Design, Synthesis, *In Vivo* and *In Silico* Evaluation of Benzothiazoles Bearing 1,3,4-Oxadiazole Moiety as New Antiepileptic Agents

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Supporting Information

Spectral Data

5-benzothiazol-2-yl-2-methoxy-phenol (3)

Yield 70%, m.p. 160-170°C. IR (KBr), Vmax (cm-1): 3244 (str, OH), 3065 (str, C-H, Ar), 2932-2845 (str, C-H, alkane), 1586 (str, C=N), 1530-1431 (C=C, Ar), 1174 (C-O), 1127(C-N), 731 (C-S-C); 1H NMR (CDCl3) (300 MHz): δ (ppm) = 8.032-8.003 (J= 8.7 Hz, d, 2H, benzothiazolyl), 7.493-7.436 (J=17.1 Hz, t, 1H, benzothiazolyl), 7.372-7.320 (J= 15.6 Hz, t, 1H, benzothiazolyl), 6.978-6.952 (J= 7.8 Hz, d, 2H, Ar), 6.078 (s, 1H, Ar), 5.002 (s, 1H, OH), 3.738 (s, 3H, -OCH3); 13C NMR: δ (ppm) = 168.42 (N=C-S), 149.01 (=C-O), 134.01-116.20 (11C, Ar), 56.29 (OCH3); EI-MS (m/z): 257 (M+); Anal. calcd. for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; O, 12.44; S, 12.46. Found: C, 65.65; H, 4.01; N, 5.24; O, 12.14; S, 12.66.

3.1.3. (5-benzothiazol-2-yl-2-methoxy-phenoxy)-acetic acid ethyl ester (4)

Yield 69%, m.p. 160-165°C. IR (KBr), Vmax (cm-1): 3064 (str, C-H, Ar), 2935-2849 (str, C-H, alkane), 1763 (str, C=O), 1586 (str, C=N), 1523-1432 (C=C, Ar), 1193 (C-O), 1136 (C-N), 727 (C-S-C); 1H NMR (CDCl3) (300 MHz): δ (ppm) = 8.023-7.993 (J= 9 Hz, d, 2H, benzothiazolyl), 7.492-7.434 (J=17.4 Hz, t, 1H, benzothiazolyl), 7.371-7.320 (J= 15.3 Hz, t, 1H, benzothiazolyl), 6.980-6.950 (J= 9 Hz, d, 2H, Ar), 6.088 (s, 1H, Ar), 4.090 (s, 2H, -CH2-), 4.014 (q, 4H, -CH2-), 3.736 (s, 3H, -OCH3), 1.252 (s, 3H, -CH3); 13C NMR: δ (ppm) = 169.02 (C=O), 168.92 (N=C-S), 152.32 (=C-O), 140.12-113.21 (10C, Ar), 77.23 (-

CH2-), 58.22 (OCH3), 14.28 (CH3); EI-MS (m/z): 343 (M+); Anal. calcd. for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08; O, 18.64; S, 9.34. Found: C, 62.76; H, 4.74; N, 4.16; O, 18.85; S, 9.54.

3.1.4. (5-benzothiazol-2-yl-2-methoxy-phenoxy)-acetic acid hydrazide (5)

Yield 72%, m.p. 170- 175°C. IR (KBr), Vmax (cm-1): 3648 (str, N-H), 3065 (str, C-H, Ar), 2932-2849 (str, C-H, alkane), 1757 (str, C=O), 1558 (str, C=N), 1554-1435 (C=C, Ar), 1173 (C-O), 1146 (C-N), 729 (C-S-C); 1H NMR (CDCl3) (300 MHz): δ (ppm) = 8.023-7.994 (J=8.7 Hz, d, 2H, benzothiazolyl), 7.489-7.431 (J= 17.4 Hz, t, 1H, benzothiazolyl), 7.371-7.320 (J=15.3 Hz, t, 1H, benzothiazolyl), 7.265 (s, 1H, NH), 6.979-6.949 (J= 9 Hz, d, 2H, Ar), 6.087 (s, 1H, Ar), 4.089 (s, 2H, -CH2-), 3.736 (s, 3H, OCH3), 1.981 (s, 2H, NH2); 13C NMR: δ (ppm) = 169.03 (C=O), 168.93 (N=C-S), 152.31 (=C-O), 140.10-113.20 (11C, Ar), 77.22 (-CH_2-), 58.21 (OCH_3); EI-MS (m/z): 329 (M+); Anal. calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76; O, 14.57; S, 9.74. Found: C, 58.04; H, 4.69; N, 12.94; O, 14.65; S, 9.56.

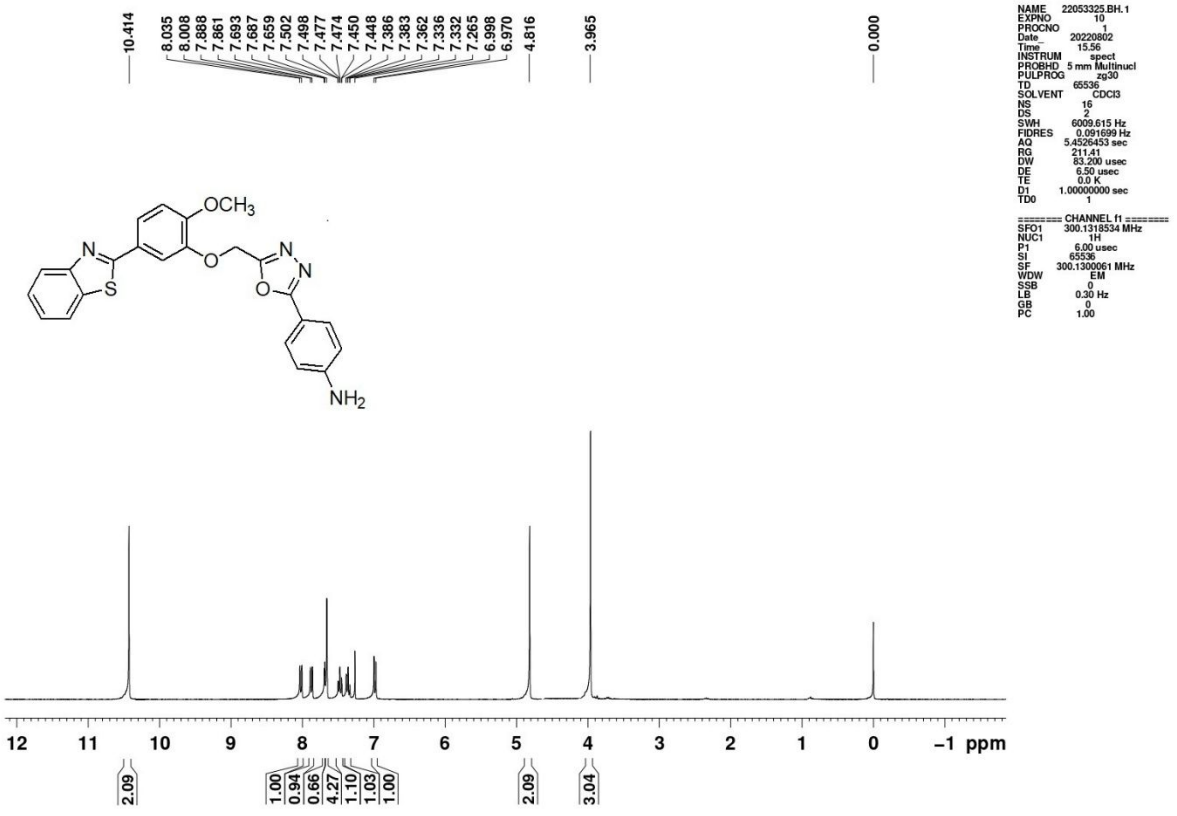

Figure 1: [1]H-NMR spectra of compound **6a**

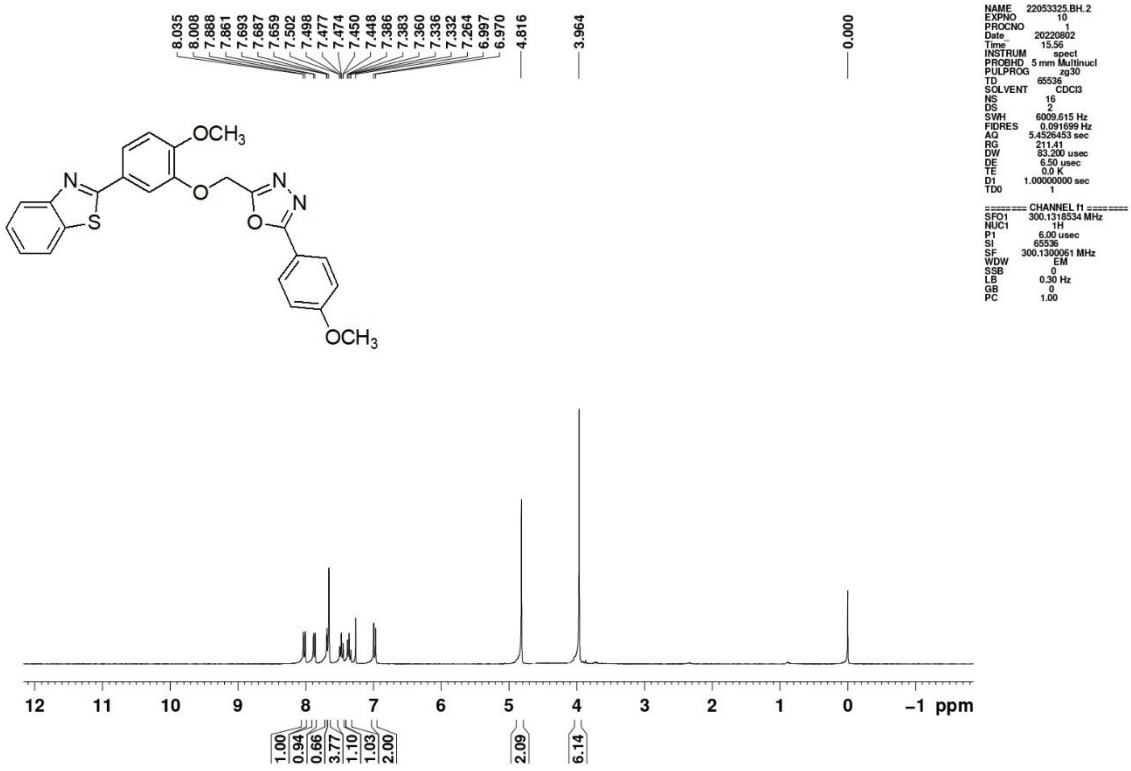

Figure 2: ^{1}H-NMR spectra of compound **6b**

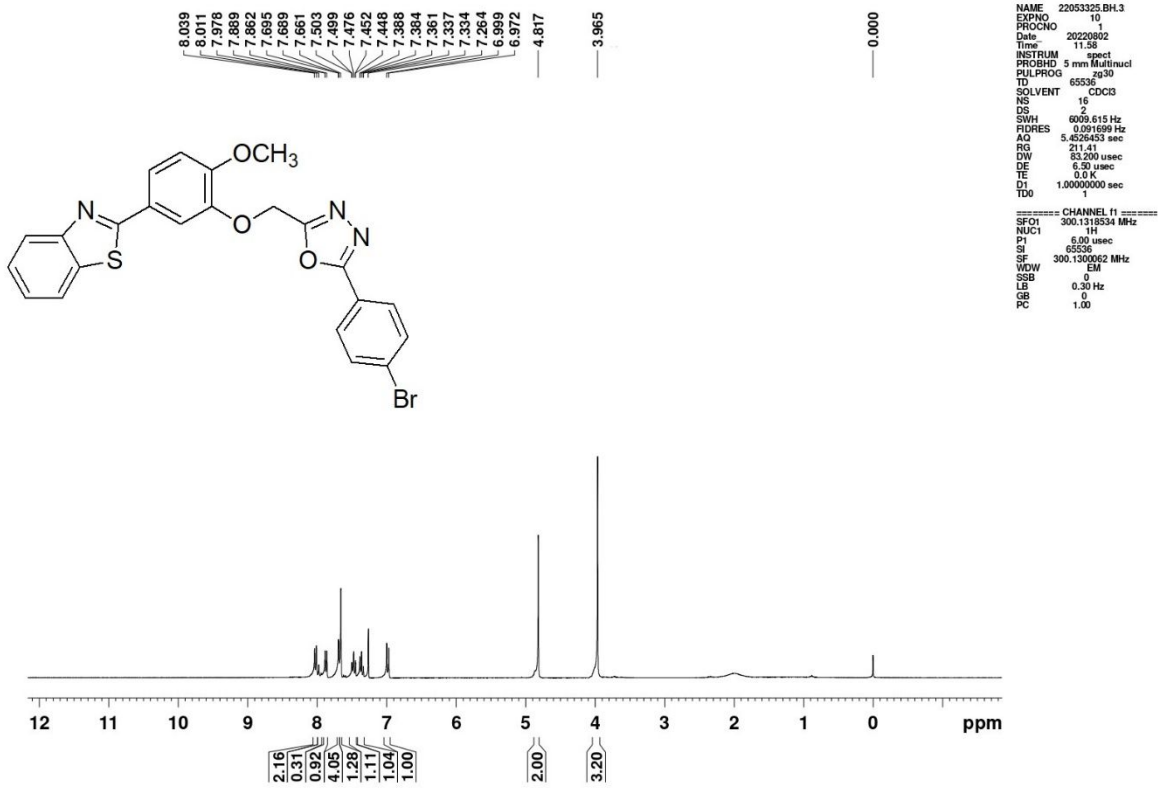

Figure 3: [1]H-NMR spectra of compound **6c**

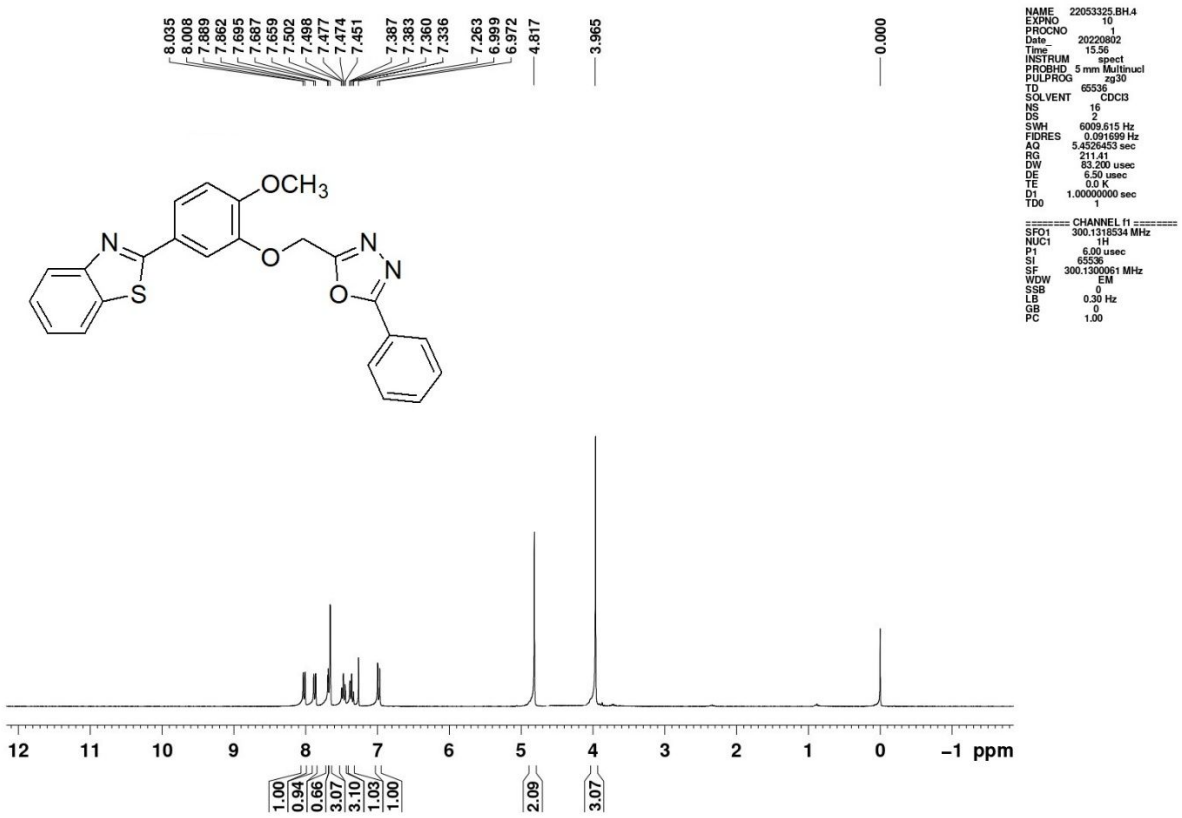

Figure 4: [1]H-NMR spectra of compound **6d**

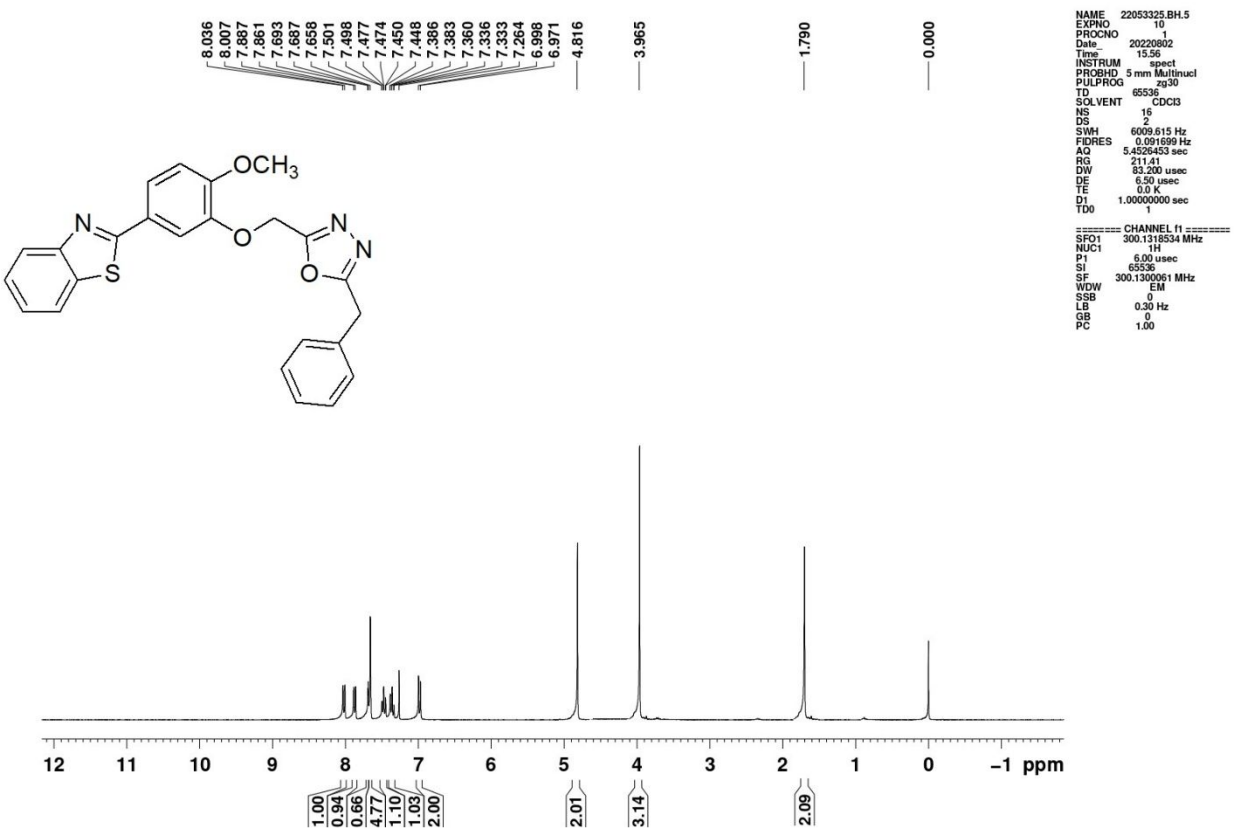

Figure 5: ^{1}H-NMR spectra of compound **6e**

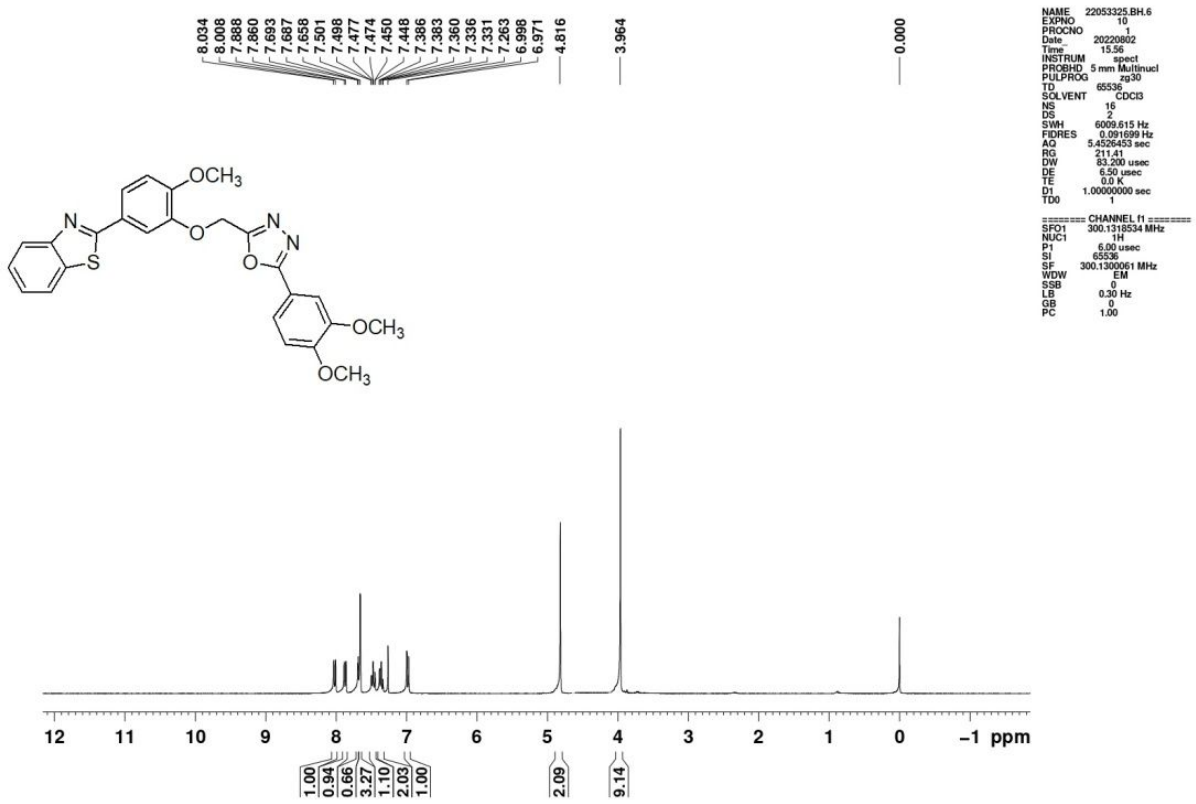

Figure 6: [1]H-NMR spectra of compound **6f**

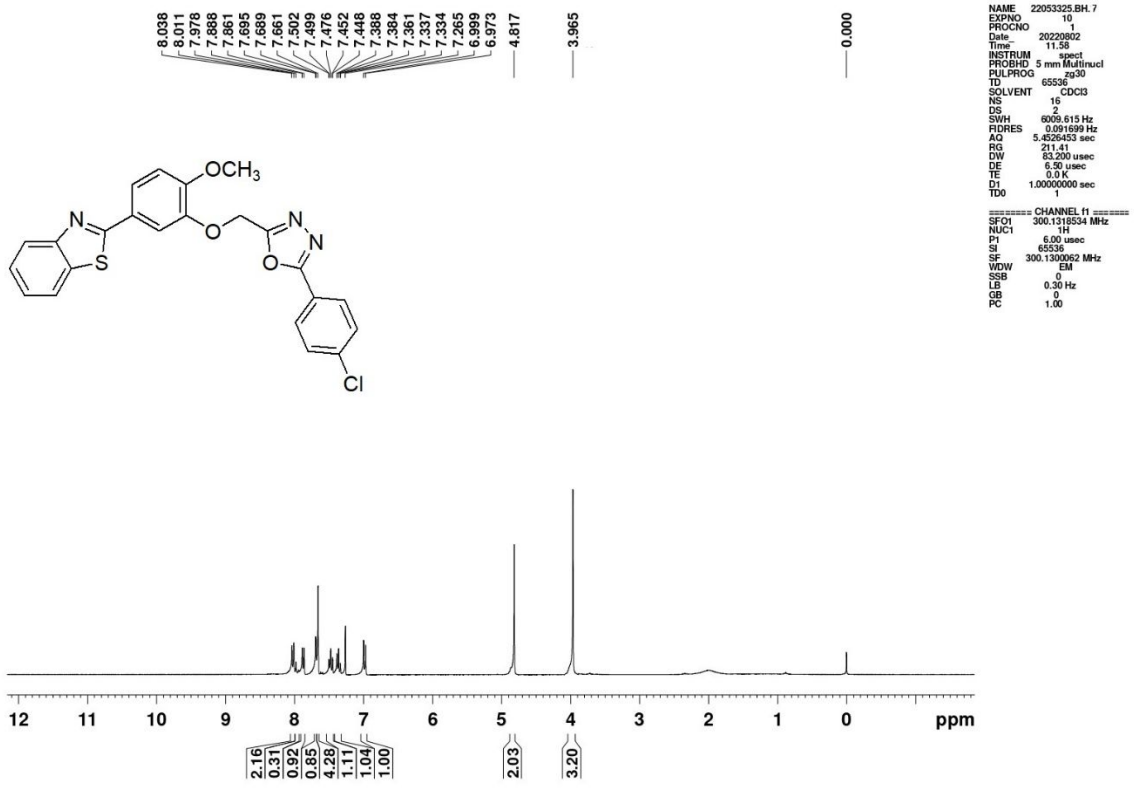

Figure 7: ^{1}H-NMR spectra of compound **6g**

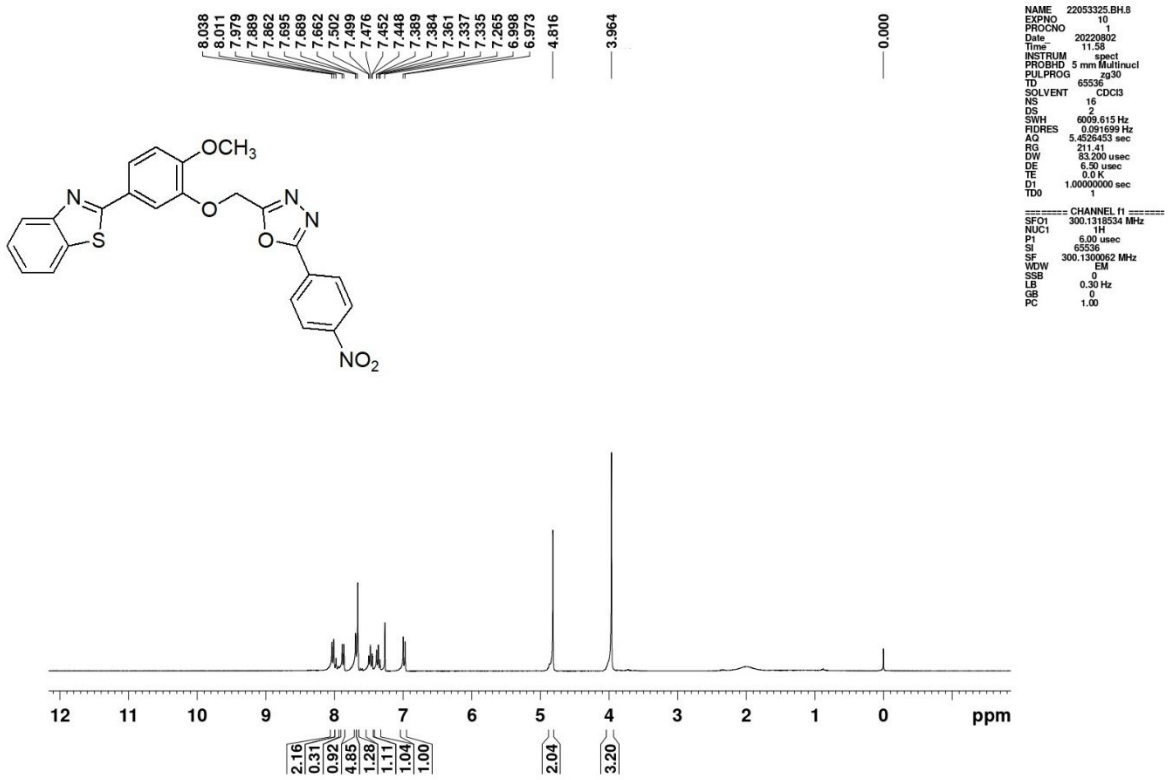

Figure 8: ^{1}H-NMR spectra of compound **6h**

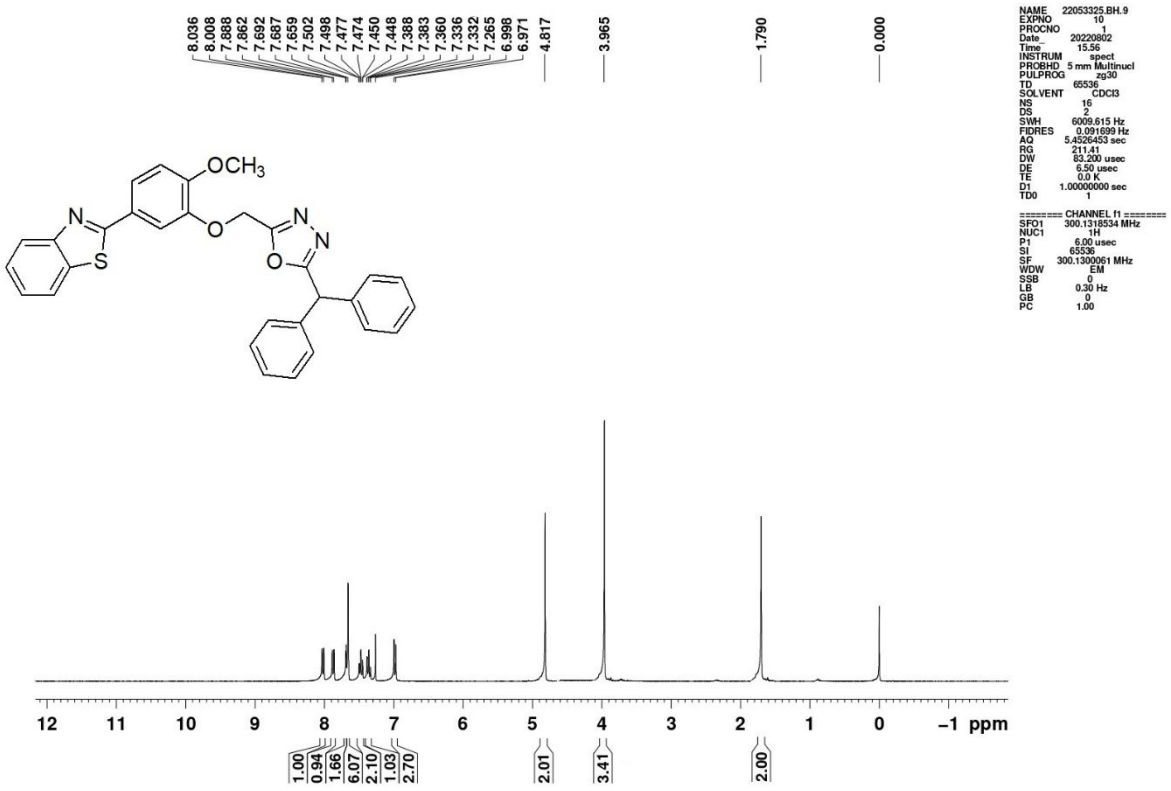

Figure 9: [1]H-NMR spectra of compound **6i**

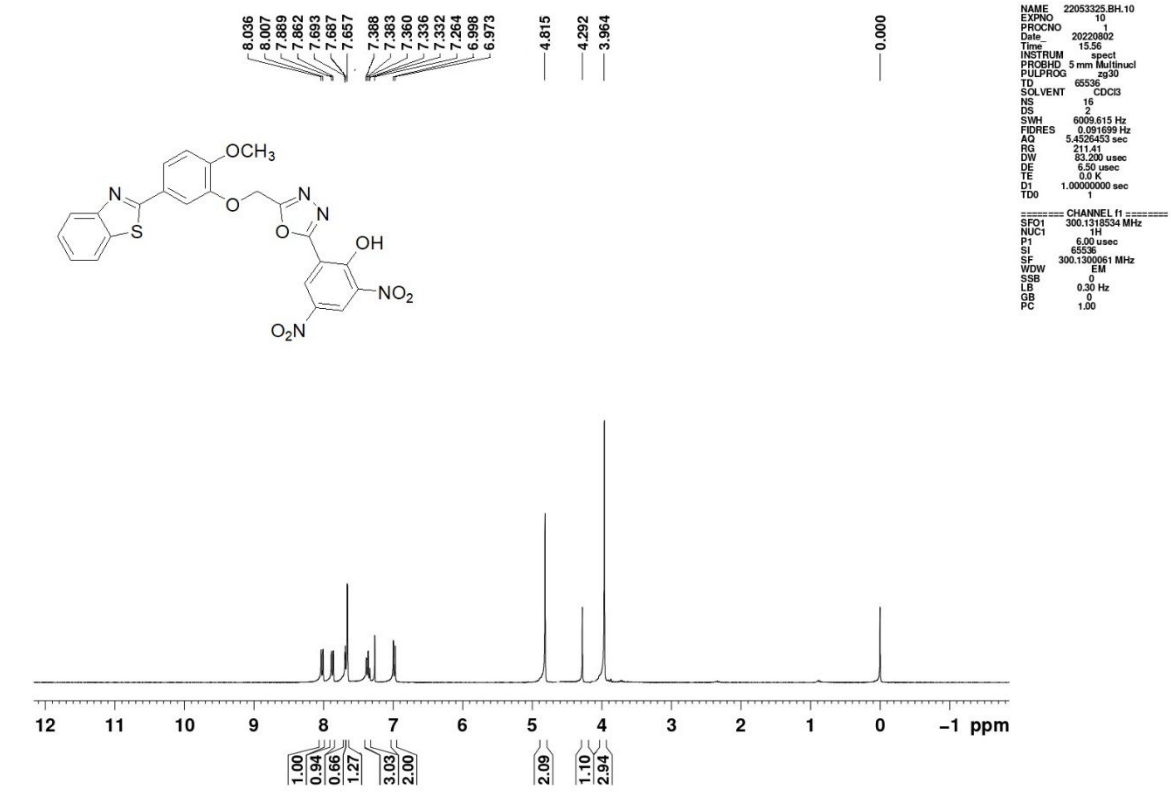

Figure 10: ^{1}H-NMR spectra of compound **6j**

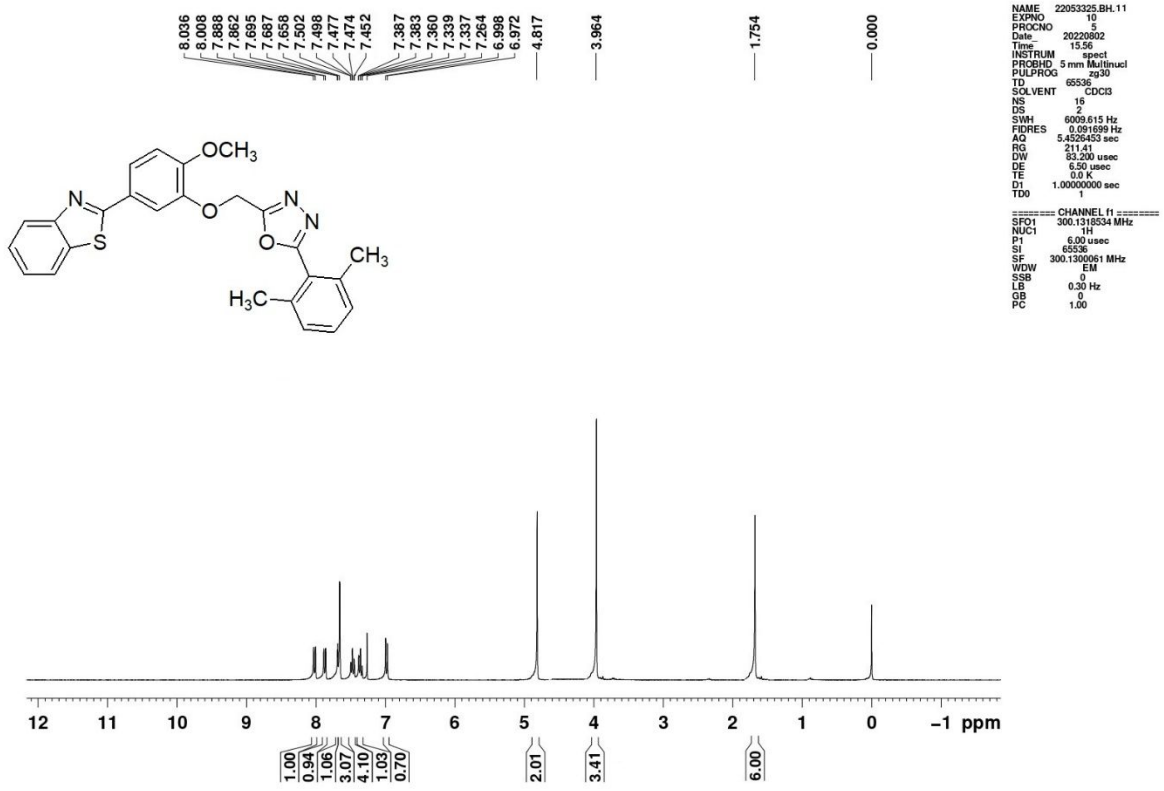

Figure 11: ^{1}H-NMR spectra of compound **6k**

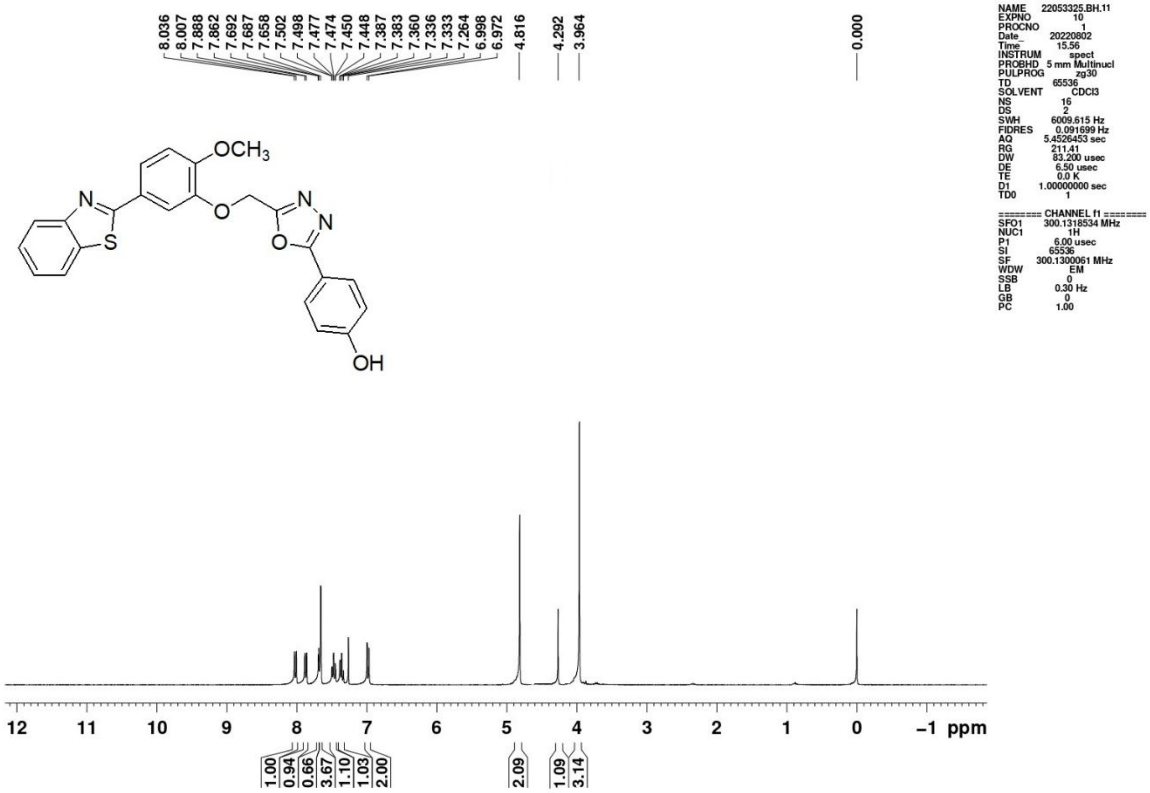

Figure 12: [1]H-NMR spectra of compound **6l**

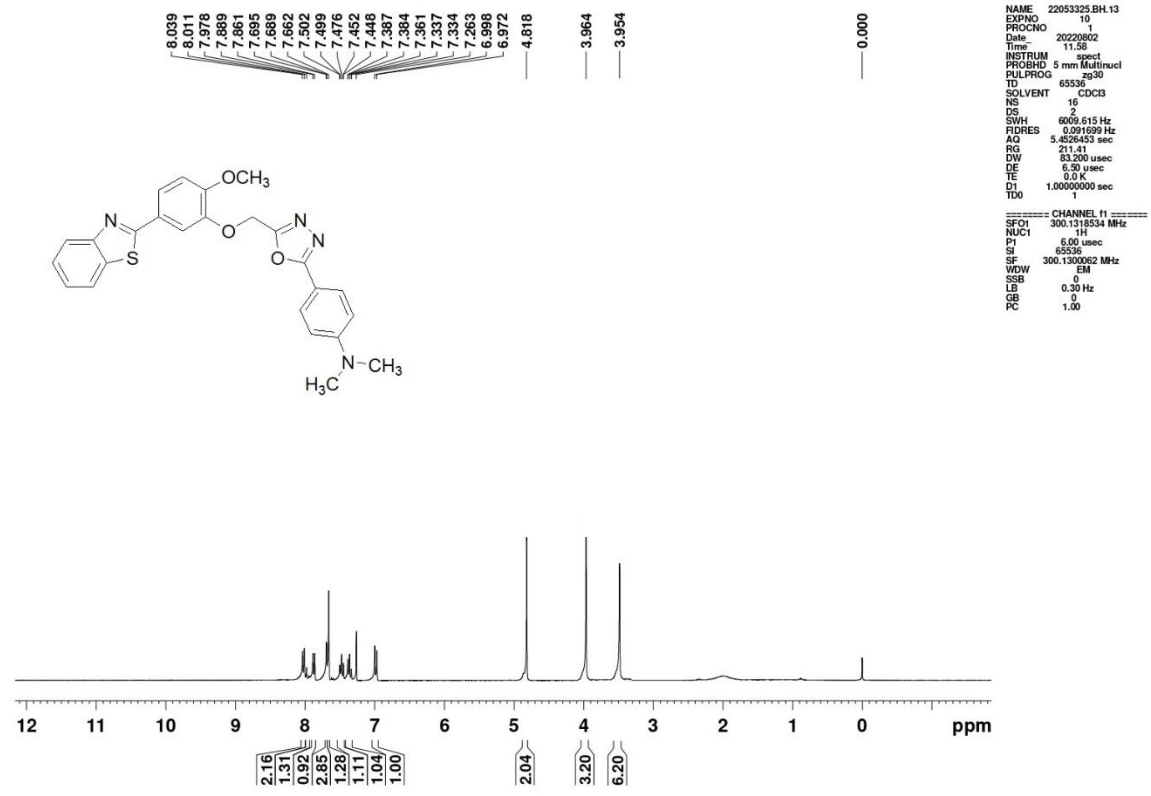

Figure 13: [1]H-NMR spectra of compound **6m**

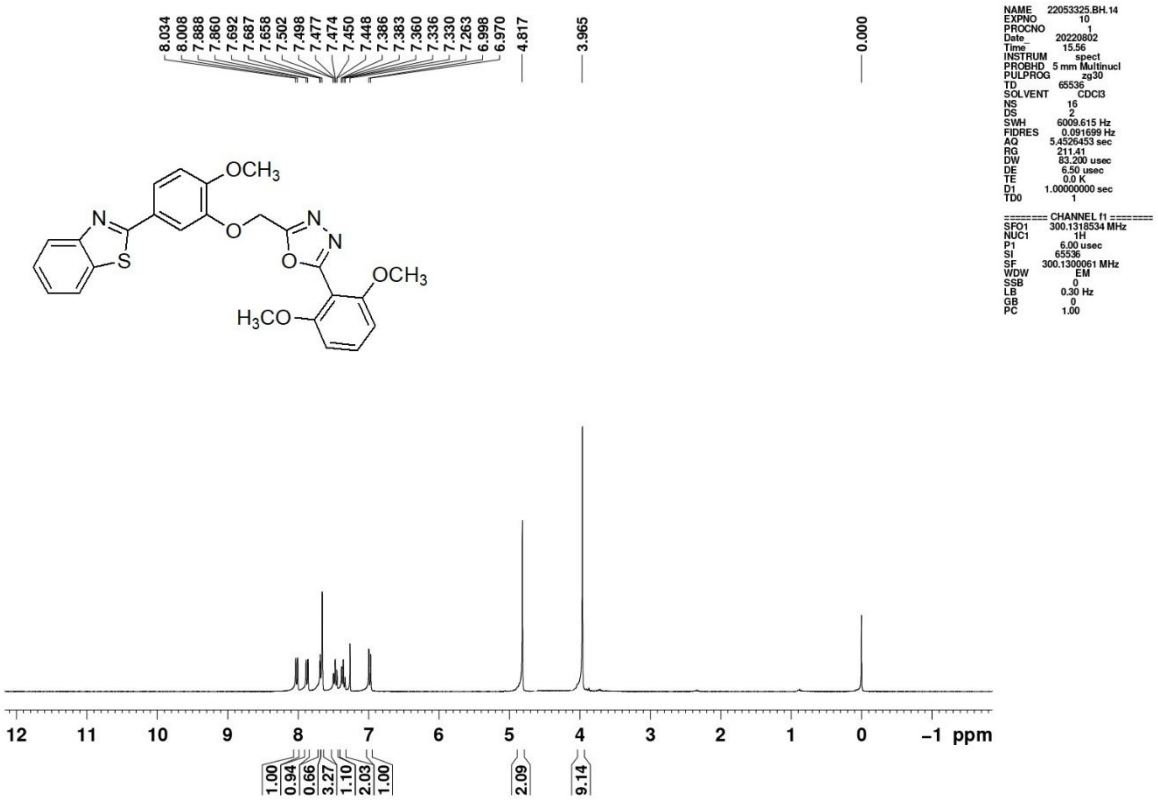

Figure 14: [1]H-NMR spectra of compound **6n**

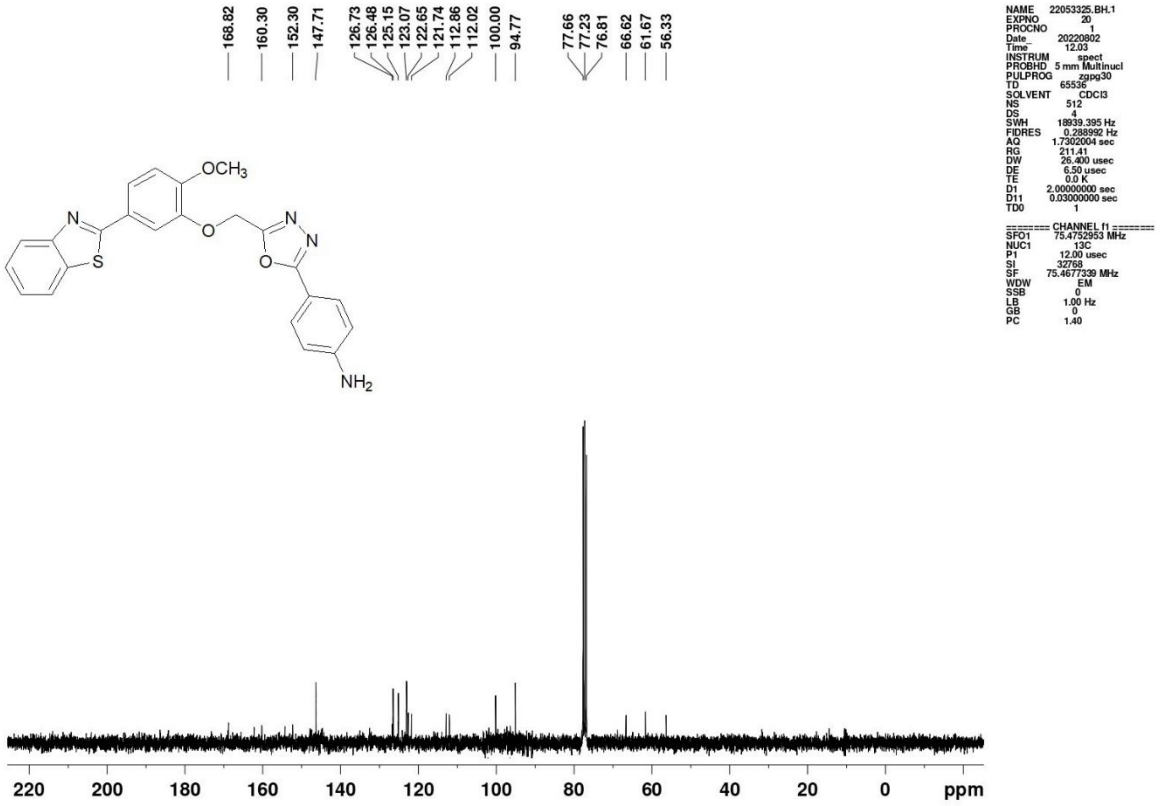

Figure 15: ^{13}C-NMR spectra of compound **6a**

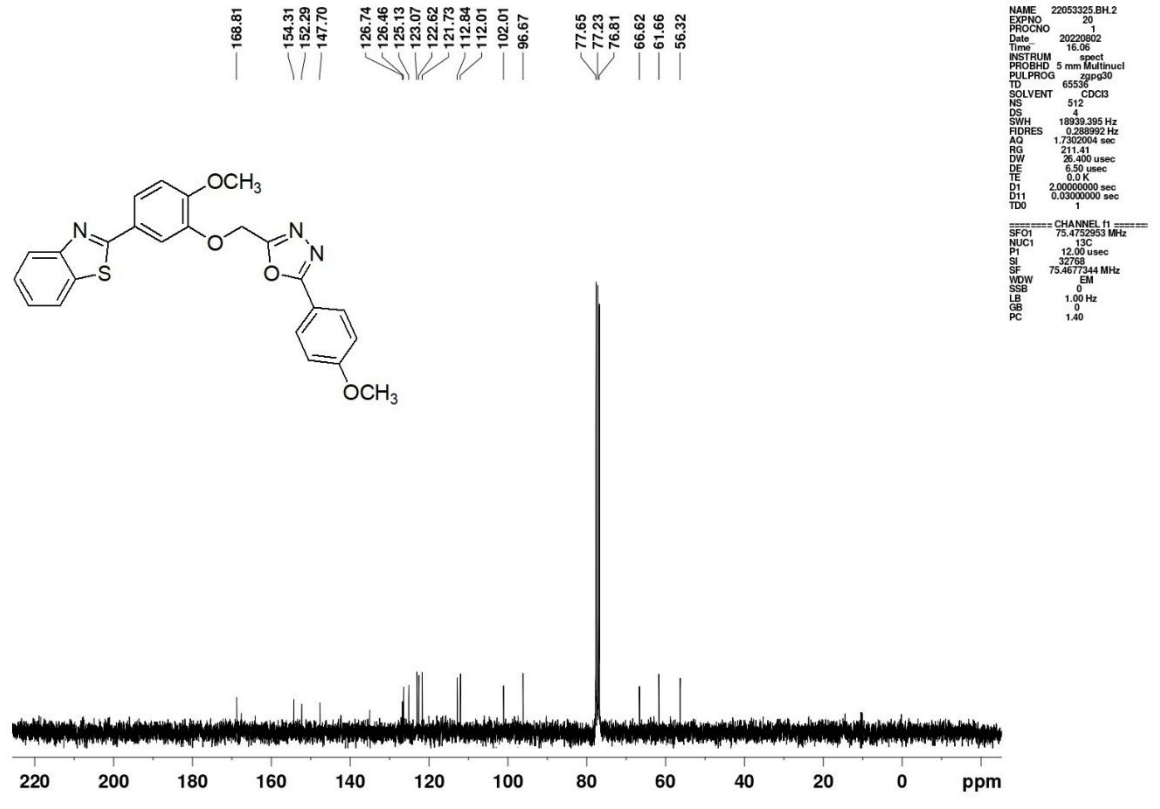

Figure 16: ^{13}C-NMR spectra of compound **6b**

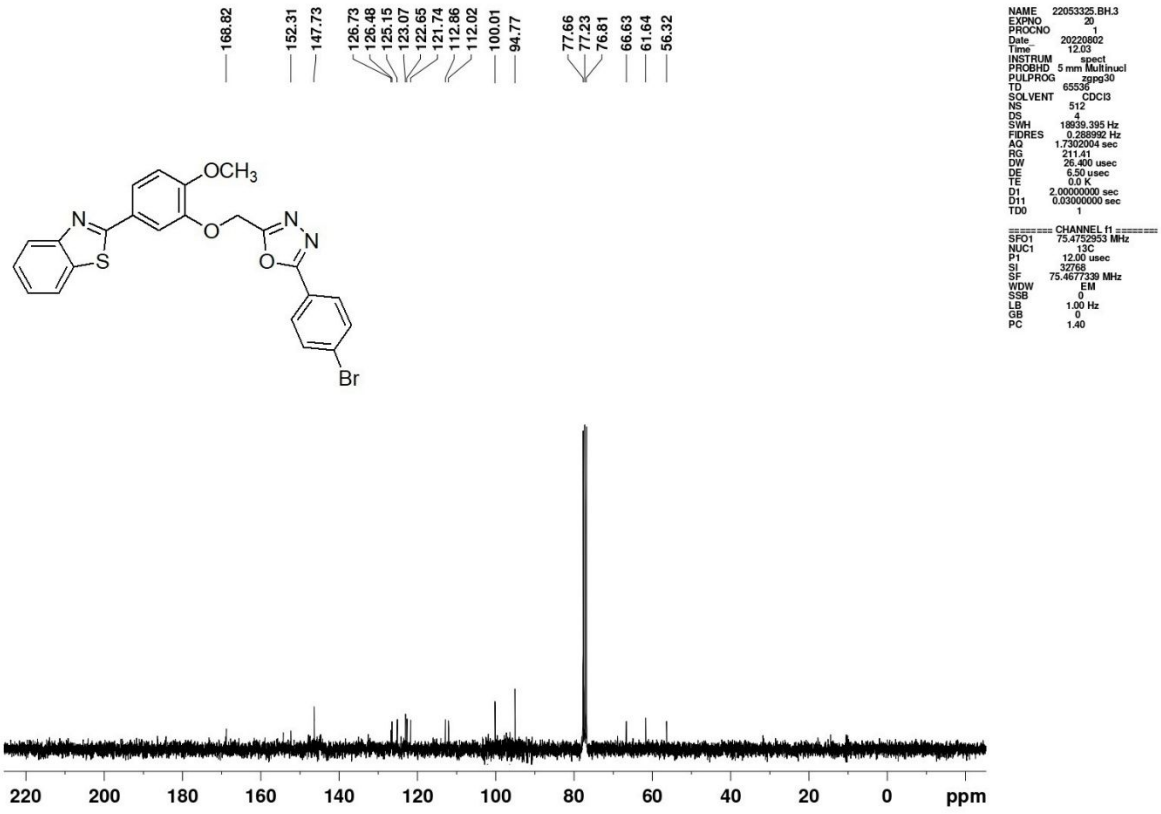

Figure 17: ^{13}C-NMR spectra of compound **6c**

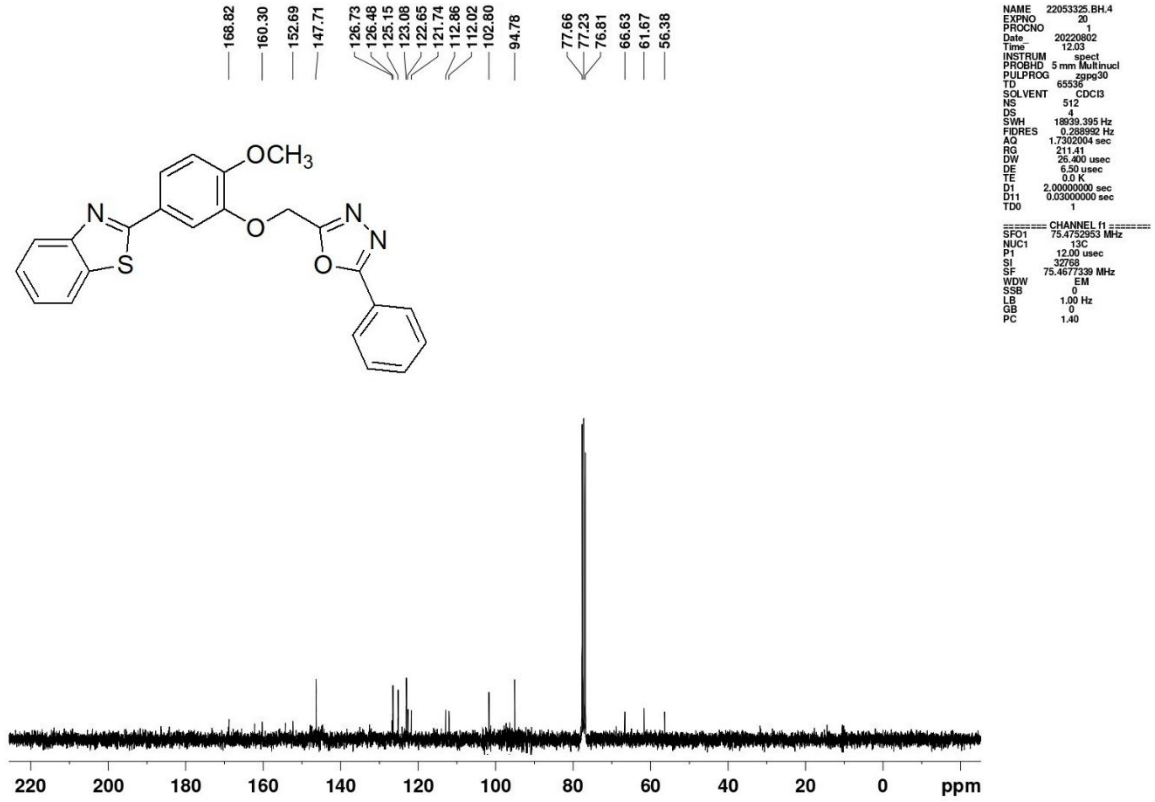

Figure 18: ^{13}C-NMR spectra of compound **6d**

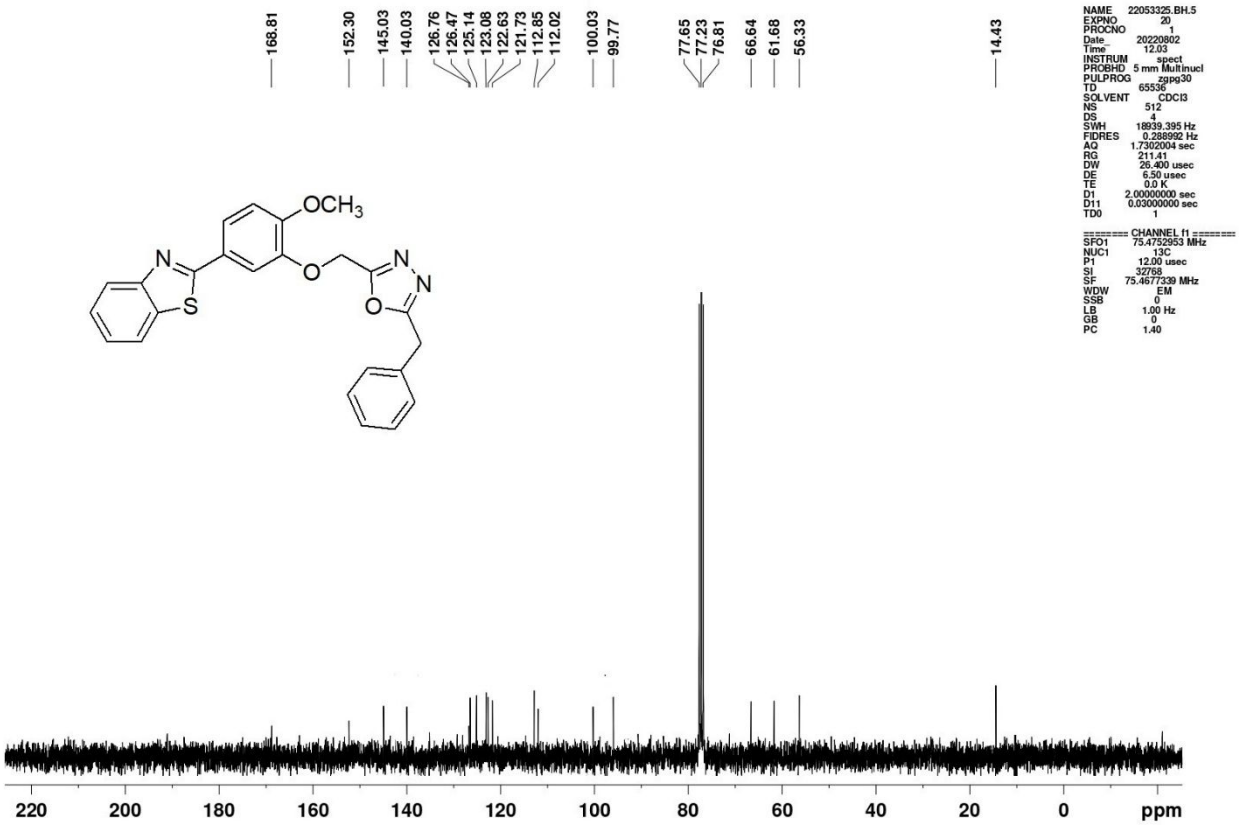

Figure 19: ^{13}C-NMR spectra of compound **6e**

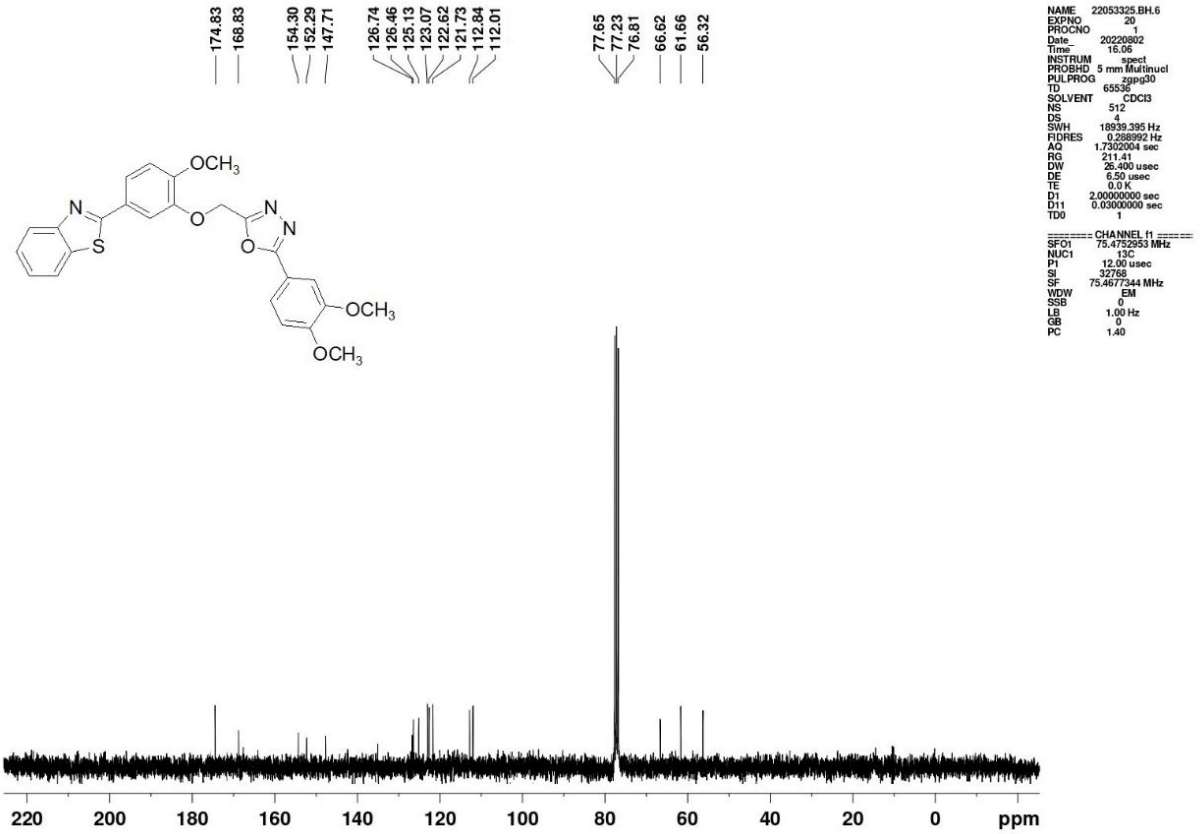

Figure 20: ^{13}C-NMR spectra of compound **6f**

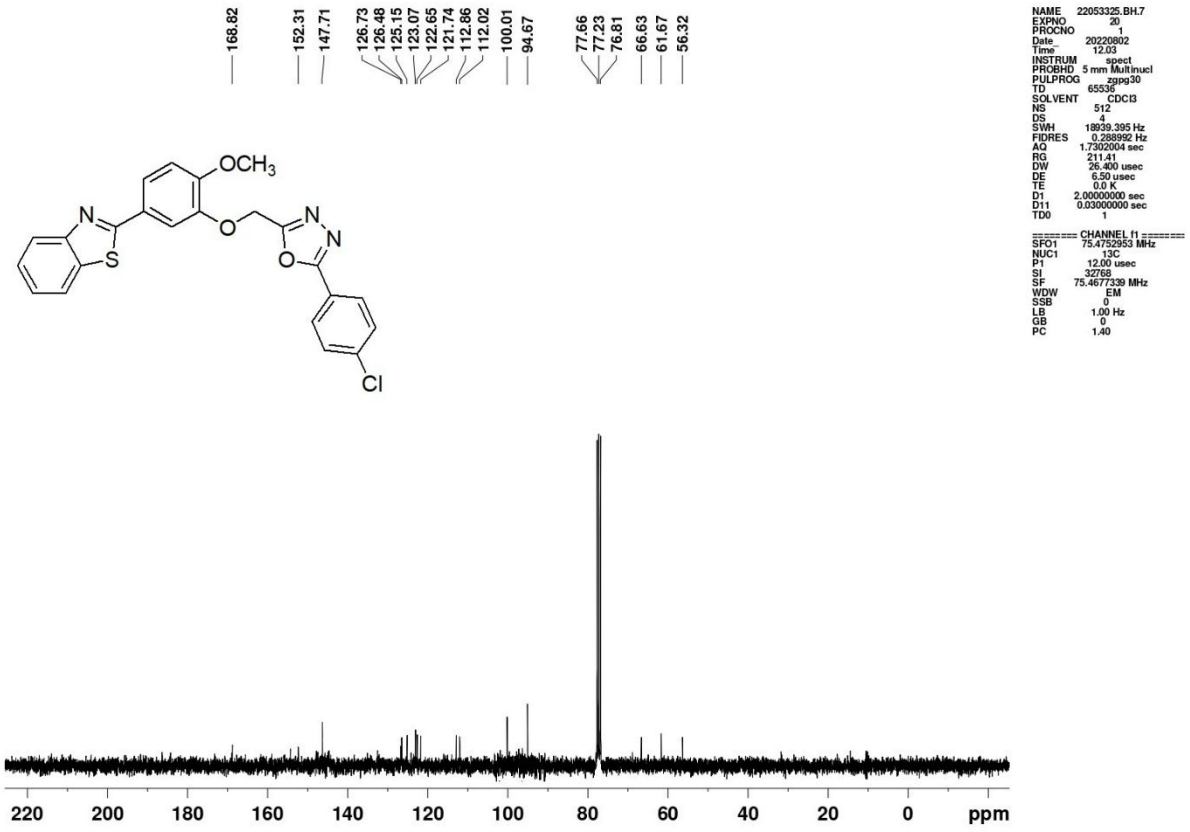

Figure 21: ^{13}C-NMR spectra of compound **6g**

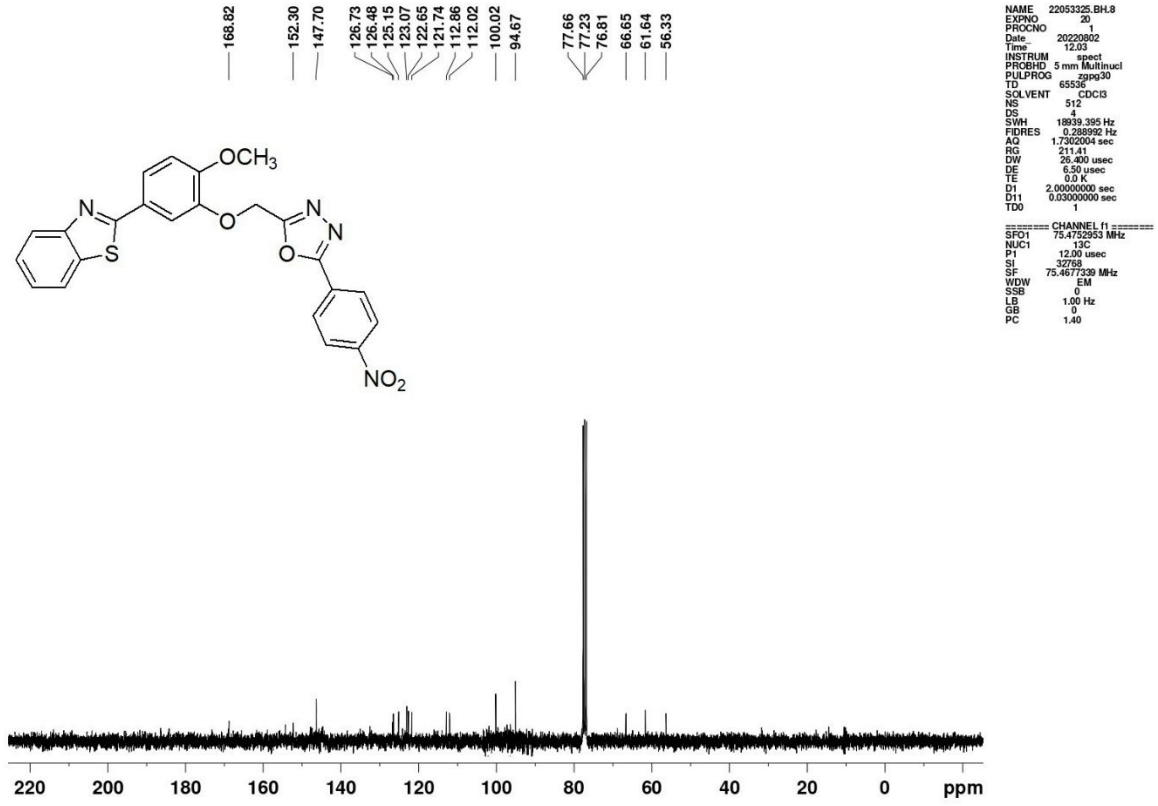

Figure 22: ^{13}C-NMR spectra of compound **6h**

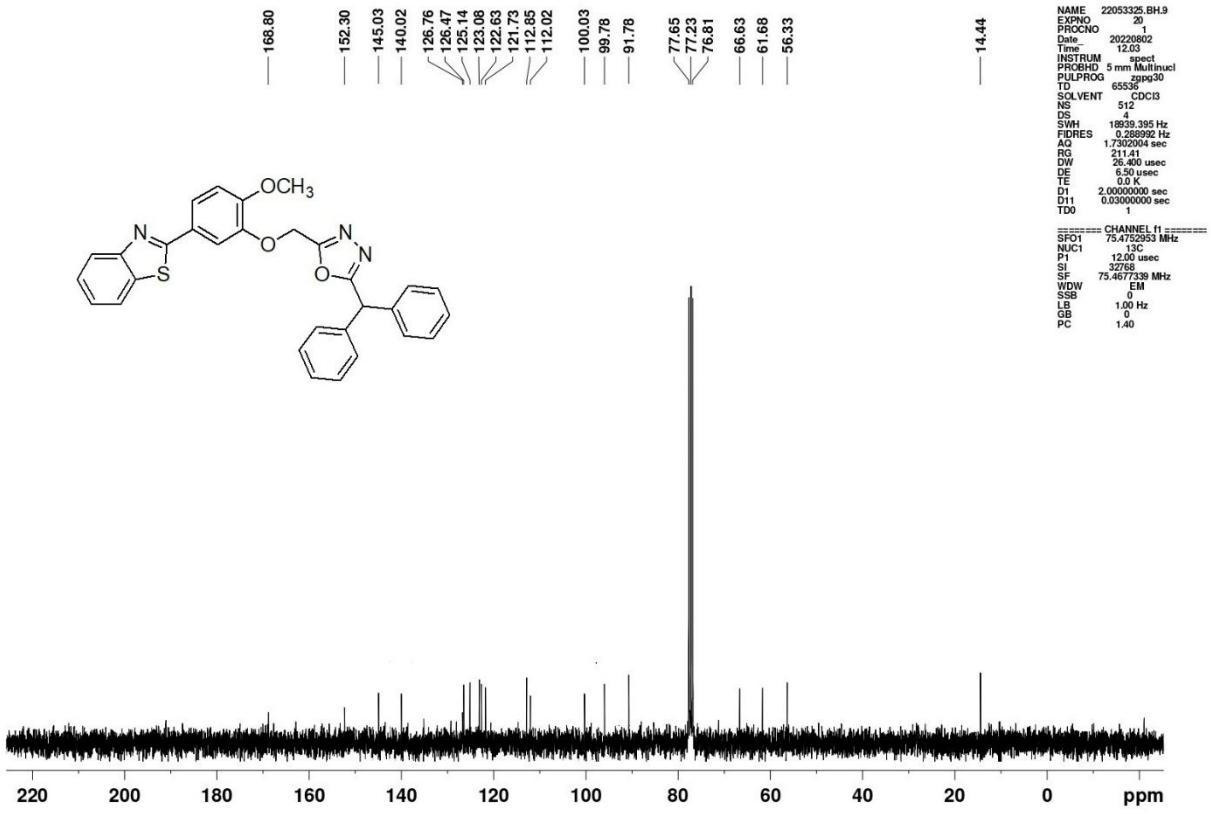

Figure 23: ^{13}C-NMR spectra of compound **6i**

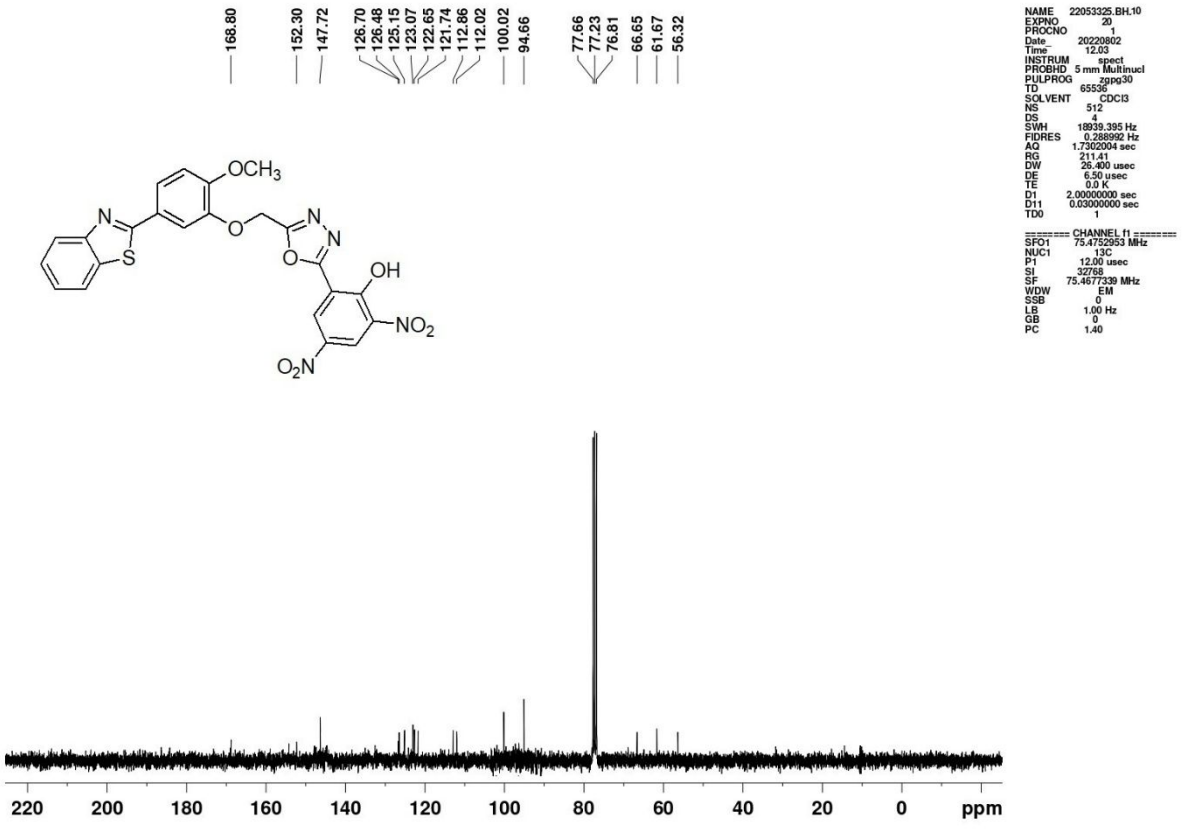

Figure 24: ^{13}C-NMR spectra of compound **6j**

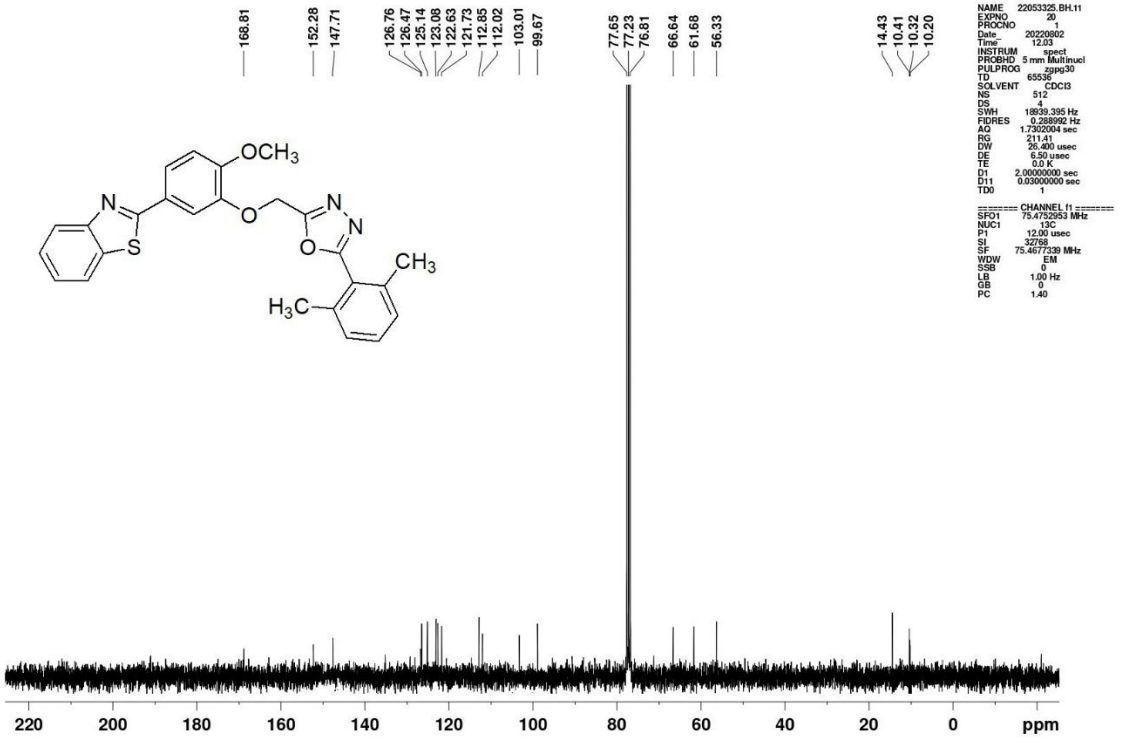

Figure 25: ^{13}C-NMR spectra of compound **6k**

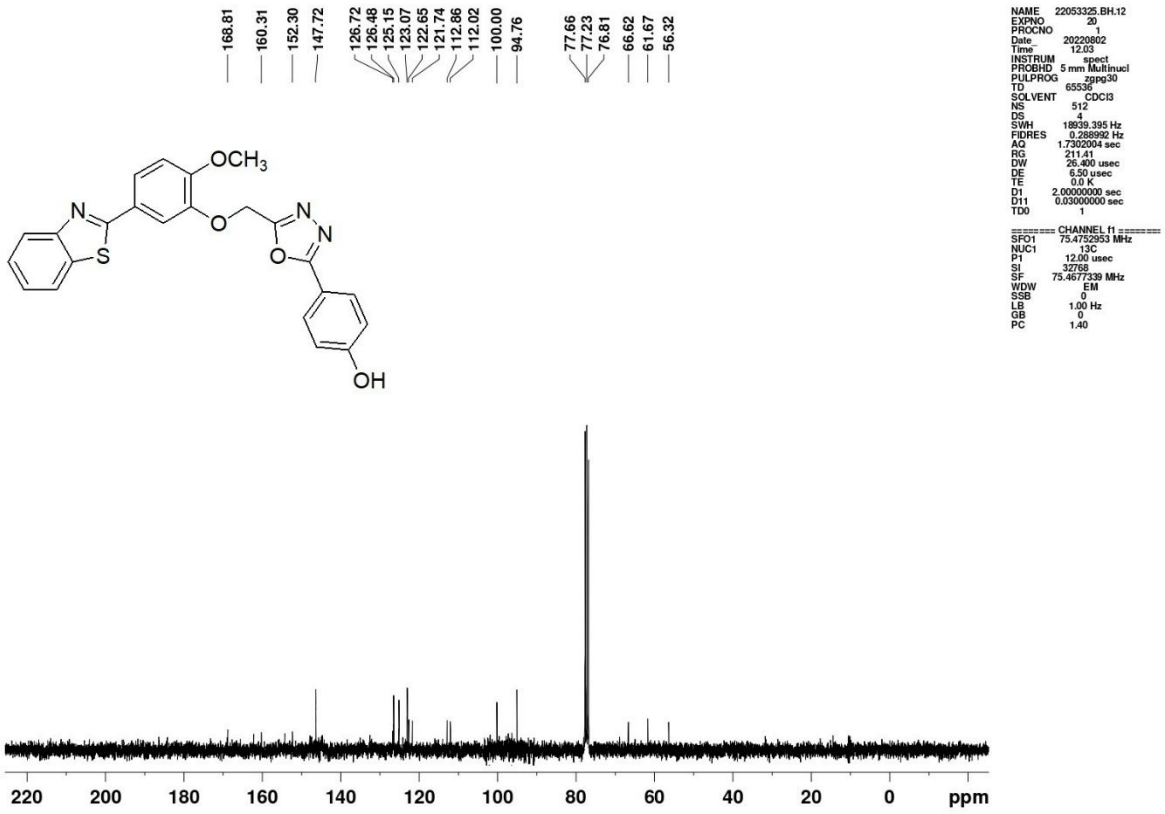

Figure 26: ^{13}C-NMR spectra of compound **6l**

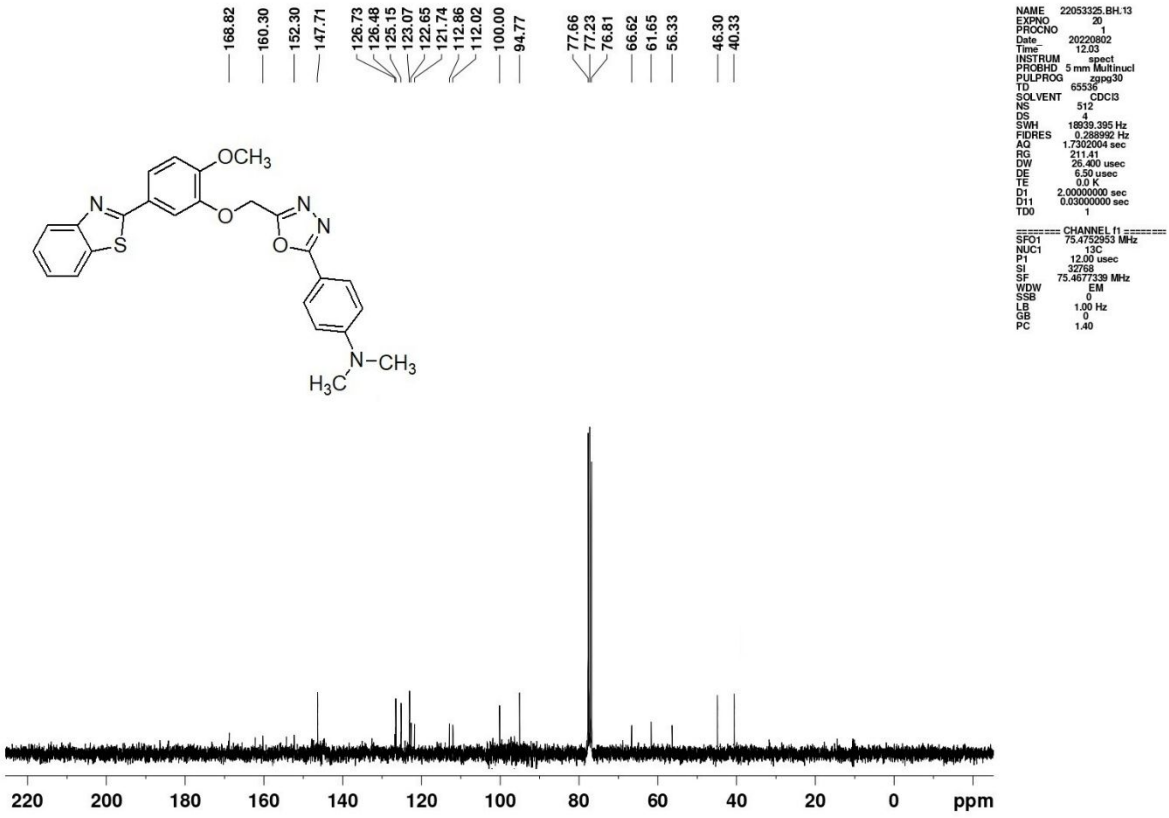

Figure 27: ^{13}C-NMR spectra of compound **6m**

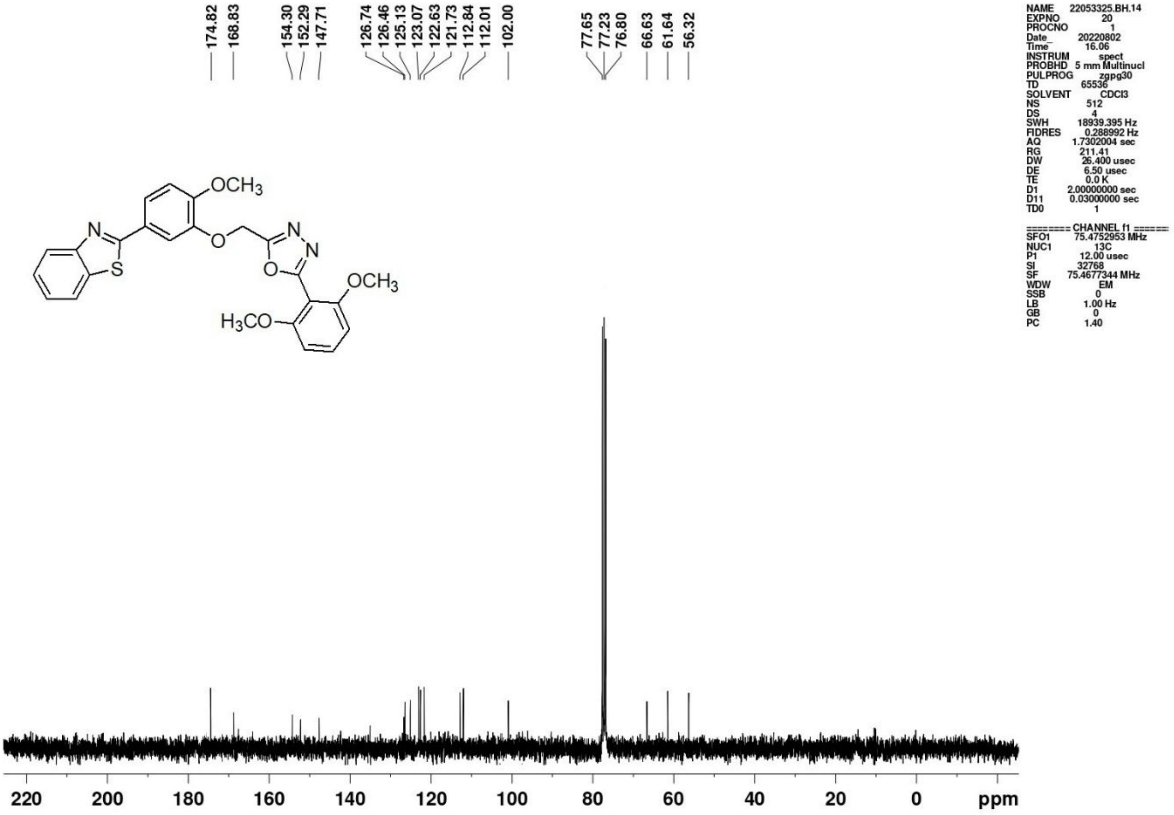

Figure 28: ^{13}C-NMR spectra of compound **6n**

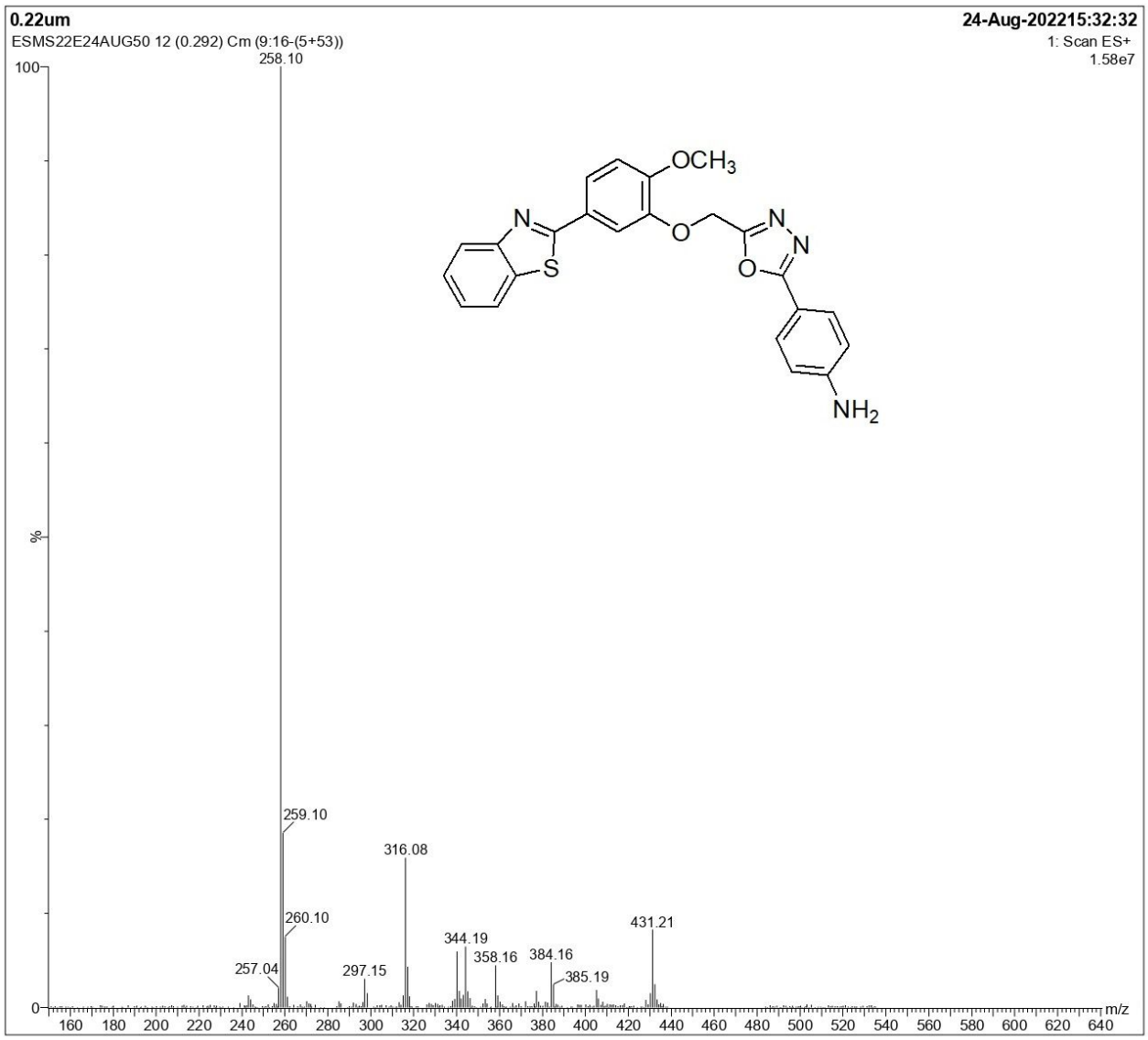

Figure 29: Mass spectra of compound **6a**

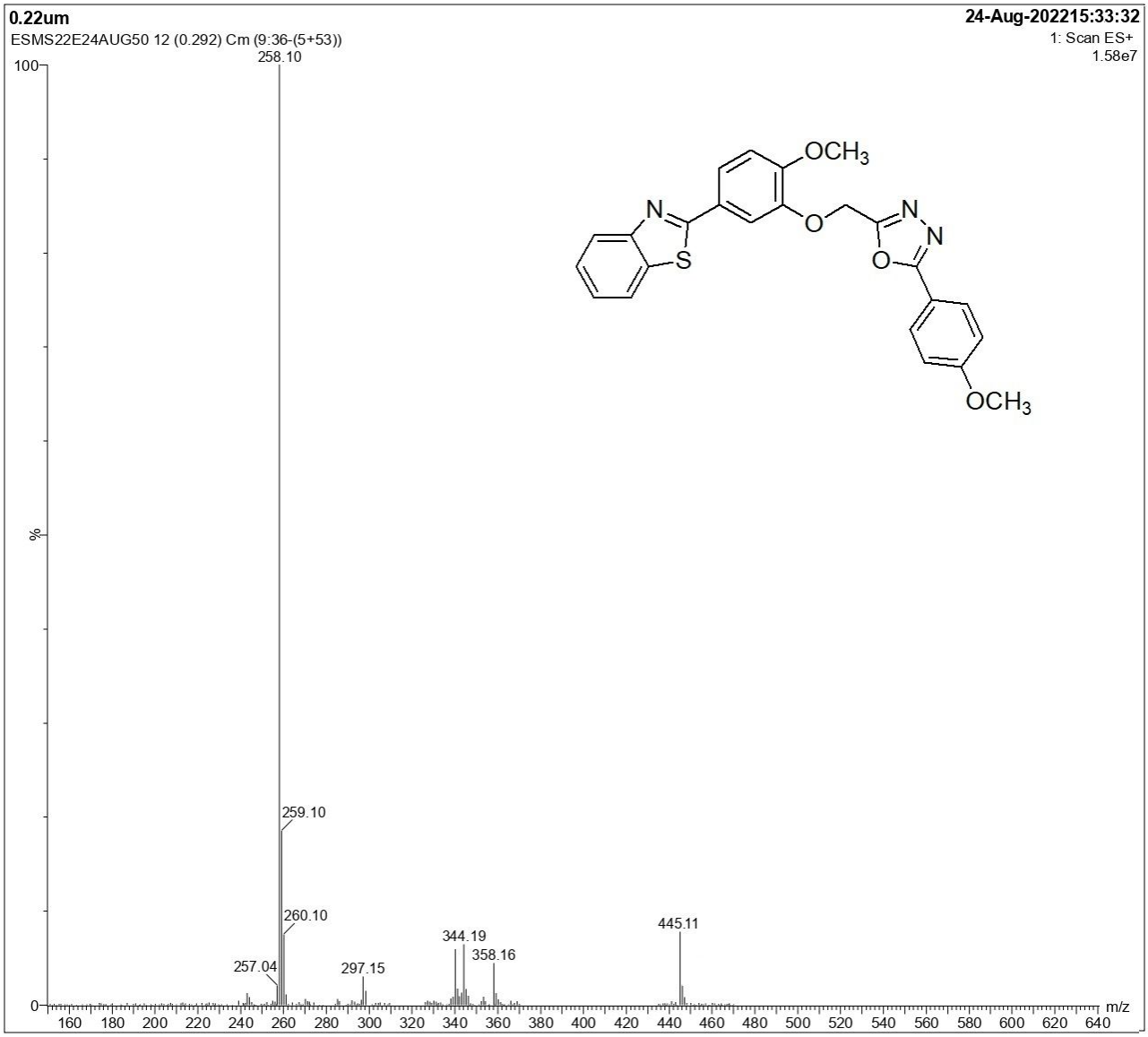

Figure 30: Mass spectra of compound **6b**

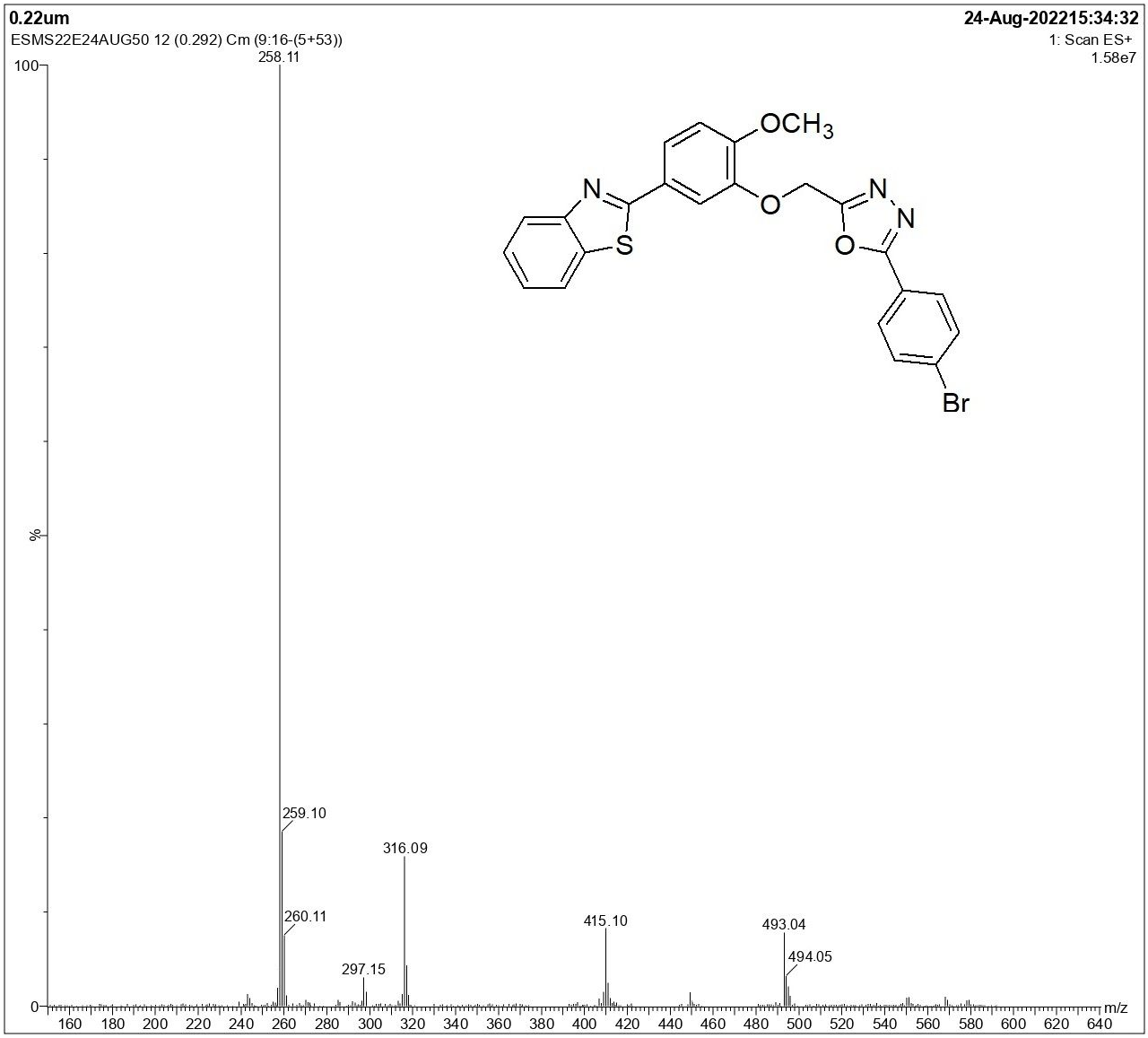

Figure 31: Mass spectra of compound **6c**

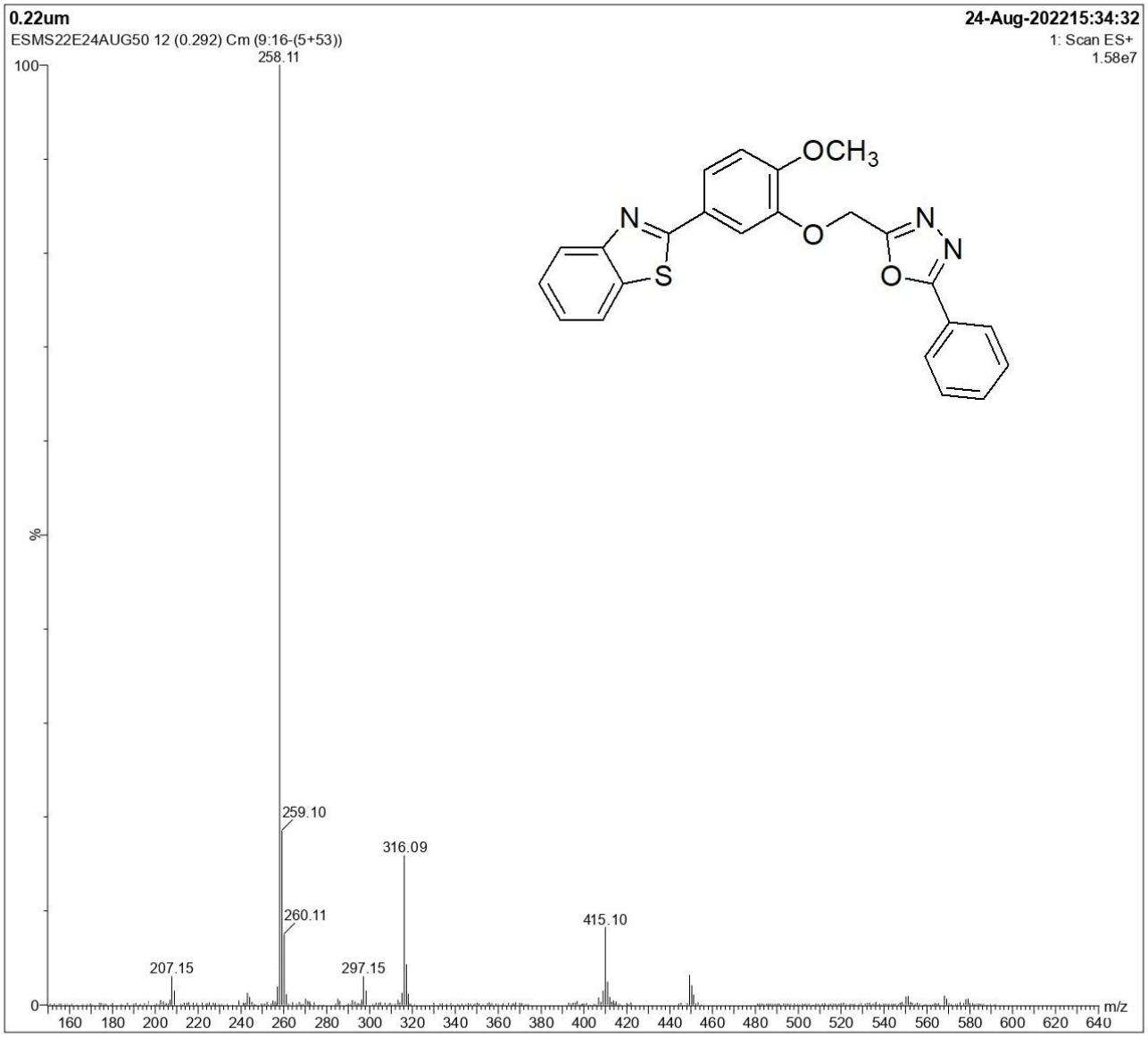

Figure 32: Mass spectra of compound **6d**

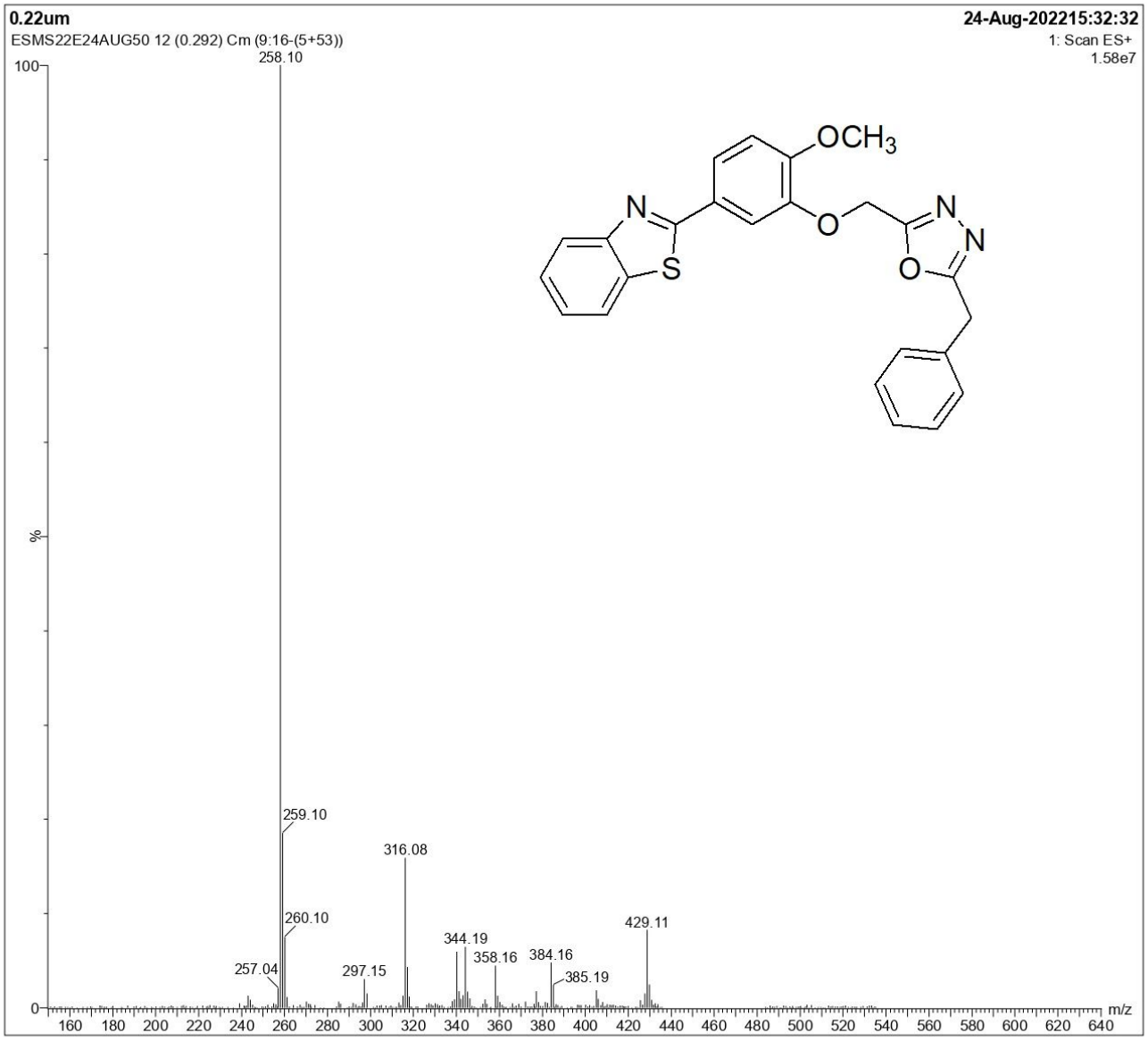

Figure 33: Mass spectra of compound **6e**

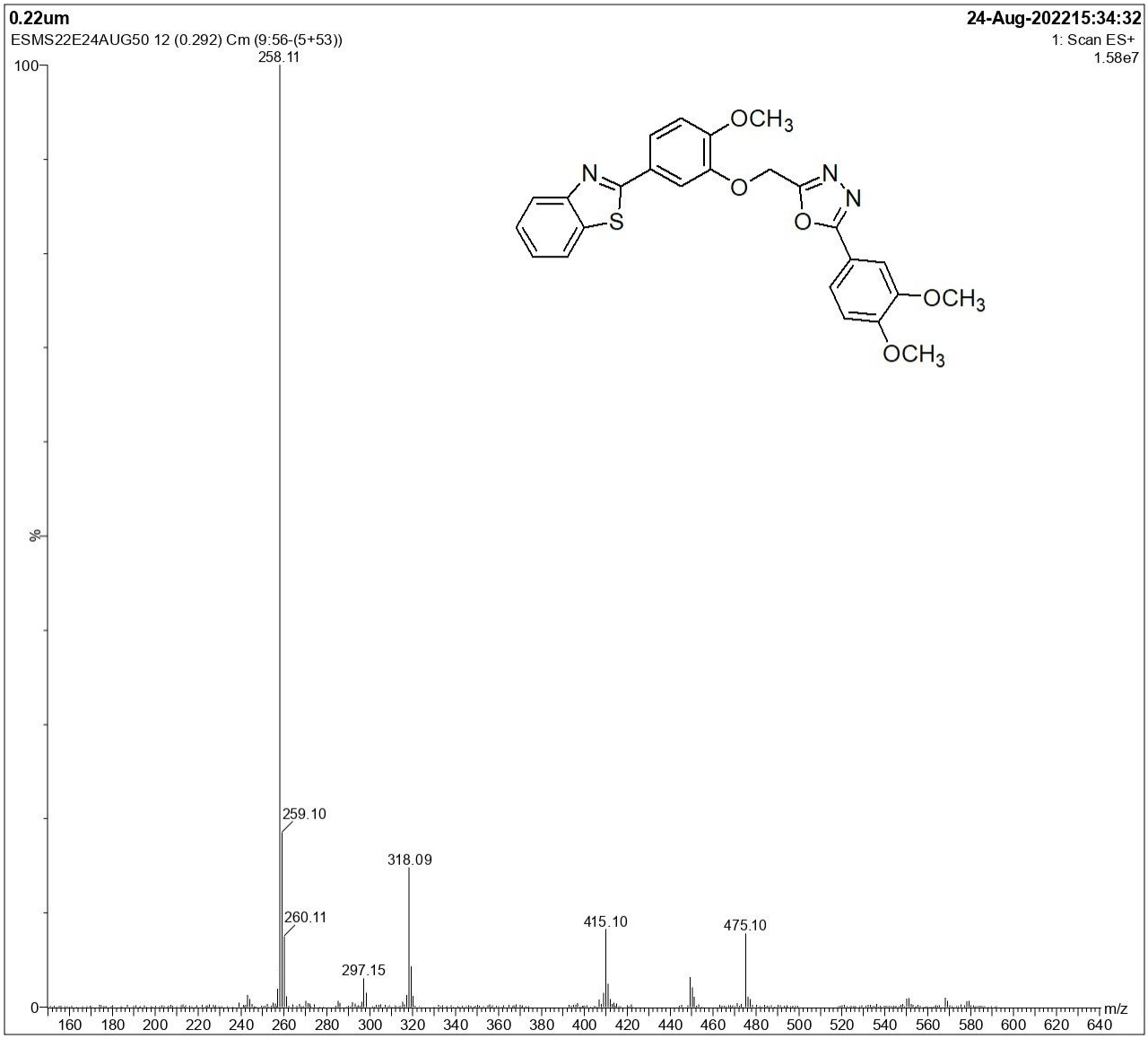

Figure 34: Mass spectra of compound **6f**

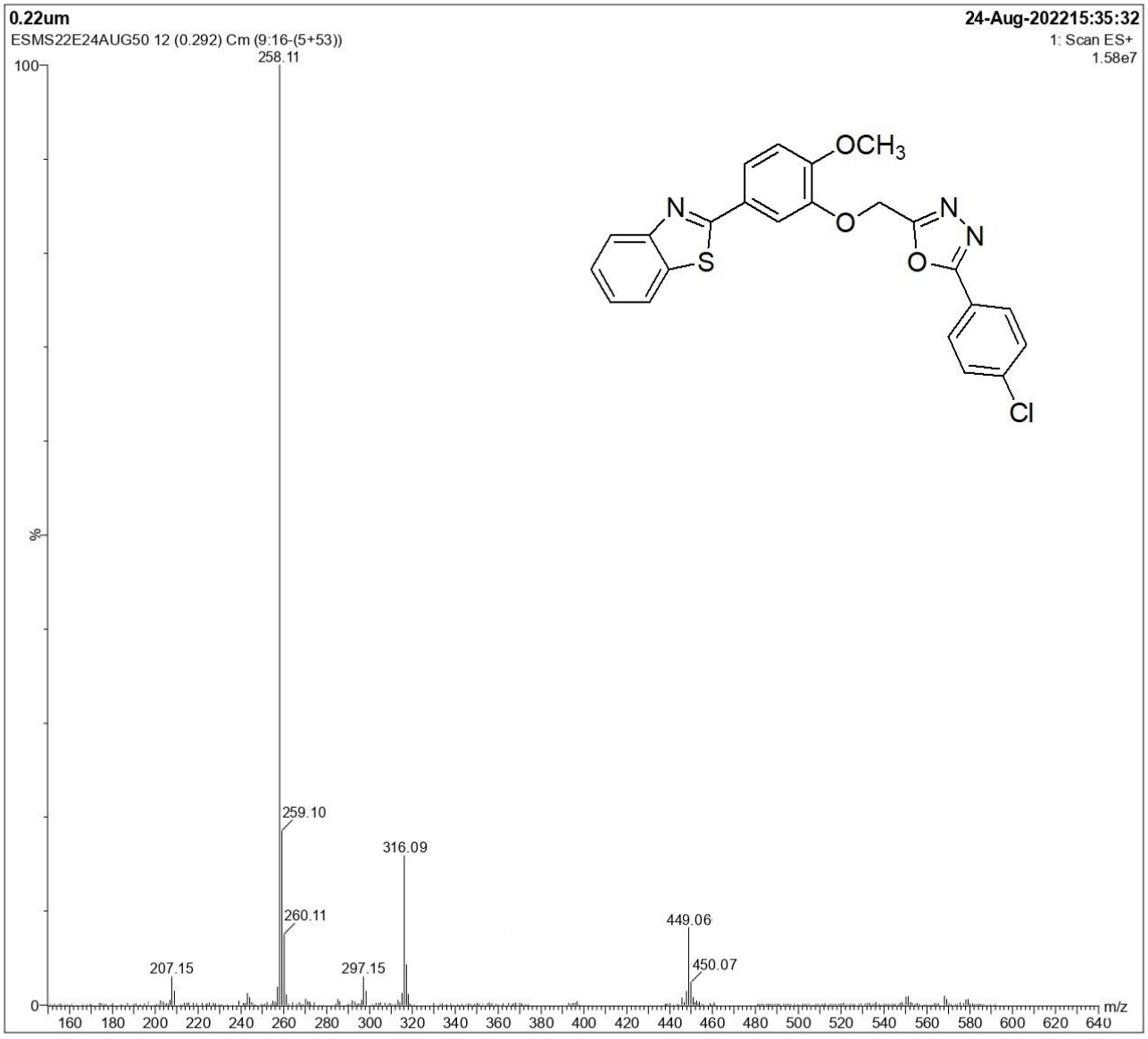

Figure 35: Mass spectra of compound **6g**

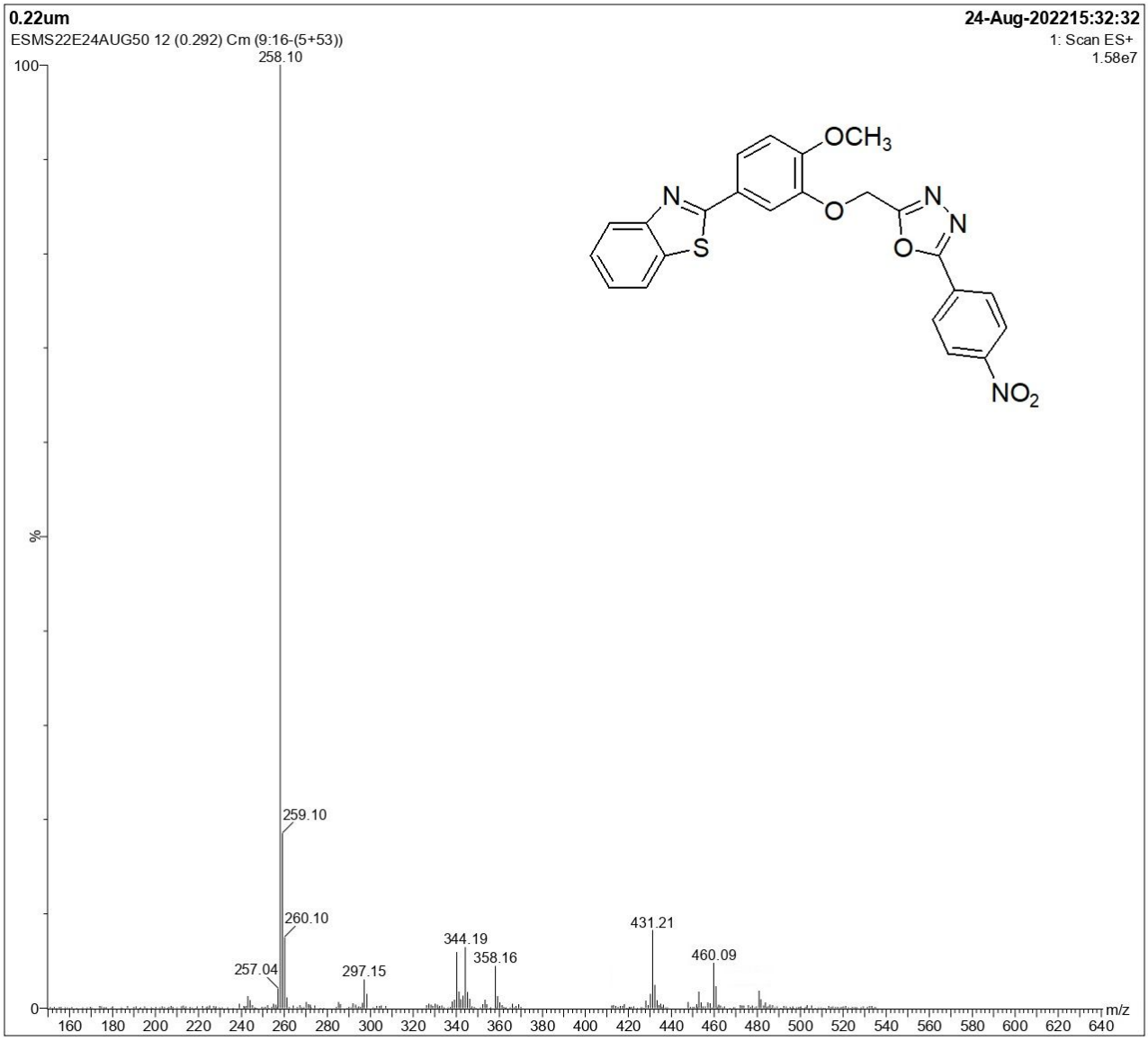

Figure 36: Mass spectra of compound **6h**

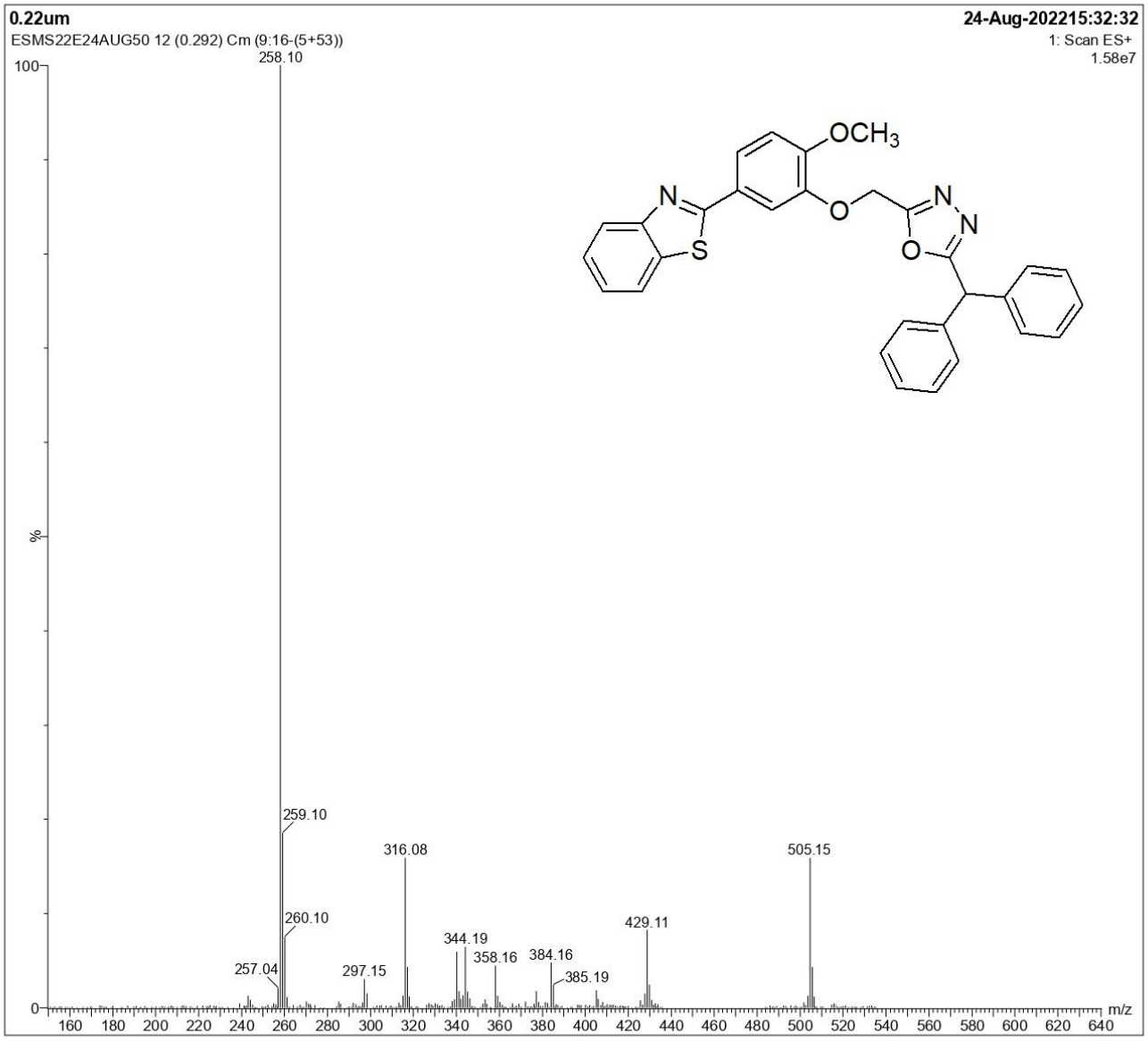

Figure 37: Mass spectra of compound **6i**

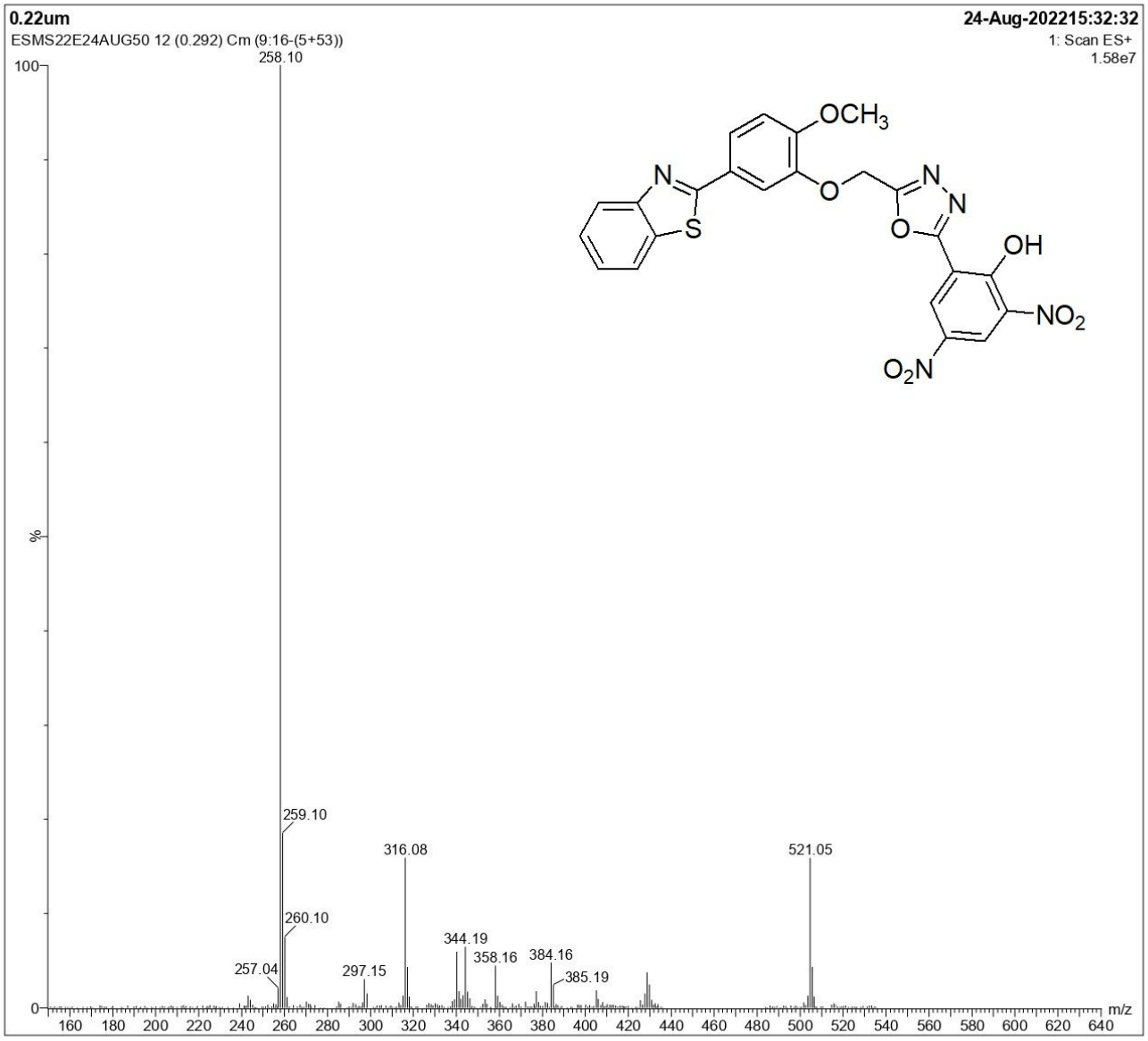

Figure 38: Mass spectra of compound **6j**

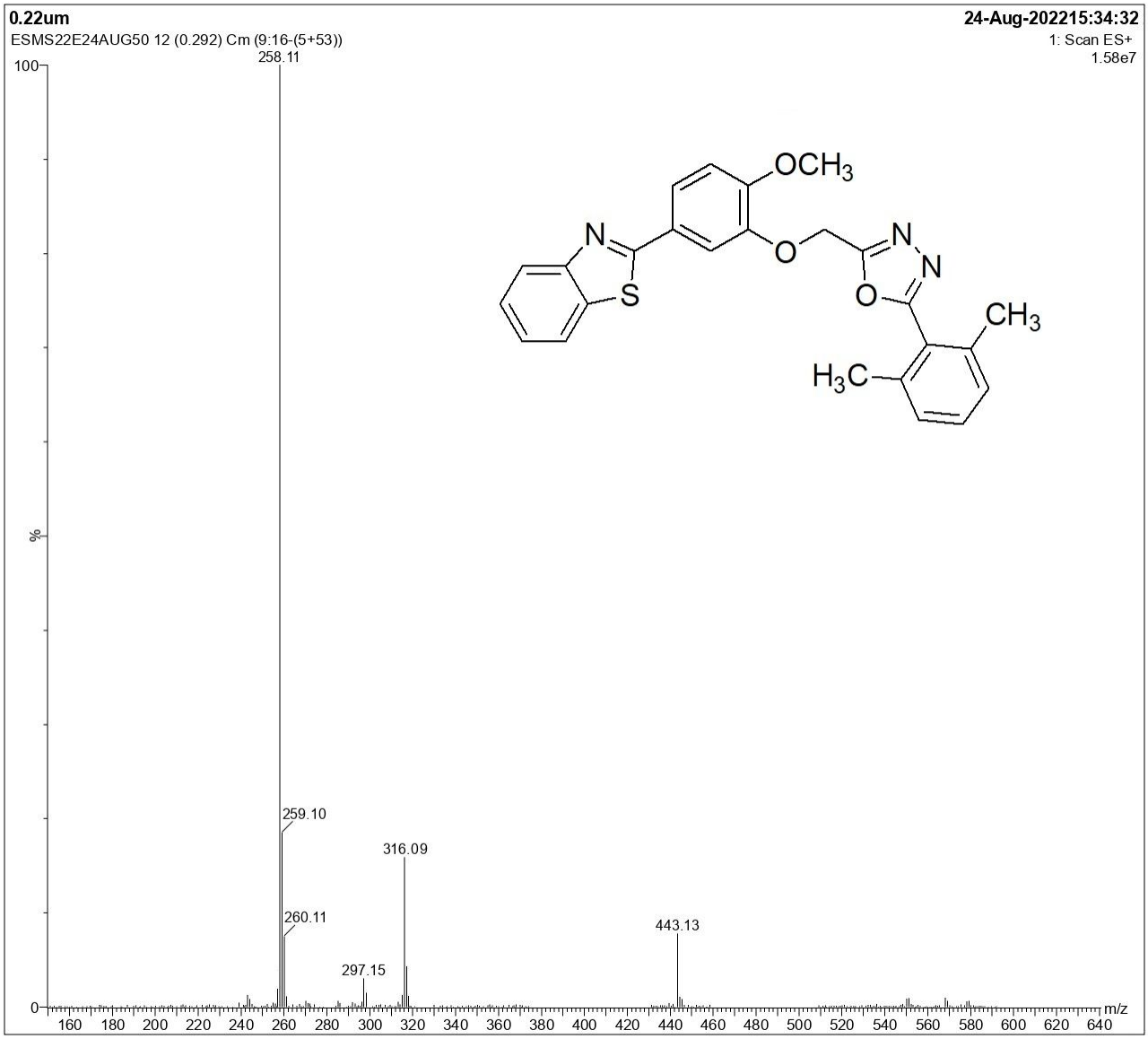

Figure 39: Mass spectra of compound **6k**

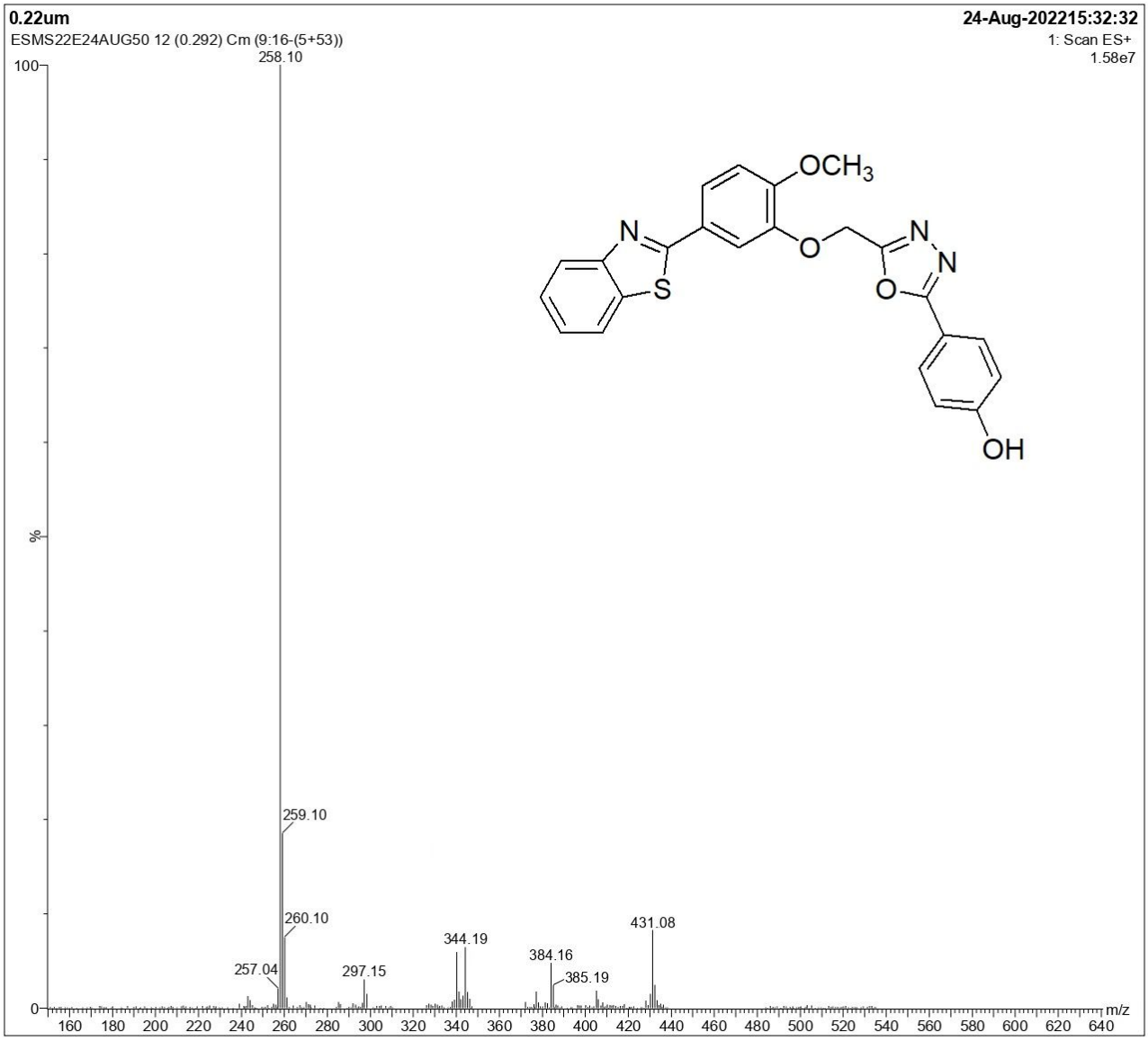

Figure 40: Mass spectra of compound **6l**

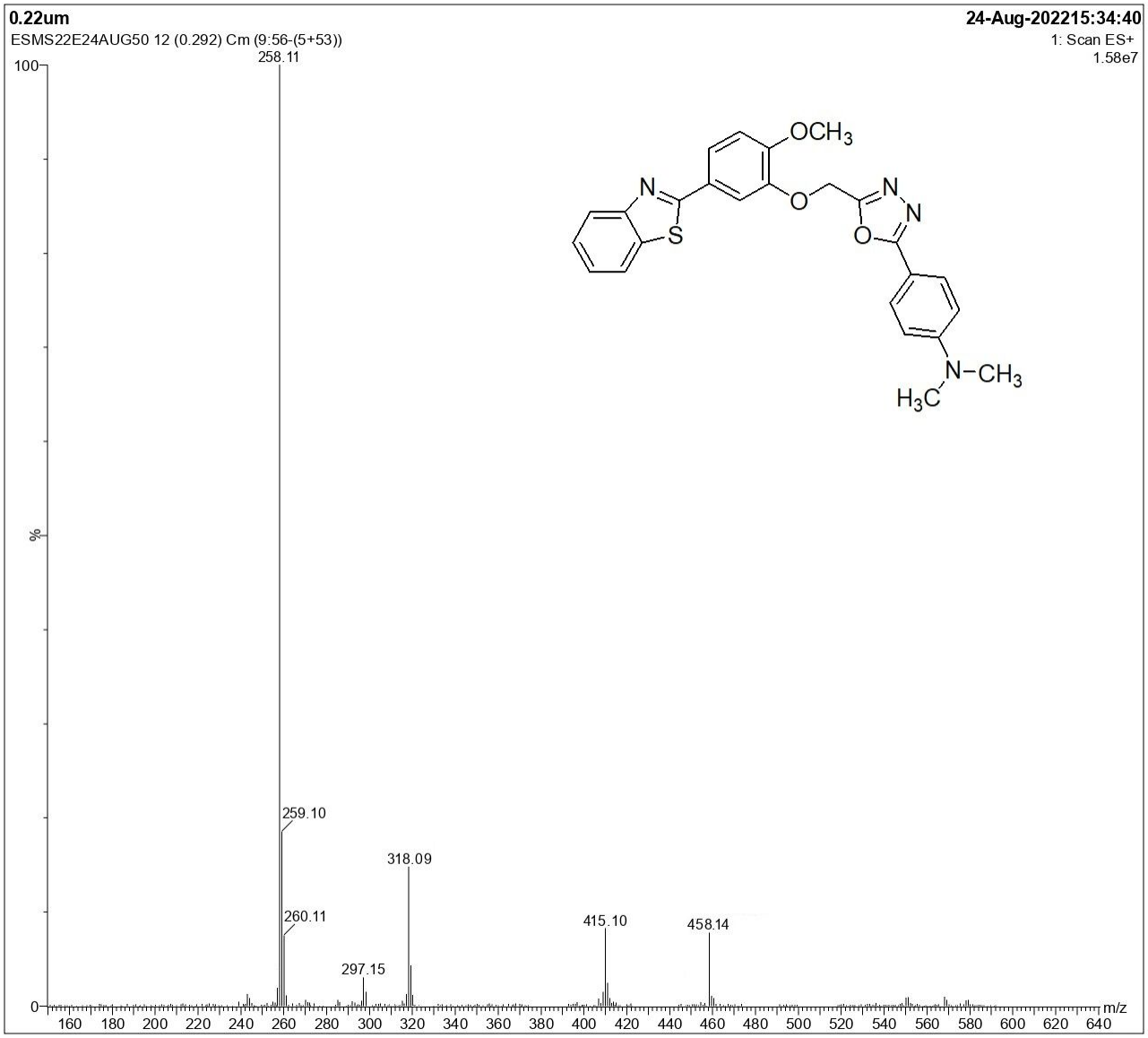

Figure 41: Mass spectra of compound **6m**

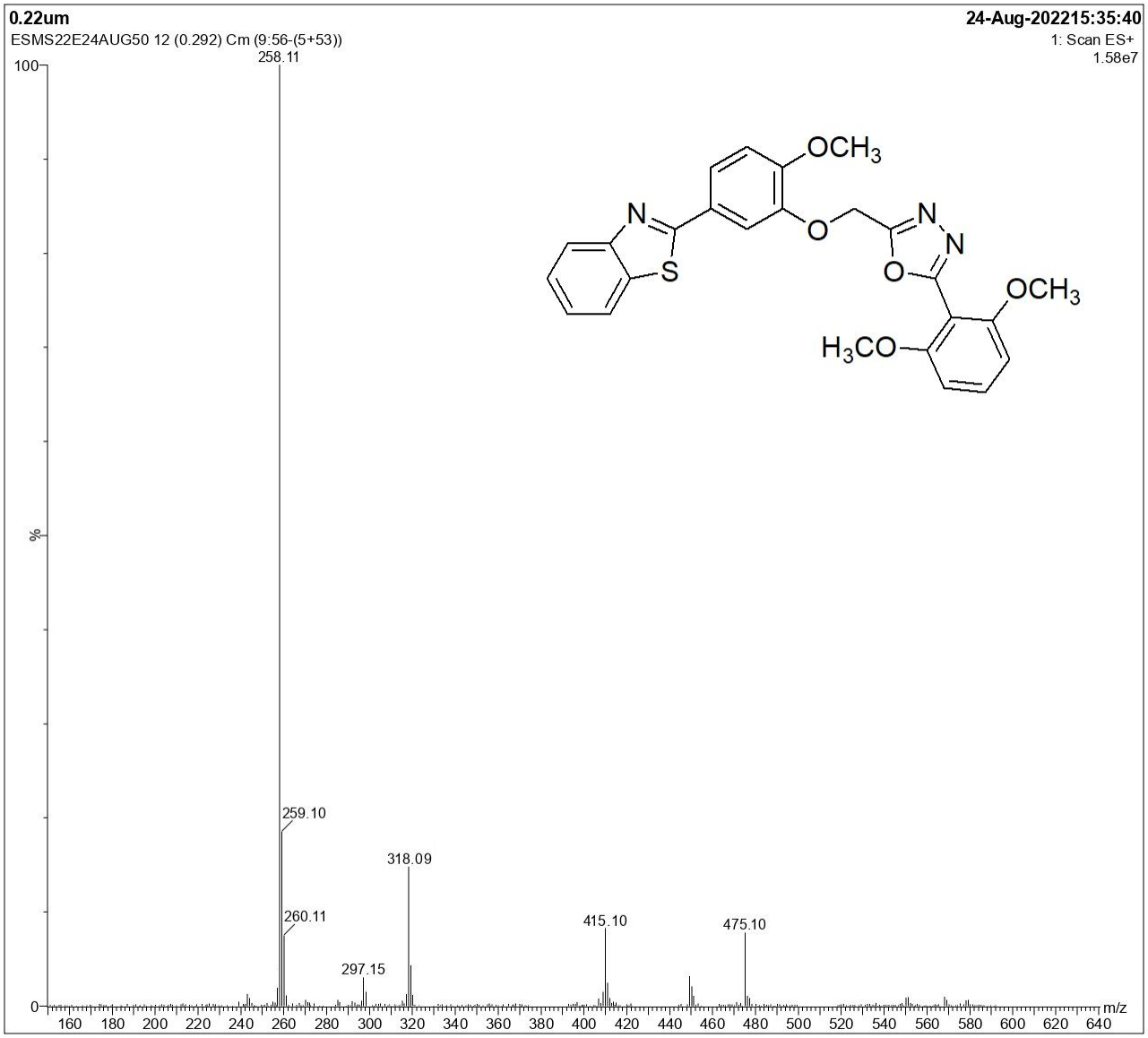

Figure 42: Mass spectra of compound **6n**

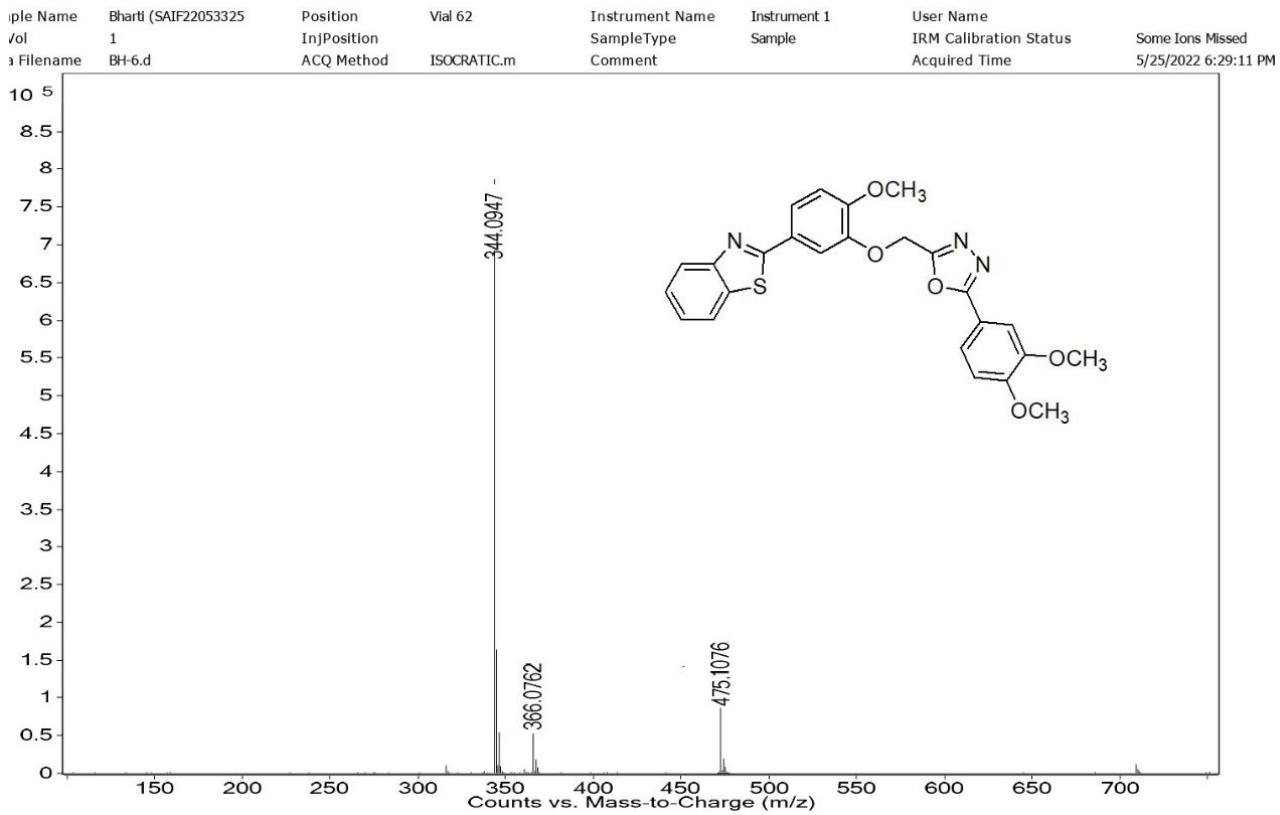

Figure 43: HRMS Spectra of compound **6f**

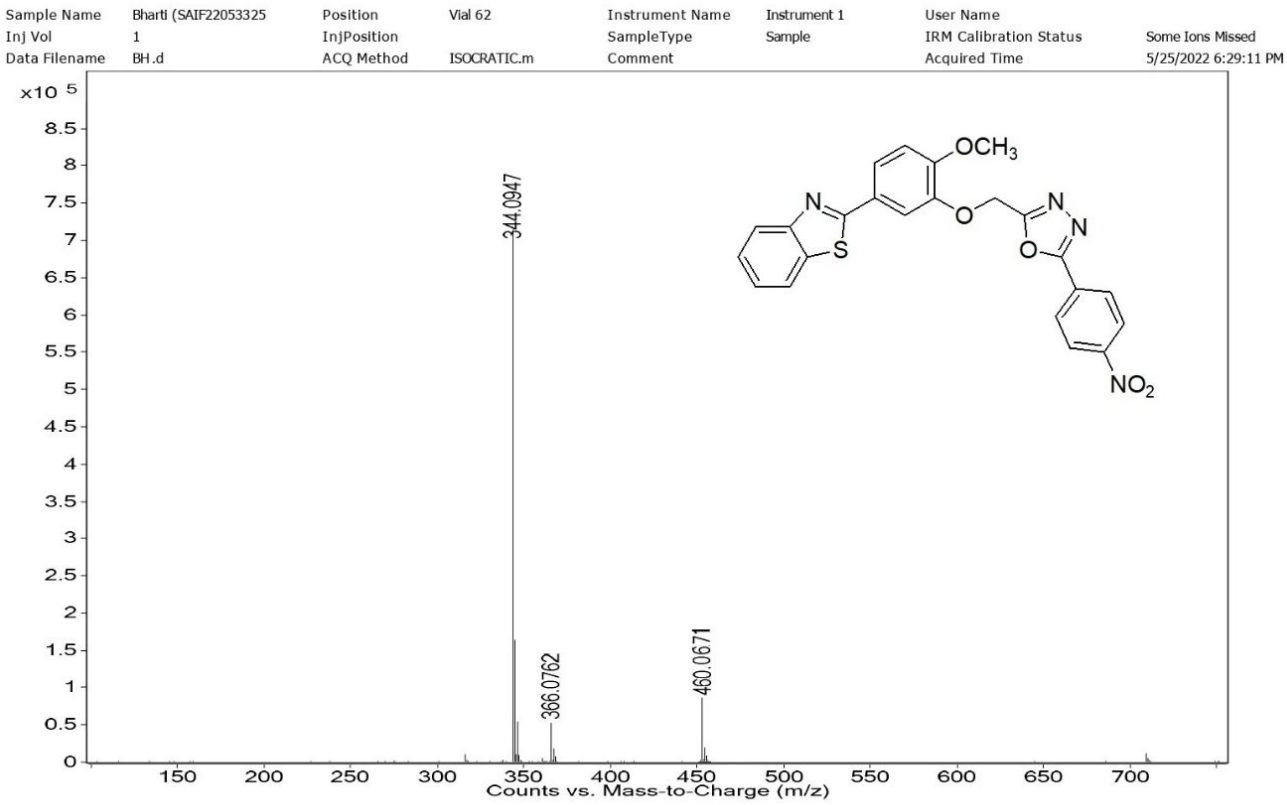

Figure 44: HRMS Spectra of compound **6h**

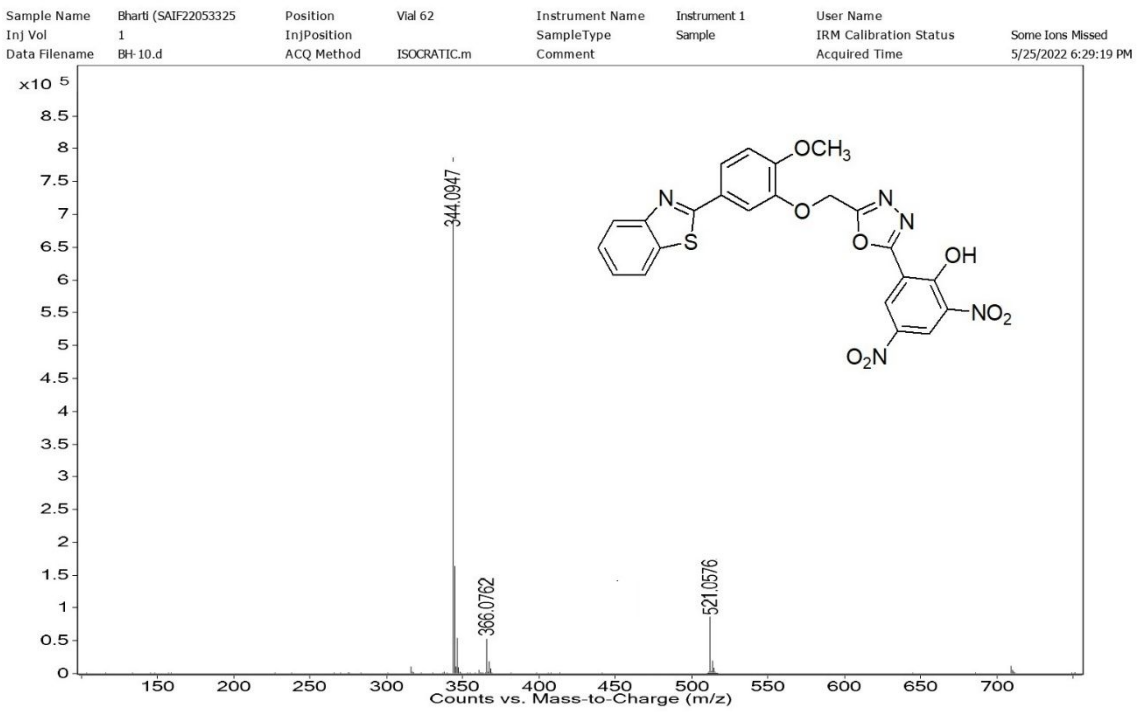

Figure 45: HRMS spectra of compound **6j**

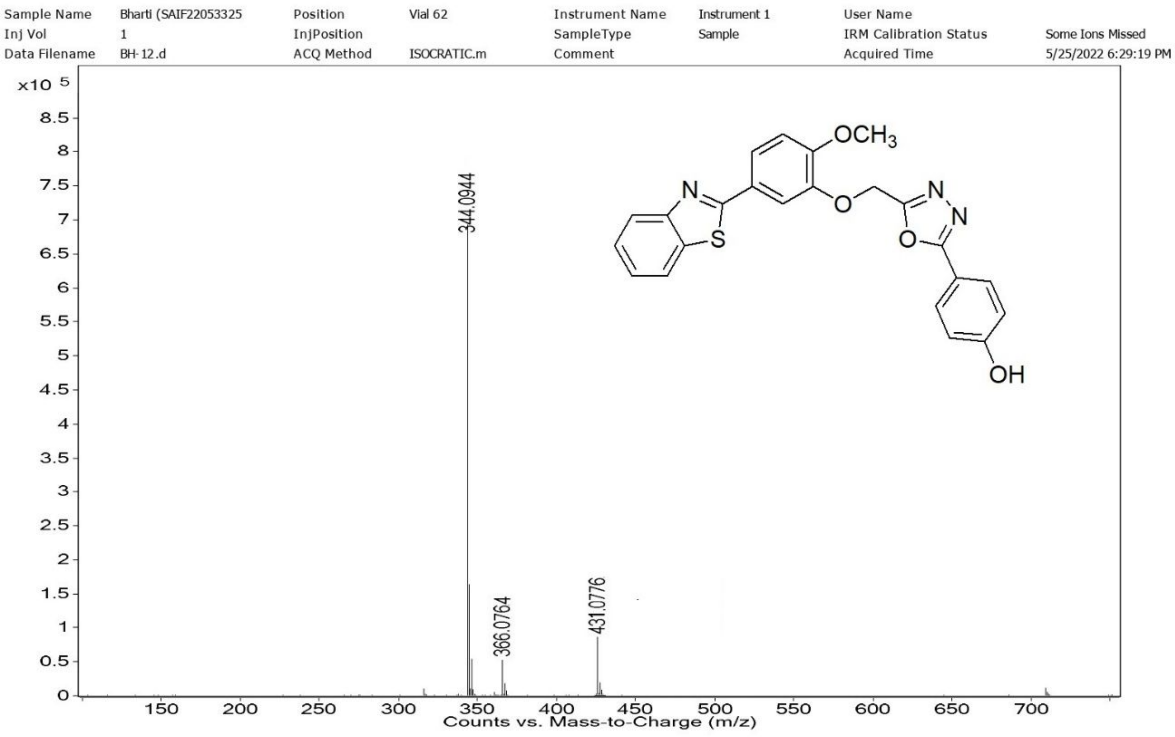

Figure 46: HRMS spectra of compound **6l**

Table 4. Molecular Properties and ADME profile of synthesized compounds **(6a-n)**

Compound	**% ABS**	**TPSA**	**n-ROTB**	**MW**	**nAOHNH**	**nAON**	**miLogP**	**Violation**	**BBB permeability**	**CNS permeability**	**Total clearance**	**Renal OCT2 substrate**	**Water solubility**
Rule				**<500**	**<5**	**<10**	**<5**	**<1**					
6a	100	96.31	6	430.49	2	7	4.03	0	-1.217	-2.184	0.009	No	-4.09
6b	96.722	79.52	7	445.50	0	7	5.01	1	-1.268	-3.256	0.252	No	-3.86
6c	94.722	70.28	6	494.37	0	6	5.76	1	-1.216	-1.872	0.07	No	-4.30

6d	96.255	70.28	6	415.47	0	6	4.95	0	-1.045	-2.184	0.214	No	-3.64
6e	98.036	70.28	7	429.50	0	6	4.55	0	-1.015	-2.215	0.304	No	-4.13
6f	96.456	88.75	8	475.53	0	8	4.60	0	-1.48	-3.494	0.443	No	-3.76
6g	94.862	70.28	6	449.92	0	6	5.63	1	-1.208	-1.895	0.091	No	-4.29
6h	100	116.11	7	460.47	0	9	4.91	0	-1.564	-2.222	0.24	No	-4.26
6i	98.83	70.28	8	505.60	0	6	5.75	2	-1.094	-2.013	0.249	No	-3.22
6j	93.534	182.16	8	521.47	1	13	4.51	2	-1.832	-3.548	0.528	No	-3.52
6k	96.993	70.28	6	443.53	0	6	5.75	1	-1.035	-1.852	0.128	No	-4.31
6l	97.083	73.52	7	458.54	0	7	5.06	1	-1.193	-2.102	0.197	No	-4.11
6m	93.566	90.51	6	431.47	1	7	4.47	0	-1.265	-3.139	0.103	No	-4.32
6n	97.508	88.75	8	475.53	0	8	4.97	0	-1.49	-3.499	0.536	No	-3.48
Phenytoin	95.329	58.20	2	252.27	2	4	2.18	0	-0.048	-2.299	0.277	No	-3.64
Phenobarbital	63.936	75.27	3	246.27	2	5	1.57	0	-0.06	-2.554	0.209	No	-2.26

Table 5. Binding energies and no. of hydrogen bonds of synthesized derivatives **(6a, 6d-h, 6j-l,** and **6n)**, phenytoin, and phenobarbital on two different receptors in (Kcal/mol).

Compound Name	**2coj**			**5iov**		
	Binding energy	**No. of Hydrogen Bonds**		**Binding energy**	**No. of Hydrogen Bonds**	
		Conventional	**Carbon-Hydrogen**		**Conventional**	**Carbon-Hydrogen**

6a	-8.78	1	0	-7.79	2	1
6b	-8.29	3	0	-6.68	2	1
6c	-8.1	0	0	-7.54	0	0
6d	-6.94	1	0	-6.33	2	2
6e	-7.74	0	0	-7.96	1	3
6f	-7.85	4	1	-7.17	3	2
6g	-7.5	1	1	-7.48	2	0
6h	-10.31	4	2	-7.49	3	2
6i	-8.01	0	0	-6.86	1	1
6j	-8.57	4	1	-7.05	2	2
6k	-8.86	0	0	-6.47	1	2
6l	-8.81	0	0	-7.47	2	0
6m	-8.06	2	2	-7.10	0	2
6n	-8.56	2	1	-6.19	1	1
Phenytoin	-7.28	4	1	-5.48	2	1
Phenobarbital	-5.28	4	0	-5.36	1	2