

Supplementary Material

From simple phenols to potent chain-breaking antioxidants by transposition of benzo[1,4]oxathiines to benzo[*b*]thiophenes

Caterina Viglianisi,^{*a} Leonardo Di Pietro,^a Valentina Meoni,^a Riccardo Amorati,^b and Stefano Menichetti^a

^aDepartment of Chemistry "U. Schiff", University of Firenze,
Via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy

^bDepartment of Chemistry "G. Ciamician", University of Bologna, Via San Giacomo 11, 40126 Bologna, Italy
Email: caterina.viglianisi@unifi.it

Table of Contents

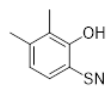
| | |
|--|----|
| General informations | S2 |
| General sulfenylation procedure for the synthesis of derivatives 2 | S2 |
| Synthesis of phenols | S3 |
| NMR Spectra | S5 |

General information

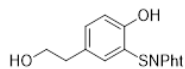
^1H and ^{13}C NMR spectra were recorded with Varian Mercury Plus 400, using CDCl_3 as solvent. Residual CHCl_3 at 7.26 ppm and central line of CDCl_3 at 77.00 ppm were used as the reference of ^1H and ^{13}C NMR spectra respectively. FT-IR spectra were recorded with Spectrum Two FT-IR Spectrometer. GC-MS spectra were recorded with a QMD 100 Carlo Erba. ESI-MS spectra were recorded with a JEOL MStation JMS700. Melting points were measured with Stuart SMP50 Automatic Melting Point Apparatus. All the reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F 254) and the products were visualized with acidic vanillin solution. Silica gel 60 (230–400 mesh) was used for column chromatography. Dry solvents were obtained by The PureSolv Micro Solvent Purification System. Chloroform was washed with water several times and stored over calcium chloride. Pyridine and TEA were freshly distilled over KOH. Phthalimide sulfonyl chloride was prepared from the corresponding commercially available disulfide (purchased from Chemper snc) as reported elsewhere. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Derivatives **1b**, **1c**, **1d** are commercially available, **2a** and **4ac** were prepared as reported in a previous paper.⁴

General sulfonylation procedure for the synthesis of derivatives 2

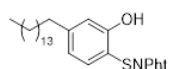
To a solution of phenol in CHCl_3 (0.5 M), was added dropwise at 0°C a solution of PhtNSCl in CHCl_3 (0.5 M) and the mixture was stirred at room temperature until TLC analysis indicated complete consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (200 mL) washed with a saturated solution of NaHCO_3 (200 mL) and with H_2O (200 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated *in vacuo* to yield the crude product.



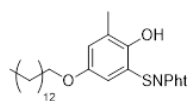
2b. The crude was purified by silica gel column chromatography, using a mixture of petroleum ether and CH_2Cl_2 1:10 as eluent. The purified product was obtained as a white solid in 63% of yield. IR (cm^{-1}) ν 3403, 1782, 1730, 1707, 1348, 1282, 1238. MP: 170-178 $^\circ\text{C}$ Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_3\text{S}$: C 64.20, H 4.38, N 4.68; found C 65.21, H 3.01, N 4.51. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (bs, 1H), 7.89 – 7.85 (m, 2H), 7.76 – 7.72 (m, 2H), 7.58 (d, $J = 8.0$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 2.23 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.4, 156.7, 144.1, 134.9, 134.7, 131.9, 124.6, 124.1, 121.8, 115.4, 20.4, 12.3.



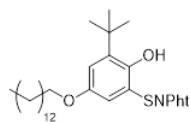
2c. The crude was purified by silica gel column chromatography, using a mixture of CH_2Cl_2 and AcOEt 14:3 as eluent. The purified product was obtained as a white solid in 16% of yield. ^1H -NMR (400 MHz, CDCl_3) δ 1.40-1.55 (br s, 1H), 2.77 (pt, 2H), 3.81 (pt, 2H), 6.96 (d, $J = 4.3$ Hz, 1H), 7.25 (dd, $J = 4.3, 1.2$ Hz, 1H), 7.70 (d, $J = 1.2$ Hz, 1H), 7.83 (m, 4H), 8.24 (br s, 1H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 37.7, 63.5, 117.03, 118.2, 124.2, 130.8, 131.8, 134.9, 135.6, 138.4, 157.5, 168.4



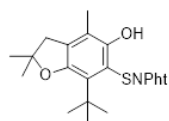
2d. The product was obtained as a white solid in quantitative yield and was used without silica gel column chromatography purification. ^1H -NMR (200 MHz, CDCl_3) δ 0.80-0.95 (m, 3H), 1.19-1.62 (m, 26 H), 2.45-2.60 (pt, 2H), 6.69 (dd, $J = 8.0$ Hz e 1.8 Hz, 1H), 6.84 (d, $J = 1.4$ Hz, 1H), 7.65- 8.00 (m, 5H), 8.25 (s, 1H).



2e. The product was obtained as soft beige solid in quantitative yield and was used without silica gel column chromatography purification. ^1H NMR (400 MHz, CDCl_3) δ 7.90 – 7.88 (m, 2H), 7.76 – 7.74 (m, 2H), 7.20 – 7.18 (m, 1H), 6.85 – 6.84 (m, 1H), 3.87 (t, $J = 6.5$ Hz, 2H), 2.23 (s, 3H), 1.75 – 1.70 (m, 2H), 1.46 – 1.41 (m, 2H), 1.30 – 1.26 (m, 20H), 0.87 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.5 (2C), 151.4, 134.8 (2C), 131.9 (2C), 127.3, 124.2 (2C), 118.8, 117.2, 115.4, 112.5, 68.7, 31.9, 29.6, 29.5, 29.4, 29.3 (4 signals for 9 non-equivalent CH_2 groups), 26.0, 22.7, 16.8, 14.1.

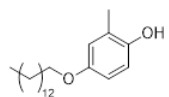


2f. The product was obtained as yellow solid in quantitative yield and was used without silica gel column chromatography purification. MS (EI) m/z (I_{rel} , %): 539 (15.41); 103 (99.25); 146 (95.35); 75 (100.00). ^1H NMR (400 MHz, CDCl_3) δ 7.91 – 7.89 (m, 2H), 7.77 – 7.75 (m, 2H), 7.24 (d, $J = 3.1$ Hz, 1H), 7.01 (d, $J = 3.0$ Hz, 1H), 3.90 (t, $J = 6.6$ Hz, 2H), 1.76 – 1.72 (m, 2H), 1.38 (s, 9H), 1.33 – 1.26 (m, 22H), 0.88 (t, $J = 6.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.4 (2C), 151.9, 151.4, 139.1, 134.7 (2C), 132.0, 124.1 (2C), 121.4, 118.4, 118.2, 68.4, 35.4, 31.9, 29.7, 29.6, 29.4 (3 signals for 9 non-equivalent CH_2 groups), 29.3, 26.0, 22.7, 14.1.

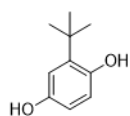


2g. The product was obtained as yellow solid in quantitative yield and was used without silica gel column chromatography purification. IR (CDCl_3 , 0.05M, cm^{-1}) ν 3606, 3424, 2928, 2856, 1782, 1732, 1710, 1609, 1468, 1340, 1282, 1221, 1199, 1060. ^1H NMR (400 MHz, CDCl_3) δ 7.87 – 7.84 (m, 2H), 7.74 – 7.72 (m, 2H), 2.84 (s, 2H), 2.07 (s, 3H), 1.75 (s, 9H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 169.0 (2C), 151.2, 150.4, 134.6 (2C), 133.6, 132.8, 131.9 (2C), 123.9 (2C), 119.4, 115.6, 84.6, 42.3, 39.2, 32.0, 28.2, 13.5.

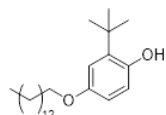
Synthesis of phenols



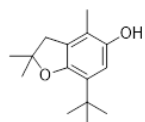
1e. In a two-necked round-bottomed flask containing K_2CO_3 (1.11 g, 8.06 mmol) and toluhydroquinone (1.00 g, 8.06 mmol) was added anhydrous CH_3CN (20 mL) previously degassed for 1h with N_2 , and at last was added 1-bromotetradecane (2.2 mL, 8.06 mmol). The reaction mixture was stirred under nitrogen atmosphere at reflux (80°C) and after 46 h was diluted with H_2O (50 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4 , filtered and evaporated *in vacuo*. The crude was purified by silica-gel column chromatography, using a mixture of petroleum ether and ethyl acetate 10 : 1 as eluent. The purified product was obtained as a light pink solid (370 mg, yield 14 %). ^1H NMR (400 MHz, CDCl_3) δ 6.69 – 6.67 (m, 2H), 6.63 – 6.60 (m, 1H), 4.33 (s, 1H), 3.88 (t, $J = 6.6$ Hz, 2H), 2.22 (s, 3H), 1.77 – 1.70 (m, 2H), 1.47 – 1.39 (m, 2H), 1.33 – 1.26 (m, 20H), 0.90 – 0.86 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 153.2, 124.7, 117.4, 115.5, 112.6, 68.6, 31.9, 29.7, 29.6, 29.4 (3 signal for 9 non-equivalent CH_2 groups), 26.1, 22.7, 16.1, 14.1.



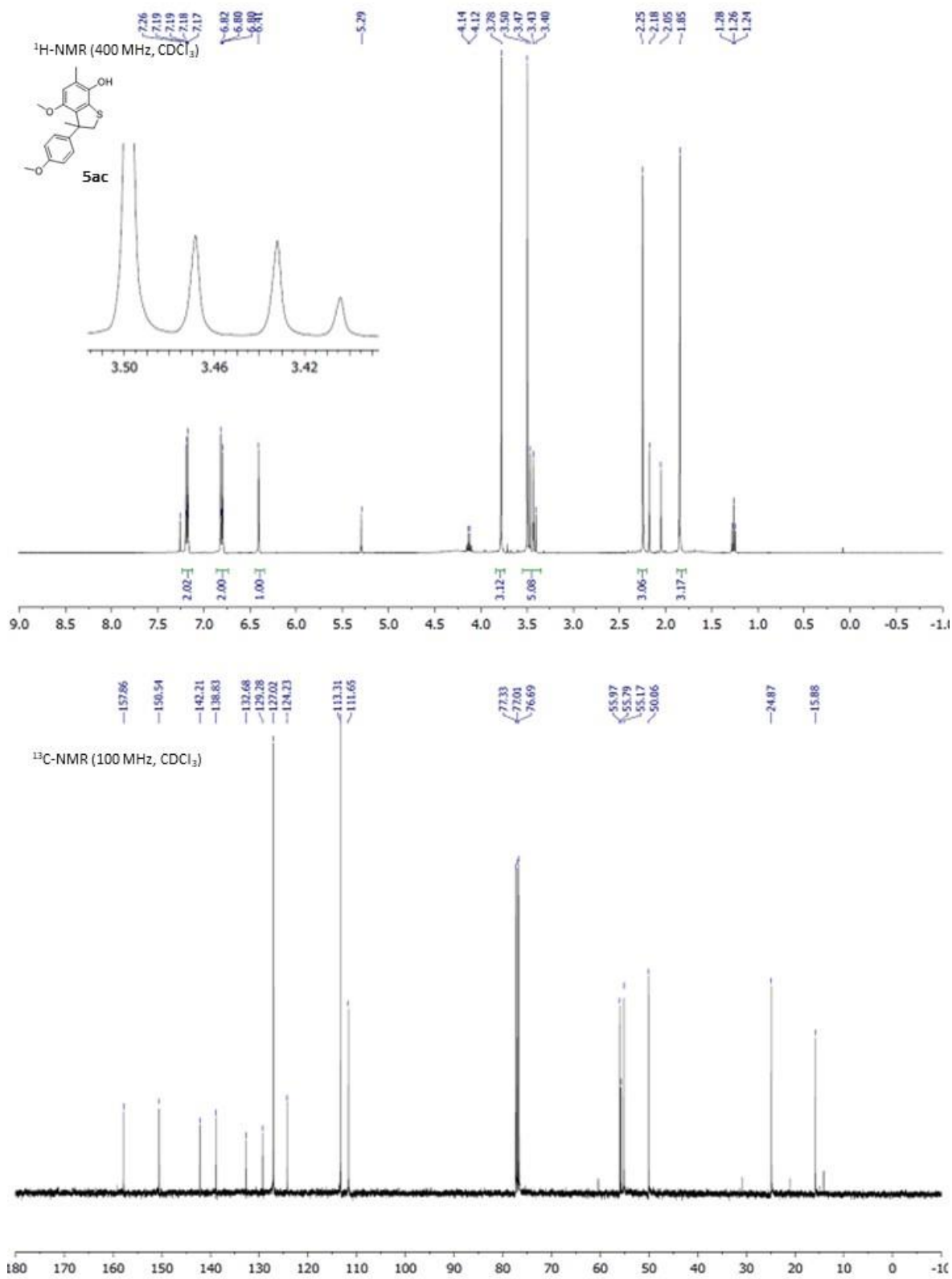
Under stirring, urea (6 g, 100 mmol) and tert-butyl alcohol (7.4 g, 99 mmol) were added to 75% H₂SO₄ (100 mL) slowly at room temperature. After 2h30' toluhydroquinone (10 g, 80 mmol) was added to the reaction mixture at 0-5 °C. After stirring at room temperature for 3h, the reaction mixture was quenched and extracted with ethyl acetate (3×100 mL). The organic layer was washed successively with saturated aqueous sodium bicarbonate (3×100 mL), brine (100 mL) and water (100 mL), then dried over anhydrous sodium sulfate. After removing the drying agent by filtration, the solvent was evaporated *in vacuo* to give the product as a light brown solid (10.6 g, yield 74%). ¹H NMR (400 MHz, CDCl₃) δ 6.72 (s, 1H), 6.46 (s, 1H), 4.52 (bs, 1H), 2.16 (s, 3H), 1.38 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 147.7, 147.0, 134.9, 121.7, 118.9, 114.1, 34.2, 29.6, 15.1. MP: 109-111°C IR (CDCl₃, 0.05M, cm⁻¹) ν 3603, 3448, 2961, 2871, 1652, 1515, 1452, 1409, 1176, 1134.

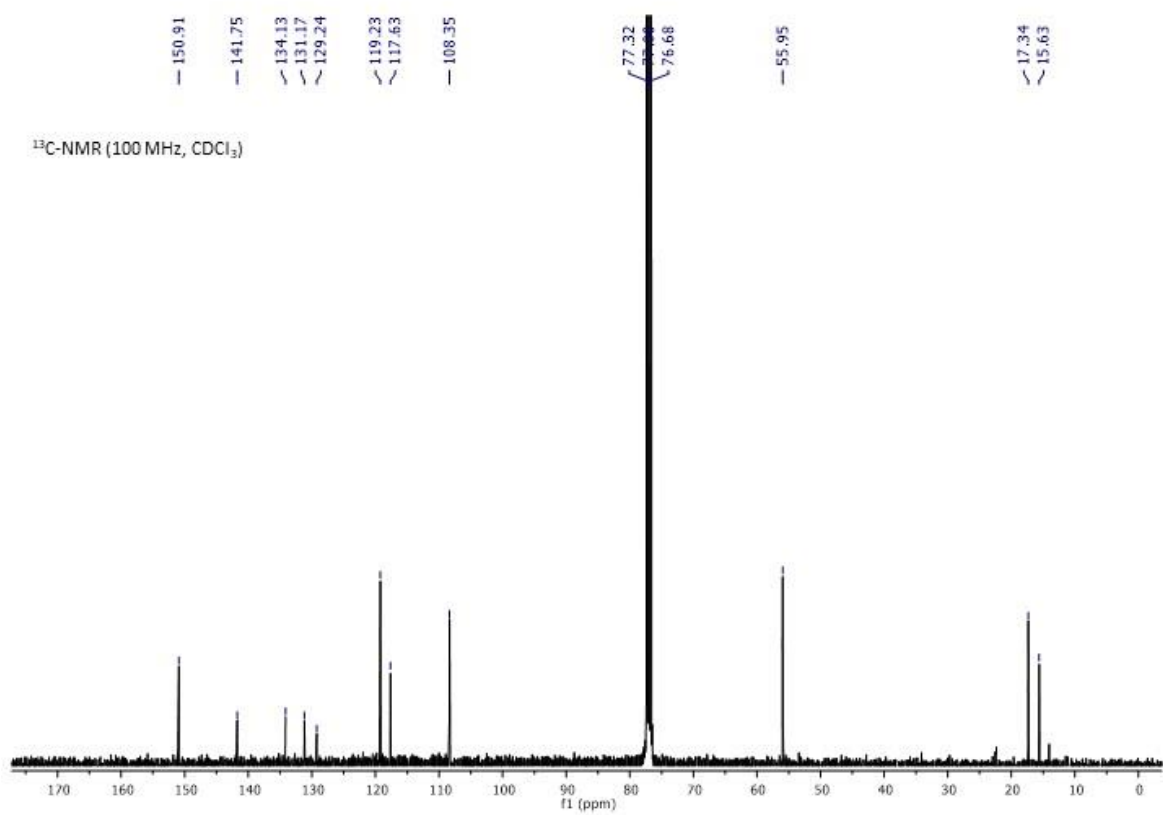
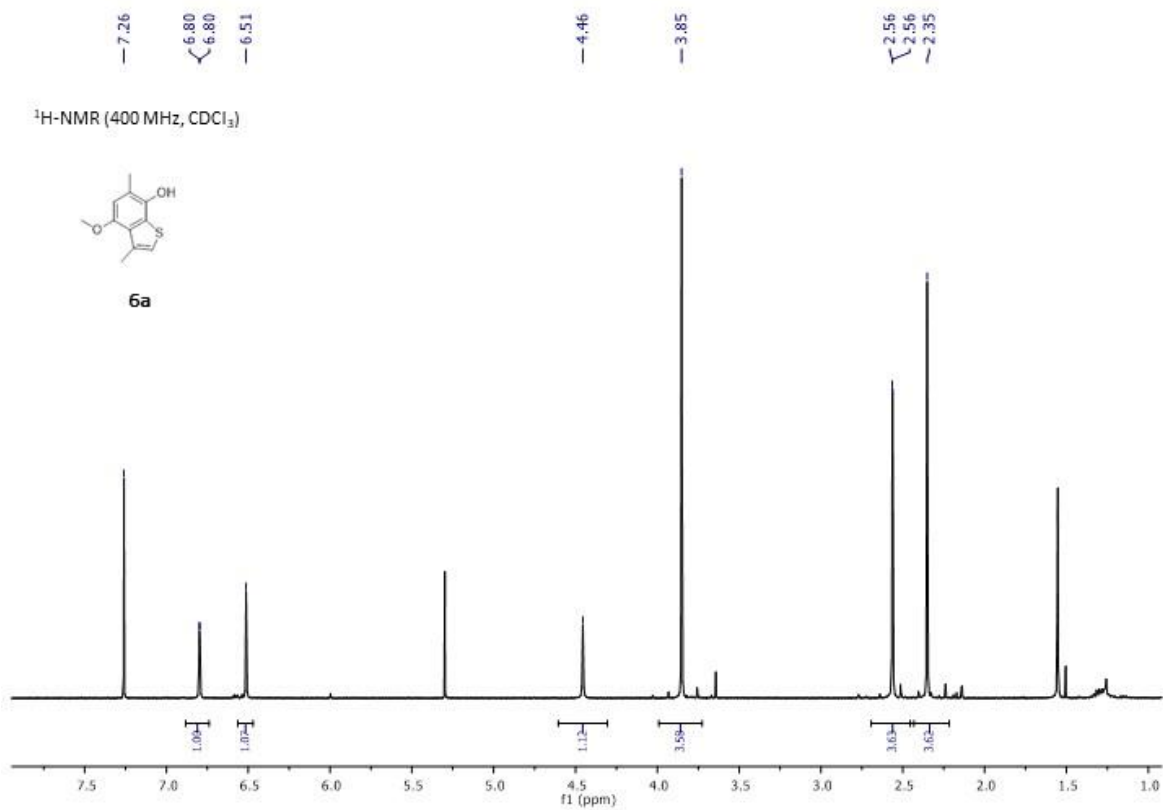


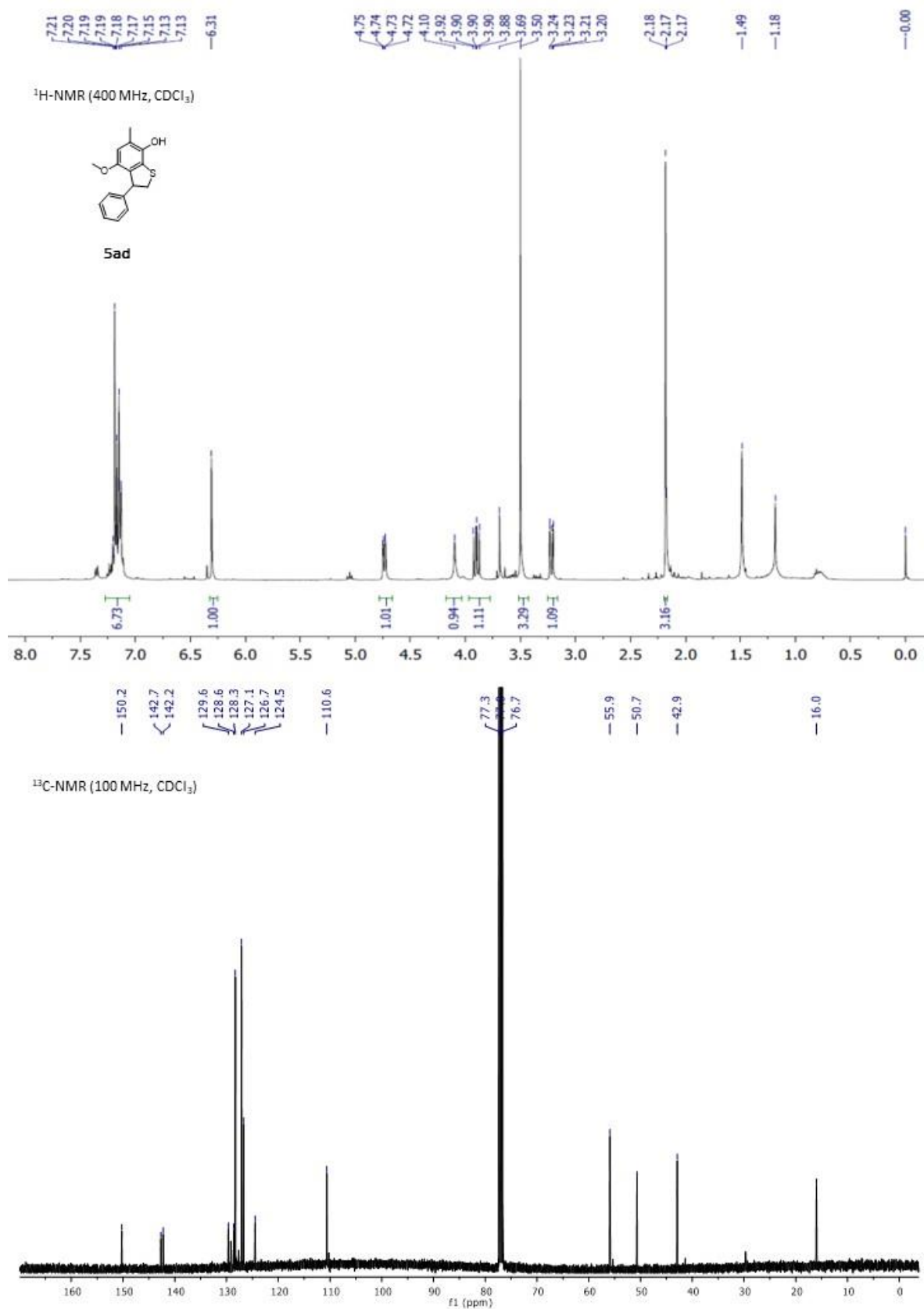
1f. In a schlenk tube containing 2-tert-butyl-hydroquinone (200 mg, 1.2 mmol) and potassium carbonate (166 mg, 1.2 mmol) was added anhydrous CH₃CN (3 mL) and 1-bromotetradecane (360 μL, 1.2 mmol). The mixture was left under magnetic stirring and heated at reflux under nitrogen atmosphere for 96h. The brown mixture was diluted with H₂O and extracted with Et₂O twice. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude product obtained was purified by silica-gel column chromatography using a mixture of dichloromethane and petroleum ether 1:1 as eluent, to give a brown oil (190 mg), yield 44%). ¹H NMR (200 MHz, CDCl₃) δ 6.87 (bs, 1H), 6.60 – 6.59 (m, 2H), 4.50 (bs, 1H), 3.89 (t, *J* = 6.6 Hz, 2H), 1.80 – 1.69 (m, 2H), 1.49 – 1.27 (m, 22H), 1.40 (s, 9H), 0.89 (t, *J* = 6.6 Hz, 3H). IR (CDCl₃, 0.05M, cm⁻¹) ν 3601, 2928, 2854.

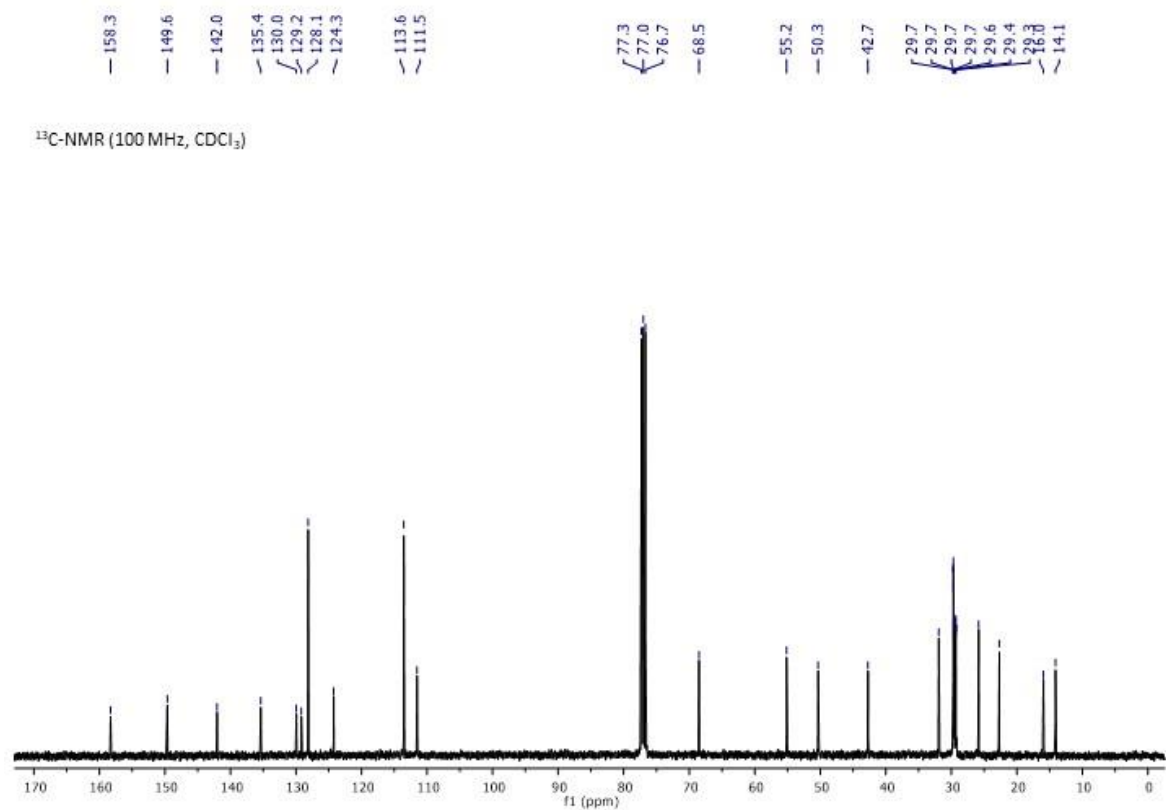
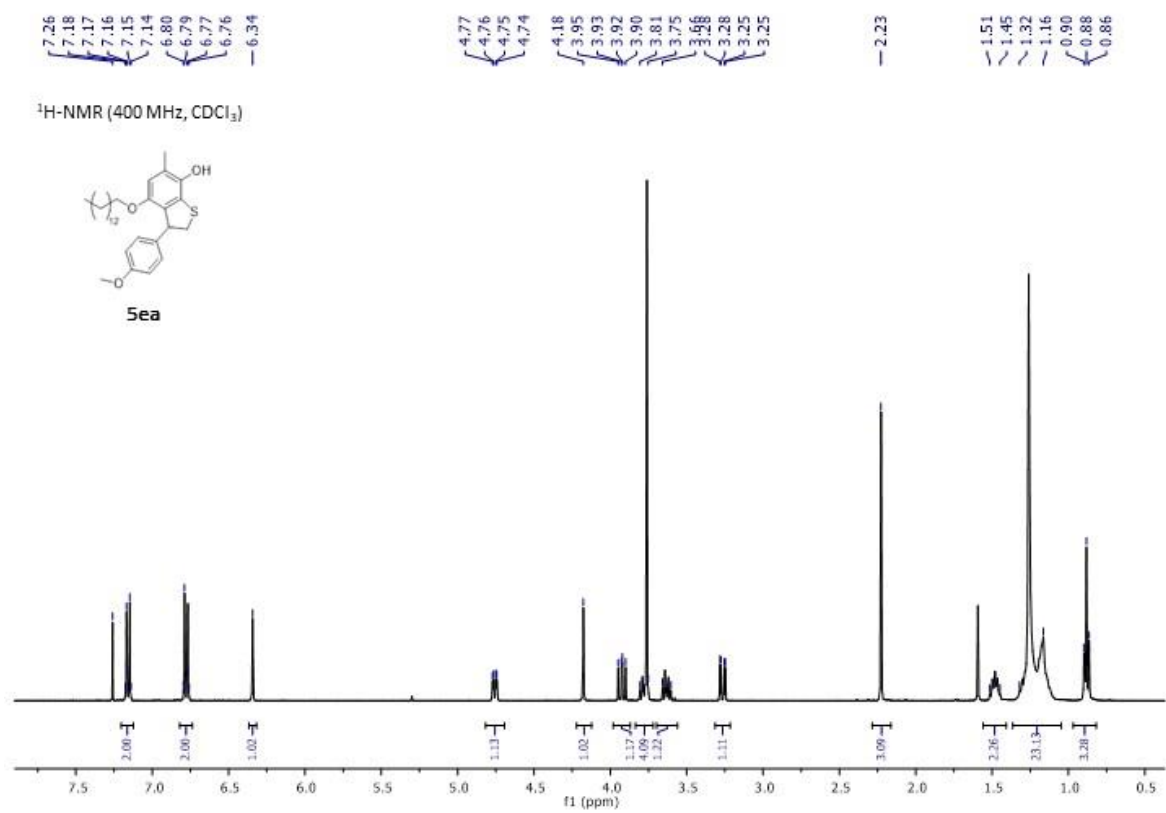


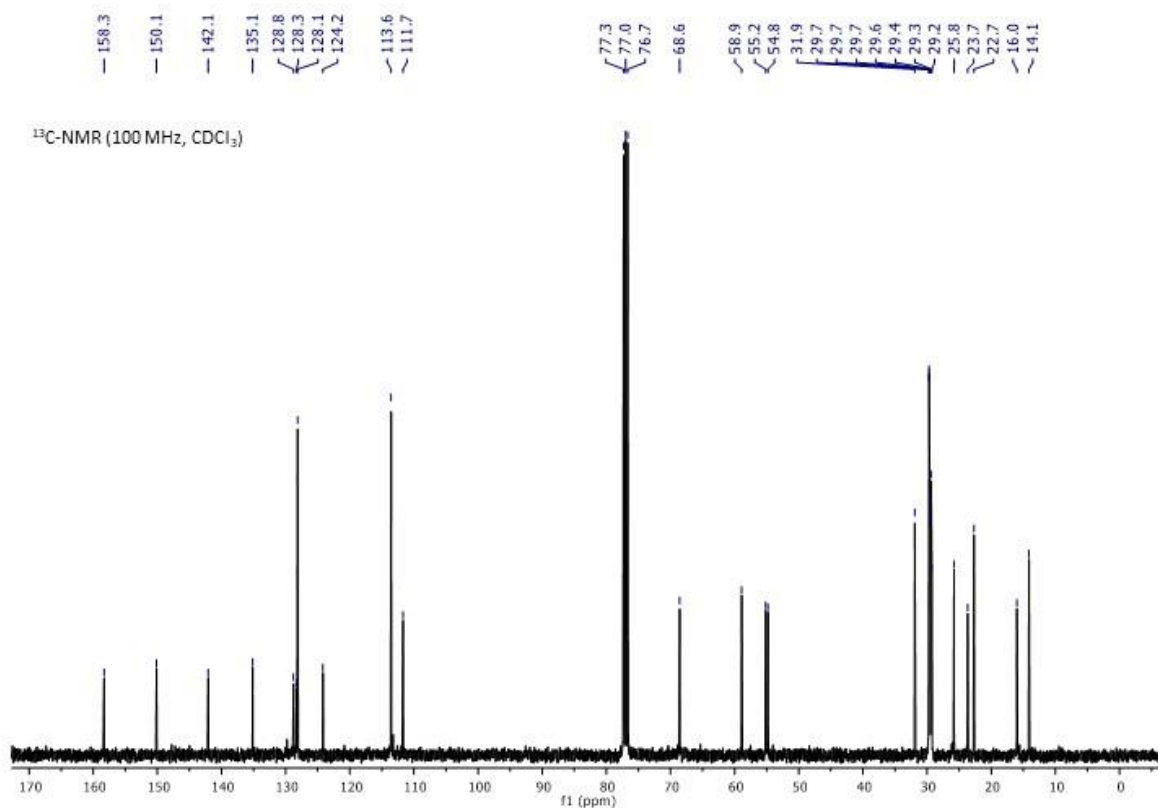
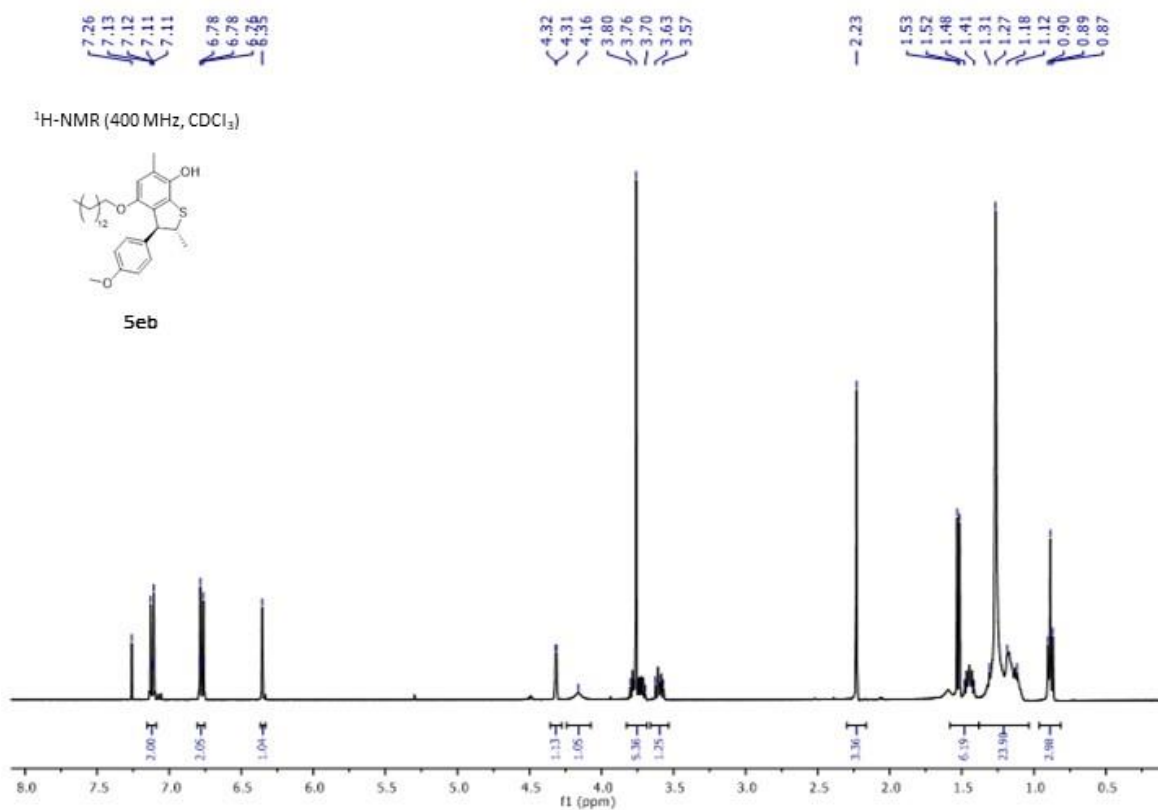
1g To a solution of 2-tert-Butyl-5-methylhydroquinone (500 mg, 2.77 mmol) in DCE (4 mL) were added 2-methyl-2-propen-1-ol (78 μL, 0.92 mmol) and p-toluensulfonic acid (17.6 mg, 0.09 mmol), then the mixture was left under magnetic stirring for 1h at room temperature. Subsequently the reaction mixture was stirred for 18 h at reflux temperature (T= 80°C), then poured into saturated aqueous NH₄Cl solution (100 mL) and the crude reaction products were extracted using petroleum ether (3 x 100 mL). The combined organic solution was washed with water (2 x 100 mL) and then dried over anhydrous Na₂SO₄. After removing the drying agent by filtration, the solvent was evaporated *in vacuo*. The crude product was purified by silica-gel column chromatography using CH₂Cl₂ as eluent. The purified product was obtained as a light brown oil (160 mg, yield 74%). ¹H NMR (400 MHz, CDCl₃) δ 6.54 (s, 1H), 4.20 (s, 1H), 2.87 (s, 2H), 2.09 (3H), 1.45 (s, 6H), 1.31 (s, 9H). ¹³C NMR (100MHz, CDCl₃) δ 150.5, 146.6, 130.5, 127.7, 118.0, 111.4, 85.4, 42.2, 33.8, 29.1, 28.3, 12.3. IR (CDCl₃, 0.05M, cm⁻¹) ν 3607, 2969, 2244, 1491, 1411, 1391, 1244, 1170, 1148, 1066.

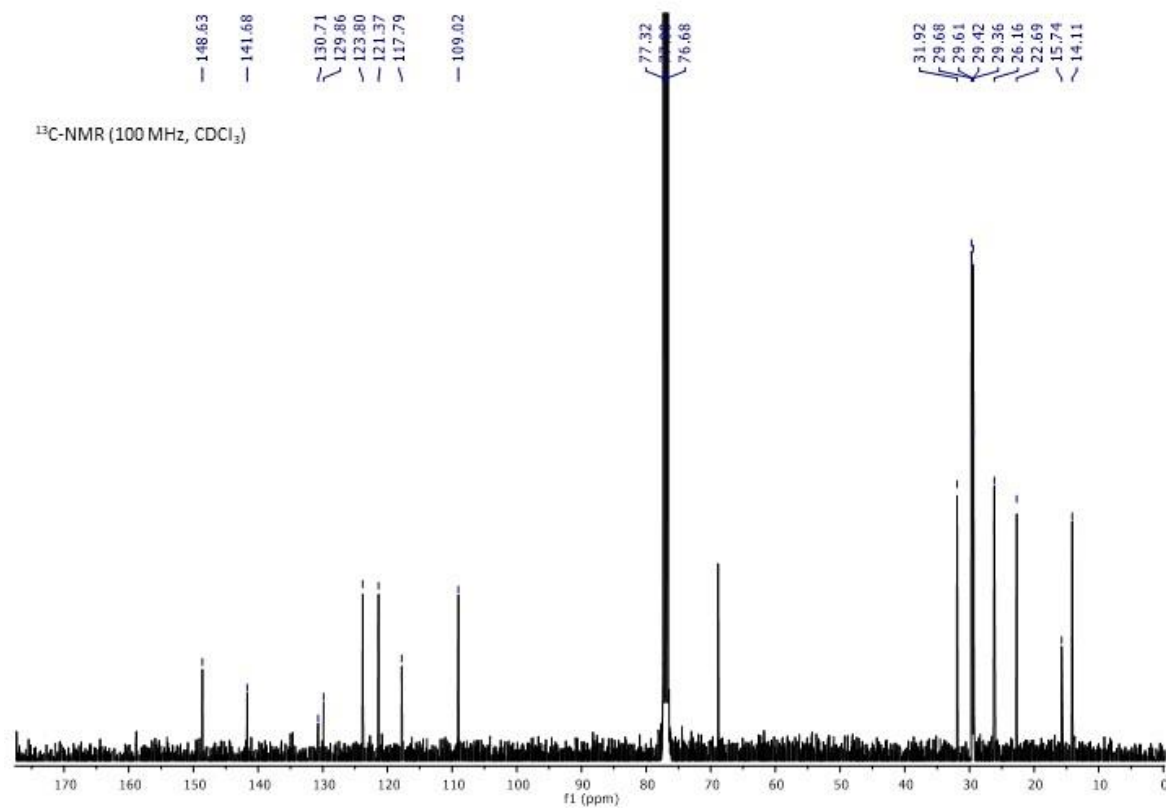
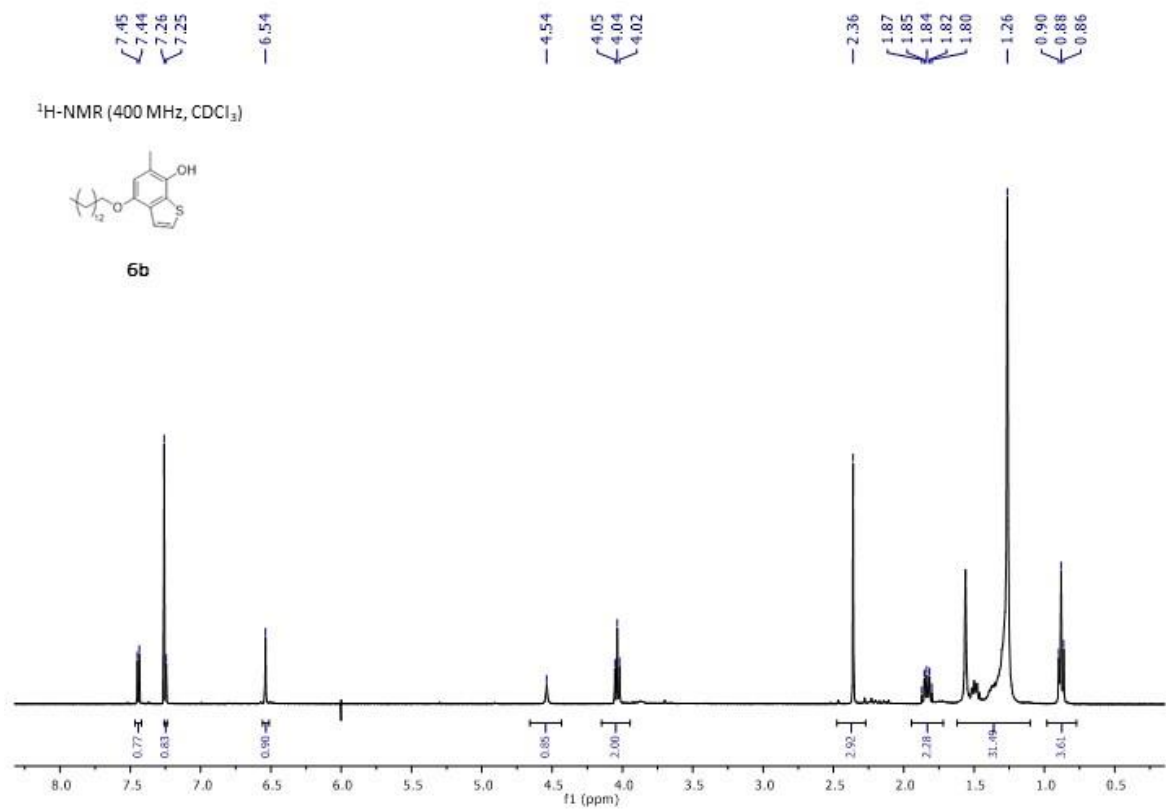


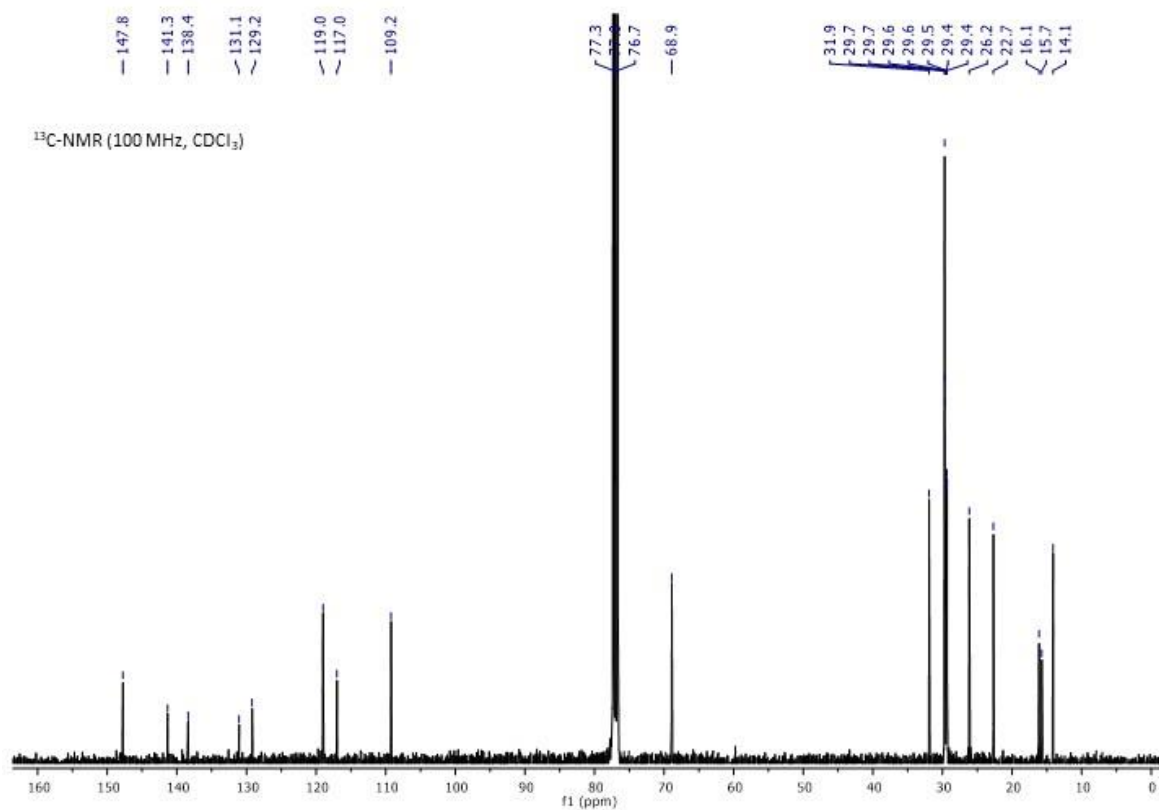
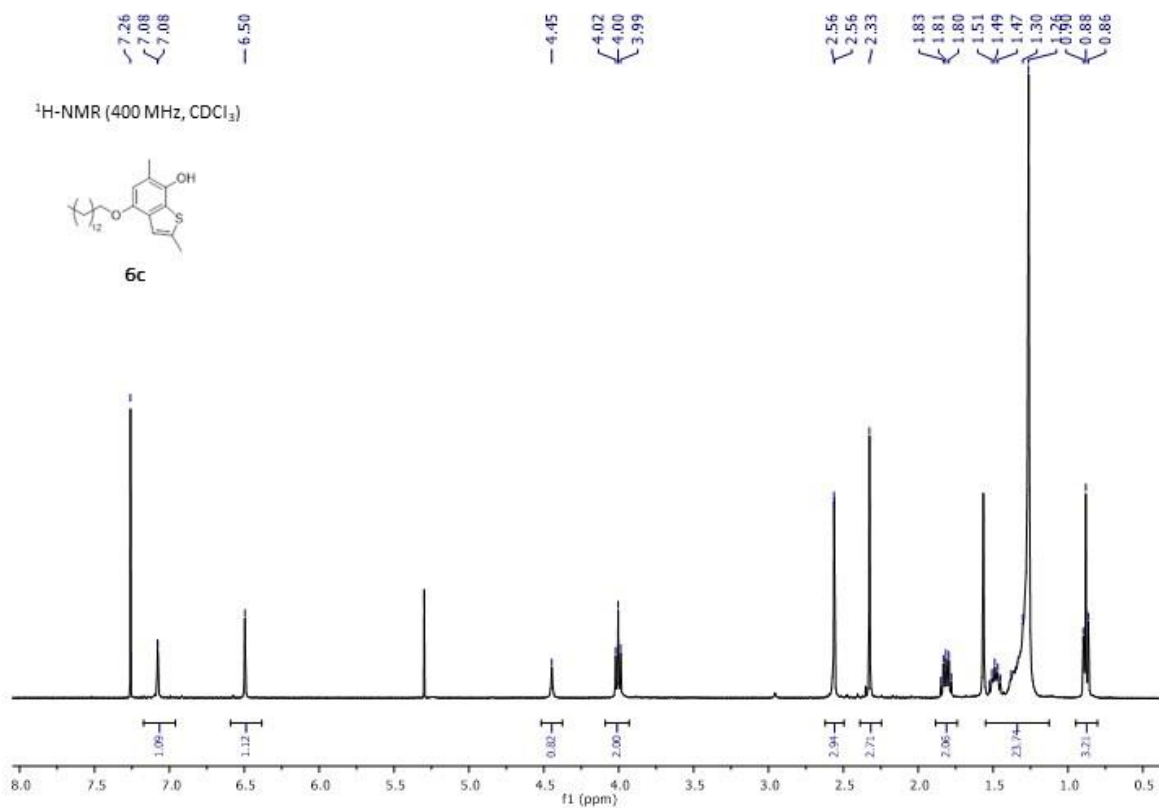


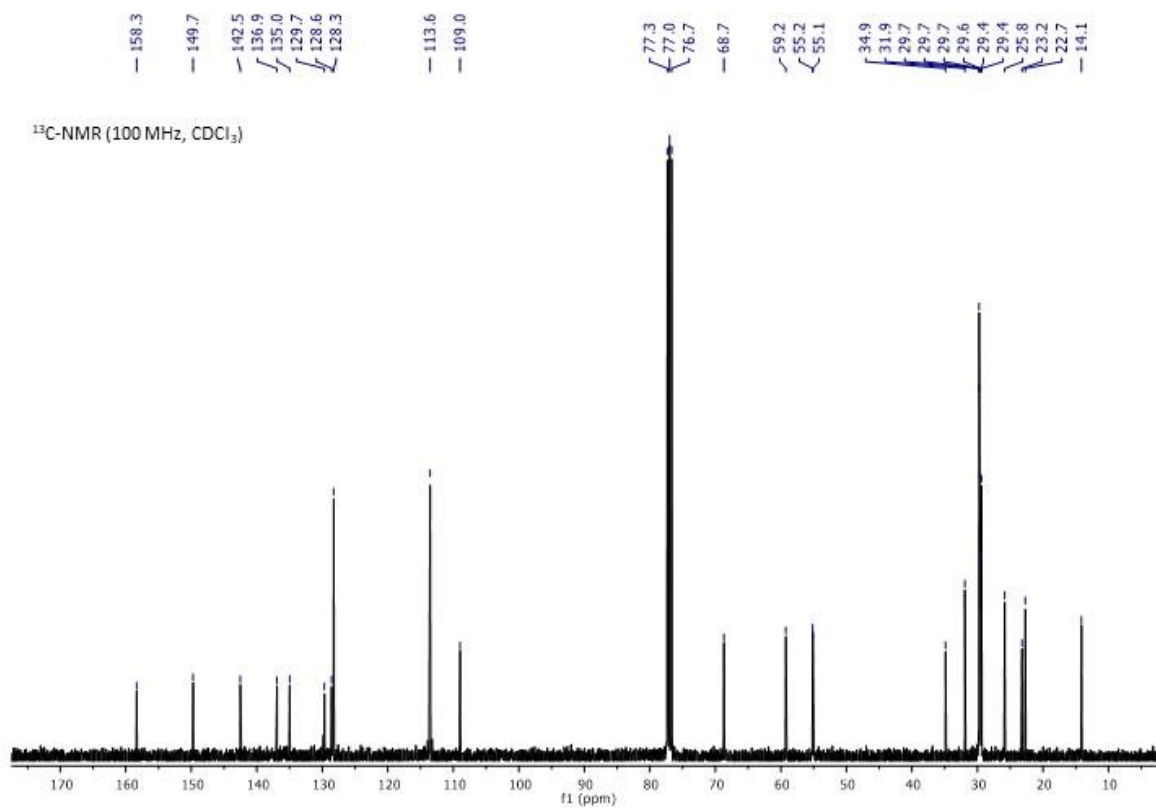
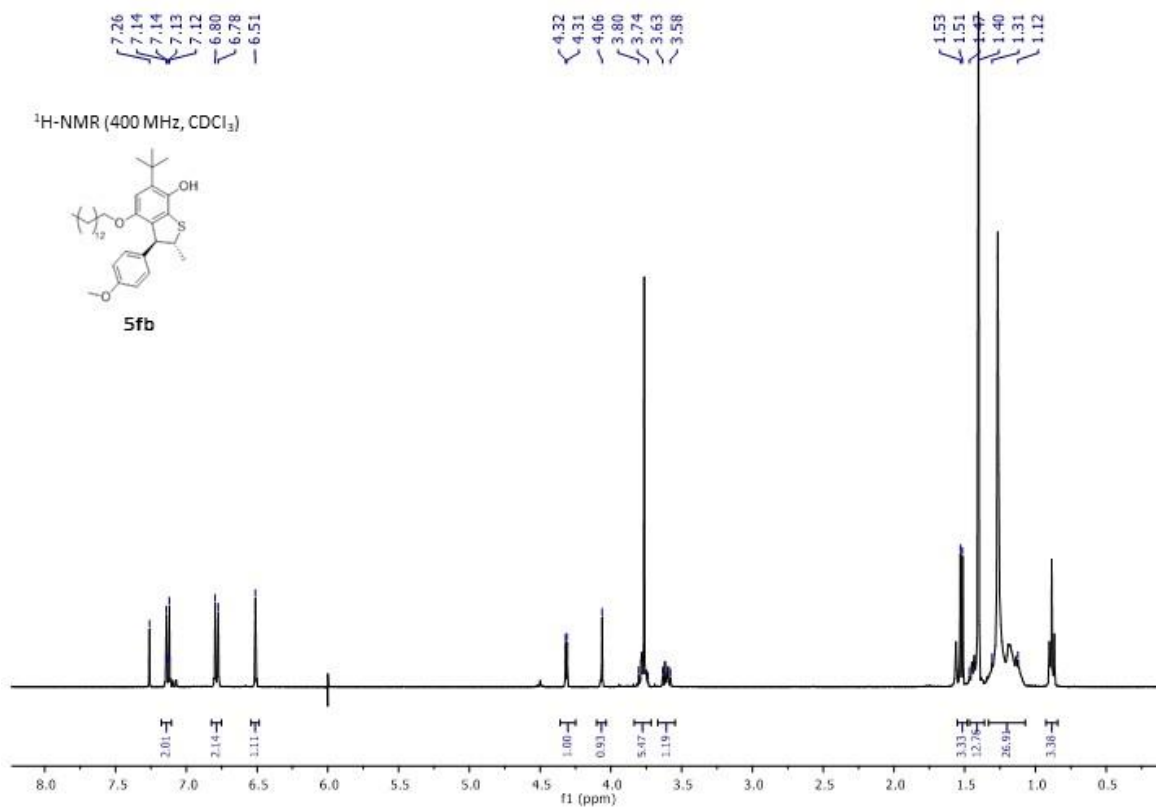


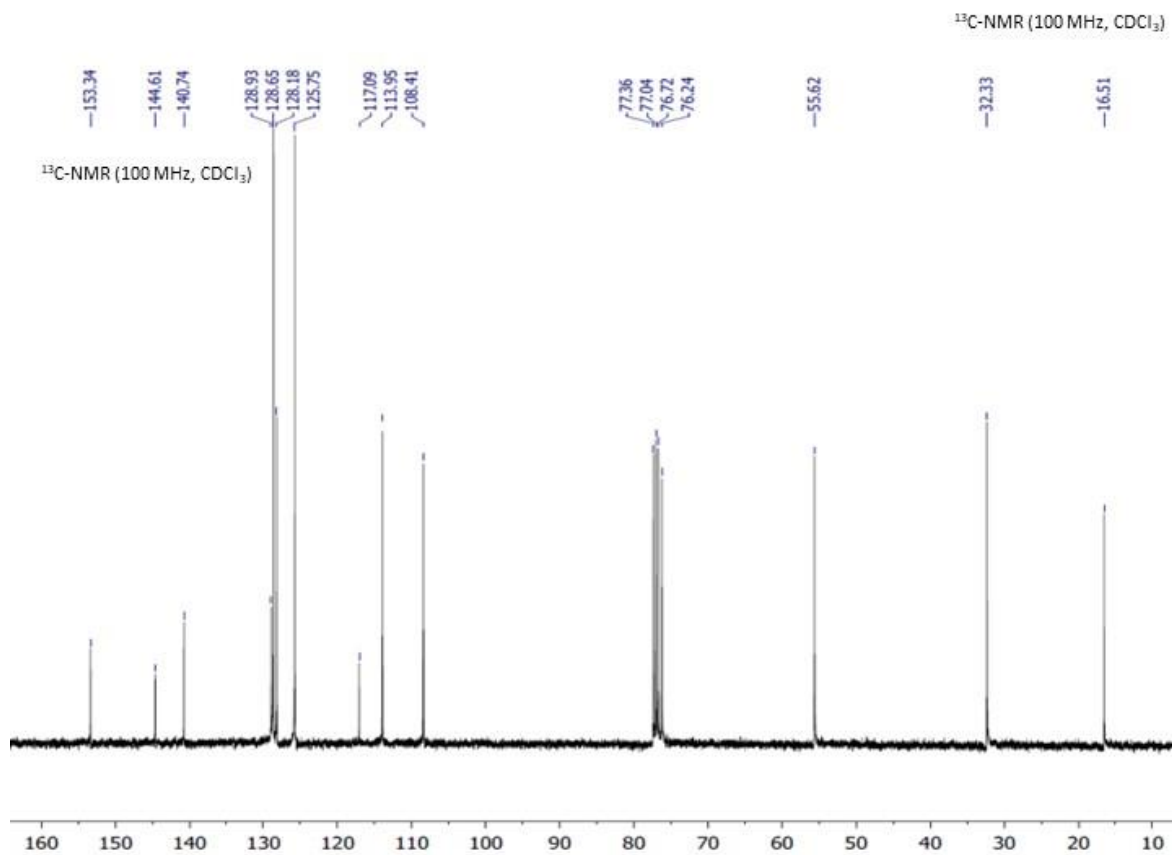
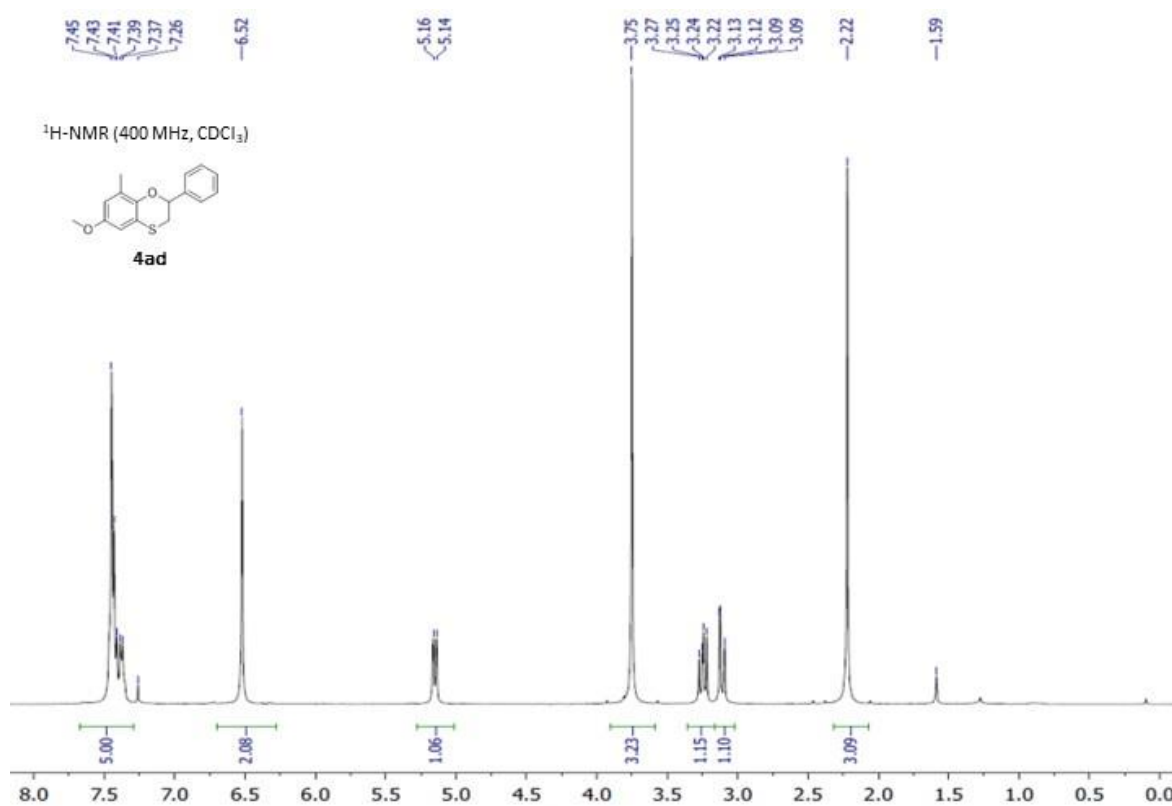


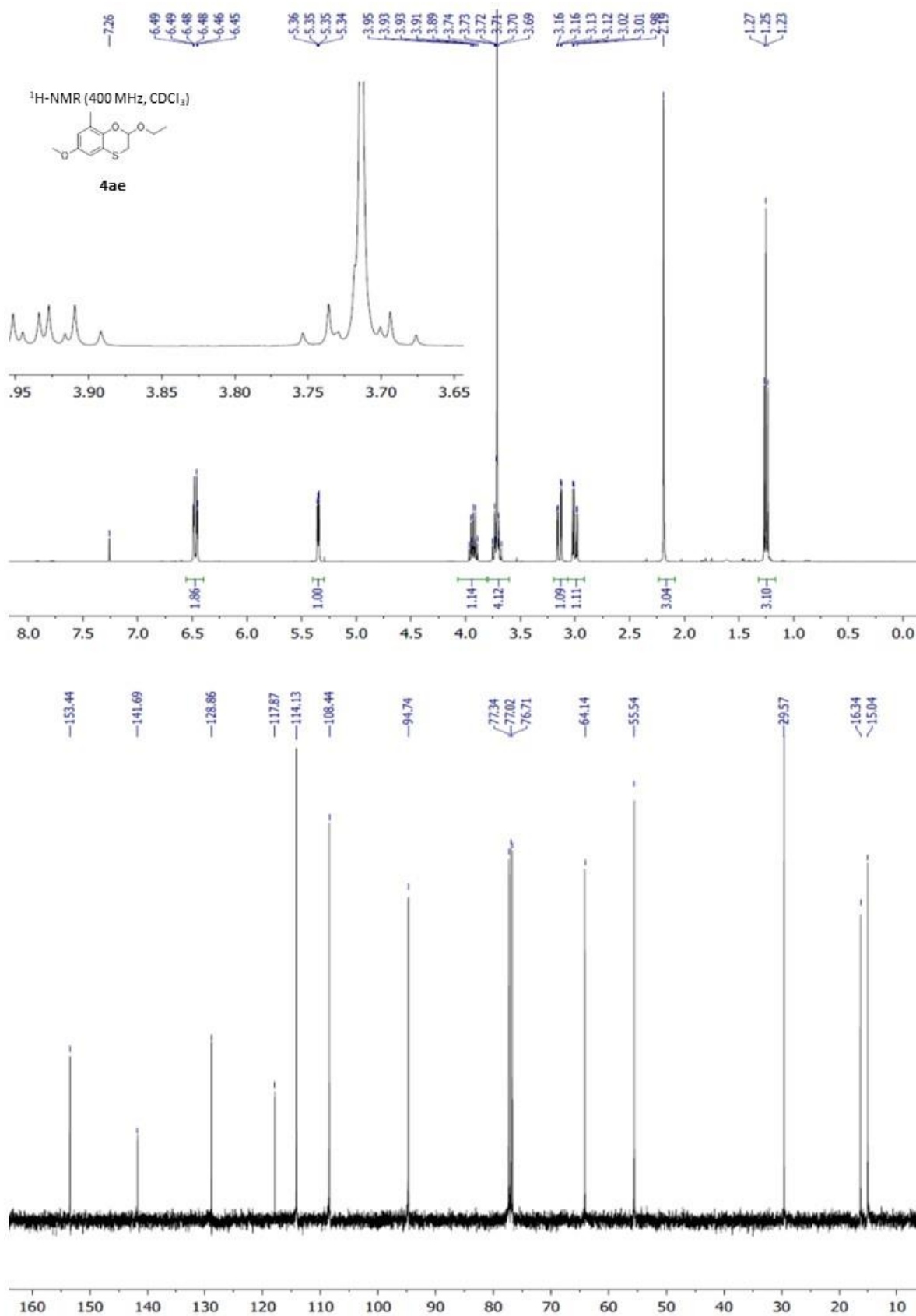


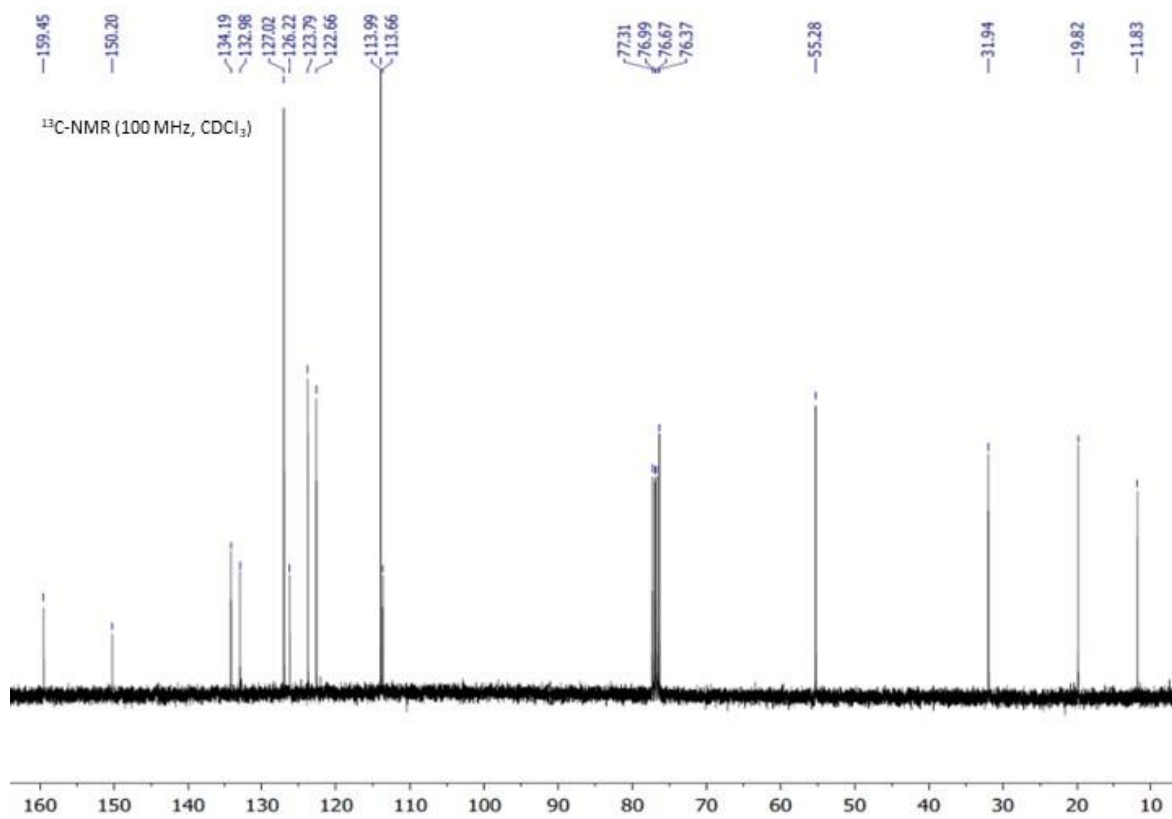
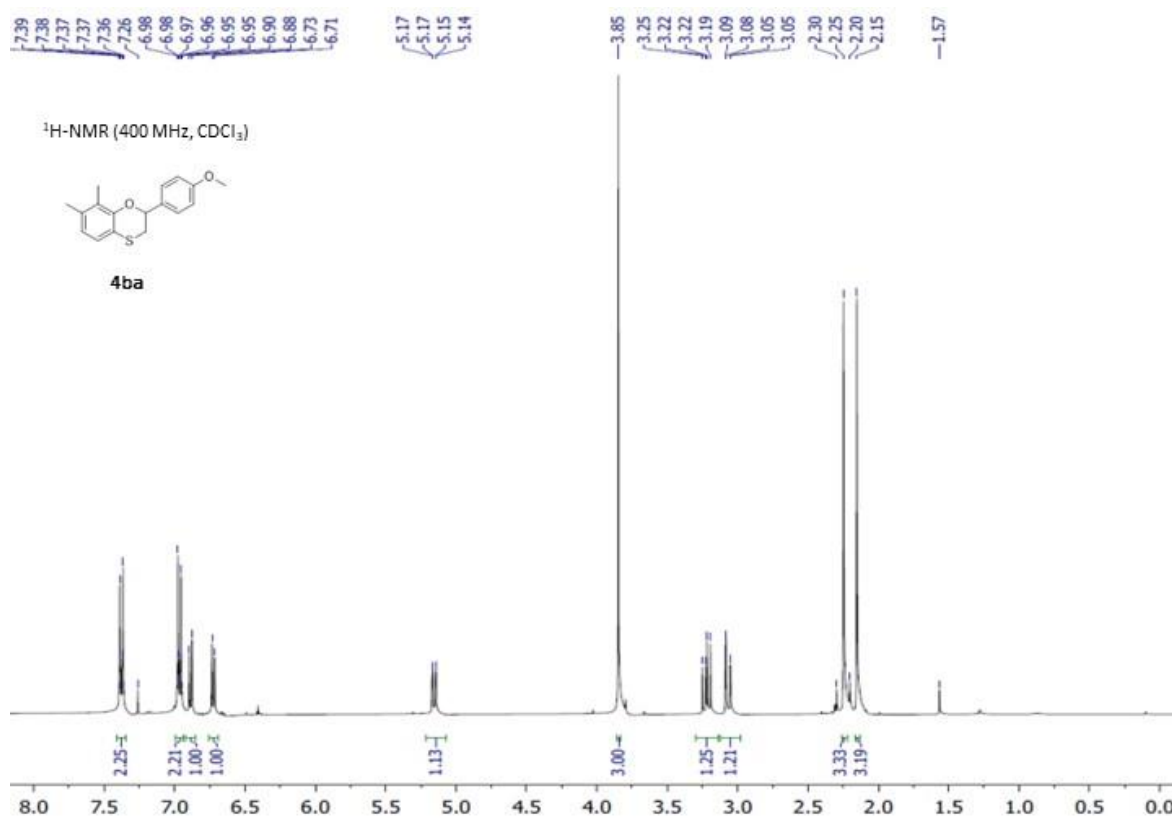


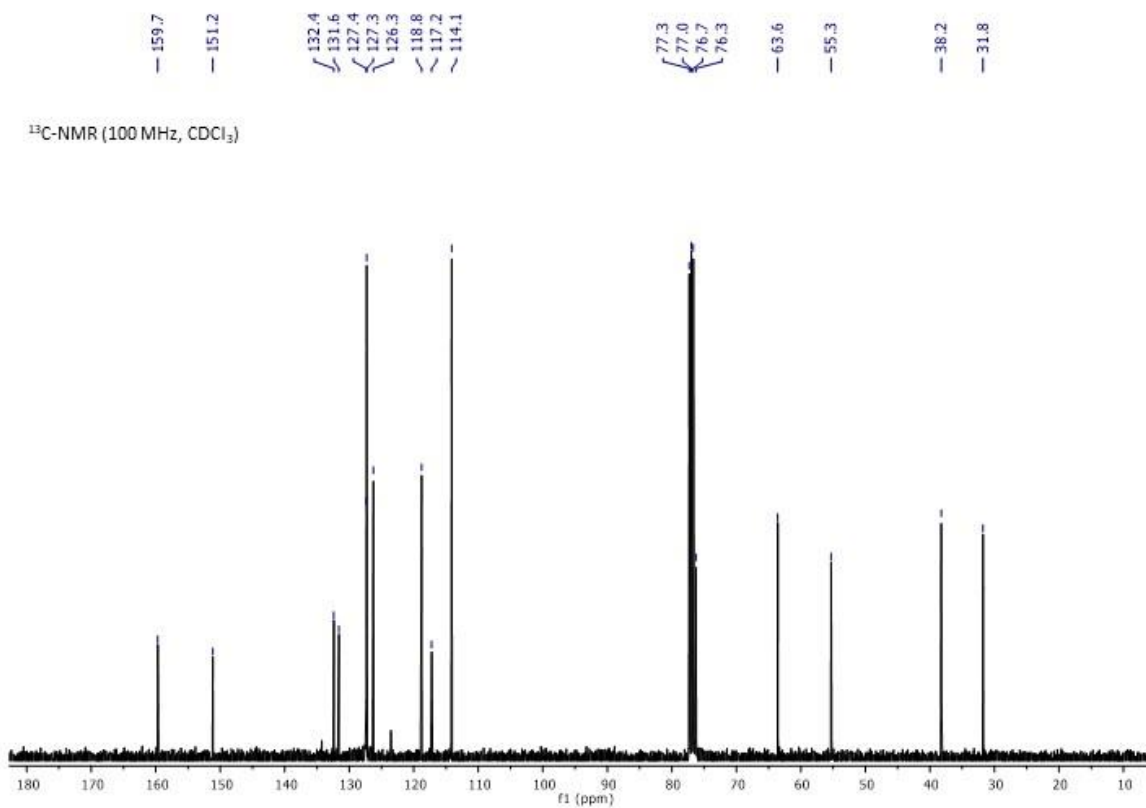
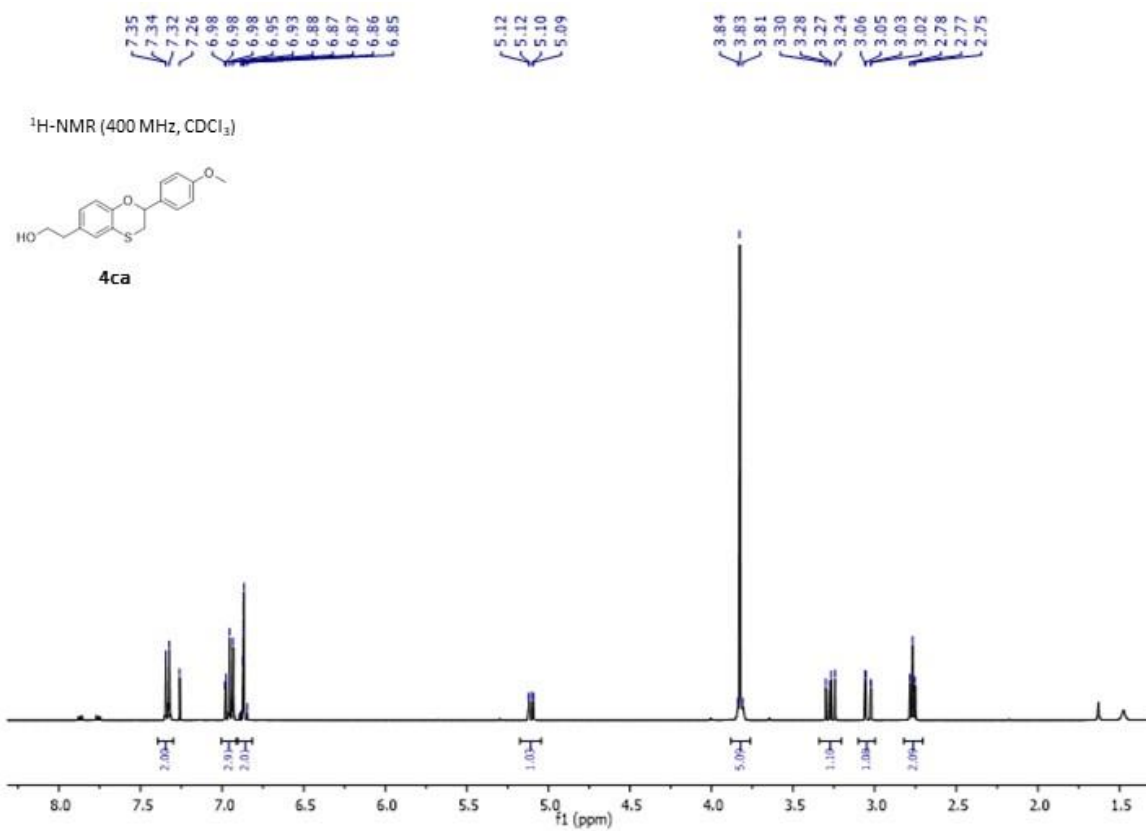


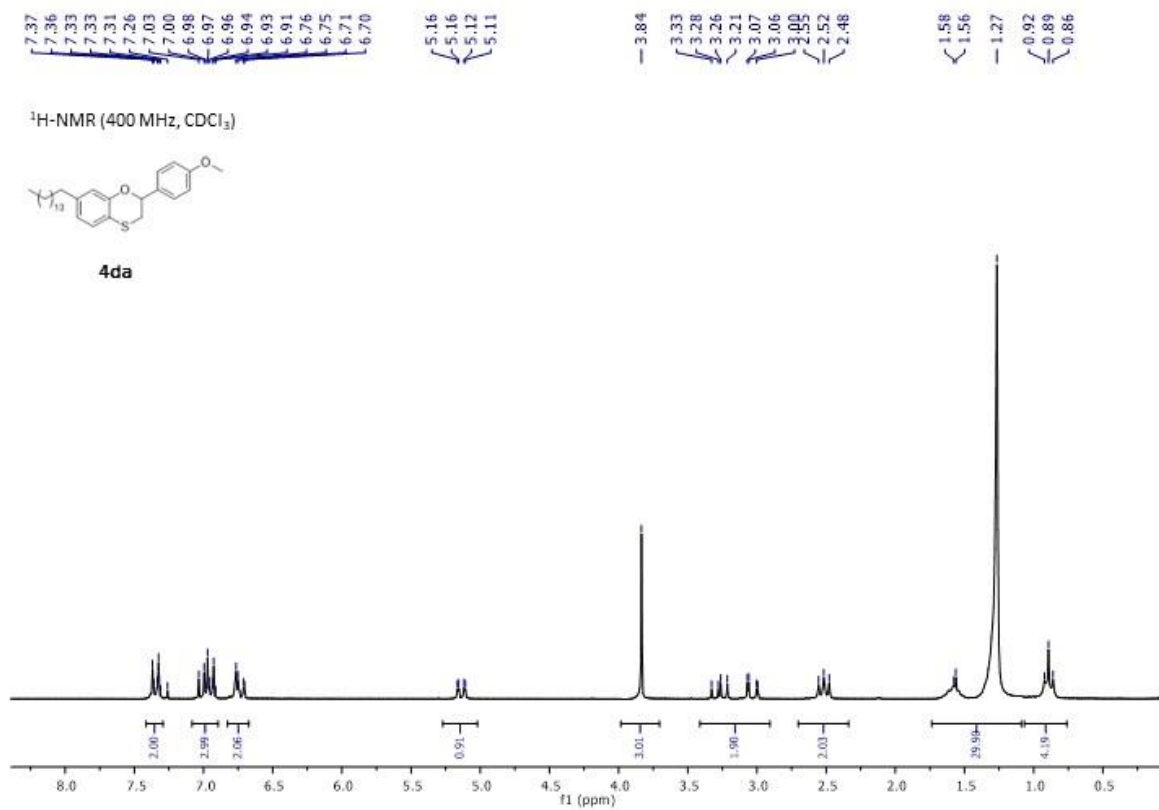


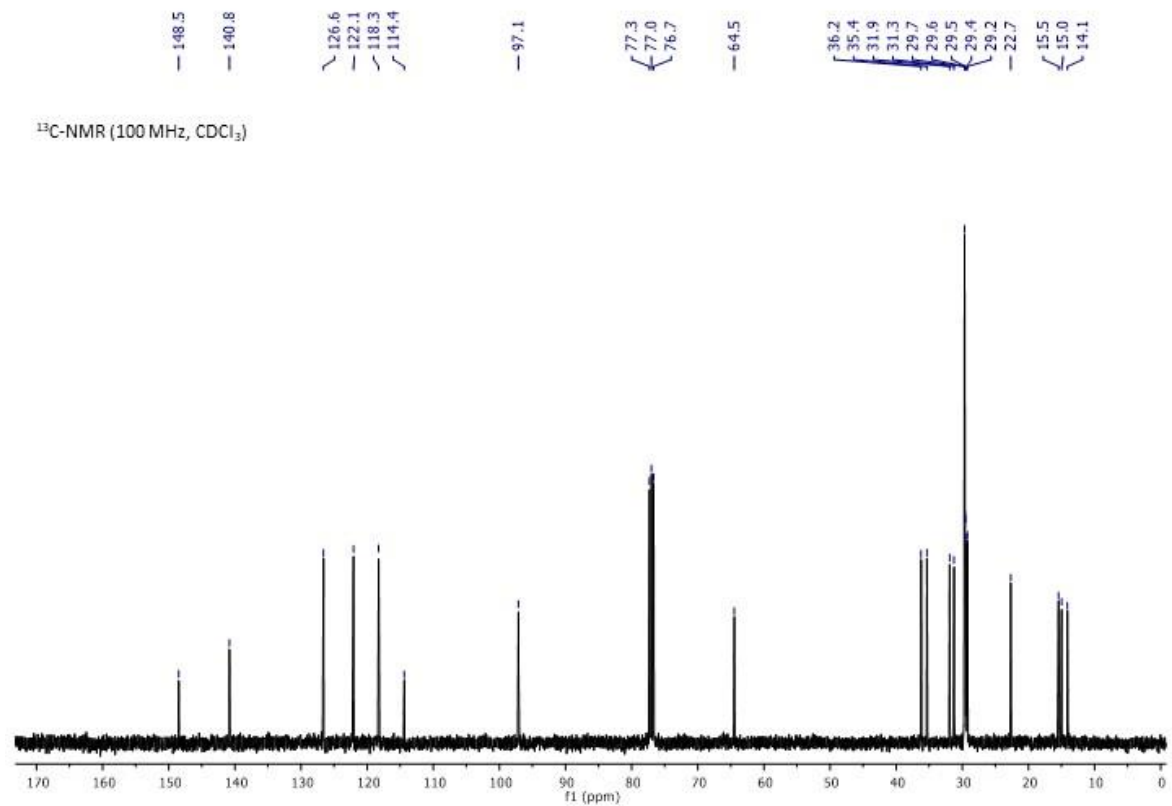
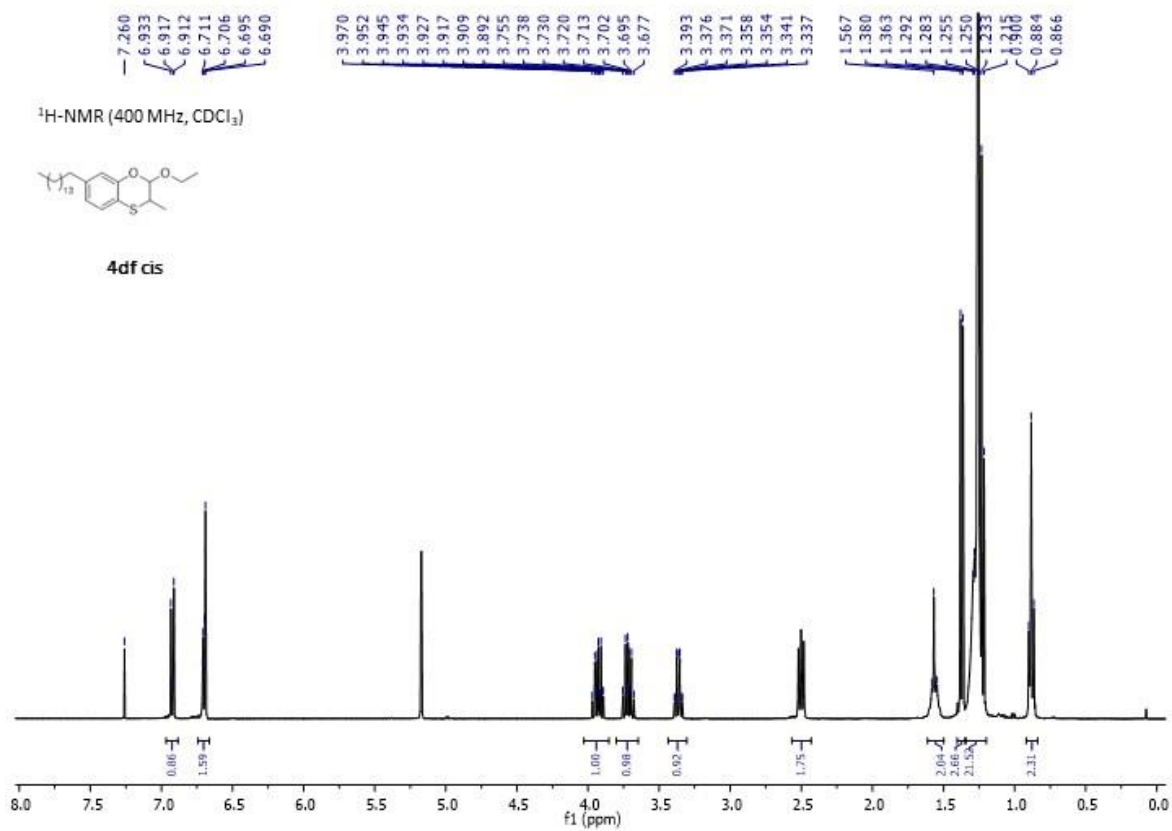


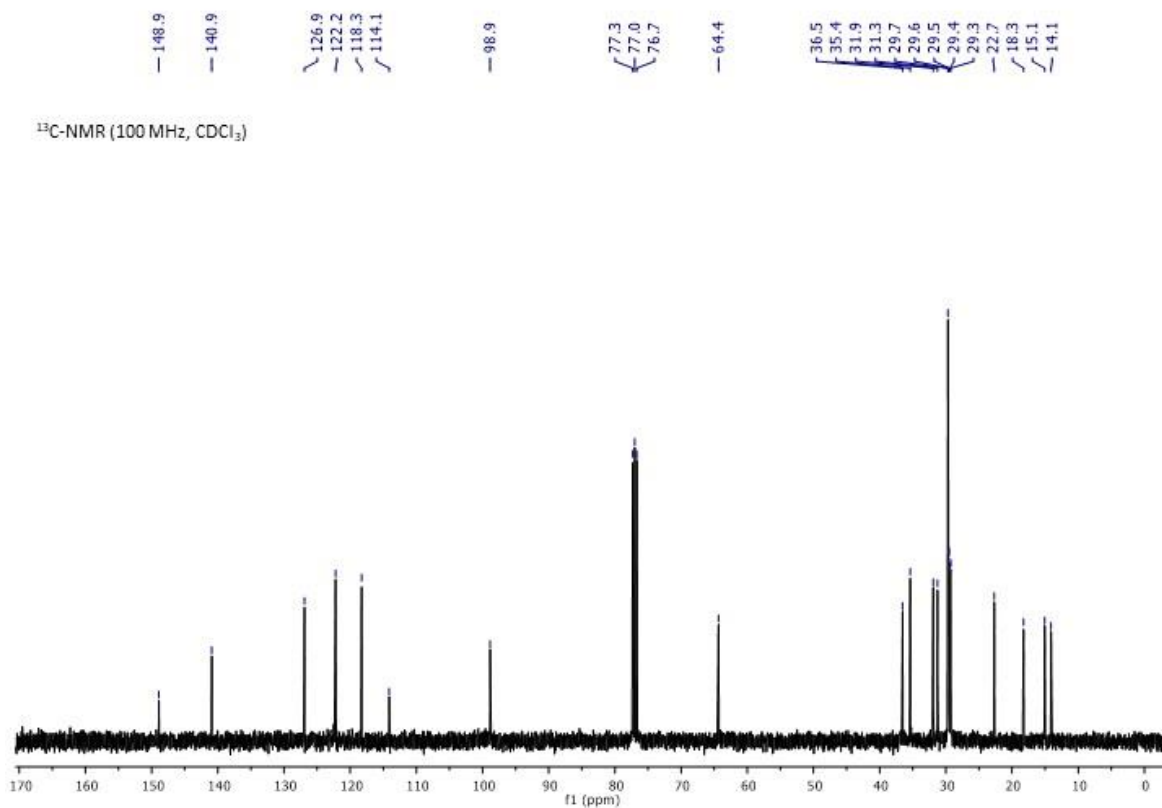
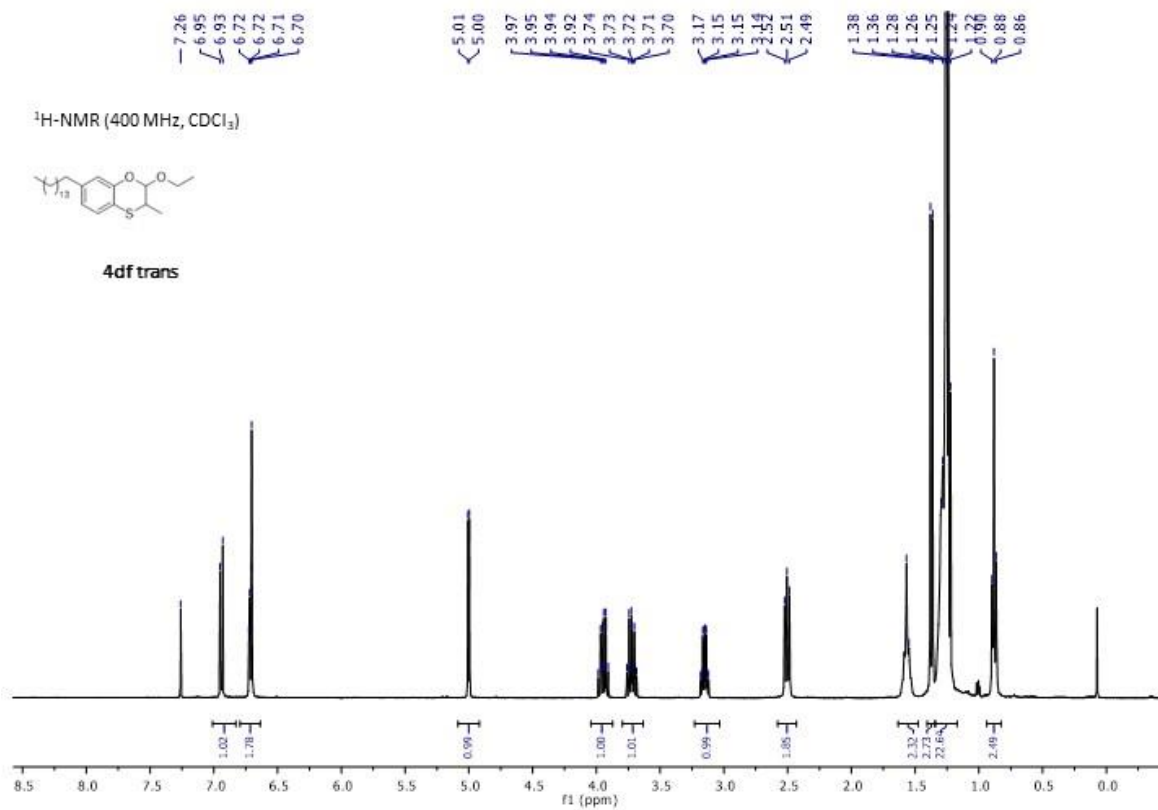


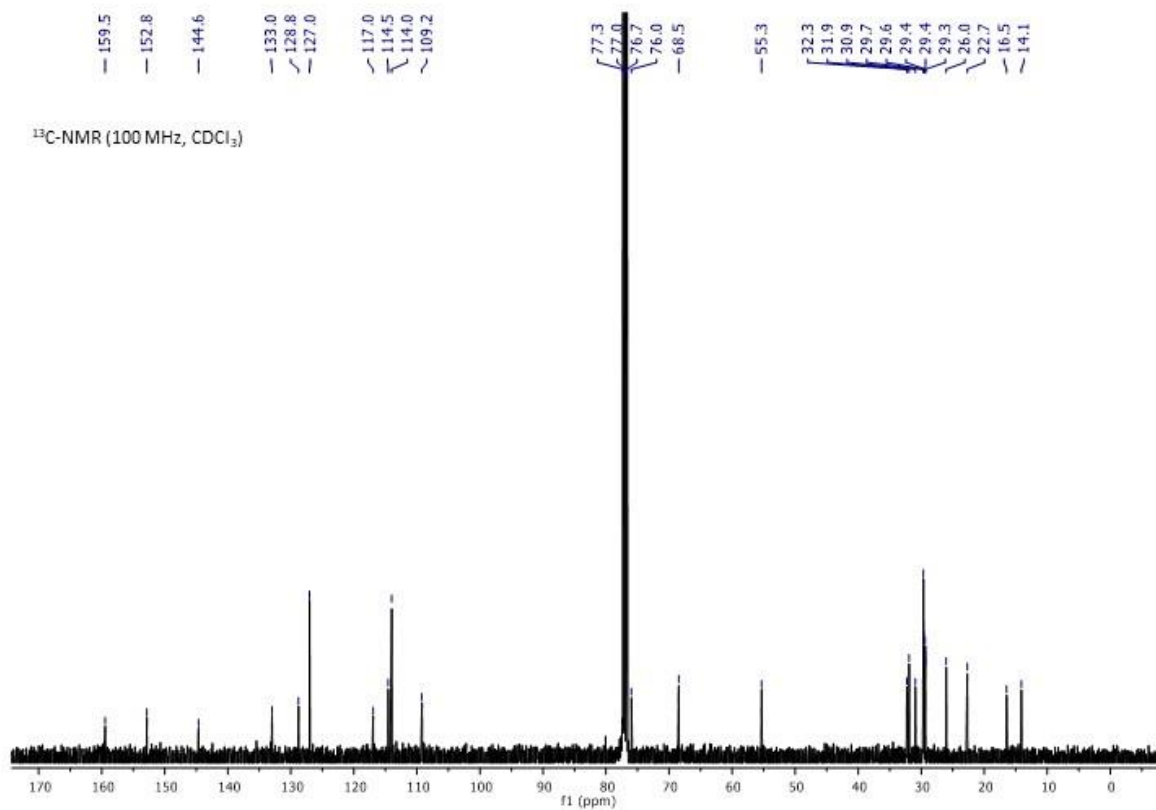
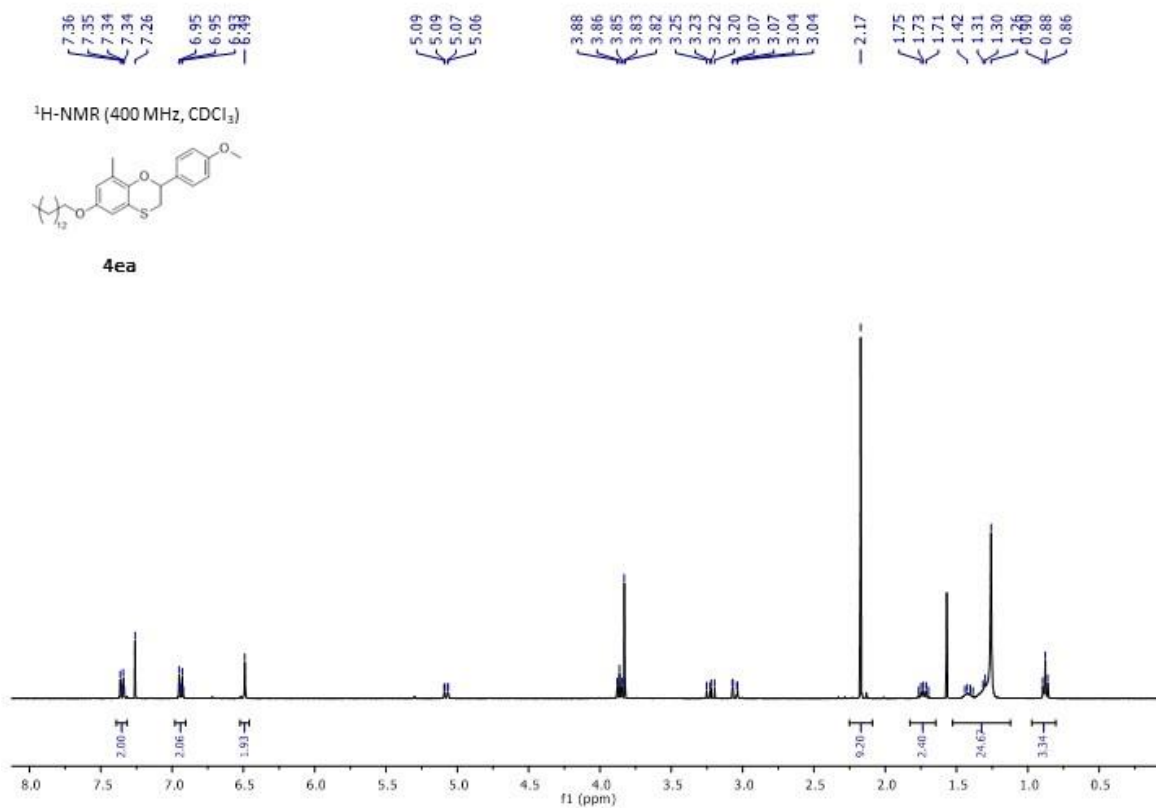


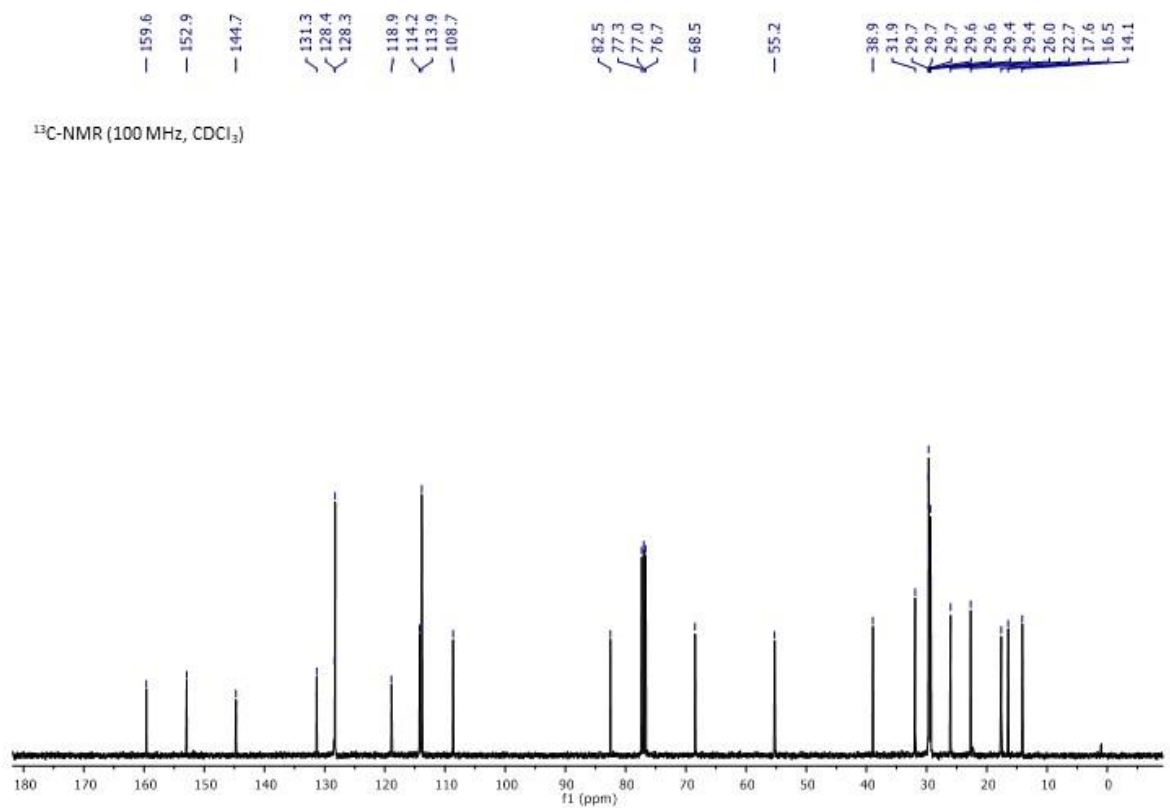
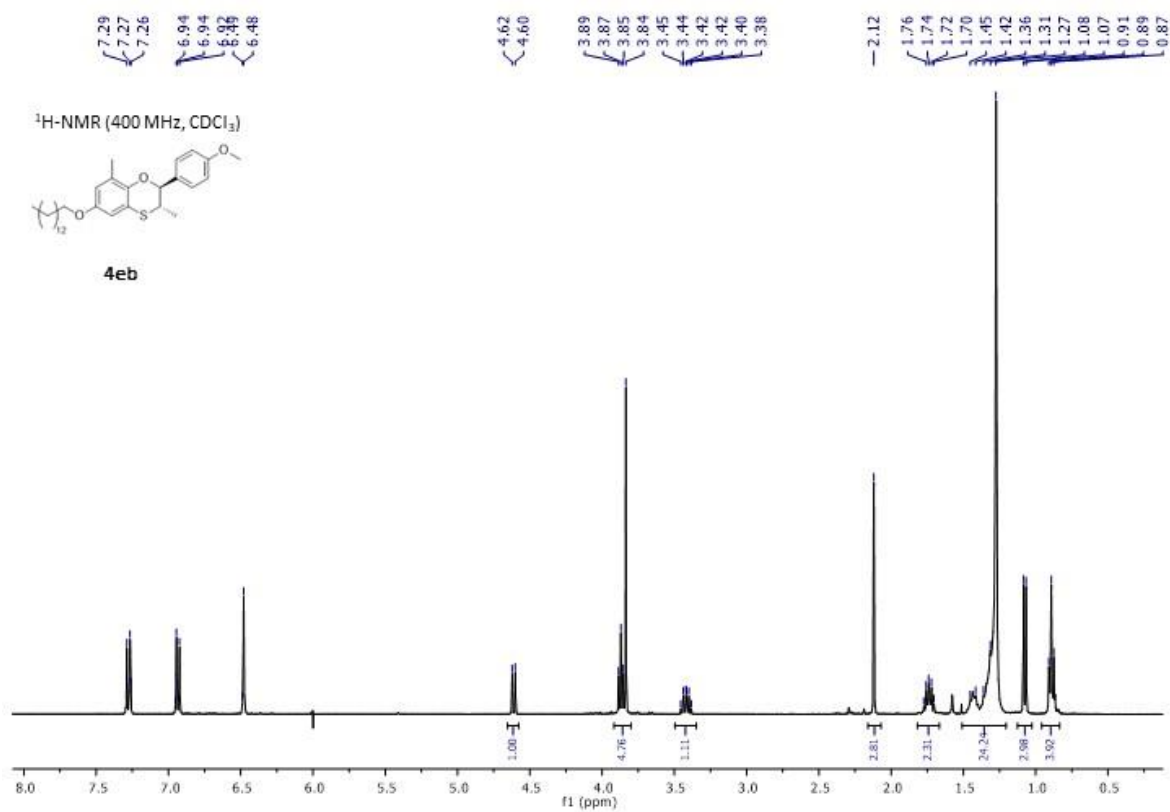


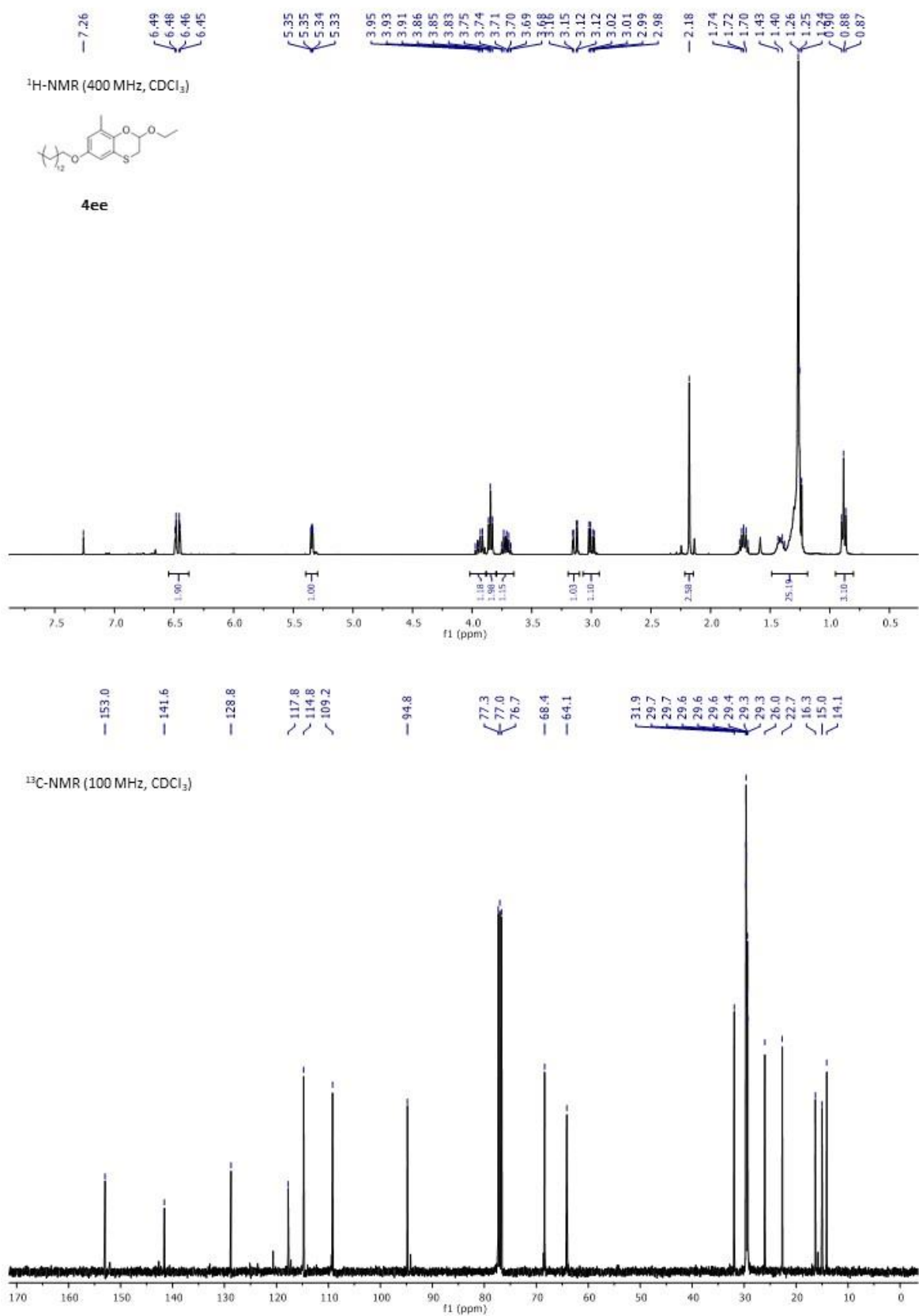


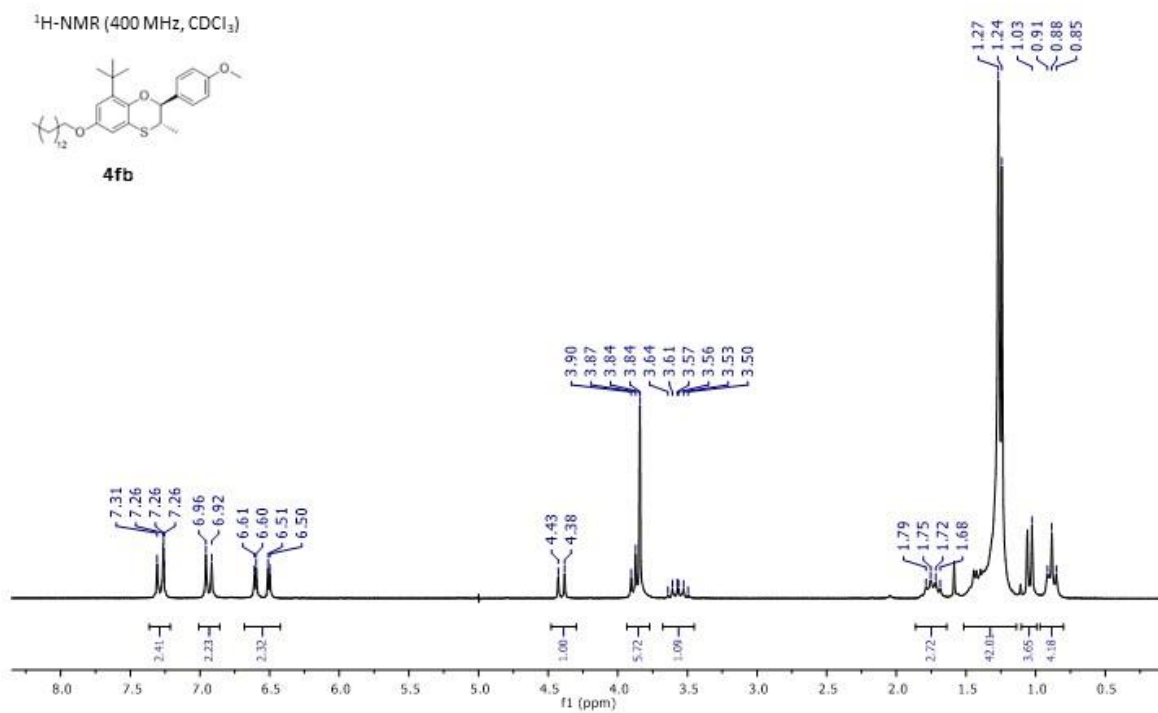


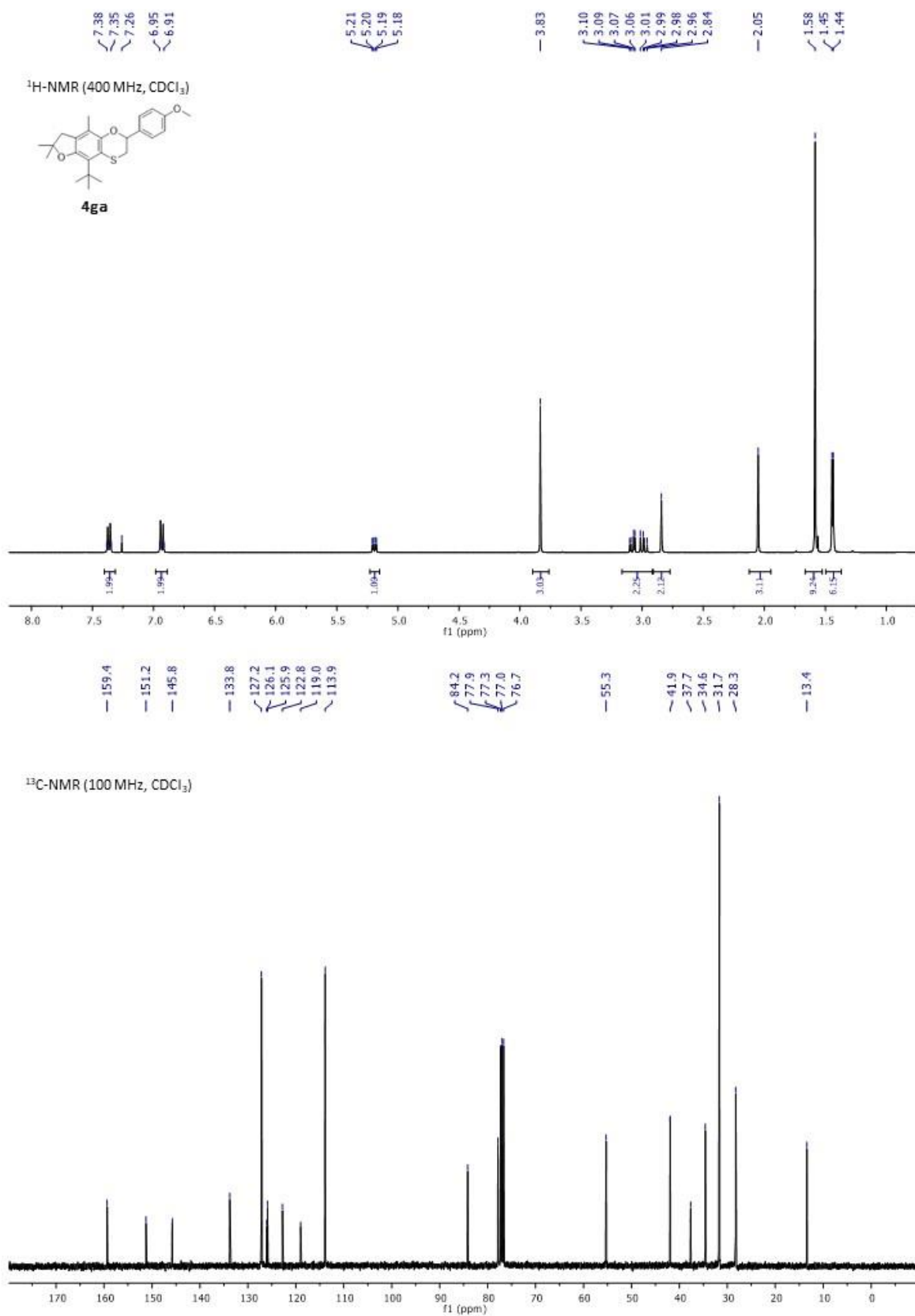


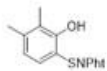
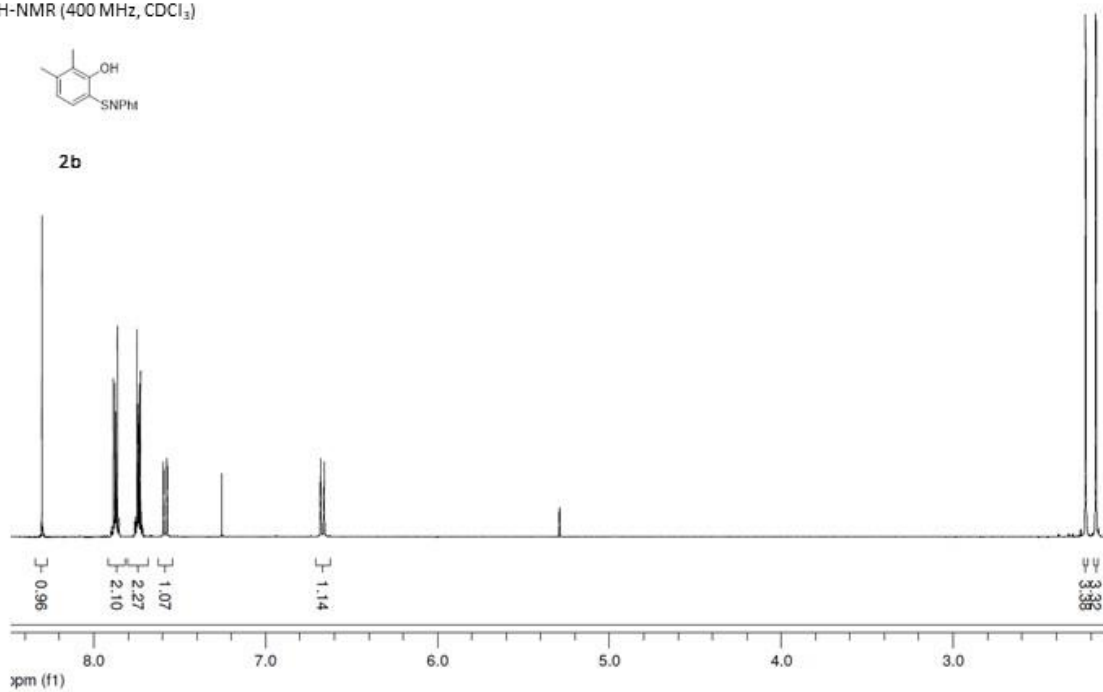










¹H-NMR (400 MHz, CDCl₃)**2b**¹³C-NMR (100 MHz, CDCl₃)