Supporting Information

Investigating the Anti-inflammatory Potential of *N*-Amidic Acids Organoselenium Candidates: Biological Assessments, Molecular Docking, and Molecular Dynamic Simulations

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SI1. Chemistry

1.1. Material and methods

Melting points were recorded in degree centigrade on a Gallenkamp instrument using the standard open capillary method. The IR spectra were recorded on FTIR 5000 Mattson spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO–d_6 on a Varian 400 and 500 Spectrophotometer (^{1}H: 400 and 500 MHz, ^{13}C: 101 and 125 MHz) at 295 K. The chemical shifts (δ) are given in parts per million (ppm) downfield relative to tetramethyl silane (TMS). Mass Spectra were recorded on Bruker micrOTOFQ II APPI mass spectrometer. Compounds **2–6** were obtained according to our literature reports [1-2], and the new compounds **7**–**12** obtained according to our literature reports[3].

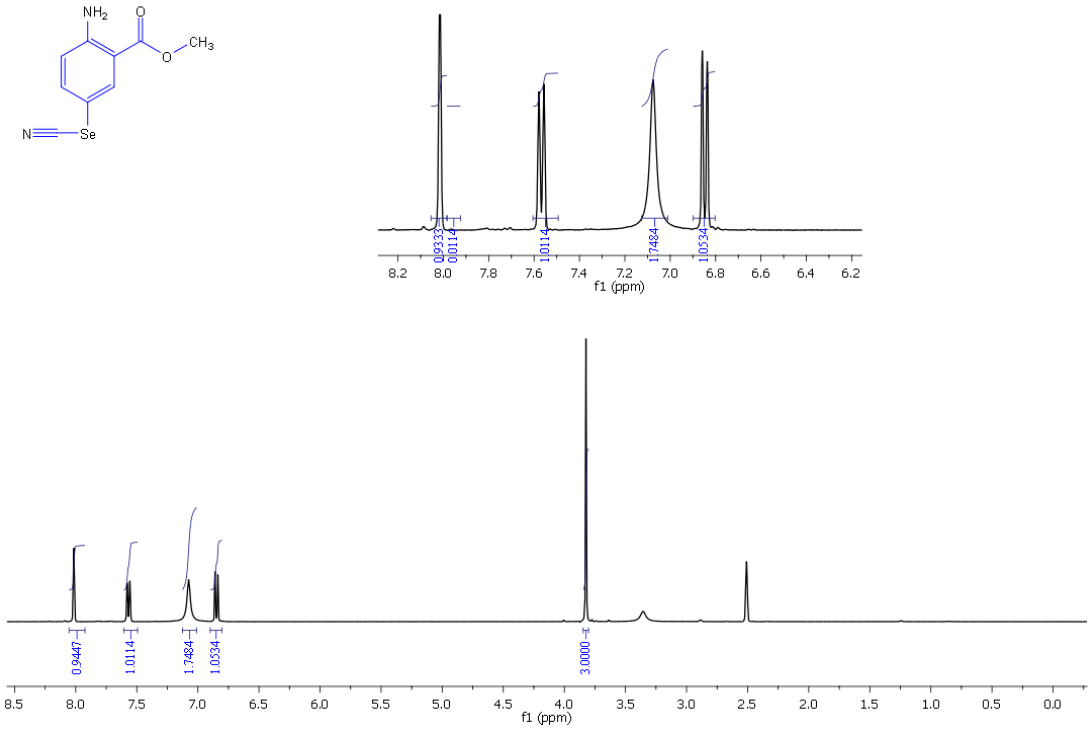
1.2. Synthesis and characterization

The synthesis of OSe maleanilic 7, 9, and 11 and succinanilic 8, 10, and 12 derivatives

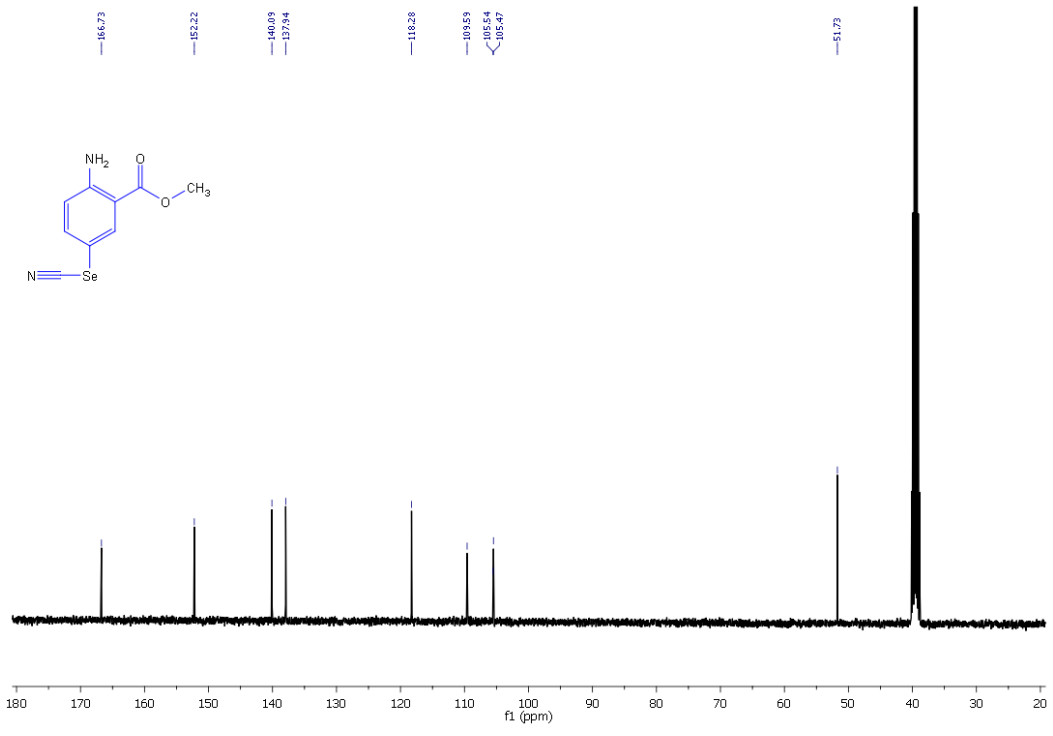
Maleic or succinic anhydride (1.3 mmol) was added to OSe amine (1.0 mmol) in methylbenzene (3.0 mL). The solution was stirred for 8 hrs. Then, the formed precipitate was filtered and washed with warm methylbenzene and water. The acids were obtained in enough purity, and no further purifications were needed.

Synthesis of methyl 2-amino-5-selenocyanatobnzoate (2) [1, 4]

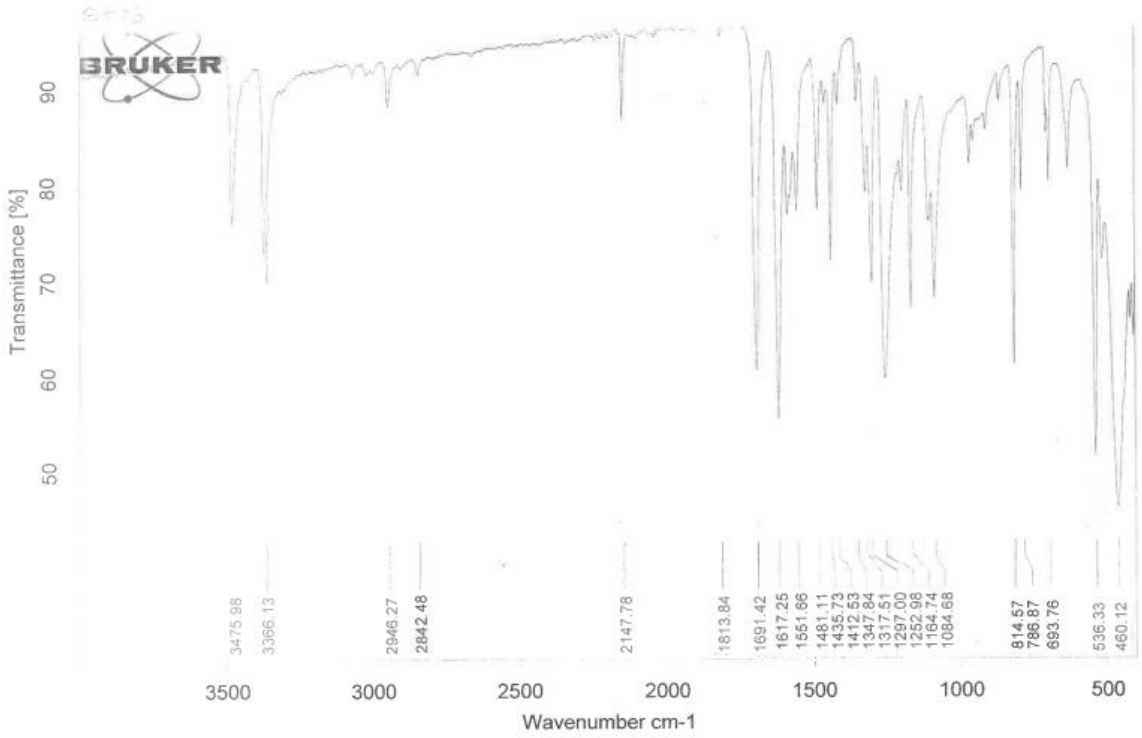
Methyl 2-amino-5-selenocyanatobenzoate (**2**) was synthesized from methyl 2-aminobenzoate (12.5 mmol, 1.80 g) with triselenium dicyanide prepared *in situ* from malononitrile (15 mmol, 1.00 g) and selenium dioxide (30 mmol, 3.30 g). It was isolated as reddish solid; yield:3.07 g (96%); m.p. = 118–119 °C; Rf = 0.4 (petroleum ether / ethyl acetate 4:2, *v*/*v*). IR (KBr): ν 3475 (N-H), 3366 (N-H), 2946 (C_{aliph}-H), 2842 (C_{aliph}-H), 2148 (CN), 1691 (C=O), 1551 (C=C), 1253 (C_{Ar}–N), 1085 (C–O), 910, 815 (C-H bending), 556 (C-Se), 536 (C-H rocking), 460; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H, Ar-H), 7.57 (d, J = 8.8 Hz, 1H, Ar-H), 7.08 (s, br, 2H, NH_2), 6.84 (d, *J* = 8.8 Hz, 1H, Ar-H), 3.82 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.73, 152.22, 140.09, 137.94, 118.28, 109.59, 105.54, 105.47, 51.73. MS (EI, 70 ev) m/z (%) = 259.35 (M+3H, 2.39), 117 (29.02), 87 (26.6), 75 (2.70), 59 (100.0, base peak).



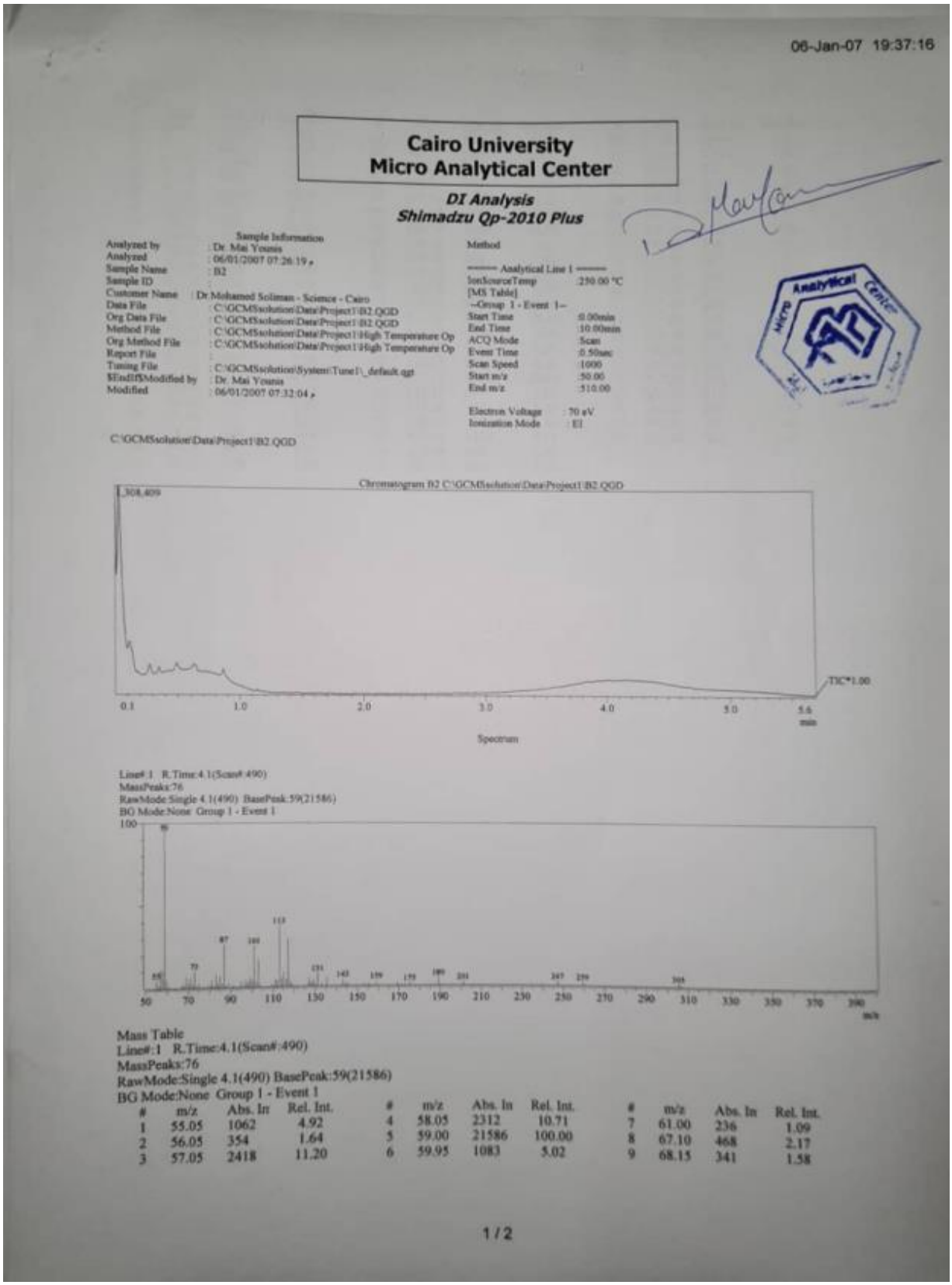
^{1}H NMR chart of compound **2**



^{13}C NMR chart of compound **2**



IR chart of compound **2**



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Cairo University
Micro Analytical Center

DI Analysis
Shimadzu Qp-2010 Plus

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2	56.05	354	1.64	5	59.00	21586	100.00	8	67.10	468	2.17
3	57.05	2418	11.20	6	59.95	1083	5.02	9	68.15	341	1.58

1 / 2

Mass chart of compound **2**

#	m/z	Abs. In	Rel. Int.
10	69.05	1515	7.02
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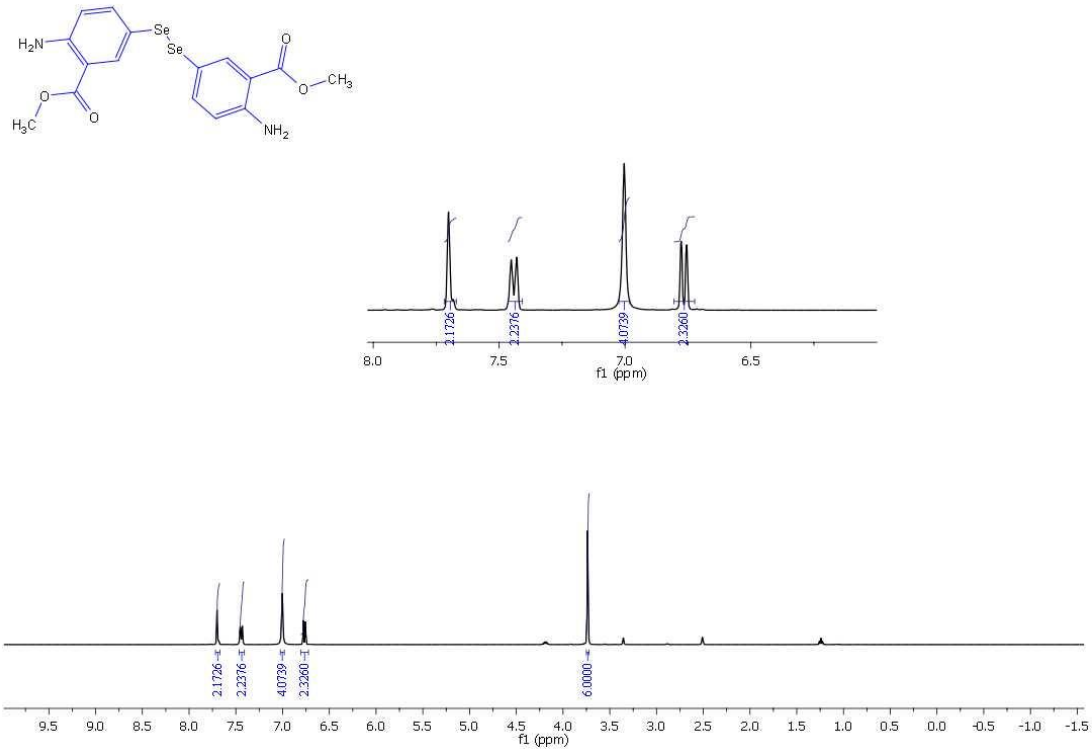
12	71.05	1365	6.32
13	72.05	440	2.04
14	73.00	2258	10.46
15	74.00	302	1.40
16	75.05	583	2.70
17	77.00	268	1.24
18	79.00	223	1.03
19	80.10	324	1.50
20	81.10	954	4.42
21	82.15	315	1.46
22	83.10	1628	7.54
23	84.10	481	2.23
24	85.05	1397	6.47
25	86.05	492	2.28
26	87.05	5752	26.65
27	88.00	314	1.45
28	89.05	560	2.59
29	91.10	327	1.51
30	94.10	202	0.94
31	95.10	807	3.74
32	96.10	278	1.29
33	97.10	945	4.38
34	98.15	599	2.77
35	99.10	1268	5.87
36	100.15	840	3.89
37	101.10	5503	25.49
38	102.15	699	3.24
39	103.10	3649	16.90
40	104.10	322	1.49
41	109.10	401	1.86
42	110.10	220	1.02
43	111.10	969	4.49
44	112.15	807	3.74
45	113.10	8084	37.45
46	114.10	1199	5.55
47	115.10	2001	9.27
48	116.25	936	4.34
49	117.15	6264	29.02
50	118.15	607	2.81
51	119.20	271	1.26
52	126.15	310	1.44
53	127.10	1102	5.11
54	128.15	589	2.73
55	129.10	740	3.43
56	130.15	304	1.41
57	131.10	1722	7.98
58	133.15	432	2.00
59	135.20	1132	5.24
60	143.10	908	4.21
61	144.10	210	0.97
62	145.20	492	2.28
63	153.20	234	1.08
64	155.20	281	1.30
65	159.15	662	3.07
66	169.20	334	1.55
67	171.20	204	0.95
68	173.20	202	0.94
69	175.20	346	1.60
70	189.20	1038	4.81
71	201.15	502	2.33
72	247.20	575	2.66
73	259.35	515	2.39
74	260.40	207	0.96
75	305.40	401	1.86
76	306.40	281	1.30

2 / 2

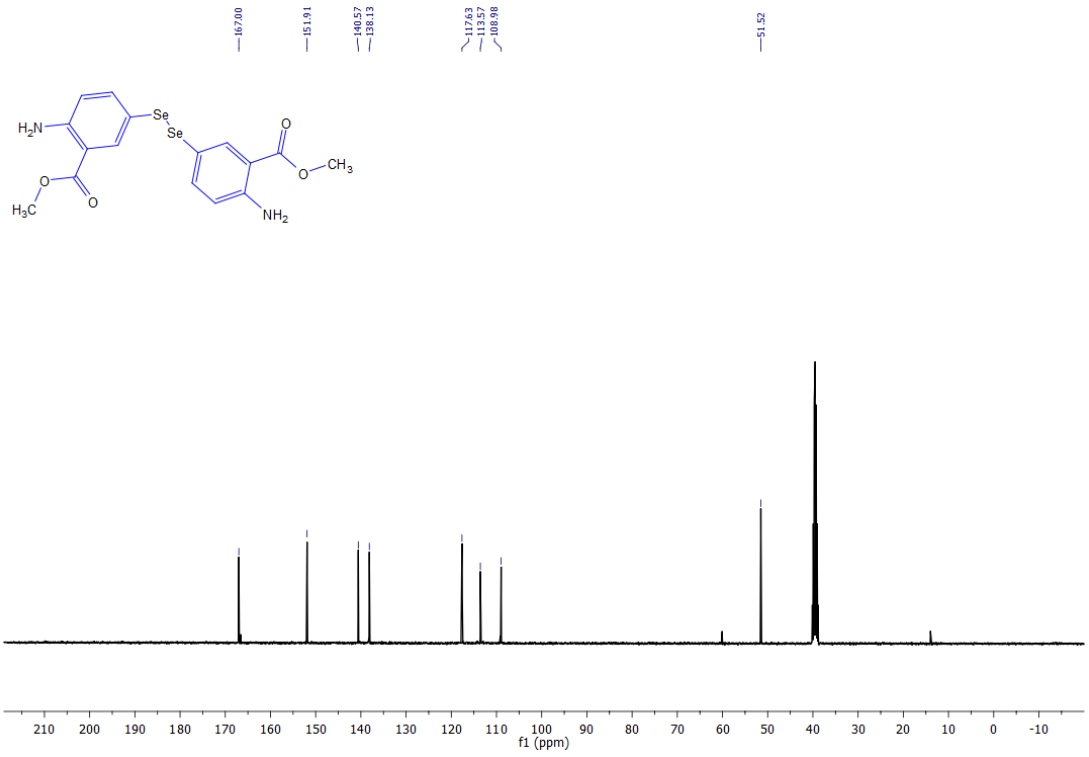
Mass chart of compound **2**

Synthesis of dimethyl 5,5'-diselanediylbis(2-aminobenzoate) (3)[1, 4]

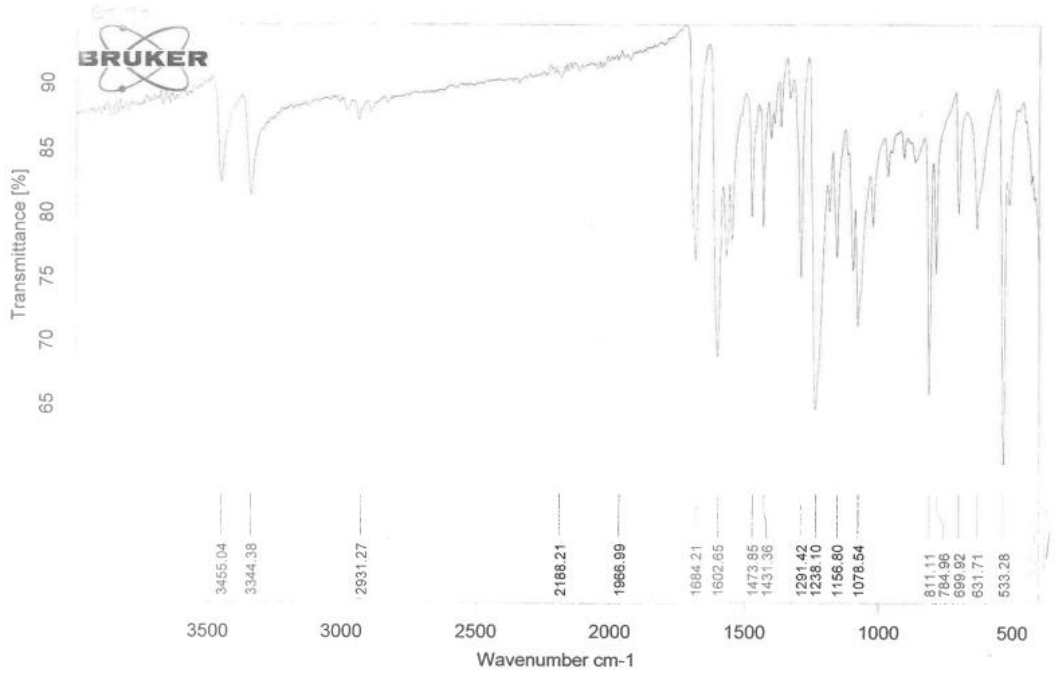
Compound dimethyl 5,5-diselanediylbis(2-aminobenzoate) (**3**) was synthesized from methyl 2-amino-5-selenocyanatobenzoate (4 mmol, 1.00 g) and sodium hydroxide (4 mmol, 1.60 g) in anhydrous ethanol (20 mL). Dimethyl 5,5'-diselanediylbis(2-aminobenzoate) (**3**) appeared as a single compound on TLC and was isolated as a yellow solid; yield: 1.69 g (92%); m.p. = 138–139 °C; Rf = 0.5 (petroleum ether / ethyl acetate 4:3, *v*/*v*). IR (KBr): ν 3455 (N-H), 3344 (N-H), 2931 (C_{aliph}-H), 2890 (C_{aliph}-H), 2168 (CN), 1684 (C=O), 1560 (C=C), 1603, 1238 (C_{Ar}–N), 1079 (C–O), 811, 784 (C-H bending), 699 (C-H rocking), 533 (C-Se); ^{1}H NMR (400 MHz, DMSO- d_6) δ 7.70 (s, 2H, Ar-H), 7.44 (d, J = 8.6 Hz, 2H, Ar-H), 7.00 (s, 4H, $2NH_2$), 6.77 (d, J = 8.6 Hz, 2H, Ar-H), 3.74 (s, 6H, $2OCH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.00, 151.91, 140.57, 138.13, 117.63, 113.57, 108.98, 51.52. MS (EI, 70 ev) *m/z* (%) = 460.15 (M+H, 20.76), 459.15 (M, 5.20) or 230 (24.42), 119 (9.45), 91 (100.0, base peak), 65 (8.88).



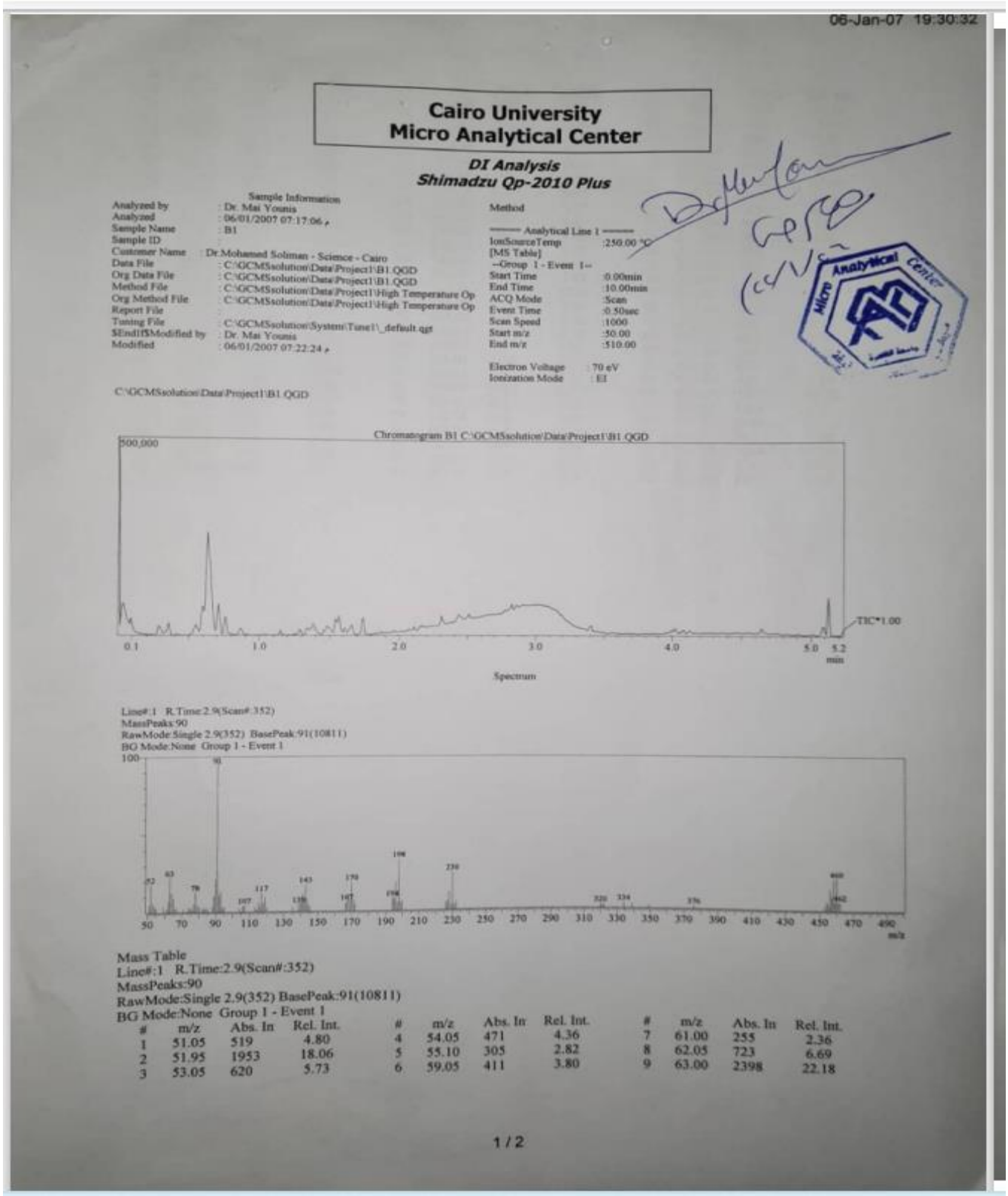
^{1}H NMR chart of compound **3**



^{13}C NMR chart of compound **3**



IR chart of compound **3**



06-Jan-07 19:30:32

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Micro Analytical Center

DI Analysis
Shimadzu Qp-2010 Plus

Sample Information

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Chromatogram B1 C:\GCMSsolution\Data\Project1\B1.QGD

500,000

TIC*1.00

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1	51.05	519	4.80	4	54.05	471	4.36	7	61.00	255	2.36
2	51.95	1953	18.06	5	55.10	305	2.82	8	62.05	723	6.69
3	53.05	620	5.73	6	59.05	411	3.80	9	63.00	2398	22.18

1 / 2

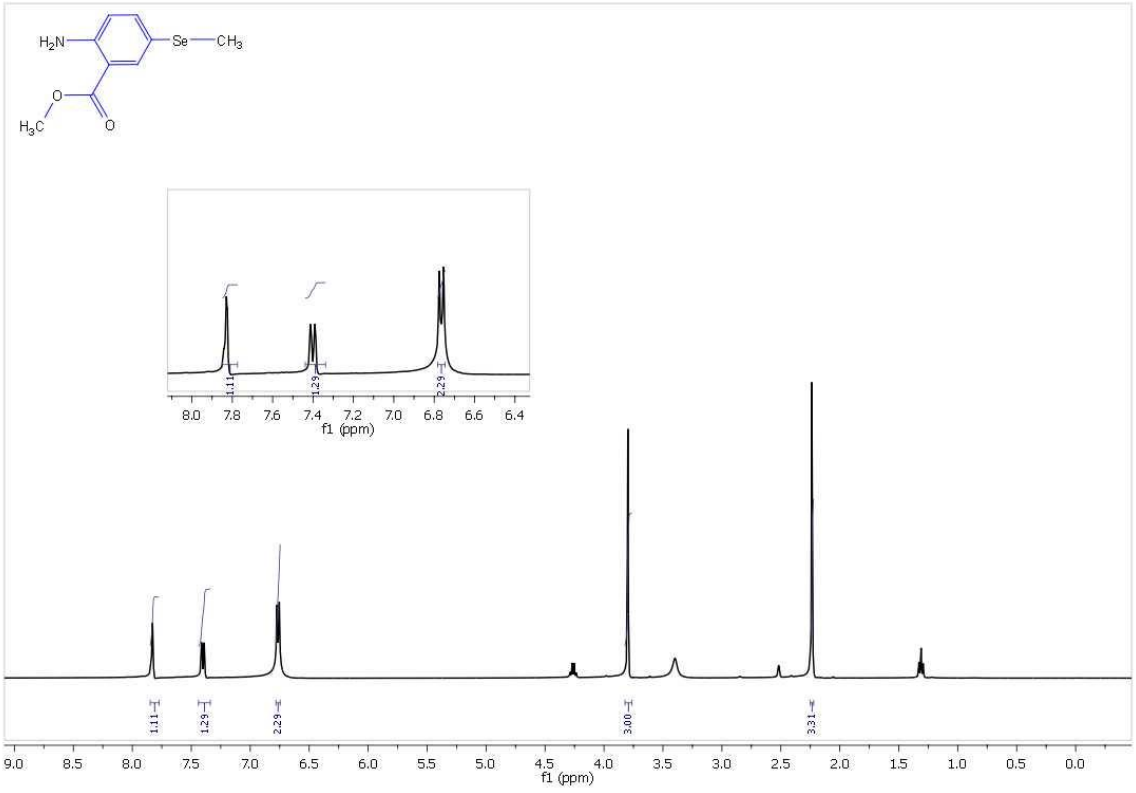
Mass chart of compound **3**

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
10	64.05	1311	12.13	37	113.00	308	2.85	64	198.00	3602	33.32
11	65.05	960	8.88	38	113.90	222	2.05	65	199.00	591	5.47
12	66.00	278	2.57	39	114.90	636	5.88	66	200.05	690	6.38
13	67.00	247	2.28	40	116.05	385	3.56	67	226.05	505	4.67
14	71.00	202	1.87	41	117.00	1319	12.20	68	227.05	655	6.06
15	74.00	313	2.90	42	118.05	599	5.54	69	228.00	1222	11.30
16	75.00	255	2.36	43	119.10	1022	9.45	70	229.15	316	2.92
17	76.00	214	1.98	44	120.10	310	2.87	71	230.05	2640	24.42
18	77.05	571	5.28	45	135.10	289	2.67	72	231.05	347	3.21
19	78.05	1366	12.64	46	139.00	482	4.46	73	232.05	594	5.49
20	79.10	466	4.31	47	140.00	614	5.68	74	320.00	290	2.68
21	80.10	388	3.59	48	141.05	1196	11.06	75	321.00	222	2.05
22	82.10	233	2.16	49	142.05	619	5.73	76	322.00	228	2.11
23	83.10	260	2.40	50	143.00	1894	17.52	77	334.00	398	3.68
24	84.10	220	2.03	51	144.00	850	7.86	78	339.00	318	2.94
25	85.10	278	2.57	52	144.95	409	3.78	79	349.00	230	2.13
26	88.05	377	3.49	53	166.05	493	4.56	80	376.00	215	1.99
27	89.05	1081	10.00	54	167.05	639	5.91	81	453.00	263	2.43
28	90.05	2287	21.15	55	168.05	1148	10.62	82	454.20	604	5.59
29	91.05	10811	100.00	56	169.15	688	6.36	83	455.20	425	3.93
30	92.05	1150	10.64	57	170.05	2031	18.79	84	456.25	1479	13.68
31	92.95	1429	13.22	58	171.10	802	7.42	85	457.20	1015	9.39
32	94.00	254	2.35	59	172.10	420	3.88	86	458.20	2169	20.06
33	95.00	354	3.27	60	194.05	863	7.98	87	459.15	562	5.20
34	104.00	249	2.30	61	195.05	858	7.94	88	460.15	2244	20.76
35	106.10	398	3.68	62	196.00	1993	18.43	89	461.15	521	4.82
36	107.00	444	4.11	63	197.05	575	5.32	90	462.10	618	5.72

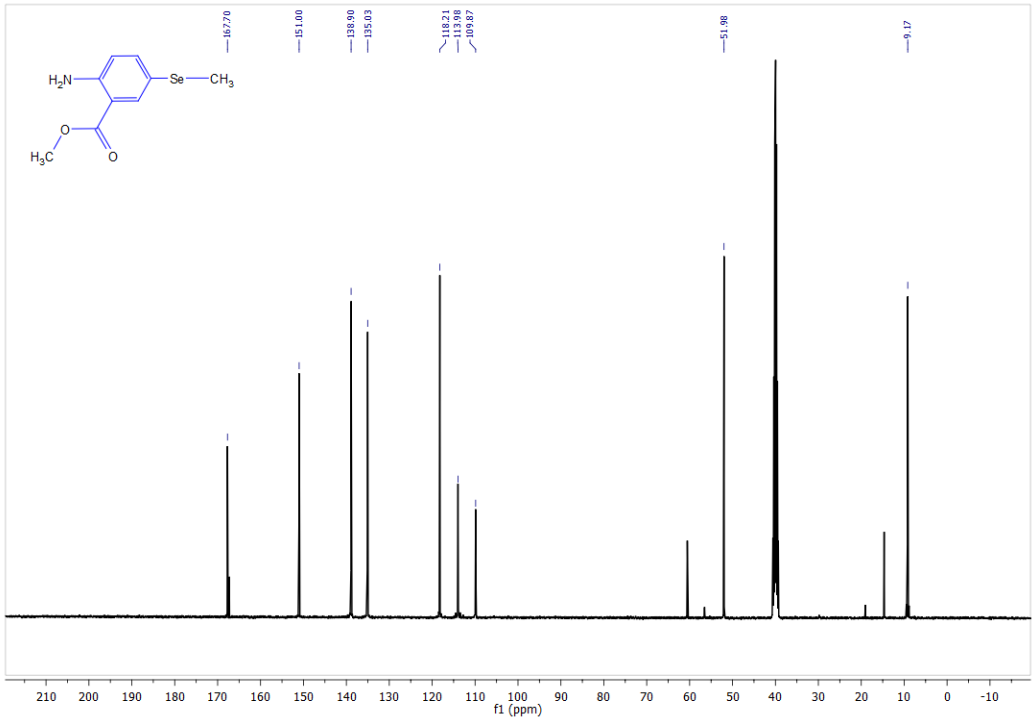
Mass chart of compound **3**

Synthesis of methyl 2-amino-5-(methylselanyl) benzoate (4)[1, 4]

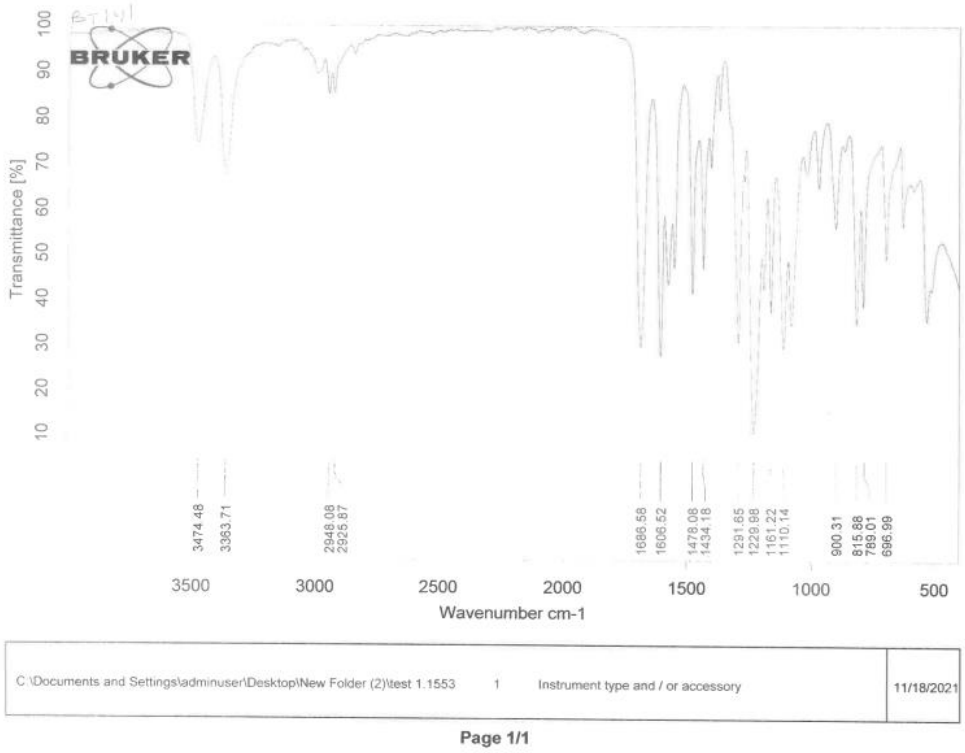
Compound **4** was synthesized from dimethyl 5,5'-diselanediylbis (2-aminobenzoate) (**3**) (2 mmol, 916 mg) and methyl iodide (4.4 mmol, 0.27 mL). It was isolated as brown oil; yield: 402 mg (82%); Rf = 0.6 (petroleum ether / ethyl acetate 4:2, *v*/*v*). IR (KBr): ν 3474 (N-H), 3364 (N-H), 2948 (C_{aliph}-H), 2926 (C_{aliph}-H), 1686 (C=O), 1607, 1292 (C_{Ar}–N), 1110 (C–O), 815, 789, 696 (C-H bending), 559 (C-Se); ^{1}H NMR (400 MHz, DMSO- d_6) δ 7.82 (s, 1H, Ar-H), 7.40 (d, J = 8.6 Hz, 1H, Ar-H), 6.77 (d, J = 8.6 Hz, 1H, Ar-H), 6.75 (s, 2H, NH_2), 3.62 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO- d_6) δ 167.70, 151.00, 138.90, 135.03, 118.21, 113.98, 109.87, 51.98, 9.17. MS (EI, 70 ev) *m/z* (%) = 245.10 (M, 100.0, base peak), 230 (38.06),186 (10.46), 170 (35.08), 91 (91.10).



^{1}H NMR chart of compound **4**



^{13}C NMR chart of compound **4**



IR chart of compound **4**

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DI Analysis
Shimadzu Qp-2010 Plus

Sample Information	
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Analyzed	: 16/01/2007 03:02:11 ص
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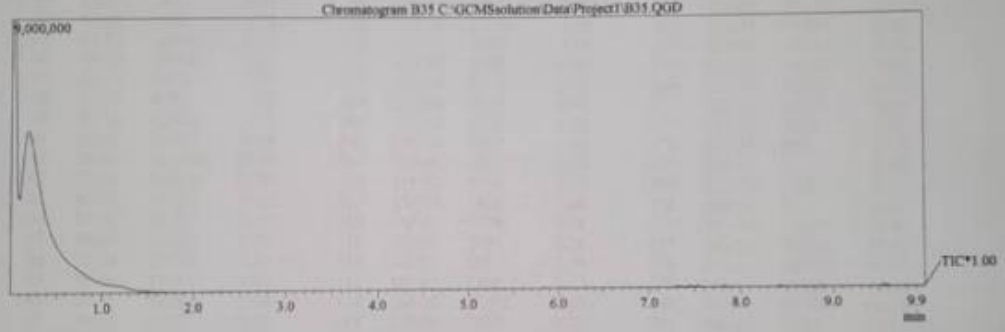

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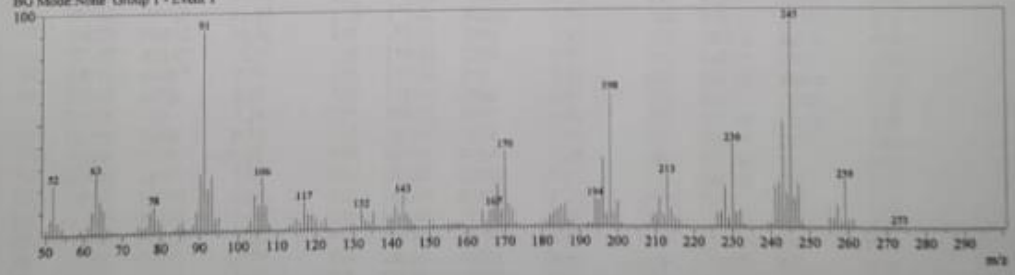

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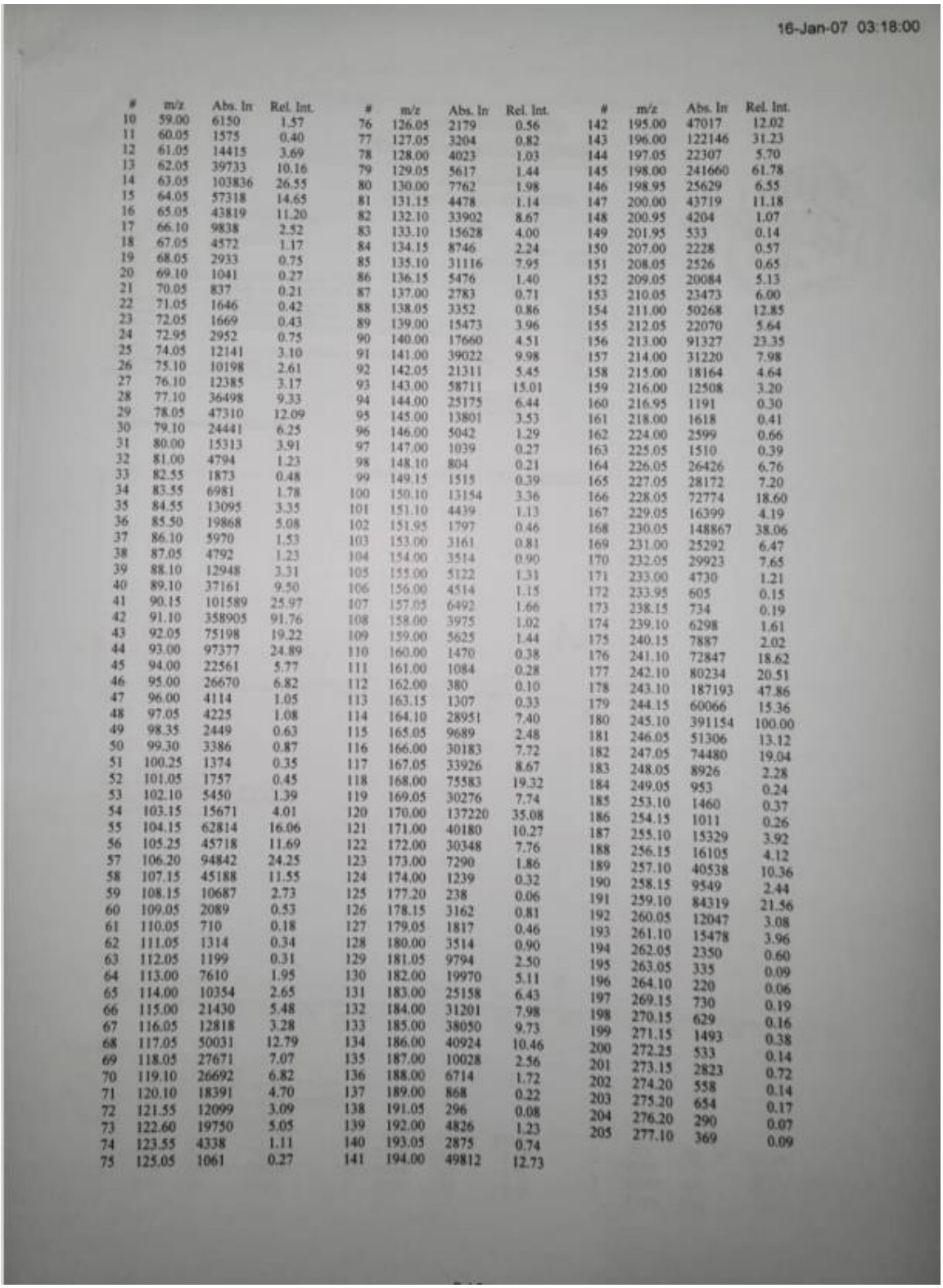
2	51.05	26260	6.71	5	54.05	11184	2.86	8	57.05	709	0.18
3	52.00	89298	22.83	6	55.00	2246	0.57	9	58.05	1164	0.30

1 / 2

Mass chart of compound **4**



16-Jan-07 03:18:00

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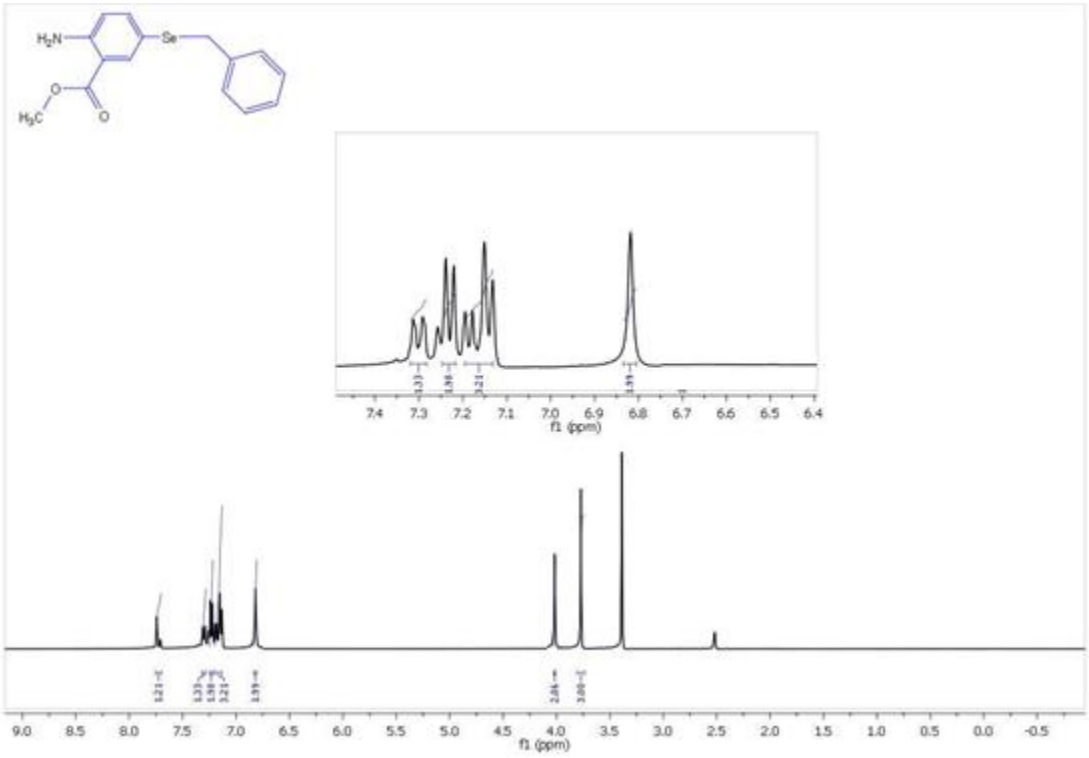
11	60.05	1575	0.40	77	127.05	3204	0.82	143	196.00	122146	31.23
12	61.05	14415	3.69	78	128.00	4023	1.03	144	197.05	22307	5.70
13	62.05	39733	10.16	79	129.05	5617	1.44	145	198.00	241660	61.78
14	63.05	103836	26.55	80	130.00	7762	1.98	146	198.95	25629	6.55
15	64.05	57318	14.65	81	131.15	4478	1.14	147	200.00	43719	11.18
16	65.05	43819	11.20	82	132.10	33902	8.67	148	200.95	4204	1.07
17	66.10	9838	2.52	83	133.10	15628	4.00	149	201.95	533	0.14
18	67.05	4572	1.17	84	134.15	8746	2.24	150	207.00	2228	0.57
19	68.05	2933	0.75	85	135.10	31116	7.95	151	208.05	2526	0.65
20	69.10	1041	0.27	86	136.15	5476	1.40	152	209.05	20084	5.13
21	70.05	837	0.21	87	137.00	2783	0.71	153	210.05	23473	6.00
22	71.05	1646	0.42	88	138.05	3352	0.86	154	211.00	50268	12.85
23	72.05	1669	0.43	89	139.00	15473	3.96	155	212.05	22070	5.64
24	72.95	2952	0.75	90	140.00	17660	4.51	156	213.00	91327	23.35
25	74.05	12141	3.10	91	141.00	39022	9.98	157	214.00	31220	7.98
26	75.10	10198	2.61	92	142.05	21311	5.45	158	215.00	18164	4.64
27	76.10	12385	3.17	93	143.00	58711	15.01	159	216.00	12508	3.20
28	77.10	36498	9.33	94	144.00	25175	6.44	160	216.95	1191	0.30
29	78.05	47310	12.09	95	145.00	13801	3.53	161	218.00	1618	0.41
30	79.10	24441	6.25	96	146.00	5042	1.29	162	224.00	2599	0.66
31	80.00	15313	3.91	97	147.00	1039	0.27	163	225.05	1510	0.39
32	81.00	4794	1.23	98	148.10	804	0.21	164	226.05	26426	6.76
33	82.55	1873	0.48	99	149.15	1515	0.39	165	227.05	28172	7.20
34	83.55	6981	1.78	100	150.10	13154	3.36	166	228.05	72774	18.60
35	84.55	13095	3.35	101	151.10	4439	1.13	167	229.05	16399	4.19
36	85.50	19868	5.08	102	151.95	1797	0.46	168	230.05	148867	38.06
37	86.10	5970	1.53	103	153.00	3161	0.81	169	231.00	25292	6.47
38	87.05	4792	1.23	104	154.00	3514	0.90	170	232.05	29923	7.65
39	88.10	12948	3.31	105	155.00	5122	1.31	171	233.00	4730	1.21
40	89.10	37161	9.50	106	156.00	4514	1.15	172	233.95	605	0.15
41	90.15	101589	25.97	107	157.05	6492	1.66	173	238.15	734	0.19
42	91.10	358905	91.76	108	158.00	3975	1.02	174	239.10	6298	1.61
43	92.05	75198	19.22	109	159.00	5625	1.44	175	240.15	7887	2.02
44	93.00	97377	24.89	110	160.00	1470	0.38	176	241.10	72847	18.62
45	94.00	22561	5.77	111	161.00	1084	0.28	177	242.10	80234	20.51
46	95.00	26670	6.82	112	162.00	380	0.10	178	243.10	187193	47.86
47	96.00	4114	1.05	113	163.15	1307	0.33	179	244.15	60066	15.36
48	97.05	4225	1.08	114	164.10	28951	7.40	180	245.10	391154	100.00
49	98.35	2449	0.63	115	165.05	9689	2.48	181	246.05	51306	13.12
50	99.30	3386	0.87	116	166.00	30183	7.72	182	247.05	74480	19.04
51	100.25	1374	0.35	117	167.05	33926	8.67	183	248.05	8926	2.28
52	101.05	1757	0.45	118	168.00	75583	19.32	184	249.05	953	0.24
53	102.10	5450	1.39	119	169.05	30276	7.74	185	253.10	1460	0.37
54	103.15	15671	4.01	120	170.00	137220	35.08	186	254.15	1011	0.26
55	104.15	62814	16.06	121	171.00	40180	10.27	187	255.10	15329	3.92
56	105.25	45718	11.69	122	172.00	30348	7.76	188	256.15	16105	4.12
57	106.20	94842	24.25	123	173.00	7290	1.86	189	257.10	40538	10.36
58	107.15	45188	11.55	124	174.00	1239	0.32	190	258.15	9549	2.44
59	108.15	10687	2.73	125	177.20	238	0.06	191	259.10	84319	21.56
60	109.05	2089	0.53	126	178.15	3162	0.81	192	260.05	12047	3.08
61	110.05	710	0.18	127	179.05	1817	0.46	193	261.10	15478	3.96
62	111.05	1314	0.34	128	180.00	3514	0.90	194	262.05	2350	0.60
63	112.05	1199	0.31	129	181.05	9794	2.50	195	263.05	335	0.09
64	113.00	7610	1.95	130	182.00	19970	5.11	196	264.10	220	0.06
65	114.00	10354	2.65	131	183.00	25158	6.43	197	269.15	730	0.19
66	115.00	21430	5.48	132	184.00	31201	7.98	198	270.15	629	0.16
67	116.05	12818	3.28	133	185.00	38050	9.73	199	271.15	1493	0.38
68	117.05	50031	12.79	134	186.00	40924	10.46	200	272.25	533	0.14
69	118.05	27671	7.07	135	187.00	10028	2.56	201	273.15	2823	0.72
70	119.10	26692	6.82	136	188.00	6714	1.72	202	274.20	558	0.14
71	120.10	18391	4.70	137	189.00	868	0.22	203	275.20	654	0.17
72	121.55	12099	3.09	138	191.05	296	0.08	204	276.20	290	0.07
73	122.60	19750	5.05	139	192.00	4826	1.23	205	277.10	369	0.09
74	123.55	4338	1.11	140	193.05	2875	0.74				
75	125.05	1061	0.27	141	194.00	49812	12.73				

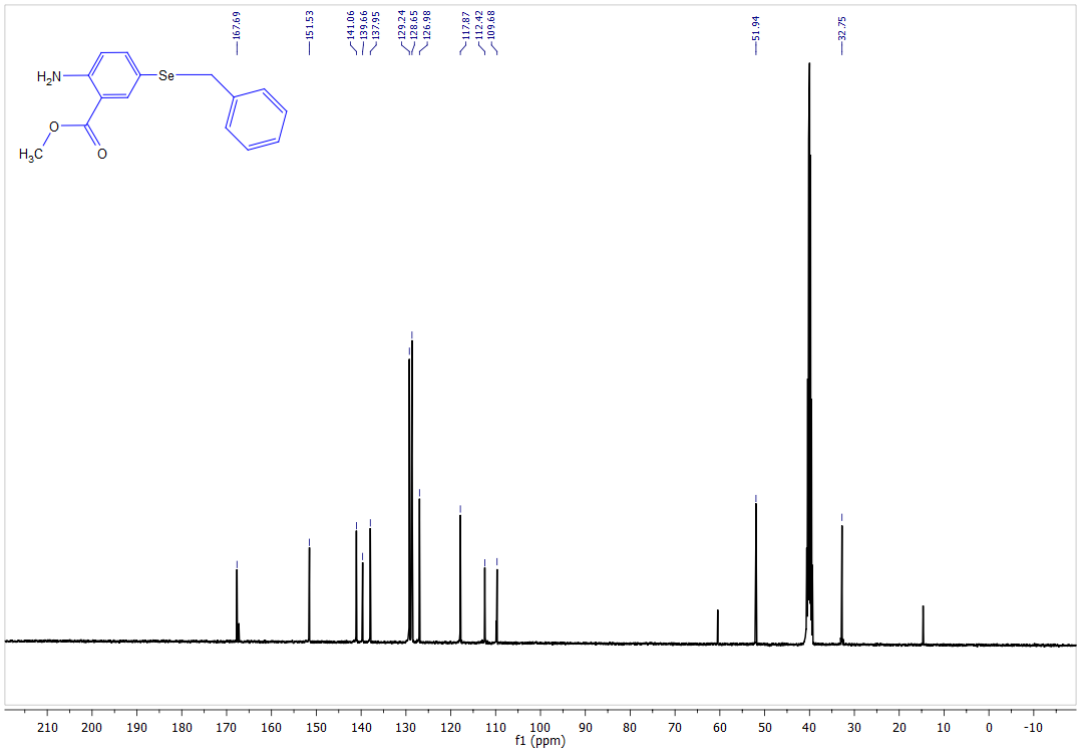
Mass chart of compound **4**

Synthesis of methyl 2-amino-5-(benzylselanyl) benzoate (5)[1, 4]

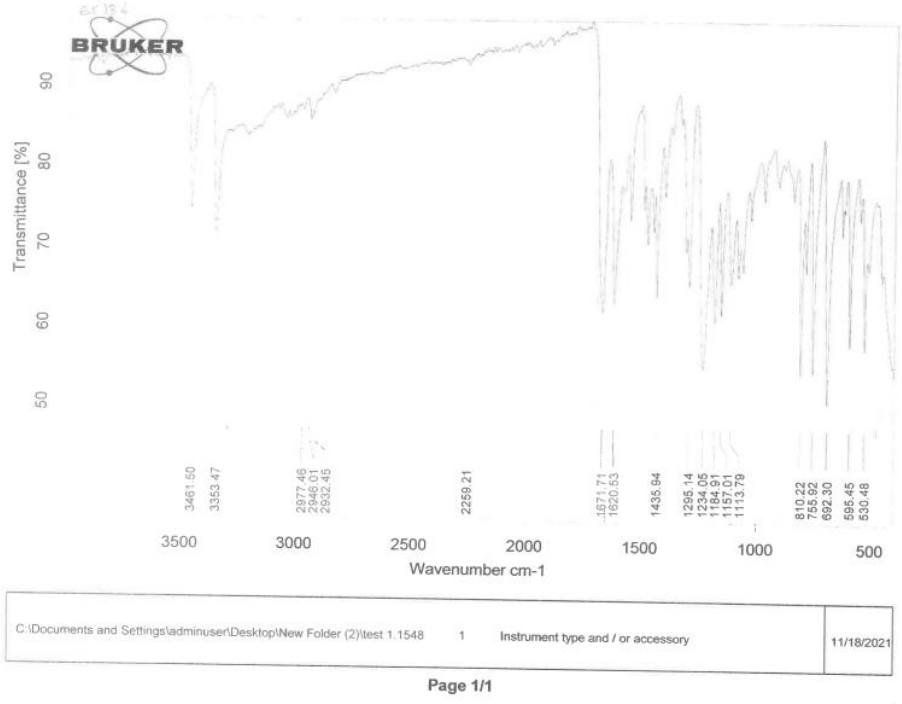
Compound **5** was synthesized from dimethyl 5,5'-diselanediylbis(2-aminobenzoate) (**3**) (2 mmol, 916 mg) and benzyl chloride (4.4 mmol, 0.50 mL). It was isolated as light brown solid; yield: 597 mg (93%); m.p. = 78 ^{o}C; Rf = 0.6 (petroleum ether / ethyl acetate 4:3, *v*/*v*). IR (KBr): ν 3462 (N-H), 3353 (N-H), 2977 (C_{aliph}-H), 2946 (C_{aliph}-H), 1672 (C=O), 1621, 1436, 1234 (C_{Ar}-N), 1114 (C-O), 810 (C-H bending), 692 (C-H rocking), 595 (C-Se); ^{1}H NMR (400 MHz, DMSO- d_6) δ 7.70 (s, 1H, Ar-H), 7.30 (d, J = 8.6 Hz, 1H, Ar-H), 7.23 (dd, J = 8.6 Hz, J = 2.1 Hz, 2H, Ar-H), 7.19 (d, J = 8.7 Hz, 2H, Ar-H), 7.14 (d, J = 8.6 Hz, 2H, Ar-H), 6.82 (s, 2H, NH_2), 4.00 (s, 2H, $SeCH_2$), 3.77 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, DMSO- d_6) δ 167.69, 151.53, 141.06, 139.66, 137.95, 129.24, 128.65, 126.98, 117.87, 112.42, 109.68, 51.94, 32.75. MS (EI, 70 ev) *m/z* (%) = 321.20 (M, 46.87), 244.10 (2.77), 230 (34.88), 150.15 (1.02), 91.05 (100.0, base peak).



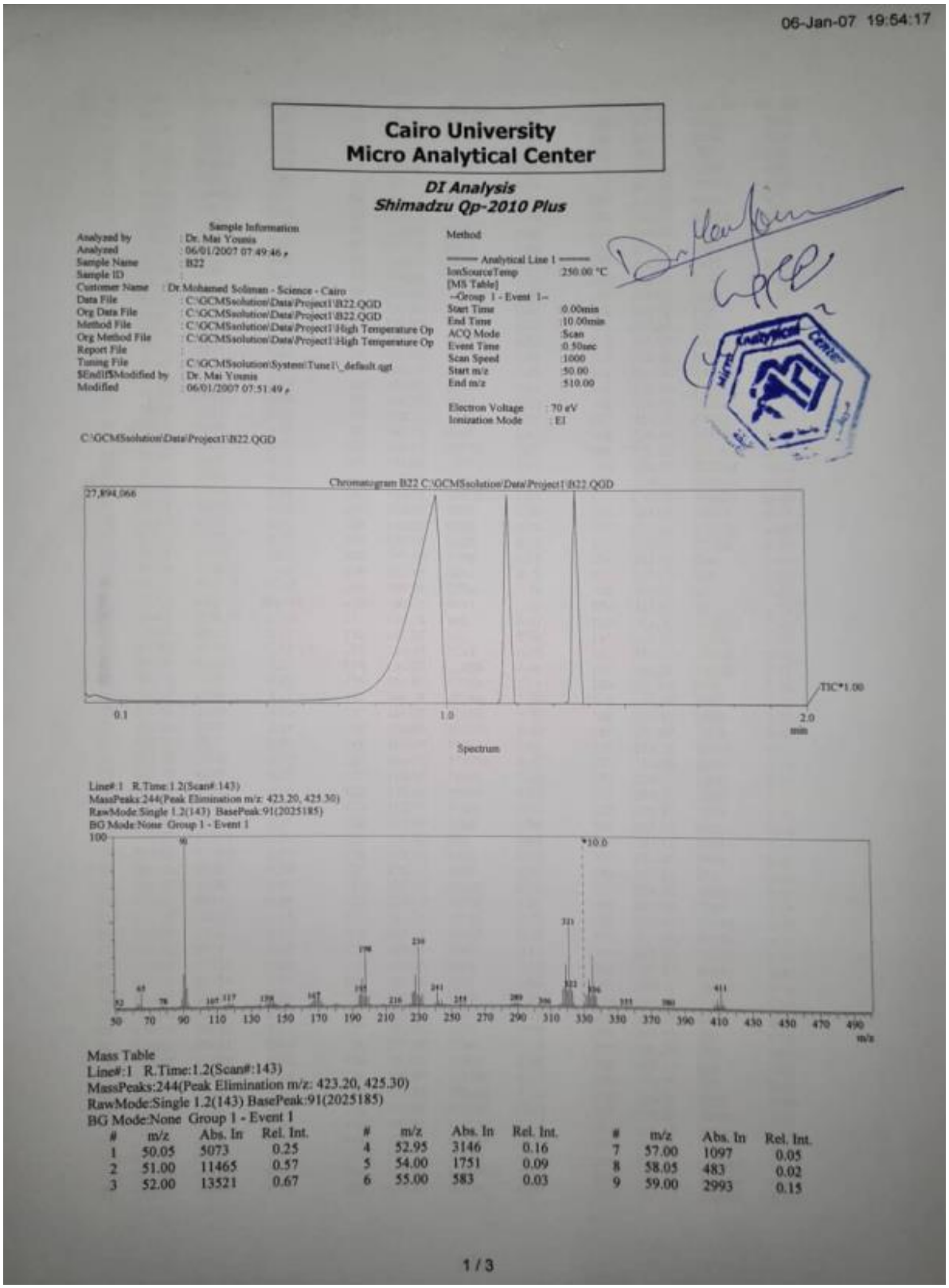
^{1}H NMR chart of compound **5**



^{13}C NMR chart of compound **5**



IR chart of compound **5**



Mass Table
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RawMode:Single 1.2(143) BasePeak:91(2025185)
BG Mode:None Group 1 - Event 1

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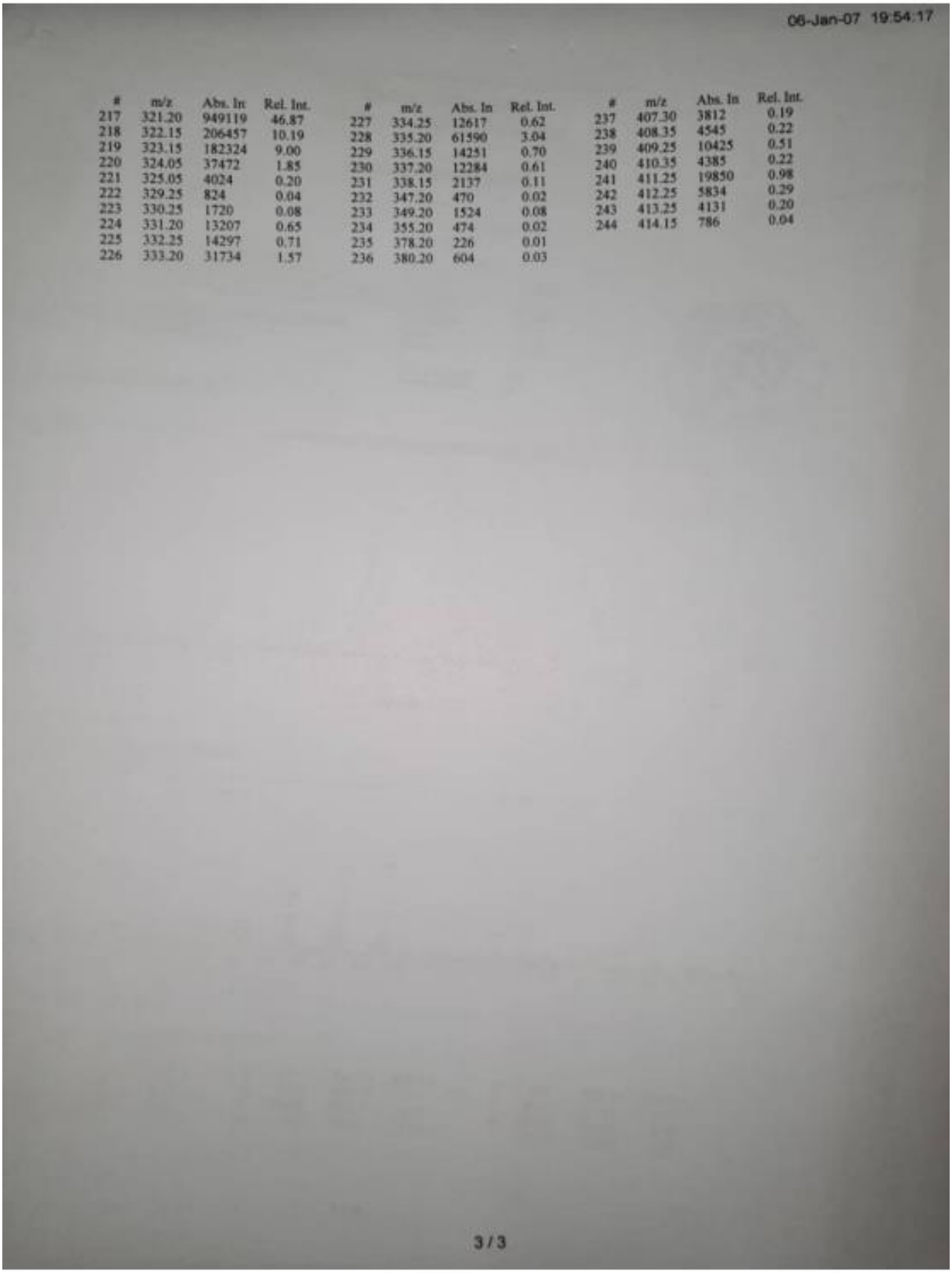
1	50.05	5073	0.25	4	52.95	3146	0.16	7	57.00	1097	0.05
2	51.00	11465	0.57	5	54.00	1751	0.09	8	58.05	483	0.02
3	52.00	13521	0.67	6	55.00	583	0.03	9	59.00	2993	0.15

1 / 3

Mass chart of compound **5**

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
10	60.05	391	0.02	79	129.05	9313	0.46	148	201.95	1028	0.05
11	61.05	3772	0.19	80	130.05	11086	0.55	149	204.25	5464	0.27
12	62.05	17107	0.84	81	131.10	5054	0.25	150	205.15	701	0.03
13	63.00	56926	2.81	82	132.05	10987	0.54	151	206.20	1020	0.05
14	64.05	36812	1.82	83	133.10	3684	0.18	152	207.25	2877	0.14
15	65.00	176463	8.71	84	134.15	9264	0.46	153	208.20	14284	0.71
16	65.95	12878	0.64	85	135.05	30121	1.49	154	209.15	17645	0.87
17	67.00	1580	0.08	86	136.05	4109	0.20	155	210.05	5896	0.29
18	68.05	483	0.02	87	137.05	5343	0.26	156	211.15	1898	0.09
19	69.10	985	0.05	88	138.05	7879	0.39	157	212.05	5471	0.27
20	70.10	1497	0.07	89	139.00	35607	1.76	158	213.10	2154	0.11
21	71.10	1663	0.08	90	140.05	41787	2.06	159	214.05	4336	0.21
22	72.05	379	0.02	91	141.00	77244	3.81	160	215.15	994	0.05
23	73.05	2080	0.10	92	142.05	47101	2.33	161	216.10	6855	0.34
24	74.05	4921	0.24	93	142.95	126529	6.25	162	217.05	395	0.02
25	75.05	5212	0.26	94	143.95	48735	2.41	163	218.10	921	0.05
26	76.05	6114	0.30	95	144.95	28945	1.43	164	221.20	846	0.04
27	77.05	10886	0.54	96	146.05	23129	1.14	165	223.15	1595	0.08
28	78.05	20811	1.03	97	146.95	4067	0.20	166	224.10	14468	0.71
29	79.05	8101	0.40	98	148.15	1843	0.09	167	225.15	19403	0.96
30	80.00	5090	0.25	99	149.15	8597	0.42	168	226.10	153471	7.58
31	81.05	1605	0.08	100	150.15	20578	1.02	169	227.15	166163	8.20
32	82.15	1045	0.05	101	151.05	33271	1.64	170	228.10	368934	18.22
33	83.10	2590	0.13	102	152.05	32505	1.61	171	229.15	120571	5.95
34	84.15	2599	0.13	103	153.05	20872	1.03	172	230.10	706377	34.88
35	85.15	4470	0.22	104	154.05	7855	0.39	173	231.05	94541	4.67
36	86.05	4174	0.21	105	155.00	4855	0.24	174	232.10	132870	6.56
37	87.15	6312	0.31	106	155.95	3585	0.18	175	233.05	15116	0.75
38	88.15	20787	1.03	107	157.00	3398	0.17	176	234.05	960	0.05
39	89.15	110480	5.46	108	157.95	2693	0.13	177	238.15	969	0.05
40	90.15	391518	19.33	109	159.05	2274	0.11	178	239.25	4131	0.20
41	91.05	202518	100.00	110	160.05	4165	0.21	179	240.25	35113	1.73
42	92.05	228419	11.28	111	161.00	602	0.03	180	241.25	155831	7.69
43	93.05	46032	2.27	112	162.05	482	0.02	181	242.10	54386	2.69
44	94.00	4180	0.21	113	163.05	3714	0.18	182	243.15	12588	0.62
45	95.00	8522	0.42	114	164.05	12889	0.64	183	244.10	56178	2.77
46	96.15	1388	0.07	115	165.05	22436	1.11	184	245.05	8044	0.40
47	97.10	2596	0.13	116	166.05	47284	2.33	185	246.10	9770	0.48
48	98.10	2490	0.12	117	167.05	66556	3.29	186	247.10	1503	0.07
49	99.10	2721	0.13	118	168.00	102111	5.04	187	254.35	1823	0.09
50	100.15	911	0.04	119	169.05	77098	3.81	188	255.25	10721	0.53
51	101.10	2750	0.14	120	169.95	174770	8.63	189	256.15	3888	0.19
52	102.10	4402	0.22	121	170.95	74461	3.68	190	257.15	1891	0.09
53	103.10	7242	0.36	122	172.00	39018	1.93	191	258.15	4289	0.21
54	104.05	11796	0.58	123	172.95	11808	0.58	192	259.15	3074	0.15
55	105.05	7012	0.35	124	173.95	1305	0.06	193	260.15	2910	0.14
56	106.10	11636	0.57	125	176.15	889	0.04	194	261.15	2231	0.11
57	107.05	13258	0.65	126	177.15	2401	0.12	195	262.20	1594	0.08
58	108.00	3873	0.19	127	178.15	5969	0.29	196	283.25	376	0.02
59	109.15	1378	0.07	128	179.15	10187	0.50	197	284.25	1803	0.09
60	110.05	979	0.05	129	180.15	36701	1.81	198	285.20	7185	0.35
61	111.05	2440	0.12	130	181.10	18865	0.93	199	286.20	14742	0.73
62	112.05	2793	0.14	131	182.15	14965	0.74	200	287.15	23239	1.15
63	113.05	9979	0.49	132	183.05	3441	0.17	201	288.20	24534	1.21
64	114.05	12822	0.63	133	184.00	2350	0.12	202	289.15	36611	1.81
65	115.00	27724	1.37	134	185.10	1281	0.06	203	290.15	36028	1.78
66	116.05	18052	0.89	135	186.05	1167	0.06	204	291.10	11612	0.57
67	117.00	53988	2.67	136	190.05	602	0.03	205	292.15	6462	0.32
68	118.05	26835	1.33	137	191.05	1736	0.09	206	293.15	552	0.03
69	119.05	43451	2.15	138	192.05	12467	0.62	207	306.20	302	0.01
70	120.05	15785	0.78	139	193.05	17901	0.88	208	308.10	636	0.03
71	121.10	4878	0.24	140	194.05	131489	6.49	209	310.05	707	0.03
72	122.05	2063	0.10	141	195.05	146464	7.23	210	314.25	1728	0.09
73	123.10	1527	0.08	142	196.00	323593	15.98	211	315.20	18481	0.91
74	124.05	682	0.03	143	197.05	113333	5.60	212	316.25	23945	1.18
75	125.05	4002	0.20	144	198.00	620129	30.62	213	317.20	196281	9.69
76	126.05	5459	0.27	145	198.95	99120	4.89	214	318.25	227987	11.26
77	127.05	10480	0.52	146	200.00	113441	5.60	215	319.20	494574	24.42
78	128.05	10844	0.54	147	200.95	16159	0.80	216	320.25	188395	9.30

Mass chart of compound **5**



06-Jan-07 19:54:17

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218	322.15	206457	10.19	228	335.20	61590	3.04	238	408.35	4545	0.22
219	323.15	182324	9.00	229	336.15	14251	0.70	239	409.25	10425	0.51
220	324.05	37472	1.85	230	337.20	12284	0.61	240	410.35	4385	0.22
221	325.05	4024	0.20	231	338.15	2137	0.11	241	411.25	19850	0.98
222	329.25	824	0.04	232	347.20	470	0.02	242	412.25	5834	0.29
223	330.25	1720	0.08	233	349.20	1524	0.08	243	413.25	4131	0.20
224	331.20	13207	0.65	234	355.20	474	0.02	244	414.15	786	0.04
225	332.25	14297	0.71	235	378.20	226	0.01				
226	333.20	31734	1.57	236	380.20	604	0.03				

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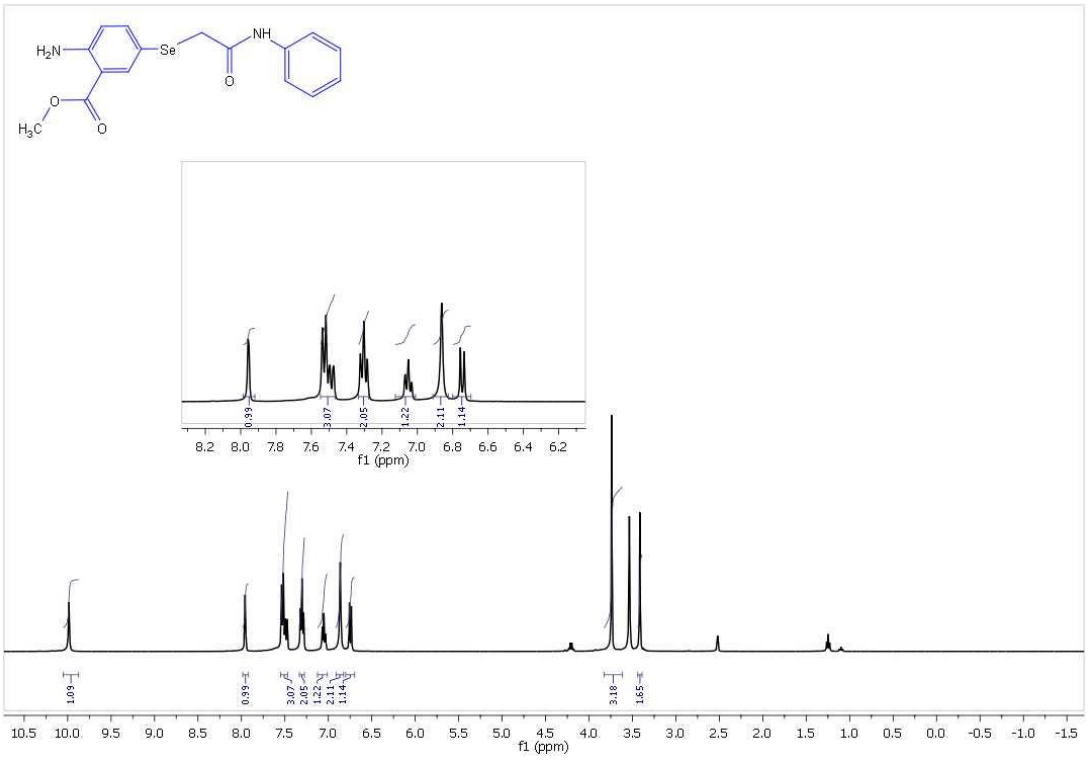
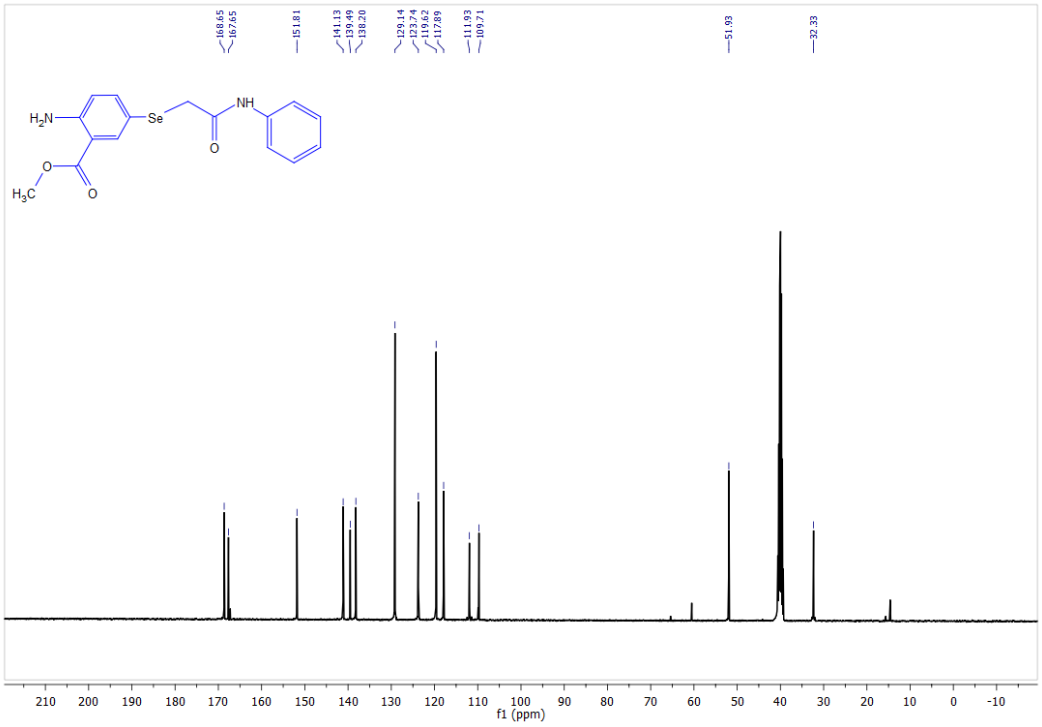
Mass chart of compound **5**

Synthesis of methyl 2-amino-5-((2-oxo-2-(phenylamino) ethyl) selanyl) benzoate (6)[1, 4]

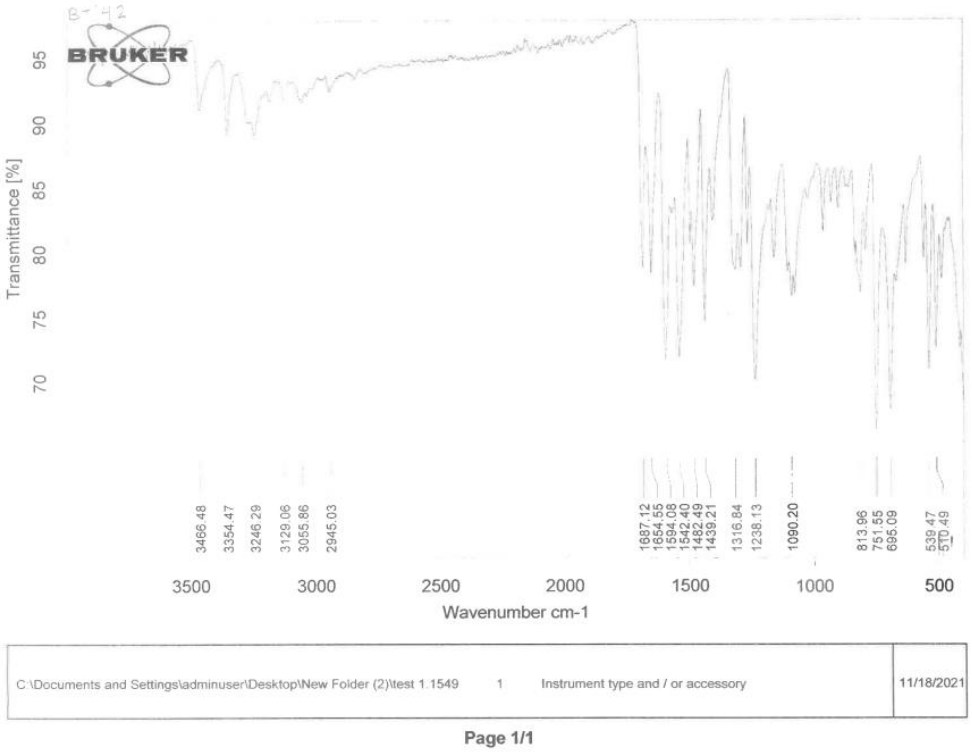
Compound **6** was synthesized from dimethyl 5,5'-diselanediylbis (2-aminobenzoate) (**3**) (2.0 mmol, 916 mg) and 2-chloro-*N*-phenylacetamide (4.4 mmol, 744 mg). It was isolated as violet solid; yield: 699 mg (96%); m.p. = 126–128 °C; Rf = 0.50 (petroleum ether / ethyl acetate 4:2, *v*/*v*). IR (KBr): ν 3466 (N-H), 3354 (N-H), 3246 (N-H), 2945 (C_{aliph}-H), 1678, 1594 (C=O), 1542 (C=C), 1439, 1238 (C_{Ar}-N), 1090 (C-O), 752 (C-H bending), 695, 552 (C-Se), 539 (C-H rocking); ^{1}H NMR (400 MHz, DMSO- d_6) δ 9.99 (s, 1H, NH), 7.96 (s, 1H, Ar-H), 7.53 (d, J = 8.6 Hz, 2H, ArH), 7.48 (d, J = 8.6 Hz, 1H, ArH), 7.30 (dd, J = 8.6 Hz, J = 2.1 Hz, 2H, Ar-H), 7.04 (t, 1H, J = 8.6 Hz, Ar-H), 6.86 (s, 2H, NH_2), 6.75 (d, J = 8.6 Hz, 1H, Ar-H), 3.74 (s, 3H, OCH_3), 3.42 (s, 2H, $SeCH_2$); ^{13}C NMR (101 MHz, DMSO- d_6) δ 168.65, 167.65, 151.81, 141.13, 139.49, 138.20, 129.14, 123.74, 119.62, 117.89, 111, 109.71, 51.93, 32.33. MS (EI, 70 ev) *m/z* (%) = 364.20 (M, 100.0, base peak), 230 (40.48), 91.10 (31), 77.05 (24.13), 59 (14.56).



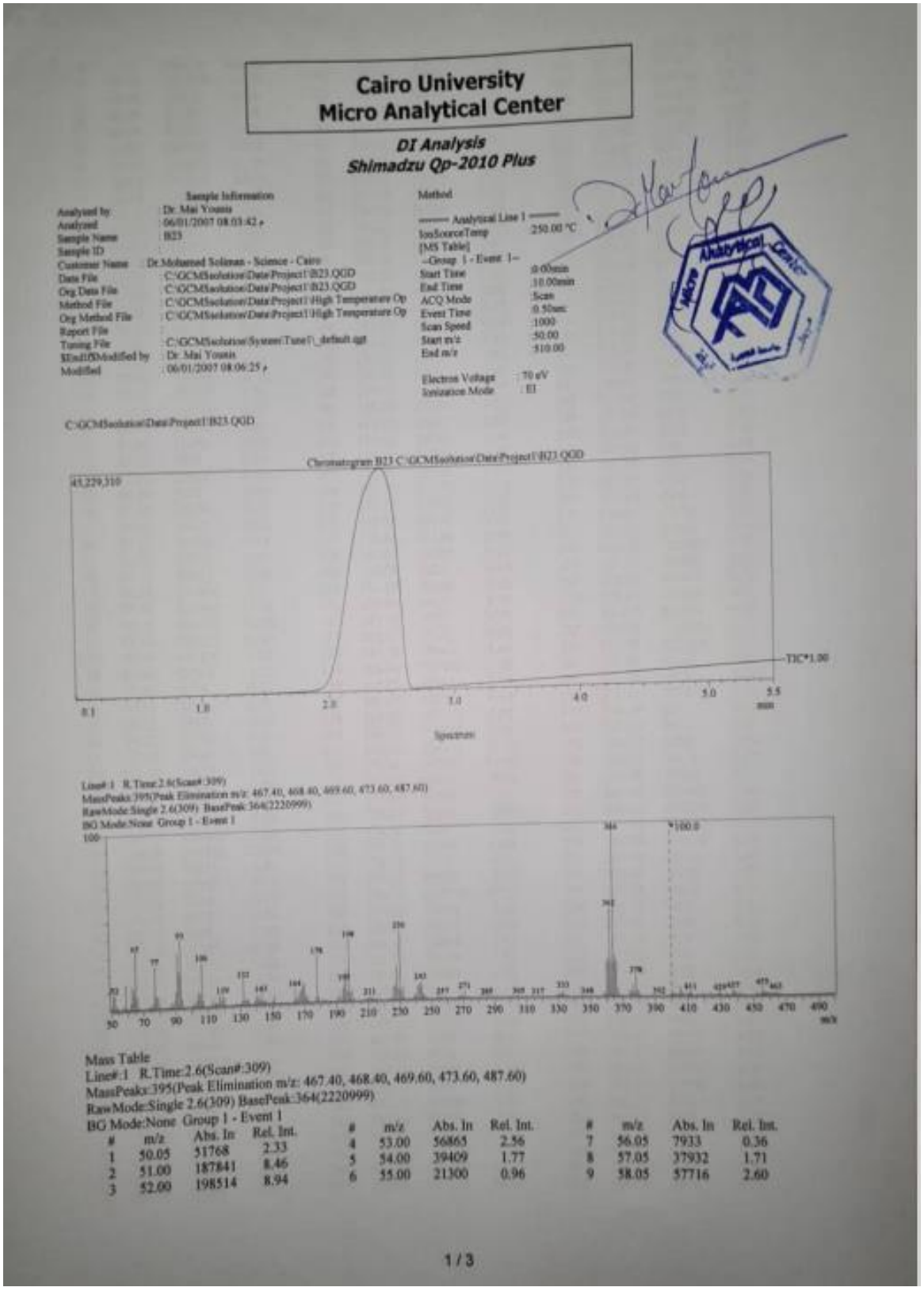
^{1}H NMR chart of compound **6**



^{13}C NMR chart of compound **6**



IR chart of compound **6**



Cairo University
Micro Analytical Center

DI Analysis
Shimadzu Qp-2010 Plus

Sample Information

Analysed by	Dr. Mai Younis
Analyzed	06/01/2007 08:03:42
Sample Name	B23
Sample ID	
Customer Name	Dr.Mohamed Soliman - Science - Cairo
Data File	C:\GCMSsolution\Data\Project1\B23.QGD
Org.Data File	C:\GCMSsolution\Data\Project1\B23.QGD
Method File	C:\GCMSsolution\Data\Project1\High Temperature Op
Org.Method File	C:\GCMSsolution\Data\Project1\High Temperature Op
Report File	
Tuning File	C:\GCMSsolution\System\Tune1_default.qgt
ReEdit/Modified by	Dr. Mai Younis
Modified	06/01/2007 08:06:25

Method

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[MS Table]	
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End Time	10.00min
ACQ Mode	Scan
Event Time	0.50sec
Scan Speed	1000
Start m/z	50.00
End m/z	510.00
Electron Voltage	70 eV
Ionization Mode	EI

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Chromatogram B23 C:\GCMSsolution\Data\Project1\B23.QGD

45,229,310

TIC*1.00

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Spectrum

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RawMode:Single 2.6(309) BasePeak:364(2220999)
BG Mode:None Group 1 - Event 1

100.0

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Mass Table
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RawMode:Single 2.6(309) BasePeak:364(2220999)
BG Mode:None Group 1 - Event 1

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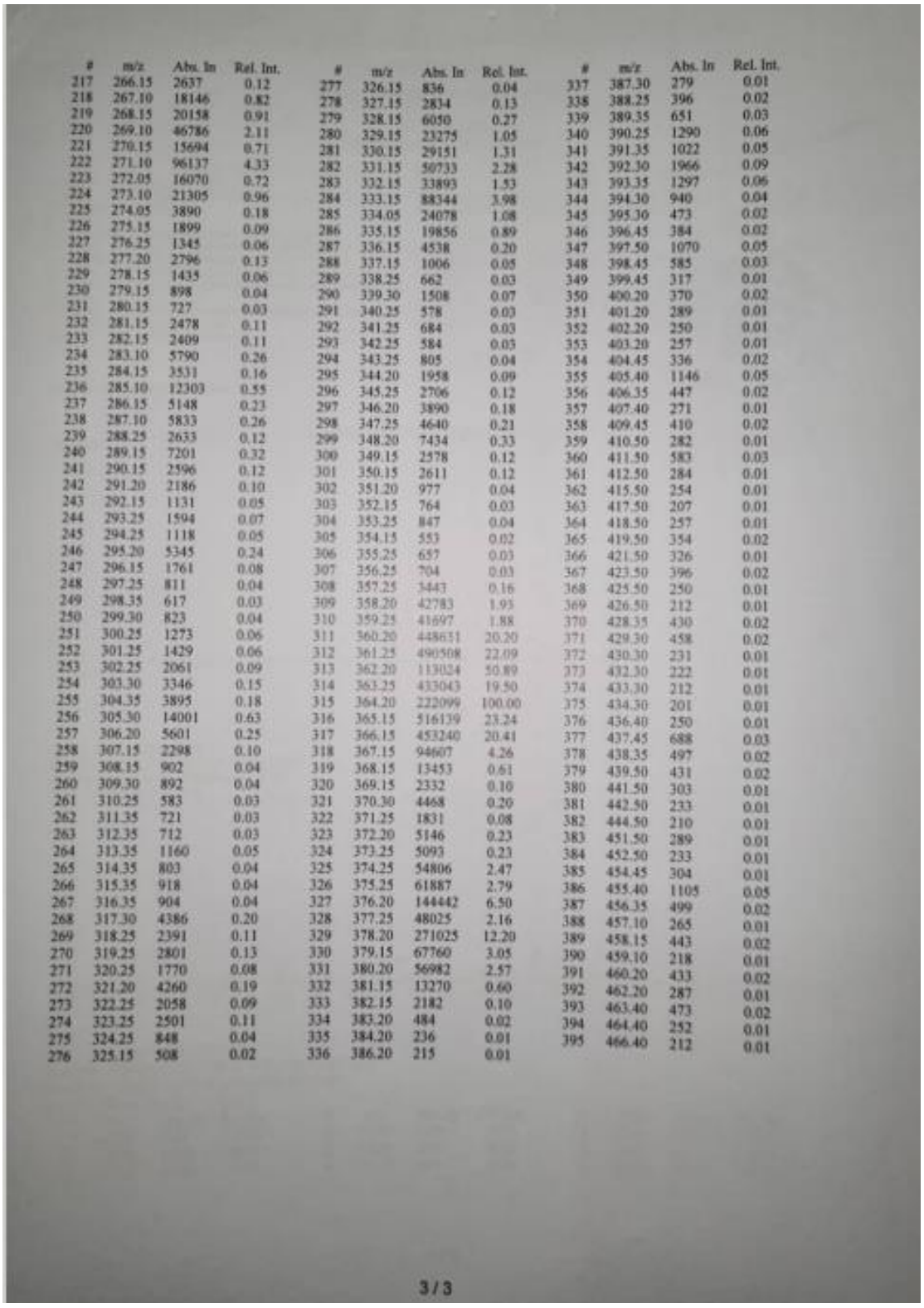
2	51.00	187841	8.46	5	54.00	39409	1.77	8	57.05	37932	1.71
3	52.00	198514	8.94	6	55.00	21300	0.96	9	58.05	57716	2.60

1 / 3

Mass chart of compound **6**

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
10	59.00	323380	14.56	79	128.15	17920	0.81	148	197.05	127657	5.75
11	60.00	19518	0.88	80	129.15	16582	0.75	149	198.00	802486	36.13
12	61.05	25294	1.14	81	130.15	23991	1.08	150	198.95	111117	5.00
13	62.05	85663	3.86	82	131.15	62358	2.81	151	200.00	147049	6.62
14	63.05	284974	12.83	83	132.10	333977	15.04	152	201.00	27327	1.23
15	64.05	250676	11.29	84	133.15	66067	2.97	153	202.05	6591	0.30
16	65.00	718538	32.35	85	134.15	78340	3.53	154	203.15	3651	0.16
17	66.00	152620	6.87	86	135.15	69517	3.13	155	204.15	2634	0.12
18	66.95	28433	1.28	87	136.15	11769	0.53	156	205.10	8610	0.39
19	68.05	8877	0.40	88	137.10	7681	0.35	157	206.05	3512	0.16
20	69.05	15359	0.69	89	138.15	13090	0.59	158	207.05	11680	0.53
21	70.05	8547	0.38	90	139.15	52322	2.36	159	208.05	15928	0.72
22	71.05	14796	0.67	91	140.10	117575	5.29	160	209.05	33769	1.52
23	72.05	7256	0.33	92	141.05	90195	4.06	161	210.05	30291	1.36
24	73.05	29968	1.35	93	142.05	52676	2.37	162	211.05	55042	2.48
25	74.05	26922	1.21	94	143.00	141599	6.38	163	212.05	30408	1.37
26	75.05	38018	1.71	95	144.00	54009	2.43	164	213.05	31320	1.41
27	76.05	89648	4.04	96	145.05	43425	1.96	165	214.05	18869	0.85
28	77.05	535908	24.13	97	146.05	54032	2.43	166	215.05	9367	0.42
29	78.05	171575	7.73	98	147.10	12569	0.57	167	216.05	19840	0.89
30	79.05	144276	6.50	99	148.10	17756	0.80	168	217.05	4333	0.20
31	80.05	37639	1.69	100	149.15	8208	0.37	169	218.05	4479	0.20
32	81.05	11176	0.50	101	150.15	38743	1.74	170	219.10	2612	0.12
33	82.15	5419	0.24	102	151.10	102964	4.64	171	220.10	778	0.04
34	83.10	15562	0.70	103	152.05	16710	0.75	172	221.15	1397	0.06
35	84.15	7935	0.36	104	153.10	11177	0.50	173	222.15	1142	0.05
36	85.10	16374	0.74	105	154.10	14711	0.66	174	223.15	4881	0.22
37	86.15	16002	0.72	106	155.05	15641	0.70	175	224.05	17976	0.81
38	87.10	69636	3.14	107	156.05	11100	0.50	176	225.15	20916	0.94
39	88.15	32733	1.47	108	157.05	15214	0.69	177	226.10	174902	7.87
40	89.15	88448	3.98	109	158.05	8233	0.37	178	227.15	189200	8.52
41	90.15	210874	9.49	110	159.10	16986	0.76	179	228.05	447454	20.15
42	91.10	688561	31.00	111	160.05	4503	0.20	180	229.15	133404	6.01
43	92.15	463765	20.88	112	161.15	4537	0.20	181	230.05	899020	40.48
44	93.10	862055	38.81	113	162.15	5173	0.23	182	231.05	114924	5.17
45	94.05	112159	5.05	114	163.15	35647	1.60	183	232.05	173318	7.80
46	95.00	27708	1.25	115	164.10	195450	8.80	184	233.05	21637	0.97
47	96.10	5274	0.24	116	165.05	50811	2.29	185	234.05	3484	0.16
48	97.10	9146	0.41	117	166.05	92270	4.15	186	235.15	3179	0.14
49	98.15	5237	0.24	118	167.05	149172	6.72	187	236.15	3807	0.17
50	99.10	12962	0.58	119	168.05	172761	7.78	188	237.05	8985	0.40
51	100.15	13487	0.61	120	169.05	226041	10.18	189	238.15	10887	0.49
52	101.10	60012	2.70	121	170.00	257615	11.60	190	239.10	48174	2.17
53	102.15	30642	1.38	122	171.00	96798	4.36	191	240.10	75681	3.41
54	103.15	88585	3.99	123	172.00	69998	3.15	192	241.10	157647	7.10
55	104.10	204116	9.19	124	173.00	21033	0.95	193	242.15	186228	8.38
56	105.15	159966	7.20	125	174.10	7897	0.36	194	243.10	230793	10.39
57	106.10	568420	25.59	126	175.15	17735	0.80	195	244.05	179124	8.07
58	107.10	76871	3.46	127	176.15	7737	0.35	196	245.05	65413	2.95
59	108.05	12580	0.57	128	177.15	62536	2.82	197	246.05	36727	1.65
60	109.10	3719	0.17	129	178.10	605762	27.27	198	247.20	22822	1.03
61	110.15	3039	0.14	130	179.05	72024	3.24	199	248.15	7827	0.35
62	111.15	9856	0.44	131	180.05	20815	0.94	200	249.15	2124	0.10
63	112.15	15347	0.69	132	181.10	26969	1.21	201	250.25	1855	0.08
64	113.10	93678	4.22	133	182.05	36544	1.65	202	251.20	7351	0.33
65	114.15	34219	1.54	134	183.10	28086	1.26	203	252.15	3123	0.14
66	115.10	49390	2.22	135	184.05	26423	1.19	204	253.15	6626	0.30
67	116.15	38664	1.74	136	185.00	19938	0.90	205	254.15	7024	0.32
68	117.10	130407	5.87	137	186.00	10751	0.48	206	255.10	19212	0.87
69	118.15	63644	2.87	138	187.05	6516	0.29	207	256.15	19273	0.87
70	119.10	142945	6.44	139	188.25	4750	0.21	208	257.10	29007	1.31
71	120.10	98100	4.42	140	189.15	25047	1.13	209	258.15	10175	0.46
72	121.05	14291	0.64	141	190.15	9994	0.45	210	259.20	21718	0.98
73	122.10	5969	0.27	142	191.15	57570	2.59	211	260.15	6061	0.27
74	123.05	3081	0.14	143	192.10	82754	3.73	212	261.15	4356	0.20
75	124.15	1538	0.07	144	193.05	33585	1.51	213	262.15	3391	0.15
76	125.15	3955	0.18	145	194.05	172249	7.76	214	263.15	3353	0.15
77	126.15	7068	0.32	146	195.05	249002	11.21	215	264.10	1687	0.08
78	127.15	19469	0.88	147	196.00	413670	18.63	216	265.15	3515	0.16

Mass chart of compound **6**



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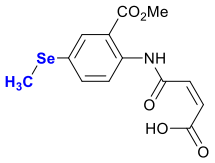
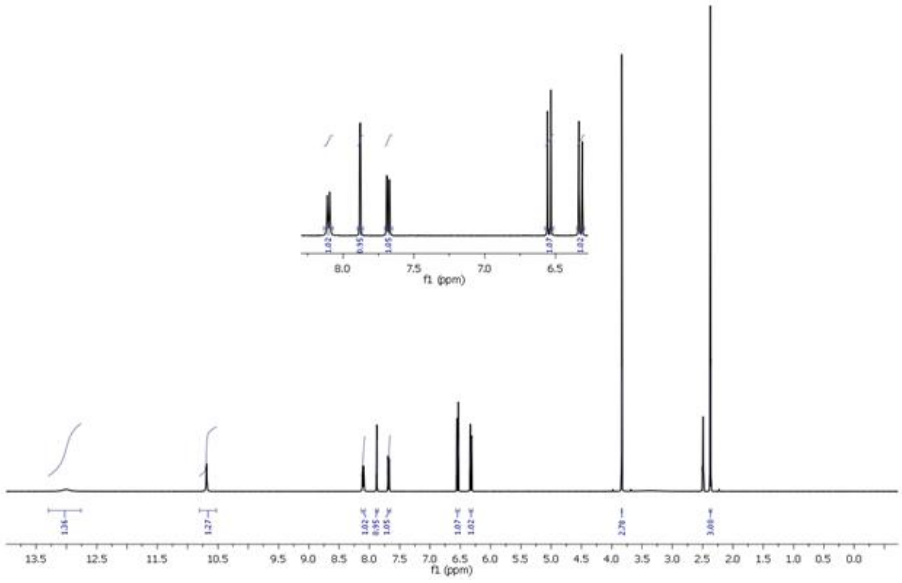
218	267.10	18146	0.82	278	327.15	2834	0.13	338	388.25	396	0.02
219	268.15	20158	0.91	279	328.15	6050	0.27	339	389.35	651	0.03
220	269.10	46786	2.11	280	329.15	23275	1.05	340	390.25	1290	0.06
221	270.15	15694	0.71	281	330.15	29151	1.31	341	391.35	1022	0.05
222	271.10	96137	4.33	282	331.15	50733	2.28	342	392.30	1966	0.09
223	272.05	16070	0.72	283	332.15	33893	1.53	343	393.35	1297	0.06
224	273.10	21305	0.96	284	333.15	88344	3.98	344	394.30	940	0.04
225	274.05	3890	0.18	285	334.05	24078	1.08	345	395.30	473	0.02
226	275.15	1899	0.09	286	335.15	19856	0.89	346	396.45	384	0.02
227	276.25	1345	0.06	287	336.15	4538	0.20	347	397.50	1070	0.05
228	277.20	2796	0.13	288	337.15	1006	0.05	348	398.45	585	0.03
229	278.15	1435	0.06	289	338.25	662	0.03	349	399.45	317	0.01
230	279.15	898	0.04	290	339.30	1508	0.07	350	400.20	370	0.02
231	280.15	727	0.03	291	340.25	578	0.03	351	401.20	289	0.01
232	281.15	2478	0.11	292	341.25	684	0.03	352	402.20	250	0.01
233	282.15	2409	0.11	293	342.25	584	0.03	353	403.20	257	0.01
234	283.10	5790	0.26	294	343.25	805	0.04	354	404.45	336	0.02
235	284.15	3531	0.16	295	344.20	1958	0.09	355	405.40	1146	0.05
236	285.10	12303	0.55	296	345.25	2706	0.12	356	406.35	447	0.02
237	286.15	5148	0.23	297	346.20	3890	0.18	357	407.40	271	0.01
238	287.10	5833	0.26	298	347.25	4640	0.21	358	409.45	410	0.02
239	288.25	2633	0.12	299	348.20	7434	0.33	359	410.50	282	0.01
240	289.15	7201	0.32	300	349.15	2578	0.12	360	411.50	583	0.03
241	290.15	2596	0.12	301	350.15	2611	0.12	361	412.50	284	0.01
242	291.20	2186	0.10	302	351.20	977	0.04	362	415.50	254	0.01
243	292.15	1131	0.05	303	352.15	764	0.03	363	417.50	207	0.01
244	293.25	1594	0.07	304	353.25	847	0.04	364	418.50	257	0.01
245	294.25	1118	0.05	305	354.15	553	0.02	365	419.50	354	0.02
246	295.20	5345	0.24	306	355.25	657	0.03	366	421.50	326	0.01
247	296.15	1761	0.08	307	356.25	704	0.03	367	423.50	396	0.02
248	297.25	811	0.04	308	357.25	3443	0.16	368	425.50	250	0.01
249	298.35	617	0.03	309	358.20	42783	1.93	369	426.50	212	0.01
250	299.30	823	0.04	310	359.25	41697	1.88	370	428.35	430	0.02
251	300.25	1273	0.06	311	360.20	448651	20.20	371	429.30	458	0.02
252	301.25	1429	0.06	312	361.25	490508	22.09	372	430.30	231	0.01
253	302.25	2061	0.09	313	362.20	113024	50.89	373	432.30	222	0.01
254	303.30	3346	0.15	314	363.25	433043	19.50	374	433.30	212	0.01
255	304.35	3895	0.18	315	364.20	222099	100.00	375	434.30	201	0.01
256	305.30	14001	0.63	316	365.15	516139	23.24	376	436.40	250	0.01
257	306.20	5601	0.25	317	366.15	453240	20.41	377	437.45	688	0.03
258	307.15	2298	0.10	318	367.15	94607	4.26	378	438.35	497	0.02
259	308.15	902	0.04	319	368.15	13453	0.61	379	439.50	431	0.02
260	309.30	892	0.04	320	369.15	2332	0.10	380	441.50	303	0.01
261	310.25	583	0.03	321	370.30	4468	0.20	381	442.50	233	0.01
262	311.35	721	0.03	322	371.25	1831	0.08	382	444.50	210	0.01
263	312.35	712	0.03	323	372.20	5146	0.23	383	451.50	289	0.01
264	313.35	1160	0.05	324	373.25	5093	0.23	384	452.50	233	0.01
265	314.35	803	0.04	325	374.25	54806	2.47	385	454.45	304	0.01
266	315.35	918	0.04	326	375.25	61887	2.79	386	455.40	1105	0.05
267	316.35	904	0.04	327	376.20	144442	6.50	387	456.35	499	0.02
268	317.30	4386	0.20	328	377.25	48025	2.16	388	457.10	265	0.01
269	318.25	2391	0.11	329	378.20	271025	12.20	389	458.15	443	0.02
270	319.25	2801	0.13	330	379.15	67760	3.05	390	459.10	218	0.01
271	320.25	1770	0.08	331	380.20	56982	2.57	391	460.20	433	0.02
272	321.20	4260	0.19	332	381.15	13270	0.60	392	462.20	287	0.01
273	322.25	2058	0.09	333	382.15	2182	0.10	393	463.40	473	0.02
274	323.25	2501	0.11	334	383.20	484	0.02	394	464.40	252	0.01
275	324.25	848	0.04	335	384.20	236	0.01	395	466.40	212	0.01
276	325.15	508	0.02	336	386.20	215	0.01				

3 / 3

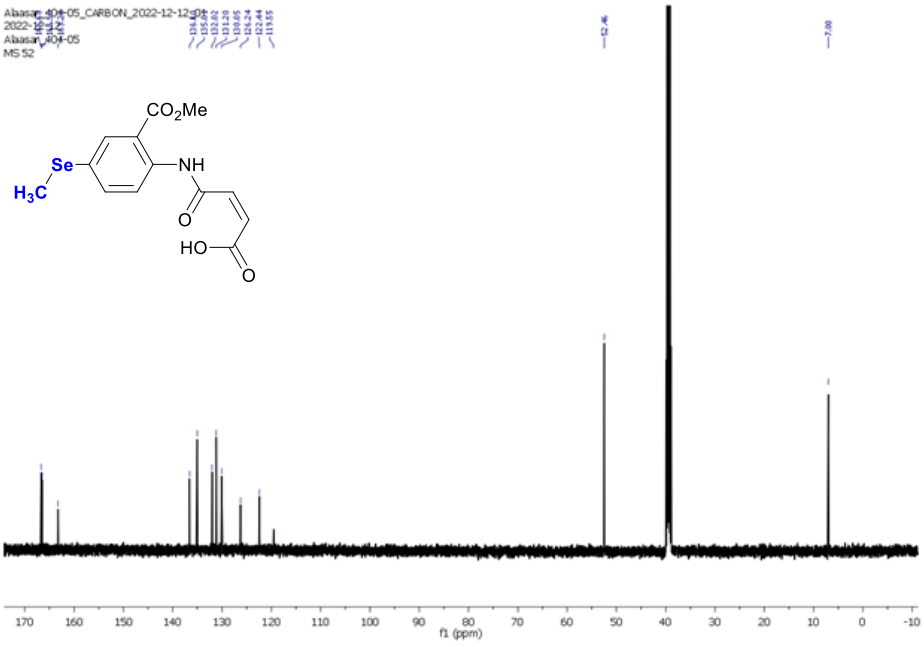
Mass chart of compound **6**

4-((2-(methoxycarbonyl)-4-(methylselanyl)phenyl)amino)-4-oxobut-2-enoic acid (7)

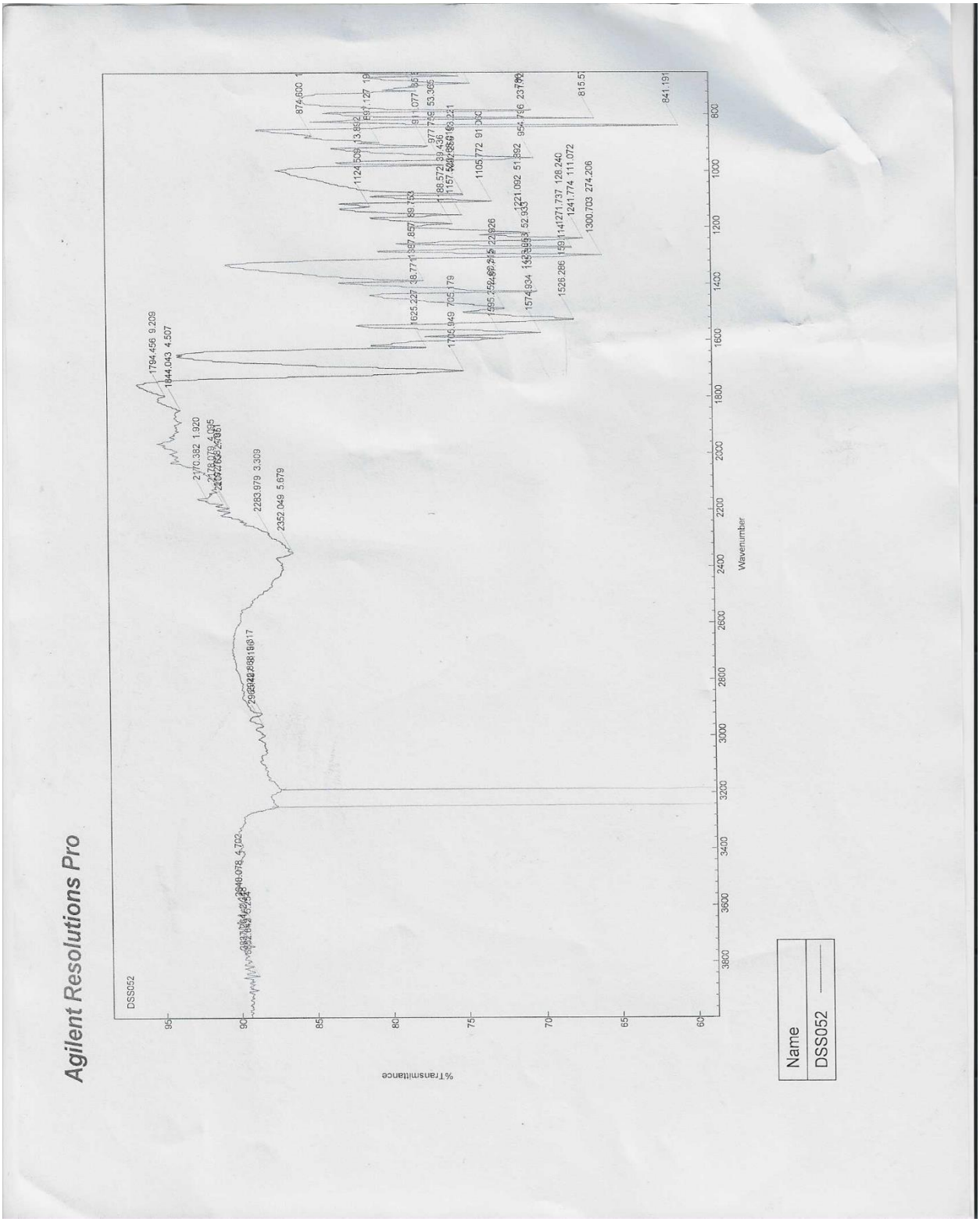




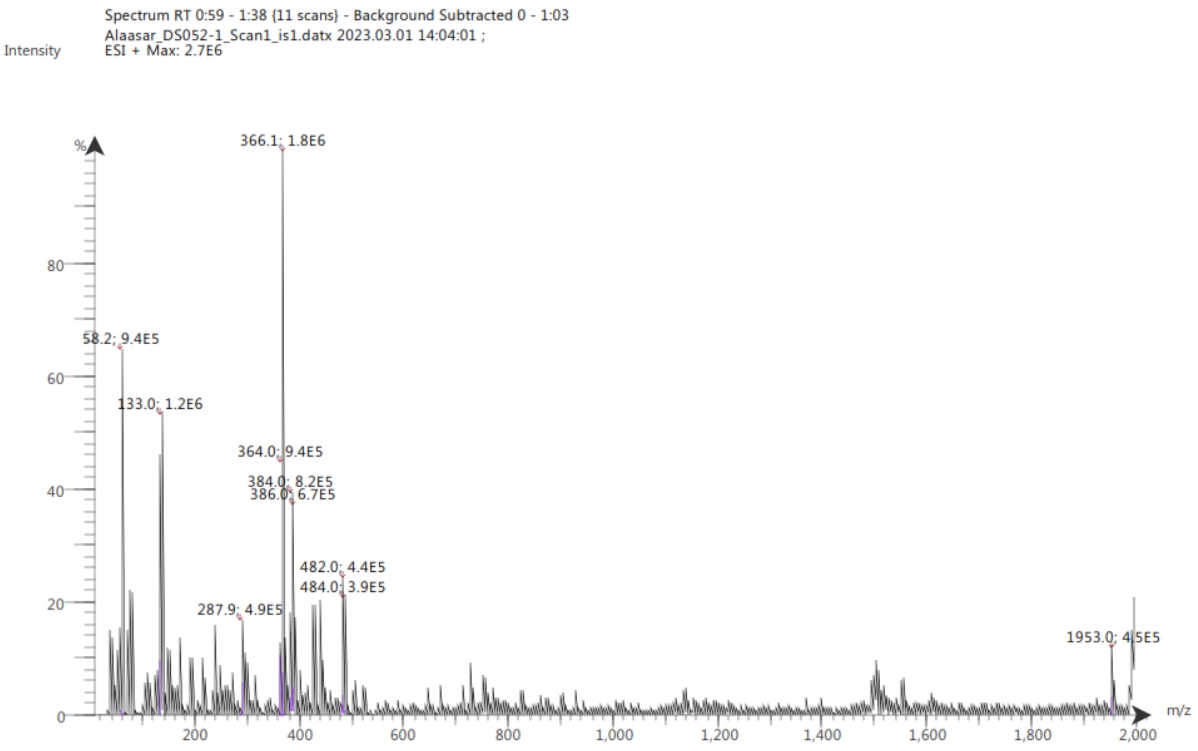
^{1}H NMR chart of compound **7**



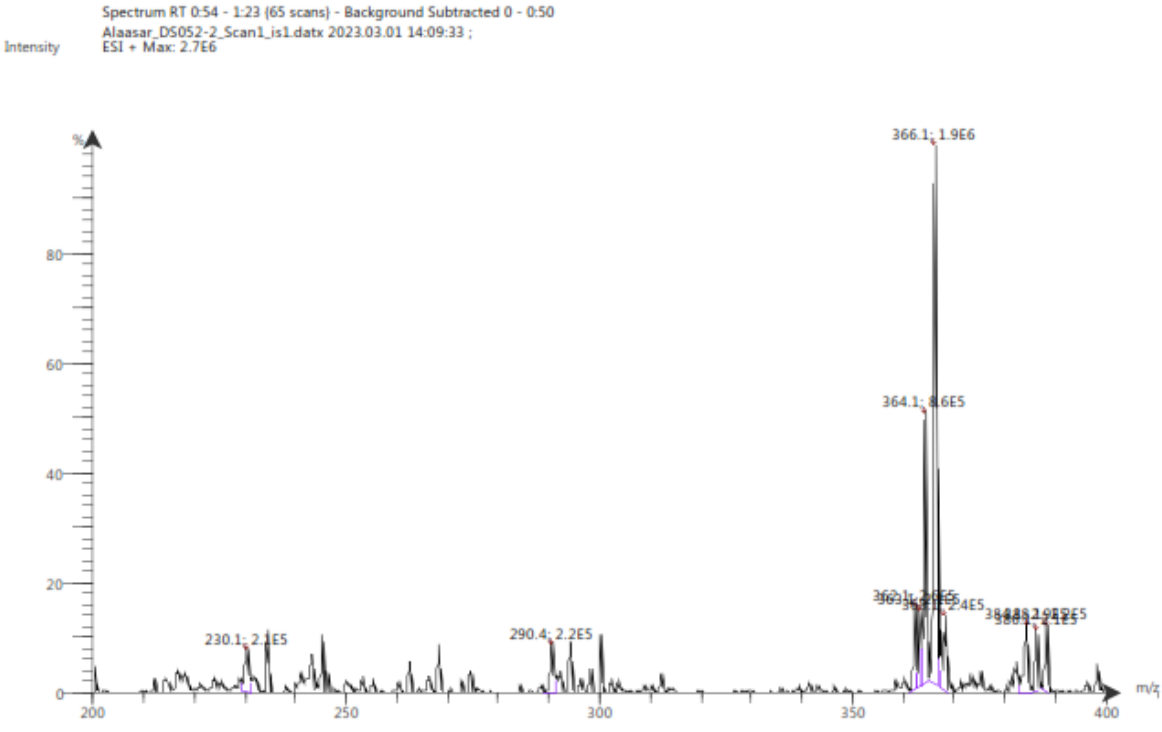
^{13}C NMR chart of compound **7**



IR chart of compound **7**

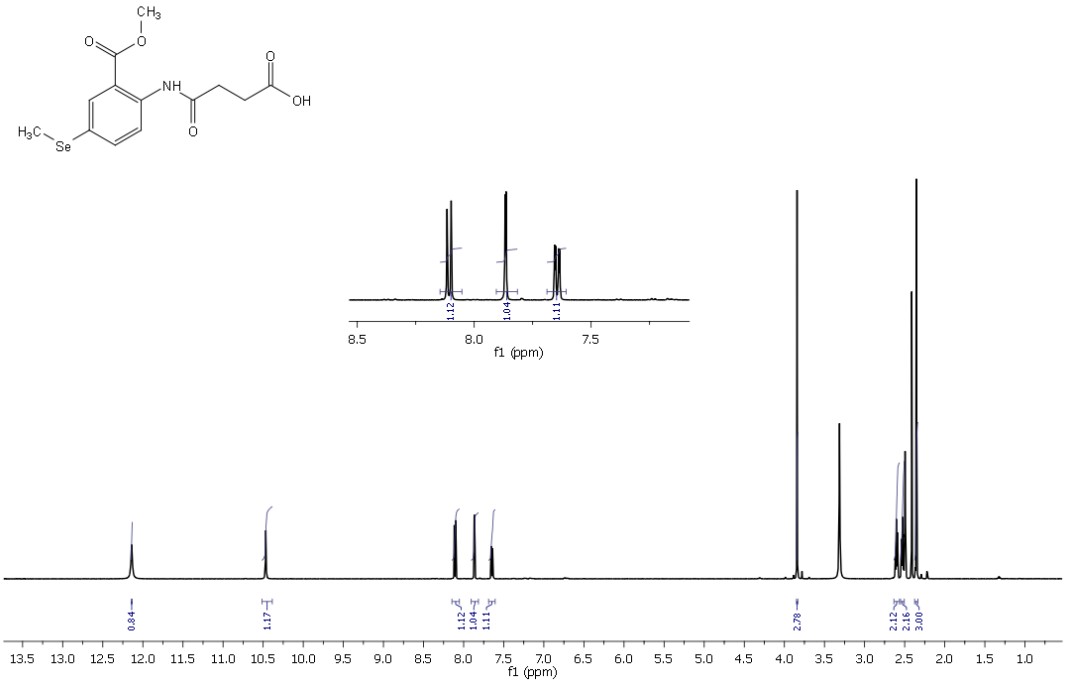


MS chart of compound **7**

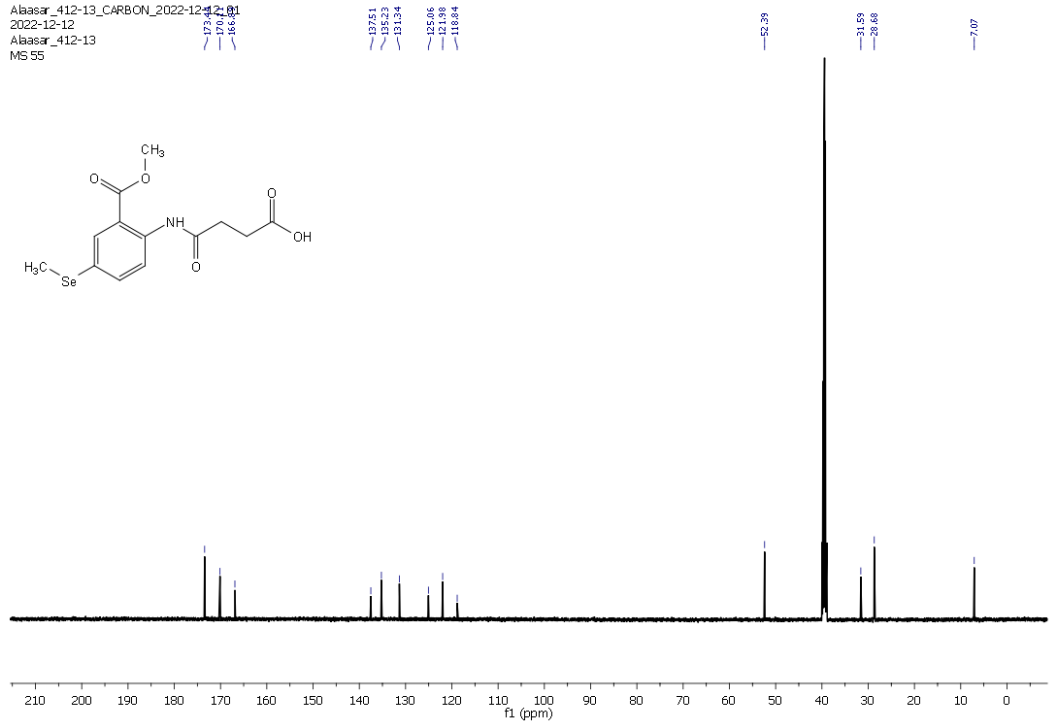


MS chart of compound **7**

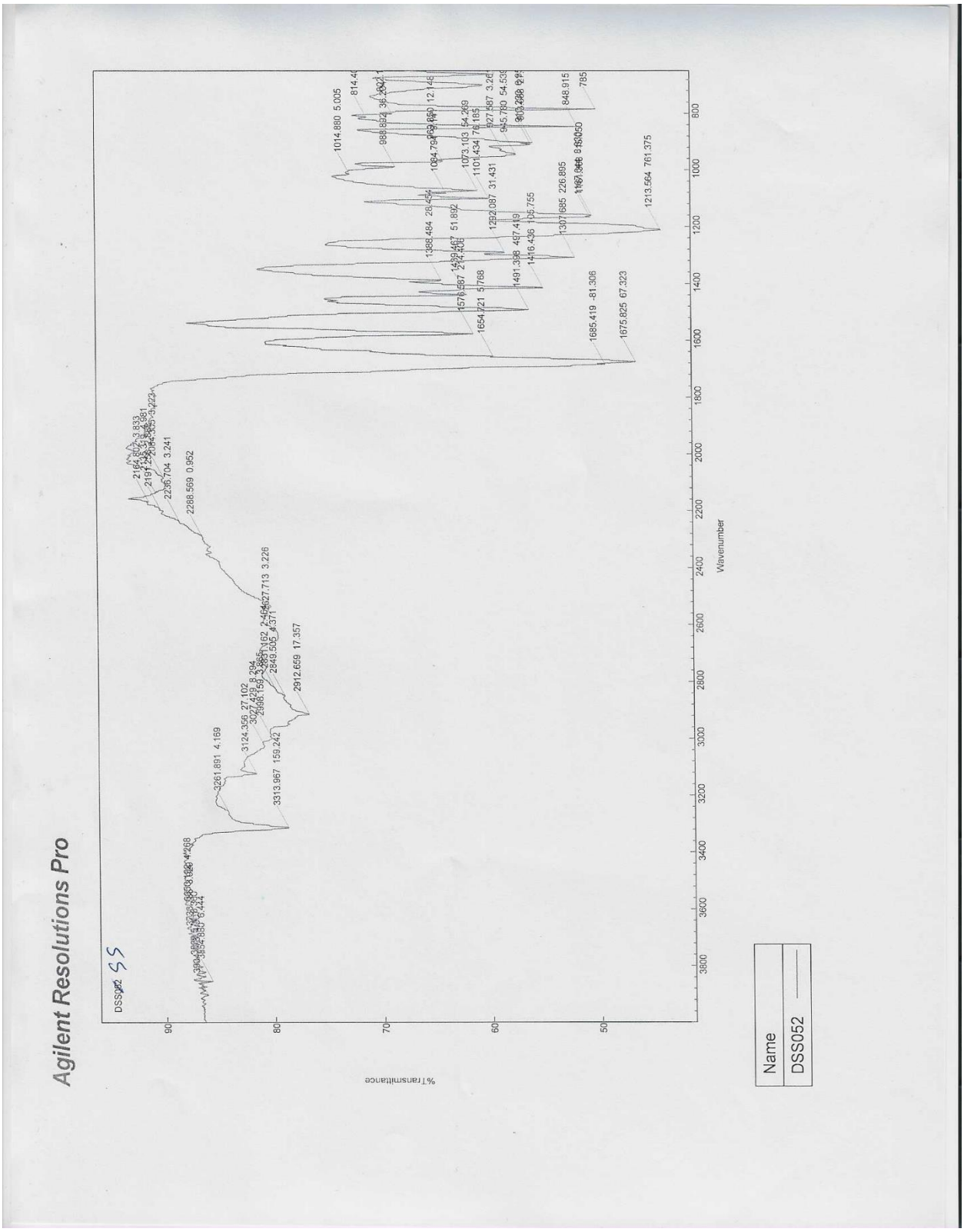
4-((2-(methoxycarbonyl)-4-(methylselanyl)phenyl)amino)-4-oxobut-2-enoic acid (8)



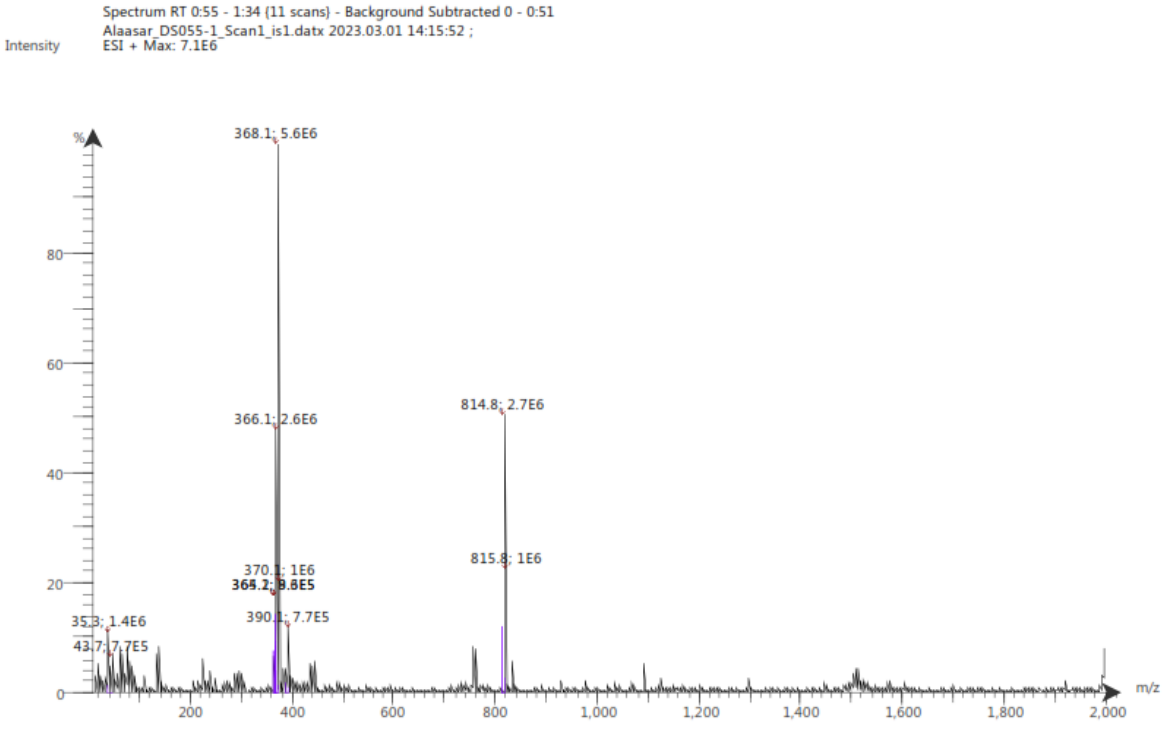
^{1}H NMR chart of compound **8**



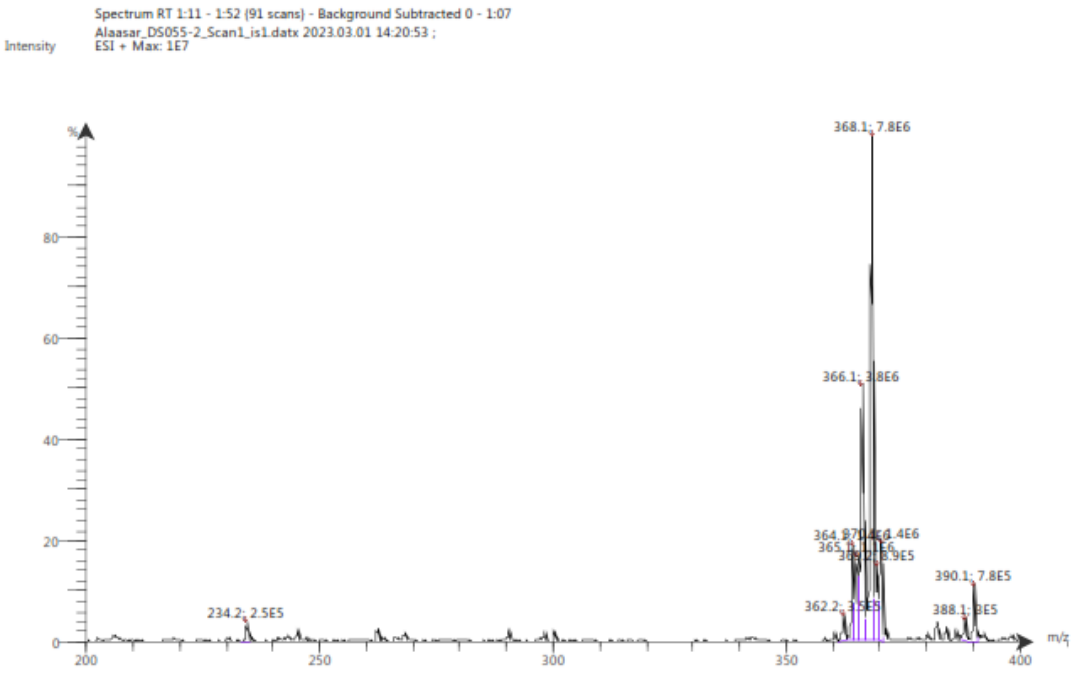
^{13}C NMR chart of compound **8**



IR chart of compound **8**

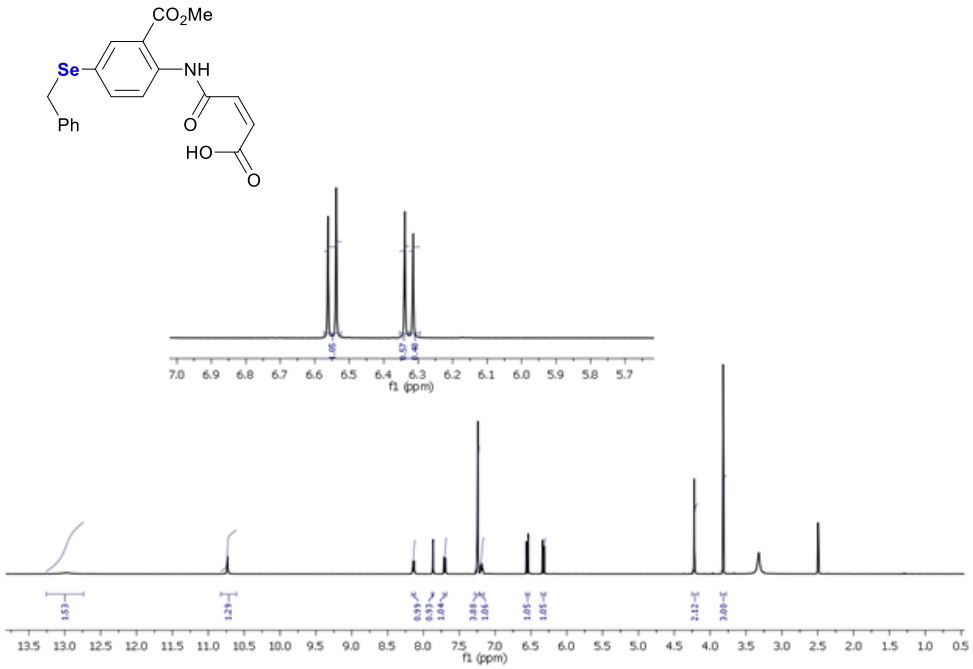


MS chart of compound **8**

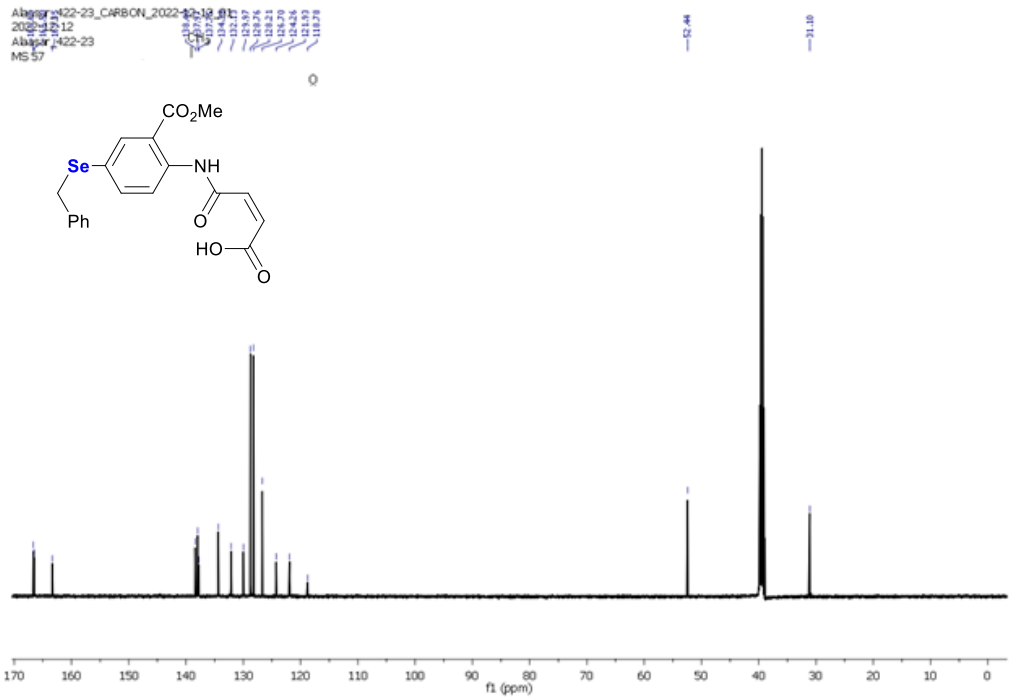


MS chart of compound **8**

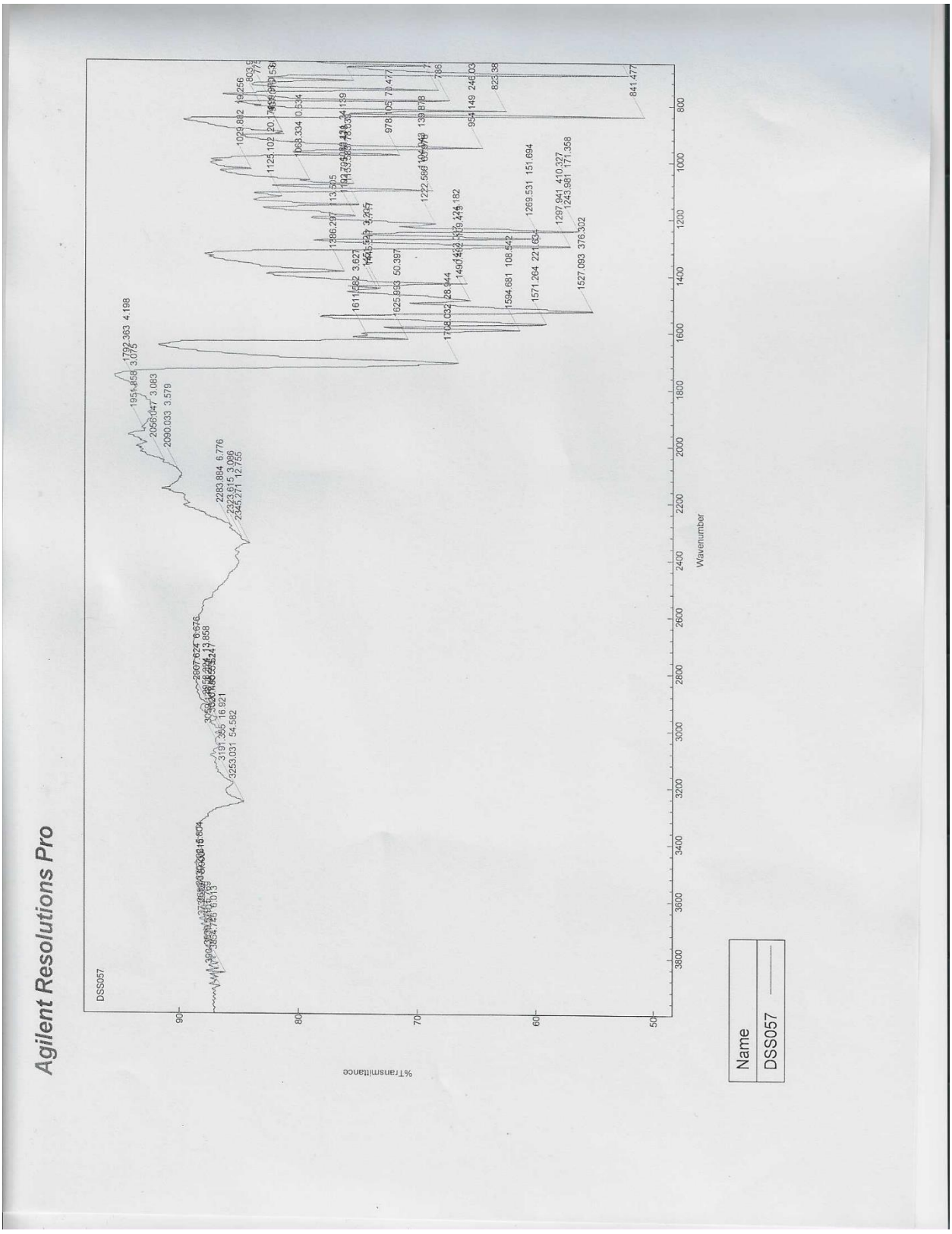
4-((2-(methoxycarbonyl)-4-(methylselanyl)phenyl)amino)-4-oxobut-2-enoic acid (9)



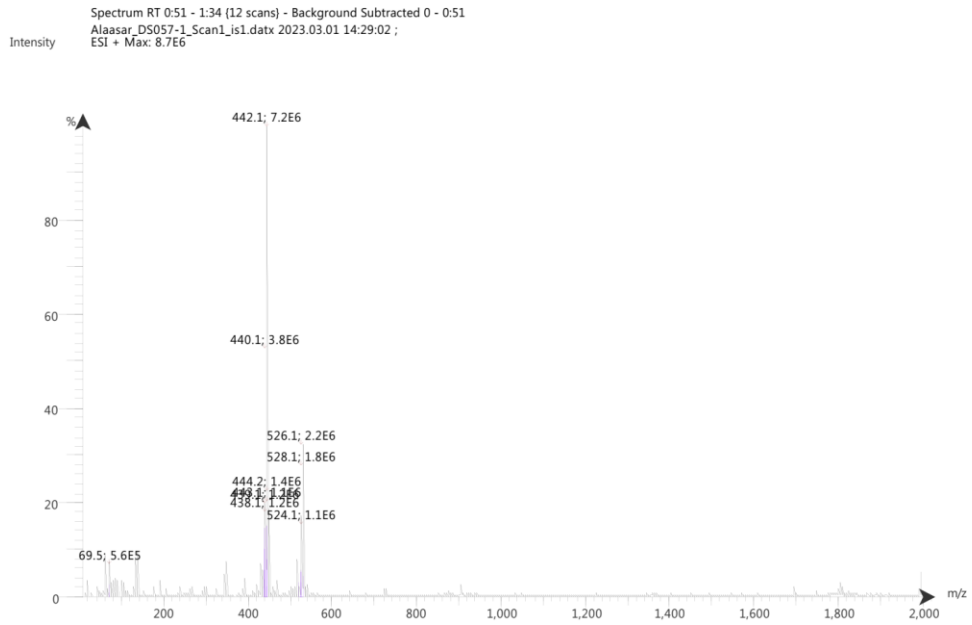
^{1}H NMR chart of compound **9**



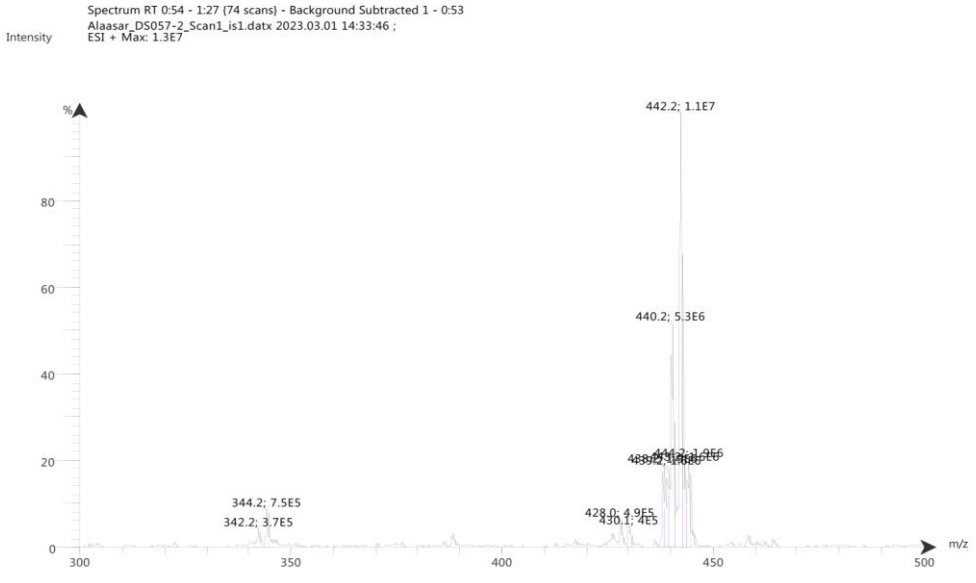
^{13}C NMR chart of compound **9**



IR chart of compound **9**

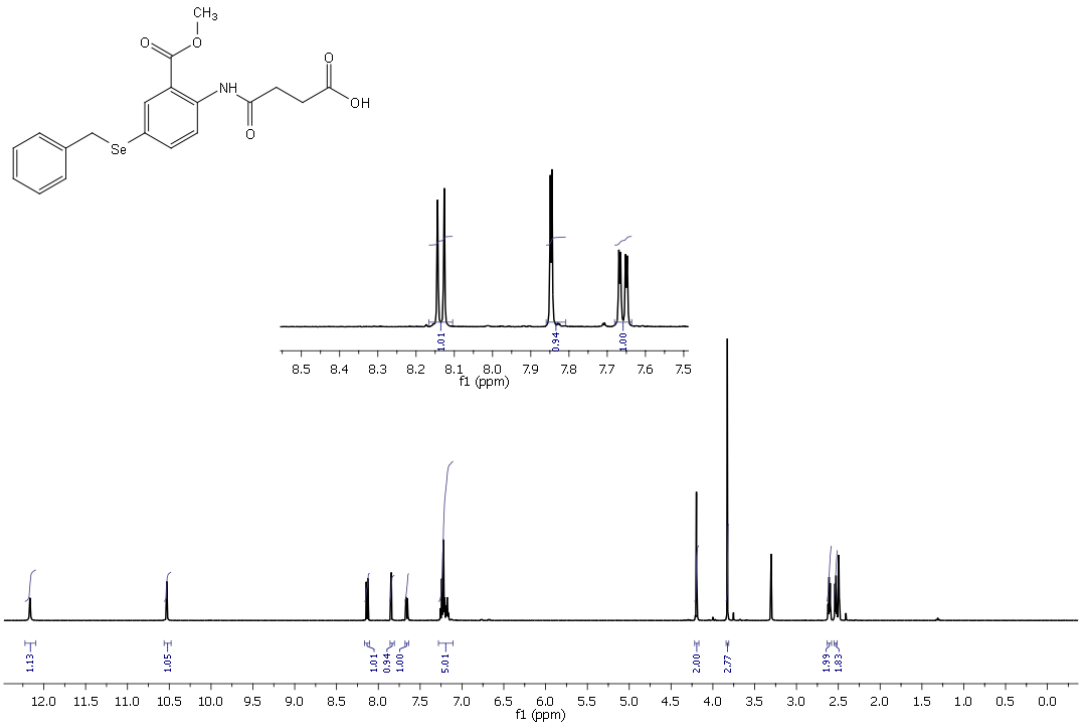


MS chart of compound **9**

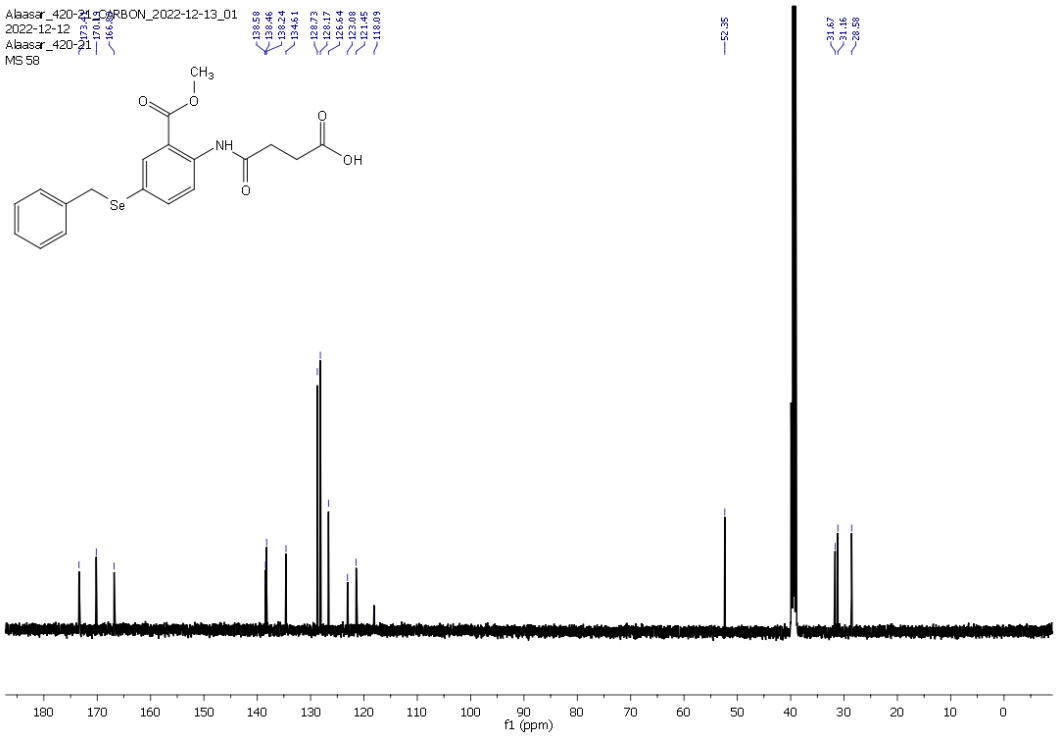


MS chart of compound **9**

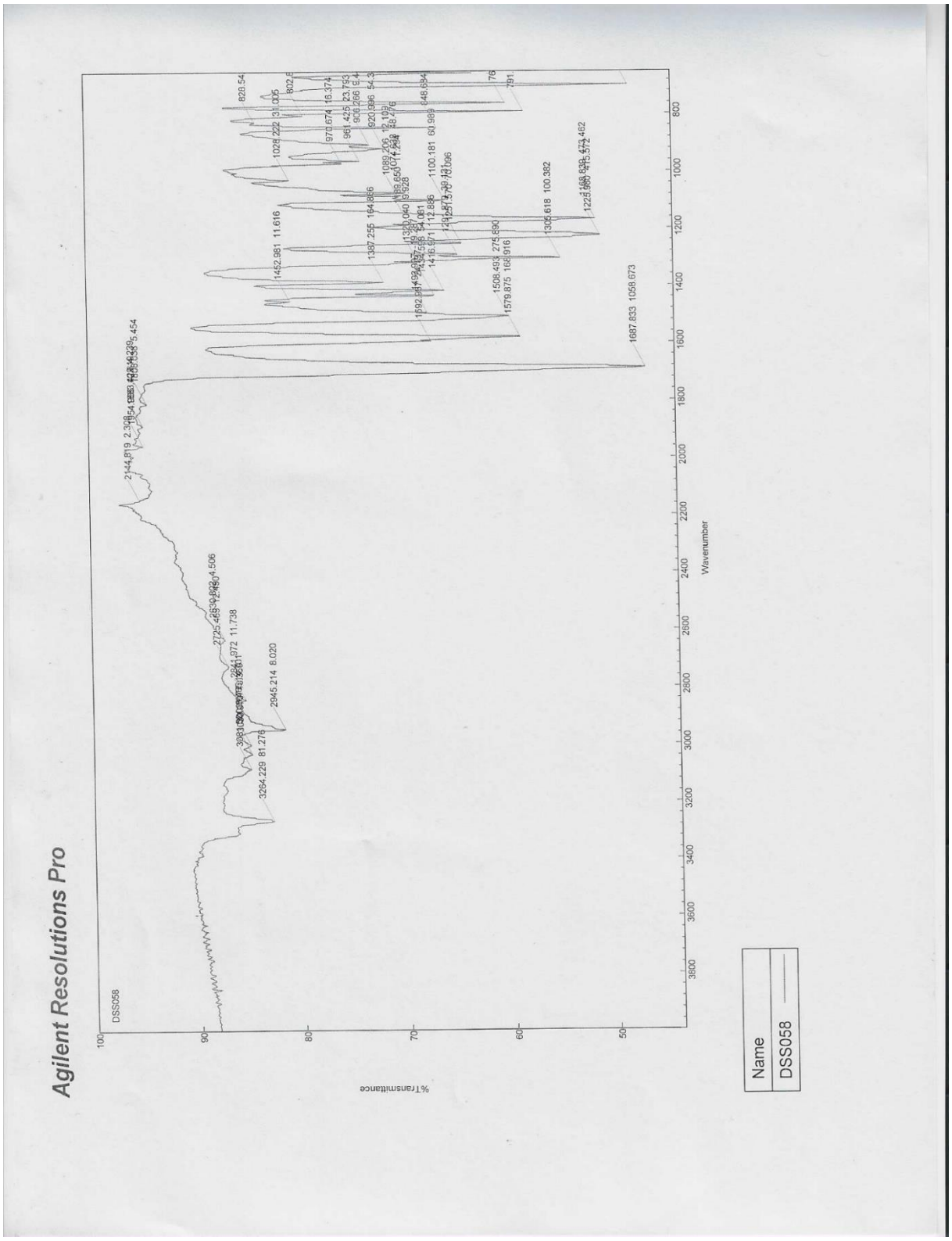
4-((2-(methoxycarbonyl)-4-(methylselanyl)phenyl)amino)-4-oxobut-2-enoic acid (10)



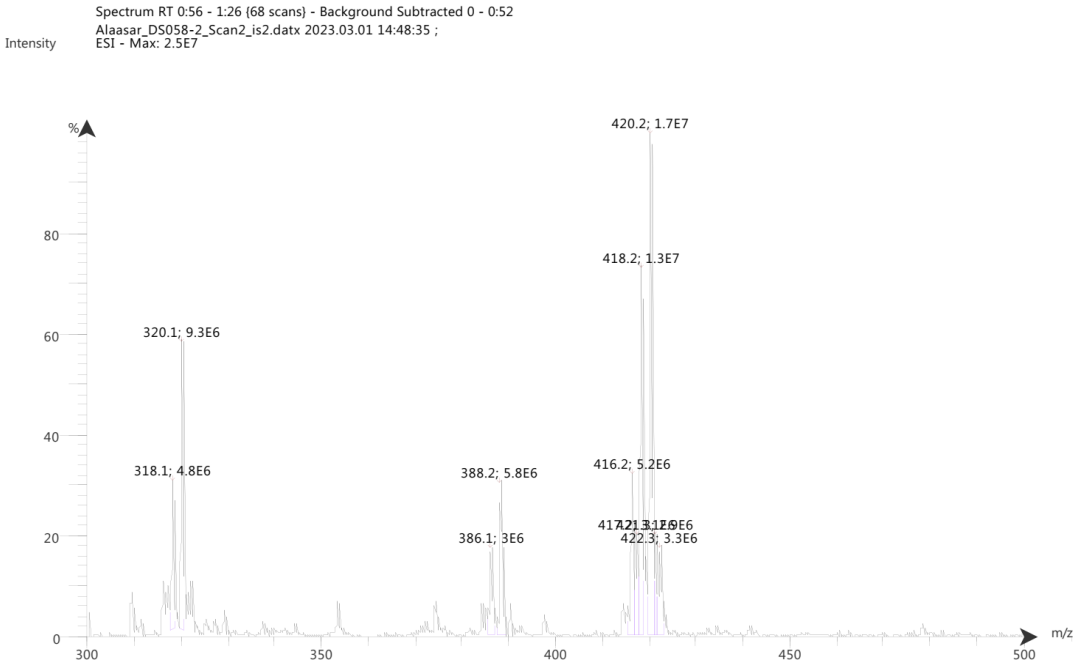
^{1}H NMR chart of compound **10**



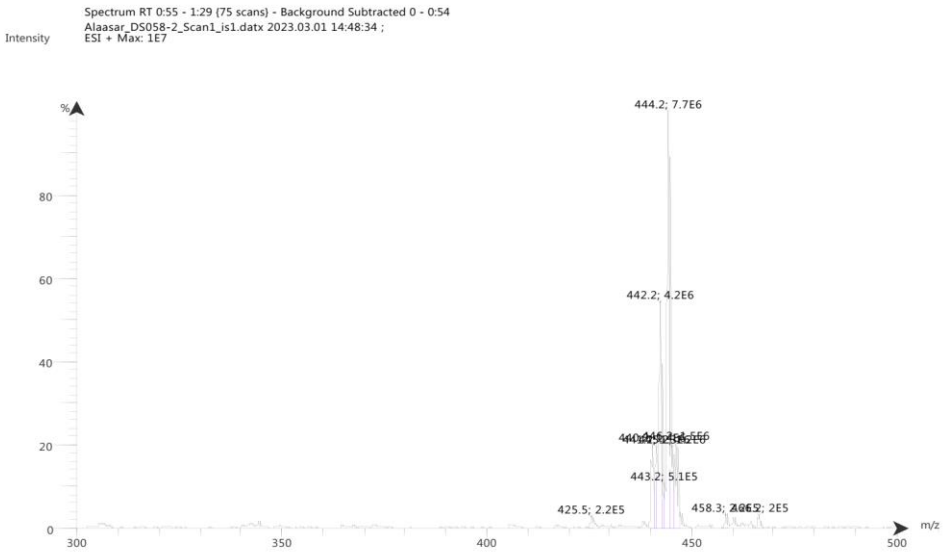
^{13}C NMR chart of compound **10**



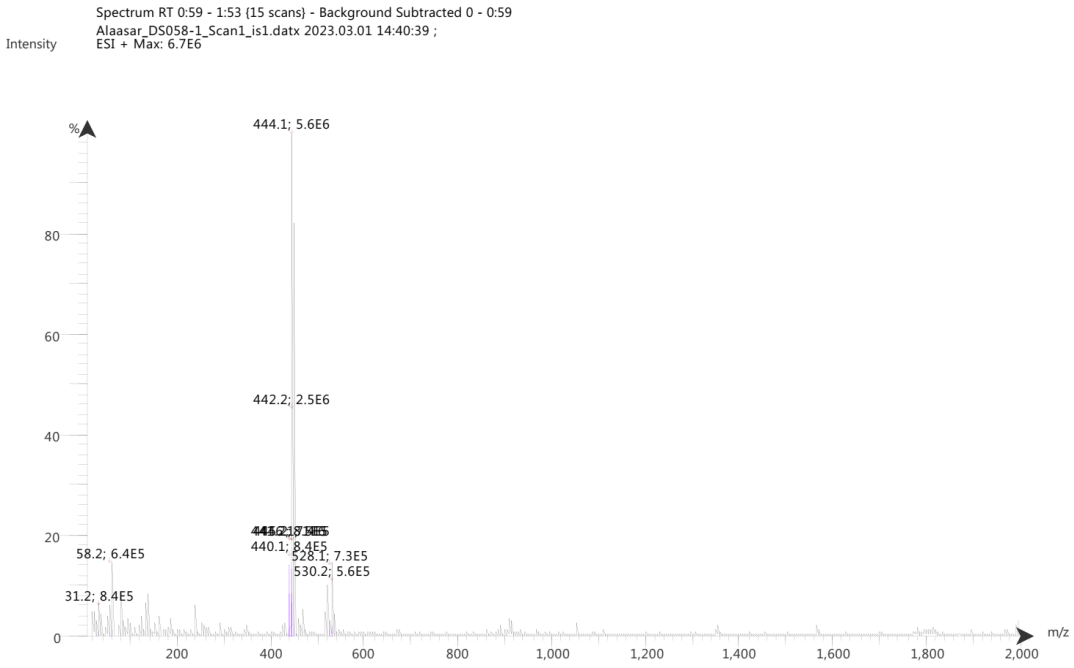
IR chart of compound **10**



MS chart of compound **10**

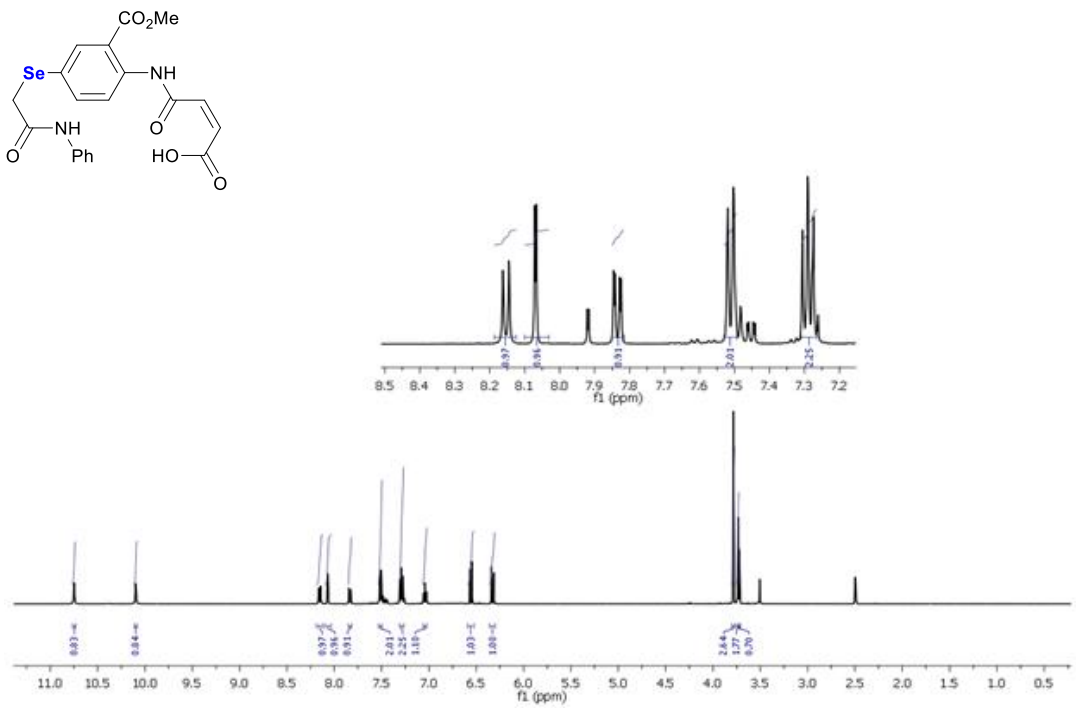


MS chart of compound **10**

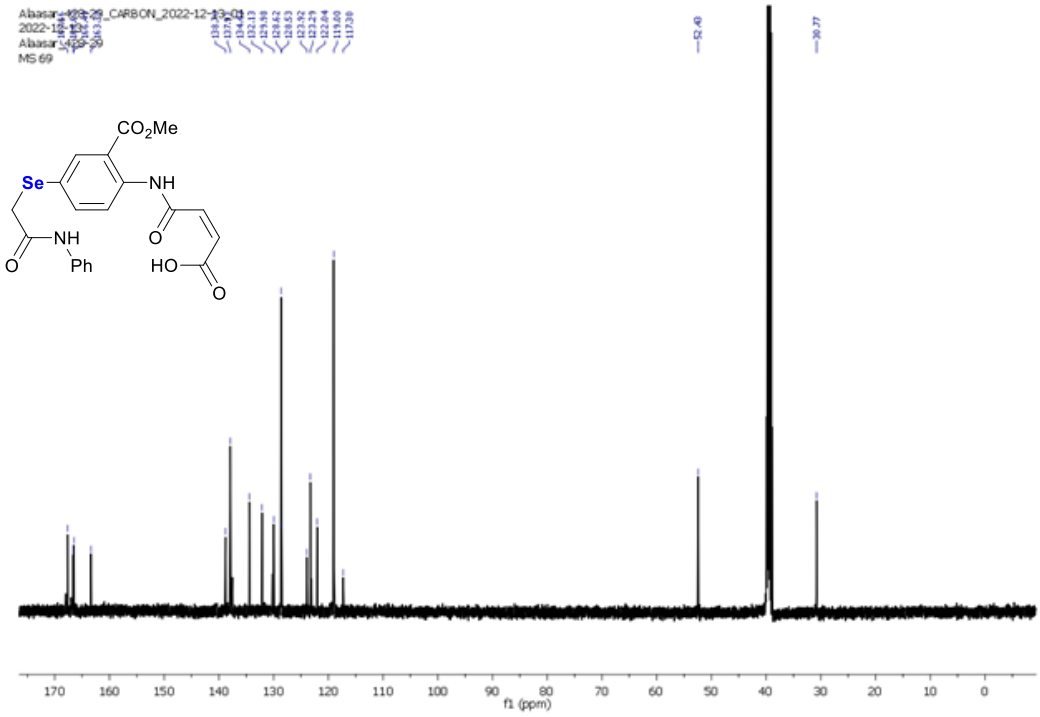


MS chart of compound **10**

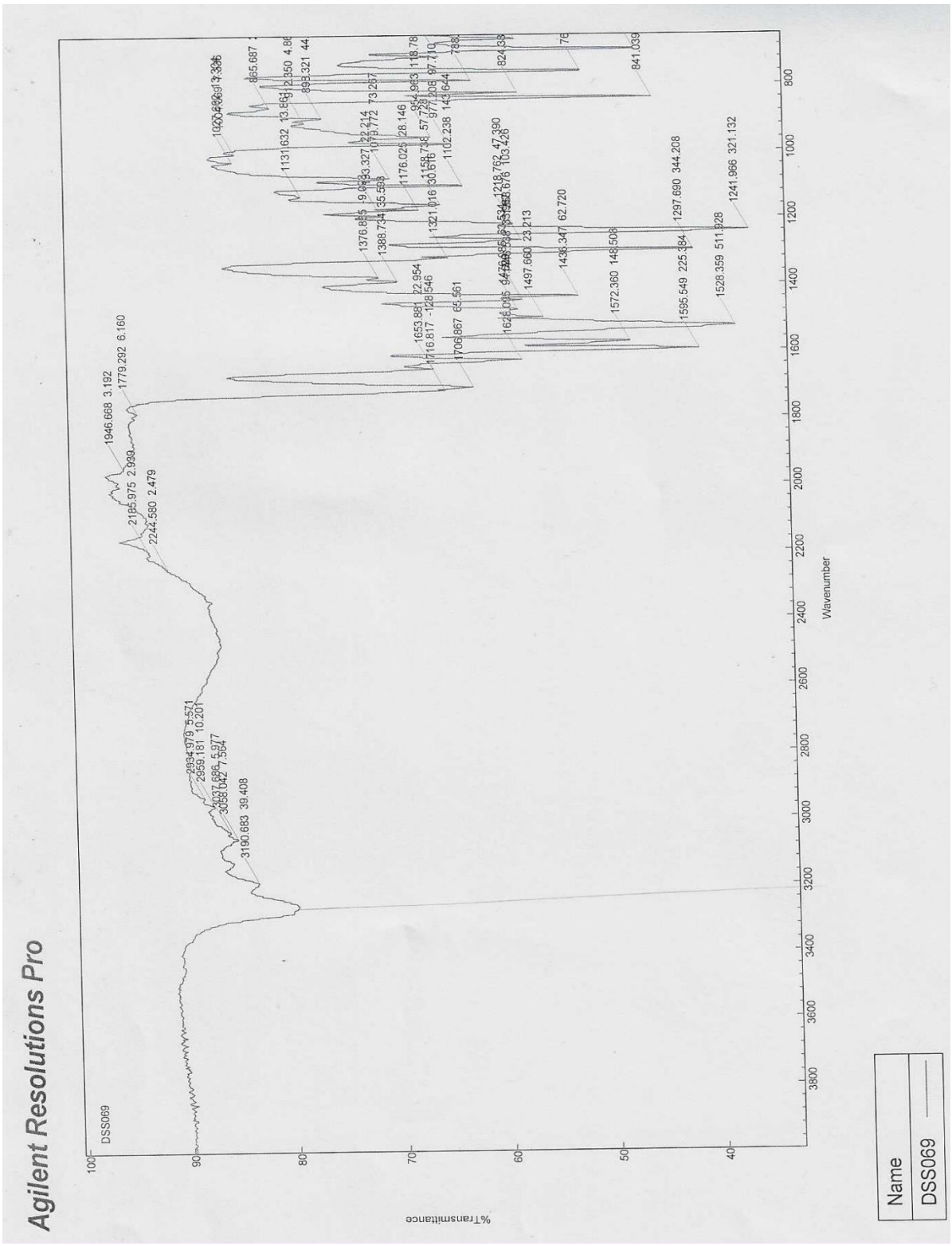
4-((2-(methoxycarbonyl)-4-(methylselanyl)phenyl)amino)-4-oxobut-2-enoic acid (11)



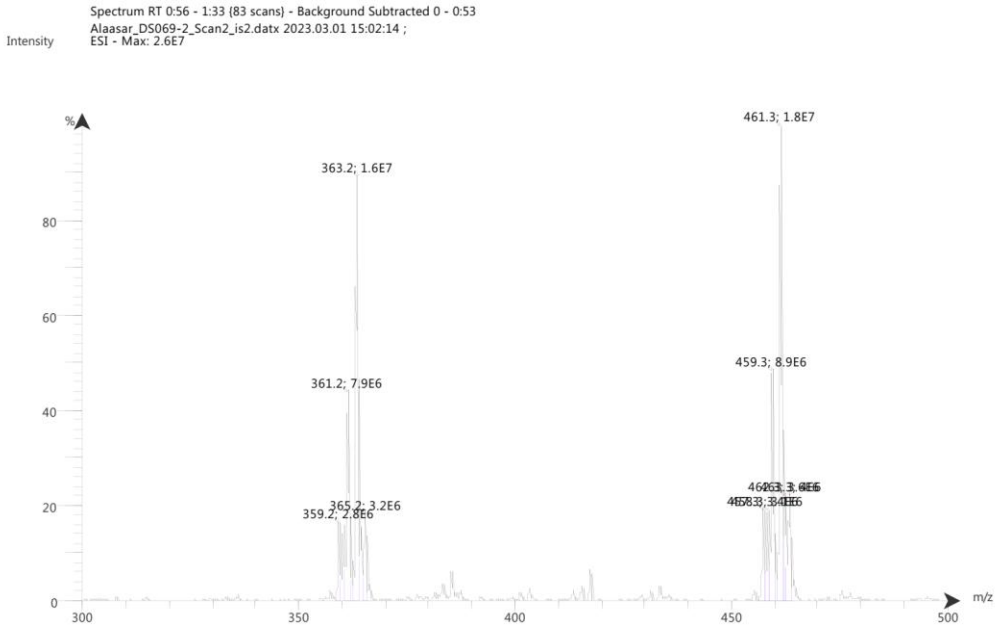
^{1}H NMR chart of compound **11**



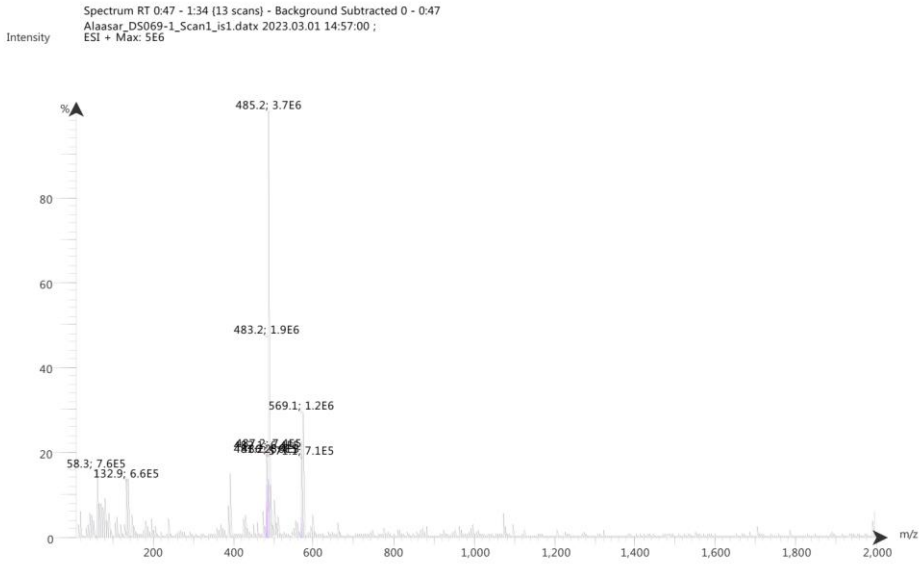
^{13}C NMR chart of compound **11**



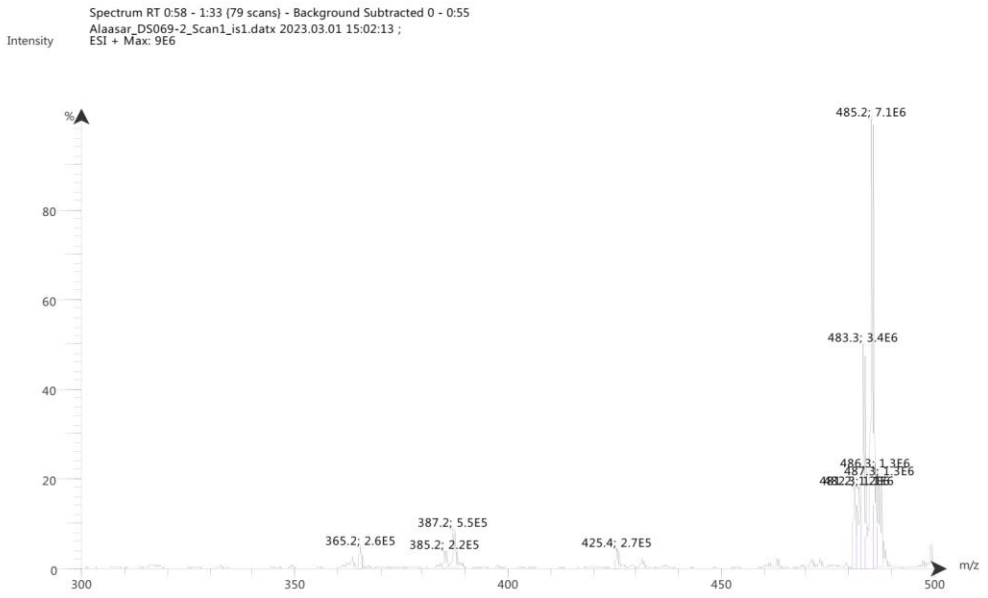
IR chart of compound **11**



MS chart of compound **11**

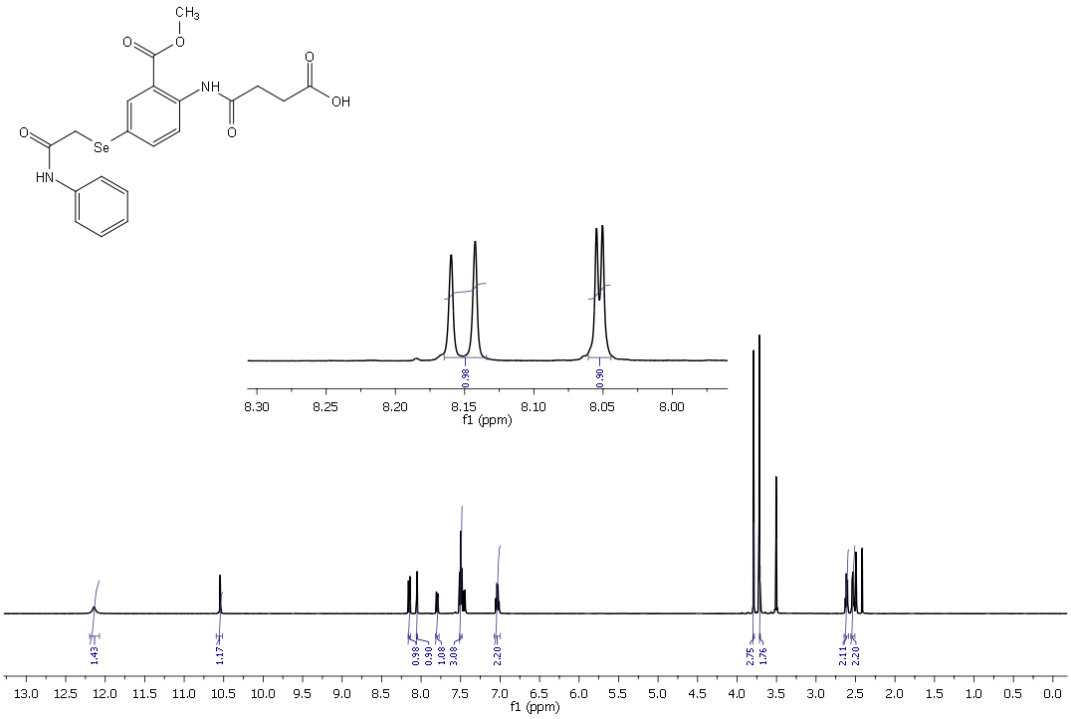


MS chart of compound **11**

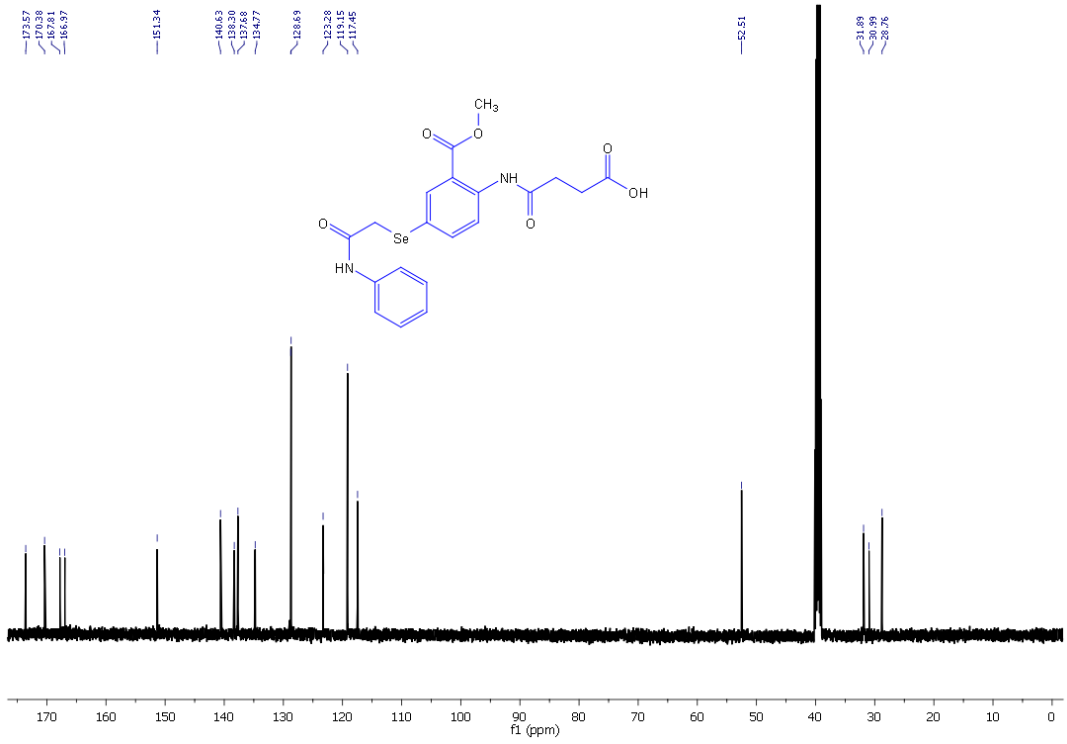


MS chart of compound **11**

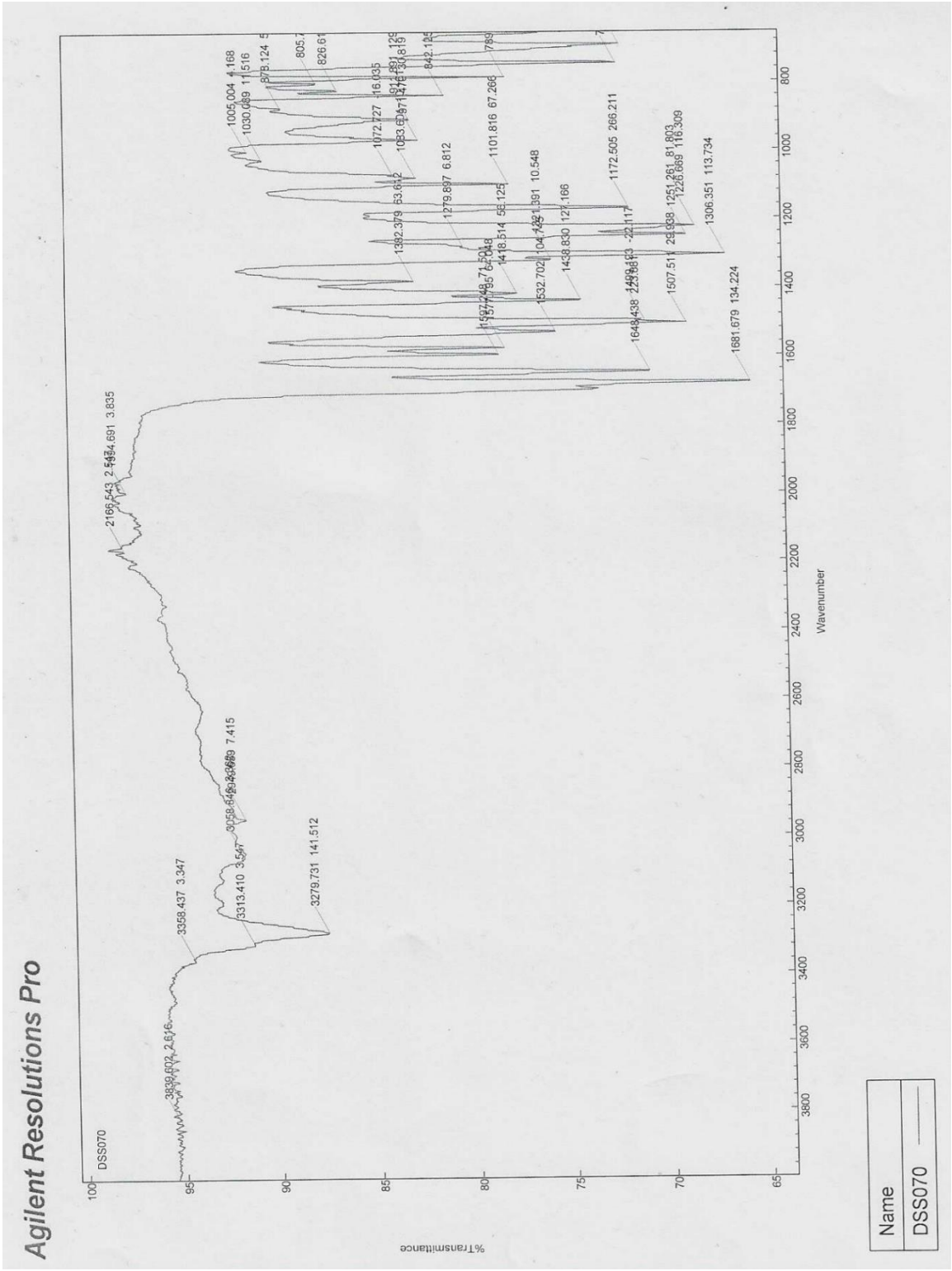
4-((2-(methoxycarbonyl)-4-(methylselanyl)phenyl)amino)-4-oxobut-2-enoic acid (12)



^{1}H NMR chart of compound **12**

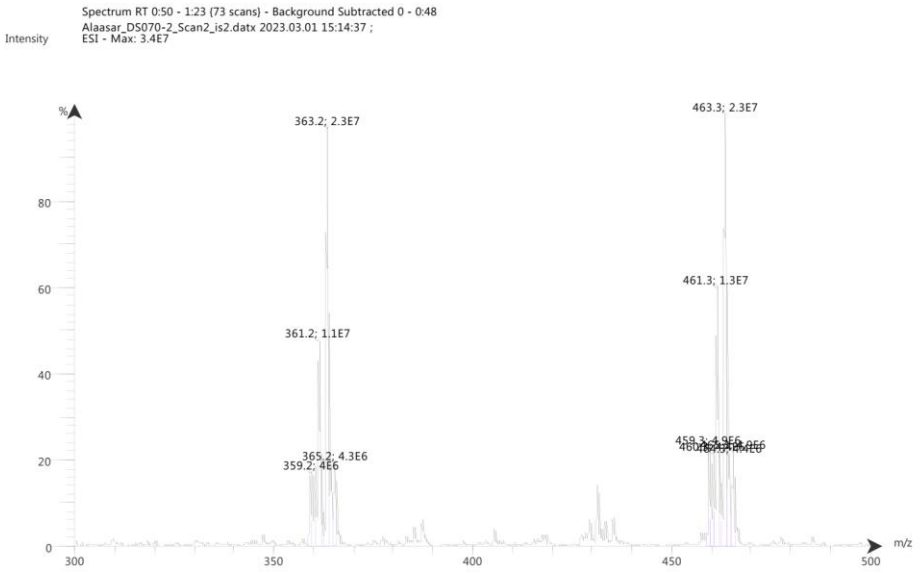


^{13}C NMR chart of compound **12**

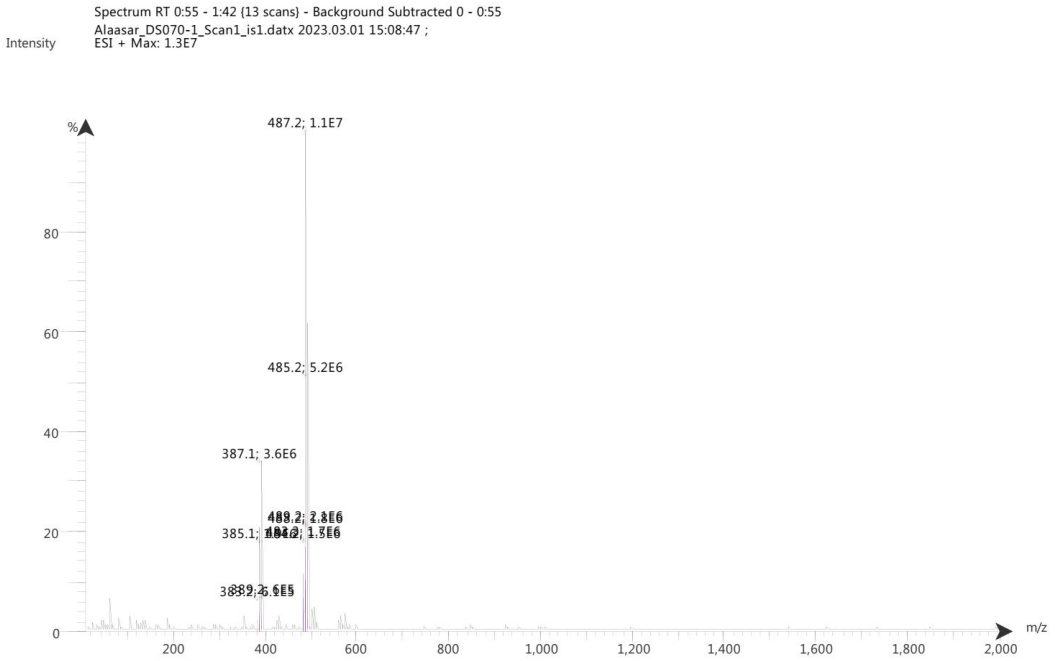


IR chart of compound **12**

MS chart of compound **12**



MS chart of compound **12**



MS chart of compound **12**

SI2. Anti-inflammatory markers assay (Enzyme-linked Immunosorbent Assay)

The microplate provided in this kit has been pre-coated with an antibody specific to COX-2, IL-6, and IL-1β. Standards or samples are then added to the appropriate microplate wells with a biotin-conjugated antibody specific to COX-2, IL-6, and IL-1β. Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. After the TMB substrate solution is added, only those wells that contain COX-2, IL-6, and IL-1β, biotin-conjugated antibody, and enzyme-conjugated Avidin will exhibit a color change. The enzyme-substrate reaction is terminated by the addition of sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 10 nm. The concentration of COX-2, IL-6, and IL-1β in the samples is then determined by comparing the O.D. of the samples to the standard curve. Average the duplicate readings for each standard, control, and sample, and subtract the average zero standard optical density. Construct a standard curve by plotting the mean O.D. and concentration for each standard and draw a best-fit curve through the points on the graph or create a standard curve on log-log graph paper with COX-2, IL-6, and IL-1β concentration on the y-axis and absorbance on the x-axis. Using some plot software, for instance, Curve Expert 1.30, is also recommended. If samples have been diluted, the concentration read from the standard curve must be multiplied by the dilution factor.

Procedure

1. Determine wells for diluted standard, blank, and sample (**3a**, **3b**, **3c**, or **5a**). Prepare 7 wells for standard, 1 well for blank. Add 100 μL each of dilutions of standard, blank, and samples into the appropriate wells. Cover with the Plate sealer. Incubate for 1 h at 37 ºC.

2. Remove the liquid from each well, don't wash.

3. Add 100 μL of Detection Reagent A working solution to each well, cover the wells with the plate sealer, and incubate for 1 h at 37 ºC.

4. Aspirate the solution and wash with 350 μL of 1× Wash Solution to each well using a squirt bottle, multi-channel pipette, manifold dispenser, or autowasher, and let it sit for 1~2 min. Remove the remaining liquid from all wells completely by snapping the plate onto absorbent paper. Totally wash 3 times. After the last wash, remove any remaining Wash Buffer by aspirating or decanting. Invert the plate and blot it against absorbent paper.

5. Add 100 μL of Detection Reagent B working solution to each well, cover the wells with the plate sealer, and incubate for 30 min at 37 ºC.

6. Repeat the aspiration/wash process for a total of 5 times as conducted in step 4.

7. Add 90 μL of Substrate Solution to each well. Cover with a new Plate sealer. Incubate for 10-20 min at 37 ºC (Don't exceed 30 min). Protect from light. The liquid will turn blue with the addition of a Substrate Solution.

8. Add 50 μL of Stop Solution to each well. The liquid will turn yellow with the addition of the stop solution. Mix the liquid by tapping the side of the plate. If the color change does not appear uniform, gently tap the plate to ensure thorough mixing.

9. Remove any drop of water and fingerprint on the bottom of the plate and confirm there is no bubble on the surface of the liquid. Then, run the microplate reader and conduct measurement at 450 nm immediately.

SI3. Molecular dynamic simulations

The molecular dynamic simulations were carried out using the Desmond simulation package of Schrödinger LLC.[5-7] The NPγT ensemble with the temperature 300 K and a pressure 1.01 bar was applied in all runs. The simulation length was 200 ns with a relaxation time of 1 ps. The OPLS3 force field parameters were used in all simulations.[8] The cutoff radius in Coulomb interactions was 9.0 Å. The orthorhombic periodic box boundaries were set 10 Å away from the protein atoms. The water molecules were explicitly described using the transferable intermolecular potential with the three points (TIP3P) model.[9] Salt concentration was set to 0.15 M NaCl and was built using the System Builder utility of Desmond. The Martyna−Tuckerman−Klein chain coupling scheme with a coupling constant of 2.0 ps was used for the pressure control and the Nosé−Hoover chain coupling scheme for the temperature control.[10-11] Nonbonded forces were calculated using a RESPA integrator where the short-range forces were updated every step, and the long-range forces were updated every three steps. The trajectories were saved at 300 ps intervals for analysis. The behavior and interactions between the ligands and protein were analyzed using the Simulation Interaction Diagram tool implemented in the Desmond MD package. The stability of MD simulations was monitored by looking at the RMSD of the ligand and protein atom positions as a function of simulation time.

SI4. MD trajectory analysis and prime MM-GBSA calculations

Simulation interactions diagram panel of Maestro software was used to monitoring interactions contribution in the ligand-protein stability. The molecular mechanics generalized born/solvent accessibility (MM – GBSA) was performed to calculate the ligand binding free energies and ligand strain energies for docked compounds over the last 50 ns with thermal_mmgbsa.py python script provided by Schrodinger which takes a Desmond trajectory file, splits it into individual snapshots, runs the MM-GBSA calculations on each frame, and outputs the average computed binding energy.

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