Supplementary information

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

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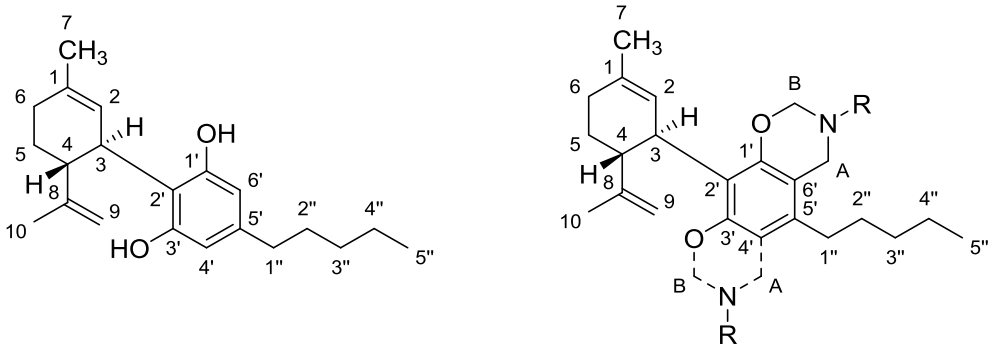
1. Antibacterial data against Gram-positive bacteria

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

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

2. NMR data of CBD and its derivatives

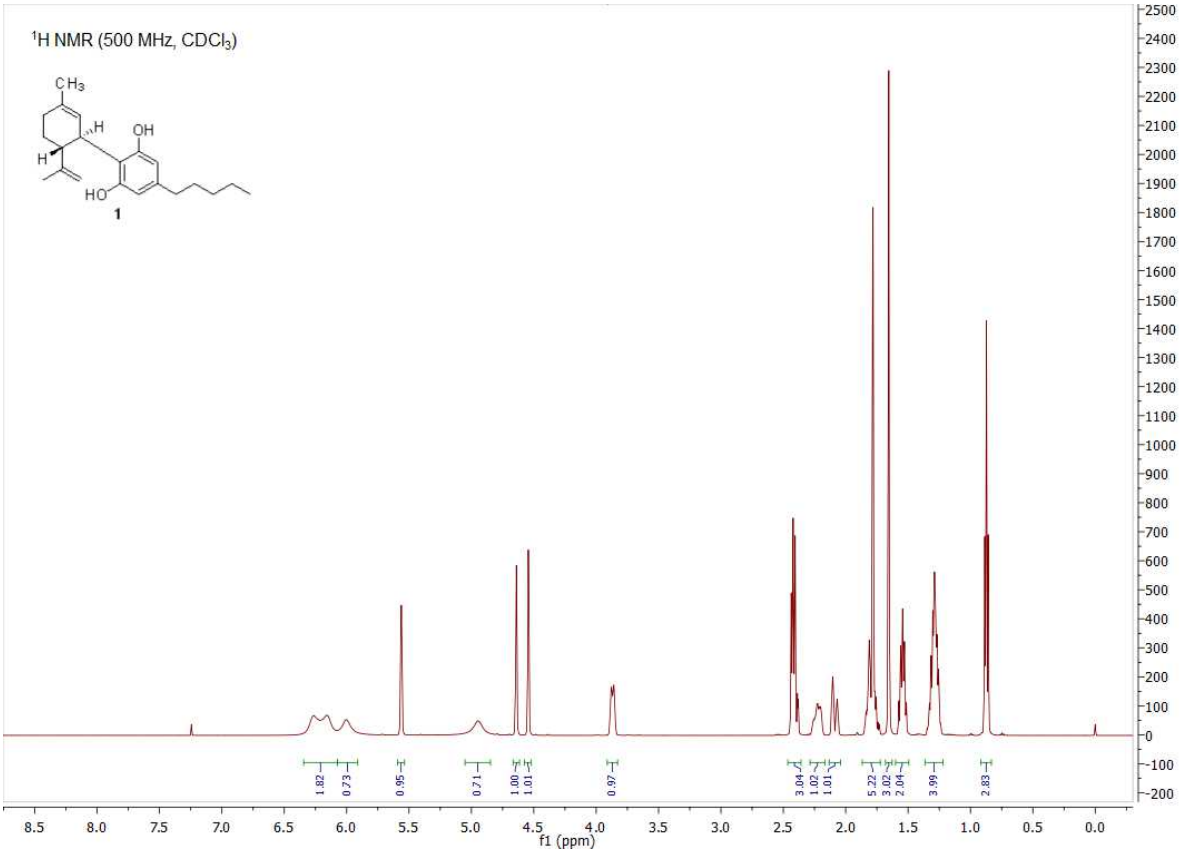


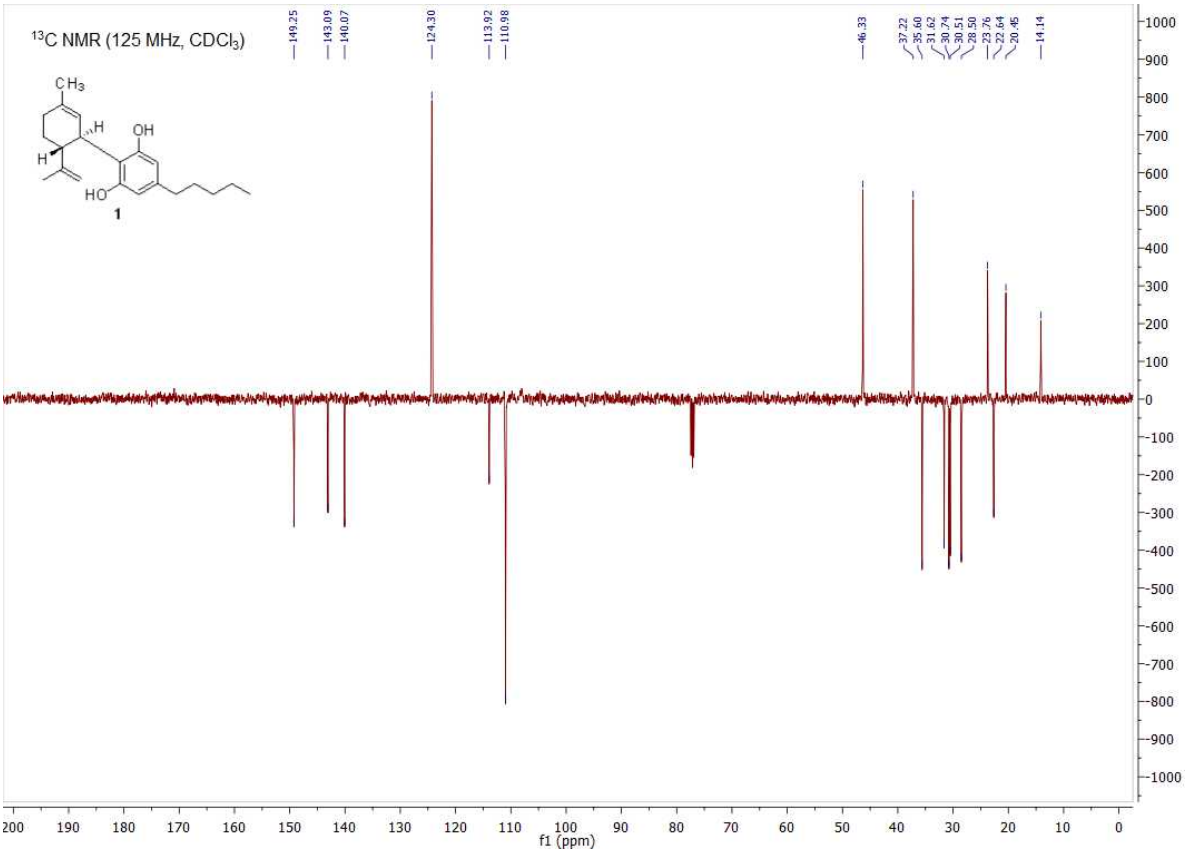
Scheme S1. Numbering of CBD and its derivatives

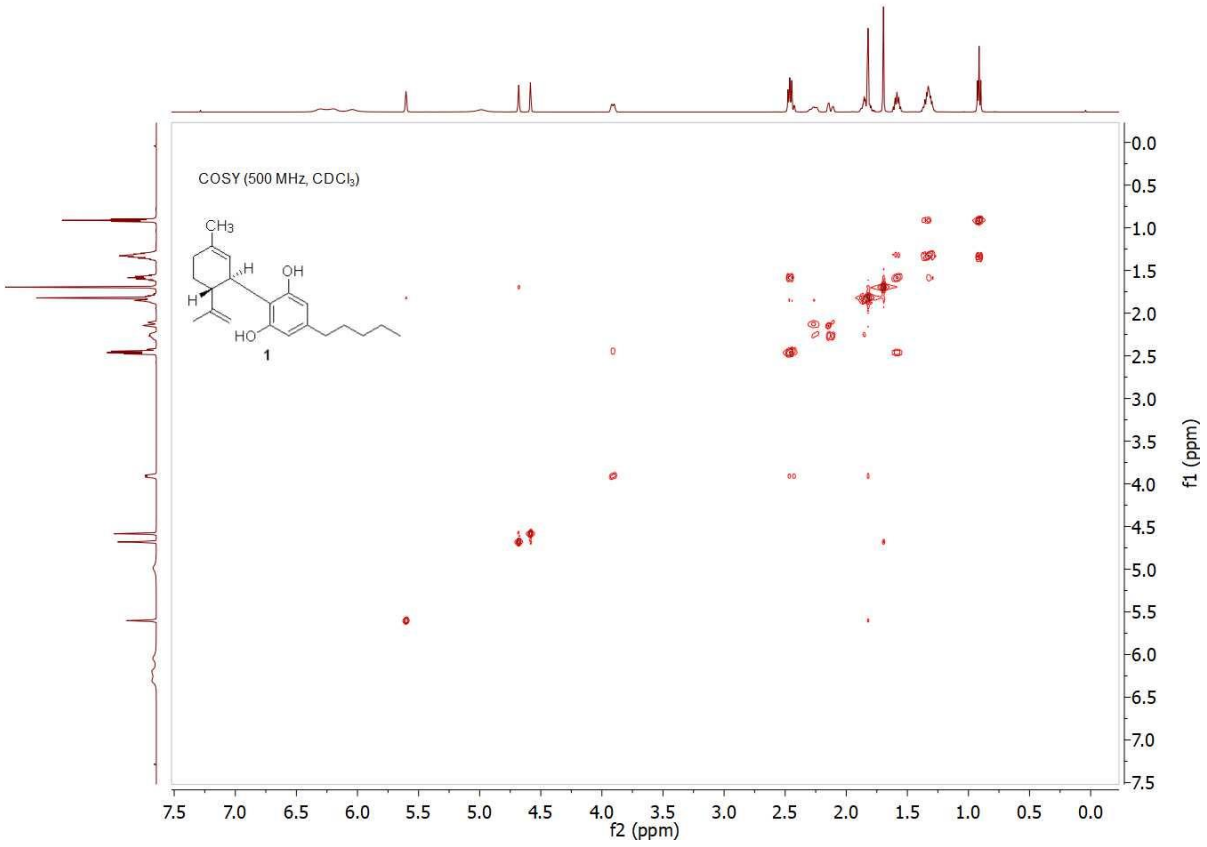
NMD data of cannabidiol:

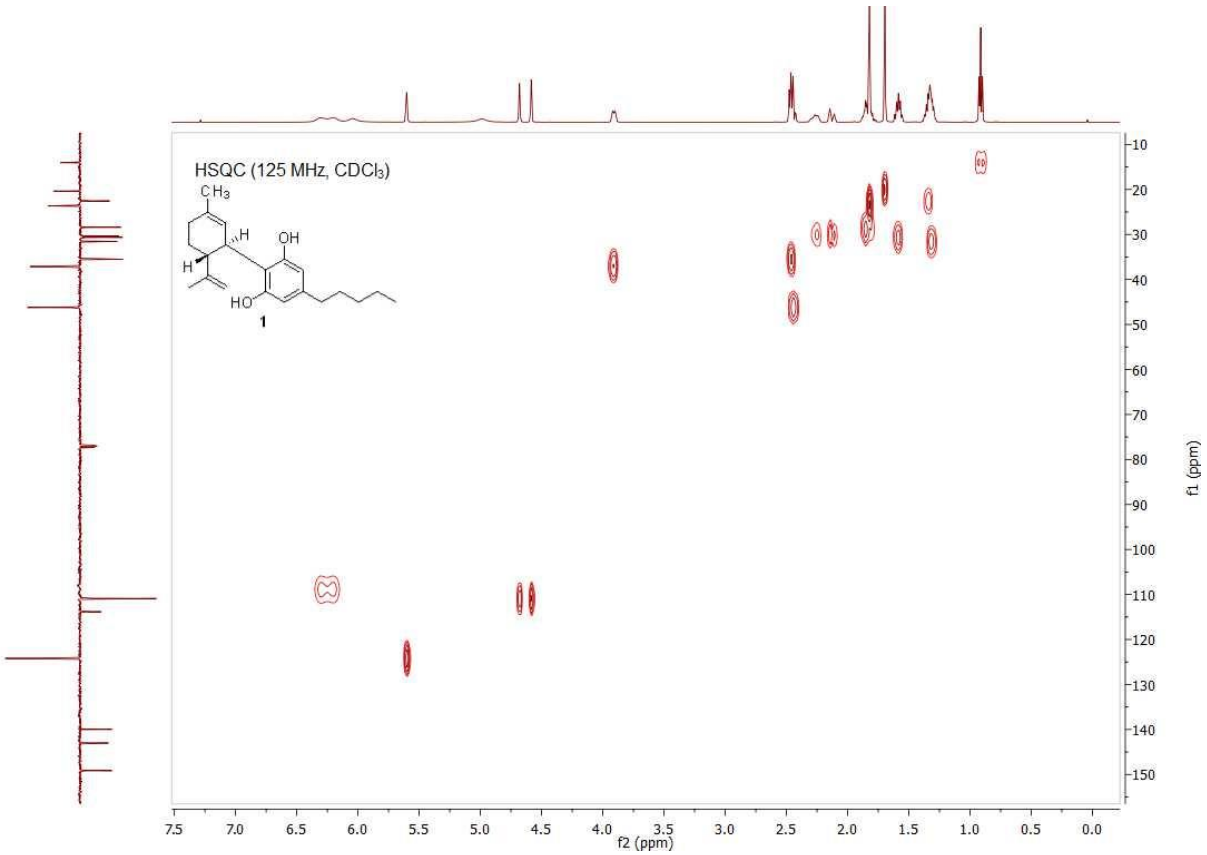
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.34-6.09 (m, 2H, aromatic C*H*), 6.00 (bs, 1H, O*H*), 5.56 (m, 1H, H-2 C*H*), 4.95 (bs, 1H, O*H*), 4.64 (m, 1H, H-9 CH_2a), 4.54 (m, 1H, H-9 CH_2b), 3.90-3.83 (m, 1H, H-3 C*H*), 2.46-2.36 (m, 3H, H-1" CH_2 and H-4 C*H*), 2.29-2.17 (m, 1H, H-6 CH_2a), 2.13-2.04 (m, 1H, H-6 CH_2b), 1.86-1.72 (m, 5H, H-5 CH_2 and H-7 CH_3), 1.66 (s, 3H, H-10 CH_3), 1.59-1.50 (m, 2H, H-2" CH_2), 1.35-1.22 (m, 4H, H-3" and H-4" CH_2), 0.87 (t, 3H, J = 6.9 Hz, H-5" CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 149.3 (1C, C-8, quat.), 143.1 (1C, C-3', quat.), 140.1 (1C, C-1, quat.), 124.3 (1C, C-2, *C*H), 113.9 (1C, C-6', quat.), 111.0 (1C, C-9, *C*H_2), 46.3 (1C, C-4, *C*H), 37.2 (1C, C-3, *C*H), 35.6 (1C, C-1", *C*H_2), 31.6 (1C, C-3", *C*H_2), 30.7 (1C, C-2", *C*H_2), 30.5 (1C, C-6, *C*H_2), 28.5 (1C, C-5, *C*H_2), 23.8 (1C, C-7, *C*H_3), 22.6 (1C, C-4", *C*H_2), 20.5 (1C, C-10, *C*H_3), 14.1 (1C, C-5", *C*H_3).

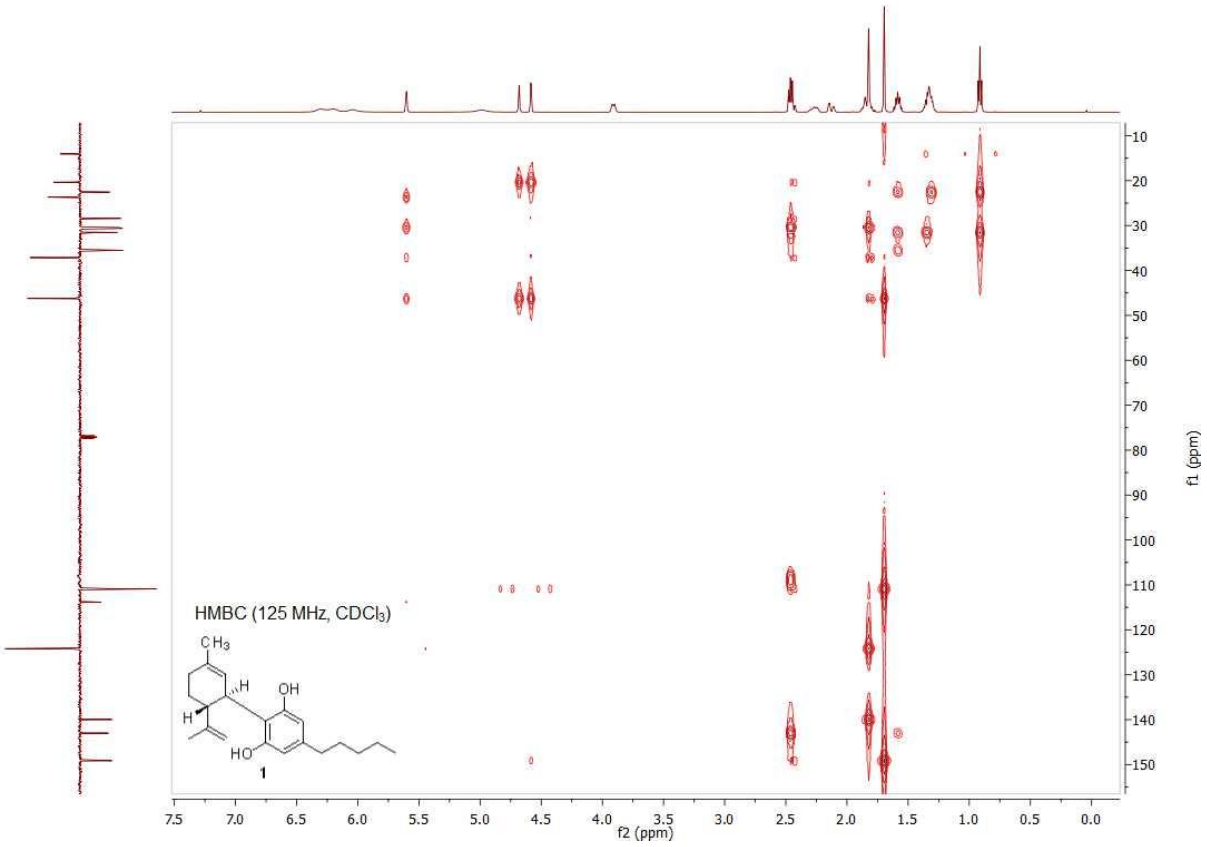
NMR spectra of CBD



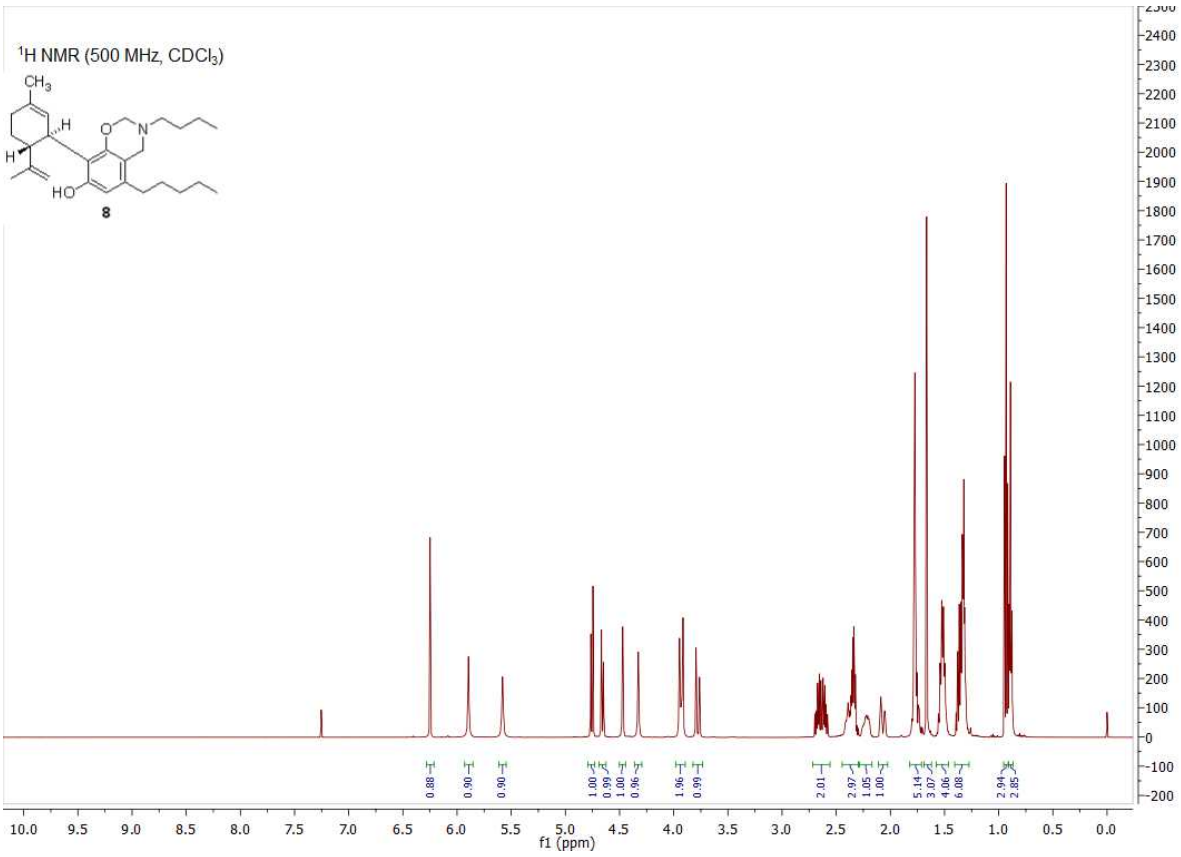


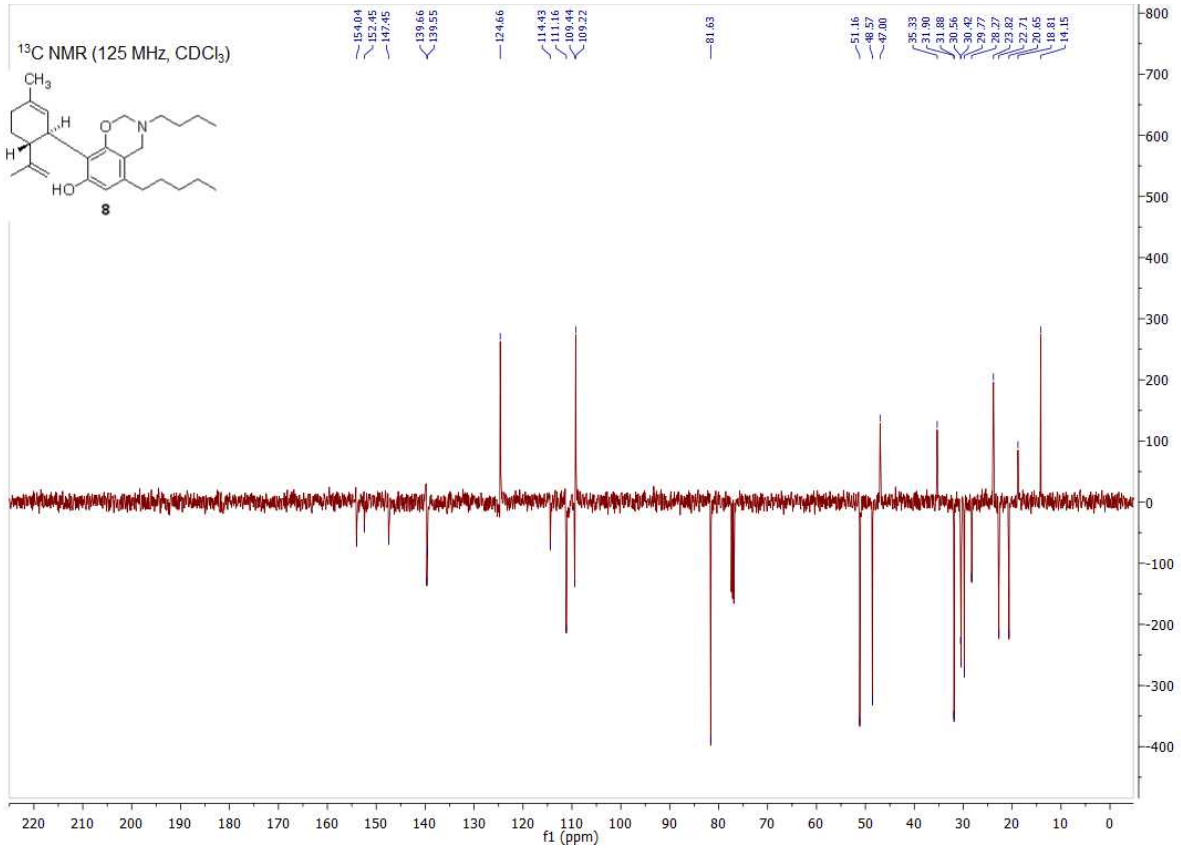

COSY (500 MHz, CDCl3)
CH3
H
OH
H
HO
1
f2 (ppm)
f1 (ppm)

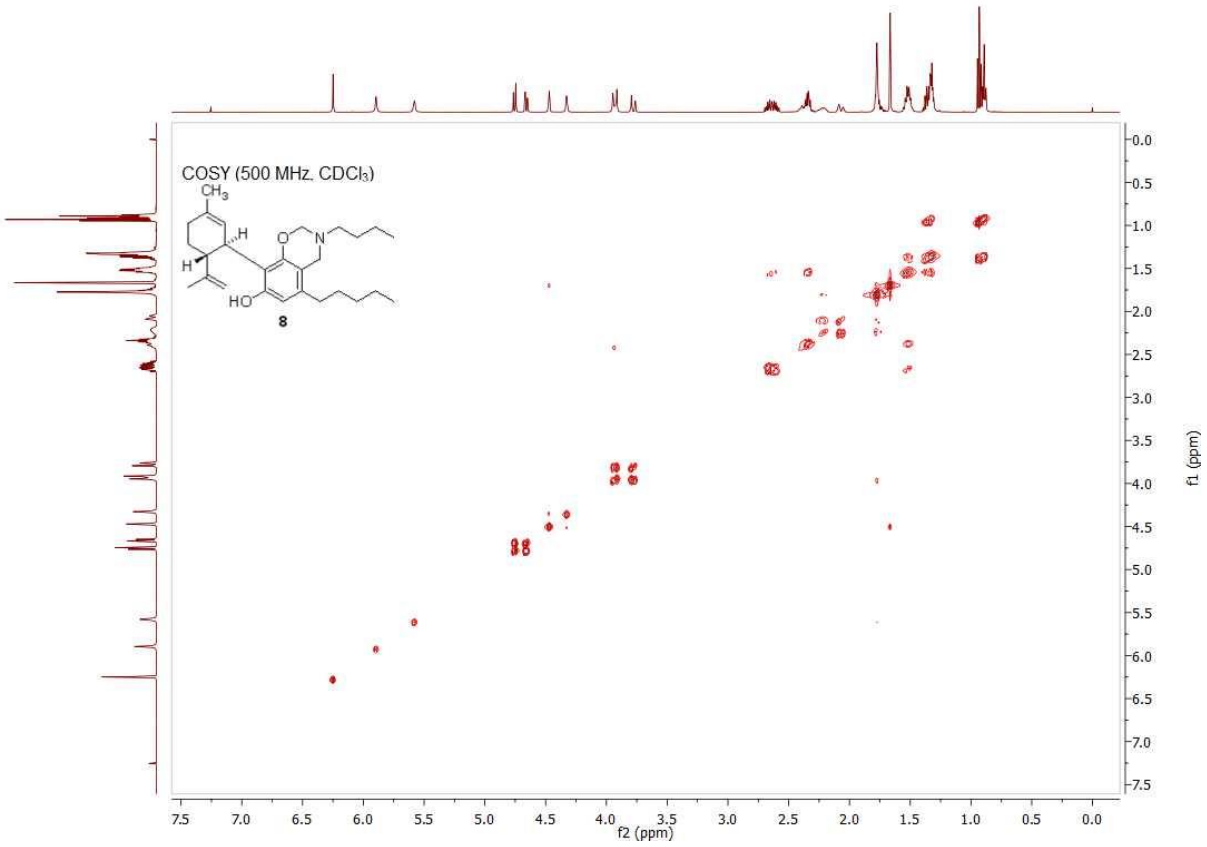

HSQC (125 MHz, CDCl3)
CH3
H
OH
H
HO
1
f2 (ppm)
f1 (ppm)

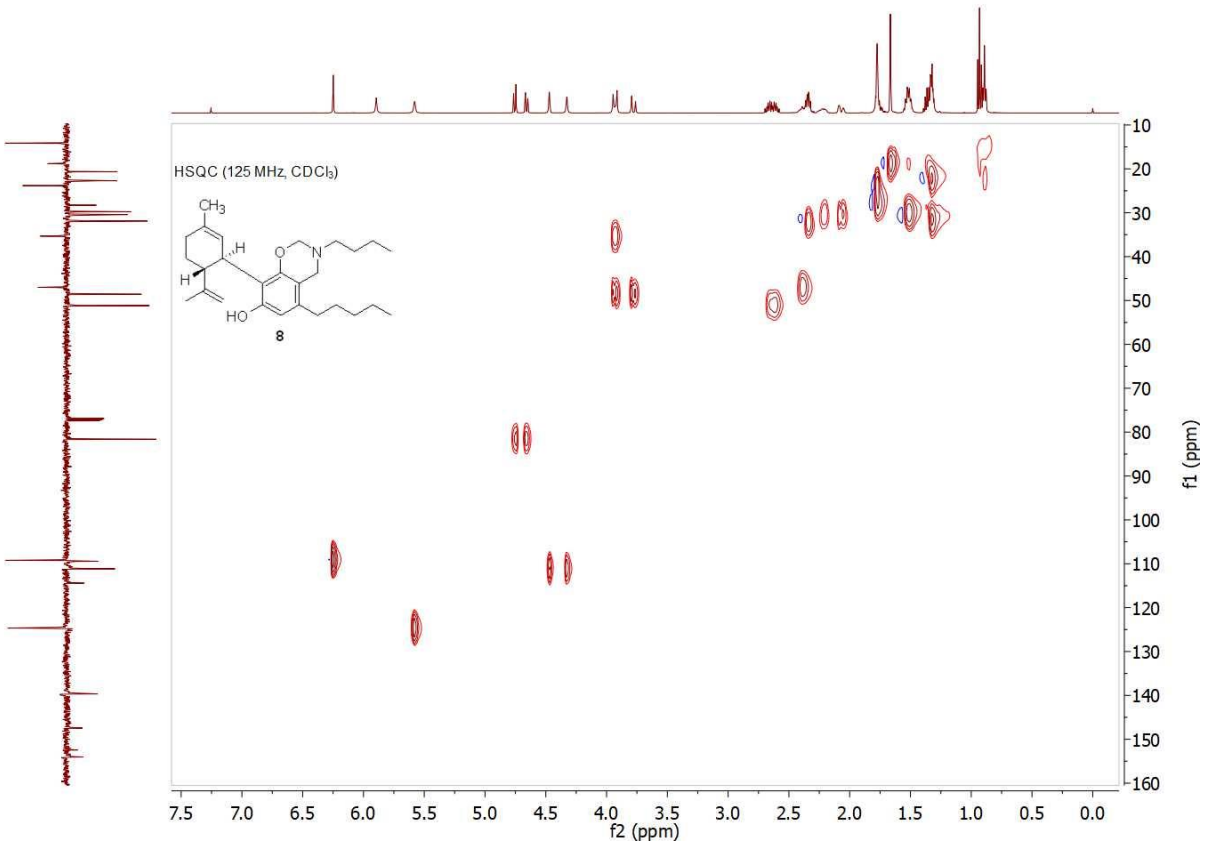

HMBC (125 MHz, CDCl3)
CH3
H
OH
H
HO
1
f1 (ppm)
f2 (ppm)

NMR spectra of compound 8

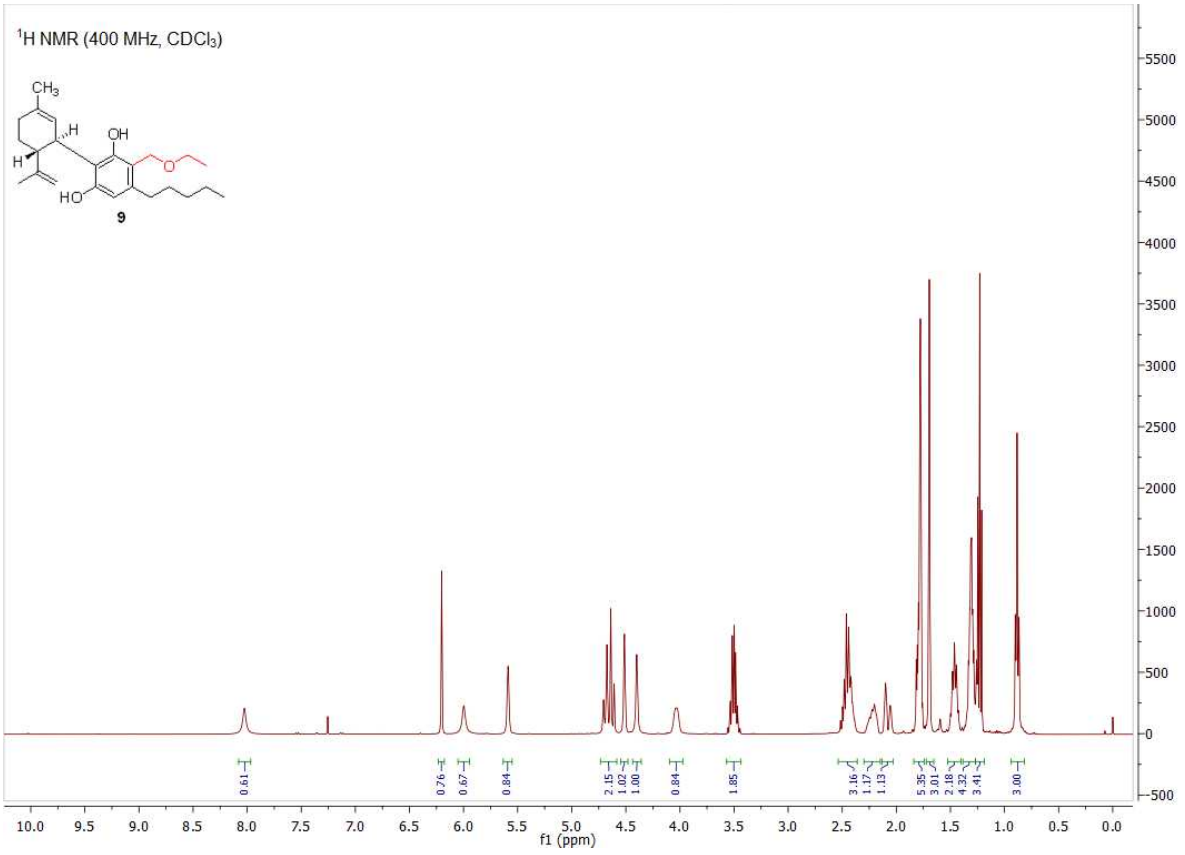


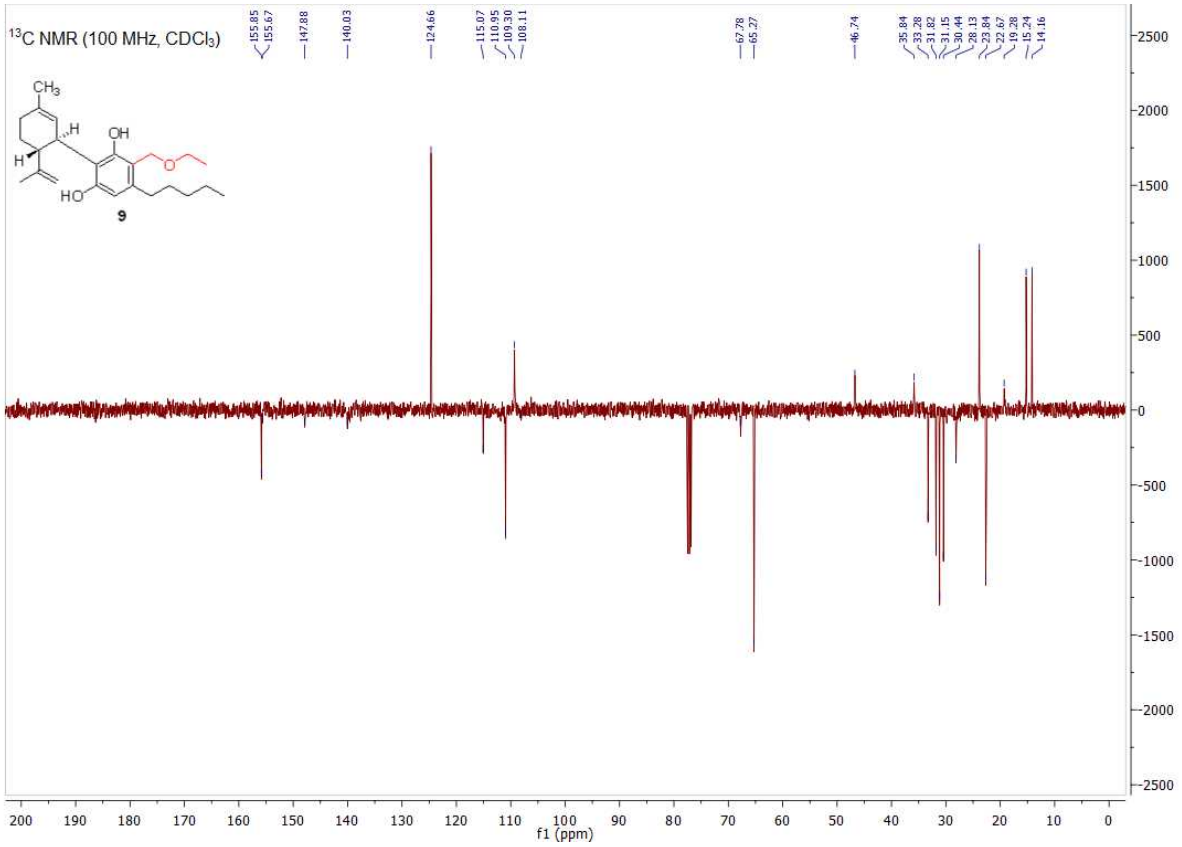


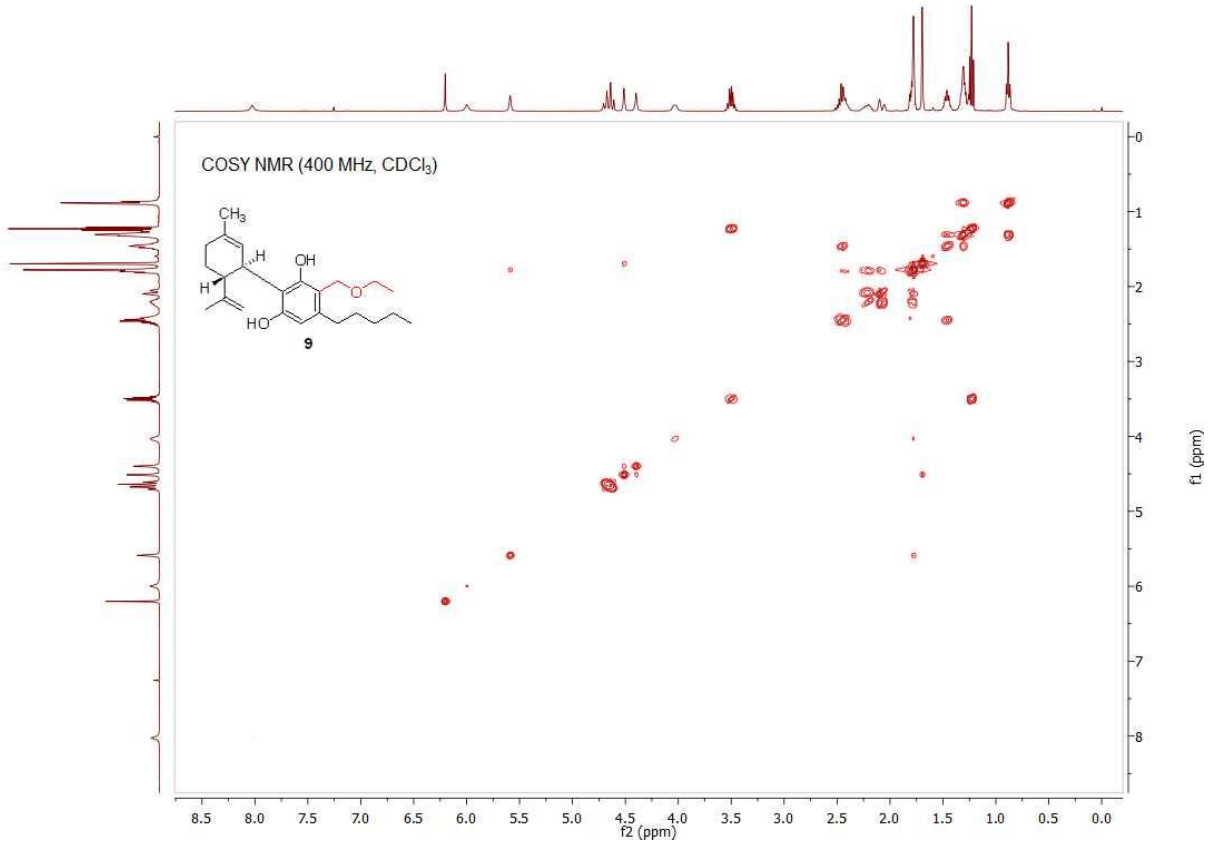

COSY (500 MHz, CDCl3)
CH3
H
O
N
H
HO
8
f1 (ppm)
f2 (ppm)

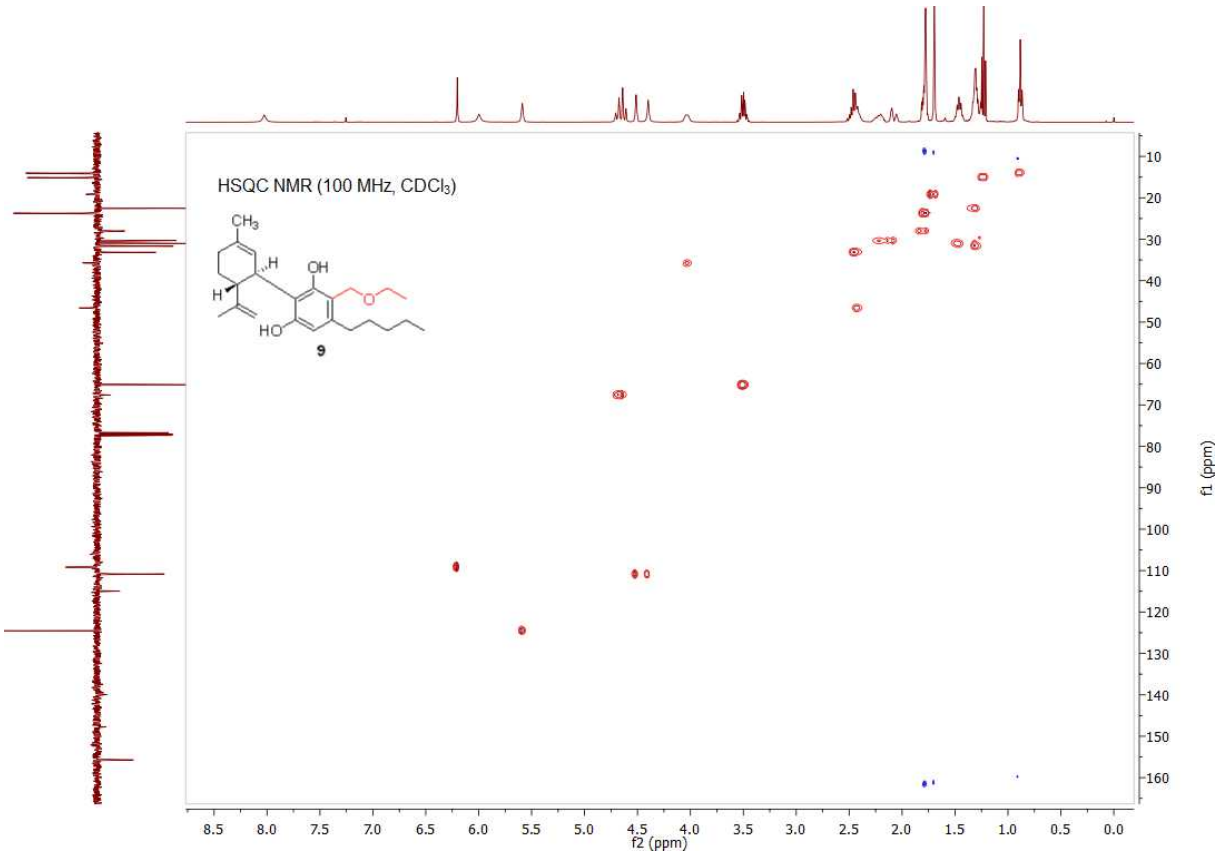

HSQC (125 MHz, CDCl3)
CH3
H
O
N
H
HO
8
f1 (ppm)
f2 (ppm)

NMR spectra of compound 9

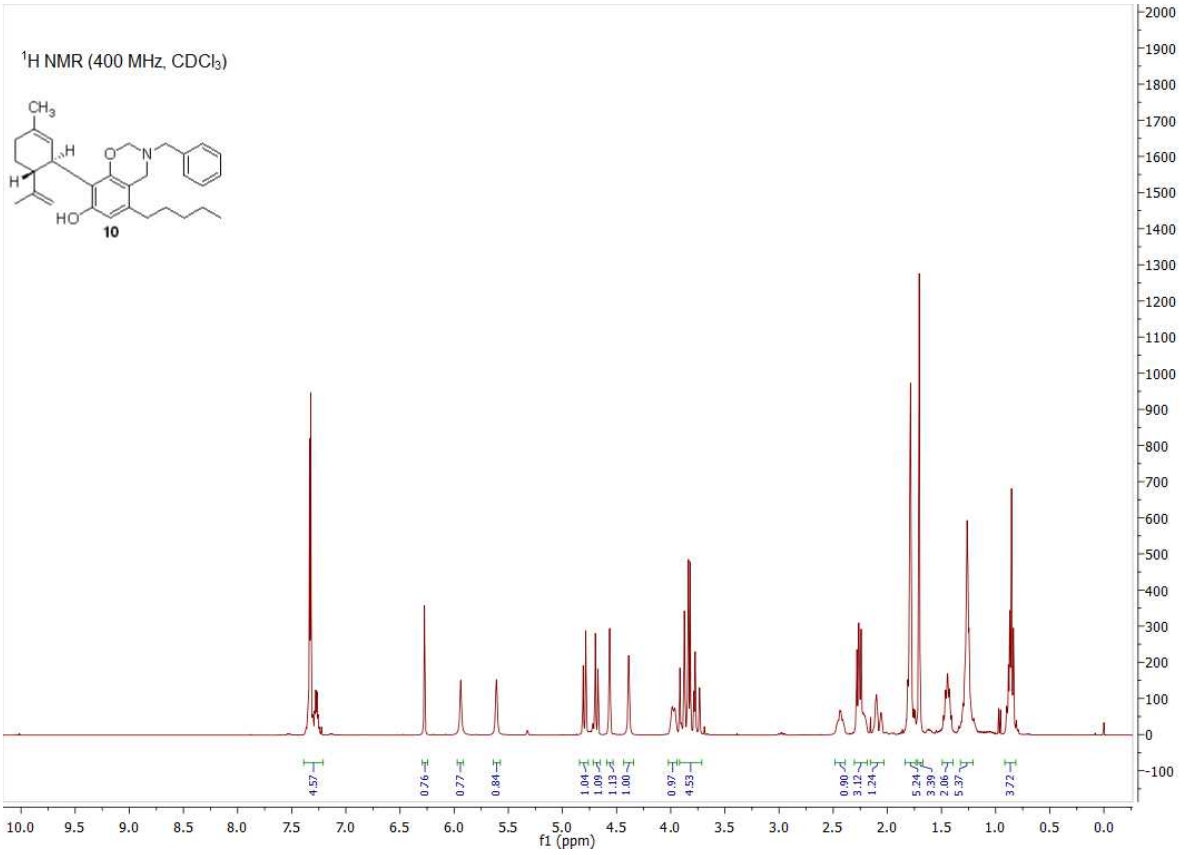


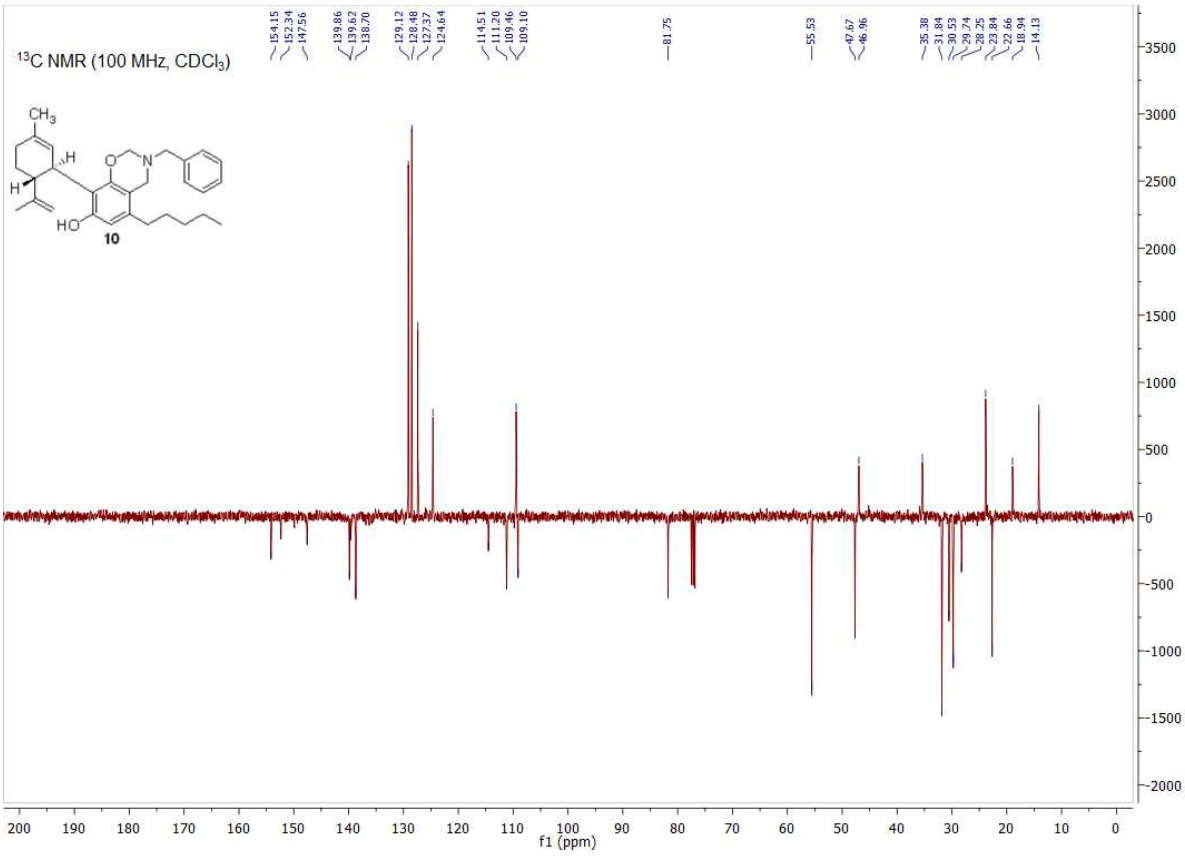


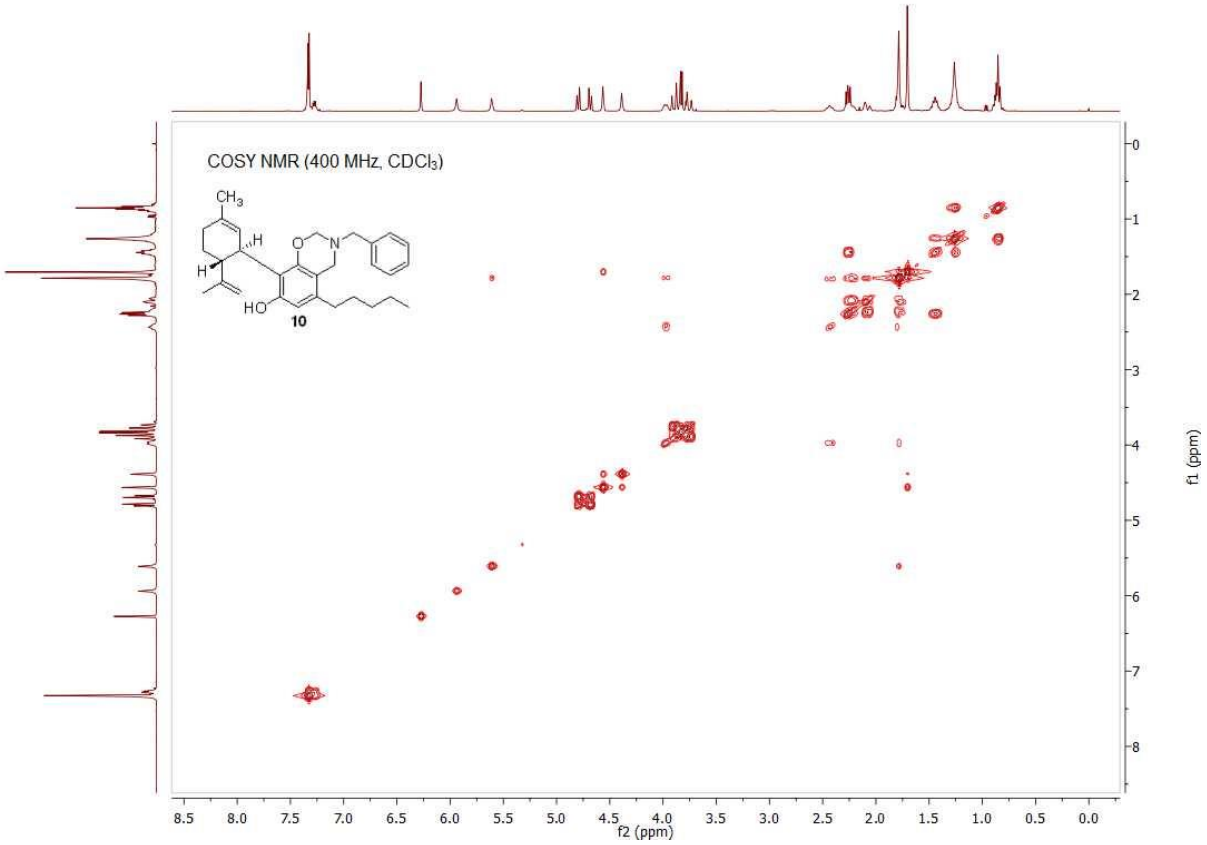

COSY NMR (400 MHz, CDCl3)
CH3
H
OH
O
HO
9
f1 (ppm)
f2 (ppm)

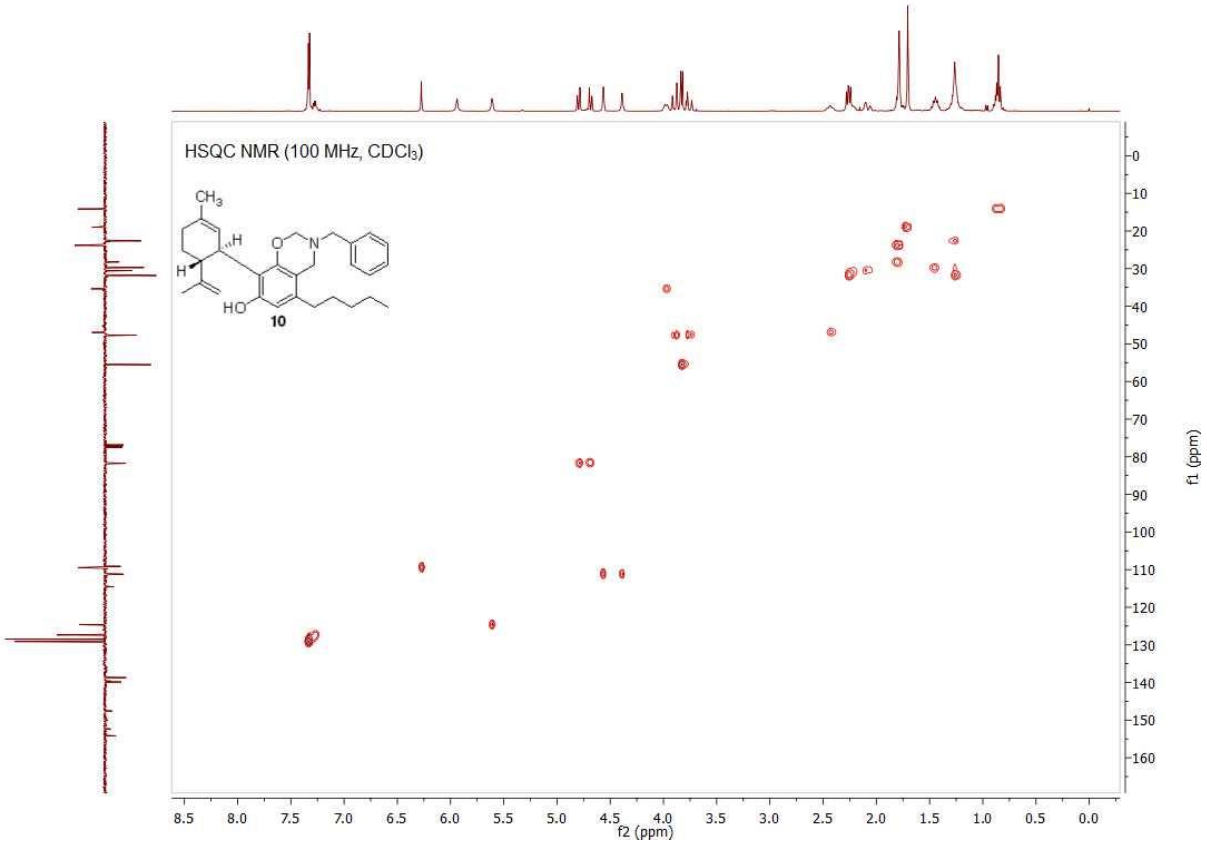

HSQC NMR (100 MHz, CDCl3)
CH3
H
OH
O
HO
9
f1 (ppm)
f2 (ppm)

NMR spectra of compound 10

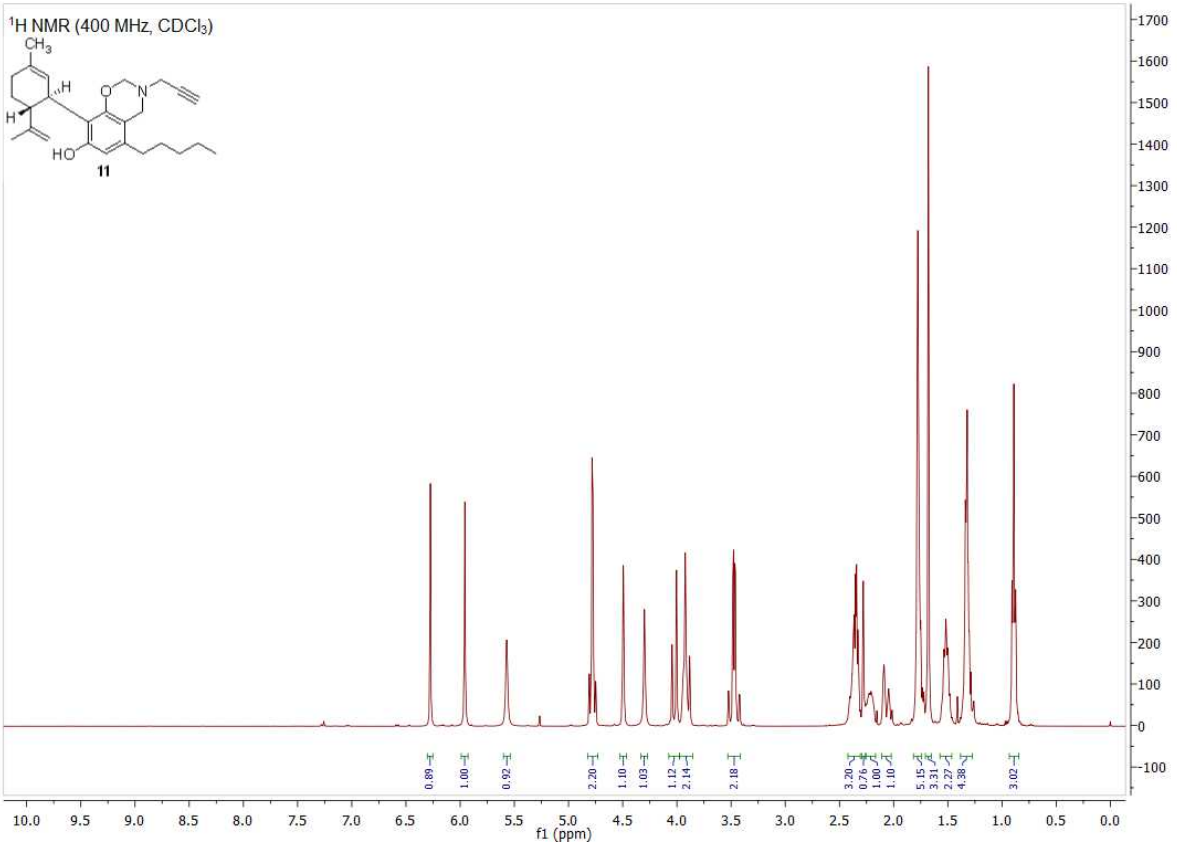


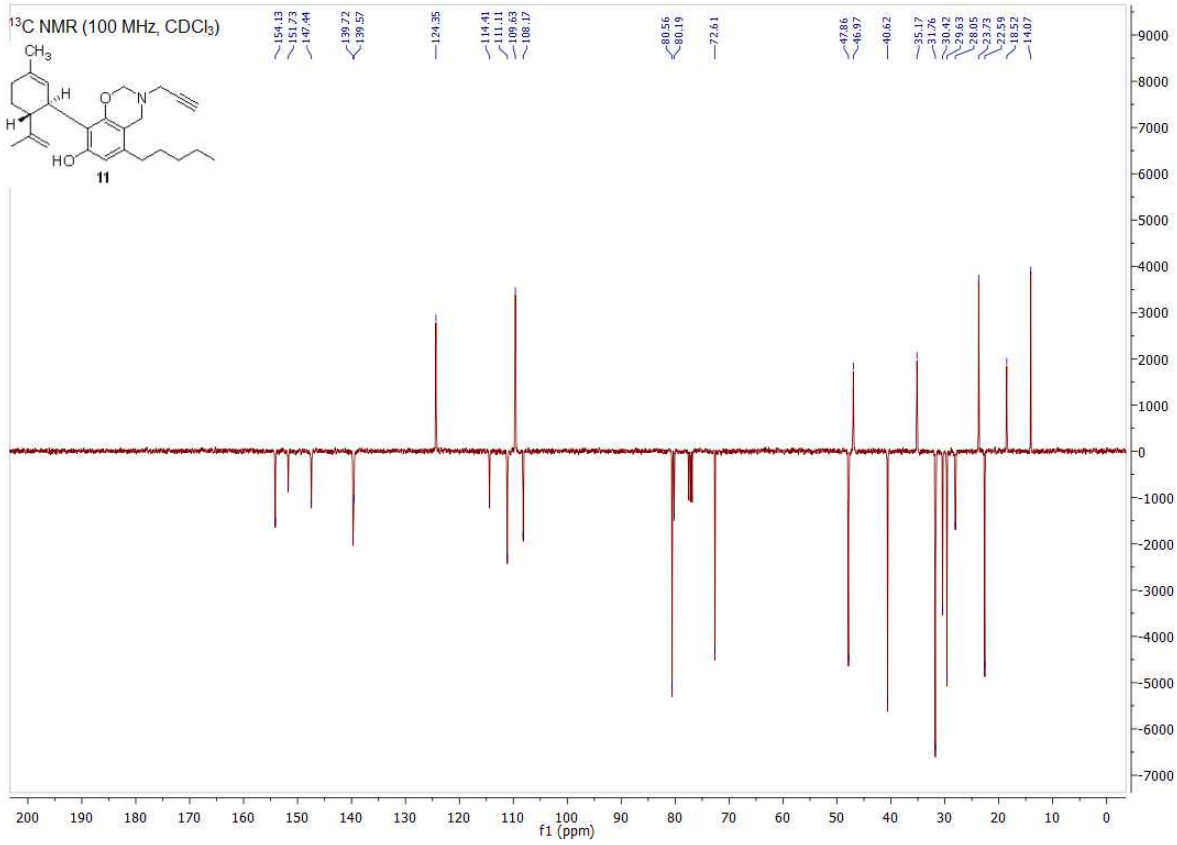


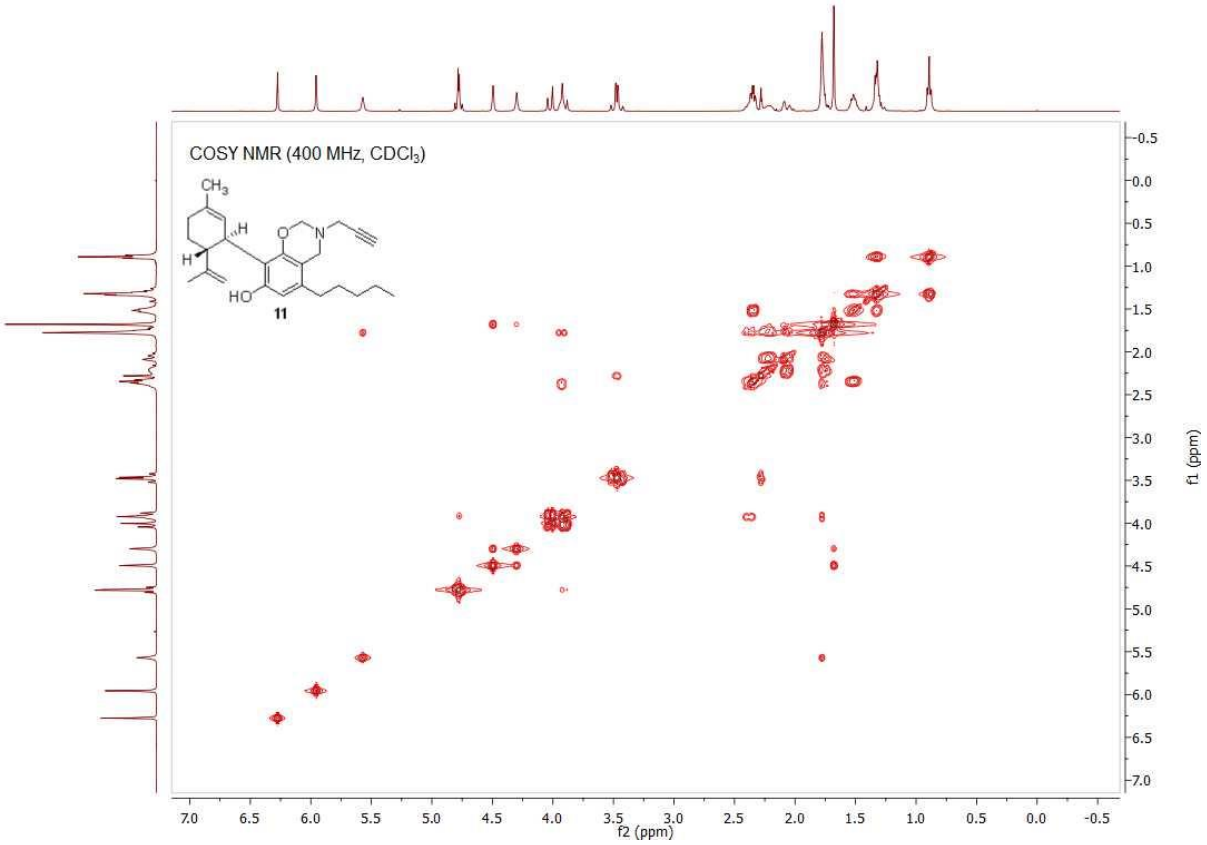

COSY NMR (400 MHz, CDCl3)
CH3
H
H
O
N
HO
10
f1 (ppm)
f2 (ppm)

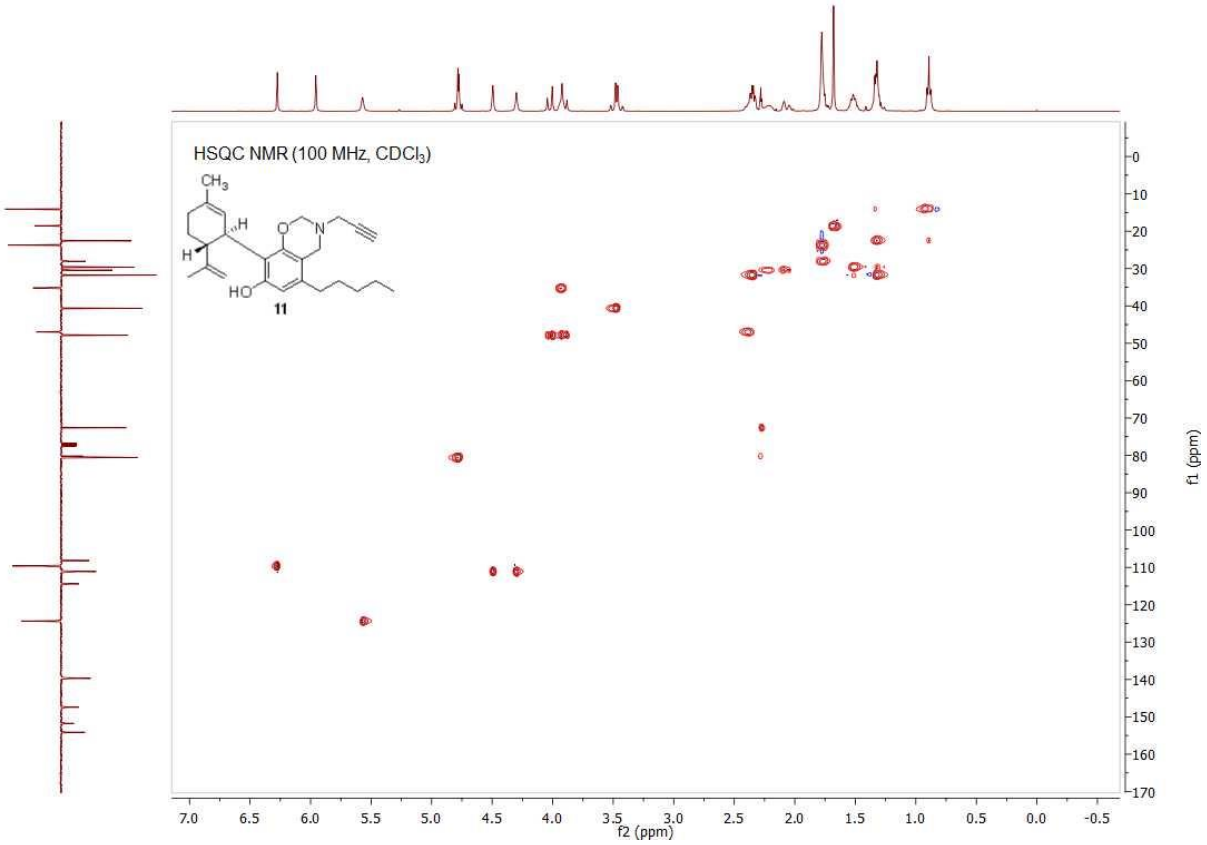

HSQC NMR (100 MHz, CDCl3)
CH3
H
H
O
N
HO
10
f1 (ppm)
f2 (ppm)

NMR spectra of compound 11

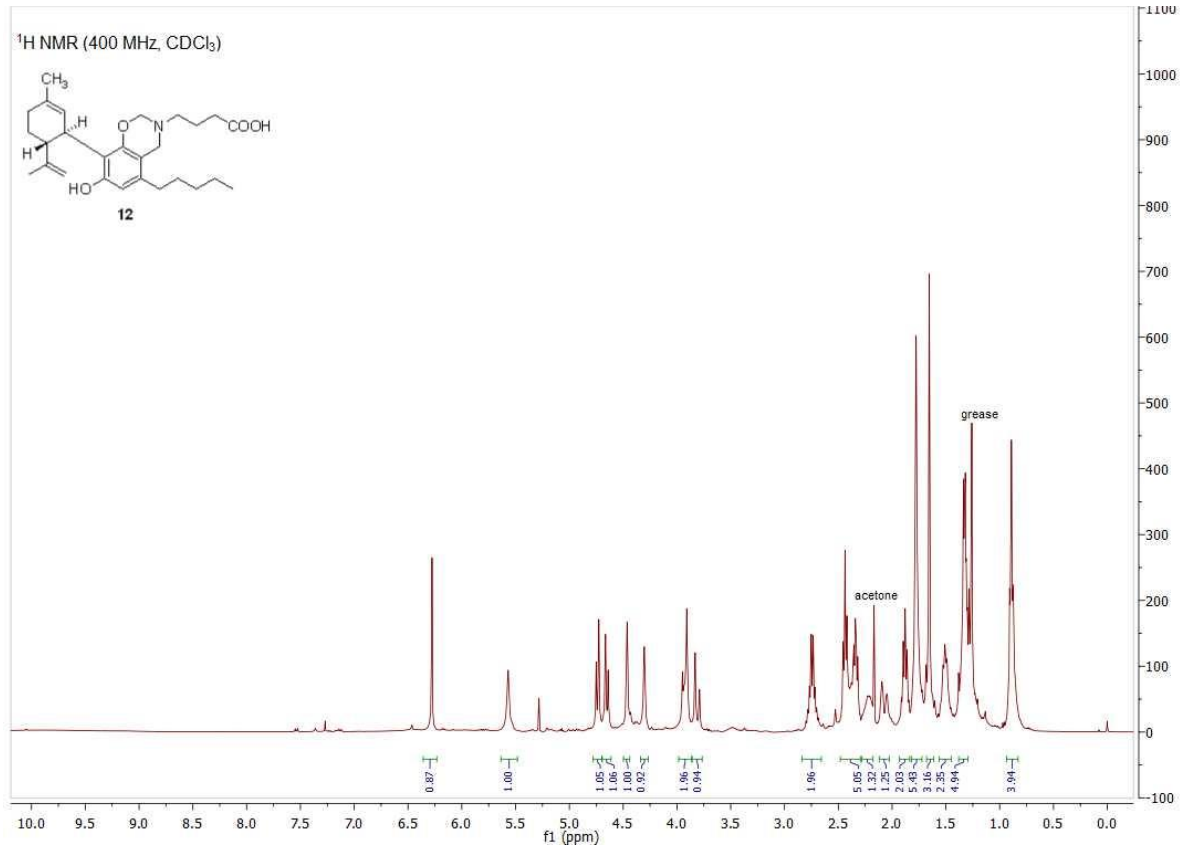


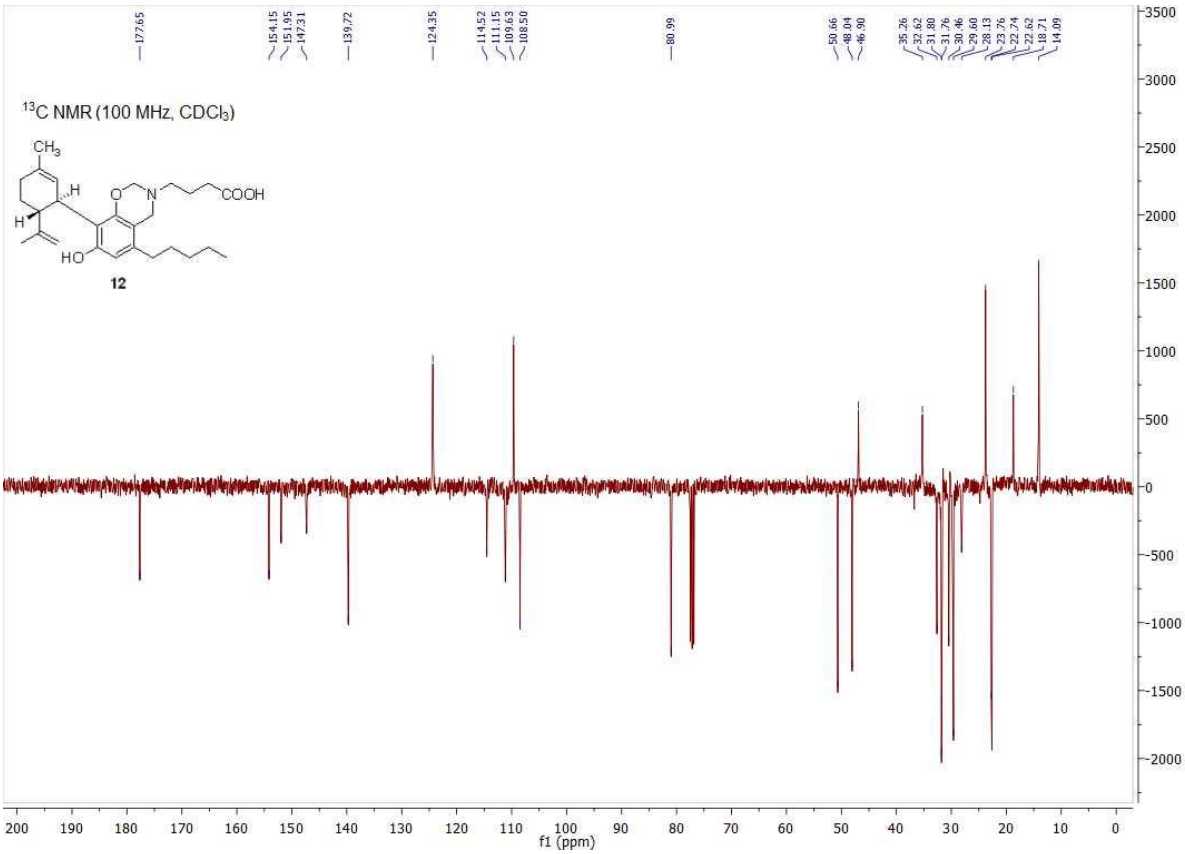


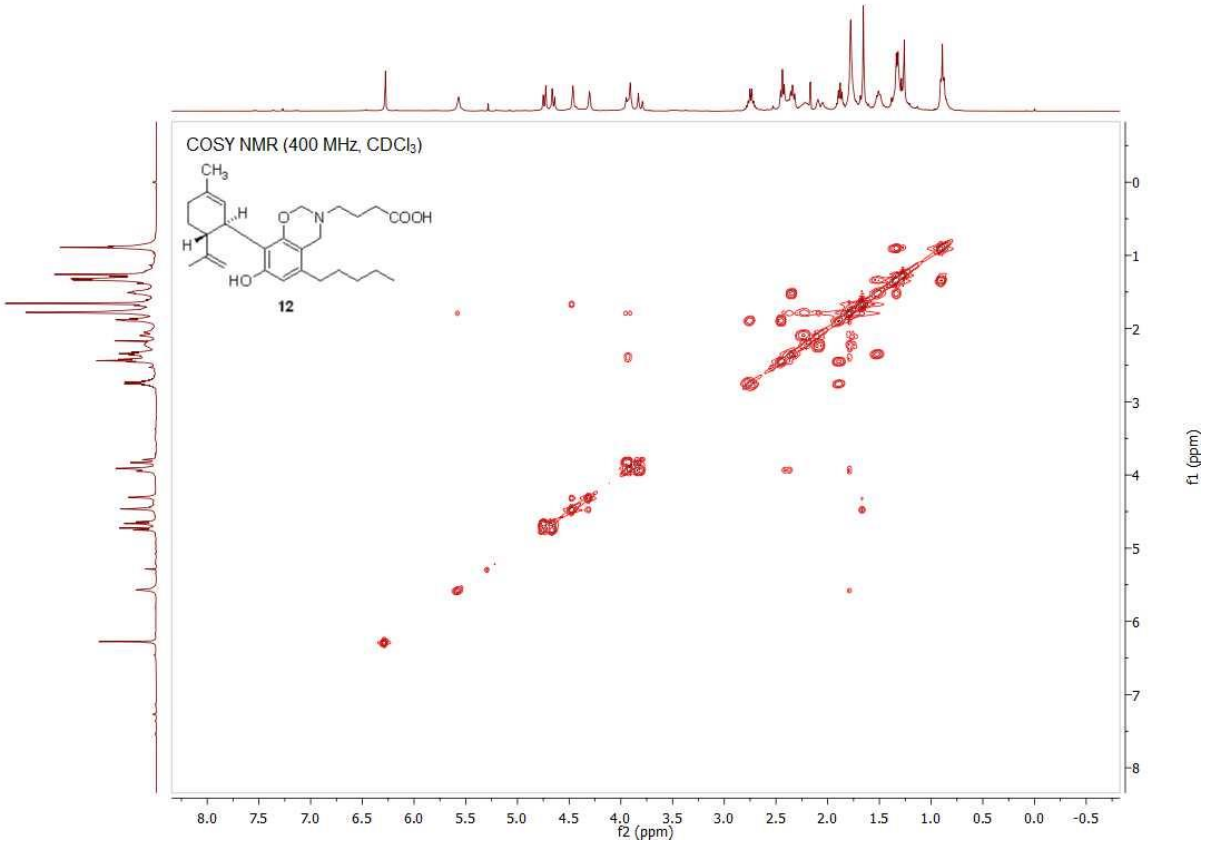

COSY NMR (400 MHz, CDCl3)
CH3
H
H
O
N
HO
11
f2 (ppm)
f1 (ppm)

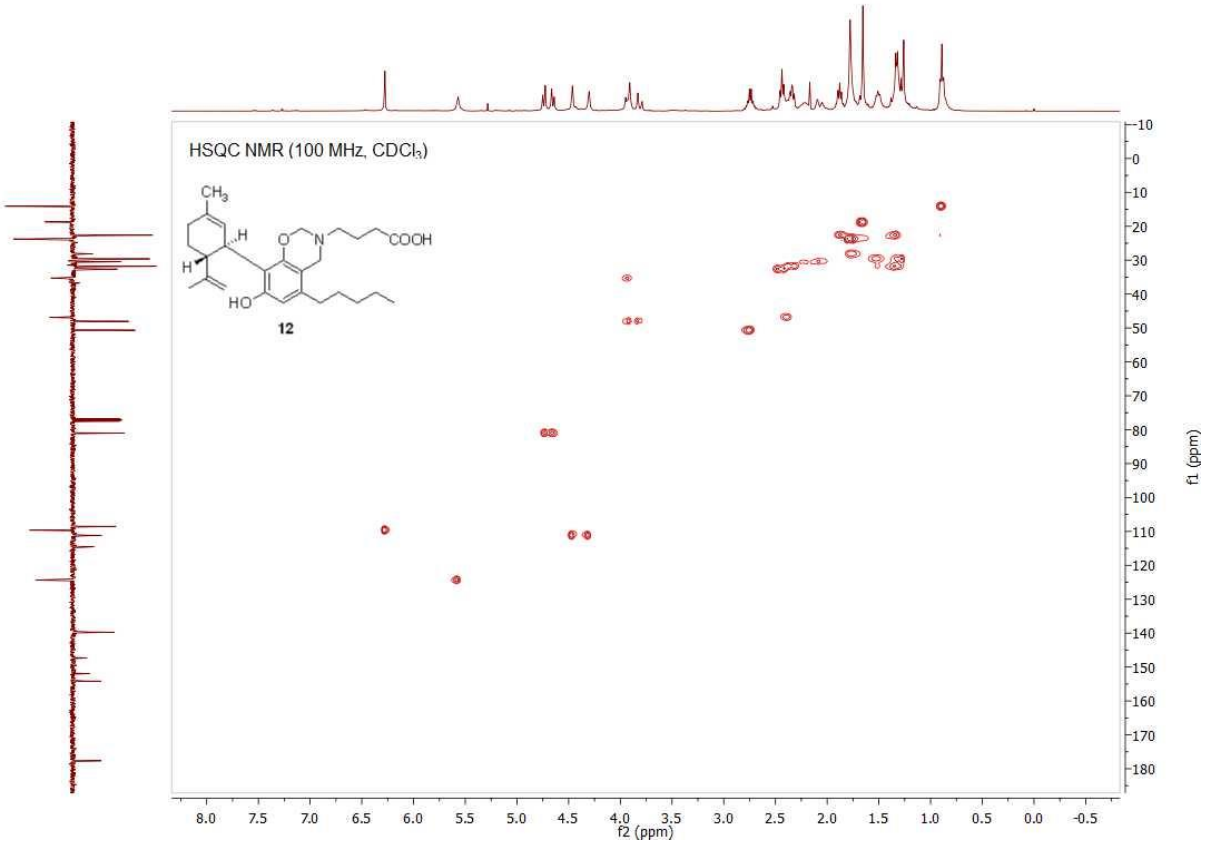

HSQC NMR (100 MHz, CDCl3)
CH3
H
H
O
N
HO
11
f2 (ppm)
f1 (ppm)

NMR spectra of compound 12

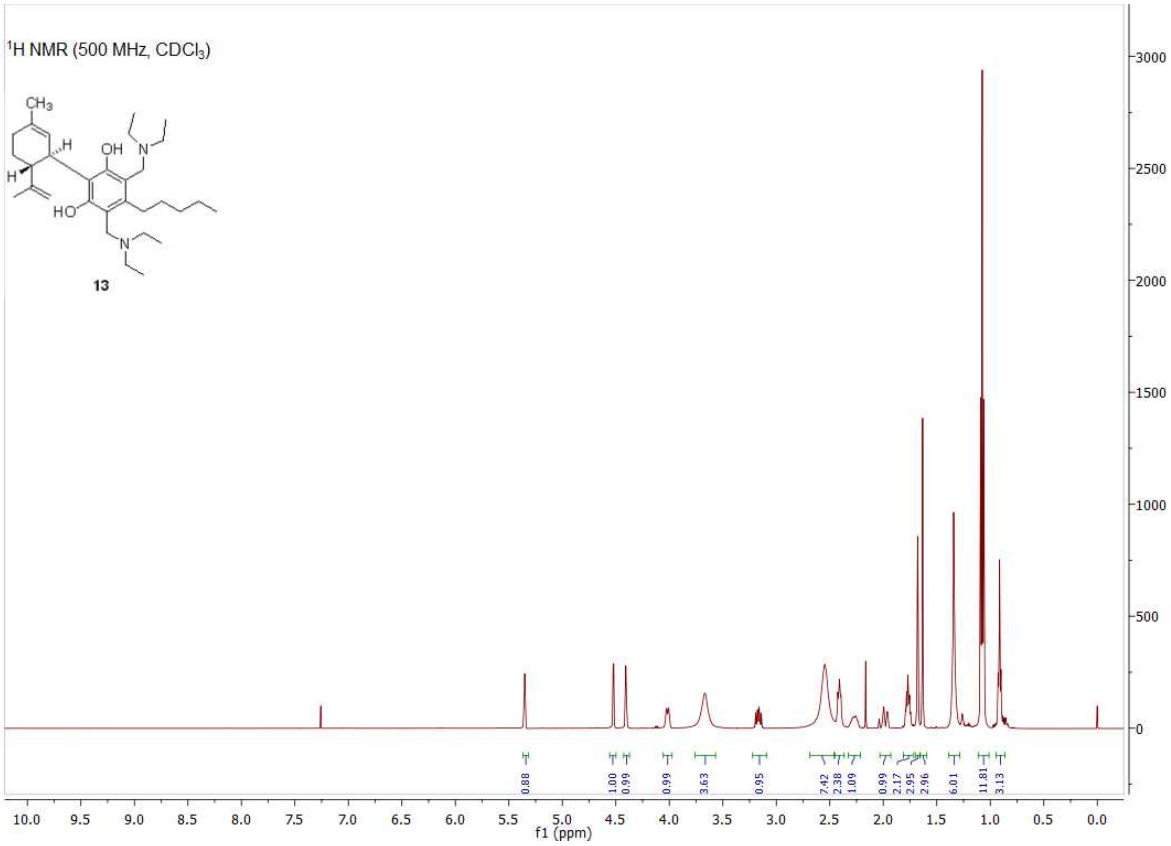


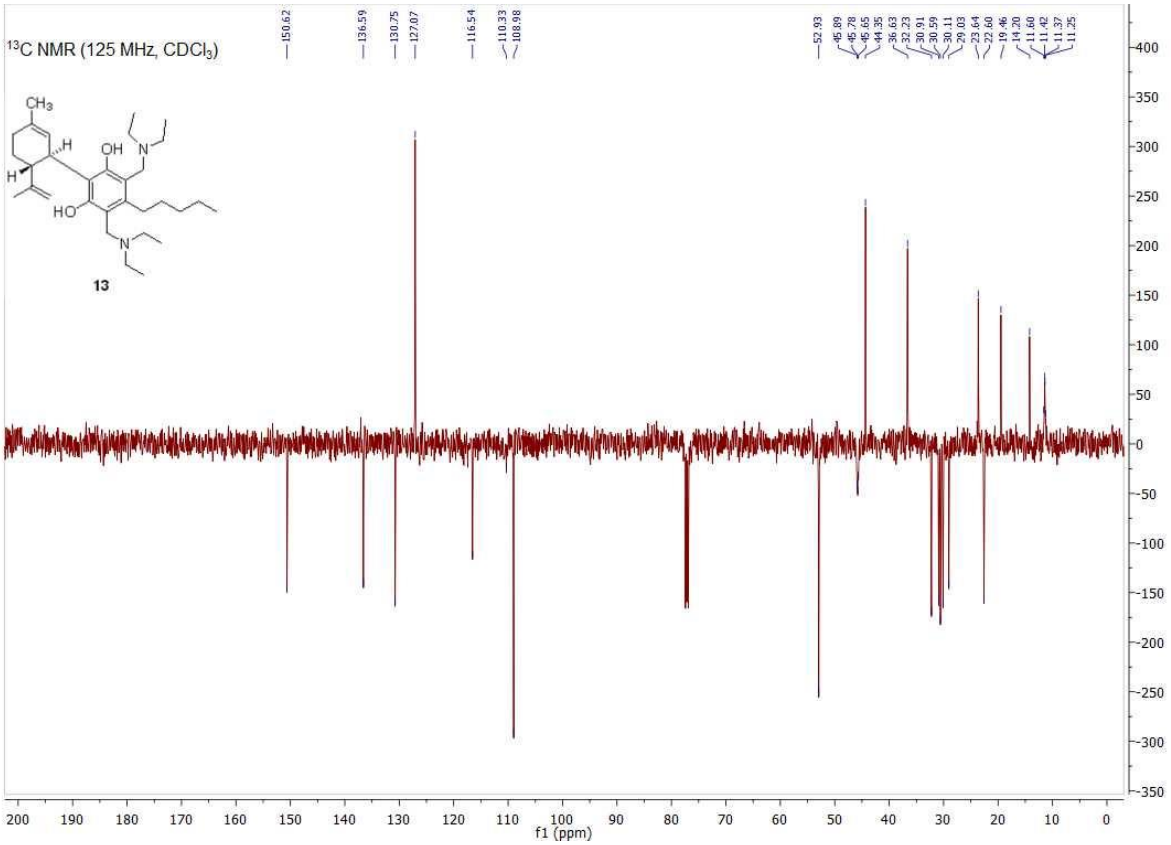


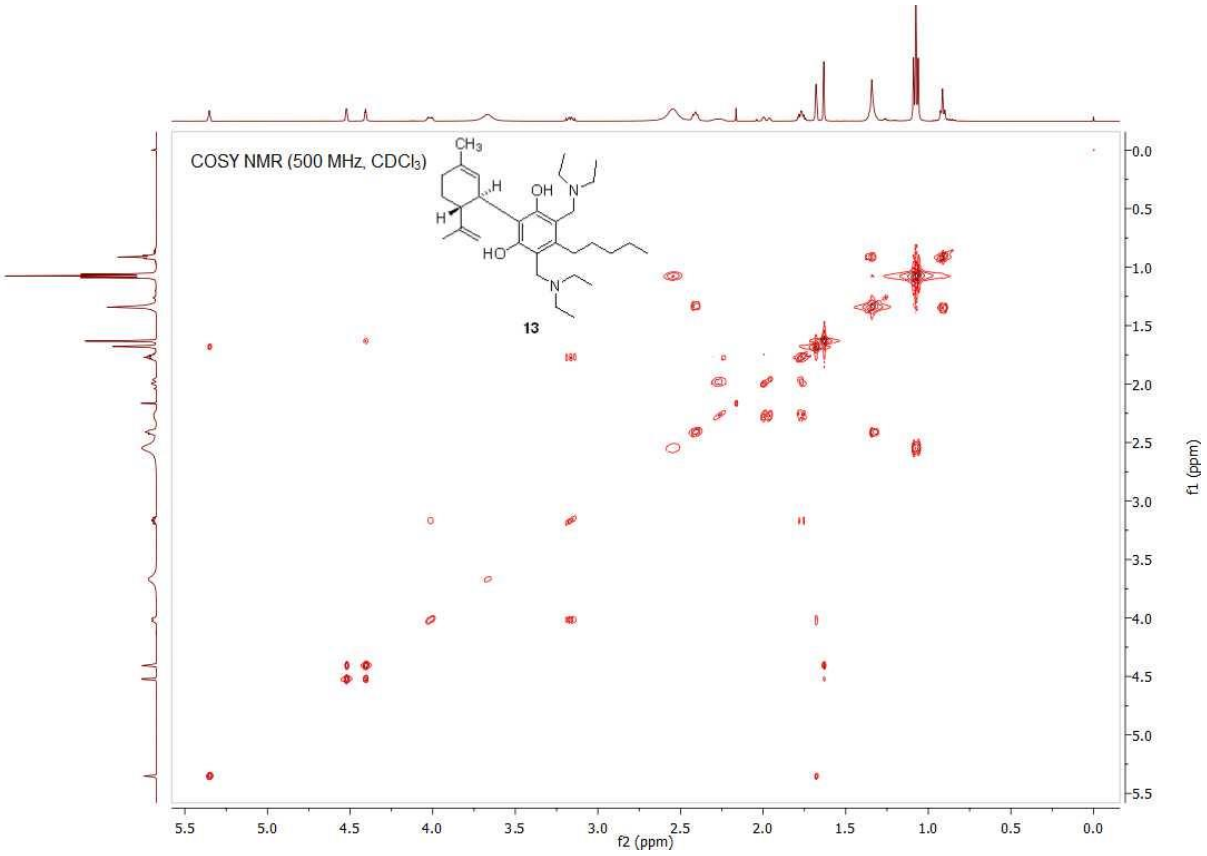

COSY NMR (400 MHz, CDCl3)
CH3
H
O
N
COOH
H
HO
12
f1 (ppm)
f2 (ppm)

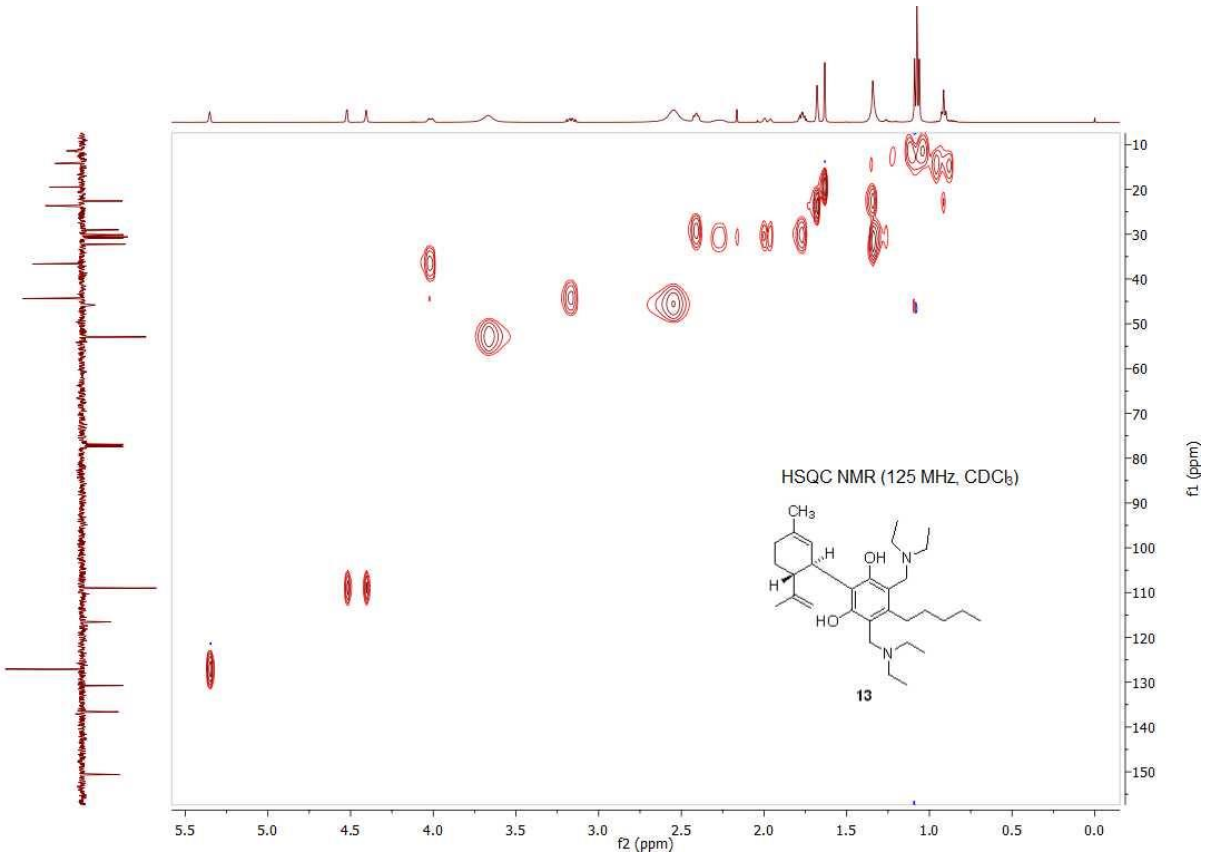

HSQC NMR (100 MHz, CDCl3)
CH3
H
O
N
COOH
H
HO
12
f1 (ppm)
f2 (ppm)

NMR spectra of compound 13

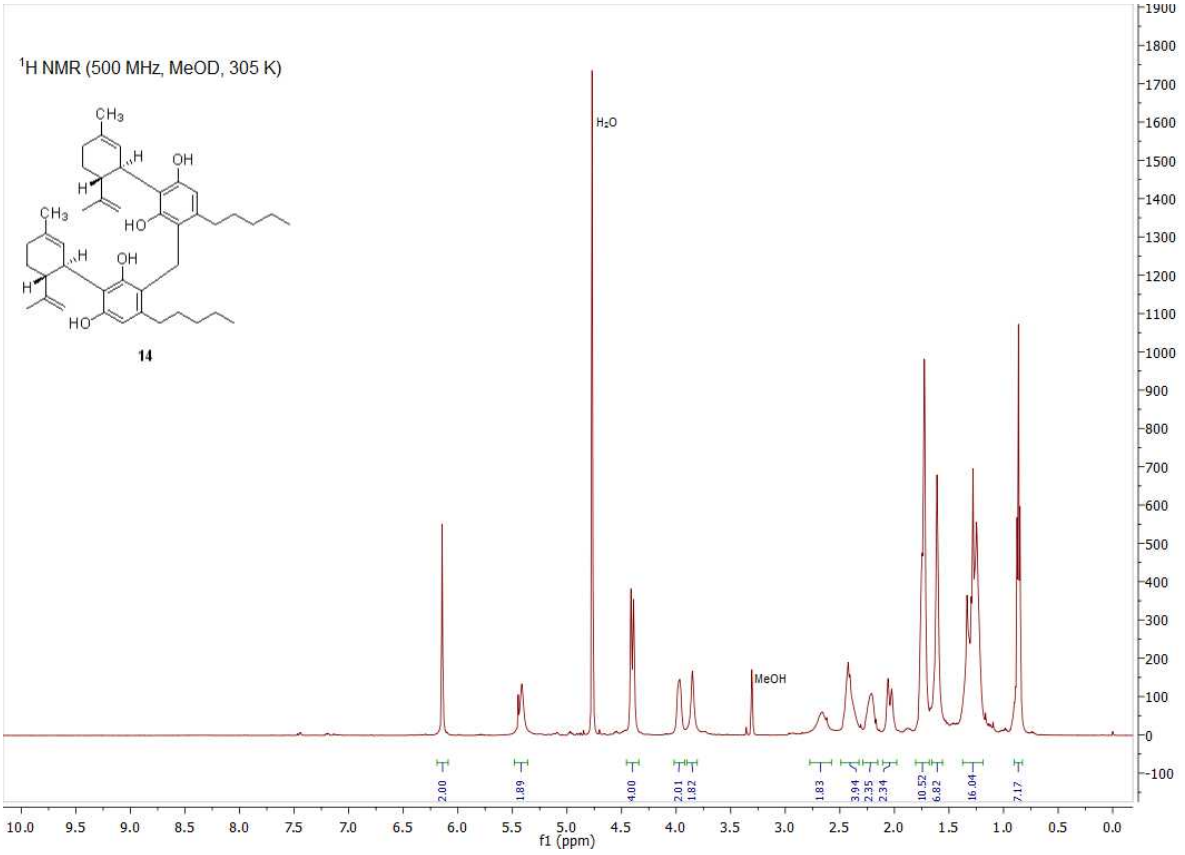


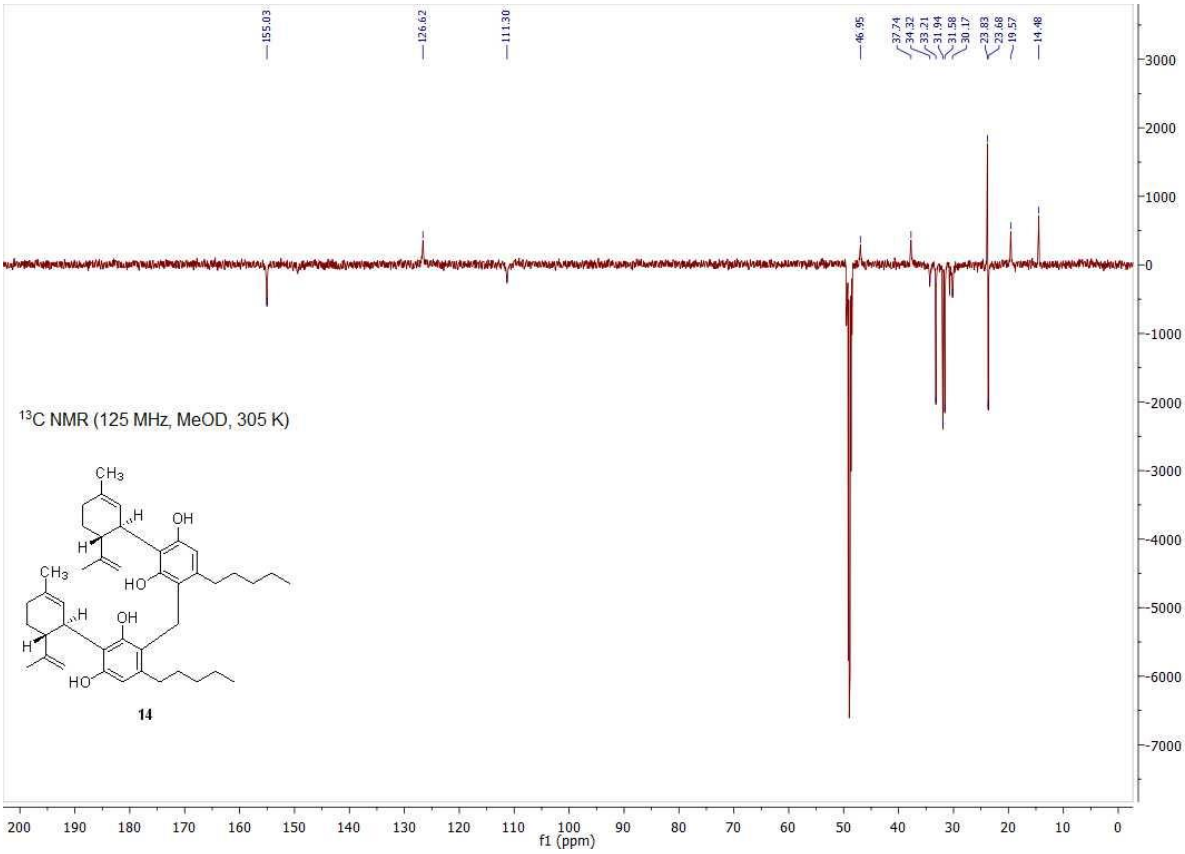


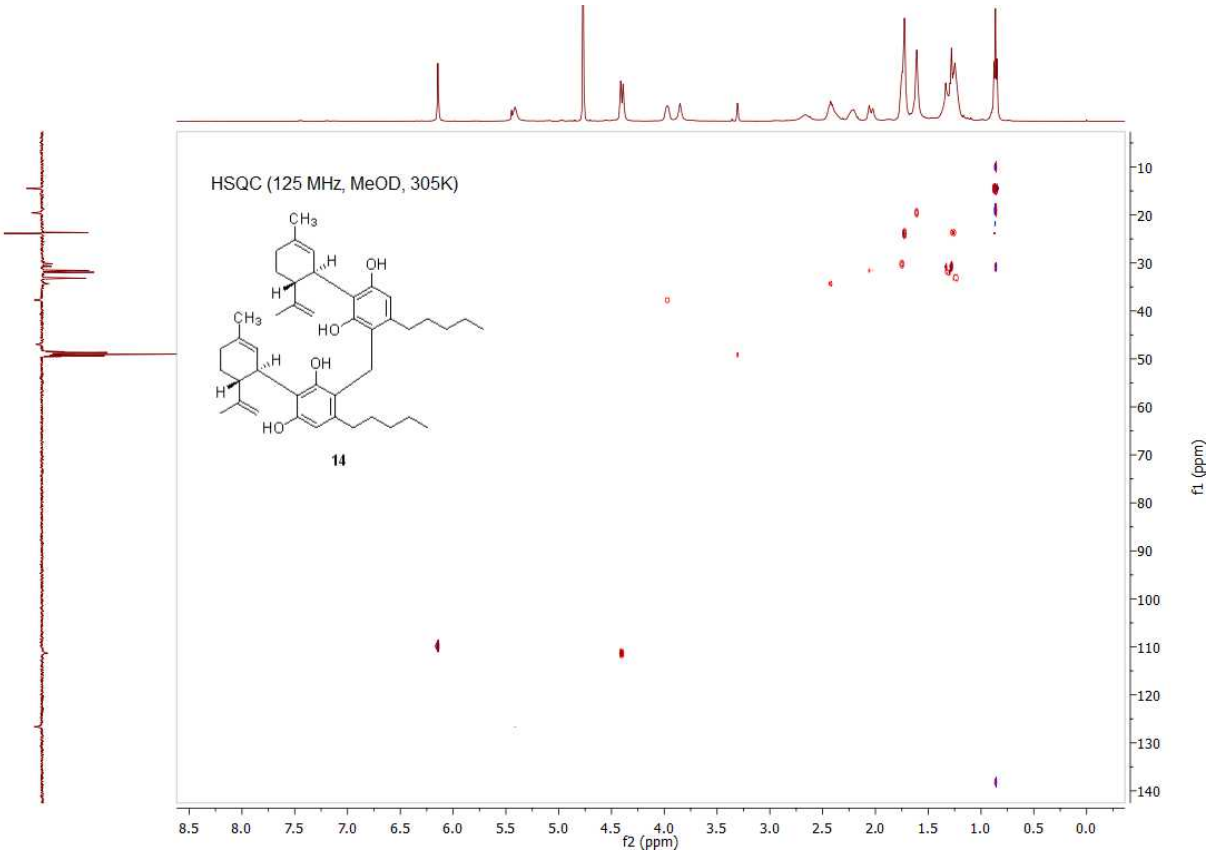

COSY NMR (500 MHz, CDCl3)
13
f2 (ppm)
f1 (ppm)


HSQC NMR (125 MHz, CDCl3)
13
f2 (ppm)
f1 (ppm)

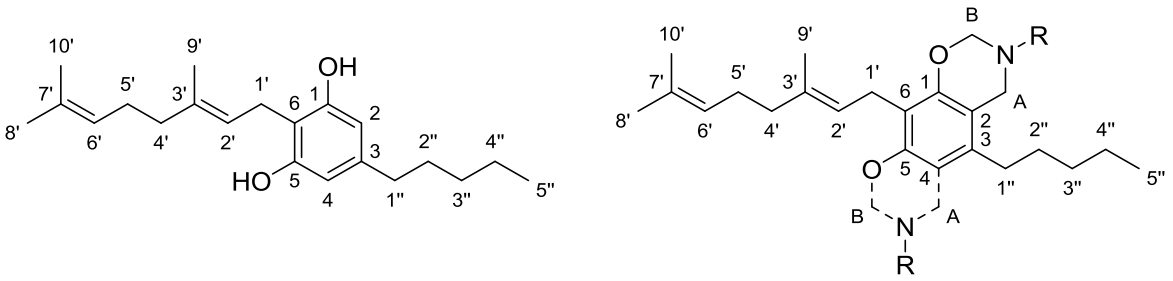
NMR spectra of compound 14






HSQC (125 MHz, MeOD, 305K)
CH3
H
OH
H
HO
CH3
H
OH
H
HO
14
f1 (ppm)
f2 (ppm)

3. NMR data of CBG and its derivatives

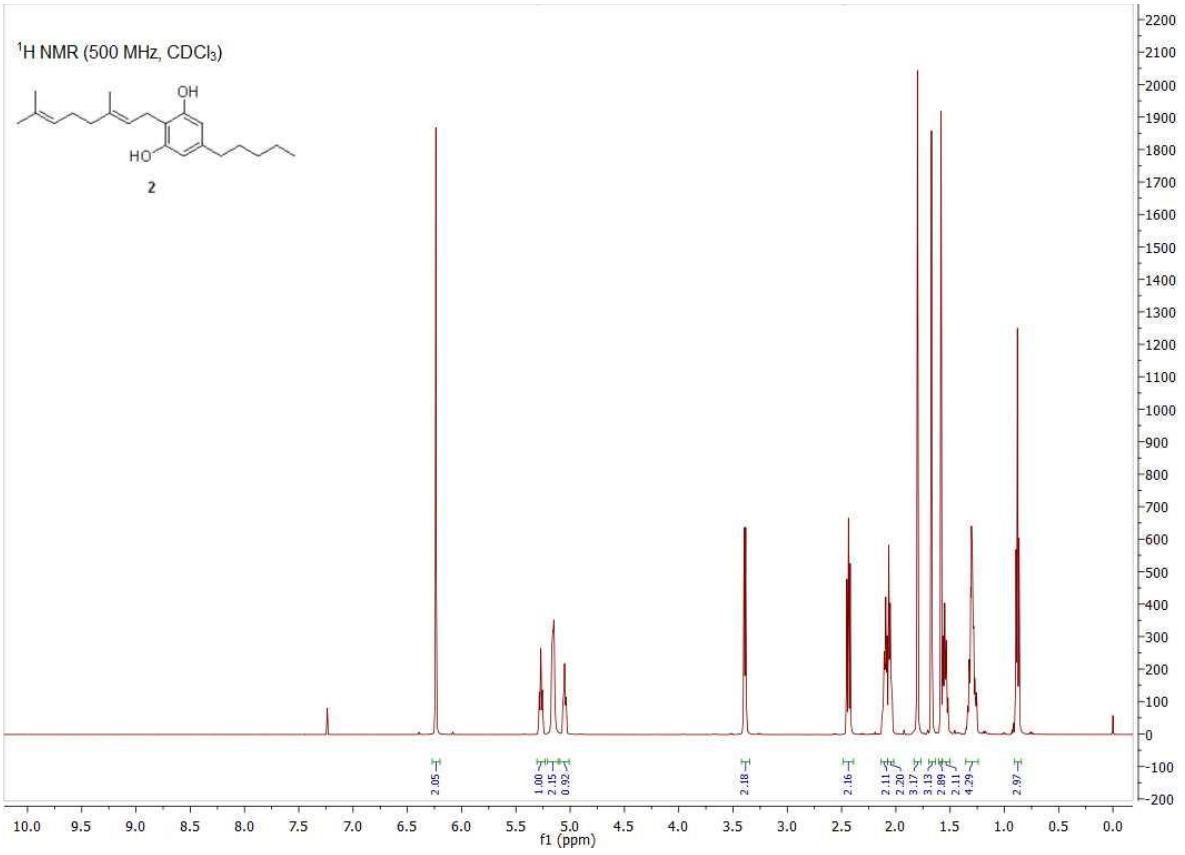


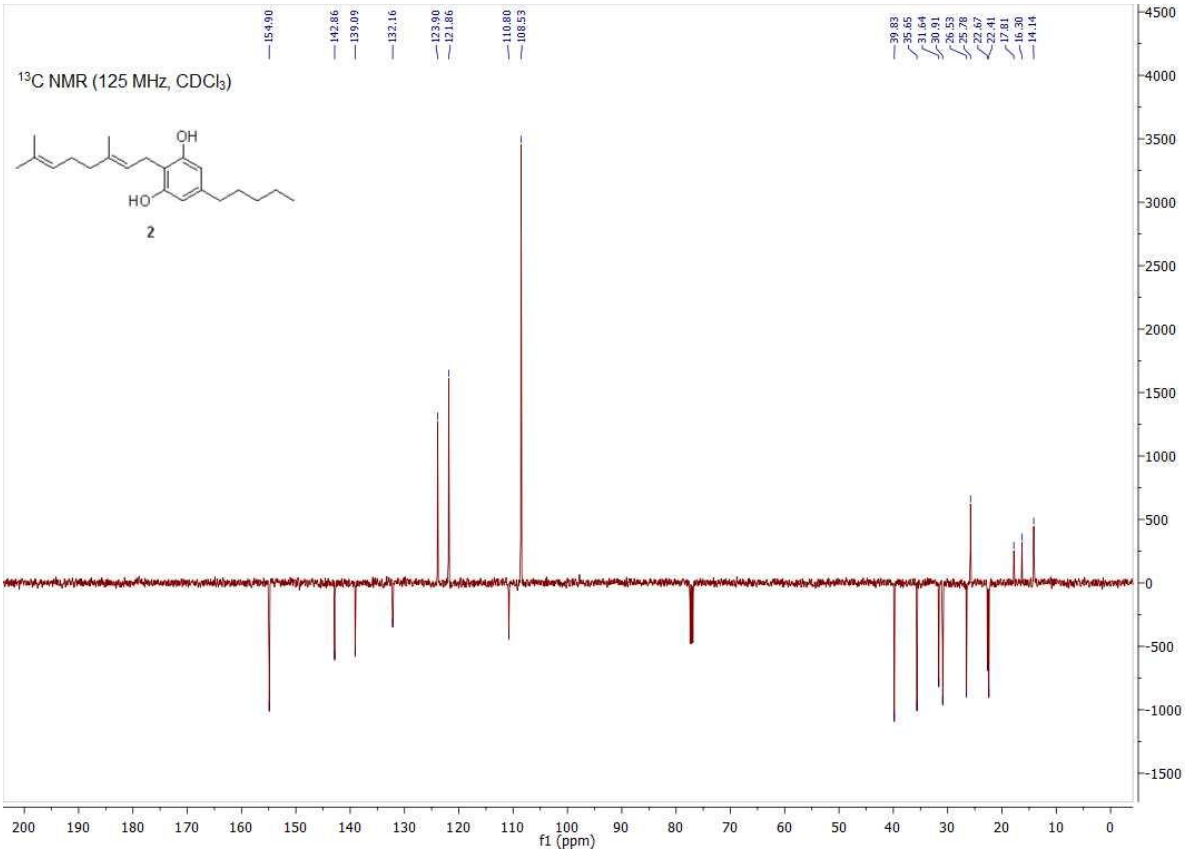
Scheme S2. Numbering of CBG and its derivatives

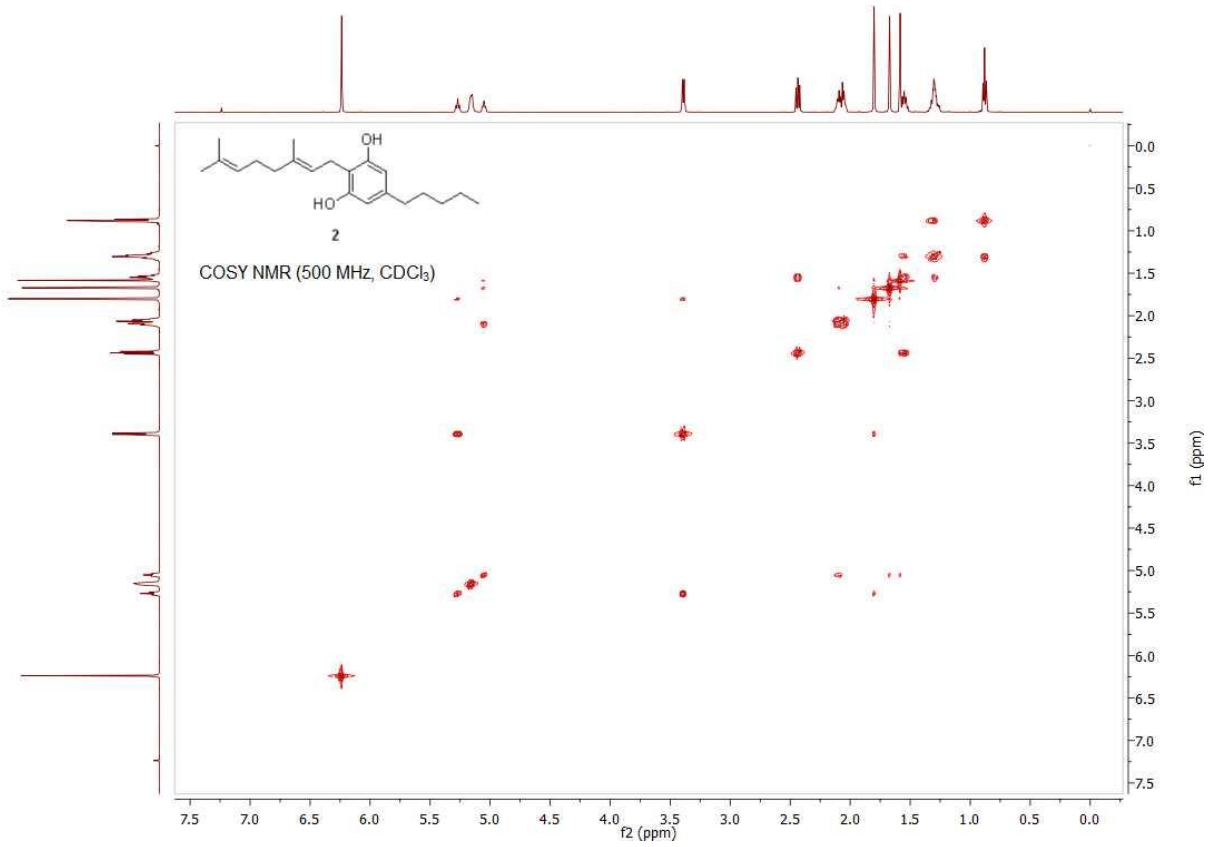
NMR data of CBG:

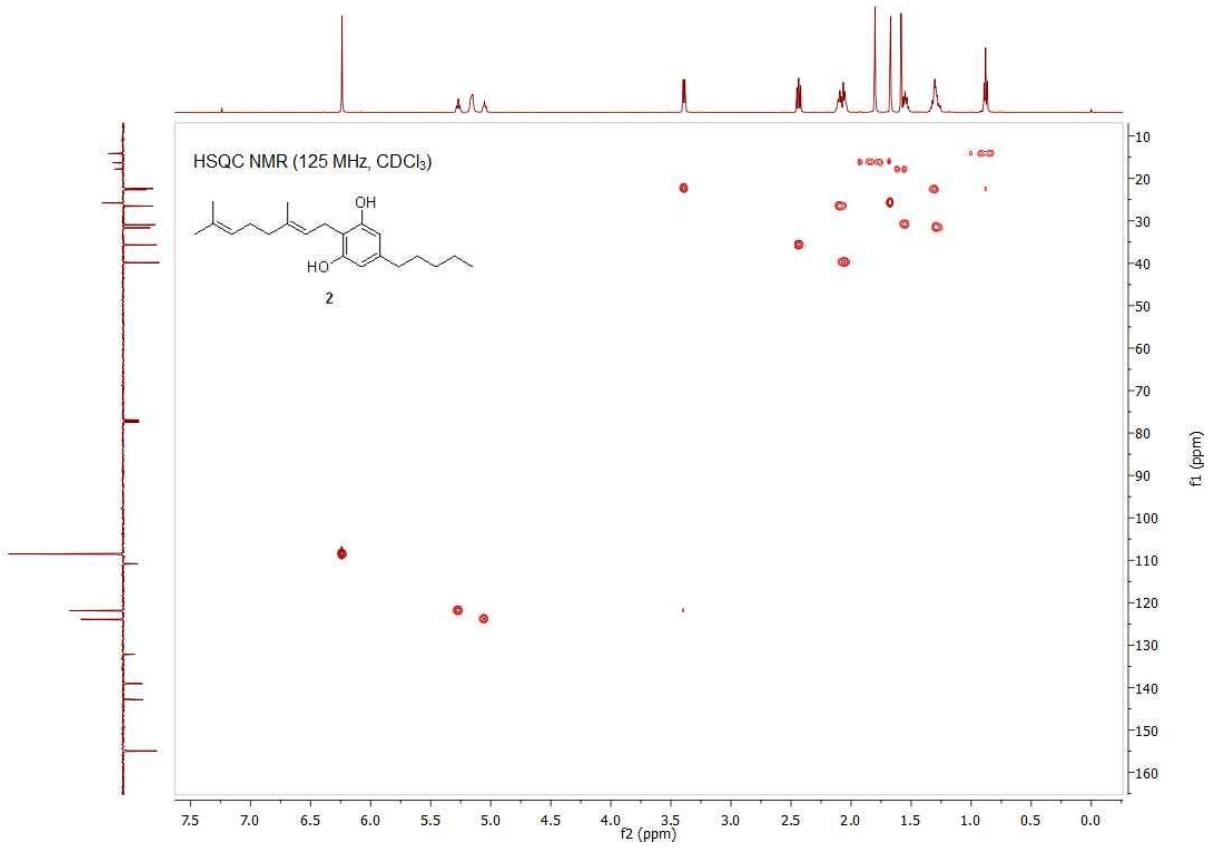
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.24 (s, 2H aromatic C*H*), 5.29-5.24 (m, 1H, H-2'C*H*), 5.15 (s, 2H, O*H*), 5.07-5.02 (m, 1H, H-6' C*H*), 3.39 (d, 2H, J = 7.1 Hz, H-1' CH_2), 2.46-2.41 (m, 2H, H-1" CH_2), 2.13-2.07 (m, 2H, H-5' CH_2), 2.07-2.02 (m, 2H, H-4' CH_2), 1.80 (s, 3H, H-9' CH_3), 1.58, 1.67 (2s, 6H, H-8' and H-10' CH_3), 1.57-1.51 (m, 2H, H-2" CH_2), 1.36-1.24 (m, 4H, H-3" and H-4" CH_2), 0.88 (t, 3H, J = 6.9 Hz, H-5" CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 154.9, 142.9, 139.1, 132.2 (4C, quat.), 123.9 (1C, C-6' *C*H), 121.9 (1C, C-2' *C*H), 110.8 (1C, quat.), 108.5 (2C, aromatic *C*H), 39.8 (1C, C-4' *C*H_2), 35.7 (1C, C-1" *C*H_2), 31.6 (1C, C-3" *C*H_2), 30.9 (1C, C-2" *C*H_2), 26.5 (1C, C-5' *C*H_2), 25.8 (1C, C-8'or C-10' *C*H_3), 22.7 (1C, C-4" *C*H_2), 22.4 (1C, C-1' *C*H_2), 17.8 (1C, C-8'or C-10' *C*H_3), 16.3 (1C, C-9' *C*H_3), 14.1 (1C, C-5" *C*H_3).

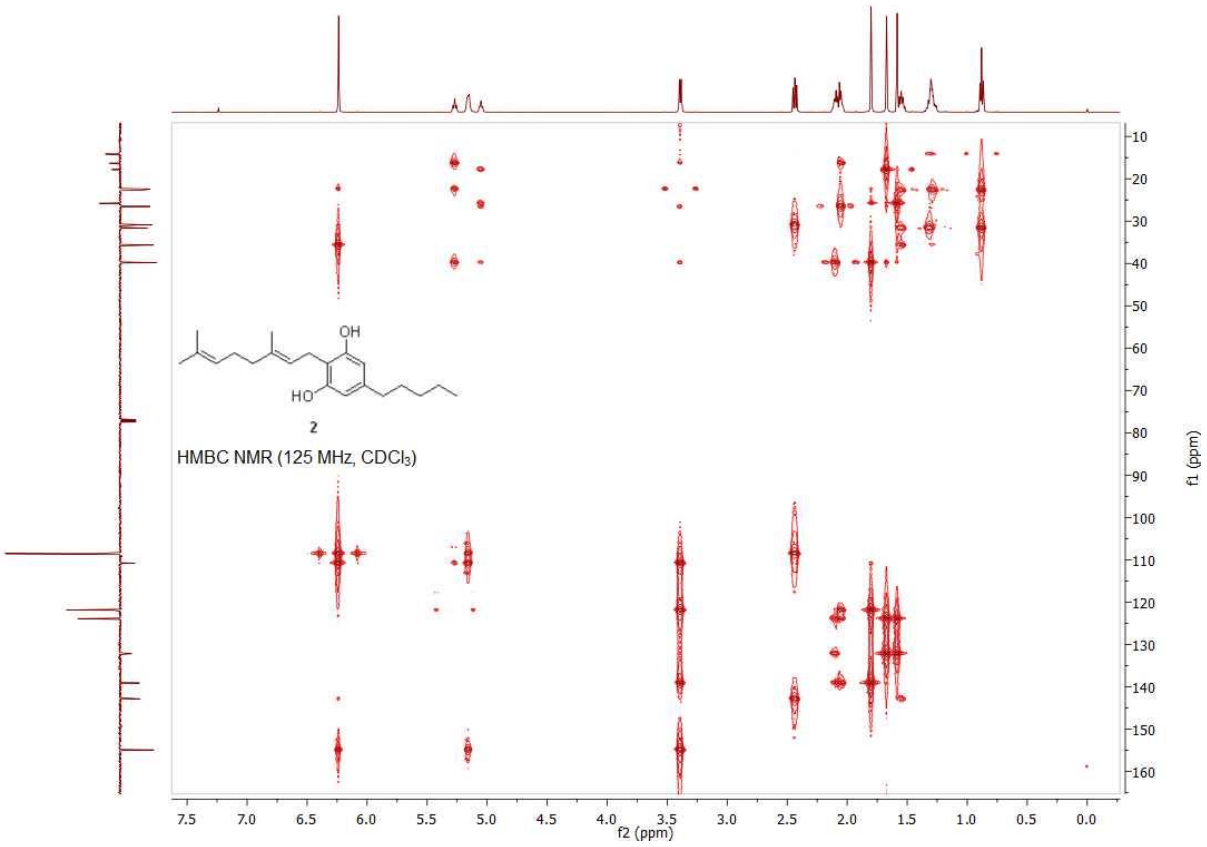
NMR spectra of CBG



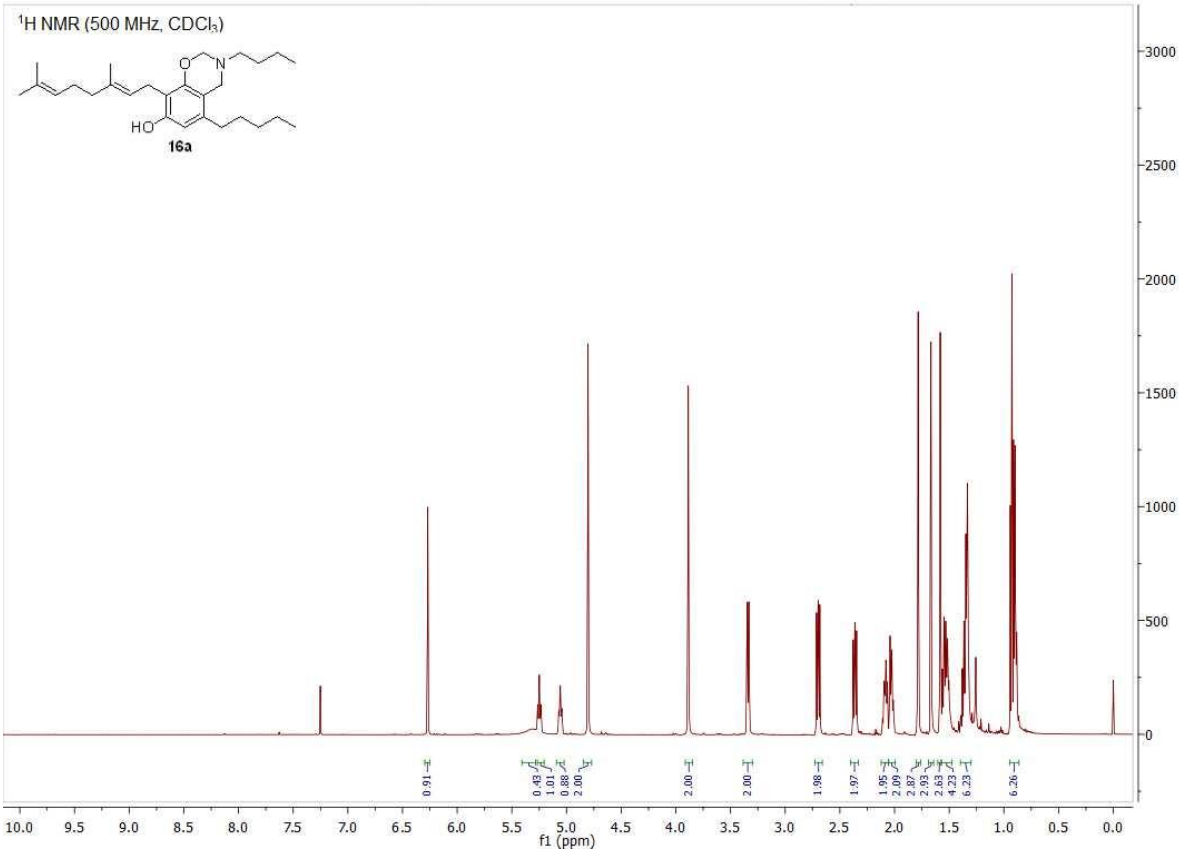


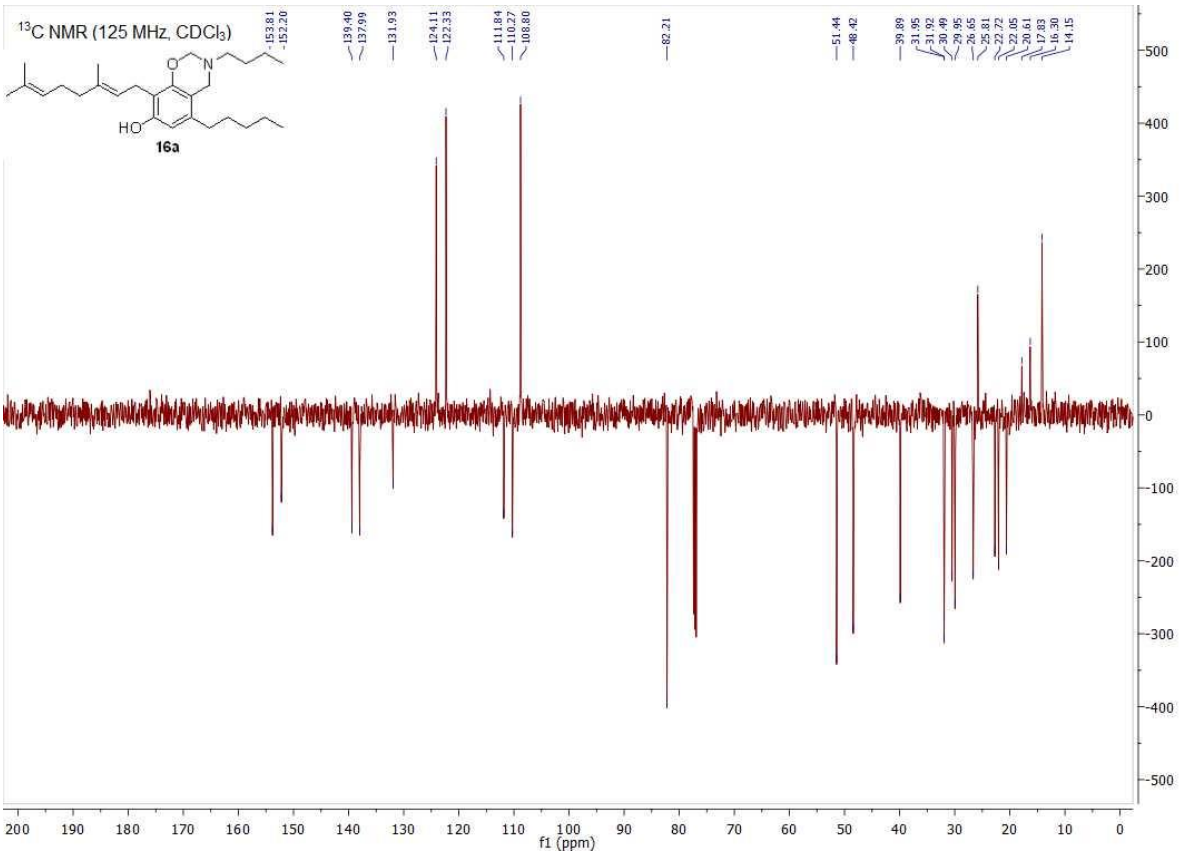

OH
HO
2
COSY NMR (500 MHz, CDCl3)
f1 (ppm)
f2 (ppm)

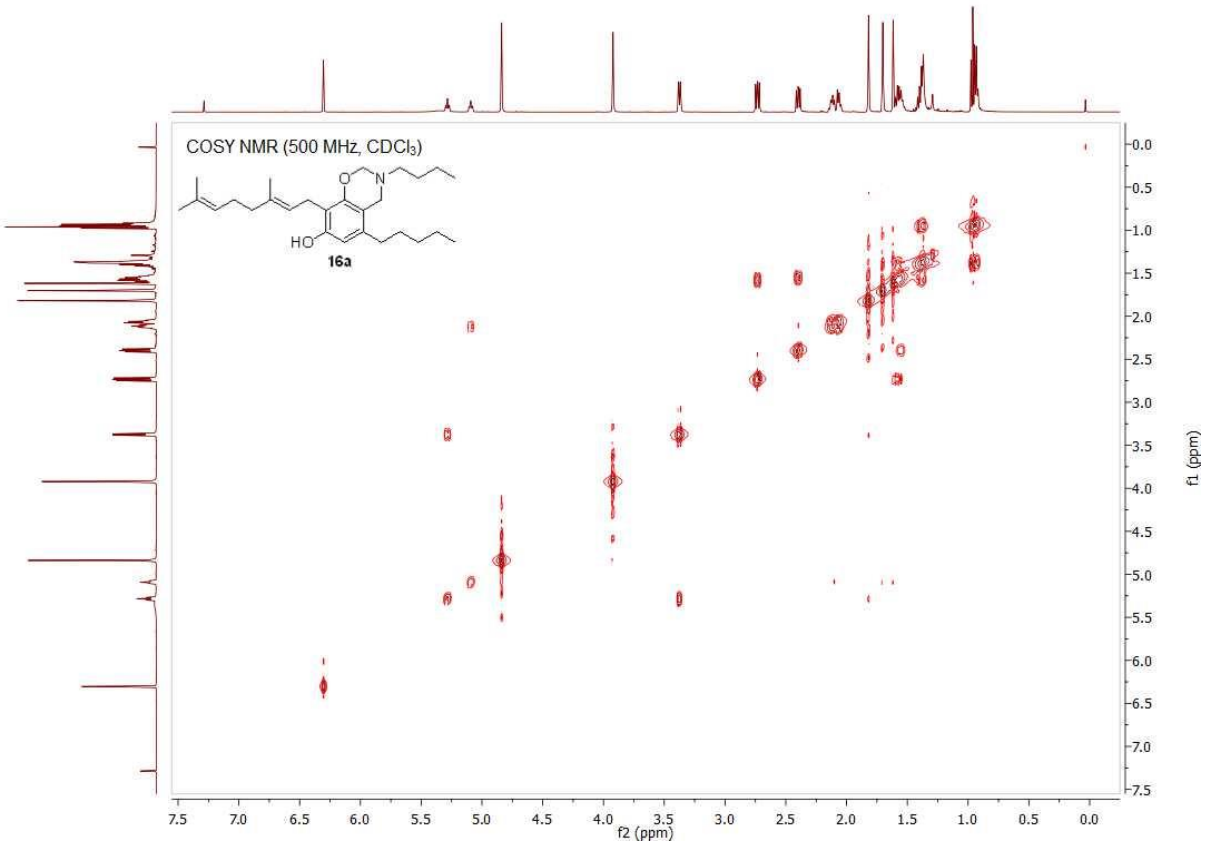

HSQC NMR (125 MHz, CDCl3)
OH
HO
2
f1 (ppm)
f2 (ppm)

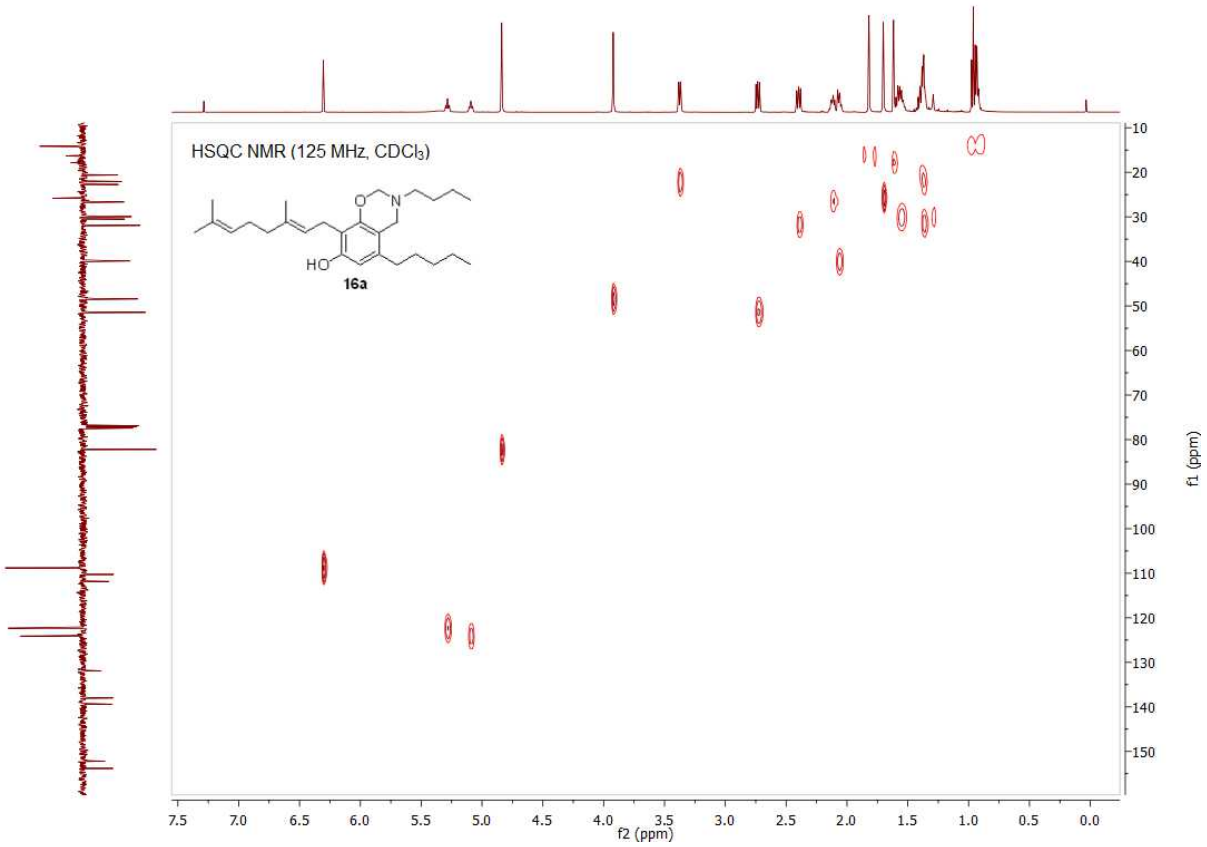

OH
HO
2
HMBC NMR (125 MHz, CDCl3)
f2 (ppm)
f1 (ppm)

NMR spectra of compound 16a

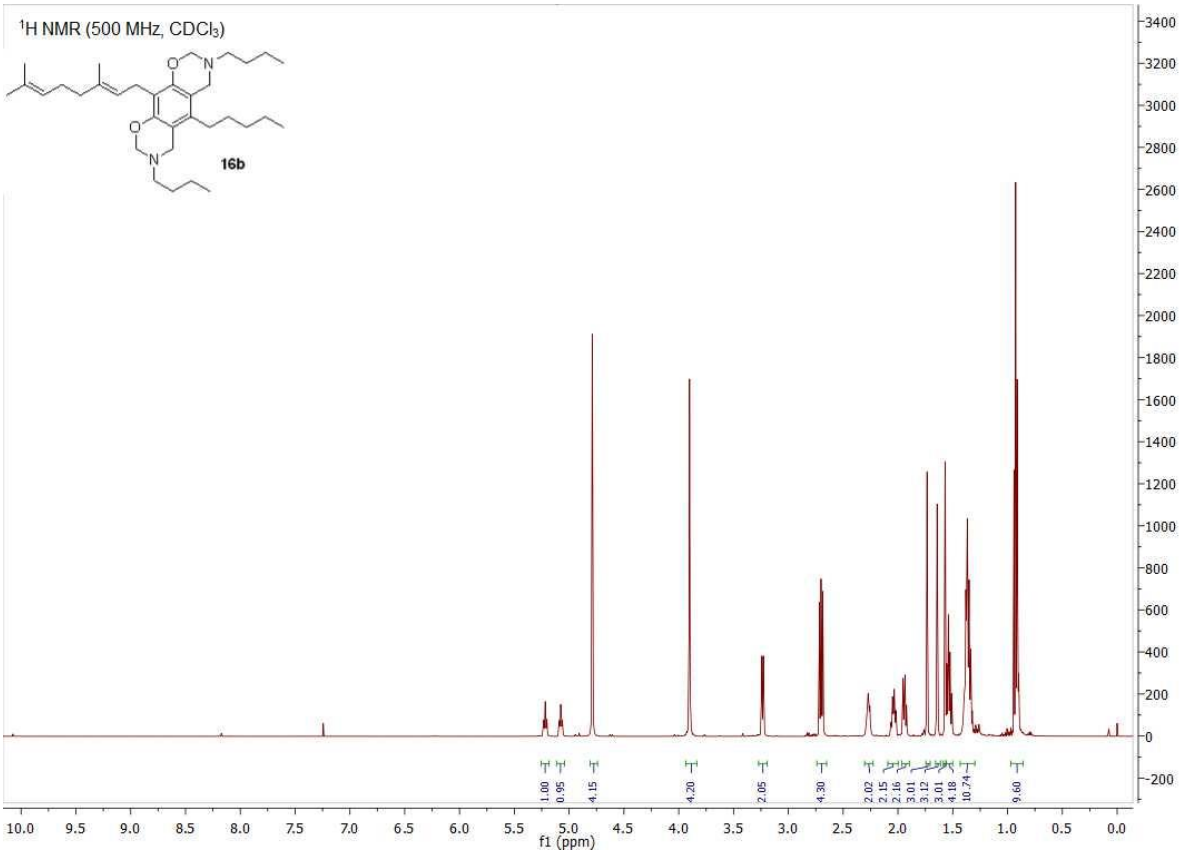


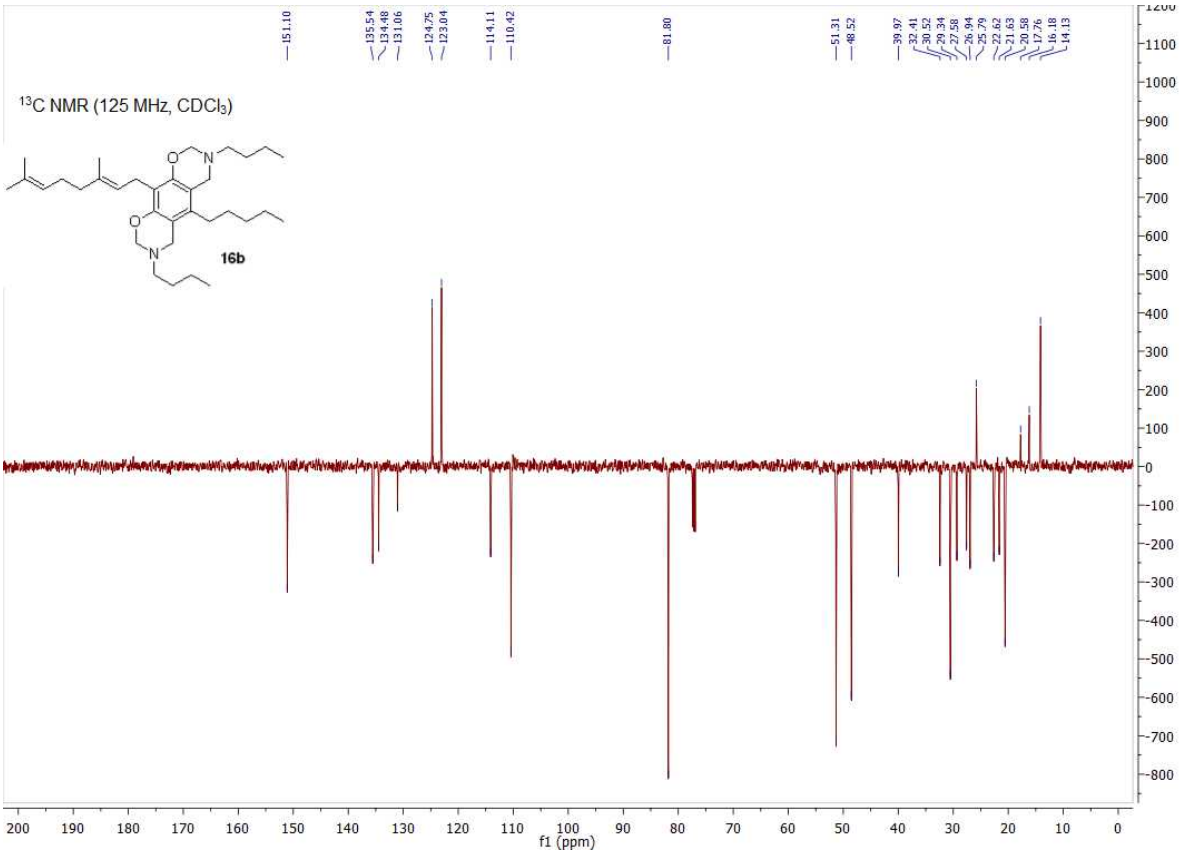


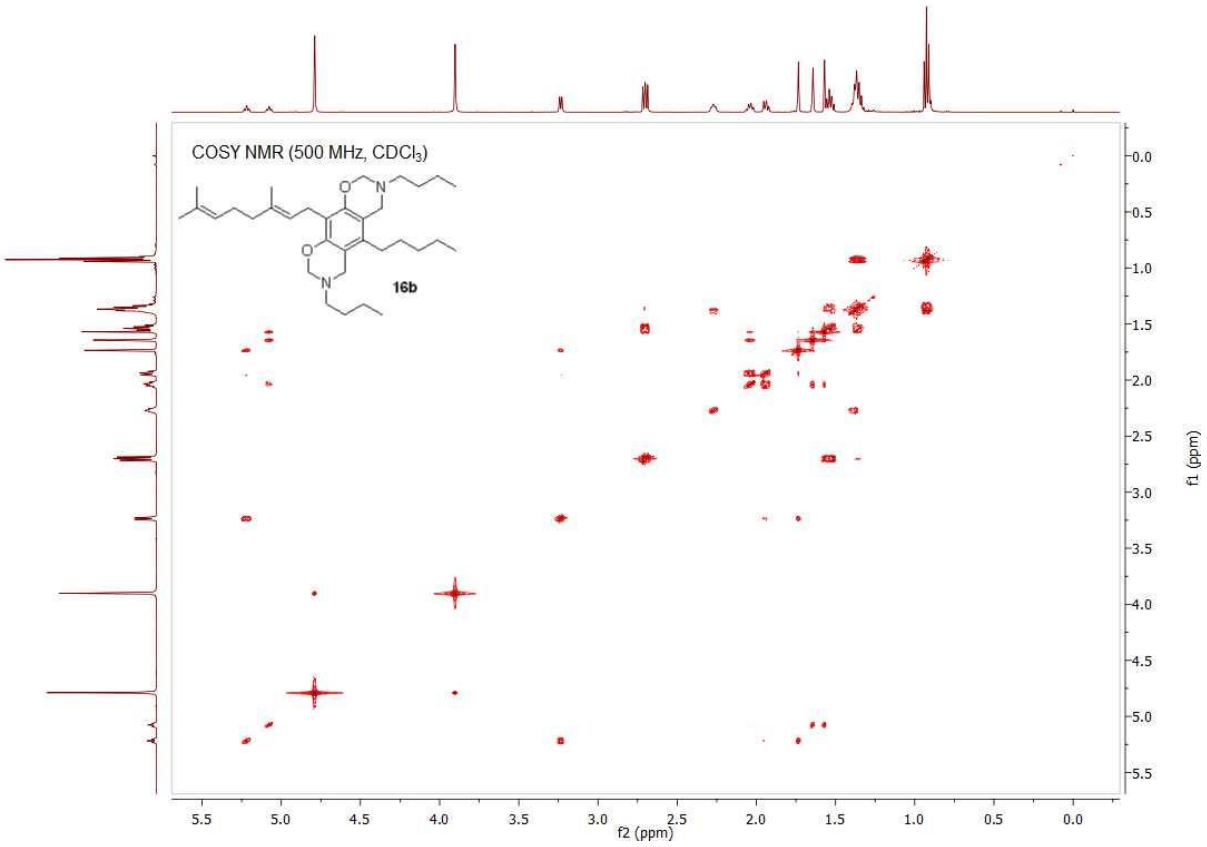

COSY NMR (500 MHz, CDCl3)
HO
16a
f2 (ppm)
f1 (ppm)

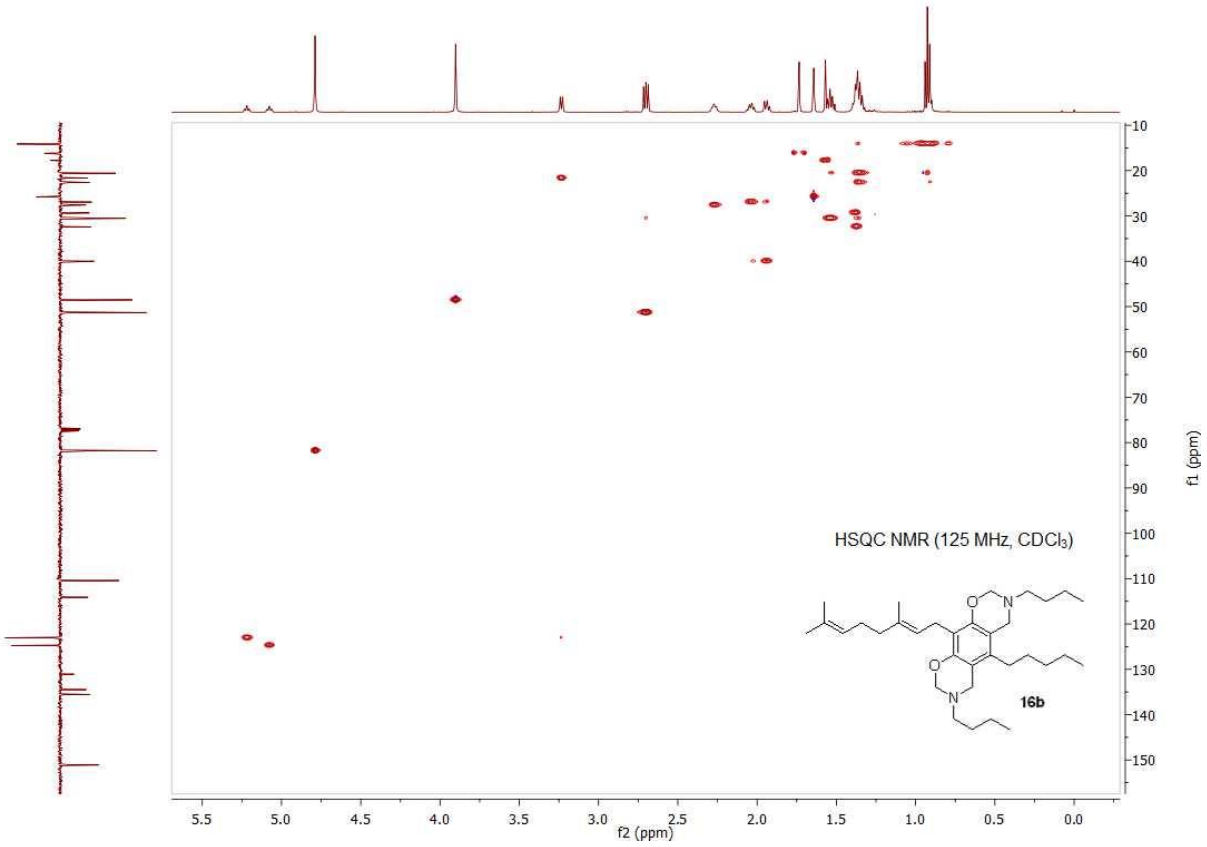

HSQC NMR (125 MHz, CDCl3)
HO
16a
f2 (ppm)
f1 (ppm)

NMR spectra of compound 16b

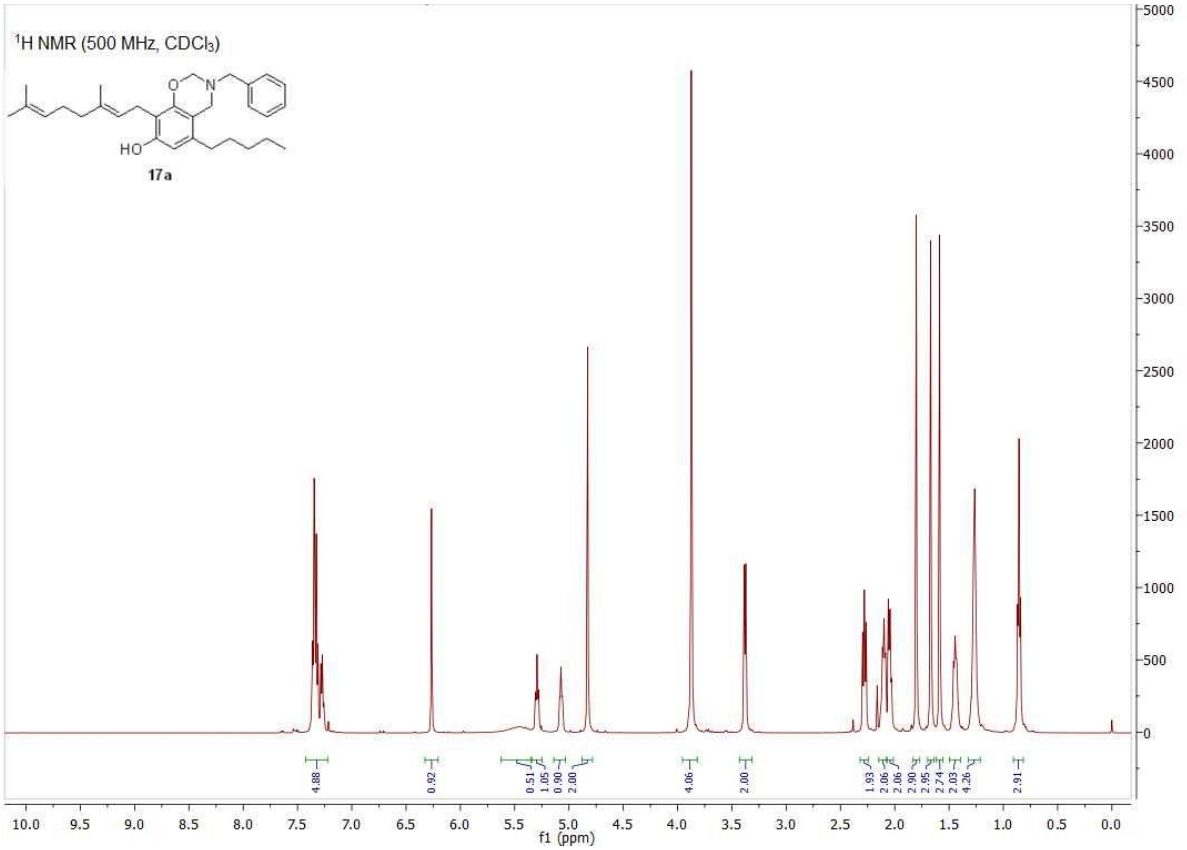


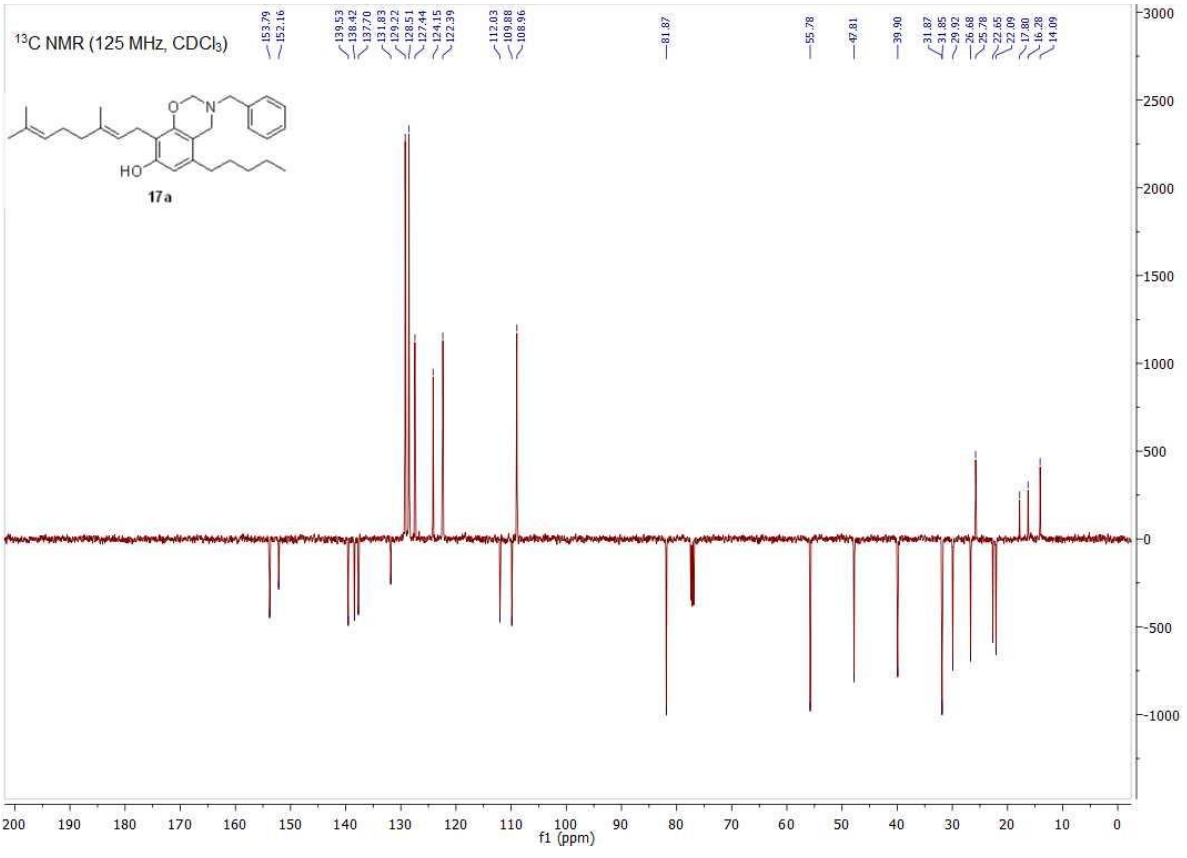


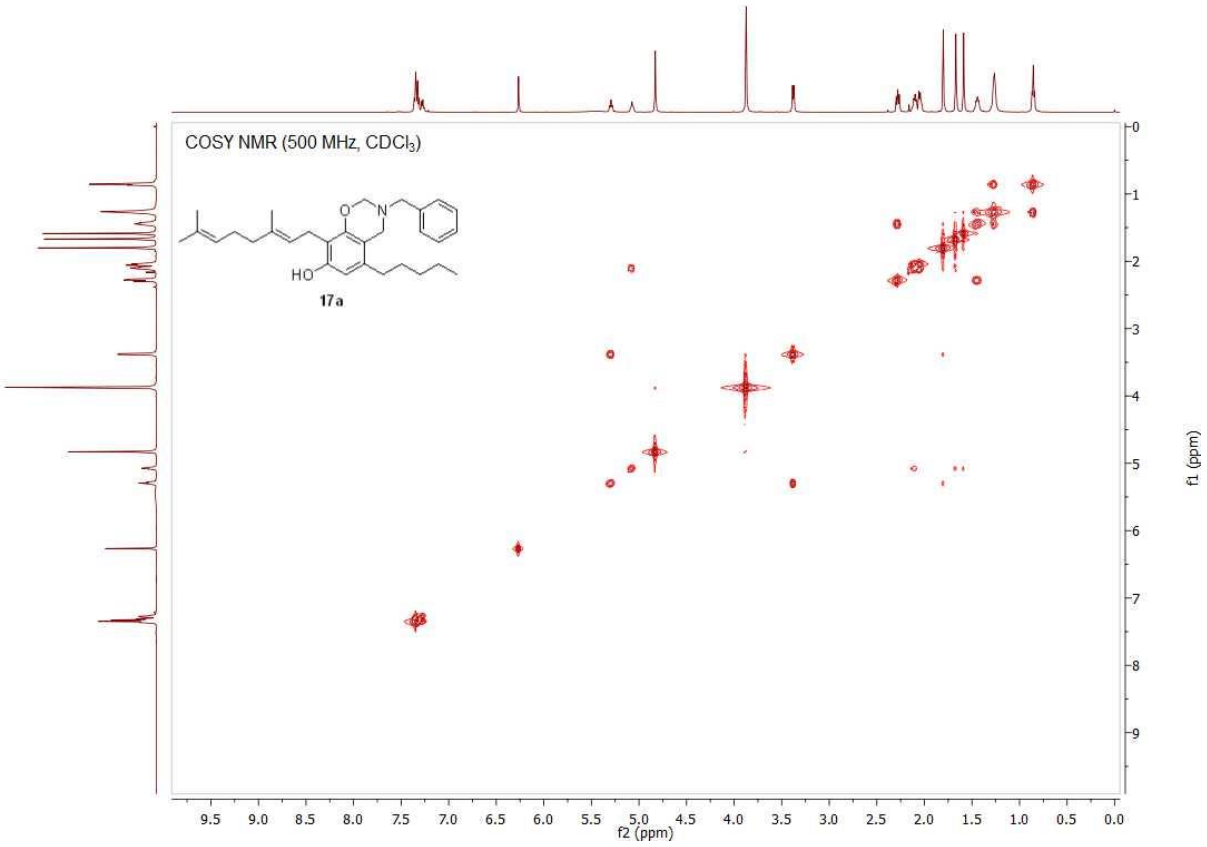

COSY NMR (500 MHz, CDCl3)
16b
f2 (ppm)
f1 (ppm)

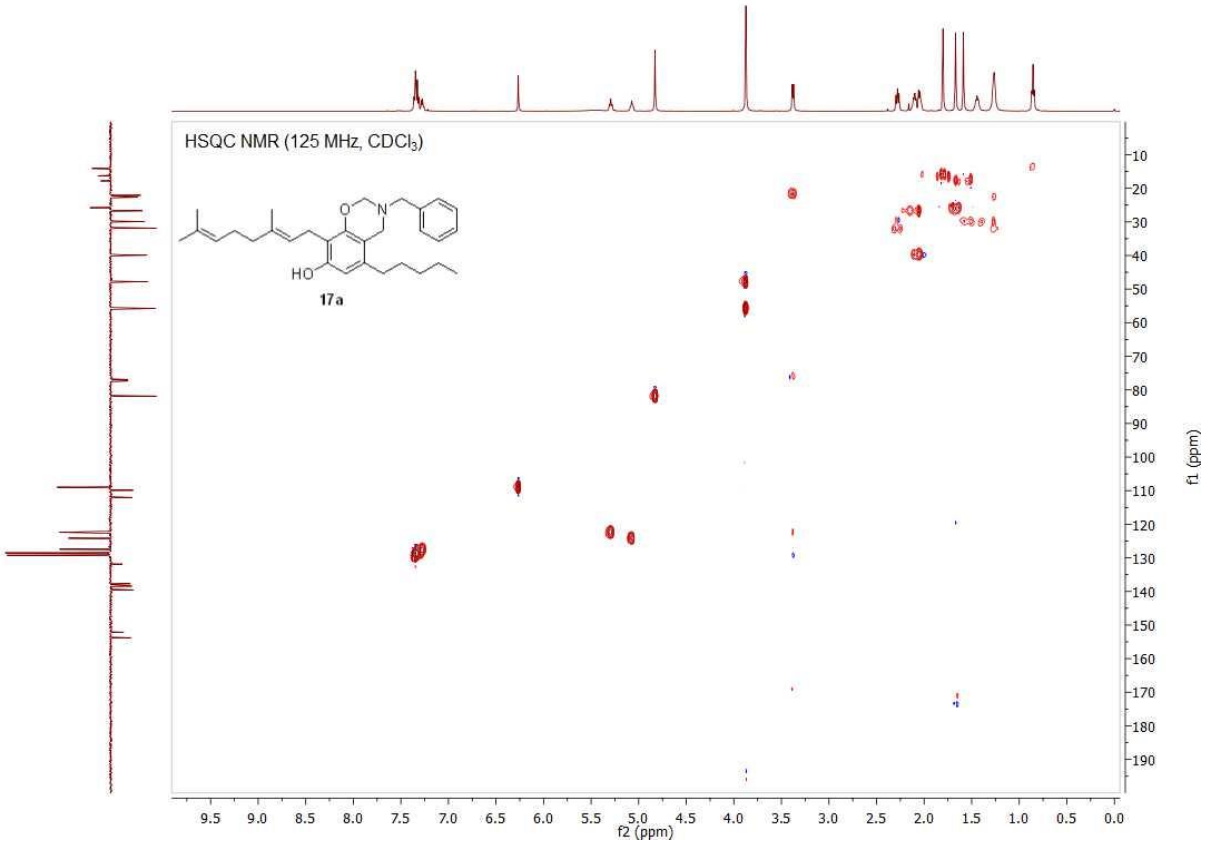

HSQC NMR (125 MHz, CDCl3)
16b
f2 (ppm)
f1 (ppm)

NMR spectra of compound 17a

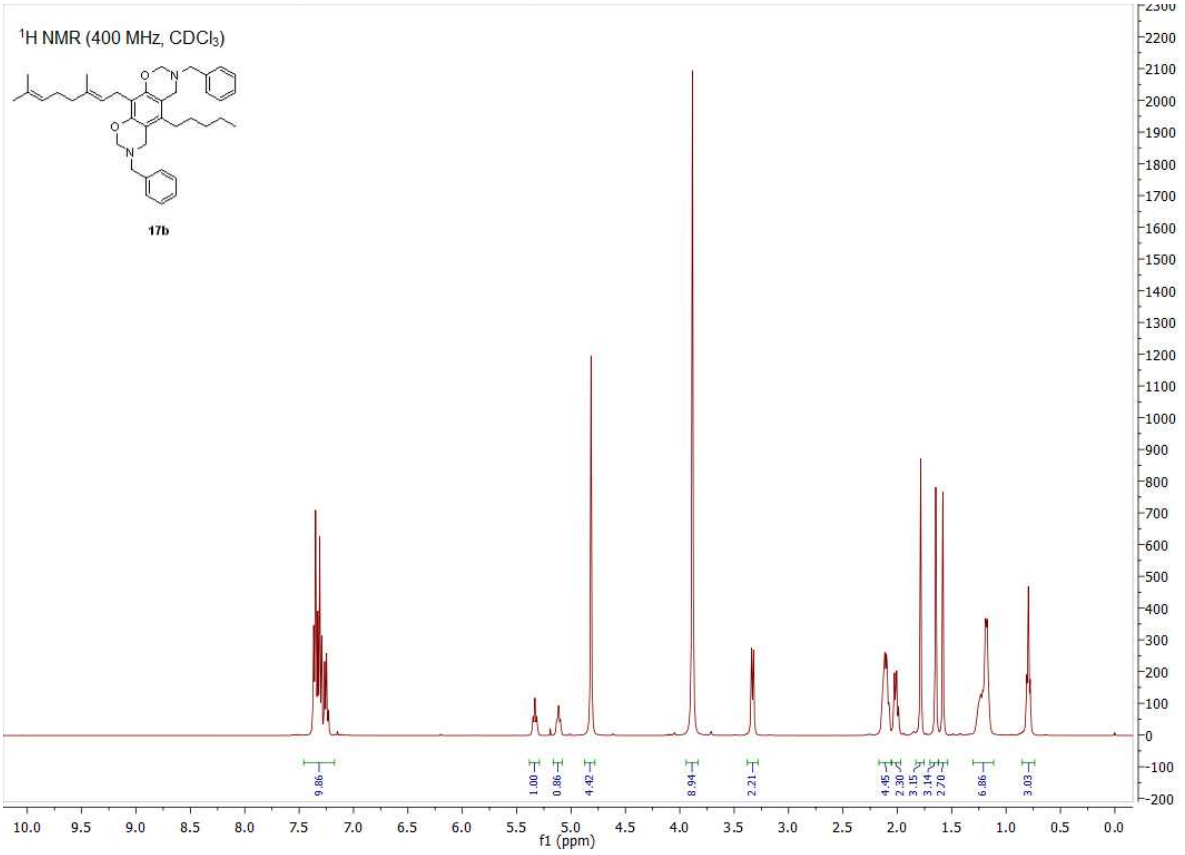


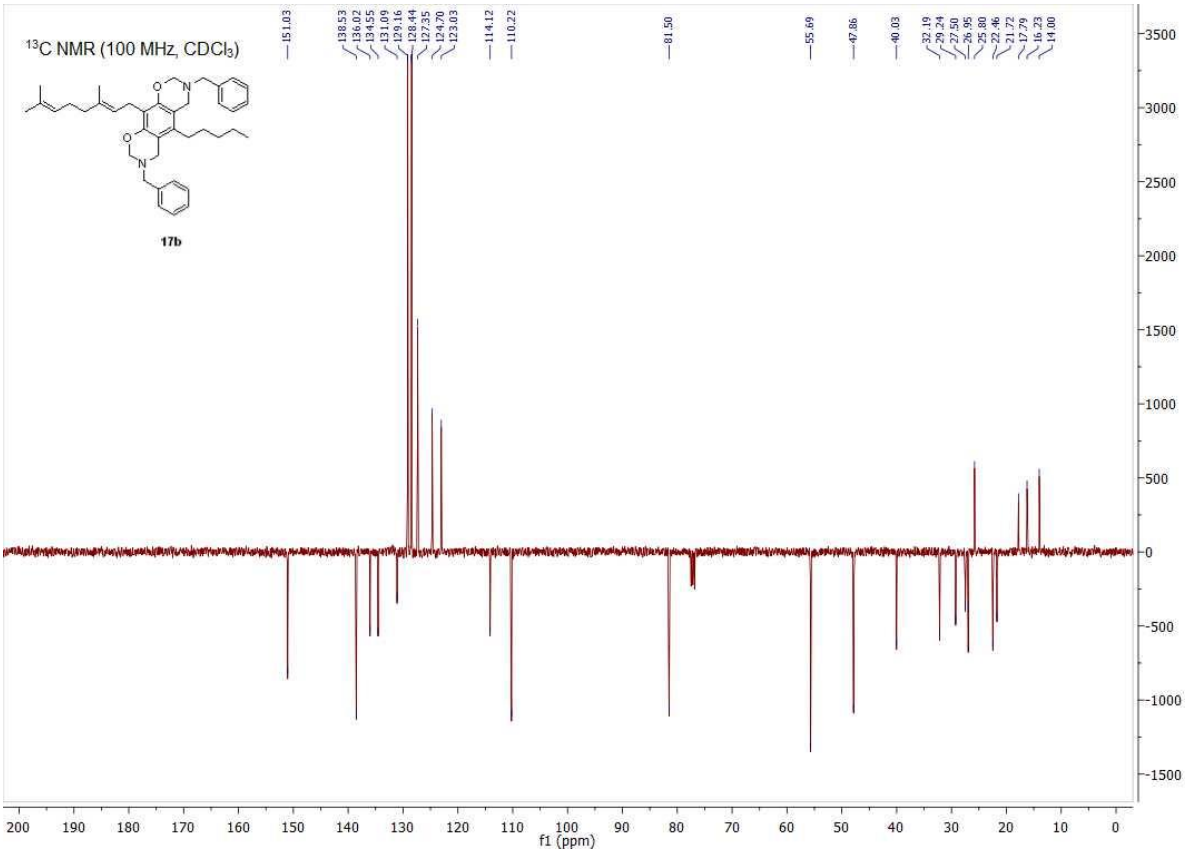


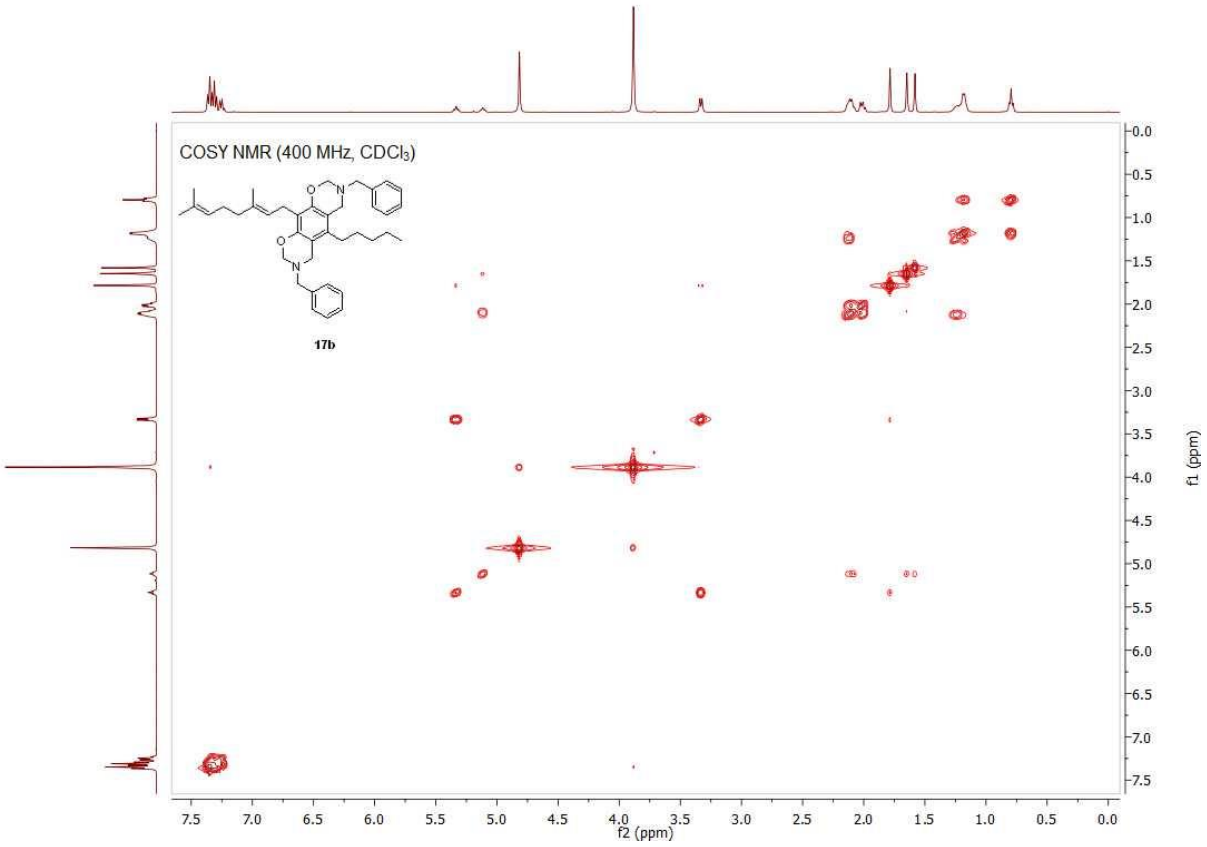

COSY NMR (500 MHz, $CDCl_3$)
HO
17a
f2 (ppm)
f1 (ppm)

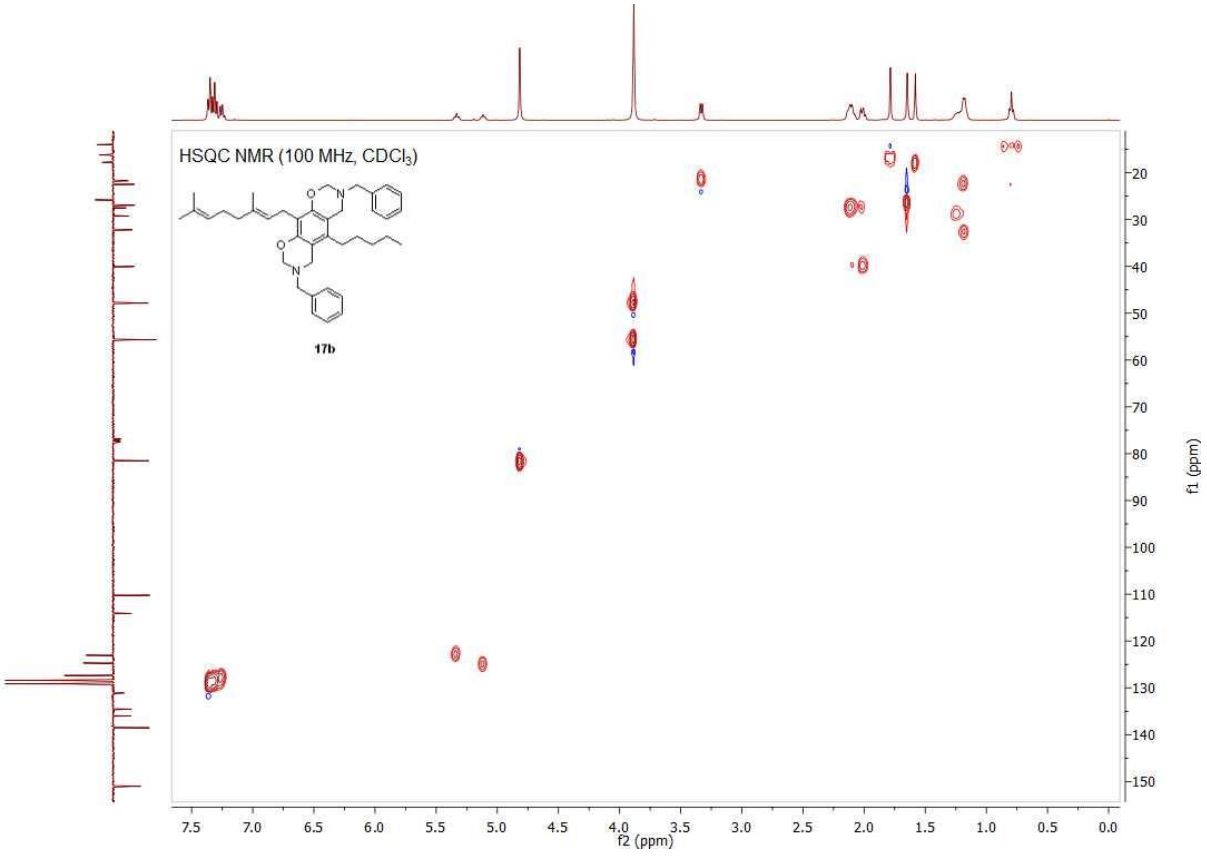

HSQC NMR (125 MHz, $CDCl_3$)
HO
17a
f2 (ppm)
f1 (ppm)

NMR spectra of compound 17b

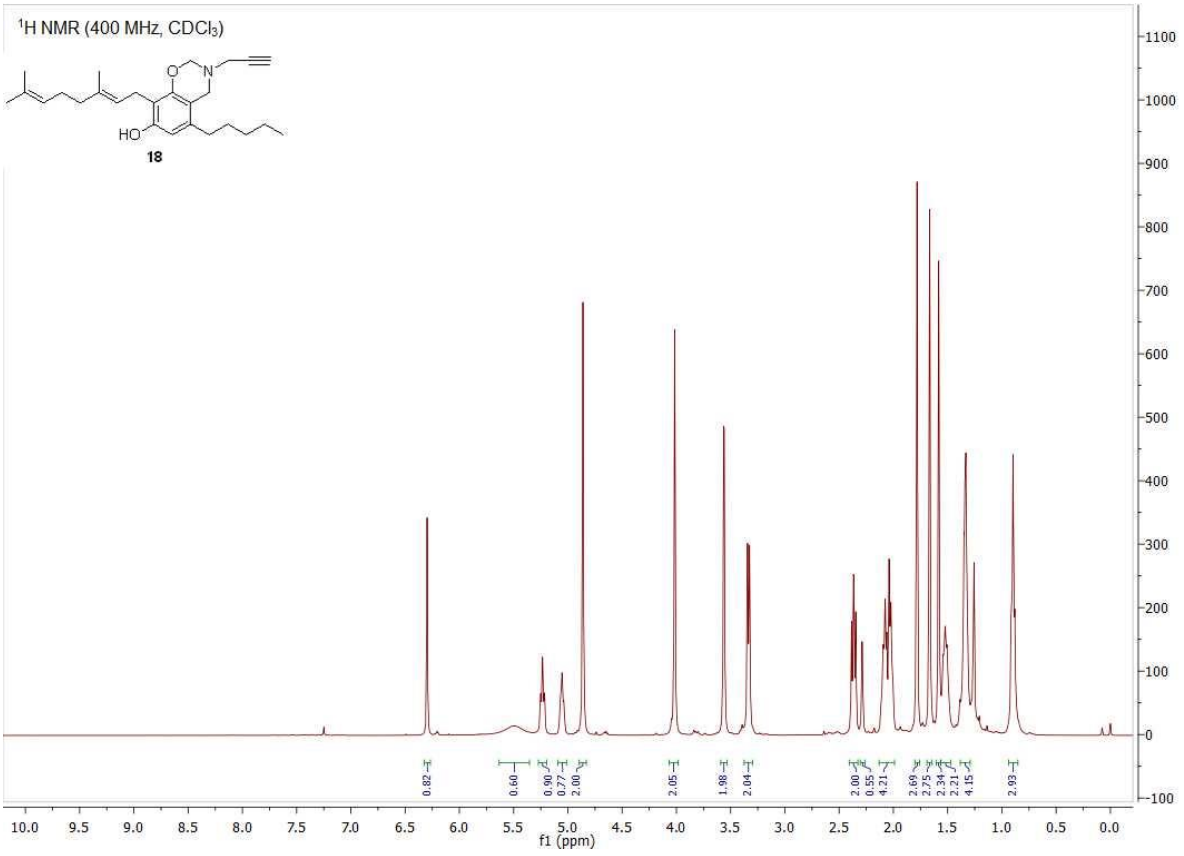


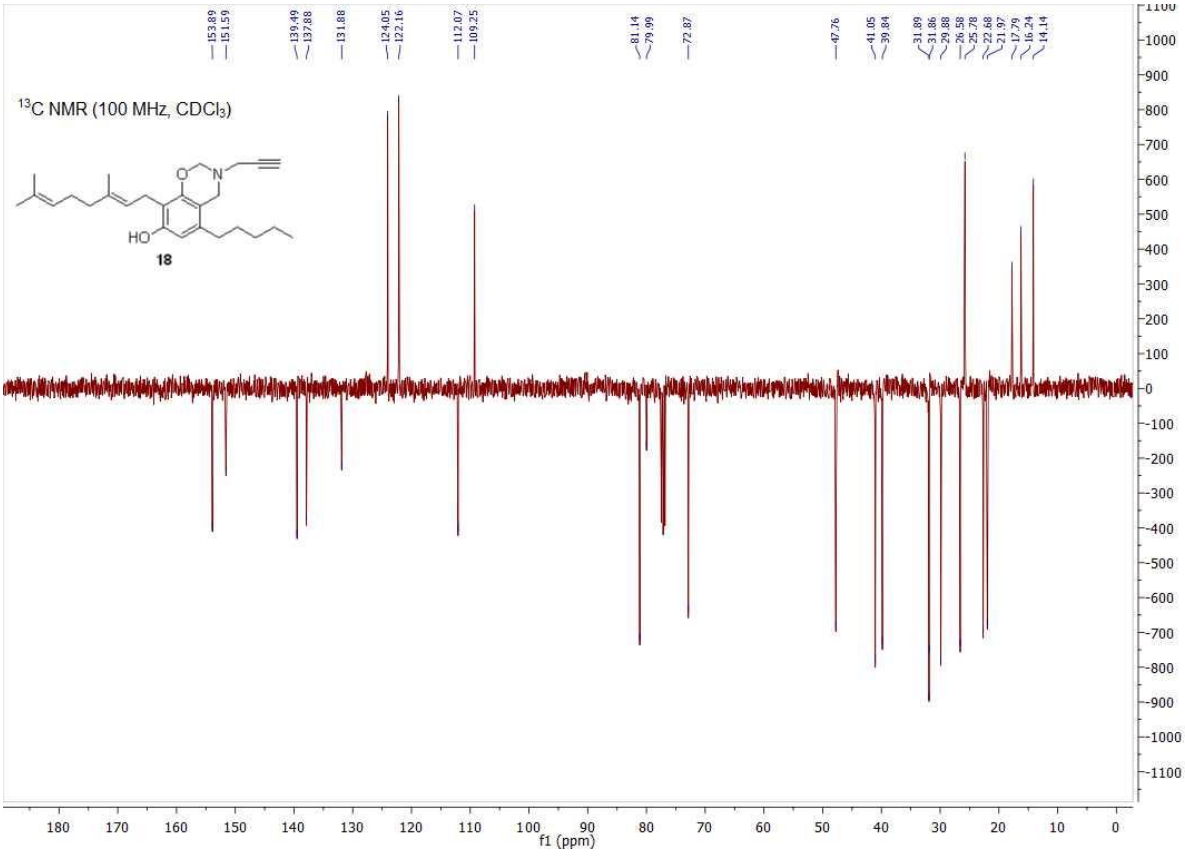


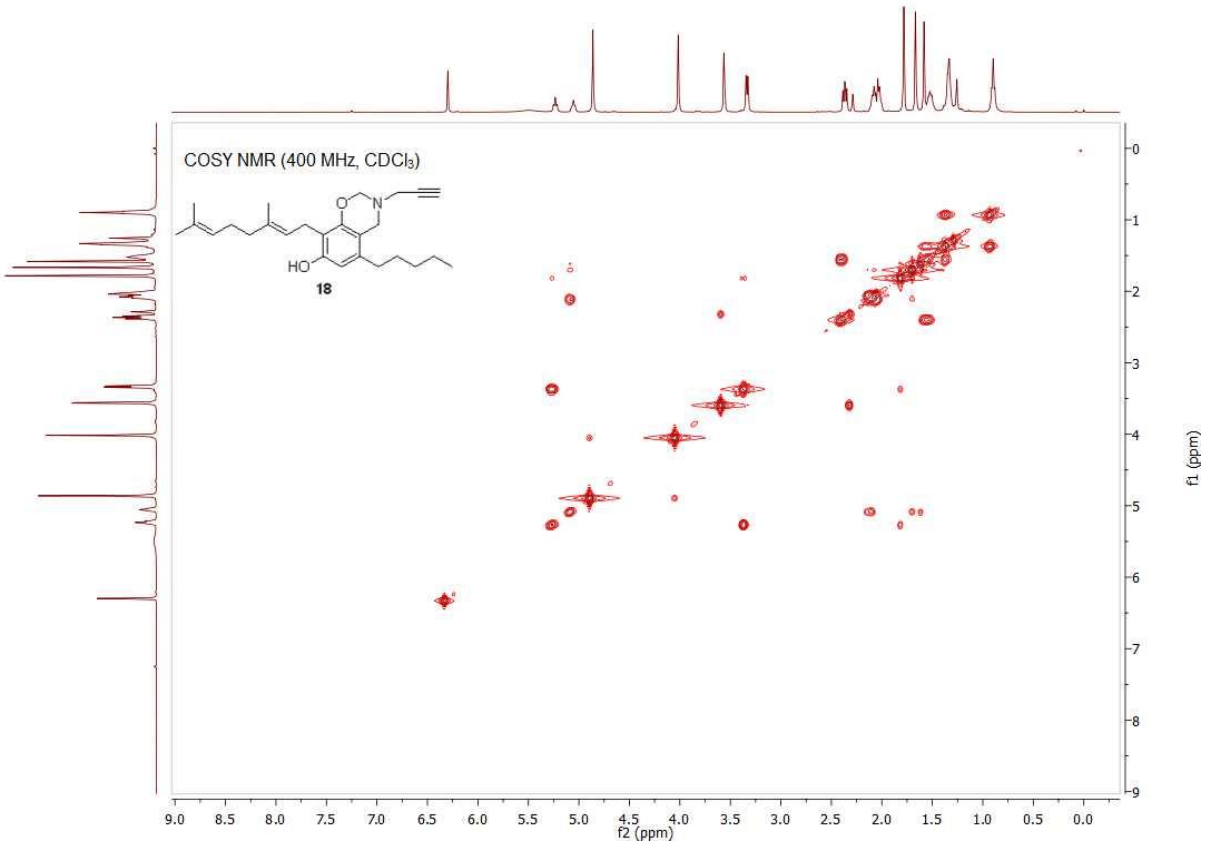

COSY NMR (400 MHz, CDCl3)
17b
f2 (ppm)
f1 (ppm)

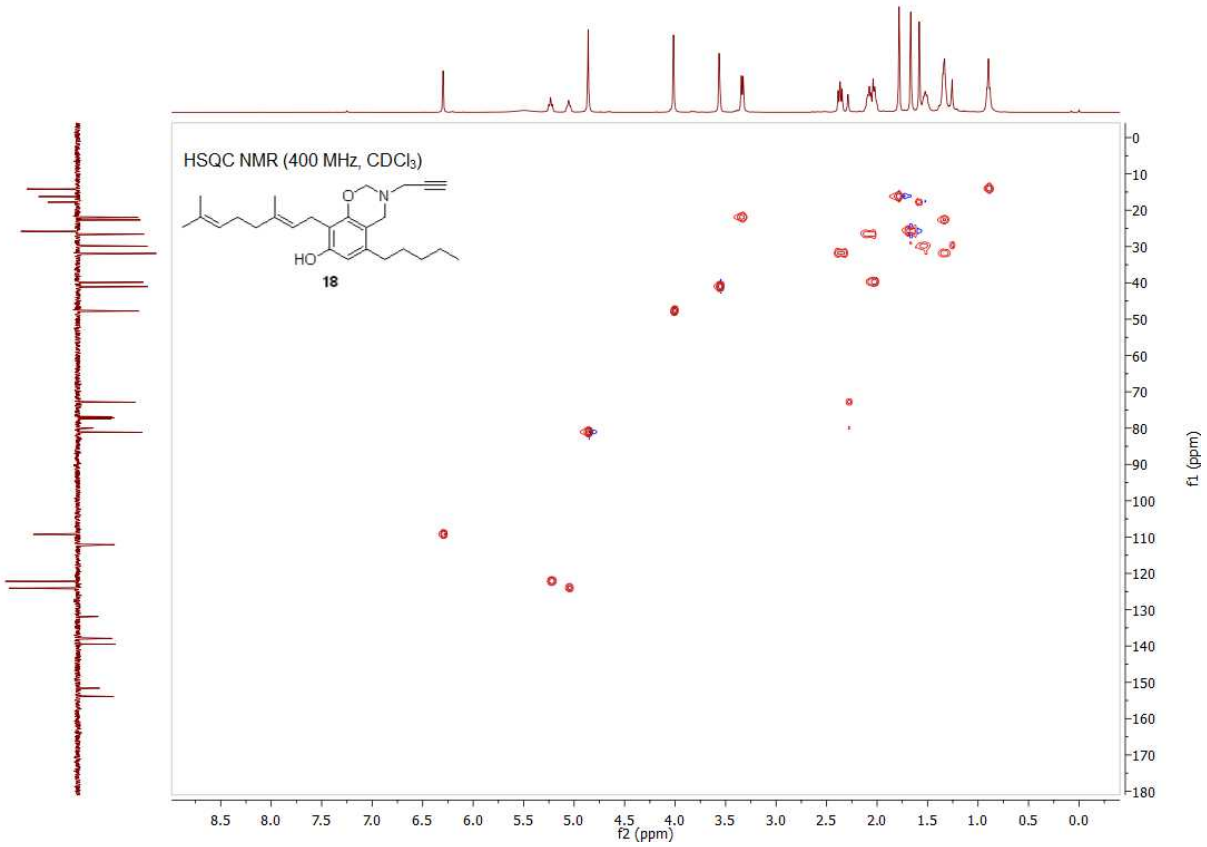

HSQC NMR (100 MHz, CDCl3)
17b
f2 (ppm)
f1 (ppm)

NMR spectra of compound 18

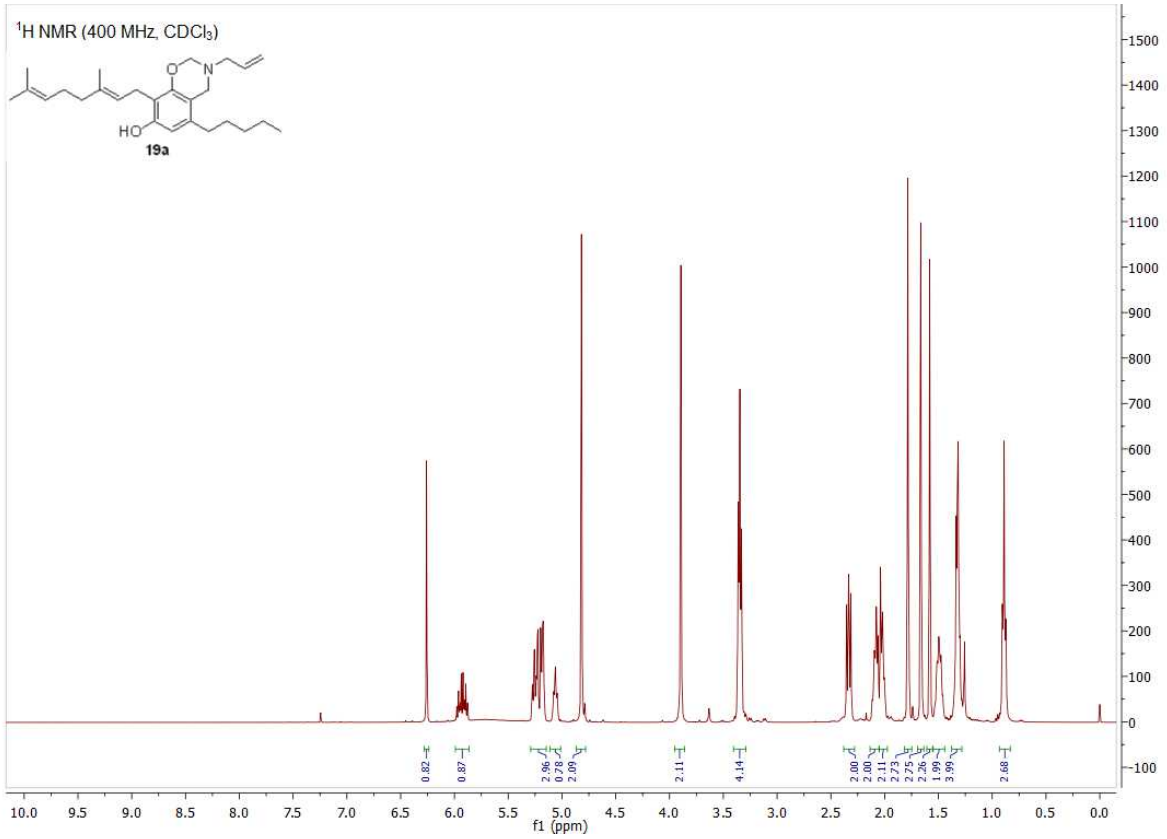


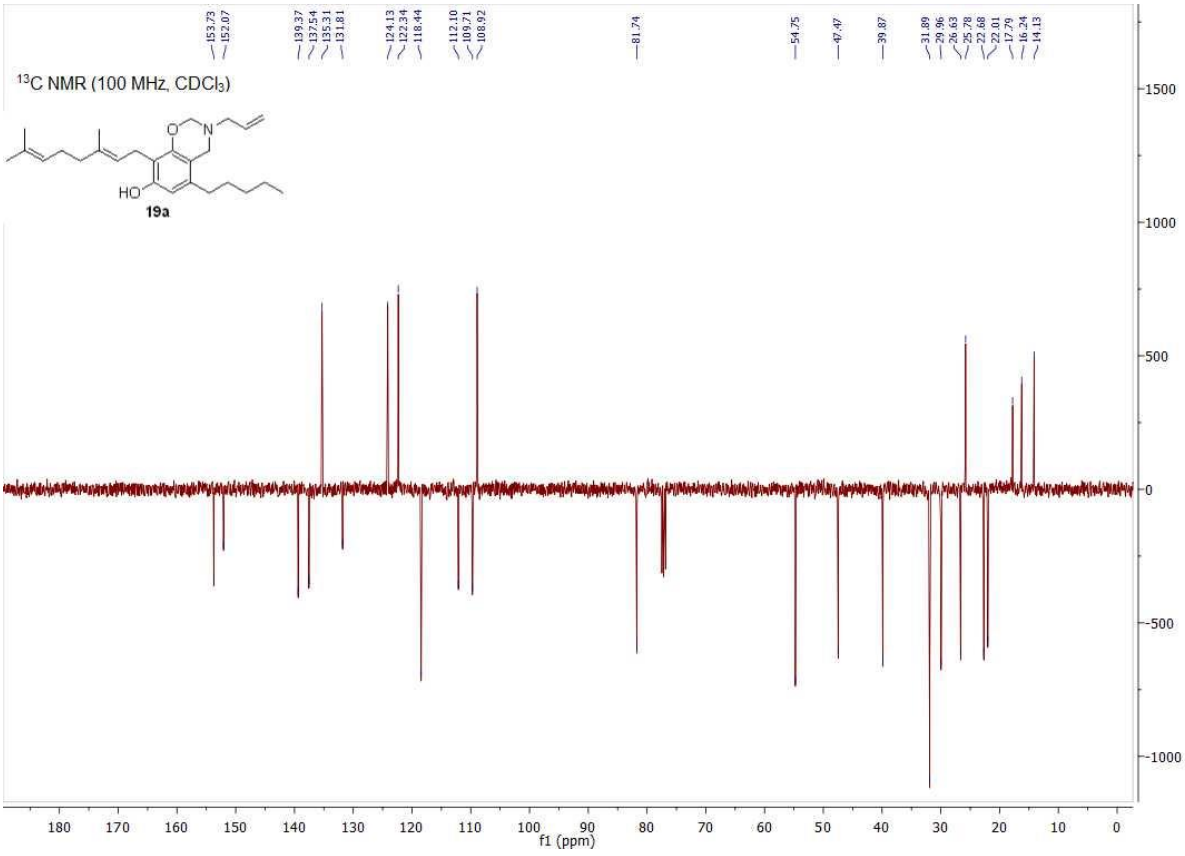


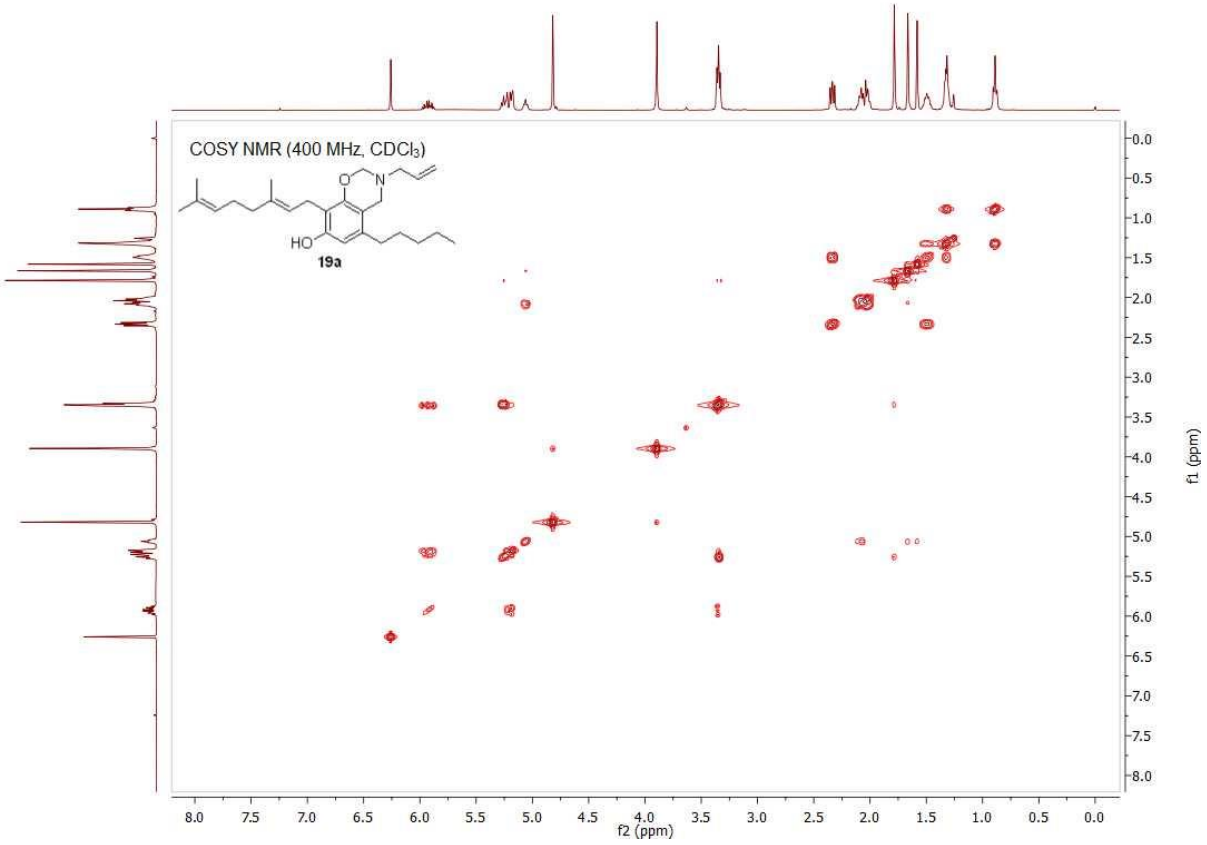

COSY NMR (400 MHz, CDCl3)
HO
18
f2 (ppm)
f1 (ppm)

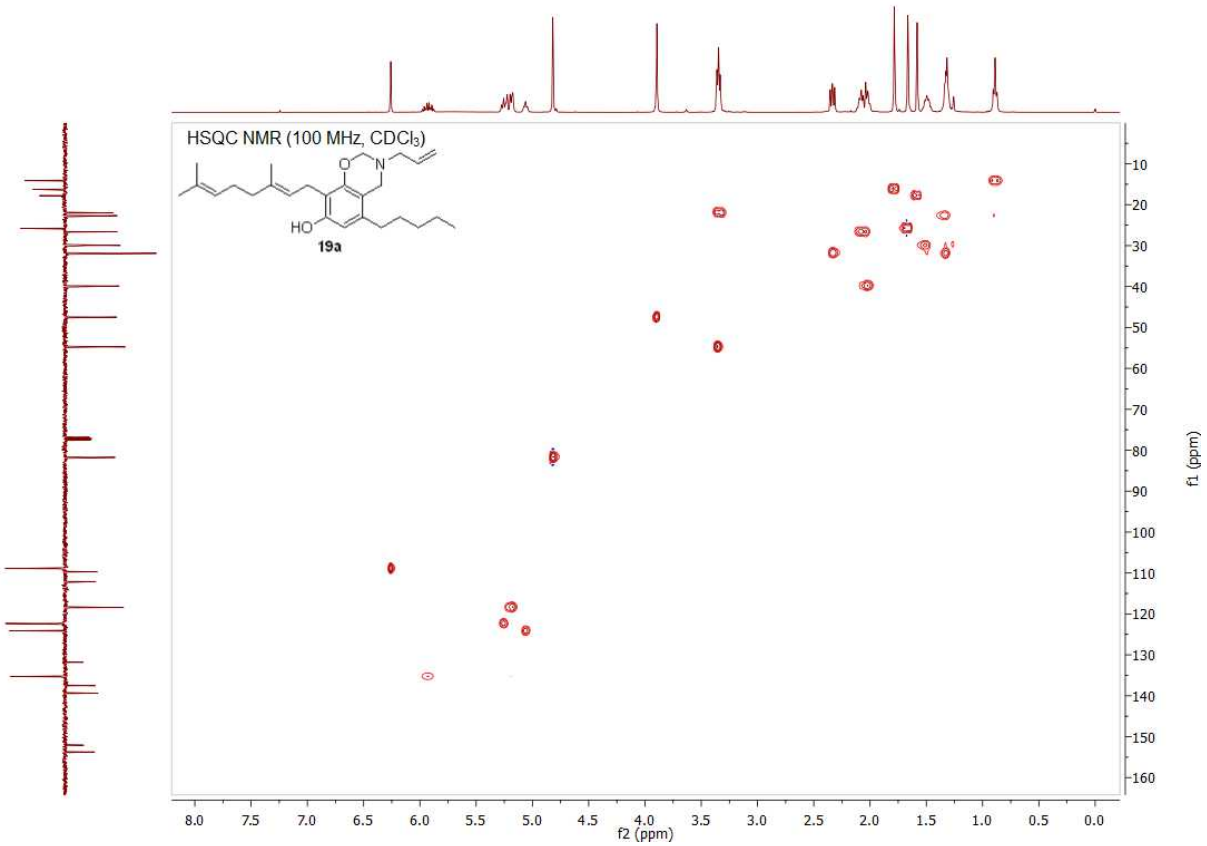

HSQC NMR (400 MHz, CDCl3)
HO
18
f2 (ppm)
f1 (ppm)

NMR spectra of compound 19a

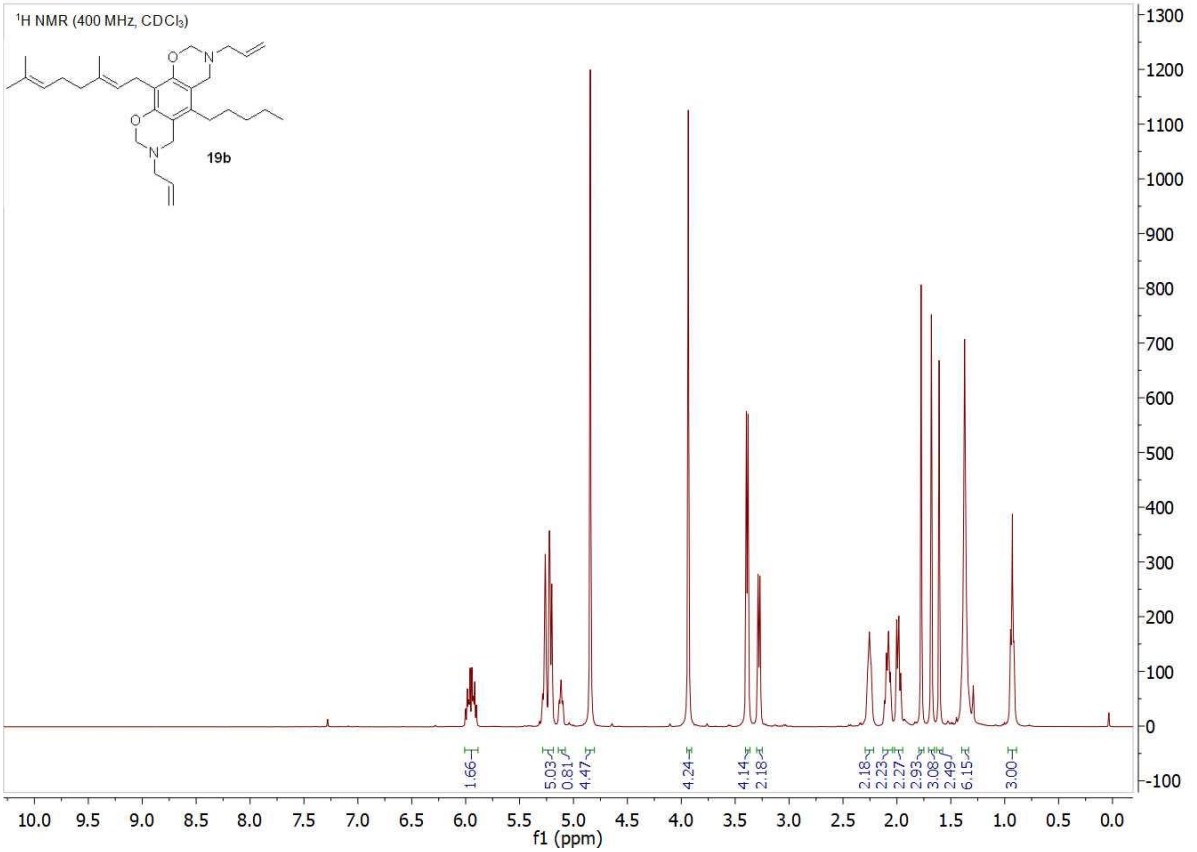


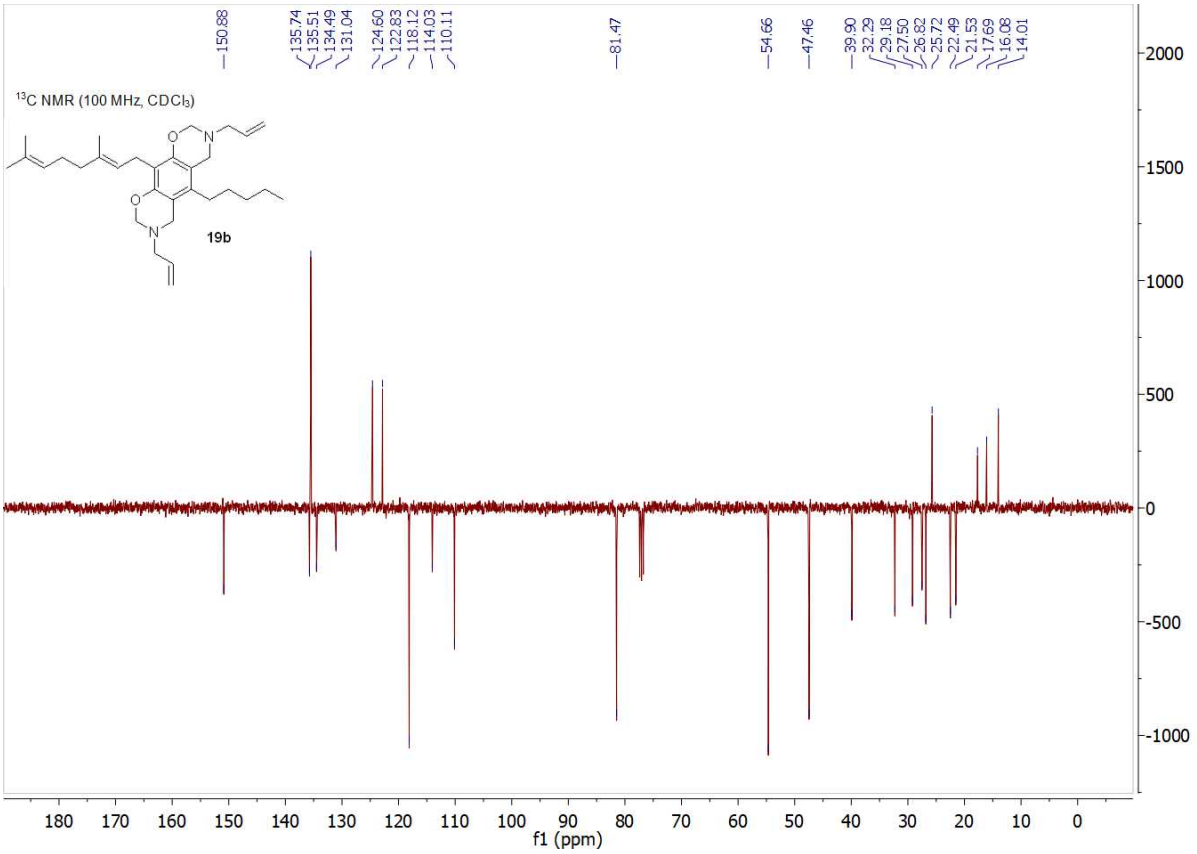



COSY NMR (400 MHz, CDCl3)
HO
19a
f2 (ppm)
f1 (ppm)

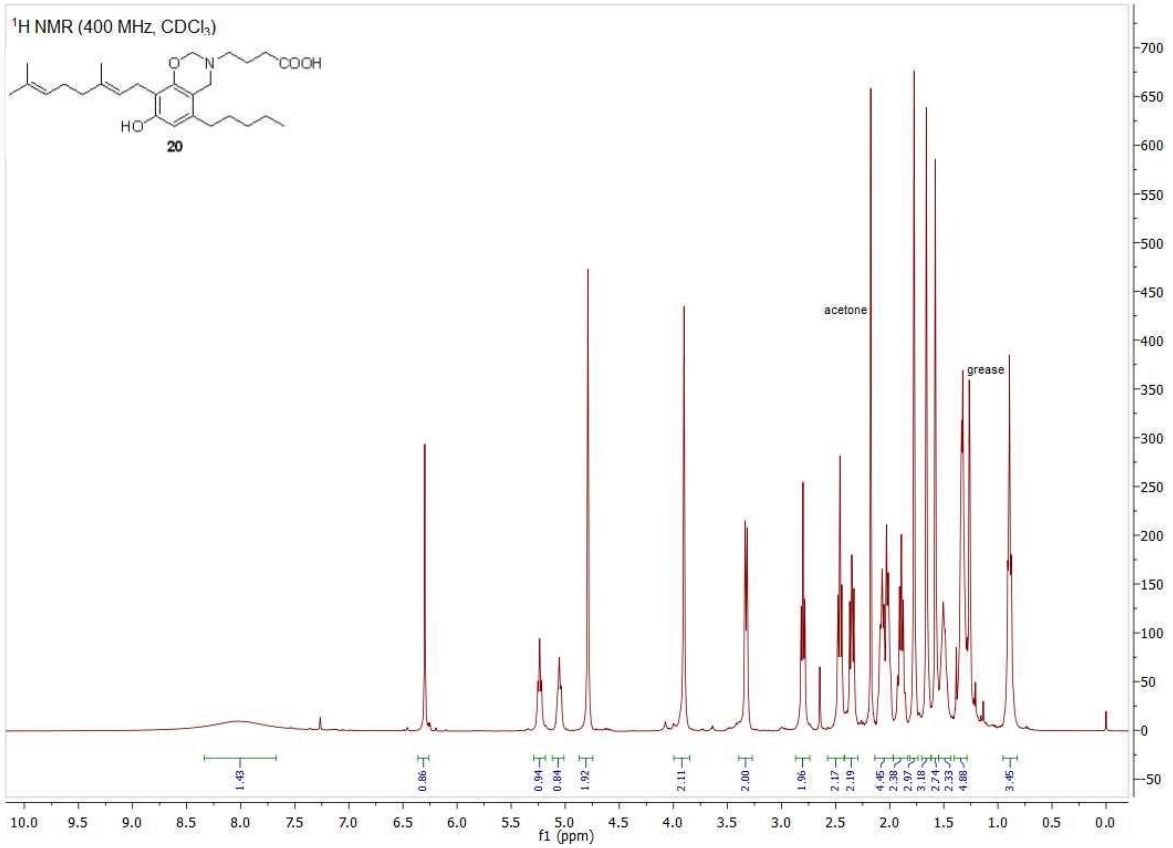

HSQC NMR (100 MHz, CDCl3)
HO
19a
f2 (ppm)
f1 (ppm)

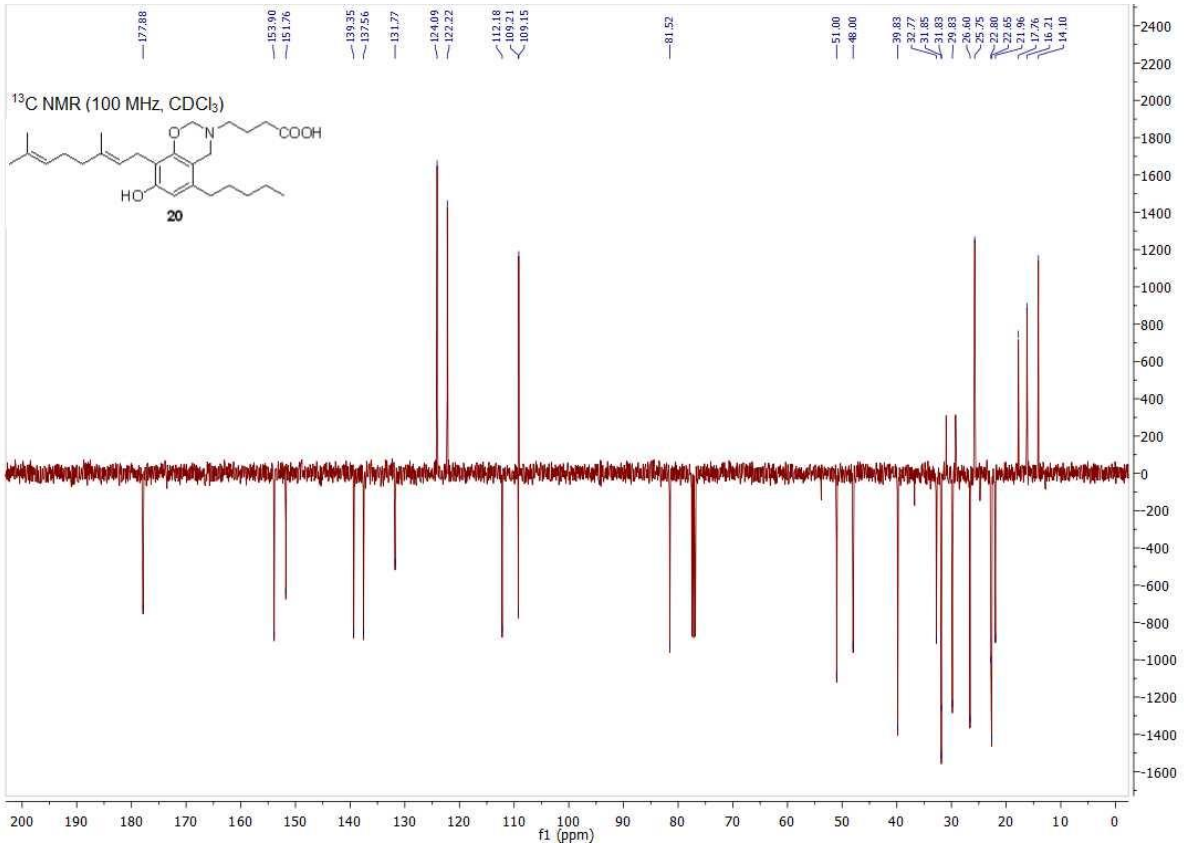
NMR spectra of compound 19b

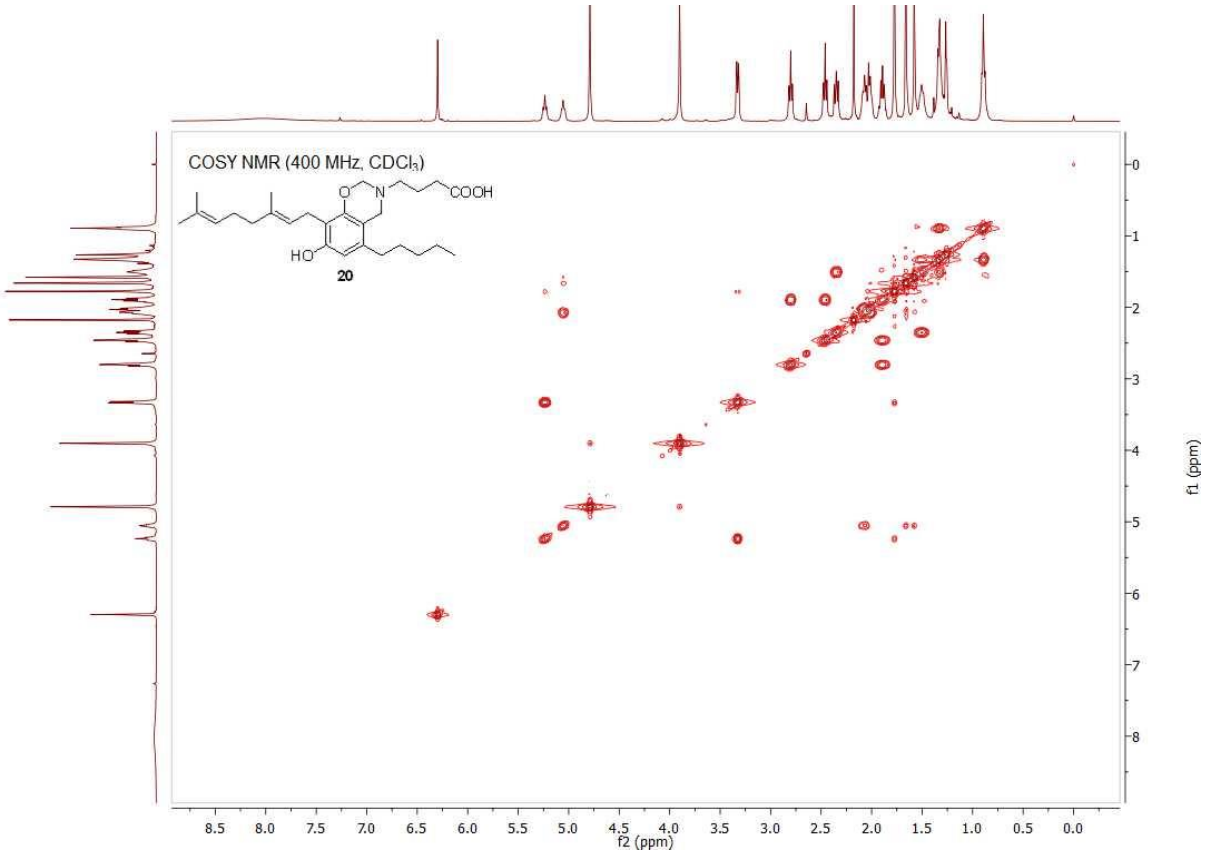


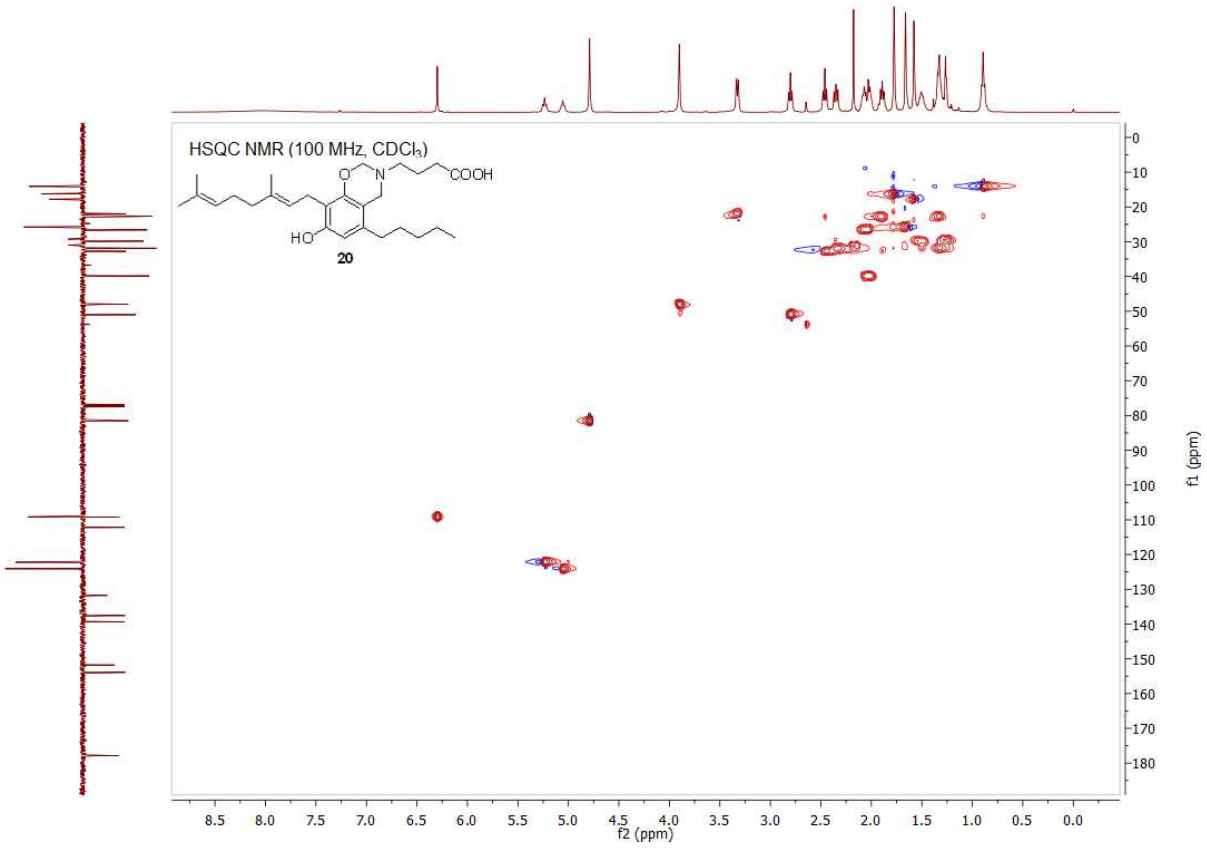


NMR spectra of compound 20

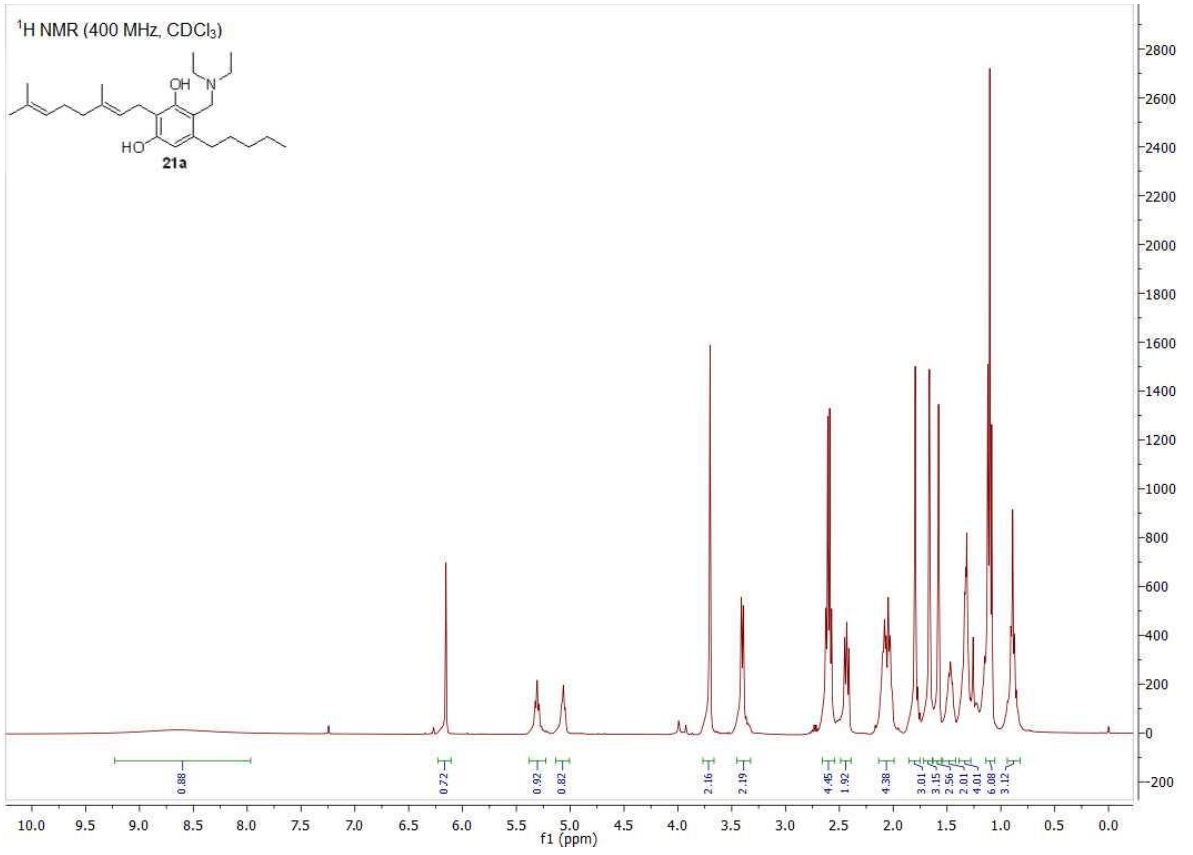


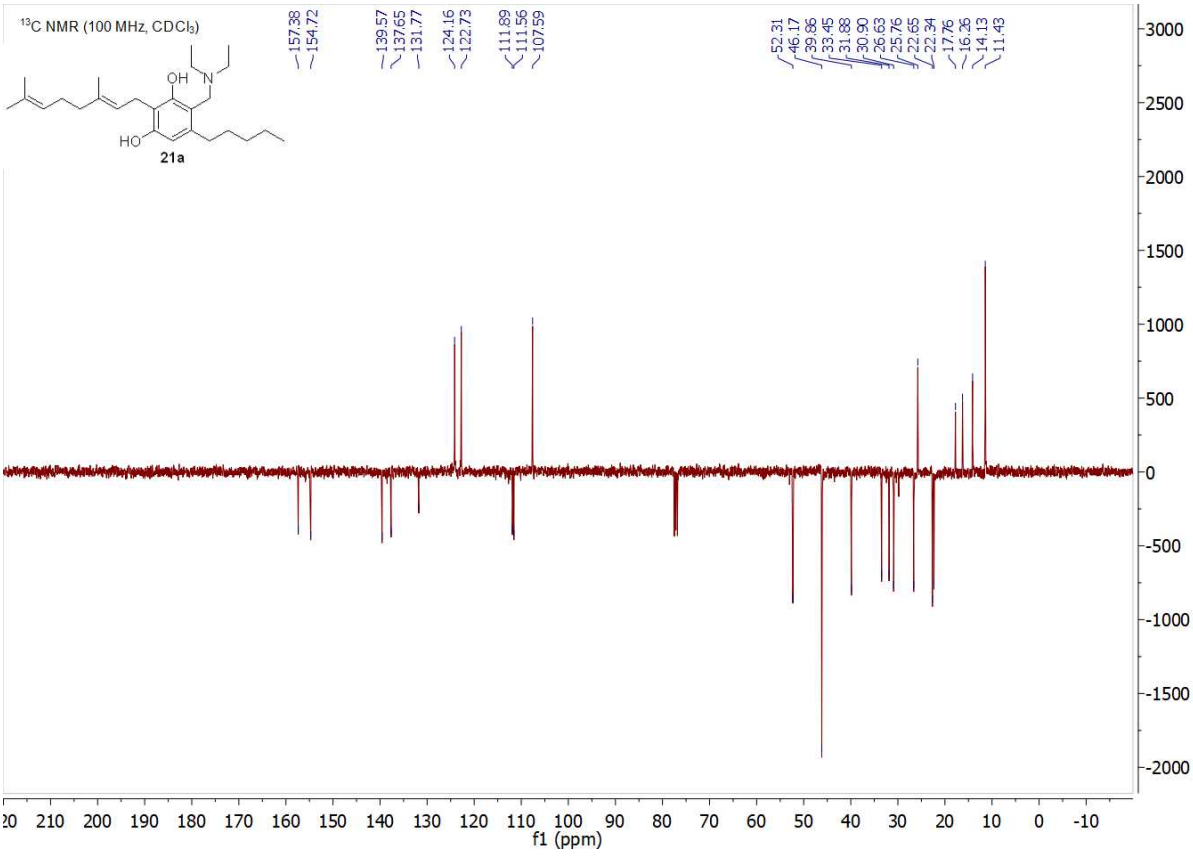


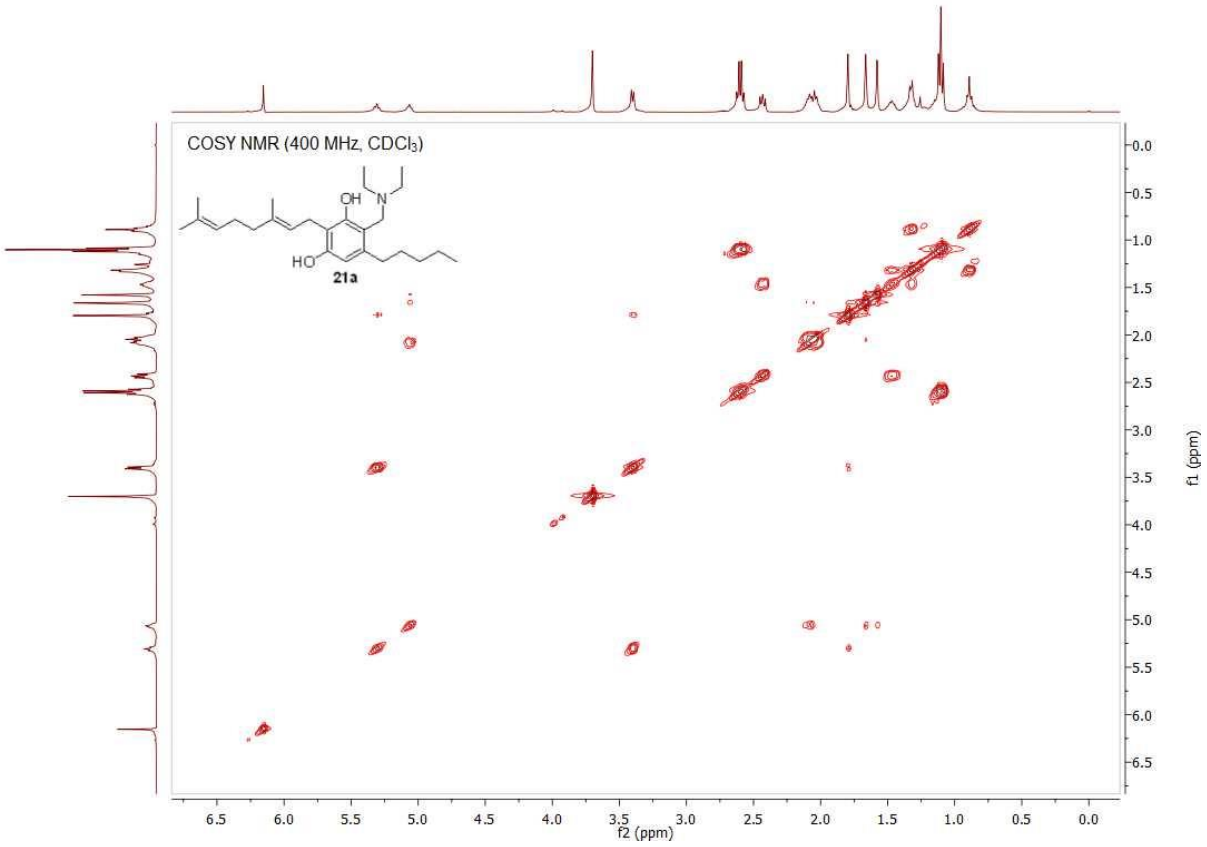

COSY NMR (400 MHz, CDCl3)
COOH
HO
20
f2 (ppm)
f1 (ppm)

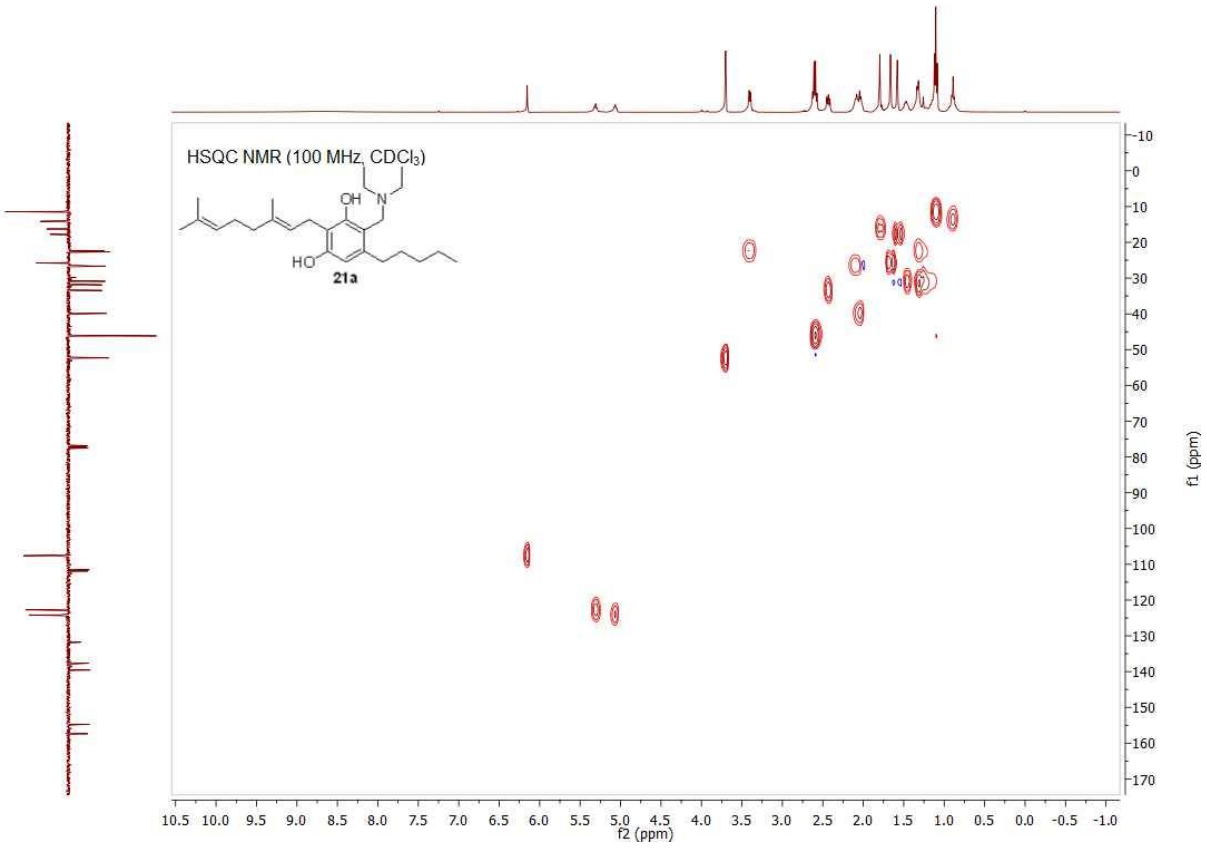

HSQC NMR (100 MHz, CDCl3)
COOH
HO
20
f2 (ppm)
f1 (ppm)

NMR spectra of compound 21a






COSY NMR (400 MHz, CDCl3)
OH
N
HO
21a
f2 (ppm)
f1 (ppm)


HSQC NMR (100 MHz, CDCl3)
OH
N
HO
21a
f2 (ppm)
f1 (ppm)

NMR spectra of compound 21b