

## A Green, Inexpensive and Efficient Organocatalyzed Procedure for Aqueous Aldol Condensations

M. Saeed Abaee,<sup>\*,a</sup> Mohammad M. Mojtahedi,<sup>\*,a</sup> Soudabeh Forghani,<sup>a</sup>  
Nafiseh M. Ghandchi,<sup>b</sup> Mehdi Forouzani,<sup>c</sup> Roholah Sharifi<sup>a</sup> and Behnam Chaharnazm<sup>c</sup>

<sup>a</sup>Faculty of Organic Chemistry and Natural Products, Chemistry and Chemical Engineering  
Research Center of Iran, Pajouhesh Blvd., Km 17<sup>th</sup> of Tehran-Karaj Highway,  
P.O.Box 14335-186, 1496813151 Tehran, Iran

<sup>b</sup>Department of Chemistry, Islamic Azad University, Tehran Central Branch, Shahrak Gharb,  
Simaye Iran St., 1467686831 Tehran, Iran

<sup>c</sup>Department of Chemistry, Payam Noor University, Farhang St., Sari Center, 4818858565 Sari, Iran

É apresentado um procedimento simples e geral para a condensação aldólica cruzada dupla de cetonas cíclicas com vários aldeídos aromáticos catalisada por dietilamina em condições aquosas. Foram obtidos 3,5-bis(arylmetilideno) de cetonas homocíclicas e heterocíclicas em um procedimento one-pot em excelentes rendimentos. Além disto, a metodologia é aplicada eficientemente à síntese de chalconas a partir das metil cetonas correspondentes. Na maioria dos casos estudados, os produtos precipitam das misturas de reação e o meio é reciclado em várias reações subsequentes sem perda significativa de atividade.

A facile and general procedure is presented for diethylamine-catalyzed double crossed aldol condensation of cyclic ketones with various aromatic aldehydes under aqueous conditions. Excellent yields of 3,5-bis(aryl)methylidenes of homocyclic and heterocyclic ketones are achieved in a one-pot procedure. Furthermore, the methodology is efficiently applied to the synthesis of chalcones from their corresponding methyl ketones. In the majority of the cases studied, products precipitate from the reaction mixtures and the medium is recycled in subsequent several reactions without significant loss of activity.

**Keywords:** aldol condensation, aqueous conditions, organocatalyst, bis(aryl)methylidenes, chalcones

### Introduction

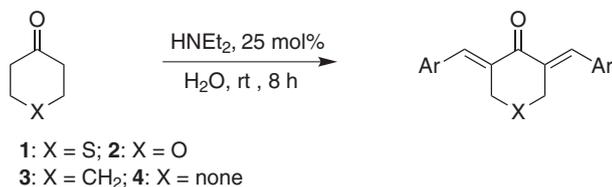
The use of water, the most abundant chemical on earth, as a solvent has been neglected for many years by organic chemists since water has been traditionally considered to have destructive effects on many reagents and synthetic reactions, unless water is used as a reagent or in workup procedures. It was believed so until pioneering experiments by Breslow's<sup>1</sup> and Grieco's<sup>2</sup> groups conducted in aqueous media led to unexpected rate and selectivity enhancement in Diels-Alder reactions. Since then, numerous papers<sup>3</sup> and reviews<sup>4</sup> on various aqueous-conditioned organic transformations have been released and more additions are expected in the upcoming years. On another "green

chemistry" front, acceleration of chemical reactions caused by addition of substoichiometric quantities of organic compounds containing no metal in their structures, known as organocatalysis, has increasingly gained popularity among synthetic organic chemists in recent years.<sup>5</sup>

Crossed aldol condensation of cyclic ketones with aromatic aldehydes has been extensively employed for the synthesis of bis(aryl)methylidene)cycloalkanones.<sup>6</sup> Many efforts have been devoted in recent years to widen the synthetic scope of bis(aryl)methylidene)cycloalkanones by using microwave radiation,<sup>7</sup> ultrasound irradiation,<sup>8</sup> and Lewis acid catalysis.<sup>9</sup> Despite these developments, even very recent reports still involve the use of either acidic or alkaline conditions or require organic solvents during the reaction or at workup stage.<sup>10</sup> In the framework of our studies on aldol condensation reactions<sup>11</sup> and in

\*e-mail: abae@ccerci.ac.ir; mojtahedi@ccerci.ac.ir

continuation of our previous research on the development of environmentally friendly processes,<sup>12</sup> we would like to report herein an efficient protocol for aldol condensation of ketones with various aldehydes using deficient quantities of diethylamine (Et<sub>2</sub>NH) under aqueous conditions (Scheme 1). As far as we know, this is one of the most inexpensive and environmentally friendly procedures offered so far for aldol condensation reactions.



Scheme 1.

## Results and Discussion

Initially, thiopyran **1** was subjected to condensation with benzaldehyde in the presence of an amine and water (Table 1). Optimum results were obtained by the use of deficient amounts of Et<sub>2</sub>NH leading to formation of **1a** in 92% yield after 8 h treatment at room temperature (entry 1). The generality of the method was demonstrated by the synthesis of similar products **1b-f** obtained from the reactions of other aromatic aldehydes with **1** under the same conditions (entry 2 - 6). Similarly, pyran **2** was subjected to react with the same aldehydes under the cited

**Table 1.** Et<sub>2</sub>NH/H<sub>2</sub>O promoted condensation of heterocyclic ketones with aldehydes

Entry	Aldehyde	Ketone	Product <sup>a</sup>	Yield (%) <sup>b</sup>
1	benzaldehyde	<b>1</b>	<b>1a</b>	92
2	<i>p</i> -methylbenzaldehyde	<b>1</b>	<b>1b</b>	90
3	<i>p</i> -anisaldehyde	<b>1</b>	<b>1c</b>	95
4	<i>p</i> -chlorobenzaldehyde	<b>1</b>	<b>1d</b>	91
5	Thiophene-2-carbaldehyde	<b>1</b>	<b>1e</b>	93
6	nicotinaldehyde	<b>1</b>	<b>1f</b>	93
7	benzaldehyde	<b>2</b>	<b>2a</b>	90
8	<i>p</i> -methylbenzaldehyde	<b>2</b>	<b>2b</b>	91
9	<i>p</i> -anisaldehyde	<b>2</b>	<b>2c</b>	96
10	<i>p</i> -chlorobenzaldehyde	<b>2</b>	<b>2d</b>	92
11	Thiophene-2-carbaldehyde	<b>2</b>	<b>2e</b>	94
12	nicotinaldehyde	<b>2</b>	<b>2f</b>	93

<sup>a</sup>A mixture of **1** or **2** (1 mmol), aldehyde (2 mmol), and Et<sub>2</sub>NH (0.25 mmol) was treated in 0.5 mL H<sub>2</sub>O for 8 h. All products precipitate spontaneously in the reaction mixtures; <sup>b</sup>Isolated yields.

conditions and complete formation of **2a-f** was observed (entry 7 - 12). All reactions proceeded rapidly at room temperature and complete conversions were observed in less than 8 h to obtain 90 - 96% of the respective products. In all cases, products separated out spontaneously allowing an easy solvent-free workup and efficient reuse of the H<sub>2</sub>O/Et<sub>2</sub>NH filtrate in the next reactions.

In comparison with many previously related reports,<sup>7,8,10</sup> the present procedure is very mild, takes place at room temperature, and involves a very straightforward and easy workup. Therefore, the procedure was next employed to evaluate the same chemistry in homocyclic ketones. In similar series of reactions, **3** and **4** were subjected to condensation with aldehydes to synthesize their respective bisarylmethylidene products, as summarized in Table 2. All aldehydes reacted in a similar manner producing high yields of the expected products. The products were easily solidified and separated by a simple filtration after acidification of the reaction mixtures by dilute HCl solution.

**Table 2.** Et<sub>2</sub>NH/H<sub>2</sub>O promoted condensation of homocyclic ketones with aldehydes

Entry	Aldehyde	Ketone	Product <sup>a</sup>	Yield (%) <sup>b</sup>
1	benzaldehyde	<b>3</b>	<b>3a</b>	90
2	<i>p</i> -methylbenzaldehyde	<b>3</b>	<b>3b</b>	91
3	<i>p</i> -anisaldehyde	<b>3</b>	<b>3c</b>	90
4	<i>p</i> -chlorobenzaldehyde	<b>3</b>	<b>3d</b>	94
5	Thiophene-2-carbaldehyde	<b>3</b>	<b>3e</b>	96
6	nicotinaldehyde	<b>3</b>	<b>3f</b>	95
7	<i>p</i> -nitrobenzaldehyde	<b>3</b>	<b>3g</b>	84
8	benzaldehyde	<b>4</b>	<b>4a</b>	96
9	<i>p</i> -anisaldehyde	<b>4</b>	<b>4c</b>	94
10	<i>p</i> -chlorobenzaldehyde	<b>4</b>	<b>4d</b>	96
11	furaldehyde	<b>4</b>	<b>4h</b>	95

<sup>a</sup>A mixture of **3** or **4** (1 mmol), aldehyde (2 mmol), and Et<sub>2</sub>NH (0.25 mmol) was treated in 0.5 mL H<sub>2</sub>O for 8 h; <sup>b</sup>Isolated yields.

Moreover, methyl ketones were subjected to condensation with aldehydes in the presence of an amine and water (Scheme 2) under the same conditions. Condensation of acetophenone **5** with various aromatic aldehydes bearing electron-releasing or electron-withdrawing substituents led to rapid and high yield formation of chalcones, which are the central core of a variety of important biologically active compounds (Table 3, entries 1 - 7).<sup>13</sup> Under the above conditions, acetone **6** also efficiently yielded its respective bisarylmethylidene products (entries 8 - 12). For reactions of **6**, products spontaneously precipitated in the medium and allowed a convenient solvent-free workup and efficient reuse of the H<sub>2</sub>O/Et<sub>2</sub>NH filtrate in subsequent reactions,



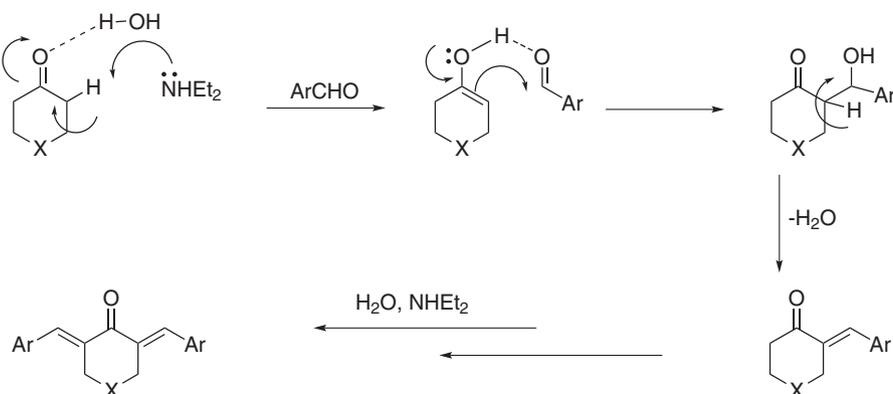


Figure 1. Suggested mechanistic overview of the reaction.

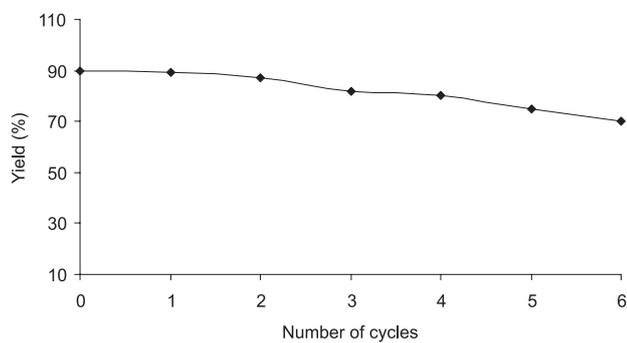


Figure 2. Efficient recovery of the catalyst for the synthesis of **1b**.

## Experimental

Reactions were monitored by TLC using silica gel coated plates and ethyl acetate/hexane solutions as the mobile phase. Melting points are uncorrected. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers ( $\text{cm}^{-1}$ ).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained on a Bruker AC 80 MHz or Bruker Ultra Shield<sup>TM</sup> (500 MHz) instrument as  $\text{CDCl}_3$  solutions and the chemical shifts are expressed as  $\delta$  units with  $\text{Me}_4\text{Si}$  as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Compound **1** was prepared using available methods.<sup>18</sup> All other reagents were purchased from commercial sources and were freshly used after being purified by standard procedures.

### General synthetic procedure for the reactions of ketones **1**, **2**, and **6**

A ketone (1.0 mmol) was added to a mixture of an aldehyde (2.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), and  $\text{Et}_2\text{NH}$  (25 mol%) and the mixture was stirred at room temperature for 8 h. The course of the reaction was monitored by TLC. After completion of the reaction, the precipitated product

was filtered and purified by recrystallization from ethyl acetate.

### General synthetic procedure for the reactions of ketones **3-4**

A ketone (1.0 mmol) was added to a mixture of an aldehyde (2.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), and  $\text{Et}_2\text{NH}$  (25 mol%) and the mixture was stirred at room temperature for 8 h. The course of the reaction was monitored by TLC. After completion of the reaction, the mixture was treated with 3 mL of HCl (5%) to solidify the product. The precipitated product was filtered and purified by recrystallization from ethyl acetate.

### General synthetic procedure for the reactions of ketones **5**

Ketone **5** (1.0 mmol) was added to a mixture of an aldehyde (1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), and  $\text{Et}_2\text{NH}$  (25 mol%) and the mixture was stirred at room temperature for 10 h. The course of the reaction was monitored by TLC. After completion of the reaction, the mixture was treated with 3 mL of HCl (5%) to solidify the product. The precipitated product was filtered and purified by recrystallization from ethyl acetate.

### Selected spectral data

#### (3*Z*,5*Z*)-3,5-Dibenzylidene-tetrahydrothiopyran-4-one (**1a**)

Obtained as yellow solid, yield 92%, mp 142–144 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1599, 1444, 1269.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.84 (s, 4H,  $\text{SCH}_2$ ), 7.30 (s, 10H, Ar-H), 7.72 (s, 2H, =CH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  30.0 ( $\text{SCH}_2$ ), 128.4, 128.7, 129.8, 133.7, 134.9, 136.6, 188.6 (C=O). MS  $m/z$  292 ( $\text{M}^+$ , 27%), 147 (40), 115 (100).

#### (3*Z*,5*Z*)-3,5-Bis(4-methylbenzylidene)-tetrahydrothiopyran-4-one (**1b**)

Obtained as yellow solid, yield 90%, mp 186–188 °C.

IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1657, 1595, 1275. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.31 (s, 6H, CH<sub>3</sub>), 3.84 (s, 4H, SCH<sub>2</sub>), 7.20-7.45 (m, 8H, Ar-H), 7.68 (s, 2H, =CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  21.4 (CH<sub>3</sub>), 30.1 (SCH<sub>2</sub>), 129.1, 129.9, 132.4, 133.3, 136.8, 139.2, 185.5 (C=O). MS  $m/z$  320 (M<sup>+</sup>, 21%), 305 (19), 147 (30), 130 (62), 115 (100).

*(3Z,5Z)-3,5-Bis(4-methoxybenzylidene)-tetrahydrothiopyran-4-one (1c)*

Obtained as yellow solid, yield 95%, mp 174-176 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1654, 1592, 1505, 1252. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.76 (s, 6H, OCH<sub>3</sub>), 3.80 (s, 4H, SCH<sub>2</sub>), 6.85 (d, 4H, *J* 9.8 Hz, Ar-H), 7.30 (d, 4H, *J* 9.8 Hz, Ar-H), 7.66 (s, 2H, =CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  30.2 (SCH<sub>2</sub>), 55.3 (OCH<sub>3</sub>), 114.1, 127.5, 131.9, 136.1, 160.2, 185.4 (C=O). MS  $m/z$  352 (M<sup>+</sup>, 49%), 146 (98), 103 (100).

*(3E,5E)-3,5-Bis(4-chlorobenzylidene)-tetrahydropyran-4-one (2d)*

Obtained as yellow solid, yield 92%, mp 168-170 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1671, 1612, 1559, 1263, 1090. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.80 (s, 4H, OCH<sub>2</sub>), 7.25 (d, 4H, *J* 6.4 Hz, Ar-H), 7.40 (d, 4H, *J* 6.4 Hz, Ar-H), 7.70 (s, 2H, =CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  68.2 (OCH<sub>2</sub>), 128.0, 128.8, 131.4, 133.1, 133.3, 135.0, 188.4 (C=O). MS  $m/z$  344 (M<sup>+</sup>, 22%), 253 (13), 141 (82), 115 (100).

*(3E,5E)-Tetrahydro-3,5-bis((thiophen-2-yl)methylene)pyran-4-one (2e)*

Obtained as yellow solid, yield 94%, mp 195-197 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1662, 1592, 1186. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.90 (s, 4H, OCH<sub>2</sub>), 7.00-7.50 (m, 6H, H's of thienyl), 7.87 (br s, 2H, =CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  68.3 (OCH<sub>2</sub>), 127.9, 128.2, 130.9, 133.3, 138.3, 184.2 (C=O). MS  $m/z$  288 (M<sup>+</sup>, 20%), 260 (6), 122 (100).

*(3E,5E)-Tetrahydro-3,5-bis((pyridine-3-yl)methylene)pyran-4-one (2f)*

Obtained as yellow solid, yield 93%, mp 192-194 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1672, 1616, 1272. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.86 (s, 4H, OCH<sub>2</sub>), 7.18-7.70 (m, 8H, H's of pyridyl), 8.50 (br s, 2H, =CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  68.2 (OCH<sub>2</sub>), 123.4, 130.4, 132.8, 134.6, 136.9, 149.9, 150.9, 187.0 (C=O). MS  $m/z$  278 (M<sup>+</sup>, 18%), 117 (100), 90 (75).

*2,6-Dibenzylidenecyclohexanone (3a)*

Obtained as yellow solid, yield 90%, mp 113-114 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1661, 1607. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.76-1.83 (m, 2H, -CH<sub>2</sub>-), 2.96 (t, *J* 6.5 Hz, 4H, CH<sub>2</sub>), 7.30-7.49 (m, 10H, Ar-H), 7.81 (s, 2H, =CH). <sup>13</sup>C NMR  $\delta$  23.5 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 128.8, 129.0, 130.8, 136.4, 136.6, 137.4, 190.8

(C=O). MS  $m/z$  274 (M<sup>+</sup>, 85%), 273 (100), 129 (36), 115 (90).

*2,6-Bis-thiophen-2-yl-methylenecyclohexanone (3e)*

Obtained as yellowish brown solid, yield 96%, mp 142-143 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1663, 1608. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.95-2.00 (m, 2H, -CH<sub>2</sub>-), 2.94 (t, *J* 5 Hz, 4H, CH<sub>2</sub>), 7.16 (t, *J* 4 Hz, 2H, H of thienyl), 7.40 (d, *J* 2.5 Hz, 2H, H of thienyl), 7.54 (d, *J* 5 Hz, 2H, H of thienyl), 7.98 (s, 2H, =CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  22.1 (CH<sub>2</sub>), 28.6, 128.0, 130.1, 130.3, 133.3, 133.4, 140.0, 189.4 (C=O). MS  $m/z$  286 (M<sup>+</sup>, 100%), 229 (77), 115 (28).

*2,5-Dibenzylidenecyclopentanone (4a)*

Obtained as yellow solid, yield 96%, mp 186-187 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1655, 1625. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.12 (s, 4H, CH<sub>2</sub>), 7.35-7.62 (m, 12H, Ar-H and =CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  27.0 (CH<sub>2</sub>), 129.2, 129.8, 131.2, 134.3, 136.3, 137.7, 196.8 (C=O). MS  $m/z$  260 (M<sup>+</sup>, 84%), 129 (42), 115 (95).

*2,5-Bis-(4-chlorobenzylidene)-cyclopentanone (4d)*

Obtained as yellow solid, yield 96%, mp 226-227 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1694, 1607. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.01 (s, 4H, CH<sub>2</sub>), 7.30-7.45 (m, 10H, Ar-H and =CH). <sup>13</sup>C NMR  $\delta$  26.8 (CH<sub>2</sub>), 129.5, 132.3, 133.1, 134.6, 135.9, 137.9, 196.3 (C=O). MS  $m/z$  328 (M<sup>+</sup>, 40%), 207 (42), 115 (100).

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## Supplementary Information

<sup>1</sup>H NMR, <sup>13</sup>C NMR, mass and IR spectra of the data mentioned above are available free of charge at <http://jbc.ssbq.org.br>, as a PDF file.

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## A Green, Inexpensive and Efficient Organocatalyzed Procedure for Aqueous Aldol Condensations

M. Saeed Abaee,<sup>\*a</sup> Mohammad M. Mojtahedi,<sup>\*a</sup> Soudabeh Forghani,<sup>a</sup>  
Nafiseh M. Ghandchi,<sup>b</sup> Mehdi Forouzani,<sup>c</sup> Roholah Sharifi<sup>a</sup> and Behnam Chaharnazm<sup>c</sup>

<sup>a</sup>Faculty of Organic Chemistry and Natural Products, Chemistry and Chemical Engineering  
Research Center of Iran, Pajouhesh Blvd., Km 17<sup>th</sup> of Tehran-Karaj Highway,  
P.O.Box 14335-186, 1496813151 Tehran, Iran

<sup>b</sup>Department of Chemistry, Islamic Azad University, Tehran Central Branch, Shahrak Gharb,  
Simaye Iran St., 1467686831 Tehran, Iran

<sup>c</sup>Department of Chemistry, Payam Noor University, Farhang St., Sari Center, 4818858565 Sari, Iran

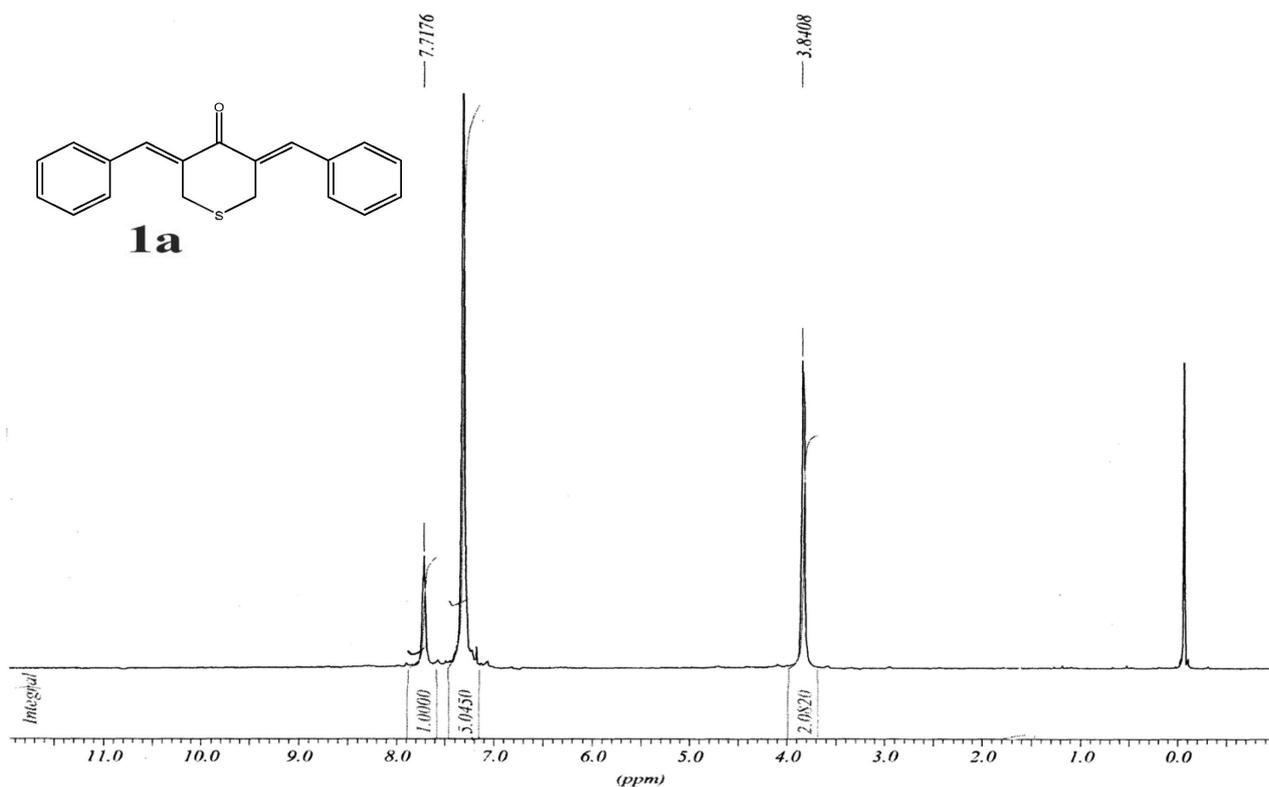
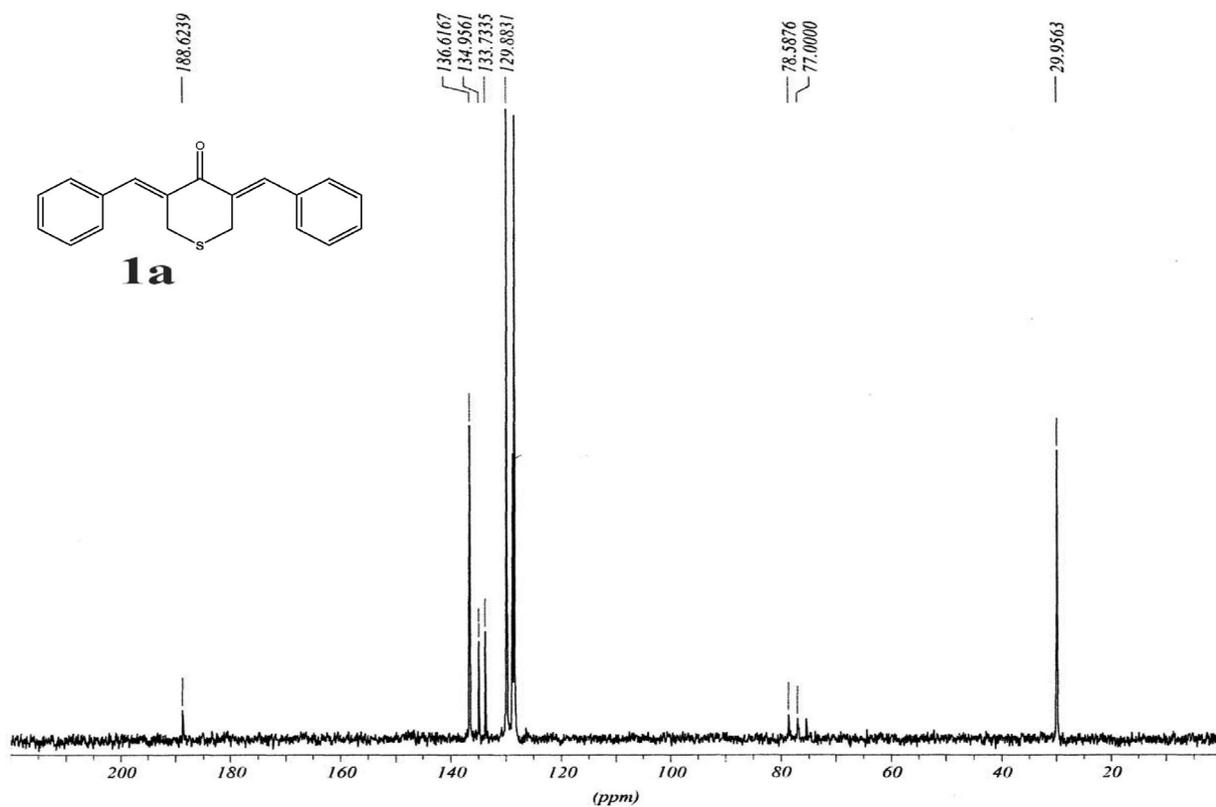
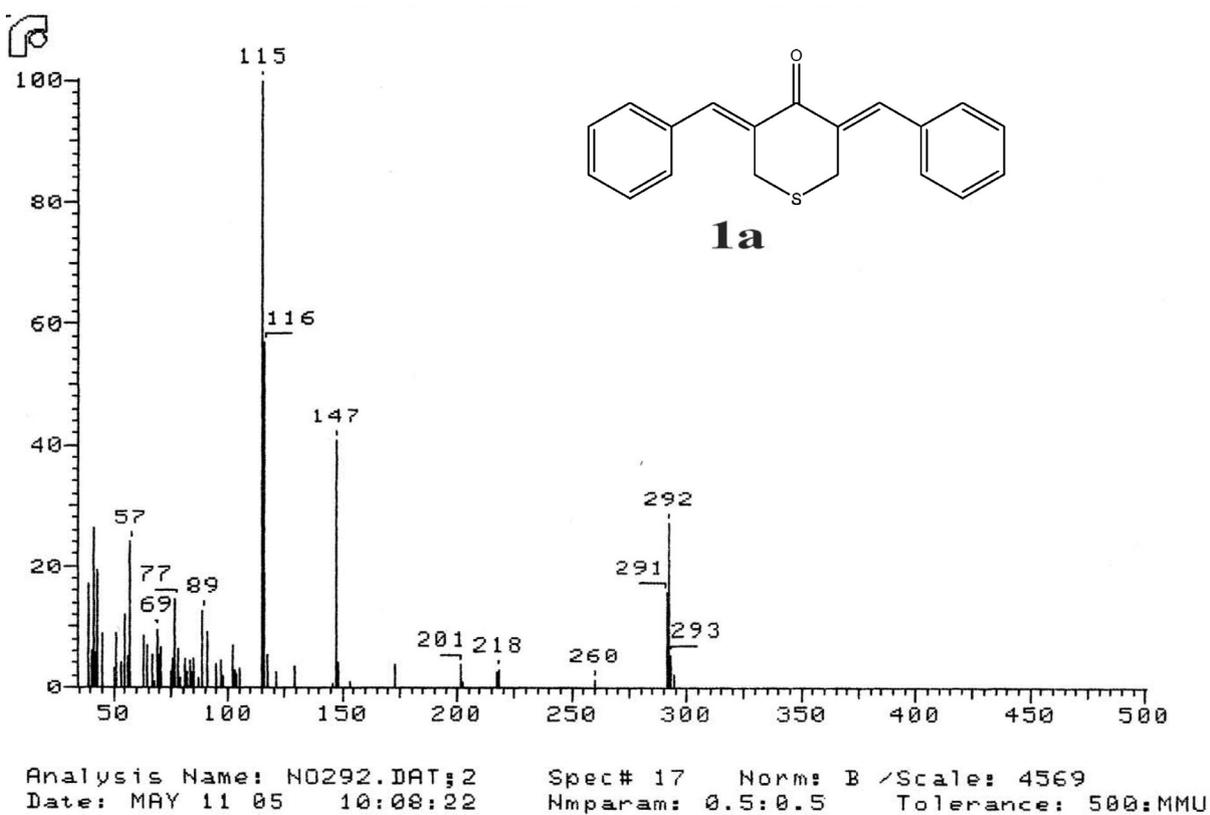
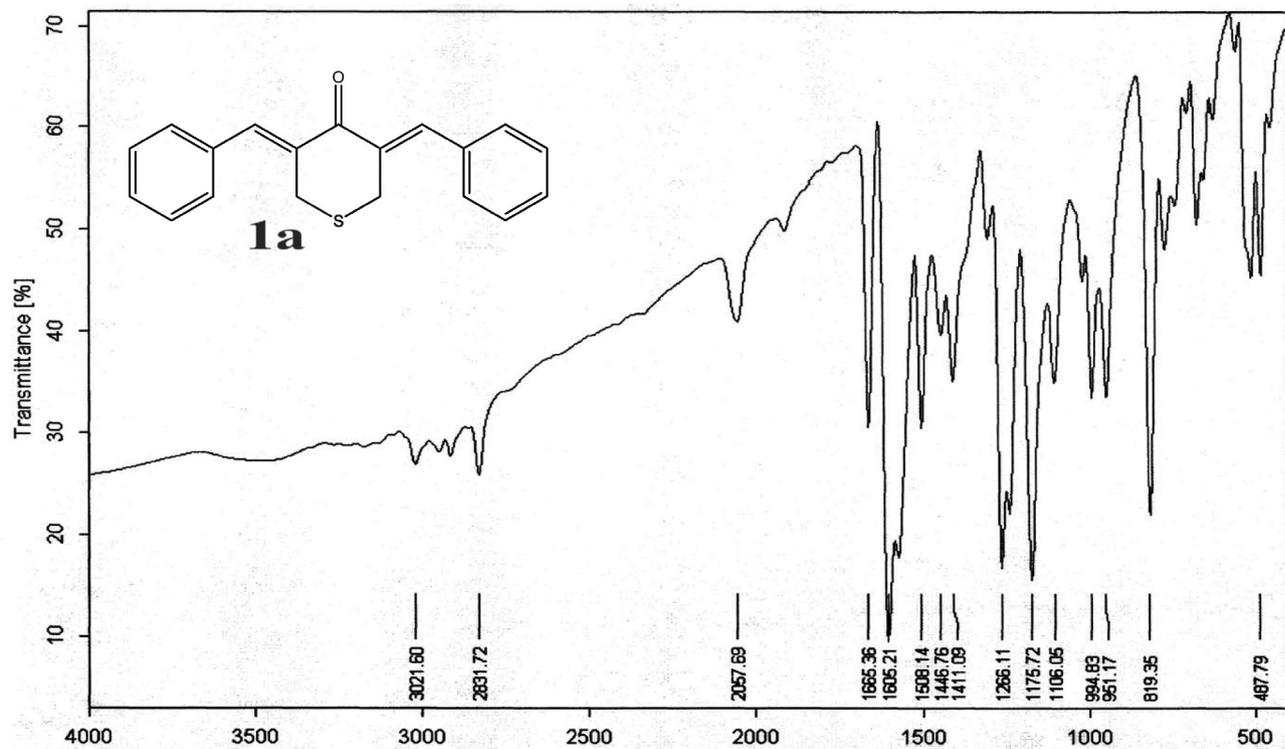
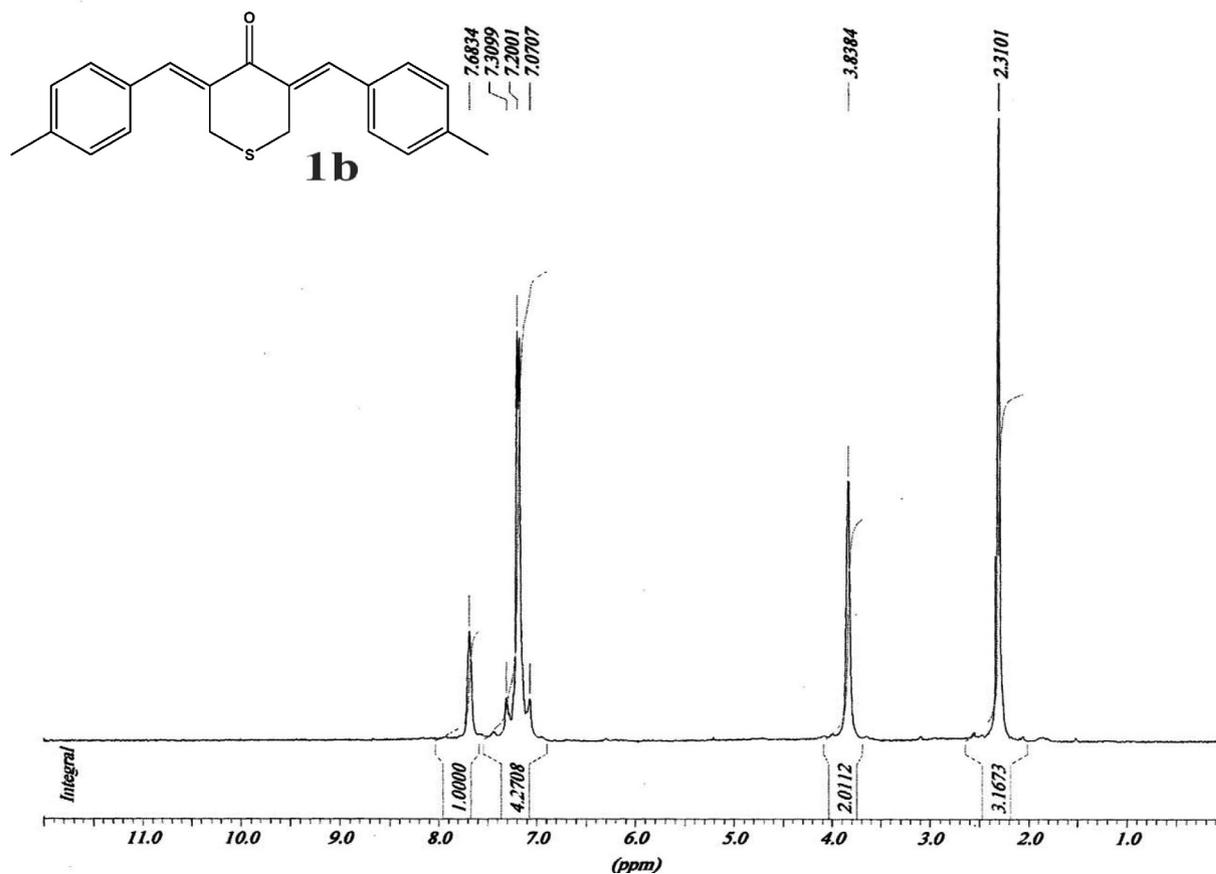
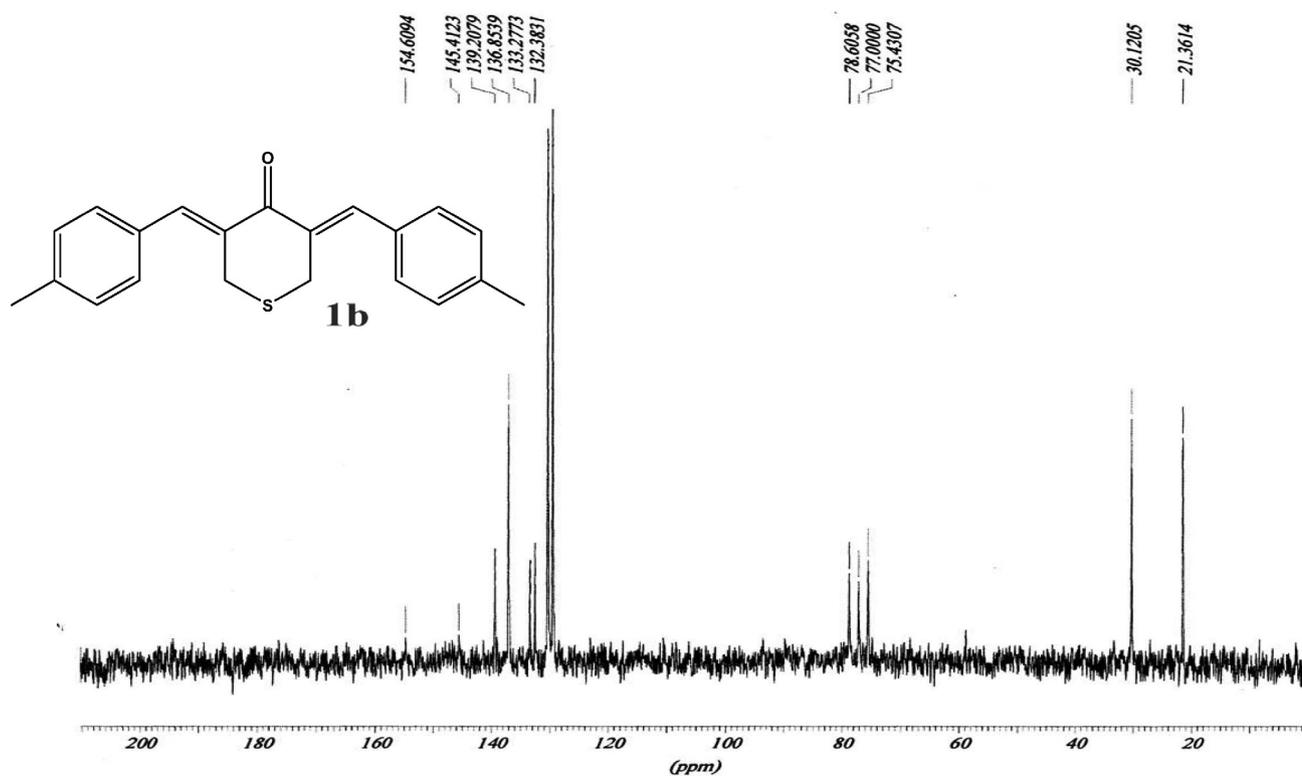
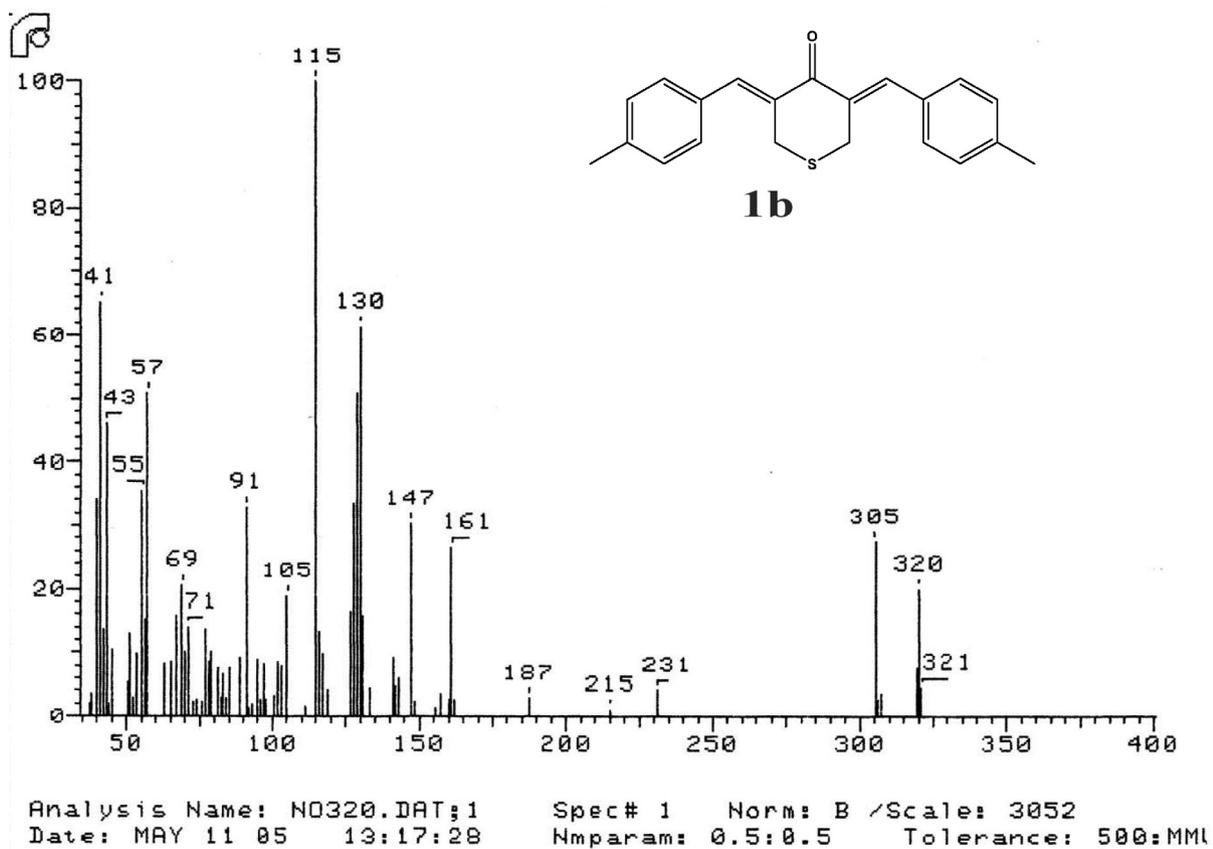


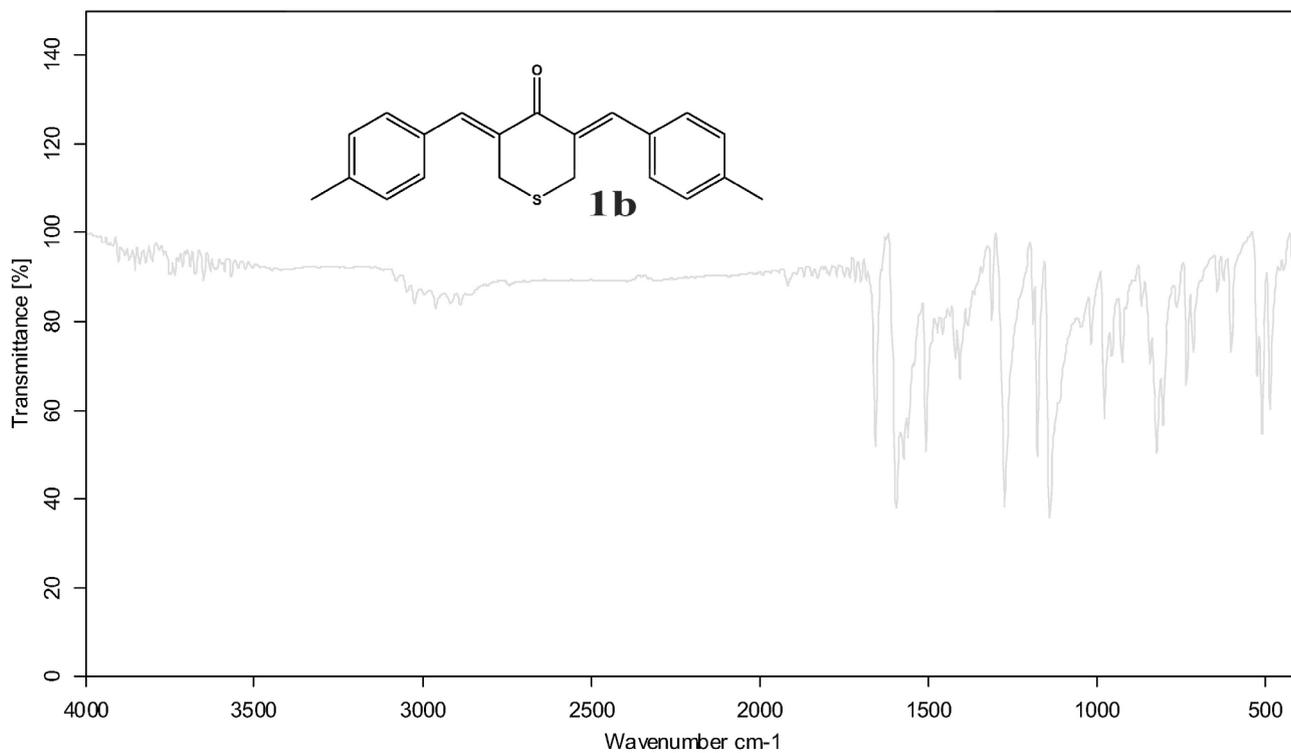
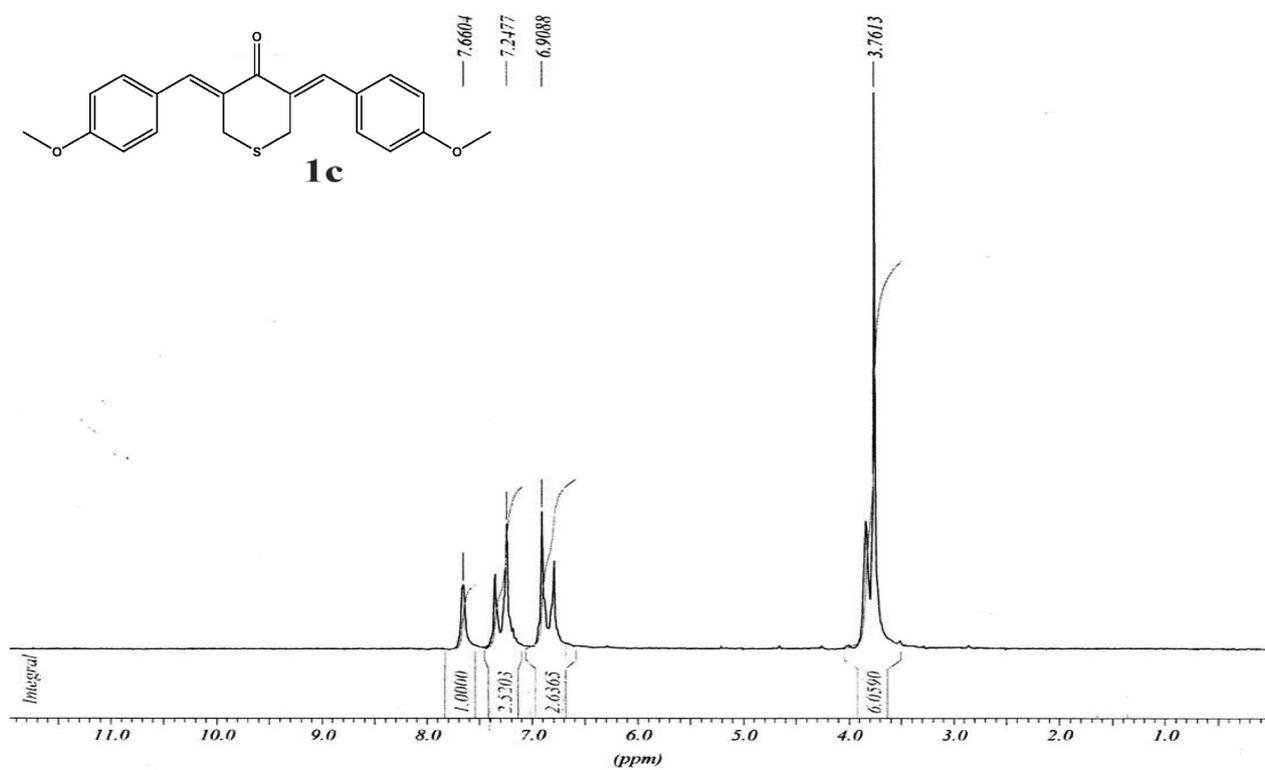
Figure S1. <sup>1</sup>H NMR spectrum of **1a**.

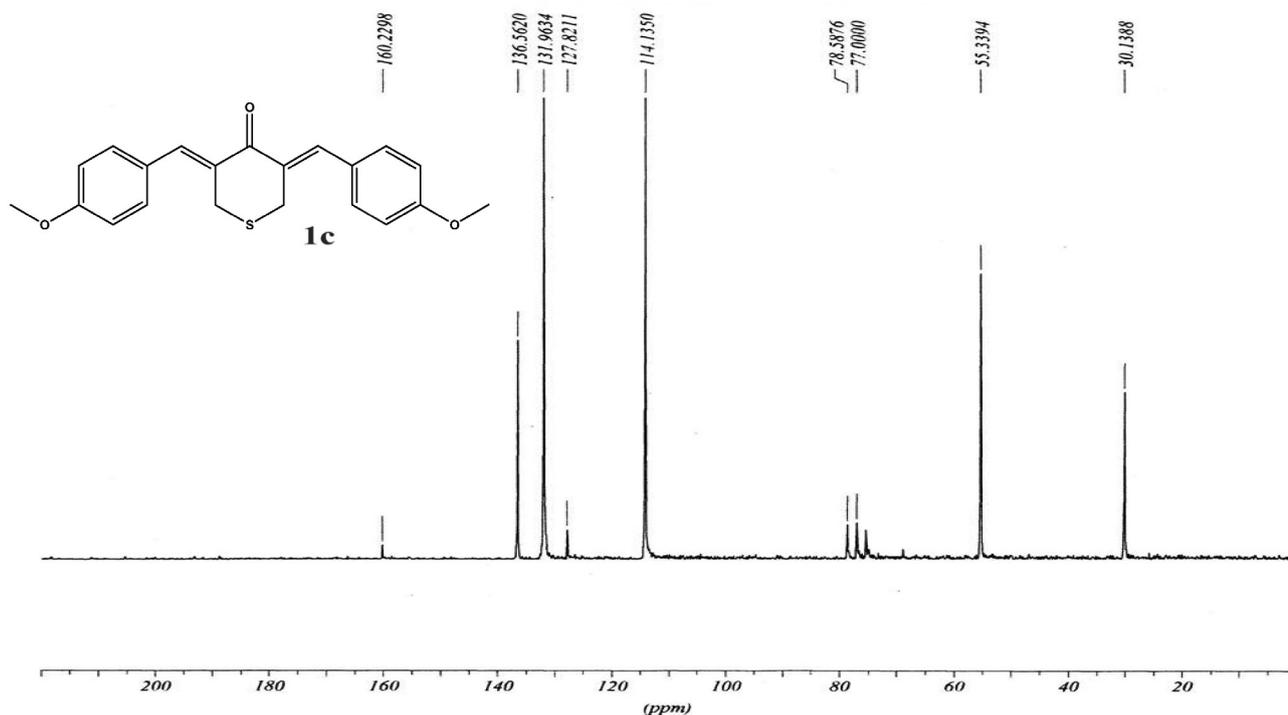
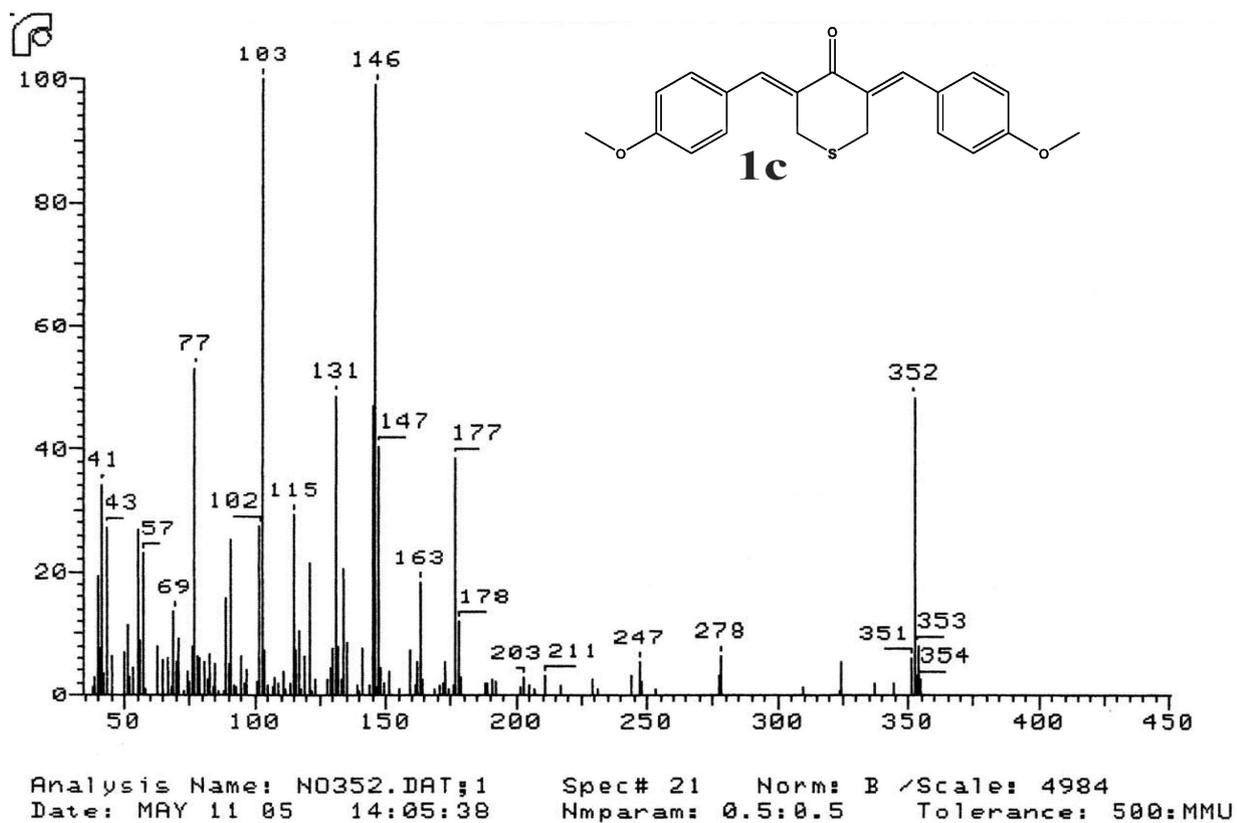
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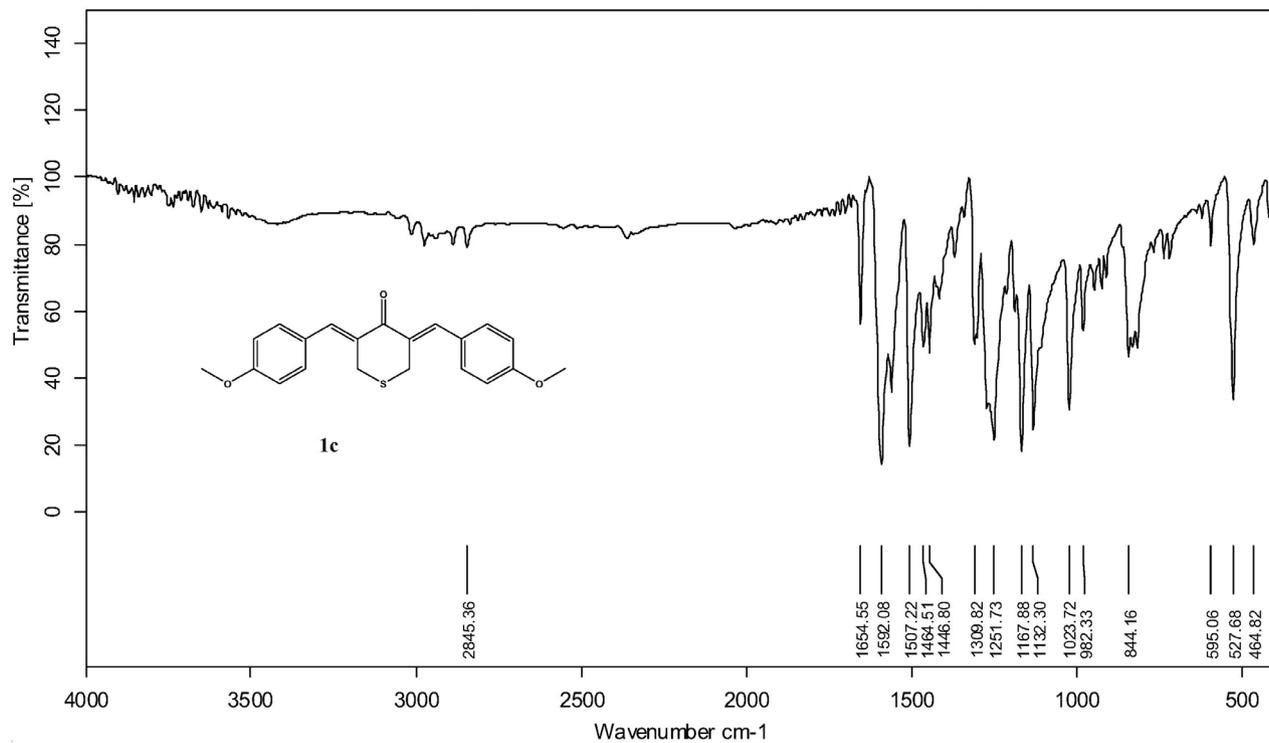
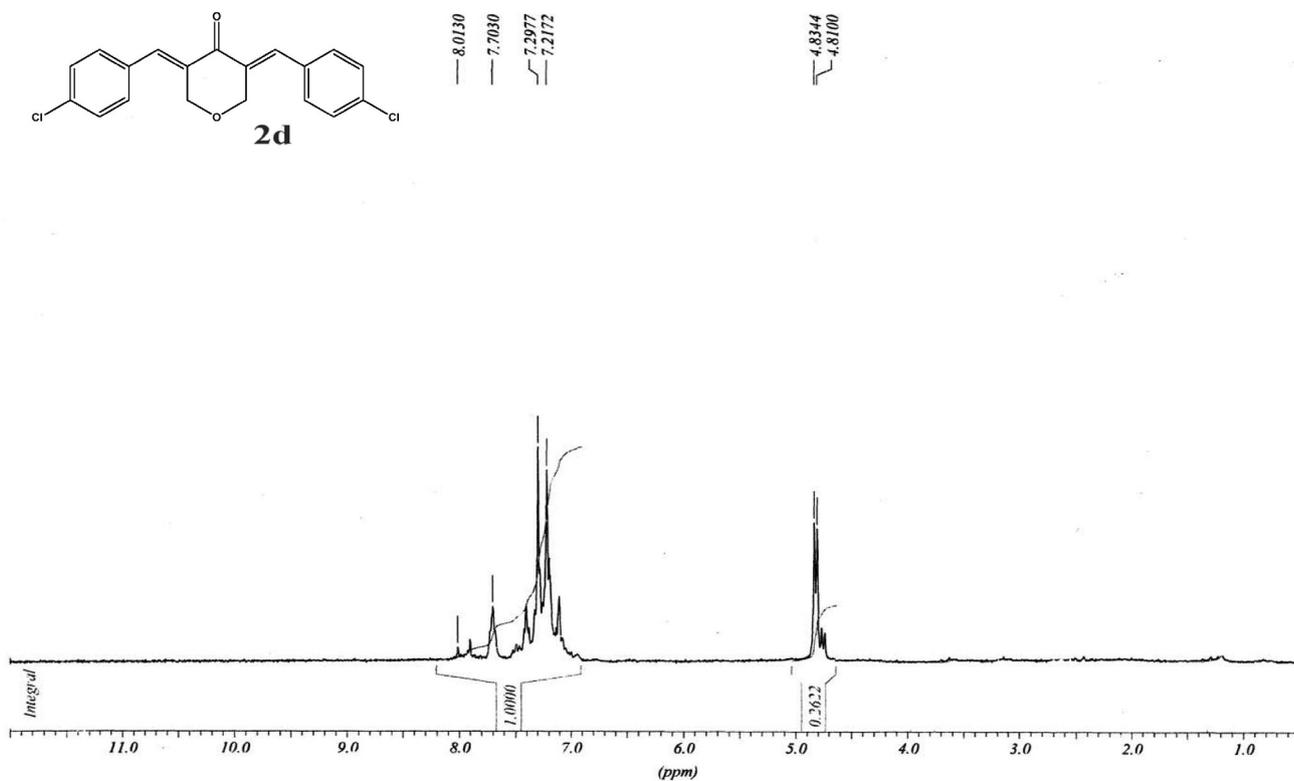
Figure S2. <sup>13</sup>C NMR spectrum of **1a**.Figure S3. Mass spectrum of **1a**.

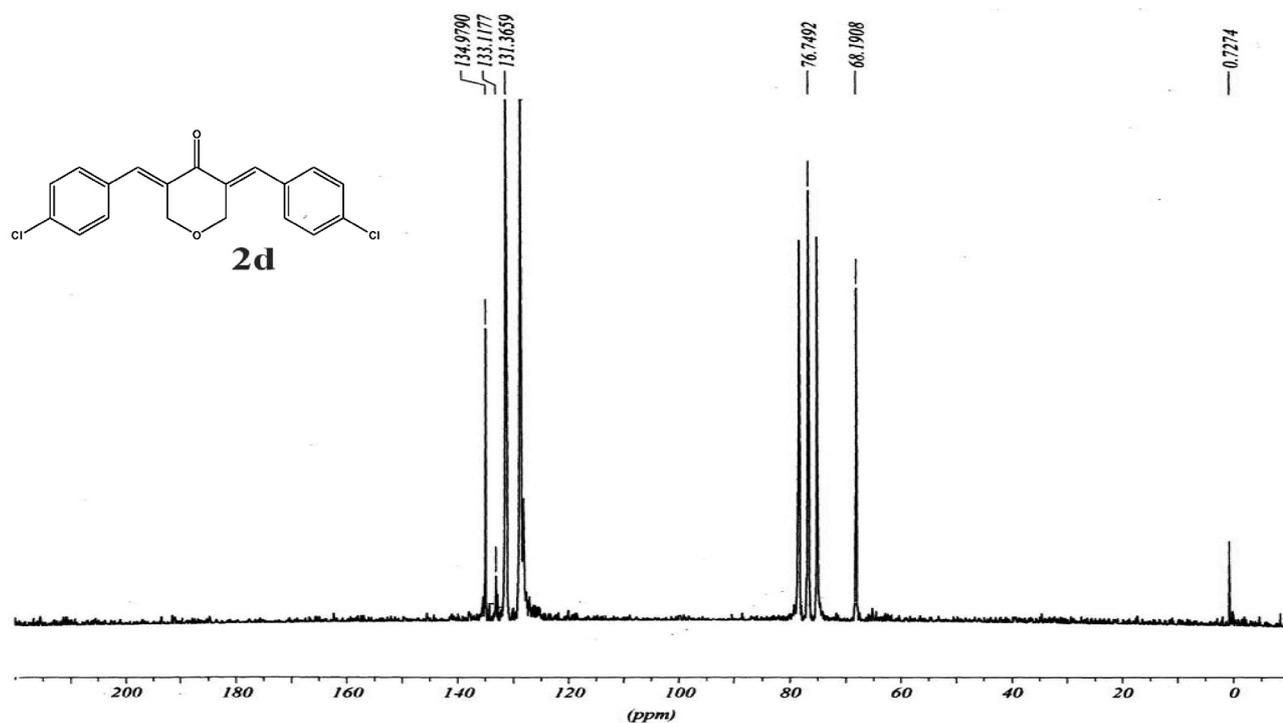
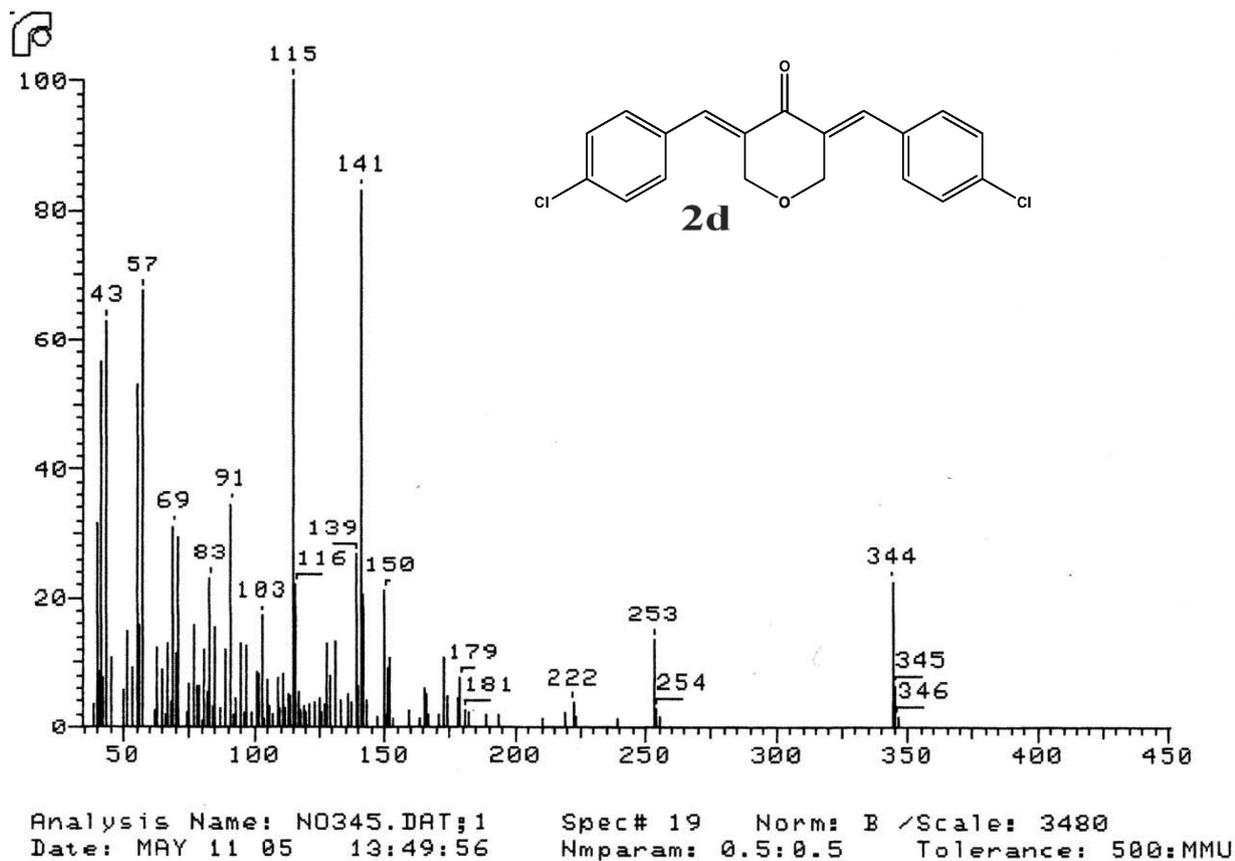
Figure S4. IR spectrum of **1a**.Figure S5. <sup>1</sup>H NMR spectrum of **1b**.

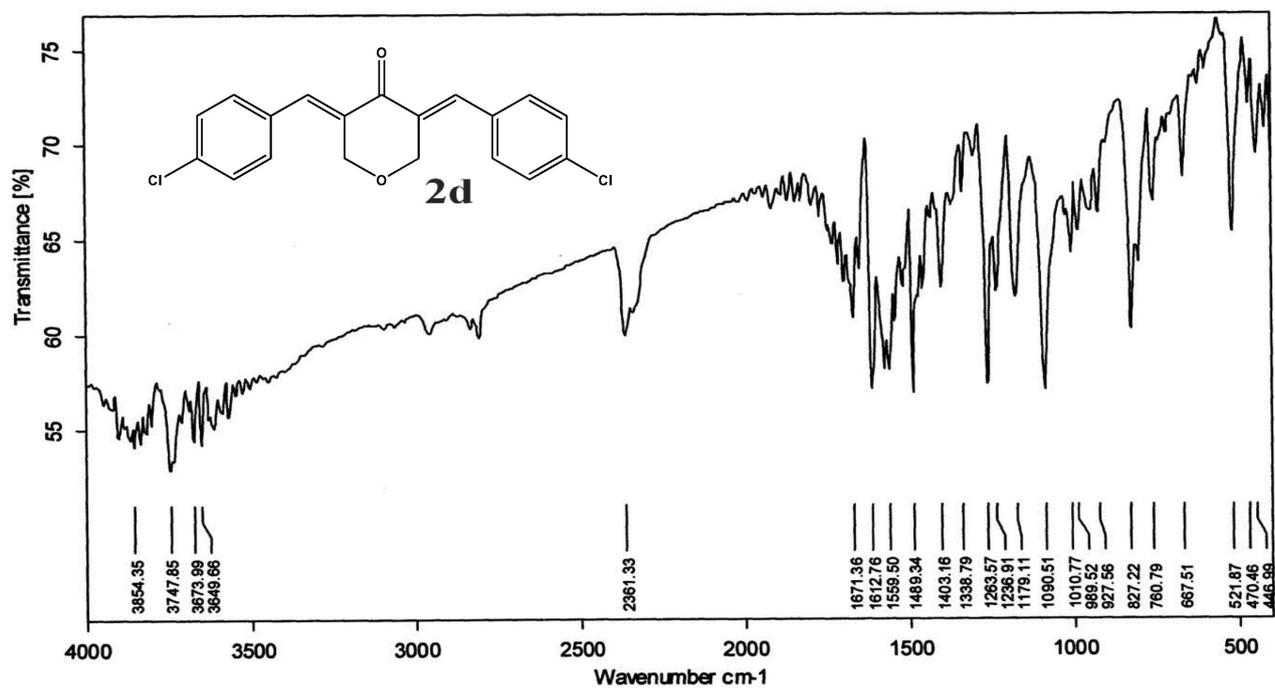
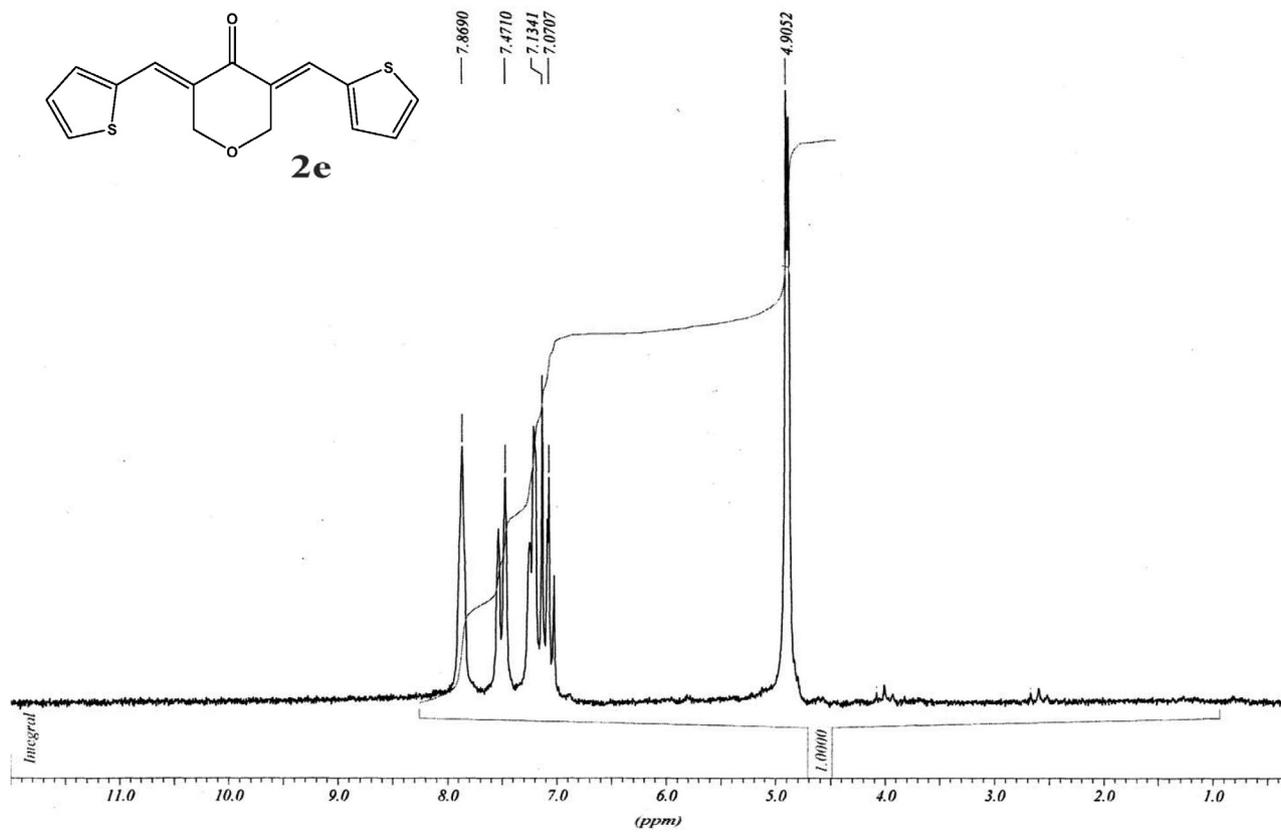
Figure S6. <sup>13</sup>C NMR spectrum of **1b**.Figure S7. Mass spectrum of **1b**.

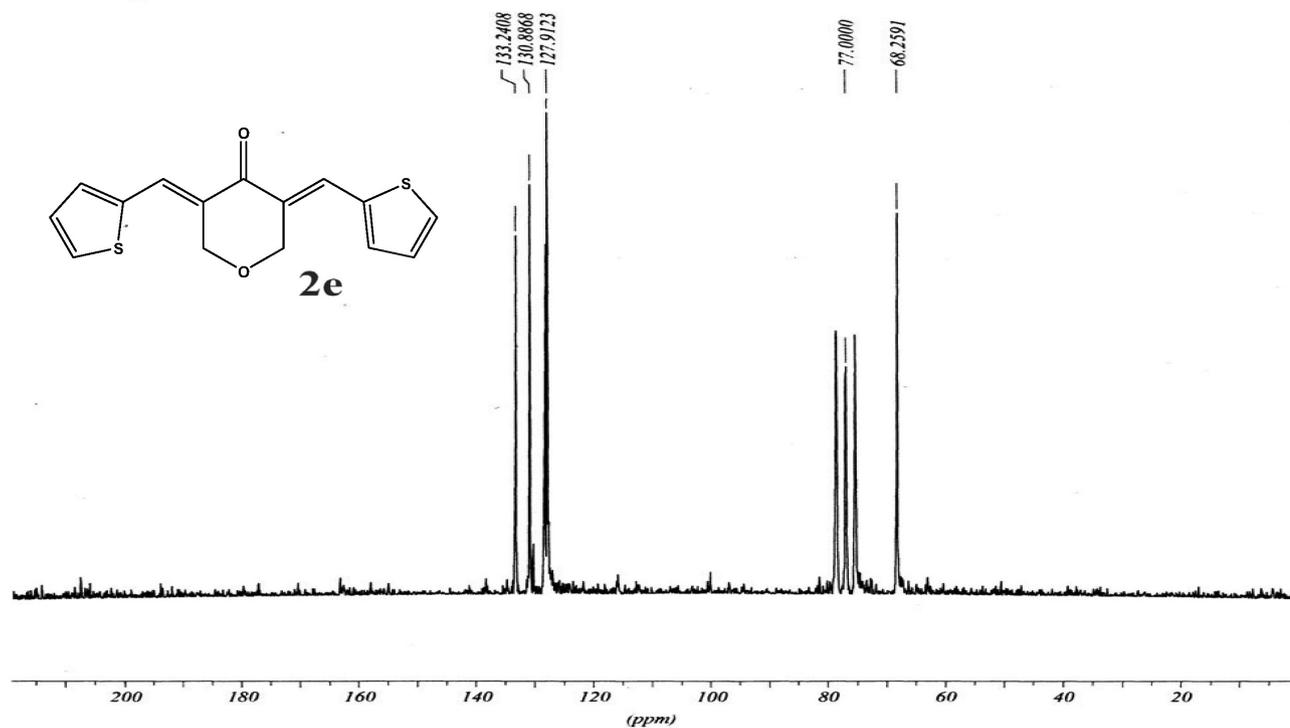
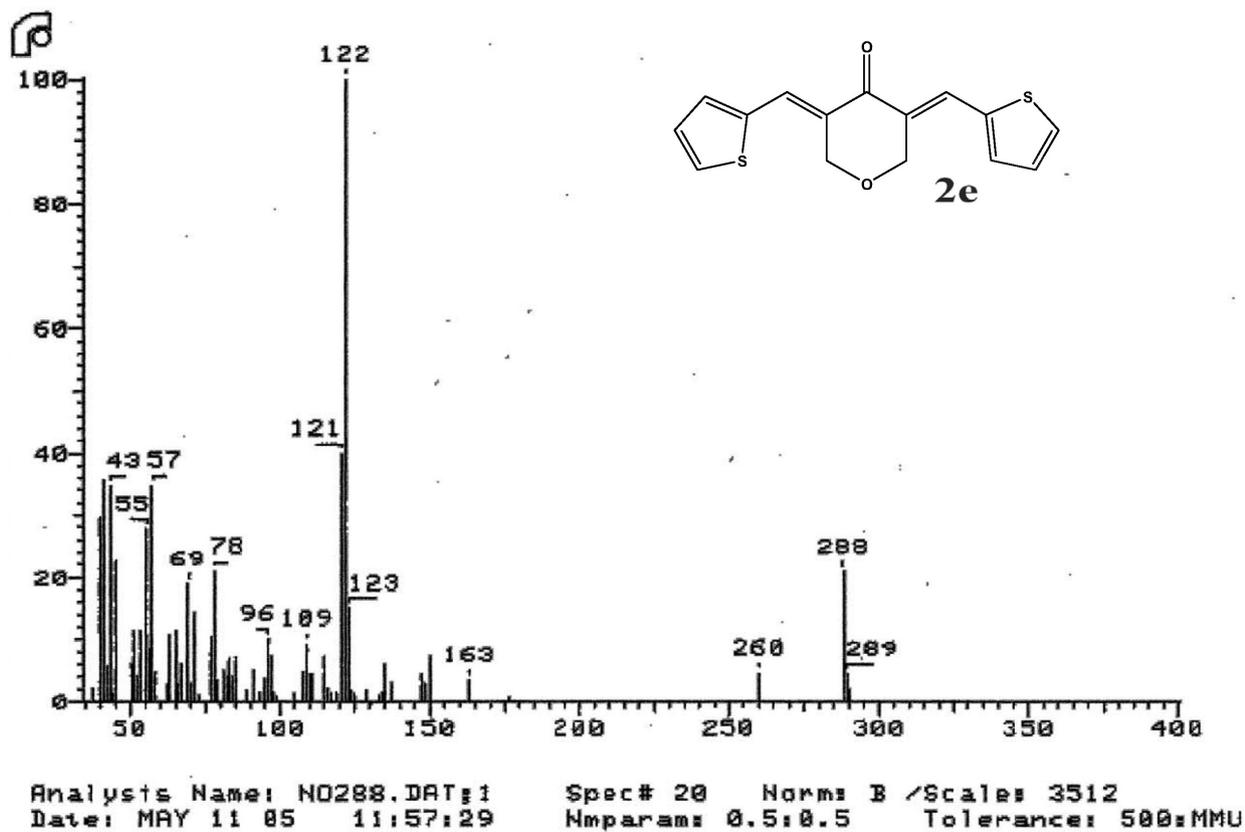
Figure S8. IR spectrum of **1b**.Figure S9. <sup>1</sup>H NMR spectrum of **1c**.

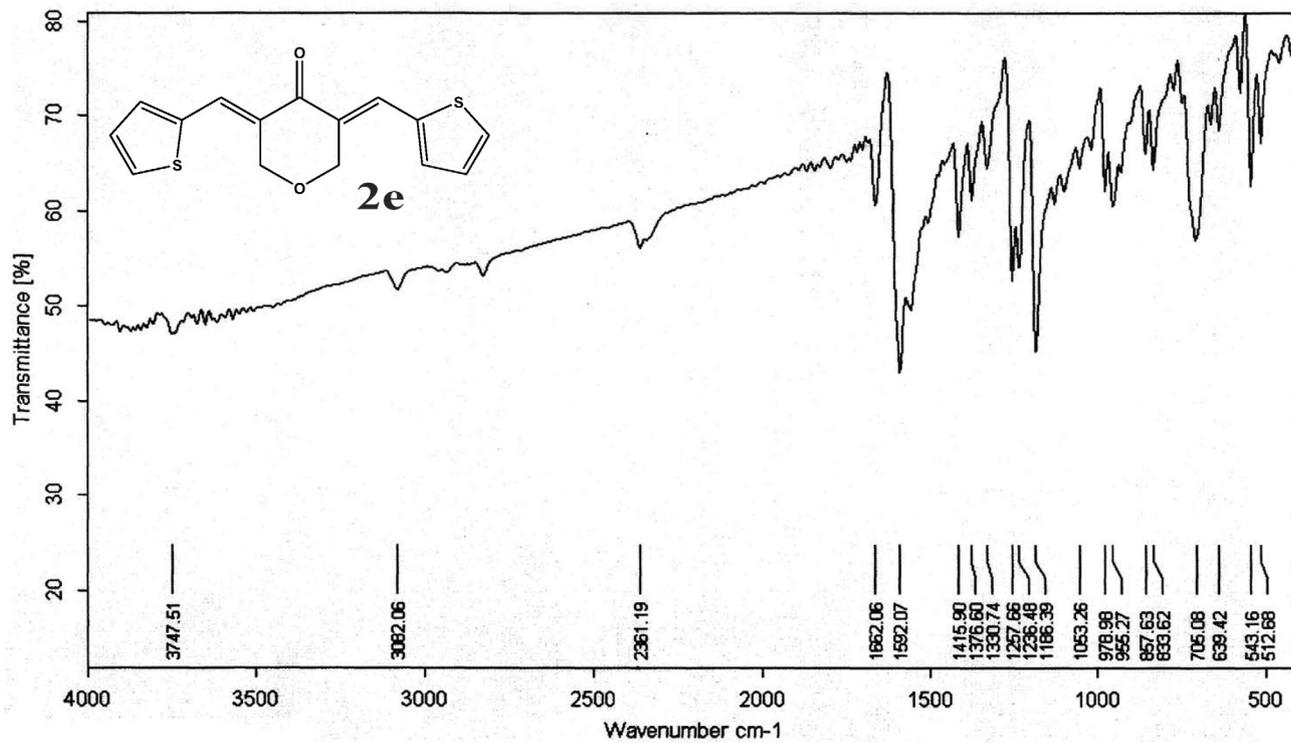
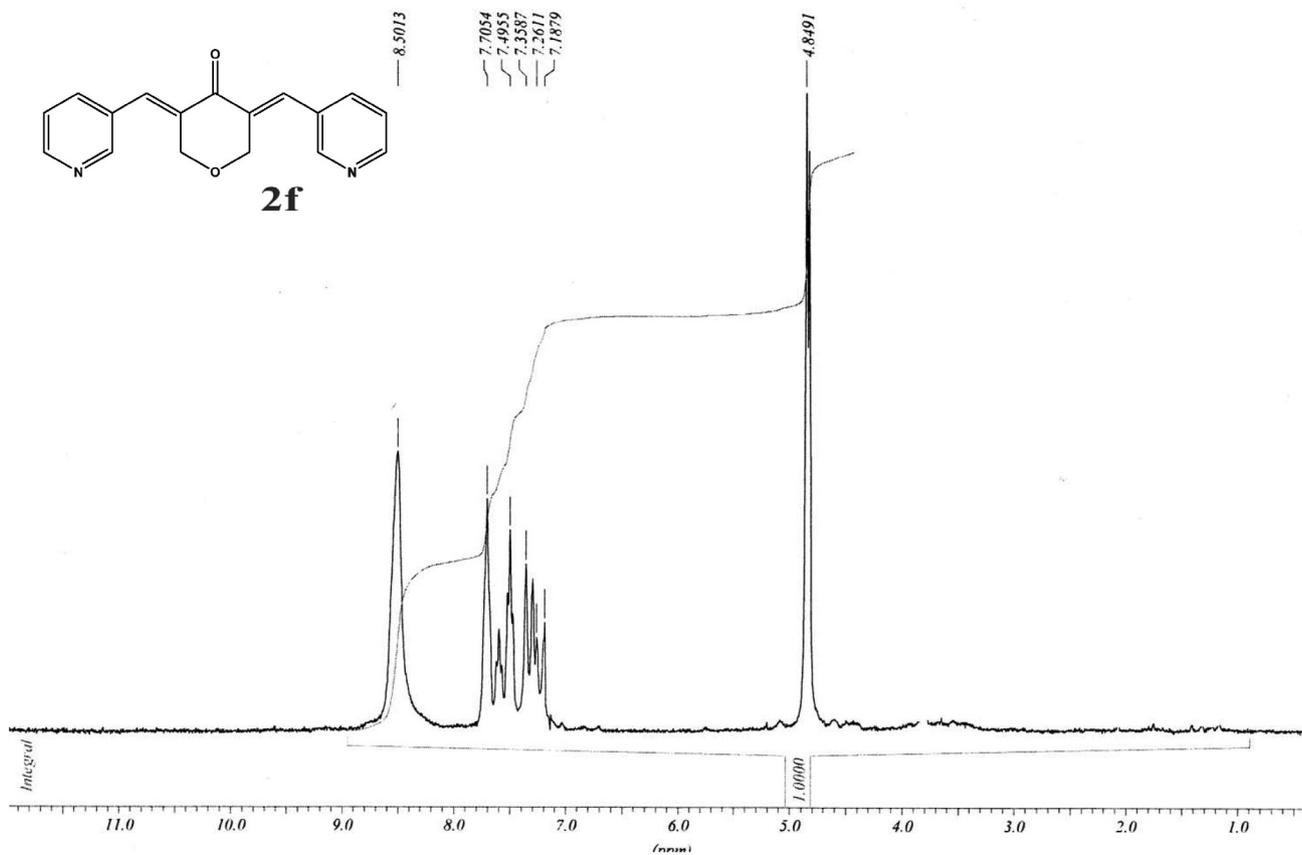
Figure S10. <sup>13</sup>C NMR spectrum of **1c**.Figure S11. Mass spectrum of **1c**.

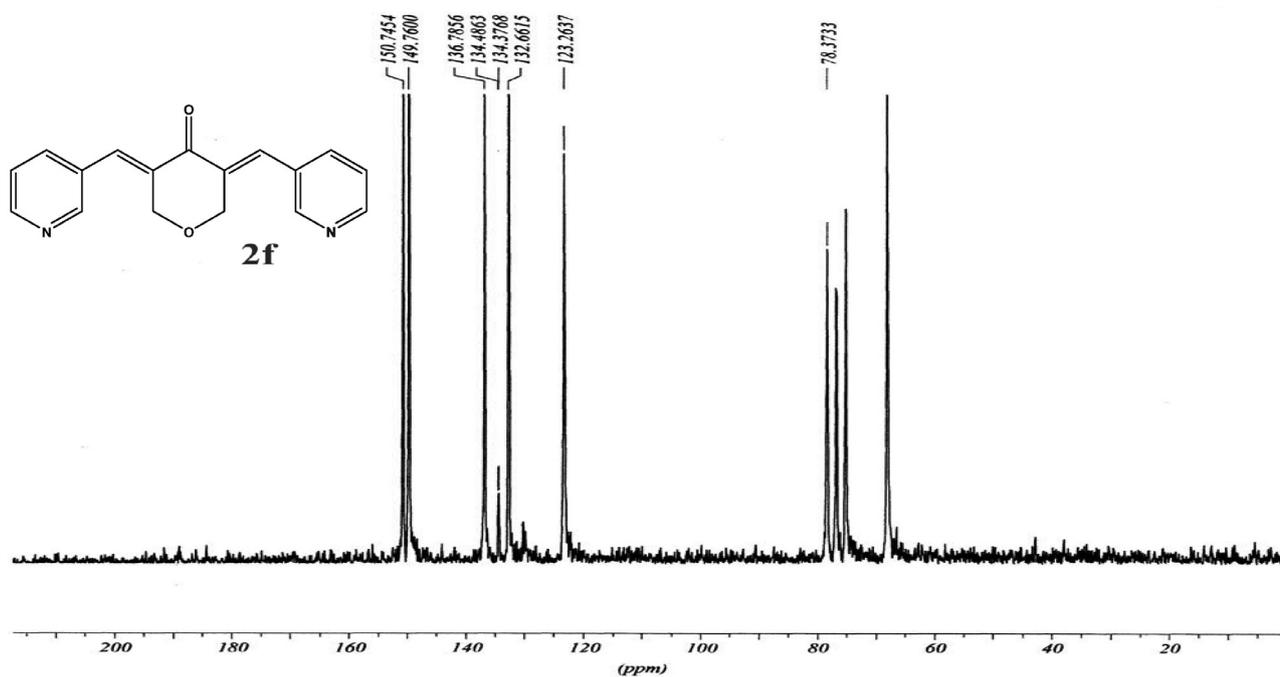
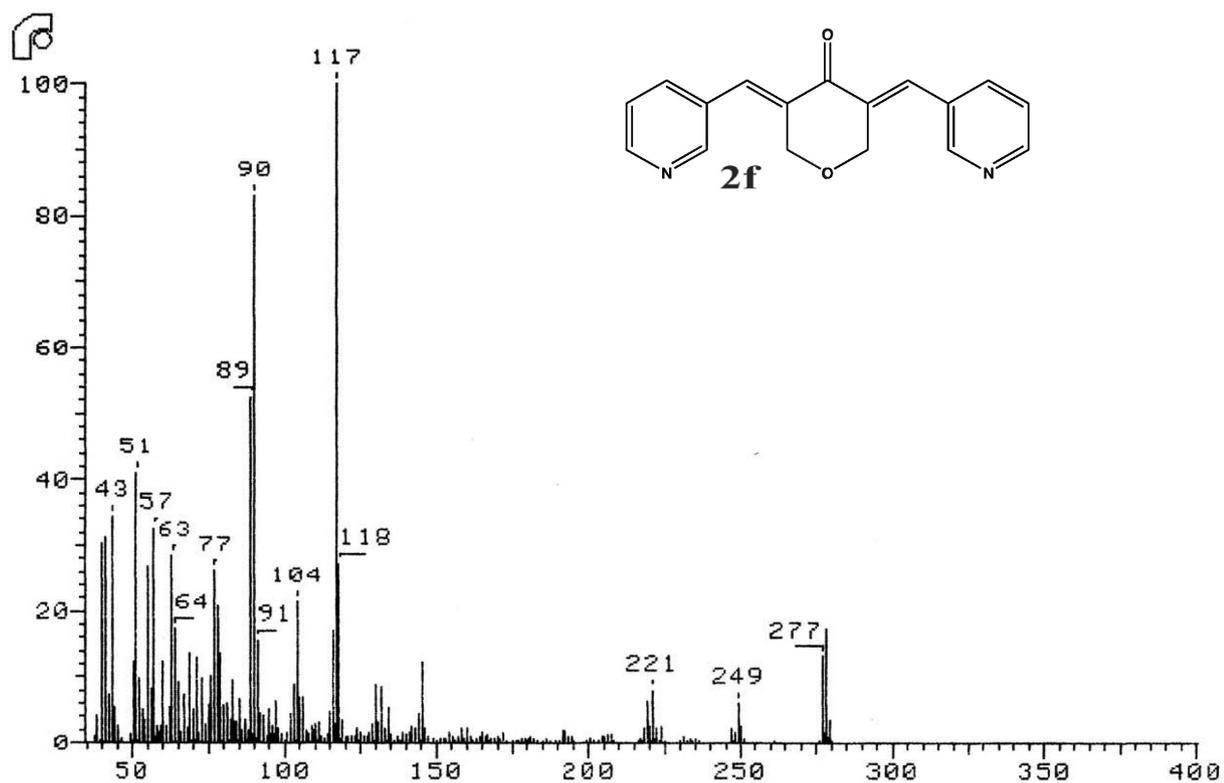
Figure S12. IR spectrum of **1c**.Figure S13. <sup>1</sup>H NMR spectrum of **2d**.

Figure S14. <sup>13</sup>C NMR spectrum of **2d**.Figure S15. Mass spectrum of **2d**.

Figure S16. IR spectrum of **2d**.Figure S17.  $^1\text{H}$  NMR spectrum of **2e**.

Figure S18. <sup>13</sup>C NMR spectrum of **2e**.Figure S19. Mass spectrum of **2e**.

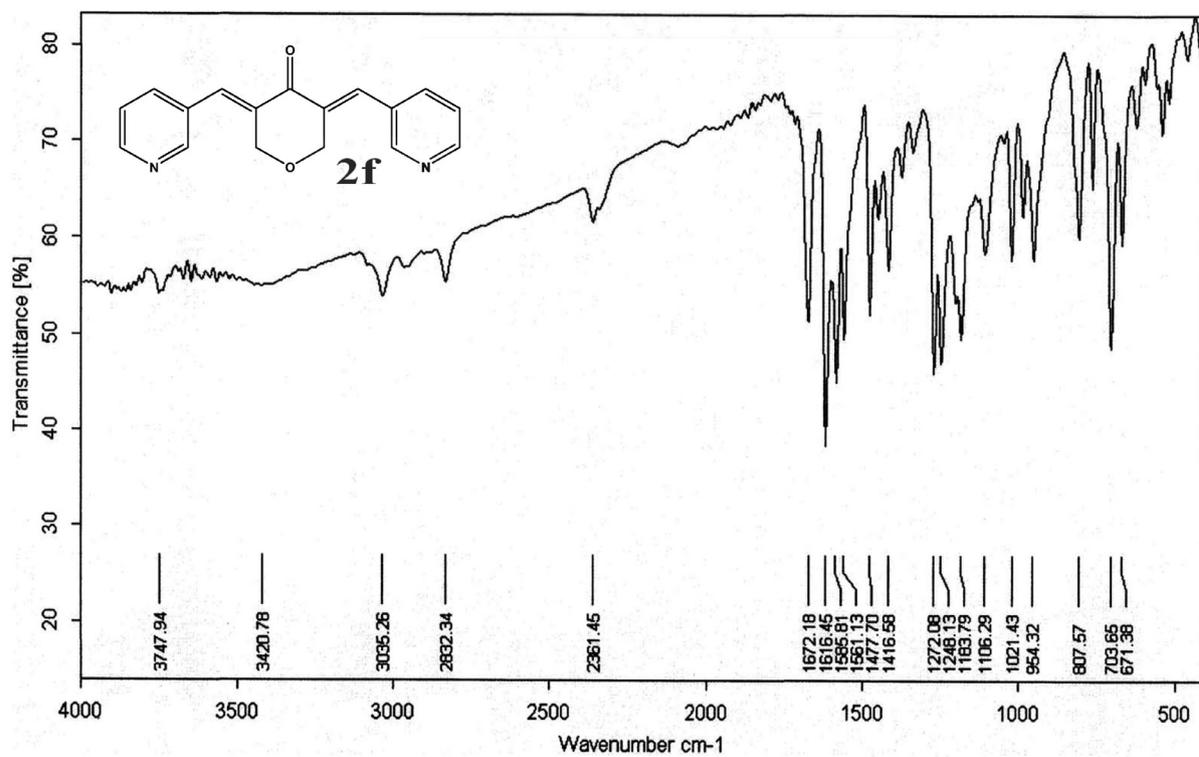
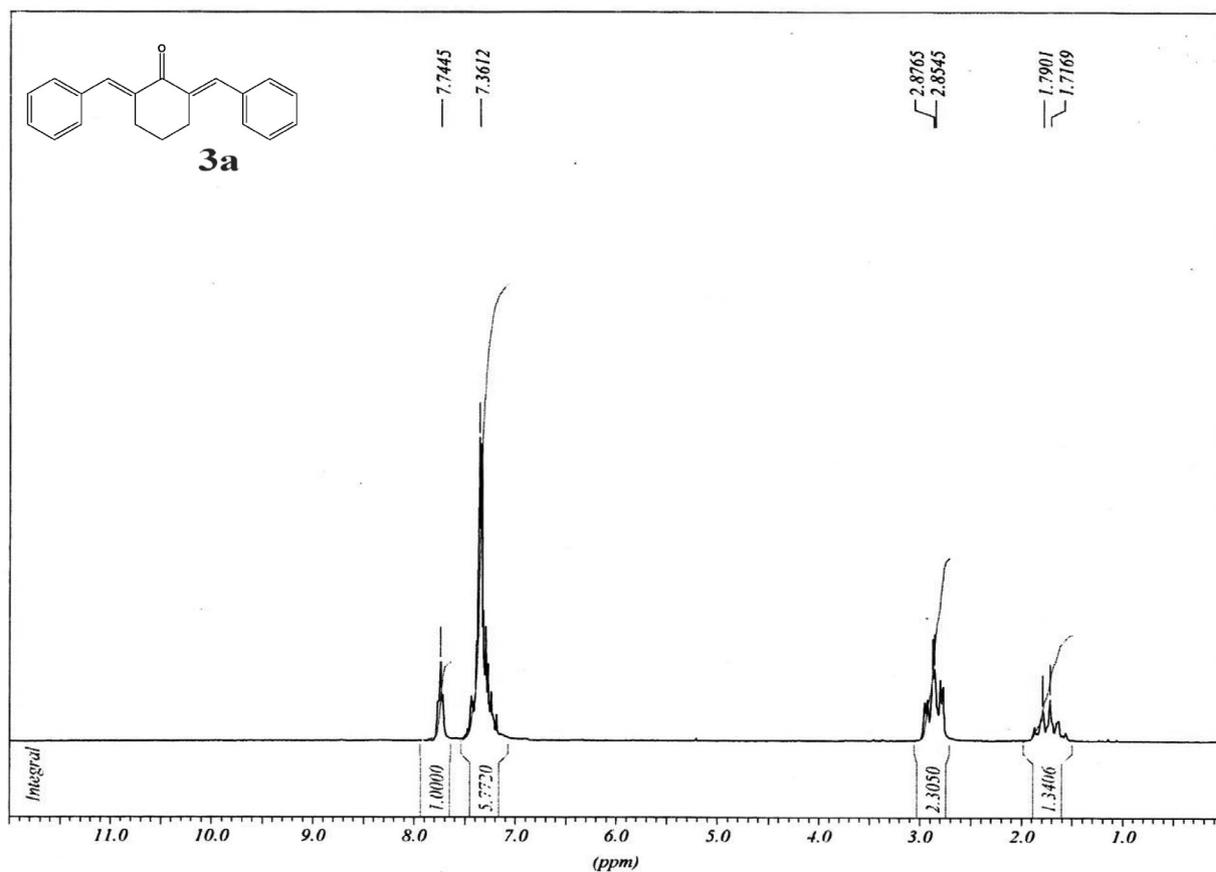
Figure S20. IR spectrum of **2e**.Figure S21. <sup>1</sup>H NMR spectrum of **2f**.

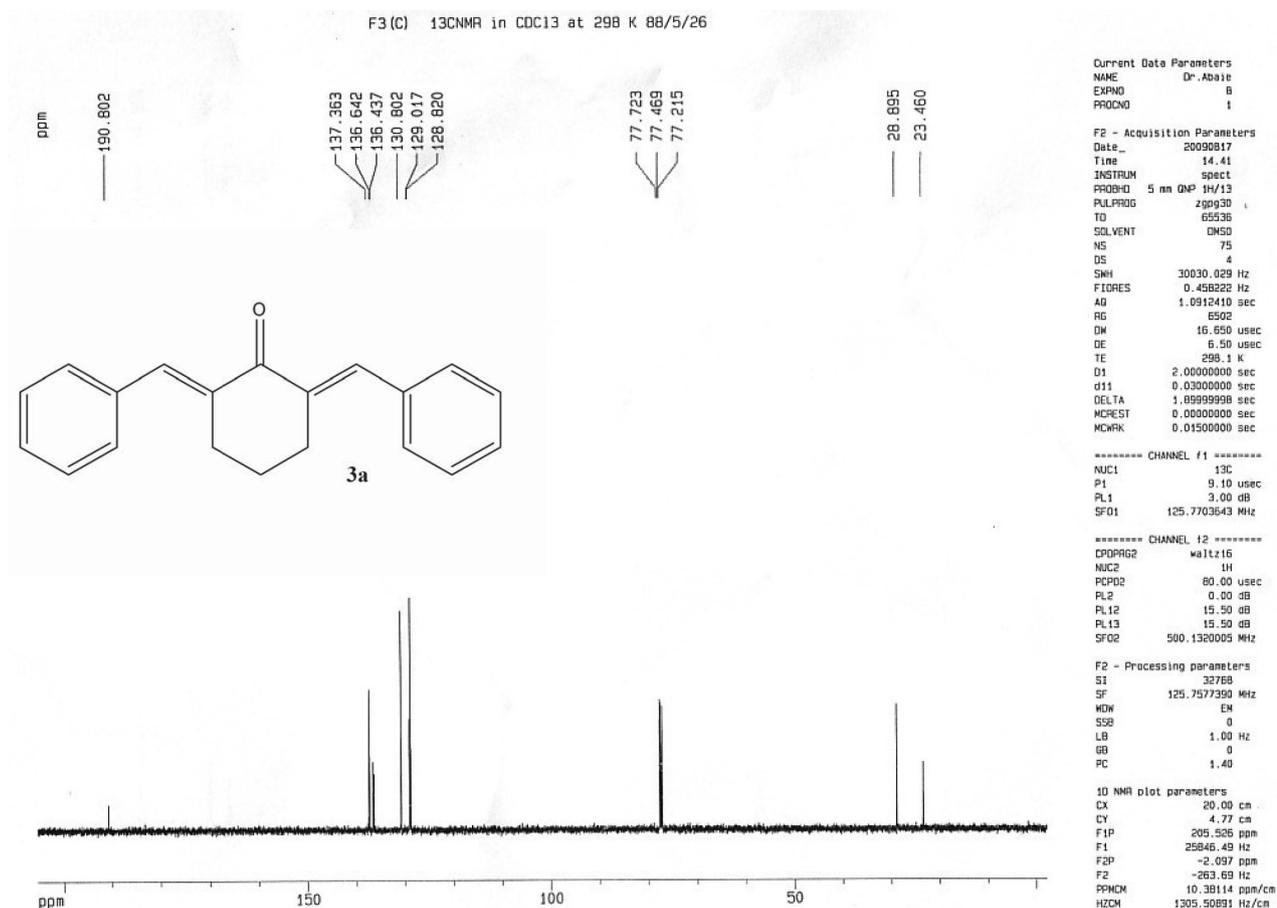
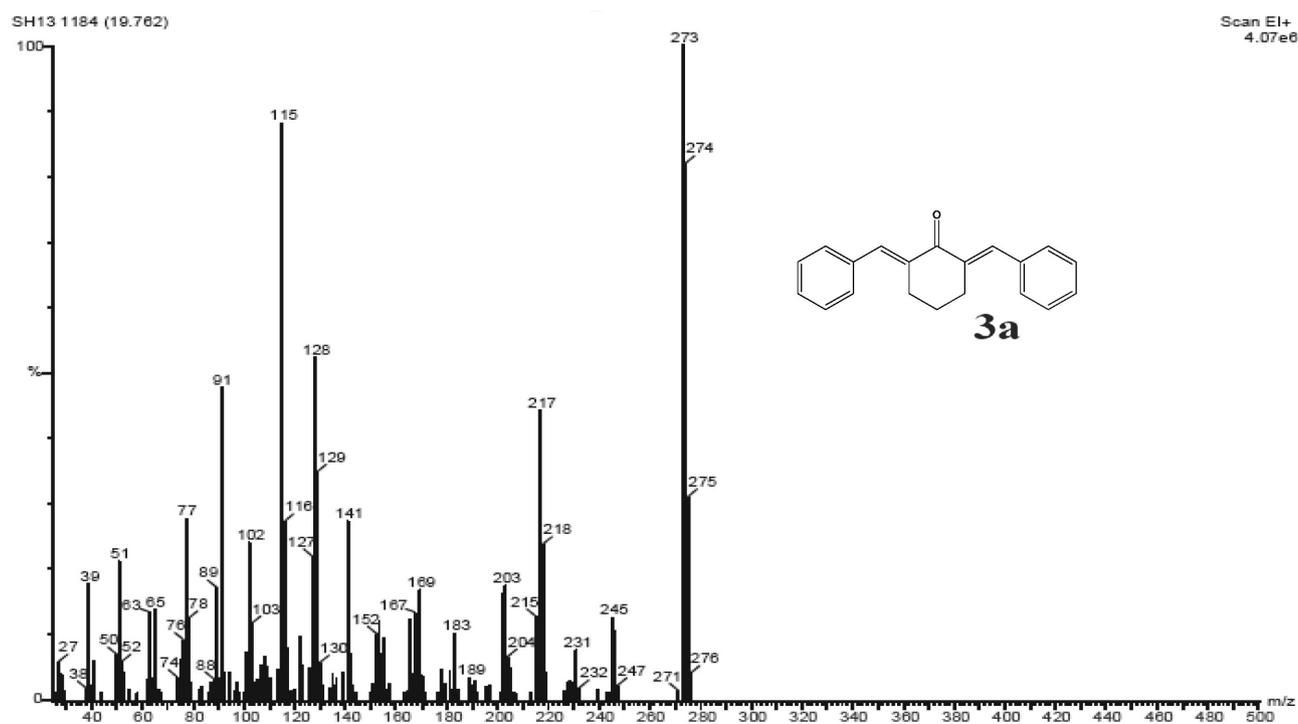
Figure S22. <sup>13</sup>C NMR spectrum of **2f**.

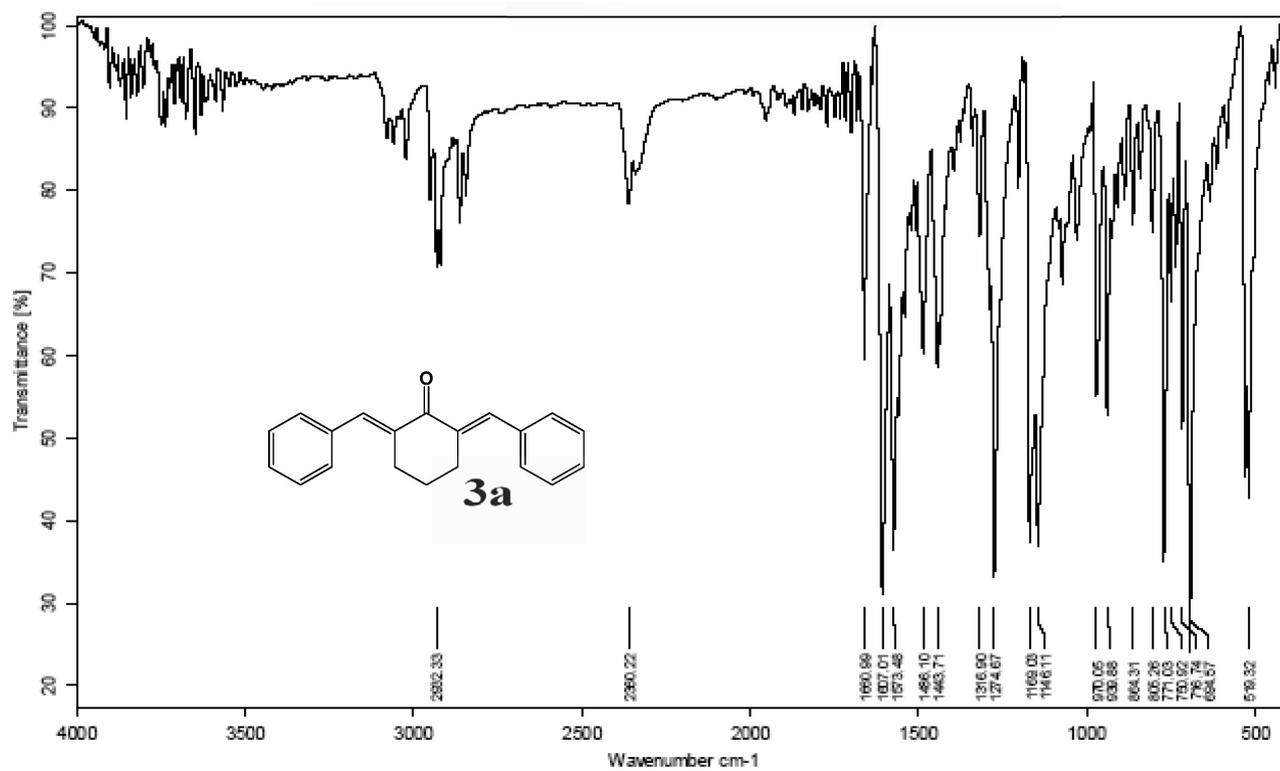
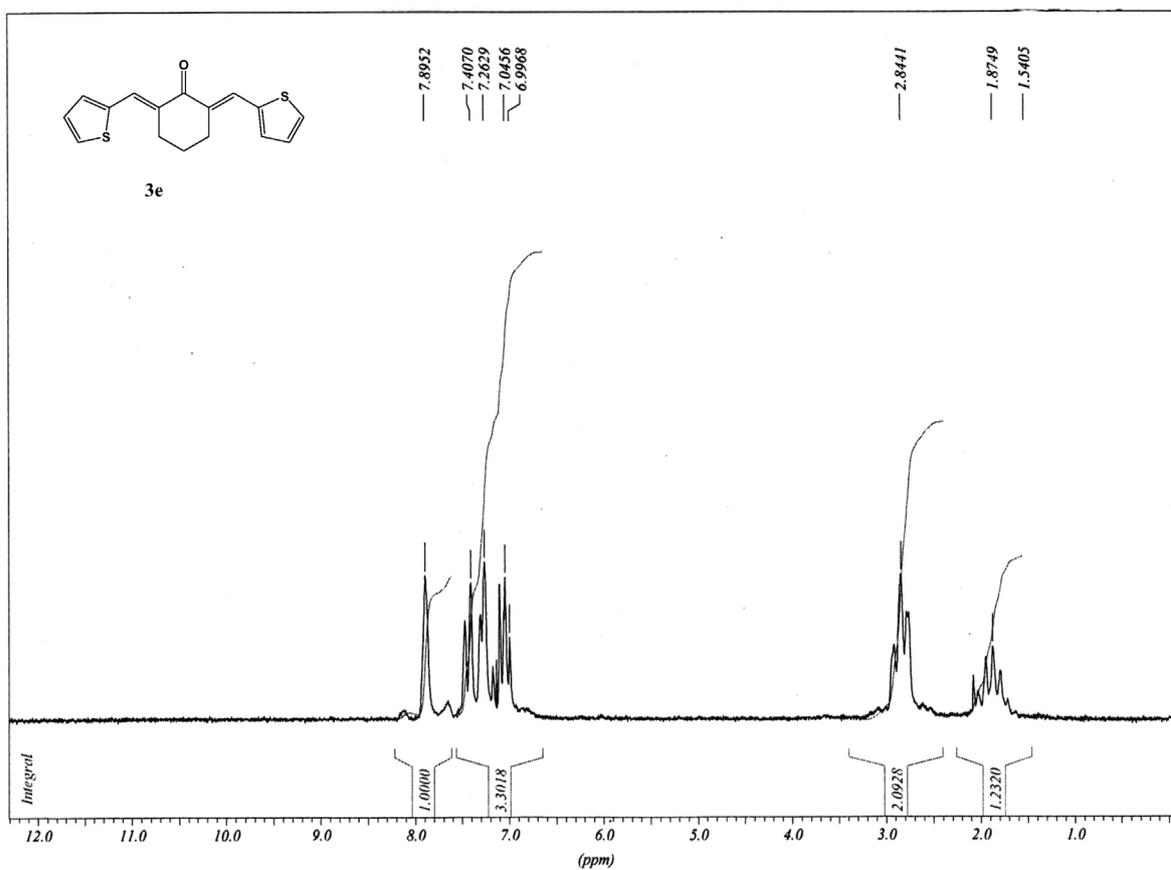
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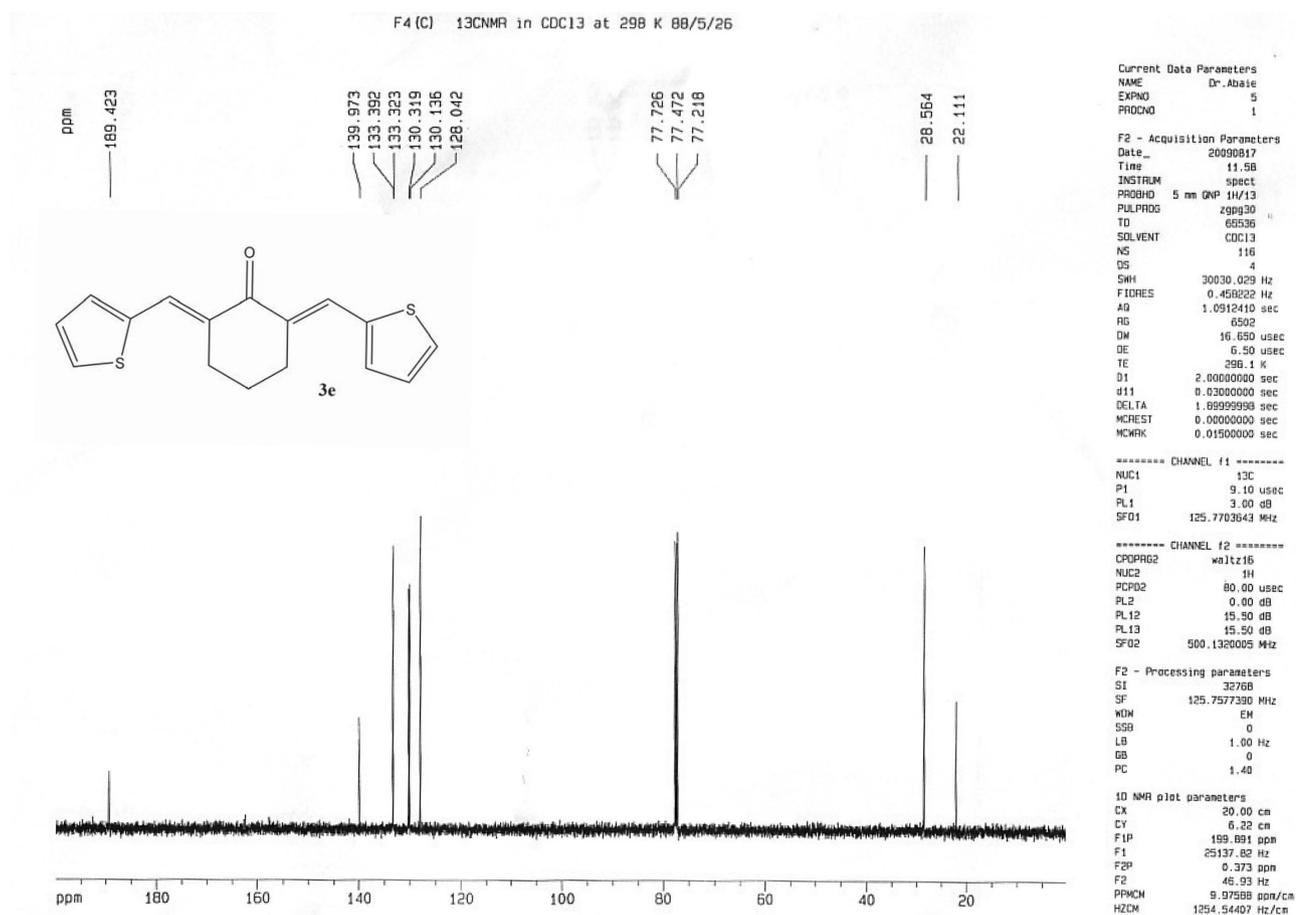
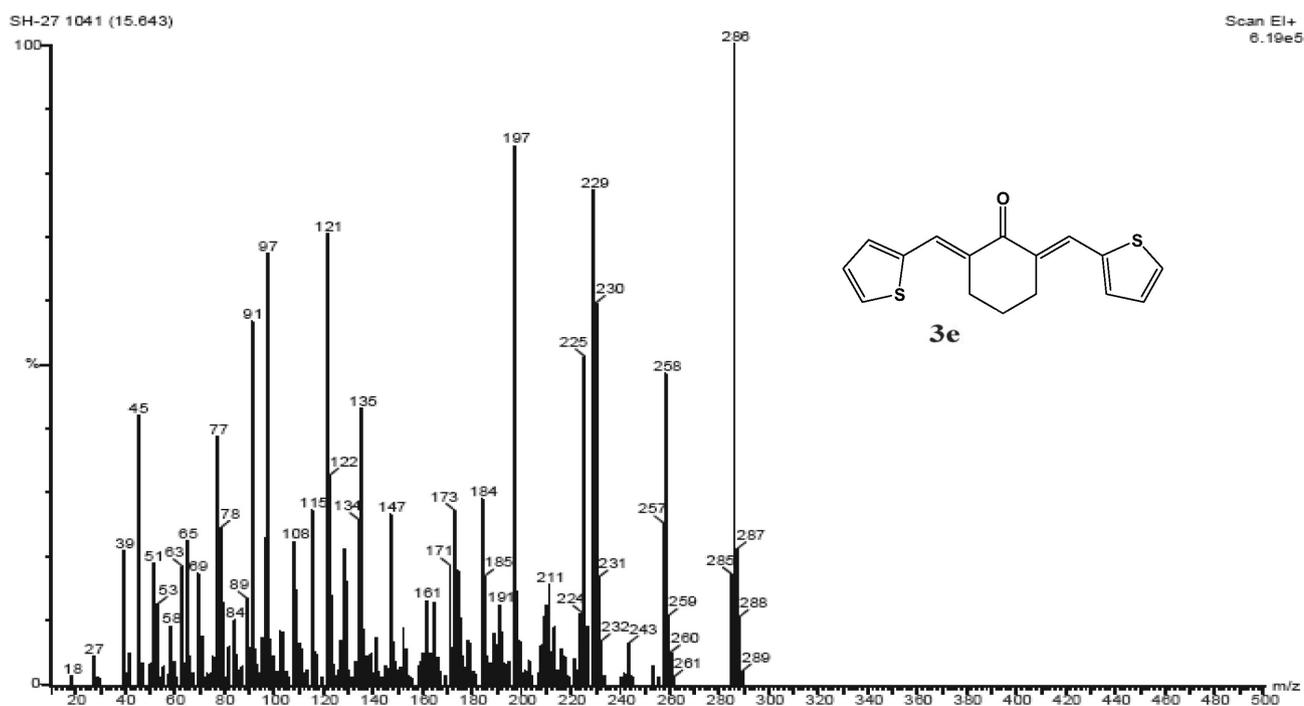
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Figure S23. Mass spectrum of **2f**.

Figure S24. IR spectrum of **2f**.Figure S25. <sup>1</sup>H NMR spectrum of **3a**.

Figure S26. <sup>13</sup>C NMR spectrum of **3a**.Figure S27. Mass spectrum of **3a**.

Figure S28. IR spectrum of **3a**.Figure S29.  $^1\text{H}$  NMR spectrum of **3e**.

Figure S30. <sup>13</sup>C NMR spectrum of **3e**.Figure S31. Mass spectrum of **3e**.



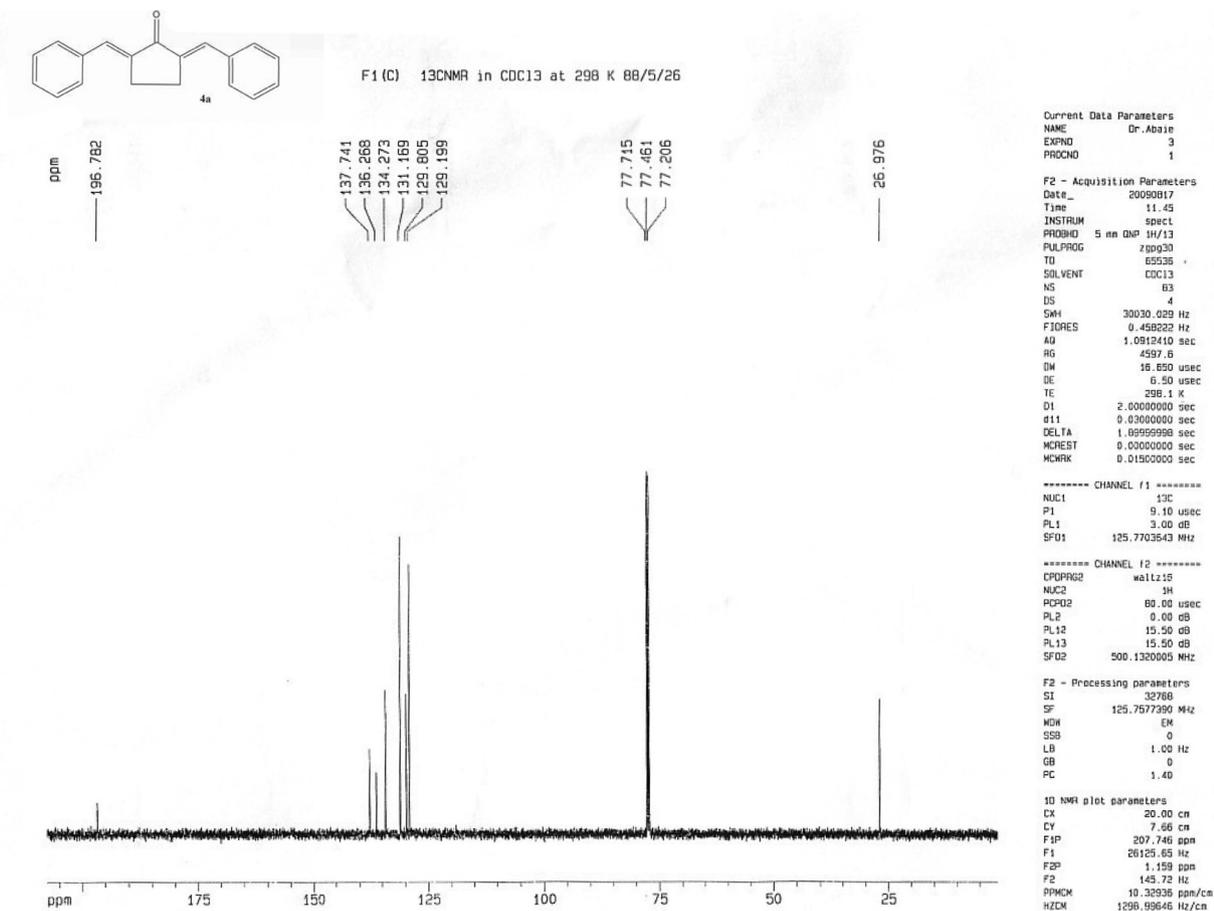
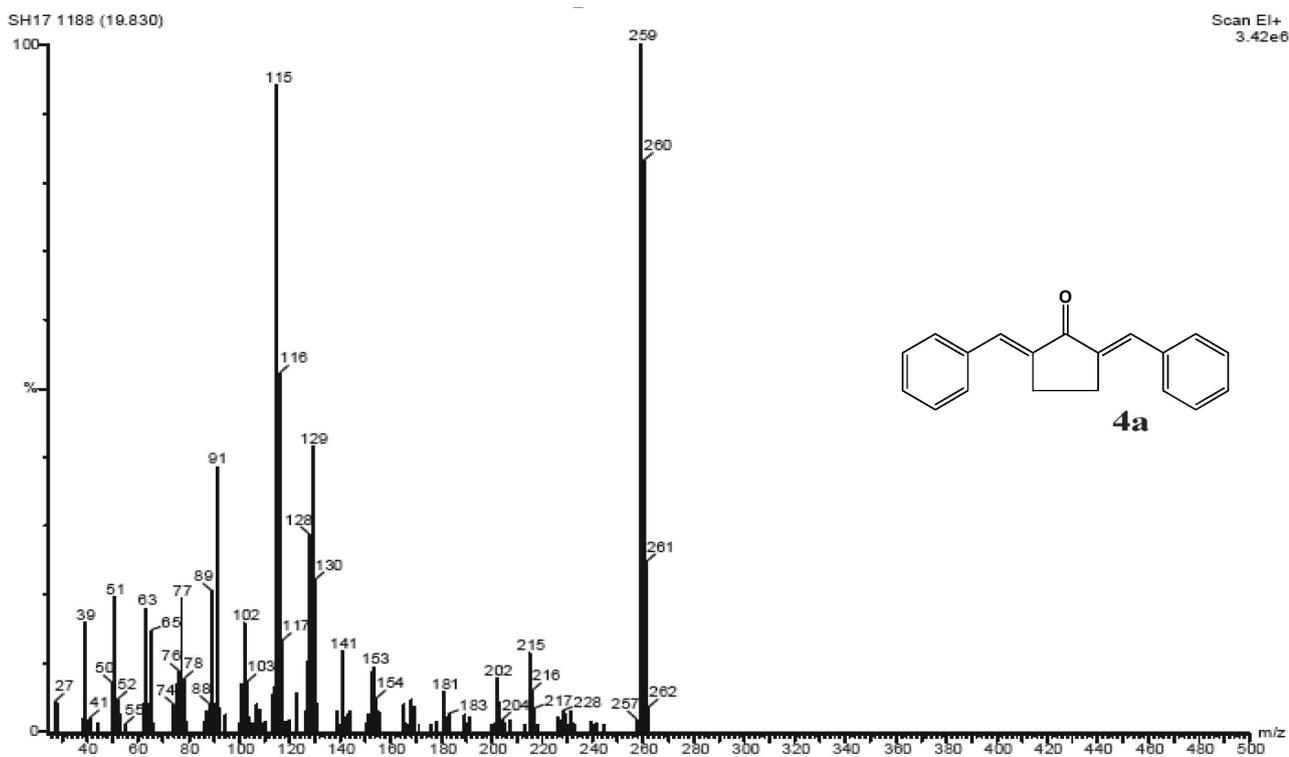
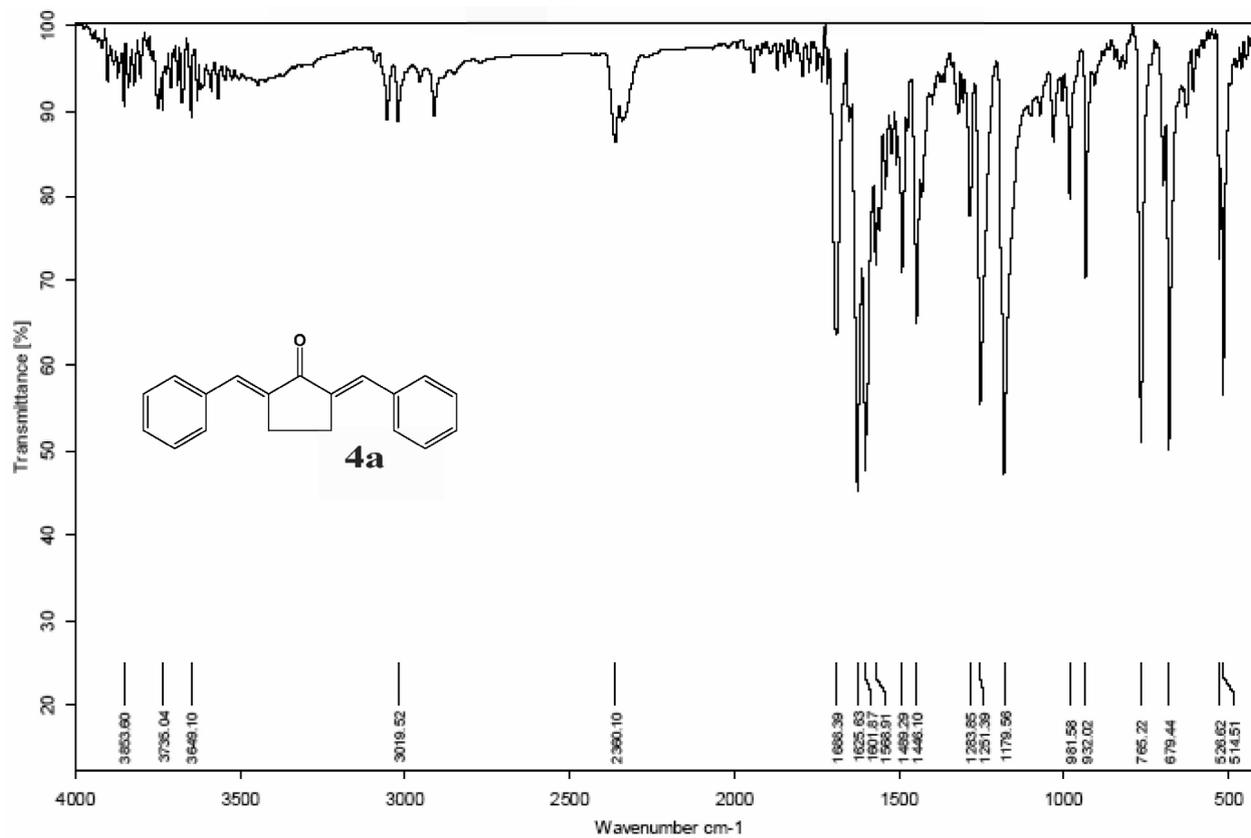
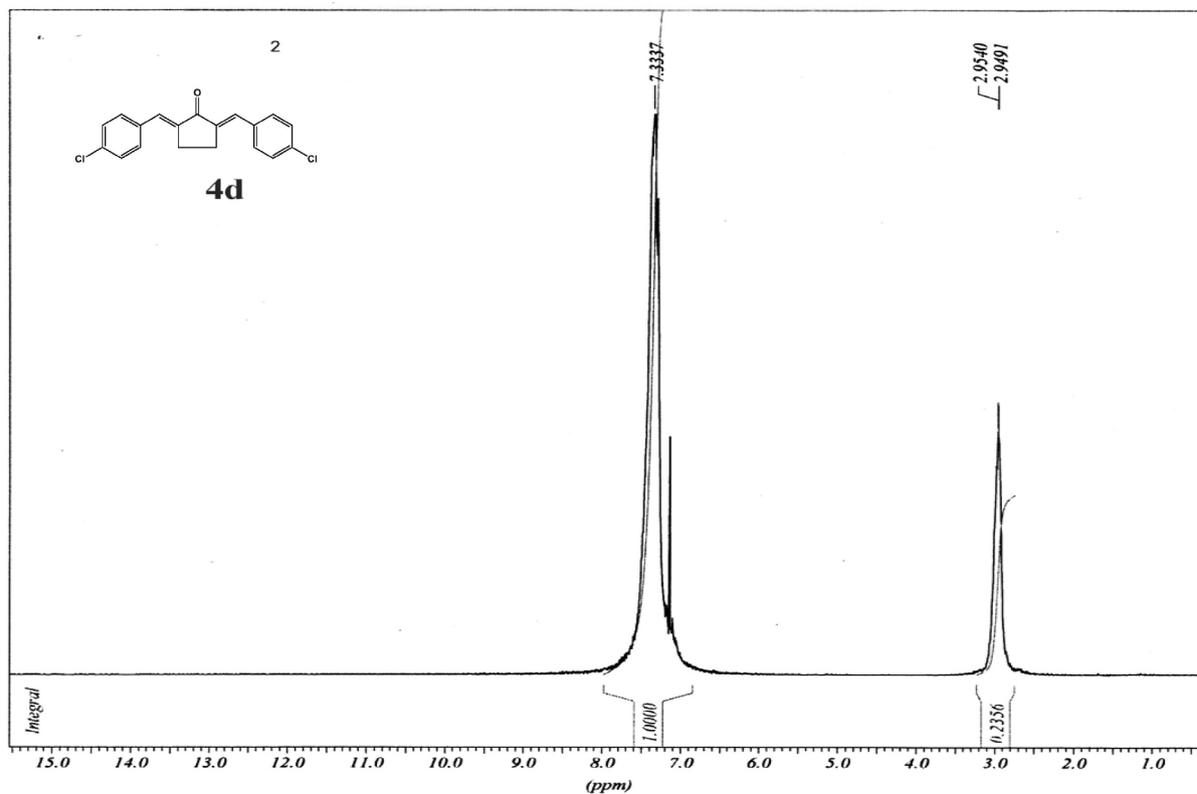
Figure S34. <sup>13</sup>C NMR spectrum of 4a.

Figure S35. Mass spectrum of 4a.

Figure S36. IR spectrum of **4a**.Figure S37. <sup>1</sup>H NMR spectrum of **4d**.

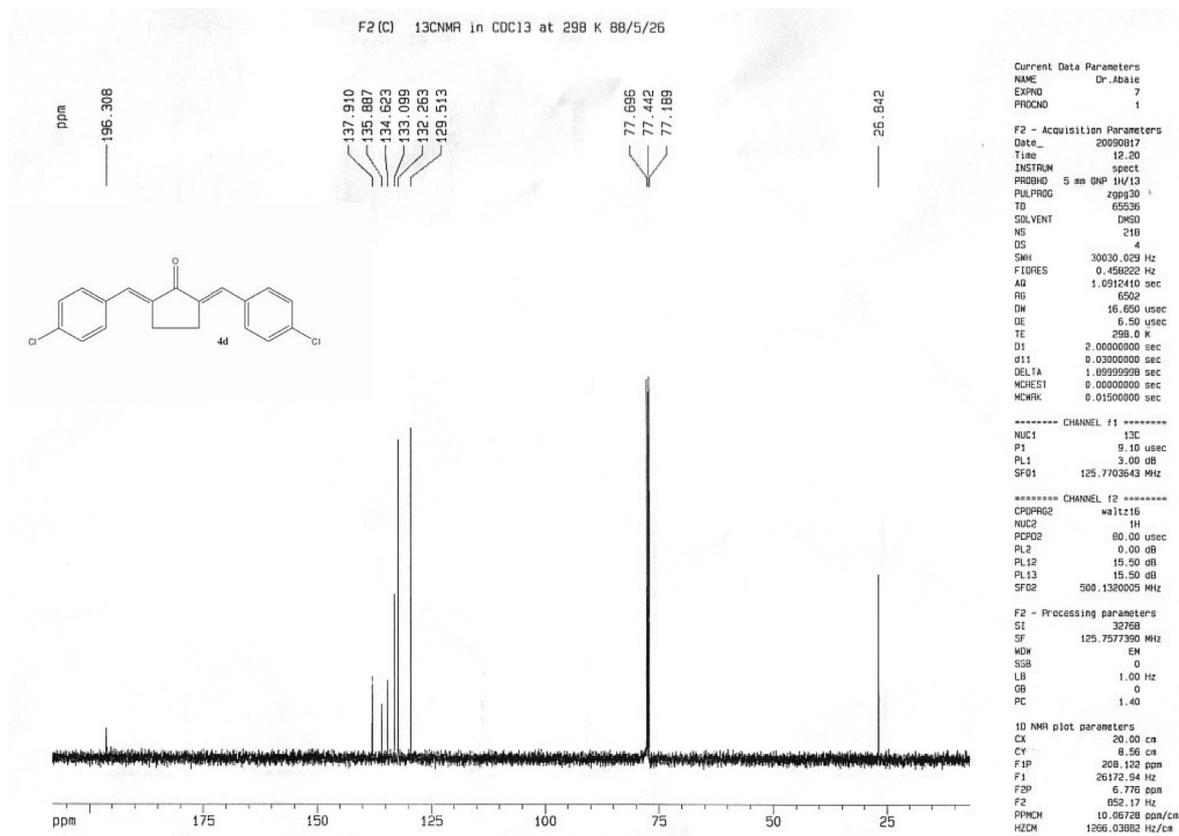
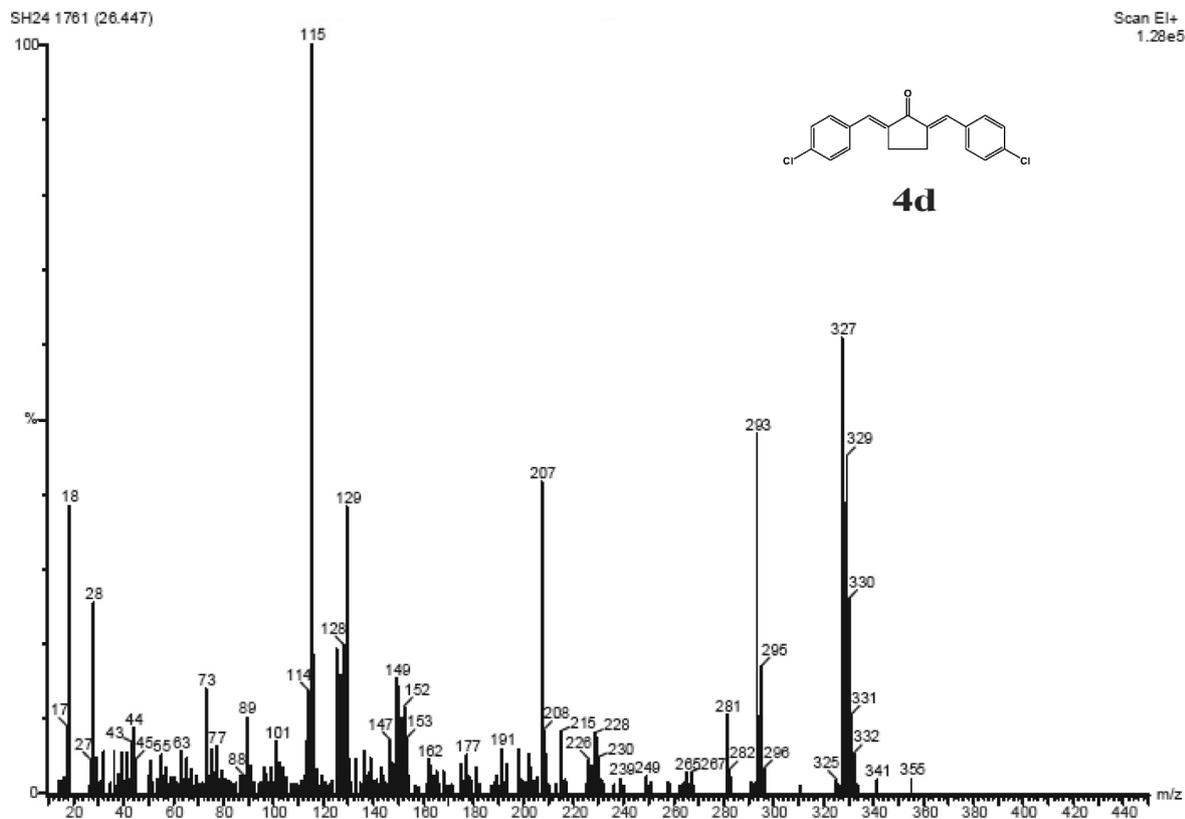
Figure S38. <sup>13</sup>C NMR spectrum of 4d.

Figure S39. Mass spectrum of 4d.

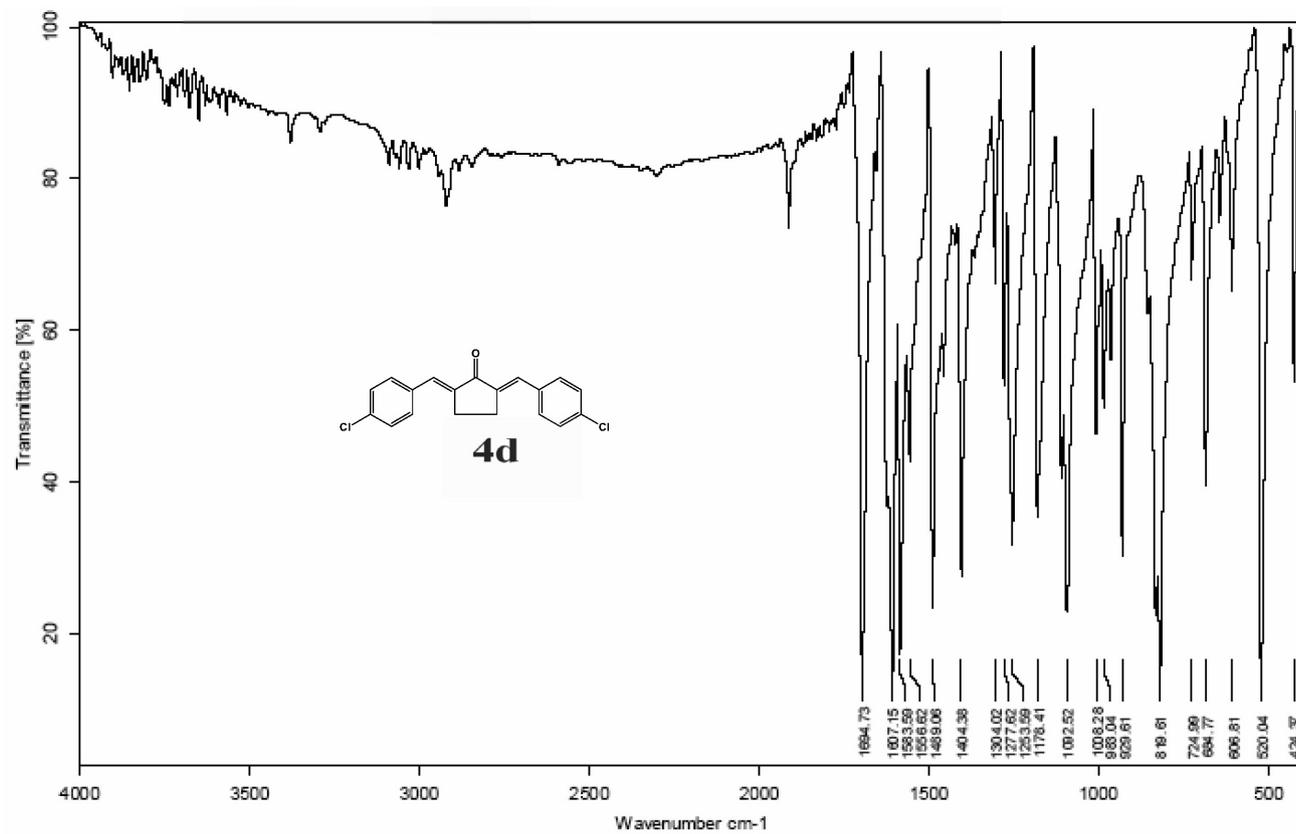


Figure S40. IR spectrum of 4d.