A Synthesis of Chalcones and Study of their Antimicrobial Activities

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ABSTRACT

The term Chalcones is used to describe compounds with the 1, 3 – diphenylprop-2-en-1-one framework. Chalcones are natural substances found in a number of plantsor synthetically prepared. These compounds have special interest due to their use as starting material, intermediates in the biosynthesis of flavonoids and in the synthesis of number of biologically active heterocyclic compounds. Some of these chalcones exhibit anti-cancer properties, cytotoxicity, anti-inflammatory, analgesic and also antipyretic properties. Many chalcones are potential antibacterial, antifungal and anti-ulcer agents. Besides biological activity certain chalcones have ability to block voltage-dependent potassium channels. Introduction of various substituted heterocyclic nucleus instead of aryl ring is also a subject of interest because it leads to SAR conclusion which helps us to synthesize pharmacologically active chalcones. This finding explains the significant interest of chemists, biochemists, and pharmacist in this particular group of compounds. In this article we synthesized the some chloro and nitro substituted chalcones and characterized them by using spectroscopic methods then products are screened for their antimicrobial properties. Most of the tested compounds exhibited significant antimicrobial activities.

Keywords: Chalcones, Flavonoids, Synthesis, Antibacterial, Antifungal.

INTRODUCTION:

The organic compound containing chalcone (1,3-diaryl-2-propen-1-ones) has wide application in medicinal chemistry and which has been possess wide spectrum of biological activities, including antibacterial, antifungal, anti-inflammatory, antitumor, antihypertensive [4], antifeedant [5], antioxidant [6]. Chalcones are also precursors in the synthesis of many biologically important heterocycles such as benzothiazepines [7], as pyrazolines [8], 1,4-diketones [9]. Due to their wide spectrum biological activity chalcones used as starting materials in the synthesis of a series of heterocyclic compound like isoxazoles, quinolinones, thiadiazines, benzofuranones and flavones [10, 11].Their simple structure and ease of preparation make chalcones as an attractive scaffold for structure-activity relationship (SAR) and a wide number of substituted chalcones have been synthesized to evaluate the effect of various functional groups on biological activity [15].

METHODOLOGY:

Completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapors for detection, IR spectra were recorded in KBr on a Shimadzu spectrometer (Japan). 1H NMR spectra were recorded in DMSO-*d6* with an Advance spectrometer 300-MHz frequency using TMS as an internal standard. Mass spectra were recorded on an EI-Shimadzu QP 2010 PLUS GC-MS system (Shimadzu, Japan). Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedure for the synthesis some substituted 1,3-diarylprop-2-en-1-one:

An equimolar mixture of substituted acetophenone **1** (1 mmol), aromatic aldehyde **2** (1 mmol) in piperidine (2-4drops) was stirred in 2-methyl propanol (10 mL) at 60-80°C for 45-50 min. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100 mL). The product which separated out was filtered and dried which on further recrystallized from acetic acid or ethanol.

Spectroscopic data of synthesized derivatives:

(3a):IR (cm^{-1},KBr): 3130 (-OH), 1690 (>C=O), 1585(>C=C<),690 (-C-Cl). ^{1}H NMR (DMSO-*d6*), δ7.12-8.10 (m, 10H, Ar-H, -CH=CH-), 12.85(s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 258 [M+], 260[M+2] Ana. Calcd for $C_{15}H_{11}ClO_2$C, 67.40; H, 4.42; %. Found: C, 68.41; H, 4.13;

(3c):IR (cm^{-1},KBr): 3163 (-OH), 1697 (>C=O), 1595(>C=C<),712 (-C-Cl). ^{1}H NMR (DMSO-*d6*), δ7.02-8.02 (m, 10H, Ar-H, -CH=CH-), 12.76 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 258 [M+], 260[M+2] Ana.Calcd for $C_{15}H_{11}ClO_2$ C, 69.60; H, 4.25; %. Found: C, 69.49; H, 4.10;

(3e):IR (cm^{-1},KBr): 3248 (-OH), 1689 (>C=O), 1595(>C=C<), ^{1}H NMR (DMSO-*d6*), δ6.98-8.24 (m, 10H, Ar-H, -CH=CH-), δ 12.58 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 269 [M+], Ana. Calcd for $C_{15}H_{11}NO_4$ C, 66.91; H, 4.12; N, 5,20 %. Found: C, 66.78; H, 4.02, N, 5.04%.

Antimicrobial Activity:

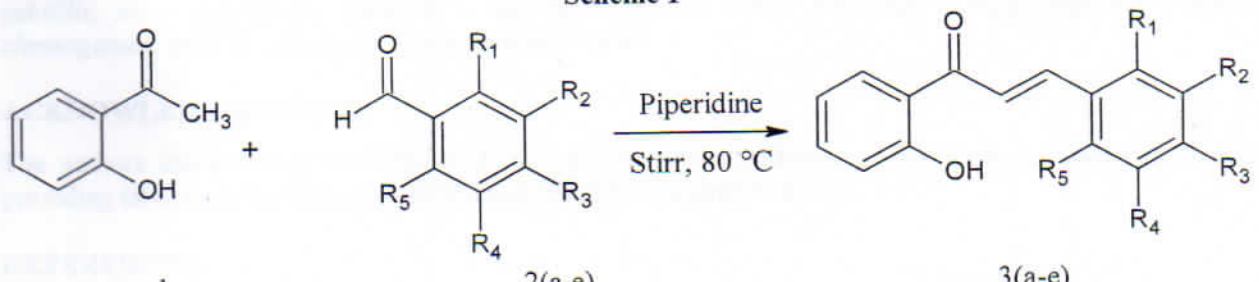
The antimicrobial activities of the synthesized compounds 3 (a-e) were determined by agar diffusion method.The compounds were evaluated for antibacterial activity against bacteria *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtillis*. The culture strains of bacteria were maintained on a nutrient agar slant at 37 ± 2°C for 24–48 hrs. Antifungal activity was studied against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, *Fusarium moneliforme*. The results were compared with penicillin and nystatin. All the culture strains of fungi were maintained on a potato dextrose agar (PDA) slant at 27 ± 2 °C for 24–28 h, until sporulation. Spores were transferred into 5 mL of sterile distilled water containing 1% Tween-80 (to suspend the spores properly). The spores were counted with a haemocytometer (106 CFU mL–1). Sterile PDA plates containing 2% agar were prepared; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27 ± 2°C for 12 h. After incubation a hole was made using a sterile cork borer and each agar well was filled with 0.1 mL chalcone solution of 50, 100 and 250 mg mL–1 separately to get the minimum inhibitory concentration (*MIC*) value of chalcones. Dimethyl sulphoxide (DMSO) was used as a solvent for chalcones and as well as a control, while distilled water used as solvent for standard drugs. The plates were kept in refrigerator for 20 minutes for diffusion and then incubated at 27 ± 2 °C for 24–28 h in an incubator. After incubation, the zone of inhibition of compounds was measured in mm and standard and minimum inhibitory concentrations *MICs*) were noted. The results of antimicrobial studies are given in Table 2 was measured in mm standard and minimum inhibitory concentrations (*MICs*) were noted.

RESULTS AND DISCUSSION:

Synthesis:

The Claisen-Schmidt condensation is an important C-C bond formation for the synthesis of 1,3-diaryl-2-propen-1-ones (chalcones). It is generally carried out by the use of base such as piperidine in polar solvents (2-Methyl propanol).Physico-chemical data of synthesized chalcone derivatives 3(a-e) are shown in table-1.

Scheme 1



1 2(a-e) 3(a-e)

IR spectra of chalcones showed characteristic bands at 1680–1698 cm^{-1}due to >C=O stretching vibration. Lowering of normal >C=O frequency was observed due to the presence of conjugated -C=C- in chalcones. 1H NMR spectra of the compounds showed characteristic doublet signals at δ 7.3 and 7.8 ppm due to α,β alkene protons respectively. However, these doublets coalesced with aromatic protons. The phenolic proton (2-OH) was observed as a singlet at δ 11–13.0 ppm due to hydrogen bonding with the adjacent carbonyl group while other aromatic and aliphatic protons were found at expected regions.

Table 1: Physico-chemical data of synthesized chalcone derivatives 3(a-e)

Sr. No.	R_1	R_2	R_3	R_4	R_5	Yield(%)	M.P(^{0}C)
3a	H	H	H	H	Cl	87	168
3b	H	H	H	Cl	H	89	156
3c	H	H	Cl	H	H	86	154
3d	H	H	H	H	NO_2	90	190
3e	H	H	NO_2	H	H	92	154

Antimicrobial Data:

All the synthesized compounds were tested for their *in vitro* antimicrobial activity. The results are given in Table 2. Compounds 3b, 3d and 3e showed good activity against all tested bacteria at concentration of 50 mg mL–1. Compound 3d showed a maximum zone of inhibition (20 mm) against *B.subtillis* compared to penicillin. Compounds 3b and 3d showed an effective zone of inhibition (18–20 mm) against *S. aureus* in comparison with the standard. Compounds 3a and 3c were found to be less active against the tested bacterial strains (*MIC* = 100 mg mL^{-1}). Antifungal screening data showed that most of the compounds were active against all fungi. Compounds 3b, 3d and 3e showed effective activity against all fungal strains at *MIC* of 50 mg mL–1. When structure and activity relationships (SAR) are investigated, we can inform from the results that halogen is responsible for antibacterial and antifungal activity.

Table 2: Antibacterial activity of synthesized compounds

Comp-ound	Zone of inhibition, mm (MIC µg/mL) Value							
	Bacteria				Fungi			
	Ec	St	Sa	Bs	An	Af	Pc	Fm
3a	12(100)	---	15(100)	13(100)	11(100)	13(100)	12(100)	14(100)
3b	15(50)	18(50)	19(50)	19(50)	18(50)	20(50)	18(50)	15(50)
3c	10(100)	12(100)	---	14(100)	9(100)	13(100)	---	16(100)
3d	17(50)	16(50)	19(50)	20(50)	18(50)	19(50)	18(50)	19(50)
3e	17(50)	18(50)	14(50)	16(50)	16(50)	18(50)	16(50)	16(50)
Penicillin	22(50)	22(50)	24(50)	22(50)	NA	NA	NA	NA
Nystatin	NA	NA	NA	NA	20(50)	22(50)	24(50)	24(50)

Solvents: DMSO, water :*Ec –Escherichia coli, St –Salmonella typhi*, Sa- *Staphylococcus aureus, Bs –Bacillus subtillis, An – Aspergillus niger, Af – Aspergillus flavus, Fm – Fusarium moneliforme, Pc – Penicillium chrysogenum,* MIC ≥ 100 µg mL^{-1}, NA –not applicable.

ACKNOWLEDGMENTS:

The authors are sincerely thankful to Principal, Loknete Vyankatrao Hiray College,Panchvati Nashik for providing laboratory facilities and IICT Hyderabad for spectral analysis.

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