SUPPLEMENTARY INFORMATION

Figure S1. Cytotoxicity of compounds NMR ^{1}H and ^{13}C spectra of compounds **25**, **30** and **33**–**38.**

Tables S1 to S3 for the computer aided drug design

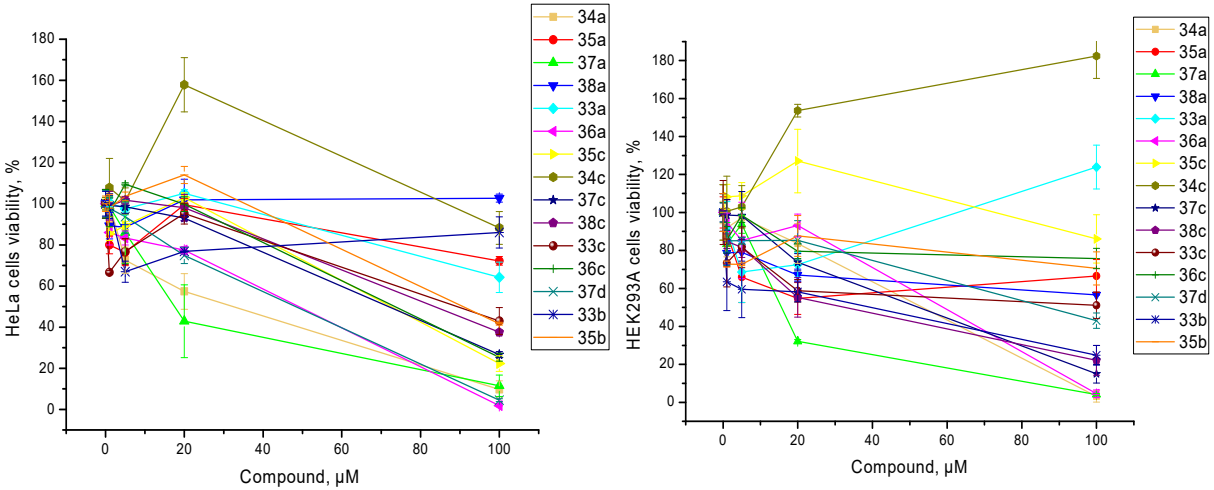
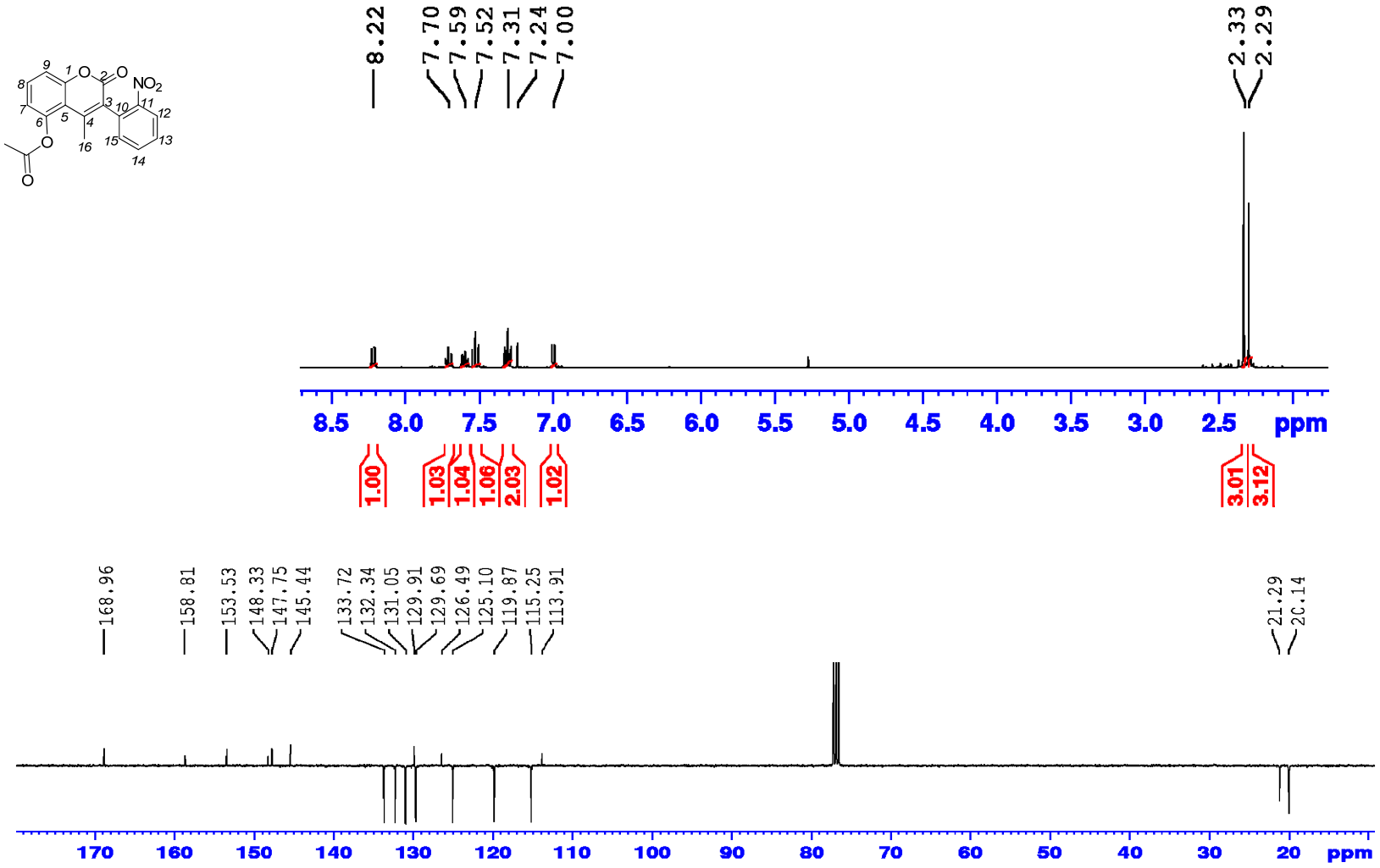
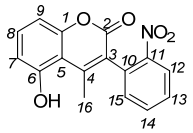


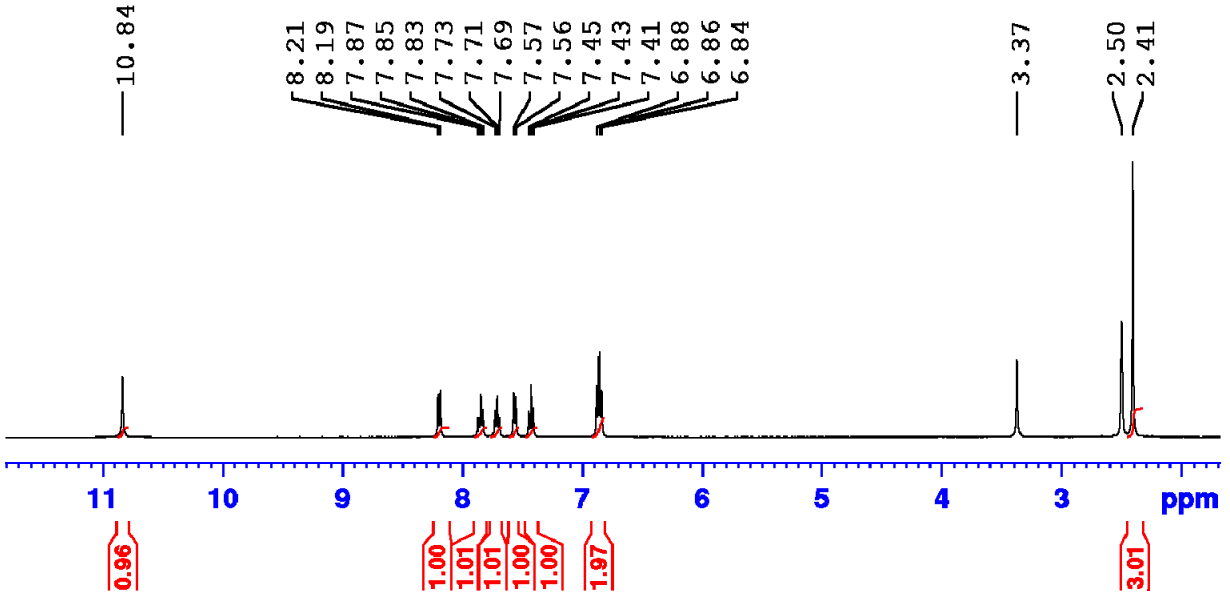
Figure S1. The effect of compounds on the survival of HeLa (**left**) and HEK293A (**right**) cells.

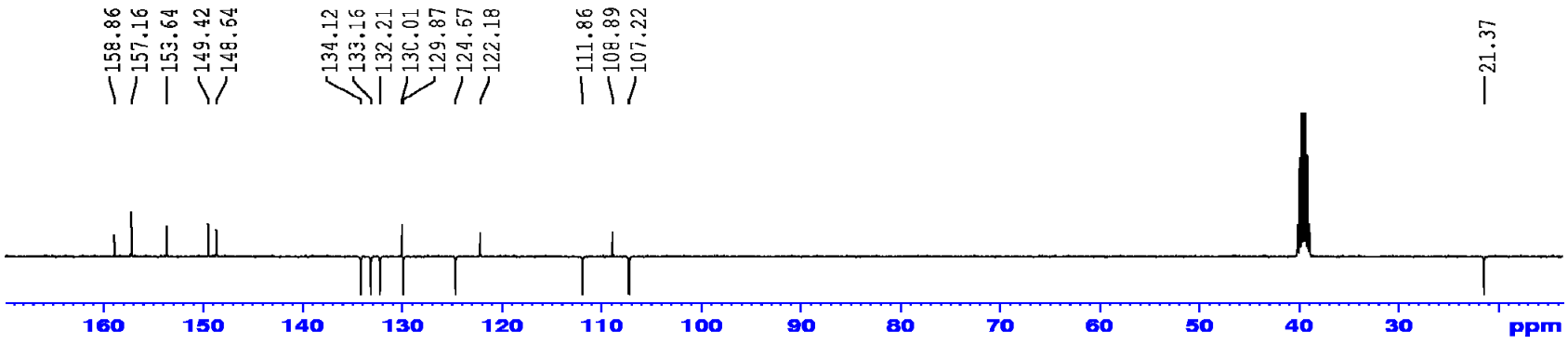
Compound **25**


8.22
7.70
7.59
7.52
7.31
7.24
7.00
2.33
2.29
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
1.00
1.03
1.04
1.06
2.03
1.02
3.01
3.12
168.96
158.81
153.53
148.33
147.75
145.44
133.72
132.34
131.05
129.91
129.69
126.49
125.10
119.87
115.25
113.91
21.29
20.14
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

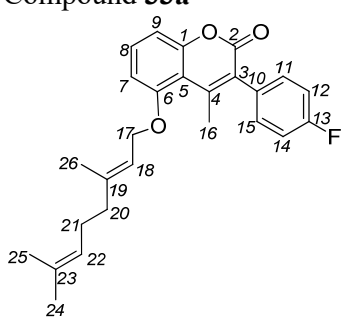
Compound **30**


9
1
O
2
O
NO2
8
3
10
11
12
7
6
5
4
OH
16
15
13
14

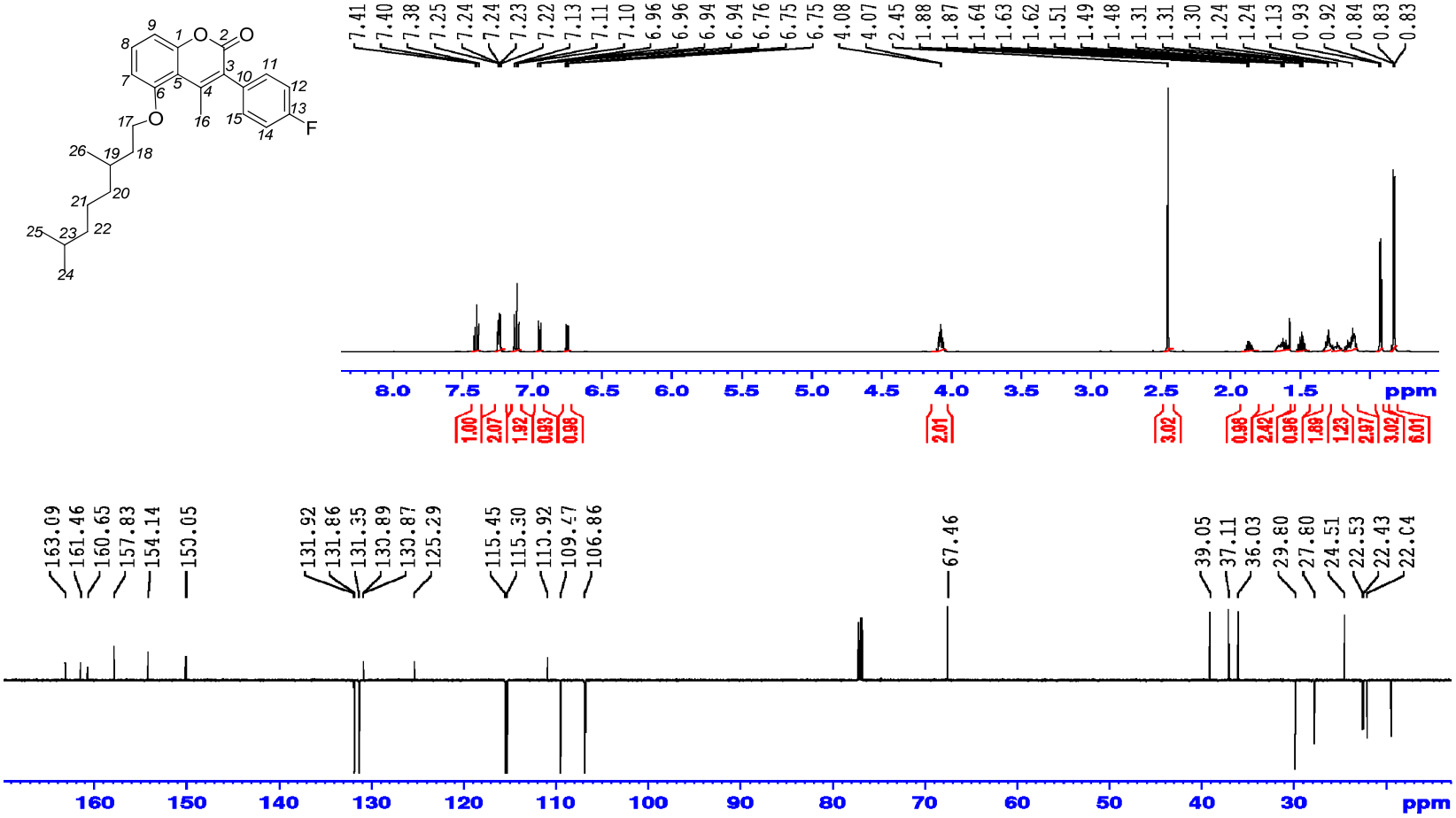

10.84
8.21
8.19
7.87
7.85
7.83
7.73
7.71
7.69
7.57
7.56
7.45
7.43
7.41
6.88
6.86
6.84
3.37
2.50
2.41
11
10
9
8
7
6
5
4
3
ppm
0.96
1.00
1.01
1.01
1.00
1.00
1.97
3.01


158.86
157.16
153.64
149.42
148.64
134.12
133.16
132.21
130.01
129.87
124.67
122.18
111.86
108.89
107.22
21.37
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

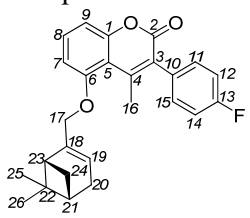
Compound **33a**

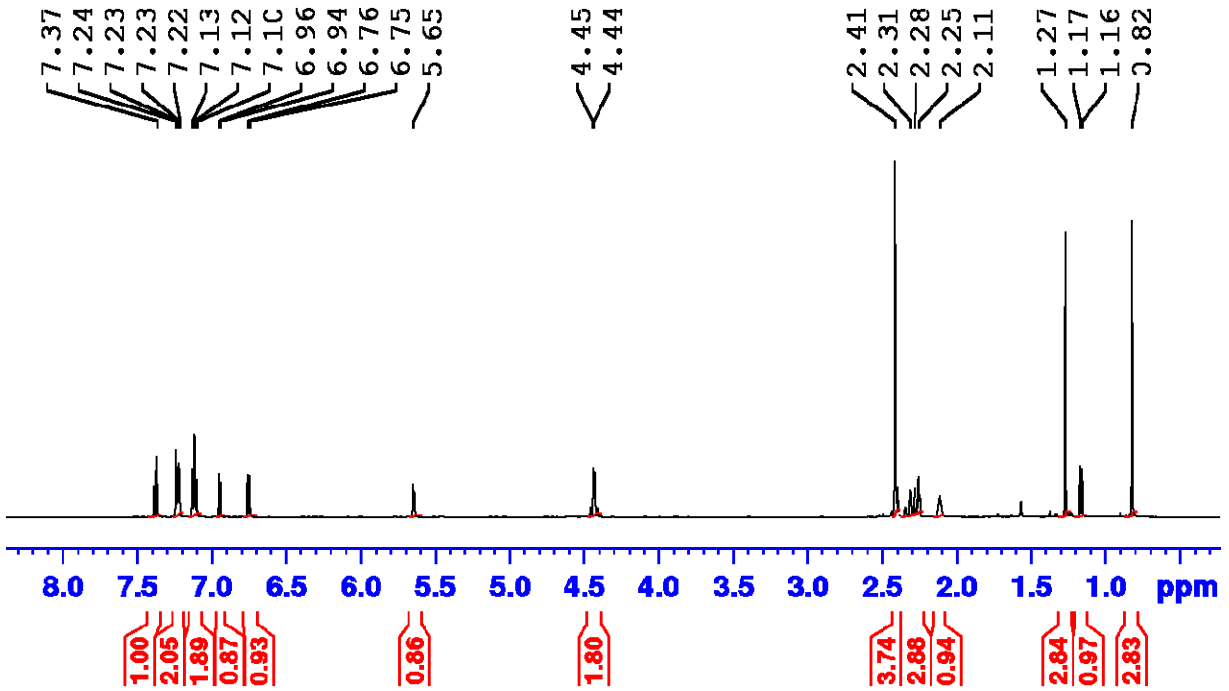


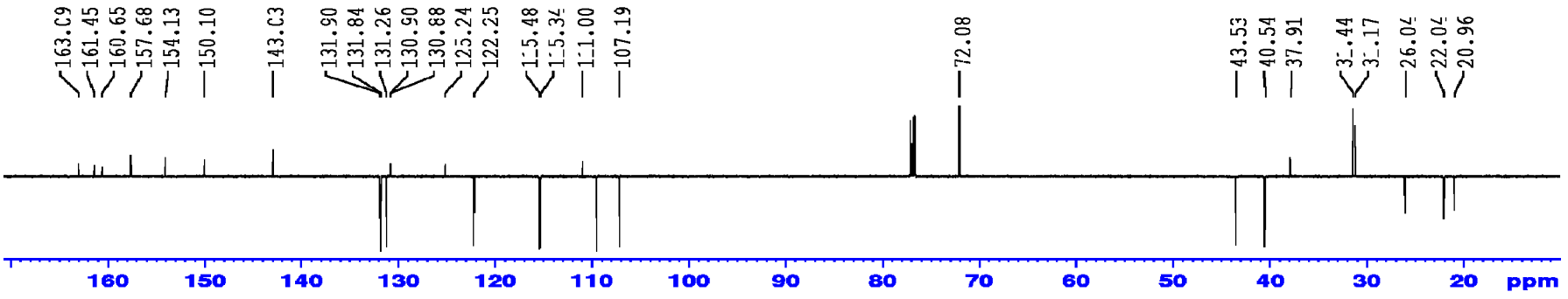
Compound **33b**



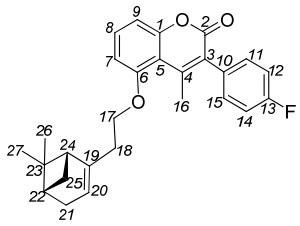
Compound **33c**

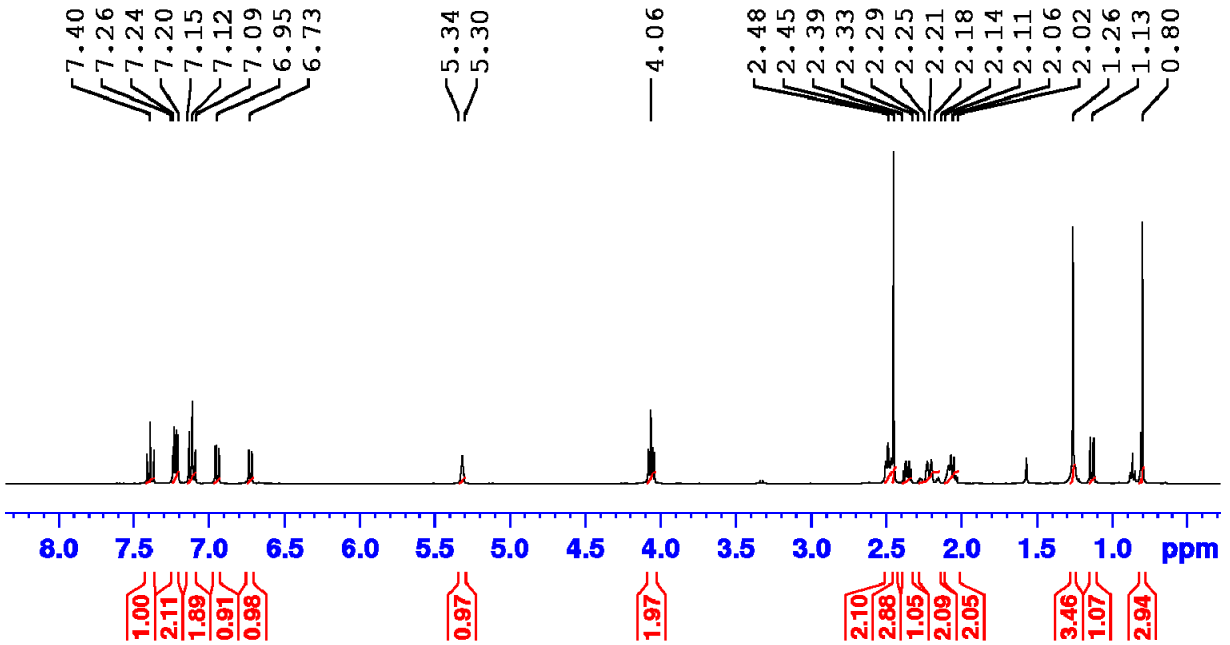


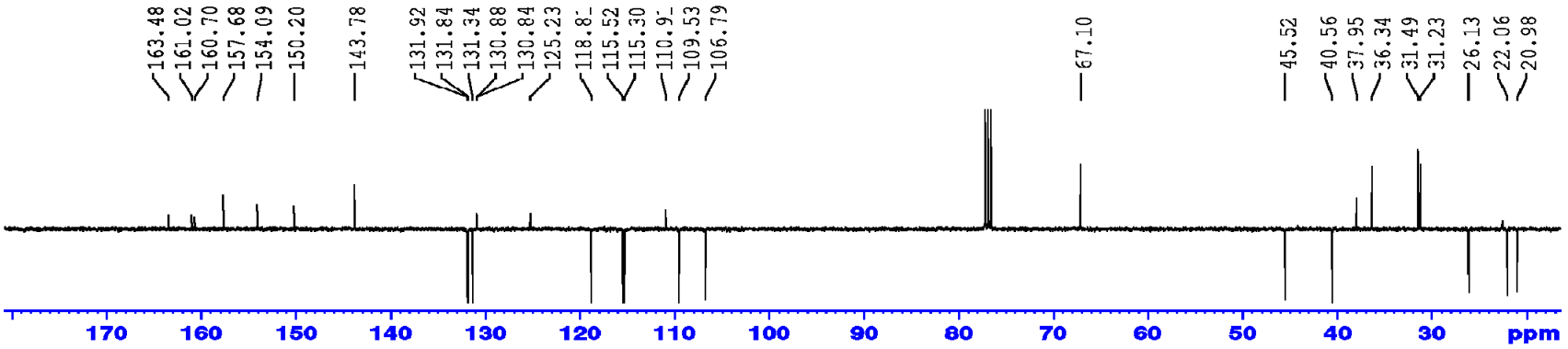




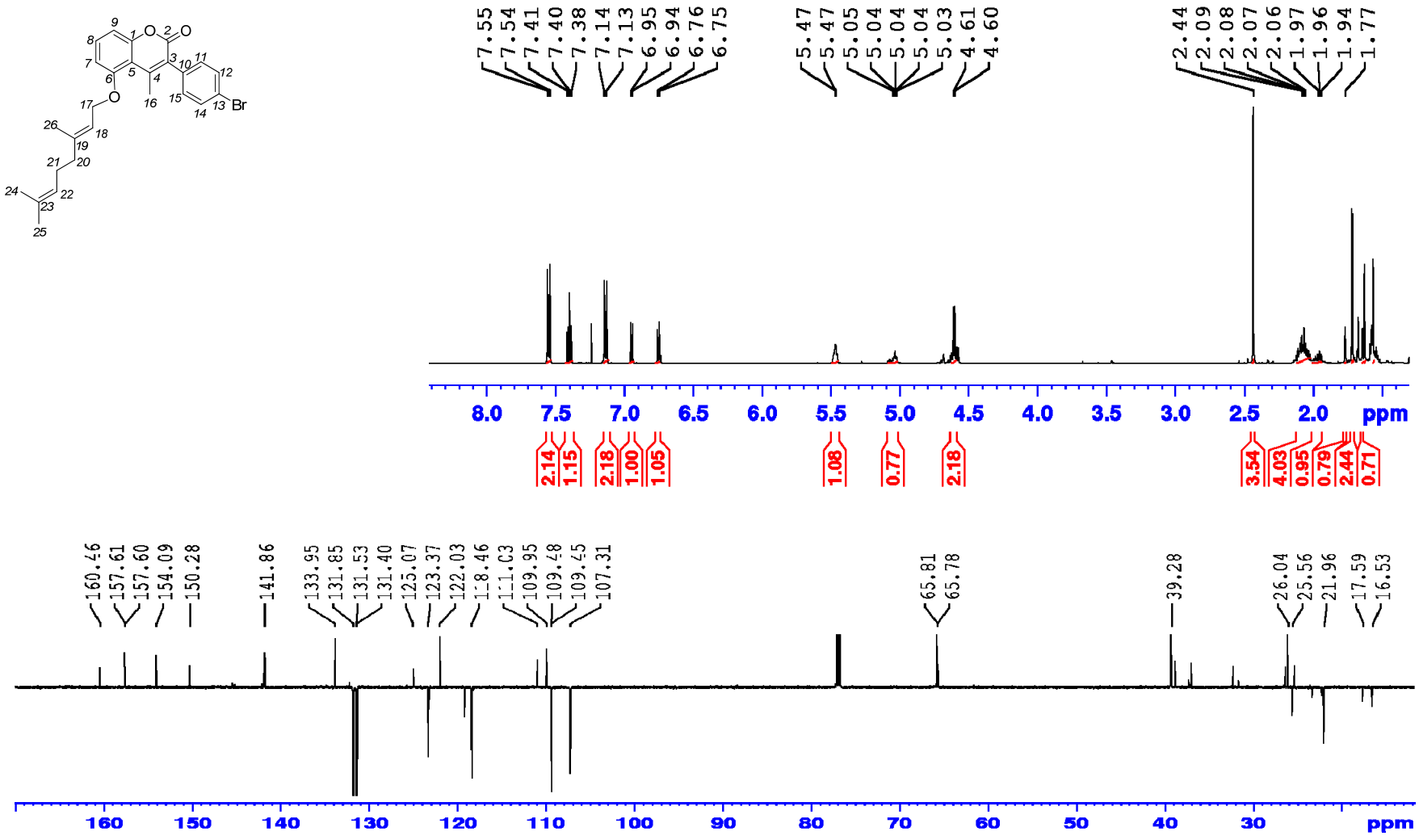
Compound **33d**



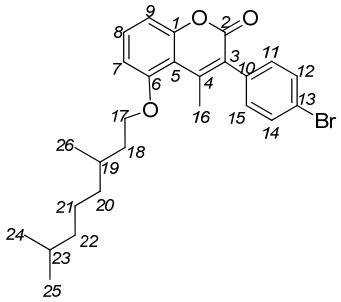


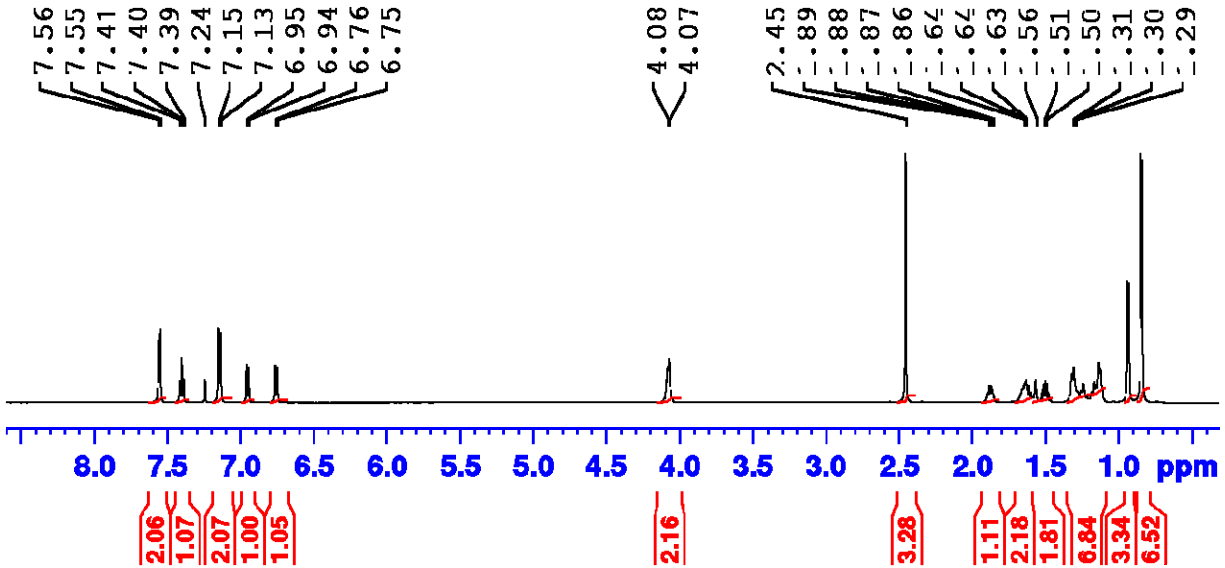


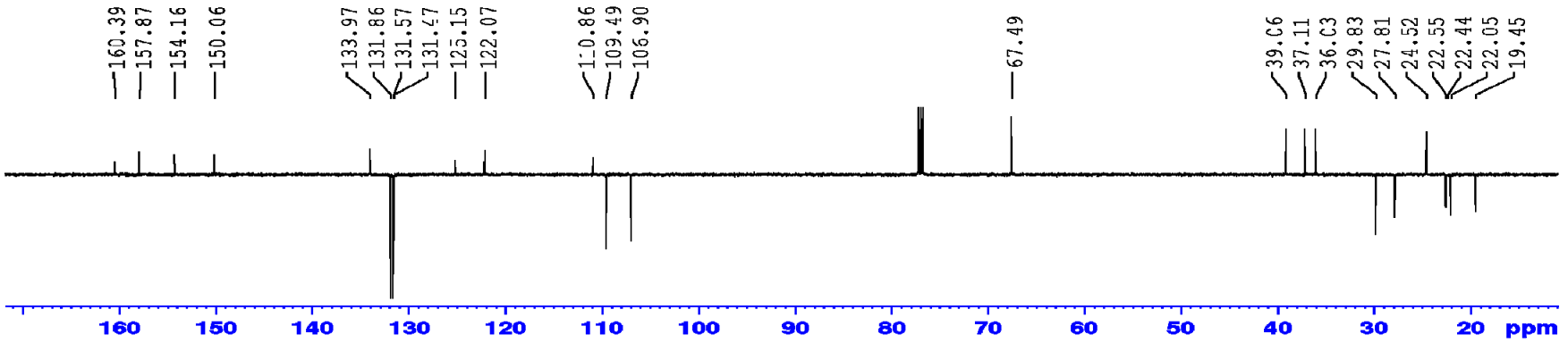
Compound **34a**



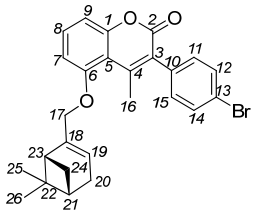
Compound **34b**

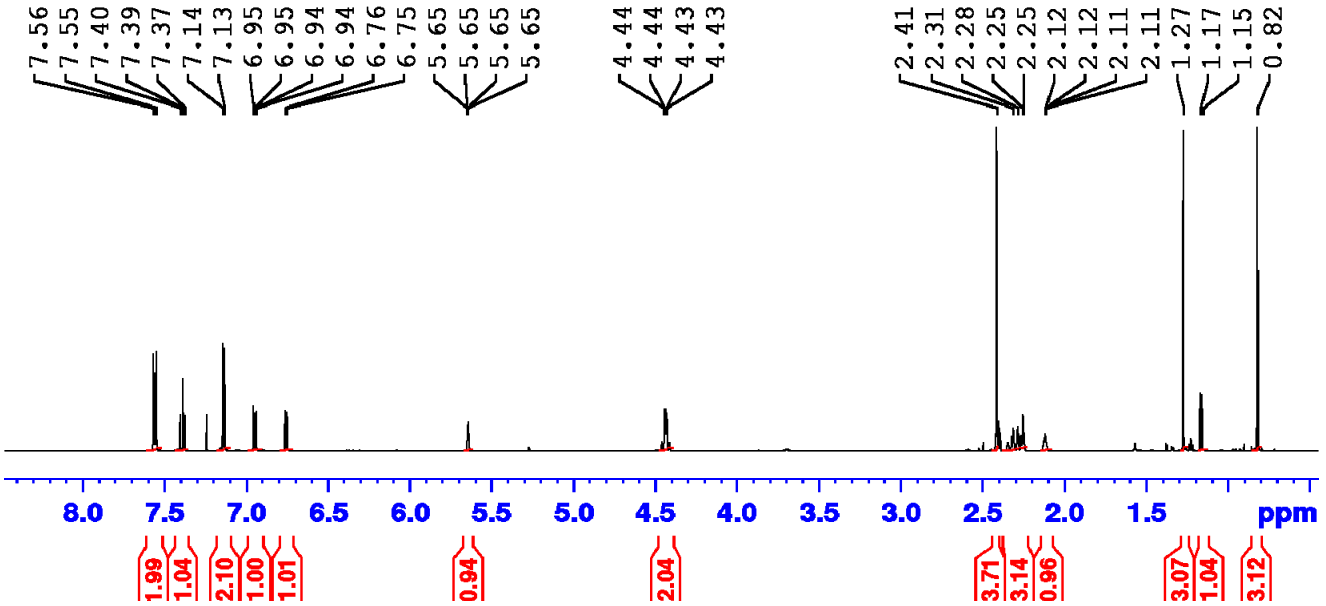


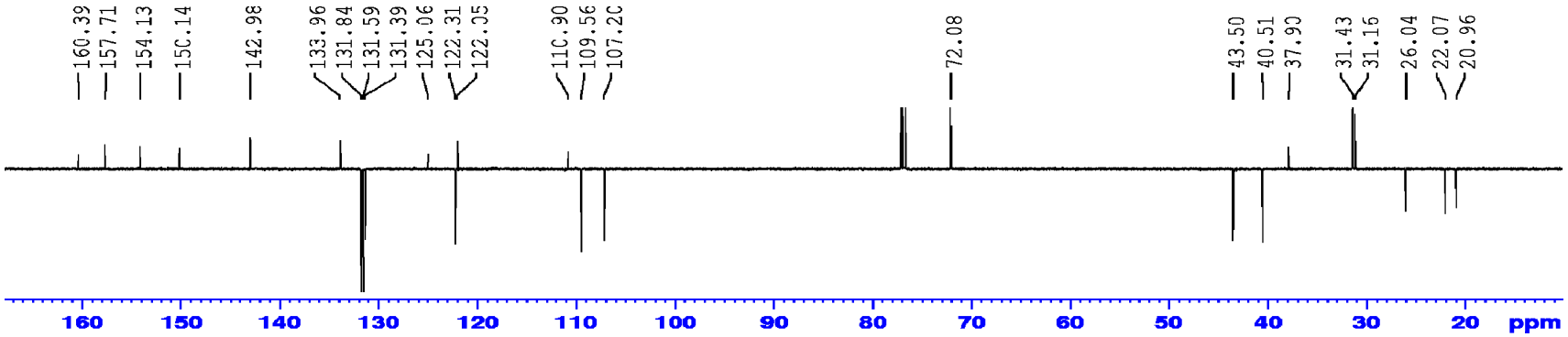




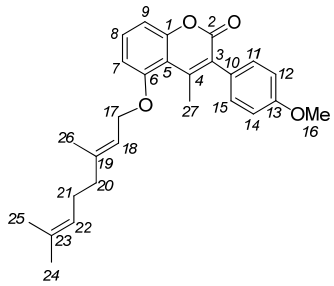
Compound **34c**

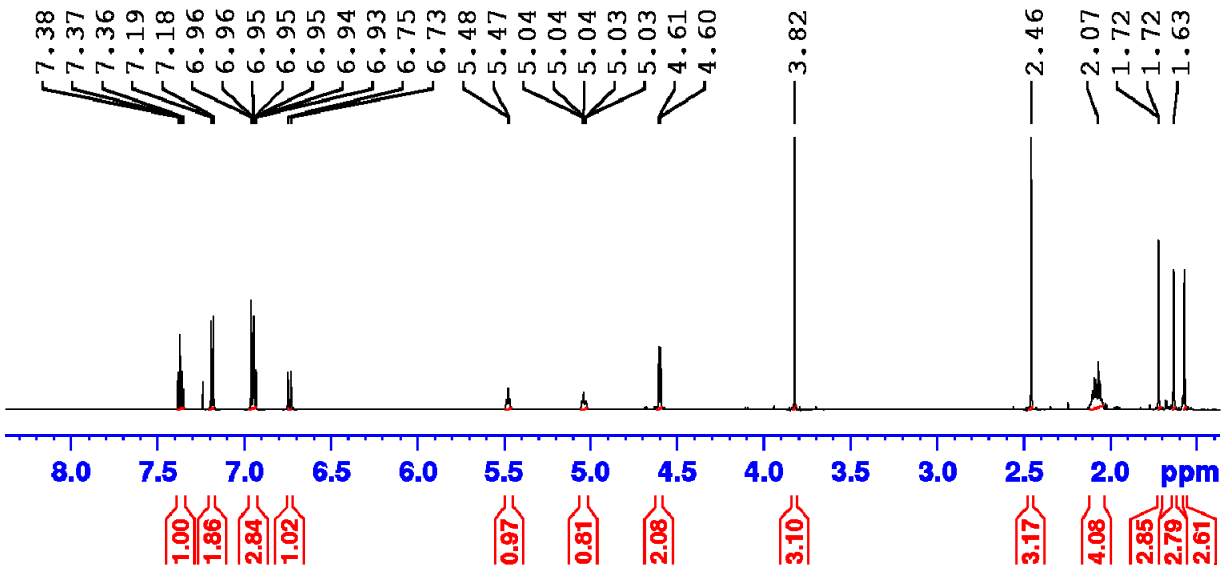


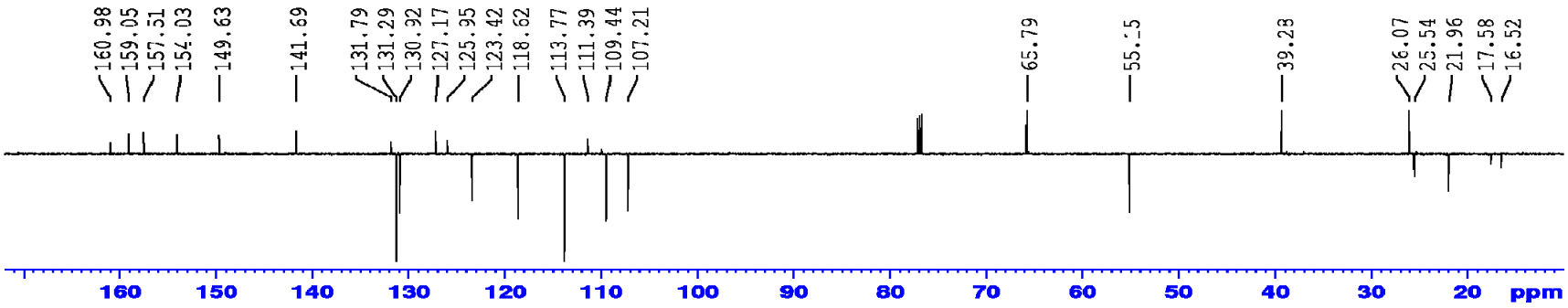




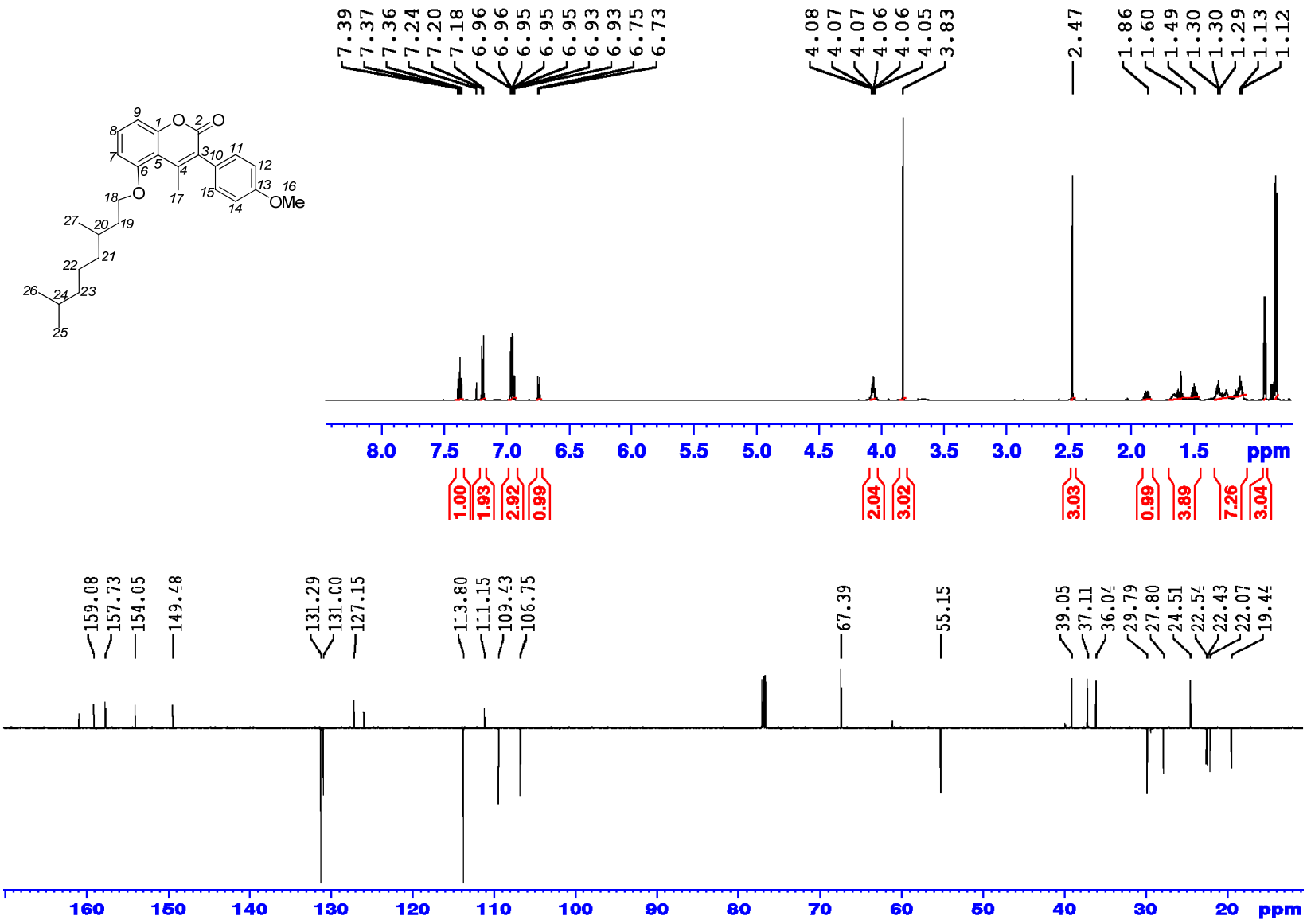
Compound **35a**



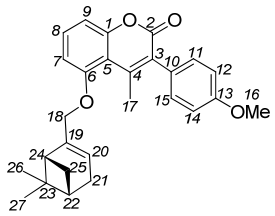


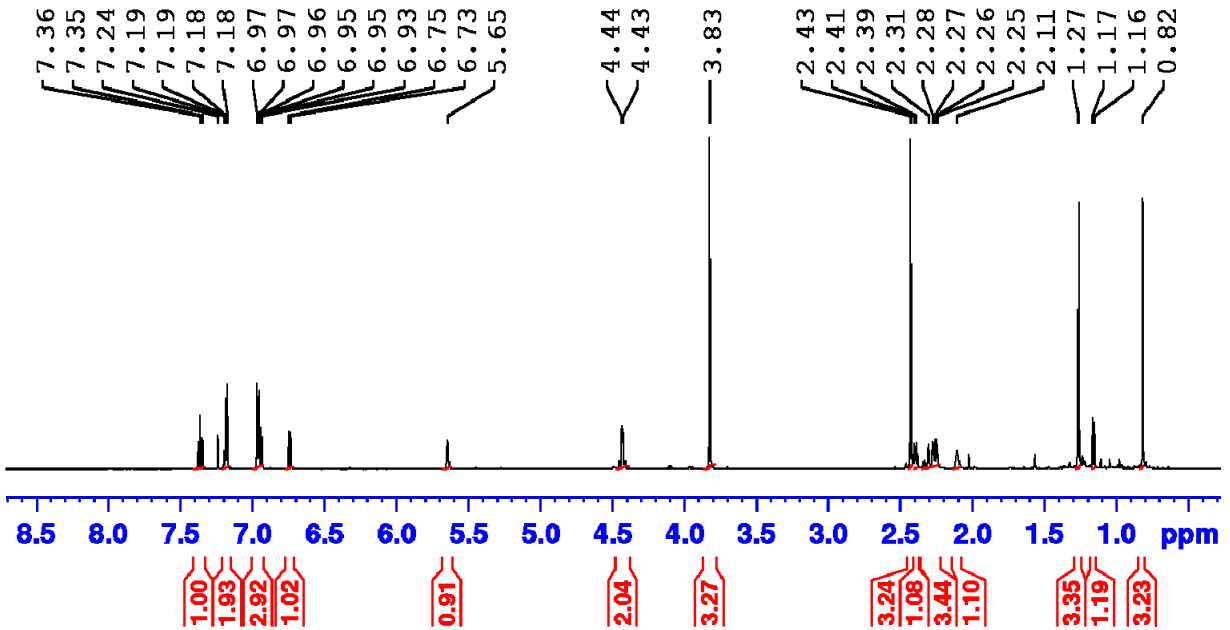


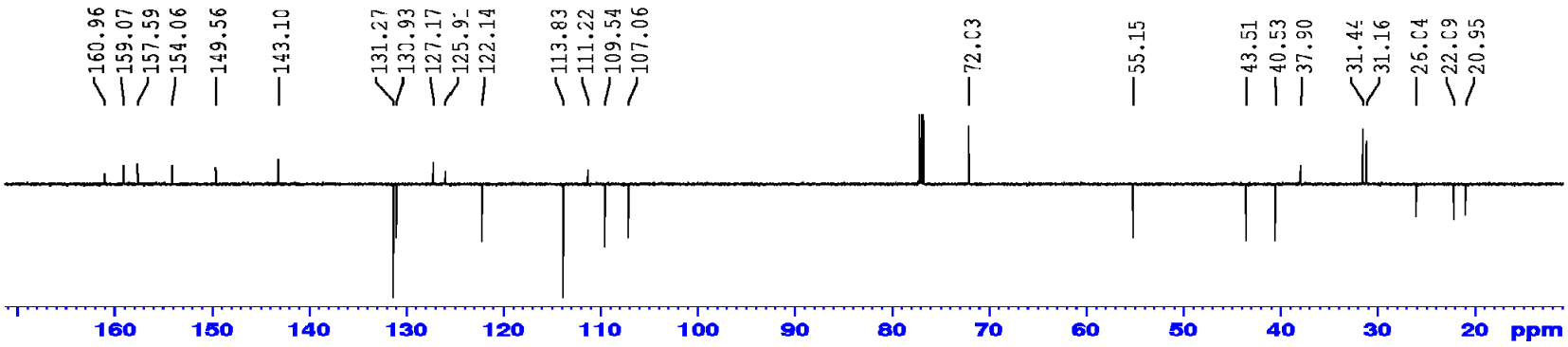
Compound **35b**



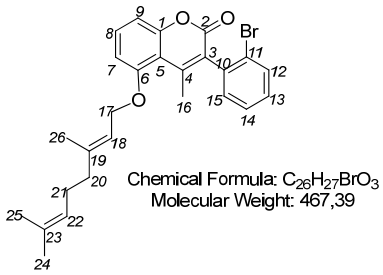
Compound **35c**

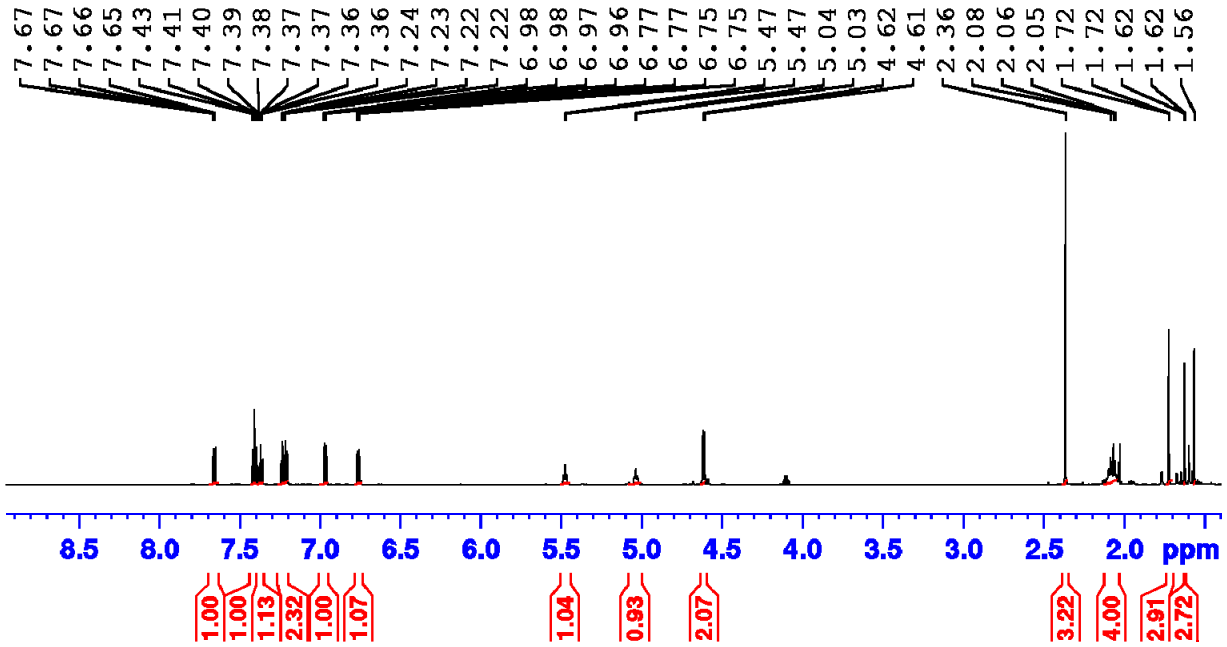


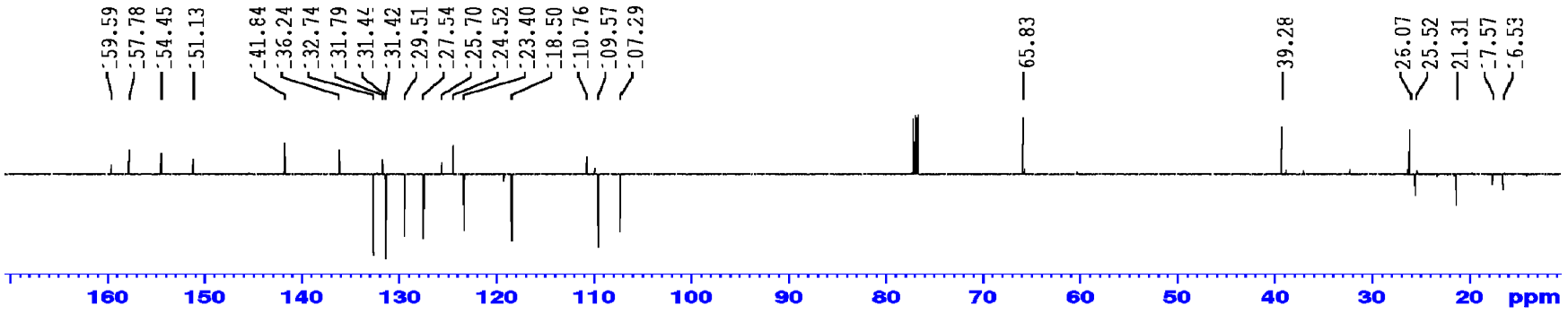




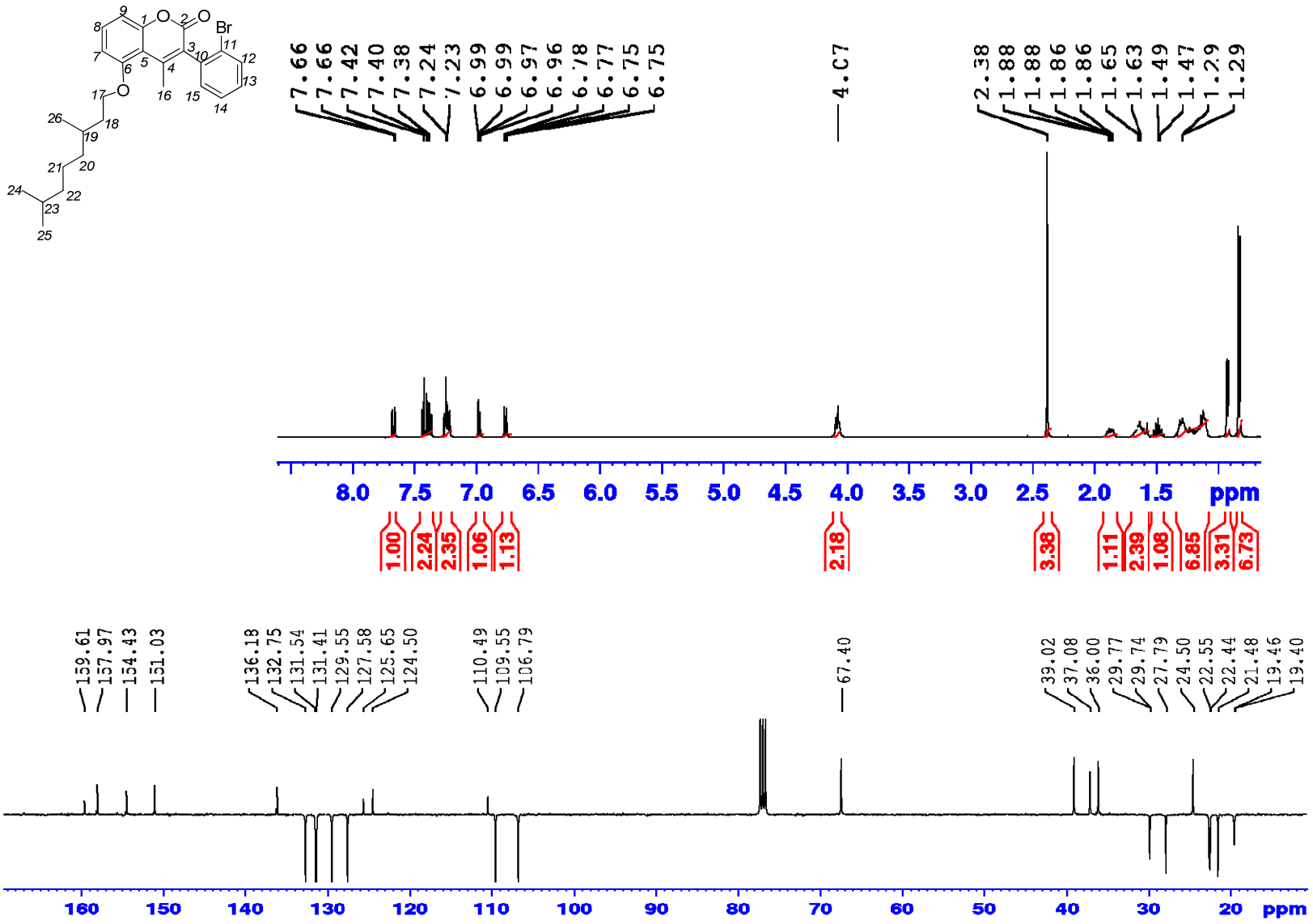
Compound **36a**



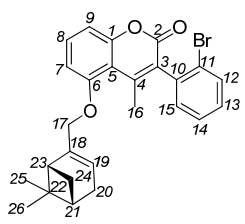




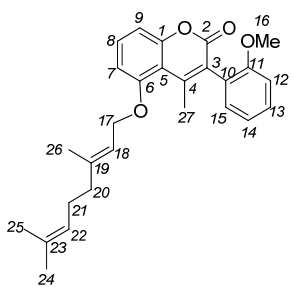
Compound **36b**

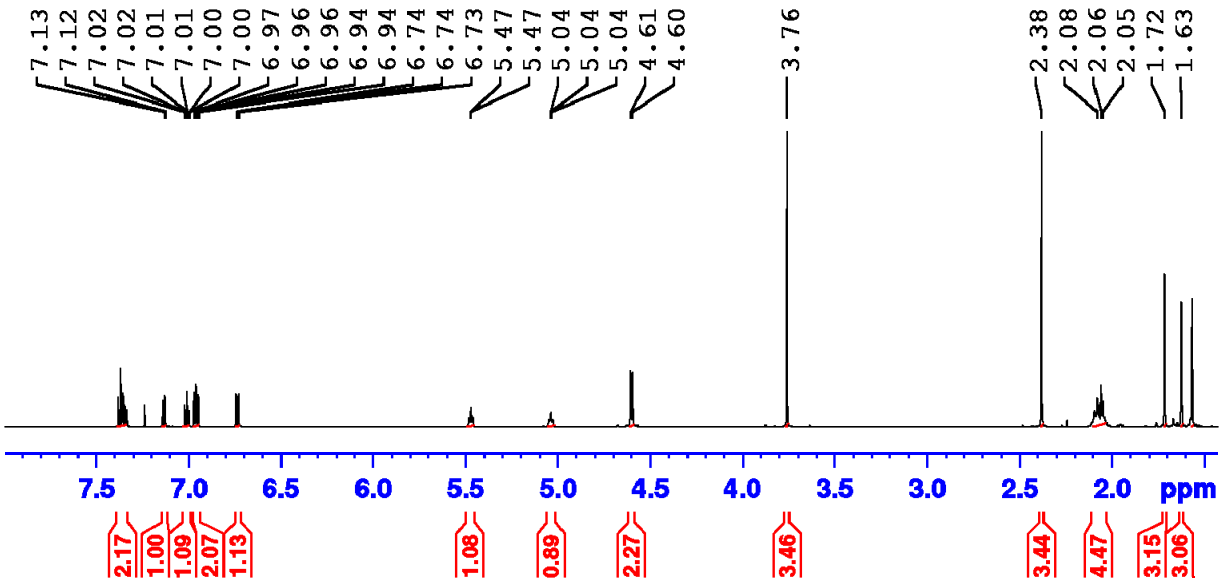


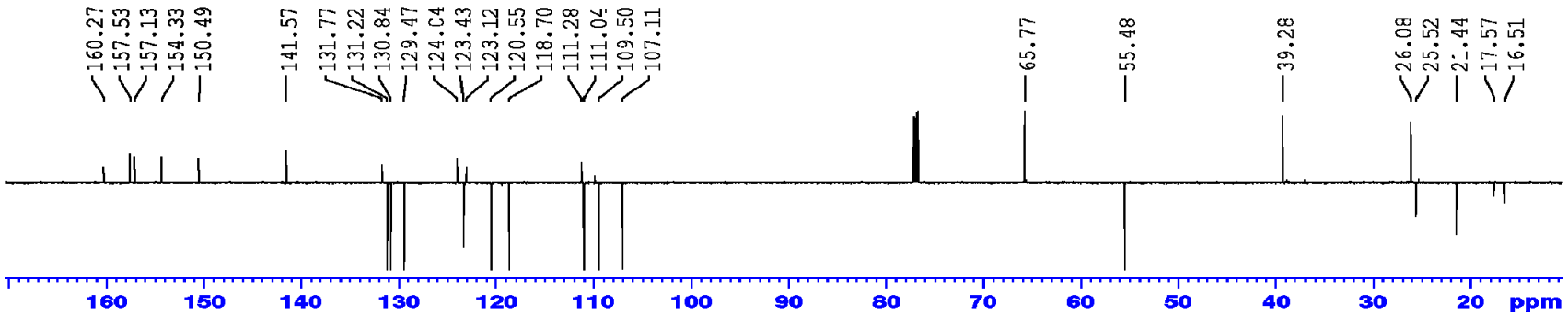
Compound **36c**



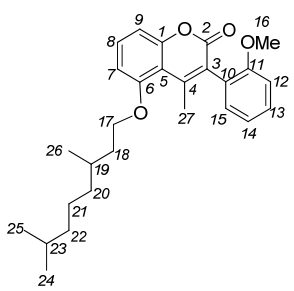
Compound **37a**



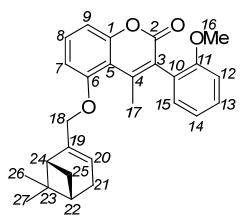




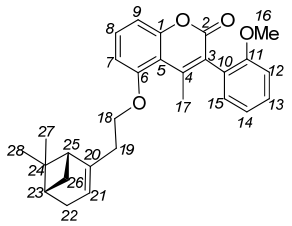
Compound **37b**

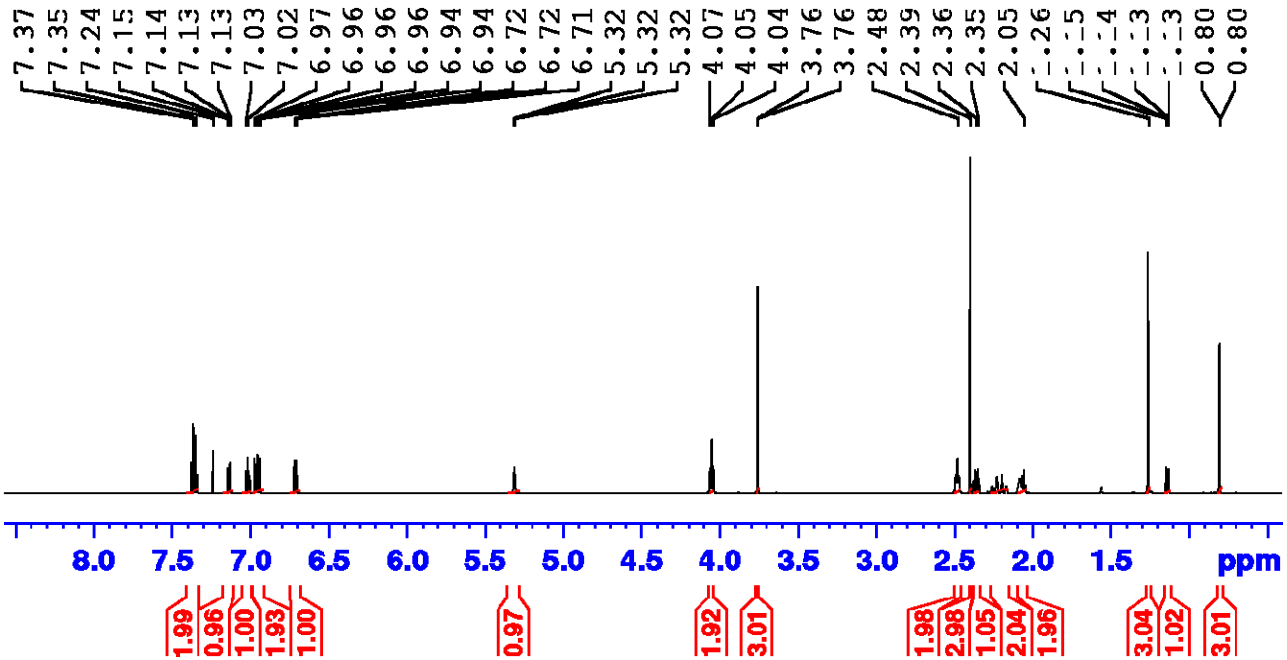


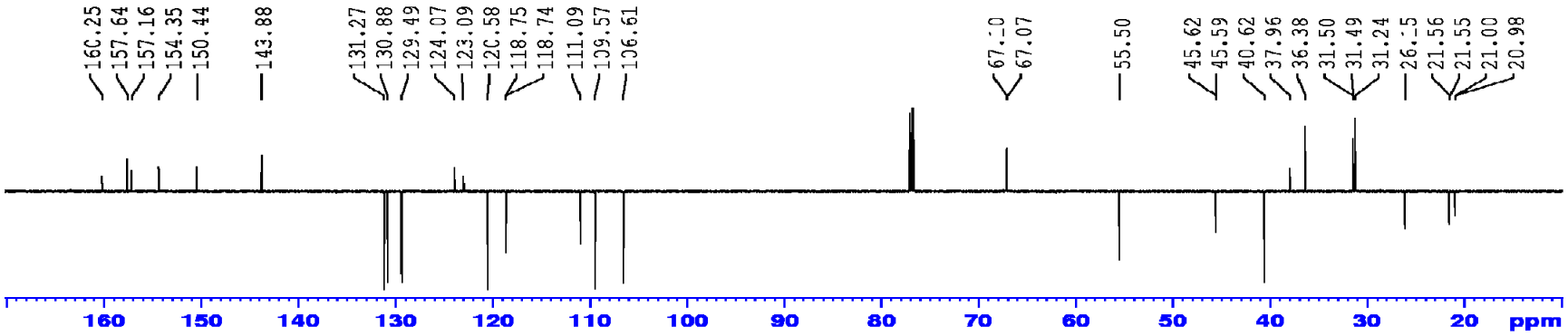
Compound **37c**



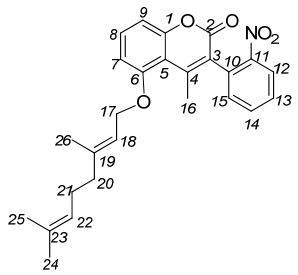
Compound **37d**



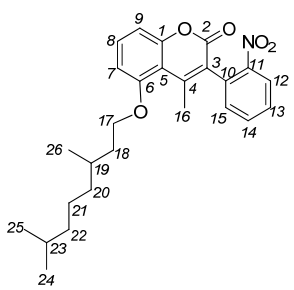




Compound **38a**



Compound **38b**



Compound **38c**

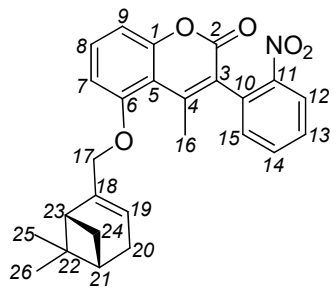


Table S1. The binding affinities as predicted by the scoring functions used to the catalytic Tdp1 binding pocket and their measured IC_{50} values.

Ligand	ASP	ChemPLP	CS	GS	IC_{50}, μM
34a	39	62	27.1	58.4	1.06±0.06
35a	35.9	60.8	26.1	57.2	6.63±1.12
37a	40.7	66.2	28.6	55.2	1.22±0.04
38a	40.9	61	25.5	52.1	1.03±0.08
33a	38.9	65.1	26.1	55.4	0.13±0.03
36a	35.9	63	28	61.6	0.85±0.15
35c	37.6	54.7	27	47.3	1.14±0.15
34c	34.8	54.3	26.8	47.6	0.9±0.07
37c	37.7	55.5	26.9	53.6	0.79±0.06
38c	37	54.4	27.2	53.5	3.83±0.29
33c	37	54.6	26.5	49.8	5.25±0.04
36c	35.9	54.1	29	53.3	4.36±1.14
37d	42.8	60	31.1	52.4	3.93±0.77
33b	39.2	62.3	25.3	52.9	0.29±0.07
35b	38.3	63.2	25.3	58.2	0.37±0.16
36b	36.5	58.1	28.4	56.3	≥50
37b	39.8	61.2	28.2	56.4	2.60±0.35
38b	41.2	62.7	28.0	58.3	2.18±0.13
33d	36.8	57.6	27.7	52.6	2.51±0.14

Table S2. The molecular descriptors and their corresponding Known Drug Indexes 2a and 2b ($KDI_{2a/2b}$).

	RB	MW	HD	HA	Log P	PSA	KDI_{2A}	KDI_{2B}	IC_{50}, µM
34a	8	418.5	0	4	6.8	44.8	3.92	0.04	1.06±0.06
35a	8	433.5	0	4.25	6.0	79.0	4.25	0.09	6.63±1.12
37a	7	406.5	0	3.25	6.7	36.1	3.90	0.04	1.22±0.04
38a	7	467.4	0	3.25	7.1	40.2	3.63	0.02	1.03±0.08
33a	5	416.5	0	4	6.0	46.9	4.48	0.12	0.13±0.03
36a	4	465.4	0	3.25	6.5	39.4	3.95	0.05	0.85±0.15
35c	5	416.5	0	4	6.1	44.5	4.44	0.11	1.14±0.15
34c	5	431.5	0	4.25	5.3	78.6	4.81	0.22	0.9±0.07
37c	4	404.5	0	3.25	6.2	39.4	4.26	0.09	0.79±0.06
38c	4	465.4	0	3.25	6.4	39.4	3.96	0.05	3.83±0.29
33c	6	430.5	0	4	6.4	44.6	4.24	0.08	5.25±0.04
36c	9	410.5	0	3.25	7.0	39.6	3.55	0.02	4.36±1.14
37d	10	422.6	0	4	6.8	47.0	3.60	0.02	3.93±0.77
33b	7	467.4	0	3.25	7.0	36.1	3.59	0.02	0.29±0.07
35b	8	418.5	0	4	6.7	47.0	3.95	0.05	0.37±0.16
36b	9	457.4	0	3.25	6.9	44.4	3.41	0.02	≥50
37b	10	408.5	0	4	6.6	48.8	3.71	0.03	2.60±0.35
38b	10	423.5	0	4.25	5.8	83.2	4.01	0.05	2.18±0.13
33d	5	404.5	0	3.25	6.2	43.2	4.28	0.09	2.51±0.14

Table S3. Definition of lead-like, drug-like and Known Drug Space (KDS) in terms of molecular descriptors. The values given are the maxima for each descriptor for the volumes of chemical space used.

	Lead-like Space	**Drug-like Space**	**Known Drug Space**
Molecular weight (g mol^{-1})	300	500	800
Lipophilicity (Log P)	3	5	6.5
Hydrogen bond donors (HD)	3	5	7
Hydrogen bond acceptors (HA)	3	10	15
Polar surface area ($Å^2$) (PSA)	60	140	180
Rotatable bonds (RB)	3	10	17