



## SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS DERIVED FROM CHALCONES

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### ABSTRACT

Chalcone derivatives were synthesized by reaction of some benzaldehyde derivatives with acetophenone, then the products obtained were allowed to react with urea, thiourea and hydroxylamine, to give the heterocyclic derivatives of oxazine, thiazine and isoxazole, respectively. The final products have been characterized by elemental analysis, IR and proton NMR spectra. These compounds were also screened for their antibacterial activities.

**Key words:** Synthesis, Heterocyclic compounds, Chalcone, Antibacterial.

### INTRODUCTION

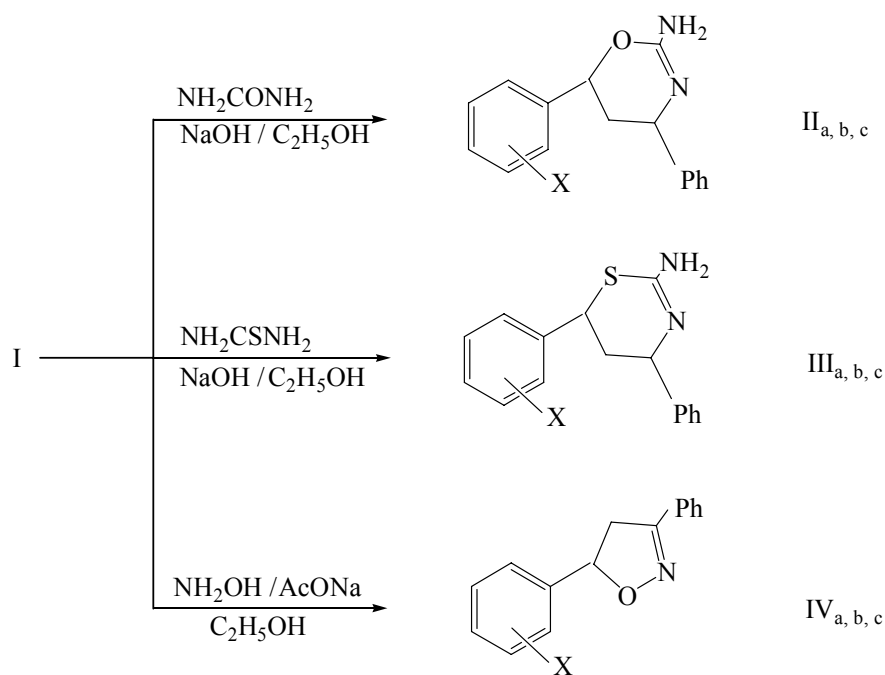
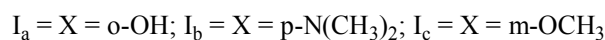
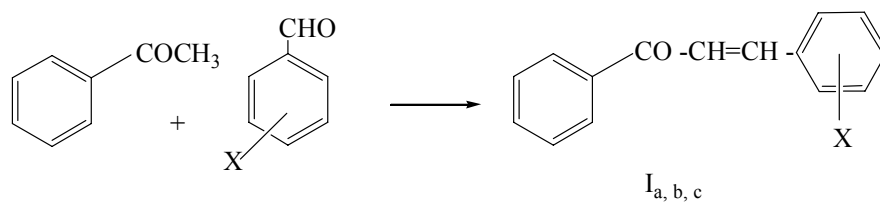
Chalcones were prepared by condensation of acetophenone with aromatic aldehydes in presence of suitable condensing agent<sup>1,2</sup>. They undergo a variety of chemical reactions that leads to many heterocyclic compounds<sup>3-6</sup>. Chalcones have been used as intermediates for the preparation of compounds having therapeutic value<sup>7,8</sup>. Many reviews reveal that chalcone derivatives exhibit diverse pharmacological activities, such as potential cytotoxic agents, antimicrobial agents, antiviral, anti-inflammatory, anesthetic, etc.<sup>9,10</sup>. In the view of the varied biological and pharmacological applications, we have planned to synthesize some heterocyclic derivatives of chalcone and test their antibacterial activity.

### EXPERIMENTAL

Melting points were determined on Stuart apparatus and were uncorrected. IR spectra were recorded on FT IR Perkin-Elmer spectrophotometer using KBr disc method. <sup>1</sup>H NMR spectra were recorded on Bruker AMX-300 MHz spectrometer in d<sub>6</sub>-DMSO. Chemical shifts relative to TMS used as internal standard were obtained in  $\delta$  unit. All analysis were carried out at Cairo University, Egypt. Physical and spectral data are shown in Tables 1 and 2 below.

The heterocyclic derivatives of chalcone were subjected to antimicrobial screening using nutrient agar medium by well diffusion method<sup>8</sup>. The antibacterial activity was tested against various types of bacteria and compared with standard drugs (Ampicillin and Vibromycin) and were carried out at the Botany Department, Garyounis University, the results are given in Table 3.

The chalcones then the heterocyclic derivatives were prepared as shown in the following scheme:



### Reaction scheme

#### Synthesis of chalcones ( $I_{a-c}$ )

Benzaldehyde derivative (0.01 mol) and acetophenone (0.01 mol) were dissolved in ethanol (25 mL). Sodium hydroxide solution, 10% (25 mL) was added slowly and the mixture stirred for 4 hrs then it was poured into 400 mL of water with constant stirring and left overnight in Refrigerator. The precipitate obtained was filtered, washed and recrystallized from ethanol.

#### Preparation of Thiazine/Oxazine derivatives ( $II_{a-c}; III_{a-c}$ )

A mixture of chalcone (0.02 mol), thiourea/urea (0.02 mol) were dissolved in ethanolic sodium hydroxide solution (10 mL) was stirred for 3 hrs, then it was poured into 400 mL of cold water with continuous stirring for 1 hr then left overnight. The precipitate formed was filtered, washed and recrystallized from ethanol.

#### Preparation of Isoxazole derivatives ( $IV_{a-c}$ )

A mixture of chalcone (0.02 mol), hydroxylamine hydrochloride (0.02 mol) and sodium acetate in ethanol (25 mL) was refluxed for 6 hrs, and then the reaction mixture was poured into ice water (50 mL). The precipitate obtained was filtered, washed and recrystallized from ethanol.

**Table 1: Physical and elemental analysis of synthesized compounds**

Compd. No.	Mol. formula	Mol. Wt.	M.P. (°C)	Yield (%)	Microanalysis Calc. / Found %			
					C	H	I	S
I <sub>a</sub>	C <sub>15</sub> H <sub>12</sub> O <sub>2</sub>	224	150-3	50	80.35 (80.66)	5.35 (5.85)	-----	-----
I <sub>b</sub>	C <sub>17</sub> H <sub>17</sub> NO	251	95-9	80	81.27 (81.76)	6.77 (6.04)	5.57 (5.03)	-----
I <sub>c</sub>	C <sub>16</sub> H <sub>14</sub> O <sub>2</sub>	238		40	80.67 (80.23)	5.88 (6.24)	-----	-----
II <sub>a</sub>	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> OS	282	148-9	40	68.08 (67.86)	4.96 (5.54)	9.92	11.34
II <sub>b</sub>	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> S	309	73-5	60	69.90 (69.45)	6.14 (6.48)	13.59 (13.21)	10.35 (10.68)
II <sub>c</sub>	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> OS	296		40	68.91 (68.34)	5.40 (5.96)	9.45 (9.92)	10.81 (10.36)
III <sub>a</sub>	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	266	144-5	50	72.18 (72.58)	5.26 (5.68)	10.52 (10.86)	-----
III <sub>b</sub>	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> O	293	65-6	60	73.72 (73.34)	6.48 (6.78)	14.33 (14.84)	-----
III <sub>c</sub>	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	280		45	72.85 (72.34)	5.71 (6.34)	10.00 (10.56)	-----
IV <sub>a</sub>	C <sub>15</sub> H <sub>11</sub> NO <sub>2</sub>	237	140-2	35	75.94 (75.36)	4.64 (4.16)	5.90 (5.23)	-----
IV <sub>b</sub>	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O	264	76-8	40	77.27 (76.93)	60.60 (60.22)	10.60 (10.16)	-----
IV <sub>c</sub>	C <sub>16</sub> H <sub>13</sub> NO <sub>2</sub>	251		30	76.49 (77.01)	5.17 (5.67)	5.57 (6.21)	-----

**Table 2: Spectral data of the synthesized compounds**

Compd.	IR (KBr) $\nu$ cm <sup>-1</sup>	<sup>1</sup> H NMR (d <sub>6</sub> -DMSO) $\delta$ ppm
I <sub>a</sub>	3350 (Ar-OH); 1675 (CH = CH-CO); 1640 (C = C); 1480 (Ar-C = C)	4.4 (d,2H,2CH); 5.0 (s,1H,Ar-OH); 7.0-7.8 (m,9H, Ar-H)
I <sub>b</sub>	3400 (Ar-I); 1680(CH = CH-CO); 1635 (C = C); 1520 (Ar-C = C)	2.47 (s,6H,I(CH <sub>3</sub> ) <sub>2</sub> ); 4.6 (d,2H,2CH); 7.1-7.8 (m,9H,Ar-H)
I <sub>c</sub>	1670 (CH = CH-CO); 1645 (C = C); 1528 (Ar-C = C); 1100 (Ar-OC)	3.4 (s,3H,OCH <sub>3</sub> ); 4.5 (d,2H,2CH); 6.9-7.8 (m,9H,Ar-H)
II <sub>a</sub>	3370 (Ar-OH); 2370 (C-S-C); 1655 (C = C); 1624 (C = N); 1610 (NH <sub>2</sub> )	2.1 (s,2H,NH <sub>2</sub> ); 3.5 (s,1H); 5.2 (s,1H,Ar-OH); 5.7 (s,1H); 6.8-7.9 (m,9H,Ar-H)
II <sub>b</sub>	3430 (Ar-N); 2356 (C-S-C); 1650 (C = C); 1620 (C = N); 1590 (NH <sub>2</sub> )	2.0 (s,2H,NH <sub>2</sub> ); 2.4 (s,6H,N(CH <sub>3</sub> ) <sub>2</sub> ); 3.4 (s,1H); 5.6 (s,1H); 6.9-8.0 (m,9H,Ar-H)

Cont...

### Biological assay of the synthesized products

Antibacterial activity of the heterocyclic derivatives of chalcone have been carried out against several types of bacteria such as, *E. coli*; *S. aureus*; and *P. aregenosa*, using nutrient agar medium by well diffusion method<sup>11</sup>. All compounds were suspended in aqueous solutions in different concentrations ranged from 10-100 mg/mL, the results are expressed on MIC (minimal inhibitory concentration), solvent blanks were run against each test organism in all assays and the experimental biological data is given in Table 3.

**Table 3: Antibacterial activity data of the heterocyclic derivatives of chalcone**

Compound	<i>E. coli</i>	<i>S. aureus</i>	<i>P. aregenosa</i>
II <sub>a</sub>	18	19	17
II <sub>b</sub>	21	18	20
II <sub>c</sub>	22	20	18
III <sub>a</sub>	18	20	22
III <sub>b</sub>	22	21	19
III <sub>c</sub>	23	21	20
IV <sub>a</sub>	17	19	18
IV <sub>b</sub>	20	20	19
IV <sub>c</sub>	22	21	18
Antibiotics	-----	-----	-----
Ampicillin	23	20	21
Vibromycin	24	22	20

## RESULTS AND DISCUSSION

All synthesized compounds as well as the reactions that carried out were characterized and monitored by TLC, melting points, elemental analysis, IR and <sup>1</sup>H NMR, and they all gave satisfactory results as shown in Tables 1 and 2.

The compounds were evaluated for their antibacterial activities against various types of bacteria, and they showed comparable activity with that of standard drugs.

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