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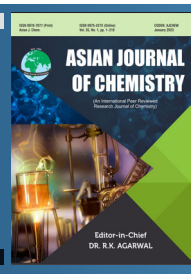

Antimicrobial and Antioxidant Study of Some Newly Synthesized Chalcones and Cyclohexenone Derivatives

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Chalcones and cyclohexenone derivatives obtained from various substituted aldehydes and substituted acetophenones are described. Chalcones were obtained by the Claisen-Schmidt condensation reaction of aldehydes with substituted acetophenones. Base catalyzed cyclocondensation of ethyl acetoacetate to chalcones under microwave irradiation leads to the formation of cyclohexenone derivatives. The prepared compounds are characterized by IR, ^{1}H NMR and ^{13}C NMR spectral methods. These are screened for their antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli, Aspergillus niger*, *Aspergillus flavus* and also, for their antioxidant properties.

Keywords: Chalcone, Microwave assisted synthesis, Cyclocondensation, Antimicrobial study, Antioxidant study.

INTRODUCTION

Natural chalcones and their synthetic derivatives have attracted great interest because of their many potential applications in scientific disciplines like synthetic and medicinal chemistry [1,2]. From a chemical point of view, these are valuable intermediates in organic synthesis and has the ability to act as activated unsaturated systems in conjugated addition reaction of carbanions in the presence of basic catalysis [3,4]. This type of reaction may be exploited with the view of obtaining highly functionalized cyclohexenone derivatives [5,6]. Chalcones are associated with impressive array of biological activities, including antimalarial, anti-inflammatory, anticancer, antiasthmatic, antibacterial, antihypertensive, tyrosine kinase inhibiting agents, antituberculars, antiparkinsons, CNS depressant and antihelmintics and also blood platelet anti-aggregating activity [7-15]. In addition of its biological importance, chalcones and its derivatives find wide range of applications in dyes [16] and cosmetic compositions [17] too.

Cyclohexenone derivatives of chalcones represent another class of cyclic compounds with interesting biological activities, among which its antimicrobial activity is well documented [18,19]. As a consequence cyclohexenones are very attractive target molecules in synthetic organic chemistry. The more common application of chalcone found in the synthesis of cyclohexenones, efficient precursor in the synthesis of benzisoxazoles, carbazole derivatives [20,21], indazoline [22] pyrazolone and isoxazolones [23]. Cyclohexenone derivatives are well known lead molecules for the treatment of inflammation and autoimmune diseases [24].

Chemical reactions can be accelerated and selectivity of the ensuing products can be obtained under microwave irradiation conditions [25]. This method offers several advantages over conventional heating, such as instantaneous and rapid heating, high temperature homogeneity and selective heating [26-28]. Microwave-assisted synthesis fulfils the promise of being a fast synthesis practice hence the use of the microwave heating technique has become prominent method in synthetic organic chemistry. Keeping in view the chemical and biological importance of the cyclohexenone derivatives of chalcones, the synthesis of cyclohexenone derivatives by choosing microwave technique in high yield is reported. The synthesized compounds are structurally elucidated and screened for *in vitro* antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger* and *Aspergillus flavus*. The promising results obtained prompted us to further screen them for antioxidant activity.

EXPERIMENTAL

All the chemicals and solvents were purchased from Merck and Sigma-Aldrich and used as received without further purification. Melting points were recorded on the melting point apparatus and are uncorrected. The purity of the compounds were confirmed by thin layer chromatography using Merck silica gel G 25-UV254 pre-coated aluminum plates in hexane:ethyl acetate (3:1) medium. IR spectra were recorded on a Thermoscientific Nicolet iS5 FTIR using ATR technique and iD7 ZnS diamond. The ^{1}H NMR was recorded in deuterated chloroform and DMSO on a Bruker (400 MHz) spectrometer using TMS as internal standard.

General procedure for the synthesis of chalcones (1a-e): Equimolar concentrations of substituted benzaldehydes and substituted acetophenones were dissolved in ethanol and then the reaction mixture was kept for stirring overnight at room temperature in the presence of catalytic amount of 10% NaOH. The progress of the reaction was monitored by TLC using ethylacetate and *n*-hexane (1:3) as solvents. The product obtained was recrystallized using ethanol and dried.

1-(4-Bromophenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (1a): Yield: 89%, m.p.: 94-96 ºC. IR (KBr, ν_{max}, cm^{-1}): 1654 (C=O), 1602 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.86 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 7.46 (d, 1H, H_b, J = 15.6 Hz), 8.02 (d, 1H, H_a, J = 15.6 Hz), 6.47-7.87 (m, 7H).

1-(3,4-Dichlorophenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (1b): Yield: 91%, m.p.: 97-99 ºC. IR (KBr, ν_{max}, cm^{-1}): 1657 (C=O), 1585 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.86 (s, 3H), 3.91 (s, 3H), 7.43 (d, 1H, H_b, J = 15.6 Hz), 6.47-8.0 (m, 8H, 7 aromatic protons and one doublet for 1H (H_a) merged together).

3-(4-Chlorophenyl)-1-(3,4-dichlorophenyl)prop-2-en-1-one (1c): Yield: 92%, m.p.: 117-119 ºC. IR (KBr, ν_{max}, cm^{-1}): 1650 (C=O), 1600 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.26 (d, 1H, H_b, J = 15.6 Hz), 7.77 (d, 1H, H_a, J = 15.6 Hz), δ 6.90-8.10 (m, 7H, Ar-H).

1-(4-Chlorophenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (1d): Yield: 91%, m.p.: 115-119 ºC. IR (KBr, ν_{max}, cm^{-1}): 1666 (C=O), 1576 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ7.73 (d, 1H, H_b, J = 16 Hz), δ 7.95 (d, 1H, H_a, J = 15.6 Hz), δ 3.85 (s, 3H, OCH_3), δ 3.91 (s, 3H, OCH_3), δ 6.62-8.14 (m, 7H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 188.00 (C=O), 55.8, 55.5 (aliphatic carbons), 98.26, 106.42, 115.79, 118.62, 128.81, 130.19, 136.68, 137.69, 139.25 (olefinic and aromatic carbons).

3-(2,6-Dichlorophenyl)-1-(3,4-dichlorophenyl)prop-2-en-1-one (1e): Yield: 94%, m.p.: 122-125 ºC. IR (KBr, ν_{max}, cm^{-1}): 1647 (C=O), 1589 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.79 (d, 1H, H_b, J = 16 Hz), 7.16-8.03 (m, 7H, 6 aromatic protons and one doublet for 1H (H_a) merged together).

General procedure for the microwave assisted synthesis of cyclohexenone derivatives (2a-e): A mixture of chalcones (0.01 mol) and ethylacetoaetate (0.01 mol) were dissolved in absolute alcohol and added 4 drops of 10% NaOH as the catalyst and subjected to microwave irradiation for 10-14 min (300 watt). After completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature and recrystallized from ethanol to get the desired product.

Ethyl 4-(4-bromophenyl)-6-(2,4-dimethoxyphenyl)-2-oxocyclohex-3-ene-1-carboxylate (2a): Yield: 92%, m.p.: 96-98 ºC. IR (KBr, ν_{max}, cm^{-1}): 3005, 2971 (CH_3,CH_2), 1726 (C=O ester), 1658 (C=O ketone), 1609 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.045 (t, 3H, J = 7.0 Hz), 2.92 (m, 1H, H_a), 2.96 (m, 1H, H_b), 3.79 (s, 3H. OCH_3), 3.81 (s, 3H. OCH_3), 3.83 (m, 1H, H_c), 4.04 (q, 2H, OCH_2, J = 7.0 Hz), 4.08 (d, 1H, CHCOOEt, J = 13.2 Hz), 6.45 (s, 1H, =CH-CO), 6.47-7.54 (m, 7H, Ar-H).

Ethyl 4-(3,4-dichlorophenyl)-6-(2,4-dimethoxyphenyl)-2-oxocyclohex-3-ene-1-carboxylate (2b): Yield: 84%, m.p.: 104-106 ºC. IR (KBr, ν_{max}, cm^{-1}): 2979, 2935 (CH_3, CH_2), 1727 (C=O ester), 1668 (C=O ketone), 1606 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.97 (t, 3H, J = 7.0 Hz), 3.0 (m, 1H, H_a), 2.86 (m, 1H, H_b), 3.72 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.83 (m, 1H, H_c), 3.92 (q, 2H, OCH_2, J = 7.0 Hz), 4.01 (d, 1H, CHCOOEt, J = 13.6 Hz), 6.36 (s, 1H, =CH-CO), 6.38-7.54 (m, 6H, Ar-H).

Ethyl 6-(4-chlorophenyl)- 4-(3,4-dichlorophenyl)-2-oxocyclohex-3-ene-1-carboxylate (2c): Yield: 82%, m.p.: 123-126 ºC. IR (KBr, ν_{max}, cm^{-1}): 2937, 2900 (CH_3, CH_2), 1734 (C=O ester), 1664 (C=O ketone), 1591 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.99 (t, 3H, J = 7.0 Hz), 2.96 (m, 1H, H_a), 2.81 (m, 1H, H_b), 3.62 (m, 1H, H_c), 3.90 (q, 2H, OCH_2, J = 7.0 Hz), 4.11 (d, 1H, CHCOOEt, J = 13.6 Hz), 6.64 (s, 1H, =CH-CO), 7.40-8.01 (m, 7H, Ar-H).

Ethyl 4-(4-chlorophenyl)-6-(2,4-dimethoxyphenyl)-2-oxocyclohex-3-ene-1-carboxylate (2d): Yield: 95%, m.p.: 128-131 ºC. IR (KBr, ν_{max}, cm^{-1}): 2928 (aliphatic CH), 1740 (C=O ester), 1658 (C=O ketone), 1616 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.04 (t, 3H, J = 7.2 Hz), 3.08 (m, 1H, H_a), 2.92 (m, 1H, H_c), 3.79 (s, 3H. OCH_3), 3.81 (s, 3H. OCH_3), 3.91-4.78 (m, 4H, H_b proton of cyclohexenone ring, ester OCH_2 proton, CHCOOEt proton), 6.45 (s, 1H, =CH-CO), 6.43-7.49 (m, 7H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.52 (keto C=O), 159.0 (ester C=O), 135.11- 121.00 (aromatic C's), 59.85-13.14 (aliphatic C's).

Ethyl 6-(2, 6-dichlorophenyl)-4-(3,4-dichlorophenyl)-2-oxocyclohex-3-ene-1-carboxylate (2e): Yield: 89%, m.p.: 136-138 ºC. IR (KBr, ν_{max}, cm^{-1}): 2979, 2917 (CH_3, CH_2), 1729 (C=O ester), 1668 (C=O ketone), 1606 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.97 (t, 3H, J = 7.2 Hz), 3.55 (m, 1H, H_a), 2.72 (m, 1H, H_b), 4.73 (m, 1H, H_c), 3.98 (q, 2H, OCH_2, J = 7.2 Hz), 3.98 (d, 1H, CHCOOEt, J = 13.6 Hz), 6.45 (s, 1H, =CH-CO), 7.08-7.56 (m, 6H, Ar-H).

Antimicrobial activity: The *in vitro* antibacterial and antifungal activities of newly synthesized compounds were carried out as per the reported method [29,30]. Newly synthesized chalcones and cyclohexenone derivatives were evaluated for antibacterial activity against Gram-positive *Staphylococcus aureus*, Gram-negative *Escherichia coli* and antifungal activity against *Aspergillus niger* and *Aspergillus flavus*. The concentration of tested compounds was 40 µg/mL against both bacterial and fungal strains. The standard drugs used for comparison of antibacterial and antifungal activities were ciprofloxacin and

fluconazole respectively. The zone of inhibition was compared with standard drug after 24 h of incubation at 37 ºC for antibacterial activity and 72 h at 25 ºC for antifungal activity.

Antioxidant activity: Antioxidant activity was measured by DPPH radical scavenging assay [31] to understand the free radical scavenging capacity of newly prepared compounds. A solution of DPPH in ethanol (1 mM) was prepared and this solution (1 mL) was added to sample solutions 1 mg/mL of distilled water. The above mixture was shaken vigorously and allowed to stand at room temperature for 20 min. At 517 nm, the absorbance was measured in a spectrophotometer. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The following equation was used to calculate the ability to scavenge the DPPH radical:

$$\text{DPPH scavenging effect (\%)} = \frac{A_0 - A_1}{A_0} \times 100$$

where, A_0 is the absorbance of the control and A_1 is the absorbance in the presence of the samples or standards. Each sample was evaluated at 1 mg/mL and all experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Newly synthesized chalcones, 1-(substituted phenyl)-3-(substituted phenyl)prop-2-en-1-one (**1a-e**) were obtained by the reaction between a substituted acetophenones and aldehydes by Claisen-Schmidt condensation. Base catalyzed cyclocondensation of ethyl acetoacetate resulted in the formation of cyclohexenone derivatives, ethyl 4-(substitutedphenyl)-6-(substituted phenyl)-2-oxocyclohex-3-ene-1- carboxylate (**2a-e**). Synthesis of target compounds (**2a-e**) by microwave assisted method resulted into high yield within 10-14 min as compared to conventional method which took 12 to 24 h [32]. The synthesis of chalcones and their cyclohexenone derivatives were carried out according to the reaction sequences depicted in **Scheme-I**. This cyclocondensation of ethylacetoacetate with chalcones generate two chiral carbon atoms and so formed diastereomeric cyclohexenones was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral analyses.

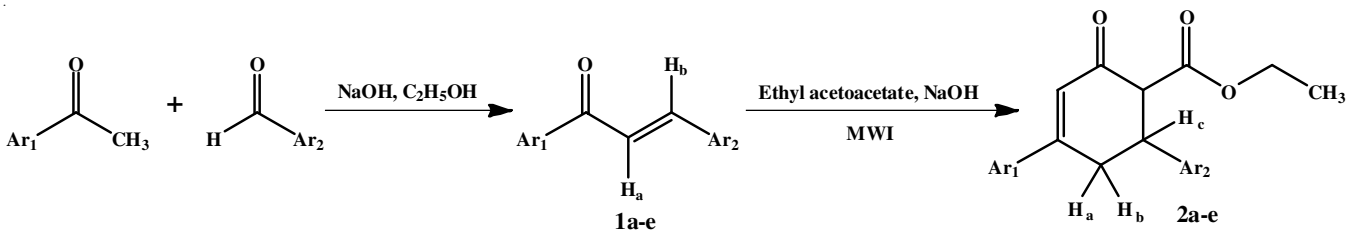
In IR spectrum of compound **1d**, a strong and sharp absorption band at 1666 cm^{-1} are seen, which confirmed the presence of C=O group. An absorption band at 1576 cm^{-1} confirms ethylenic group of chalcone. The presence of doublets at δ 7.95 ppm (J = 15.6 Hz) and δ 7.73 ppm (J = 16 Hz) for ethylenic protons conjugated to carbonyl group in the ^{1}H NMR spectrum of chalcone **1d** confirmed the formation of *E*-isomer. In the ^{13}C NMR spectrum of compound **1d**, the signals in the region δ 188.0 ppm (for C=O carbon), δ 55.5-55.8 ppm (for OCH_3 carbons) and δ 98.26, 106.42, 115.79, 118.62, 128.81, 130.19, 136.68, 137.69, 139.25 ppm (olefinic and aromatic carbons) were observed.

In IR spectrum of cyclohexenone derivative (**2d**), the C=O stretching was at 1658 cm^{-1}, which was due to the carbonyl group conjugated with a C=C and another sharp, strong absorption band at 1740 cm^{-1} revealed the presence of ester carbonyl group. The ^{1}H NMR spectrum of cyclohexenone derivative **2d**, confirmed the formation of desired product. The CH_3 protons of the ethyl ester group resonated as triplet at δ 1.04 ppm with J = 7.2 Hz. Two multiplets at δ 2.92 ppm and δ 3.08 ppm could be attributed to the protons (H_c and H_a) of cyclohexenone ring. Signals for the H_b proton of cyclohexenone ring, CHCOOEt proton and ester OCH_2 protons merged together and appeared as a multiplet in the range δ 3.91-4.78 ppm. A singlet for vinylic proton (=CH-CO) of cyclohexenone ring appeared at δ 6.45 ppm. In the ^{13}C NMR spectra o fcompound **2d**, presence of keto carbonyl at 169.52 ppm and ester carbonyl at 159.00 ppm confirmed the formation of desired product. Similarly, the structures of all newly synthesized compounds were confirmed by spectral analysis data.

Antimicrobial activity: The antimicrobial activity of the synthesized derivatives were tested against Gram-positive *S. aureus*, Gram-negative *E. coli* and two fungal strains *A. niger* and *A. flavus* under identical conditions. The ciprofloxacin is used as standard antibiotics against bacterial strains and fluconazole against fungal strains for comparison purpose. Results obtained for *in vitro* antibacterial and antifungal activity are summarized in Table-1.

All of the compounds exhibited activity however some did not exhibit similar bioactivity against all the tested strains. Among the tested compounds, **1a**, **1b**, **1d**, **2a** and **2d** exhibited inhibition against *S. aureus* as that of the standard ciprofloxacin with zone of inhibition 22 mm at MIC 20 µg/mL. Other compounds exhibited moderate activity against *S. aureus.* Compounds **1a** and **2a** were active against the bacteria *Escherichia coli* with zone of inhibition 23 mm at MIC 20 µg/mL, which is comparable to that of the standard drug.

The antifungal activity studies showed that compounds **1a**, **1d**, **2a**, **2d** and **2e** were active against *A. niger* whereas compounds **2a** and **2b** were active against *A. flavus* with zone of inhibition 22 mm at MIC 20 µg/mL. All other compounds exhibited moderate activity against the tested fungal strains. The cyclohexenone derivative **2a** exhibited excellent inhibition as compared with standard antibiotics against all tested strains, which may be due to the presence of electron releasing groups like bromo, methoxy and ester group in the aromatic ring, which enhances the antimicrobial activity.



Scheme-I: Synthesis of chalcones (**1a-e**) and its cyclohexenone derivatives (**2a-e**) [for Ar_1 and Ar_2 please refer Table-1]

TABLE-1
ANTIMICROBIAL ACTIVITY AND DPPH SCAVENGING DATA OF NEWLY SYNTHESIZED COMPOUNDS (**1a-e** AND **2a-e**)

Compound	Ar_1	Ar_2	m.f.	Zone of inhibition (mm)				DPPH scavenging assay (%)
				S. aureus	*E. coli*	*A. niger*	*A. flavus*	
1a	4-Bromophenyl	2,4-Dimethoxyphenyl	$C_{17}H_{15}O_3Br$	20 (22)	20 (23)	20 (22)	20 (21)	74.13±2.31
1b	3,4-Dichlorophenyl	2,4-Dimethoxyphenyl	$C_{17}H_{14}O_3Cl_2$	20 (22)	20 (18)	30 (21)	30 (18)	54.21±1.12
1c	3,4-Dichlorophenyl	4-Chlorophenyl	$C_{15}H_9OCl_3$	30 (18)	40 (20)	20 (21)	20 (18)	36.77±2.25
1d	4-Chlorophenyl	2,4-Dimethoxyphenyl	$C_{17}H_{15}O_3Cl$	20 (22)	20 (20)	20 (22)	20 (21)	51.16±1.32
1e	3,4-Dichlorophenyl	2,6-Dichlorophenyl	$C_{17}H_9OCl_4$	30 (16)	40 (18)	20 (21)	30 (18)	28.43±3.43
2a	4-Bromophenyl	2,4-Dimethoxyphenyl	$C_{23}H_{23}O_5Br$	20 (22)	20 (23)	20 (22)	20 (22)	82.03±1.64
2b	3,4-Dichlorophenyl	2,4-Dimethoxyphenyl	$C_{23}H_{22}O_5Cl_2$	30 (19)	20 (22)	20 (19)	20 (22)	49.21±1.26
2c	3,4-Dichlorophenyl	4-Chlorophenyl	$C_{21}H_{17}O_3Cl_3$	20 (20)	20 (21)	20 (18)	20 (21)	39.56±2.05
2d	4-Chlorophenyl	2,4-Dimethoxyphenyl	$C_{18}H_{23}O_5Cl$	20 (22)	20 (22)	20 (22)	20 (21)	58.34±1.55
2e	3,4-Dichlorophenyl	2,6-Dichlorophenyl	$C_{16}H_{15}O_3Cl_4$	20 (21)	20 (21)	20 (22)	20 (21)	37.21±1.21
Ciprofloxacin	–	–	–	20 (22)	20 (23)	–	–	–
Fluconazole	–	–	–	–	–	20 (22)	20 (22)	–
Glutathione	–	–	–	–	–	–	–	92.03±1.05

Antioxidant activity: Among the synthesized compounds, compound **2a** with bromo and methoxy substitution, exhibited good radical scavenging capacity whereas compounds **1c**, **1e**, **2c** and **2e** showed low activity, which may be due to the presence of chloro substitution in the aromatic ring, while other compounds showed the moderate scavenging capacity (Table-1). The variation in the scavenging capacity may be attributed to the presence of various substituents.

Conclusion

The study reports the efficient synthesis of chalcones and its base catalyzed cyclization to cyclohexenone derivatives. These cyclohexenone derivatives can be used as useful intermediates in the synthesis of various heterocyclic compounds. Also, newly synthesized compounds showed the antimicrobial activity against all the tested strains. Among all, compound **2a** showed good inhibition against all tested microorganisms. The compound **2a** with bromo and methoxy substitution, exhibited good radical scavenging capacity whereas compounds **1b**, **1d**, **2d** shown moderate radical scavenging capacity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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