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Anthelmintic and anti-microbial activity of some novel chalcone derivatives

Biswajit Chandra Das[*], G. Mariappan[+], Sudip Saha[*], Debjit Bhowmik[*], Chiranjib[*]

[*]*Rajeev Gandhi College of Pharmacy, Nautanwa, Maharajganj (U.P.)*
[+]*Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim.*

Abstract

In this study, substituted chalcone derivatives were synthesized and their Anthelmintic and Anti-microbial activities were carried out. Chalcone derivatives were obtained by the treatment of substituted acetophenone with substituted aromatic and hetero aromatic aldehydes. The structure elucidation of the compounds was performed by UV, IR, ^{1}H NMR. Generally the prepared compound exhibited only moderate Anthelmintic and Anti-microbial activity; however, a few of them exhibited good activity.

Key Words: Chalcone, anthelmintic activity, anti-microbial activity.

Introduction

The chalcones are α, β unsaturated ketones containing the reactive keto ethylene group –CO–CH=CH–. Presence of α, β unsaturated carbonyl system in chalcone makes it biologically active. Some substituted chalcones and their derivatives have been reported to possess some interesting biological properties such as antibacterial, anthelmintic, antifungal, insecticidal, ulcerogenic, anticancer, anti-inflammatory, anaesthetic, analgesic, antileishmanial, antimalarial, antioxidant etc. These compounds are precursors of flavonoids and isoflavonoids, which are abundant in edible plants. It has incidental antiviral activity against herpes and vaccinia infections.

As per the recent literature some novel synthetic chalcones that inhibit *in vivo* eosinophilia, but clearly show differential effects on eosinophil functions. Both chalcones inhibit cytokine-

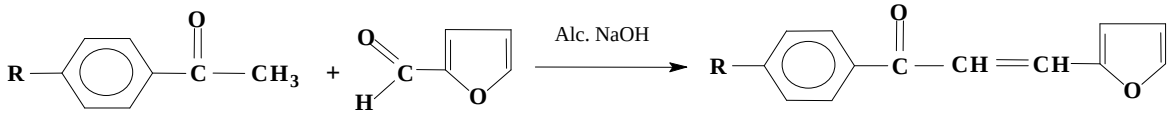
induced VCAM-1 protein expression and block IL-5-mediated survival of eosinophils. Inhibition of de-granulation is another property exhibited by some chalcones that may prove useful in developing novel therapeutic strategies for inhibition of eosinophil-related inflammatory diseases such as asthma[1-7].

Experimental Section

Melting points of the compounds were determined using Open Capillary Melting Point apparatus and were reported uncorrected. Ultra violet visible spectroscopic analysis has been carried out in UV Pharma Spec. 1700 (SHIMADZU) UV-visible spectrophotometer IR spectra were detected in KBr pellets using a Schimadzu FTIR- 8400S spectrophotometer. The ^{1}H NMR spectra were recorded in DMSO-d6 by NMR 300MHZ spectrometers using tetramethylsilane as an internal standard. All the chemicals and solvents used in this study were of analytical grade (S.D. FINE Chem. Limited, Mumbai).

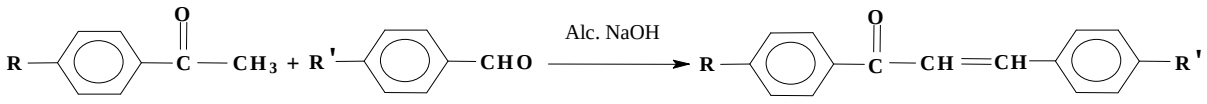
General procedure for the synthesis of chalcone derivatives

A mixture of substituted aromatic aldehyde and substituted acetophenone were dissolved in rectified spirit in a 250 ml round-bottomed flask equipped with a mechanical stirrer. Sodium hydroxide solution was added drop wise to the reaction mixture on vigorous stirring for 30 minutes when solution became turbid. The reaction temperature was maintained between 20-25°C using a cold water bath on the mechanical stirrer. After vigorous stirring for 4-5 hours, the reaction mixture was neutralized by 0.1- 0.2N HCl whereby the precipitation occurred. On filtering off, the crude chalcone was dried in air and recrystallized from rectified spirit.



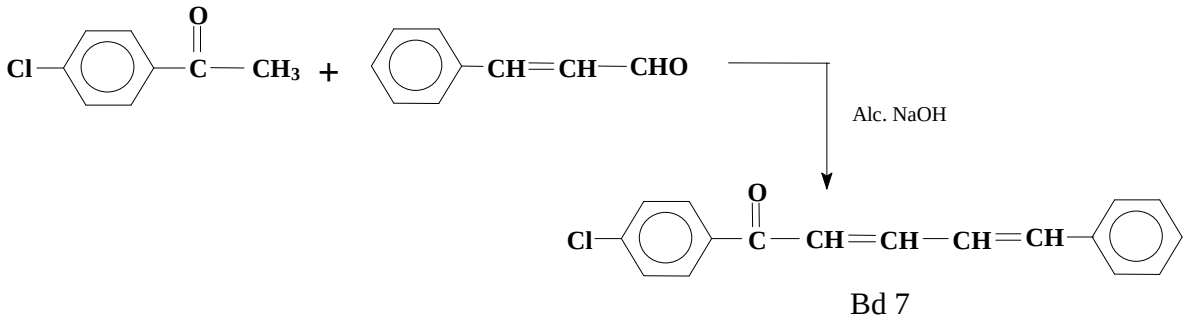
Bd 1 – Bd 4

Scheme of synthesis of chalcone with five membered heterocyclic aromatic aldehyde



Bd 5 and Bd 6

Scheme of synthesis of chalcone with six membered aromatic aldehyde



Bd 7

Scheme of synthesis of chalcone with cinnamaldehyde

Screening for Anthelmintic activity

The newly synthesiszed compounds were tested for Anthelmintic activity according to method described in detail by Kailasraj and Kurupa. *Pheretima posthuma* (earth worms obtained from Shibpur Botanical Garden, Kolkata) of nearly equal size (6cm±1) were selected for present study.The anthelmintic activity was evaluated on adult Indian earthworm (*Pheretima posthuma*) due to its anatomical and physiological similarity with the intestinal round worm parasites of human beings[8-10].

Albendazole diluted with normal saline solution to obtained 0.1%, 0.2%, 0.5% and 1% served as standard and poured into petridishes. The synthesized compounds were prepared in minimum quantity of ethanol and diluted to prepare four concentrations i.e. 0.1%, 0.2%, 0.5% and 1%. These solutions were taken in four petridishes. Normal saline serves as control. Six earth worms were nearly equal size (6cm±1) are taken for each concentration and placed in petridishes at room temperatures. The time taken for complete paralysis and death are recorded. The mean paralysis time and mean lethal time for each sample was recorded (each reading were taken triplicate). The time taken by worms to become motionless was noted as paralysis time and to ascertain the death. Earth worms were frequently applied with external stimuli which stimulates and induce movement in the earth worms, if alive. The observations were recorded and tabulated in Table.3 and Figure 1,2

Screening for anti-microbial activity

The MICs were determined by the standard agar dilution method. The synthesized compounds were dissolved in 10µg/ml of DMF, as they were not fully soluble in water and then diluted by sterile distilled water to make up the solution. The drug solutions were then added to the molten nutrient agar in different tubes to give final concentration of 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 700, 800, 900 and 1000 µg/ml. The molten nutrient agar media containing various concentrations of the synthesized compounds were poured and solidified into sterile 100 mm petridishes to give sterile nutrient agar plates with varying dilution of synthesized compounds. Then these plates were kept in a refrigerator (4^{o} C) for 24 hours for uniform diffusion of the synthesized compounds into the nutrient agar media[11,12].

The plates were then dried at 37° C for 2 hours before spot inoculation. One loop full (diameter: 3mm) of the overnight grown peptone water culture of each test organism was placed in petridish marked by Checker Board Technique (Mazumdar et al., 2000). The final number of cfu inoculated on to the agar plates 10^{10} for all stains. The spot inoculated plates were incubated at 37°C for 24 hours and the MIC values were obtained. The lowest concentration of the plates, which did not show any visible growth after incubation, was considered as MIC. The agar plate containing only sterile distilled water served as control. The observations were recorded and tabulated in Table 4 and Figure 3.

Results and Discussion

The novel chalcones have been synthesized by Claisen–Schmidt condensation reaction. All the synthesized compounds were critically analyzed to ascertain the structure by melting point, UV spectra, IR spectra and ^{1}H NMR spectra. The new derivatives were screened for anthelmintic and anti-microbial activity. The result of the anthelmintic activity was given in table 3 and figure 1 and 2. From this table it was found that the compound Bd1 has more activity than the other analogs but less than the standard Albendazole. The result of the anti-microbial activity was given in table 4 and figure 3. From this table it was concluded that almost all the derivatives have same biological response. It was also found that the heterocyclic aldehyde substituted chalcone showed more activity than the aromatic aldehyde. Results were presented as mean±SEM (standard error of mean).

Table-1 Physico-chemical data of chalcone derivatives

Entry	*R*	*R*^{1}	M.F	M.W	M.P	Yield (%)	Nomenclature
Bd 1	H	-	$C_{13}H_{10}O_2$	198	37-40	46.00	1-[phenyl-3-furfuryl prop-2-en-1-one]
Bd 2	2 – OH	-	$C_{13}H_{10}O_3$	214	155-157	19.19	1-[2-hydroxyphenyl]-3-[furfuryl] prop-2-en-1-one.
Bd 3	4 – Cl	-	$C_{13}H_9OCl$	216.5	70-72	40.47	1-[4-chlorophenyl]-3-furfuryl prop-2-en-1-one.
Bd 4	3-OMe, 4-OMe	-	$C_{15}H_{14}O_4$	258	80-83	75.74	1-[3,4-dimethoxyphenyl]-3-[furfuryl] prop-2-en-1-one.
Bd 5	4-OMe	4-OMe	$C_{17}H_{16}O_3$	268	120-122	16.74	1-[4-methoxy phenyl]-3-[4-methoxy-phenyl] prop-2-en-1-one
Bd 6	4-OMe	4- F	$C_{16}H_{13}O_2F$	256	140-142	91.02	1-[4-methoxyphenyl]-3-[4-flurophenyl] prop-2-en-1-one
Bd 7	4-Cl	Phenyl ethenyl	$C_{17}H_{13}OCl$	268.5	115-117	29.53	5-phenyl-1-[4-chlorophenyl] penta 2,4-dien-1-one

Table-2 Spectroscopic data of chalcone derivatives

Entry	UV (λ-max)	IR (KBr, cm^{-1})	^{1}H-NMR (300 MHz) (DMSO-*d*6) (ppm)
Bd 1	331	1660 (C=C); 1766 (C=O); 3061, 3122 (furan-H, alkenyl C-H); 638,704 (Ar-H)	7.70 (1H, d, H-α), 7.91 (1H, d, H- β), 6.90 (2H, dd, H-2 and H-6), 7.56 (2H, dd, H-3 and H-5)
Bd 2	334	1606,1668(C=C); 764(C=O); 3105 (furan-H, alkenyl C-H); 617,769 (Ar-H)	7.68 (1H, d, H-α), 7.91 (1H, d, H- β), 8.16 (1H, s, OH-5H), 6.86 (1H, d, H-3), 7.16 (1H, dd, H-4), 7.63 (1H, d, H-6), 7.69 (1H, d, H-5)

Bd 3	335	1473,1597(C=C); 656(C=O); 3059, 3124 (furan-H, alkenyl C-H); 677,746 (Ar-H)	7.38 (1H, d, H-α), 7.91 (1H, d, H- β), 6.91 (1H, d, H-3), 7.03 (1H, dd, H-4), 7.24 (1H, d, H-6), 7.4(1H, dd, H-6), 7.46 (1H, d, H-5)
Bd 4	340	1599,1419(C=C); 653(C=O); 3317 (furan-H, alkenyl C-H); 700,765 (Ar-H)	7.45 (1H, d, H-α), 7.91 (1H, d, H-β), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 6.94 (1H, d, H-3), 7.04 (1H, dd, H-4), 7.19 (1H, d, H-6)
Bd 5	343	1593 (C=C); 1654 (C=O); 3014, 3072 (alkenyl C-H), 607,813 (Ar-H)	7.40 (1H, d, H-α), 7.91 (1H, d, H-β), 3.72 (3H, s, OMe), 3.78 (3H, s, OMe), 6.86 (1H, d, H-3), 6.91 (1H, dd, H-4), 7.02 (2H, dd, H-3 and H-6), 7.14 (1H, d, H-6)
Bd 6	341	1587 (C=C); 1651 (C=O), 3026 (aliphatic C-H), 684,725 (Ar-H)	7.02 (1H, d, H-α), 7.48 (1H, d, H- β), 3.83 (3H, s, OMe), 6.88(2H, dd, H-3 and H-5), 6.93 (1H, d, H-3), 7.02 (1H, dd, H-4), 7.15 (1H, d, H-6), 7.46(2H, dd, H-2 and H-6)
Bd 7	313	1506 (C=C); 1656 (C=O); 3076 (aliphatic C-H); 613, 744 (Ar-H)	7.44 (1H, d, H-α), 7.48 (1H, d, H β), 6.41 (1H, d, CH), 7.73 (1H, d, CH), 6.93 (1H, d, H-3), 7.06 (1H, dd, H-4), 7.35 (1H, d, H-6), 7.39 (1H, dd, H-4), 7.42 (1H, dd, H-5), 7.65 (1H, dd, H-2)

Table-3 Effect of synthesized compound on *pheretima posthuma*

Sl No.	Treatment	Concentration Used (mg/ml)	Time taken for paralysis (Mean ± SEM)	Time taken for death (mean± SEM)
1	Control	0.1% 0.2% 0.5% 1%	- - - -	- - - -
2	Albendazole	0.1% 0.2% 0.5% 1%	2.37±0.04 2.04±0.23 1.21±0.06 0.72±0.15	4.54±0.02 4.30±0.21 3.42±0.04 2.49±0.31
3	Bd 1	0.1% 0.2% 0.5% 1%	2.45±0.21 2.09±0.36 1.54±0.03 1.12±0.17	7.37±0.95 5.20±0.22 4.07±0.75 2.08±0.20
4	Bd 2	0.1% 0.2% 0.5% 1%	6.02±0.32 5.05±0.17 4.10±0.22 3.52±0.29	11.51±0.24 10.41±0.06 9.02±0.22 8.27±0.03
5	Bd 3	0.1% 0.2% 0.5% 1%	6.10±0.28 4.83±0.17 4.37±0.43 3.12±0.42	16.23±0.46 13.31±0.43 11.15±0.43 8.42±0.39
6	Bd 4	0.1% 0.2% 0.5% 1%	5.44±0.26 4.94±0.41 4.30±0.26 3.24±0.32	10.07±0.48 9.37±0.80 7.69±0.19 6.90±0.93

7	Bd 5	0.1% 0.2% 0.5% 1%	5.30±0.25 4.57±0.18 4.17±0.25 3.04±0.29	10.46±0.38 9.35±0.08 7.40±0.21 5.45±0.04
8	Bd 6	0.1% 0.2% 0.5% 1%	8.98±0.79 8.18±0.39 5.54±0.23 4.37±0.31	20.91±0.42 19.09±0.32 15.32±0.98 13.32±0.37
9	Bd 7	0.1% 0.2% 0.5% 1%	11.17±0.46 9.01±0.42 7.42±0.48 6.10±0.21	25.45±1.17 22.23±1.09 21.25±0.37 18.04±0.89

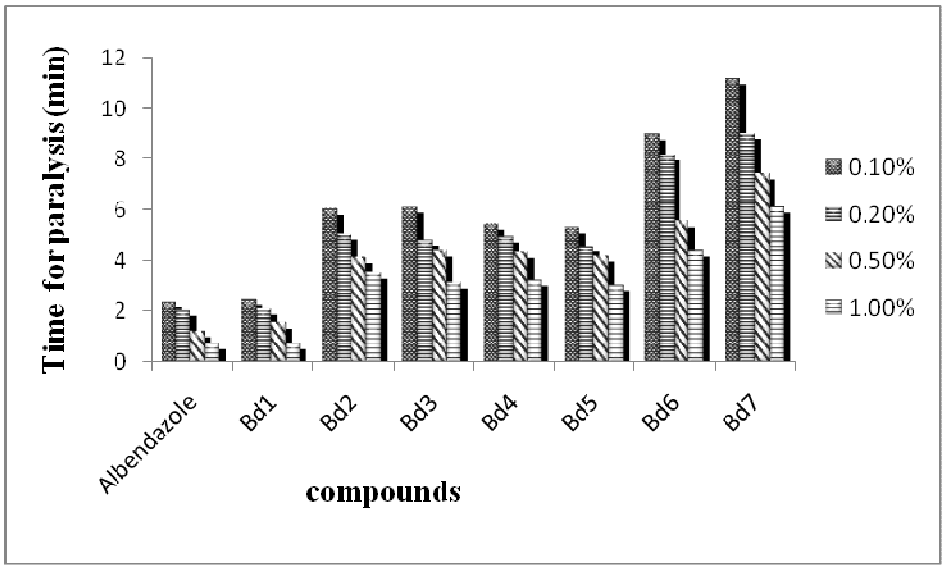


Figure:1 Anthelmintic activity of compounds: (in case of paralysis)

Table-4 Minimum inhibitory concentration data for synthesized compounds

Strains used	Concentration of the synthesized compounds(µg/ml)						
	Bd 1	**Bd 2**	**Bd 3**	**Bd 4**	**Bd 5**	**Bd 6**	**Bd 7**
S_1^+	150*	700*	500*	500*	700*	700*	700*
S_2^+	400*	600*	500*	500*	500*	500*	800*

S_8^+	250*	500*	500*	500*	600*	600*	700*
E_6^-	150*	700*	500*	500*	500*	600*	600*
V_6^-	150*	700*	600*	400*	600*	600*	700*
SG_7^-	150*	800*	700*	600*	700*	700*	900*

*Solvent DMF, S_1^+, S_2^+, S_8^+, E_6^-, V_6^- and SG_7^- indicates *S. aureus* NCTC 6571, *S. aureus* NCTC 8530, *S. aureus* ML 27, *E. coli* HD 10, *V. cholera* 71 and *S. dysentriae* 6 respectively.

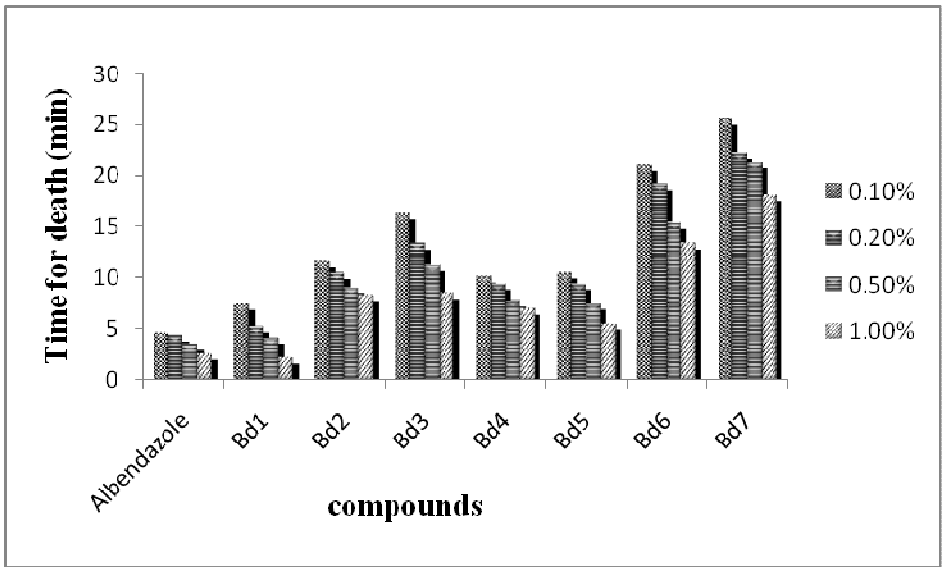


Figure:2 Anthelmintic activity of compounds: (in case of death)

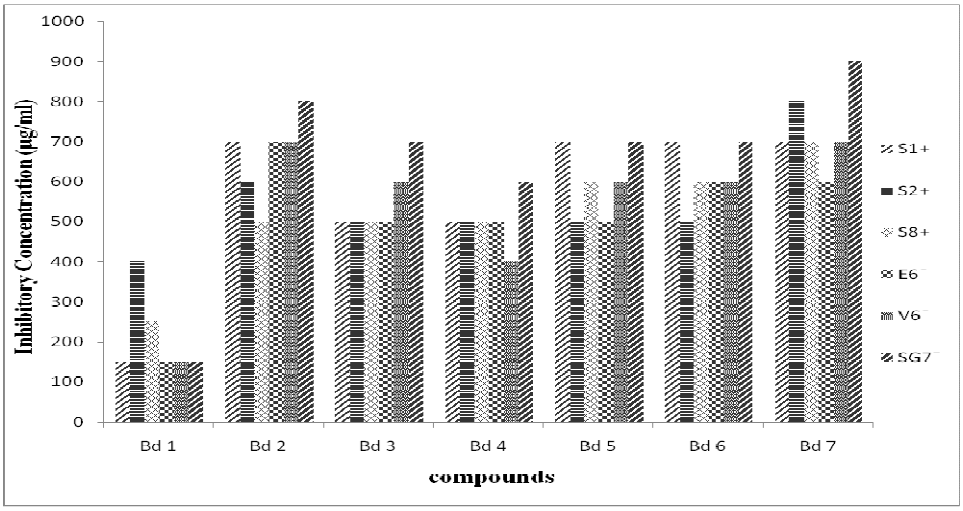


Figure-3 Minimum inhibitory concentration of the synthesized compound in different strains of bacteria

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