

New Inhibitors of Respiratory Syncytial Virus (RSV) Replication Based on Monoterpene-Substituted Arylcoumarins

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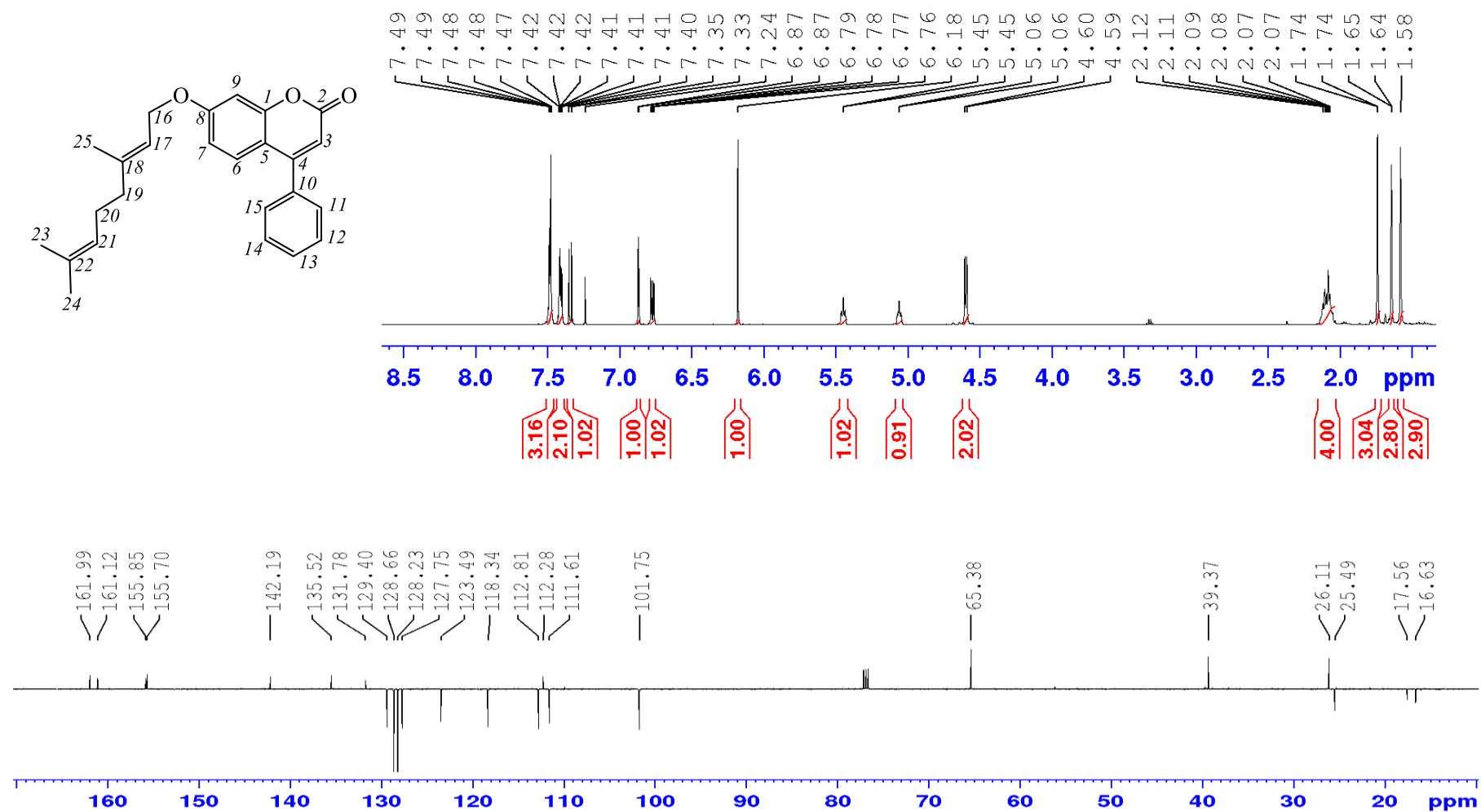
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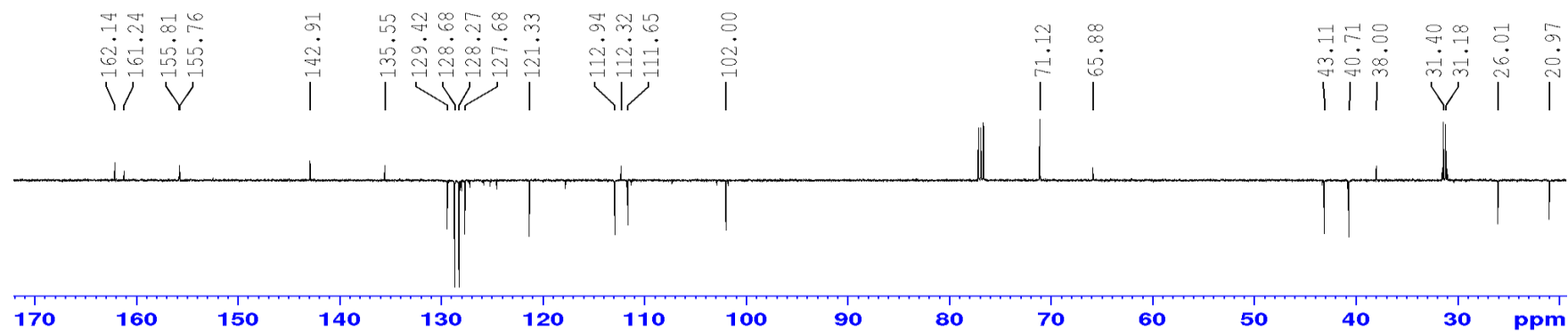
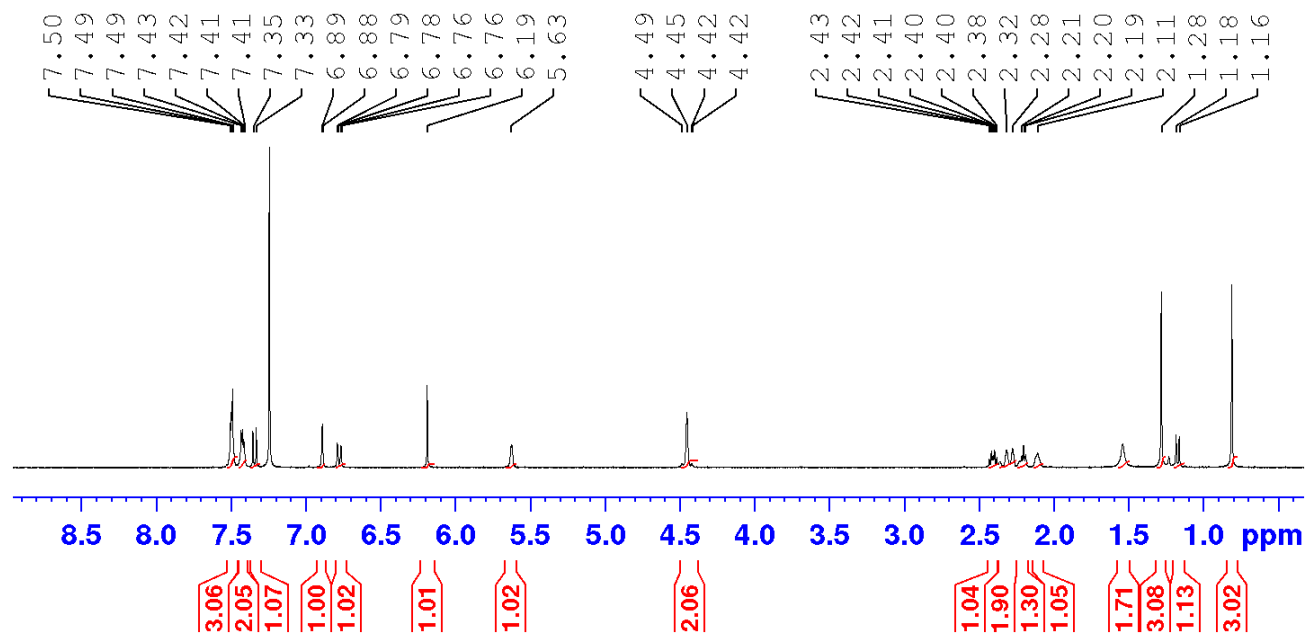
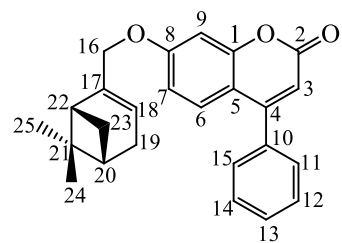
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1. NMR ¹H and ¹³C spectra of the compounds **14-17**, **21** and **22**.
2. Table S1: Analysis of structural descriptors and pharmacophoric features of the ligand as a function of linker length.
3. Table S2: Analysis of structural descriptors and pharmacophoric features of the ligand as a function of the nature of the substituent
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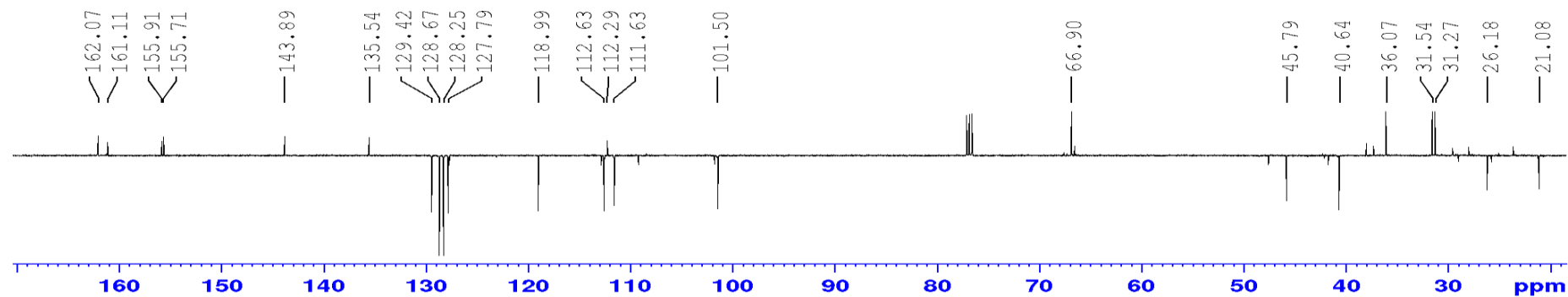
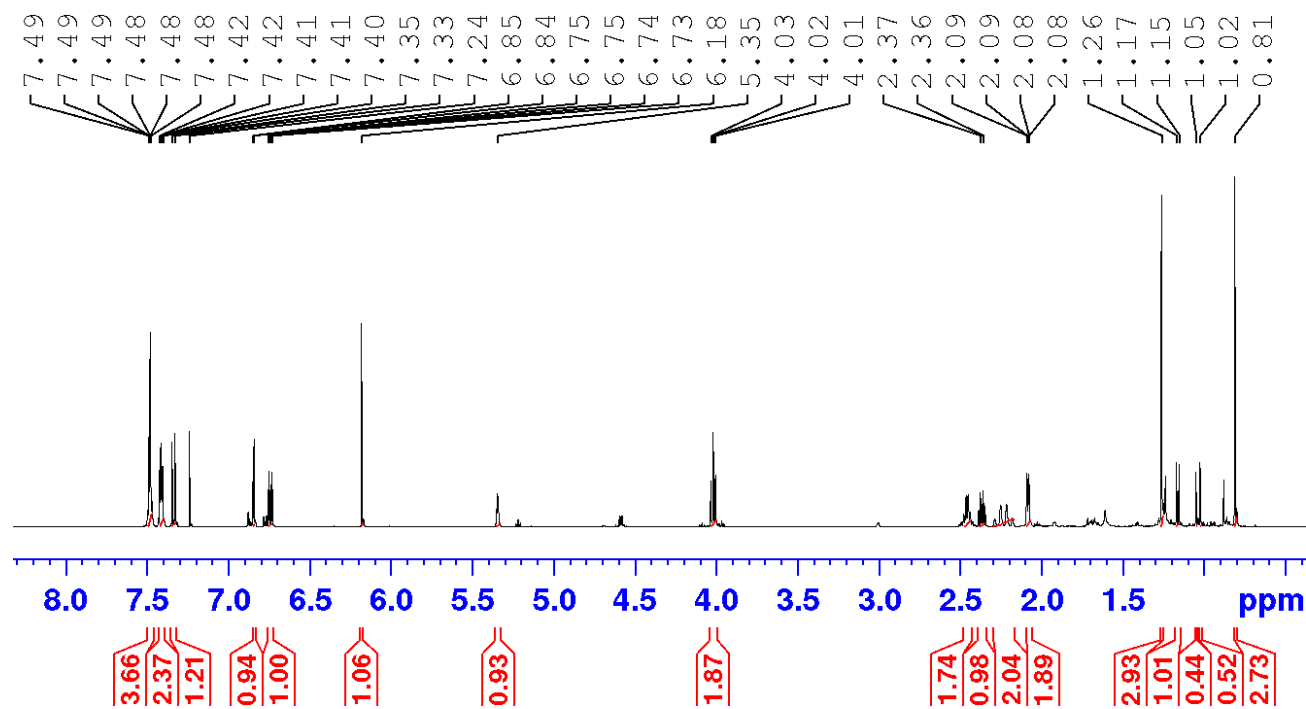
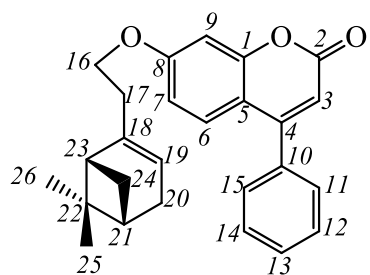
Compound **14a**



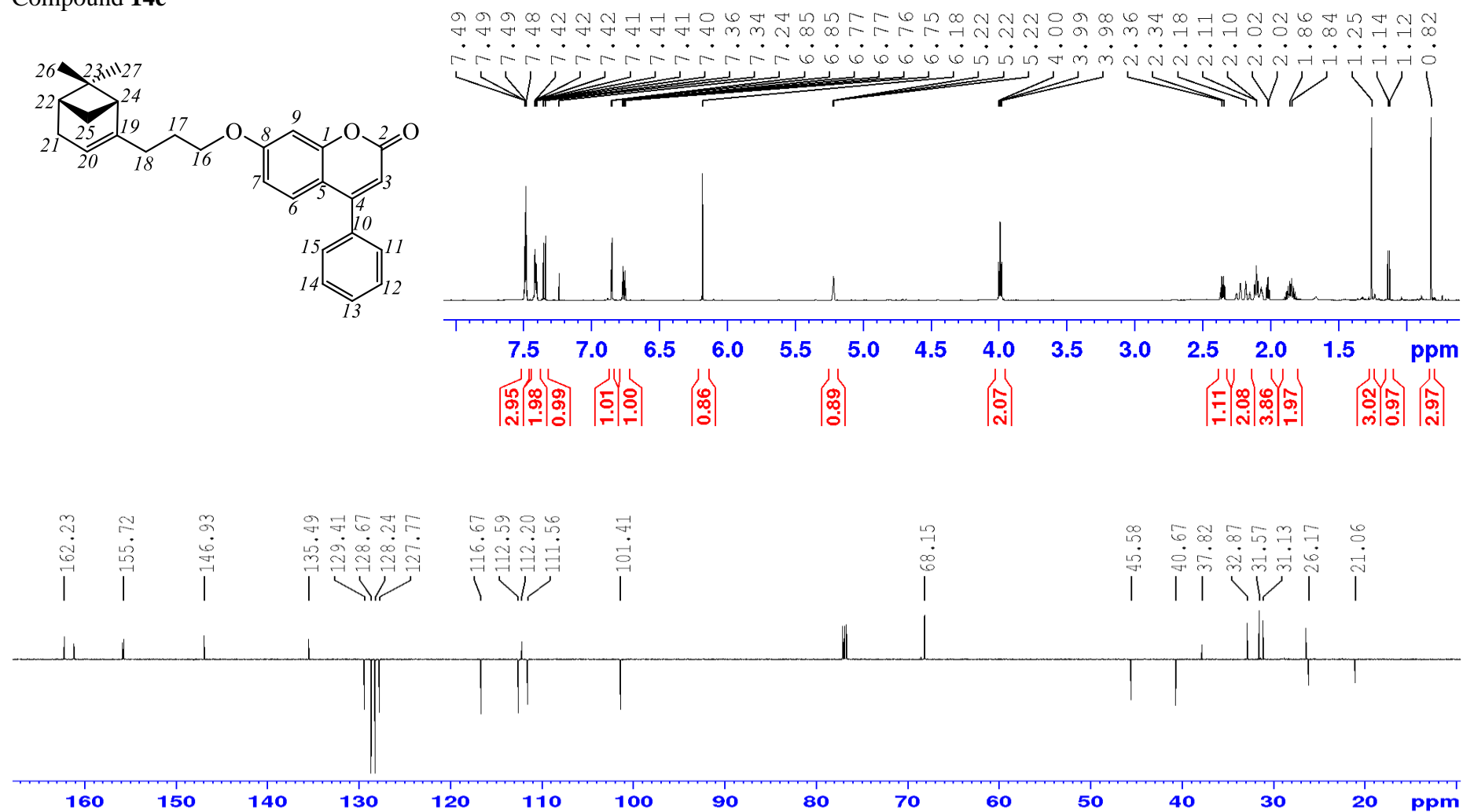
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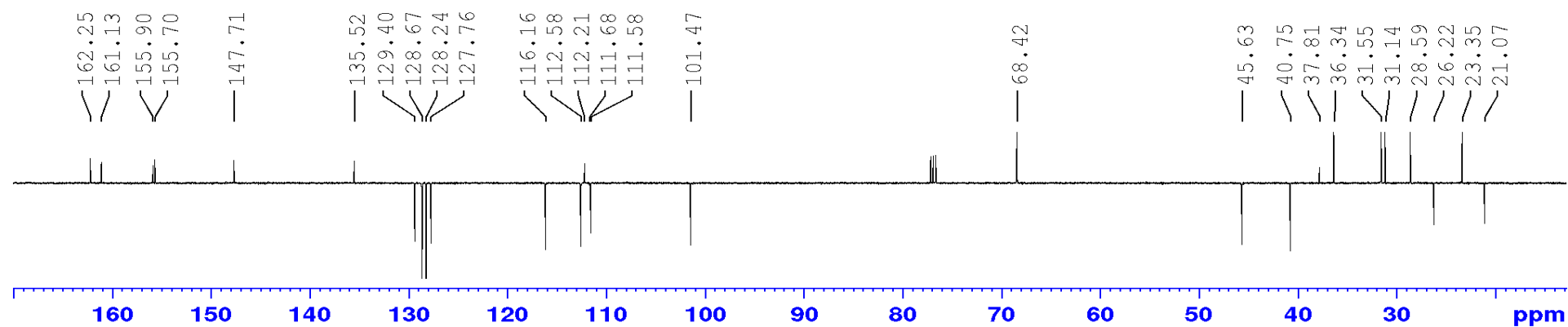
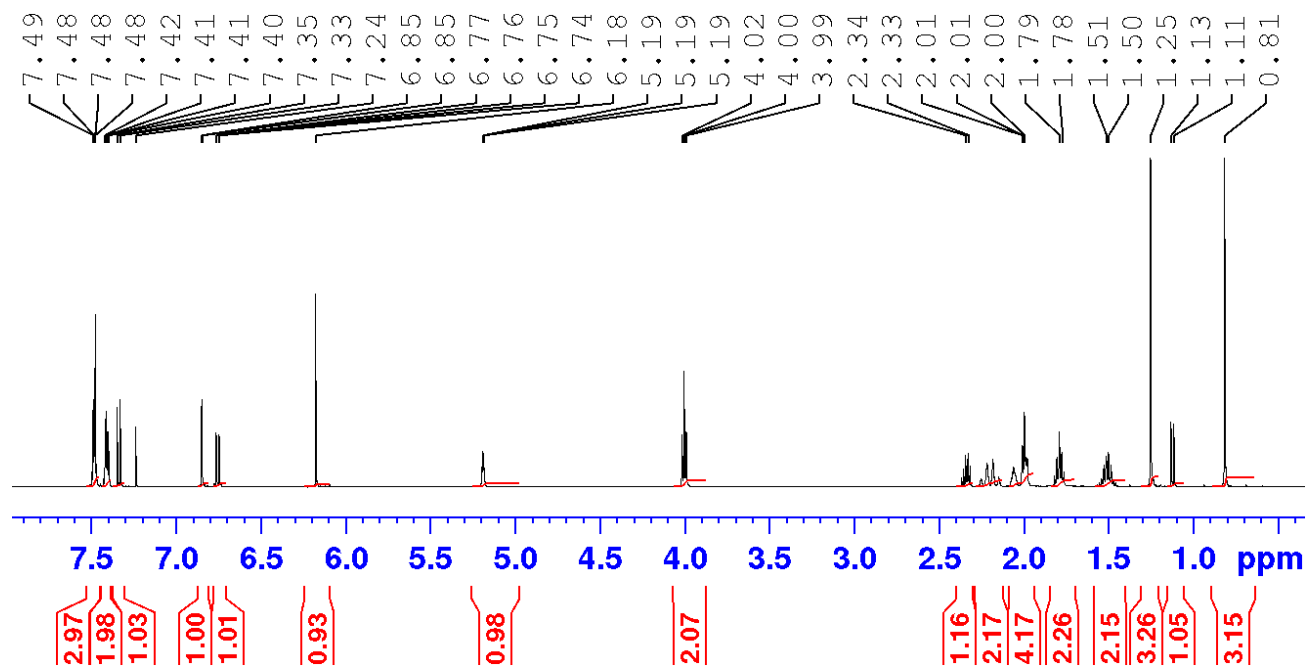
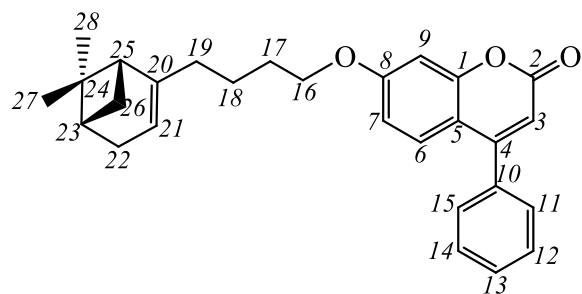
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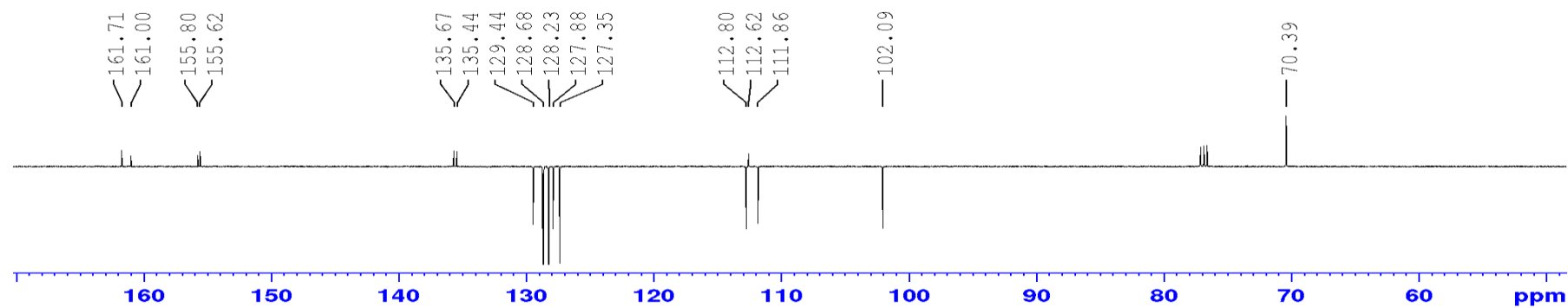
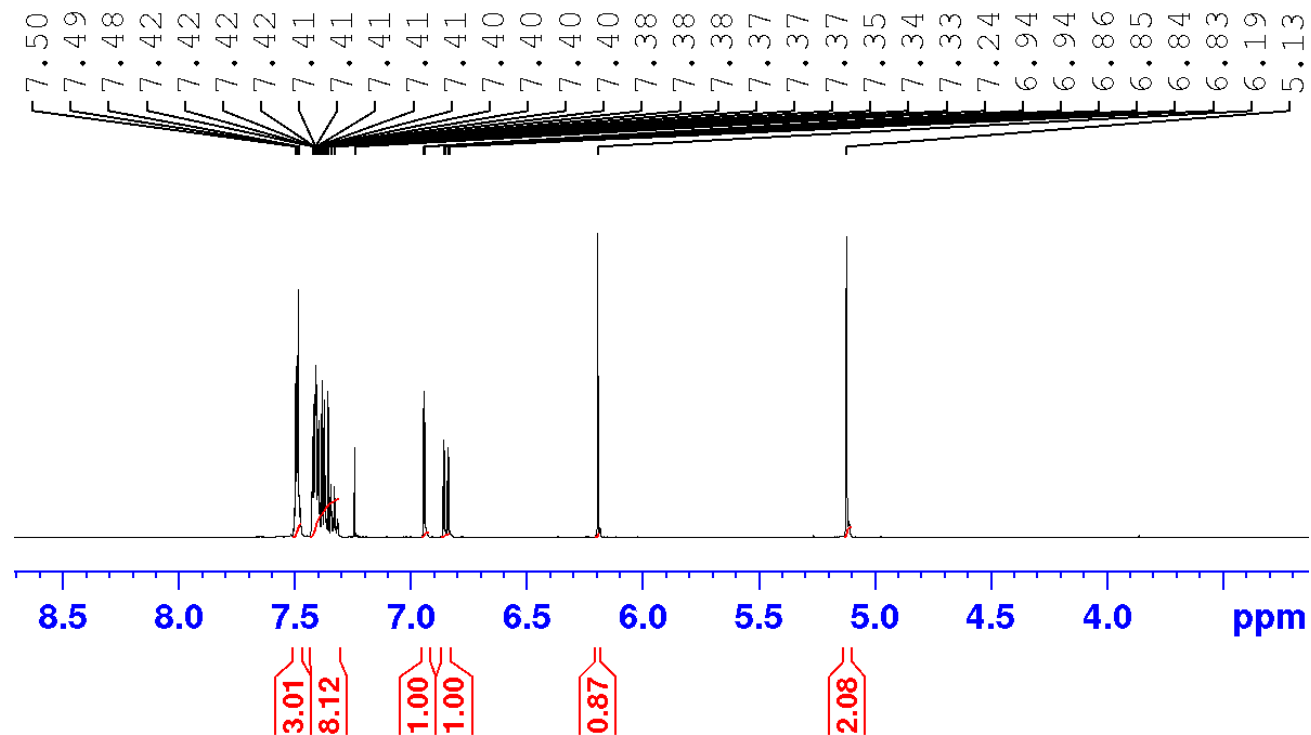
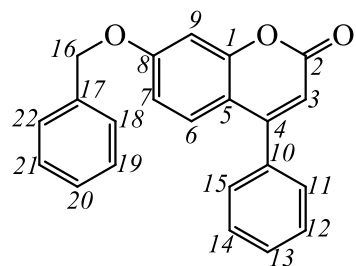
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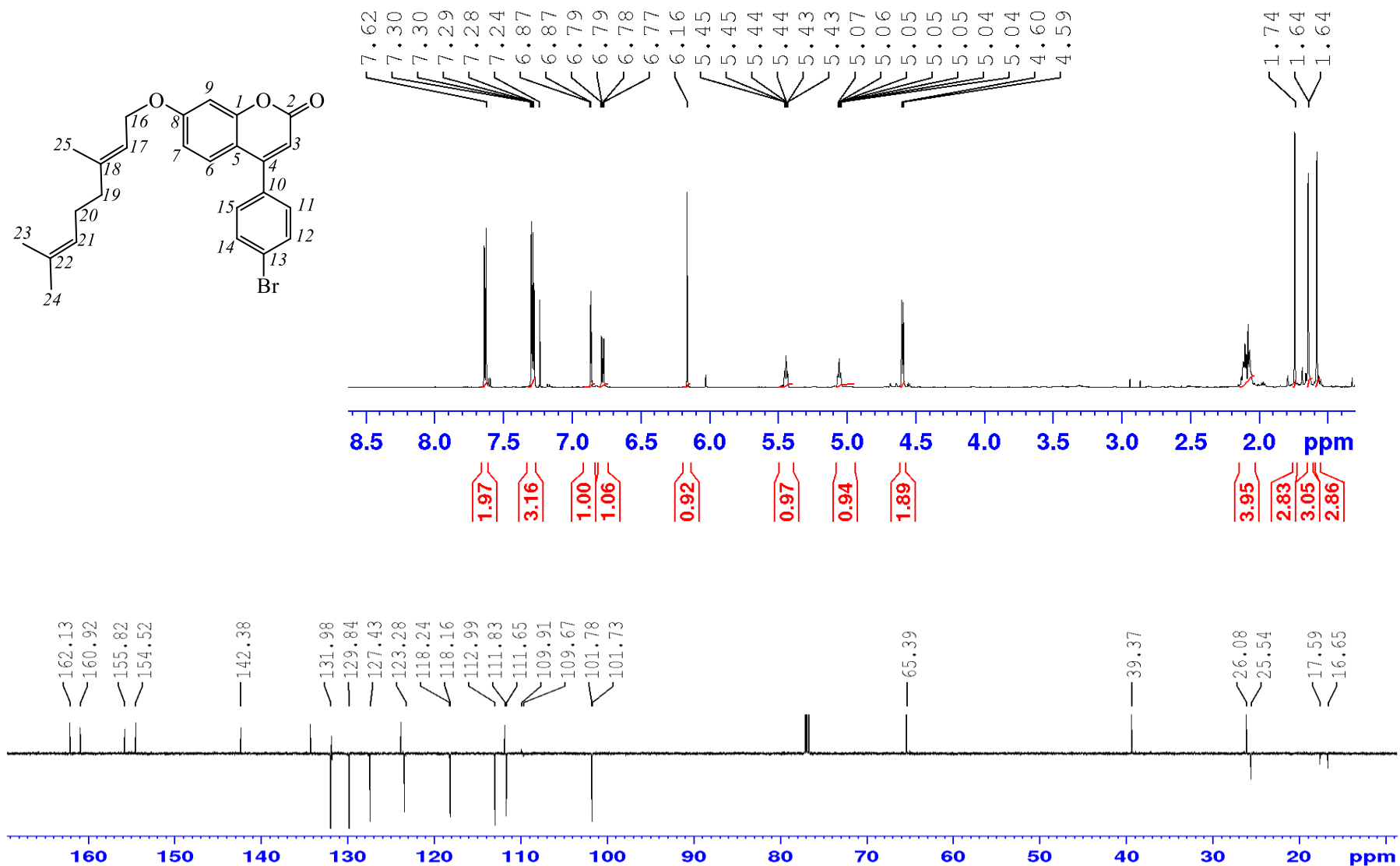
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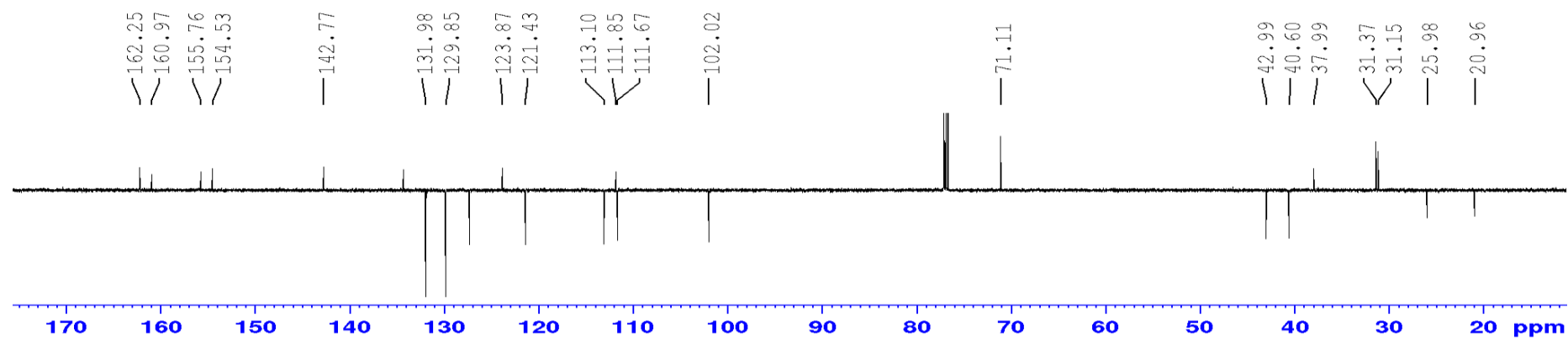
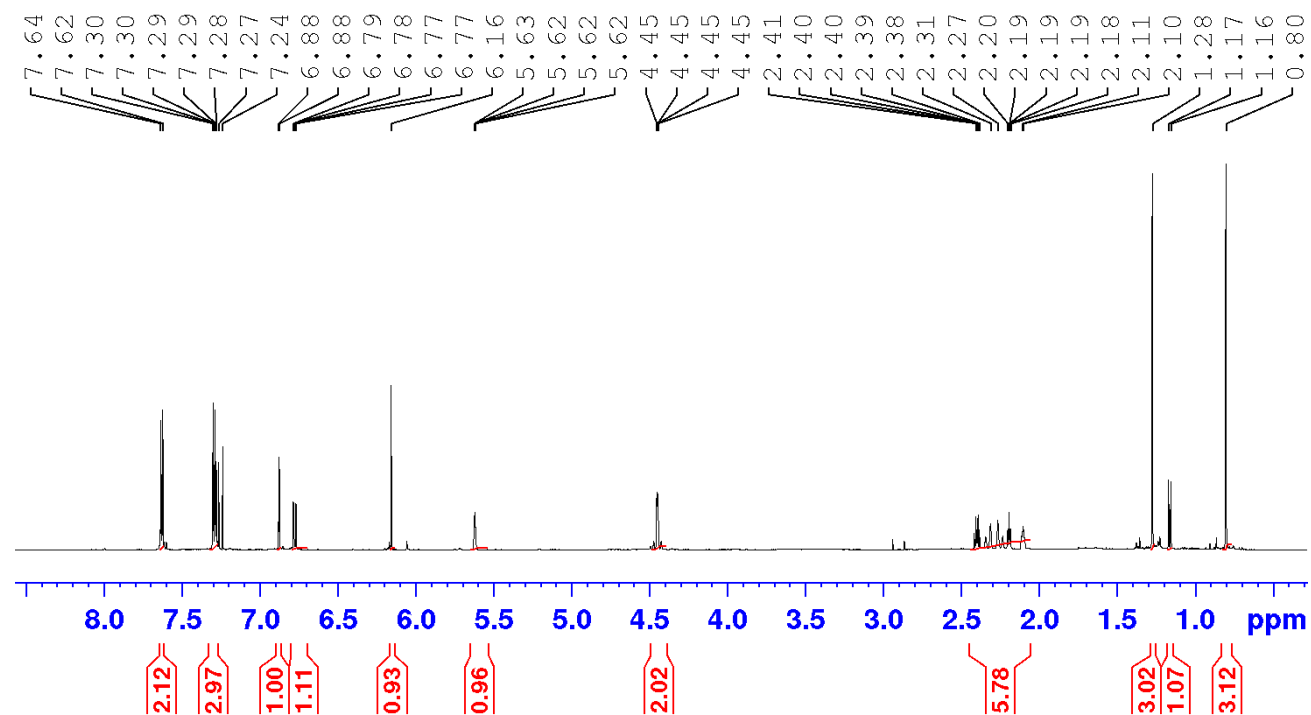
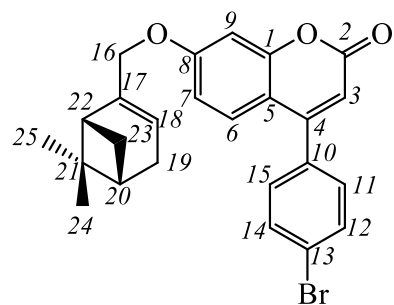
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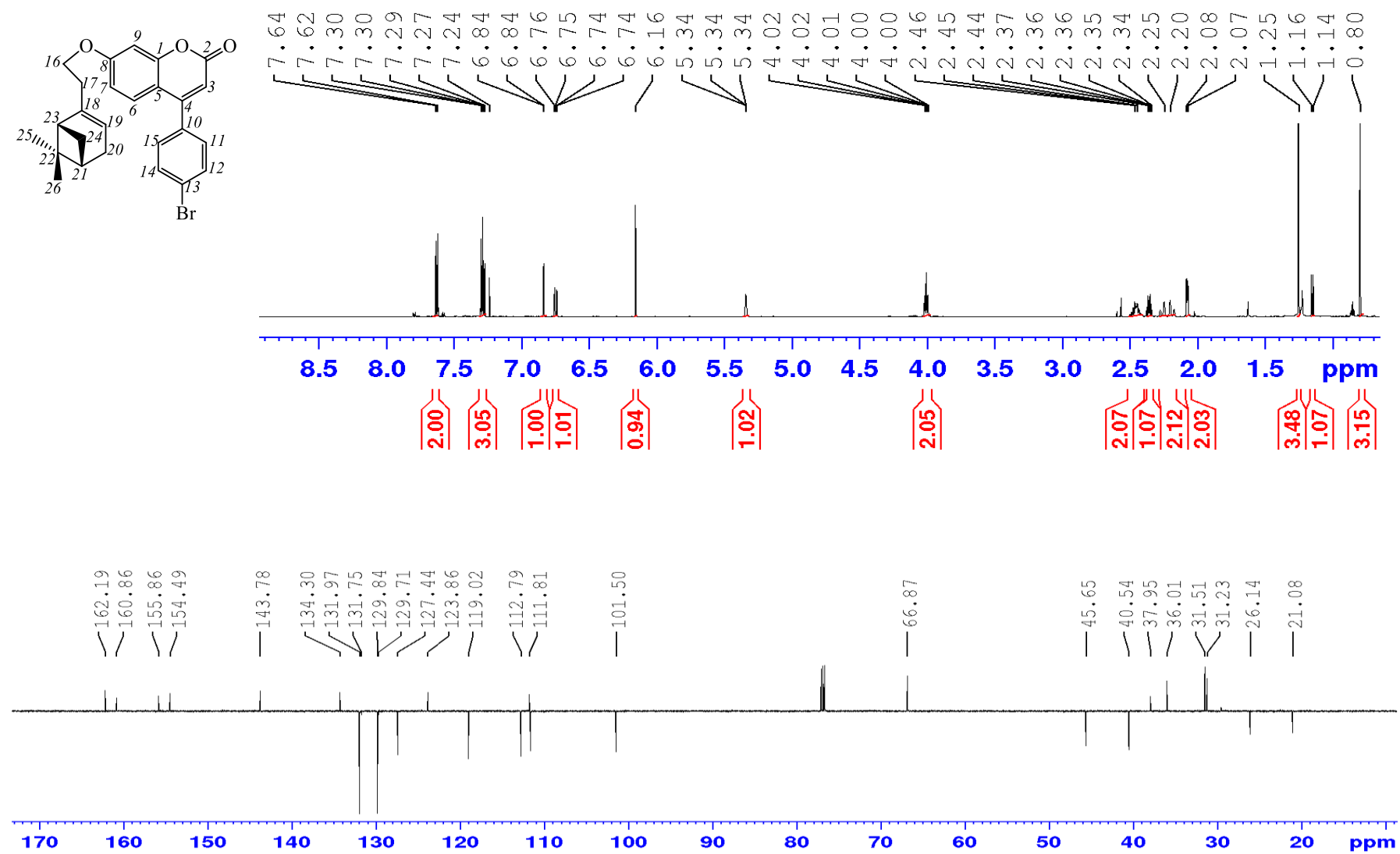
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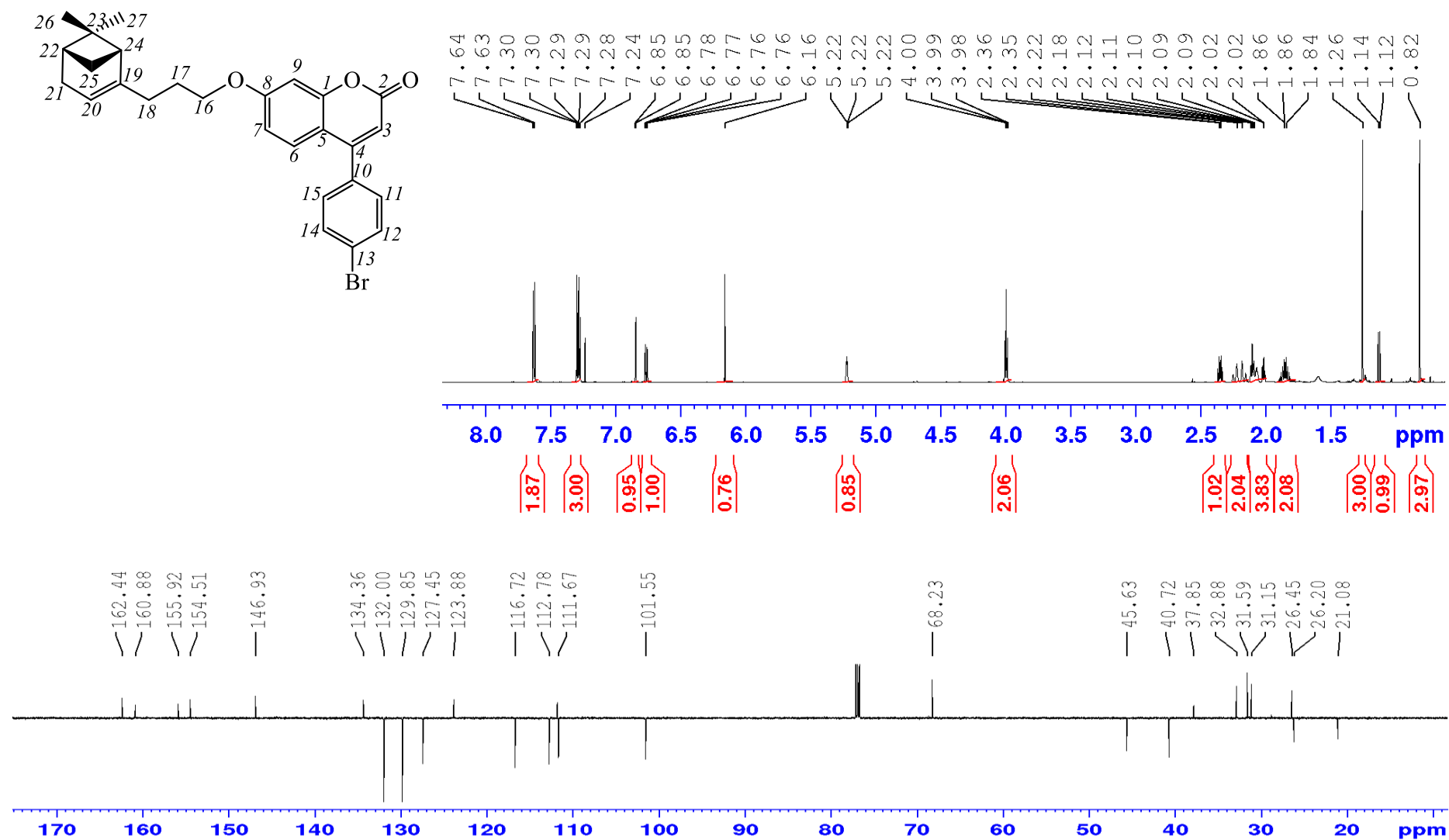
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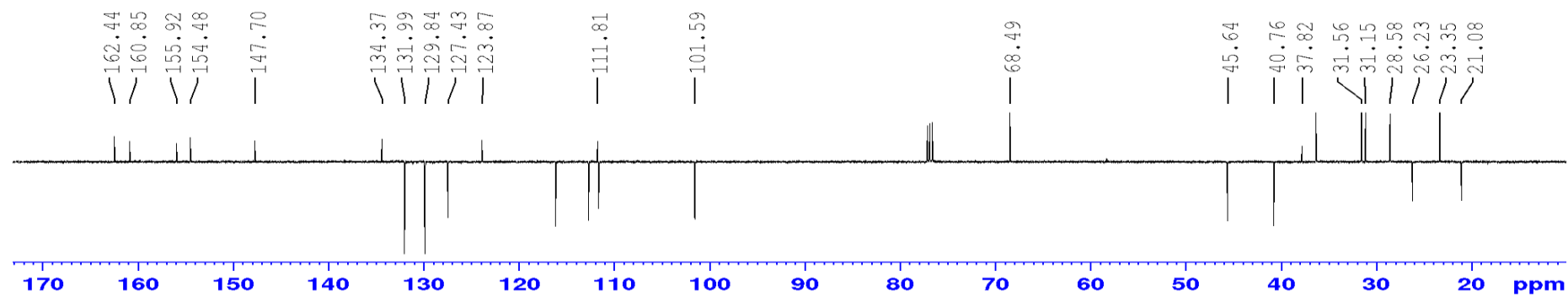
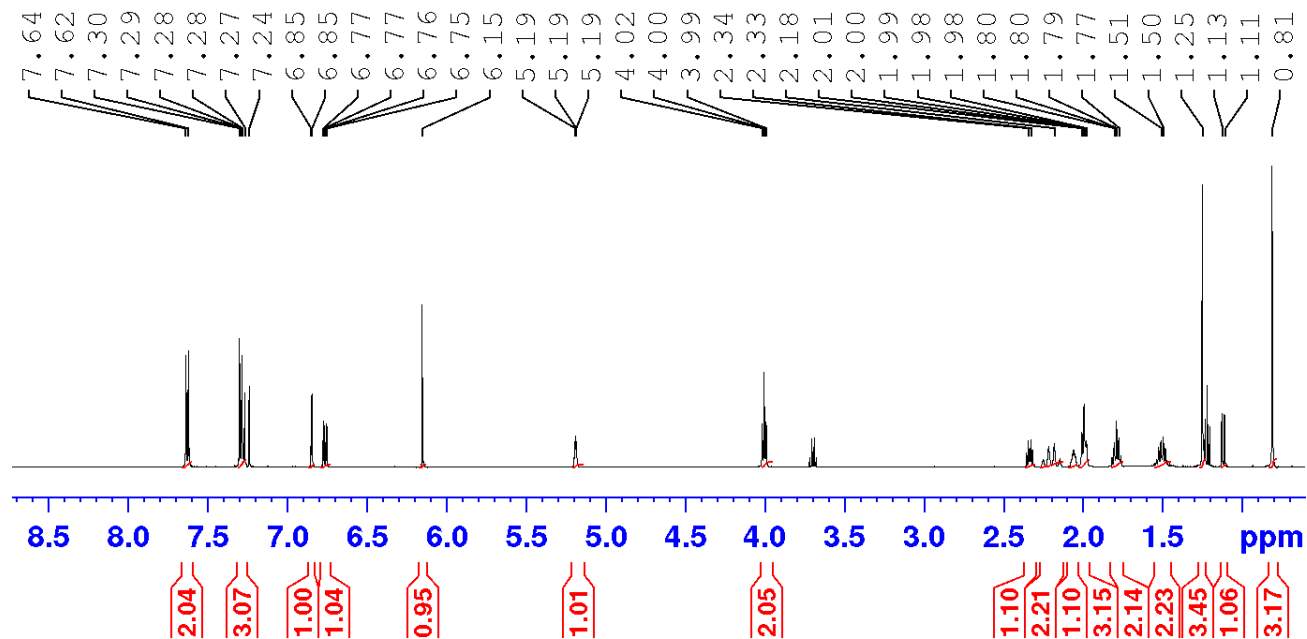
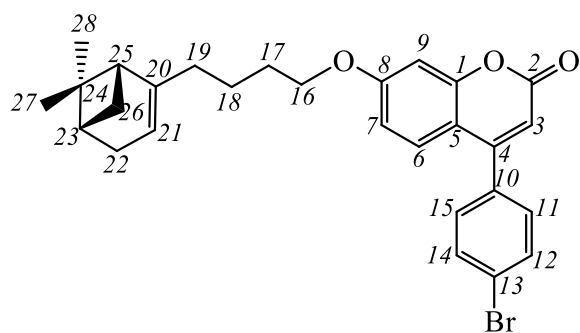
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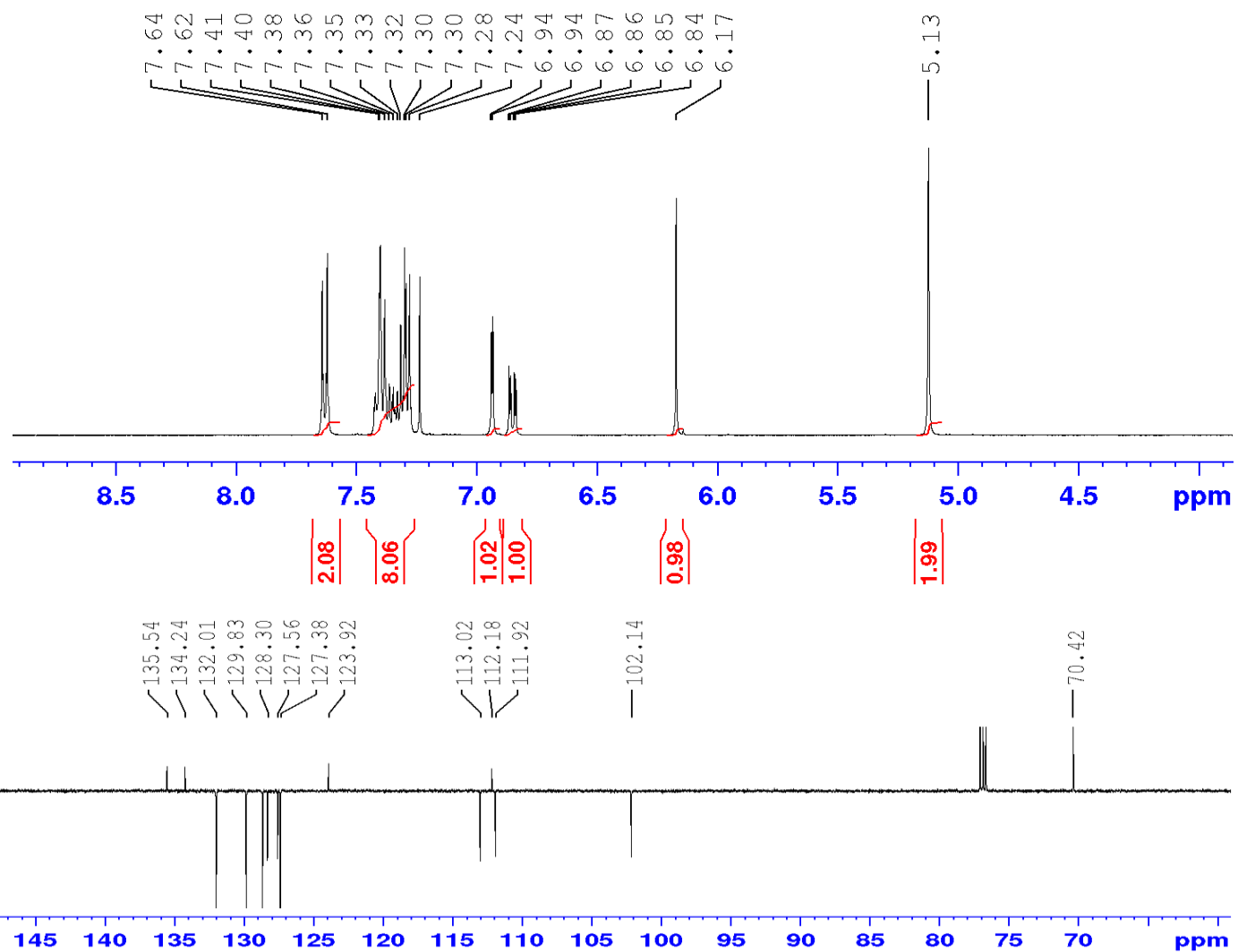
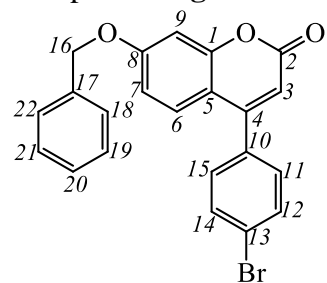
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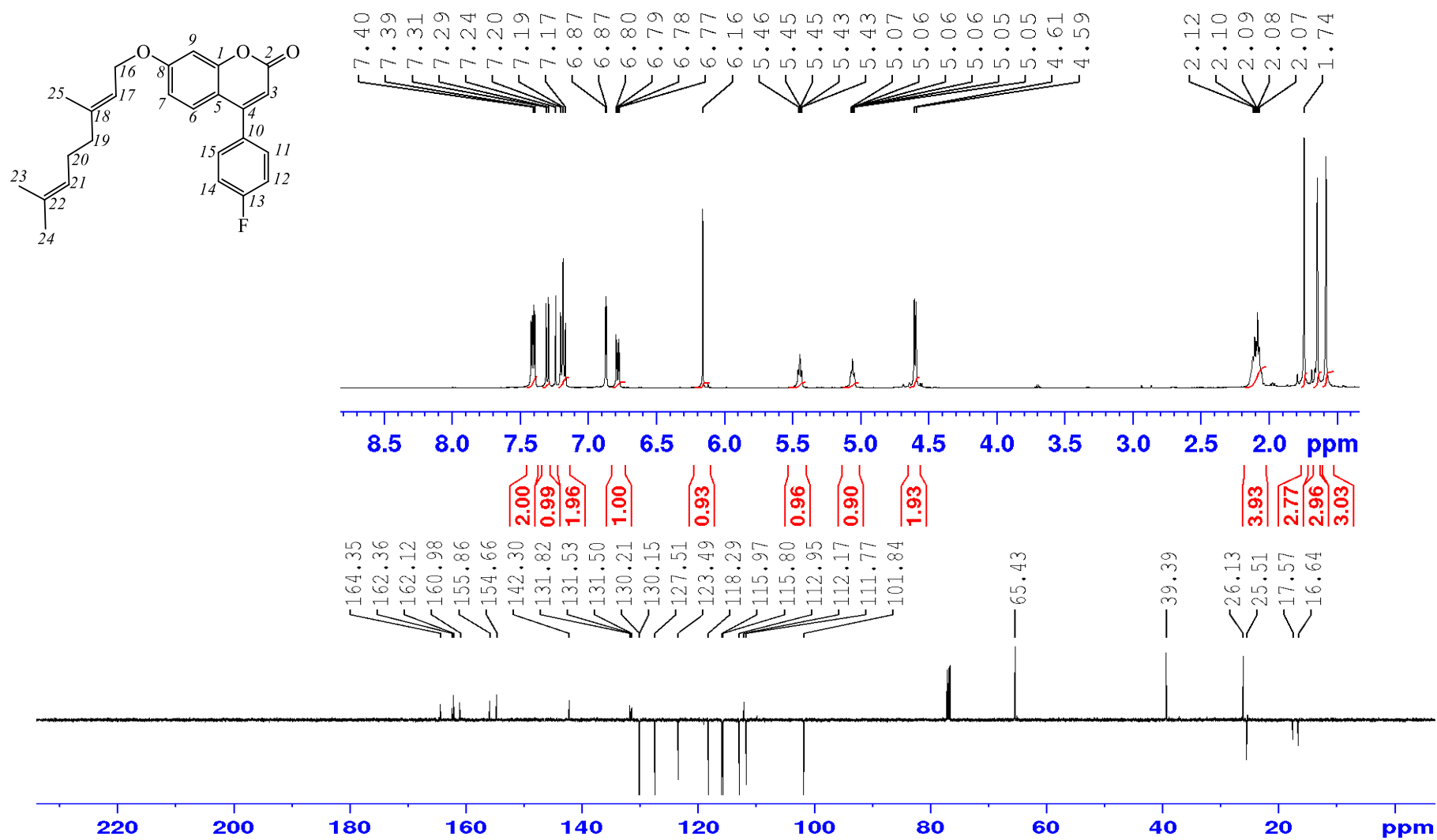
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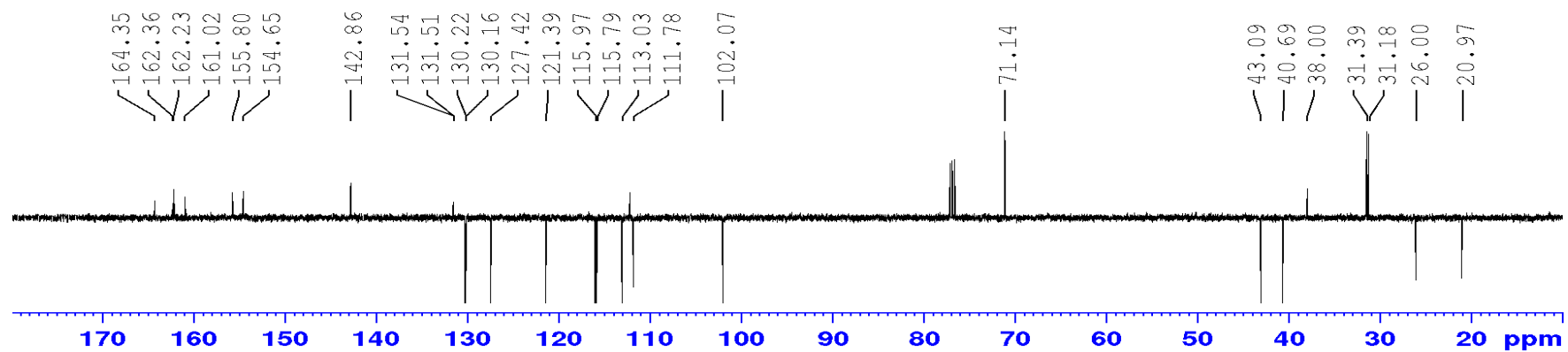
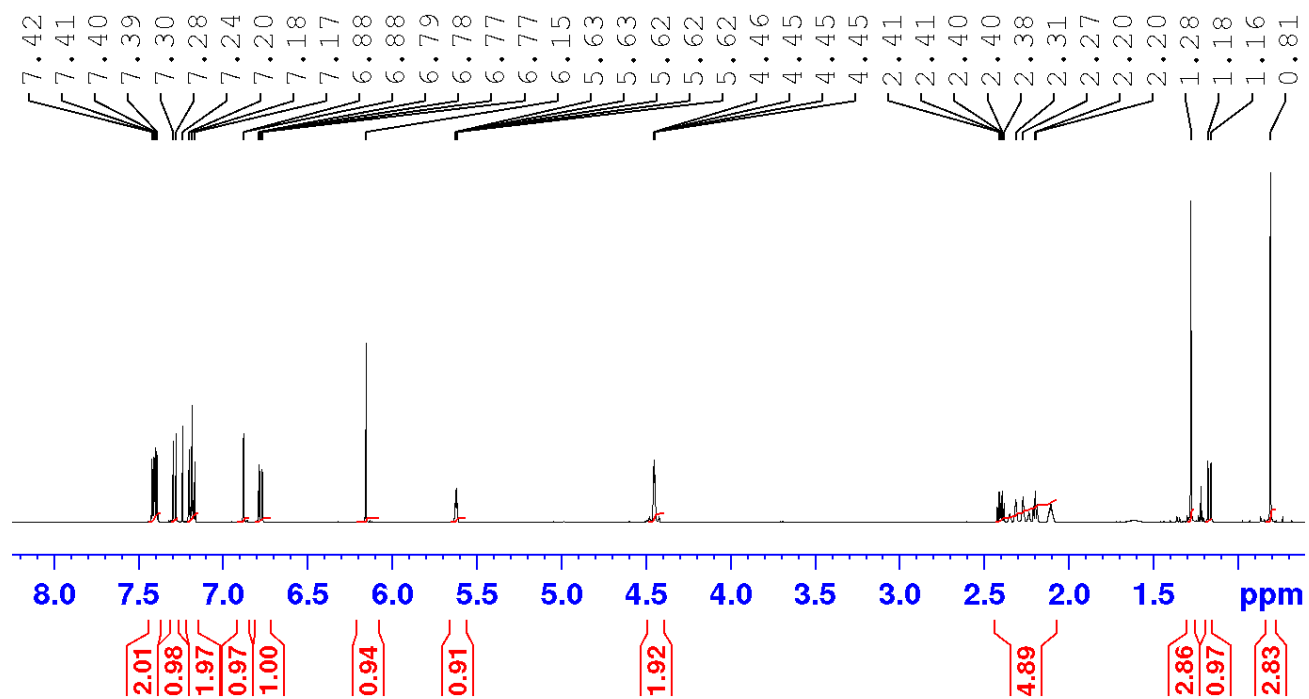
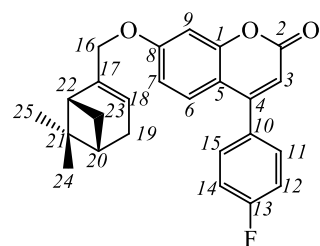
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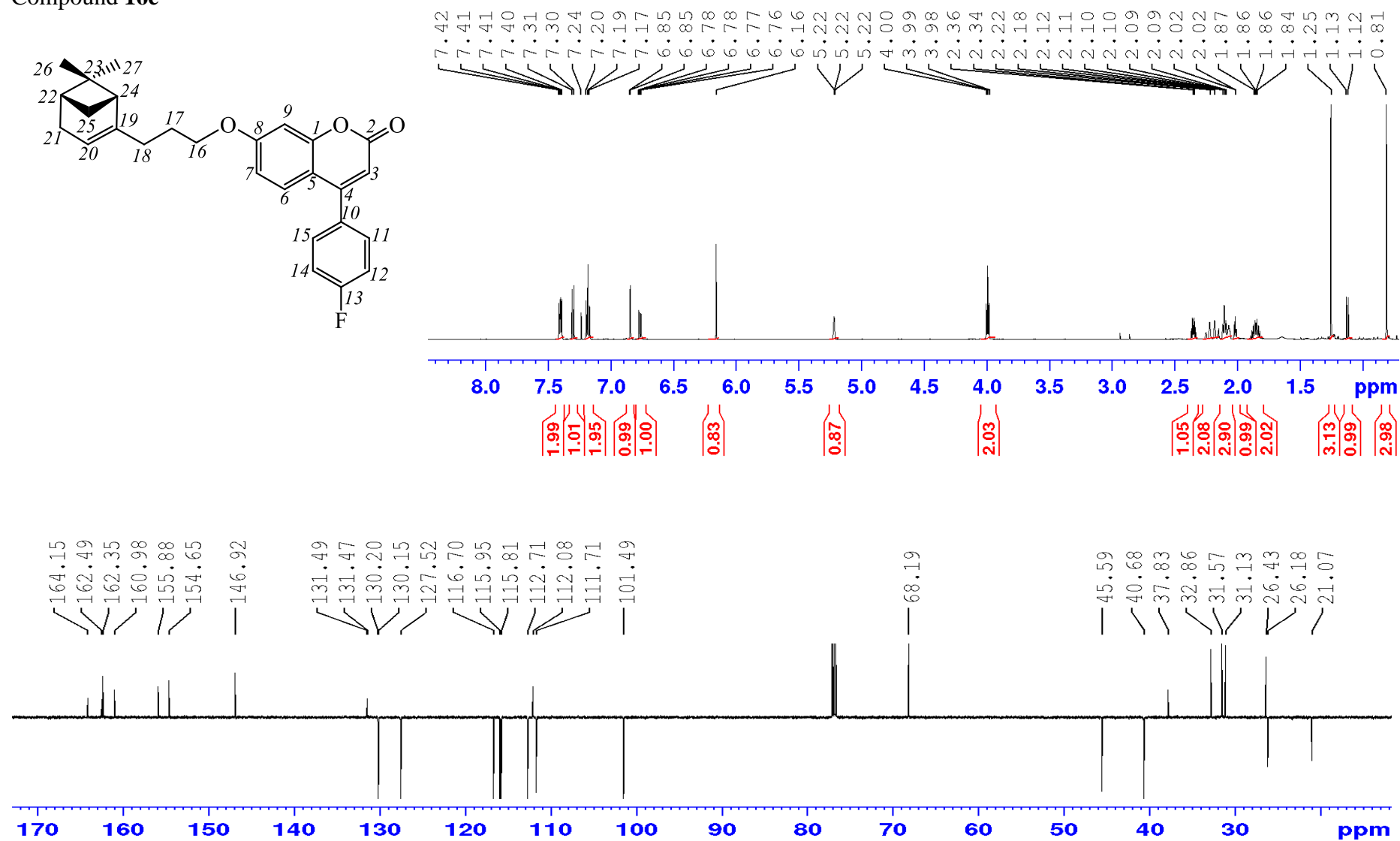
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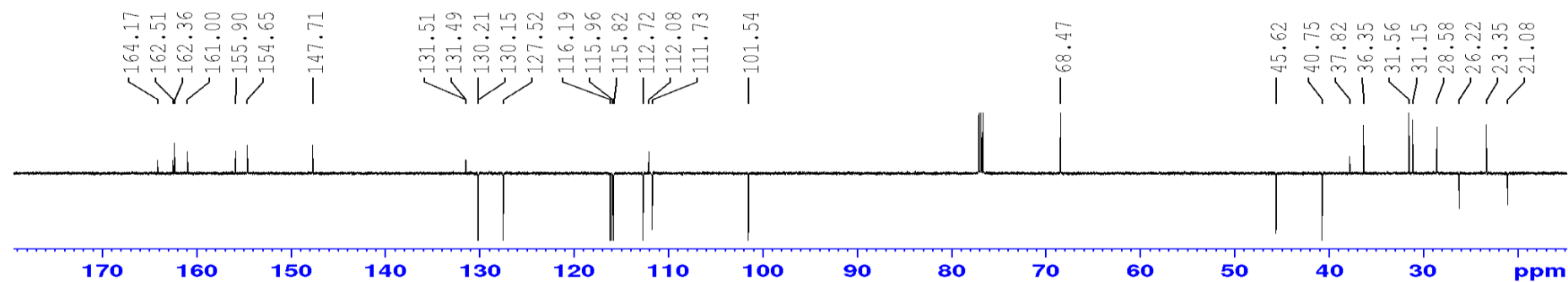
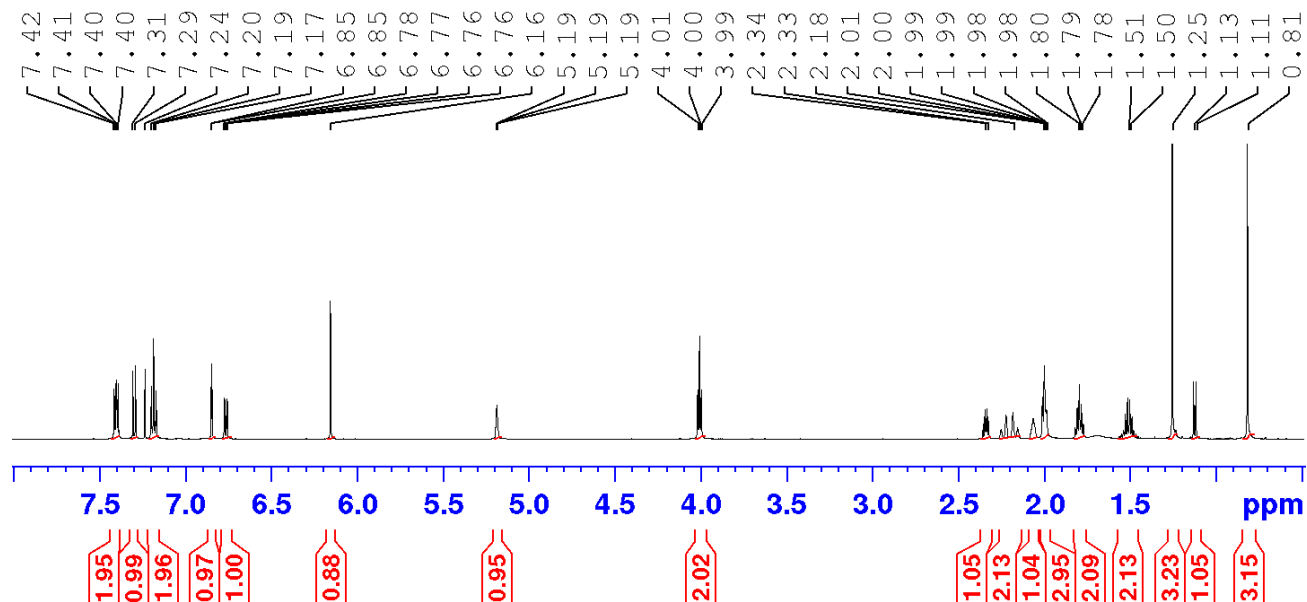
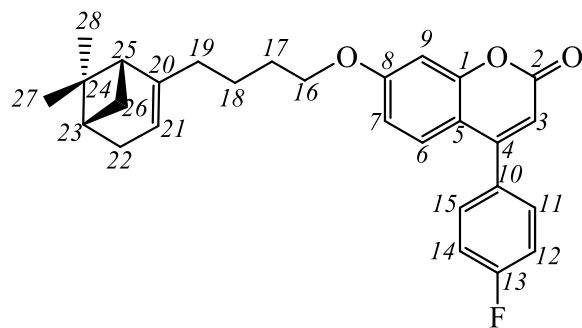
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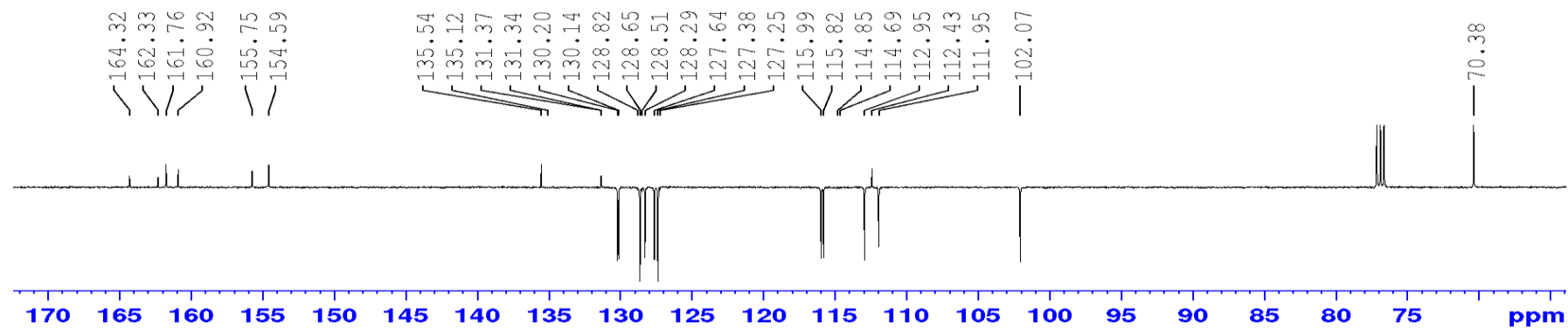
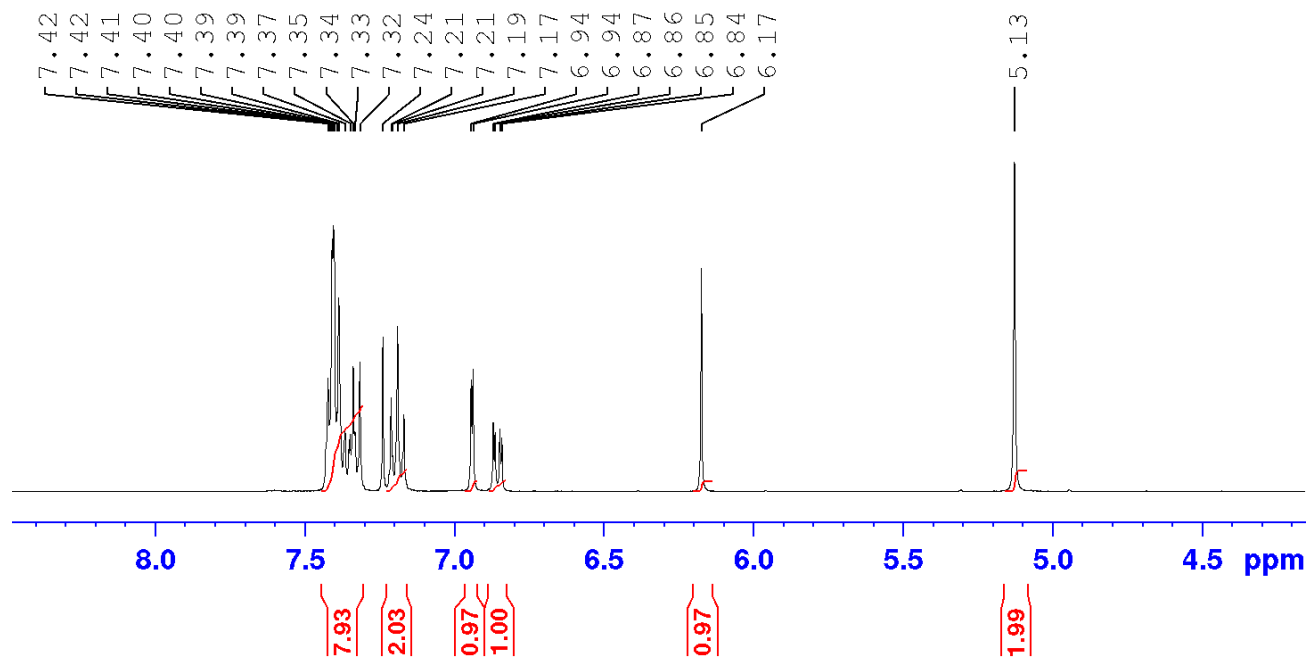
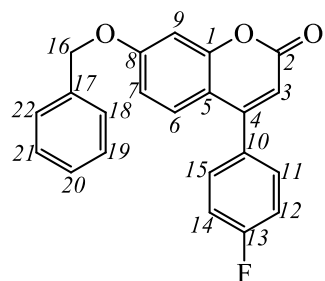
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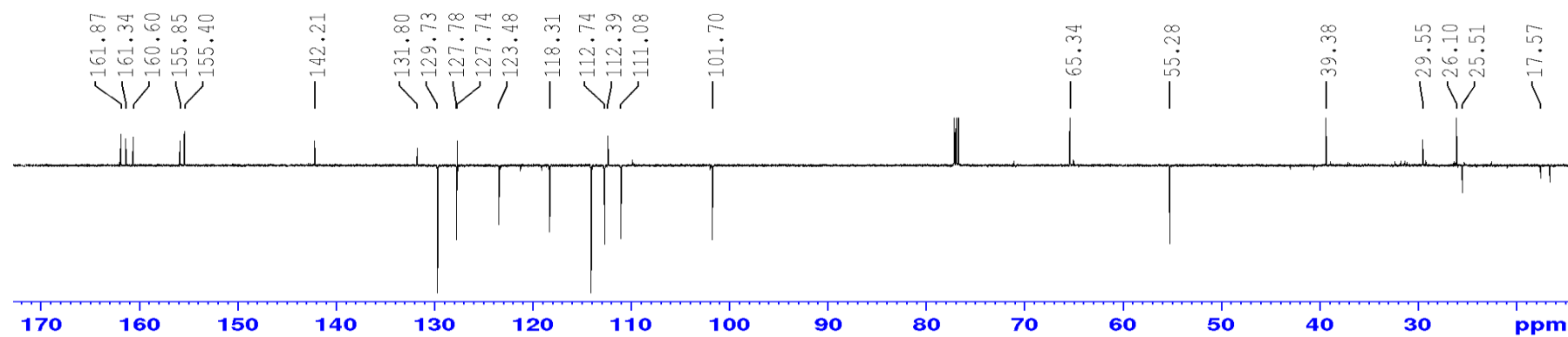
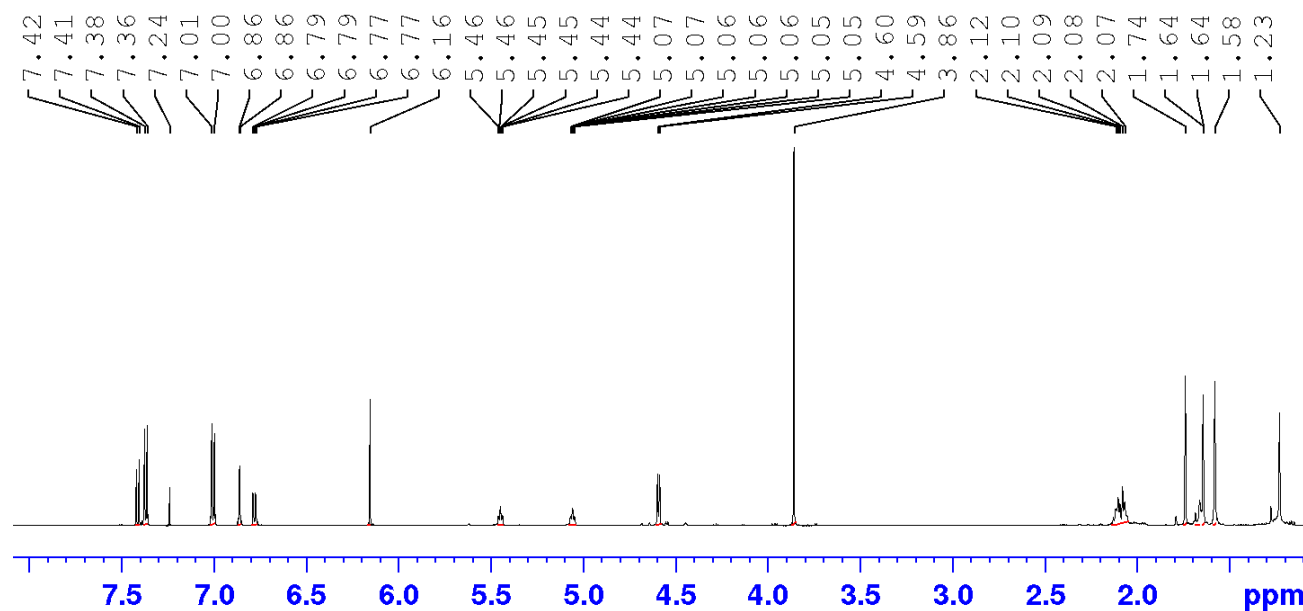
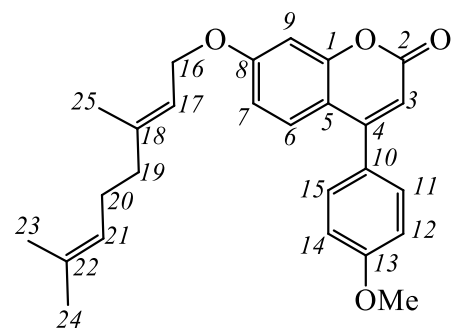
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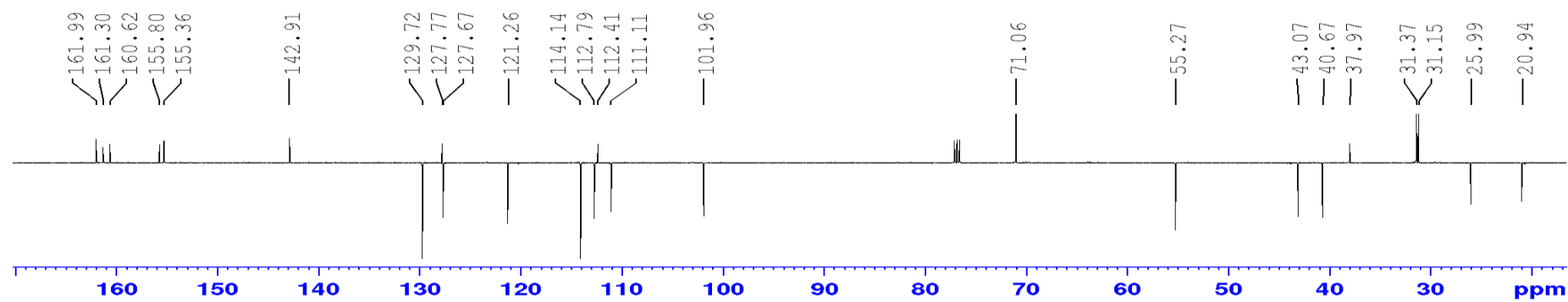
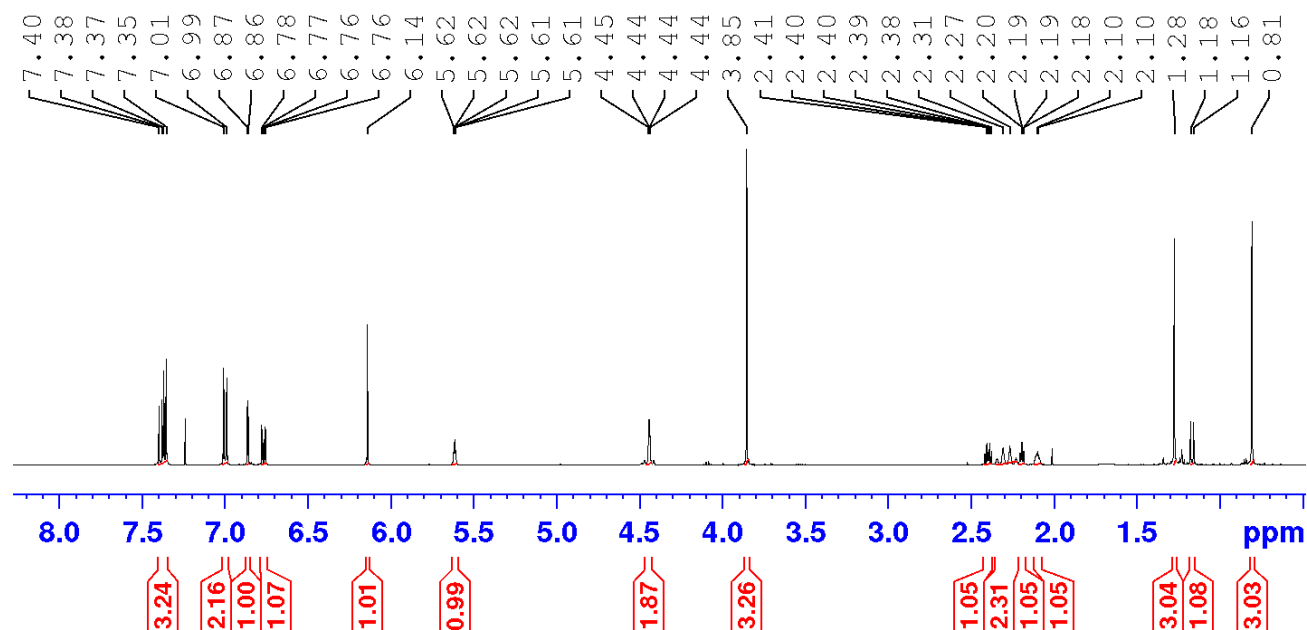
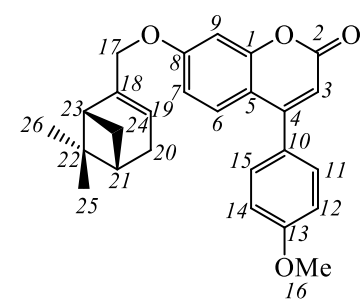
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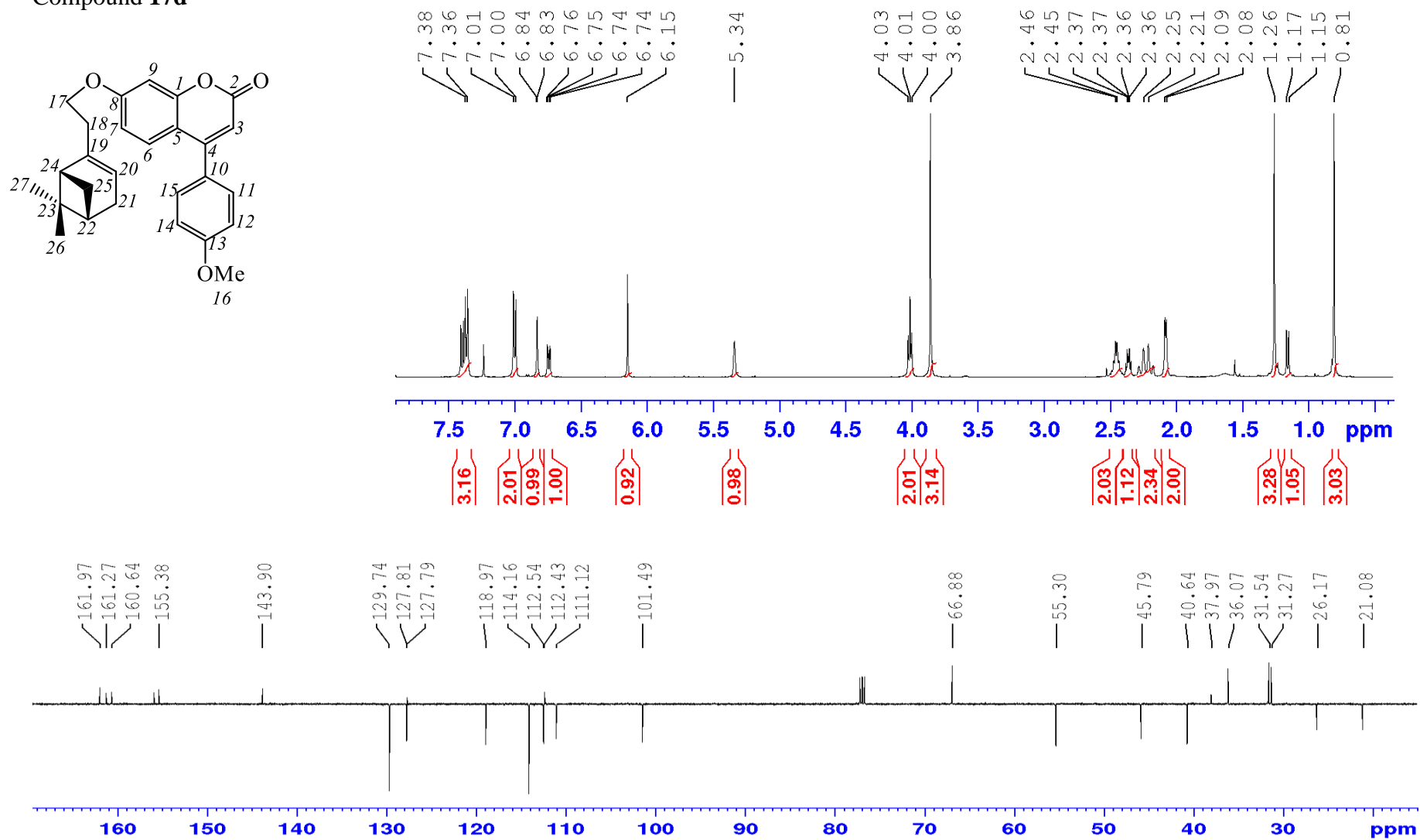
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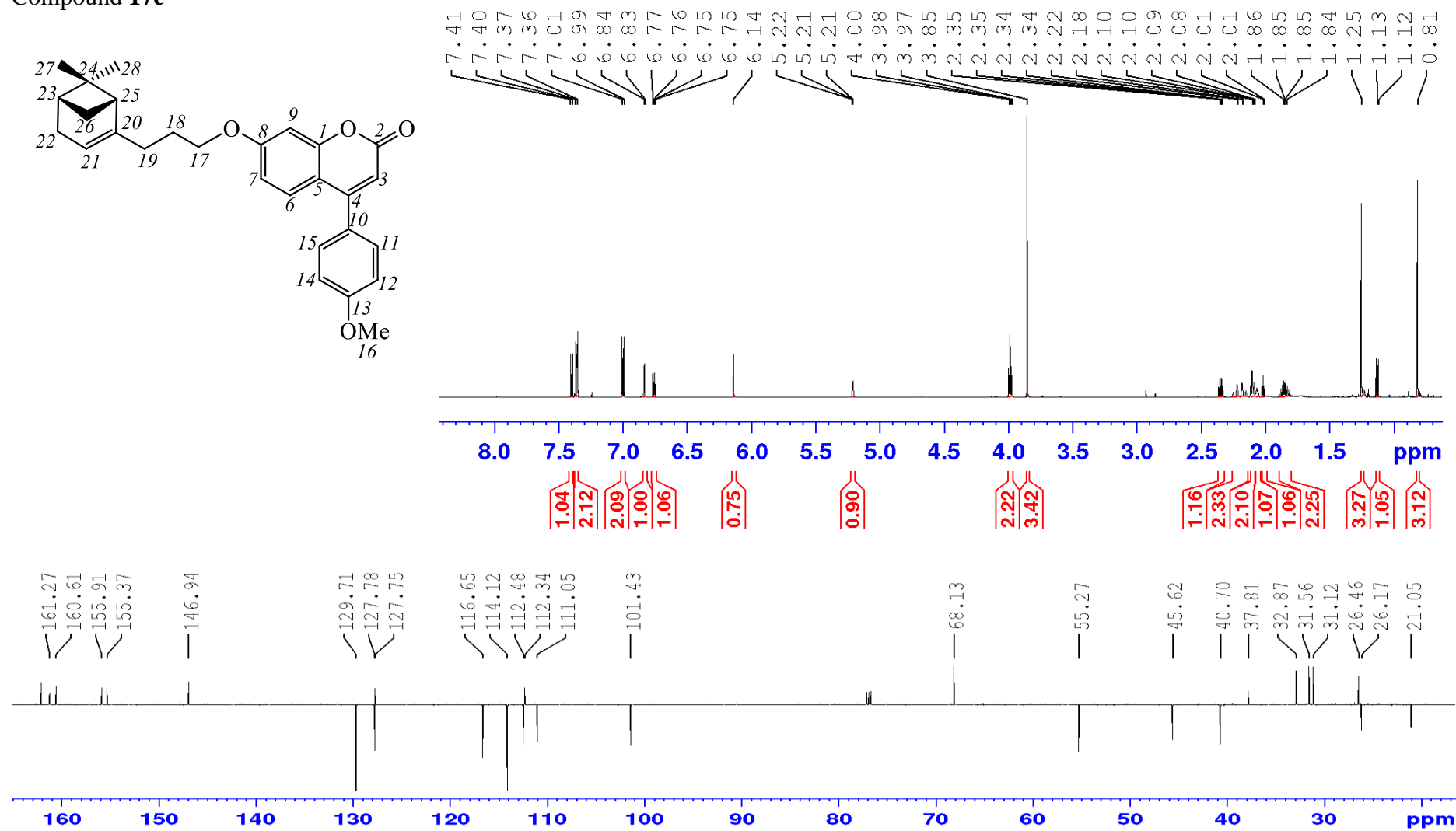
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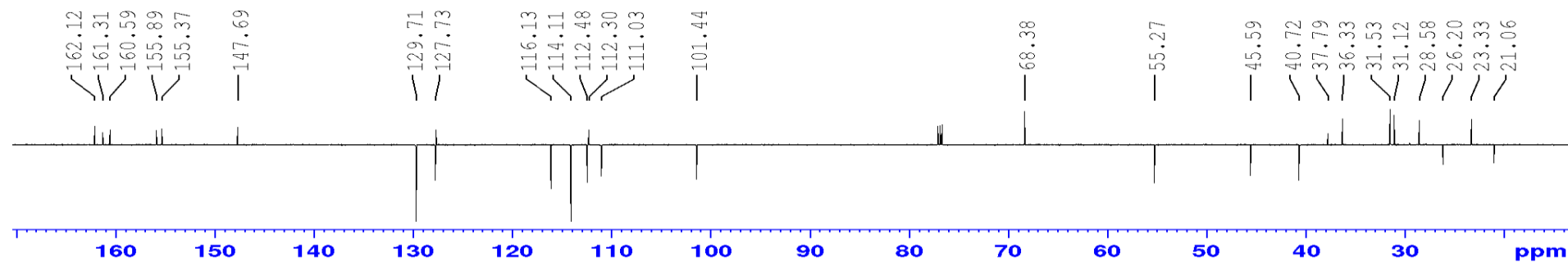
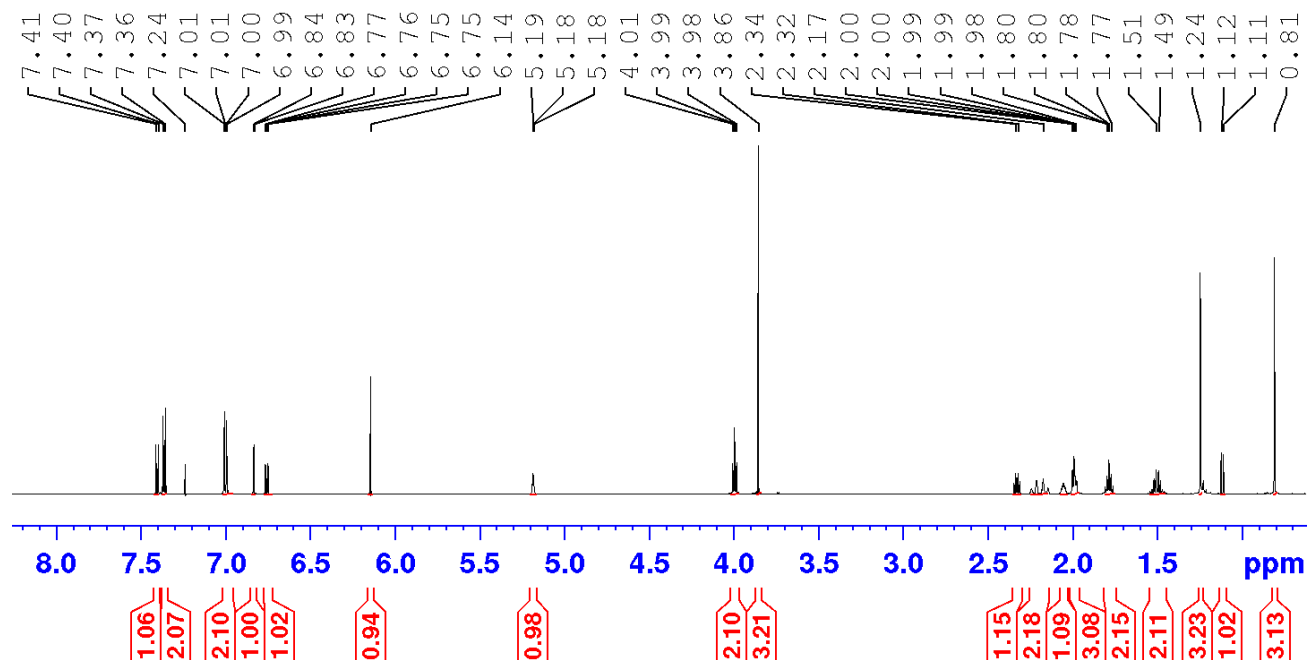
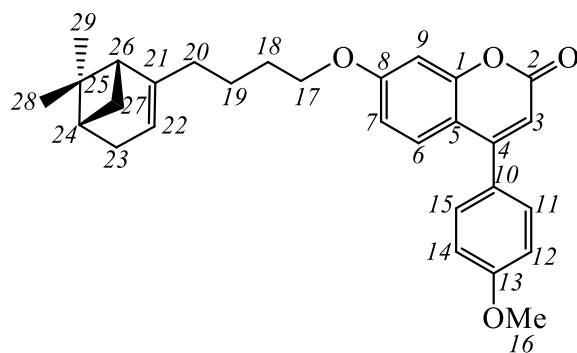
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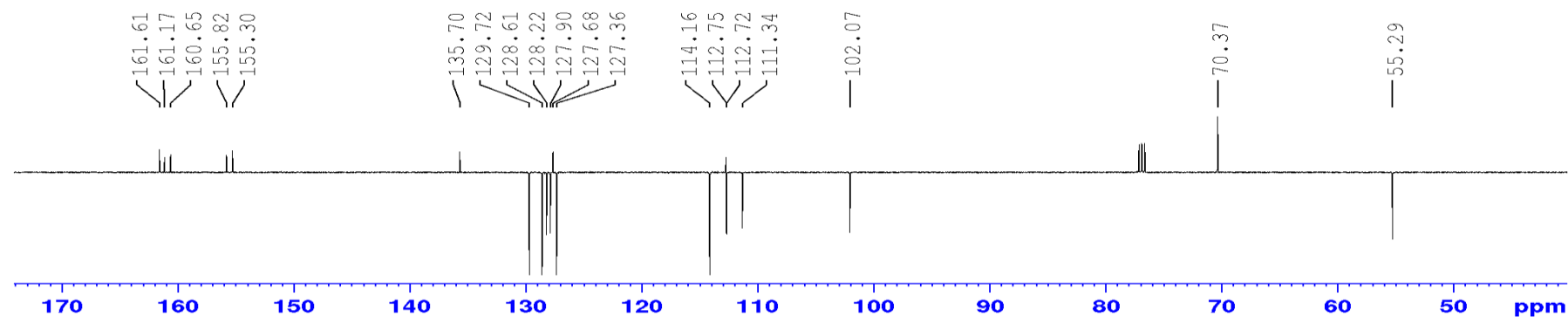
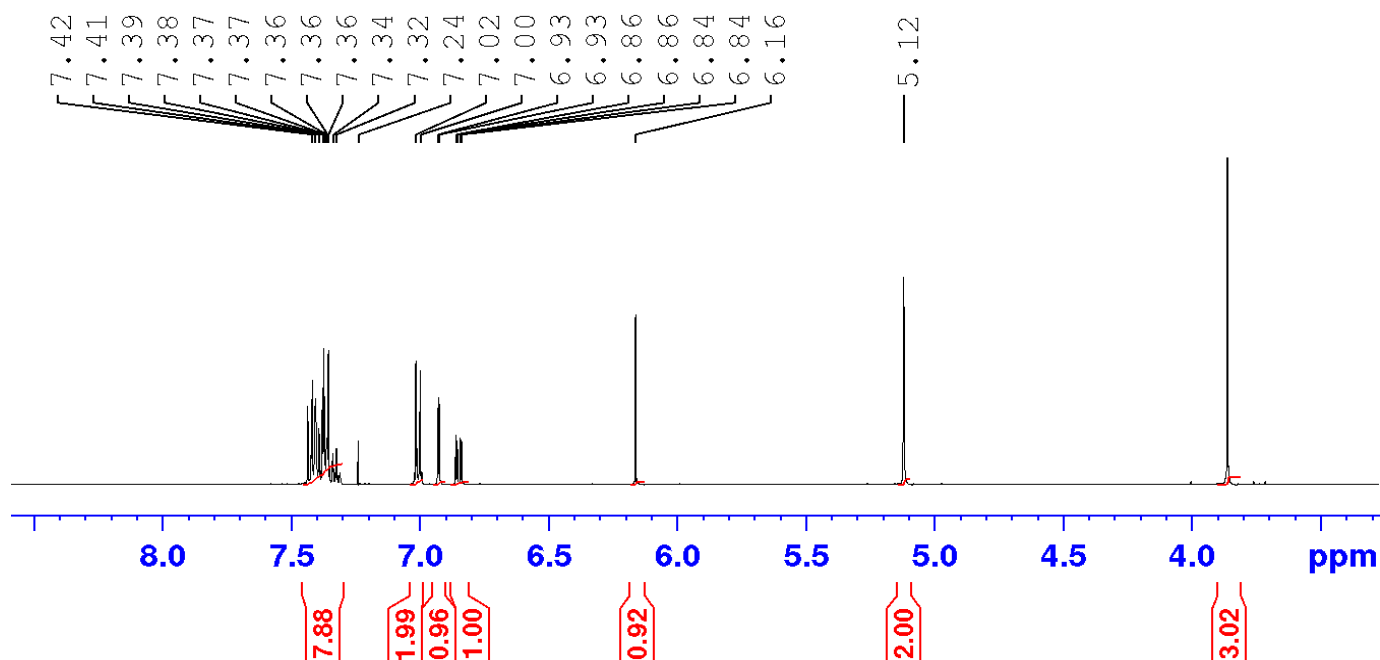
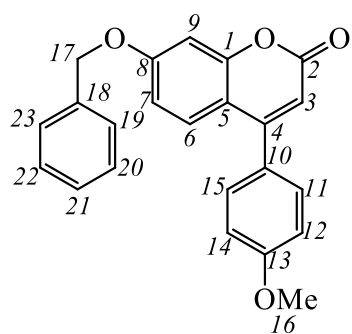
Compound 17e



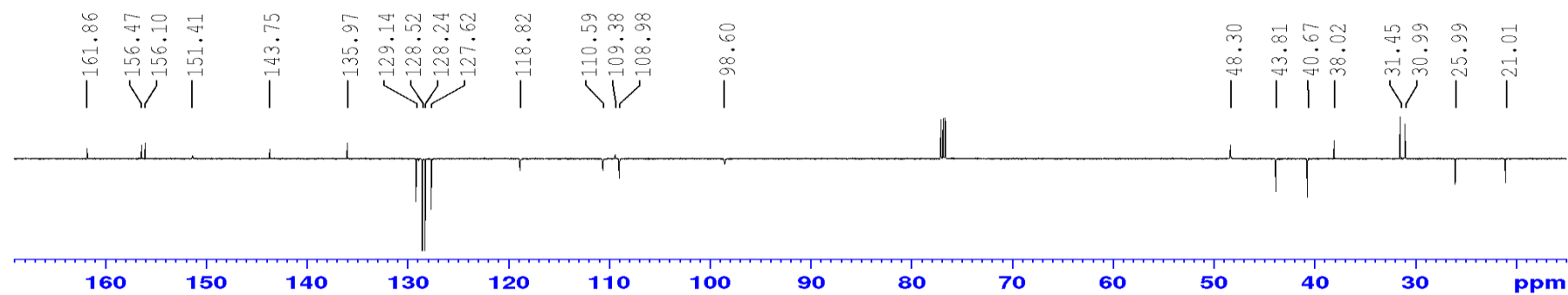
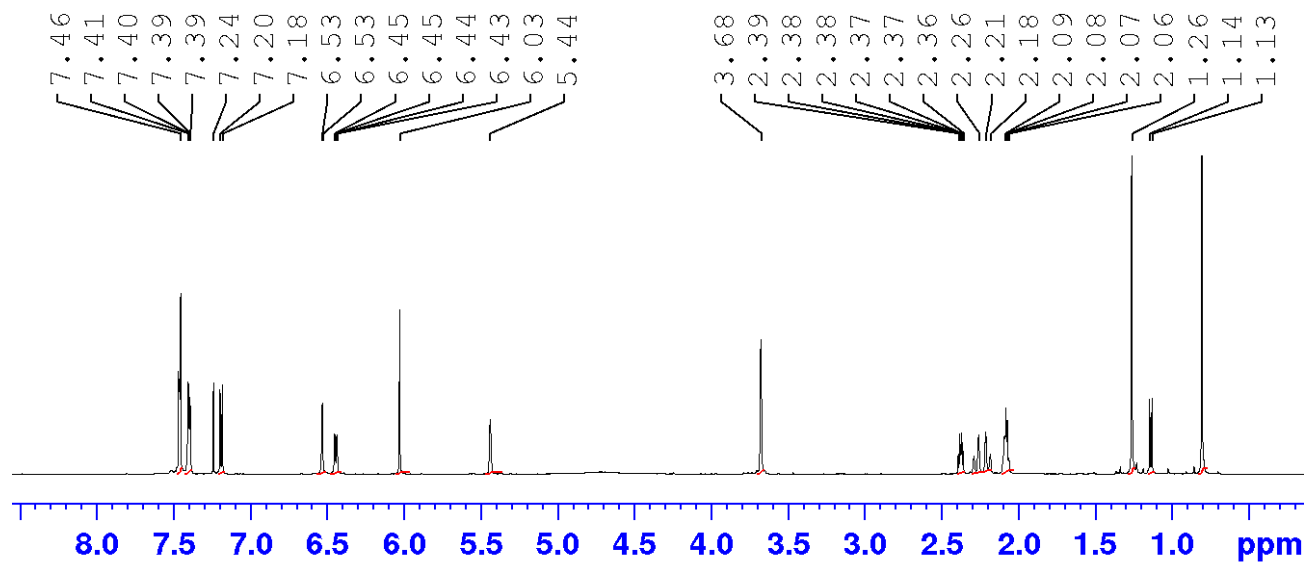
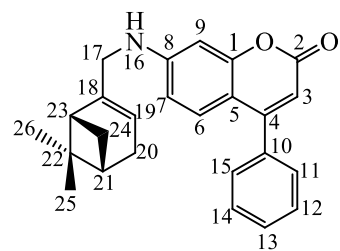
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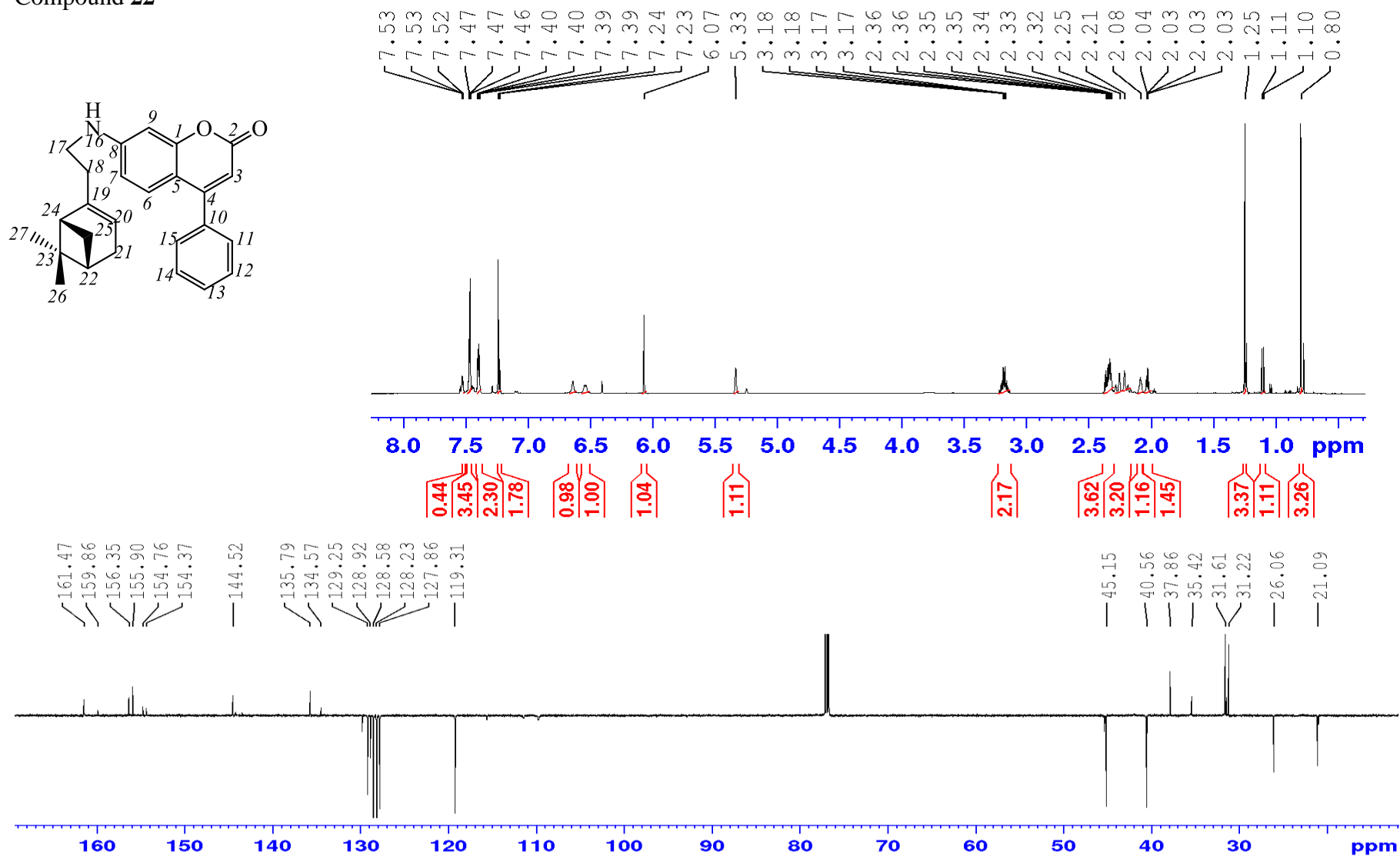
Compound **17g**



Compound 21



Compound **22**



Correspondence of ligands' pharmacophores to the pharmacophore features of the binding site

The structural descriptors of the studied ligands are presented in Tables SM-1-3: M – molecular weight, AlogP – the predicted octanol/water partial coefficient based on atomic contributions shows the value of the lipophilicity of the compounds under consideration, PSA – polar surface area or the sum of the surface of all polar atoms, according to (Pajouhesh and Lenz 2005) PSA value greater than 140 Å² characteristic of compounds with poor membrane permeability, HBD and HBA are donor atoms and hydrogen bond acceptors, respectively. pIC₅₀ – -lg[IC₅₀]; c; SI is the selectivity index, the ratio of cytotoxicity to inhibitory activity. Based on the SI value of the connection, the leaders are colored green. Matched ligand sites – the ratio of ligands to the pharmacophore profile of the binding site: A – the presence of a hydrogen bond acceptor; R – the presence of an aromatic ring; HP – the presence of a hydrophobic fragment; D – the presence of a fragment – a donor of the hydrogen bond.

Table S1. Analysis of structural descriptors and pharmacophoric features of the ligand as a function of linker length.

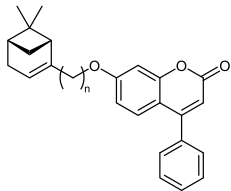
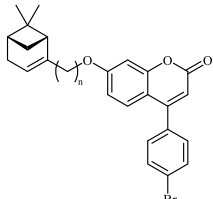
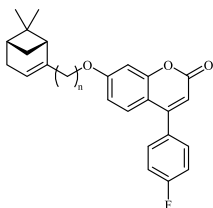
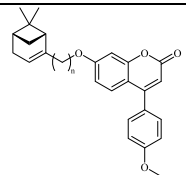
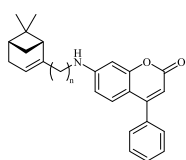
ID structures		-(CH ₂) _n	M, Da	AlogP	PSA, Å ²	HBD	HBA	Matched ligand sites	pIC ₅₀	SI
	14b	1	372.5	5.65	39.44	0	3	3: A-1 ; R-2	4.75	32.8
	14d	2	386.5	5.97	39.44	0	3	3: HP-1 ; R-2	4.08	7.9
	14e	3	400.5	6.43	39.44	0	3	3: HP-1 ; R-2	5.12	192.6
	14f	4	414.5	6.89	39.44	0	3	< 3	3.95	11.4
	15b	1	451.2	6.40	39.44	0	3	3: A-1 ; R-2	4.82	3.0
	15d	2	465.4	6.72	39.44	0	3	3: HP-1 ; R-2	< 4.7	< 0.8
	15e	3	479.4	7.18	39.44	0	3	3: HP-1 ; R-2	< 4.9	< 1
	15f	4	493.4	7.64	39.44	0	3	< 3	5.02	9.6
	16b	1	390.5	5.86	39.44	0	3	3: A-1 ; R-2	3.99	2.9
	16e	3	418.5	6.64	39.44	0	3	3: HP-1 ; R-2	3.96	9.0
	16f	4	432.5	7.09	39.44	0	3	< 3	5.03	11.8
	17b	1	402.5	5.64	48.67	0	4	3: A-1 ; R-2	< 4.9	< 1
	17d	2	416.5	5.96	48.67	0	4	3: HP-1 ; R-2	4.19	10.6
	17f	4	444.5	6.87	48.67	0	4	3: HP-1 ; R-2	< 4.9	< 1
	21	1	371.5	5.48	42.24	1	2	4: D-1 ; HP-1 ; R-2	< 4.9	< 1.5
	22	2	385.5	5.80	42.24	1	2	3: HP-1 ; R-2	4.10	6.0

Table S2. Analysis of structural descriptors and pharmacophoric features of the ligand as a function of the nature of the substituent.

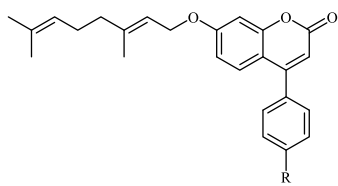
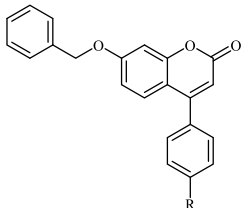
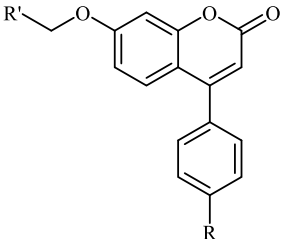








ID structures		-R	M, Da	AlogP	PSA	HBD	HBA	pIC ₅₀	SI	Matched ligand sites
	14a	-H	374.5	6.81	39.44	0	3	4.17	11.9	< 3
	15a	-Br	453.4	7.55	39.44	0	3	5.05	1.0	< 3
	16a	-F	392.5	7.01	39.44	0	3	4.32	5.8	< 3
	17a	-OCH ₃	404.5	6.79	48.67	0	4	4.23	5.8	< 3
	14g	-H	328.4	5.10	39.44	0	3	< 2.80	< 0.9	< 3
	15g	-Br	407.3	5.85	39.44	0	3	4.08	3.2	3: R – 3
	16g	-F	346.4	5.30	39.44	0	3	3.16	< 0.9	3: R – 3
	17g	-OCH ₃	358.4	5.08	48.67	0	4	< 4.77	< 1	3: R – 3

Table S3. Analysis of structural descriptors and pharmacophoric features of the different stereoisomers.

ID structures	-R -R'	M, Da	AlogP	PSA	HBD	HBA	pIC ₅₀	SI	Matched ligand sites
	14b R = H R' = 	372.5	5.65	39.44	0	3	4.75	32.8	3: A - 1 ; R - 2
	14c R' = 	372.5	5.65	39.44	0	3	3.63	3.5	< 3
	15b R = Br R' = 	451.2	6.40	39.44	0	3	4.82	3.0	3: A - 1 ; R - 2
	15c R' = 	451.2	6.40	39.44	0	3	4.31	1.9	< 3
	16b R = F R' = 	390.5	5.86	39.44	0	3	3.99	2.9	3: A - 1 ; R - 2
	16c R' = 	390.5	5.86	39.44	0	3	4.84	1.4	< 3
	17b R = -OCH ₃ R' = 	402.5	5.64	48.67	0	4	< 4.9	< 1	3: A - 1 ; R - 2
	17c R' = 	402.5	5.64	48.67	0	4	< 4.8	< 0.98	< 3

Molecular docking

Table S4. Molecular docking results.

ID compounds	pIC50	Pose (max 20)	GC	IDF	H-bond	Other interactions
14a	4.17	17	-8.70	-3108.00	None	A: Phe488 – π - π A: Phe140 – HP B: Phe140 – π - π D: Phe137; Leu138; Met396; Phe488 – HP D: Phe140 – π - π
14b	4.75	12	-9.27	-3108.97	None	A: Phe488 – π - π B: Phe488 – π - π B: Phe140; Leu141 – HP D: Phe488 – π - π
14c	3.63	9	-8.31	-3106.42	None	A: Phe488 – π - π B: Phe488 – π - π D: Phe137; Leu138; Phe140; Leu141 – HP
14d	4.08	16	-9.05	-3106.64	None	D: Phe488 – π - π D: Phe137; Leu138; Phe140; Leu141 – HP
14e	5.12	17	-10.26	-3108.15	None	A: Phe140 – HP B: Phe140 – π - π B: Phe488 – π - π B: Phe137; Leu138; Phe140; Leu141 – HP D: Phe137; Leu138; Phe140; Leu141 – HP
14f	3.95	17	-9.22	-3107.32	None	A: Phe488 – π - π B: Phe488 – π - π
14g	2.80	8	-7.60	-3104.82	None	A: Phe140; Phe488 – π - π A: Met396 – HP D: Phe488 – π - π
15a	5.05	17	-9.40	-3110.11	None	A: Phe488 – π - π A: Phe137; Phe140 – HP

						B: Phe140; Leu141 – HP B: Phe488 – π - π D: Phe140; Phe488 – π - π
15b	4.82	14	-9.70	-3108.88	None	A: Phe488 – π - π A: Phe137; Phe140 – HP B: Phe140; Leu141 – HP B: Phe488 – π - π D: Phe140; Phe488 – π - π
15c	4.30	19	-8.14	-3106.38	A: Asp489	D: Phe137; Leu138; Phe140 – HP
15d	4.70	16	-9.47	-3110.81	A: Phe488 Asp489	A: Phe137 – HP B: Phe488 – π - π B: Phe137; Leu138; Phe140 – HP
15e	4.90	12	-8.73	-3109.03	A: Phe488 Asp489	A: Phe488 – π - π B: Phe137; Leu138; Phe140 – HP
15f	5.02	12	-9.72	-3110.20	A: Phe488 D: Asp486	A: Phe140 – HP B: Phe488 – HP D: Phe137, Phe138 – HP. D: Phe488 – π - π
15g	4.08	8	-8.99	-3109.05	None	A: Phe488 – π - π B: Phe140; Phe488 – π - π B: Phe140; Leu141 – HP D: Phe140; Phe488 – π - π
16a	4.32	15	-8.86	-3108.25	A: Asp489 Phe488	A: Lys498 – π -cation B: Phe137; Phe140; Phe488 – HP D: Phe140; Phe488 – HP
16b	3.99	17	-9.03	-3107.49	None	A: Phe488 – π - π D: Phe488 – π - π D: Phe137; Leu138; Phe140 – HP
16c	4.84	6	-9.07	-3109.40	None	A: Phe488 – π - π A: Phe137; Phe140 – HP B: Phe140; Leu141 – HP

						D: Phe140; Phe488 – π - π
16e	3.96	17	-9.20	-3107.86	None	A: Phe140 – π - π A: Phe140 – HP B: Met396 – HP B: Phe140 – π - π D: Phe137; Leu138; Phe140 – HP
16f	5.03	13	-9.99	-3108.68	None	A: Phe488 – π - π B: Phe140 – π - π D: Phe140 – π - π D: Phe137; Leu138; Phe140 – HP
16g	3.20	11	-8.17	-3107.30	None	A: Phe140; Phe488 – π - π B: Phe488 – π - π D: Phe488 – π - π D: Phe137; Leu138; Phe140 – HP
17a	4.20	13	-8.97	-3109.54	A: Asp489 Phe488	B: Phe488 – π - π B: Phe137; Leu138; Phe140 – HP
17b	4.90	14	-9.16	-3108.81	None	B: Phe140; Phe488 – π - π B: Phe137; Leu138; Phe140 – HP D: Phe137; Leu138; Phe140 – HP
17c	4.80	10	-9.59	-3109.31	None	A: Phe140; Phe488 – π - π B: Phe137; Leu138; Phe140 – HP D: Phe140; Phe488 – π - π D: Phe137; Leu138; Phe140; Met396 – HP
17d	4.19	18	-8.53	-3107.42	A: Phe488 A: Asp489	A: Lys498 – π -cation D: Phe488 – π - π D: Phe137; Leu138; Phe140; Leu141 – HP
17f	4.97	18	-9.86	-3110.34	A: Phe488 A: Asp489 B: Lys498	B: Pro484 – HP D: Phe488 – HP

17g	4.80	11	-9.72	-3109.89	None	A: Phe488 – π - π B: Phe488 – π - π D: Phe137; Leu138; Phe140 – HP
21	4.90	16	-10.36	-3106.98	B: Phe137	A: Phe488 – π - π B: Phe488 – π - π B: Phe137; Leu138; Phe140 – HP
22	4.10	17	-8.86	-3106.99	None	A: Phe140 – HP A: Phe488 – π - π B: Phe488 – π - π D: Phe137; Leu138; Phe140; Leu141 – HP D: Phe140 – π - π

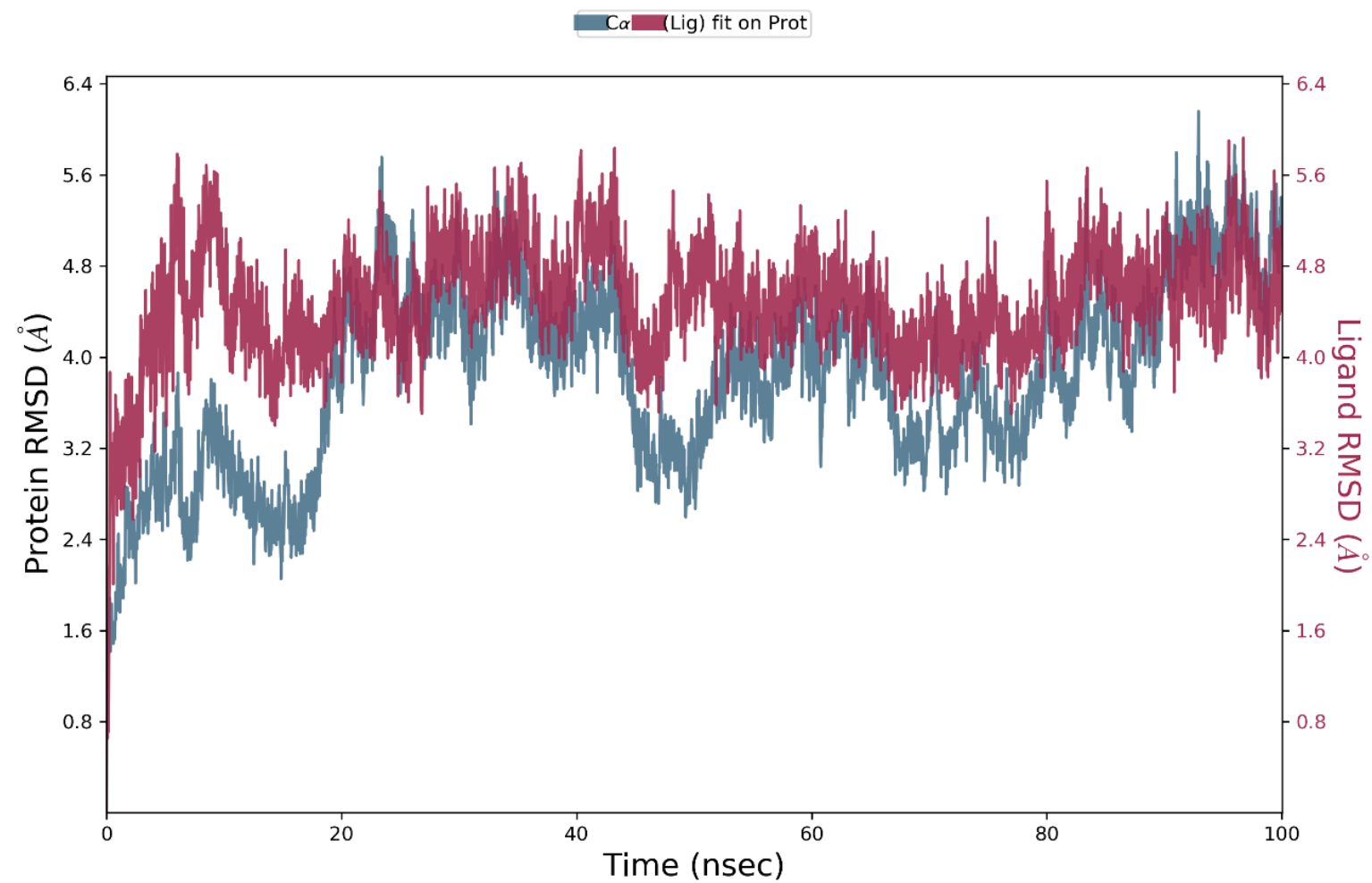


Figure S1. RMSD fluctuations.

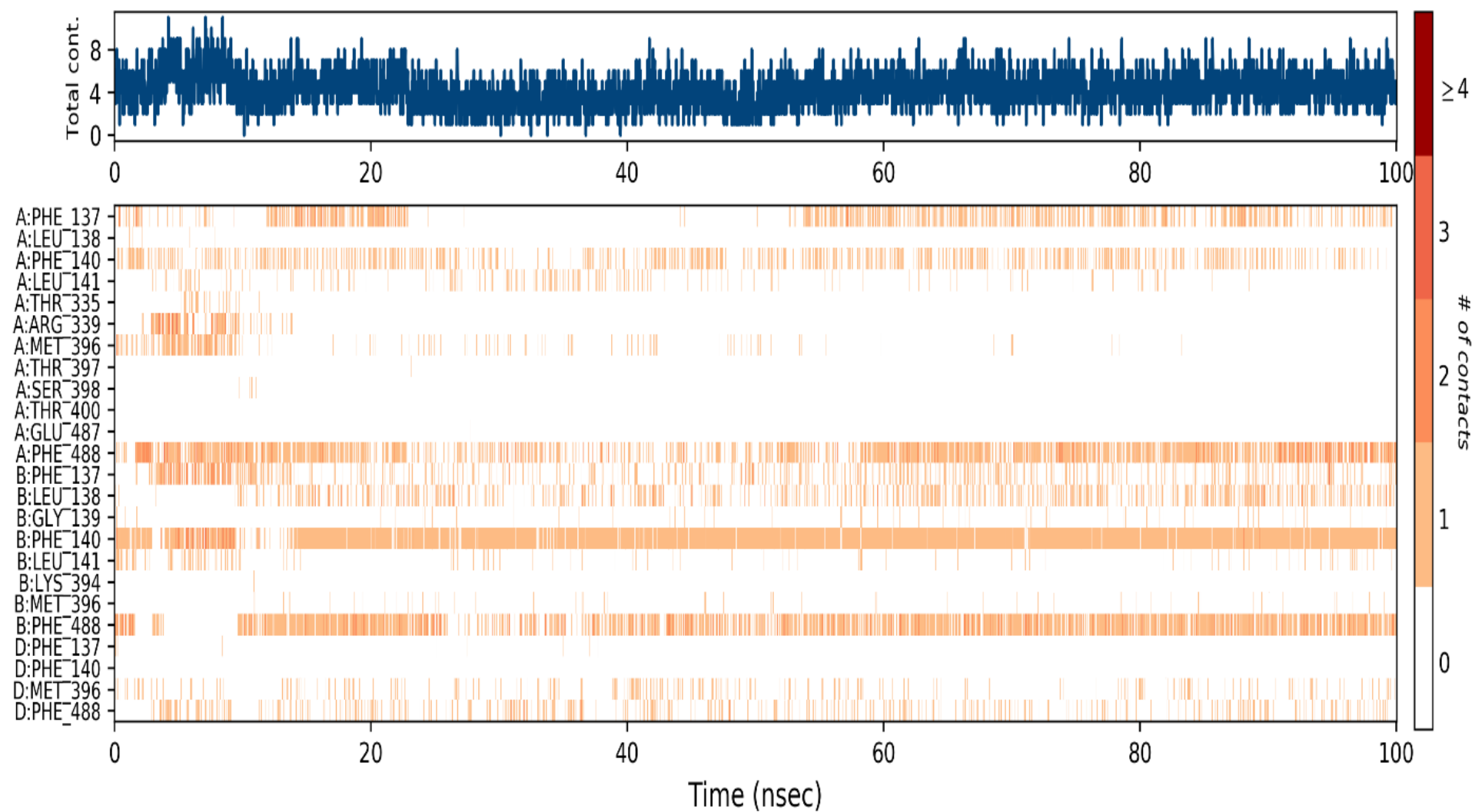


Figure S2. The total number of protein-ligand contacts.