Supplementary Data

Figure S1: 1HNMR of compound 2a

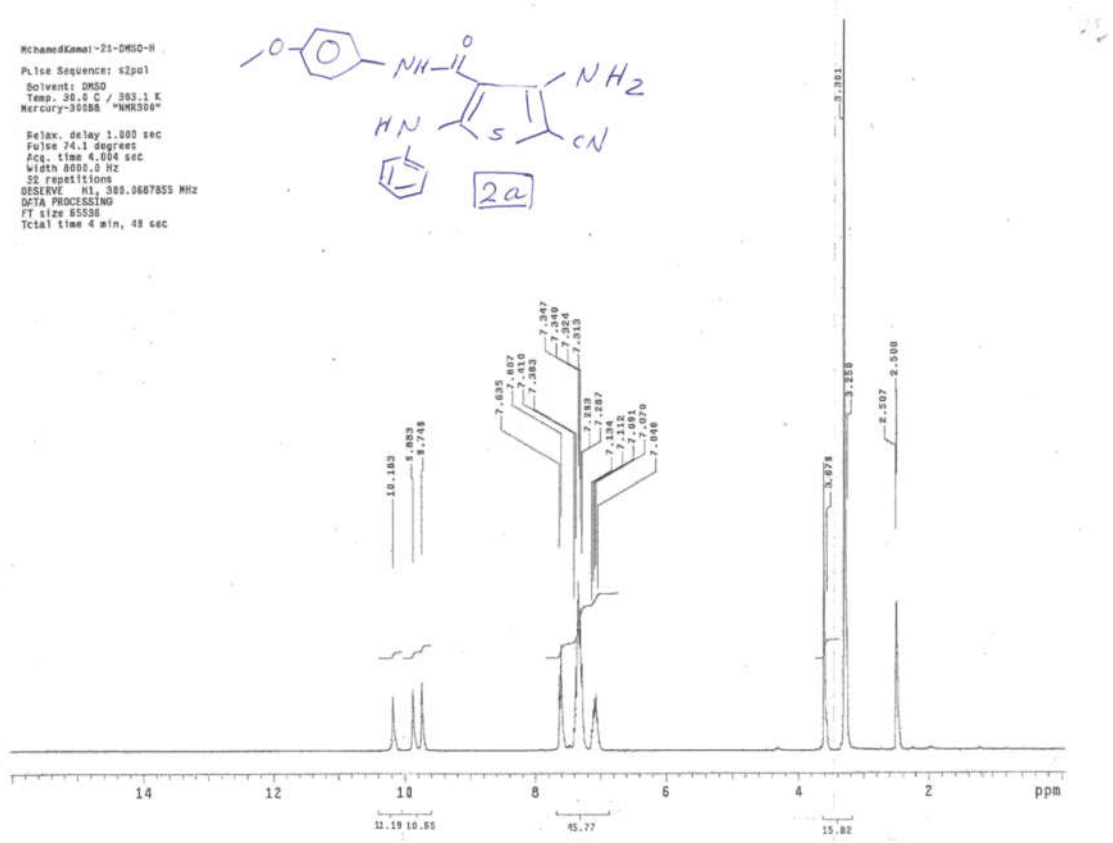


Figure S2: mass spectrum of compound 2a

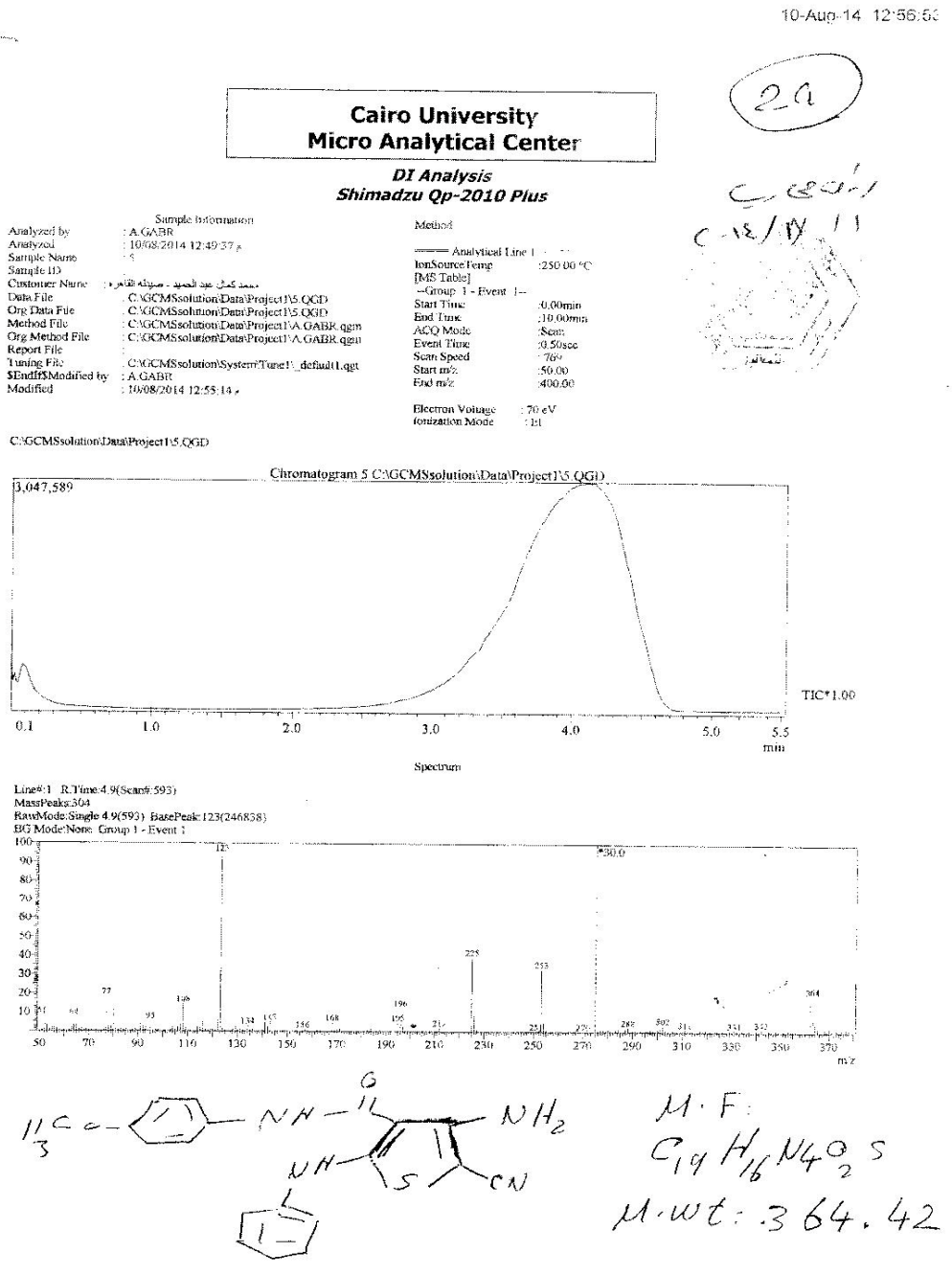


Figure S3: 1HNMR of compound 2b

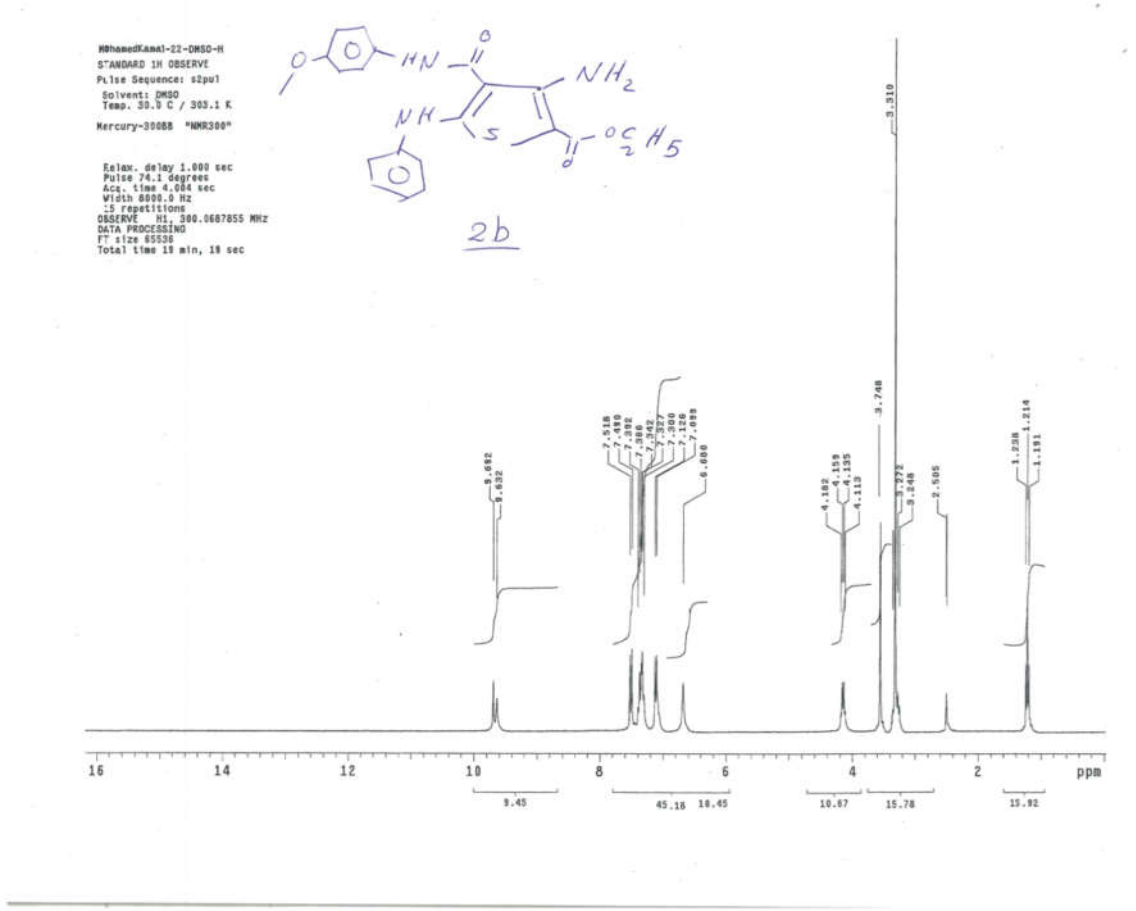


Figure S4: mass spectrum of compound 2b

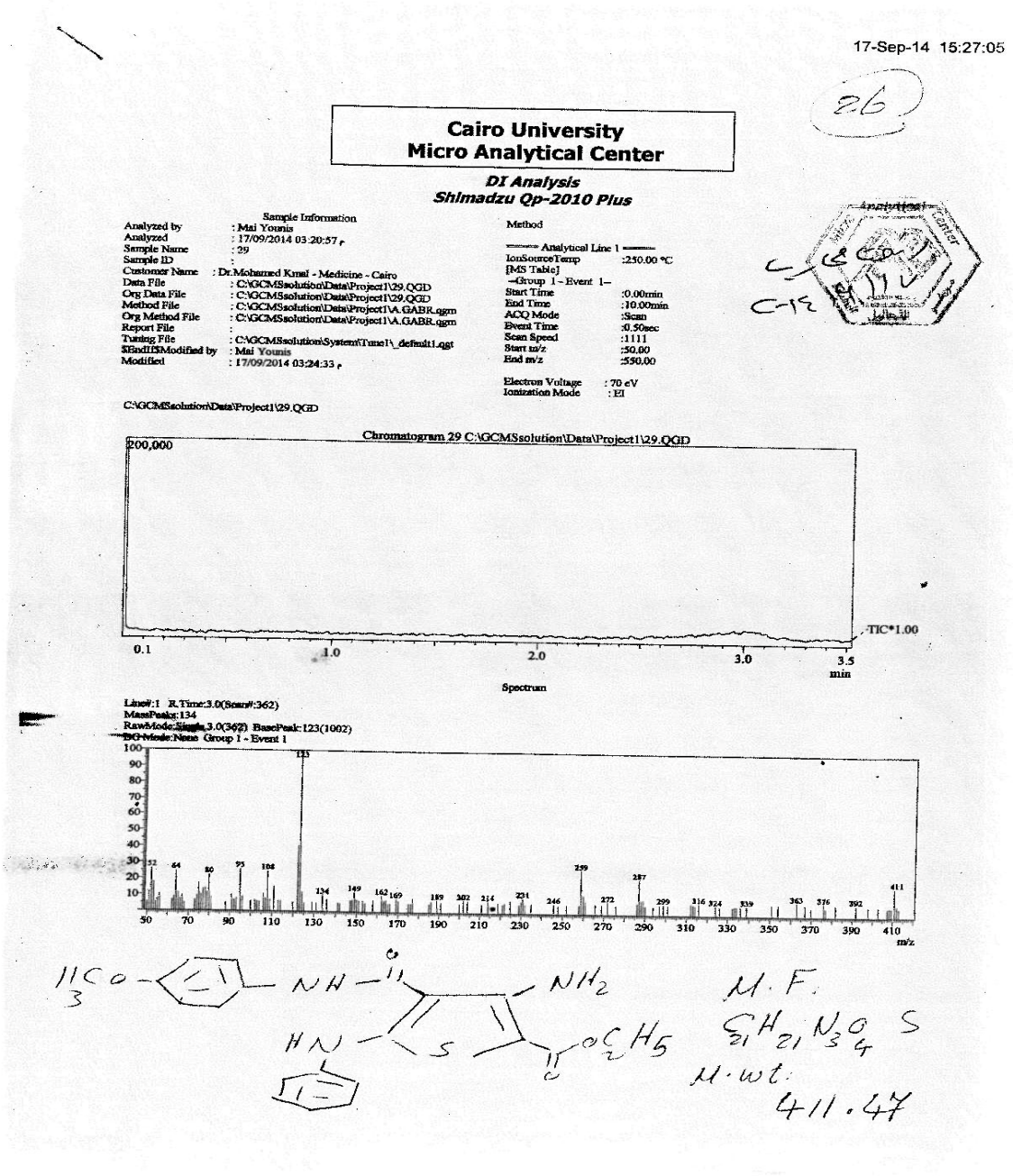


Figure S5: 1HNMR of compound 3

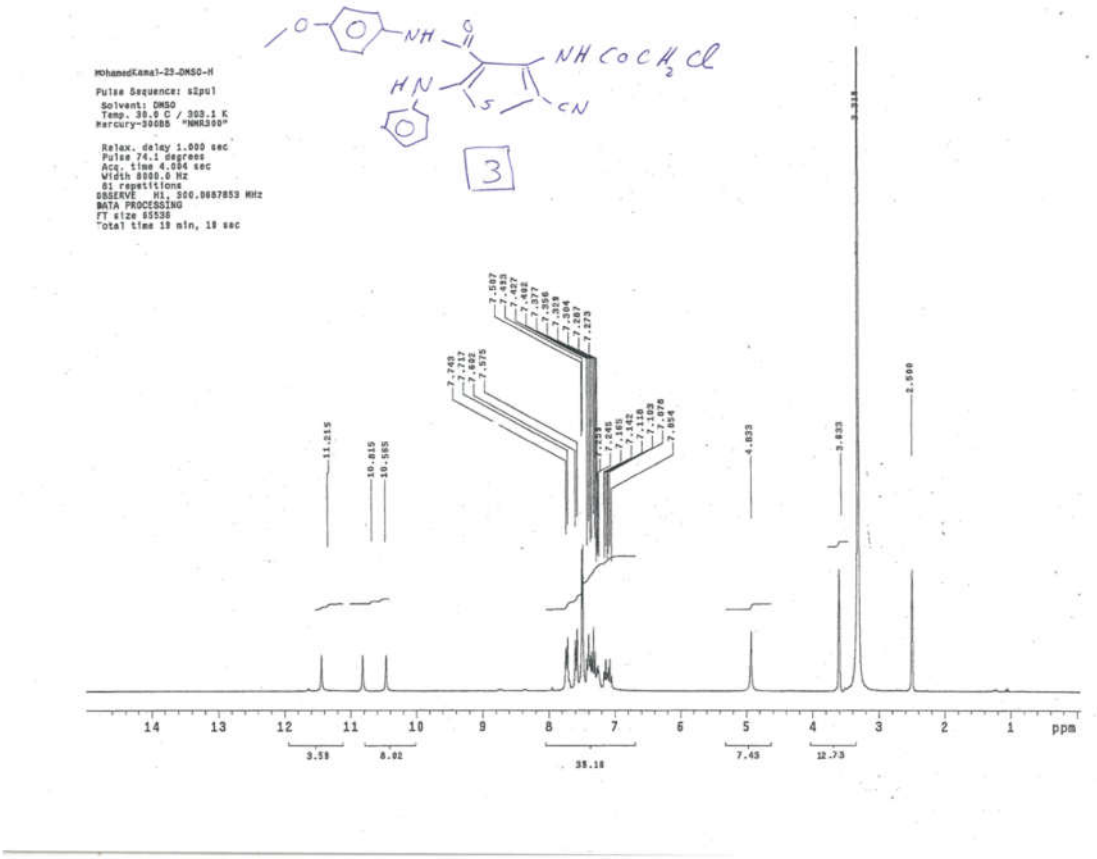


Figure S6: mass spectrum of compound 3

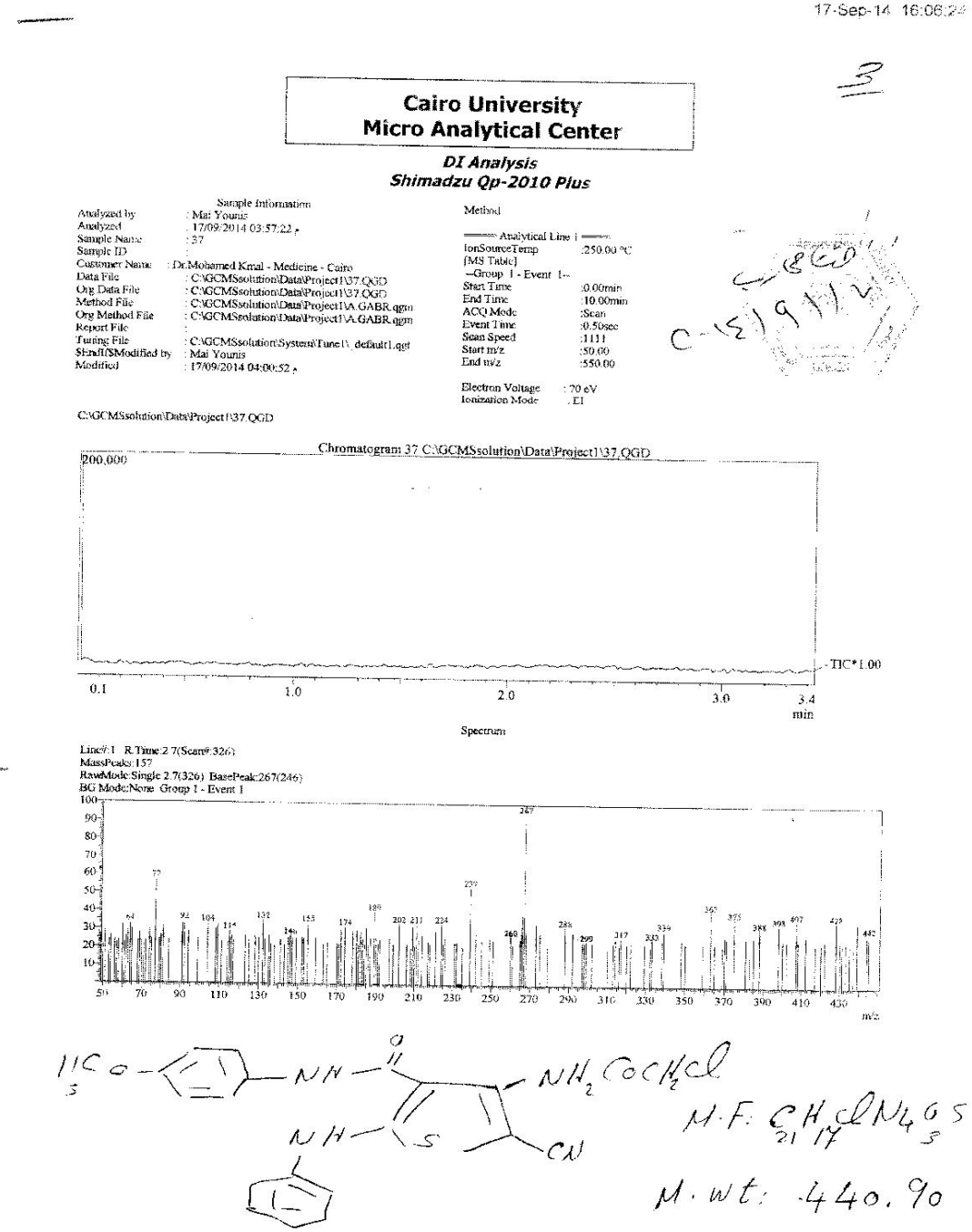


Figure S7: 1HNMR of compound 4

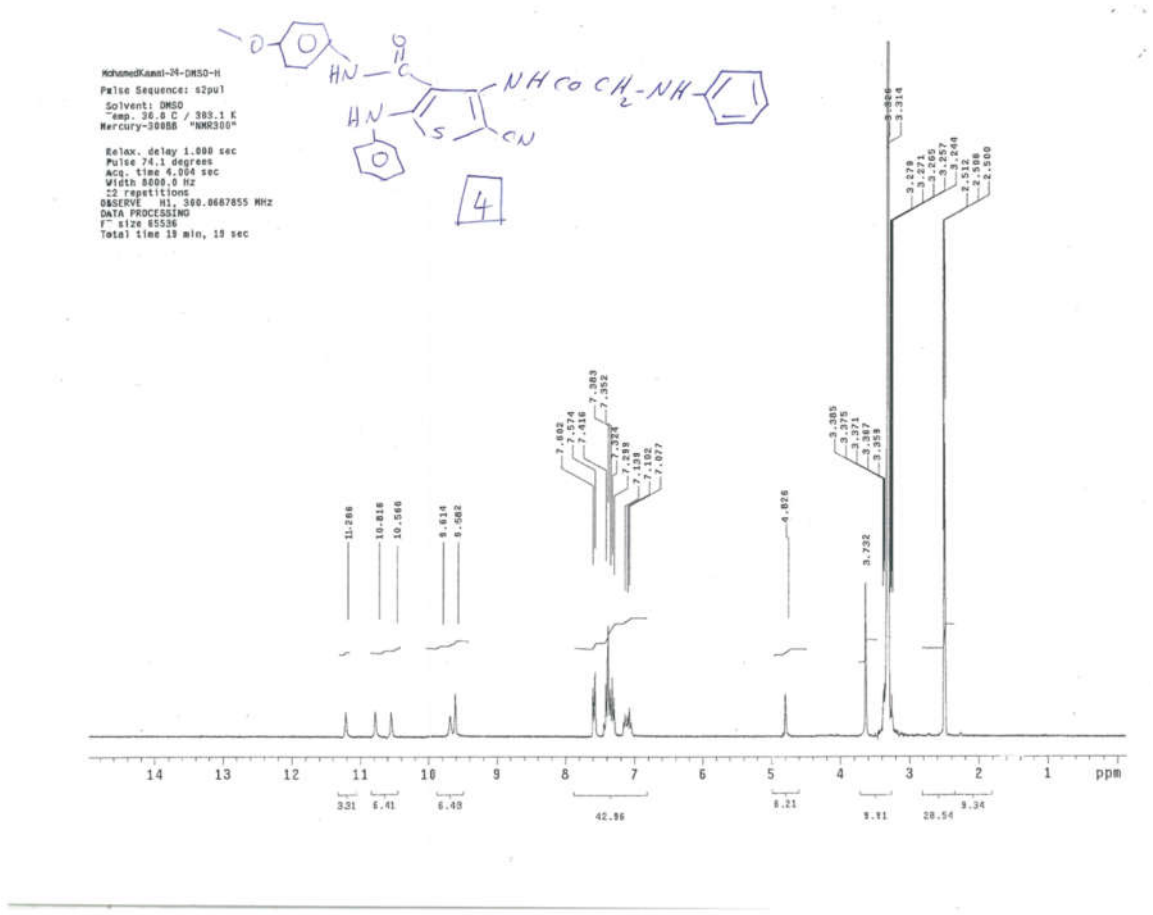


Figure S8: 13CNMR of compound 4

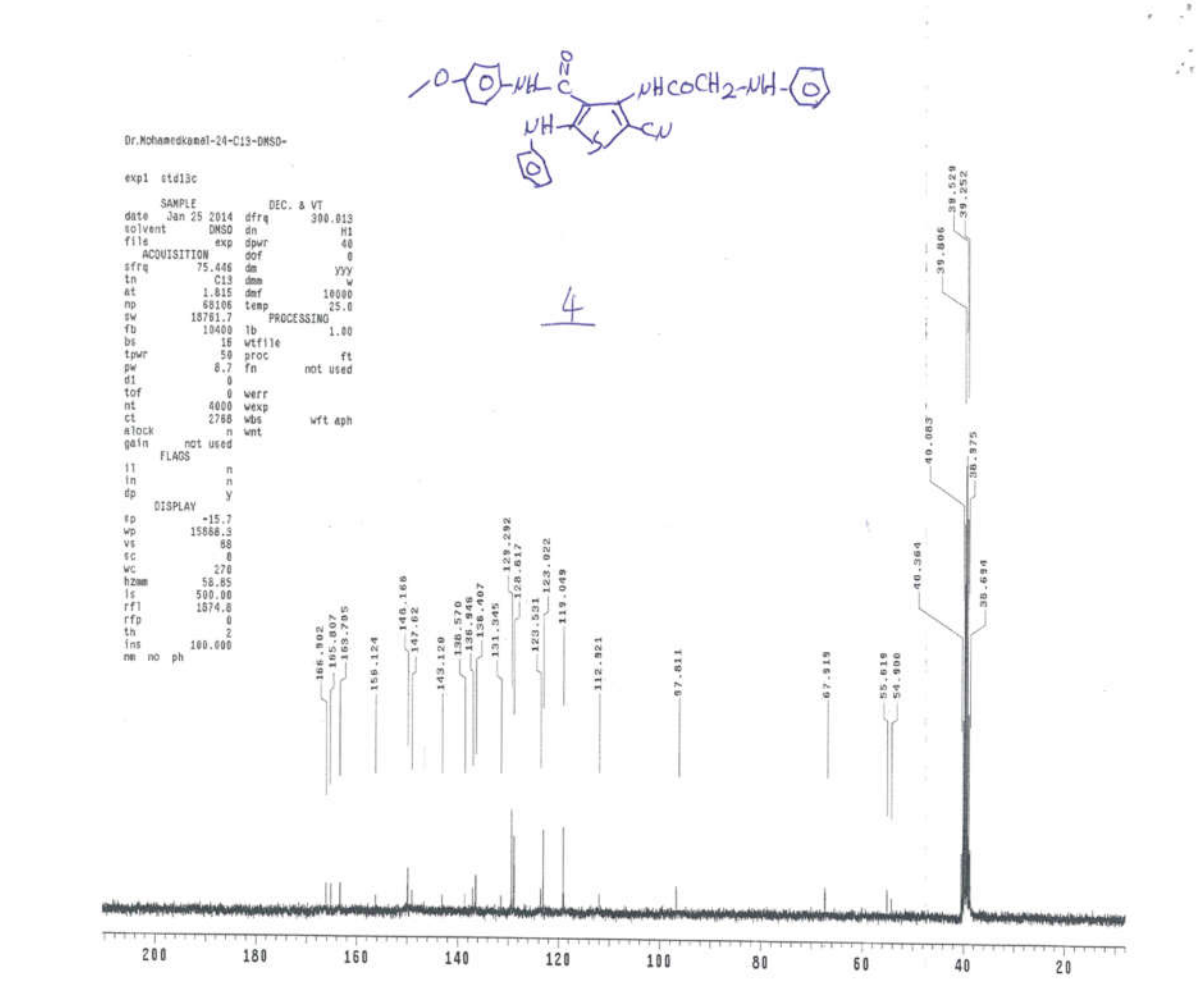


Figure S9: 1HNMR of compound 5

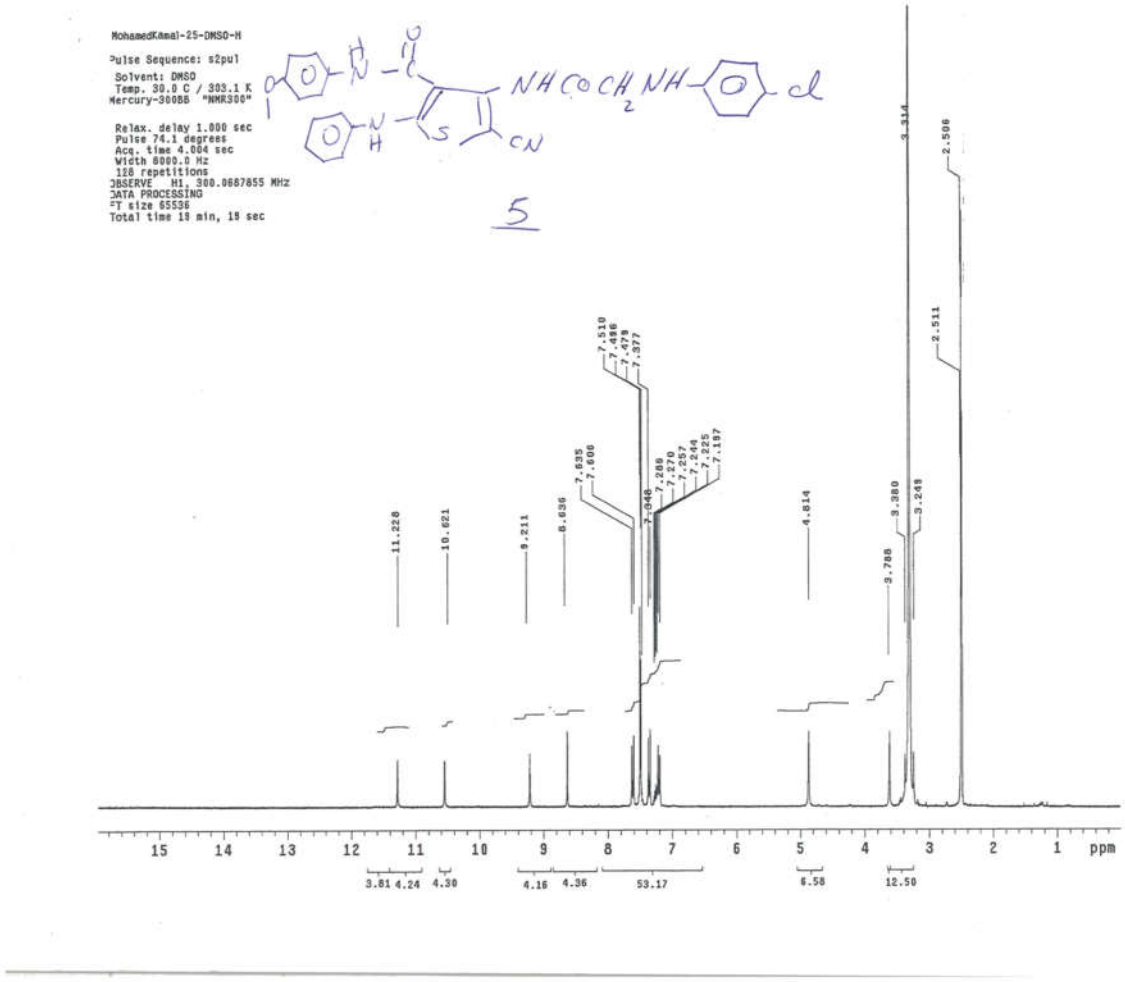


Figure S10: 13CNMR of compound 5

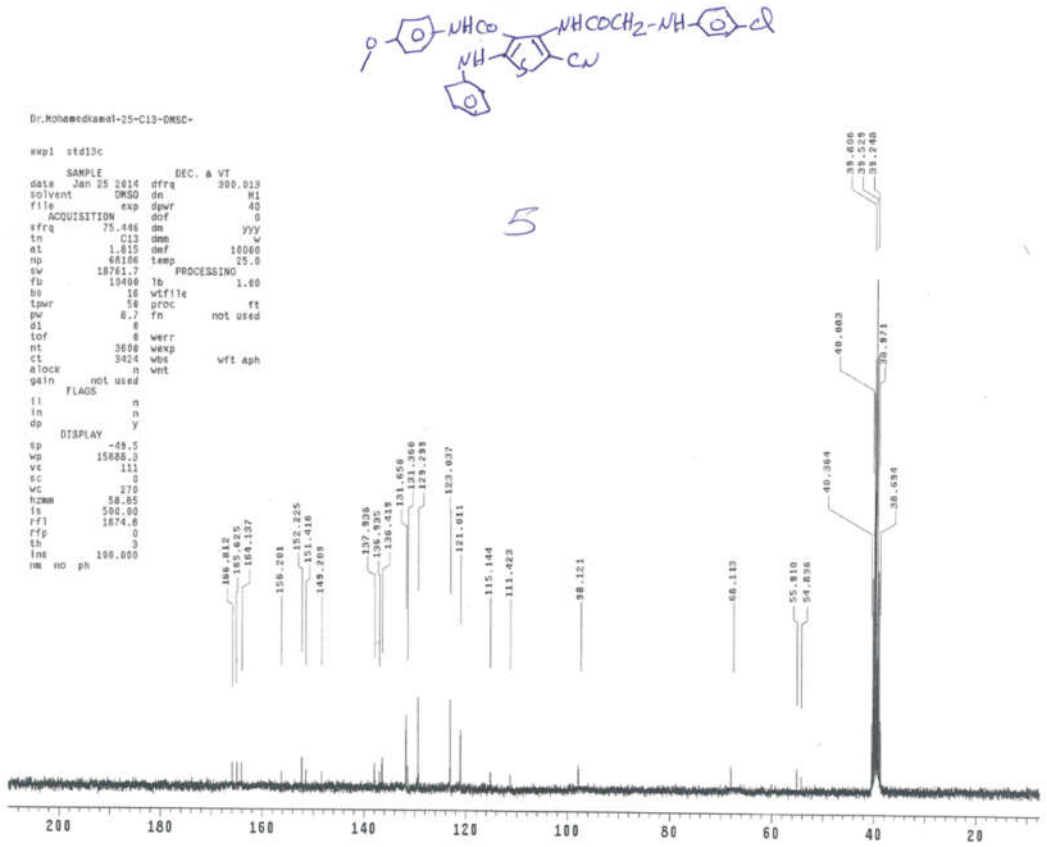


Figure S11: mass spectrum of compound 5

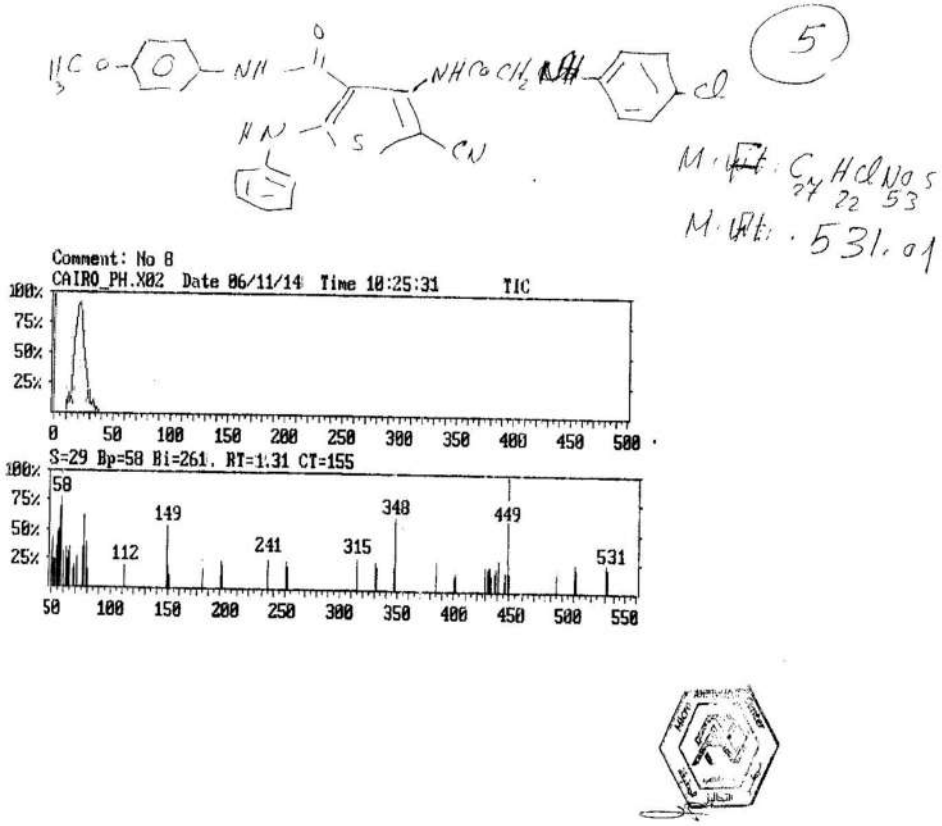


Figure S12: 1HNMR of compound 6

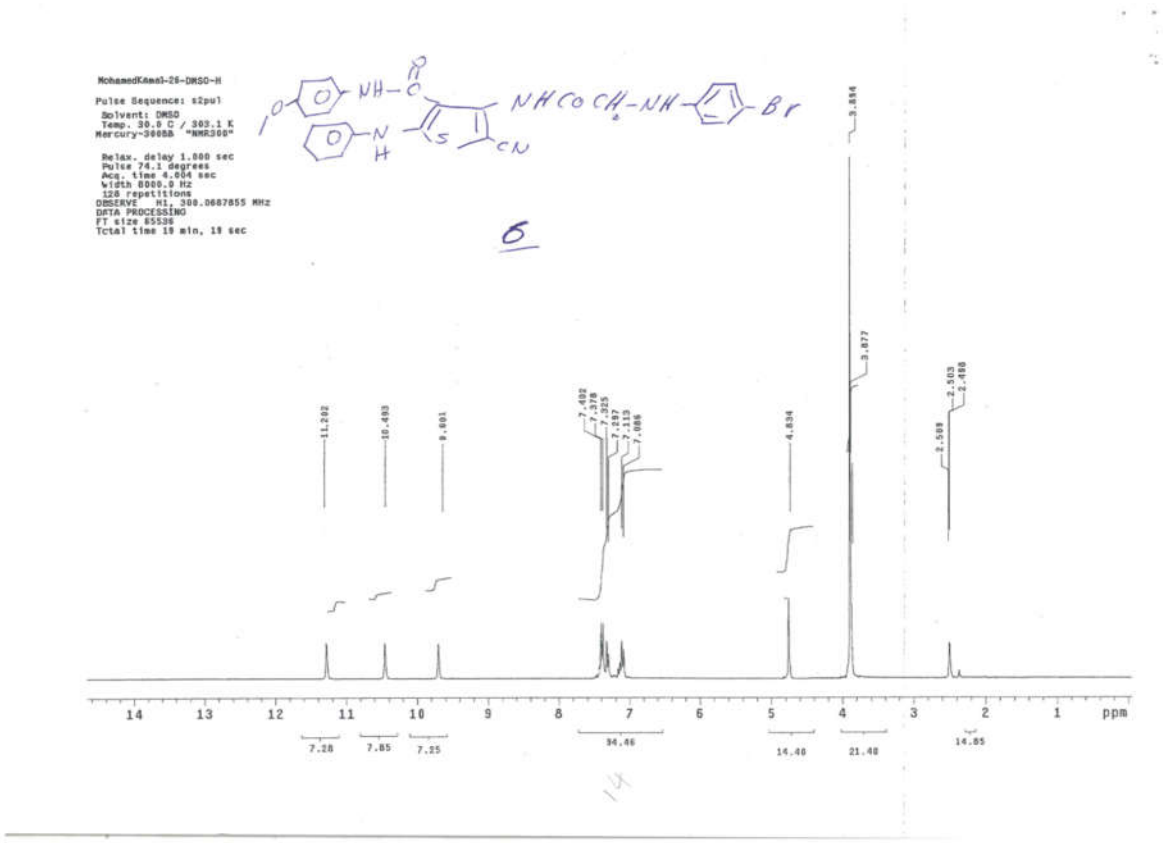


Figure S13: 13CNMR of compound 6

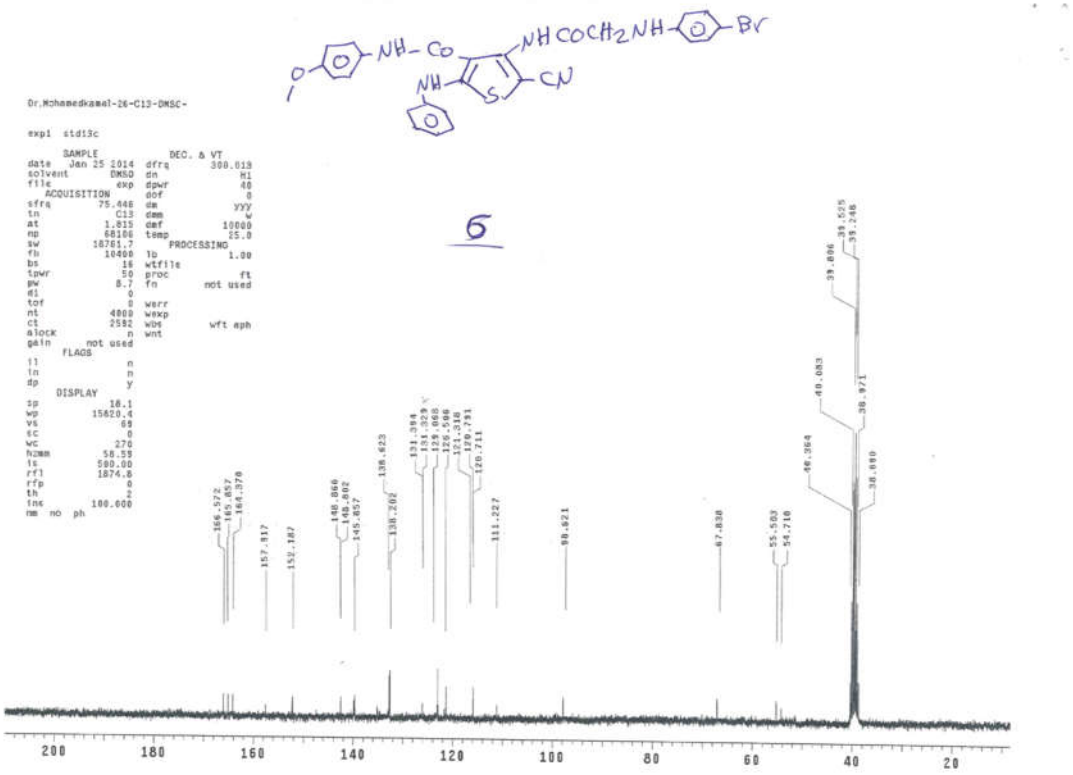


Figure S14: mass spectrum of compound 6

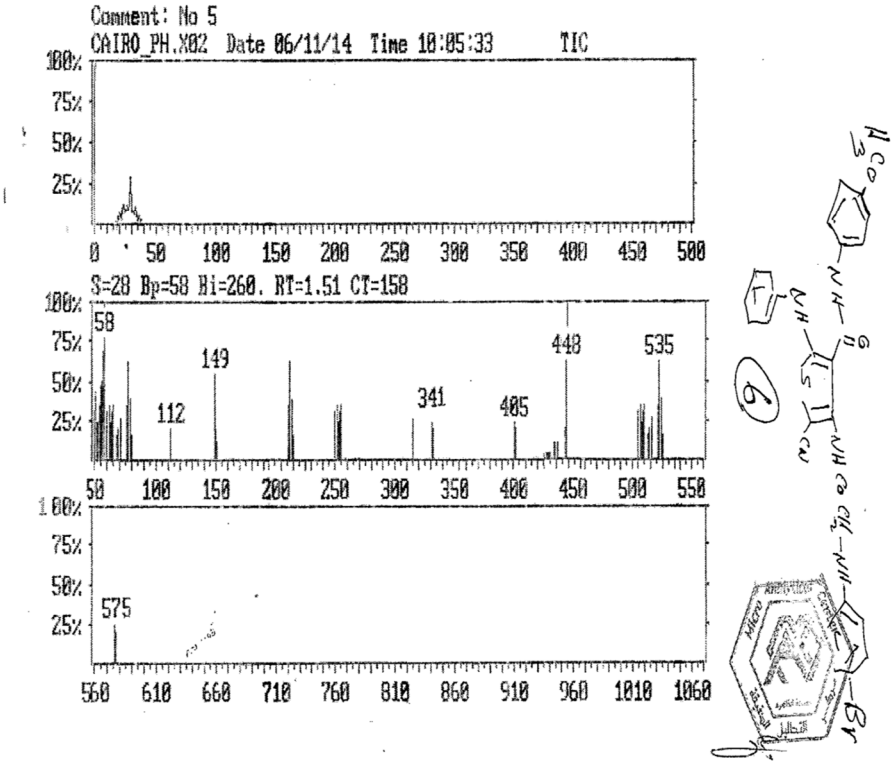


Figure S15: 1HNMR of compound 7

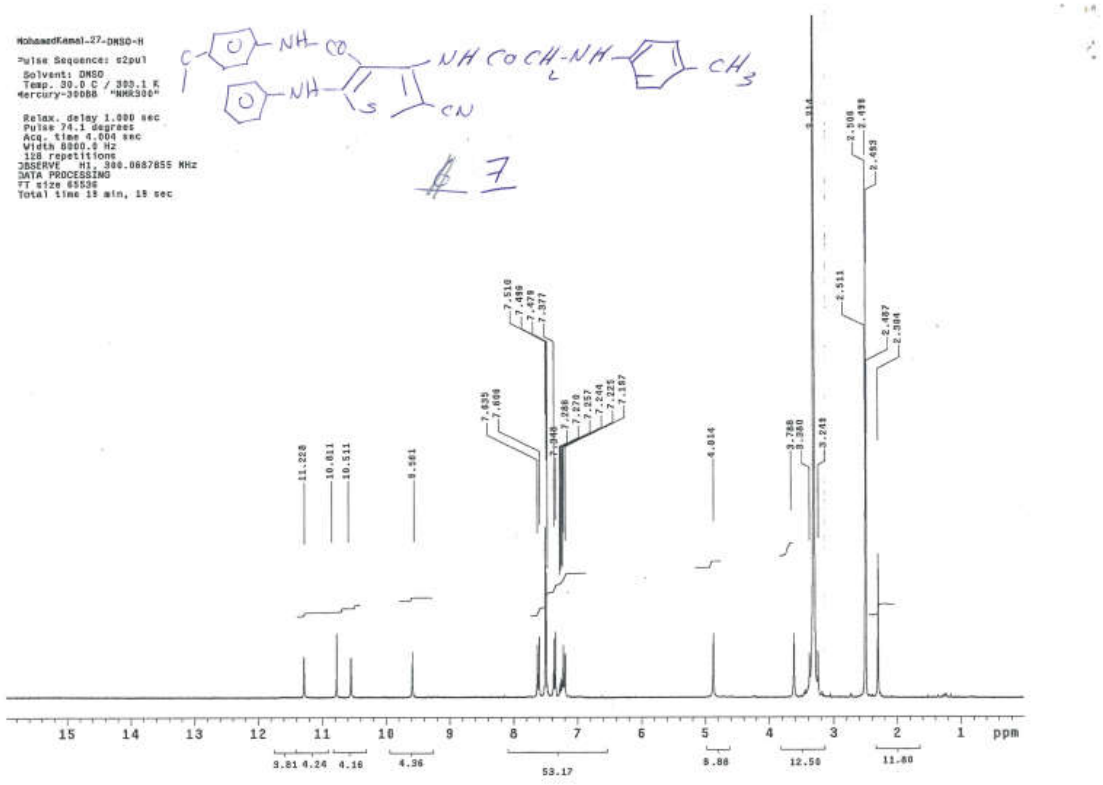


Figure S16: 13CNMR of compound 7

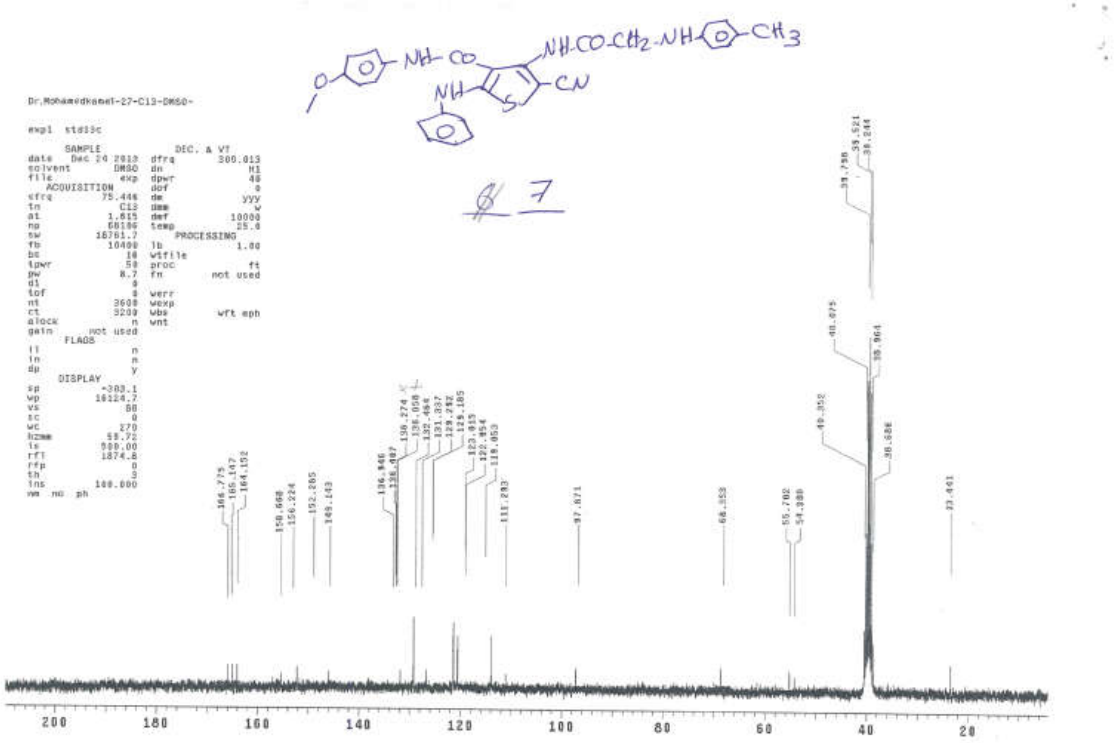


Figure S17: 1HNMR of compound 8

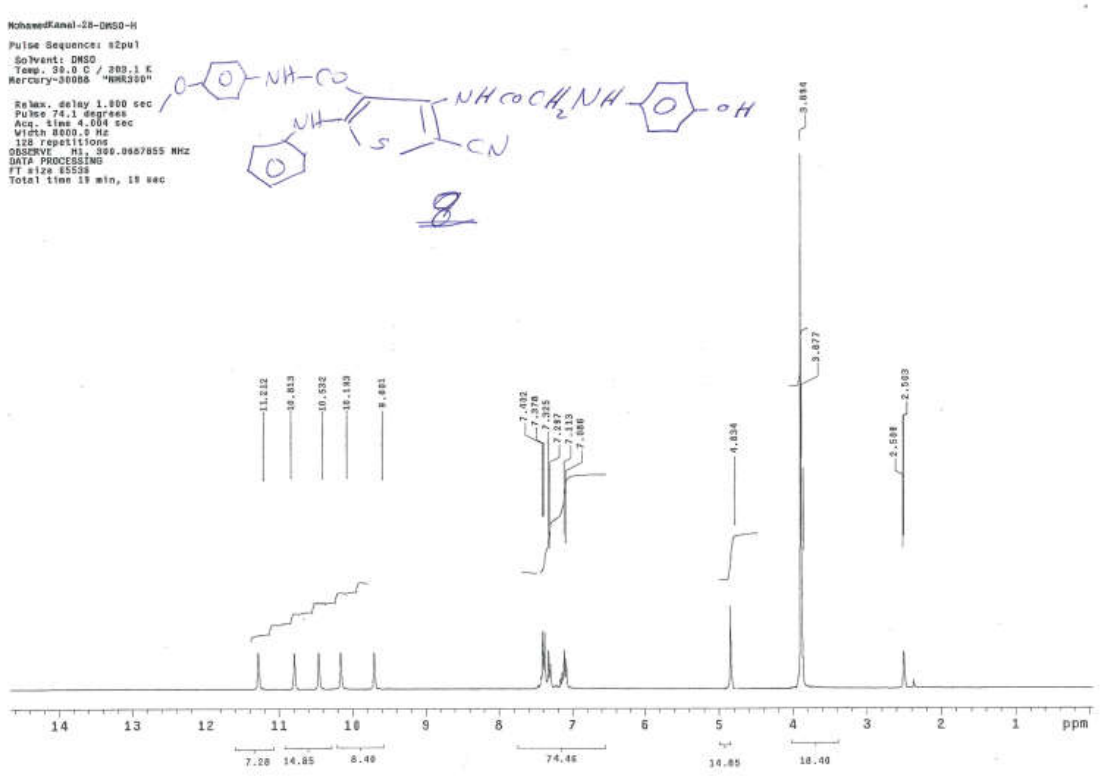


Figure S18: 13CNMR of compound 8

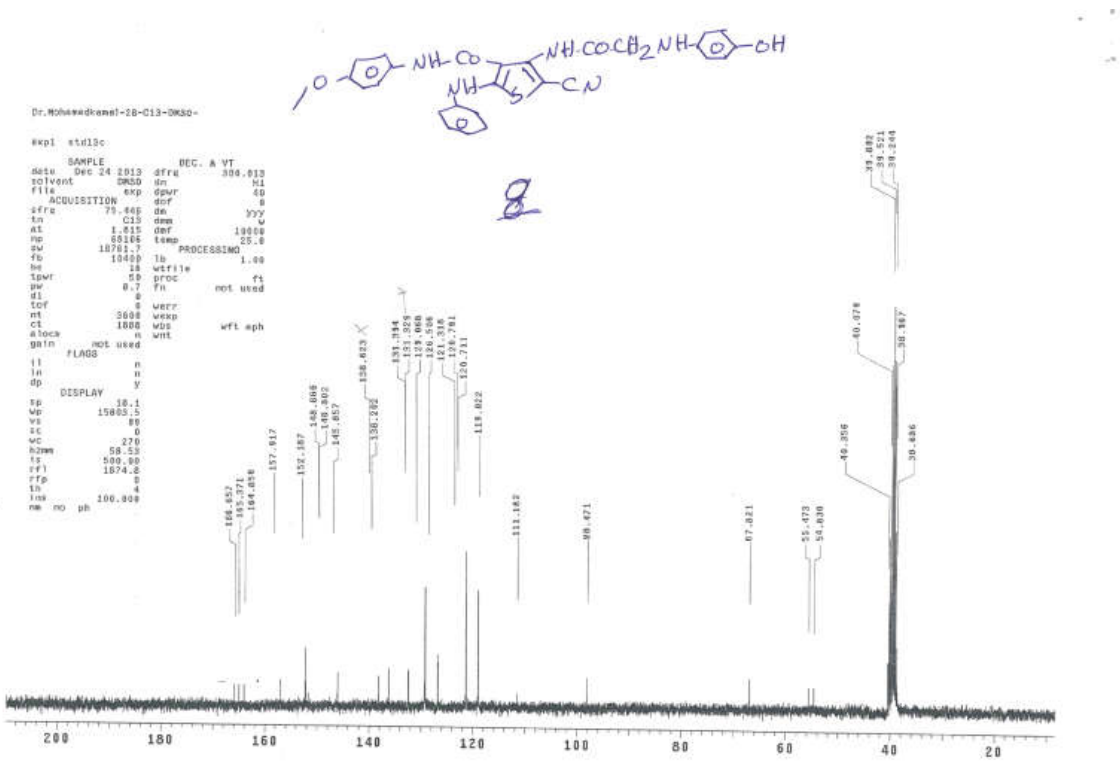


Figure S19: 1HNMR of compound 9

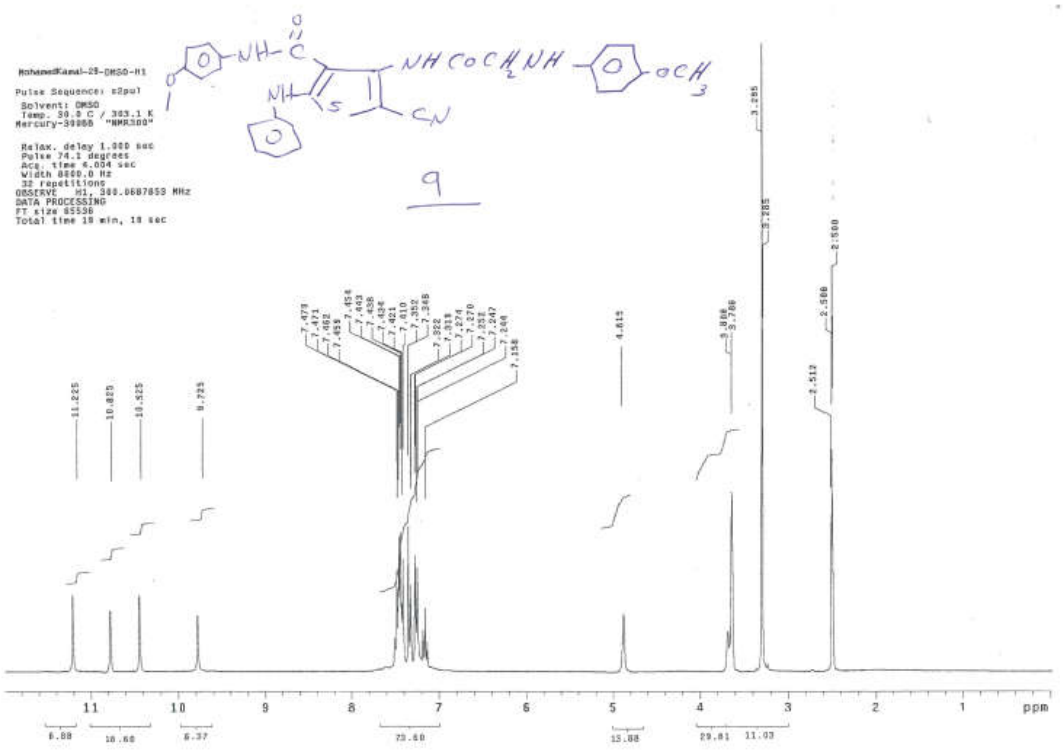


Figure S20: 13CNMR of compound 9

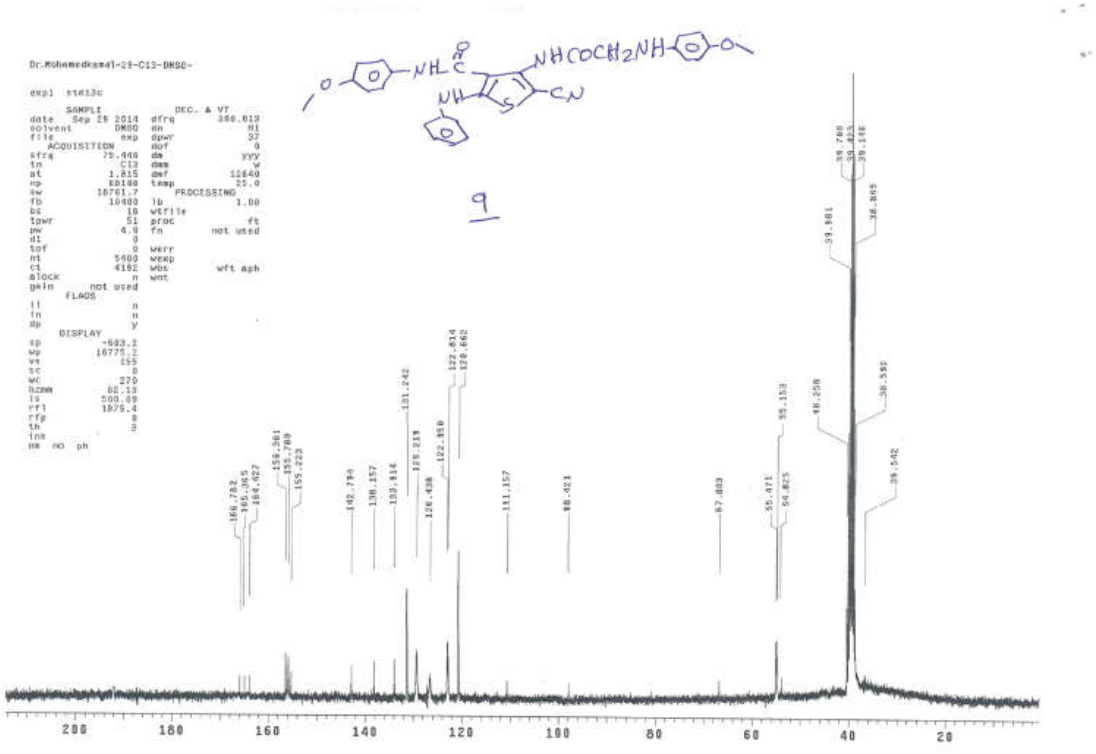


Figure S21: 1HNMR of compound 10

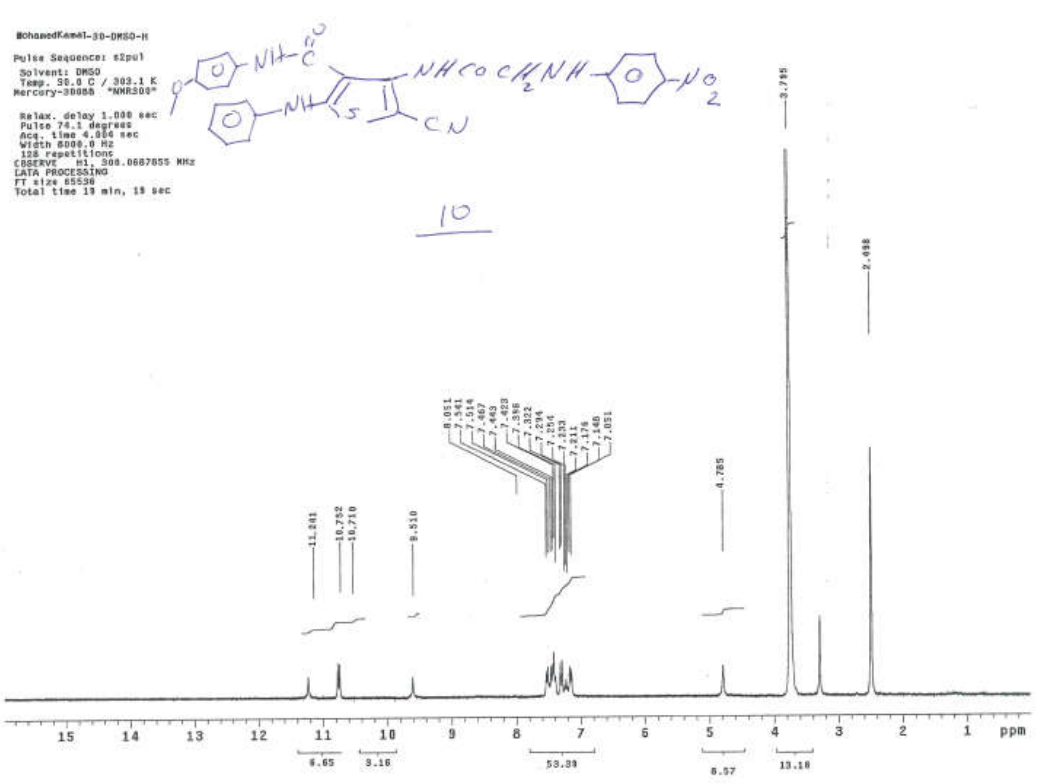


Figure S22: 13CNMR of compound 10

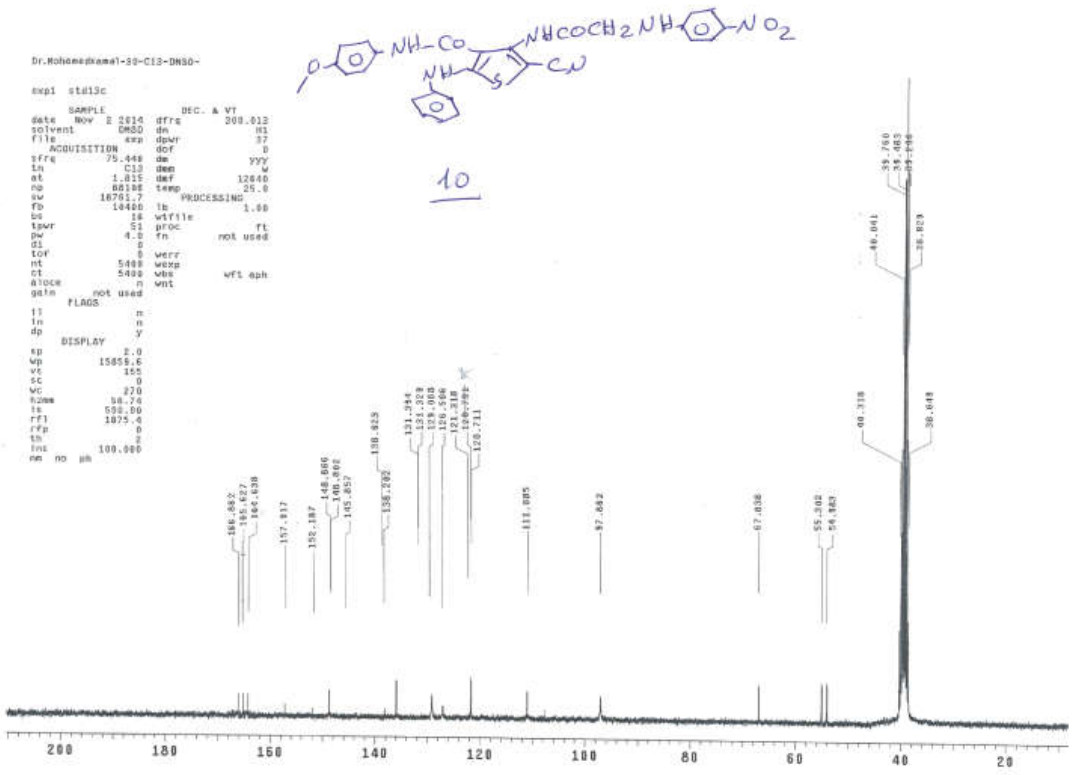


Figure S23: mass spectrum of compound 10

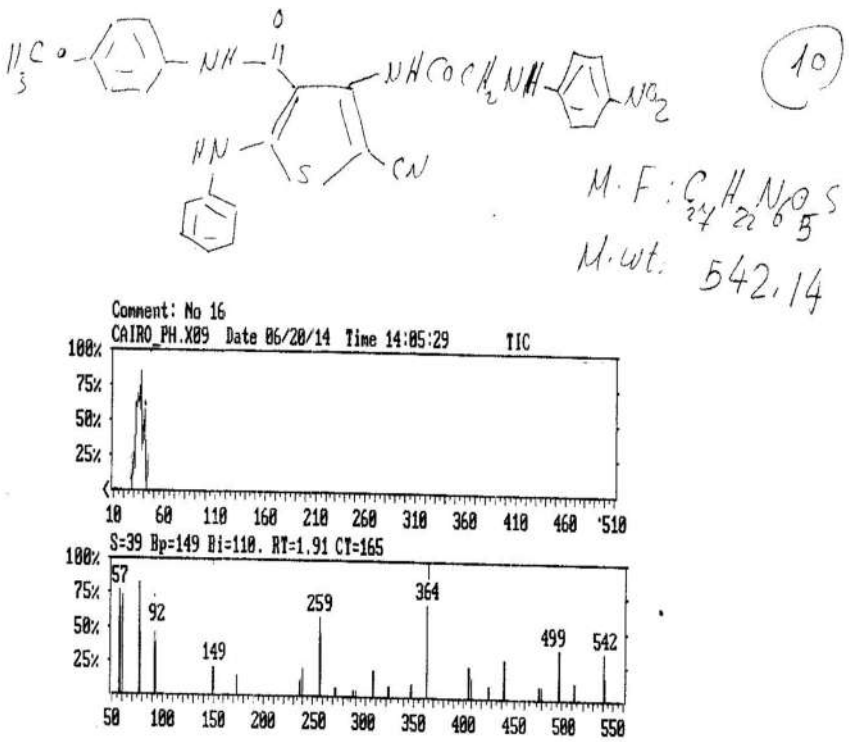


Figure S24: 1HNMR of compound 11

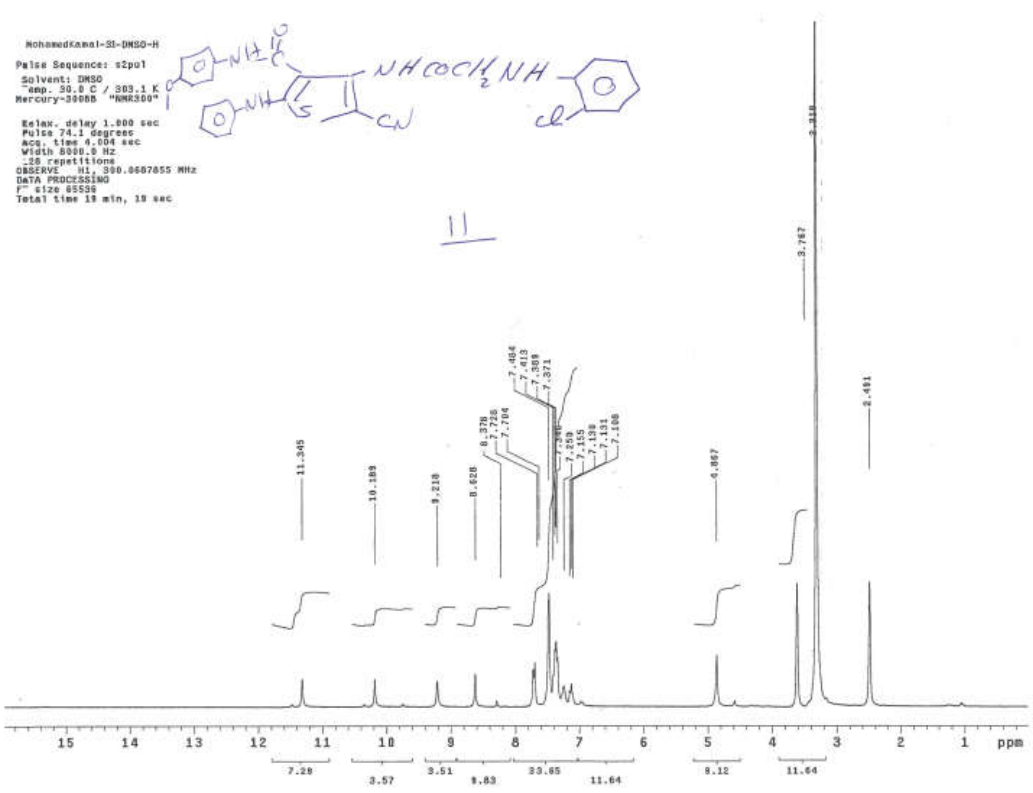


Figure S25: 13CNMR of compound 11

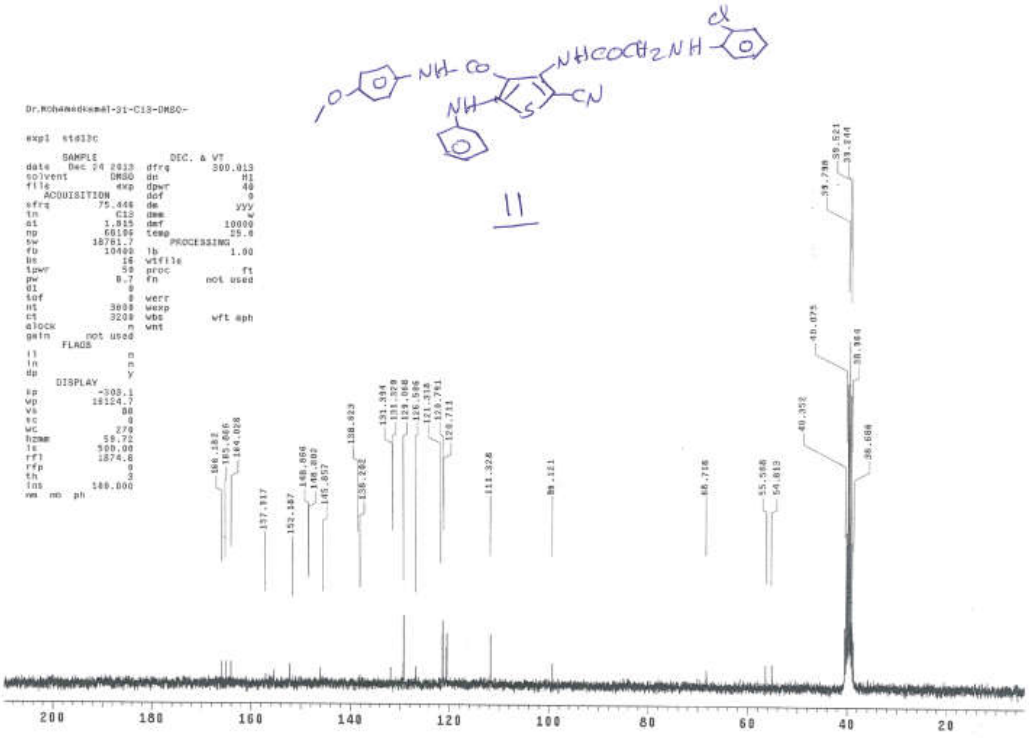


Figure S26: 1HNMR of compound 12

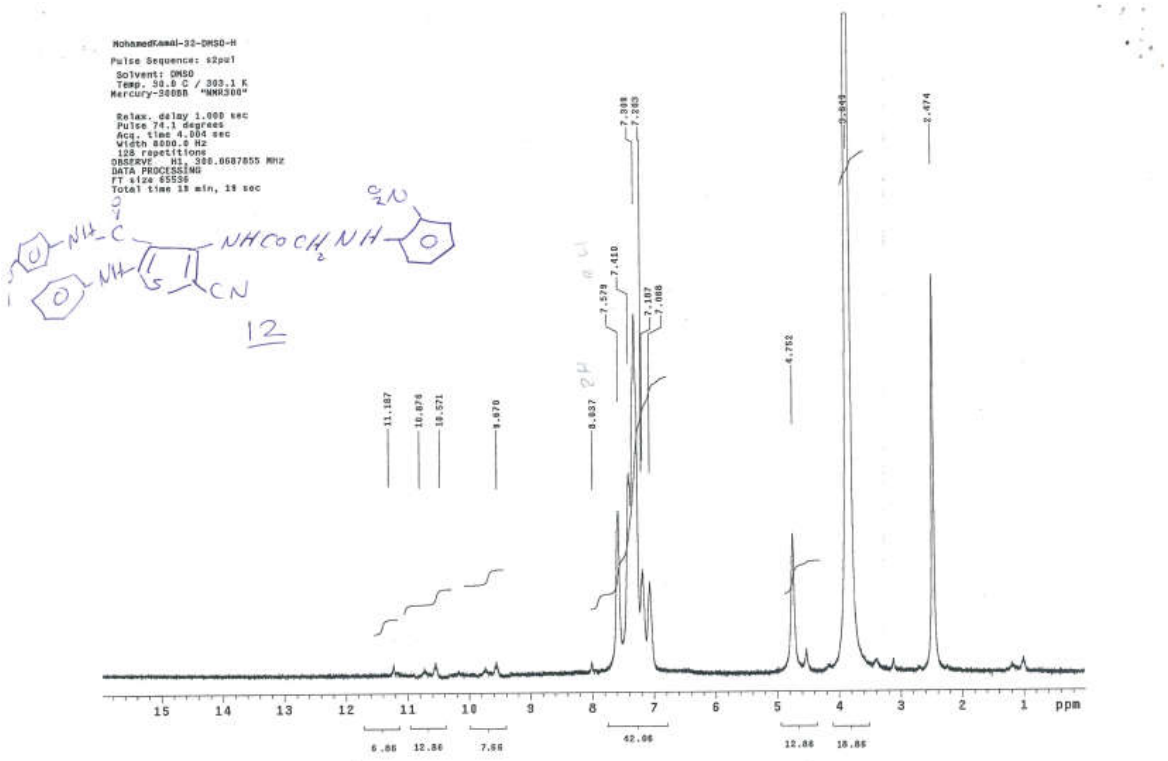


Figure S27: 13CNMR of compound 12

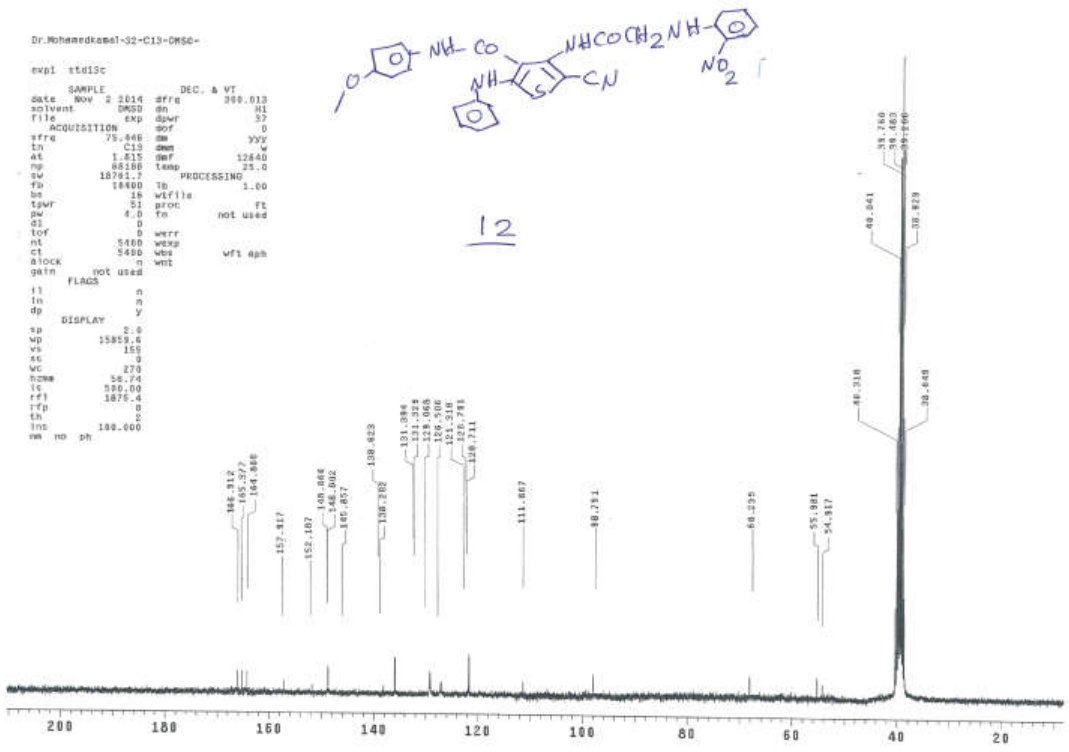


Figure S28: 1HNMR of compound 13

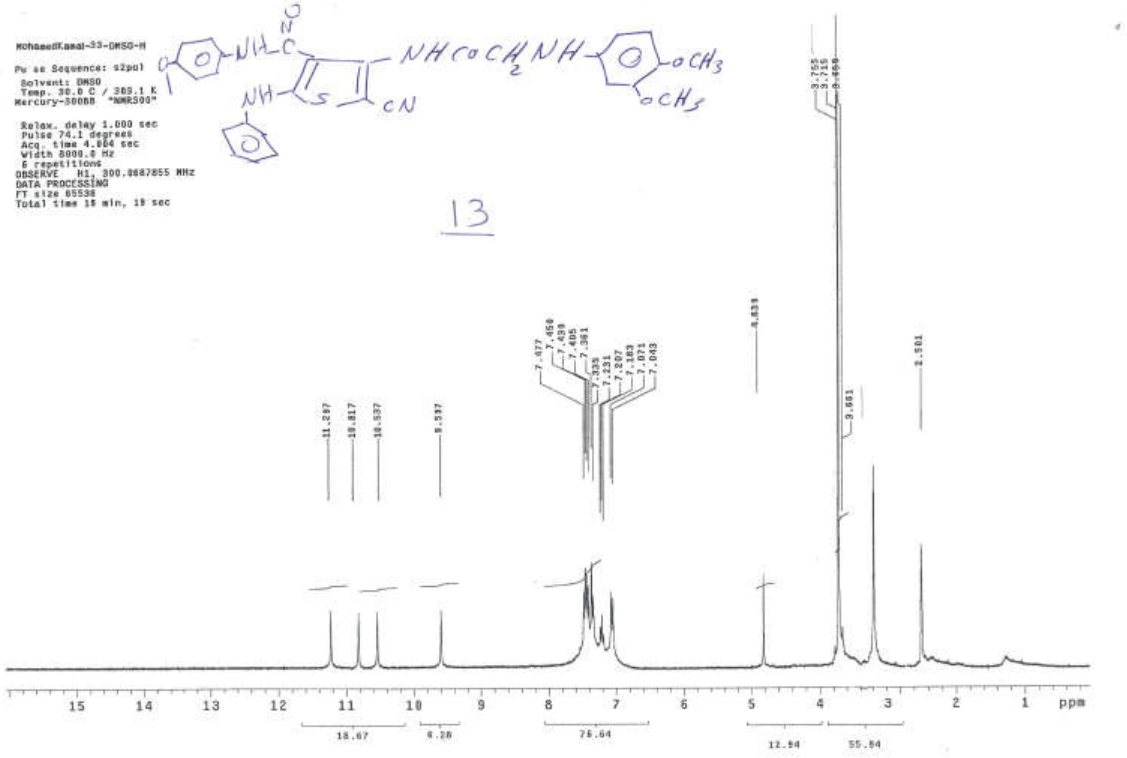


Figure S29: 13CNMR of compound 13

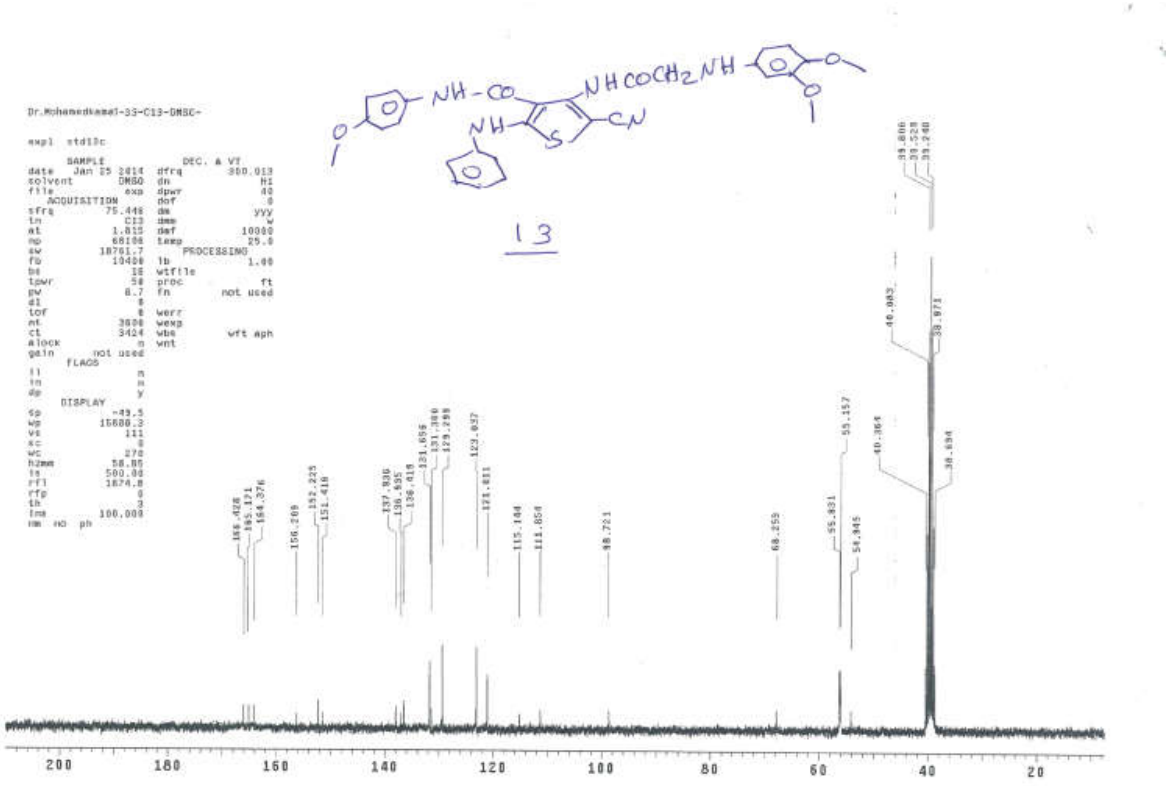


Figure S30: 1HNMR of compound 14

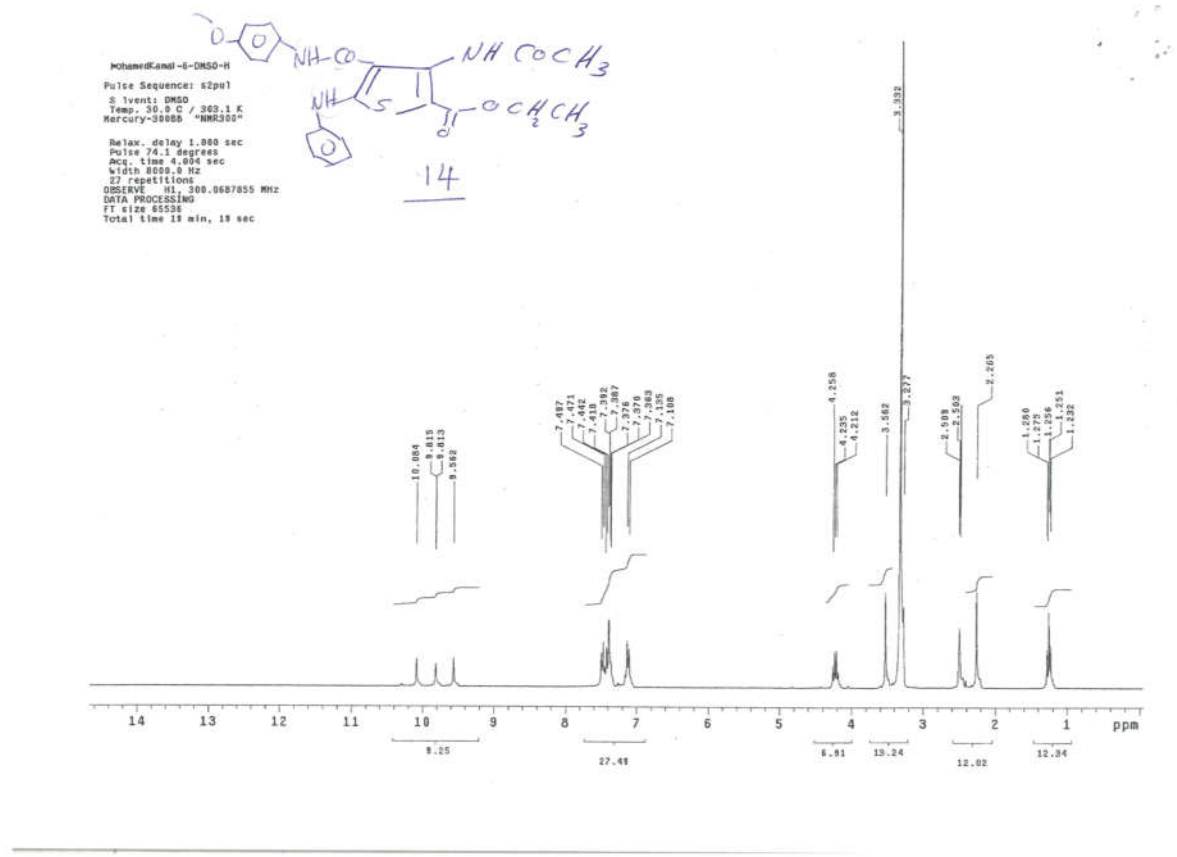


Figure S31: 13CNMR of compound 14

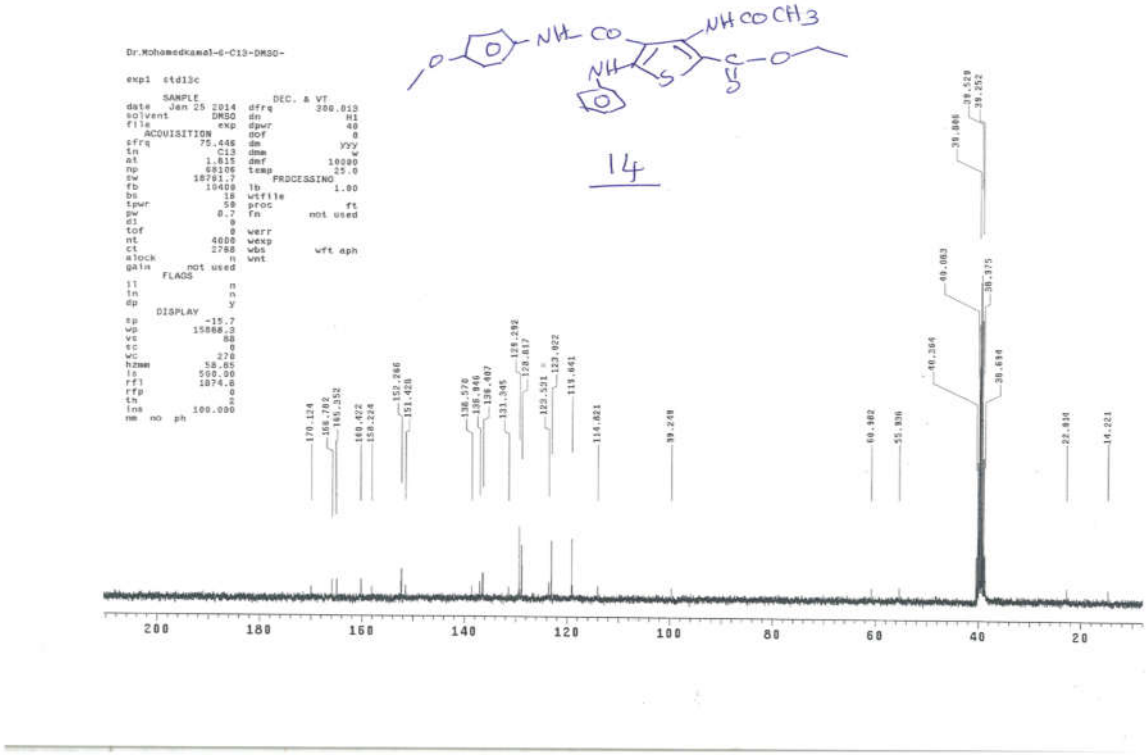


Figure S32: mass spectrum of compound 14

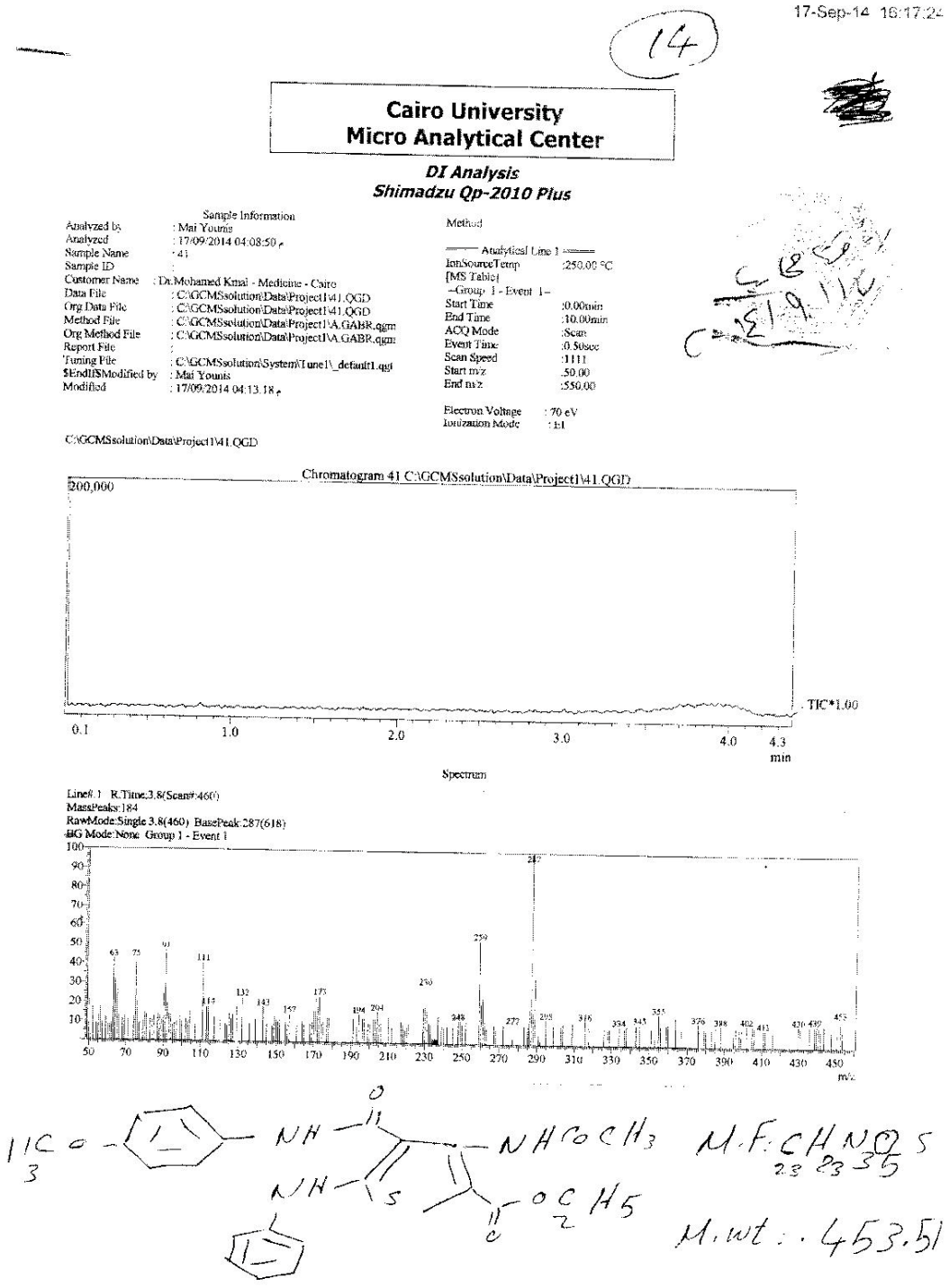


Figure S33: 1HNMR of compound 15

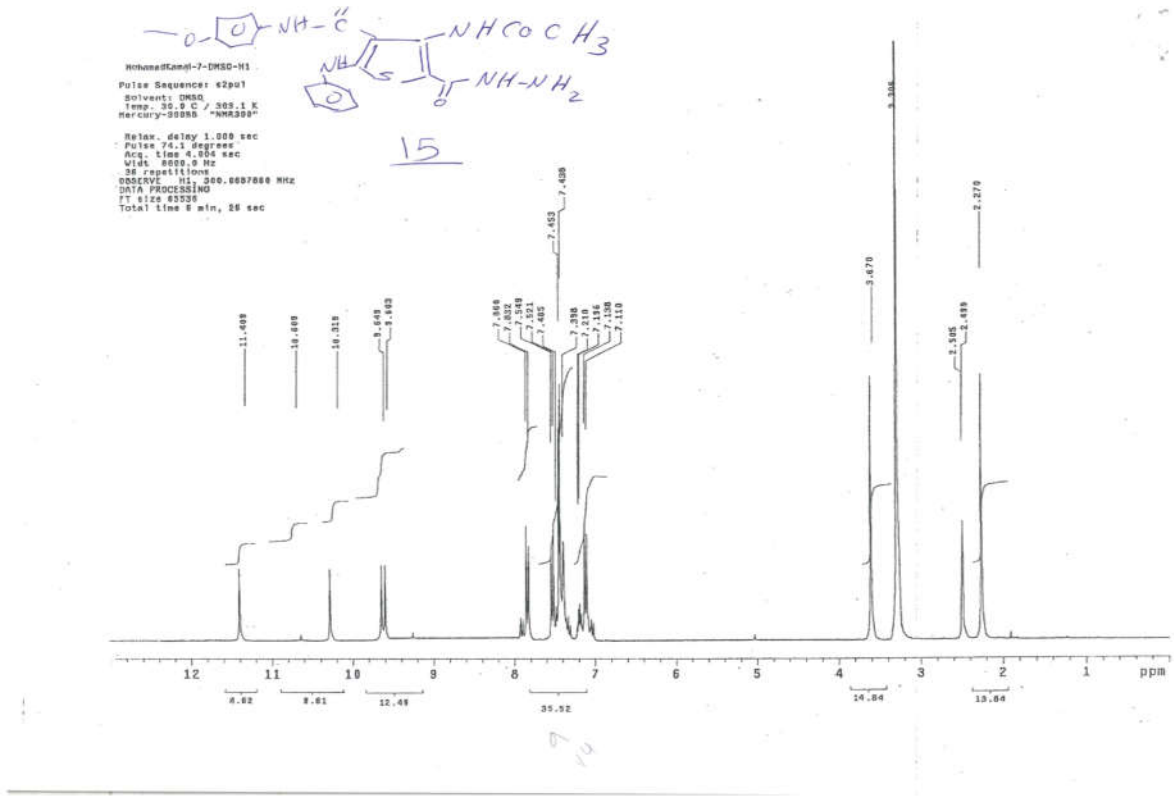


Figure S34: 13CNMR of compound 15

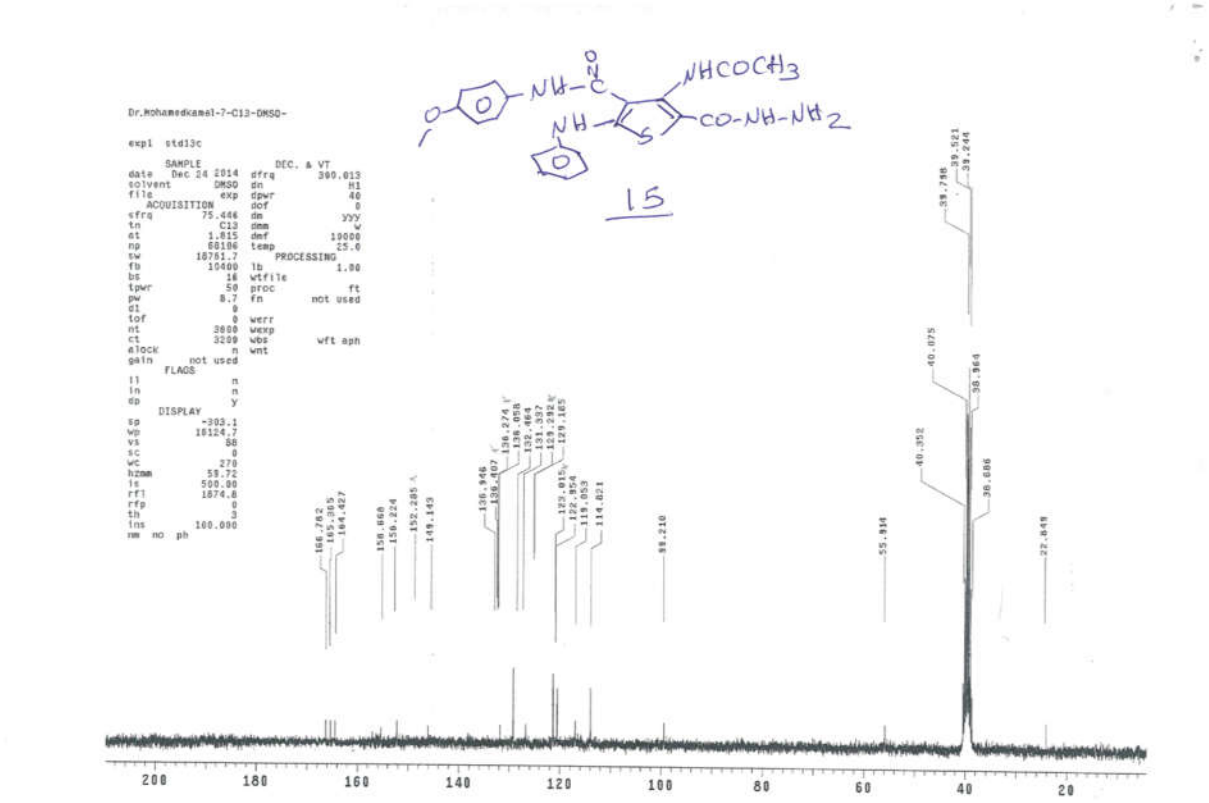


Figure S35: mass spectrum of compound 15

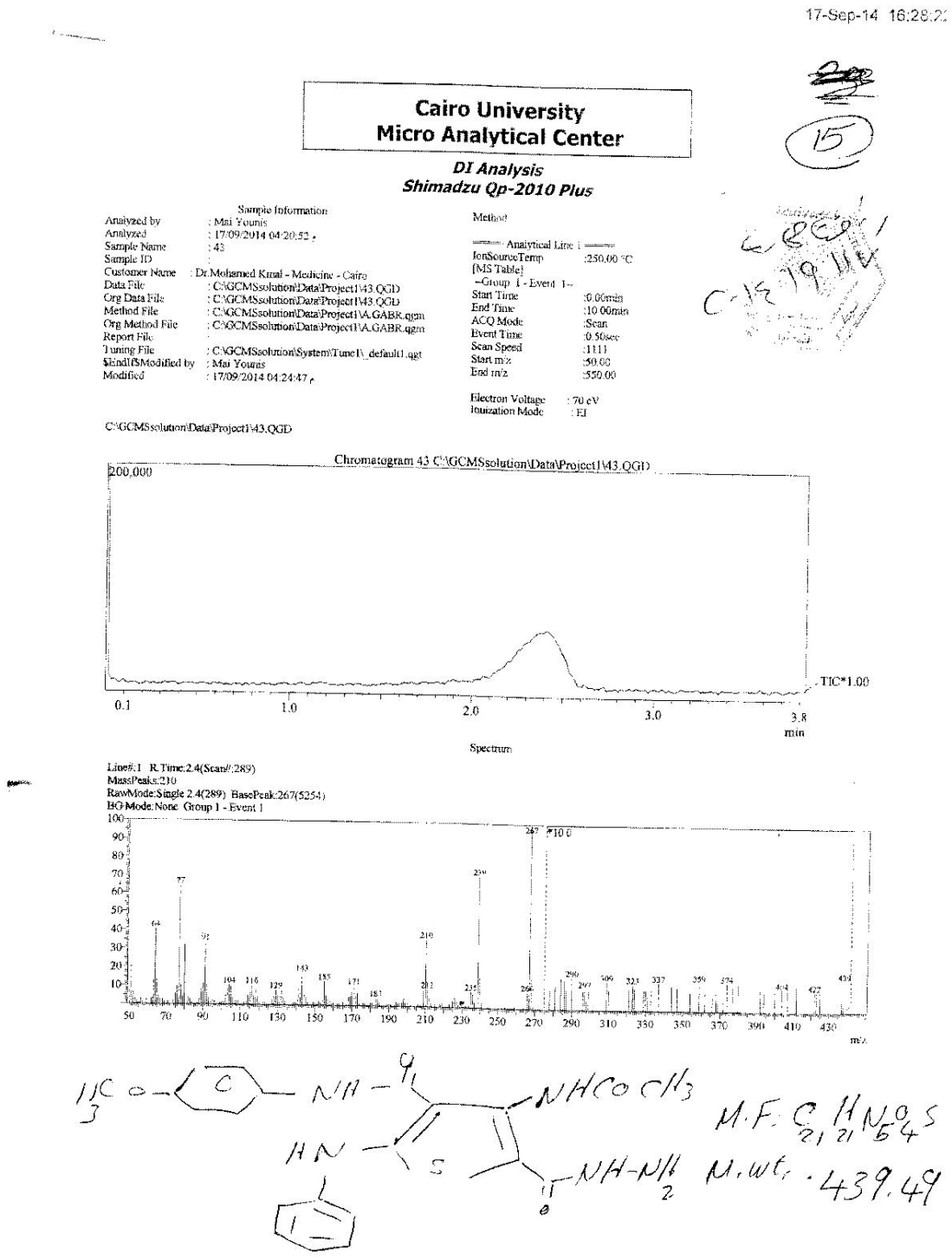


Figure S36: 1HNMR of compound 16

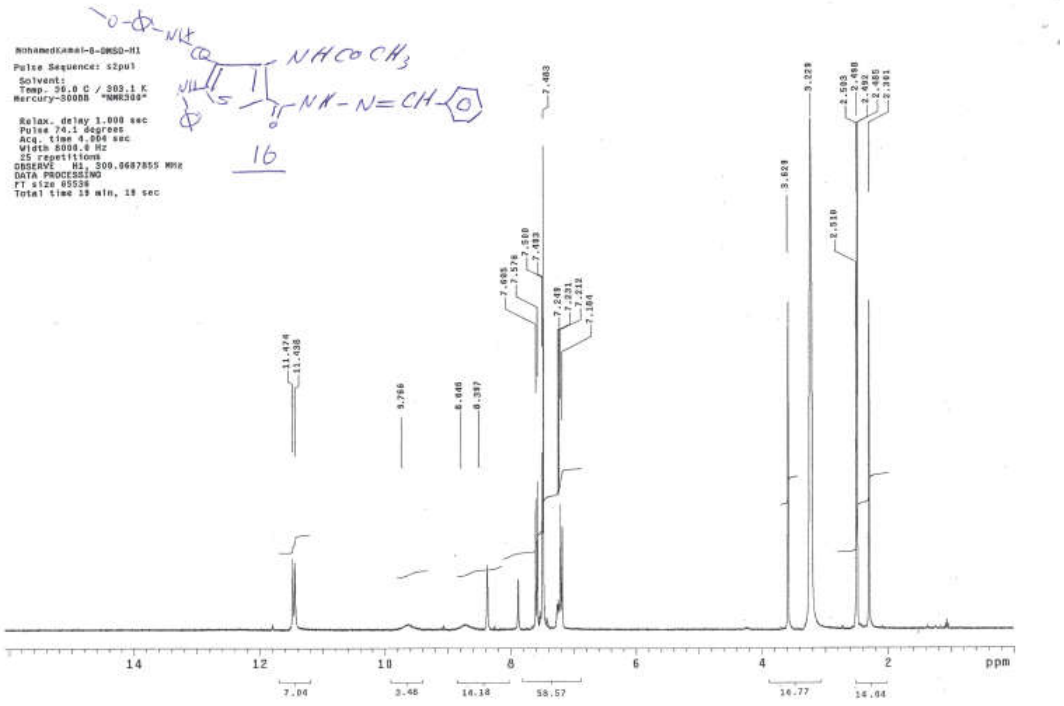


Figure S37: 13CNMR of compound 16

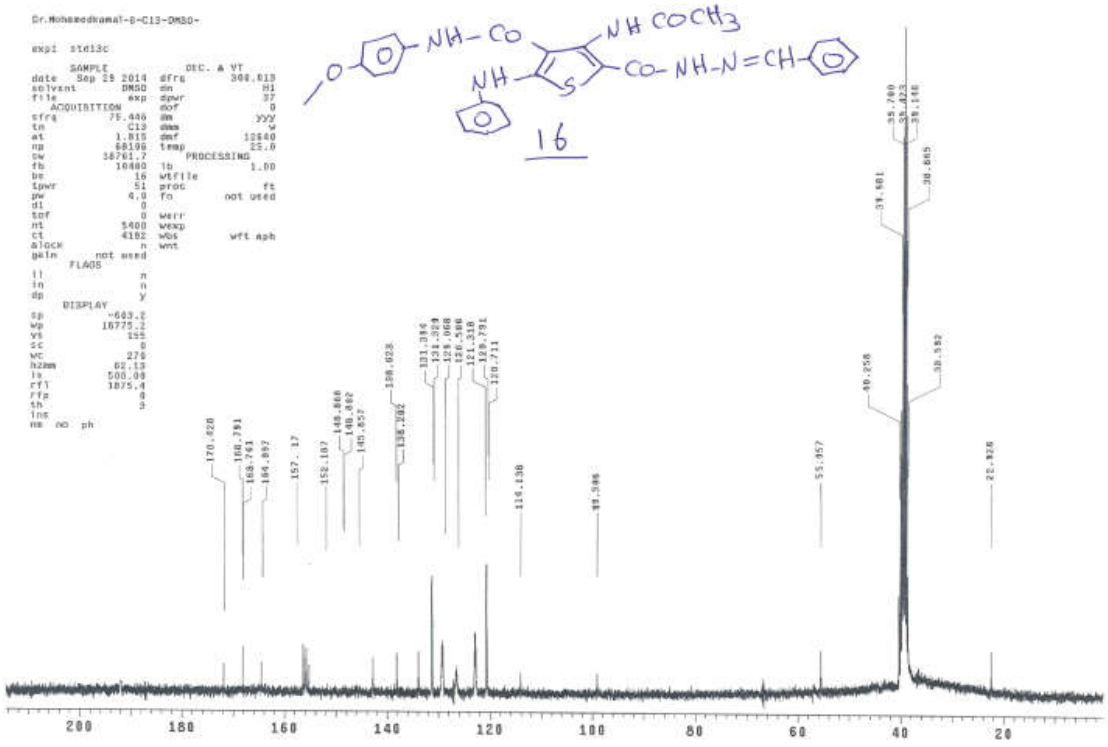


Figure S38: mass spectrum of compound 16

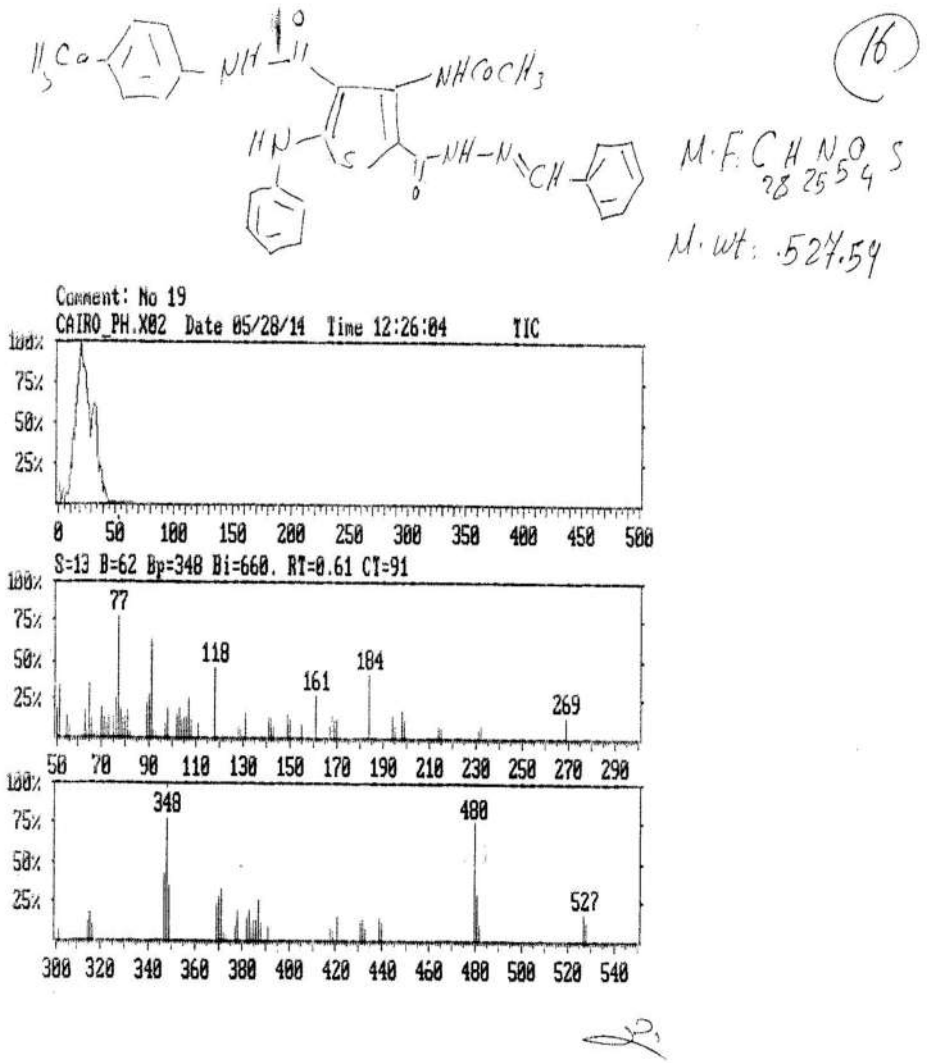


Figure S39: 1HNMR of compound 17

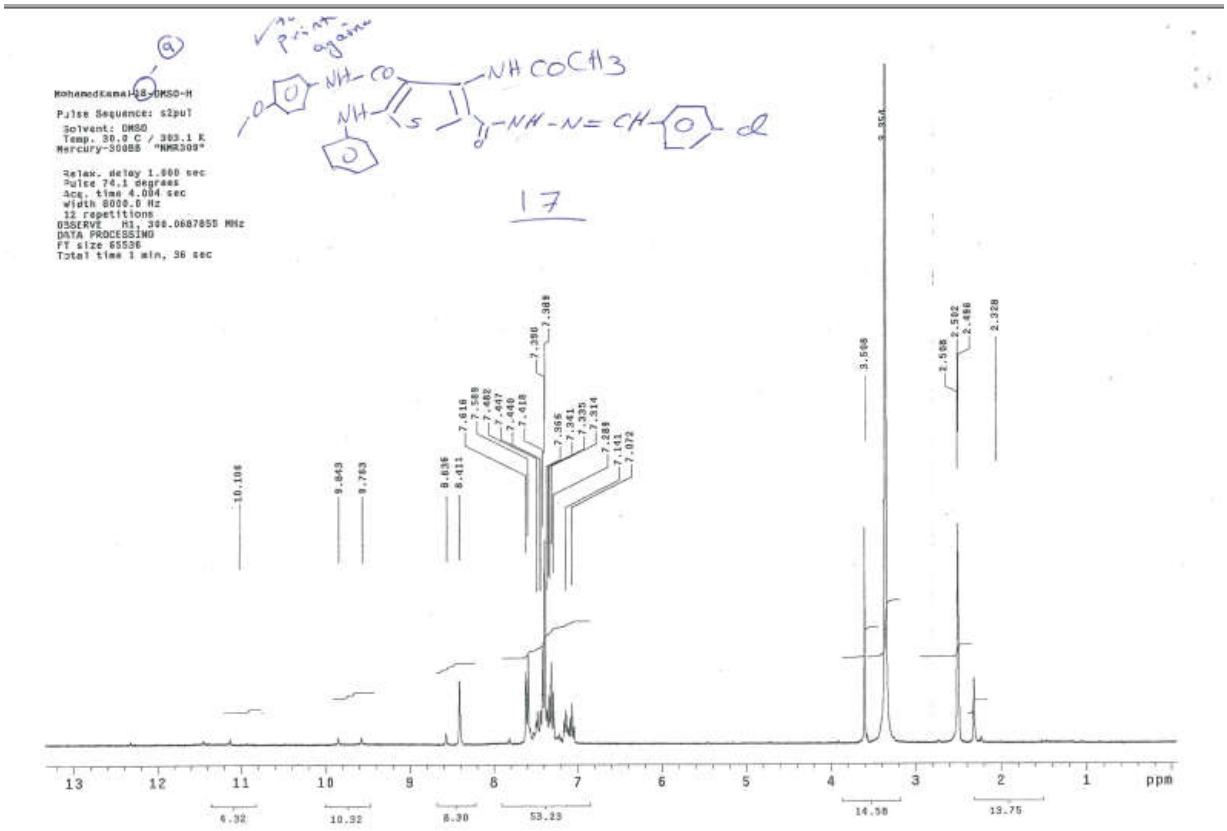


Figure S40: 13CNMR of compound 17

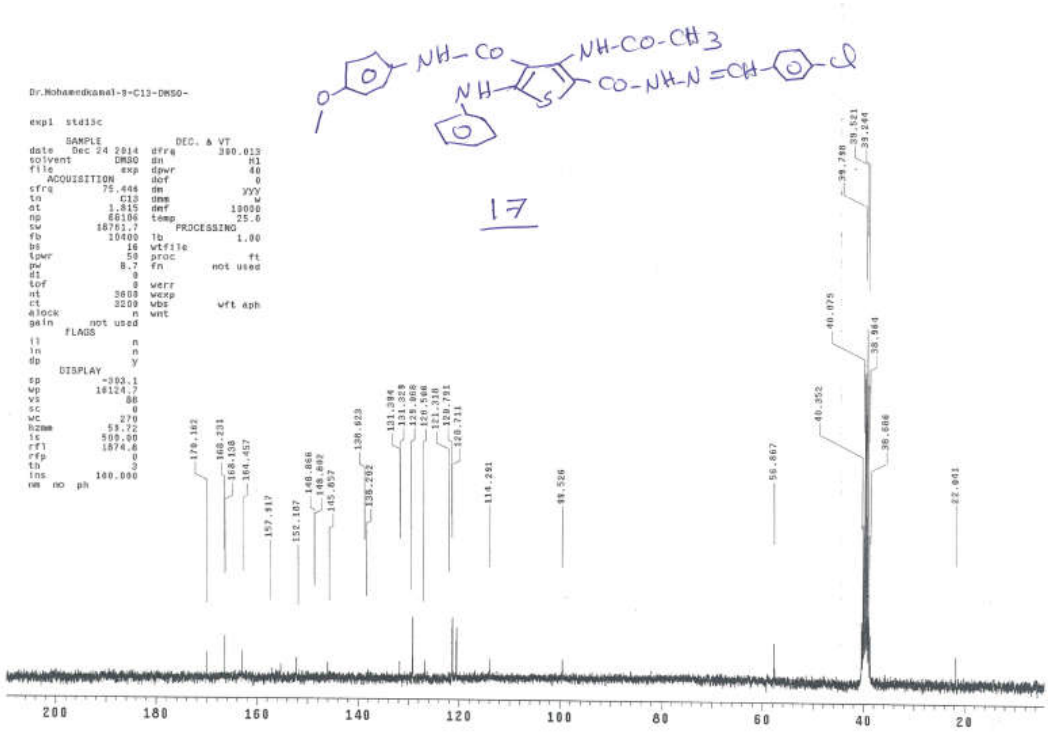


Figure S41: mass spectrum of compound 17

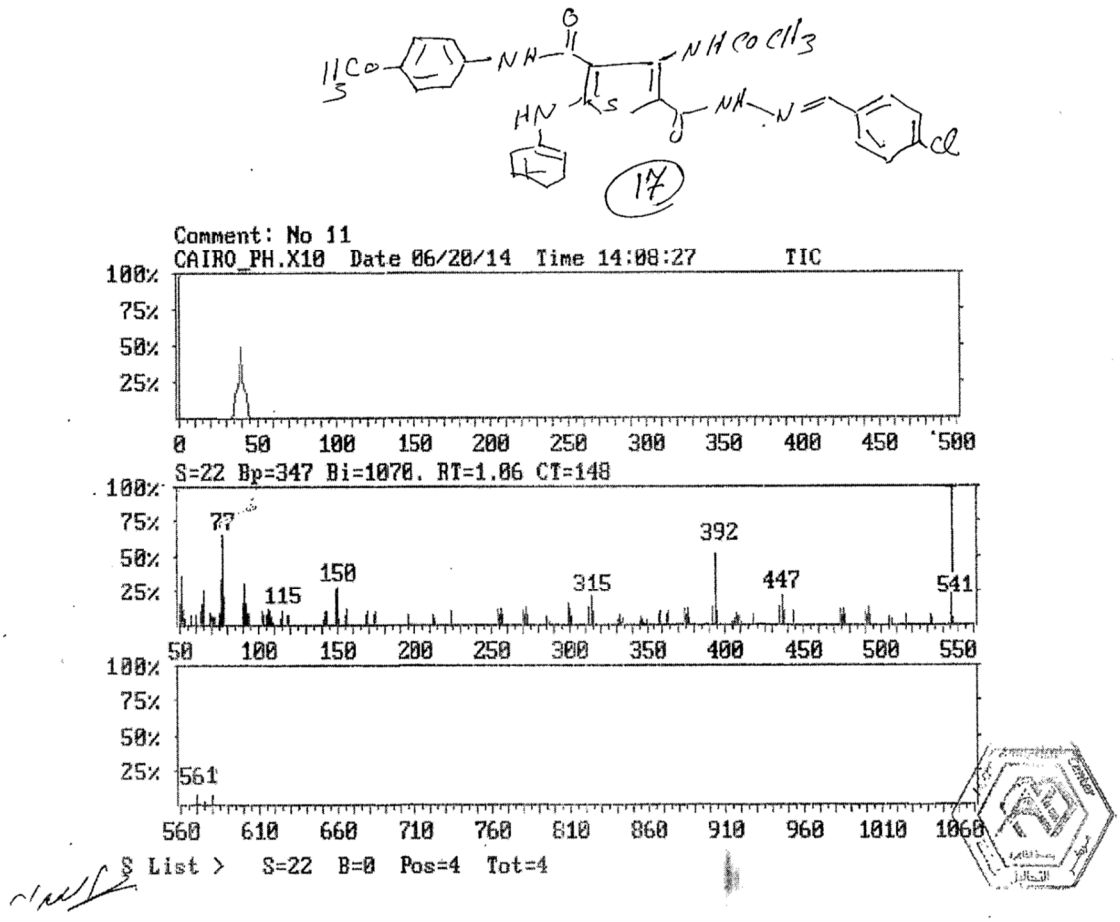


Figure S42: 1HNMR of compound 18

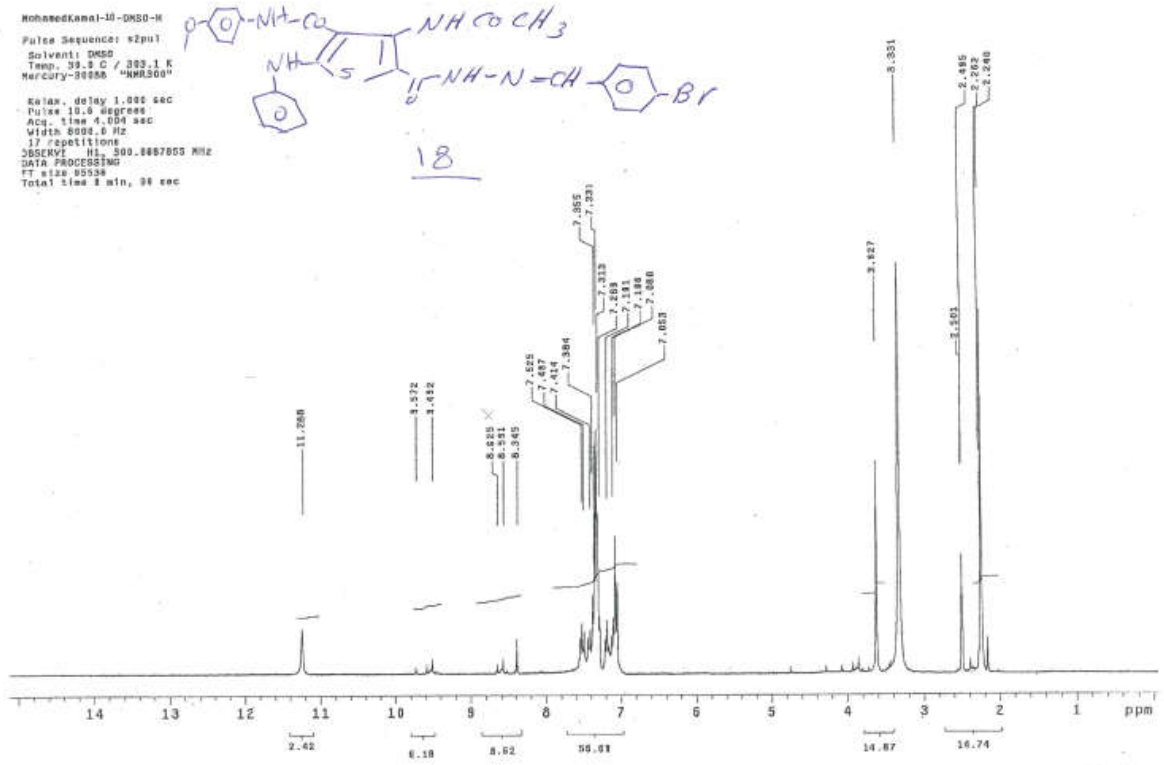


Figure S43: 13CNMR of compound 18

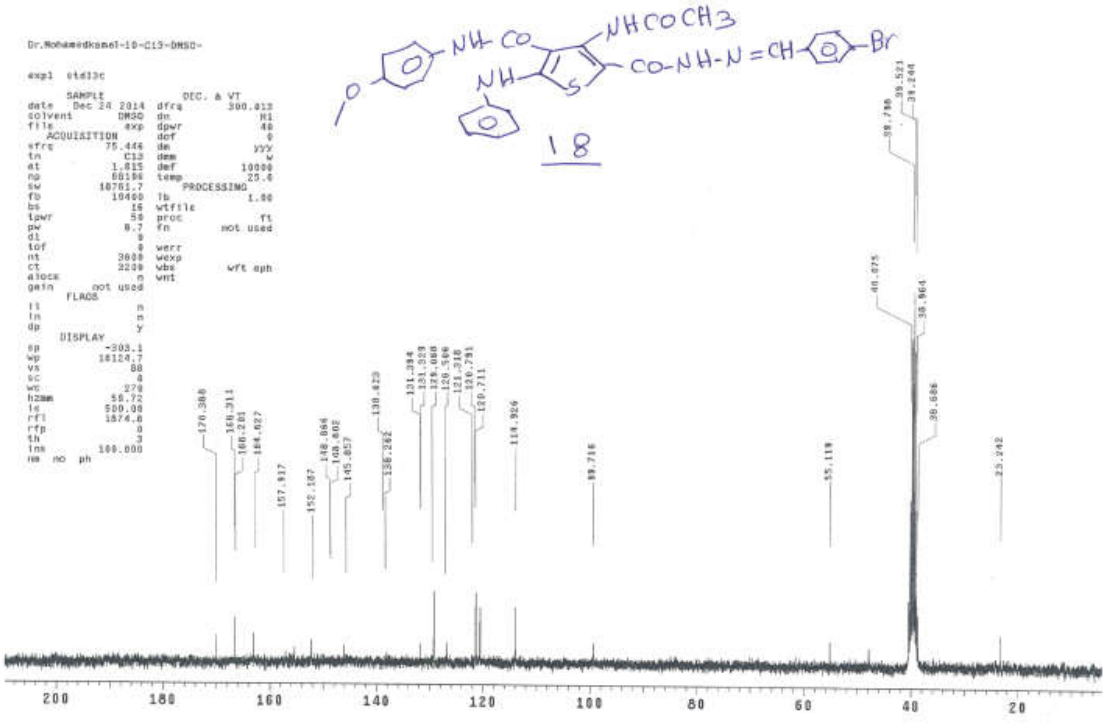


Figure S44: 1HNMR of compound 19

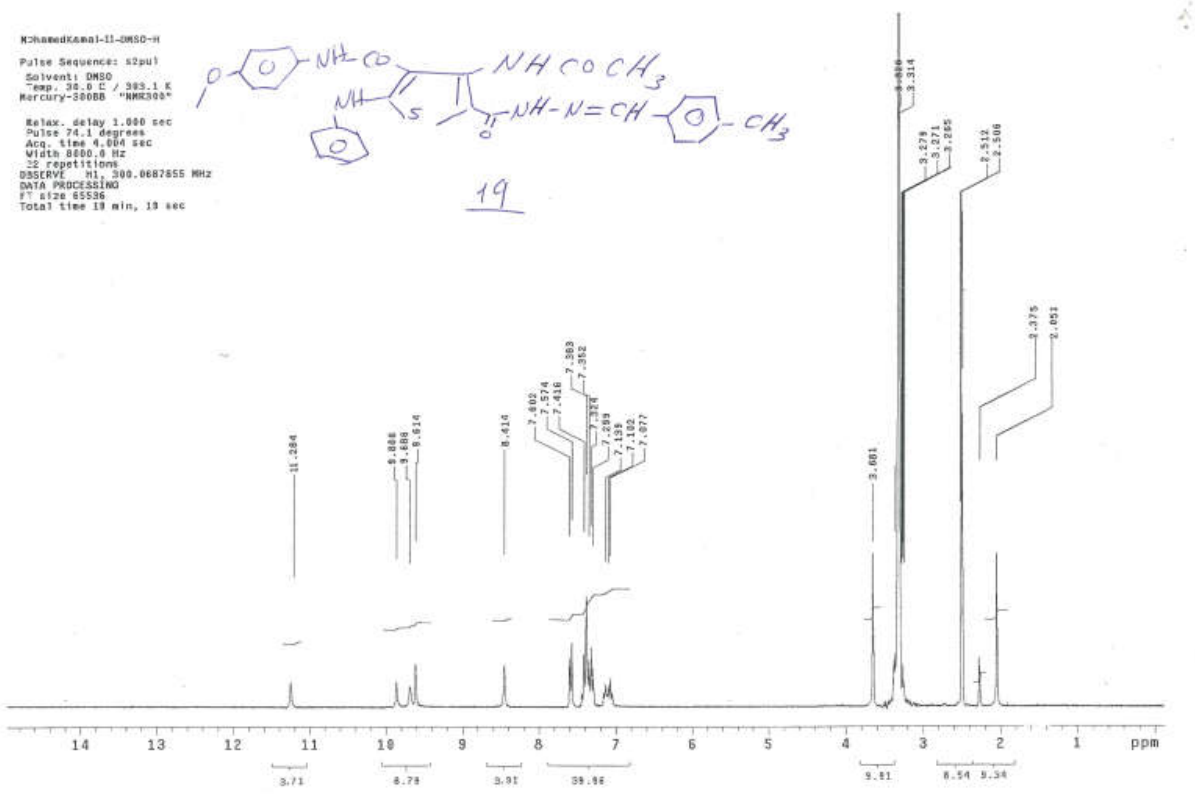


Figure S45: 13CNMR of compound 19

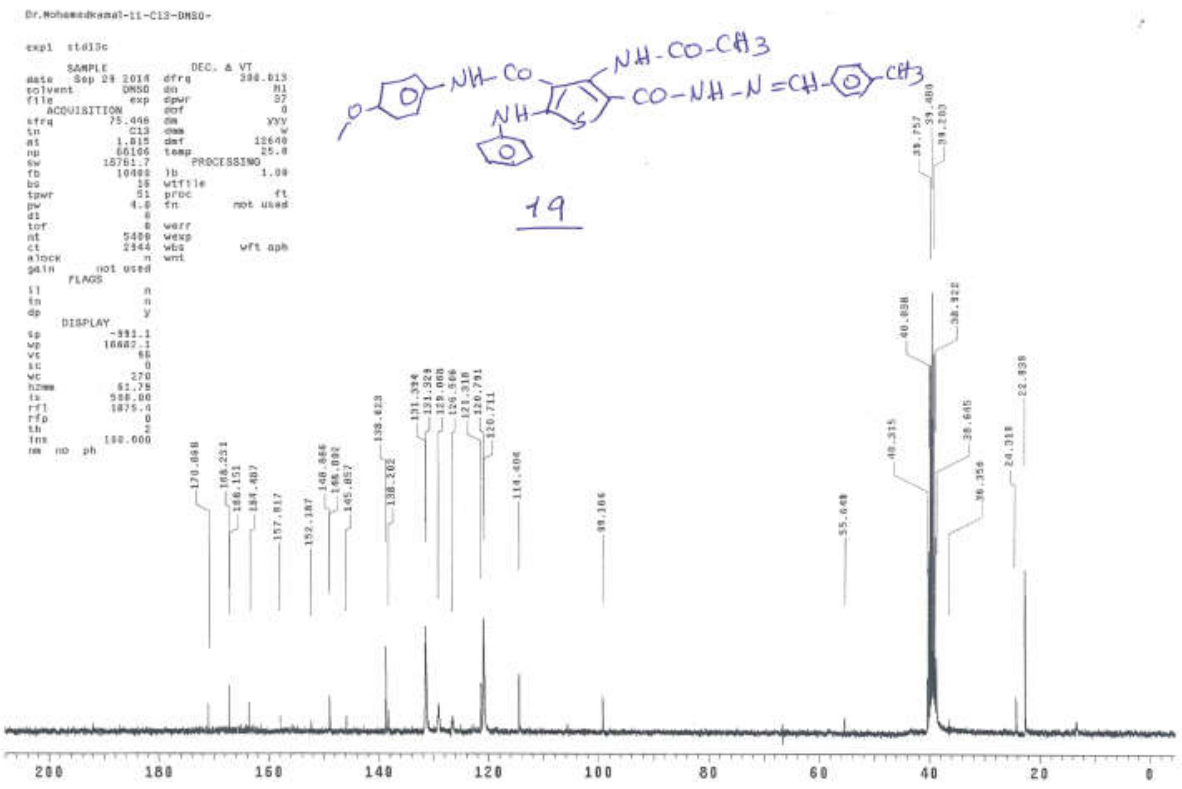
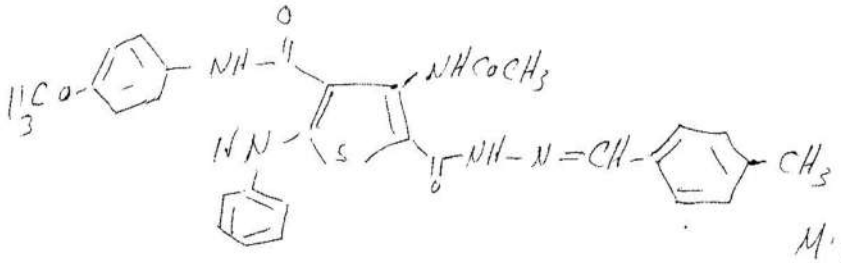


Figure S46: mass spectrum of compound 19



19

M.F: $C_{29}H_{24}N_4O_4S$

M.wt: 541.62

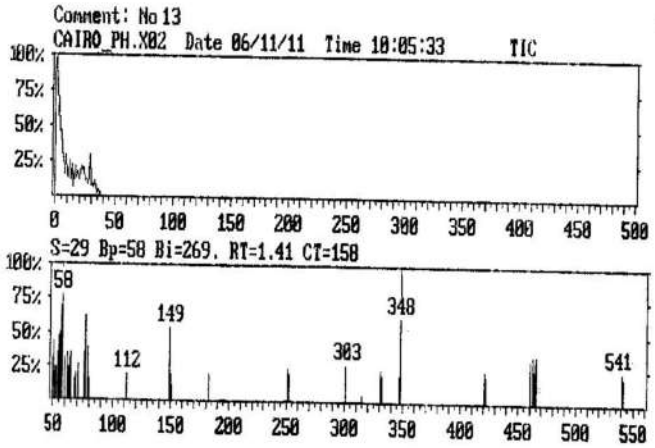


Figure S47: 1HNMR of compound 20

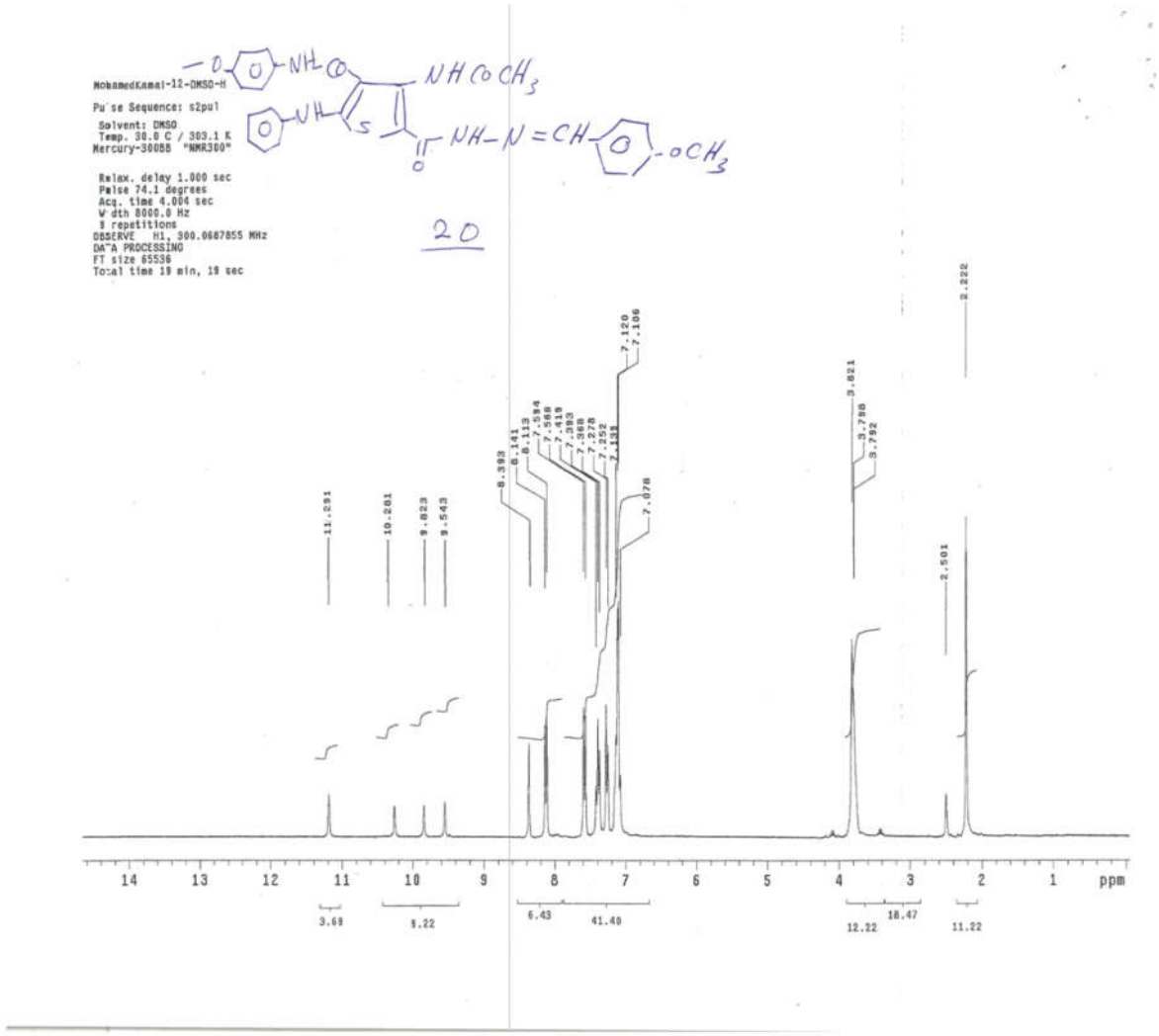


Figure S48: 13CNMR of compound 20

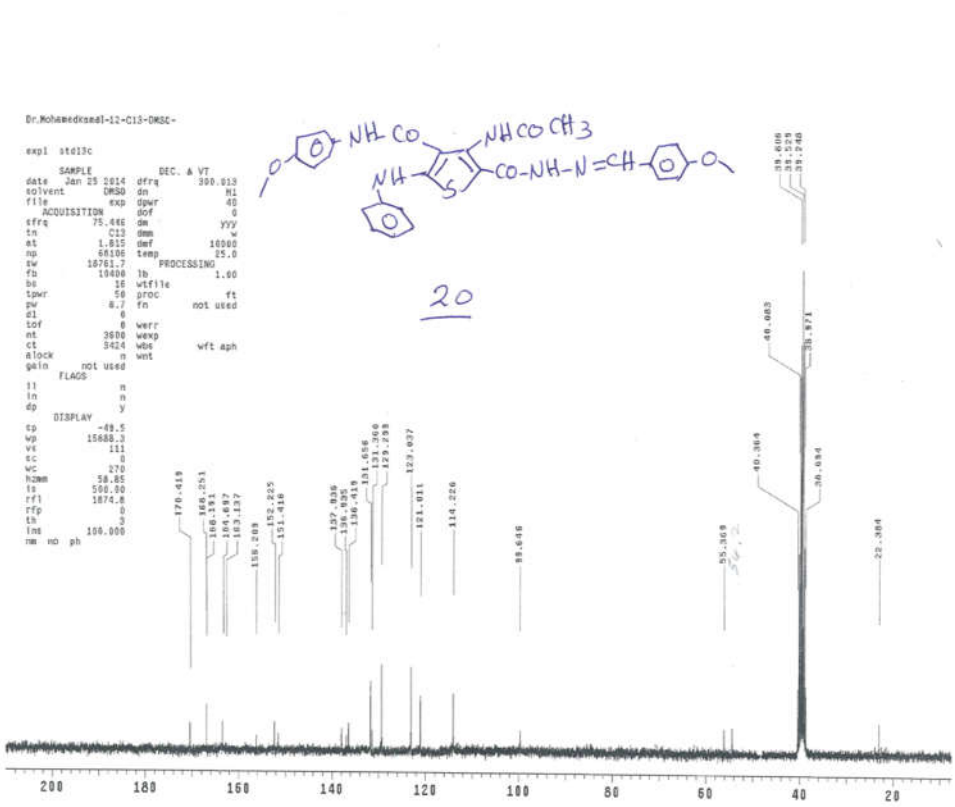


Figure S49: 1HNMR of compound 21

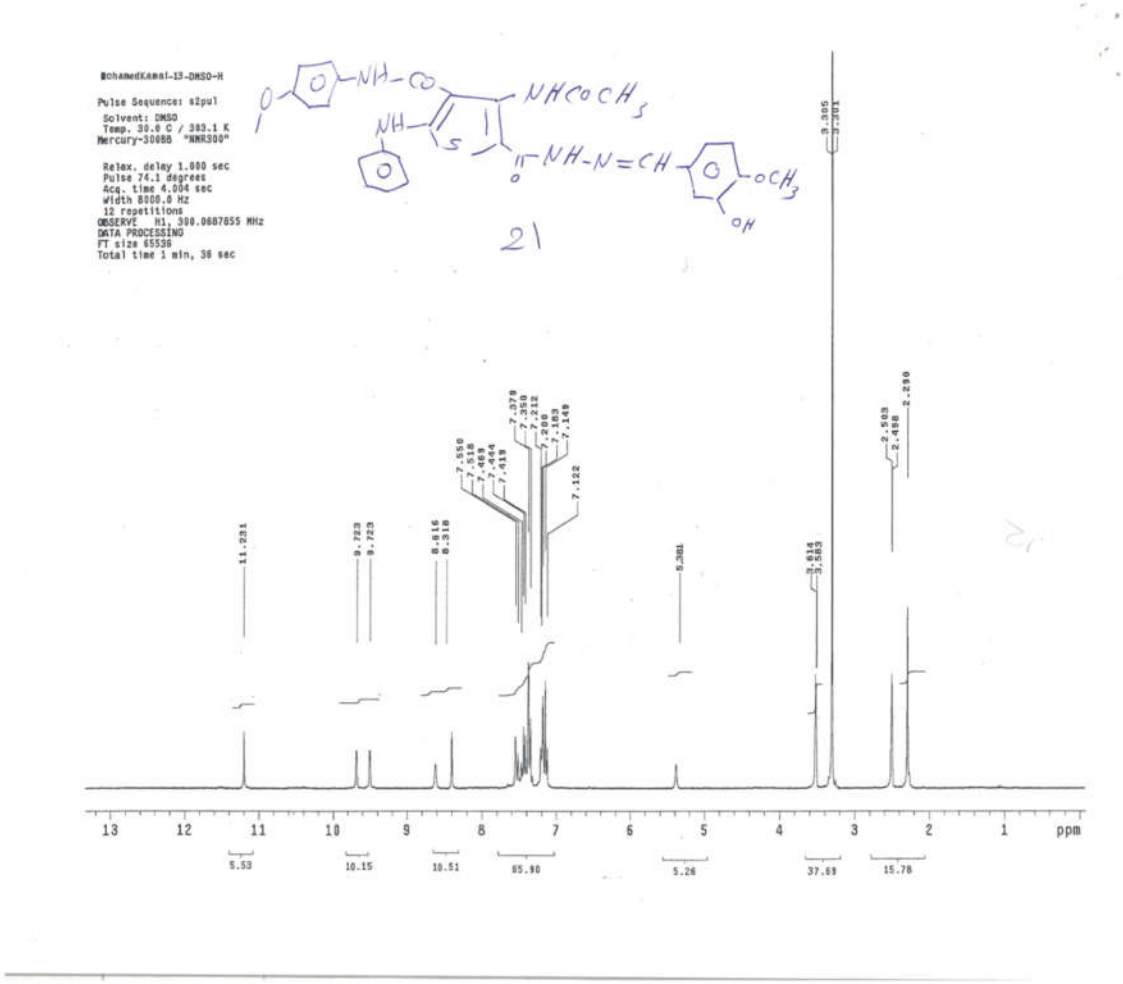


Figure S50: 13CNMR of compound 21

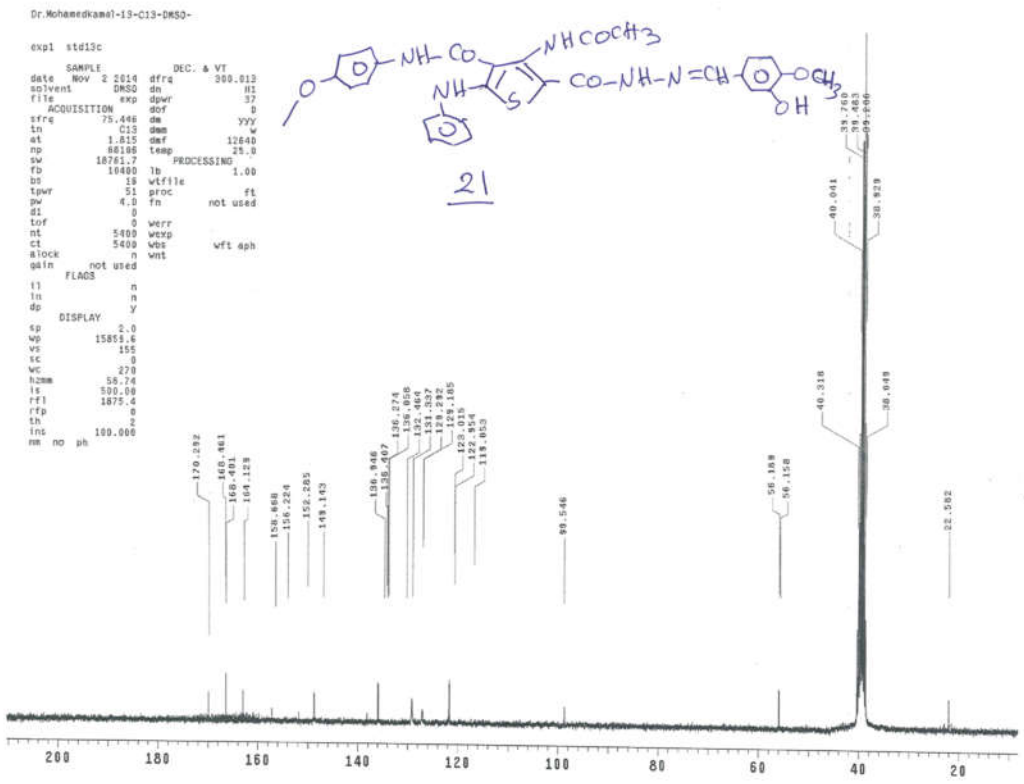


Figure S51: mass spectrum of compound 21

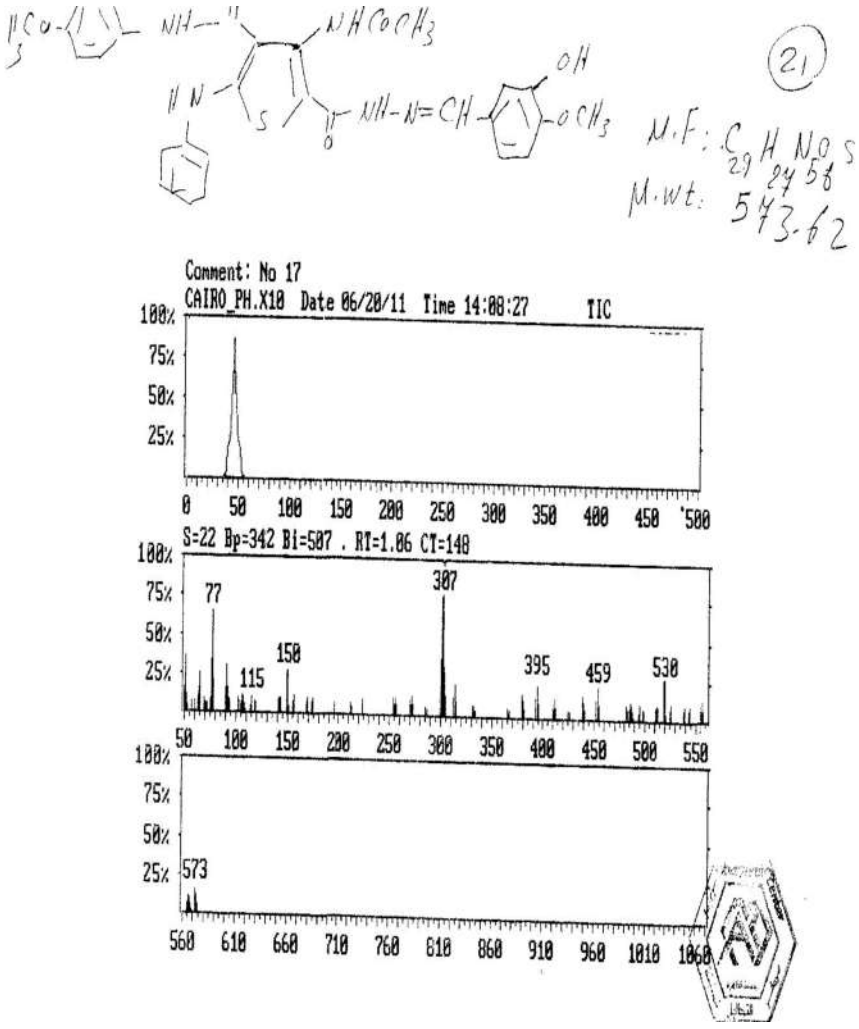


Figure S52: 1HNMR of compound 22

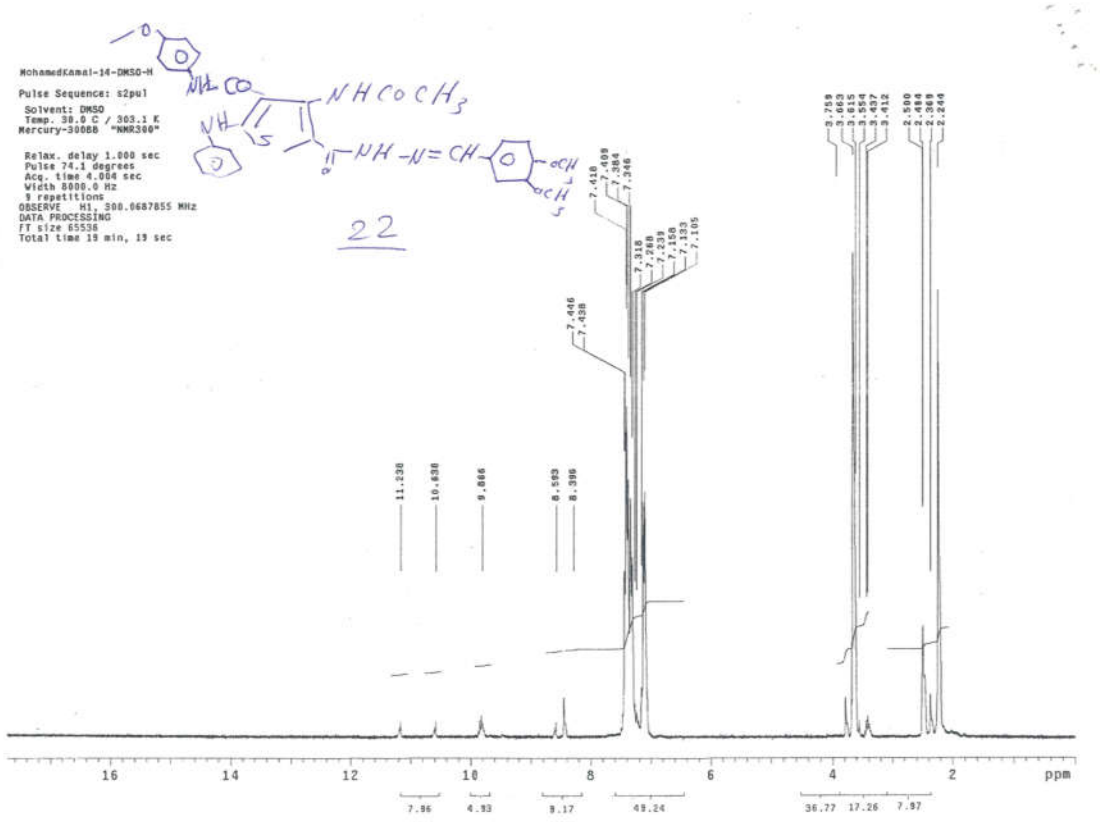


Figure S53: 13CNMR of compound 22

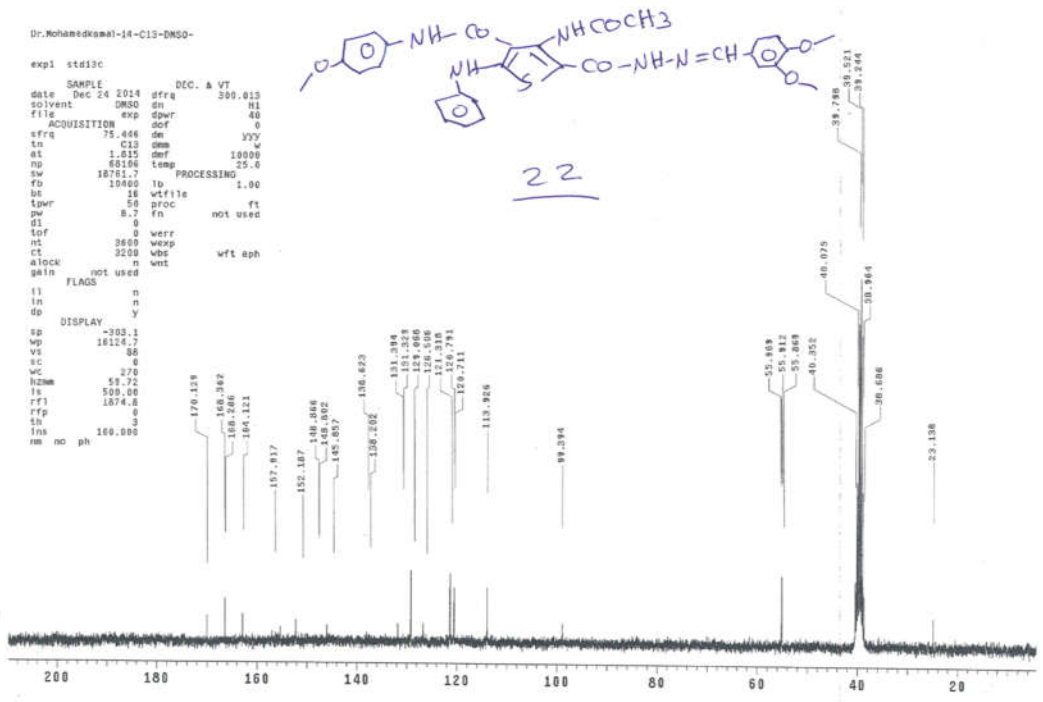
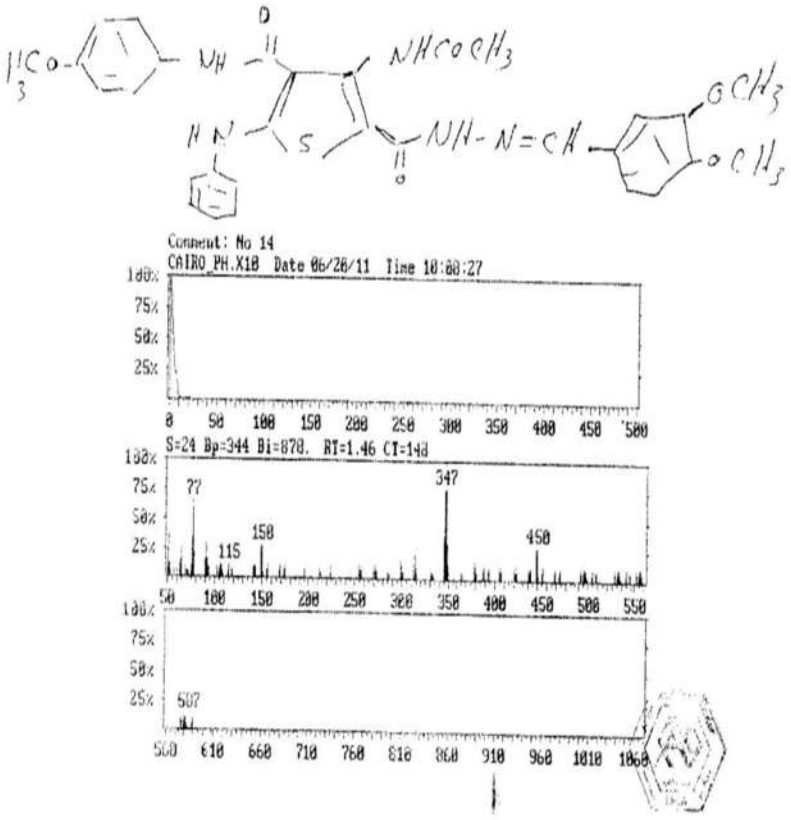


Figure S54: mass spectrum of compound 22



22

M.F. $C_{30}H_{29}NO_5S$

M.wt: 587.65

Figure S55: 1HNMR of compound 23

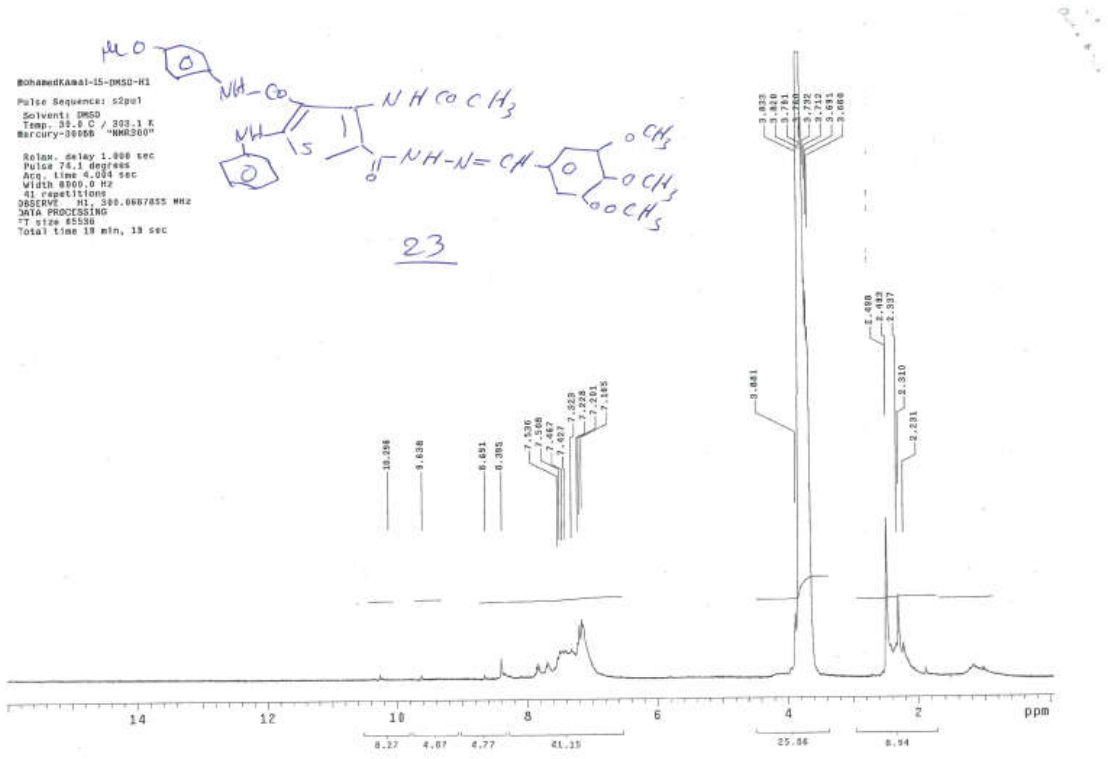


Figure S56: 13CNMR of compound 23

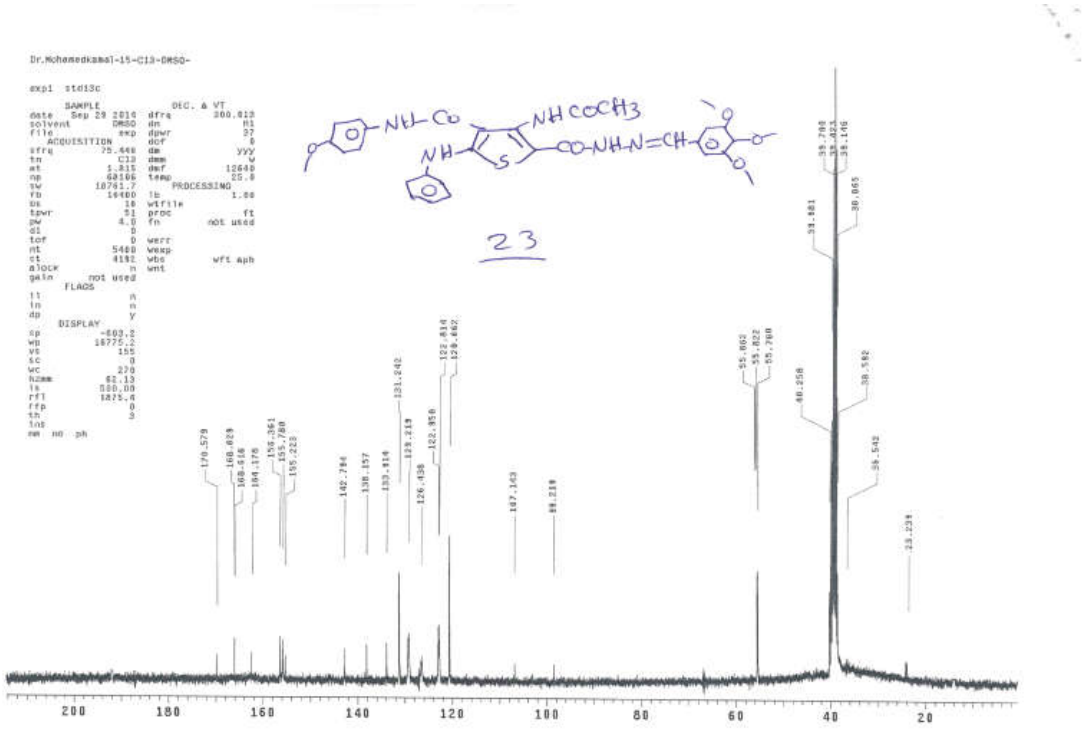


Figure S57: mass spectrum of compound 23

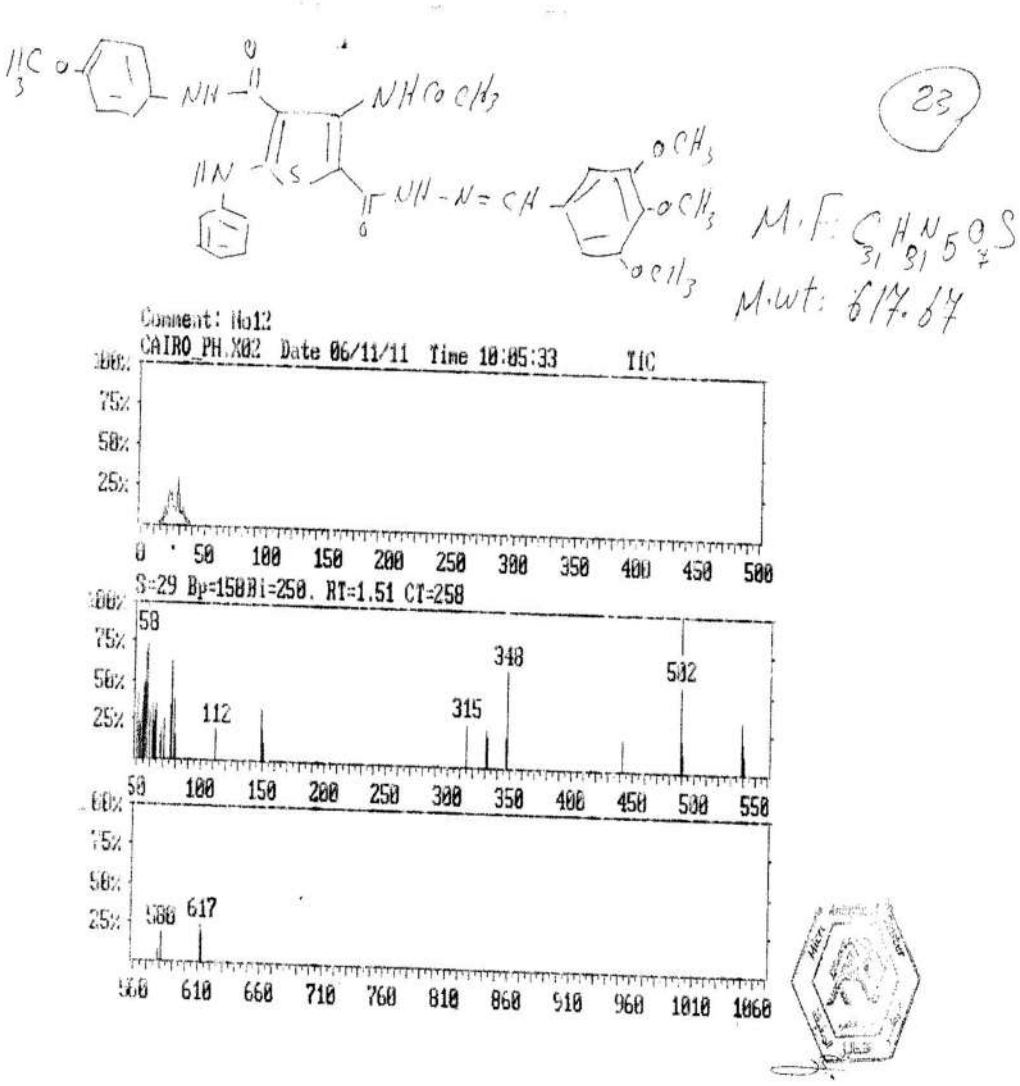


Figure S58: Docking pose displaying 2D interactions of sorafenib with VEGFR-2 active site.

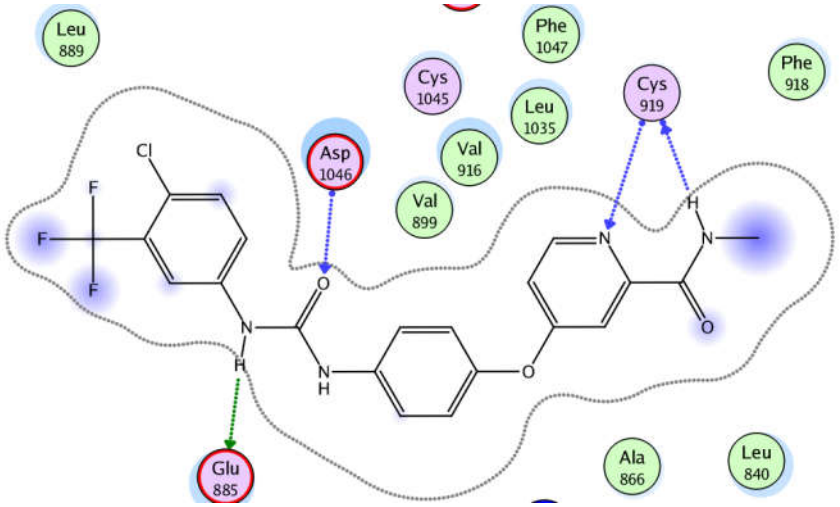


Table S1: Viability % with 8 different concentration (µM) for each compound of thiophene-3-carboxamides **4-13** and **16-23** and their IC_{50} (µM) on HCT-116 cell line. [a]

Compound	Viability % at each concentration (µM)						IC_{50}(µM)
	0.001	**0.01**	**0.1**	**1**	**10**	**100**	
4	102.02±7.8	92.6±6.7	81.2±4.5	91.1±2.3	87.22±1.2	75.73±0.9	64.11±7.51
5	100.01±7.8	85.2±7.1	72.01±6.2	60.12±5.4	48.61±2.9	33.54±1.1	7.83±0.61
6	101.02±7.8	95.23±6.6	80.6±5.7	64.47±4.9	55.31±3.6	45.35±2.64	3.13±.21
7	100.04±7.8	92.4±7.1	86.74±6.2	75.36±5.4	68.44±2.9	60.3±1.1	18.41±1.23
8	100.6±7.8	93.1±7.1	87.87±6.2	77.8±5.4	69.4±2.9	56.9±1.1	16.23±1.52
9	99.45±7.7	82.6±6.8	74.2±6.1	70.17±4.6	65.47±2.7	63.29±0.5	21.35±1.92
10	102.8±7.8	92.4±6.7	83.9±4.5	71.4±2.3	56.2±1.2	41.32±0.9	5.12±0.42
11	99.2±7.8	87.67±6.6	64.34±4.5	54.54±2.1	62.89±1.2	80.26±1.03	52.21±5.54
12	102.3±7.8	90.41±6.7	83.9±4.5	81.47±2.3	72.66±1.2	86.48±0.9	60.11±7.41
13	98.1±7.7	87.28±7.2	76.04±6.8	65.21±4.2	53.64±2.7	50.34±1.6	10.28±1.31
16	100.9±7.8	93.54±7.1	87.14±6.2	77.3±5.4	64.21±2.9	58.37±1.1	19.21±1.46
17	101.06±7.8	95.14±6.6	82.46±5.7	74.21±4.9	61.32±3.6	50.87±2.6	9.24±1.02
18	99.7±7.8	91.31±6.6	85.14±4.5	72.78±2.1	59.65±1.2	47.34±1.08	7.41±0.62
19	100.2±7.8	90.17±7.1	80.48±6.2	76.37±5.4	76.26±2.9	76.07±1.1	21.45±1.82
20	99.4±7.8	86.12±6.6	72.55±4.5	59.4±2.1	46.8±1.2	40.2±1.05	3.12±0.31
21	100.24±7.8	83.73±7.1	61.44±6.2	46.39±5.4	35.64±2.9	29.1±1.1	4.32±0.11
22	102.6±7.8	81.28±6.7	63.54±4.5	48.14±2.3	39.42±1.2	32.36±0.6	5.33 ±0.37
23	99.05±7.8	95.63±6.6	86.12±4.5	78.39±2.1	56.34±1.2	43.25±1.06	6.46±0.49
Sorafenib	100.1±7.8	85.7±6.6	72.8±4.5	46.6±2.1	37.14±1.2	34.2±0.4	3.22±0.24

[a] Values given are means of three experiments

Table S2: Viability % with 8 different concentration (µM) for each compound of thiophene-3-carboxamides **4-13** and **16-23** and their IC_{50} (µM) on HepG-2 cell line. [a]

Compound	Viability % at each concentration (µM)						IC_{50}(µM)
	0.001	**0.01**	**0.1**	**1**	**10**	**100**	
4	102.05±7.8	90.3±6.7	82.41±4.5	88.6±2.3	90.37±1.2	95±0.9	74.32±5.98
5	99.14±7.8	86.1±6.6	72.38±4.5	45.28±2.1	33.16±1.2	30.14±0.4	1.92±0.12
6	102.3±7.8	89.6±6.7	70.36±4.5	58.31±2.3	46.21±1.2	39.74±0.9	3.51±0.22
7	98.1±7.6	88.31±6.7	81.22±5.9	75.88±4.7	68.24±2.5	62.26±0.9	24.31±1.96
8	101.9±7.8	92.12±6.6	85.61±5.7	77.21±4.9	61.65±3.6	53.89±2.6	10.42±1.08
9	97.2±7.7	91.09±6.8	84.37±6.1	71.64±4.6	52.39±2.7	50.33±0.5	14.26±1.23
10	100.3±7.7	86.36±7.2	75.24±6.8	68.38±4.2	54.11±2.7	46.24±1.6	9.71±0.86
11	100.96±7.8	88.3±6.6	95.69±4.5	77.25±2.1	79.19±1.2	90.3±1.02	31.34±3.61
12	102.4±7.8	92.47±6.7	88.31±4.5	67.29±2.3	84.6±1.2	89.7±0.9	43.32±4.23
13	100.11±7.8	96.14±7.1	88.29±6.2	83.68±5.4	71.44±2.9	60.6±1.1	15.21±1.62
16	99.3±7.7	85.33±6.8	78.14±6.1	71.99±4.6	65.3±2.7	60.24±0.5	21.41±2.91
17	100.1±7.7	95.21±7.2	92.35±6.8	84.34±4.2	71.2±2.7	52.6±1.6	9.50±0.86
18	100.6±7.7	92.69±7.2	90.26±6.8	85.19±4.2	73.9±2.7	54.14±1.6	10.13±1.12
19	100.01±7.7	96.34±7.2	89.15±6.8	82.67±4.2	68.16±2.7	57.33±1.6	12.21±1.31
20	101.68±7.8	89.28±6.6	76.48±5.7	68.44±4.9	56.27±3.6	49.21±2.6	4.96±0.45
21	100.14±7.8	82.64±7.1	63.67±6.2	46.54±5.4	31.6±2.9	22.44±1.1	2.61±0.12
22	99.87±7.8	86.37±6.6	73.95±4.5	64.97±2.1	53.2±1.2	40.17±1.06	5.12±0.45
23	97.32±7.8	89.19±6.7	76.46±4.5	58.23±2.3	42.94±1.2	33.87±0.9	10.82±.065
Sorafenib	100.48±7.8	89.17±6.7	70.43±4.5	58.06±2.3	42.61±1.2	40.3±0.9	4.43±0.32

[a] Values given are means of three experiments

Table S3: cell cycle distribution of HepG-2 cells after treatment with thiophene-3-carboxamides 5 and 21 for 24 h with their IC_{50} values (1.92 and 2.61 μM) compared with control

Compound	Percentage cells in cell cycle phase			
	Apoptosis	G1	S	G2/M
Control	0.10±0.05	58.59±6.31	31.25±4.21	10.16±1.31
5	8.23±0.23	45.35±5.12	33.48±4.32	21.17±3.12
21	6.07±0.42	49.499±3.54	31.10±2.93	19.41±2.24

*The values given are means of three experiments.

Table S4: Percentage of the cells at the indicated stage after treatment with compounds **5** and **21** and staining with Annexin-V

Compound	Percentage cells			
	Normal cells Q3	Early apoptosis Q4	Late apoptosis Q2	Dead cells &cells debris Q1
Control	96.57±8.42	0.72±0.09	0.34±0.032	0.53±0.04
5	81.41±9.30	5.47±0.42	7.851±0.95	3.14±1.30
21	84.61±6.23	4.19±0.21	7.02±0.81	2.06±

Table S5: *In* vitro ELISA immunoassay measurement of p53, Bcl-2,Bax,caspase-3,caspase-7 proteins expression level in HepG-2cells after treatment for 24h with thiophene-3-carboxamides**5** (1.92 μM)or **21**(2.61 μM).

Compound	Conc.(pg/ml)				
	p53	Bcl-2	Bax	Caspase-3	Caspase-7
5	327.70±20.86	408.3±18.5	120.59±13.64	321.2±24.78	245.9±18.62
21	165.70±11.0	357.4±21.3	215.35±30.15	263.0±16.05	211.7±20.86
Control	96.29±13.15	899.0±32.9	18.19±1.29	28.59±1.14	35.64±13.15

*The values given are means of three experiments.

Table S6: VEGFR-2 enzyme activity % at the indicated concentration of inhibitors (μM)[a]

Compound	Enzyme activity % at each concentration (μM)					IC_{50}(μM)
	0.01	0.1	1	10	100	
5	98.±7.21	61.34±6.85	41.11±4.22	29.61±2.72	16.54±1.60	0.59±0.21
6	93.±7.83	66.22±6.72	51.31±4.50	35.42±2.34	22.33±1.20	0.93±0.19
10	98.±7.61	86.12±6.74	79.11±4.52	71.76±2.33	68.78±1.22	3.92±0.16
17	96.14±7.13	88.29±6.23	83.68±5.41	71.44±2.90	60.62±1.12	5.91±0.23
20	96.±7.87	79.41±6.61	65.52±5.73	48.61±4.81	35.11±3.61	1.71±0.21
21	99.±6.33	83.21±5.32	63.21±2.11	46.11±1.23	28.31±2.0.6	1.29±0.13
22	96.±7.85	81.33±6.65	65.34±4.54	44.32±2.11	38.12±1.21	1.80±0.17
23	100±7.84	95.42±6.71	82.09±4.52	71.14±2.33	72.22±1.26	5.21± 0.32
Sorafenib	89.17±6.71	70.43±4.50	58.06±2.31	42.61±1.22	30.31±0.94	2.07±0.15

[a] Values given are means of three experiments

Table S7: β-tubulin polymerization inhibition percentage for compounds **5** and **21** at their IC_{50}values on HepG-2 cells [a]

Compound	percentage β-tubulin polymerization inhibition	IC_{50}(μM)
5	72.61±4.21	1.92
21	85.95±6.51	2.61
Colchicine	90.62±7.32	6.6

[a] Values given are means of two experiments.

Table S8: Calculated descriptors (Jurs-RPCS, Rad of Gyration, PMI-mag, PMI-X and PMI-Z) of the training and test sets.

Compound	Jurs-RPCS	Rad of Gyration	PMI-mag	PMI-X	PMI-Z
4	0.46334	6.11878	6275.22	513.81	4384.21
5	0.46297	6.11979	6275.33	513.819	4384.24
6	0.48150	5.74944	6231.28	513.216	4372.26
7	0.48923	5.73846	6230.26	513.206	4372.09
8	0.48728	5.73861	6230.25	513.205	4372.08
9	0.48813	5.73846	6230.27	513.207	4372.10
10	0.48857	5.73844	6230.27	513.207	4372.10
11	0.47628	5.98973	6253.25	513.303	4375.28
13	0.46399	6.09423	6273.34	513.813	4384.16
16	0.46114	6.12616	6275.82	513.821	4384.26
17	0.45895	6.14137	6276.12	513.822	4384.46
19	0.48142	5.74949	6231.27	513.215	4372.25
20	0.49974	5.73711	6230.17	513.202	4372.07
22	0.49747	5.73749	6230.19	513.203	4372.07
12	0.60342	6.76955	6,828.57	445.616	5,033.59
18	0.60342	6.76454	6,819.87	445.119	5,027.21
21	0.58567	6.76782	6,824.31	445.008	5,030.22