

## Synthesis and characterization of unsaturated diacyl and alkyl-acyl piperazine derivatives

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**Abstract:** The aim of this study is to obtain new unsaturated piperazine compounds by the reactions of piperazine (**1a**) and piperazine derivatives (**1b–1d**) with acylation reactive groups (**2a–2j**). Methacryloyl piperazine (**1b**) was synthesized from the reaction of methacrylic anhydride with piperazine (**1a**). Acyl chlorides (**2b–2d**) were prepared from the reaction of thionyl chloride with carboxylic acids (**3a–3c**) obtained as a result of the reaction with malonic acid and suitable aldehyde (5-methylfuran-2-carbaldehyde for **3a**, cinnamaldehyde for **3b**, and thiophene-2-carbaldehyde for **3c**), respectively, by literature methods. Acyl chlorides **2e** and **2f** were obtained from the reaction of commercially purchased carboxylic acids **3d** and **3e** with thionyl chloride. Acyl chlorides (**2g–2j**) were synthesized from the reaction of thionyl chloride with carboxylic acids (**3d–3g**) transformed from hydrolyzation of esters (**4a–4d**) obtained as a result of the reaction of triethyl phosphonoacetate with a suitable ketone (acetophenone for **4a**, benzophenone for **4b**, 1-(5-methylfuran-2-yl)ethan-1-one for **4c**, and 1-(thiophen-2-yl)ethan-1-one for **4d**), respectively, by literature methods. Unsaturated piperazine derivatives **5a** and **5b** were obtained from the reaction of **1b** with **2b** and **2e**, respectively. In addition, from the reaction of **1b** and acyl chlorides (**2b–2j**), unsaturated piperazines (**5c–5k**) were synthesized in medium to good yields (63%–84%). Also, **5l–5g** and **5r–5w** were obtained from the reaction of allyl piperazine (**2c**) and cinnamyl piperazine (**2d**) with acyl chlorides (**2a–2f**).

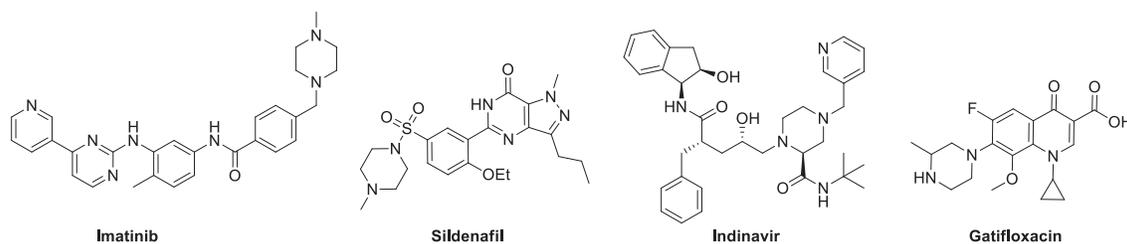
**Key words:** Piperazine, acylation, heterocycle

### 1. Introduction

Heterocycles are organic molecules that have great importance both biologically and industrially. Many synthetic and naturally occurring drugs contain heterocyclic moieties [1–3]. Heterocycles bearing nitrogen (piperazine, thiazole, imidazole, etc.) have drawn much attention due to their biological properties [4,5]. In medicinal chemistry the piperazine scaffold is considered a privileged structure for its capability of binding to multiple receptors with high affinity [6] and it can be found in drugs such as imatinib [7], sildenafil [8], indinavir [9], and gatifloxacin [10] (Figure 1). Piperazine is also a useful linker for bioactive structures. Many biological activity studies were performed on piperazine-containing structures, such as anticonvulsant [11], antibacterial [12], antituberculosis [13], antiviral [14], anticancer [15], antimalarial [16], and acetylcholine esterase inhibition [17].

Cinnamyl piperazine derivatives were reported to show anticonvulsant activity [18], monoacylglycerol lipase inhibition [19], and antimicrobial [20] and antiinflammatory activity [21]. Some acrylamide piperazine

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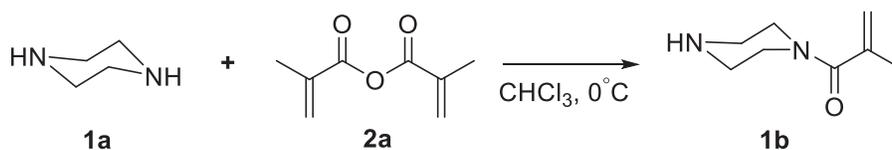


**Figure 1.** Structure of imatinib, sildenafil, indinavir, and gatifloxacin.

derivatives were also reported to show antimycobacterial [22], antiischemic [23], and antiparasitic activities [24]. Additionally, some dienoyl-substituted piperazines were reported to show  $\gamma$ -aminobutyric acid receptor [25], monoamine oxidase [26], and *Staphylococcus aureus* [27] inhibition. In this study, based on these properties of piperazines, we obtained various unsaturated diacyl and alkyl-acyl cinnamyl, ally, and acrylamide piperazines bearing unsaturated moieties, which are potential bioactive compounds and starting reagents for synthesizing many other potential bioactive molecules. All new synthesized compounds were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HRMS, and FTIR spectroscopy. Other compounds that are available in the literature were characterized by  $^1\text{H}$  NMR spectroscopy.

## 2. Results and discussion

Synthesis of methacryloyl piperazine (**1b**) was performed by the reaction of piperazine (**1a**) and methacryloyl chloride as an acylating reagent in the literature [28]. However, we did not succeed in synthesizing **1b** using this method; dimethacryloyl piperazine was obtained instead. In this study, synthesis of **1b** (77%) was achieved by the reaction of methacrylic anhydride (**2a**) with piperazine (**1a**) in mild conditions (Figure 2).



**Figure 2.** Synthesis of methacryloyl piperazine (**1b**).

Unsaturated acyl chlorides (**2b–2j**) were prepared from the reaction of suitable carboxylic acid and  $\text{SOCl}_2$  according to literature (see Section 3). Diacyl (**5a–5k**) and alkyl-acyl (**5l–5w**) piperazine compounds were obtained from the reactions of these acyl chlorides with piperazine (**1a**) and piperazine derivatives (**1b–1d**).

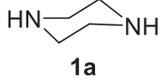
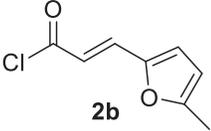
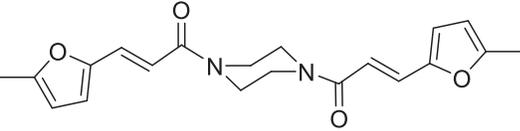
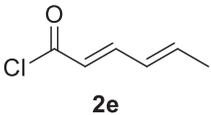
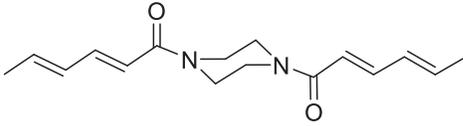
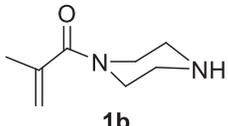
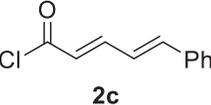
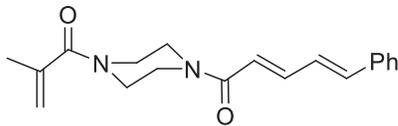
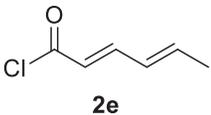
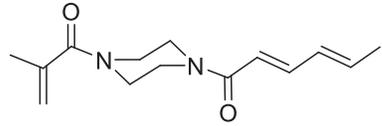
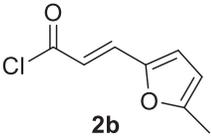
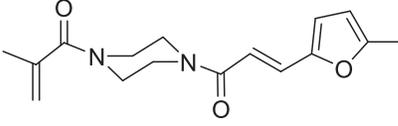
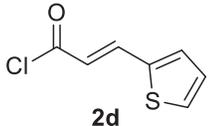
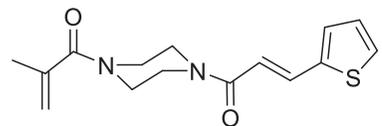
As can be seen in Table 1, symmetrical unsaturated piperazine derivatives **5a** (84%) and **5b** (66%) were synthesized from the reactions of piperazine (**1a**) and (*E*)-3-(5-methylfuran-2-yl)acryloyl chloride (**2b**) and (*2E,4E*)-hexa-2,4-dienoyl chloride (**2e**), respectively.

Reactions of **1b** with (*2E,4E*)-5-phenylpenta-2,4-dienoyl chloride (**2c**) and **2e** gave **5c** (72%) and **5d** (66%) in high yields, respectively. Additionally, reactions of **1b** with **2b** and (*E*)-3-(thiophen-2-yl)acryloyl chloride (**2d**) gave piperazine derivatives **5e** (75%) and **5f** (81%), respectively.

Diacyl piperazine compounds **5g** (65%), **5h** (79%), and **5i** (70%) were obtained from the reaction of **1b** with cinnamoyl chloride (**2f**), (*E*)-3-phenylbut-2-enoyl chloride (**2g**), and 3,3-diphenylacryloyl chloride (**2h**) in medium to high yields, respectively (Table 2).

Similarly, **5j** (65%) and **5k** (63%) were synthesized from the reaction of **1b** with (*E*)-3-(5-methylfuran-

**Table 1.** Synthesis diacyl piperazine compounds **5a-f**.

Entry	Piperazine	Acylating reagent	Diacyl piperazine product	Product and Yield (%) <sup>a</sup>
1				<b>5a</b> , 84
2	<b>1a</b>			<b>5b</b> , 66
3				<b>5c</b> , 72
4	<b>1b</b>			<b>5d</b> , 66
5	<b>1b</b>			<b>5e</b> , 75
6	<b>1b</b>			<b>5f</b> , 81

a) Isolated yields are based on piperazine derivative (**1a** or **1b**).

2-yl)but-2-enoyl chloride (**2i**) and (*E*)-3-(thiophen-2-yl)but-2-enoyl chloride (**2j**), respectively.

Synthesis of alkyl-acyl piperazine (**5l–5q**) compounds obtained from the reactions of allyl piperazine (**1c**) and suitable acyl chloride (**2a–2f**) can be seen in Table 3.

Piperazine compounds **5l** (63%) and **5m** (70%) were obtained from the reaction of **1c** with **2b** and **2d**, respectively. Treatments of **1c** with **2f** and **2a** also gave piperazine derivatives **5n** (90%) and **5o** (76%) in high yields, respectively. Moreover, reactions of **1c** with **2c** and **2e** gave **5p** (75%) and **5q** (81%), respectively.

Syntheses of alkyl-acyl piperazines (**5r–5w**) were obtained from the reactions of cinnamyl piperazine (**1d**) and suitable acyl chloride (**2a–2f**) (Table 4).

Reactions of **1d** with **2b** and **2d** gave piperazine compounds **5r** (87%) and **5s** (81%) in high yields, respectively. Additionally, **5t** (87%) and **5u** (94%) were obtained from the reactions of **1d** with **2f** and **2a**.

**Table 2.** Synthesis diacyl piperazine compounds **5g-k**.

Entry	Piperazine	Acylating reagent	Diacyl piperazine product	Product and Yield (%) <sup>a</sup>
1				<b>5g</b> , 65
2	<b>1b</b>			<b>5h</b> , 79
3	<b>1b</b>			<b>5i</b> , 70
4	<b>1b</b>			<b>5j</b> , 65
5	<b>1b</b>			<b>5k</b> , 63

a) Isolated yields are based on piperazine derivative (**1b**).

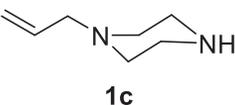
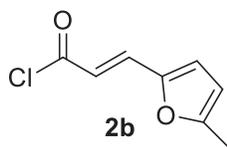
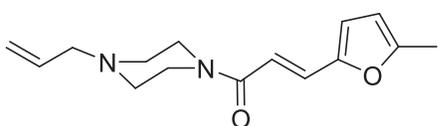
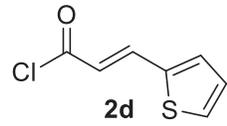
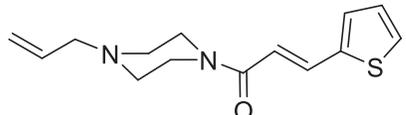
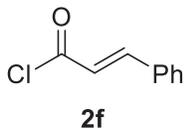
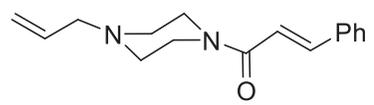
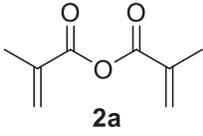
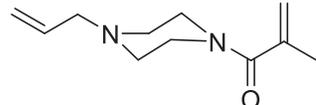
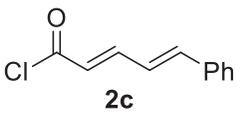
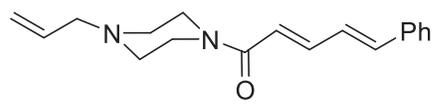
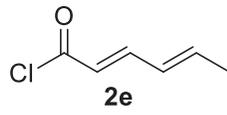
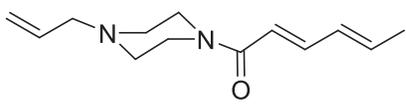
Moreover, **5v** (75%) and **5w** (81%) were synthesized from the reactions of **1d** with **2c** and **2e** in high yields.

In conclusion, novel diacyl (**5a–5k**) and alkyl-acyl (**5l–5w**) unsaturated piperazine compounds were synthesized by the acylation reactions of piperazine (**1a**), methacryloyl piperazine (**1b**), allyl piperazine (**1c**), and cinnamyl piperazine (**1d**) with suitable acyl chlorides and methacrylic anhydride in medium to high yields for the first time. All new compounds were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS, and FTIR spectroscopy. The others were characterized by only <sup>1</sup>H NMR.

Many piperazine derivatives are known for their bioactive properties and can be used as linkers for many other bioactive structures like imatinib [7], sildenafil [8], indinavir [9], and gatifloxacin [10]. On the other hand, these diacyl (**5a–5k**) and alkyl-acyl (**5l–5w**) piperazine compounds bear unsaturated moieties and for that reason they are potential starting reagents for many reactions such as Heck coupling, polymerizations, and  $\alpha$ - $\beta$  unsaturated Michael additions.

These compounds are also starting reagents for Mn(OAc)<sub>3</sub> mediated radical cyclization reactions for

**Table 3.** Synthesis of allyl-acyl piperazine compounds (**5l-q**).

Entry	Piperazine	Acylating reagent	Alkly-Acyl piperazine product	Product and Yield (%) <sup>a</sup>
1				<b>5l</b> , 63
2	<b>1c</b>			<b>5m</b> , 70
3	<b>1c</b>			<b>5n</b> , 90
4	<b>1c</b>			<b>5o</b> , 76
5	<b>1c</b>			<b>5p</b> , 75
6	<b>1c</b>			<b>5q</b> , 81

a) Isolated yields are based on piperazine derivative (**1c**).

synthesizing acetylcholine esterase inhibitor dihydrofuran-piperazine molecules and this work is an ongoing research interest of our group.

### 3. Experimental

#### 3.1. Equipment and used chemicals

Melting points were determined on a Gallenkamp capillary melting point apparatus. IR spectra (ATR) were obtained with a Bruker Tensor27 spectrophotometer in the 400–4000  $\text{cm}^{-1}$  range with 2  $\text{cm}^{-1}$  resolution.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Varian Mercury-400 High Performance Digital FT-NMR and

**Table 4.** Synthesis of cinnamyl-acyl piperazine compounds (**5r-w**).

Entry	Piperazine	Acylating reagent	Alkyl-Acyl piperazine product	Product and Yield (%) <sup>a</sup>
1				<b>5r</b> , 87
2	<b>1d</b>			<b>5s</b> , 81
3	<b>1d</b>			<b>5t</b> , 87
4	<b>1d</b>			<b>5u</b> , 94
5	<b>1d</b>			<b>5v</b> , 75
6	<b>1d</b>			<b>5w</b> , 81

a) Isolated yields are based on piperazine derivative (**1d**).

Varian Oxford NMR300 spectrometers. High-resolution mass time-of-flight spectra (TOF) were measured on an Agilent 1200/6210 LC/MS spectrophotometer. Thin-layer chromatography (TLC) was performed on Merck aluminum-packed silica gel plates. Purification of products was performed by column chromatography on silica gel (Merck silica gel 60, 40–60  $\mu\text{m}$ ) or preparative TLC on silica gel (Merck, PF<sub>254–366</sub> nm). All solvents (chloroform, methanol, ethyl acetate, hexane, THF, diethyl ether, ethanol, HCl) were of the highest purity and anhydrous. Malonic acid, 5-methyl-2-carbaldehyde, cinnamaldehyde, thiophene-2-carbaldehyde, pyridine, piperidine, SOCl<sub>2</sub>, NaH, triethyl phosphonoacetate, acetophenone, benzophenone, 2-acetyl-5-methylfuran, 2-acetyl-thiophene, NaOH, Na<sub>2</sub>SO<sub>4</sub>, 2,4-hexadienoic acid, cinnamic acid, piperazine, 1-allylpiperazine, 1-cinnamylpiperazine, and metacrylic anhydride were purchased from Sigma Aldrich. Please note that the <sup>1</sup>H

NMR spectra for known compounds and  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and HRMS spectra for all novel compounds can be found in the Supplementary information.

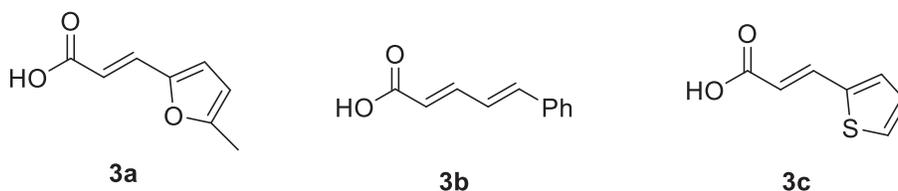
### 3.2. General synthesis of unsaturated acyl chlorides (2b–2j)

Thionyl chloride (22 mL, 0.3 mol, freshly distilled) was added to a solution of suitable carboxylic acid (**3a–3g**) (0.1 mol) in 100 mL of chloroform at room temperature. The mixture was allowed to stand for 12 h. Then the solvent and excess  $\text{SOCl}_2$  were distilled in vacuo. The residue was pure enough to be used as an acylating reagent without further purification.

All necessary carboxylic acids (except 2,4-hexadienoic acid and cinnamic acid) were prepared according to methods described in Sections 3.3 and 3.4.

### 3.3. General synthesis of (E)-3-(5-methylfuran-2-yl)acrylic acid (**3a**), (2E,4E)-5-phenylpenta-2,4-dienoic acid (**3b**), and (E)-3-(thiophen-2-yl)acrylic acid (**3c**)

Molecular structures of carboxylic acids (**3a–3c**) are given in Figure 3.



**Figure 3.** Carboxylic acids (**3a–3c**).

Malonic acid (20 g, 0.2 mol), the corresponding aldehyde (0.1 mol), (5-methylfuran-2-carbaldehyde for **3a**, cinnamaldehyde for **3b**, and thiophene-2-carbaldehyde for **3c**), 50 mL of freshly distilled pyridine, and 1 mL of piperidine were put into a two-necked reaction flask. The mixture was heated for 2 h to a temperature not exceeding 90–95 °C and boiled for 5 min after that. The mixture was left to cool and diluted with water. After cooling, concentrated HCl was added dropwise. Formed precipitates were filtered and crystallized in EtOH-water.

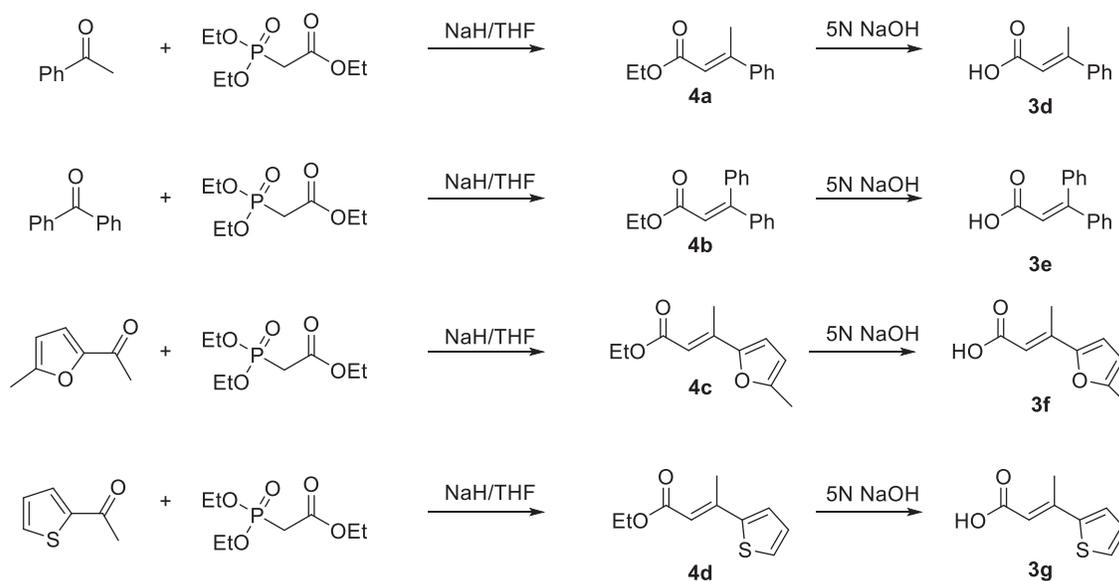
(*E*)-3-(5-Methylfuran-2-yl)acrylic acid (**3a**) [29]: Yield: 13 g, 85%. Mp: 155–156 °C, (lit: 154–155 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.43 (1H, d,  $J = 15.6$  Hz), 6.56 (1H, d,  $J = 3.2$  Hz), 6.22 (1H, d,  $J = 15.6$  Hz), 6.10 (1H, d,  $J = 3.2$  Hz), 2.35 (3H, s).

(2*E*,4*E*)-5-Phenylpenta-2,4-dienoic acid (**3b**) [30]: Yield: 12 g, 70%. Mp: 164–166 °C, (lit: 164–166 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.57–7.46 (3H, m), 7.39–7.30 (3H, m), 6.98–6.87 (2H, m), 6.00 (1H, d,  $J = 15.2$  Hz).

(*E*)-3-(Thiophen-2-yl)acrylic acid (**3c**) [31]: Yield: 13.8 g, 90%. Mp: 140–141 °C, (lit: 140–142 °C).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.88 (1H, d,  $J = 15.6$  Hz), 7.42 (1H, d,  $J = 4.8$  Hz), 7.30 (1H, d,  $J = 3.2$  Hz), 7.07 (1H, dd,  $J = 4.8, 3.2$  Hz), 6.24 (1H, d,  $J = 15.6$  Hz).

### 3.4. General synthesis of substituted carboxylic acids (3d–3g)

Carboxylic acids (**3d–3g**) were prepared from the hydrolysis of esters (**4a–4d**) synthesized from the reaction of suitable ketones and triethyl phosphonoacetate in  $\text{NAH}/\text{THF}$  (Figure 4).



**Figure 4.** Synthesis of unsaturated esters (**4a–4d**) and carboxylic acids (**3d–3g**).

### 3.4.1. General synthesis of unsaturated esters (**4a–4d**)

To a suspension of NaH (60%, 8.3 g, 0.12 mol) in THF, a solution of triethyl phosphonoacetate (34.5 mL, 0.12 mol) in THF was added dropwise in an ice bath. After instillation the mixture was stirred for 30 min at room temperature and a solution of corresponding ketone (0.1 mol) (acetophenone for **4a**, benzophenone for **4b**, 1-(5-methylfuran-2-yl)ethan-1-one for **4c**, and 1-(thiophen-2-yl)ethan-1-one for **4d**) in THF was poured into the reaction mixture and stirred for 2–3 h. The reaction was monitored with TLC, and in the case of remaining ketone, the mixture was heated until no more ketone remained. THF was evaporated and water was added. The mixture was extracted with diethyl ether. The combined organic phase was dried with  $\text{Na}_2\text{SO}_4$  and ether was evaporated. The crude product was purified with column chromatography with hexane/ethyl acetate (5:1) as eluent.

(*E*)-Ethyl 3-phenylbut-2-enoate (**4a**) [32]: Yield: 17.81 g, 94%. Oily product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.51 (2H, m), 7.40 (3H, m), 6.17 (1H, m), 4.25 (2H, q,  $J = 7.2$  Hz), 2.62 (3H, d,  $J = 1.2$  Hz), 1.36 (3H, t,  $J = 7.2$  Hz).

Ethyl 3,3-diphenylacrylate (**4b**) [32]: Yield: 23.5 g, 93%. Oily product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.27–7.45 (10H, m), 6.44 (1H, s), 4.11 (2H, q,  $J = 7.2$  Hz), 1.17 (3H, t,  $J = 7.2$  Hz).

Ethyl (*E*)-3-(5-methylfuran-2-yl)but-2-enoate (**4c**): Yield: 17.9 g, 92%. Oily product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 6.52 (1H, d,  $J = 3.6$  Hz), 6.28 (1H, d,  $J = 1.2$  Hz), 6.03 (1H, d,  $J = 3.6$  Hz), 4.17 (2H, q,  $J = 7.2$  Hz), 2.40 (3H, d,  $J = 1.2$  Hz), 2.30 (3H, s), 1.28 (3H, t,  $J = 7.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 167.35, 154.35, 152.78, 142.24, 112.71, 110.82, 108.36, 59.57, 14.48, 14.33, 13.74.

Ethyl (*E*)-3-(thiophen-2-yl)but-2-enoate (**4d**) [33]: Yield: 16 g, 93%. Oily product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.34 (2H, d,  $J = 4.2$  Hz), 7.06 (1H, t,  $J = 4.2$  Hz), 6.22 (1H, d,  $J = 1.2$  Hz), 4.22 (2H, q,  $J = 7.2$  Hz), 2.63 (3H, d,  $J = 1.2$  Hz), 1.34 (3H, t,  $J = 7.2$  Hz).

### 3.4.2. General synthesis of unsaturated carboxylic acids (3d–3g)

Unsaturated esters (**4a–4d**) obtained by the method described above were transformed into their corresponding carboxylic acids (**3d–3g**) by the method described below.

Unsaturated ester (**4a–4d**) (0.1 mol) was boiled with 5 N NaOH under a reflux condenser for 2–3 h and left to stir at room temperature overnight. The formed carboxylate salt was dissolved in water and diluted HCl was added. The obtained solid product was filtered and crystallized with EtOH-water.

(*E*)-3-Phenylbut-2-enoic acid (**3d**) [34]: Yield: 15 g, 94%. Mp: 90–92 °C, (lit: 90–92 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ (ppm): 7.51–7.49 (3H, m), 7.40–7.38 (2H, m), 6.18 (1H, s), 2.61 (3H, s).

3,3-Diphenylacrylic acid (**3e**) [35]: Yield: 14.5 g, 65%. Mp: 159–161 °C (lit: 161–162 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ (ppm): 7.38–7.19 (10H, m), 6.33 (1H, s).

(*E*)-3-(5-Methylfuran-2-yl)but-2-enoic acid (**3f**): Yield: 10 g, 60%. Mp: 138–140 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ (ppm): 6.08 (1H, d, *J* = 3.2 Hz), 6.33 (1H, d, *J* = 1.2 Hz), 6.07 (1H, d, *J* = 3.2 Hz), 2.43 (3H, d, *J* = 1.2 Hz), 2.43 (3H, s). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ (ppm): 172.3, 155, 152.6, 144.5, 113.7, 109.8, 108.6, 14.8, 13.8.

(*E*)-3-(Thiophen-2-yl)but-2-enoic acid (**3g**) [36]: Yield: 11 g, 65%. Mp: 113–115 °C (lit: 114–114.8 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ (ppm): 7.37 (2H, d, *J* = 4.4 Hz), 7.07 (1H, t, *J* = 4.4 Hz), 6.29 (1H, s), 2.63 (3H, s).

### 3.5. Synthesis procedure for 2-methyl-1-(piperazin-1-yl)prop-2-en-1-one (1b) [28]

Piperazine (**1a**) (20 g, 0.232 mol) was dissolved in 50 mL of chloroform in a reaction flask. The solution was stirred in an ice-salt bath for 15 min. Then a dilute solution of methacrylic anhydride (**2a**) (18 g, 0.116 mol) was added. After instillation, the reaction was removed from the ice-salt bath and allowed to stir overnight. Water was added and crude product was extracted with chloroform. Combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-methanol (1:1) as eluent. Yield: 30 g, 77%. Oily product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 5.16 (1H, q, *J* = 1.6 Hz), 5.00 (1H, q, *J* = 1.2 Hz) 3.55 (4H, s) 2.84 (4H, s), 1.93 (3H, t, *J* = 1.2 Hz).

### 3.6. General synthesis procedure for symmetrical diacyl piperazine compounds (5a, 5b)

Piperazine (**2a**) (860 mg, 10 mmol) and Et<sub>3</sub>N (22 mmol) were dissolved in 10 mL of chloroform in a reaction flask. The solution was stirred in an ice bath for 15 min. Then a dilute solution of the related acylating agent (**1a**, **1b**) (22 mmol) in CHCl<sub>3</sub> was added dropwise. After instillation, the reaction was removed from the ice bath and allowed to stir overnight. Water was added and crude product was extracted with chloroform. Combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-methanol (1:1) as eluent.

(**2E,2'E**)-1,1'-(Piperazine-1,4-diyl)bis(3-(5-methylfuran-2-yl)prop-2-en-1-one) (**5a**): Yield: 3.1 g, 84%. Mp: 275–277 °C. IR (ATR): 980, 1209, 1426, 1603, 1644, 1748, 2850, 2921, 3686 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ (ppm): 7.43 (2H, d, *J* = 14.8 Hz), 6.69 (2H, d, *J* = 14.8 Hz), 6.47 (2H, d, *J* = 2.8 Hz), 6.07 (2H, d, *J* = 2.8 Hz), 3.74 (8H, s), 2.35 (6H, s). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ (ppm): 165.80, 154.83, 150.09, 130.48, 116.06, 111.81, 108.75, 45.6, 42.3, 13.89. HRMS (ESI): (m/z) calcd. for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>, (M+Na)<sup>+</sup> 377.14717, found: 377.14695.

**(2E,2'E,4E,4'E)-1,1'-(Piperazine-1,4-diyl)bis(hexa-2,4-dien-1-one) (5b):** Yield: 1.9 g, 66%. Mp: 153–155 °C. IR (ATR): 938, 1207, 1236, 1426, 1620, 1648, 2336, 2912  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.28 (2H, dd,  $J = 14.8, 10$  Hz), 6.25–6.07 (6H, m), 3.64 (8H, s), 1.85 (6H, d,  $J = 6.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 166.02, 143.99, 138.40, 129.99, 117.07, 41.99, 38.70, 18.59. HRMS (ESI): (m/z) calcd. for  $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2$ , (M+Na) $^+$  297.15734, found: 297.15706.

### 3.7. General synthesis procedure for nonsymmetrical diacyl piperazine compounds (5c-k)

Methacryloyl piperazine (**1b**, 10 mmol) and  $\text{Et}_3\text{N}$  (22 mmol) was dissolved in 10 mL of chloroform in a reaction flask. The solution was stirred in an ice bath for 15 min. Then a dilute solution of the related acylating agent (**2c–2j**) (22 mmol) in  $\text{CHCl}_3$  was added dropwise. After instillation, the reaction was removed from the ice bath and allowed to stir overnight. Water was added and crude product was extracted with chloroform. Combined organic phases were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-methanol (1:1) as eluent.

**(2E,4E)-1-(4-Methacryloylpiperazine-1-yl)-5-phenylpenta-2,4-dien-1-one (5c):** Yield: 2.2 g, 72%. Mp: 178–180 °C. IR (ATR): 759, 989, 1194, 1225, 1430, 1460, 1615, 2861, 2908  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.51–7.44 (3H, m), 7.36–7.25 (3H, m), 6.89 (2H, t,  $J = 15.2$  Hz), 6.43 (1H, d,  $J = 15.2$  Hz), 5.24 (1H, s), 5.06 (1H, s), 3.63 (8H, s), 1.96 (3H, s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.38, 165.71, 143.75, 139.71, 136.18, 128.78, 127.04, 126.52, 119.39, 116.12, 45.22, 41.56, 20.47. HRMS (ESI): (m/z) calcd. for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ , HRMS (ESI): (m/z) calcd. for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ , (M+H) $^+$  311.17540, found: 311.17543.

**(2E,4E)-1-(4-Methacryloylpiperazine-1-yl)hexa-2,4-dien-1-one (5d):** Yield: 1.78 g, 66%. Mp: 110–112 °C. IR (ATR): 924, 1198, 1253, 1432, 1614, 1645, 2912  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.30 (1H, t,  $J = 14.8$  Hz), 6.24–6.09 (3H, m), 5.24 (1H, t,  $J = 1.6$  Hz), 5.05 (1H, t,  $J = 1.2$  Hz), 3.60 (8H, s), 1.96 (3H, t,  $J = 1.6$  Hz), 1.84 (3H, d,  $J = 6.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.38, 166.03, 144.10, 139.97, 138.49, 129.97, 116.99, 116.08, 42, 46, 20.46, 18.60. HRMS (ESI): (m/z) calcd. for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$ , (M+Na) $^+$  271.14169, found: 271.14216.

**(E)-1-(4-Methacryloylpiperazine-1-yl)-3-(5-methylfuran-2-yl)prop-2-en-1-one (5e):** Yield: 2.33 g, 75%. Mp: 142–144 °C. IR (ATR): 977, 1196, 1247, 1426, 1606, 1644, 1705, 2859, 2919, 3047  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.40 (1H, d,  $J = 15.2$  Hz), 6.66 (1H, d,  $J = 15.2$ ), 6.45 (1H, d,  $J = 3.2$  Hz), 6.05 (1H, m), 5.23 (1H, t,  $J = 1.2$  Hz), 5.05 (1H, t,  $J = 1.2$  Hz), 3.66 (8H, s), 2.33 (3H, s), 1.96 (3H, t,  $J = 1.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.36, 165.75, 154.81, 150.05, 139.97, 130.49, 116.06, 111.75, 108.75, 45.47, 42.19, 20.46, 13.87. HRMS (ESI): (m/z) calcd. for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3$ , (M+Na) $^+$  311.13661, found: 311.13582.

**(E)-1-(4-Methacryloylpiperazine-1-yl)-3-(thiophen-2-yl)prop-2-en-1-one (5f):** Yield: 2.5 g, 81%. Mp: 101–103 °C. IR (ATR): 967, 1202, 1271, 1433, 1606, 1642, 2190, 2860, 2923, 2997  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.84 (1H, d,  $J = 15.2$  Hz), 7.51 (1H, dd,  $J = 5.2, 3.6$  Hz), 7.34 (1H, d,  $J = 5.2$  Hz), 7.24 (1H, d,  $J = 3.6$  Hz), 6.65 (1H, d,  $J = 15.2$  Hz), 5.25 (1H, t,  $J = 1.6$  Hz), 5.07 (1H, t,  $J = 1.6$  Hz), 3.66 (8H, s), 1.98 (3H, t,  $J = 1.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.38, 165.33, 140.13, 139.94, 136.46, 130.67, 128.08, 127.57, 116.13, 114.96, 46, 42, 20.4. HRMS (ESI): (m/z) calcd. for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ , (M+Na) $^+$  313.09811, found: 313.09941.

**(E)-1-(4-Cinnamoylpiperazine-1-yl)-2-methylprop-2-en-1-one (5g):**

Yield: 1.9 g, 65%. Mp: 100–102 °C. IR (ATR): 748, 996, 1133, 1209, 1367, 1436, 1618, 1739, 2362, 3003  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.71 (1H, d,  $J = 16$  Hz), 7.54–7.52 (2H, m), 7.41–7.36 (3H, m), 6.86 (1H, d,  $J = 16$  Hz), 5.26 (1H, s), 5.08 (1H, s), 3.60 (8H, s), 1.98 (3H, s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.38, 165.68, 143.66, 139.94, 134.97, 129.88, 128.85, 127.82, 116.39, 116.14, 42, 46, 20.47. HRMS (ESI): (m/z) calcd. for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$ , (M+Na) $^+$  307.14169, found: 307.14038.

**(E)-1-(4-Methacryloylpiperazine-1-yl)-3-phenylbut-2-en-1-one (5h):**

Yield: 2.6 g, 79%. Mp: 84–86 °C. IR (ATR): 766, 910, 1208, 1433, 1460, 1612, 2867, 2917, 2995  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.46–7.43 (2H, m), 7.38–7.33 (3H, m), 6.25 (1H, t,  $J = 1.2$  Hz), 5.24 (1H, d,  $J = 1.2$  Hz), 5.06 (1H, d,  $J = 1.2$  Hz), 3.62 (8H, s), 2.28 (3H, d,  $J = 1.2$  Hz), 1.96 (3H, t,  $J = 1.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.4, 167.3, 146.9, 141.4, 140, 128.54, 128.51, 125.9, 118.83, 116.1, 46.89, 42.29, 20.47, 18.05. HRMS (ESI): (m/z) calcd. for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$ , (M+Na) $^+$  337.13129, found: 337.13041.

**1-(4-Methacryloylpiperazine-1-yl)-3,3-diphenylprop-2-en-1-one (5i):**

Yield: 2.7 g, 70%. Mp: 126–128 °C. IR (ATR): 760, 916, 1199, 1431, 1592, 1628, 2856, 2890, 2978  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.37–7.27 (10H, m), 6.30 (1H, s), 5.171 (1H, s), 4.94 (1H, s), 3.5 (2H, s), 3.30 (4H, s), 2.91 (2H, s), 1.88 (3H, s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.09, 167.31, 147.68, 140.54, 139.84, 138.65, 129.50, 128.84, 128.77, 128.44, 128.40, 128.08, 120.11, 115.92, 46.20, 41.32, 20.39. HRMS (ESI): (m/z) calcd. for  $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2$ , (M+Na) $^+$  383.17300, found: 383.17366.

**(E)-1-(4-Methacryloylpiperazine-1-yl)-2-methyl-3-(5-methylfuran-2-yl)prop-2-en-1-one (5j):**

Yield: 2.1 g, 65%. Mp: 142–144 °C. IR (ATR): 988, 1195, 1219, 1421, 1441, 1611, 1631, 1738, 2854, 2923, 3013  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 6.45 (1H, d,  $J = 1.2$  Hz), 6.39 (1H, d,  $J = 2.8$  Hz), 6.00 (1H, m), 5.21 (1H, t,  $J = 1.6$  Hz), 5.03 (1H, t,  $J = 1.2$  Hz), 3.62 (8H, s), 2.3 (3H, s), 2.19 (3H, d,  $J = 1.2$  Hz), 1.94 (3H, t,  $J = 1.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.33, 167.03, 153.45, 152.67, 140, 136.70, 115.98, 112.15, 111.12, 108.10, 46.66, 41.54, 20.46, 14.93, 13.78. HRMS (ESI): (m/z) calcd. for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$ , (M+Na) $^+$  325.15226, found: 325.15113.

**(E)-1-(4-Methacryloylpiperazine-1-yl)-2-methyl-3-(thiophen-2-yl)prop-2-en-1-one (5k):**

Yield: 2 g, 63%. Mp: 102–104 °C. IR (ATR): 856, 1196, 1428, 1462, 1616, 2911, 2974  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.26 (1H, d,  $J = 1.2$  Hz), 7.19 (1H, dd,  $J = 3.6, 1.2$  Hz), 7.02 (1H, dd,  $J = 5.2, 3.6$  Hz), 6.37 (1H, d,  $J = 1.2$  Hz), 5.24 (1H, t,  $J = 1.2$  Hz), 5.06 (1H, t,  $J = 1.6$  Hz), 3.61 (8H, s), 2.33 (3H, d,  $J = 1.2$  Hz), 1.96 (3H, t,  $J = 1.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.37, 166.61, 145.17, 140.69, 139.96, 127.80, 125.82, 125.54, 116.2, 116.09, 46, 42, 20.5, 17.8. HRMS (ESI): (m/z) calcd. for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ , (M+Na) $^+$  327.11376, found: 327.11506.

**3.8. General synthesis procedure for alkyl-acyl piperazine compounds (5l–5w)**

Allyl piperazine (**2c**) or cinnamyl piperazine (**2d**) (10 mmol) and  $\text{Et}_3\text{N}$  (20 mmol) were dissolved in 10 mL of chloroform. The solution was stirred in an ice bath for 15 min. Then a dilute solution of related acylating reagents (13 mmol) in  $\text{CHCl}_3$  was added dropwise. After instillation, the reaction was removed from the ice bath and allowed to stir overnight. Water was added and crude product was extracted with chloroform. Combined

organic phases were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-methanol (1:1) as eluent.

**3.8.1. (*E*)-1-(4-Allylpiperazine-1-yl)-3-(5-methylfuran-2-yl)prop-2-en-1-one (5l):**

Yield: 1.7 g, 63%. Oily product. IR (ATR): 1001, 1220, 1367, 1428, 1647, 1739, 2360, 2799, 2943  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.39 (1H, d,  $J = 14.8$  Hz), 6.69 (1H, d,  $J = 14.8$  Hz), 6.44 (1H, d,  $J = 3.2$  Hz), 6.05 (1H, d,  $J = 3.2$  Hz), 5.87 (1H, ddt,  $J = 17.2, 10, 6$  Hz), 5.24 (1H, dd,  $J = 17.2, 1.2$  Hz), 5.20 (1H, dd,  $J = 10, 1.2$  Hz), 3.73 (4H, s), 3.06 (2H, d,  $J = 6.8$  Hz), 2.51 (4H, t,  $J = 5.2$  Hz), 2.34 (3H, s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.45, 154.47, 150.24, 133.94, 129.87, 118.90, 115.50, 112.40, 108.60, 61.42, 53.16, 52.58, 45.45, 41.88, 14. HRMS (ESI): (m/z) calcd. for  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$ , (M+Na) $^+$  283.1417, found: 283.14169.

**(*E*)-1-(4-Allylpiperazine-1-yl)-3-(thiophen-2-yl)prop-2-en-1-one (5m):**

Yield: 1.9 g, 70%. Mp: 64–66 °C. IR (ATR): 971, 1223, 1366, 1441, 1582, 1630, 1739, 2359, 2818, 2941  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.80 (1H, d,  $J = 15.2$  Hz), 7.31 (1H, d,  $J = 5.2$  Hz), 7.20 (1H, d,  $J = 3.6$  Hz), 7.03 (1H, dd,  $J = 5.2, 3.6$  Hz), 6.67 (1H, d,  $J = 15.2$  Hz), 5.87 (1H, ddt,  $J = 17.2, 10.8, 6$  Hz), 5.21 (1H, dd,  $J = 17.2, 1.2$  Hz), 5.19 (1H, dd,  $J = 10.8, 1.2$  Hz), 3.70 (4H, s), 3.04 (2H, d,  $J = 6$  Hz), 2.49 (4H, s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 164.96, 140.42, 135.60, 134.13, 130.20, 127.96, 127.15, 118.73, 115.70, 61.45, 53.16, 52.62, 45.60, 42.02. HRMS (ESI): (m/z) calcd. for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{OS}$ , (M+Na) $^+$  285.10321, found: 285.10448.

**(*E*)-1-(4-Allylpiperazine-1-yl)-3-phenylprop-2-en-1-one (5n):**

Yield: 2.5 g, 90%. Mp: 85–87 °C. IR (ATR): 987, 1221, 1436, 1590, 1643, 1739, 2360, 2943  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.66 (1H, d,  $J = 15.2$  Hz), 7.51 (2H, d,  $J = 1.6$  Hz), 7.39–7.33 (3H, m), 6.87 (1H, d,  $J = 15.2$  Hz), 5.86 (1H, ddt,  $J = 17.2, 10.4, 6.4$  Hz), 5.23 (1H, dd,  $J = 17.2, 1.2$  Hz), 5.18 (1H, dd,  $J = 10.4, 1.2$  Hz), 3.71 (4H, s), 3.03 (2H, dd,  $J = 6.4, 1.2$  Hz), 2.48 (4H, s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.39, 142.69, 135.29, 134.42, 129.56, 128.76, 127.71, 118.48, 117.12, 61.52, 53.24, 52.67, 45.79, 42.13, 29.66. HRMS (ESI): (m/z) calcd. for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$ , (M+Na) $^+$  279.14678, found: 279.14752.

**1-(4-Allylpiperazine-1-yl)-2-methylprop-2-en-1-one (5o):** Yield: 1.48 g, 76%. Mp: 128–130 °C. IR (ATR): 791, 920, 998, 1207, 1368, 1435, 1624, 1739, 2360, 2967  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 5.82 (1H, ddt,  $J = 17.2, 10, 6$  Hz), 5.20 (1H, d,  $J = 1.2$  Hz), 5.16 (2H, m), 5.00 (1H, d,  $J = 1.2$  Hz), 3.57 (4H, s), 2.99 (2H, dd,  $J = 6, 1.2$  Hz), 2.41 (4H, s), 1.96 (3H, t,  $J = 1.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.04, 140.42, 134.36, 118.37, 115.27, 61.49, 52.88, 42, 46, 20.44. HRMS (ESI): (m/z) calcd. for  $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}$ , (M+H) $^+$  195.14919, found: 195.14906.

**(2E,4E)-1-(4-Allylpiperazine-1-yl)-5-phenylpenta-2,4-dien-1-one (5p):**

Yield: 2.1 g, 76%. Oily product. IR (ATR): 758, 1009, 1227, 1447, 1595, 1636, 1739, 2360, 2792, 3005  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.48–7.42 (3H, m), 7.36–7.26 (3H, m), 6.88 (2H, q,  $J = 14.4$  Hz), 6.44 (1H, d,  $J = 14.4$  Hz), 5.85 (1H, ddt,  $J = 17.2, 10.4, 6.4$  Hz), 5.22 (1H, dd,  $J = 17.2, 1.2$  Hz), 5.19 (1H, dd,  $J = 10.4, 1.2$  Hz), 3.73 (2H, s), 3.61 (2H, s), 3.03 (2H, d,  $J = 6.4$  Hz), 2.47 (4H, t,  $J = 5.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.42, 142.88, 138.99, 136.35, 134.39, 128.74, 128.66, 126.97, 126.81, 120.19, 118.53, 61.53, 53.21, 52.68, 45.68, 41.99. HRMS (ESI): (m/z) calcd. for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$ , (M+H) $^+$  283.18049, found: 283.18153.

**(2E,4E)-1-(4-Allylpiperazine-1-yl)hexa-2,4-dien-1-one (5q):**

Yield: 2 g, 84%. Mp: 62–64 °C. IR (ATR): 923, 1228, 1266, 1421, 1621, 1648, 1739, 2360, 2810, 2958  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.25 (1H, dd,  $J = 14.8, 10.4$  Hz), 6.23–6.04 (3H, m), 5.85 (1H, ddt,  $J = 17.2, 10.4, 6.4$  Hz), 5.23–5.16 (2H, m), 3.70 (2H, s), 3.58 (2H, s), 3.01 (2H, d,  $J = 6.4$  Hz), 2.45 (4H, t,  $J = 5.2$  Hz), 1.83 (3H, d,  $J = 6.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.71, 143.17, 137.55, 134.27, 130.12, 118.56, 117.68, 61.49, 53.14, 52.66, 45.51, 41.86, 18.53. HRMS (ESI): (m/z) calcd. for  $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$ , (M+Na) $^+$  243.14678, found: 243.14626.

**(E)-1-(4-Cinnamylpiperazine-1-yl)-3-(5-methylfuran-2-yl)prop-2-en-1-one (5r):**

Yield: 3.1 g, 87%. Mp: 122–124 °C. IR (ATR): 969, 1212, 1366, 1432, 1647, 1739, 2360, 2801, 2944  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.39 (1H, d,  $J = 14.8$  Hz), 7.37–7.21 (5H, m), 6.69 (1H, d,  $J = 14.8$  Hz), 6.53 (1H, d,  $J = 16$  Hz), 6.42 (1H, d,  $J = 3.2$  Hz), 6.26 (1H, dt,  $J = 16, 6.8$  Hz), 6.04 (1H, d,  $J = 3.2$  Hz), 3.75 (2H, s), 3.60 (2H, s), 3.18 (2H, d,  $J = 6.8$  Hz), 2.52 (4H, t,  $J = 4.8$  Hz), 2.33 (3H, s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.46, 154.44, 150.29, 136.70, 133.51, 129.82, 128.59, 127.64, 126.33, 115.44, 112.53, 108.60, 60.89, 53.44, 52.86, 45.66, 42.11, 13.86. HRMS (ESI): (m/z) calcd. for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2$ , (M+Na) $^+$  359.173, found: 359.17447.

**(E)-1-(4-Cinnamylpiperazine-1-yl)-3-(thiophen-2-yl)prop-2-en-1-one (5s):** Yield: 2.9 g, 81%. Mp: 111–113 °C. IR (ATR): 965, 1208, 1230, 1421, 1587, 1629, 2152, 2941  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.80 (1H, d,  $J = 14.8$  Hz), 7.38–7.20 (7H, m), 7.02 (1H, dd,  $J = 5.2, 3.6$  Hz), 6.67 (1H, d,  $J = 14.8$  Hz), 6.53 (1H, d,  $J = 16.4$  Hz), 6.25 (1H, dt,  $J = 16.4, 7.2$  Hz), 3.70 (2H, s), 3.60 (2H, s), 3.18 (2H, d,  $J = 7.2$  Hz), 2.53 (4H, t,  $J = 4.8$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.01, 140.47, 136.70, 135.60, 133.52, 130.20, 128.60, 127.98, 127.64, 127.14, 126.33, 125.89, 115.76, 60.88, 53.44, 52.86, 44.1. HRMS (ESI): (m/z) calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{OS}$ , (M+Na) $^+$  361.13451, found: 361.13598.

**(E)-1-(4-Cinnamylpiperazine-1-yl)-3-phenylprop-2-en-1-one (5t):**

Yield: 3 g, 87%. Mp: 104–106 °C. IR (ATR): 978, 1226, 1428, 1648, 1738, 2358, 2949  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.67 (1H, d,  $J = 15.2$  Hz), 7.51 (2H, dd,  $J = 7.6, 2$  Hz), 7.39–7.22 (8H, m), 6.87 (1H, d,  $J = 15.2$  Hz), 6.54 (1H, d,  $J = 16$  Hz), 6.26 (1H, dt,  $J = 16, 6.8$  Hz), 3.73 (2H, s), 3.62 (2H, s), 3.19 (2H, d,  $J = 6.8$  Hz), 2.54 (4H, t,  $J = 4.8$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.40, 142.75, 136.70, 135.29, 133.50, 129.57, 128.77, 128.60, 127.73, 127.65, 126.33, 125.91, 117.11, 60.89, 53.40, 52.86, 45.85, 42.17. HRMS (ESI): (m/z) calcd. for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}$ , (M+Na) $^+$  355.17918, found: 355.17952.

**(E)-1-(4-Cinnamylpiperazine-1-yl)-2-methylprop-2-en-1-one (5u):**

Yield: 2.7 g, 94%. Mp: 100–102 °C. IR (ATR): 748, 996, 1133, 1209, 1367, 1436, 1618, 1739, 2362, 3003  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.36–7.35 (2H, m), 7.34–7.19 (3H, m), 6.5 (1H, d,  $J = 16$  Hz), 6.22 (1H, dt,  $J = 16, 6.8$  Hz), 5.15 (1H, t,  $J = 1.6$  Hz), 5.00 (1H, t,  $J = 1.2$  Hz), 3.60 (4H, s), 3.15 (2H, dd,  $J = 6.4, 1.2$  Hz), 2.46 (4H, s), 1.93 (3H, t,  $J = 1.6$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 171.09, 140.33, 136.64, 133.53, 128.57, 127.64, 126.32, 125.78, 115.40, 60.87, 53.45, 52.78, 46.85, 41.30, 20.5. HRMS (ESI): (m/z) calcd. for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$ , (M+Na) $^+$  293.16243, found: 293.16291.

**(2E,4E)-1-(4-Cinnamylpiperazine-1-yl)-5-phenylpenta-2,4-dien-1-one (5v):**

Yield: 2.8 g, 75%. Mp: 120–121 °C. IR (ATR): 787, 1000, 1241, 1437, 1596, 1640, 1738, 2359, 2803, 2945  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.49–7.22 (11H, m), 6.91 (1H, d,  $J = 14.8$  Hz), 6.87 (1H, d,  $J = 14.8$  Hz), 6.53 (1H, d,  $J = 15.6$  Hz), 6.44 (1H, d,  $J = 14.8$  Hz), 6.26 (1H, dt,  $J = 15.6, 7.2$  Hz), 3.68

(4H, s), 3.18 (2H, d,  $J = 7.2$  Hz), 2.52 (4H, t,  $J = 5.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.44, 142.94, 139.03, 136.68, 136.35, 133.57, 128.76, 128.68, 128.61, 127.68, 126.99, 126.81, 126.35, 125.82, 120.17, 60.88, 53.33, 52.85, 45.68, 42.03. HRMS (ESI): (m/z) calcd. for  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}$ , (M+Na) $^+$  381.19373, found: 381.19241.

**(2E,4E)-1-(4-Cinnamylpiperazine-1-yl)hexa-2,4-dien-1-one (5w):**

Yield: 2.5 g, 81%. Mp: 85–87 °C. IR (ATR): 787, 1048, 1242, 1433, 1617, 1734, 2359, 2764, 2907  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 7.36–7.18 (6H, m), 6.49 (1H, d,  $J = 15.6$  Hz), 6.22 (1H, dt,  $J = 15.6, 7.2$  Hz), 6.18–6.00 (3H, m), 3.61 (4H, s), 3.13 (2H, d,  $J = 7.2$  Hz), 2.46 (4H, t,  $J = 5.2$  Hz), 1.80 (3H, d,  $J = 6.8$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 165.70, 143.15, 137.50, 136.69, 133.40, 130.16, 128.57, 127.61, 126.31, 125.96, 117.75, 60.85, 53.31, 52.85, 45.61, 41.97, 18.55. HRMS (ESI): (m/z) calcd. for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}$ , (M+Na) $^+$  319.17808, found: 319.17952.

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## SUPPLEMENTARY INFORMATION

### Synthesis and characterization of unsaturated diacyl and alkyl-acyl piperazine derivatives

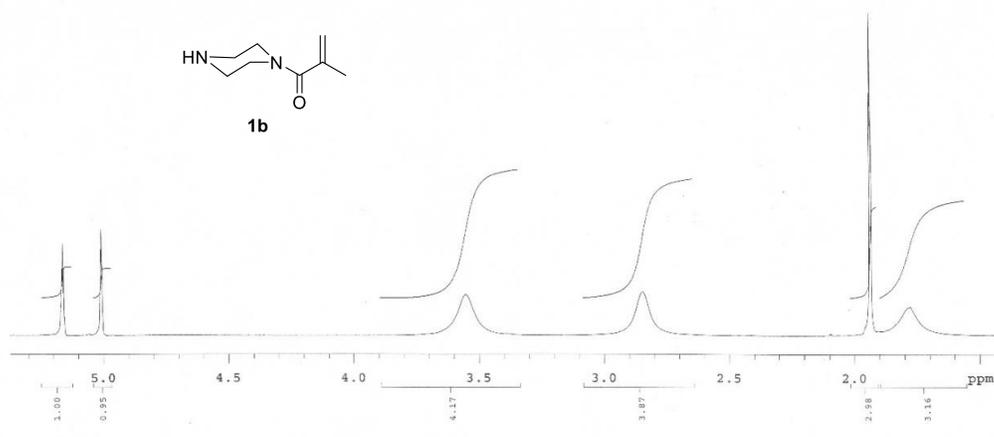
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Umuttepe, Kocaeli, Turkey*

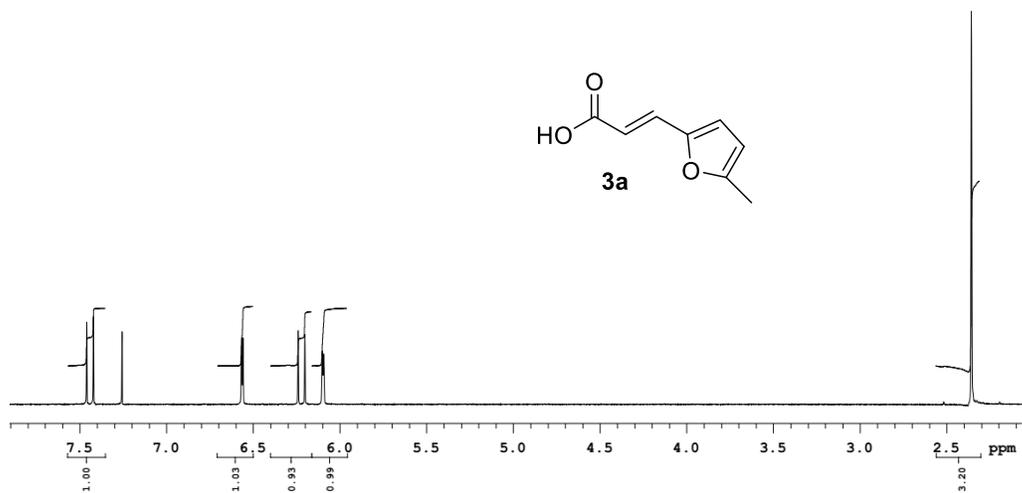
\*Correspondence: [mehmet.yilmaz@kocaeli.edu.tr](mailto:mehmet.yilmaz@kocaeli.edu.tr)

#### <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra

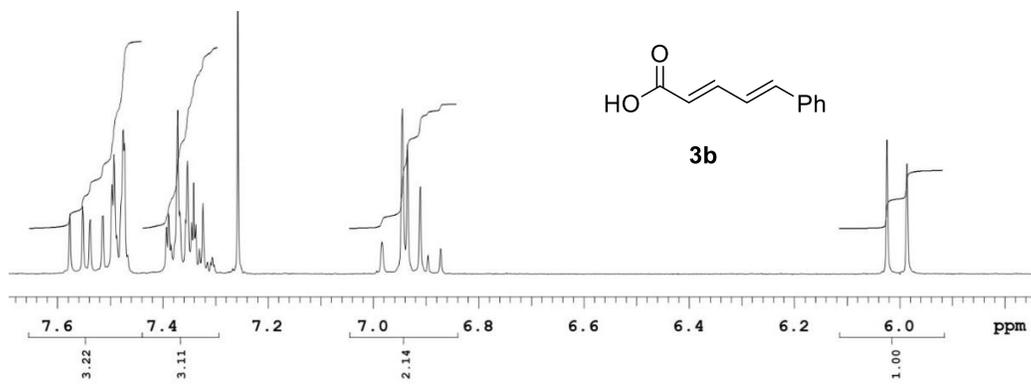
##### 1b. <sup>1</sup>H-NMR



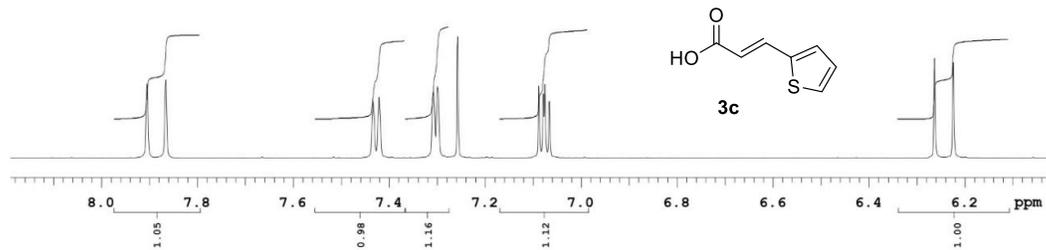
18 **3a.**  $^1\text{H-NMR}$



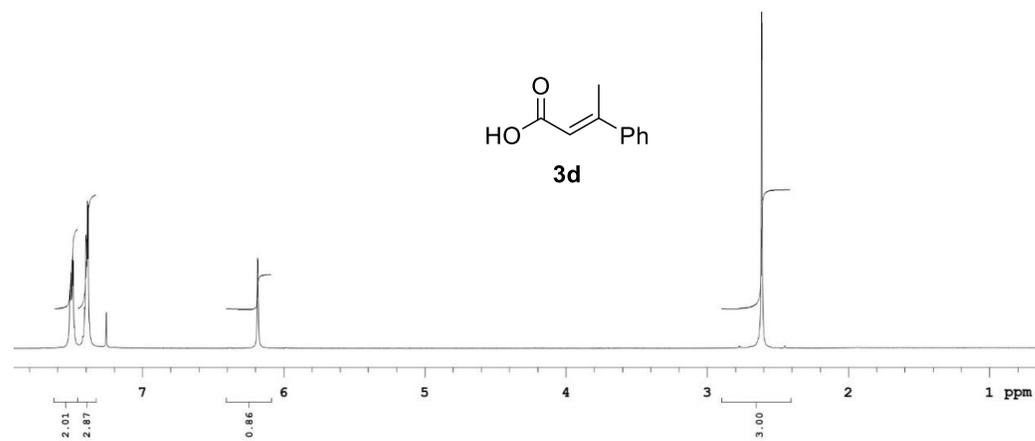
**3b.**  $^1\text{H-NMR}$



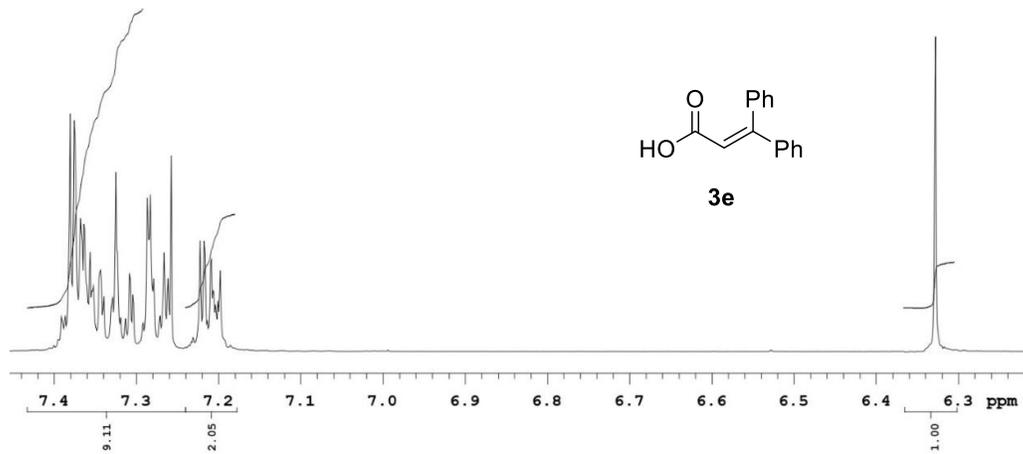
**3c.**  $^1\text{H-NMR}$



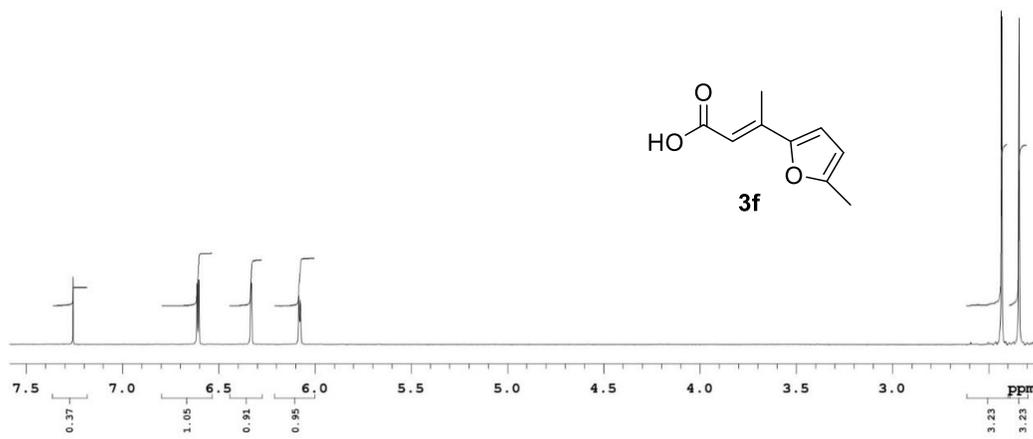
**3d.**  $^1\text{H-NMR}$



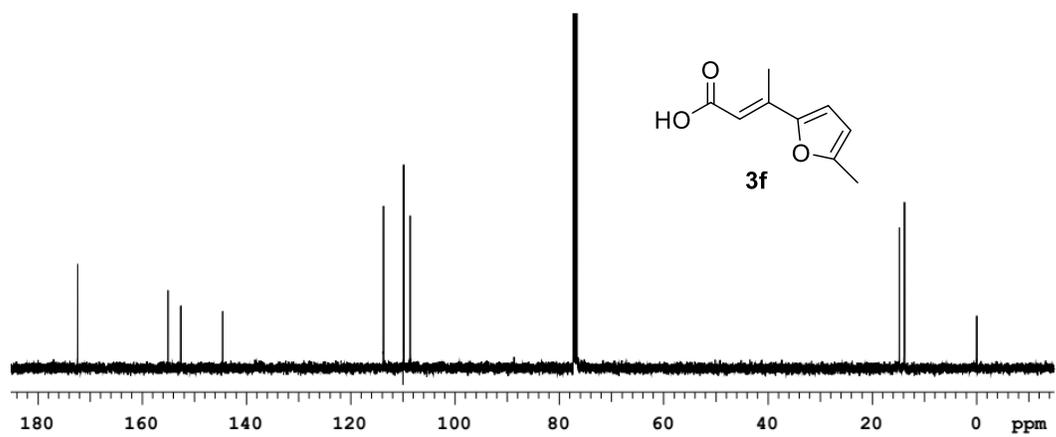
3e. <sup>1</sup>H-NMR



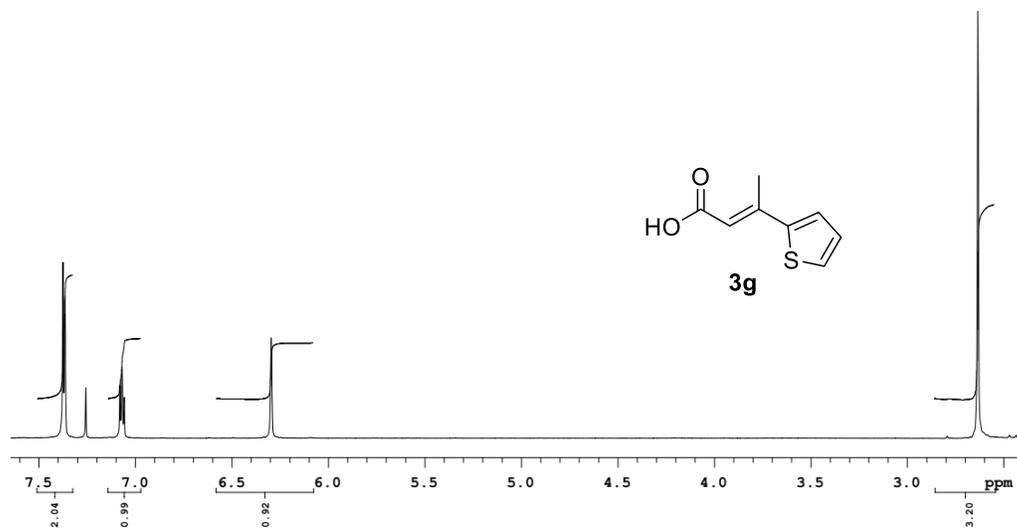
3f. <sup>1</sup>H-NMR



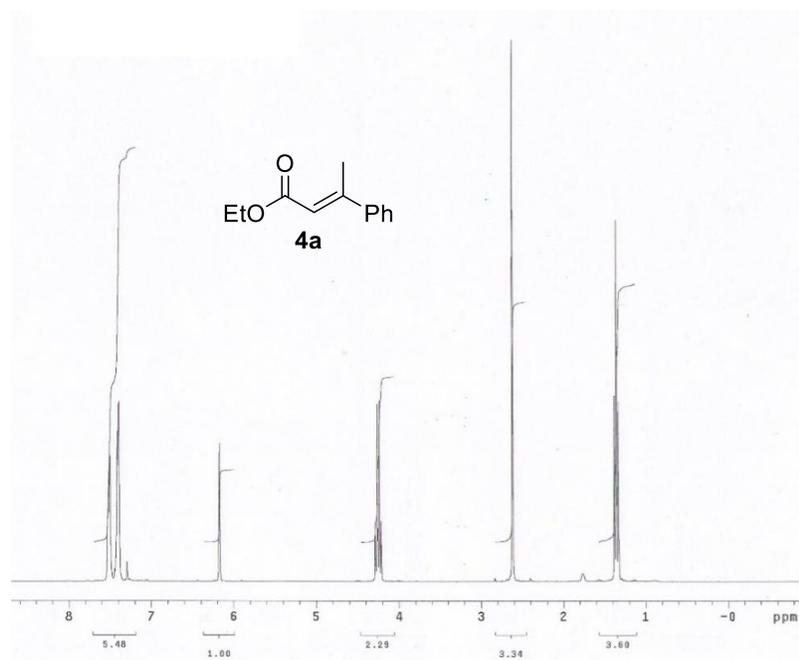
3f.  $^{13}\text{C}$ -NMR



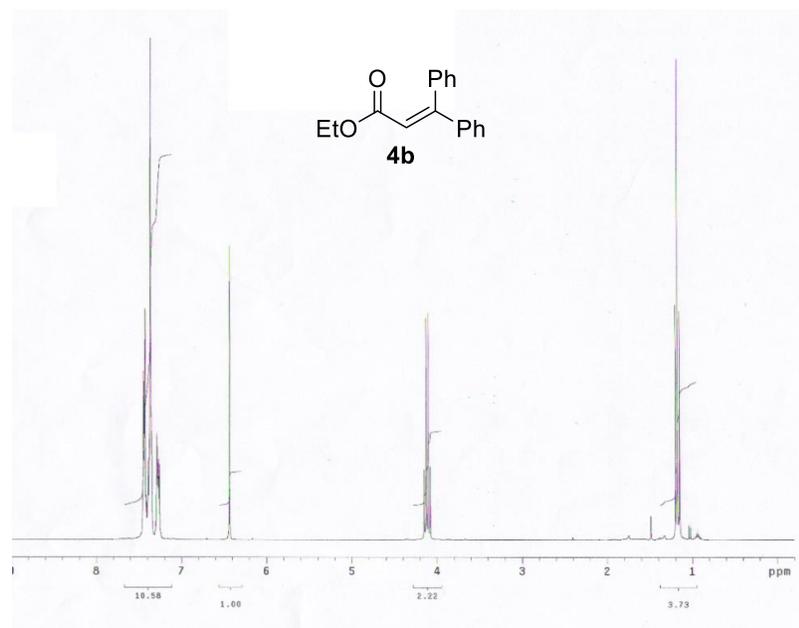
3g.  $^1\text{H}$ -NMR



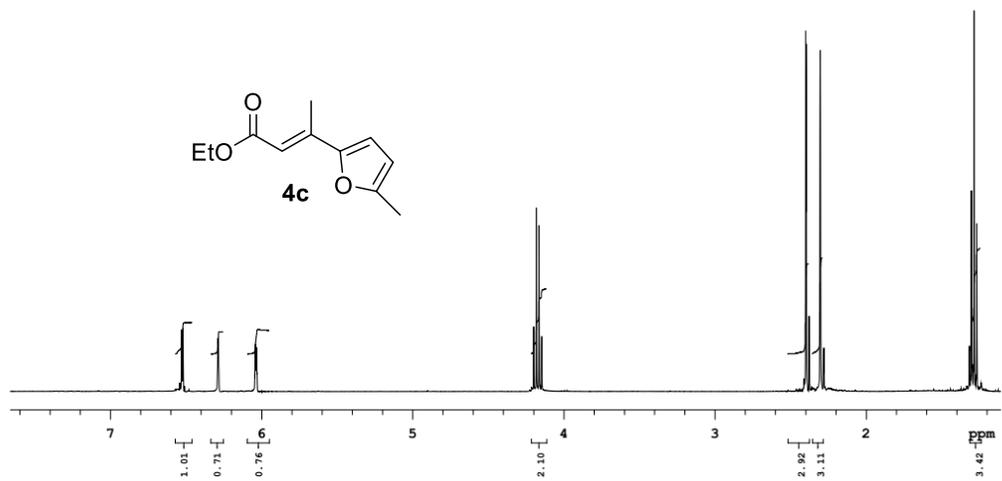
4a. <sup>1</sup>H-NMR



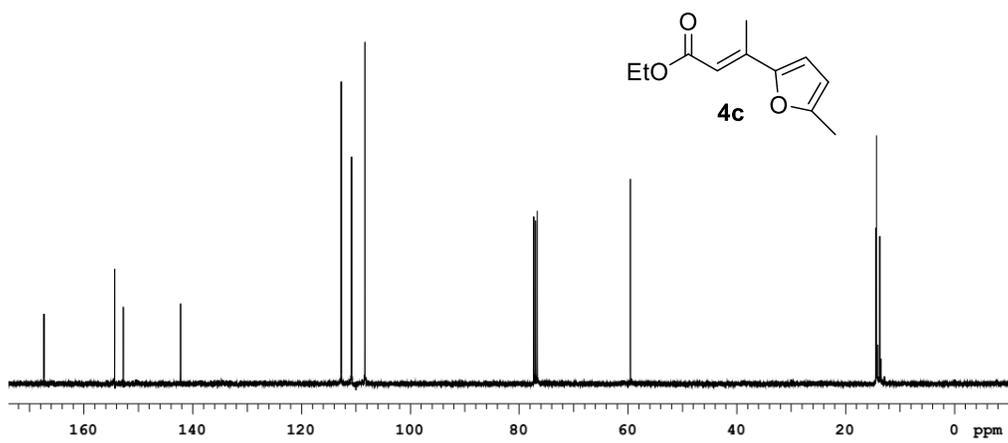
4b. <sup>1</sup>H-NMR



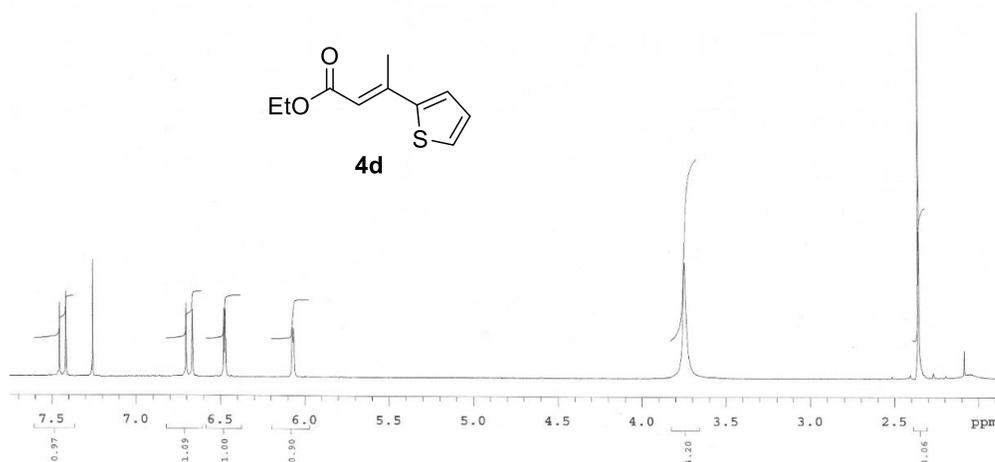
4c.  $^1\text{H-NMR}$



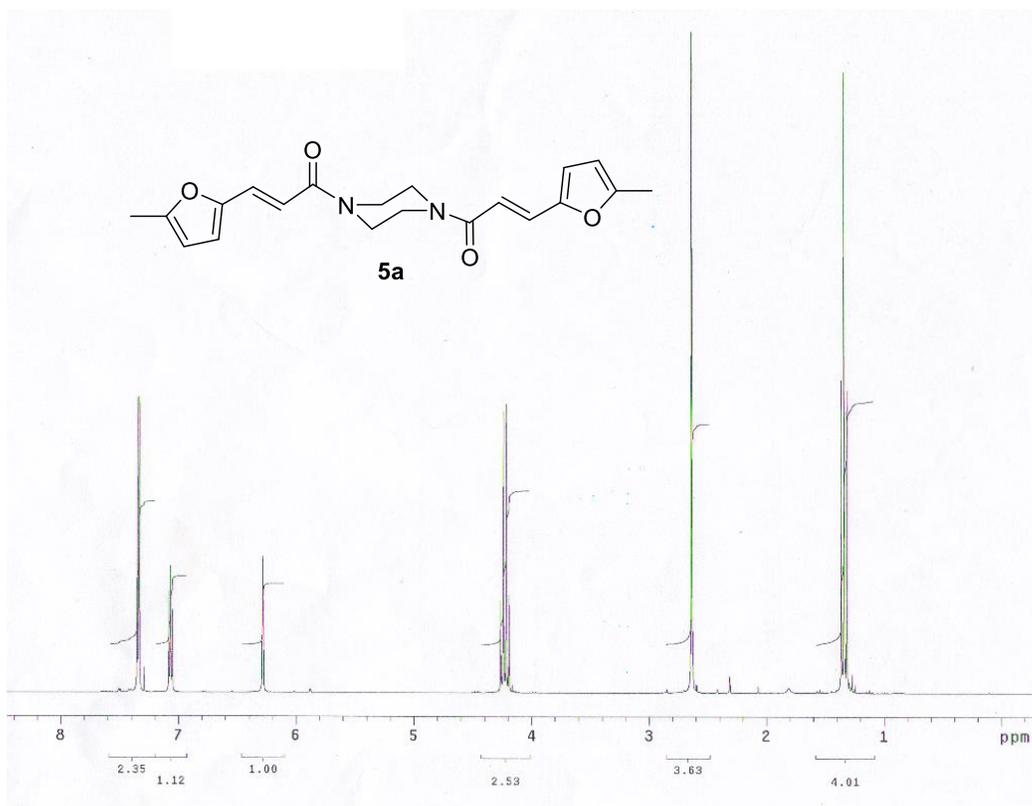
4c.  $^{13}\text{C-NMR}$



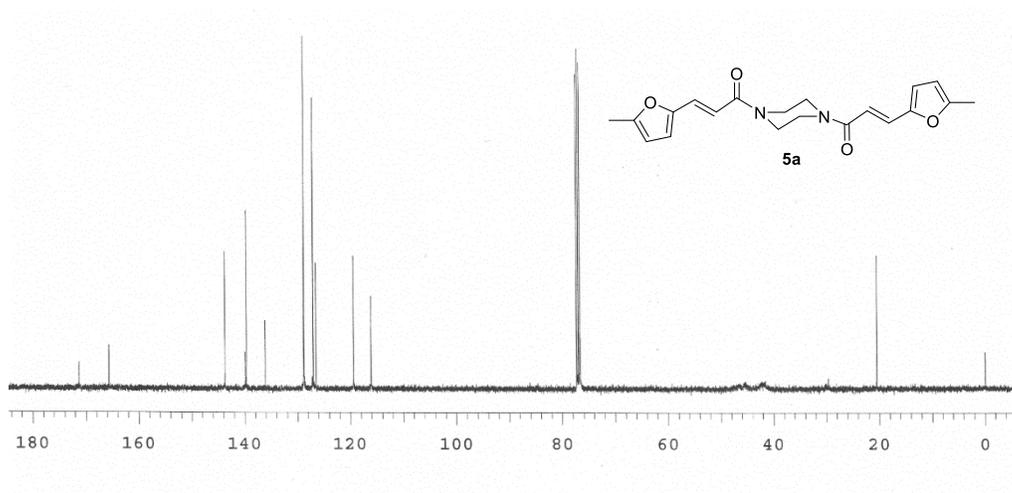
4d. <sup>1</sup>H-NMR



5a. <sup>1</sup>H-NMR

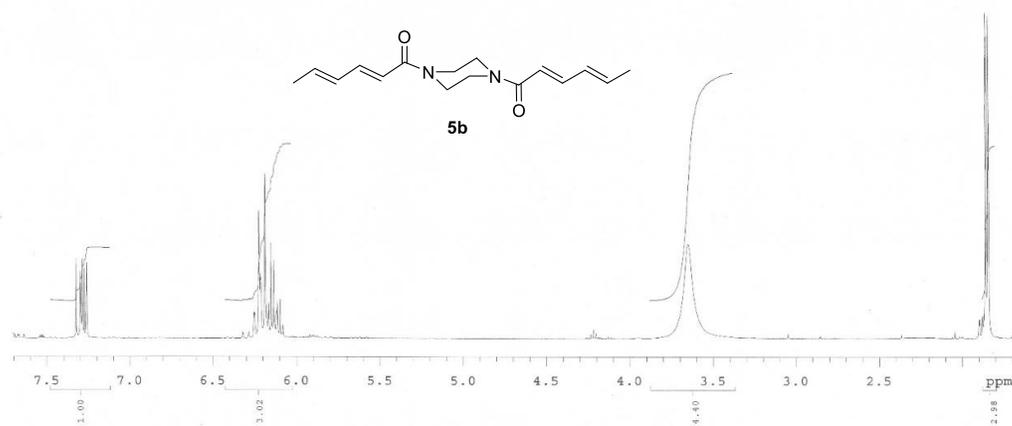


5a.  $^{13}\text{C}$ -NMR

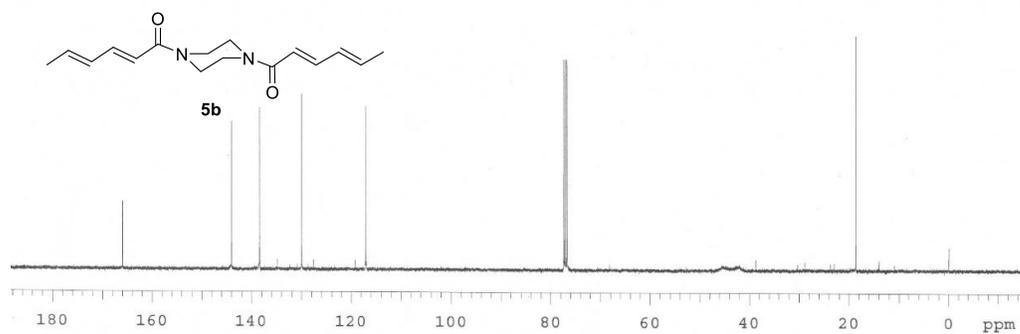


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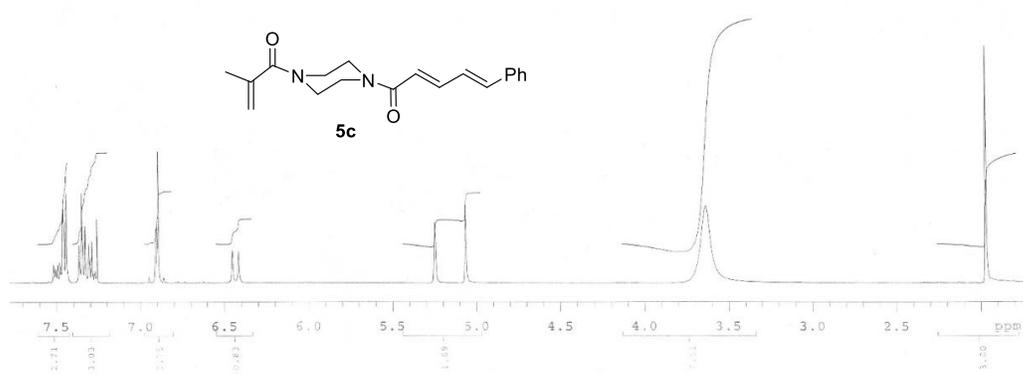
5b.  $^1\text{H}$ -NMR



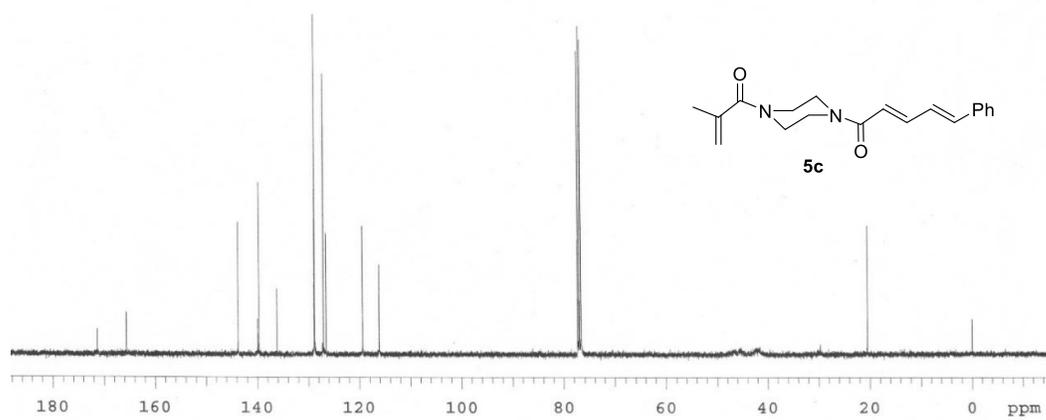
**5b.**  $^{13}\text{C}$ -NMR



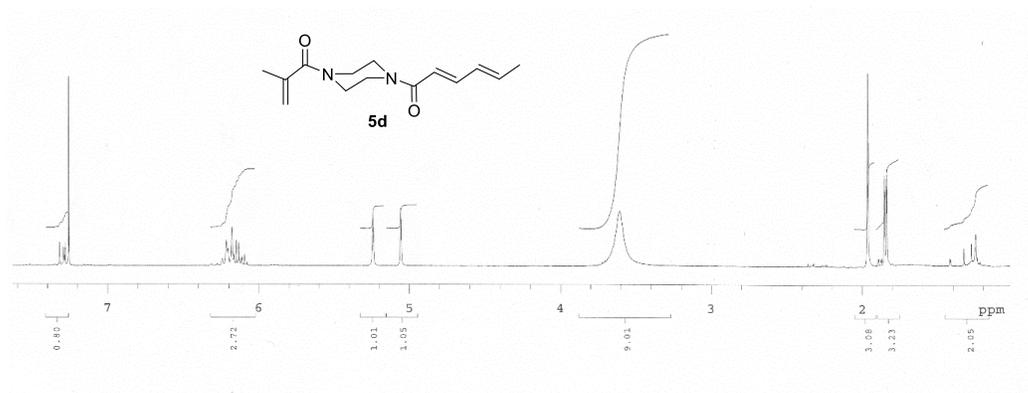
**5c.**  $^1\text{H}$ -NMR



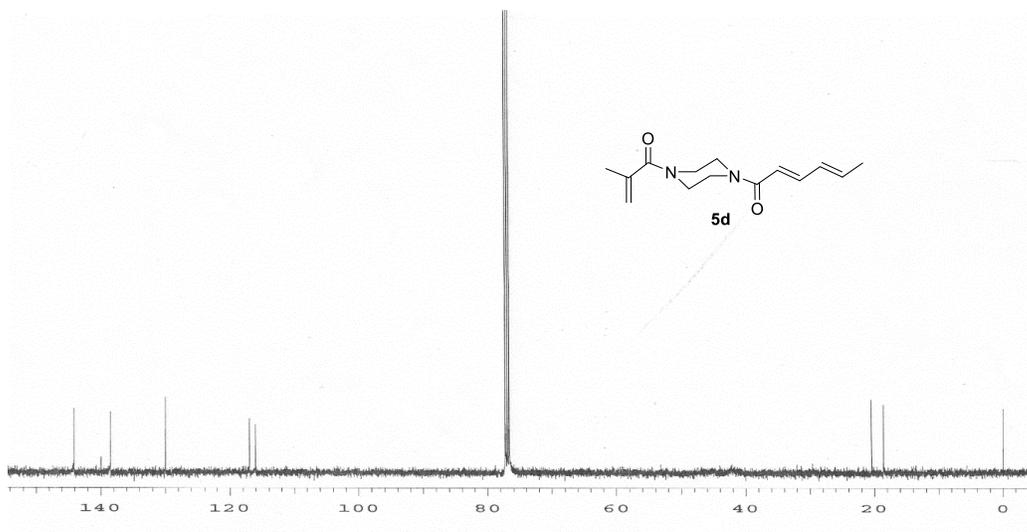
**5c**  $^{13}\text{C}$ -NMR



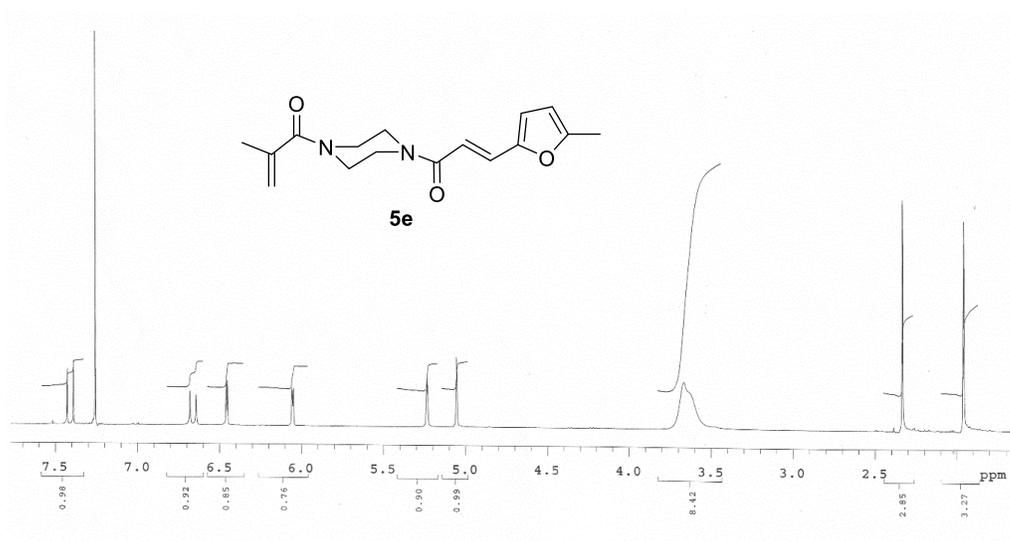
**5d**.  $^1\text{H}$ -NMR



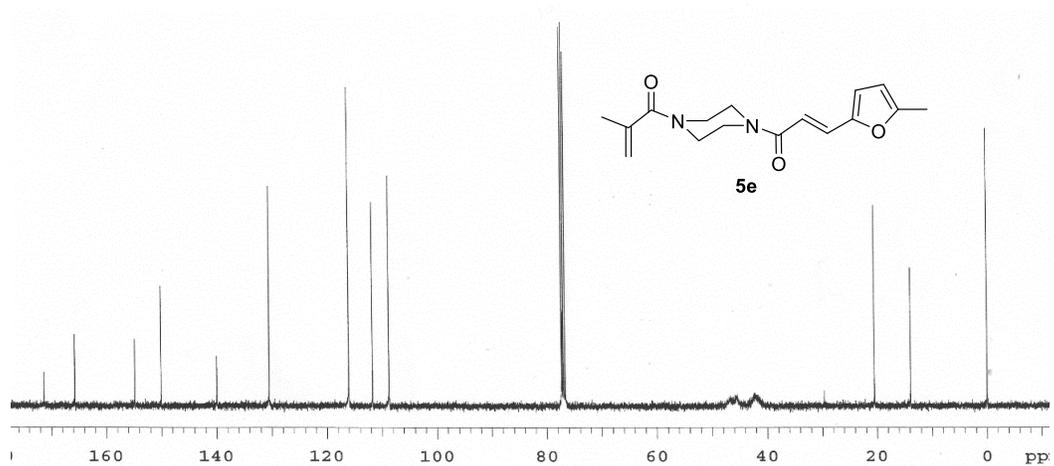
5d.  $^{13}\text{C}$ -NMR



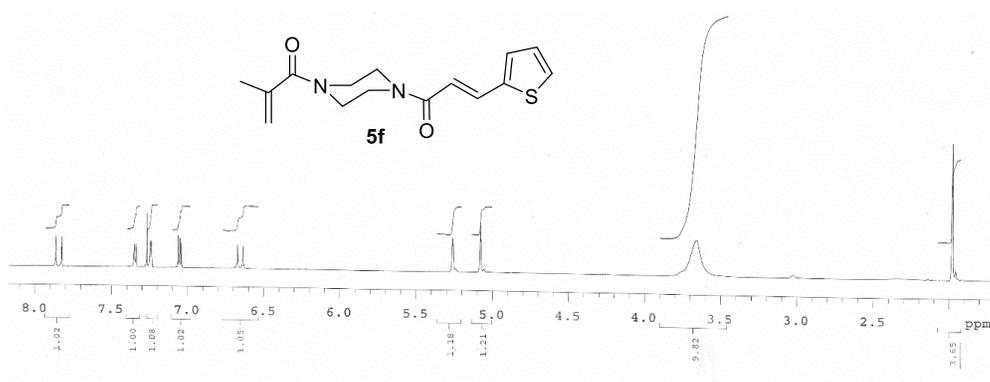
5e.  $^1\text{H}$ -NMR



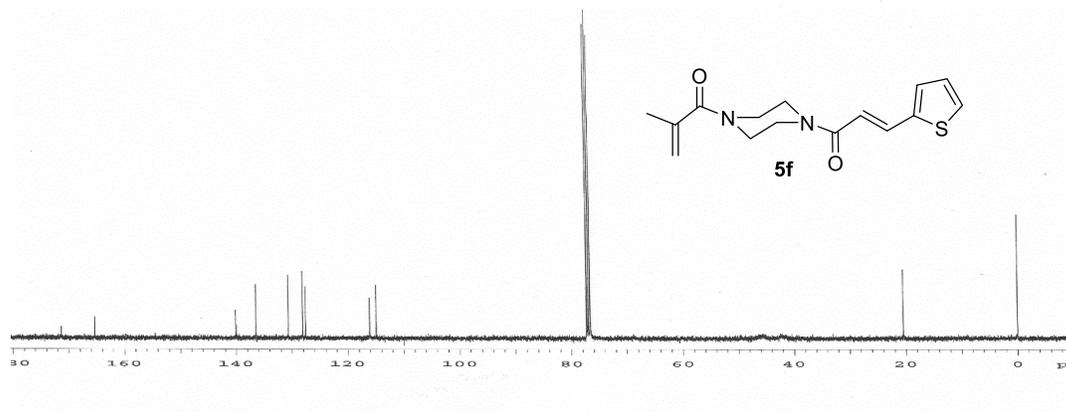
5e.  $^{13}\text{C}$ -NMR



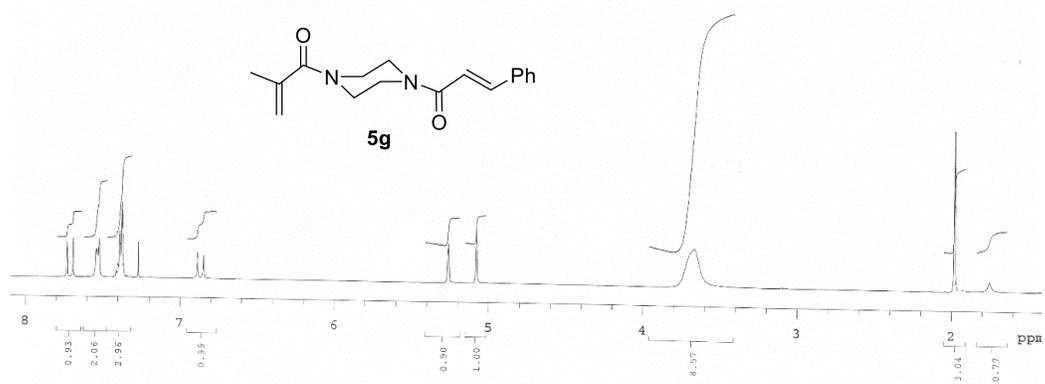
5f.  $^1\text{H}$ -NMR



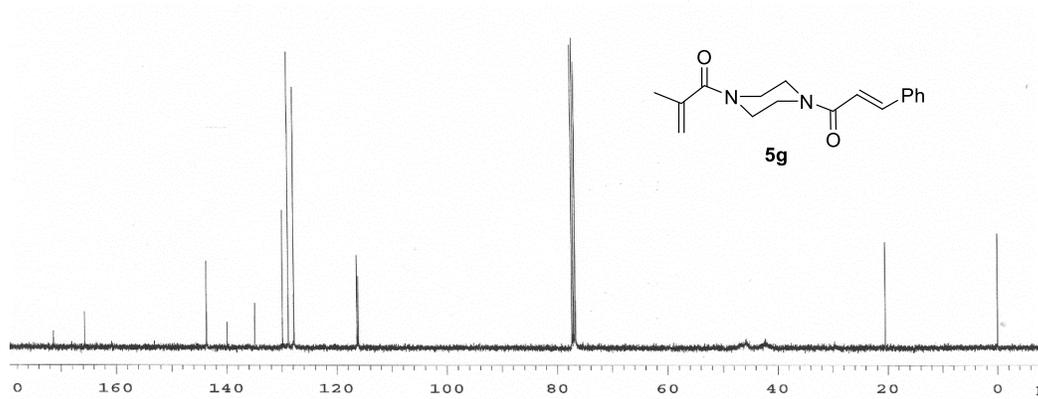
5f.  $^{13}\text{C}$ -NMR



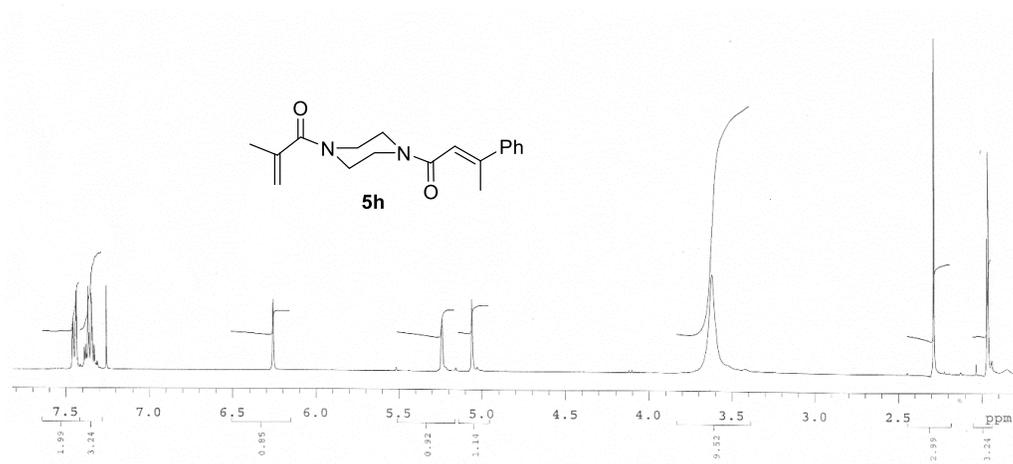
5g.  $^1\text{H}$ -NMR



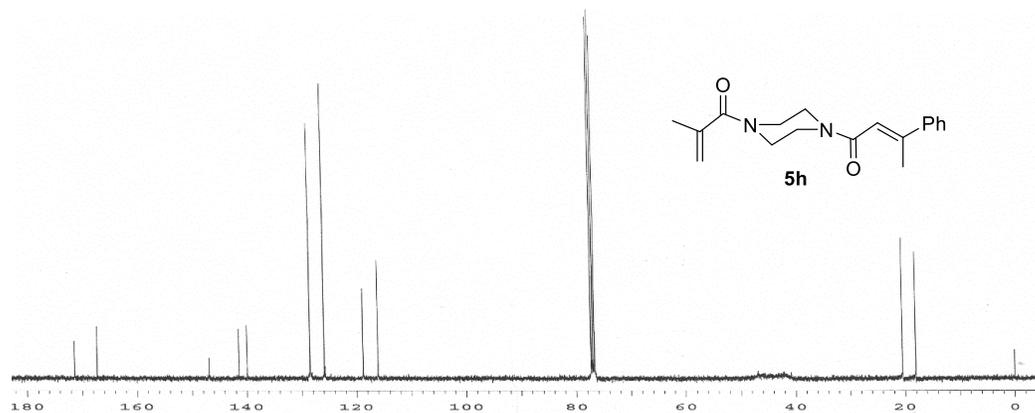
5g.  $^{13}\text{C}$ -NMR



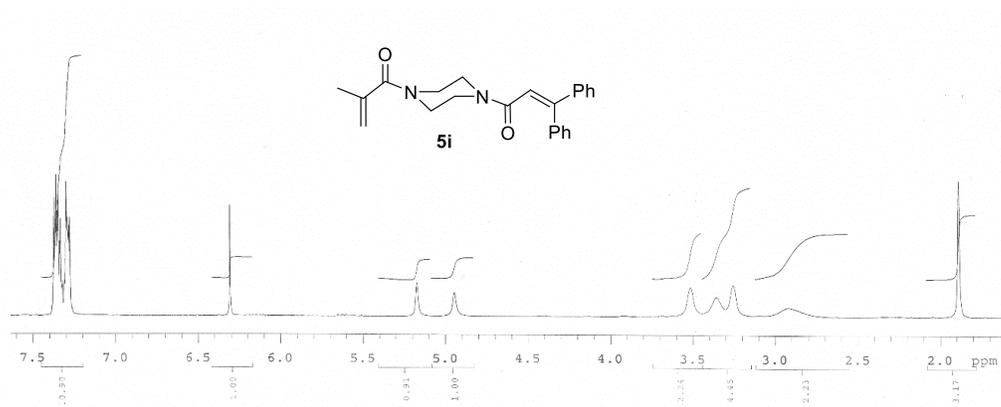
5h.  $^1\text{H}$ -NMR



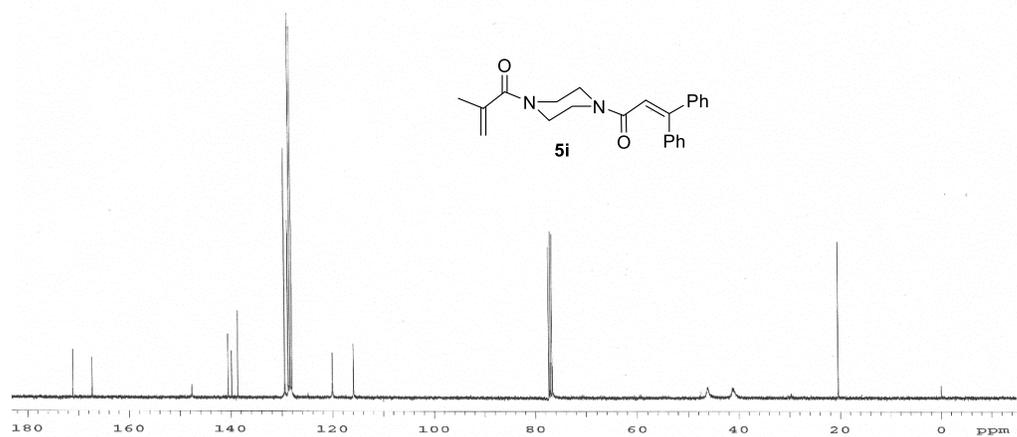
5h.  $^{13}\text{C}$ -NMR



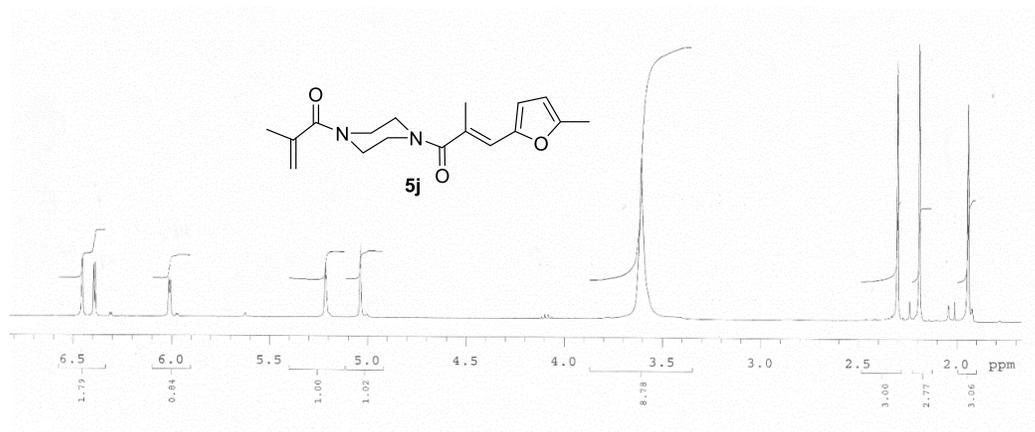
5i.  $^1\text{H}$ -NMR



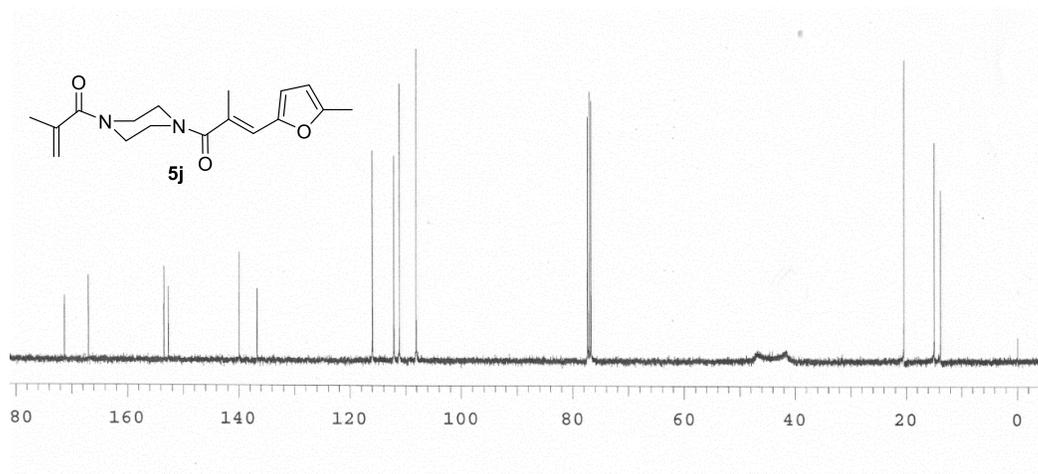
5i.  $^{13}\text{C}$ -NMR



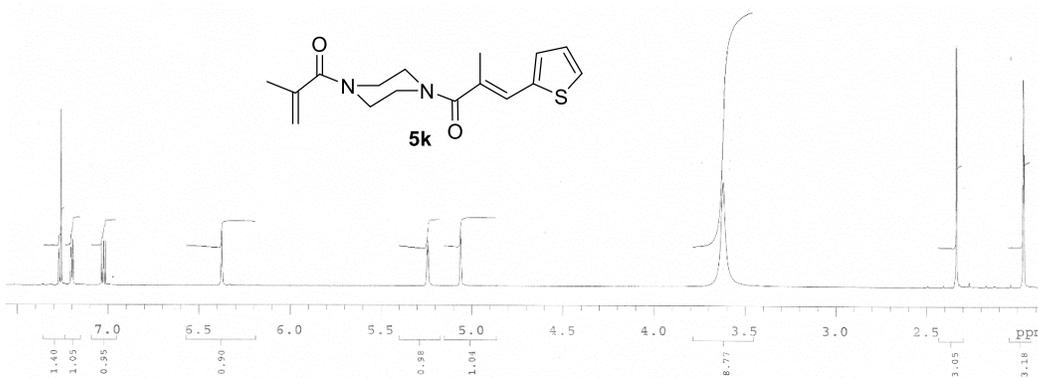
5j.  $^1\text{H}$ -NMR



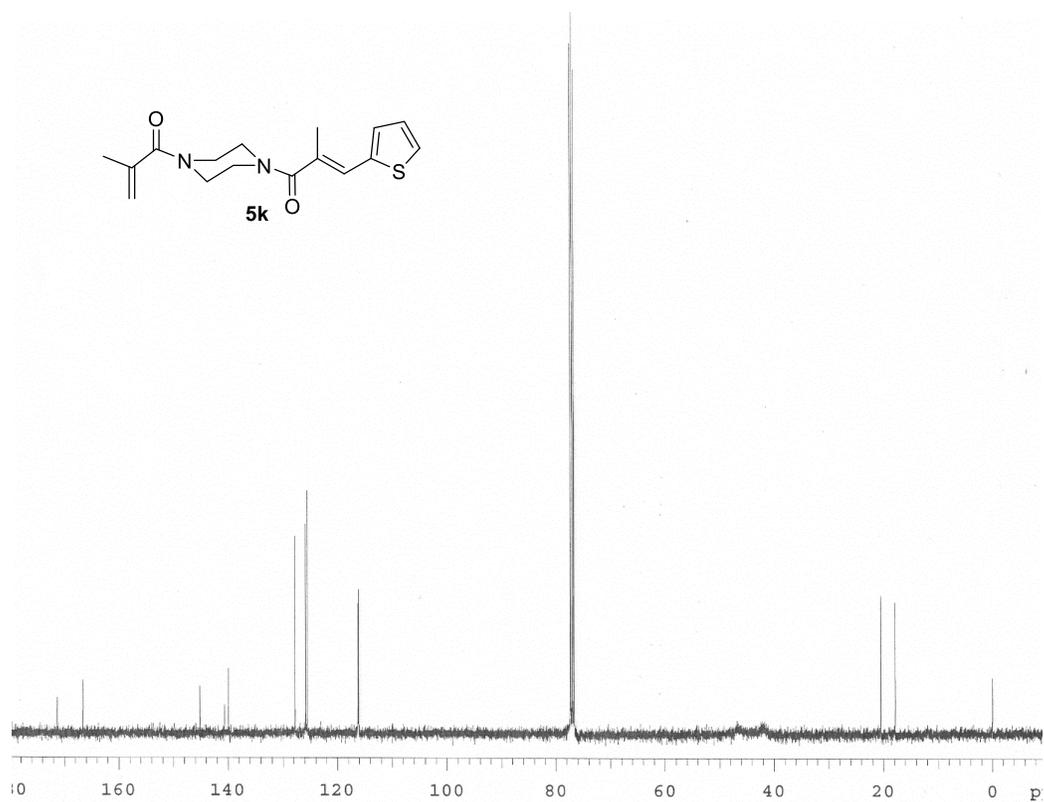
5j.  $^{13}\text{C}$ -NMR



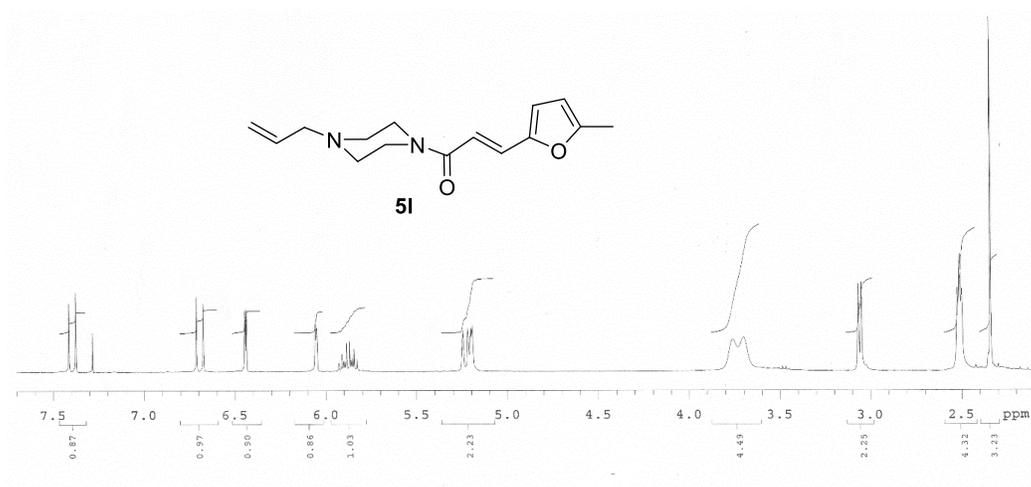
5k.  $^1\text{H}$ -NMR



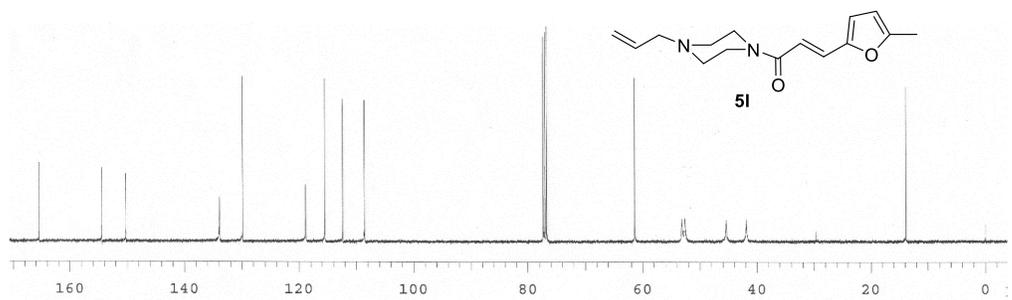
5k.  $^{13}\text{C}$ -NMR



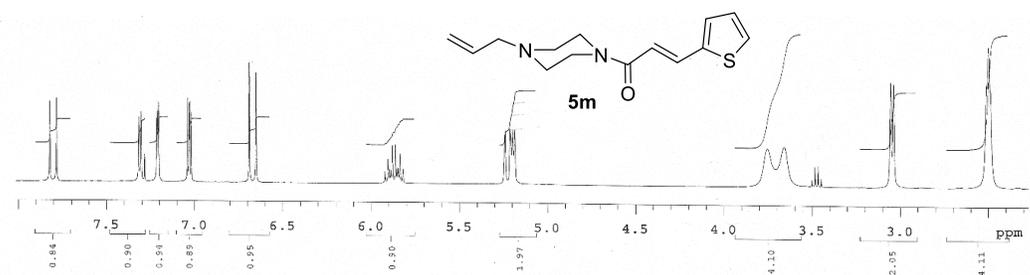
5l.  $^1\text{H}$ -NMR



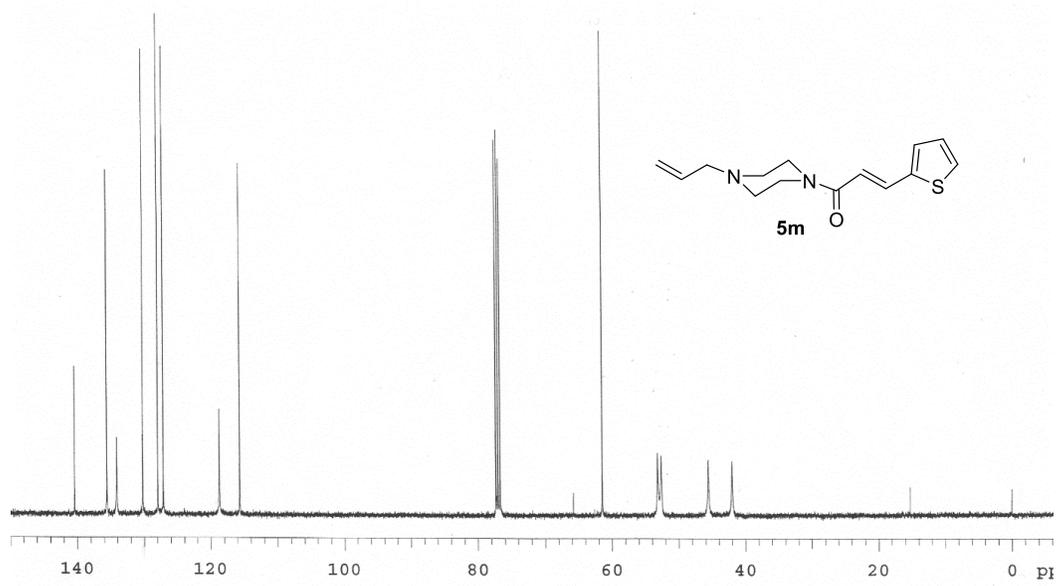
5l.  $^{13}\text{C}$ -NMR



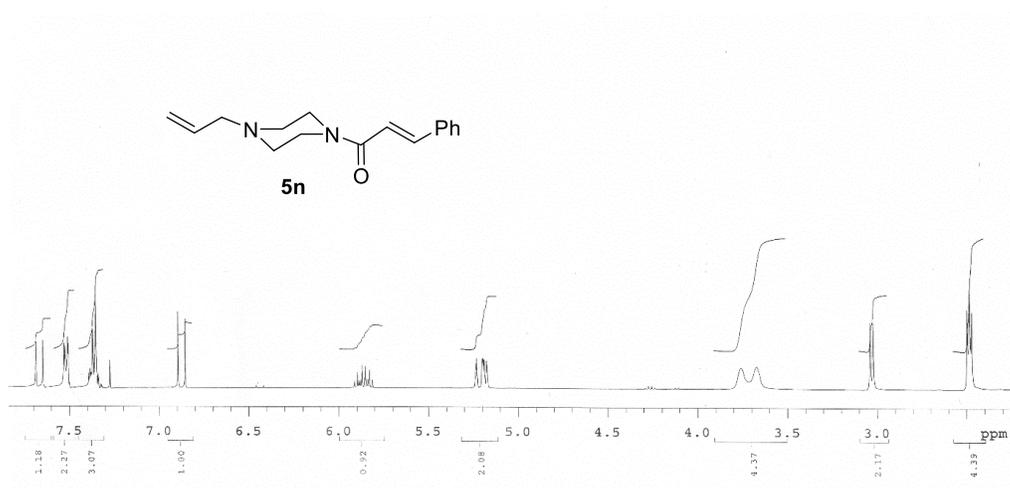
5m.  $^1\text{H}$ -NMR



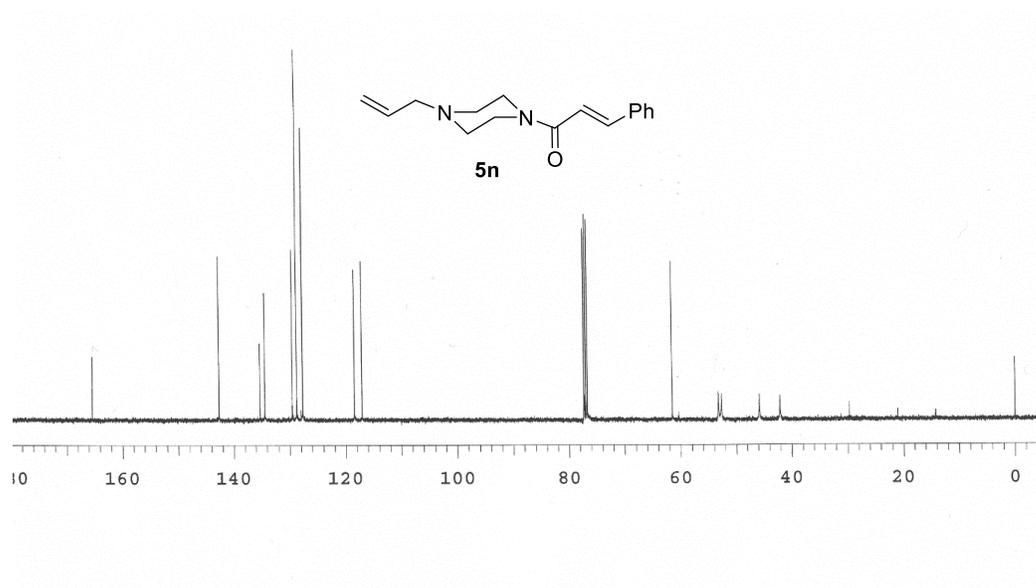
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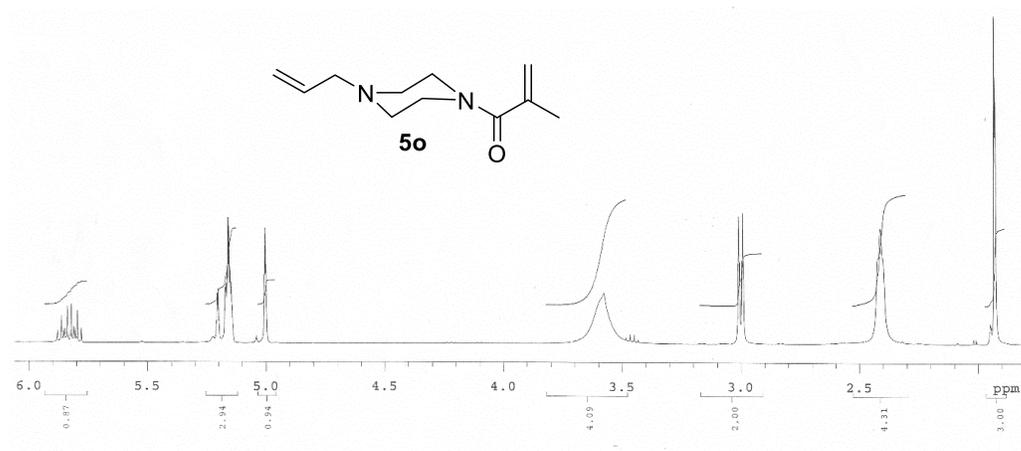
223 5n.  $^1\text{H}$ -NMR



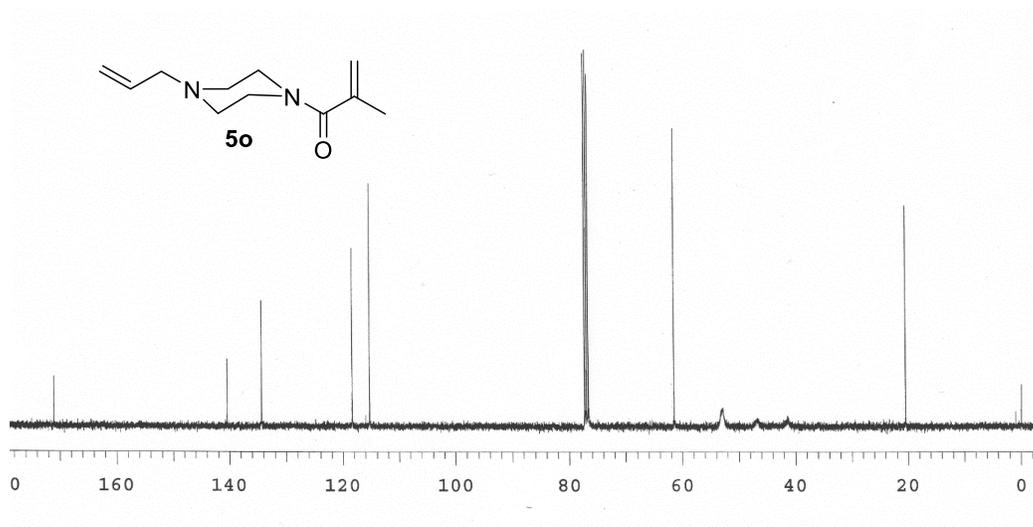
5n.  $^{13}\text{C}$ -NMR



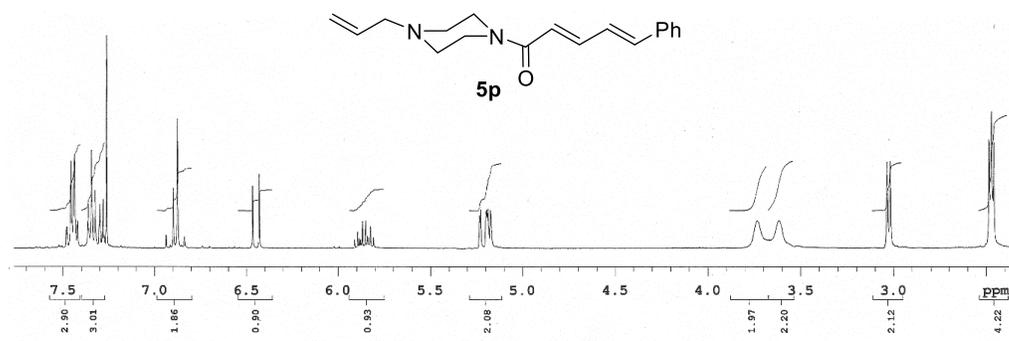
5o.  $^1\text{H}$ -NMR



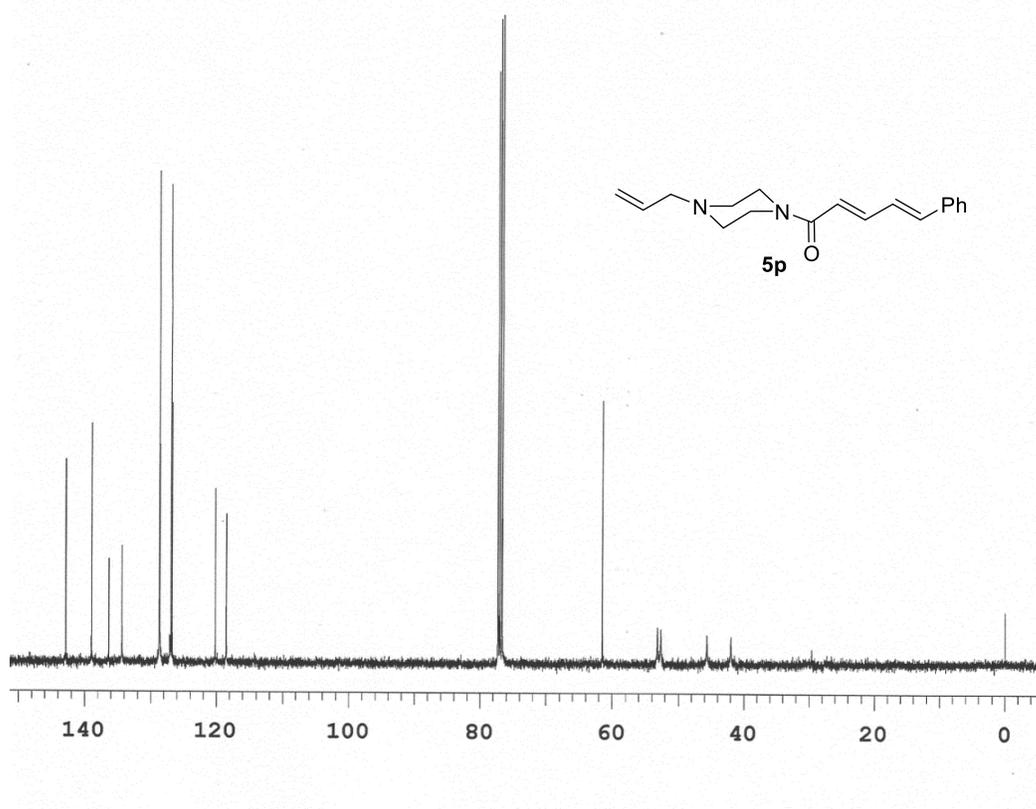
5o.  $^{13}\text{C}$ -NMR



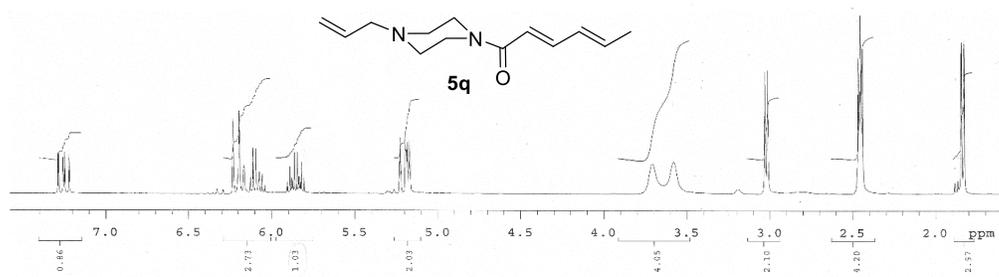
5p  $^1\text{H}$ -NMR



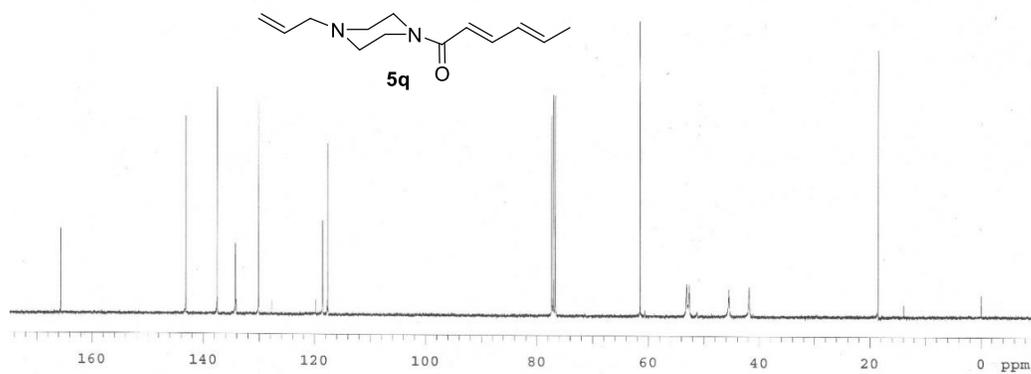
5p.  $^{13}\text{C}$ -NMR



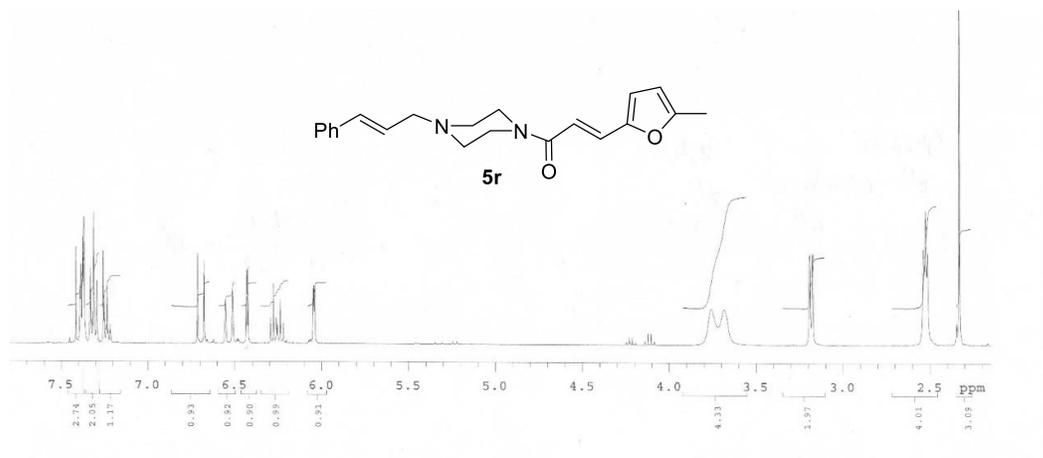
5q.  $^1\text{H}$ -NMR



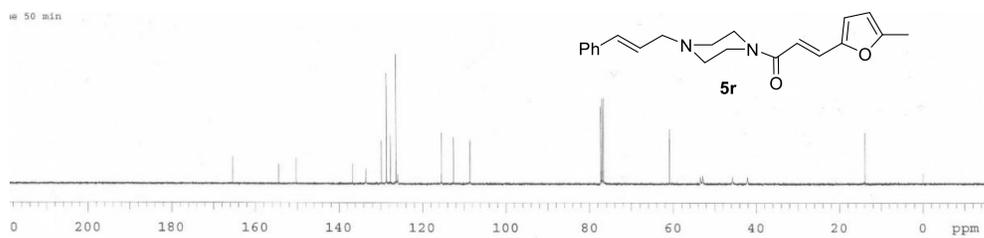
5q.  $^{13}\text{C}$ -NMR



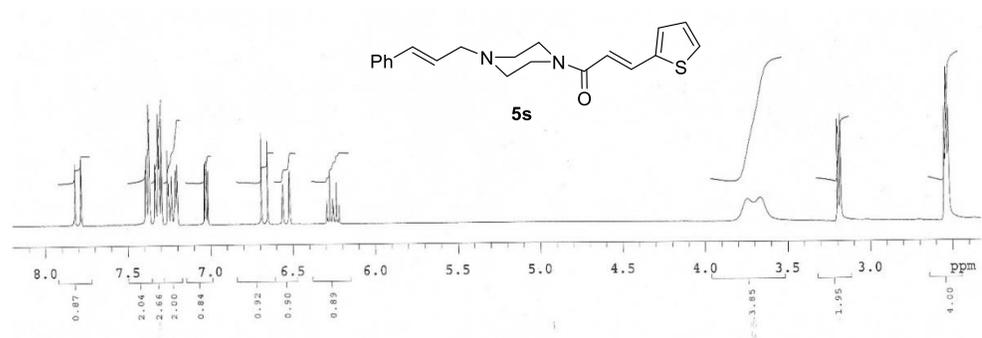
5r.  $^1\text{H}$ -NMR



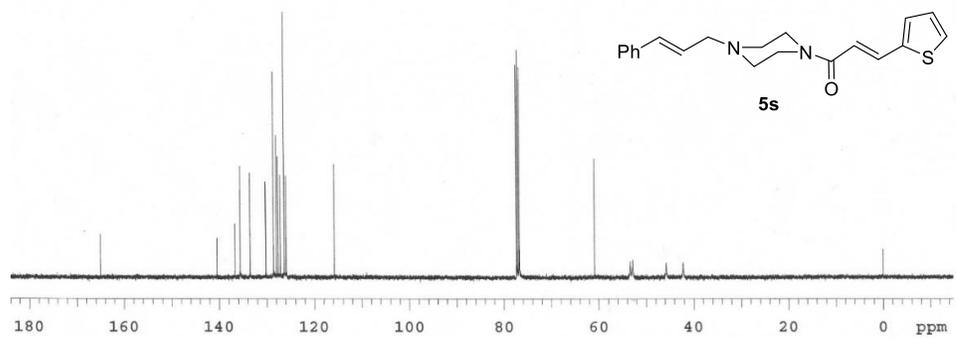
**5r.**  $^{13}\text{C}$ -NMR



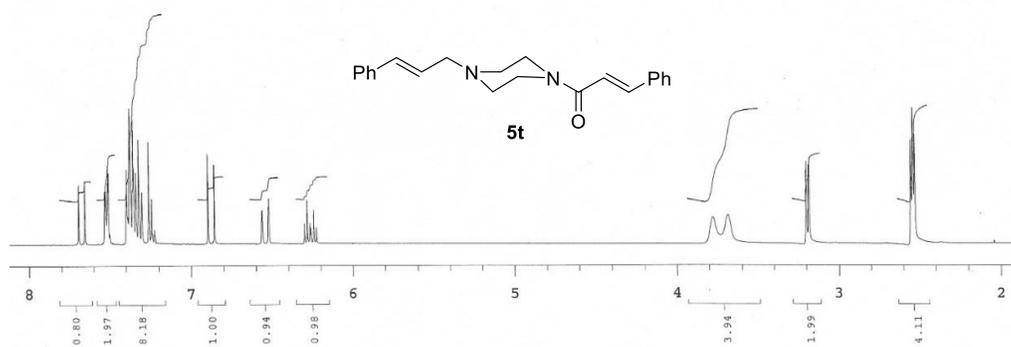
**5s.**  $^1\text{H}$ -NMR



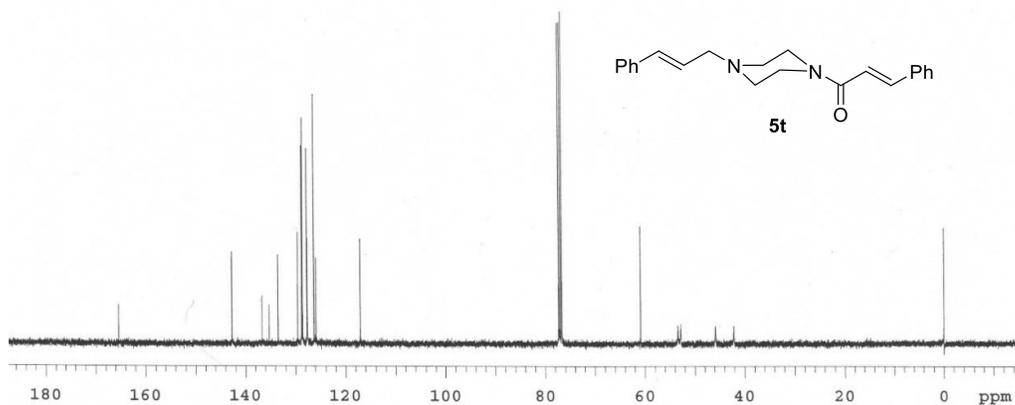
**5s.**  $^{13}\text{C}$ -NMR



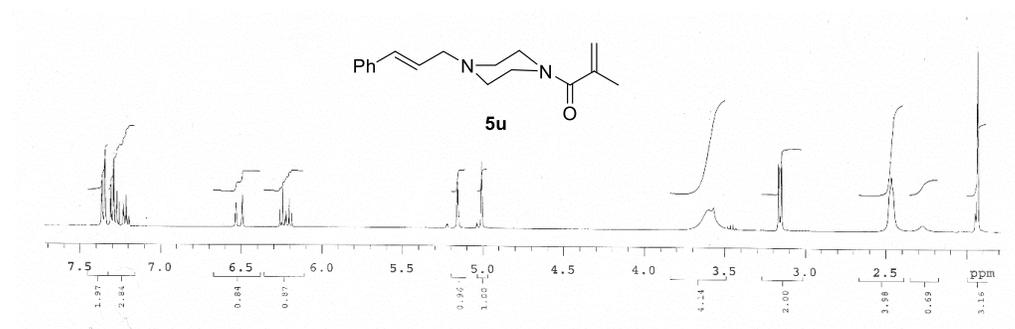
**5t.**  $^1\text{H}$ -NMR



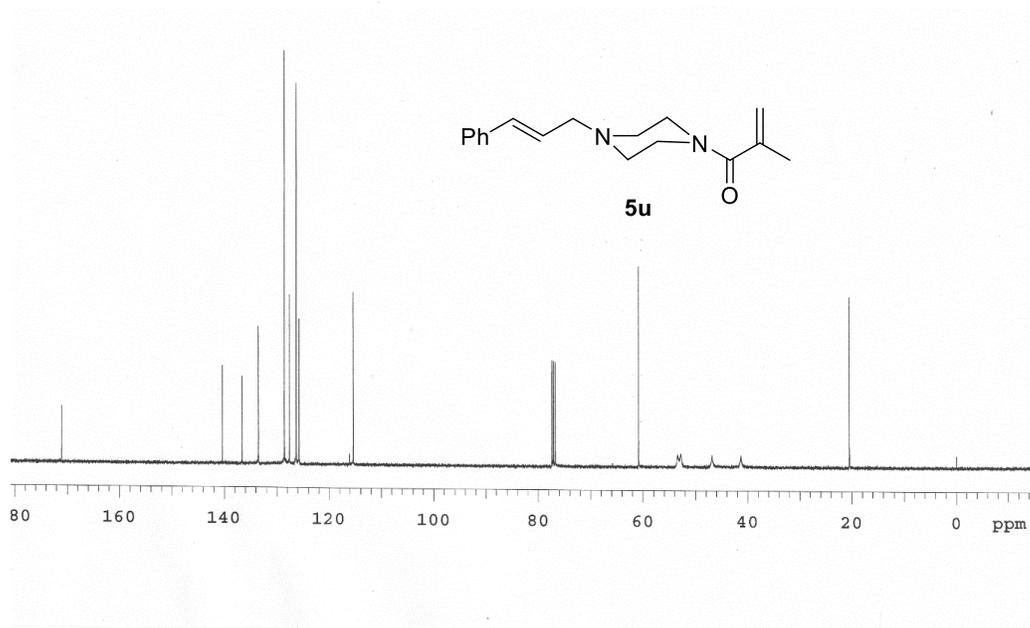
5t.  $^{13}\text{C}$ -NMR



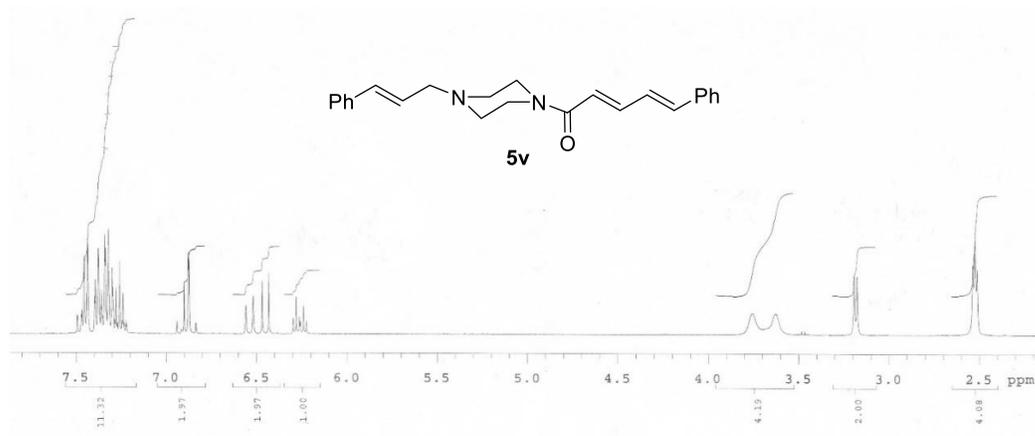
5u.  $^1\text{H}$ -NMR



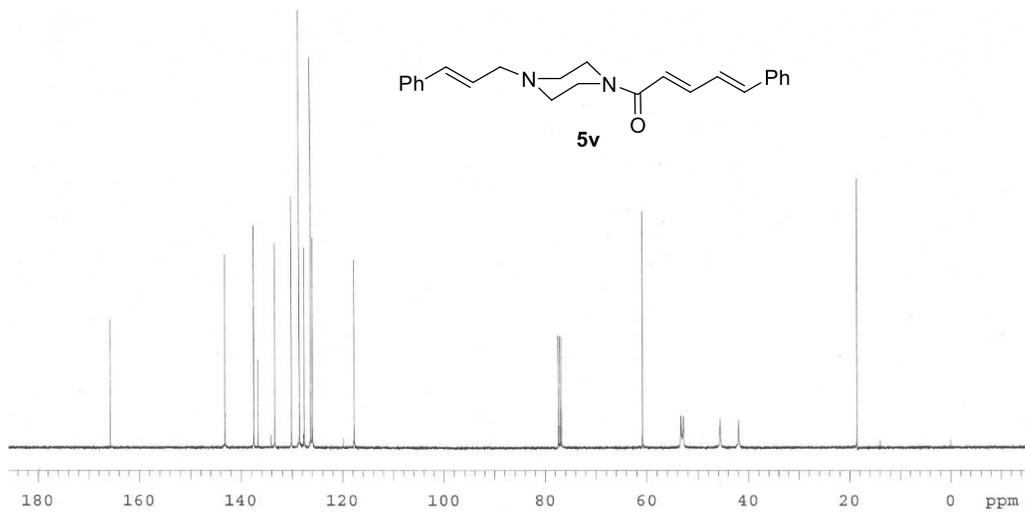
5u.  $^{13}\text{C}$ -NMR



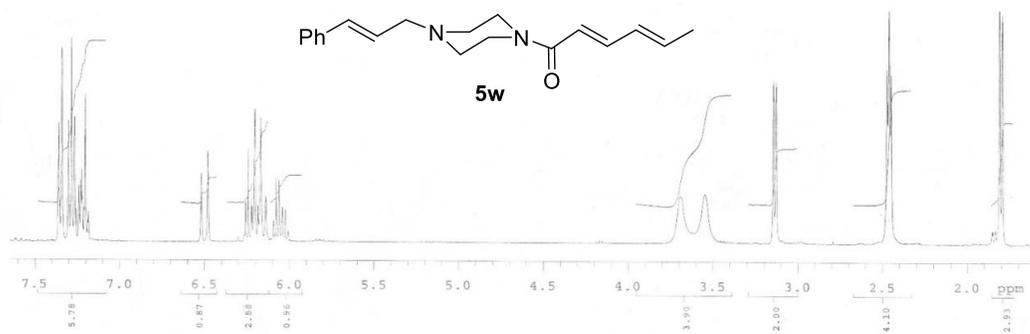
5v.  $^1\text{H}$ -NMR



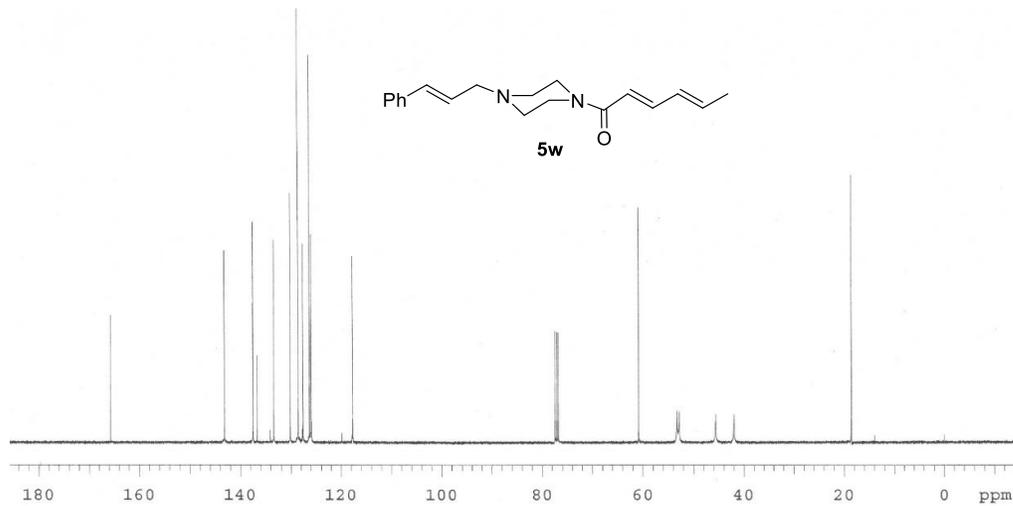
**5v.**  $^{13}\text{C}$ -NMR



**5w.**  $^1\text{H}$ -NMR

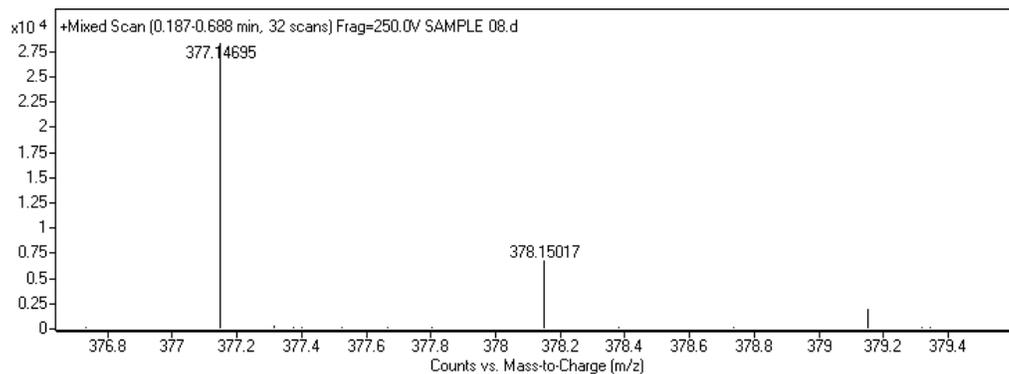


5w.  $^{13}\text{C}$ -NMR

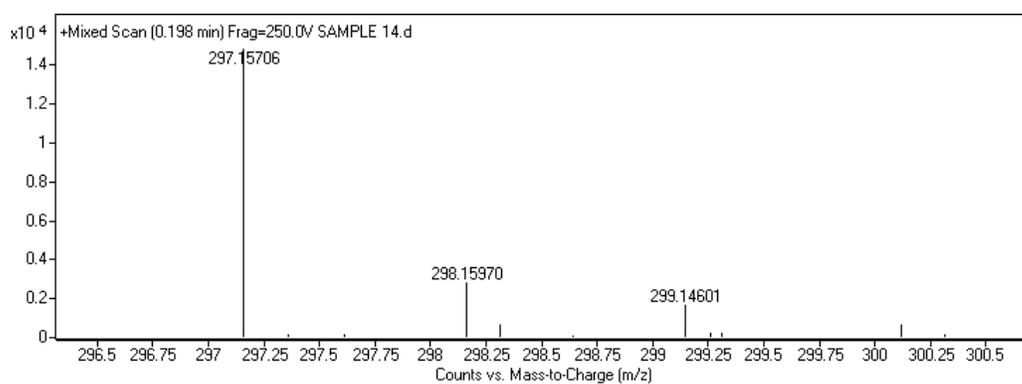


## HRMS spectra

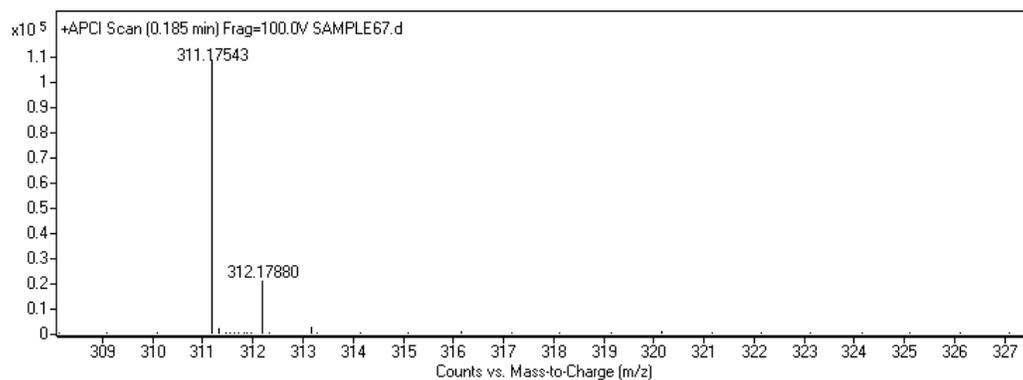
5a



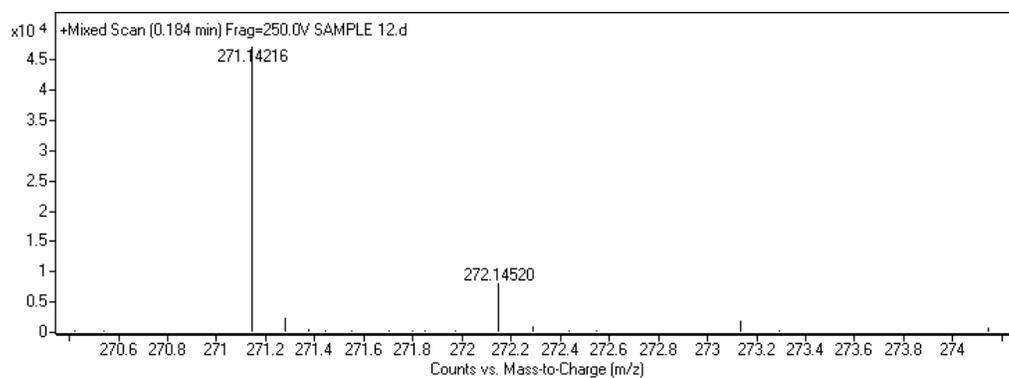
5b



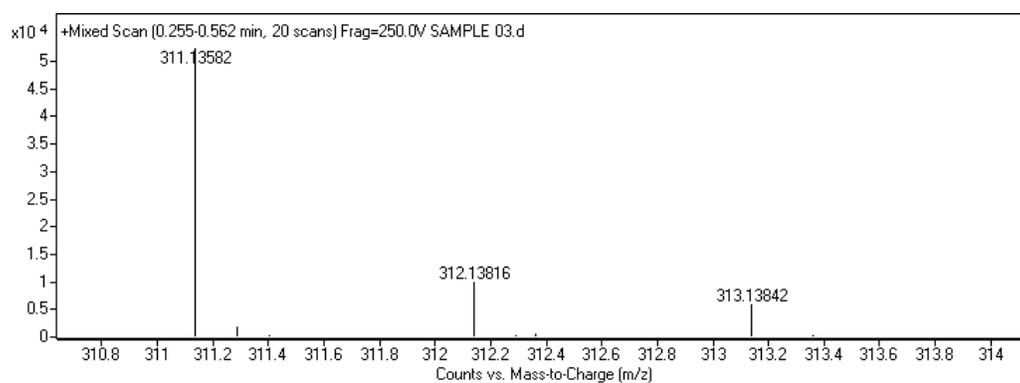
5c



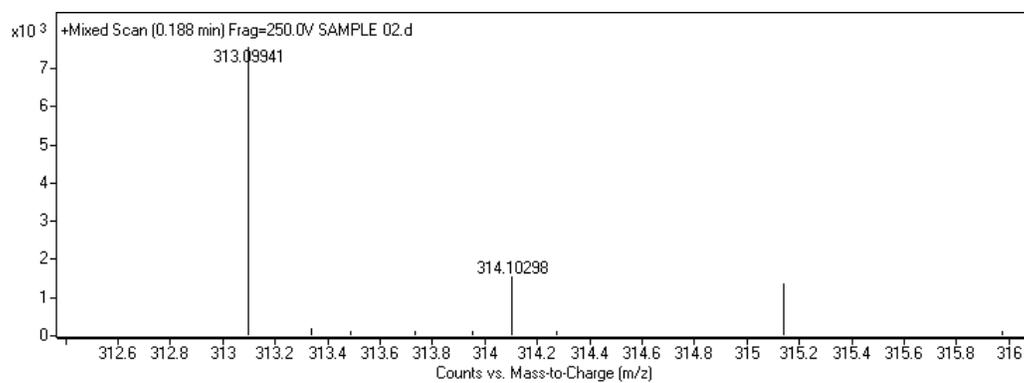
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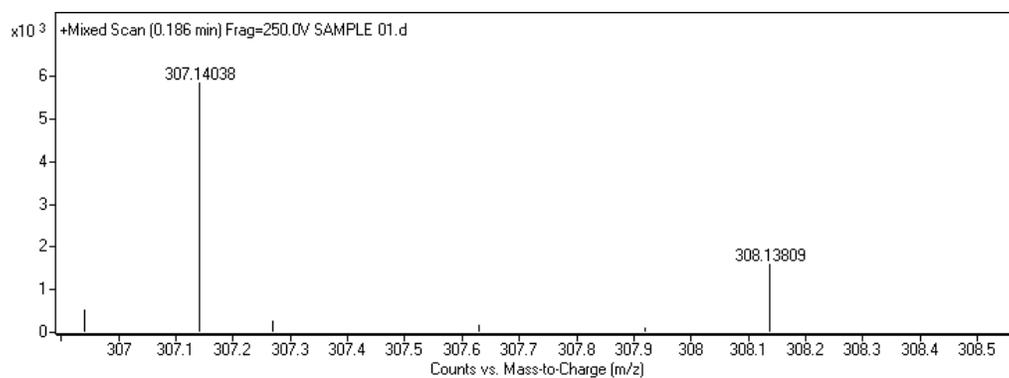
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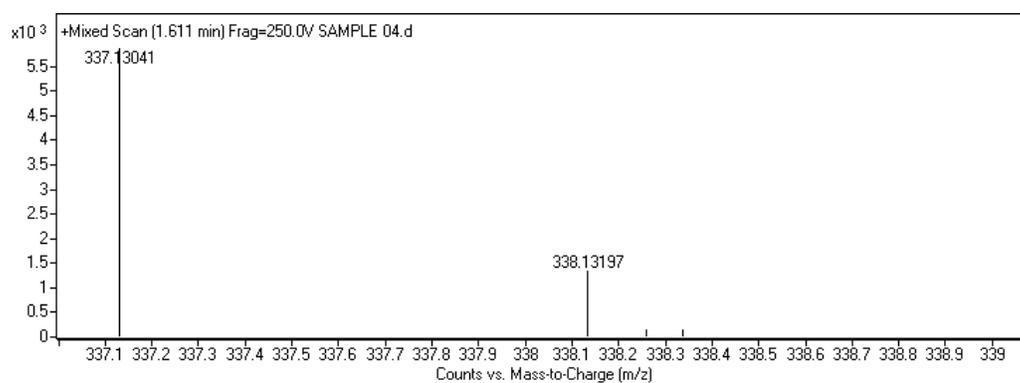
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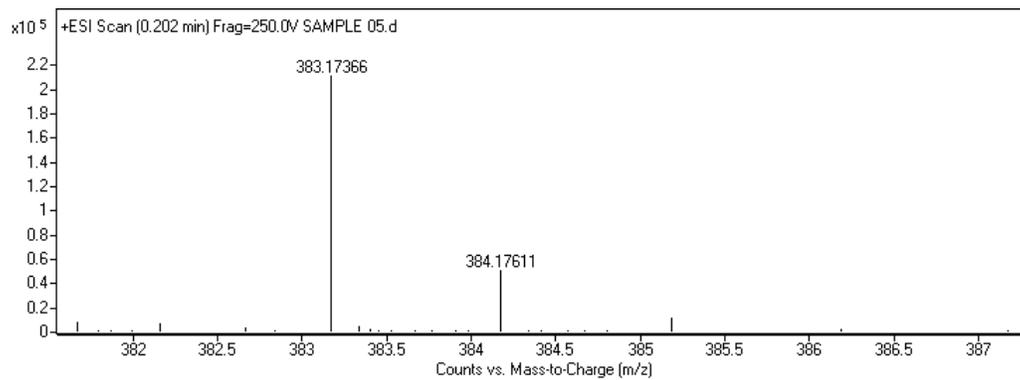
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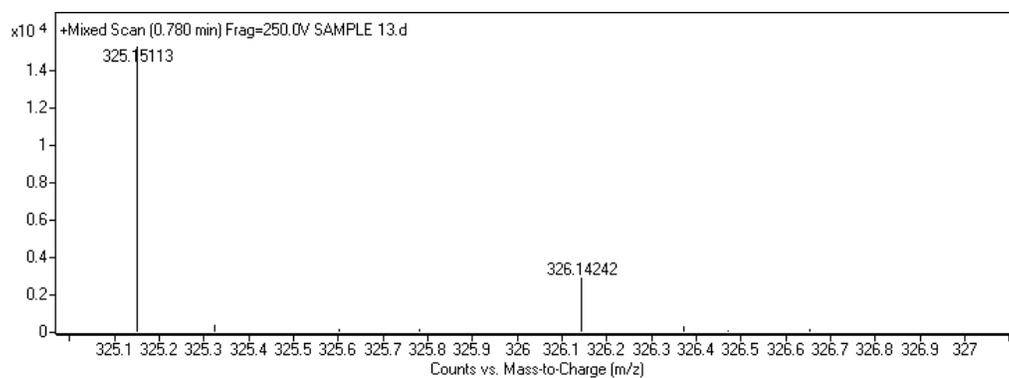
5h



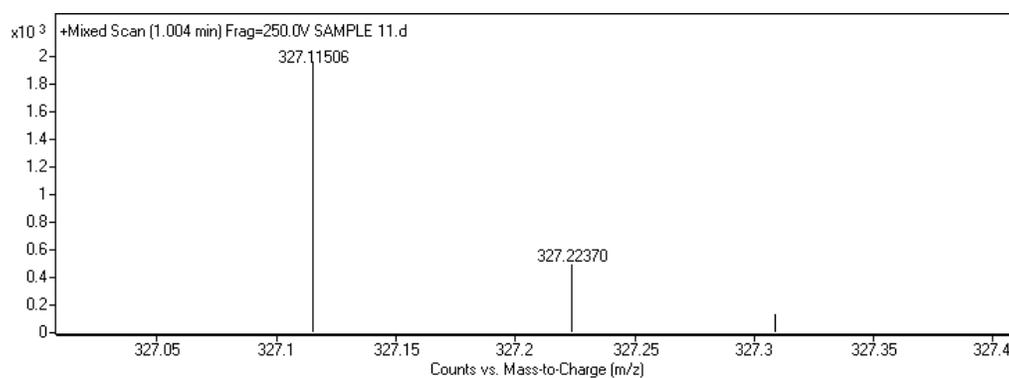
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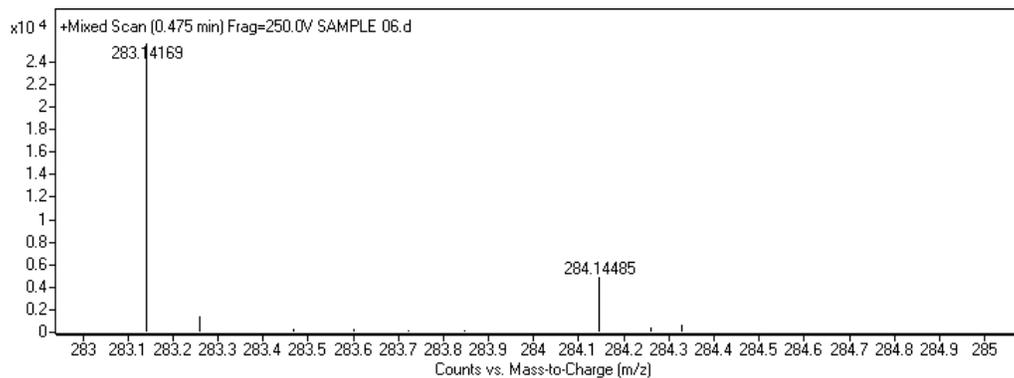
5j



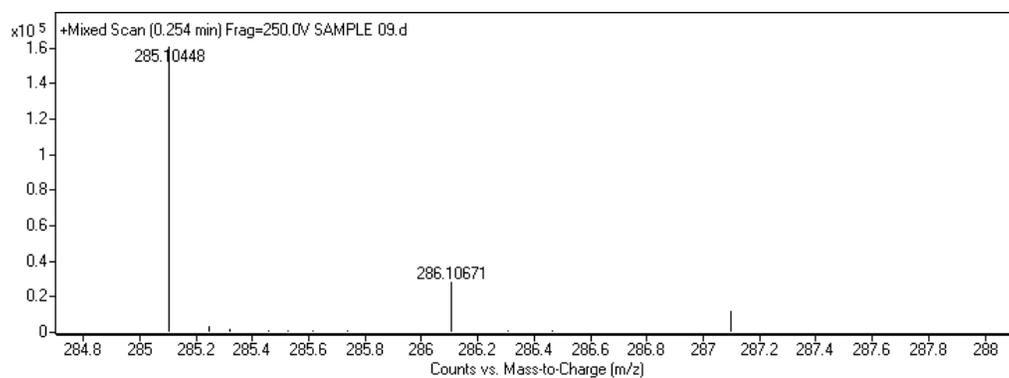
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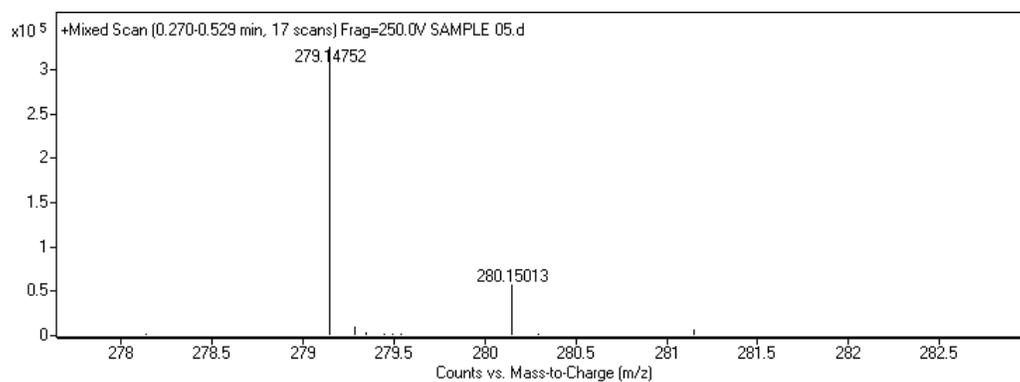
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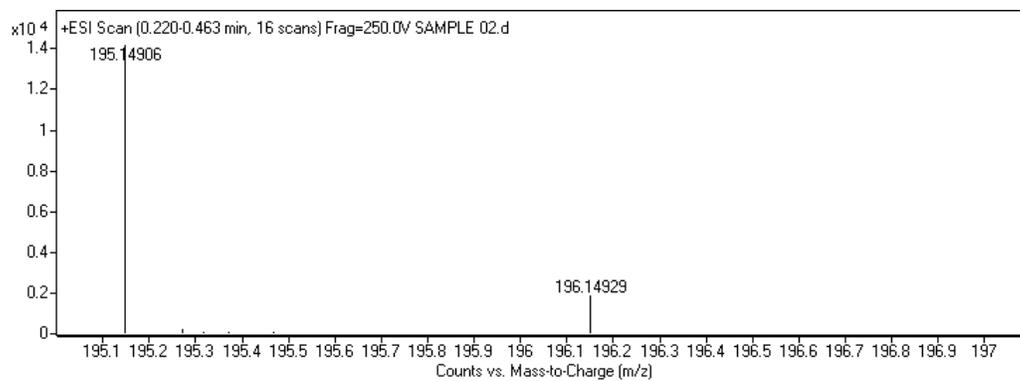
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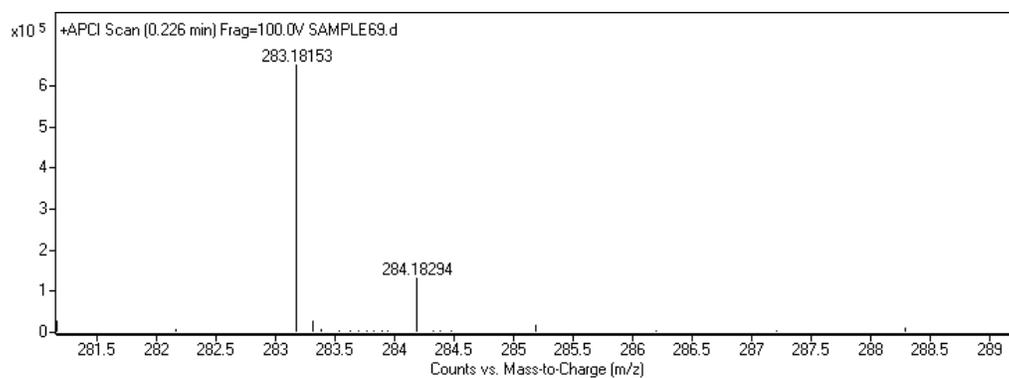
### 5n



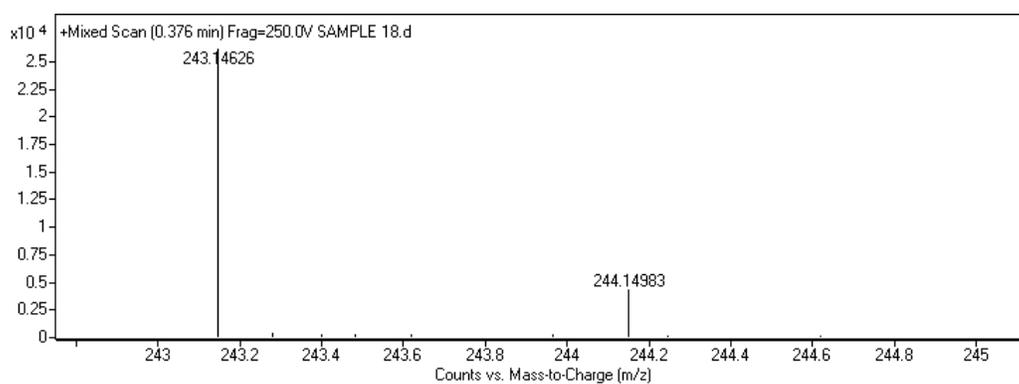
### 5o



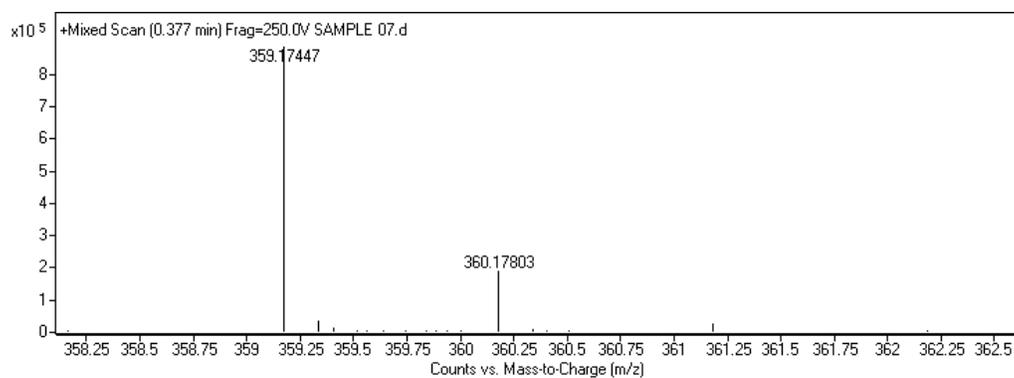
5p



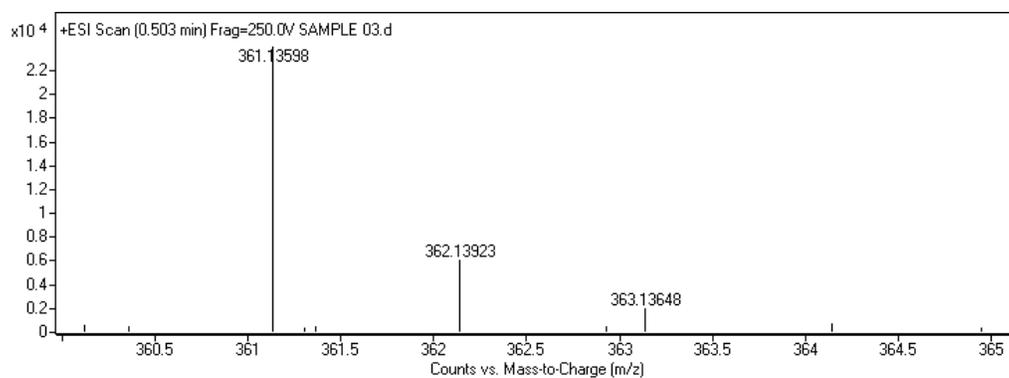
5q



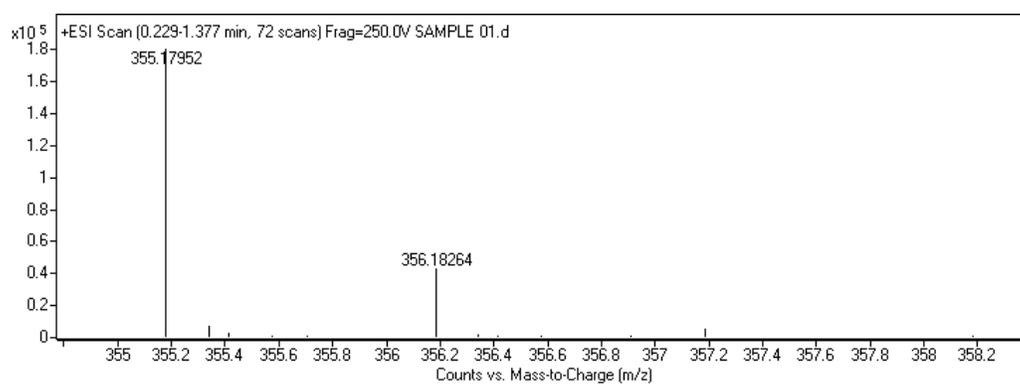
5r



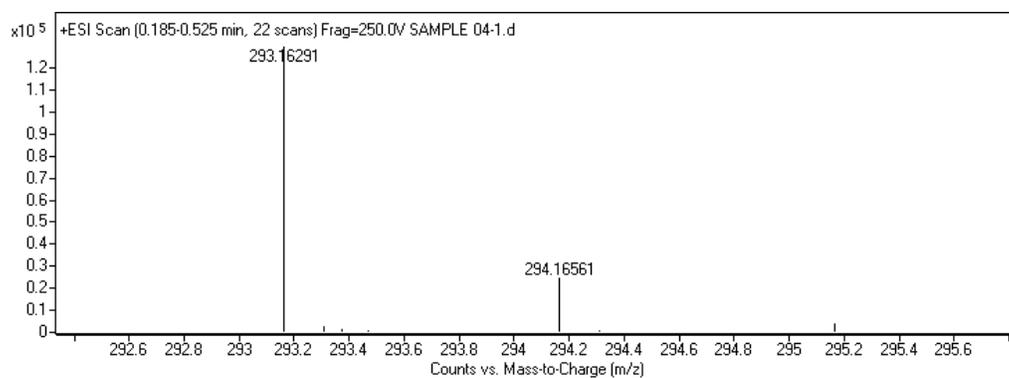
5s



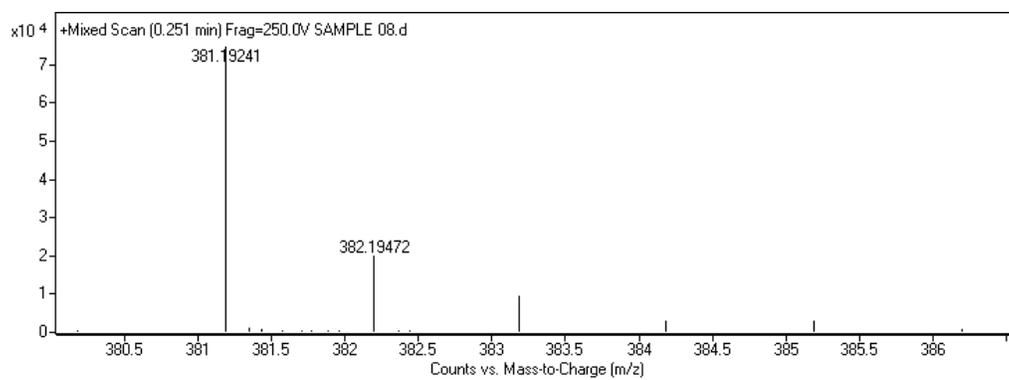
5t



5u



5v



5w

