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# Synthesis and Biological Evaluation of Some Novel Chalcone Derivatives

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In this study, substituted chalcone derivatives were synthesized and their analgesic and antiinflammatory activities were assayed. Chalcone derivatives were prepared 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 analgesic and antiinflammatory activities in mice at the dose of 100 mg/kg i.p.; however, a few of them exhibited good activity, almost equivalent to that of aspirin at 1 mg/kg was observed. At the above dosage, no toxicity was observed for all compounds.

**Key Words: Chalcone, Antiinflammatory, Analgesic activity.**

## INTRODUCTION

The chalcones are α, β unsaturated ketones containing the reactive keto ethylenic 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[1], antifungal[2], insecticidal[3], ulcerogenic[4], anticancer[5], *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[6].

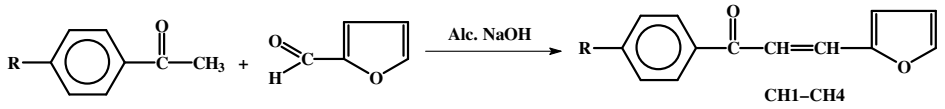
As per the recent literature some novel synthetic chalcones that inhibit *in vivo* eosinophilia, but clearly show differential effects on eosinophil functions. Both chalcones inhibit cytokine-induced VCAM-1 protein expression and block IL-5-mediated survival of eosinophils. Inhibition of de-granulation 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[7].

## EXPERIMENTAL

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 and IR spectra were recorded in KBr pellets using a Shimadzu FTIR-8400S spectrophotometer. The $^1$H NMR spectra were recorded in DMSO-$d_6$

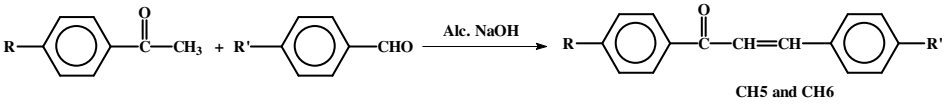
by NMR 300 MHz spectrometers using tetramethyl silane as an internal standard. All the chemicals and solvents used in this study were of analytical grade (S.D. Fine Chem. Limited, Mumbai).

**General scheme of 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 0.5 h 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 h, the reaction mixture was neutralized by 0.1-0.2 N HCl whereby the precipitation occurred. On filtering off, the crude chalcone was dried in air and recrystallized from rectified spirit.



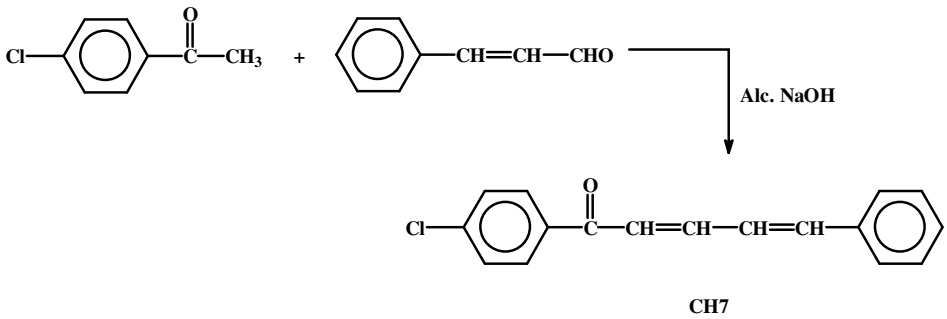

CH1–CH4

**Scheme-I:** Synthesis of chalcone with 5 membered heterocyclic aromatic aldehyde




CH5 and CH6

**Scheme-II:** Synthesis of chalcone with 6 membered aromatic aldehyde




CH7

**Scheme-III:** Synthesis of chalcone with cinnamaldehyde

**Animals:** The Swiss albino mice (20-25 g) and adult Wistar albino rats of either sex weighing between 120-150 g maintained in our college animal house were used for the study. The animals were maintained at a well-ventilated, temperature-controlled (30 ± 1 °C) animal room for 7 d prior to the experimental period and provided with pelleted diet, water *ad libitum* and kept in 12 h light-dark cycle. All animal experiments were performed following the approval of study protocols by the Institutional Animal Ethics Committee (HPI/08/60/IAEC, 0026).

TABLE-1
PHYSICO-CHEMICAL DATA OF CHALCONE DERIVATIVES

| Entry | R | $R^1$ | m.f. | m.w. | m.p. (ºC) | Yield (%) | Nomenclature |
|---|---|---|---|---|---|---|---|
| CH1 | H | - | $C_{13}H_{10}O_2$ | 198.0 | 37-40 | 46.00 | 1-[phenyl-3-furfuryl]prop-2-en-1-one |
| CH2 | 2 – OH | - | $C_{13}H_{10}O_3$ | 214.0 | 155-157 | 19.19 | 1-[2-hydroxyphenyl]-3-[furfuryl]prop-2-en-1-one. |
| CH3 | 4 – Cl | - | $C_{13}H_9OCl$ | 216.5 | 70-72 | 40.47 | 1-[4-chlorophenyl]-3-furfuryl prop-2-en-1-one. |
| CH4 | 3-OMe, 4-OMe | - | $C_{15}H_{14}O_4$ | 258.0 | 80-83 | 75.74 | 1-[3,4-dimethoxyphenyl]-3-[furfuryl]prop-2-en-1-one. |
| CH5 | 4-OMe | 4-OMe | $C_{17}H_{16}O_3$ | 268.0 | 120-122 | 16.74 | 1-[4-methoxy phenyl]-3-[4-methoxy-phenyl]prop-2-en-1-one |
| CH6 | 4-OMe | 4- F | $C_{16}H_{13}O_2F$ | 256.0 | 140-142 | 91.02 | 1-[4-methoxyphenyl]-3-[4-flurophenyl]prop-2-en-1-one |
| CH7 | 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 ($\lambda_{max}$) | IR (KBr, $\nu_{max}$, $cm^{-1}$) | $^1$H-NMR (300 MHz) (DMSO-*d*6) (ppm) |
|---|---|---|---|
| CH1 | 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) |
| CH2 | 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) |
| CH3 | 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) |
| CH4 | 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) |
| CH5 | 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) |
| CH6 | 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) |
| CH7 | 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) |

**Screening of analgesic activity:** The analgesic activity of synthesized compounds has been performed by Tail flick method[8]. In this method heat is used as a source of pain. The tips of the tail of the animals are individually placed on the radiant heat source at constant temperature 55 °C and the reaction of the animals, like flicking of the tail is noted. All the mice were weighed and divided into 9 groups (6 mice in each group). The group I served as control, given distilled water (1 mL/kg), while group II was given aspirin (100 mg/kg) i.p. as a standard drug. The remaining group III to IX was given synthesized compounds (CH1, CH2, CH3, CH4, CH5, CH6 and CH7) i.p. at dose (80 mg/kg, 1/10th of the LD50 dose). The tail-flick latency was assessed by the analgesiometer (Techno, India). Basal reaction time to radiant heat was taken by placing the tip of the tail of the mice on the radiant heat source. The tail withdrawal from the heat (flicking response) was taken as the end point. The reaction time was noted at 0.5, 1.0, 2.0 and 3.0 h time interval of the above mentioned groups after administration of compounds. The cut-off reaction time was fixed at 10 sec to avoid tissue damage[9-11]. The observations were recorded and tabulated in Table-3.

TABLE-3
EFFECT OF COMPOUNDS ON THERMALLY INDUCED NOCICEPTION IN MICE

| Group | Treatment | Dose (mg/kg) | Reaction time for tail flick in sec (Mean ± SEM) | | | |
|---|---|---|---|---|---|---|
| | | | 0.5 h | 1 h | 2 h | 3 h |
| 1 | Control | - | 2.20±0.30 | 2.28±0.25 | 2.37±0.25 | 2.49±0.20 |
| II | Aspirin | 100 | 3.57±0.15 | 4.4±0.26 | 5.46±0.31 | 6.02±0.23 |
| III | CH1 | 80 | 3.17±0.06 | 3.92±0.21 | 5.01±0.11 | 5.62±0.11 |
| IV | CH2 | 80 | 3.21±0.19 | 4.14±0.19 | 5.12±0.12 | 5.71±0.02 |
| V | CH3 | 80 | 3.14±0.10 | 3.89±0.05 | 4.94±0.03 | 5.49±0.11 |
| VI | CH4 | 80 | 3.15±0.11 | 3.90±0.15 | 4.96±0.14 | 5.56±0.19 |
| VII | CH5 | 80 | 3.18±0.12 | 4.10±0.31 | 5.02±0.05 | 5.72±0.09 |
| VIII | CH6 | 80 | 3.11±0.11 | 4.01±0.06 | 4.99±0.09 | 5.63±0.14 |
| IX | CH7 | 80 | 3.01±0.06 | 3.92±0.02 | 4.89±0.04 | 5.51±0.13 |

ANOVA and Dunnett multiple comparisons test (after 3 h)

| Source of variation | Degree of freedom (df) | Sum of square | Mean square | F | F-crit |
|---|---|---|---|---|---|
| Treatments (between groups) | 8 | 54.77 | 6.846 | 48.95 | 2.1521 |
| Residual (within groups) | 45 | 6.294 | 0.1399 | | |
| Total | 53 | 61.06 | | | |

n = 6 in each group. *p < 0.01 compared to control.

**Screening of antiinflammatory activity:** Antiinflammatory activity was determined by carrageenan-induced rat paw oedema method[12]. Wistar rats of either sex (120-150 g) were used in this study. All the rats were weighed and divided into 9 groups (6 rats in each group). The control (group I) received 0.2 % Tween suspension 5 mL/kg i.p. while group II was given aspirin (100 mg/kg) i.p. as a standard drug. The remaining group III to IX was given synthesized compounds (CH1, CH2, CH3,

CH4, CH5, CH6 and CH7) i.p. at dose (80 mg/kg, 1/10th of the LD50 dose). A mark was made on left paws just beyond tibio-tarsal junction (knee joint) of each animal of all groups, so that every time the paw was dipped in the water column of paw edema meter (520-R, IITC Life Science, USA) up to the fixed mark to ensure constant paw volume[13]. After 0.5 h carrageenan solution (1 % w/v) was injected in the planter region of the left paw of control, standard and test groups. After the administration of carrageenan solution, the paw volume of all groups was noted at 1, 2, 3 and 4 h time interval[14,15]. The initial volume of paw was measured immediately before the injection. The percentage inhibition of inflammation after 4 h was calculated by using following equation. The observations were tabulated in Table-4.

$$\% \text{ Inhibition} = 100\ [1 - (V_t)/(V_c)]$$

where, $V_t$ = Mean relative changes in the paw volume of each of the rats after the administration of carrageenan and test or standard compound. $V_c$ = Mean relative changes in the paw volume of each of the rats after the administration of carrageenan in the control group.

TABLE-4
EFFECT OF COMPOUNDS ON CARRAGEENAN-INDUCED PAW OEDEMA METHOD IN RATS

| Group | Treatment (100 mg/kg) | Dose (mg/kg) | Paw volume in mL (Mean ± SEM) (% inhibition of paw) | | | |
|---|---|---|---|---|---|---|
| | | | 1 h | 2 h | 3 h | 4 h |
| 1 | Control | 10 mL/kg | 0.75±0.03 | 0.95±0.01 | 1.02±0.02 | 1.17±0.01 |
| 2 | Aspirin | 100 | 0.52±0.02 (30.66) | 0.65±0.01 (31.57) | 0.69±0.02 (32.35) | 0.75±0.03 (35.89) |
| 3 | CH1 | 80 | 0.61±0.01 (18.66) | 0.71±0.01 (25.26) | 0.76±0.02 (25.49) | 0.77±0.01 (34.18) |
| 4 | CH2 | 80 | 0.56±0.01 (25.33) | 0.70±0.02 (26.31) | 0.75±0.03 (26.47) | 0.78±0.04 (33.33) |
| 5 | CH3 | 80 | 0.60±0.01 (20) | 0.75±0.03 (21.05) | 0.78±0.02 (23.52) | 0.84±0.03 (28.20) |
| 6 | CH4 | 80 | 0.62±0.01 (17.33) | 0.73±0.01 (23.15) | 0.83±0.01 (18.62) | 0.84±0.01 (28.20) |
| 7 | CH5 | 80 | 0.49±0.02 (34.67) | 0.64±0.02 (32.63) | 0.71±0.02 (30.39) | 0.80±0.01 (31.62) |
| 8 | CH6 | 80 | 0.59±0.01 (21.33) | 0.69±0.01 (27.36) | 0.79±0.01 (22.54) | 0.83±0.02 (29.05) |
| 9 | CH7 | 80 | 0.60±0.01 (20) | 0.67±0.01 (29.47) | 0.79±0.02 (22.54) | 0.81±0.02 (30.76) |

ANOVA and Dunnett multiple comparisons test (after 4 h)

| Source of variation | Degree of freedom (df) | Sum of square | Mean square | F | F-crit |
|---|---|---|---|---|---|
| Treatments (between groups) | 8 | 0.7531 | 0.09413 | 36.60 | 2.1521 |
| Residual (within groups) | 45 | 0.1157 | 0.002572 | | |
| Total | 53 | 0.8688 | | | |

n = 6 in each group. *p < 0.01 compared to control.

## 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 analgesic and antiinflammatory activities. The result of the analgesic activity was given in Table-3. From this table it was concluded that almost all the derivatives have same biological response. The result of the anti-inflammatory activity was given in Table-4. From this table it was found that the compound CH1 has more activity than the other analogues but less than the standard aspirin. 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). Statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Dunnett's test for multiple comparisons, using Graph-pad software package. All statistical data are significant at $p < 0.05$ level.

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