SUPPORTING MATERIALS

Synthesis, structural assignments and antiinfective activities of 3-*O*-benzyl-carvotacetone and 3-hydroxy-2-isopropyl-5-methyl-*p*-benzoquinone

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ABSTRACT

In an attempt to synthesize carvotacetone analogues, new 3-*O*-benzyl-carvotacetone (**10)** and previously reported 3-hydroxy-2-isopropyl-5-methyl-*p*-benzoquinone (**11**) were synthesized from piperitone (**7**). In this work, we describe synthesis of **10** and other analogues from **7**. Luche reduction of **7** to *cis*-piperitol **(8)**, followed by benzylation yielded 3-*O*-benzyl-piperitol (**9**). Riley oxidation of **9** afforded corresponding ketone **10**, **11** and 3-benzyloxy-4-isopropylcyclohex-1-enecarbaldehyde (**12)**. Structures of these compounds were determined based on NMR, IR and LC-MS spectral data. Compound **11**, exhibited antiplasmodial activities against chloroquine-sensitive (D6) and resistant (W2) strains of *Plasmodium falciparum* with IC_{50} values of 0.697 and 0.653 µg/mL, respectively. In addition, compound **11** was active against *Cryptococcus neoformans* with an IC_{50} value of 3.11 µg/mL, compared to reference standard fluconazole (IC_{50} value of 1.87 µg/mL), while **10** and **12** were

inactive against both organisms. This is the first report of the antiplasmodial and anticryptococcal activity of compound **11**.

Key words: Piperitone, Riley oxidation, 3-Hydroxy-2-isopropyl-5-methyl-*p*-benzoquinone, 3-*O*-benzyl-carvotacetone, Anti-plasmodial, Cryptococcosis.

SUPPLEMENTARY INFORMATION

Table S1: ^{1}H and ^{13}C-NMR spectral Data assignment of compound 9 by 2D experiments

Position	^{13}C NMR, δ, ppm	^{1}H NMR, δ, ppm	HMBC
1	140.3		
2	121.1	5.82, *m*, 1H	C-7, C-6, C-4, C-3
3	71.7	3.89, (*t*), 1H	C-7′, C-5, C-2, C-1
4	46.2	1.09, 1H	C-9, C-8, C-6, C-5
5	21.4	1.63, (*m*), 2H	C-6, C-4, C-3, C-1
6	31.7	2.02, (*dd*)/2.07, (*dd*), 2H	C-5, C-4, C-2, C-1
7	23.7	1.77, (*s*), 3H	C-6, C-2, C-1
8	28.3	1.86, (*m*), 1H	C-10, C-9, C-4
9	21.0	0.98, (*d*), 3H, J = 6.5 *Hz*	C-10, C-8, C-4
10	21.1	1.0, (*d*), 3H, J = 6.5 *Hz*	C-9, C-8, C-4
1′	139.6		
2′/6′	127.5	7.39, (*m*), 2H	C-4′, C-1′
3′/5′	128.2	7.36, (*m*), 2H	C-3′/5′, C-1′
4′	127.2	7.28, (*m*), 1H	C-2′/C-6′, C-1′
7′	70.1	4.73, (*d*), J= 11.7*Hz*/ 4.49, (*d*), J=11.7*Hz*	C-3, C-1′, C-2′/C-6′

Figure S2: ^{1}H-NMR spectrum of compound 9

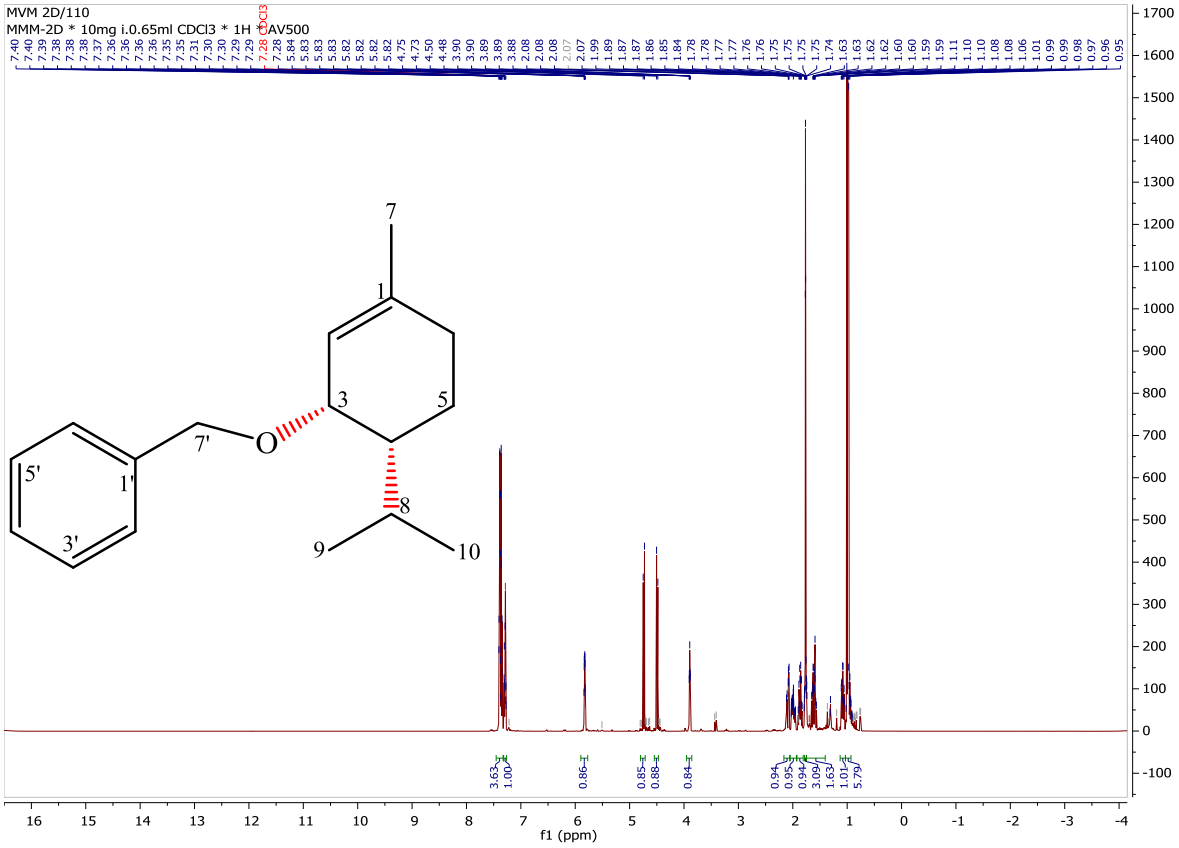

Figure S3: ^{13}C-NMR spectrum of compound 9

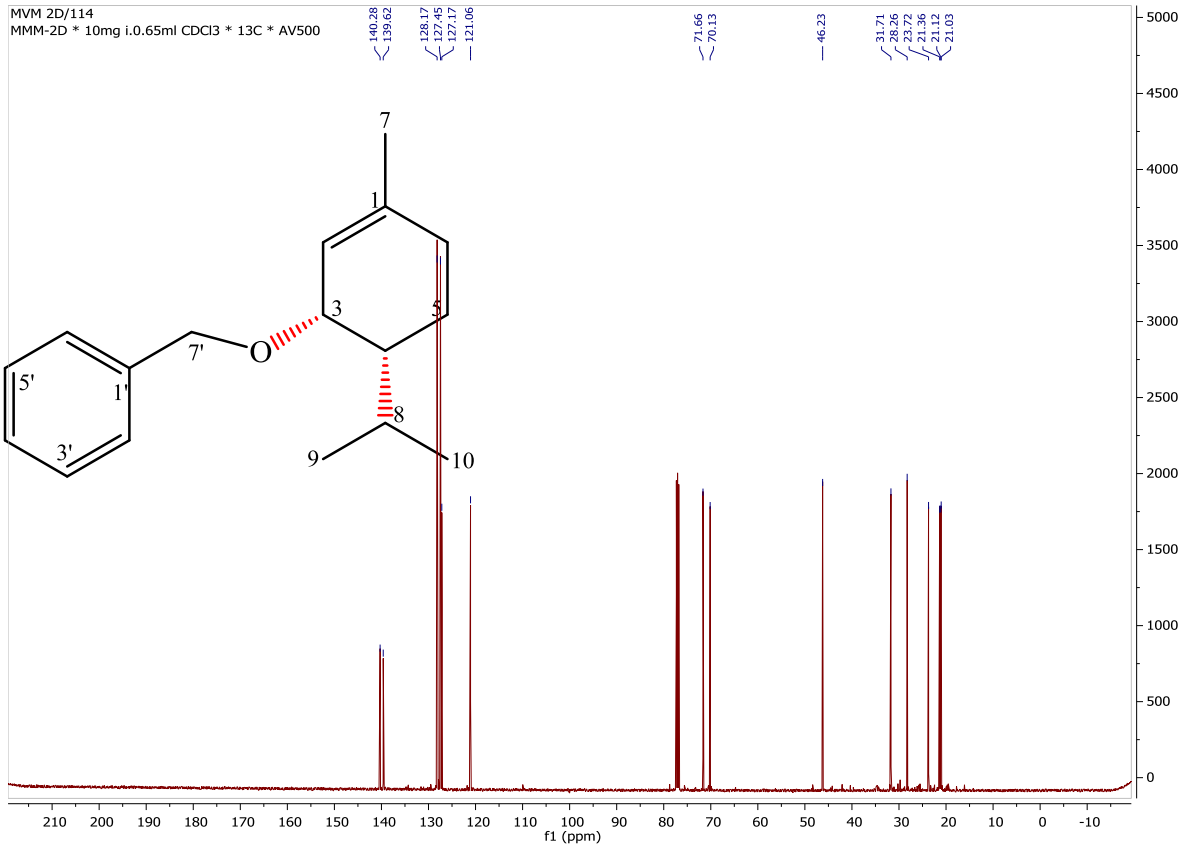

Figure S4: COSY spectrum of compound 9

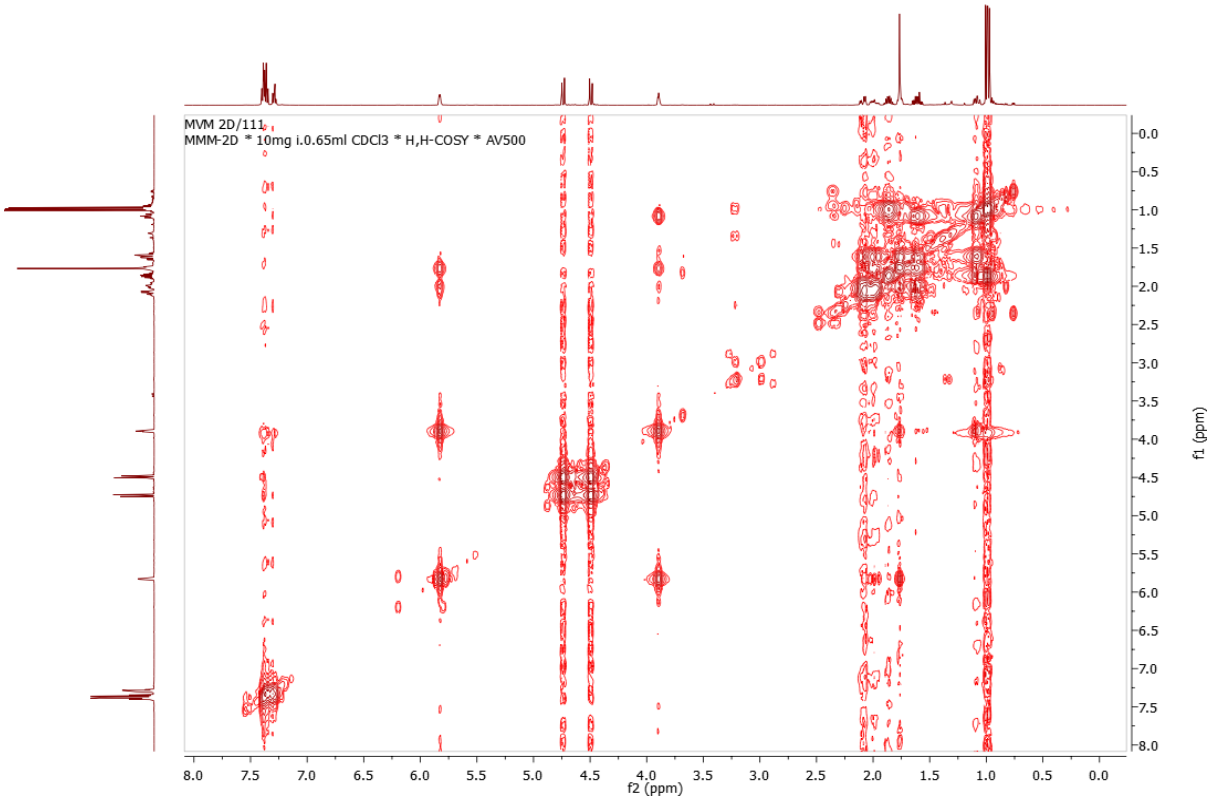

Figure S5: HSQC spectrum of compound 9

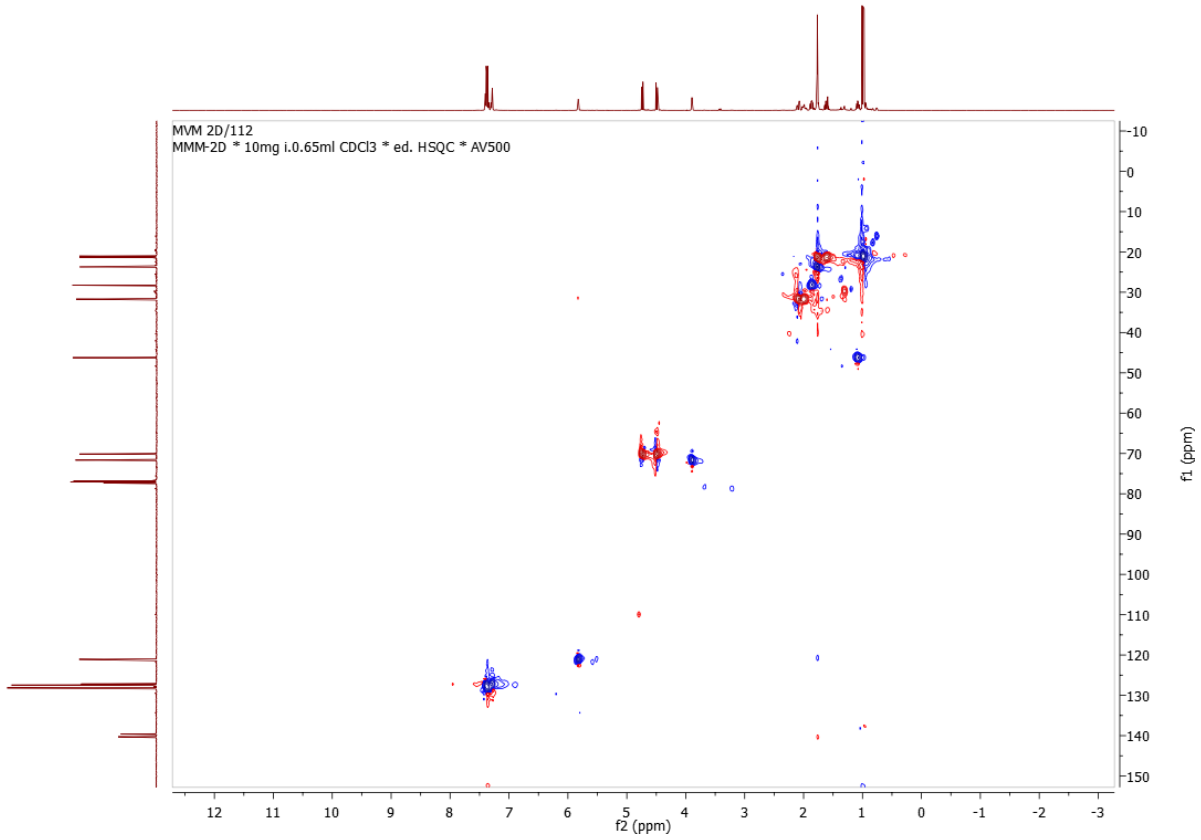

Figure S6: HMBC spectrum of compound 9

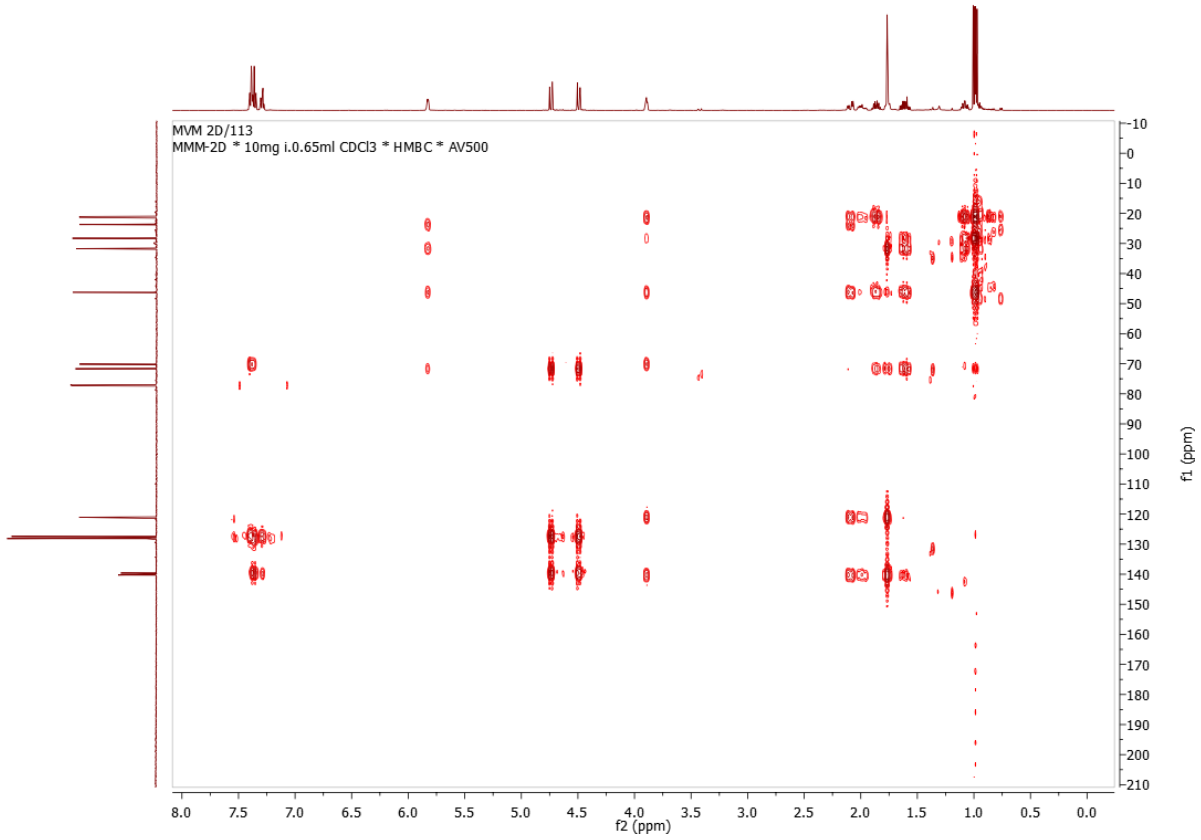

Figure S7: LC-MS spectrum for compound 9

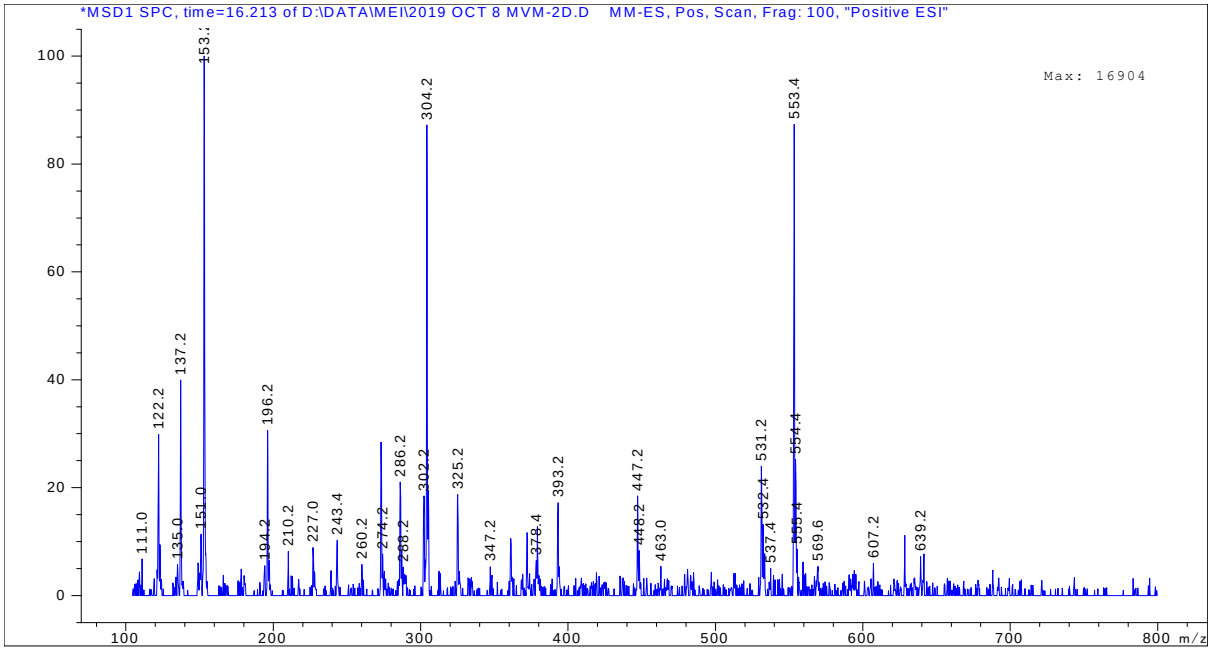

Figure S8: IR spectrum of compound 9

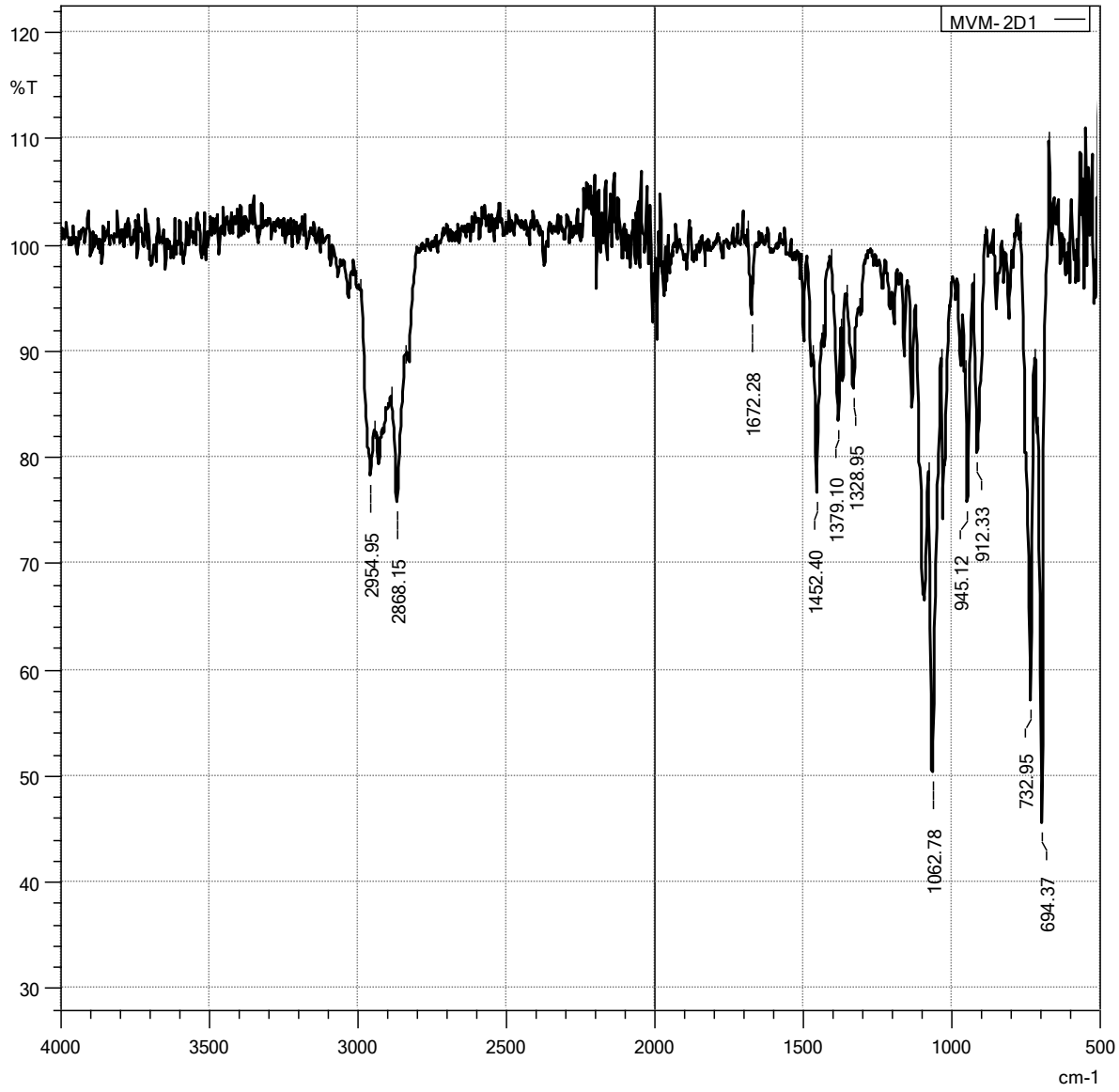

Table S9: ^{1}H and ^{13} C-NMR spectral Data assignment of compound 10 by 2D experiments

Position	^{13}C NMR, δ, ppm	^{1}H NMR, δ, ppm	HMBC
1	132.7		
2	146.4	6.78, *m*, 1H	C-6, C-7, C-4
3	78.7	3.85, *d*, J = 2.4 *Hz*, 1H	C-7′, C-5, C-4, C-2
4	46.9	1.65, *m*, 1H	C-10, C-9, C-8
5	27.3	2.39, *m*, 2H	C-4, C-3, C-1
6	198.1		
7	15.6	1.83, *s*, 3H	C-6, C-2, C-1
8	28.2	1.94, *m*, 1H	C-10, C-9, C-4
9	20.5*	0.86, *d*, 3H, J=6.6Hz	C-10, C-8
10	20.4*	0.96, *d*, 3H, J=6.6Hz	C-9, C-8
1′	138.1		
2′/6′	127.9	7.33, *m*, 2H	C-7′, C-4′
3′/5′	128.3	7.36, *m*, 2H	C-2′/6′, C′4, C-1′
4′	127.6	7.30, *m*, 2H	C-3′/5′, C-2′/6″
7′	71.3	4.48, *d*, J = 12.0 *Hz*, 1H 4.58, *d*, J = 12.0 *Hz*, 1H	C-3, C-2′/6′, C-1′ C-3, C-2′/6′, C-1′

Figure S10: ^{1}H-NMR spectrum data of compound 10

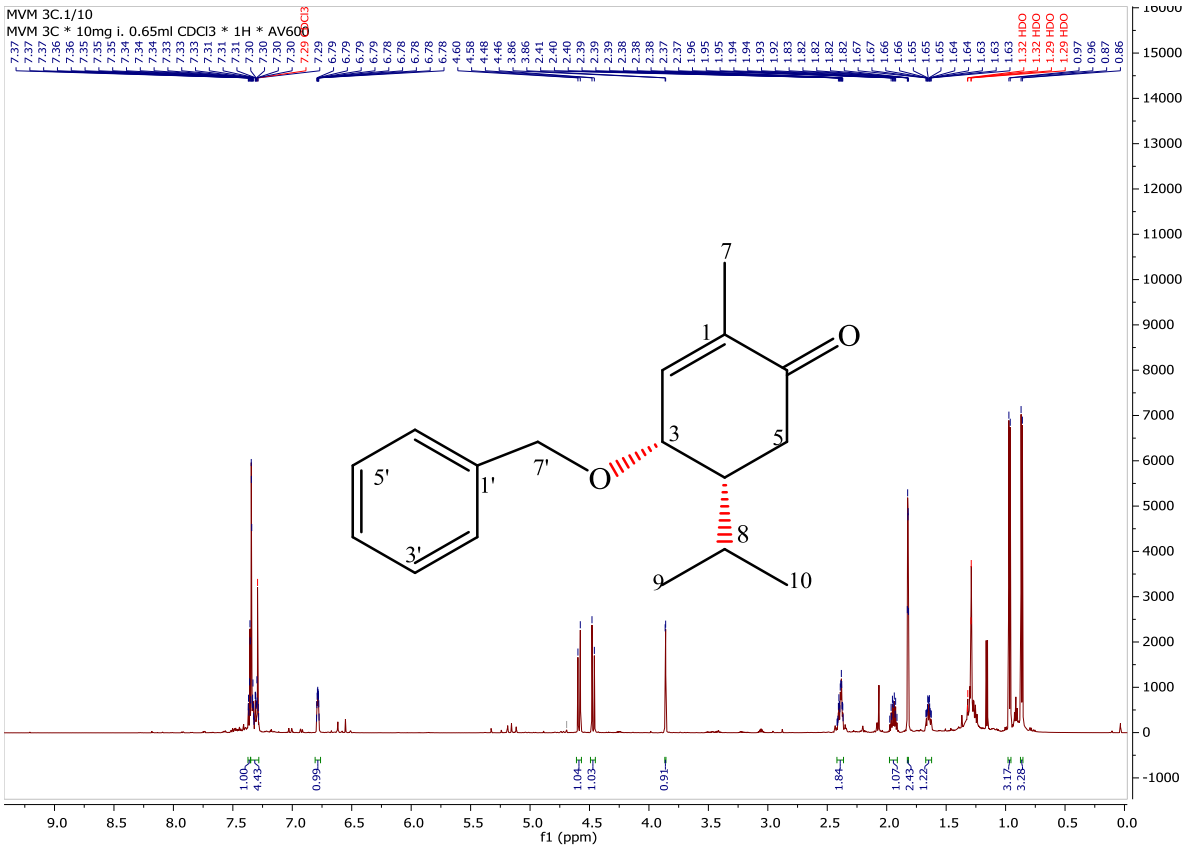

Figure S11: ^{13}C-NMR spectrum data of compound 10

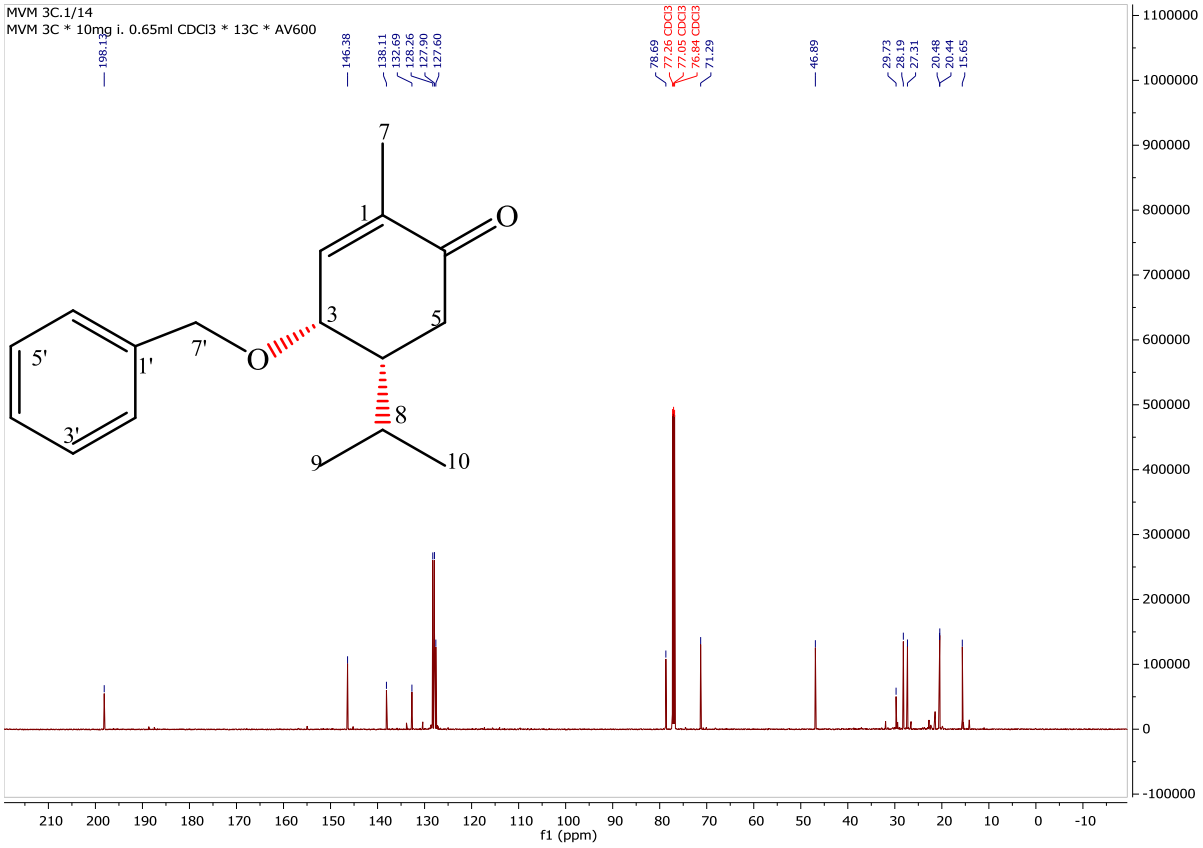

Figure S12: COSY spectrum of compound 10

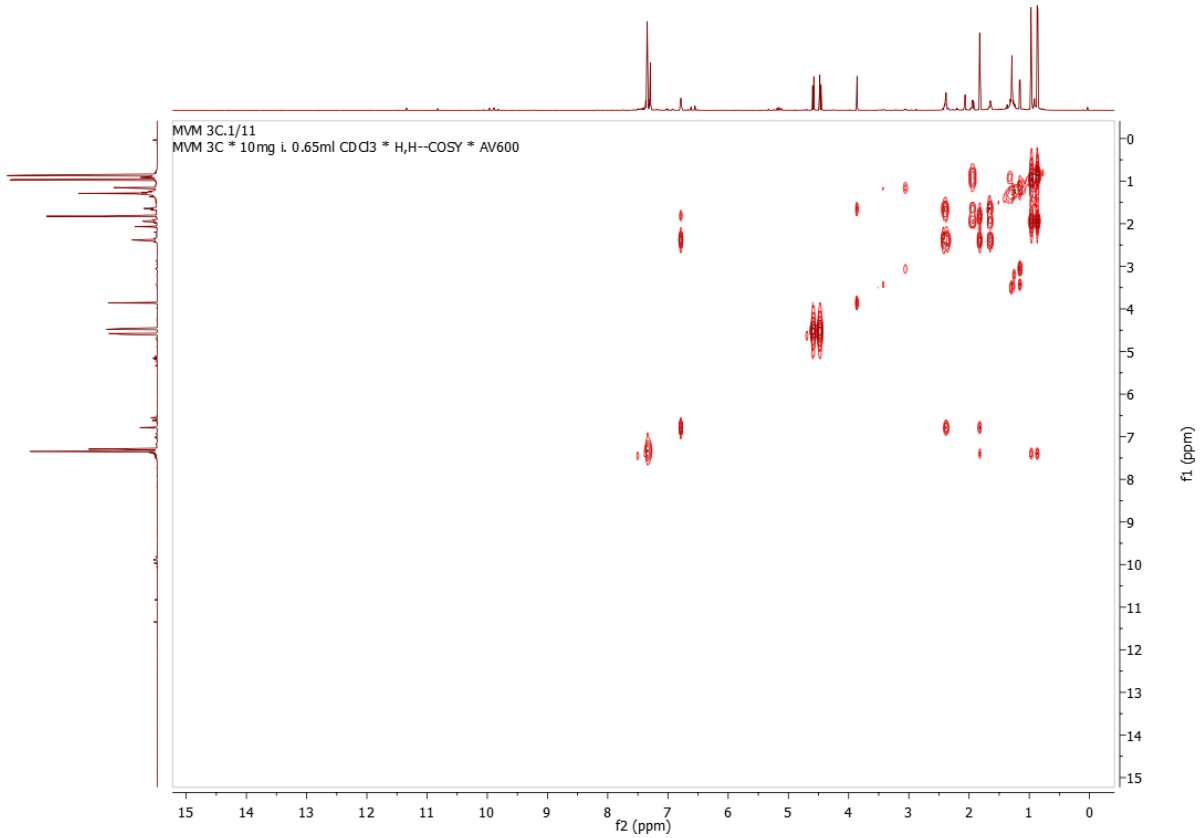

Figure S13: HSQC spectrum of compound 10

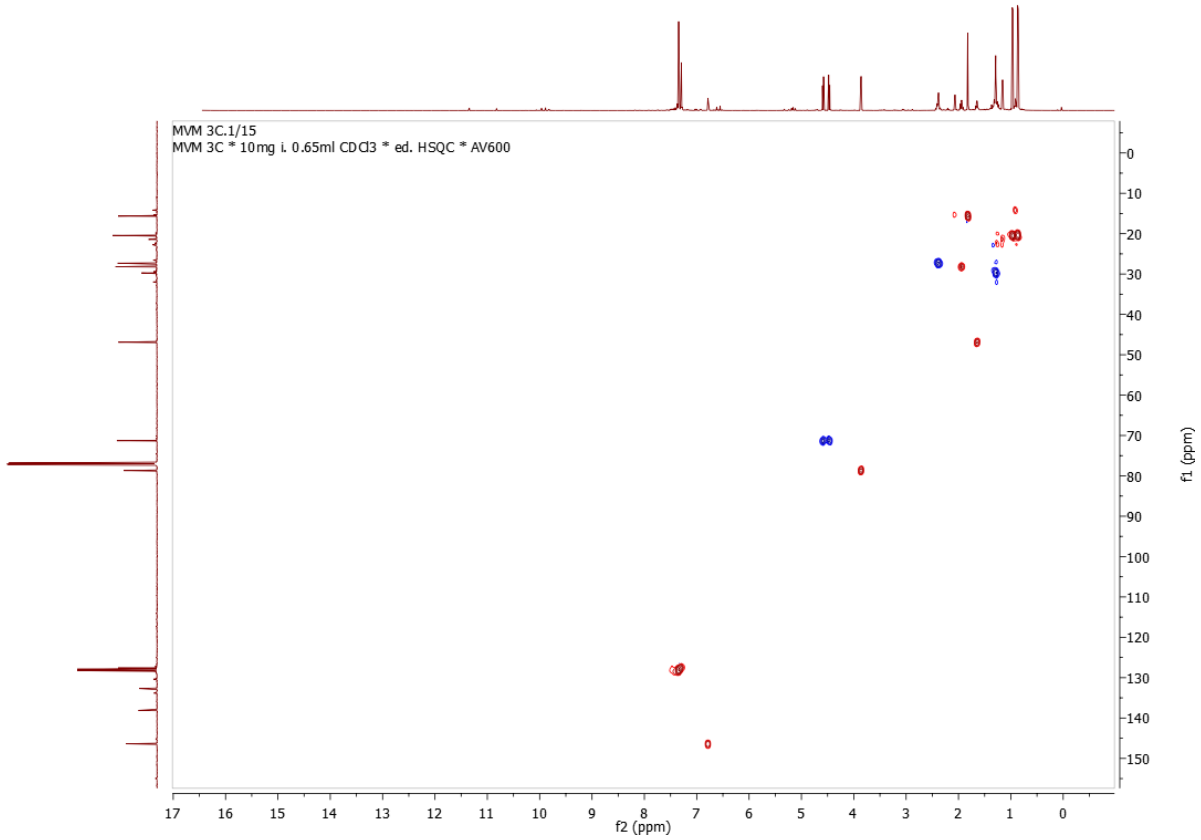

Figure S14: HMBC spectrum of compound 10

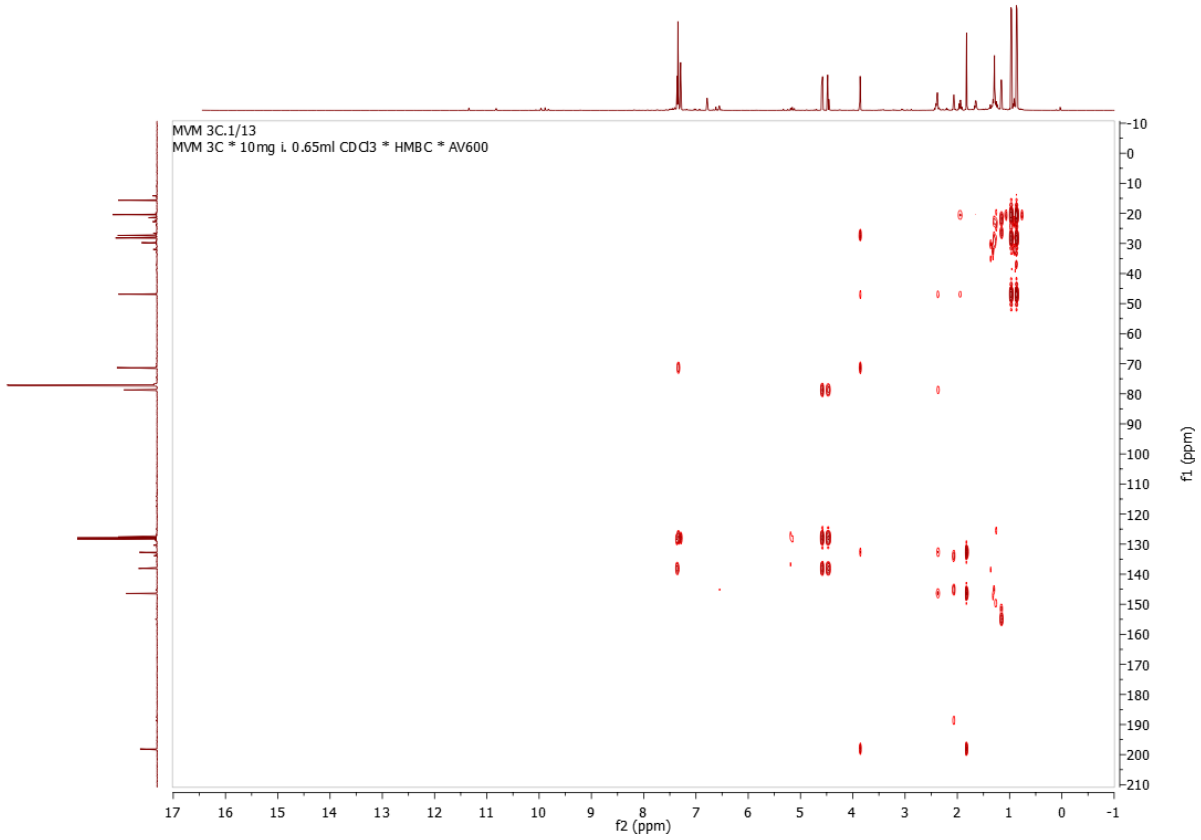

Figure S15: LC-MS spectrum for compound 10

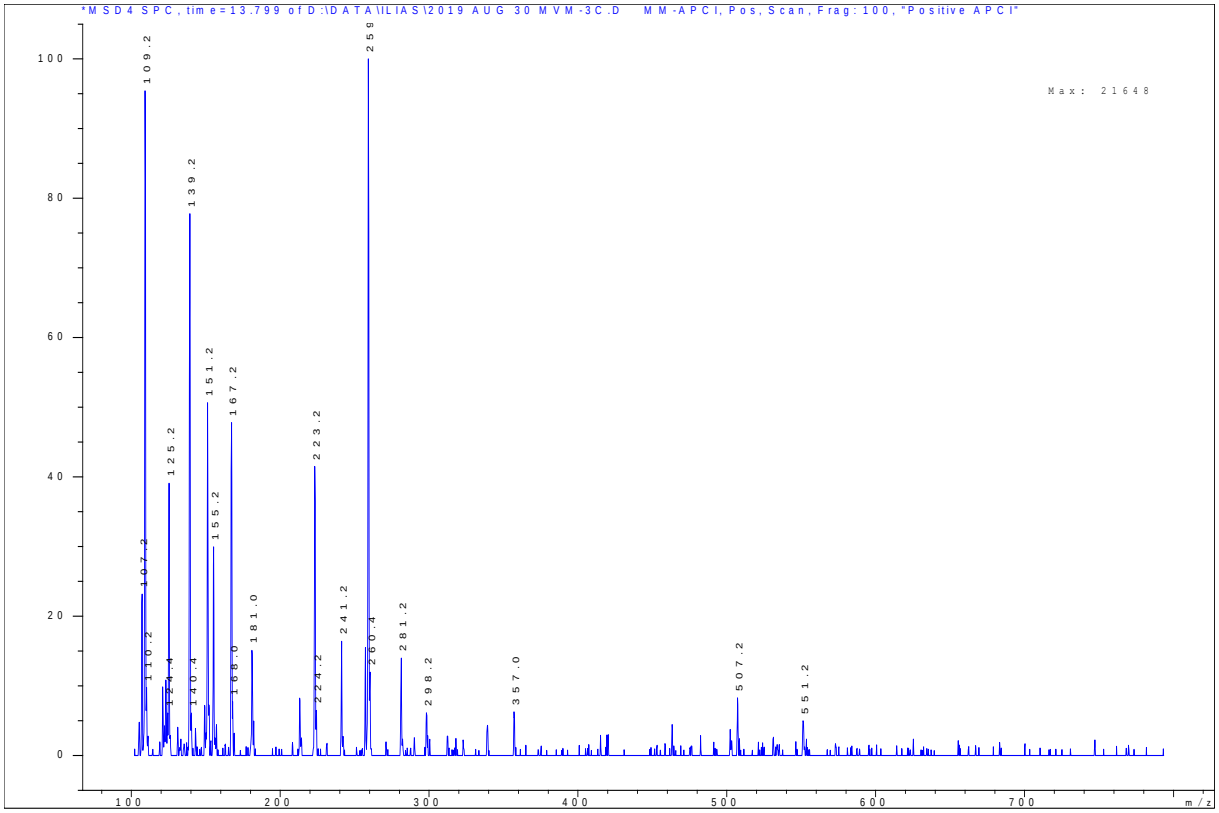

Figure S16: IR spectrum of compound 10

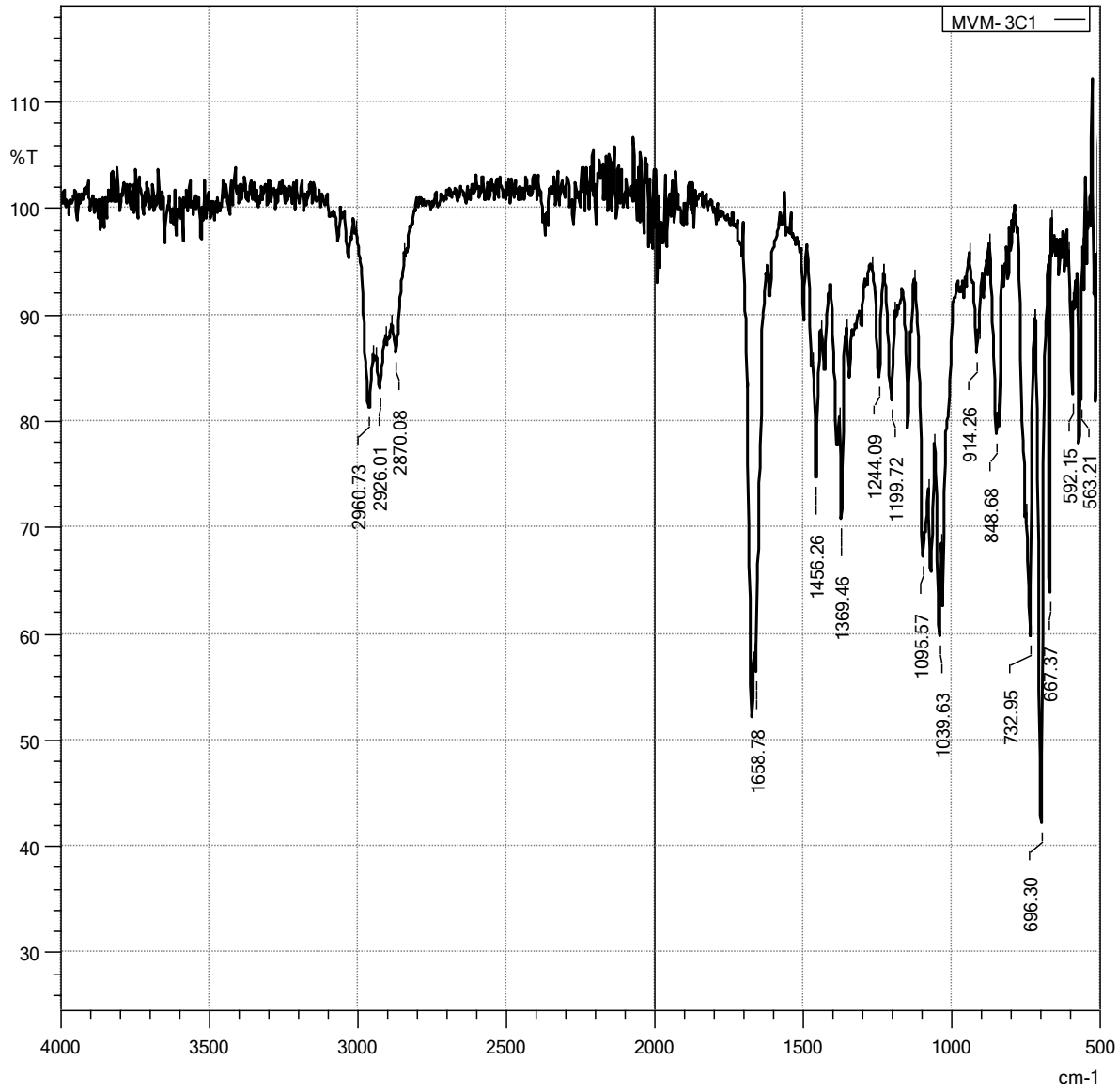

Table S17: ^{1}H and ^{13} C-NMR spectral Data assignment of compound 12 by 2D experiments

Position	^{13}C NMR, δ, ppm	^{1}H NMR, δ, ppm	HMBC
1	143.7		
2	146.4	6.93 1H	C-6, C-5
3	71.4	4.20 *t, 1H*	C-6, C-7′
4	46.4	1.19 *m, 1H*	C-10, C-9, C-8
5	20.1	1.55 *m* 1H 1.89 *m*,1H	C-5, C-4, C-3, C-1
6	22.7	2.53 *m,* 1H 2.03 *m,* 1H	C-7, C-5, C-4, C-2, C-1
7	194.7	9.54 *s,* 1H	C-5, C-2, C-1
8	28	1.89 *m,* 1H	C-4, C-3
9	21.1*	1.02 *d,* 3H	C-10, C-8, C-4
10	21.0*	1.02 *d,* 3H	C-9, C-8, C-4
1′	138.6		
2′/6′	128.4	7.38 *d J = 4.8Hz*	C-7′, C-4′, C-3′/5′, C-1′
3′/5′	127.6	7.32 *m*	C-2′/6′, C-1′
4′	127.7	7.34 *m*	C-3′, C-2′
7′	71.5	4.76 *d* J=11.5 *Hz*/ 4.64 *d* J=11.5 *Hz*	C-3, C-2′/6′, C-1′

Figure S18: ^{1}H-NMR spectrum of compound 12

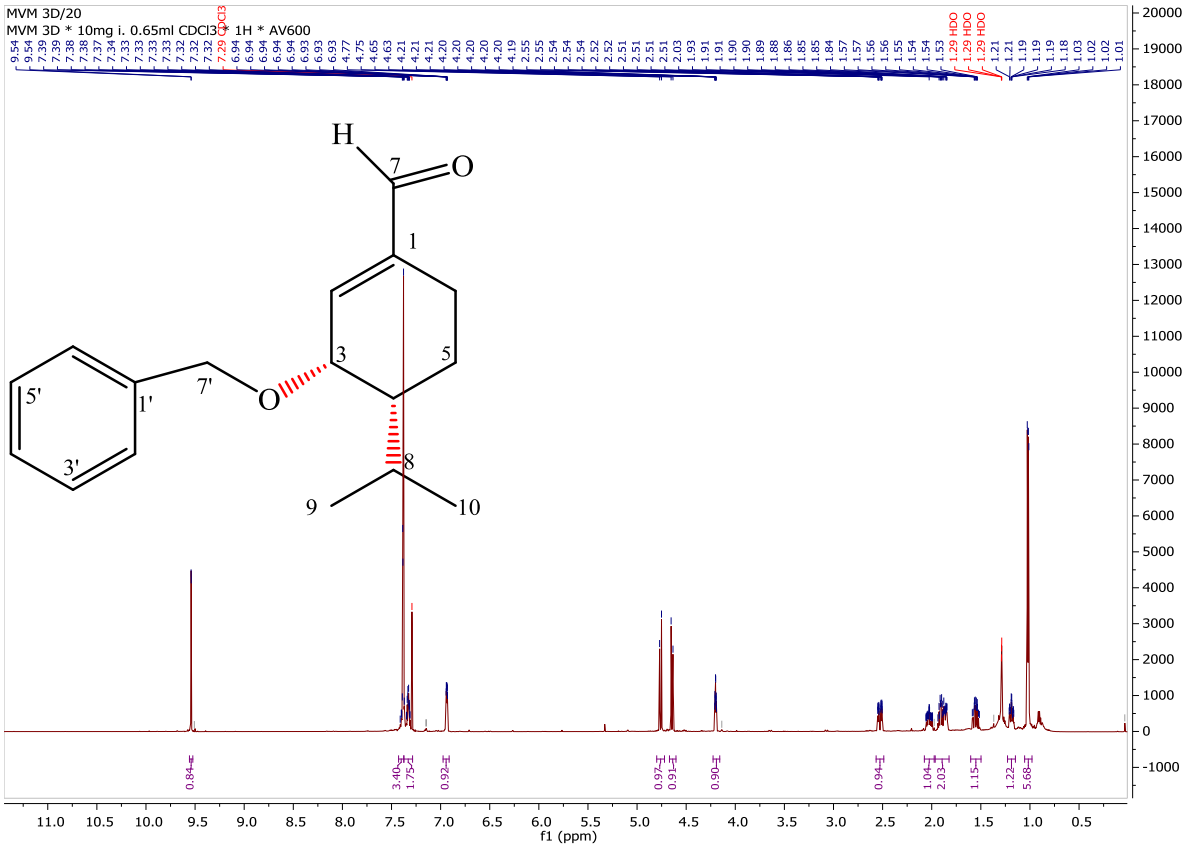

Figure S19: ^{13}C-NMR spectrumof compound 12

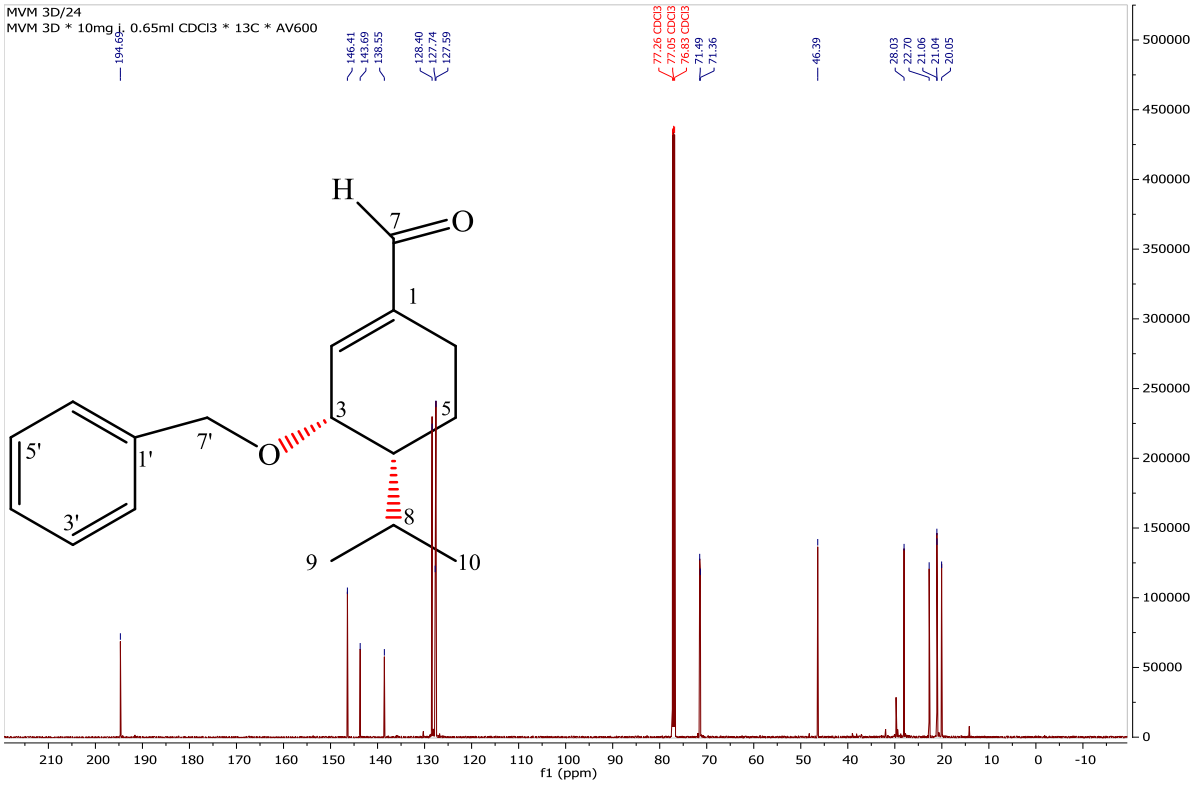

Figure S20: COSY spectrum of compound 12

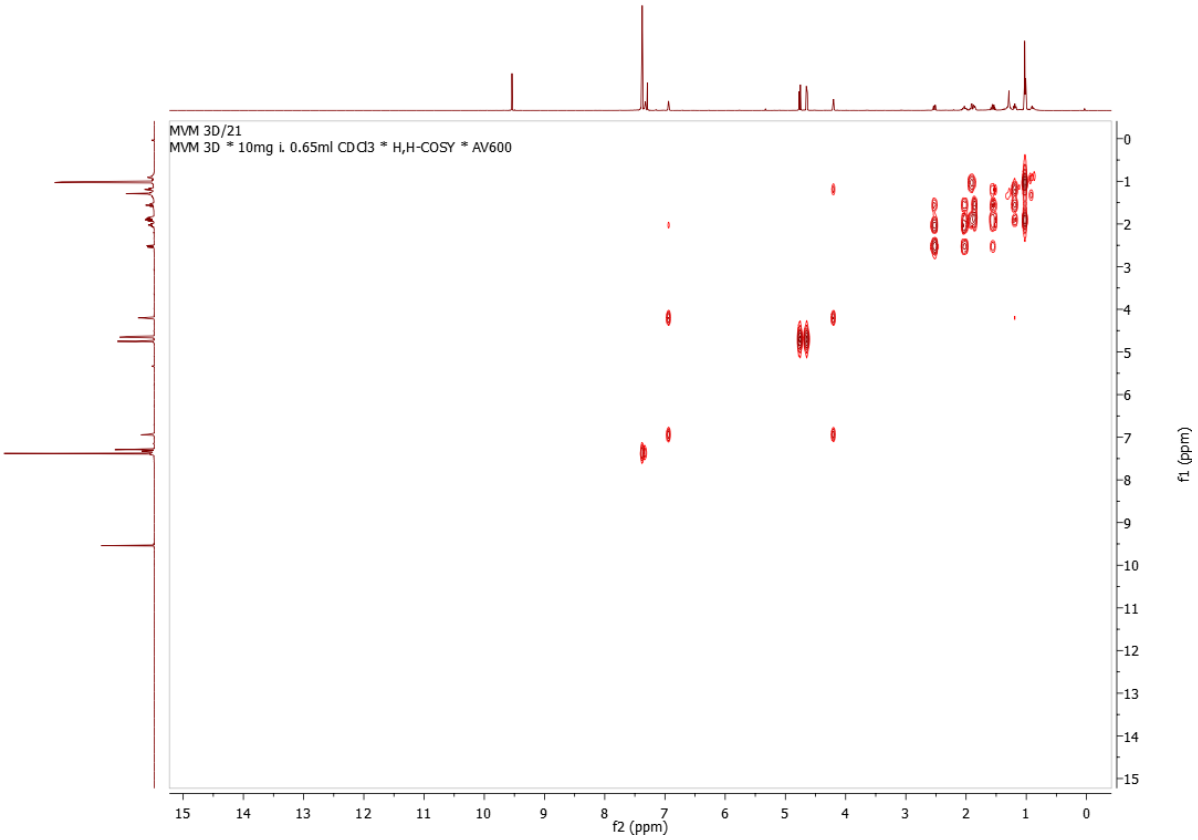

Figure S21: HSQC spectrum of compound 12

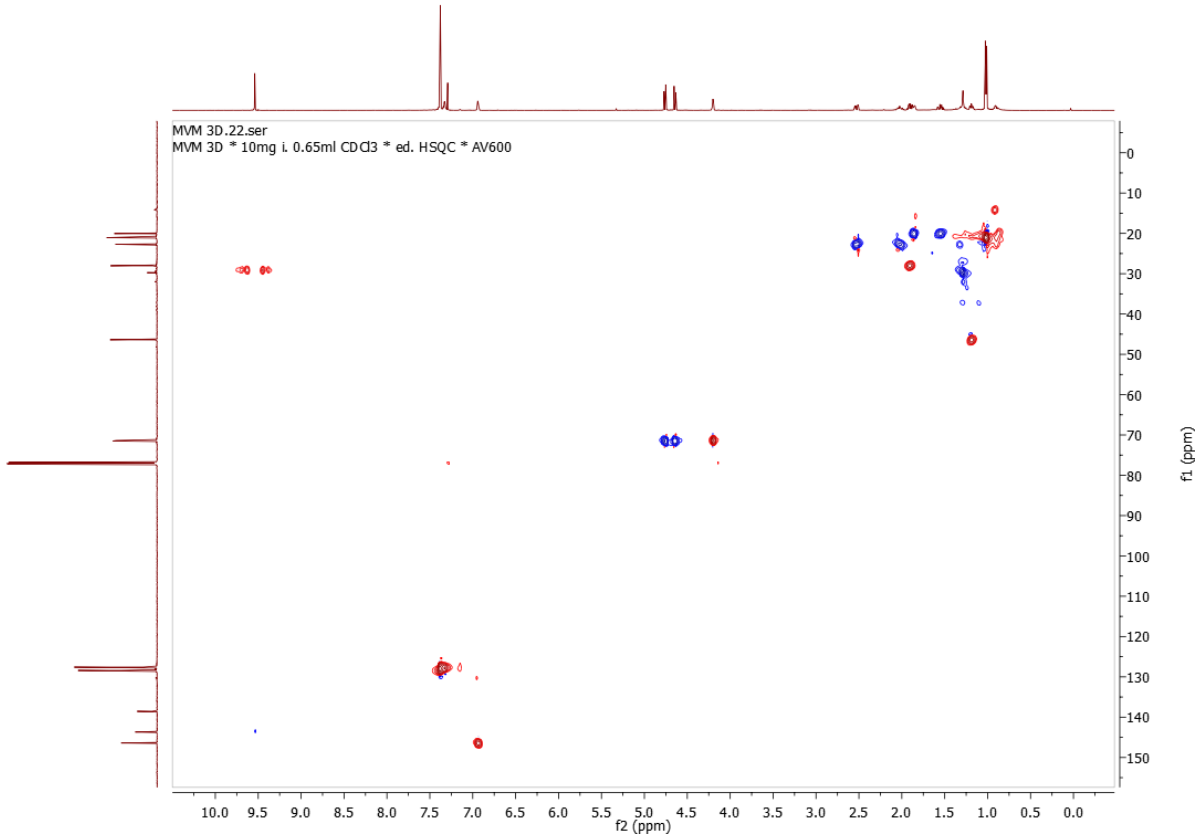

Figure S22: : HMBC spectrum of compound 12

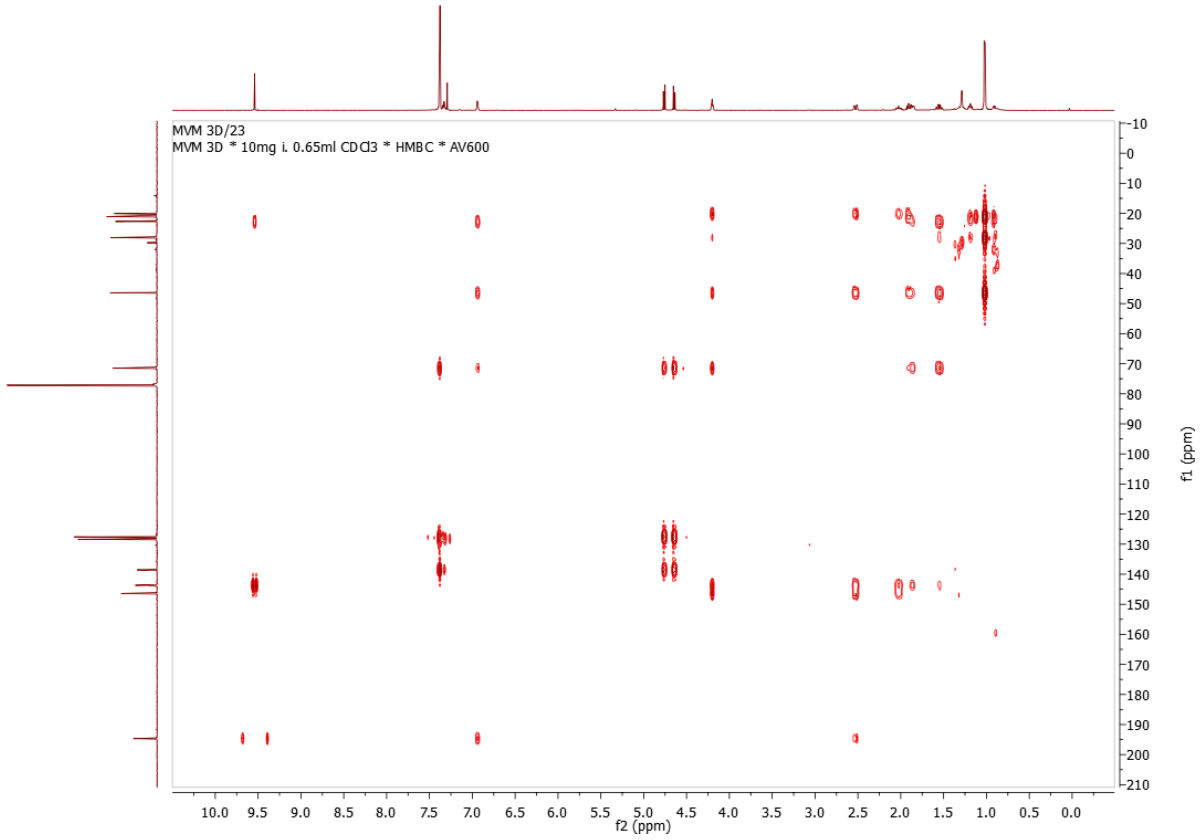

Figure S23: IR spectrum of compound 12

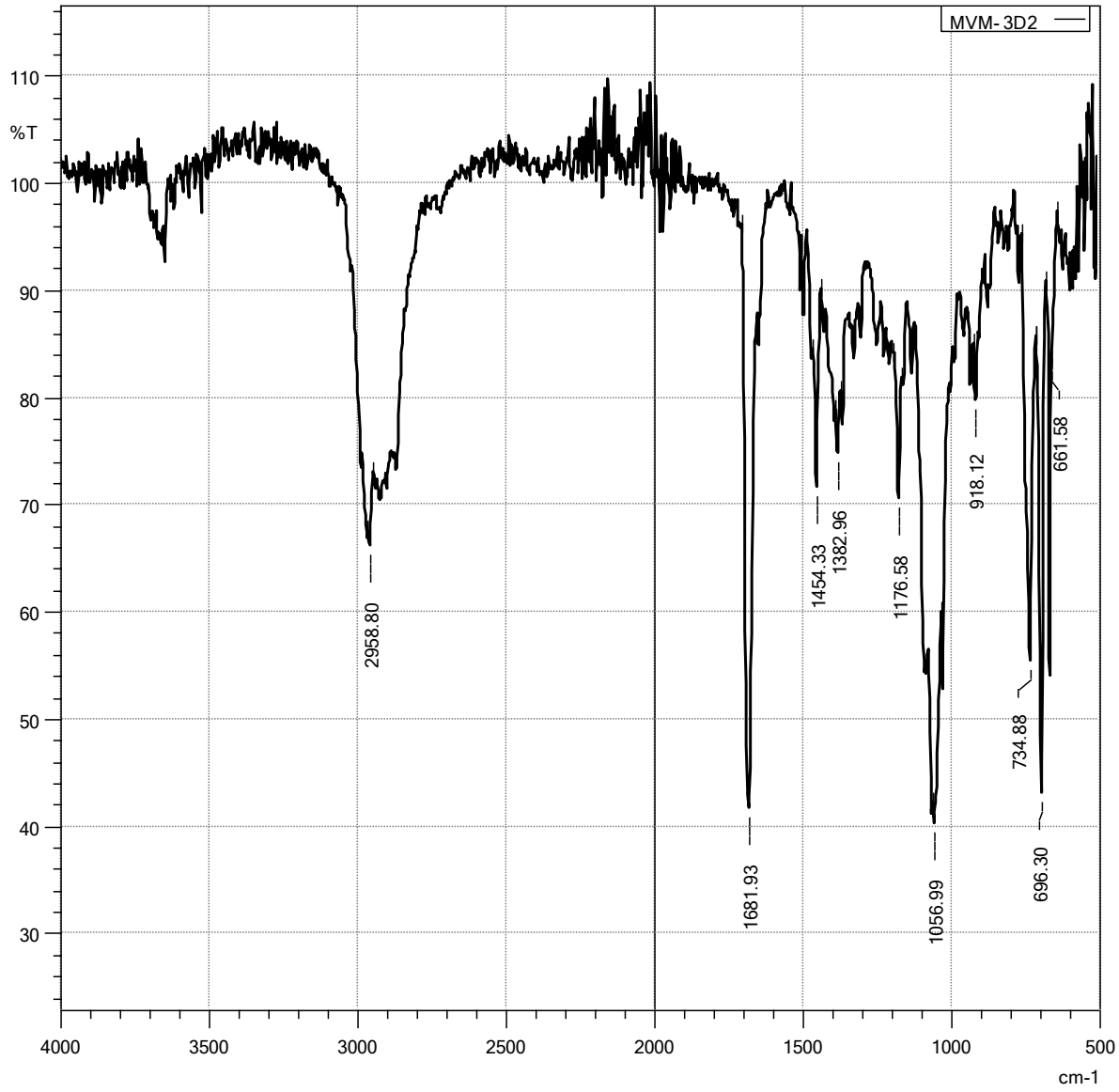

Figure S24: LC-MS spectrum for compound 12