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Synthesis of some new aryl substituted chalcones and their antimicrobial study

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Abstract
Synthesis and characterization of some new biologically active class of chalcones using a base in ethanol as reaction solvent under mild reaction condition. Chalcones are of great interest due to their use as starting materials in the synthesis of a series of different heterocyclic compounds and the precursors of all flavonoids are chalcones with oxygenated function on the aromatic rings. Structures of the newly synthesized compounds were confirmed by spectroscopic methods and newly synthesized compounds were studies for bioactivity (antibacterial and antifungal) by using *Micrococcus caseolyticus, Bacillus subtilis* and two gram negative bacteria *viz*., *Escherichia coli, Pseudomonas putida*, *Aspergillus niger, Rhizopus oryzae* and *Aspergillus flavus.* 1a-1d reported strong antimicrobial activity in this current study against all the bacteria used. 1a-1c have shown high potency especially against *A.niger, A. flavus* and *Rhizopus oryzae*.

Keywords: substituted chalcones, synthesis and bioactivity, antibacterial activity, antifungal activity

Introduction

Nitrogen containing Chalcones are heterocyclic compounds of unsaturated ring structure having three carbon atoms. Chalcones are of a high interest due to their use as starting materials in the synthesis of a series of various heterocyclic compounds and especially chalcones bearing oxygenated function on the aromatic rings are the precursors of all flavonoids. Thus the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemist. This class exhibits a broad spectrum of biological properties including antinociceptive, anti-inflammatory, antitumor, antibacterial, antifungal and antileischmanial. Some chalcones derivatives also showed a profound influence on the cardiovascular, cerebrovascular and neuromuscular systems including the vital organs of the experimental animals. Several chalcones derivatives possess important pharmacological activities and therefore they are useful materials in drug research. Chlacones are biologically active scaffolds with a variety of biological activities like antimicrobial [1], antitubercular [2], anti-inflammatory [3], anticancer [4], antitumor [5], anticonvulsant [6], and anti-HIV [7].

Experimental Methods

Melting points were determined by in an open capillary method and are uncorrected. The chemicals and solvents used for laboratory grade and were purified. ^{1}H NMR spectra were recorded (in DMSO-d_6) on Avance-300 MHz spectrometer using TMS as an internal standard. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. The mass was recorded on EI-Shimadzu-GC-MS spectrometer.

General Experimental Procedure for the Synthesis of Chalcones (1a-H)

Equimolar mixture of substituted acetophenone (1 mmol), and aromatic aldehyde (1 mmol) was mixed in 15 mL in ethanol taken in 100 mL conical flask. Then 2-3 mL of saturated solution of KOH (aprox 40%) was added into the flask. The solution becomes reddish brown color. The reaction mixture was kept for overnight at room temperature. On the next day morning, the completion of the reaction was monitored by TLC. After completion of the reaction, then the contents of the flask were poured into 50 mL ice cold water. The corresponding solid was separated then filtered. The crude product was recrystallized from suitable solvent. The yield and M.P. of the product was noted.

Similarly, all the compounds were synthesized by the same procedure. The physical and analytical data of the compounds were mentioned in Table-1.

Spectroscopic Data of Selected Compounds

(1a): IR (KBr): 3162 (-OH), 1648 (>C=O), 1598 (-C=N); ^{1}H NMR (DMSO-d_6): δ 3.48 (s, 3H, OCH_3), δ 7.06-8.89 (m, 9H, Ar-H + CH=CH), δ 11.26 (s, 1H, OH) ppm; M.S. (m/z): 288[M^+], 290[M^{+2}];

(1f): IR (KBr): 3148 (-OH), 1654 (>C=O), 1592 (-C=N); ^{1}H NMR (DMSO-d_6): δ 5.21 (s, 1H, OH), δ 7.11-8.42 (m, 10H, Ar-H + CH=CH) ppm; M.S. (m/z): 258[M^+], 260[M^{+2}];

(1g): IR (KBr): 1668 (>C=O), 1602 (-C=N); ^{1}H NMR (DMSO-d_6): δ 7.18-8.28 (m, 10H, Ar-H + CH=CH) ppm; M.S. (m/z): 276 [M^+], 278[M^{+2}], 280[M^{+2}]

Antimicrobial Activity

The newly synthesized compounds were screened for their antibacterial activity against two Gram positive bacteria *viz*., *Micrococcus caseolyticus*, *Bacillus subtilis* and two gram negative bacteria *viz*., *Escherichia coli*, *Pseudomonas putida* by using cup plate method8-9. The agar medium was purchased from HI media Laboratories Ltd., Aurangabad, India. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Discs measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper. 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 □g/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 (0.05 and 0.1 mL) were added separately in the cups and petri plates were subsequently incubated. A reference standard for both Gram positive and Gram negative bacteria was made by dissolving accurately weighed quantity of chloramphenicol (200 and 1000 □g/mL, respectively) in sterile distilled water, separately. The incubation was carried out at 37ºC for 24h. 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 compound was measured in mm.

All those compounds screened for antibacterial activity were also tested for their antifungal activity using potato-dextrose-agar (PDA) medium by same cup plate method against *Aspergillus niger*, *Rhizopus oryzae* and *Aspergillus flavus.* The PDA medium was purchased from HI media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. The solutions of test compounds were prepared by a similar procedure described under the antibacterial activity. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulphoxide (1000 □g/mL). Volumes of 0.05 and 0.1 mL of each compound were used for testing. A reference standard drug fluconazole (200 and 1000 □g/mL respectively) and dimethylsulphoxide as a control which did not reveal any inhibition. The experiments were performed in triplicate in order to minimize the errors. Zone of inhibition produced by each compound was measured in mm.

Results and Discussion

The starting chalcones 1(a-h) were prepared by the Claisen-Schmidt condensation method. The aromatic acetophenones and aldehydes were mixed ethanol taken in a conical flask. The aqueous KOH solution was added to it and kept for overnight. On the next day morning, the progress of the reaction was monitored by the TLC and worked up with water to yielded corresponding chalcones 1(a-h) (Scheme-1, Table-1).

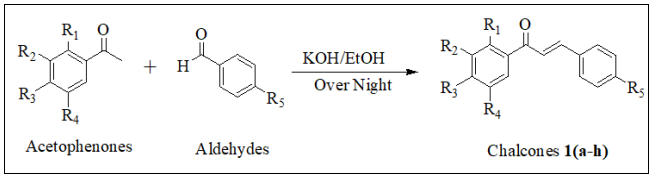

Fig 1: Synthesis of chalcones using KOH in ethanol 1(a-h)

Table 1: The physical and analytical data of synthesized chalcone derivatives

Entry (1a-h)	Substitution					Mol. Formula	Yield (%)	M.P (°C)
	R_1	R_2	R_3	R_4	R_5			
a	OH	H	H	Cl	Br	$C_{15}H_{10}O_2BrCl$	86	96-98
b	OH	H	H	F	OMe	$C_{16}H_{13}O_3F$	85	138-140
c	H	H	CH_3	H	OMe	$C_{17}H_{16}O_2$	86	106-108
d	OH	H	H	Cl	Cl	$C_{15}H_{10}O_2Cl_2$	90	126-128
e	OH	H	H	Cl	OH	$C_{15}H_{11}O_3Cl$	90	130-132
F	H	H	Cl	H	OH	$C_{15}H_{11}O_2Cl$	85	127-129
G	H	H	Cl	H	Cl	$C_{15}H_{10}OCl_2$	95	134-136
H	H	H	Cl	H	Br	$C_{15}H_{10}OBrCl$	92	116-118

Antimicrobial activity

Table 2: The results of antibacterial studies were given in following table.

Compound	Micrococcus Caseolyticus		Bacillus Subtilus		Escherichia Coli		Pseudomonas putida	
	0.05	0.1	0.05	0.1	0.05	0.1	0.05	0.1
1a	5	8	7	9	6	8	6	8
1b	6	8	8	9	7	09	-	-
1c	7	9	6	8	8	10	6	5
1d	9	10	8	10	-	-	8	10
1e	-	-	8	10	6	8	-	-
1f	8	10	-	-	6	8	-	-
1g	-	-	5	7	-	-	-	-
1h	-	-	8	10	8	10	-	-

(-) indicates no zone of inhibition.

Table 3: The results of antifungal studies are given in following table

Compound	Aspergillus niger		Aspergillus flavus		Rhizopus orazae	
	0.05	0.1	0.05	0.1	0.05	0.1
1a	9	10	8	9	-	-
1b	7	8	6	9	9	11
1c	5	8	7	10	6	8
1d	-	-	8	11	-	-
1e	6	8	7	9	-	-
1f	6	8	-	-	8	9
1g	-	-	8	9	6	8
1h	7	8	-	-	7	8

(-) indicates no zone of inhibition.

The screening results revealed that the compounds 1a-1d showed significant antimicrobial activity against all bacteria used in this current study. In particular compounds 1e, 1f, 1h showed mild inhibitory action on *B. subtilis* and *E. coli.* Compound 1g showed minimum activity against *B. subtilis*. Compound 1a-1c have shown high potency especially against *A.niger*, *A. flavus* and *R.oryzae*. Compounds 1e, 1f and 1g showed mild inhibition. While 1d showed minimum inhibition. All the organisms employed at a concentration of 1000 □g/mL (0.01 mL dose level) showed considerable

antibacterial and antifungal activities and are comparable to that of standard drugs chloramphenicol and fluconazole, respectively.

Conclusion

In summary, we synthesized some new aryl substituted chalcone developed with simple and efficient system. The advantages of the present protocol are the simple and easy work up procedure, high yields of products and shorter reaction time is reported. Synthesized compounds showed antibacterial and antifungal activity.

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