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SYNTHESIS OF SOME CHALCONE DERIVATIVES AND SCREENING OF THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT: In present work, we synthesized different chalcones by the use of Claisen-Schmidt condensation reaction. Substituted acetophenones and different aromatic aldehydes were grinded mechanically by using morter and pestle in alkaline medium. Reaction was monitored by TLC and synthesized products were characterized by IR, ^{1}H-NMR, MASS spectroscopic methods and further screened for their antimicrobial activity.

KEYWORDS: Chalcones, Claisen-Schmidt Reaction, Substituted Aromatic Aldehydes, Substituted Acetophenones etc.

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1.INTRODUCTION

There is growing interest in the synthesis of different heterocyclic compounds with pharmacological potential[1-5]. Chalcones are the important building blocks in the synthesis of variety of such heterocyclic compounds[6-8]. Also they constitute an important class of bioactive natural products[9-11]. Chemically, they consist of open chain flavonoids in which the two aromatic rings are joined by a three carbon α-β unsaturated carbonyl system. The presence of reactive α-β unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity[12-14]. In recent years a variety of chalcones have been reviewed for their cytotoxic, anticancer, antiviral, insecticidal and enzyme inhibitory properties[15,16]. A number of chalcones having hydroxyl, alkoxy groups in different position have been reported to possess antibacterial[17-20], antiulcer[21], antifungal[22], antioxidant[23], antimalarial[24,25] and antidiabetic[26] activities.

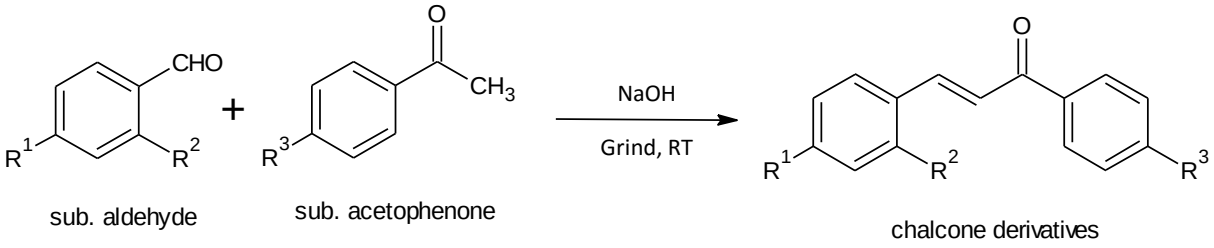
Library of such biological activities of chalcone derivatives motivated us to synthesize different chalcones derivatives.

2. MATERIALS AND METHODS

Melting points were determined with Melting point apparatus using open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^1H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker spectrometer at 400 MHz and their chemical shifts are recorded in δ (parts per million) unit. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Purity of the compounds was checked by TLC on silica-G plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber.

Experimental Procedure

Chalcones were synthesized by base catalyzed Claisen-Schmidt condensation reaction of substituted acetophenones and substituted aromatic aldehydes by grinding method. A mixture of aromatic aldehyde (1 mmol) and acetophenone (1 mmol) were taken in clean mortar. A small pellete of sodium hydroxide added to above mixture and reaction mixture was grinded mechanically at room temperature with the help of pestle for about half an hour. The progress of reaction was monitored by TLC. Then, the reaction mixture in mortar was covered with filter paper and kept overnight. Then product formed was poured in water taken in beaker, the washings of mortar were collected in same beaker. The excess of alkali was neuralised by 1:1 HCl and the solid obtained was filtered, washed with water, dried and recrystalized from ethanol.



Scheme 1

Synthesis of (E)-3-(4-ethoxy-phenyl)-1-(4-methoxy-phenyl)-propenone [1a]

p-Methoxyacetophenone 1.50 g (1 mmol) and p-ethoxybenzeldehyde 2.82 g (1 mmol) were grinded along with sodium hydroxide as in general procedure to give 1a. The excess of alkali was neuralised by 1:1 HCl and the solid obtained was filtered, washed with water, dried and recrystalized from ethanol to get Yield 86% of [1a].

Mol. Formula: $C_{18}H_{18}O_3$, Mol.Wt: 282.33, M.P. 116-118^{0}C, IR (KBr): 1040 cm^{-1} (C-O), 1209 cm^{-1} (O-CH_3), 1410 cm^{-1} (CH=CH), 1515 cm^{-1} (C-C), 1670 cm^{-1} (C=O), 3019 cm^{-1} (Ar-CH). ^{1}H-NMR($CDCl_3$): *δ*, 1.42-1.45 (3H, t, CH_3), 3.82 (3H, s, OCH_3), 4.09-4.12 (2H, q, OCH_2), 8.02-8.04 (2H, d, Ar-2',6'), 7.45–7.47 (1H, d,=CH), 6.97-6.99 (2H, d, Ar-3',5'), 7.79-7.81(1H, d,=CH),7.55-7.57(2H, d, Ar-2'',6''), 6.81-6.83 (2H, d, Ar-2'', 6'') ppm.

Synthesis of (E)-3-(2,4-dichloro-phenyl)-1-(4-methoxy-phenyl) propenone[1b]

By the same method 4-methoxyacetophenone and 2, 4 di-chlorobenzaldehyde were grinded with sodium hydroxide to get 1b with 75% yield. Recrystalization from ethanol.

Mol. Formula: $C_{16}H_{12}Cl_2O_2$ Mol. Wt. 307.18, M.P. 155-158^{0}C, IR(KBr): 3019 cm^{-1} (Ar-CH), 1670 cm^{-1} (C=O), 1515 cm^{-1} (C-C), 1410 cm^{-1} (CH=CH), 1040 cm^{-1} (-OCH_3). ^{1}H-NMR($CDCl_3$):δ, 3.82 (3H, s, OCH_3), 6.97-6.99(2H, d, Ar-3',5'), 8.02-8.04 (2H, d, Ar-2',6'), 7.45-7.47(1H, d, Ar-6''), 7.79-7.81 (1H, d, Ar-5''), 7.48-7.50(1H,d,=CH), 7.20-7.22(1H, d,=CH), 7.37 (1H,s, Ar3'') ppm.

Synthesis of (E)-3-(4-methoxy-phenyl)-1-(4-methoxy-phenyl) propenone [1c]

By Using the same method p-methoxy acetophenone and p-methoxy benzaldehyde were grinded with sodium hydroxide to get 1c with 70% yield. Recrystalization from ethanol.

Mol. Formula: $C_{17}H_{16}O_3$ Mol. Wt. 268.304, M.P. 175-177^{0}C, IR(KBr): 3020 cm^{-1} (Ar-CH), 1640 cm^{-1} (C=O), 1515 cm^{-1} (C-C), 1599, 1528 cm^{-1} (CH=CH), 1017 cm^{-1} (-OCH_3). ^{1}H-NMR ($CDCl_3$), δ, 3.87 (3H, s, OCH_3), 6.98 (2H, d, Ar-3',5'), 8.02 (2H, d, Ar-2',6') 7.41(1H, d,=CH), 7.76 (1H, d,=CH), 7.61 (2H, d, Ar-2'',6''), 6.92 (2H, d, Ar-3'',5'') ppm.

Synthesis of (E)-3-(4-hydroxy-phenyl)-1-(4-methoxy-phenyl) propenone[1d]

By Using the same method p-methoxy acetophenone and p-hydroxy benzaldehyde were grinded with sodium hydroxide to get (1d) with 52% yield. Recrystalization from ethanol. Mol. Formula: $C_{16}H_{14}O_3$ Mol. Wt. 230.280, M.P. 238-240^{0}C IR(KBr): 1640 cm^{-1} (C=O), 1598, 1528 cm^{-1} (>C=C<), 1020 cm^{-1} (OCH_3), 3659 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$), δ, 3.87 (3H, s, OCH_3), 6.89 (2H, d, Ar-3',5'), 7.94 (2H, d, Ar-2',6'), 7.51(1H, d,=CH), 7.71(1H, d,=CH), 7.45 (2H, d, Ar-2'',6''), 6.96 (2H, d, Ar-3'',5''), 8.03(1H, s, OH) ppm.

Synthesis of (E)-3-(4-methoxy-phenyl)-1-(4-ethoxy-phenyl) propenone[1e]

By Using the same method p-ethoxy acetophenone and p-methoxy benzaldehyde were grinded with sodium hydroxide to get (1e) with 65% yield. Recrystalization from ethanol. Mol. Formula: $C_{18}H_{18}O_3$ Mol. Wt. 282.330, M.P. 186-188^{0}C. IR(KBr): 1654 cm^{-1} (C=O), 1599, 1526 cm^{-1} (>C=C<), 1026 cm^{-1} (OCH_3), 1048 cm^{-1} (OC_2H_5). ^{1}H-NMR ($CDCl_3$), δ, 1.40-1.42 (3H, t, CH_3), 4.02-4.06 (2H, q, CH_2), 3.83 (3H, s, OCH_3), 6.95 (2H, d, Ar-3',5'), 8.02 (2H, d, Ar-2',6'), 7.50(1H, d, =CH), 7.76 (1H, d, =CH), 6.61 (2H, d, Ar-2'',6'') 6.91 (2H, d, Ar-3'', 5'') ppm.

Synthesis of (E)-3-phenyl-1-(4-ethoxy-phenyl) propenone[1f]

By Using the same method p-ethoxy acetophenone and benzaldehyde were grinded with sodium hydroxide to get (1f) with 84% yield. Recrystalization from ethanol.

Mol. Formula: $C_{17}H_{16}O_2$ Mol. Wt. 252.1151, M.P. 140-143^{0}C. IR(KBr): 1648 cm^{-1} (C=O), 1576, 1534 cm^{-1} (>C=C<), 1048 cm^{-1} (OC_2H_5). ^{1}H-NMR ($CDCl_3$), δ, 1.39-1.43 (3H, t, CH_3), 4.03-4.08 (2H, q, CH_2), 6.95 (2H, d, Ar-3',5'), 8.02(2H, d, Ar-2',6'), 7.51 (1H, d, =CH), 7.76 (1H, d, =CH), 7.61 (2H, d, Ar-2'',6''), 7.36-7.39 (3H, m, Ar) ppm.

Synthesis of (E)-3-(4-methoxy-phenyl)-1-(4-bromophenyl) propenone[1g]

By Using the same method p-bromo acetophenone and p-methoxy benzaldehyde were grinded with sodium hydroxide to get (1g) with 88% yield. Recrystalization from ethanol. Mol. Formula: $C_{16}H_{13}BrO_2$ Mol. Wt. 317.177, M.P. 197-199^{0}C. IR (KBr): 1658 cm^{-1} (C=O), 1596, 1540 cm^{-1} (>C=C<), 1026 cm^{-1} (OCH_3), 722 cm^{-1} (Br). ^{1}H-NMR ($CDCl_3$), δ, 3.84, (3H, OCH_3), 7.85 (2H, d, Ar-3', 5'), 7.87 (2H, d, Ar-2',6'), 7.58 (1H, d, =CH), 7.61 (1H, d, =CH), 6.92 (2H, d, Ar-2'', 6''), 6.94 (2H, d, Ar-3'', 5'') ppm.

Synthesis of (E)-3-(4-methoxy-phenyl)-1-(4-bromophenyl) propenone[1h]

By Using the same method p-bromo acetophenone and p-hydroxy benzaldehyde were grinded with sodium hydroxide to get (1h) with 30% yield. Recrystalization from ethanol. Mol. Formula: $C_{15}H_{11}BrO_2$ Mol. Wt. 301.9942, M.P. 265-268^{0}C, IR(KBr):1650 cm^{-1} (C=O), 1590, 1548 cm^{-1} (>C=C<), 1365 cm^{-1} (-OH), 654 cm^{-1} (Br). ^{1}H-NMR ($CDCl_3$), δ, 8.92, (1H, s, OH), 7.55 (2H, d, Ar3', 5'), 7.72 (2H, d, Ar-2', 6'), 7.12 (1H, d, =CH), 7.76 (1H, d, =CH), 7.42 (2H, d, Ar-2'', 6''), 6.56 (2H, d, Ar-3'', 5'') ppm.

Synthesis of (E)-3-(4-methoxy-phenyl)-1-(4-bromophenyl) propenone[1i]

By Using the same method p-bromo acetophenone and benzaldehyde were grinded with sodium hydroxide to get (1i) with 88% yield. Recrystalization from ethanol.

Mol. Formula: $C_{15}H_{11}BrO$ Mol. Wt.285.999, M.P. 155-157^{0}C, IR(KBr): 1652 cm^{-1} (C=O), 1568, 1517 cm^{-1} (>C=C<), 678 cm^{-1} (Br). ^{1}H-NMR ($CDCl_3$), δ, 7.44 (2H, d, Ar3', 5'), 7.89 (2H, d, Ar-2', 6'), 7.44 (1H, d, =CH), 7.78 (1H, d, =CH), 7.61 (2H, d, Ar-2'', 6''), 7.40 (2H, d, Ar-3'', 5''), 7.22 (1H, s) ppm.

3. RESULTS AND DISCUSSION

The structures of synthesized compounds were confirmed by IR, ^{1}H-NMR and Mass spectral analysis. Titled compounds were confirmed by IR spectral data showing sharp bands in the range between 1030-1660 cm^{-1} indicated the presence of C=O group. Compounds (1a-1i) were also confirmed by ^{1}H-NMR spectral analysis. Inspection of the ^{1}H-NMR spectra suggested that the chalcones were geometrically pure and configured trans. The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against Gram positive bacteria shown in Table 2. The 1g showed excellent activity against *Staphylococcus aureus* at both concentration i.e. 500 µg/ml and 1000 µg/ml. The compounds 1g, 1b, 1e, 1i and 1h, 1a have shown good to moderate activity against *Staphylococcus aureus* at both concentration i.e. 500 µg/ ml and 1000 µg/ ml. Three of the chalcones with anti-staphylocaccal activity (1c, 1d and 1f) gave no inhibitory zones probably due to their low diffusion potential into agar media. Finally, no activity was observed for compounds against *Pseudomonas aeruginosa*, a Gram negative organism. It is widely known that Gram positive and negative organism have significantly different membrane composition and architecture which would explain the selectivity of the present compounds against Gram positive *Staphylococcus aureus*.

Antibacterial activity

Antimicrobial activity of all synthesized compounds were determined by disc diffusion method [27-29]. All human pathogenic bacteria viz. *Staphylococcus aurenus* (737), *Pseudomonas aeruginosa* (1688) were used for activity determination. Preparation of nutrient broth, Subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Disc measuring 6.25 mm in diameter were punched from Whatman no.1 filter paper. Stock solution of synthesized compounds diluted in dimethylsulfoxide (1% DMSO) to give final concentration of 500 µg/ml and 1000 µg/ml. A reference standard for both gram positive and gram negative bacteria was made by dissolving accurately weighed quantity of chloramphenicol (500 and 1000 µg/ml, respectively) in sterile distilled water separately. The incubation was carried out at 37 ^{0}C for 24 hrs. All the experiments were carried out in triplicate. Simultaneously, controls were maintained by employing 0.1 mL of dimethyl sulfoxide which did not reveal any inhibition. Zones of inhibition produced by each compounds was measured in mm. The results of antibacterial studies are given in Table 1.

Table 1: Antimicrobial activity of the synthesized compounds

Compound	Antimicrobial activity (%inhibition)			
	Staphylococcus aureus (737)		*Pseudomonas aeruginosa* (1688)	
	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml
1a	21.4	32.6	------	------
1b	24.3	33.6	------	------
1c	------	------	------	------
1d	------	------	------	------
1e	23.8	33.6	------	------
1f	--------	--------	------	------
1g	**25.0**	**34.8**	------	------
1h	22.6	32.8	------	------
1i	23.0	33.3	------	------
Chloramphenicol	42.3	55.2	63.7	78.9
DMSO	1.4	------	1.2	--------

4. CONCLUSION

Grinding method easily afforded the desired products with higher yields. The synthesized compounds showed moderate to good antimicrobial activities against *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

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CONFLICT OF INTEREST

Authors declare that no conflict of interest exists.

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