Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Design, Synthesis, Biological Evaluation, and SAR Studies of Novel Cyclopentaquinoline Derivatives as DNA Intercalators, Topoisomerase II Inhibitors, and Apoptotic Inducers

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Figure SI 1. 2D overlay diagram showing the superimposition of the native co-crystallized EVP, and the redocked co-crystallized one at human topoisomerase II-DNA complex target protein with **PDB:** 3QX3 with RMSD value 1.42 Å after the re-docking process for MOE program validation.

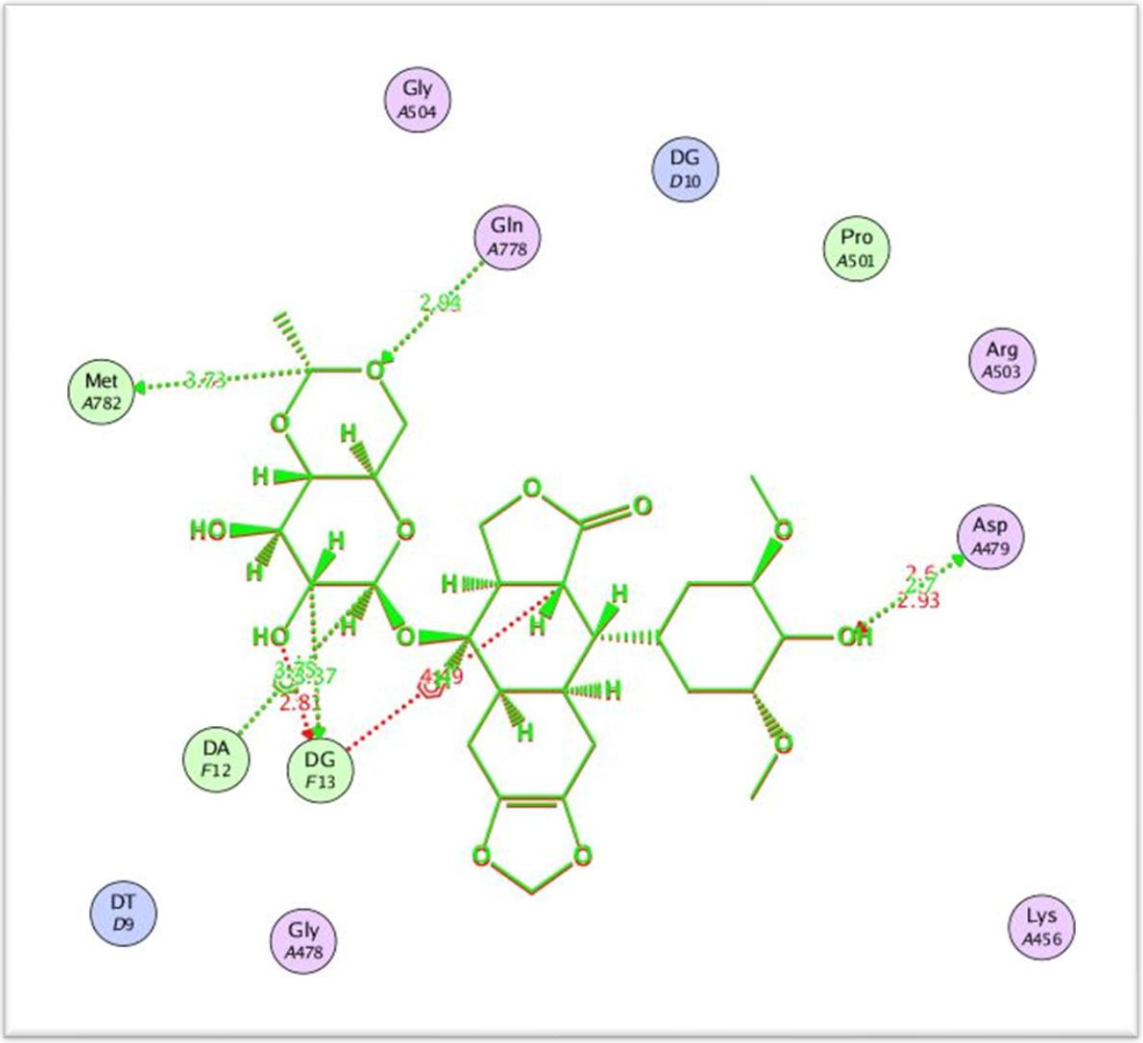


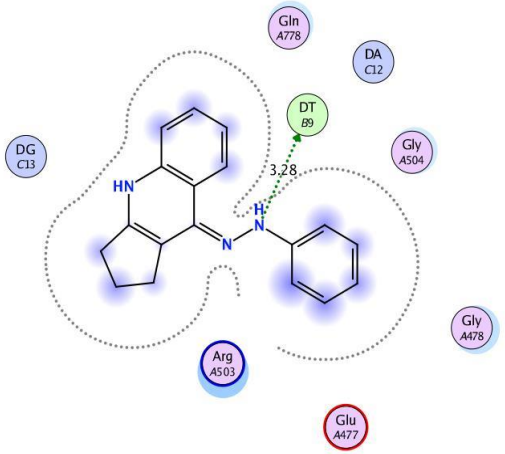
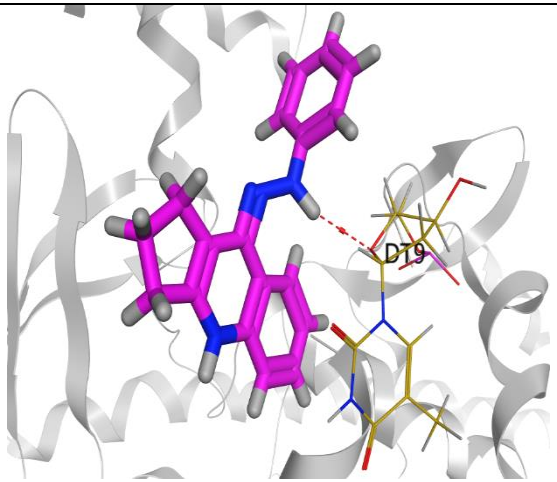
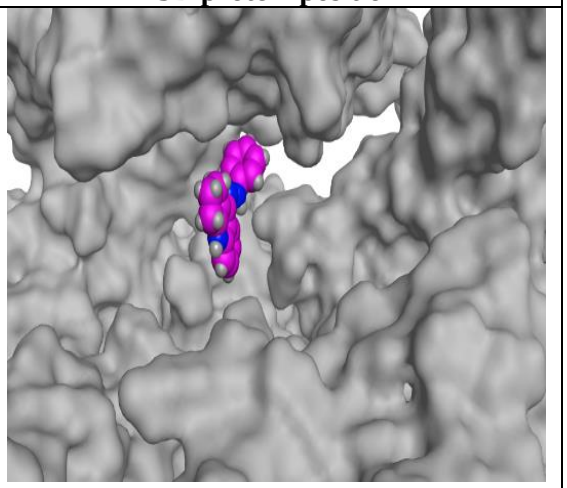
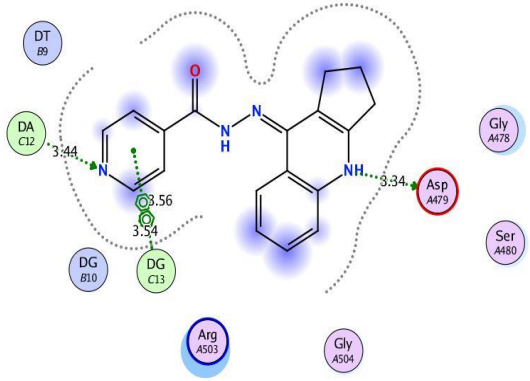
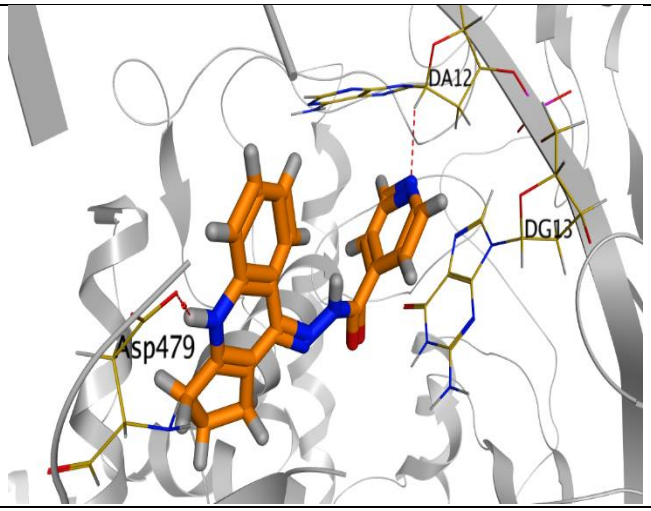
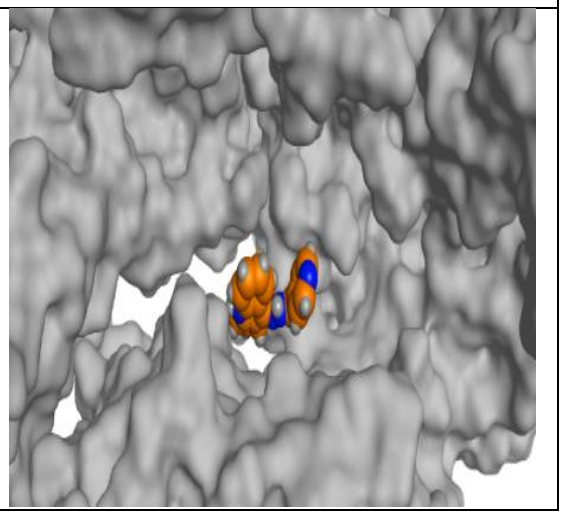
Table SI 1. Cytotoxic activity of some compounds against Liver, Breast, and Colon cancer cell lines.

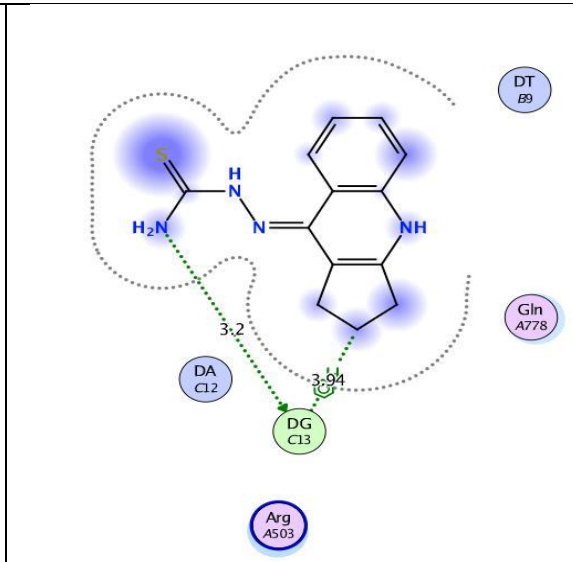
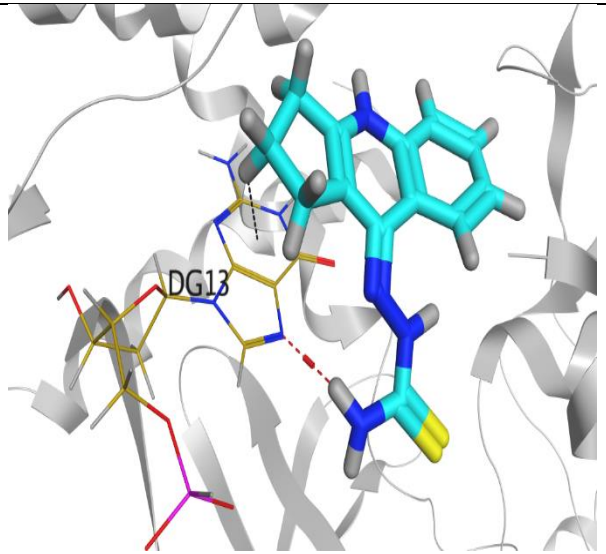
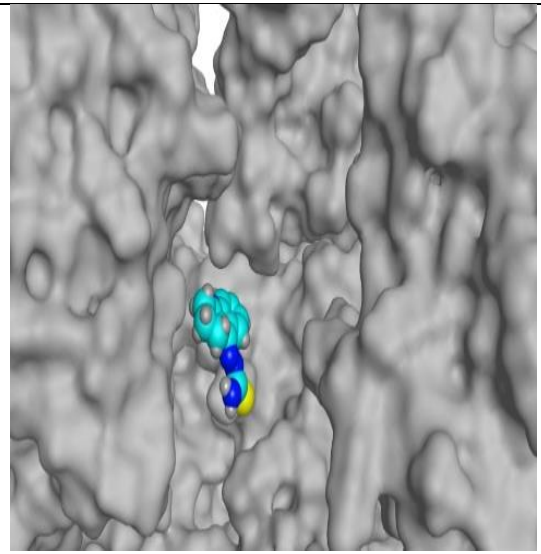
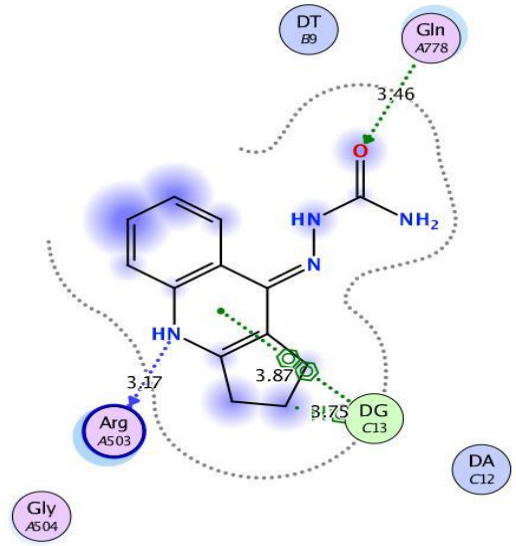
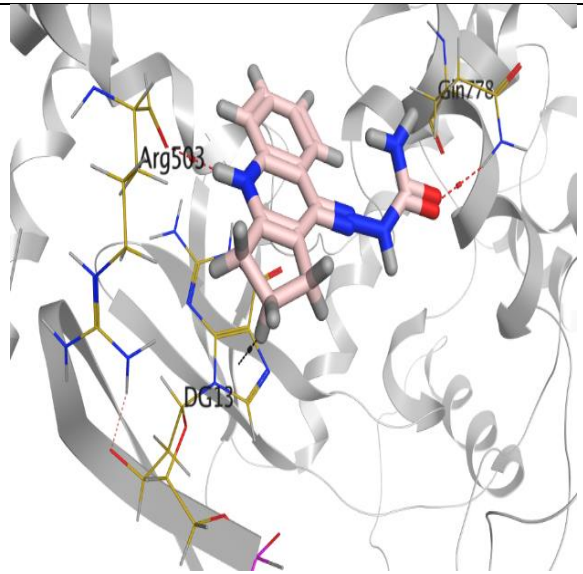
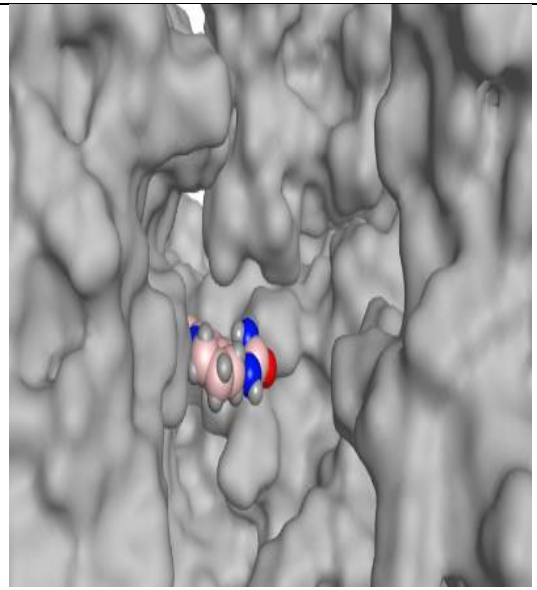
Comp.	In vitro Cytotoxicity IC_{50} (µM)•				
	HePG-2	**MCF-7**	**HCT-116**	**MDA-231**	**Caco-2**
5	10.45±0.8	36.33±2.3	22.49±1.8	17.09±1.4	57.39±3.2
6a	64.28±2.8	56.48±3.1	49.12±2.7	62.27±3.2	74.28±3.8
6b	28.43±1.9	23.87±1.8	30.04±2.2	34.62±2.4	45.49±2.9
6c	19.57±1.4	15.92±1.2	13.55±1.1	26.86±2.0	31.02±2.5
6d	7.06±0.4	11.61±0.8	6.28±0.3	8.32±0.6	18.76±1.4
6e	46.60±2.3	41.52±2.5	37.25±2.4	50.39±2.9	67.01±3.5
6f	2.31±0.1	6.83±0.4	3.67±0.2	4.78±0.3	9.83±0.7
6g	72.14±3.2	82.36±3.9	68.43±3.1	75.41±3.5	92.53±4.2
Doxorubicin	4.50±0.2	4.17±0.2	5.23±0.3	3.18±0.1	12.49±1.1

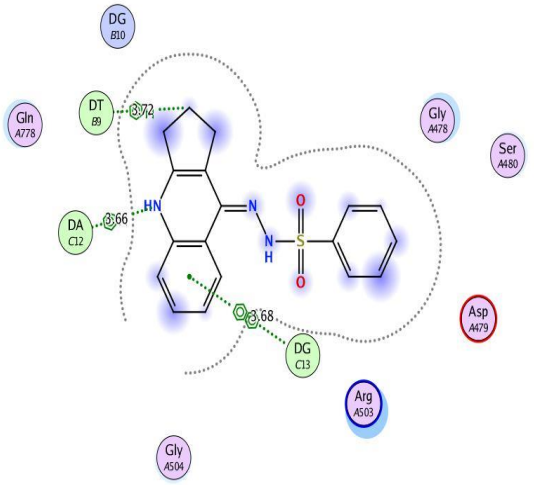
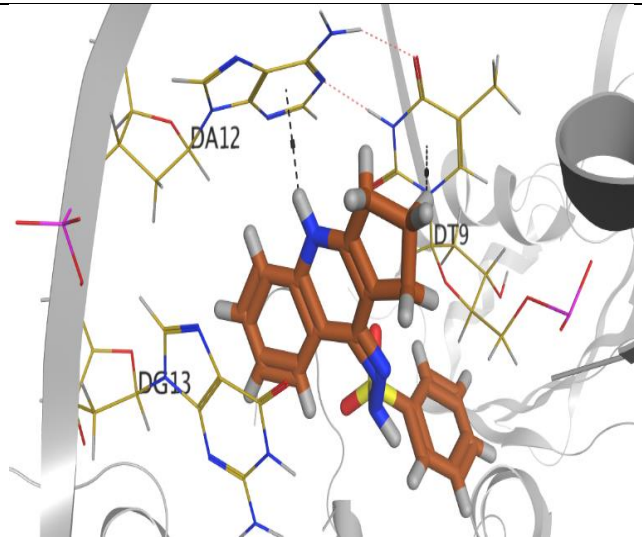
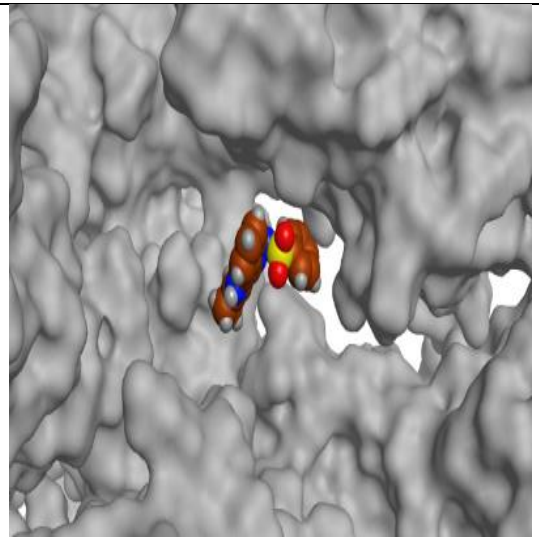
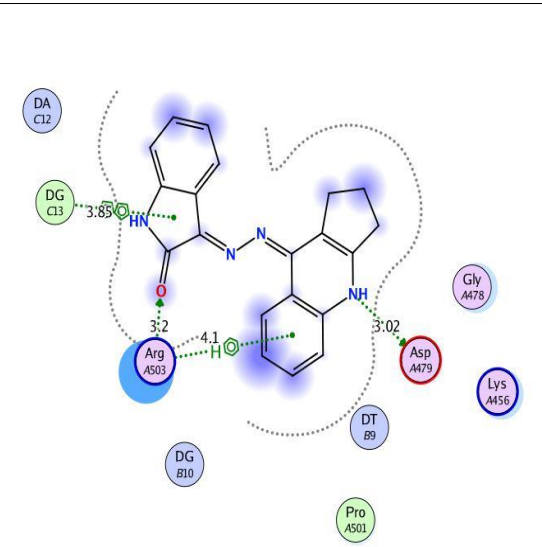
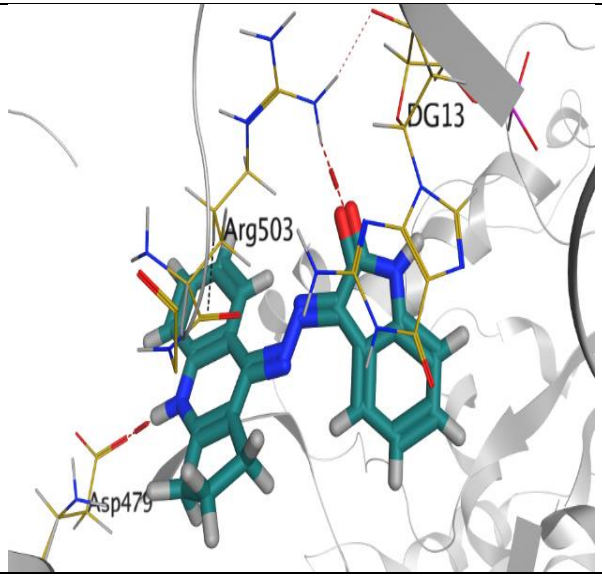
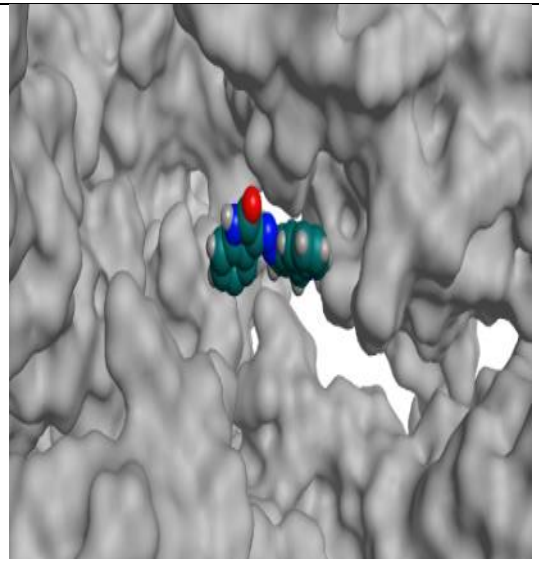
Table SI 2. Binding scores, RMSD values, and amino acid/nucleotides interactions of the synthesized compounds (**6a-g**) into DNA–topo II complex along with doxorubicin and the co-crystallized ligand (EVP) as two reference standards.

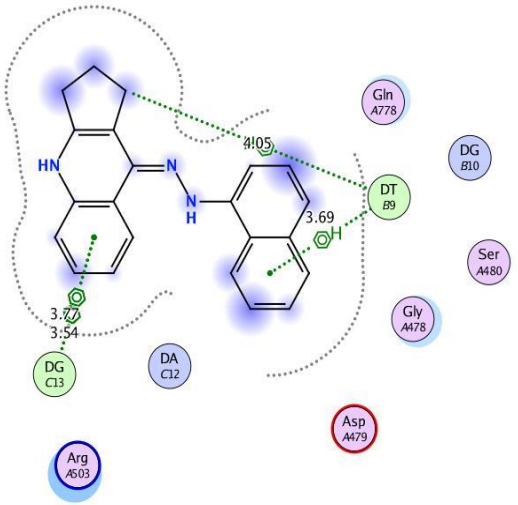
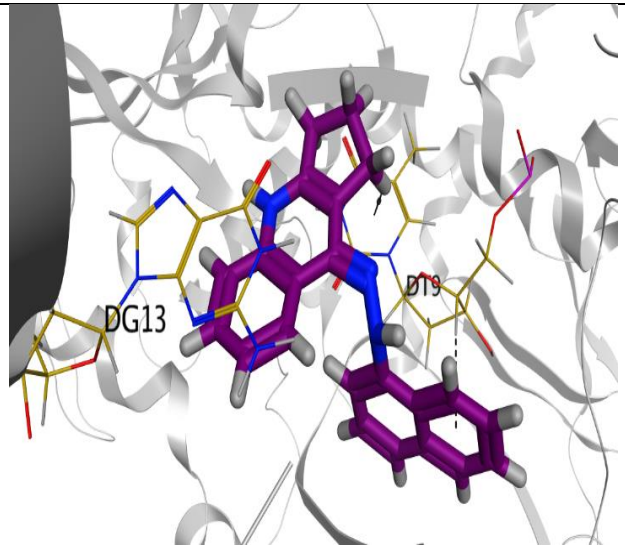
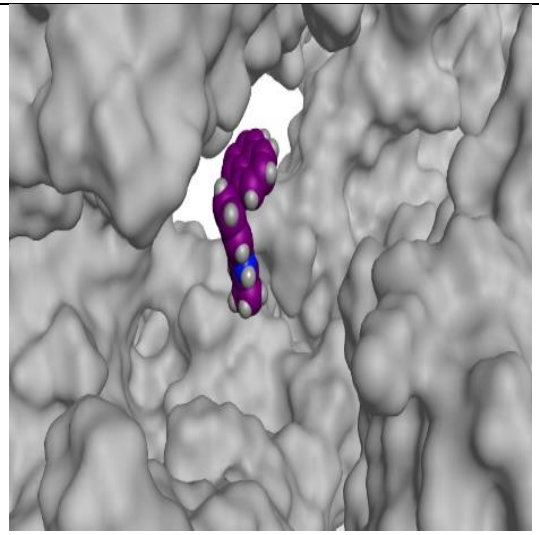
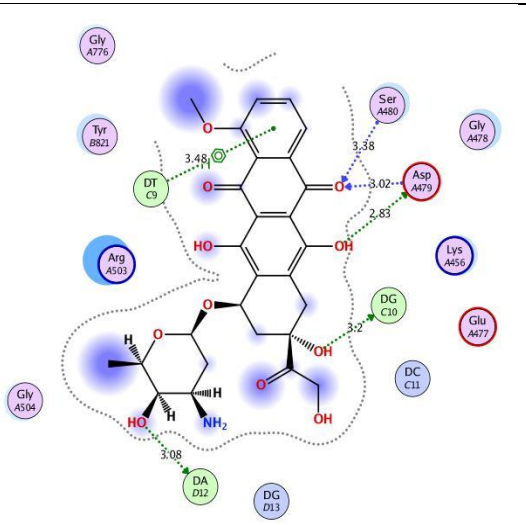
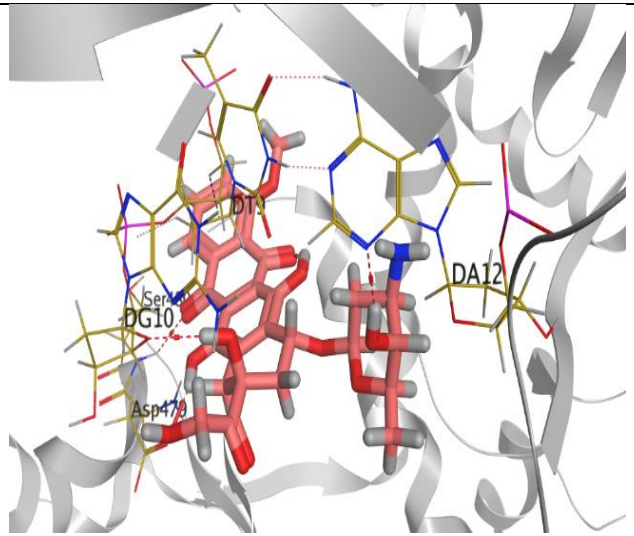
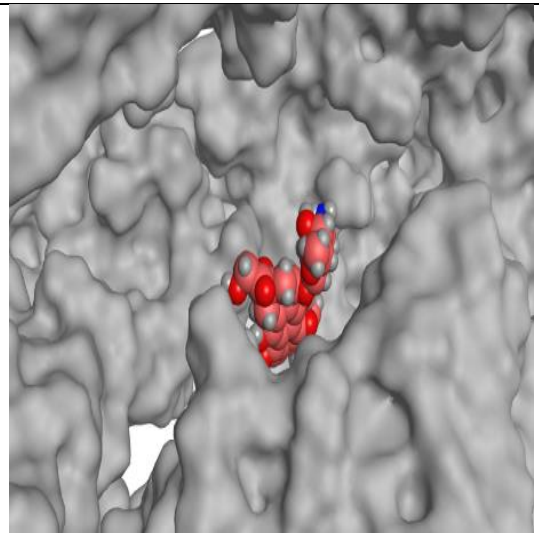
Compound	Score[a]	RMSD_refine[b]	Interactions	Distance Å
6a	-6.22	0.65	DT9/H-donor	3.28
6b	-6.49	1.94	ASP479/H-donor	3.34
			DA12/H-acceptor	3.44
			DG13/pi-pi	3.54
			DG13/pi-pi	3.56
6c	-5.81	1.12	DG13/H-donor	3.20
			DG13/H-pi	3.94
6d	-5.75	0.73	ARG503/H-donor	3.17
			GLN778/H-acceptor	3.46
			DG13/H-pi	3.75
			DG13/pi-pi	3.87
6e	-6.99	1.75	DA12/H-pi	3.66
			DT9/H-pi	3.72
			DG13/pi-pi	3.68
6f	-6.62	0.93	ASP479/H-donor	3.02
			ARG503/H-acceptor	3.20
			ARG503/pi-H	4.10
			DG13/pi-pi	3.85
6g	-6.96	1.54	DT9/H-pi	4.05
			DT9/pi-H	3.69
			DG13/pi-pi	3.77
			DG/13/pi-pi	3.54
Doxorubicin	-8.92	1.35	ASP479/H-donor	2.83
			DG10/H-donor	3.20
			DA12/H-donor	3.08
			ASP479/H-acceptor	3.02
			SER480/H-acceptor	3.38
			DT9/pi-H	3.48
EVP	-10.52	1.41	ASP479/H-donor	2.70
			MET782/H-donor	3.73
			DG13/H-donor	3.37
			GLN778/H-acceptor	2.94
			DA12/H-pi	3.75

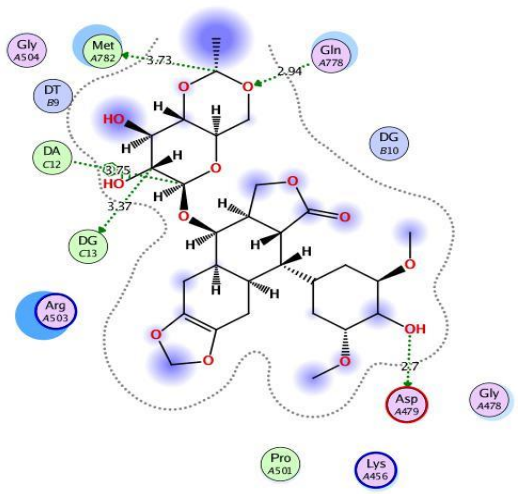
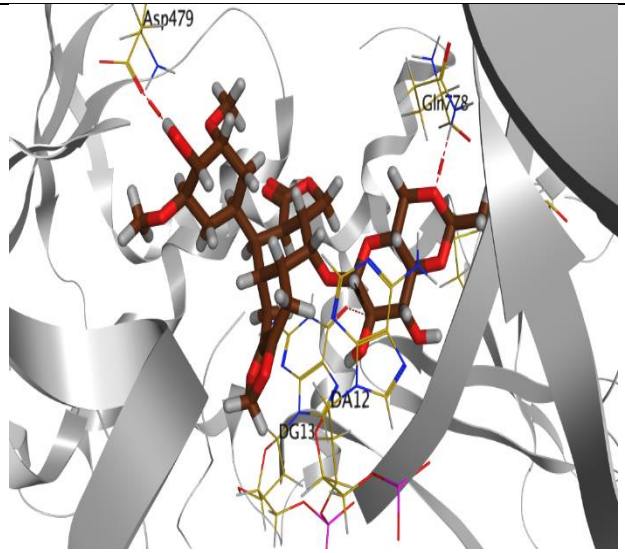
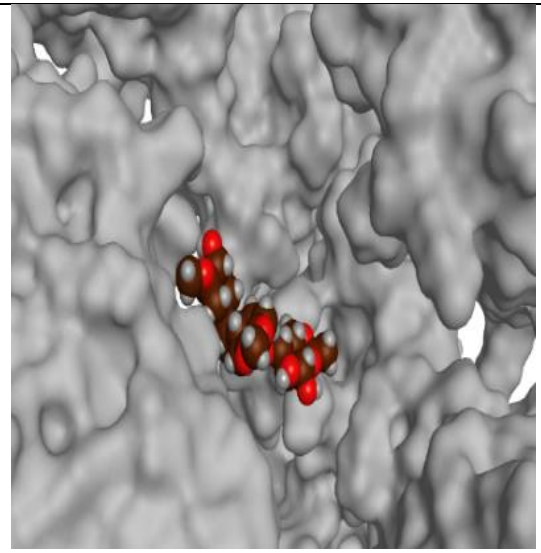
Table SI 3. 2D pictures, 3D interactions and 3D protein positioning pictures representing the binding interactions of the investigated compounds (**6a-6g**) into human topoisomerase II-DNA complex target protein with the redocked co-crystallized ligand EVP and doxorubicin as reference controls.

Compound	2D picture	3D interactions	3D protein position
6a			
6b			

6c	 DT B9 Gln A778 DA C12 DG C13 Arg A503 3.2 3.94	 DG13	
6d	 DT B9 Gln A778 3.46 3.17 3.87 3.75 Arg A503 DG C13 DA C12 Gly A504	 Arg503 Gln778 DG13	

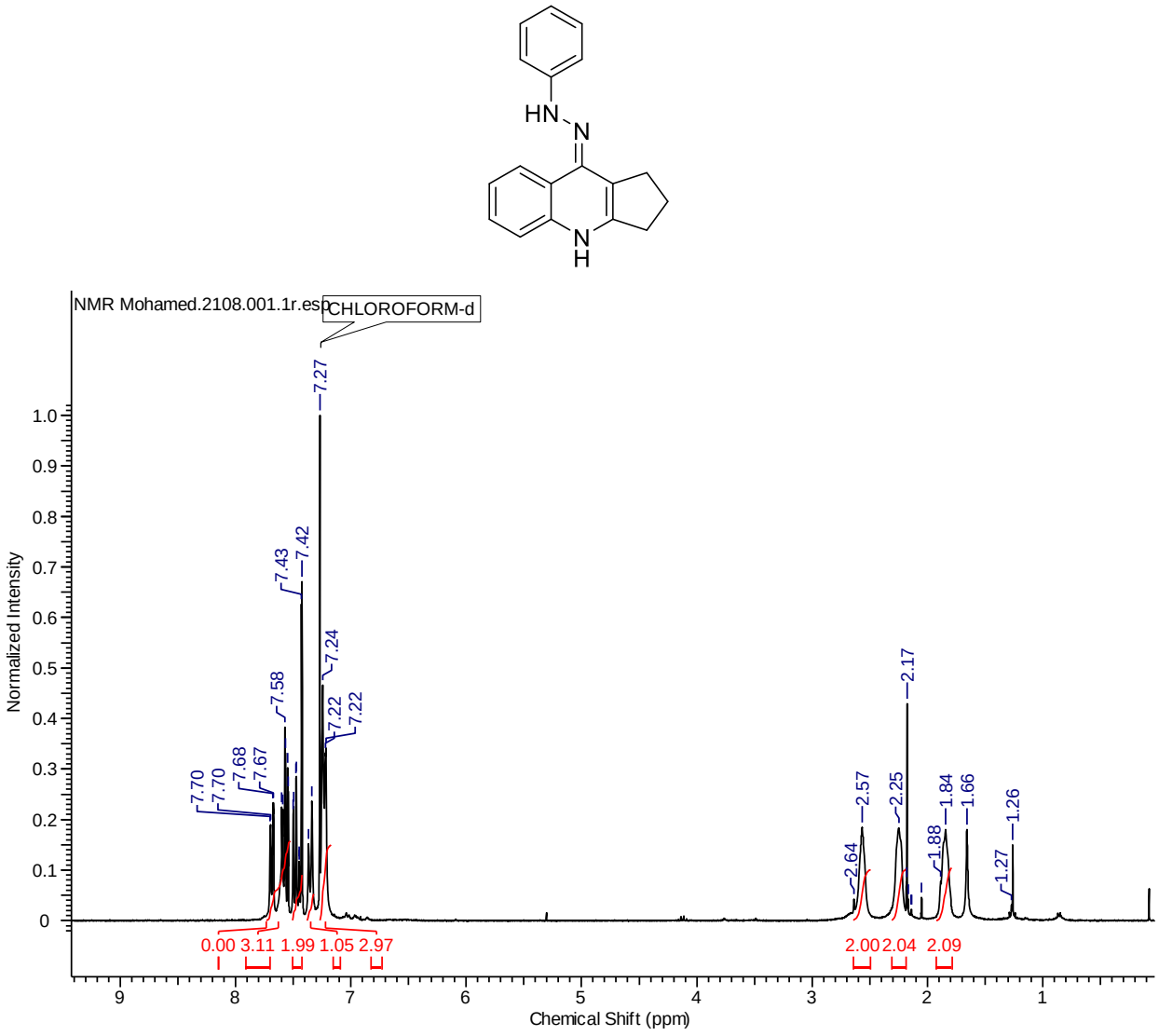
6e	 DG B10 Gln A778 DT B9 3.72 Gly A478 Ser A480 DA C12 3.66 HN N N H O S O 3.68 Asp A479 DG C13 Arg A503 Gly A504	 DA12 DT9 DG13	
6f	 DA C12 DG C13 3.85 HN N N O NH Gly A478 3.2 4.1 H 3.02 Arg A503 Asp A479 Lys A456 DT B9 DG B10 Pro A501	 DG13 Arg503 Asp479	

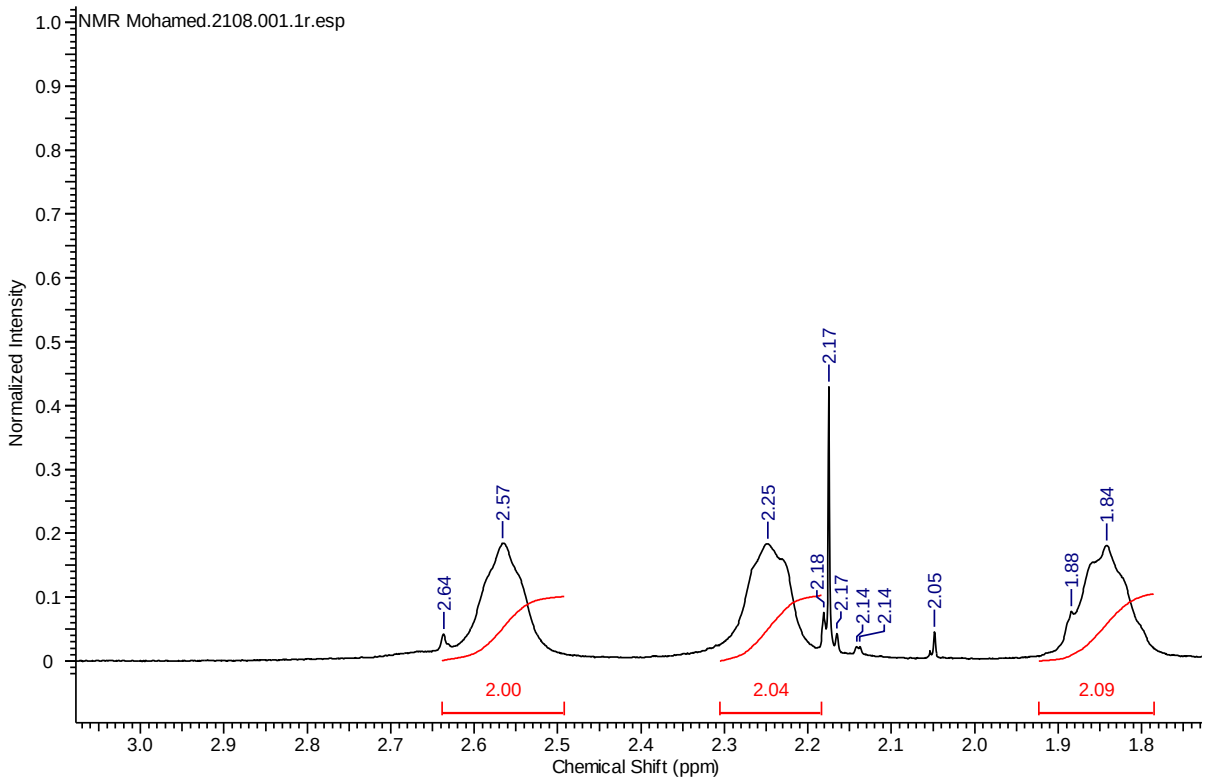
6g			
Doxorubicin			

Re-docked EVP			

SI 1. Spectral data of compounds (**6a-g**), (IR, ^{1}HNMR, ^{13}CNMR, DEPT, and Mass spectroscopy).

(Z)-9-(2-phenylhydrazono)-2,3,4,9-tetrahydro-1H-cyclopenta[b]quinoline (6a).

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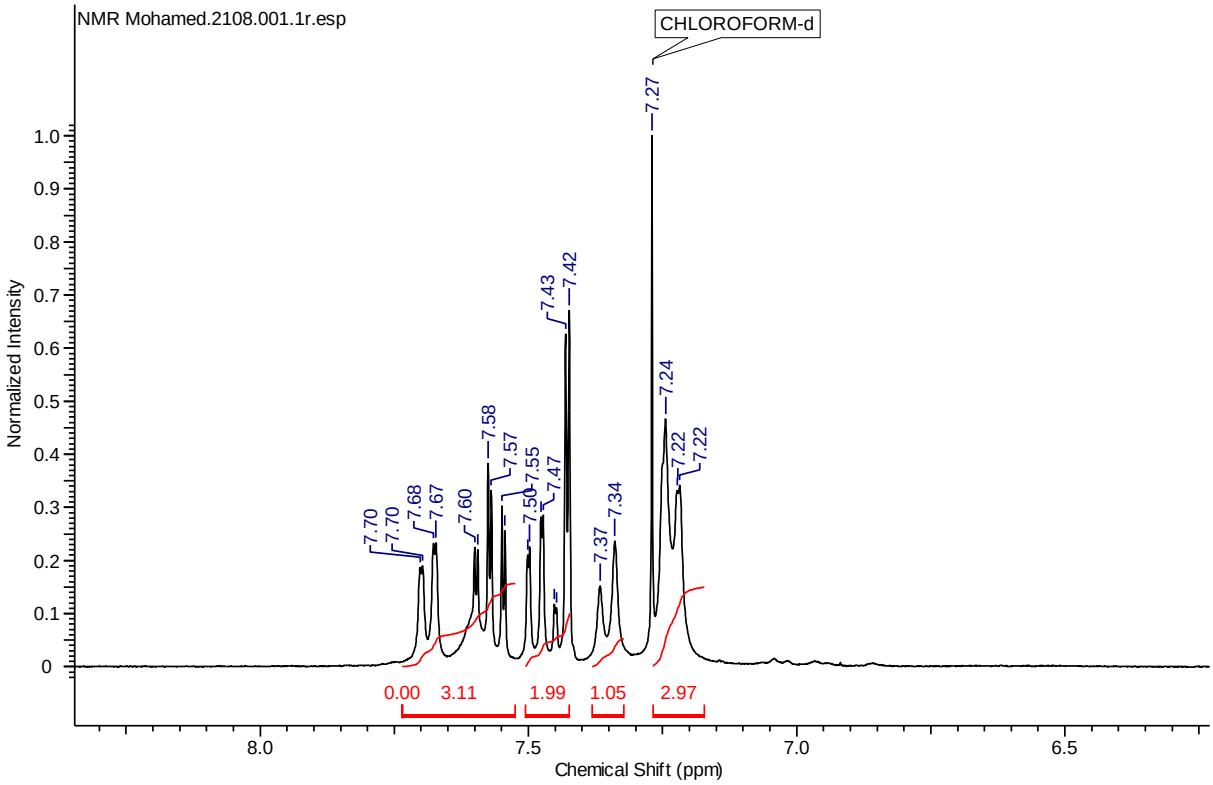
2.09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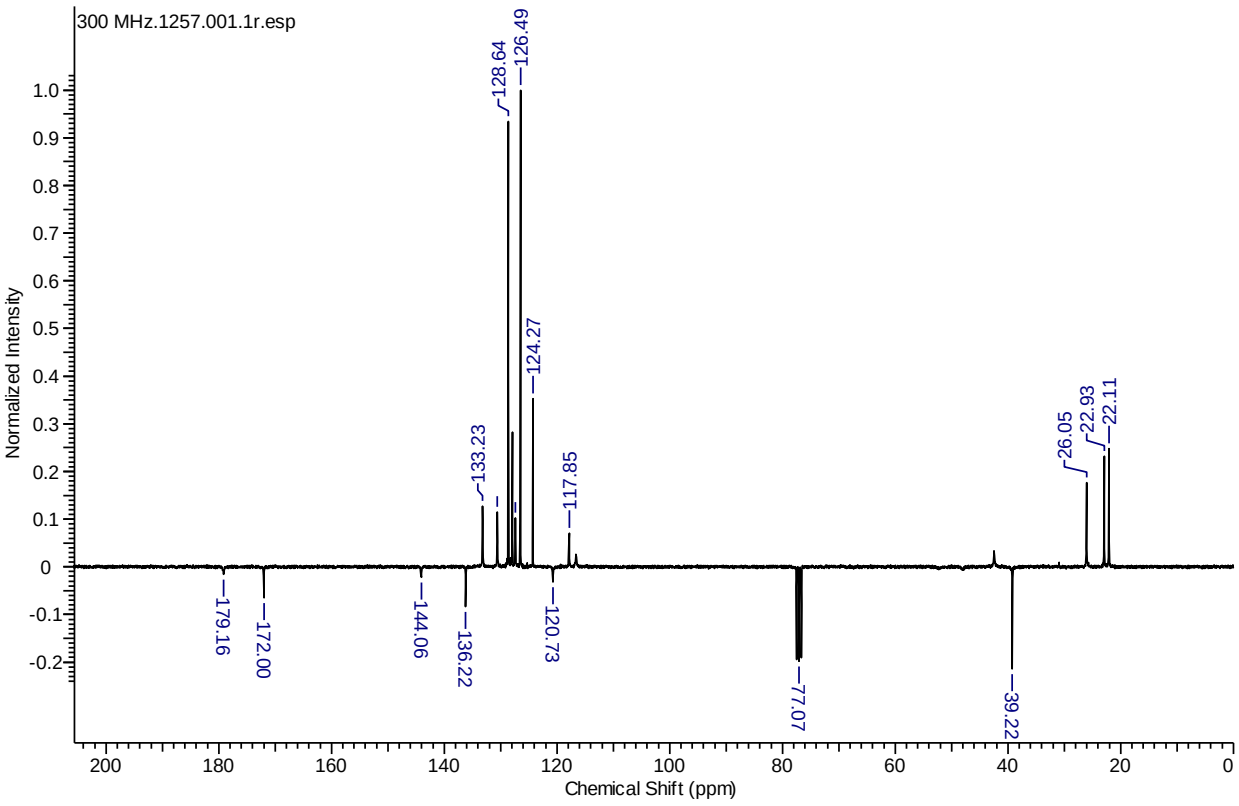
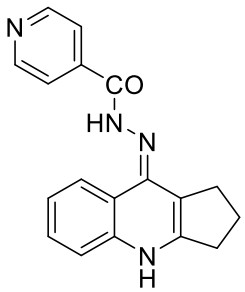
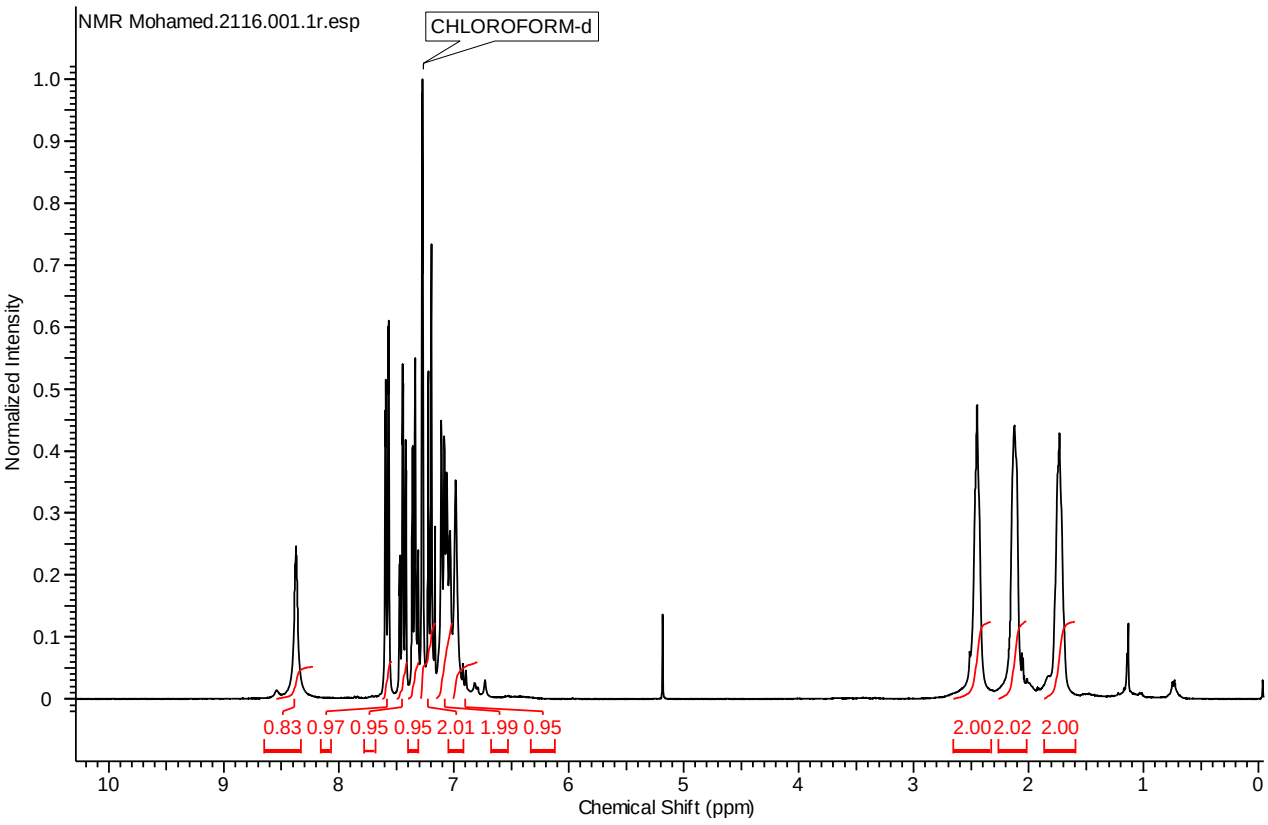
2.97



(Z)-N'-(1,2,3,4-tetrahydro-9H-cyclopenta[b]quinolin-9-ylidene)nicotinohydrazide (6b).

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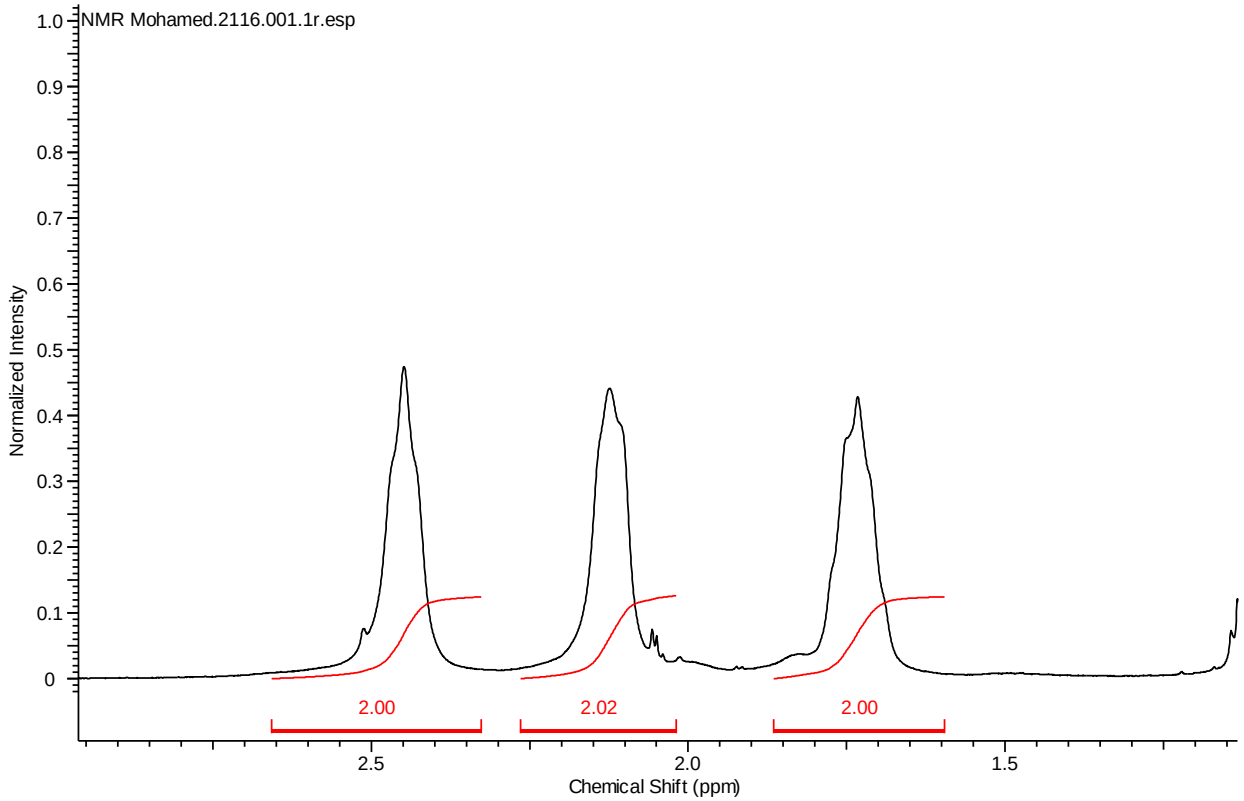
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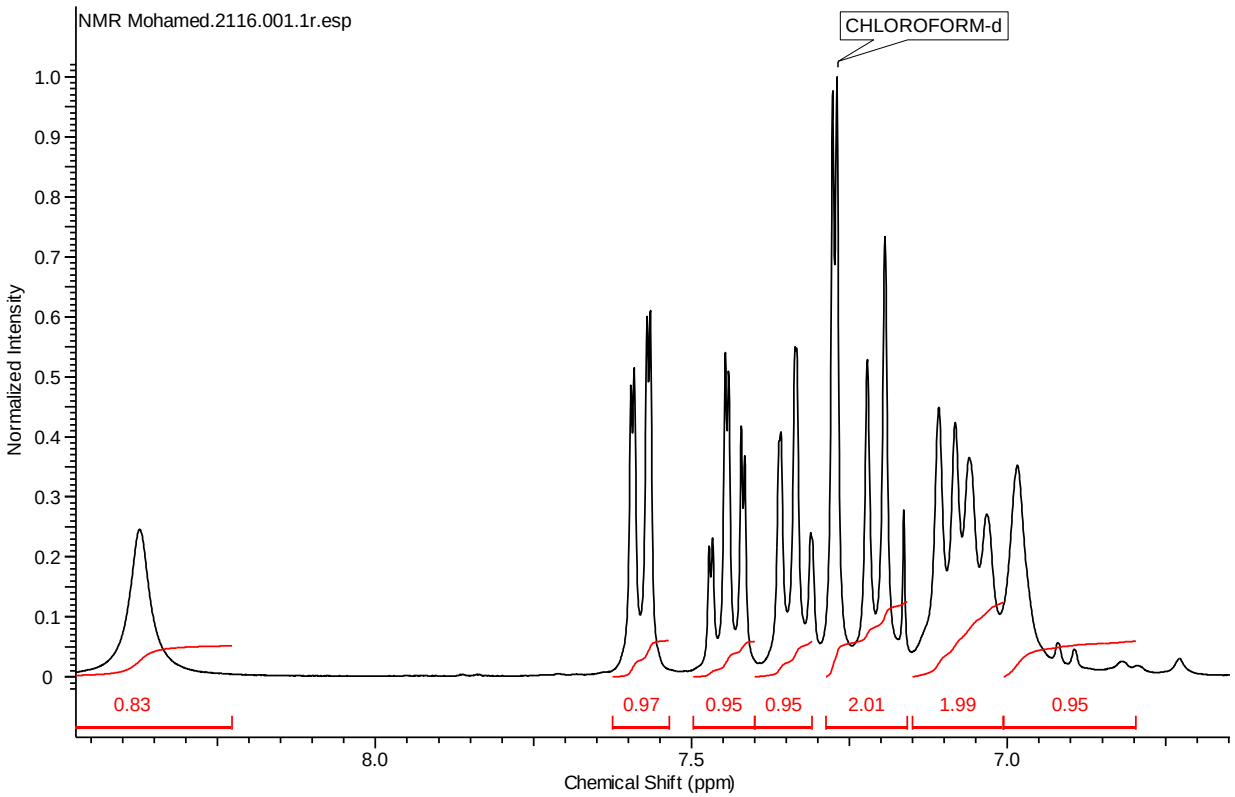
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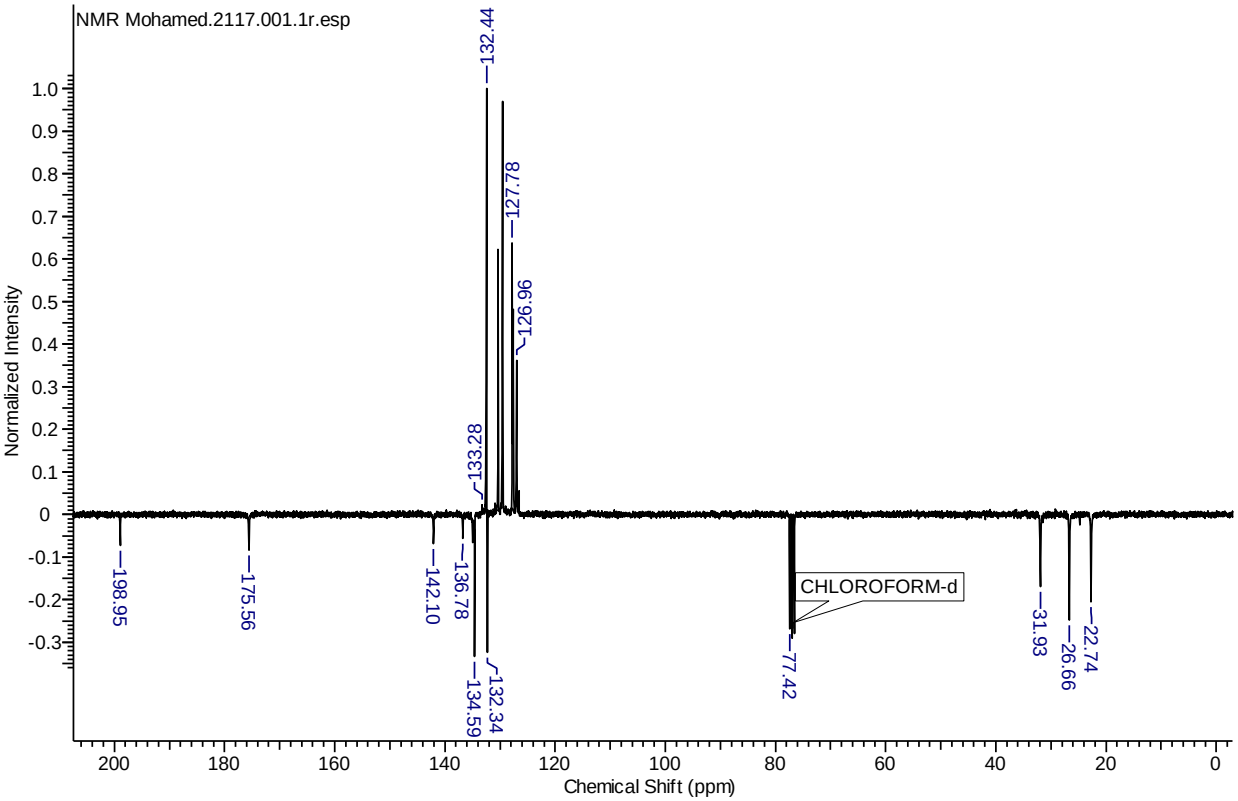
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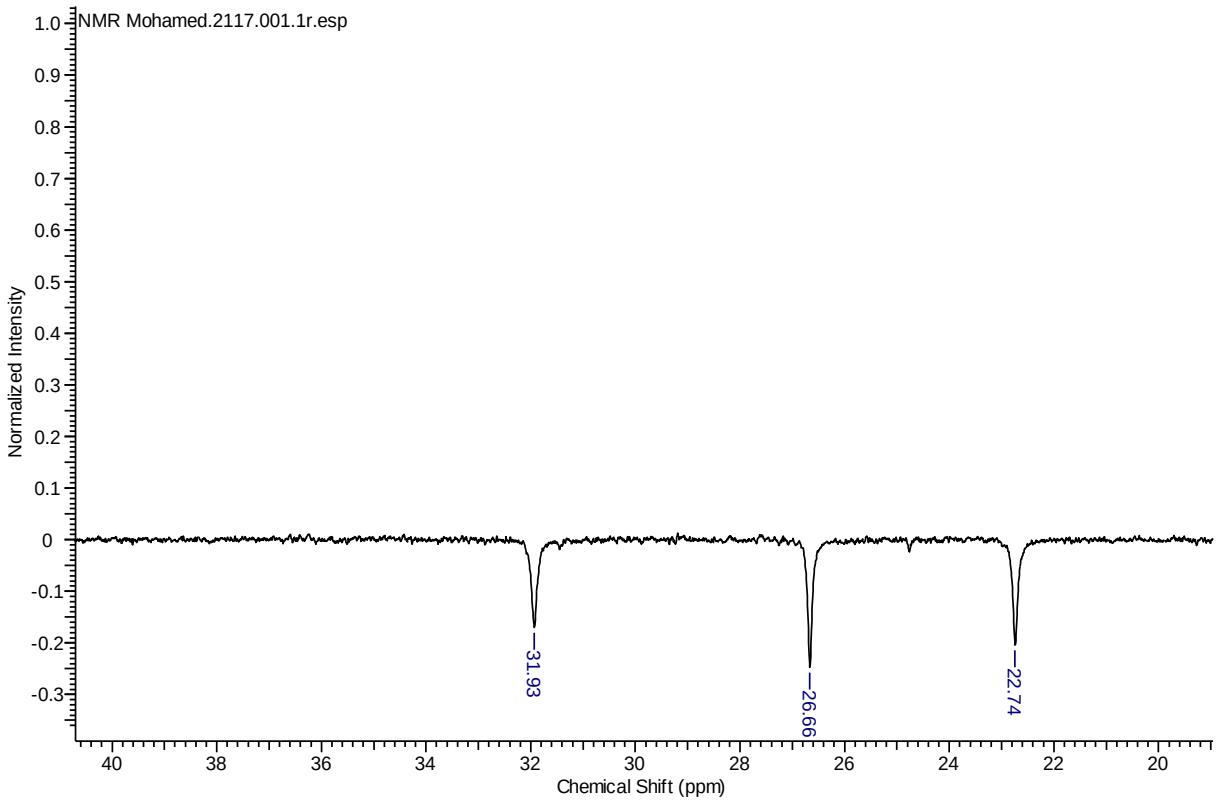
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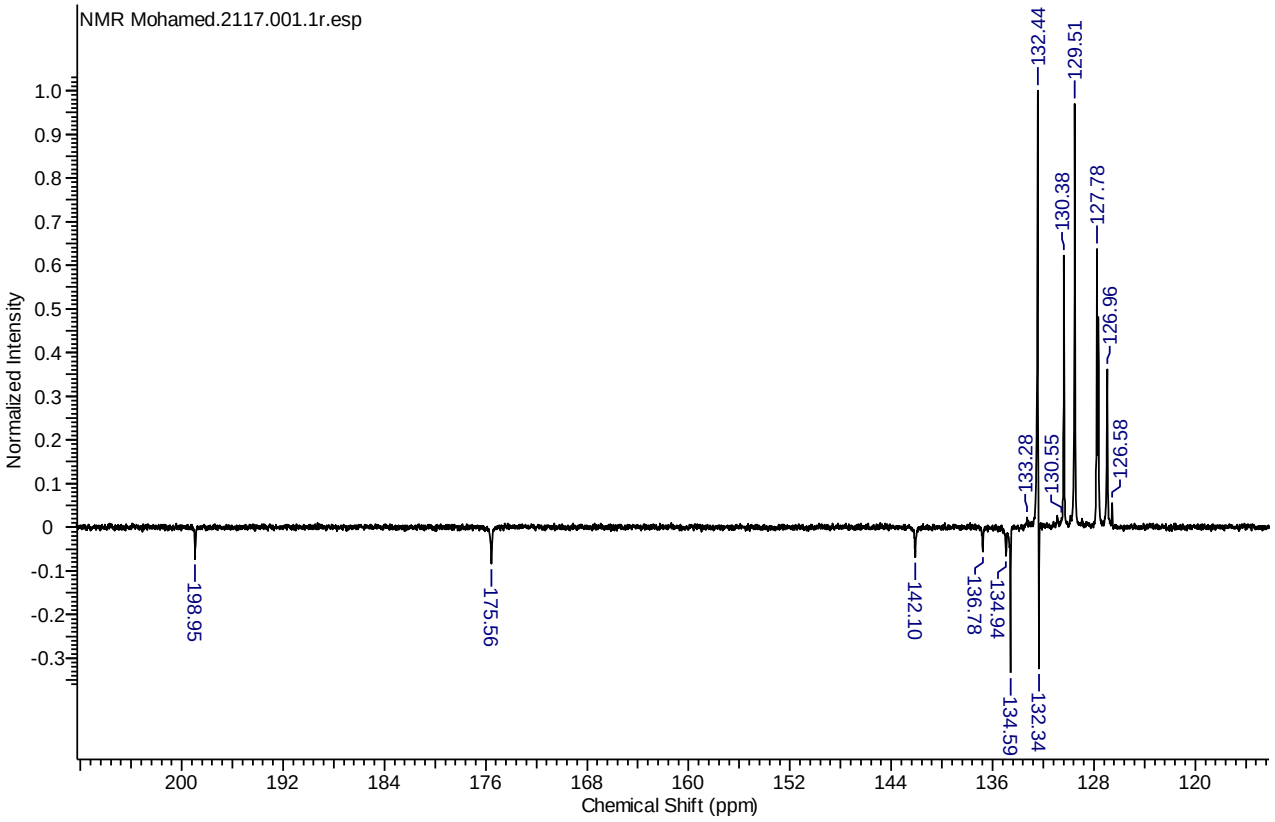
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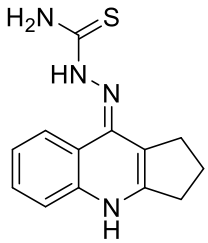
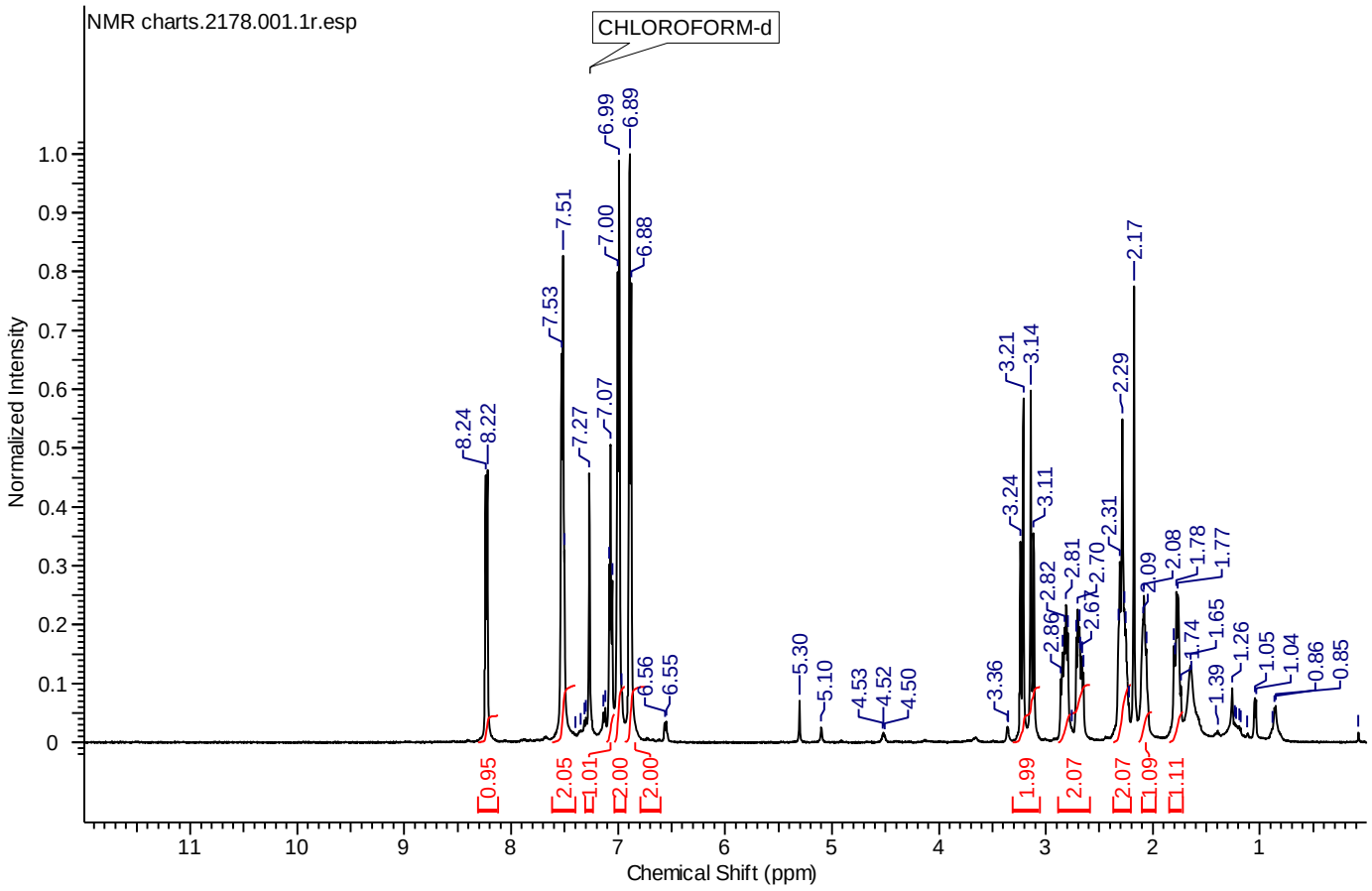
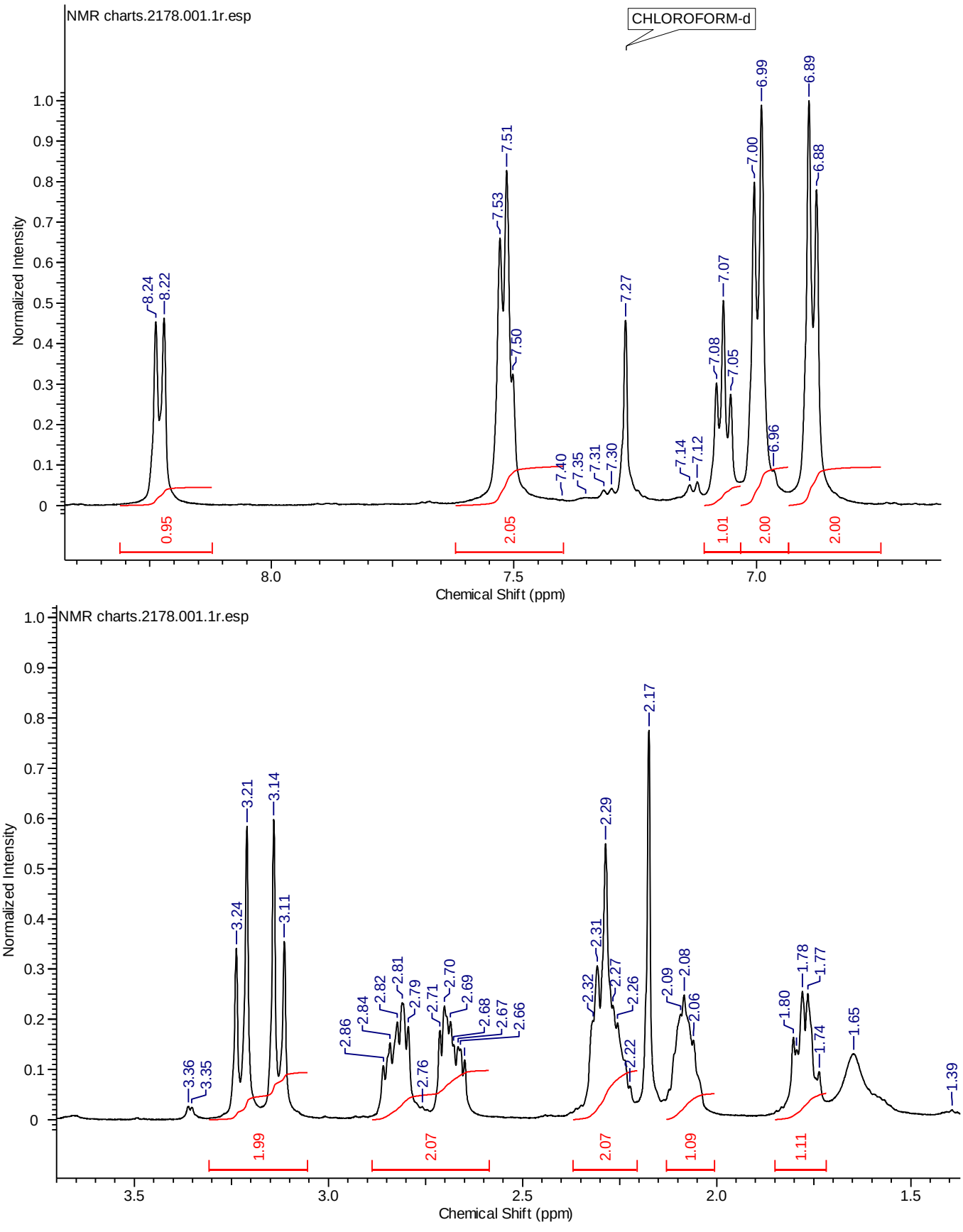
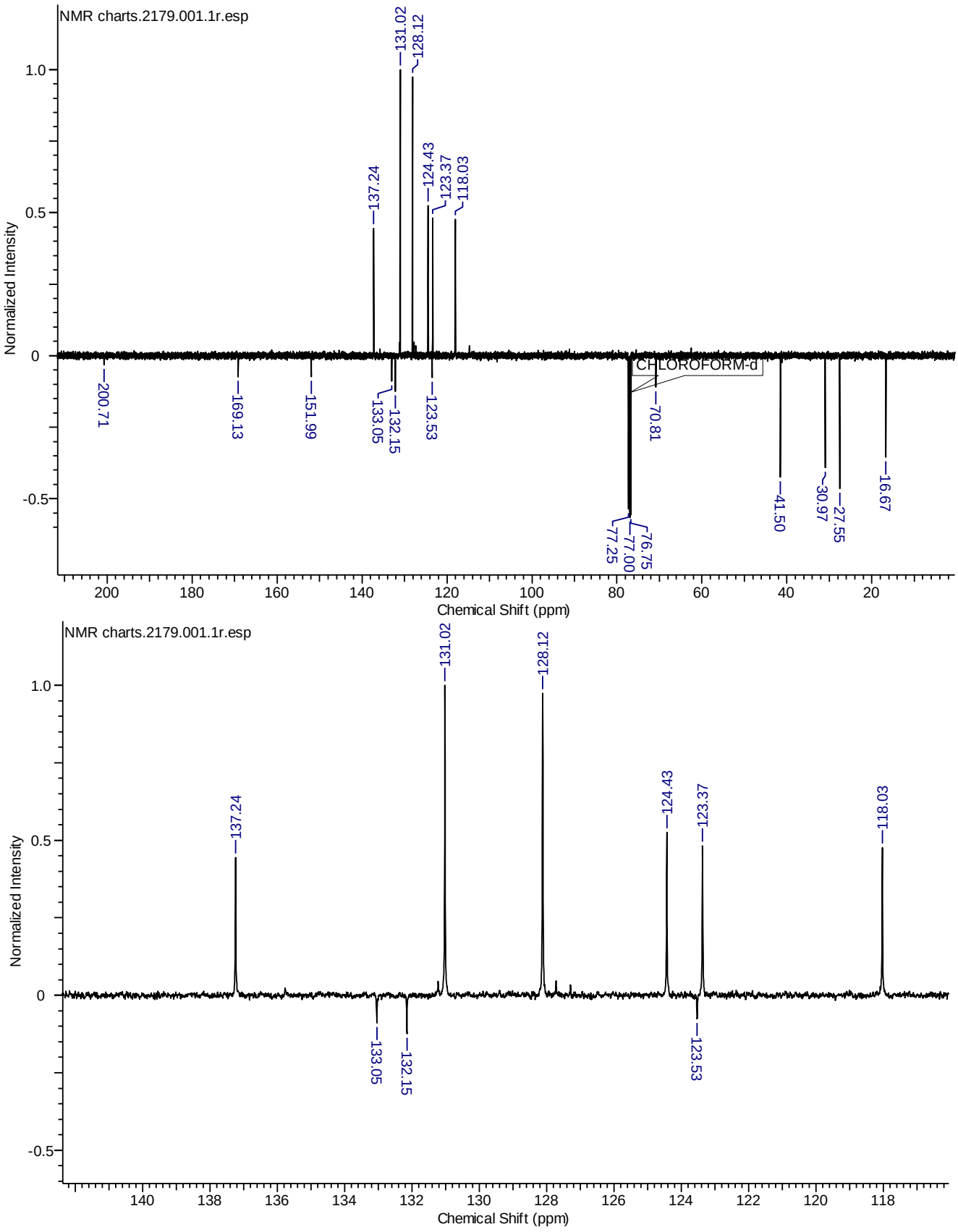
132.44
129.51
130.38
127.78
126.96
126.58

(Z)-2-(1,2,3,4-tetrahydro-9H-cyclopenta[b]quinolin-9-ylidene)hydrazine-1-carbothioamide (6c).

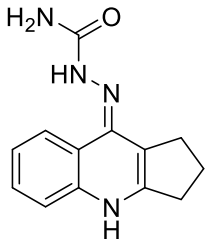


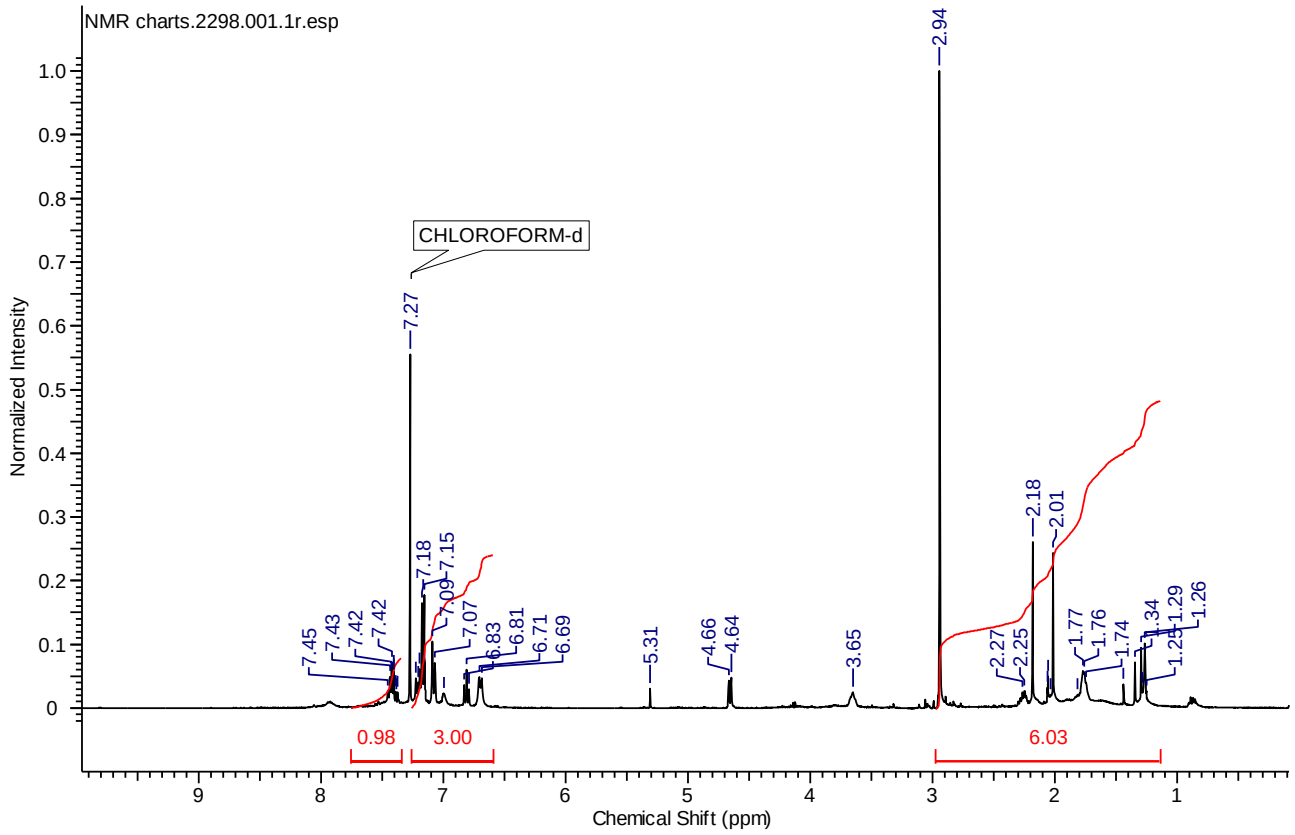


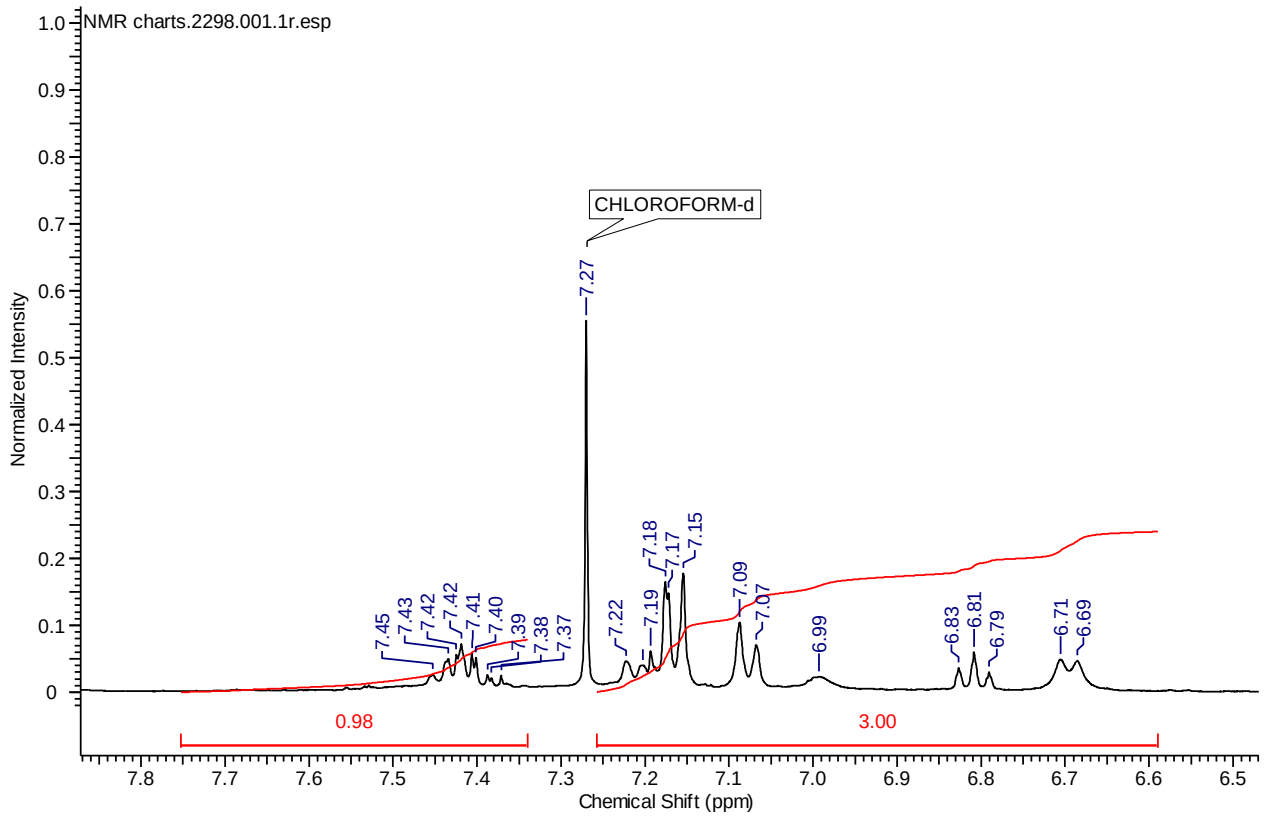

NMR charts.2178.001.1r.esp
CHLOROFORM-d
Normalized Intensity
Chemical Shift (ppm)
8.24
8.22
7.53
7.51
7.50
7.40
7.35
7.31
7.30
7.27
7.14
7.12
7.08
7.07
7.05
7.00
6.99
6.96
6.89
6.88
0.95
2.05
1.01
2.00
2.00
NMR charts.2178.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
3.36
3.35
3.24
3.21
3.14
3.11
2.86
2.84
2.82
2.81
2.79
2.76
2.71
2.70
2.69
2.68
2.67
2.66
2.32
2.31
2.29
2.27
2.26
2.22
2.17
2.09
2.08
2.06
1.80
1.78
1.77
1.74
1.65
1.39
1.99
2.07
2.07
1.09
1.11

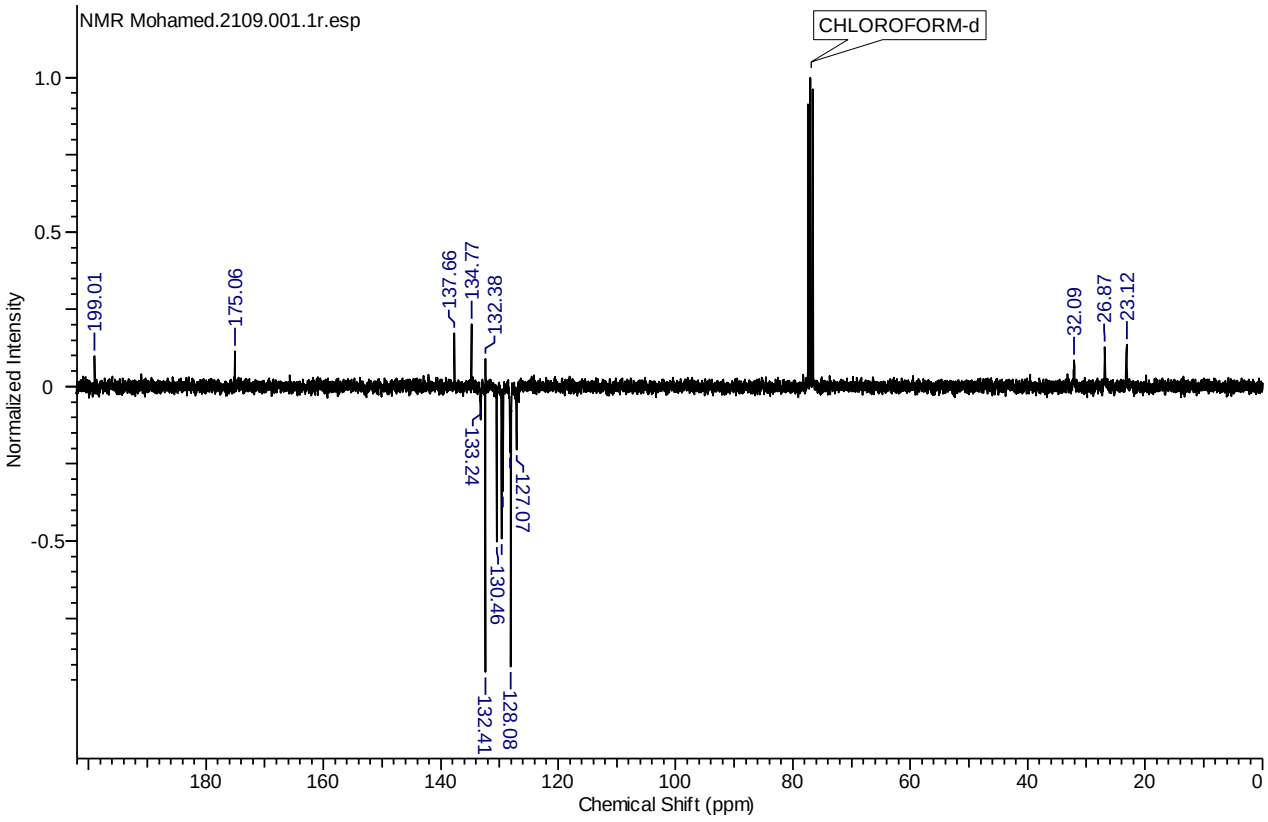

NMR charts.2179.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
131.02
128.12
137.24
124.43
123.37
118.03
200.71
169.13
151.99
133.05
132.15
123.53
CHLOROFORM-d
70.81
77.25
77.00
76.75
41.50
30.97
27.55
16.67
NMR charts.2179.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
131.02
128.12
137.24
124.43
123.37
118.03
133.05
132.15
123.53

(Z)-2-(1,2,3,4-tetrahydro-9H-cyclopenta[b]quinolin-9-ylidene)hydrazine-1-carboxamide (6d).

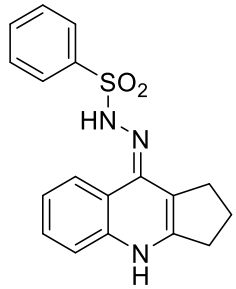


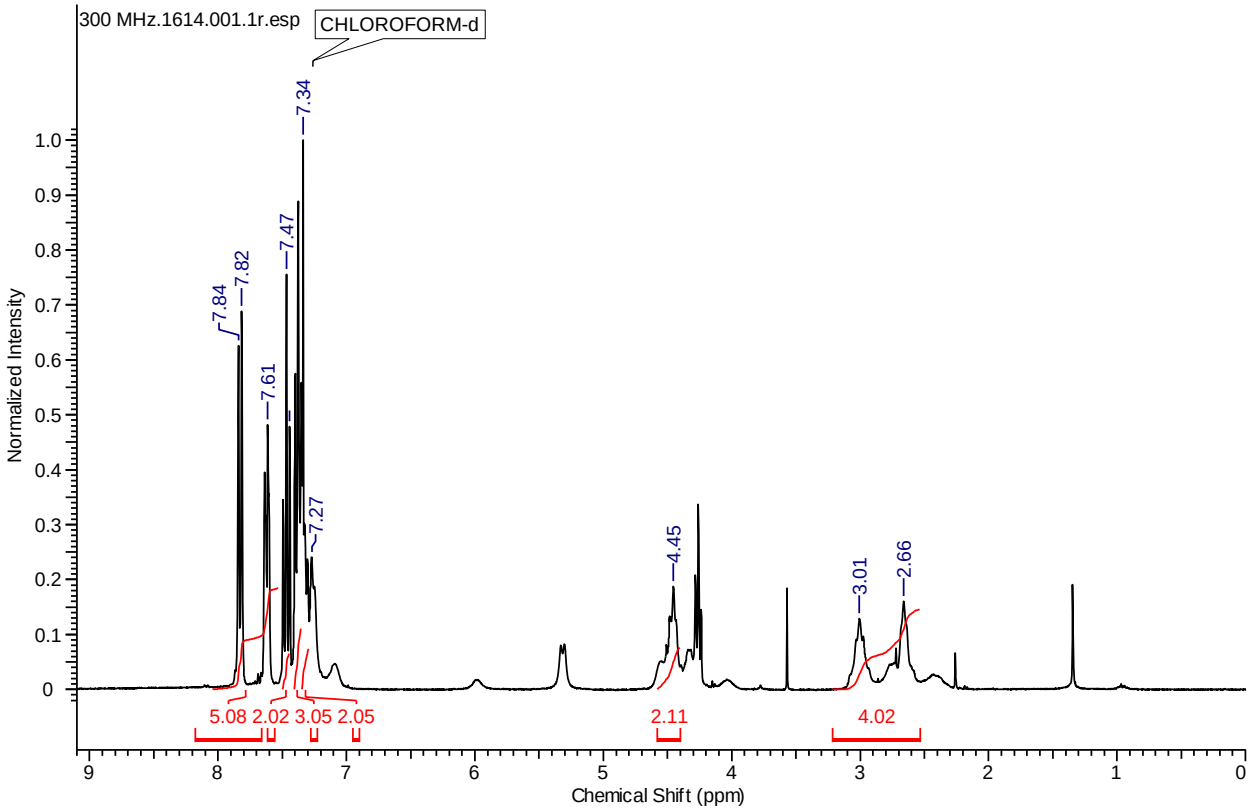


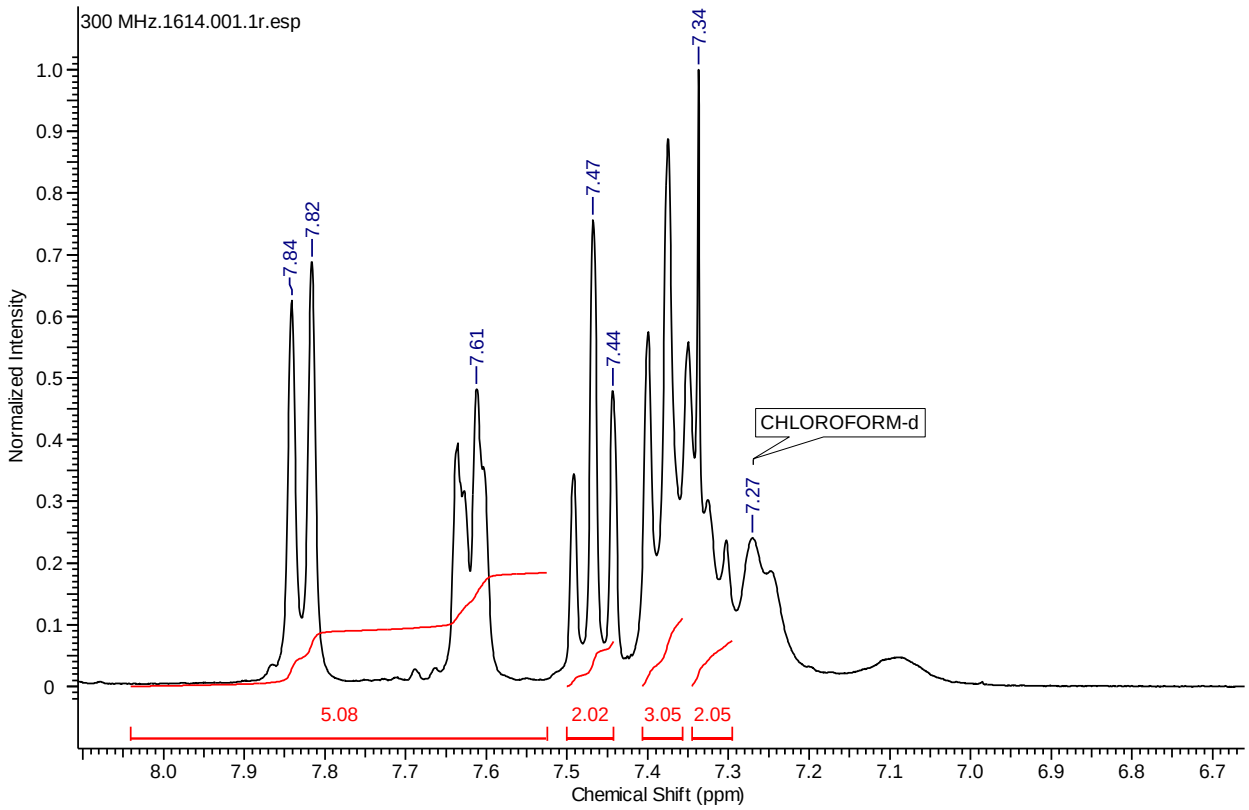

NMR charts.2298.001.1r.esp
CHLOROFORM-d
7.27
7.45
7.43
7.42
7.42
7.41
7.40
7.39
7.38
7.37
7.22
7.19
7.18
7.17
7.15
7.09
7.07
6.99
6.83
6.81
6.79
6.71
6.69
0.98
3.00
Normalized Intensity
Chemical Shift (ppm)

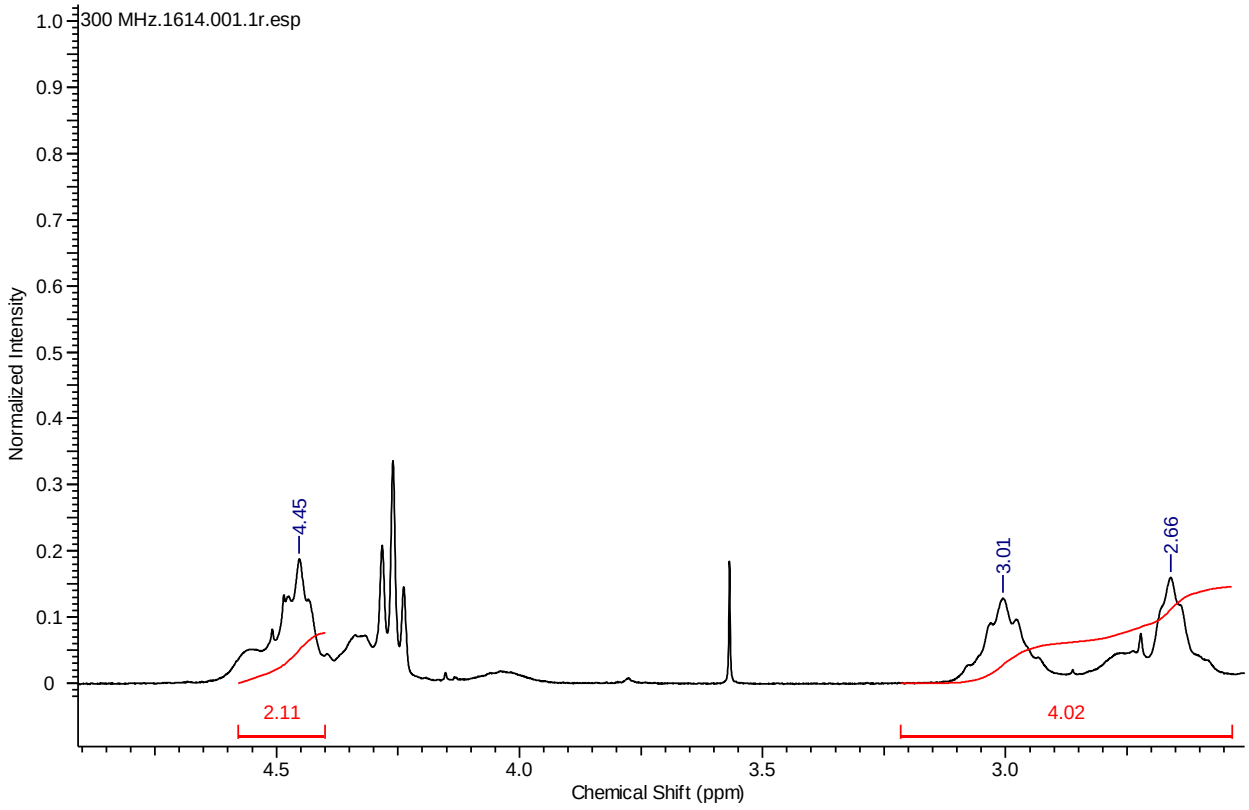

NMR Mohamed.2109.001.1r.esp
CHLOROFORM-d
199.01
175.06
137.66
134.77
132.38
133.24
130.46
132.41
128.08
127.07
32.09
26.87
23.12
Normalized Intensity
Chemical Shift (ppm)

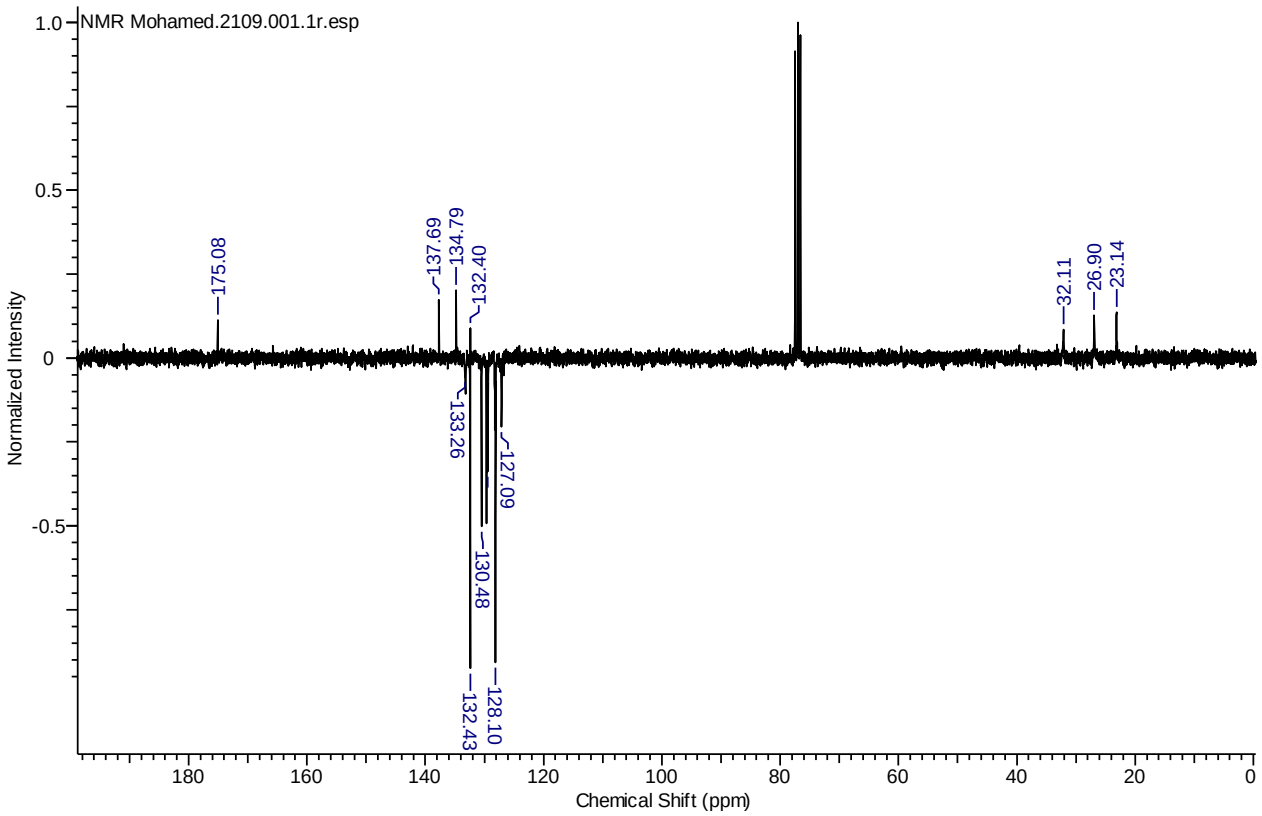
(Z)-N'-(1,2,3,4-tetrahydro-9H-cyclopenta[b]quinolin-9 ylidene)benzenesulfonohydrazide (6e).

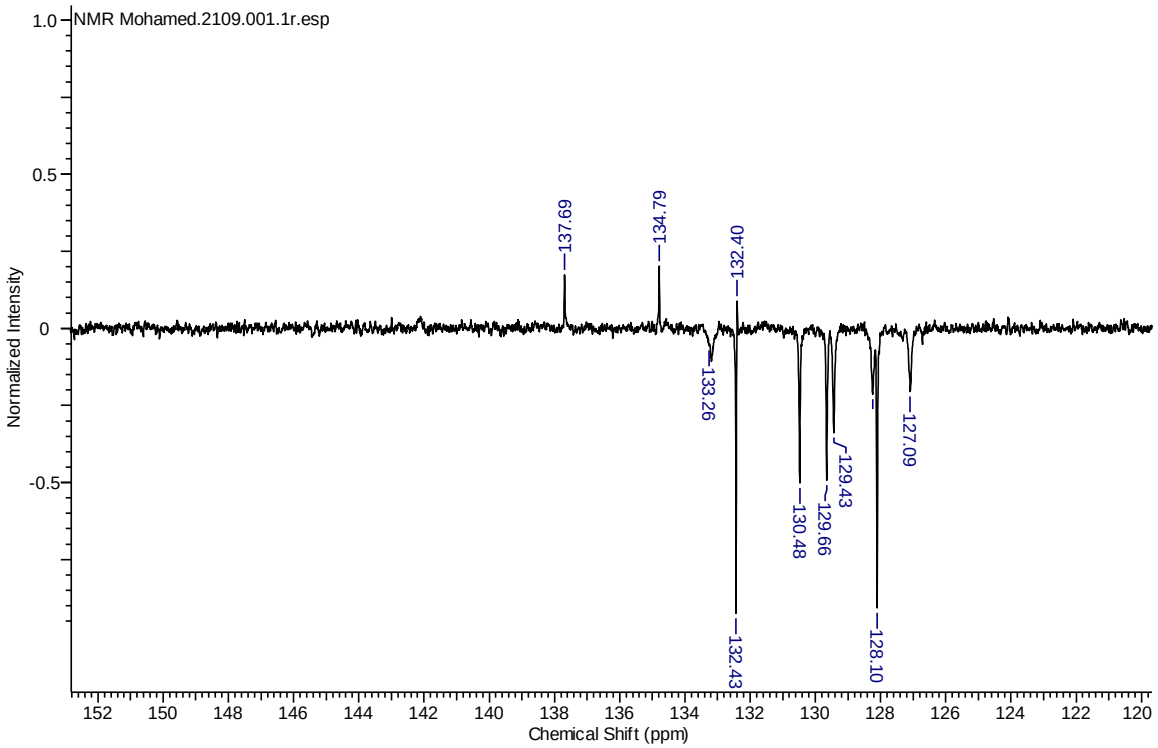




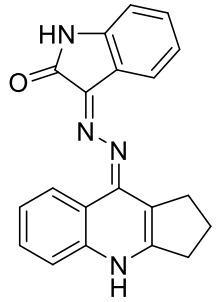

300 MHz.1614.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
7.84
7.82
7.61
7.47
7.44
7.34
7.27
CHLOROFORM-d
5.08
2.02
3.05
2.05

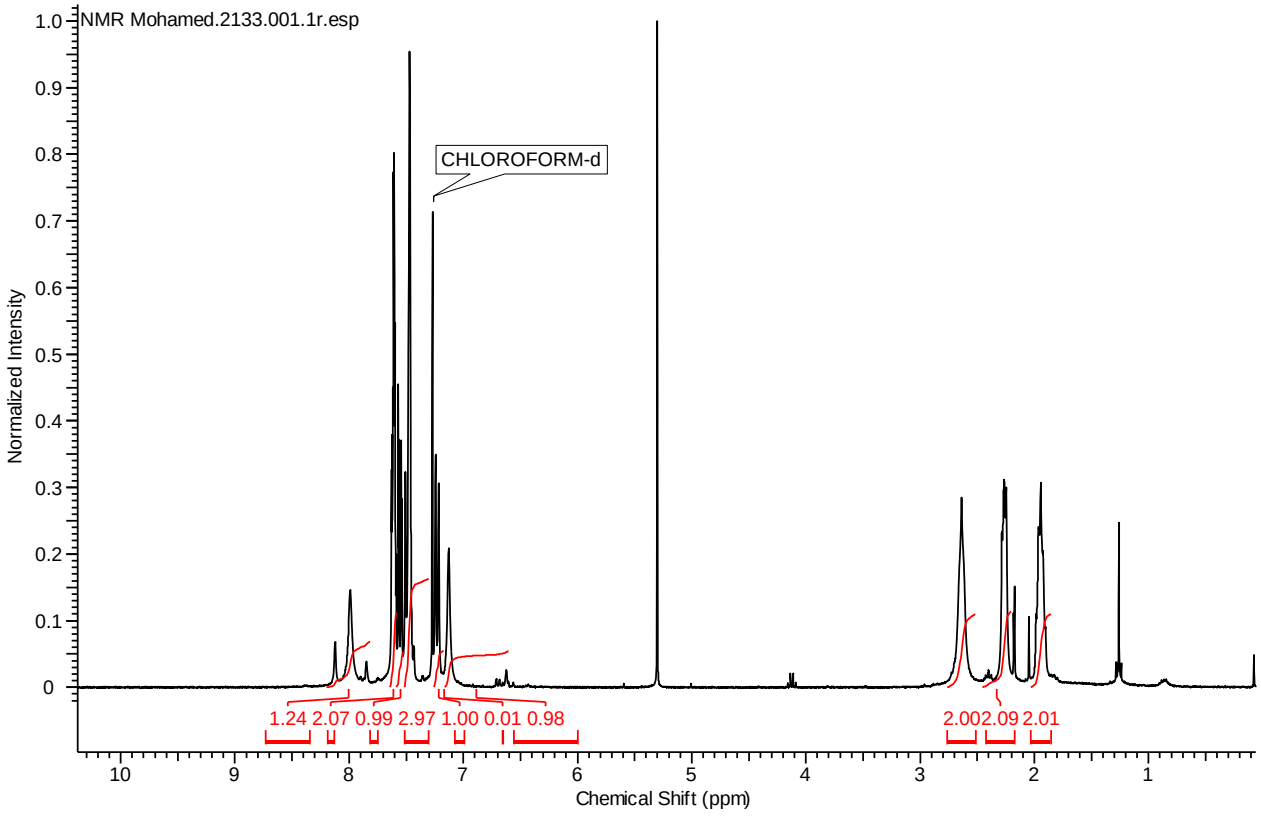

300 MHz.1614.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
4.45
3.01
2.66
2.11
4.02

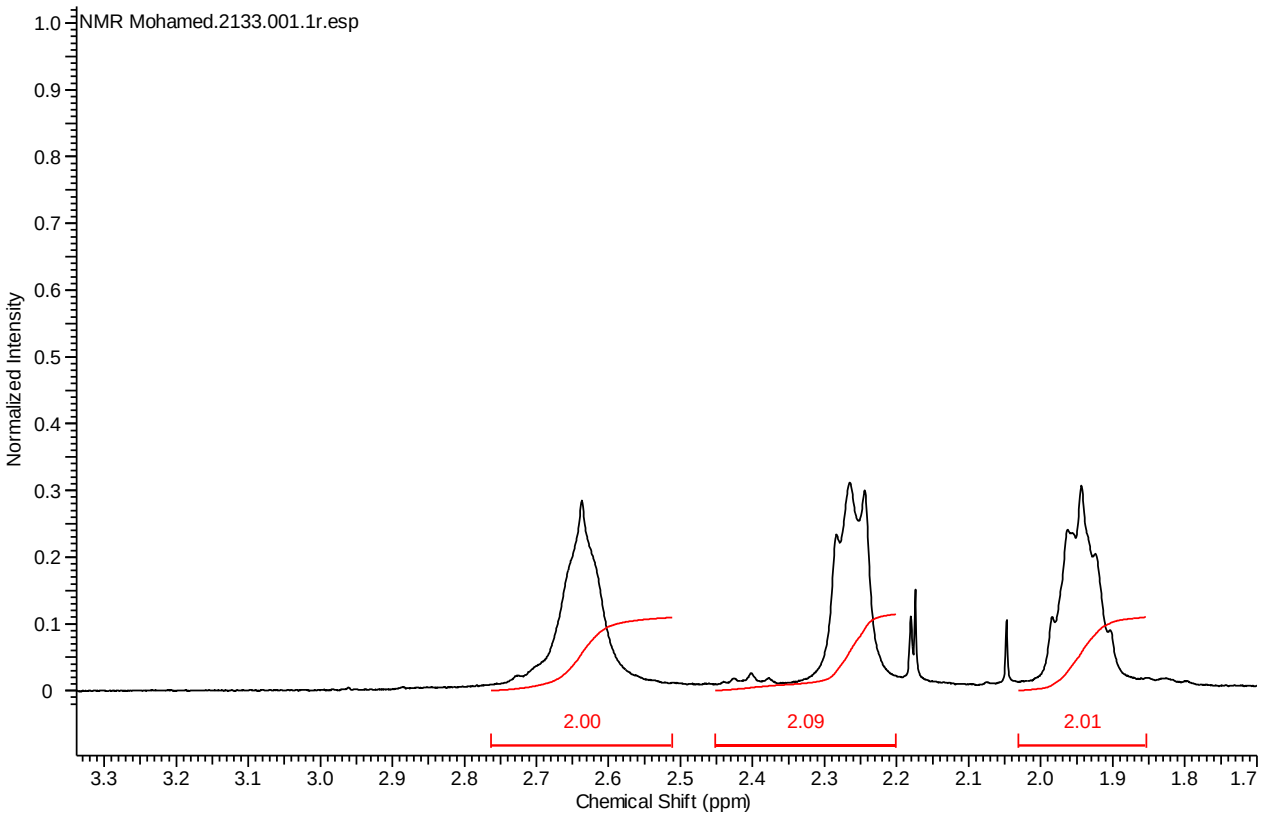

NMR Mohamed.2109.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
175.08
137.69
134.79
132.40
133.26
130.48
132.43
128.10
127.09
32.11
26.90
23.14

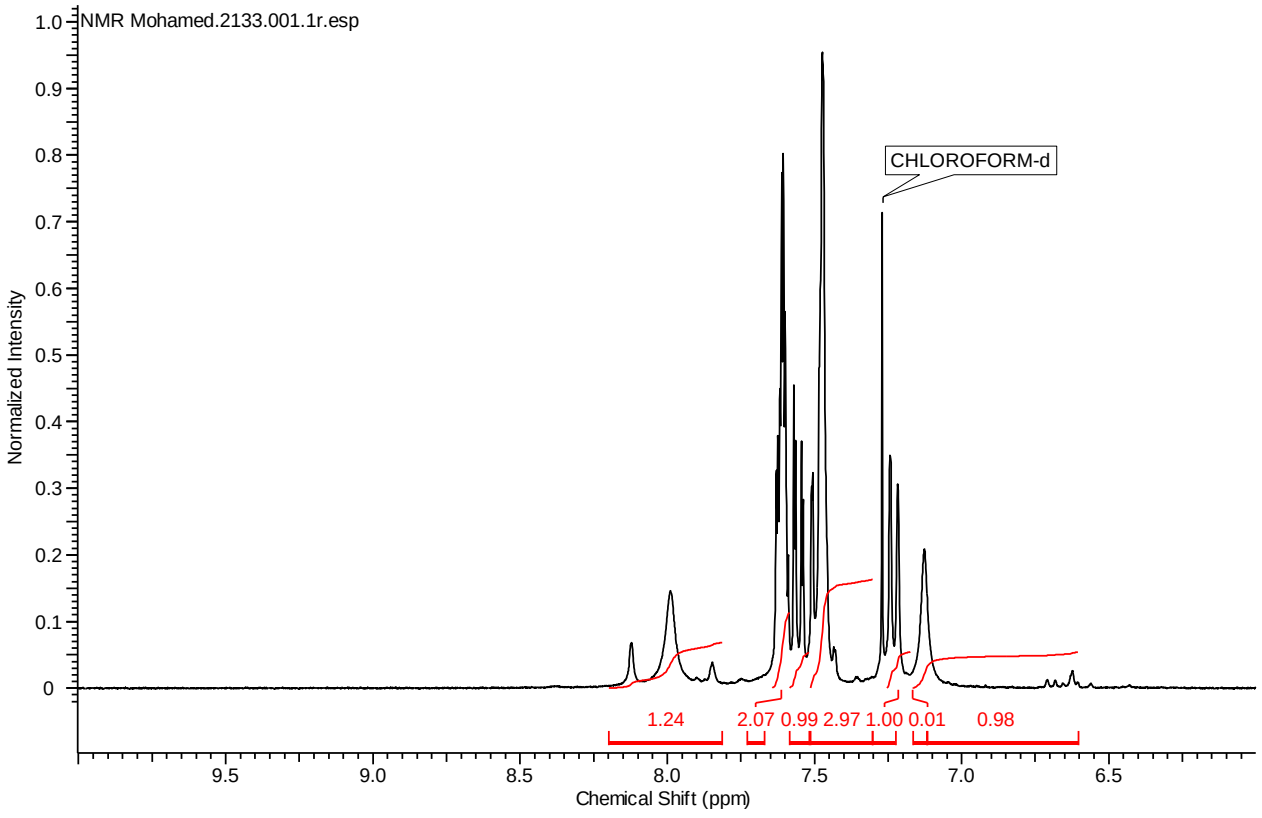

NMR Mohamed.2109.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
137.69
134.79
132.40
133.26
132.43
130.48
129.66
129.43
128.10
127.09

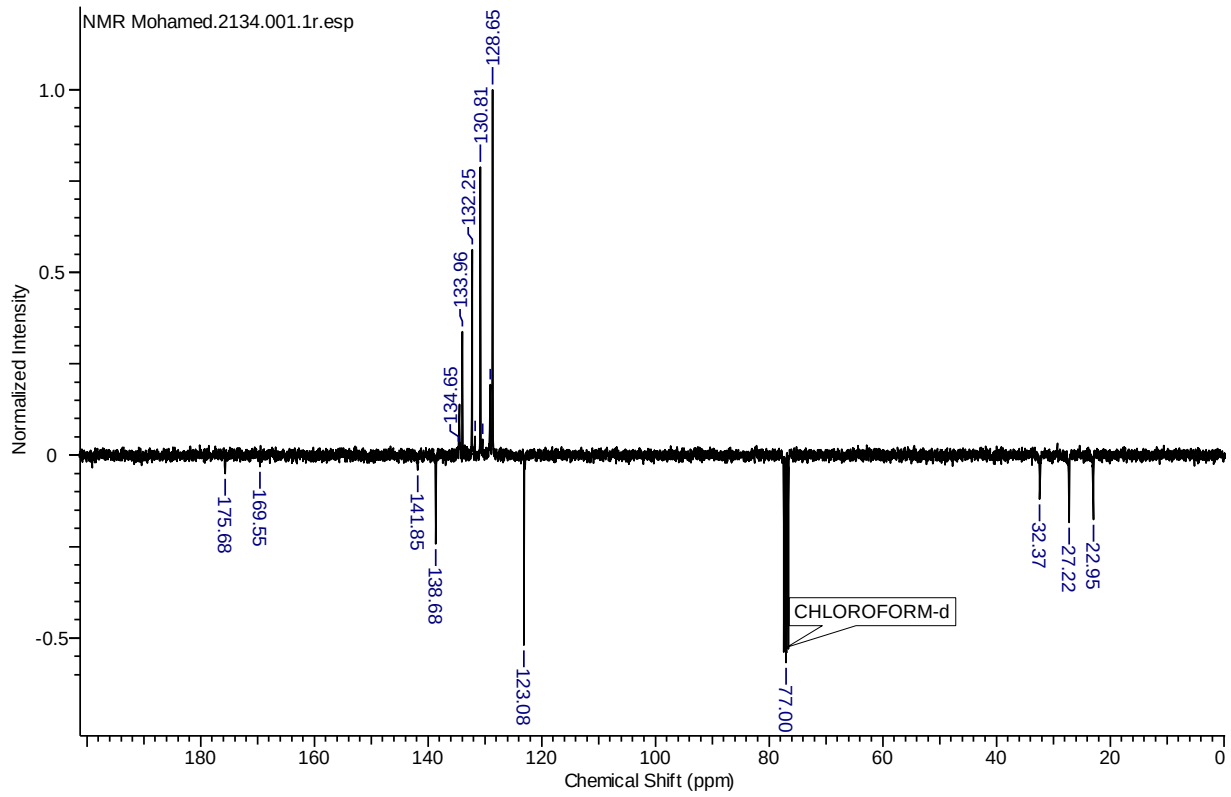
(E)-3-(((Z)-1,2,3,4-tetrahydro-9H-cyclopenta[b]quinolin-9-ylidene)hydrazono)indolin-2-one (6f).

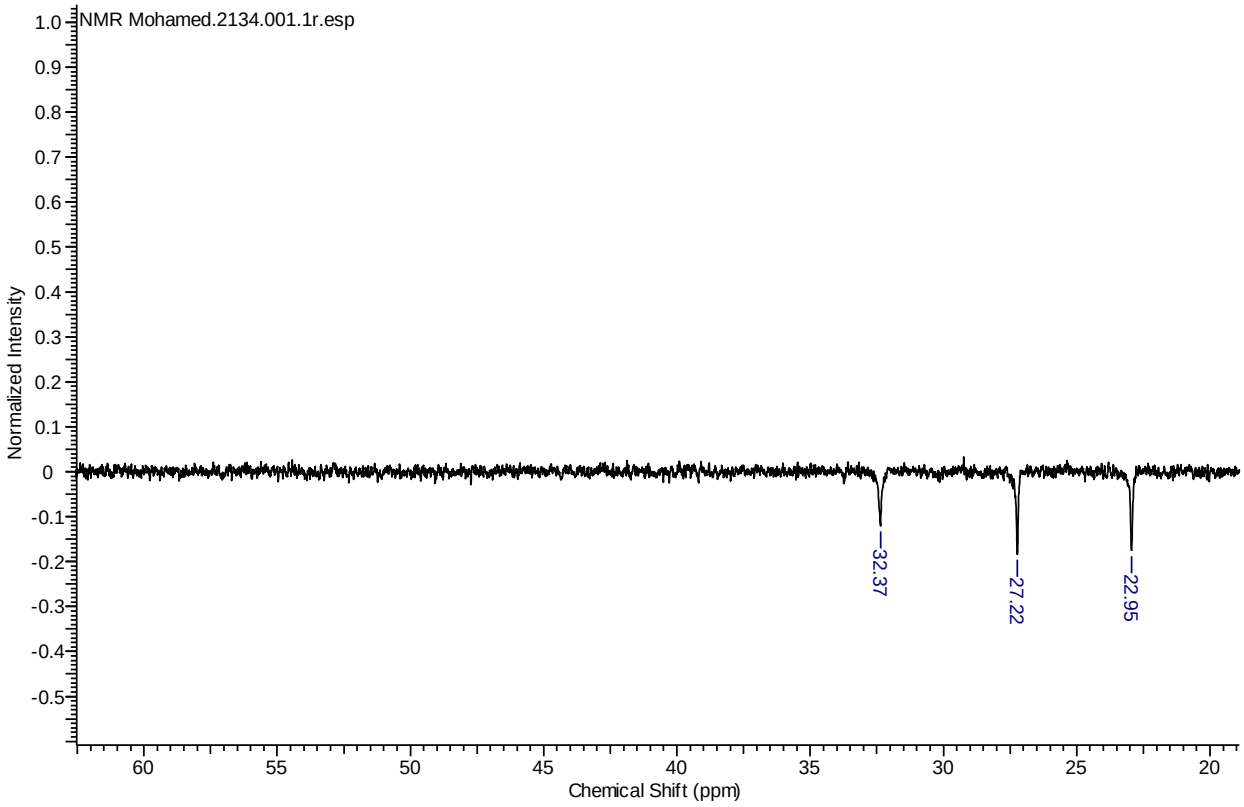


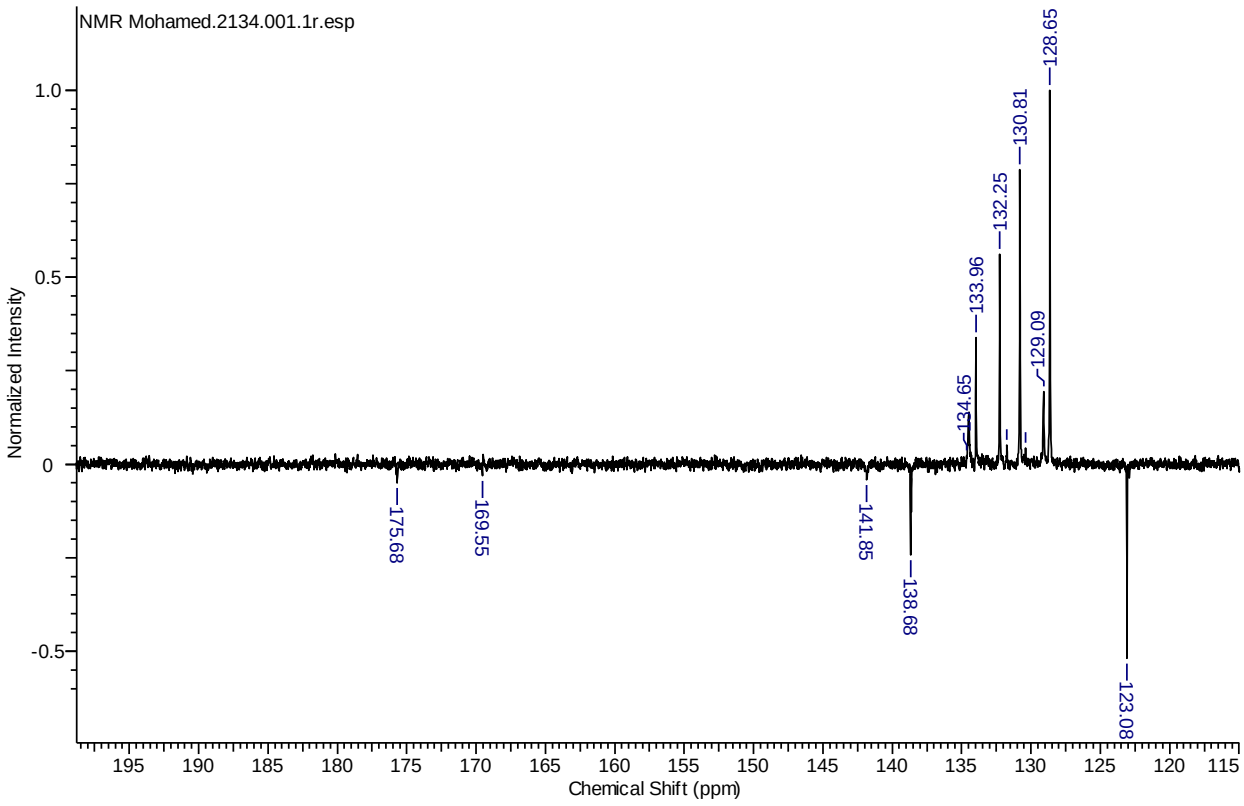



NMR Mohamed.2133.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
2.00
2.09
2.01

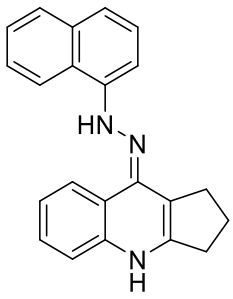

NMR Mohamed.2133.001.1r.esp
CHLOROFORM-d
Normalized Intensity
Chemical Shift (ppm)
1.24
2.07
0.99
2.97
1.00
0.01
0.98

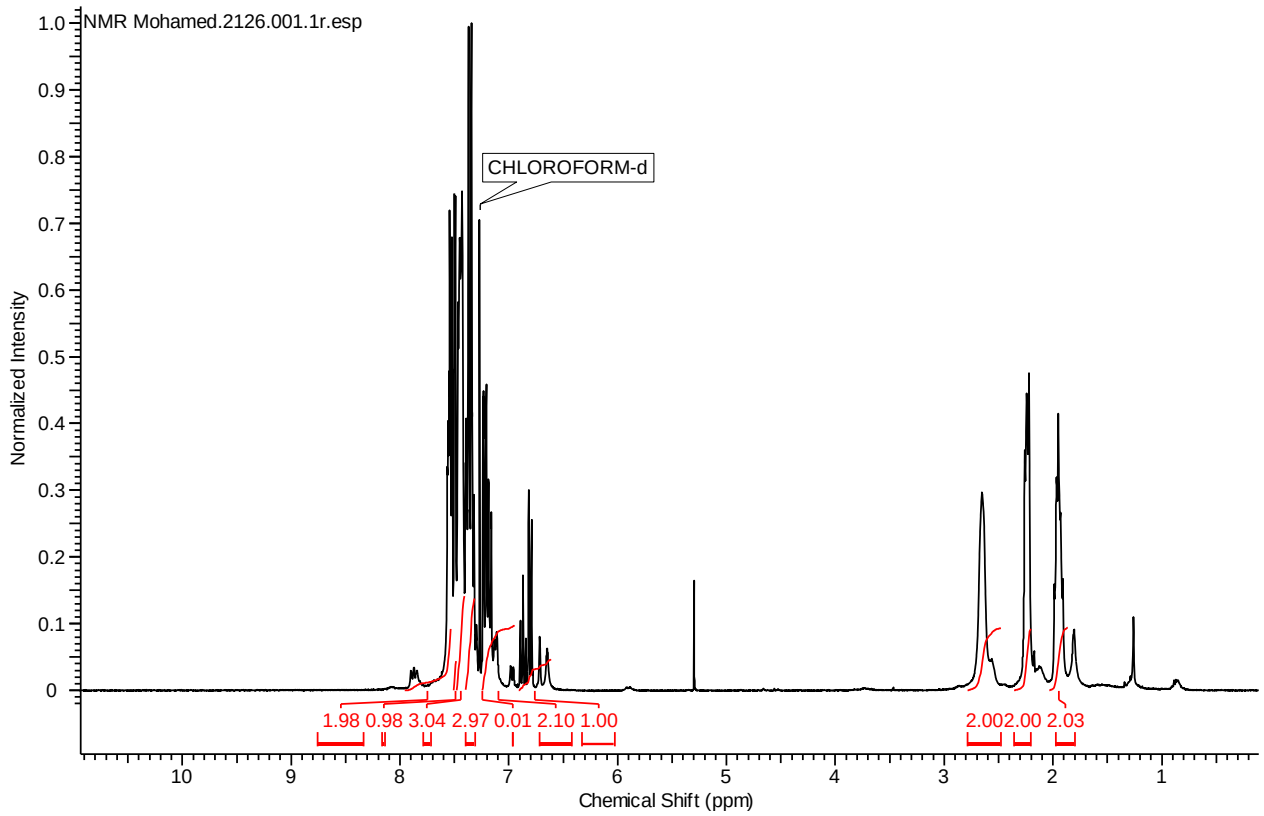

NMR Mohamed.2134.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
128.65
130.81
132.25
133.96
134.65
175.68
169.55
141.85
138.68
123.08
77.00
CHLOROFORM-d
32.37
27.22
22.95

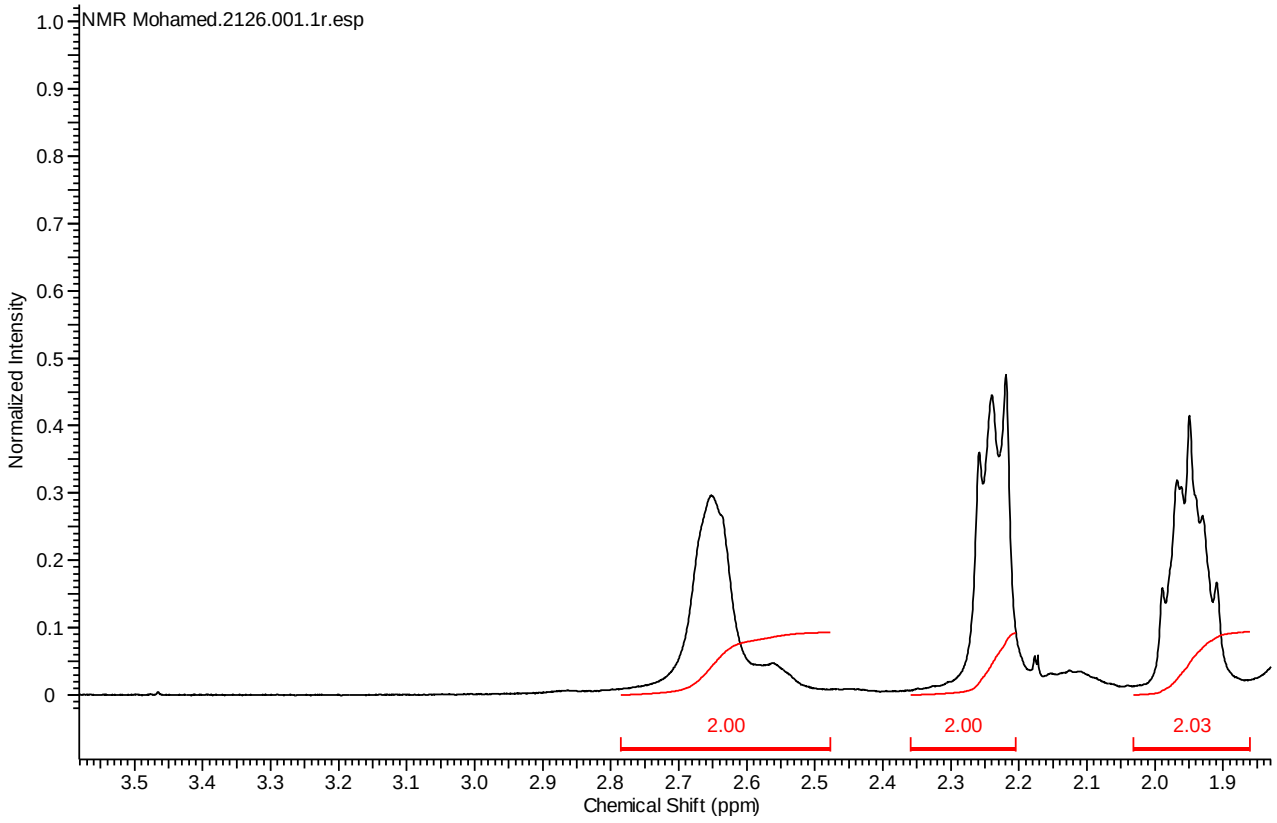

NMR Mohamed.2134.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
32.37
27.22
22.95

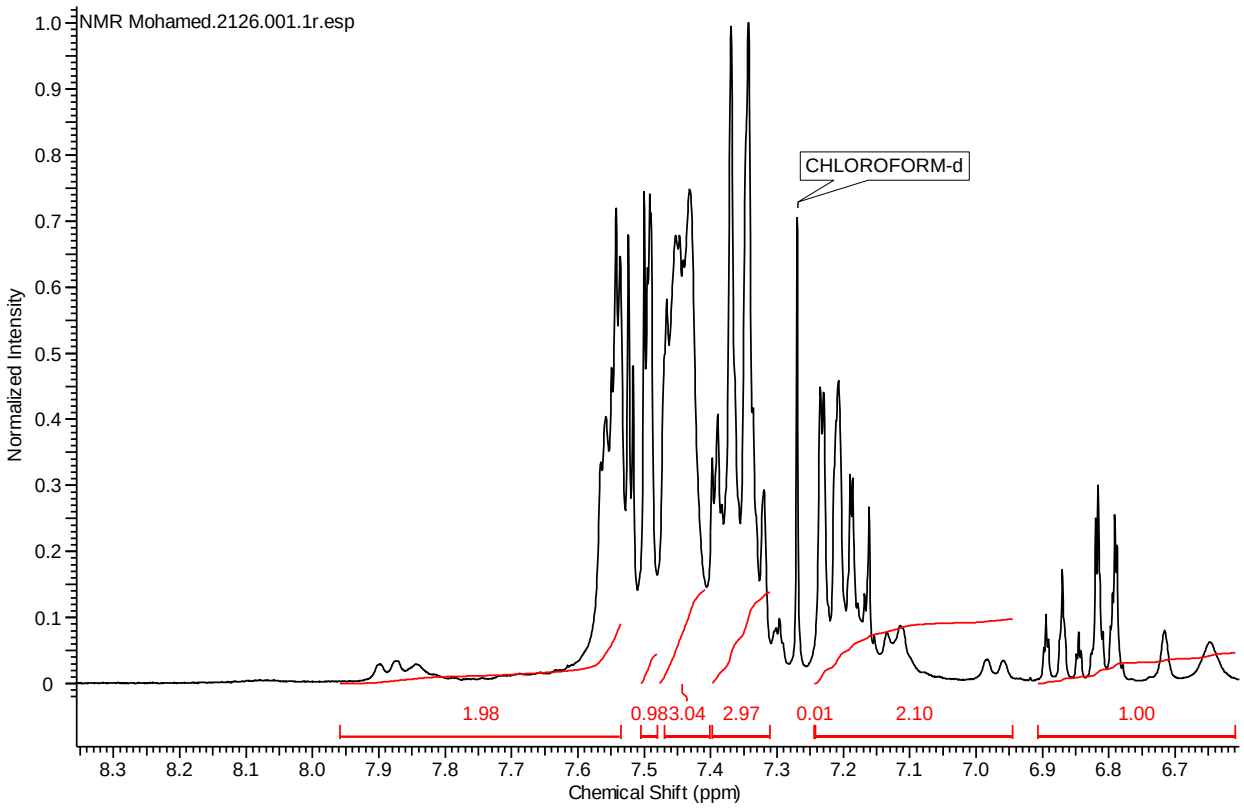


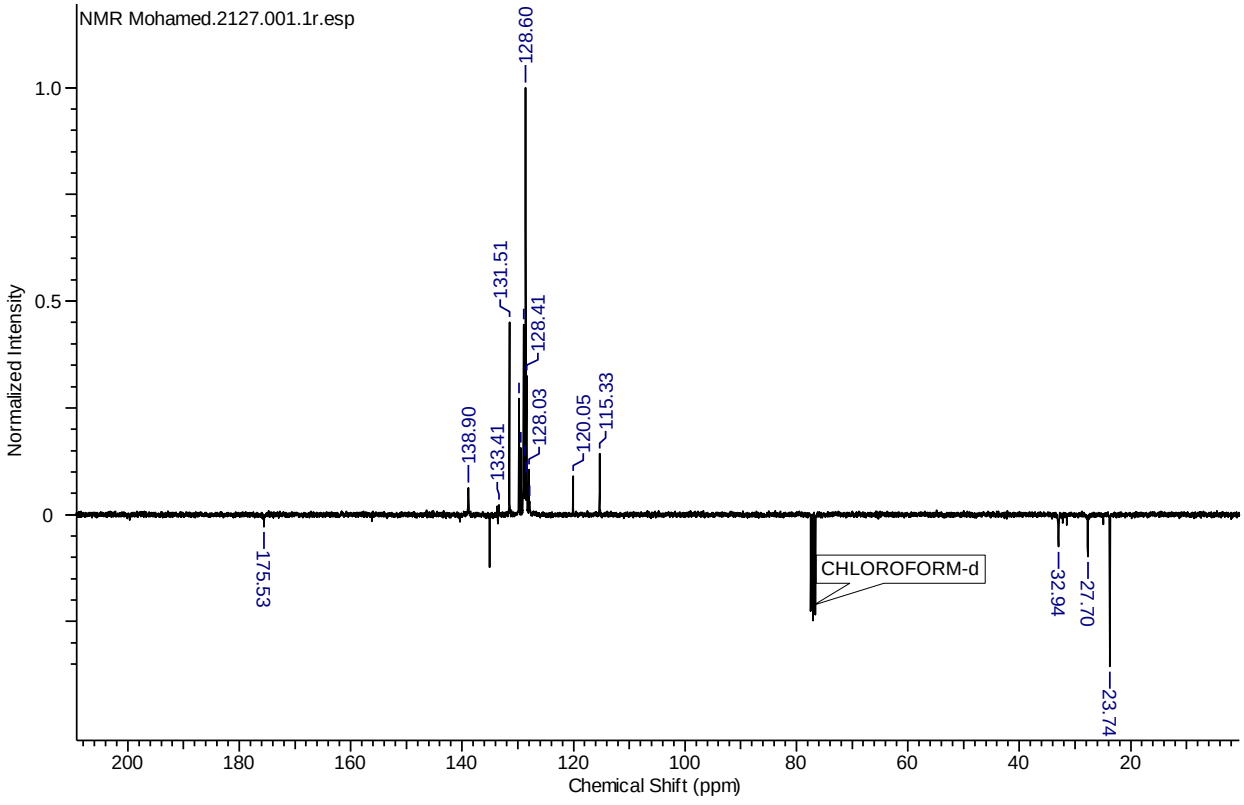
(Z)-9-(2-(naphthalen-1-yl)hydrazono)-2,3,4,9-tetrahydro-1H-cyclopenta[b]quinoline (6g).

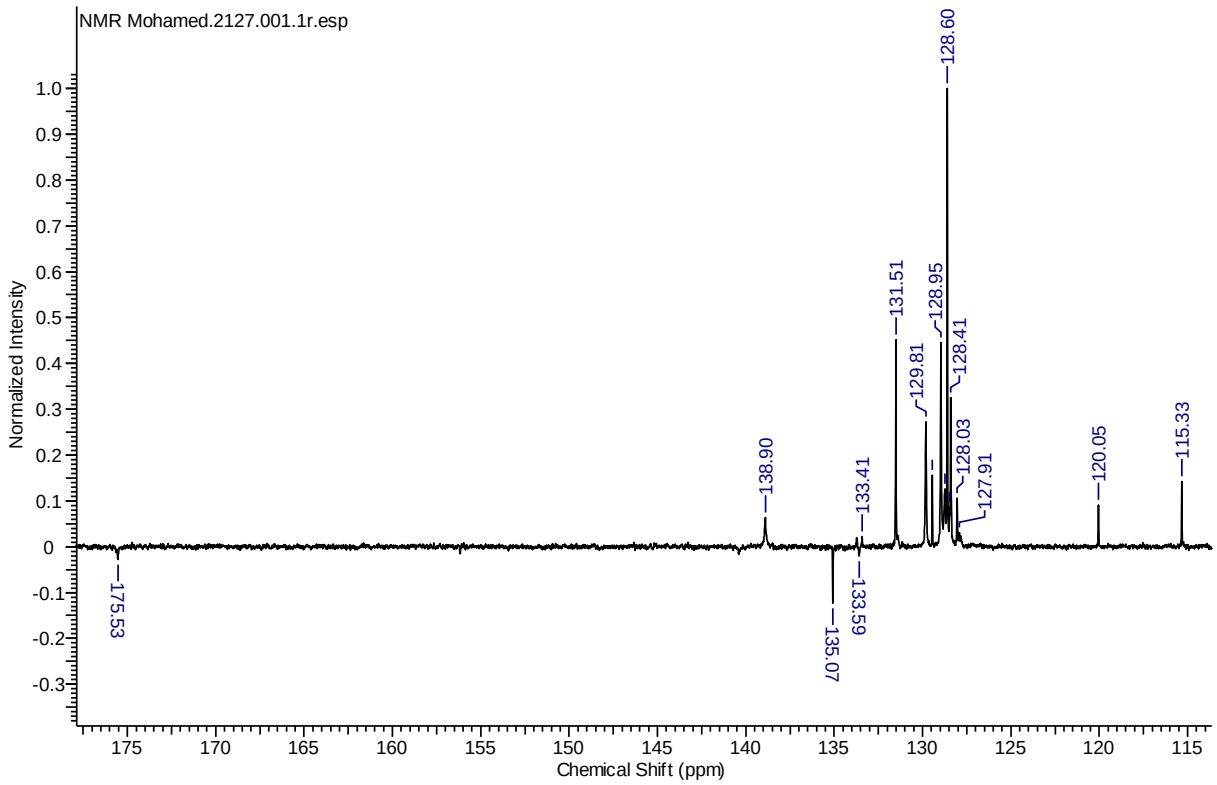


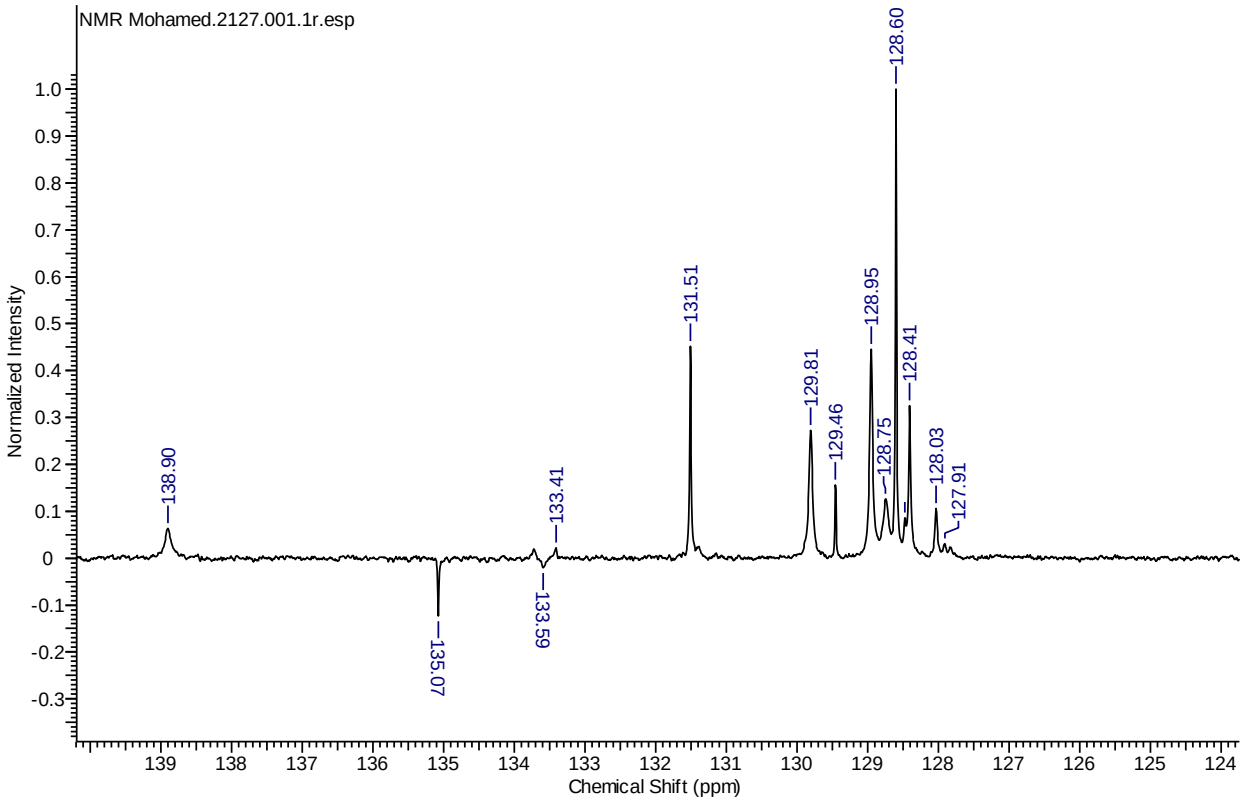

NMR Mohamed.2126.001.1r.esp
CHLOROFORM-d
Normalized Intensity
Chemical Shift (ppm)
1.98 0.98 3.04 2.97 0.01 2.10 1.00
2.00 2.00 2.03


NMR Mohamed.2126.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
2.00
2.00
2.03


NMR Mohamed.2126.001.1r.esp
Normalized Intensity
CHLOROFORM-d
1.98
0.98
3.04
2.97
0.01
2.10
1.00
Chemical Shift (ppm)


NMR Mohamed.2127.001.1r.esp
Normalized Intensity
128.60
131.51
128.41
138.90
133.41
128.03
120.05
115.33
175.53
CHLOROFORM-d
32.94
27.70
23.74
Chemical Shift (ppm)


NMR Mohamed.2127.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
128.60
131.51
128.95
129.81
128.41
128.03
127.91
138.90
133.41
120.05
115.33
175.53
135.07
133.59


NMR Mohamed.2127.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
128.60
131.51
128.95
129.81
128.41
129.46
128.75
128.03
127.91
138.90
133.41
135.07
133.59