Development of Certain Benzylidene Coumarin Derivatives as Anti-Prostate Cancer Targeting EGFR and PI3Kβ Kinases

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Supplementary data:

The data are divided into three parts, experimental part and spectral data (^{1}HNMR, ^{13}C NMR and MS) of the synthesized compounds, the biological studies and the docking studies.

Part 1:

A: Experimental part:

The starting materials 1a-c, 2a-c and 3a-c were synthesized according adopted procedures at literatures. [1-6]

General procedure for synthesis of 4-methyl-7-hydroxy-3,8-substituted-2*H*-1-chromene-2-ones (1a-c).

A cooled mixture of resorcinol or 2-methylresorcinol (0.1 mol) and ethyl 2-ethylacetoacetate or ethyl 2-benzylacetoacetate (0.1 mol) was slowly added with stirring to cooled concentrated sulphuric acid (50 mL) in an ice bath over 90 min. The mixture was left overnight in the refrigerator then poured onto ice. The formed precipitate was filtered, dried and recrystallized from isopropanol to afford compounds **1a-c** in good yield.

General procedure for synthesis of 2-(4-methyl-3,8-disubstituted-2-oxo-2*H*-chromen-7-yl)oxyacetate (2a-c).

A mixture of the appropriate chromen-2-one derivative **1a-c** (0.1 mol), anhydrous potassium carbonate (27.64 g, 0.2 mol) and ethyl chloroacetate (14.64 g, 0.12 mol) in dry acetone (200 mL) was heated under reflux with stirring for 24 h. After cooling the reaction mixture, the formed precipitate was filtered and washed with acetone. The crude product was crystallized from ethanol to give compounds **2a-c.**

General procedure for synthesis of 2-(4-methyl-3,8-disubstituted -2-oxo-2*H*-chromen-7-yl)oxyacetohydrazide (3a-c).

A mixture of the appropriate ester derivative **2a-c** (0.01 mol) and hydrazine hydrate 99% (1 mL, 0.02 mol) in absolute ethanol (30 mL) was heated under reflux for 2 h. The precipitate was

filtered, washed with water and dried. The crude product was crystallized from acetic acid to give compounds **3a-c**

B: Spectral data:

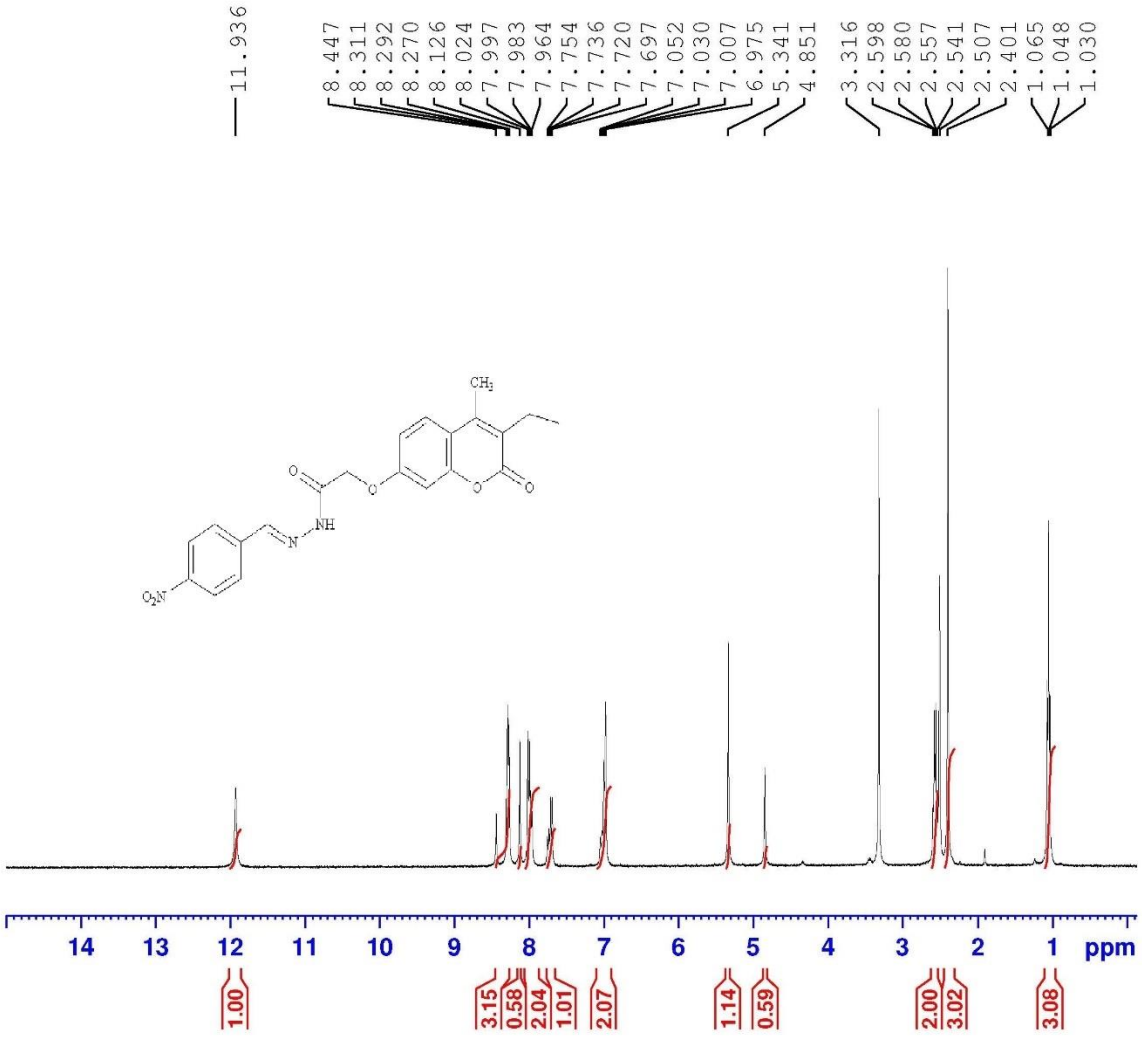

Figure S1: ^{1}H NMR spectrum of the compound **4a**.

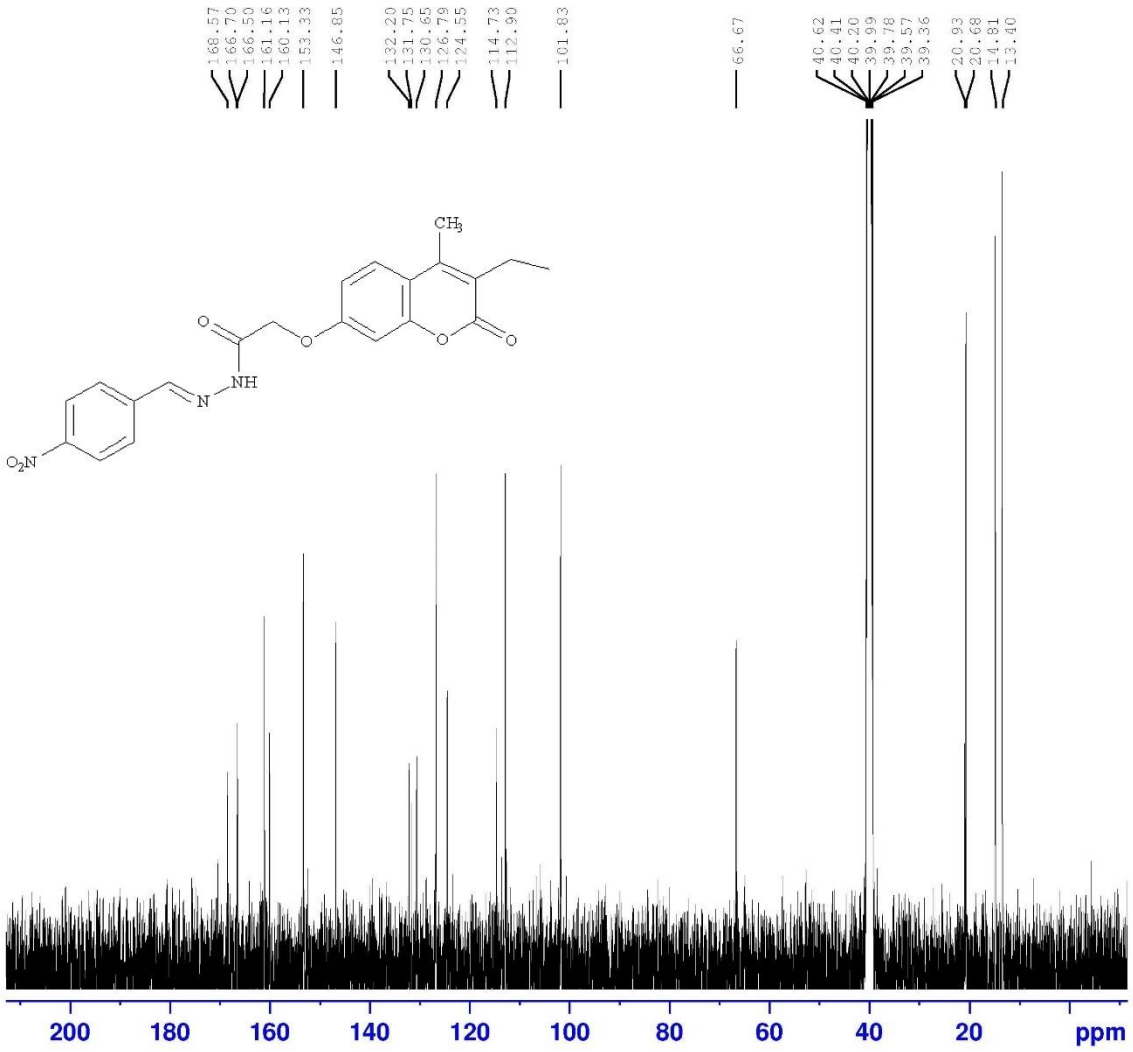

Figure S2: ^{13}C NMR spectrum of the compound **4a**.

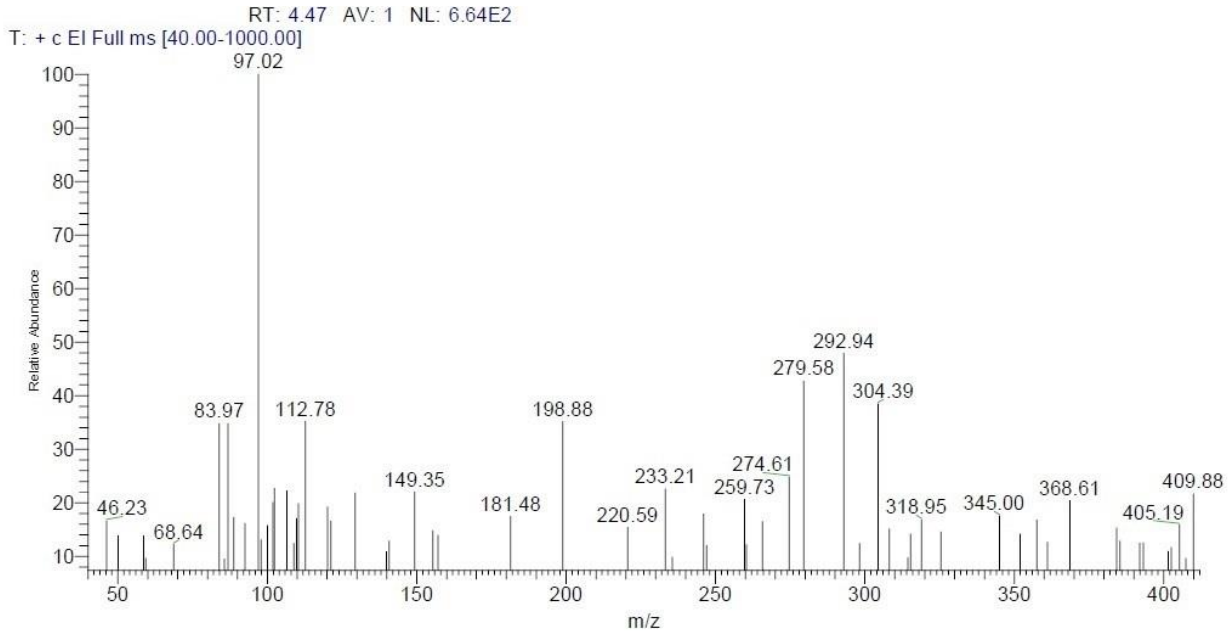

Figure S3: MS of the compound **4a**.

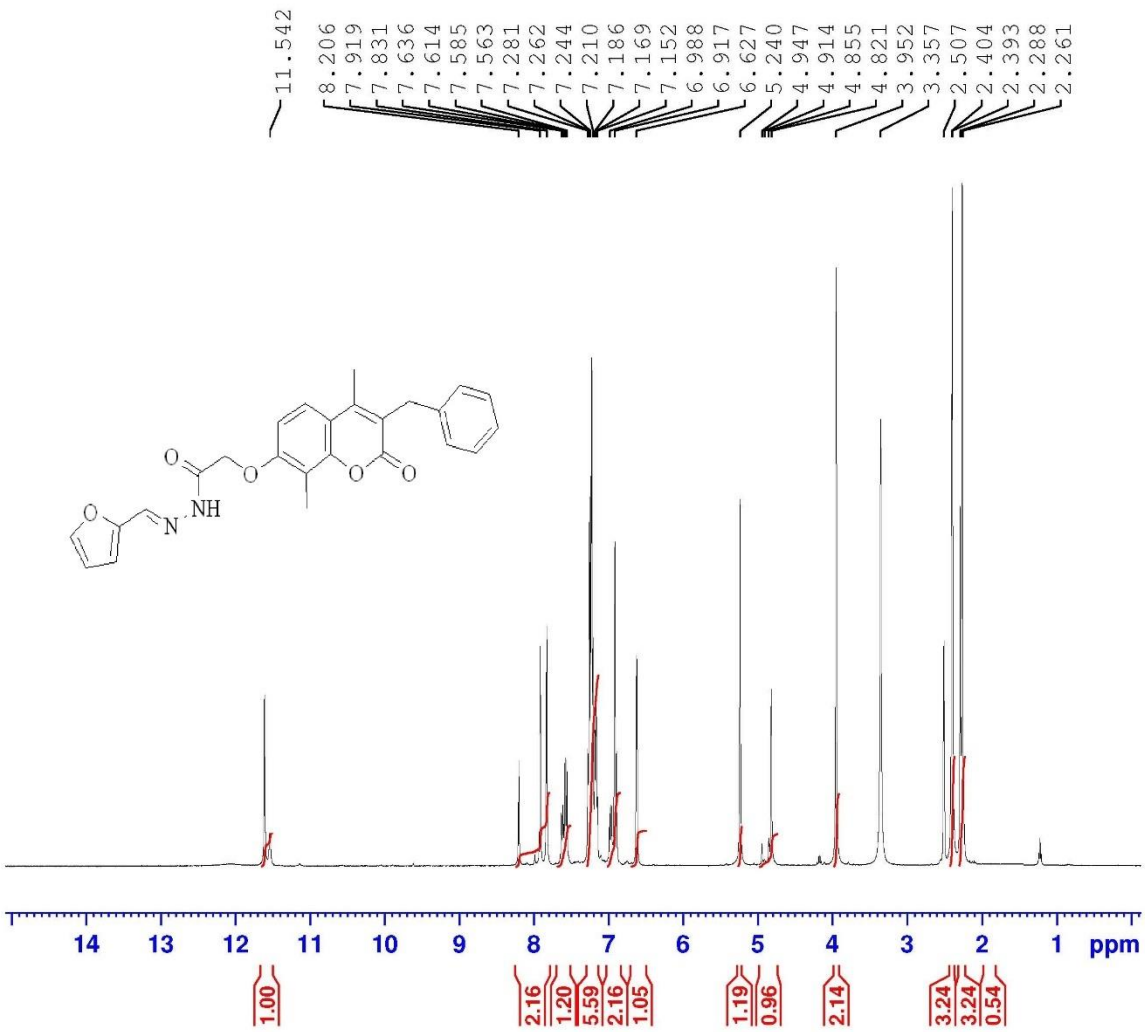

Figure S4: ^{1}H NMR spectrum of the compound **4b**.

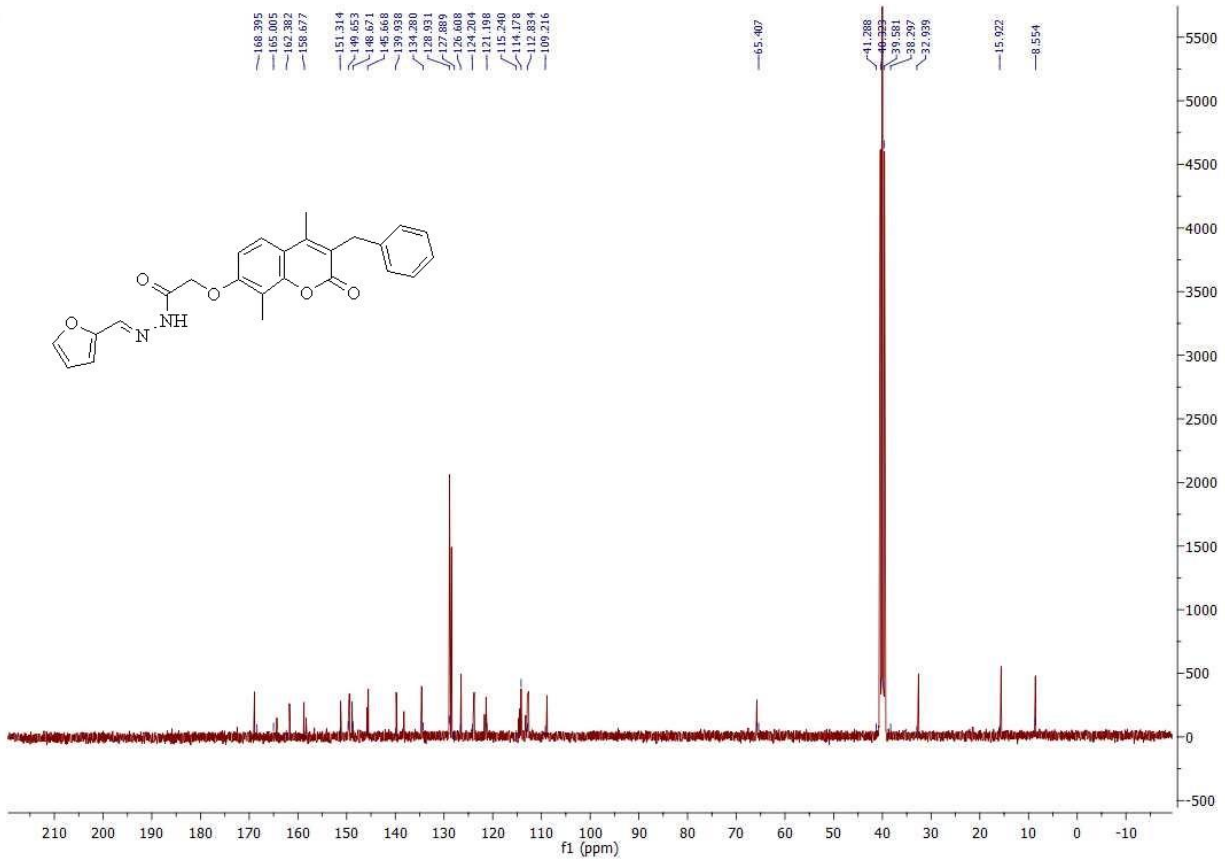

Figure S5: ^{13}C NMR spectrum of the compound **4b**.

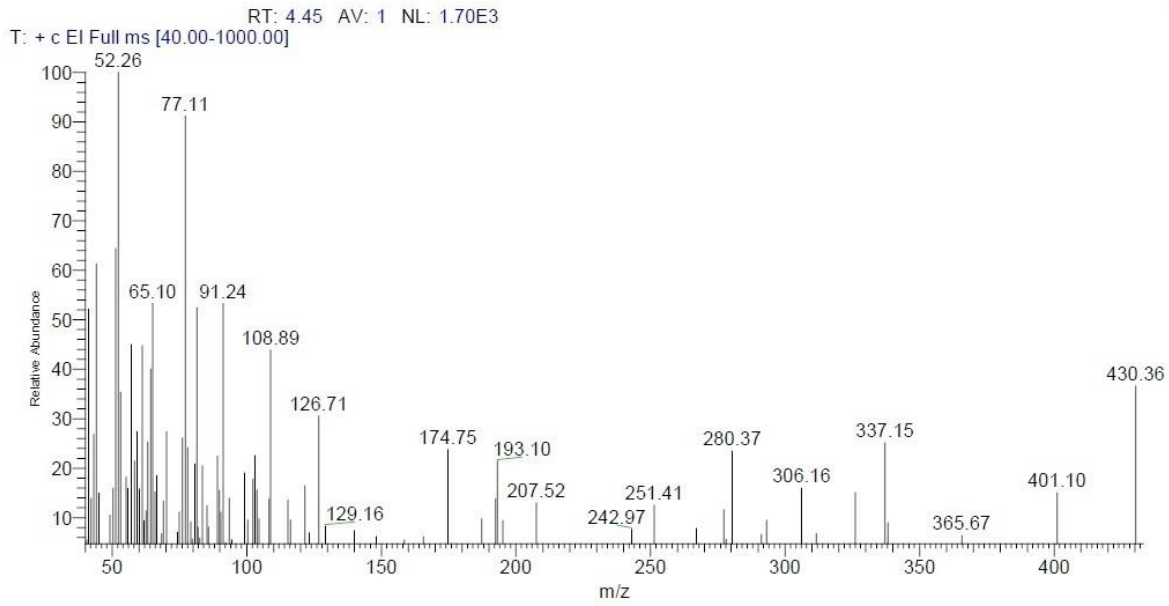

Figure S6: MS of the compound **4b**.

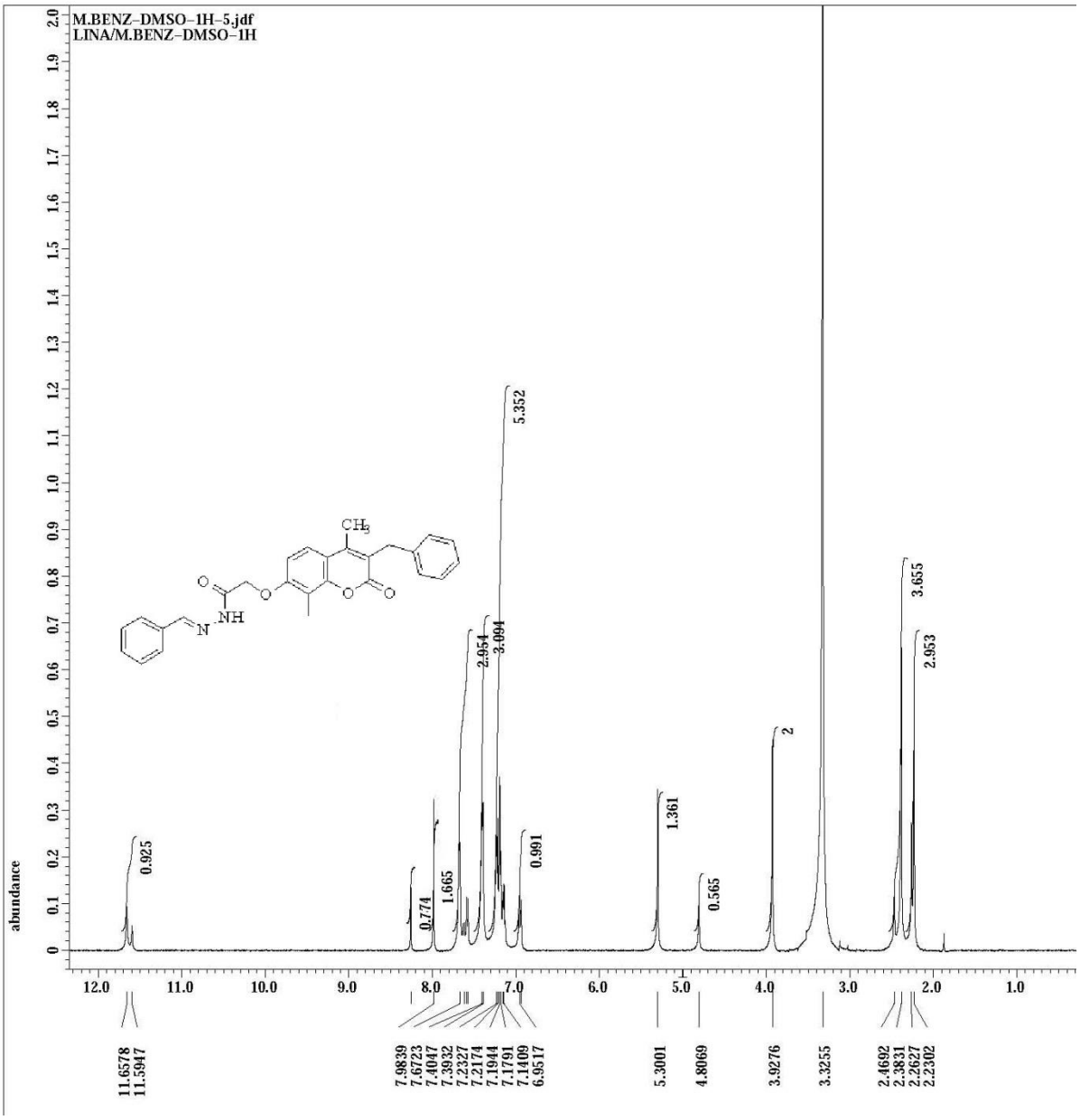

Figure S7: ^{1}H NMR spectrum of the compound **4c**.

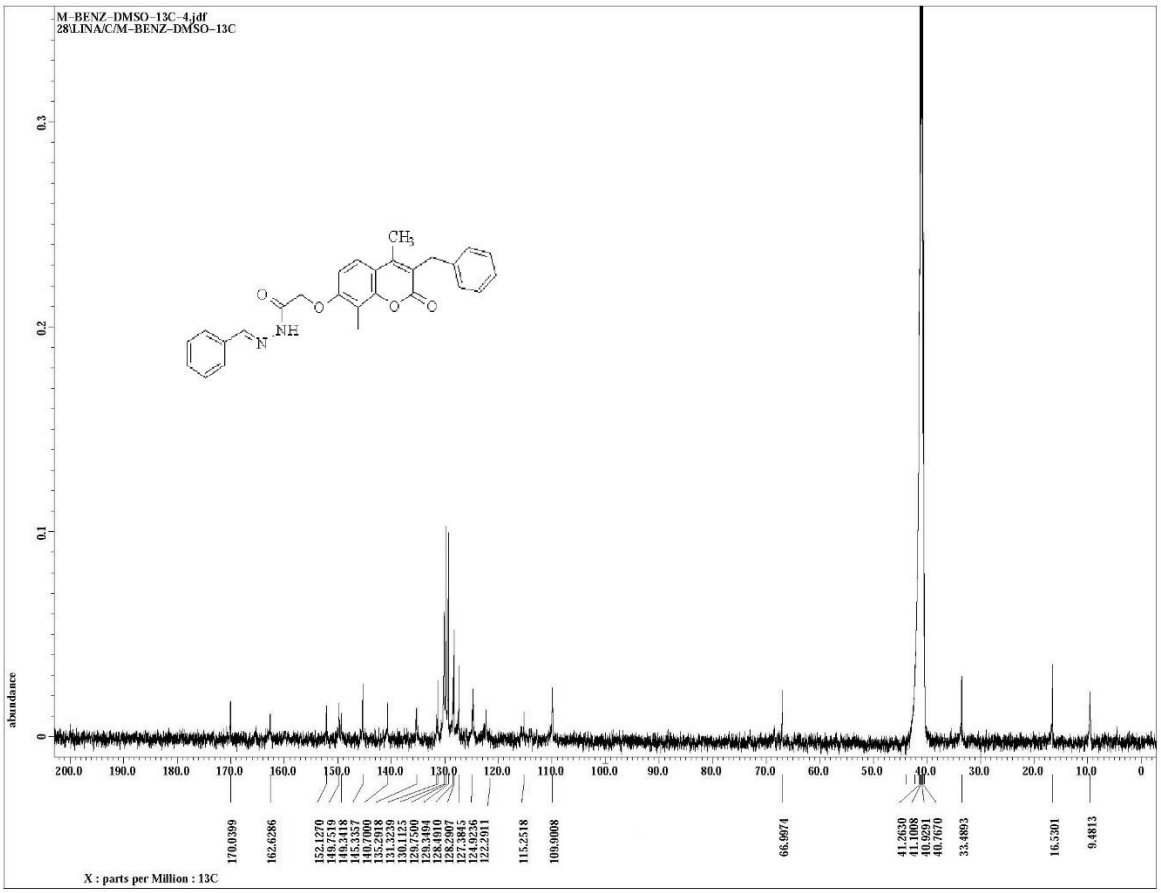

Figure S8: ^{13}C NMR spectrum of the compound **4c**.

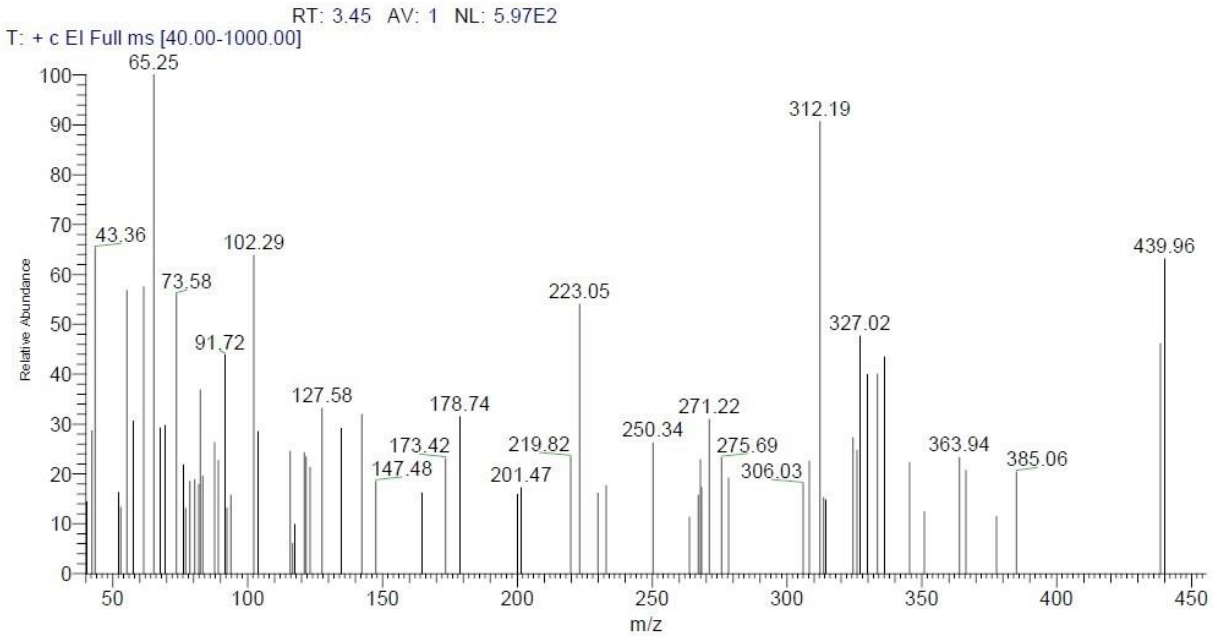

Figure S9: MS of the compound **4c**.

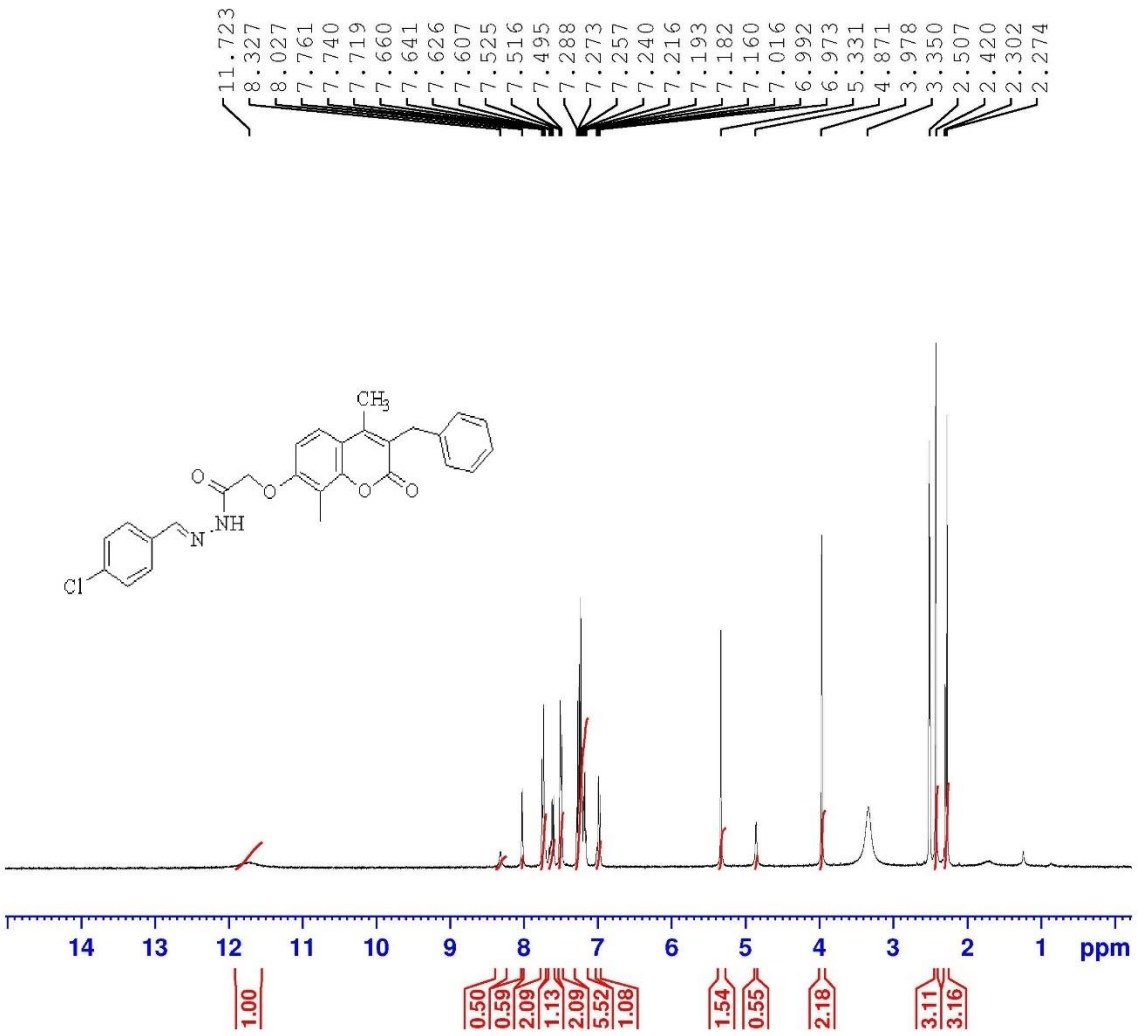

Figure S10: [1]H NMR spectrum of the compound **4d**.

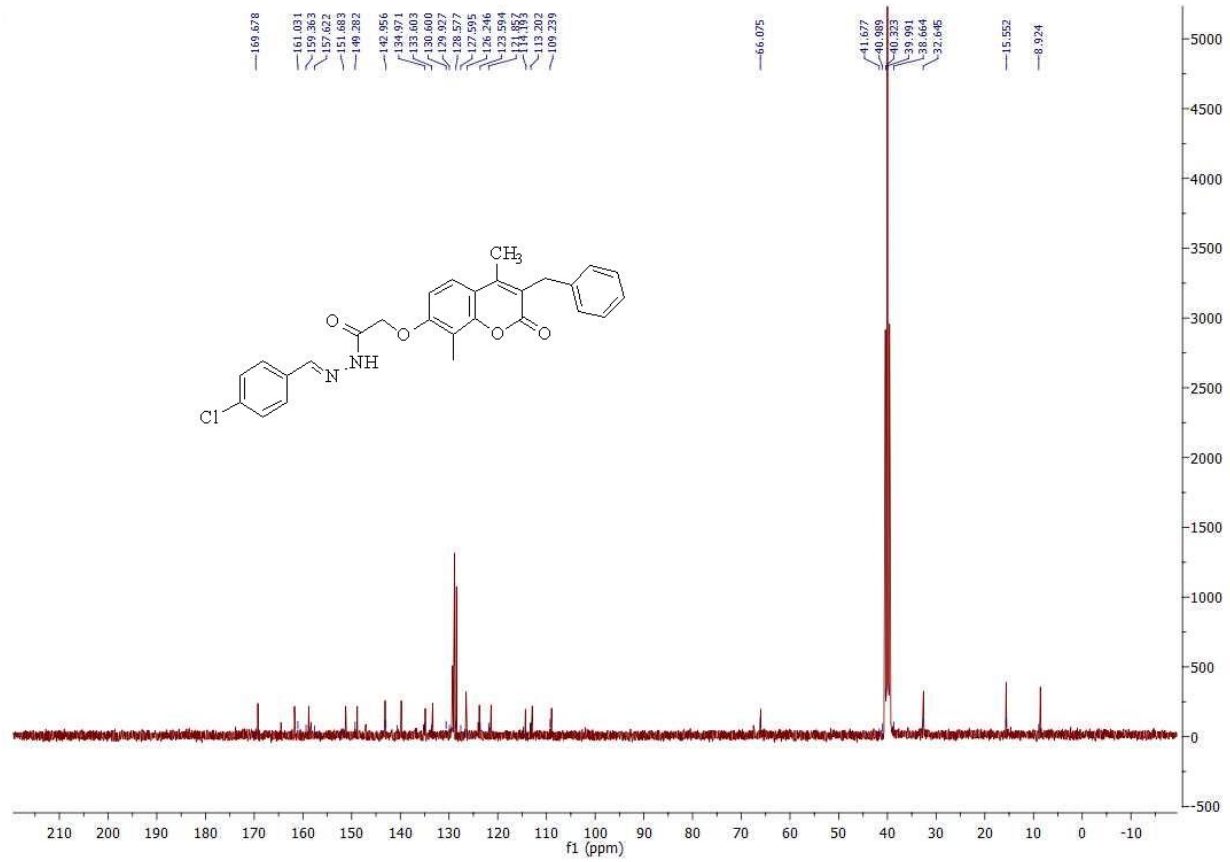

Figure S11: ^{13}C NMR spectrum of the compound **4d**.

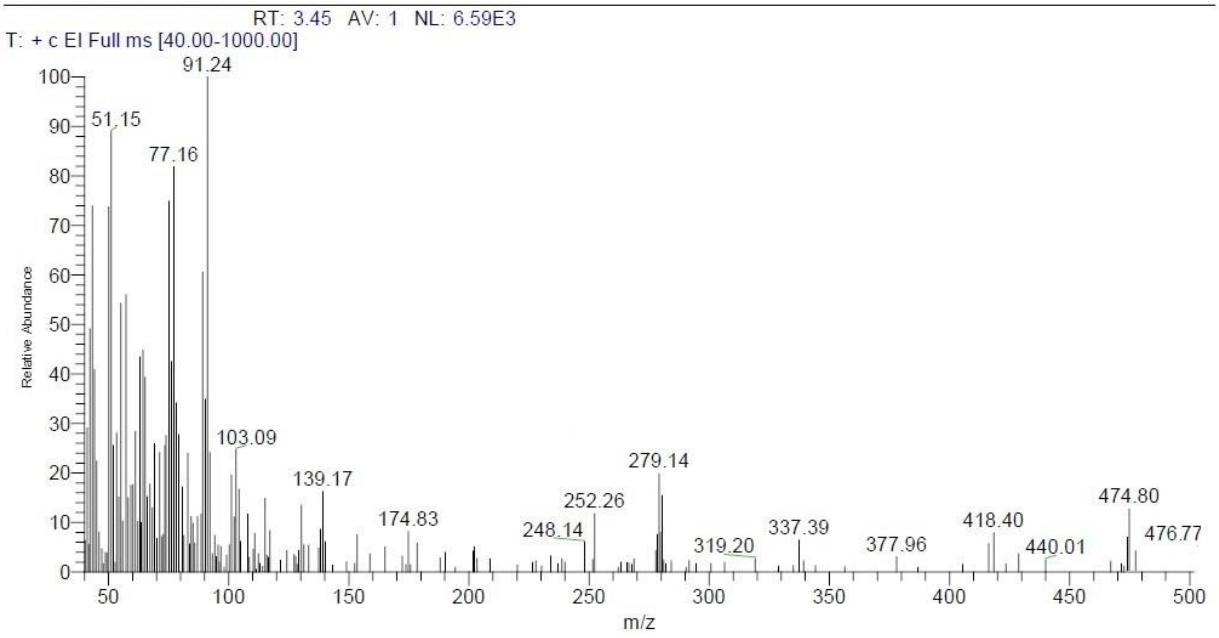

Figure S12: MS of the compound **4d**.

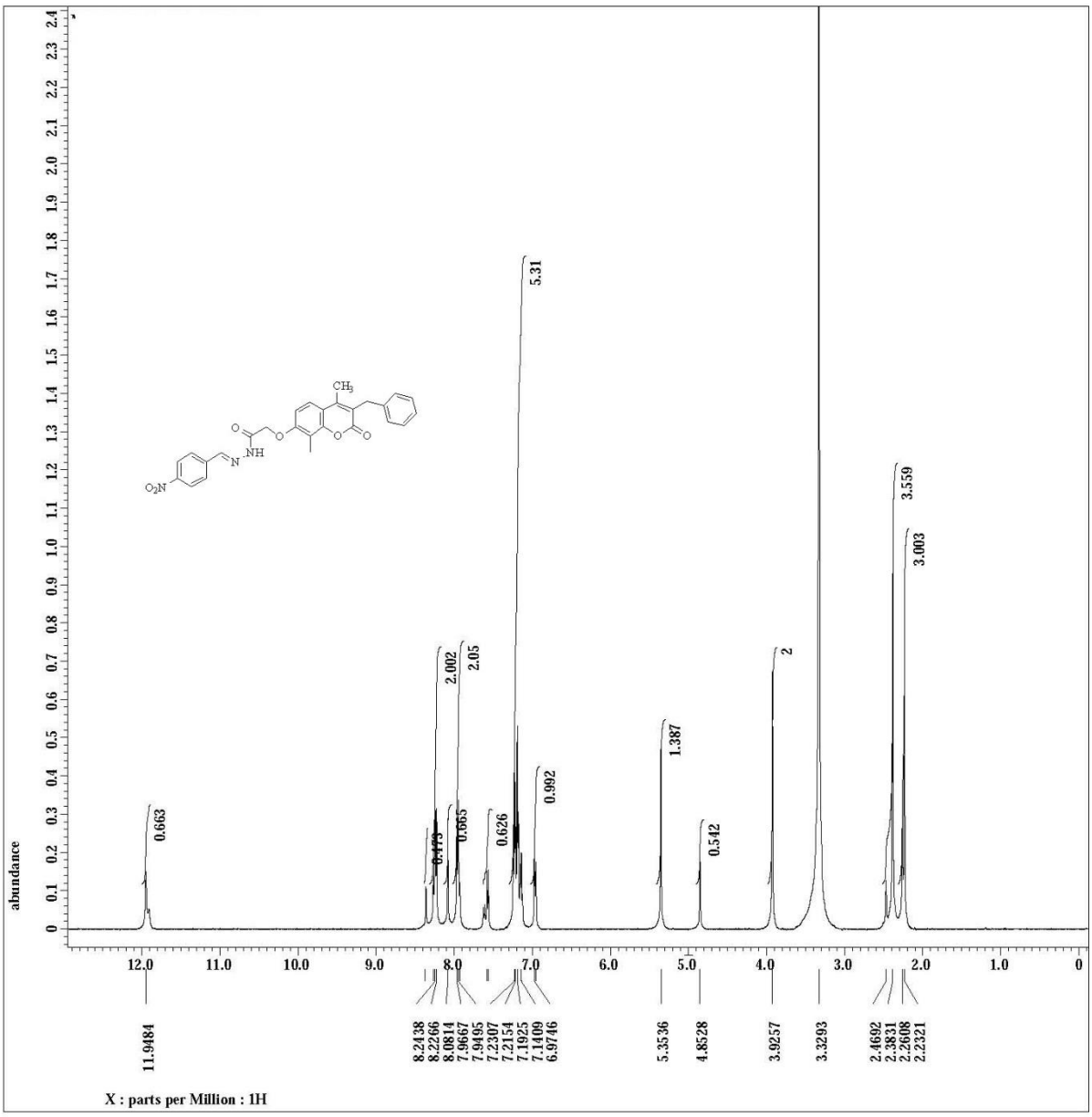

Figure S13: ^{1}H NMR spectrum of the compounds **4e**.

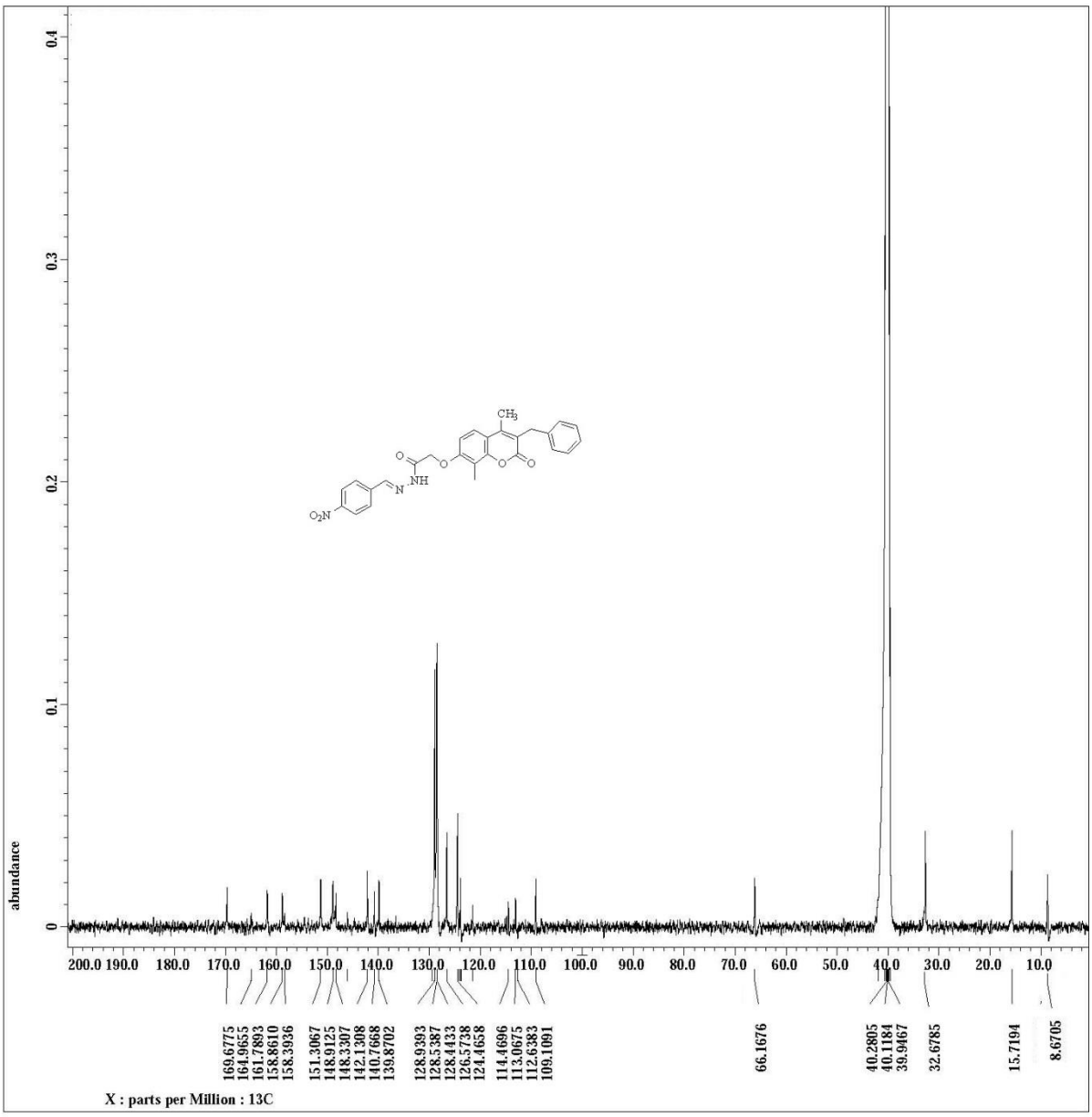

Figure S14: ^{13}C NMR spectrum of the compound **4e**.

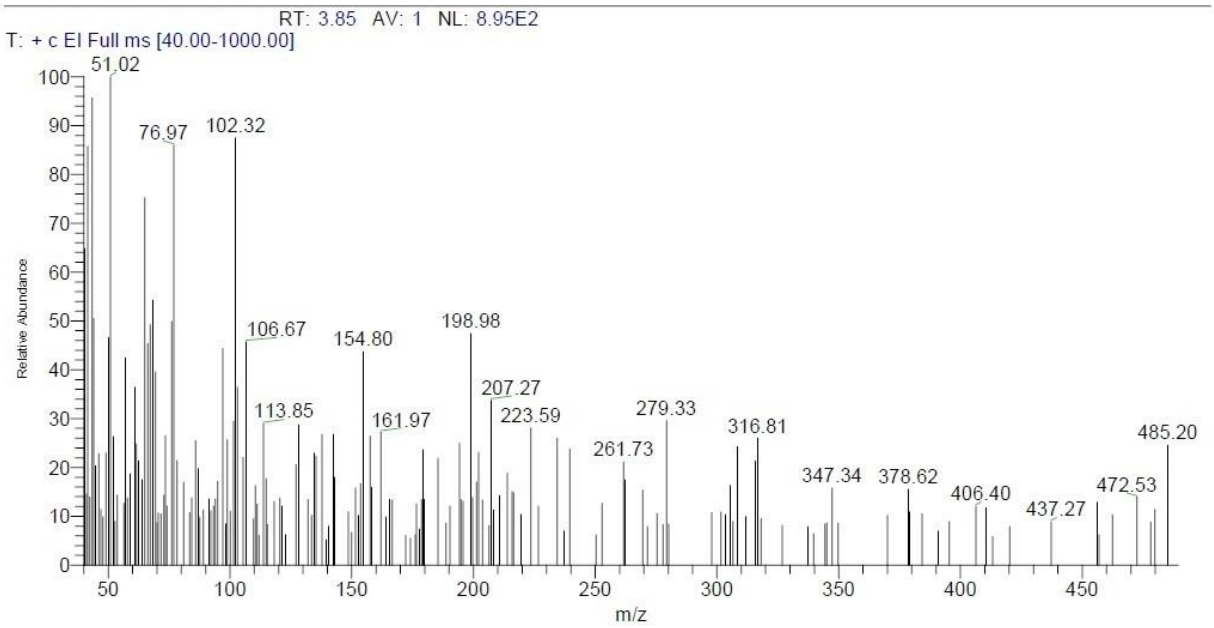

Figure S15: MS of the compound **4e**.

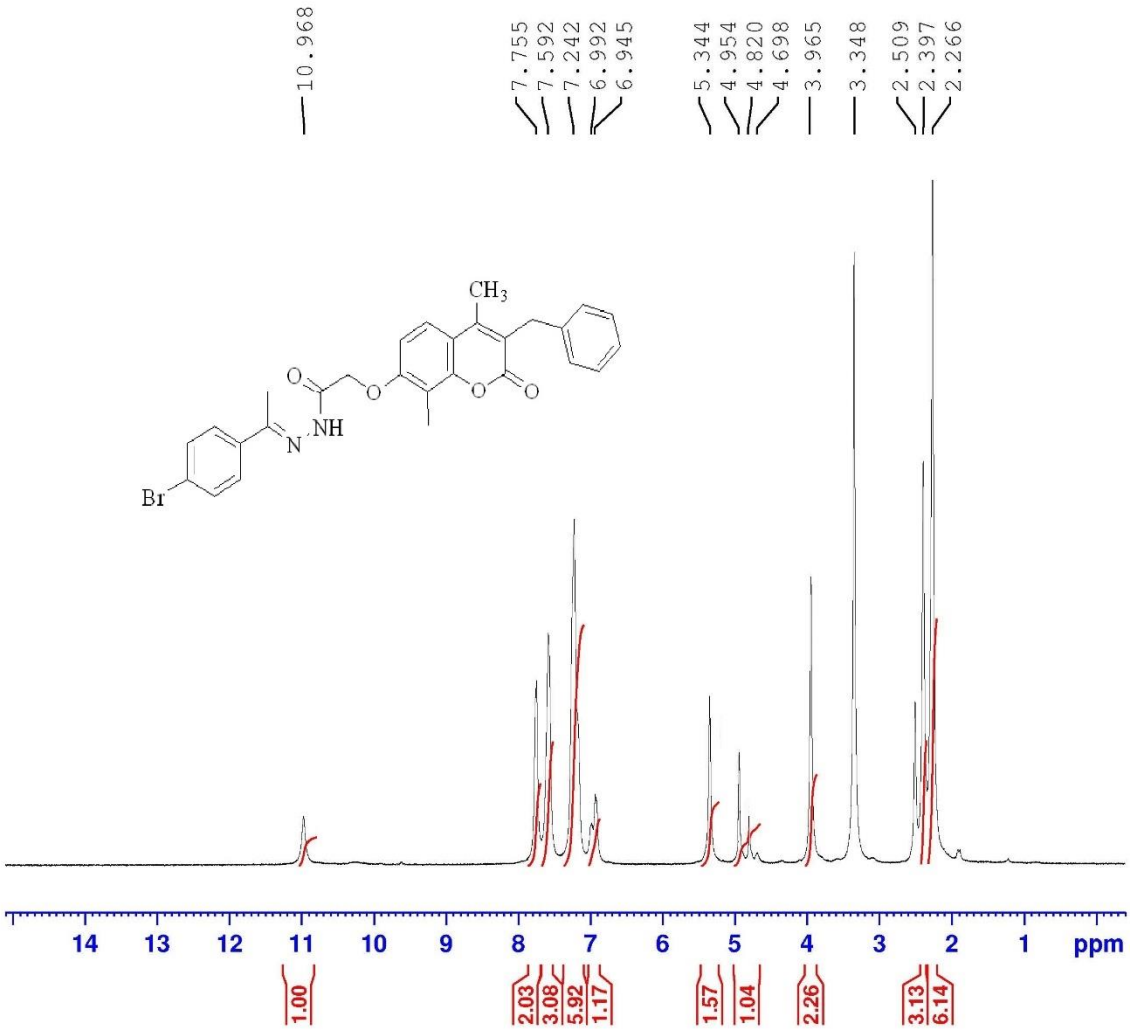

Figure S16: [1]H NMR spectrum of the compound **5**.

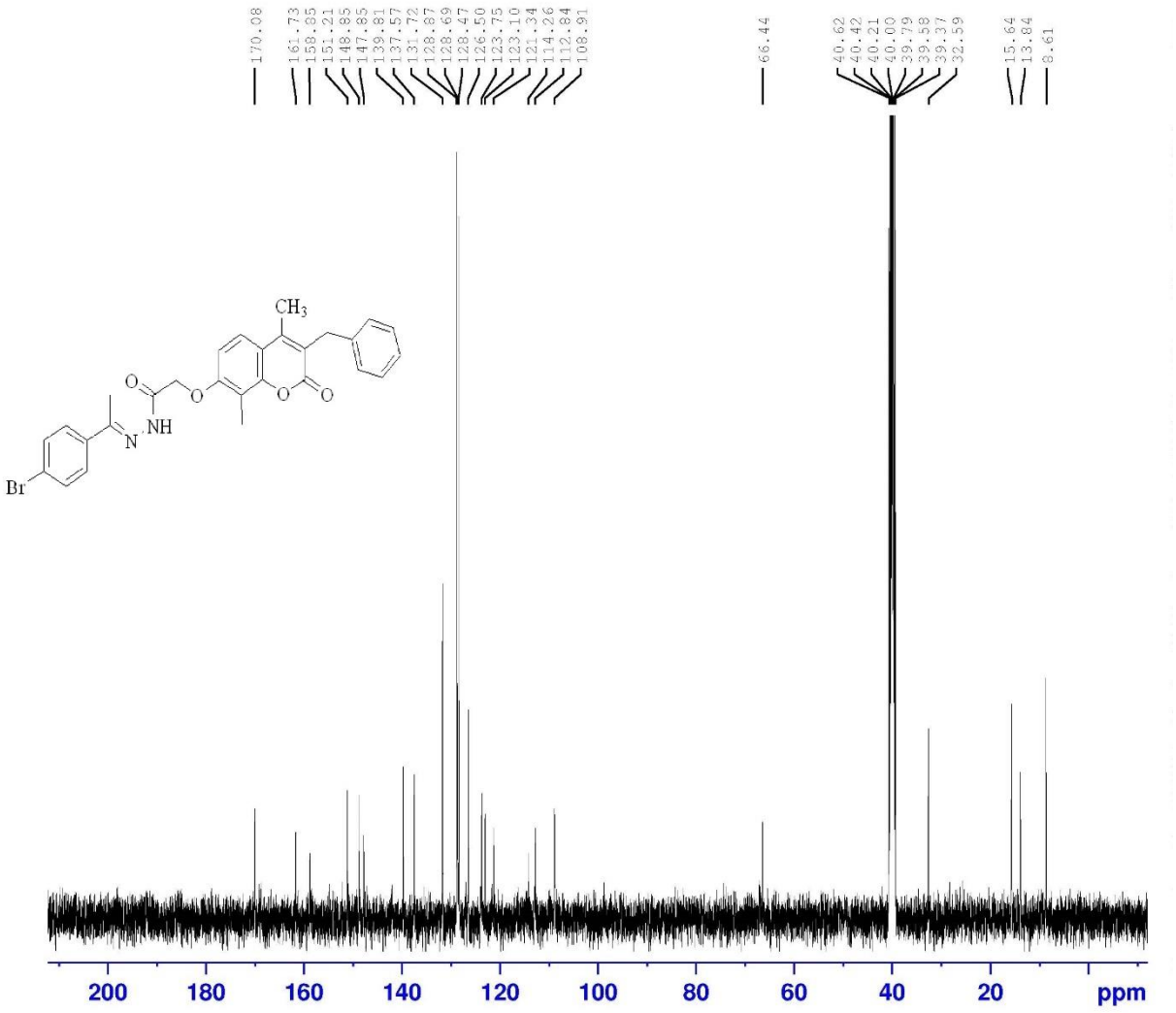

Figure S17: ^{13}C NMR spectrum of the compound **5**.

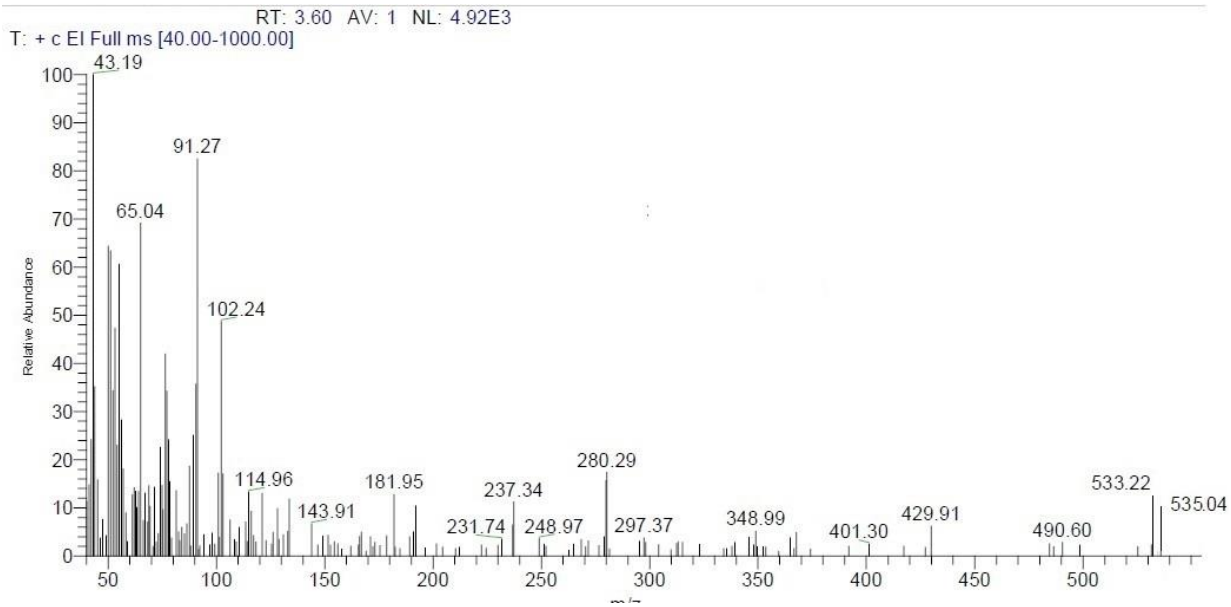

Figure S18: MS of the compound **5**.

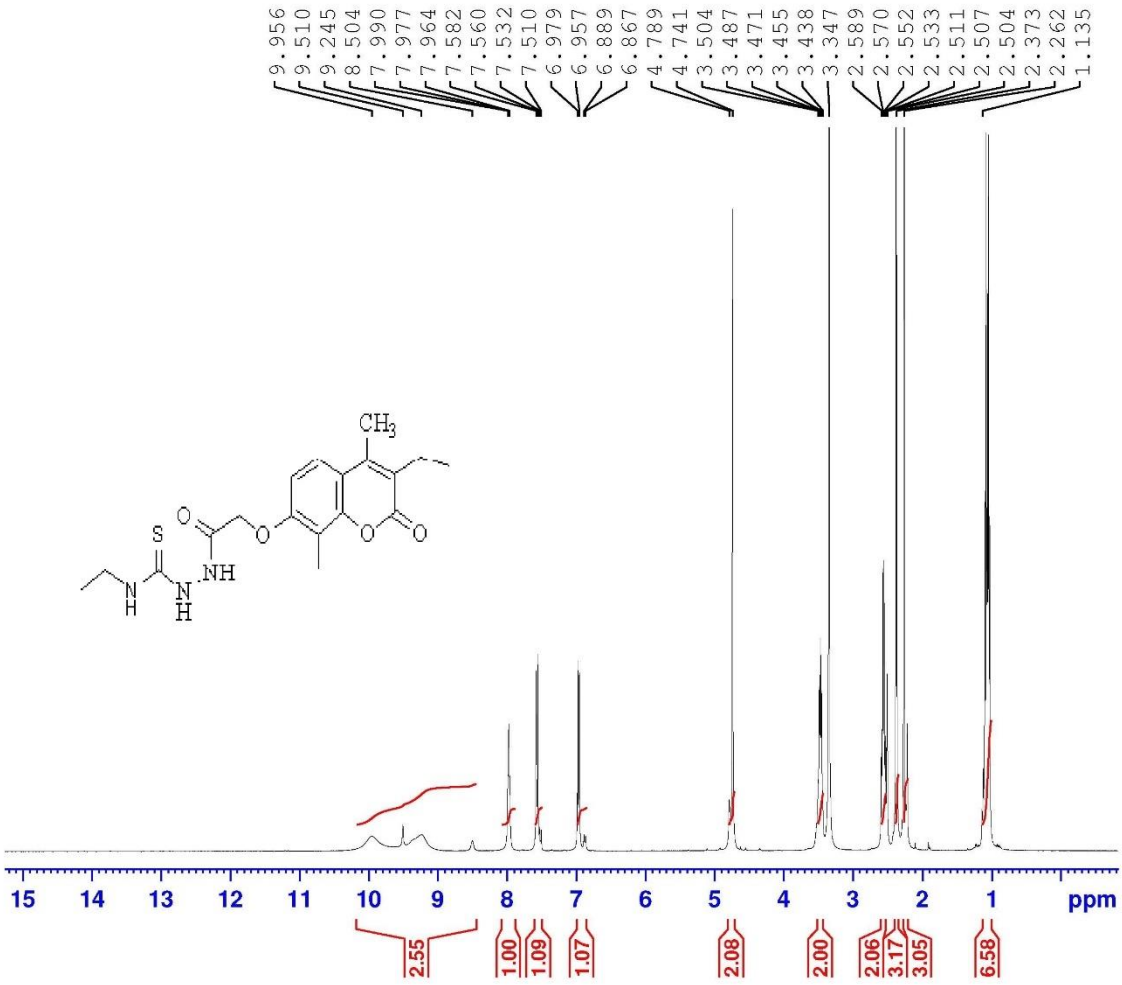

Figure S19: [1]H NMR spectrum of the compound **6a**.

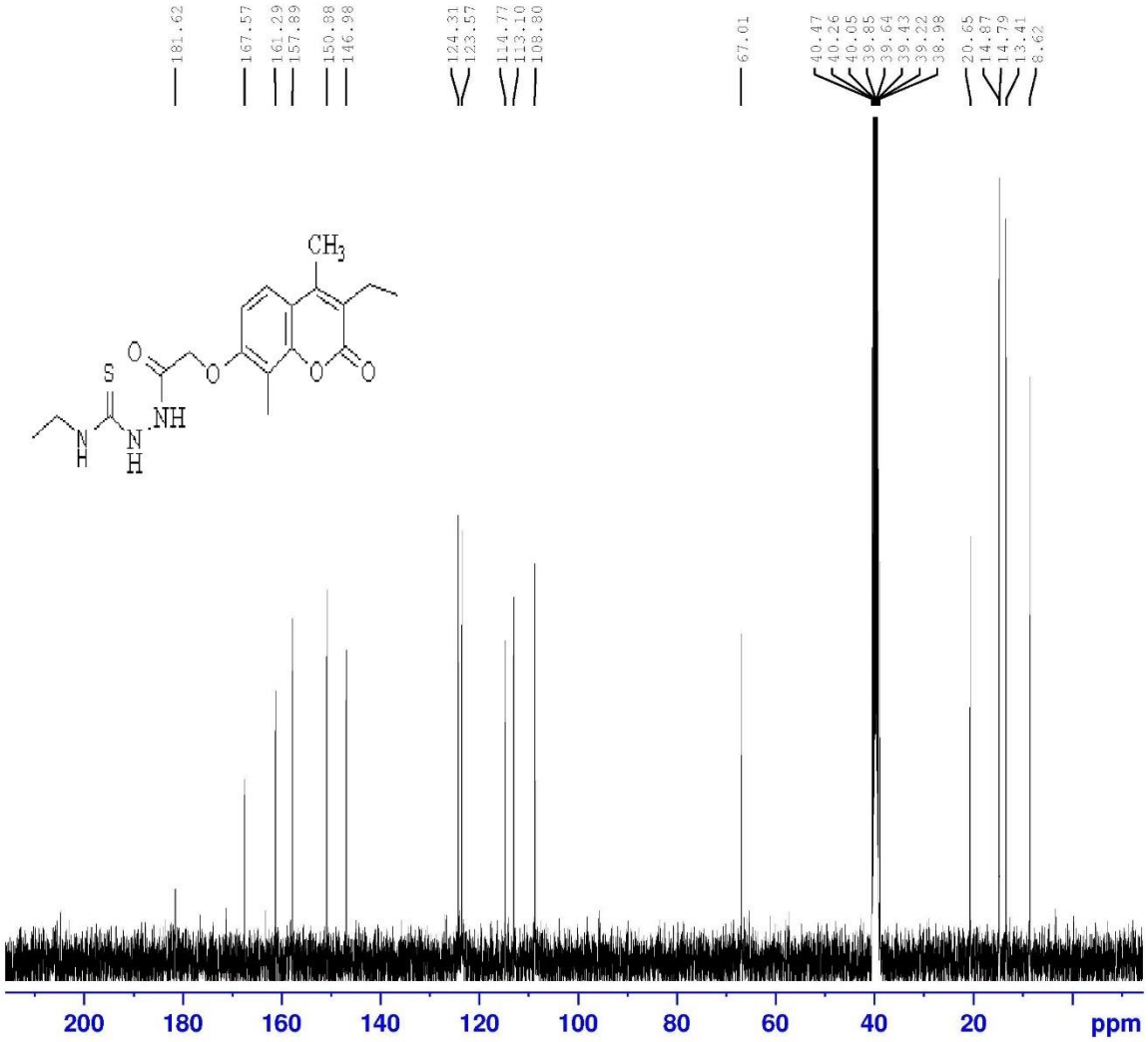

Figure S20: ^{13}C NMR spectrum of the compound **6a**.

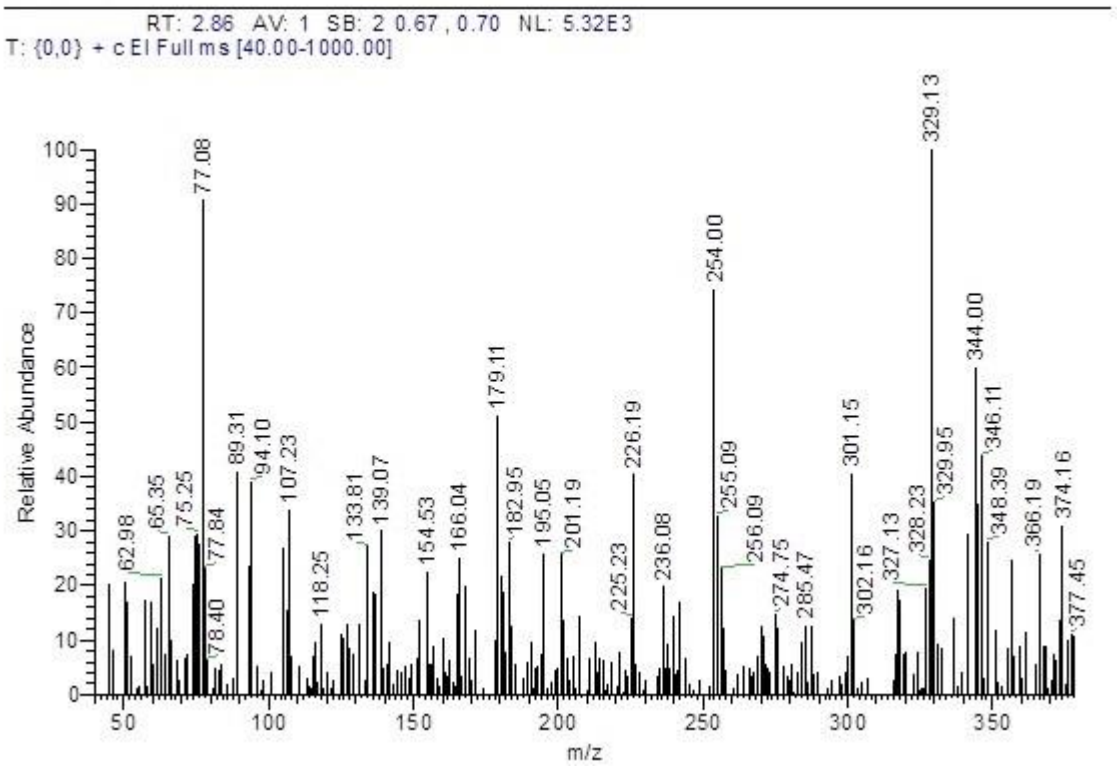

Figure S21: MS of the compound **6a**.

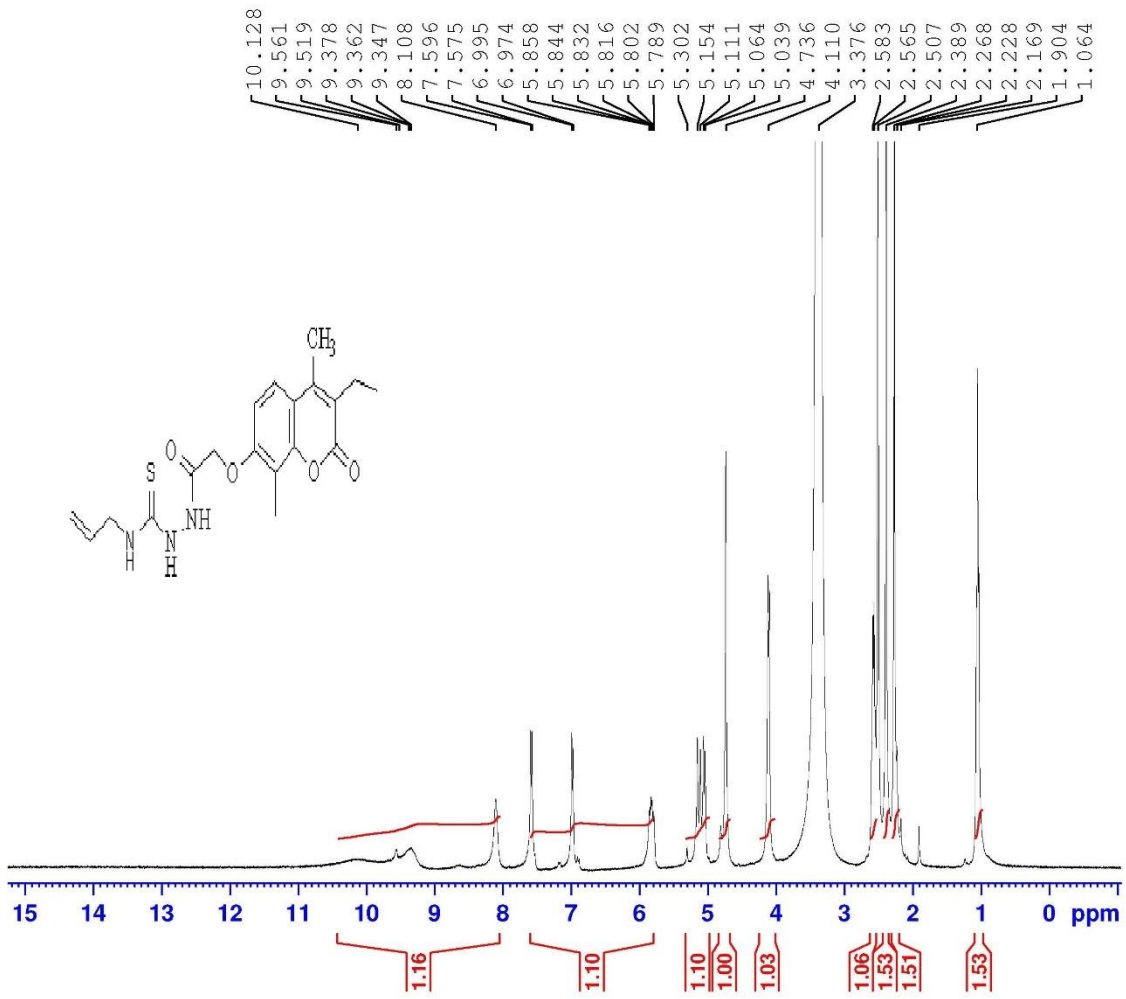

Figure S22: [1]H NMR spectrum of the compound **6b**.

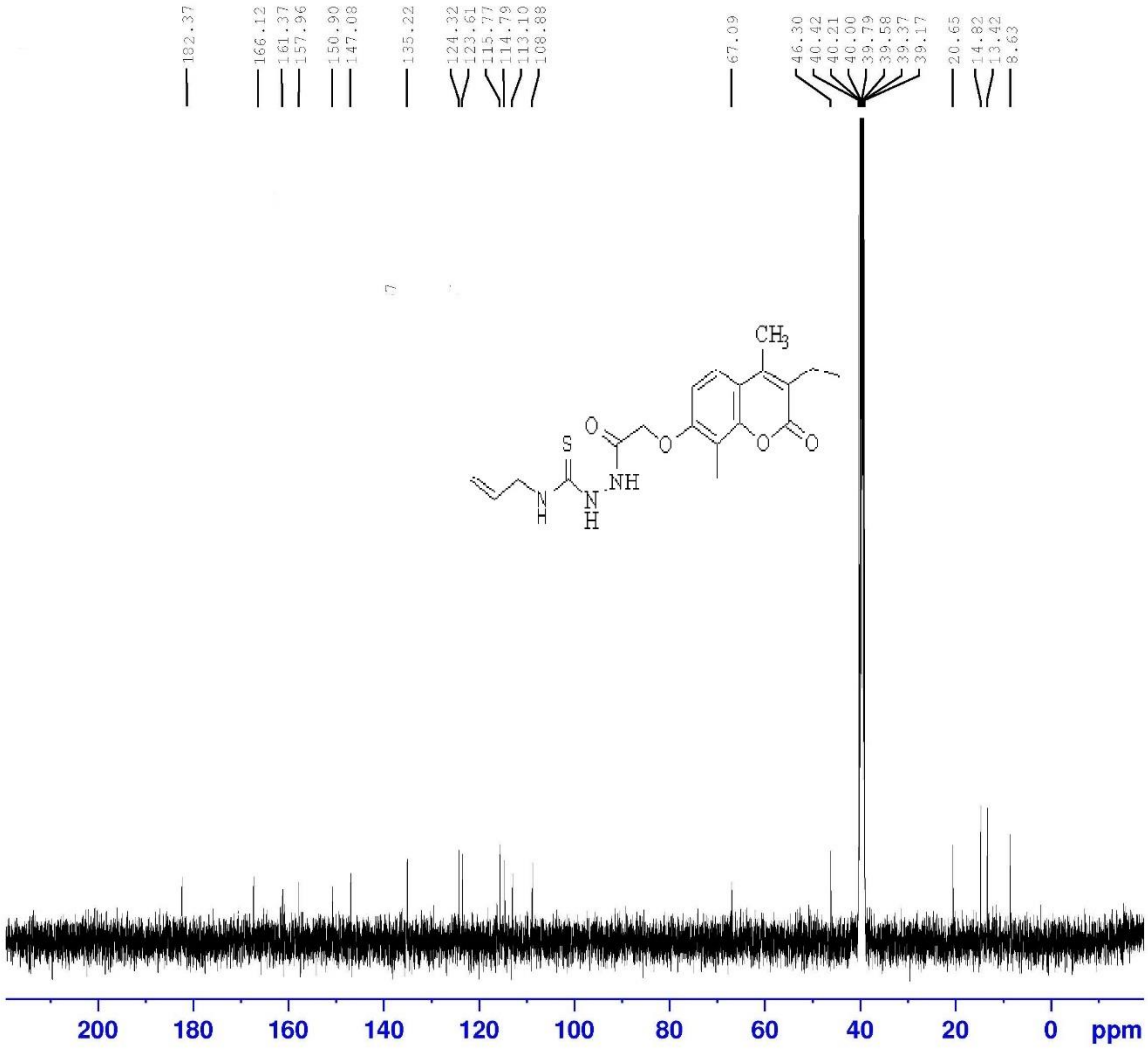

Figure S23: ^{13}C NMR spectrum of the compound **6b**.

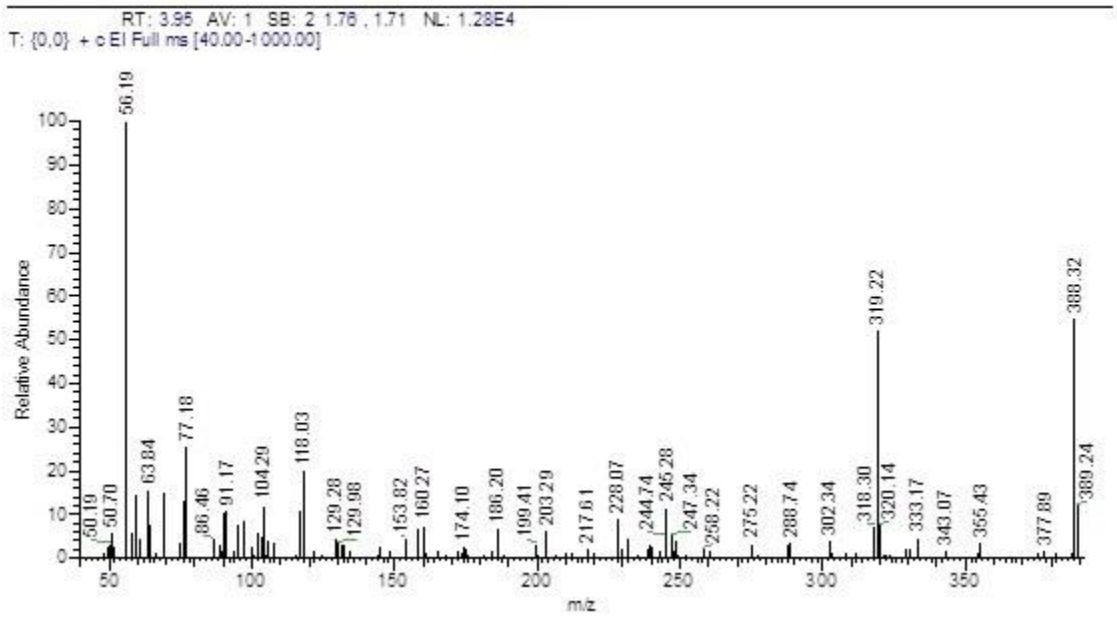

Figure S24: MS of the compound **6b**.

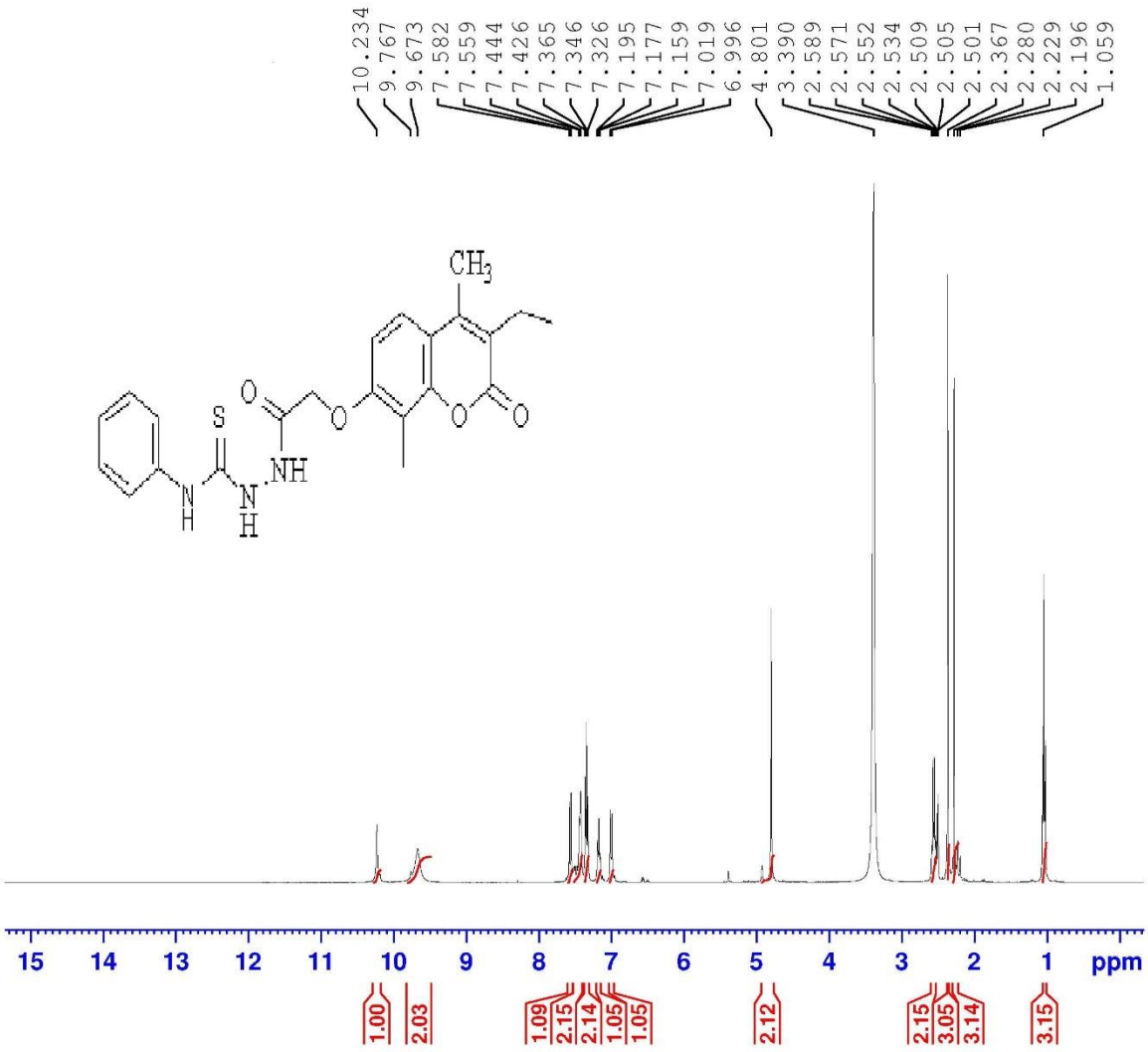

Figure S25: ^{1}H NMR spectrum of the compound **6c**.

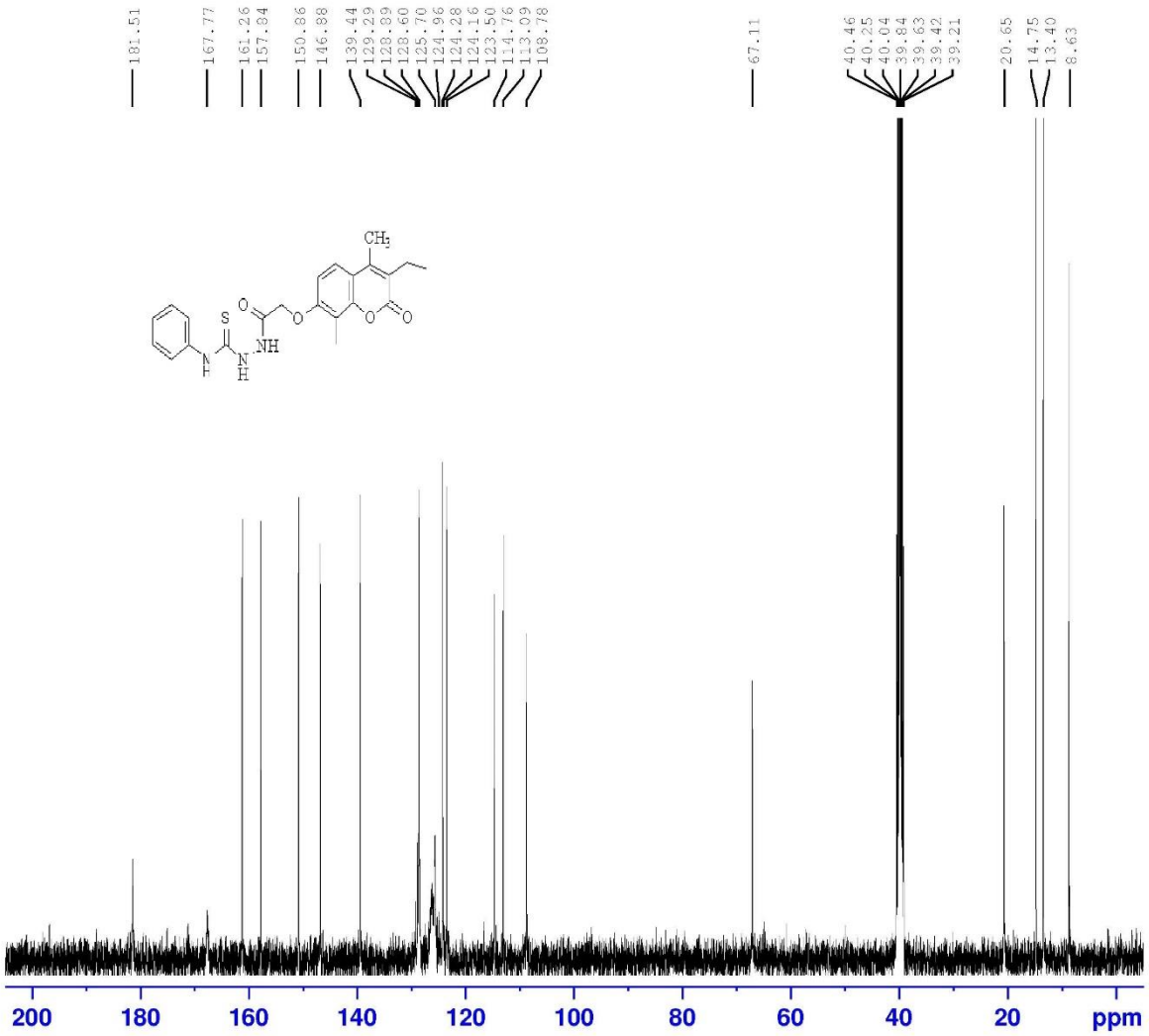

Figure S26: ^{13}C NMR spectrum of the compound **6c**.

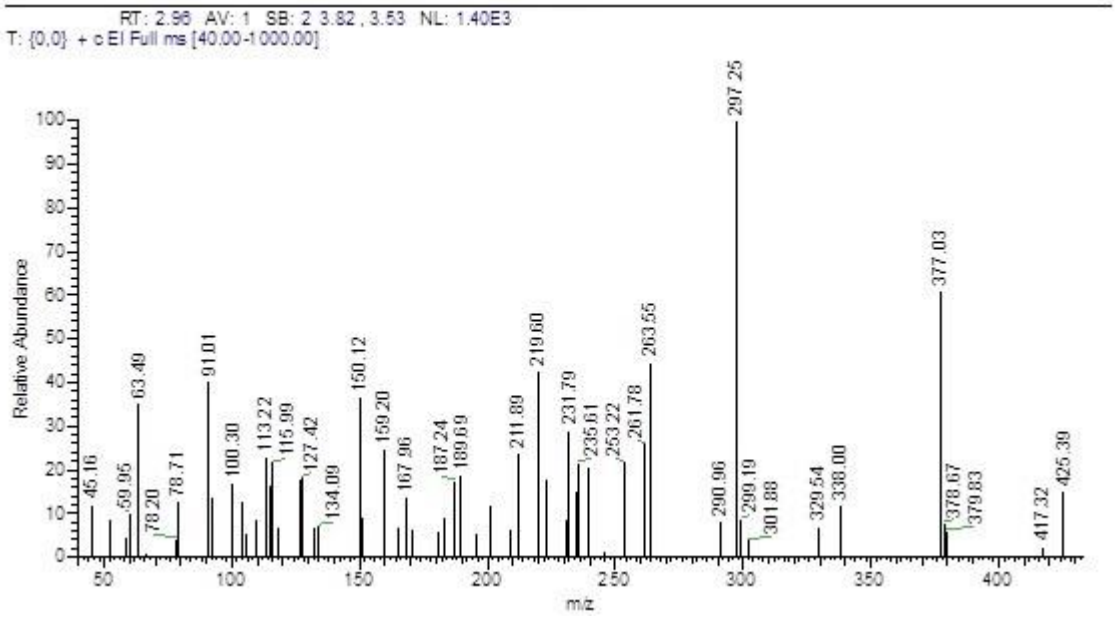

Figure S27: MS of the compound **6c**.

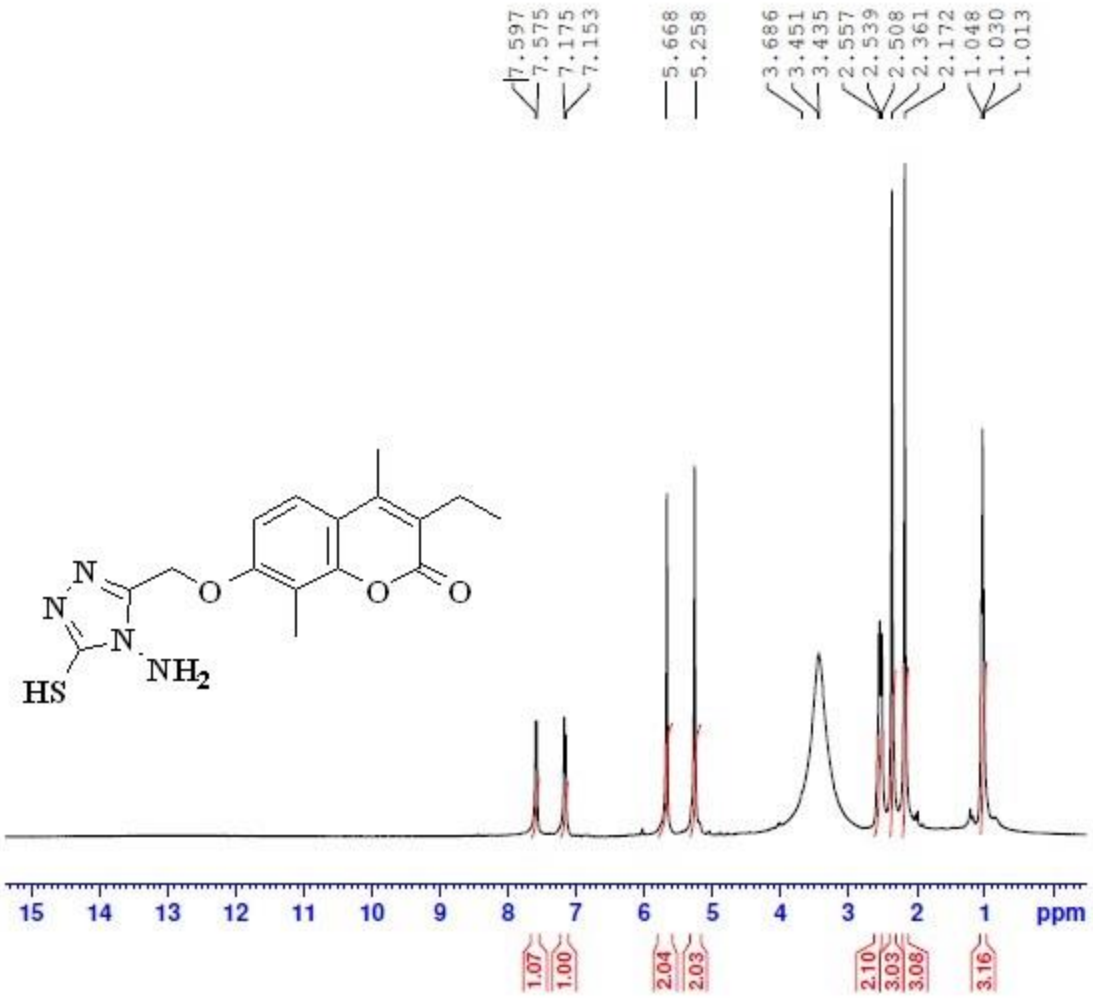

Figure S28: ^{1}H NMR spectrum of the compound **7**.

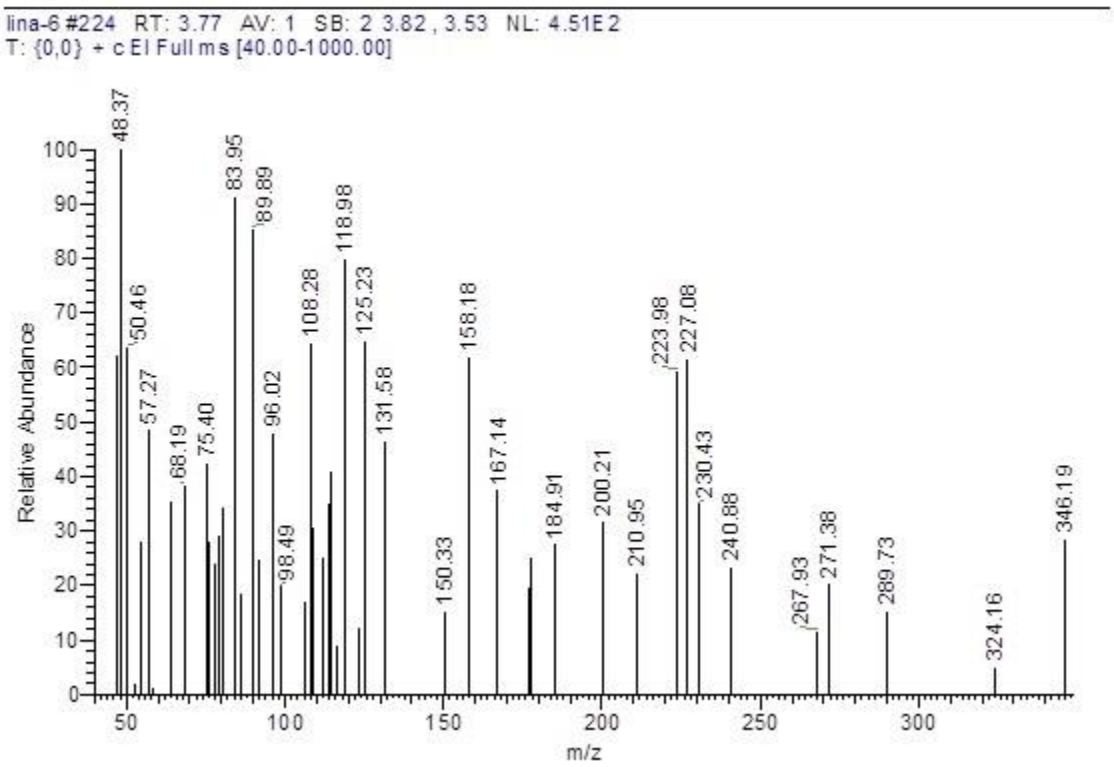

Figure S29: MS of the compound **7**.

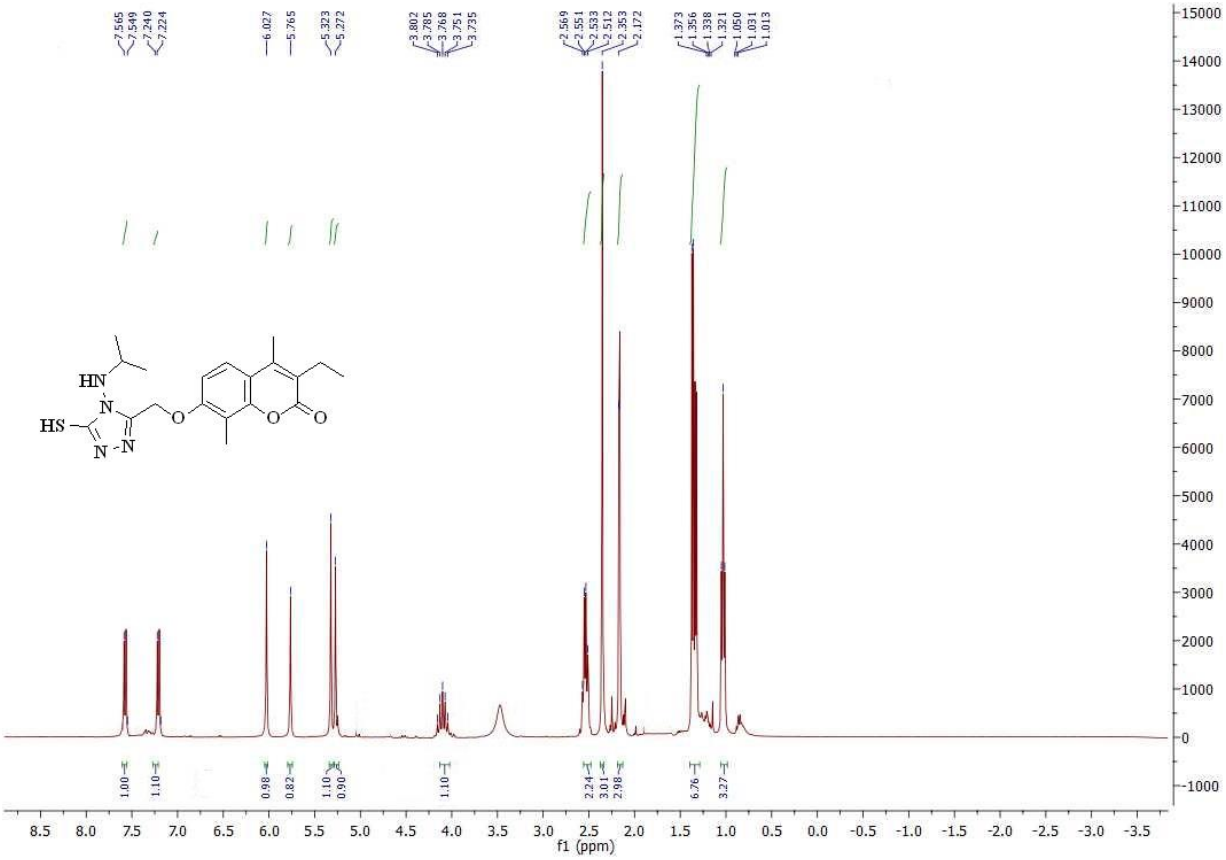

Figure S30: ^{1}H NMR spectrum of the compound **8**.

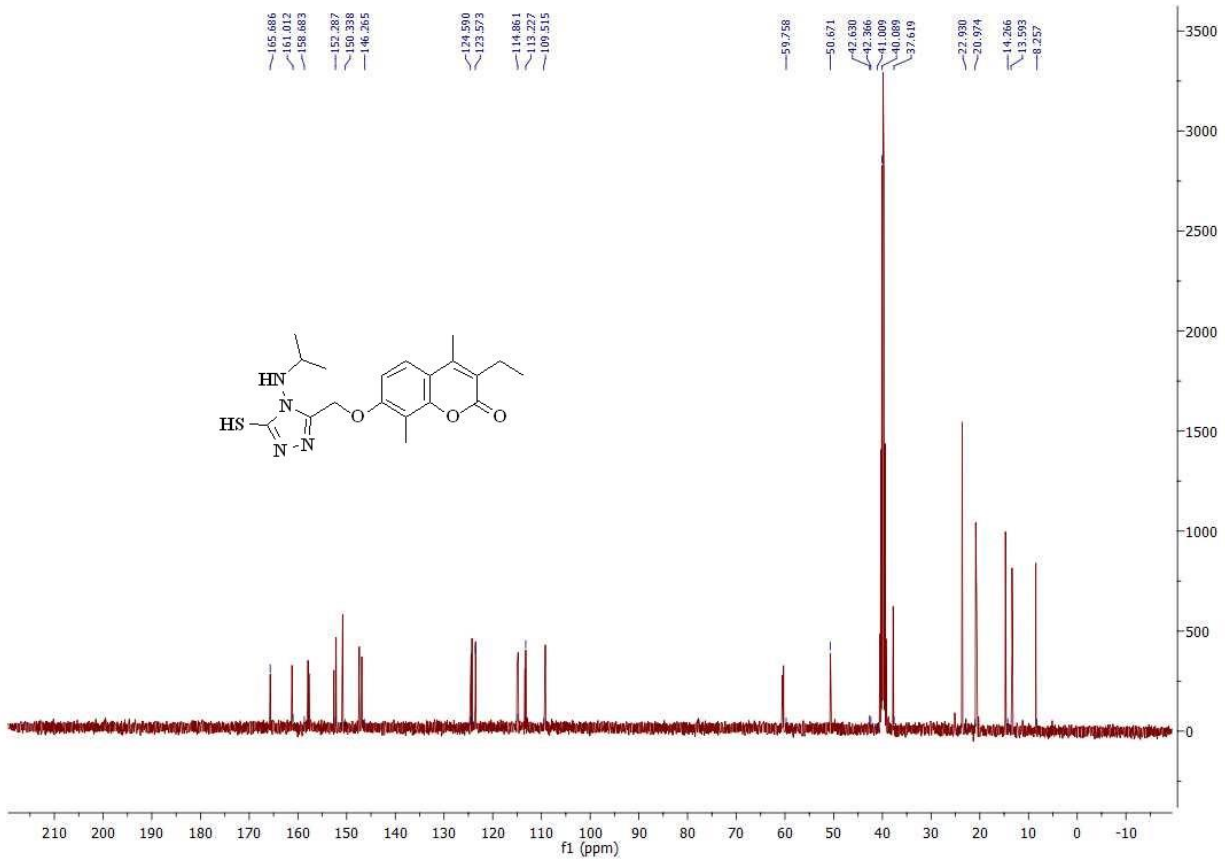

Figure S31: ^{13}C NMR spectrum of the compound **8**.

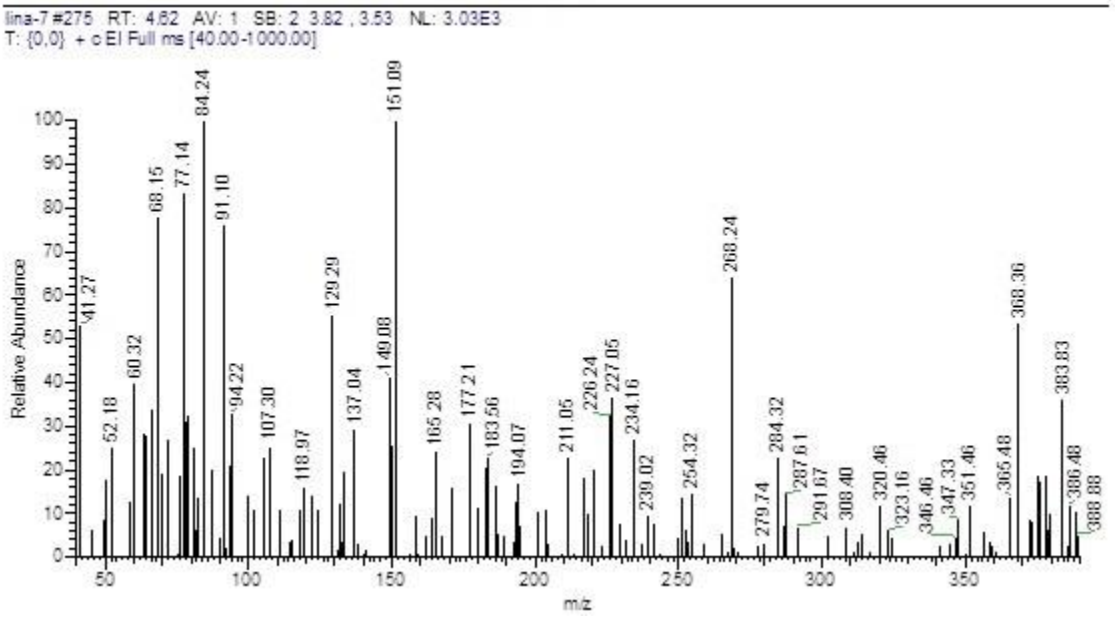

Figure S32: MS of the compound **8**.

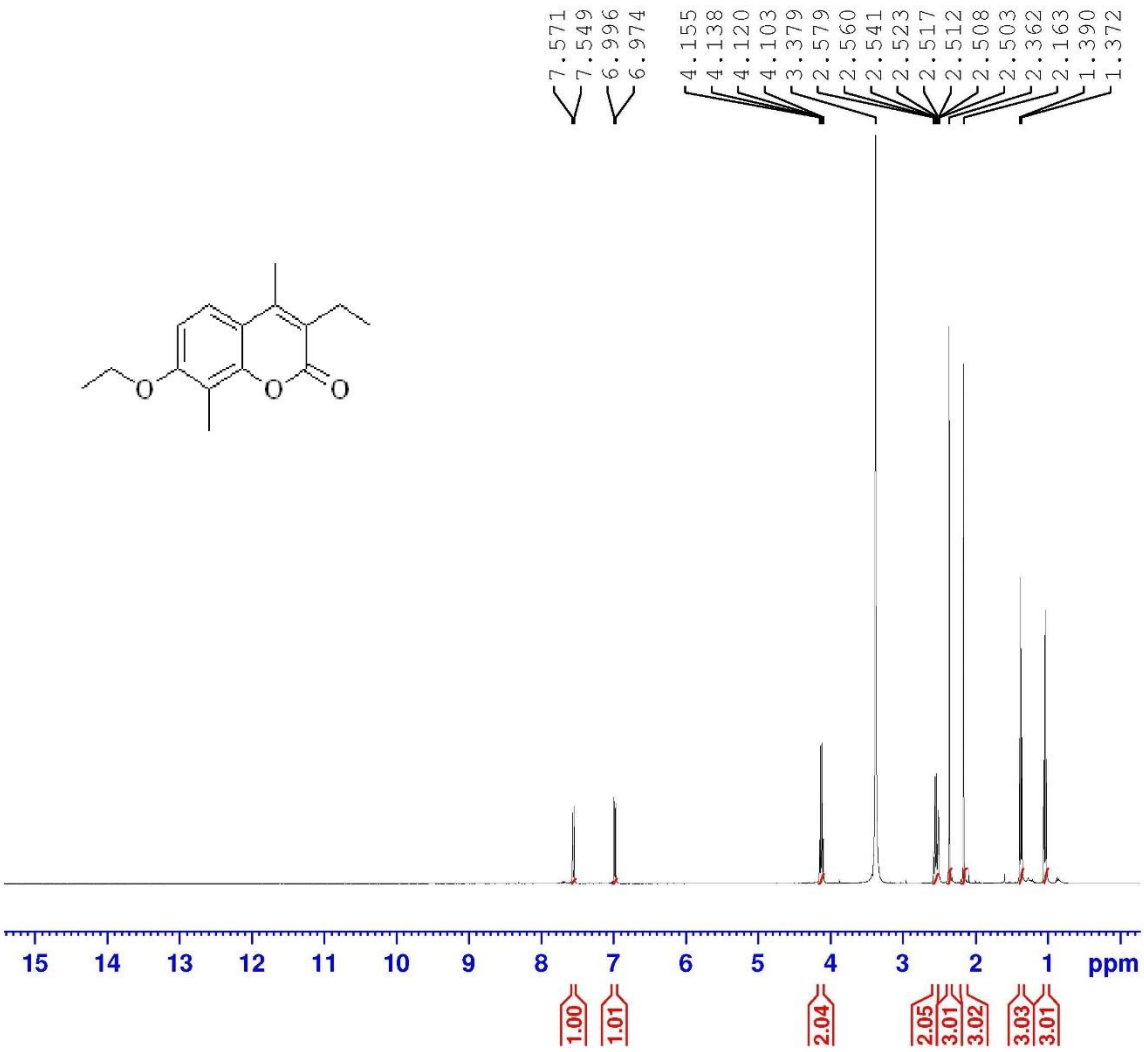

Figure S33: ^{1}H NMR spectrum of the compound **9a**.

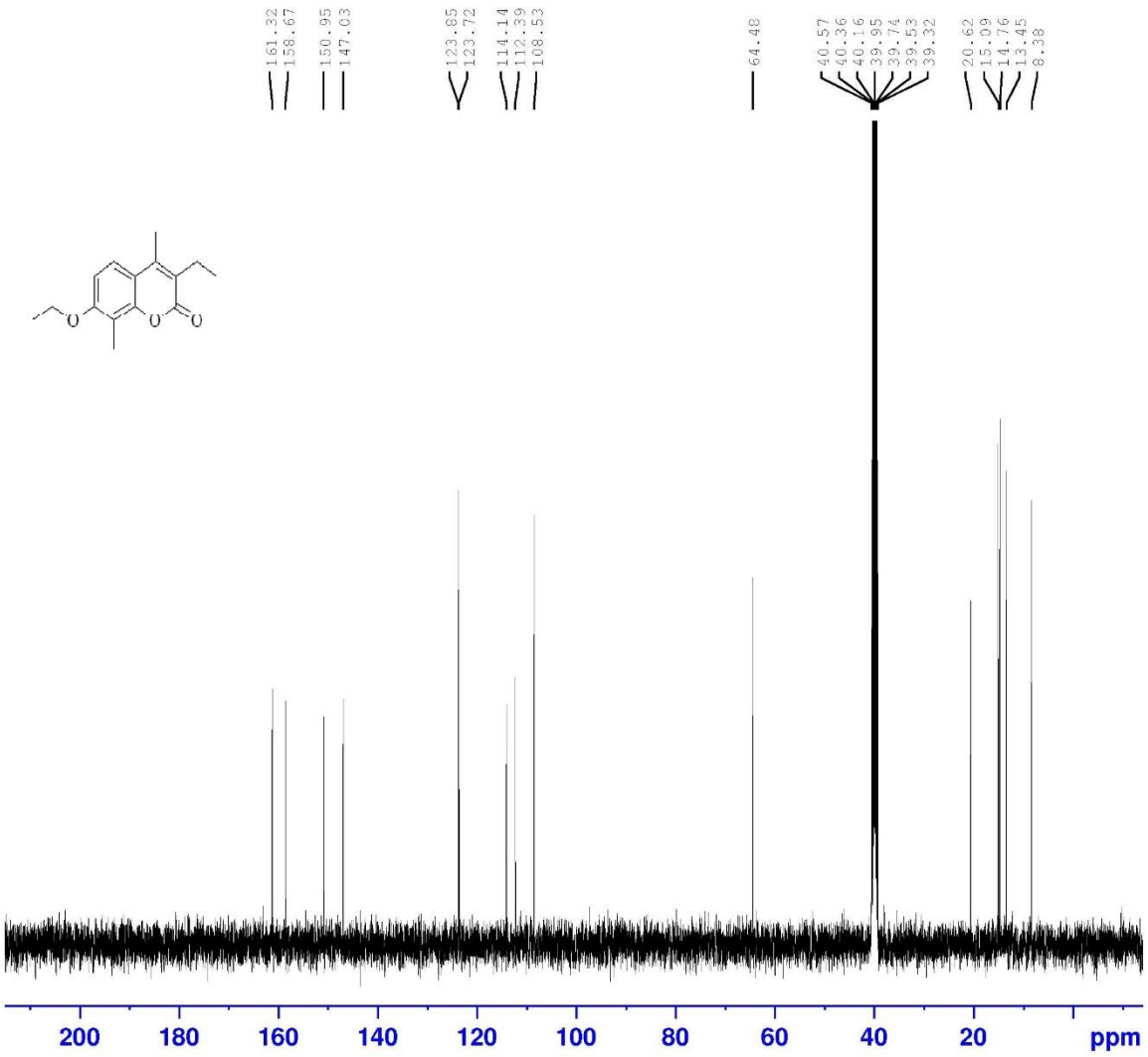

Figure S34: ^{13}C NMR spectrum of the compound **9a**.

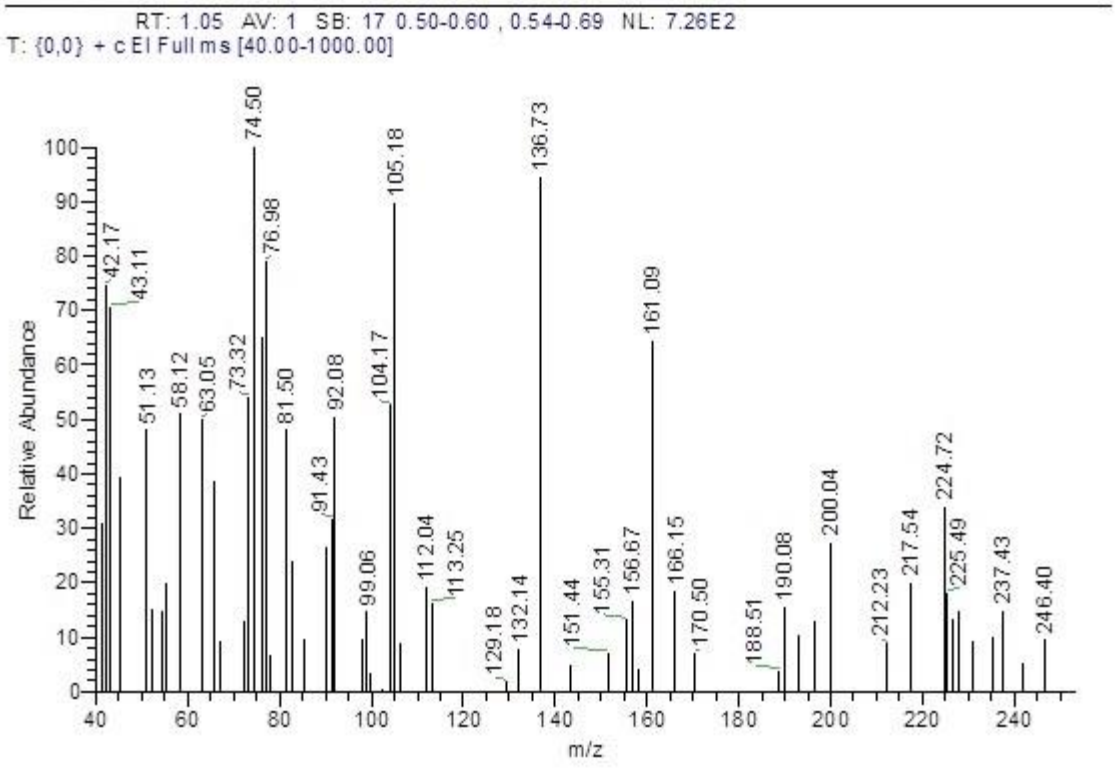

Figure S35: MS of the compound **9a**.

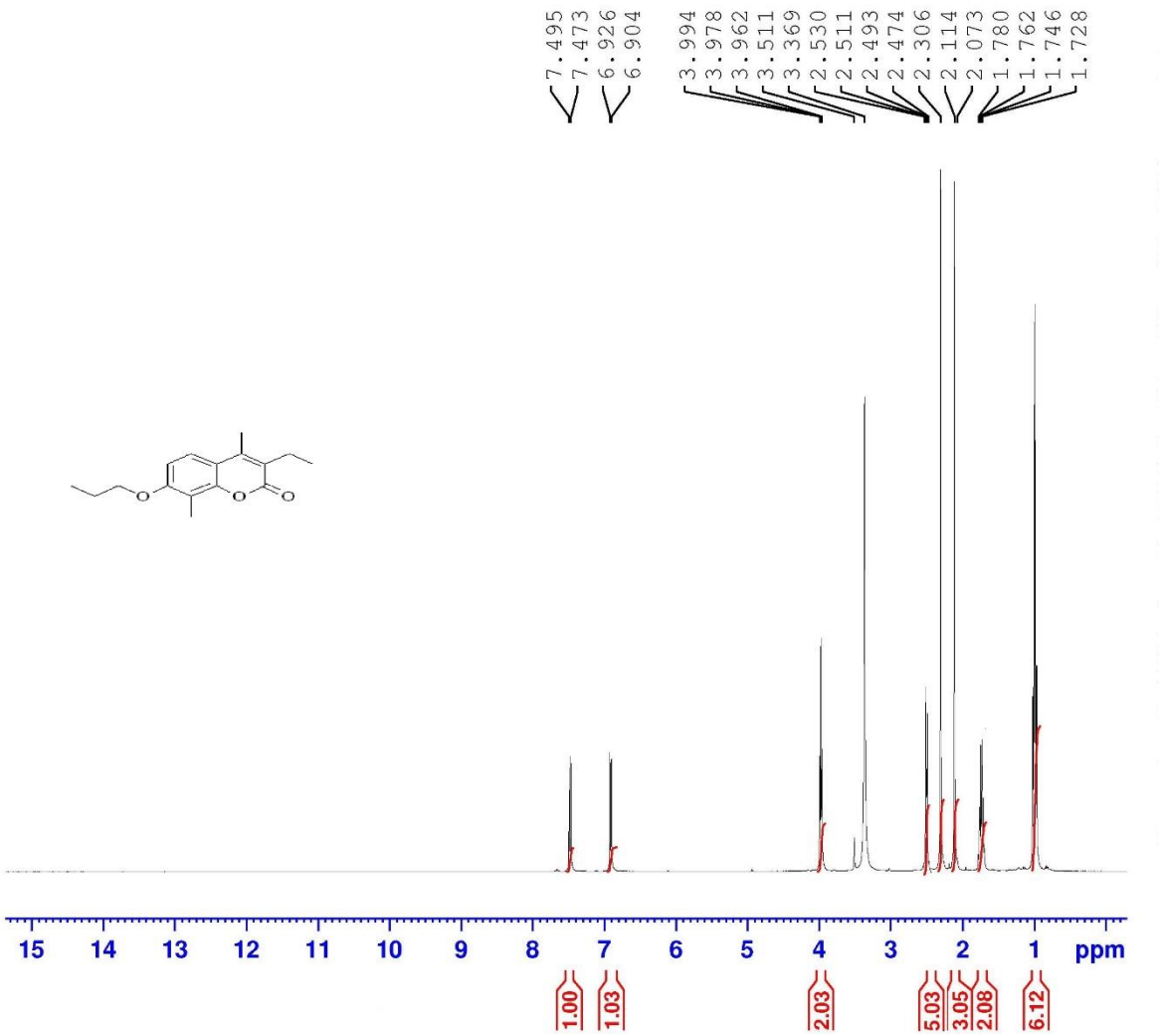

Figure S36: [1]H NMR spectrum of the compound **9b**.

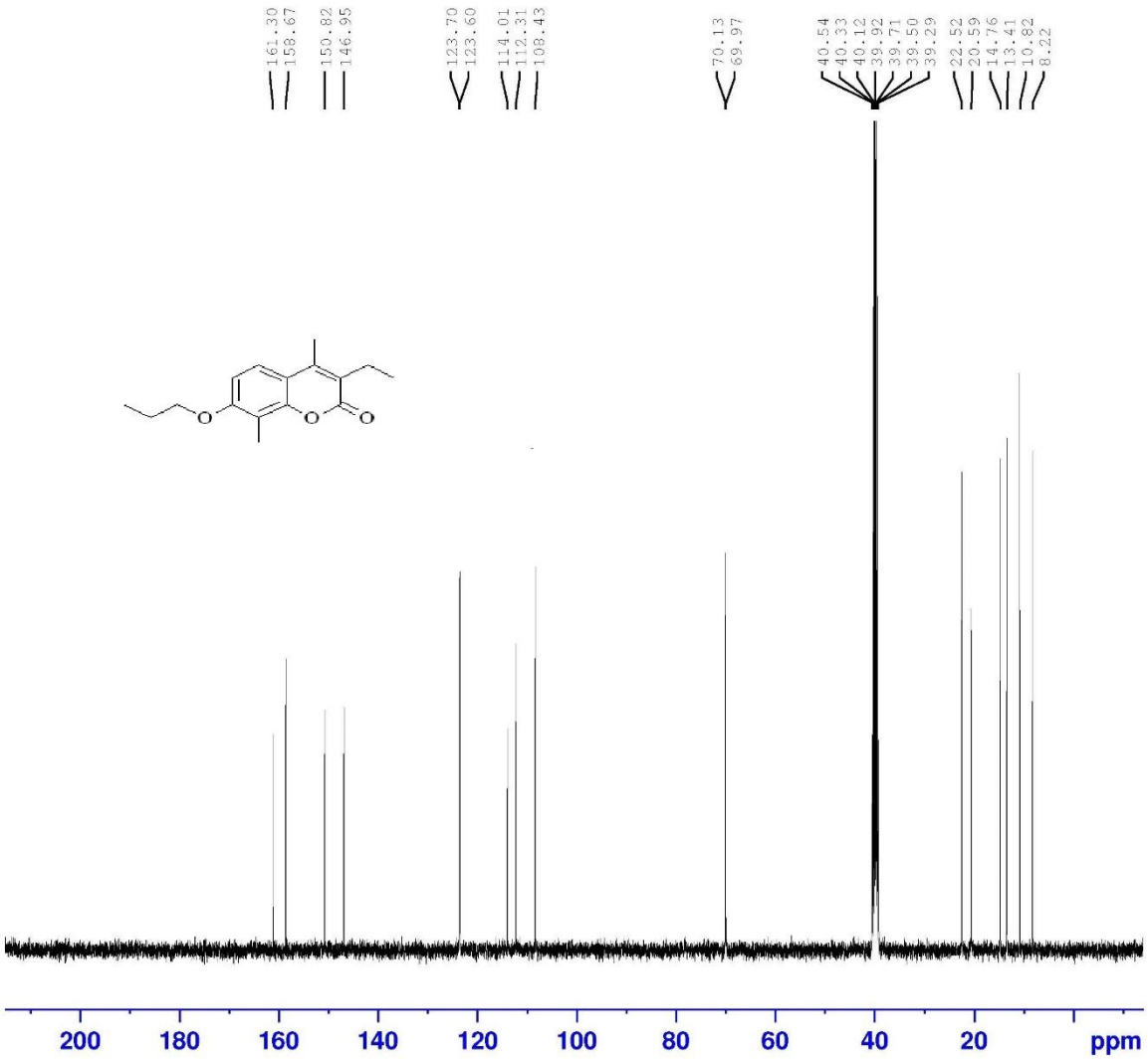

Figure S37: ^{13}C NMR spectrum of the compound **9b**.

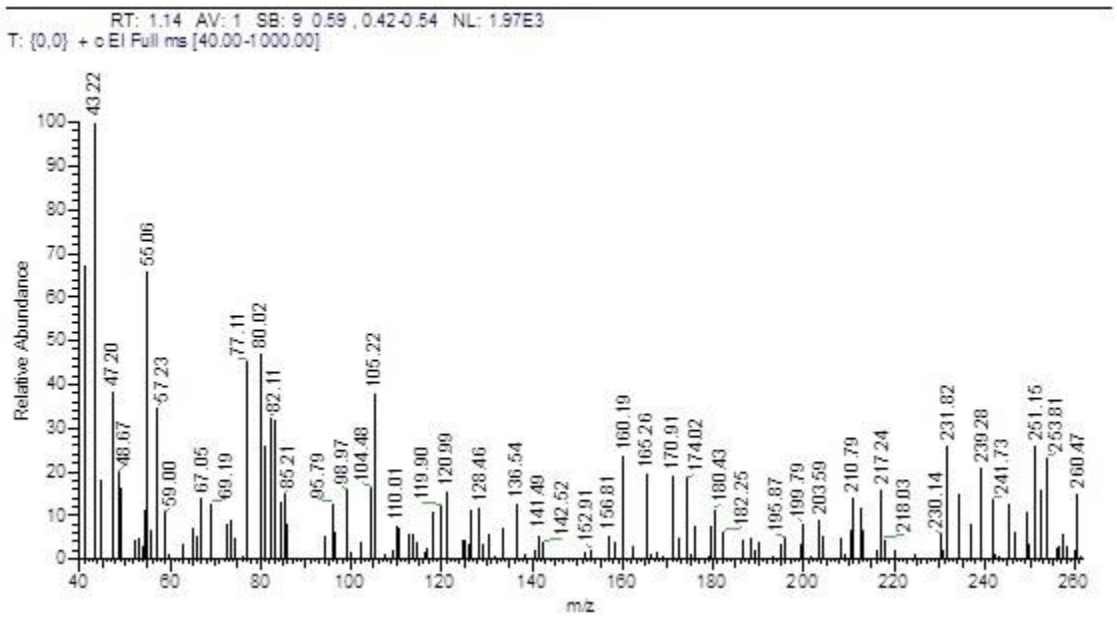

Figure S38: MS of the compound **9b**.

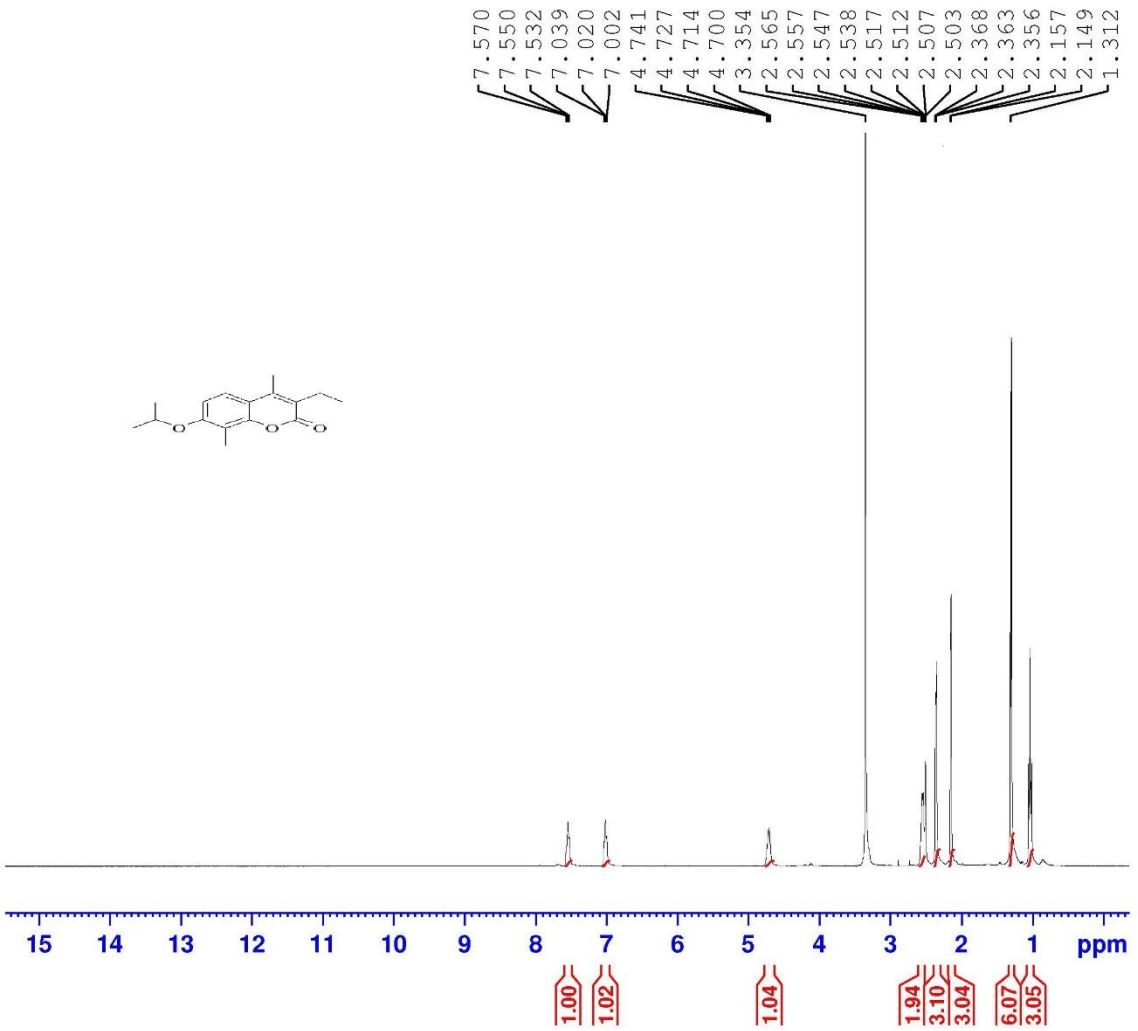

Figure S39: [1]H NMR spectrum of the compound **9c**.

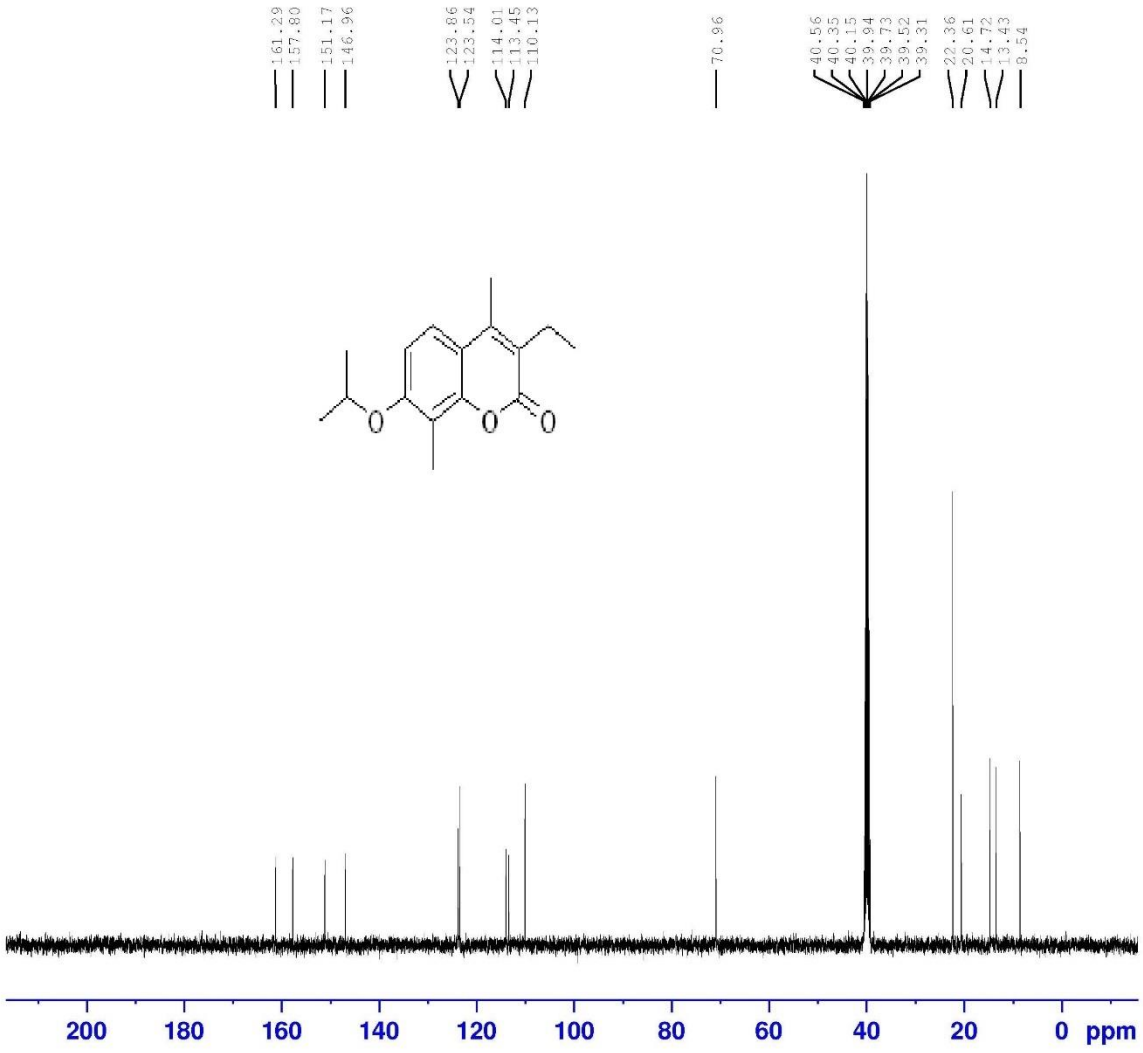

Figure S40: ^{13}C NMR spectrum of the compound **9c**.

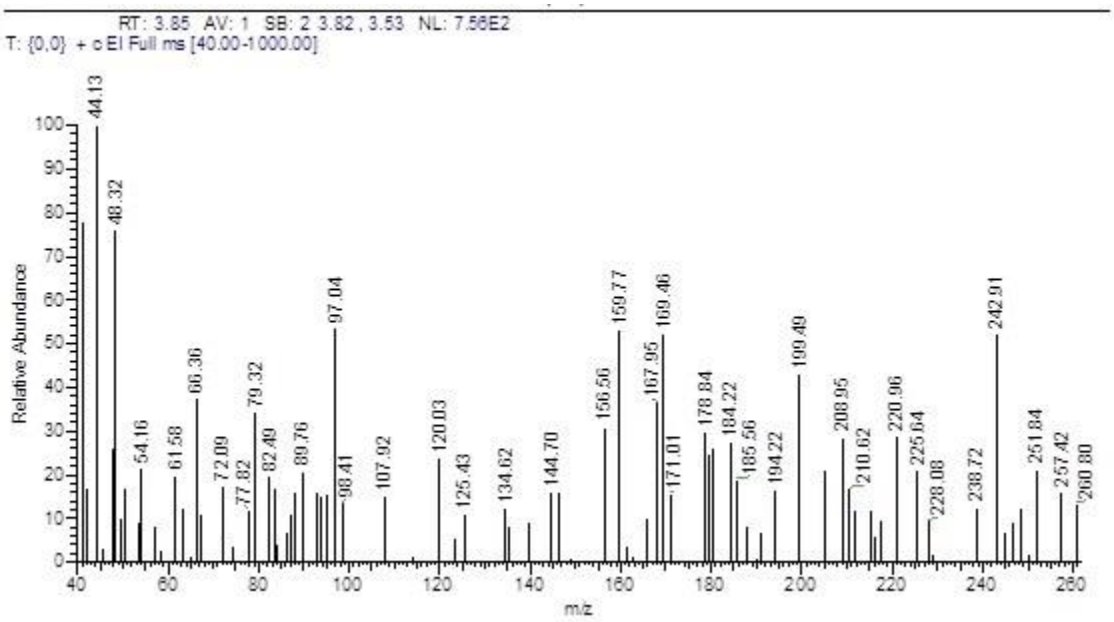

Figure S41: MS of the compound**9c**.

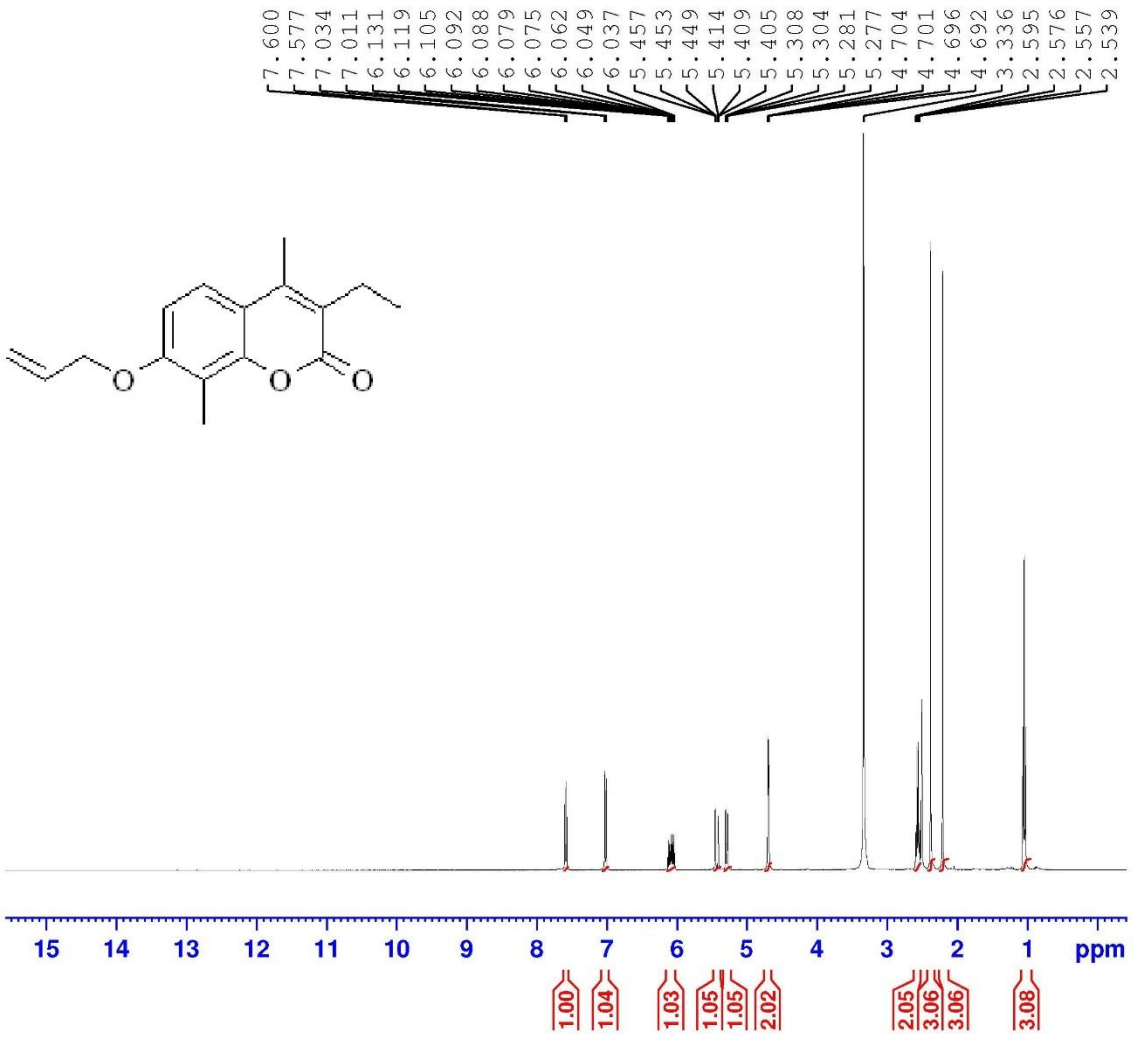

Figure S42: ^{1}H NMR spectrum of the compound **9d.**

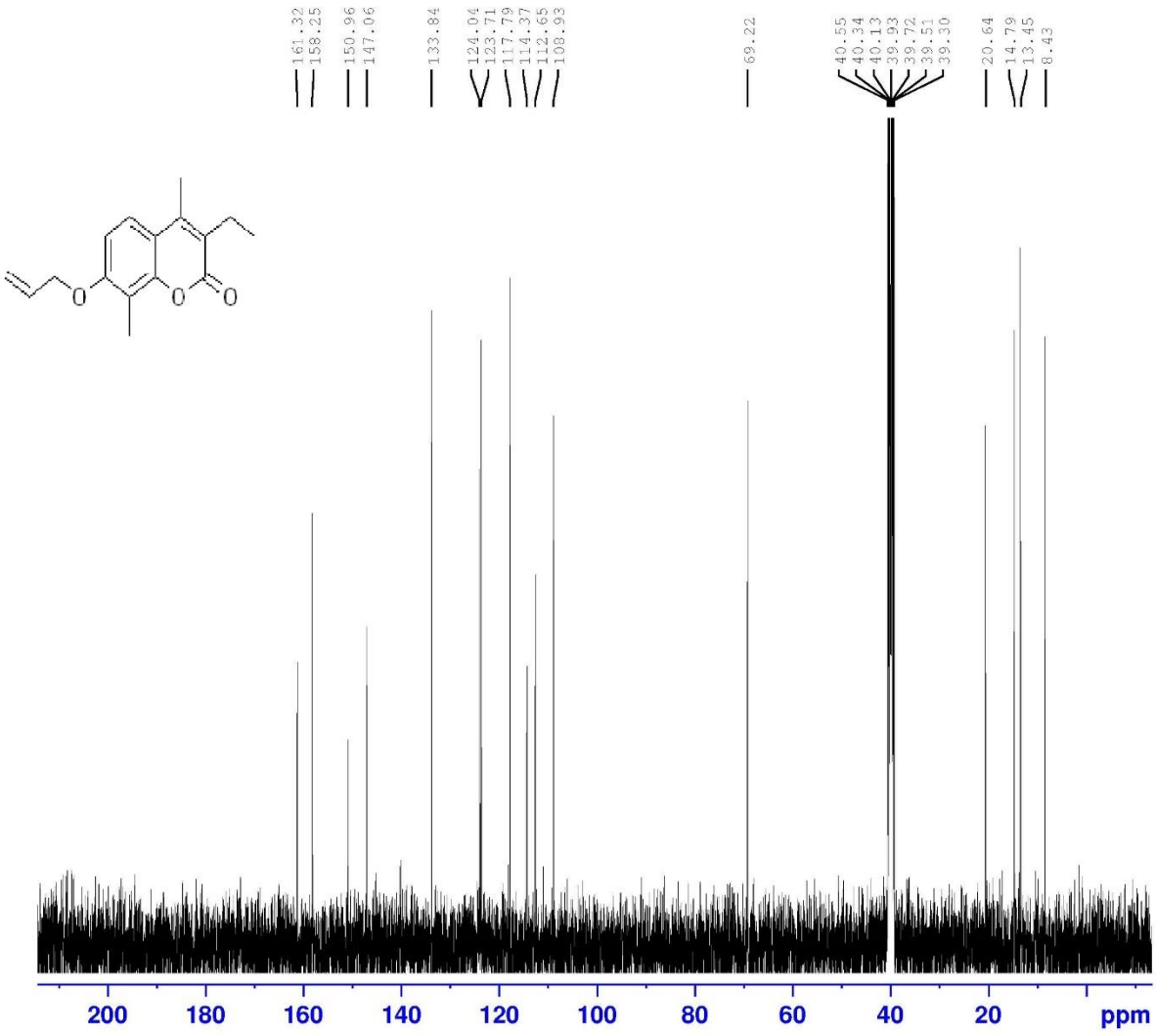

Figure S43: ^{13}C NMR spectrum of the compound **9d**.

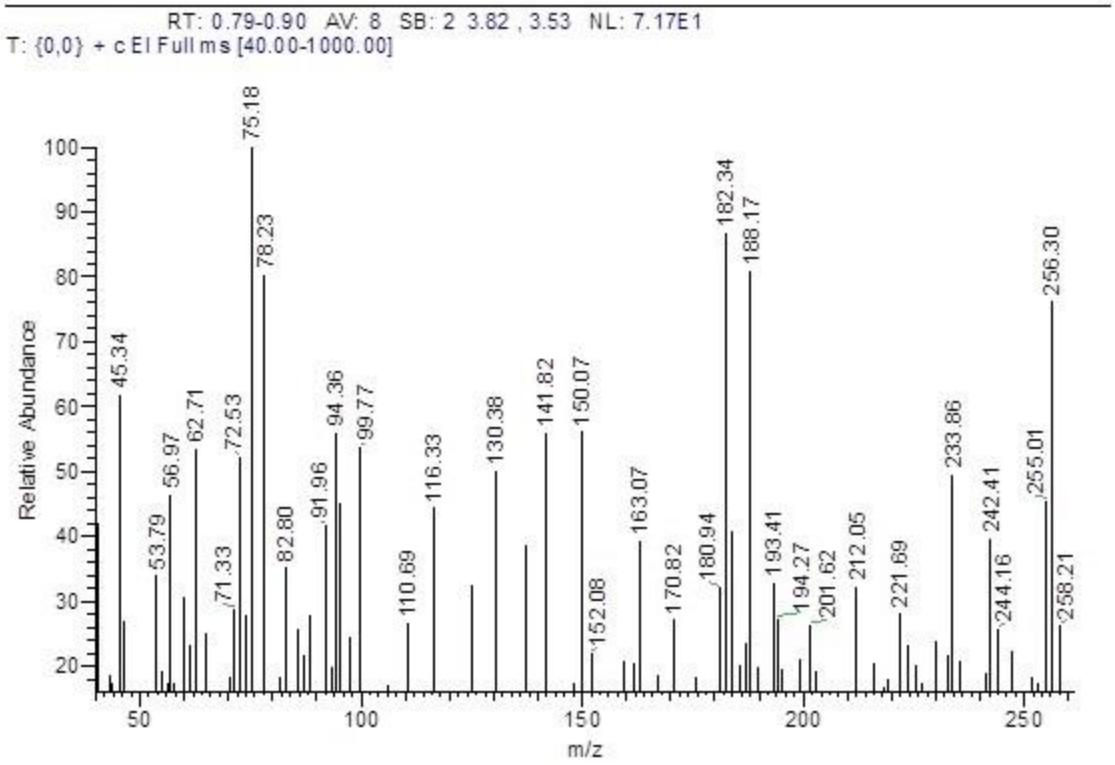

Figure S44: MS of the compound **9d**.

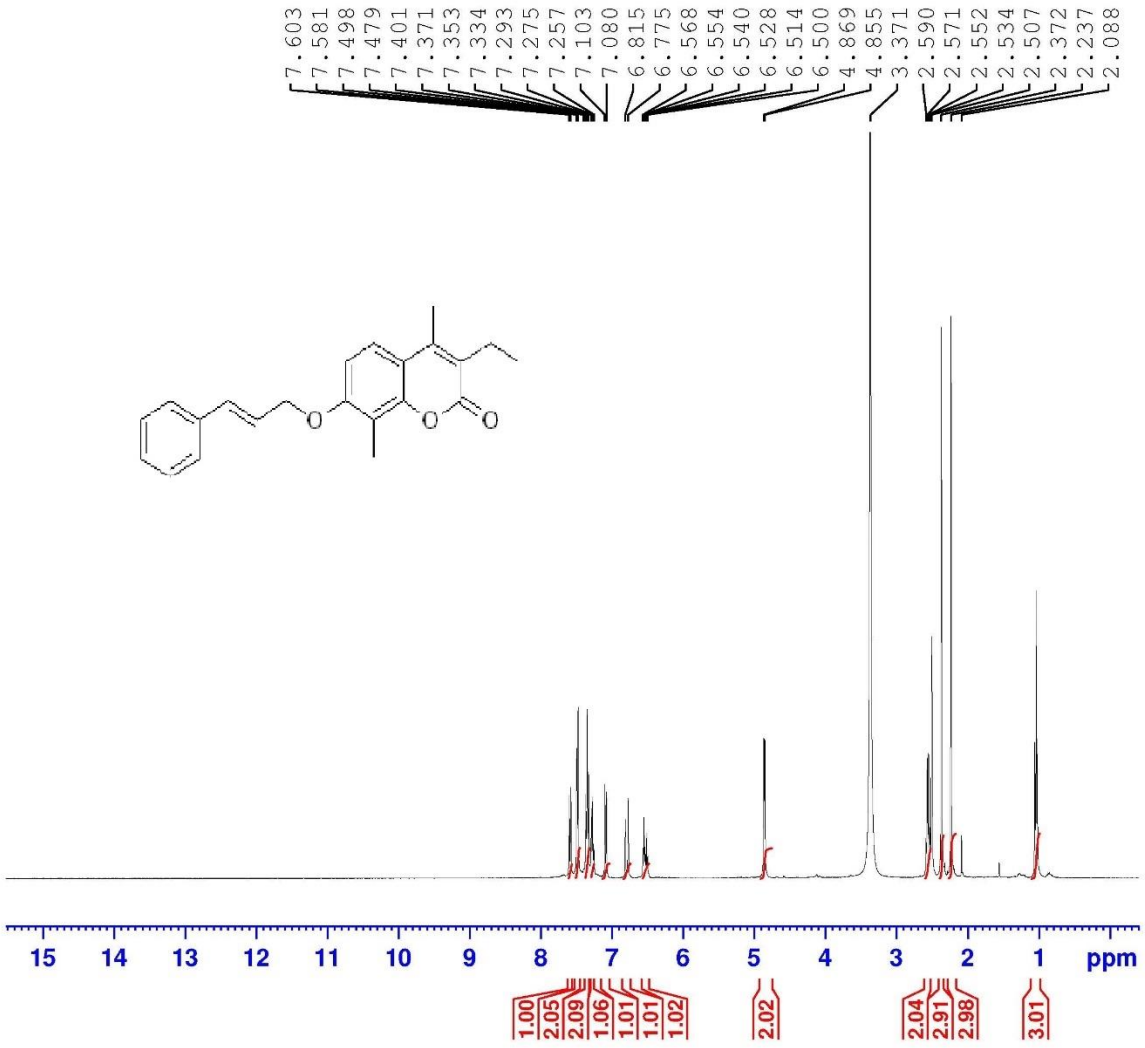

Figure S45: ^{1}H NMR spectrum of the compound **9e.**

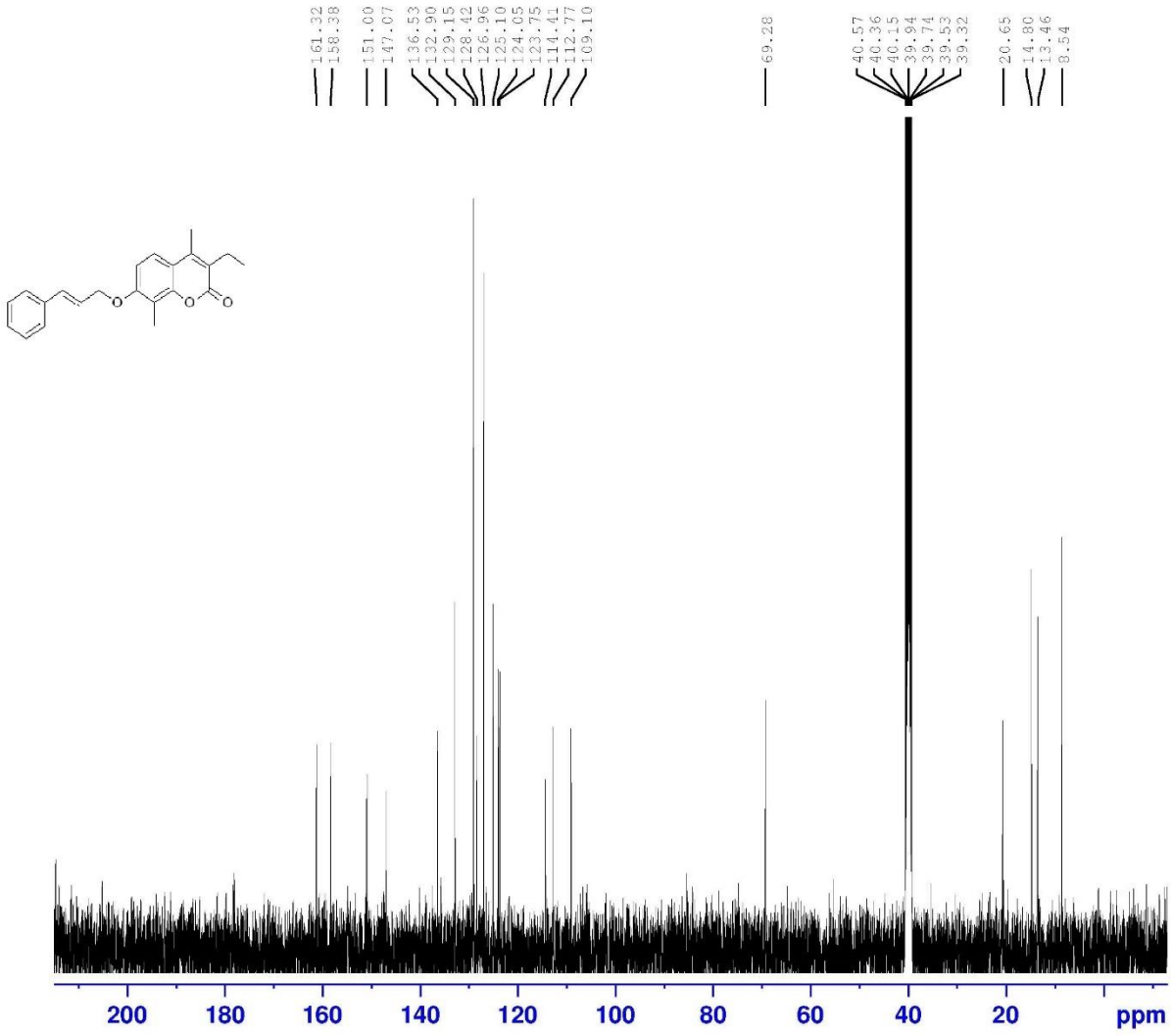

Figure S46: ^{13}C NMR spectrum of the compound **9e**.

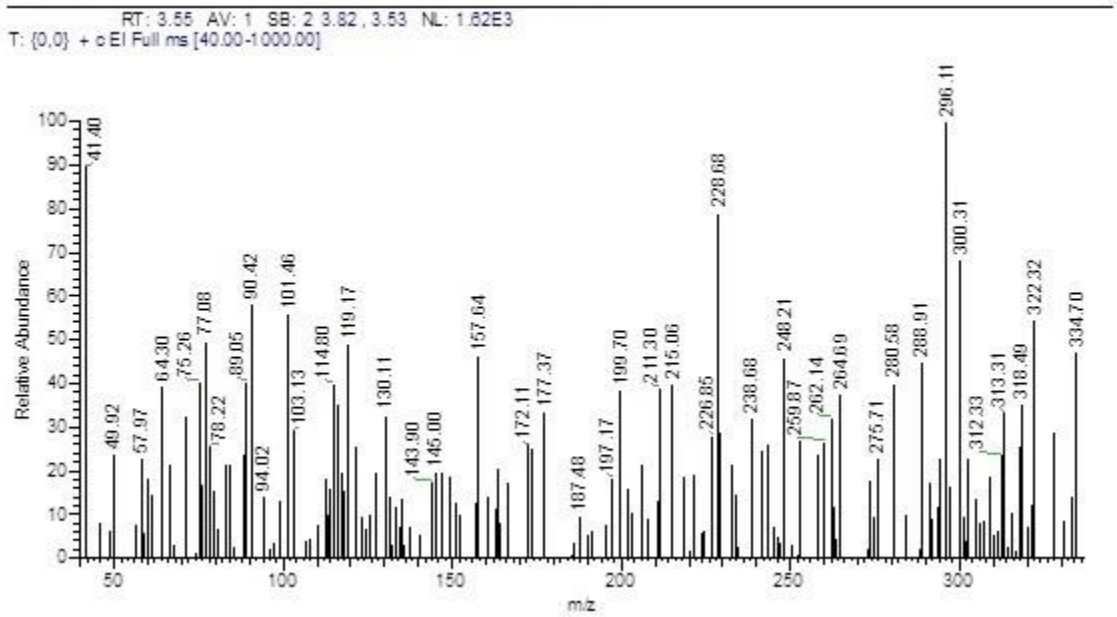

Figure S47: MS of the compound **9e**.

Part 2: Biological studies:

Table S. 1: The viability percentage for 6 concentrations (µM) for each compound and their IC_{50} on PC-3 cell line.

ID	Mwt	ug/ml	O.D			Viability %			Mean Viability %	IC50 ug/ml			MeanIC50 ug/ml	SD	IC50 UM			MeanIC50 ug/ml	SD
Pc3		-------	0.722	0.719	0.7	100	100	100	100										
4a	**409**	1000	0.025	0.018	0	3.46	2.503	3.1	3.03	4	4.05	4.5	4.183	0.237	9.9	9.9	10.9	10.218	0.579
		500	0.038	0.037	0	5.26	5.146	5.5	5.32										
		250	0.059	0.058	0.1	8.17	8.067	8	8.06										
		125	0.074	0.079	0.1	10.2	10.99	10	10.4										
		62.5	0.127	0.129	0.1	17.6	17.94	18	18										
		31.25	0.161	0.157	0.2	22.3	21.84	23	22.2										
4b	**430**	1000	0.055	0.048	0.1	7.62	6.676	7.4	7.23	3.5	3.68	4.4	3.871	0.493	8.13	8.55	10.3	8.9927	1.146
		500	0.058	0.058	0.1	8.03	8.067	8.5	8.21										
		250	0.084	0.079	0.1	11.6	10.99	11	11.1										
		125	0.122	0.125	0.1	16.9	17.39	17	17.1										
		62.5	0.148	0.143	0.1	20.5	19.89	20	20.1										
		31.25	0.192	0.19	0.2	26.6	26.43	28	27										
4c	**441**	1000	0.051	0.048	0.1	7.06	6.676	8.1	7.28	16	16.8	17	16.55	0.523	36.2	38.2	38.3	37.579	1.188
		500	0.08	0.07	0.	11.	10.9	11	11										

				9	1	1	9												
		250	0.104	0.101	0.1	14.4	14.05	14	14.1										
		125	0.149	0.155	0.2	20.6	21.56	21	21.2										
		62.5	0.191	0.188	0.2	26.5	26.15	26	26.3										
		31.25	0.299	0.303	0.3	41.4	42.14	43	42.1										
4d	**475**	1000	0.018	0.017	0	2.49	2.364	1.8	2.23	55.1	57	60	57.2	2.247	116	120	125	120.43	4.731
		500	0.04	0.036	0	5.54	5.007	5.3	5.27										
		250	0.209	0.205	0.2	28.9	28.51	30	29										
		125	0.249	0.251	0.3	34.5	34.91	36	35.1										
		62.5	0.341	0.348	0.3	47.2	48.4	48	48										
		31.25	0.435	0.438	0.4	60.2	60.92	62	61.2										
4e	**486**	1000	0.031	0.027	0	4.29	3.755	4.1	4.06	10.6	11.4	12	11.22	0.584	21.8	23.6	24.1	23.134	1.204
		500	0.039	0.036	0	5.4	5.007	4.7	5.03										
		250	0.061	0.059	0.1	8.45	8.206	8	8.2										
		125	0.069	0.066	0.1	9.56	9.179	8.7	9.13										
		62.5	0.121	0.119	0.1	16.8	16.55	17	16.8										
		31.25	0.222	0.223	0.2	30.7	31.02	32	31.3										
5	**533**	1000	0.012	0.015	0	1.66	2.086	2	1.91	1.89	1.95	1.9	1.91	0.035	3.54	3.66	3.54	3.5807	0.065
		500	0.018	0.016	0	2.49	2.225	2.3	2.33										
		250	0.024	0.02	0	3.32	2.782	3.1	3.08										

		125	0.064	0.058	0.1	8.86	8.067	8.7	8.53										
		62.5	0.094	0.086	0.1	13	11.96	13	12.5										
		31.25	0.102	0.1	0.1	14.1	13.91	14	14										
6a	**377**	1000	0.019	0.02	0	2.63	2.782	2.8	2.75	135	130	133	132.6	2.511	357	344	353	351.21	6.651
		500	0.052	0.066	0.1	7.2	9.179	7.7	8.02										
		250	0.083	0.091	0.1	11.5	12.66	11	11.7										
		125	0.417	0.377	0.4	57.8	52.43	56	55.4										
		62.5	0.657	0.672	0.7	91	93.46	95	93.2										
		31.25	0.711	0.719	0.7	98.5	100	99	99										
6b	**389**	1000	0.023	0.019	0	3.19	2.643	2.1	2.65	97	94.4	97	96	1.432	249	242	248	246.48	3.677
		500	0.022	0.019	0	3.05	2.643	2.8	2.84										
		250	0.083	0.11	0.1	11.5	15.3	14	13.7										
		125	0.183	0.167	0.2	25.3	23.23	24	24.3										
		62.5	0.638	0.619	0.6	88.4	86.09	88	87.6										
		31.25	0.711	0.709	0.7	98.5	98.61	103	99.9										
6c	**426**	1000	0.018	0.016	0	2.49	2.225	2.7	2.47	28.9	30.8	30	29.84	0.93	67.9	72.3	70.2	70.137	2.186
		500	0.018	0.019	0	2.49	2.643	2.7	2.61										
		250	0.02	0.02	0	2.77	2.782	2.7	2.75										
		125	0.033	0.028	0	4.57	3.894	5.8	4.76										
		62.5	0.12	0.14	0.	17.	20.4	16	17.9										

			8	7	1	7	5												
		31.25	0.338	0.357	0.3	46.8	49.65	49	48.3										
7	**346**	1000	0.028	0.02	0	3.88	2.782	3.1	3.26	41.6	40.6	40	40.65	0.97	120	117	115	117.34	2.8
		500	0.019	0.026	0	2.63	3.616	3	3.08										
		250	0.02	0.02	0	2.77	2.782	4.8	3.46										
		125	0.066	0.081	0.1	9.14	11.27	13	11.3										
		62.5	0.273	0.291	0.3	37.8	40.47	38	38.8										
		31.25	0.438	0.413	0.4	60.7	57.44	57	58.5										
8	**388**	1000	0.032	0.028	0	4.43	3.894	5.3	4.53	444	441	469	451.4	15.4	1143	1135	1207	1161.9	39.63
		500	0.267	0.253	0.3	37	35.19	40	37.5										
		250	0.699	0.701	0.7	96.8	97.5	102	98.7										
		125	0.726	0.72	0.7	101	100.1	99	99.8										
		62.5	0.684	0.72	0.7	94.7	100.1	102	98.9										
		31.25	0.718	0.712	0.7	99.4	99.03	101	100										
9a	**246**	1000	0.018	0.017	0	2.49	2.364	2.4	2.42	123	129	127	126.2	2.838	500	523	514	512.23	11.52
		500	0.063	0.048	0.1	8.73	6.676	7.4	7.6										
		250	0.055	0.073	0.1	7.62	10.15	8.5	8.76										
		125	0.352	0.377	0.4	48.8	52.43	52	51										
		62.5	0.713	0.719	0.7	98.8	100	101	99.9										
		31.25	0.721	0.716	0.7	99.9	99.58	101	100										

9b	**260**	1000	0.042	0.029	0	5.82	4.033	4.7	4.85	147	155	156	152.4	5.086	563	593	600	585.41	19.54
		500	0.073	0.058	0.1	10.1	8.067	10	9.47										
		250	0.194	0.183	0.2	26.9	25.45	27	26.3										
		125	0.379	0.427	0.4	52.5	59.39	58	56.8										
		62.5	0.682	0.703	0.7	94.5	97.77	98	96.7										
		31.25	0.726	0.707	0.7	101	98.33	98	99.1										
9c	**260**	1000	0.017	0.015	0	2.35	2.086	2.3	2.24	36.3	36.6	37	36.55	0.211	140	140	141	140.4	0.809
		500	0.018	0.016	0	2.49	2.225	2.7	2.47										
		250	0.018	0.018	0	2.49	2.503	3.4	2.8										
		125	0.044	0.038	0	6.09	5.285	5.1	5.5										
		62.5	0.089	0.116	0.1	12.3	16.13	15	14.5										
		31.25	0.463	0.451	0.4	64.1	62.73	64	63.5										
9d	**258**	1000	0.048	0.062	0	6.65	8.623	5.5	6.94	224	216	223	220.9	4.636	867	835	864	855.27	17.95
		500	0.05	0.058	0	6.93	8.067	6.3	7.08										
		250	0.289	0.234	0.3	40	32.55	38	36.7										
		125	0.672	0.699	0.7	93.1	97.22	97	95.8										
		62.5	0.716	0.711	0.7	99.2	98.89	101	99.7										
		31.25	0.727	0.703	0.7	101	97.77	101	99.7										
9e	**334**	1000	0.052	0.038	0	7.2	5.285	7	6.48	84.6	86.2	85	85.32	0.805	253	258	255	255.14	2.406
		500	0.03	0.05	0.	4.9	8.06	7.2	6.77										

			6	8	1	9	7												
		250	0.117	0.143	0.1	16.2	19.89	18	18.1										
		125	0.273	0.288	0.3	37.8	40.06	37	38.3										
		62.5	0.388	0.368	0.4	53.7	51.18	51	52										
		31.25	0.672	0.659	0.7	93.1	91.66	97	93.9										
erlotinib	**393**	1000	0.018	0.033	0	2.49	4.59	3.8	3.64	5.22	4.85	4.5	4.84	0.385	13.3	12.3	11.3	12.302	0.979
		50	0.02	0.031	0	2.77	4.312	4.1	3.73										
		25	0.025	0.027	0	3.46	3.755	4.3	3.83										
		12.5	0.063	0.058	0.1	8.73	8.067	9.9	8.91										
		6.25	0.07	0.079	0.1	9.7	10.99	12	10.7										
		3.125	0.144	0.152	0.2	19.9	21.14	21	20.8										

Table S. 2: The viability percentage for 6 concentrations (μM) for each compound and their IC_{50} on MDA-MB-231cell line.

ID	Mwt	ug/ml	O.D			Viability %			Mean Viability %	IC50 ug/ml			MeanIC50 ug/ml	SD	IC50 UM			Mean IC50 Um	SD
MDA-MB-231		----------	0.648	0.666	0.651	100	100	100	100										
4a	409.4	1000	0.088	0.082	0.086	13.58025	12.31231	13.21	13.0343	9.52	9.65	9.82	9.663	0.15	23.3	23.6	23.99	23.604	0.36775
		500	0.091	0.09	0.088	14.04321	13.51351	13.518	13.6915										
		250	0.116	0.111	0.113	17.90123	16.66667	17.3 58	17.3086										
		125	0.149	0.154	0.152	22.99383	23.12312	23.349	23.1552										
		62.5	0.211	0.217	0.219	32.56173	32.58258	33.641	32.9283										
		31.25	0.239	0.239	0.235	36.88272	35.88589	36.098	36.289										
4b	430.46	1000	0.009	0.005	0.007	1.388889	0.750751	1.0753	1.07164	5.39	4.59	5.235	5.072	0.424	12.52	10.66	12.161	11.782	0.9856
		500	0.008	0.006	0.009	1.234568	0.900901	1.3825	1.17265										
		250	0.011	0.015	0.01	1.697531	2.252252	1.5361	1.82863										
		125	0.029	0.034	0.03	4.475309	5.105105	4.6083	4.72957										
		62.5	0.064	0.061	0.069	9.876543	9.159159	10.599	9.87826										
		31.25	0.101	0.099	0.101	15.58642	14.86486	15.515	15.322										
4c	440.5	1000	0.022	0.031	0.017	3.395062	4.654655	2.6114	3.55369	3.31	3.97	3.96	3.747	0.378	7.514	9.012	8.9898	8.5055	0.8586

		500	0.033	0.029	0.022	5.092593	4.354354	3.3794	4.27545										
		250	0.041	0.044	0.037	6.32716	6.606607	5.6836	6.20578										
		125	0.06	0.061	0.055	9.259259	9.159159	8.4485	8.95565										
		62.5	0.118	0.116	0.111	18.20988	17.41742	17.051	17.5593										
		31.25	0.128	0.142	0.132	19.75309	21.32132	20.276	20.4503										
4d	**474.94**	1000	0.113	0.111	0.112	17.43827	16.66667	17.204	17.1031	38.55	36.43	37	37.33	1.097	81.17	76.7	77.905	78.592	2.31
		500	0.125	0.127	0.129	19.29012	19.06907	19.816	19.3916										
		250	0.141	0.139	0.137	21.75926	20.87087	21.045	21.2249										
		125	0.203	0.204	0.199	31.32716	30.63063	30.568	30.842										
		62.5	0.307	0.311	0.308	47.37654	46.6967	47.312	47.1284										
		31.25	0.341	0.344	0.338	52.62346	51.65165	51.92	52.0651										
4e	**485.5**	1000	0.068	0.069	0.083	10.49383	10.36036	12.75	11.2013	12.89	11.77	10.67	11.78	1.11	26.58	24.27	22	24.282	2.2887
		500	0.098	0.099	0.087	15.12346	14.86486	13.364	14.4508										
		250	0.083	0.083	0.107	12.80864	12.46246	16.436	13.9025										
		125	0.153	0.153	0.16	23.61111	22.97297	24.578	23.7206										
		62.5	0.221	0.223	0.199	34.10494	33.48348	30.568	32.7189										
		31.25	0.242	0.242	0.247	37.34568	36.33634	37.942	37.2079										
5	**533.42**	1000	0.099	0.088	0.109	15.27778	13.21321	16.743	15.0782	25.61	26.41	23.61	25.21	1.442	48.01	49.51	44.262	47.261	2.7037
		500	0.127	0.133	0.132	19.59877	19.96997	20.276	19.9484										

		250	0.151	0.149	0.147	23.30247	22.37237	22.581	22.7518											
		125	0.223	0.228	0.119	34.41358	34.23423	18.28	28.9758											
		62.5	0.243	0.279	0.261	37.5	41.89189	40.092	39.828											
		31.25	0.315	0.305	0.326	48.61111	45.795 8	50.077	48.1612											
6a	**377.46**	1000	0.025	0.036	0.032	3.858025	5.405405	4.9155	4.72631	129.2	120.8	125	125	4.2	342.3	320	331.16	331.16	11.127	
		500	0.055	0.073	0.068	8.487654	10.96096	10.445	9.96469											
		250	0.138	0.153	0.16	21.2963	22.97297	24.578	22.9489											
		125	0.319	0.276	0.288	49.2284	41.44144	44.24	44.9698											
		62.5	0.551	0.568	0.542	85.03086	85.28529	83.257	84.5242											
		31.25	0.649	0.621	0.63	100.1543	93.24324	96.774	96.7239											
6b	**389.47**	1000	0.018	0.019	0.016	2.777778	2.852853	2.4578	2.69613	93.63	92.65	95.36	93.88	1.372	240.4	237.9	244.85	241.05	3.5232	
		500	0.018	0.019	0.022	2.777778	2.852853	3.3794	3.00335											
		250	0.041	0.028	0.046	6.32716	4.204204	7.0661	5.86581											
		125	0.13	0.126	0.145	20.06173	18.91892	22.273	20.418											
		62.5	0.577	0.593	0.582	89.04321	89.03904	89.401	89.1611											
		31.25	0.66	0.652	0.65	101.8519	97.8979	99.846	99.8654											
6c	**425.5**	1000	0.018	0.018	0.02	2.777778	2.702703	3.0722	2.85089	39.38	35.77	38.41	37.85	1.868	92.55	84.07	90.27	88.962	4.3908	
		500	0.033	0.023	0.027	5.092593	3.453453	4.1475	4.23117											
		250	0.033	0.048	0.051	5.092593	7.207207	7.8341	6.7113											

		125	0.062	0.049	0.055	9.567901	7.357357	8.4485	8.45793										
		62.5	0.138	0.124	0.152	21.2963	18.61862	23.349	21.0879										
		31.25	0.429	0.398	0.411	66.2037	59.75976	63.134	63.0324										
7	**346.41**	1000	0.027	0.046	0.033	4.166667	6.906907	5.0691	5.3809	77.19	73.3	77.6	76.03	2.373	222.8	211.6	224.01	219.48	6.8506
		500	0.02	0.018	0.018	3.08642	2.702703	2.765	2.85137										
		250	0.019	0.019	0.019	2.932099	2.852853	2.9186	2.90118										
		125	0.073	0.089	0.103	11.26543	13.36336	15.822	13.4835										
		62.5	0.472	0.439	0.452	72.83951	65.91592	69.432	69.3957										
		31.25	0.619	0.599	0.634	95.52469	89.93994	97.389	94.2844										
8	**388.49**	1000	0.022	0.015	0.017	3.395062	2.252252	2.6114	2.75289	257	253	251.8	253.9	2.723	661.5	651.2	648.15	653.64	7.0085
		500	0.096	0.112	0.109	14.81481	16.81682	16.743	16.125										
		250	0.328	0.333	0.312	50.61728	50	47.926	49.5145										
		125	0.62	0.598	0.613	95.67901	89.78979	94.163	93.2105										
		62.5	0.657	0.653	0.644	101.3889	98.04805	98.925	99.4539										
		31.25	0.655	0.66	0.65	101.0802	99.0991	99.846	100.009										
9a	**246.31**	1000	0.015	0.017	0.016	2.314815	2.552553	2.4578	2.44171	189.5	189.7	186.8	188.7	1.62	769.4	770.2	758.39	765.97	6.5757
		500	0.052	0.038	0.049	8.024691	5.705706	7.5269	7.08576										
		250	0.217	0.22	0.198	33.48765	33.03303	30.415	32.3118										
		125	0.489	0.512	0.502	75.46296	76.87688	77.112	76.484										

		62.5	0.617	0.639	0.632	95.21605	95.94595	97.081	96.0811										
		31.25	0.653	0.661	0.65	100.7716	99.24925	99.846	99.9557										
9b	**260.33**	1000	0.016	0.023	0.018	2.469136	3.453453	2.765	2.89586	215.8	204.6	211.3	210.6	5.636	828.9	785.9	811.66	808.85	21.649
		500	0.07	0.092	0.078	10.80247	13.81381	11.982	12.1993										
		250	0.241	0.225	0.23	37.19136	33.78378	35.33	35.4351										
		125	0.573	0.553	0.569	88.42593	83.03303	87.404	86.2877										
		62.5	0.66	0.652	0.648	101.8519	97.8979	99.539	99.763										
		31.25	0.659	0.642	0.643	101.6975	96.3964	98.771	98.955										
9c	**260.33**	1000	0.021	0.018	0.019	3.240741	2.702703	2.9186	2.95401	48.41	46.74	50.17	48.44	1.715	186	179.5	192.72	186.07	6.5885
		500	0.032	0.047	0.036	4.938272	7.057057	5.53	5.84176										
		250	0.055	0.032	0.047	8.487654	4.804805	7.2197	6.83737										
		125	0.062	0.058	0.063	9.567901	8.708709	9.6774	9.31801										
		62.5	0.152	0.158	0.172	23.45679	23.72372	26.421	24.5338										
		31.25	0.583	0.563	0.599	89.96914	84.53453	92.012	88.8387										
9d	**258.32**	1000	0.016	0.025	0.02	2.469136	3.753754	3.0722	3.09836	153.6	156.4	158.5	156.2	2.458	594.6	605.5	613.58	604.55	9.5166
		500	0.028	0.044	0.032	4.320988	6.606607	4.9155	5.28104										
		250	0.118	0.147	0.132	18.20988	22.07207	20.276	20.1861										
		125	0.426	0.431	0.44	65.74074	64.71471	67.588	66.0146										
		62.5	0.658	0.643	0.651	101.5432	96.54655	100	99.3633										

		31.25	0.663	0.647	0.649	102.3148	97.14715	99.693	99.7182										
9e	**334.42**	1000	0.019	0.017	0.018	2.932099	2.552553	2.765	2.74988	195.2	190.1	196.2	193.8	3.272	583.7	568.4	586.69	579.61	9.7829
		500	0.079	0.093	0.083	12.19136	13.96396	12.75	12.9683										
		250	0.162	0.166	0.183	25	24.92492	28.111	26.0118										
		125	0.583	0.569	0.56	89.96914	85.43544	86.022	87.142										
		62.5	0.646	0.657	0.652	99.69136	98.64865	100.15	99.4979										
		31.25	0.658	0.657	0.65	101.5432	98.64865	99.846	100.013										
Erlotinib	**393.44**	1000	0.017	0.022	0.021	2.623457	3.303303	3.2258	3.05086	4.27	4.87	4.016	4.385	0.439	10.85	12.38	10.208	11.146	1.1146
		50	0.031	0.019	0.025	4.783951	2.852853	3.8402	3.82568										
		25	0.051	0.038	0.04	7.87037	5.705706	6.1444	6.57349										
		12.5	0.073	0.069	0.083	11.26543	10.36036	12.75	11.4585										
		6.25	0.128	0.142	0.132	19.75309	21.32132	20.276	20.4503										
		3.125	0.14	0.136	0.133	21.60494	20.42042	20.43	20.8185										

Table S.3: The viability percentage (μM) for compound **5** and erlotinib showing their IC_{50} on HCT-116 cell line.

ID	Mwt	ug/ml	O.D			Viability %			Mean Viability %	IC50 ug/ml			MeanIC50 ug/ml	SD	IC50 UM			MeanIC50 UM	SD
HCT-116		----------	0.502	0.497	0.479	100	100	100	100										
5	**533.4**	100	0.163	0.177	0.157	32.47	35.6	32.8	33.62	10.91	10.42	10.37	10.57	0.298	20.45	19.53	19.441	19.80928	0.5594
		25	0.227	0.19	0.225	45.219	38.2	47	43.47										
		6.3	0.242	0.246	0.249	48.207	49.5	52	49.9										
		1.6	0.314	0.311	0.287	62.55	62.6	59.9	61.68										
		0.4	0.324	0.326	0.3	64.542	65.6	62.6	64.26										
		0.2	0.339	0.34	0.298	67.53	68.4	62.2	66.05										
erlotinib	**393.4**	100	0.131	0.129	0.144	26.096	26	30.1	27.37	6.55	7.02	7.46	7.013	0.455	16.65	17.84	18.961	17.81738	1.1567
		25	0.159	0.155	0.165	31.673	31.2	34.4	32.44										
		6.3	0.225	0.246	0.227	44.821	49.5	47.4	47.24										
		1.6	0.322	0.308	0.307	64.143	62	64.1	63.4										
		0.4	0.331	0.338	0.313	65.936	68	65.3	66.43										
		0.2	0.348	0.342	0.32	69.323	68.8	66.8	68.31										

Table S.4: The viability percentage (μM) for compound **5** and erlotinib showing their IC_{50} on HEPG-2 cell line.

ID	Mwt	ug/ml	O.D			Viability %			Mean Viability %	IC50 ug/ml			MeanIC50 ug/ml	SD	IC50 UM			MeanIC50 UM	SD
HEPG-2		----------	0.549	0.561	0.586	100	100	100	100										
5	**533.4**	100	0.192	0.181	0.216	34.973	32.3	36.9	34.7	8.33	7.39	7.07	7.5967	0.655	15.62	13.85	13.254	14.241	1.2278
		25	0.255	0.231	0.264	46.448	41.2	45.1	44.23										
		6.3	0.279	0.292	0.286	50.82	52	48.8	50.56										
		1.6	0.298	0.319	0.312	54.281	56.9	53.2	54.8										
		0.4	0.323	0.329	0.331	58.834	58.6	56.5	57.99										
		0.2	0.341	0.36	0.366	62.113	64.2	62.5	62.91										
erlotinib	**393.4**	100	0.136	0.129	0.137	24.772	23	23.4	23.72	8.66	8.51	8.87	25.08	0.181	22.01	21.63	22.545	22.062	0.46
		25	0.215	0.222	0.221	39.162	39.6	37.7	38.82										
		6.3	0.254	0.261	0.344	46.266	46.5	58.7	50.5										
		1.6	0.321	0.326	0.319	58.47	58.1	54.4	57.01										
		0.4	0.394	0.411	0.377	71.767	73.3	64.3	69.79										
		0.2	0.414	0.421	0.44	75.41	75	75.1	75.18										

Table S.5: The viability percentage (μM) for compound **5** and erlotinib showing their IC_{50} on HPrEC cell line.

ID	Mwt	ug/ml	O.D			Viability %			Mean Viability %	IC50 ug/ml			MeanIC50 ug/ml	SD	IC50 UM			MeanIC50 UM	SD
HPrEC		-------	0.545	0.531	0.529	100	100	100	100										
5	**533.4**	100	0.248	0.239	0.231	45.505	45	43.7	44.73	50.9	51.7	50.32	50.96	0.695	95.37	96.92	94.335	95.541	1.3024
		25	0.311	0.305	0.311	57.064	57.4	58.8	57.76										
		6.3	0.354	0.344	0.357	64.954	64.8	67.5	65.74										
		1.6	0.39	0.388	0.394	71.56	73.1	74.5	73.04										
		0.4	0.432	0.444	0.505	79.266	83.6	95.5	86.12										
		0.2	0.511	0.469	0.517	93.761	88.3	97.7	93.27										
erlotinib	**393.4**	100	0.216	0.202	0.217	39.633	38	41	39.57	22.7	24.98	27.19	25.08	2.225	57.8	63.49	69.109	63.466	5.6553
		25	0.257	0.277	0.252	47.156	52.2	47.6	48.99										
		6.3	0.339	0.319	0.344	62.202	60.1	65	62.44										
		1.6	0.37	0.37	0.37	67.89	69.7	69.9	69.17										
		0.4	0.433	0.441	0.428	79.45	83.1	80.9	81.14										
		0.2	0.466	0.459	0.463	85.505	86.4	87.5	86.49										

Table S6: IC_{50} values of PI3Kβ and EGFR inhibition for compounds **4a, 4b, 4c, 4e** and **5** over PC-3 cells

Comp no.	IC_{50} PI3Kβ (µM)	IC_{50} EGFR (µM)
4a	0.7918 ±0.0318	0.4140 ±0.0025
4b	0.4844 ±0.0289	0.5587 ±0.0215
4c	0.5335 ±0.0525	0.3073 ±0.0259
4e	0.9923 ±0.0042	0.3132±0.0008
5	0.2612 ±0.0196	0.1812 ±0.0037
Erlotinib	ND	0.1344 ±0.0135
LY294002	0.5254 ±0.0393	ND

Values are means ± SD, n=3, p value using independent t-test for the tested compounds vs Erlotinib and LY294002

ND= not determined

Part 3: Docking studies:

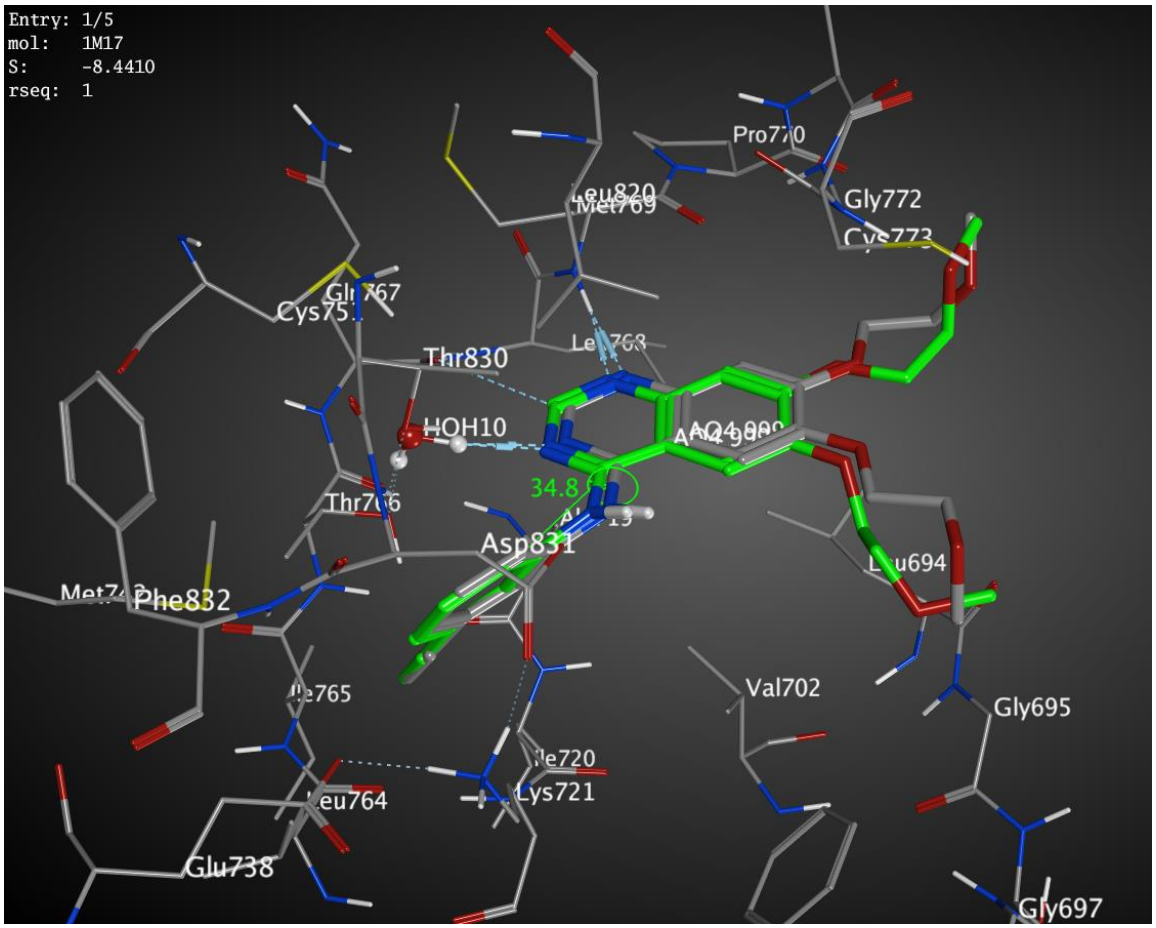

Figure S.48: Alignment between x-ray bioactive conformation of Erlotinib (colored in grey) and best-fitted docked pose (colored with green) within the binding site of EGFR tyrosine kinase. RMSD refine score = 1.254137

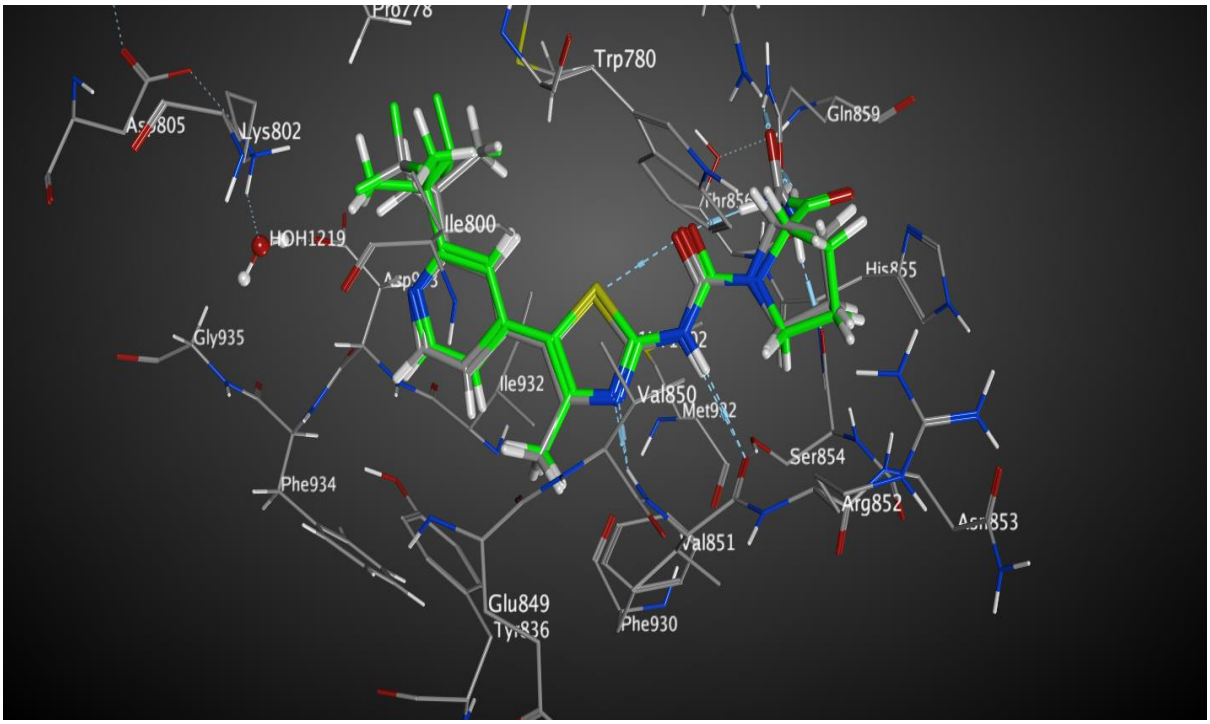

Figure S.49: Alignment between x-ray bioactive conformation of Alpelisib (colored in grey) and its best-fitted docked pose (colored with green) within the binding site of PI3Kβ kinase. RMSD refine score = 1.862