

## Supplementary information

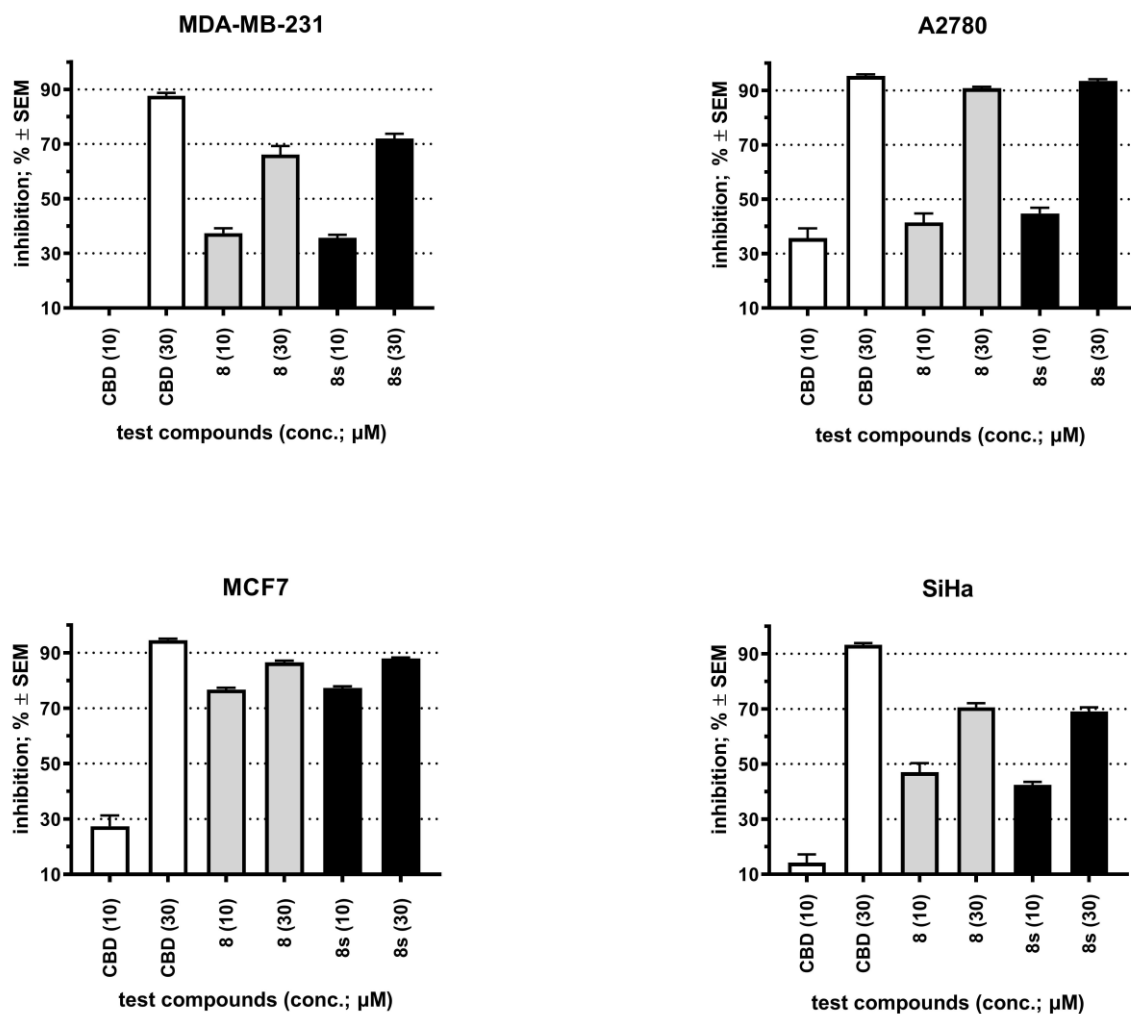
### Mannich-Type Modifications Of (-)-Cannabidiol And (-)-Cannabigerol Leading To New, Bioactive Derivatives

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## 1. Antiproliferative effect of the salt derivative compound **8s**



**Figure S1.** Antiproliferative properties of compound **8s** compared to CBD and its free base derivative (**8**) (10 and 30 μM). Inhibition values less than 10% are considered negligible and not presented for clarity.

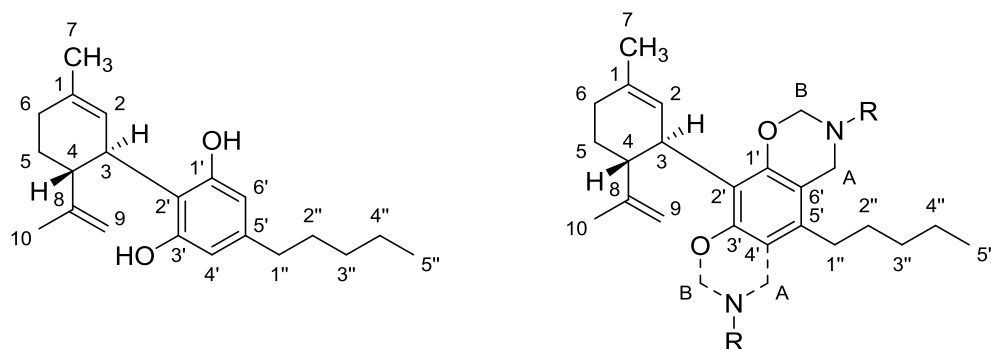
## 2. Antibacterial data against Gram-positive bacteria

**Table S1.** Antibacterial effects of CBD, CBG and their derivatives against Gram-positive bacteria

	CBD	8	8s	9	10/12/13	11	CBG	16b/17a/ 18/21b	20
	(MIC, µg/ml)								
<i>Bacillus subtilis</i>	4	>256	128	>256	>256	>256	2	>256	>256
MSSA	4	>256	128	>256	>256	>256	4	>256	>256
MRSA	4	>256	128	>256	>256	>256	4	>256	>256
<i>Staphylococcus epidermidis</i> biofilm forming	8	>256	128	>256	>256	>256	8	>256	>256
<i>Staphylococcus epidermidis</i> mecA	8	>256	128	>256	>256	>256	8	>256	>256
<i>Enterococcus faecalis</i> 29 212	2	2	2	8	>256	128	4	64	64
<i>Enterococcus faecalis</i> 15 376 VanA	4	>256	128	128	>256	>256	4	>256	128
<i>Enterococcus faecalis</i> 51299 VanB	4	2	2	8	>256	128	4	64	128

MIC: Minimum Inhibitory Concentration; MSSA: Methicillin Sensitive *Staphylococcus aureus*; MRSA: Methicillin Resistant *Staphylococcus aureus*; mecA: mecA gene expression; vanA: vanA gene positive; vanB: vanB gene positive.

### 3. NMR data of CBD and its derivatives

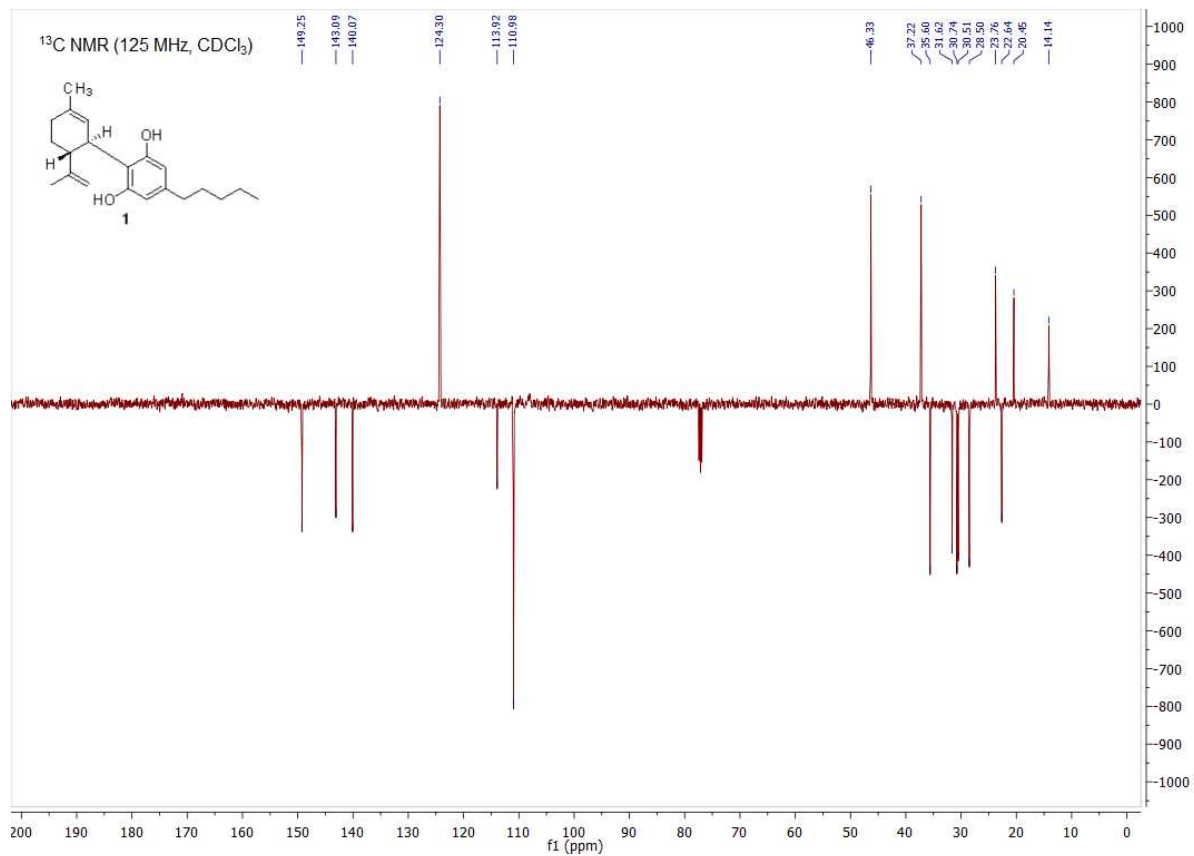
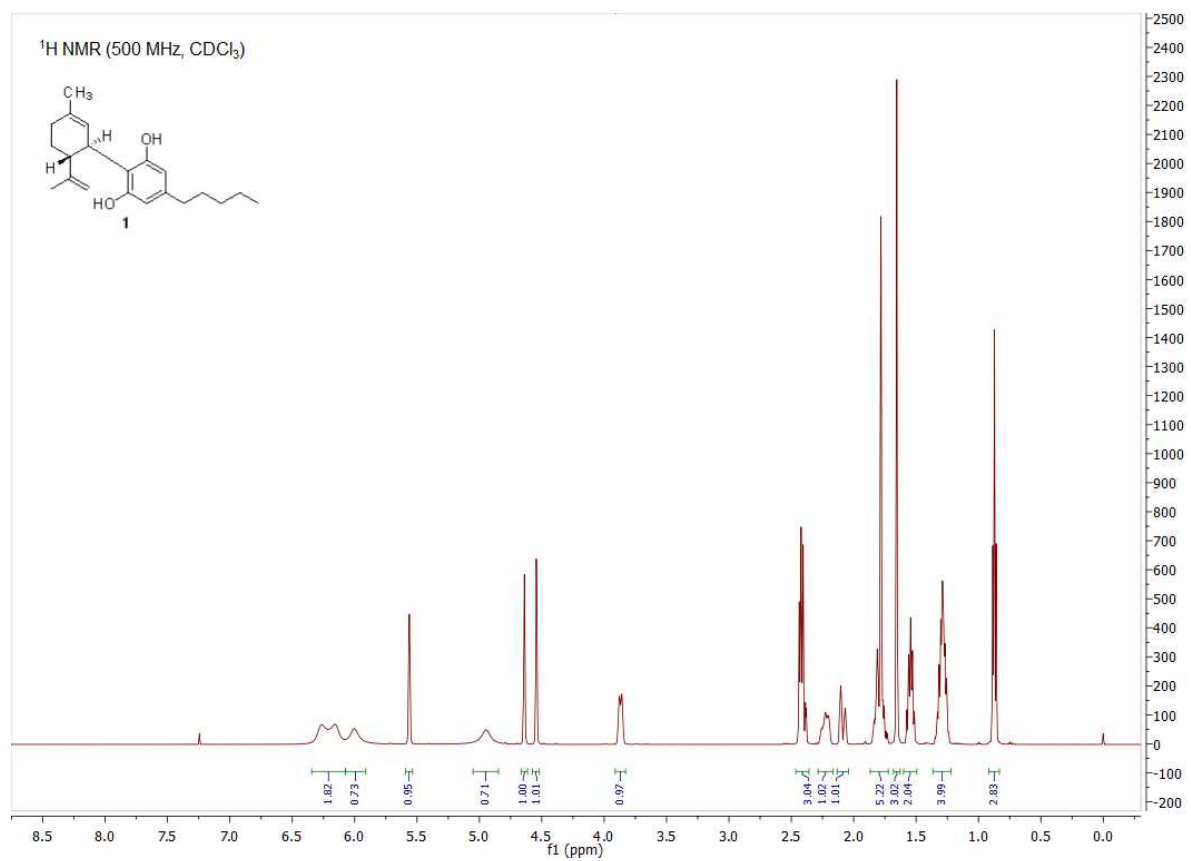


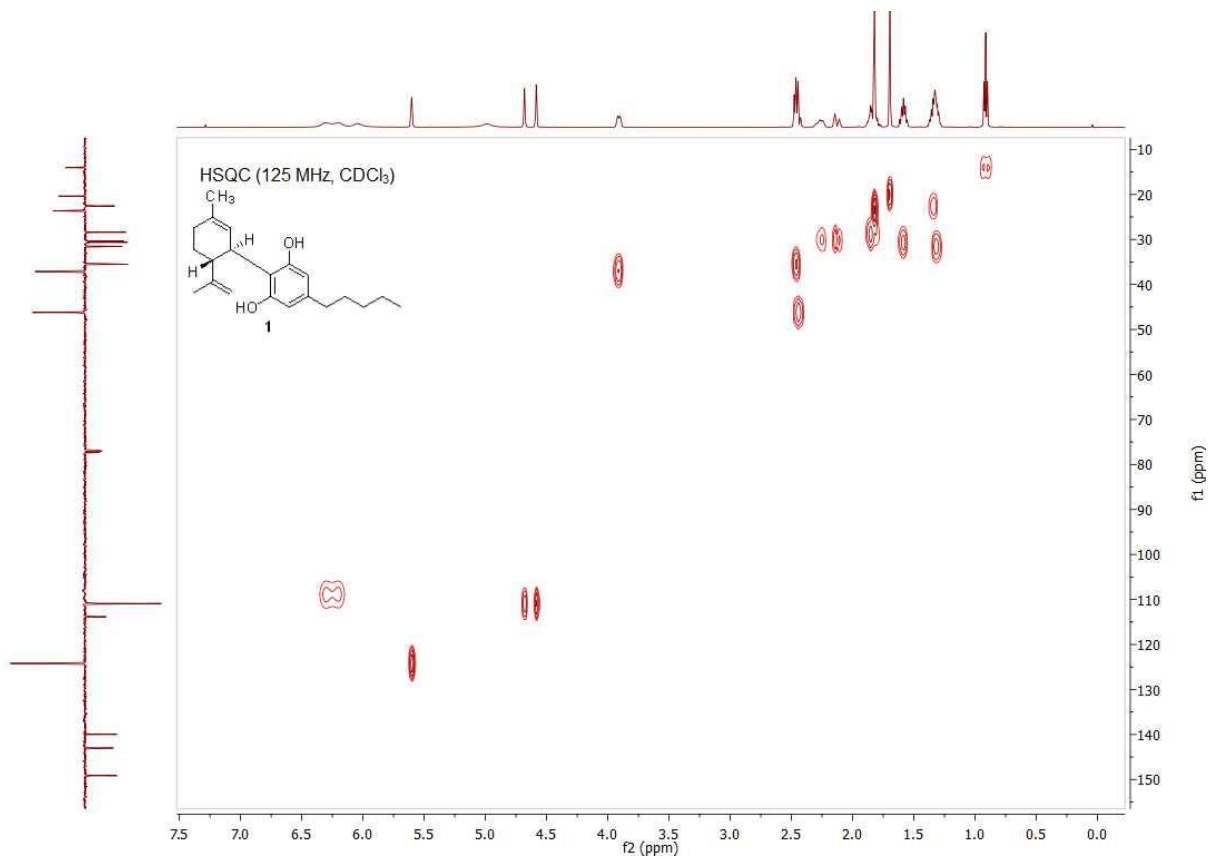
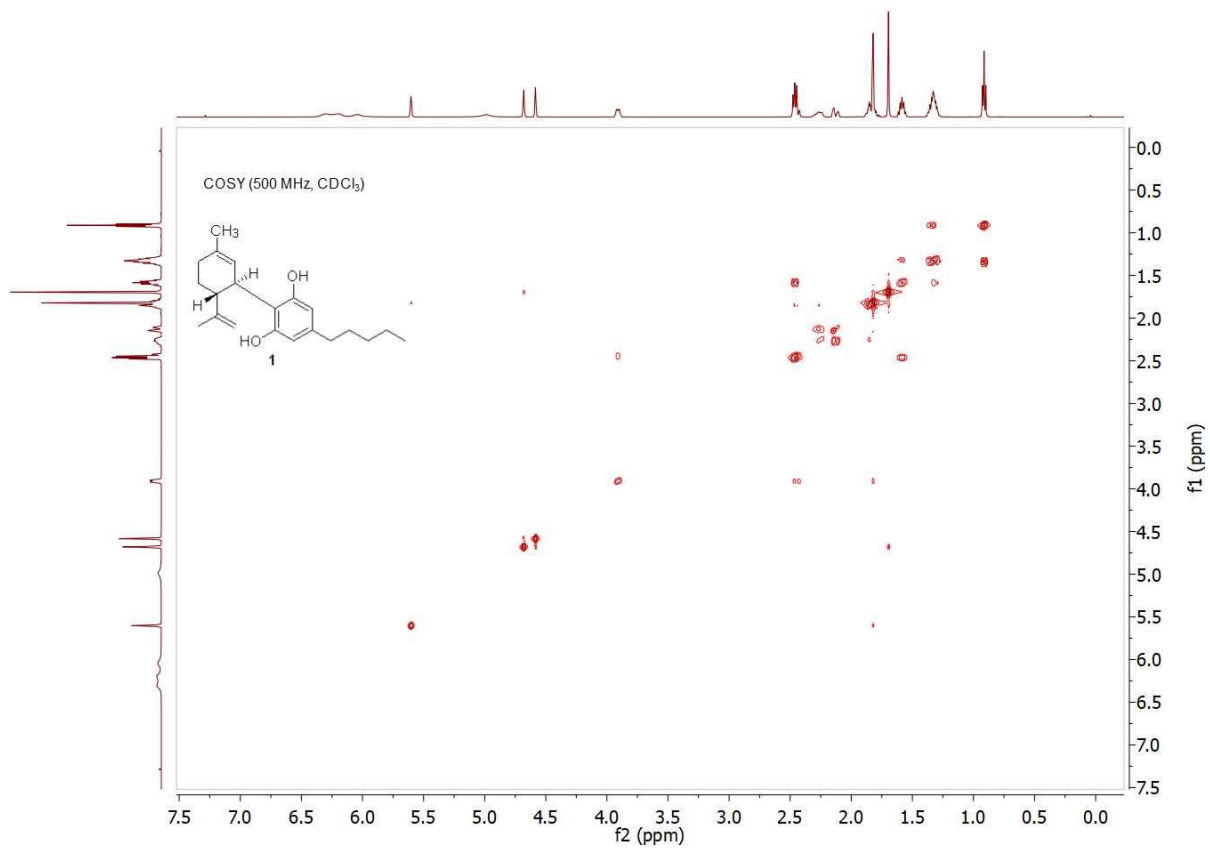
**Figure S2.** Numbering of CBD and its derivatives.

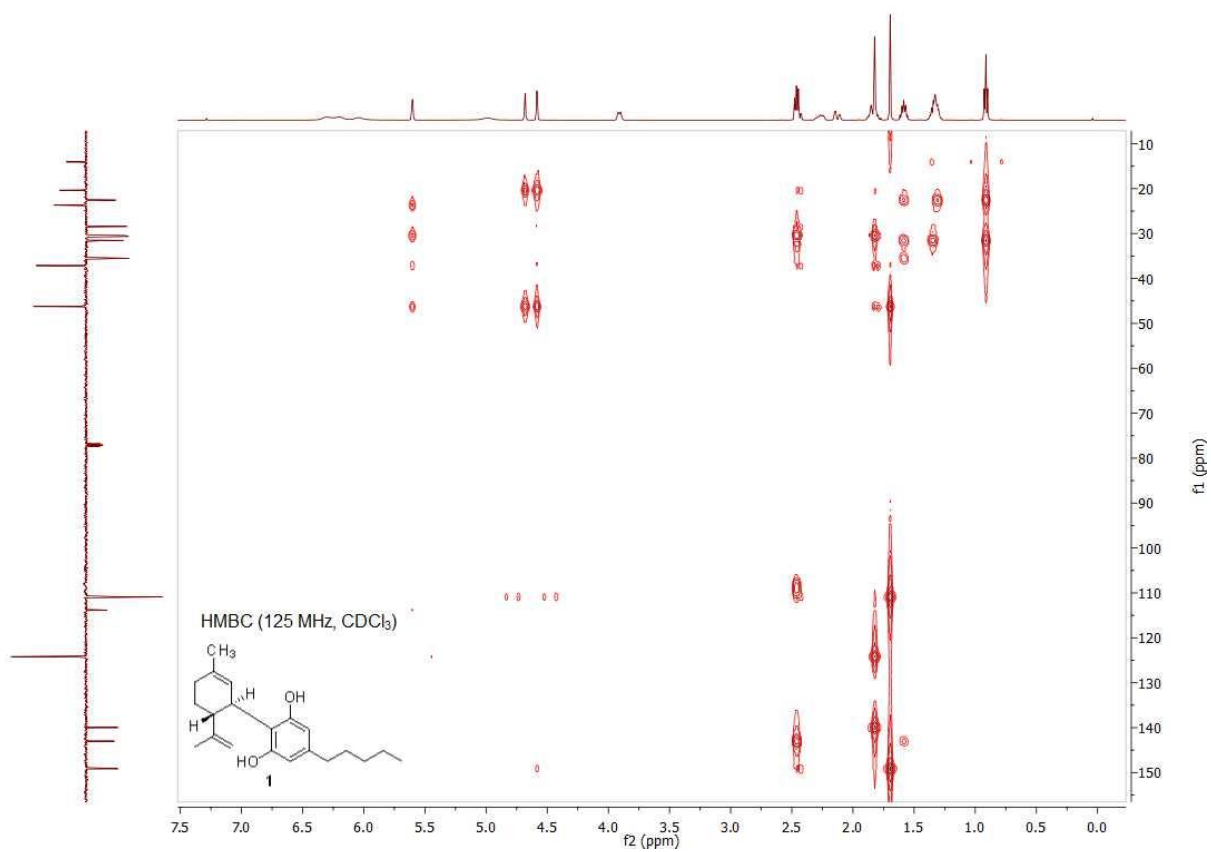
#### NMR data of cannabidiol:

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 6.34-6.09 (m, 2H, aromatic CH), 6.00 (bs, 1H, OH), 5.56 (m, 1H, H-2 CH), 4.95 (bs, 1H, OH), 4.64 (m, 1H, H-9  $\text{CH}_2\text{a}$ ), 4.54 (m, 1H, H-9  $\text{CH}_2\text{b}$ ), 3.90-3.83 (m, 1H, H-3 CH), 2.46-2.36 (m, 3H, H-1''  $\text{CH}_2$  and H-4 CH), 2.29-2.17 (m, 1H, H-6  $\text{CH}_2\text{a}$ ), 2.13-2.04 (m, 1H, H-6  $\text{CH}_2\text{b}$ ), 1.86-1.72 (m, 5H, H-5  $\text{CH}_2$  and H-7  $\text{CH}_3$ ), 1.66 (s, 3H, H-10  $\text{CH}_3$ ), 1.59-1.50 (m, 2H, H-2''  $\text{CH}_2$ ), 1.35-1.22 (m, 4H, H-3'' and H-4''  $\text{CH}_2$ ), 0.87 (t, 3H,  $J = 6.9$  Hz, H-5''  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 149.3 (1C, C-8, quat.), 143.1 (1C, C-3', quat.), 140.1 (1C, C-1, quat.), 124.3 (1C, C-2, CH), 113.9 (1C, C-6', quat.), 111.0 (1C, C-9,  $\text{CH}_2$ ), 46.3 (1C, C-4, CH), 37.2 (1C, C-3, CH), 35.6 (1C, C-1'',  $\text{CH}_2$ ), 31.6 (1C, C-3'',  $\text{CH}_2$ ), 30.7 (1C, C-2'',  $\text{CH}_2$ ), 30.5 (1C, C-6,  $\text{CH}_2$ ), 28.5 (1C, C-5,  $\text{CH}_2$ ), 23.8 (1C, C-7,  $\text{CH}_3$ ), 22.6 (1C, C-4'',  $\text{CH}_2$ ), 20.5 (1C, C-10,  $\text{CH}_3$ ), 14.1 (1C, C-5'',  $\text{CH}_3$ ).

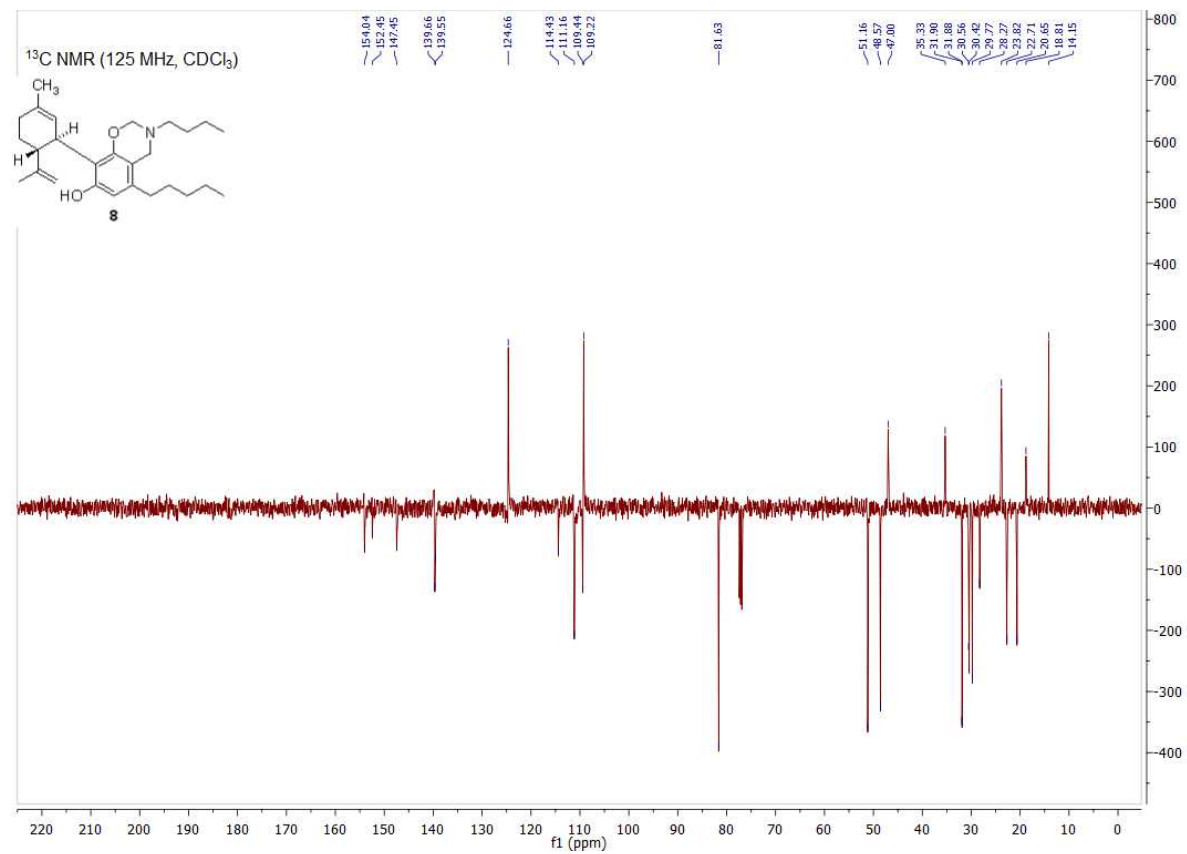
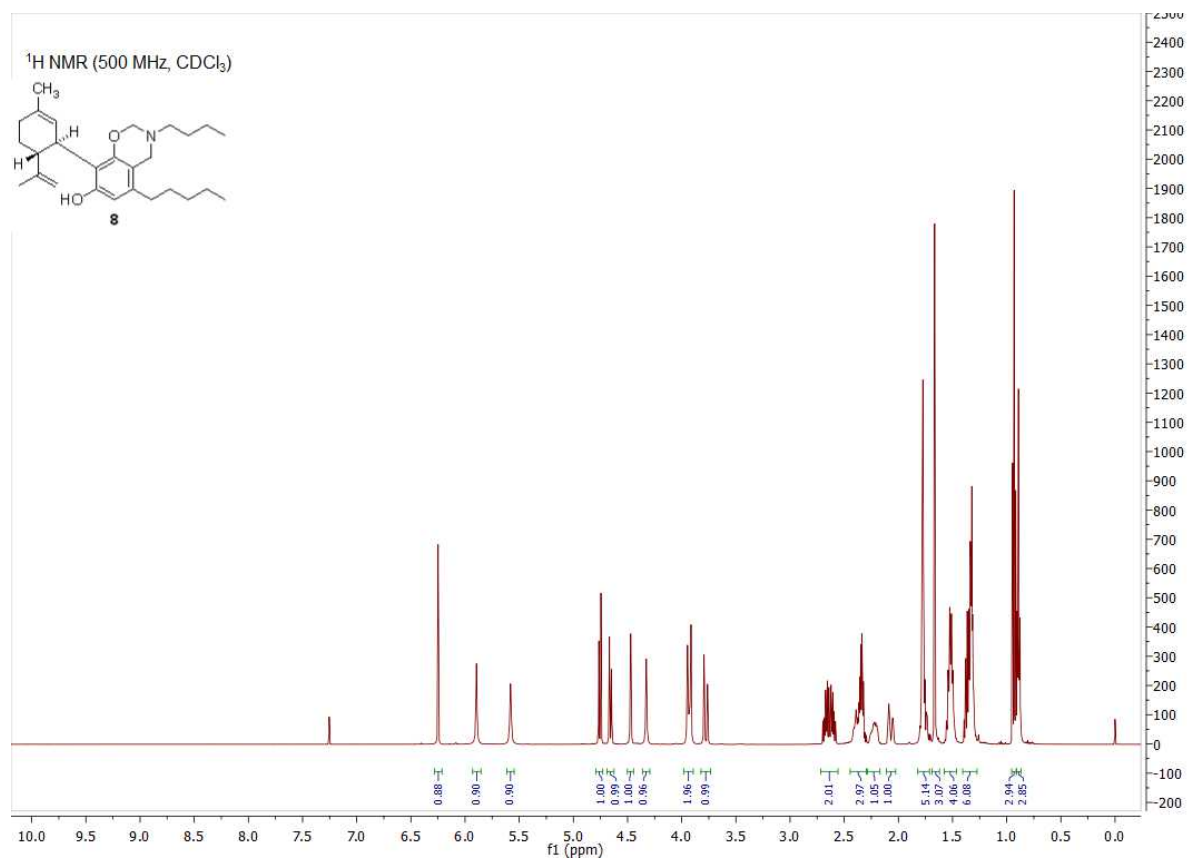
# NMR spectra of CBD

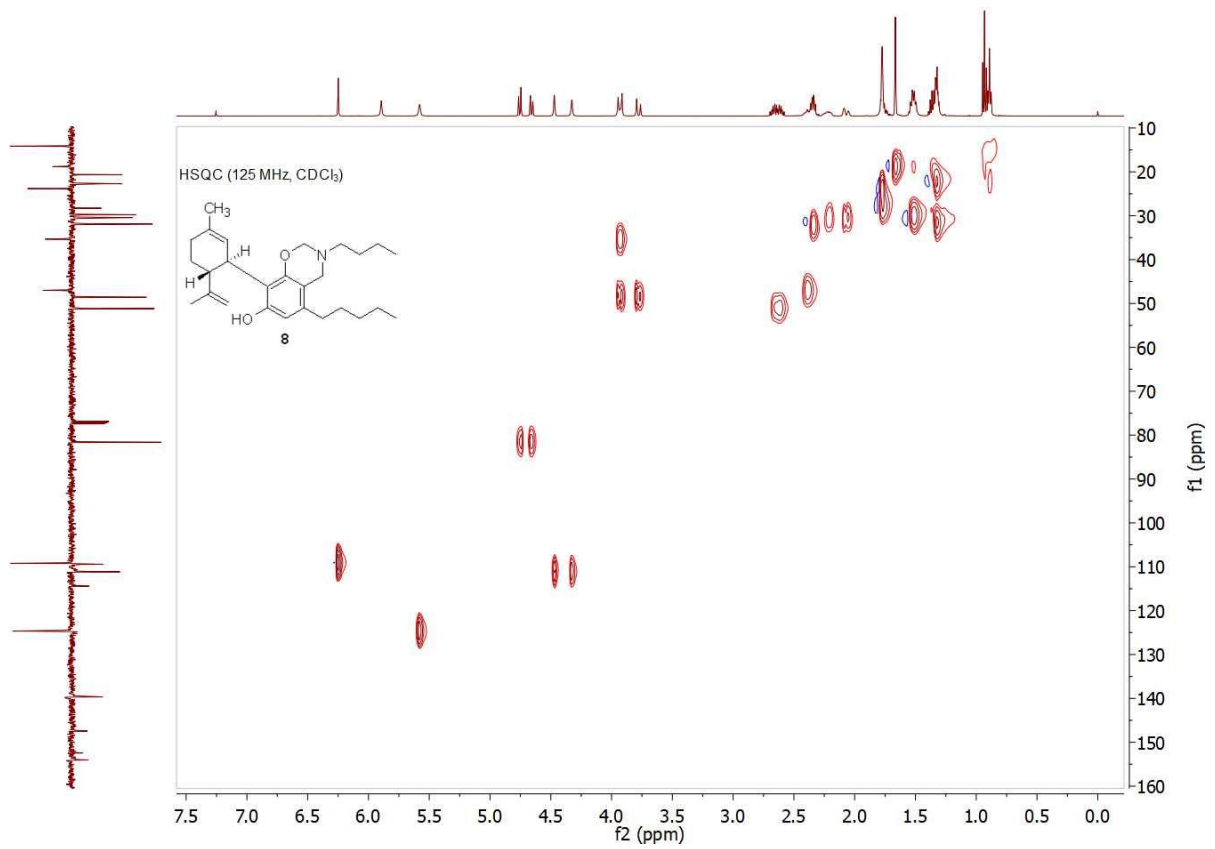
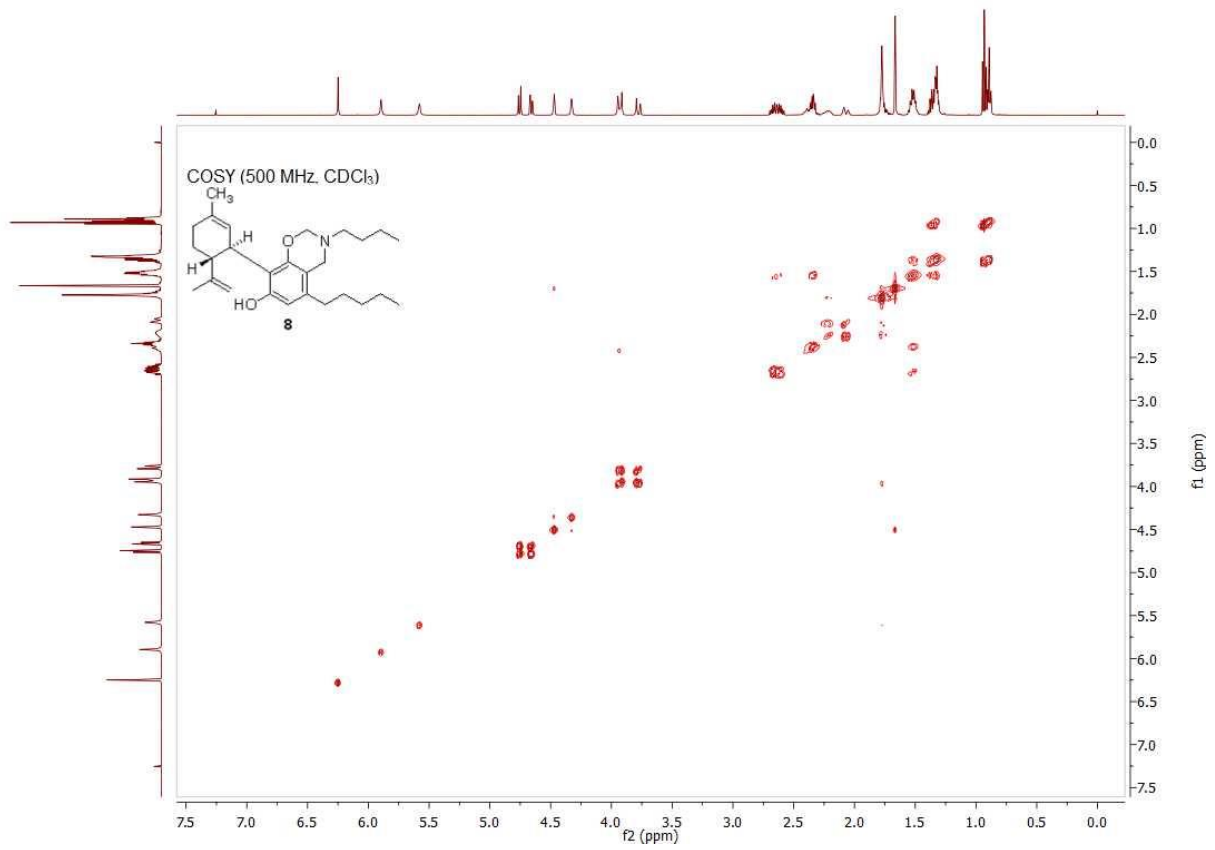




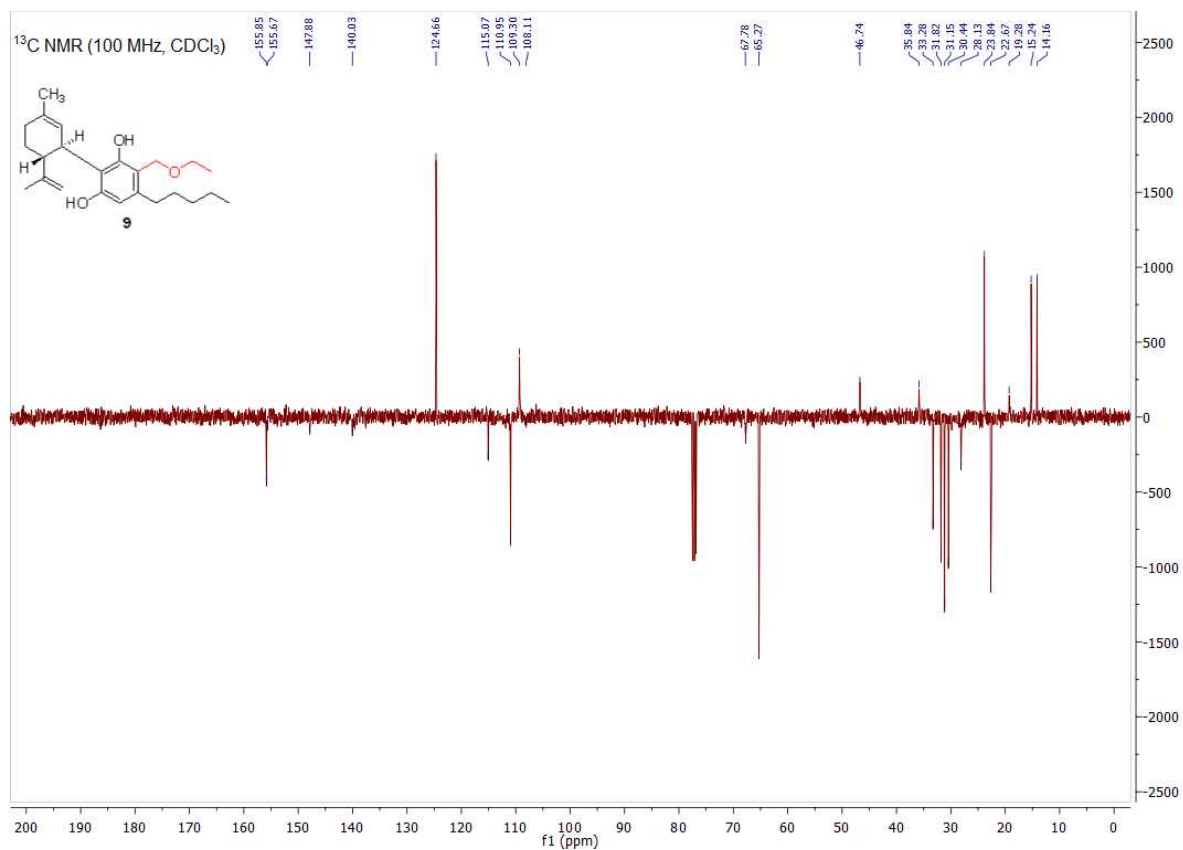
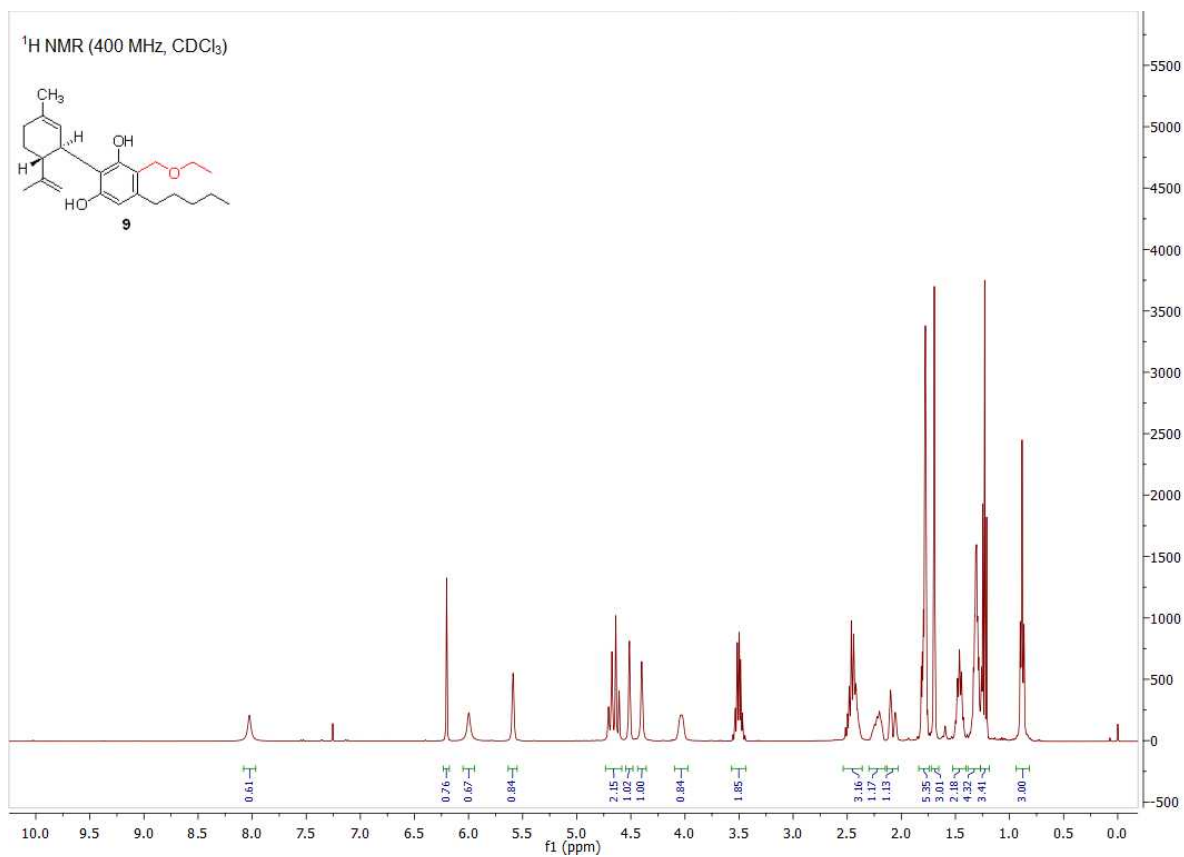


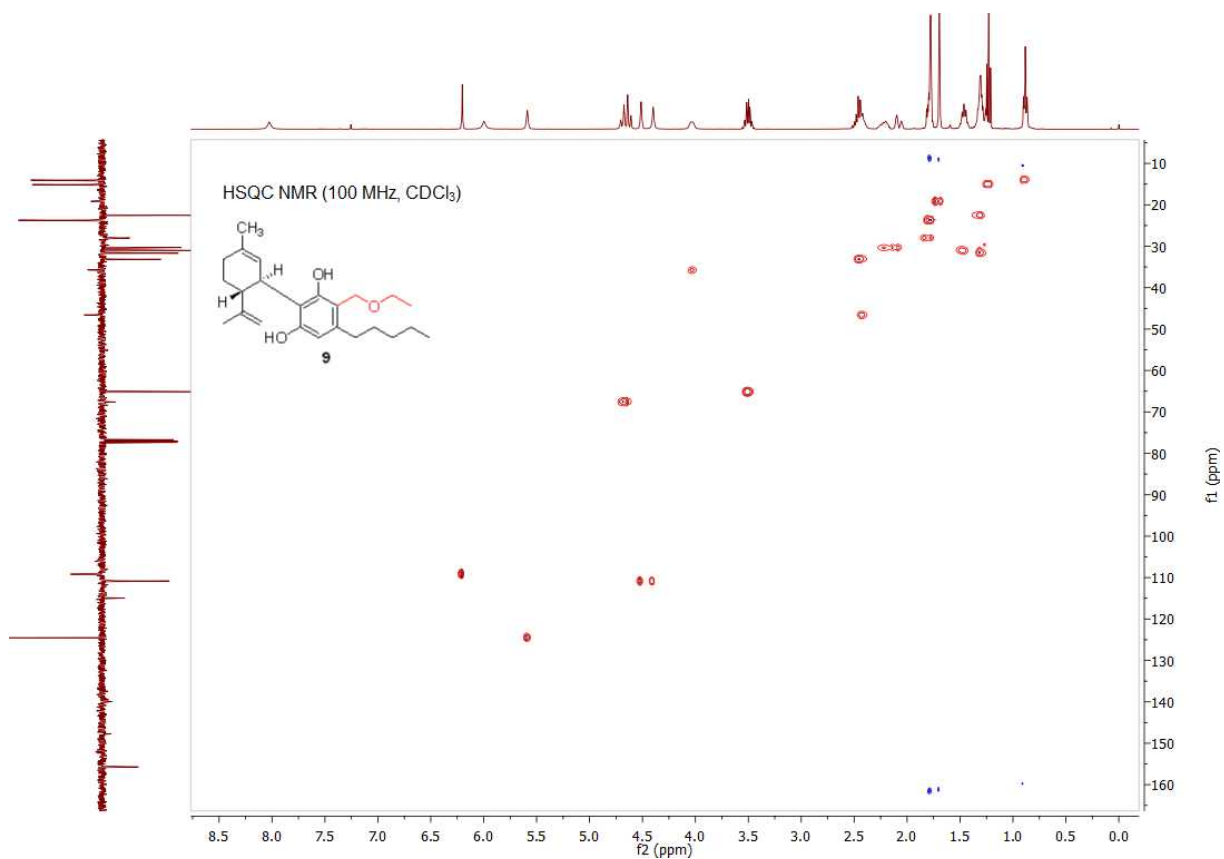
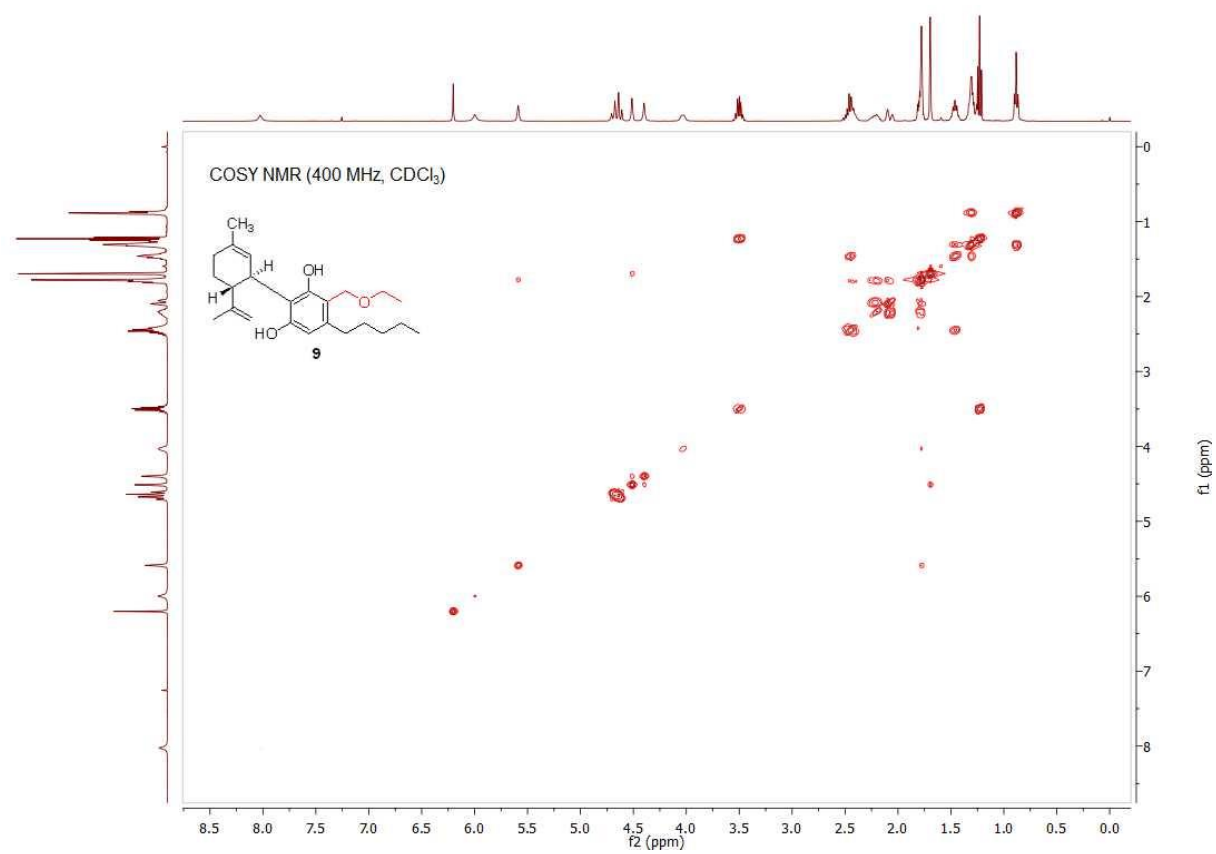
# NMR spectra of compound 8



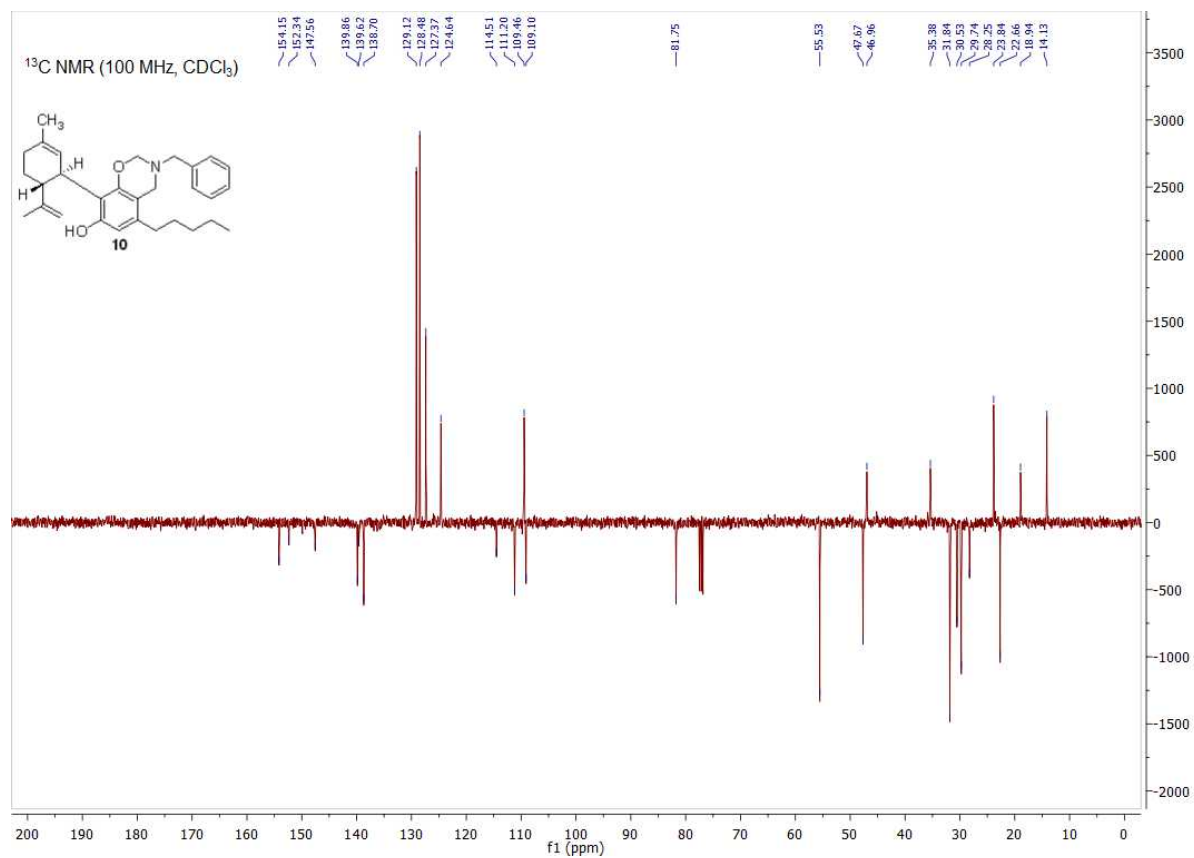
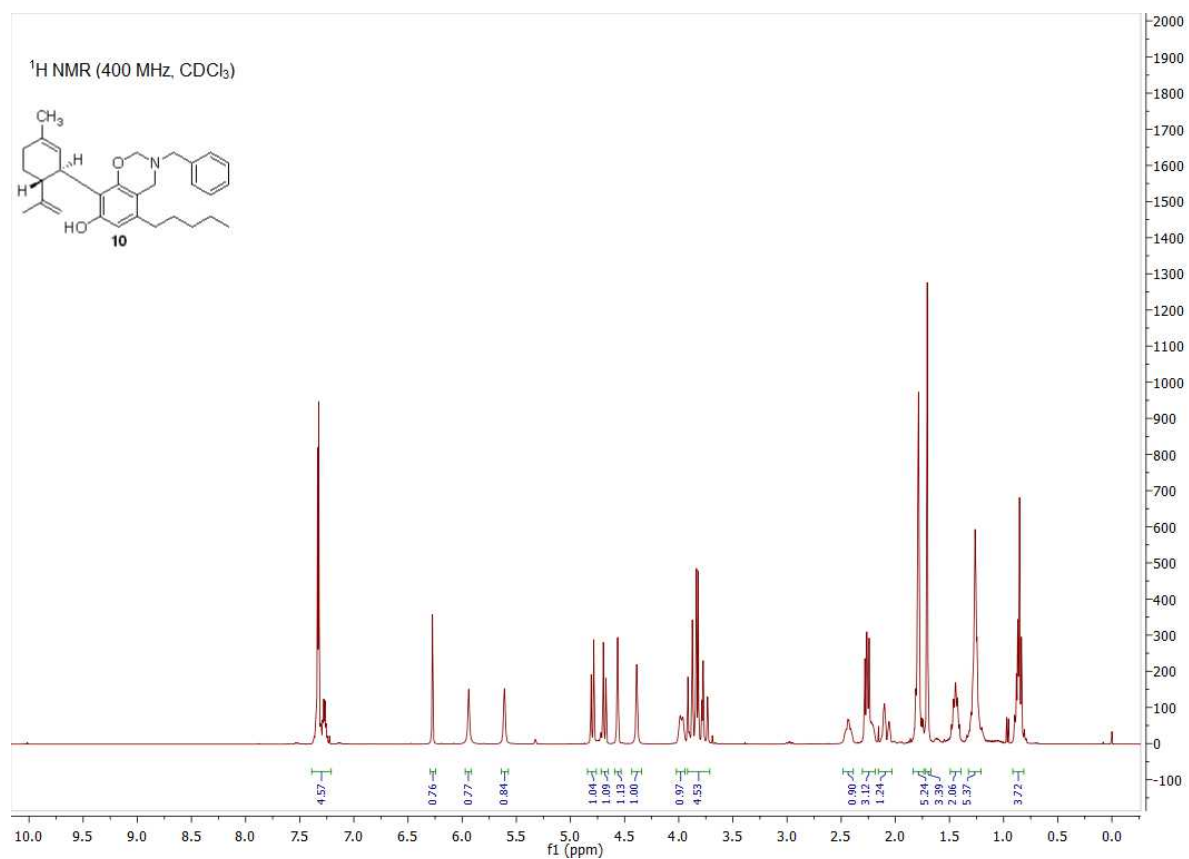


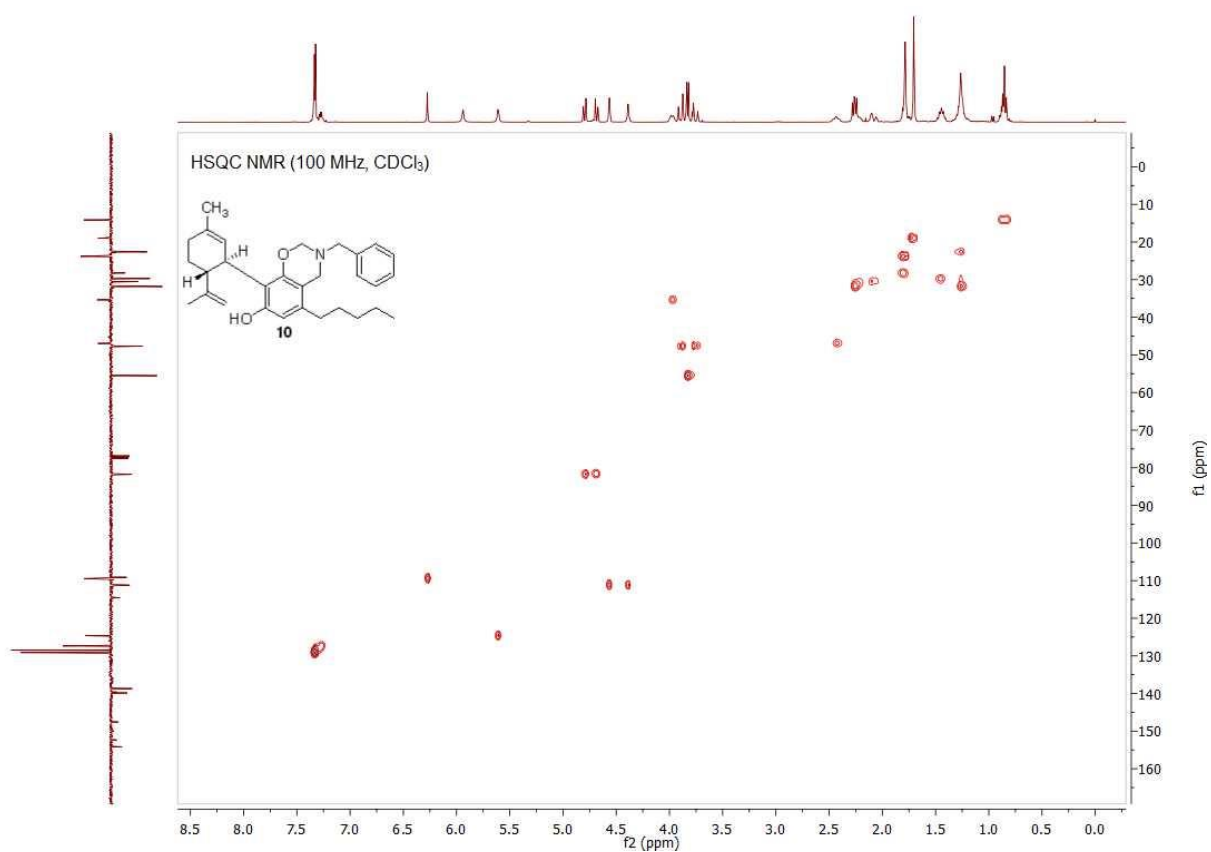
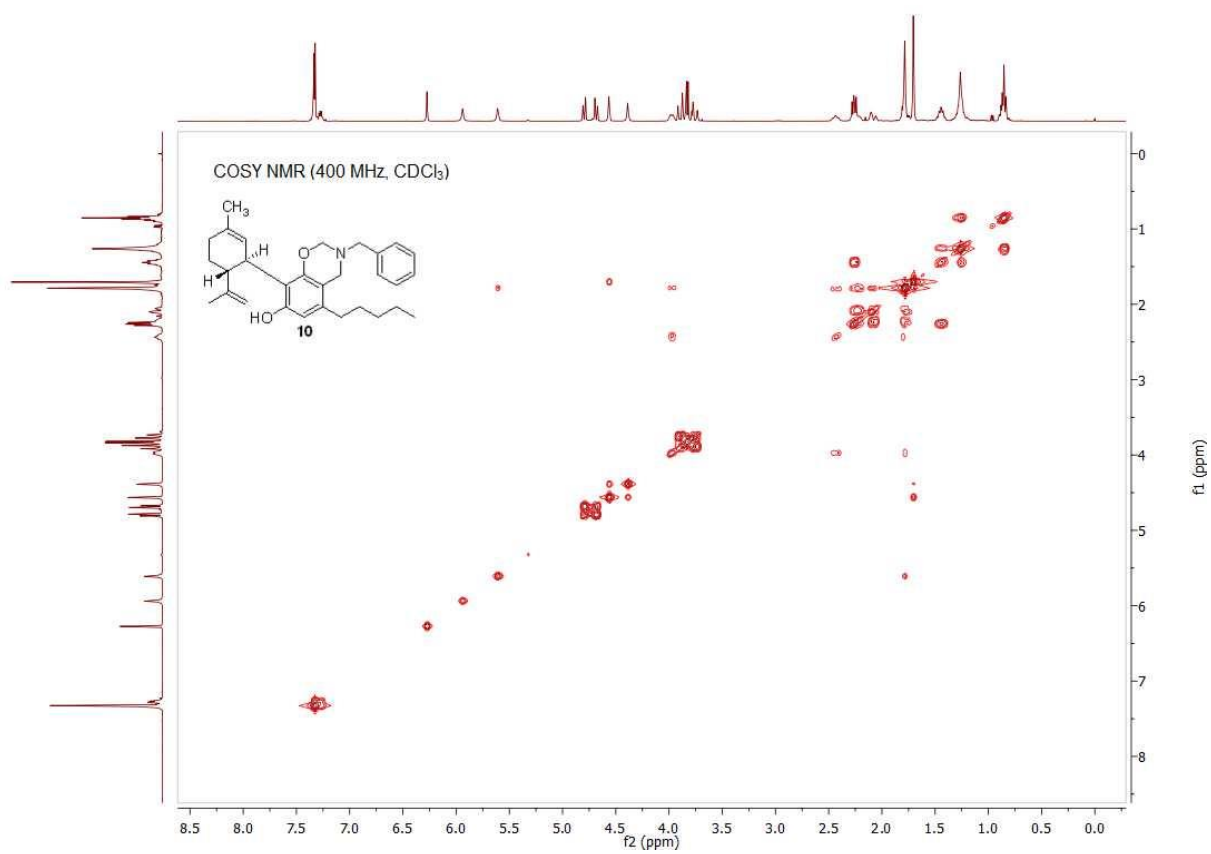
# NMR spectra of compound 9



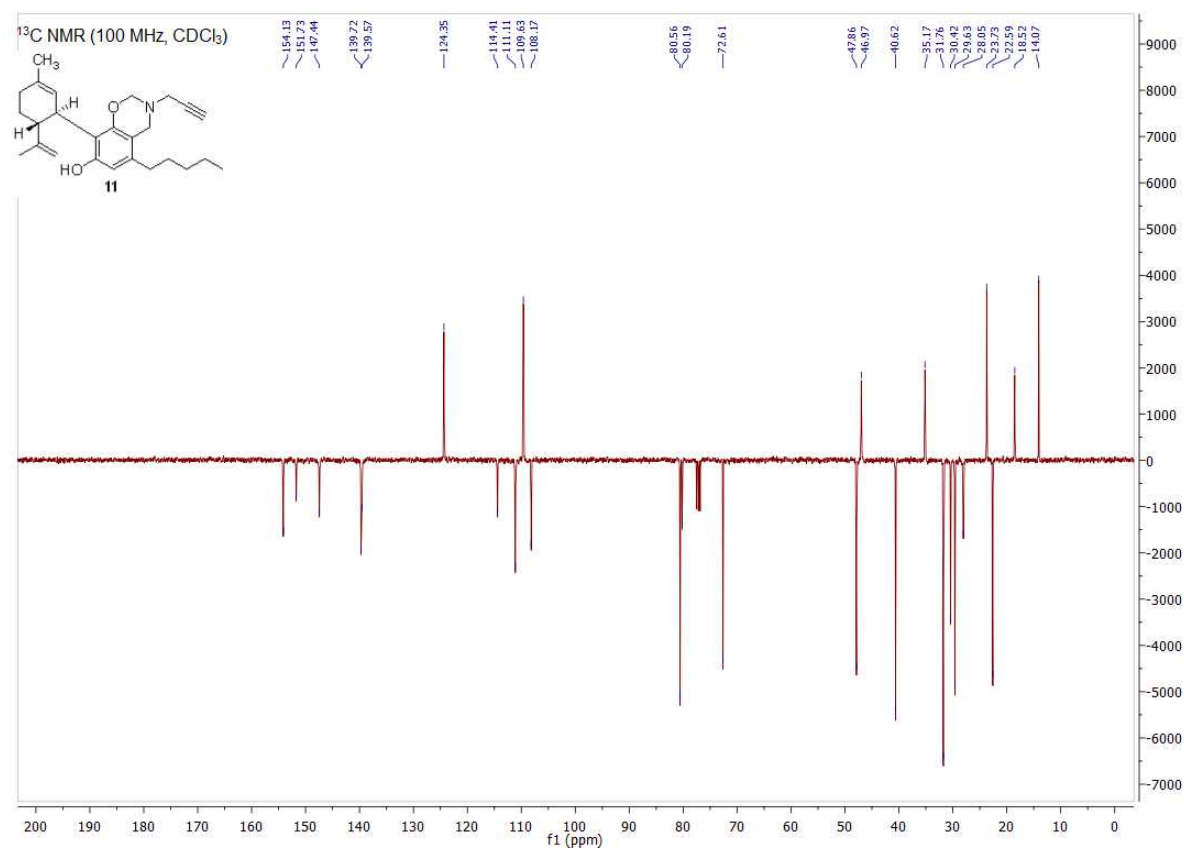
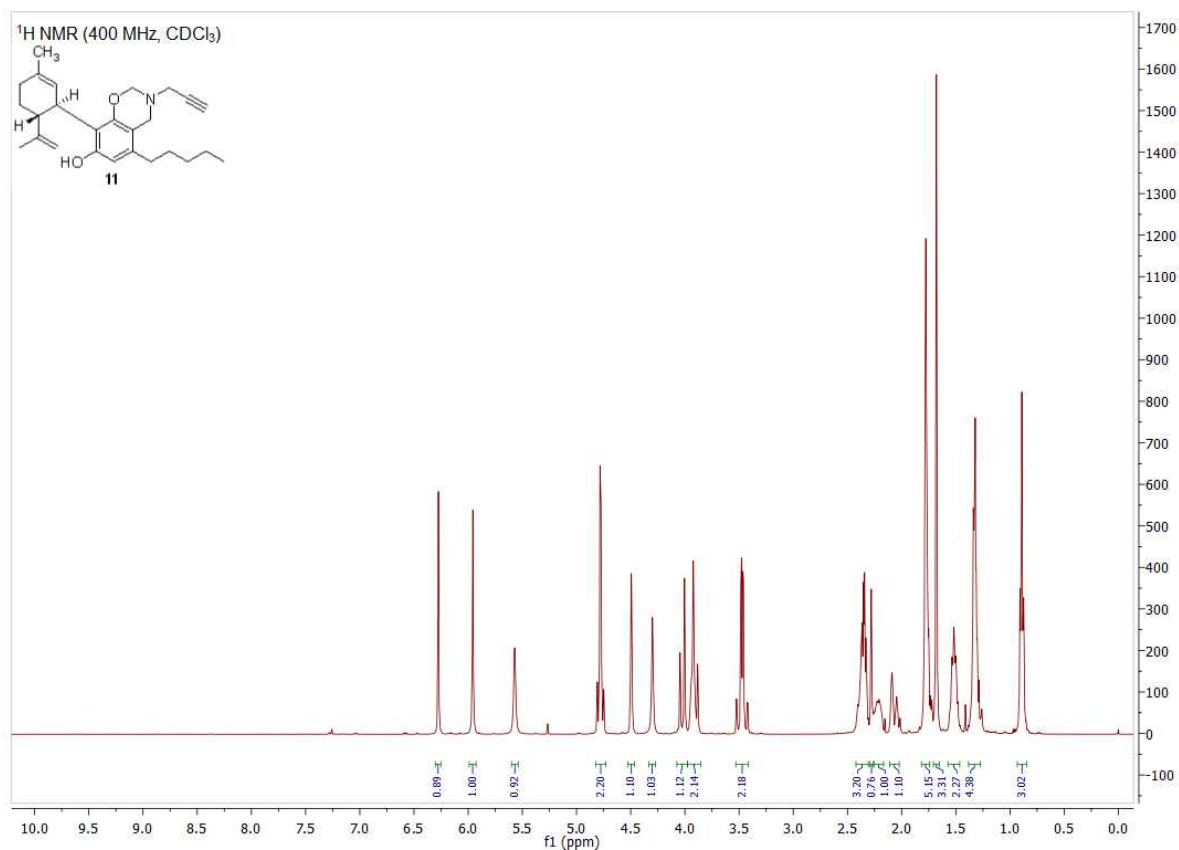


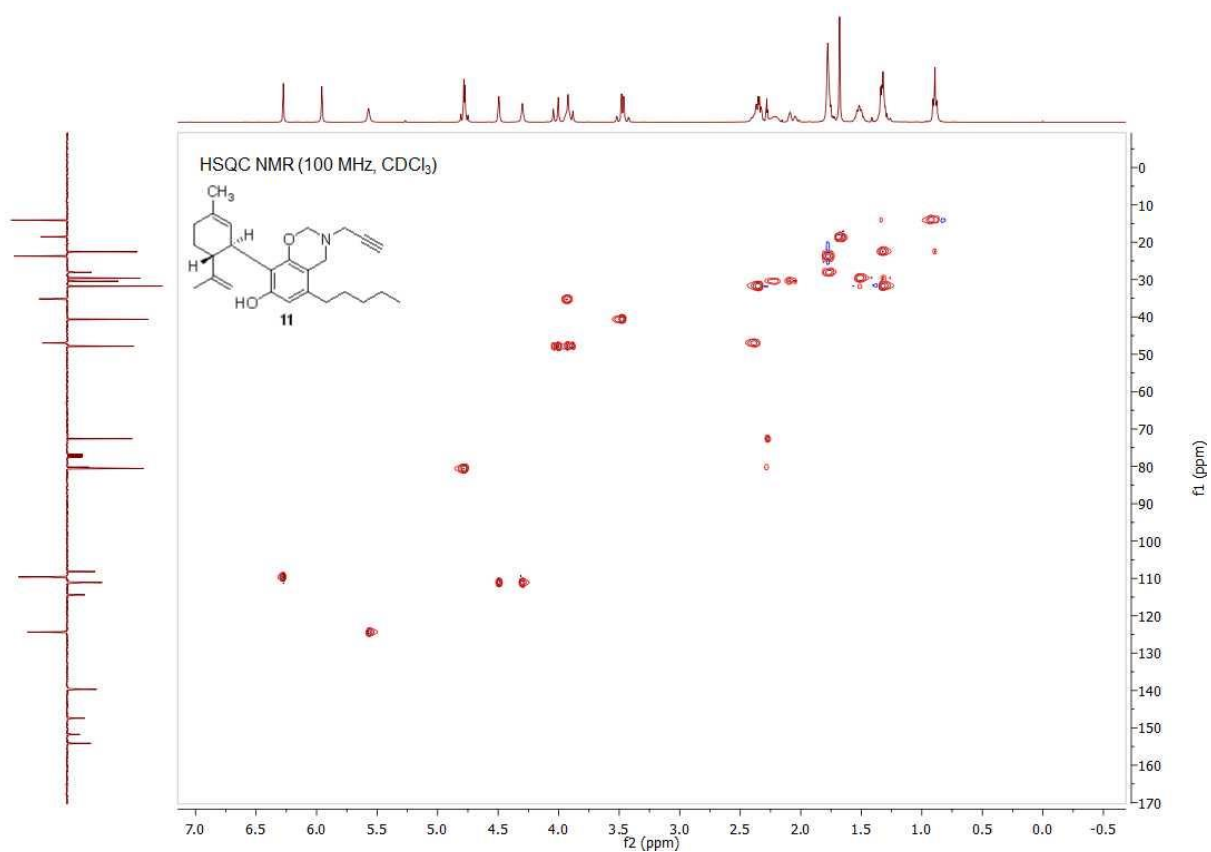
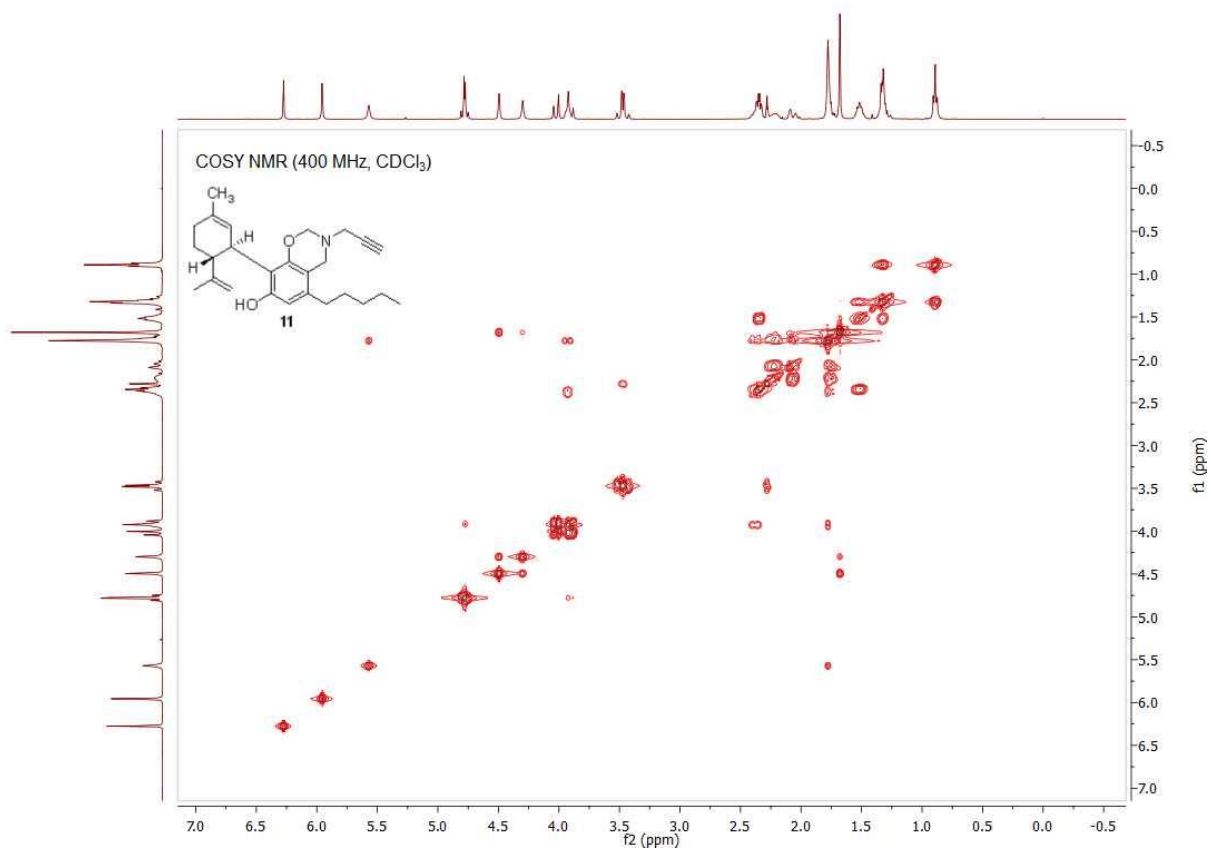
# NMR spectra of compound 10



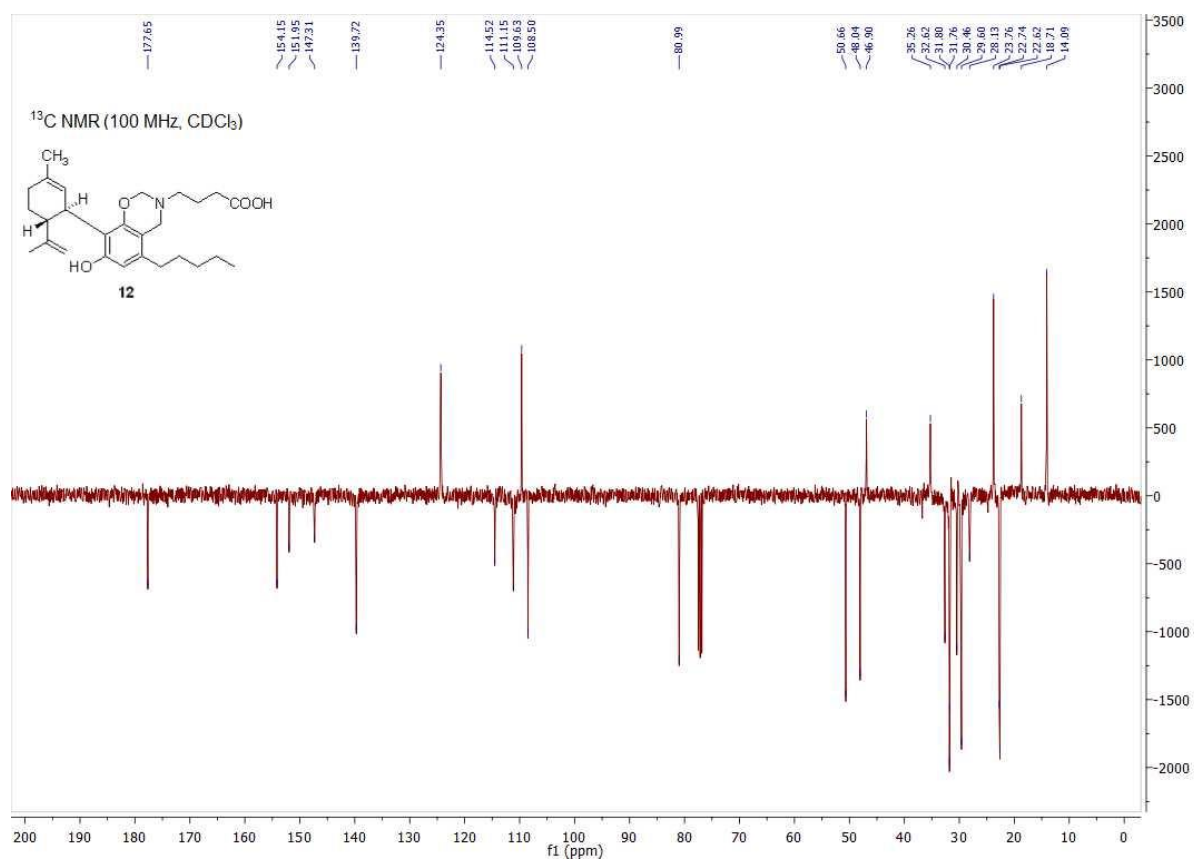
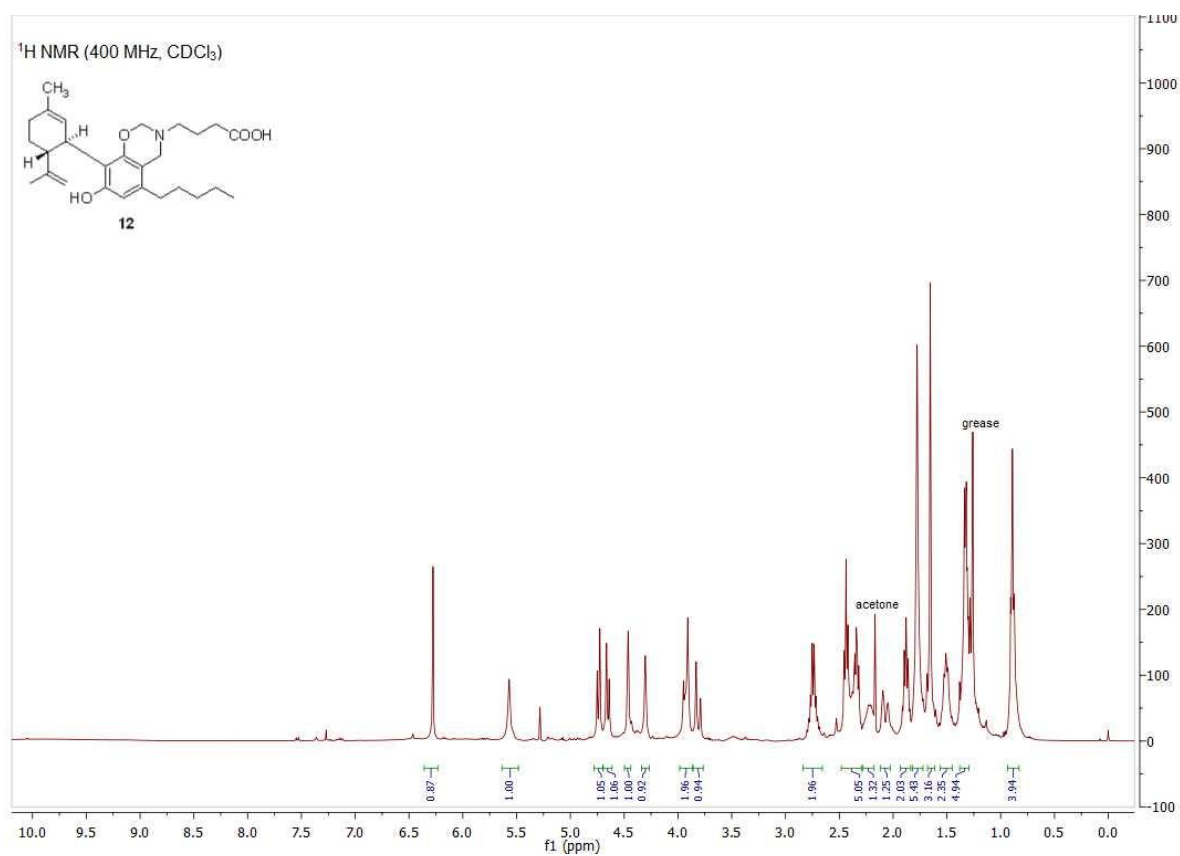


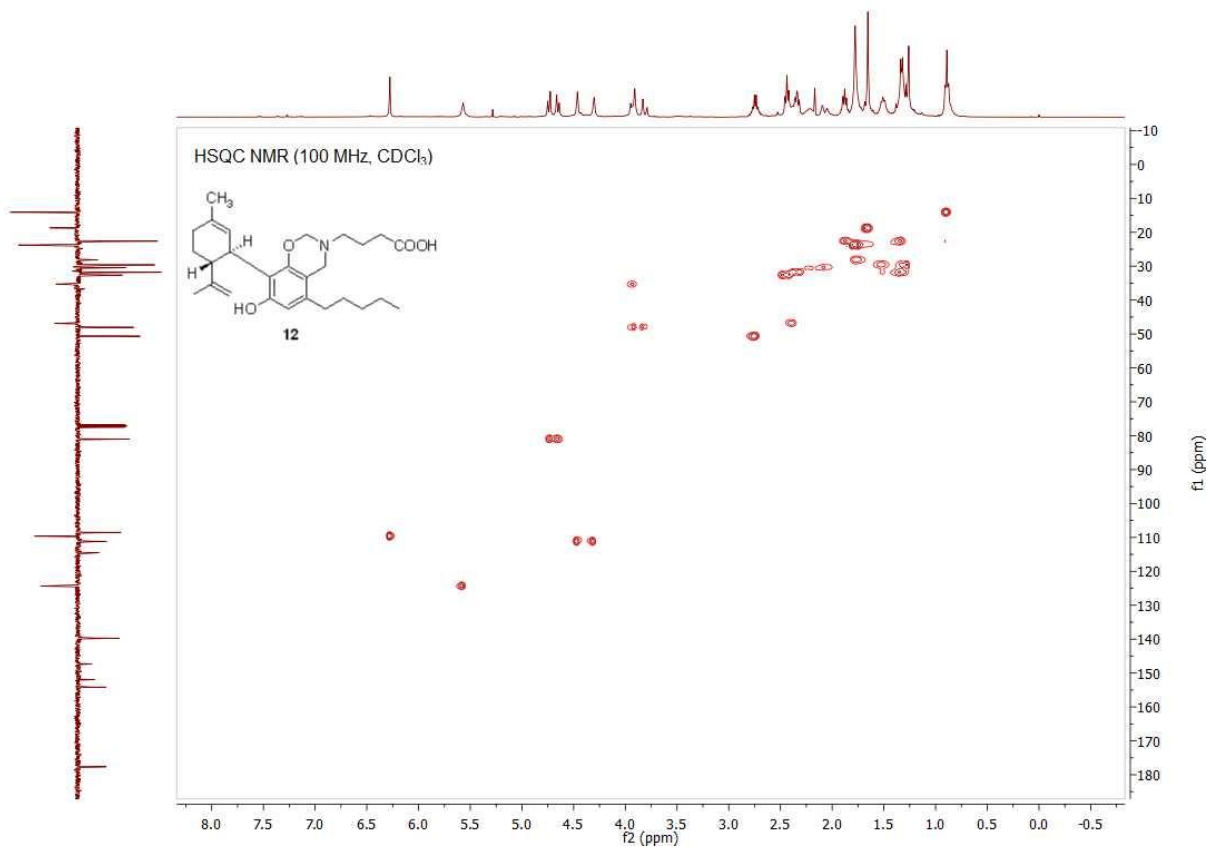
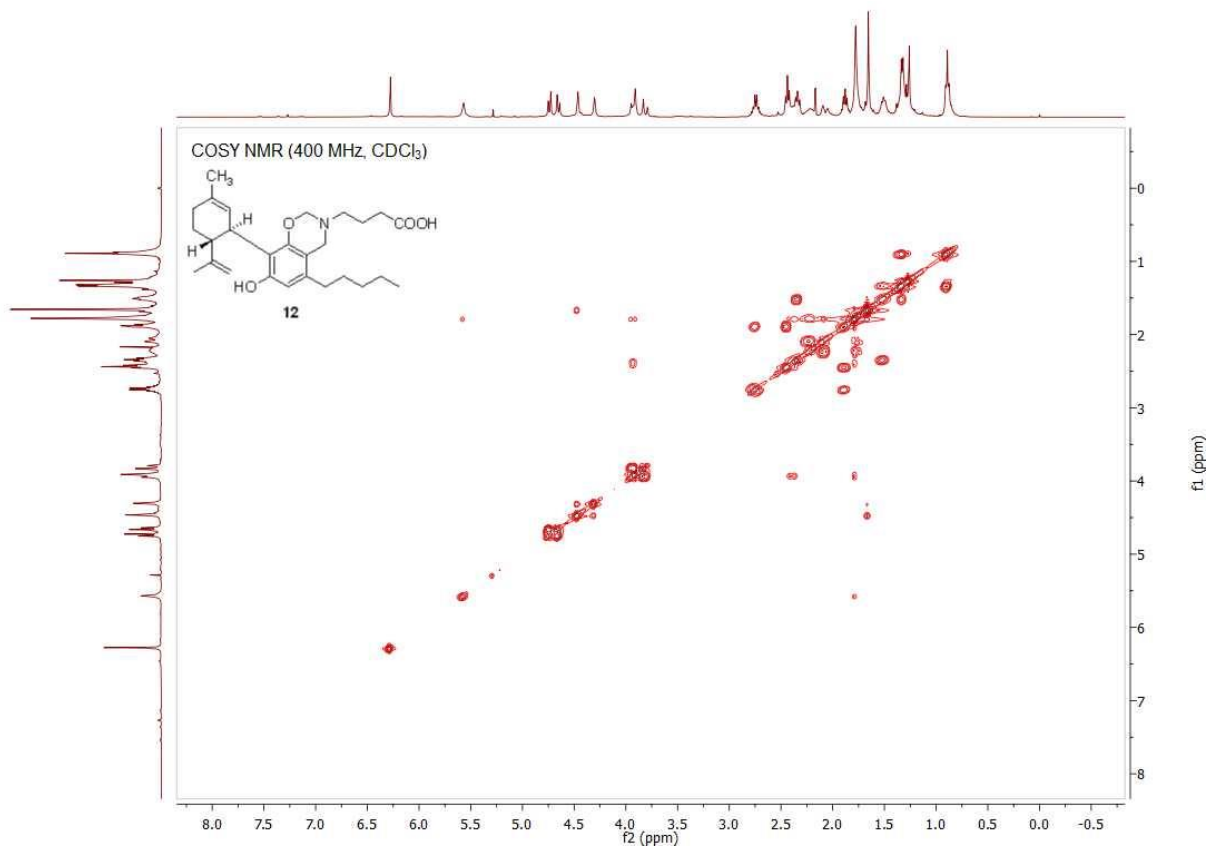
# NMR spectra of compound 11



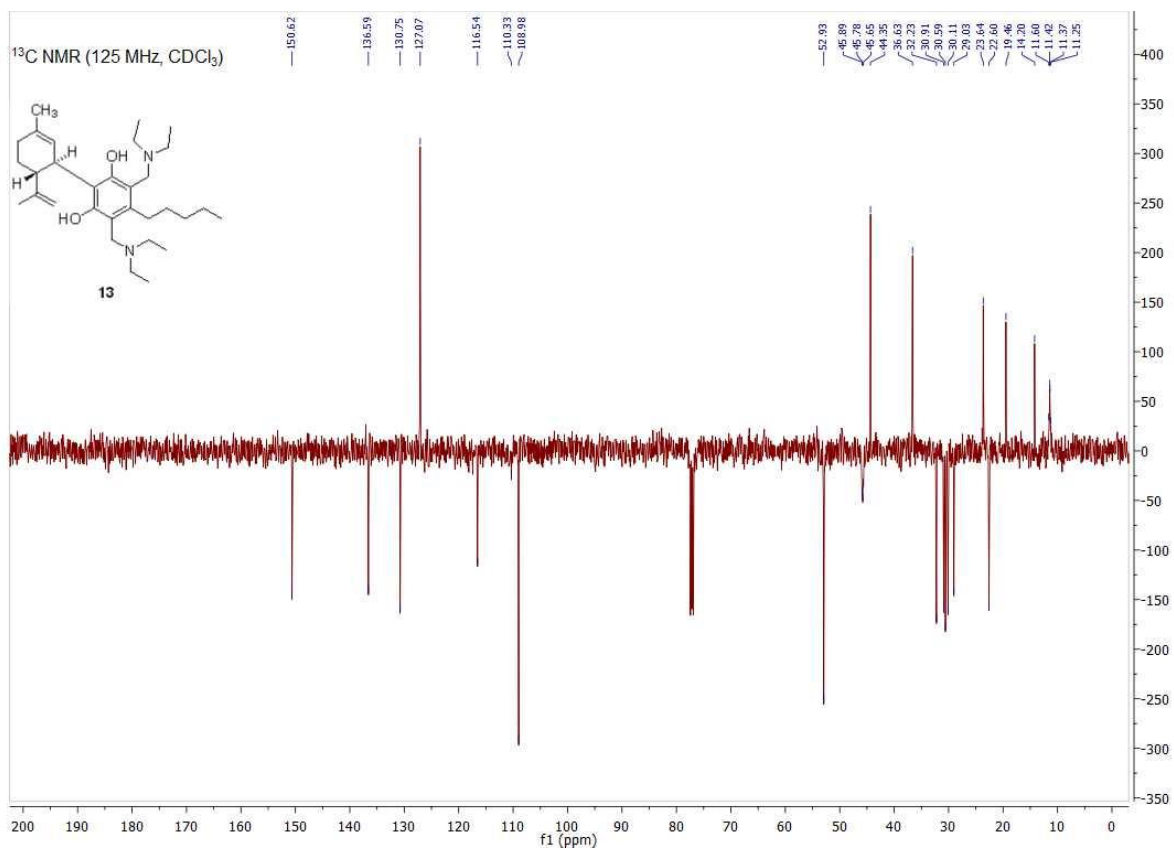
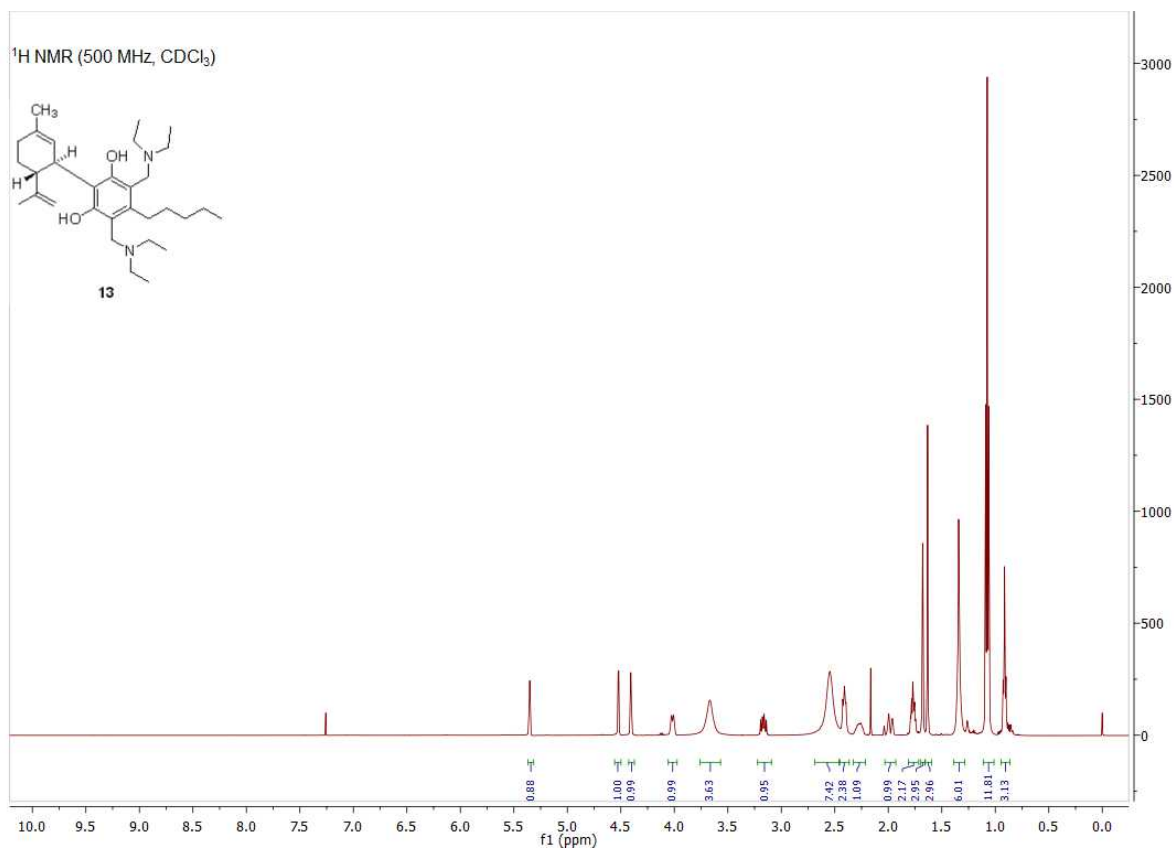


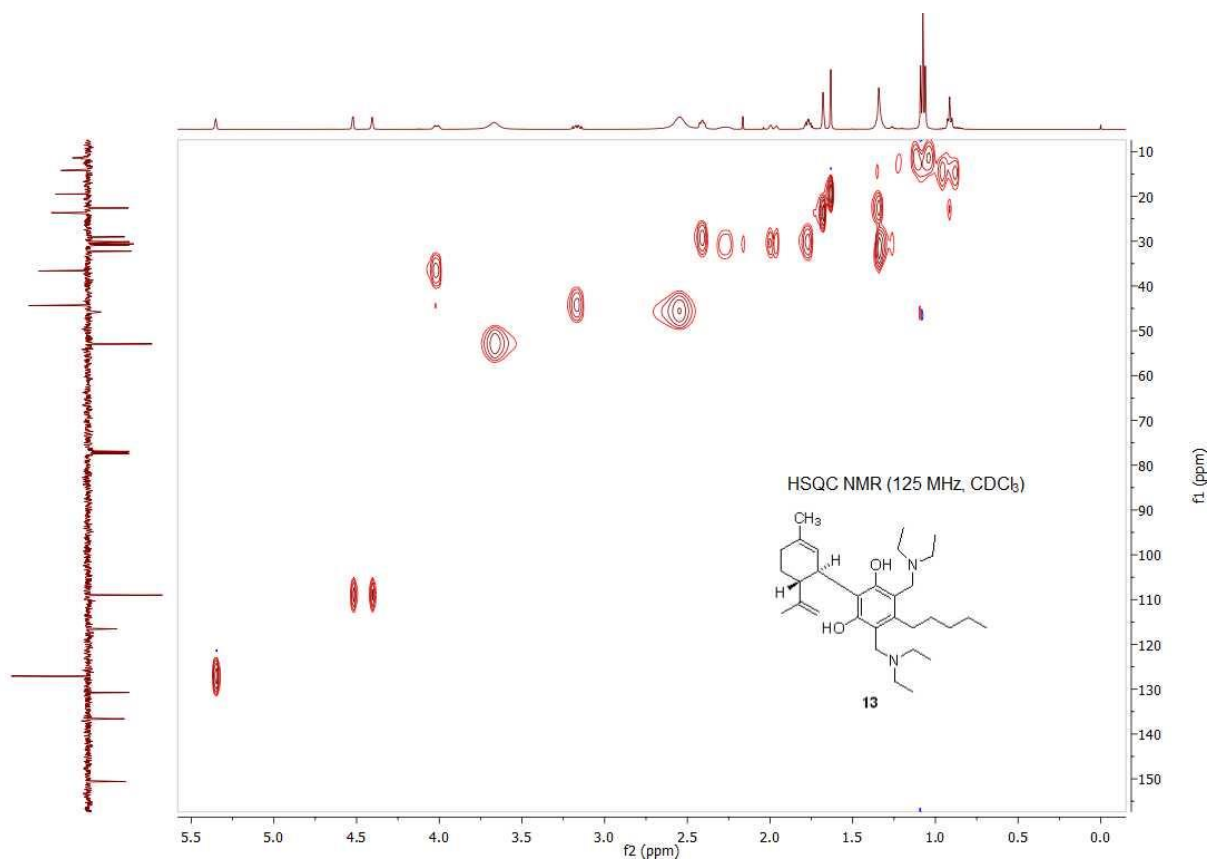
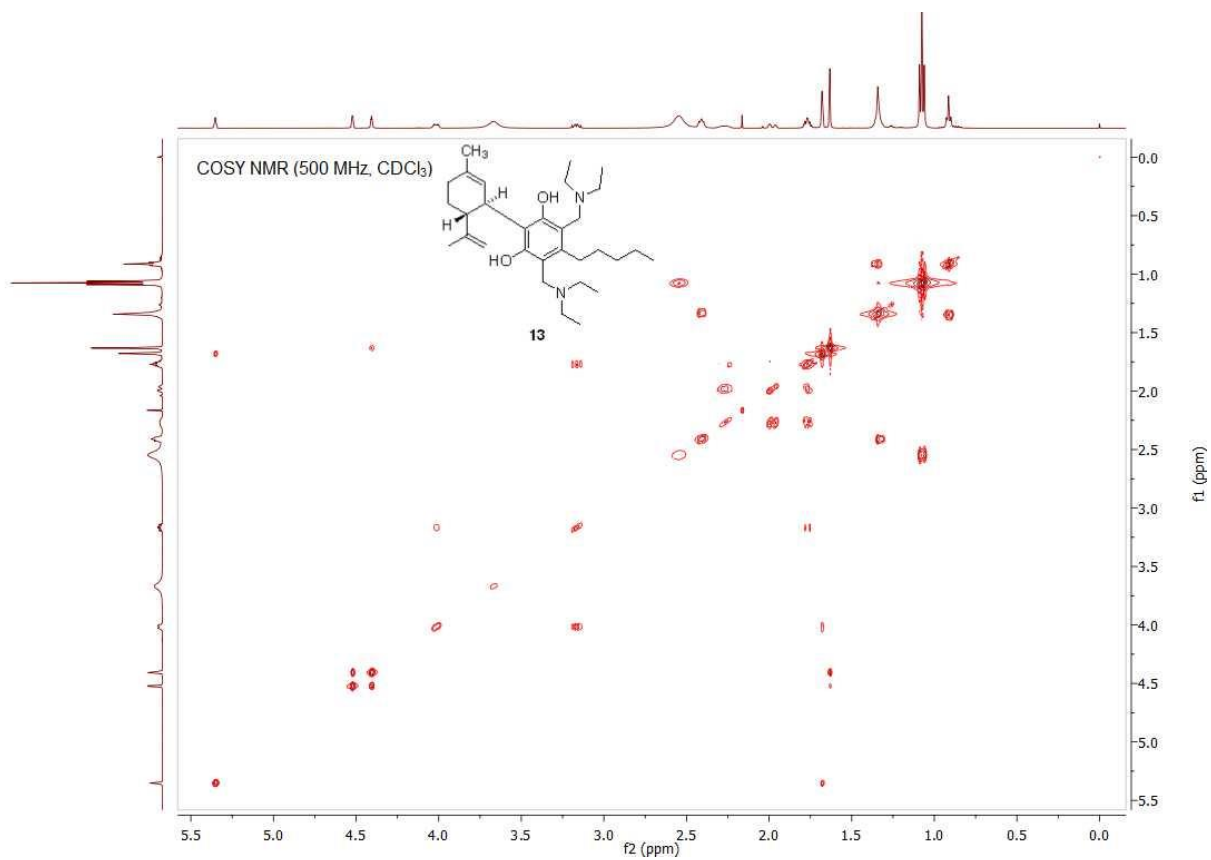
## NMR spectra of compound 12



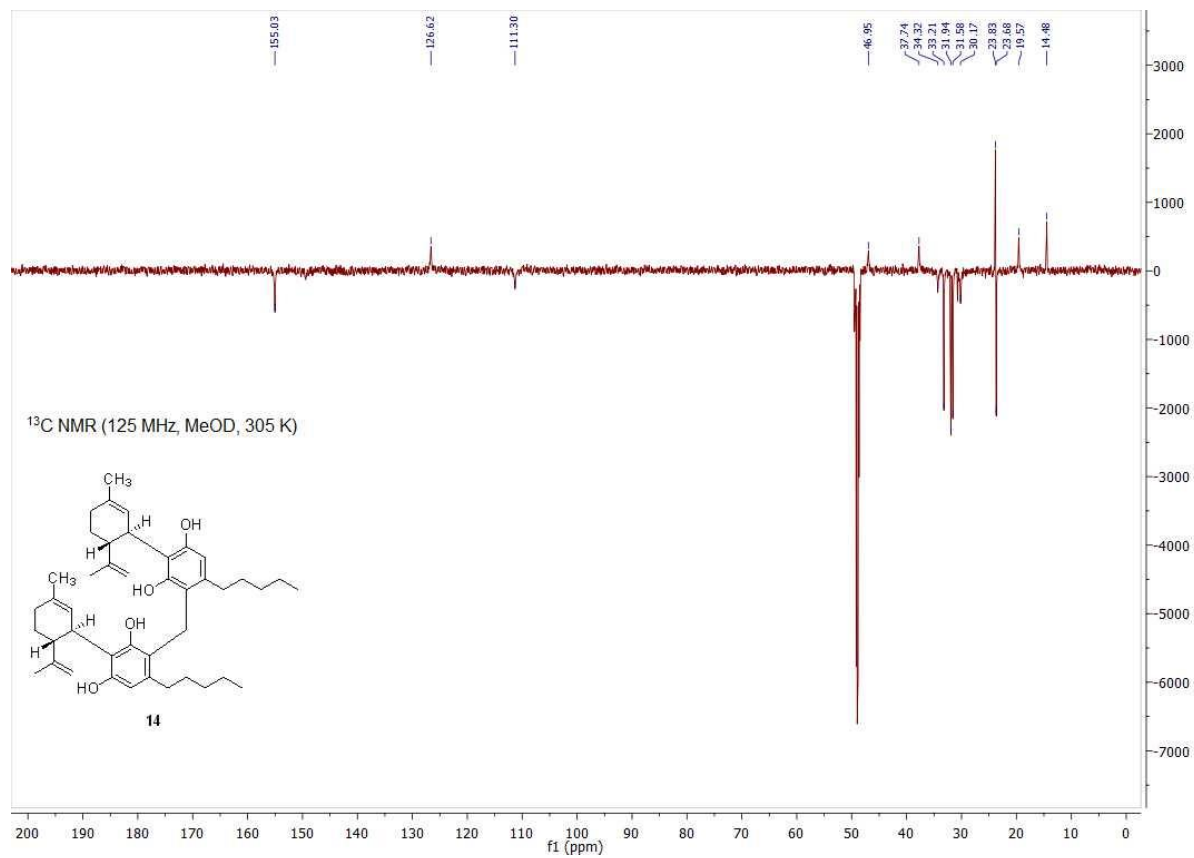
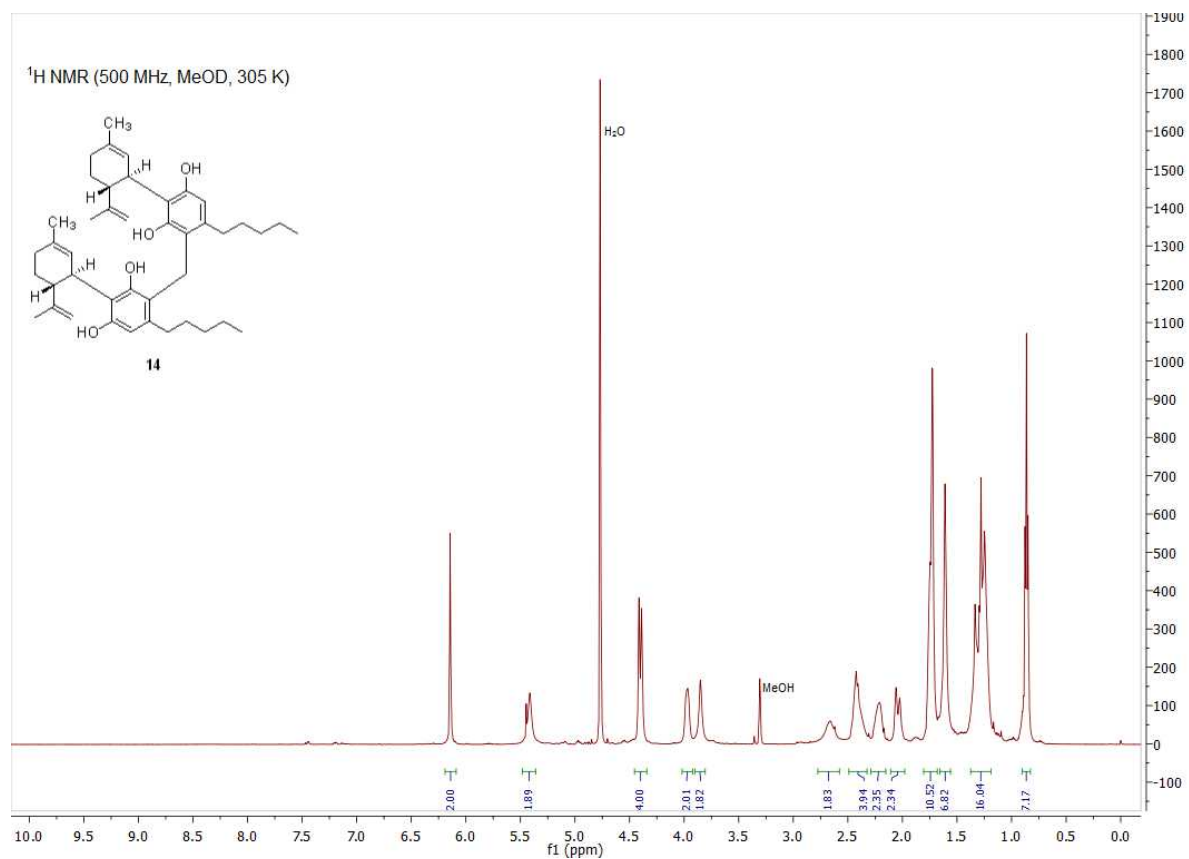


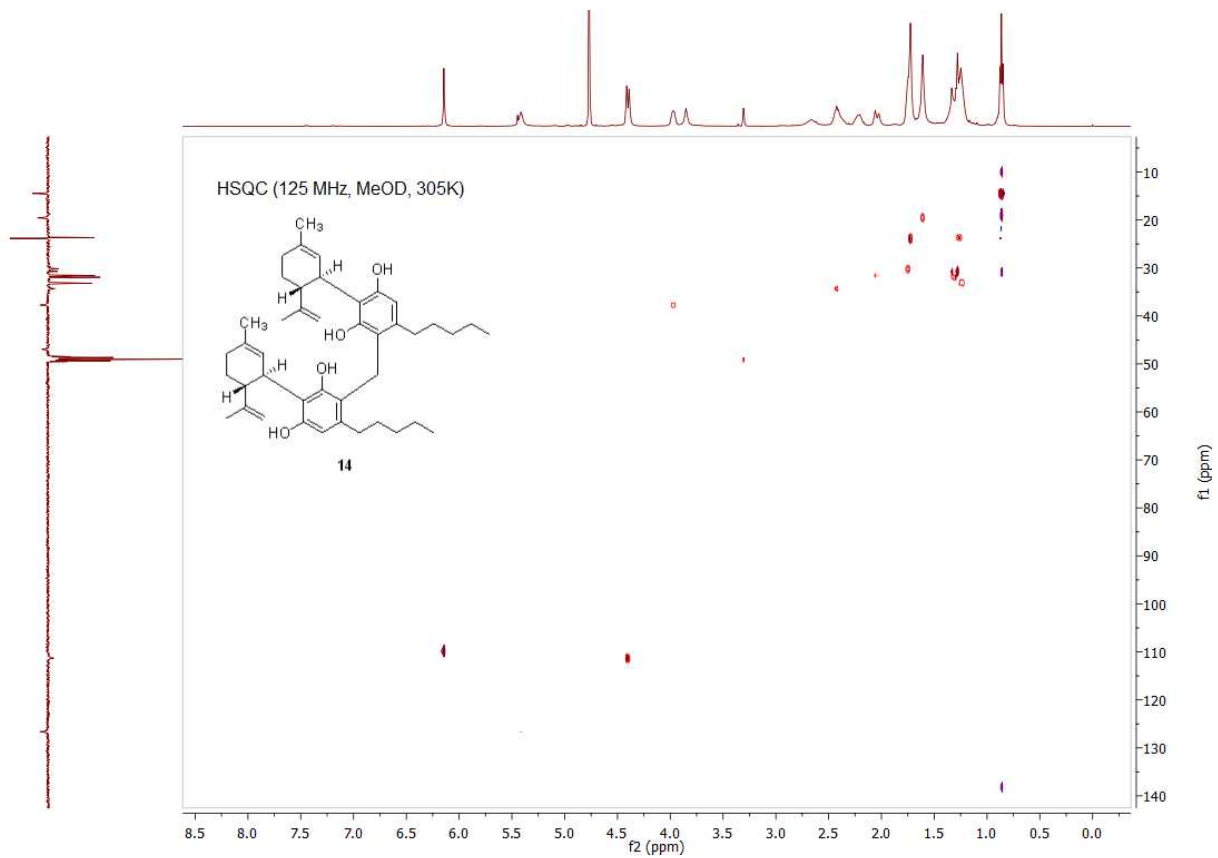
# NMR spectra of compound 13



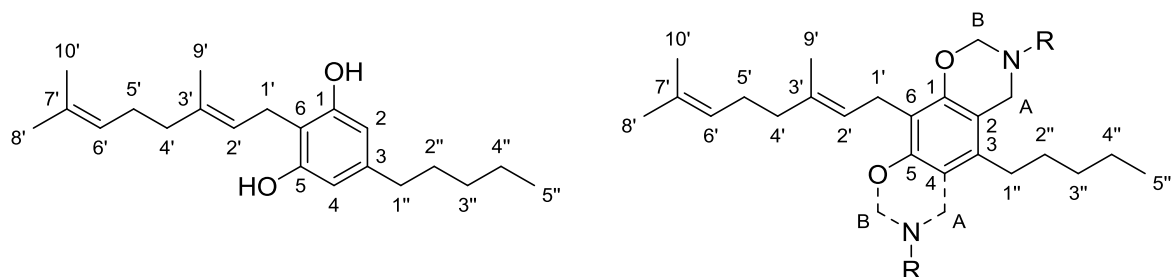


# NMR spectra of compound 14





#### 4. NMR data of CBG and its derivatives

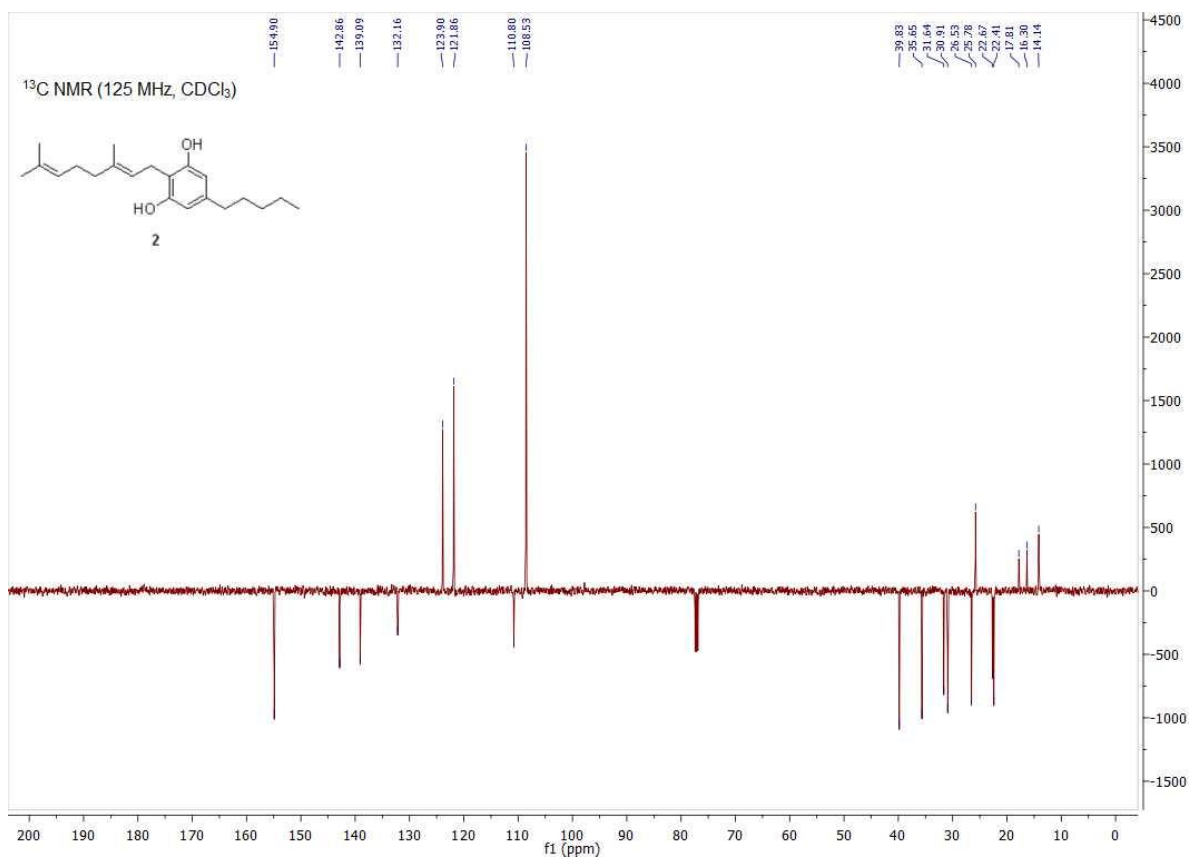
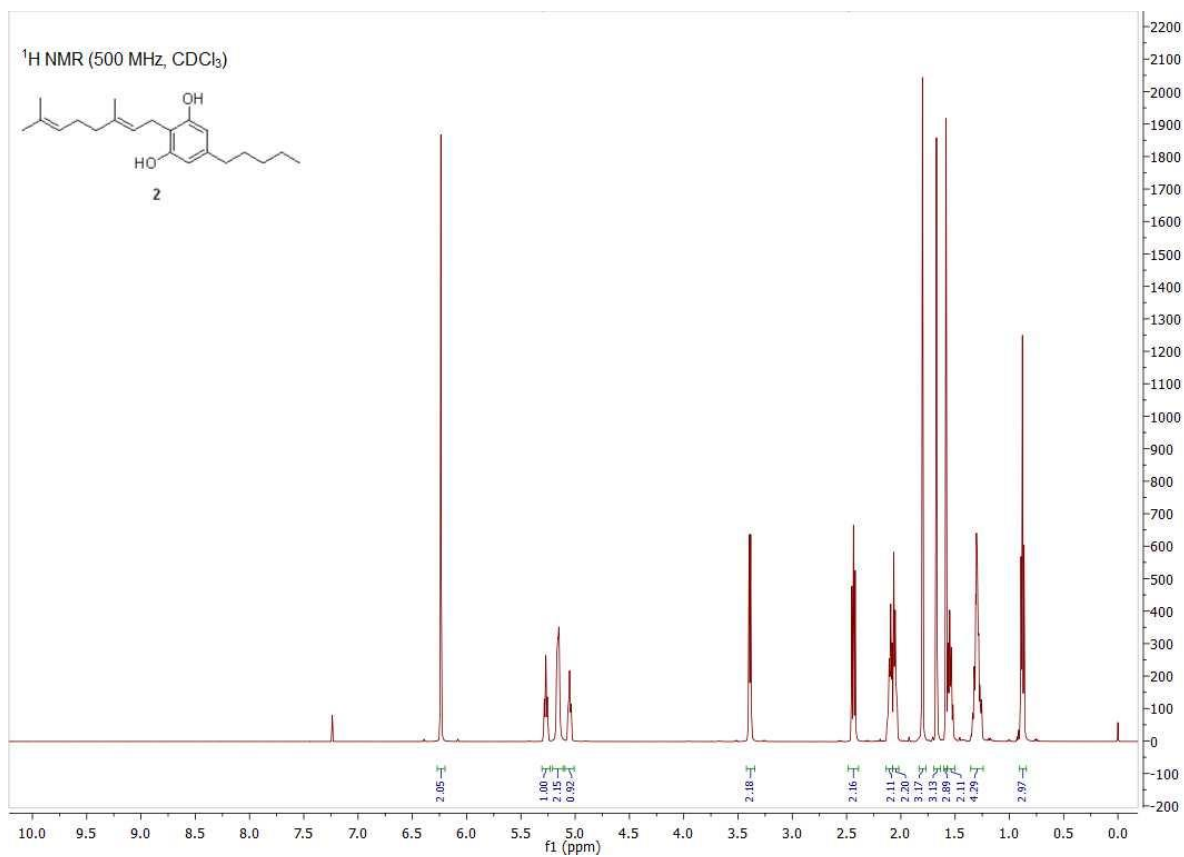


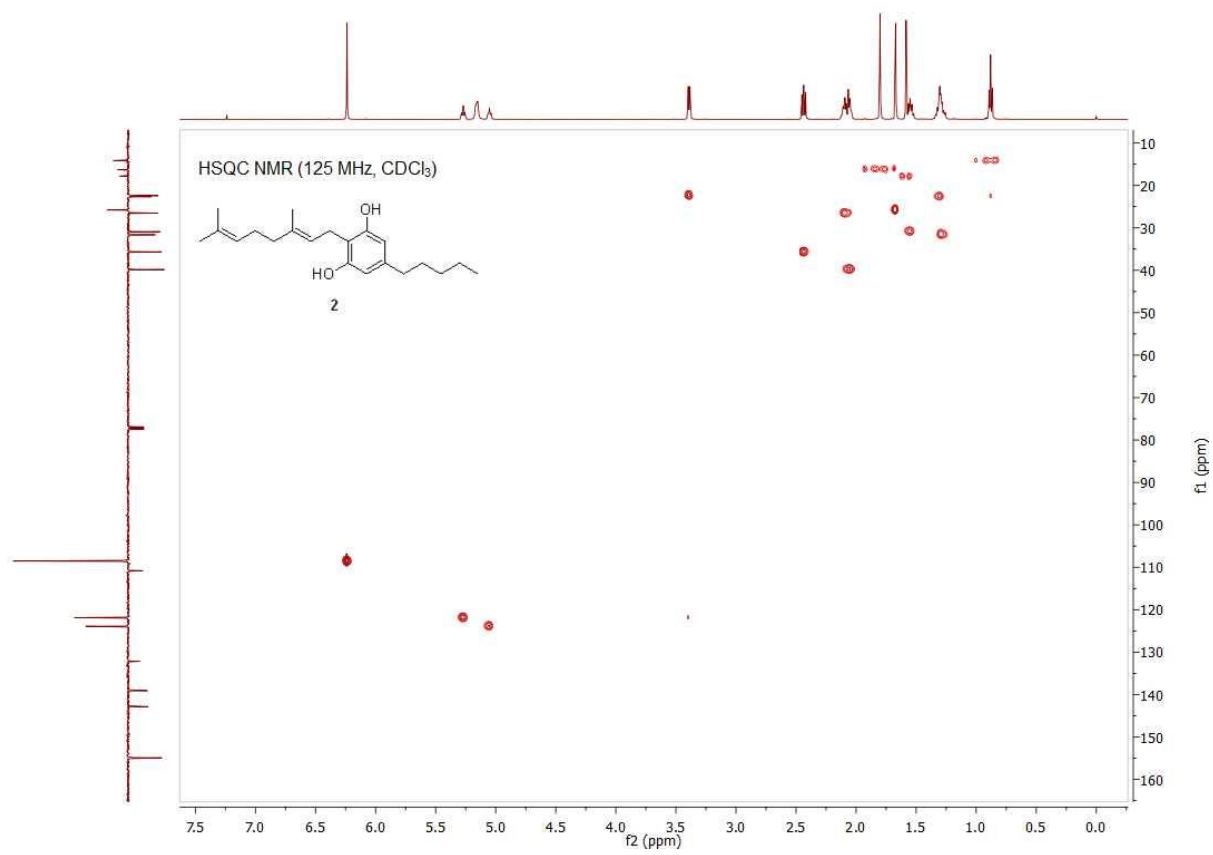
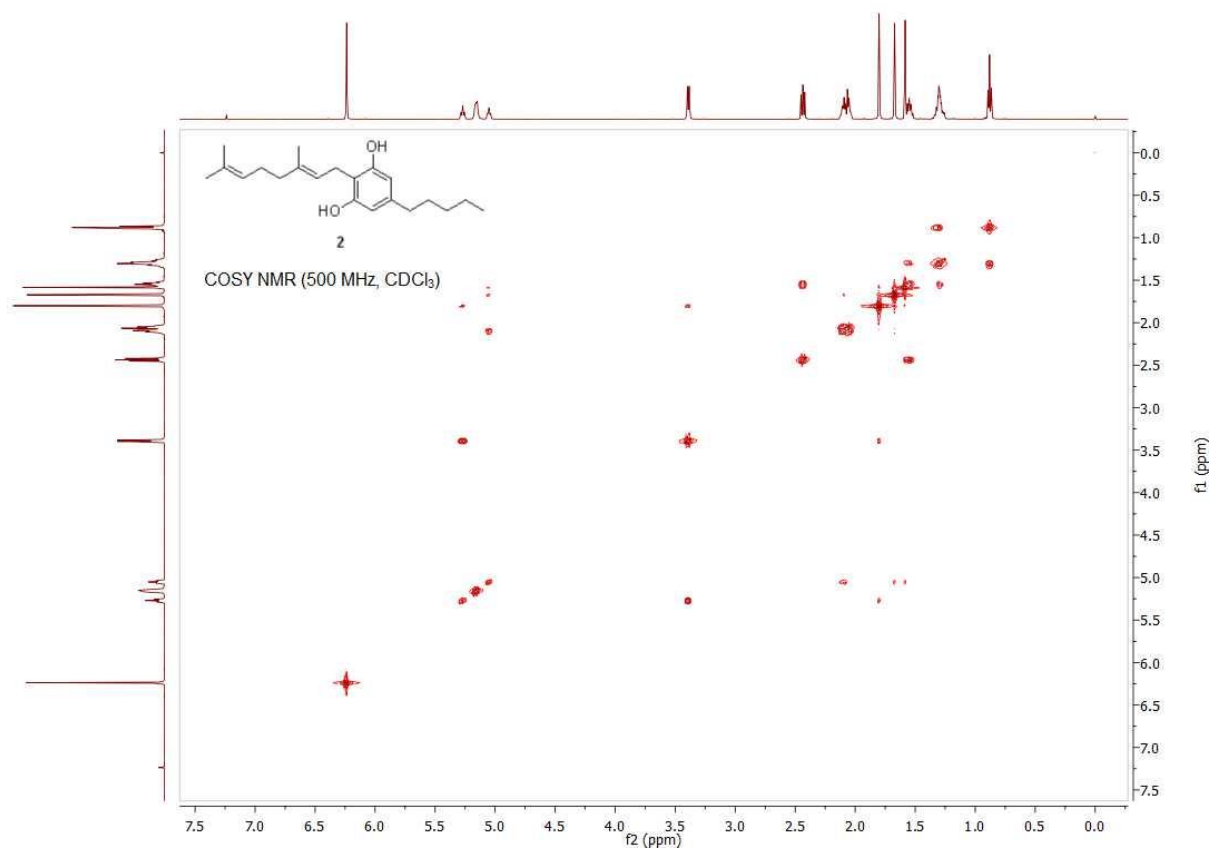
**Figure S3.** Numbering of CBG and its derivatives

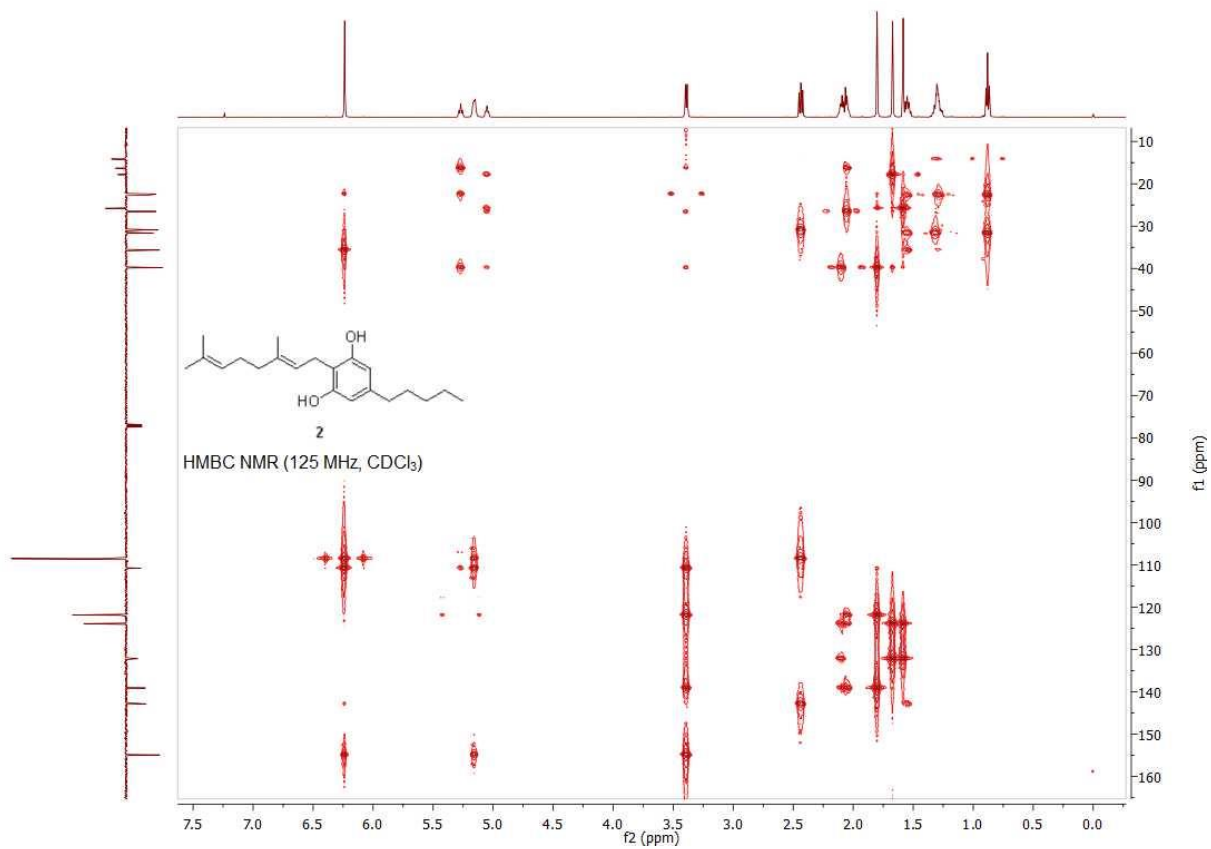
##### NMR data of CBG:

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 6.24 (s, 2H aromatic CH), 5.29-5.24 (m, 1H, H-2'CH), 5.15 (s, 2H, OH), 5.07-5.02 (m, 1H, H-6' CH), 3.39 (d, 2H,  $J = 7.1$  Hz, H-1'  $\text{CH}_2$ ), 2.46-2.41 (m, 2H, H-1''  $\text{CH}_2$ ), 2.13-2.07 (m, 2H, H-5'  $\text{CH}_2$ ), 2.07-2.02 (m, 2H, H-4'  $\text{CH}_2$ ), 1.80 (s, 3H, H-9'  $\text{CH}_3$ ), 1.58, 1.67 (2s, 6H, H-8' and H-10'  $\text{CH}_3$ ), 1.57-1.51 (m, 2H, H-2''  $\text{CH}_2$ ), 1.36-1.24 (m, 4H, H-3'' and H-4''  $\text{CH}_2$ ), 0.88 (t, 3H,  $J = 6.9$  Hz, H-5''  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 154.9, 142.9, 139.1, 132.2 (4C, quat.), 123.9 (1C, C-6' CH), 121.9 (1C, C-2' CH), 110.8 (1C, quat.), 108.5 (2C, aromatic CH), 39.8 (1C, C-4'  $\text{CH}_2$ ), 35.7 (1C, C-1''  $\text{CH}_2$ ), 31.6 (1C, C-3''  $\text{CH}_2$ ), 30.9 (1C, C-2''  $\text{CH}_2$ ), 26.5 (1C, C-5'  $\text{CH}_2$ ), 25.8 (1C, C-8' or C-10'  $\text{CH}_3$ ), 22.7 (1C, C-4''  $\text{CH}_2$ ), 22.4 (1C, C-1'  $\text{CH}_2$ ), 17.8 (1C, C-8' or C-10'  $\text{CH}_3$ ), 16.3 (1C, C-9'  $\text{CH}_3$ ), 14.1 (1C, C-5''  $\text{CH}_3$ ).

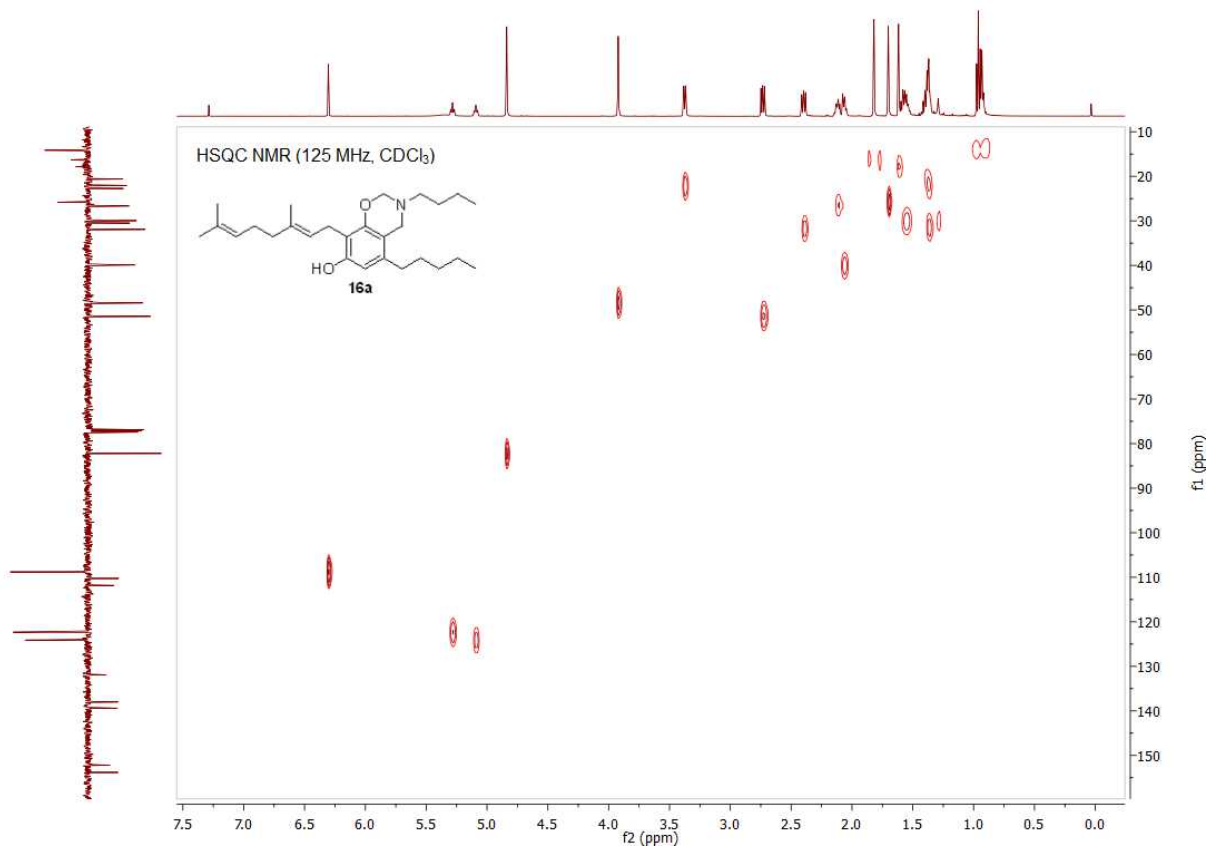
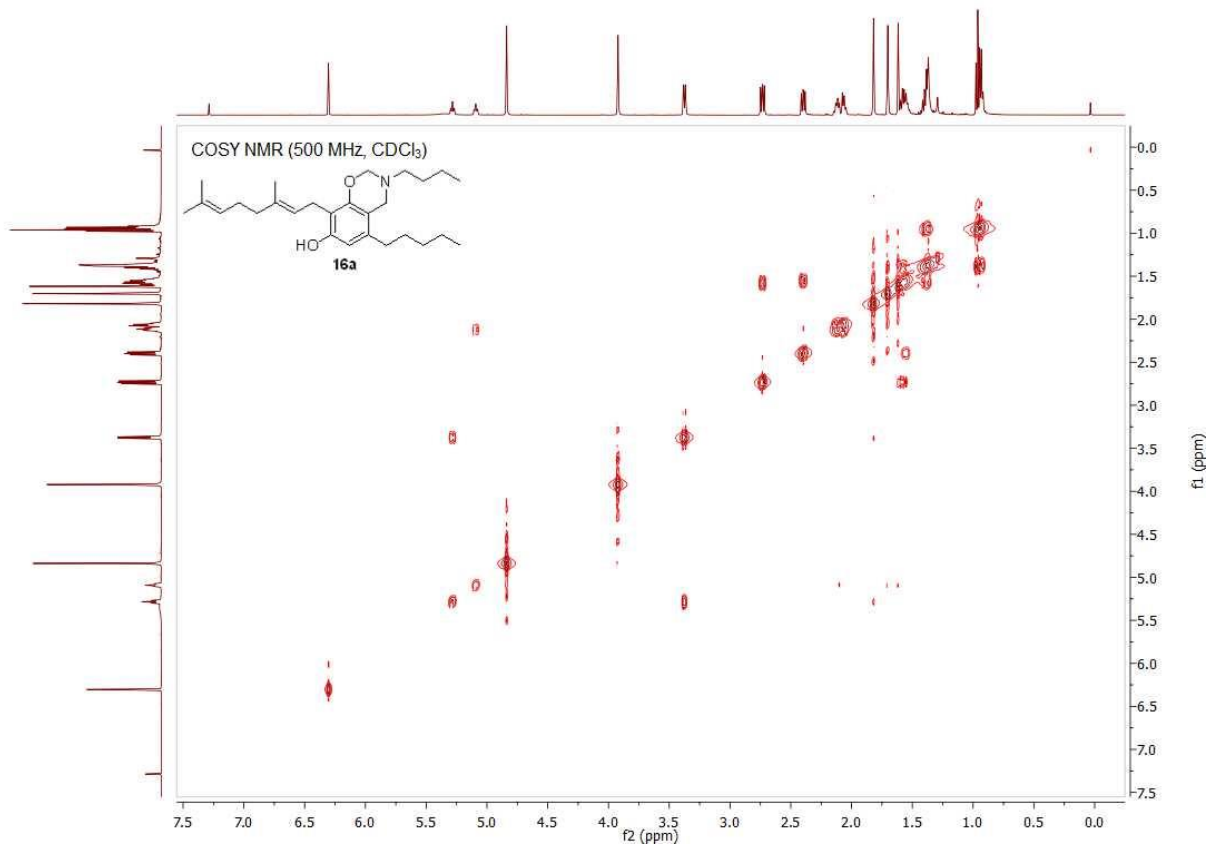
# NMR spectra of CBG



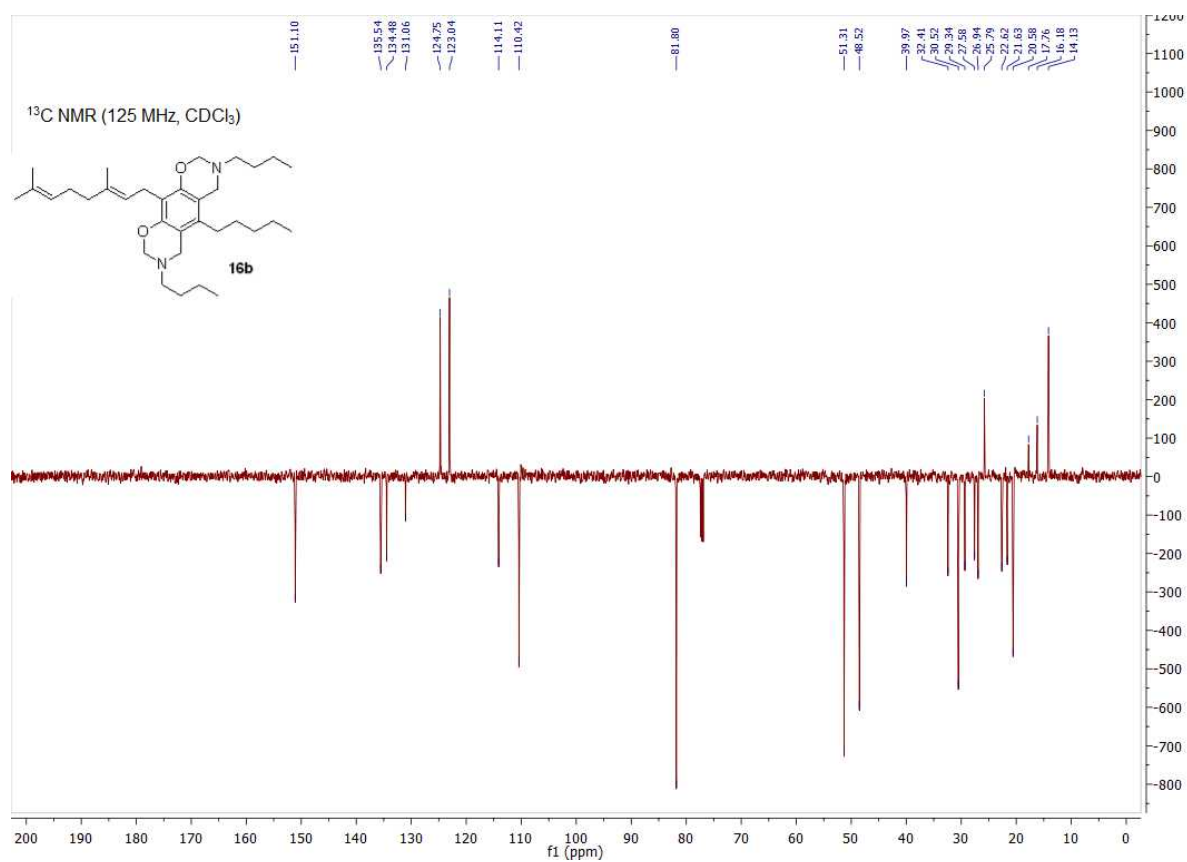
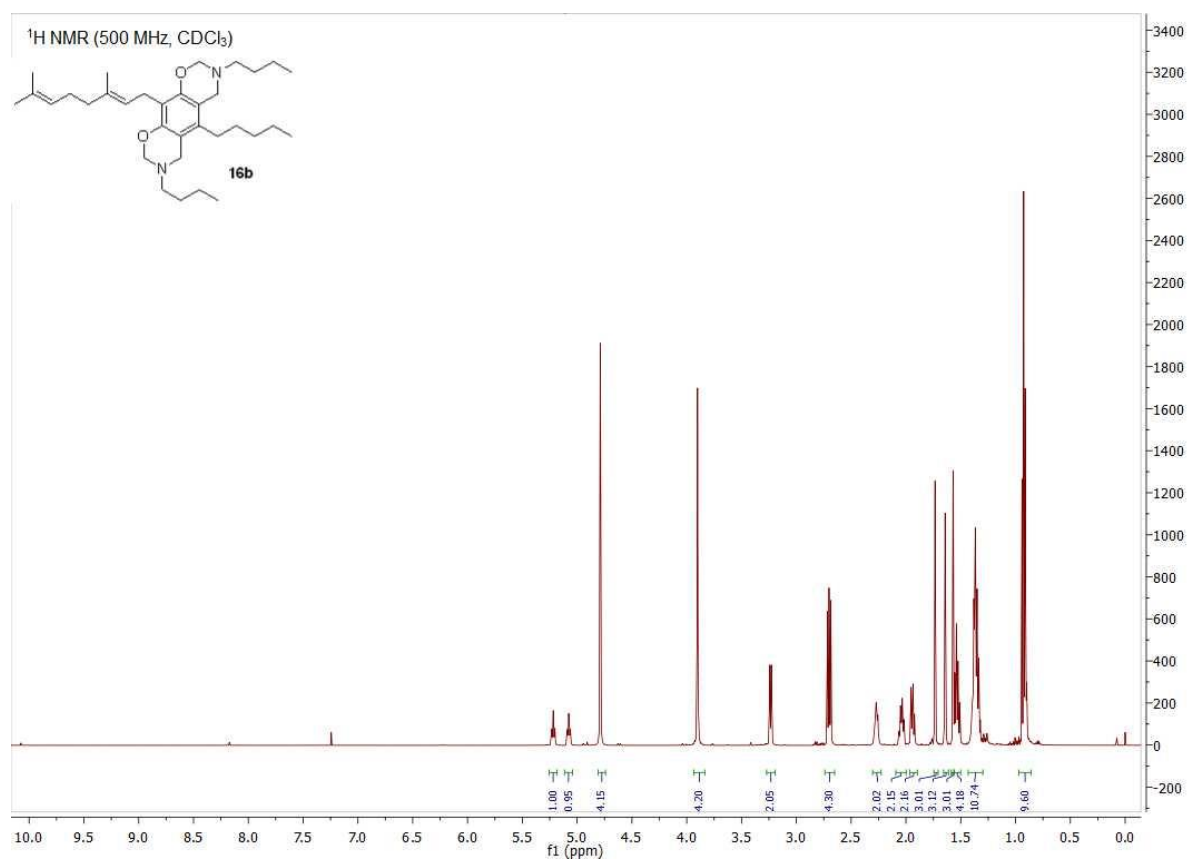


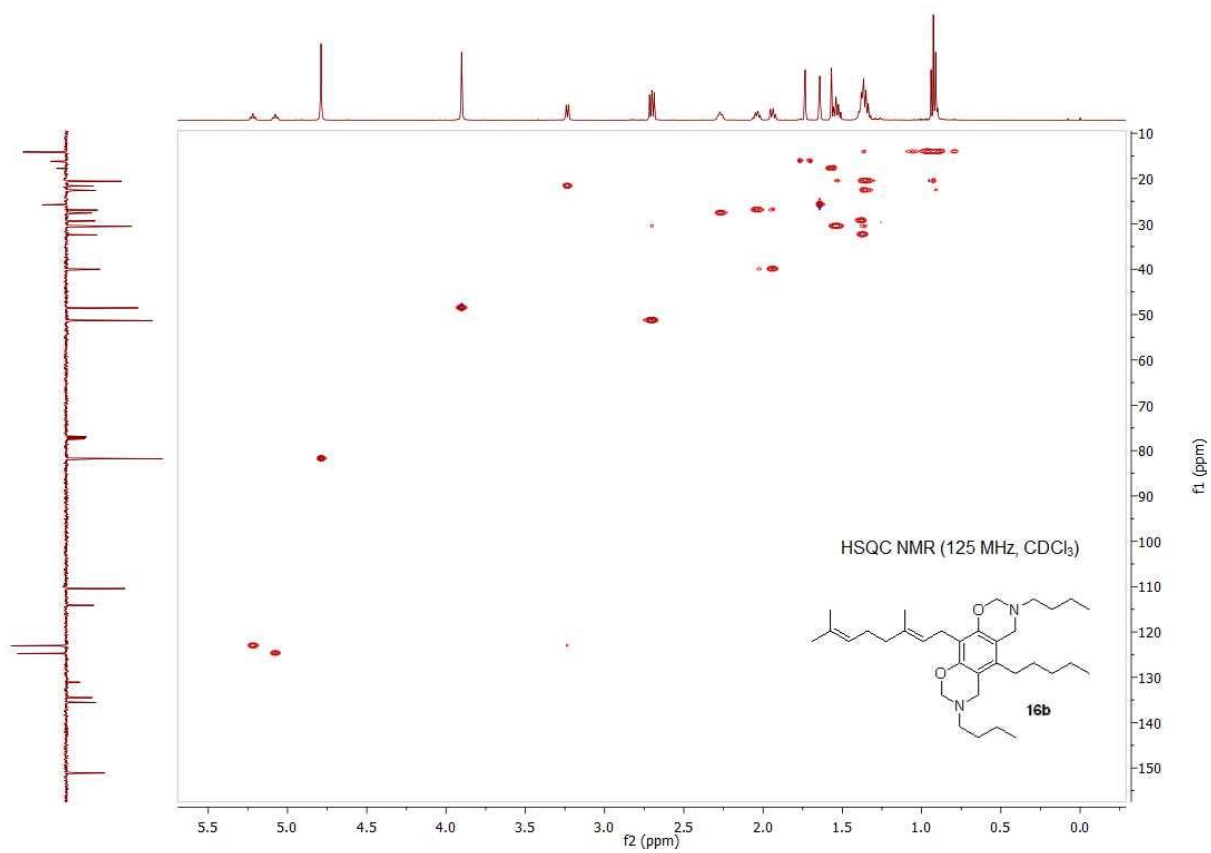
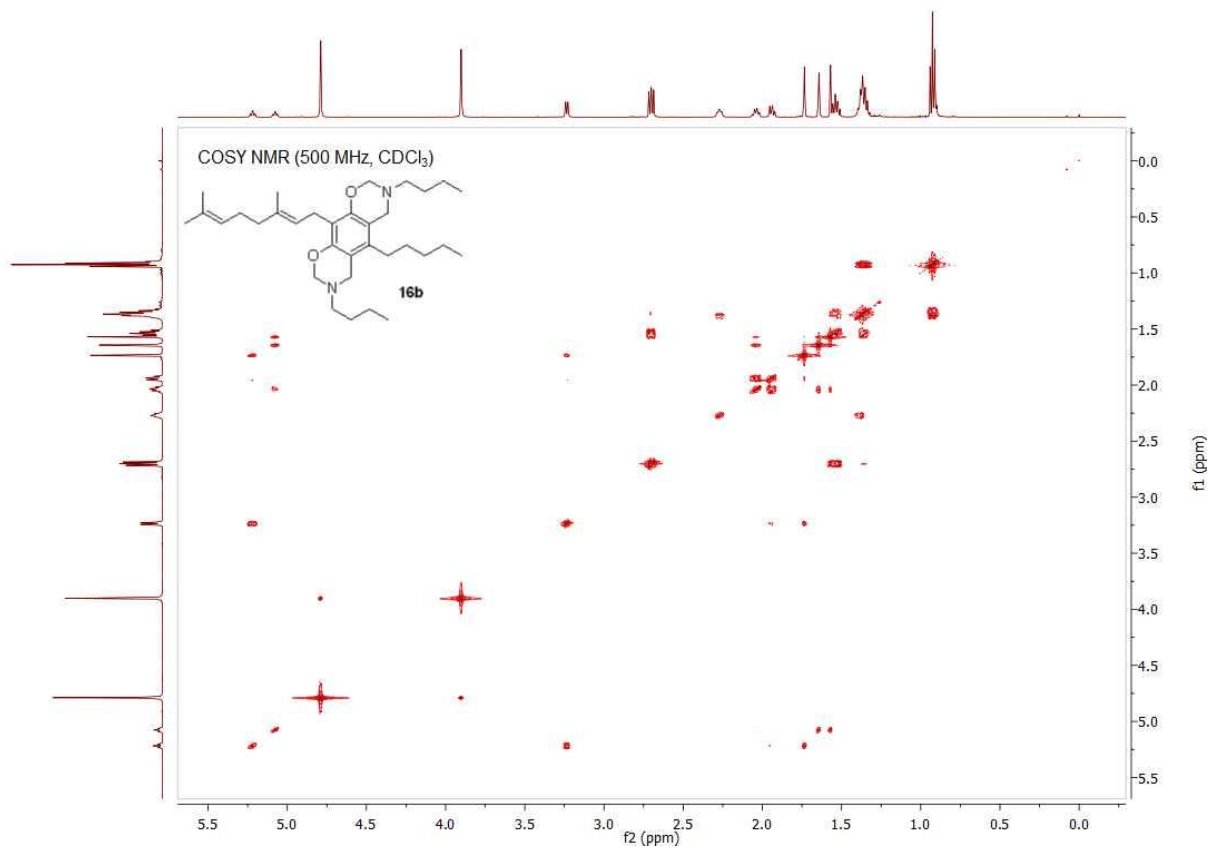




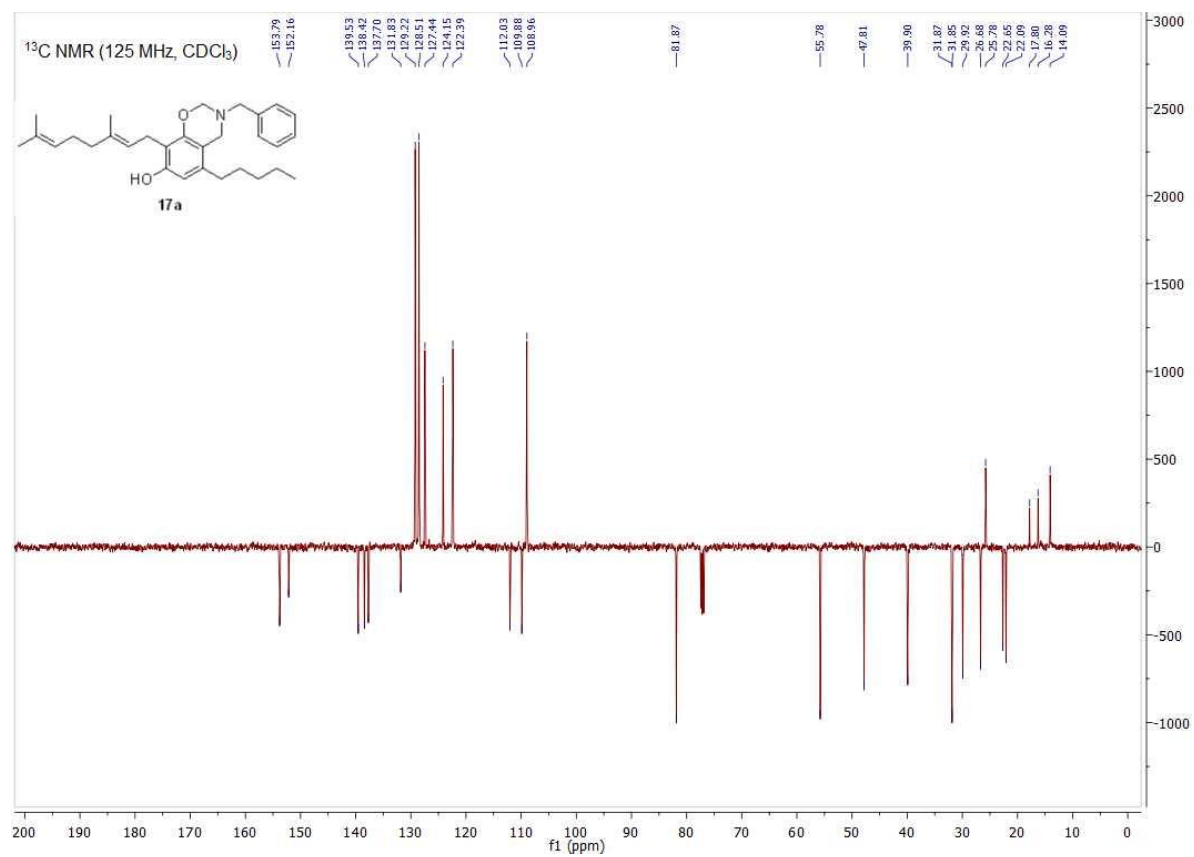
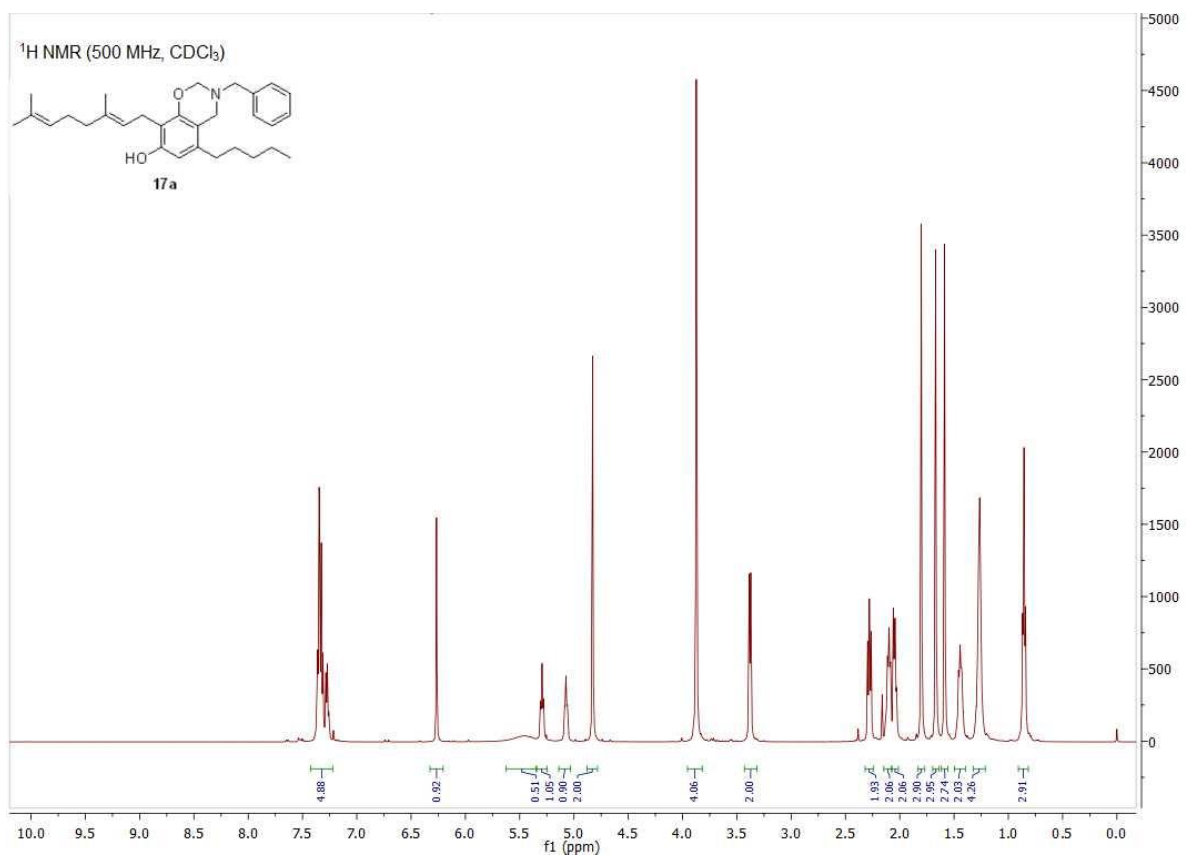


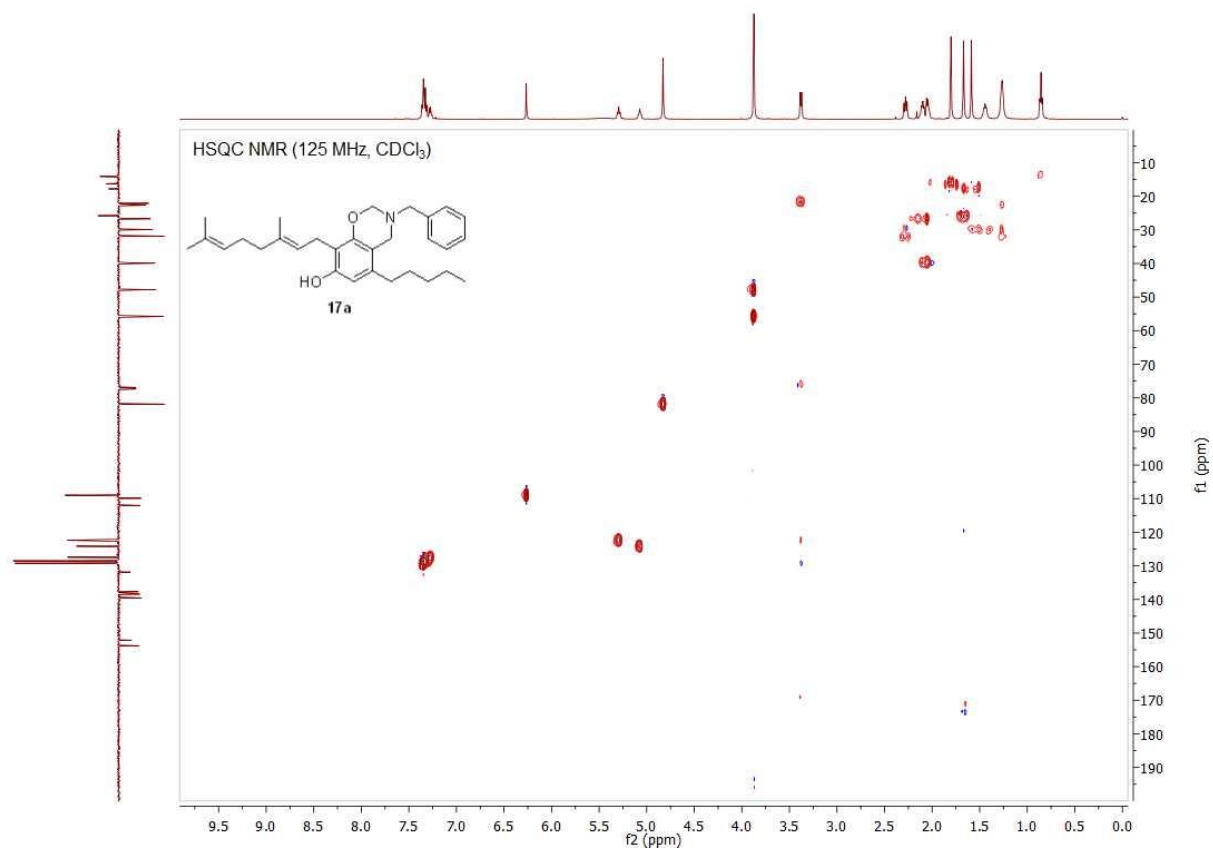
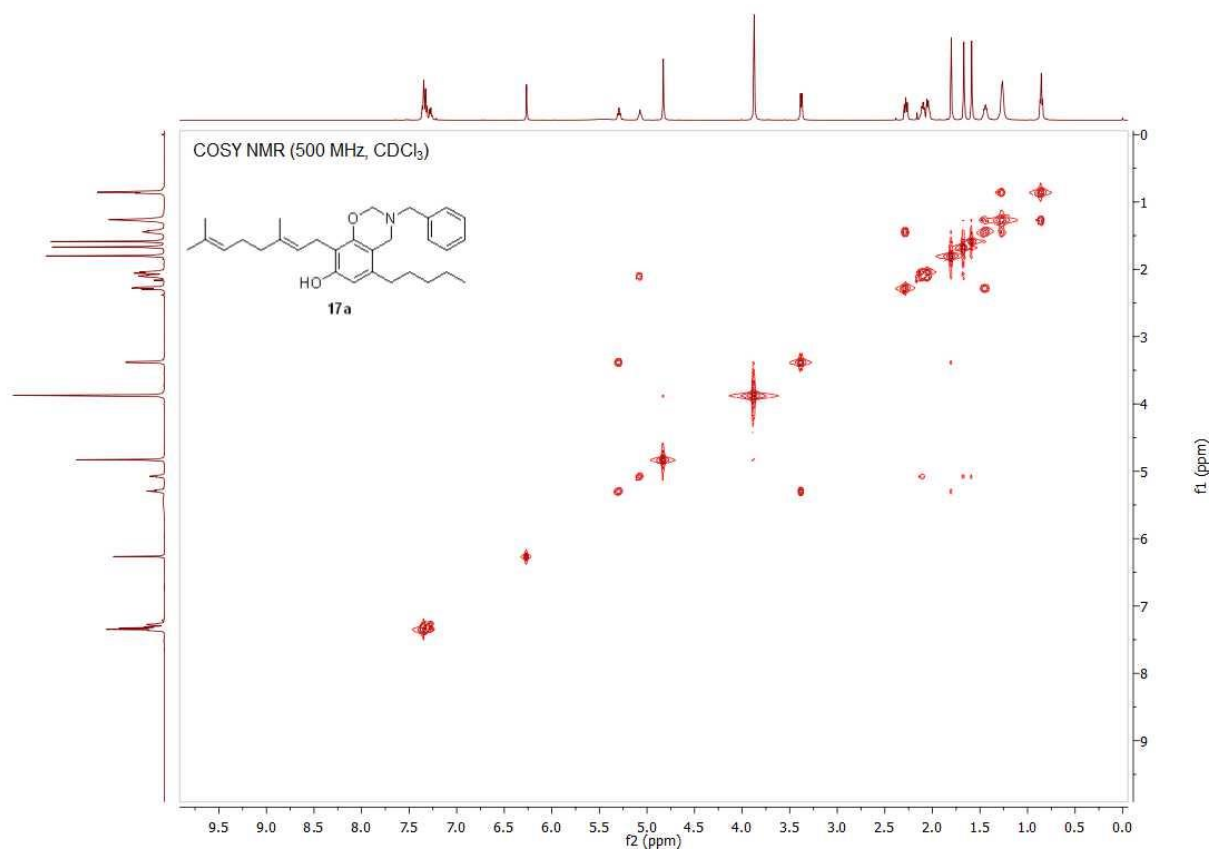
# NMR spectra of compound 16b



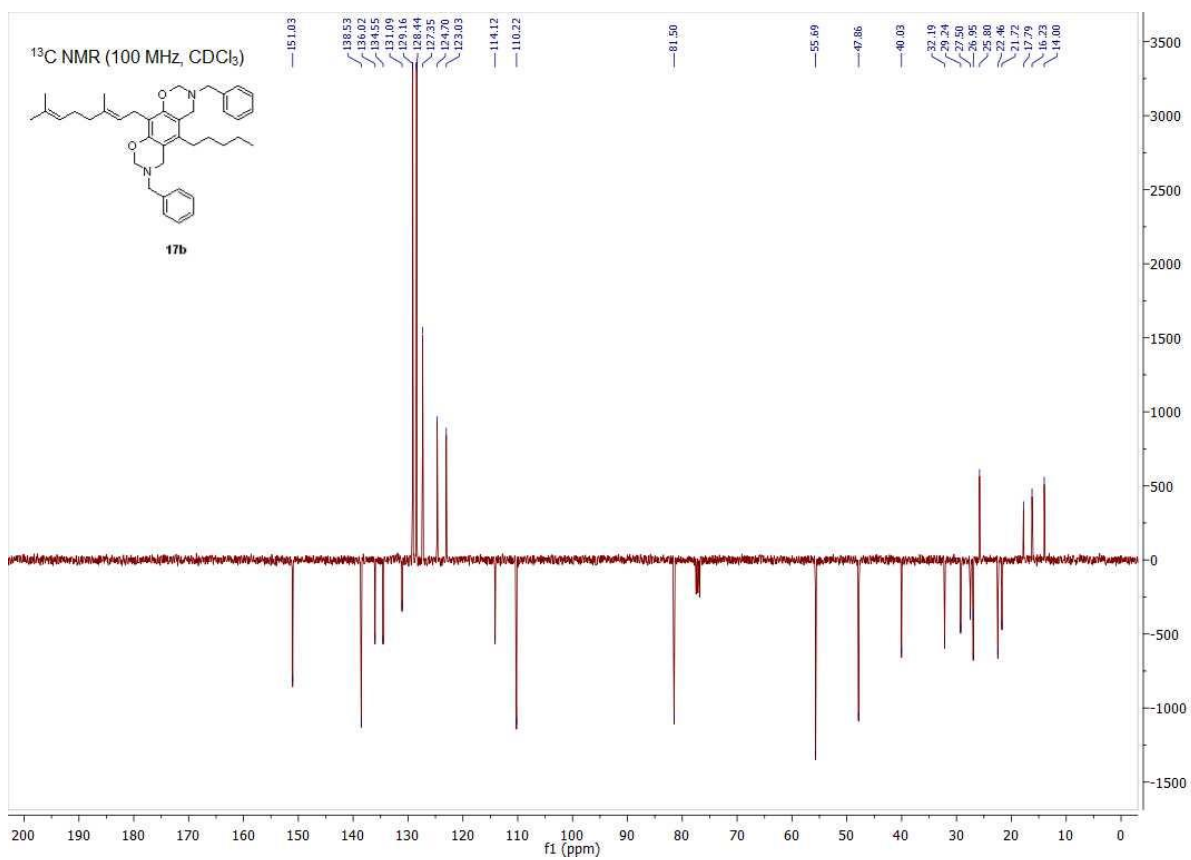
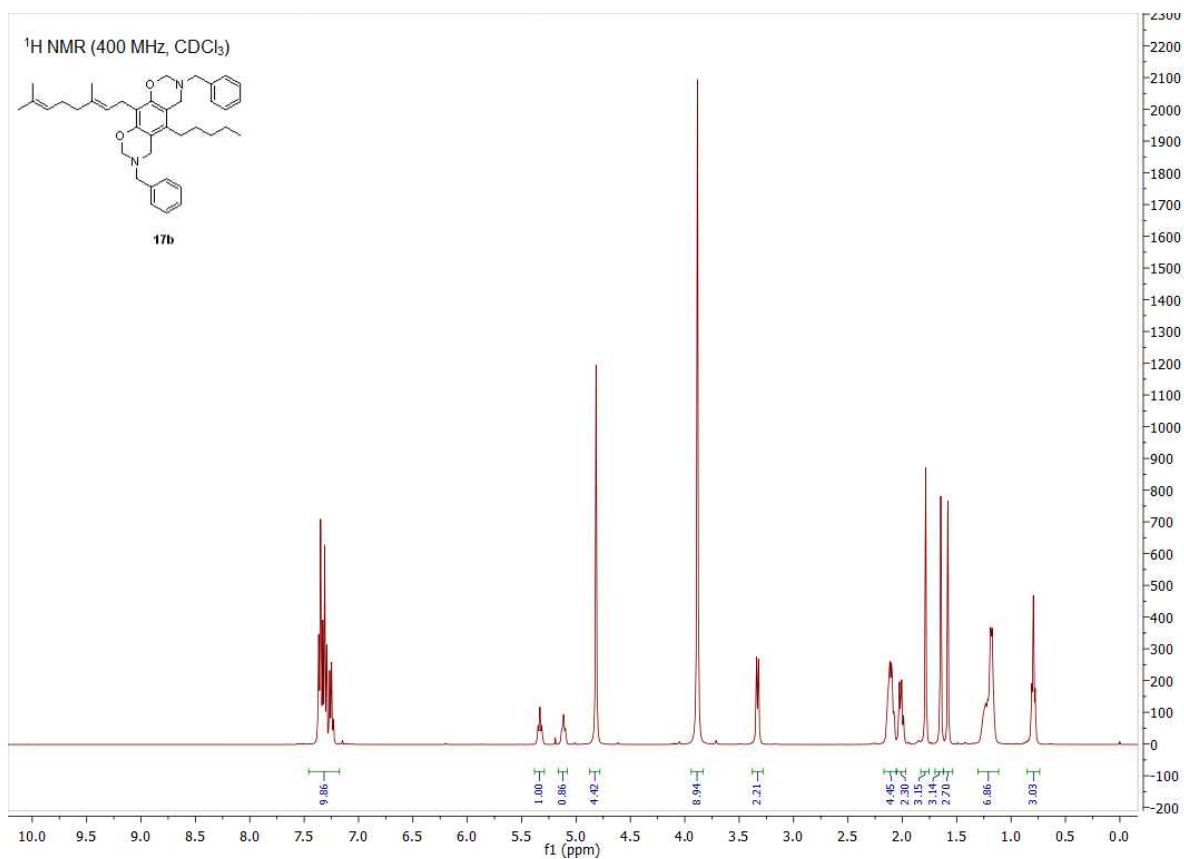


# NMR spectra of compound 17a



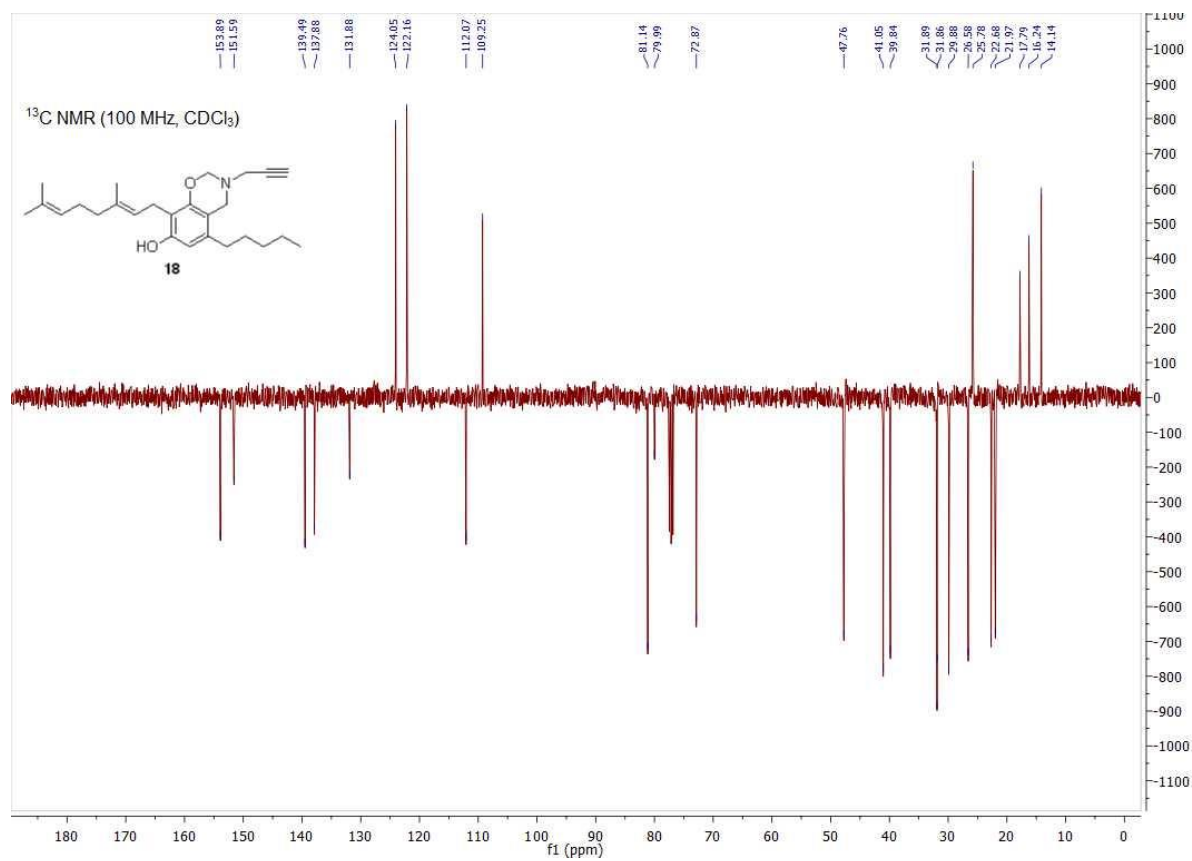
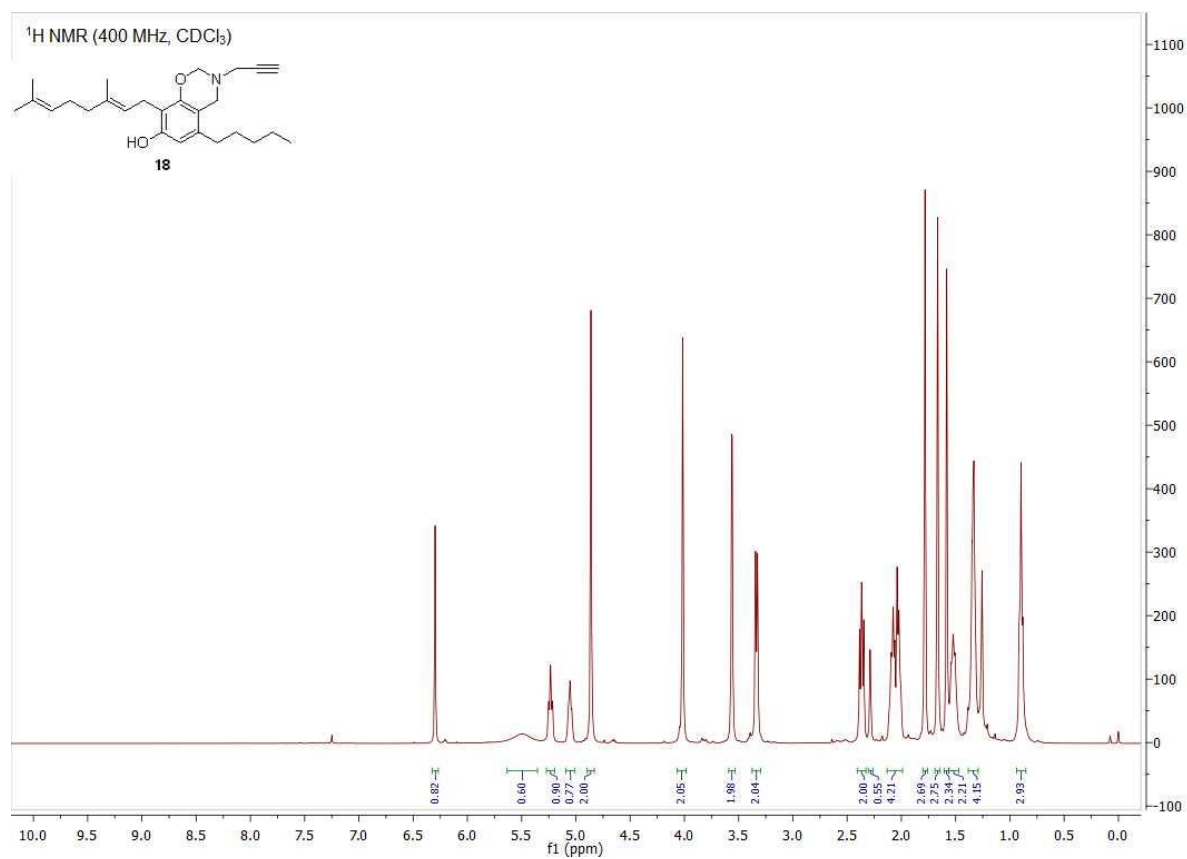


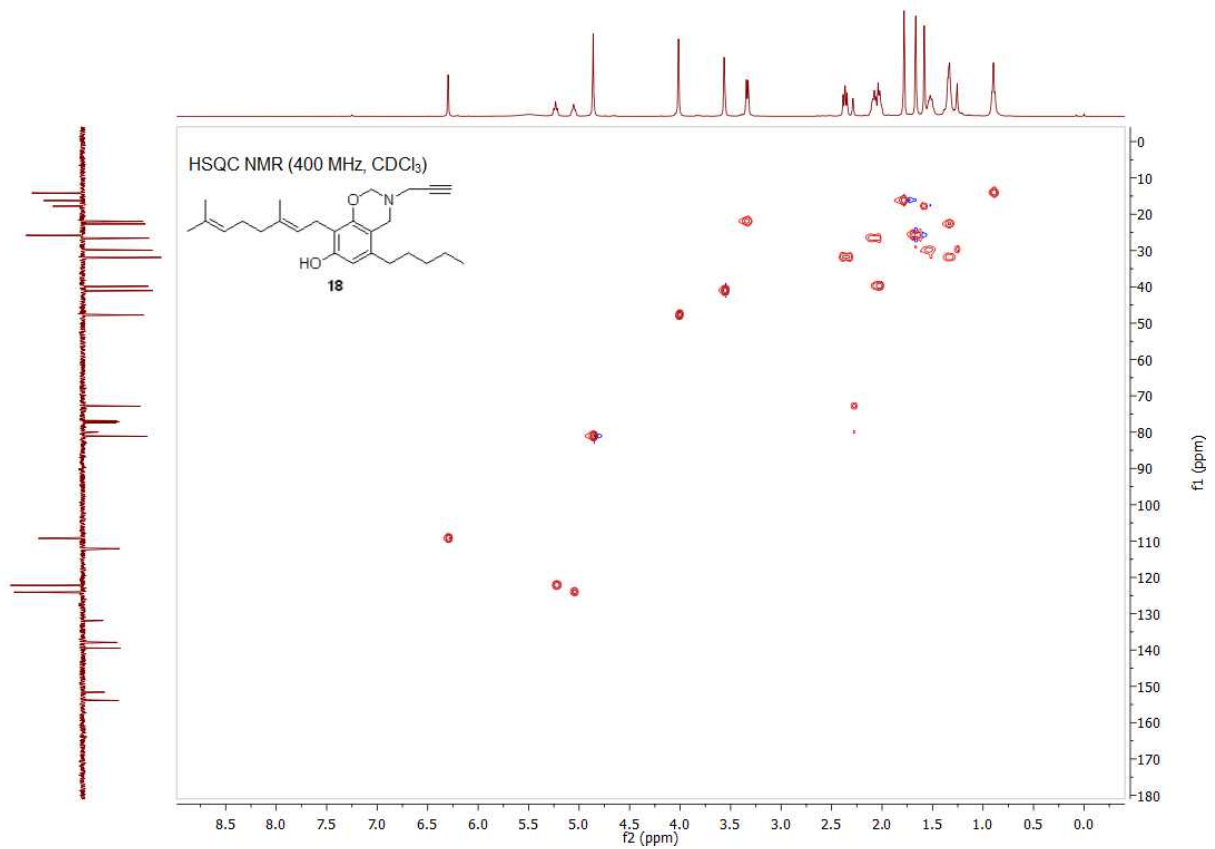
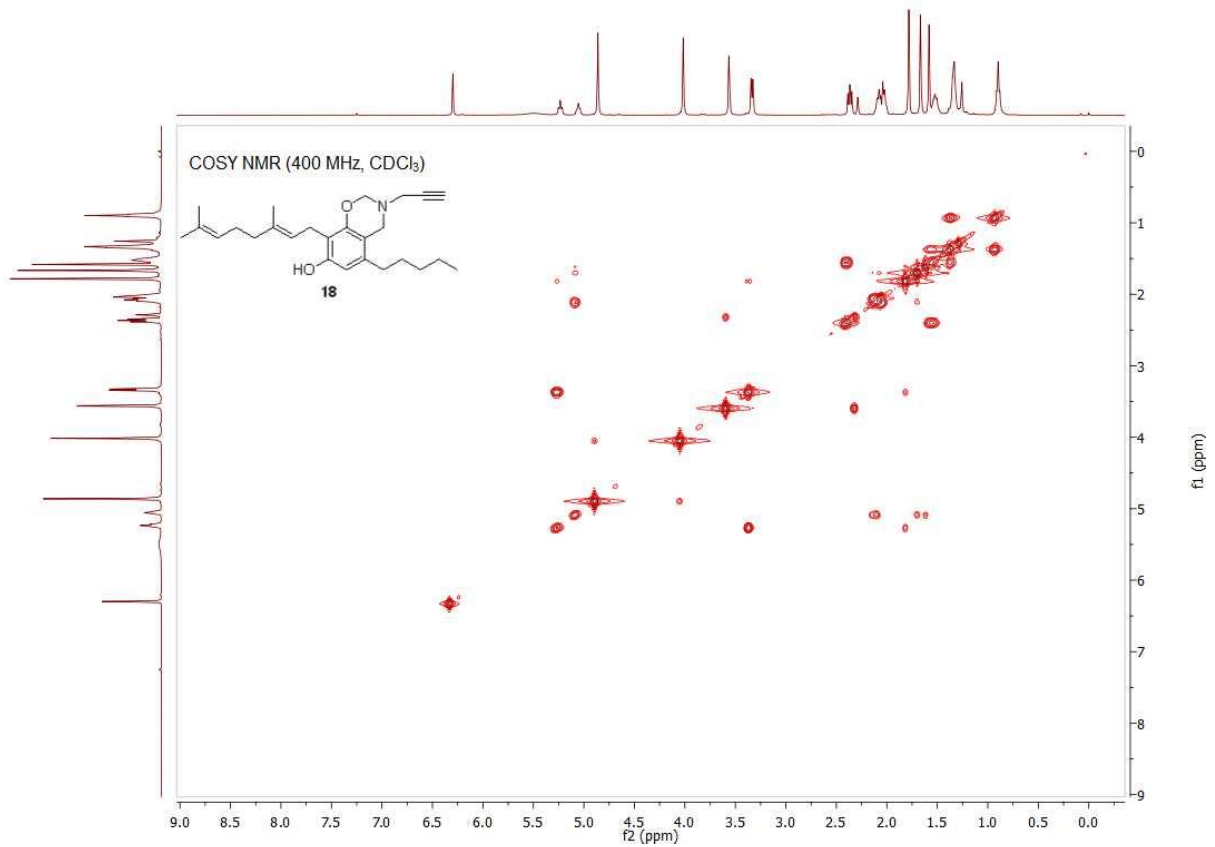
# NMR spectra of compound 17b



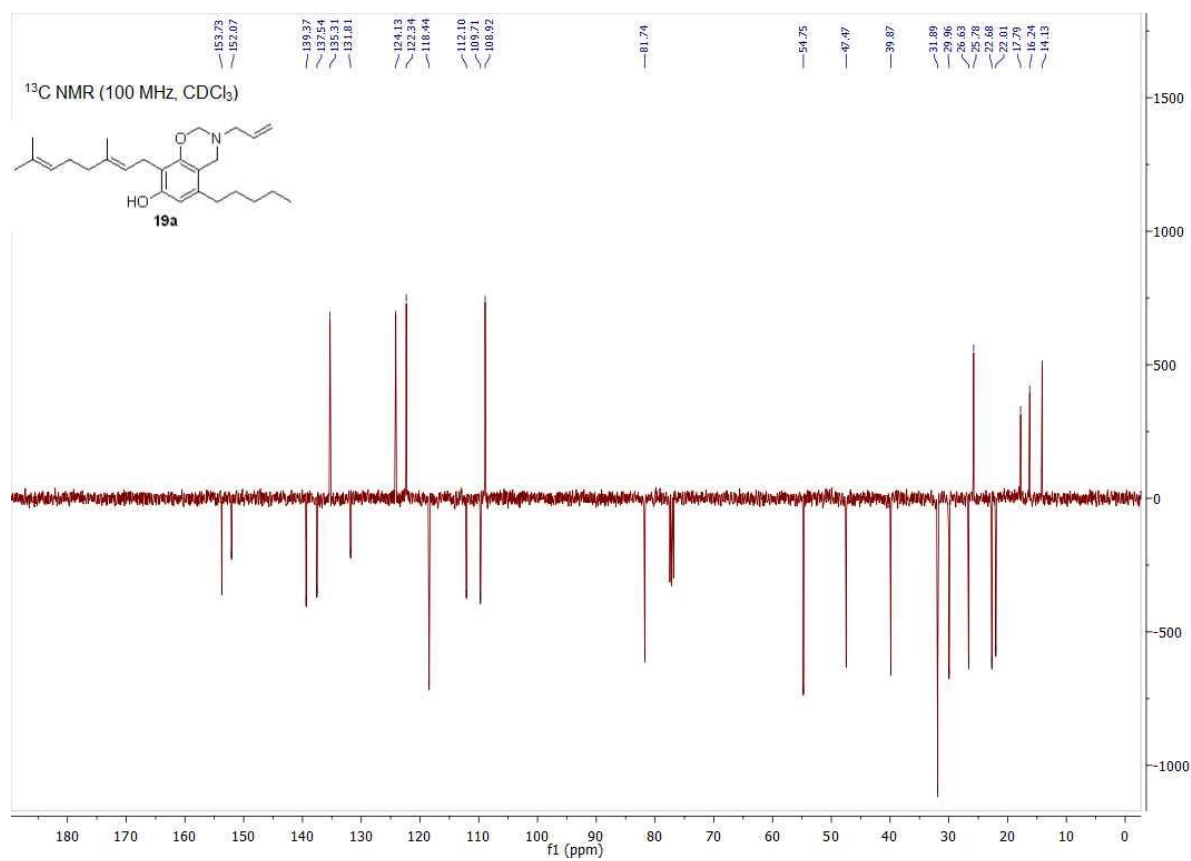
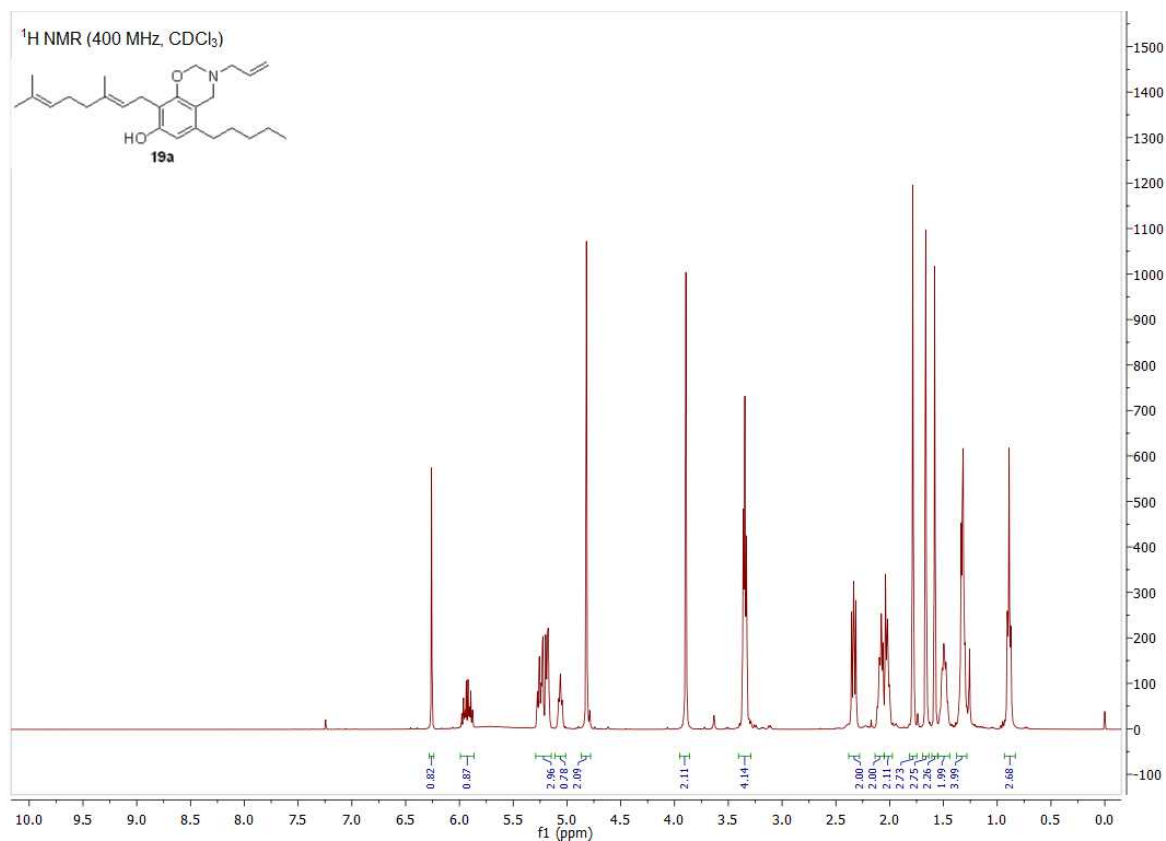


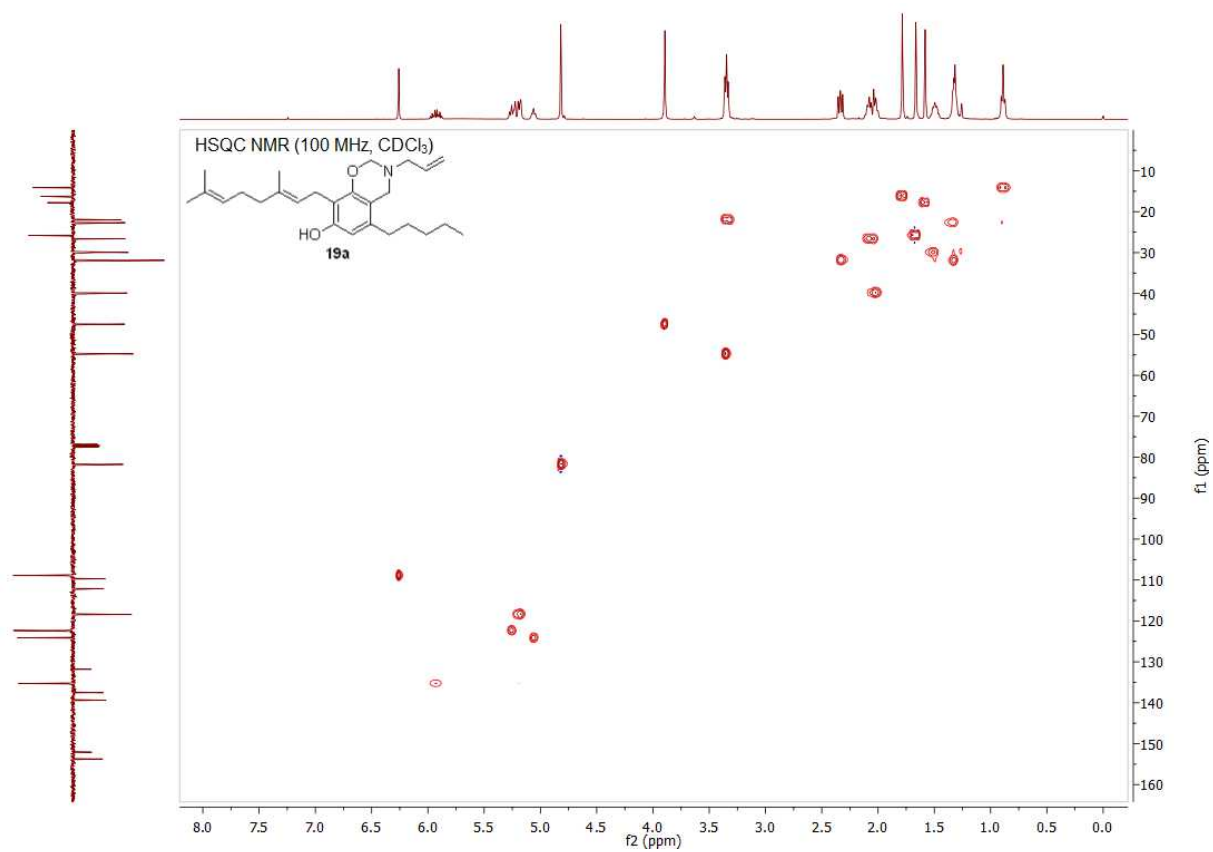
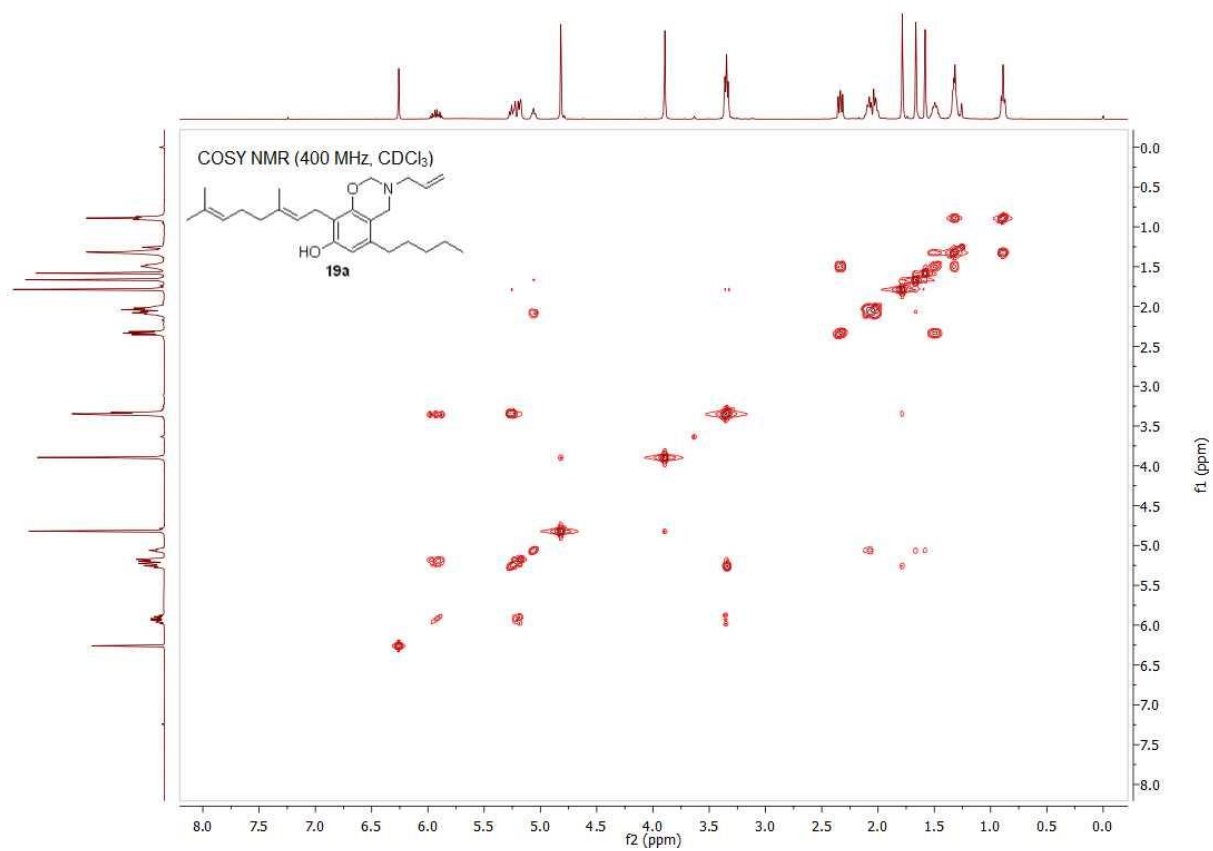
# NMR spectra of compound 18



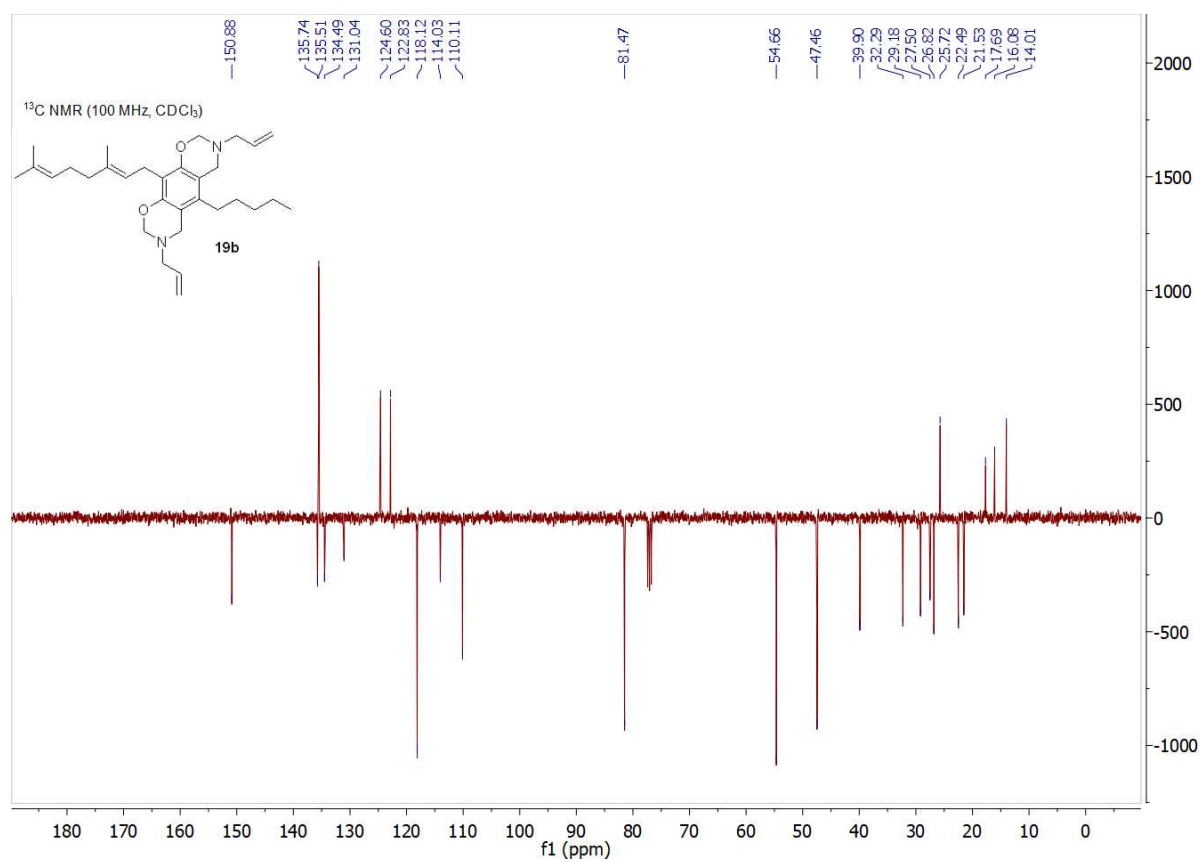
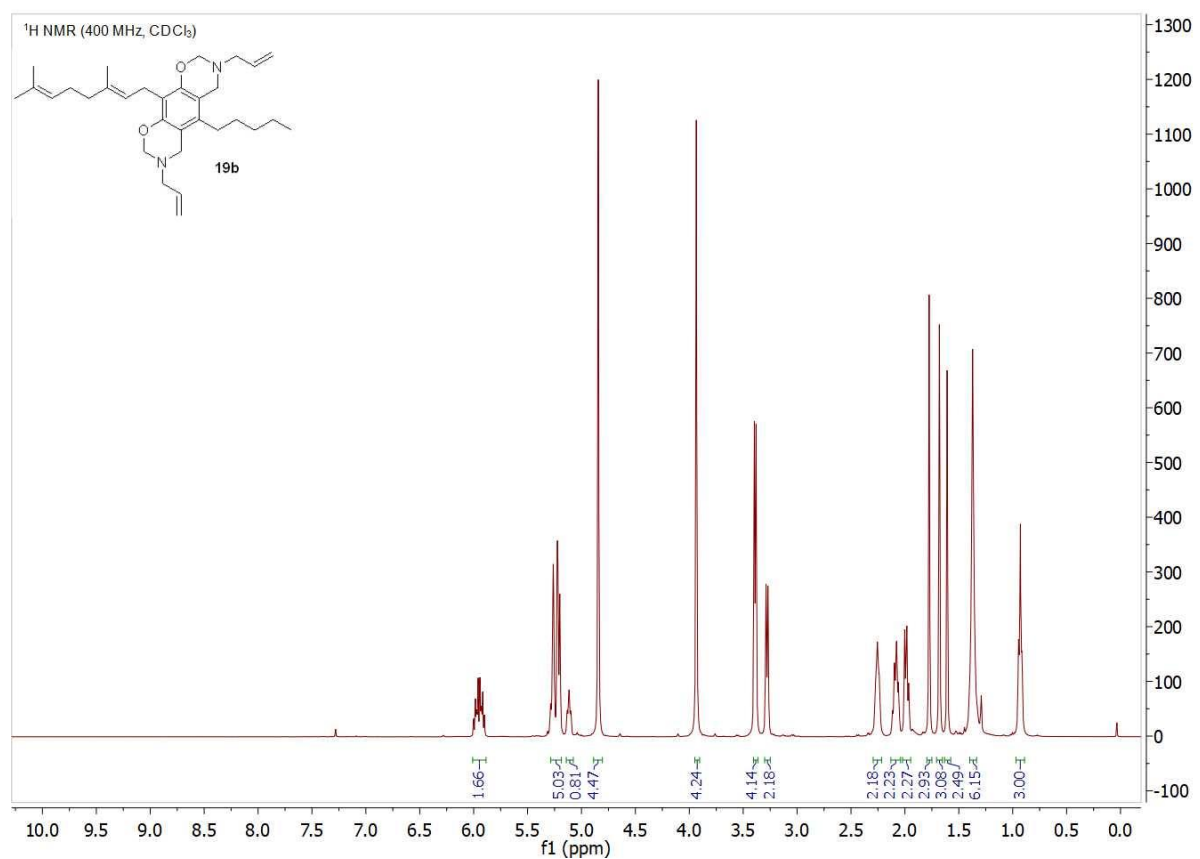


# NMR spectra of compound 19a

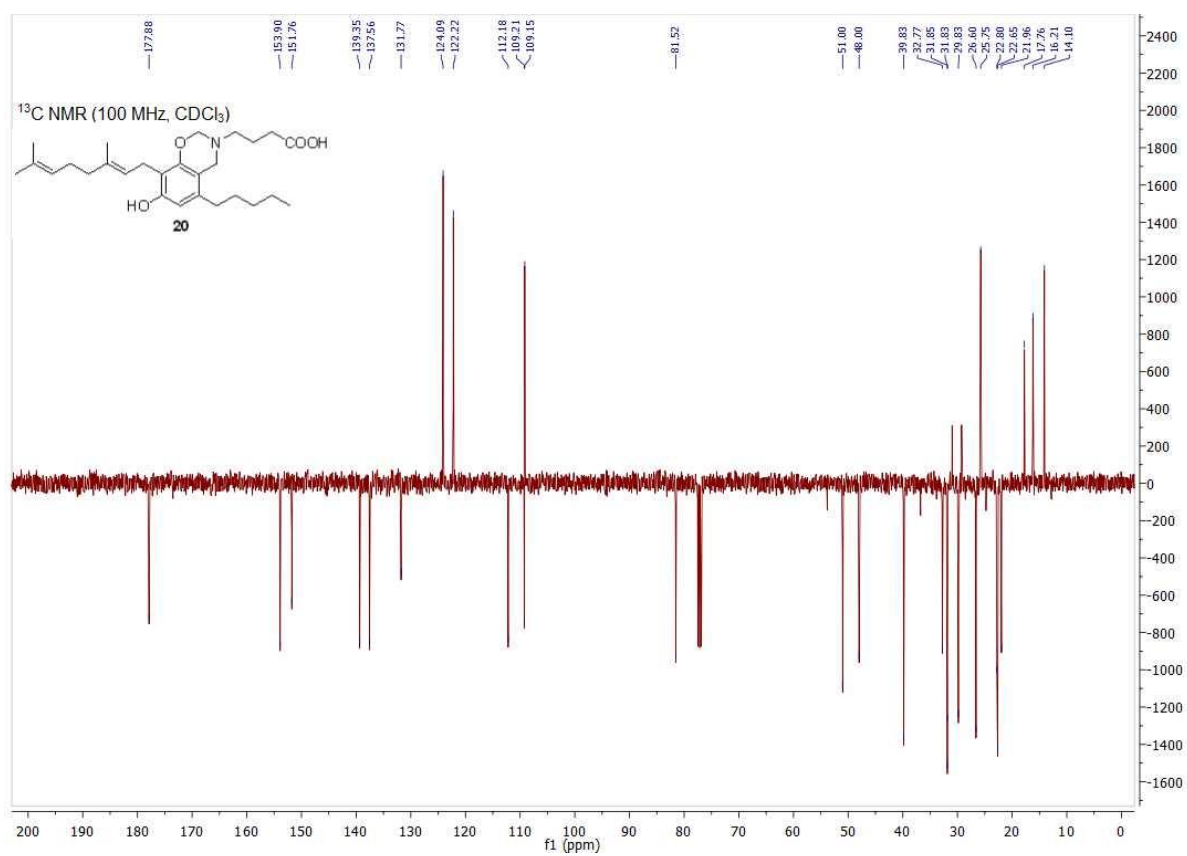
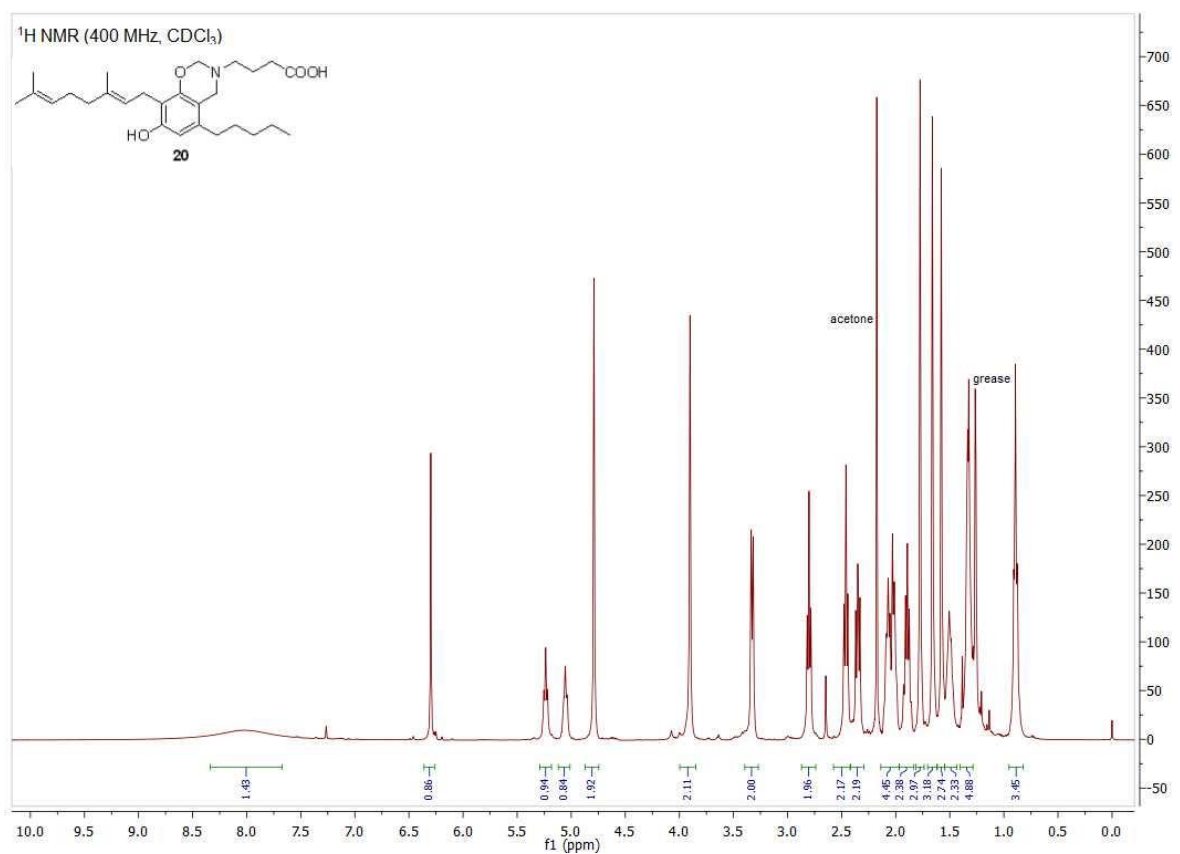


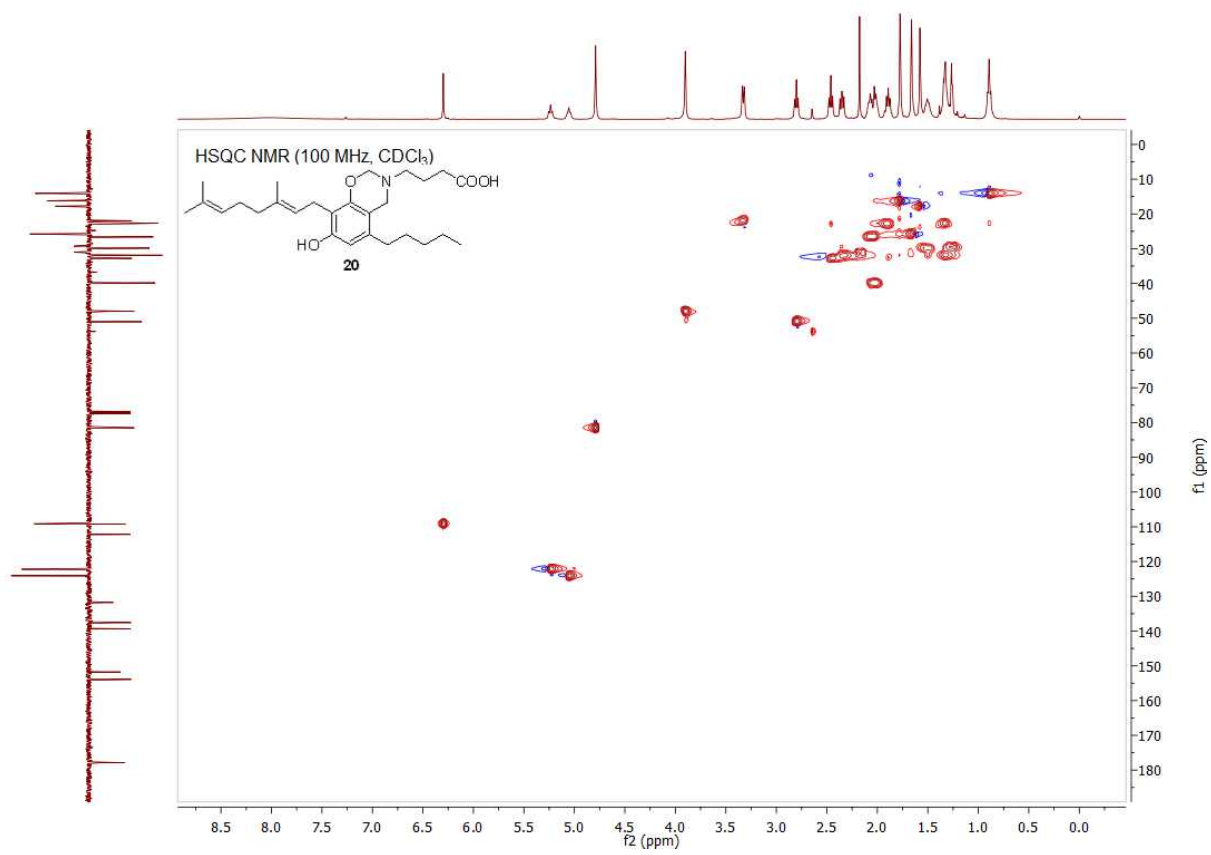
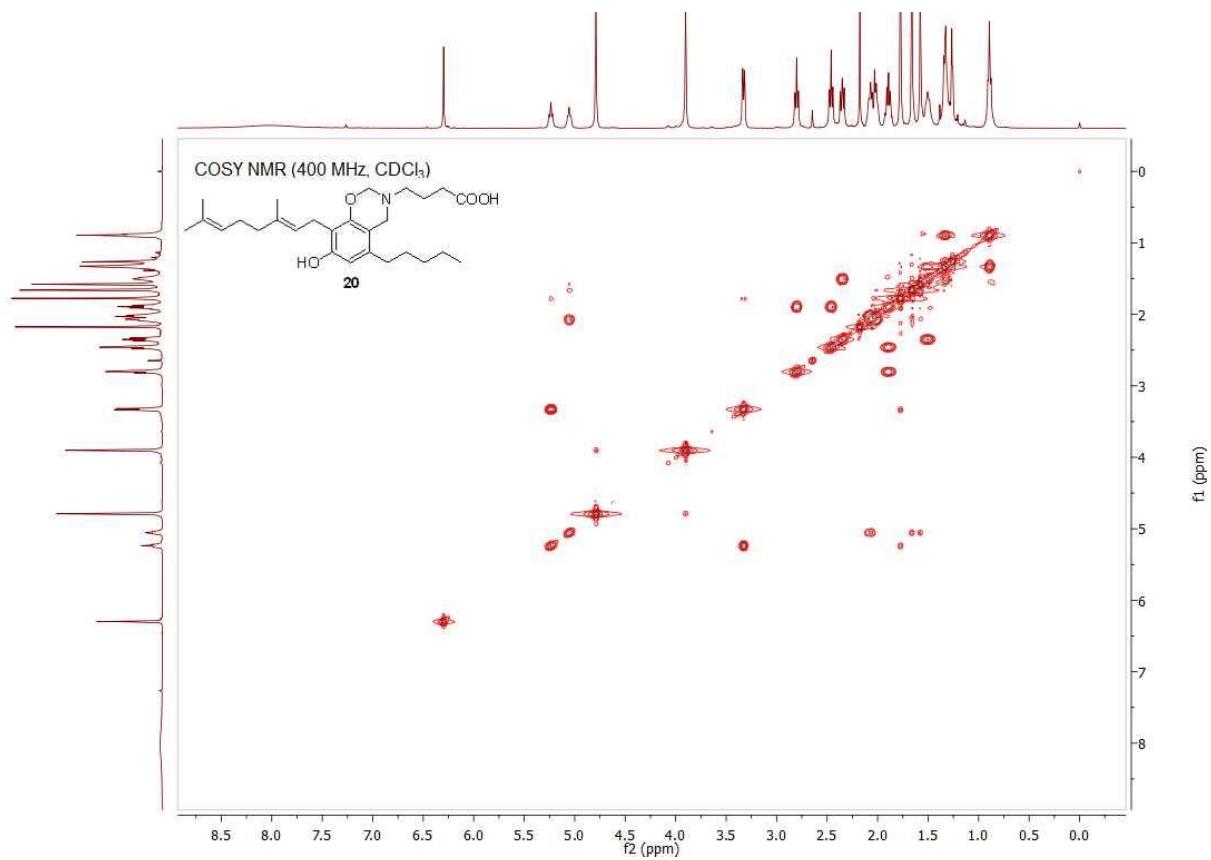


# NMR spectra of compound 19b

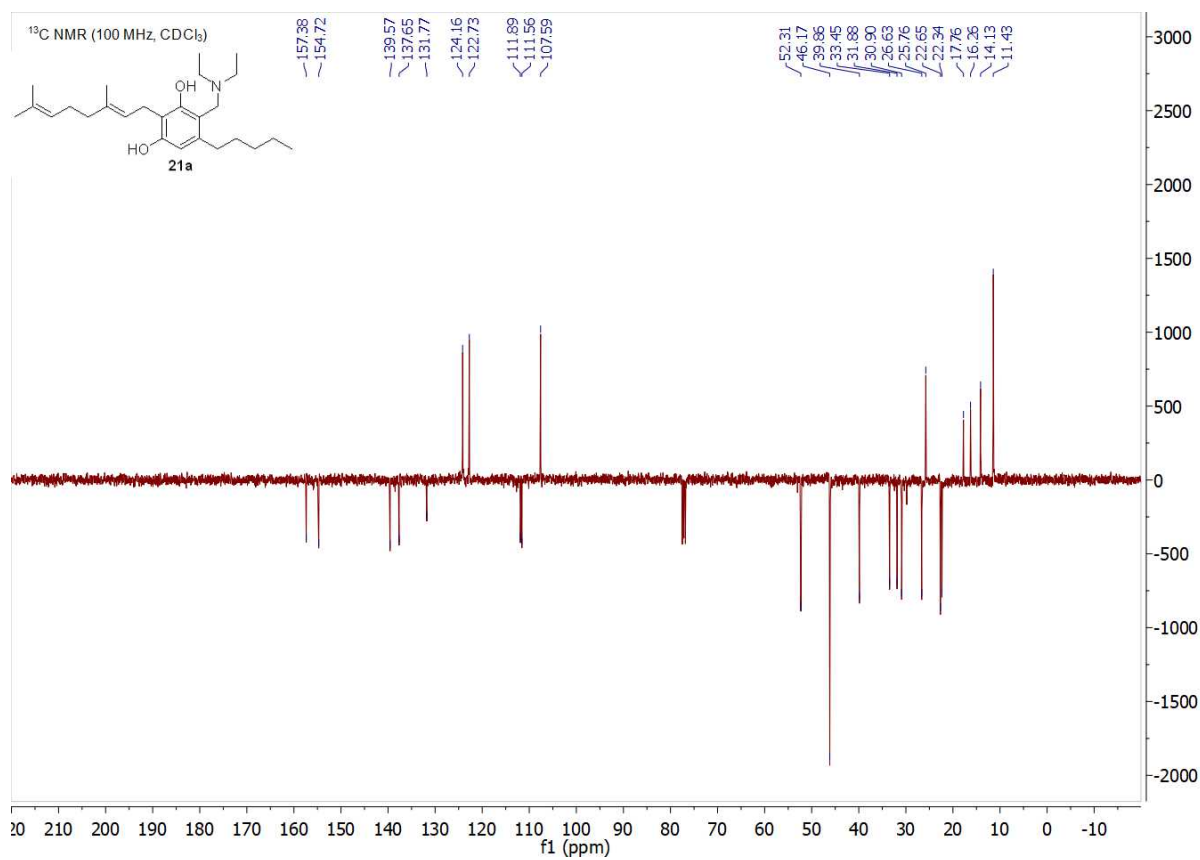
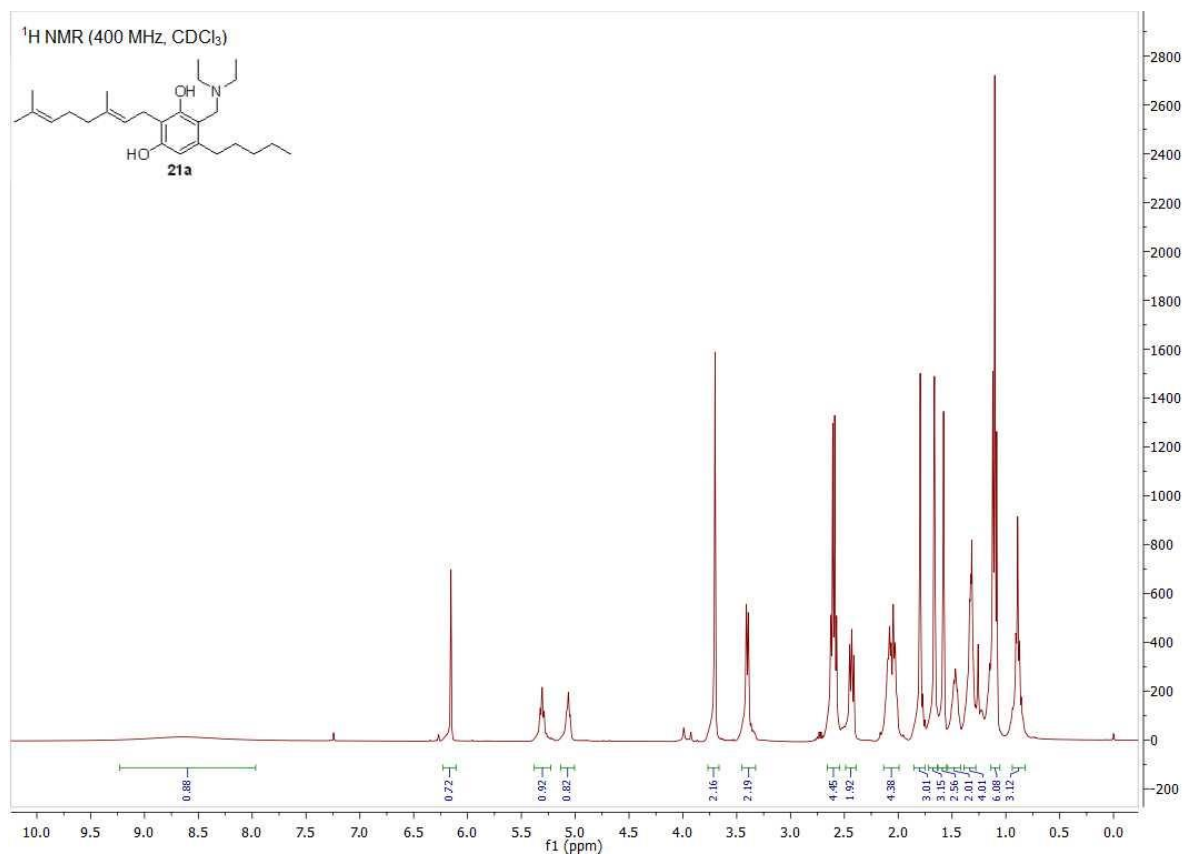


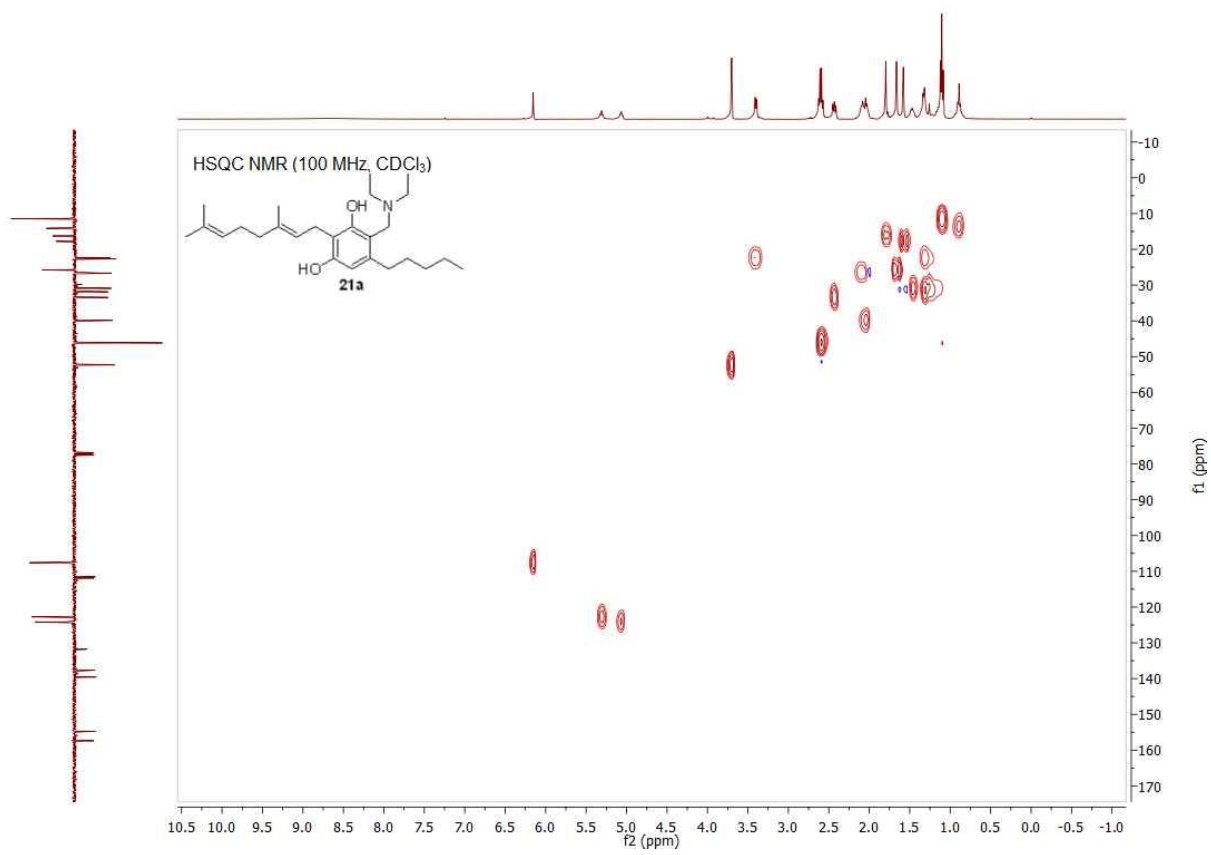
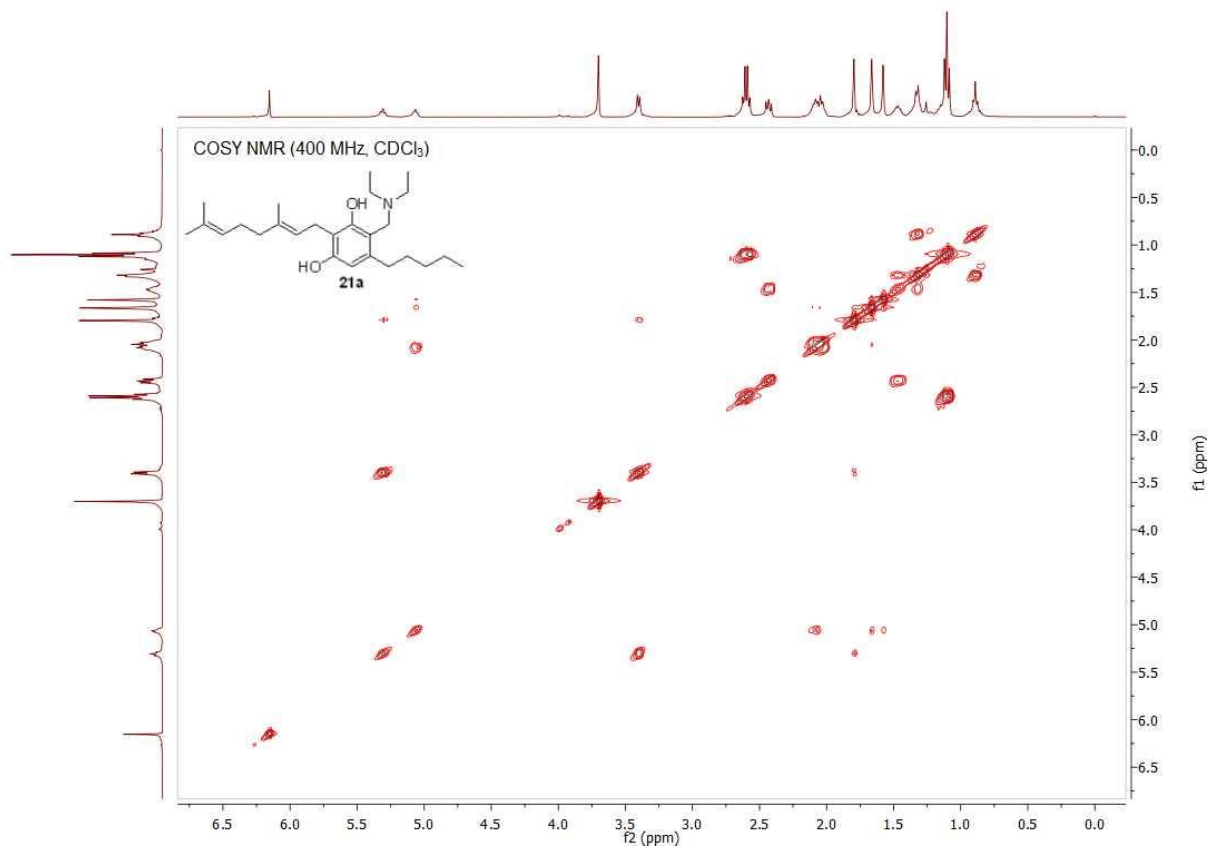
## NMR spectra of compound 20





# NMR spectra of compound 21a





# NMR spectra of compound 21b

