

Investigation of Direct and Retro Chromone-2-carboxamides based Analogs of *Pseudomonas aeruginosa* Quorum Sensing Signal as New Anti-biofilm Agents

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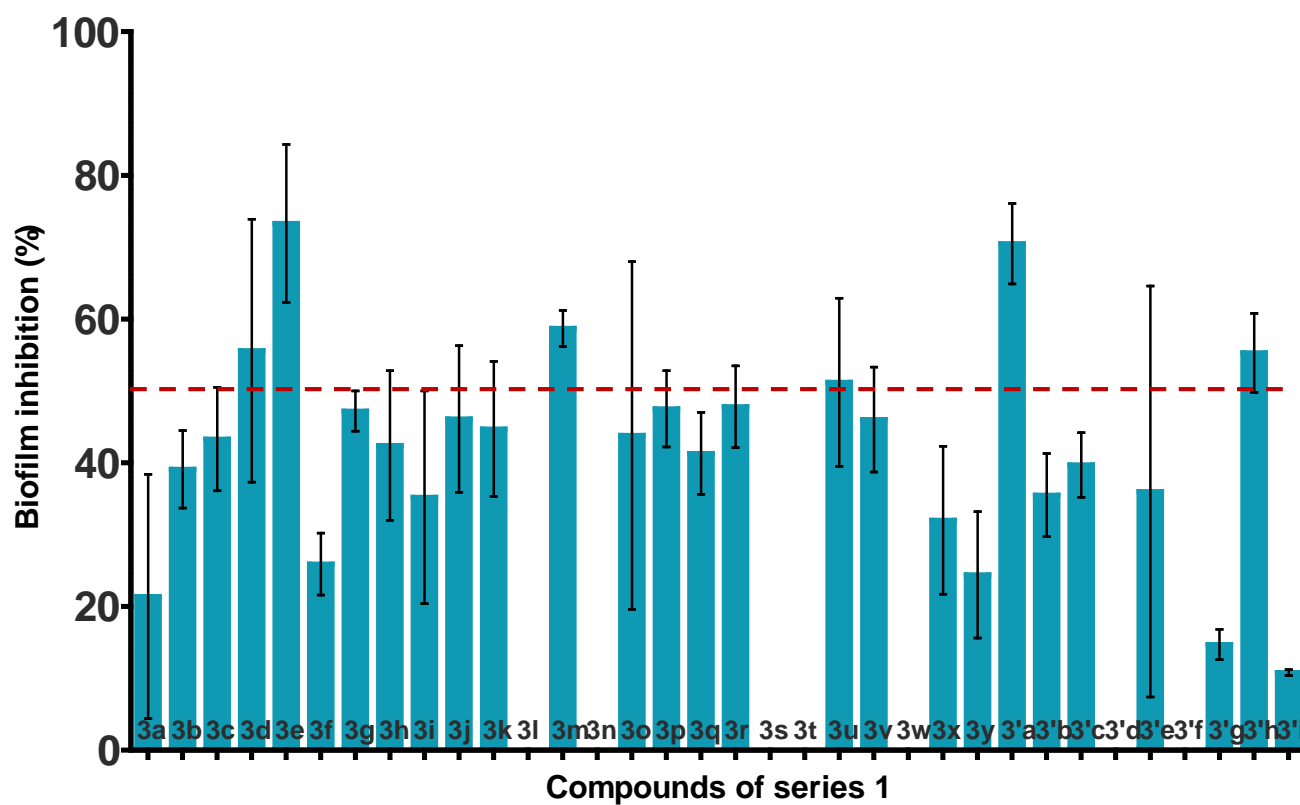
Supplementary Material

Table S1: Structural properties and Lipinski's parameters of chromone carboxamides

Code	MW	LogS	LogP	pKa	non-H atoms	VdW surface area (Å ²)
Series 1						
3a	265.0	-4.6	2.73	12.11	20	338.8
3b	279.0	-5.1	3.24	12.19	21	370.1
3c	293.0	-5.6	3.69	12.2	22	400.4
3d	307.0	-6.1	4.13	12.19	23	431.1
3e	283.0	-4.9	2.87	12.18	21	345.8
3f	299.0	-5.3	3.34	12.09	21	355.2
3g	344.2	-5.6	3.50	12.09	21	359.6
3h	283.0	-4.9	2.87	10.9	21	345.6
3i	299.0	-5.3	3.34	11.41	21	354.8
3j	344.2	-5.6	3.50	11.55	21	358.7
3k	317.7	-5.6	3.48	11.51	22	361.8
3m	310.3	-5.3	2.67	11.58	23	376.9
3o	355.3	-5.9	2.61	11.32	26	413.3
3p	295.3	-4.6	2.57	12.24	22	386.4
3q	295.3	-4.6	2.57	11.27	22	385.5
3r	311.4	-5.3	3.36	11.67	22	392.4
3u	350.3	-4.9	2.62	15.21	26	472.3
3v	267.2	-3.9	1.49	0.69	20	324.1
3x	271.3	-4.4	2.51	13.97	20	386.6
3y	323.4	-5.6	2.81	13.56	24	447.0
3'a	293.0	-5.6	3.69	12.11	22	400.9
3'b	366.0	-4.2	2.43	9.01	21	350.2
3'c	281.0	-4.1	3.08	8.06	27	530.1
3'e	386.2	-4.4	2.1	14.03	28	579.2
3'g	330.0	-1.8	2.44	9.32	24	537.6
3'i	384.0	-3.4	0.31	5.03	28	532.9
Series 2						
6a	265.3	-4.9	2.84	12.85	20	338.1
6b	279.3	-5.4	3.35	13.08	21	370.1
6c	293.3	-5.9	3.80	13.06	22	400.9
6d	307.3	-6.4	4.24	13.05	23	433.2
6e	283.3	-5.2	2.98	12.62	21	345.2
6f	300.4	-5.6	3.45	12.60	21	354.3
6g	344.2	-5.9	3.61	12.64	21	358.6
6h	283.2	-5.2	2.98	9.84	21	343.8
6i	300.4	-5.6	3.45	10.09	21	352.9
6j	344.2	-5.9	3.61	10.07	21	356.3
6k	317.7	-5.9	3.59	9.93	22	360.0

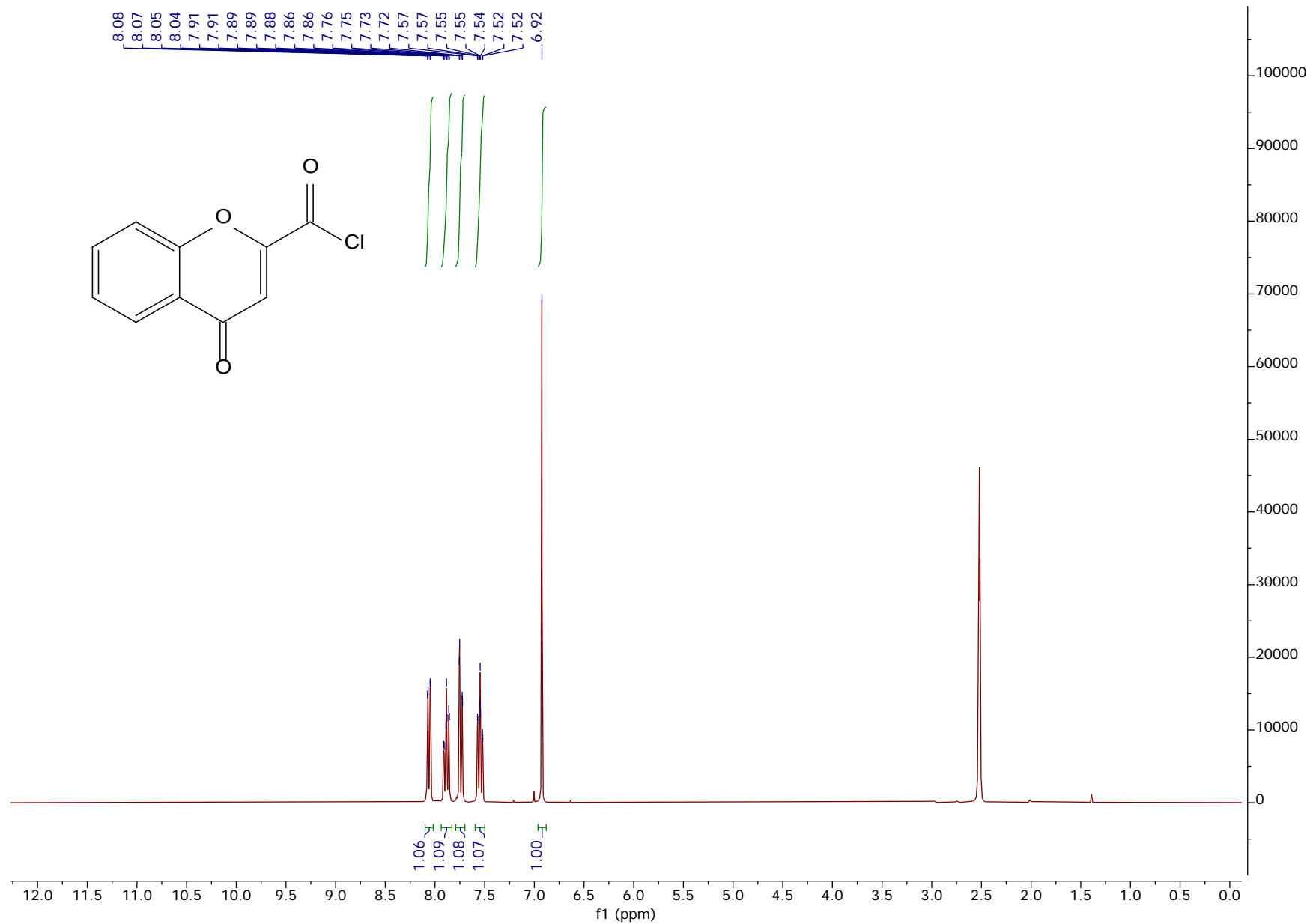
6l	317.7	-5.9	3.59	12.28	22	360.5
6m	310.3	-5.6	2.78	10.16	23	376.1
6n	357.3	-5.0	2.72	8.79	26	419.0
6o	357.3	-5.0	2.72	9.38	26	421.0
6p	295.3	-4.9	2.68	12.93	22	386.3
6q	296.3	-4.9	2.68	10.61	22	385.5
6r	312.4	-5.6	3.47	10.9	22	392.7
6s	327.3	-4.9	2.53	12.57	24	434.9
6t	325.3	-4.9	2.53	10.65	24	435.1
6u	350.4	-5.2	2.73	13.53	26	473.8
6v	267.2	-3.2	1.46	12.07	20	323.6
6w	231.3	-3.8	2.13	12.43	17	326.4
6x	271.3	-5.2	3.10	12.40	20	385.5
6y	323.4	-6.3	3.59	12.36	24	447.3

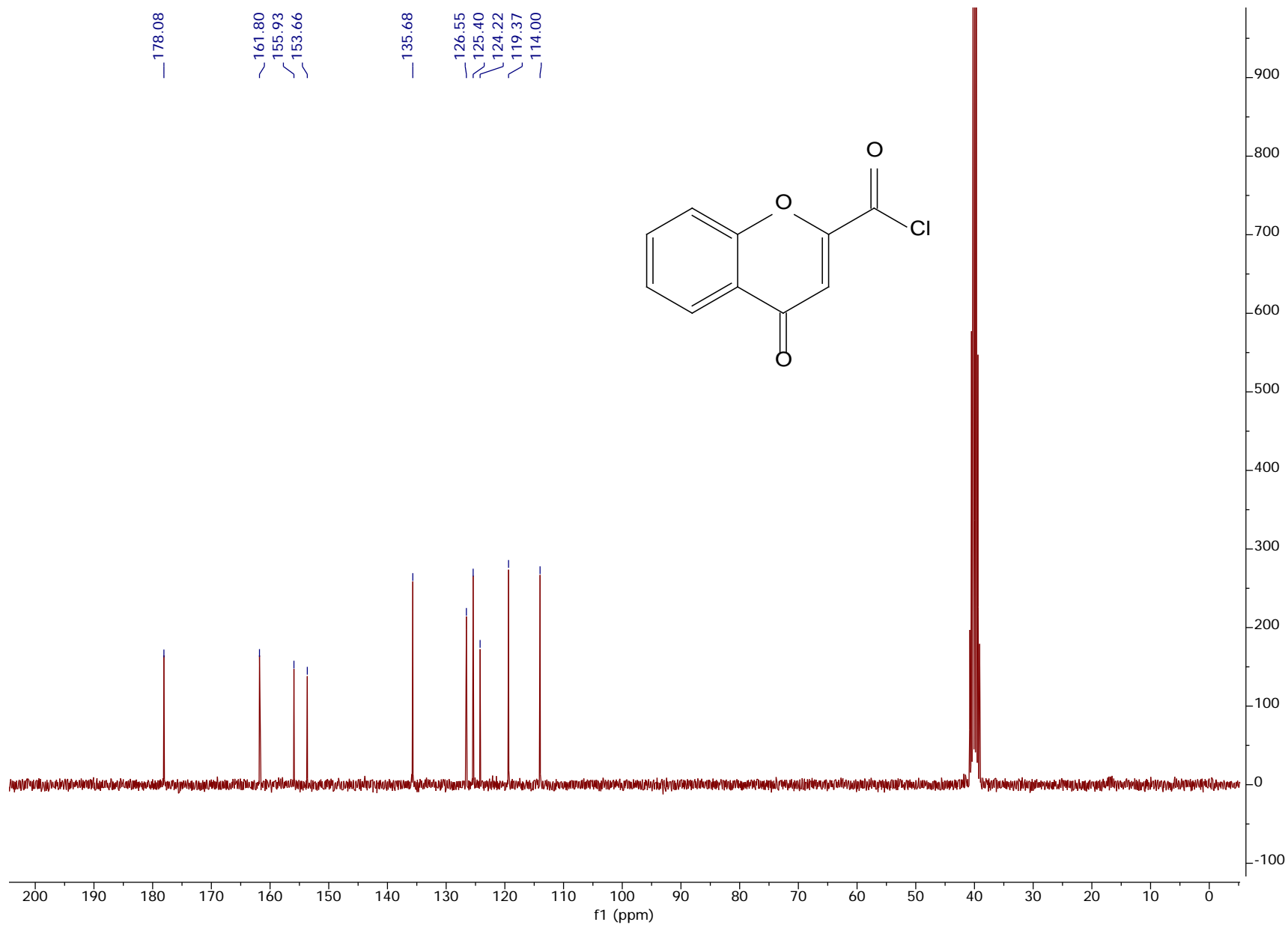
Figure S1. Anti-biofilm activity against *P. aeruginosa* PAO1 of direct chromone carboxamides (**3a-y** and **3'a-i**) at 50 μ M, expressed as inhibition % (GraphPad 5.0)



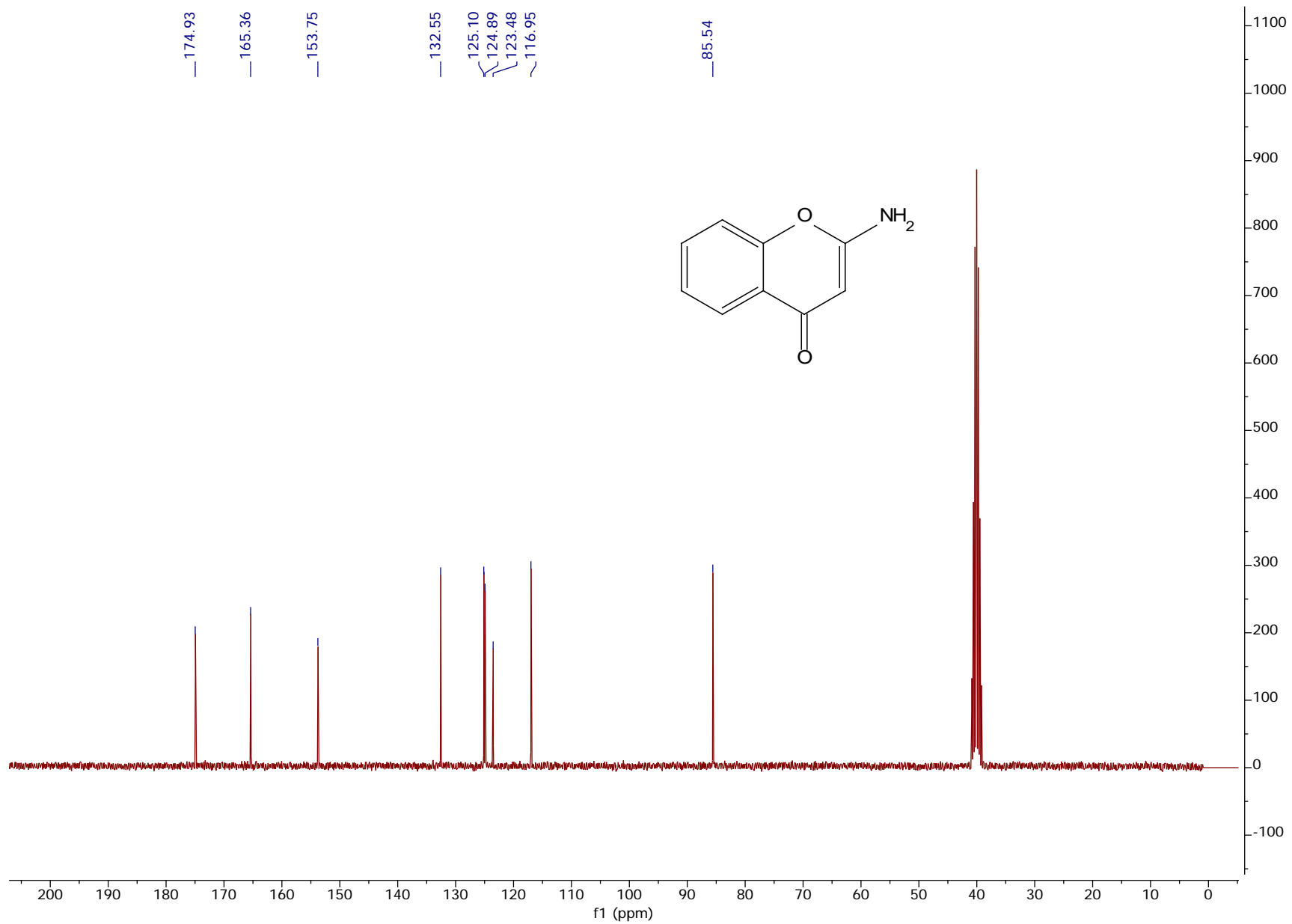
Figures S2 to S123: ^1H (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6) spectra of final compounds

4-Oxo-4H-chromene-2-carbonyl chloride (2)

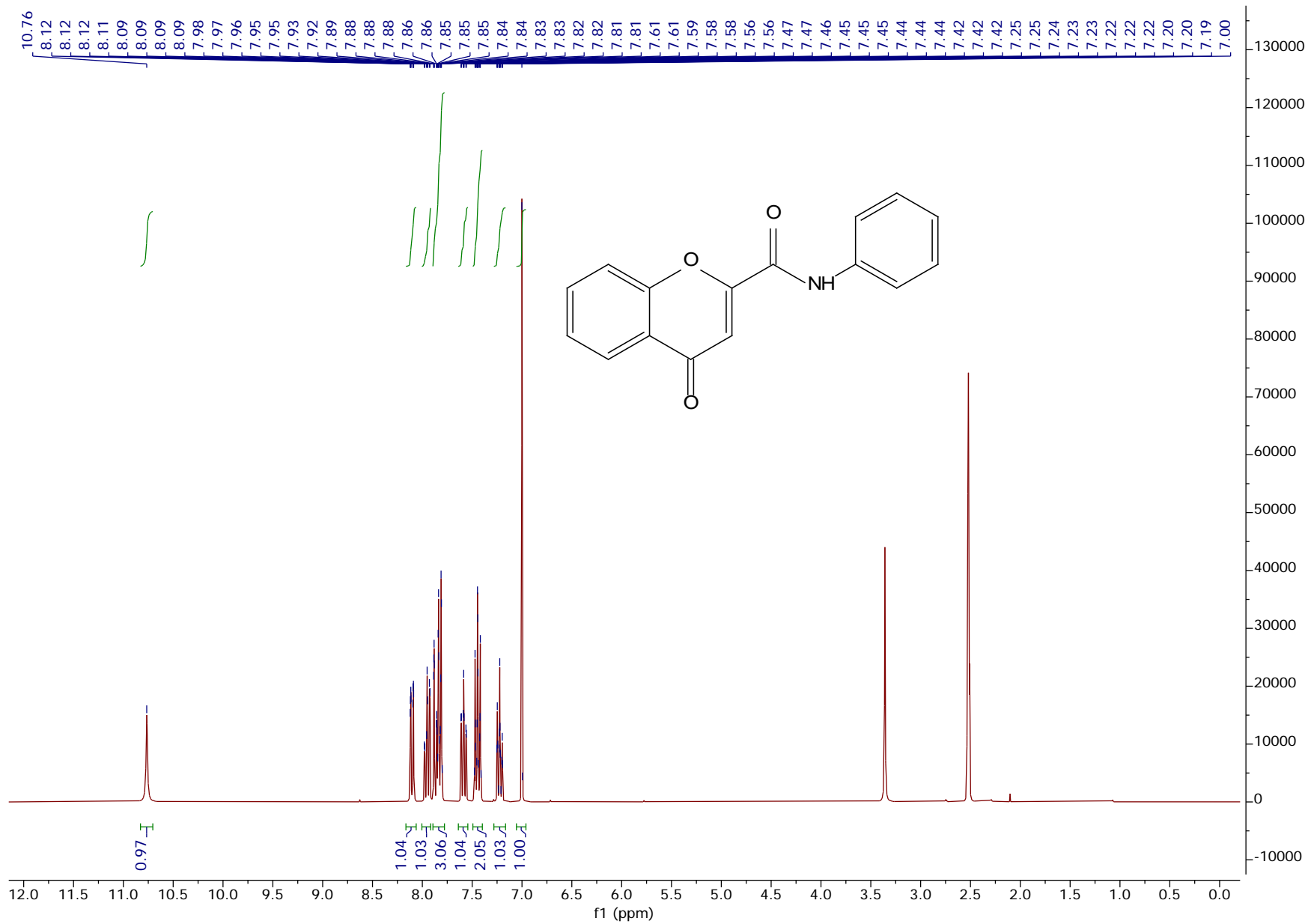


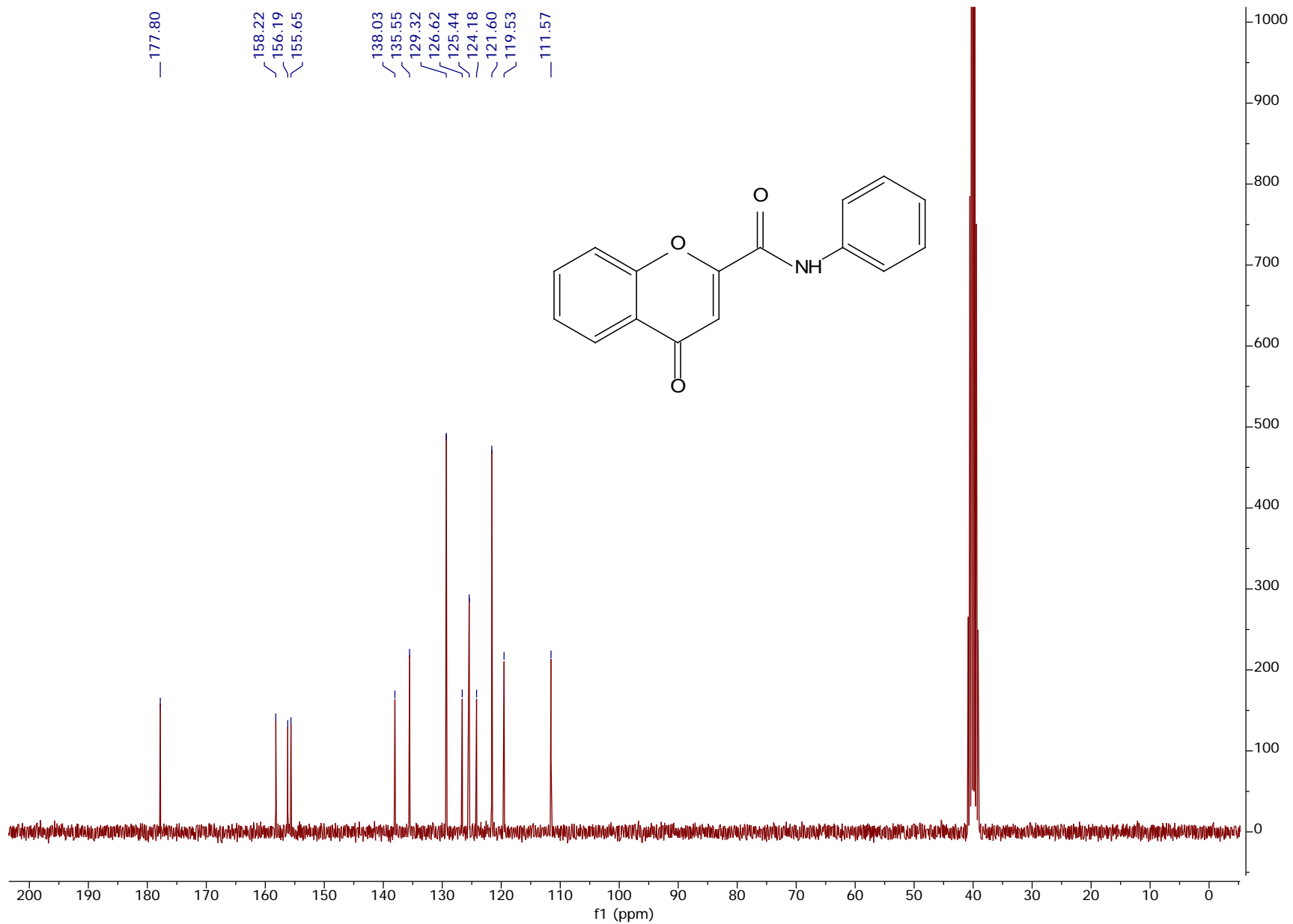


2-Amino-4H-chromen-4-one (4)

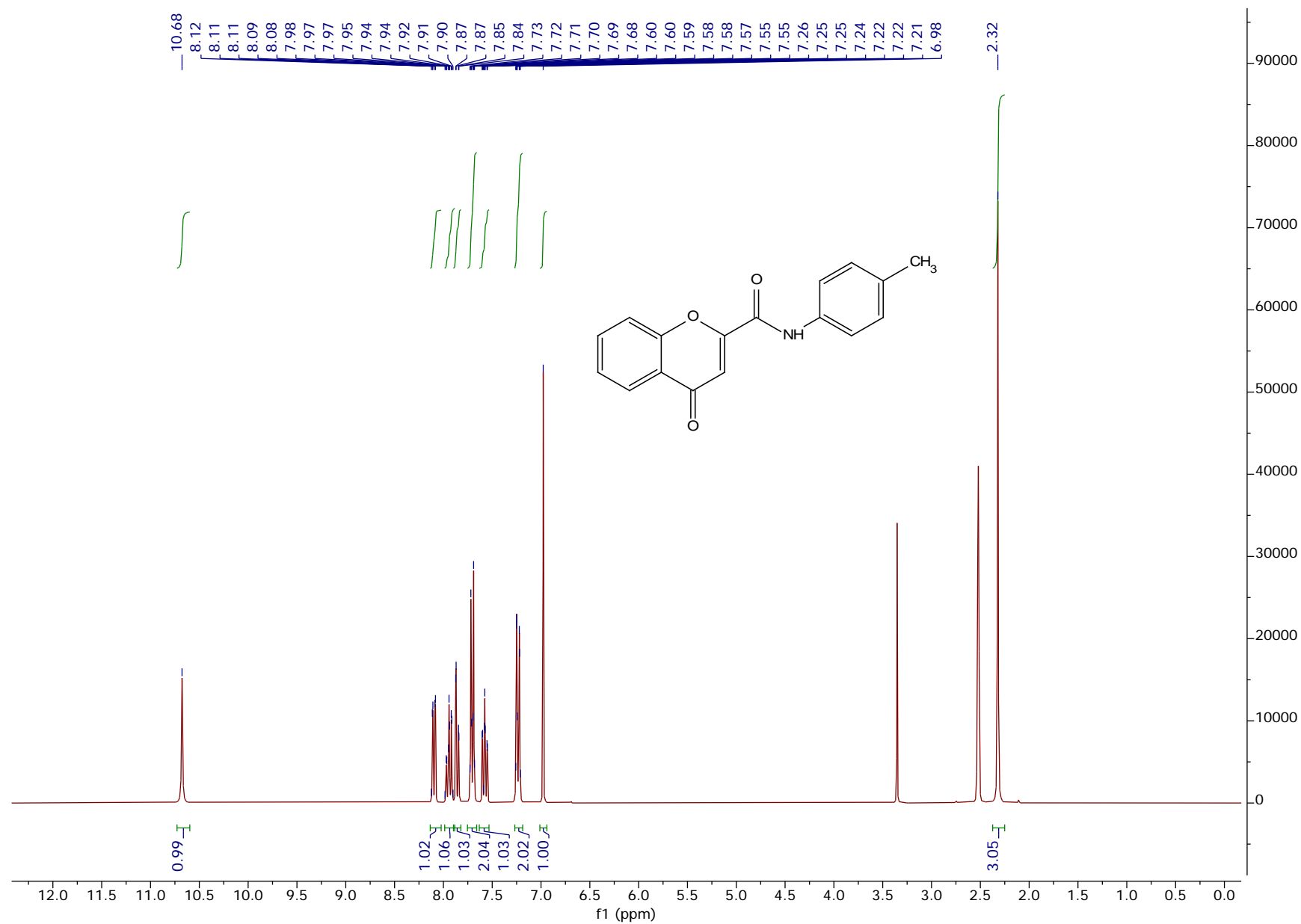


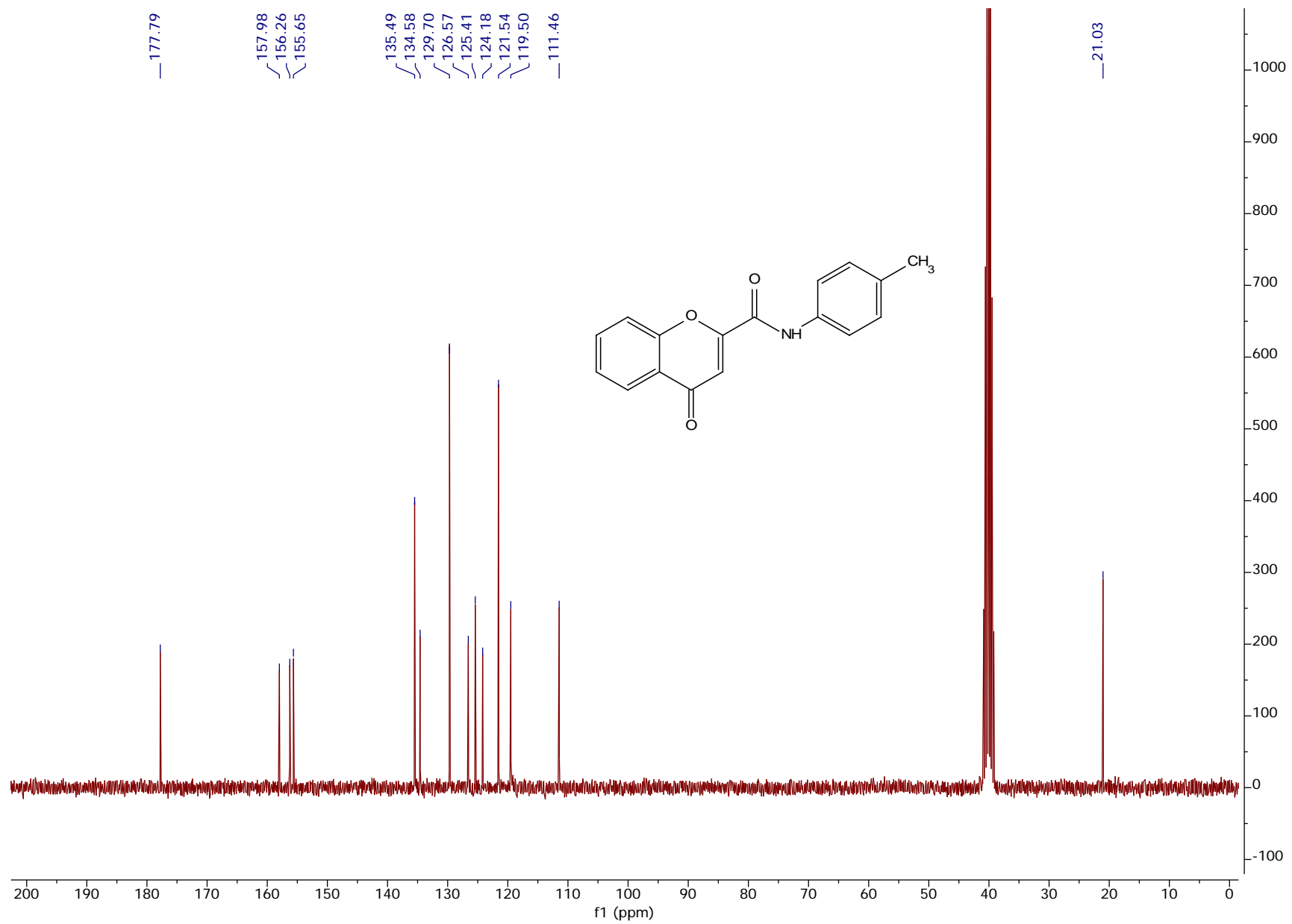
4-Oxo-N-phenyl-4H-chromene-2-carboxamide (3a)



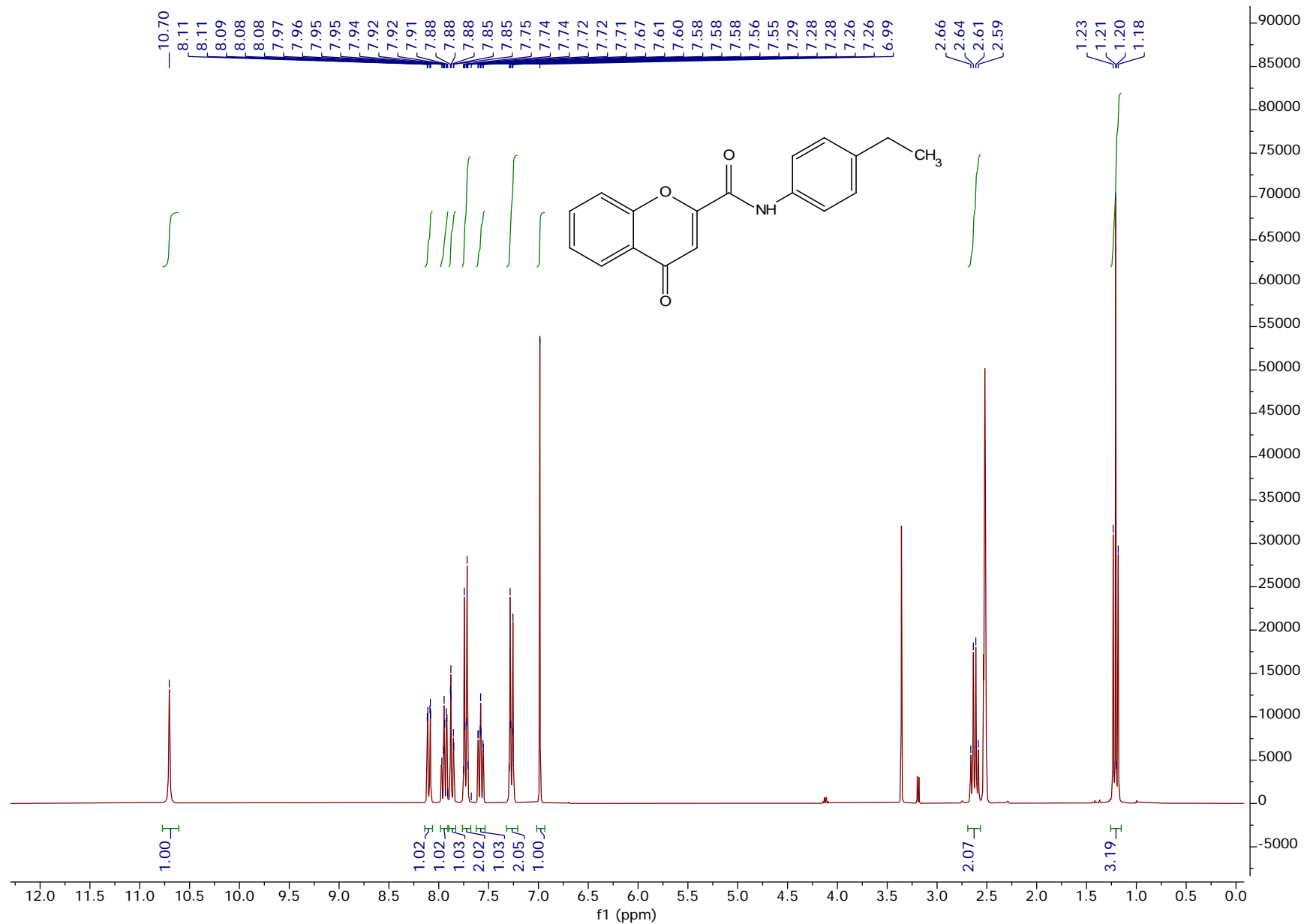


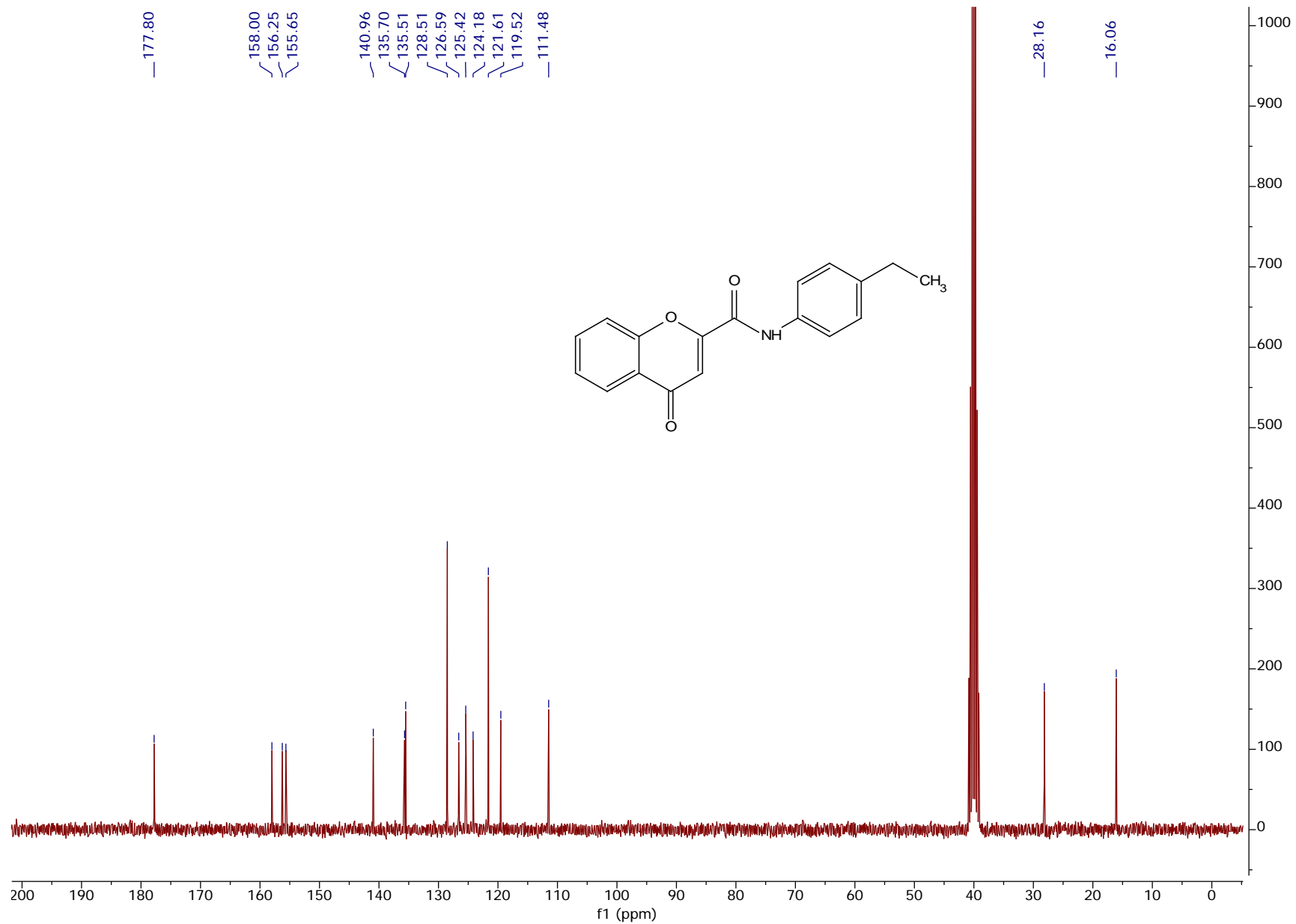
4-Oxo-N-(p-tolyl)-4H-chromene-2-carboxamide (3b)



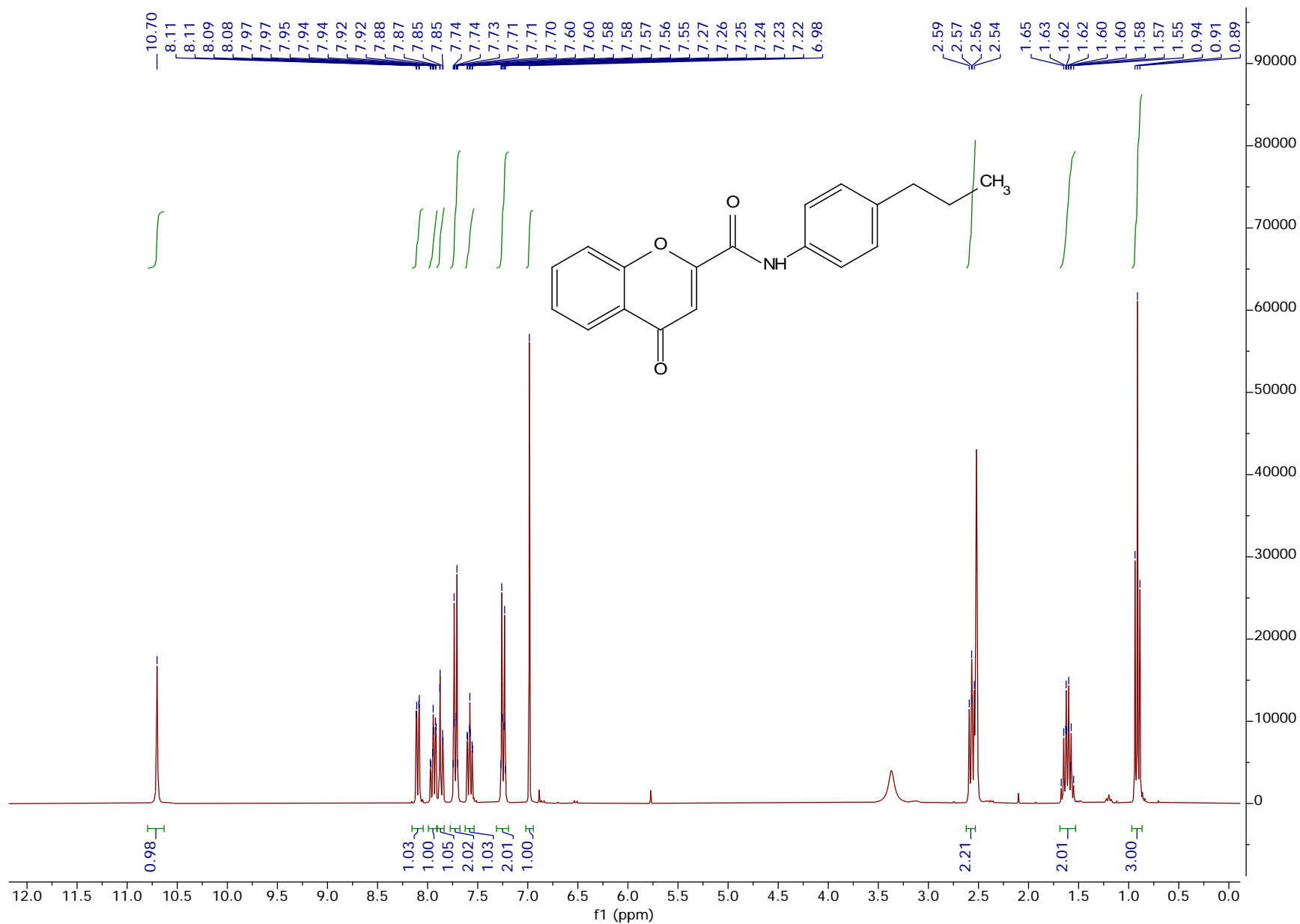


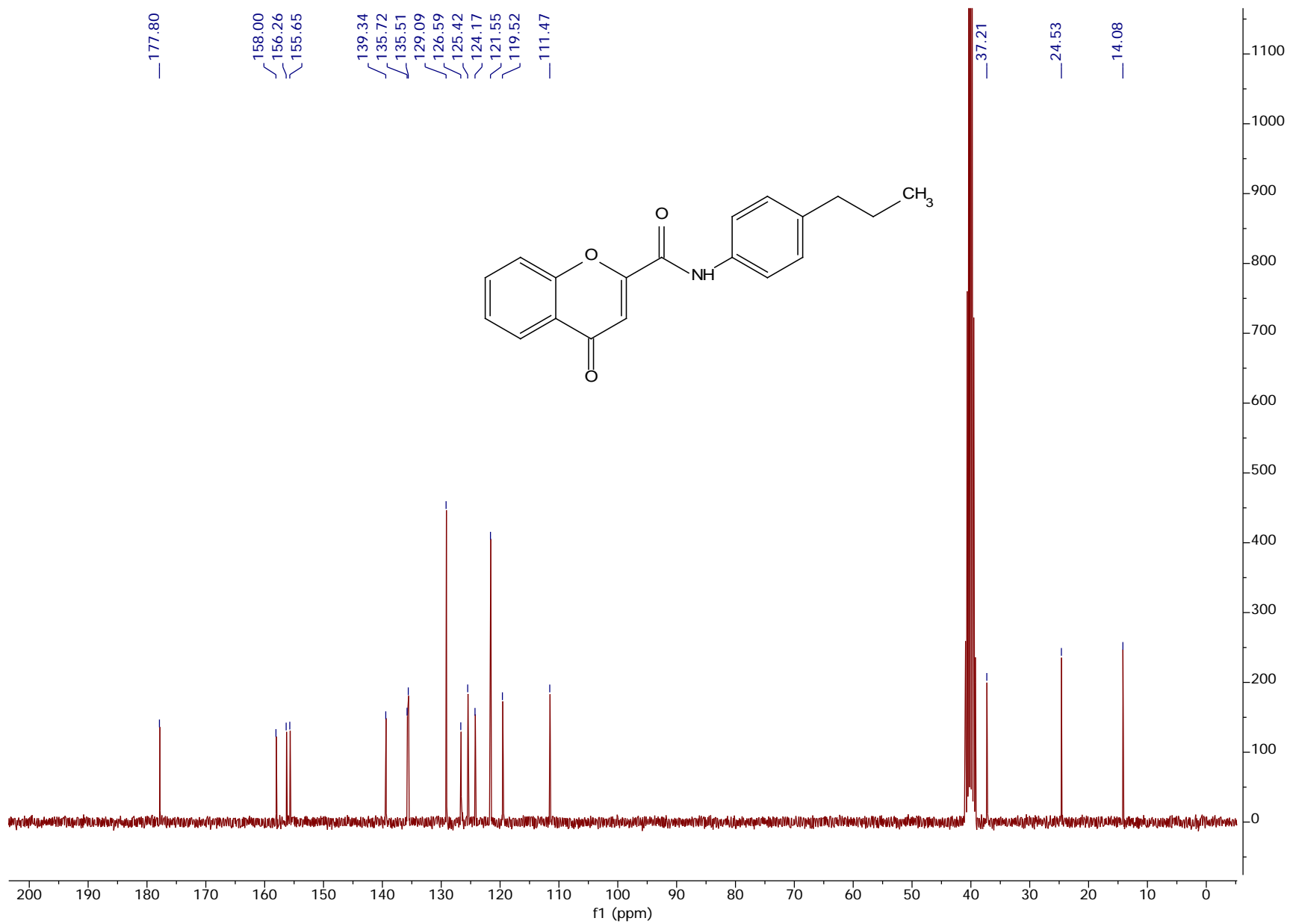
***N*-(4-Ethylphenyl)-4-oxo-4*H*-chromene-2-carboxamide (3c)**



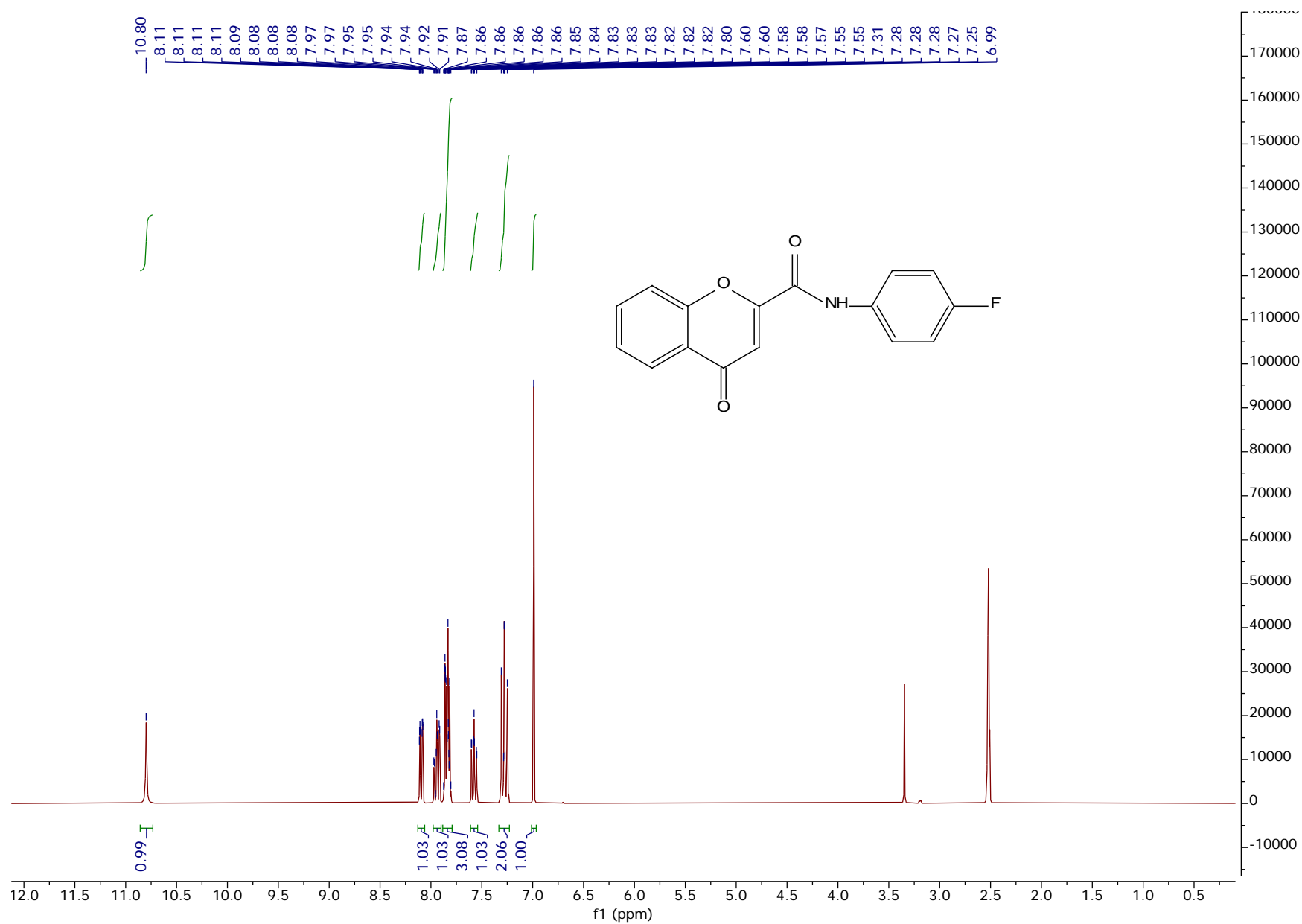


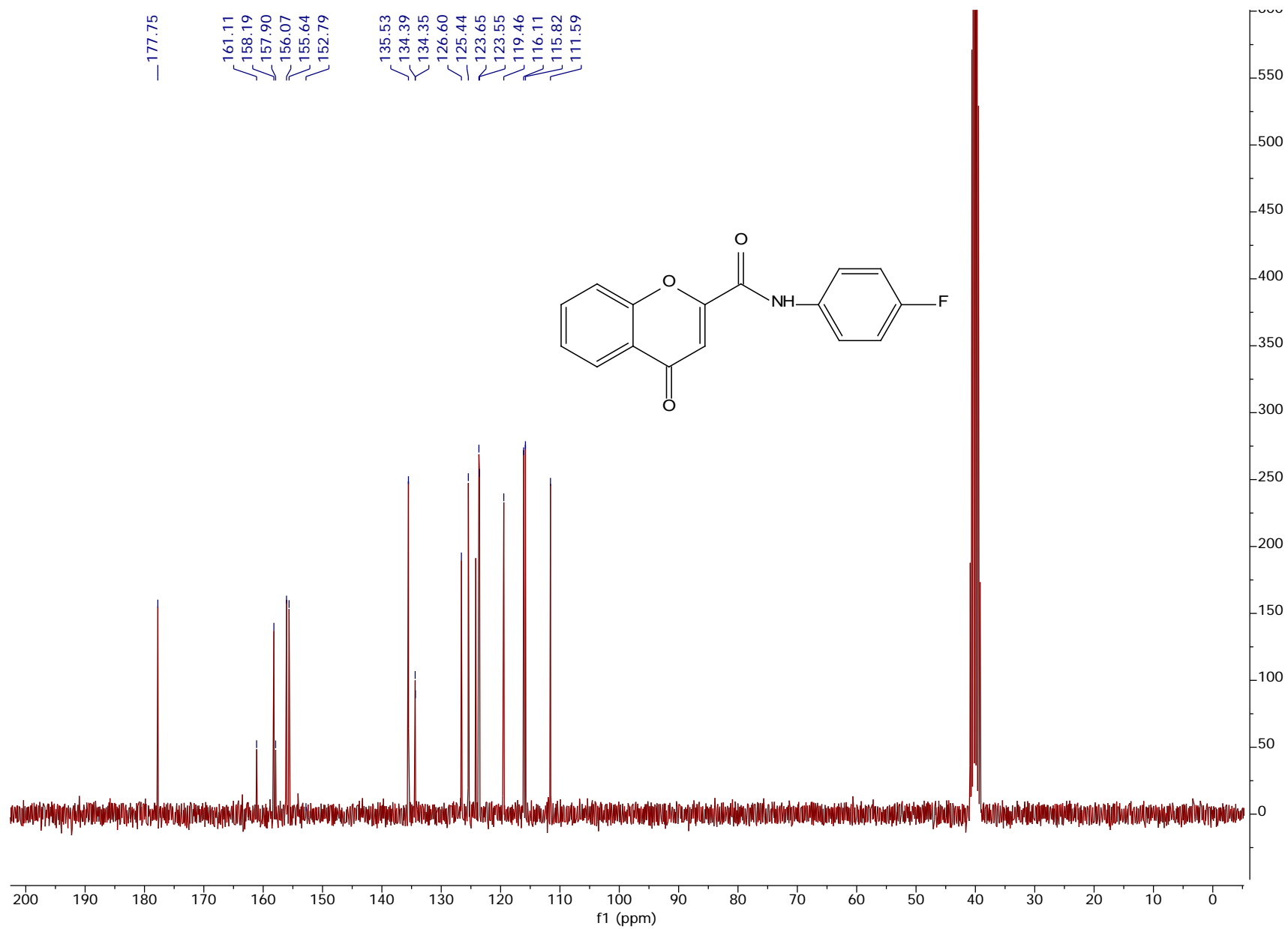
4-Oxo-N-(4-propylphenyl)-4H-chromene-2-carboxamide (3d)



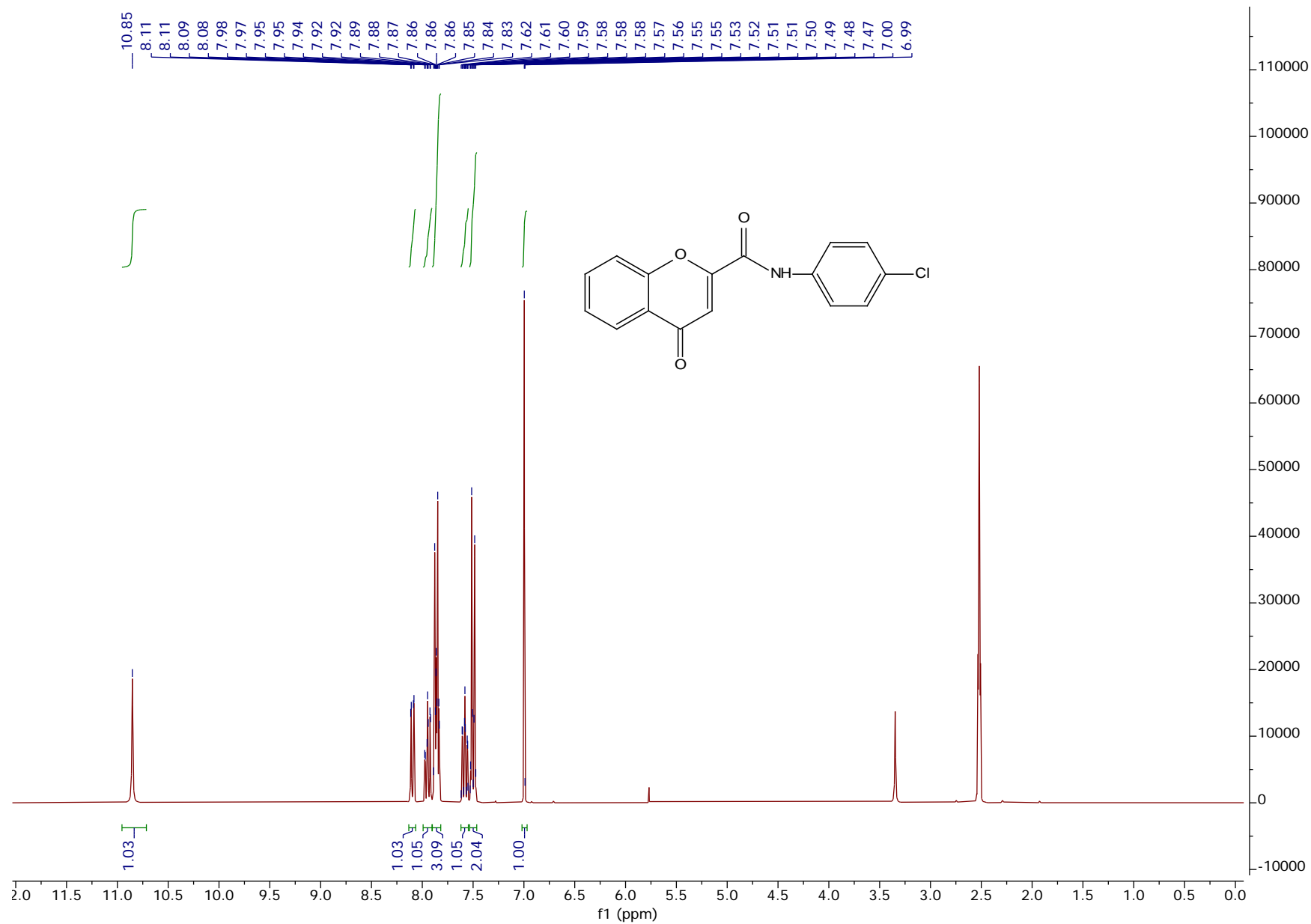


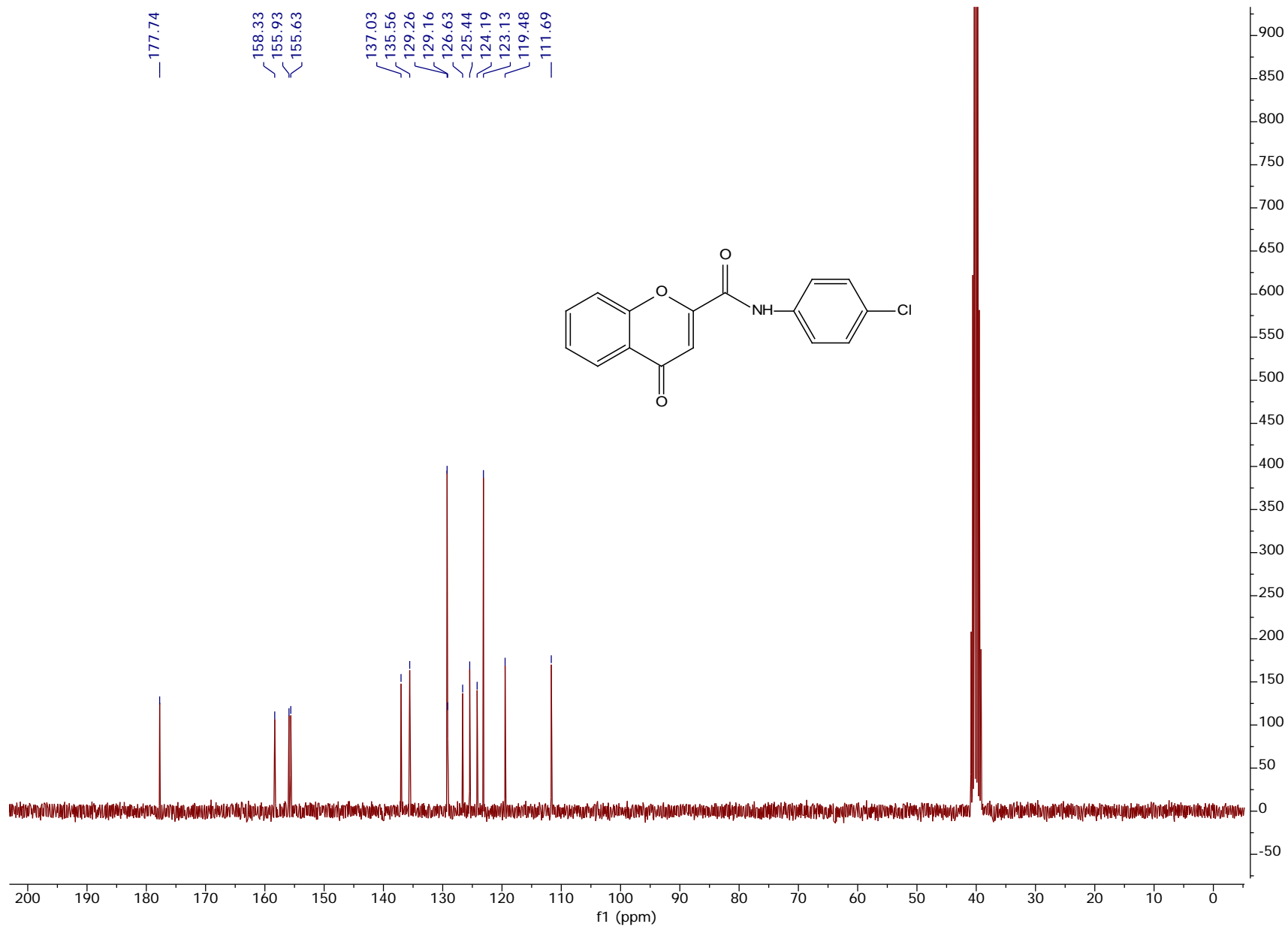
***N*-(4-Fluorophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3e)**



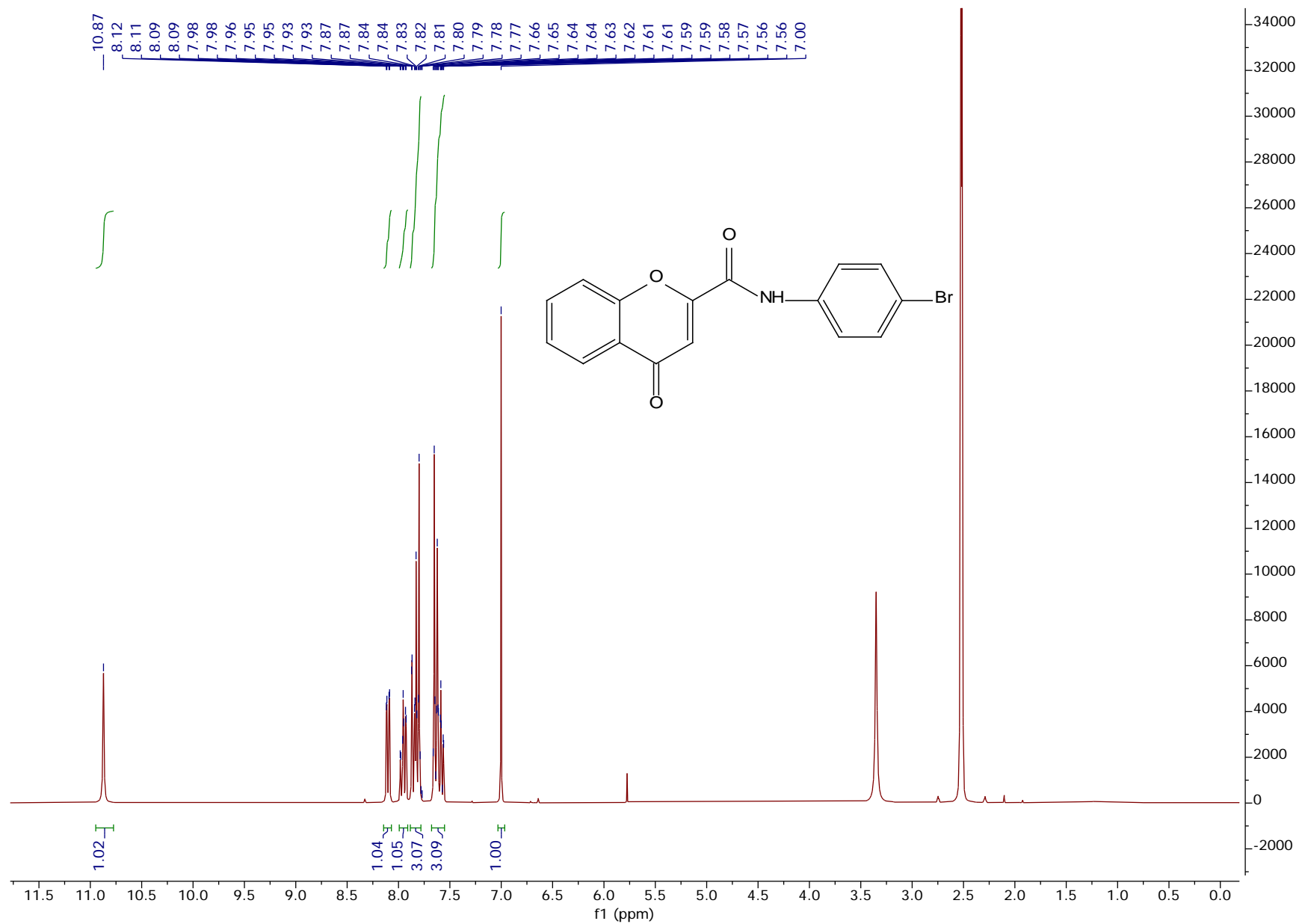


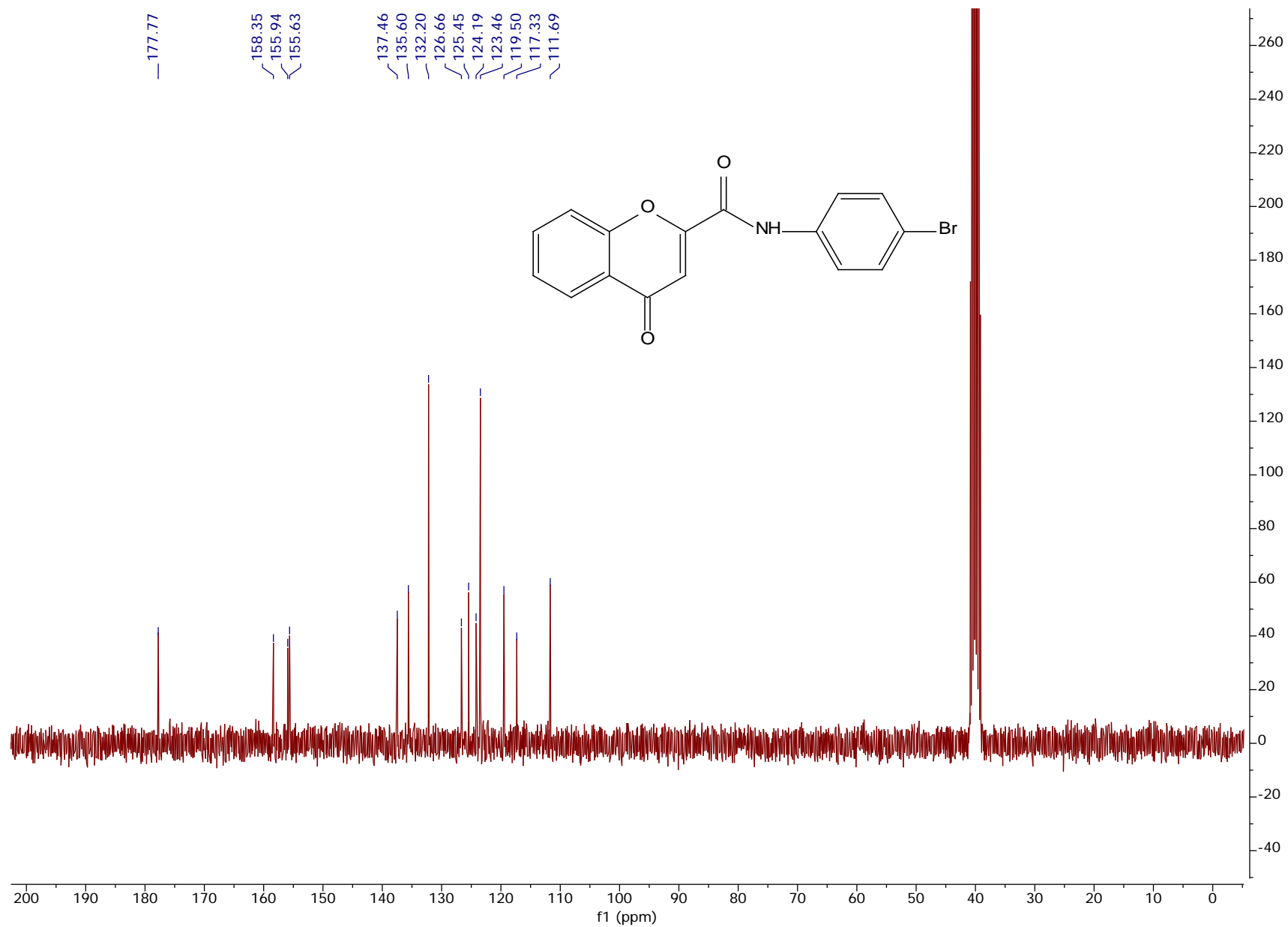
***N*-(4-Chlorophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3f)**



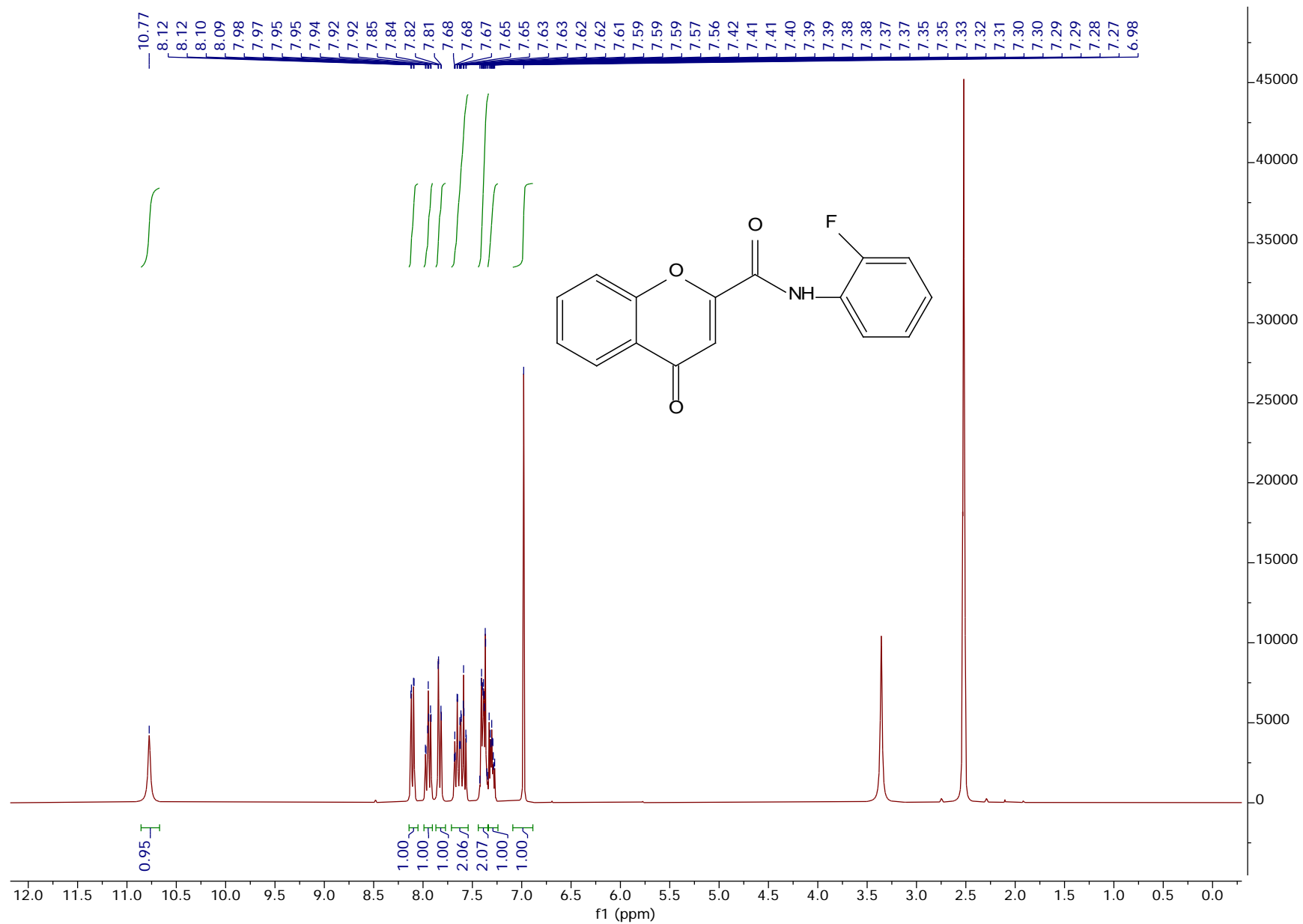


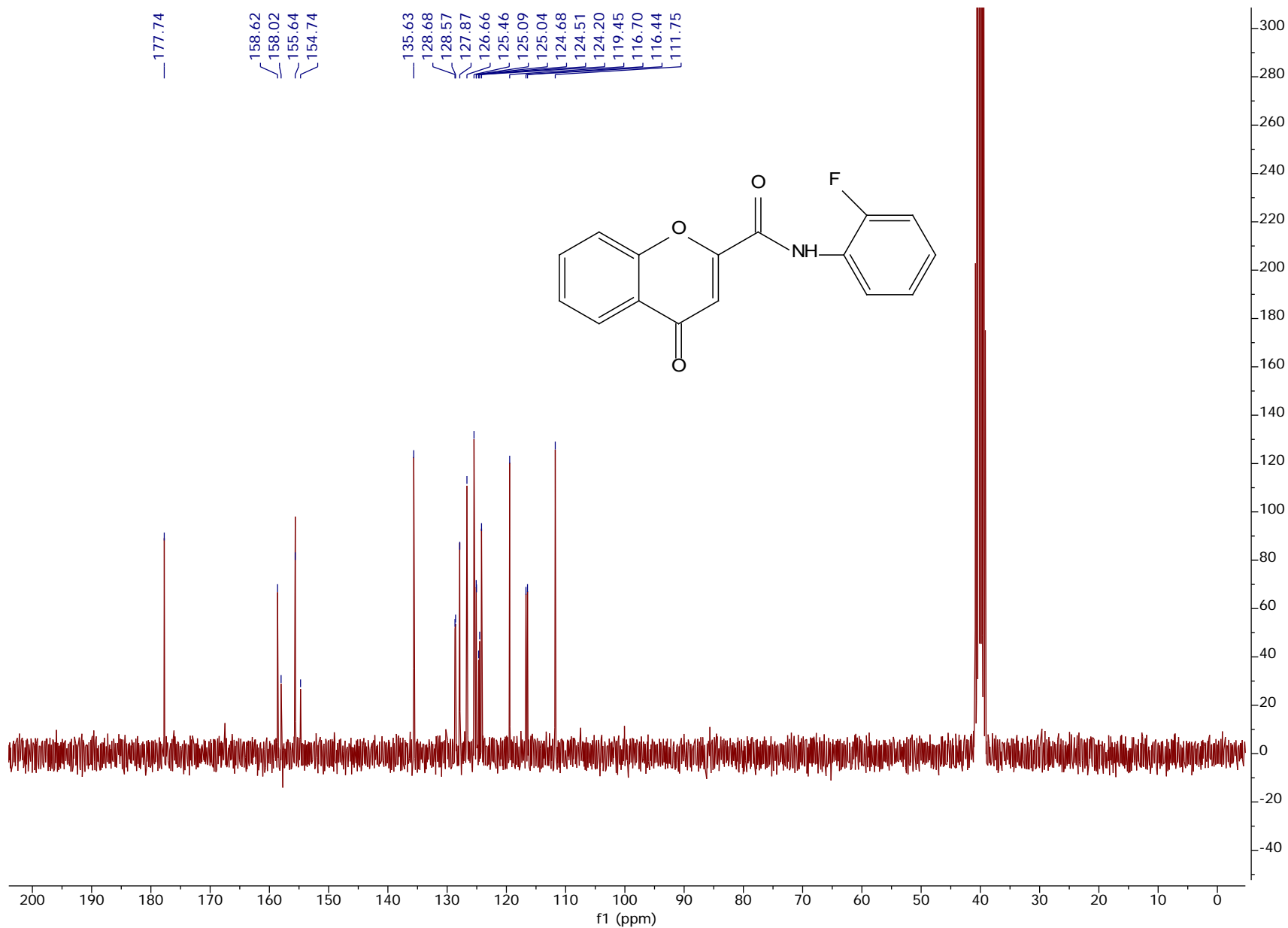
***N*-(4-Bromophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3g)**



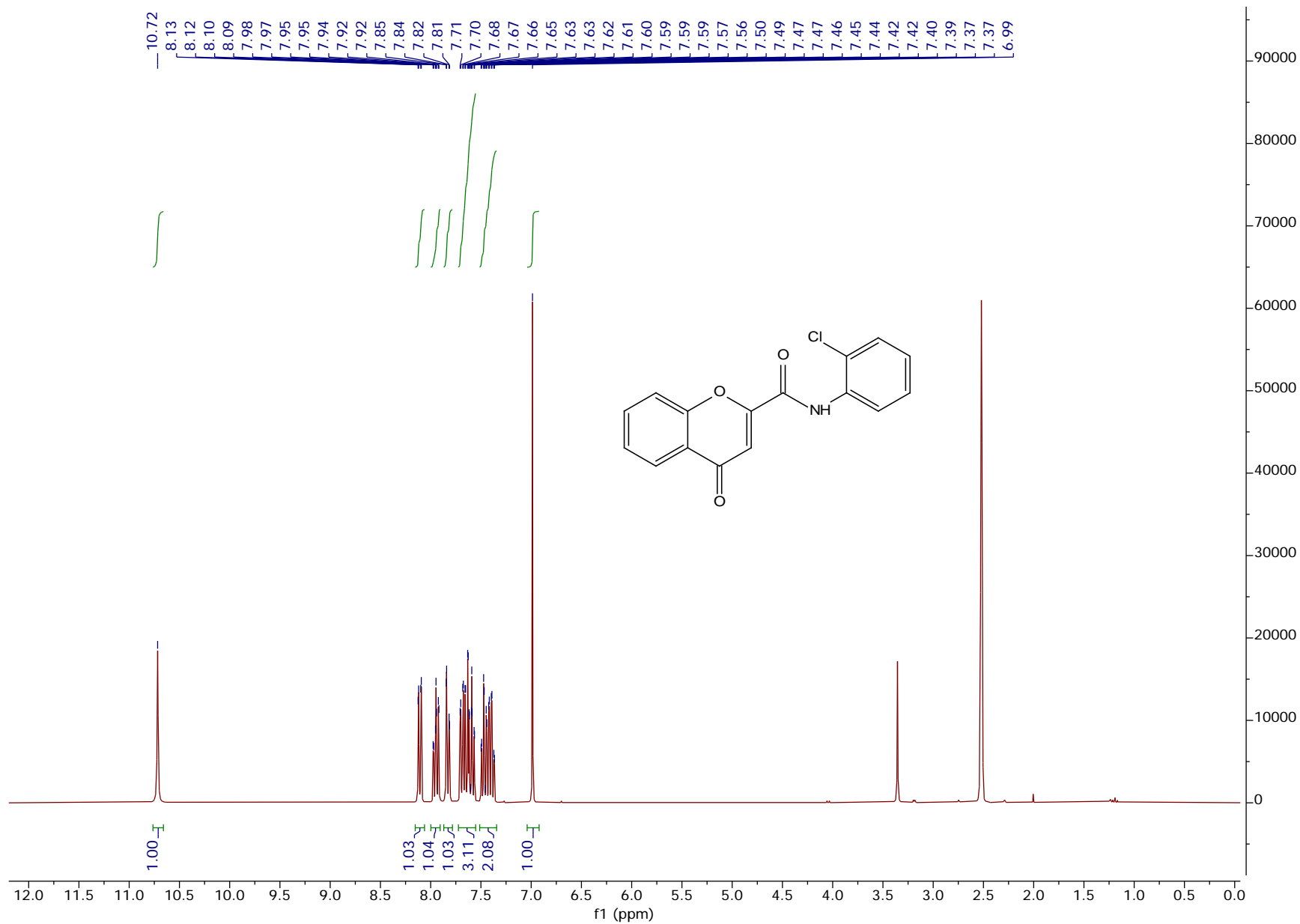


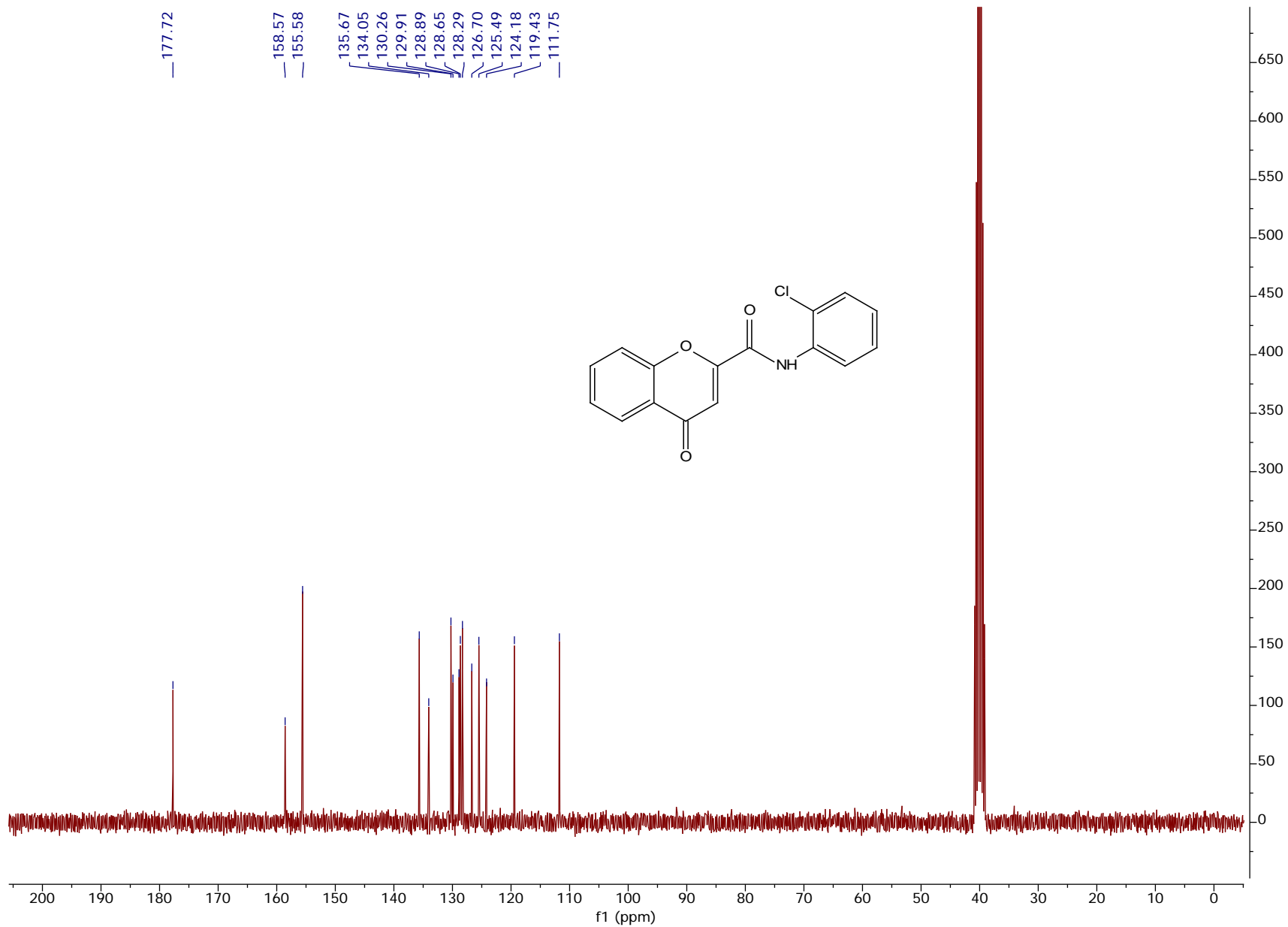
***N*-(2-Fluorophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3h)**





***N*-(2-Chlorophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3i)**

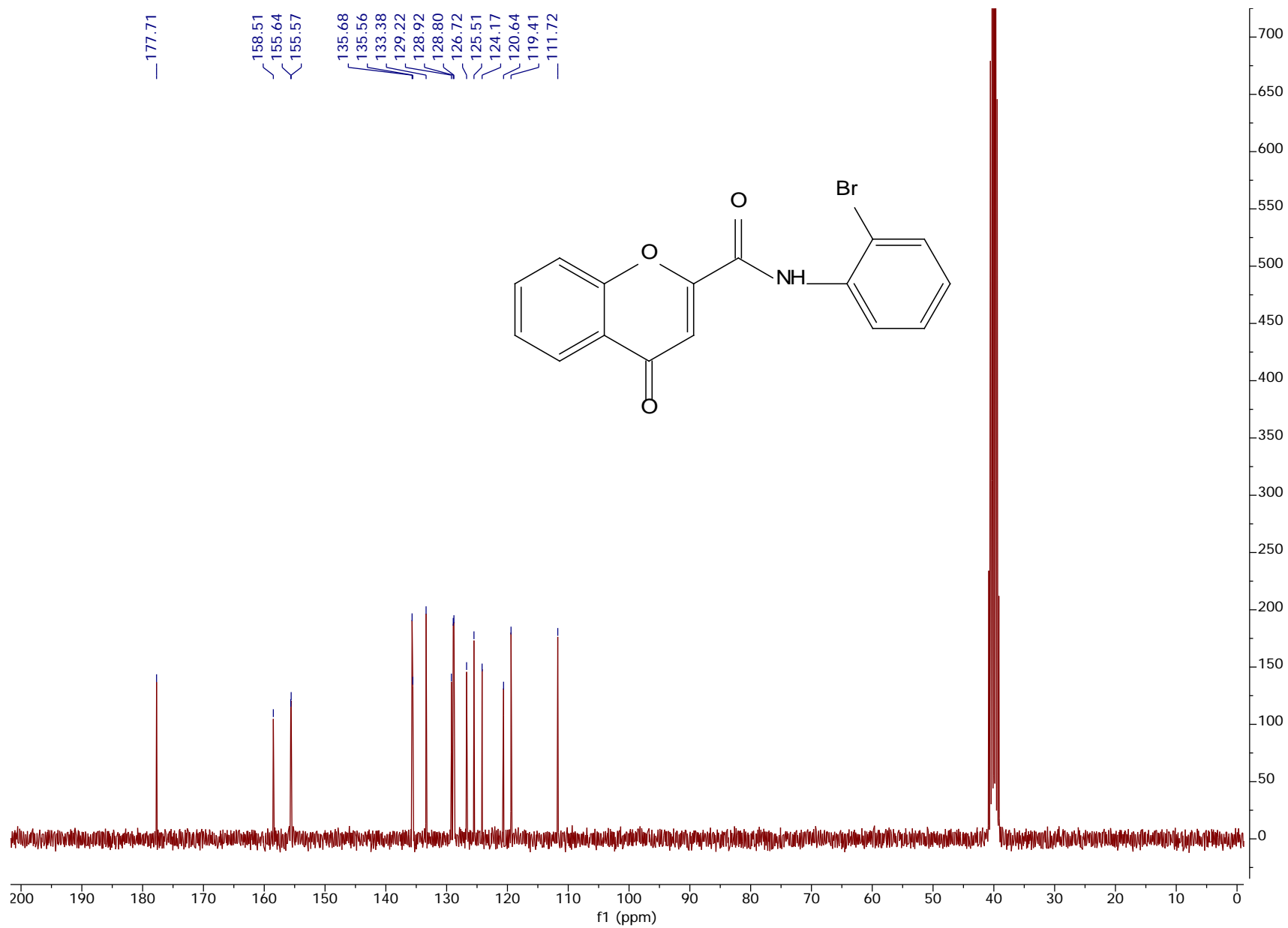




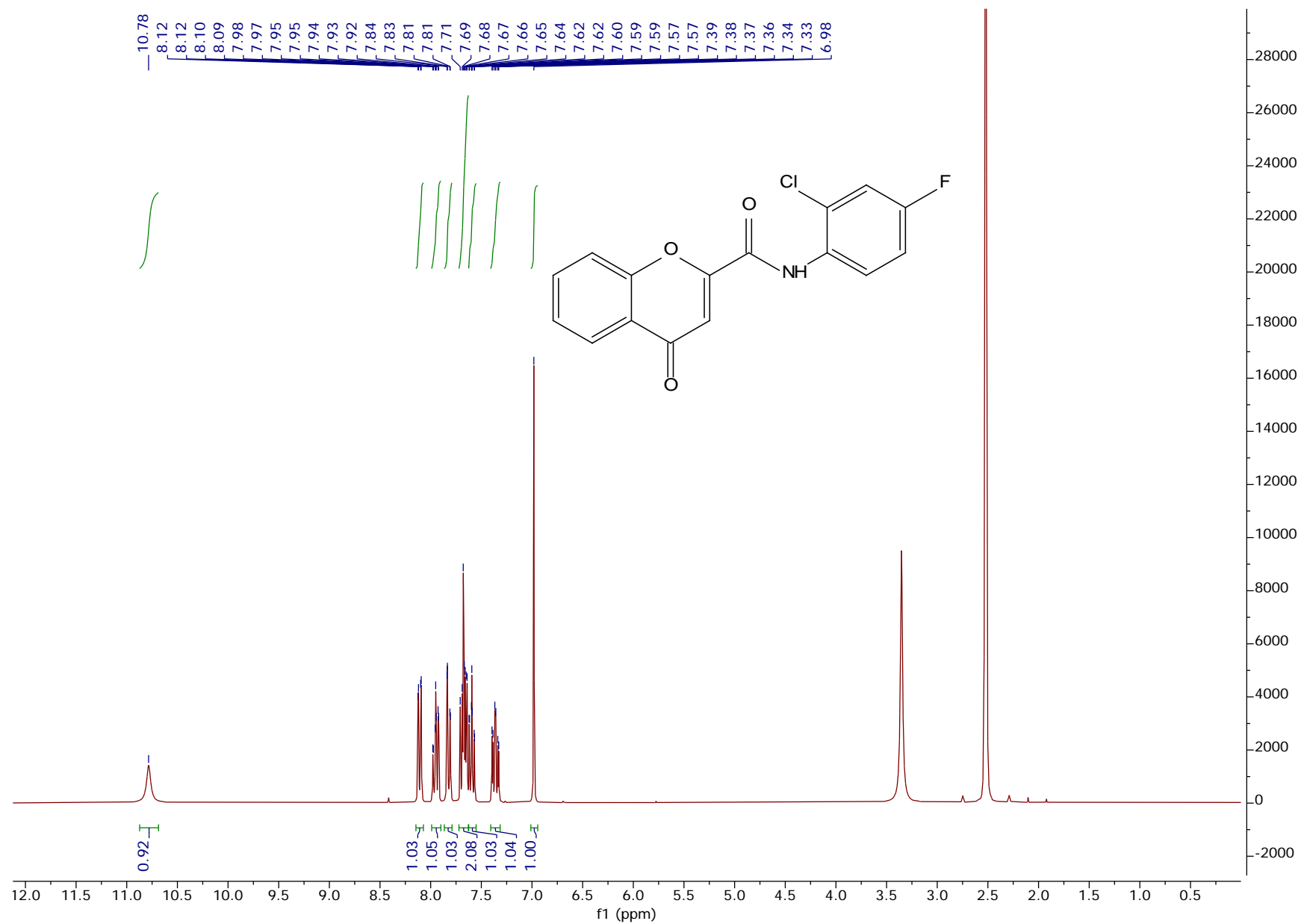
Chemical structure: O=C1C(=O)C(=C(NC2=CC=CC=C2)C3=CC=CC=C3)OC4=CC=CC=C14

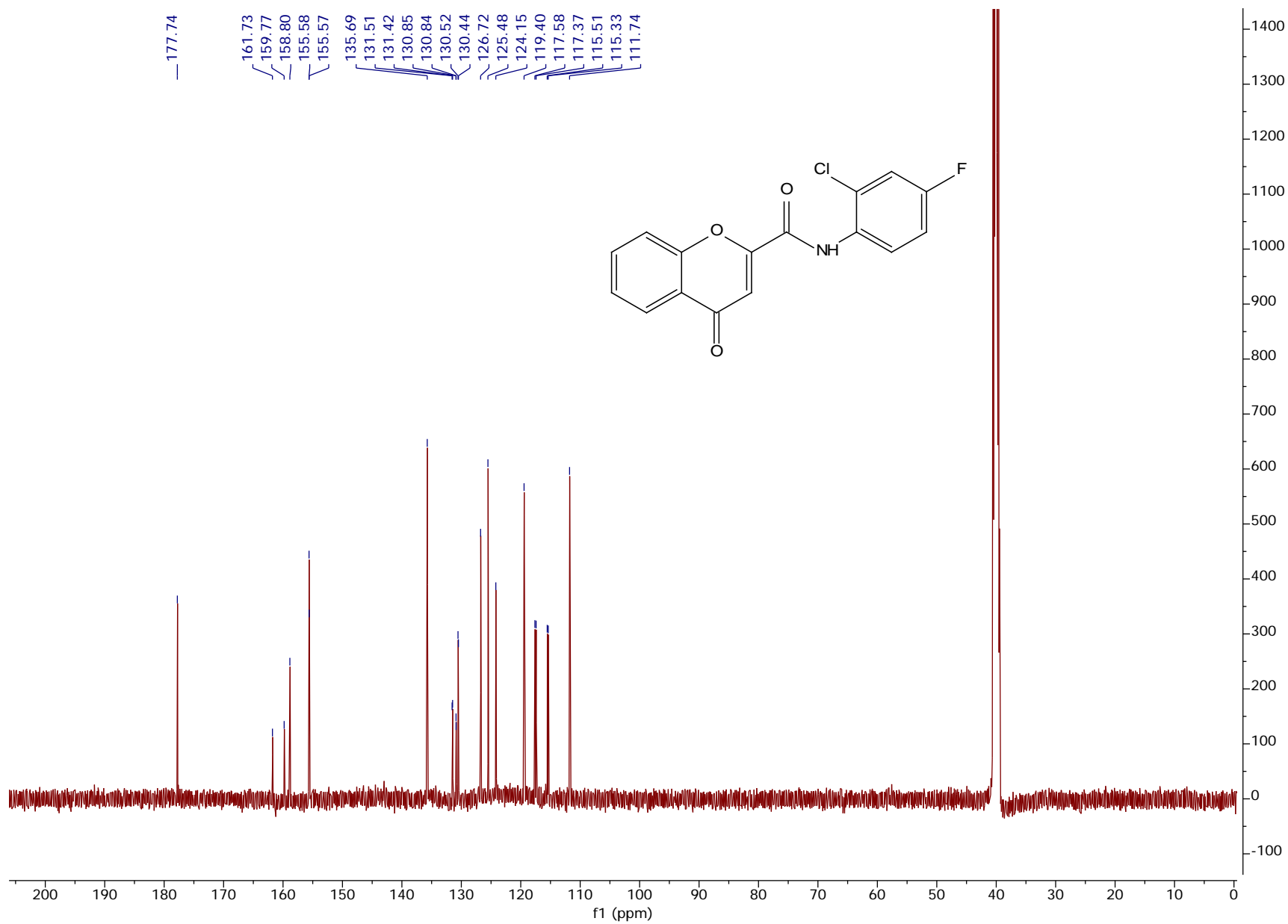
¹H NMR spectrum (ppm):

- 10.69 (s, 1H, integration 0.98)
- 7.94-7.78 (m, 8H, integration 1.00, 1.03, 1.02, 1.01, 1.02, 1.02, 1.02, 1.01)
- 7.33 (s, 2H, integration 0.97)
- 7.31 (s, 2H, integration 0.97)

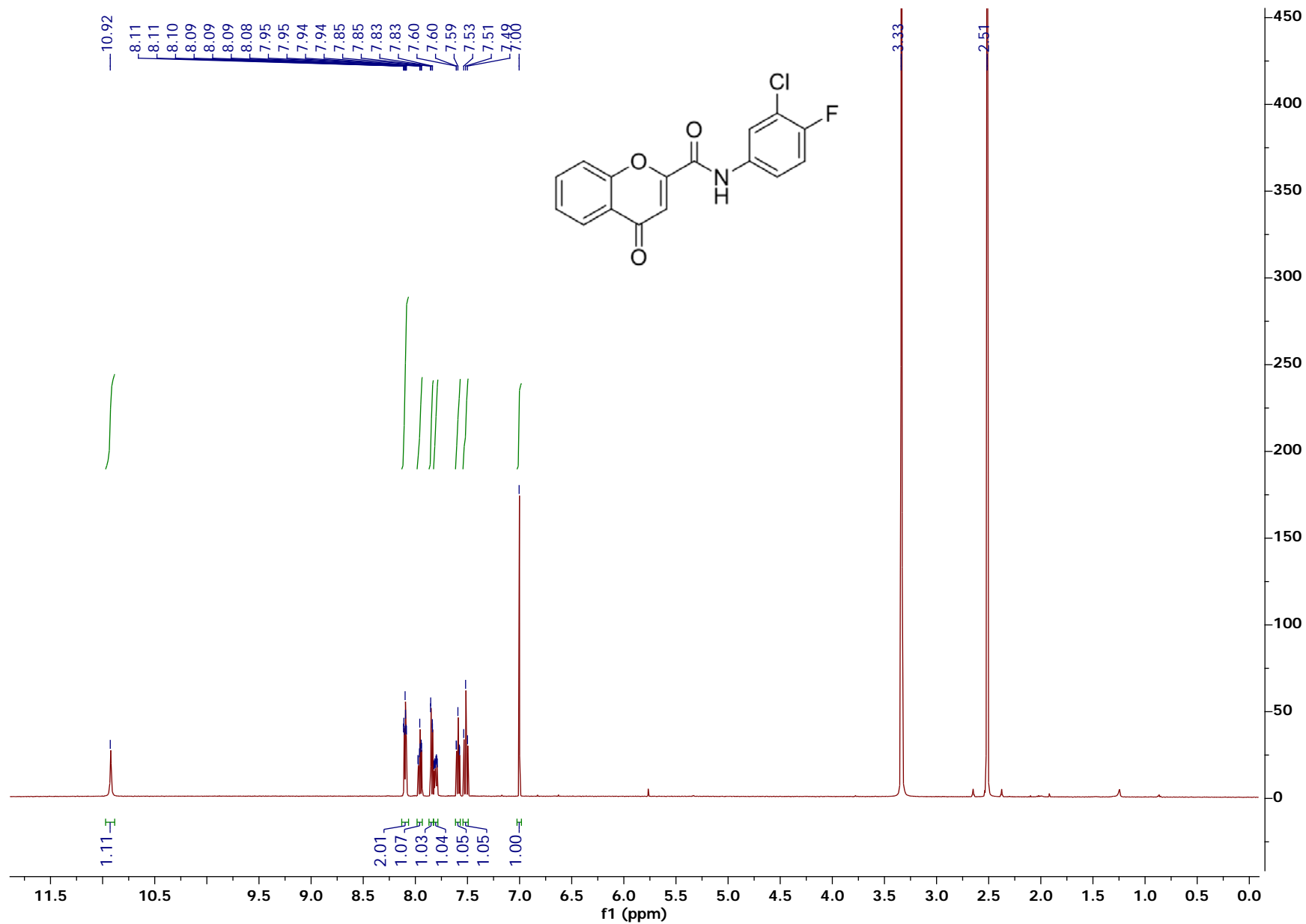


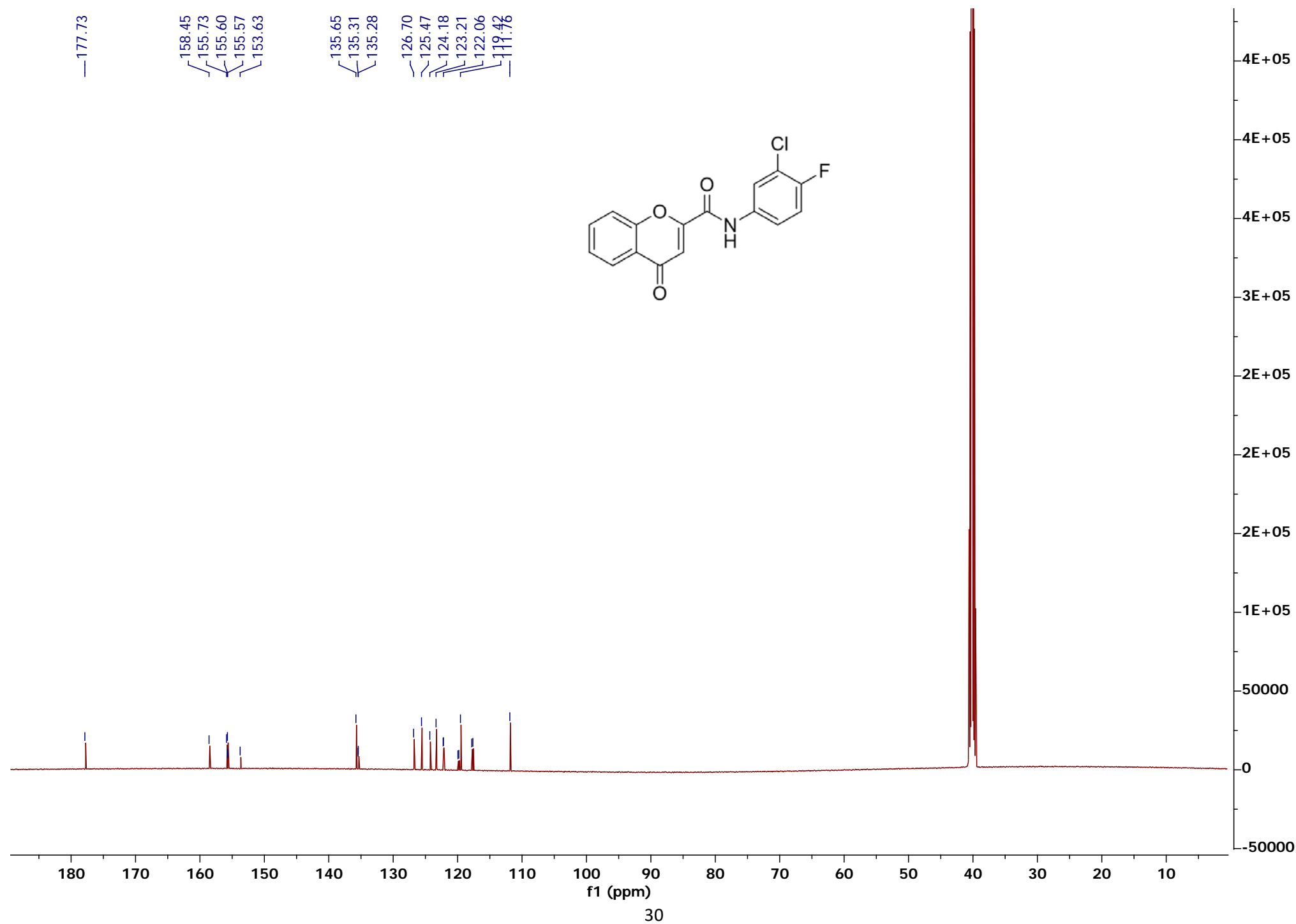
***N*-(2-Chloro-4-fluorophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3k)**



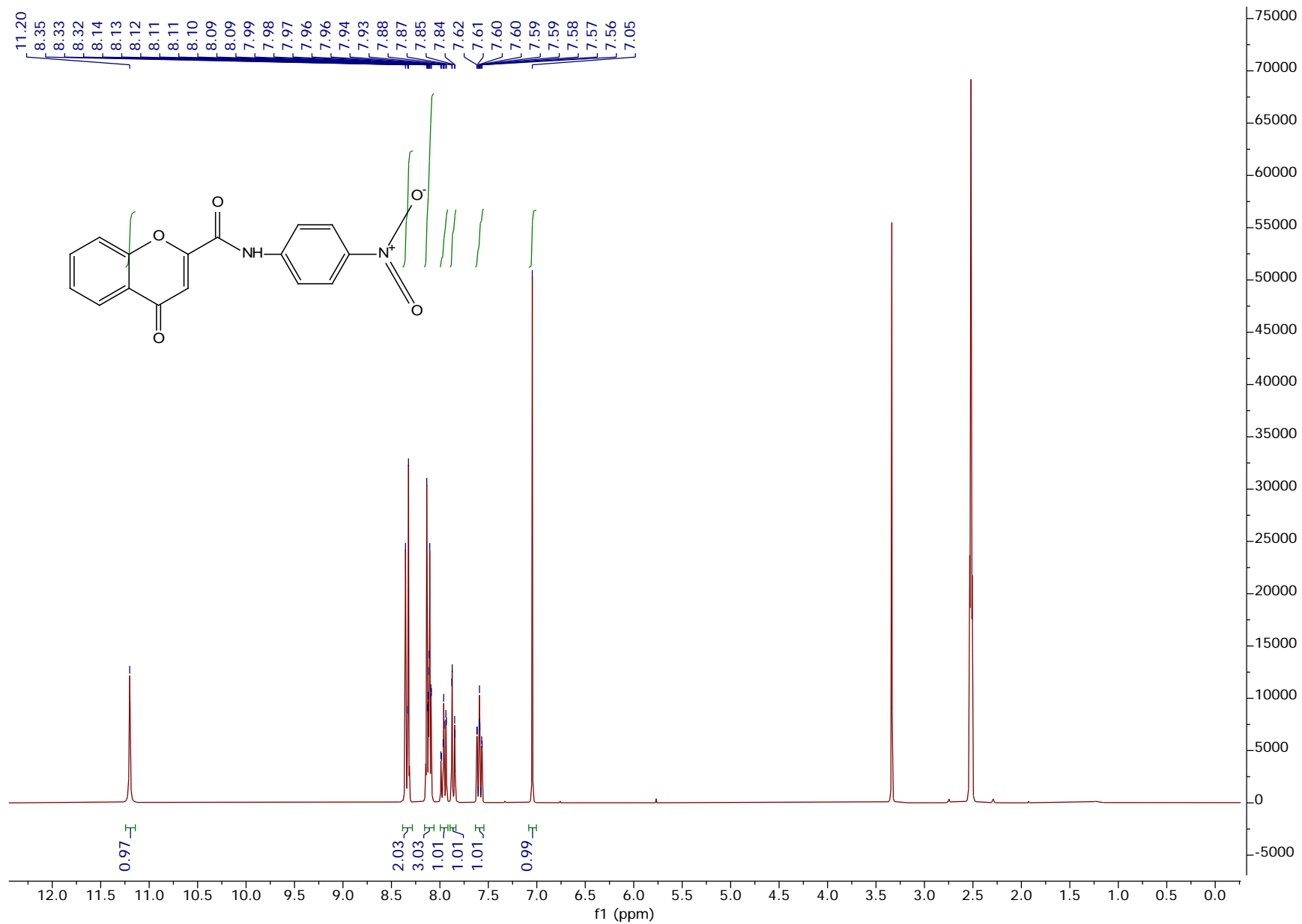


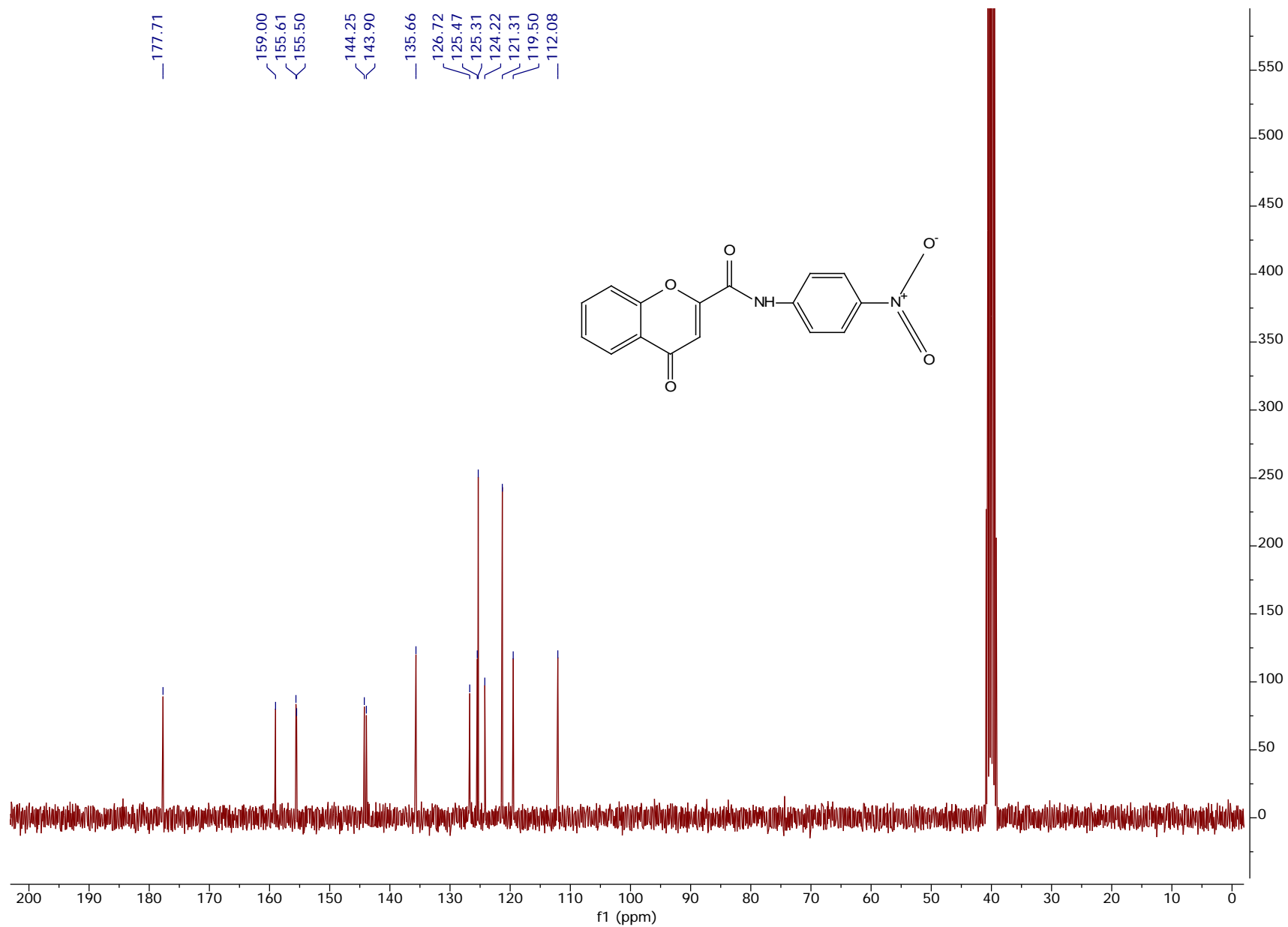
N-(3-Chloro-4-fluorophenyl)-4-oxo-4H-chromene-2-carboxamide (3I)



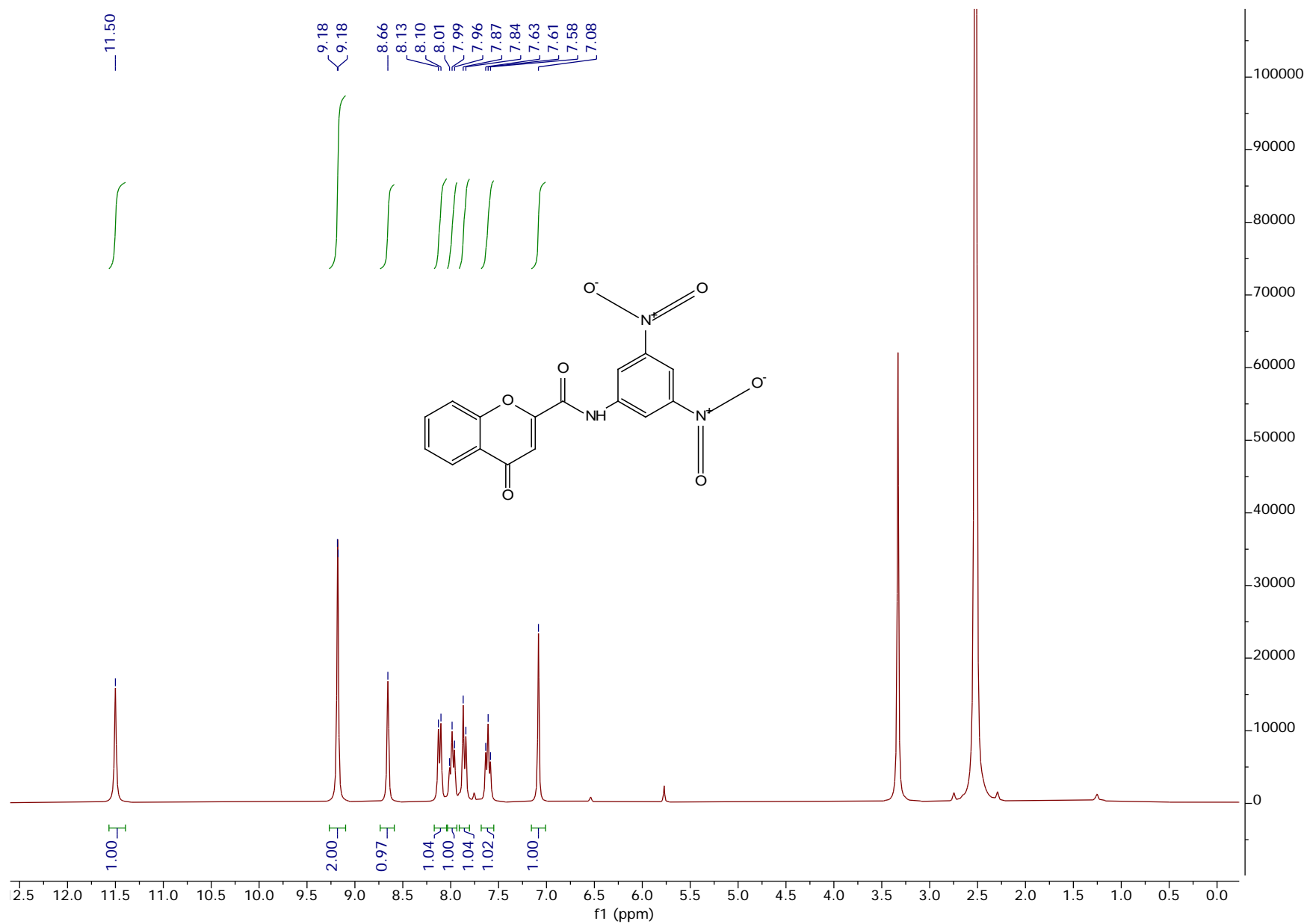


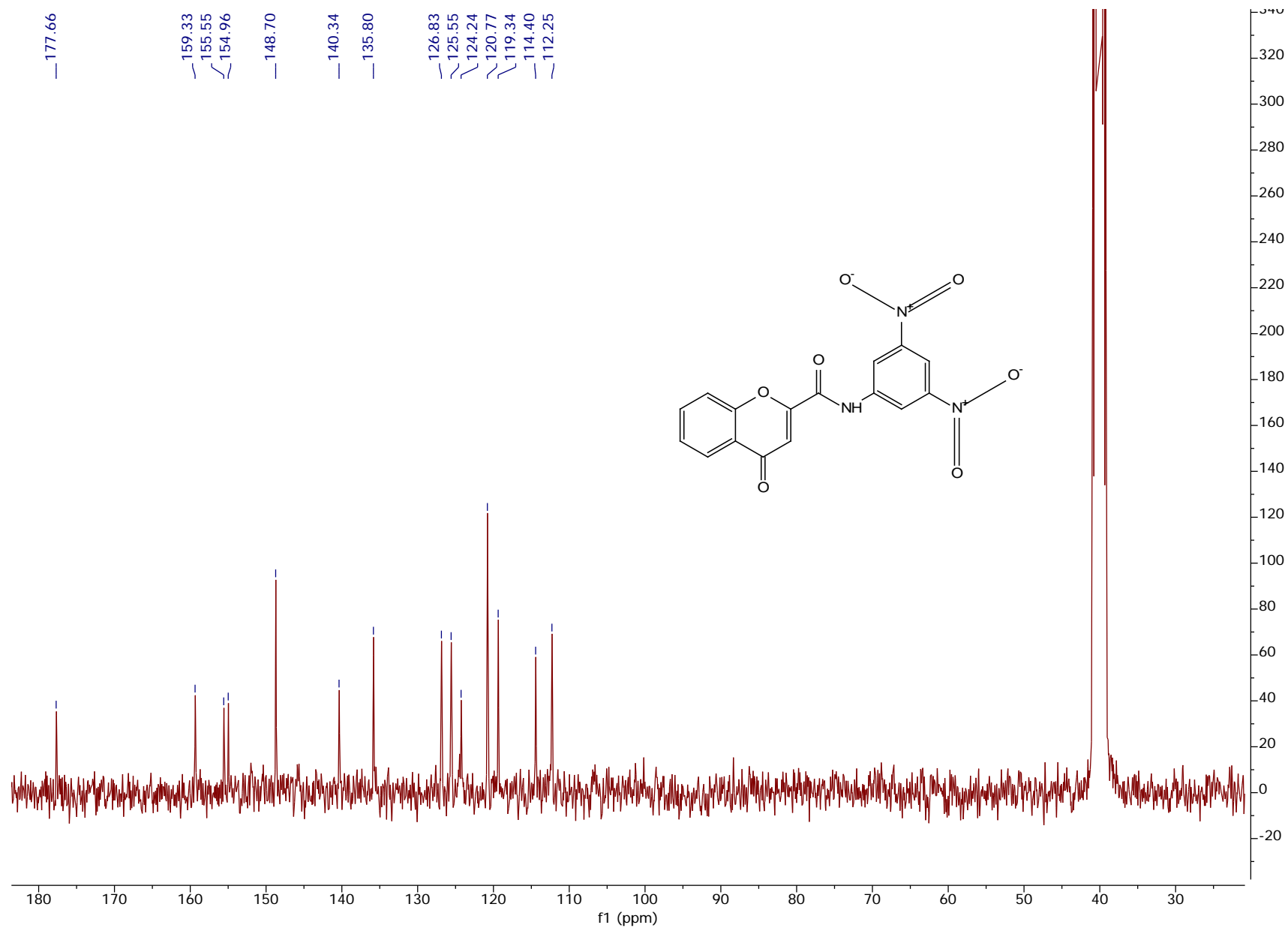
***N*-(4-Nitrophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3m)**



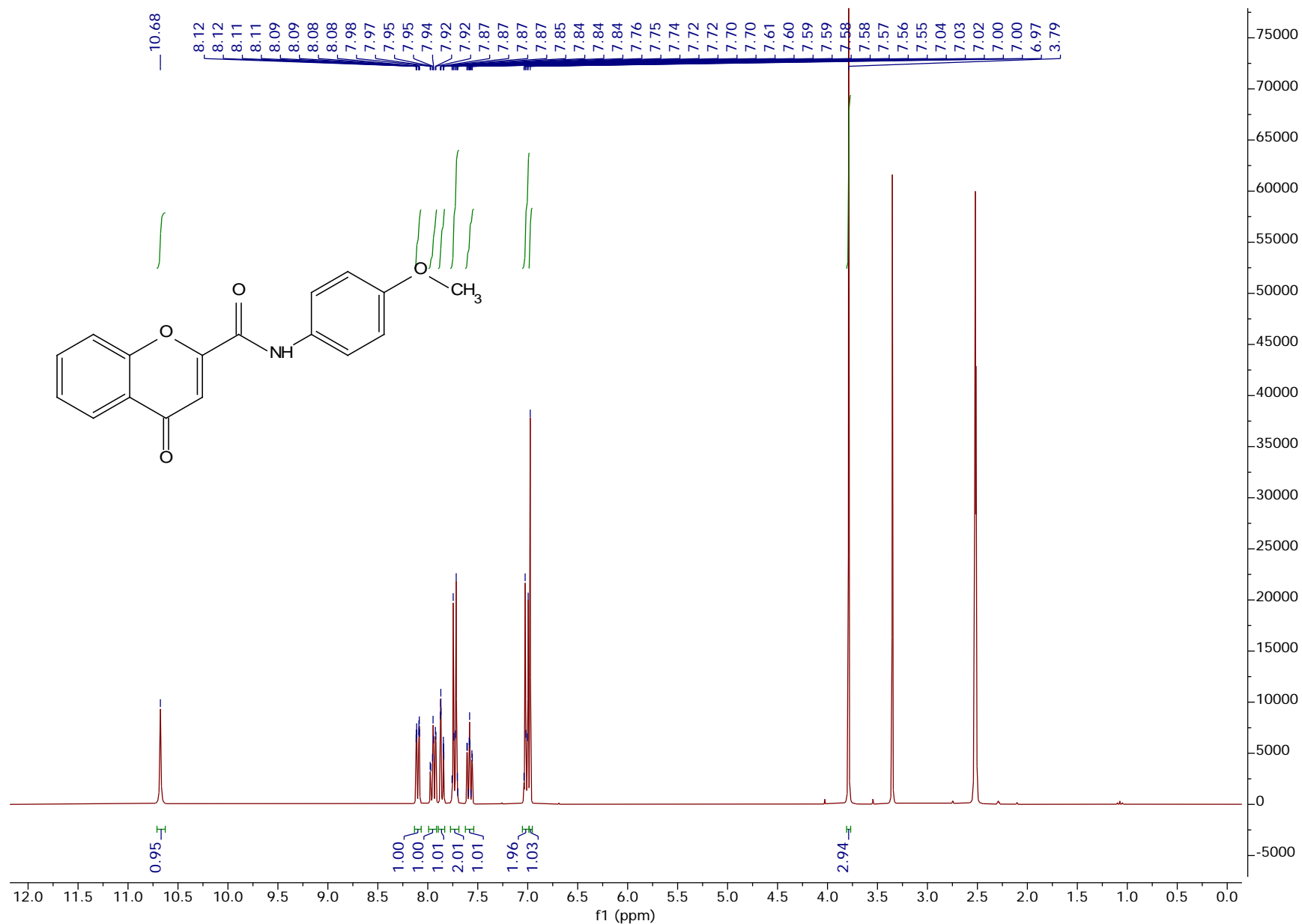


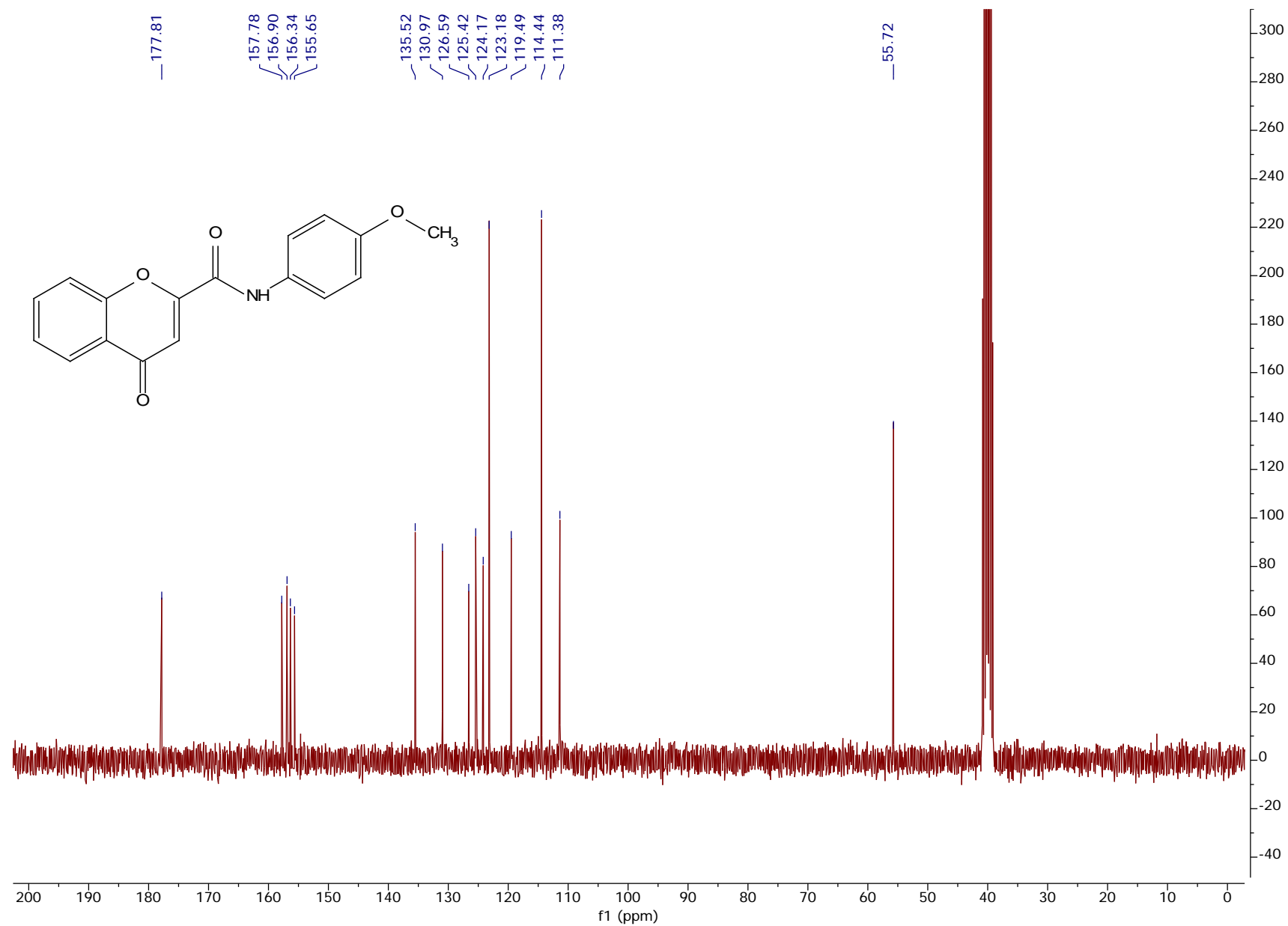
***N*-(3,5-Dinitrophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3o)**



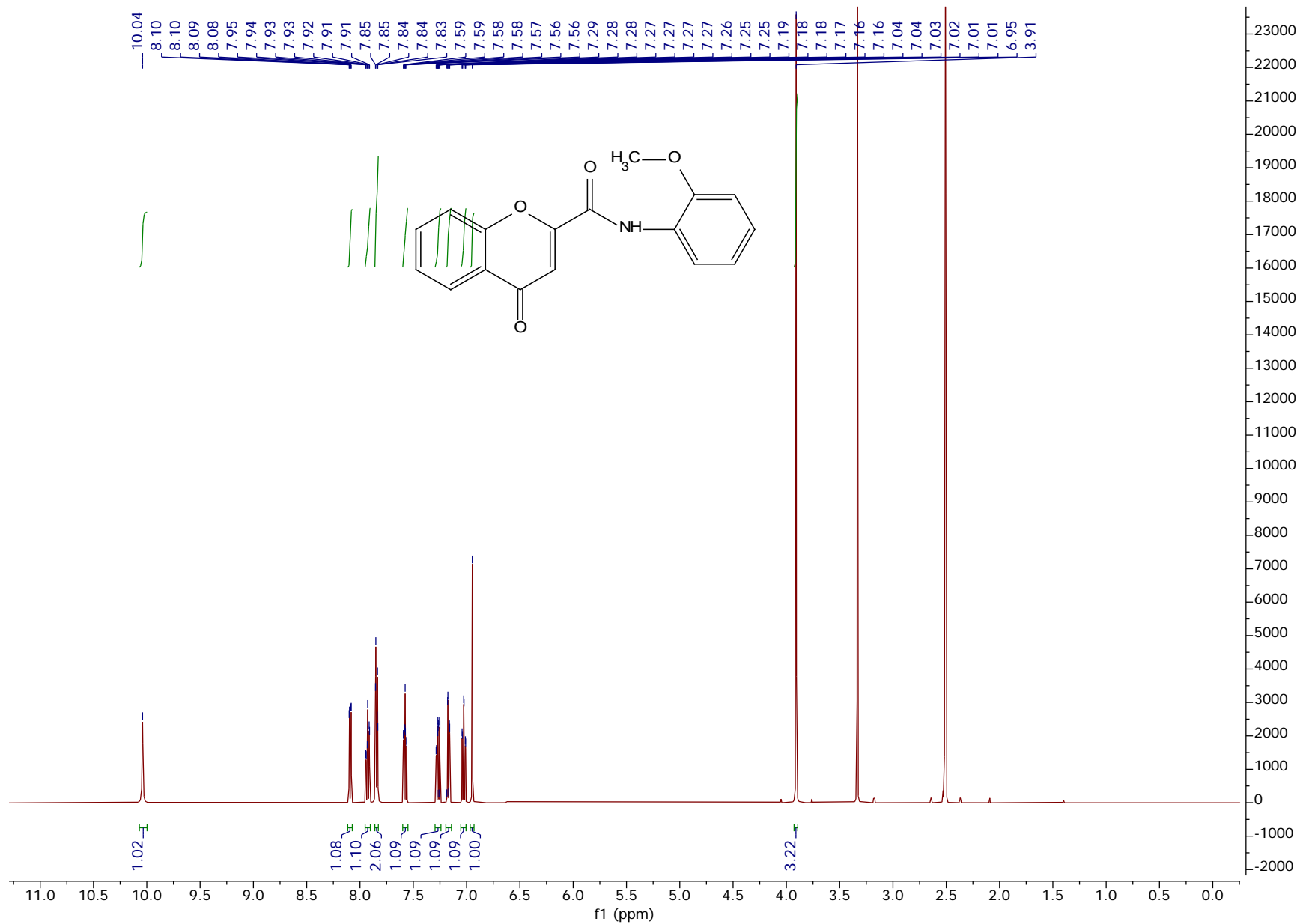


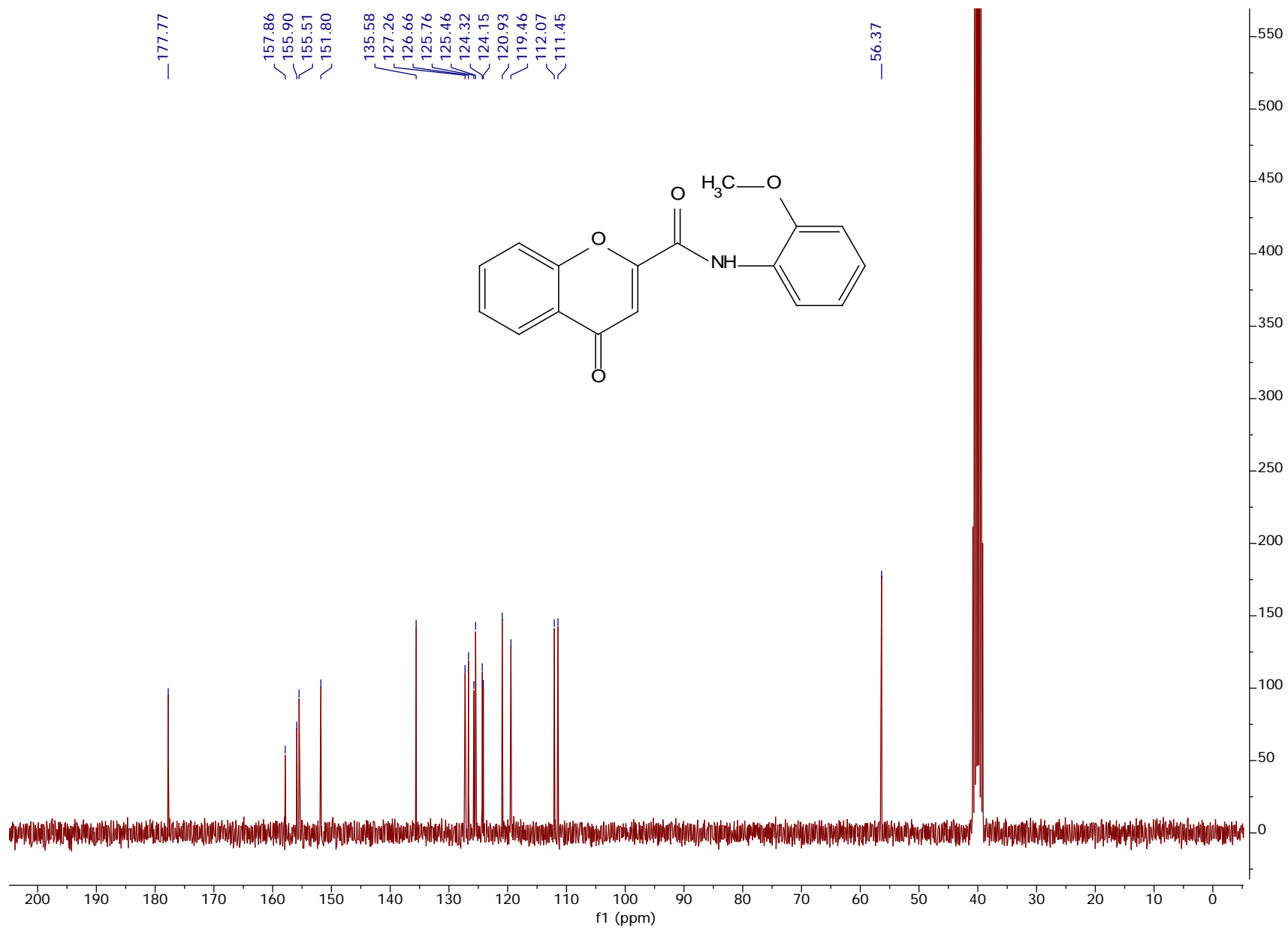
***N*-(4-Methoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide (3p)**



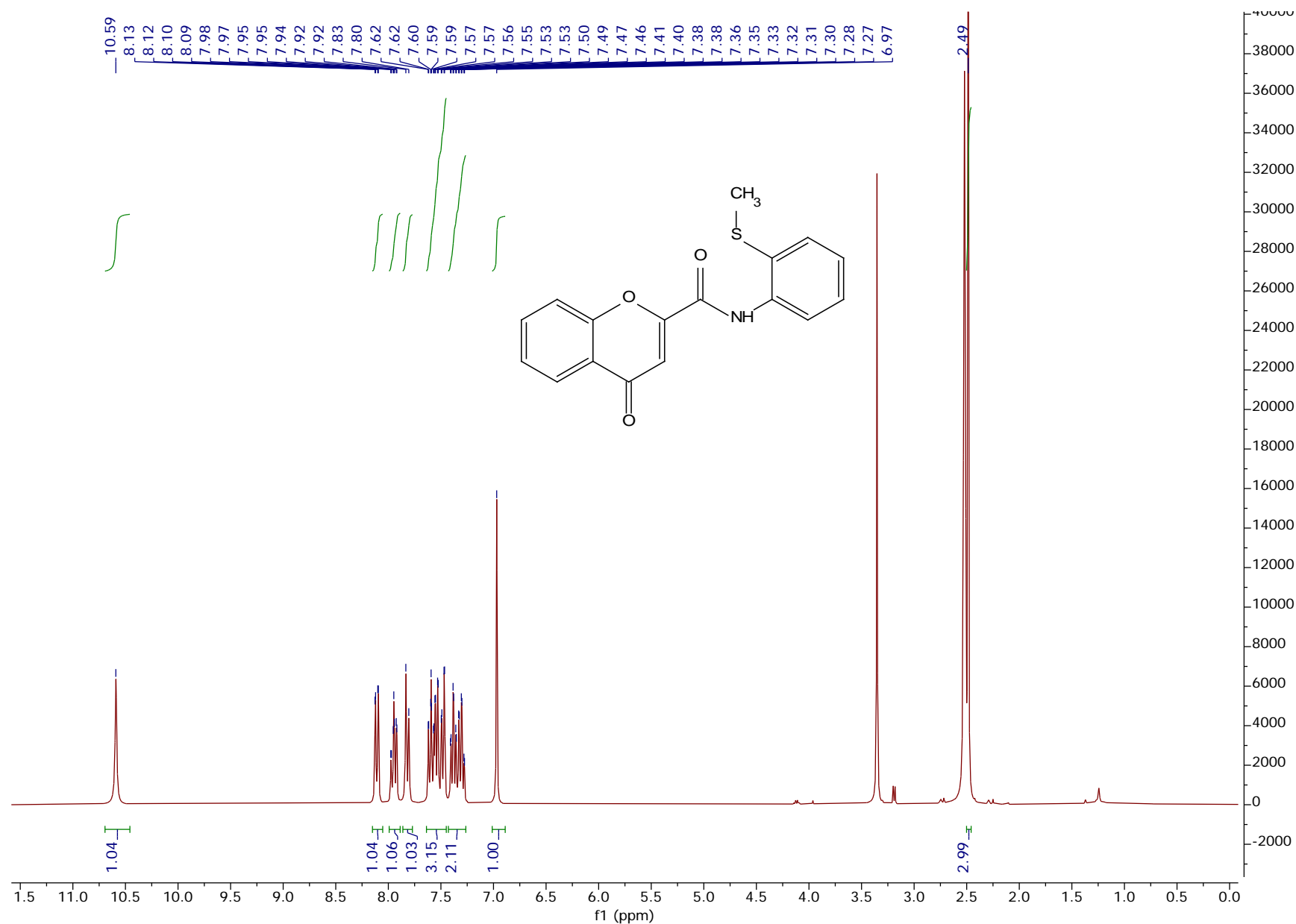


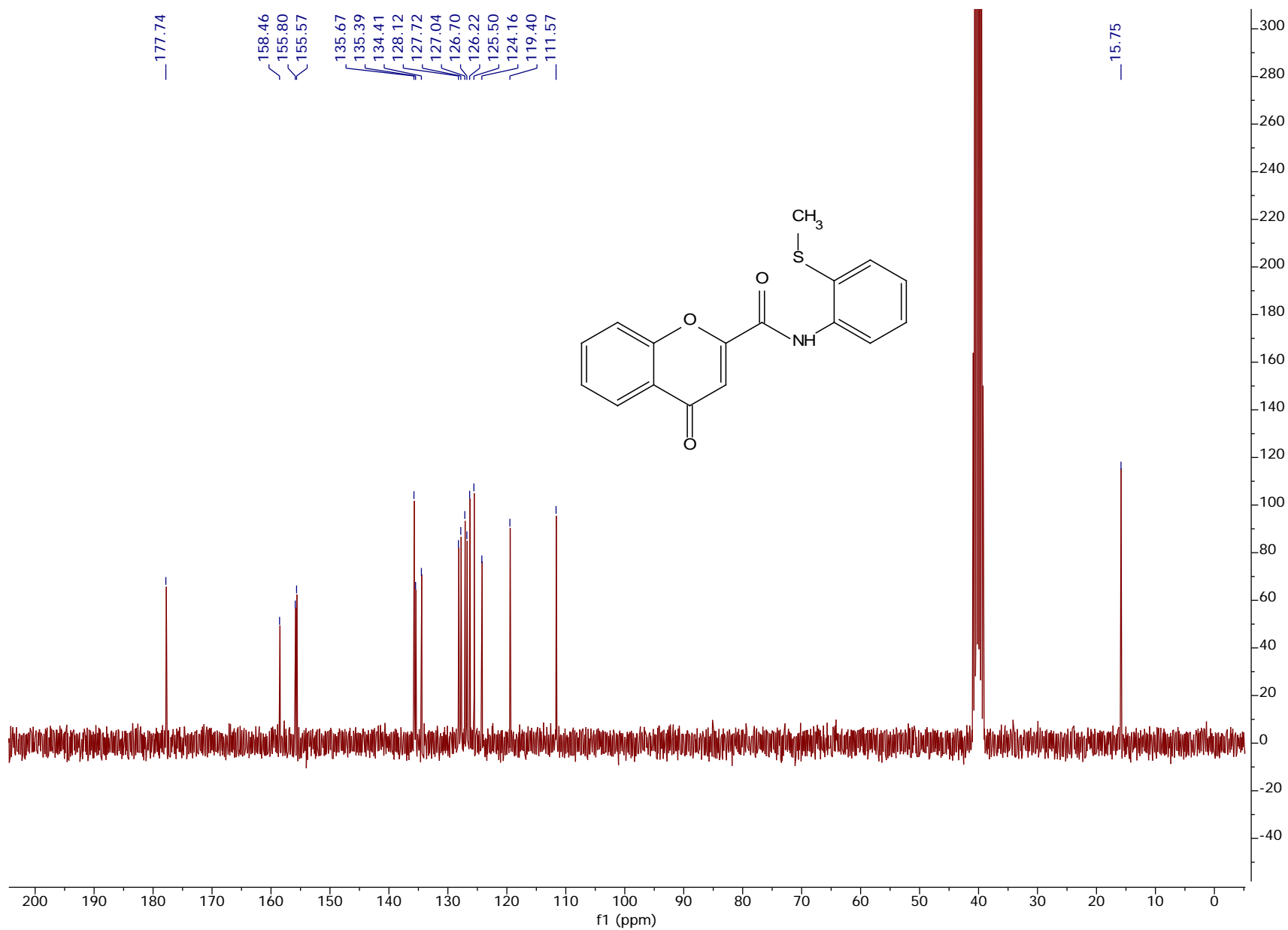
***N*-(2-Methoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide (3q)**



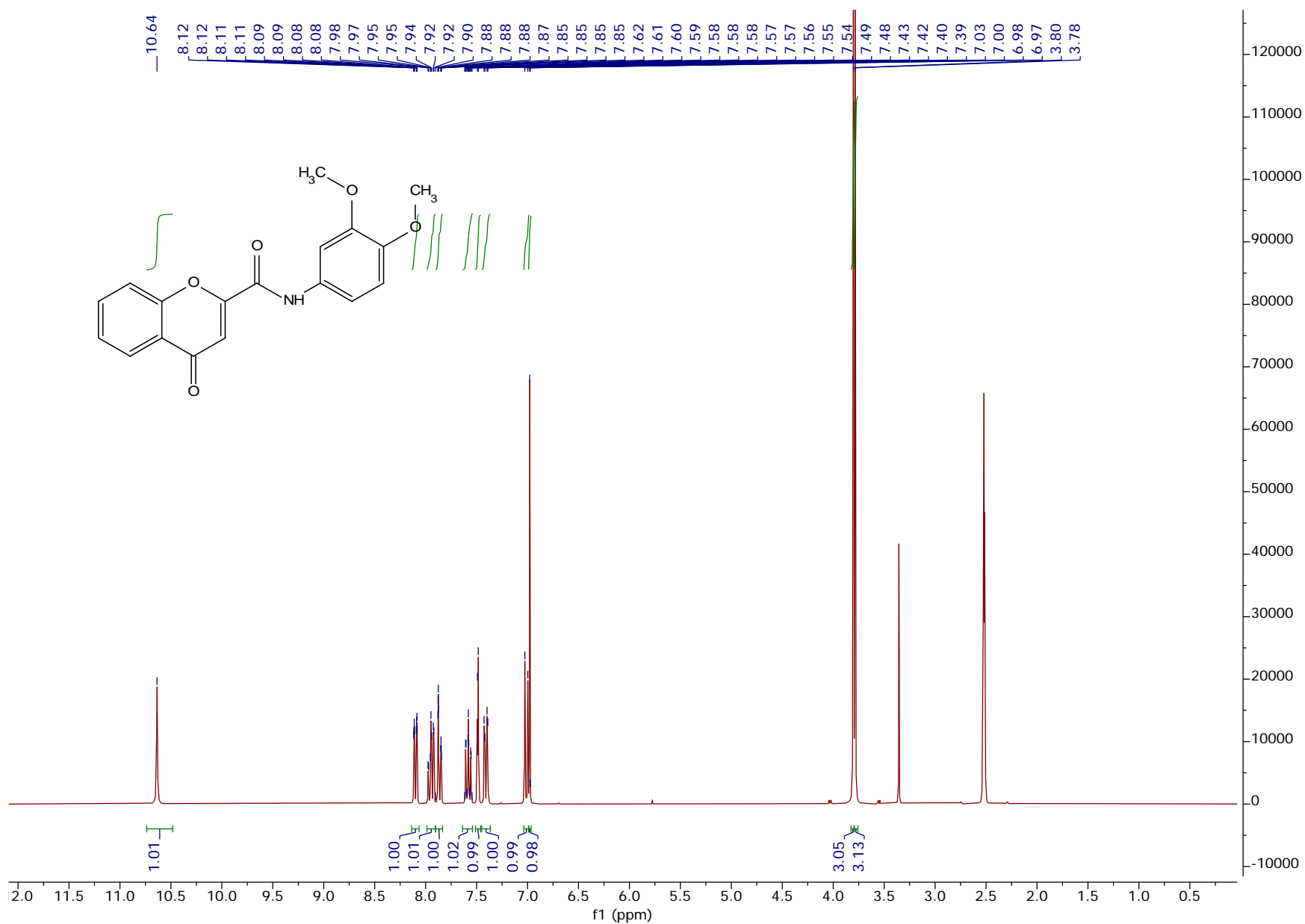


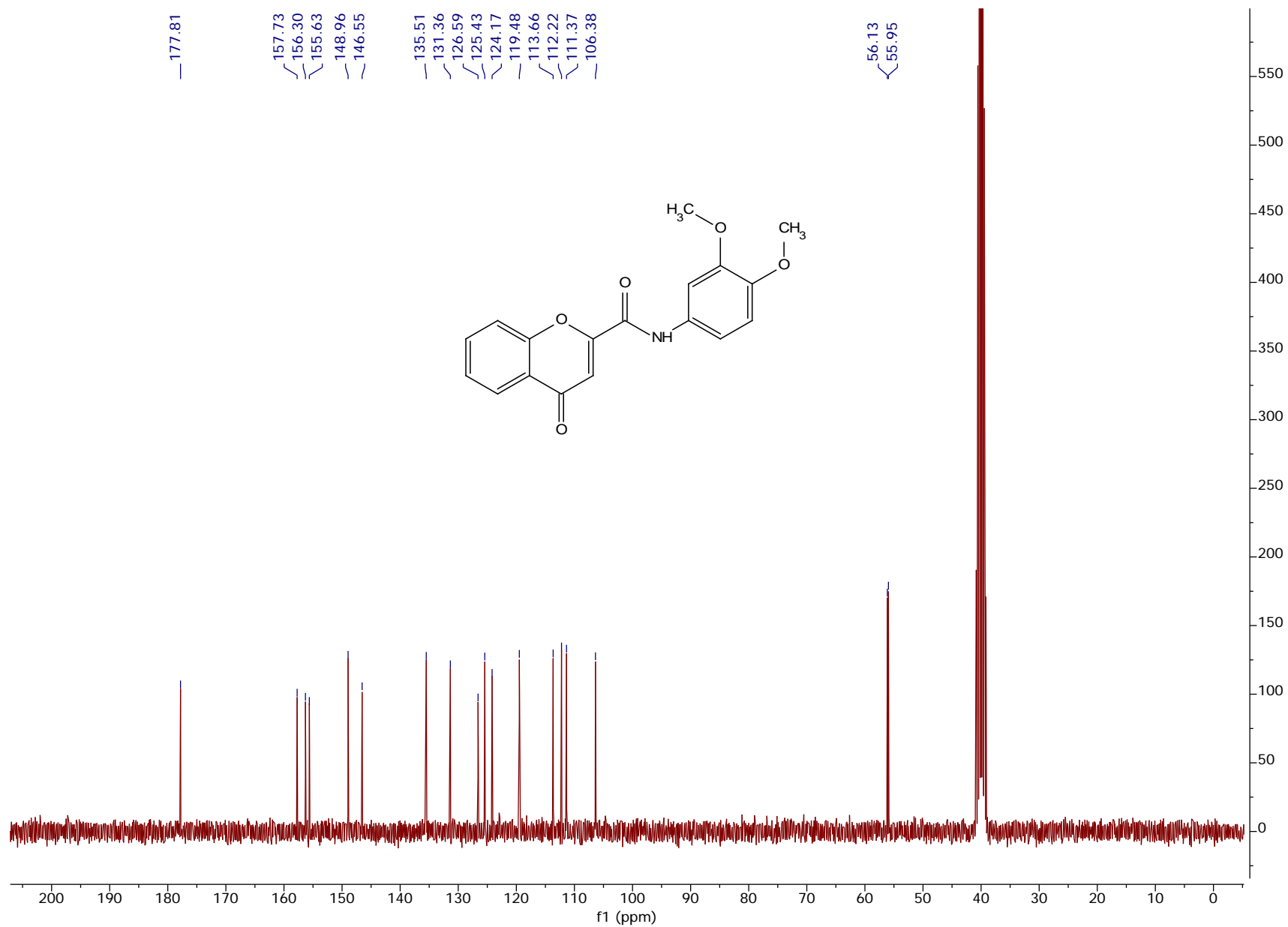
***N*-(2-(Methylthio)phenyl)-4-oxo-4*H*-chromene-2-carboxamide (3r)**



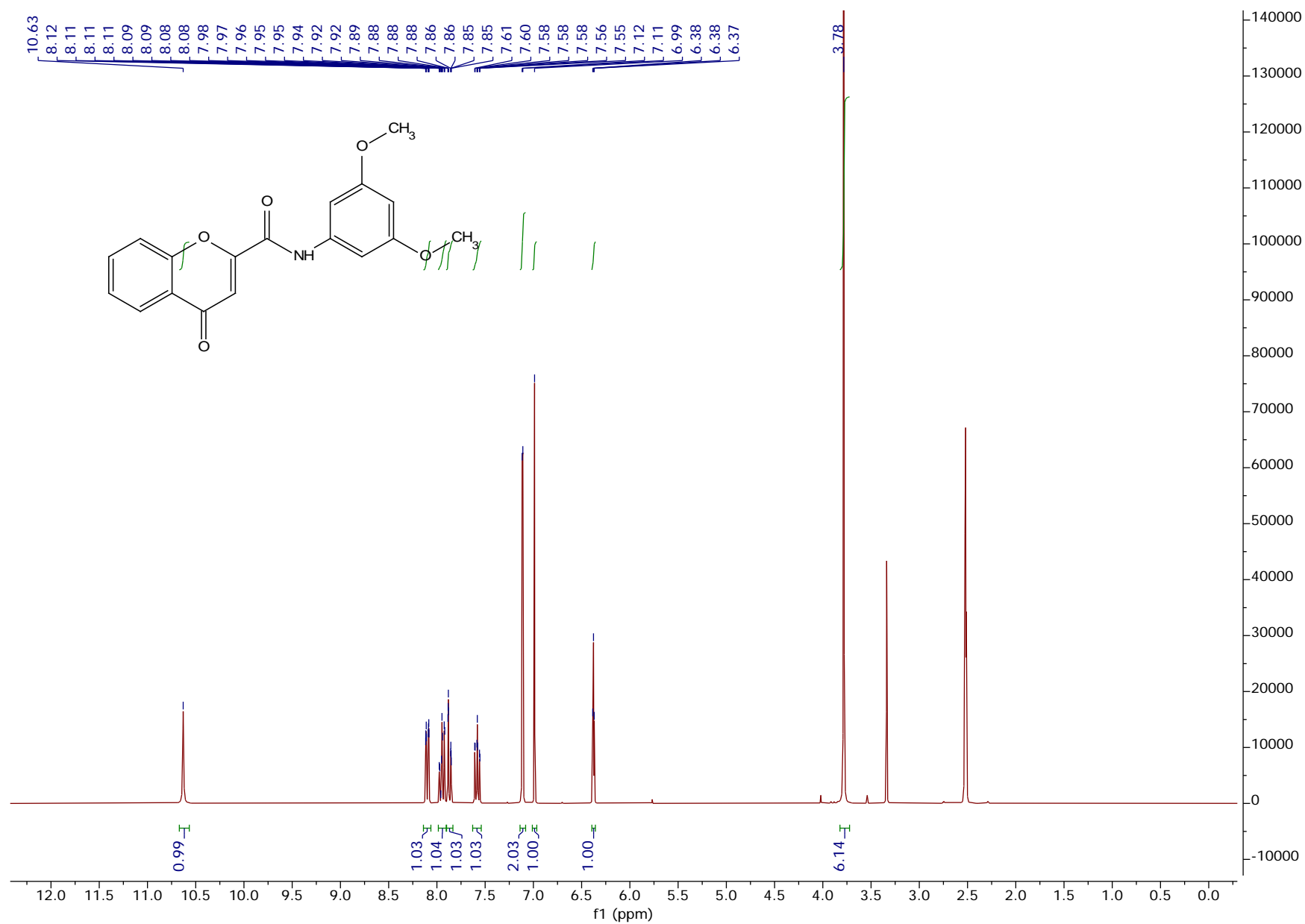


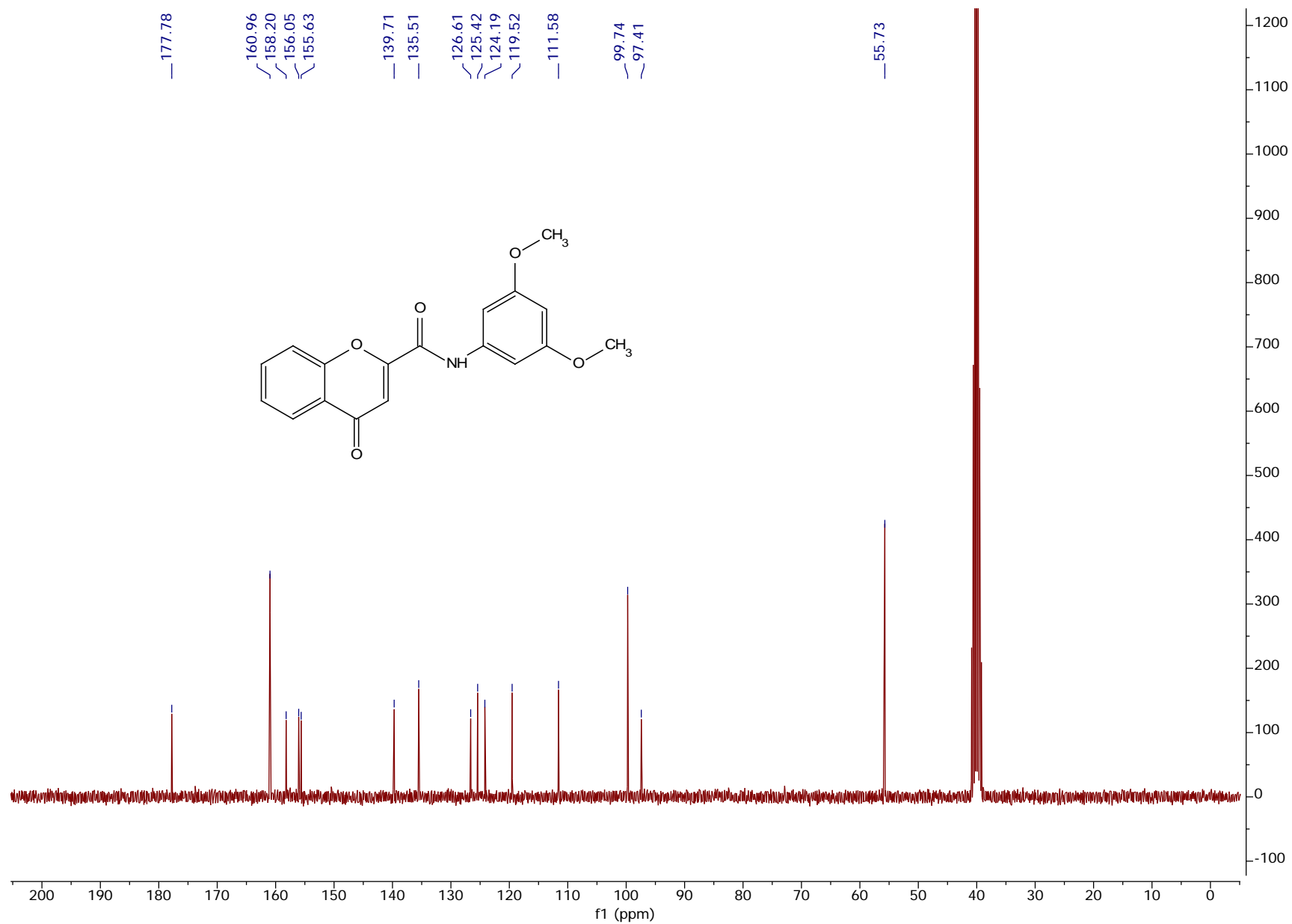
***N*-(3,4-Dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide (3s)**



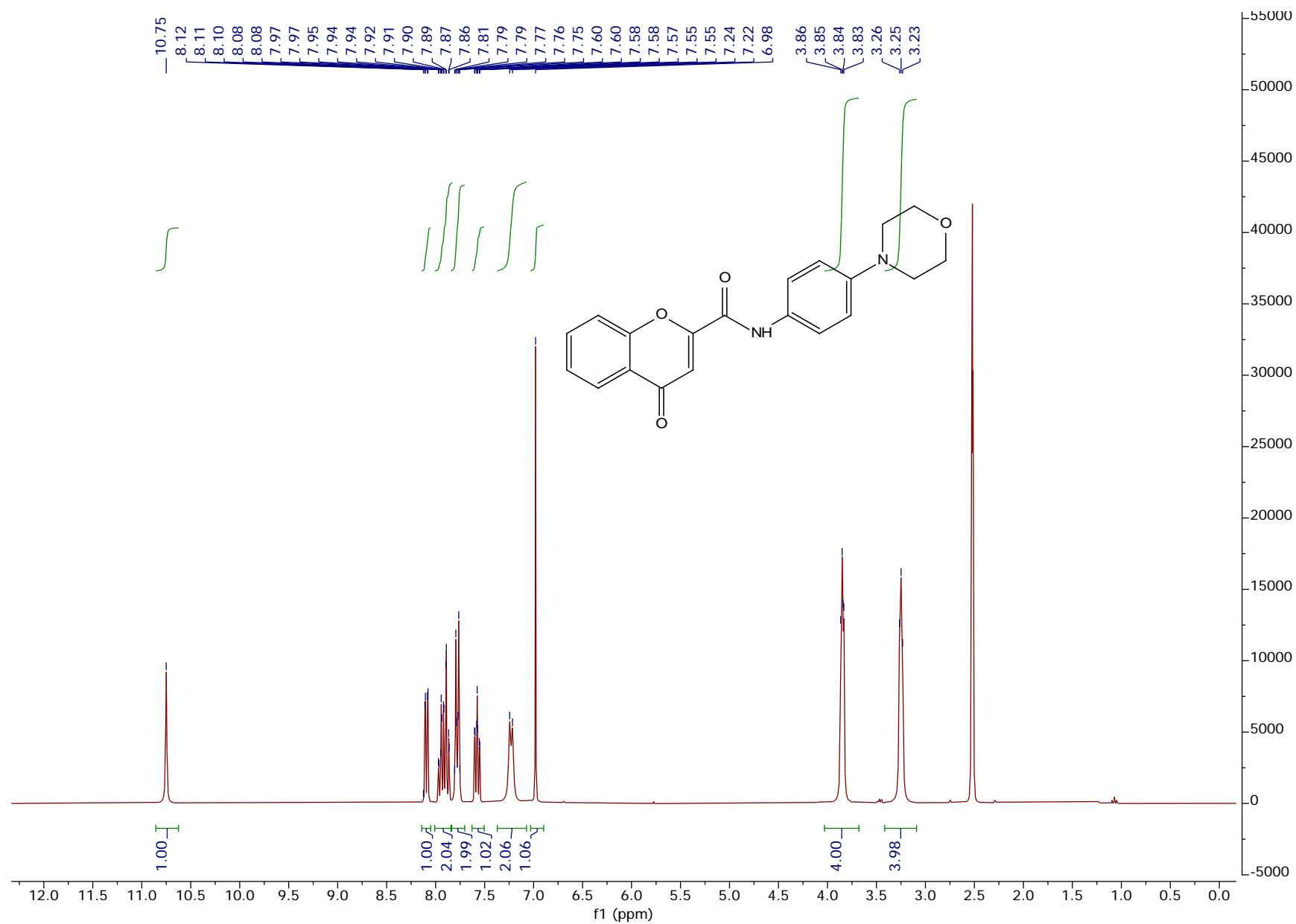


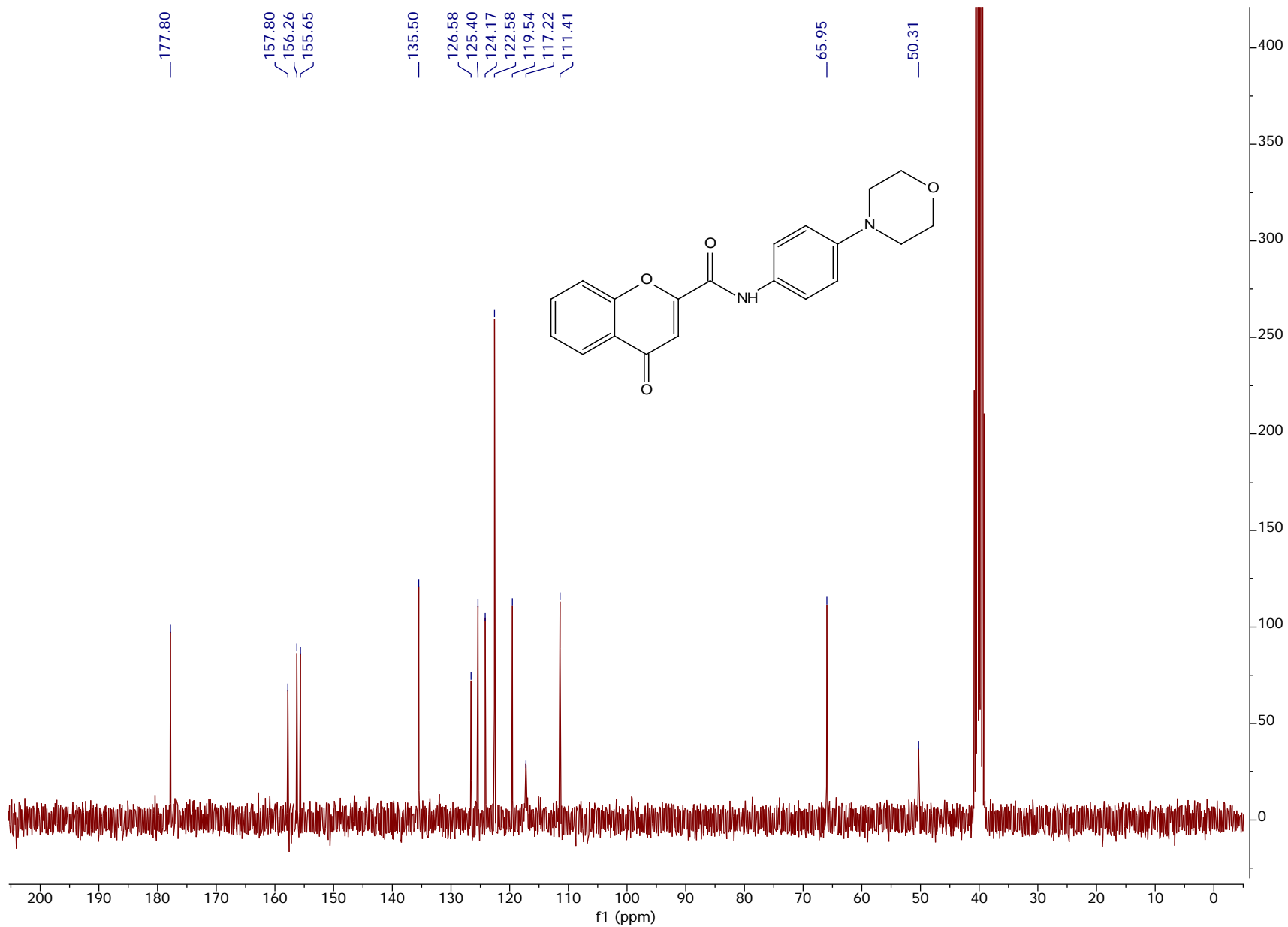
***N*-(3,5-Dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide (3t)**



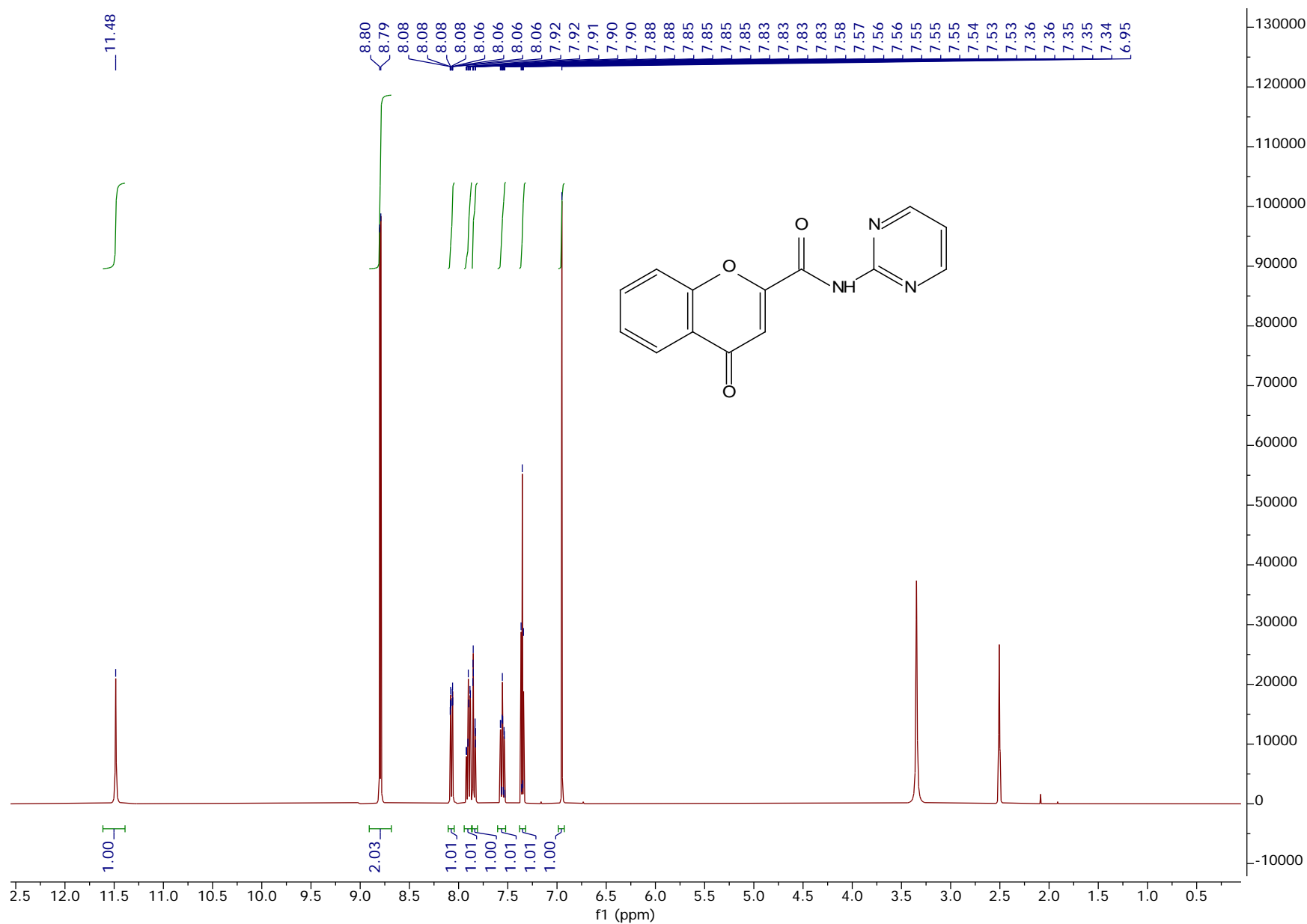


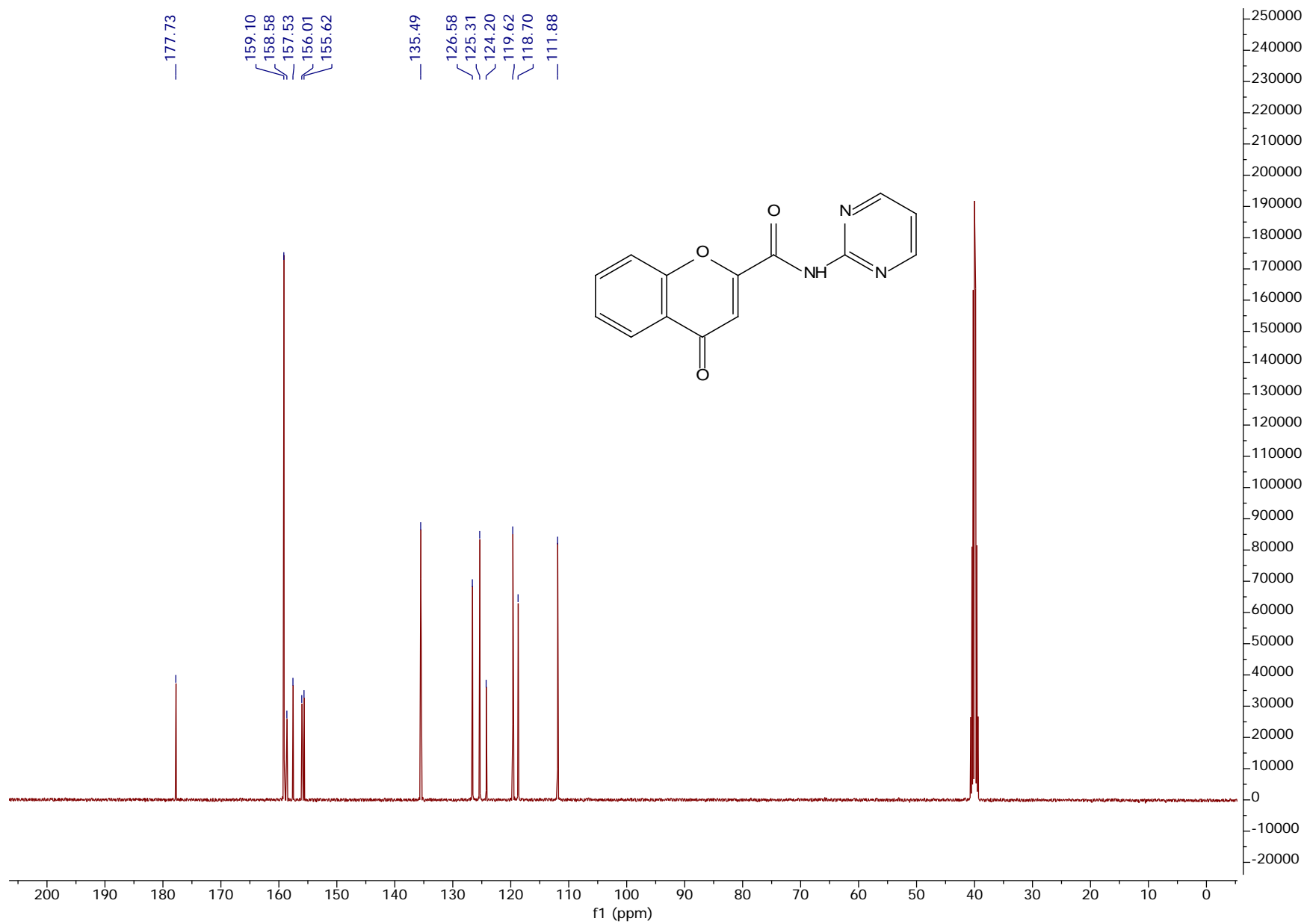
***N*-(4-Morpholinophenyl)-4-oxo-4*H*-chromene-2-carboxamide (3u)**



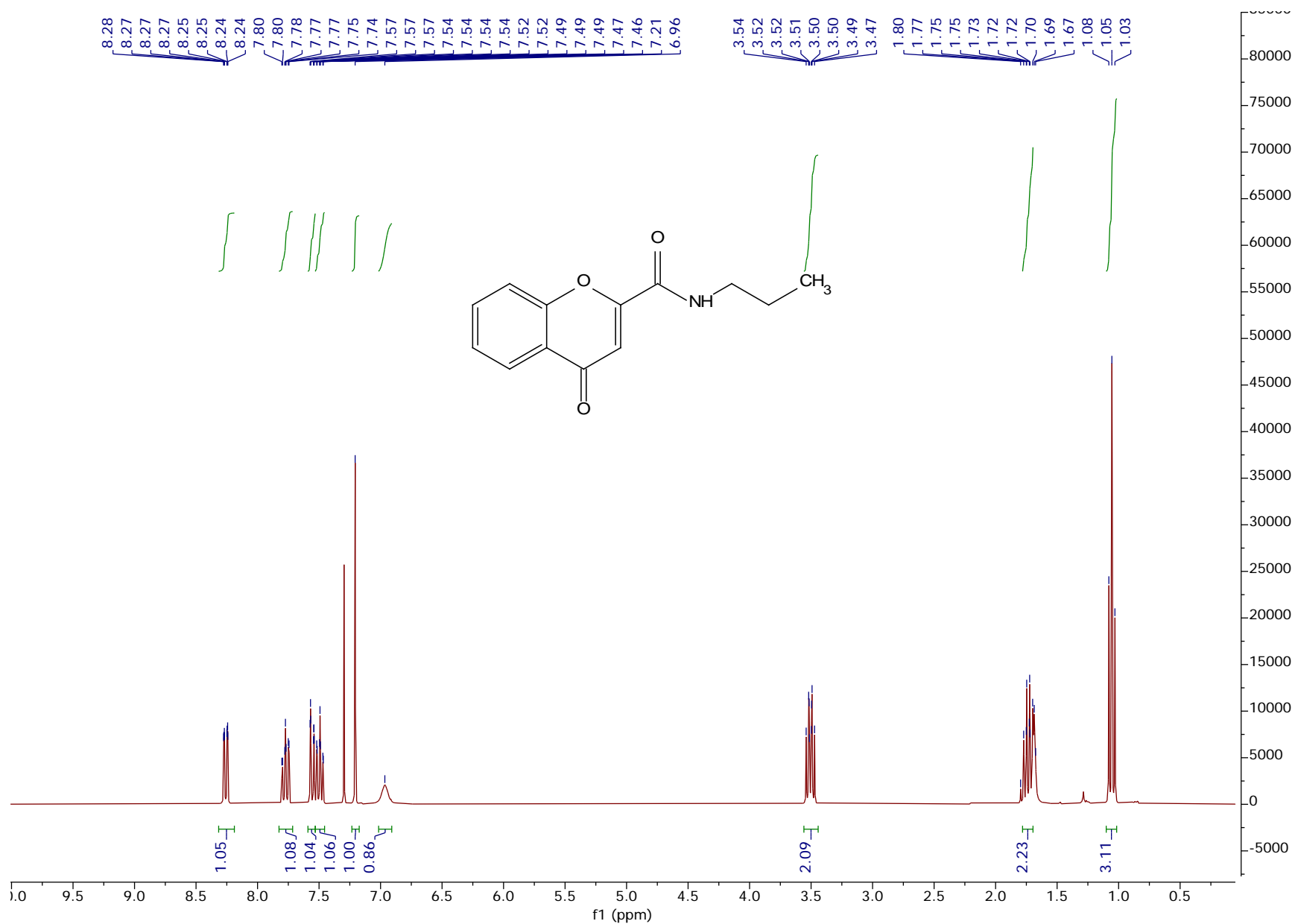


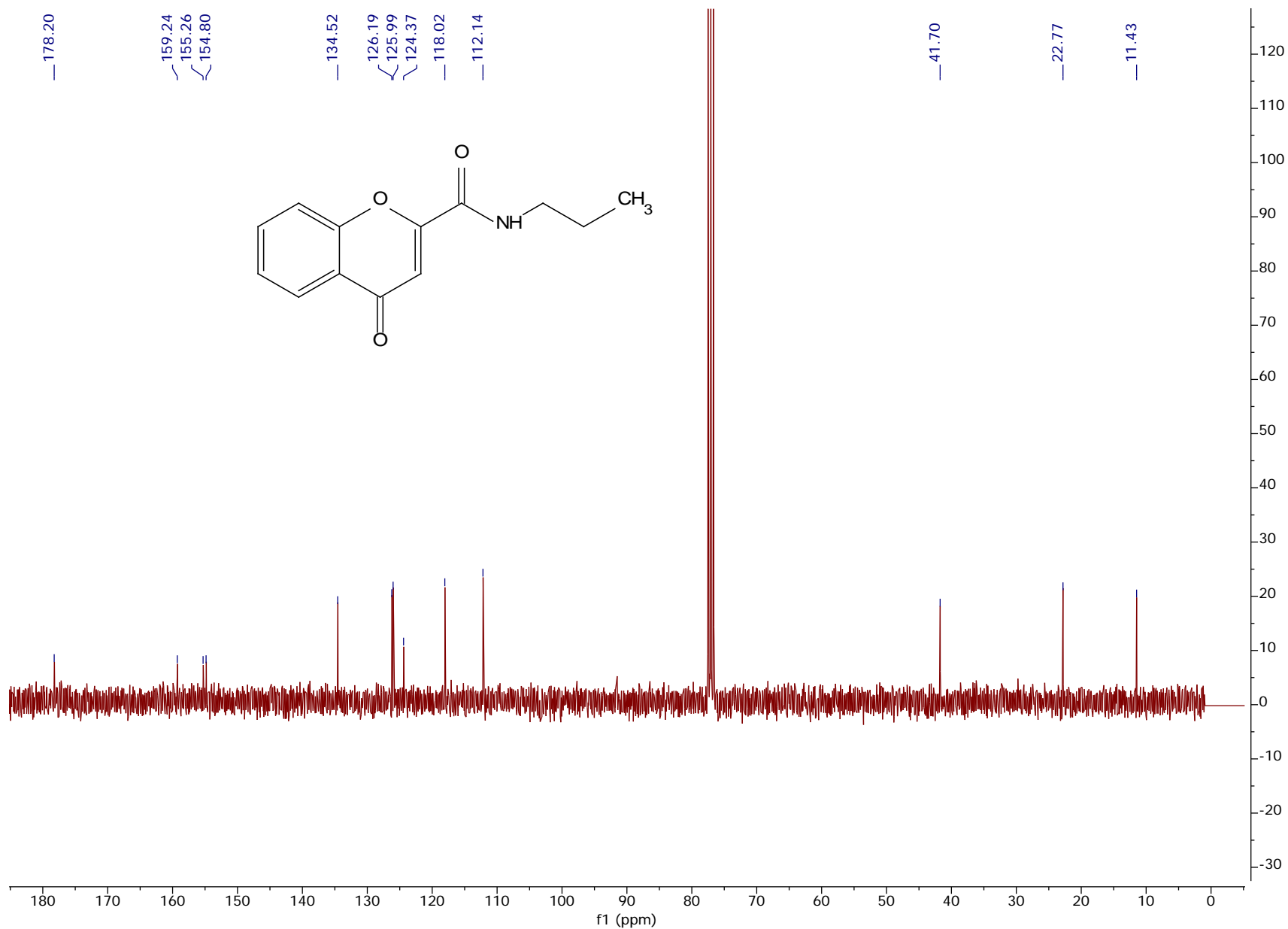
4-Oxo-*N*-(pyrimidin-2-yl)-4*H*-chromene-2-carboxamide (3v)



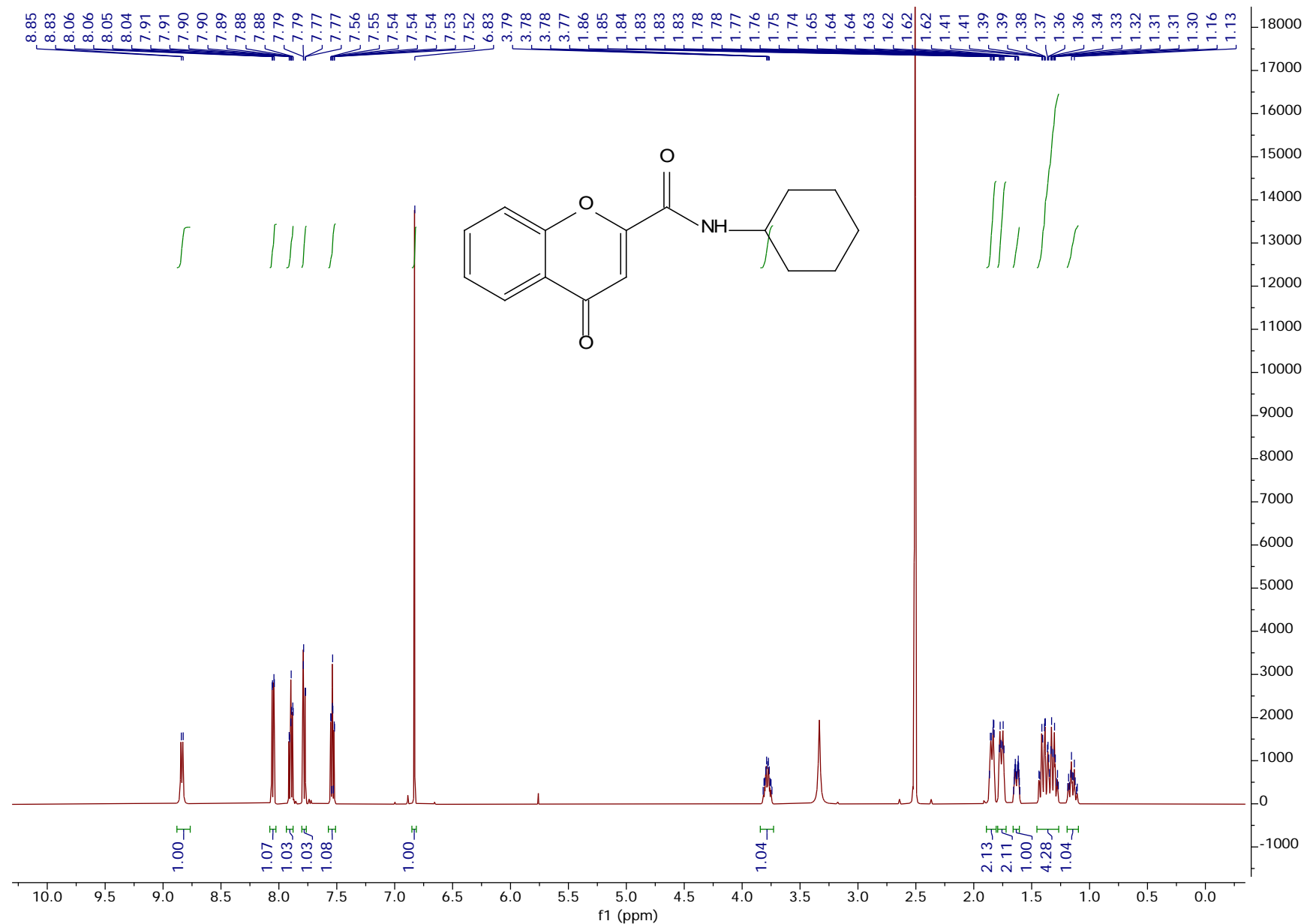


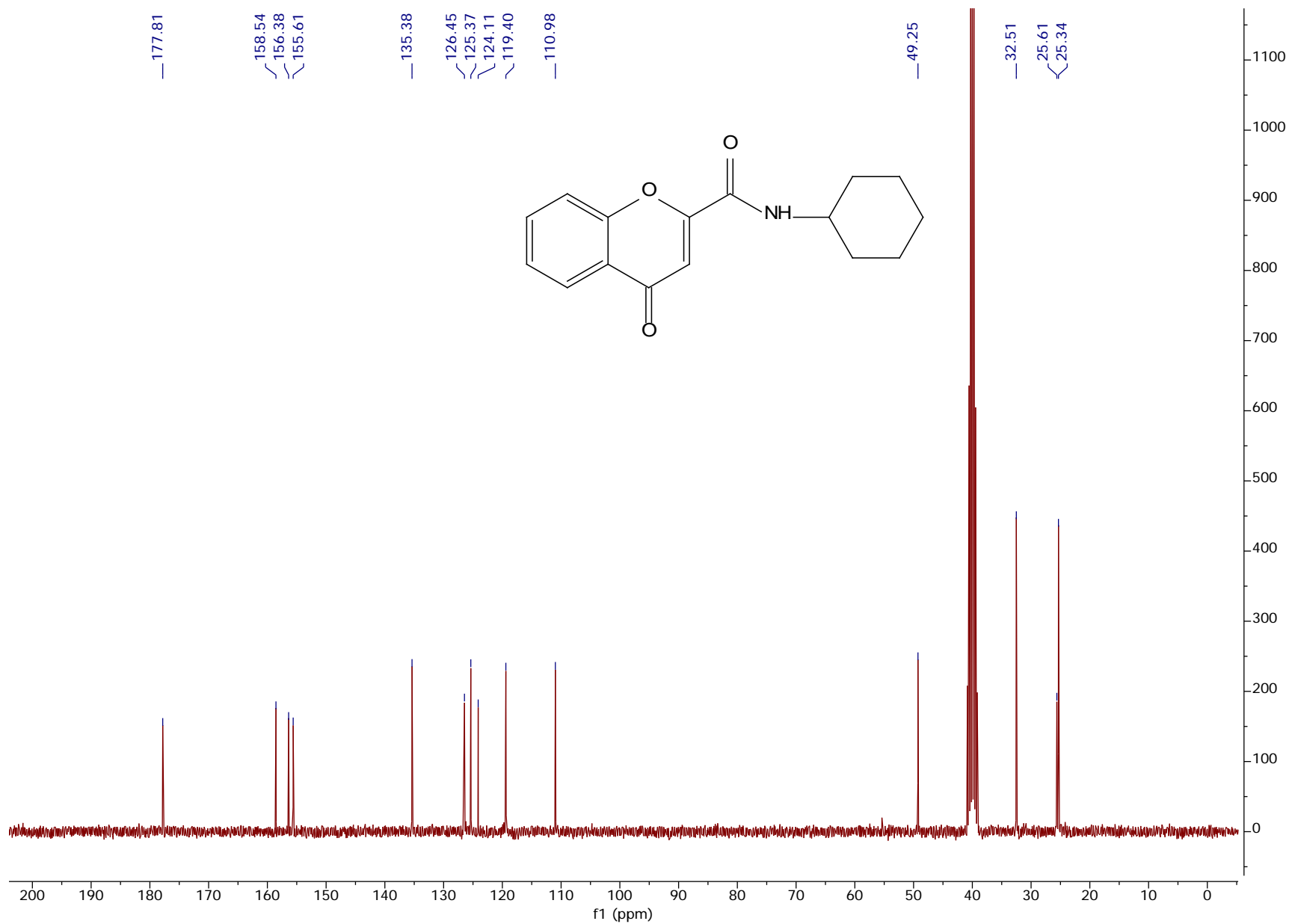
4-Oxo-N-propyl-4H-chromene-2-carboxamide (3w)



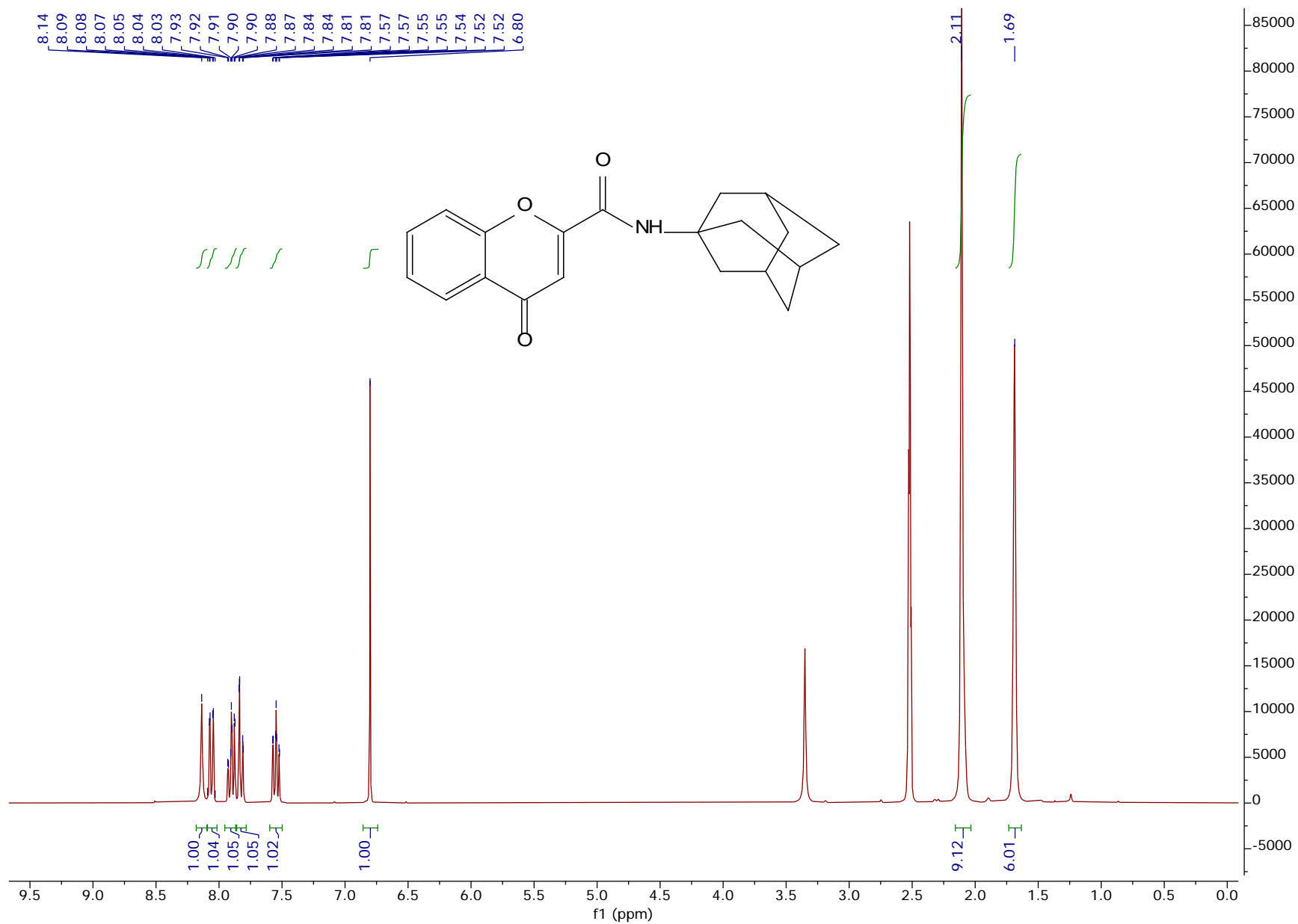


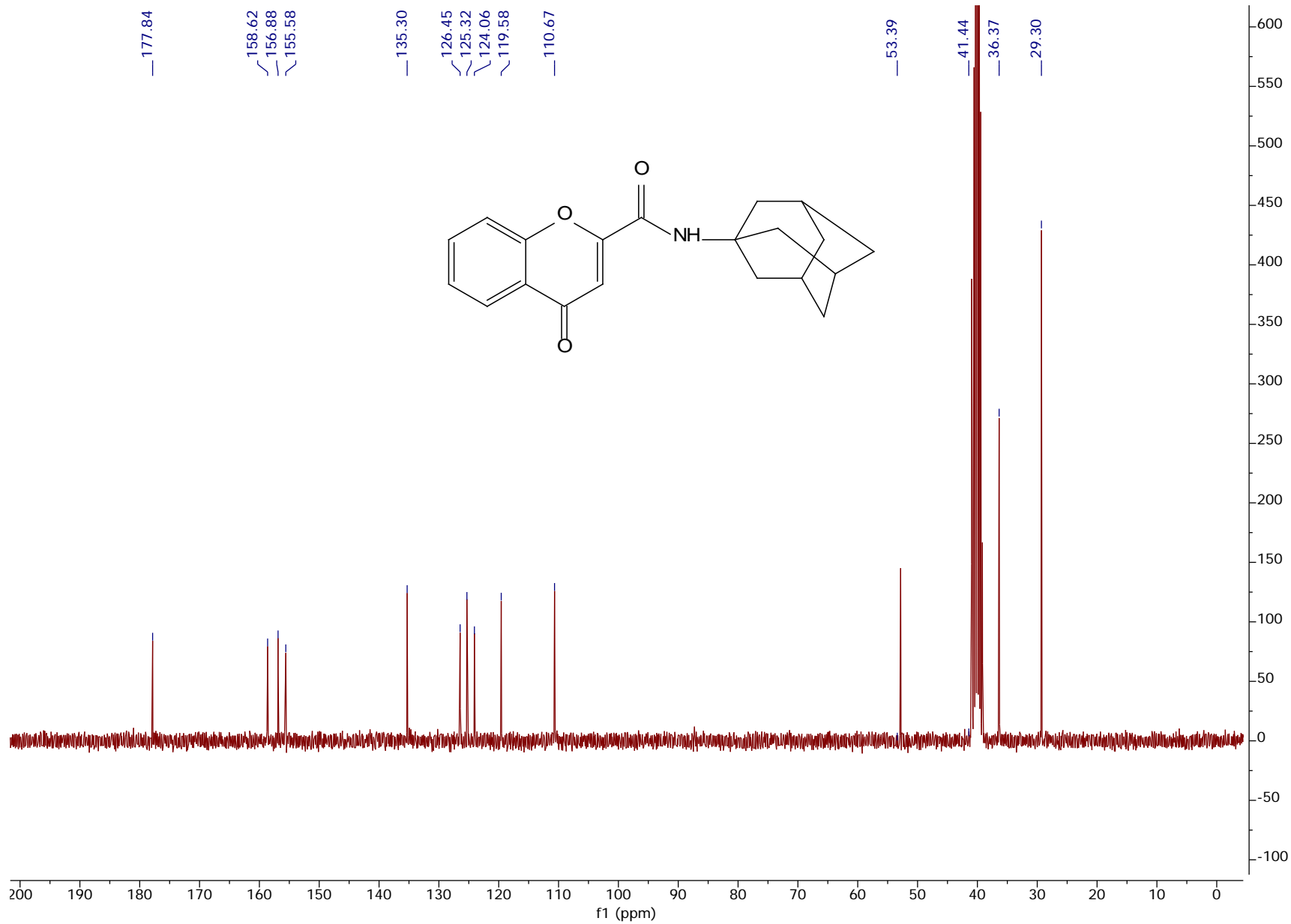
***N*-Cyclohexyl-4-oxo-4*H*-chromene-2-carboxamide (3x)**



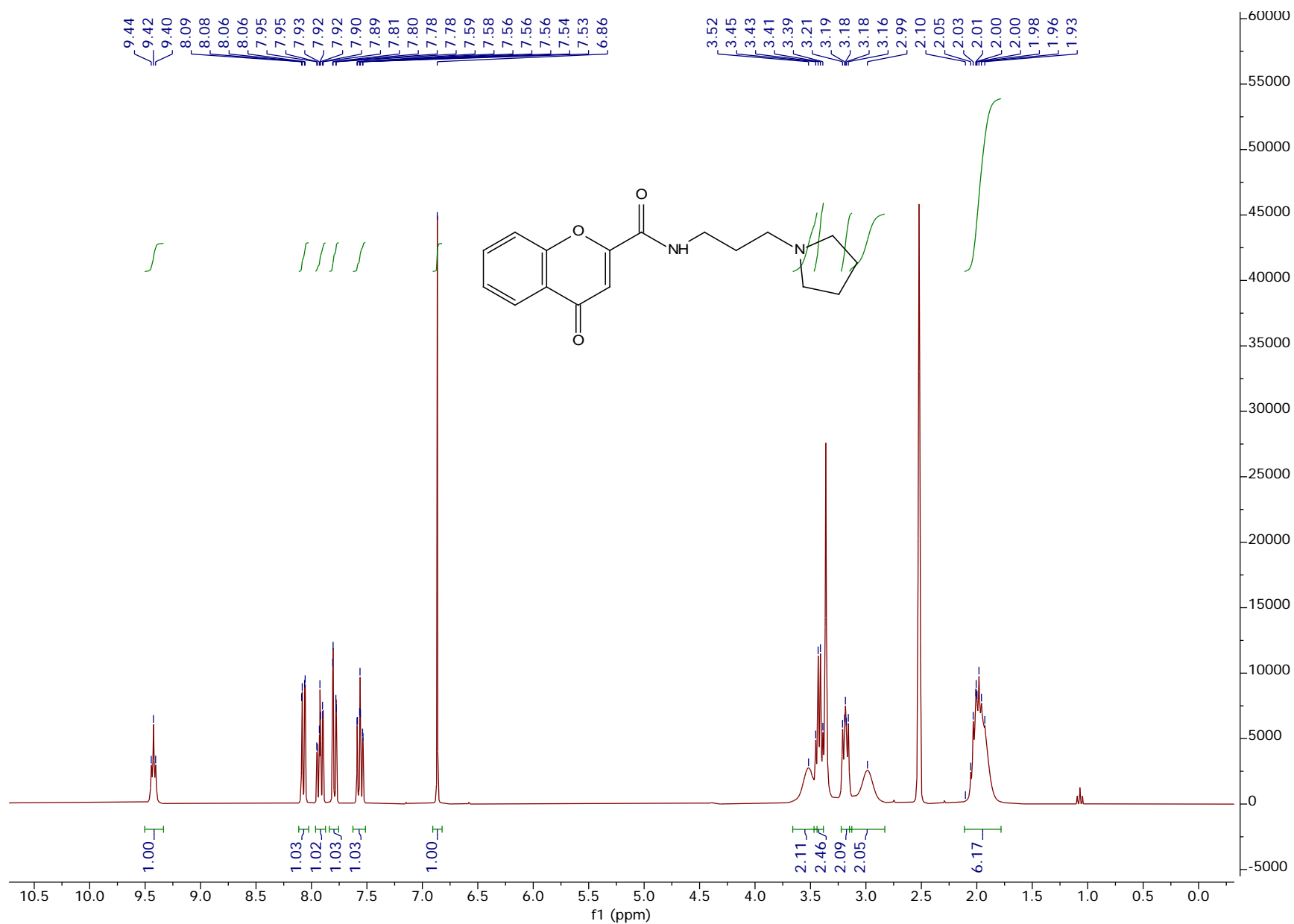


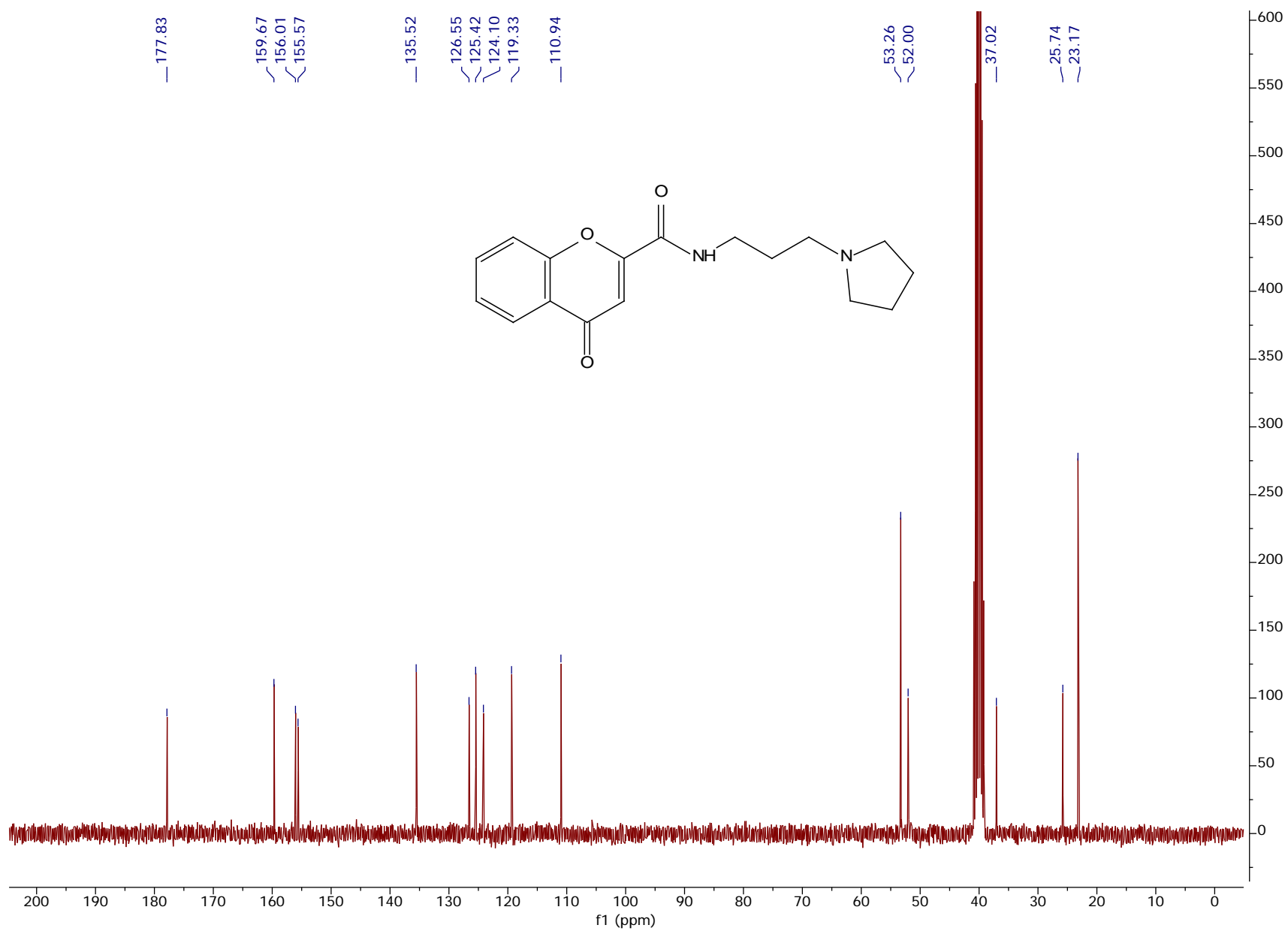
***N*-((3*s*,5*s*,7*s*)-Adamantan-1-yl)-4-oxo-4*H*-chromene-2-carboxamide (3y)**



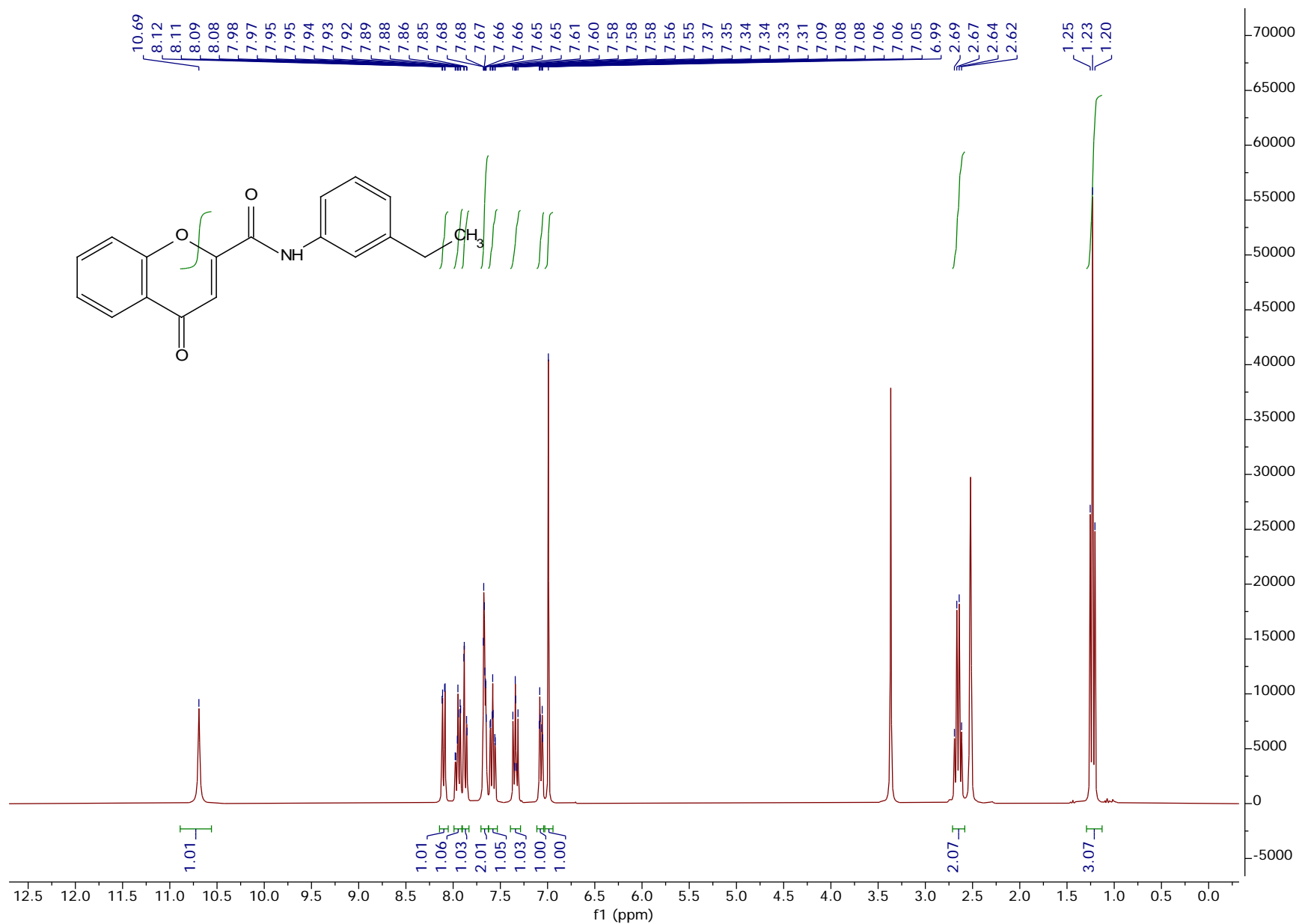


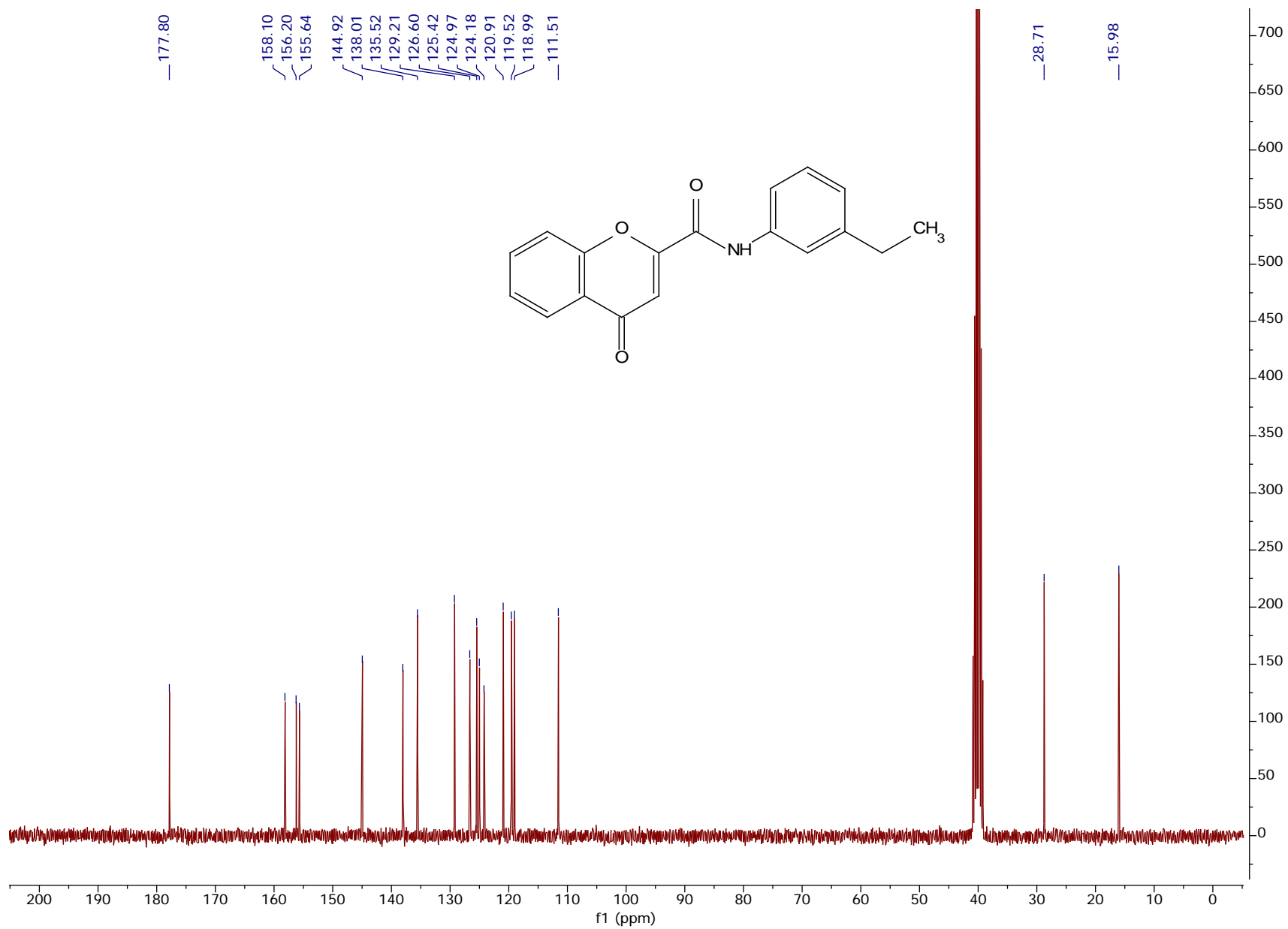
4-Oxo-N-(3-(pyrrolidin-1-yl)propyl)-4H-chromene-2-carboxamide (3z)



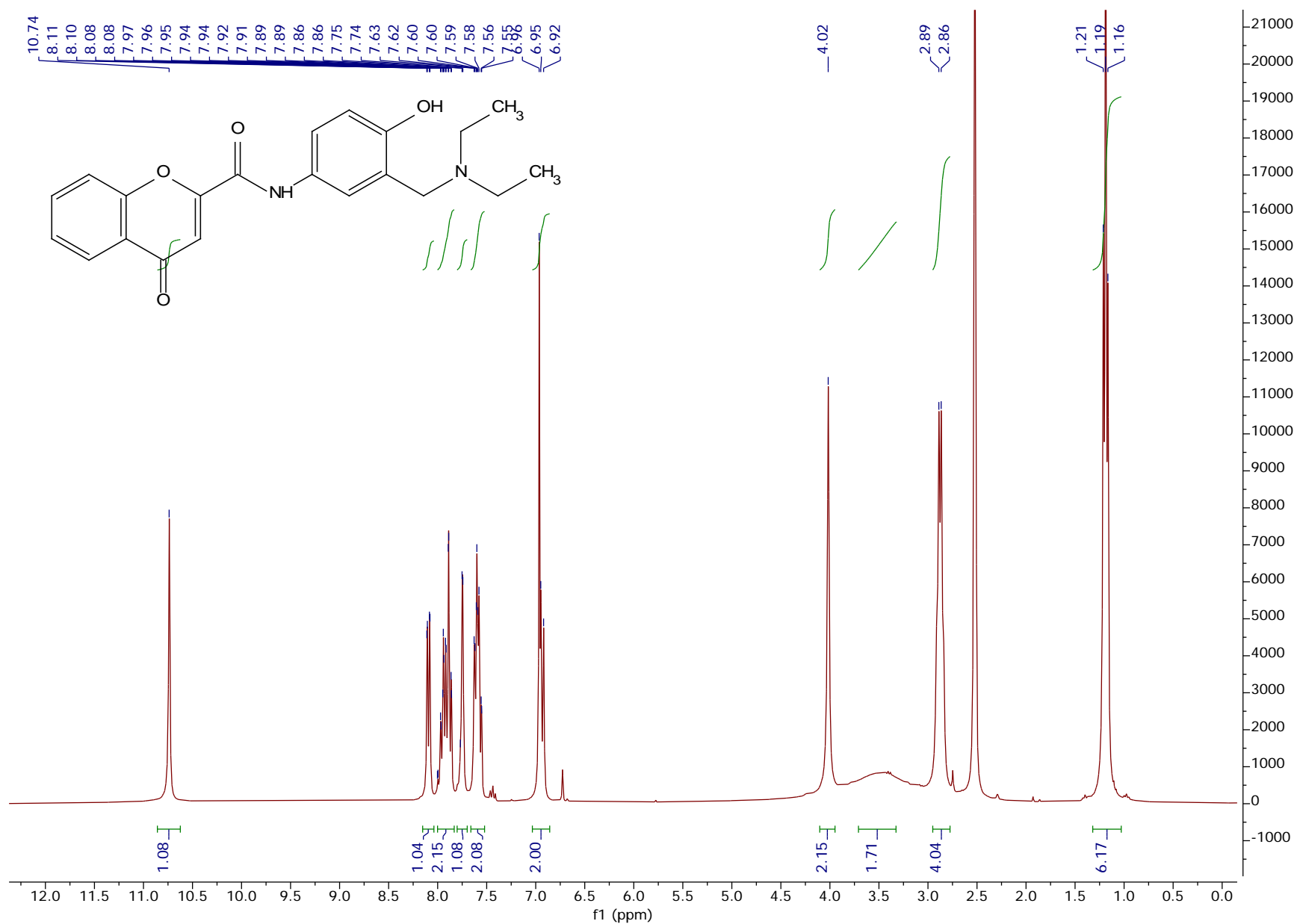


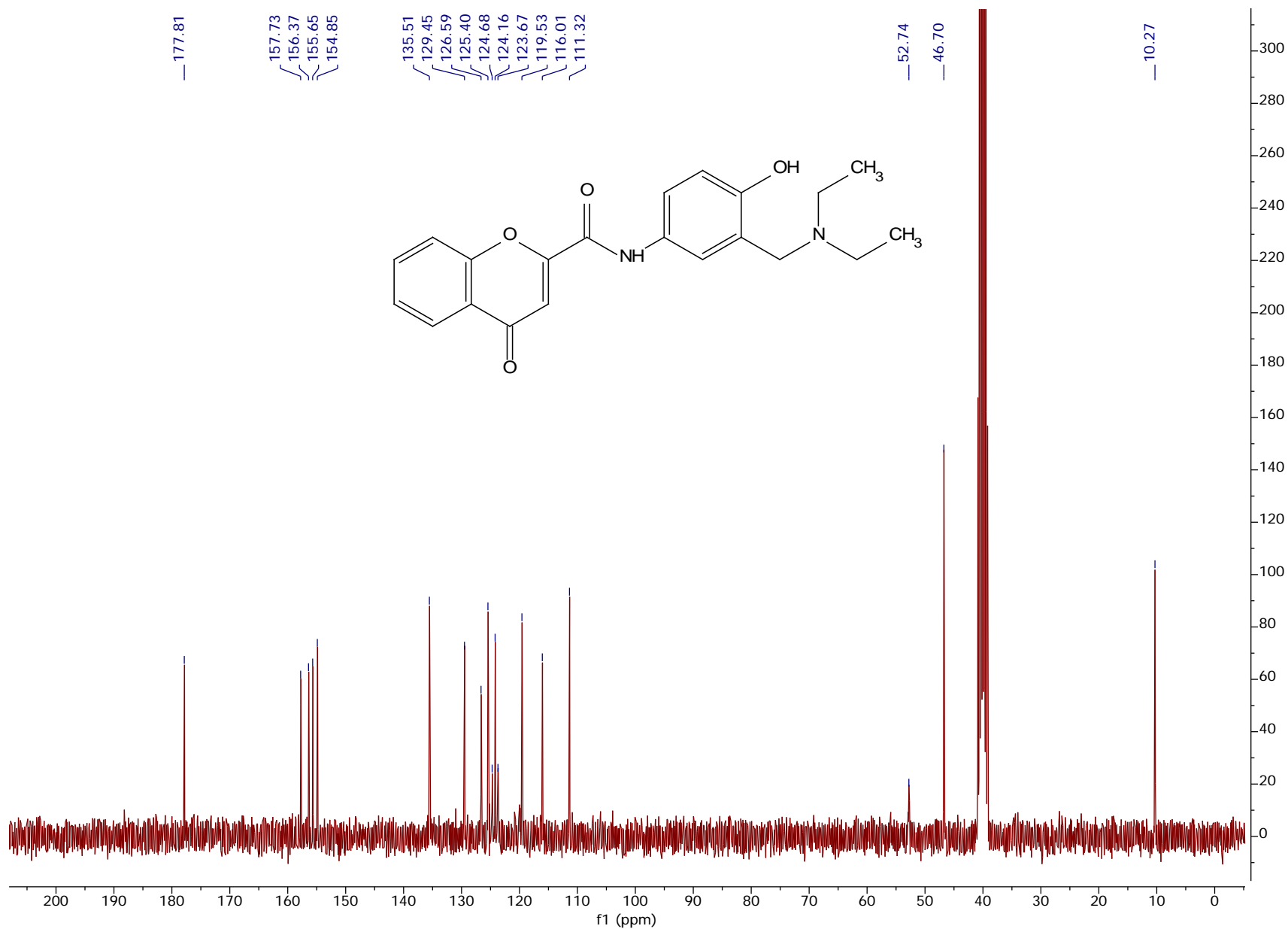
***N*-(3-Ethylphenyl)-4-oxo-4*H*-chromene-2-carboxamide (3'a)**



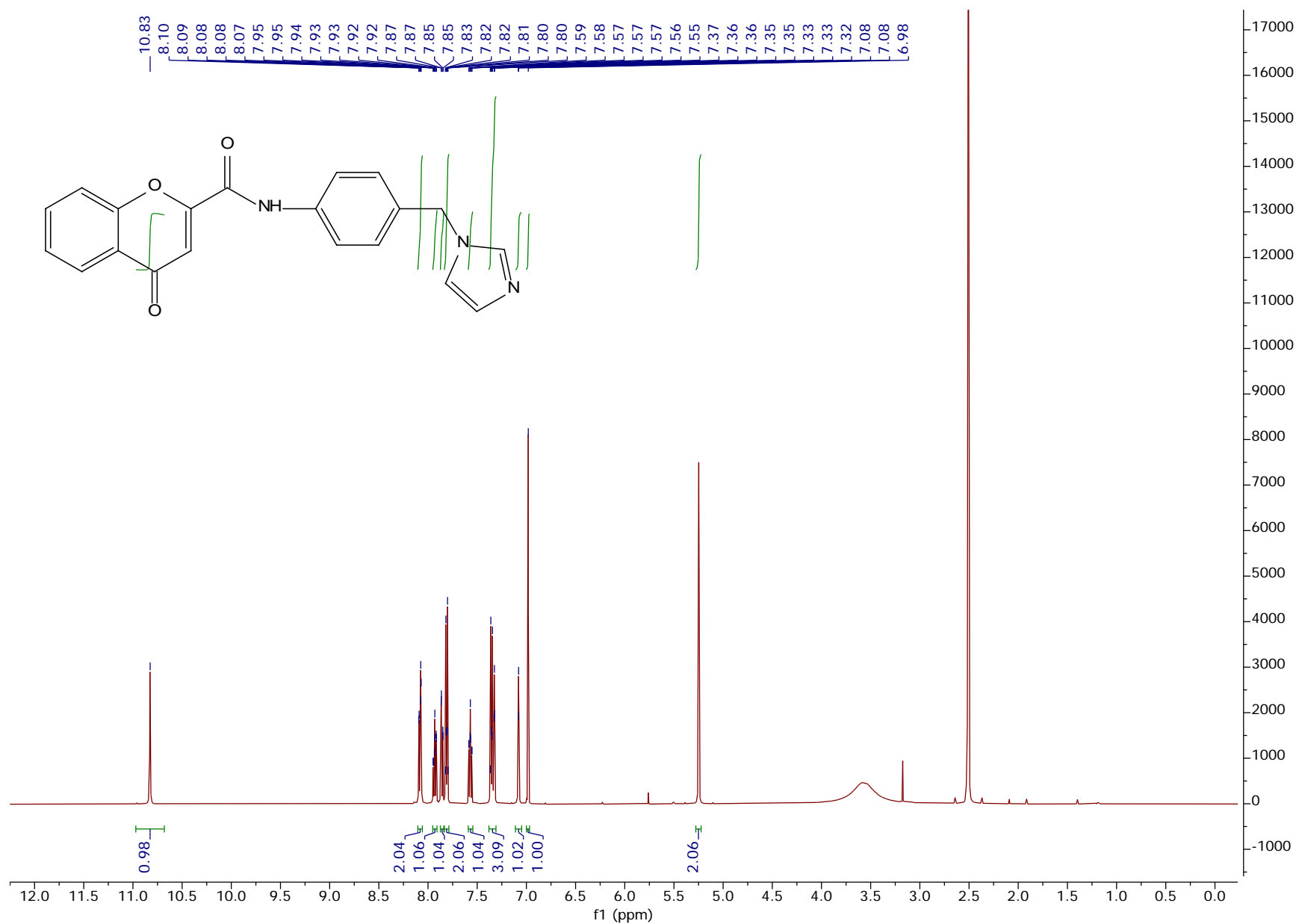


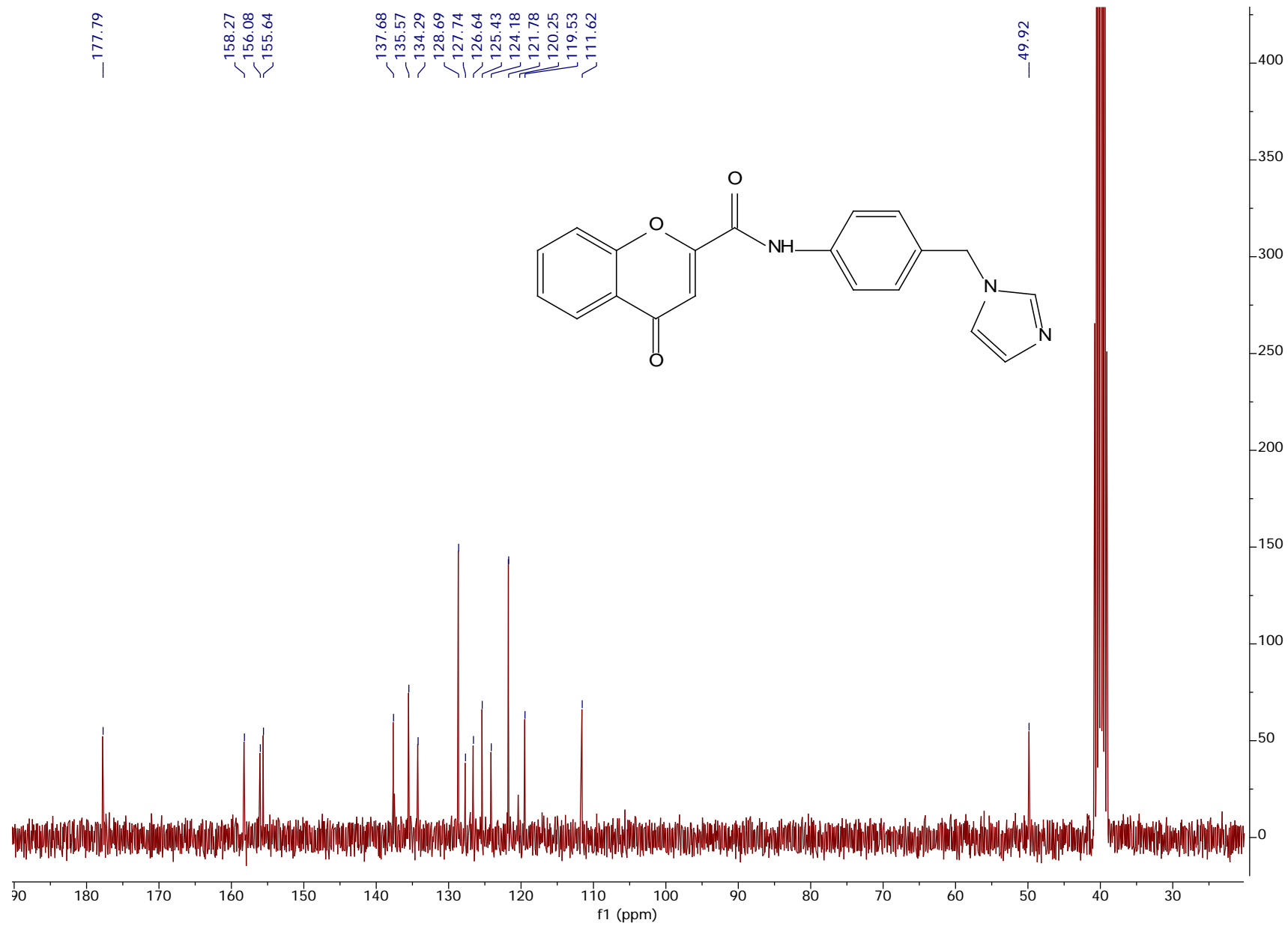
***N*-(3-((Diethylamino)methyl)-4-hydroxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide (3'b)**



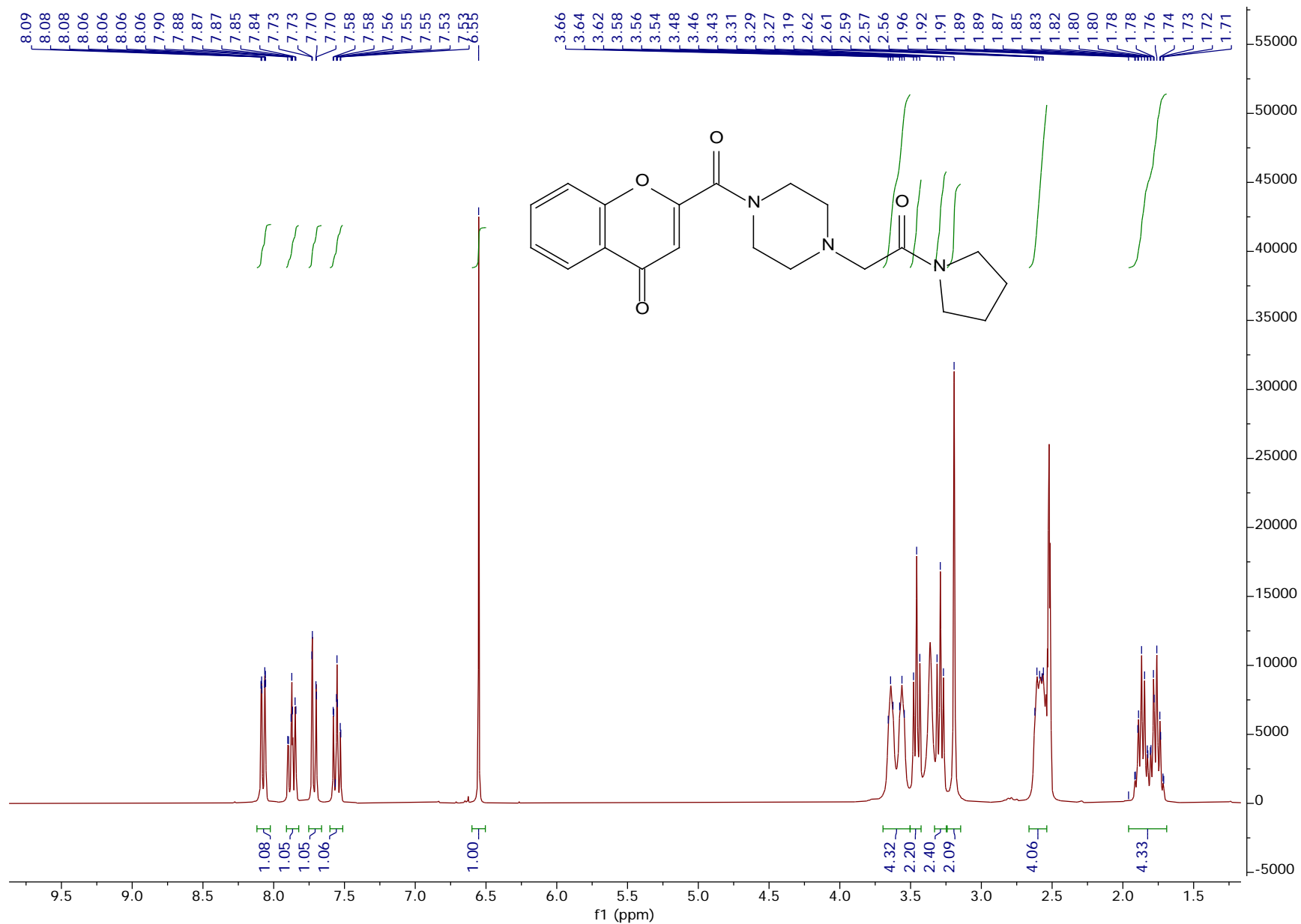


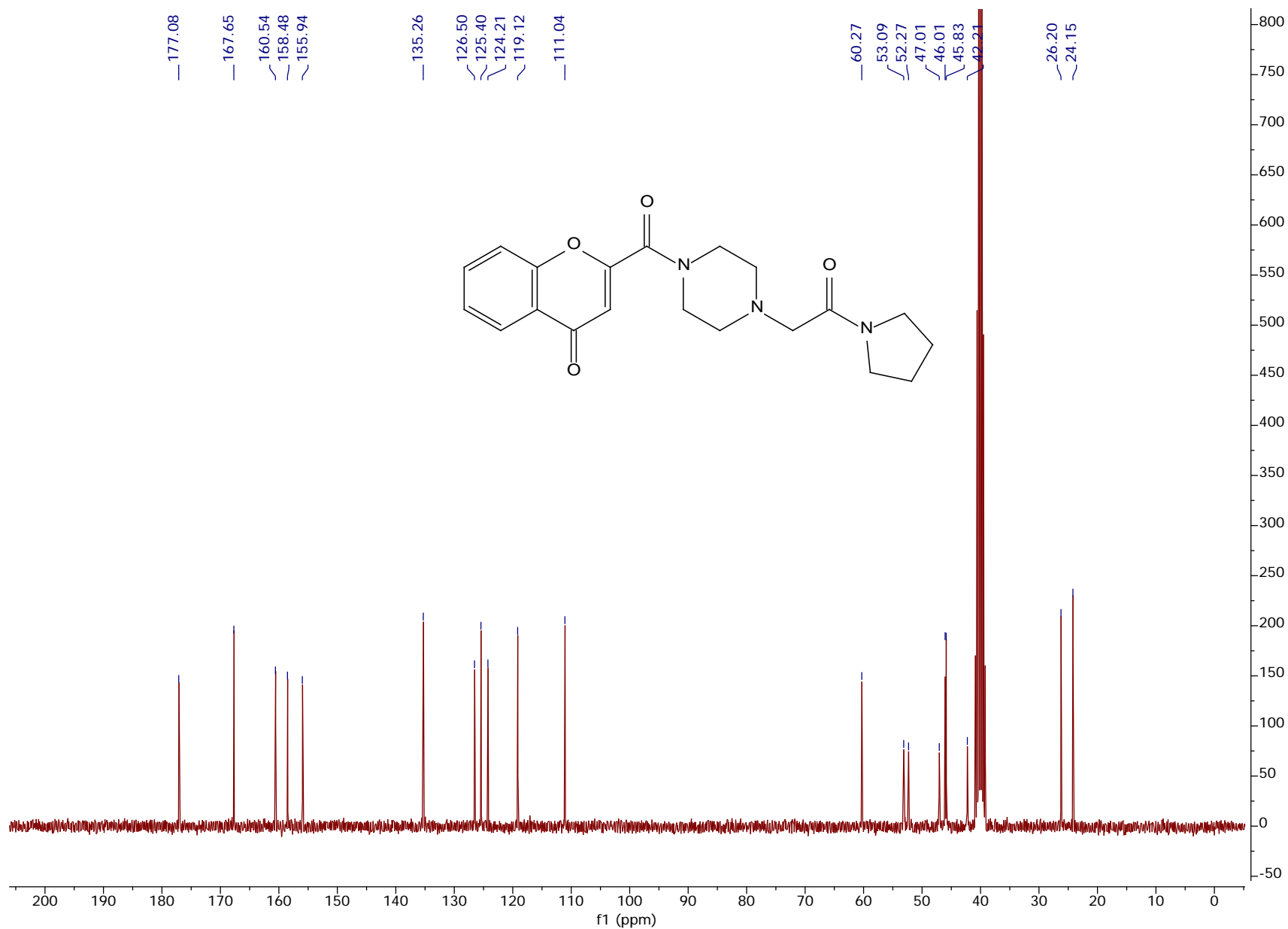
***N*-(4-((1*H*-imidazol-1-yl)methyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide (3'*c*)**



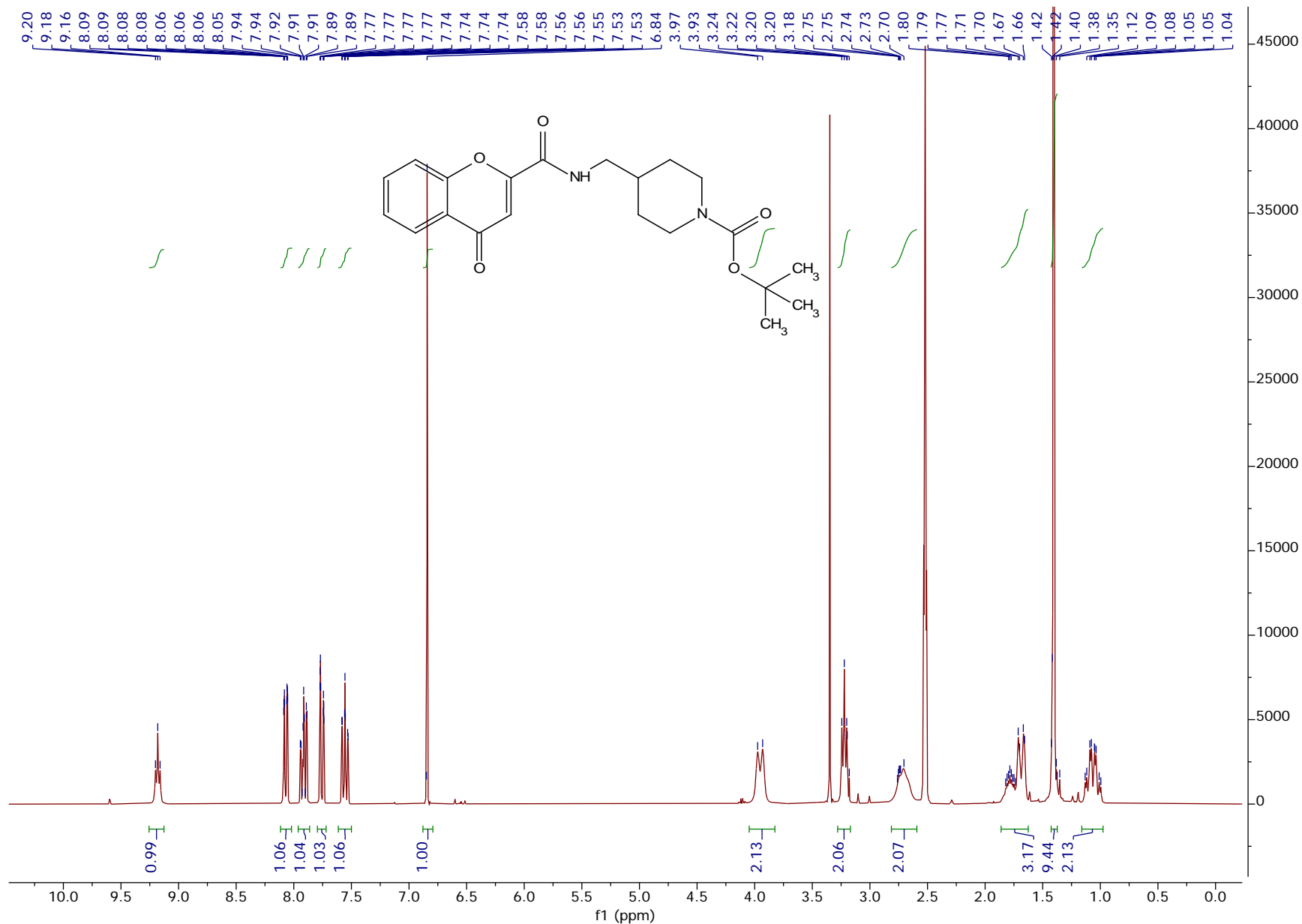


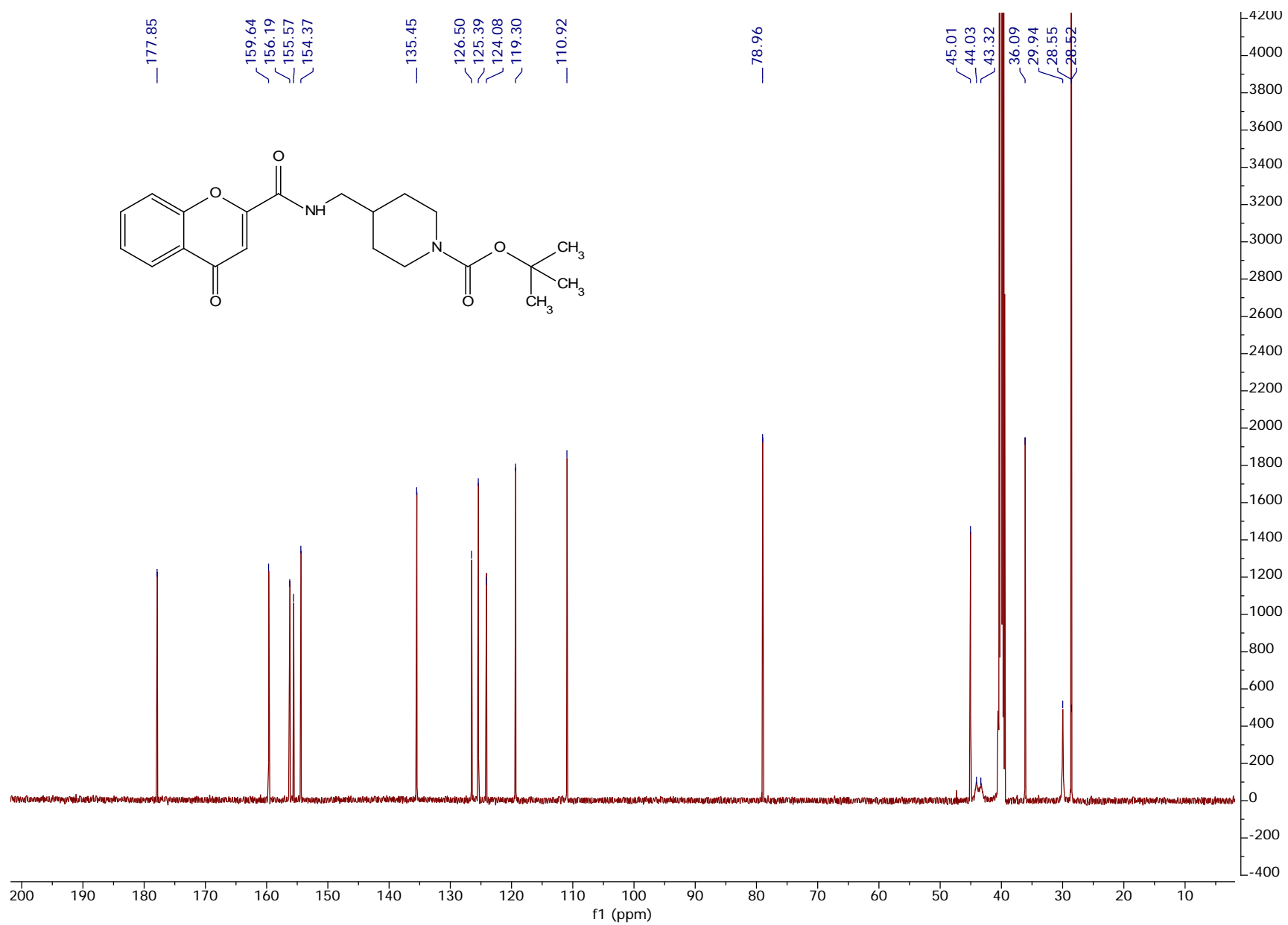
2-(4-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)piperazine-1-carbonyl)-4*H*-chromen-4-one (3'd)



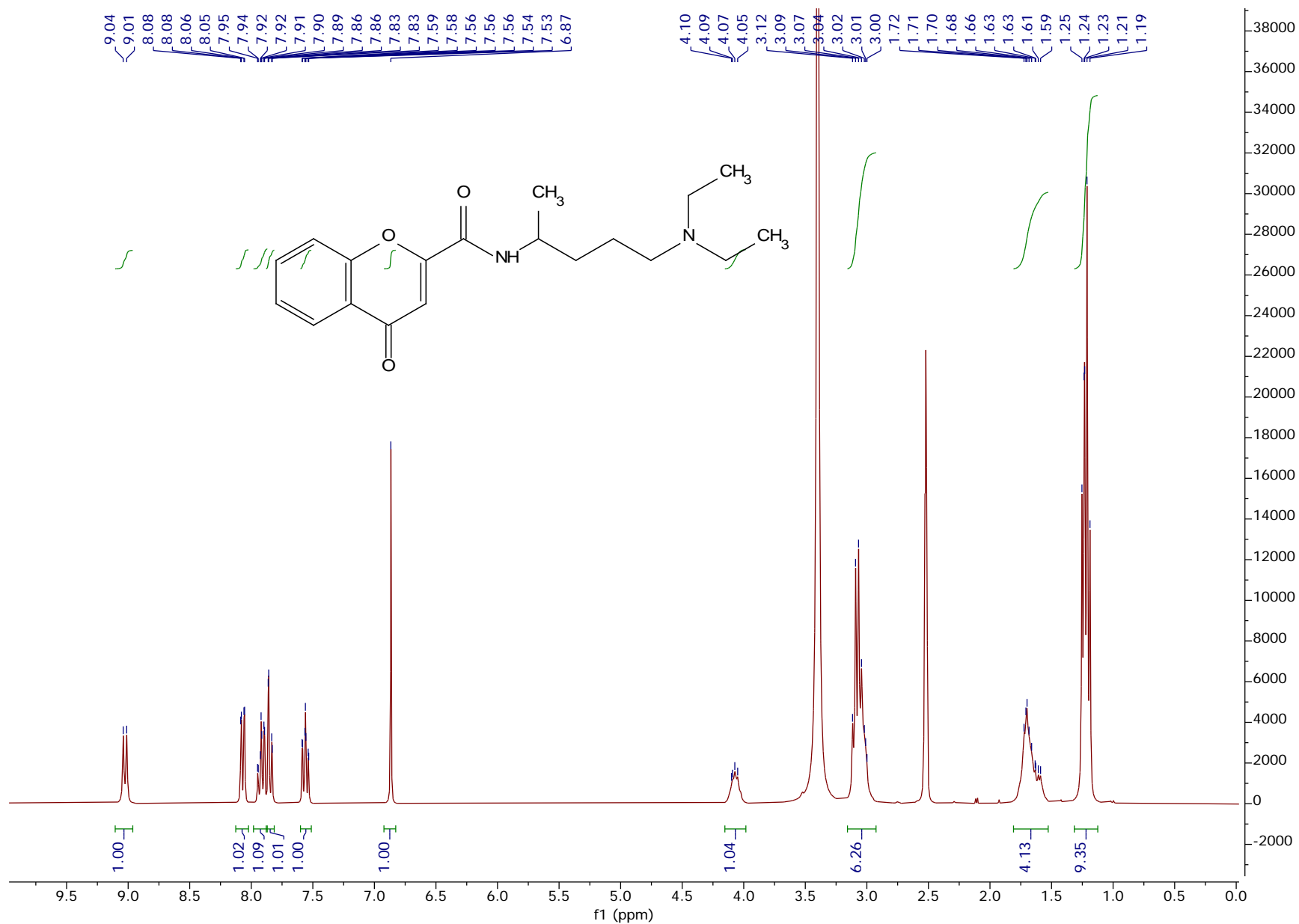


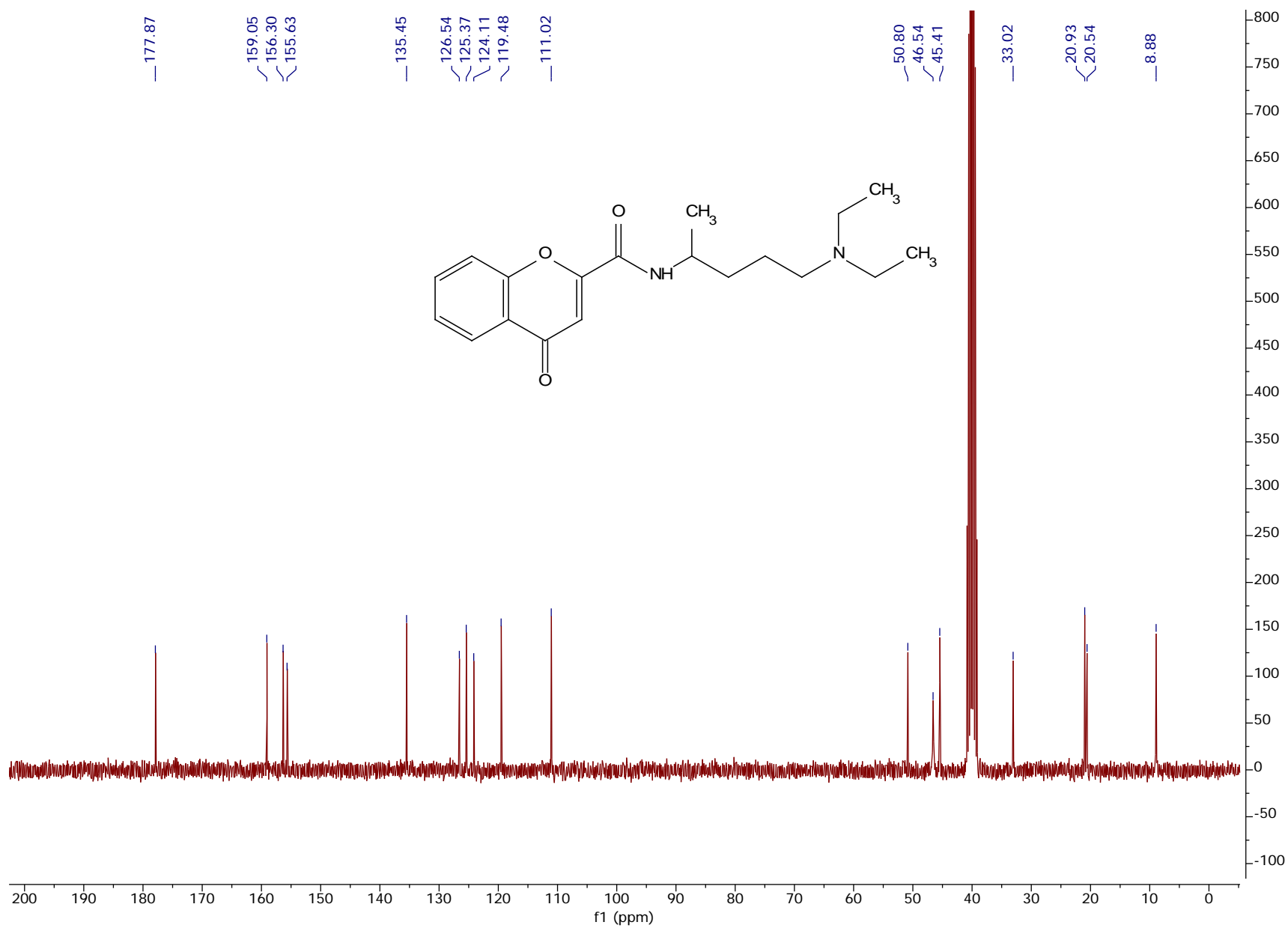
tert-Butyl 4-((4-oxo-4H-chromene-2-carboxamido)methyl)piperidine-1-carboxylate (3'e)



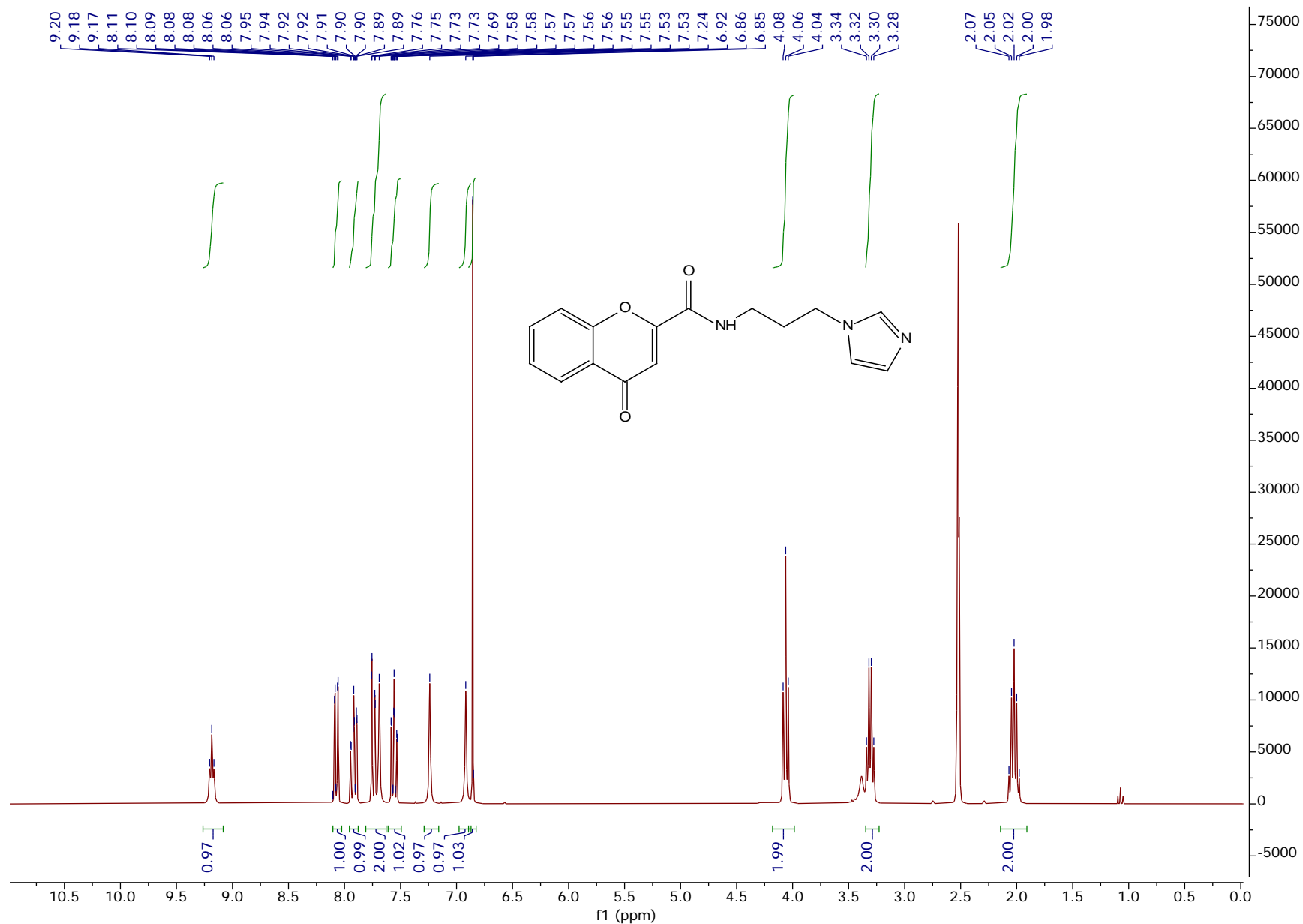


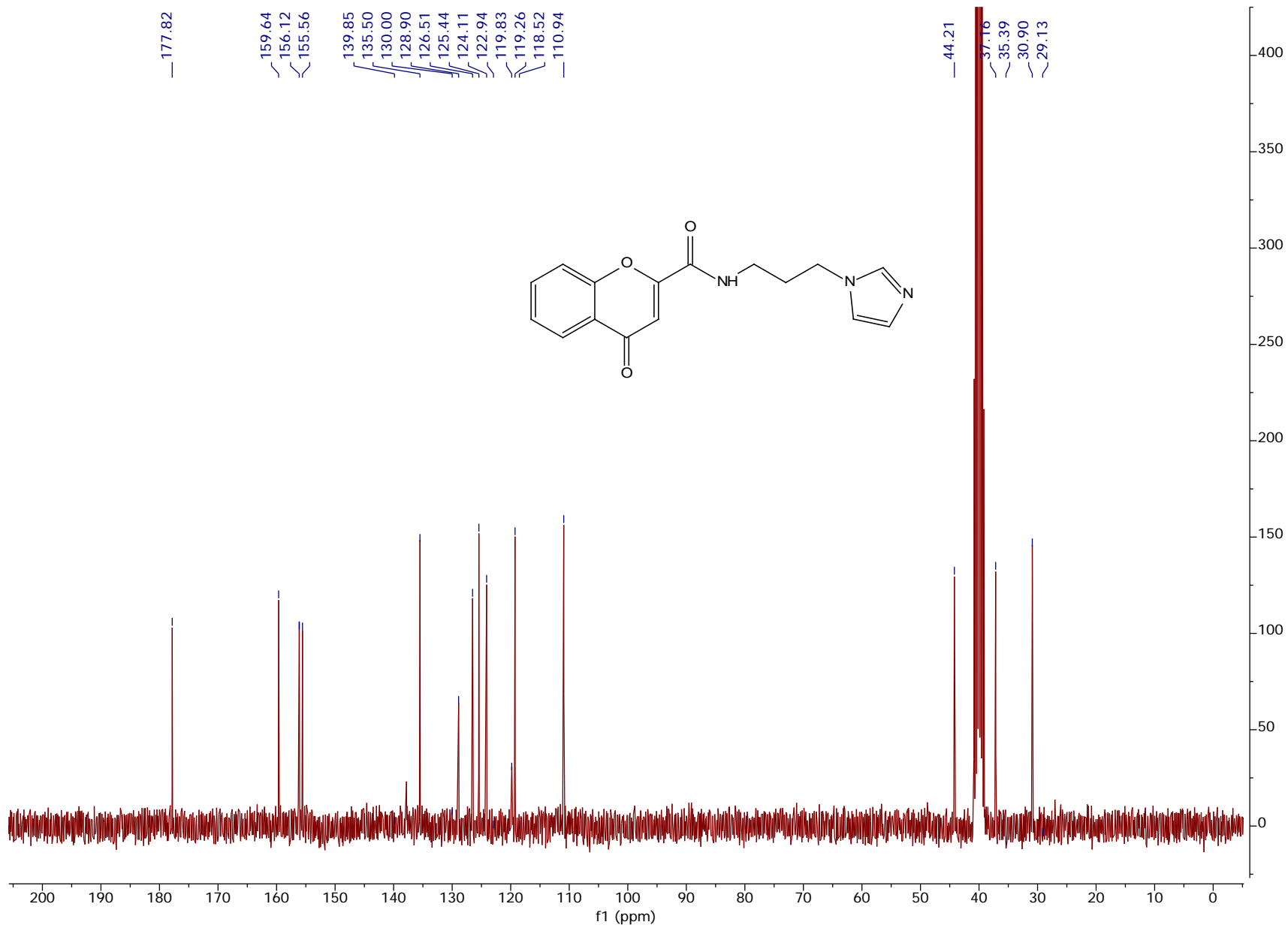
***N*-(5-(Diethylamino)pentan-2-yl)-4-oxo-4*H*-chromene-2-carboxamide (3'f)**



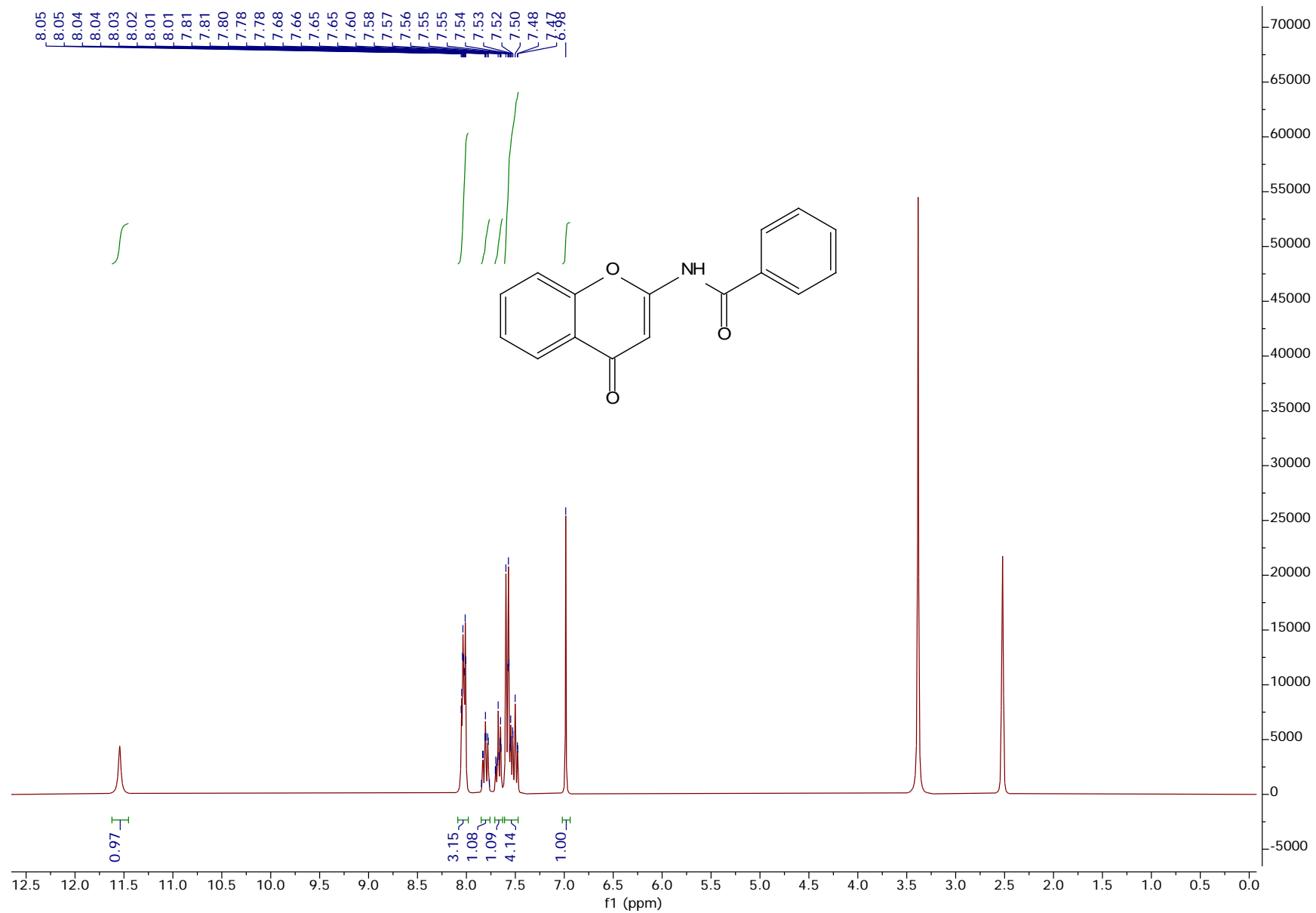


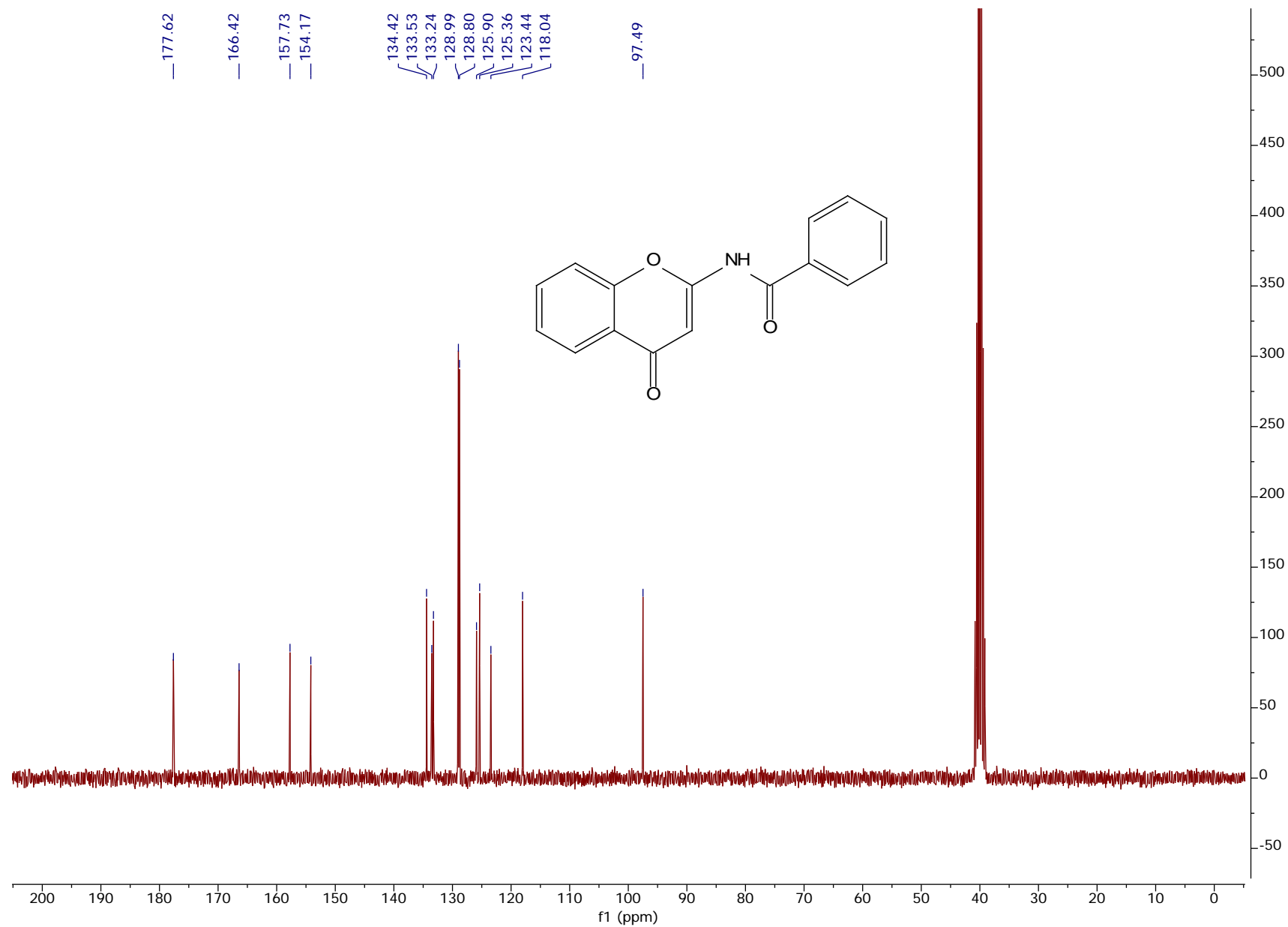
***N*-(3-(1*H*-Imidazol-1-yl)propyl)-4-oxo-4*H*-chromene-2-carboxamide (3'g)**



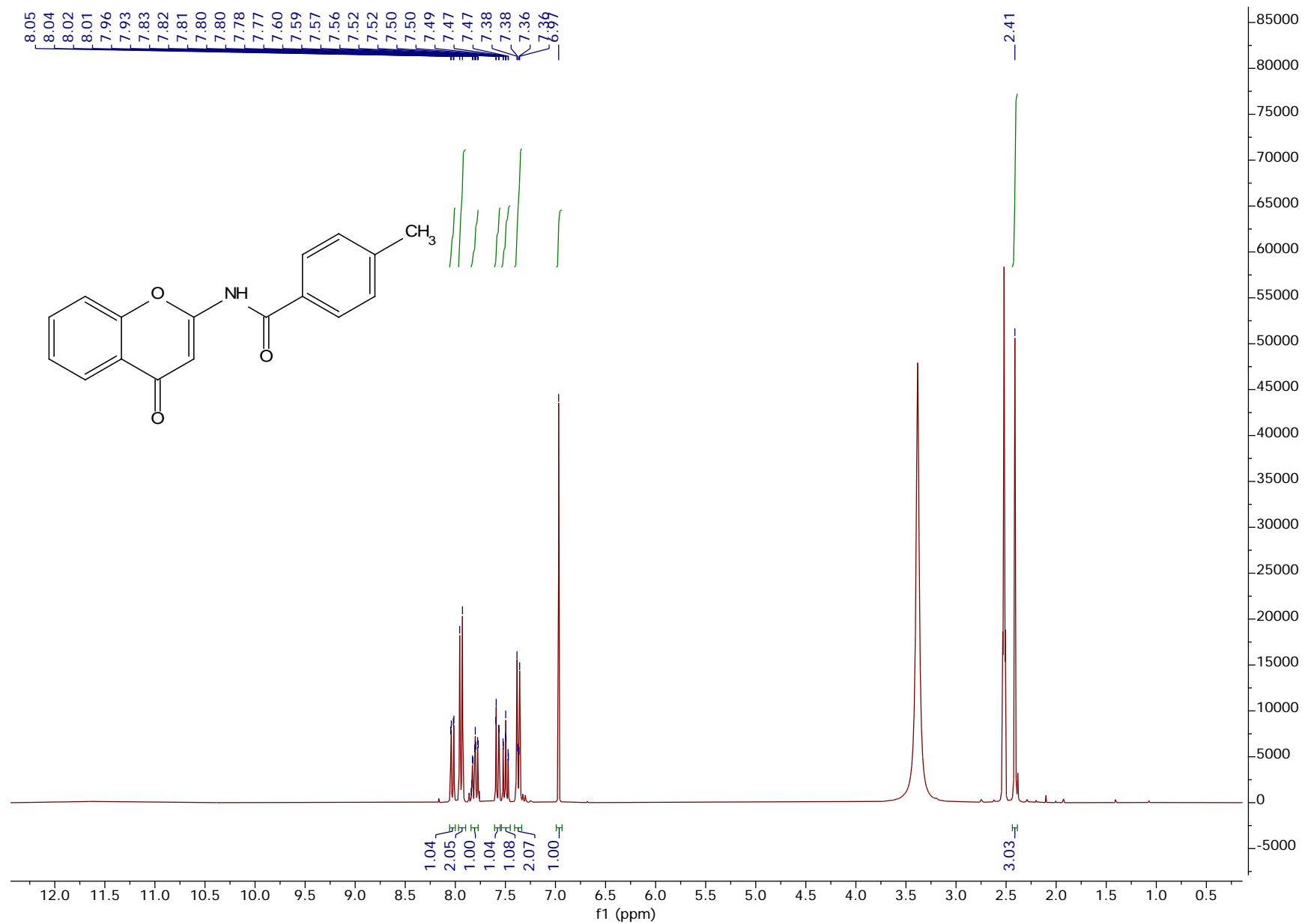


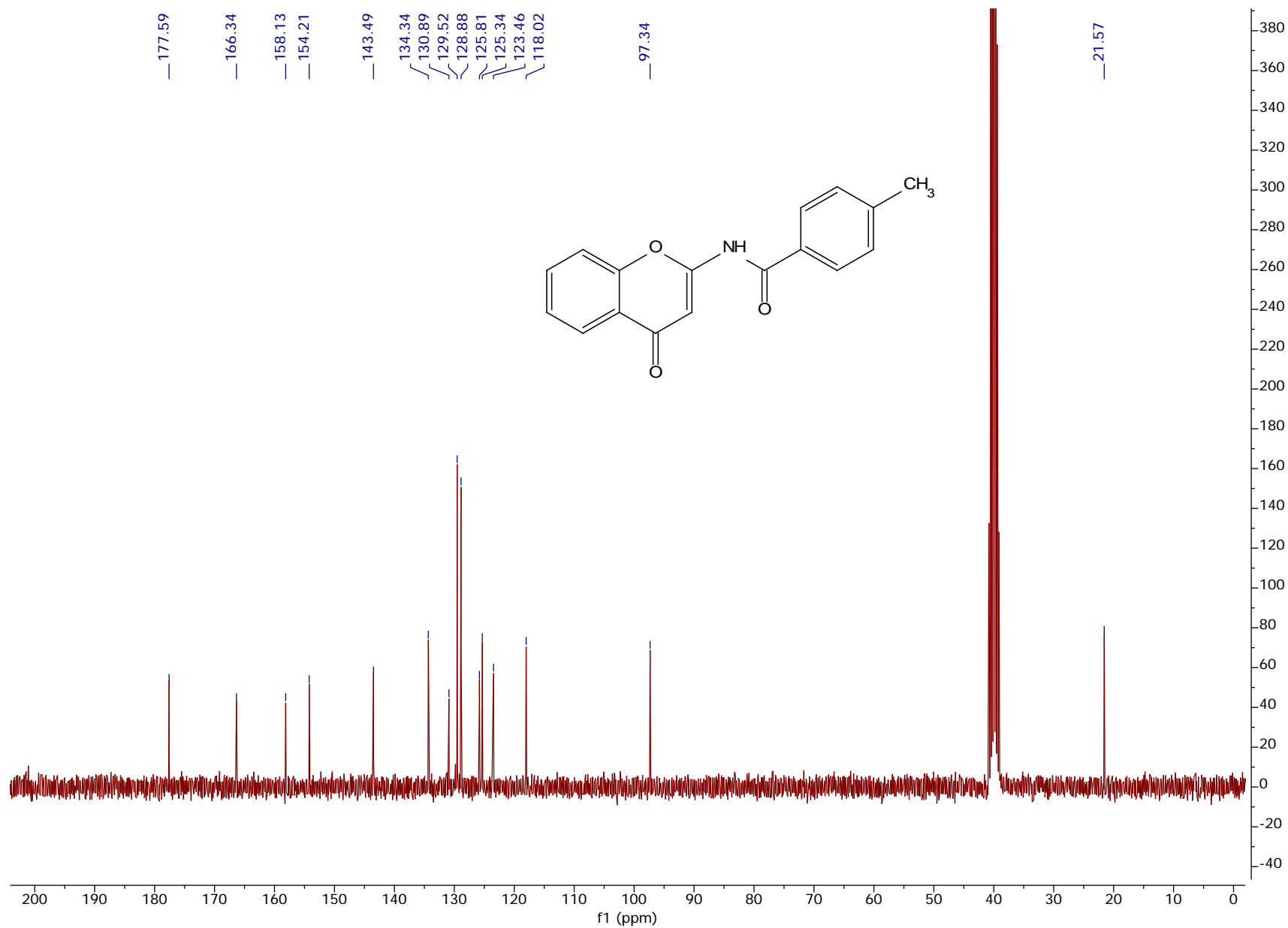
***N*-(4-Oxo-4*H*-chromen-2-yl)benzamide (6a)**



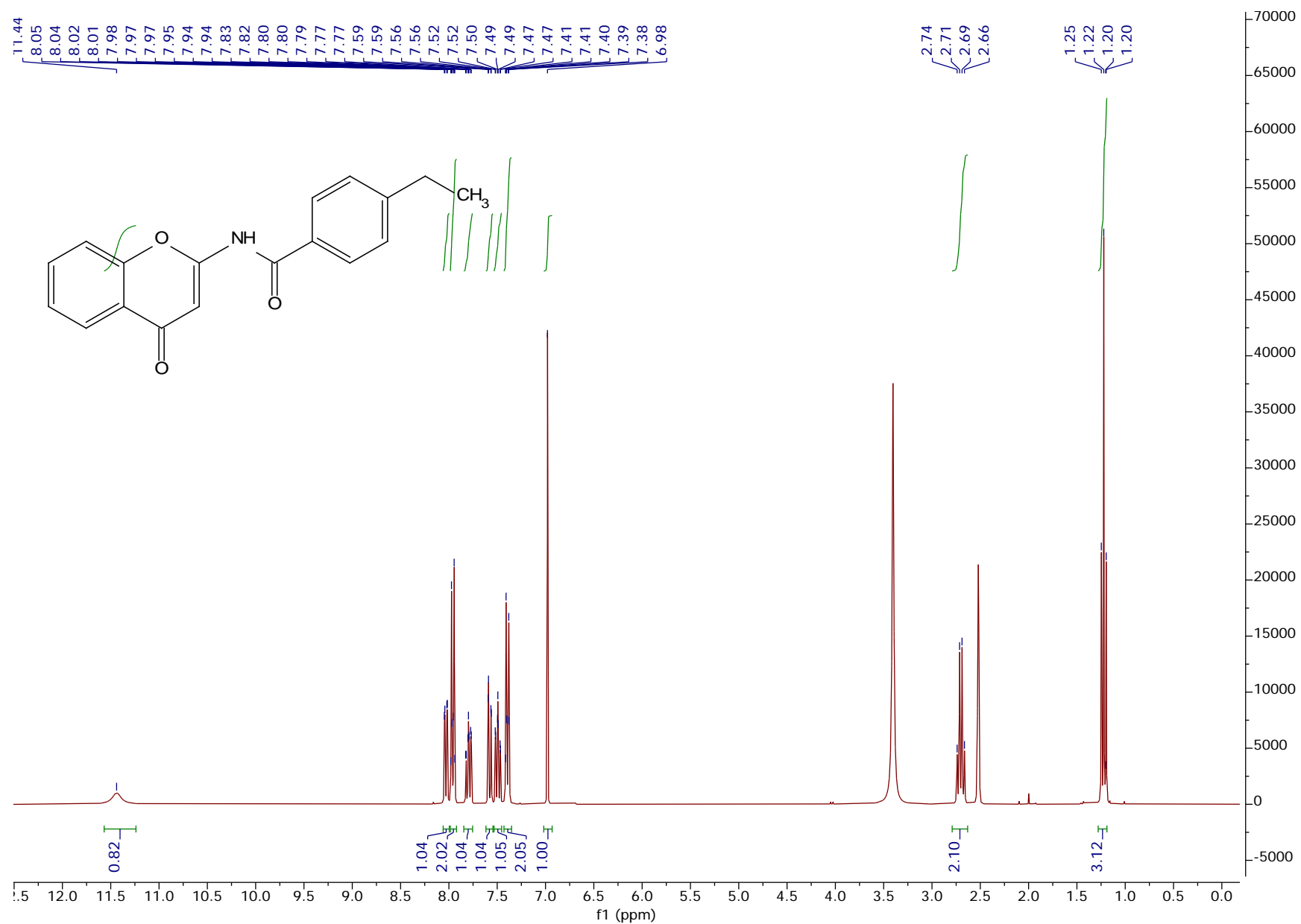


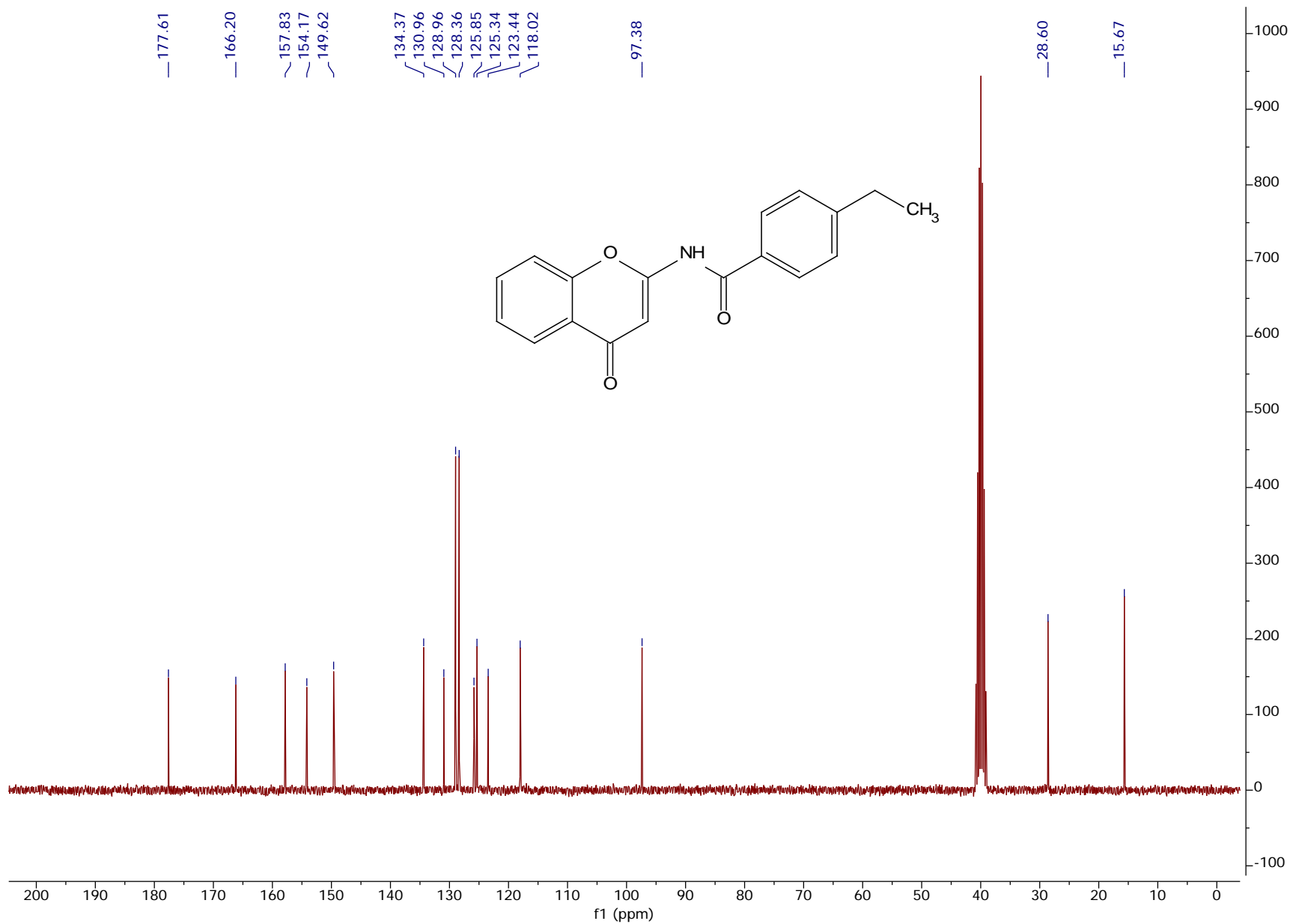
4-Methyl-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6b)



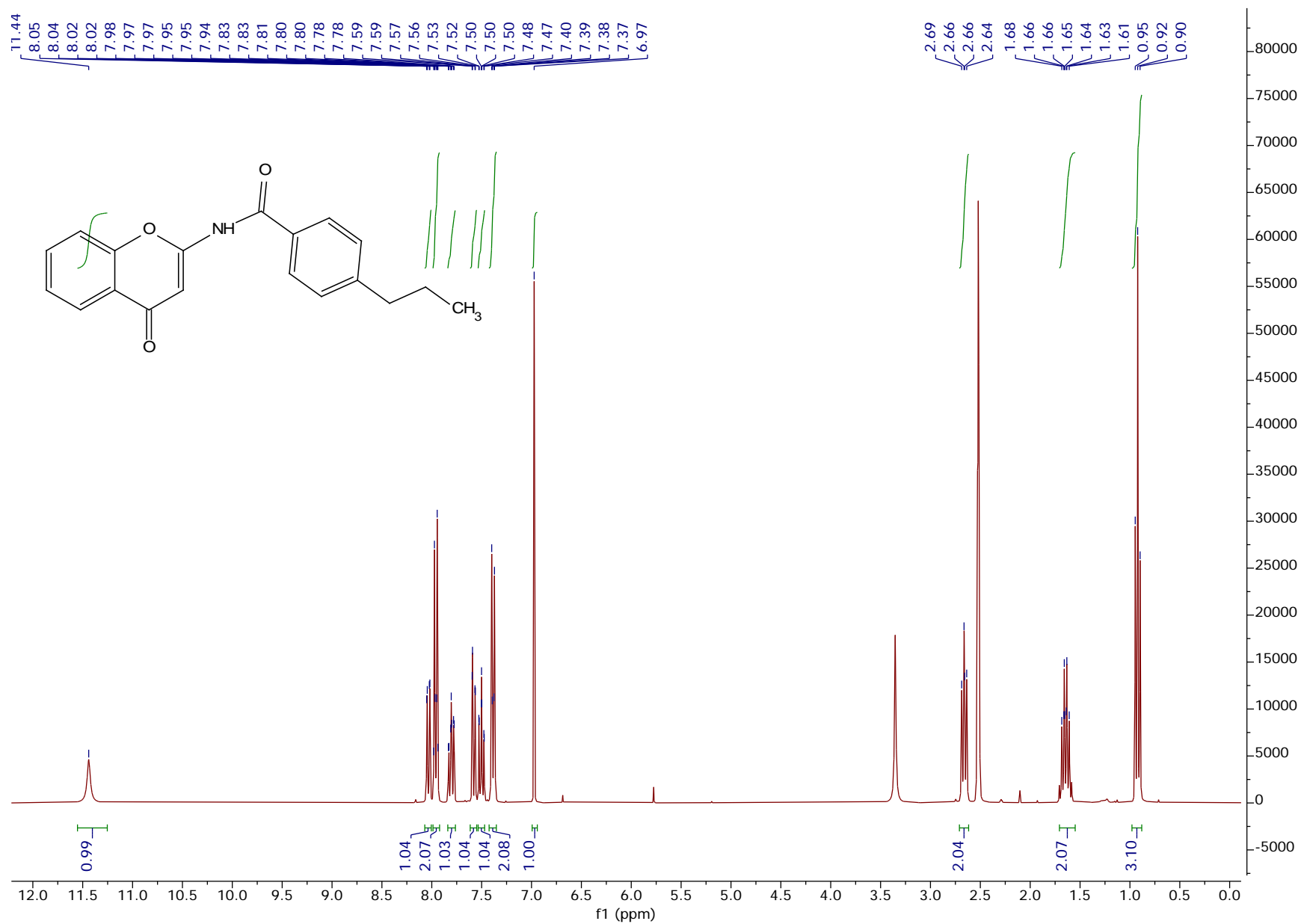


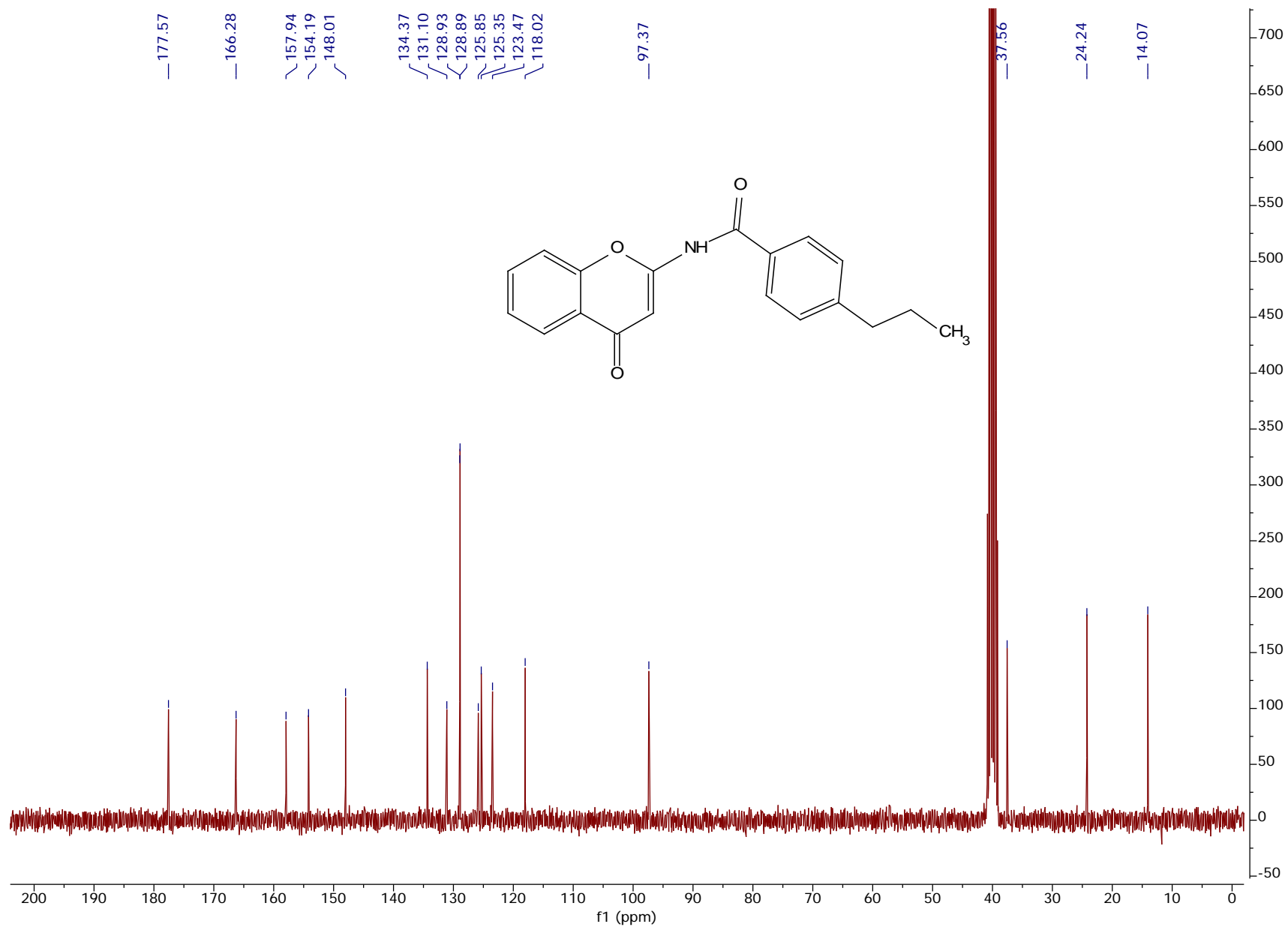
4-Ethyl-N-(4-oxo-4H-chromen-2-yl)benzamide (6c)



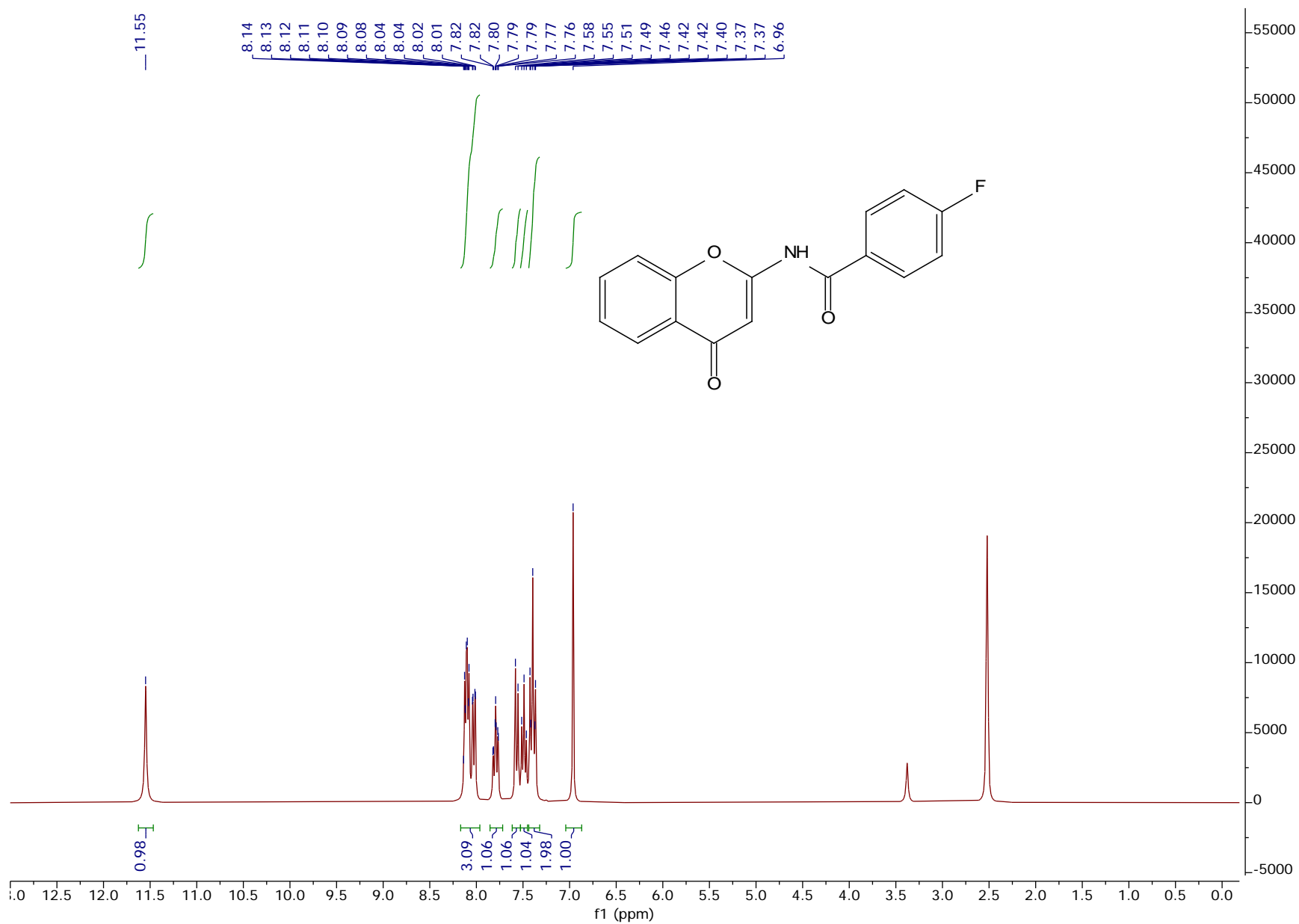


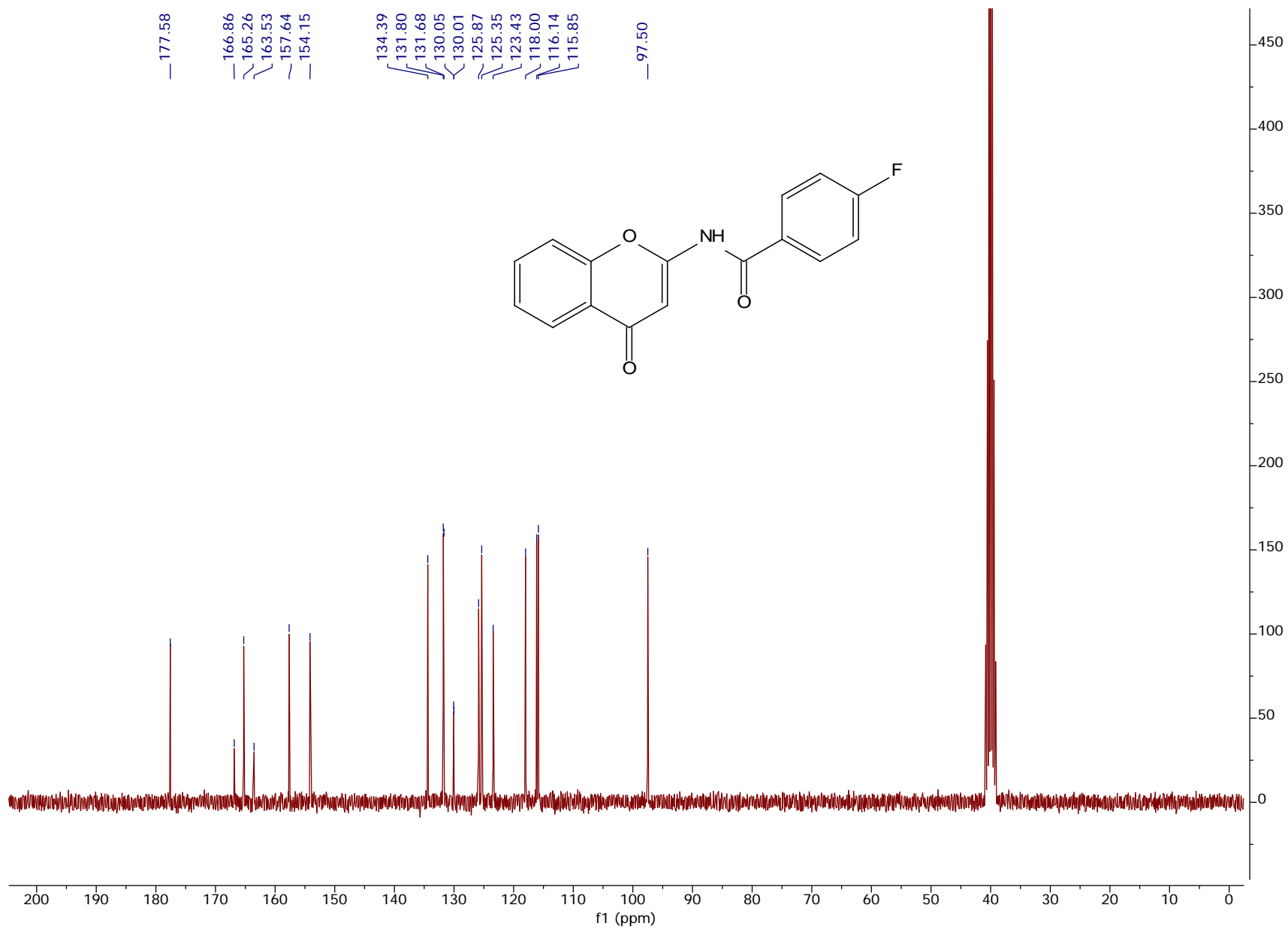
***N*-(4-Oxo-4*H*-chromen-2-yl)-4-propylbenzamide (6d)**



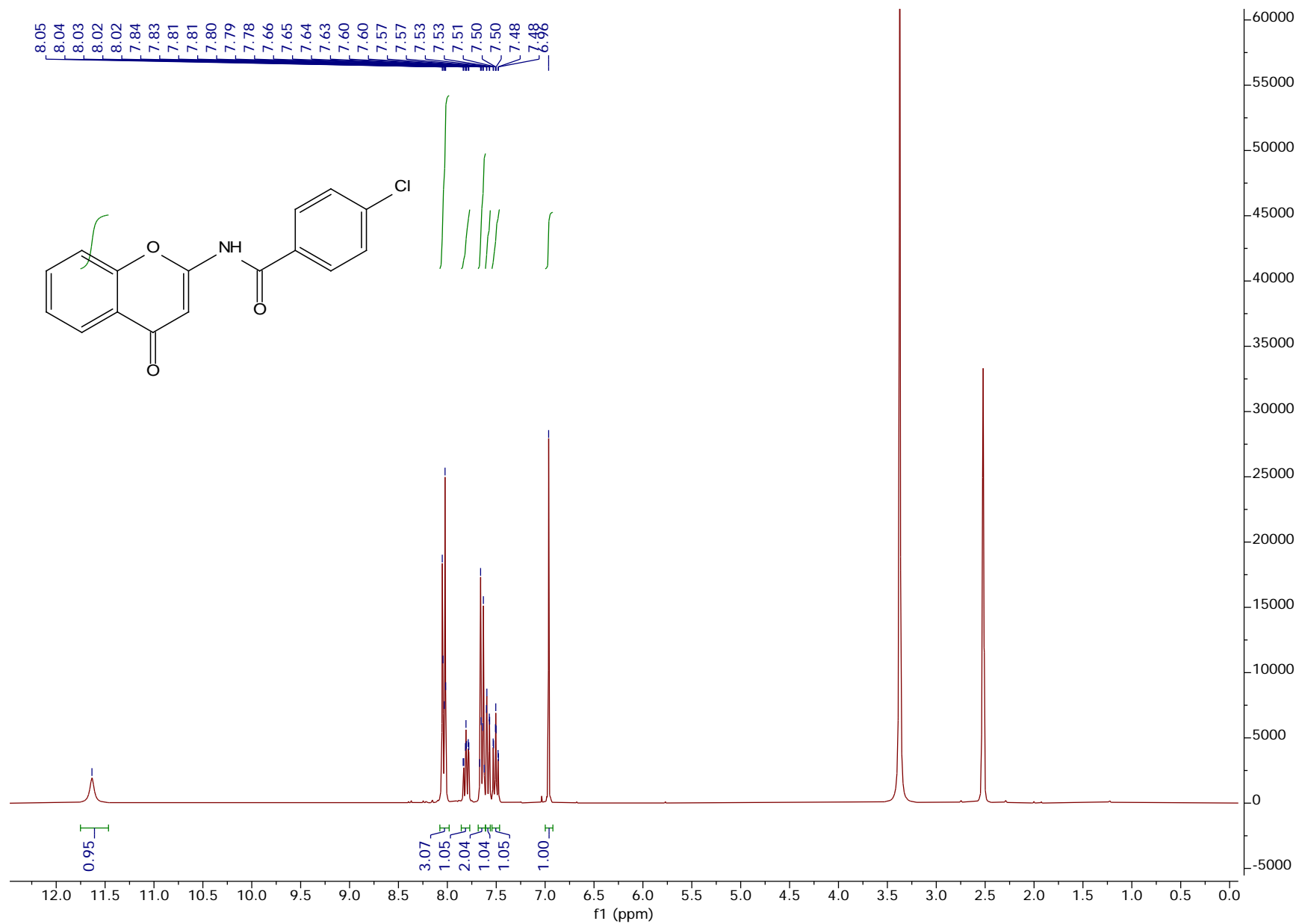


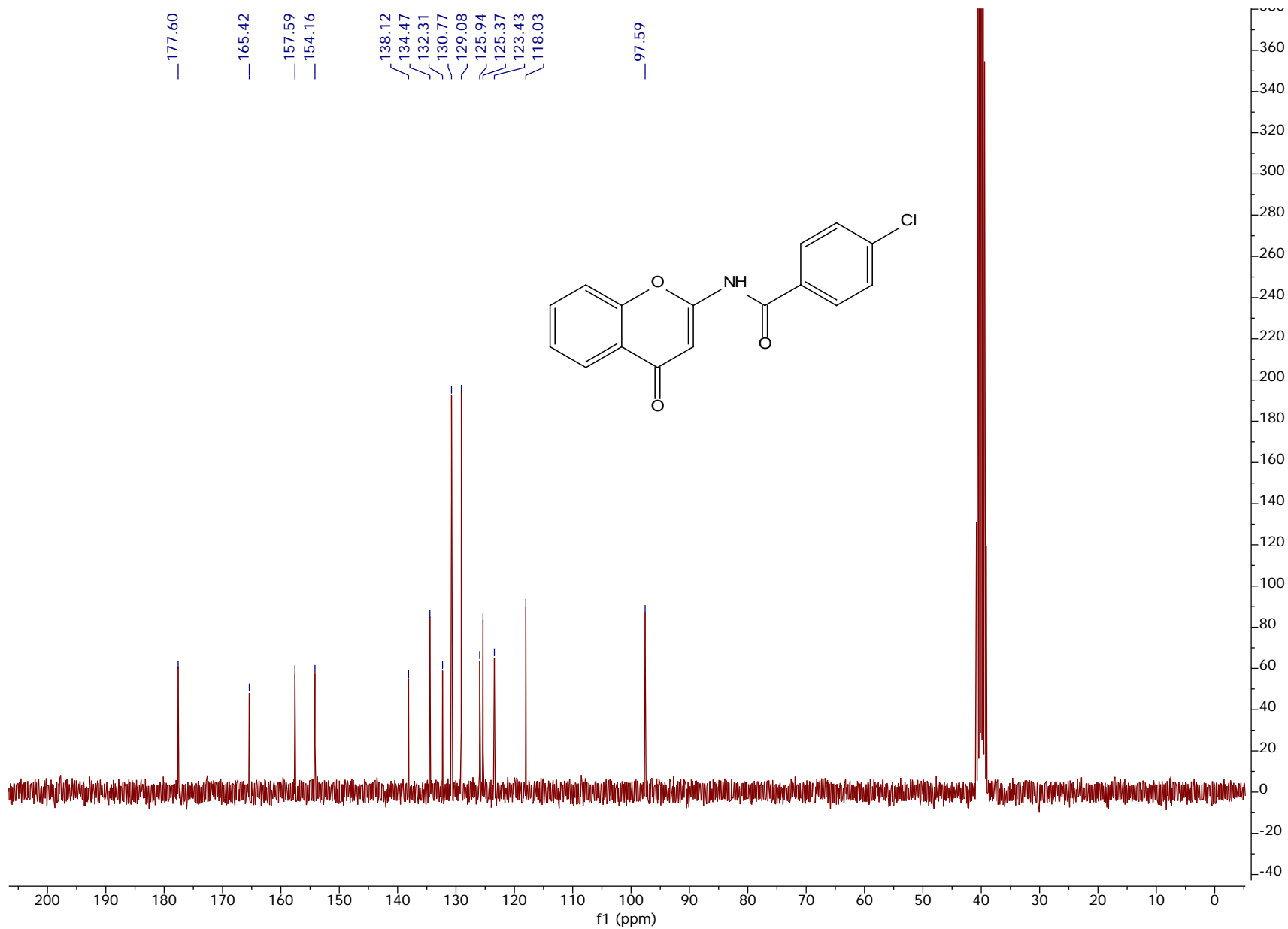
4-Fluoro-N-(4-oxo-4H-chromen-2-yl)benzamide (6e)



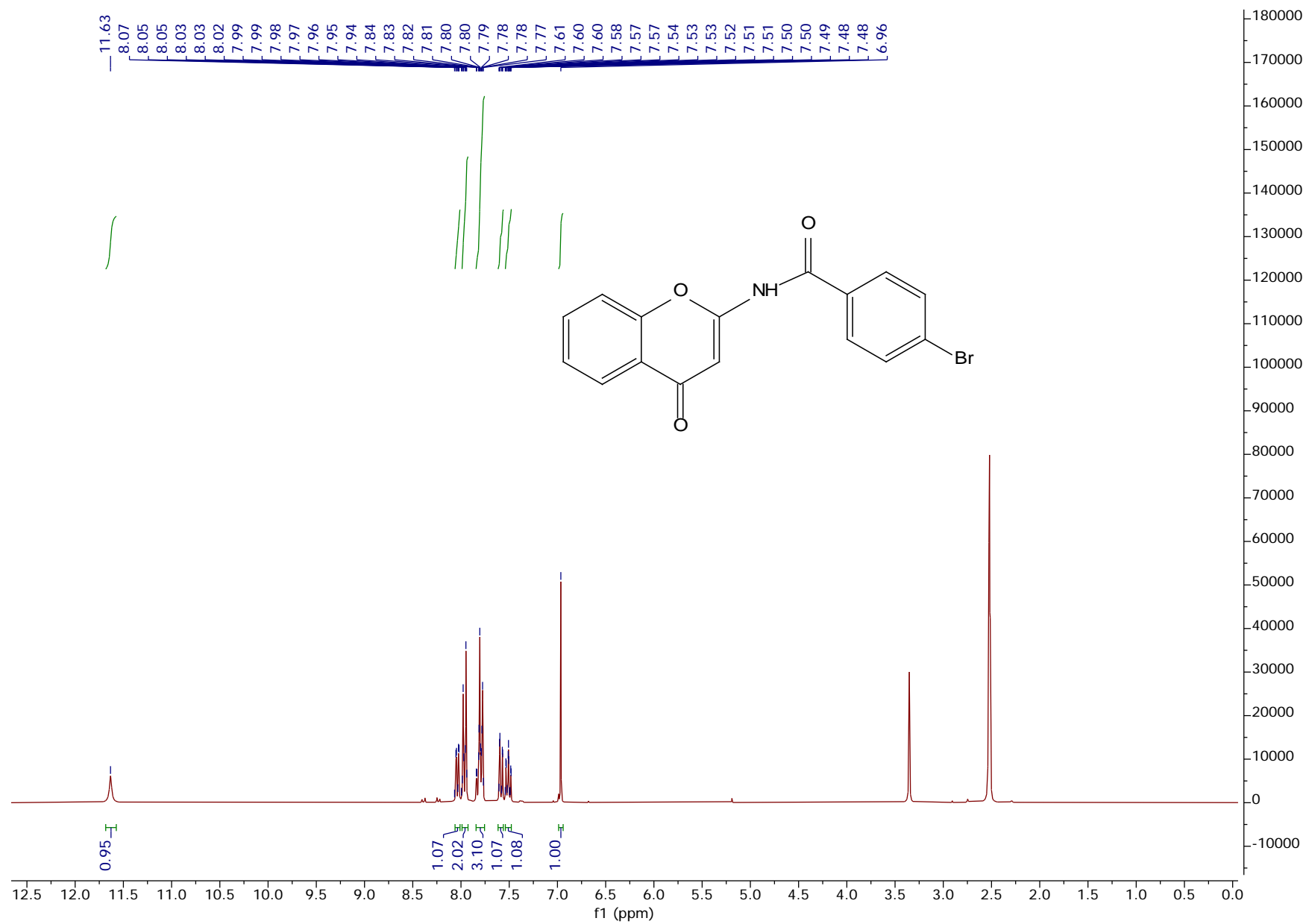


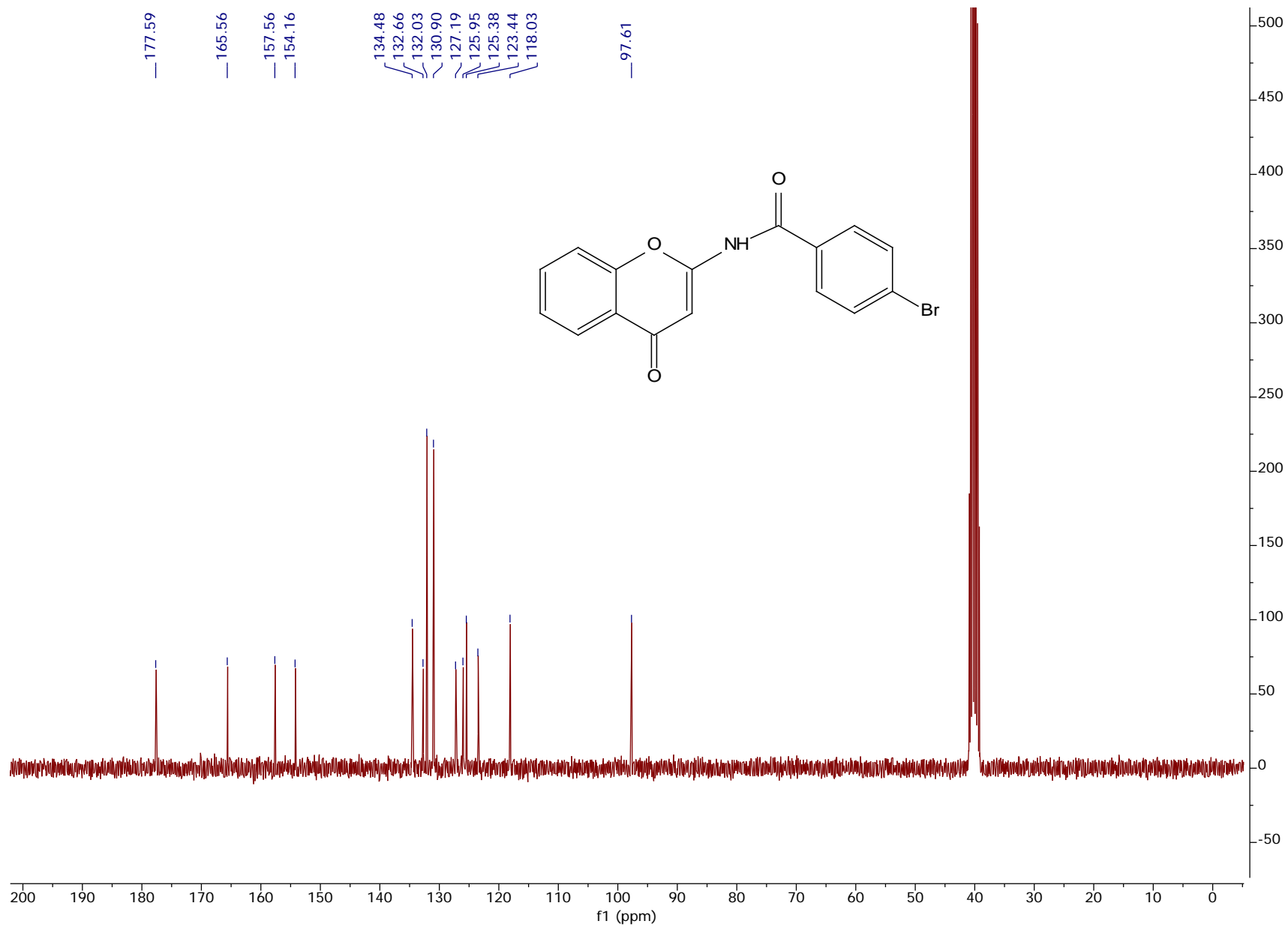
4-Chloro-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6f)



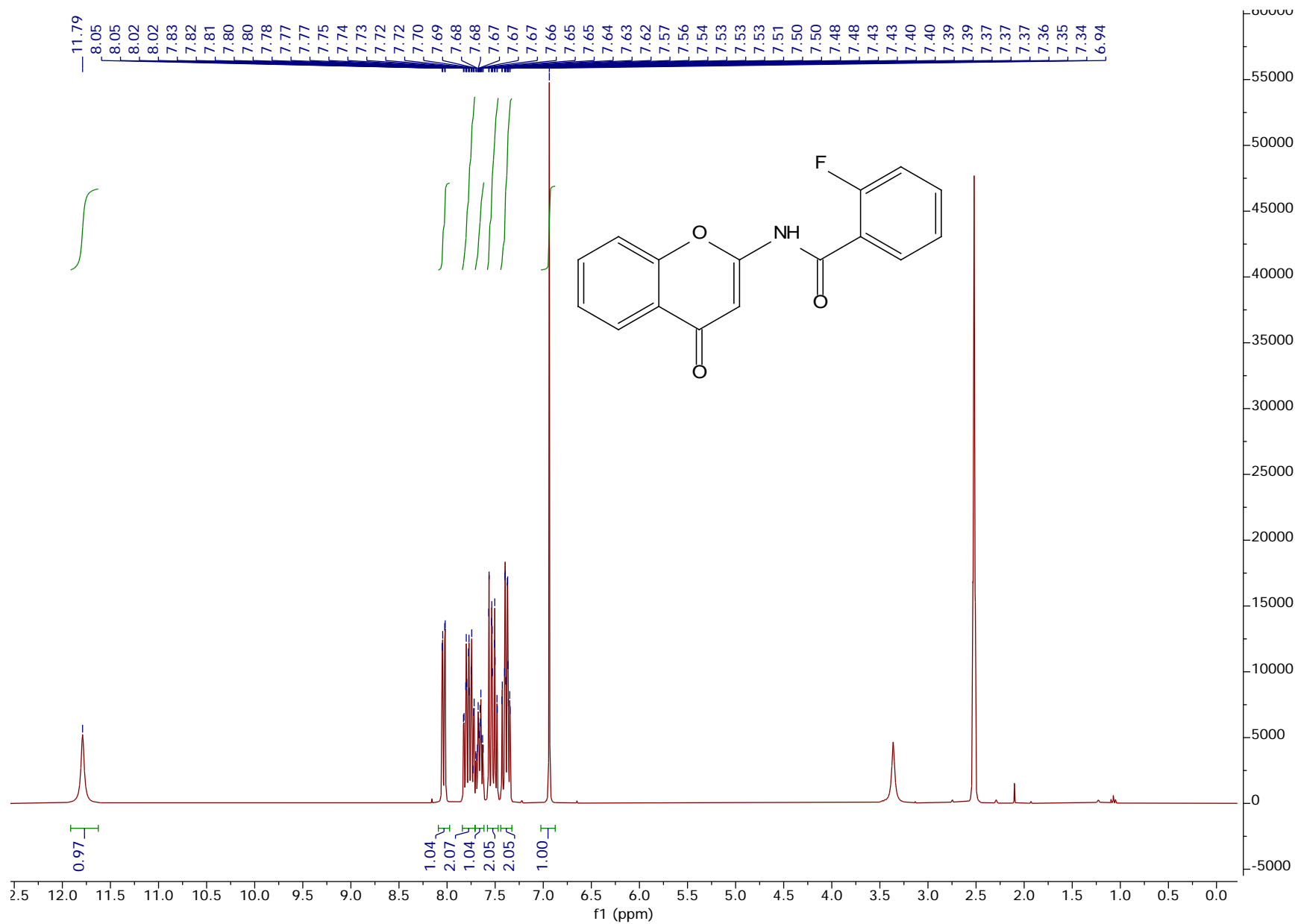


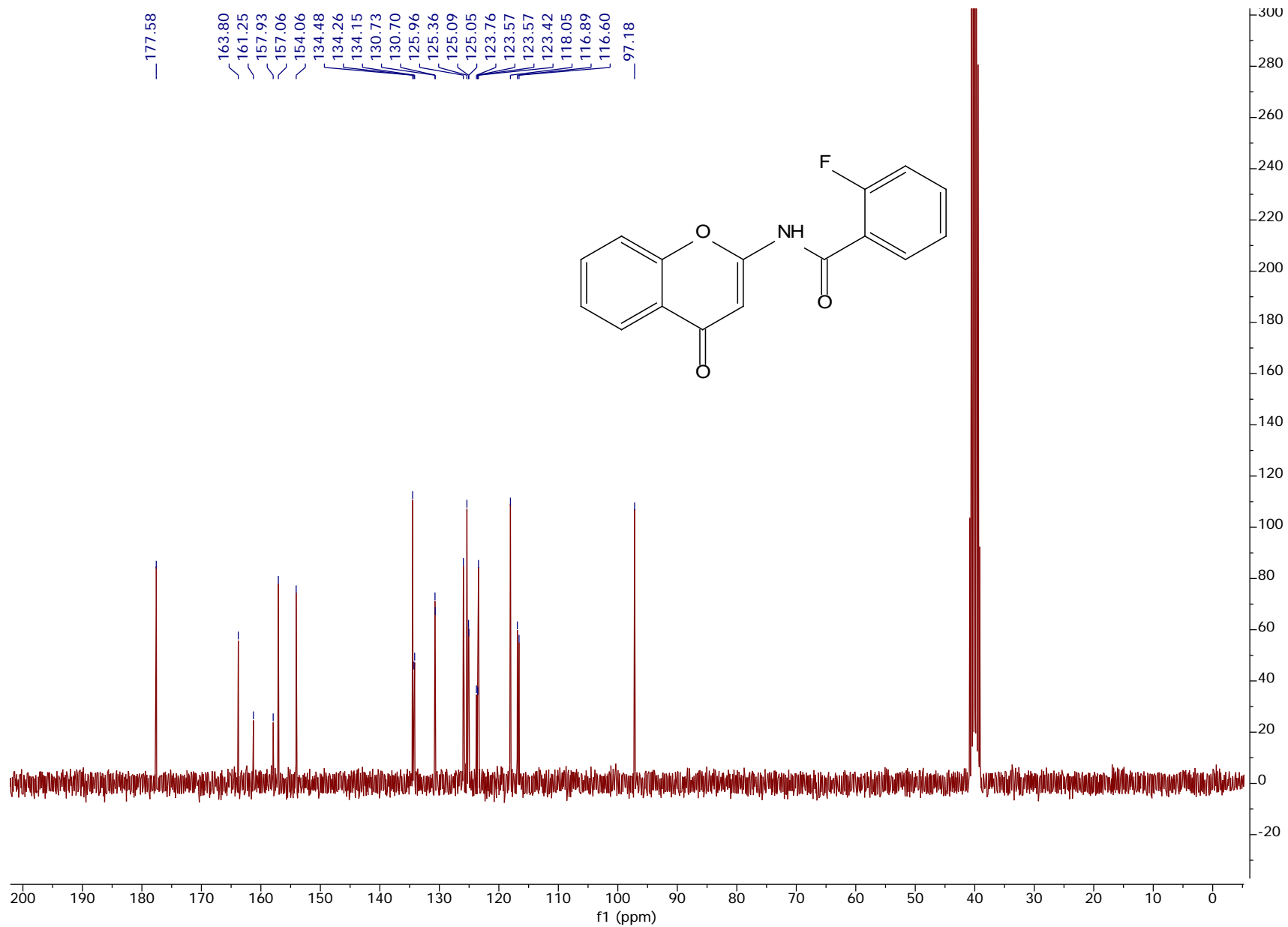
4-Bromo-N-(4-oxo-4H-chromen-2-yl)benzamide (6g)



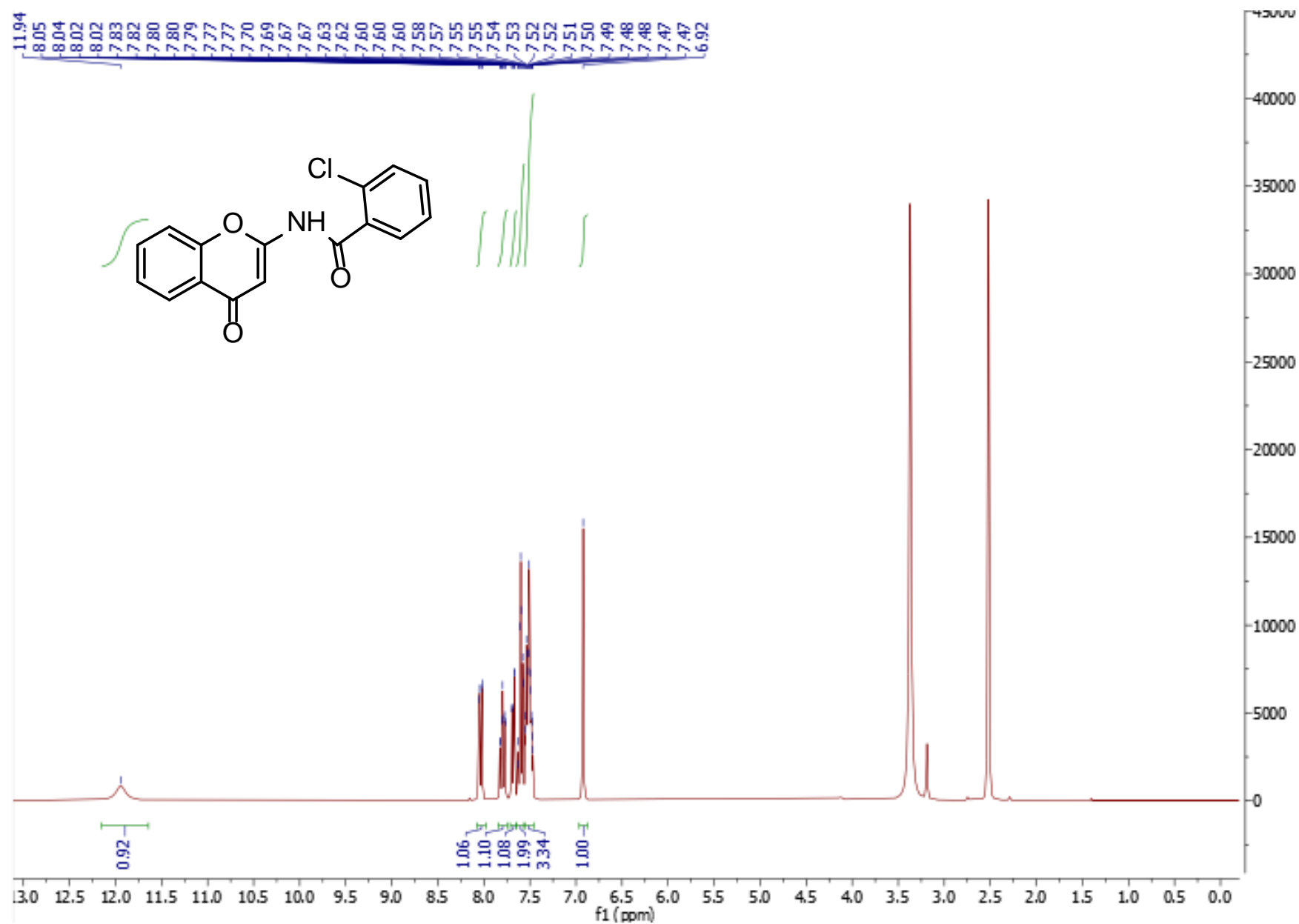


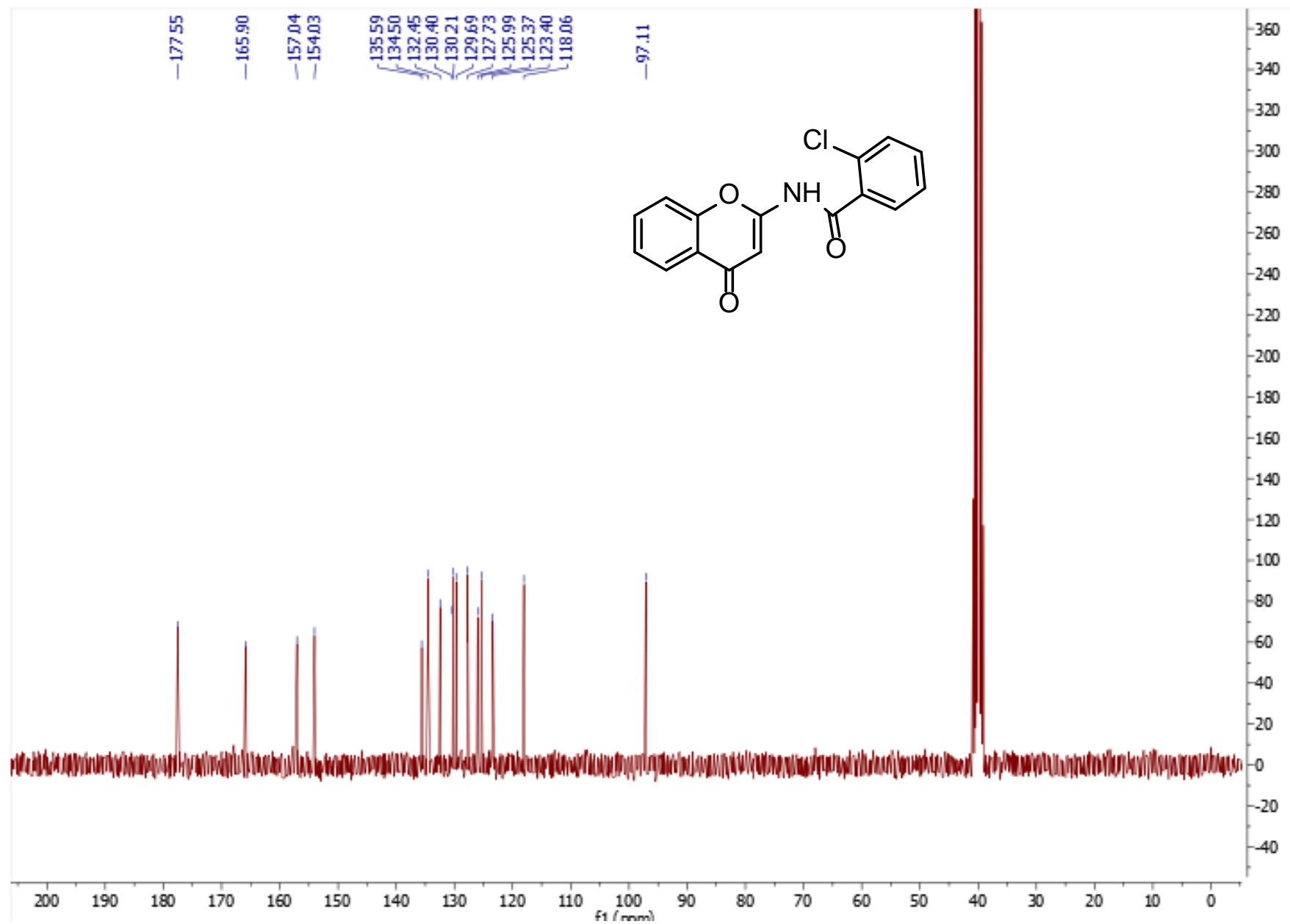
2-Fluoro-N-(4-oxo-4H-chromen-2-yl)benzamide (6h)



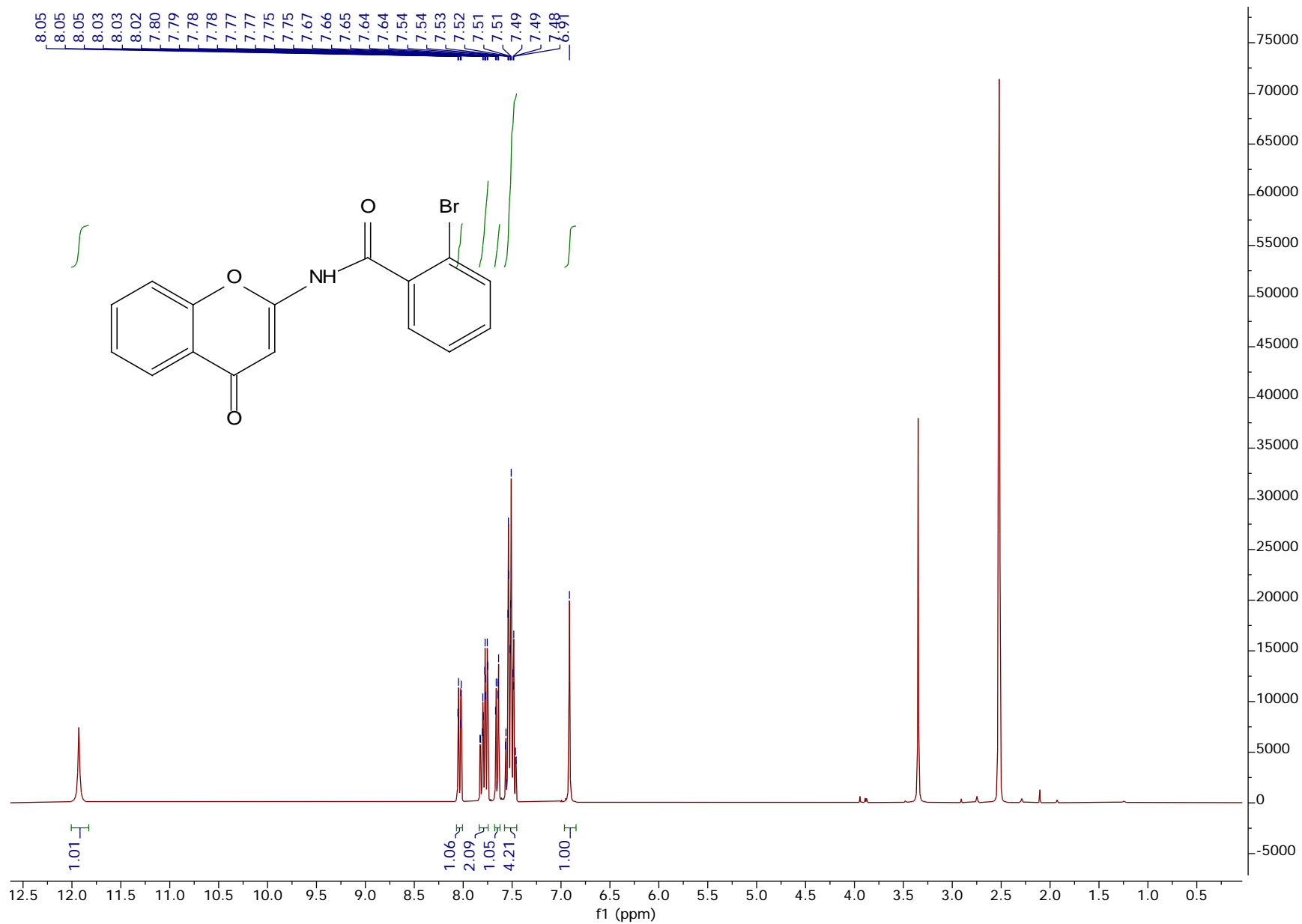


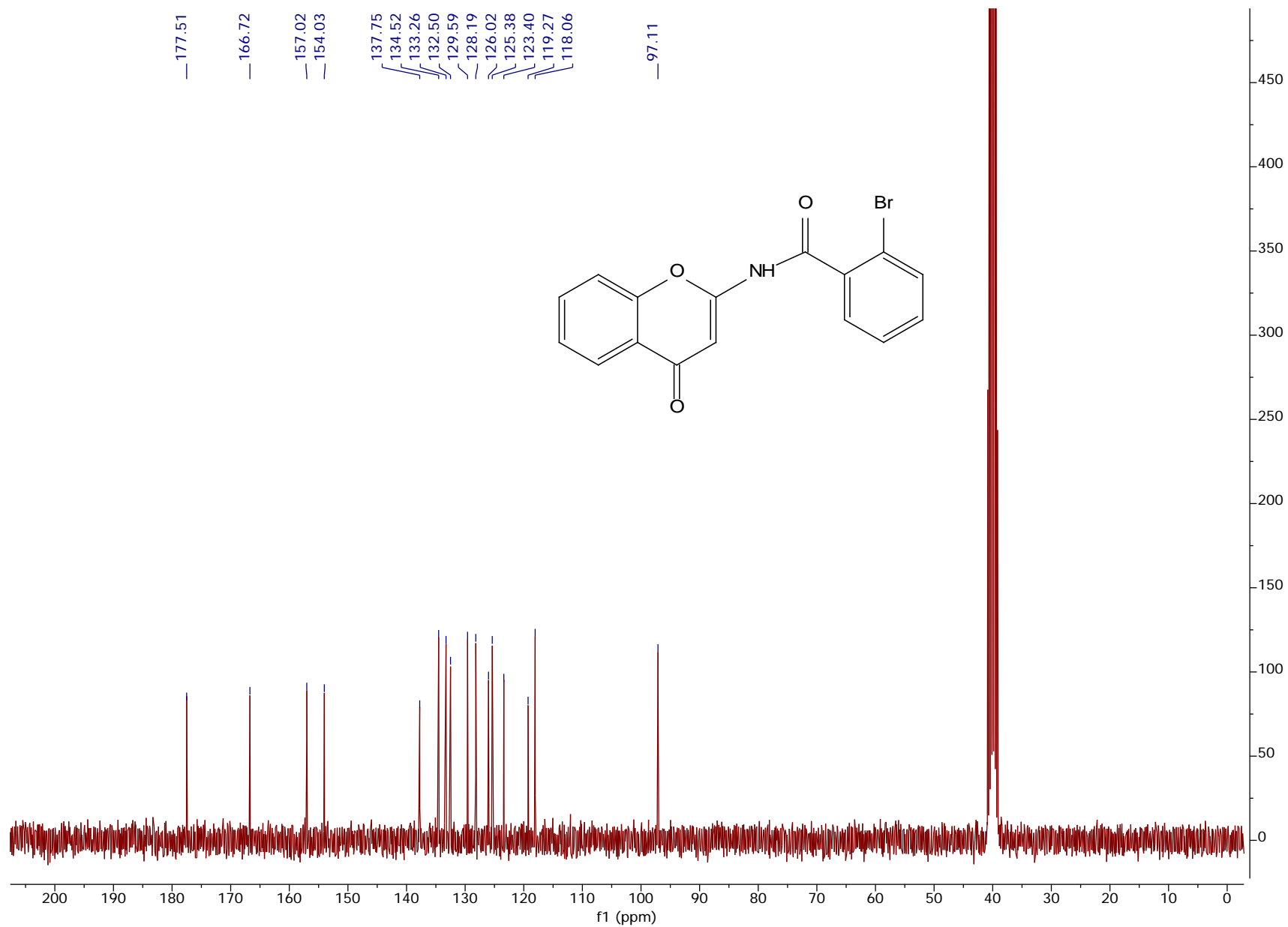
2-Chloro-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6i)



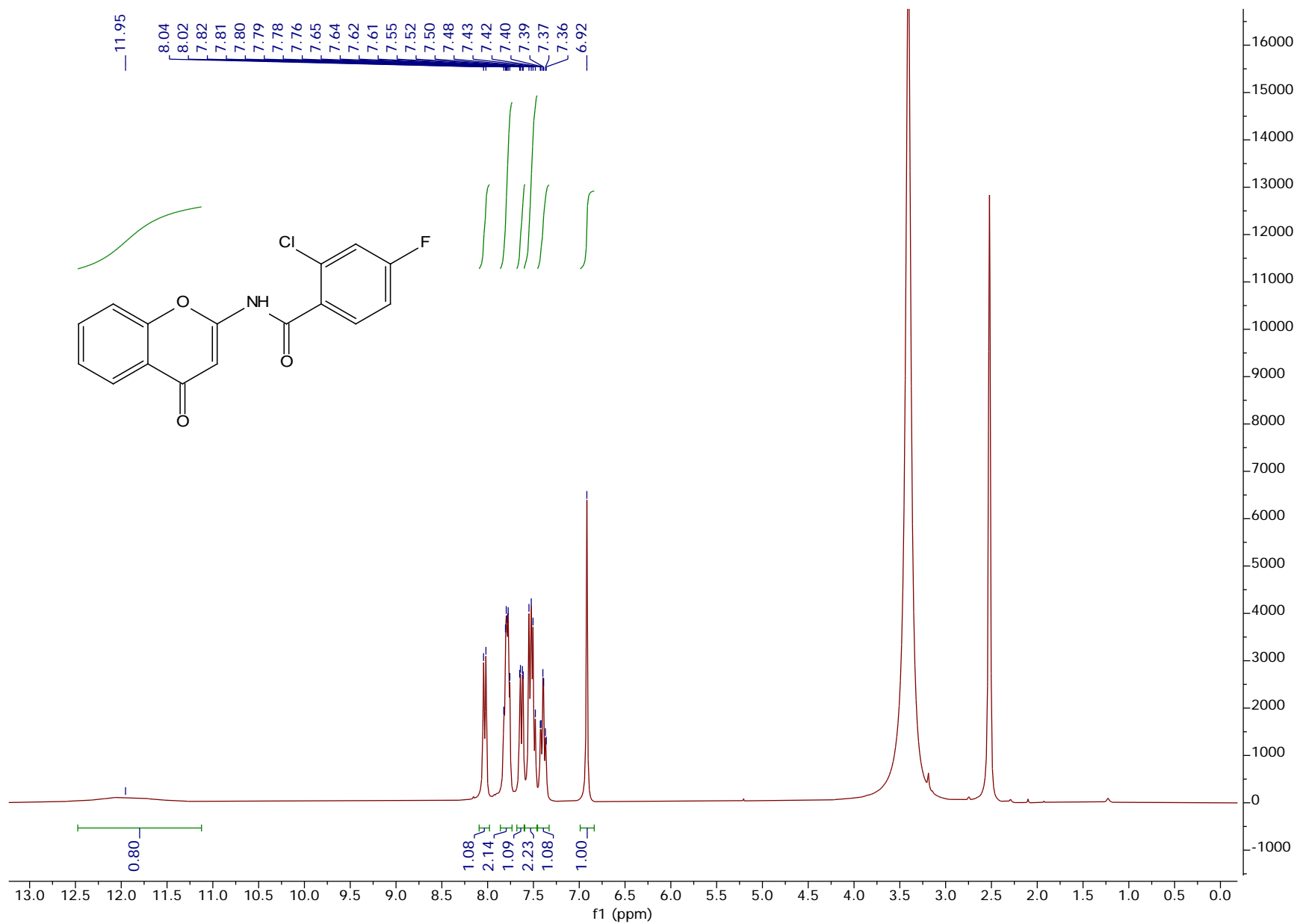


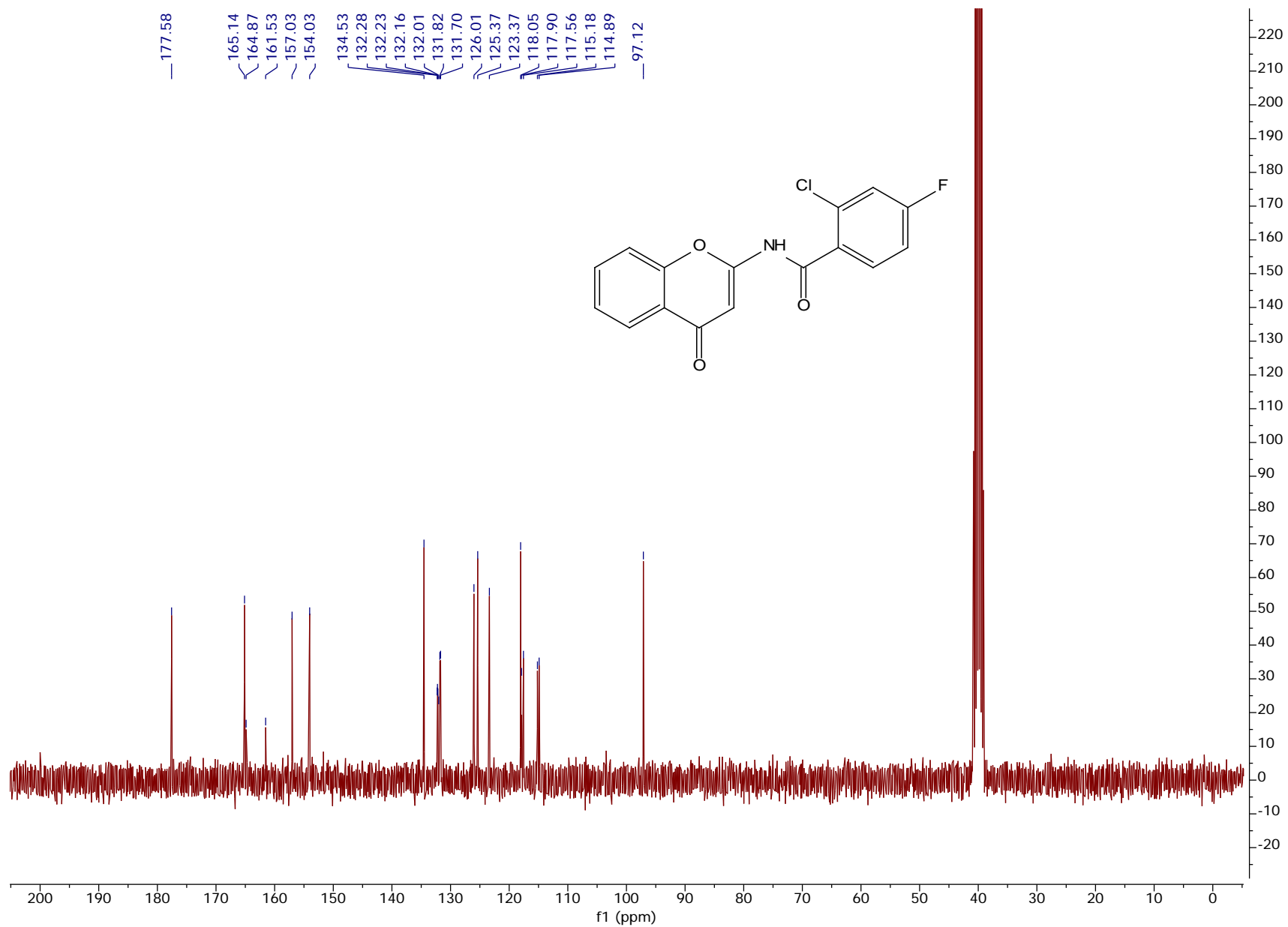
2-Bromo-N-(4-oxo-4H-chromen-2-yl)benzamide (6j)



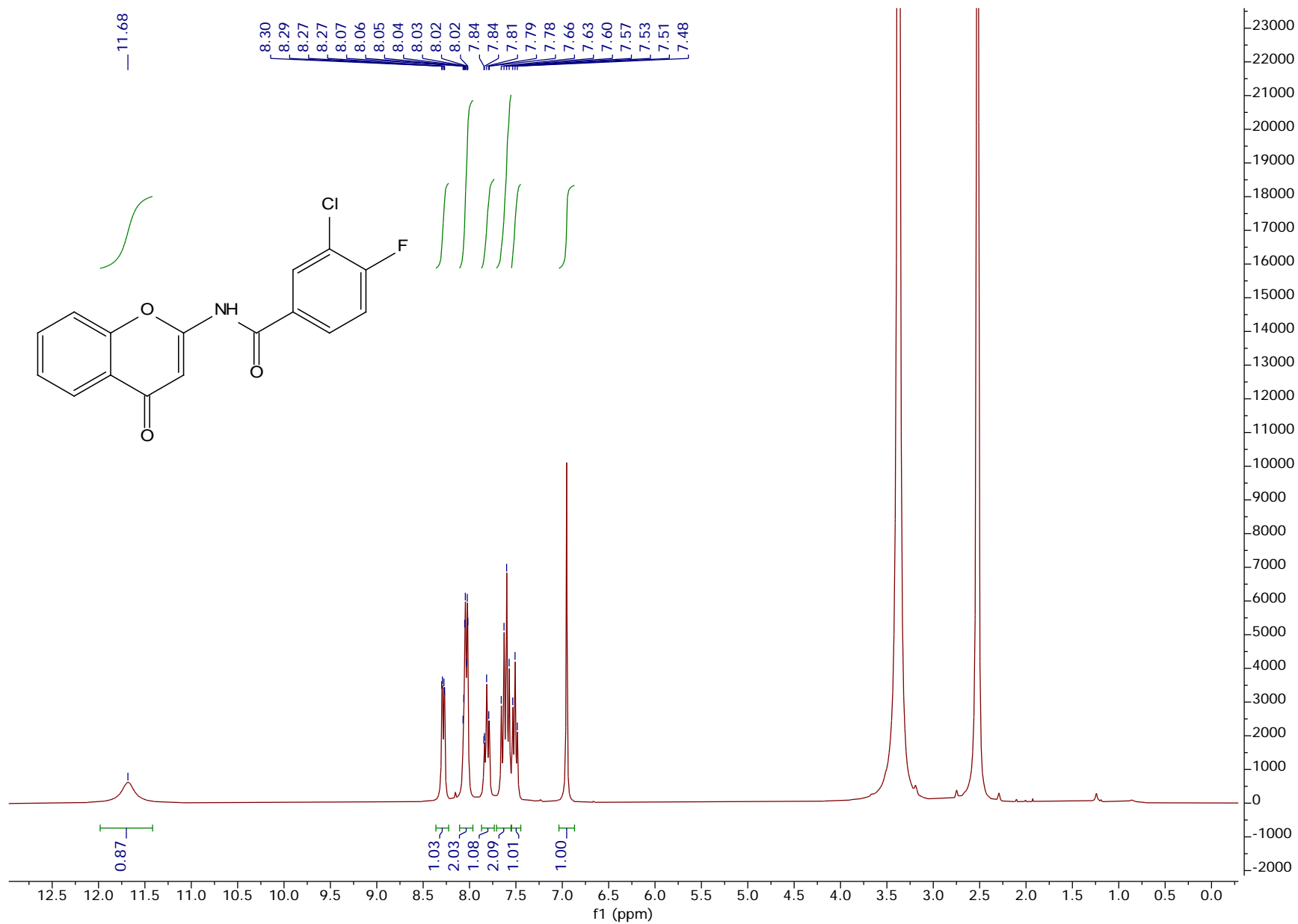


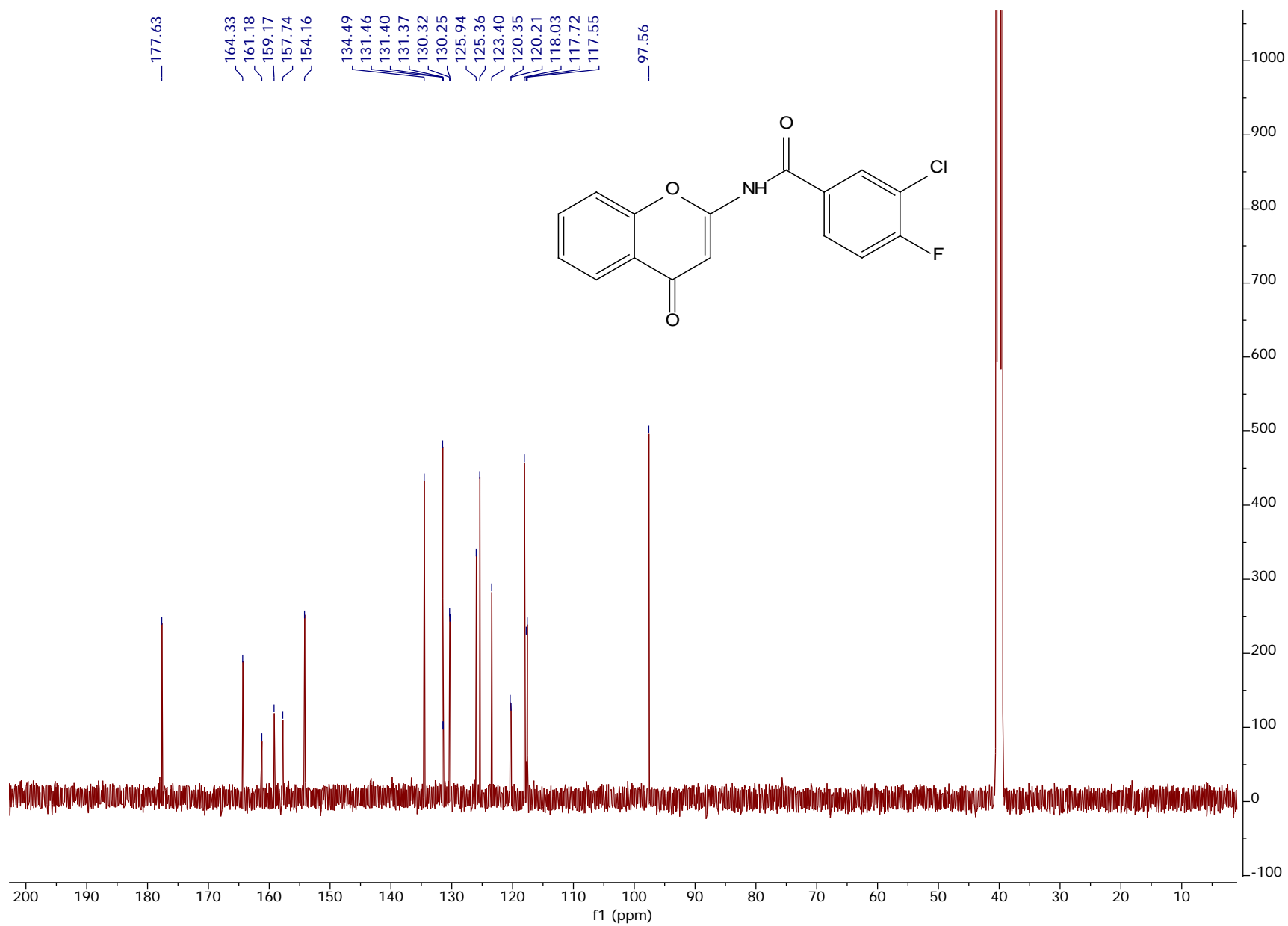
2-Chloro-4-fluoro-N-(4-oxo-4H-chromen-2-yl)benzamide (6k)



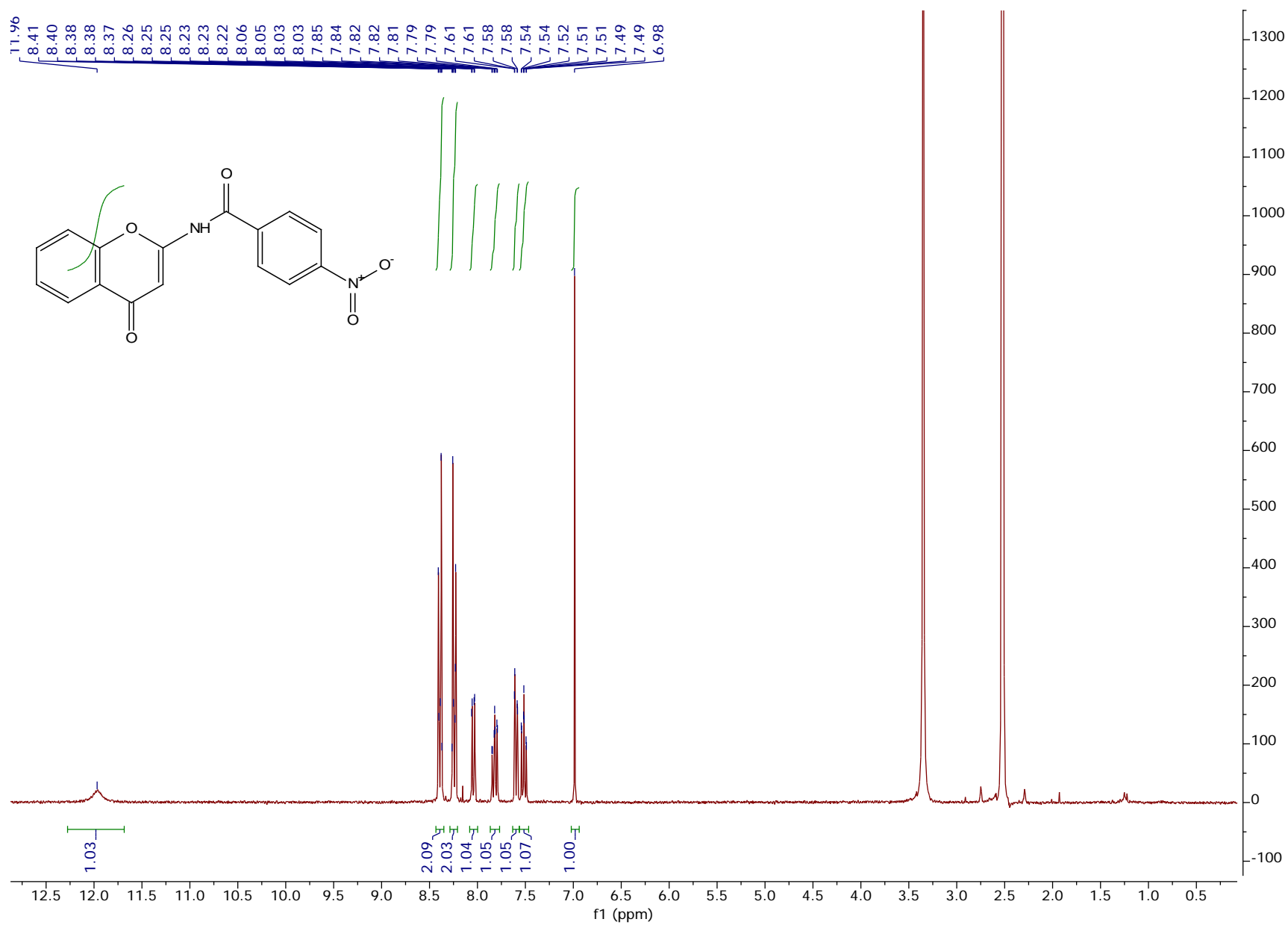


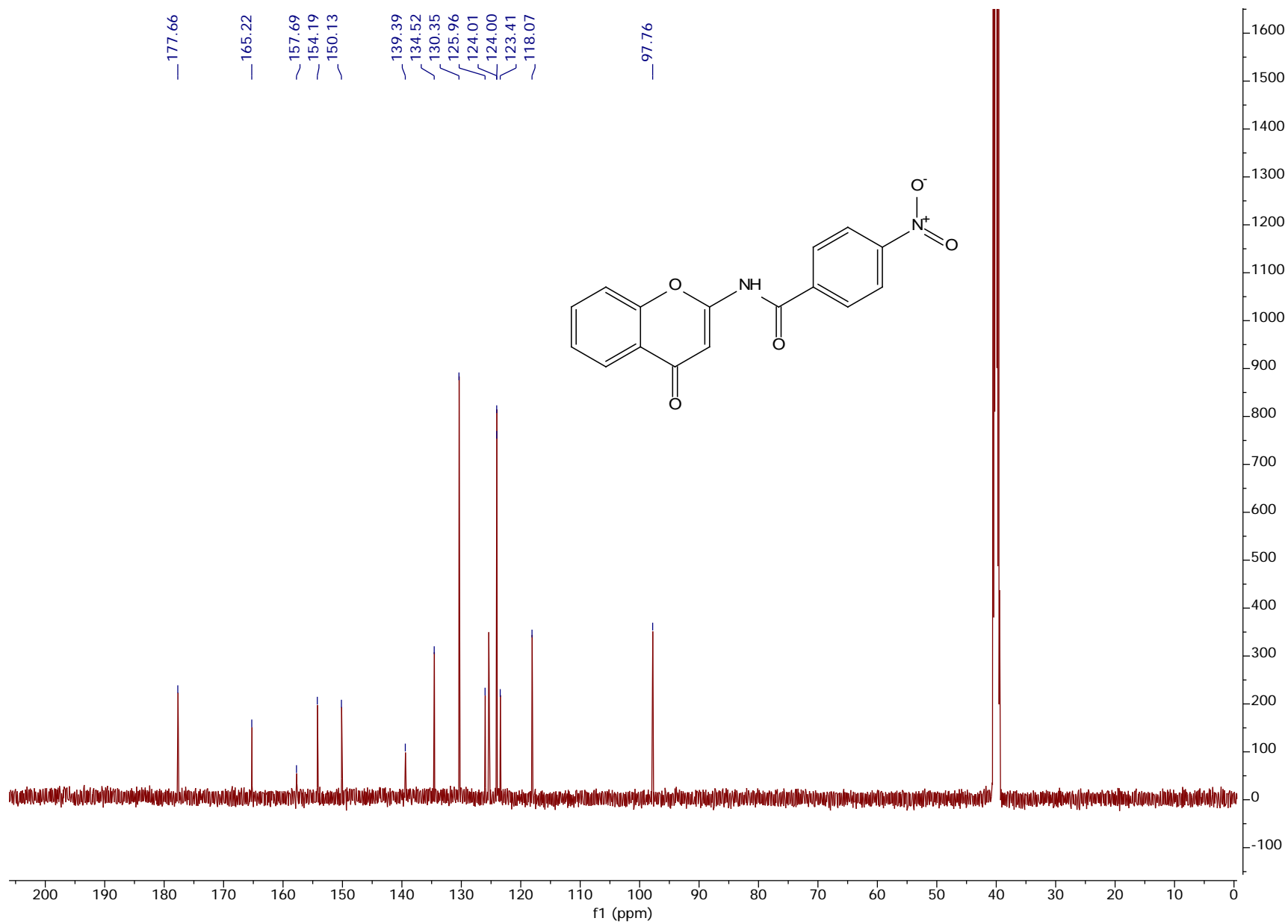
3-Chloro-4-fluoro-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6l)



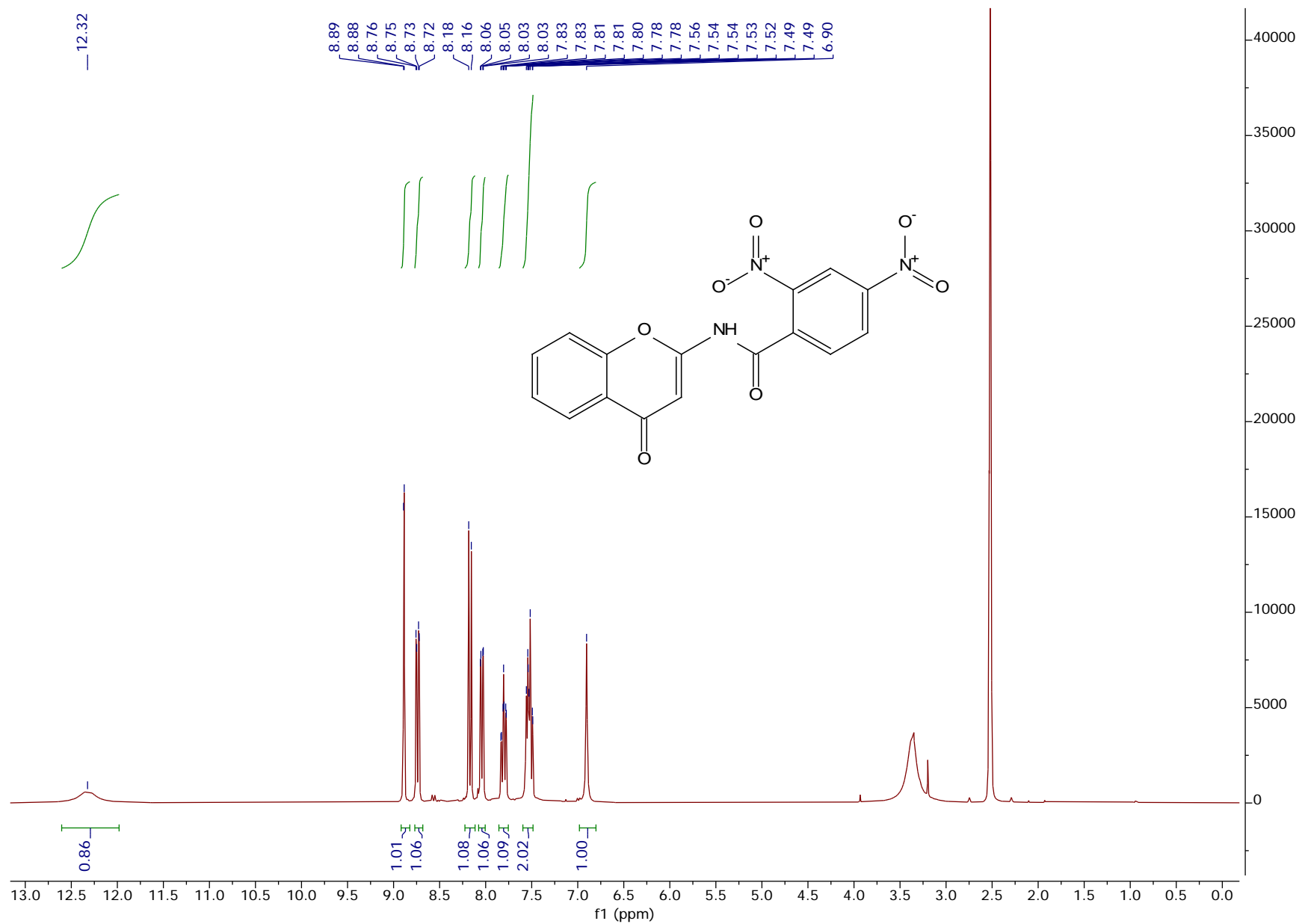


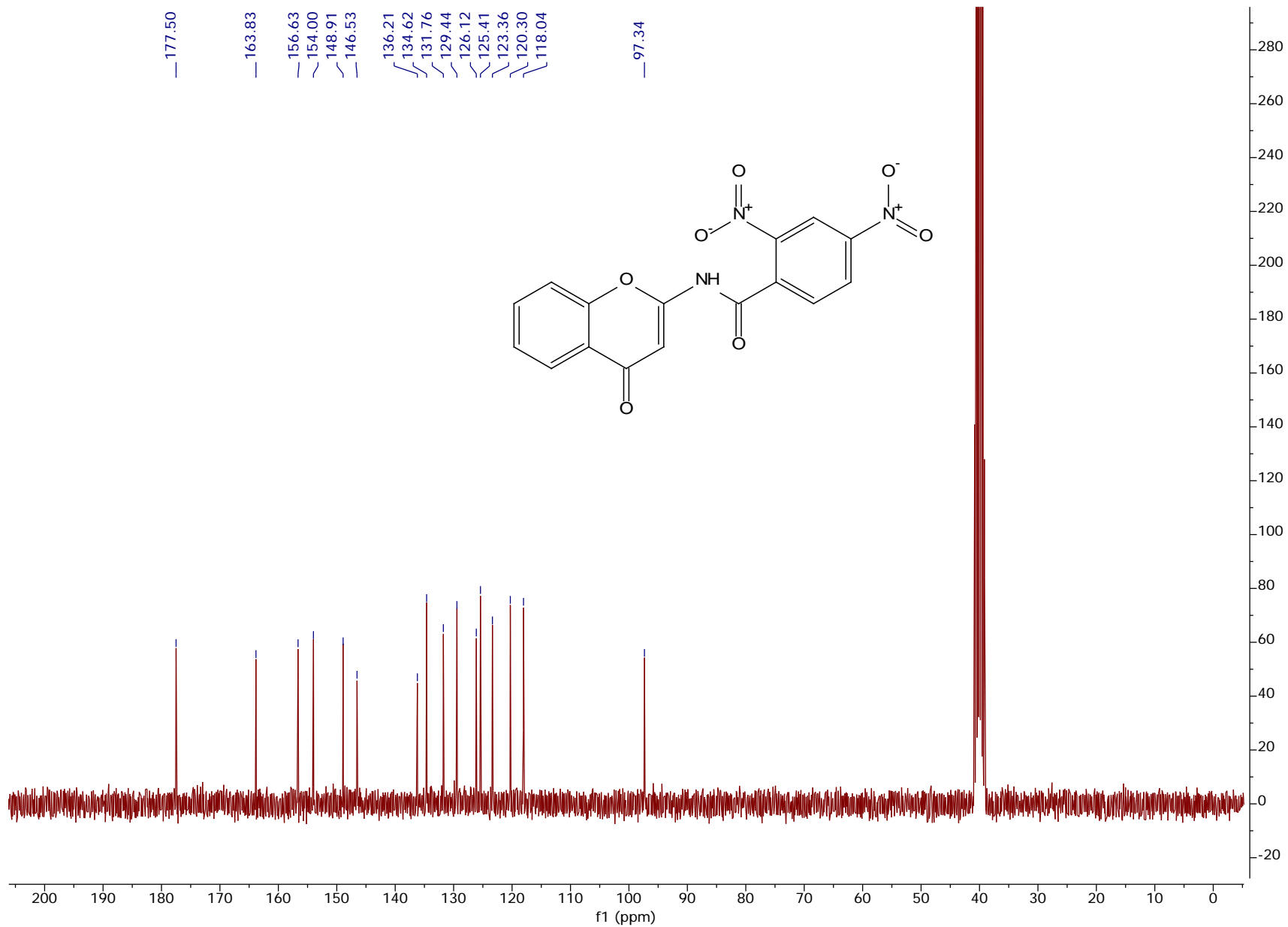
4-Nitro-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6m)



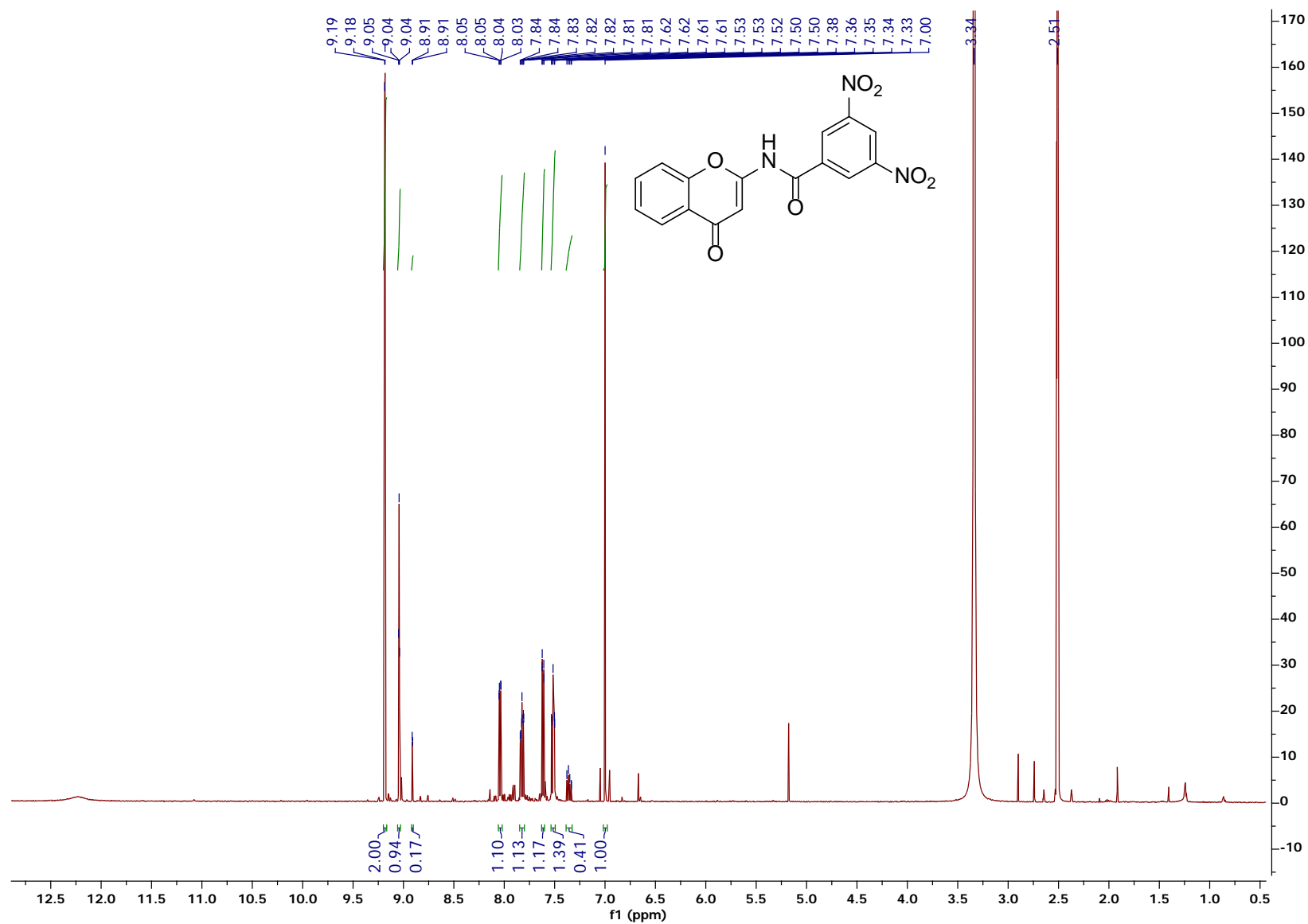


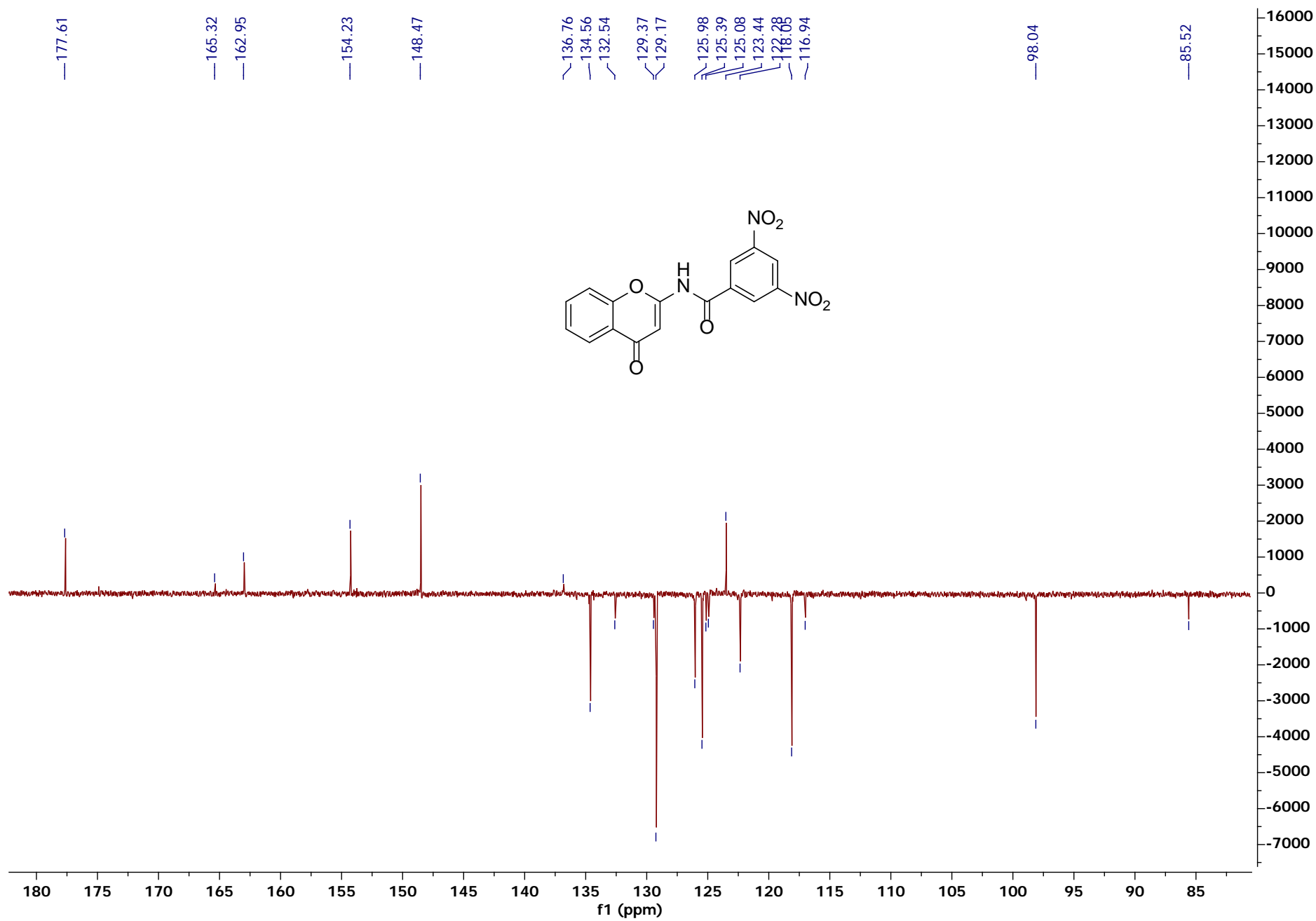
2,4-Dinitro-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6n)



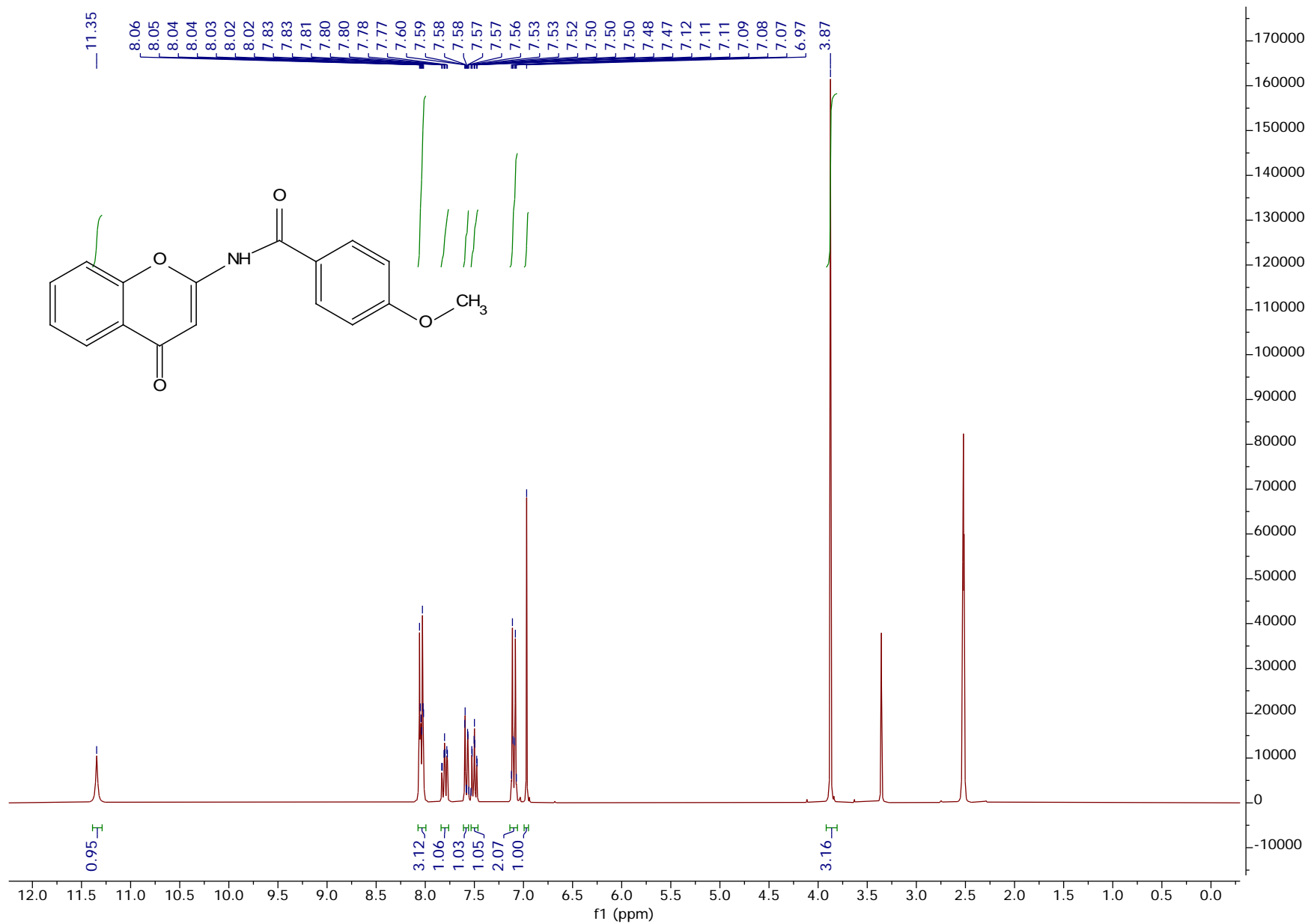


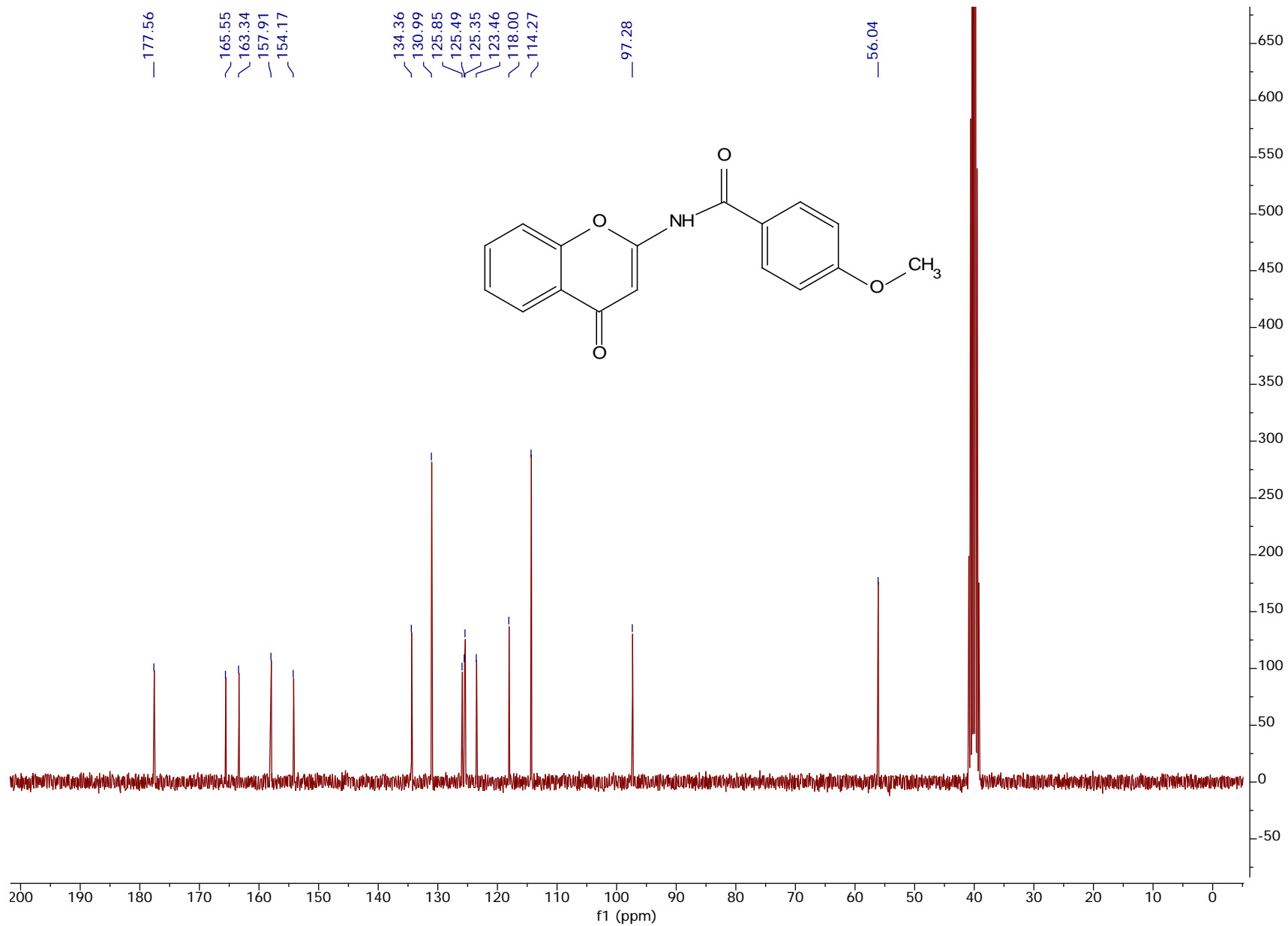
2,4-Dinitro-N-(4-oxo-4H-chromen-2-yl)benzamide (6n)



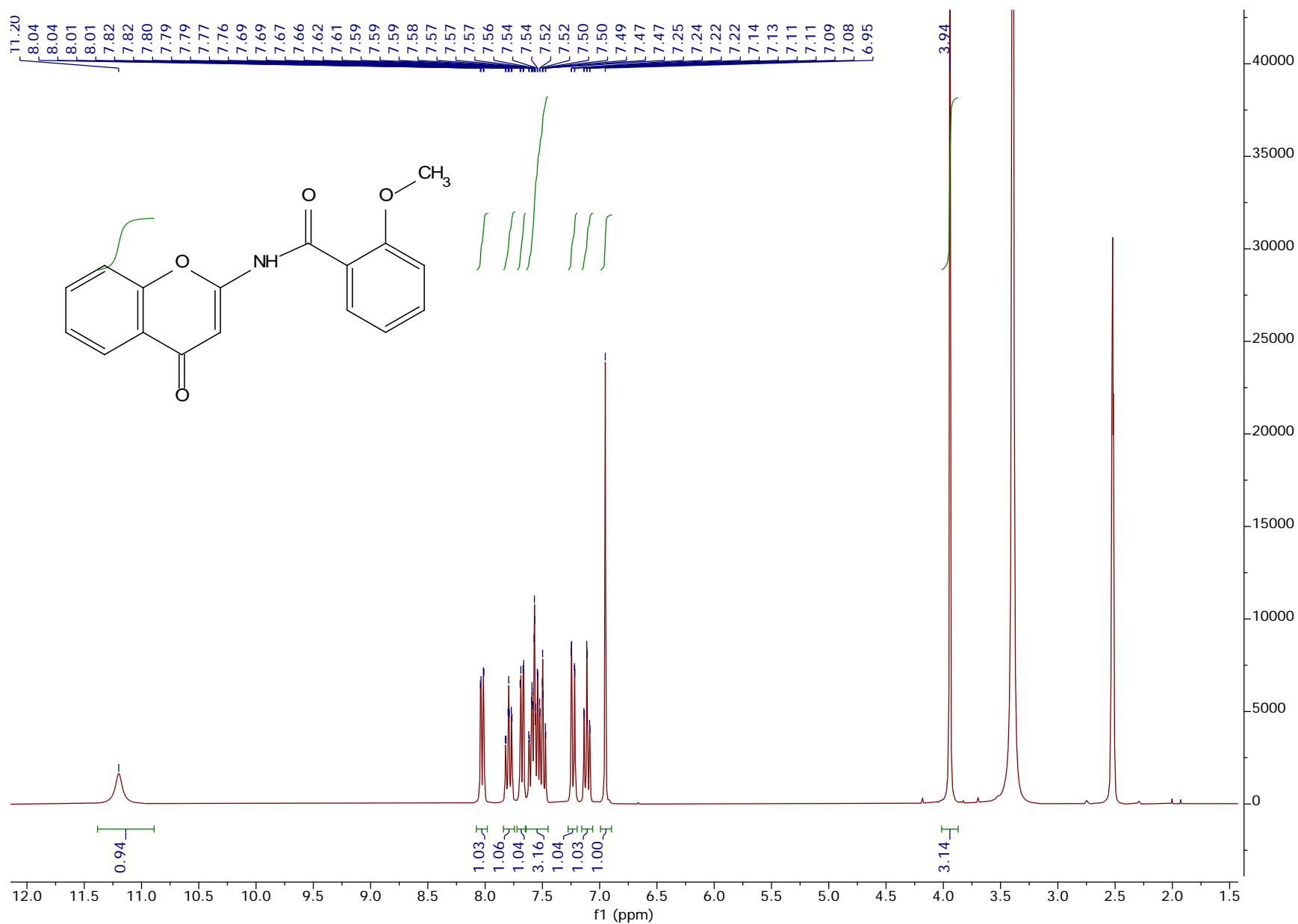


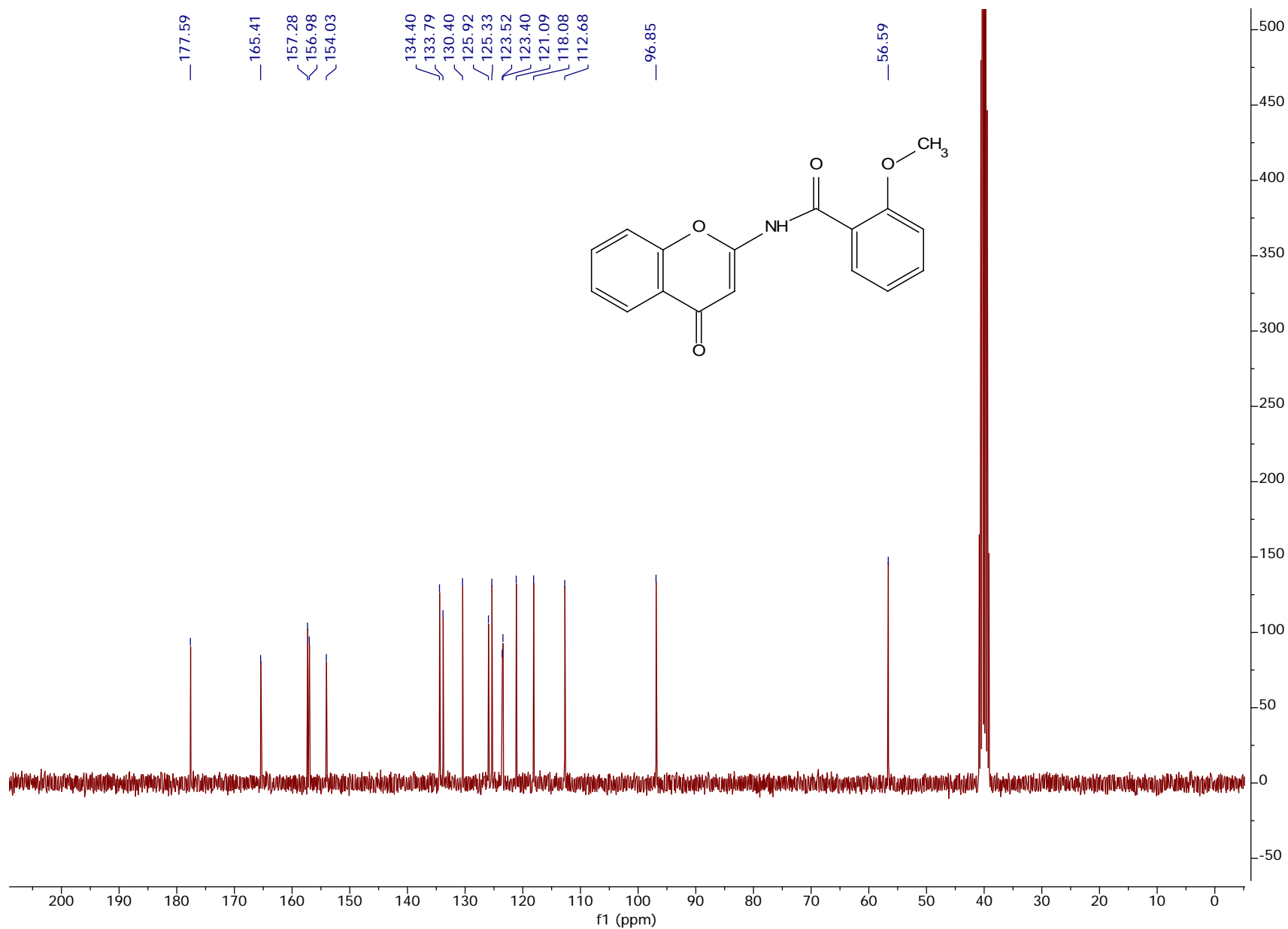
4-Methoxy-N-(4-oxo-4H-chromen-2-yl)benzamide (6p)



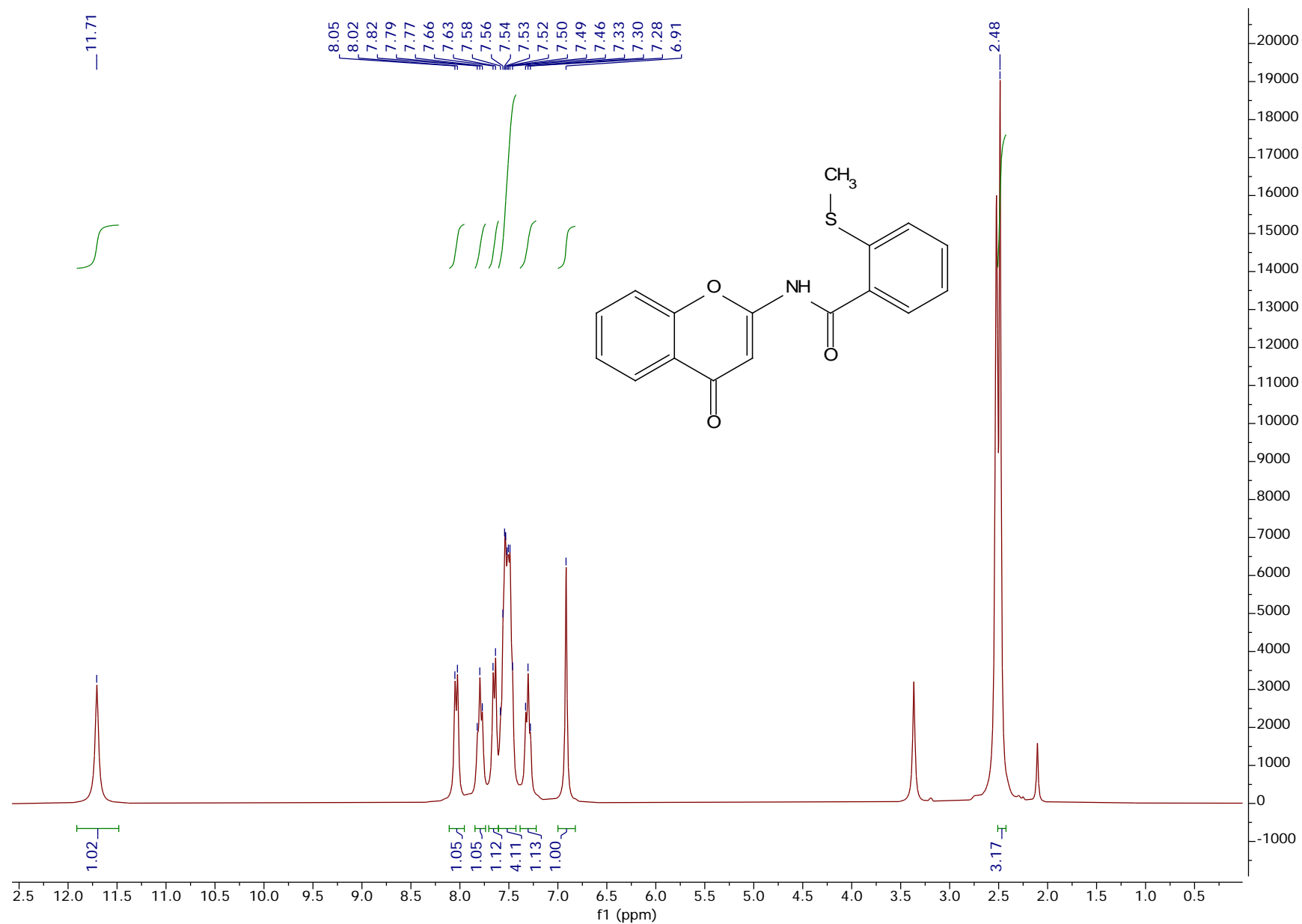


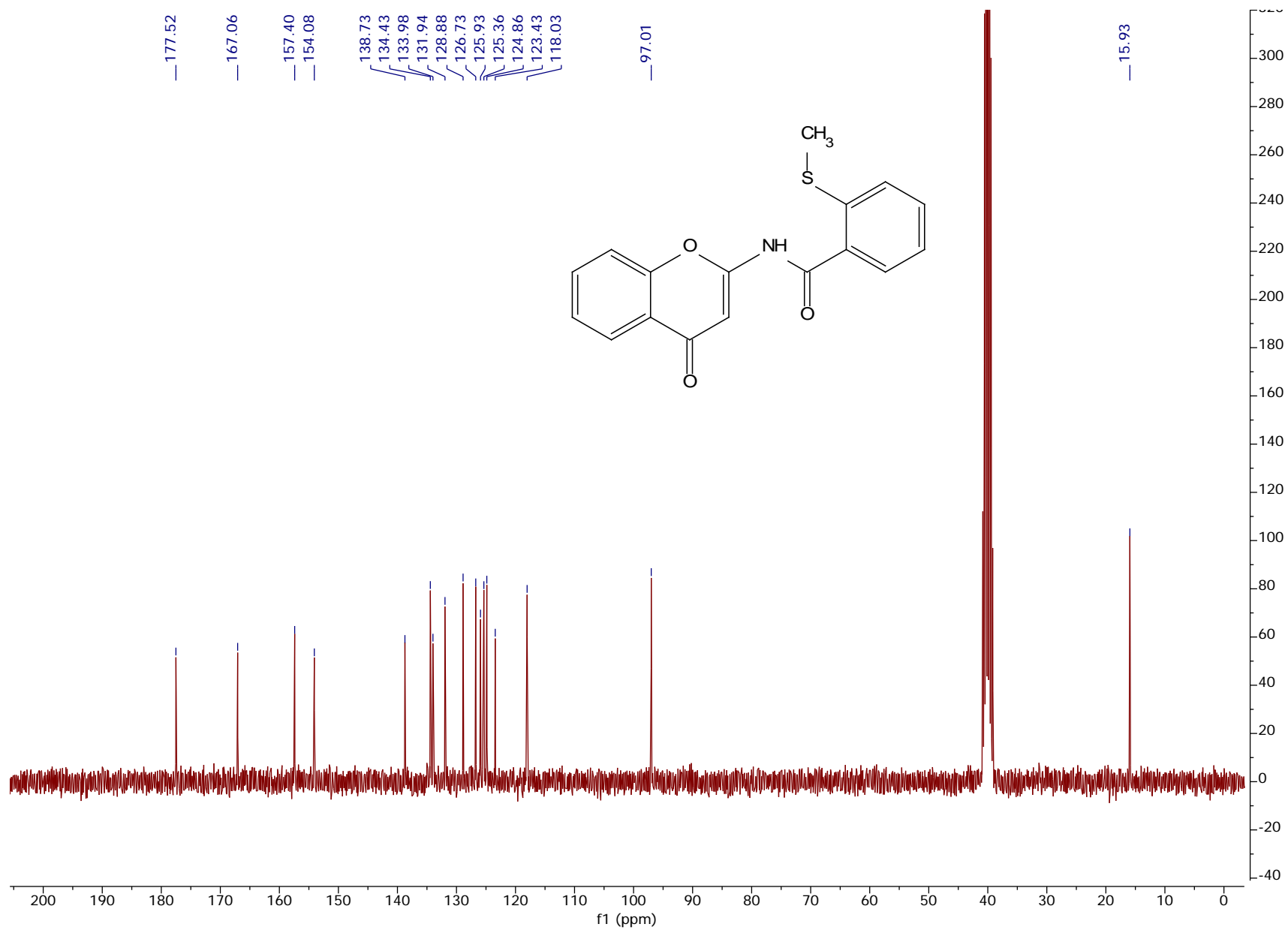
2-Methoxy-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6q)



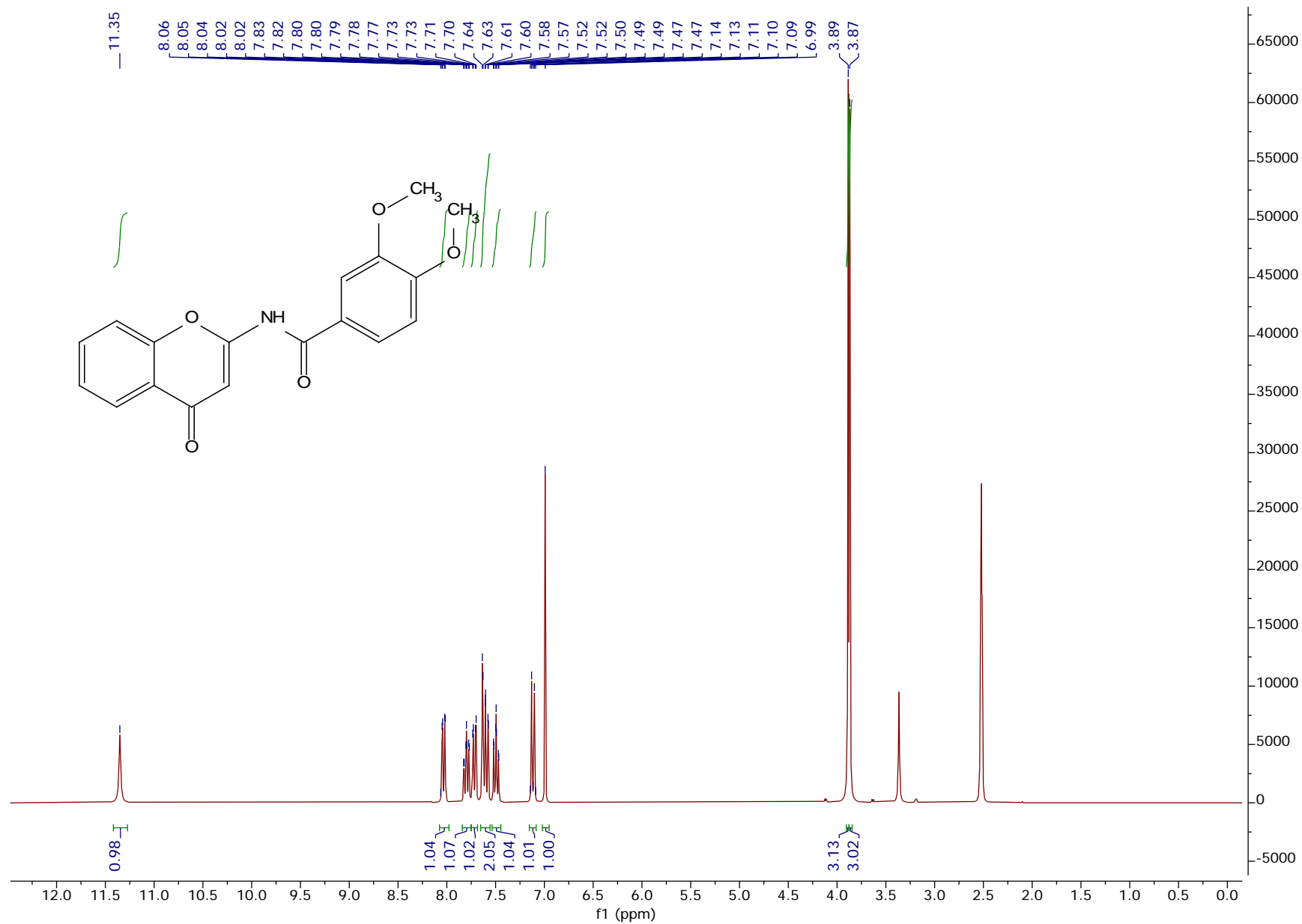


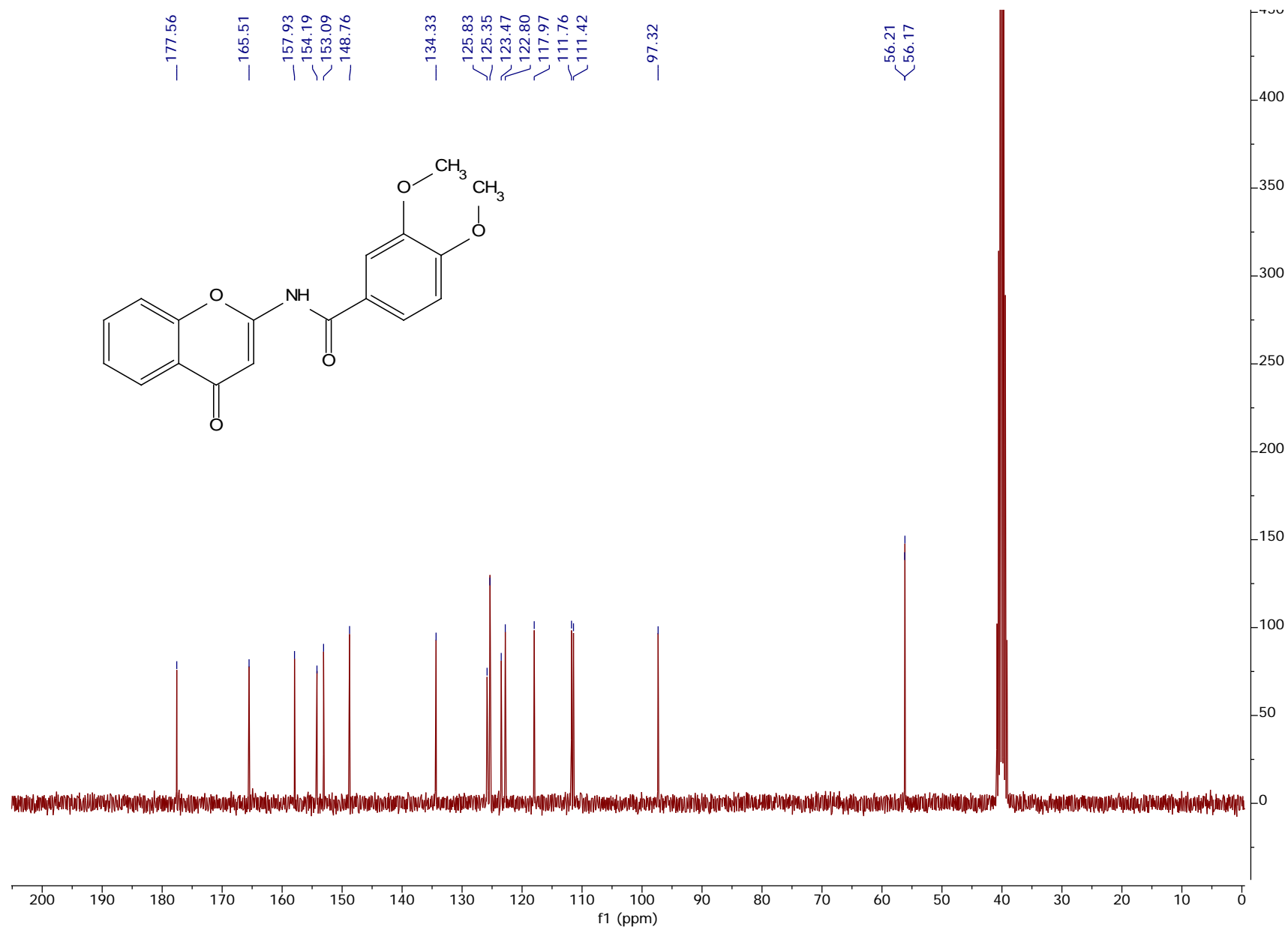
2-(Methylthio)-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6r)



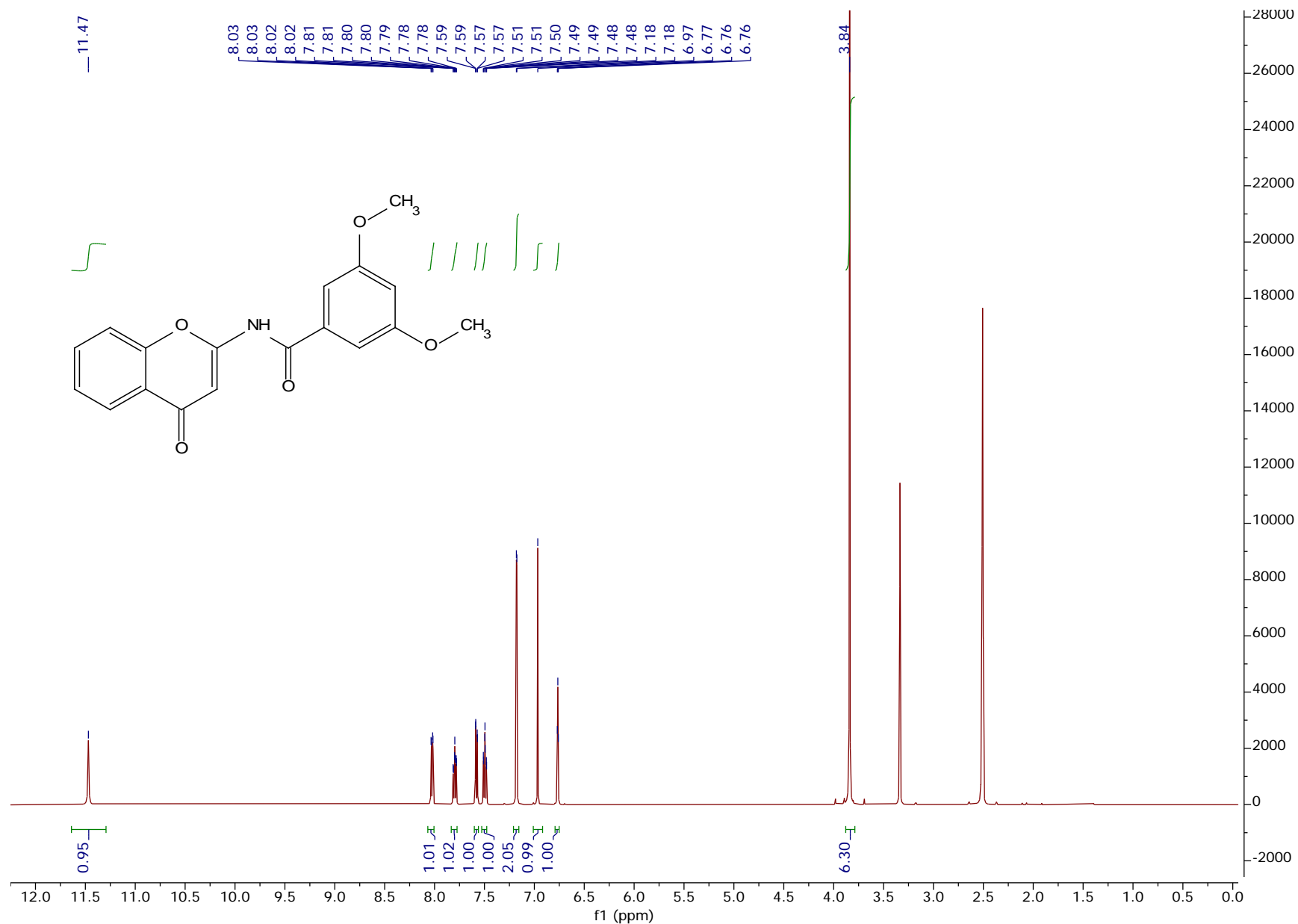


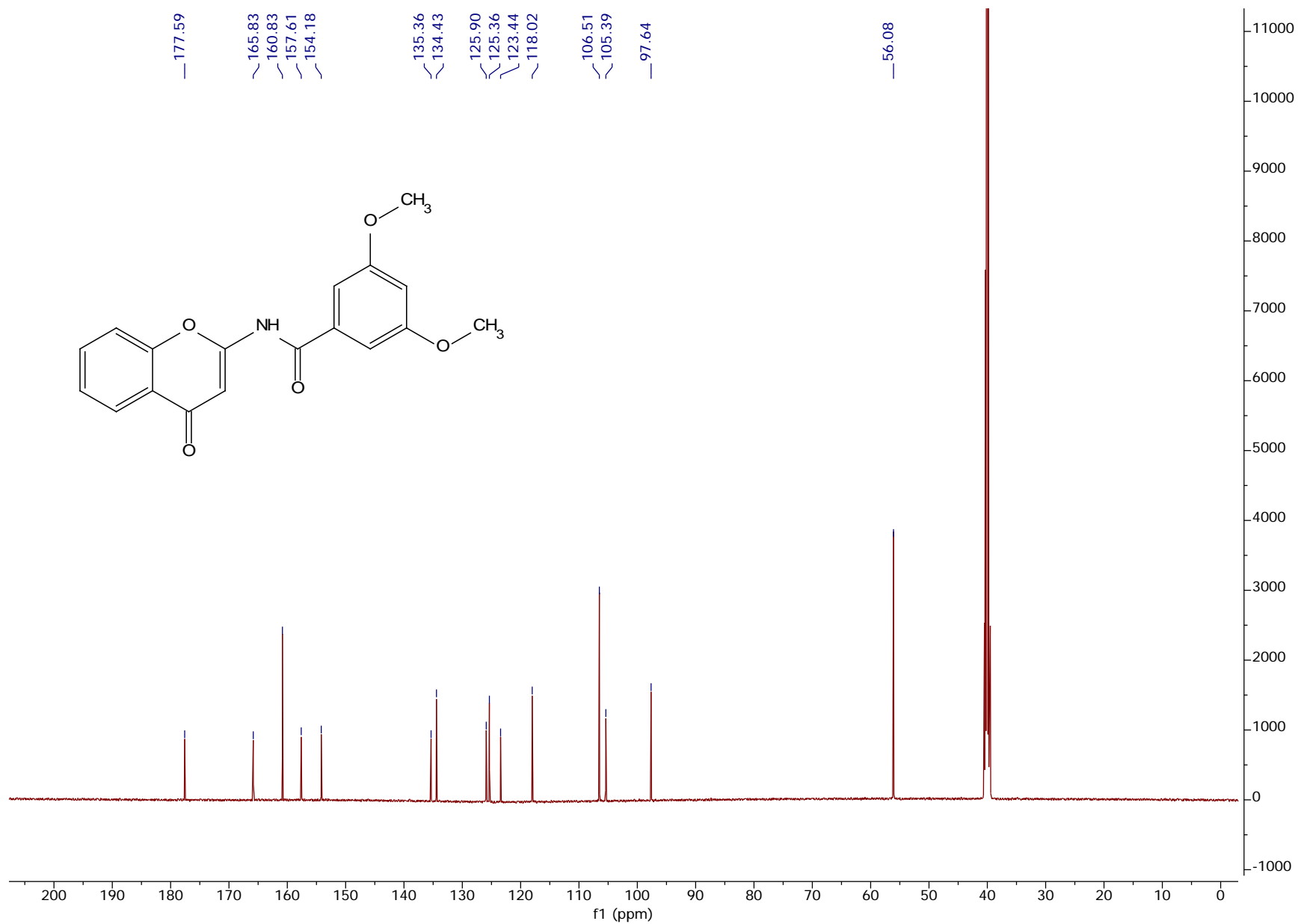
3,4-Dimethoxy-N-(4-oxo-4H-chromen-2-yl)benzamide (6s)



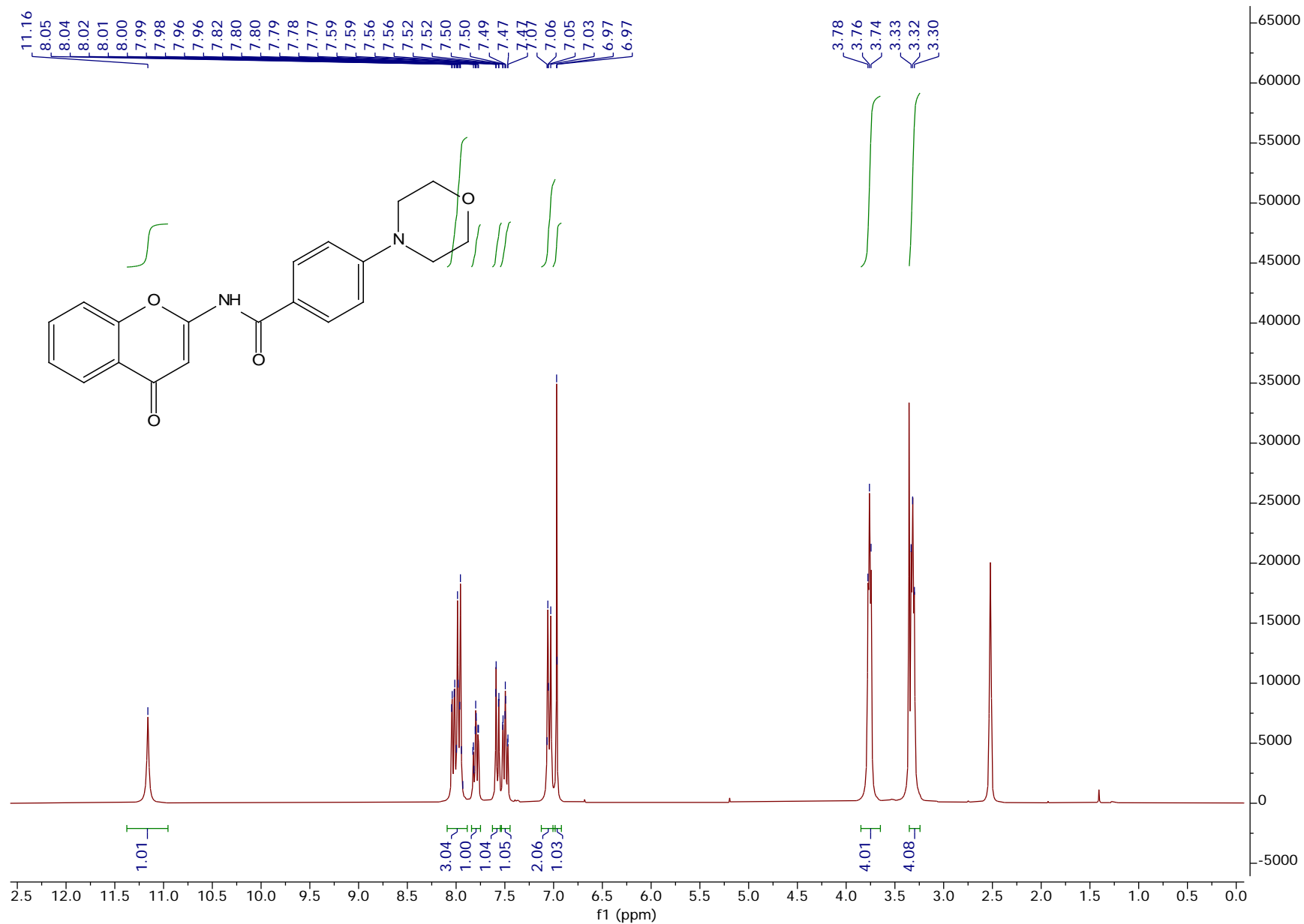


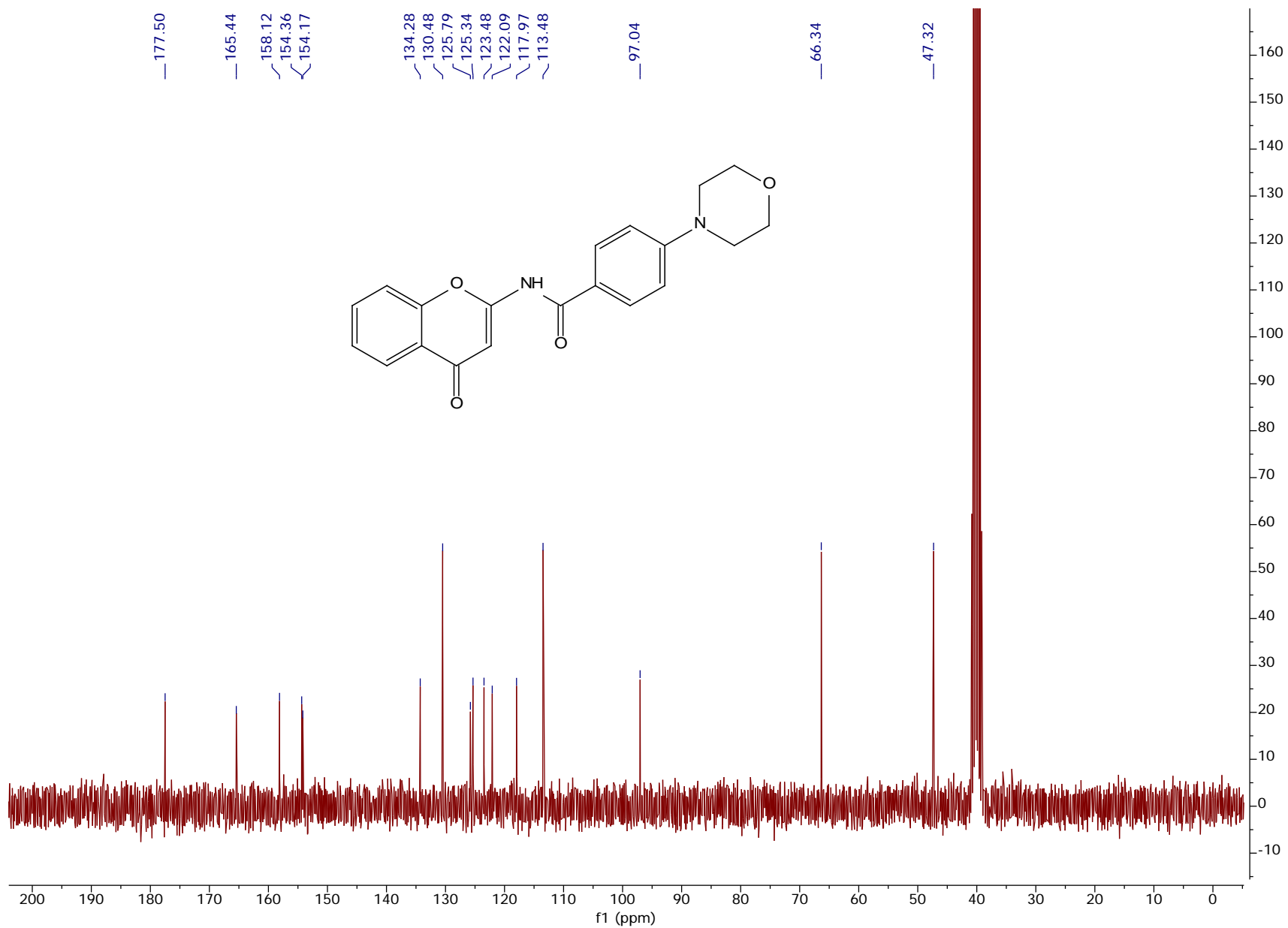
3,5-Dimethoxy-N-(4-oxo-4H-chromen-2-yl)benzamide (6t)



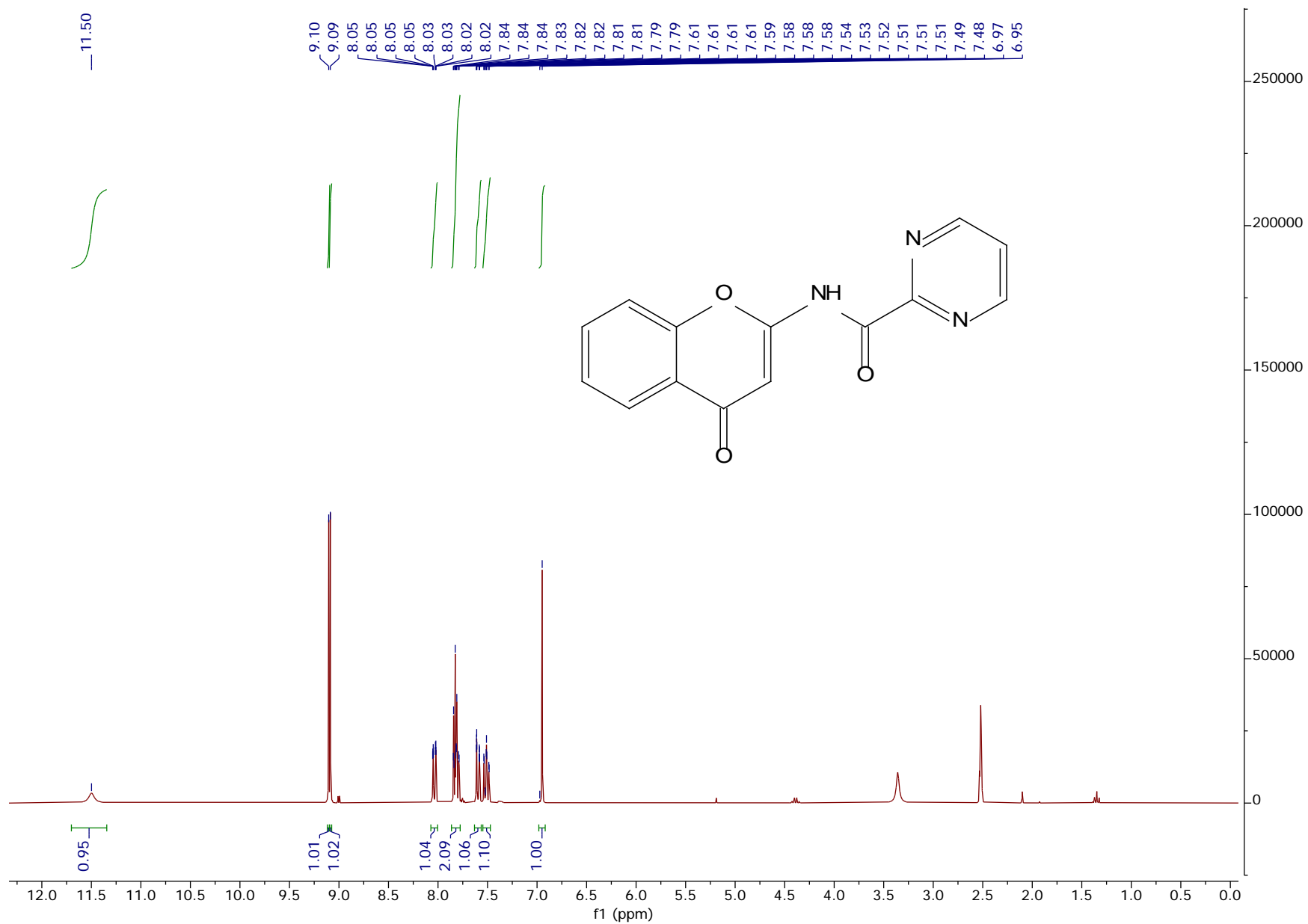


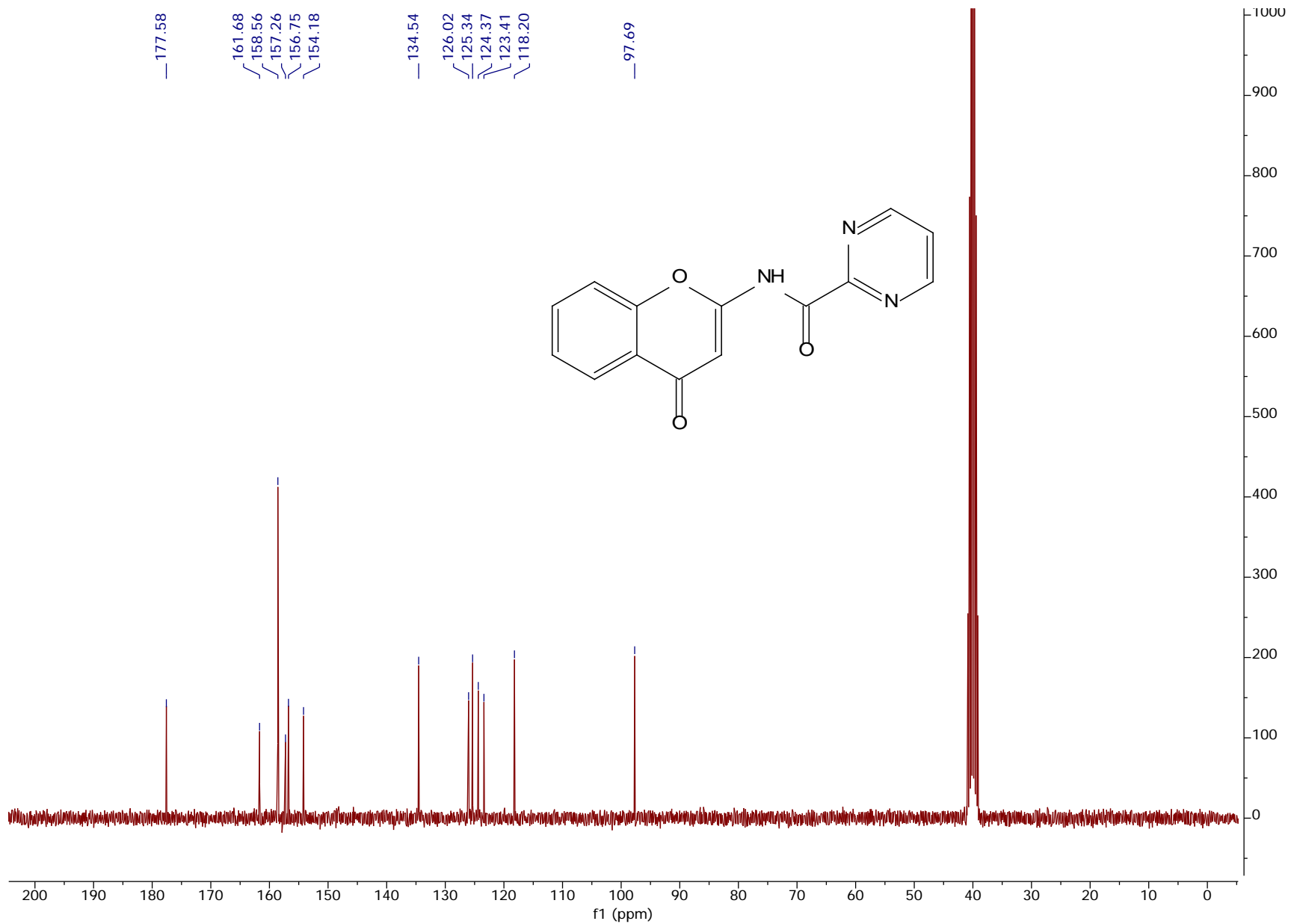
4-Morpholino-*N*-(4-oxo-4*H*-chromen-2-yl)benzamide (6u)



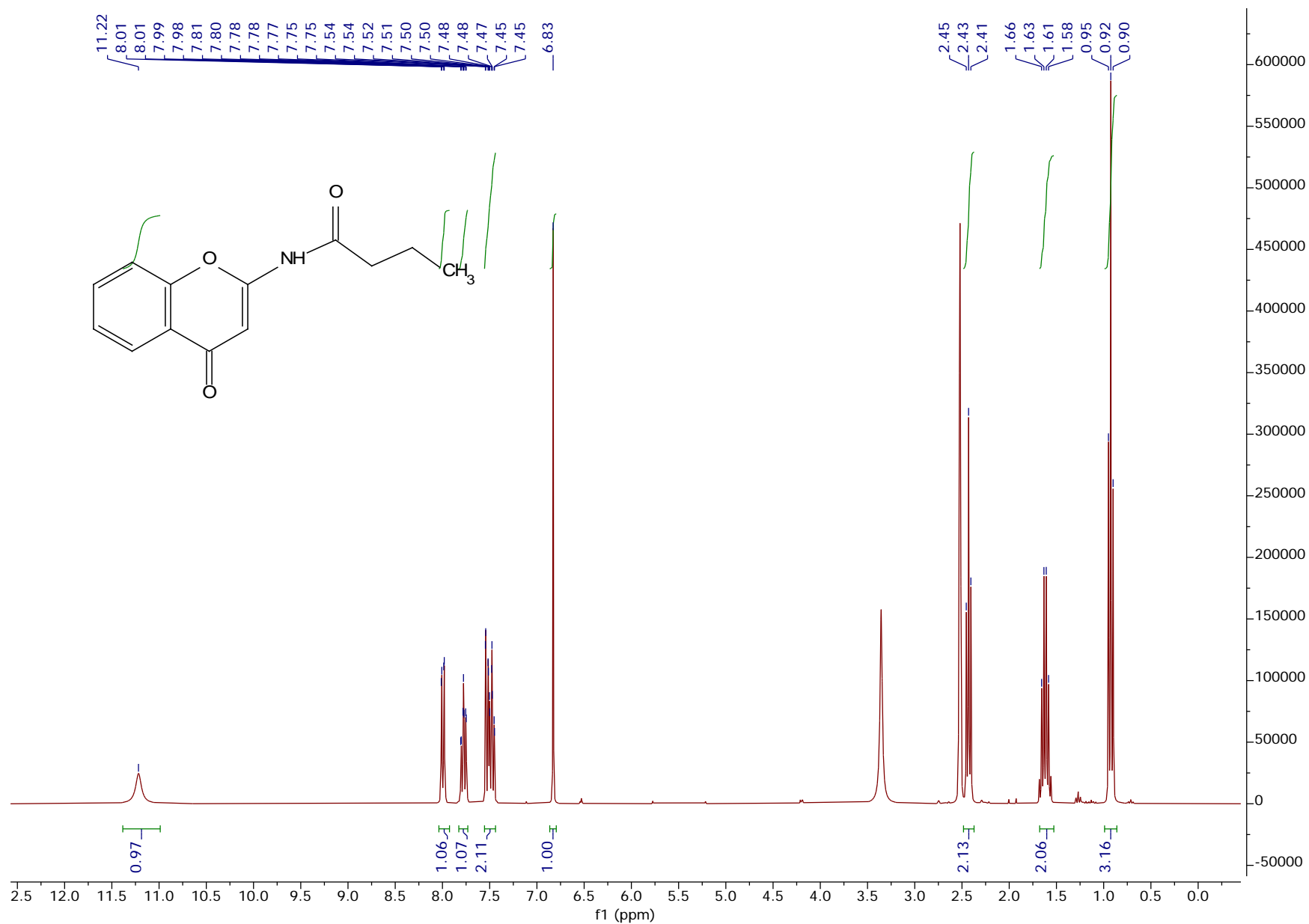


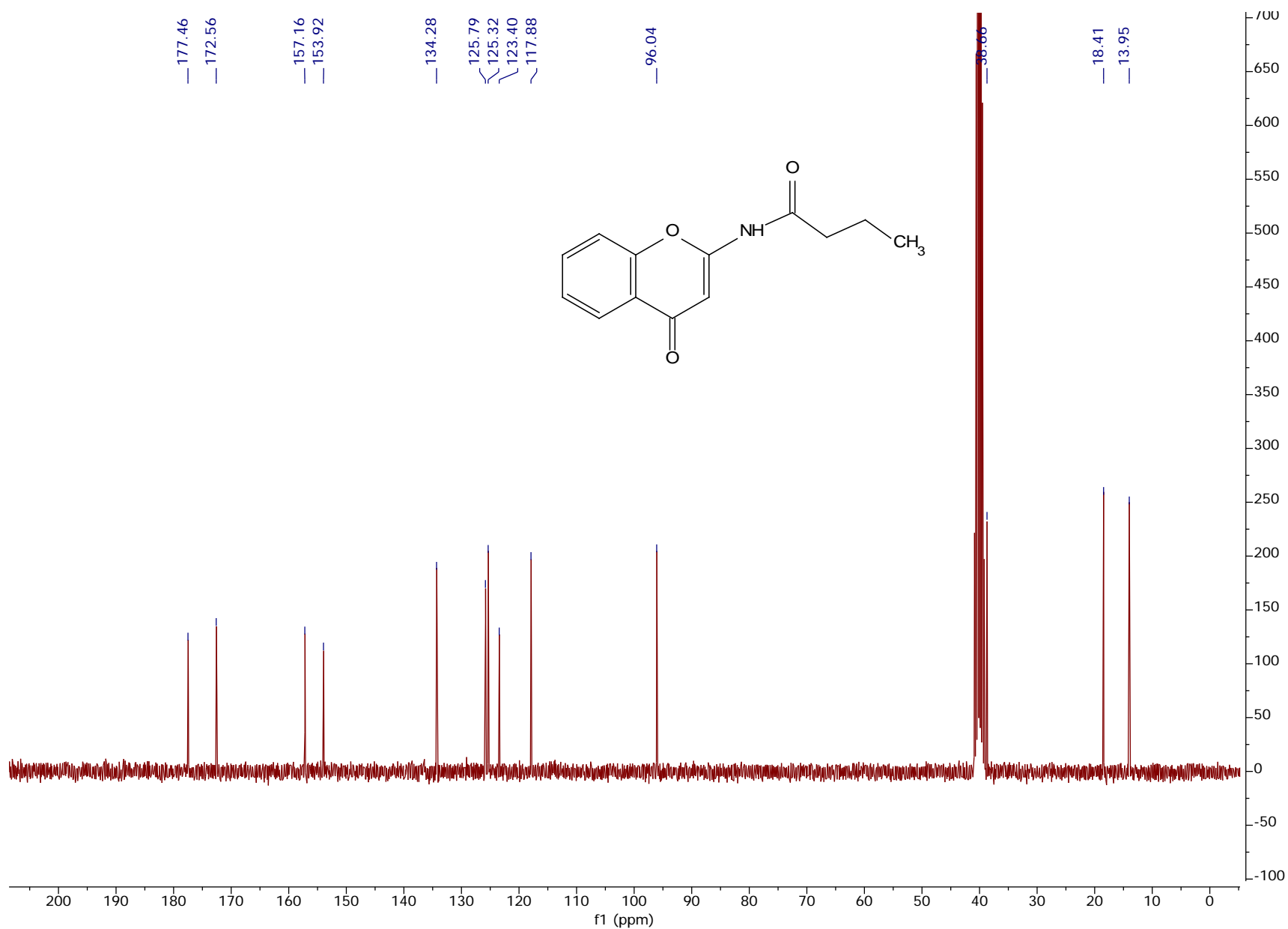
***N*-(4-Oxo-4*H*-chromen-2-yl)pyrimidine-2-carboxamide (6v)**



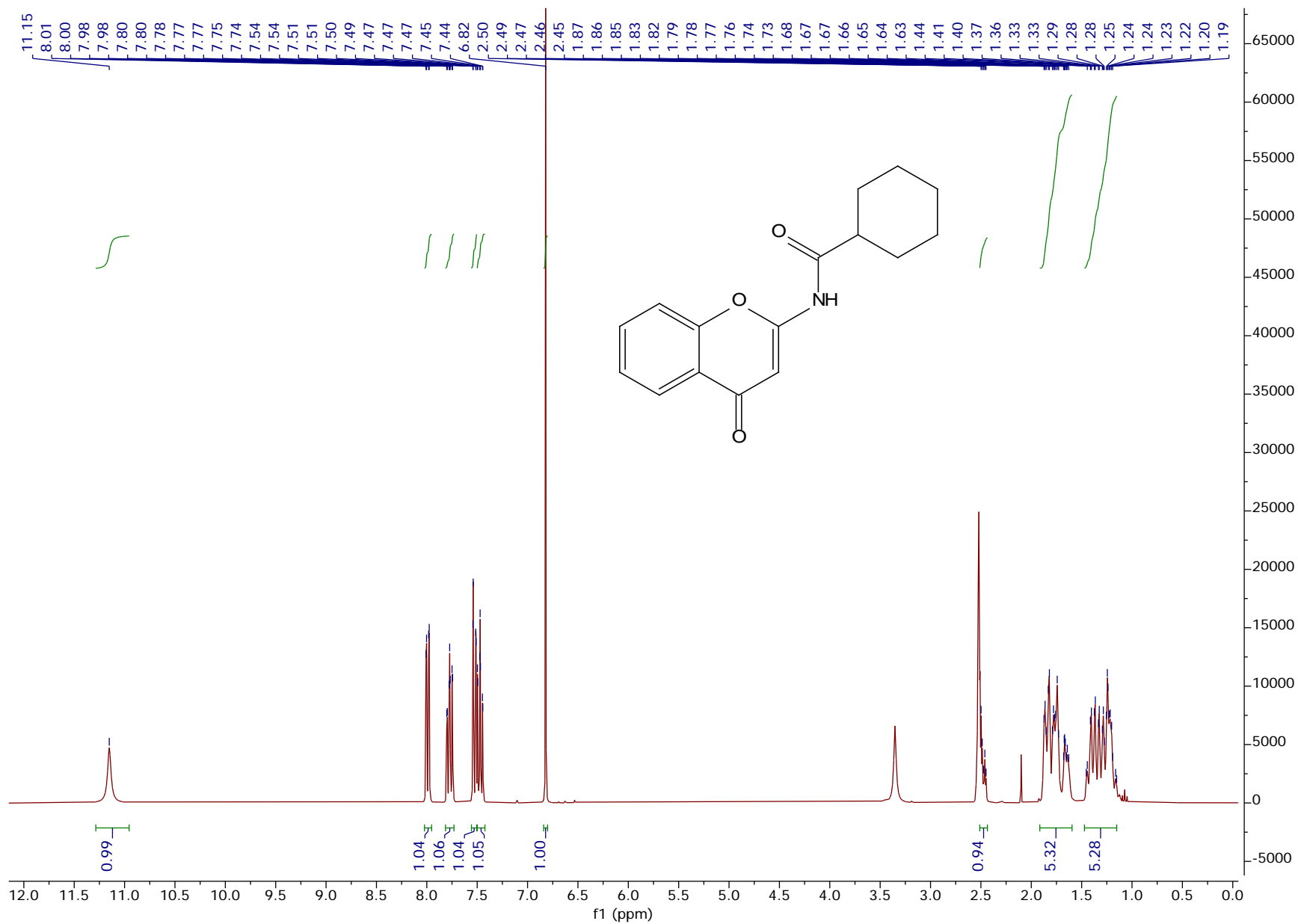


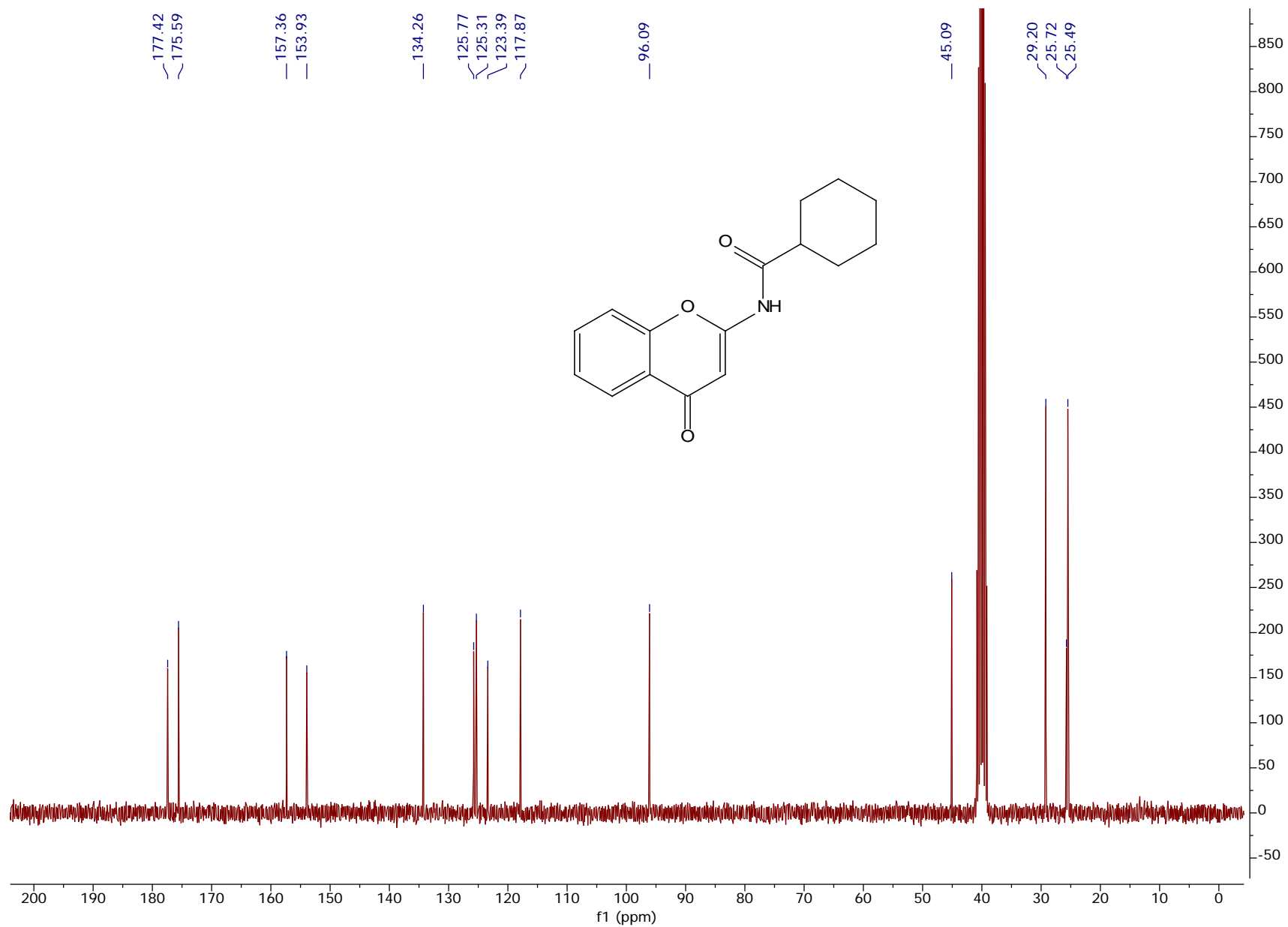
***N*-(4-Oxo-4*H*-chromen-2-yl)butyramide (6w)**



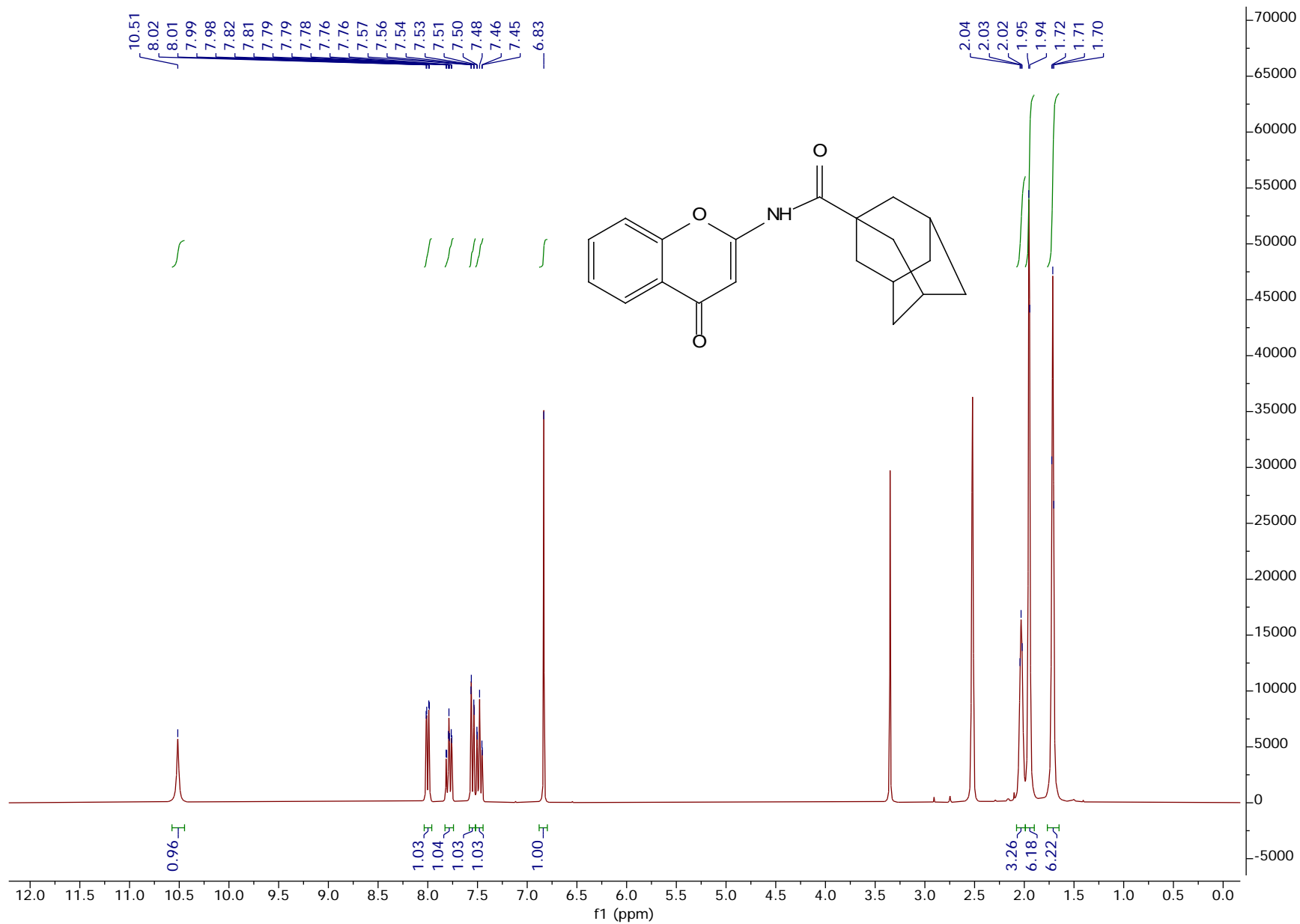


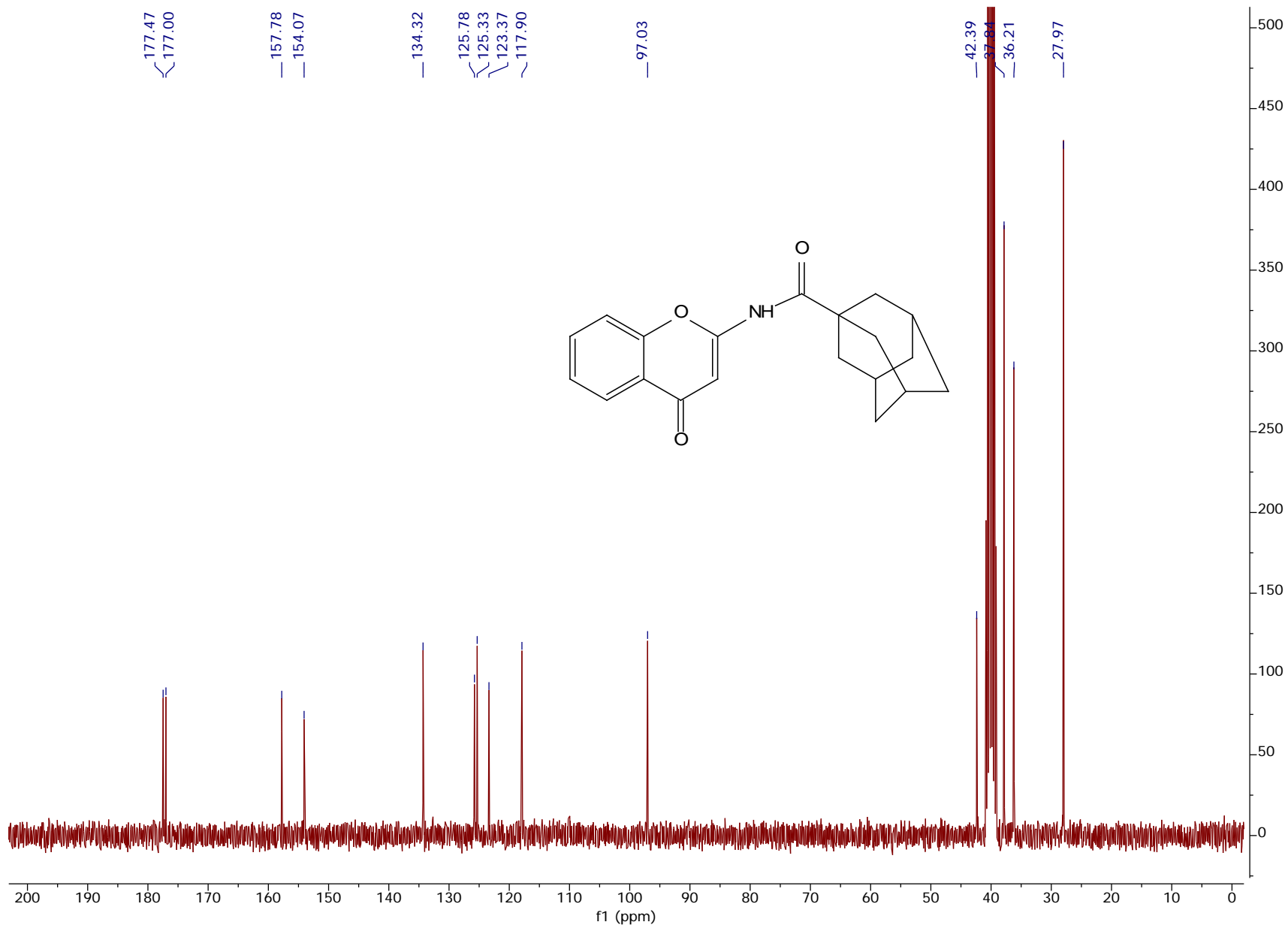
***N*-(4-Oxo-4*H*-chromen-2-yl)cyclohexanecarboxamide (6x)**



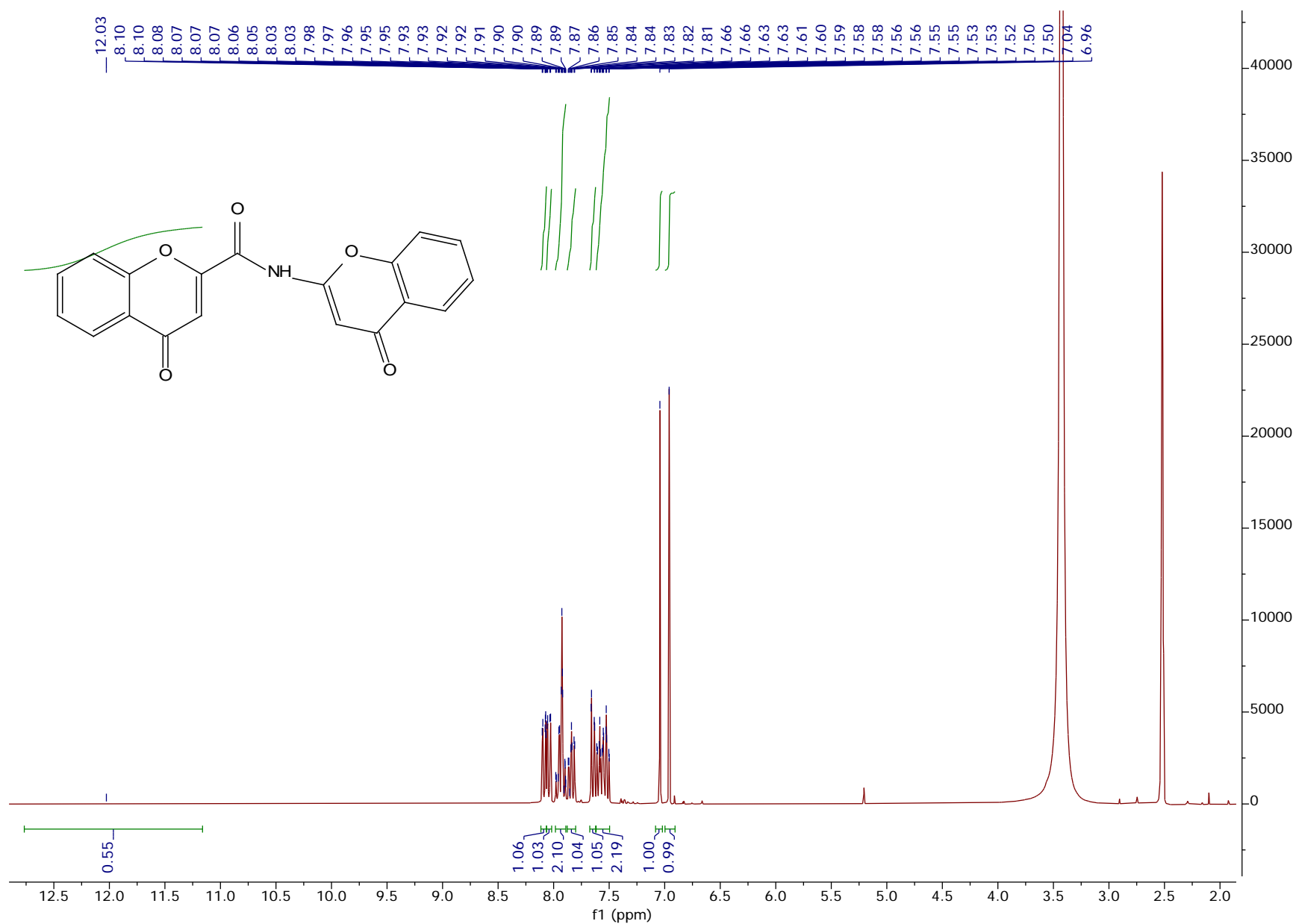


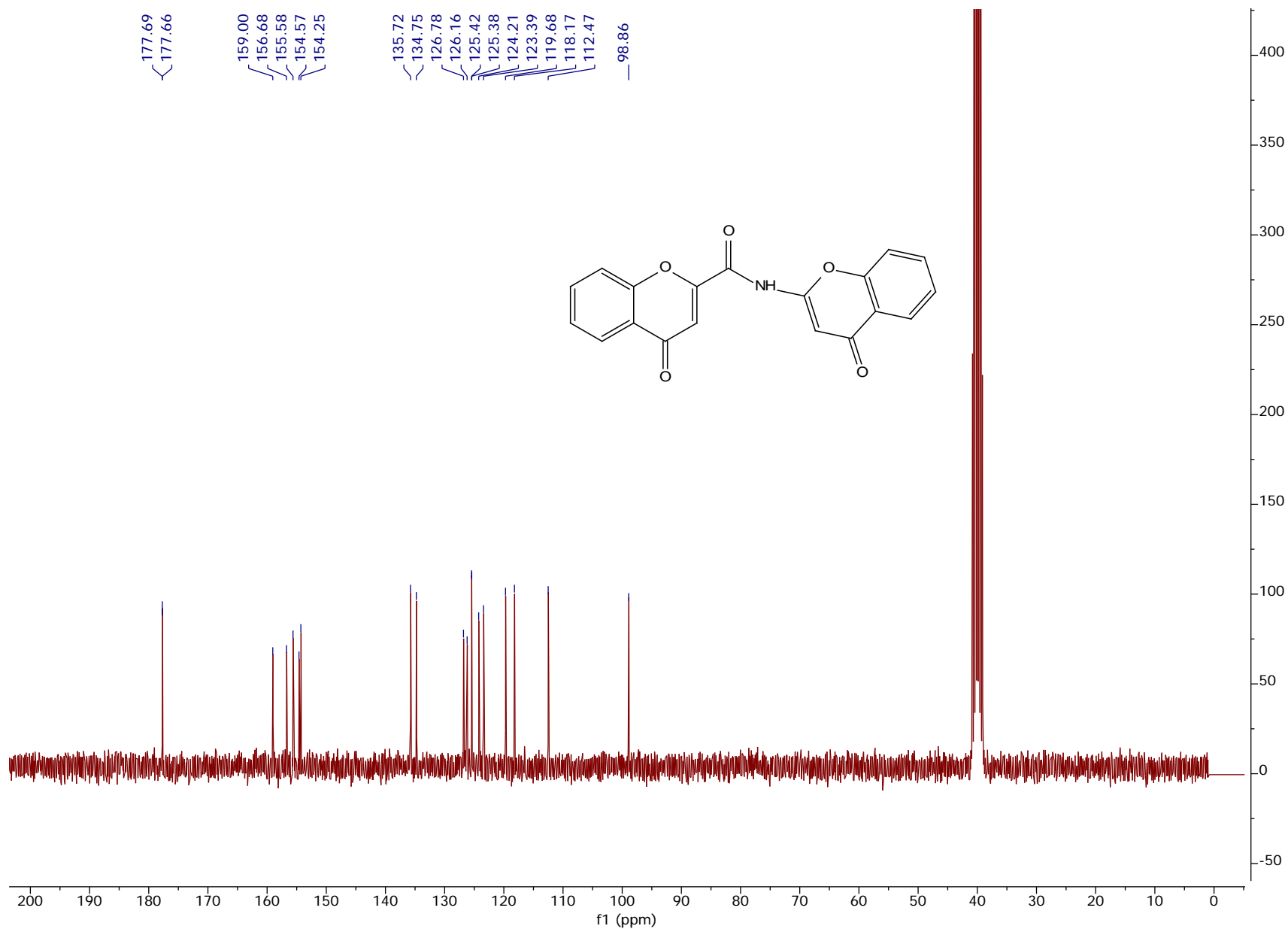
(3R,5R,7R)-N-(4-Oxo-4H-chromen-2-yl)adamantane-1-carboxamide (6y)





4-Oxo-N-(4-oxo-4H-chromen-2-yl)-4H-chromene-2-carboxamide (6z)





3-(4-Bromophenyl)-2-isocyanato-4H-chromen-4-one (7)

