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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 1-(2'',4''-DICHLOROPHENYL)-3-(SUBSTITUTED ARYL)-2-PROPENE-1-ONES

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ABSTRACT

According to Claisen-Schmidt condensation a series of eight novel chalcones were synthesised by condensing 2,4-Dichloro acetophenone with various aromatic aldehydes in dilute ethanolic potassium hydroxide solution at room temperature. All these compounds were characterized by means of their IR, ^{1}H NMR spectroscopic data and elemental analysis. The antimicrobial activity of these compounds was evaluated by the cup plate method. The particular compounds FC-4,6,7,8 showed maximum antibacterial acitivity because of having electron releasing groups such as methoxy (FC-4) and naphthyl groups (FC-8). Similarly compounds FC-1,2,3 halogen having pharmacophores such as chloro, dichloro and bromo groups exhibited moderate to considerable antifungal activity. These results suggest that the chalcone derivatives have excellent scope for further development as commercial antimicrobial agents.

KEYWORDS : Chalcones, Claisen Schmidt condensation, antimicrobial & antifungal activity.

INTRODUCTION

Chalcones[1] are condensation products of substituted aromatic aldehydes with acetophenone derivatives in presence of alkali. These are well known intermediates for synthesizing various heterocyclic compounds. Chalcones have been reported to possess various biological activities such as antimicrobial[2], antiviral[3], anticancer[4], analgesic[5], anti-inflammatory[6], antitubercular[7], antiplatelet[8], antiulcerative[9], antimalarial[10], antileishmanial[11], antioxidant[12], antihyperglycemic[13], immunomodulatory[14] and inhibition of aldose reductase[15] activities. The presence of a reactive α,β-unsaturated keto functional group in chalcones is found to be responsible for their antimicrobial activity. In the present communication we report the reaction of 2,4-dichloro acetophenone with different aromatic aldehyde derivatives to form chalcones . The structures of the various synthesized compounds were assigned on the basis of IR, ^{1}H NMR spectral data and elemental analysis. These compounds were also screened for their antimicrobial and antifungal activity.

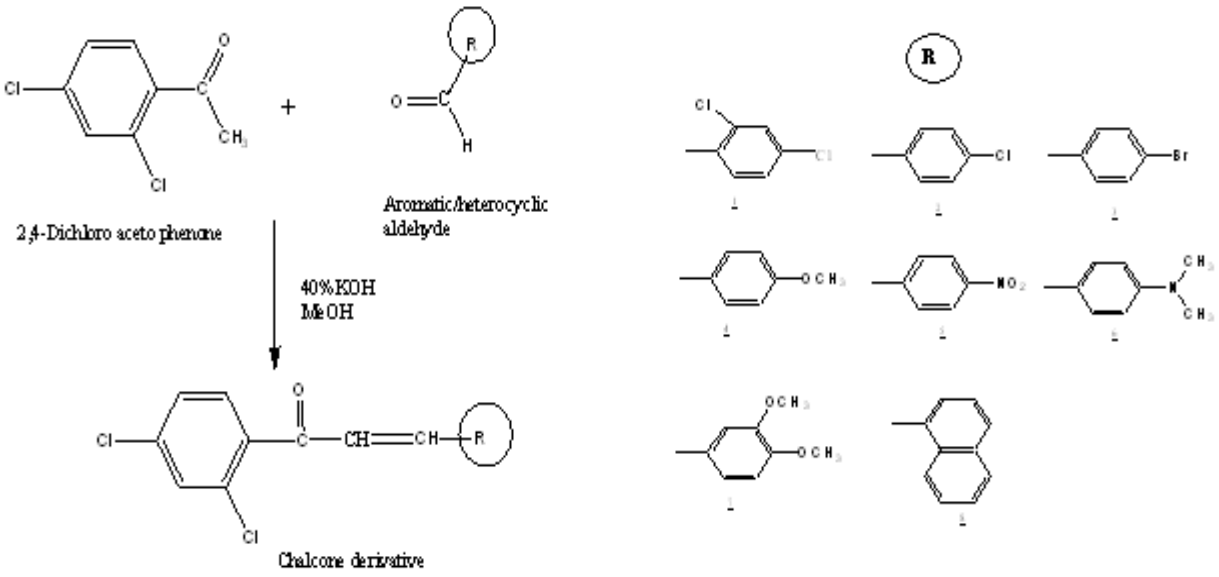
MATERIALS AND METHODS

The melting point of the compounds was determined in open capillaries, using Elico digital melting point apparatus and expressed in ºC and the values were uncorrected. IR spectra of the compounds were recorded on on Perkin-Elmer 337 Spectrophotometer using KBr discs and the values are expressed in cm^{-1}. ^{1}H NMR spectra were recorded on Bruker AV 400 MHz Spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. All the solvents used were of analytical grade. The purity of the compounds was checked by TLC using Silicagel-G (Merck). Column chromatography was performed on Silica gel (Merck, 60-120 mesh). 2,4-dichloroacetophenone, methanol, Potassium Hydroxide, 2,4-dichloro benzaldehyde, *p*-nitrobenzaldehyde, *p*-chloro

benzaldehyde, *p*-bromo benzaldehyde, dimethylamino benzaldehyde, naphthaldehyde, sparfloxacin, Griseofulvin Silica gel (Merck, 60-120 mesh) etc. were used as chemicals.

General procedure for the preparation of chalcones FC(1-8)

A mixture of 2,4-Dichloro acetophenone (0.01moles) and aryl aldehyde (0.01 mol) was stirred in methanol (30 ml) and then an aqueous solution of KOH (40%, 15 ml) added to it. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The chalcone derivative precipitates out as solid. Then it was filtered and crystallized from ethanol (Scheme-1). Characterization data of the synthesized compounds are reported in Table-1.



Scheme -1: ***Synthesis of chalcones of 2,4-Dichloro acetophenone***

Table 1 : ***Characterization data of Chalcone compounds***

Compound	R	Molecular Formula	% yield	M.P (^{0}C)
FC-1	2',4'-dichloro phenyl	$C_{15}H_8OCl_4$	68	120
FC-2	4'-chloro phenyl	$C_{15}H_9OCl_3$	62	118
FC-3	4'-bromo phenyl	$C_{15}H_9OBrCl_2$	65.5	126
FC-4	4'-methoxy phenyl	$C_{16}H_{12}O_2Cl_2$	60	121
FC-5	4'-nitro phenyl	$C_{15}H_9O_3NCl_2$	74	120
FC-6	N,N-dimethyl aminophenyl	$C_{17}H_{15}ONCl_2$	66.5	122
FC-7	3',4'-dimethoxy phenyl	$C_{17}H_{14}O_3Cl_2$	63.5	125
FC-8	naphthyl	$C_{19}H_{12}OCl_2$	51.5	236

Spectral data of the compounds FC-1 to FC-8:

(FC-1):1-(2'',4''-dichlorophenyl)-3-(2′,4′-dichlorophenyl)-2-propene-1-one:

IR(in *cm*$^{-1}$): 1671(C=0), 1606(C=C), 870.2(C-Cl) **^{1}H NMR (in δppm):** 7.409 (1H, d, J=14Hz, C-2H), 8.083 (1H, d, J=5.2Hz, C-3H),7.321-8.096 (6H, m,Ar-H). **Elemental analysis for $C_{15}H_8OCl_4$(in %):** Calculated: C- 52.02; H- 2.31; O- 4.62; Cl- 41.02. Found: C- 52.16; H- 2.38; O- 4.76; Cl- 40.05.

(FC- 2):1-(2'',4''-dichlorophenyl)-3-(4′-chlorophenyl)-2-propene-1-one:

IR(in *cm*$^{-1}$): 1665(C=0), 1600(C=C), 866.7(C-Cl); **^{1}H NMR (in δppm):** 7.635 (1H, d, J=8.4Hz, C-2H), .820 (1H, d, J=8.4Hz, C-3H), 7.283-7.789 (7H, m,Ar-H).**Elemental analysis for $C_{15}H_9OCl_3$(in %):** Calculated: C- 57.78; H-2.89; O-5.13; Cl-34.18. Found: C- 50.46; H- 2.49; O-4.56 ; Cl-34.

(FC- 3):1-(2'',4''-dichlorophenyl)-3-(4′-bromo phenyl)-2-propene-1-one:

IR(in *cm*$^{-1}$): 1663(C=0), 1605(C=C), 864.3(C-Cl); **^{1}H NMR (in δppm):** 7.652 (1H, d, J=4.8Hz, C-2H), 7.79 (1H, d, J=11.2Hz, C-3H), 7.342-7.785 (7H, m,Ar-H).**Elemental analysis for $C_{15}H_9OBrCl_2$(in %):** C- 51.01; H-2.54; O, 4.53; Cl-20.11; Br-21.81. Found: C-50.46; H-2.49; O-4.56 ; Cl-20.05; Br-21.31.

(FC- 4):1-(2',4''-dichlorophenyl)-3-(4′-methoxy phenyl)-2-propene-1-one:

IR(in *cm*$^{-1}$): 1695(C=0), 1653(C=C), 864.2(C-Cl); **^{1}H NMR (in δppm):** 3.817(3H, s,-OCH_3), 6.90(1H, d, J=8.8Hz, C-3H),7.20(1H, d, J=16.4Hz, C-2H),7.2-8.0(7H, m,Ar-H) **Elemental analysis for $C_{16}H_{12}O_2Cl_2$(in %):** C- 62.54; H-3.91; O- 10.42; Cl-23.12. Found: C-50.46; H-2.49; O- 4.56; Cl-23.21.

(FC– 5):1-(2'',4''-dichlorophenyl)-3-(4′-nitrophenyl)-2-propene-1-one:

IR(in *cm*$^{-1}$): 1667(C=0), 1590(C=C), 830.0(C-Cl); **^{1}H NMR (in δppm):** 7.687(1H, d, J=8 Hz, C-2H), 8.066(1H, d, J=8.4Hz, C-3H), 7.467-8.273(7H, m,Ar-H).**Elemental analysis for $C_{15}H_9O_3NCl_2$ (in %):** C- 55.90; H- 2.79; O-14.90;N-4.35;Cl-22.05. Found: C- 55.25; H- 2.82; O- 14.50; Cl-22.18.

(FC- 6):1-(2'',4''-dichlorophenyl)-3-(4′-N,N dimethylaminophenyl)-2-propene-1-one:

IR(in *cm*$^{-1}$): 1625(C=0), 1587(C=C), 860.8 (C-Cl); **^{1}H NMR (in δppm):** 6.767(1H, d, J=8Hz, C-2H), 7.762(1H, d, J=8.4, C-3H), 6.767-7.782(7H,m, Ar-H). **Elemental analysis for $C_{17}H_{15}ONCl_2$(in %):** C-63.75; H-4.68; O-5.01; N-4.38; Cl-22.18. Found: C-63.42; H-4.34; O-5.20; . N-4.15; Cl-22.10.

(FC- 7):1-(2'',4''-dichlorophenyl)-3-(3′,4′-dimethoxy phenyl)-2-propene-1-one:

IR(in *cm*$^{-1}$):1660(C=0),1588(C=C),861.6(C-Cl); **^{1}H NMR (in δppm):**3.820(6H, s ,-OCH_3), 7.004(1H, d, J=8.4Hz, C-2H),7.319(1H, d, J=6.4Hz, C-3H), 6.997-7.777(6H, m,Ar-H), **Elemental analysis for $C_{17}H_{14}O_3Cl_2$(in %):** C-60.53; H-4.15; O-14.24; Cl-21.07. Found: C-60.22; H-4.05; O-14.05; Br-21.12.

(FC- 8):1-(2'',4''-dichlorophenyl)-3-naphthyl-2-propene-1-one:

IR(in *cm*$^{-1}$):1660(C=0), 1590(C=C), 859.8(C-Cl) ; **^{1}H NMR (in δppm):** 7.82(1H ,d , J=8.4Hz, C-2H), 7.635 (1H, d, J=8.4Hz, C-3H), 7.283-7.789(10H, Ar-H), **C^{13}NMR(δppm) :** 191.82 (1C, C-1), 40.18(2C, C-2), 22.75-142.46 (Ar-H). **Elemental analysis for $C_{19}H_{12}OCl_2$(in %):** C-69.72; H-3.67; O-4.89; Cl-21.71. Found: C-69.46; H-3.34; O-4.45; Cl-21.92.

RESULTS AND DISCUSSION

Antibacterial activity

The newly synthesized compounds (FC-1 to FC-8) were screened for their antibacterial activity against gram positive bacteria viz., *Bacillus subtilis* and gram negative bacteria *viz*., *Escherichia coli* by using cup plate method[16,17]. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. The test compounds were prepared in different concentrations using dimethyl sulfoxide. Solutions of the test compounds were prepared by dissolving 5 mg each in 5 ml of dimethyl sulfoxide at a concentration of 1000 µg / ml.

Volumes of 0.05 ml and 0.1 ml of each compound were used for testing. The cups each of 9 mm diameter were made by scooping out medium with a sterilized cork borer in a petri dish, which was streaked with the organisms.

The solutions of each test compound (0.05ml and 0.1 ml) were added separately in the cups and petri dishes were subsequently incubated. A reference standard for both gram positive and gram negative bacteria was made by dissolving accurately weighed quantity of sparfloxacin (50 and 100 µg/ml, respectively) in sterile distilled water, separately. The incubation was carried out at 37ºC for 24hr. All the experiments were carried out in triplicate. Simultaneously, controls were maintained by employing 0.1 ml of dimethylsulfoxide which did not reveal any inhibition. Zones of inhibition produced by each compound was measured in mm. The results of antibacterial studies are given in Table 2.

Table 2. ***Antibacterial activity of chalcone derivatives***

Zone of inhibition (in mm)								
Compound	***B.pumilis***		***B.subtilis***		***E.coli***		***P.vulgaris***	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
FC-1	7	9	10	13	11	15	-	-
FC-2	5	6	9	12	10	14	_	_
FC-3	7	8	14	18	12	16	7	9
FC-4	_	7	11	13	13	16	-	-
FC-5	6	8	10	13	11	14	8	11
FC-6	_	9	12	15	12	15	_	_
FC-7	7	10	12	14	14	16	_	8
FC-8	8	10	13	16	15	17	-	_
Sparfloxacin	12	14	17	22	16	19	13	15
Control	_	_	_	_	_	_	_	_

(-) indicates no zone of inhibition

Antifungal Activity

All these compounds screened for their antifungal activity by same cup plate method[16,17] against Aspergillus *niger* and *Candida albicans.* The solutions of test compounds were prepared by a similar procedure described under the antibacterial activity. A reference standard drug Griseofulvin (50 and 100 µg / ml respectively) and dimethyl sulphoxide as a control which did not reveal any inhibition. The results of antifungal studies are given in Table 3.

Table 3. ***Antifungal activity of chalcone derivates***

Zone of inhibition (in mm)				
Compound	***Candida albicans***		***Asperagillus niger***	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
FC-1	6	11	10	12
FC-2	_	6	12	15
FC-3	5	7	9	11
FC-4	6	8	12	14
FC-5	_	_	10	13
FC-6	_	5	_	6
FC-7	5	8	8	10
FC-8	_	_	7	9
Control	_	_	_	_
Griseofulvin	18	22	18	22

(-) indicates no zone of inhibition

CONCLUSION

The screening results revealed that the synthesised chalcone compounds FC-1 to FC-8 showed significant broad spectrum antibacterial activity. In particular compounds FC-4,6,7,8 showed maximum anti bacterial acitivity because of having electron releasing groups such as methoxy (FC-4) and naphthyl groups (FC-8). Similarly compounds FC-1,2,3 halogen having pharmacophores such as chloro, dichloro and bromo groups exhibited moderate to considerable antifungal activity. These results suggest that the chalcone derivatives have excellent scope for further development as commercial antimicrobial agents.

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REFERENCES

1. Maayan, Shmuel; Ohad, nerya and Soliman, K., Chalcones as potent tyrosinase inhibitors: the importance of a 2,4-substituted resorcinol moiety Bioorganic & medicinal chemistry 2005;13(2):433-41.
2. Mokle S S, Sayeed M A, Kothawar and Chopde., Synthesis and Antimicrobial Activity of Some Chalcone Derivatives *Int. J. Chem. Sci*. 2004, 2(1), 96.
3. Onyilagna J C, Malhotra B, Elder M and Towers G H N, *Can. J. Plant Pathol*, 1997,19, 133.
4. Francesco E, Salvatore G, Luigi M and Massimo C, *Phytochem*, 2007, 68, 939.
5. Viana G S, Bandeira M A. and Matos F, *J. Phytomedicine*, 2003, 10, 189.
6. Hsieh H K, Tsao L T and Wang J P, *J. Pharm. Pharmacol*., 2000, 52, 163.
7. Sivakumar PM, Seenivasan SP, Kumar V, Doble M., Synthesis, antimycobacterial activity evaluation, and QSAR studies of chalcone derivatives. Bioorg Med Chem Lett. 2007,17(6),1695-700
8. Zhao L M, Jin H S, Sun L P, Piao H R and Quan Z S, Synthesis and evaluation of

antiplatelet activity of trihydroxychalcone derivatives.*Bioorg. Med. Chem. Lett*, 2005,15, 5027.
9. Mukarami S, Muramatsu M, Aihara H and Otomo S, *Biochem. Pharmacol*, 1991, 42, 1447.
10. Liu M, Wilairat P and Go L M, Antimalarial alkoxylated and hydroxylated chalcones *J. Med. Chem*, 2001, 44, 4443.
11. Nielsen S F, Chen M, Theander T G, Kharazmi A and Christensen S B, Synthesis of antiparasitic licorice chalcones Bioorg. Med. Chem. Lett. 1995, 5, 449– 452.
12. Miranda C L, Aponso G L M, Stevens J F, Deinzer M L and Buhler D R, *J Agric.Food Chem*, 2000, 48, 3876.
13. Satyanarayana M, Priti Tiwari, Tripathi K, Srivastava A K and Ram Pratap,*Bioorg. Med. Chem*, 2004, 12, 883.
14. Barford L, Kemp K, Hansen M and Kharazmi A, *Int. Immunopharmacol*, 2002, 2, 545.
15. Severi F, Benvenuti S, Costantino L, Vampa G, Melegari M and Antolini L, *Eur.J. Med. Chem*, 1998, 33, 859.
16. Banty A L, The Antimicrobial Susceptability Test: Principle and Practice, Ed.,by Illus Lea and Febiger (Philadelphia, PA, USA), 1976, 180.
17. Seely H W and Van Demark P J, Microbes in Action: A Laboratory Manual of Microbiology, D.B.Taraporewala Sons and Co., Bombay, 1975, 55.