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Synthesis, Characterization and Antiulcer Activity of Halogen Containing Chalcones

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ABSTRACT

In the present study, a series of ten chalcone derivatives were synthesized by Claisen-Schmidt condensation and evaluated for their antiulcer activity. Chalcones are a group of naturally occurring compounds and precursor of flavonoids, isoflavonoids and important constituents of natural products such as fruits, vegetables, spices, tea and soya based food stuff. The structures of the compounds were characterized by Infra-Red (IR), Proton Nuclear Magnetic Resonance (^{1}H-NMR) and mass spectral analysis. All the chalcones were evaluated for their antiulcer activity by using albino rats and the activity was measured by using methanol induced gastric ulcer model. The results of the best synthesized chalcones suggested that the presence of electron releasing groups and halogen moieties on aromatic ring showed best antiulcer activity and it was measured in terms of % antiulcer activity.

Keywords: Chalcones, Claisen-Schmidt condensation, Antiulcer activity

INTRODUCTION

Chalcones are medicinally important class of compounds, acts as precursors of flavonoid and isoflavonoid. The name chalcone was given by Kostanecki and Tambor [1]. Recent studies on biological evaluation of chalcones revealed that most of them are found to exhibit pharmacological activities such as antimalarial [2,3], antiplatelet [4], anticancer [5-7], antiulcer [8], antioxidant [9-11], anti-inflammatory [12-14], antiviral [15], antimicrobial [16,17], antileishmanial [18], antifungal [19,20]. Chalcone forms the central core for the variety of biological compounds and chemically 4-bromoactophenone in which two aromatic rings are liked by highly electrophilic three carbons α, β-unsaturated carbonyl system [21]. The presence of α, β-unsaturated functional group make chalcone biologically active [22].

Among worldwide Non-steroidal Anti-inflammatory Drugs (NSAID's) still remain among the most extensively drugs and have been used in the treatment of rheumatoid arthritis, osteoarthritis, orthopedic injuries etc, [23,24]. But the use of conventional NSAID's has been restricted due to its side effects especially gastric erosion and ulcers [25-27]. Chalcones containing radical quenching properties of phenolic group have raised interest in using the compounds [28,29]. The aim of the present study is to design, synthesize and evaluate the antiulcer activity of chalcones containing halogen moiety.

MATERIALS AND METHODS

The chemicals used in the present work were AR grade and LR grade, purchased from Avra Synthesis Pvt. Ltd. The synthesized compounds were scaled for yield and purified by recrystallization with suitable solvent system. The melting points were recorded in open capillaries with electrical melting point apparatus and were uncorrected. The Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded at 400 MHZ at Bruker NMR spectrophotometer in sodium Carboxy Methyl Cellulose (CMC) and chemical shifts are expressed in parts per million (s) relative to Tetramethylsilane (TMS). ^{1}H-NMR spectral was recorded at room temperature on a 300 MHZ Varian spectrophotometer in Ethanol using TMS as internal standard [30]. The IR spectra were recorded on Schimadzu FTIR using 8400 s using KBr pellet technique. Purification was done by Thin Layer Chromatography (TLC) using precoated plates silica gel (HF254-200mgh) aluminium plate from E-Merk using ethyl acetate, n-hexane (4:1) as the mobile phase detection of the spots was done under UV chamber [31].

General method of preparation of halogen substituted chalcones (CH 01-CH 10)

Chalcone derivatives was synthesized by Clasien-Schmidt condensation reaction, by taking a mixture of 4-bromo acetophenone and substituted benzaldehyde (1-10) were dissolved in 20 ml of methanol and sufficient volume of 30% Potassium Hydroxide (KOH) drop wise with continuous stirring [32]. The reaction mixture was stirred at room temperature for 24 h. The sodium salts of chalcones (CH 01-CH 10) were separated with ice cold Hydrochloric Acid (10% HCl).

The separated solid precipitated was filtered and washed with ice cold water until filtrate was neutralized; the crude chalcones were dried in hot air oven and recrystallized by rectified sprit [33].

3-[4-(benzyloxy)phenyl]-1-(4-bromophenyl)prop-2-en-1-one (CH 01)

Yield: 76%; m.p: 245°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1656.3, C=C stretching 1608.7; ^{1}H-NMR (400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 8.06 (1H, s, β-H), 7.59 (1H, s, α-H), 7.62 (2H, d, C-2, C-6, Ar-H), 6.94 (2H, d, C-3, C-5, Ar-H), 5.16 (1H, s, α-H), 7.47 (2H, d, C-2, C-6, Ar-H), 7.38 (3H, t, C-3, C-4, C-5, Ar-H), MS (m/z): $C_{22}H_{17}BrO_2$, C, 67.19; H, 4.36; Br, 20.32; O, 8.14.

1-(4-bromophenyl)-3-[4-(methylsulfanyl)phenyl]prop-2-en-1-one (CH 02)

Yield: 75%; m.p: 214°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1656.3, C=C stretching 1608.7; ^{1}H-NMR (400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 8.06 (1H, s, β-H), 7.59 (1H, s, α-H), 7.28 (2H, d, C-2, C-6, Ar-H), 7.35 (2H, d, C-3, C-5, Ar-H), 2.53 (3H, s, S-CH_3), $C_{16}H_{13}BrOS$, C, 57.67; H, 3.98; Br, 23.98; O, 4.80; S, 9.62.

1-(4-bromophenyl)-3-(2-chloro-6-fluorophenyl)prop-2-en-1-one (CH 03)

Yield: 73%; m.p: 237°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1656.3, C=C stretching 1608.7; ^{1}H-NMR (400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 7.42 (1H, s, α-H), 8.33 (1H, s, β-H), 7.21 (1H, d, C-3, Ar-H), 7.14 (1H, t, C-4, Ar-H), 7.07 (1H, d, C-5, Ar-H), $C_{16}H_{13}BrOS$, C, 53.05; H, 2.67; Br, 23.53; Cl, 10.44; F, 5.59; 0, 4.71.

1-(4-bromophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (CH 04)

Yield: 84%; m.p: 210°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1656.3, C=C stretching 1608.7; ^{1}H-NMR (400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 8.06 (1H, s, β-H), 7.59 (1H, s, α-H), 7.68 (2H, d, C-2, C-6, Ar-H), 7.44 (2H, d, C-3, C-5, Ar-H), $C_{15}H_{10}BrClO$, C, 56.02; H, 3.13; Br, 24.85; Cl, 11.02; O, 4.97.

1-(4-bromophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (CH 05)

Yield: 57%; m.p: 258°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1656.3, C=C stretching 1608.7; ^{1}H-NMR (400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 8.06 (1H, s, β-H), 7.59 (1H, s, α-H), 7.62 (2H, d, C-2, C-6, Ar-H), 6.94 (2H, d, C-3, C-5, Ar-H), 3.83(3H, s, OCH_3), $C_{16}H_{13}BrO_2$, C, 60.59; H, 4.13; Br, 25.19; O, 10.09.

1-(4-bromophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (CH 06)

Yield: 81%; m.p: 231°C; IR (KBr, cm^{-1}): C-H stretching 3128.7, C=O stretching 1636.3, C=C stretching 1618.7; ^{1}H-NMR (400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 8.06 (1H, s, β-H), 7.59 (1H, s, α-H), 6.78 (2H, s, C-2, C-6, Ar-H), 3.38 (9H, t, OCH_3), $C_{18}H_{17}BrO_4$, C, 57.31; H, 4.54; Br, 21.18; O, 16.97.

1-(4-bromophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (CH 07)

Yield: 82%; m.p: 221°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1643.3, C=C stretching 1608.7; ^{1}H-NMR(400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 8.06 (1H, s, β-H), 7.59 (1H, s, α-H), 7.56 (2H, d, C-2, C-6, Ar-H), 6.65 (2H, d, C-3, C-5, Ar-H), 5.35 (1H, s, -OH), $C_{15}H_{11}BrO_2$, C, 60.21; H, 4.74; Br, 25.03; O, 10.02.

1-(4-bromophenyl)-3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (CH 08)

Yield: 83%; m.p: 215°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1652.3, C=C stretching 1608.7; ^{1}H-NMR(400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 7.42 (1H, s, α-H), 8.33 (1H, s, β-H), 6.09 (2H, s, C-3, C-5 Ar-H), 3.83 (9H, s, OCH_3), C18$H_{16}BrO_4$, C, 52.52; H, 3.92; Br, 19.41; Cl, 8.61; O, 15.55.

1-(4-bromophenyl)-3-(4-ethylphenyl)prop-2-en-1-one (CH 09)

Yield: 78%; m.p: 222°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1616.3, C=C stretching 1608.7; ^{1}H-NMR(400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 8.06 (1H, s, β-H), 7.59 (1H, s, α-H), 7.66 (2H, d, C-2, C-6, Ar-H), 6.77 (2H, d, C-3, C-5), 2.60 (1H, s, Al-H), 1.25 (3H, s, CH_3), $C_{17}H_{15}BrO$, C, 64.78; H, 4.80; Br, 25.35; O, 5.08.

1-(4-bromophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one(CH 10)

Yield: 88%; m.p: 207°C; IR (KBr, cm^{-1}): C-H stretching 3138.7, C=O stretching 1661.3, C=C stretching 1608.7; ^{1}H-NMR (400 mHz, DMSO, δ ppm): 7.79 (2H, d, C-3, C-5, Ar-H), 8.01 (2H, d, C-2, C-6, Ar-H), 7.42 (1H, s, α-H), 8.33 (1H, s, β-H), 5.35 (1H, s, OH), 6.72 (1H, d, Ar-H), 7.16 (1H, t, Ar-H), 6.96 (1H, t, Ar-H), 7.60 (1H, d, Ar-H); MS (m/z): $C_{15}H_{11}BrO_2$, C, 59.43; H, 3.66; Br, 26.36; O, 10.56.

Antiulcer activity

Anti-ulcer activity of all synthesized compounds was evaluated by using alcohol (ethanol) induced ulcer model in albino rats. Albino rats weighing 150-200 g were divided into 13 groups each group consisting of 6 animals and starved for 24 h. The test compounds were administered orally 30 min prior to ethanol administration (100 mg/kg). Normal group received only vehicle (1% sodium CMC) where as the standard group received omeprazole (30 mg/kg body weight) and test groups were treated with synthesized novel compounds CH 01-CH 10. After 1 h of drug treatment all the animals were sacrificed according to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines and stomach was cut open in the greater curvature, washed with ice cold saline solution and cleaned. The gastric mucosa was examined for ulcer scoring by using 4X binocular magnifier. The ulcer score was measured according to its severity in comparison with that of the standard. Ulcer scores were recorded as follows. (0) Normal, no ulcer, (1) Isolated hemorrhagic spot, (2) Dense hemorrhagic spot, (3) Small ulcer, (4) Large ulcer, (5) Peroration. The severity of the mucosal damage was assessed by Ulcer Index (UI) and it was calculated by using the formula [34-37]:

$$U_I = (U_N + U_S + U_P) \times 10^{-1}$$

Where, (U_N) Average of number of ulcers per animal, (U_S) Average of severity score and (U_P) Percentage of animals with ulcers. The mean ulcer index and percentage protection produced by different test compounds are presented in Table 1 along with their statistical significance in Figures 1 and 2.

Table 1: Antiulcer activity of synthesized chalcones

Groups (Treatment)	Ulcer index	Ulcer score	% Protection
Normal (Sodium CMC)	0.000 ± 0.000	0.000 ± 0.000	100
Control (Ethanol)	10.3 ± 0.0258	2.17 ± 0.307	0
Standard (Omeprazole)	0.000 ± 0.000	0.000 ± 0.000	100
CH 01	6.94 ± 0.0211***	2.00 ± 0.365	17
CH 02	5.15 ± 0.0224***	1.00 ± 0.365	53
CH 03	8.65 ± 0.0167***	2.33 ± 0.333	17
CH 04	8.61 ± 0.0307***	2.00 ± 0.365	17
CH 05	5.15 ± 0.0224***	1.00 ± 0.365	52
CH 06	1.72 ± 0.0167***	0.333 ± 0.211**	83
CH 07	6.87 ± 0.0211***	1.33 ± 0.422	33
CH 08	3.41 ± 0.0211***	0.500 ± 0.224**	67
CH 09	8.53 ± 0.0307***	1.17 ± 0.307	33
CH 10	5.17 ± 0.0224***	1.17 ± 0.477	50

All the data was expressed n mean ± SEM and was analyzed with one way ANNOVA using Dunnet's post hoc test comparing with control and was found satisfactorily at **P<0.01; ***P<0.001

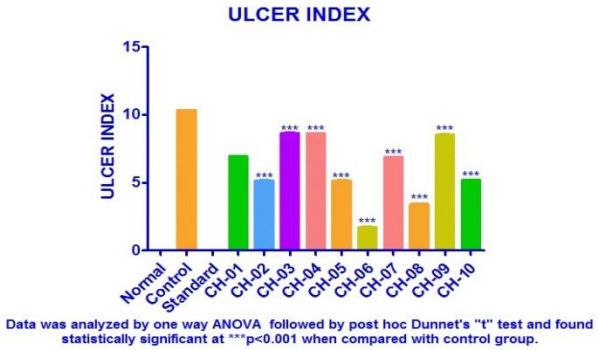


Figure 1: Ulcer index values of synthesized chalcones (CH-01-CH-10)

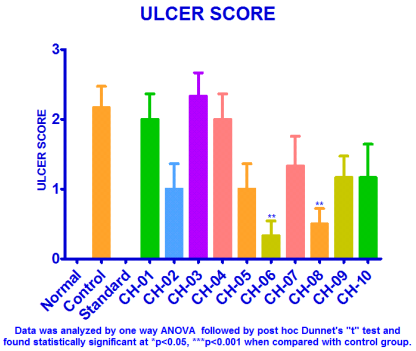
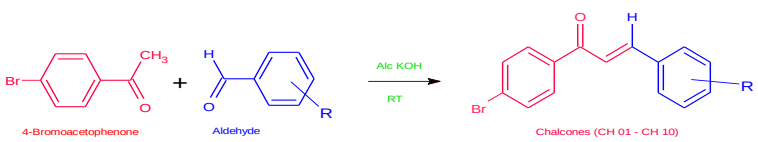


Figure 2: Ulcer scores of synthesized chalcones (CH 01-CH 10)

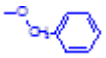
RESULTS AND DISCUSSION

Chemistry

The synthesis of 1-(4-bromophenyl)-3-(substituted aryl)prop-2-en-1-one (CH 01-CH 10) were represented in Scheme 1. The synthesized compounds are structurally elucidated by elemental and spectral analysis (^{1}H-NMR, FTIR, Mass spectra). The IR spectrum of synthesized compounds (CH 01-CH 10) showed a characteristic bands within the range of 1656.3 cm^{-1}, 3138.7 cm^{-1} and 1608.7 cm^{-1} due to C=O, C-H and C=C respectively. The proton spectrum (^{1}H-NMR) of all the synthesized compounds showed doublet signal with the chemical shift value of α-hydrogens at 7.42 ppm, β hydrogens at 8.33 ppm and multiplet signals of aromatic hydrogens in than range of 6.9-7.6 ppm.



Scheme 1: Synthesized chalcones (CH 01-CH 10)

Chalcone	Radicals				
	R_2	R_3	R_4	R_5	R_6
CH 01	-H	-H		-H	-H
CH 02	-H	-H	-S-CH_3	-H	-H
CH 03	-H	-H	-Cl	-H	-H
CH 04	-Cl	-H	-H	-H	-F
CH 05	-H	-H	-O-CH_3	-H	-H
CH 06	-H	-O-CH_3	-O-CH_3	-O-CH_3	-H
CH 07	-H	-H	-OH	-H	-H
CH 08	-O-CH_3	-H	-O-CH_3	-H	-O-CH_3
CH 09	-H	-H	-C_2H_5	-H	-H
CH 10	-OH	-H	-H	-H	-H

Biological activity

The ethanol induced acute gastric mucosal injury model is considered to be one of the important and widely used experimental models for ulcer disease. Ethanol causes the gastric damage by altering protective factors, including decreasing the mucus production and blood circulation within the mucosa. In this alcohol induced gastric lesion model, the chalcones CH 06 and CH 08 showed 83% and 67% ulcer protection respectively with low ulcer index and ulcer score values compared with the ulcer control group respectively as shown in Table 1; Figures 1 and 2.

CONCLUSION

The concept of antiulcer activity signifies protection against mucosal injury by a mechanism other than inhibition of acid secretion. Among all the synthesized chalcones, methoxylated derivatives are the future promising molecules while showing a significant protection in ethanol induced gastric lesions in rats, to a greater degree than the reference drug omeprazole which showed 64.56% protection ($P<0.01$). Omeprazole is an oral cytoprotective drug, primarily indicated for the treatment of active duodenal ulcers.

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