Synthesis, Isolation and Structure Determination of Cannabidiol Derivatives and their cytotoxic potential

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ABSTRACT

In a continuing effort to explore the structural diversity and pharmacological activities of natural products based scaffolds, herein, we report the isolation, synthesis, and structure determination of cannabidiol and its derivatives along with their cytotoxic activities. Treatment of cannabidiol (**1**) with acid catalyst $POCl_3$ afforded a new derivative **6** along with six known molecules **2**−**5**, **7** and, **8**. The structure of **6** was elucidated by extensive spectroscopic analyses and DFT calculations of the NMR and ECD data. All the compounds (**2**–**8**) were evaluated for their cytotoxic potential against a panel of eight cancer cell lines. Compounds **4**, **5**, **7**, and **8** showed pronounced *in vitro* cytotoxic activity with GI50 values ranging from 5.6 to 60 μM. Out of the active molecules, compounds **4**, and **7** were found to be comparable to that of the parent molecule **1** on the inhibition of almost all the tested cancer cell lines.

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Table S3. ^{1}H experimental and calculated NMR chemical shifts for **6a** and **6b**, with $^{a}|\Delta\delta|(^{1}H)$ and ^{c}MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 carbons, and tetramethylsilane (TMS) for sp^3 carbons.

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Table S6. $^{13}C/^{1}H$ MAE values, and DP4+ probabilities computed for compounds **6a** and **6b**.

Figure S1. $^{13}C/^{1}H$ MAE instagrams related to compounds **6a** and **6b** (values reported in Table 1).

Figure S2. a) Superposition of the measured ECD spectrum of **6** and that computed for compound **6b** (6*S*,9*R*,10*R*); b)Superposition of the measured ECD spectrum of **6** and that computed for compound $\mathbf{6b_{enant}}$ (6*R*,9*S*,10*S*).

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Figure S19. NOESY spectrum of compound **6** in DMSO-d6

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Figure S21. HPLC chromatogram of fraction **Fr.3**

Table S8. *In vitro* Growth %age inhibition of all screened derivatives using MTT assay

Table S1. ^{1}H NMR (400 MHz) &^{13}C NMR (100 MHz) NMR Spectroscopic Data for Compound **6** in $CDCl_3$

C.No	δ_H(*J*Hz)	δ_C	HMBC
1	-	157.7	
2	6.26 s	108.4	C-1, C-10a, C-4, C-1'
3	-	143.0	
4	6.06 s	105.8	C-5, C-10a, C-4, C-1'
5	-	153.5	
6	-	74.2	
7	1.96 – 1.78 m	35.5	C-6, C-8, C-9, C-15
8	1.51 m 1.34 m	28.5	C-10, C-12
9	-	76.2	
10	3.26 d (1.6)	34.4	C-6, C-9, C-1, C-5, C-10a
10a	-	109.2	
11	2.42 – 2.36 m	31.7	C-10, C-10a
	1.48 m		
12	1.69 dt (13.4, 6.7)	32.7	C-13, C-14, C-10
13	1.11 d (6.6)	17.2	C-14, C-9
14	0.78 d (6.8)	16.6	C-13, C-9
15	1.37 s	28.5	C-6, C-7, C-11
1'	2.47 – 2.42 m	35.8	C-2, C-3, C-4, C-2', C-3'
2'	1.31 m	31.6	C-3, C-3'
3'	1.58 m	30.6	C-4', C-2'
4'	1.33 m	22.5	C-3'
5'	0.89 t (6.9)	14.0	C-3', C-4', C-2'

All assignments were based on HSQC and HMBC experiments.

Table S2. ^{13}C experimental and calculated NMR chemical shifts for **6a** and **6b**, with [a]$|\Delta\delta|(^{13}C)$ and [c]MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 carbons, and tetramethylsilane (TMS) for sp^3 carbons.

	δ_{exp}, ppm	δ_{calc} (^{13}C), ppm		$\|\Delta\delta\|$ (^{13}C), ppm[a]	
#		6a	6b	6a	6b
1	157.7	155.9[b]	153.6[b]	1.78	4.07
2	108.4	110.3[b]	105.2[b]	1.94	3.23
3	143.0	144.5[b]	143.0[b]	1.51	0.03
4	105.8	109.1[b]	110.2[b]	3.26	4.44
5	153.5	156.6[b]	158.0[b]	3.09	4.52
6	74.2	70.7	72.5	3.54	1.69
7	35.5	37.7	36.6	2.24	1.13
8	28.5	31.1	29.1	2.61	0.58
9	76.2	77.2	76.1	0.95	0.14
10	34.4	37.6	37.4	3.17	3.03
10a	109.2	109.1[b]	109.7[b]	0.13	0.54
11	31.7	33.1	31.8	1.39	0.12
12	32.7	31.0	33.5	1.73	0.84
13	17.2	18.2	17.9	1.02	0.67
14	16.6	17.2	17.9	0.59	1.25
15	28.5	29.0	29.1	0.49	0.63
1'	35.8	38.4	37.9	2.64	2.10
2'	31.6	34.5	34.3	2.91	2.74
3'	30.6	32.4	32.0	1.84	1.41
4'	22.5	25.2	24.9	2.74	2.37
5'	14.0	16.0	15.9	2.03	1.86
MAE, ppm[c]				1.98	1.78

[a] **$|\Delta\delta|(^{13}C)$** = $|\delta_{exp} - \delta_{calc}|$ (^{13}C), ppm: absolute differences for experimental versus calculated ^{13}C NMR chemical shifts

[b] ^{13}C chemical shifts calculated using benzene as reference compound; all the remaining values calculated using TMS as reference compound.

[c] **MAE** = $(\Sigma[|(\delta_{exp} - \delta_{calc})|])/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and ^{13}C chemical shifts), normalized to the number of the chemical shifts

Table S3. ^{1}H experimental and calculated NMR chemical shifts for **6a** and **6b**, with [a]|Δδ|(^{1}H) and [c]MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 carbons, and tetramethylsilane (TMS) for sp^3 carbons.

	δ_{exp}, ppm	δ_{calc} (^{1}H), ppm		|Δδ| (^{1}H), ppm[a]	
#		6a	6b	6a	6b
2	6.26	5.89[b]	5.27[b]	0.37	0.99
4	6.06	5.81[b]	5.81[b]	0.25	0.25
7	1.78	1.58	1.70	0.20	0.08
7	1.96	1.81	2.02	0.15	0.06
8	1.51	1.80	1.59	0.29	0.08
8	1.34	1.28	1.37	0.06	0.03
10	3.26	3.40	3.12	0.14	0.14
11	2.42	1.87	2.51	0.55	0.09
11	1.48	1.58	1.24	0.10	0.24
12	1.69	2.20	1.85	0.51	0.16
13	1.11	1.18	1.02	0.07	0.09
14	0.78	1.07	0.81	0.29	0.03
15	1.37	1.24	1.24	0.13	0.13
1'	2.47	2.43	2.37	0.04	0.10
2'	1.31	1.55	1.53	0.24	0.22
3'	1.58	1.28	1.27	0.30	0.31
4'	1.33	1.31	1.32	0.02	0.01
5'	0.89	0.90	0.90	0.01	0.01
MAE, ppm[c]				0.21	0.17

[a] **|Δδ|(^{1}H)** = $|\delta_{exp} - \delta_{calc}|$ (^{1}H), ppm: absolute differences for experimental versus calculated ^{1}H NMR chemical shifts

[b]^{1}H chemical shifts calculated using benzene as reference compound; all the remaining values calculated using TMS as reference compound.

[c] **MAE** = $(\Sigma[|(\delta_{exp} - \delta_{calc})|])/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and ^{1}H chemical shifts), normalized to the number of the chemical shifts

Table S4. ^{13}C experimental and calculated NMR chemical shifts for **6a** and **6b**, with [a]$|\Delta\delta|(^{13}C)$ and [b]MAE values. Chemical shift data here reported were produced using tetramethylsilane (TMS) as reference compound.

	δ_{exp}, ppm	δ_{calc} (^{13}C), ppm		$\|\Delta\delta\|$ (^{13}C), ppm[a]	
#		6a	6b	6a	6b
1	157.7	151.2	148.9	6.50	8.79
2	108.4	105.6	100.4	2.79	7.96
3	143.0	139.8	138.3	3.22	4.70
4	105.8	104.3	105.5	1.47	0.28
5	153.5	151.9	153.3	1.64	0.20
6	74.2	70.7	72.5	3.54	1.69
7	35.5	37.7	36.6	2.24	1.13
8	28.5	31.1	29.1	2.61	0.58
9	76.2	77.2	76.1	0.95	0.14
10	34.4	37.6	37.4	3.17	3.03
10a	109.2	104.3	105.0	4.86	4.19
11	31.7	33.1	31.8	1.39	0.12
12	32.7	31.0	33.5	1.73	0.84
13	17.2	18.2	17.9	1.02	0.67
14	16.6	17.2	17.9	0.59	1.25
15	28.5	29.0	29.1	0.49	0.63
1'	35.8	38.4	37.9	2.64	2.10
2'	31.6	34.5	34.3	2.91	2.74
3'	30.6	32.4	32.0	1.84	1.41
4'	22.5	25.2	24.9	2.74	2.37
5'	14.0	16.0	15.9	2.03	1.86
MAE, ppm[b]				2.40	2.22

[a] **$|\Delta\delta|(^{13}C)$** = $|\delta_{exp} - \delta_{calc}|$ (^{13}C), ppm: absolute differences for experimental versus calculated ^{13}C NMR chemical shifts

[b] **MAE** = $(\Sigma[|(\delta_{exp} - \delta_{calc})|])/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and ^{13}C chemical shifts), normalized to the number of the chemical shifts

Table S5. ^{1}H experimental and calculated NMR chemical shifts for **6a** and **6b**, with [a]|Δδ|(^{1}H) and [b]MAE values. Chemical shift data here reported were produced using tetramethylsilane (TMS) as reference compound.

	δ_{exp}, ppm	δ_{calc} (^{1}H), ppm		|Δδ| (^{1}H), ppm[a]	
#		6a	6b	6a	6b
2	6.26	6.45	5.84	0.19	0.42
4	6.06	6.37	6.37	0.31	0.31
7	1.78	1.58	1.70	0.20	0.08
7	1.96	1.81	2.02	0.15	0.06
8	1.51	1.80	1.59	0.29	0.08
8	1.34	1.28	1.37	0.06	0.03
10	3.26	3.40	3.12	0.14	0.14
11	2.42	1.87	2.51	0.55	0.09
11	1.48	1.58	1.24	0.10	0.24
12	1.69	2.20	1.85	0.51	0.16
13	1.11	1.18	1.02	0.07	0.09
14	0.78	1.07	0.81	0.29	0.03
15	1.37	1.24	1.24	0.13	0.13
1'	2.47	2.43	2.37	0.04	0.10
2'	1.31	1.55	1.53	0.24	0.22
3'	1.58	1.28	1.27	0.30	0.31
4'	1.33	1.31	1.32	0.02	0.01
5'	0.89	0.90	0.90	0.01	0.01
MAE, ppm[b]				0.20	0.14

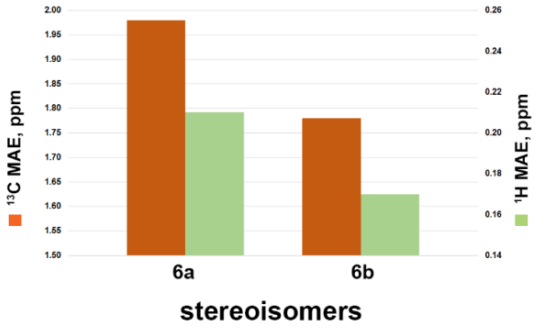
[a] **|Δδ|(^{1}H)** = $|\delta_{exp} - \delta_{calc}|$ (^{1}H), ppm: absolute differences for experimental versus calculated ^{1}H NMR chemical shifts

[b] **MAE** = $(\Sigma[|(\delta_{exp} - \delta_{calc})|])/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and ^{1}H chemical shifts), normalized to the number of the chemical shifts

Table S6. $^{13}C/^{1}H$ MAE values, and DP4+ probabilities computed for compounds **6a** and **6b**.

Compound	^{13}C MAE, ppm	^{1}H MAE, ppm	DP4+ probability
6a	1.98	0.21	0.00%
6b	1.78	0.17	100.00%

Figure S1. $^{13}C/^{1}H$ MAE instagrams related to compounds **6a** and **6b** (values reported in Table S6).



A QM/NMR approach (Bifulco et al. 2007, Di Micco et al. 2010) was employed to compare the sets of experimental ^{13}C and ^{1}H NMR chemical shifts with those calculated for **6a** and **6b** isomers. Firstly, all the conformers obtained at the empirical level were submitted to a geometry and energy optimization step at the DFT (density functional theory) using the MPW1PW91/6-31G(d) functional/basis set (see computational details, experimental section). Then, ^{13}C and ^{1}H NMR chemical shifts were predicted at the MPW1PW91/6-31G(d,p) level, and the mean absolute error (MAE) values were used to compare calculated and experimental values (Tables S1-S5) for **6a** and **6b**. As shown in Figure S1, compound **6b** showed the lowest ^{13}C and ^{1}H MAE values, 1.78 and 0.17 ppm, respectively. To further confirm our findings, we also employed the recently introduced DP4+ method (Grimblat et al. 2015). Again, the isomer **6b** showed the highest DP4+ probabilities (100.00%) (Table S6). Interestingly, the NOESY correlations were also found to be consistent with the **6b** isomer. Finally, the absolute configurations were established by comparison of the experimental ECD spectrum of **6** with those predicted for **6b** (6*R*, 9*S*, 10*S*) and for its enantiomer $\mathbf{6b_{enant}}$ (6*S*, 9*R*, 10*R*) (Cerulli et al. 2017). The results showed that the calculated ECD spectrum of **6b** was in accordance with the experimental spectrum (Figure S2). Accordingly, the absolute configuration of **6** was confidently assigned as 6*R*, 9*S*, 10*S*.

Figure S2. a) Superposition of the measured ECD spectrum of **6** and that computed for compound **6b** (6*S*,9*R*,10*R*); b)Superposition of the measured ECD spectrum of **6** and that computed for compound **6b$_{enant}$** (6*R*,9*S*,10*S*).

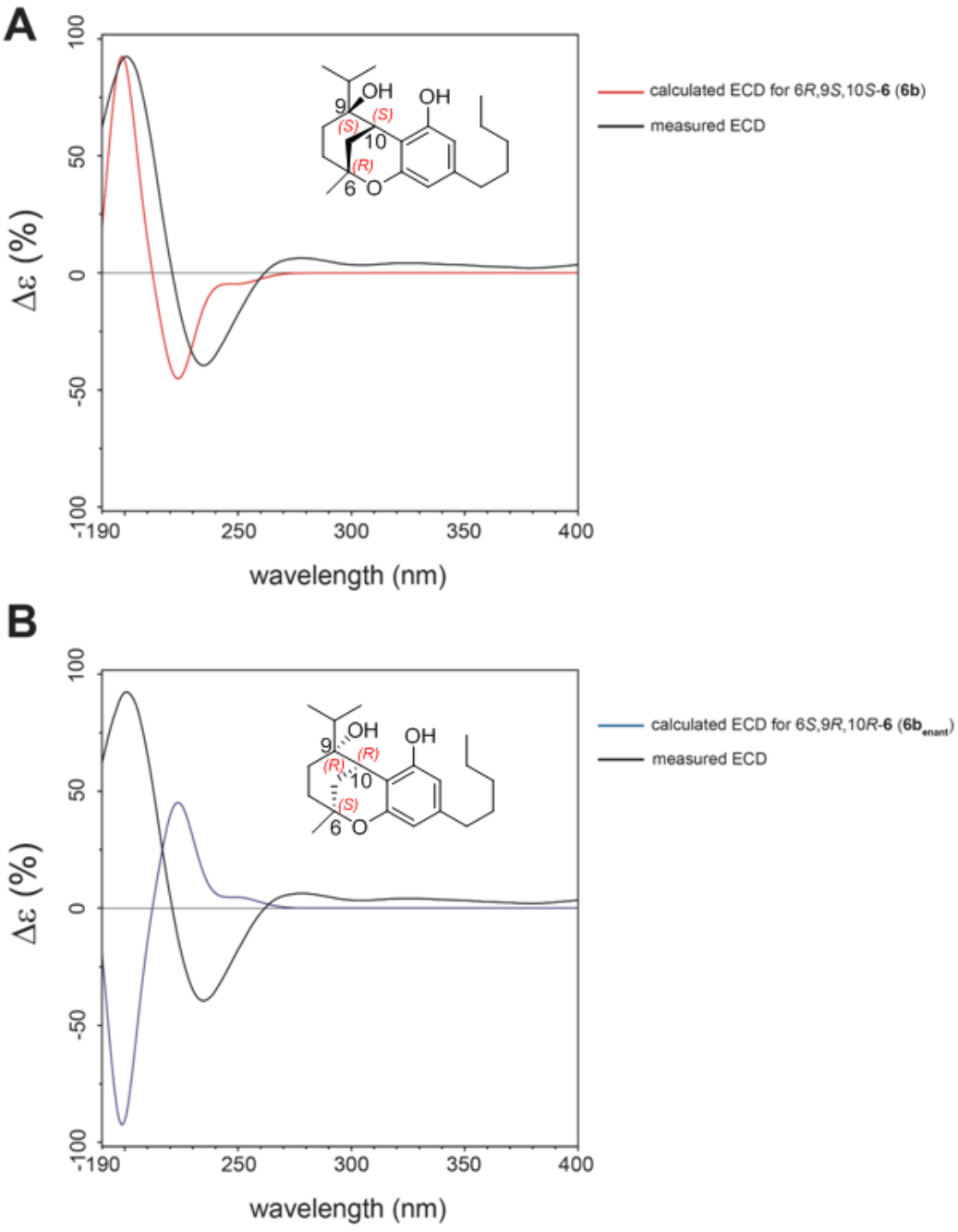
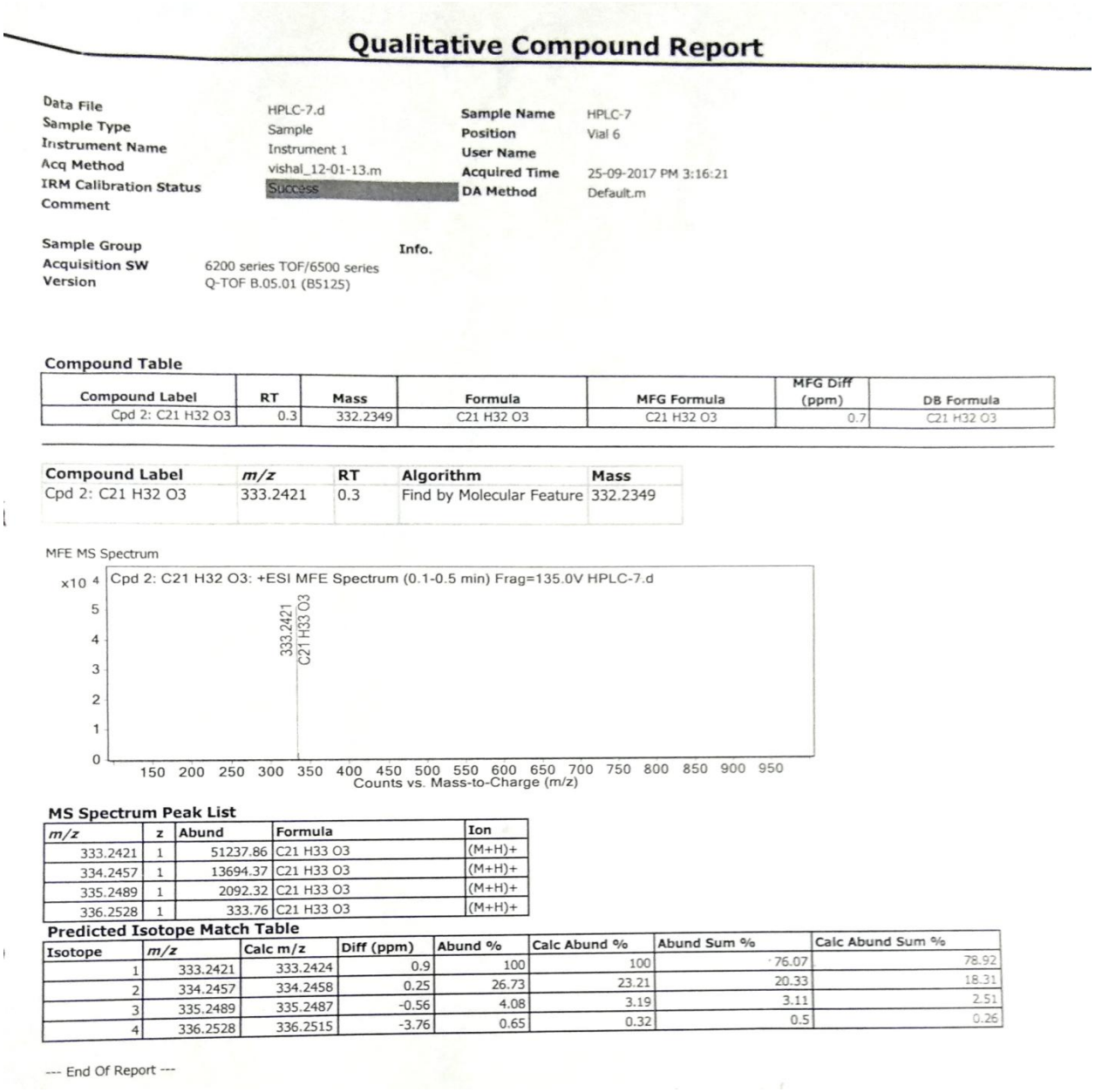


Figure S3. (+) HR-ESI-MS of compound **6**



Qualitative Compound Report

Data File	HPLC-7.d	Sample Name	HPLC-7
Sample Type	Sample	Position	Vial 6
Instrument Name	Instrument 1	User Name	
Acq Method	vishal_12-01-13.m	Acquired Time	25-09-2017 PM 3:16:21
IRM Calibration Status	Success	DA Method	Default.m
Comment			

Sample Group	Info.
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125)

Compound Table

Compound Label	RT	Mass	Formula	MFG Formula	MFG Diff (ppm)	DB Formula
Cpd 2: C21 H32 O3	0.3	332.2349	C21 H32 O3	C21 H32 O3	0.7	C21 H32 O3

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 2: C21 H32 O3	333.2421	0.3	Find by Molecular Feature	332.2349

MFE MS Spectrum

MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
333.2421	1	51237.86	C21 H33 O3	(M+H)+
334.2457	1	13694.37	C21 H33 O3	(M+H)+
335.2489	1	2092.32	C21 H33 O3	(M+H)+
336.2528	1	333.76	C21 H33 O3	(M+H)+

Predicted Isotope Match Table

Isotope	*m/z*	Calc m/z	Diff (ppm)	Abund %	Calc Abund %	Abund Sum %	Calc Abund Sum %
1	333.2421	333.2424	0.9	100	100	76.07	78.92
2	334.2457	334.2458	0.25	26.73	23.21	20.33	18.31
3	335.2489	335.2487	-0.56	4.08	3.19	3.11	2.51
4	336.2528	336.2515	-3.76	0.65	0.32	0.5	0.26

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Figure S4. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6**

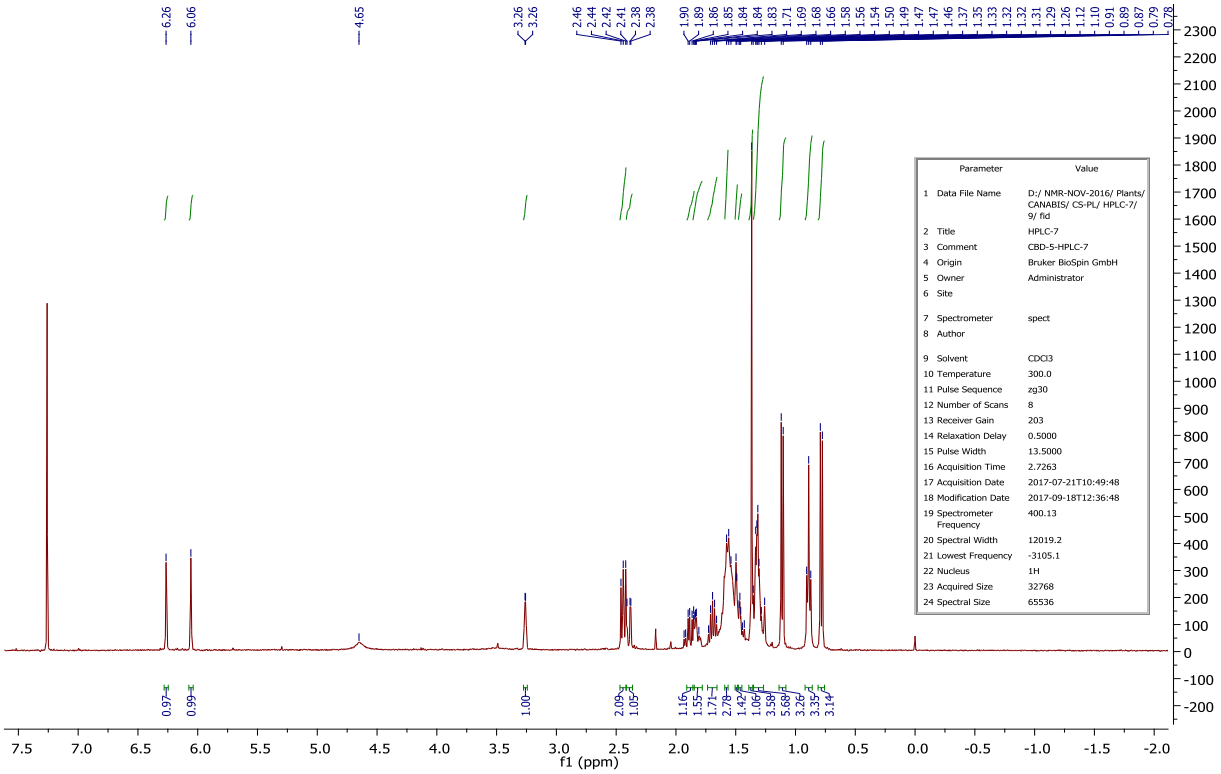


Figure S5. ^{13}C NMR & DEPT-135 (100 MHz, $CDCl_3$) spectrum of compound **6**

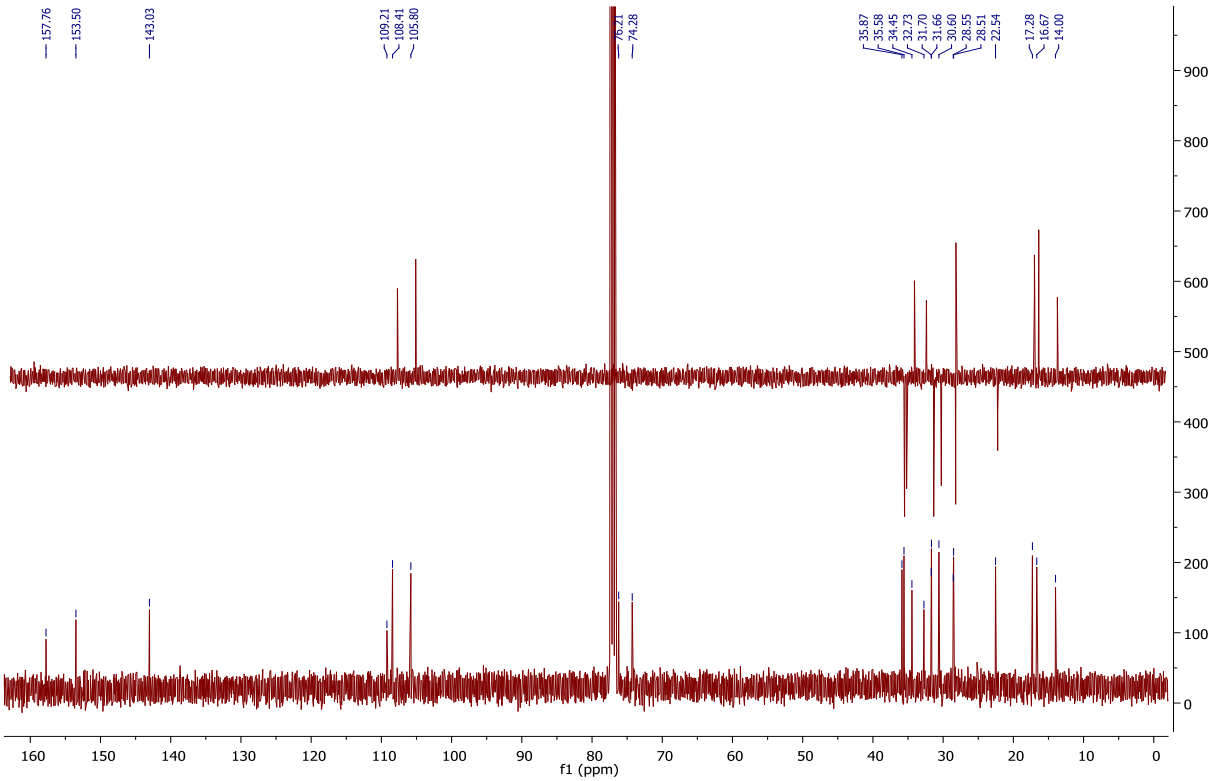


Figure S6. COSY spectrum of compound **6**

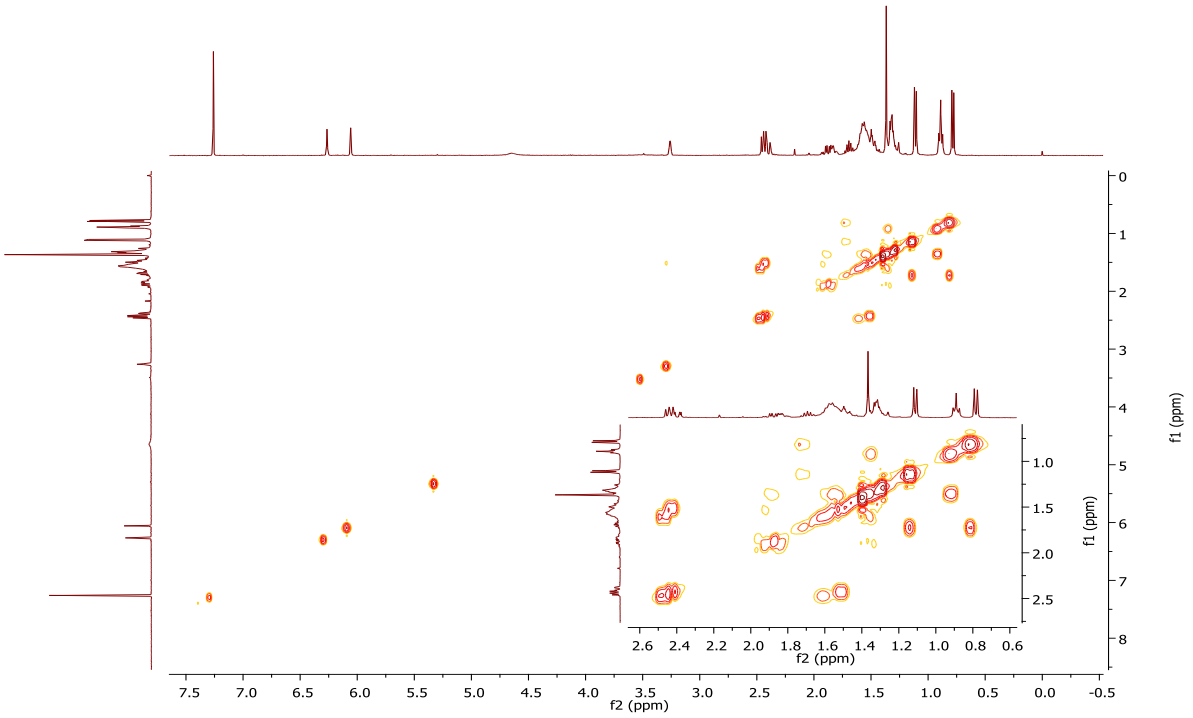


Figure S7. HSQC spectrum of compound **6**

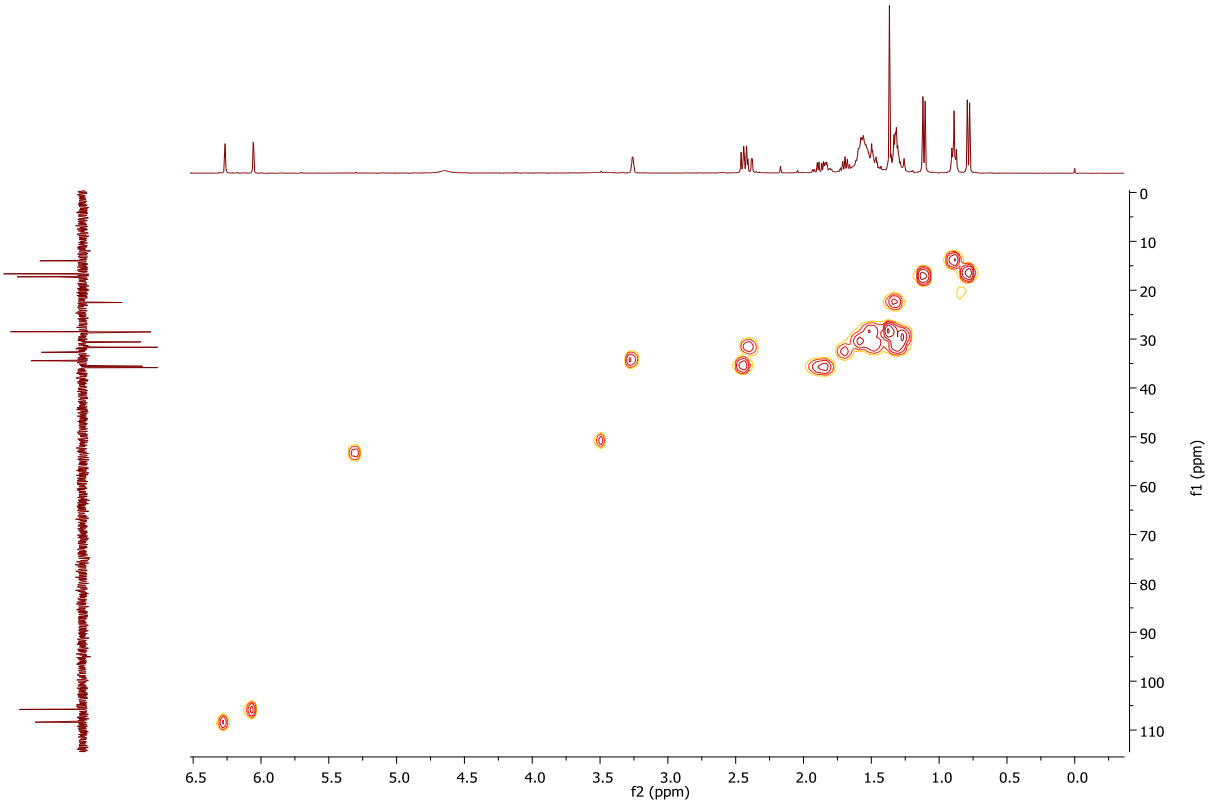


Figure S8. HMBC spectrum of compound **6**

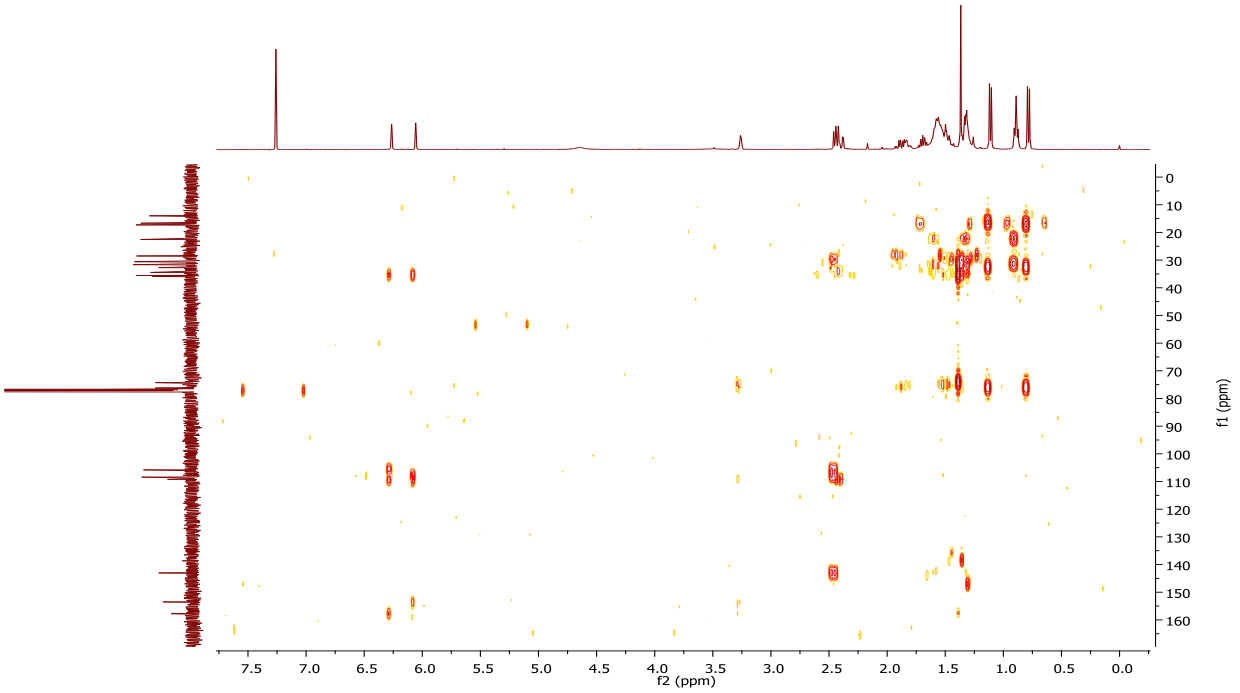


Figure S9. NOESY spectrum of compound **6**

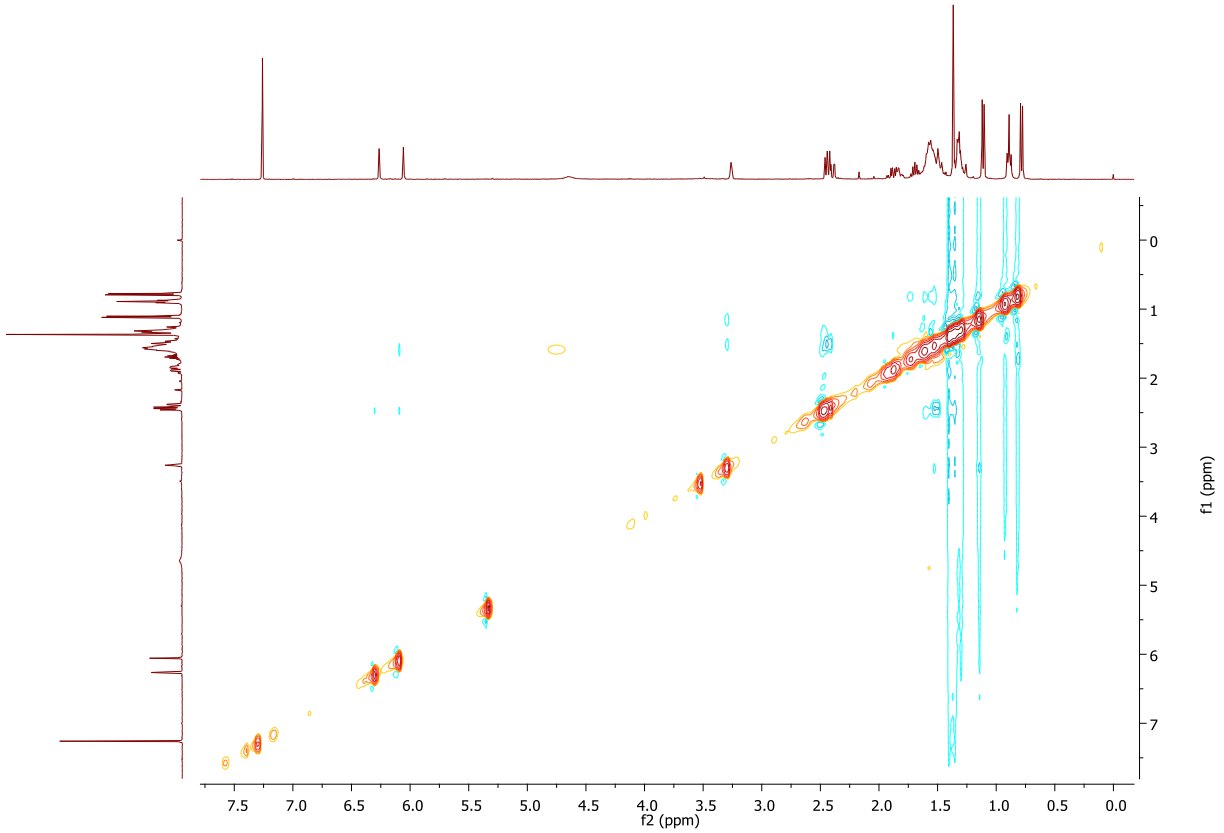


Figure S10. Key COSY, HMBC and NOESY correlations of compound **6**

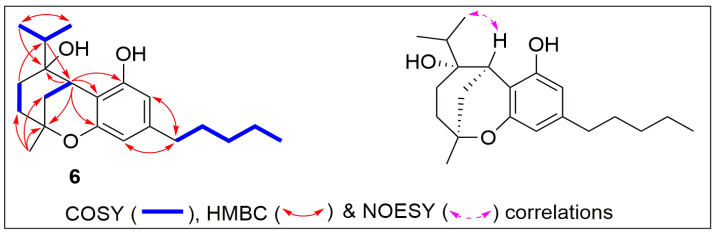


Table S7. ^{1}H NMR (400 MHz, DMSO) & ^{13}C NMR (100 MHz, DMSO) Spectroscopic Data of Compound **6**

	C.No	δ_H (mult., *J* Hz, no. H)	δ_C	HMBC
Q2	1		155.81	-
2	2	6.12 (d, *J* = 1.2 Hz, 1H)	105.96	C-1, C-10a, C-4, C-1'
Q3	3	-	141.66	-
1	4	6.04 (s, 1H)	106.53	C-1, C-10a, C-2, C-1'
	C1-OH	9.10 (s, 1H)	-	C-1, C-10a
Q1	5	-	157.62	-
Q6	6	-	74.08	-
3	7	1.89 (td, *J* = 13.3, 5.0 Hz, 1H) 1.69 – 1.63 (m, 1H)	36.11	C-8
11	8	1.41 – 1.38 (m, 1H), 1.15 – 1.09 (m, 1H)^{A}	28.68	C-7
Q5	9		74.87	
5	10	3.20 (*brs*, 1H)	33.86	C-6, C-9, C-1, C-5, C-10a
Q4	10a		110.03	
7	11	2.41 – 2.34 (1H)^{B}, 1.27 – 1.21 (1H)^{A}	32.14	C-15
6	12	1.58 – 1.45 (1H)^{C}	33.12	C-13, C-14, C-10
13	13	1.06 (d, *J* = 6.5 Hz, 3H)	18.71	C-14, C-9, C-12
14	14	0.73 (d, *J* = 6.8 Hz, 3H)	17.26	C-13, C-9, C-12
10	15	1.31 (s, 3H)^{A}	29.05	C-6, C-7, C-11
4	1'	2.41 – 2.34 (2H)^{B}	35.44	C-2, C-3, C-4, C-2', C-3'
9	2'	1.58 – 1.45 (2H)^{C}	30.71	C-3, C-1', C-3', C-4'
8	3'	1.30 – 1.27 (2H)^{A}	31.52	C-4'
12	4'	1.36 – 1.31 (2H)^{A}	22.43	C-2'
15	5'	0.91 (t, *J* = 6.9 Hz, 3H)	14.37	C-3', C-4'

All assignments were based on HSQC and HMBC experiments; *A, B, C* represents overlapped signals

Figure S11. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **6**

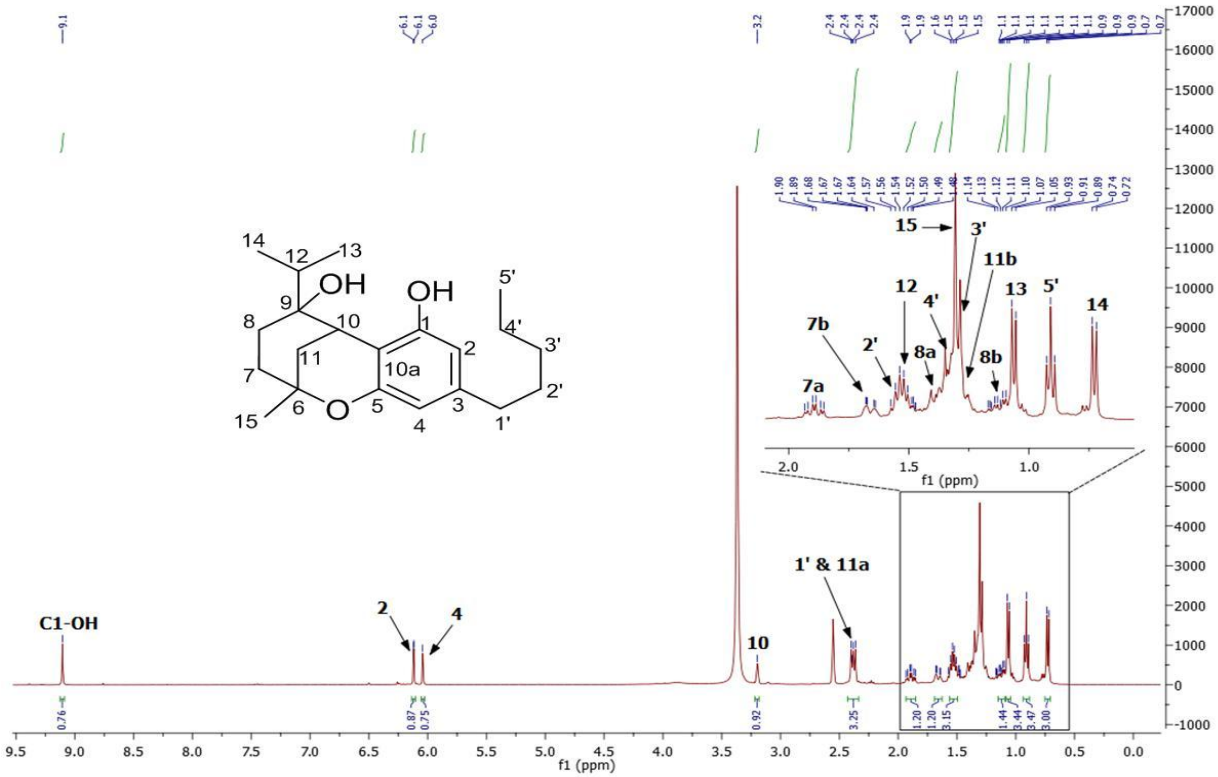


Figure S12. ^{13}C NMR & DEPT-135 (100 MHz, DMSO-d6) spectrum of compound **6**

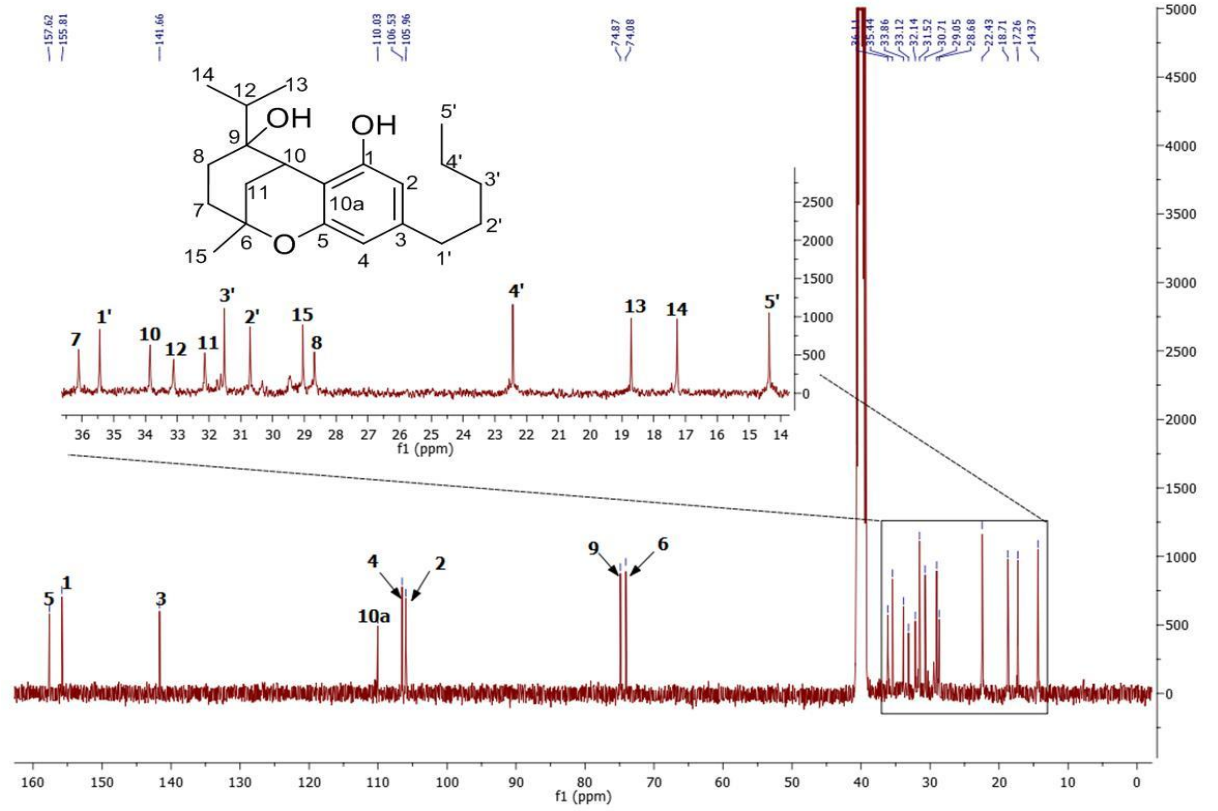


Figure S13. DEPT-135 (100 MHz, DMSO-d6) spectrum of compound **6**

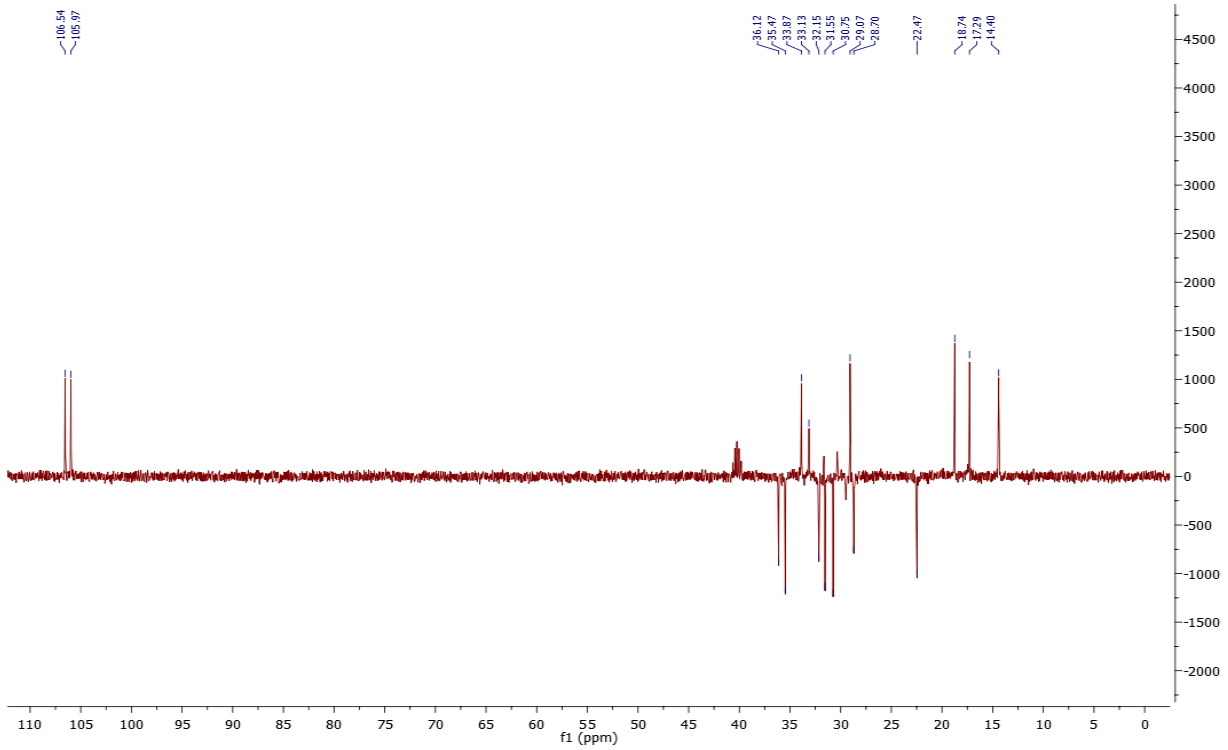


Figure S14. COSY spectrum of compound **6** in DMSO-d6

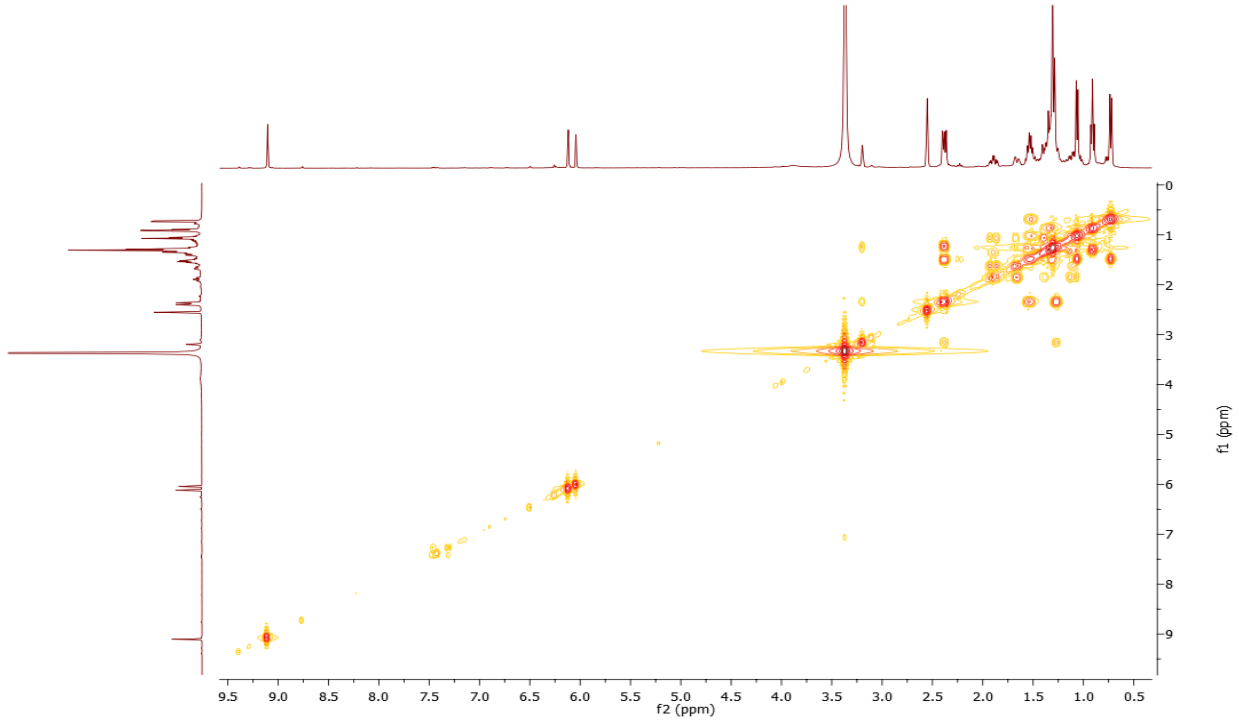


Figure S14a. Expantion of COSY spectrum of compound **6** in DMSO-d6

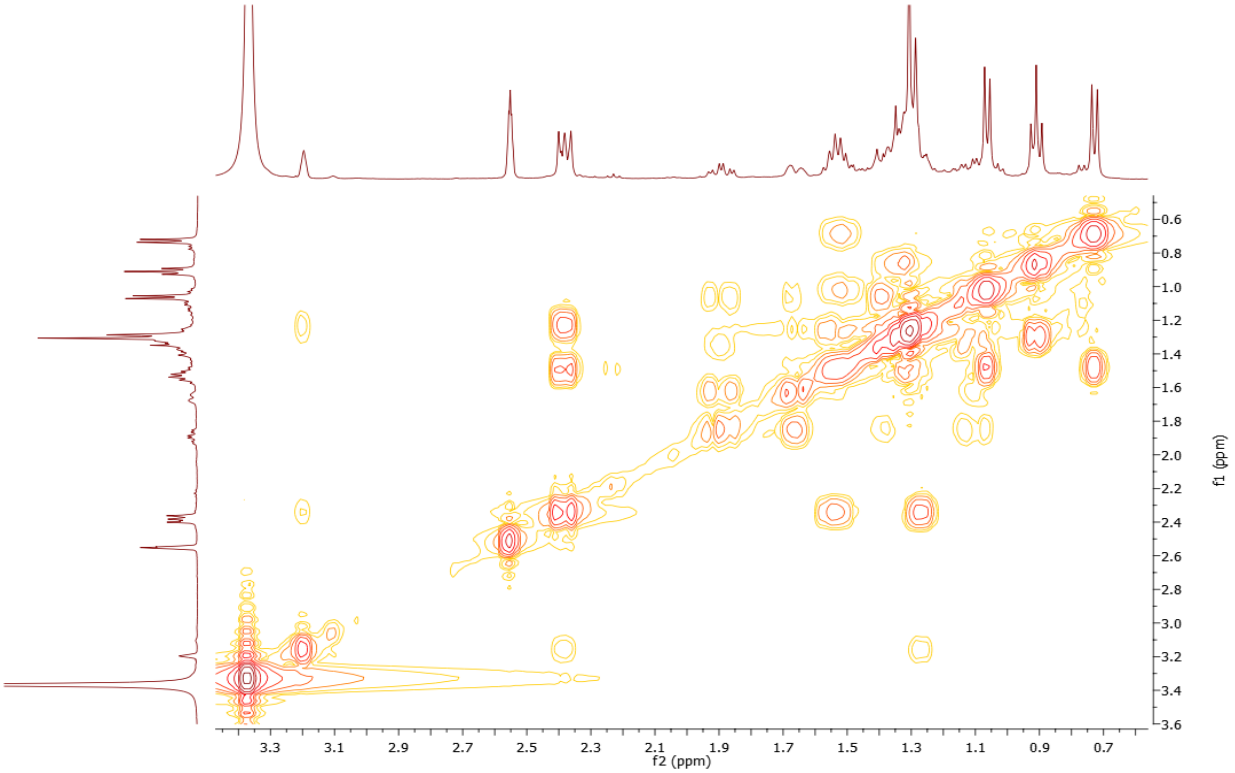


Figure S15. HSQC spectrum of compound **6** in DMSO-d6

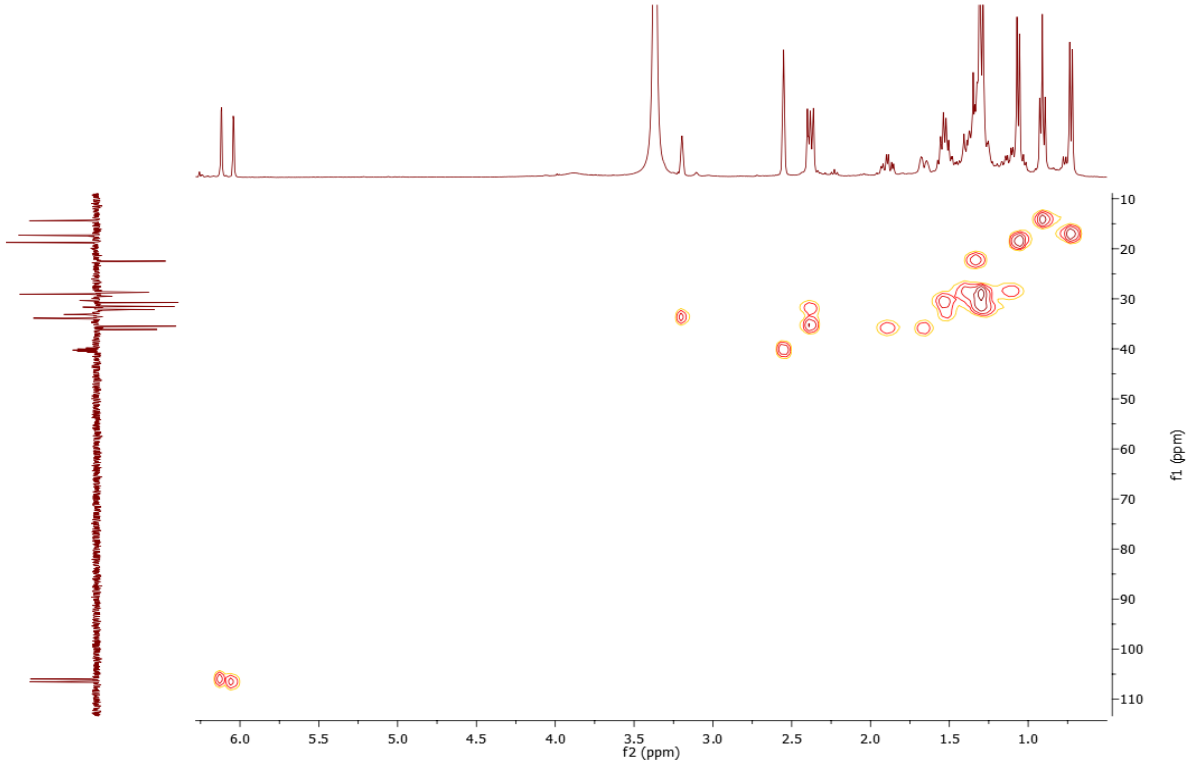


Figure S16a. Expantion of HSQC spectrum of compound **6** in DMSO-d6

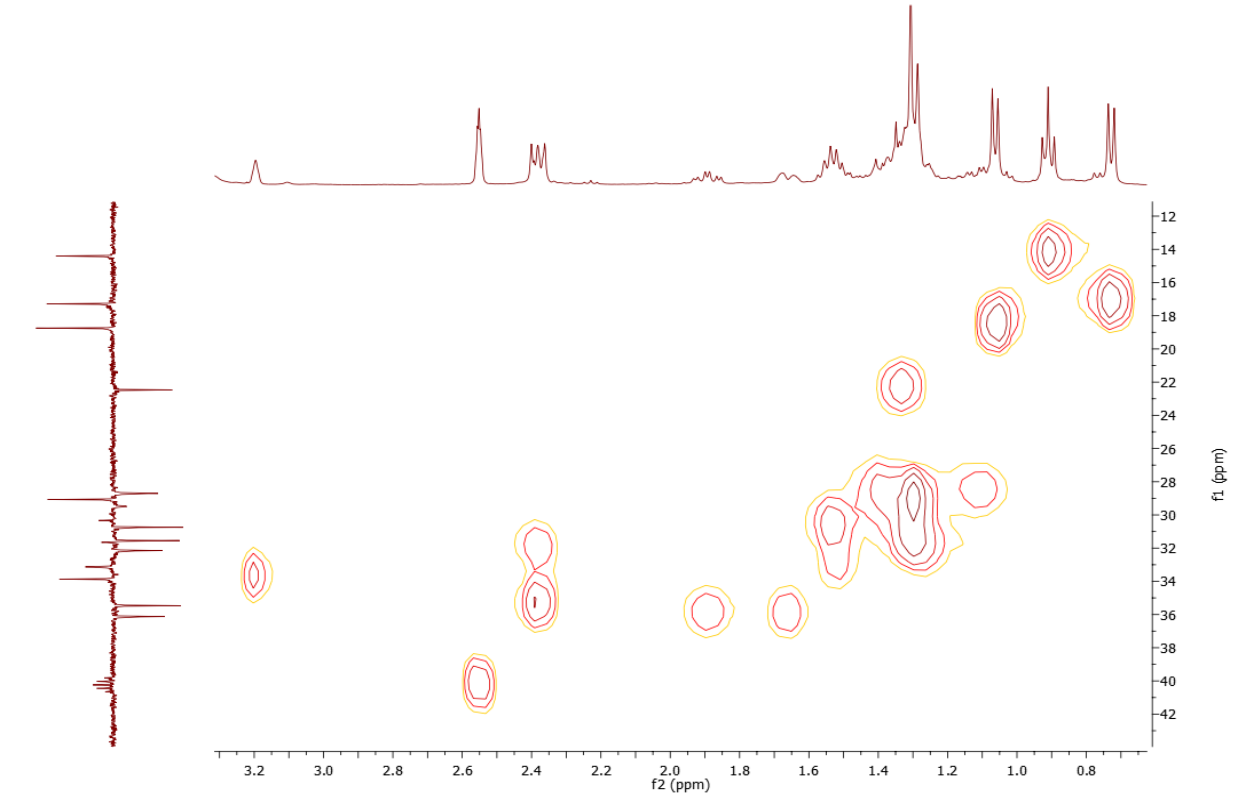


Figure S17. HMBC spectrum of compound **6** in DMSO-d6

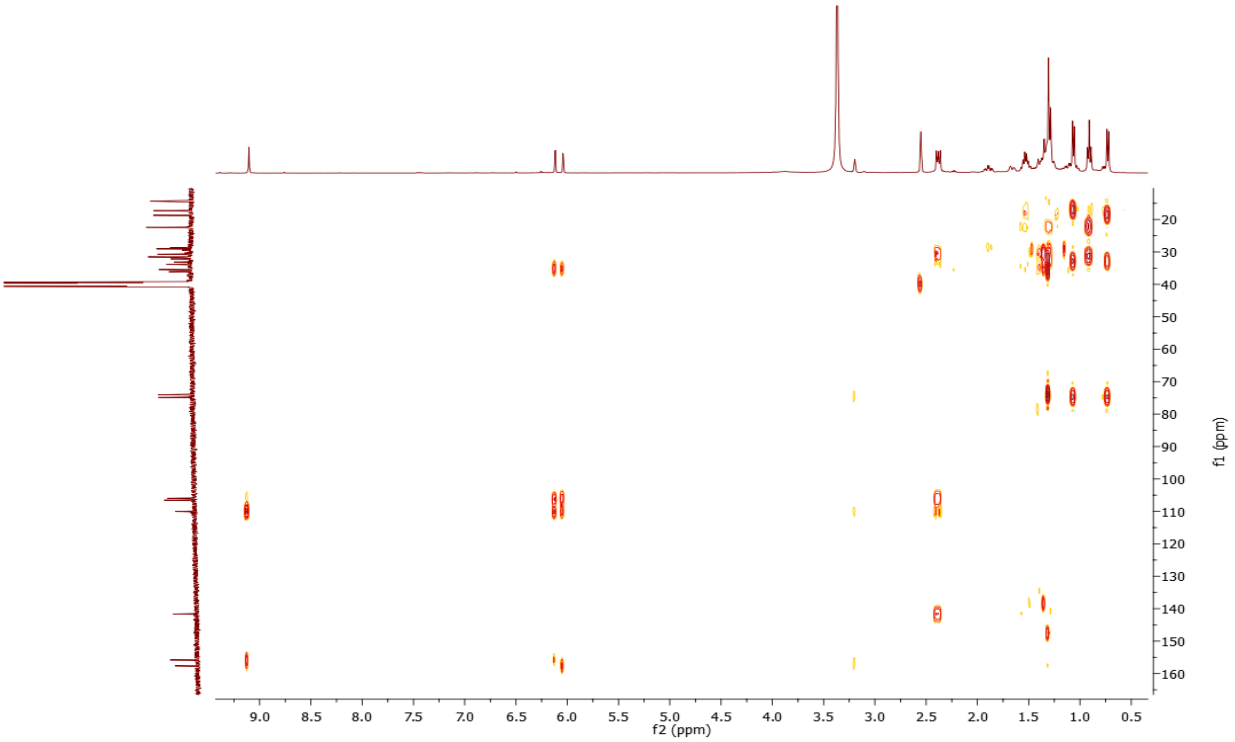


Figure S18. NOESY spectrum of compound **6** in DMSO-d6

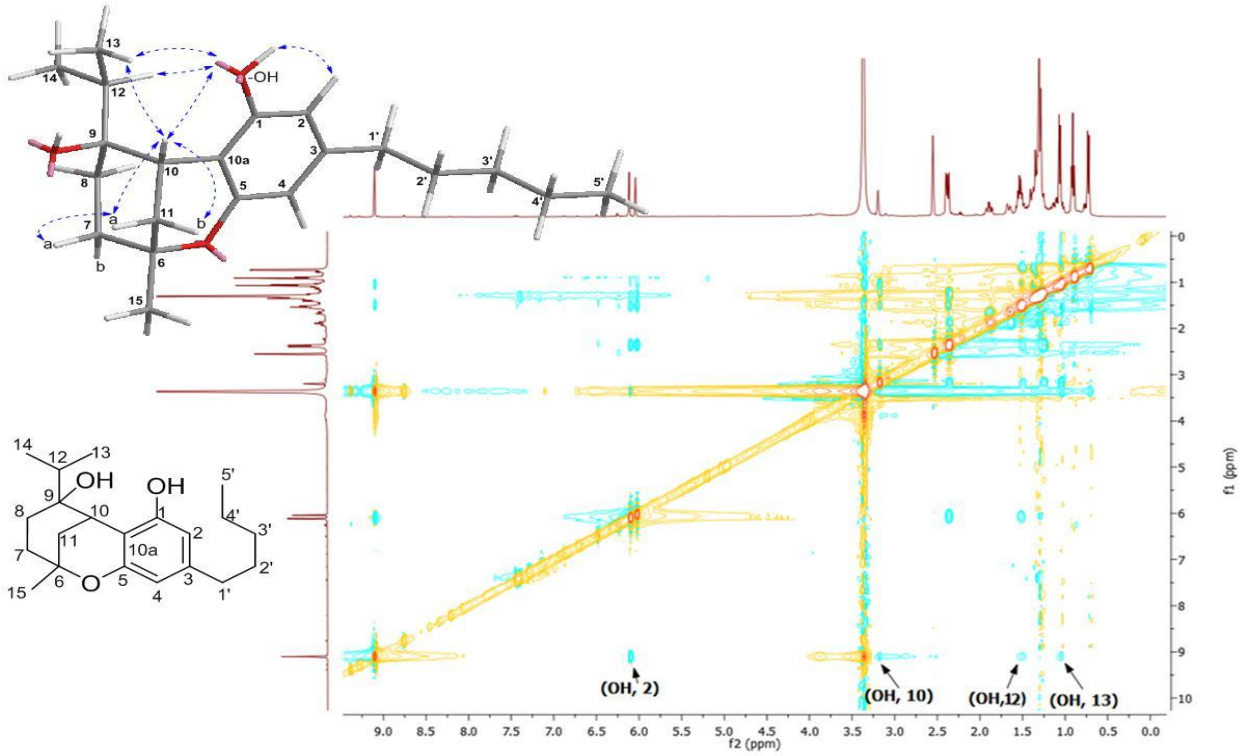


Figure S19. Expantion of NOESY spectrum of compound **6** in DMSO-d6

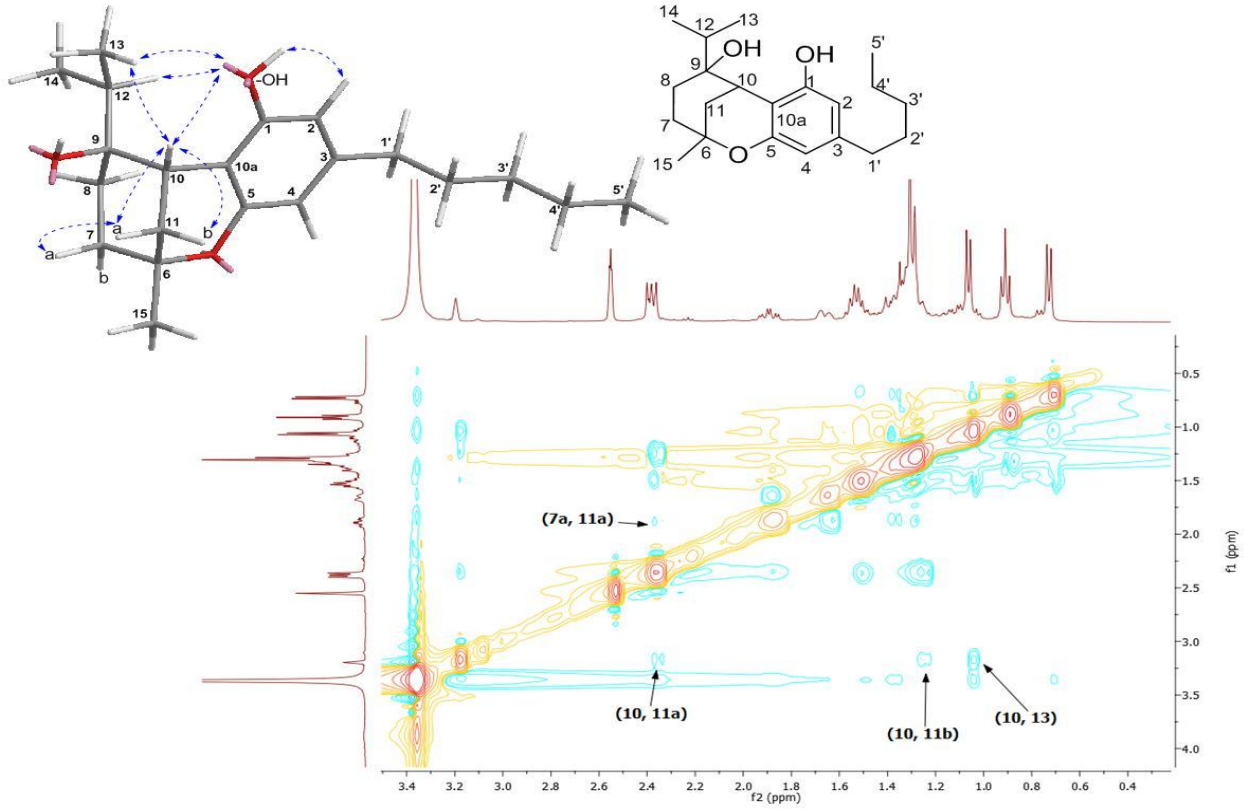


Figure S20. HPLC chromatogram of fraction **Fr.1**

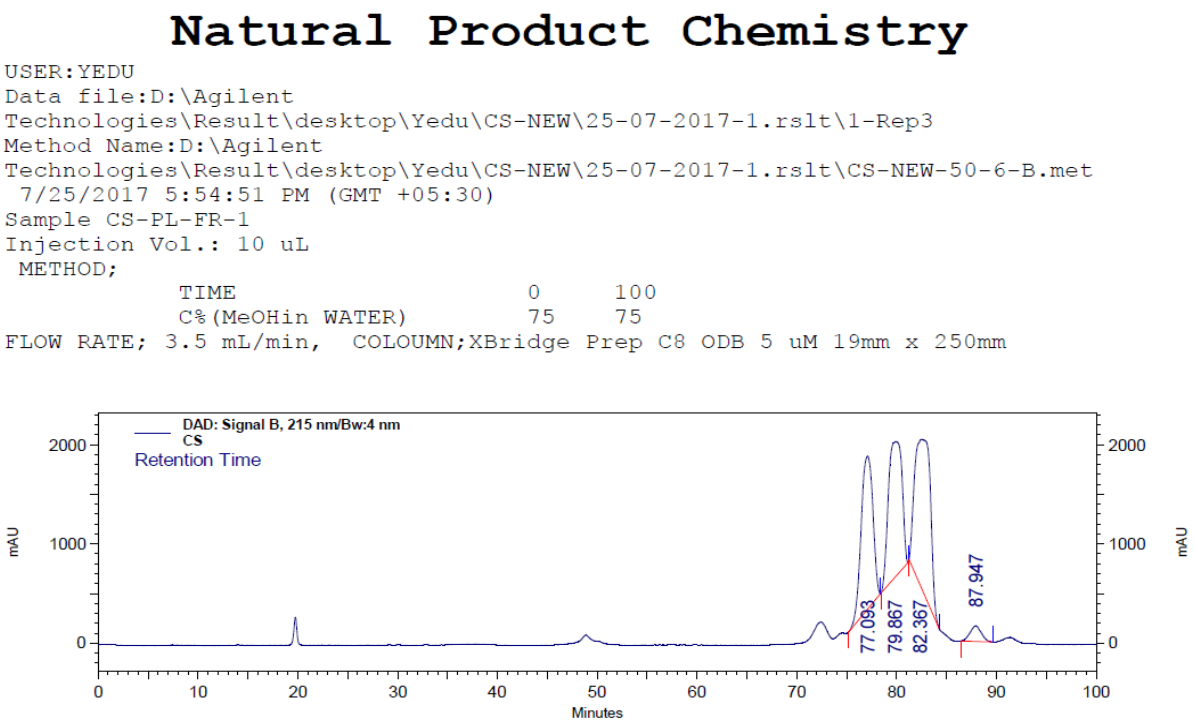


Figure S21. HPLC chromatogram of fraction **Fr.3**

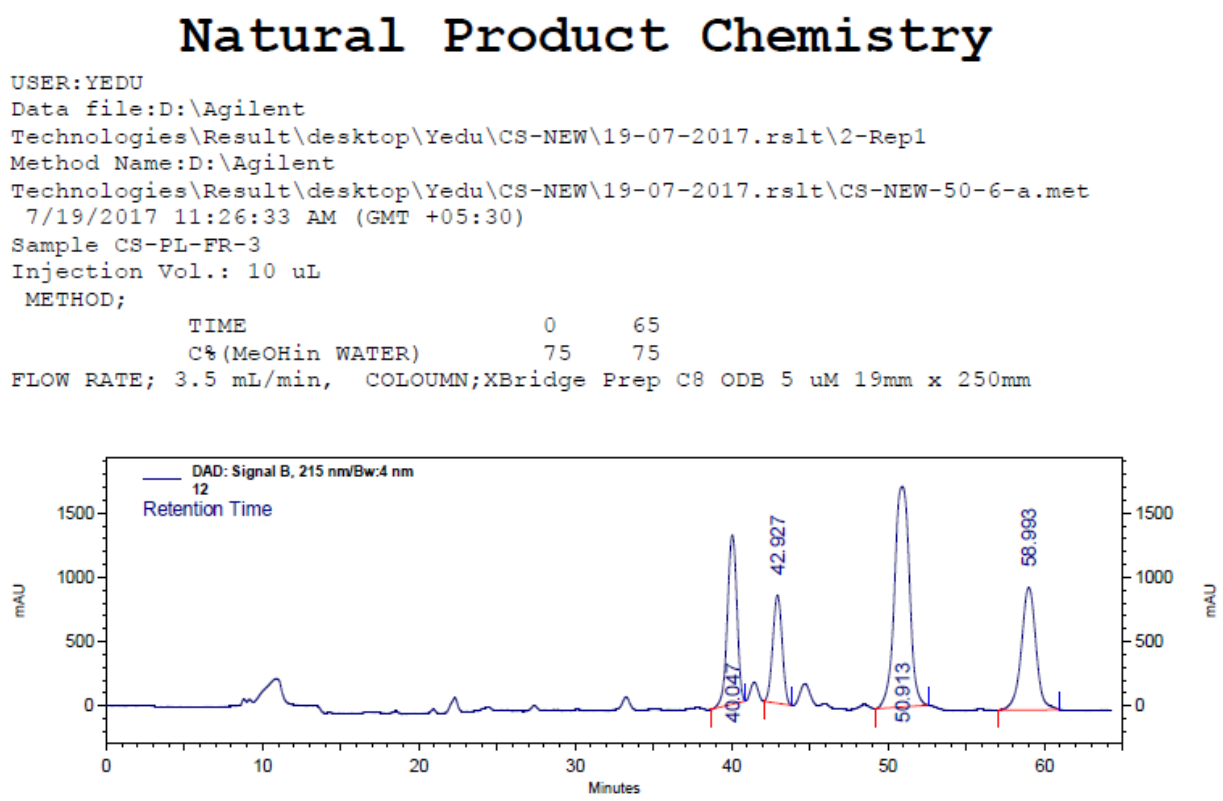


Table S8. *In vitro* Growth %age inhibition of all screened derivatives using MTT assay

Cells	**GI**50 (μM)				
	1	4	5	7	8
HCT-116	10.47±1.58	15.11±2.10	24.94±3.45	24.39±4.21	>60
MCF-7	13.52±3.06	15.60±1.82	28.06±2.74	15.23±3.30	54.62±3.92
K562	20.03±2.85	11.07±3.01	28.29±4.12	22.23±1.87	54.62±4.38
MIAPaCa-2	15.57±1.95	10.22±3.23	28.43±2.78	27.37±3.63	43.02±5.03
PANC-1	9.743±1.04	24.97±2.21	19.95±2.65	20.39±5.06	44.24±2.78
A549	10.41±1.25	13.36±1.26	39.38±1.38	28.71±4.27	51.12±1.94
PC3	5.678±1.05	15.66±3.22	21.30±2.81	16.51±2.02	34.25±3.38
SW	18.30±1.86	21.69±2.07	60.13±3.21	33.74±5.19	>60
Results are expressed as the mean value of IC50± SD					

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