Electronic Supplementary Material (ESI) for RSC Advances.

Antiulcer secondary metabolites from *Elaeocarpus grandis*., family Elaeocarpaceae supported by in silico studies.

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Key words:

Elaeoacarpus, anti-ulcer, Heterophyllin A, phenolics, docking.

Abstract:

Elaeocarpus grandis has a very potent analgesic effect especially to δ- opioid receptor, but its anti-ulcer activity has not been validated. Therefore, the present study was carried out to evaluate the anti-ulcer potential of the total methanolic extract and its derived fractions of the aerial parts of the plant using indomethacin- induced gastric ulcer method. Six compounds named Grandisine H, *P*-methoxy benzaldehyde, Methyl gallate, Kaempferol, Quercetin and Heterophylliin A (**1**-**6**), were isolated from the ethyl acetate fraction which was the most potent one with an ulcer index value of 5± 1.95 ** (*P<0.05, **P<0.01) and preventive index of 92.9%, following a bioassay-guided fractionation. The isolated compounds were subjected to molecular docking study in an attempt to explain their significant antiulcer potential, and the results revealed that Kampferol and Quercetin bind to the active site of M3 receptor with a strong binding affinity via strong hydrogen bonds. In addition, Quercetin and Heterophyllin A showed a binding affinity with gastric proton pump receptor and a strong hydrogen bond interaction with the amino acids active sites in case of H_2-modeled receptor. These results clarify the effectiveness and importance of the ethyl acetate fraction as natural anti-ulcer remedy.

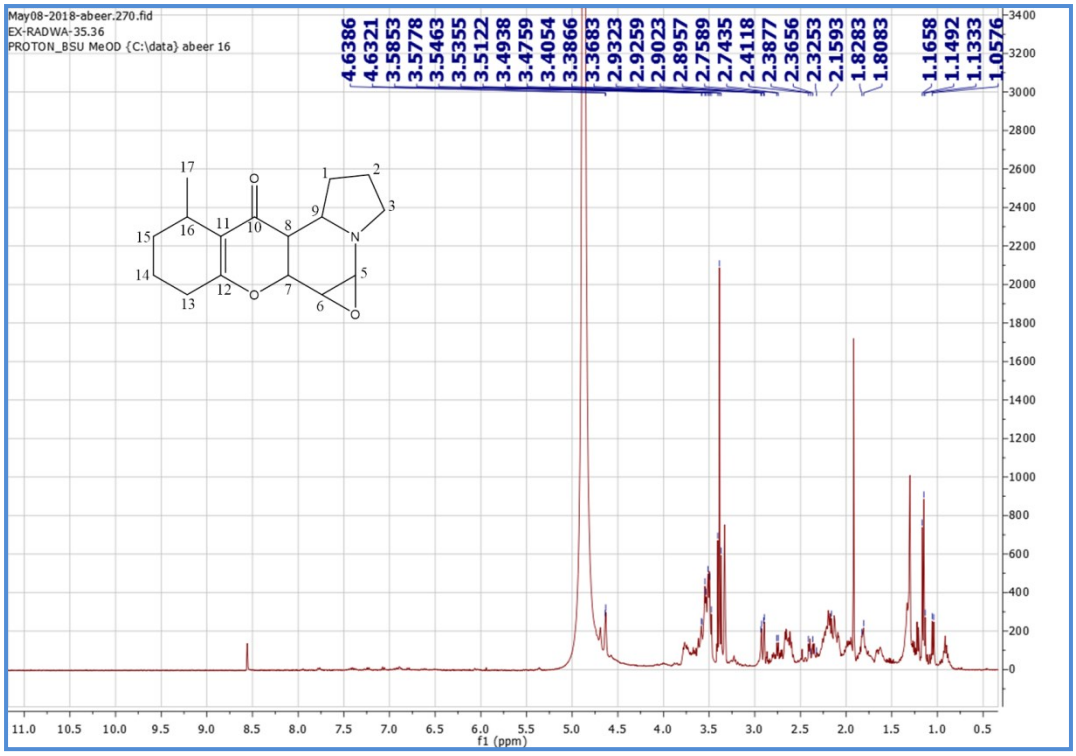

Fig. S_1: ^{1}H-NMR spectrum of compound 1 (MeOD, 400 MHz).

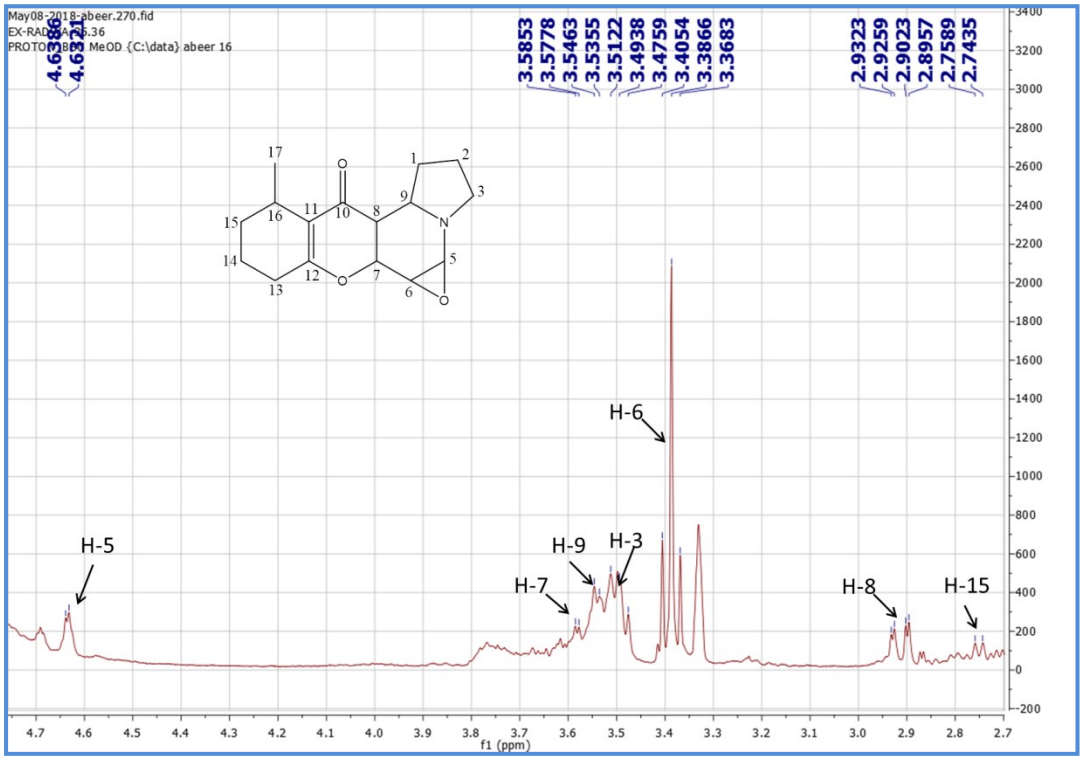

Fig. S_2: Expanded ^{1}H-NMR spectrum of compound 1 (MeOD, 400 MHz).

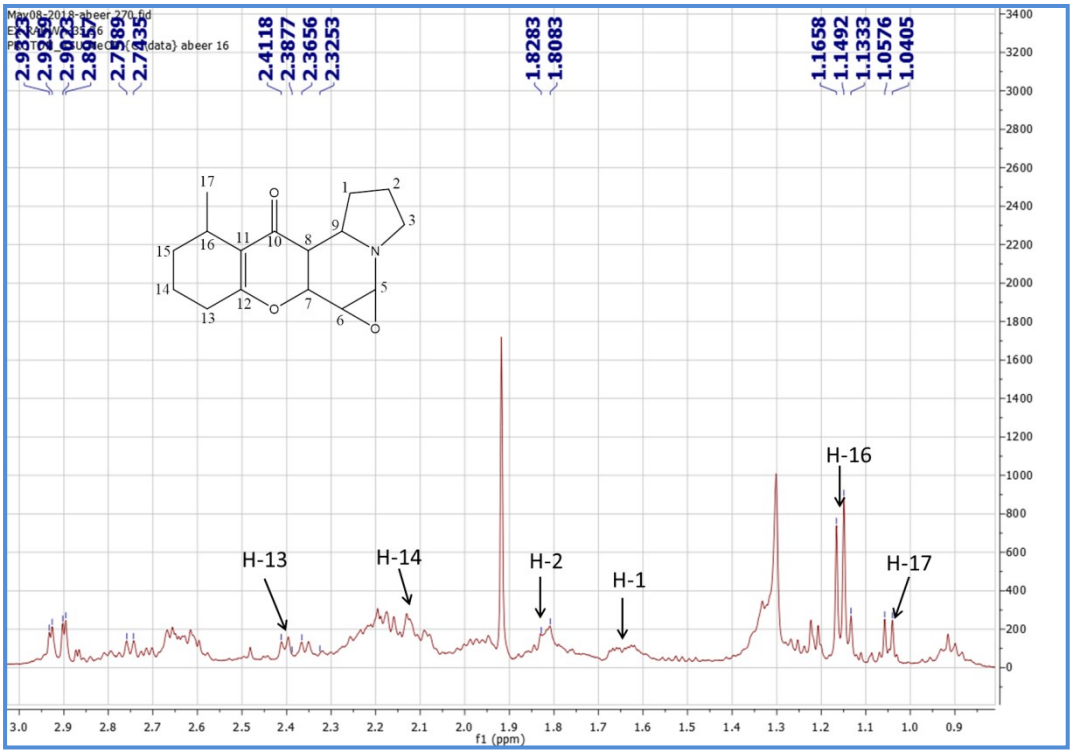

Fig. S_3: Expanded ^{1}H-NMR spectrum of compound 1 (MeOD, 400 MHz).

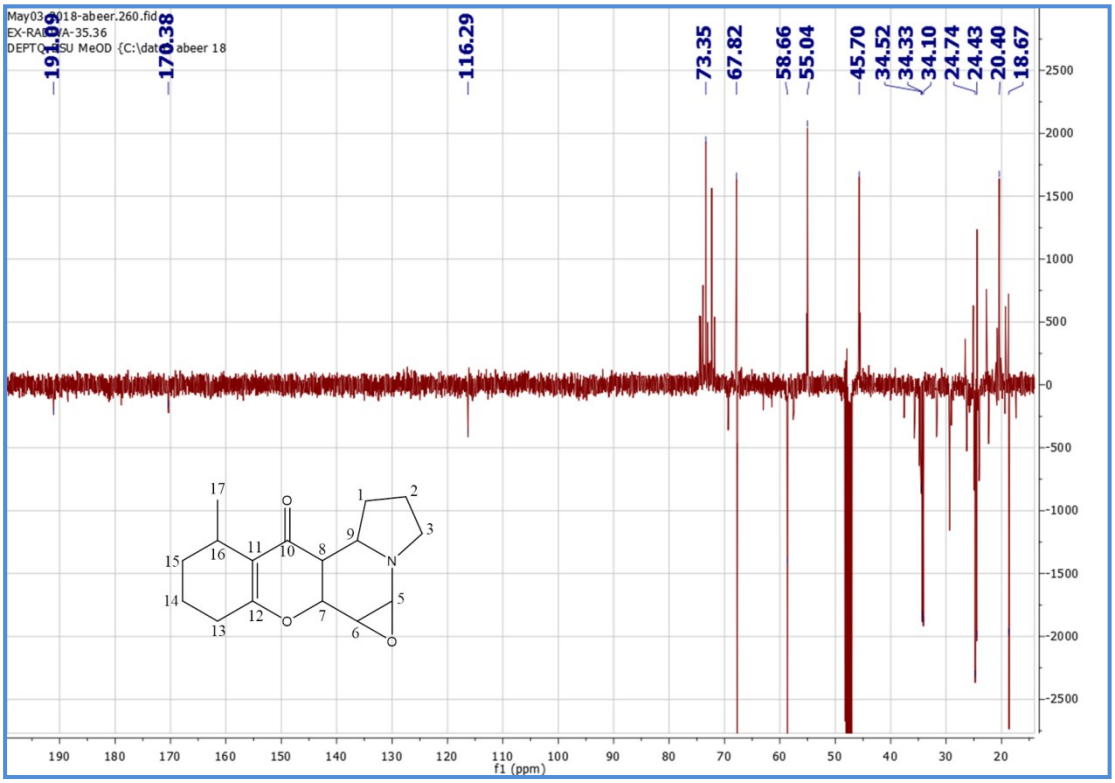

Fig.S_4: DEPT-Q spectrum of compound 1 (MeOD, 100 MHz).

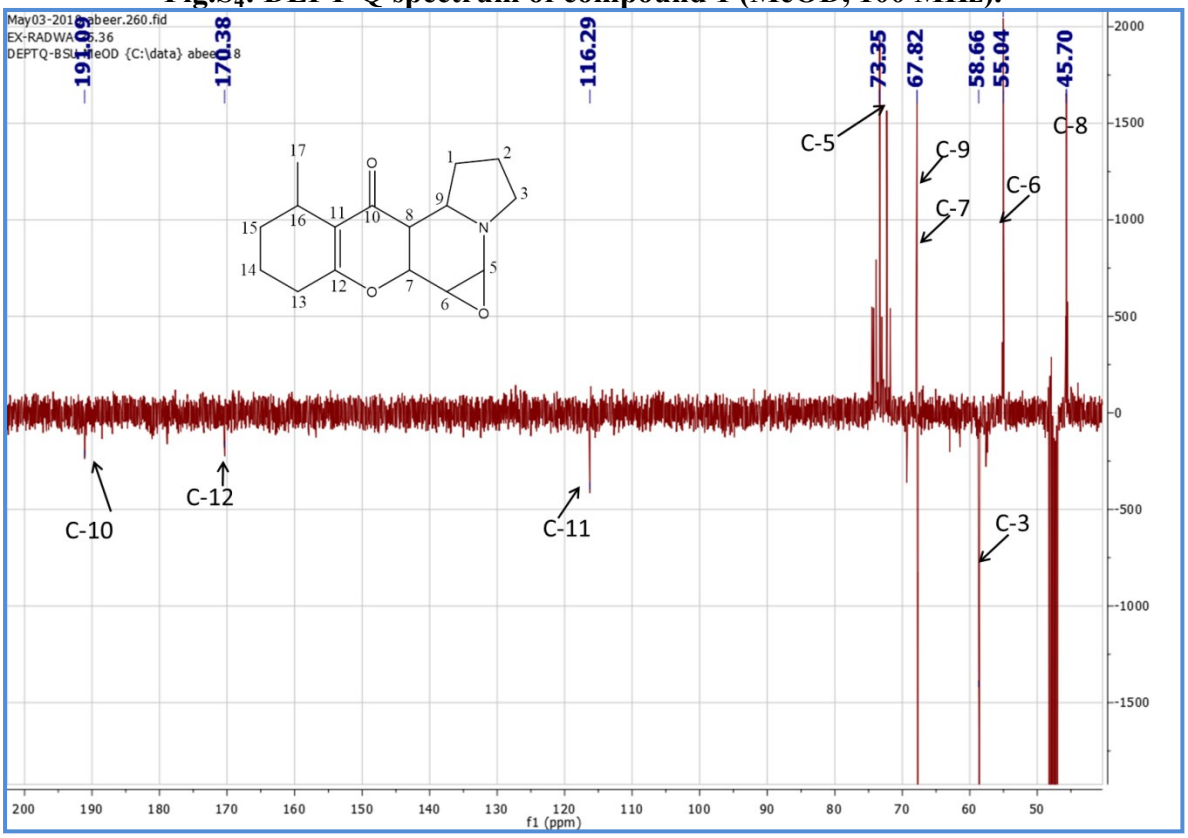

Fig. S_5: Expanded DEPT-Q spectrum of compound 1 (MeOD, 100 MHz).

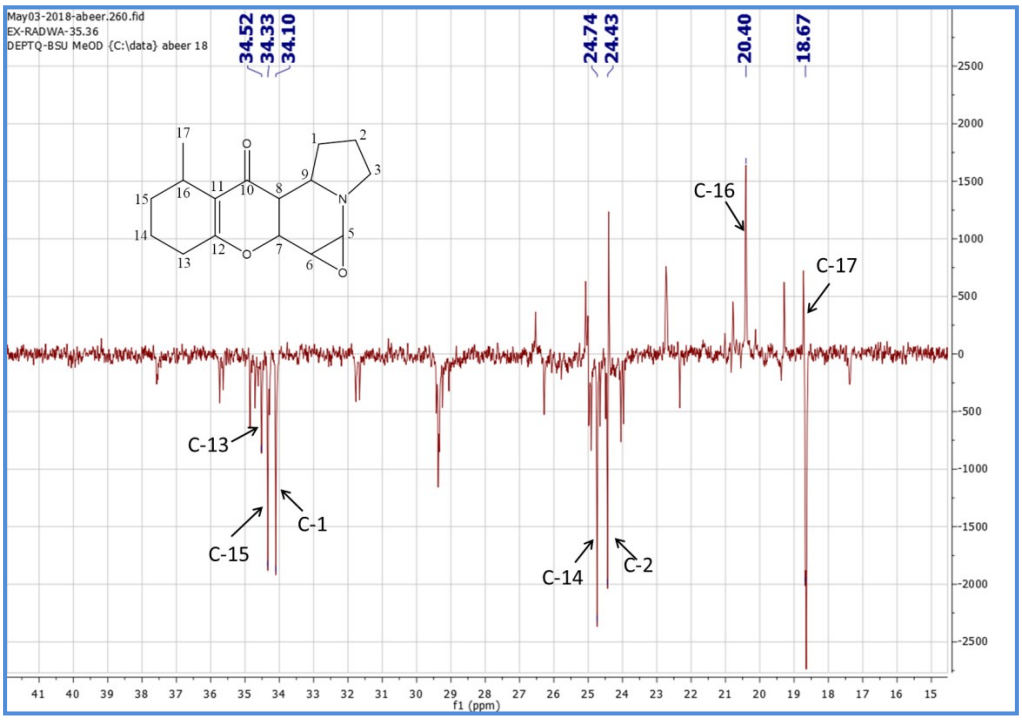

Fig. S_6: Expanded DEPT-Q spectrum of compound 1 (MeOD, 100 MHz).

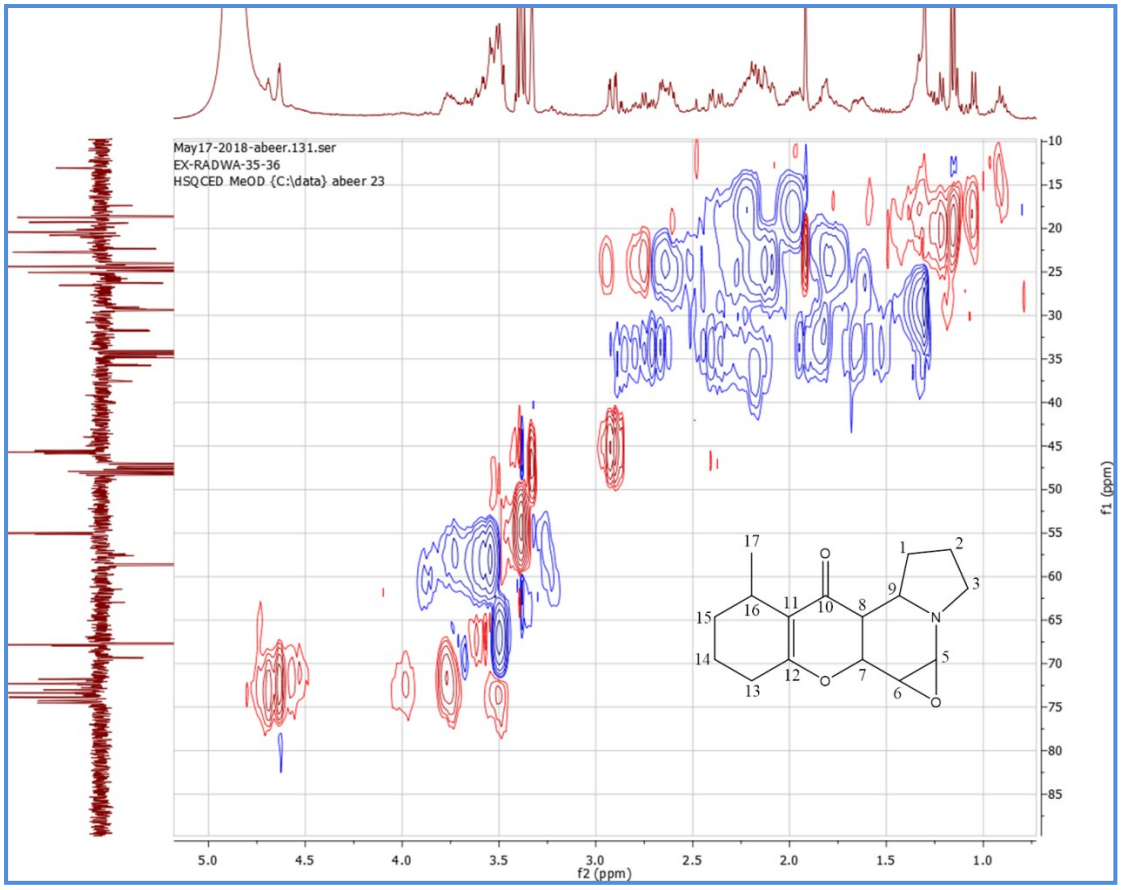

Fig. S_7: HSQC spectrum of compound 1.

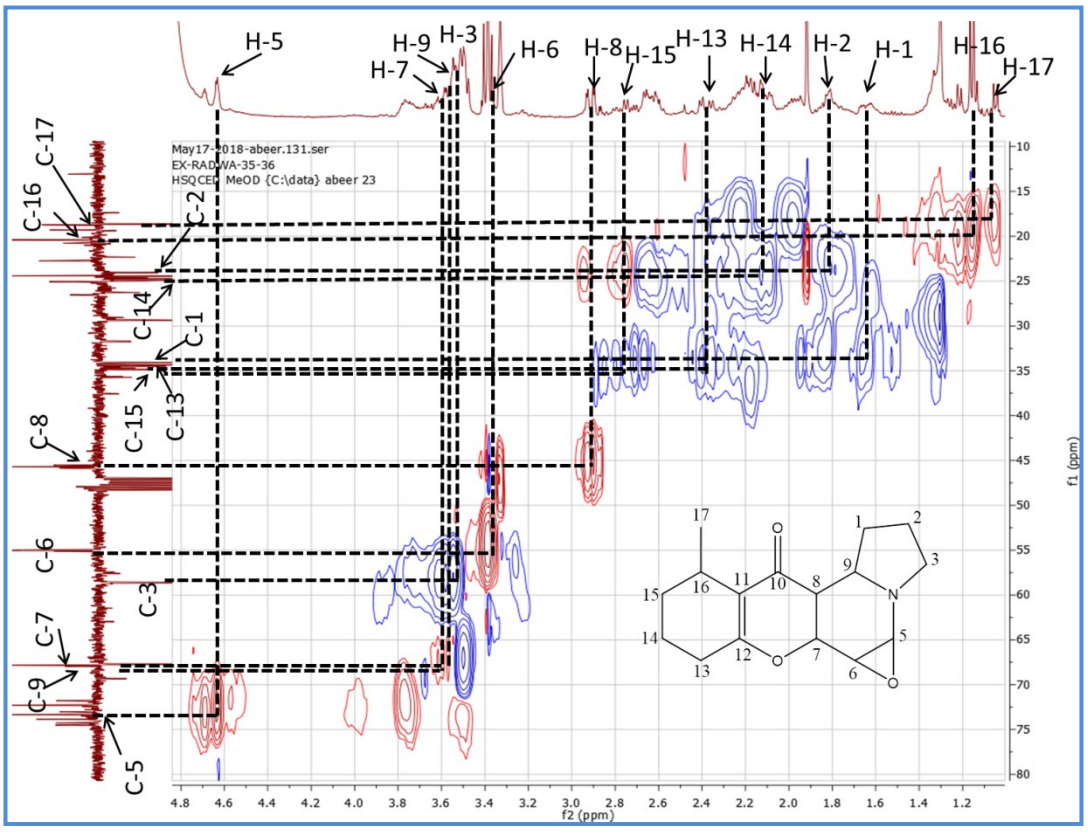

Fig.S$_8$: Expanded HSQC spectrum of compound 1.

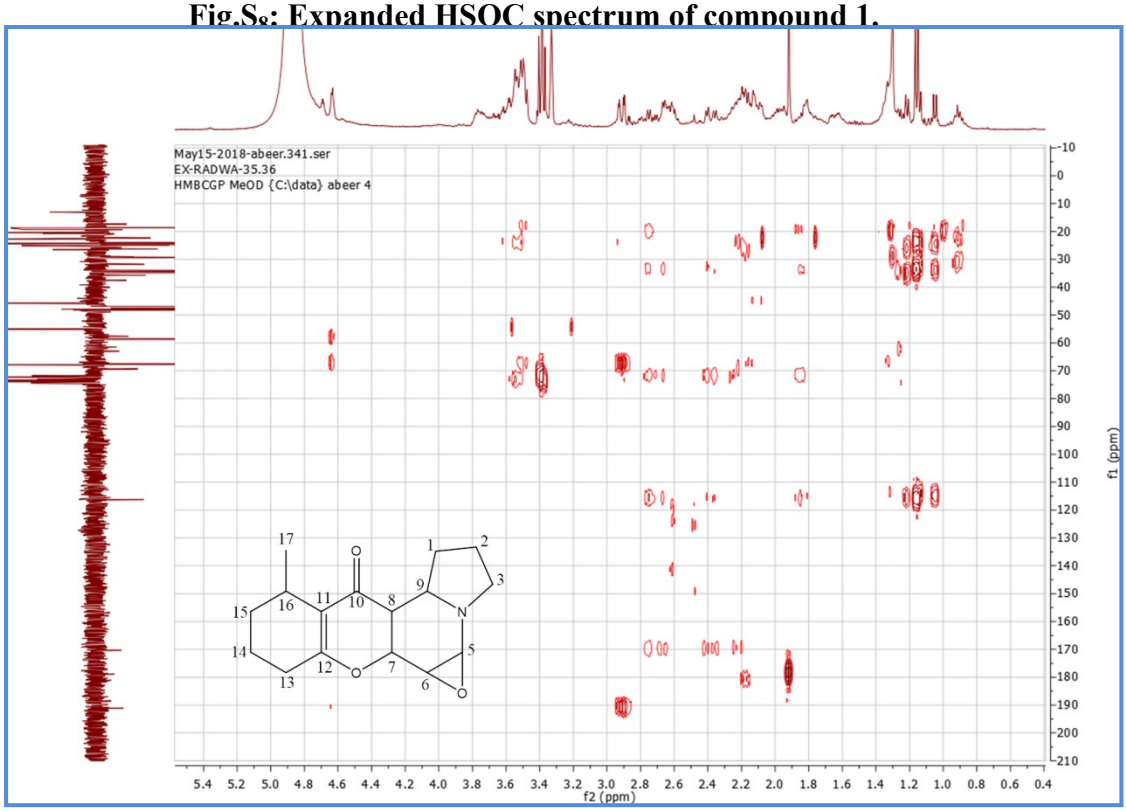

Fig.S$_9$: HMBC spectrum of compound 1.

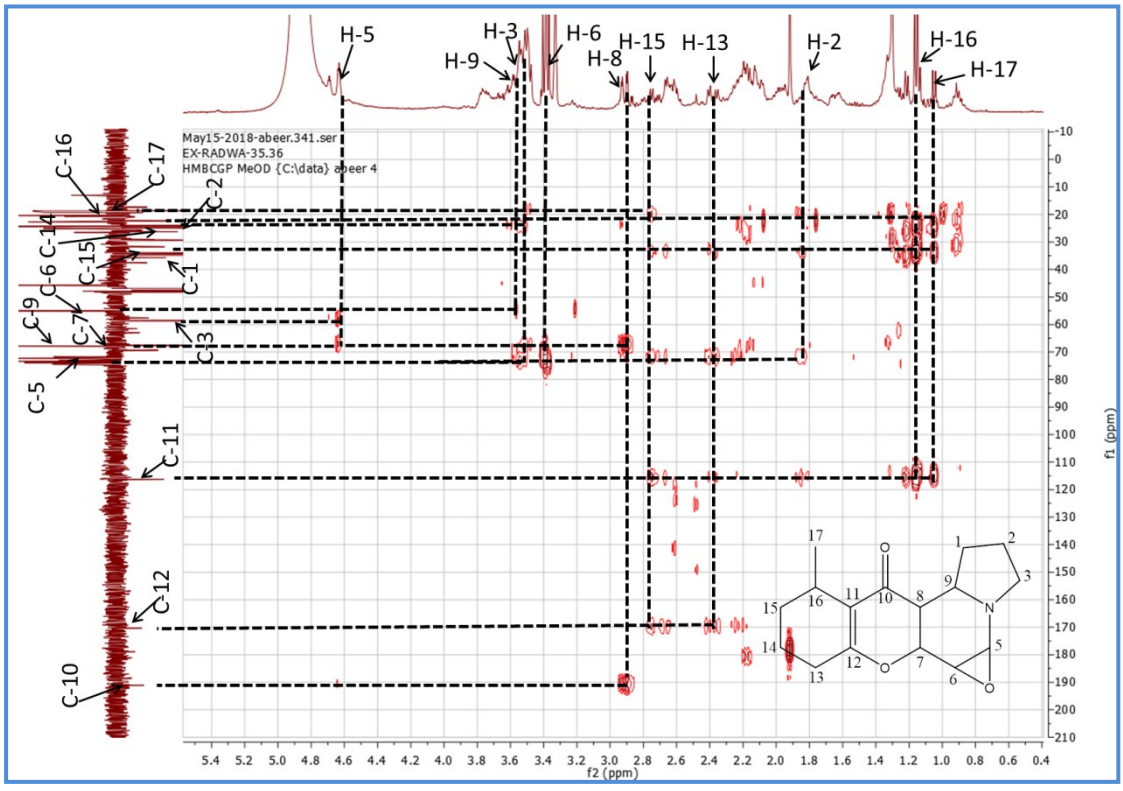

Fig. S$_{10}$: Expanded HMBC spectrum of compound 1.

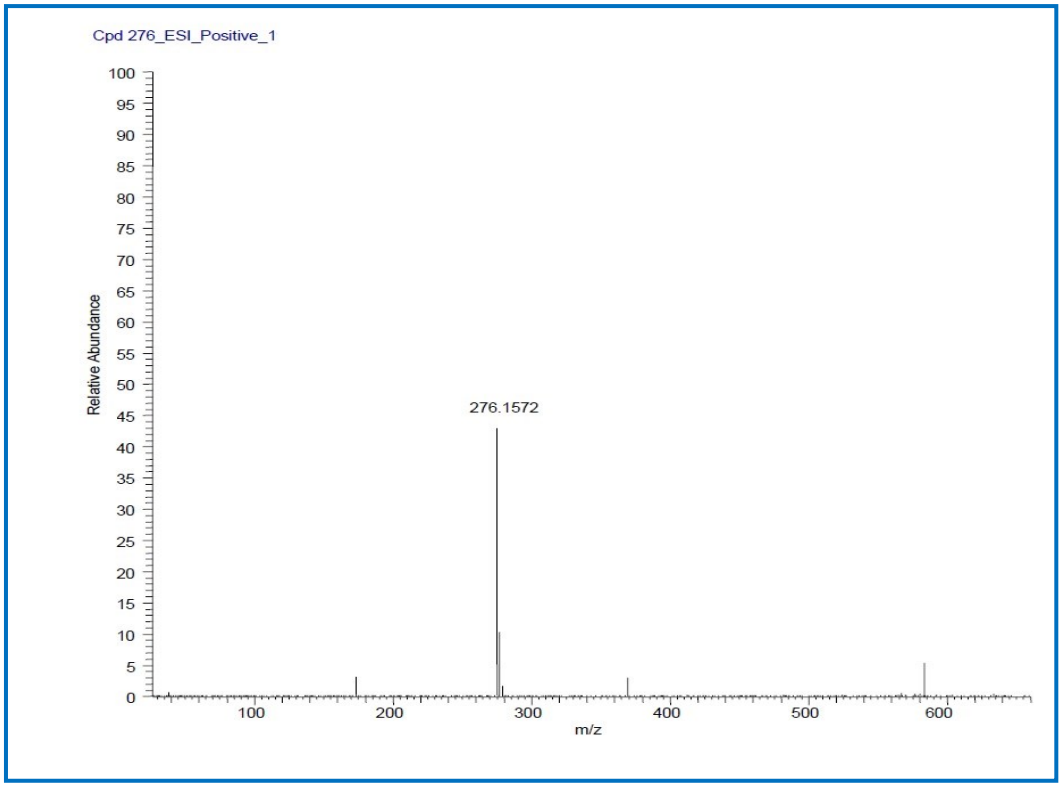

Fig. S_{11}: HR-ESI-MS of compound 1.

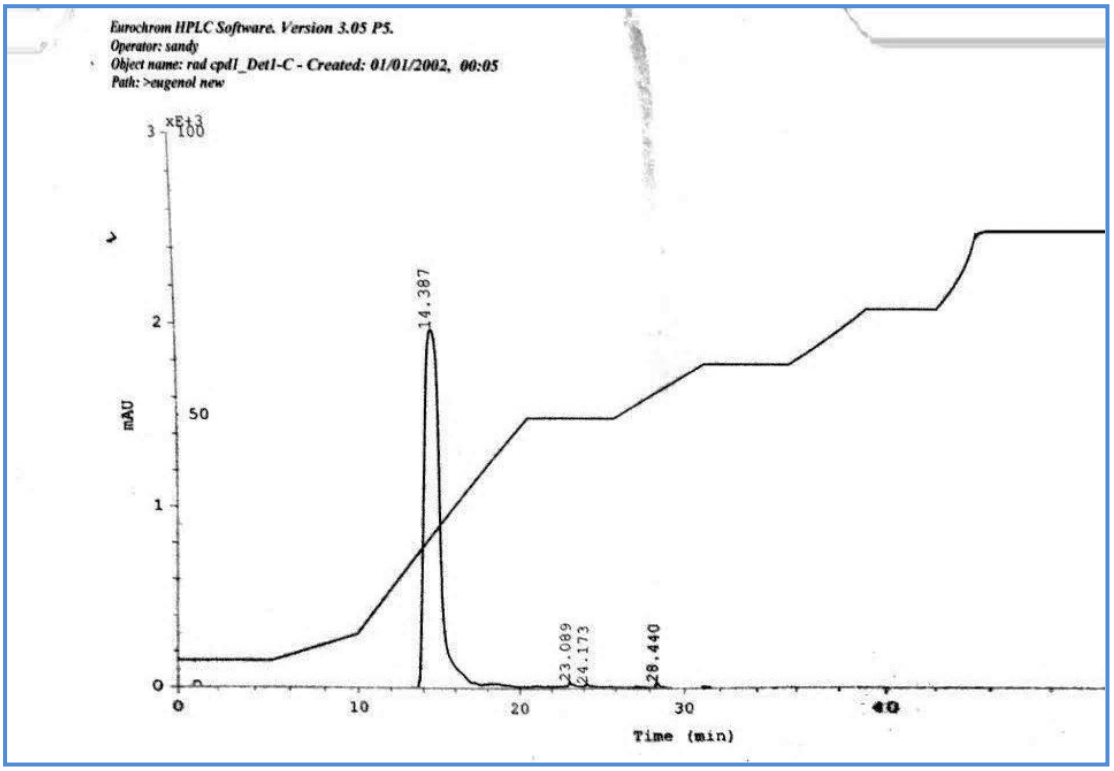

Fig. S_{12}: HPLC chromatogram of compound 2.

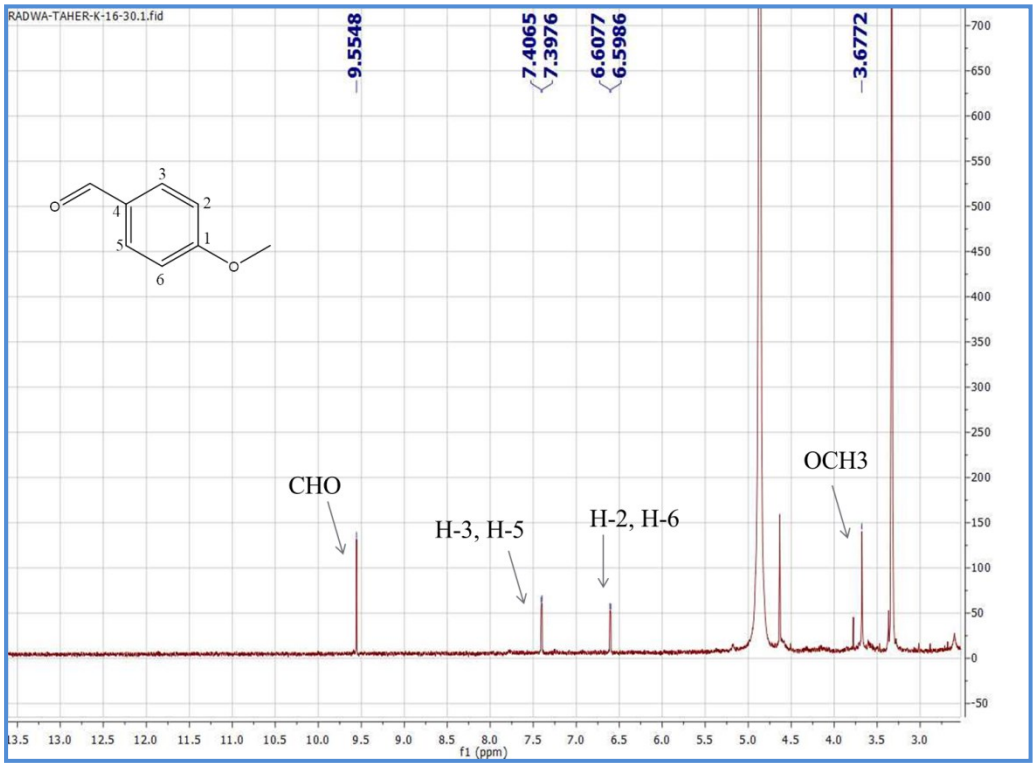

Fig. S_{13}: ^{1}H-NMR spectrum of compound 2 (MeOD, 400 MHz).

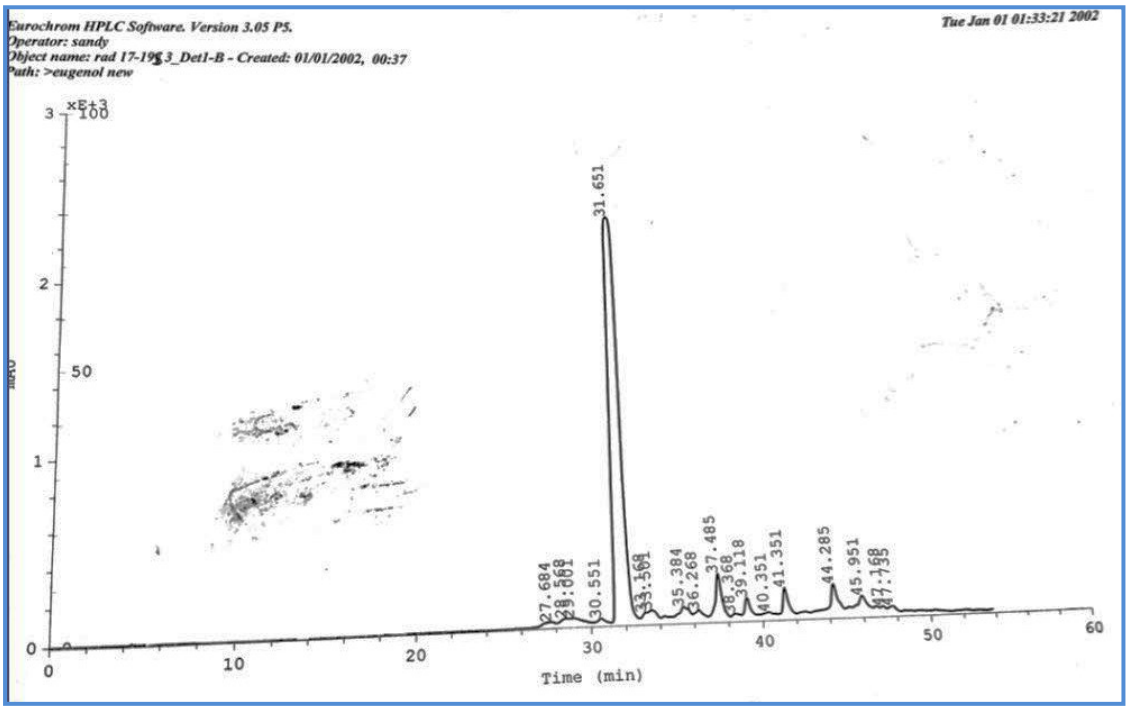

Fig. S_{14}: HPLC chromatogram of compound 3.

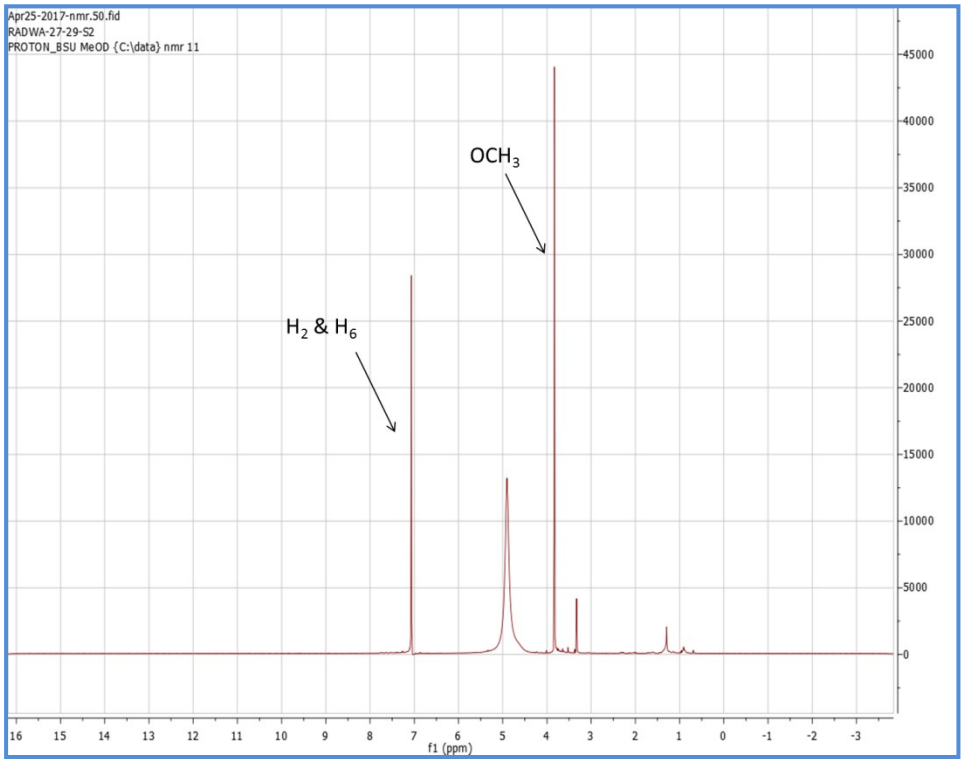

Fig.S$_{15}$: ^{1}H-NMR spectrum of compound 3 (MeOD, 400 MHz).

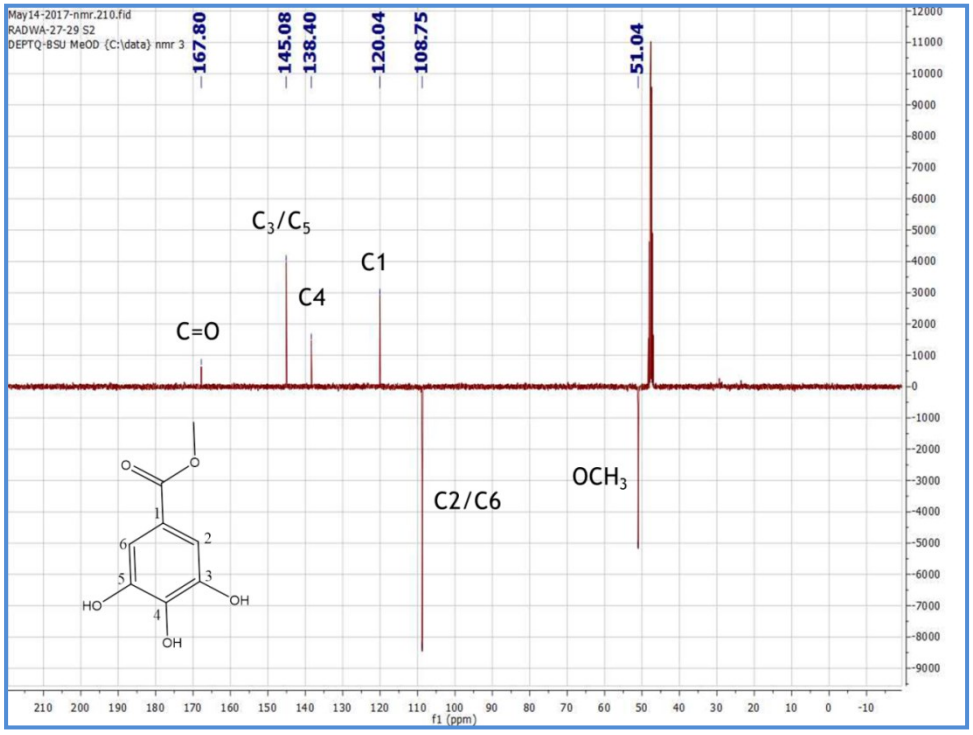

Fig.S$_{16}$: DEPT-Q spectrum of compound 3 (MeOD, 100 MHz).

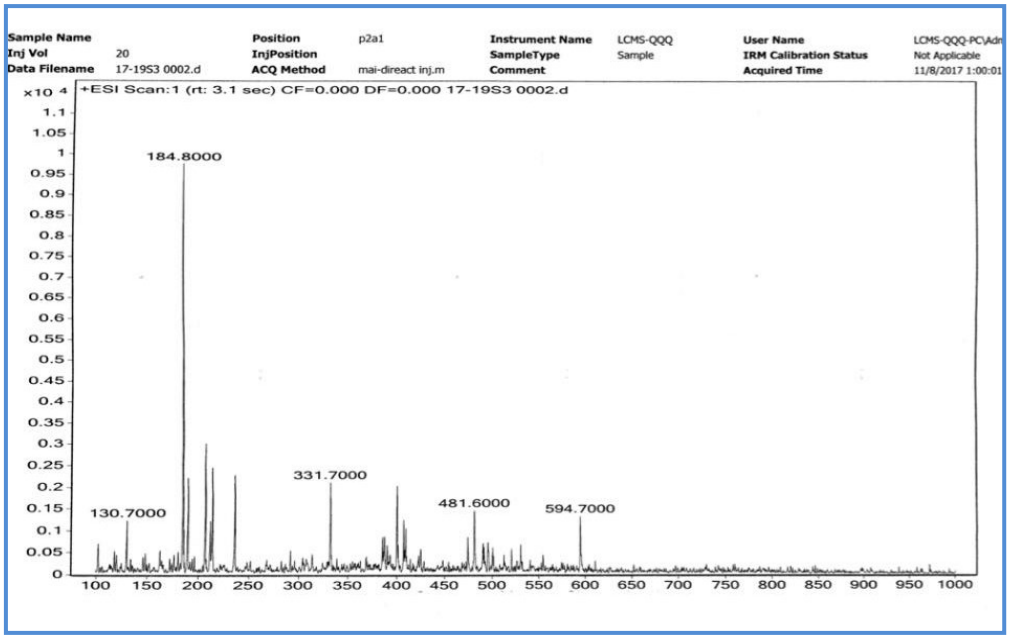

Fig. S_{17}: +ESI- MS spectrum of compound 3.

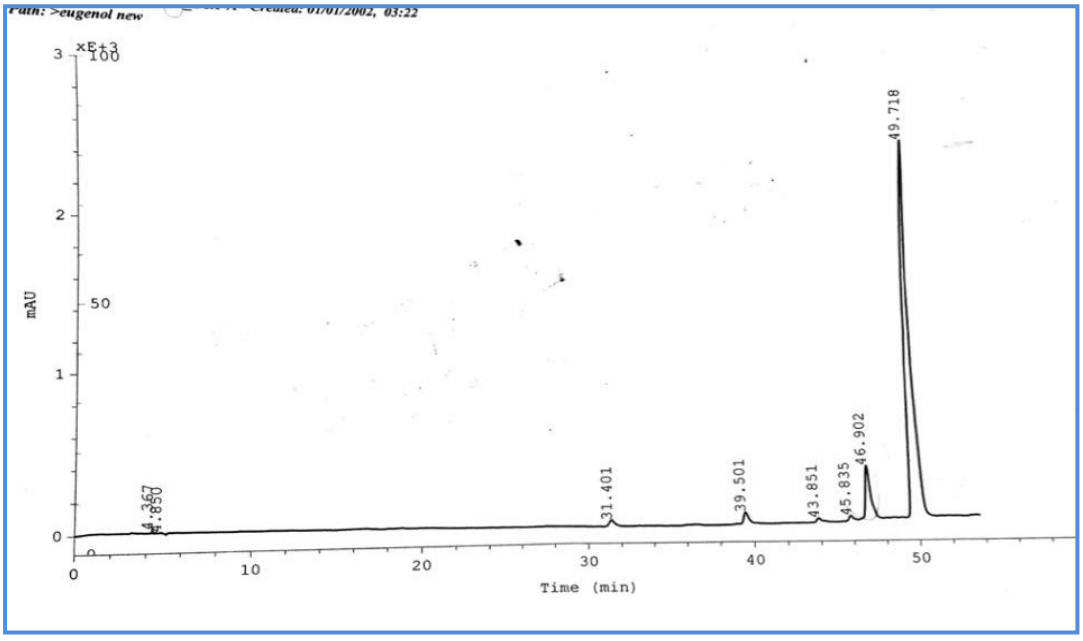

Fig. S_{18}: HPLC chromatogram of compound 4.

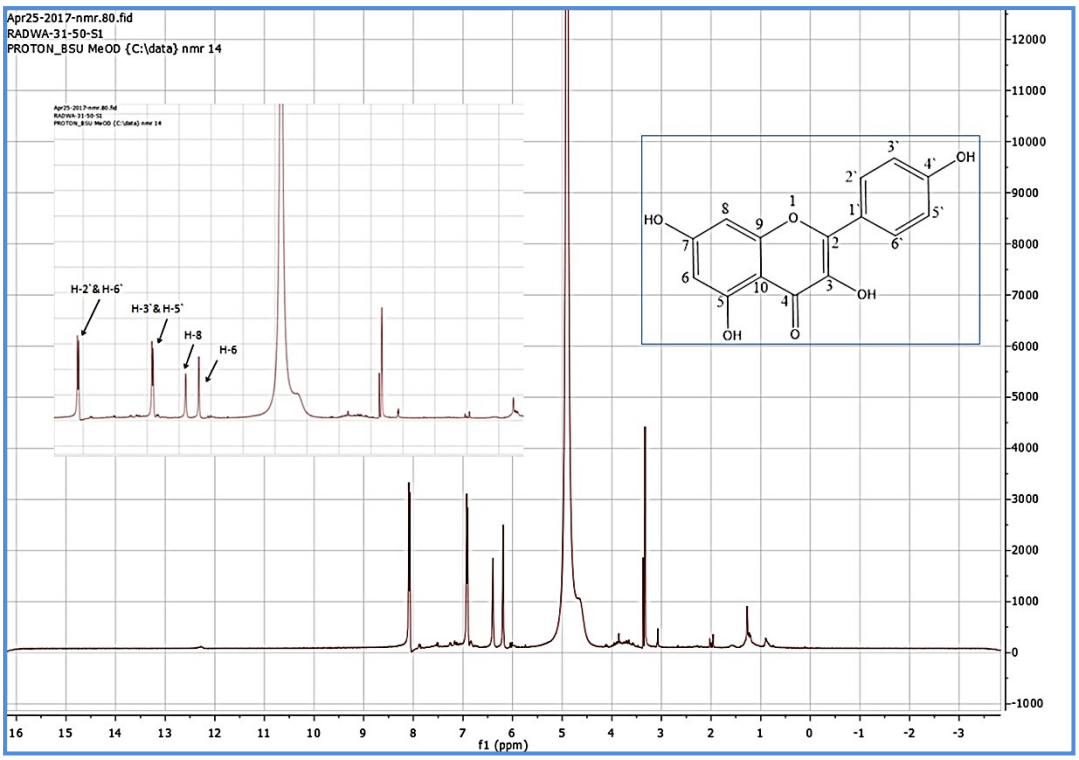

Fig. S_{19}:^{1}H-NMR spectrum of compound 4 (MeOD, 400 MHz).

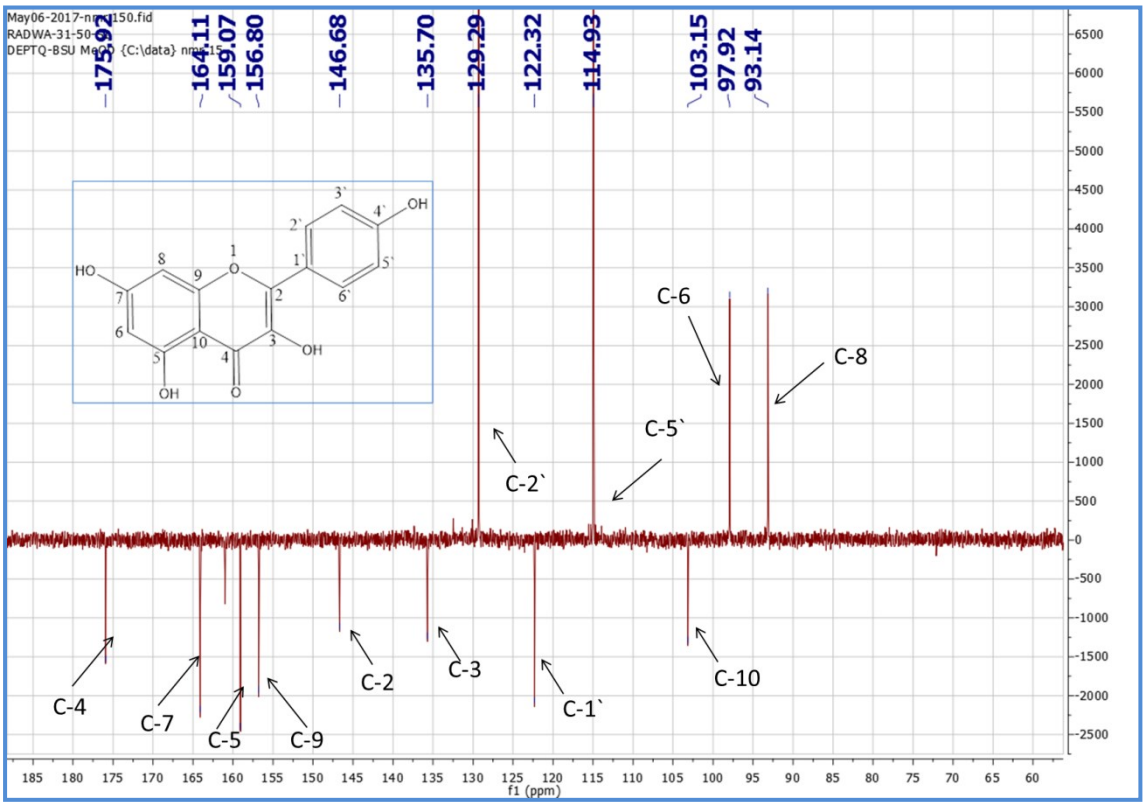

Fig. S_{20}: DEPT-Q spectrum of compound 4 (MeOD, 100 MHz).

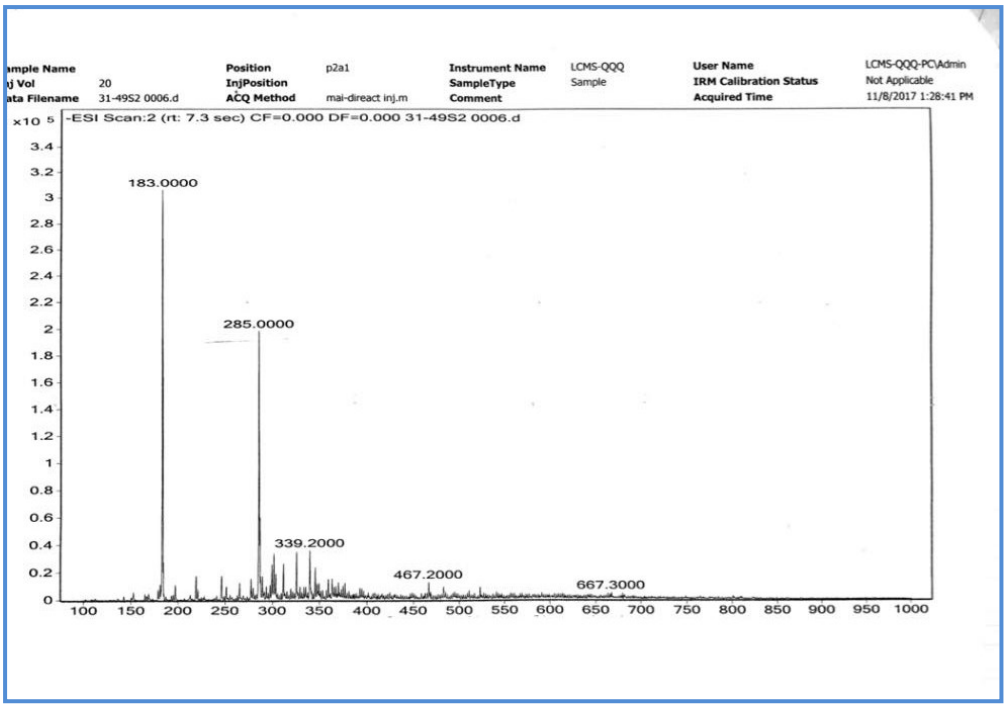

Fig. S_{21}: -ESI- MS spectrum of compound 4.

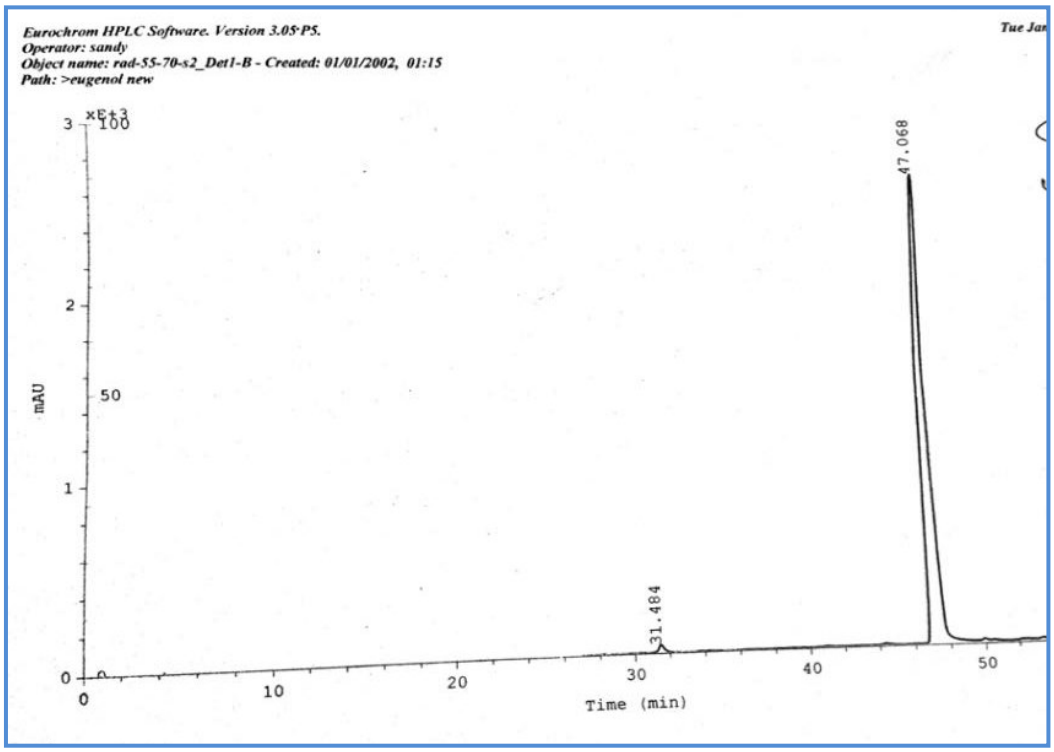

Fig. S_{22}: HPLC chromatogram of compound 5.

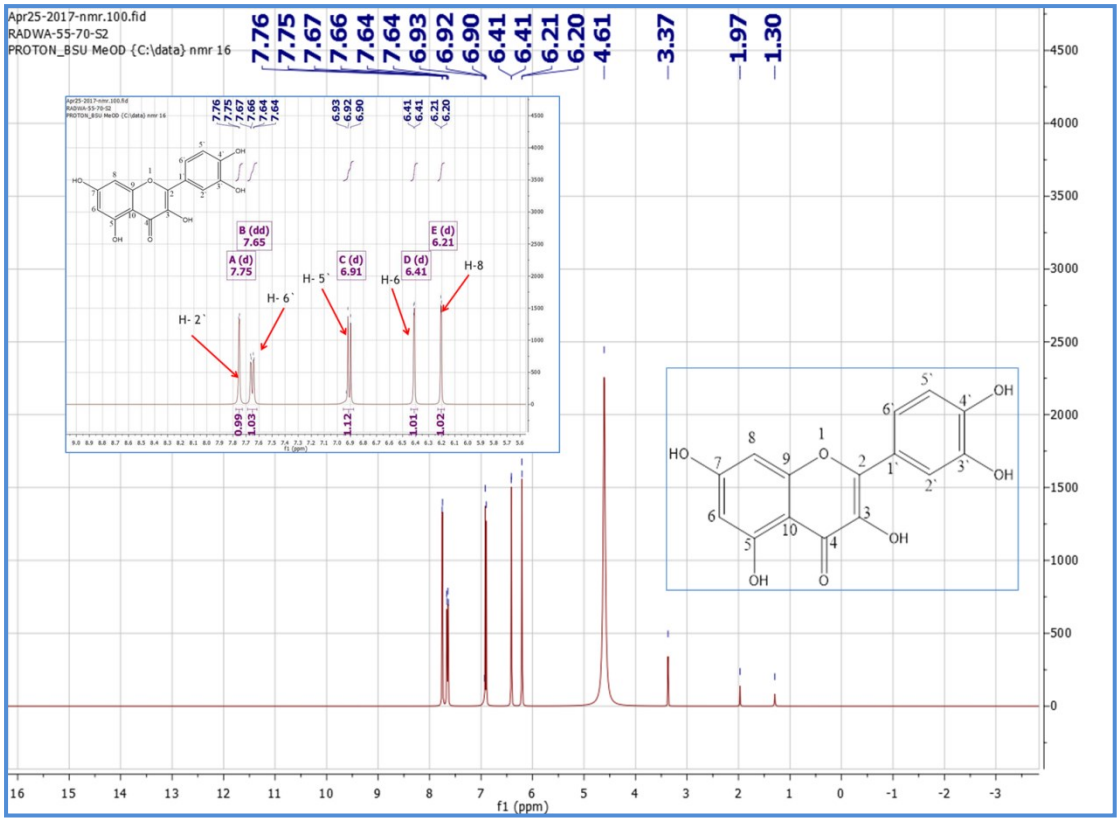

Fig. S_{23}: ^{1}H-NMR spectrum of compound 5 (MeOD, 400 MHz).

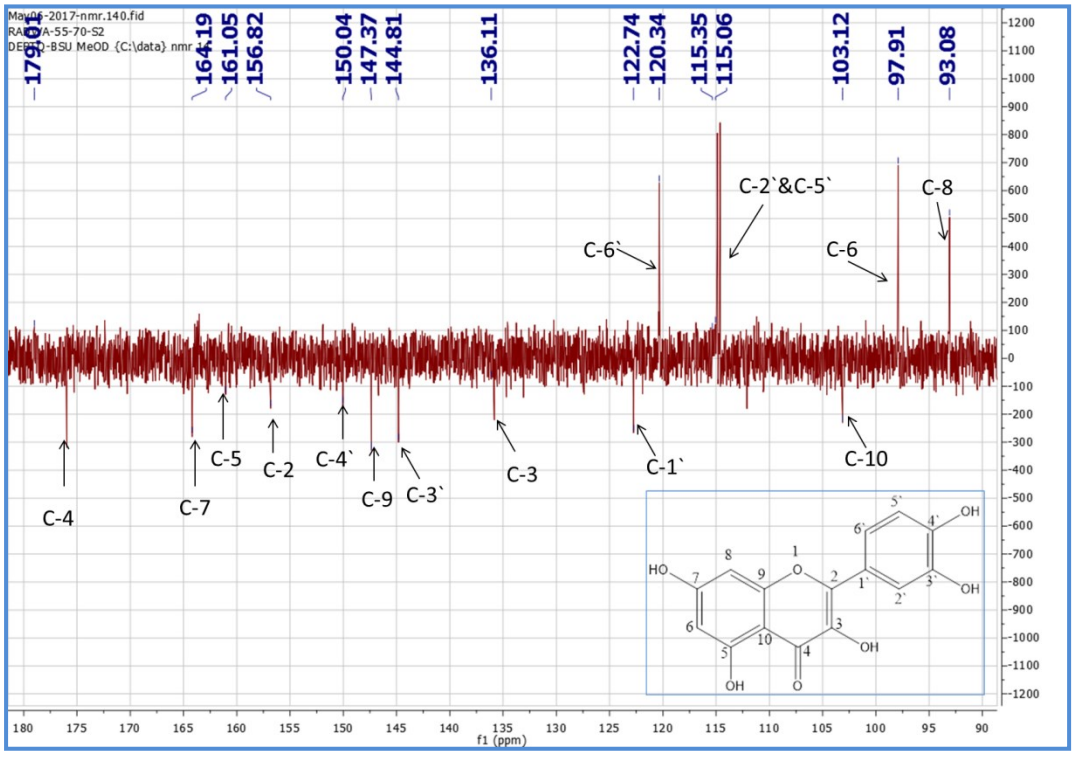

Fig. S_{24}: DEPT-Q spectrum of compound 5 (MeOD, 100 MHz).

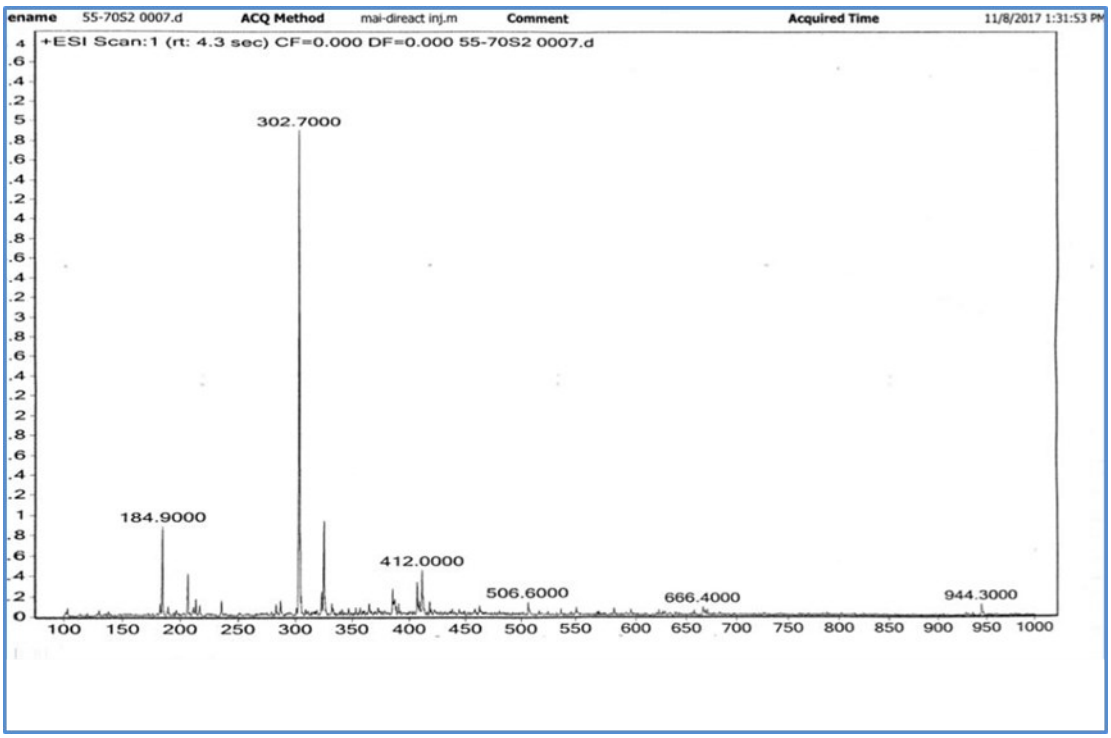

Fig. S_{25}: +ESI- MS spectrum of compound 5.

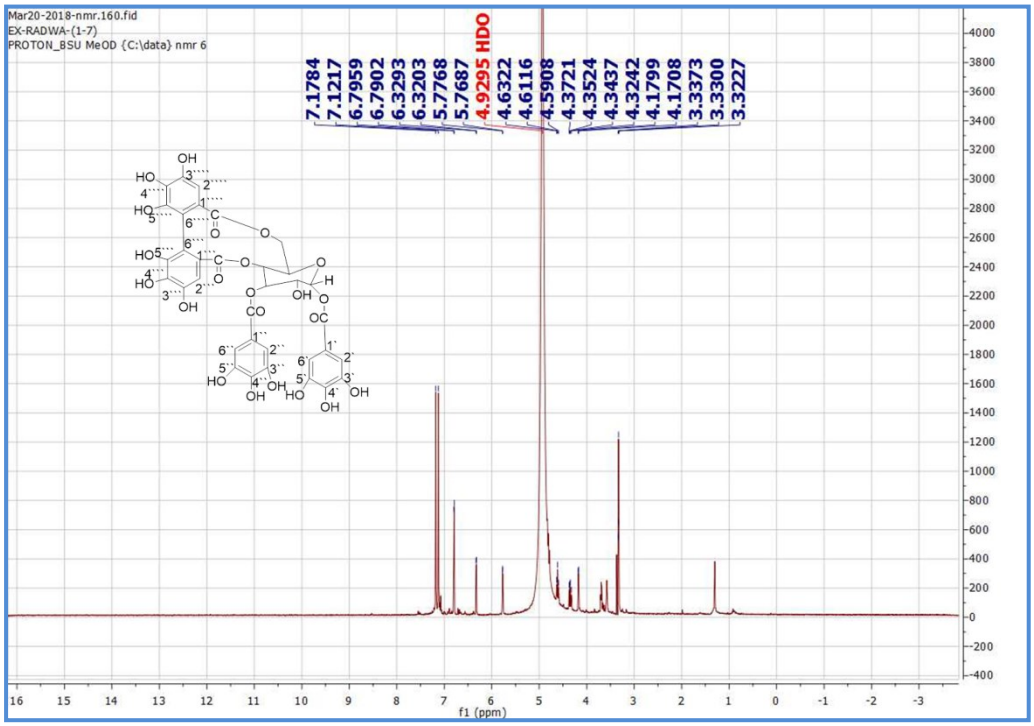

Fig.S_{26}: ^{1}H-NMR spectrum of compound 6 (MeOD, 400 MHz).

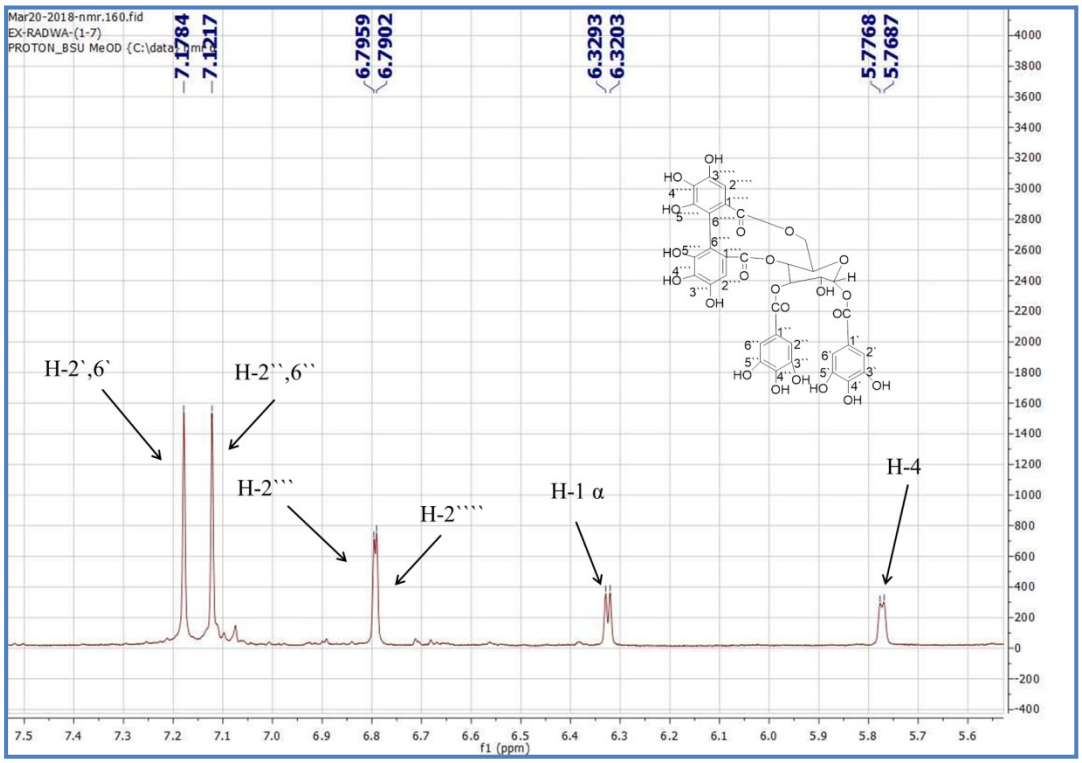

Fig. S_{27}: Expanded ^{1}H-NMR spectrum of compound 6 (MeOD, 400 MHz).

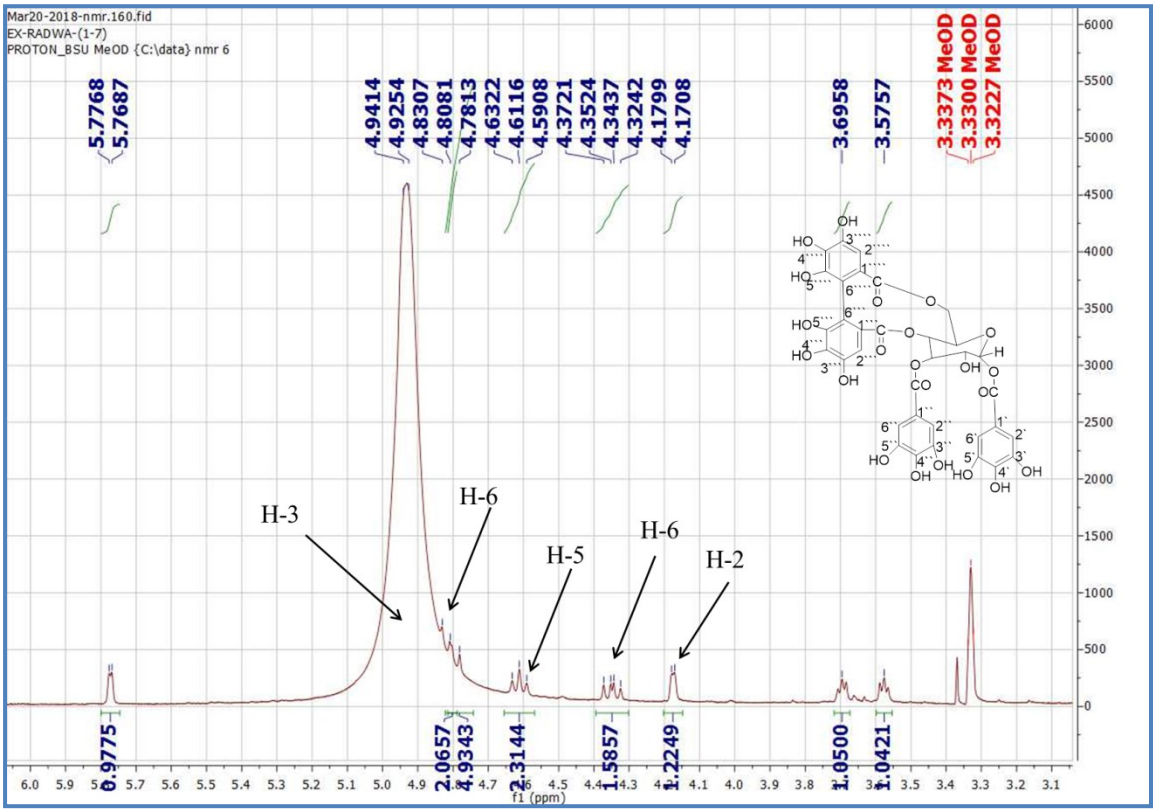

Fig. S_{28}: Expanded ^{1}H-NMR spectrum of compound 6 (MeOD, 400 MHz).

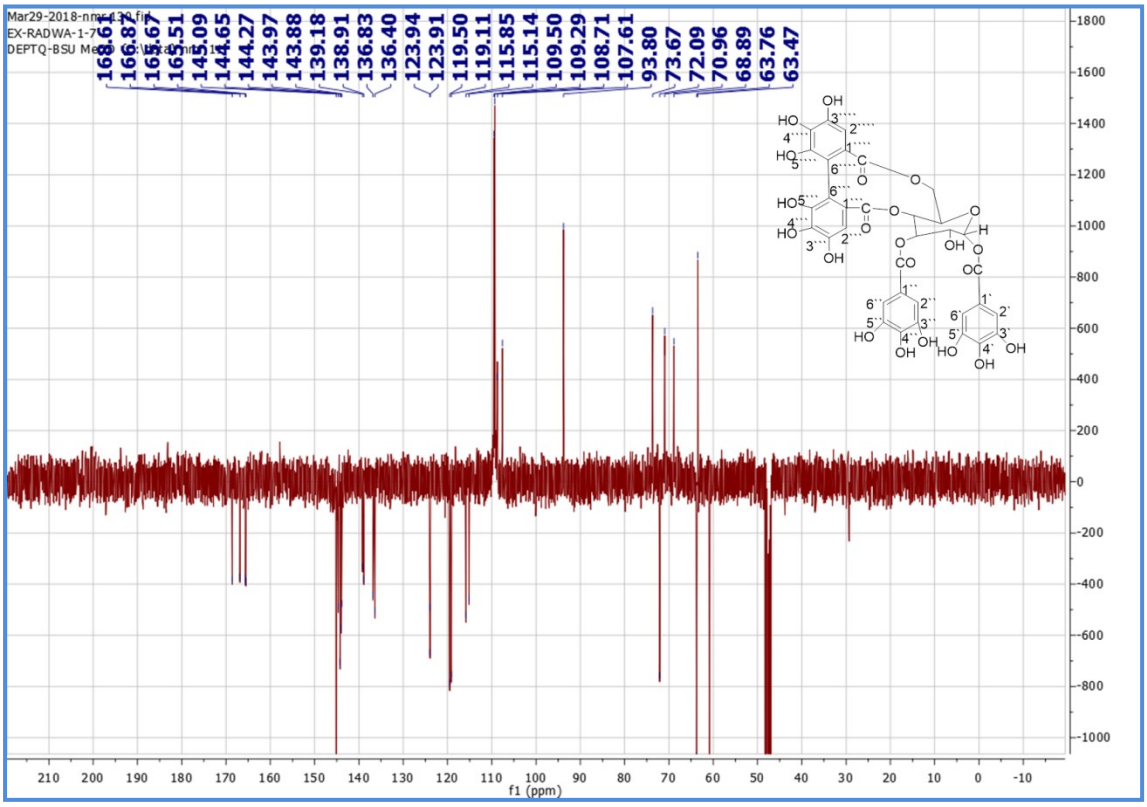

Fig. S_{29}: DEPT-Q spectrum of compound 6 (MeOD, 100 MHz).

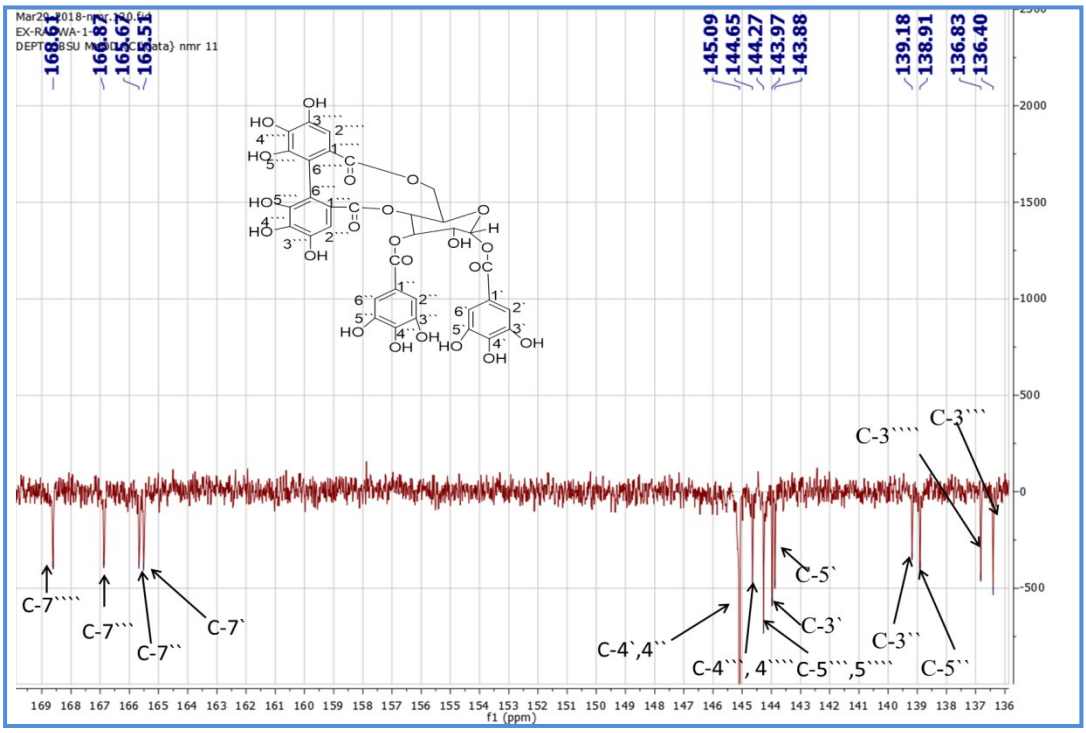

Fig. S_{30}: Expanded DEPT-Q spectrum of compound 6 (MeOD, 100 MHz).

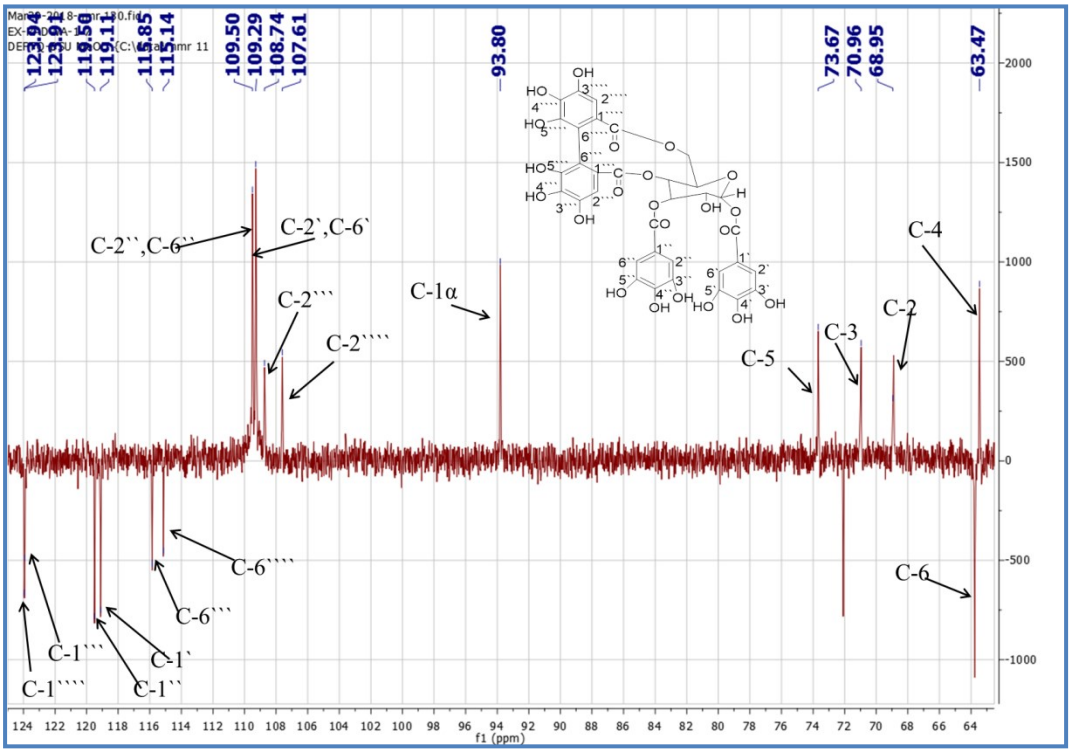

Fig. S_{31}: Expanded DEPT-Q spectrum of compound 6 (MeOD, 100 MHz).

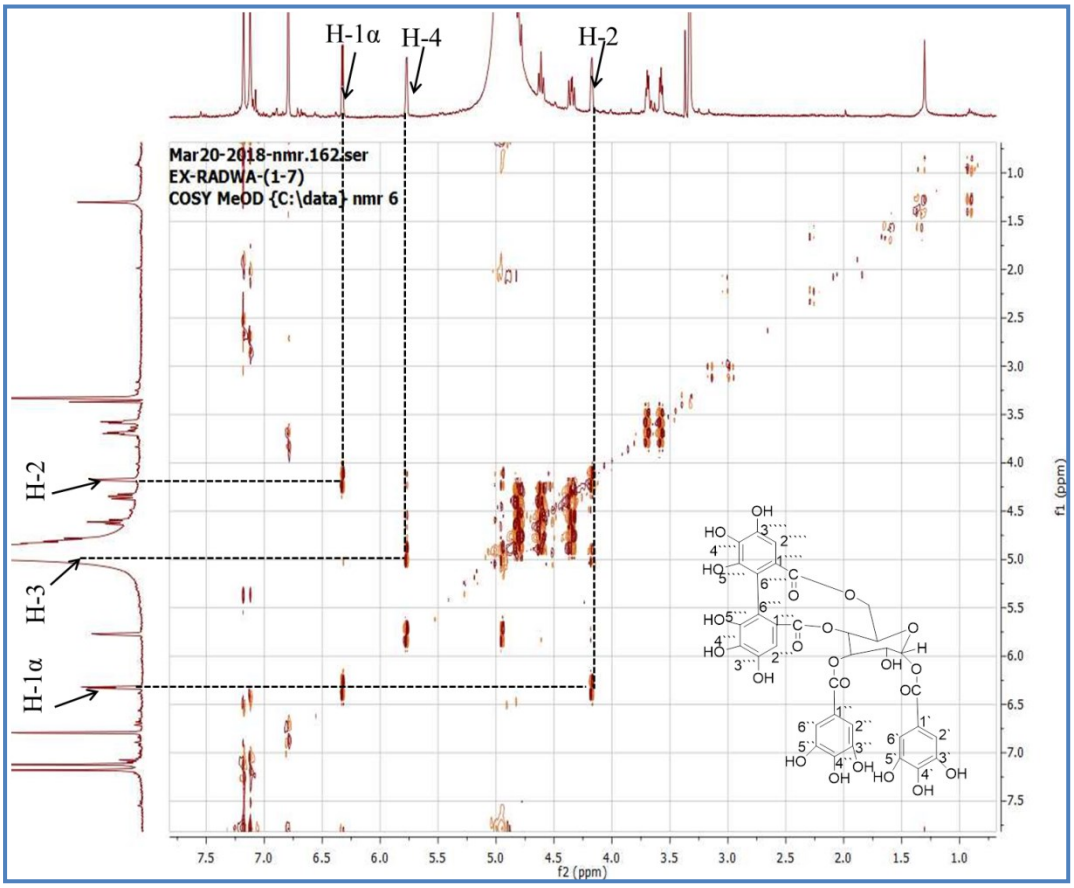

Fig. S_{32}: Expanded ^{1}H- ^{1}H COSY spectrum of compound 6.

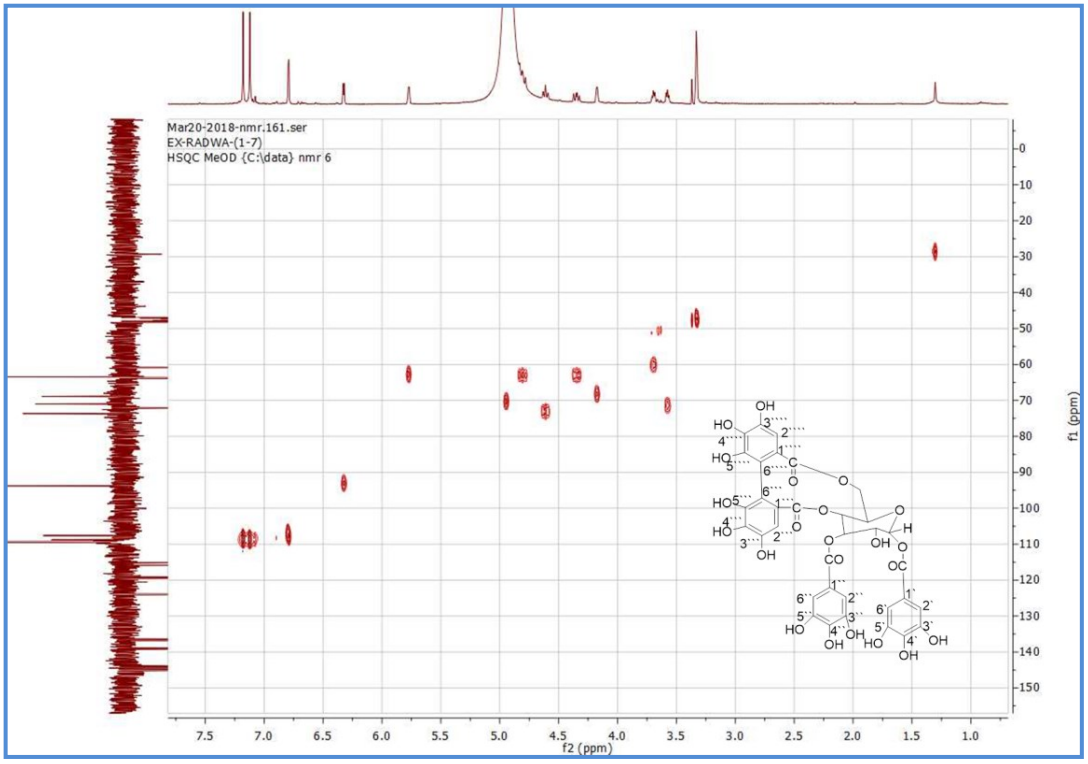

Fig. S_{33}: HSQC spectrum of compound 6.

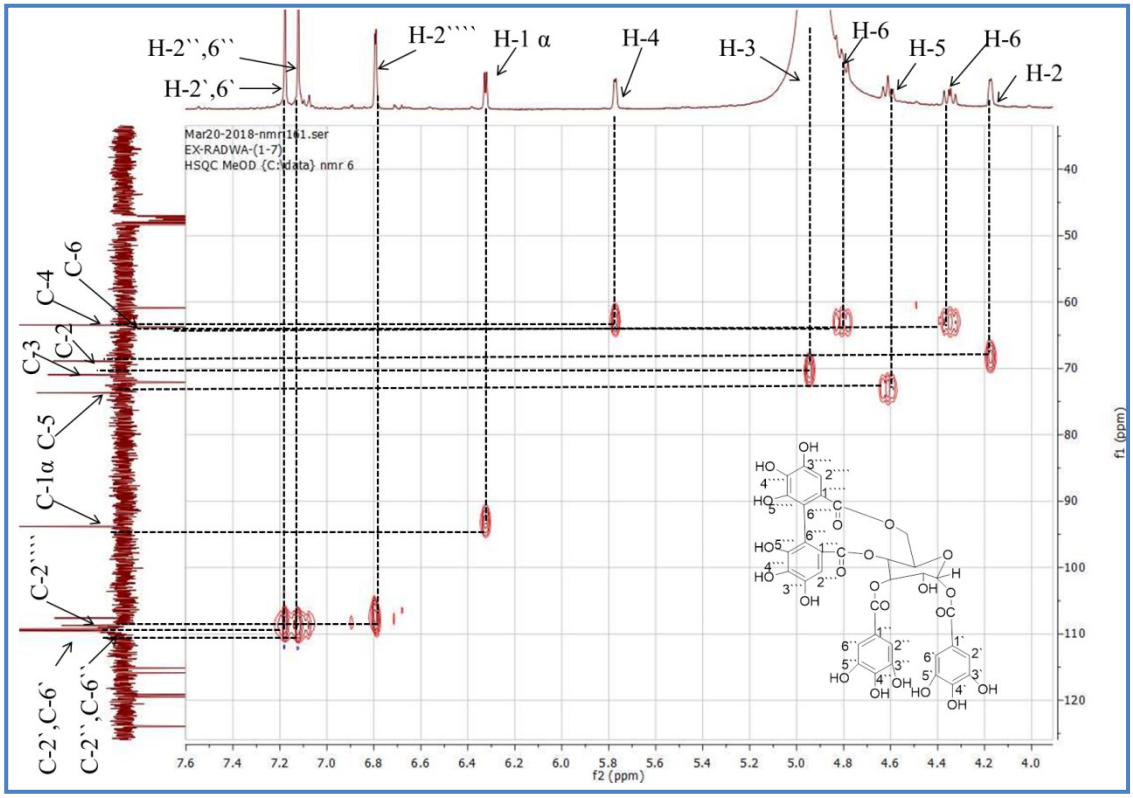

Fig. S_{34}: Expanded HSQC spectrum of compound 6.

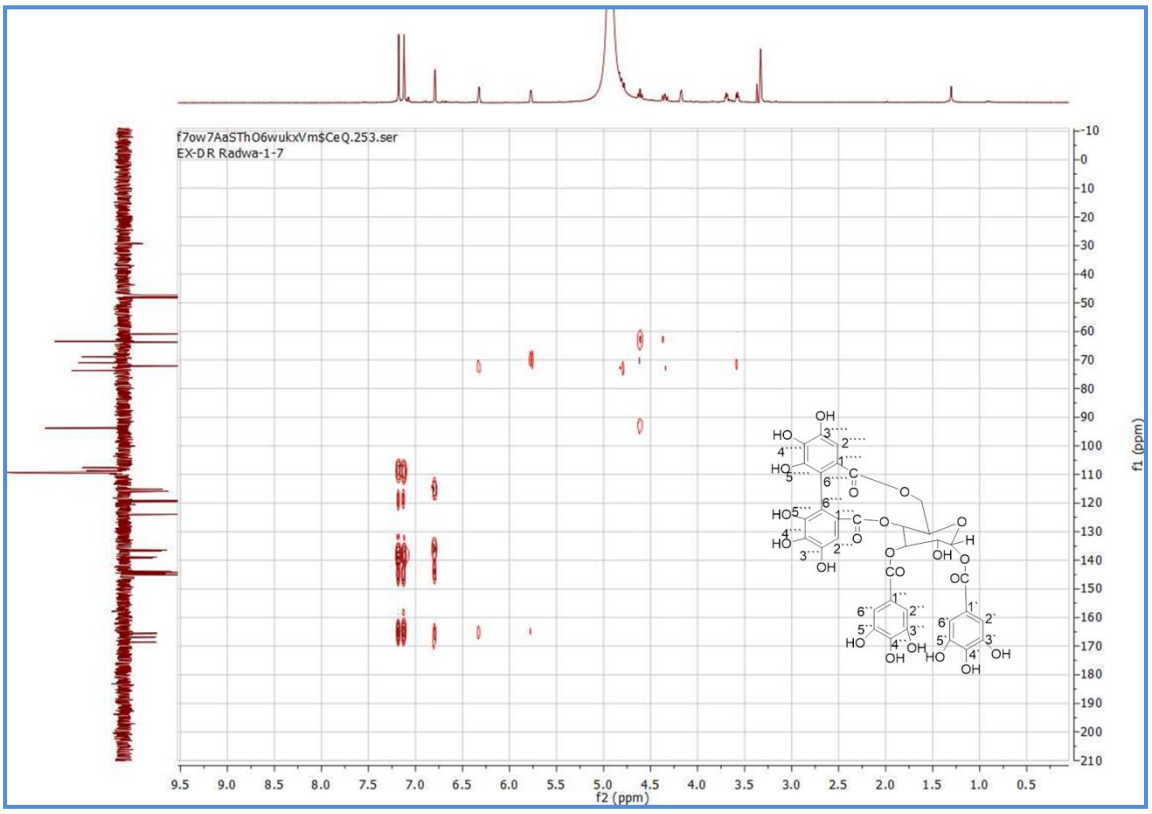

Fig. S_{35}: HMBC spectrum of compound 6.

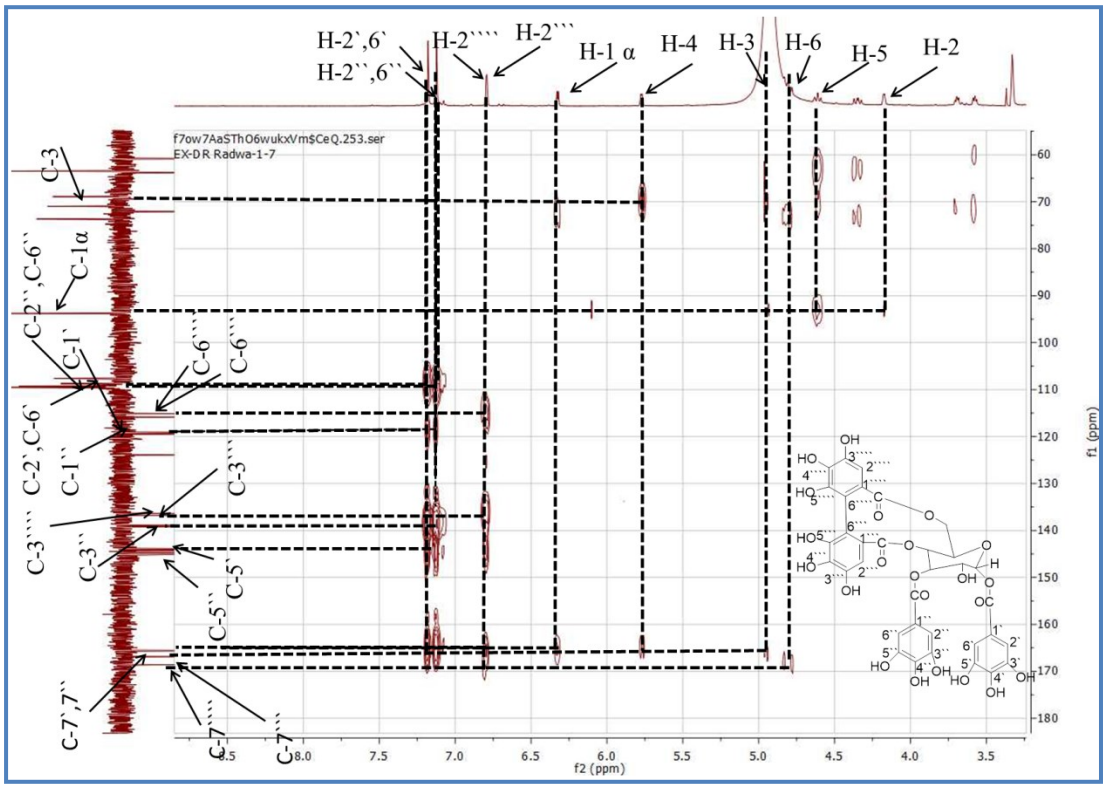

Fig. S_{36}: Expanded HMBC spectrum of compound 6.

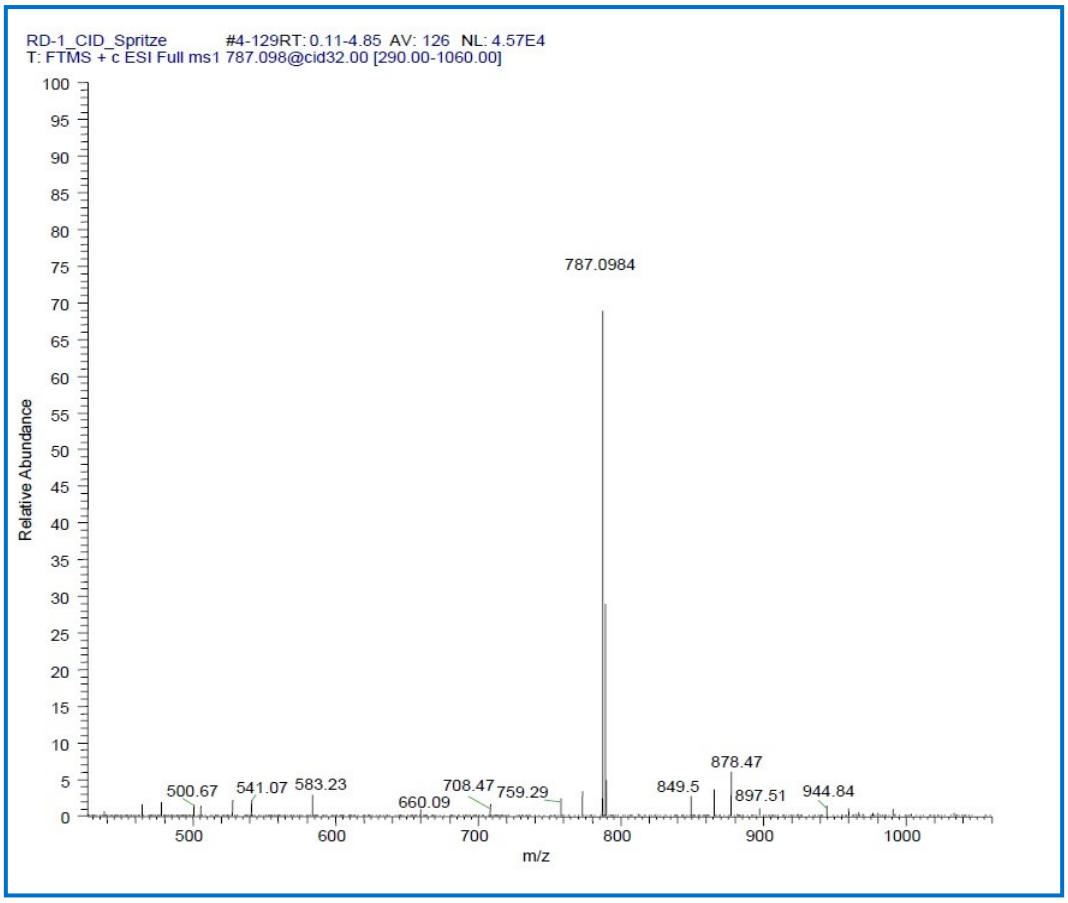

Fig. S_{37}: HR-ESI-MS of compound 6.

Assignment	**Chemical shift (ppm)**	**Multiplicity**	***J* (Hz)**	**Published data in MeOH** (Harish *et al.*, 2005)
OCH_3	3.67	3H, S	-	3H, S, 3.71
CHO	9.5	1H, S	-	1H, S, 9.75
H-2, H-6	6.6	2H, d	8.5	2H, d, 6.99

H-3, H-5	7.23	2H, d	8.5	2H, d,7.39

Table. S_1: ^{1}H NMR spectral data of compound 2 (MeOD, 400 MHz).

Table. S_2: ^{1}H-NMR spectral data of compound 3 (MeOD, 400 MHz).

Assignment	**Chemical shift (ppm)**	**Multiplicity**	***J* (Hz)**	**Published data in MeOH** (Banday *et al.,* 2012)
OCH_3	3.8	3H, S	-	3.97
H-2 & H-6	7.0	2H, S	-	7.1

Table.S_3: UV spectral data of compound 4 in methanol as well as with different ionizing and complexing reagents.

Band	MeoH	+NaOMe		+NaOAc		+$AlCl_3$		+$AlCl_3$/HCl
	λ_{max}	λ_{max}	$\Delta\lambda$	λ_{max}	$\Delta\lambda$	λ_{max}	$\Delta\lambda$	λ_{max}
Band I	364	420	+56	372	+8	420	+56	398
Band II	268	282	+14	270	+2	306	+38	274

Table.S$_4$: ^{1}H-NMR spectral data of compound 4 (MeOD, 400 MHz).

Assignment	**Chemical shift (ppm)**	**Multiplicity**	***J* (Hz)**	**Published data in MeOH** (Wahab *et al.,* 2014)
H-2`& H-6`	8.11	d	8.5	8.09, d, J=8.7
H-3`& H-5`	6.93	d	8.6	6.91, d, J=8.7
H-8	6.42	d	2.1	6.43, d, J=1.8
H-6	6.21	d	1.9	6.19, d, J=1.8

Table.S_5: DEPT-Q spectral data of compound 4 (MeOD, 100 MHz).

Assignment	**Chemical shift (ppm)**	**Published data** (Wahab *et al.,* 2014)
C-2	146.7	146.3
C-3	135.7	135.2
C-4	175.9	175.2
C-5	159.1	160.4
C-6	97.9	98.4
C-7	164.1	163.7
C-8	93.1	93.8
C-9	156.8	156.7
C-10	103.1	103.1
C-1`	122.3	122.1
C-2`	129.3	129.4
C-3`	114.9	115.3
C-4`	159.1	158.7
C-5`	114.9	115.3
C-6`	129.3	129.4

Table.S_6: UV spectral data of compound 5 in methanol as well as with different ionizing and complexing reagents.

Band	MeoH	+NaOMe		+NaOAc		+$AlCl_3$		+$AlCl_3$/HCl
	λ_{max}	λ_{max}	$\Delta\lambda$	λ_{max}	$\Delta\lambda$	λ_{max}	$\Delta\lambda$	λ_{max}
Band I	372	432	+62	378	+8	449	+77	421
Band II	258	330	+72	260	+2	270	+12	266

Table.S_7: DEPT-Q spectral data of compound 5 (MeOD, 100 MHz).

Assignment	**Chemical shift (ppm)**	**Published data** (Metwally *et al*., 2010)
C-2	156.9	156.82
C-3	136.1	136.11
C-4	179.0	179.01
C-5	161.0	161.05
C-6	97.9	97.91
C-7	164.1	164.19
C-8	93.0	93.08
C-9	147.4	146.70
C-10	103.1	104.78
C-1`	122.7	123.31
C-3`	144.8	145.19
C-4`	150.0	147.98
C-2` & C-5`	115.0, 115.3	115.06, 115.35

C-6`	120.3	120.39

Table.S_8: ^{1}H, ^{13}C and HMBC NMR spectral data of compound 7 (MeOD, 400 and 100 MHz).

Assignment	Chemical shift (δ_H ppm)	Multiplicity	*J* (Hz)	Chemical shift (δ_C ppm)	HMBC ^{1}H to ^{13}C
1α	6.33	d	3.6	93.8	C-7`
2	4.17	d	3.64	68.8	C-1α, C-3
3	4.95 Under water peak	-	Overlapped	70.9	C-1α, C-4, C-7``
4	5.77	d	3.24	63.4	C-7```, C-3
5	4.64	t	8.24	73.7	C-1α, C-4
6	4.8 Under water peak 4.33	- dd	Overlapped 11.3, 7.8	63.7	C-4, C-7````
1`	-	-	-	119.1	-
1``	-	-	-	119.5	-

2`,6`	7.17	S	-	109.2	C-7`, C-1`, C-3`, C-5`
2``,6``	7.12	S	-	109.5	C-7``, C-1``, C-3``, C-5``
3`	-	-	-	143.9	-
3``	-	-	-	139.8	-
4` & 4``	-	-	-	145.1	-
5`	-	-	-	143.8	-
5``	-	-	-	138.9	-
C-7`	-	-	-	165.5	-
C-7``	-	-	-	165.9	-
1````, 1```	-	-	-	123.9	-
2```	6.79	S	-	108.7	C-6```, C-3```, C-7```
2`````	6.79	S	-	107.6	C-6````, C-3````, C-7````
3````, 3```	-	-	-	136.8,136.4 exchangeable	-
4``` & 4````	-	-	-	144.6	-
5````` & 5```	-	-	-	144.3	-
6```, 6`````	-	-	-	115.8, 115.1 exchangeable	-
C-7````	-	-	-	168.6	-
C-7```	-	-	-	166.8	-