



**[DBU][Ac] mediated: Step wise and four-component synthesis of 2,2-dimethyl-4-oxo-4,5-dihydropyrano[2,3-d][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-diones**

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## Abstract

Green synthesis of 2,2-dimethyl-4-oxo-4,5-dihydropyrano[2,3-d][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-diones **7** were developed by the reaction of diethylphthalate **1** with ethyl cyanohydrazide **2** to form 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile **3**. Then, **3** reacted with benzaldehydes **4** by Knoevenagel condensation to form **chalcones** (E)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-phenylacrylonitriles **5**. Compound **5** undergo further condensation with Meldrum's acid **6** to form **7** with good yields in [DBU][Ac]. Compound **7** could also be synthesized by one-pot four component synthesis with excellent yields with short time.

**Keywords:** Multi-component synthesis, Diethylphthalate, Benzaldehydes and Meldrum's acid.

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## Introduction:

Multi-component reactions (MCRs) are major tools for the rapid and efficient synthesis of a wide variety of organic molecules. These reactions have been investigated widely in organic and diversely oriented synthesis, primarily due to their ability to produce complex molecular functionality from simple starting materials via one-pot reaction<sup>1, 2</sup>. In the past few decades, the synthesis of novel heterocyclic compounds has been received a great deal of attention, most notably for the construction of heterocycles<sup>3</sup>. Heterocyclic compounds occur very extensively in nature and are essential to life. Among a large variety of heterocyclic compounds, heterocycles containing phthalazine moiety<sup>4,5</sup> are of importance because they show some pharmacological and biological

activities<sup>6</sup>. Phthalazine derivatives were reported to possess anticonvulsant<sup>7</sup>, cardiotoxic<sup>8</sup>, and vasorelaxant activities<sup>9</sup>.

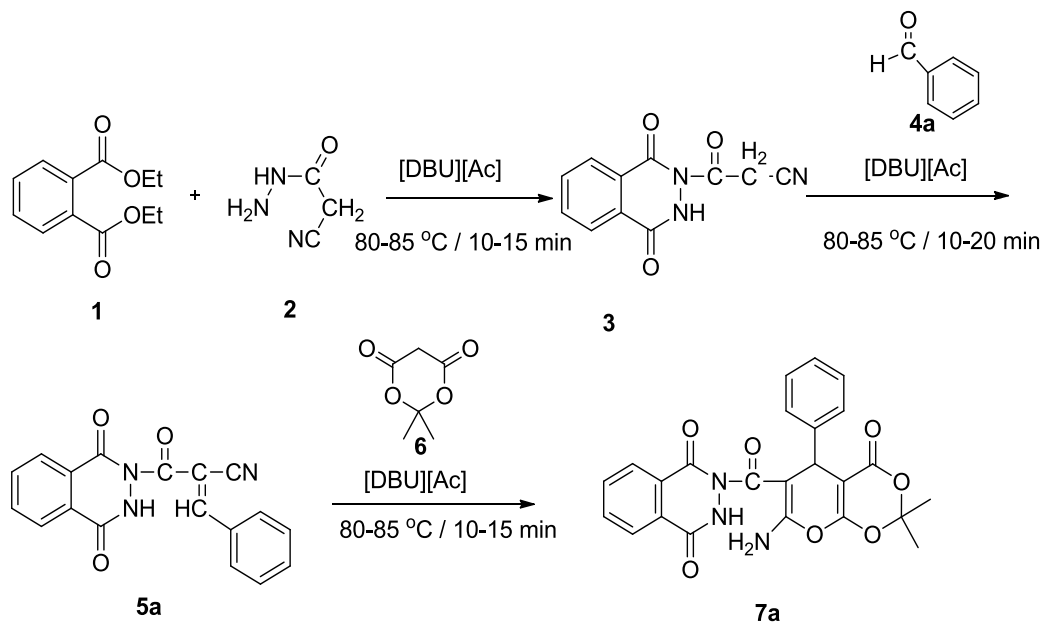
Heterocycles containing the phthalazine moiety are of interest because they show some pharmacological and biological activities<sup>10-13</sup>. Mogilaiah et al<sup>14</sup> reported the synthesis of 1,8-naphthyridine-3-carbonylphthalazine-1,4-diones by the condensation of 1,8-naphthyridine-3-carboxylic acid hydrazides with phthalic anhydride using p-toluene sulphonic acid (PTSA) as a catalyst under solid state conditions. Mogilaiah et al<sup>15</sup> also reported the microwave irradiation of a mixture of 3-aryl-2-hydrazino-1, 8-naphthyridines with phthalic anhydride in the presence of a catalytic amount of DMF resulting in 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydrophthalazine-1,4-diones.

Ionic liquids as catalysts<sup>16</sup> and /or media<sup>17</sup> in reactions have been widely used in organic transformations due to their advantages such as good solvating ability, negligible vapor pressure, high polarity and ease of work-up. [DBU][Ac] is one such task-specified ionic liquid which acts as reaction medium as well as a basic catalyst and has got varied applications in the field of synthetic methodology development.

Keeping these observations in mind, we now wish to report green & efficient, one-pot, four component synthesis of 2,2-dimethyl-4-oxo-4,5-dihydropyrano[2,3-d][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-diones **7** compounds in [DBU][Ac] at 80-85 °C.

### Results and Discussion:

As illustrated in **Scheme-1**, we have developed the condensation of diethyl phthalate **1** (1 mmol), ethyl cyanohydrazide **2** (1 mmol) to form 3-(1, 4-dioxo-3, 4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile<sup>18</sup> **3** in the presence of [DBU][Ac] (5 ml) (1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate) at 80-85 °C for 10-15 min. Compound **3** (1mmol) was reacted with benzaldehyde **4a** (1mmol) in the presence of [DBU][Ac] (5 ml) at 80-85 °C for 10-20 min to form (E)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-phenylacrylonitriles<sup>18</sup> **5a**. Compound **5a** (1mmol) was reacted with Meldrum's acid **6** (1mmol) in the presence of [DBU][Ac] (5 ml) at 80-85 °C for 10-15 min to form title compound **7a**. The overall yield is 88% for this step wise route. The gross structure of this product was assigned on the basis of its spectral data. Furthermore, the compound was assigned E - configuration on the presumption that bulky groups in a trans position would confer thermal stability on the molecule. This has been found to be case by a careful examination of the Frame-work molecular models of both E and Z - configurations of **5a** wherein it was observed that there were minimum number of steric interactions in the E – configuration.



**Scheme-1: Synthesis of 7a by step-wise reaction.**

Encouraged by above results, the preparation **7a** was carried out in one-pot reaction by heating a mixture of **1** (1 mmol) and **2** (1 mmol) (**Scheme 3**) in [DBU][Ac] (8 ml) at 80-85 °C for 10-15 min. Then, added **4a** & **6** and continued heating the reaction mass at 80-85 °C for 20-25 to get product **7a** with good yield (90 %) and no side products were detected. Structure of the product has been established by comparison with authentic samples which were prepared in step wise fashion in Scheme-1. (**Scheme-2**)

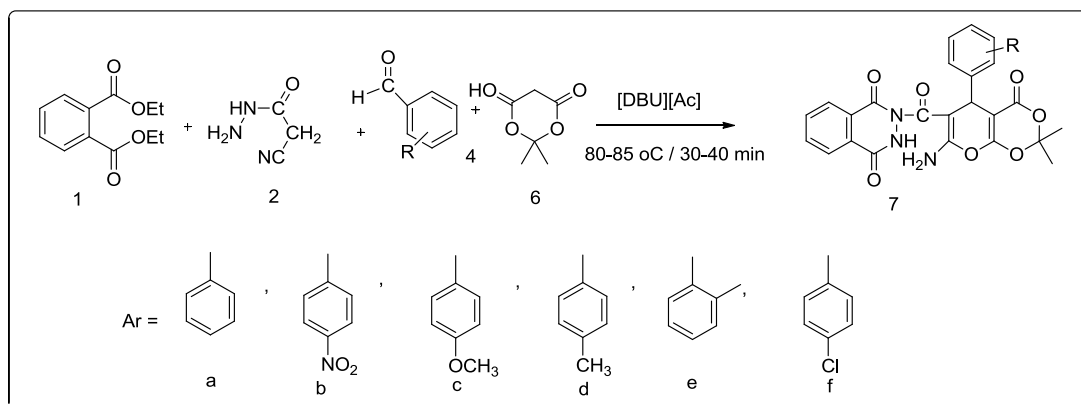
The above one-pot reaction was examined by carrying out in the presence of different ionic liquids ([Bmim]Br, [Bmim]BF<sub>4</sub> and [Bmim]AlCl<sub>4</sub>) at different temperature (**TABLE 1**). However, the one-pot four component reaction of **1**, **2**, **4a** & **6** using [DBU][Ac] as a catalyst and solvent media at 80-85 °C for 30-40 min gave the best yield (90%) of **7a**.

**TABLE 1** Effect of ionic liquid & temperature on one-pot reaction

Entry	Ionic liquid	Temperature	Time/min	7a (%)
1	[DBU][Ac]	80-85°C	30	90
2	[Bmim]Br	80-85°C	50	80
3	[Bmim]BF <sub>4</sub>	80-85°C	55	70
4	[Bmim]AlCl <sub>4</sub>	80-85°C	75	80
5	[DBU][Ac]	95-100 °C	25	85
6	[Bmim]Br	95-100 °C	40	75
7	[Bmim]BF <sub>4</sub>	95-100 °C	50	70
8	[Bmim]AlCl <sub>4</sub>	95-100 °C	45	75
9	[DBU][Ac]	25-30 °C	240	80

10	[Bmim]Br	25-30 °C	360	80
11	[Bmim]BF <sub>4</sub>	25-30 °C	300	75
12	[Bmim]AlCl <sub>4</sub>	25-30 °C	360	75

After having optimized the one-pot reaction conditions, the generality of the reaction was confirmed by carrying out the condensation of several others **4a-4f** using [DBU][Ac] as catalyst and solvent medium at 80-85 °C for 30-40 min to giving **7a-7f** in excellent yields and no side product formation was detected. As shown in experiment section, it was found that this method works with a wide variety of substrates.



**Scheme-2: Synthesis of 7a-7f by one-pot reaction.**

### Experimental section

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. <sup>1</sup>H NMR spectra were recorded in DMSO – d<sub>6</sub> using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument.

### Preparation of 7a-7f from 1, 2, 4a-4f & 6 by one-pot synthesis:

A mixture of **1** (10 mM), **2** (10 mM), **4** (10 mM) and **6** (10mM) and [DBU][Ac] (10 ml) were heated at 80-85 °C for 30-40 min. At the end of this period, poured water (50 ml) to generate solid. Stirred reaction mass for 10-15 min followed by filtered the separated solid out from reaction mass, washed with hexane (10 ml) and dried the wet solid at 60-65 °C for 10-12 hr to obtain desired **7a-7f**.

**7a:** Mp: 159–161 °C; IR (KBr) : 3146-3434 cm<sup>-1</sup> (-NH-), 1793 Cm<sup>-1</sup> (-CO-), 1740 Cm<sup>-1</sup> (-CO-), 1693 cm<sup>-1</sup> (-CO-NH-), <sup>1</sup>H- NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 1.32 (s, 1H, -CH<sub>3</sub>), 1.53 (s, 1H, -CH<sub>3</sub>), 5.31 (s, 1H, -CH), 7.1-7.8 (m, 9H, Ar-H), 8.18 (s, 2H, -NH<sub>2</sub>), 11.32 (s, 1H, -NH); <sup>13</sup>C-NMR

(DMSO-d<sub>6</sub>, 100 MHz):  $\delta$  21.5, 22.1, 43.7, 72.9, 74.9, 78.2, 99.7, 118.5, 123.6, 125.4, 127.3, 127.6, 128.1, 129.2, 135.2, 142.9, 155.2, 158.9, 165.0; [M+H]<sup>+</sup>: 462.

**7b:** Mp: 170–171 °C; IR (KBr) : 3132-3443 cm<sup>-1</sup> (-NH-), 1786 Cm<sup>-1</sup> (-CO-), 1752 Cm<sup>-1</sup> (-CO-), 1693 cm<sup>-1</sup> (-CO-NH-), <sup>1</sup>H- NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  1.41 (s, 1H, -CH<sub>3</sub>), 1.72 (s, 1H, -CH<sub>3</sub>), 5.44 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.41 (s, 2H, -NH<sub>2</sub>), 11.31 (s, 1H, -NH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 100 MHz):  $\delta$  21.1, 22.1, 43.3, 72.5, 74.7, 78.3, 99.4, 118.2, 123.3, 125.5, 127.3, 127.6, 128.6, 129.2, 135.3, 142.5, 155.1, 158.6, 165.7; [M+H]<sup>+</sup>: 507.

**7c:** Mp: 158–160 °C; IR (KBr) : 3143-3445 cm<sup>-1</sup> (-NH-), 1781 Cm<sup>-1</sup> (-CO-), 1755 Cm<sup>-1</sup> (-CO-), 1692 cm<sup>-1</sup> (-CO-), <sup>1</sup>H- NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  1.31 (s, 1H, -CH<sub>3</sub>), 1.62 (s, 1H, -CH<sub>3</sub>), 3.91 (s, 1H, -CH<sub>3</sub>), 5.31 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.22 (s, 2H, -NH<sub>2</sub>), 11.24 (s, 1H, -NH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 100 MHz):  $\delta$  21.4, 22.3, 42.4, 72.8, 74.6, 76.2, 98.5, 118.3, 122.4, 125.4, 127.4, 127.5, 128.2, 129.1, 134.2, 142.8, 154.2, 158.5, 164.5; [M+H]<sup>+</sup>: 492.

**7d:** Mp: 169–171 °C; IR (KBr) : 3146-3435 cm<sup>-1</sup> (-NH-), 1791 Cm<sup>-1</sup> (-CO-), 1752 Cm<sup>-1</sup> (-CO-), 1698 cm<sup>-1</sup> (-CO-NH-), <sup>1</sup>H- NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  1.33 (s, 1H, -CH<sub>3</sub>), 1.62 (s, 1H, -CH<sub>3</sub>), 2.24 (s, 1H, -CH<sub>3</sub>), 5.41 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.15 (s, 2H, -NH<sub>2</sub>), 11.43 (s, 1H, -NH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 100 MHz):  $\delta$  20.4, 21.2, 42.6, 72.8, 73.9, 77.1, 99.6, 117.4, 123.5, 124.3, 127.3, 127.6, 128.2, 128.5, 135.2, 142.9, 155.1, 157.8, 165.1; [M+H]<sup>+</sup>: 476.

**7e:** Mp: 165–167 °C; IR (KBr) : 3142-3435 cm<sup>-1</sup> (-NH-), 1791 Cm<sup>-1</sup> (-CO-), 1752 Cm<sup>-1</sup> (-CO-), 1694 cm<sup>-1</sup> (-CO-NH-), <sup>1</sup>H- NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  1.31 (s, 1H, -CH<sub>3</sub>), 1.62 (s, 1H, -CH<sub>3</sub>), 2.34 (s, 1H, -CH<sub>3</sub>), 5.31 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.12 (s, 2H, -NH<sub>2</sub>), 11.32 (s, 1H, -NH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 100 MHz):  $\delta$  21.3, 22.3, 43.5, 72.7, 74.8, 78.2, 99.7, 118.3, 123.5, 125.3, 127.3, 127.4, 128.2, 129.3, 135.3, 142.8, 155.4, 158.6, 165.2; [M+H]<sup>+</sup>: 476.

**7f:** Mp: 153–155 °C; IR (KBr) : 3121-3394 cm<sup>-1</sup> (-NH-), 1771 Cm<sup>-1</sup> (-CO-), 1768 Cm<sup>-1</sup> (-CO-), 1674 cm<sup>-1</sup> (-CO-NH-), <sup>1</sup>H- NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  1.31 (s, 1H, -CH<sub>3</sub>), 1.83 (s, 1H, -CH<sub>3</sub>), 5.15 (s, 1H, -CH), 7.1-7.9 (m, 8H, Ar-H), 8.13 (s, 2H, -NH<sub>2</sub>), 11.31 (s, 1H, -NH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 100 MHz):  $\delta$  20.4, 21.5, 43.2, 71.4, 73.6, 77.4, 96.3, 116.1, 122.1, 125.4, 127.1, 127.4, 128.5, 129.1, 135.3, 142.5, 154.2, 158.4, 164.4; [M+H]<sup>+</sup>: 496.

## Conclusion

In summary, we have successfully developed one-pot four component reaction for 2,2-dimethyl-4-oxo-4,5-dihydropyrano[2,3-d][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-diones under green conditions using ionic liquid without formation of any by-products with excellent yields.

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## Graphical Abstract:

### [DBU][Ac] mediated: Step wise and four-component synthesis of 2,2-dimethyl-4-oxo-4,5-dihydropyrano[2,3-d][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-diones CHEKRAPANI KESARI<sup>1\*</sup>, Dr. MENKA SURANA<sup>2</sup>, Dr. SHRAVANKUMAR KANKALA<sup>3</sup>

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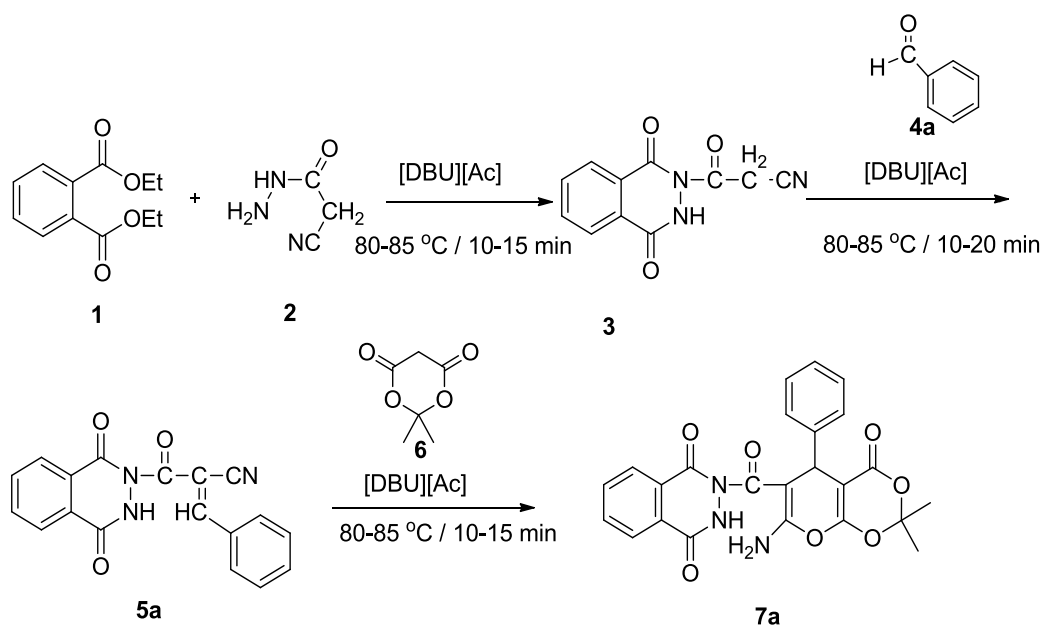
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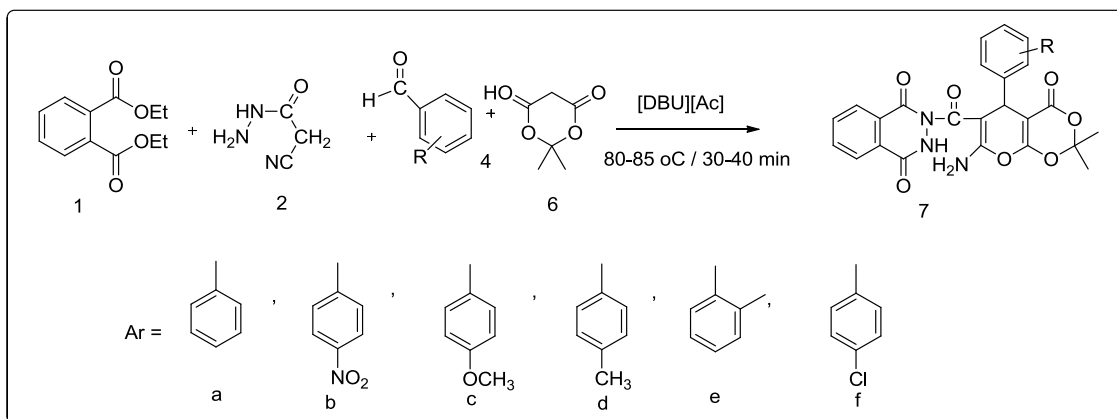
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**Preparation of 7a-7f from 1, 2, 4a-4f & 6 by one-pot synthesis:**

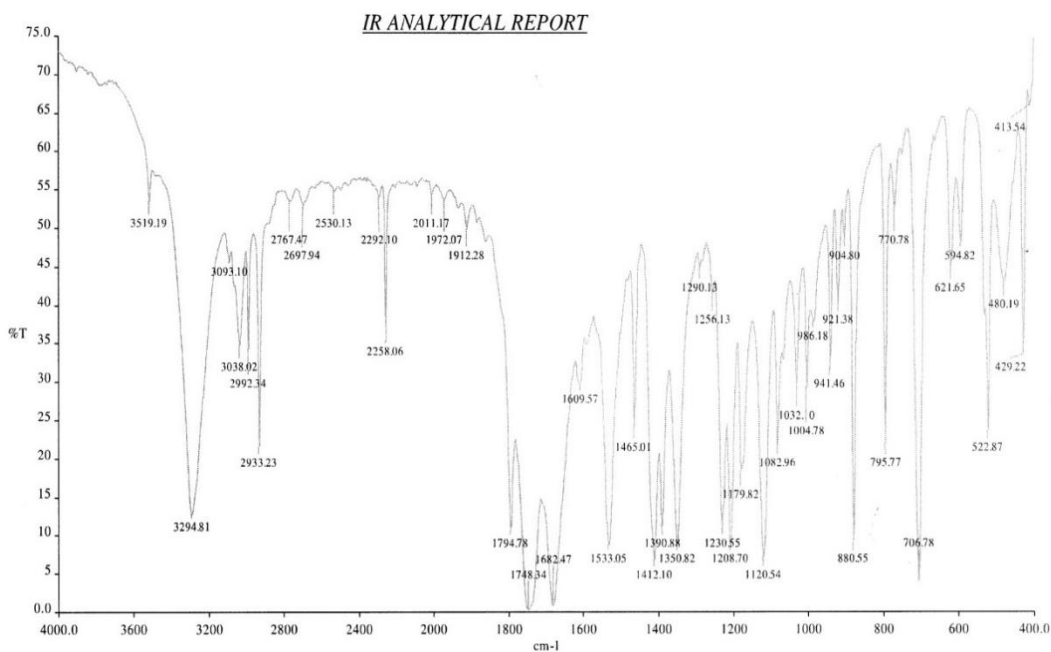
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A mixture of **1** (10 mM), **2** (10 mM), **4** (10 mM) and **6** (10mM) and [DBU][Ac] (10 ml) were heated at 80-85 °C for 30-40 min. At the end of this period, poured water (50 ml) to generate solid. Stirred reaction mass for 10-15 min followed by filtered the separated solid out from reaction mass, washed with hexane (10 ml) and dried the wet solid at 60-65 °C for 10-12 hr to obtain desired **7a-7f**



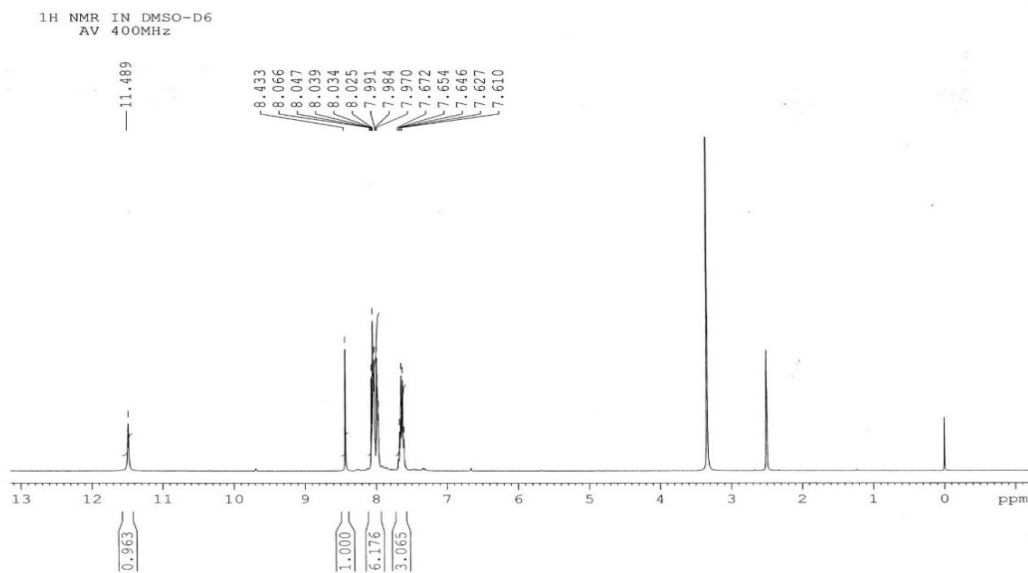
## Supporting information

### IR spectra of compound-5a

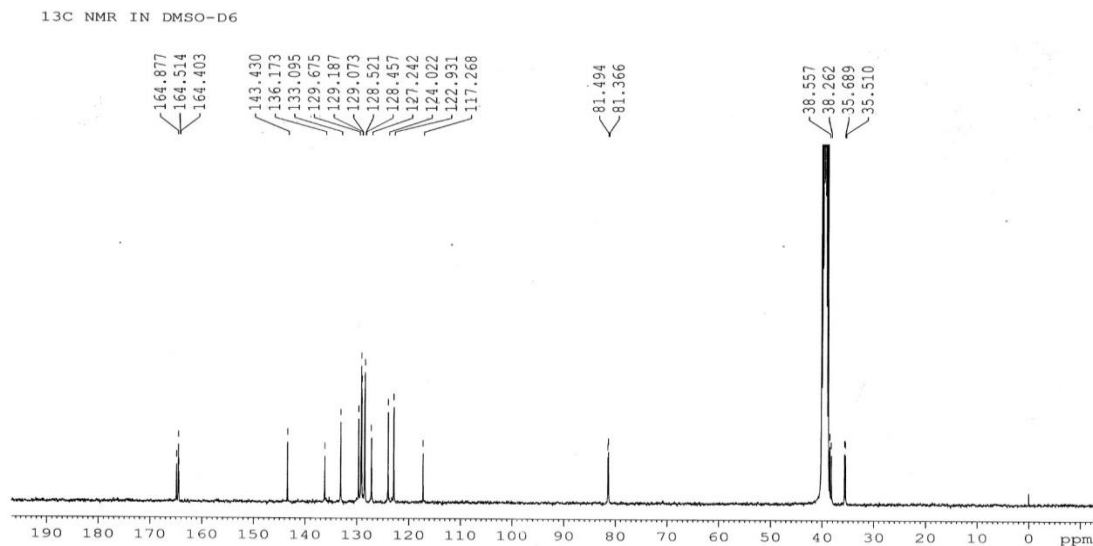




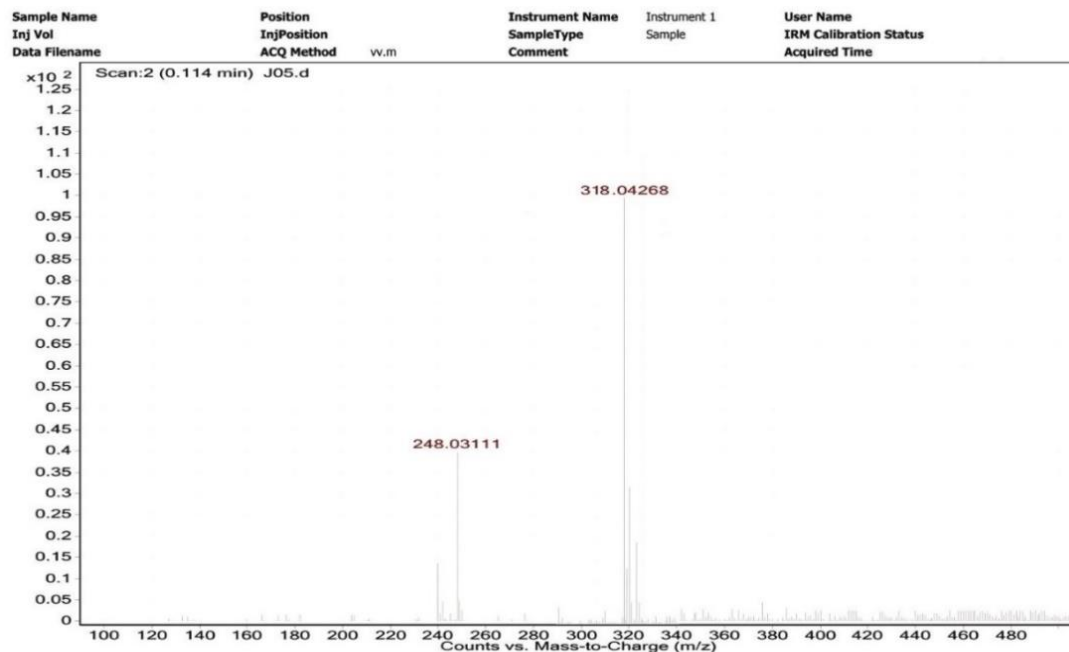
### <sup>1</sup>H NMR spectra of compound-5a



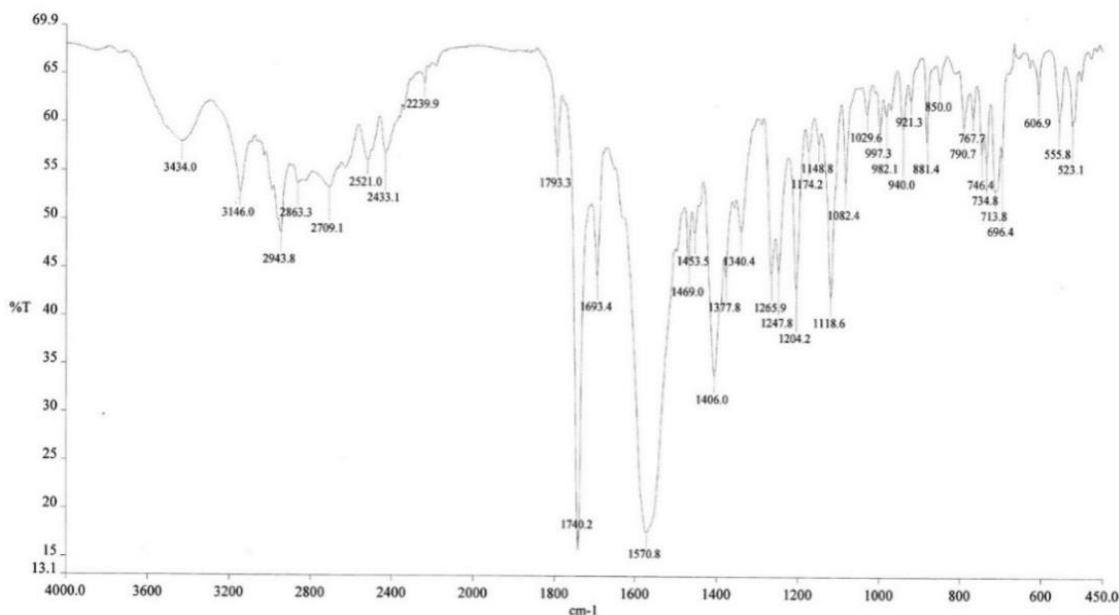
### <sup>13</sup>C NMR spectra of compound-5a



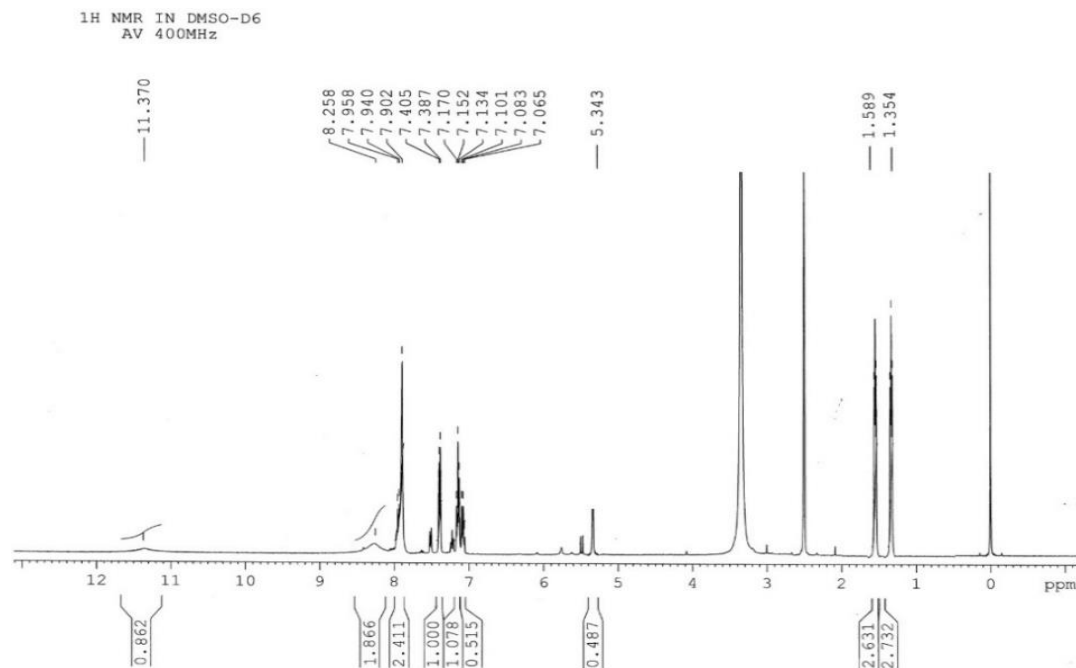
### Mass spectra of compound-5a



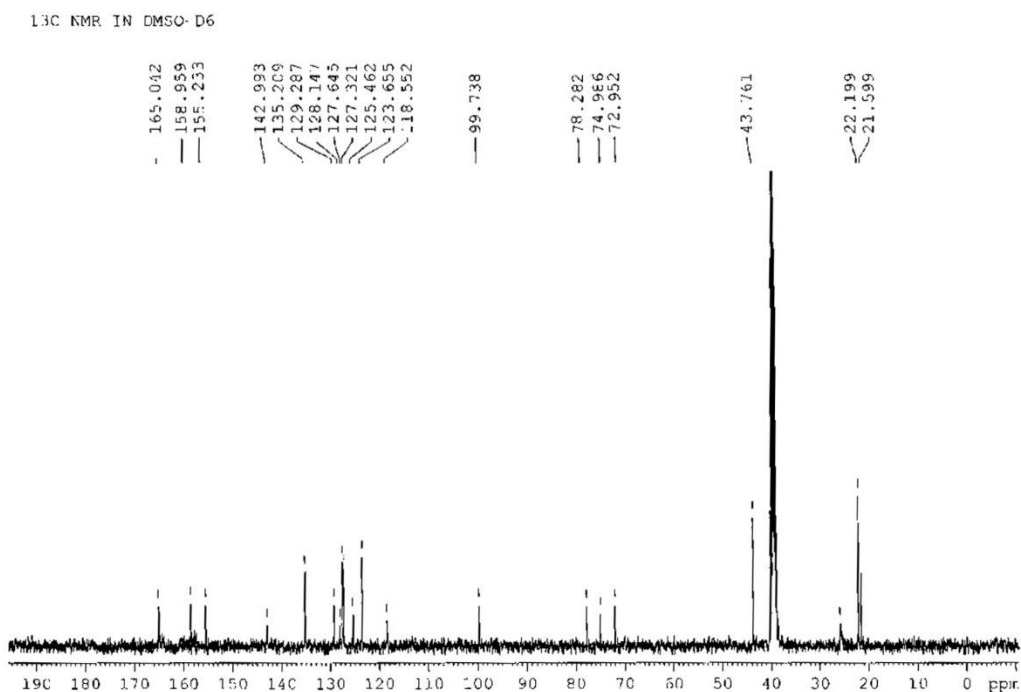
### IR spectra of compound-7a



### <sup>1</sup>H NMR spectra of compound-7a



### <sup>13</sup>C NMR spectra of compound-7a



## Mass spectra of compound-7a

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IRM Calibration Status	Success	DA Method	Default.m
Comment			

### User Spectra

