

## PhSeBr-Catalyzed Selective Addition of Thiols to $\alpha,\beta$ -Unsaturated Carbonyl Compounds: Regioselective Synthesis of Thioacetals vs. $\beta$ -Mercapto Ketones

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Apresentamos aqui nossos resultados da adição de tióis, catalisada por PhSeBr, a compostos carbonílicos  $\alpha,\beta$ -insaturados sob condições brandas para obter regioseletivamente  $\beta$ -mercapto cetonas ou tioacetais com altos rendimentos e seletividade. A reação foi principalmente controlada pela temperatura, na qual os produtos de adição 1,4 foram obtidos à temperatura de  $-20\text{ }^{\circ}\text{C}$ . Inversamente quando a reação foi realizada sob refluxo, tioacetais foram obtidos como único produto. O método admite diversos grupos funcionais, como alquílicos, benzílicos e arílicos com substituintes neutros, deficientes e ricos em elétrons no anel aromático.

We present herein results on the PhSeBr-catalyzed addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds under mild conditions to afford regioselectively  $\beta$ -mercapto ketones or thioacetals in high yields and selectivity. The reaction was highly controlled by the temperature in which, the 1,4-addition products were obtained when the temperature was  $-20\text{ }^{\circ}\text{C}$ , conversely when the reaction was carried out at reflux, the thioacetals were obtained as a sole product. The developed protocol stands a wide range of functional groups, in which alkyl, benzyl and aryl with neutral, electron deficient and electron rich substituents on the aromatic ring.

**Keywords:** thioacetals,  $\beta$ -mercapto ketones, chalcogenides

### Introduction

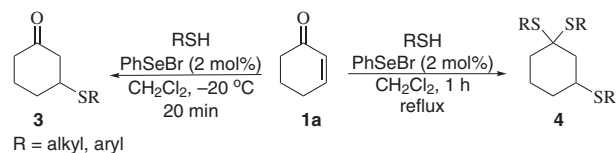
Thioacetals are useful intermediates in organic synthesis and are often used as masked carbonyl groups, in particular  $\alpha$ -lithiated thioacetals that are synthetic equivalents of carbonyl anions.<sup>1,2</sup> Thioacetals and thioketals are particularly attractive as carbonyl protecting groups in complex molecule synthesis because of their added stability to acidic conditions. In this view, there have been continued improvements in the thioacetal synthesis methods. Usually, these compounds are prepared by protic or Lewis acid-catalyzed condensation of carbonyl compounds with thiols. Lewis acid catalysts such as  $\text{ZnCl}_2$ ,<sup>3</sup>  $\text{LnCl}_3$ ,<sup>4</sup>  $\text{FeCl}_3/\text{SiO}_2$ ,<sup>5</sup>  $\text{AlCl}_3$ ,<sup>6</sup>  $\text{ZrCl}_4/\text{SiO}_2$ ,<sup>7</sup>  $\text{TeCl}_4$ ,<sup>8</sup>  $\text{SnCl}_2$ ,<sup>9</sup>  $\text{SiCl}_4$ ,<sup>10</sup>  $\text{TiCl}_4$ ,<sup>11</sup>  $\text{BF}_3\cdot\text{OEt}_2$ <sup>12</sup> and others methods<sup>13-15</sup> have been used for this purpose. Despite those methods reported

in the literature, some problems were found as, difficulties in work-up, isolation, requirement of inert atmosphere, harsh reaction conditions, expensive and stoichiometric reagents, incompatibility with other protecting groups and failure to protect deactivated and hindered substrates. In contrast, none of the reported methods describe the selective catalytic preparation of  $\beta$ -mercapto ketones or thioacetals from  $\alpha,\beta$ -unsaturated carbonyl compounds with thiols, catalyzed by PhSeBr. Therefore, it would be of interest to define a method in order to prepare selectively  $\beta$ -mercapto ketones or thioacetals starting from  $\alpha,\beta$ -unsaturated carbonyl compounds and thiols (Scheme 1).

### Results and Discussion

Our initial studies have focused on the development of an optimum set of reaction conditions to obtain  $\beta$ -mercapto ketones in the absence of thioacetals. In

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**Scheme 1.** General scheme.

this way, cyclohex-2-enone **1a** and benzenethiol **2a** were used as standard substrates and the variation in the temperature, time, presence or absence of catalyst were investigated. At first, the reaction was tested under room temperature, using  $\text{CH}_2\text{Cl}_2$  as solvent in the presence

of PhSeBr (2 mol%); thus after 10 min the product of 1,4-addition was obtained in 65% yield. However, under this reaction condition traces of the thioacetal were also obtained. In attempt to avoid the thioacetal by-product and to select the  $\beta$ -mercapto ketones, as a sole product, we carried out the reaction at 0 and  $-20^\circ\text{C}$ . At  $0^\circ\text{C}$  a mixture of both  $\beta$ -mercapto ketone and thioacetal was yet obtained, but changing the temperature to  $-20^\circ\text{C}$ , after 20 min, the desired product in 79% yield was found with no mixture. Regarding the influence of the catalyst, neither  $\beta$ -mercapto ketones nor thioacetals

**Table 1.** Addition of thiols in the carbonyl group; synthesis of  $\beta$ -mercapto ketones

Reaction 1: $\text{1a-b} + \text{RSH} \xrightarrow[\text{20 min}]{\text{PhSeBr (2 mol\%)}, \text{CH}_2\text{Cl}_2, -20^\circ\text{C}}$ $\text{3a-o}$				
Entry	Ketone	Thiol	Product	Yield (%)
1	<b>1a</b>	<b>2a</b>	<b>3a</b>	79
2	<b>1a</b>	<b>2b</b>	<b>3b</b>	74
3	<b>1a</b>	<b>2c</b>	<b>3c</b>	63
4	<b>1a</b>	<b>2d</b>	<b>3d</b>	74
5	<b>1a</b>	$\text{C}_{12}\text{H}_{25}\text{SH2e}$	<b>3e</b>	76
6	<b>1a</b>	<b>2f</b>	<b>3f</b>	61
7	<b>1a</b>	<b>2g</b>	<b>3g</b>	95
8	<b>1a</b>	<b>2h</b>	<b>3h</b>	75
9	<b>1a</b>	<b>2i</b>	<b>3i</b>	84
10	<b>1a</b>	<b>2j</b>	no product	N.R.
11	<b>1a</b>	<b>2k</b>	<b>3k</b>	71
12	<b>1b</b>	<b>2i</b>	<b>3l</b>	78
13	<b>1b</b>	<b>2a</b>	<b>3m</b>	62
14	<b>1b</b>	<b>2k</b>	<b>3n</b>	56
15	<b>1b</b>	<b>2g</b>	<b>3o</b>	50

N.R.: no reaction.

were obtained when the reactions was carried out in the absence of PhSeBr. Thus, the analysis of the optimized reaction conditions demonstrated that the optimal ones for this procedure were the addition of cyclohex-2-enone **1a** (1 mmol), benzenethiol **2a** (1.1 mmol), PhSeBr (2 mol%) and  $\text{CH}_2\text{Cl}_2$  (1 mL) as a solvent. After the addition, the reaction was stirred for 20 min at  $-20^\circ\text{C}$  and the product **3a** was obtained in 79% yield. These reactions conditions were systematically applied to other substrates to demonstrate the efficiency of this method, and the results are summarized in Table 1.

Inspections of Table 1 show that in general, all of the reactions proceeded smoothly with good yields. Most

importantly, the addition turned out to be general with respect to a diverse array of functional thiol sources. Our experiments showed that the reaction with thiols having aryl and aryl substituted, was sensitive to the electronic nature of functional groups present in the aromatic ring. Electron donating group such as methoxy gave the conjugated addition product in high yield 95%, in contrast to this, electron withdrawing group decrease the yield (Table 1, entries 7, 8 and 11). We also observed that hindered and non-hindered alkyl thiols gave the desired products in good yields (Table 1; entries 2, 4 and 6). As shown in Table 1, bulky carbonyl ketone afforded the 1,4-addition product in moderated yields (Table 1, entries 13-15). A limitation

**Table 2.** Addition of thiols in the carbonyl group; synthesis of thioacetals *Aqui corrigir só o 1 h*

Entry	ketone	Thiol	Product	Yield (%)	Entry	ketone	Thiol	Product	Yield (%)
1				81	8	<b>1a</b>			82
2	<b>1a</b>			83	9	<b>1a</b>		no product <b>4i</b>	N.R.
3	<b>1a</b>			95	10	<b>1a</b>			N.R.
4	<b>1a</b>			N.R.	11				76
5	<b>1a</b>			88	12	<b>1b</b>			89
6	<b>1a</b>			60	13	<b>1b</b>			92
7	<b>1a</b>			86	14	<b>1b</b>			78

N.R.: no reaction.

in this methodology was observed when oxazolethiol derivative **2j** was used as thiol source. In this case no product was obtained, even under long reaction time, probably due to steric effects.

It was gratifying to discover the use of cyclohex-2-enone **1a** and benzenethiol **2a** as standard substrates and the simply changing in the temperature from -20 °C to reflux, in the procedure described to obtain  $\beta$ -mercapto ketones **3**, had a dramatic effect. Thus, the reaction of cyclohex-2-enone **1a** (1 mmol), benzenethiol **2a** (4.0 equiv.) with PhSeBr (2 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at reflux, gave thioacetal **4a** as the sole product in 85% yield. Using the optimized reaction conditions, a wide variety of thiols containing useful functional groups can be successfully used as substrate (Table 2). The results revealed that the aryl, alkyl and benzyl thiols, gave the product efficiently under these conditions. The exception was the bulky thiols **2d**, **2j** and **2k**, which did not give the desired product, even changing the reaction conditions.

The fact that the protection of thiols has found widespread applications in the organic transformations<sup>16</sup> associated with the simple preparation, low cost and easy handling of PhSeBr, prompted us to study its application on the thiol reaction with dihydropyran. Thus, the standard reaction condition applied to prepare the  $\beta$ -mercapto ketones **3** was also tested for the reaction of thiols and dihydropyran. In this way, the reaction of

dihydropyran **1c** (1 mmol), benzenethiol **2a** (1.1 mmol), PhSeBr (2 mol%) and CH<sub>2</sub>Cl<sub>2</sub> (1 mL) as a solvent, at 0 °C for 10 min gave THP thioether in 75% yield. The scope and limitations of this protection are summarized in Table 3.

The results showed that the reaction is not sensitive to the electronic effect at aromatic ring in the thiol. For example, both arylthiol bearing electron-donating (OMe) and electron-withdrawing (Cl) group gave the product in good yields. Differentiation in the reactivity between chlorine and sulfur atoms of thiol can also be seen by the reaction of thiols **2k** and **2f** to provide only the THP thioether products in 85 and 90% yields, respectively, without any side-product observed. In this case, the chlorine substituent was not affected.

## Conclusions

We described herein an efficient method for PhSeBr-mediated addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds providing a versatile and regioselective synthesis of 1,4-addition products or thioacetals. The reaction was highly controlled by the temperature in which, the 1,4-addition products were obtained when the temperature was -20 °C; conversely when the reaction was carried out at reflux thioacetals were obtained as a sole product. With this protocol, we were also able to prepare THP thioethers under mild conditions in fair to excellent yields demonstrating the versatility of the PhSeBr in this catalytic system. The advantages of this method include, the use of cheap, easy and handle catalyst, non anhydrous reaction conditions, non aqueous work-up and ease of product isolation, besides short reaction times and high yields. This reaction associated with the ease in which the protect group can be removed from thiol, can contribute to an interesting alternative route for preparation of more functionalized organothiols.


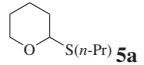
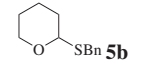
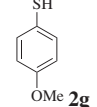
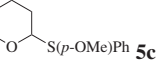
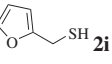
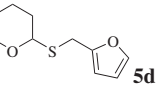
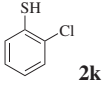
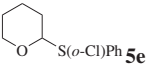
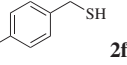
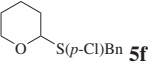
## Supplementary Information

Experimental details and spectra are available free of charge at <http://jbc.sbc.org.br>, as PDF file.

## Acknowledgments

We are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (SAUX) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul, for the fellowships and financial support (PRONEX-10-0005-1).

**Table 3** Addition of thiols in dihydropyran; synthesis of thioethers

Entry	Thiol	Product	Yield (%)
1	 <b>2b</b>	 <b>5a</b>	75
2	<b>2c</b>	 <b>5b</b>	91
3	 <b>2g</b>	 <b>5c</b>	87
4	 <b>2i</b>	 <b>5d</b>	61
5	 <b>2k</b>	 <b>5e</b>	85
6	 <b>2f</b>	 <b>5f</b>	90

## References

- Greene, T. W.; Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999, pp. 297-348.
- Cordes, E. H.; Bull, H. G.; *Chem. Rev.* **1974**, *74*, 581.
- Truce, W. E.; Roberts, F. E.; *J. Org. Chem.* **1963**, *28*, 961.
- Garlaschelli, L.; Vidari, G.; *Tetrahedron Lett.* **1990**, *31*, 5815.
- Patney, H. K.; *Tetrahedron Lett.* **1991**, *32*, 2259.
- Ong, B. S.; *Tetrahedron Lett.* **1980**, *21*, 4225.
- Patney, H. K.; Margan, S.; *Tetrahedron Lett.* **1996**, *37*, 4621.
- Tani, H.; Masumoto, K.; Inamasu, T.; *Tetrahedron Lett.* **1991**, *32*, 2039.
- Das, N. B.; Nayak, A.; Sharma, R. P.; *J. Chem. Res. (S)* **1993**, 242.
- Ku, B.; Oh, D. Y.; *Synth. Commun.* **1989**, *19*, 433.
- Kumar, V.; Dev, S.; *Tetrahedron Lett.* **1983**, *24*, 1289.
- Fieser, L. F.; *J. Am. Chem. Soc.* **1954**, *76*, 1945.
- Khurana, J. M.; Agrawal, A.; Kumar, S.; *J. Braz. Chem. Soc.* **2009**, *20*, 1256.
- Lenardão, E. J.; Trecha, D. O.; Ferreira, P. C.; Jacob, R. G.; Perin, G.; *J. Braz. Chem. Soc.* **2009**, *20*, 93.
- Almeida, Q. A. R.; Pereira, M. L. D. O.; Coelho, R. B.; *J. Braz. Chem. Soc.* **2008**, *19*, 894.
- Masaki, Y.; Tanaka, N.; Miura, T.; *Tetrahedron Lett.* **1998**, *39*, 5799.
- General procedure for  $\beta$ -mercapto ketones formation:* To a Schlenck tube, under air atmosphere containing an appropriate  $\alpha,\beta$ -unsaturated carbonyl compound (0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL), was added the thiol (0.6 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 20 min at  $-20^\circ\text{C}$ . After that, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. *3-(Phenylthio)cyclohexanone (3a)*: Yield 0.162 g (79%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.43-7.40 (m, 2H), 7.33-7.25 (m, 3H), 3.46-3.37 (m, 1H), 2.68 (d,  $J$  9.7 Hz, 1H), 2.40-2.25 (m, 3H), 2.17-2.08 (m, 2H), 1.80-1.63 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  208.63, 133.09, 132.88, 128.95, 127.66, 47.63, 45.98, 40.75, 31.09, 23.90. HRMS calc. for  $\text{C}_{12}\text{H}_{24}\text{OS}$ : 206.0765. Found: 206.0769.
- General procedure for thioacetals formation:* To a Schlenck tube, under air atmosphere containing an appropriate  $\alpha,\beta$ -unsaturated carbonyl compounds (0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL), was added the thiol (2.0 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 1 h under reflux. After that, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. *1,1,3-tris(Phenylthio)cyclohexane (4a)*: Yield 0.330 g (81%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz),  $\delta$ : 7.70-7.65 (m, 2H), 7.54-7.50 (m, 2H), 7.35-7.20 (m, 11H), 3.56 (tt,  $J$  12.0/3.5 Hz, 1H), 2.28-2.19 (m, 1H), 2.03-1.75 (m, 3H), 1.69-1.50 (m, 3H), 1.16-0.94 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 137.33, 136.11, 133.67, 132.63, 130.90, 130.72, 129.16, 128.96, 128.77, 128.61, 128.55, 127.08, 65.05, 43.37, 42.73, 36.12, 32.15, 22.66. HRMS calc. for  $\text{C}_{24}\text{H}_{24}\text{S}_3$ : 408.1040. Found: 408.1043.
- General procedure for thioethers formation:* To a Schlenck tube, under air atmosphere containing an appropriate dihydropyran (0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL), was added the thiol (0.6 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 20 min at  $0^\circ\text{C}$ . After this, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. *2-(Propylthio)-tetrahydro-2H-pyran (5a)*: Yield 0.120 g (75%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 4.16-3.71 (m, 2H), 3.53-3.36 (m, 1H), 2.72-2.49 (m, 2H), 1.92-1.51 (m, 8H), 0.99 (t,  $J$  7.20 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 98.80, 67.26, 62.26, 51.81, 35.98, 29.21, 25.44, 19.59. HRMS calc. for  $\text{C}_9\text{H}_{16}\text{OS}$ : 160.0921. Found: 160.0918.

Submitted: March 30, 2010

Published online: July 8, 2010

## PhSeBr-Catalyzed Selective Addition of Thiols to $\alpha,\beta$ -Unsaturated Carbonyl Compounds: Regioselective Synthesis of Thioacetals vs. $\beta$ -Mercapto Ketones

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Proton nuclear magnetic resonance spectra (<sup>1</sup>H NMR) were obtained at 200 MHz on a DPX-200 NMR spectrometer or at 400 MHz on DPX-400 NMR spectrometer. Spectra were recorded in CDCl<sub>3</sub> solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of CDCl<sub>3</sub> or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift ( $\delta$ ), multiplicity, coupling constant ( $J$ ) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (<sup>13</sup>C NMR) were obtained either at 50 MHz on a DPX-200 NMR spectrometer or at 100 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in CDCl<sub>3</sub> solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of CDCl<sub>3</sub>. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet) and m (multiplet). High resolution mass spectra were recorded on a MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Column chromatography was performed using Silica Gel (230-400 mesh) following the methods described by Still (Still, W. C.; Kahn, M.; Mitra, A.; *J. Org. Chem.* **1978**, *43*, 2923). Thin layer chromatography (TLC) was performed using Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapour, or acidic vanillin. Most reactions were monitored by TLC for disappearance of starting material. Air- and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents were handled using standard

syringe techniques. Temperatures above room temperature were maintained by use of a mineral oil bath with an electrically heated coil connected to a Variac controller.

### General procedure for $\beta$ -mercapto ketones

To a Schlenk tube, under air atmosphere containing an appropriate  $\alpha,\beta$ -unsaturated carbonyl compounds (0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL), was added the thiol (0.6 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 20 min at -20 °C. After that, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

### 3-(Phenylthio)cyclohexanone (**3a**)

Yield: 0.162 g (79%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 7.43-7.40 (m, 2H), 7.33-7.25 (m, 3H), 3.46-3.37 (m, 1H), 2.68 (d,  $J$  9.7 Hz, 1H), 2.40-2.25 (m, 3H), 2.17-2.08 (m, 2H), 1.80-1.63 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  208.63, 133.09, 132.88, 128.95, 127.66, 47.63, 45.98, 40.75, 31.09, 23.90. HRMS calc. for C<sub>12</sub>H<sub>24</sub>OS: 206.0765. Found: 206.0769.

### 3-(Propylthio)cyclohexanone (**3b**)

Yield: 0.127 g (74%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 3.08-3.01 (m, 1H), 2.70 (d,  $J$  9.5 Hz, 1H), 2.53 (t,  $J$  7.4 Hz, 2H), 2.41-2.31 (m, 3H), 2.18-2.10 (m, 2H), 1.76-1.68 (m, 2H), 1.60 (sex,  $J$  7.3 Hz, 2H), 0.99 (t,  $J$  7.3 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 208.61, 48.00, 42.49, 40.70, 32.31, 31.42, 23.98, 22.82, 13.27. HRMS calc. for C<sub>9</sub>H<sub>16</sub>OS: 172.0921. Found: 172.0927.

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**3-(Benzylthio)cyclohexanone (3c)**

Yield: 0.138 g (63%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz),  $\delta$ : 7.32-7.21 (m, 5H), 3.76 (s, 2H), 3.00-2.86 (m, 1H), 2.67 (dd,  $J$  9.6/4.4 Hz, 1H), 2.40-2.29 (m, 3H), 2.17-2.02 (m, 2H), 1.73-1.61 (m, 2H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 208.13, 137.61, 128.39, 128.23, 126.75, 47.39, 41.67, 40.55, 34.55, 30.86, 23.70. MS (relative intensity)  $m/z$ : 220 (11), 123 (32), 97 (53), 91 (100). HRMS calc. for  $\text{C}_{13}\text{H}_{16}\text{OS}$ : 220.0921. Found: 220.0925.

**3-(tert-Butylthio)cyclohexanone (3d)**

Yield: 0.137 g (74%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 3.03-2.96 (m, 1H), 2.72 (dd,  $J$  9.3/4.7 Hz, 1H), 2.43-2.22 (m, 3H), 2.20-2.06 (m, 2H), 1.77-1.69 (m, 2H), 1.34 (s, 9H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 208.92, 50.66, 43.49, 40.51, 40.46, 34.13, 31.27, 24.46. MS (relative intensity)  $m/z$ : 186 (30), 171 (1), 130 (29), 96 (50). HRMS calc. for  $\text{C}_{10}\text{H}_{18}\text{OS}$ : 186.1078. Found: 186.1081.

**3-(Dodecylthio)cyclohexanone (3e)**

Yield: 0.226 g (76%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 3.09-3.01 (m, 1H), 2.71 (dd,  $J$  9.6/4.3 Hz, 1H), 2.54 (t,  $J$  7.5 Hz, 2H), 2.40-2.31 (m, 3H), 2.17-2.10 (m, 2H), 1.77-1.67 (m, 2H), 1.59-1.53 (m, 3H), 1.40-1.26 (m, 17H), 0.88 (t,  $J$  7.5 Hz, 3H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 199.60, 39.05, 37.92, 31.78, 29.50, 29.47, 29.39, 29.22, 29.11, 29.09, 28.39, 25.56, 22.55, 13.98. MS (relative intensity)  $m/z$ : 267 (1), 201 (45), 129 (4), 97 (22). HRMS calc. for  $\text{C}_{18}\text{H}_{34}\text{OS}$ : 298.2330. Found: 298.2332.

**3-(sec-Butylthio)cyclohexanone (3f)**

Yield: 0.113 g (61%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 3.14-3.04 (m, 1H), 2.77 (sex d,  $J$  7.0/2.3 Hz, 1H), 2.69 (dd,  $J$  9.5/4.2, 1H), 2.40-2.31 (m, 3H), 2.18-2.09 (m, 2H), 1.78-1.67 (m, 2H), 1.63-1.45 (m, 2H), 1.25 (d,  $J$  6.7 Hz, 3H), 0.97 (t,  $J$  7.4 Hz, 3H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 208.79, 48.54, 41.34, 40.78, 40.40, 31.89, 29.79, 24.09, 20.98, 11.10. MS (relative intensity)  $m/z$ : 186 (30), 171 (1), 157 (20), 143 (1), 129 (21), 97 (100). HRMS calc. for  $\text{C}_{10}\text{H}_{18}\text{OS}$ : 186.1078. Found: 186.1083.

**3-(4-Methoxyphenylthio)cyclohexanone (3g)**

Yield: 0.224 g (95%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.41-7.37 (m, 2H), 6.86-6.78 (m, 2H), 3.80 (s, 3H), 3.27-3.19 (m, 1H), 2.61 (dd,  $J$  9.6/4.4 Hz, 1H), 2.35-2.26 (m, 3H), 2.16-2.04 (m, 2H), 1.73-1.64 (m, 2H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 208.61, 159.70, 136.17, 122.70, 114.33, 55.05, 47.45, 46.72, 40.55, 30.91, 23.73. MS (relative intensity)  $m/z$ : 236 (70), 207 (1), 140 (100), 97 (19). HRMS calc. for  $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$ : 236.0871. Found: 236.0867.

**3-(4-Chlorophenylthio)cyclohexanone (3h)**

Yield: 0.180 g (75%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.37-7.33 (m, 2H), 7.30-7.26 (m, 2H), 3.43-3.36 (m, 1H), 2.66 (dd,  $J$  9.4/4.5 Hz, 1H), 2.39-2.26 (m, 3H), 2.18-2.09 (m, 2H), 1.77-1.67 (m, 2H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 208.28, 134.48, 133.99, 131.45, 129.17, 47.52, 46.27, 40.74, 31.05, 23.87. HRMS calc. for  $\text{C}_{12}\text{H}_{13}\text{ClOS}$ : 240.0375. Found: 240.0379.

**3-(Furan-2-ylmethylthio)cyclohexanone (3i)**

Yield: 0.176 g (84%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 7.35 (dd,  $J$  1.7/0.7 Hz, 1H), 7.30 (dd,  $J$  3.1/1.9 Hz, 1H), 6.18 (dd,  $J$  3.1/0.7 Hz, 1H), 3.77 (s, 2H), 3.08-3.00 (m, 1H), 2.69 (dd,  $J$  9.3/4.2 Hz, 1H), 2.40-2.30 (m, 3H), 2.15-2.08 (m, 2H), 1.76-1.65 (m, 2H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 208.61, 151.24, 142.10, 110.42, 107.40, 47.65, 42.32, 40.82, 31.14, 26.94, 24.05. MS (relative intensity)  $m/z$ : 210 (6), 114 (20), 97 (12), 81 (100). HRMS calc. for  $\text{C}_{11}\text{H}_{14}\text{O}_2\text{S}$ : 210.0714. Found: 210.0719.

**3-(2-Chlorophenylthio)cyclohexanone (3k)**

Yield: 0.170 g (71%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 7.45-7.39 (m, 2H), 7.25-7.18 (m, 2H), 3.69-3.52 (m, 1H), 2.69 (dd,  $J$  9.4/4.4 Hz, 1H), 2.48-2.32 (m, 3H), 2.23-2.07 (m, 2H), 1.87-1.66 (m, 2H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ : 208.19, 136.79, 133.61, 132.41, 130.07, 128.64, 127.13, 47.41, 44.74, 40.80, 30.91, 23.95. MS (relative intensity)  $m/z$ : 240 (47), 205 (1), 108 (20), 97 (80). HRMS calc. for  $\text{C}_{12}\text{H}_{13}\text{ClOS}$ : 240.0375. Found: 240.0380.

**3-(Furan-2-ylmethylthio)-4,4-dimethylcyclohexanone (3l)**

Yield: 0.185 g (78%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 7.35 (d,  $J$  0.9 Hz, 1H), 6.30 (dd,  $J$  3.0/1.8 Hz, 1H), 6.17 (d,  $J$  3.0 Hz, 1H), 3.73 (s, 2H), 2.73-4.49 (m, 3H), 2.44-2.21 (m, 2H), 1.88-1.77 (m, 1H), 1.65-1.49 (m, 1H), 1.10 (s, 6H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 209.12, 151.25, 142.15, 110.37, 107.65, 53.22, 45.59, 38.67, 37.78, 34.60, 28.39, 25.21, 20.56. MS (relative intensity)  $m/z$ : 238 (10), 125 (23), 97 (3), 81 (100), 69 (14). HRMS calc. for  $\text{C}_{15}\text{H}_{18}\text{O}_2\text{S}$ : 238.1027. Found: 238.1032.

**4,4-Dimethyl-3-(phenylthio)cyclohexanone (3m)**

Yield: 0.145 g (62%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 7.41-7.38 (m, 2H), 7.31-7.22 (m, 3H), 3.19-3.15 (m, 1H), 2.66-2.52 (m, 2H), 2.50-2.41 (m, 1H), 2.34-2.27 (m, 1H), 1.93-1.87 (m, 1H), 1.68, 1.59 (m, 1H), 1.28 (s, 3H), 1.22 (s, 3H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 208.93, 134.57, 132.64, 129.05, 127.36, 57.58, 45.37, 38.58, 37.82, 34.60, 28.99, 20.97. HRMS calc. for  $\text{C}_{14}\text{H}_{18}\text{OS}$ : 234.1078. Found: 234.1083.

### General procedure for thioacetals formation

To a Schlenck tube, under air atmosphere containing an appropriate  $\alpha,\beta$ -unsaturated carbonyl compounds (0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL), was added the thiol (2.0 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 1 h under reflux. After that, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

#### *1,1,3-tris(Phenylthio)cyclohexane (4a)*

Yield: 0.330 g (81%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 7.70-7.65 (m, 2H), 7.54-7.50 (m, 2H), 7.35-7.20 (m, 11H), 3.56 (tt,  $J$  12.0/3.5 Hz, 1H), 2.28-2.19 (m, 1H), 2.03-1.75 (m, 3H), 1.69-1.50 (m, 3H), 1.16-0.94 (m, 1H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 137.33, 136.11, 133.67, 132.63, 130.90, 130.72, 129.16, 128.96, 128.77, 128.61, 128.55, 127.08, 65.05, 43.37, 42.73, 36.12, 32.15, 22.66. HRMS calc. for  $\text{C}_{24}\text{H}_{24}\text{S}_3$ : 408.1040. Found: 408.1043.

#### *1,1,3-tris(Propylthio)cyclohexane (4b)*

Yield: 0.253 g (83%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 3.06 (tt,  $J$  11.8/3.9 Hz, 1H), 2.63 (t,  $J$  7.0 Hz, 2H), 2.51 (t,  $J$  7.0 Hz, 4H), 2.33-2.19 (m, 1H), 2.09-1.81 (m, 2H), 1.78-1.72 (m, 2H), 1.69-1.50 (m, 8H), 1.31-1.11 (m, 1H), 1.00 (t,  $J$  7.0, 3H), 0.99 (t,  $J$  7.0, 3H), 0.98 (t,  $J$  7.0, 3H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 61.14, 44.87, 39.02, 36.94, 33.13, 32.03, 30.56, 30.17, 23.16, 22.65, 22.48, 22.32, 13.73, 13.67, 13.36. MS (relative intensity)  $m/z$ : 306 (8), 263 (1), 231 (67), 155 (100). HRMS calc. for  $\text{C}_{15}\text{H}_{30}\text{S}_3$ : 306.1509. Found: 306.1513.

#### *1,1,3-tris(Benzylthio)cyclohexane (4c)*

Yield: 0.427 g (95%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 7.35-7.23 (m, 15H), 3.88 (s, 2H), 3.71 (d,  $J$  2.5 Hz, 2H), 3.69 (s, 2H), 3.02 (tt,  $J$  12.1/3.9 Hz, 1H), 2.30-2.18 (m, 1H), 2.04-1.90 (m, 2H), 1.81-1.57 (m, 4H), 1.32-1.28 (m, 1H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 138.33, 137.68, 137.27, 128.91, 128.50, 128.24, 126.72, 126.65, 62.73, 44.31, 38.98, 36.68, 34.65, 33.39, 33.21, 32.60, 22.34. HRMS calc. for  $\text{C}_{27}\text{H}_{30}\text{S}_3$ : 450.1509. Found: 450.1505.

#### *1,1,3-tris(Dodecylthio)cyclohexane (4e)*

Yield: 0.601 g (88%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ : 3.06 (tt,  $J$  12.0/3.3 Hz, 1H), 2.64 (t,  $J$  7.3 Hz, 2H), 2.57-2.46 (m, 4H), 2.30-2.20 (m, 1H), 2.08-1.81 (m, 2H), 1.78-1.66 (m, 3H), 1.64-1.49 (m, 6H), 1.40-1.19 (m, 56H), 0.88 (t,  $J$  6.7 Hz, 9H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 61.20, 44.79, 39.04, 38.91, 37.10, 33.99, 33.20, 31.80, 30.00, 29.93, 29.54, 29.45, 29.25, 29.20, 28.99, 28.87,

28.51, 28.28, 28.09, 24.35, 22.54, 13.90. HRMS calc. for  $\text{C}_{42}\text{H}_{84}\text{S}_3$ : 684.5735. Found: 684.5740.

#### *1,1,3-tris(sec-Butylthio)cyclohexane (4f)*

Yield: 0.208 g (60%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 3.18-3.08 (m, 1H), 3.03-2.96 (m, 2H), 2.81-2.73 (m, 1H), 2.32-2.23 (m, 1H), 2.05-1.91 (m, 3H), 1.79-1.42 (m, 10H), 1.31-1.21 (m, 9H), 0.96 (t,  $J$  7.3 Hz, 9H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 62.82, 46.26, 40.02, 39.21, 38.07, 33.65, 33.61, 31.62, 31.47, 31.27, 30.08, 29.95, 22.67, 22.08, 21.43, 11.21, 11.13, 11.01. MS (relative intensity)  $m/z$ : 348 (3), 259 (80), 169 (100), 113 (93). HRMS calc. for  $\text{C}_{18}\text{H}_{36}\text{S}_3$ : 348.1979. Found: 348.1982.

#### *1,1,3-tris(4-Methoxyphenylthio)cyclohexane (4g)*

Yield: 0.428 g (86%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.49 (d,  $J$  9.0 Hz, 2H), 7.39 (d,  $J$  8.5 Hz, 2H), 7.29 (d,  $J$  8.8 Hz, 2H), 6.82-6.77 (m, 6H), 3.78 (s, 9H), 3.36 (tt,  $J$  11.9/3.4 Hz, 1H), 2.07-1.93 (m, 2H), 1.92-1.70 (m, 2H), 1.58-1.49 (m, 3H), 1.04-0.95 (m, 1H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 160.40, 160.28, 159.50, 138.83, 137.99, 136.27, 123.39, 121.84, 121.09, 114.19, 113.97, 64.69, 55.08, 43.75, 42.77, 35.72, 31.98, 22.62. MS (relative intensity)  $m/z$ : 359 (38), 219 (100), 187 (27), 139 (49), 77 (13). HRMS calc. for  $\text{C}_{27}\text{H}_{30}\text{O}_3\text{S}_3$ : 498.1357. Found: 498.1355.

#### *2-((1,3-bis(Furan-2-ylmethylthio)cyclohexylthio)methyl)furan (4h)*

Yield: 0.344 g (82%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.38-7.32 (m, 3H), 6.30-6.29 (m, 3H), 6.20-6.17 (m, 3H), 3.94 (s, 2H), 3.83 (s, 2H), 3.70 (s, 2H), 3.05 (tt,  $J$  12.2/3.8 Hz, 1H), 2.27-2.22 (m, 1H), 2.02-1.92 (m, 2H), 1.82-1.56 (m, 4H), 1.20 (qd,  $J$  8.4/4.0 Hz, 1H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 151.64, 151.29, 150.93, 141.75, 141.69, 110.35, 110.28, 107.34, 107.27, 107.04, 62.76, 44.14, 39.23, 36.55, 32.43, 26.74, 25.70, 25.47, 22.32. MS (relative intensity)  $m/z$ : 339 (15), 306 (1), 225 (10), 81 (100). HRMS calc. for  $\text{C}_{21}\text{H}_{24}\text{O}_3\text{S}_3$ : 420.0887. Found: 420.0890.

#### *2-((1,3-bis(Furan-2-ylmethylthio)-4,4-dimethylcyclohexylthio)methyl)furan (4k)*

Yield: 0.340 g (76%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.35-7.33 (m, 3H), 6.31-6.28 (m, 3H), 6.19-6.18 (m, 3H), 3.92 (s, 2H), 3.82 (d,  $J$  1.7 Hz, 2H), 3.64 (d,  $J$  3.2 Hz, 2H), 2.83 (t,  $J$  8.1 Hz, 1H), 2.04 (d,  $J$  9.3 Hz, 2H), 1.93-1.84 (m, 1H), 1.81-1.73 (m, 2H), 1.29-1.24 (m, 1H), 0.99 (s, 3H), 0.85 (s, 3H).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 151.62, 151.34, 151.06, 141.88, 141.82, 110.47, 110.43, 110.33, 107.51, 107.49, 107.38, 63.11, 51.06, 41.85, 36.68, 34.50, 33.00, 29.74, 28.80, 25.87, 25.60,



19.74. MS (relative intensity)  $m/z$ : 367 (9), 334 (7), 253 (11), 221 (6), 81 (100). HRMS calc. for  $C_{23}H_{28}O_3S_3$ : 448.1200. Found: 448.1205.

*1-((5,5-bis(Benzylthio)-2,2-dimethylcyclohexylthio)methyl)benzene (4l)*

Yield: 0.425 g (89%).  $^1H$ NMR ( $CDCl_3$ , 200 MHz)  $\delta$ : 7.35-7.16 (m, 15H), 3.86 (s, 2H), 3.68 (d,  $J$  3.5 Hz, 2H), 3.58 (s, 2H), 2.85-2.76 (m, 1H), 2.08-2.03 (m, 2H), 1.92-1.69 (m, 3H), 1.31-1.22 (m, 1H), 1.00 (s, 1H), 0.86 (s, 3H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 138.50, 137.70, 137.42, 129.02, 128.99, 128.78, 128.33, 128.25, 126.80, 126.74, 63.08, 50.61, 41.88, 36.69, 34.45, 33.46, 32.97, 29.93, 19.72. HRMS calc. for  $C_{29}H_{34}S_3$ : 478.1822. Found: 478.1819.

*1-(1,3-bis(4-Methoxyphenylthio)-4,4-dimethylcyclohexylthio)-4-methoxybenzene (4m)*

Yield: 0.483 g (92%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 7.45-7.43 (m, 2H), 7.34-7.30 (m, 4H), 6.86-6.81 (m, 4H), 6.69-6.67 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.24-3.20 (m, 1H), 1.96-1.85 (m, 4H), 1.60-1.53 (m, 1H), 1.28-1.25 (m, 1H), 1.21 (s, 3H), 0.67 (s, 3H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 160.44, 160.21, 159.30, 138.83, 138.16, 135.79, 132.55, 125.77, 121.02, 114.42, 114.05, 113.94, 64.60, 56.89, 55.19, 55.07, 39.64, 37.33, 34.21, 32.21, 30.47, 19.45. MS (relative intensity)  $m/z$ : 416 (1), 387 (34), 247 (100), 139 (49), 107 (50). HRMS calc. for  $C_{29}H_{34}O_3S_3$ : 526.1670. Found: 526.1673.

*1,1-Dimethyl-2,4,4-tris(propylthio)cyclohexane (4n)*

Yield: 0.260 g (78%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 2.81 (dd,  $J$  9.5/4.4 Hz, 1H), 2.64 (t,  $J$  7.4 Hz, 2H), 2.48 (t,  $J$  7.4 Hz, 4H), 2.20-1.72 (m, 5H), 1.60 (sex,  $J$  7.4 Hz, 6H), 1.40-1.20 (m, 1H), 1.11 (s, 3H), 1.00 (t,  $J$  7.4 Hz, 3H), 1.09 (t,  $J$  7.4 Hz, 3H), 0.98 (t,  $J$  7.4 Hz, 3H), 0.88 (s, 3H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 61.39, 51.05, 42.46, 36.88, 34.55, 33.25, 30.68, 30.29, 30.19, 23.15, 22.68, 22.38, 19.54, 13.79, 13.74, 13.30. HRMS calc. for  $C_{17}H_{34}S_3$ : 334.1822. Found: 334.1820.

*General procedure for thioethers formation*

To a Schlenk tube, under air atmosphere containing an appropriate dihydropyran (0.50 mmol) in  $CH_2Cl_2$  (2.0 mL), was added the thiol (0.6 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 20 min at 0 °C for thioethers products. After that, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

*2-(Propylthio)-tetrahydro-2H-pyran (5a)*

Yield: 0.120 g (75%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 4.16-3.71 (m, 2H), 3.53-3.36 (m, 1H), 2.72-2.49 (m, 2H), 1.92-1.51 (m, 8H), 0.99 (t,  $J$  7.20 Hz, 3H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 98.80, 67.26, 62.26, 51.81, 35.98, 29.21, 25.44, 19.59. HRMS calc. for  $C_8H_{16}OS$ : 160.0921. Found: 160.0918.

*2-(Benzylthio)-tetrahydro-2H-pyran (5b)*

Yield: 0.191 g (91%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 7.33-7.20 (m, 5H), 4.72-4.69 (m, 1H), 4.14-4.08 (m, 1H), 3.87-3.81 (m, 1H), 3.75-3.70 (m, 1H), 3.53-3.47 (m, 1H), 1.89-1.75 (m, 2H), 1.67-1.49 (m, 4H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 128.26, 128.65, 128.09, 126.49, 80.14, 63.80, 34.38, 33.59, 30.49, 25.37, 21.27. HRMS calc. for  $C_{12}H_{16}OS$ : 208.0921. Found: 208.0924.

*2-(4-Methoxyphenylthio)-tetrahydro-2H-pyran (5c)*

Yield: 0.194 g (87%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 7.43 (d,  $J$  8.8 Hz, 2H), 6.84 (d,  $J$  8.8 Hz, 2H), 5.04-4.98 (m, 1H), 4.23-4.12 (m, 1H), 3.79 (s, 3H), 3.59-3.48 (m, 1H), 2.04-1.77 (m, 2H), 1.72-1.57 (m, 4H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 158.96, 133.94, 124.85, 114.00, 85.82, 64.22, 54.81, 31.15, 25.21, 21.37. HRMS calc. for  $C_{12}H_{16}O_2S$ : 224.0871. Found: 224.0874.

*2-(2-Furan-2-ylmethylthio)-tetrahydro-2H-pyran (5d)*

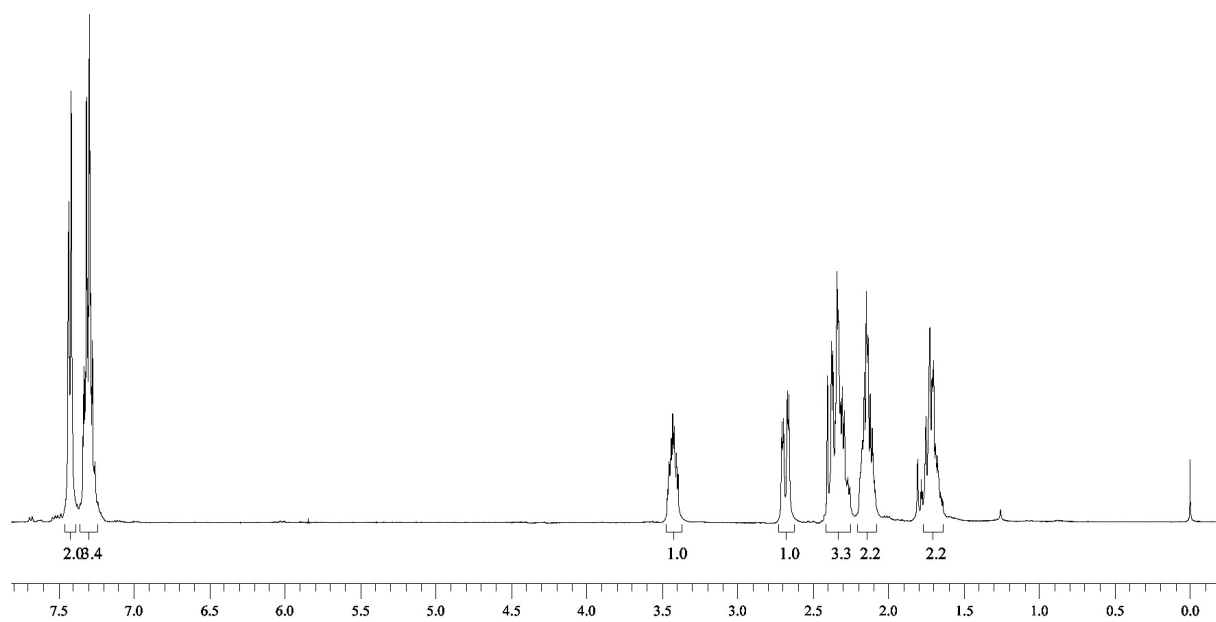
Yield: 0.120 g (61%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 7.35 (s, 1H), 6.30-6.29 (m, 1H), 6.17 (d,  $J$  2.6 Hz, 1H), 4.87-4.85 (m, 1H), 4.12-4.06 (m, 1H), 3.91 (d,  $J$  14.6 Hz, 1H), 3.69 (d,  $J$  14.6 Hz, 1H), 3.55-3.49 (m, 1H), 1.94-1.54 (m, 6H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 151.68, 141.97, 110.27, 107.28, 80.84, 64.02, 30.64, 25.89, 25.56, 21.39. HRMS calc. for  $C_{10}H_{14}O_2S$ : 198.0714. Found: 198.0716.

*2-(2-Chlorophenylthio)-tetrahydro-2H-pyran (5e)*

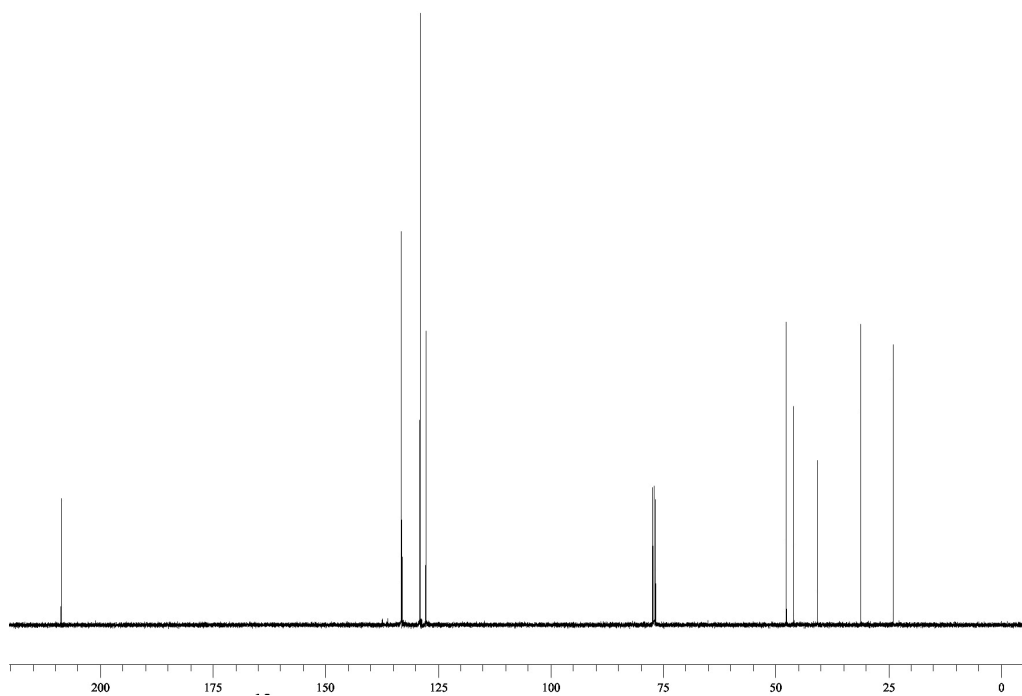
Yield: 0.194 g (85%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 7.59 (dd,  $J$  6.0/1.7 Hz, 1H), 7.36 (dd,  $J$  6.1/1.4 Hz, 1H), 7.26-7.07 (m, 2H), 5.37 (t,  $J$  4.4 Hz, 1H), 4.22-4.11 (m, 1H), 3.67-3.56 (m, 1H), 2.17-1.59 (m, 6H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 135.02, 133.27, 129.90, 129.12, 126.91, 126.65, 83.21, 63.67, 31.05, 25.19, 20.96. HRMS calc. for  $C_{11}H_{13}ClOS$ : 228.0375. Found: 228.0371.

*2-(4-Chlorobenzylthio)-tetrahydro-2H-pyran (5f)*

Yield: 0.218 g (90%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 7.28-7.15 (m, 4H), 4.69-4.66 (m, 1H), 4.11-4.06 (m, 1H), 3.83-3.75 (m, 1H), 3.69-3.64 (m, 1H), 3.51-3.46 (m, 1H), 1.89-1.46 (m, 6H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 136.93, 132.31, 130.08, 128.28, 80.18, 63.88, 32.98, 30.50, 25.40, 21.29. HRMS calc. for  $C_{12}H_{15}ClOS$ : 242.0532. Found: 242.0535.



**Figure S1.** <sup>1</sup>H NMR spectra of compound **3a** in CDCl<sub>3</sub> at 200 MHz.



**Figure S2.** <sup>13</sup>C NMR spectra of compound **3a** in CDCl<sub>3</sub> at 100 MHz.

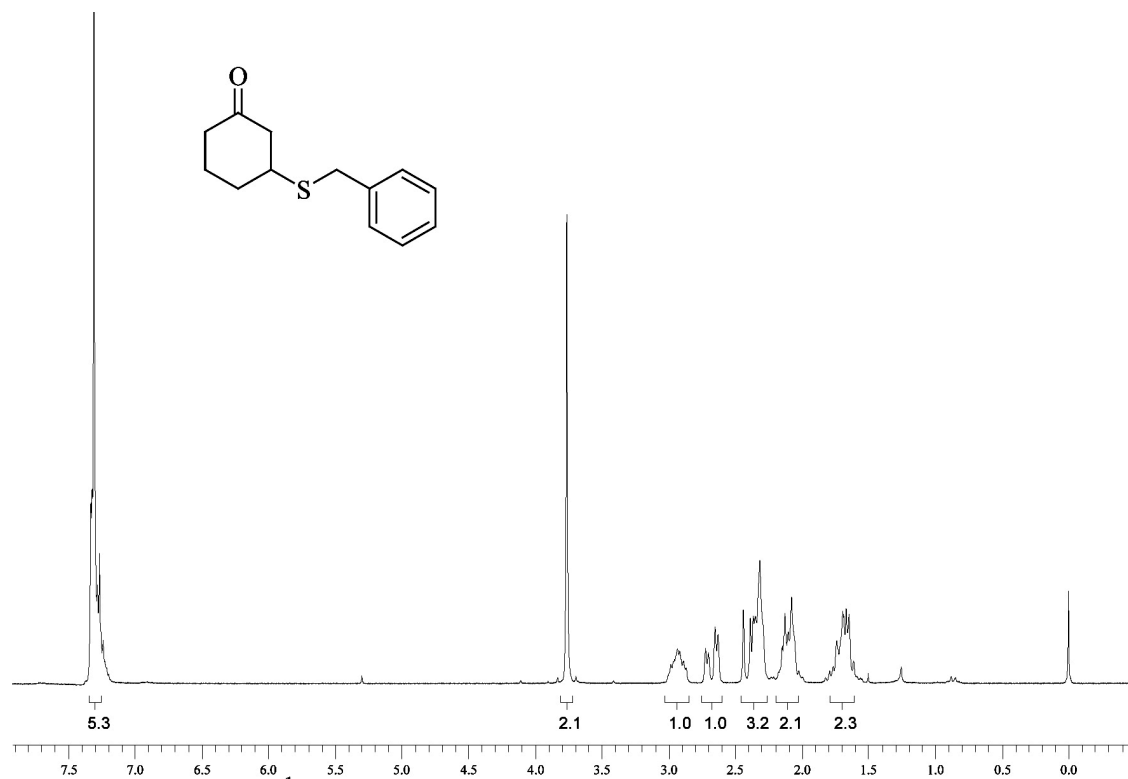


Figure S3.  $^1\text{H}$  NMR spectra of compound **3c** in  $\text{CDCl}_3$  at 200 MHz.

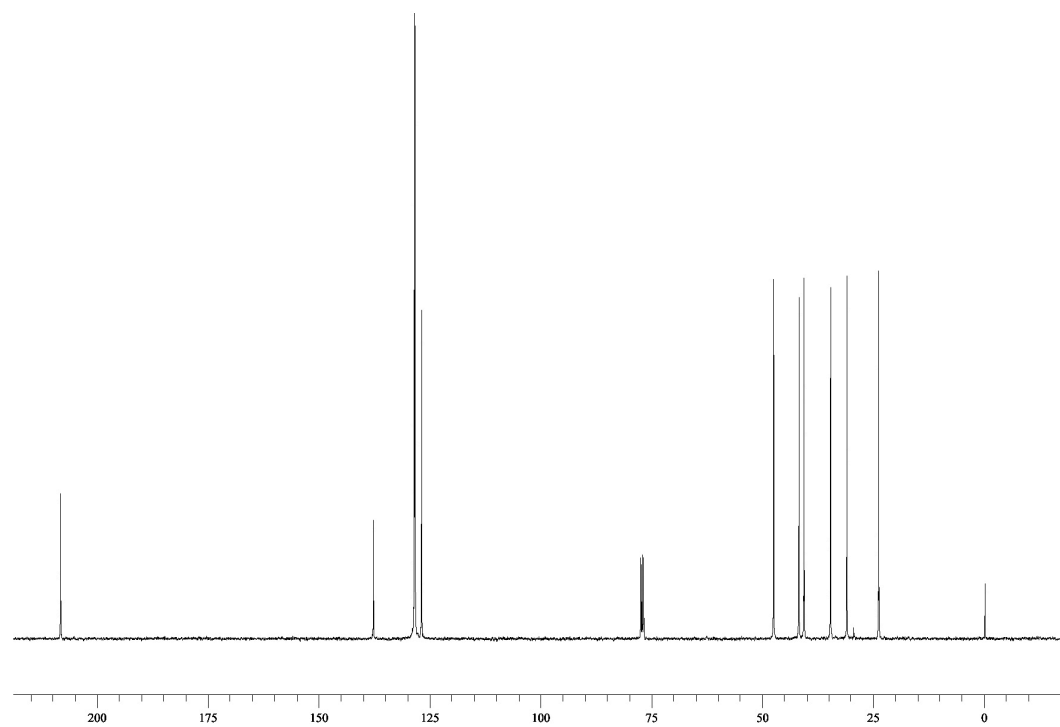
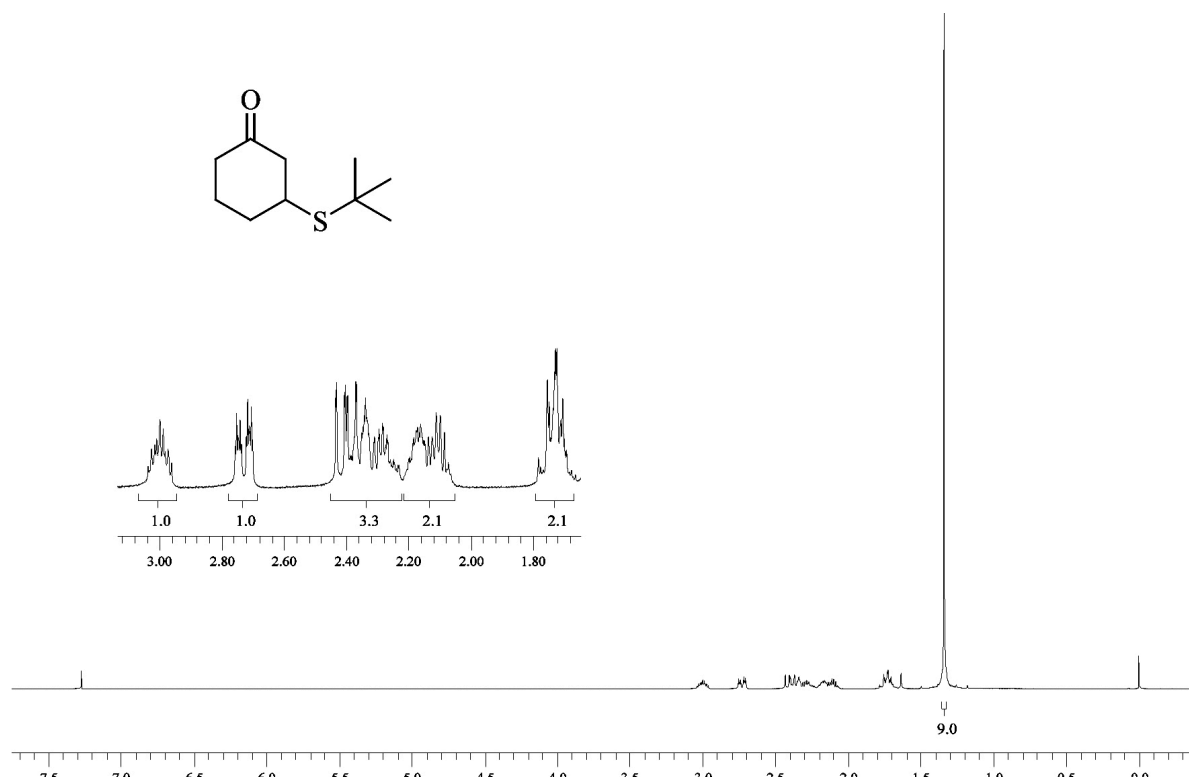
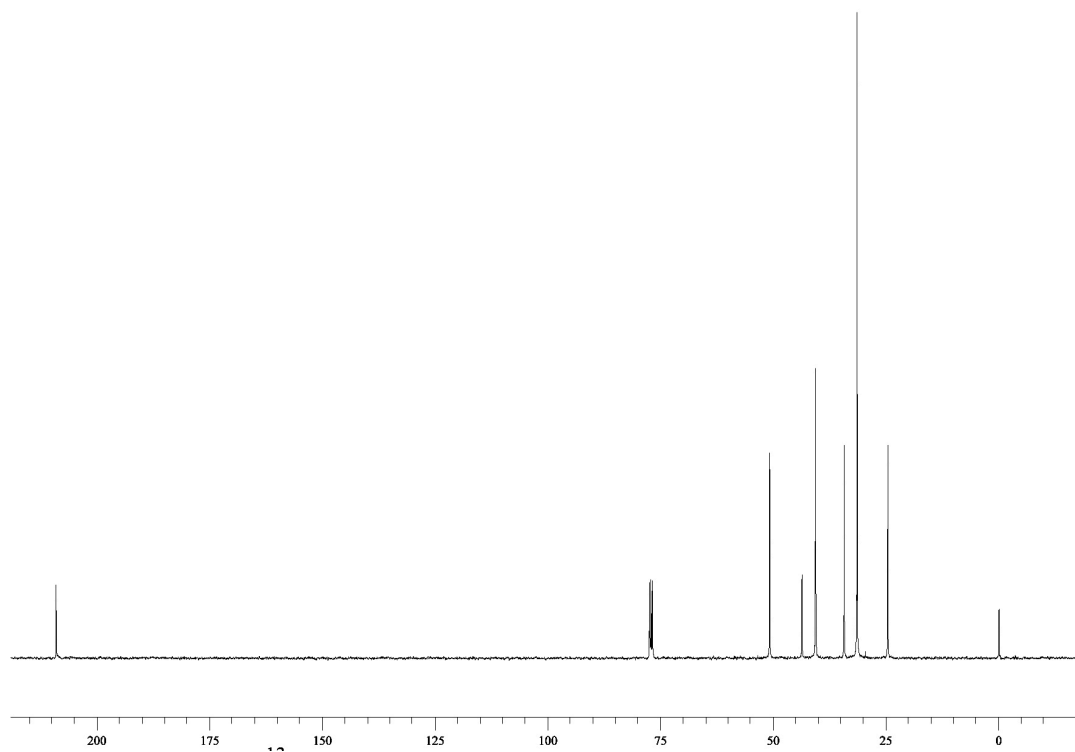


Figure S4.  $^{13}\text{C}$  NMR spectra of compound **3a** in  $\text{CDCl}_3$  at 100 MHz.



**Figure S5.** <sup>1</sup>H NMR spectra of compound **3d** in CDCl<sub>3</sub> at 200 MHz.



**Figure S6.** <sup>13</sup>C NMR spectra of compound **3d** in CDCl<sub>3</sub> at 100 MHz.

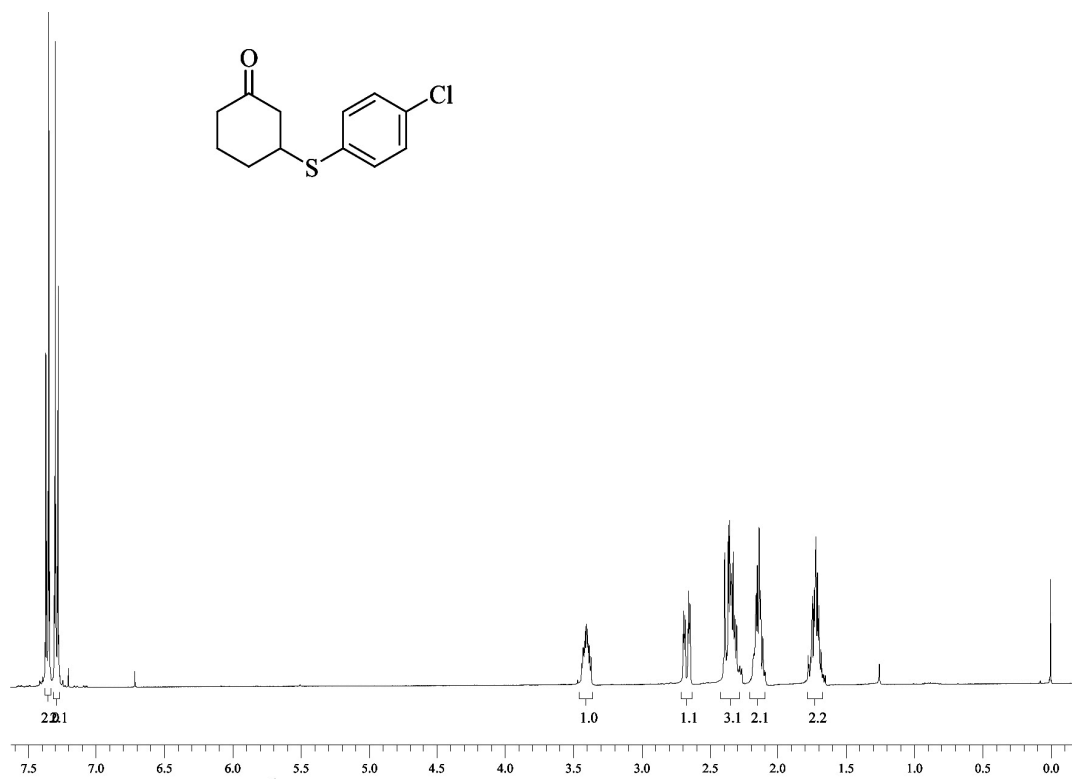


Figure S7.  $^1\text{H NMR}$  spectra of compound **3h** in  $\text{CDCl}_3$  at 400 MHz.

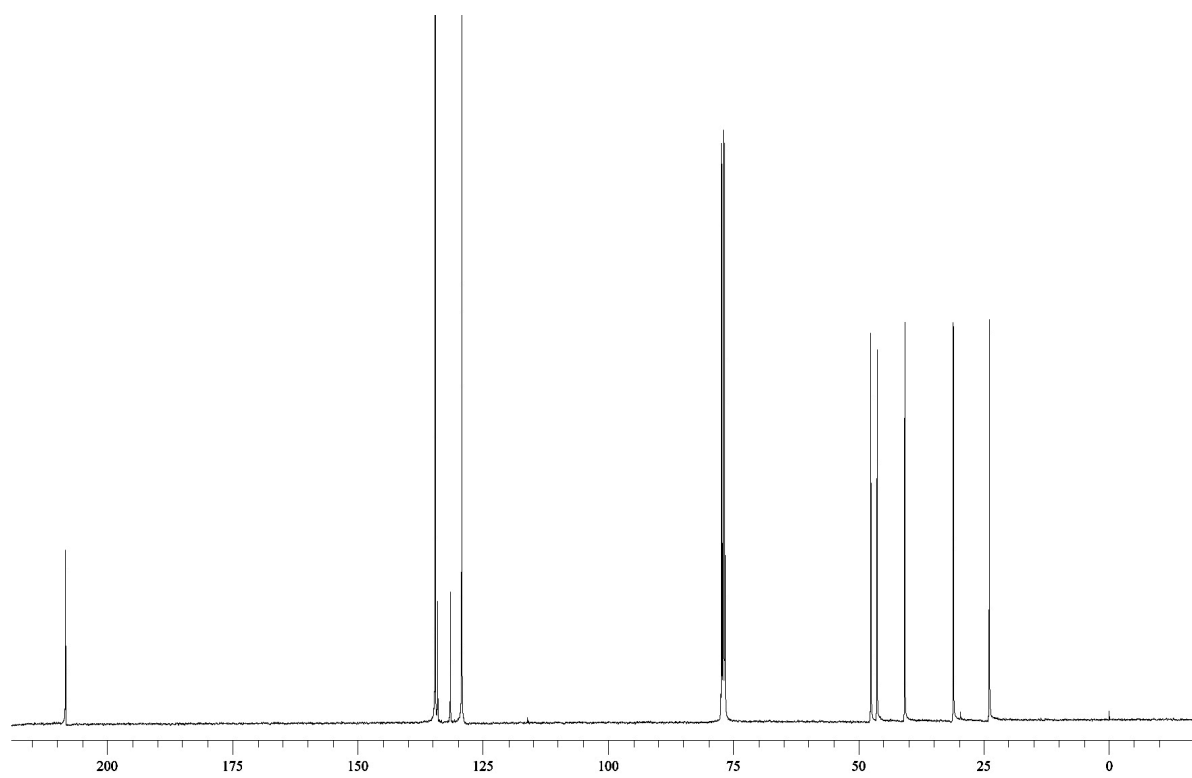
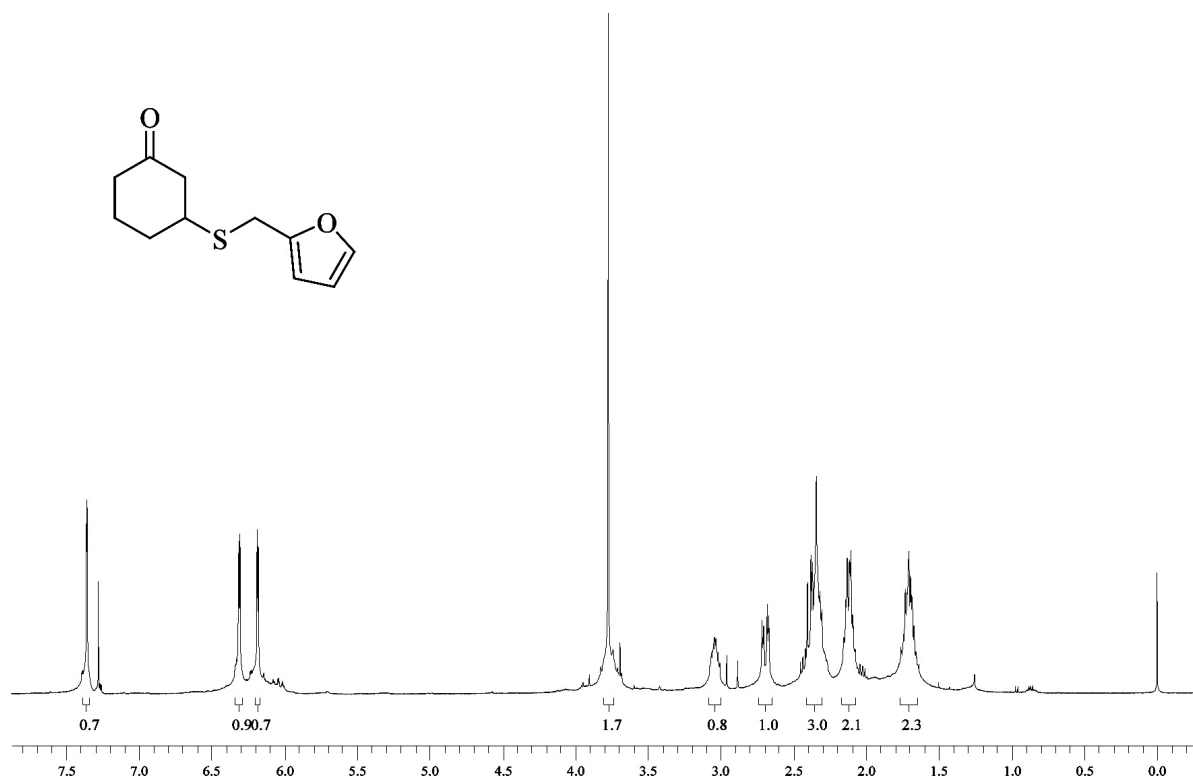
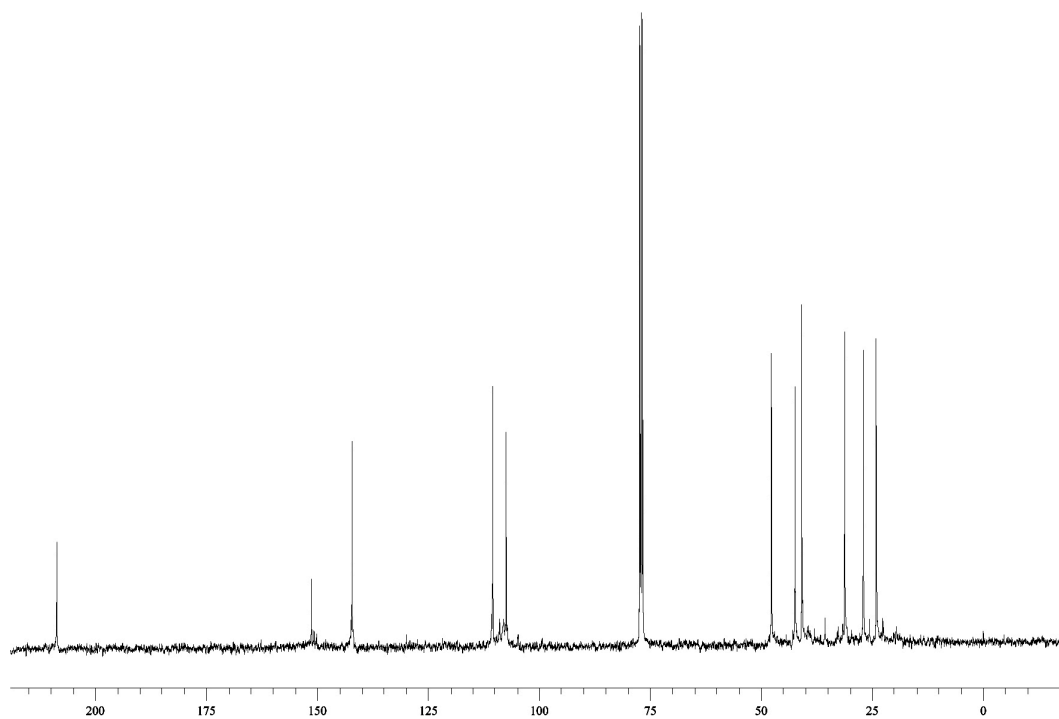


Figure S8.  $^{13}\text{C NMR}$  spectra of compound **3h** in  $\text{CDCl}_3$  at 100 MHz.



**Figure S9.** <sup>1</sup>H NMR spectra of compound **3i** in CDCl<sub>3</sub> at 200 MHz.



**Figure S10.** <sup>13</sup>C NMR spectra of compound **3i** in CDCl<sub>3</sub> at 100 MHz.

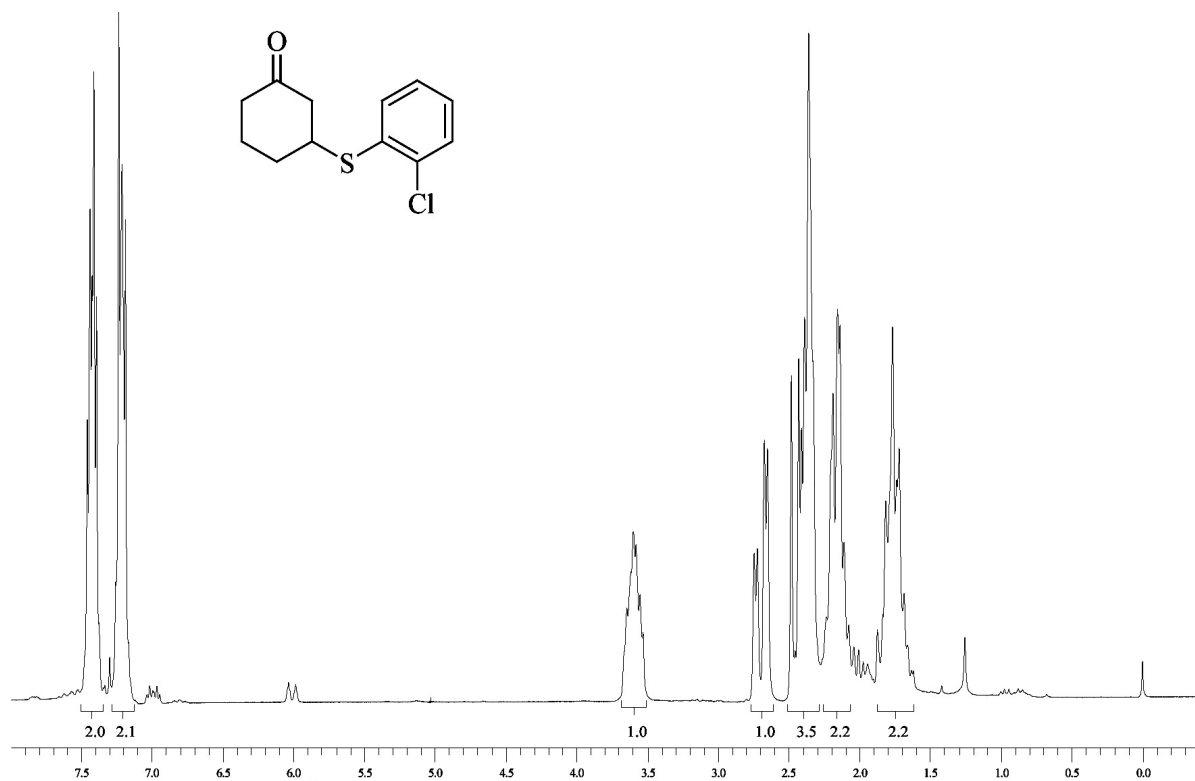


Figure S11.  $^1\text{H}$  NMR spectra of compound **3k** in  $\text{CDCl}_3$  at 200 MHz.

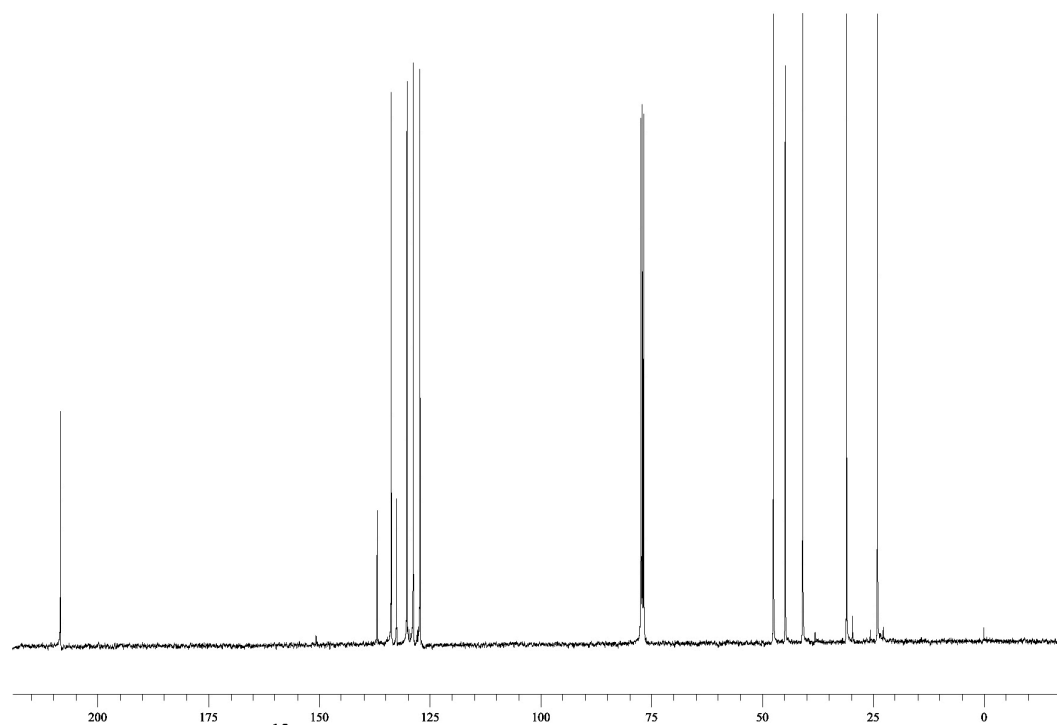


Figure S12.  $^{13}\text{C}$  NMR spectra of compound **3k** in  $\text{CDCl}_3$  at 100 MHz.

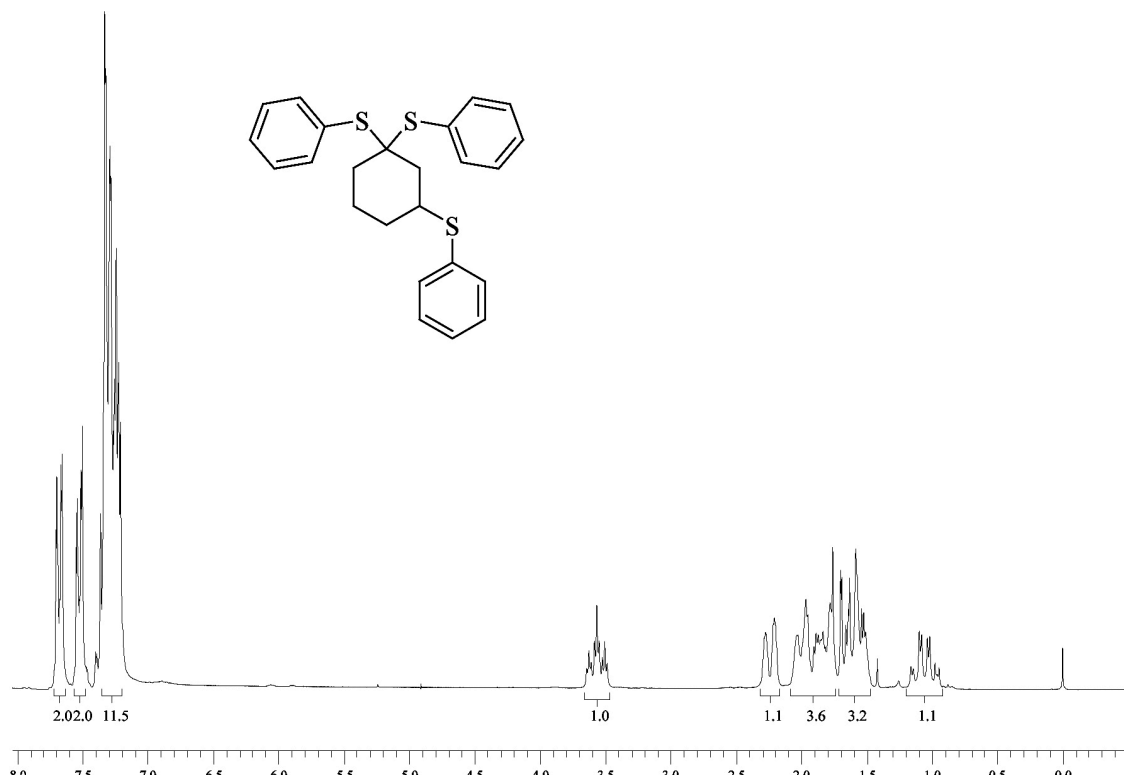


Figure S13.  $^1\text{H}$  NMR spectra of compound **4a** in  $\text{CDCl}_3$  at 200 MHz.

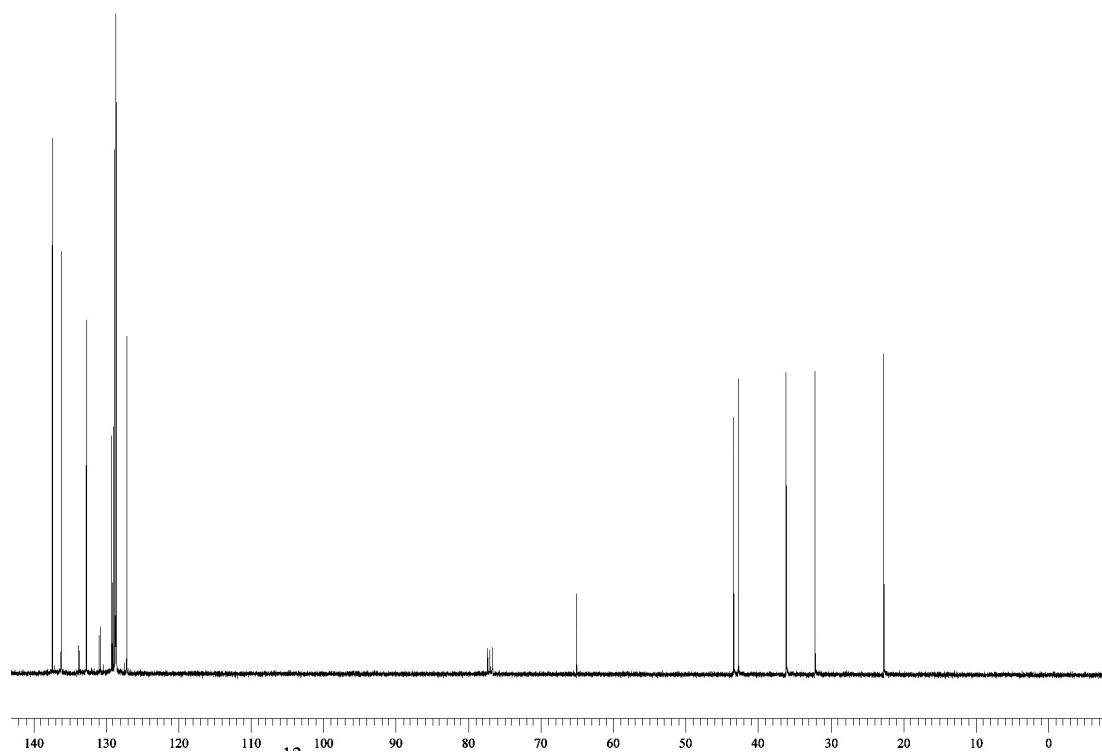


Figure S14.  $^{13}\text{C}$  NMR spectra of compound **4a** in  $\text{CDCl}_3$  at 100 MHz.



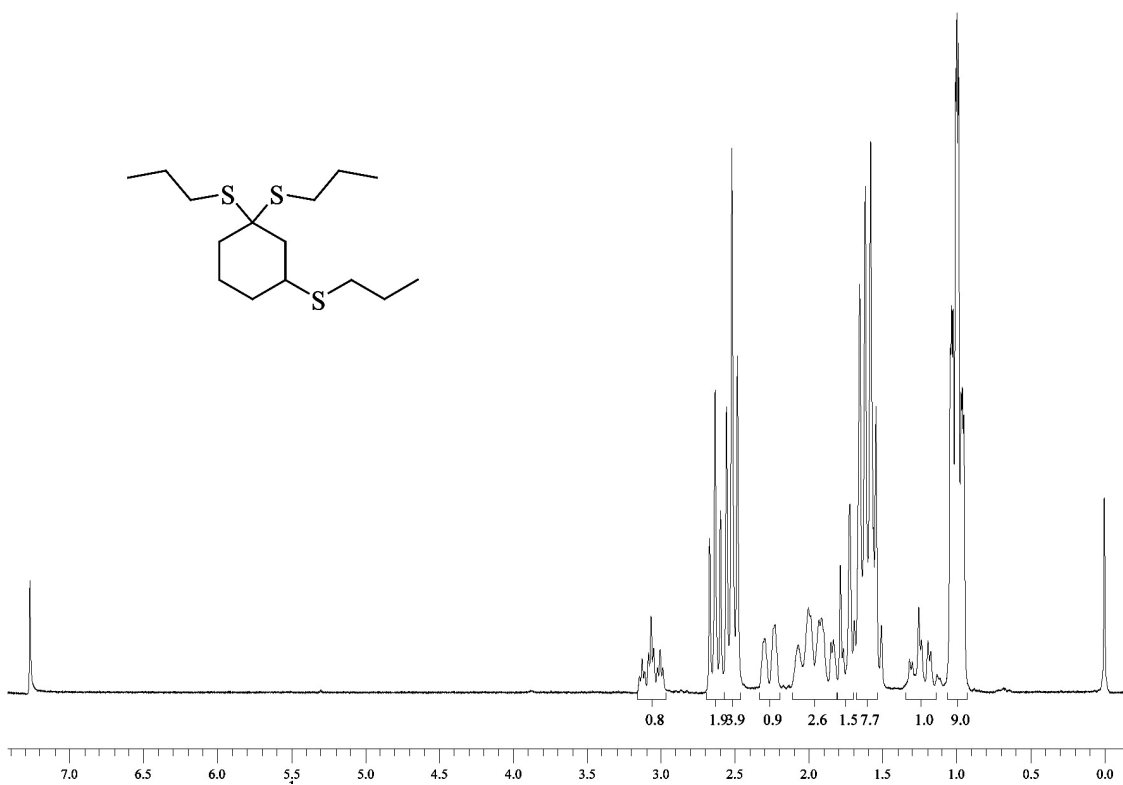


Figure S15.  $^1\text{H}$  NMR spectra of compound **4b** in  $\text{CDCl}_3$  at 200 MHz.

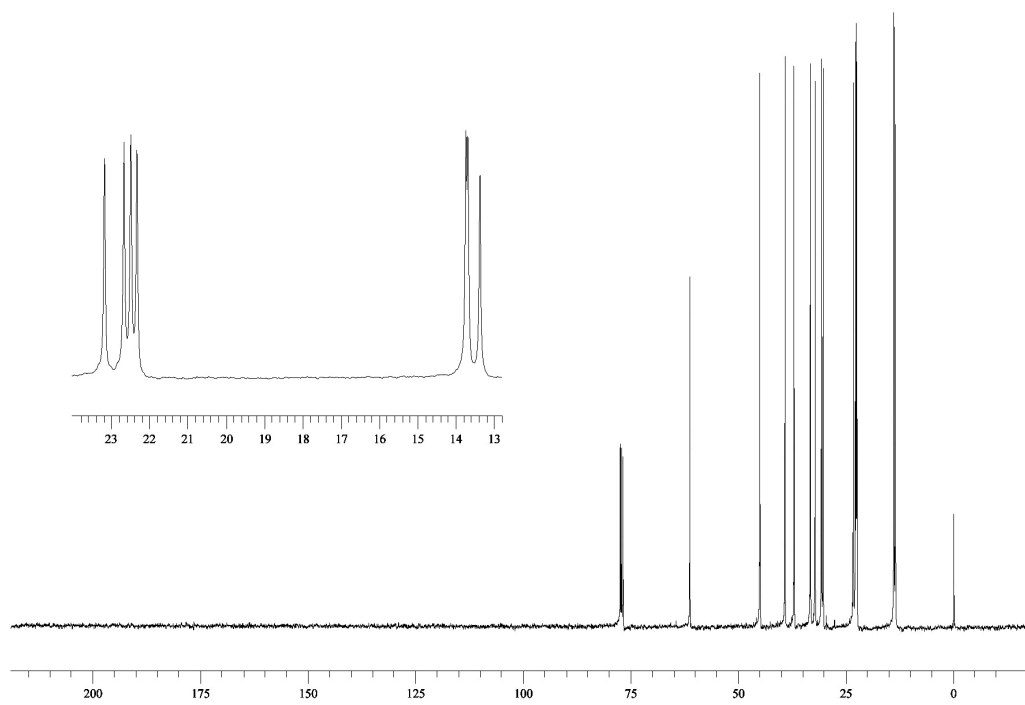
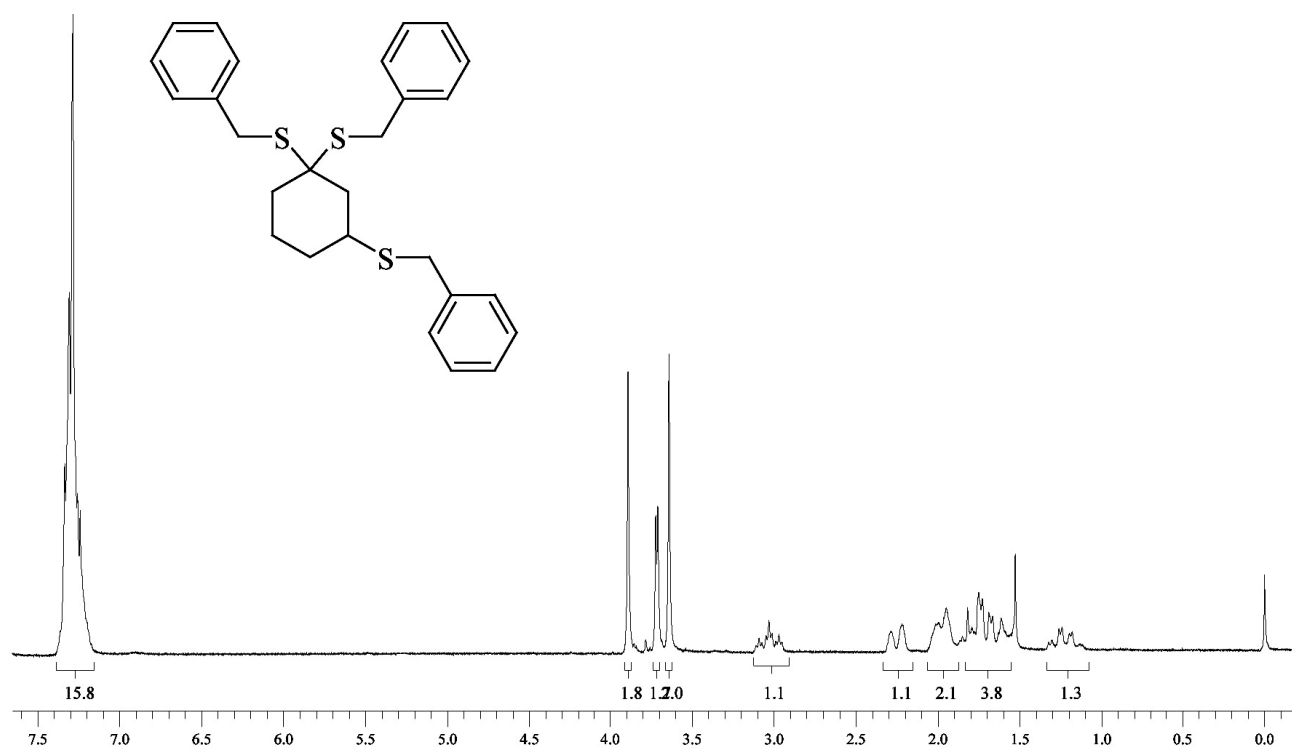
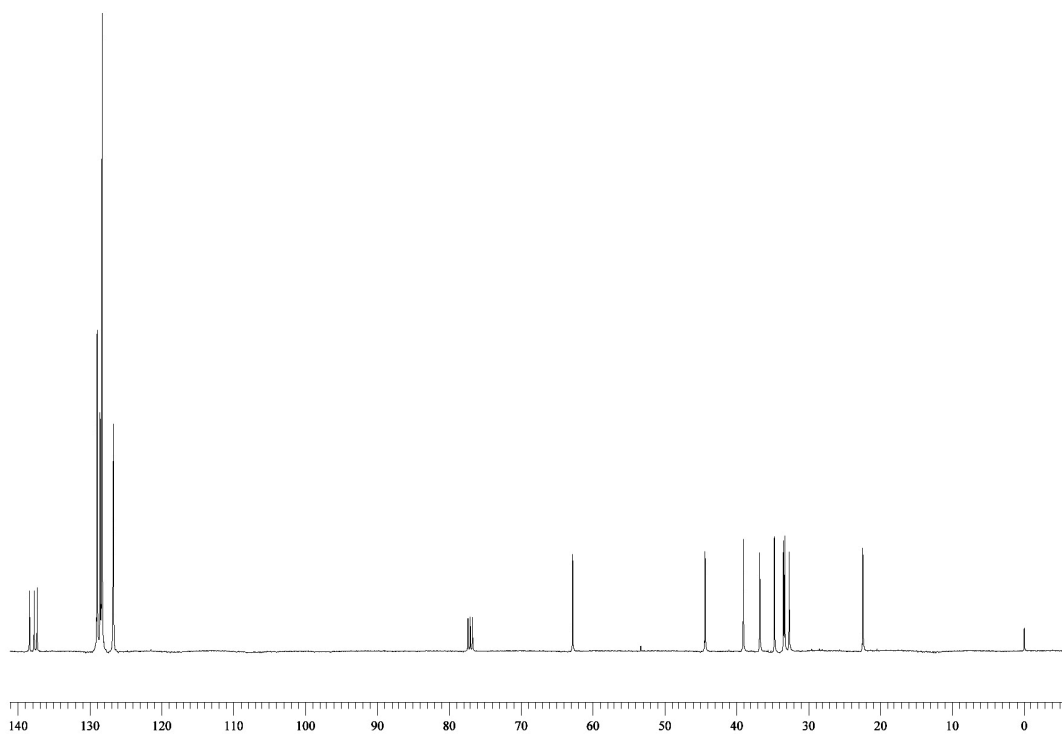


Figure S16.  $^{13}\text{C}$  NMR spectra of compound **4b** in  $\text{CDCl}_3$  at 100 MHz.



**Figure S17.** <sup>1</sup>H NMR spectra of compound **4c** in CDCl<sub>3</sub> at 200 MHz.



**Figure S18.** <sup>13</sup>C NMR spectra of compound **4c** in CDCl<sub>3</sub> at 100 MHz.

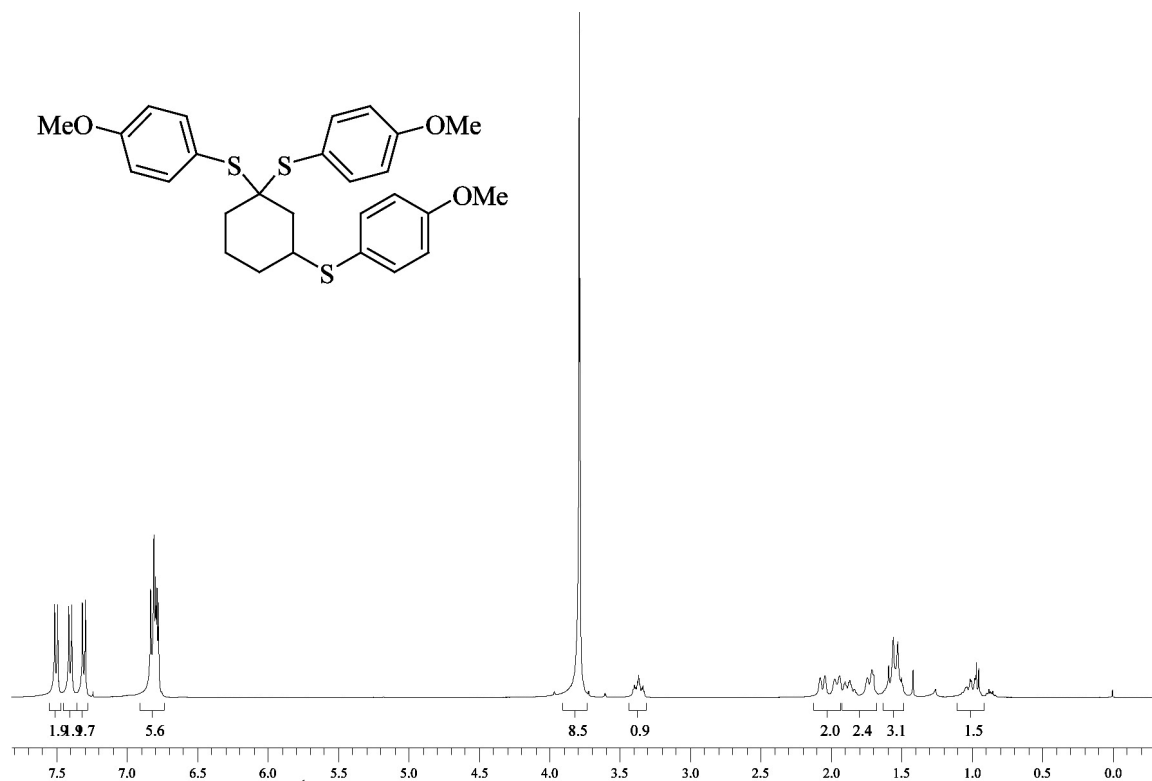


Figure S19.  $^1\text{H NMR}$  spectra of compound **4g** in  $\text{CDCl}_3$  at 400 MHz.

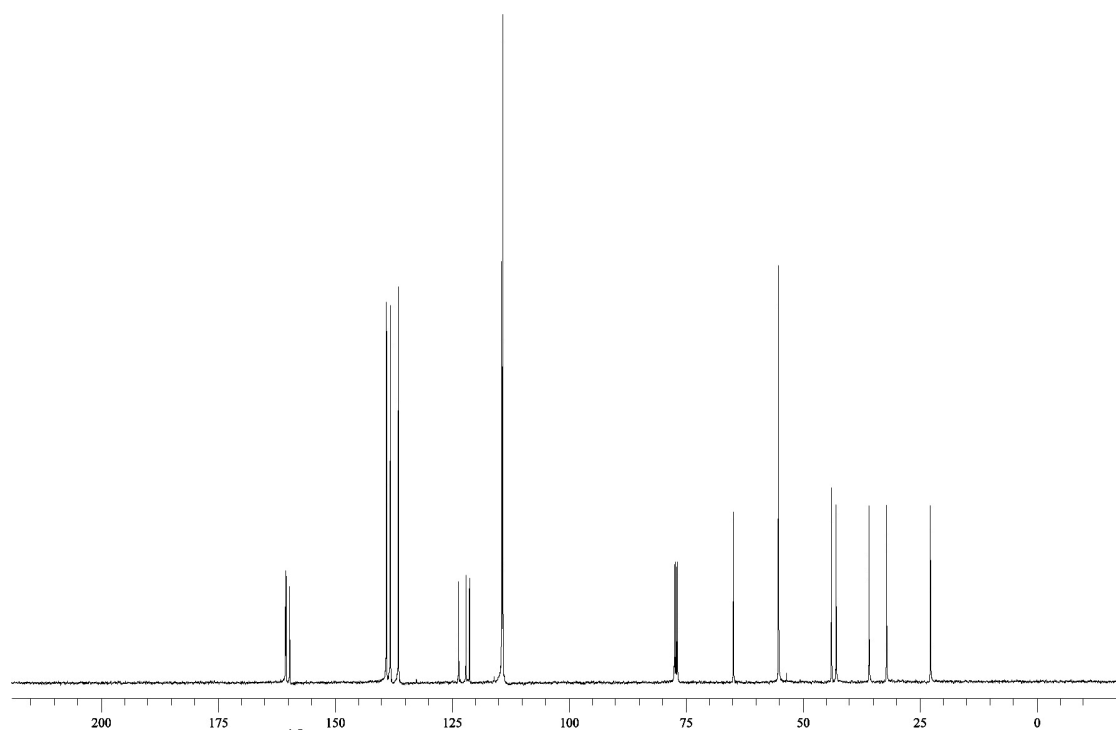
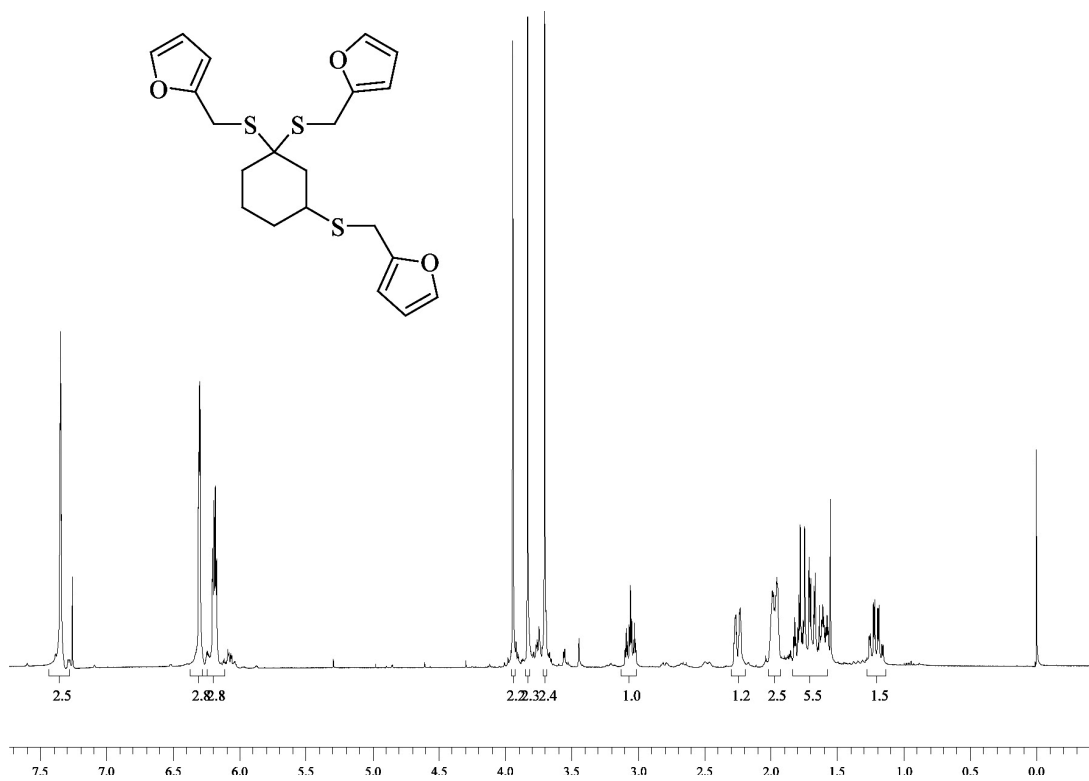
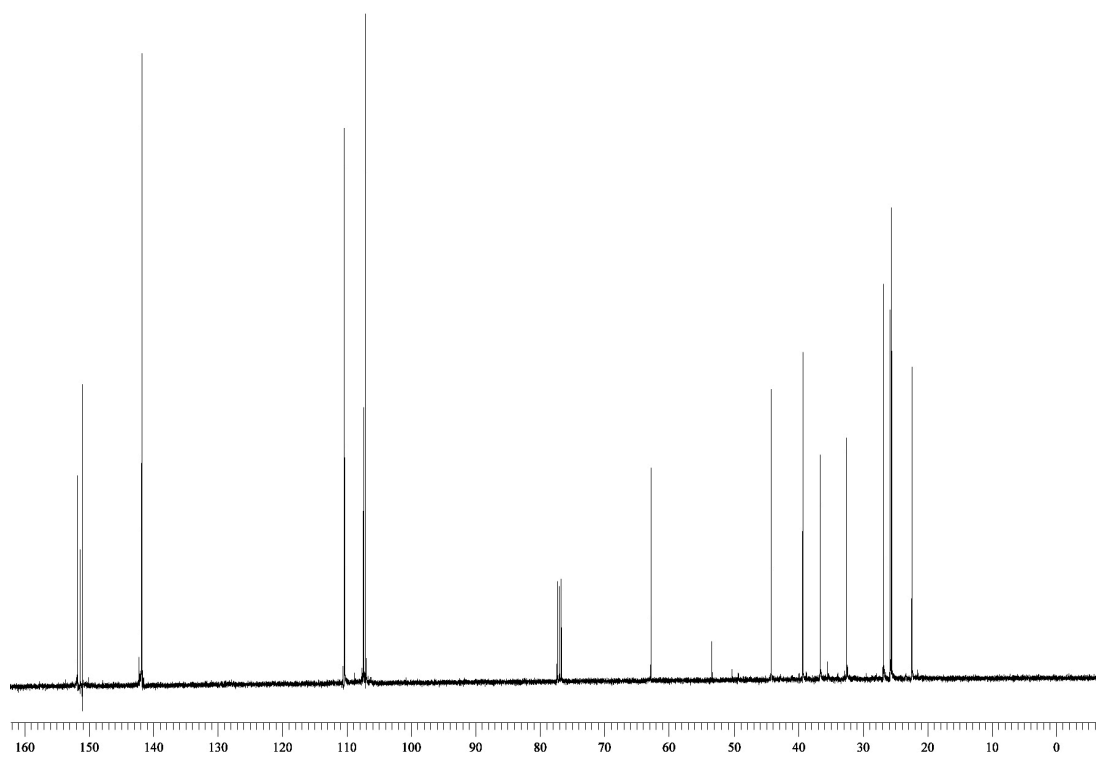


Figure S20.  $^{13}\text{C NMR}$  spectra of compound **4g** in  $\text{CDCl}_3$  at 100 MHz.



**Figure S21.** <sup>1</sup>H NMR spectra of compound **4h** in CDCl<sub>3</sub> at 400 MHz.



**Figure S22.** <sup>13</sup>C NMR spectra of compound **4h** in CDCl<sub>3</sub> at 100 MHz.

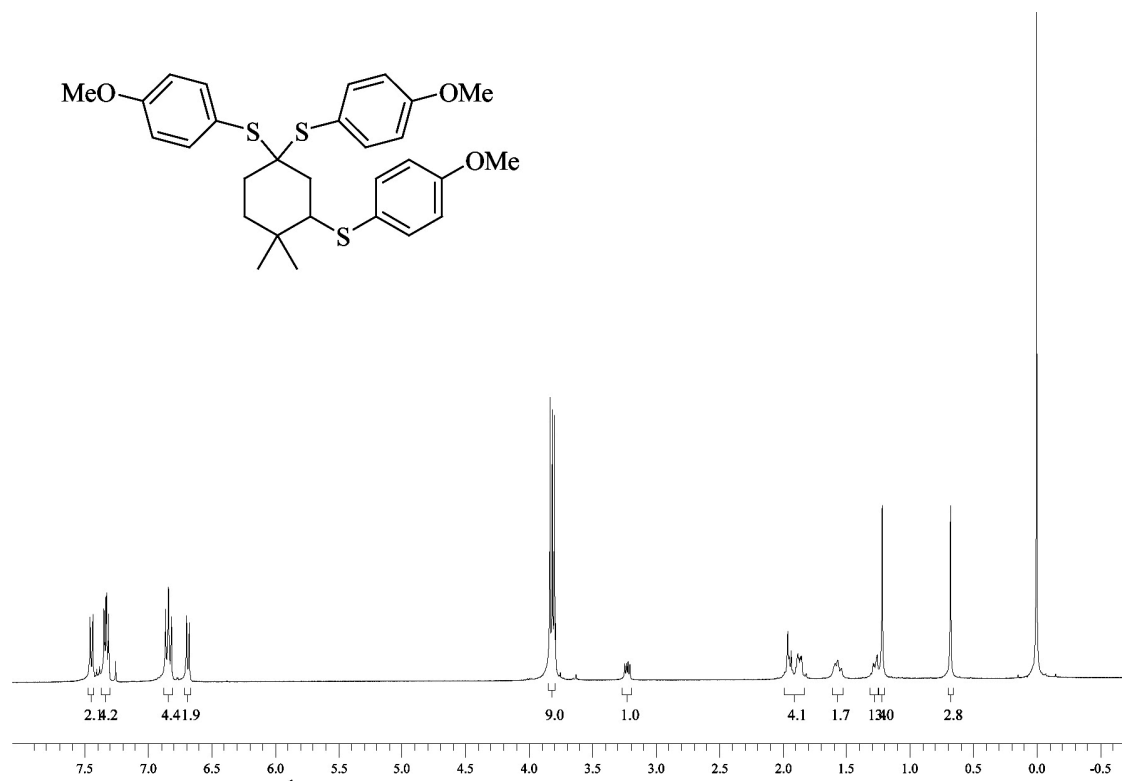


Figure S23.  $^1\text{H}$  NMR spectra of compound **4m** in  $\text{CDCl}_3$  at 400 MHz.

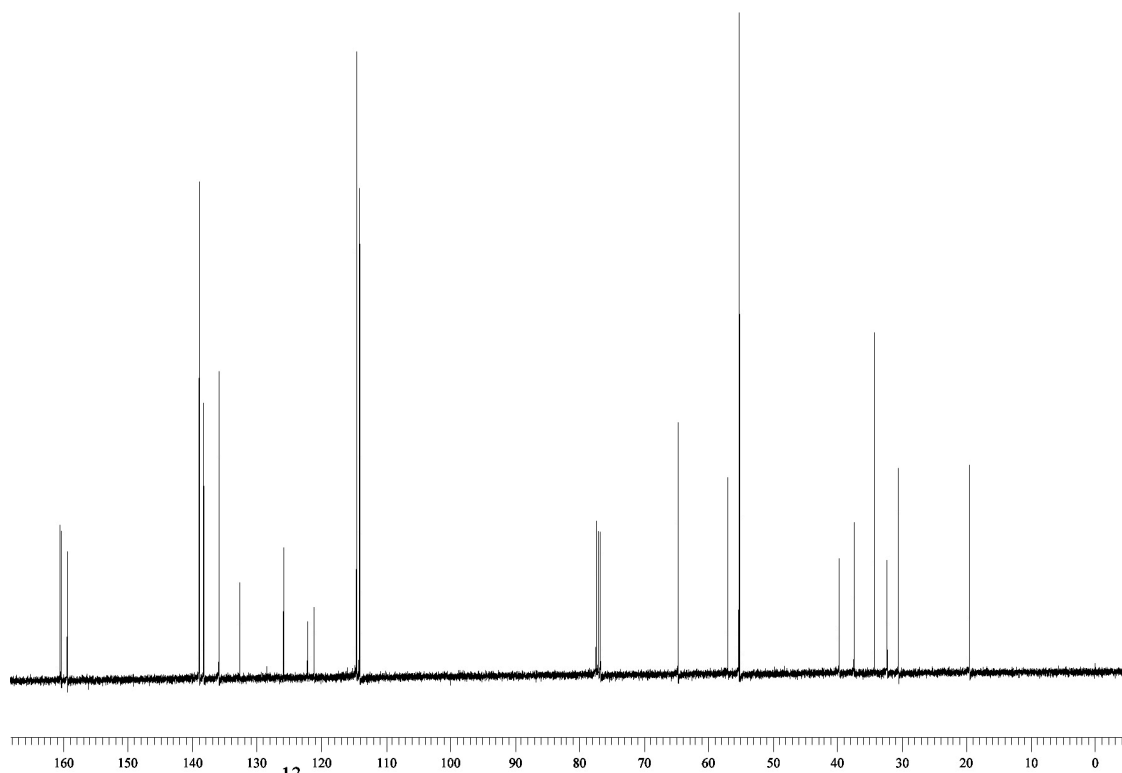


Figure S24.  $^{13}\text{C}$  NMR spectra of compound **4m** in  $\text{CDCl}_3$  at 100 MHz.

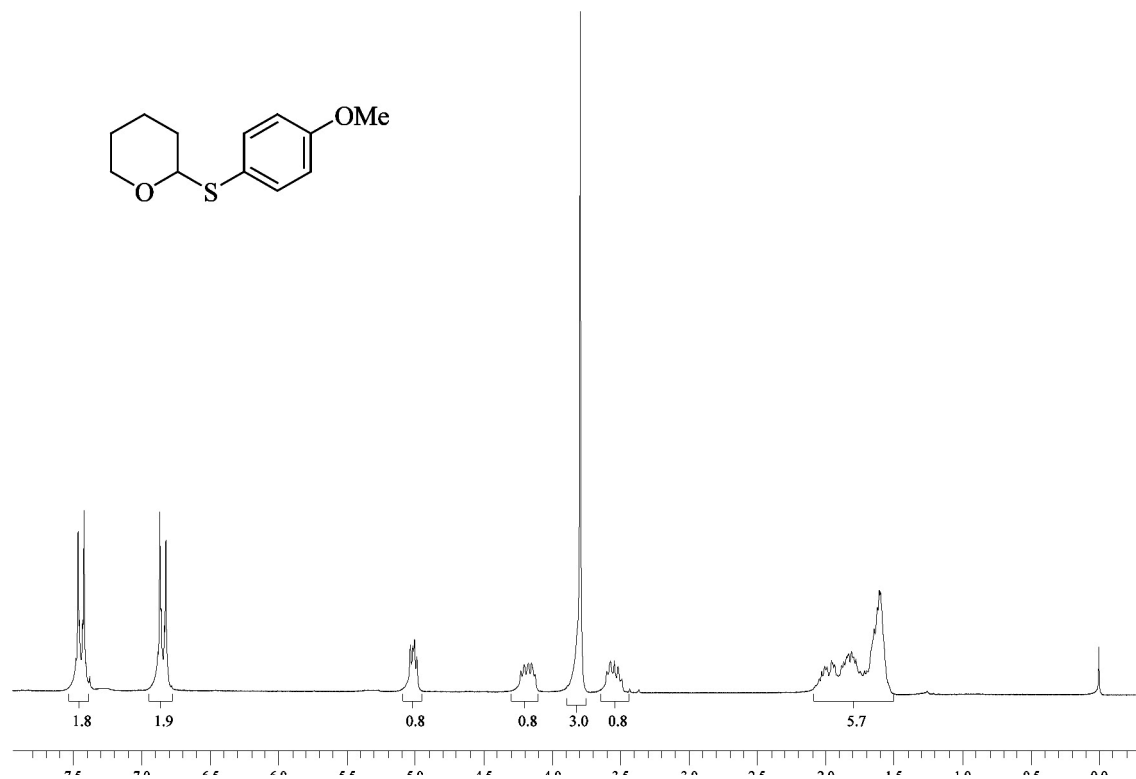


Figure S25. <sup>1</sup>H NMR spectra of compound **5c** in CDCl<sub>3</sub> at 400 MHz.

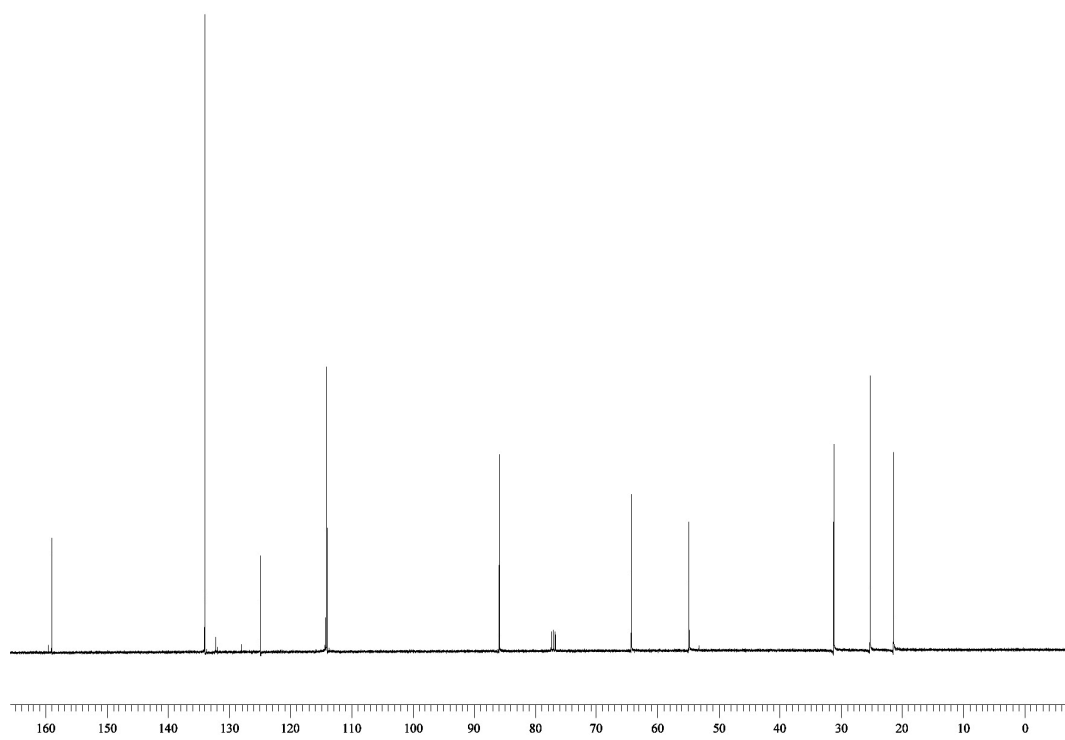
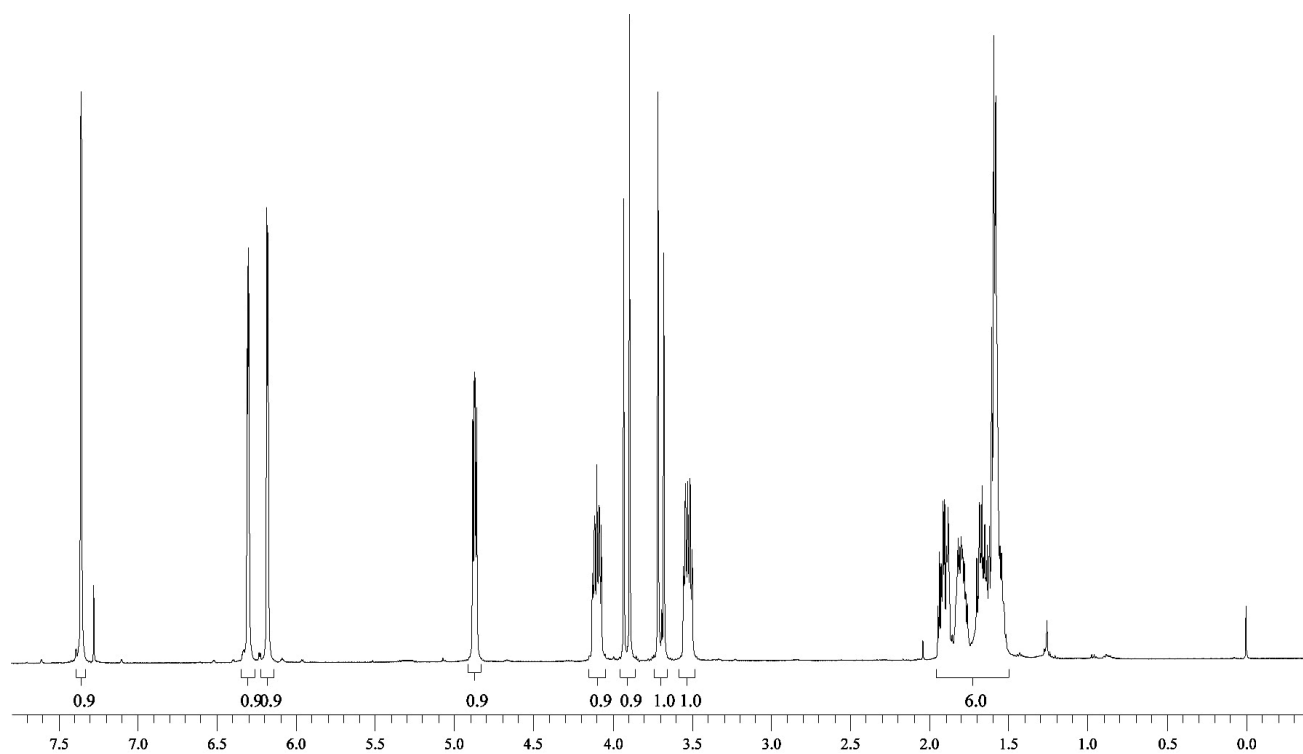
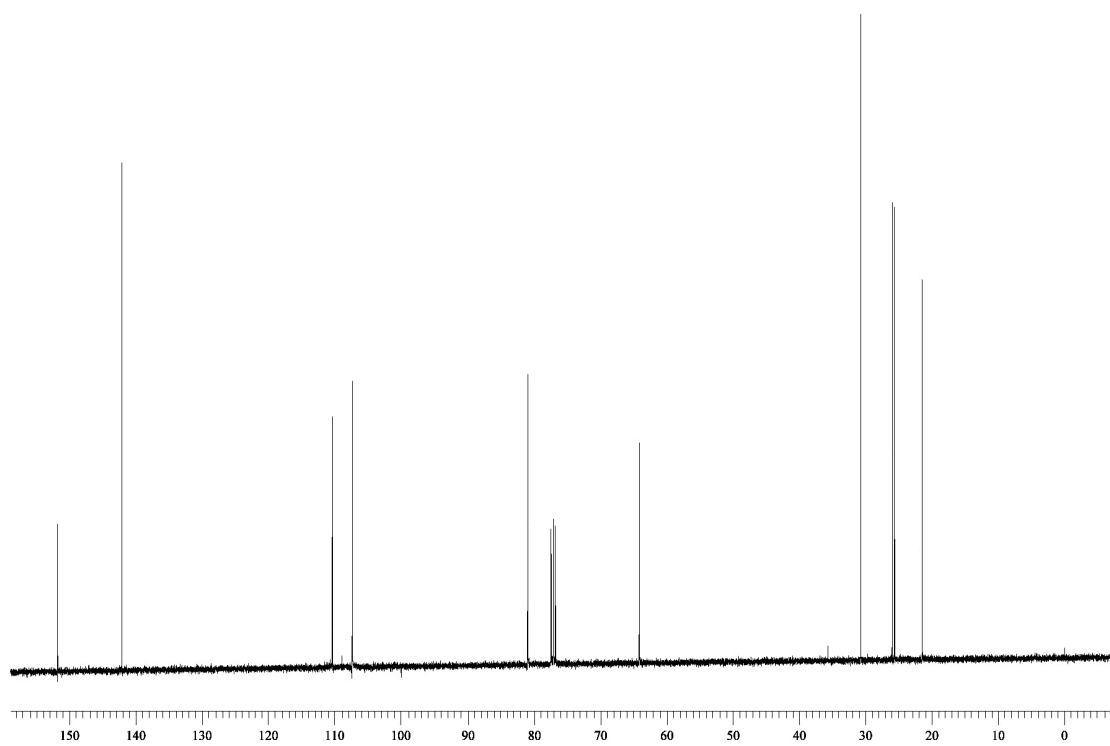


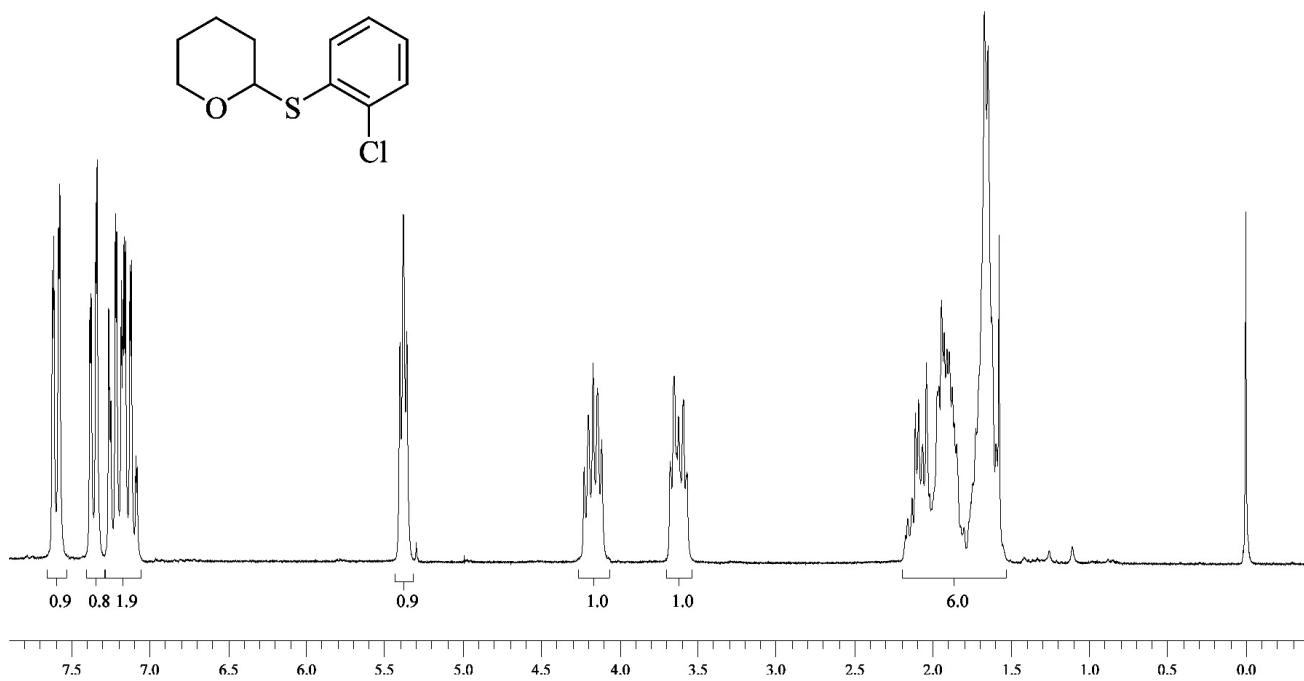
Figure S26. <sup>13</sup>C NMR spectra of compound **5c** in CDCl<sub>3</sub> at 100 MHz.



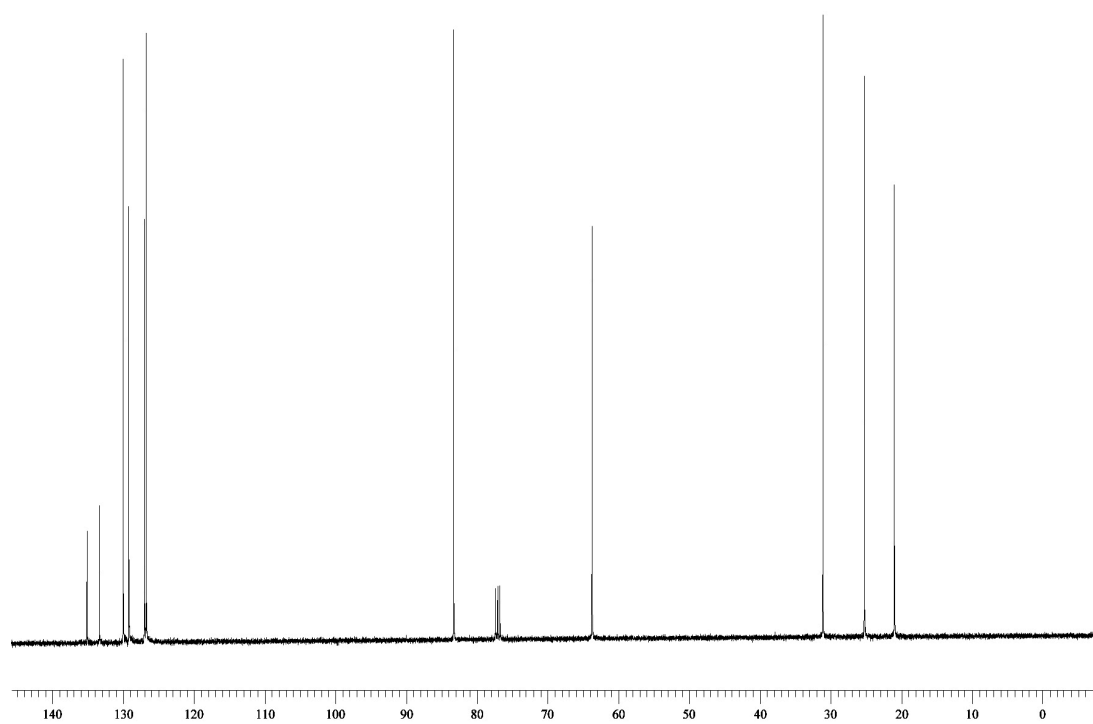
**Figure S27.**  $^1\text{H}$  NMR spectra of compound **5d** in  $\text{CDCl}_3$  at 400 MHz.



**Figure S28.**  $^{13}\text{C}$  NMR spectra of compound **5d** in  $\text{CDCl}_3$  at 100 MHz.



**Figure S29.** <sup>1</sup>H NMR spectra of compound **5e** in CDCl<sub>3</sub> at 400 MHz.



**Figure S30.** <sup>13</sup>C NMR spectra of compound **5e** in CDCl<sub>3</sub> at 100 MHz.