SUPPORTING INFORMATION FOR

Investigating the Neuroprotective Effects of Turmeric Extract: Structural Interactions of β-Amyloid Peptide with Single Curcuminoids

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[§]These authors contributed equally to this work

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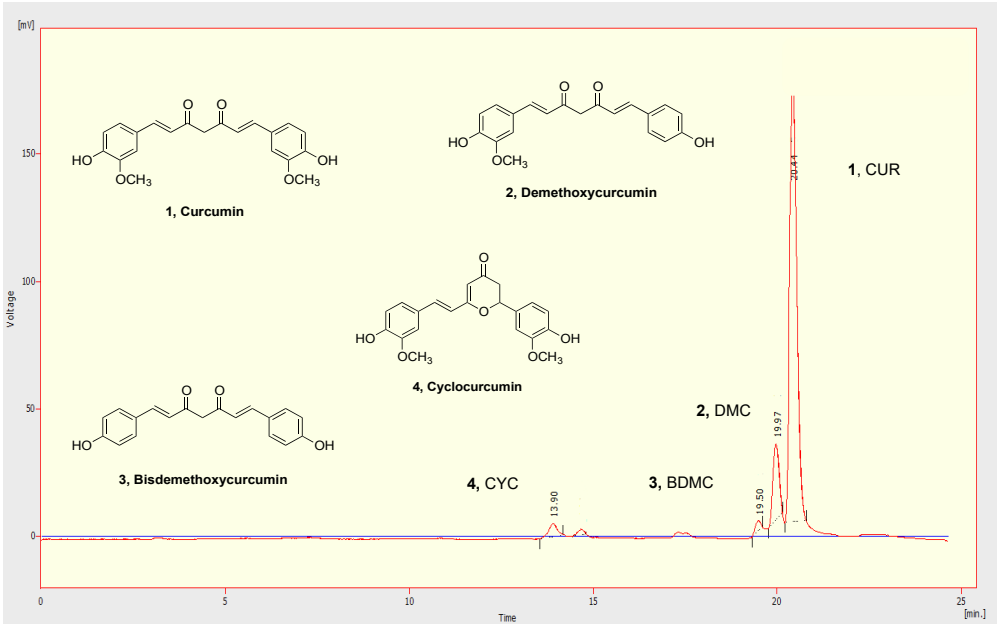
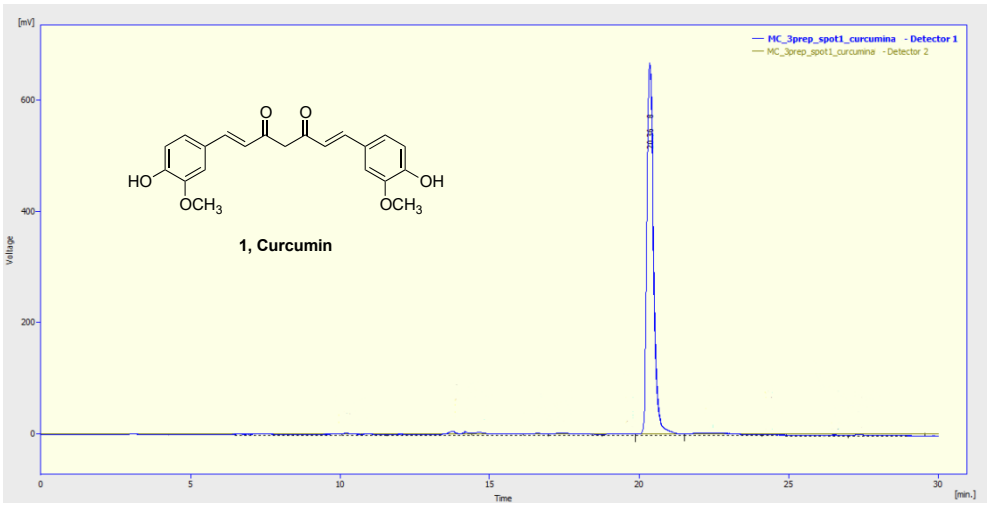
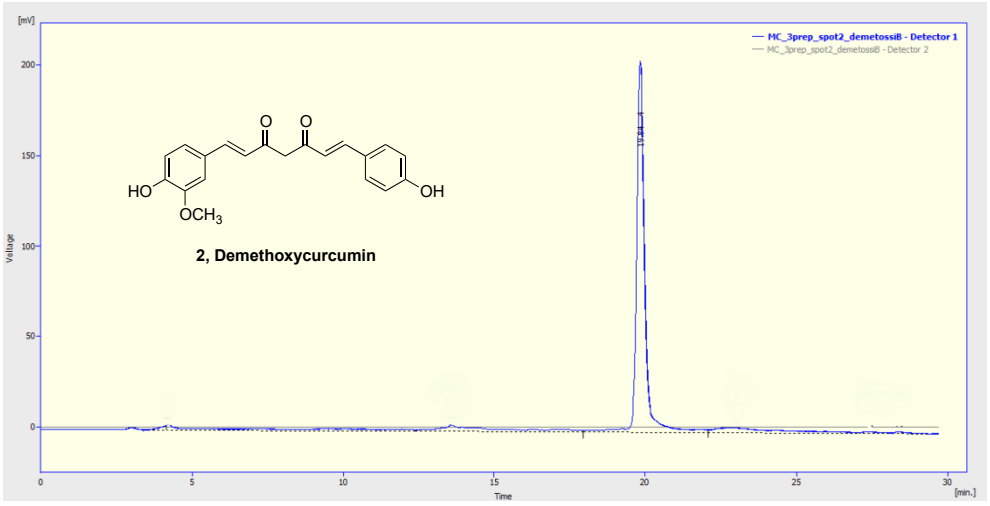


Figure 1SI. HPLC chromatogram showing composition of *Curcuma longa* extract as it is in MIX and Meriva® extract.





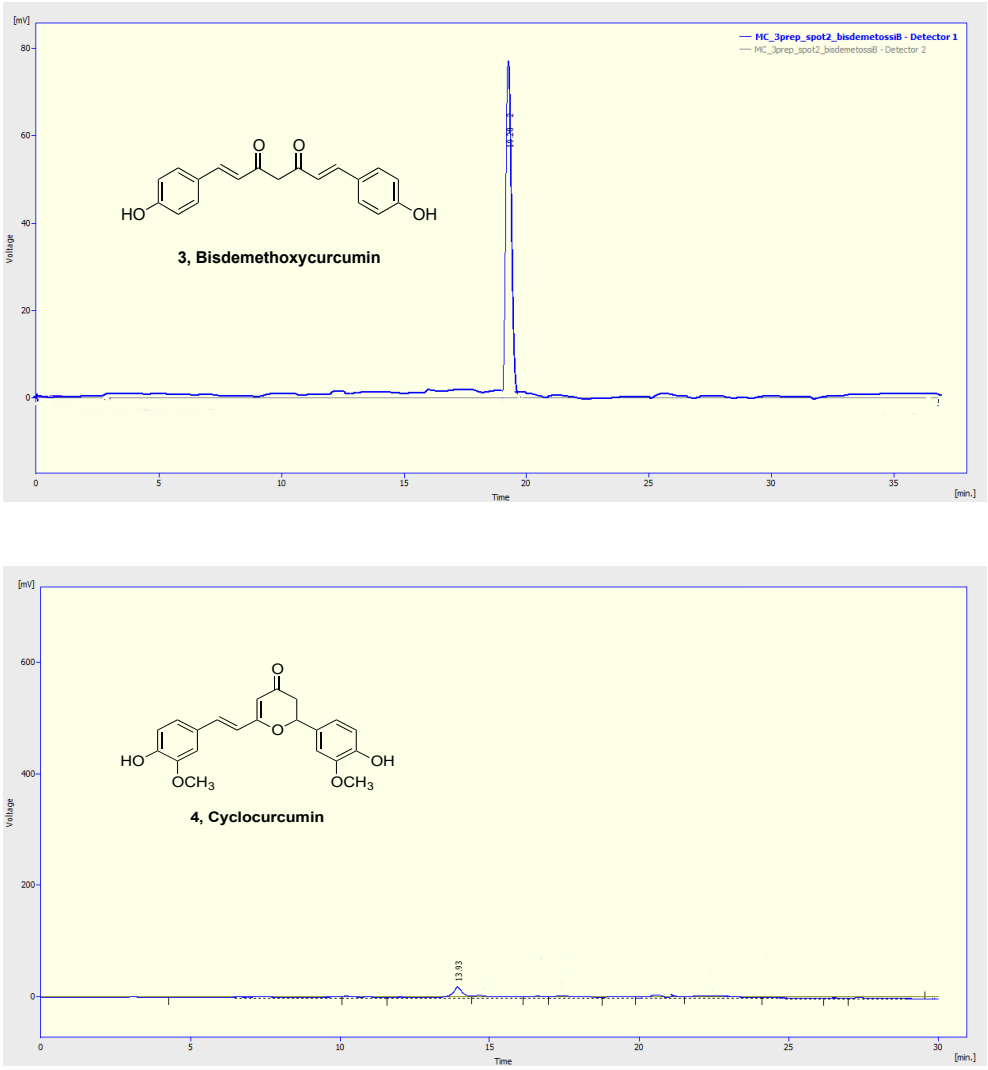


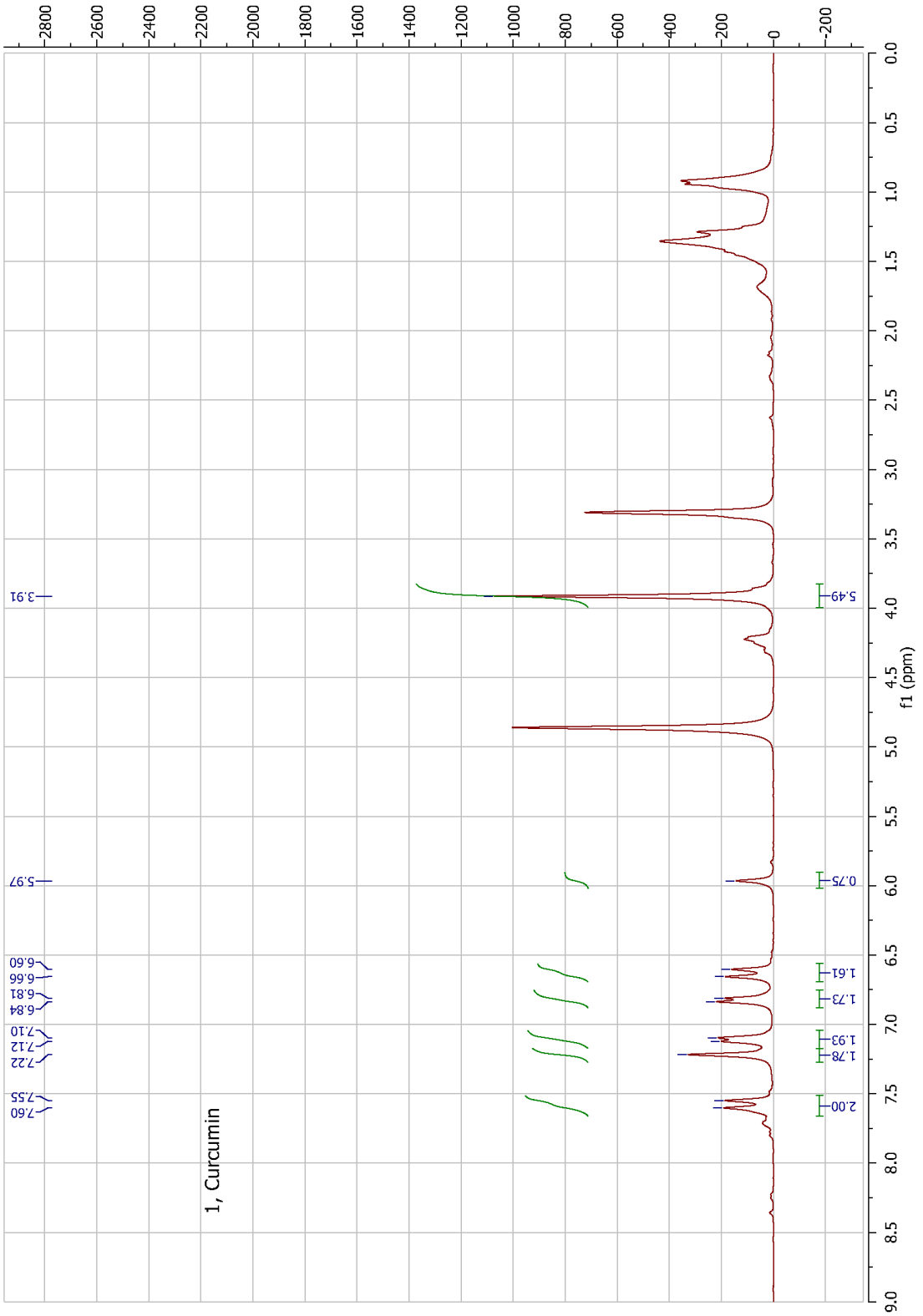
Figure 2SI. HPLC Chromatograms *of isolated CUR, DMC, BDMC and CYC.*

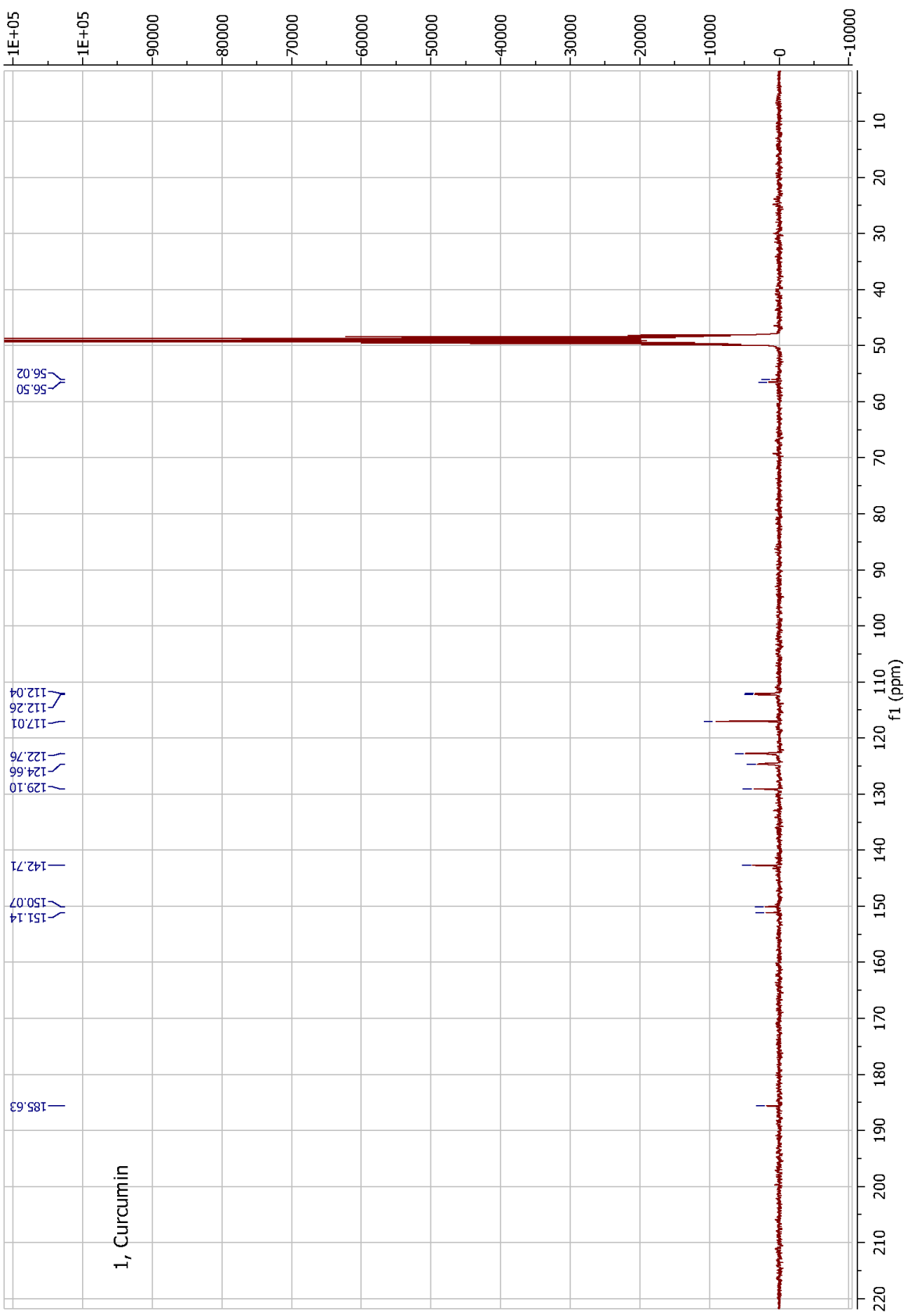
Table 1SI. Reaction conditions for cyclocurcumin synthesis.

Entry	Solvent[a]	Acid (%)	(reaction time, temperature)	Yield[b]
1	Benzene	TFA, 3%	65 h, rt, dark	5%
2	Benzene	TfOH, 3%	65 h, rt, dark	5%
MW Conditions (temperature, reaction time)				
3	Benzene	TFA, 3%	100 °C, 4x20 min,	5%
4	-	TFA, 100%	100 °C, 4 min,	**10%**

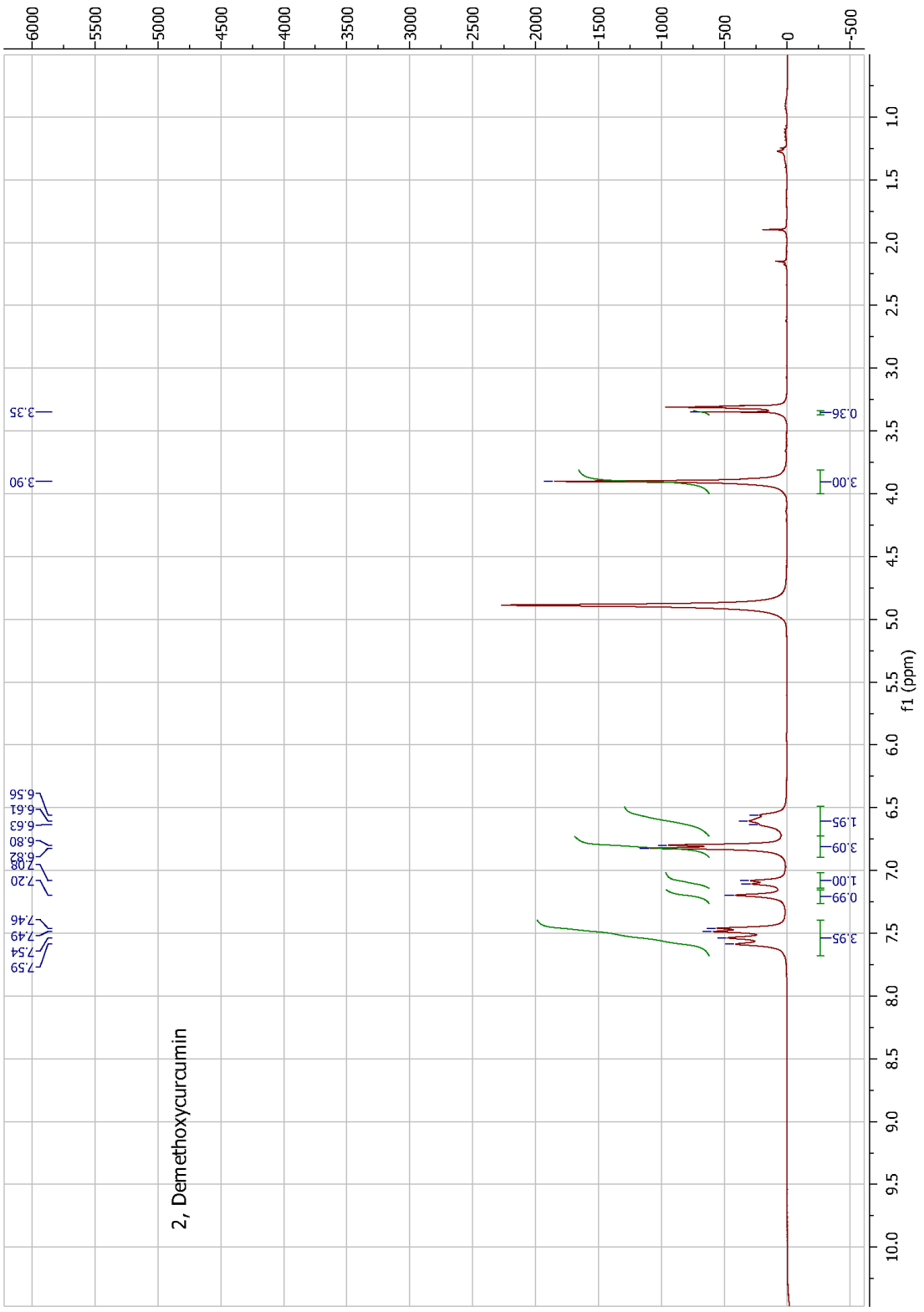
[a] Reaction was carried out in a [0.25 M] benzene solution. [b] Yields are evaluated on isolated product.

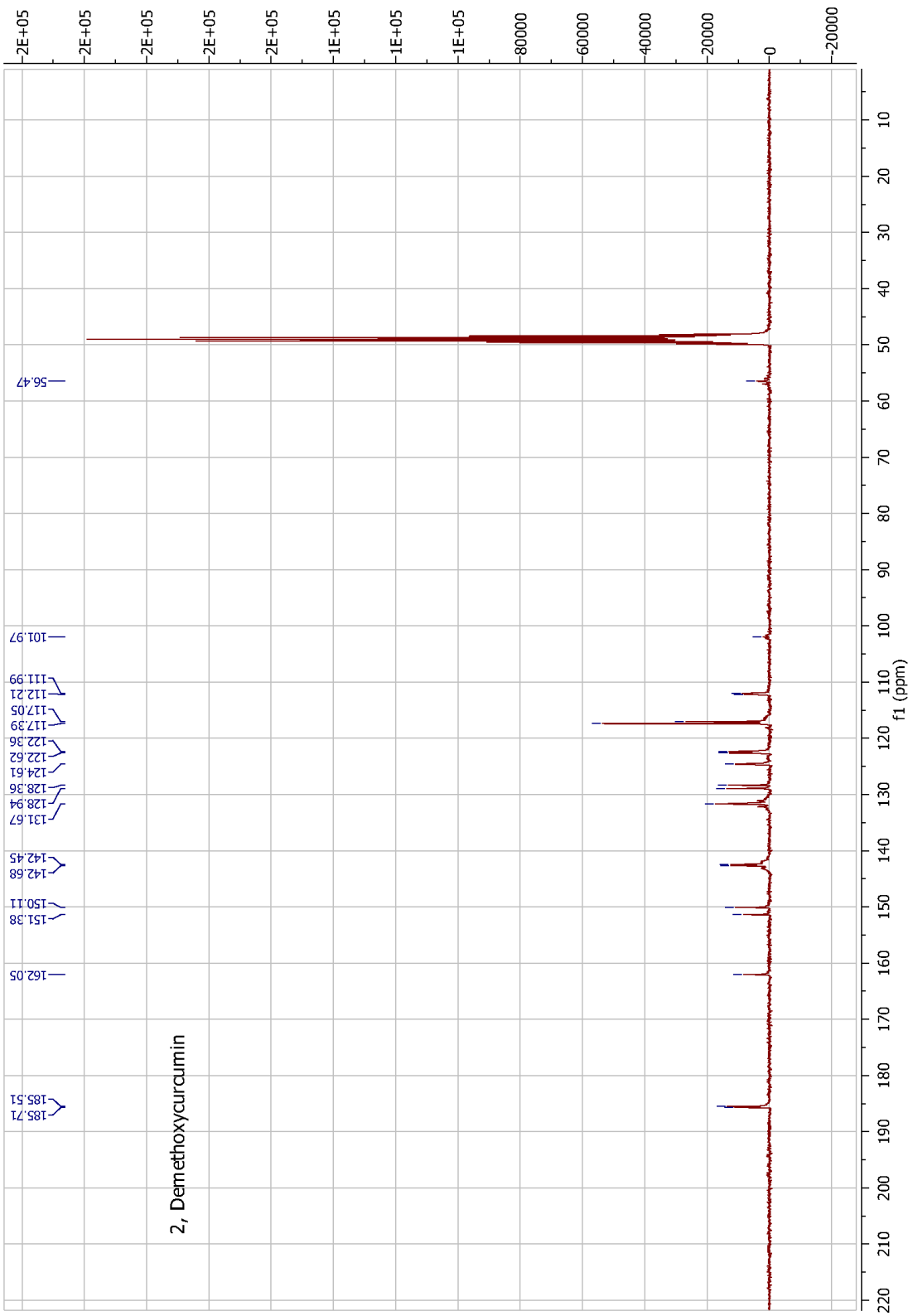
1, ***Curcumin (MeOD)***



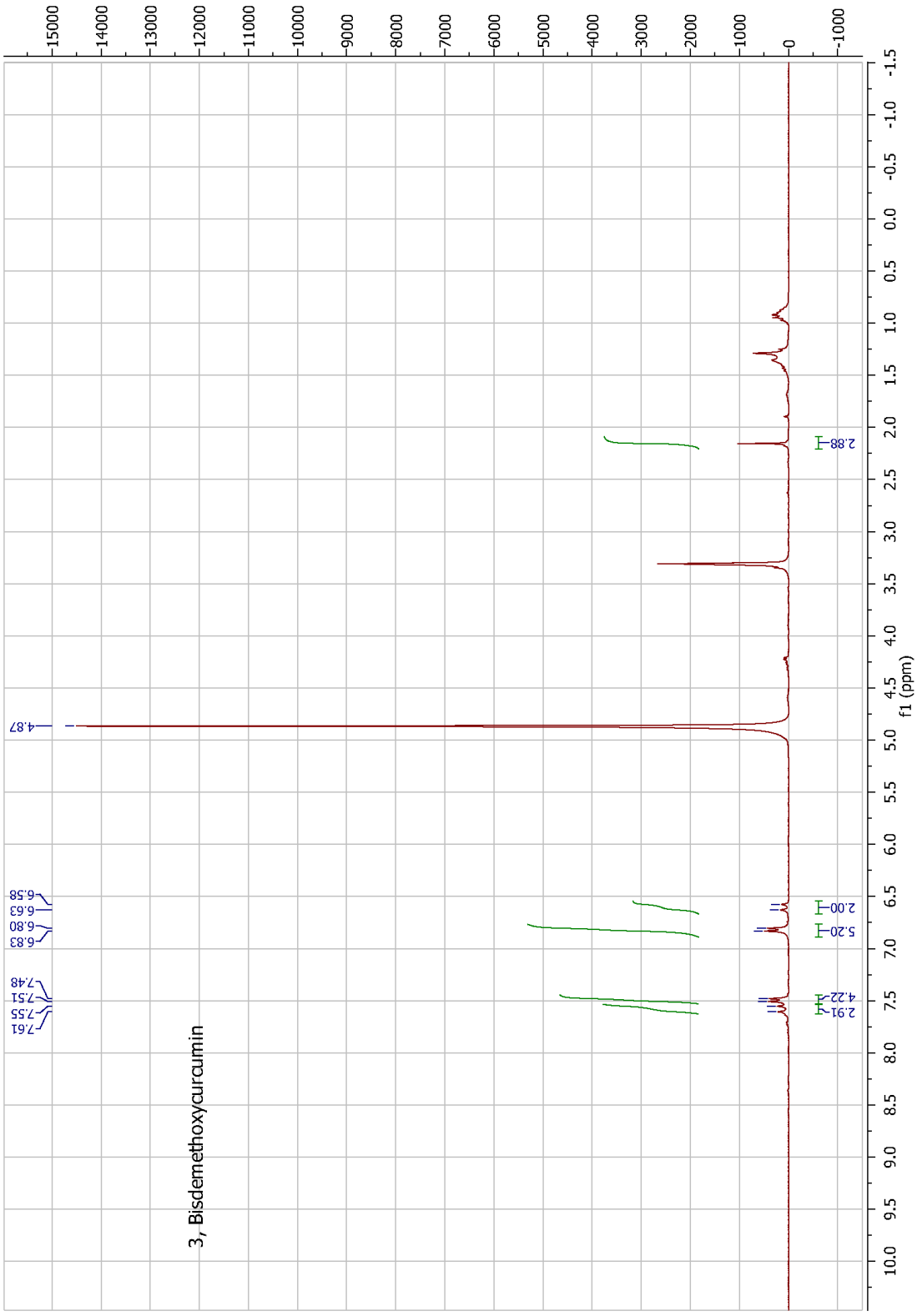

1, Curcumin
185.63
151.14
150.07
142.71
129.10
124.66
122.76
117.01
112.26
112.04
56.50
56.02
f1 (ppm)

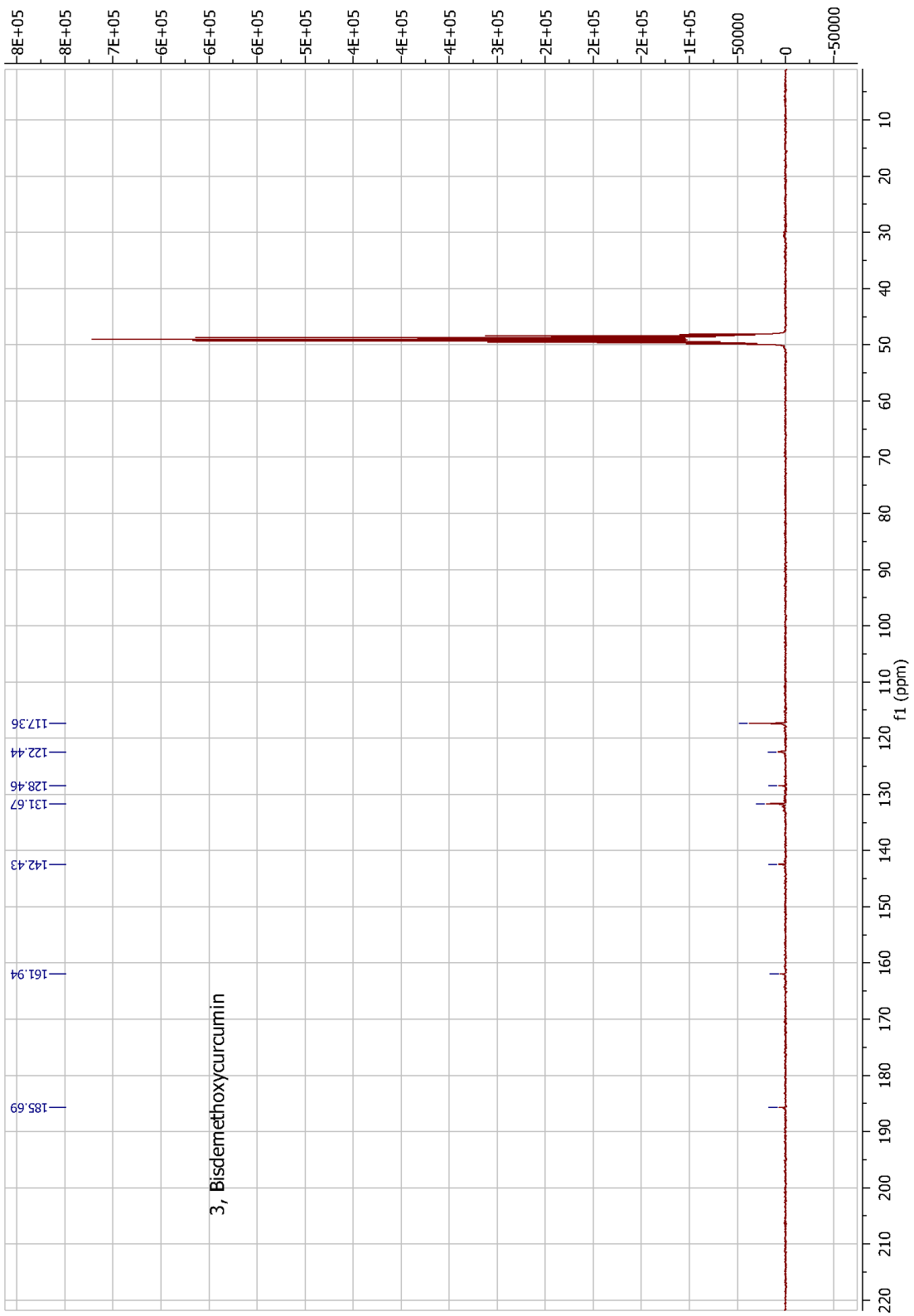
2, Demethoxycurcumin (MeOD)



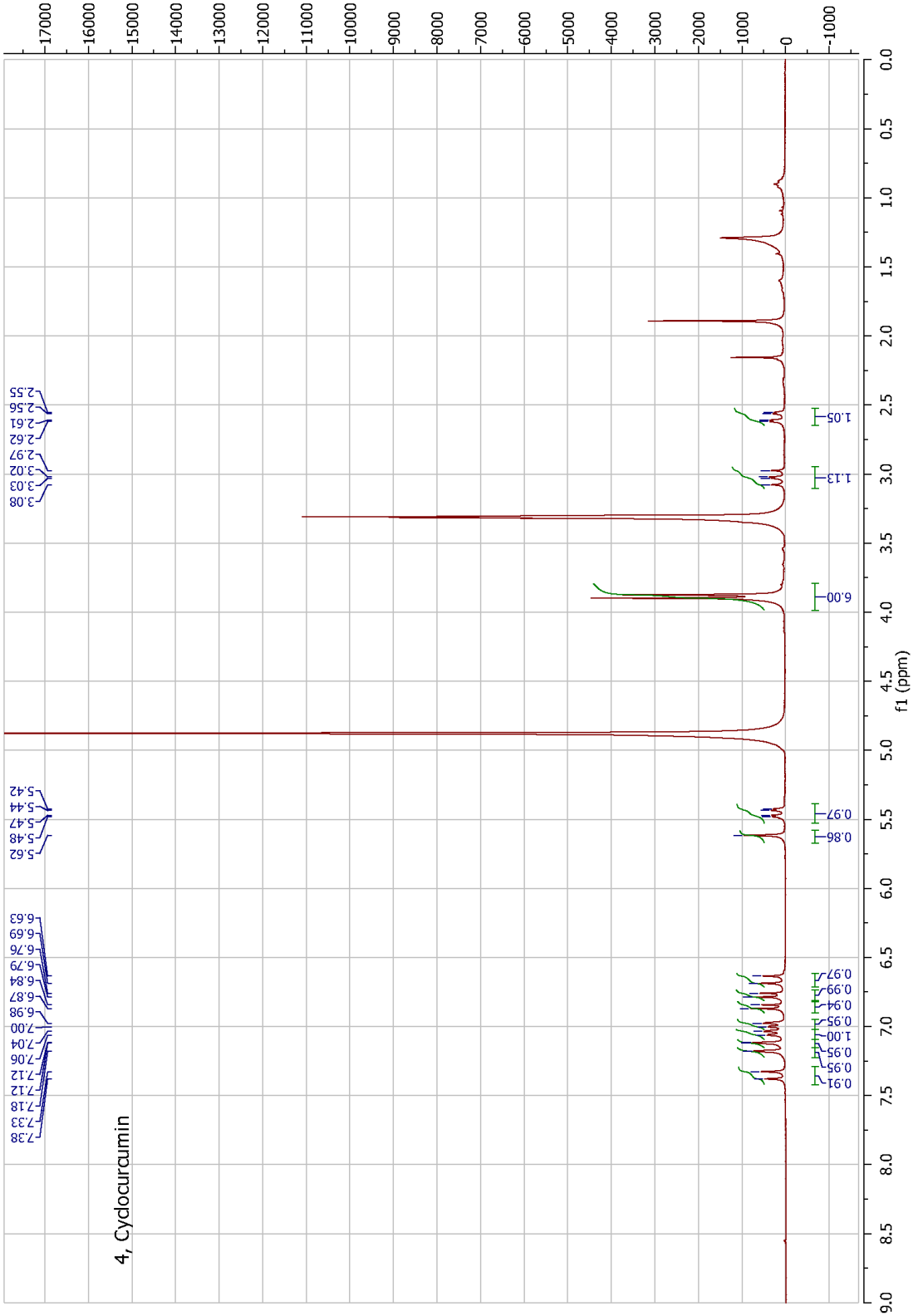

2, Demethoxycurcumin
185.71
185.51
162.05
151.38
150.11
142.68
142.45
131.67
128.94
128.56
124.61
122.62
122.36
117.39
117.05
112.21
111.99
101.97
56.47
f1 (ppm)

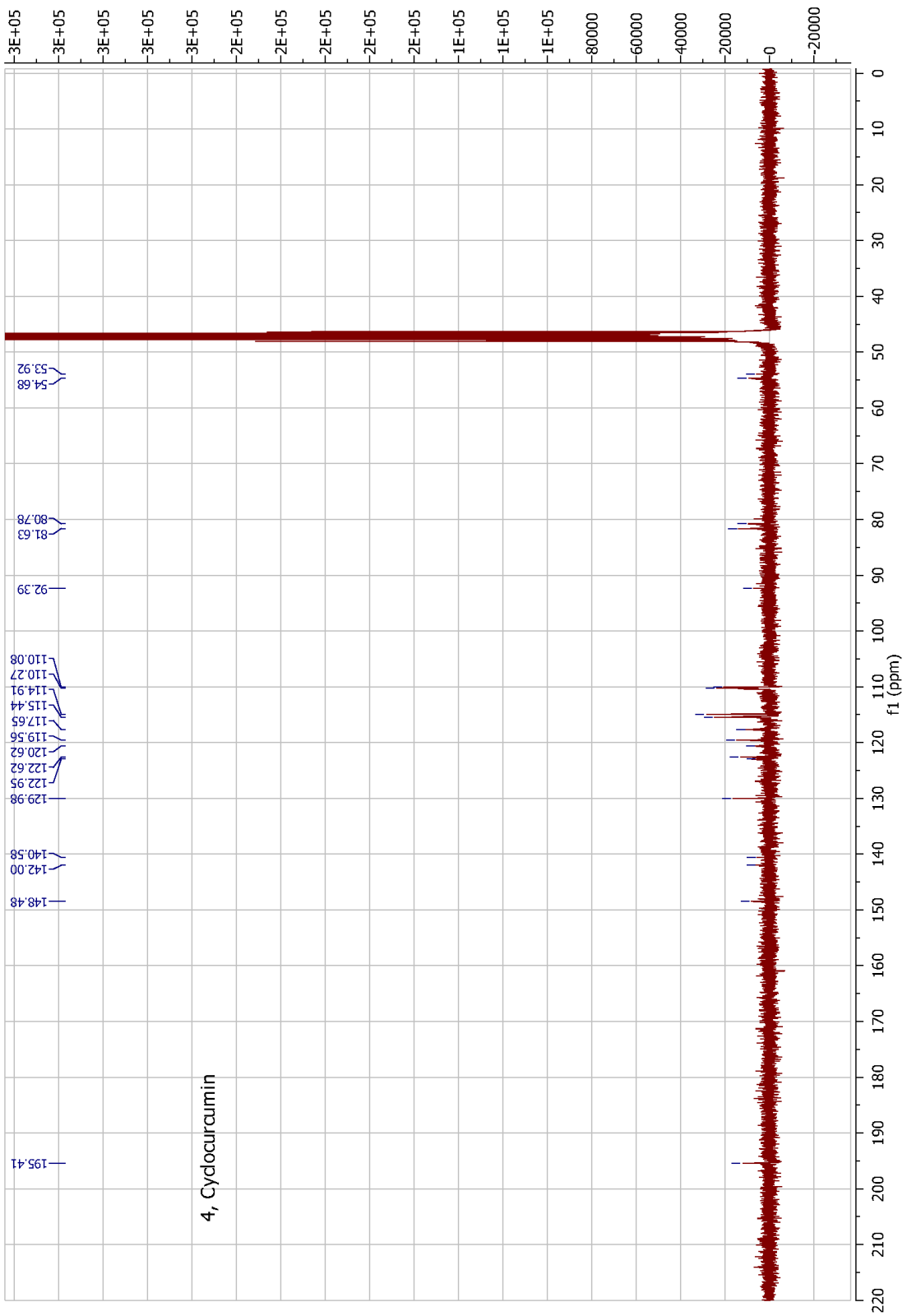
3, Bisdemethoxycurcumin (MeOD)



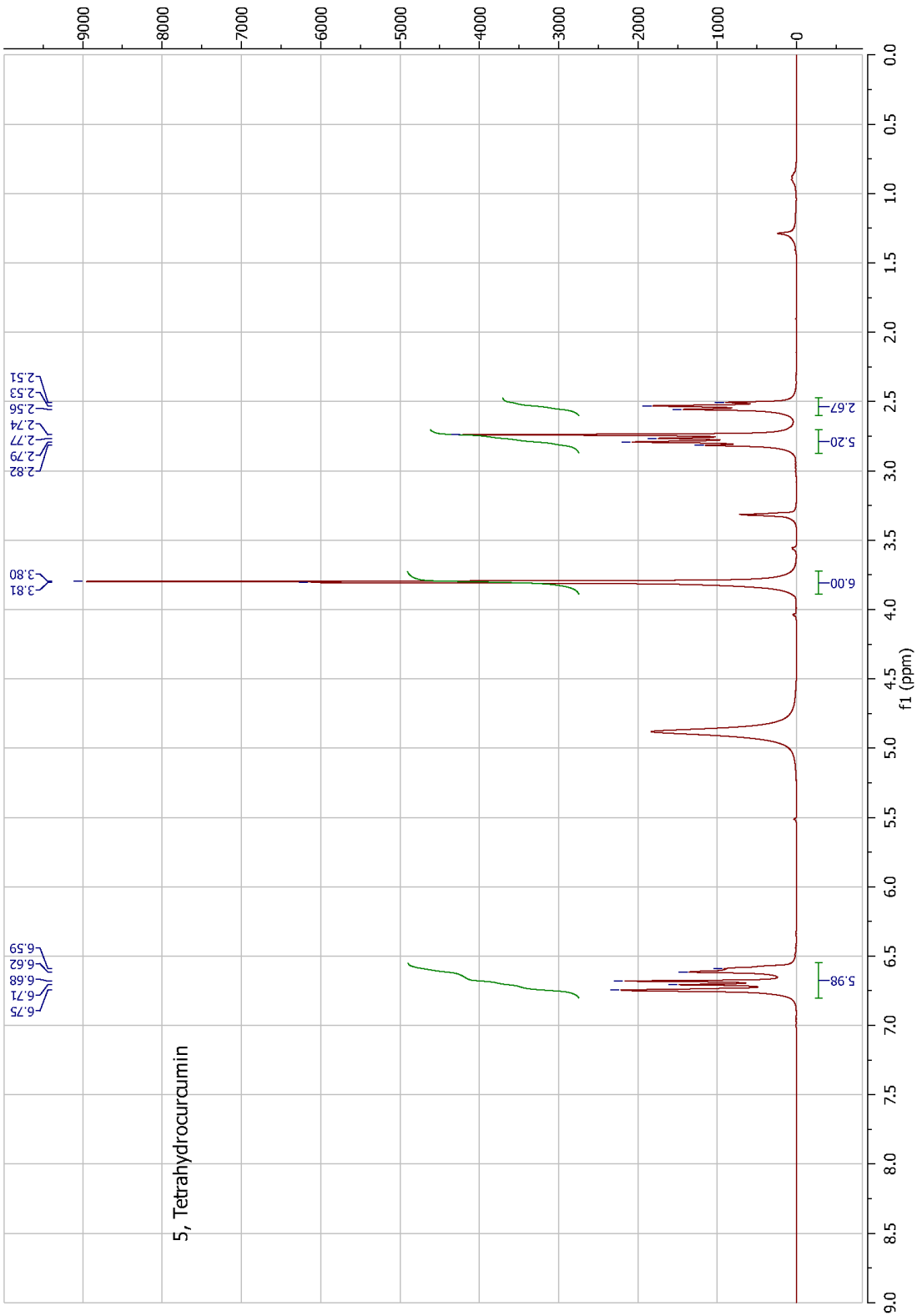

3, Bisdemethoxycurcumin
117.36
122.44
128.46
131.67
142.43
161.94
185.69
f1 (ppm)

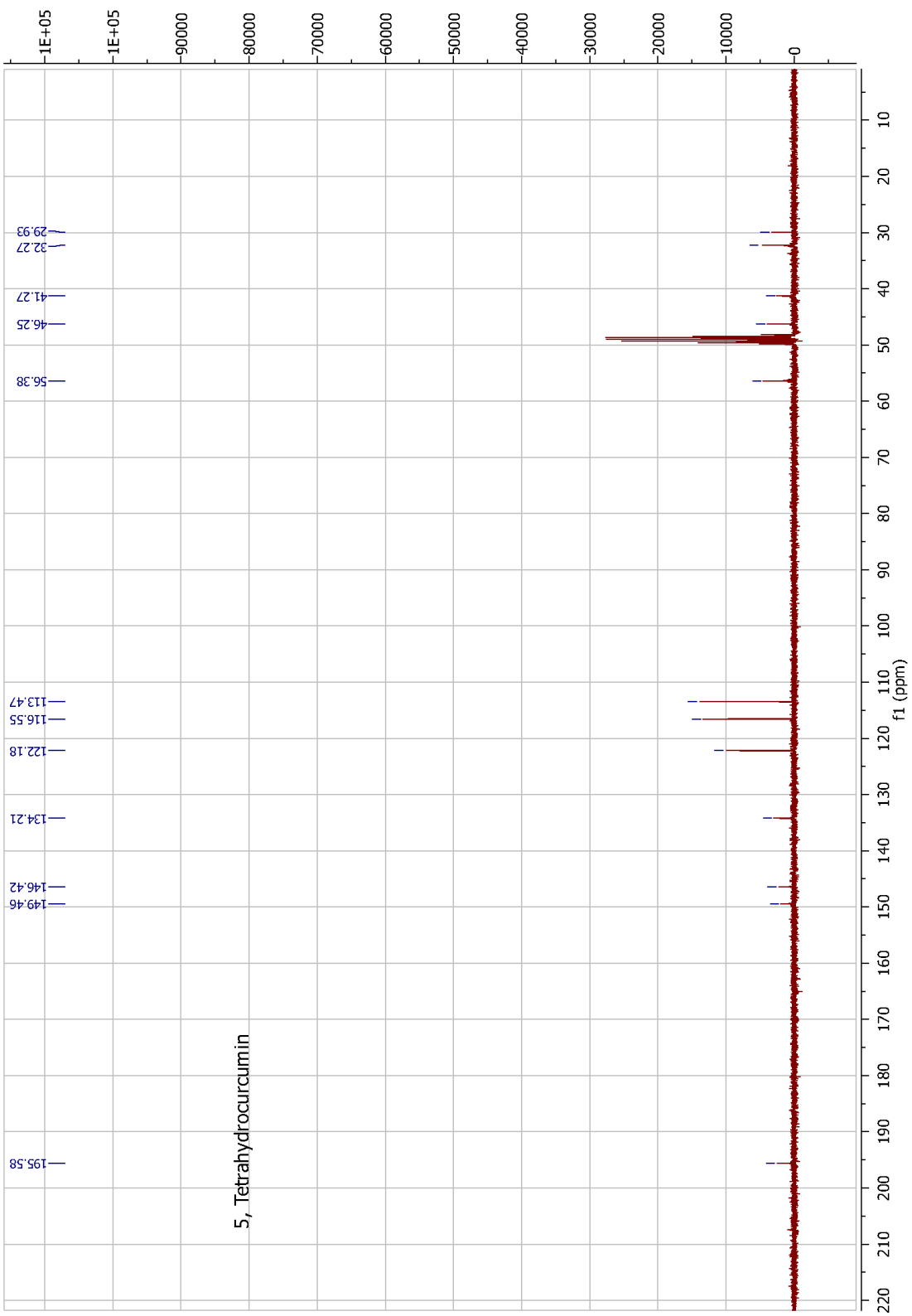
4, Cyclocurcumin (MeOD)



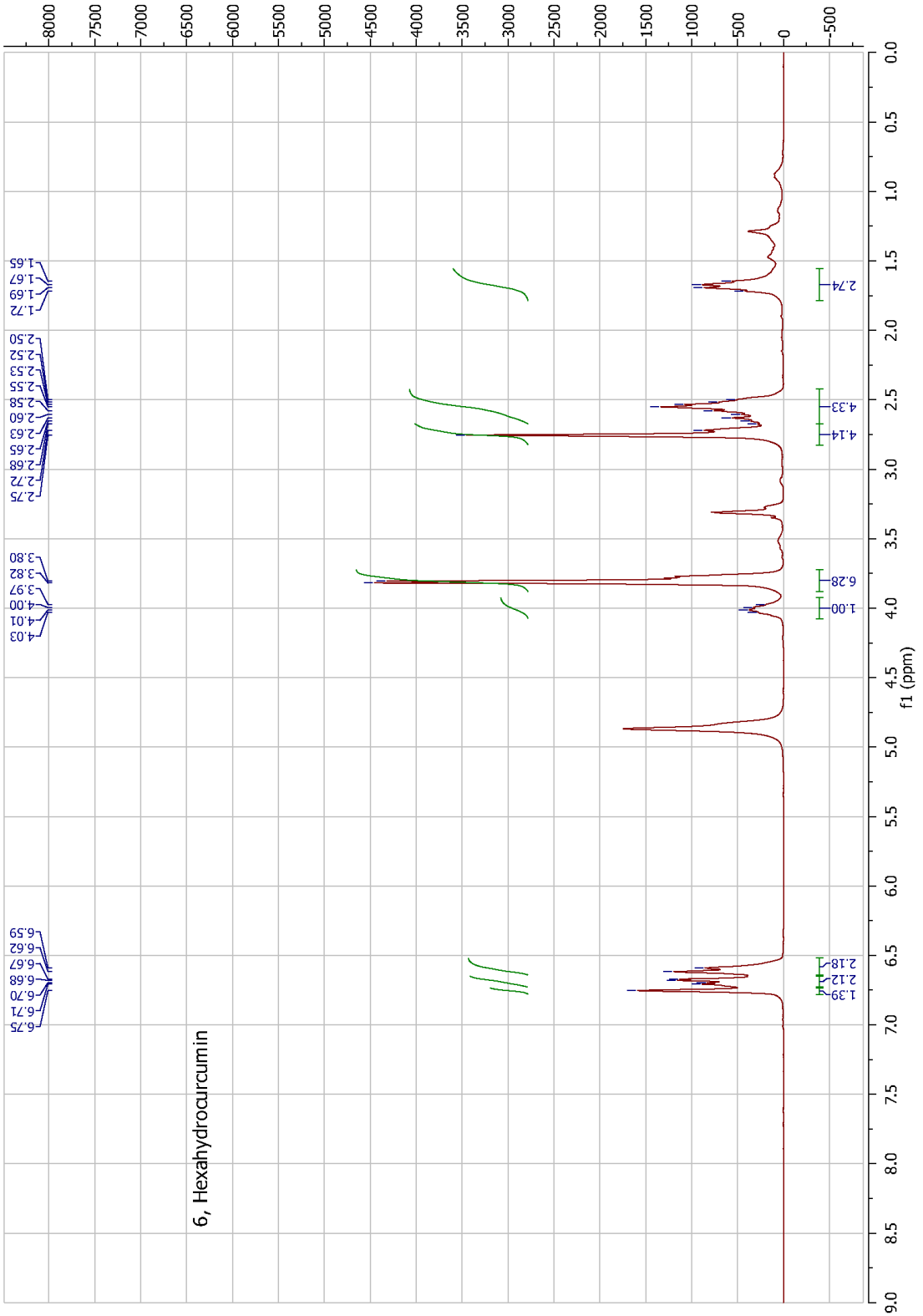

4, Cyclocurcumin
195.41
148.48
142.00
140.58
129.98
122.95
122.62
120.62
119.56
117.65
115.44
114.91
110.27
110.08
92.39
81.63
80.78
54.68
53.92
f1 (ppm)

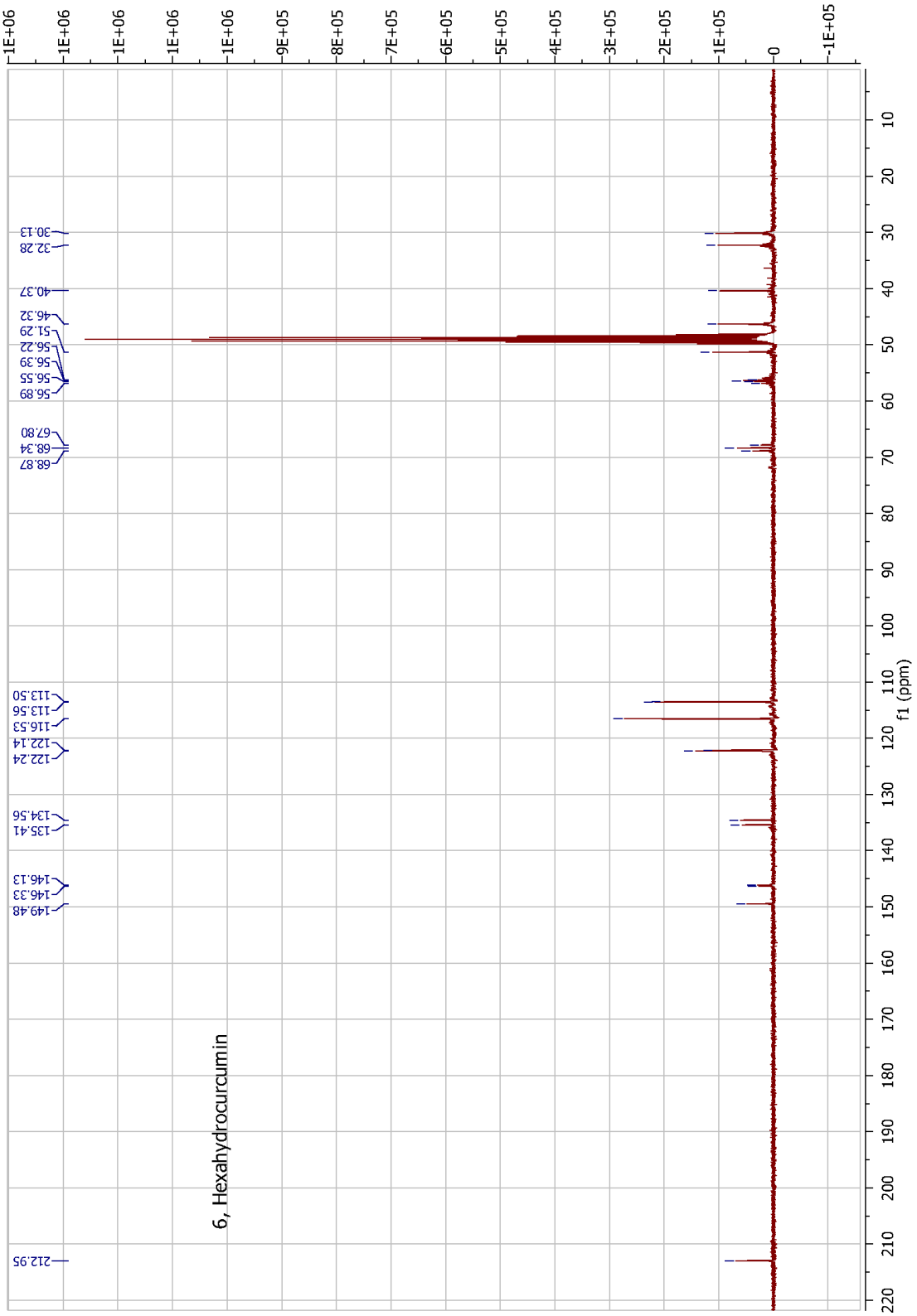
5, Tetrahydrocurcumin (MeOD)



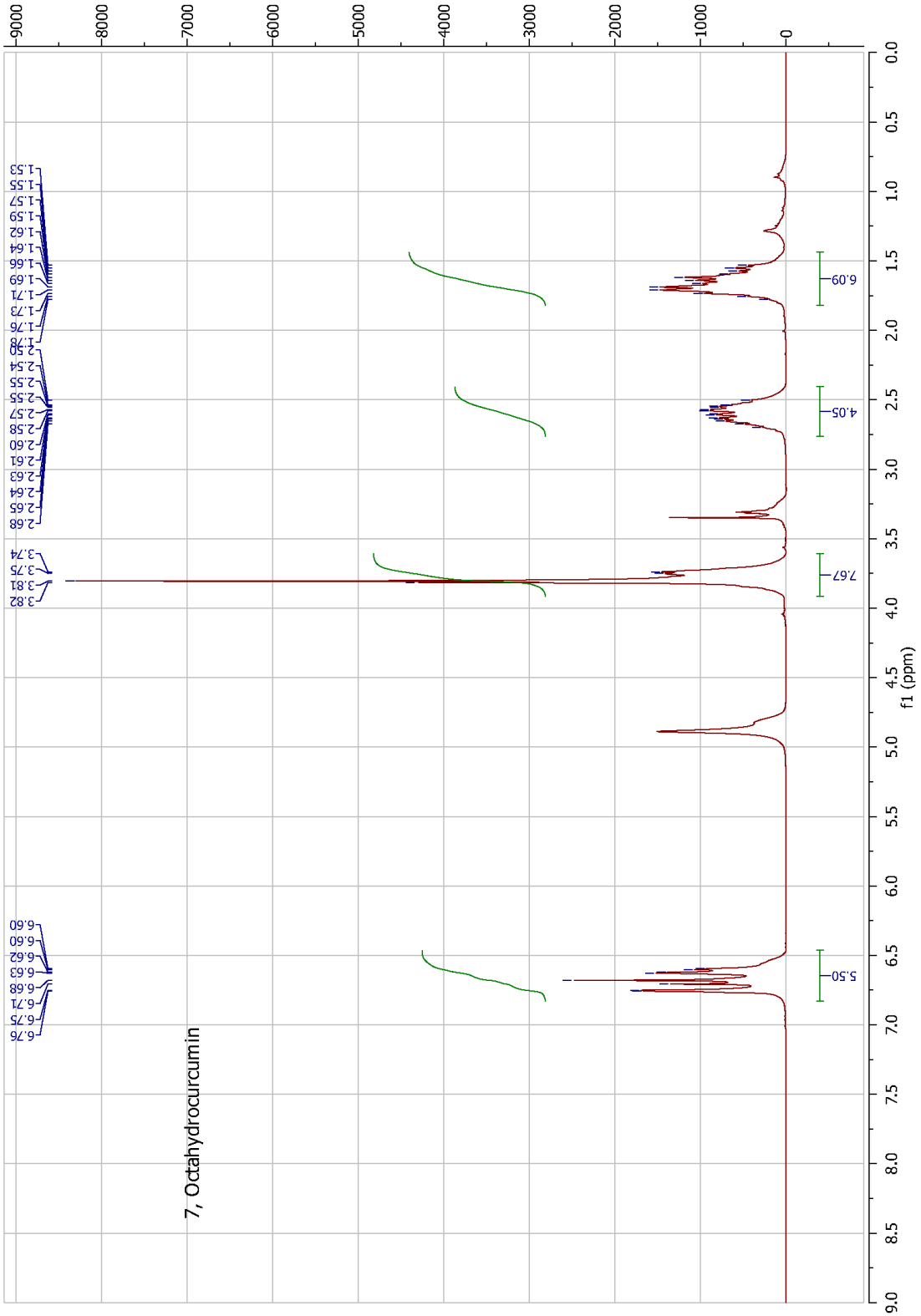

5, Tetrahydrocurcumin
29.93
32.27
41.27
46.25
56.38
113.47
116.55
122.18
134.21
146.42
149.46
195.58
f1 (ppm)

6, Hexahydrocurcumin (MeOD)




6, Hexahydrocurcumin
f1 (ppm)
212.95
149.48
146.33
146.13
135.41
134.56
122.24
122.14
116.53
113.56
113.50
68.87
68.34
67.80
56.89
56.55
56.39
56.22
51.29
46.32
40.37
32.28
30.13

7, Octahydrocurcumin (MeOD)



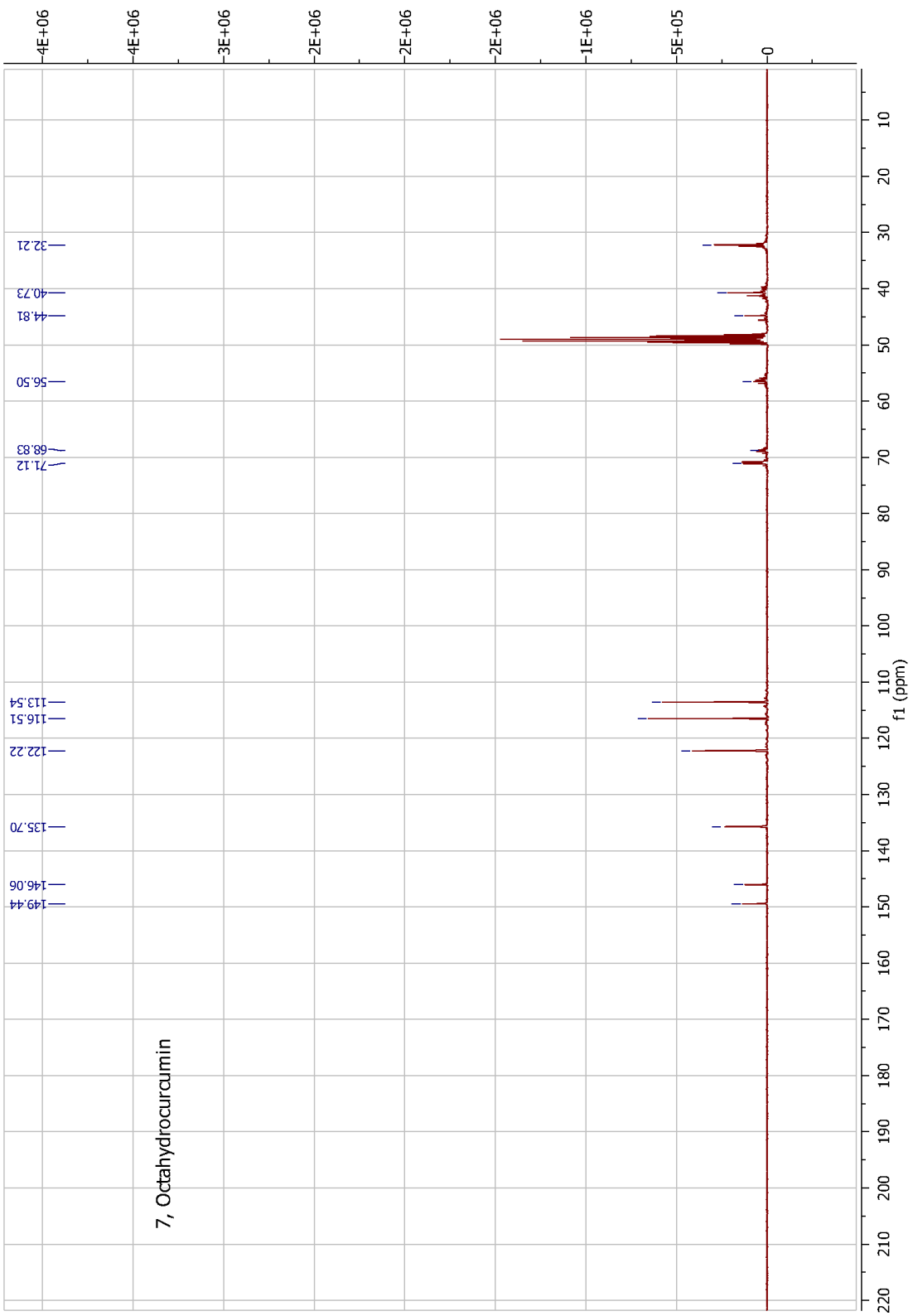

7, Octahydrocurcumin
32.21
40.73
44.81
56.50
68.83
71.12
113.54
116.51
122.22
135.70
146.06
149.44
f1 (ppm)

Table 2SI. Outer hyperfine splittings ($2A_{max}$) of spin-labeled phospholipids incorporated in DOPC, DOPG, DOPC/DOPG 90/10 lipid bilayers, in the presence of ligands (CUR, DMC, BDMC, MIX, CYC, THC, HHC and OHC) and/or A*β*(25-35).

	DOPC		***DOPG***		***DOPC/DOPG 90/10***	
	5-PCSL	***14-PCSL***	***5-PCSL***	***14-PCSL***	***5-PCSL***	***14-PCSL***
	51.5	*32.2*	*51.2*	*31.7*	*51.3*	*32.6*
+ CUR	*51.9*	*31.9*	*52.6*	*31.8*	*52.0*	*32.8*
+ DMC	*51.8*	*31.8*	*52.7*	*31.7*	*52.1*	*32.8*
+ BDMC	*52.0*	*32.0*	*52.6*	*31.5*	*51.9*	*32.5*
+ MIX	*51.9*	*31.9*	*52.8*	*31.9*	*52.0*	*32.9*
+ CYC	*52.3*	*32.3*	*53.2*	*32.1*	*52.4*	*33.1*
+ THC	*52.1*	*32.2*	*53.0*	*32.0*	*52.2*	*33.0*
+ HHC	*51.9*	*32.0*	*52.8*	*31.6*	*52.0*	*32.8*
+ OHC	*52.0*	*31.9*	*52.9*	*31.9*	*51.9*	*32.5*

+Aβ (25-35)

	DOPC		***DOPG***		***DOPC/DOPG 90/10***	
	5-PCSL	***14-PCSL***	***5-PCSL***	***14-PCSL***	***5-PCSL***	***14-PCSL***
Aβ (25-35)	*52.2*	*32.0*	*52.0*	*31.4*	*52.1*	*32.5*
+ CUR	*52.0*	*31.7*	*52.8*	*31.6*	*52.1*	*32.9*
+ DMC	*51.8*	*31.9*	*52.8*	*31.7*	*52.2*	*32.9*
+ BDMC	*52.1*	*32.0*	*52.6*	*31.8*	*51.9*	*32.8*
+ MIX	*51.8*	*31.7*	*52.7*	*31.6*	*52.1*	*32.7*
+ CYC	*52.5*	*32.1*	*53.6*	*32.0*	*52.5*	*32.9*
+ THC	*52.3*	*32.0*	*53.2*	*32.0*	*52.4*	*32.8*
+ HHC	*51.9*	*31.8*	*52.8*	*31.9*	*52.3*	*32.7*
+ OHC	*51.9*	*31.9*	*53.0*	*31.9*	*52.1*	*32.8*

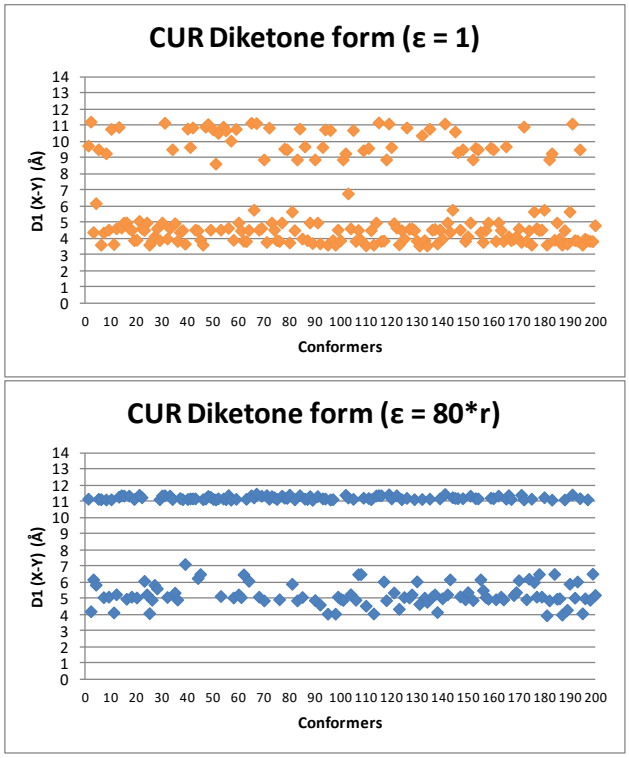


Figure 3SI. Obtained PM7 (orange) and MM (blue) conformers of di-ketone CUR plotted against the distance between the centroids of the two aromatic ring (d1).

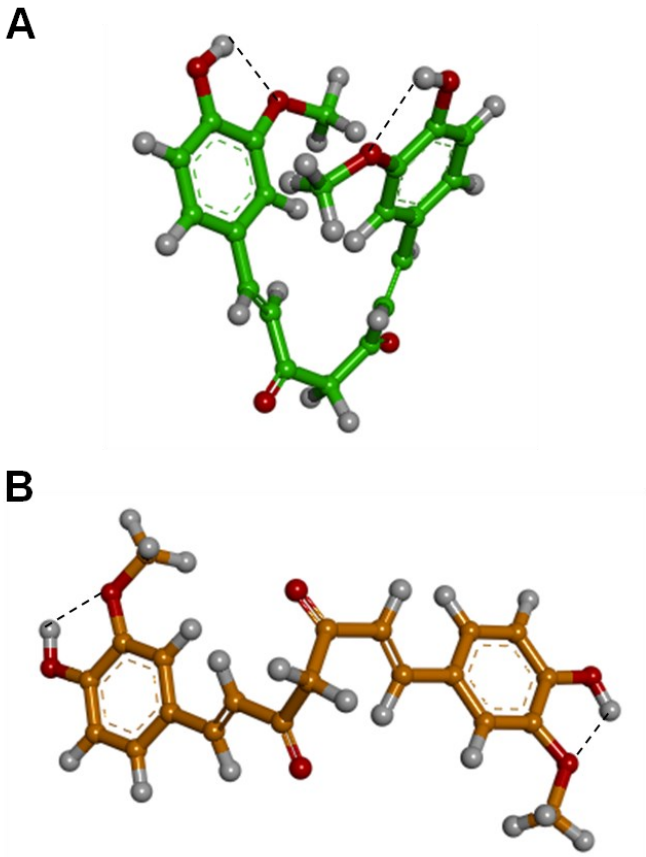


Figure 4SI. PM7 lowest energy conformers of di-ketone CUR: “folded” (A; green) and “extended” (B; orange) conformational family. The conformers are displayed as ball&sticks and colored by atom type: O, red; H, white. Hydrogen bonds are highlighted with a black dashed line.

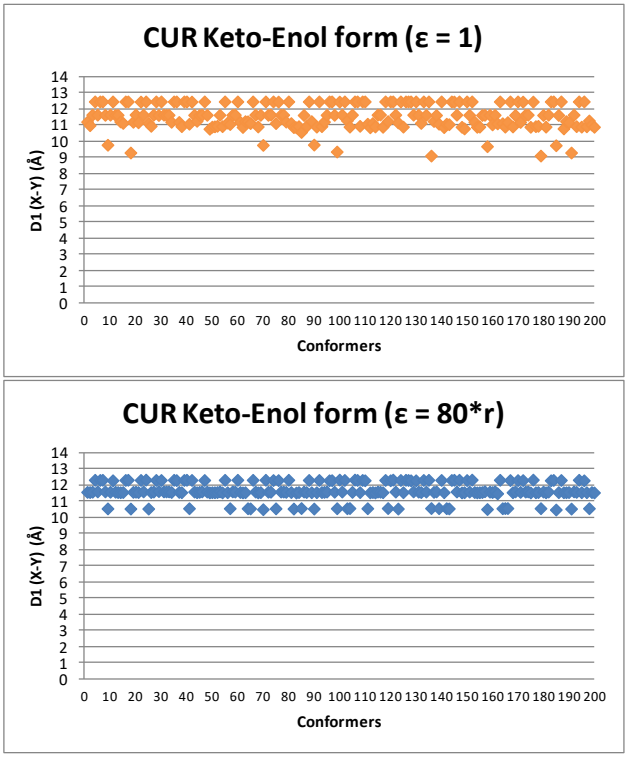


Figure 5SI. Obtained PM7 (orange) and MM (blue) conformers of keto-enol CUR plotted against the distance between the centroids of the two aromatic rings (d1).

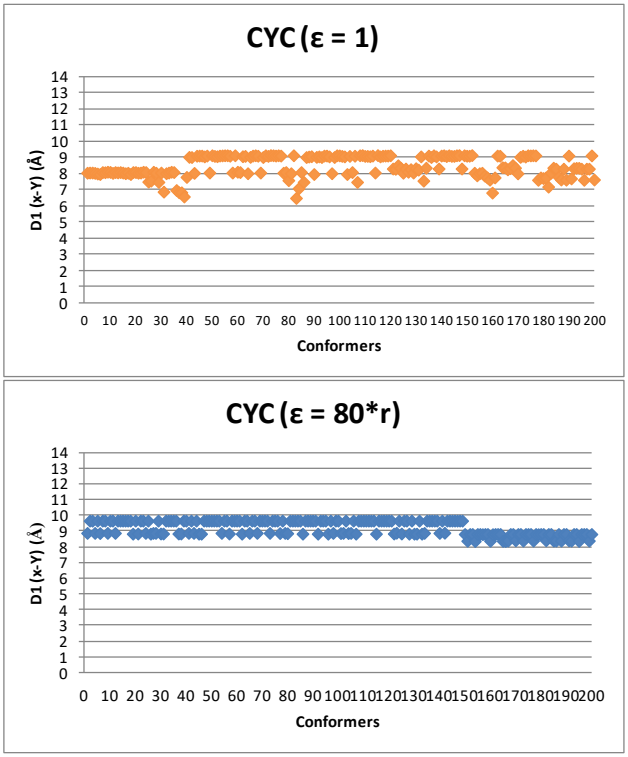


Figure 6SI. Obtained PM7 (orange) and MM (blue) conformers of CYC plotted against the distance between the centroids of the two aromatic rings (d1).

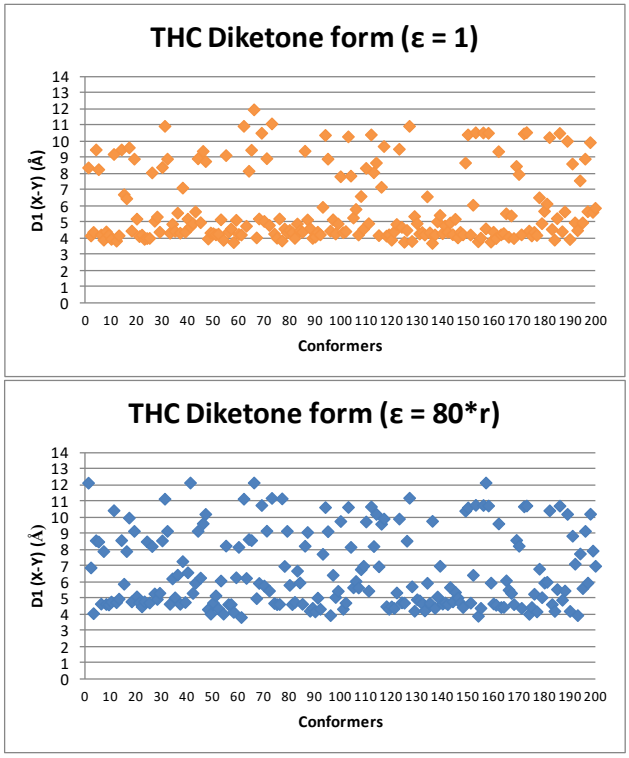


Figure 7SI. Obtained PM7 (orange) and MM (blue) conformers of di-ketone THC plotted against the distance between the centroids of the two aromatic rings (d1).

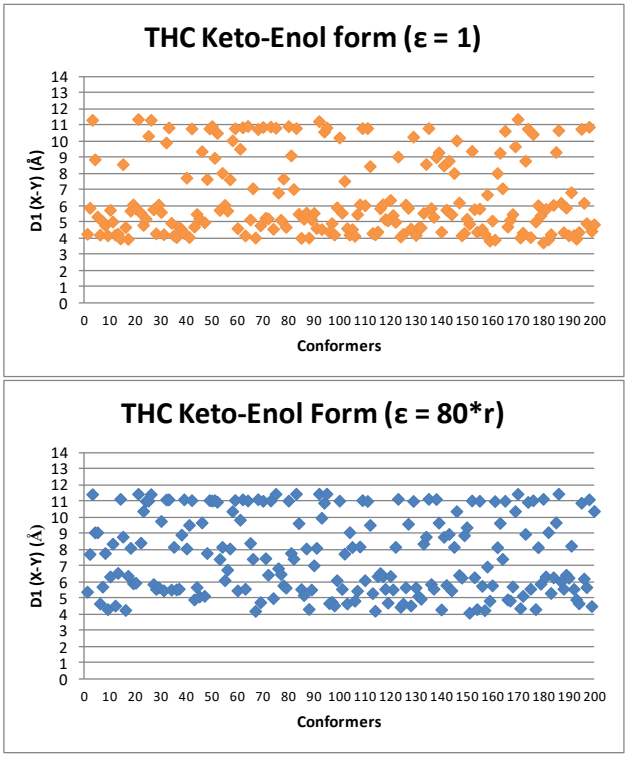


Figure 8SI. Obtained PM7 (orange) and MM (blue) conformers of keto-enol THC plotted against the distance between the centroids of the two aromatic rings (d1).

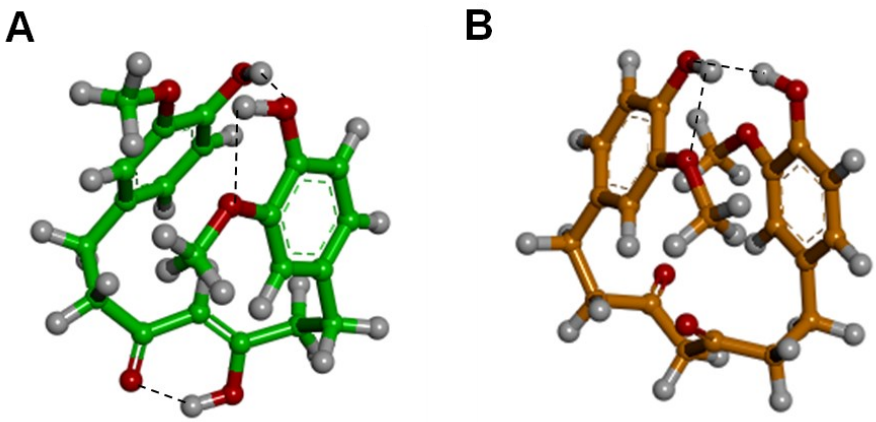


Figure 9SI. PM7 lowest energy conformers of THC in keto-enol (A; green) and diketone form (B; orange). The conformers are displayed as ball&sticks and colored by atom type: O, red; H, white. Hydrogen bonds are highlighted with a black dashed line.

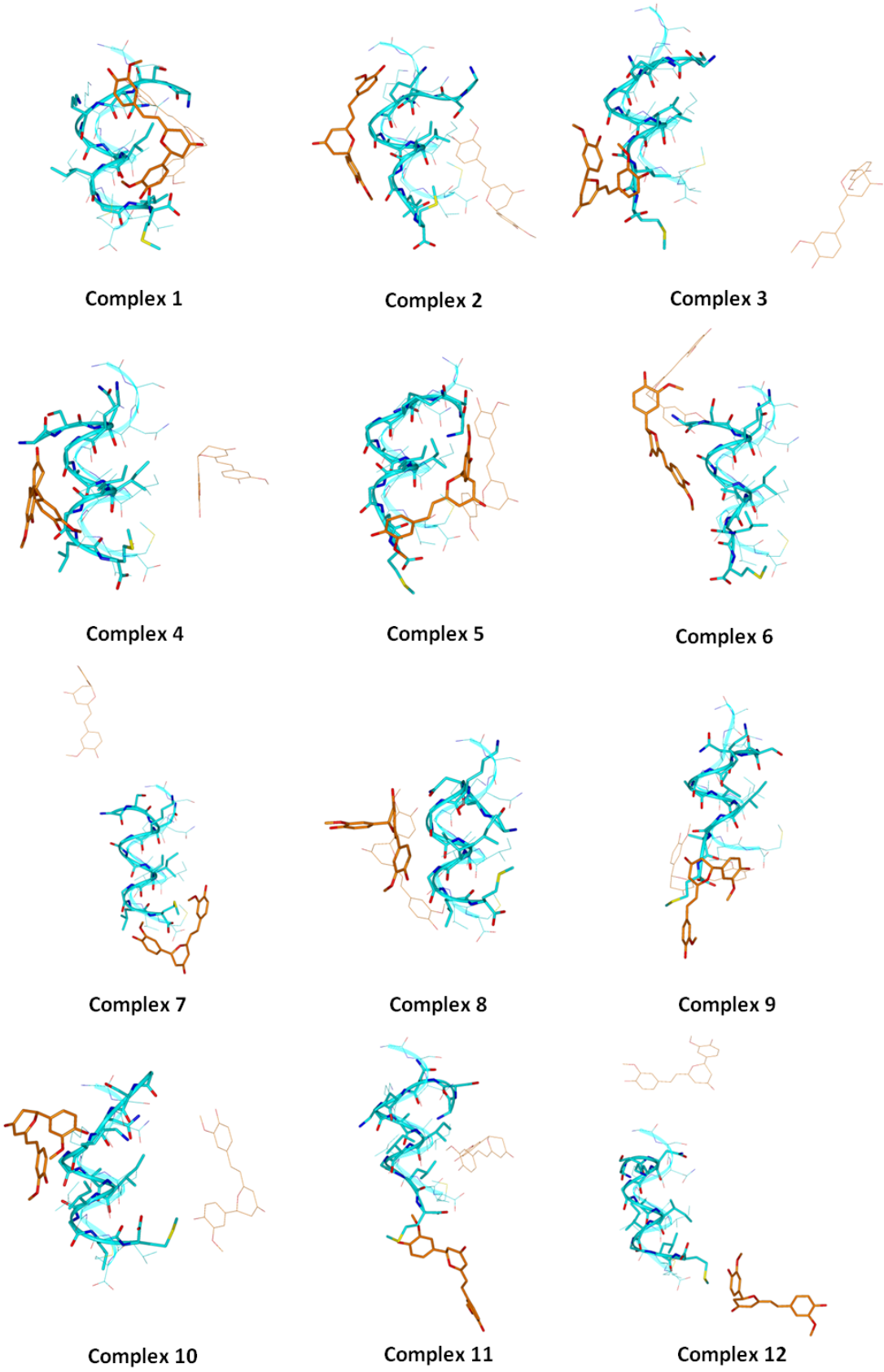


Figure 10SI. Superimposition between docked (lines) and annealed complexes (sticks) of CYC (orange) and Aβ(25–35) peptide (cyan). The peptides are displayed as ribbon. Molecules are colored by atom type (O: red; N: blue; S: yellow). Hydrogens are omitted for sake of clarity.

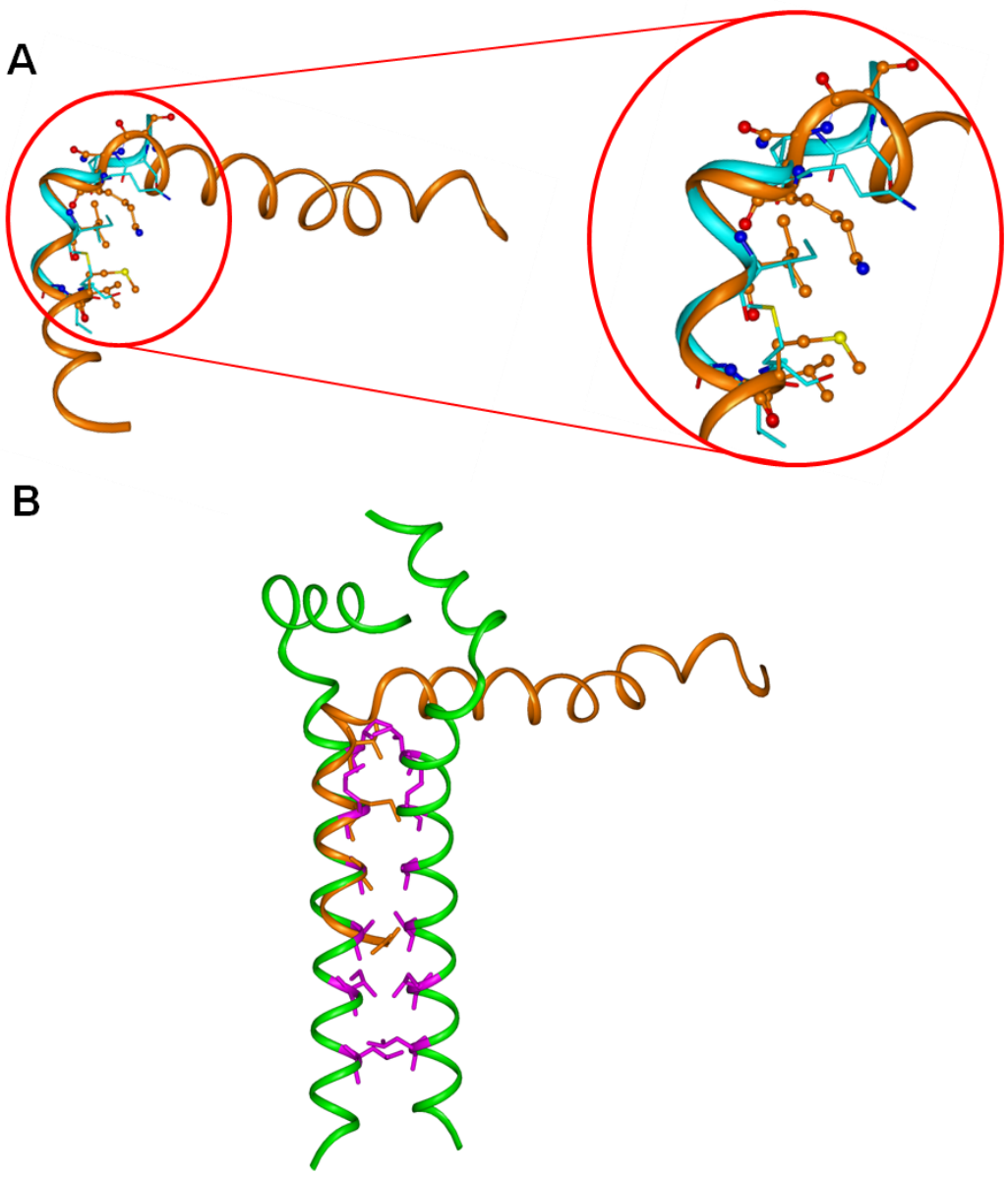
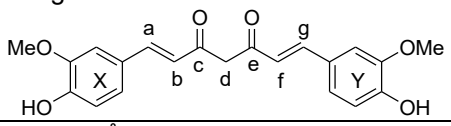


Figure 11SI. A) Superimposition between Aβ(25–35) (cyan and sticks; PDB ID: 1QWP) and Aβ(1–42) peptide (orange and ball&sticks; PDB ID: 1IYT). The peptides are displayed as ribbon and colored by atom type (O: red; N: blue; S: yellow). B) Superimposition between Aβ(1–42) peptide (orange ; PDB ID: 1IYT) and APP (green; PDB ID: 2LOH). The heptad repeat motif interacting amino acids are displayed as stick and in case of APP colored in magenta. Hydrogens are omitted for sake of clarity.

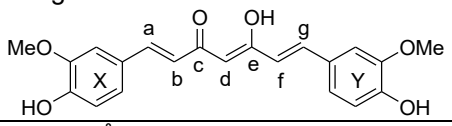
Table 3SI. ΔE range values (kcal/mol), distance X-Y (d1), torsional angle values (τ1, τ2, τ3, and τ4), and occurrence rate (%) of each conformational family of CUR in diketone form considering MM and PM7 conformers within 5 kcal/mol from the global minimum.



Fam	ΔE_{GM} (kcal/mol)[a]	d1 (Å)[a]	Torsional Angles (°)[a]				%
			τ1[b]	τ2[c]	τ3[d]	τ4[e]	
MM I	0.00	5.10	-128.37	78.66	-74.92	134.23	23
MM II	0.01	5.10	134.50	-74.85	78.67	-128.26	29
MM III	2.56	5.61	-143.50	38.42	38.48	-143.52	3
MM IV	3.17	4.87	134.07	-35.71	-35.53	133.88	1
MM V	3.76	11.35	178.37	86.74	86.73	178.36	22
MM VI	3.76	11.35	-178.39	-86.75	-86.74	-178.36	22
PM7 I	0.00	4.98	-153.51	32.16	32.09	-153.48	26
PM7 II	0.00	4.98	153.49	-32.13	-32.13	153.50	23
PM7 III	0.95	4.52	154.65	-71.99	52.78	-117.36	24
PM7 IV	0.95	4.52	-154.57	71.95	-52.85	117.48	24
PM7 V	1.45	4.64	166.86	-158.96	17.27	-75.06	1
PM7 VI	2.88	3.68	-100.07	-31.34	61.42	-152.66	1
PM7 VII	3.42	3.78	153.25	-49.10	-0.93	130.31	1

[a]The values reported refer to the lowest energy conformers of the family. [b]τ1 torsional angle is calculated considering a, b, c, and d atoms. [c]τ2 torsional angle is calculated considering b, c, d, and e atoms. [d]τ3 torsional angle is calculated considering c, d, e, and f atoms. [e]τ4 torsional angle is calculated considering d, e, f, and g atoms.

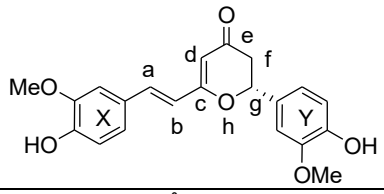
Table 4SI. ΔE range values (kcal/mol), distance X-Y (d1), torsional angle values (τ1, τ2, τ3, and τ4), and occurrence rate (%) of each conformational family of CUR in keto-enol form considering MM and PM7 conformers within 5 kcal/mol from the global minimum.



Fam	ΔE_{GM} (kcal/mol)[a]	d1 (Å)[a]	Torsional Angles (°)[a]				%
			τ1[b]	τ2[c]	τ3[d]	τ4[e]	
MM I	0.00	12.31	178.92	-179.95	-180.00	179.90	33
MM II	1.05	11.58	29.55	-174.12	179.78	-179.84	39
MM III	3.41	11.54	-174.17	42.94	179.33	179.80	18
MM IV	4.25	10.54	21.65	48.31	179.53	179.64	10
PM7 I	0.00	12.45	177.66	179.69	179.84	176.22	42.5
PM7 II	0.81	11.63	-42.74	179.36	179.71	177.96	57.5

[a] The values reported refer to the lowest energy conformers of the family. [b] τ1 torsional angle is calculated considering a, b, c, and d atoms. [c] τ2 torsional angle is calculated considering b, c, d, and e atoms. [d] τ3 torsional angle is calculated considering c, d, e, and f atoms. [e] τ4 torsional angle is calculated considering d, e, f, and g atoms.

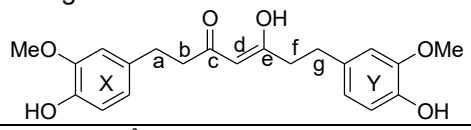
Table 5SI. ΔE range values (kcal/mol), distance X-Y (d1), torsional angle values (τ1, τ2, and τ3), and occurrence rate (%) of each conformational family of CYC considering MM and PM7 conformers within 5 kcal/mol from the global minimum.



Fam	ΔE_{GM} (kcal/mol)[a]	d1 (Å)[a]	Torsional Angles (°)[a]			%
			τ1[b]	τ2[c]	τ3[d]	
MM I	0.00	8.81	179.31	46.79	-48.30	23
MM II	1.89	8.37	179.35	-41.19	37.12	11
MM III	2.53	9.66	-0.61	46.81	-49.20	51
MM IV	4.42	8.83	0.48	-41.46	37.89	15
PM7 I	0.00	7.00	176.89	-52.12	54.91	11
PM7 II	0.39	7.60	31.83	-51.73	50.09	28
PM7 III	0.84	8.05	-166.05	51.25	-41.51	19
PM7 IV	1.57	9.02	21.02	50.69	-40.61	42

[a] The values reported refer to the lowest energy conformers of the family. [b]τ1 torsional angle is calculated considering a, b, c, and d atoms. [c]τ2 torsional angle is calculated considering e, f, g, and h atoms. [d]τ3 torsional angle is calculated considering f, g, h, and c atoms.

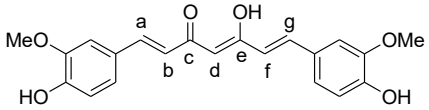
Table 6SI. ΔE range values (kcal/mol), distance X-Y (d1), torsional angle values (τ1, τ2, τ3, and τ4), and occurrence rate (%) of each conformational family of THC in keto-enol form considering MM and PM7 conformers within 5 kcal/mol from the global minimum.



Fam	ΔE_{GM} (kcal/mol)[a]	d1 (Å)[a]	Torsional Angles (°)[a]				%
			τ1[b]	τ2[c]	τ3[d]	τ4[e]	
MM I	0.00	4.37	87.13	144.17	179.27	77.36	4
MM II	0.15	4.20	-113.67	126.61	179.43	42.32	15
MM III	0.19	4.32	-85.72	-151.04	-179.45	-75.97	7
MM IV	0.64	4.53	98.50	157.16	178.34	-105.06	27
MM V	1.00	4.54	-112.37	-71.81	179.38	-105.52	8
MM VI	1.68	4.66	-117.31	32.08	178.13	-81.03	6
MM VII	2.06	4.91	52.14	36.05	-176.52	107.17	8
MM VIII	2.16	4.67	118.45	-33.51	-178.08	80.42	1
MM IX	2.31	5.86	84.09	-164.44	174.36	-89.34	8
MM X	2.32	5.94	-83.70	161.17	-174.09	90.51	5
MM XI	3.90	5.13	-60.95	-32.10	174.43	-84.24	3.5
MM XII	3.90	5.56	-108.72	55.51	-172.38	83.55	1
MM XIII	4.22	5.91	82.15	134.71	-172.26	86.85	5
XIV	4.95	6.75	107.39	-61.20	174.08	-106.06	1
PM7 I	0.00	4.03	66.27	179.47	178.72	73.41	29
PM7 II	0.00	4.03	-66.08	-179.46	-178.73	-73.58	42
PM7 III	0.68	4.27	-134.32	179.13	179.64	103.24	17
PM7 IV	2.62	4.94	84.33	-175.86	170.86	-62.62	8
PM7 V	4.95	6.03	94.46	-164.28	171.53	-13.47	4

[a] The values reported refer to the lowest energy conformers of the family. [b]τ1 torsional angle is calculated considering a, b, c, and d atoms. [c]τ2 torsional angle is calculated considering b, c, d, and e atoms. [d]τ3 torsional angle is calculated considering c, d, e, and f atoms. [e]τ4 torsional angle is calculated considering d, e, f, and g atoms.

Table 7SI. Torsional angle values (τ1, τ2, τ3, and τ4) of the experimentally determined structures of CUR.



CSD Code	Torsional Angles (°)			
	τ1[a]	**τ2[b]**	**τ3[c]**	**τ4[s]**
AXOGIE	176.19	-177.52	-178.61	179.72
AXOGOK	-176.21	178.27	-176.81	171.57
BINMEQ06	-170.44	-176.13	179.87	-173.35
BINMEQ07	170.47	175.68	-177.70	171.97
BINMEQ08	-170.61	-176.32	179.67	-173.78
BINMEQ	18.39	176.43	-178.81	-176.99
BINMEQ01	-16.63	-176.17	178.93	176.88
BINMEQ02	17.31	176.18	-178.91	-177.12
BINMEQ03	-18.32	-176.71	178.83	177.74
BINMEQ04	-18.49	-176.41	178.83	177.07
BINMEQ05	18.60	176.31	-178.84	-177.05

[a]τ1 torsional angle is calculated considering a, b, c, and d atoms. [b]τ2 torsional angle is calculated considering b, c, d, and e atoms. [c]τ3 torsional angle is calculated considering c, d, e, and f atoms. [d]τ4 torsional angle is calculated considering d, e, f, and g atoms.

Table 8SI. Conformational and interaction energy values of the CYC-Aβ(25–35) peptide complexes obtained by docking studies.

Frame	Complex Energy (kcal/mol)	Non-bond Interaction Energy (kcal/mol)
1	173.850	-17.266
2	177.898	-14.191
3	180.192	-14.528
4	182.297	-14.452
5	185.506	-12.605
6	187.292	-12.187
7	187.773	-12.320
8	188.072	-10.014
9	188.519	-9.498
10	189.290	-13.001
11	193.457	-5.615
12	198.052	-2.451