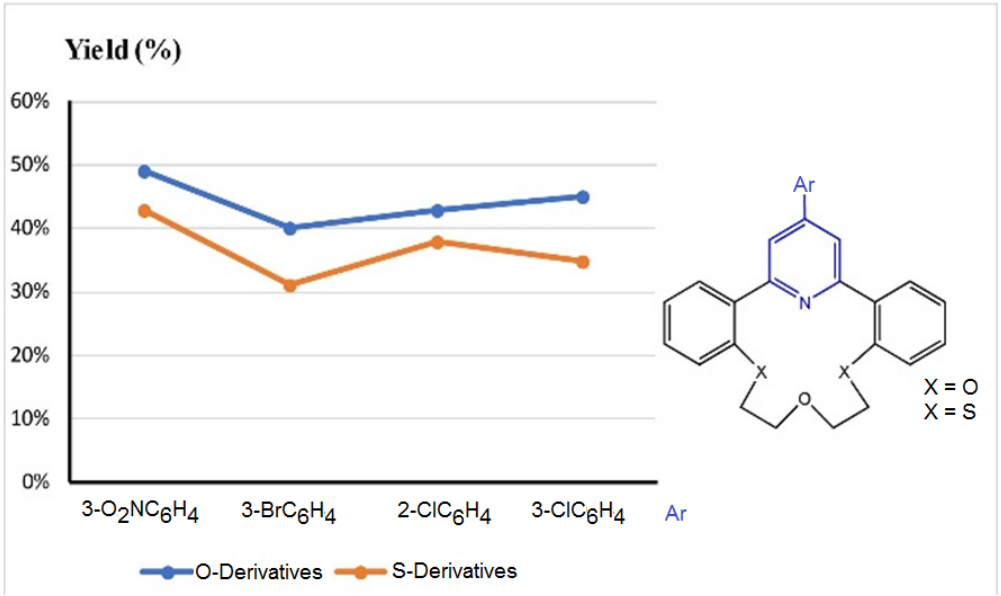
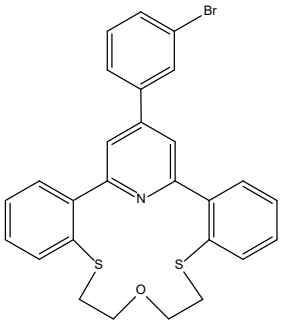


Figure S2. The yield comparison of O- and S-derivatives.

5.2. Spectral data analysis of the synthesized compounds 2a-h

Compounds **2e,f** were synthesized according to the previous publication and compared their R_f values and meting point.

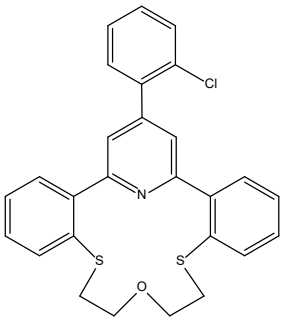
Synthesis of 2^4-(3-bromophenyl)-7-oxa-4,10-dithia-2(2,6)-pyridina-1,3(1,2)-dibenzenacyclodecaphane (2a)



Yield 23 %, R_f = 0.59 (hexane/EtOAc 3:1), Mp. 190 – 191 °C.

^{1}H-NMR (500 MHz, [D1]$CHCl_3$): δ_H (ppm) = 7.88 (t, J = 1.8 Hz, 1H, Ar-H), 7.72 – 7.64 (m, 5H, Ar-H), 7.62 (d, J = 9 Hz, 3H, ArH & H_{pyrid}), 7.44 (s, 4H, Ar-H), 7.39 (t, J=8 Hz, 1H, Ar-H), 3.399 (s, 4H, 2xCH_2), 2.908 (s, 4H, 2xCH_2).^{13}C-NMR (125 MHz, $CDCl_3$): δ_C(ppm) = 135.20; 130.88; 130.61; 130.16; 128.22; 126.28; 123.53; 68.63. HRMS (ESI$^+$), m/z Calc. for $[C_{27}H_{23}Br^{79}NOS_2]^+$:521.0462, found 521.0434 $[M+H]^+$; Calc. for $[C_{27}H_{23}Br^{81}NOS_2]^+$: 523.0544, Found: 523.0414 $[M+H]^+$.

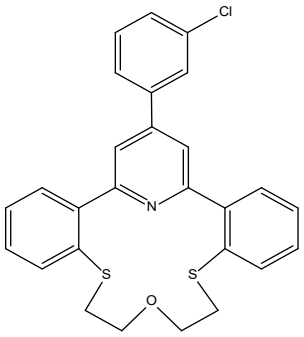
Synthesis of 2^4-(2-chlorophenyl)-7-oxa-4,10-dithia-2(2,6)-pyridina-1,3(1,2)-dibenzenacyclodecaphane (2b)



Yield 38 %, R_f = 0.55 (hexane/EtOAc 3:1), Mp. 185 – 186 °C.

^{1}H-NMR (500 MHz, [D1]$CHCl_3$): δ_H (ppm) = 7.64 (dd, J = 1.5; 7.5 Hz, 2H, Ar-H), 7.59 (s, 3H, Ar-H & H_{pyrid}), 7.58 (d.d, J = 1.5; 7.5, 1H, Ar-H), 7.50 (t.d, J = 2.1; 7.5 Hz, 2H, Ar-H), 7.41(t.d, J = 1.0; 7.5, 2H, Ar-H); 7.39 (td, J = 6.5, 2H, Ar-H), 7.37–7.33 (m, 4H, Ar-H); 3.30 (t ,4H, 2xCH_2), 2.27 (t, 4H, 2xCH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C = 158.80, 150.72, 137.79, 135.37, 133.31, 132.41, 131.32, 130.33, 130.06, 129.78, 129.07, 128.25, 127.19, 124.32, 69.15, 37.18. HRMS (ESI+), m/z Calc. for $[C_{27}H_{23}Cl^{35}NOS_2]^+$: 476.0909. Found: 476.0897 $[M+H]^+$; Calc. for $[C_{27}H_{23}Cl^{37}NOS_2]^+$: 478.0868, Found: 478.0878 $[M+H]^+$.

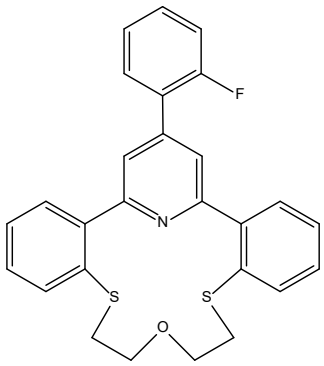
Synthesis of 2^4-(3-chlorophenyl)-7-oxa-4,10-dithia-2(2,6)-pyridina-1,3(1,2)-dibenzenacyclodecaphane (2c)



Yield 35 %, R_f = 0.5 (hexane/EtOAc 3:1), Mp. 182 – 184 ºC.

^{1}H-NMR (500 MHz, [D1]$CHCl_3$): δ_H (ppm) = 7.708 (s, 1H, Ar-H), 7.68 (d.d, *J* = 1.0, 7.5 Hz, 2H, Ar-H), 7.64 (s, 2H, H_{pyrid}); 7.62 – 7.61 (m, 1H, Ar-H), 7.55 (d, *J* = 5.5, 2H, Ar-H), 7.43 – 7.40 (m, 4H, Ar-H), 7.39 (d, *J* = 6.5, 2H, Ar-H), 3.29 (br.s, 4H, 2xCH_2), 2.80 (br.s, 4H, 2xCH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C = 135.36, 135.20, 133.31, 130.40, 129.88, 129.28, 128.25, 127.50, 125.55, 68.85, 37.51, 30.91. HRMS (ESI$^+$), m/z Calc. for $[C_{27}H_{23}Cl^{35}NOS_2]^+$: 476.0909. Found: 476.0882 $[M+H]^+$; Calc. for $[C_{27}H_{23}Cl^{37}NOS_2]^+$: 478.0868, Found: 478.0853 $[M+H]^+$.

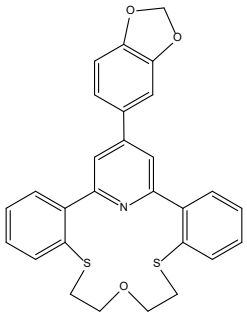
Synthesis of 2^4-(2-fluorophenyl)-7-oxa-4,10-dithia-2(2,6)-pyridina-1,3(1,2)-dibenzenacyclodecaphane (2d)



Yield 30 %, R_f = 0.69 (hexane/EtOAc 3:1), Mp. 188 – 189 ºC.

^{1}H-NMR (600 MHz, [D1]$CHCl_3$): δ_H (ppm) = 7.68-7.64 (m, 3H, Ar-H), 7.61 (td, *J* = 1.8 & 8 Hz, 1H, Ar-H), 7.57 (d.d, *J* = 1.6; 7.5 Hz, 1H, Ar-H); 7.44 – 7.37 (m, 3H, Ar-H), 7.36 (td, *J* = 7.5, 1.6 Hz, 2H, Ar-H), 7.27 (d, *J* = 1.2, 1H, Ar-H),), 7.25 (d, *J* = 1.2, 1H, Ar-H), 7.19 (ddd, *J* = 10.9, 8.2, 1.2 Hz, 1H), 3.29 (t, *J* = 6.0 Hz, 4H, 2xCH_2), 2.79 (t, *J* = 6.0 Hz, 4H, 2xCH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C = 159.182, 145.71, 142.777, 135.367, 133.259, 130.708 (J_{CF} 2.8 Hz), 130.696 (J_{CF} 4.3 Hz), 130.66, 130.006, 129.087, 129.084, 128.262, 126.310 (J_{CF} 12.47 Hz), 124.744 (J_{CF} 3.78 Hz), 123.596 (J_{CF} 2.9 Hz), 116.481 (J_{CF} 22.4 Hz), 69.02, 37.27, 0.00.. HRMS (ESI+), m/z Calc. for $[C_{27}H_{23}FNOS_2]^+$: 460.1179 $[M+H]^+$, Found: 476.1176 $[M+H]^+$.

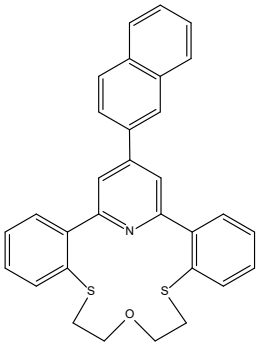
Synthesis of 2^4-(benzo[d][1,3]dioxol-5-yl)-7-oxa-4,10-dithia-2(2,6)-pyridina-1,3(1,2)-dibenzenacyclodecaphane (2g)



Yield 26 %, R_f = 0.6 (hexane/EtOAc 3:1), Mp. 205 – 206 °C.

^{1}H-NMR (600 MHz, [D1]$CHCl_3$): δ_H (ppm) = 7.65 (d.d, *J* = 1.2; 6.6 Hz, 2H, Ar-H), 7.59 (s, 2H, H-py); 7.54 (d.d, *J* = 1.8; 6.0 Hz, 2H, Ar-H); 7.4 (t.d, *J* = 1.2; 6.0 Hz, 2H, Ar-H); 7.35 (t.d, *J* = 1.2; 6.0 Hz, 2H, Ar-H); 7.24(d, *J* = 2.4 Hz, 1H, Ar-H); 7.20(d, *J* = 1.8 Hz, 1H, Ar-H), 6.9 (d, *J* = 7.8 Hz, 1H, Ar-H); 6.0 (s, 2H, OCH_2O); 3.28 (t, *J* = 6 Hz, 4H, 2xCH_2); 2.78 (t, *J* = 6 Hz, 4H, 2xCH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C = 159.38, 148.64, 148.54, 147.21, 145.86, 135.36, 133.21, 132.29, 129.90, 129.04, 128.24, 121.38, 121.33, 108.86, 107.55, 101.49, 69.00, 37.30. HRMS (ESI+), m/z Calc. for $[C_{28}H_{24}NO_3S_2]^+$: 486.1179. Found: 486.1168 $[M+H]^+$.

Synthesis of 2^4-(naphthalen-2-yl)-7-oxa-4,10-dithia-2(2,6)-pyridina-1,3(1,2)-dibenzenacyclodecaphane (2h)



Yield 32 %, R_f = 0.36 (hexane/EtOAc 2:1), Mp. 214-216 °C.

^{1}H-NMR (600 MHz, [D1]$CHCl_3$): δ_H (ppm) = 8.21 (br.d, *J* = 1.2 Hz, 1H, Ar-H), 7.96 – 7.94 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.88 (m, 1H, Ar-H), 7.85 (d.d, 1H, *J* = 1.8; 7.2 Hz, Ar-H); 7.81 (s, 2H, H-py), 7.67 (d.d, *J* = 1.2; 6.6 Hz, 2H, Ar-H), 7.59 (d.d, *J* = 1.8; 6.0 Hz, 2H, Ar-H), 7.52 (sext, *J* = 3.0 Hz, 2H, Ar-H), 7.42 (t.d, *J* = 1.2; 6.6 Hz, 2H, Ar-H); 7.37 (t.d, *J* = 1.8; 6.0 Hz, 2H, Ar-H), 3.31 (t, *J* = 6.0 Hz, 4H, 2xCH_2), 2.81(t, *J* = 6.0 Hz, 4H, 2xCH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C = 159.52, 147.56, 145.90, 135.38, 133.27, 129.93, 129.09, 128.91, 128.53, 128.26, 127.73, 126.80, 126.65, 124.83, 121.91, 69.00, 37.37. HRMS (ESI+), m/z Calc. for $[C_{31}H_{26}NOS_2]^+$: 492.1455. Found: 492.14459 $[M+H]^+$.

6. Cytotoxicity of synthesized compounds.

Table S2. The percent of cell survival induced by compounds 2a-h

Entry	Conc.[a] (mM)	Cell line (Cell survival - %)				
		Hep-G2	A549	MCF-7	HeLa	Vero
DMSO	-	100	100	100	100	100
Control	$5.85x10^{-3}$	**2.17±0.42**	**2.44±1.01**	**0.91±0.28**	**4.85±0.60**	**25.93± 1.15**
2a	0.019	98.56±0.36	99.32±1.86	97.27±0.29	98.22±1.11	
2b	0.021	99.84±0.14	99.55±0.25	98.48±1.27	97.84±1.19	
2c	0.021	99.92±0.03	99.26±0.69	97.45±0.83	99.30±0.35	
2d	0.044	**36.90±1.43**	61.43±1.73	N/A	97.25±1.85	93.25±1.53
2e	0.021	97.62±0.22	99.58±0.34	98.29±0.99	96.07±1.29	
2f	0.021	86.21±1.67	96.71±1.22	96.15±0.73	87.10±1.44	
2g	0.021	64,57±1.84	N/A	88,22±1.63	88.39±0.98	
2h	0.021	67,24±2,19	N/A	85.95±1.27	92.14±1.58	

Note: [a] Concentration

7. Single crystal X-ray Diffraction data of 2d

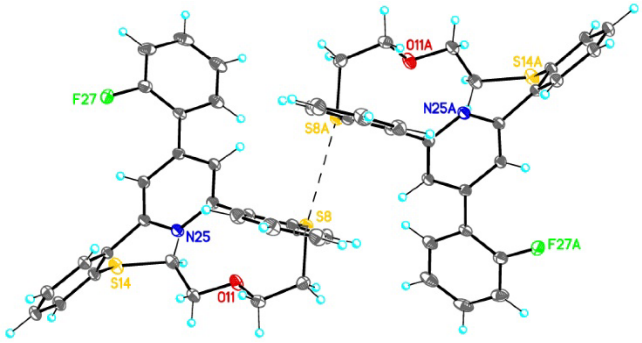


Figure S3. Dimer of the molecules **2d** *via* the intermolecular S···S interaction. The alternative positions of the disordered fluoro substituents with the minor occupancies are not shown.

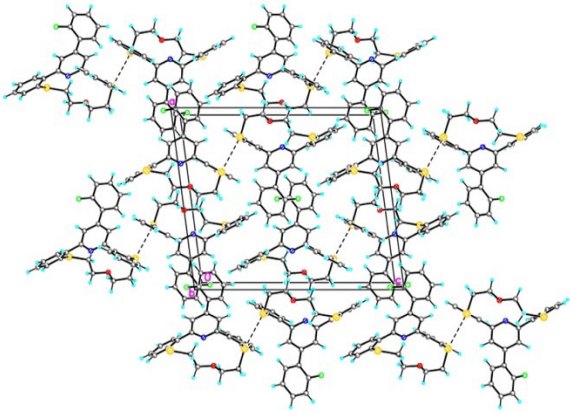


Figure S4. Crystal packing of the dimers of **2d** along the crystallographic ***b*** axis.

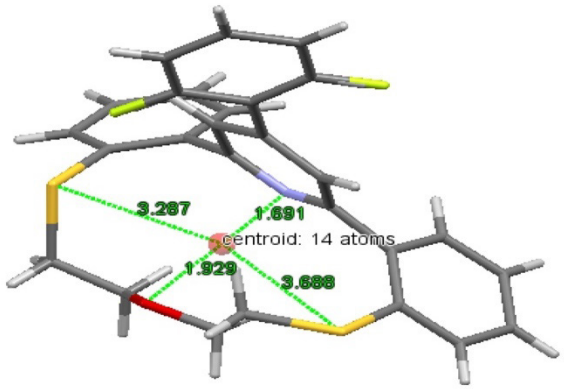


Figure S5. Determination of the internal cavity of compound **2d.**

Table S3. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2) for compound 2d

	x	*y*	*Z*	U_{iso}*/U_{eq}	Occ. (<1)
C1	0.23938 (8)	0.52038 (15)	0.56198 (7)	0.0136 (2)	
C2	0.20060 (8)	0.62920 (15)	0.61593 (7)	0.0145 (2)	
C3	0.20409 (9)	0.80219 (16)	0.60476 (7)	0.0186 (2)	
H3	0.2294	0.8441	0.5633	0.022*	
C4	0.17139 (9)	0.91373 (17)	0.65288 (8)	0.0221 (3)	
H4	0.1752	1.0309	0.6449	0.026*	
C5	0.13288 (10)	0.85283 (18)	0.71287 (8)	0.0231 (3)	
H5	0.1104	0.9286	0.7461	0.028*	
C6	0.12721 (9)	0.68143 (18)	0.72433 (7)	0.0197 (2)	
H6	0.1003	0.6406	0.7652	0.024*	
C7	0.16098 (8)	0.56817 (16)	0.67605 (7)	0.0154 (2)	
S8	0.15138 (2)	0.34979 (4)	0.69253 (2)	0.01693 (7)	
C9	0.03813 (8)	0.31559 (18)	0.65067 (8)	0.0195 (2)	
H9A	0.0192	0.2039	0.6661	0.023*	
H9B	0.0004	0.3999	0.6709	0.023*	
C10	0.02310 (8)	0.32546 (17)	0.56635 (7)	0.0189 (2)	
H10A	-0.0406	0.3203	0.5484	0.023*	
H10B	0.0460	0.4329	0.5497	0.023*	
O11	0.06675 (7)	0.18968 (12)	0.53599 (5)	0.02104 (19)	
C12	0.06101 (9)	0.19845 (18)	0.45657 (7)	0.0194 (2)	
H12A	0.0649	0.3161	0.4401	0.023*	
H12B	0.0048	0.1505	0.4327	0.023*	
C13	0.13790 (9)	0.09727 (16)	0.43598 (7)	0.0190 (2)	
H13A	0.1279	-0.0221	0.4468	0.023*	
H13B	0.1917	0.1330	0.4685	0.023*	
S14	0.15688 (2)	0.11587 (4)	0.33899 (2)	0.02112 (8)	
C15	0.15383 (8)	0.33271 (16)	0.31598 (7)	0.0159 (2)	
C16	0.11199 (9)	0.36946 (17)	0.24376 (7)	0.0191 (2)	
H16	0.0858	0.2813	0.2132	0.023*	
C17	0.10809 (9)	0.53140 (18)	0.21616 (7)	0.0198 (2)	
H17	0.0810	0.5531	0.1666	0.024*	
C18	0.14390 (8)	0.66197 (17)	0.26110 (7)	0.0186 (2)	
H18	0.1414	0.7735	0.2427	0.022*	
C19	0.18329 (8)	0.62755 (16)	0.33321 (7)	0.0162 (2)	
H19	0.2057	0.7175	0.3645	0.019*	
C20	0.19089 (8)	0.46438 (16)	0.36105 (7)	0.0144 (2)	
C21	0.23709 (8)	0.44470 (15)	0.43850 (6)	0.0137 (2)	
C22	0.31292 (8)	0.34906 (15)	0.45483 (7)	0.0142 (2)	
H22	0.3371	0.2918	0.4162	0.017*	
C23	0.35284 (8)	0.33874 (15)	0.52901 (7)	0.0133 (2)	
C24	0.31322 (8)	0.42215 (15)	0.58367 (7)	0.0145 (2)	
H24	0.3363	0.4120	0.6350	0.017*	
N25	0.20228 (7)	0.53396 (13)	0.49046 (6)	0.01441 (19)	
C26	0.43486 (8)	0.24327 (13)	0.55098 (6)	0.0147 (2)	
C27	0.50614 (8)	0.25153 (12)	0.51112 (6)	0.0186 (2)	
F27	0.49949 (6)	0.34234 (12)	0.44777 (5)	0.02190 (18)	0.9
H27	0.5000	0.3150	0.4655	0.026*	0.1
C28	0.58460 (9)	0.16957 (16)	0.53343 (8)	0.0251 (3)	
H28	0.6319	0.1780	0.5047	0.030*	
C29	0.59292 (9)	0.07493 (17)	0.59838 (9)	0.0261 (3)	
H29	0.6464	0.0184	0.6146	0.031*	
C30	0.52348 (10)	0.06253 (16)	0.63970 (8)	0.0245 (3)	
H30	0.5290	-0.0032	0.6840	0.029*	
C31	0.44566 (9)	0.14691 (15)	0.61598 (7)	0.0195 (2)	
H31	0.3983	0.1393	0.6455	0.023*	0.9

F31	0.3833 (4)	0.1265 (7)	0.6599 (3)	0.02190 (18)	0.1

Table S4. Atomic displacement parameters (Å^2) for compound 2d

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0141 (5)	0.0137 (5)	0.0129 (5)	0.0018 (4)	0.0011 (4)	-0.0006 (4)
C2	0.0149 (5)	0.0154 (5)	0.0125 (5)	0.0037 (4)	-0.0007 (4)	-0.0018 (4)
C3	0.0212 (6)	0.0161 (5)	0.0180 (6)	0.0033 (4)	0.0003 (4)	0.0000 (4)
C4	0.0257 (6)	0.0158 (6)	0.0235 (6)	0.0057 (5)	-0.0015 (5)	-0.0041 (5)
C5	0.0256 (6)	0.0225 (6)	0.0201 (6)	0.0088 (5)	-0.0006 (5)	-0.0083 (5)
C6	0.0201 (6)	0.0251 (6)	0.0141 (5)	0.0063 (5)	0.0026 (4)	-0.0037 (5)
C7	0.0155 (5)	0.0170 (5)	0.0130 (5)	0.0044 (4)	-0.0008 (4)	-0.0016 (4)
S8	0.01794 (14)	0.01758 (14)	0.01480 (14)	0.00308 (11)	0.00048 (10)	0.00165 (10)
C9	0.0167 (5)	0.0219 (6)	0.0200 (6)	0.0011 (4)	0.0036 (4)	0.0017 (5)
C10	0.0164 (5)	0.0198 (6)	0.0194 (6)	0.0030 (4)	-0.0012 (4)	0.0019 (5)
O11	0.0287 (5)	0.0187 (4)	0.0148 (4)	0.0052 (4)	-0.0003 (4)	0.0020 (3)
C12	0.0208 (6)	0.0216 (6)	0.0146 (5)	0.0004 (5)	-0.0016 (4)	0.0023 (4)
C13	0.0238 (6)	0.0152 (5)	0.0168 (6)	0.0006 (5)	-0.0016 (5)	0.0017 (4)
S14	0.02969 (17)	0.01582 (14)	0.01692 (15)	0.00324 (12)	-0.00026 (12)	-0.00317 (11)
C15	0.0168 (5)	0.0180 (5)	0.0126 (5)	0.0029 (4)	0.0006 (4)	-0.0011 (4)
C16	0.0203 (6)	0.0236 (6)	0.0125 (5)	0.0015 (5)	-0.0006 (4)	-0.0028 (4)
C17	0.0203 (6)	0.0274 (7)	0.0111 (5)	0.0032 (5)	0.0001 (4)	0.0018 (4)
C18	0.0184 (5)	0.0220 (6)	0.0154 (5)	0.0027 (5)	0.0020 (4)	0.0039 (4)
C19	0.0156 (5)	0.0184 (5)	0.0142 (5)	0.0013 (4)	0.0011 (4)	0.0011 (4)
C20	0.0132 (5)	0.0186 (5)	0.0113 (5)	0.0022 (4)	0.0009 (4)	-0.0002 (4)
C21	0.0137 (5)	0.0153 (5)	0.0115 (5)	0.0007 (4)	-0.0002 (4)	-0.0004 (4)
C22	0.0147 (5)	0.0152 (5)	0.0126 (5)	0.0022 (4)	0.0015 (4)	-0.0011 (4)
C23	0.0129 (5)	0.0132 (5)	0.0134 (5)	0.0014 (4)	0.0004 (4)	-0.0001 (4)
C24	0.0155 (5)	0.0157 (5)	0.0117 (5)	0.0024 (4)	-0.0006 (4)	-0.0006 (4)
N25	0.0149 (4)	0.0157 (5)	0.0122 (4)	0.0021 (4)	0.0002 (3)	-0.0006 (3)
C26	0.0150 (5)	0.0139 (5)	0.0141 (5)	0.0029 (4)	-0.0023 (4)	-0.0028 (4)
C27	0.0165 (5)	0.0206 (6)	0.0179 (6)	0.0028 (4)	-0.0004 (4)	-0.0037 (5)
F27	0.0187 (4)	0.0283 (5)	0.0195 (4)	0.0016 (3)	0.0052 (3)	0.0040 (3)
C28	0.0150 (5)	0.0290 (7)	0.0303 (7)	0.0052 (5)	-0.0002 (5)	-0.0116 (6)
C29	0.0217 (6)	0.0211 (6)	0.0318 (7)	0.0095 (5)	-0.0102 (5)	-0.0097 (5)
C30	0.0283 (7)	0.0178 (6)	0.0239 (7)	0.0065 (5)	-0.0090 (5)	-0.0018 (5)
C31	0.0213 (6)	0.0170 (5)	0.0187 (6)	0.0041 (5)	-0.0032 (5)	-0.0006 (4)
F31	0.0187 (4)	0.0283 (5)	0.0195 (4)	0.0016 (3)	0.0052 (3)	0.0040 (3)

Table S5. Geometric parameters – bond lengths (Å) and angles (º) for compound 2d

C1—N25	1.3438 (15)	C15—C16	1.4052 (17)
C1—C24	1.3926 (16)	C16—C17	1.3847 (19)
C1—C2	1.4882 (16)	C16—H16	0.9500
C2—C3	1.3988 (18)	C17—C18	1.3890 (19)
C2—C7	1.4010 (17)	C17—H17	0.9500
C3—C4	1.3850 (18)	C18—C19	1.3875 (18)
C3—H3	0.9500	C18—H18	0.9500
C4—C5	1.390 (2)	C19—C20	1.3963 (17)
C4—H4	0.9500	C19—H19	0.9500
C5—C6	1.389 (2)	C20—C21	1.4889 (16)
C5—H5	0.9500	C21—N25	1.3449 (15)
C6—C7	1.4031 (17)	C21—C22	1.3923 (16)
C6—H6	0.9500	C22—C23	1.3984 (16)
C7—S8	1.7793 (13)	C22—H22	0.9500
S8—C9	1.8237 (13)	C23—C24	1.3961 (16)
C9—C10	1.5102 (19)	C23—C26	1.4819 (16)
C9—H9A	0.9900	C24—H24	0.9500
C9—H9B	0.9900	C26—C27	1.3907 (18)
C10—O11	1.4233 (16)	C26—C31	1.3942 (18)
C10—H10A	0.9900	C27—F27	1.3463 (14)

C10—H10B	0.9900	C27—C28	1.3843 (18)
O11—C12	1.4257 (16)	C27—H27	0.9611
C12—C13	1.5188 (19)	C28—C29	1.386 (2)
C12—H12A	0.9900	C28—H28	0.9500
C12—H12B	0.9900	C29—C30	1.385 (2)
C13—S14	1.8186 (14)	C29—H29	0.9500
C13—H13A	0.9900	C30—C31	1.3902 (18)
C13—H13B	0.9900	C30—H30	0.9500
S14—C15	1.7806 (13)	C31—F31	1.333 (3)
C15—C20	1.4032 (17)	C31—H31	0.9600
N25—C1—C24	122.75 (11)	C17—C16—C15	121.41 (12)
N25—C1—C2	115.17 (10)	C17—C16—H16	119.3
C24—C1—C2	121.89 (11)	C15—C16—H16	119.3
C3—C2—C7	118.99 (11)	C16—C17—C18	119.81 (12)
C3—C2—C1	117.15 (11)	C16—C17—H17	120.1
C7—C2—C1	123.86 (11)	C18—C17—H17	120.1
C4—C3—C2	121.41 (13)	C19—C18—C17	119.20 (12)
C4—C3—H3	119.3	C19—C18—H18	120.4
C2—C3—H3	119.3	C17—C18—H18	120.4
C3—C4—C5	119.44 (13)	C18—C19—C20	121.84 (12)
C3—C4—H4	120.3	C18—C19—H19	119.1
C5—C4—H4	120.3	C20—C19—H19	119.1
C4—C5—C6	120.19 (12)	C19—C20—C15	118.91 (11)
C4—C5—H5	119.9	C19—C20—C21	116.28 (11)
C6—C5—H5	119.9	C15—C20—C21	124.80 (11)
C5—C6—C7	120.49 (13)	N25—C21—C22	122.93 (11)
C5—C6—H6	119.8	N25—C21—C20	114.46 (10)
C7—C6—H6	119.8	C22—C21—C20	122.51 (11)
C2—C7—C6	119.46 (12)	C21—C22—C23	118.87 (11)
C2—C7—S8	121.67 (9)	C21—C22—H22	120.6
C6—C7—S8	118.86 (10)	C23—C22—H22	120.6
C7—S8—C9	100.00 (6)	C24—C23—C22	118.10 (11)
C10—C9—S8	114.73 (9)	C24—C23—C26	119.53 (10)
C10—C9—H9A	108.6	C22—C23—C26	122.37 (10)
S8—C9—H9A	108.6	C1—C24—C23	119.13 (11)
C10—C9—H9B	108.6	C1—C24—H24	120.4
S8—C9—H9B	108.6	C23—C24—H24	120.4
H9A—C9—H9B	107.6	C1—N25—C21	117.99 (10)
O11—C10—C9	109.37 (10)	C27—C26—C31	116.61 (11)
O11—C10—H10A	109.8	C27—C26—C23	122.59 (11)
C9—C10—H10A	109.8	C31—C26—C23	120.71 (11)
O11—C10—H10B	109.8	F27—C27—C28	117.78 (12)
C9—C10—H10B	109.8	F27—C27—C26	119.29 (11)
H10A—C10—H10B	108.2	C28—C27—C26	122.93 (12)
C10—O11—C12	112.37 (10)	C28—C27—H27	118.7
O11—C12—C13	105.91 (10)	C26—C27—H27	118.3
O11—C12—H12A	110.6	C27—C28—C29	118.82 (13)
C13—C12—H12A	110.6	C27—C28—H28	120.6
O11—C12—H12B	110.6	C29—C28—H28	120.6
C13—C12—H12B	110.6	C30—C29—C28	120.24 (13)
H12A—C12—H12B	108.7	C30—C29—H29	119.9
C12—C13—S14	114.98 (9)	C28—C29—H29	119.9
C12—C13—H13A	108.5	C29—C30—C31	119.56 (14)
S14—C13—H13A	108.5	C29—C30—H30	120.2
C12—C13—H13B	108.5	C31—C30—H30	120.2
S14—C13—H13B	108.5	F31—C31—C30	114.5 (4)
H13A—C13—H13B	107.5	F31—C31—C26	123.6 (4)
C15—S14—C13	107.54 (6)	C30—C31—C26	121.84 (13)

C20—C15—C16	118.75 (12)	C30—C31—H31	119.0
C20—C15—S14	126.75 (9)	C26—C31—H31	119.2
C16—C15—S14	114.46 (10)		
N25—C1—C2—C3	-60.80 (15)	S14—C15—C20—C21	-2.47 (18)
C24—C1—C2—C3	114.28 (14)	C19—C20—C21—N25	56.59 (15)
N25—C1—C2—C7	118.80 (13)	C15—C20—C21—N25	-122.05 (13)
C24—C1—C2—C7	-66.12 (17)	C19—C20—C21—C22	-119.99 (13)
C7—C2—C3—C4	1.72 (19)	C15—C20—C21—C22	61.37 (17)
C1—C2—C3—C4	-178.65 (12)	N25—C21—C22—C23	2.95 (19)
C2—C3—C4—C5	-1.1 (2)	C20—C21—C22—C23	179.24 (11)
C3—C4—C5—C6	-0.1 (2)	C21—C22—C23—C24	1.53 (18)
C4—C5—C6—C7	0.6 (2)	C21—C22—C23—C26	-178.43 (11)
C3—C2—C7—C6	-1.13 (18)	N25—C1—C24—C23	2.47 (19)
C1—C2—C7—C6	179.27 (11)	C2—C1—C24—C23	-172.23 (11)
C3—C2—C7—S8	178.32 (10)	C22—C23—C24—C1	-4.08 (18)
C1—C2—C7—S8	-1.28 (17)	C26—C23—C24—C1	175.88 (11)
C5—C6—C7—C2	-0.02 (19)	C24—C1—N25—C21	1.88 (18)
C5—C6—C7—S8	-179.48 (10)	C2—C1—N25—C21	176.92 (11)
C2—C7—S8—C9	-98.94 (11)	C22—C21—N25—C1	-4.65 (18)
C6—C7—S8—C9	80.50 (11)	C20—C21—N25—C1	178.80 (11)
C7—S8—C9—C10	71.27 (11)	C24—C23—C26—C27	-135.84 (10)
S8—C9—C10—O11	66.74 (13)	C22—C23—C26—C27	44.12 (15)
C9—C10—O11—C12	-175.45 (11)	C24—C23—C26—C31	40.56 (15)
C10—O11—C12—C13	156.90 (11)	C22—C23—C26—C31	-139.48 (11)
O11—C12—C13—S14	-170.32 (9)	C31—C26—C27—F27	179.82 (8)
C12—C13—S14—C15	47.40 (11)	C23—C26—C27—F27	-3.65 (11)
C13—S14—C15—C20	41.54 (13)	C31—C26—C27—C28	0.03 (6)
C13—S14—C15—C16	-140.78 (10)	C23—C26—C27—C28	176.57 (10)
C20—C15—C16—C17	1.11 (19)	F27—C27—C28—C29	-179.83 (9)
S14—C15—C16—C17	-176.76 (10)	C26—C27—C28—C29	-0.05 (7)
C15—C16—C17—C18	-1.9 (2)	C27—C28—C29—C30	0.33 (13)
C16—C17—C18—C19	0.11 (19)	C28—C29—C30—C31	-0.60 (16)
C17—C18—C19—C20	2.41 (19)	C29—C30—C31—F31	-179.89 (14)
C18—C19—C20—C15	-3.13 (18)	C29—C30—C31—C26	0.60 (16)
C18—C19—C20—C21	178.14 (11)	C27—C26—C31—F31	-179.77 (12)
C16—C15—C20—C19	1.34 (18)	C23—C26—C31—F31	3.6 (2)
S14—C15—C20—C19	178.92 (10)	C27—C26—C31—C30	-0.31 (13)
C16—C15—C20—C21	179.95 (11)	C23—C26—C31—C30	-176.92 (11)

8. Spectra of synthesized compounds

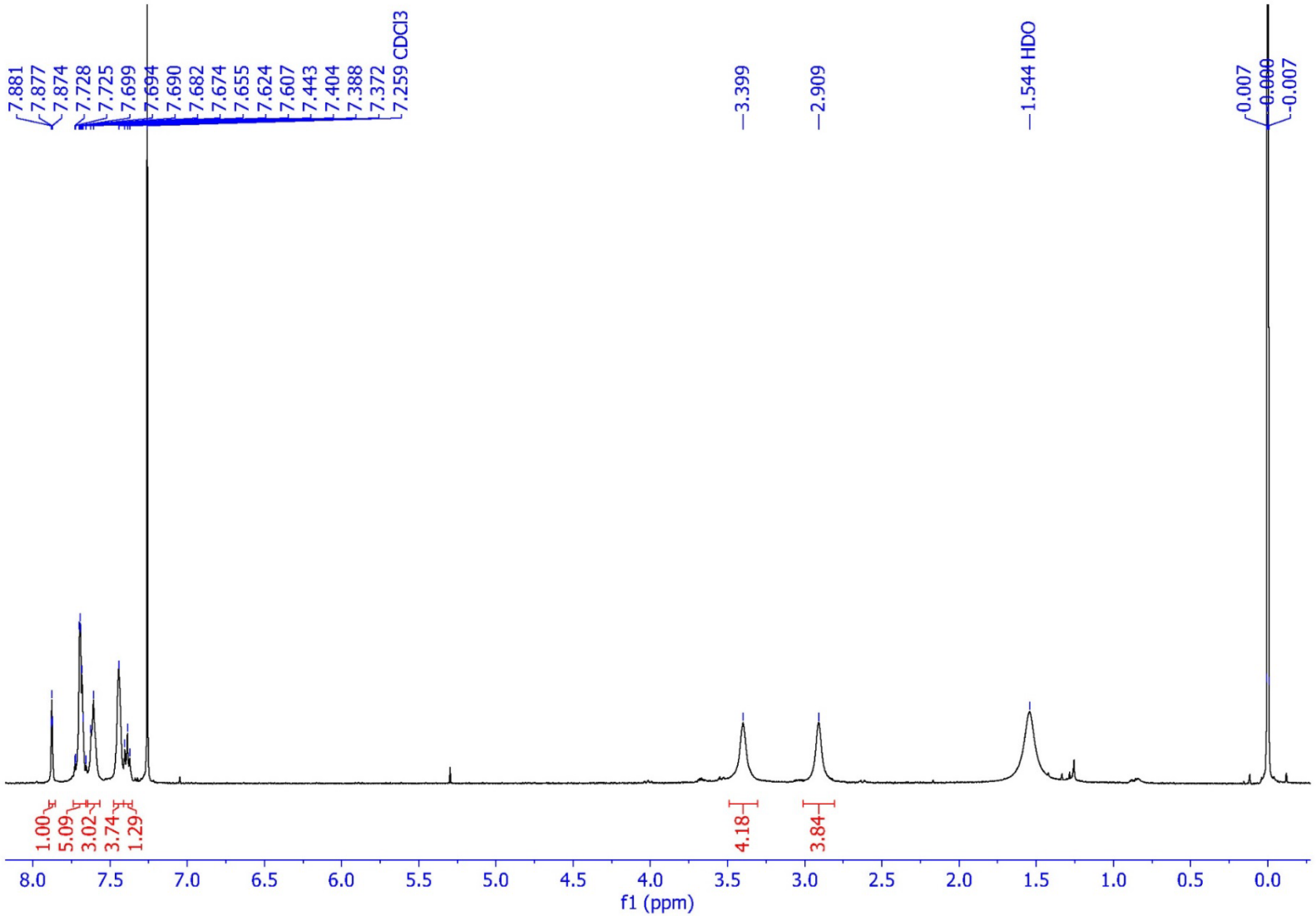


Figure S6. ^{1}H – NMR spectrum of compound 2a

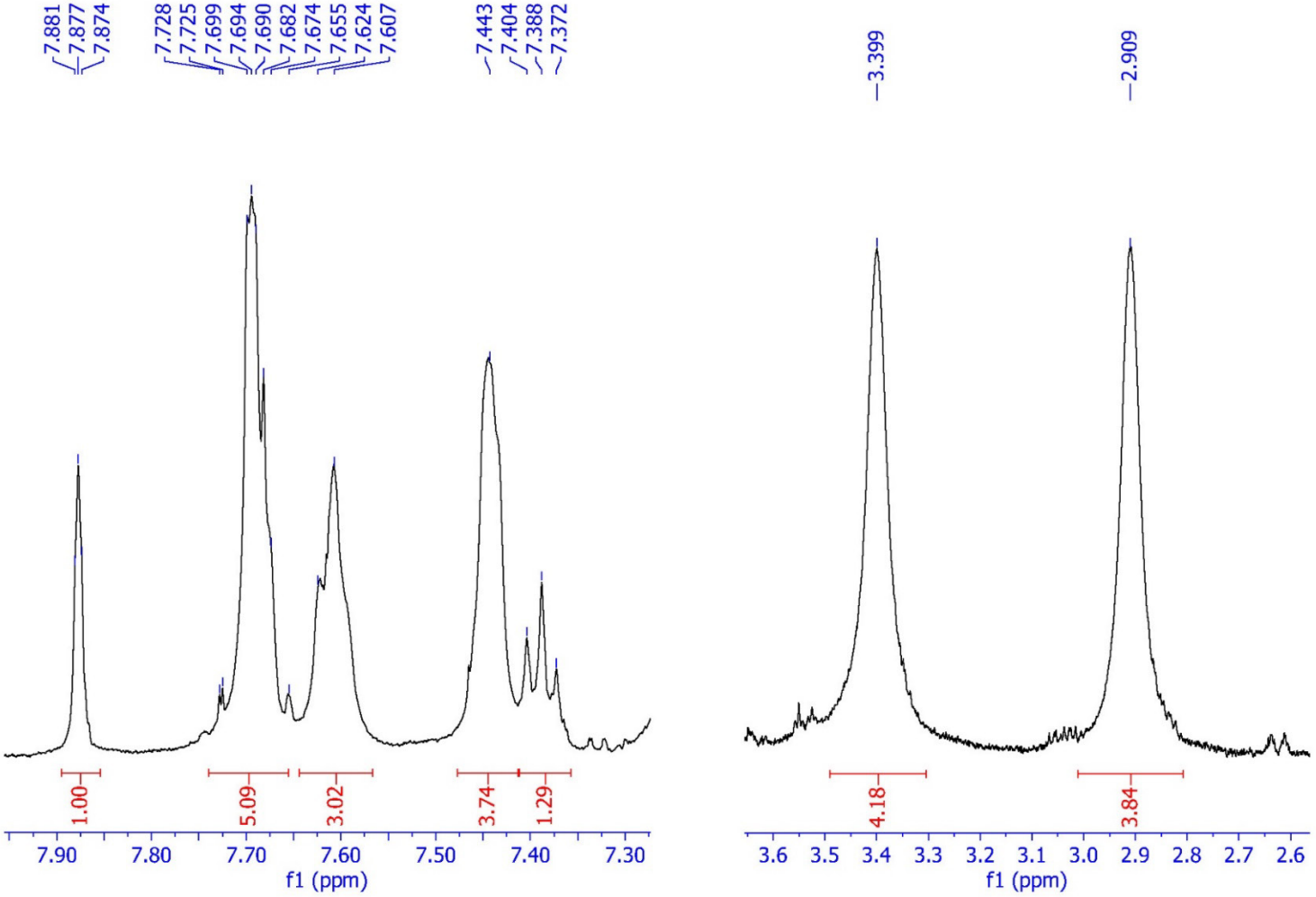


Figure S6. ^{1}H – NMR spectrum of compound 2a (*continued)*

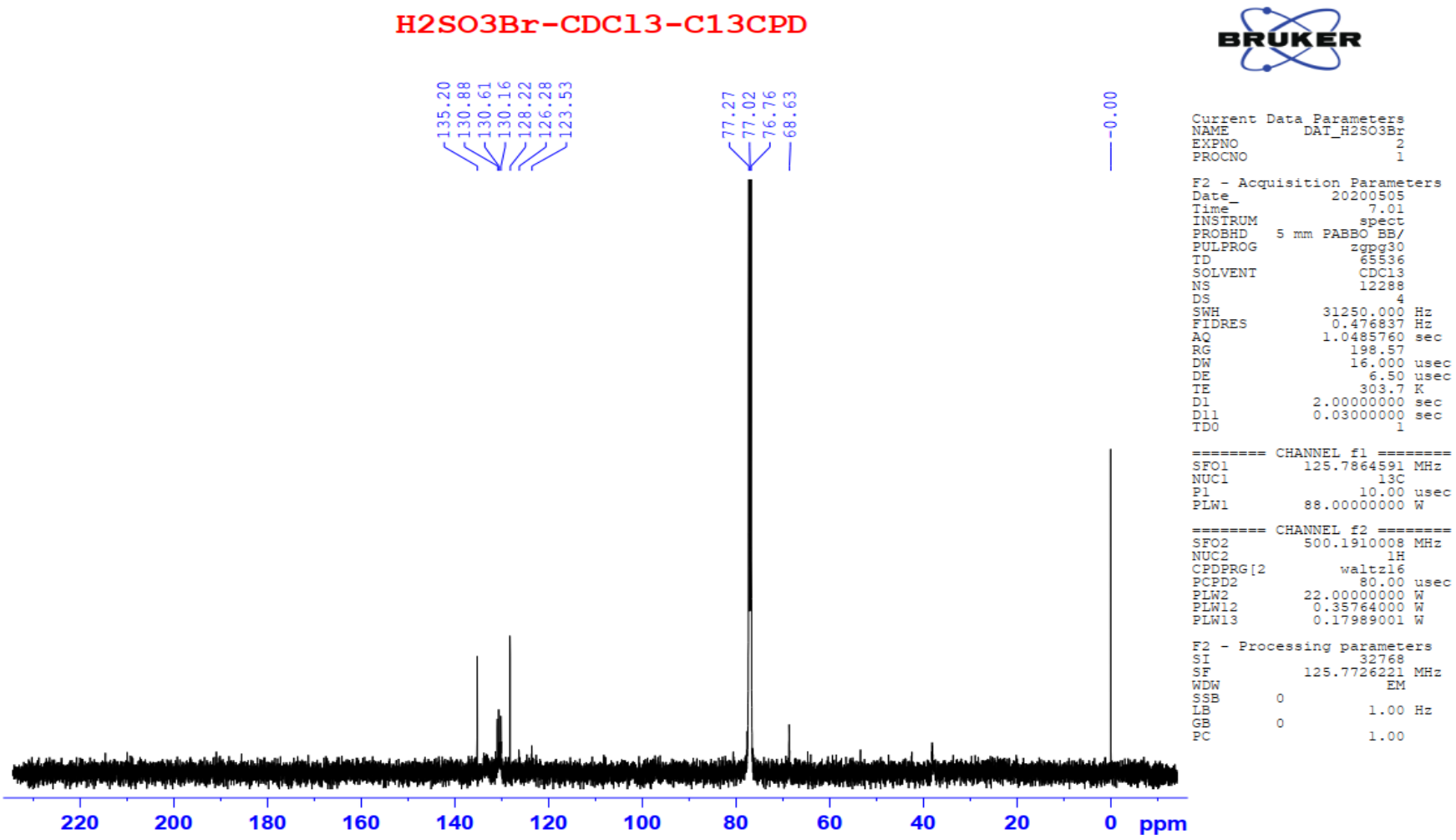
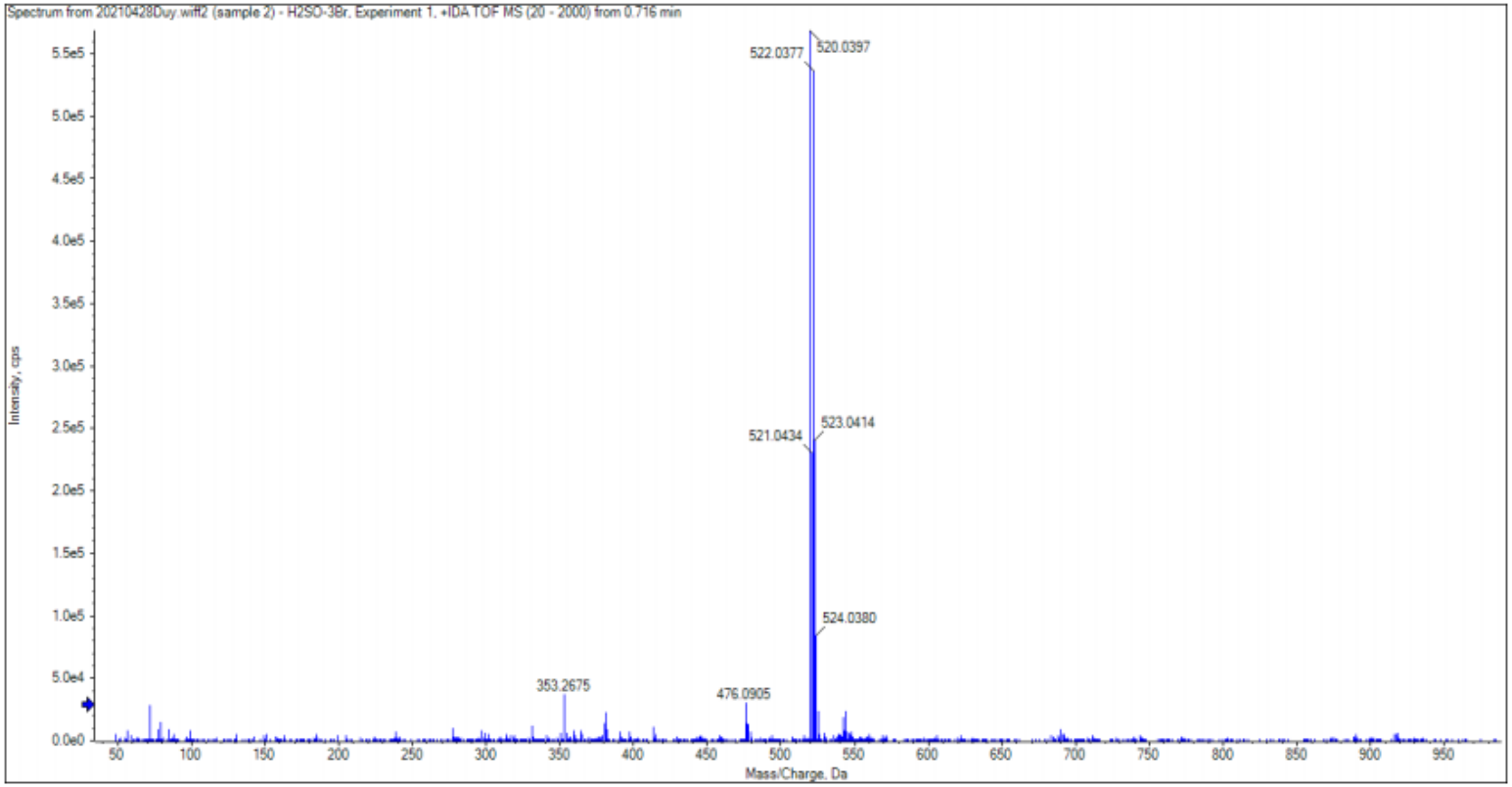


Figure S7. ^{13}C – NMR spectrum of compound 2a



Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C27H22BrNOS2	520.03990	17.0	-0.4	1			NA/NA

Figure S8. HRMS spectrum of compound 2a

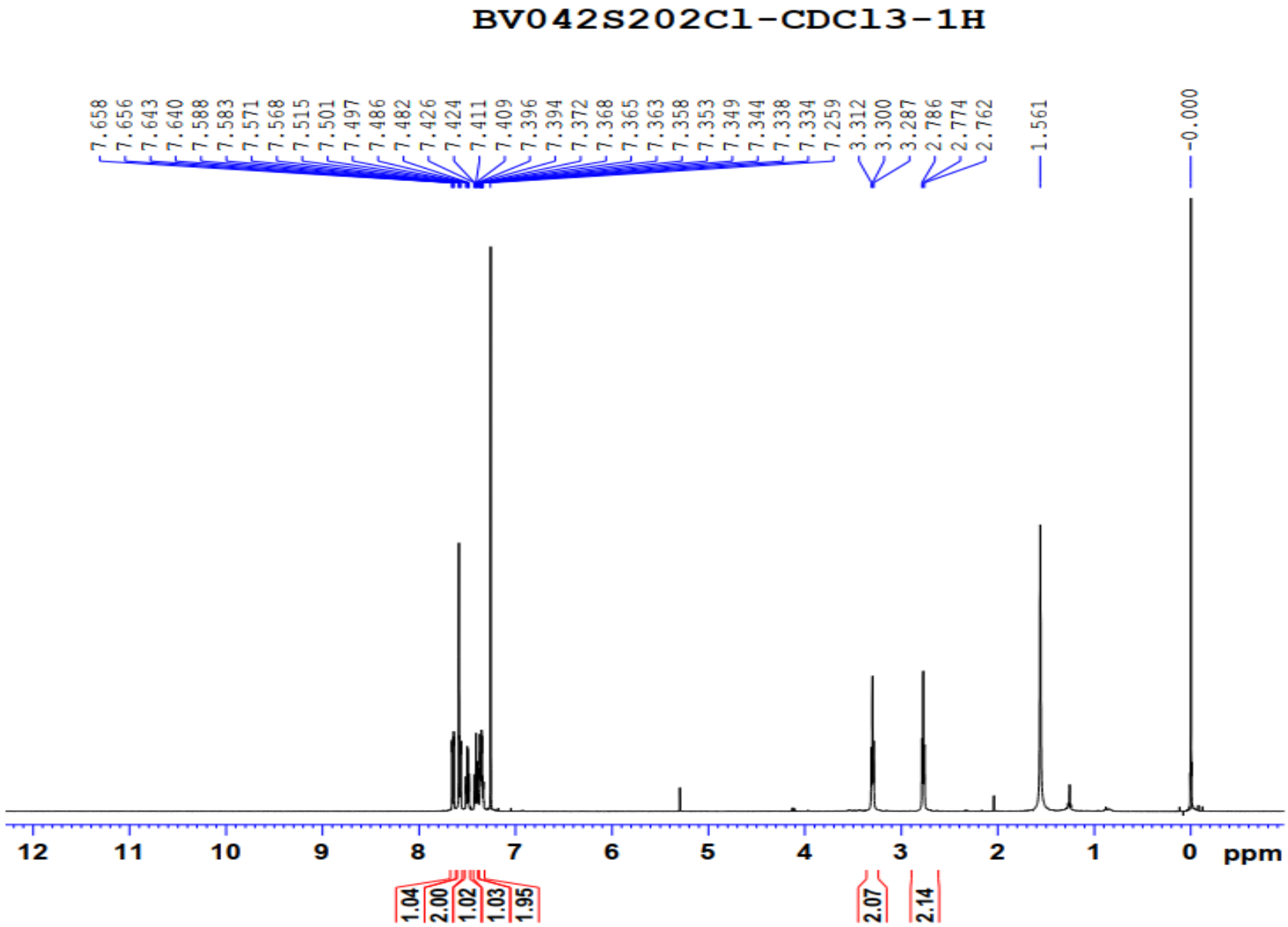


Figure S9. ^{1}H – NMR spectrum of compound 2b

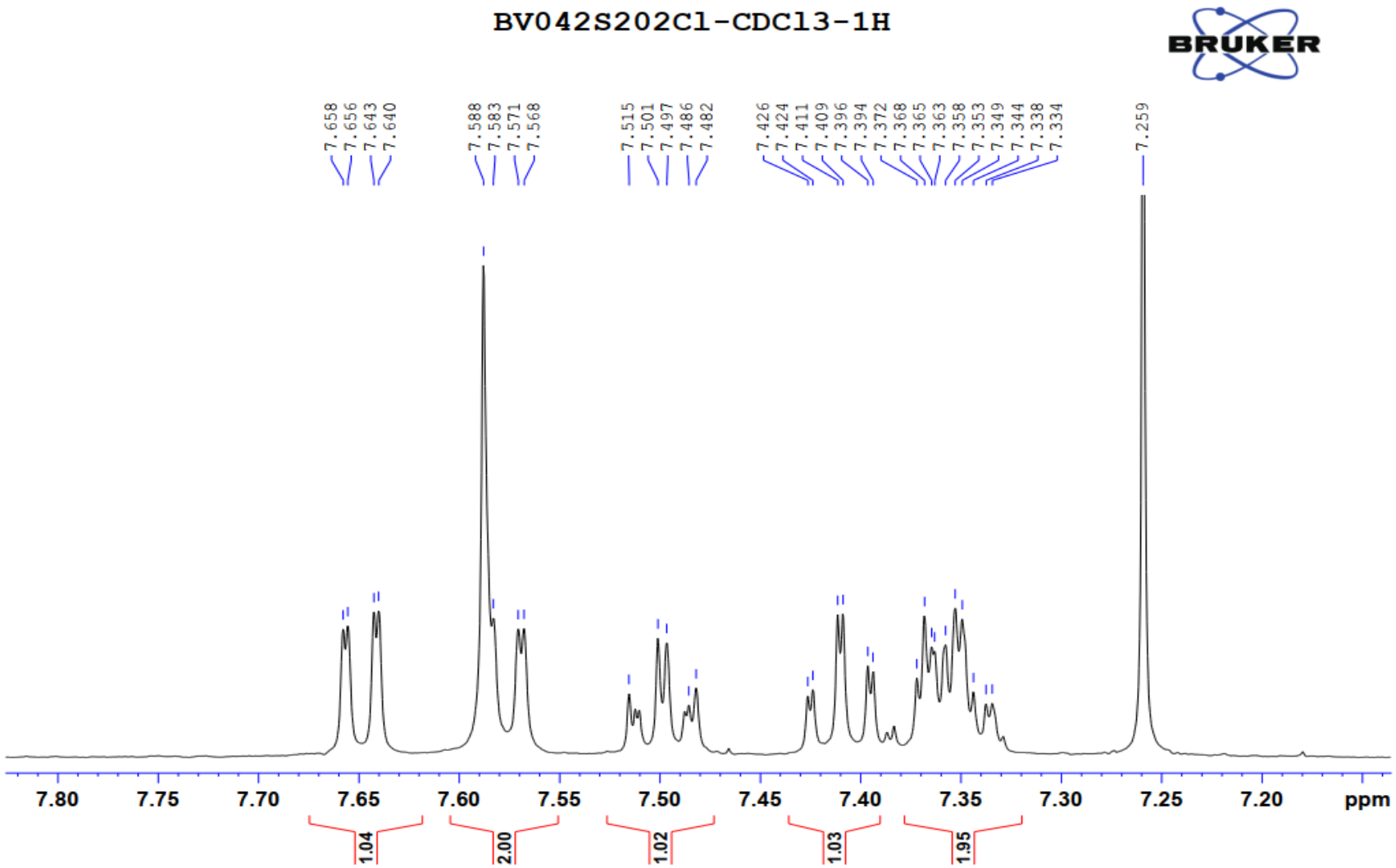


Figure S9. ^{1}H – NMR spectrum of compound 2b (*continued)*

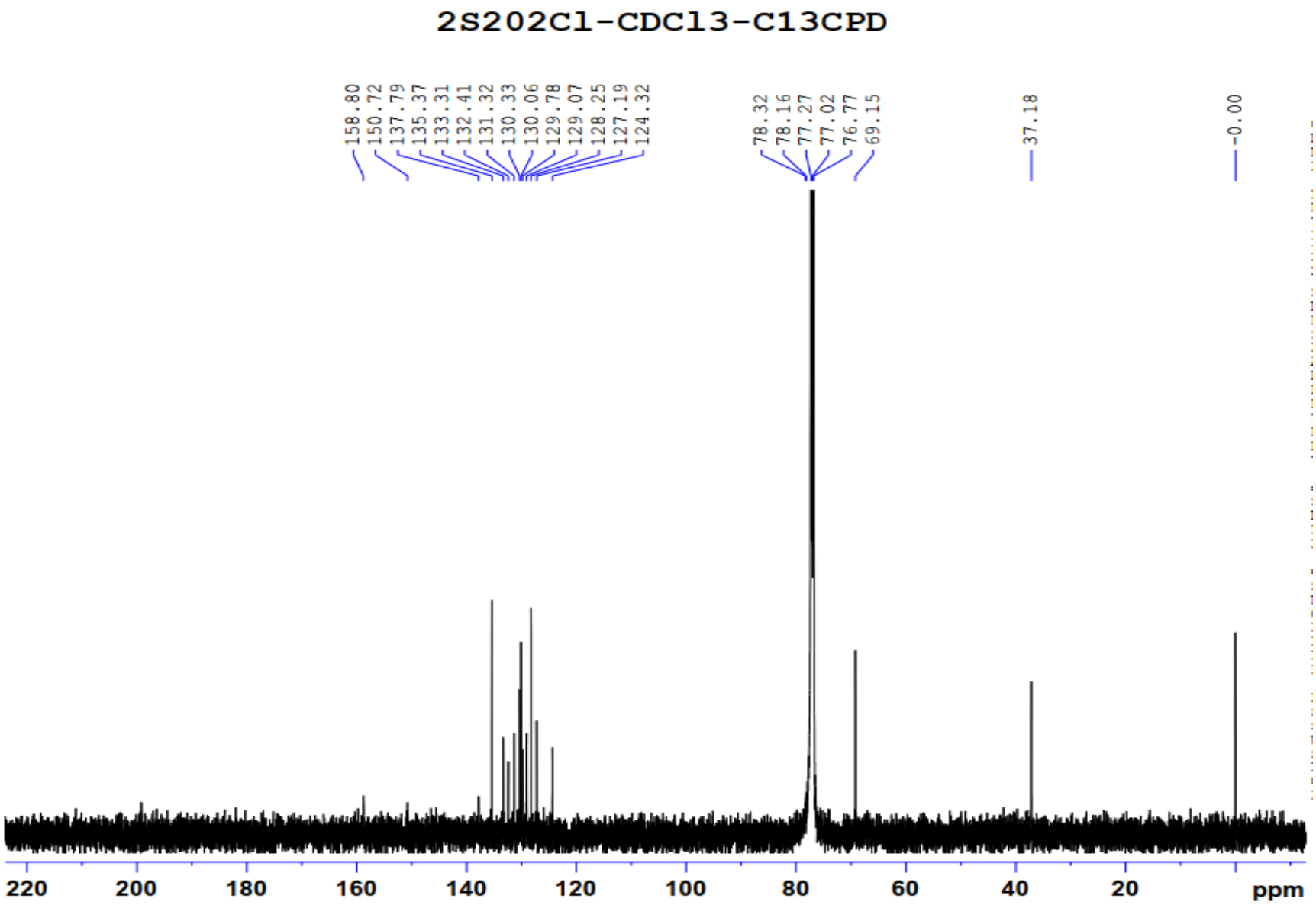
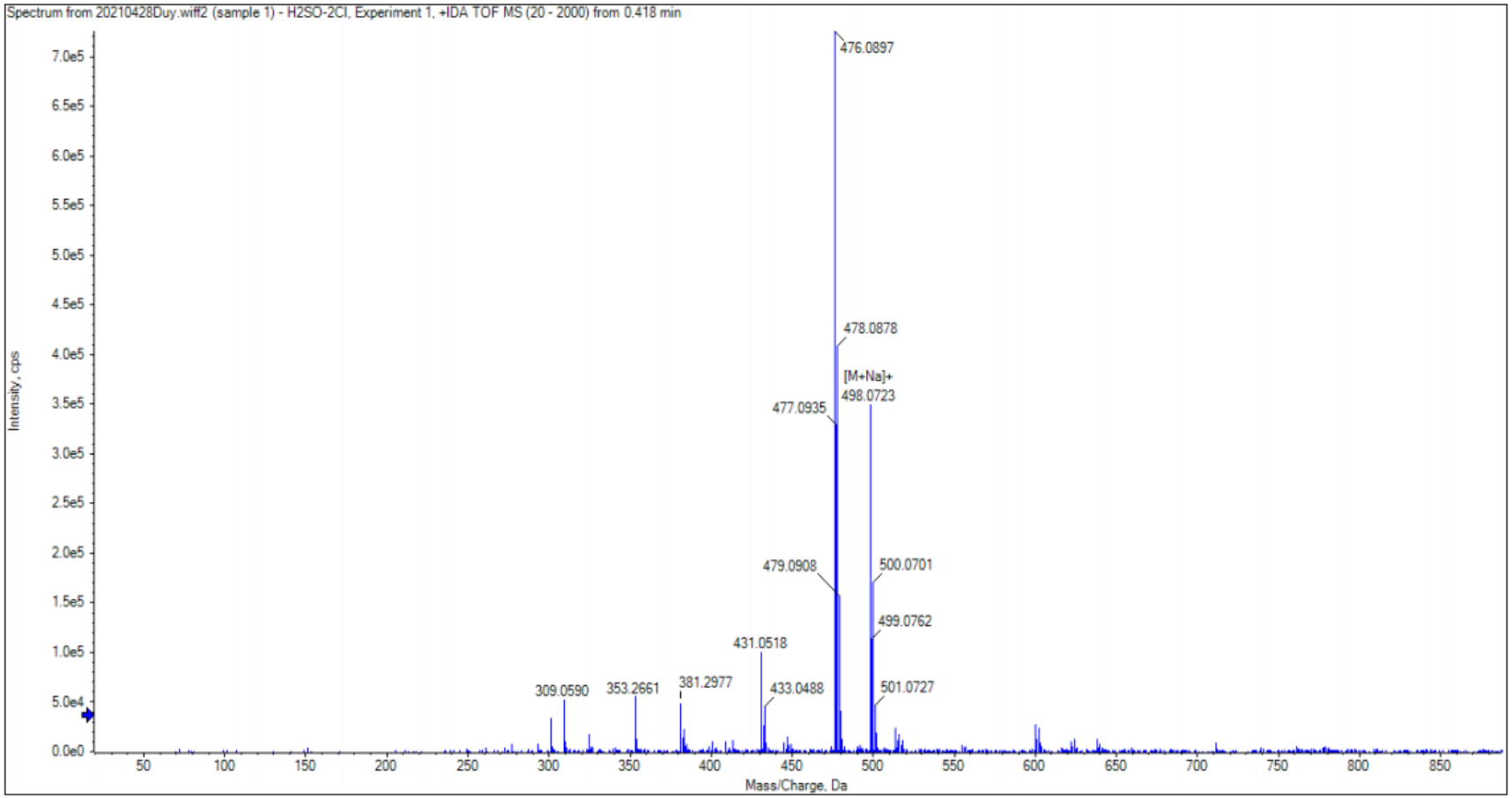


Figure S10. ^{13}C – NMR spectrum of compound 2b



Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C27H22ClNOS2	476.09041	17.0	-1.5	1			NA/NA

Figure S11. HRMS spectrum of compound 2b

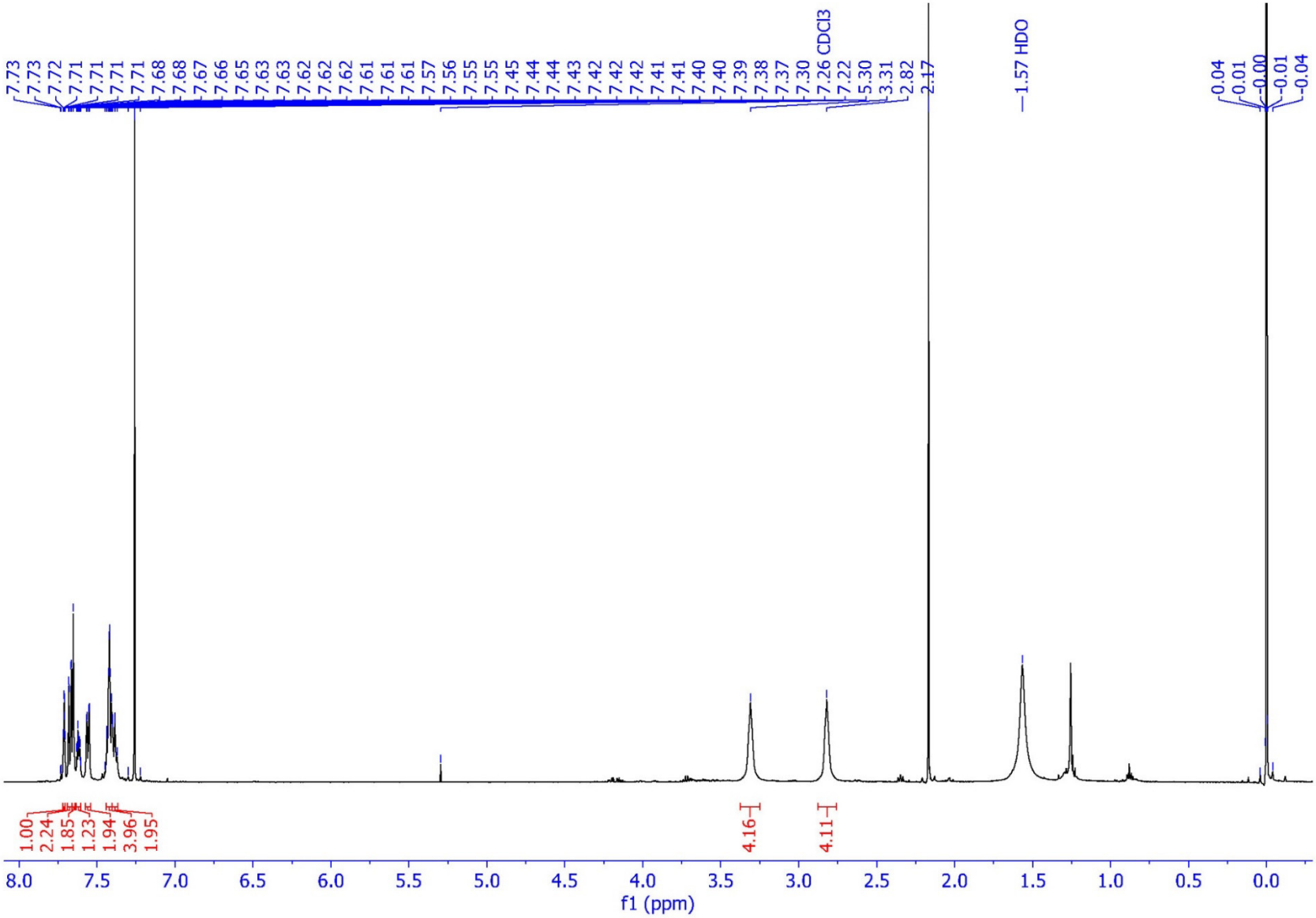


Figure S12. ^{1}H – NMR spectrum of compound 2c

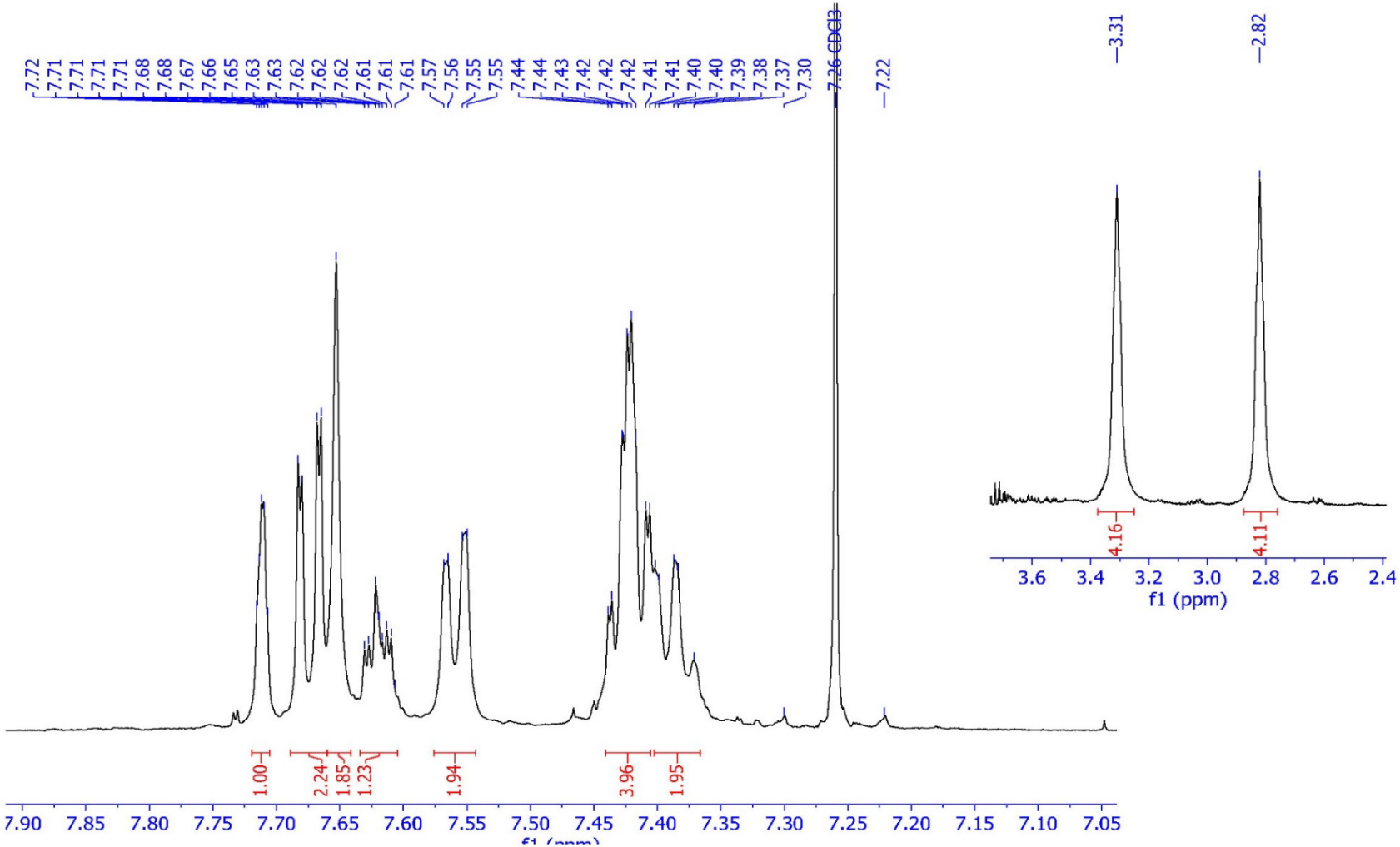


Figure S12. ^{1}H – NMR spectrum of compound 2c (continued)

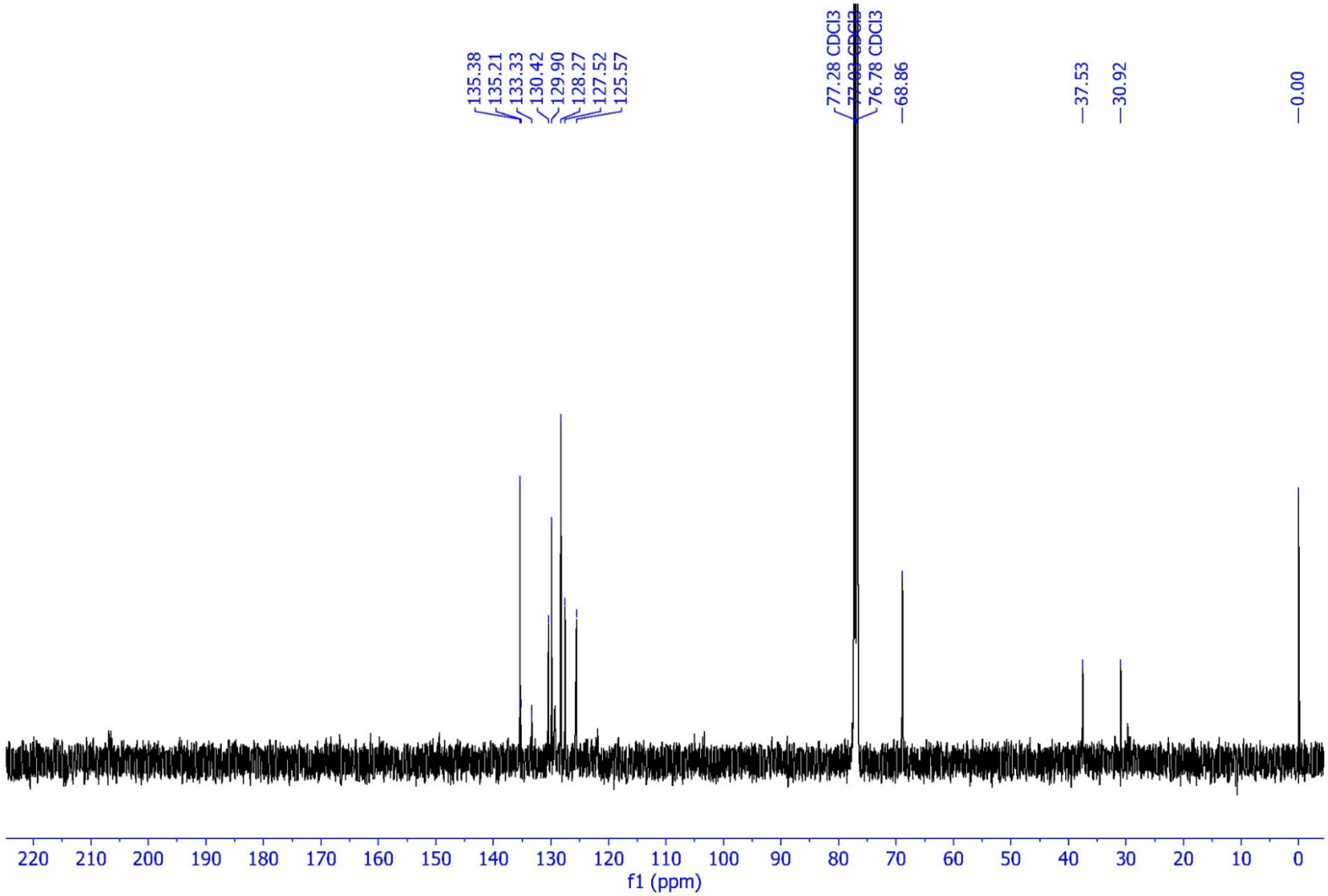


Figure S13. ^{13}C – NMR spectrum of compound 2c

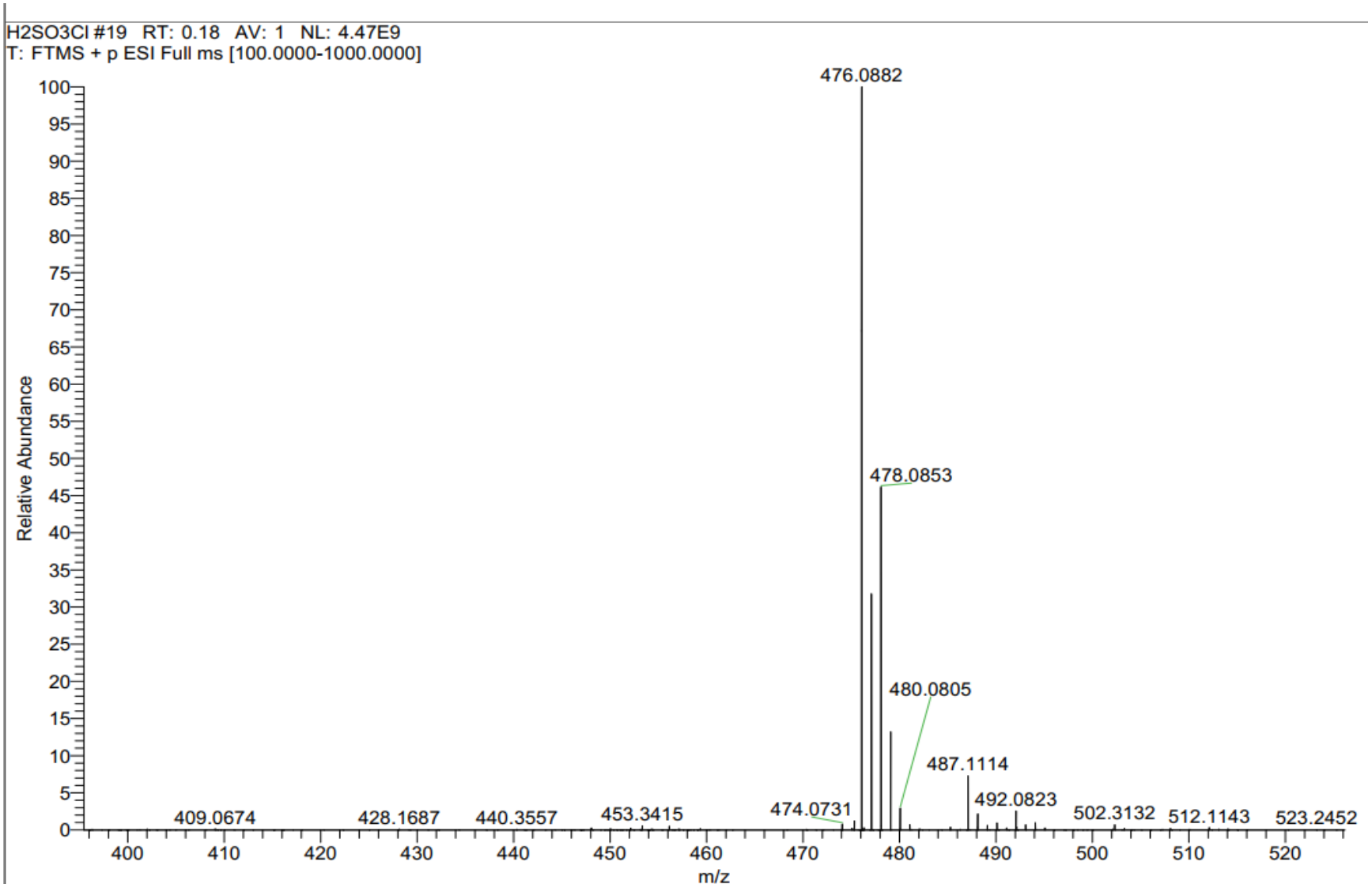


Figure S14. HRMS spectrum of compound 2c

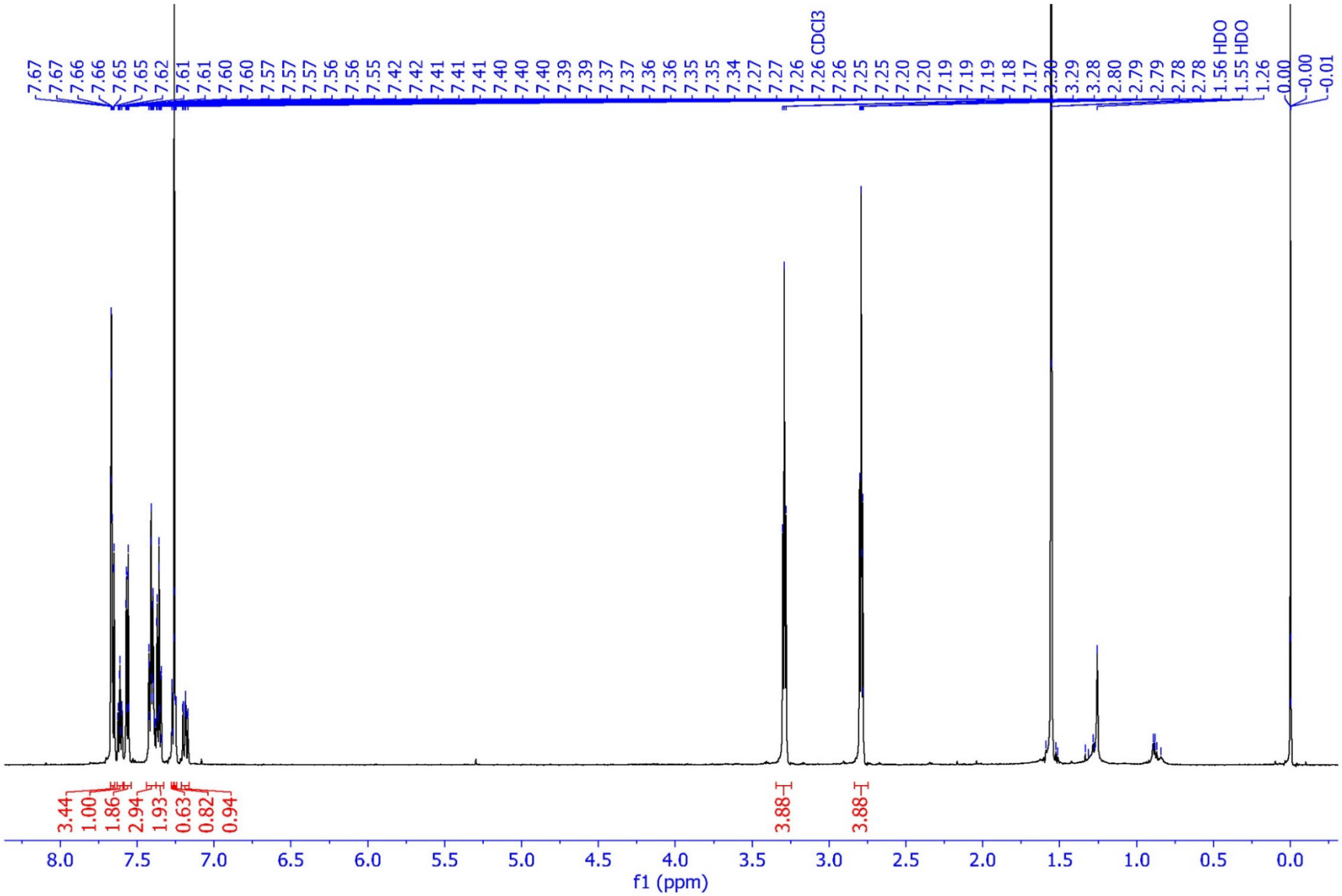


Figure S15. 1H – NMR spectrum of compound 2d

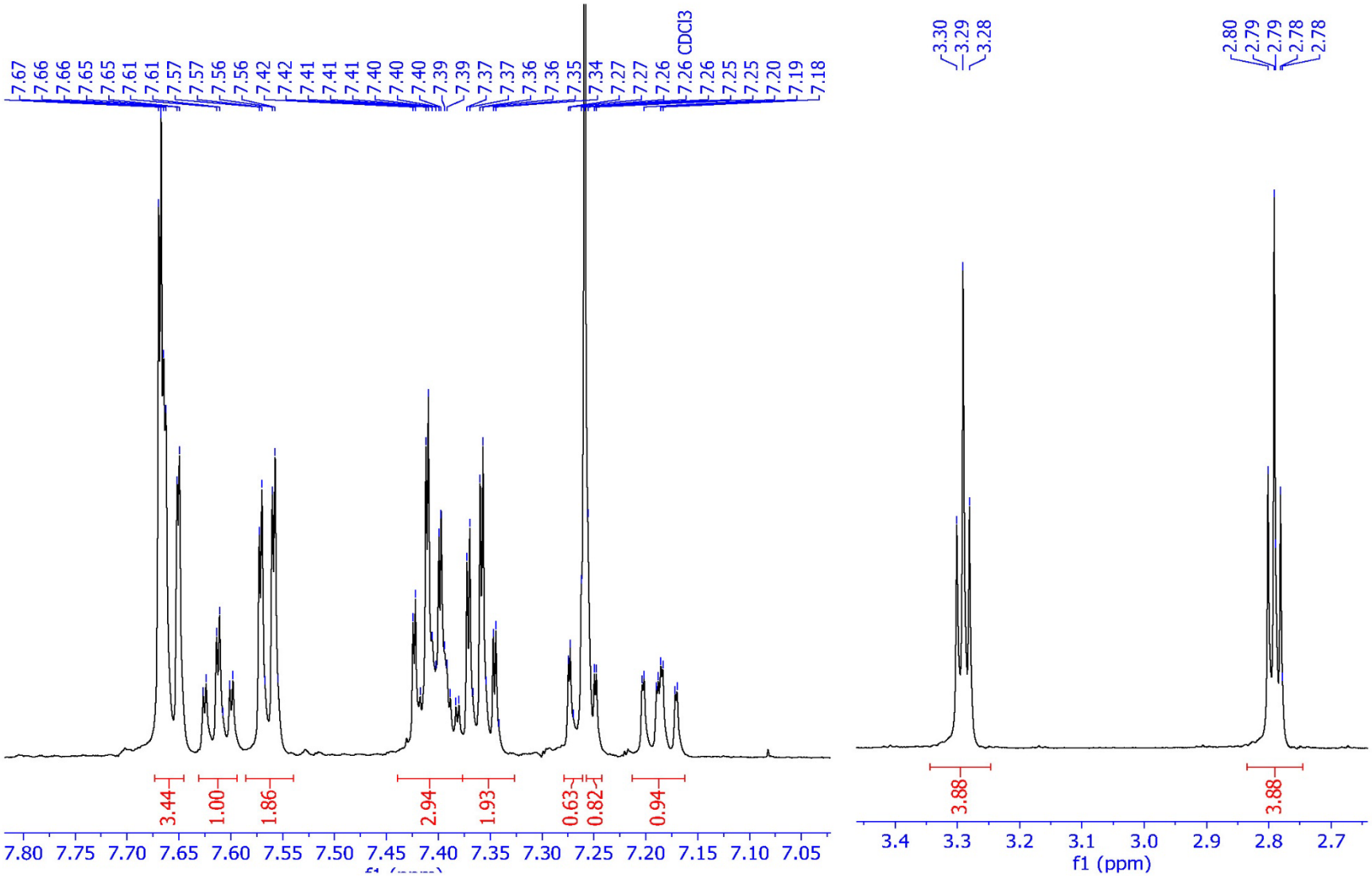


Figure S15. ^{1}H – NMR spectrum of compound 2d *(continued)*

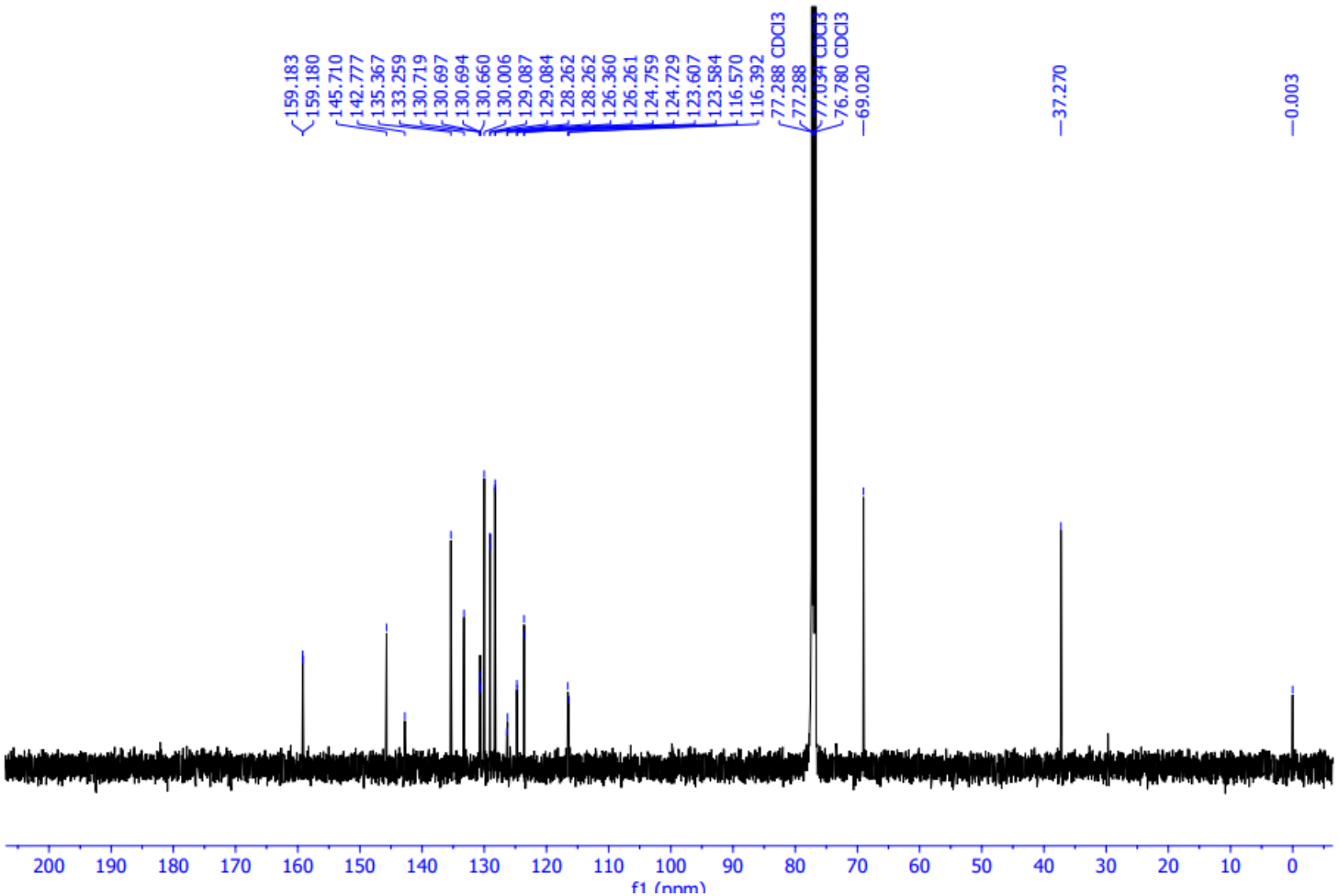


Figure S16. ^{13}C – NMR spectrum of compound 2d

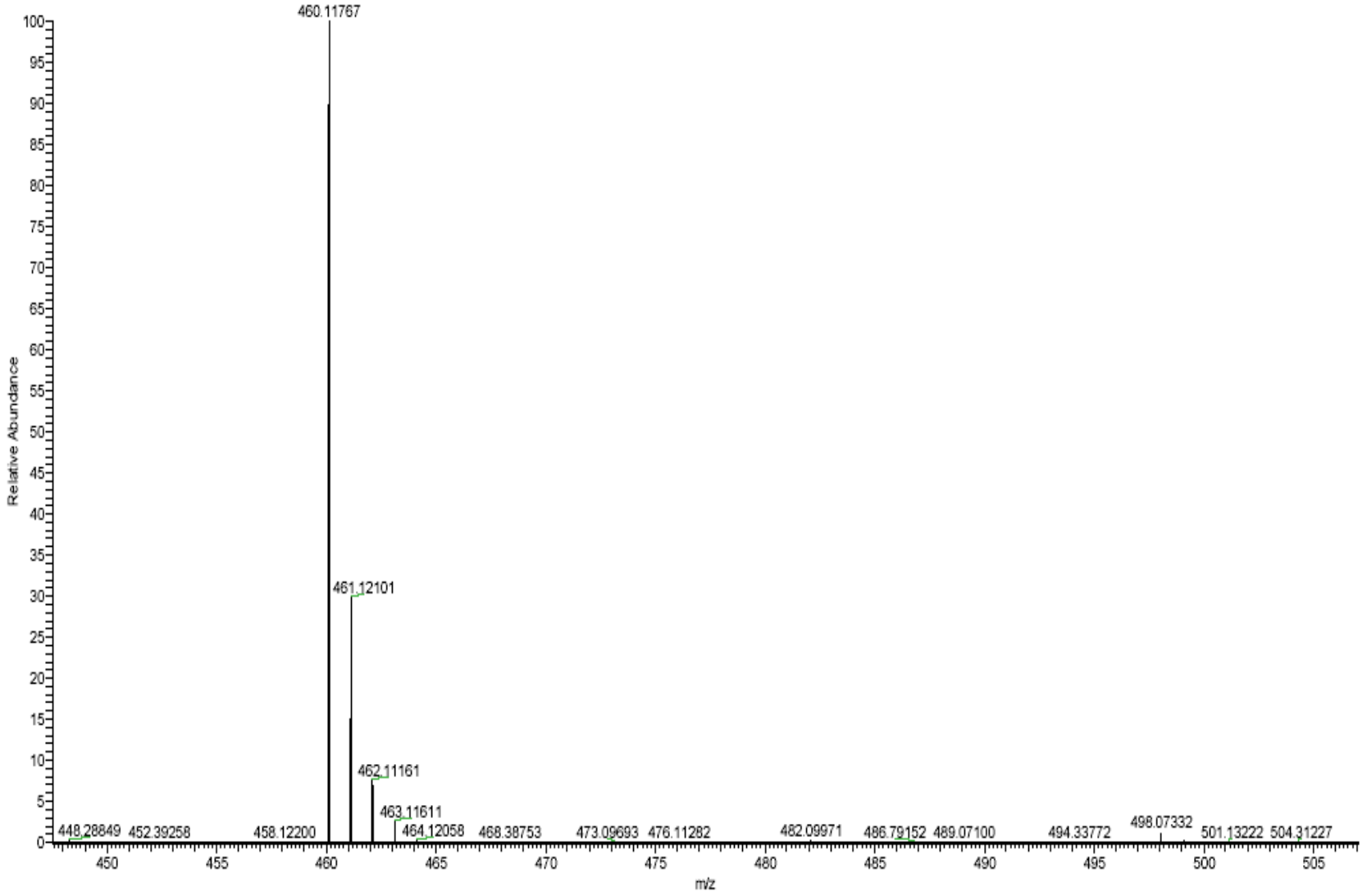


Figure S17. HRMS spectrum of compound 2d

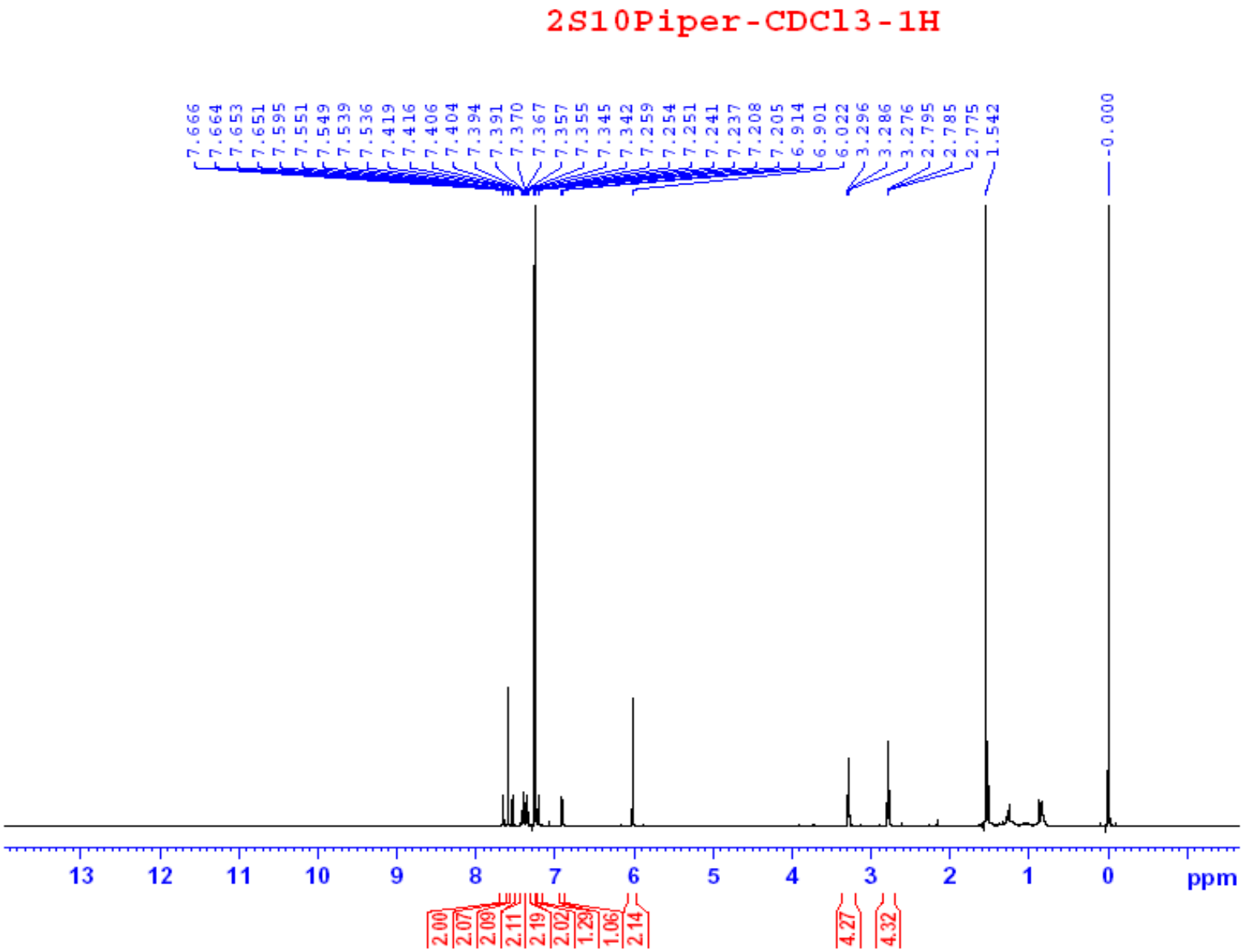


Figure S18. ^{1}H - NMR spectrum of compound 2g

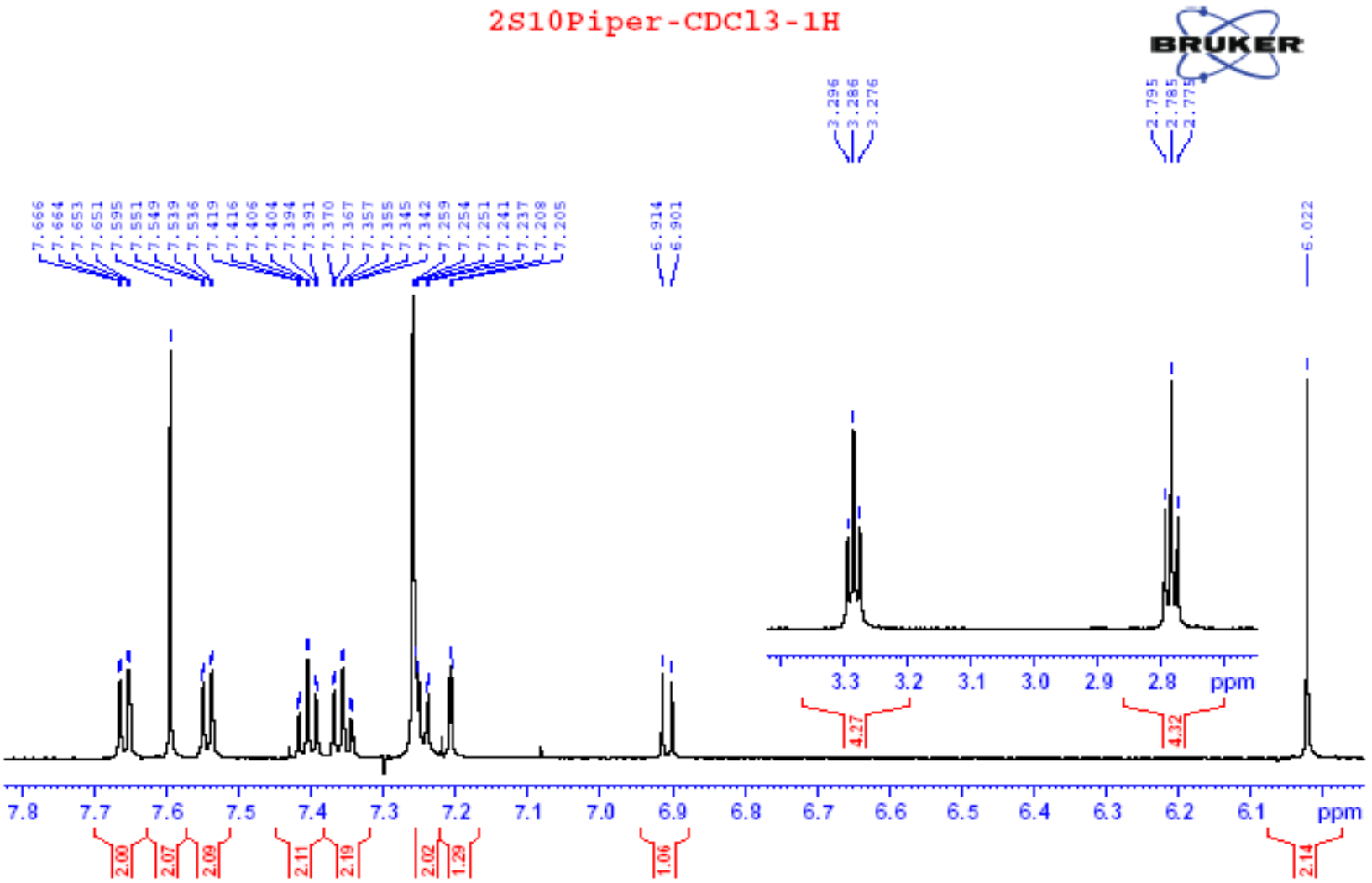


Figure S18. ^{1}H - NMR spectrum of compound 2g *(continued)*

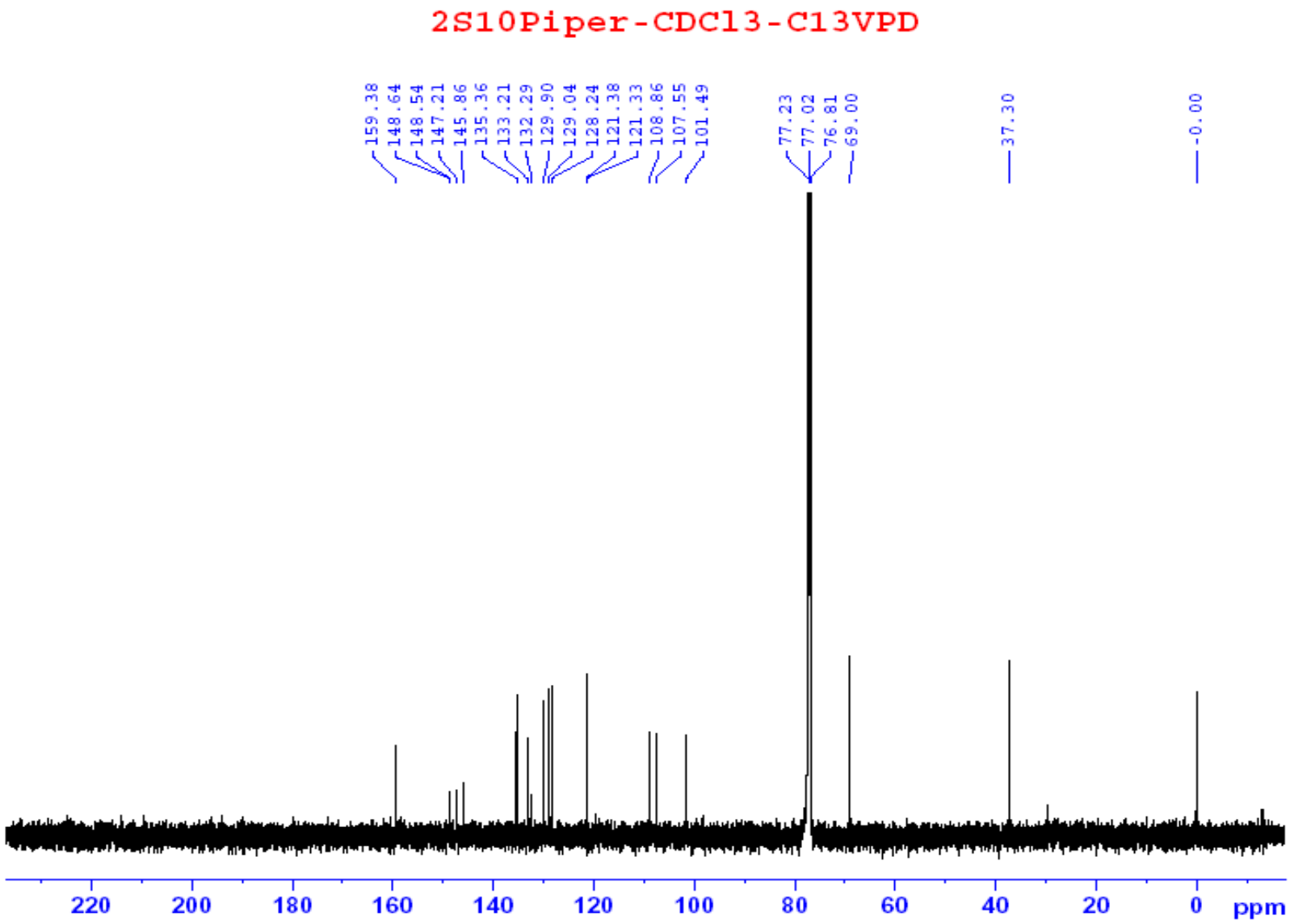


Figure S19. ^{13}C - NMR spectrum of compound 2g

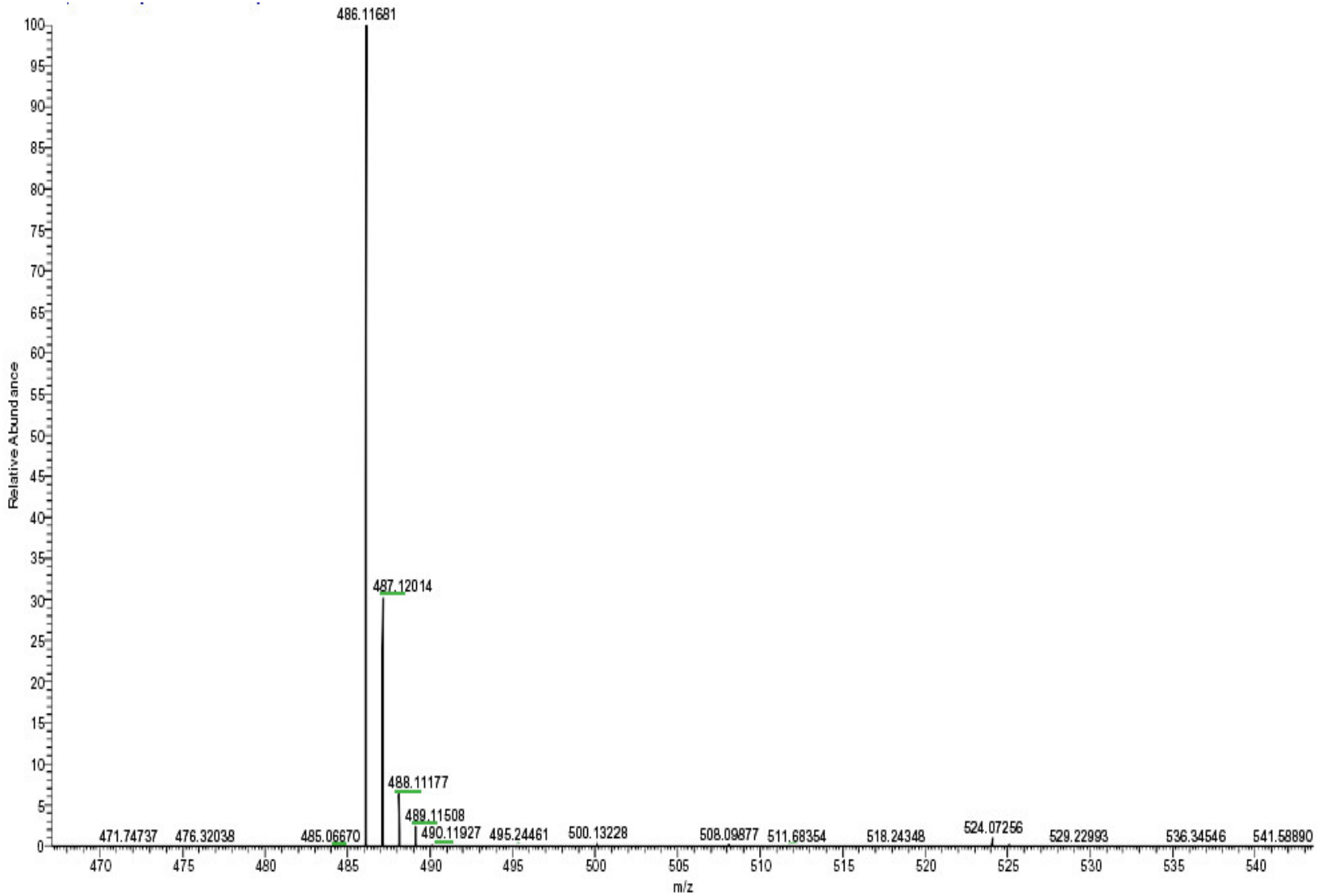


Figure S20. HRMS spectrum of compound 2g

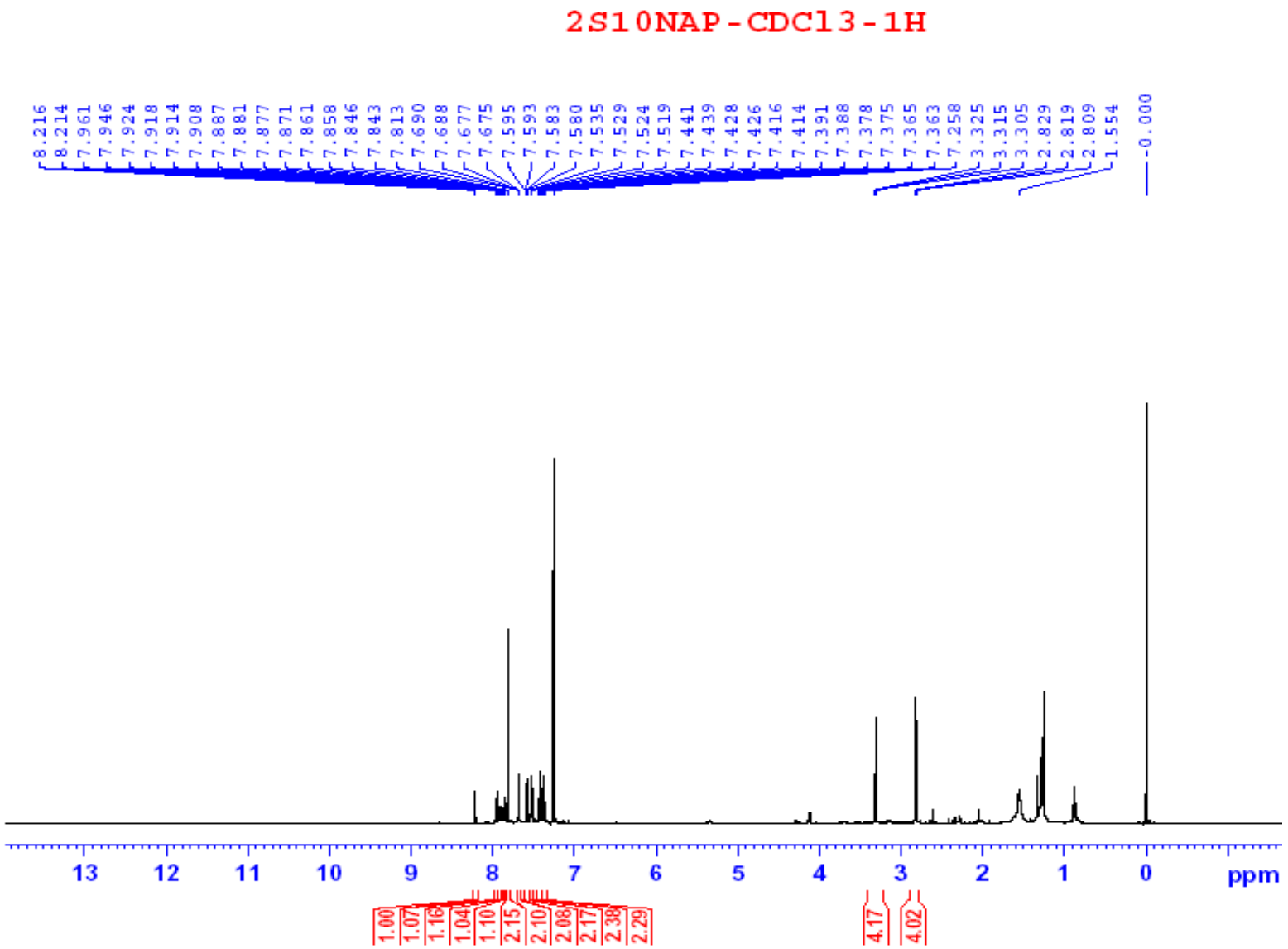


Figure S21. ^{1}H - NMR spectrum of compound 2h

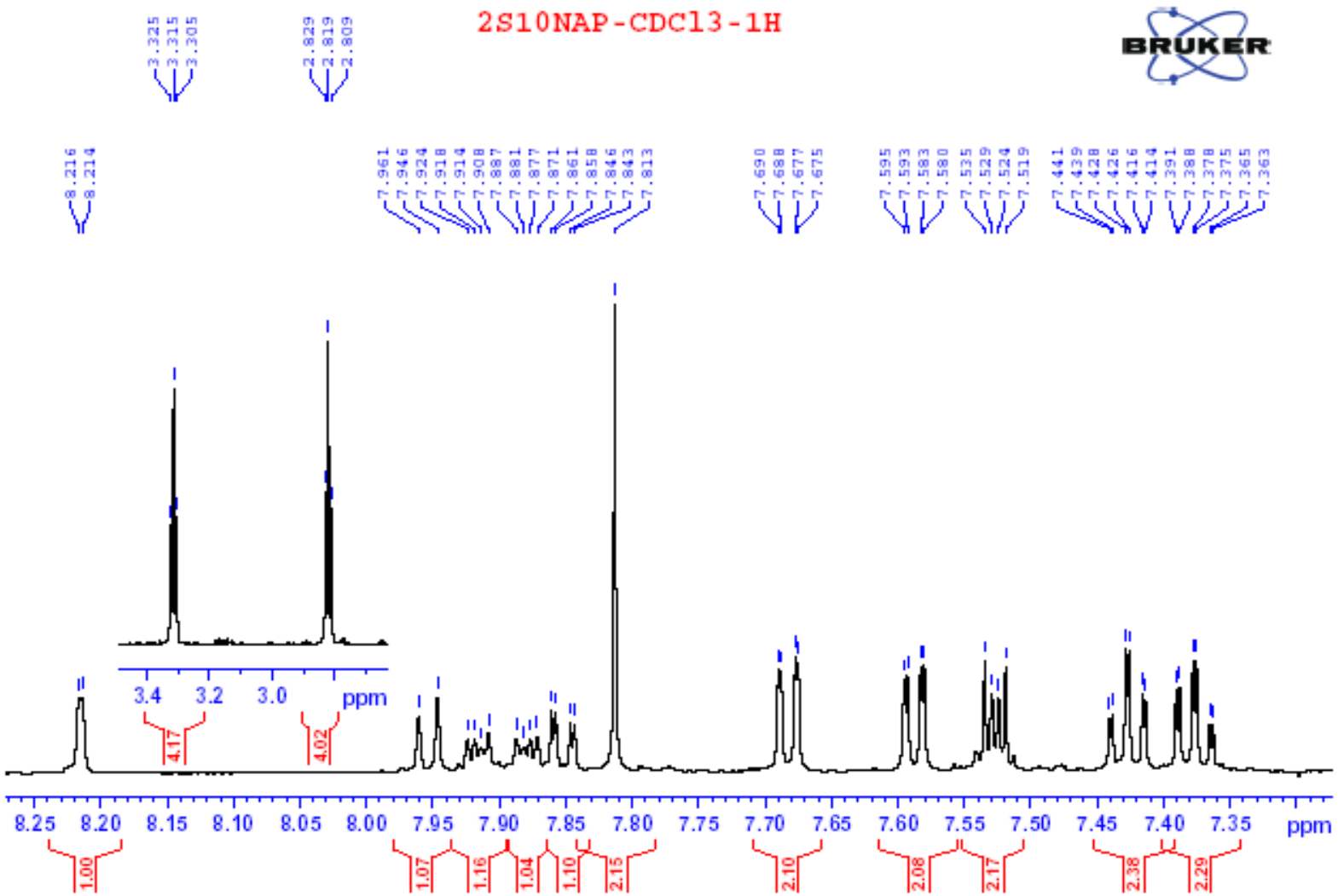


Figure S21. ^{1}H - NMR spectrum of compound 2h (*continued)*

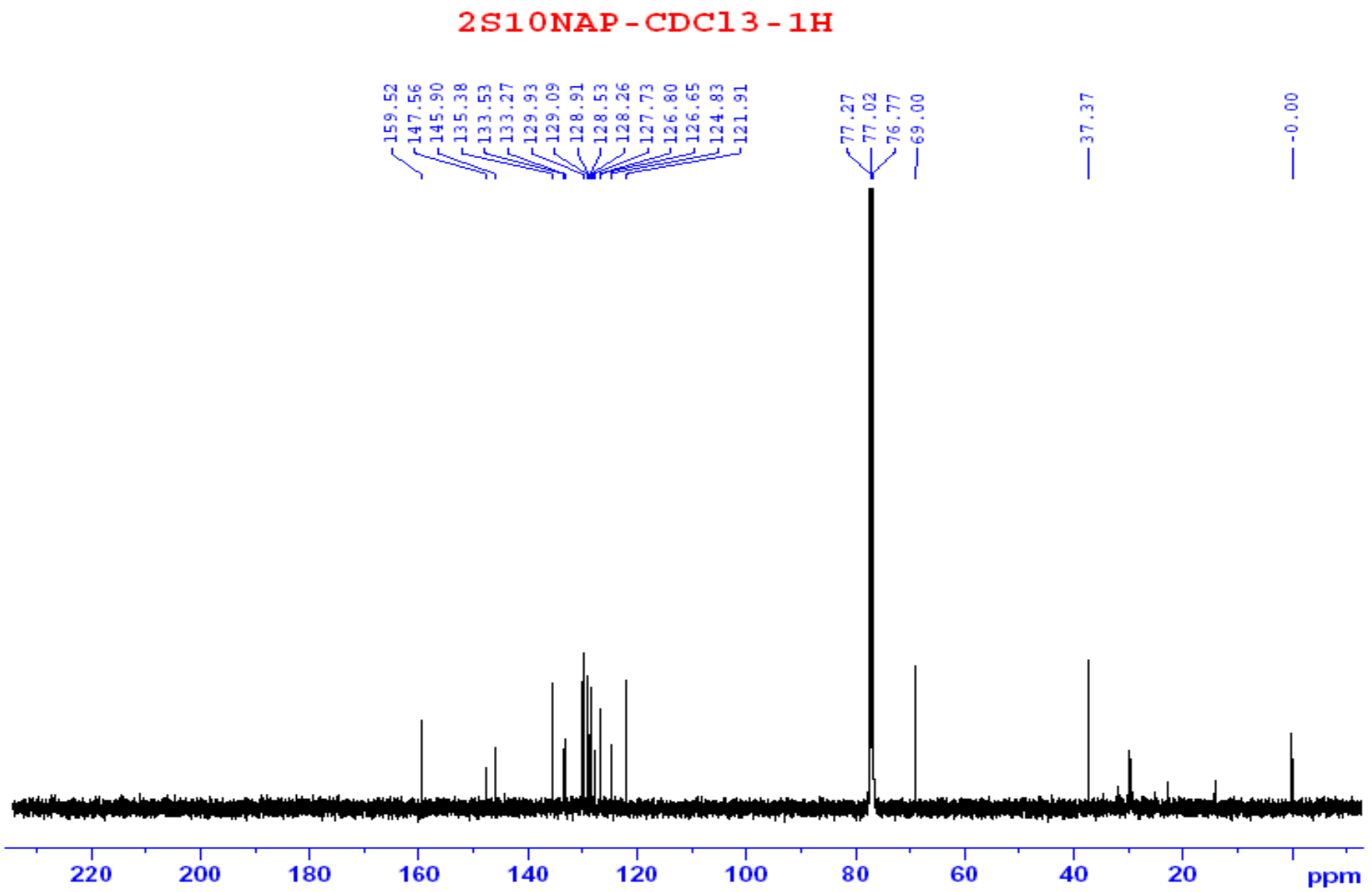


Figure S22. ^{13}C - NMR spectrum of compound 2h

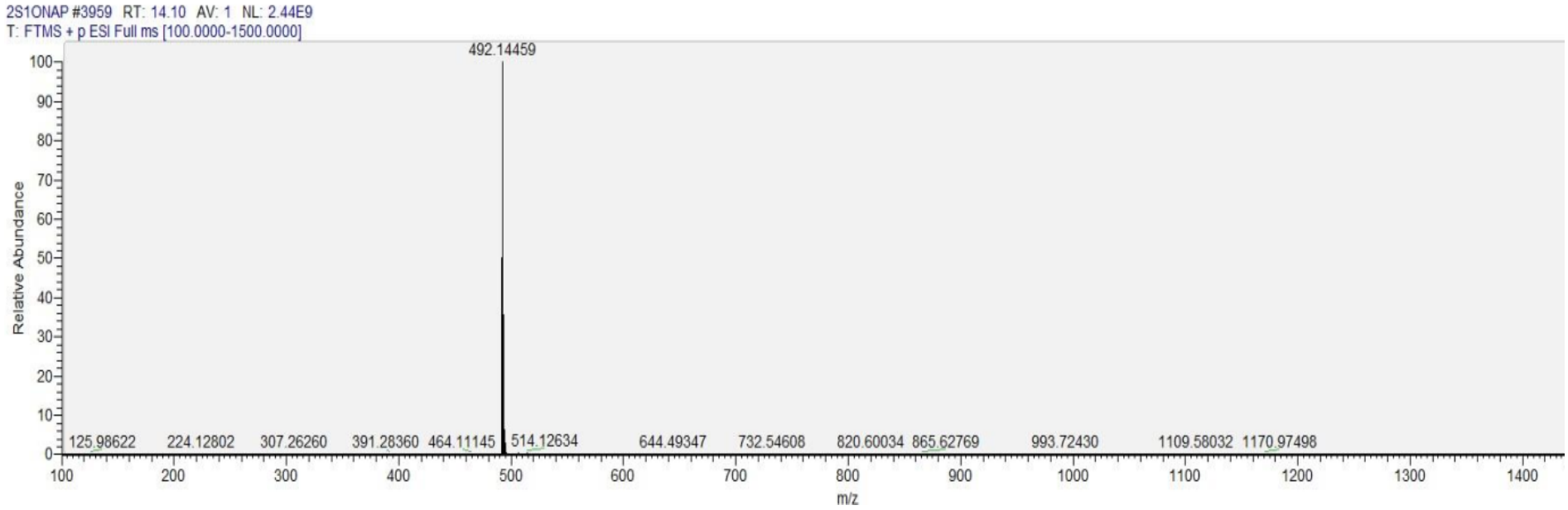


Figure S23. HRMS spectrum of compound 2h