

Supporting Information

Disulfide-based metal free sulfanylation of ketones

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Materials and Methods

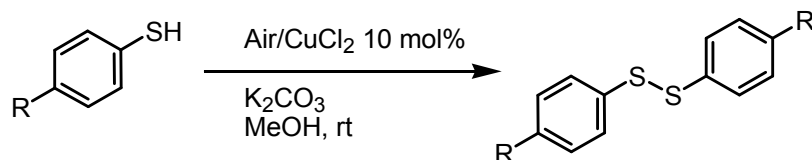
Unless stated otherwise, reaction were performed at ambient temperature (25°C). Commercially available reagents were used as received unless otherwise noted. Diphenyldisulfide, *p*-nitrophenyldisulfide, cyclobutanone **1a**, cyclopentanone **3a**, cyclohexanones **3b-e**, and ketones **5a-c** were purchased from Aldrich. Catalysts **I-VII** were purchased from Aldrich or Alfa-Aesar and used as received. ¹H NMR spectra were recorded on 400 and 500 MHz Varian spectrometers at 27°C using CDCl₃, DMF-*d*₇ or DMSO-*d*₆ as solvent. ¹³C NMR were recorded at 100 and 125 MHz at 27°C using CDCl₃, DMF-*d*₇ or DMSO-*d*₆ as solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and are reported in wavenumbers. Low Mass spectra analysis were recorded on an Agilent-HP GC-MS (E.I. 70eV). High resolution mass spectra (HRMS) were obtained using a Bruker High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode or acquired using an Bruker micrOTOF-Q II 10027.

HPLC analysis were obtained from Hitachi-LaChrome 7100-UV/7400-Pump integrated system and using chiral HPLC columns OJ, OD-H, AD-H and Phenomenex-Lux.

Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merk 70-200 mesh silica gel. Yields refer to chromatography and spectroscopically pure materials.

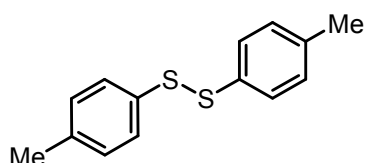
Experimental Procedures

General procedure for the synthesis of substituted disulfides **b-k**

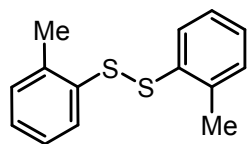


R = H, *p*-Me, *o*-Me, 3,5-dimethyl, OMe, F, Cl, Br, NO₂, naphthyl

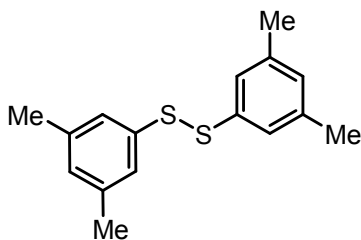
p-Substituted disulfides **b-k** were synthesized as follow: To a stirred solution of benzenethiol **b** (2.0 g, 16 mmol) in MeOH (50 mL), K₂CO₃ (4.41 g, 32 mmol) and CuCl₂ (215 mg, 1.6 mmol) were added and the resulting mixture was bubbled with air for 8-10h. the resulting reaction mixture was filtered and the solid was washed with MeOH (2x20 mL). The organic phase was washed with a saturated solution of NaHCO₃ and dried on Na₂SO₄. After filtration the solution was concentrated under reduced pressure, the crude disulfide was purified by flash chromatography (eluents hexanes-hexanes:diethyl ether 95:5) affording the corresponding pure product in 92% yield.



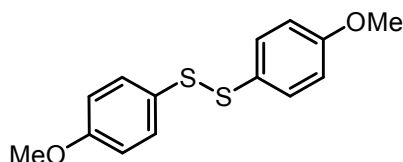
bis(*p*-tolyl)disulfide **b.** Yield 87%, white solid, Mp 44-45°C (recrystallized by *n*-hexane); FTIR neat, cm⁻¹ v: 3057, 3014, 2973, 1540, 1452, 1036; ¹H NMR (500 MHz, CDCl₃) δ: 7.36 (d, 4 H, *J* = 5.0 Hz), 7.09 (d, 4 H *J* = 5.0 Hz), 2.31 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ: 137.42, 133.89, 129.76, 128.53, 21.04. GC-MS (EI) *m/z*: (%) 246, (100) [M⁺], 213 (12), 167 (15), 123 (66), 91 (15), 77 (18). Spectroscopic data are in accordance with the previously presented.¹



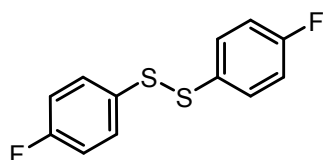
bis(*o*-tolyl)disulfide **c.** Yield 91%, yellow oil. FTIR neat, cm⁻¹ v: 3058, 3014, 2973, 1540, 1452, 1035; ¹H NMR (400 MHz, CDCl₃) δ: 7.547.48 (m, 1H), 7.17-7.09 (m, 3H), 2.42 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ: 137.34, 135.37, 130.27, 128.63, 127.29, 126.64, 19.96; GC-MS (EI) *m/z*: (%) 246, (100) [M⁺], 213 (8), 198 (6), 182 (10), 167 (6), 123 (67), 108 (9), 91 (11), 77 (13). Spectroscopic data are in accordance with the previously presented.¹



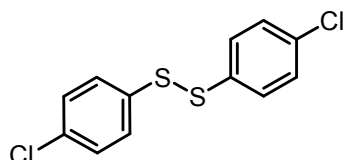
bis(3,5-phenyl)disulfide **d.** Yield 89%, yellow oil. FTIR neat, cm⁻¹ v: 3010, 2921, 2862, 1537, 1459, 1038; ¹H NMR (400 MHz, CDCl₃) δ: 7.11 (s, 2H), 6.84 (s, 4H), 2.27 (s, 12H); ¹³C NMR (100 MHz, CDCl₃) δ: 138.67, 136.79, 128.97, 125.12, 21.21; GC-MS (EI) *m/z*: (%) 274, (100) [M⁺], 259 (6), 241 (12), 226 (19), 210 (8), 195 (17), 168 (5), 137 (24), 121 (13), 105 (7), 91 (12), 77 (11). Spectroscopic data are in accordance with the previously presented.¹



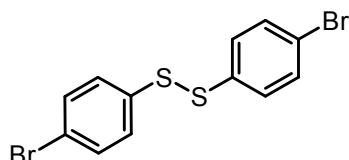
bis(*p*-methoxyphenyl)disulfide e. Yield 90%, white solid. Mp 75-78°C. ¹H NMR (400 MHz, CDCl₃) δ: 7.22-7.18 (m, 2H), 7.07 (d, 4 H, *J* = 1.1 Hz), 6.76 (dd, 2 H, *J* = 1.1 Hz *J* = 2.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ: 159.8, 132.6, 128.4, 114.5, 55.3; GC-MS (EI) *m/z*: (%) 278, (22) [M⁺], 140 (100), 139 (100), 96 (21), 77 (9). Spectroscopic data are in accordance with the previously presented.¹



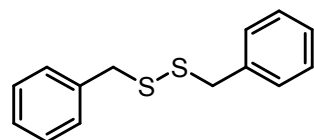
bis(*p*-fluorophenyl)disulfide f. Yield 91%, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ: 7.43 (dt, 4 H, *J* = 1.2 Hz, *J* = 2.5 Hz), 7.00 (t, 4 H, *J* = 1.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ: 162.6 (d, *J* = 308 Hz), 132.1 (d, *J* = 3.87 Hz), 131.2 (d, *J* = 10.6 Hz), 116.2 (d, *J* = 28.0 Hz); GC-MS (EI) *m/z*: (%) 254, (77), 128 (100), 96 (33), 75 (12). Spectroscopic data are in accordance with the previously presented.²



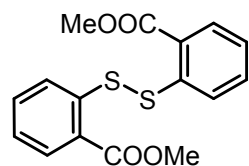
bis(*p*-chlorophenyl)disulfide g. Yield 90%, white solid. Mp 71-73°C. ¹H NMR (500 MHz, CDCl₃) δ: 7.40-7.38 (m, 2 H), 7.28-7.25 (m, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ: 135.1, 133.6, 129.3, 129.2; GC-MS (EI) *m/z*: (%) 288, (13), 287 (23) [M⁺], 222 (6), 145 (24), 143 (100), 108 (66), 99 (21), 75 (12), 63 (14). Spectroscopic data are in accordance with the previously presented.¹



bis(*p*-bromophenyl)disulfide h. Yield 93%, crystalline white solid. Mp 92-93°C. ¹H NMR (500 MHz, CDCl₃) δ: 7.43-7.41 (m, 4 H), 7.34-7.32 (m, 4); ¹³C NMR (125 MHz, CDCl₃) δ: 135.7, 132.2, 129.4, 121.5; GC-MS (EI) *m/z*: (%) 377, (72), 376 (100) [M⁺], 375 (63), 312 (8), 297 (18), 296 (17), 189 (77), 188 (74), 108 (81), 82 (15), 69 (16). Spectroscopic data are in accordance with the previously presented.³

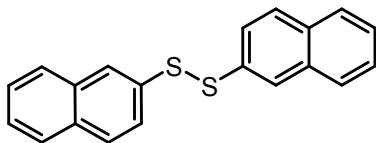


bis(benzyl)disulfide i. Yield 98%, brown solid. Mp 68-70°C. ¹H NMR (400 MHz, CDCl₃) δ: 7.32-7.22 (m, 10 H), 3.60 (s, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ: 137.3, 129.3, 128.4, 127.3, 43.3. GC-MS (EI) *m/z*: (%) 246, (7) [M⁺], 91 (100), 65 (17). Spectroscopic data are in accordance with the previously presented.¹

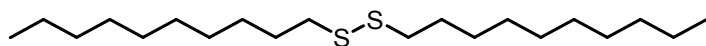


bis(*o*-carboxymethylphenyl)disulfide j. Yield 89%, white solid. Mp 196-198°C; FTIR neat, cm⁻¹ v: 2955, 1718, 1699, 1549, 1456, 1271, 1142, 1105, 1057; ¹H NMR (500 MHz, CDCl₃) δ: 8.06 (dd, 1 H, *J* = 1.0 Hz, 10.0 Hz), 7.43-7.27 (m, 1 H), 7.26 (d, 1 H, *J* = 10.0 Hz), 7.23

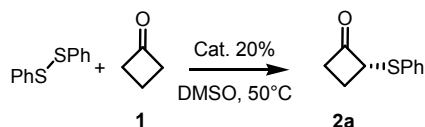
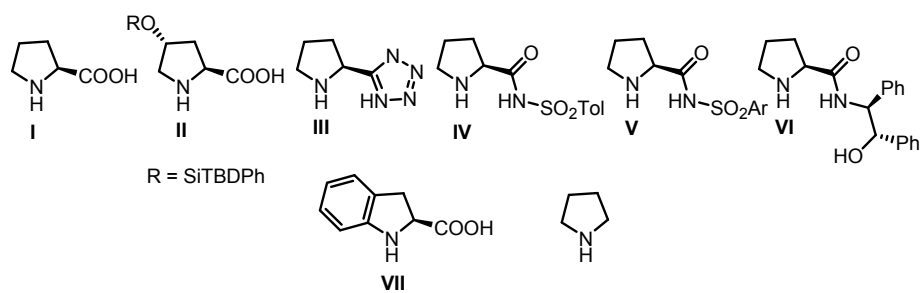
(dd, 1 H, $J = 10$ Hz, $J = 20$ Hz), 3.99 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.9, 140.3, 133.1, 131.4, 127.3, 125.8, 125.4, 52.4; GC-MS (EI) m/z : (%) 334, (21), 319 (14), 167 (100), 109 (61), 77 (47%), 65 (39%), 62 (65%). Spectroscopic data are in accordance with the previously presented.⁴



bis(naphthyl)disulfide k. Yield 93%, beige solid. Mp 140-141°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.23 (s, 2H), 7.05 (d, 2H, $J = 8.7$ Hz), 6.99 (dd, 4H, $J = 9.1$ Hz, $J = 6.9$ Hz), 6.77 (dd, 2H, $J = 8.7$ Hz, $J = 1.8$ Hz), 6.66-6.57 (m, 4H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 133.1, 133.0, 132.1, 129.3, 127.8, 127.4, 127.1, 126.7, 126.3, 125.3. Spectroscopic data are in accordance with the previously presented.¹



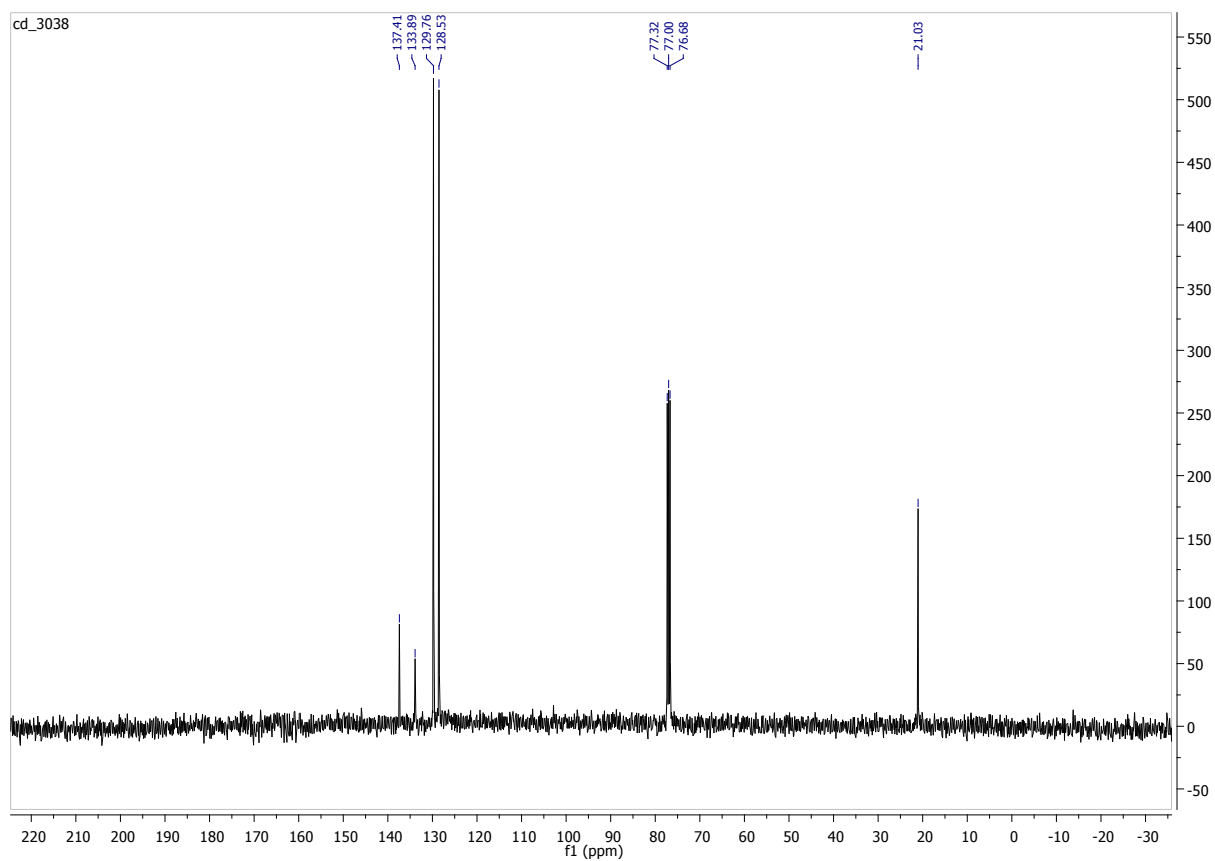
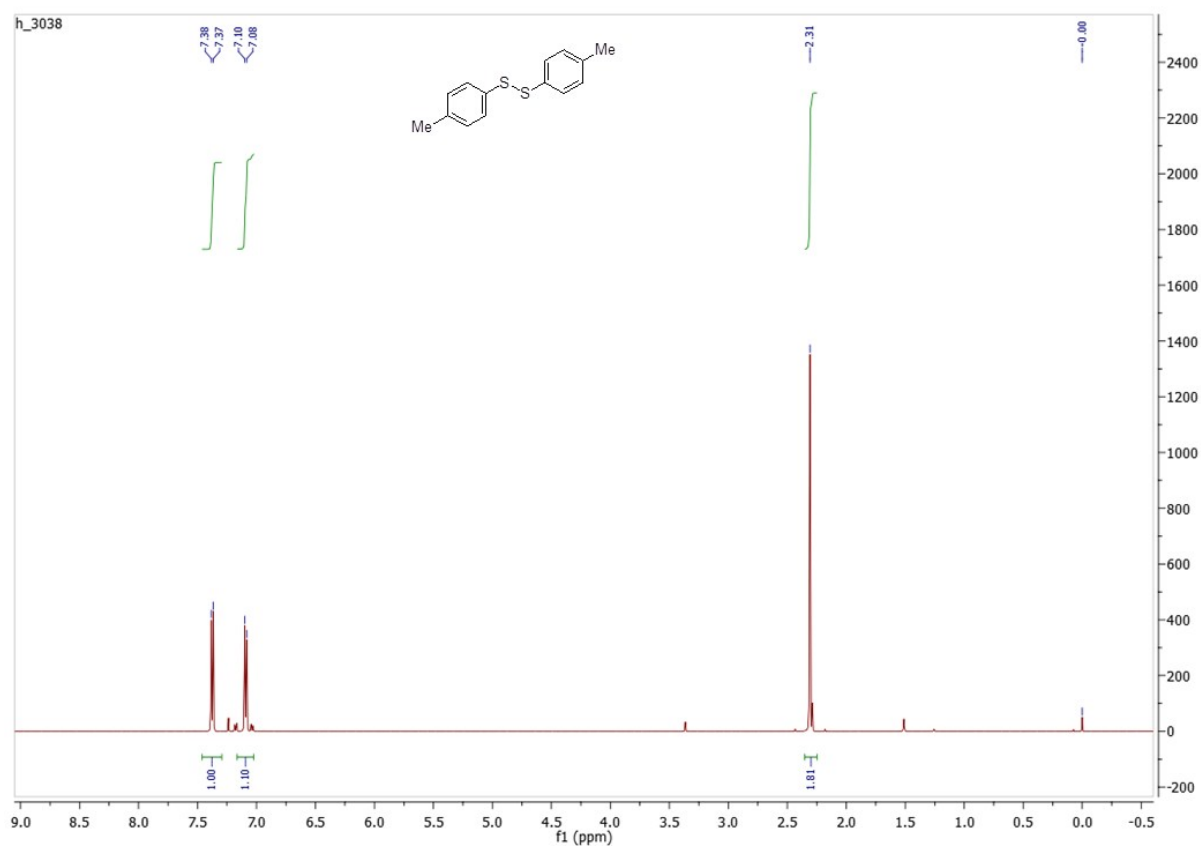
bis(decyl)disulfide l. Yield 96%, colorless oil. ^1H NMR (400 MHz, CDCl_3) δ : 2.68 (t, $J = 7.4$ Hz, 4H), 1.73 – 1.59 (m, 4H), 1.37 (dd, $J = 13.6$, 6.7 Hz, 4H), 1.26 (s, 24H), 0.88 (t, $J = 6.5$ Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ : 39.4, 32.0, 29.7, 29.6, 29.5, 29.4, 28.7, 22.8, 14.2. Spectroscopic data are in accordance with the previously presented.⁵

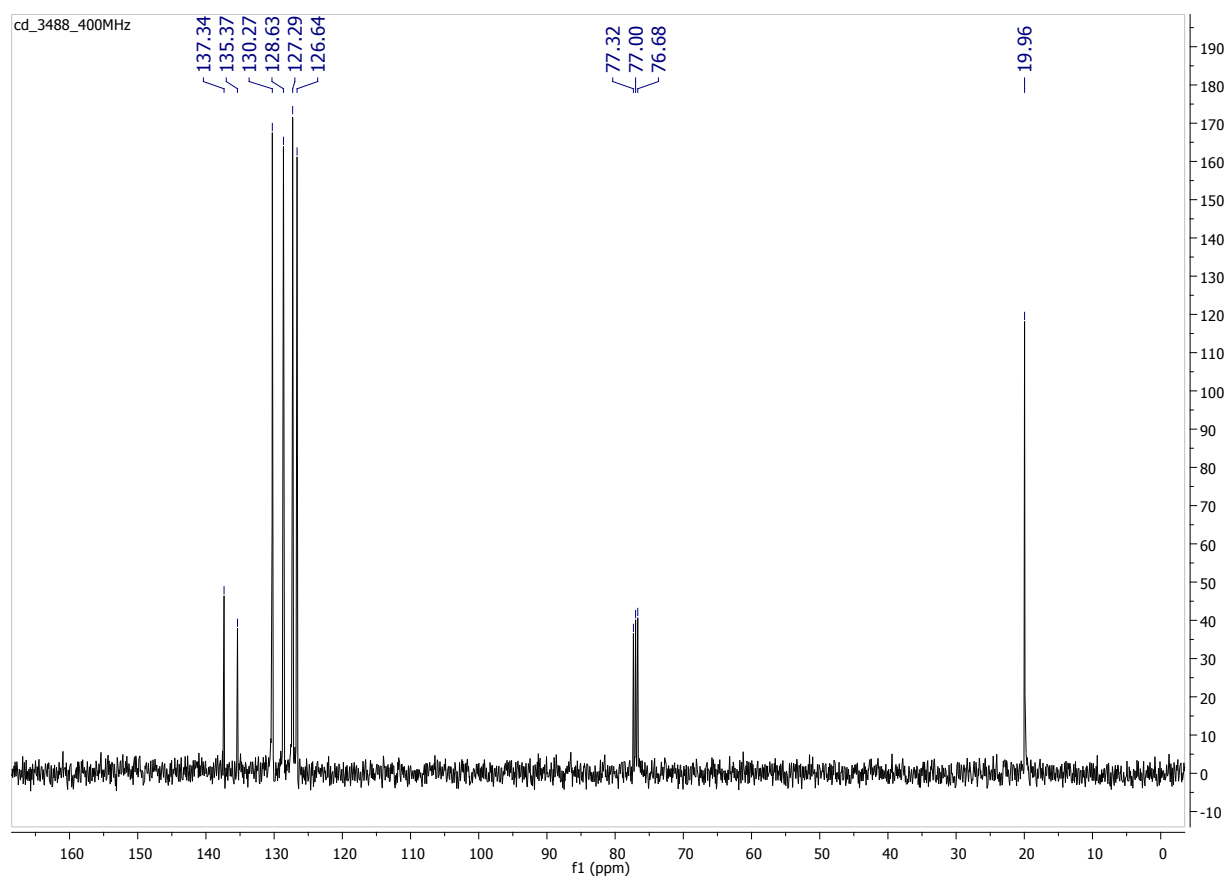
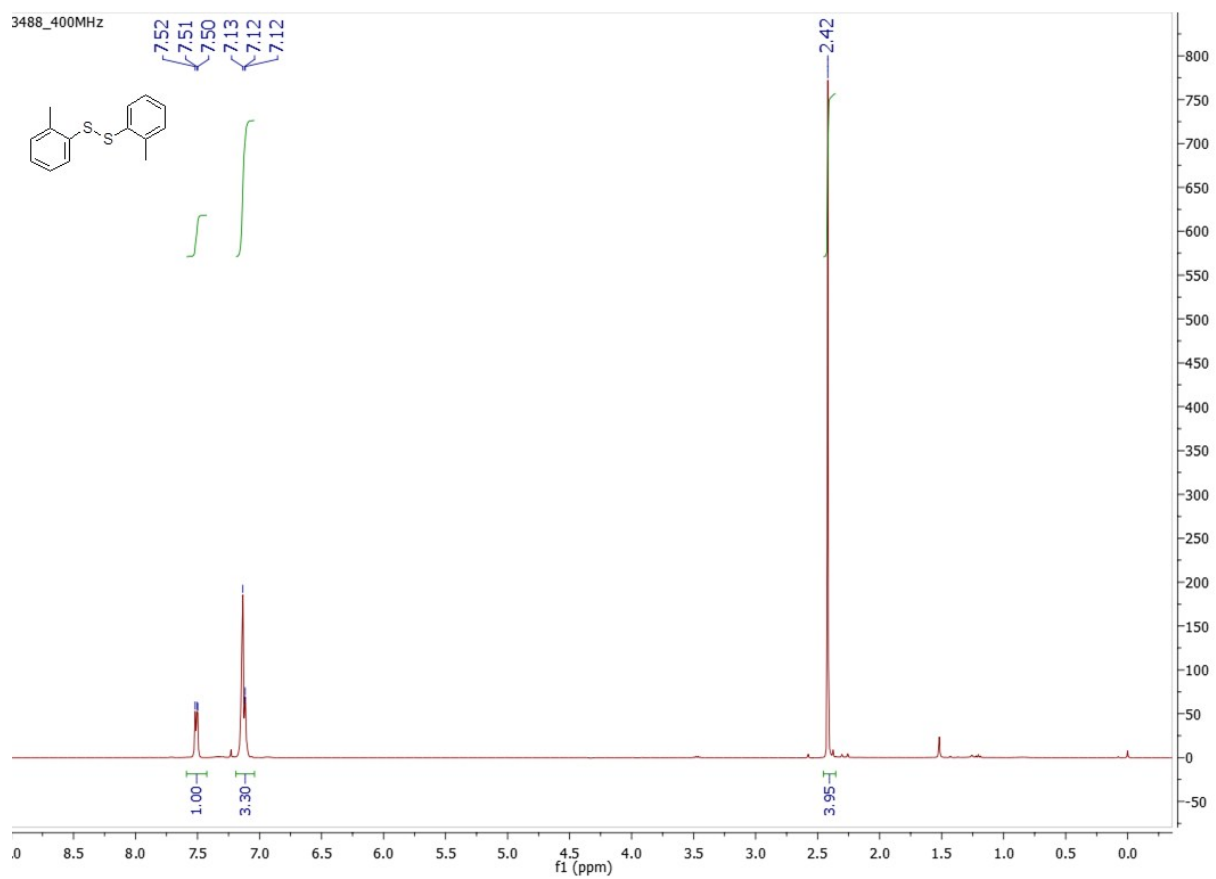
Table 1 α -sulfenylation of cyclobutanone **1a** using different pyrrolidine catalysts.^a

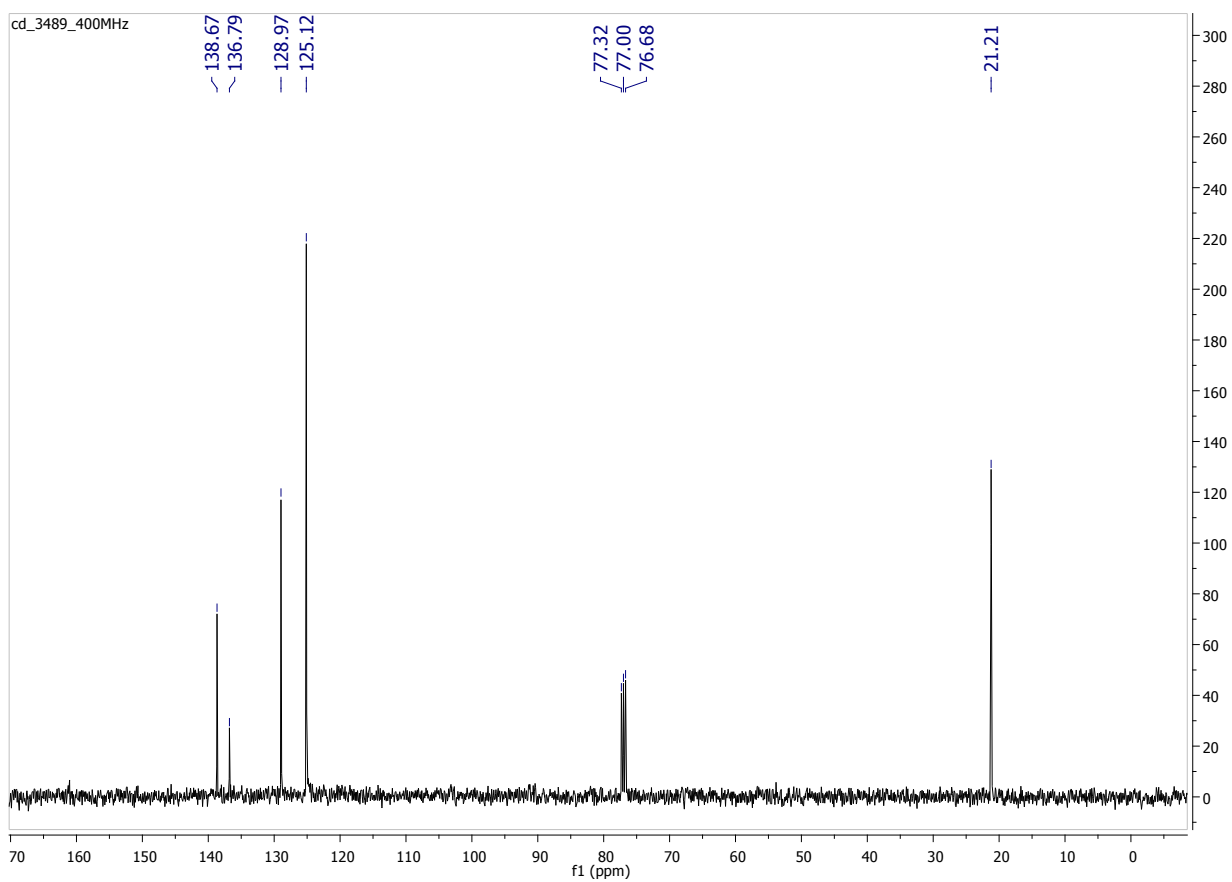
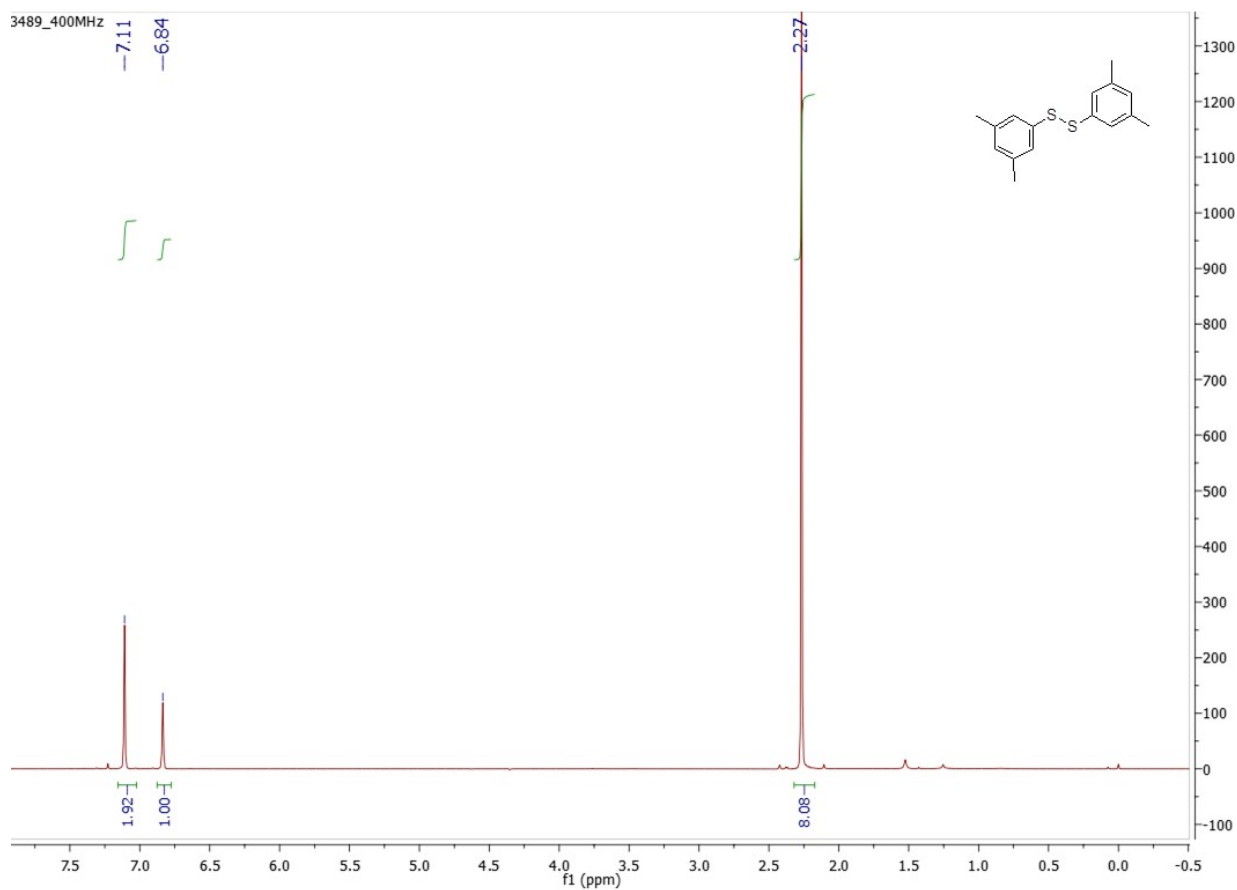
Entry	Catalyst	Yield % ^b	Time/h	e.r. ^c
1	I	90	12	48:52
2		92	12	49:51
3	II	37	24	48:52
4	III	22	24	51:49
5	IV	29 ^c	24	53:47
6	V^d	19	24	48:52
7	VI	-	36	-
8	VII	12	24	-
	Pyrrolidine			

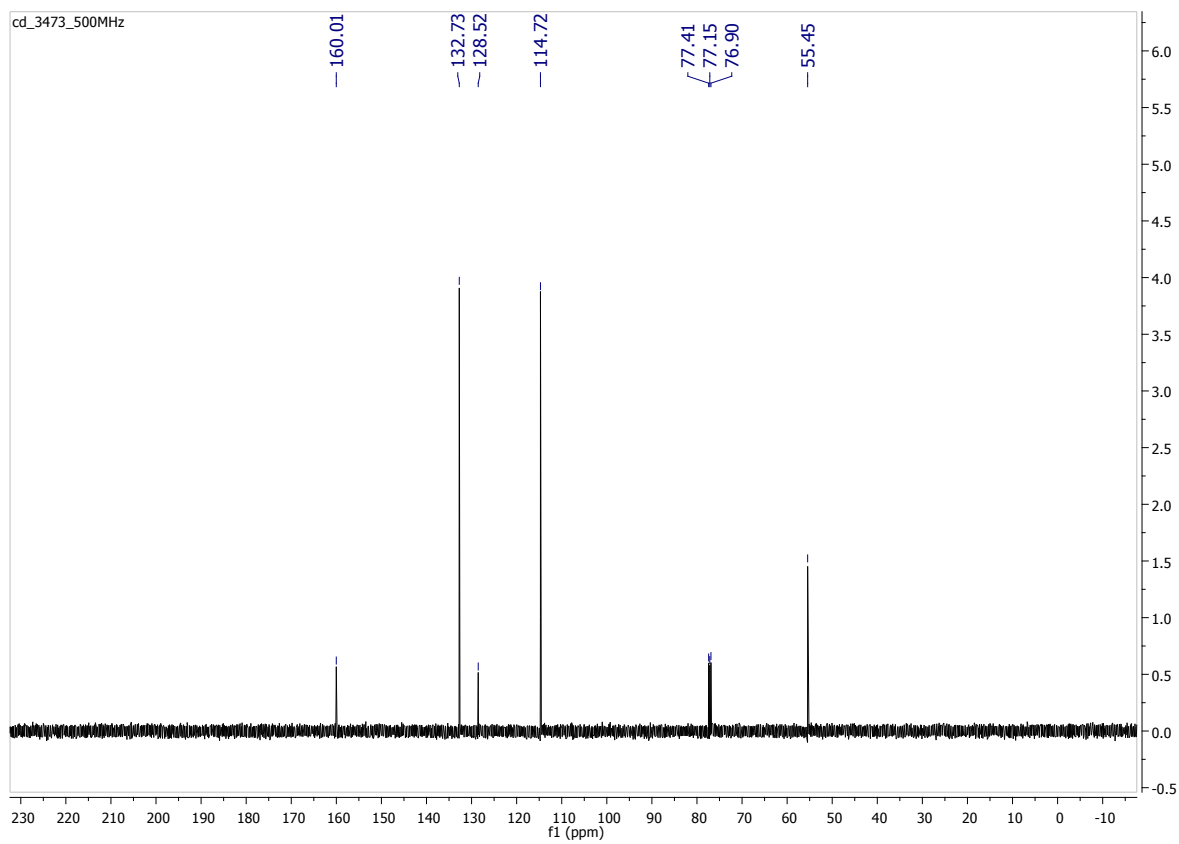
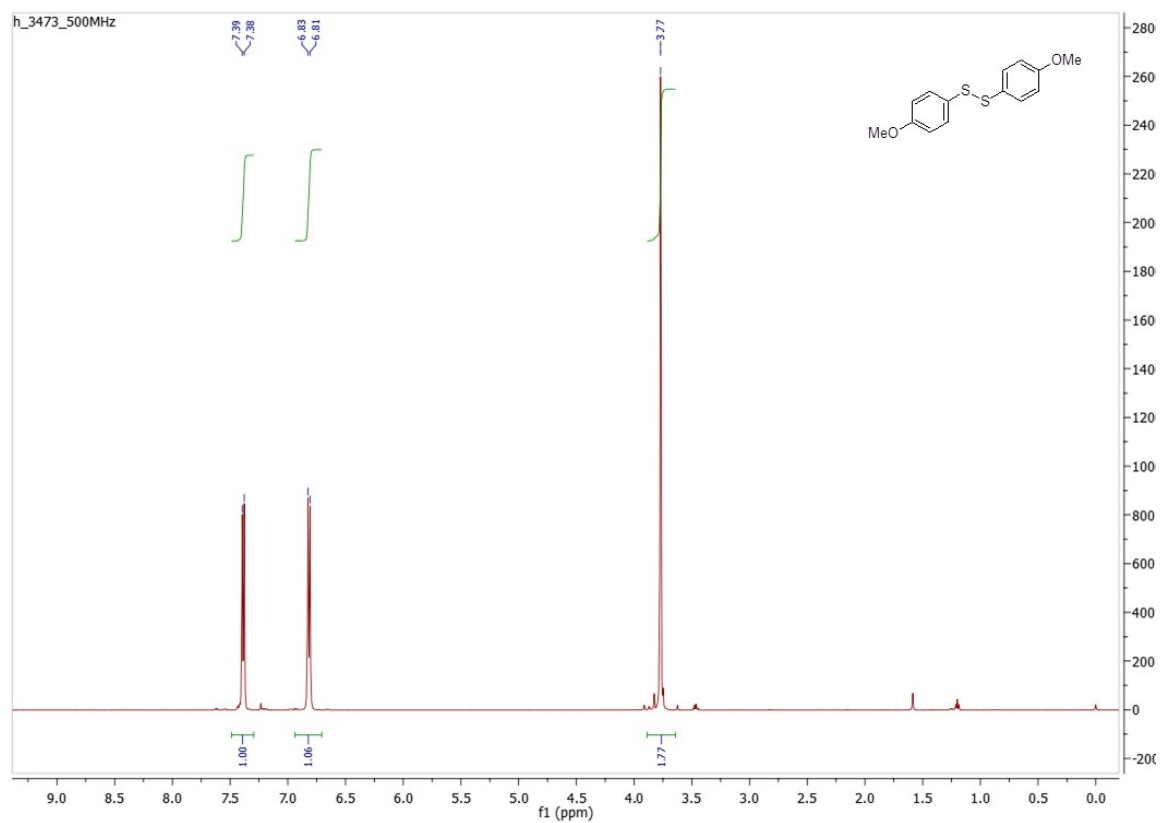
a) Reaction conditions: DMSO (1.0 mL), cyclobutanone (1.0 mmol), cat. **I-VII** (20 mol%), diphenyldisulfide (1.0 mmol), 50°C. b) Isolated yield. c) e.r. were determined by chiral-HPLC analysis. d) R = *p*-C₆H₄-C₁₂H₂₅.

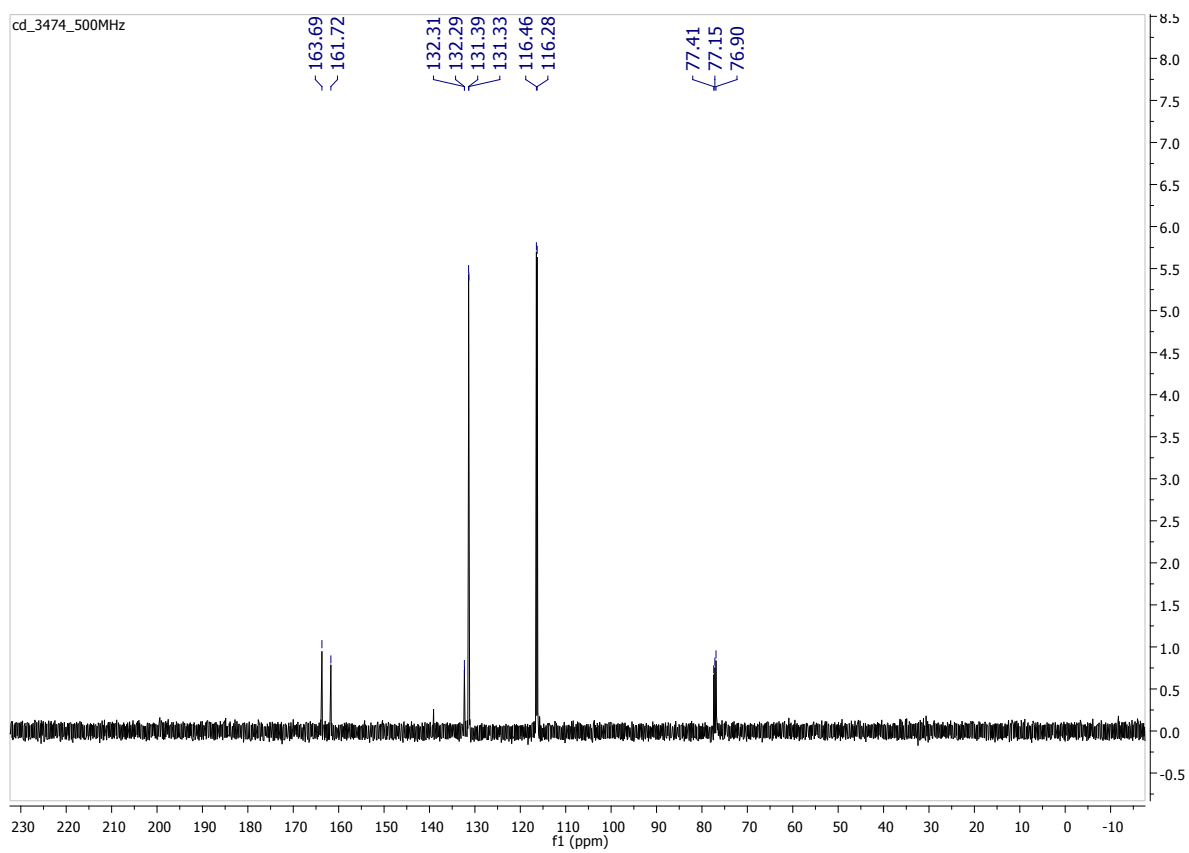
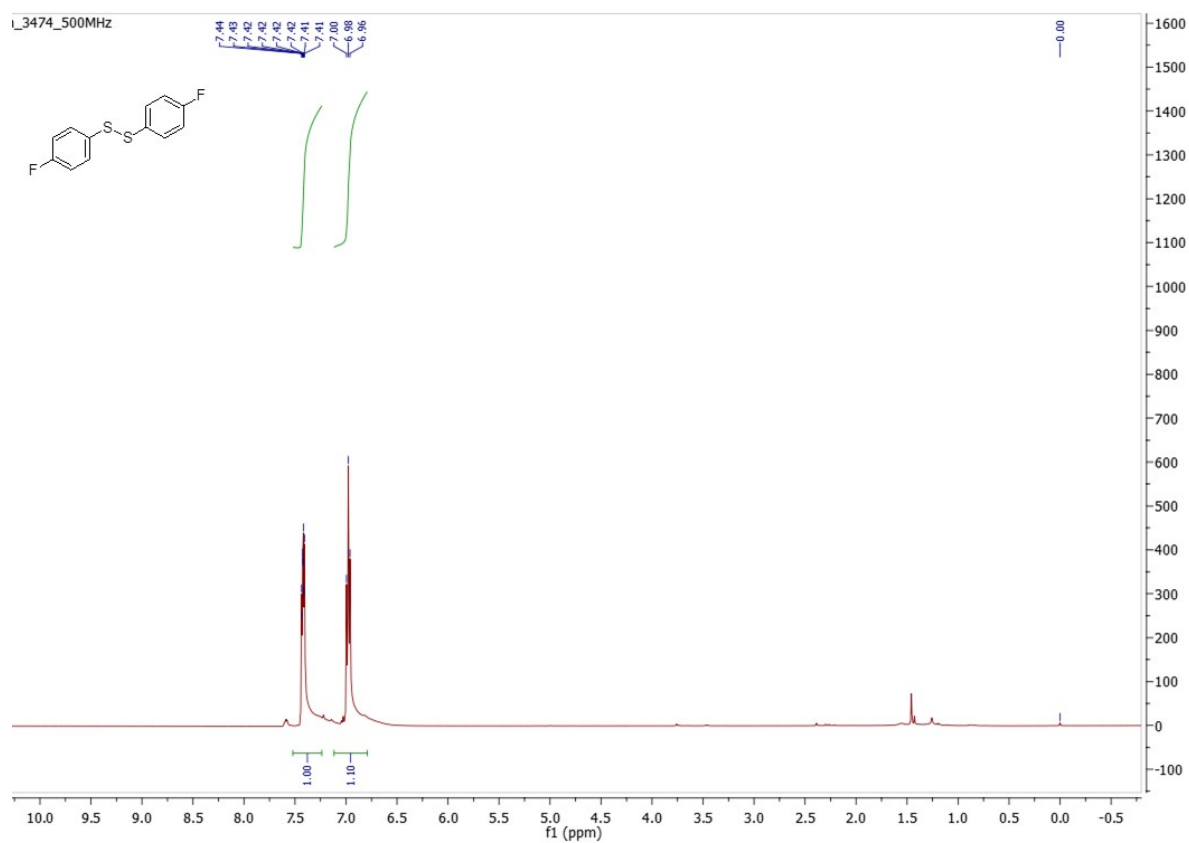
¹H and ¹³C NMR spectra of bis(aryl)disulfides b-l

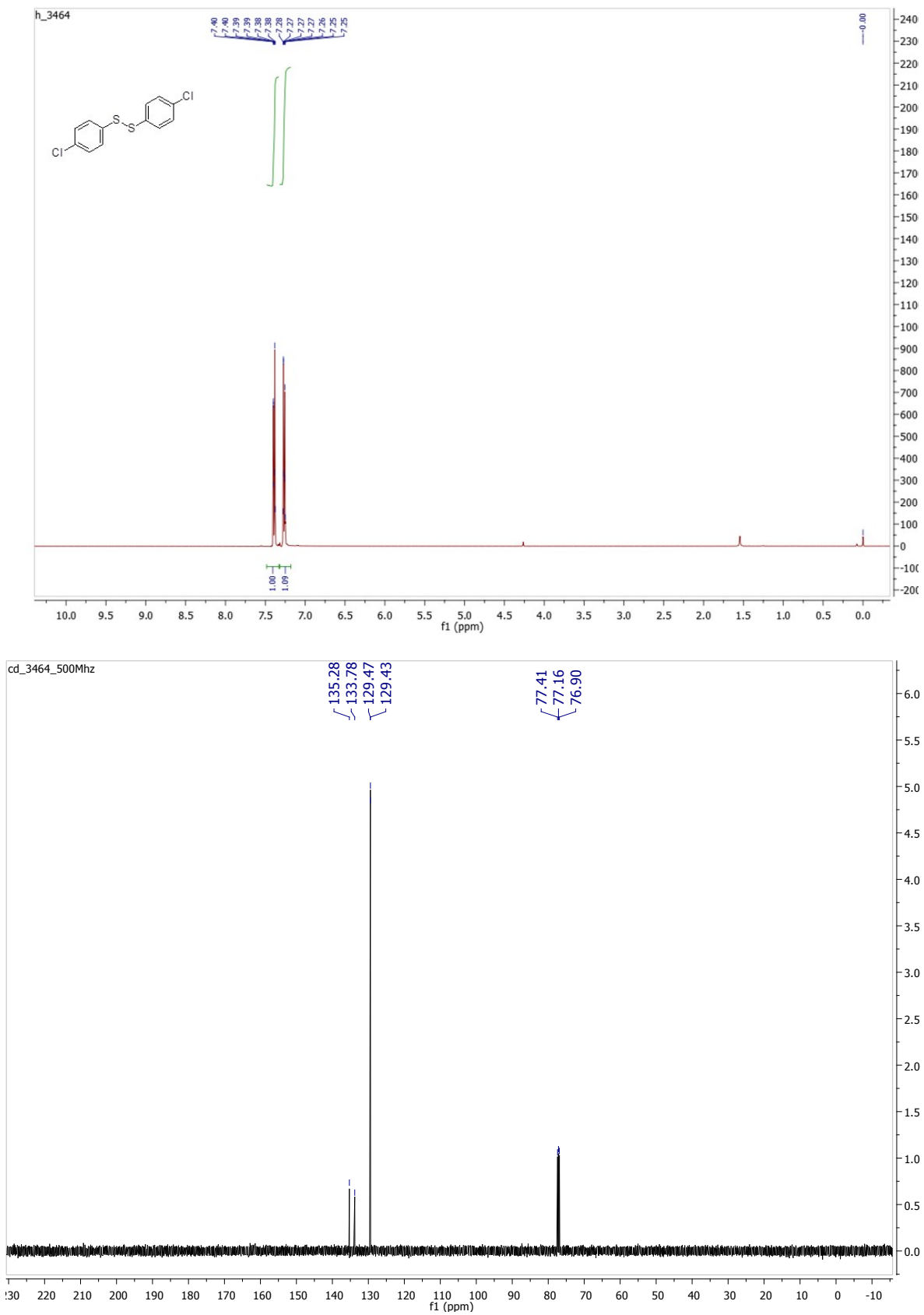


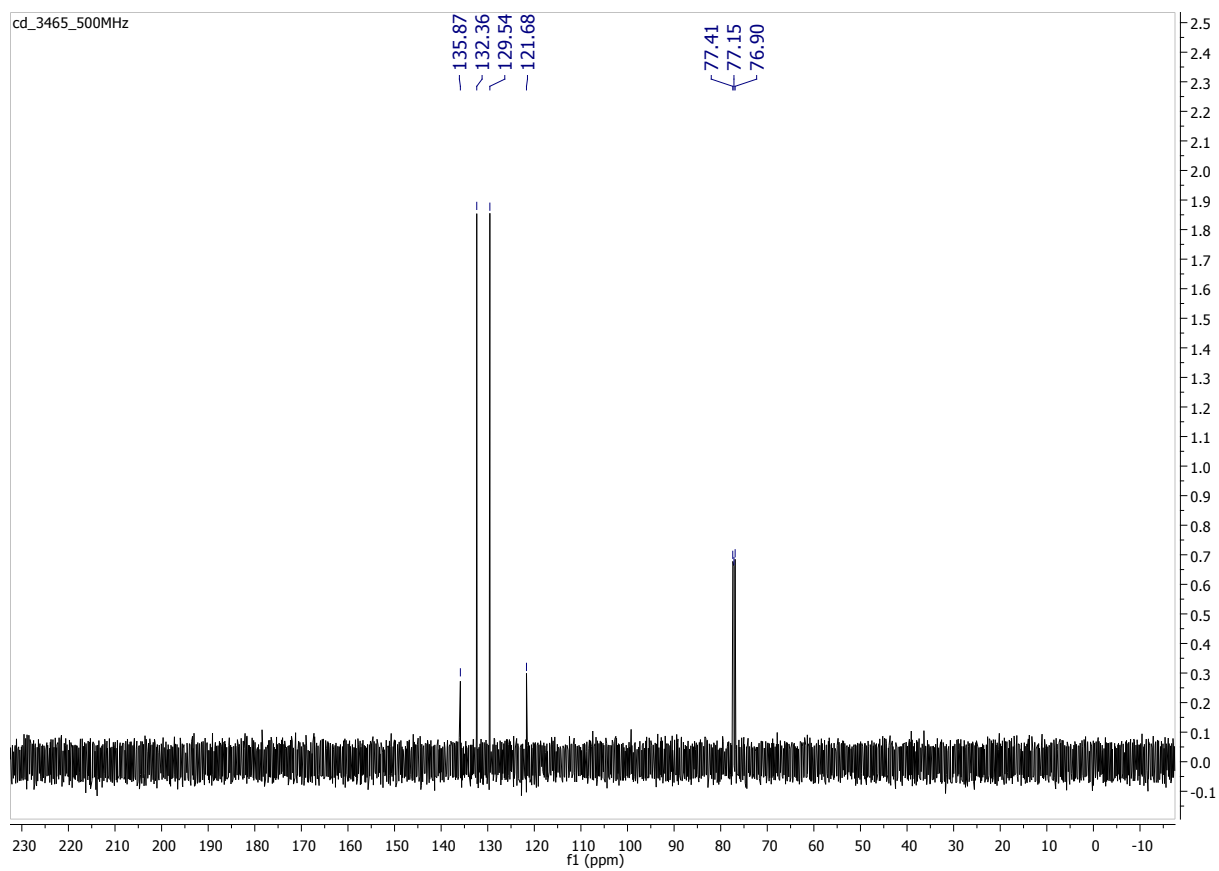
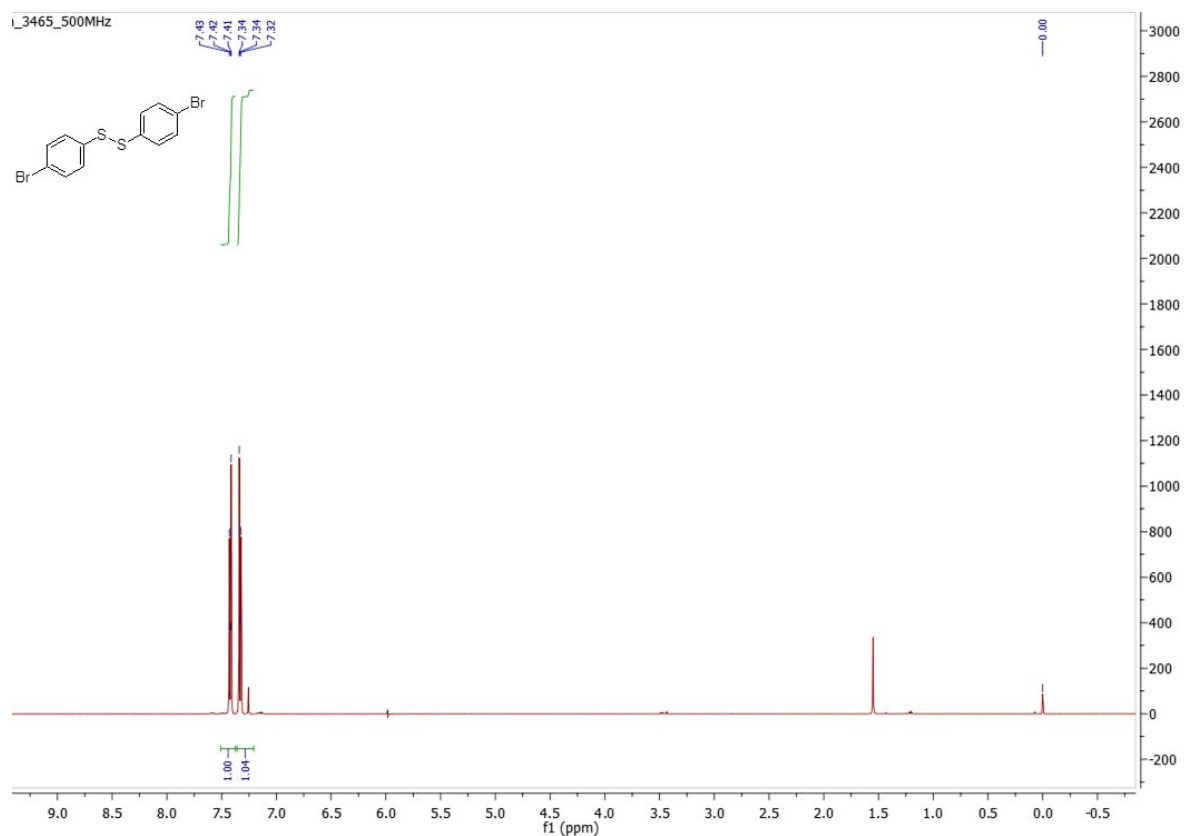


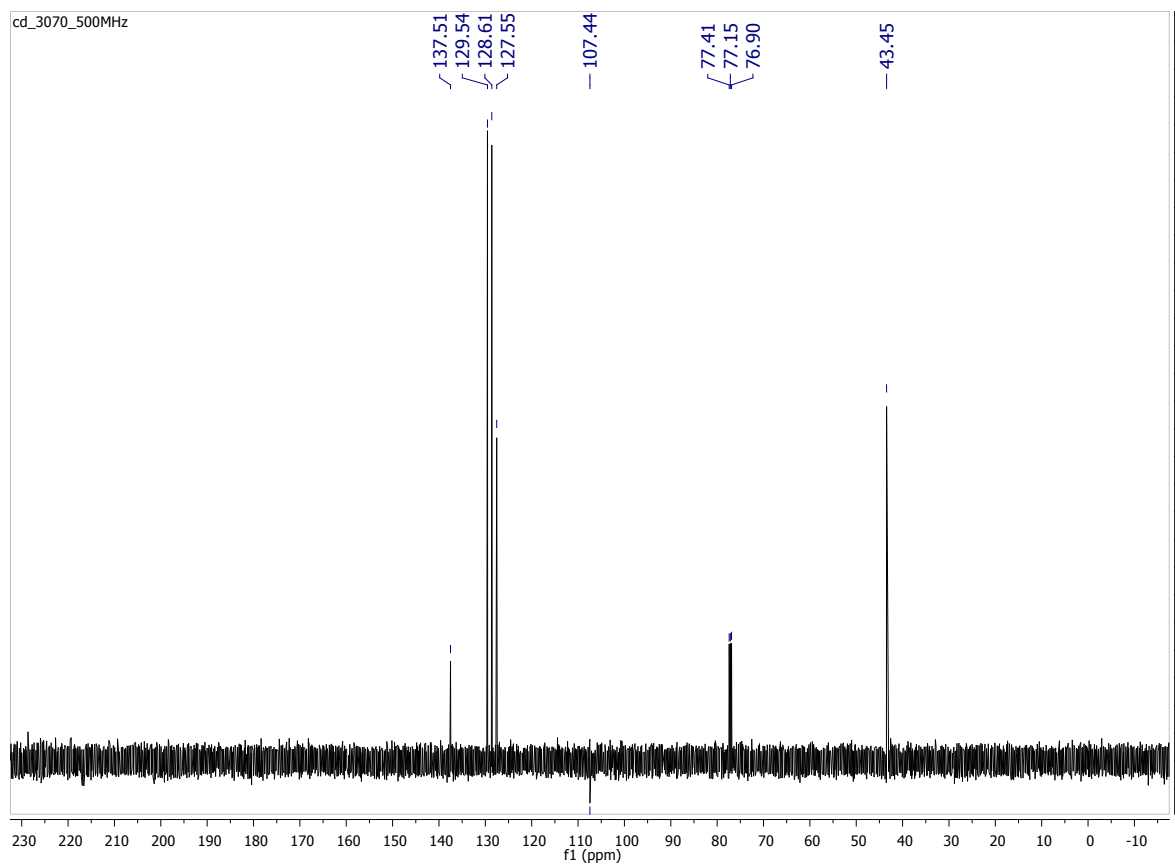
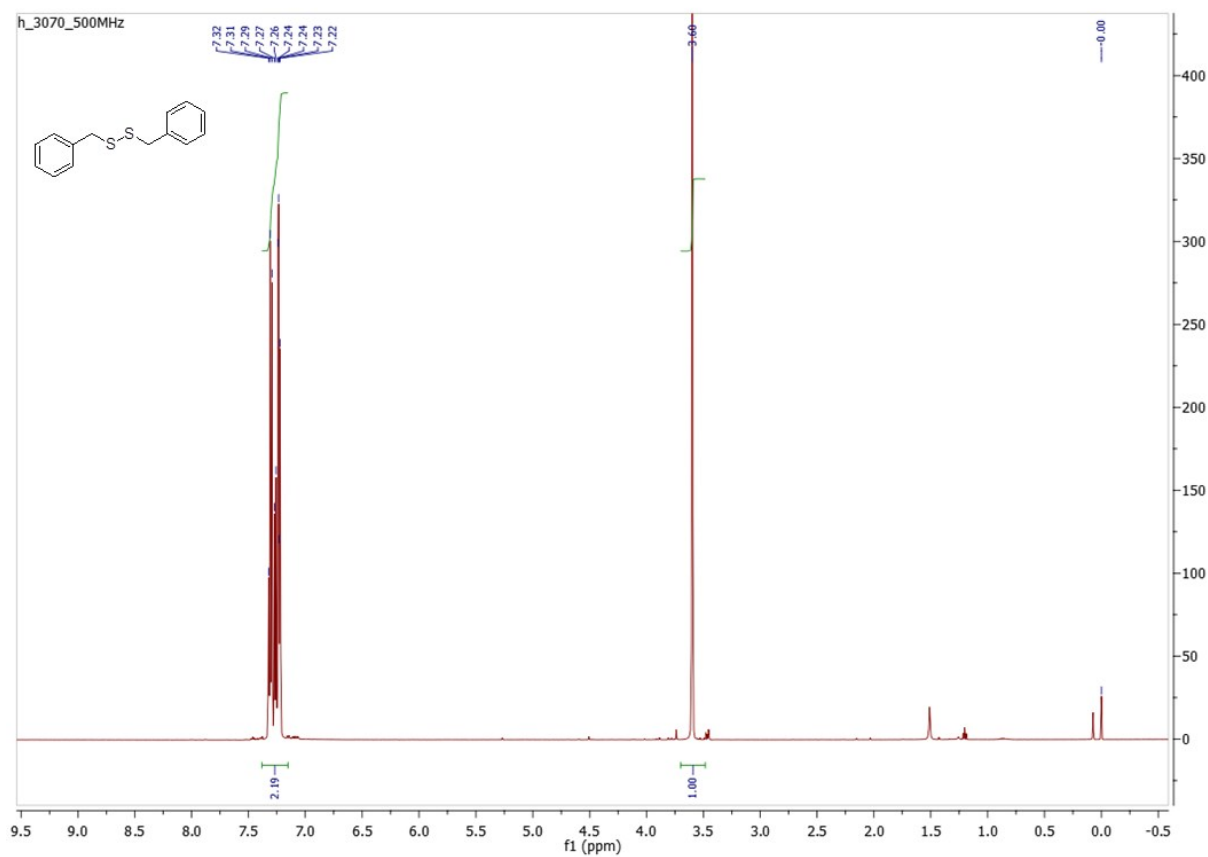


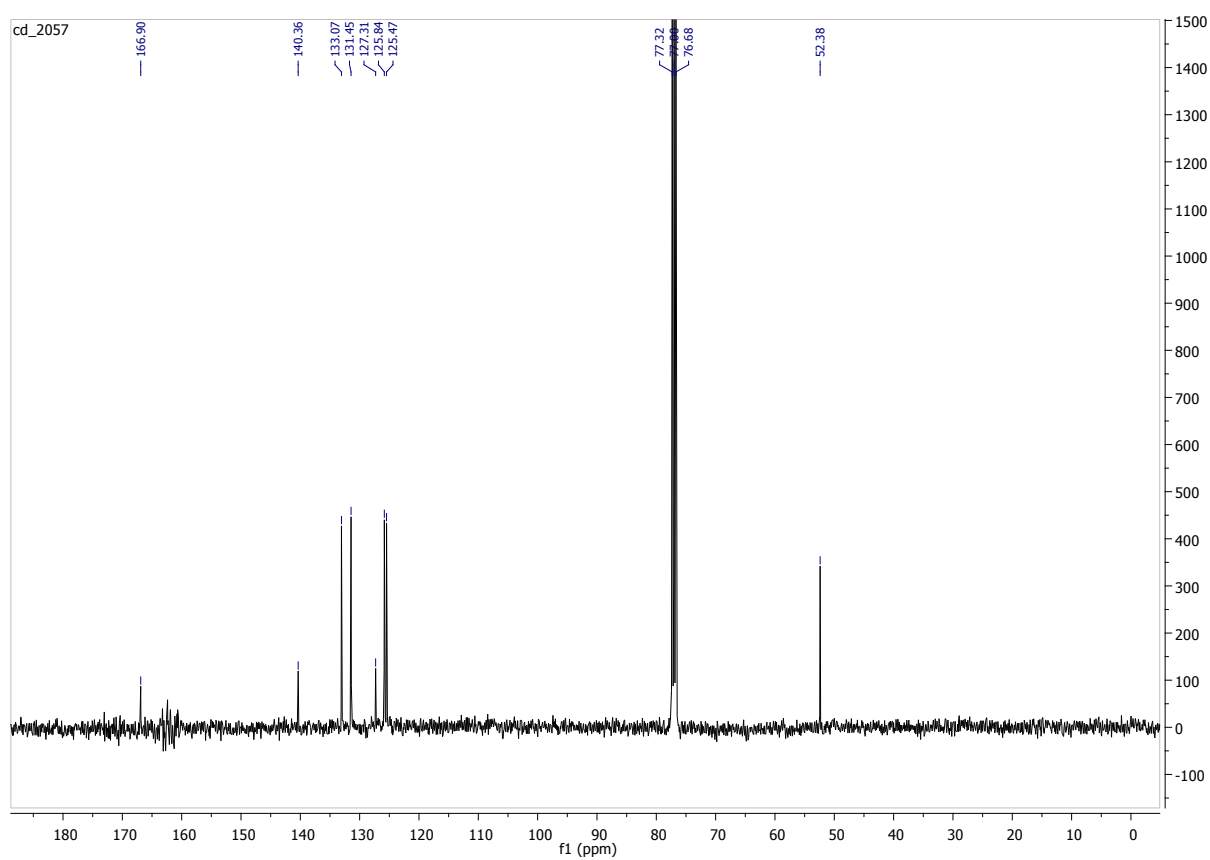
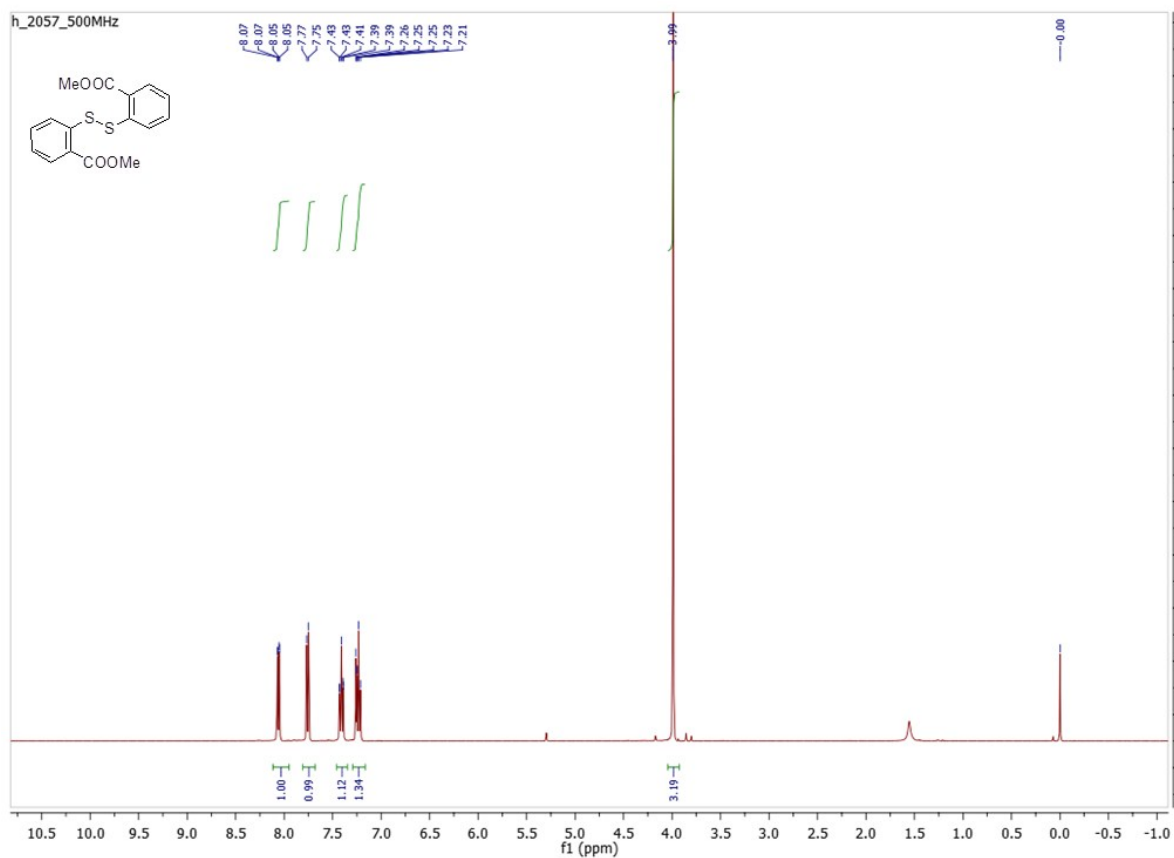


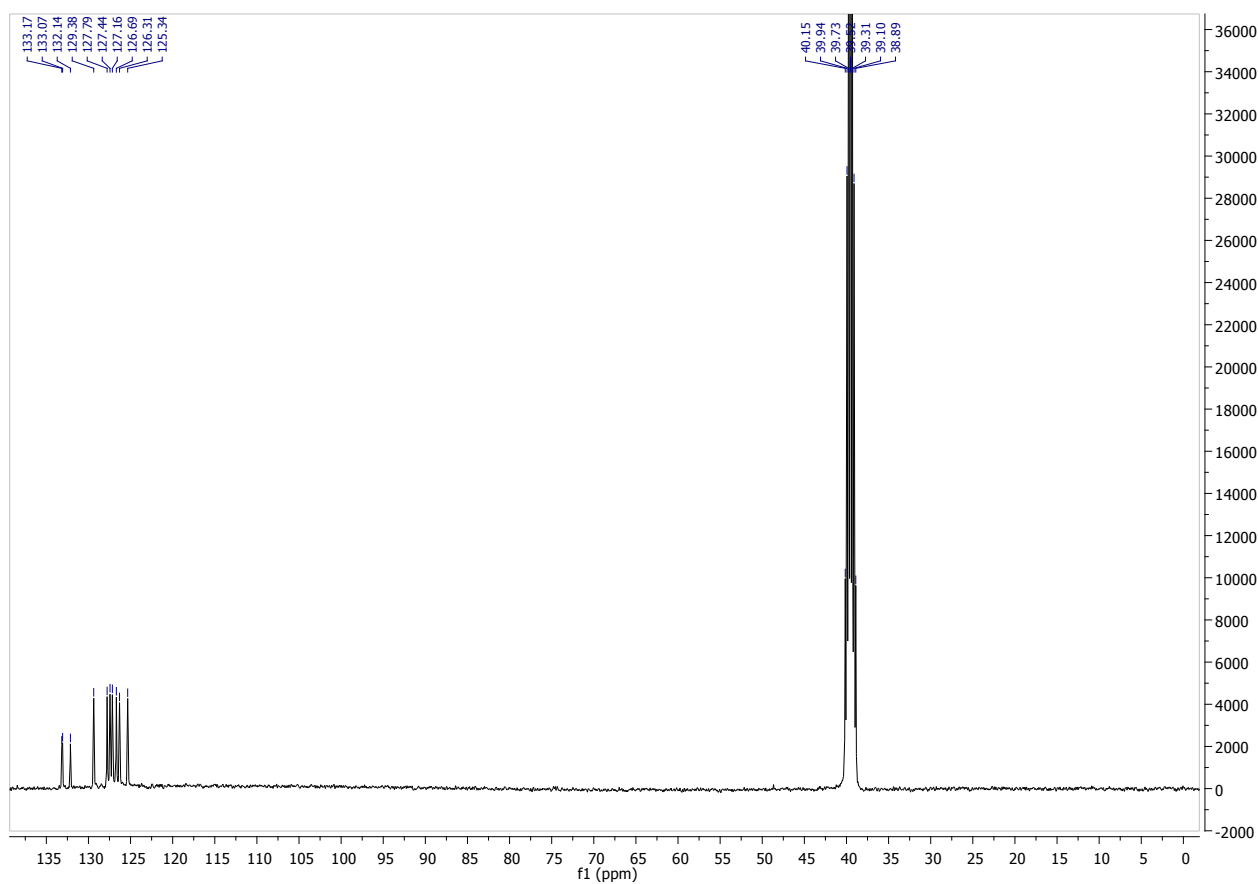
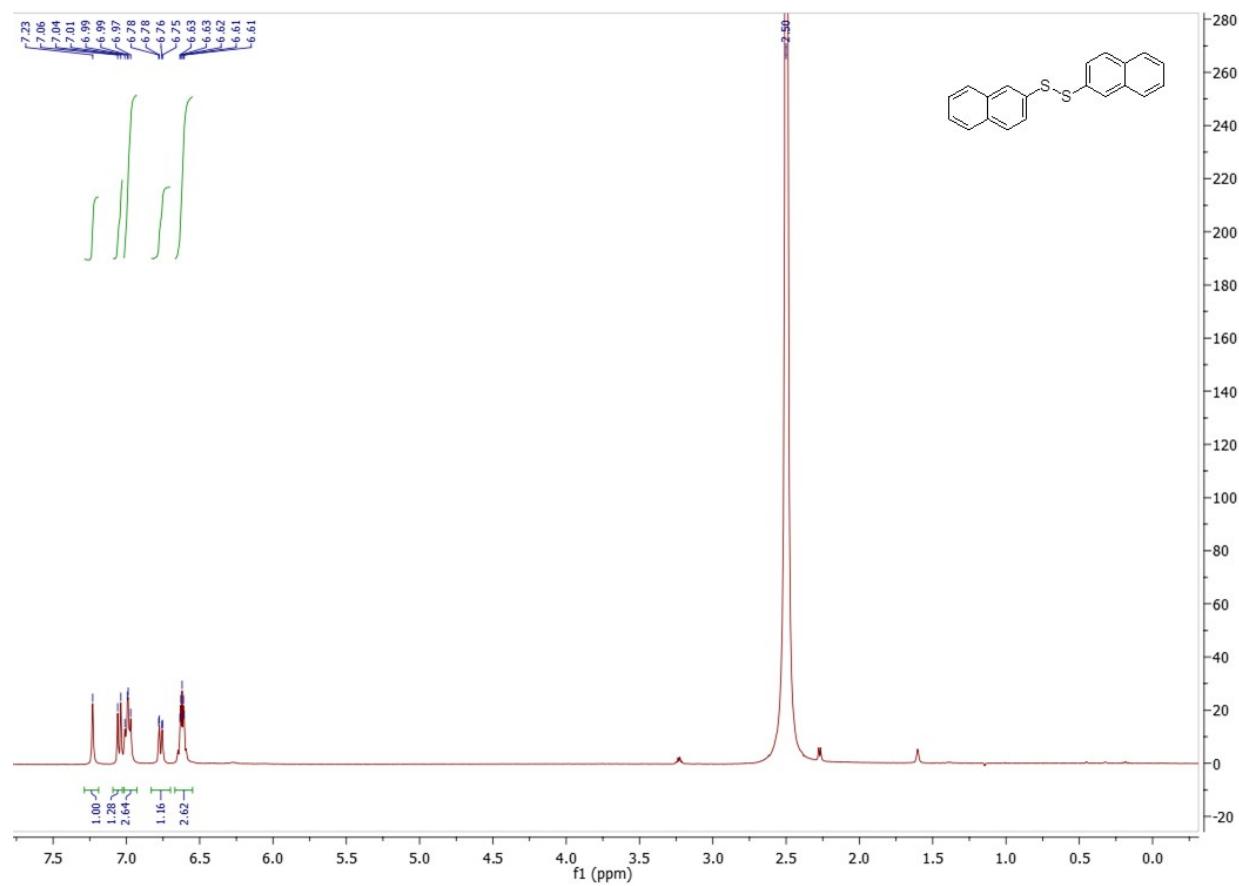


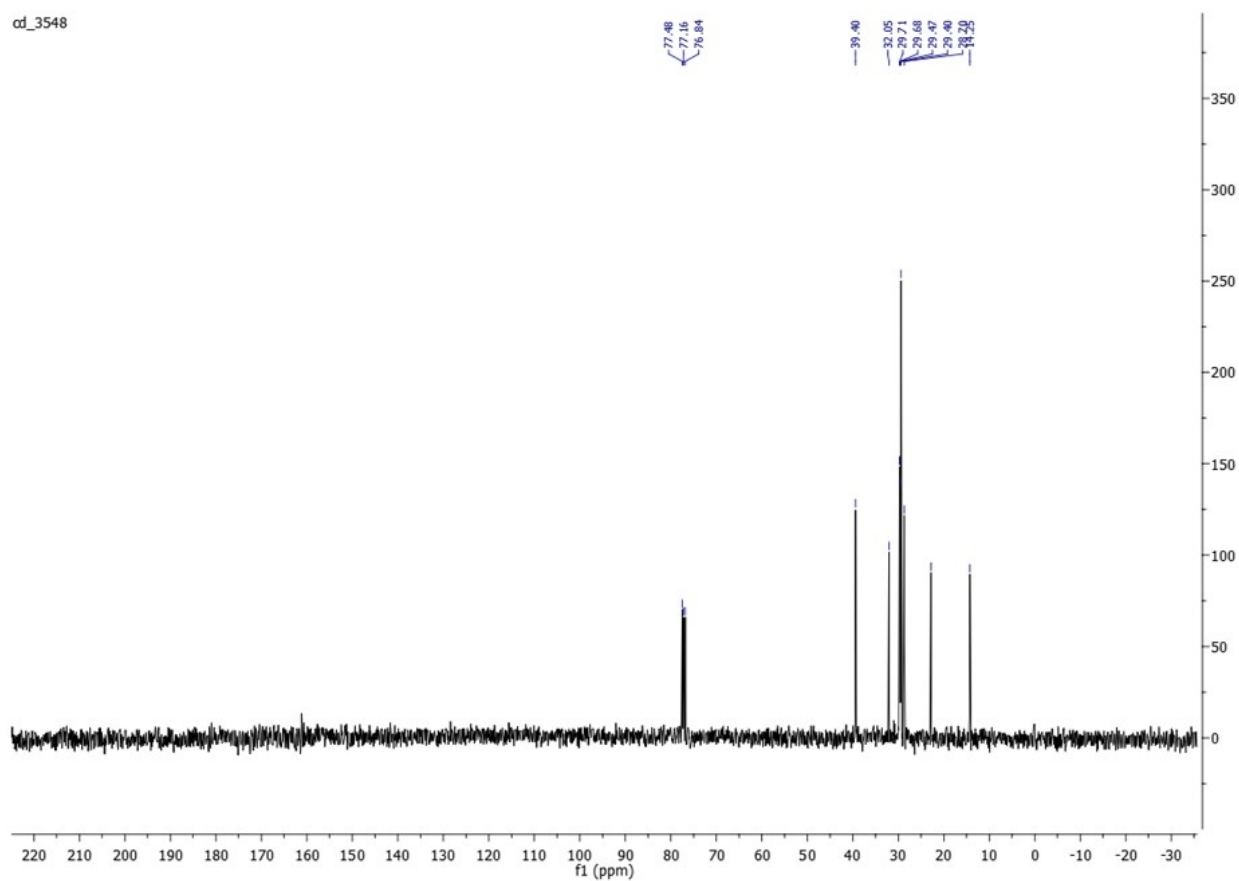
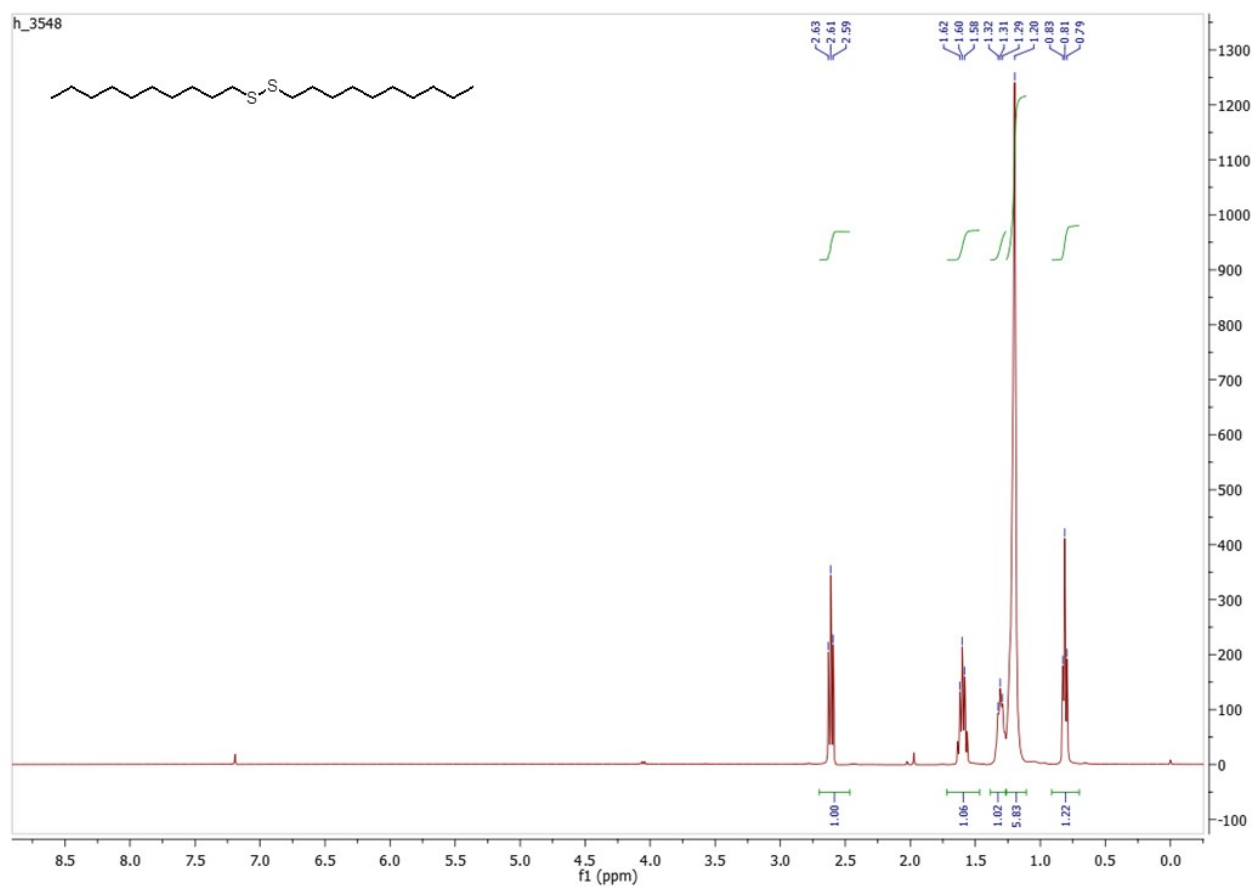




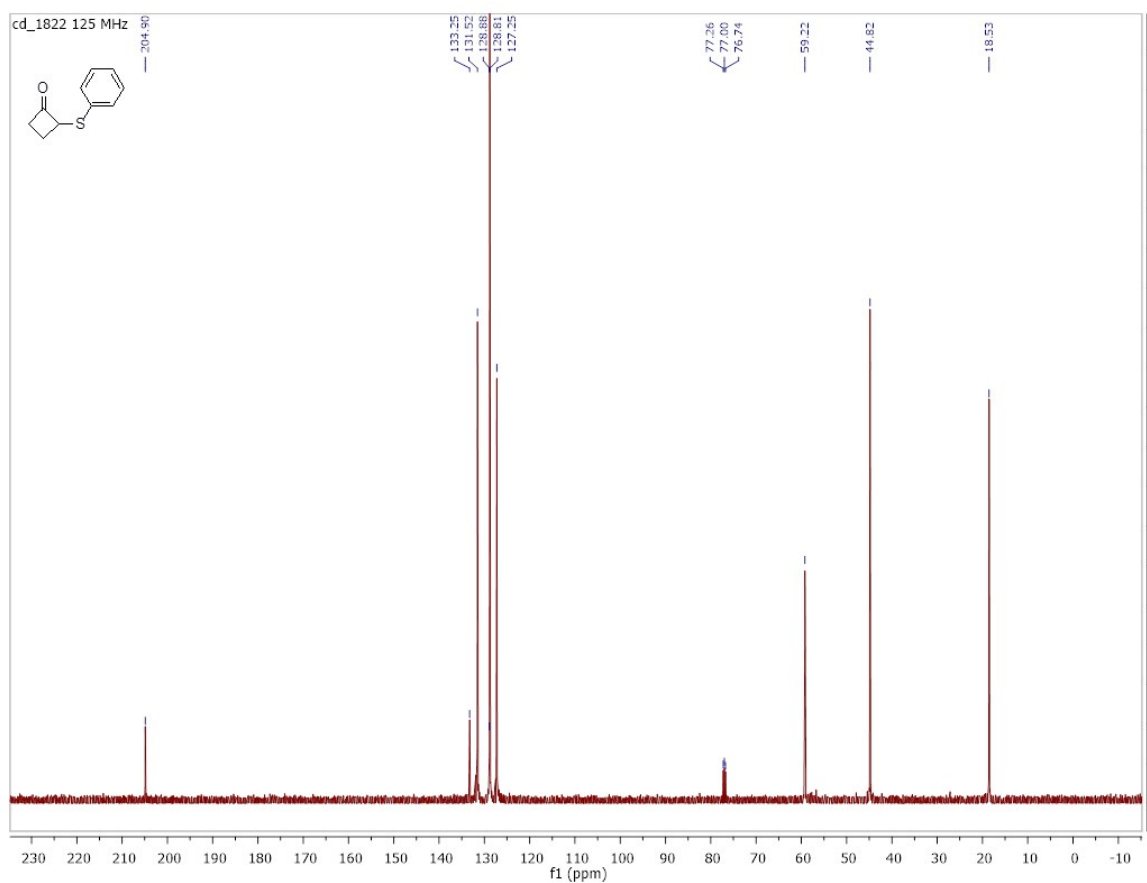
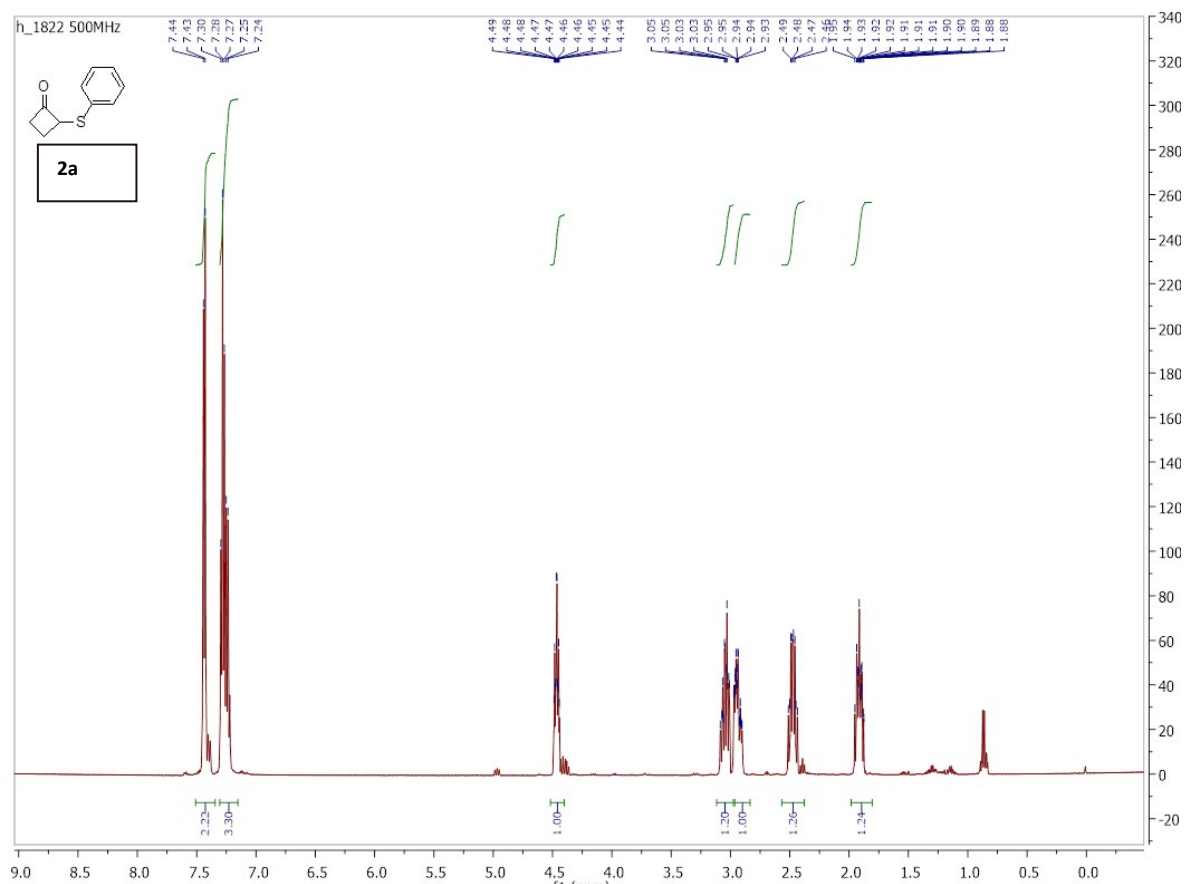


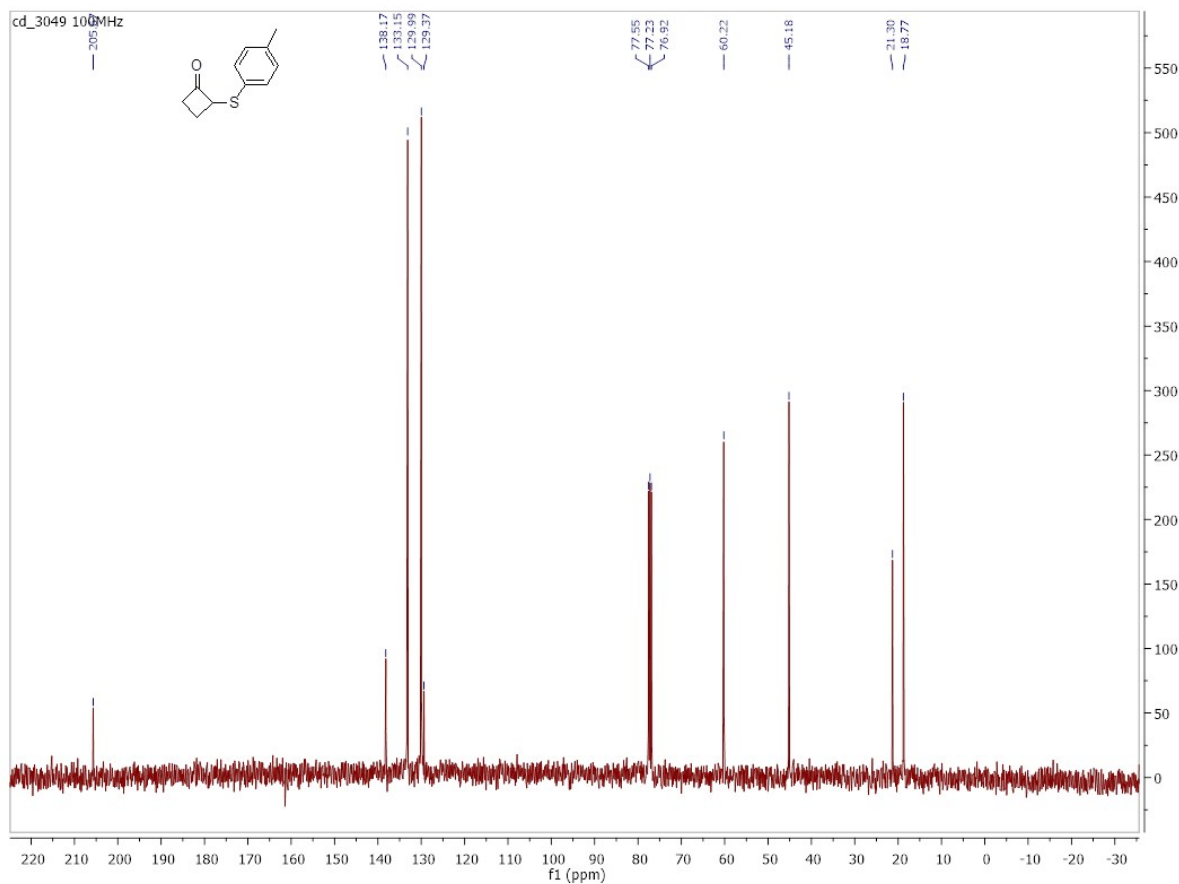
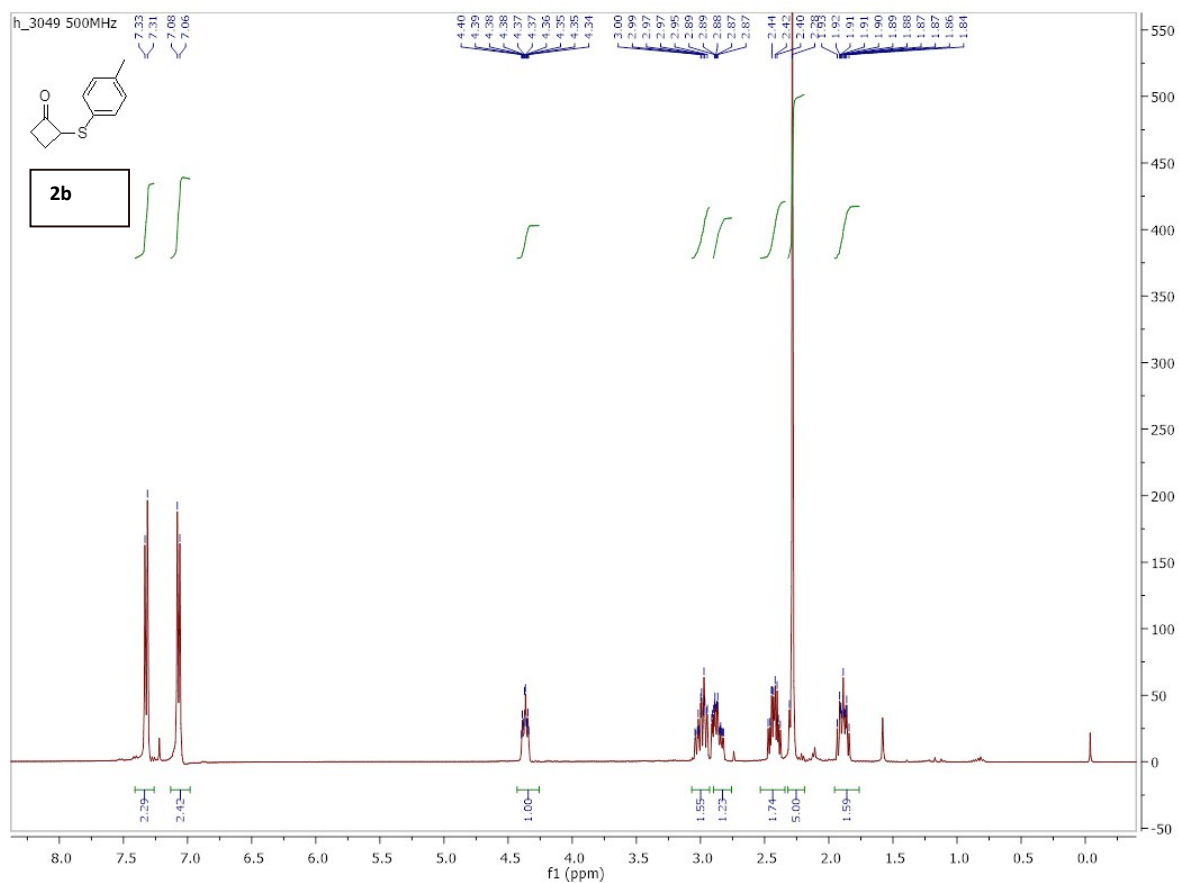


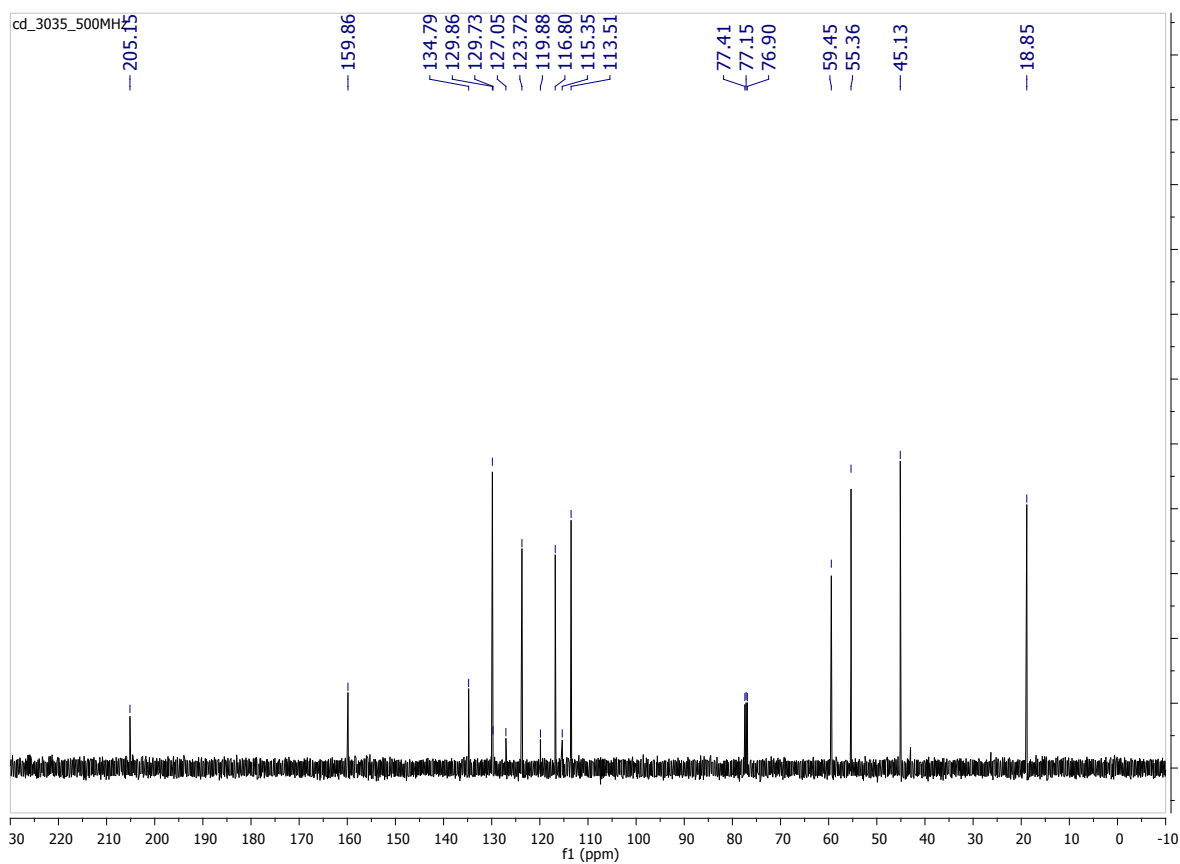
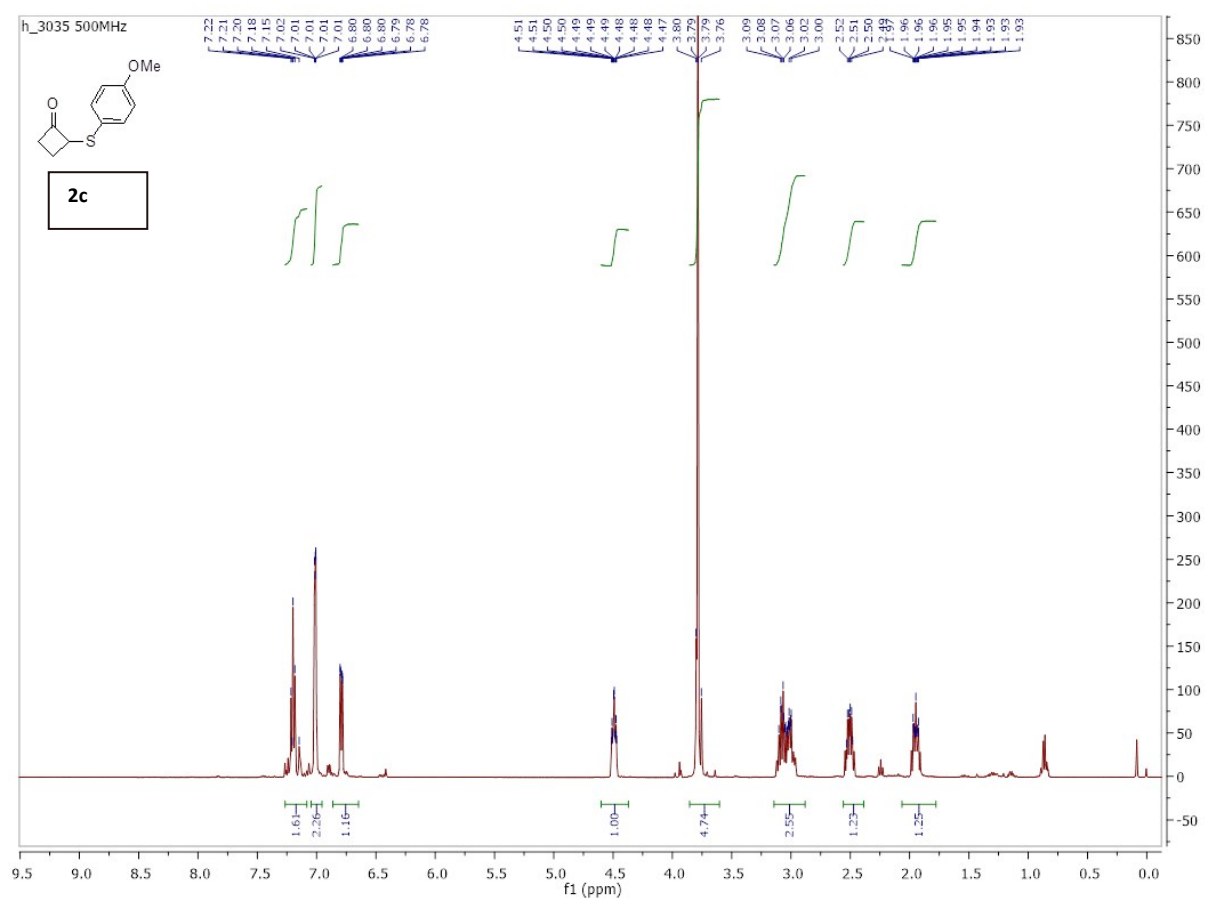


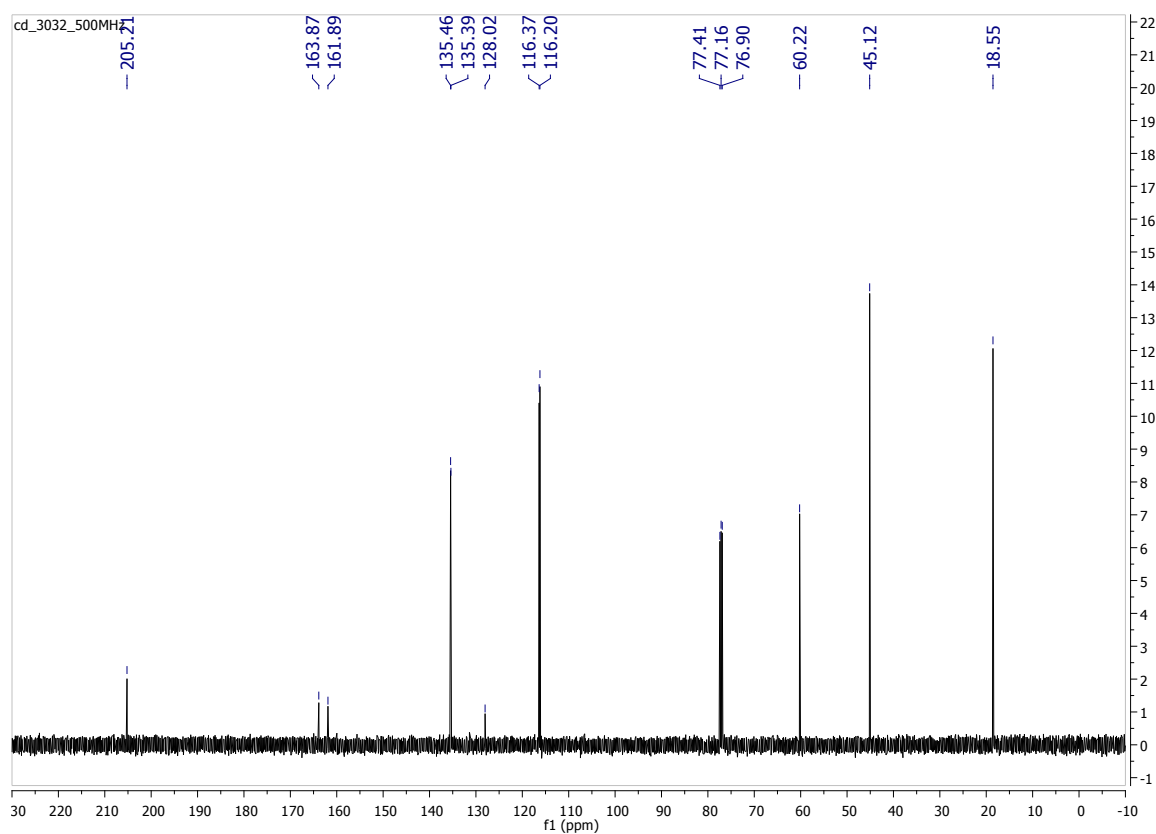
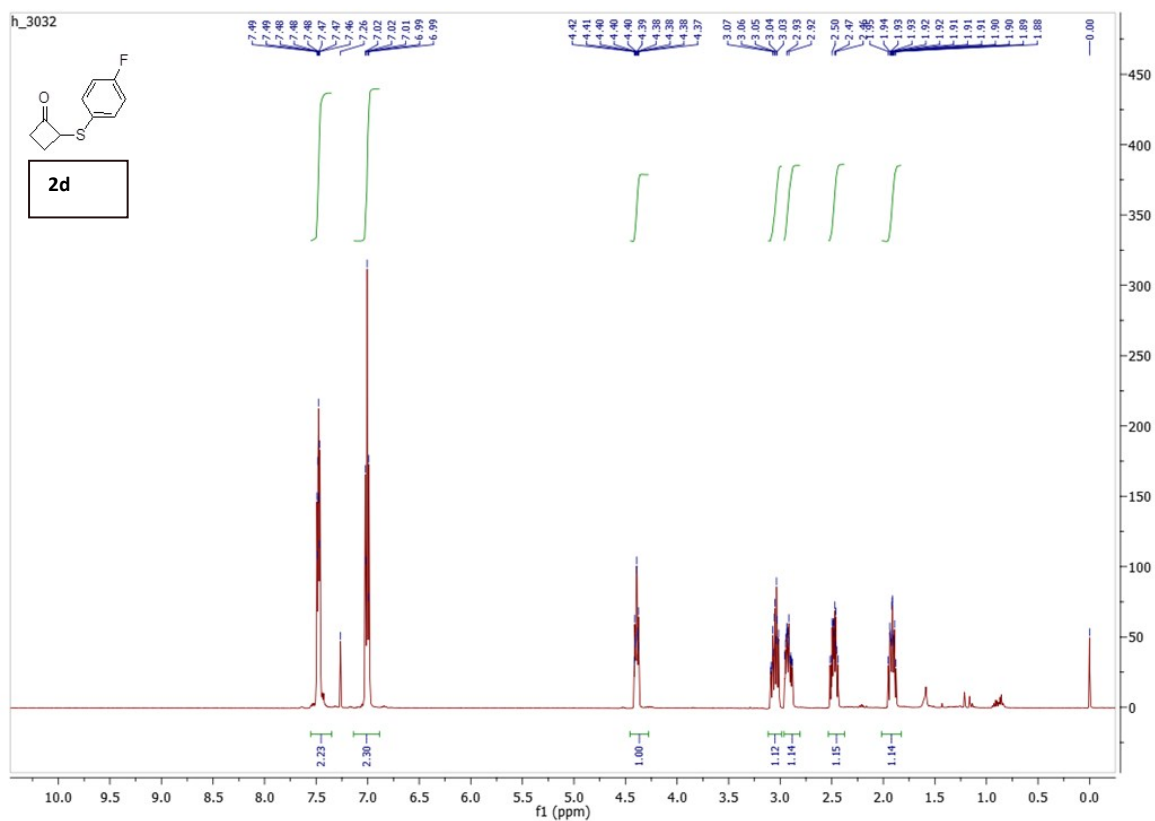


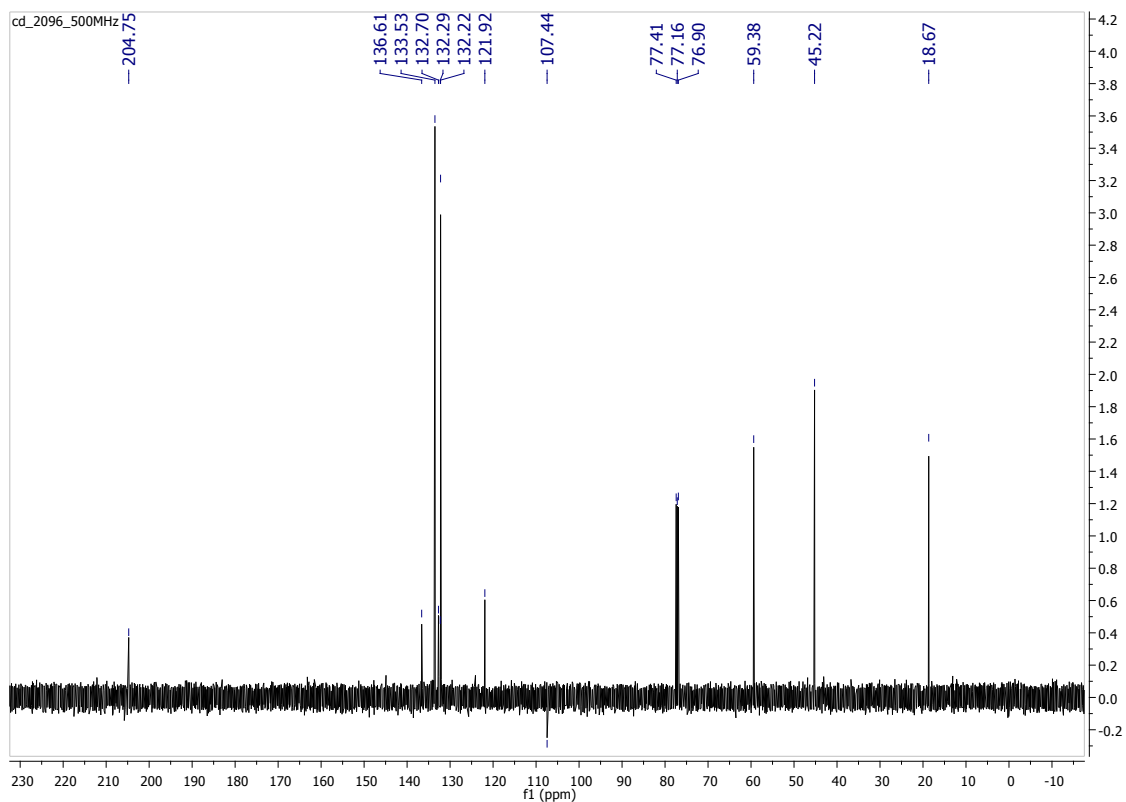
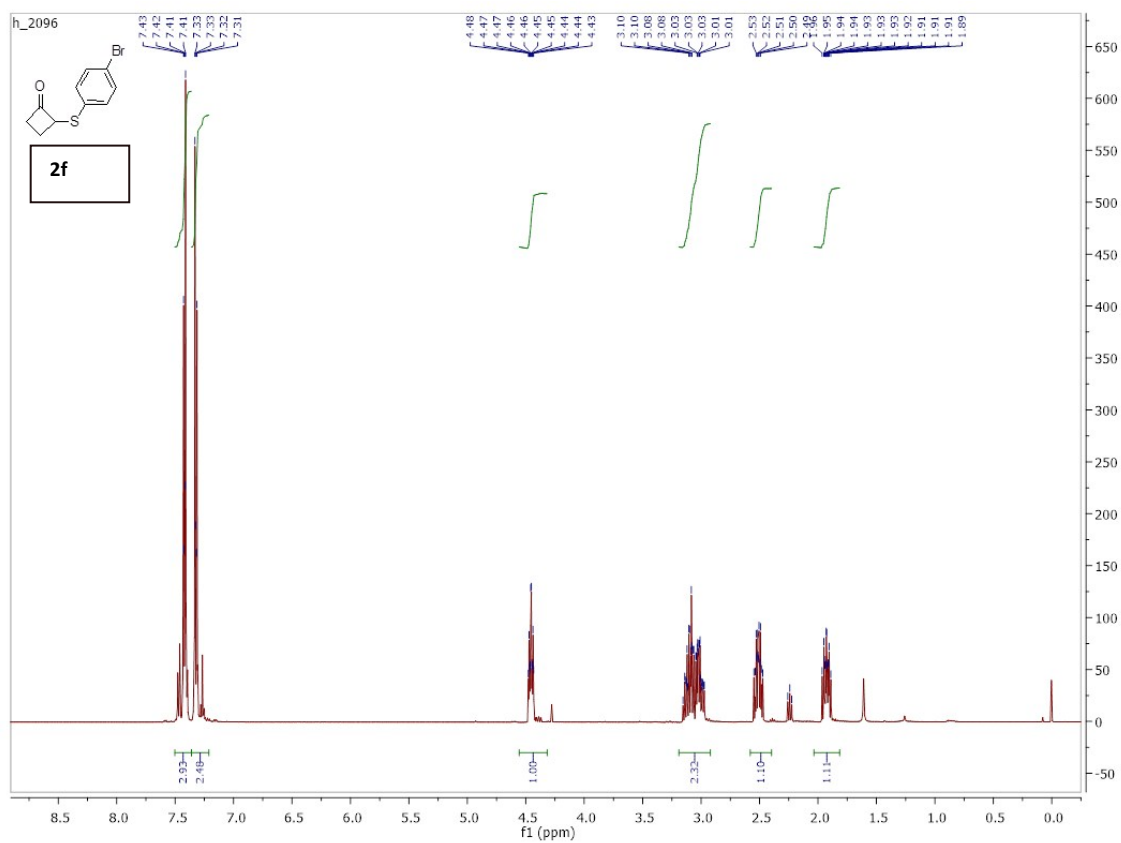
¹H and ¹³C NMR spectra of ketosulfides 2a-g, 4a-h, 6a-d and 7a-i

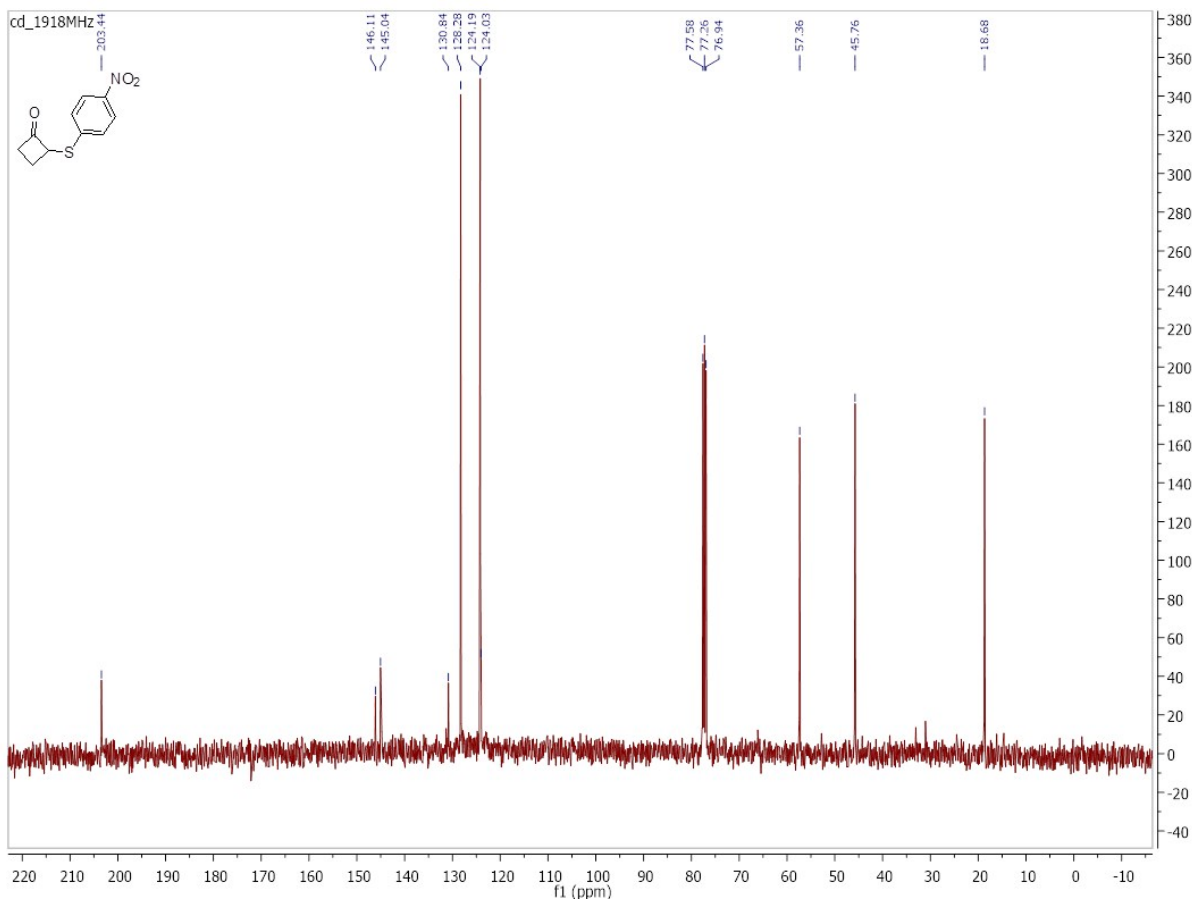
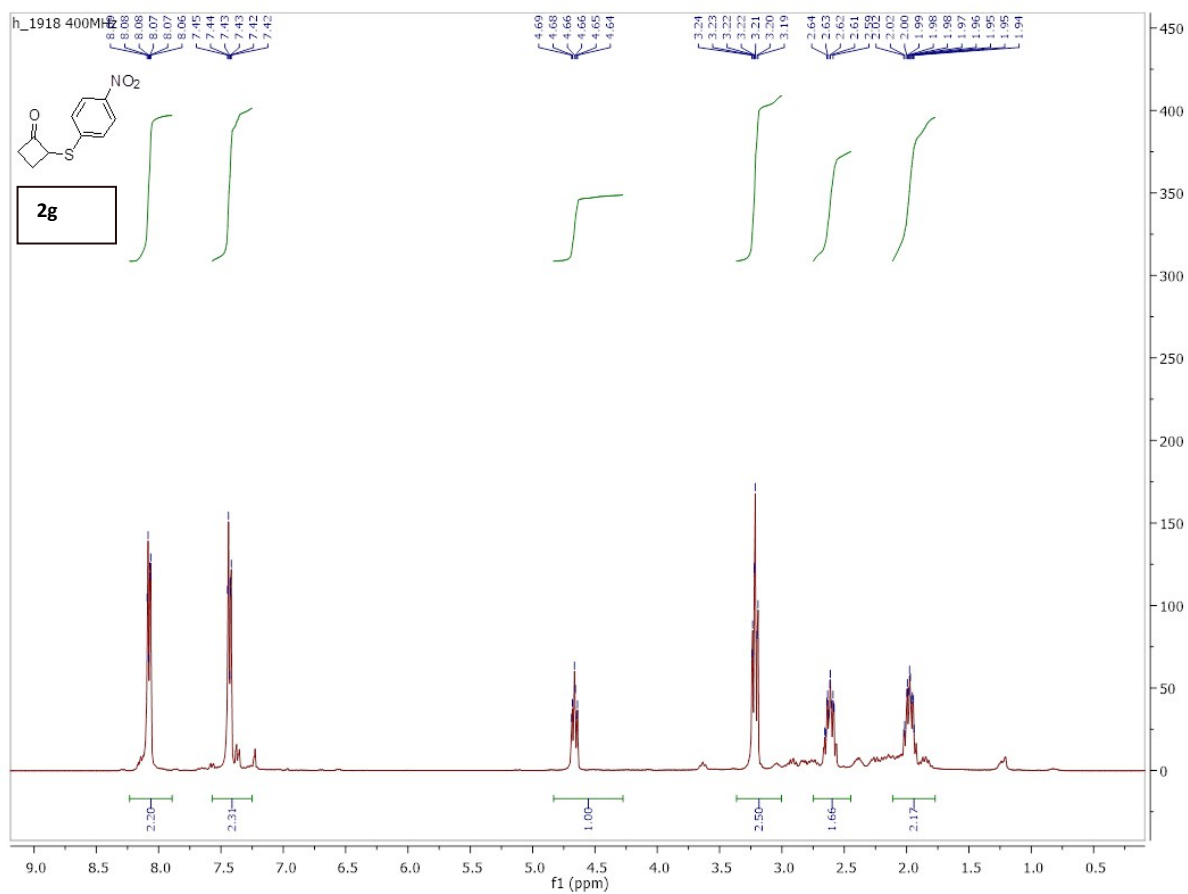


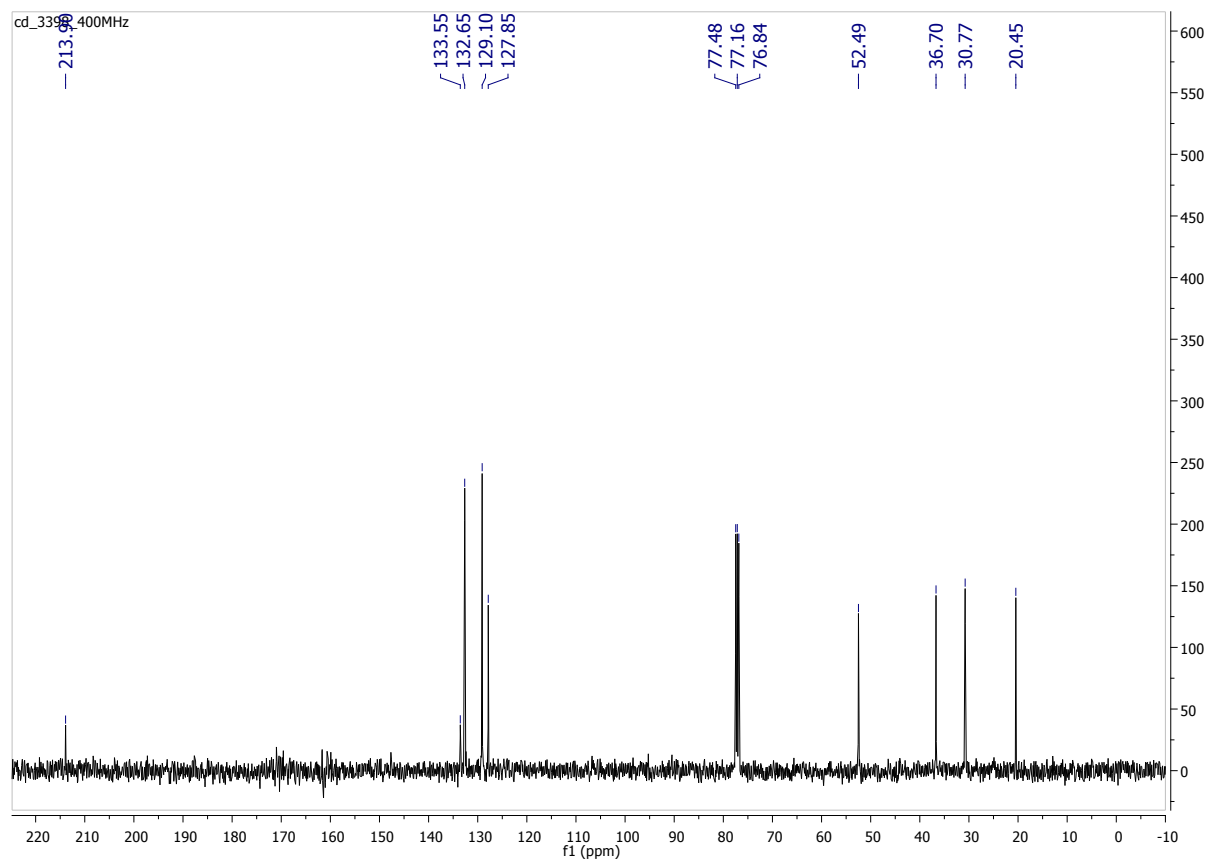
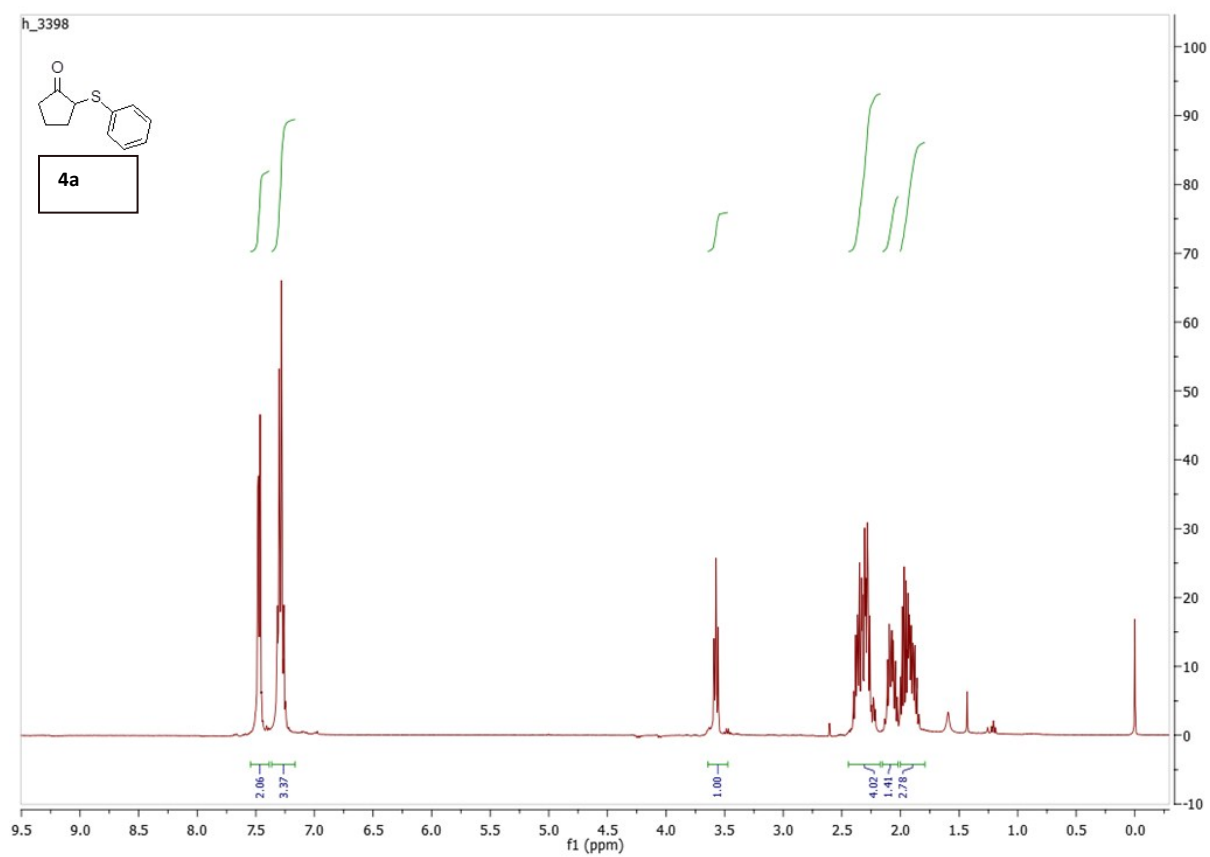


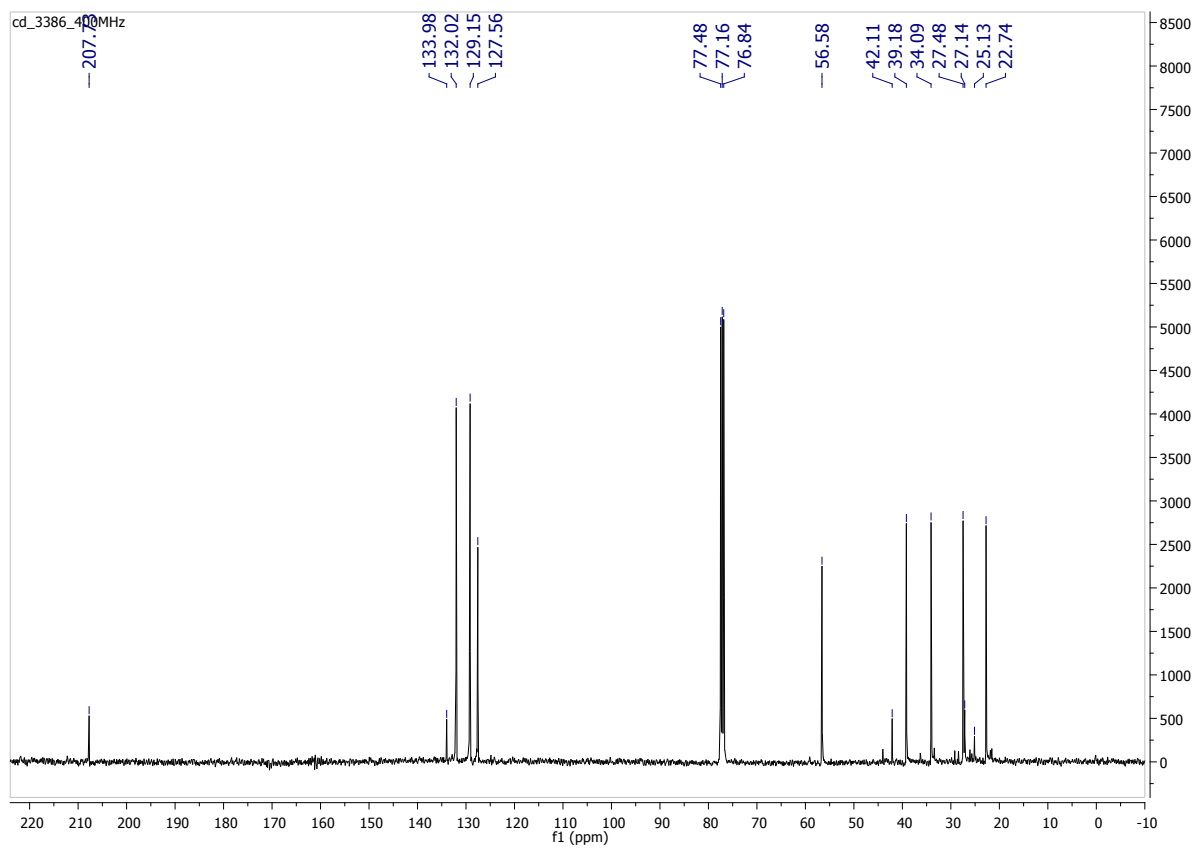
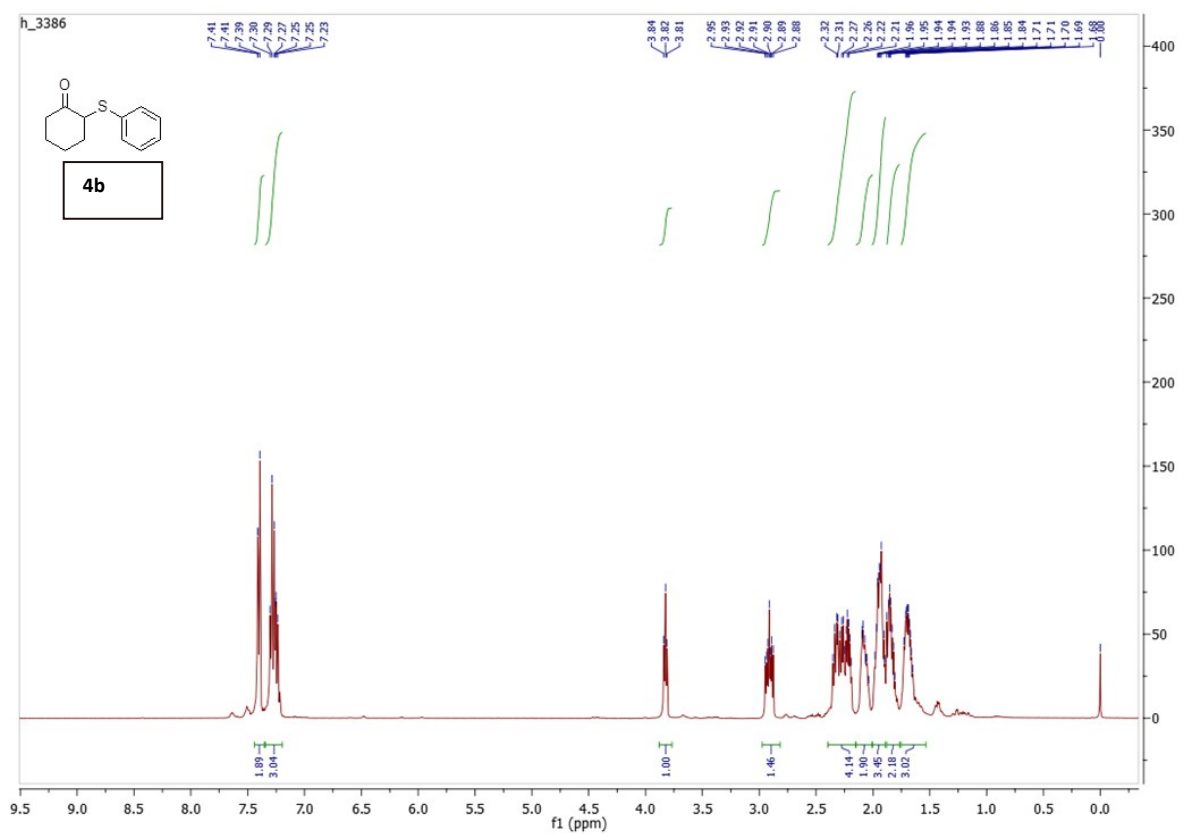


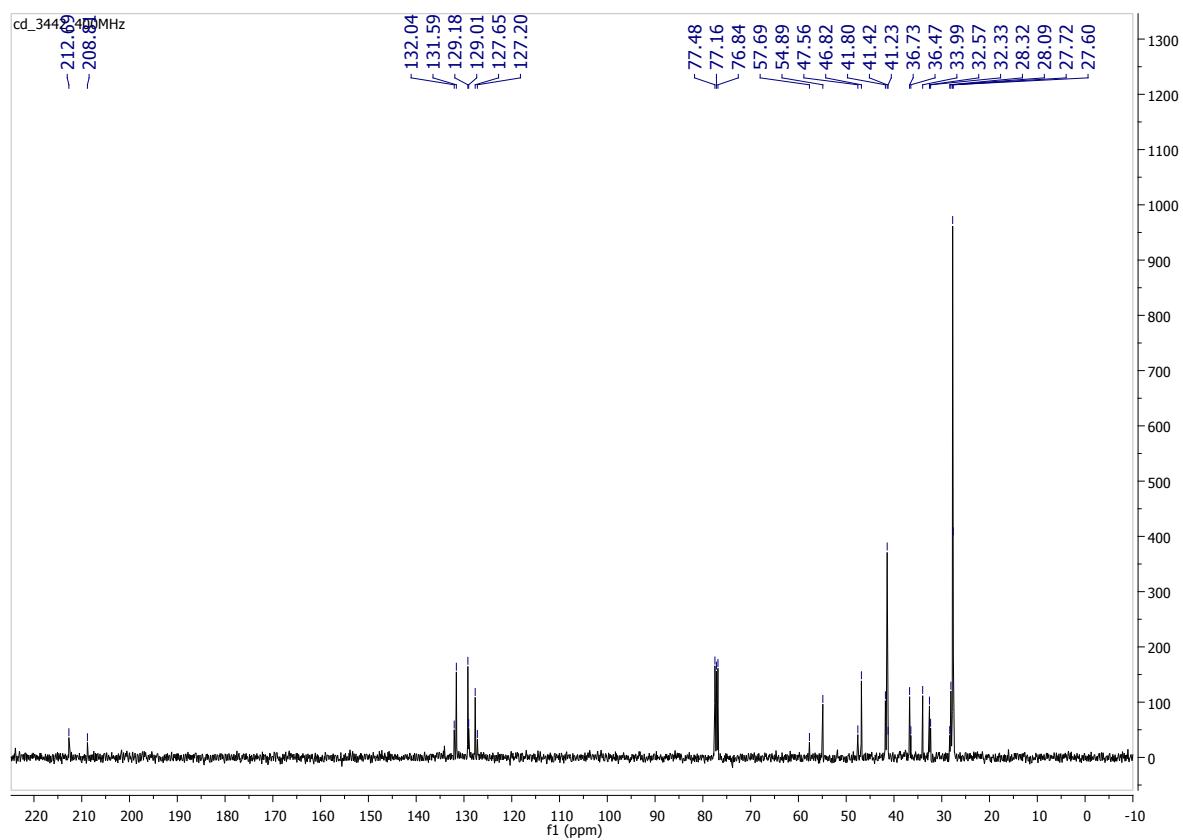
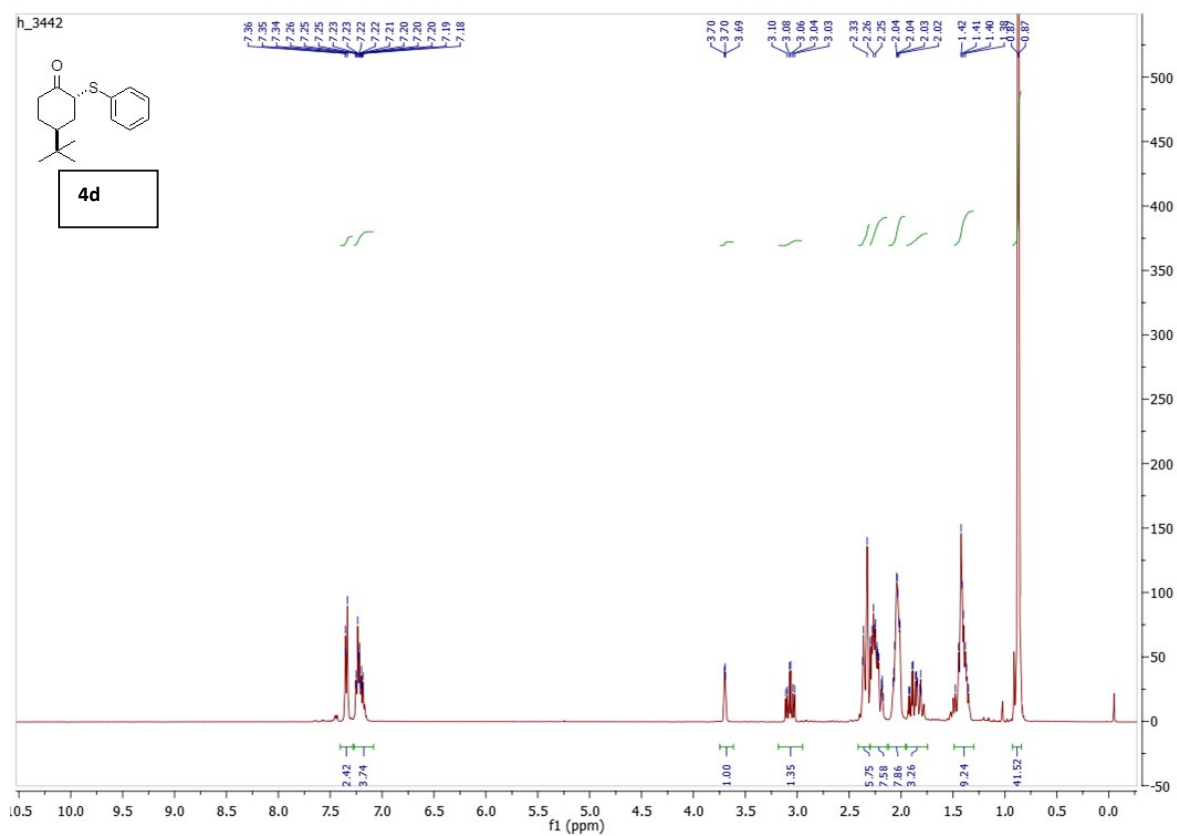


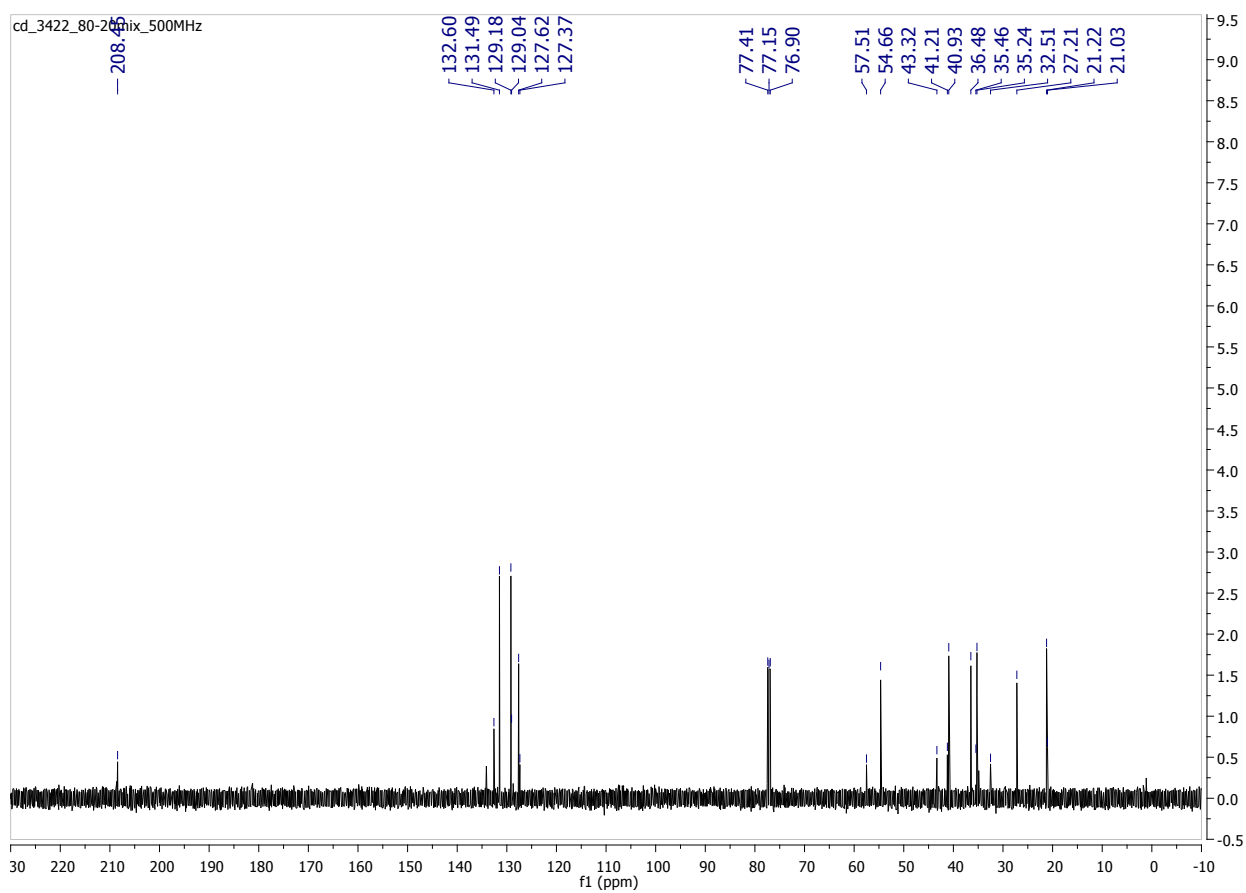
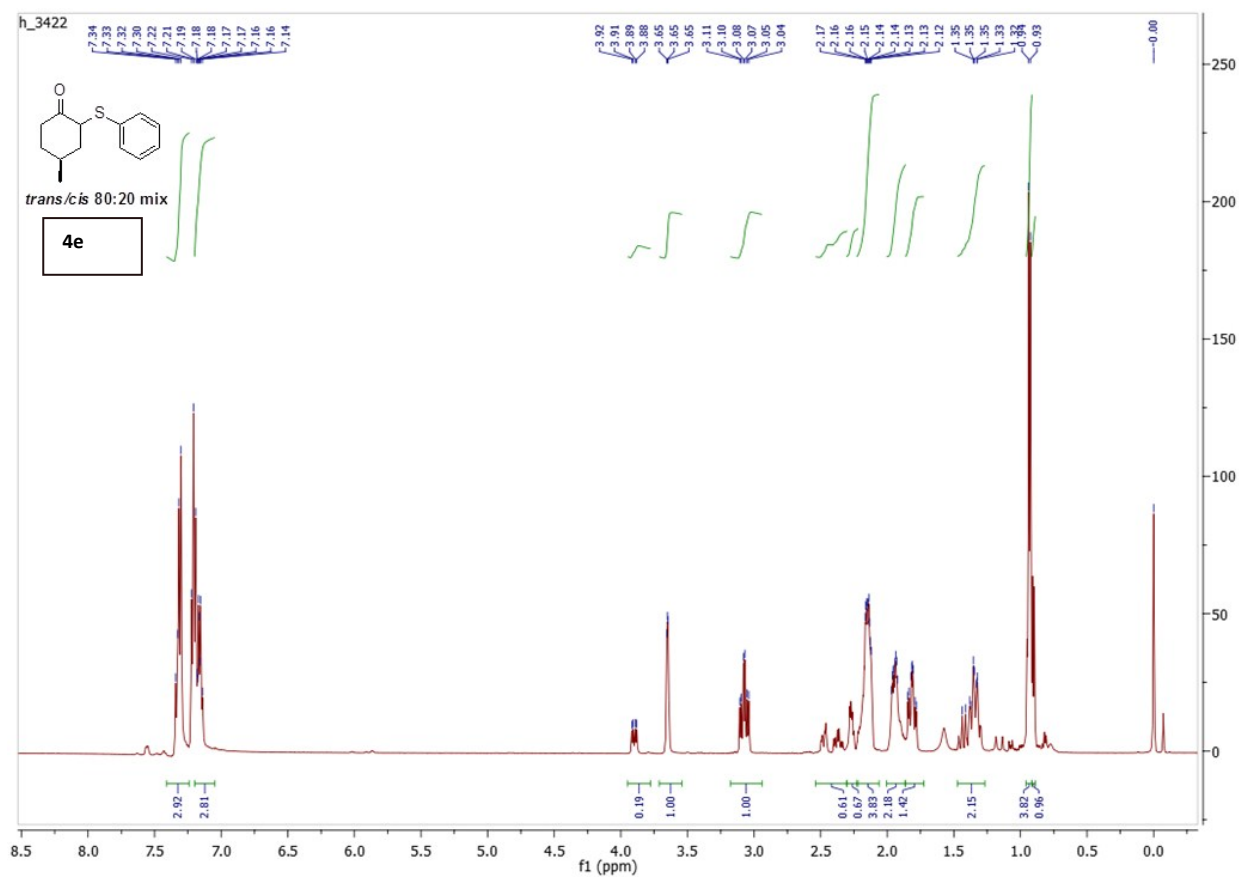


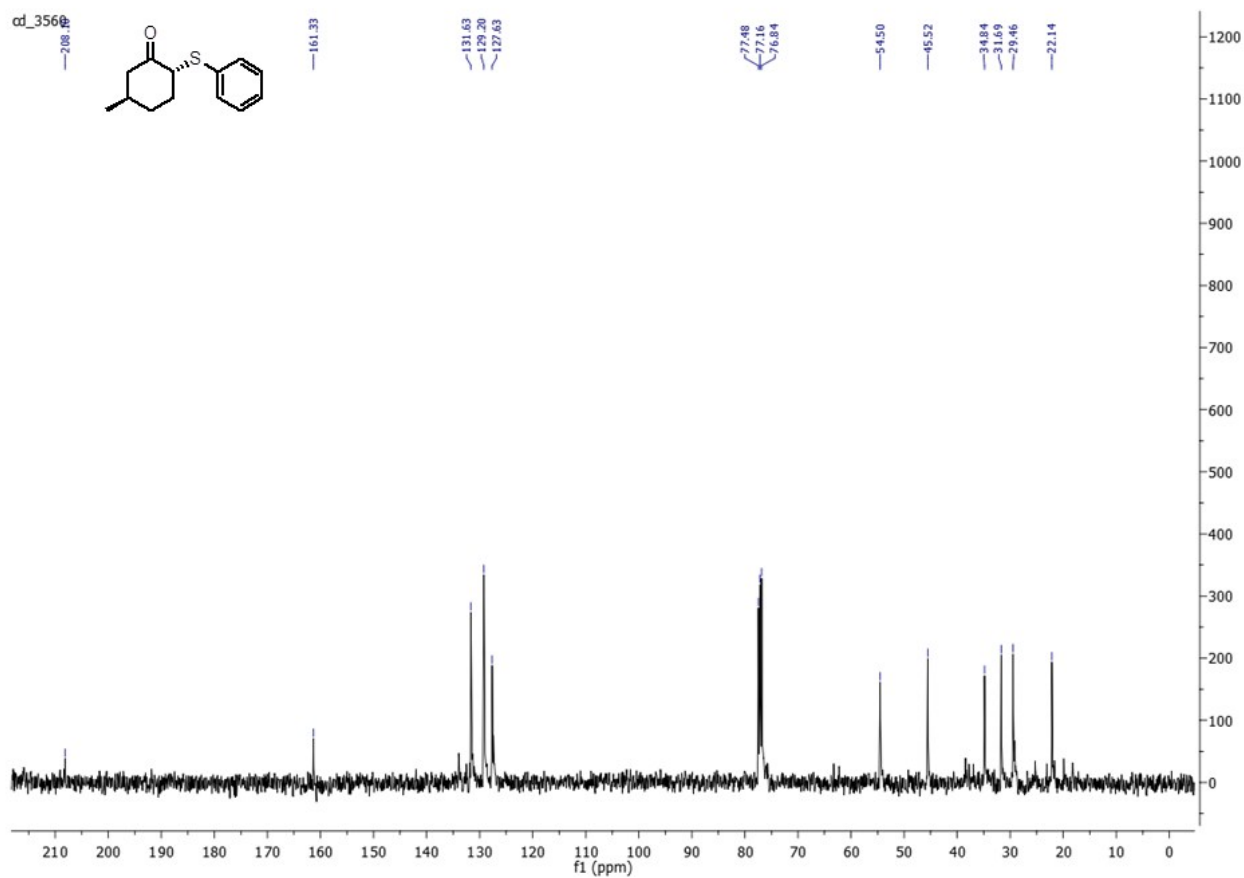
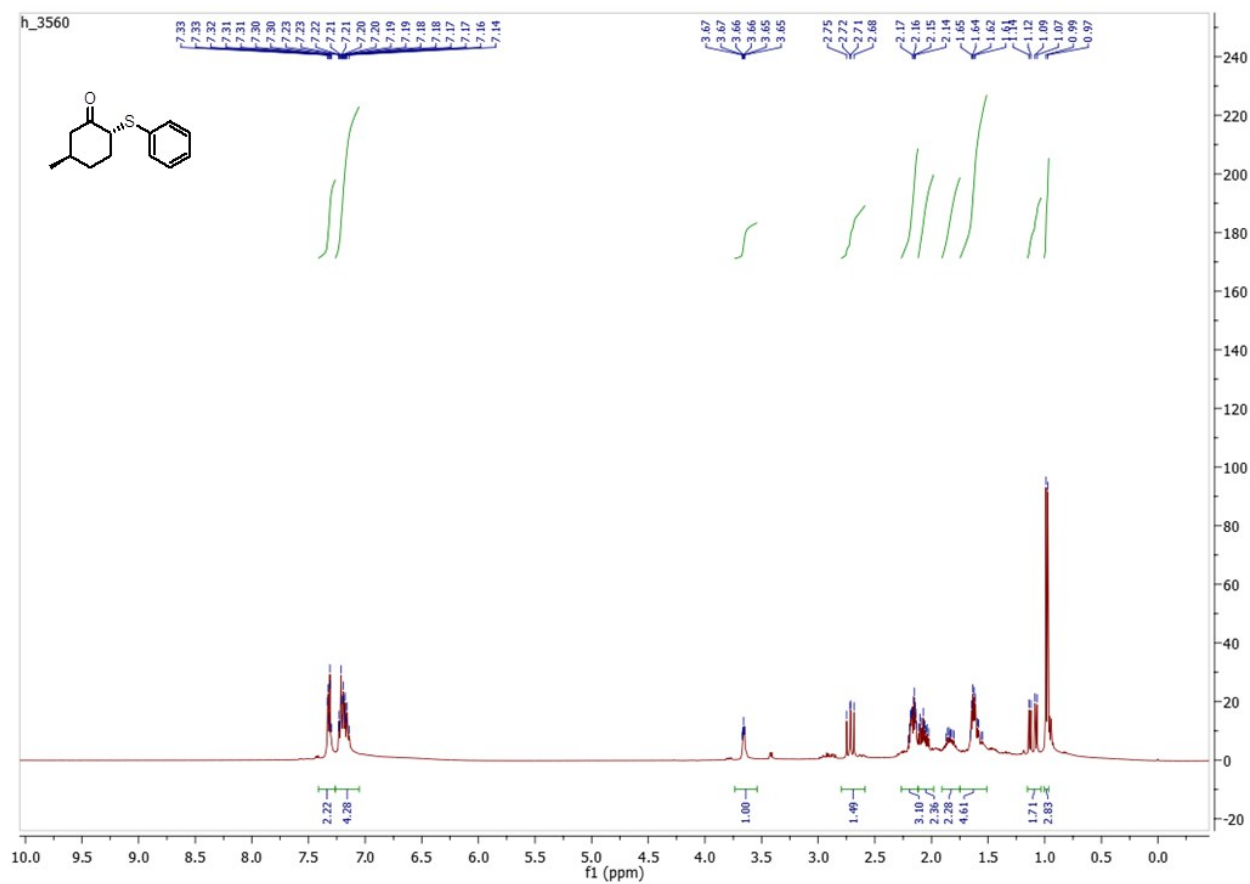


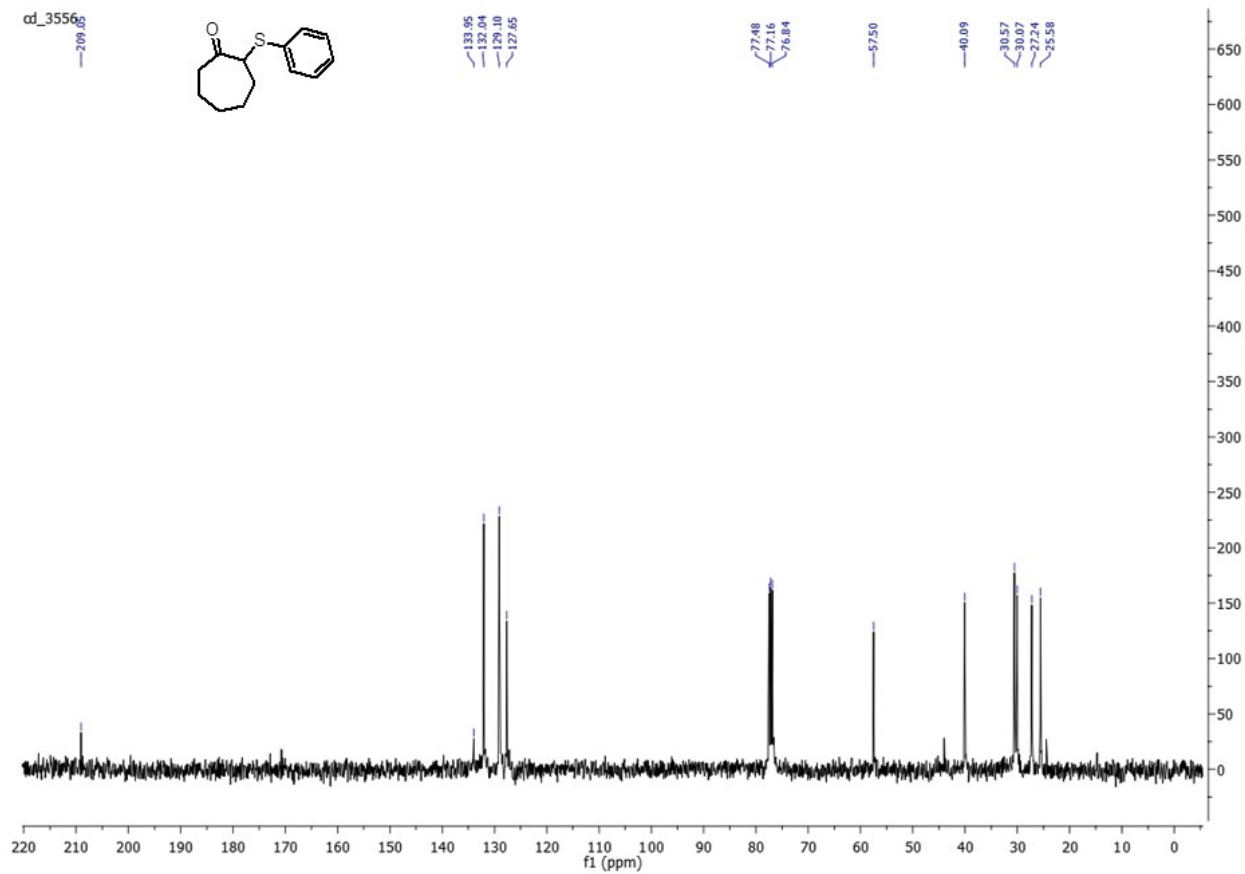
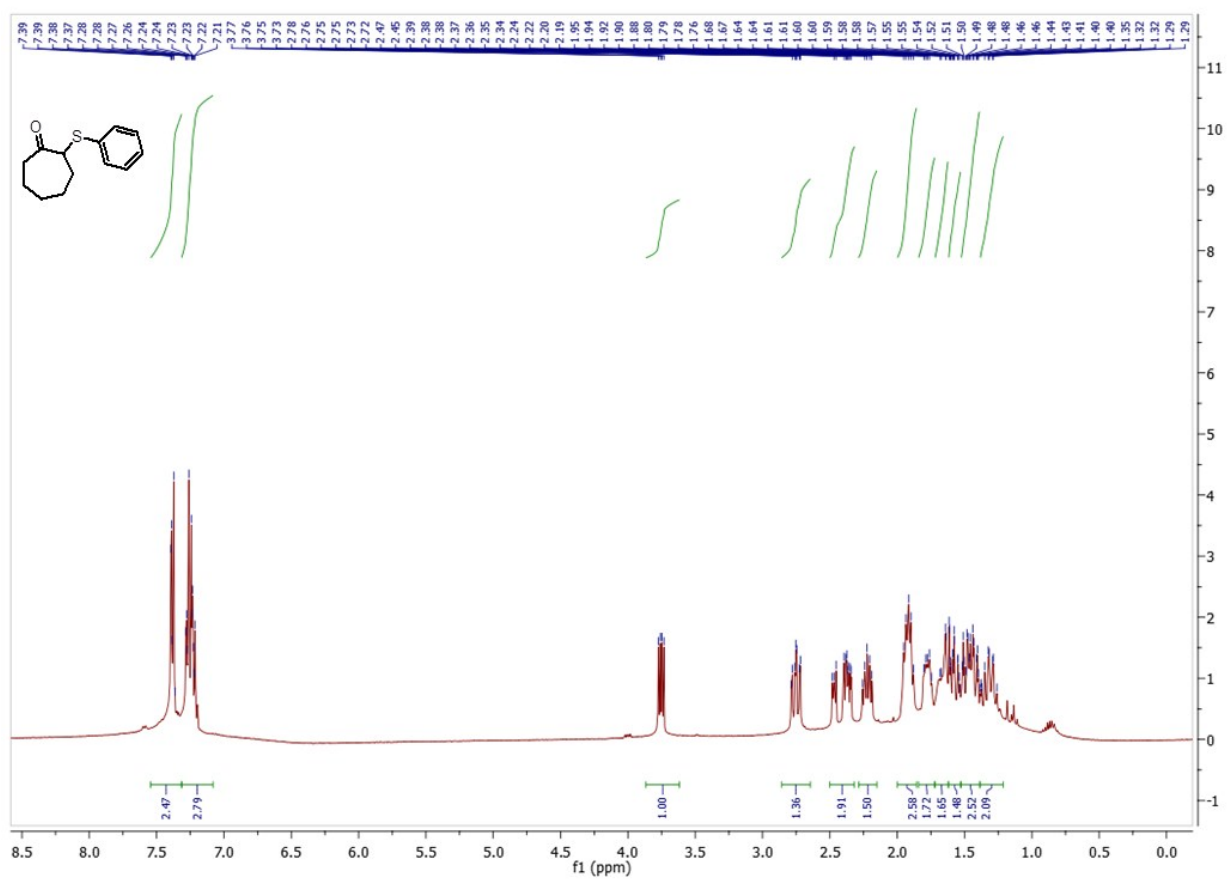


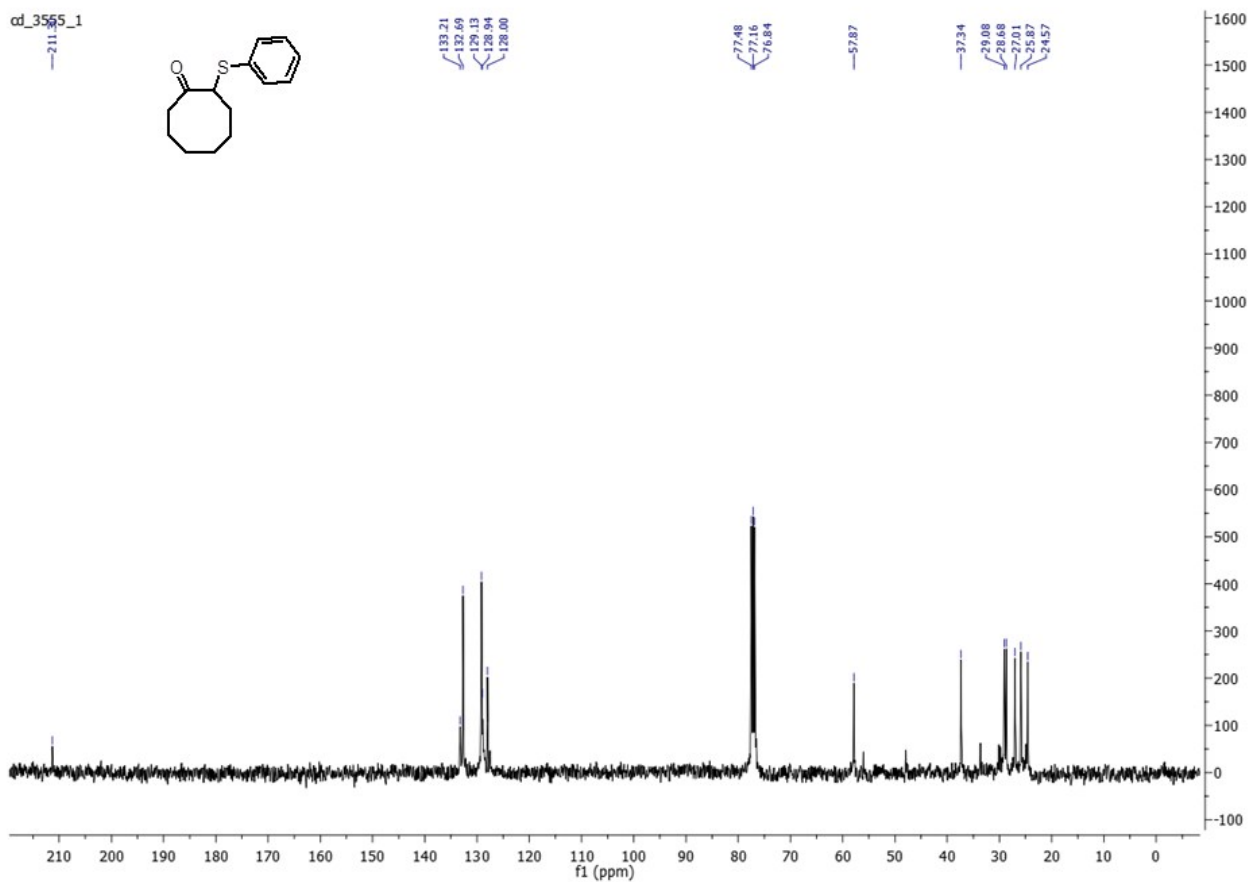
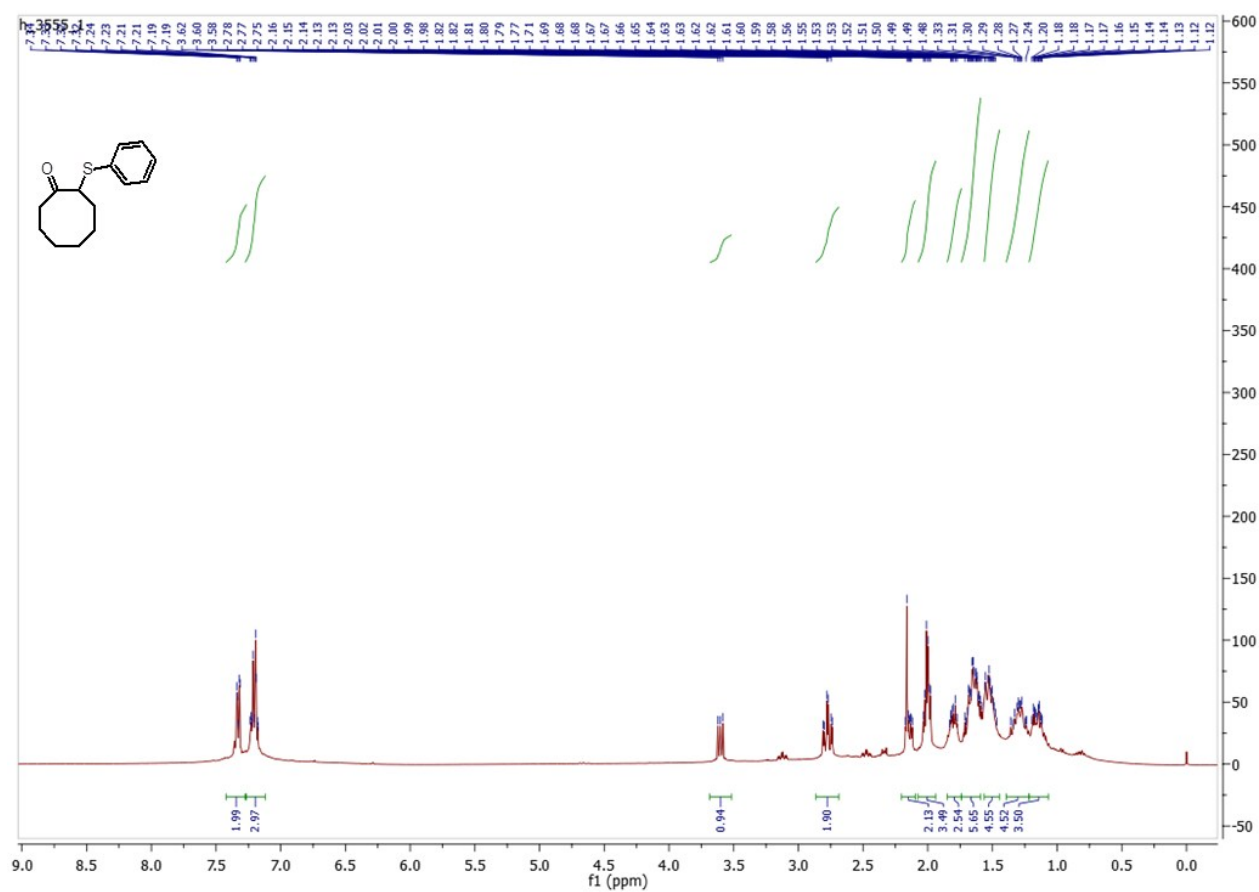


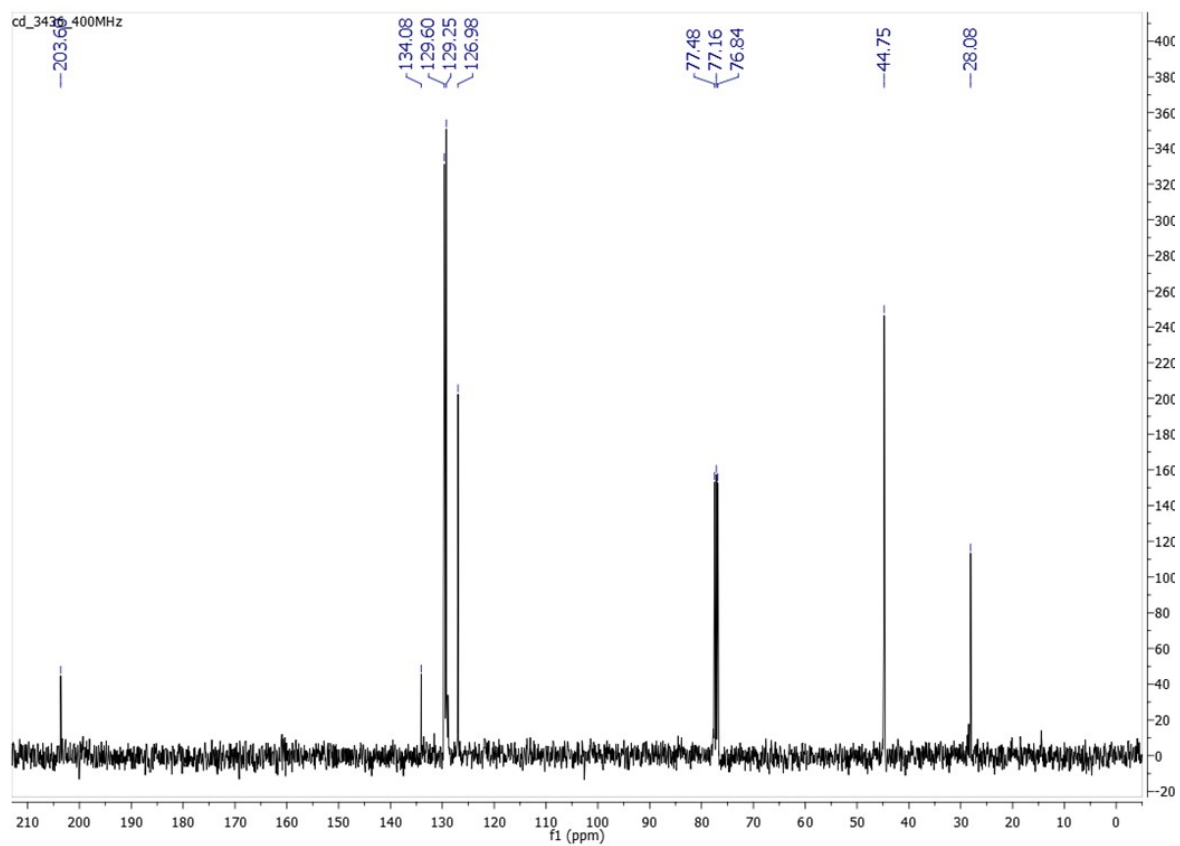
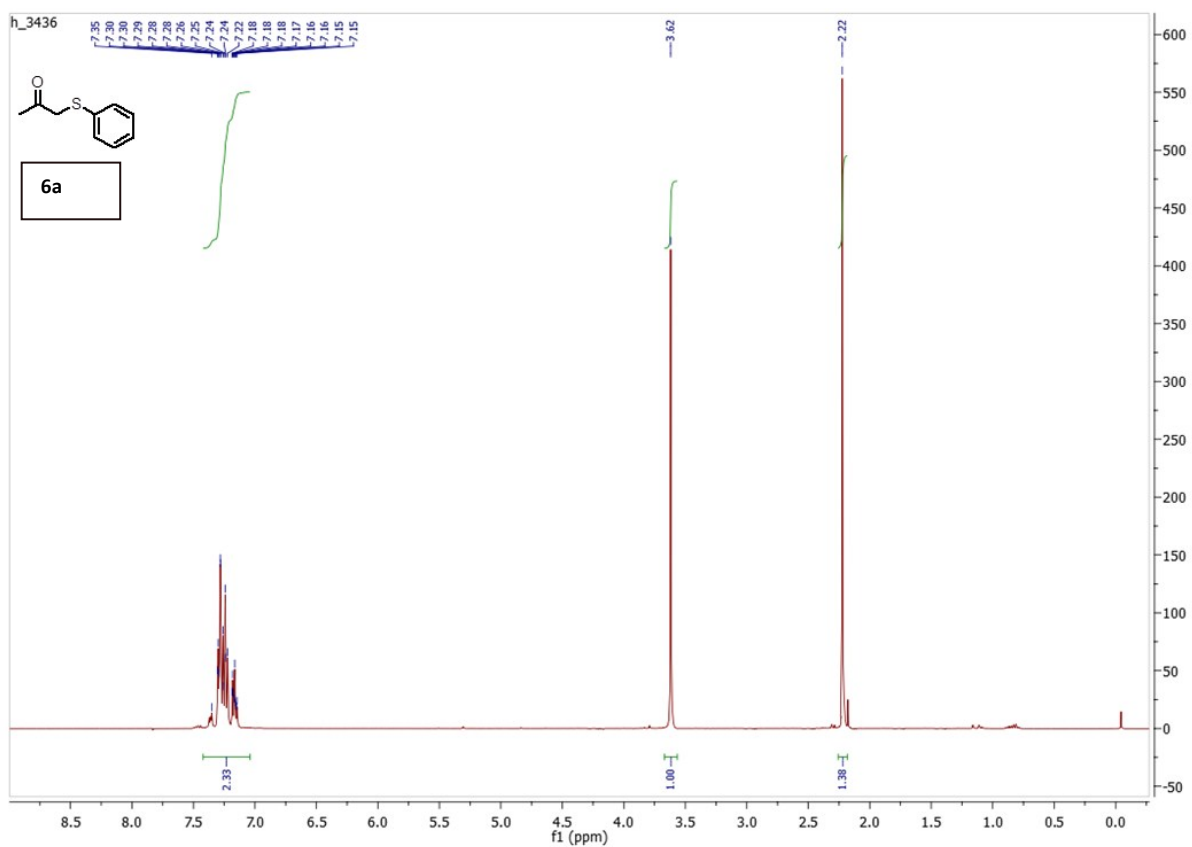


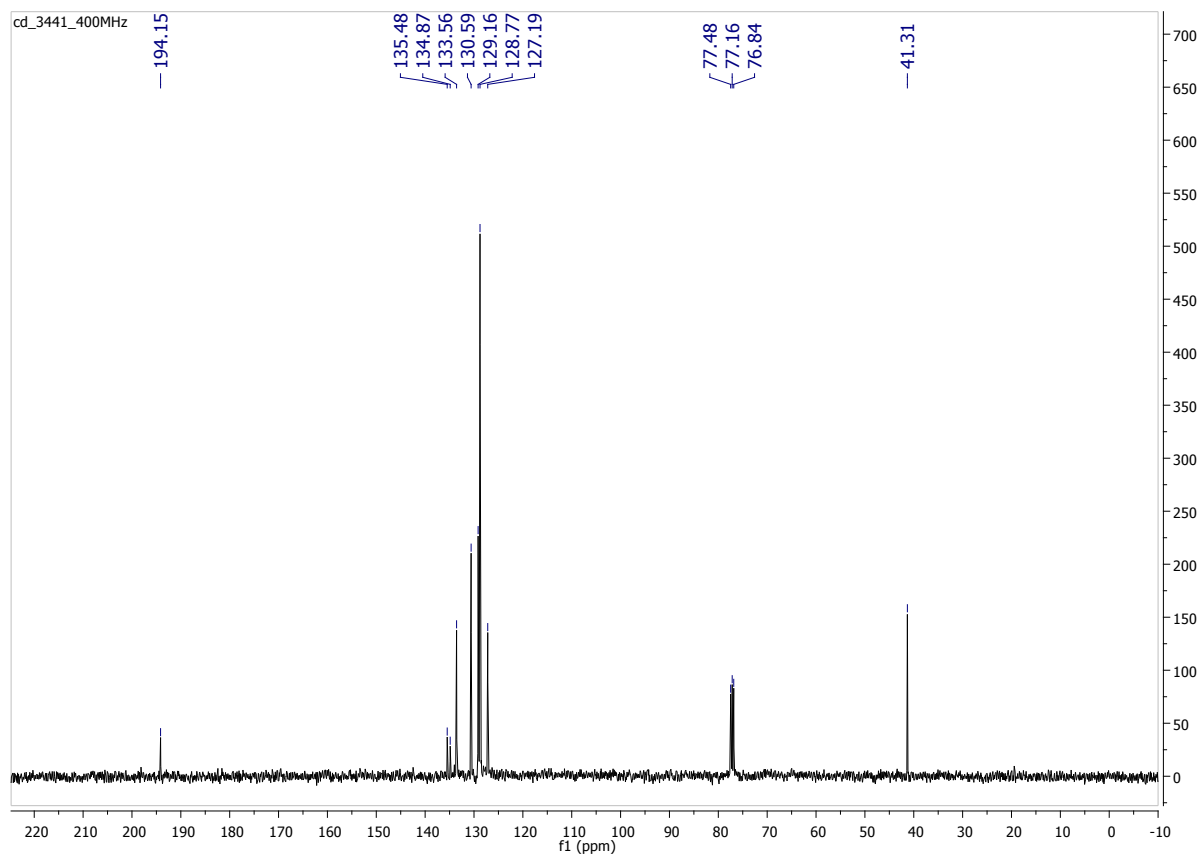
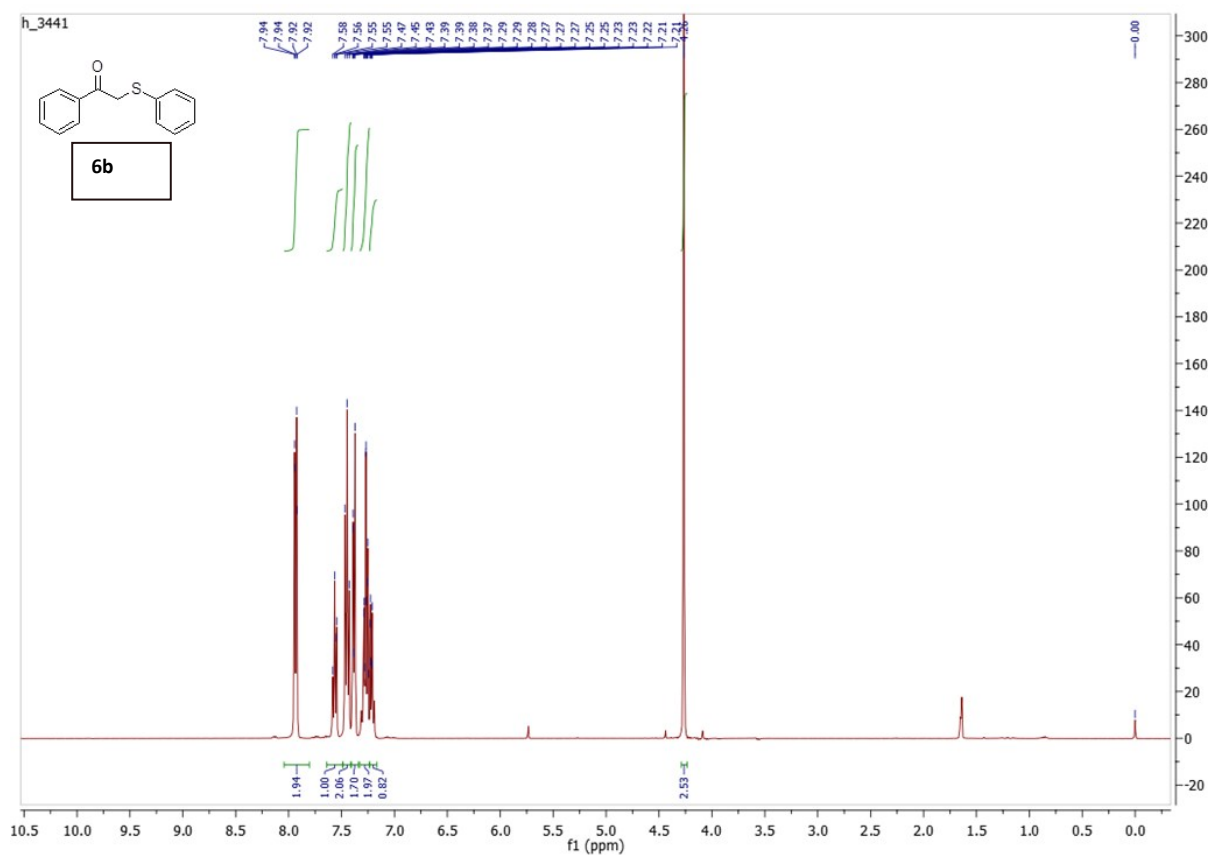


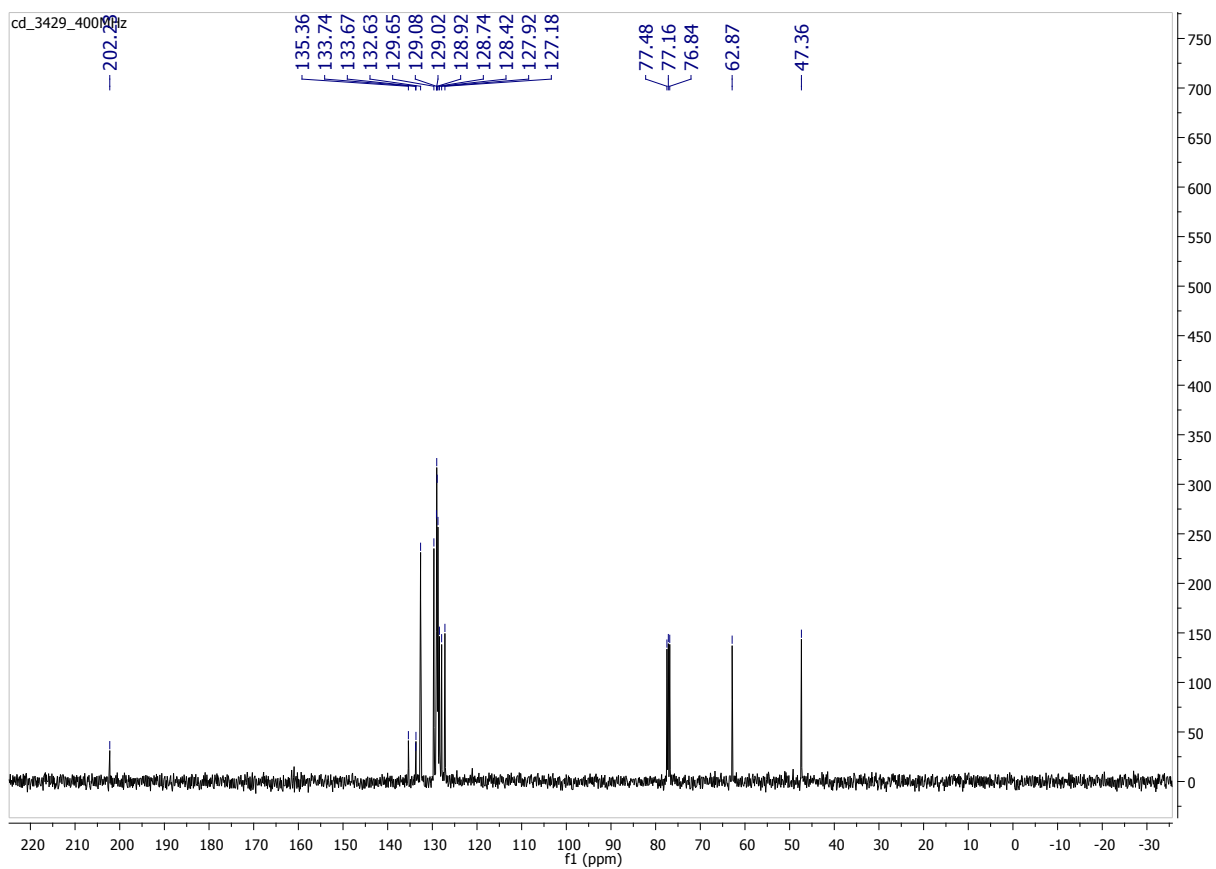
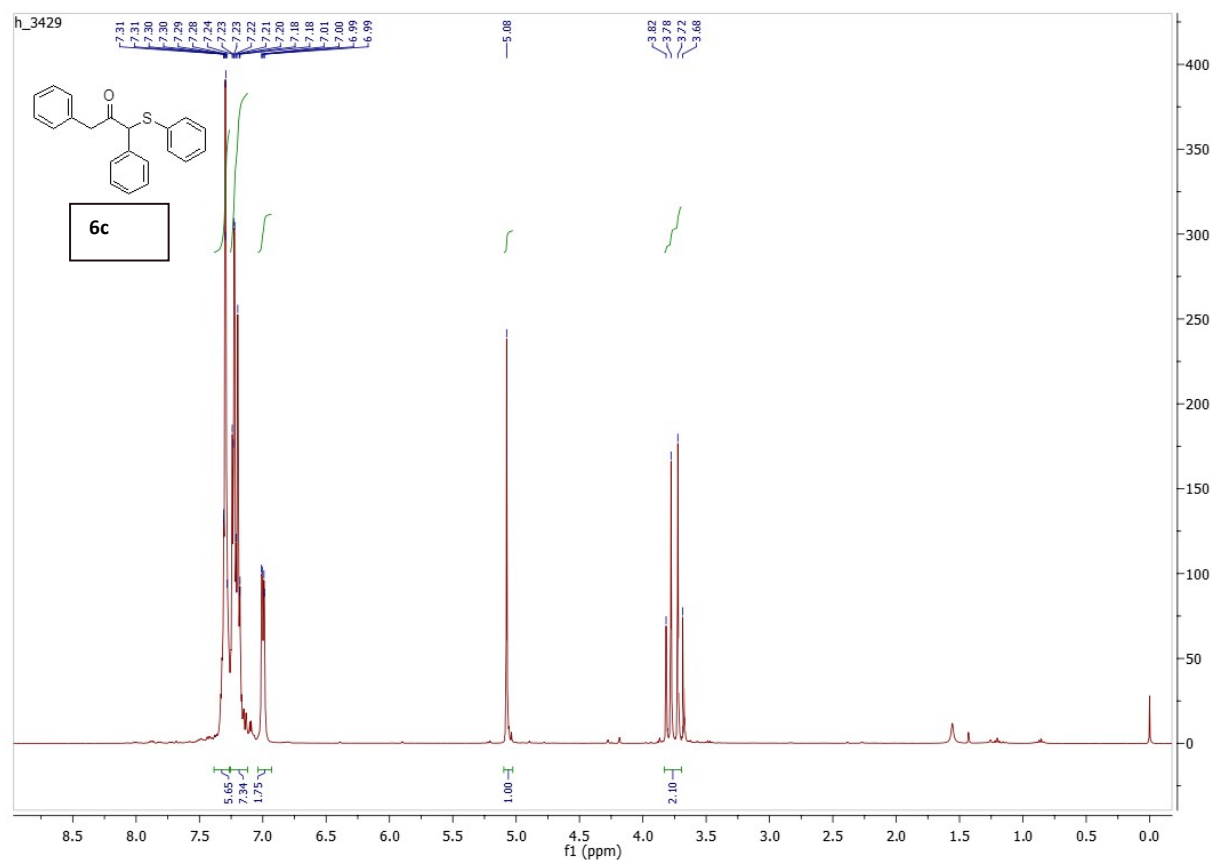


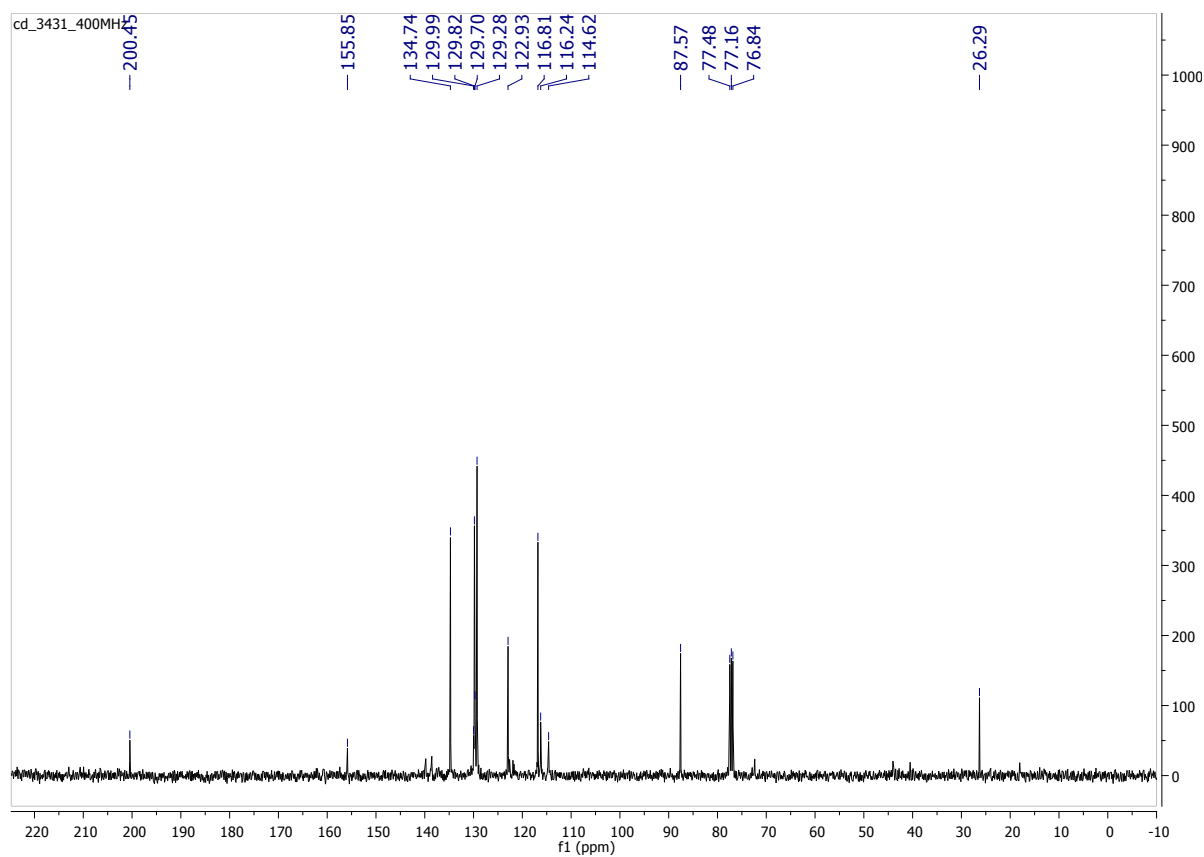
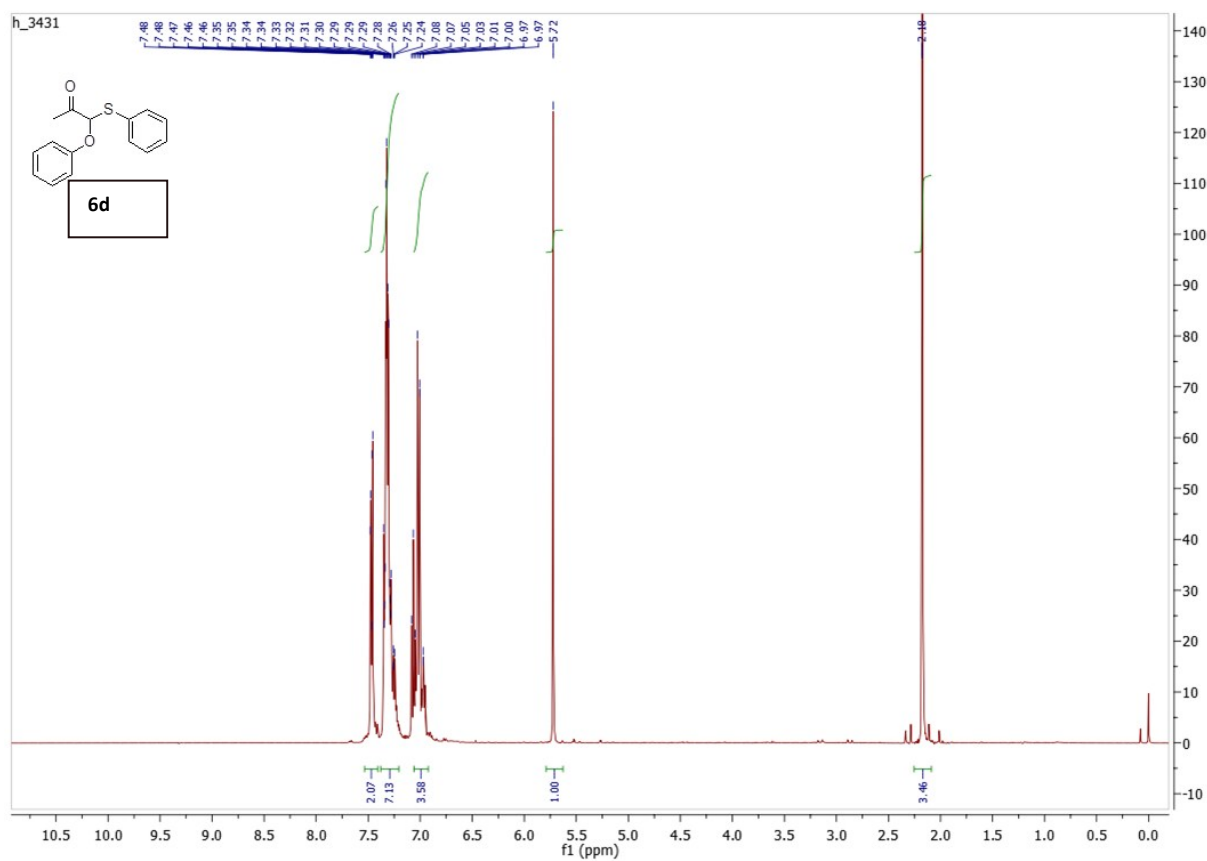


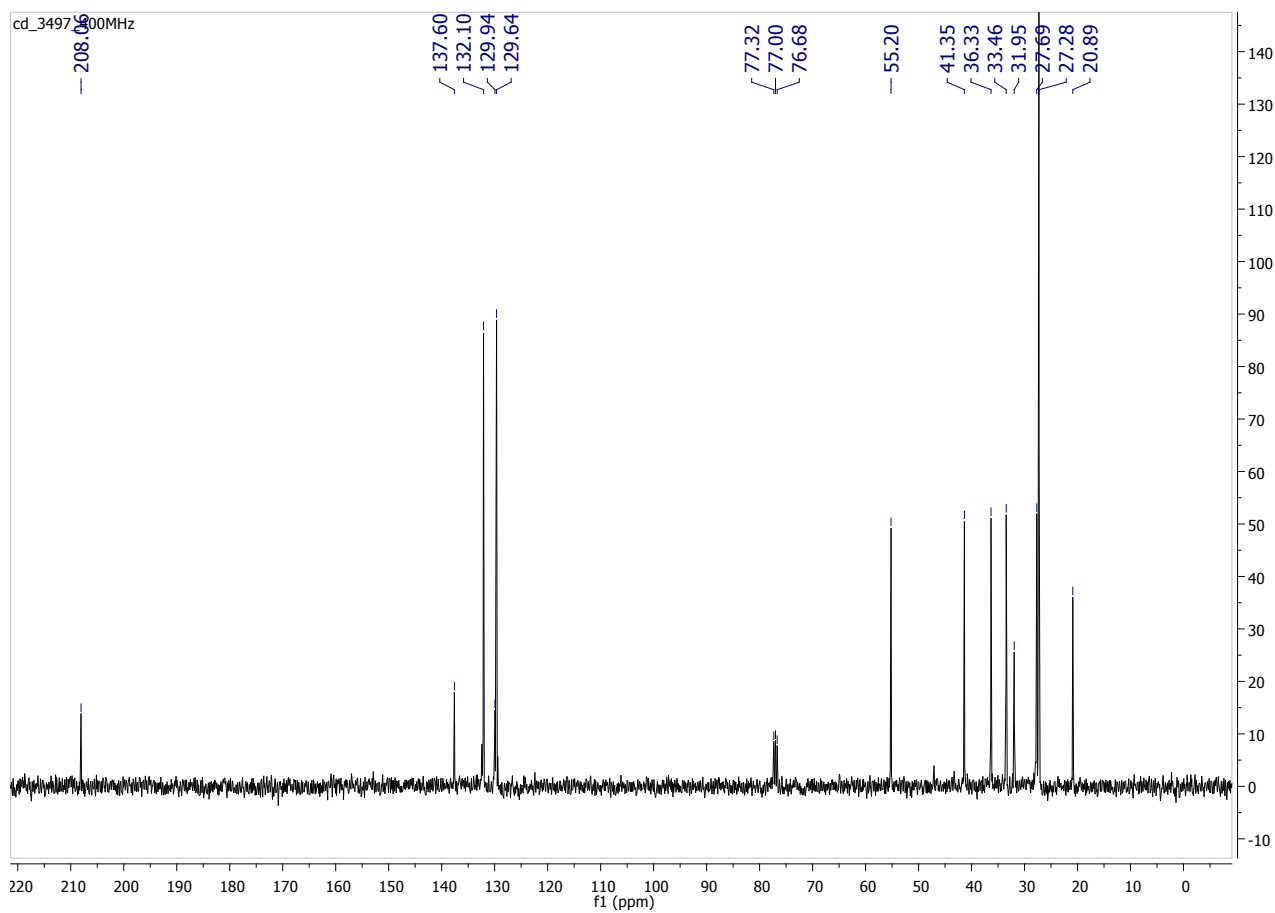
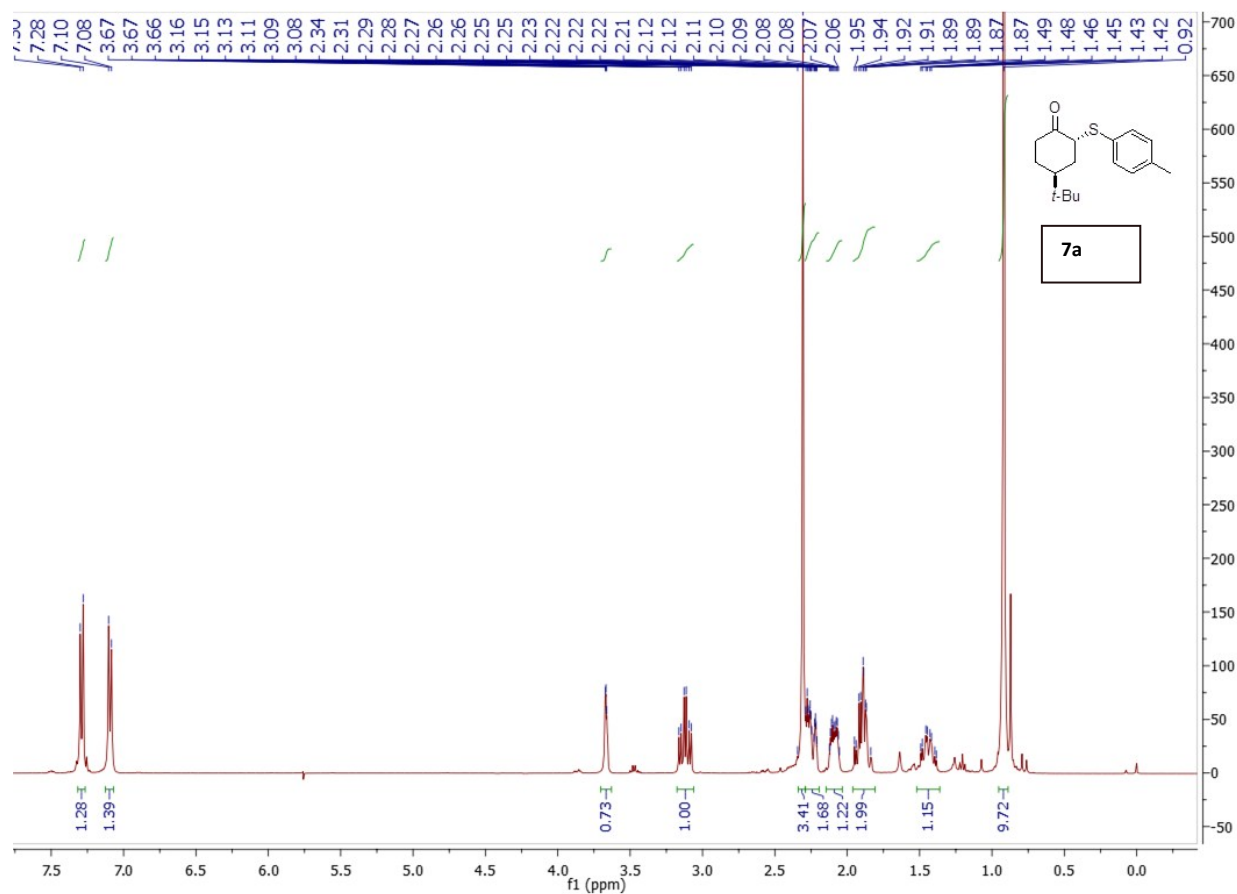


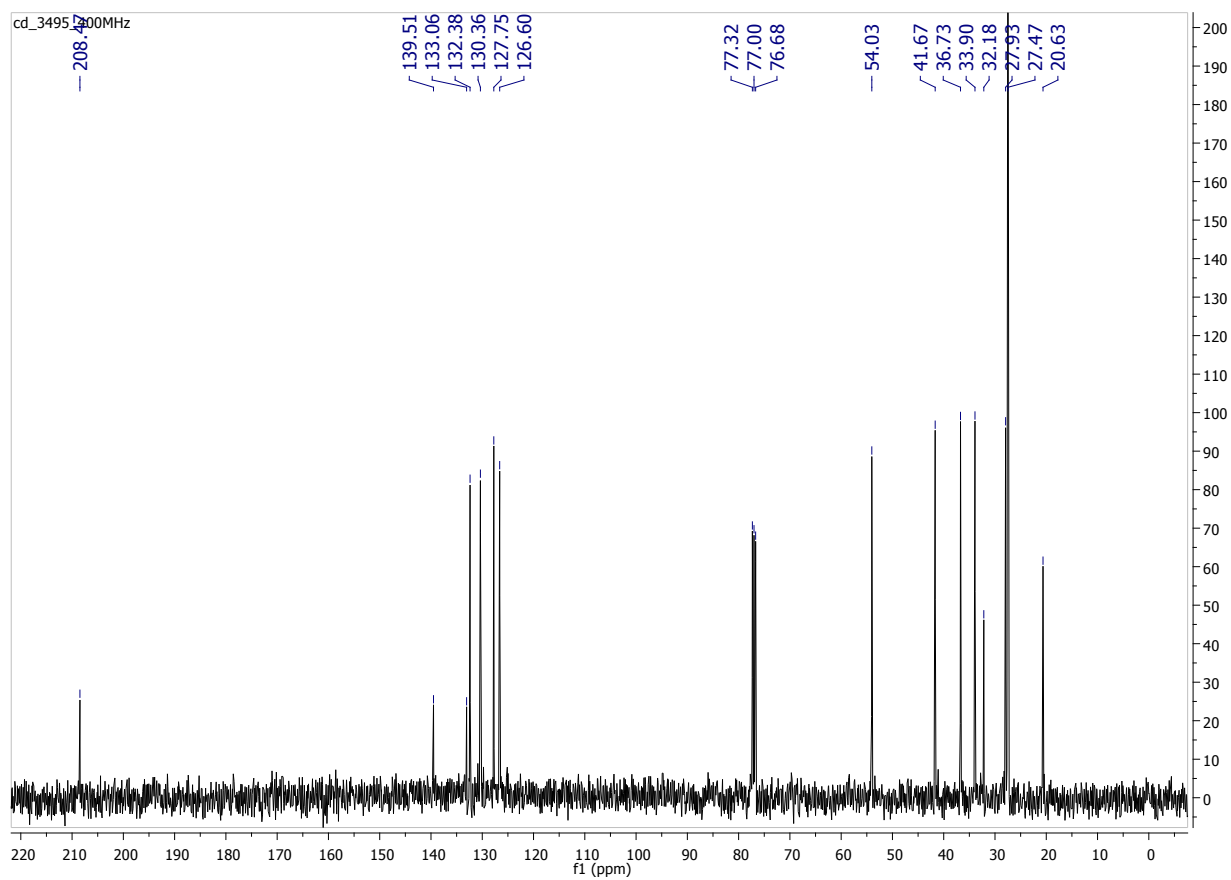
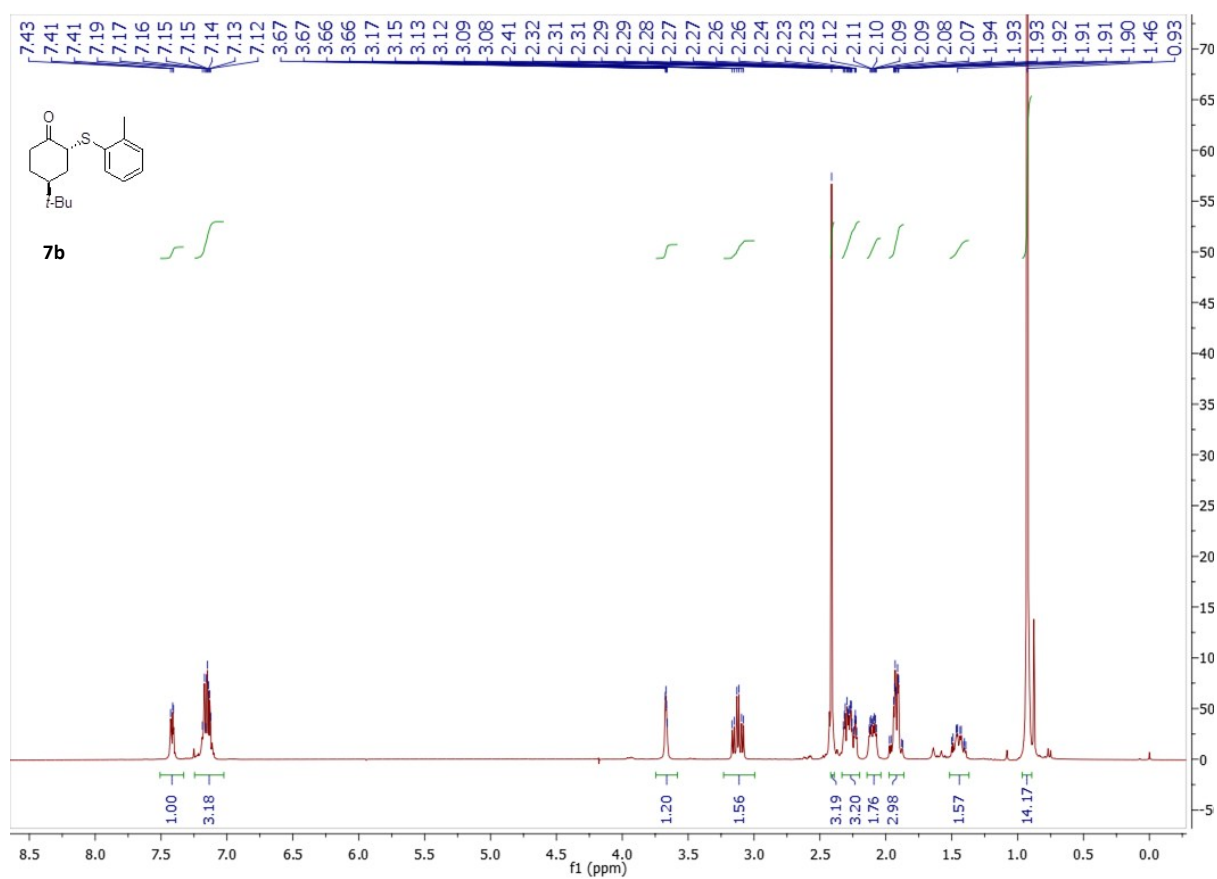


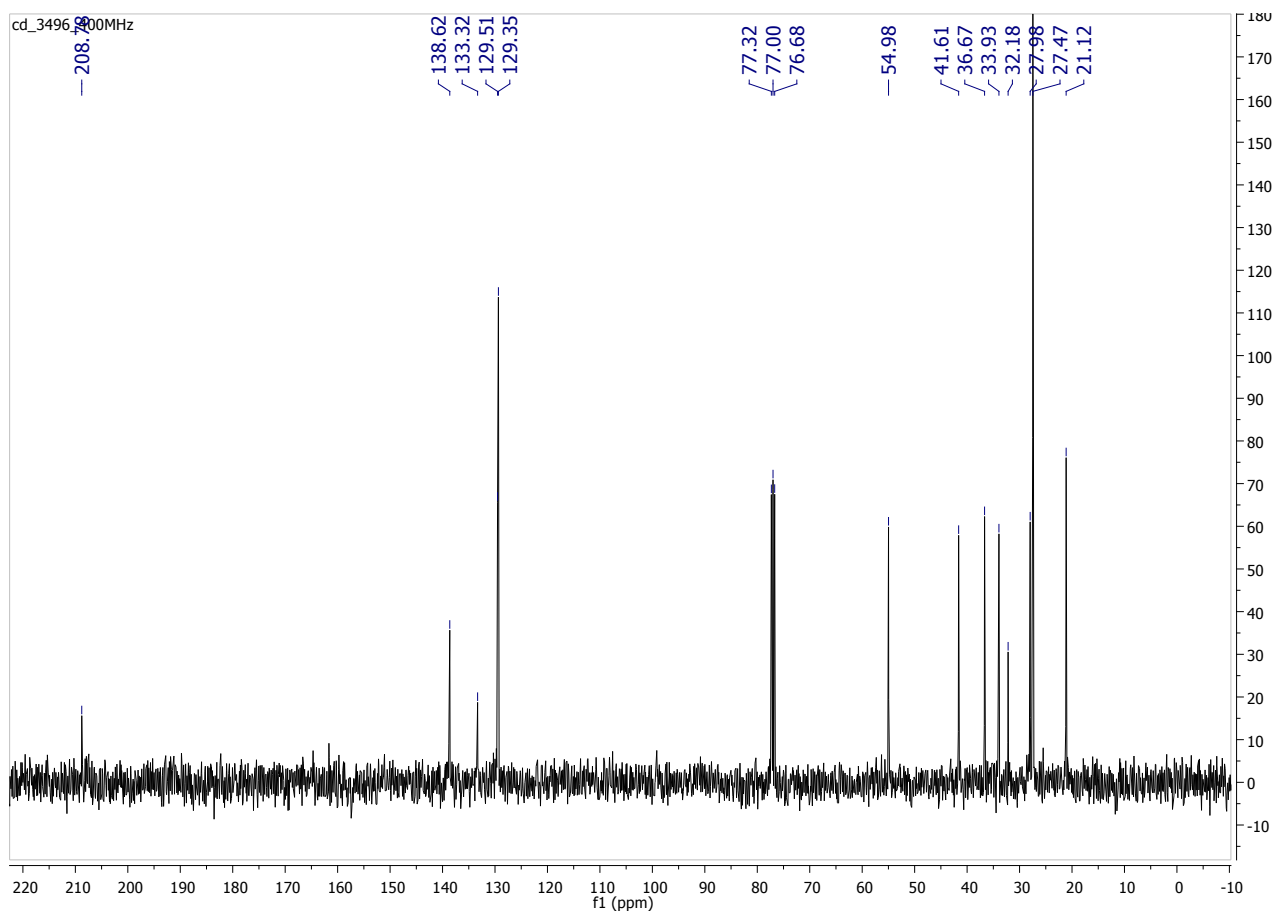
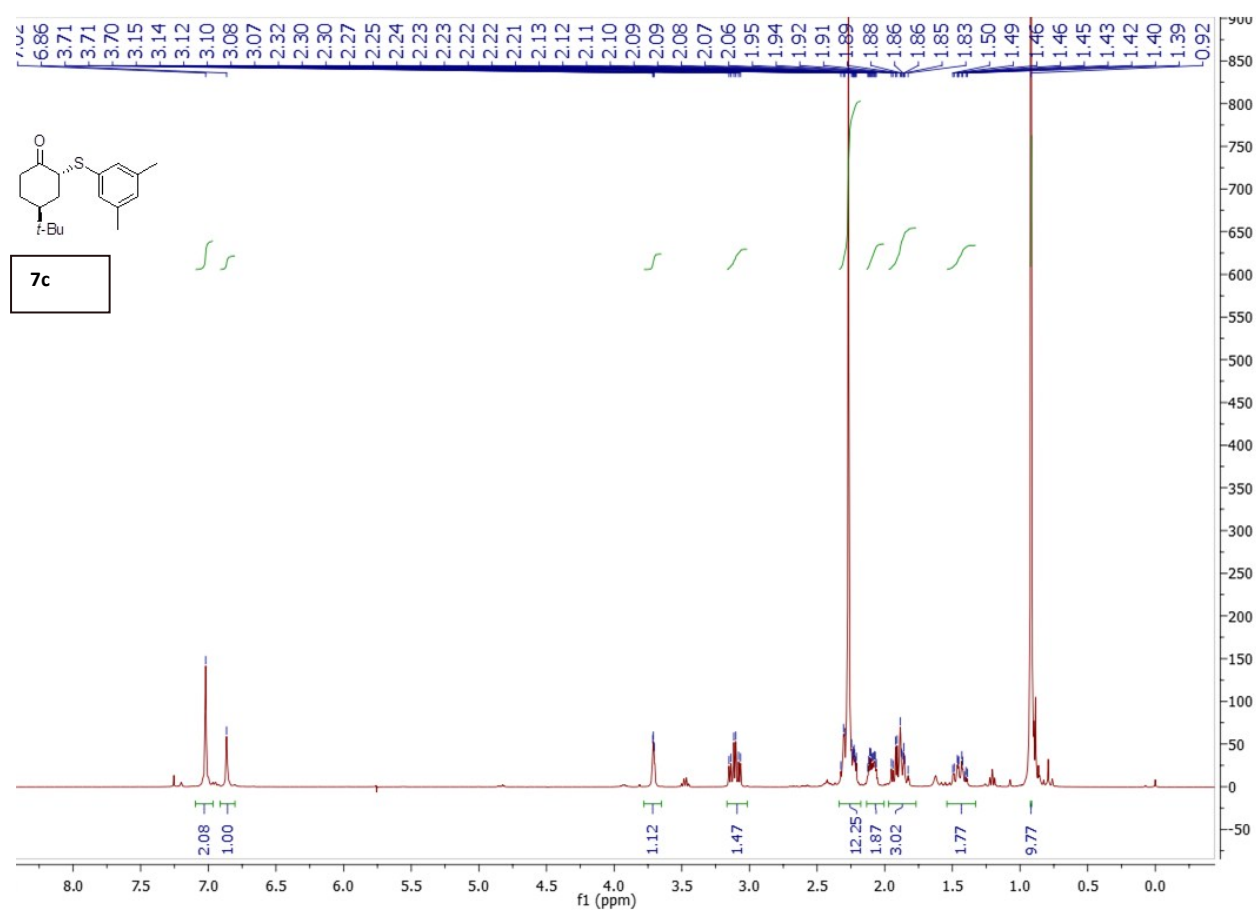


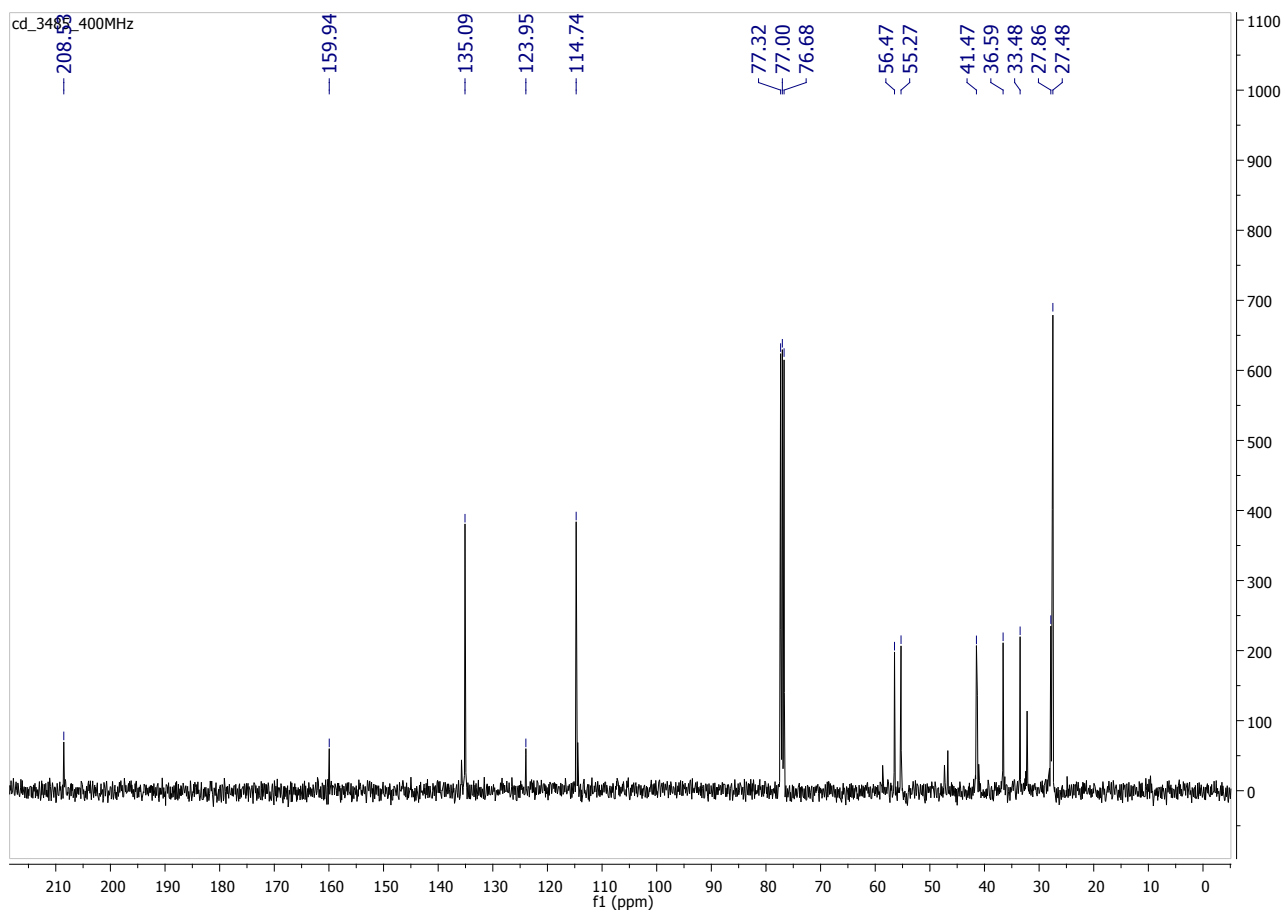
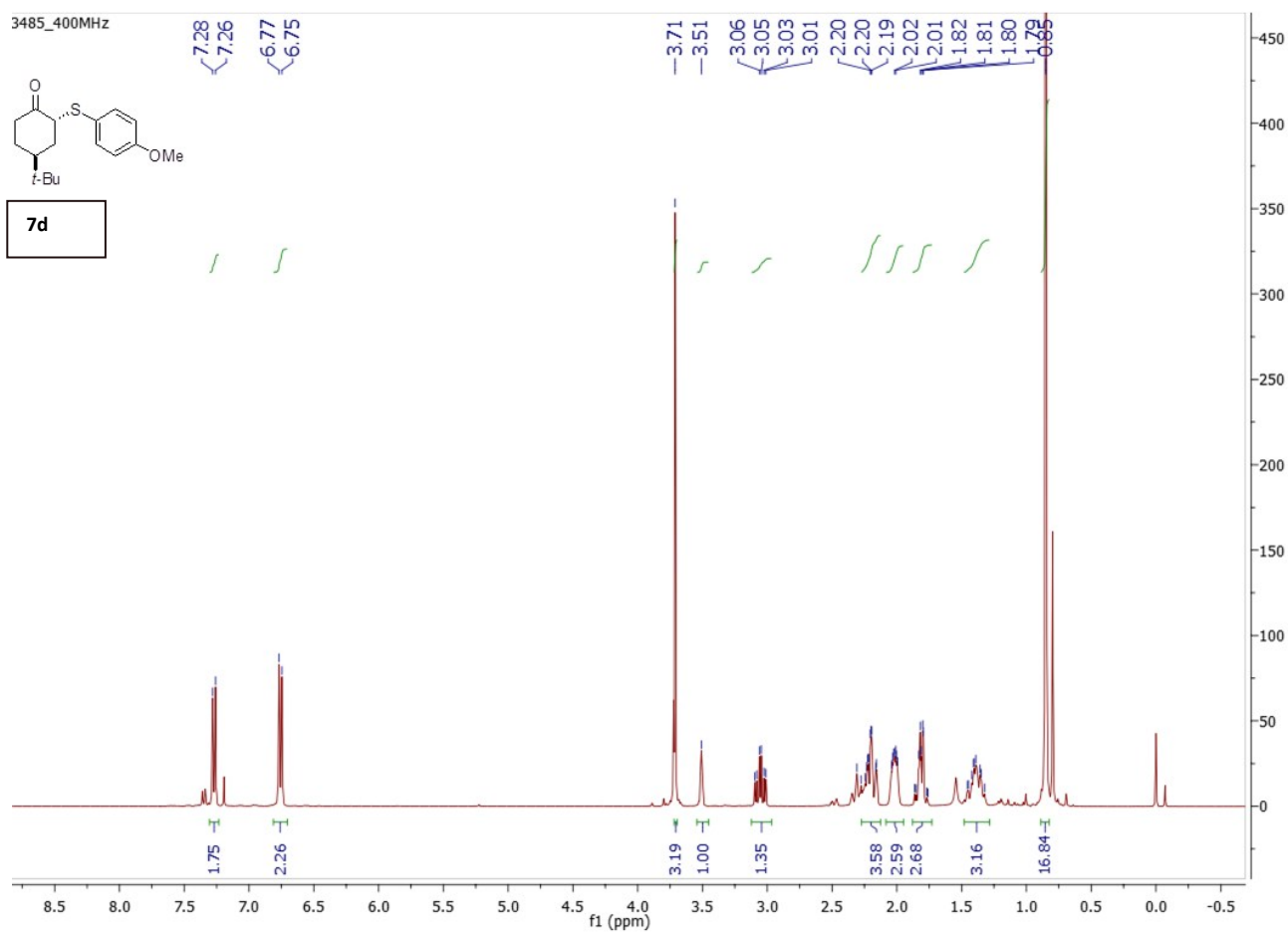


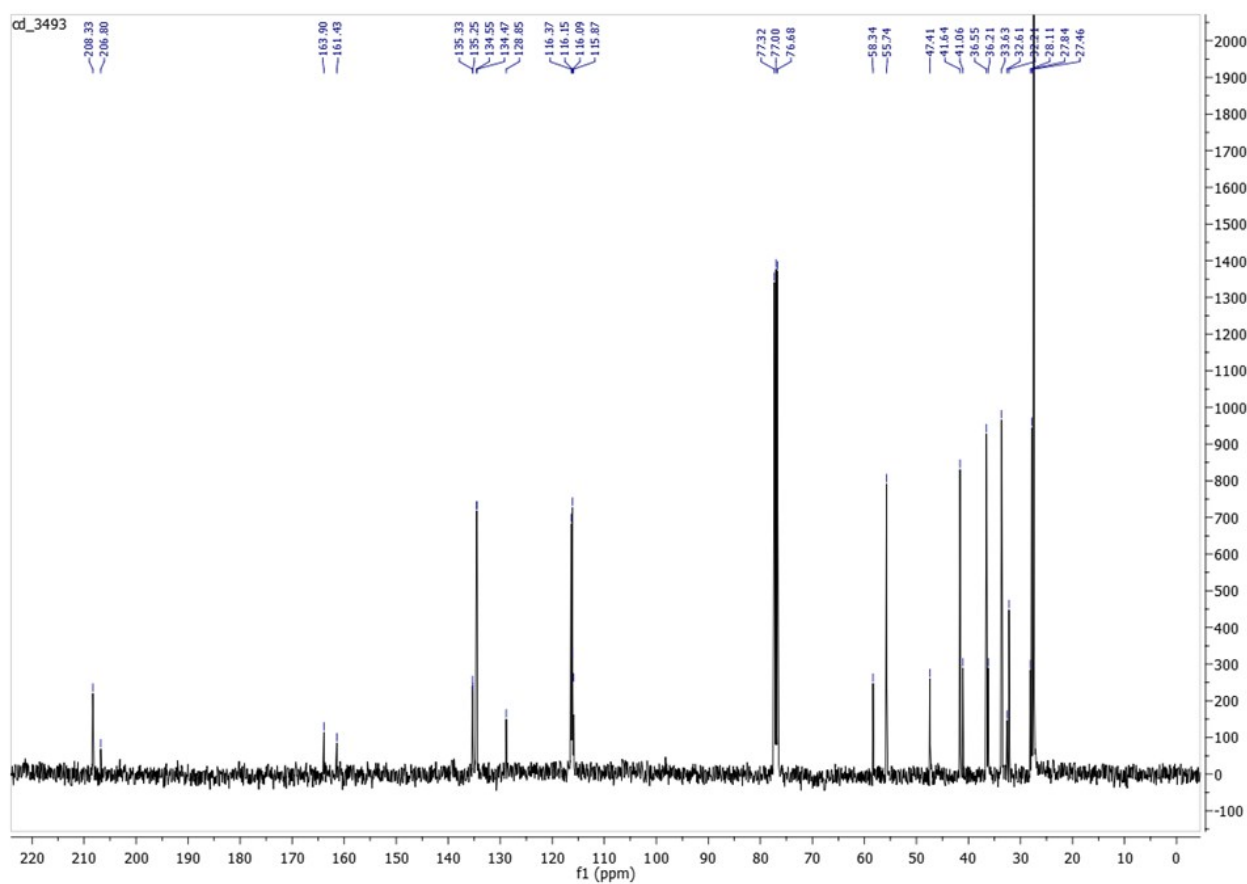
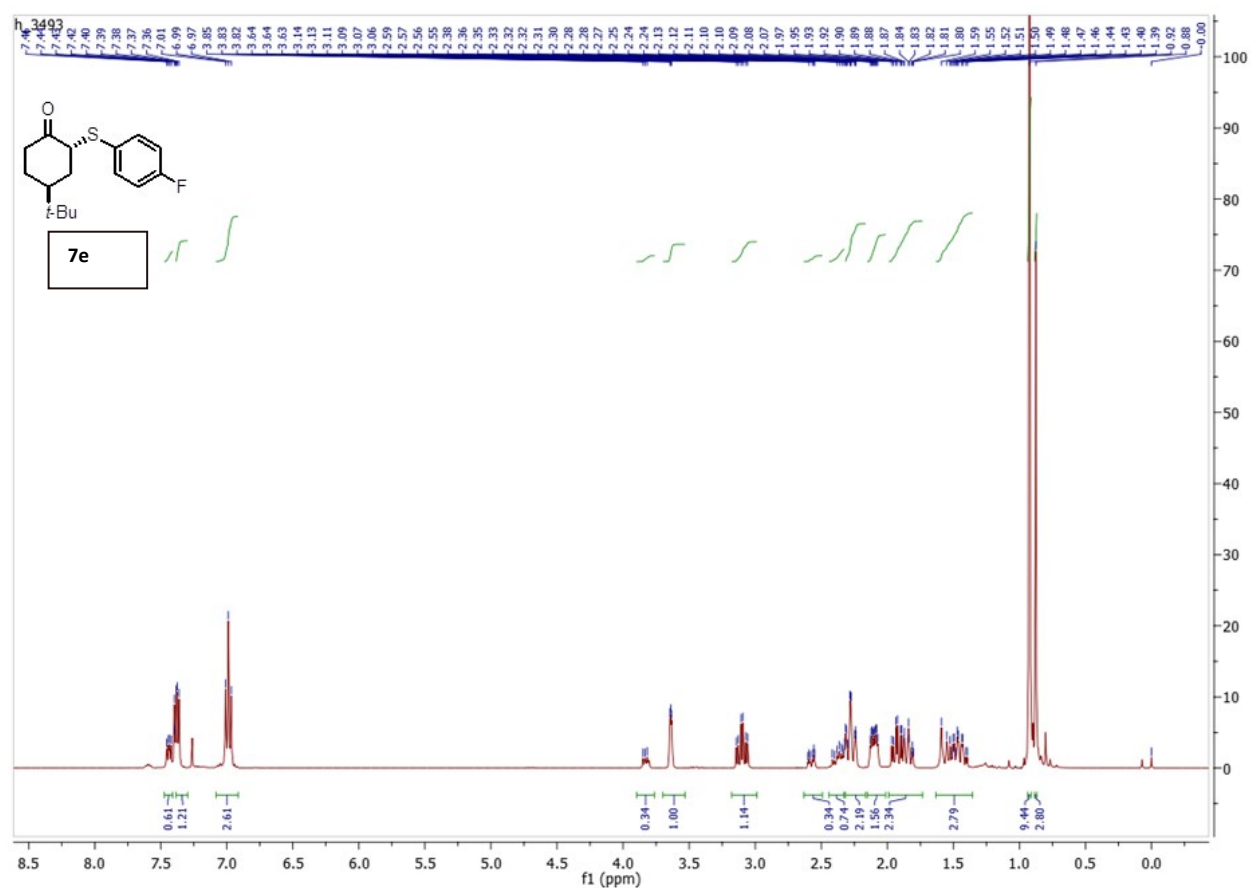


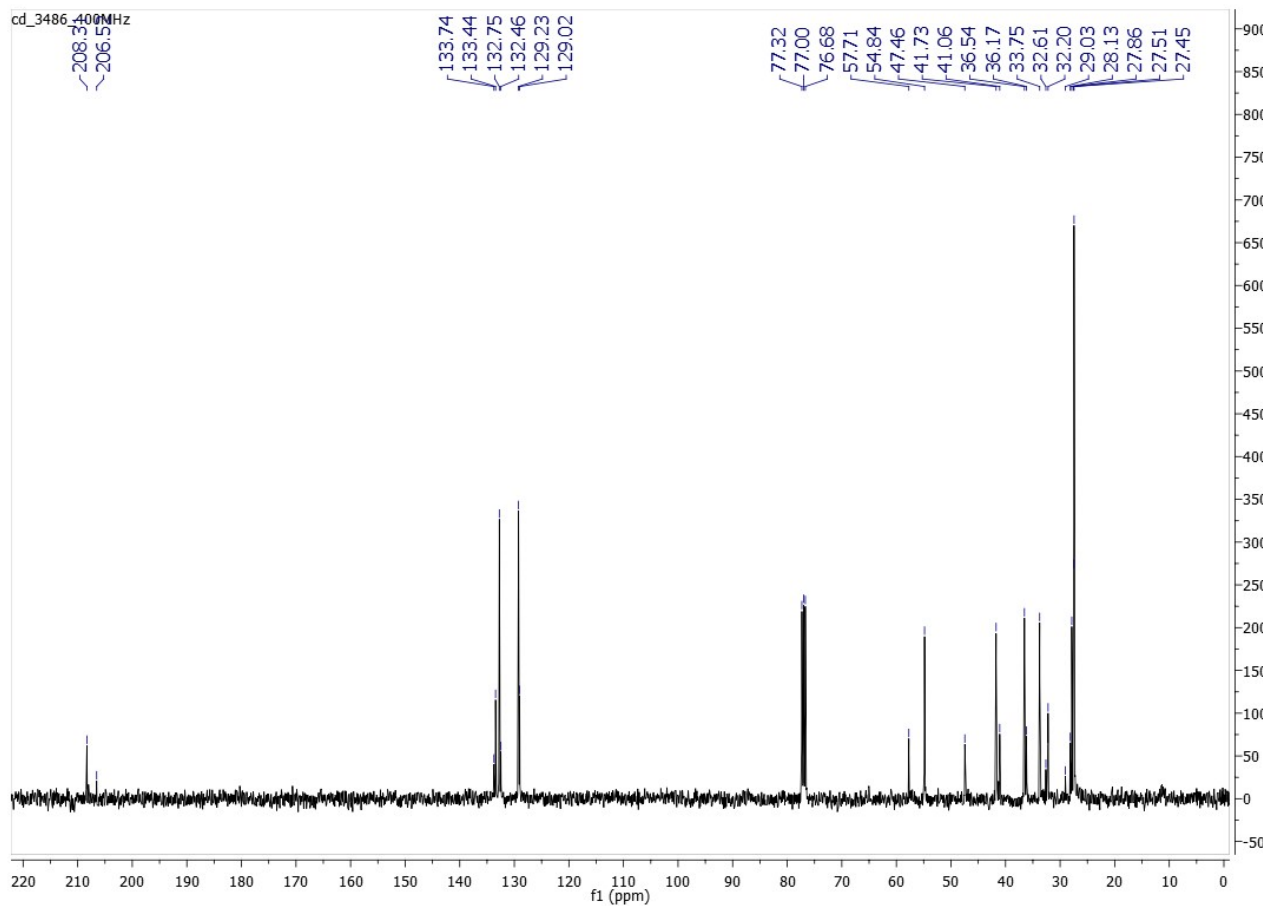
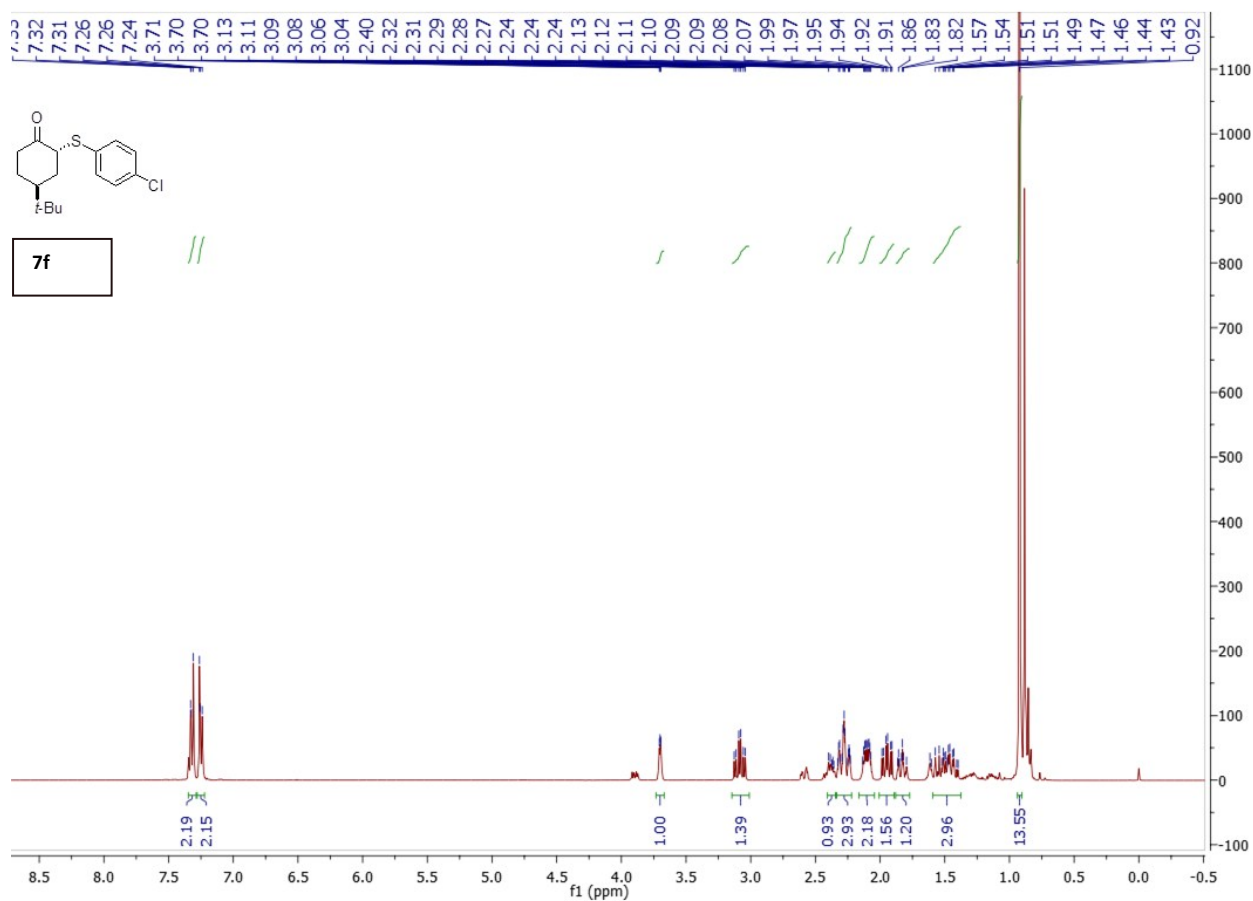


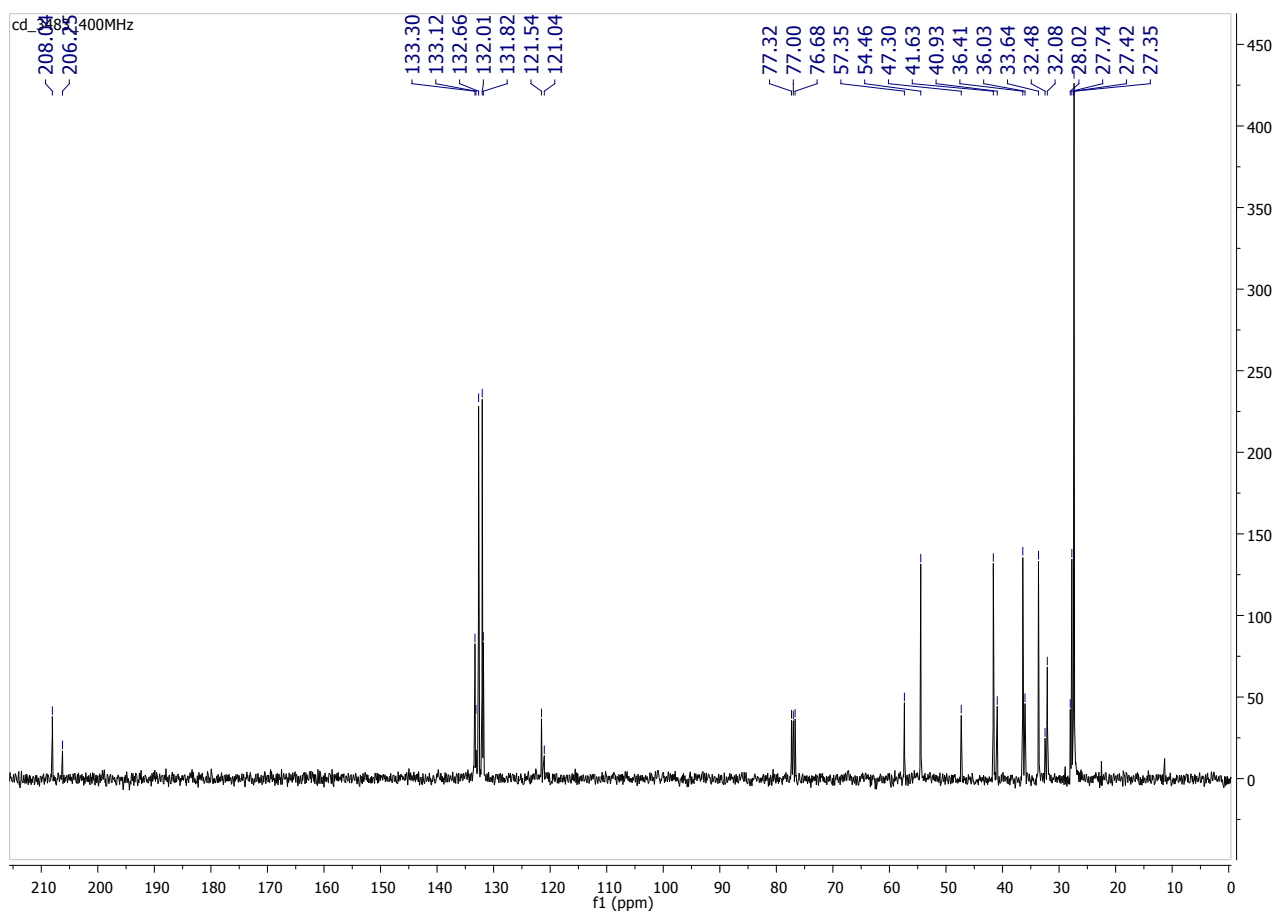
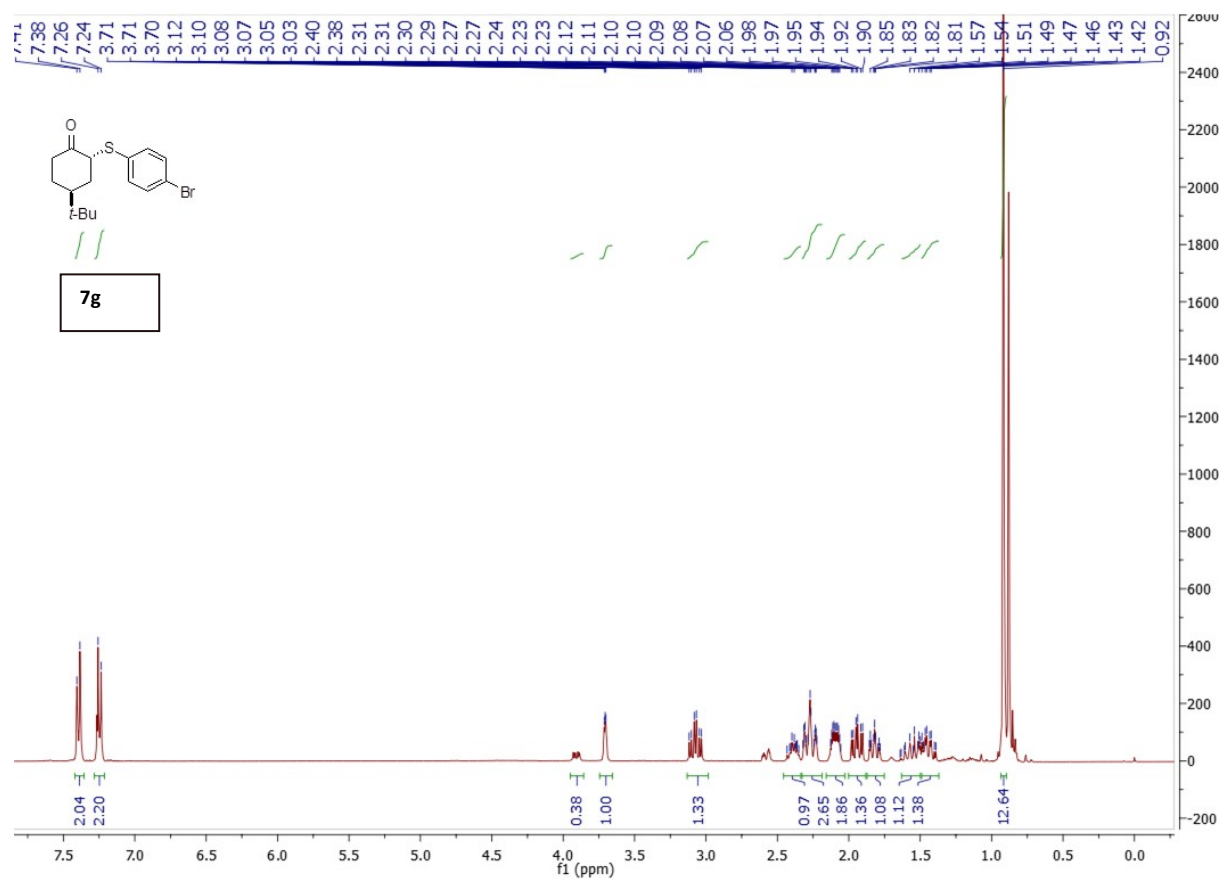


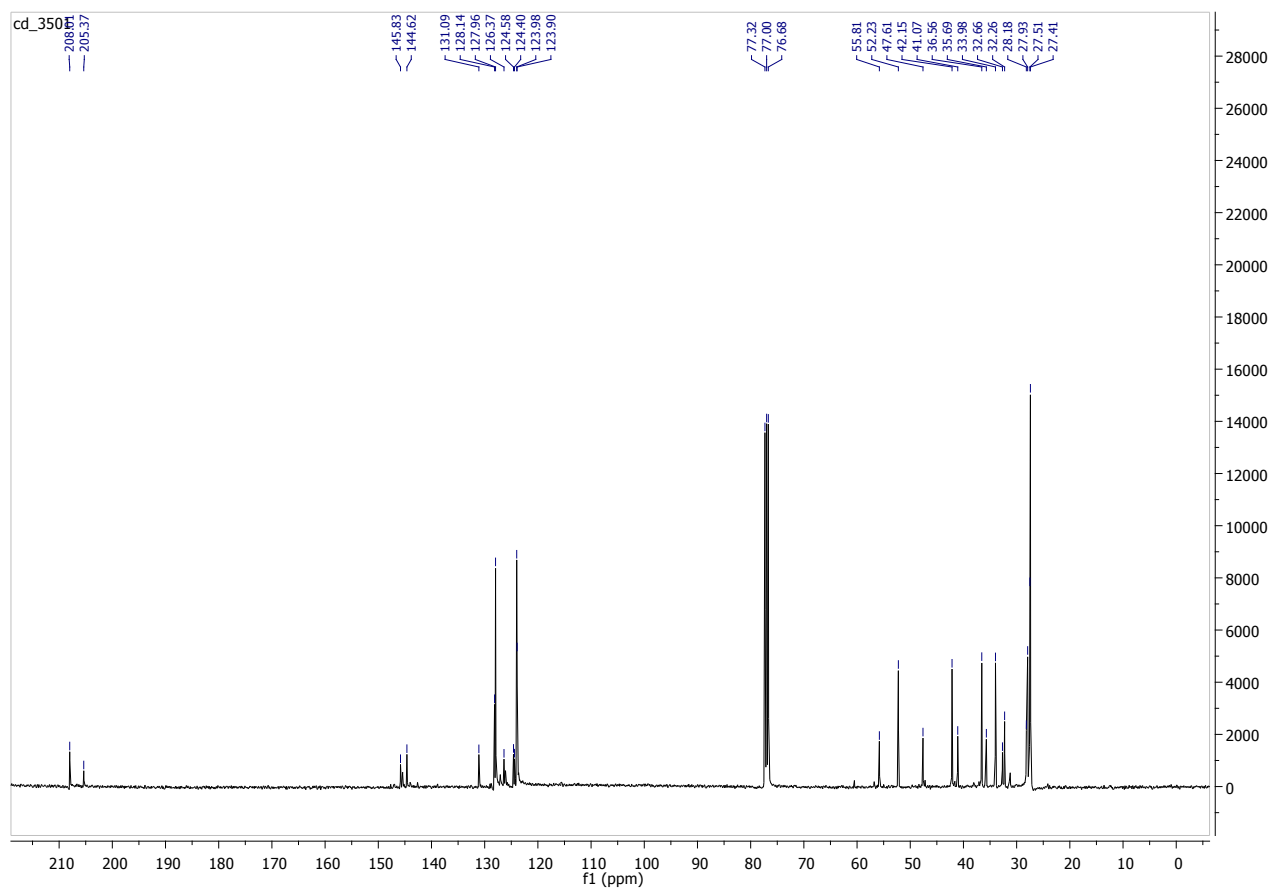
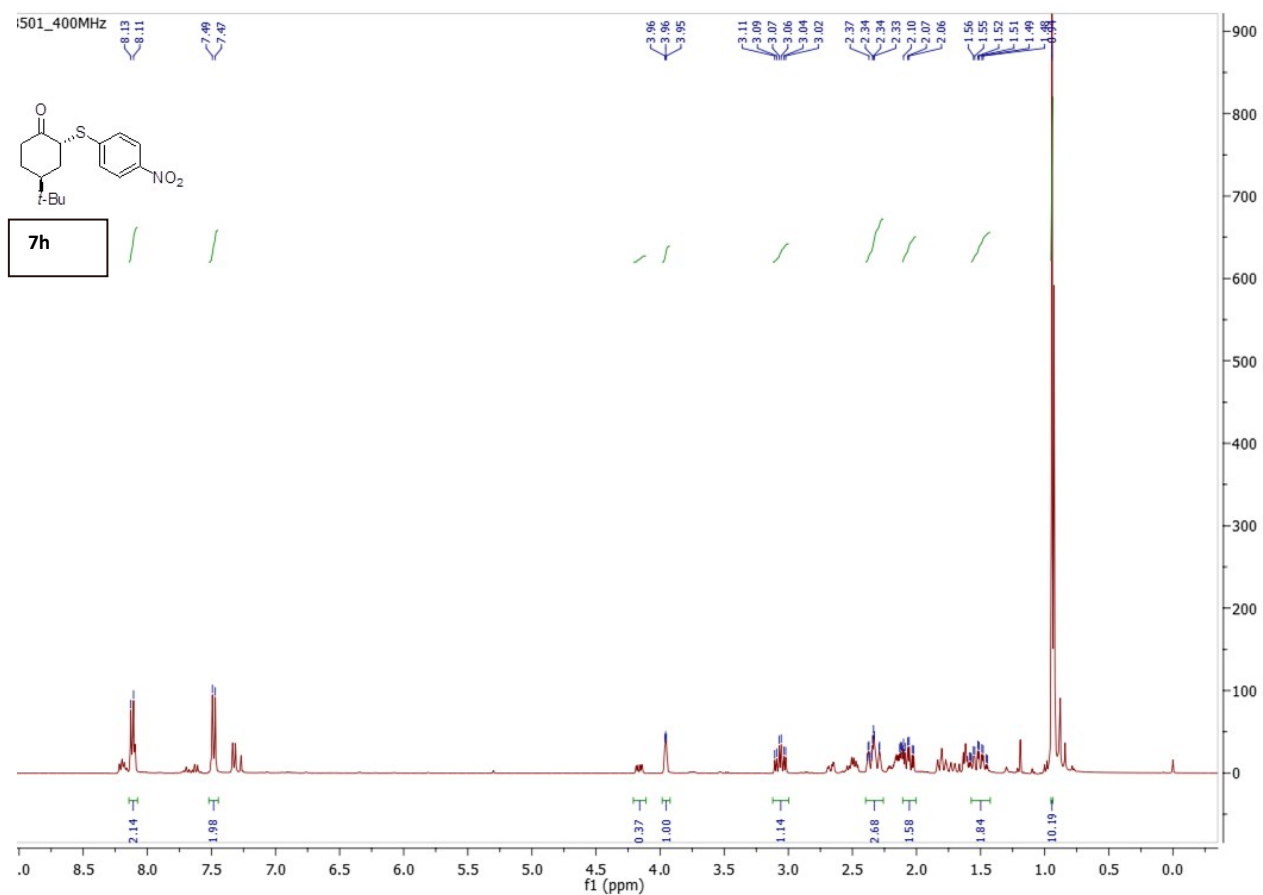


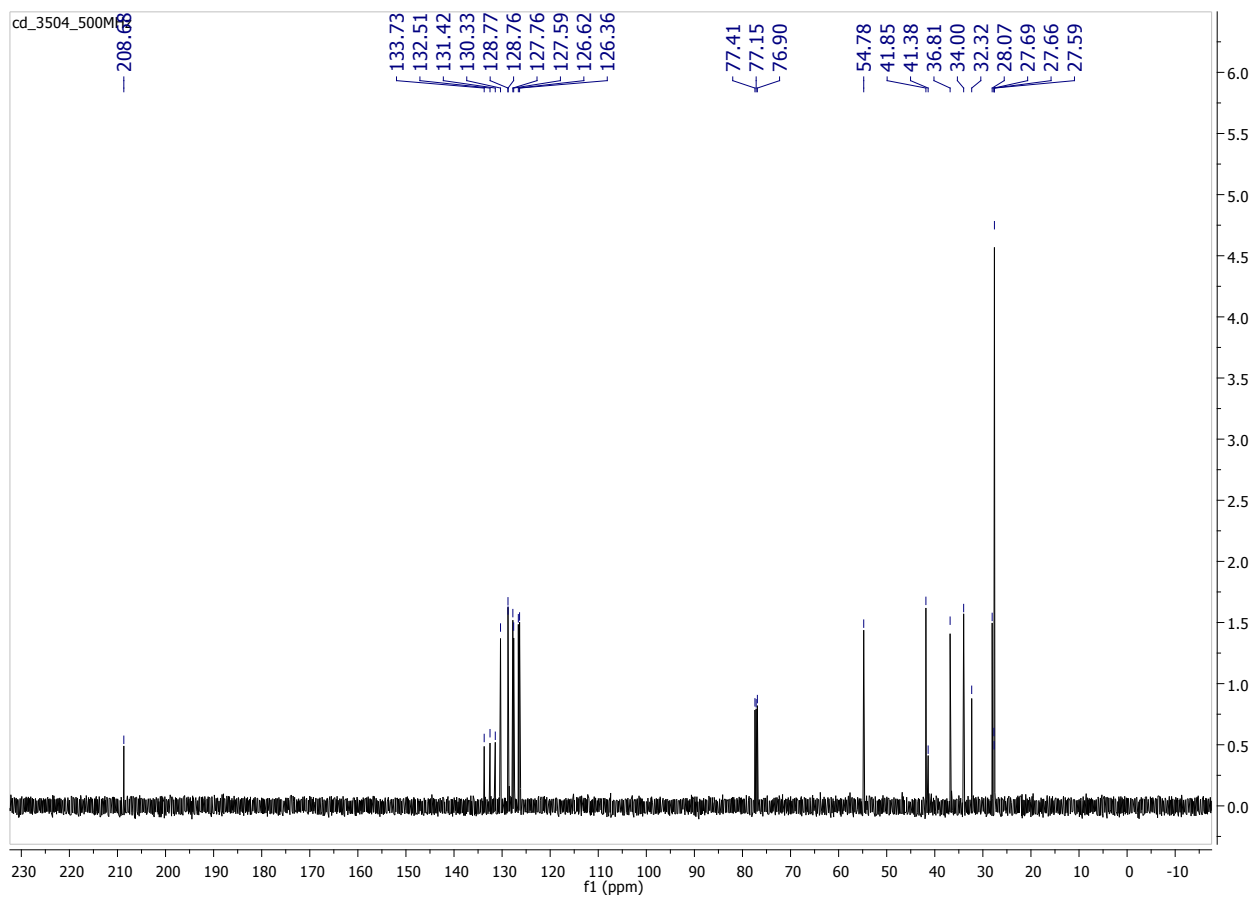
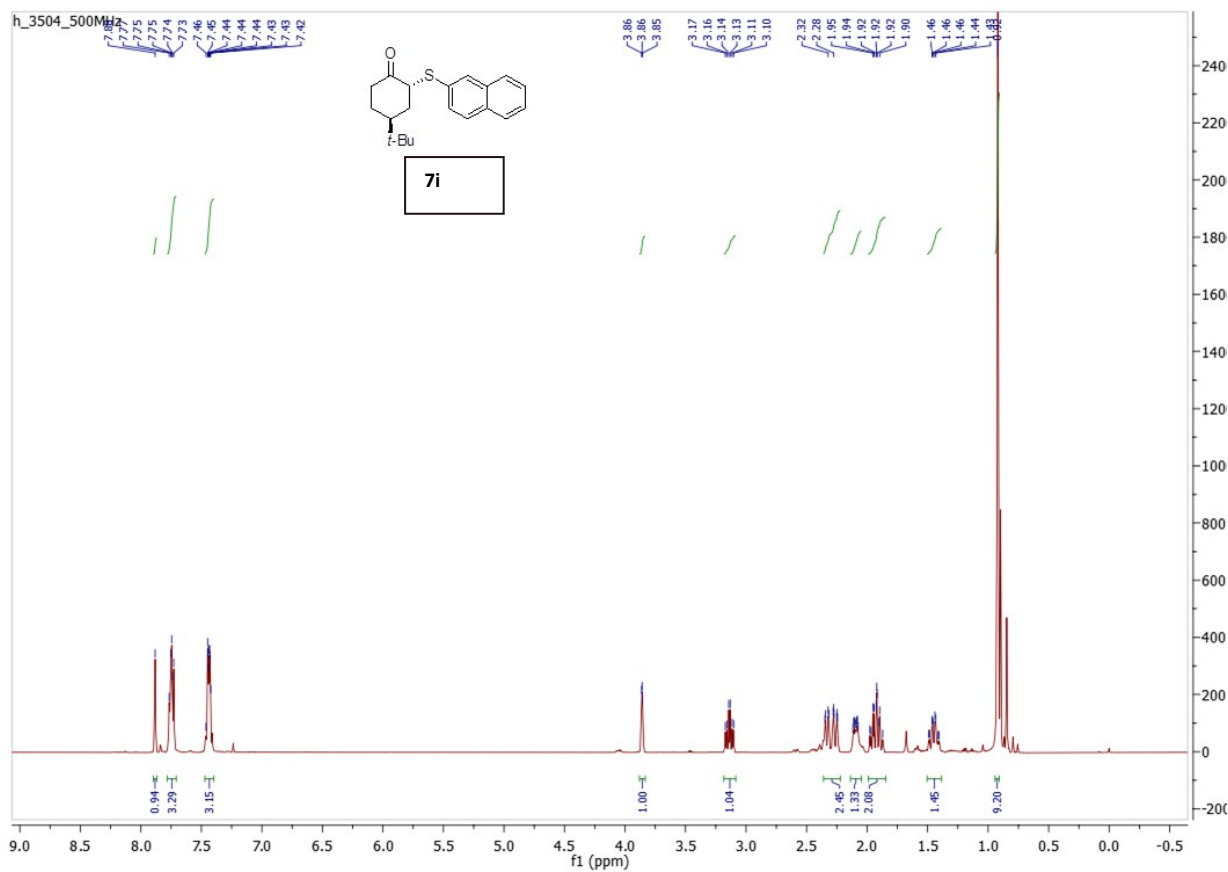












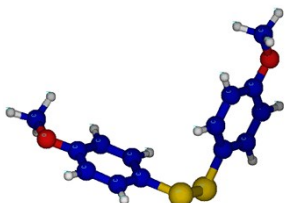
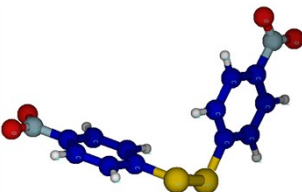
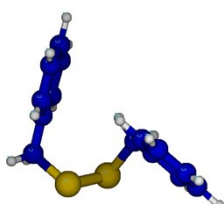
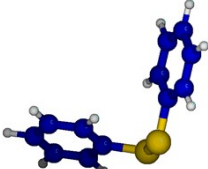
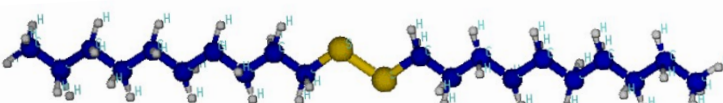
Theoretical calculations

Table 2 DFT-optimized for Sulfur atom charges on disulfide (**e,g,i,a,l**)

compounds.

Density Functional Theory (DFT) calculations were performed on compounds **e,g,i,a,l** with the commercial suite of software Gaussian09⁶. On this basis, the quantum-mechanical (QM) study aimed at investigating the S atom charge on disulfure.

All calculations were carried out with the mPW1PW hybrid functional⁷ with the split valence 6-311G^{8,9} basis sets, for all atomic species. NBO populations¹⁰ bond indices were calculated at the optimized geometries, which were verified by harmonic frequency calculations. Tight SCF convergence criteria and fine numerical integration grids were used for all calculations. The results of the calculations were examined with GaussView 5 and Molden 5.0 programs. In according to the experimental data the charge on S atom.

Ball and stick drawing and atom labelling scheme of the compounds e,g,i,a,l DFT level optimized geometry.	Compound	S-charges (medium value)	S-natural charges
	e	S 0,17852	S1 0,20755 S2 0,14950
	g	S 0,19717	S1 0,24934 S2 0,14501
	i	S 0,12628	S1 0,08212 S2 0,17044
	a	S 0,17848	S1 0,20403 S2 0,15293
	l	S 0,05961	S1 0,07011 S2 0,04911

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