INTRODUCTION

The chemistry of α, β-unsaturated ketones has generated intensive scientific studies worldwide, due to their biological and industrial applications. The α, β-unsaturated ketones, also known as chalcone derivatives, are compounds containing the reactive keto-ethylenic group i.e. -CO-CH=CH-. The presence of this moiety gives them their characteristic yellow-to-orange colors [1]. They are prepared by condensing an aromatic aldehyde (without alpha hydrogen) with aliphatic or aromatic ketone having alpha hydrogen, in the presence of a catalyst of base or acid.

This method is usually referred to as condensatio...
n of Claisen – Schmidt or condensation of aldol. The reaction has been applied in the preparation of chalcones, α,β-unsaturated ketones, cycloalkanones, flavanones, 1,3-diarylpropane derivatives and a new family of macrocycles in a single step, depending on the chemical structures of the reactants [2-4]. Not only are α,β-unsaturated ketones (Figure 1) important precursors for synthetic manipulations, they also form the major components of natural products [5]. The name chalcone was first used by Kostaecki and Tambor [6].

Figure 1: α, β-unsaturated ketone structure

The conjugation involves the double bond and the completely delocalized π electrons. The delocalization of the electrons along the α, β-unsaturated carbonyl linkage leads to electron transfer reactions that cause the carbonyl carbon–carbon bond (-CO-CH=) to show partial double bond character, while the carbonyl group shows single bond character [7]. It is believed that the presence of double bond in conjunction with carbonyl functionality accounts for the biological properties of α, β-unsaturated ketones, since removing this functionality makes them inactive [6]. A spectrum of biological effects of chalcone derivatives have been reported [8-16].

EXPERIMENTAL

Chemicals and materials

All chemicals used were supplied by Merck and Fluka. The solvents used were ethanol, chloroform, benzaldehyde, 2-acetyl cyclopentanone, 4-dimethylaminobenzaldehyde, 4-acetamidobenza-aldehyde, and 4-hydroxy benzaldehyde, all of which were of analytical grade.

General procedure for the preparation of α, β-unsaturated ketones [17]

Benzaldehyde derivatives (0.001 mol) was added to a solution of 2-acetyl cyclopentanone in 10 mL of 40 % NaOH and 15 mL of absolute ethanol, and stirred overnight (Figure 2). The colored solution was poured on crushed ice, and was acidified with acetic acid to neutralization. The precipitate obtained was washed with absolute ethanol and cold water, filtered, dried and recrystallized. Table 1 summarizes the physical properties of the synthesized compounds.

Figure 2: Synthesis of the α, β-unsaturated ketone derivatives

Determination of anti-Inflammatory effects of the synthesized chalcones [18]

Albino rats (n = 36) weighing 175 - 200 g were used. They were divided into 6 groups, with 6 rats in each. Autoclave-sterilized cotton pellets weighing 50 ± 3 mg were subcutaneously inserted into the abdominal area of each rat. The rats in control group received only the vehicle (DMSO). The second group was given the standard drug diclofenac sodium at a dose of 5 mg/kg (standard group). The four synthesized chalcone derivatives were given separately to the other 4 groups of rats, each at a dose of 20 mg/kg. The treatments were given orally for seven days. On the 8th day, the rats were anesthetized with ether, and the cotton pellets were removed along with the granuloma tissues, weighed and compared with control in an oven at 60 °C.

Inhibition (N) was calculated as shown in Eq 1.

\[ N(\%) = \frac{(Wc - Ws)}{Wc} \times 100 \] \hspace{1cm} (1)

where \( Wc \) is weight of the control pellet, and \( Ws \) is weight of the test pellet.

Edema inhibition (E) was calculated as shown in Eq 2.

\[ E(\%) = \frac{(Ewc - Ews)}{Ewc} \times 100 \] \hspace{1cm} (2)
where $E_{wc}$ is exudate weight of the control, and $E_{ws}$ is exudate weight of the test.

Granuloma inhibition (G) was calculated as shown in Equation 3:

$$G (\%) = \frac{(G_{wc} - G_{ws})}{G_{wc}} \times 100 \quad \ldots \ldots \ (3)$$

where $G_{wc}$ is weight of the control granuloma tissue, and $G_{ws}$ is weight of the test granuloma tissue.

**Determination of antibacterial effect of synthesized chalcones**

The antibacterial effect of the synthesized compounds was determined using *Bacillus cereus*, *Staph. aureus* (Gram +ve), *E. coli*, and *Pseud.s aeruginosa* (Gram –ve). All growth media were prepared in line with the manufacturer’s instructions. On the Mueller-Hinton agar was spread a pure bacterial strain (obtained from the Department of Microbiology and Parasitology, Veterinary Medicine College, Basrah University). Small filter paper disks (6 mm) were sterilized using UV light, and dipped in a solution of each chalcone of concentration 1 mg/mL or 2 mg/mL. The paper was then carefully pressed onto the surface of the nutrient agar. The nutrient agars were incubated overnight. The inhibitory effect was adjudged through the presence of growth-inhibition (triplicate) zones that were easily measurable. Cefuroxime was used as standard drug at the same concentrations as the tested chalcones [19].

**Statistical analysis**

The data are expressed as mean ± SD. The mean values of the groups had been statistically compared using the analysis of variance with the aid of SPSS software, and $p < 0.05$ was considered statistically significant.

**Computational studies**

In order to investigate the existence of consistency between the theoretical, and the experimental results, HyperChem 8 software had been used complete geometry optimization.

**RESULTS**

**Spectral characteristics of the compounds**

The physical features of the compounds are summarized in Table 1.

| Compound | R       | Color  | Melting Point | Yield (%) |
|----------|---------|--------|---------------|-----------|
| I        | H       | Yellow | Oily          | 88        |
| II       | Me$_2$N | Pale   | 77            | 90        |
| III      | CH$_3$CONH | Yellow | 167          | 80        |
| IV       | HO      | Red    | 200           | 79        |

The data obtained from all structural characteristics analysis of α, β-unsaturated ketones derivatives were characterized using UV-Visible (Figure 3), FT-IR, $^1$H-NMR, $^{13}$C-NMR and mass spectroscopy.

**Figure 3**: UV-Visible spectrum of α, β-unsaturated ketone derivatives

2-(3-phenyl acryloyl) cyclopentan-1-one (I)

Yellowish oily compound (C$_{14}$H$_{14}$O$_2$); yield = 88 %

**IR (KBr, cm$^{-1}$):** 3109 (C-H) Ar., 2983(C-H) Aliph., 1708 (C=O), 1580 (C=C), 1654 (C=O).

$^1$H-NMR (400 MHz, CDCl$_3$ $\delta$/ppm): 7.79-7.10 (m, 4H, ArH), 7.14-7.10(d, 2H), 3.14(s, 2H), 2.40 (s, 2H), 1.16 (s, 2H), 1.17 (s, 2H)

$^{13}$C-NMR (100 MHz,$\delta$/ppm): CDCl$_3$ $\delta$ =188.98 (IC), 143.3(IC), 134.8,130.7-125.4 (6C, Ar), 77.3,77.0, 76.7 (1C), 44.9, 43.9, 43.2, 41.3, 39.5 (2C), 26.5 (1C), 19.4, 19.3.

**MS:** m/z, 214(M$^+$); m/z, 131(-C$_6$H$_7$O); m/z, 205 (-H$_2$O); m/z, 103 (-C$_6$H$_5$O$_2$); m/z, 77 (Ph)

2-(3-(4-(Dimethylamino)phenyl)acryloyl)cyclopentan-1-one (II)

Pale yellow precipitate, M.P. = 77 °C, C$_{16}$H$_{19}$NO, yield = 90 %

**IR (KBr, cm$^{-1}$):** 3119 (C-H) aromatic, 2982(C-H) aliphatic, 2245 (C-N) 1650, (C=O), 1597 (C=O), 1664 (C=O).
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**H-NMR** (400 MHz, CDCl₃) δ/ppm = 7.77-6.71 (m,5H, ArH), 7.77 7.74 (d, 2H, ArH), 7.28 (s, 1H, ArH), 6.73 6.71 (d, 2H, ArH), 3.1 (s, 6H), 1.71 (s, 1H)

**13C-NMR** (100 MHz): CDCl₃ δ/ppm =190.3(2C), 154.3 (IC), 131.9, 125.1, 110.9 (6C, Ar), 77.3, 77.2, 77.0, 76.7 (1C), 40.0 (2C)

**MS:** m/z, 257 (M⁺); m/z, m/z, 247(-CO, H₂O); 243 (-CH₃); m/z, 215(-CO, -CH₃); m/z,148 (-C₁₇H₂₉N); m/z, 121(-C₆H₉O₂); m/z, 93 (C₈H₉O₂); 43 (N(CH₃)₂).

N-(4-(3-(2-oxocyclopentyl) prop-1-enyl phenyl) acetamide (III)

Yellow precipitate, M.P. =167 °C, (C₁₆H₁₇NO₃), yield = 80 %

**IR (KBr, cm⁻¹):** 3515(N-H) amide, 3115 (C-H) aromatic, 2983 (C-H) aliphatic, 1678 (C=O), 1635 (C=C), 1597 (C=O), 1640 amide (C=O)

**H-NMR** (400 MHz, CDCl₃) δ/ppm =9.76 (s, 1H, NH), 7.77 7.28 (m, 4H, ArH), 6.73 6.71 (m, 1H, ethylene).

**13C-NMR** (100 MHz): CDCl₃ δ=188.95 (IC), 143.3 (IC), 130.6, 128.9, 128.8, 128.7, 128.5, 128.4, 125.4 (6C, Ar), 77.3, 77.0, 76.7 (C, solvent), 26.5 (1C)

**MS:** m/z, 271 (M⁺); m/z, 257 (-CH₃); m/z, 194 (-NHCOCH₃, -H₂O); m/z, 161 (C₆H₇O₂); m/z; m/z, 83(C₆H₅O); m/z, 43 (COCH₃).

2-(3-(4-Hydroxyphenyl)acryloyl)cyclopentan-1-one (IV)

Red precipitate, M.P. = 200 °C (decomposition), (C₄H₁₄O₃), yield = 79 %

**IR (KBr):** 3345(OH), 3100 (C-H) aromatic, 2982 (C-H) aliphatic, 1610 (C=O), 1560 (C=C), 1654 (C=O)

**H-NMR** (400 MHz, CDCl₃) δ/ppm = 9.26 (s, 1H, OH), 8.56-8.36 (d, 2H), 7.76 -7.74 (d, 2H, ArH), 6.69-6.67 (m, 4H, ArH), 3.45 (s, 6H, cyclic), 2.58-2.56 (s, 6H, solvent), 1.67 (s, 1H)

**13C-NMR** (100 MHz): CDCl₃ δ=188.99 (IC), 130.6 (Ar-C), 113.6 (C, cyclic) 79.1 (1C), 40.3-38.8(C, solvent).

**MS:** m/z, 230 (M⁺); m/z, m/z, 189 (-CO, -CH₂); m/z, 165 (C₆H₇O₂ + H₂O); 112 (C₆H₈O₂); m/z, 83 (C₃H₇O₂).

**Anti-inflammatory activity**

α, β-unsaturated ketones derivatives showed significantly (p < 0.05) anti-inflammatory activity in dose dependent manner (Figure 4).

The antibacterial activity of chalcones derivatives and antibacterial agent cefuroxime against four pathogenic bacteria are shown in Figure 5.

**DISCUSSION**

The synthesis of α, β-unsaturated ketones is a single step process. The derivatives were synthesized under basic conditions as shown in Figure 2, according to Claisen-Schmidt condensation of 2-acetylcyclopentanone with an
aromatic aldehyde. The yield obtained was good. The products were collected and purified, and their structures were confirmed using UV-Visible, FTIR, $^1$H-NMR, $^{13}$C-NMR and mass spectral measurements.

Figure 7: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of compounds I – IV

The UV – Visible Spectra (Figure 3) showed that the functional group -C=C-CO had two types of absorbance i.e. $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$. In general, conjugation of -C=C- double bond with a carbonyl group led to increase in the intensity of $\pi\rightarrow\pi^*$ transition of the carbonyl group. The absorbance was found between 220 and 250 nm in simple enone -CH=CH-CO-. The $n\rightarrow\pi^*$ appeared at 320-380 nm because of conjugation of $\pi$ electrons of unsaturated double bond with the carbonyl group.

All the compounds gave the typical FTIR peaks which indicated the presence of different functional groups. Strong carbonyl group stretching vibration resulted in strong peaks at 1650 - 1670 cm$^{-1}$. Decreased carbonyl stretching vibration was due to the double bond combination. Double bond stretching was shown to peak in the 1580 - 1665 cm$^{-1}$ range. The aromatic ring unsaturation of $\pi$ electrons was shown in the range of 1500 - 1590 cm$^{-1}$.

The anti-inflammatory effects of the synthesized chalcones are shown in Figure 4. Compared with the standard drug, the synthesized compounds showed moderate anti-inflammatory properties. They all had a smaller effect on the percentage inhibition of granuloma tissue formation, relative to diclofenac. Similar results were obtained in the percentage inhibition of inflammation. However, compound IV exerted more anti-inflammatory effect than diclofenac, as revealed using t-test analysis for percentage edema inhibition. Indeed, compound IV generally produced the best anti-inflammatory effect among the chalcones. Its effect was comparable to that of the standard drug at the dose used, as shown in Figure 4.

The results of the antimicrobial effects of the synthesized compounds showed that when compared with cefuroxime (standard drug), the four compounds showed varying degrees of inhibition against the tested organisms i.e. two gram-positive bacteria (Staph. Aureus and Bas. Cereus) and two gram-negative bacteria (E. coli and P. aeroginosa). These results are shown in Figure 5.

A hydroxyl group on the phenyl ring enhances antibacterial effects [20]. The mechanism of the bactericidal action is thought to be due to disruption of intermolecular interactions. This may result in disruption of cellular membrane lipid bilayers, thereby impairing cellular permeability controls, leading to leakage of cellular contents [21]. Many chalcones are known to exhibit appreciable antimicrobial and

Table 2: Global chemical reactivity of chalcone compounds I, II, III and IV

| Compound | I     | II    | III   | IV    |
|----------|-------|-------|-------|-------|
| Total energy (kcal/mol) | -56762.0786 | -67753.4923 | -73819.4721 | -63538.7554 |
| Heat of formation (kcal/mol) | 44.320115 | 48.3724 | 89.23692 | 88.9020703 |
| Log P | 6.27 | 6.53 | 1.14 | 2.01 |
| Dipole moment (debye) | 1.026 | 5.128 | 3.88 | 3.817 |
| $E_{\text{HOMO}}$ (eV) | -9.440372 | -8.497168 | -9.017367 | -9.065188 |
| $E_{\text{LUMO}}$ (eV) | -0.7740081 | -0.6686261 | -0.973185 | -0.7302036 |
| $\Delta E$ (eV) | 8.6663639 | 7.8303059 | 8.044182 | 8.3349844 |
| $\eta$ (eV) | 4.33318195 | 3.91515265 | 4.022091 | 4.1674922 |
| $\mu$ (eV) | 5.10719005 | 4.5820153 | 4.995276 | 9.7953916 |
| $\omega$ (eV) | 3.00972 | 2.68121442 | 3.10195895 | 2.0837461 |

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antifungal properties due to the presence of α, β-unsaturated carbonyl groups [22].

The optimized geometries and 3D geometrical structures of compounds I, II, III and IV are shown in Figure 6. The distribution of the electronic density (electrostatic potential charges), related quantum chemical parameters, and dipole moments demonstrate that the compounds were polar molecules and soluble in polar solvents (Table 2, row 4). From log p values (indicating hydrophobicity properties), compound II had more lipophilic properties, while compound III showed more hydrophilic characteristics. The less the heat of formation of a compound, the more stable it is. Therefore, compound I was more stable than compound II, III or IV. Compound I had the highest HOMO-LUMO energy gap, indicating that it was the most stable and least reactive. These results are shown in Table 2, Figure 7.

Chemical hardness (η) is synonymous with a chemical system’s stability and reactivity. It estimates the compounds resistance to the changes in its electronic density distribution, or to transfer of electron charge. Depending on the approach of frontier molecular orbital, chemical hardness (η), is directly proportional to the energy gap between HOMO and LUMO. It is evaluated using the formula shown in Eq 4:

\[ \eta = -1/2 (E_{\text{HOMO}} - E_{\text{LUMO}}) \]  

Thus, the bigger the energy gap of the HOMO-LUMO, the harder and more stable (less reactive) the compound [23].

Table 2 shows the calculated chemical hardness (\( \eta \)) values for the four chalcone derivatives. Compound II had the lowest \( \eta \) value (3.91515265) and therefore it was the least stable of the four compounds. On the other hand, compound I was the hardest and most stable, with the highest value of \( \eta \) (4.33318195).

The electronic chemical potential (\( \mu \)) is described as the negative of a molecule's electronegativity [24]. The less the potential value of electronic chemical (\( \mu \)), the more stable the compound. On the other hand, the greater the electronic chemical potential, the less stable or more reactive the compound. Table 4 shows the calculated electronic chemical potential (\( \mu \)) values for the four studied compounds. It is clear that since compound II had the lowest \( \mu \) value (4.5820153 J/mol.), it was found to be the most stable, while the largest \( \mu \) (9.7953916 J/mol) compound IV was the least stable.

The electrophilicity parameter (\( \omega \)) was calculated using the electronic chemical potential (\( \mu \)) and the chemical hardness (\( \eta \)) according to Equation 5:

\[ \omega = \mu^2/2\eta \]  

In a chemical process, electrophilicity parameter (\( \omega \)) measures the ability of a species to accept electrons and therefore measures the stabilization in energy after a system accepts additional electronic charge.

The electrophilicity values (\( \omega \)) of the synthesized chalcones shown in Table 2. The values obtained were 3.00972 eV for compound I, 2.68121442 eV for compound II, 3.10195895 eV for compound III, and 2.0837461 eV for compound IV. Thus, with the lowest \( \omega \) value, compound IV was a good nucleophile, while compound III was the strongest electrophile, since it had the highest \( \omega \) value. These results suggest some sort of selectivity in the mechanistic chemistry of chalcone derivatives.

CONCLUSION

In the present work, new α, β-unsaturated ketone derivatives which contain cyclic moiety instead of aromatic group, were successfully prepared using conventional methods. Compound IV displays good antibacterial activity against Staph. aureus and E. coli while Compounds I, II and IV possesses good antibacterial properties against Bacil. cereus, and also exerted anti-inflammatory effects. Compound IV produced the best anti-inflammatory effect among the synthesized chalcones, with effect comparable to that of the standard drug.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.
Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. The idea behind this study came from the corresponding author who also did the experimental portion involving preparation of the chalcones. The second author worked on the diagnosis of all the synthesized compounds. The third author was involved in biological activity assays.

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