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Synthesis, characterization and antimicrobial evaluation of a series of chalcone derivatives

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ABSTRACT

To synthesis a series of six chalcones that resemble those occur in nature and to evaluate the in vitro antimicrobial activity of these chalcones against Gram positive and Gram negative bacteria and fungi. Chalcones were synthesized from acetophenone and substituted benzaldehydes via the Claisen-Schmidt condensation and utilizing a green chemistry protocol using sodium carbonate as a catalyst in pure water with excellent yields. The antimicrobial evaluation was performed by filter paper disc plate method against selected microorganisms and using amoxicillin and fluconazole as standards. The structure of the synthesized derivatives has been characterized by elemental microanalysis (CHN), FTIR Spectroscopy, and other physicochemical properties. The antimicrobial evaluation of these synthesized chalcones revealed a promised antimicrobial activity. The ease of the synthesis and purification of these chalcones in addition to the observed high yields make this green protocol the most convenient, operative and environmentally friendly protocol for the synthesis of chalcones by the Claisen-Schmidt condensation. Chalcone derivatives have an excellent promise for further development as commercial antimicrobial agents.

Keywords: Chalcones; Green chemistry; Chalcone synthesis; Antibacterial activity; Antifungal activity.

INTRODUCTION

The development of microbial resistance in all its forms in addition to the fumbling and incompetence shown by some antibiotic families has become one of the problems that encouraged the researchers to develop new and safe compounds which are active against multidrug-resistant pathogens.

Chalcones are derived from the common structure: 1,3-diphenyl-2-propen-1-one, where they are considered to be precursors of a very large and widespread group of plant constituents known collectively as the flavonoids, where they participate in the defense strategies acting as antioxidants, antifungal and antimicrobial agents. As a result, the flavonoids have a great therapeutic potential ideal for the treatment of different diseases.

Chalcones being natural or synthetic are known to display a remarkable spectrum of biological activities such as antibacterial [1-4], anti-inflammatory, analgesic [5, 6], antioxidant [7], and other activities. They are also well known as valuable intermediates in organic synthesis of many heterocycles that exhibit a multitude of biological activities [8].

The antimicrobial activity of chalcones is being increasingly documented. Many research groups were concerned with either isolated or synthesized chalcones that possess antimicrobial activity [1, 3, and 4]. The presence of a reactive Enone moiety (α,β-unsaturated ketone) in chalcones was found to undergo conjugate addition with a nucleophilic group like a thiol group in an essential protein, thus partly contributing for their antimicrobial activity, which may be altered depending on the type and position of the substituents on the aromatic rings present in chalcones [9].

The Claisen-Schmidt condensation appeared to be the most appealing one when it comes to the condensation of aryl ketones with aryl aldehydes in the presence of suitable condensing agents and accordingly a variety of methods are available for the synthesis of chalcones. Literature review showed that the usage of sodium carbonate in pure water as a catalyst for the synthesis of chalcones was accompanied with an excellent outcome (percent yields) in a short span of time without the formation of any side product. Therefore this method can be considered as the most convenient, effective and environmentally friendly protocol [10].

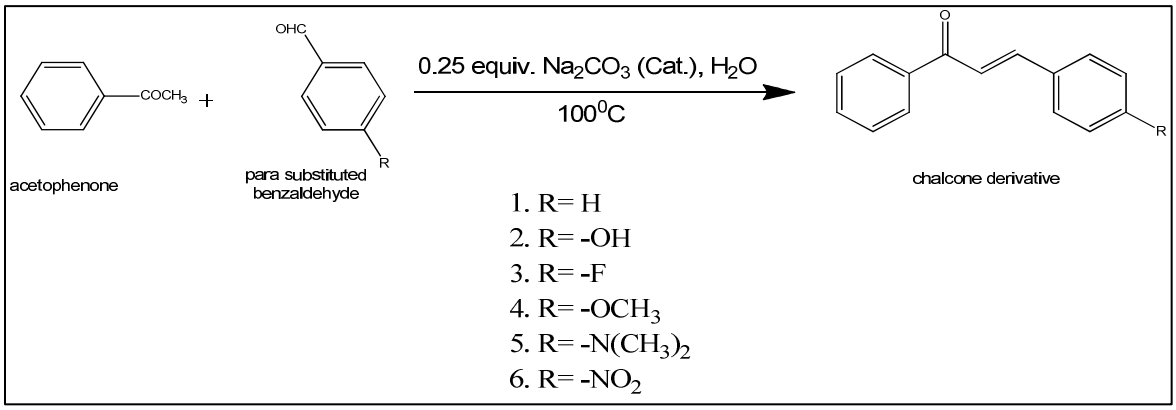
MATERIALS AND METHODS

Acetophenone, benzaldehyde, p-dimethylaminobenzaldehyde, p-fluorobenzaldehyde, p-methoxybenzaldehyde, and p-nitrobenzaldehyde were purchased from Himedia (India), and the quality of all these chemicals together with the other ones used throughout the study and obtained from standard commercial sources were of analar grade and used without further purification. The melting points were determined by the open capillary method using Thomas hoover (England) and were used uncorrected. Cooling of reactions when needed was done using a Julabo chiller VC (F30) (GMBH, Germany). Infra-red spectra were recorded in KBr disc on Shimadzu FTIR 8400 spectrophotometer (Japan), at the College of Pharmacy, University of Al-Kufa. Elemental microanalysis was performed at the Jordanian University using CHN Elemental Analyzer (Euro-vector EA3000A, Italy). The progress of the reaction was monitored by ascending thin layer chromatography which was run on Kieslgel GF_{254} (60) aluminum plates (E. Merck, Germany), which was used as well to check the purity of the product. The synthesized compound was revealed either by derivatization or reactivity toward iodine vapor or by irradiation with UV_{254} light. Chromatograms were eluted using petroleum spirit (40-60): ethyl acetate (70:30) solvent system.

The antimicrobial evaluation was performed at the Department of biology, College of Science, University of Baghdad.

Chemical synthesis of the chalcone derivatives (1-6) [10]
The synthetic method of the intended chalcones had followed ref. 10 with few minor alterations.

To an aqueous suspension of the acetophenone [10 mmol/1.16 ml] and benzaldehyde [10 mmol/1.01 ml] or one of the selected benzaldehydes (10 mmol): p-hydroxybenzaldehyde (1.22 gm), p-flourobenzaldehyde (1.07 ml), p-methoxybenzaldehyde (1.21 ml), p-nitrobenzaldehyde (1.51 gm), or p-dimethylaminobenzaldehyde (1.49 gm), in 15 ml water which was kept vigorously stirred in a preheated oil bath, a solution containing [0.25 mmol/0.265 gm] sodium carbonate in 5 ml water was added to the reaction mixture. After completion of the addition of Na_2CO_3, the reaction mixture was refluxed for (4 hours) at (100^oC) with continuous stirring on a magnetic stirrer. The reaction was followed by TLC and when completed the reaction mixture was cooled to room temperature. The solid product was collected by Buchner filtration, washed successively with distilled water (2×30ml), and cold absolute ethanol (2×10ml) and allowed to dry to afford the corresponding chalcone derivative (Table 1 and 2) without further purification and according to the following scheme:



Synthetic scheme of the chalcone derivatives (1-6)

Antimicrobial activity
The synthesized compounds (1-6) were screened for their *in vitro* antimicrobial activity against some selected microorganisms, where the antibacterial activity was evaluated against two gram positive bacteria *staphylococcus aureus* and *Bacillus* cereus and two gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*, and the antifungal activity against *Candida albicans* by measuring the zone of inhibition in mm. The antimicrobial activity

was performed by filter paper disc plate method at concentration 50, 100, 500 and 1000 µg/mL and reported in table 3 and 4. Muller Hinton agar & Sabouroud Dextrose agar were employed as culture medium and DMSO was used as solvent control for antimicrobial activity. Amoxicillin and Fluconazole were used as chemotherapeutic standards for the antibacterial and antifungal activity evaluations respectively.

RESULTS AND DISCUSSION

The present study has revealed that the employed green chemistry was a powerful tool that can be utilized to design and synthesize chalcones in pure water catalyzed by sodium carbonate and to afford α,β-unsaturated ketones in high yields. This method does not require the use of any organic solvent and the products were isolated in practically pure form simply by filtration of the final aqueous reaction mixture after cooling to room temperature.

The structures of the synthesized compounds were confirmed by using IR, elemental microanalysis (CHN), and other physicochemical parameters (Tables 1 and 2). The synthesized chalcone derivatives (1-6) showed several characteristic sharp bands in the IR region, where the bands in the range between 1635-1660 cm-1 indicated the appearance of the carbonyl C=O group of the formed ketone, which was conjugated to both the aromatic and the alkene systems. The elemental microanalysis revealed good agreement with the calculated percentages. The percent deviations of the observed/calculated values were found to be within the limits of accurate analysis (Table 1).

The antimicrobial evaluation revealed that the synthesized para substituted chalcones at the ring B possess a moderate to good potency in comparison to the standard drugs (Table 3, 4, and 5).

Table 1: Physicochemical characterization data for the synthesized compounds

Sym.	*Molecular Formula*	*Molecular Weight*	*% Yield*	*Melting point °C*	R_f	*Elemental analysis found (calculated)%*		
						C	*H*	*N*
1	$C_{15}H_{12}O$	208	70	55-57	0.6	86.51 85.34	5.81 5.88	-
2	$C_{15}H_{12}O_2$	224	88	184-186	0.45	80.34 81.243	5.39 5.381	-
3	$C_{15}H_{11}FO$	226	91	79-80	0.61	79.63 78.558	4.90 4.803	-
4	$C_{16}H_{14}O_2$	238	83	78-80	0.55	80.65 81.581	5.92 5.934	-
5	$C_{17}H_{17}NO$	251	72	250-252	0.57	81.24 80.119	6.82 6.720	5.57 5.483
6	$C_{16}H_{15}NO_4$	253	60	159-161	0.48	71.14 72.295	4.38 4.396	5.53 5.520

Table 2: IR spectral data of the synthesized compounds

Sym.	*Chemical Name*	*Characteristics IR spectral bands (KBr) v cm^{-1} with its Interpretation*
1	(E)-3-(phenyl)-1-(phenyl)prop-2-en-1-one	1665 (C=O), 1604 (C=C) trans alkene
2	(E)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one	3234 (-OH), 1649 (C=O), 1599 (C=C) trans alkene
3	(E)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one	1646 (C=O), 1609 (C=C) trans alkene, 1160 (C-F)
4	(E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one	2940, 2860 (C-H) asym. and sym. stretching vibration of -CH_3 group, 1645 (C=O), 1605 (C=C) trans alkene, 1253 (C-O-C) ether
5	(E)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one	3301 (C-N), 2970, 2812 (C-H) asym. and sym. stretching vibration of -CH3 group, 1635 (C=O), 1605 (C=C) trans alkene, 1348 aromatic (C-N) stretching vibration
6	(E)-3-(4-nitrophenyl)-1-phenyl-2-propen-1-one	1650 (C=O), 1610 (C=C) trans alkene, 1515 (N-O) asym. Stretching, 1335 (N-O) sym. Stretching

Table 3: The antibacterial activity of the chalcone derivatives aginst gram positive bacteria

Sym.	*Zone of inhibition (in mm)*							
	staphylococcus aureus				*Bacillus cereus*			
	50 µg	100 µg	500 µg	1000 µg	50 µg	100 µg	500 µg	1000 µg
1	-	9	10	11	-	-	15	22
2	16	21	21	35	18	20	22	30
3	16	17	18	35	15	15	18	19
4	-	15	17	18	-	-	16	20
5	-	10	13	14	5	10	12	13
6	-	-	12	15	13	14	15	15
Amoxicillin	15	15	20	25	14	15	17	17
Control (DMSO)	-	-	-	-	-	-	-	-

Table 4: The antibacterial activity of the chalcone derivatives aginst gram negative bacteria

Sym.	Zone of inhibition (in mm)							
	Escherichia coli				*Pseudomonas aeruginosa*			
	50 µg	100 µg	500 µg	1000 µg	50 µg	100 µg	500 µg	1000 µg
1	-	-	12	15	5	6	7	10
2	22	25	25	35	-	-	20	22
3	16	25	25	30	-	-	20	23
4	-	-	17	36	-	-	14	20
5	-	-	15	20	-	-	-	22
6	13	15	16	20	-	-	-	18
Amoxicillin	17	20	26	40	15	21	24	40
Control (DMSO)	-	-	-	-	-	-	-	-

Table 5: The antifungal activity of the chalcone derivatives

Comp.	Zone of inhibition (in mm)			
	Candida albicans			
	50 µg	100 µg	500 µg	1000 µg
1	-	10	13	15
2	-	11	11	12
3	-	14	14	15
4	-	11	15	16
5	-	-	-	15
6	-	16	18	25
Flucanazole	-	15	17	20
Control (DMSO)	-	-	-	-

CONCLUSION

The obtained results proved that the synthesized chalcones analogues have moderate antimicrobial effects including that against *Staphylococcus aureus*. The results, based on the potentially active chalcone skeleton, have pointed out the importance of the positions of the electron releasing groups (such as the methoxy and hydroxy groups or compounds 2 and 4) in the B ring in obtaining a better antibacterial activity than others when compared with the reference standard amoxicillin at both 0.5 ml (500 µg) and 1 ml (1000 µg) concentration levels. Fungicidal screening data revealed that chalcone having a pharmacophore such as a nitro group has exhibited more antifungal activity than other chalcones when compared with the reference standard fluconazole at both 0.1 ml (100 µg), 0.5 ml (500 µg), and 1 ml (1000 µg) concentration levels.

These results suggest that the chalcone derivatives can be an excellent template for designing and further development as commercial antimicrobial agents. Further experiments are needed to elucidate their mechanism of action. An interesting structure activity correlation was observed when discussing the antimicrobial findings in that electron-donating groups tended to weaken the antifungal activity, and electron-withdrawing groups increase the potency.

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