

## ANTI-INFLAMMATORY AND GASTROPROTECTIVE PROPERTIES OF SOME CHALCONES.

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**Abstract:** The synthesis of 1,3-diaryl propen-1-ones (chalcones) by the Claisen-Schmidt condensation between acetophenones and benzaldehydes in potassium hydroxide /methanol medium at room temperature yielded: 1-(4-nitrophenyl)-3-(2,4,6-trimethoxyphenyl)propen-1-one (**3a**), 1-(4-nitrophenyl)-3-(3-bromophenyl)propen-1-one (**3b**), 1-(4-methoxyphenyl)-3-(3-bromophenyl)propen-1-one (**3c**), 1-(4-methoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propen-1-one (**3d**), 1-(2,4-dihydroxyphenyl)-3-(phenyl)propen-1-one (**3e**), 1-(4-nitrophenyl)-3-(4-chlorophenyl)propen-1-one (**3f**) which were evaluated for anti-inflammatory activity at doses of 20, 40 and 80mg/kg. The compounds were found to be effective inhibitors of carrageenan-induced rat paw edema in Wistar rats and this activity was dose dependent and increased between the third and fourth hour. The gastroprotective activity of the compounds was investigated (using 200 mg/kg acetylsalicylic acid-induced ulceration) in Wistar rats at a single dose of 100 mg/kg for all the compounds synthesized and compound **3d** had significant activity ( $p < 0.001$ ) comparable to cimetidine. The compounds were found to have anti-inflammatory and anti-ulcer activities at the doses employed.

**Keywords:** Chalcones, anti-inflammatory activity, anti-ulcer activity, prostaglandin synthesis.

Chalcones or 1,3-diaryl-2-propen-1-ones are natural or synthetic compounds belonging to the flavonoid family. They exhibit a wide range of biological activities, which include antiviral and anti-cancer (1-3), anti-microbial (4-5), anti-inflammatory (3,6-8), anti-ulcer and spasmolytic (9-10) and antiproliferative (11) activities thus comprise a class with important therapeutic potentials.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used as anti-inflammatory agents but their use often causes gastric erosion and ulcers, which are among the most serious clinical problems (12-13). NSAID induced gastric damage has been attributed to suppression of endogenous prostaglandin synthesis resulting in the direct toxic effect on the gastric epithelial cells such as apoptosis or necrosis (14). The inhibition of prostaglandin biosynthesis, which has cyto-protective effect on the gastric mucosa, was thought to be the major mechanism of gastrointestinal problems with NSAIDs (15).

Therefore, the synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemists in recent years. For this purpose chalcones were prepared using a classical base catalyzed condensation reaction of substituted

acetophenones and benzaldehydes. The chalcones were evaluated for possible anti-inflammatory as well as for gastroprotective properties.

### EXPERIMENTALS

Melting points were measured on a Kofler hot stage apparatus and were uncorrected. The IR spectra were recorded on a Perkin-Elmer Paragon PC 1000 spectrophotometer in KBr pellets. The NMR spectra were recorded on a Varian Gemini 200 apparatus. Chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were acquired on a Varian MAT 44S mass spectrometer operating at 70 eV. Elemental analyses were in agreement with the calculated values. Analytical thin layer chromatography (TLC) was used to monitor the reactions.

### Chemistry

#### General procedure

Compounds **3a-3f** were obtained by reaction of appropriate acetophenone and benzaldehydes (1:1) in the presence of 10% potassium hydroxide and methanol (25-30 mL) and the reaction mixture was

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added to 50% diluted acetic acid according to the methodology previously described (16). The respective products were purified by recrystallization or column chromatography on silica gel. The purity of the compounds was determined by TLC using several solvent systems of different polarity.

**1-(4-Nitrophenyl)-3-(2,4,6-trimethoxyphenyl)propen-1-one (3a)**

To a stirred solution of 4-nitroacetophenone (1.65 g, 0.01 mol) in 25 mL of methanol 2,4,6-trimethoxybenzaldehyde (1.96 g, 0.01 mol) was added and treated as in the general procedure to give **3a**. Recrystallization from methanol; yield 2.79 g, (81%); m.p. 195-197° C; IR (KBr,  $\text{cm}^{-1}$ ): 2850 (C-H), 1700 (C=O), 1600 (C=C), 1320, 1200.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 3.75-3.84 s, 9H (3  $\times$  -OCH<sub>3</sub>); 6.07 s, 1H (Ar-H); 6.13 s, 1H (Ar-H); 6.93-6.99 d, 1H,  $J = 15.83$  Hz, (HC=CH); 7.85-7.92 d, 1H,  $J = 15.83$  Hz, (HC=CH); 8.01-8.04 d, 2H,  $J = 8.92$ , (Ar'-H); 8.20-8.27 d, 2H,  $J = 8.83$  Hz, (Ar'-H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 49.90 (OCH<sub>3</sub>), 106.65, 113.18, 128.73, 129.42, 130.59, 130.81, 137.42, 137.51, 148.01 (Ar-C), 188.13 (C=O). Anal. C<sub>18</sub>H<sub>17</sub>NO<sub>6</sub> (343.336) Calcd.: 62.97% C. 4.99% H. 4.08% N. Found: 62.87% C. 5.29% H. 4.21% N.

**1-(4-Nitrophenyl)-3-(3-bromophenyl)propen-1-one (3b)**

To a stirred solution of 4-nitroacetophenone (3.01 g, 0.018 mol) in 30 mL of methanol 3-bromobenzaldehyde (3.35 g, 0.018 mol) was added and treated as in the general procedure to give **3b**. Recrystallization from methanol; yield 5.03 g, (87%); m.p. 131-133° C; IR (KBr,  $\text{cm}^{-1}$ ): 2890 (C-H), 1730 (C=O), 1620 (C=C), 1320, 1200:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.32-7.37 d, 1H,  $J = 15.06$  Hz, (HC=CH); 7.45-7.51d, 1H,  $J = 15.68$  Hz, (HC=CH); 7.55-7.60 m, 3H (Ar'-H); 7.73 s, 1H (Ar'-H); 8.14-8.17d, 2H,  $J = 6.94$  Hz, (Ar-H); 8.34-8.38 d, 2H,  $J = 8.96$  Hz, (Ar-H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 122.38, 123.21, 123.90, 127.47, 129.43, 130.43, 131.02, 133.88, 136.35, 142.62, 144.84, 150.18 (Ar-C), 188.53 (C=O). Anal. C<sub>15</sub>H<sub>10</sub>NO<sub>3</sub>Br (332.153) Calcd. : 54.24% C. 3.03% H. 4.22% N. Found: 54.01% C. 3.20% H. 4.02% N.

**1-(4-Methoxyphenyl)-3-(3-bromophenyl)propen-1-one (3c)**

To a stirred solution of 4-methoxyacetophenone (3.01 g, 0.02 mol) in 30 mL of methanol 3-bromobenzaldehyde (3.81 g, 0.02 mol) was added and treated as in the general procedure to give **3c**.

Recrystallization from ethanol; yield 6.11 g, (96%); m.p. 108-109°C (Lit.(17) 108°C); IR (KBr,  $\text{cm}^{-1}$ ): 2890 (C-H), 1720 (C=O), 1610 (C=C), 1320, 1200, 960.  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 3.18 s, 3H (OCH<sub>3</sub>); 7.05-7.08 d, 1H,  $J = 8.93$  Hz, (Ar-H); 7.35-7.41d, 1H,  $J = 15.01$  Hz, (HC=CH); 7.78-7.84 d, 1H,  $J = 15.01$  Hz, (HC=CH); 7.97 s, 1H (Ar'-H); 8.15-8.20 m, 3H (Ar'-H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 55.36 (OCH<sub>3</sub>), 113.94, 121.38, 122.32, 123.46, 127.18, 129.59, 130.21, 139.44, 130.66, 131.00, 132.75, 137.28, 141.29 (Ar-C), 187.13 (C=O). Anal. C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>Br (317.182) Calcd.: 60.59% C. 4.13% H. Found: 60.47% C. 4.39% H.

**1-(4-Methoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propen-1-one (3d)**

To a stirred solution of 4-methoxyacetophenone (2.25 g, 0.015 mol) in 30 mL of methanol 2,4,6-trimethoxybenzaldehyde (3.00 g, 0.015 mol) was added and treated as in the general procedure to give **3d**. Recrystallization from methanol; yield 1.04 g, (21%); m.p. 135-136°C; IR (KBr,  $\text{cm}^{-1}$ ): 2980(C-H), 1710(C=O), 1600(C=C), 1200, 960.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 3.75-3.87 s, 12H (4  $\times$  -OCH<sub>3</sub>); 6.07 s, 1H (Ar-H); 6.13 s, 1H (Ar-H); 6.93-6.99 d, 1H,  $J = 15.83$  Hz, (HC=CH); 7.85-7.92 d, 1H,  $J = 15.83$  Hz, (HC=CH); 8.01-8.04 d, 2H,  $J = 8.92$ Hz, (Ar'-H); 8.20-8.27 d, 2H,  $J = 15.83$ Hz, (Ar'-H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 55.38 (OCH<sub>3</sub>), 90.22, 90.52, 106.65, 113.18, 113.54, 121.82, 130.59, 130.81, 132.14, 135.14, 162.79, 164.09, 166.22 (Ar-C), 187.70 (C=O). Anal. C<sub>19</sub>H<sub>20</sub>O<sub>5</sub> (328.365) Calcd.: 69.50% C. 6.14% H. Found: 69.27% C. 6.38% H.

**1-(2,4-Dihydroxyphenyl)-3-(phenyl)propen-1-one (3e)**

To a stirred solution of 2,4-dihydroxyacetophenone (1.39 g, 0.009 mol) in 25 mL of methanol benzaldehyde (0.97 g, 0.009 mol) was added and treated as in the general procedure to give **3e**. Recrystallization from methanol; yield 1.40 g, (64%); m.p. 138-139°C; IR (KBr,  $\text{cm}^{-1}$ ): 3210(OH), 1650 (C=O), 1570 (C=C), 1280 (C-O), 1120, 810.  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 6.24-6.25 d, 1H,  $J = 2.50$  Hz, (HC=CH); 6.33-6.34 d, 1H,  $J = 2.50$  Hz (HC=CH); 6.34-6.37 m, 5H (Ar-H); 7.68-7.72 m, 3H (Ar'-H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 26.11, 26.44, 101.69, 102.79, 108.06, 112.72, 113.50, 133.97, 164.19, 164.73, 164.90 (Ar-C), 202.52 (C=O). Anal. C<sub>15</sub>H<sub>12</sub>O<sub>3</sub> (240.258) Calcd.: 74.99% C. 5.03% H. Found: 75.21% C. 5.29% H.

Table 1. Anti-inflammatory activity of the test compounds relative to control.

Compounds	Doses (mg/kg) (p.o.)	Change in paw edema mean $\pm$ SEM in mm		% Activity	
		3 <sup>rd</sup> h	4 <sup>th</sup> h	3 <sup>rd</sup> h	4 <sup>th</sup> h
<b>3a</b>	20	2.83 $\pm$ 2.14 <sup>*</sup>	1.40 $\pm$ 2.10 <sup>**</sup>	39.40	62.67
	40	2.05 $\pm$ 2.09 <sup>**</sup>	1.30 $\pm$ 1.08 <sup>**</sup>	56.10	65.33
	80	1.42 $\pm$ 1.12 <sup>**</sup>	1.08 $\pm$ 1.25 <sup>**</sup>	69.59	71.20
<b>3b</b>	20	4.13 $\pm$ 1.51	3.80 $\pm$ 0.43	11.56	36.53
	40	3.63 $\pm$ 1.24	2.30 $\pm$ 0.24	22.27	36.67
	80	1.63 $\pm$ 1.12 <sup>**</sup>	0.38 $\pm$ 0.79 <sup>**</sup>	65.09	89.87
<b>3c</b>	20	3.39 $\pm$ 2.24	1.88 $\pm$ 2.12 <sup>*</sup>	27.62	49.87
	40	3.13 $\pm$ 2.31	1.81 $\pm$ 2.37 <sup>*</sup>	33.08	51.73
	80	2.13 $\pm$ 1.12 <sup>*</sup>	0.75 $\pm$ 1.14 <sup>**</sup>	54.50	80.00
<b>3d</b>	20	2.88 $\pm$ 2.21 <sup>*</sup>	1.88 $\pm$ 2.41 <sup>*</sup>	38.44	49.57
	40	2.38 $\pm$ 1.31 <sup>*</sup>	1.44 $\pm$ 1.21 <sup>**</sup>	49.04	61.62
	80	2.25 $\pm$ 2.14 <sup>*</sup>	1.19 $\pm$ 3.11 <sup>**</sup>	51.82	68.33
<b>3e</b>	20	3.5 $\pm$ 0.5	2.75 $\pm$ 2.43	25.05	26.67
	40	3.38 $\pm$ 0.12	2.13 $\pm$ 1.12 <sup>*</sup>	27.60	43.33
	80	3.25 $\pm$ 0.32	2.02 $\pm$ 0.28 <sup>*</sup>	30.41	46.62
<b>3f</b>	20	4.75 $\pm$ 2.75	3.75 $\pm$ 1.95	-1.17	0
	40	4.75 $\pm$ 2.25	3.63 $\pm$ 1.37	-1.71	3.20
	80	3.13 $\pm$ 1.55	2.38 $\pm$ 0.68 <sup>*</sup>	32.98	36.53
Indomethacin	10	1.21 $\pm$ 3.36 <sup>**</sup>	1.26 $\pm$ 2.24 <sup>**</sup>	74.09	66.40
Tween 80 (10%)	0.3 ml	4.67 $\pm$ 1.03	3.75 $\pm$ 2.98	-	-

Values are mean  $\pm$  S.E.M \*  $p < 0.05$ , \*\*  $p < 0.001$ , significantly different from control, Paired t- test (n = 5), p.o. = per oral, % = percentage

### 1-(4-Nitrophenyl)-3-(4-chlorophenyl) propen-1-one (3f)

To a stirred solution of 4-nitroacetophenone (1.00 g, 0.006 mol) in 25 mL of methanol 4-chlorobenzaldehyde (0.85 g, 0.006 mol) was added and treated as in the general procedure to give **3f**. Recrystallization from methanol; yield 1.42 g, (84%); mp 154-156° C; IR (KBr, cm<sup>-1</sup>): 2890(C-H), 1700 (C=O), 1620 (C=C), 1320, 1200,968. <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>)  $\delta$  (ppm): 7.17- 7.24 d, 1H,  $J = 17.52$  Hz, (HC=CH); 7.27- 7.34 d, 1H,  $J = 17.62$  Hz, (HC=CH); 7.36-7.39 d, 1H,  $J = 8.50$  Hz, (Ar-H); 7.48-7.52 d, 1H,  $J = 8.67$  Hz, (Ar-H); 7.76-7.82 m, 2H (Ar'-H); 8.01-8.37 m, 2H (Ar'-H). <sup>13</sup>C NMR (63 MHz, DMSO-d<sub>6</sub>)  $\delta$  (ppm): 122.92, 124.20, 128.68, 129.36, 130.27, 131.17, 131.59, 133.74, 135.89, 142.55, 144.40, 150.27 (Ar-C), 188.64 (C=O). MS: 288.6 [M<sup>+</sup>+ 1] (5%), 287.8 (20), 251.7 (100), 239.7 (15), 177.7 (14), 136.4 (10), 101.4 (15), 74.3 (11). Anal. C<sub>15</sub>H<sub>10</sub>NO<sub>3</sub>Cl (287.702) Calcd.: 62.62% C. 3.50% H 4.87% N. Found: 62.47% C. 3.29% H. 4.63% N.

### Pharmacological evaluation

Wistar rats (180-220 g) of either sex kept at the laboratory animal home of the Faculty of Pharmacy,

Table 2. The gastroprotective activity of the test compounds.

Compounds	Doses (mg/kg) p.o.	No. of ulcer spots counted	% Anti-ulcer activity
<b>3a</b>	100	7.67 $\pm$ 0.29 <sup>**</sup>	64.47
<b>3b</b>	100	7.33 $\pm$ 0.29 <sup>**</sup>	66.29
<b>3c</b>	100	9.00 $\pm$ 0.71 <sup>**</sup>	58.62
<b>3d</b>	100	5.50 $\pm$ 0.96 <sup>**</sup>	74.71
<b>3e</b>	100	8.75 $\pm$ 0.85 <sup>**</sup>	59.77
<b>3f</b>	100	16.67 $\pm$ 1.15 <sup>*</sup>	23.36
Cimetidine	100	3.75 $\pm$ 0.75 <sup>**</sup>	82.76
Control 10% Tween 80	0.3 ml	21.75 $\pm$ 1.18	-

Values are mean  $\pm$  S.E.M \*  $p < 0.05$ , \*\*  $p < 0.001$ , significantly different from control, Paired t- test (n = 10), p.o. = per oral, % = percentage

University of Benin, Benin City, Nigeria were used. The animals were maintained under standard environmental conditions and had free access to standard diet and water (test compounds were administered orally by gavage in 10% Tween 80 suspension at different dose levels). Ethical approval was obtained from the Animals Use and Ethics Committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

### Anti-inflammatory activity

Anti-inflammatory activity was measured using carrageenan-induced rat paw edema assay (18, 19). Groups of 5 rats of both sexes (pregnant females excluded) were given a dose of a test compound. After 1 h 0.1 mL of 1% carrageenan suspension in 0.9% NaCl solution was injected into the subplantar tissue of the right hind paw. The linear paw circumference was measured at hourly intervals for 4 h (20). Two groups of drug treated rats and one control group were used each test day and the mean paw edema value for the test group was compared with the mean value for the control group for that day.

Anti-inflammatory activity (21) was measured as the percentage of reduction in edema level when drug was present, relative to control, as shown in Table 2. Indomethacin (10 mg/kg) was administered orally as reference drug whereas 10% Tween 80 was used as negative control. All data were expressed as the mean  $\pm$  SEM; the Student's *t*-test was applied to determine the significance of the difference between the control group and treated group.

**Anti-ulcer activity:** Gastric ulcers were induced by the administration of 200 mg/kg of acetylsalicylic acid orally (22). The animals were starved for 24 h and divided into 8 groups of 10 animals each. To one group 0.3 mL 10% Tween 80 was administered as negative control. To another group 100 mg/kg, cimetidine was administered as reference drug. To the last 6 groups 100 mg/kg of each of the synthesized chalcones were administered. One hour after administration of the drugs, acetylsalicylic acid was administered at a dose of 200 mg/kg to induce ulcers. Six hours later, the animals were sacrificed by cervical dislocation and the stomach quickly removed, open out along the greater curvature, care-

fully cleaned out with a gentle stream of running distilled water and ulcers formed on the granular mucosa were counted. The activity of the drugs was calculated as  $X \pm \text{SEM}$  and the percentage of inhibition of ulcers calculated using the formula.

$$\% \text{ Inhibition of ulcers} = \frac{C - T}{C} \times 100$$

Where C = total number of ulcer spots in control group

T = total number of ulcer spots in test group

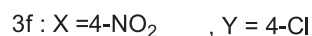
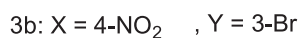
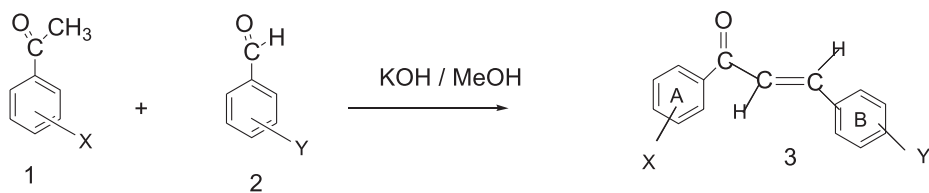
## RESULTS AND DISCUSSION

### Chemistry

The scheme shows the general synthetic procedure used. The compounds were generally obtained in good yields (64-96%). This may be attributed to the fact that the reactions took place at room temperature. When the temperature is allowed to exceed 30°C, some secondary reactions occur which diminish product yield and purity. However, 1-(4-methoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propen-1-one (**3d**) has a lower yield of 21%, which may be attributed to the methoxy groups attached to the aromatic rings of the reactants. This group has a positive mesomeric effect at the carbonyl carbon of the benzaldehydes thus leading to reduction in the yield of the product. The compounds were readily characterized by conventional spectral data. Inspection of the <sup>1</sup>H NMR spectra suggested that the chalcones were geometrically pure and configured *trans* ( $J_{\text{Ha-Hb}}$  = 15-16 Hz) (23).

### Pharmacology

The basis for the determination of anti-inflammatory activity at third and fourth hour is that with carrageenan-induced rat paw edema model peak inflam-



Scheme 1.

matory response occurs at 3-5 h (21). From the results obtained (summarized in Table 1) all the synthesized compounds show a dose-dependent inhibition of edema, with an increase in activity from 20 mg/kg to 40 mg/kg and to 80 mg/kg doses. At 20 mg/kg doses all the compounds except **3f**, had activity at third and fourth hour with increasing activities. From the pattern of anti-inflammatory activity, methoxy groups are needed for a faster onset of activity as is evident in the magnitude of activity of **3a** and **3d**.

The activities at 80 mg/kg show that the bromine atom at position 3 of ring B seems to be necessary for more inhibition of inflammation as shown with **3b** and **3c**.

The chlorine atom at position 4 of ring B seems to have caused the relatively low activity of **3f**. From the results obtained, it is evident that the synthesized compounds have increasing activity from third hour to fourth hour. However, the anti-inflammatory activity of the reference drug (indomethacin) is reduced during the same time. This may probably be due to the difference in the mechanism of action of these compounds. At the fourth hour **3b** and **3c** showed greater activity in comparison with the reference drug. It can be deduced from the above that the synthesized compounds may probably have the anti-oxidant properties (like other flavonoids). This is evident in their increase in activities at the fourth hour in comparison with indomethacin which had reduced activity at this time; indomethacin is, however, a well-known non-specific COX enzyme inhibitor. This result points to the conclusion that the compounds synthesized may not act in the same manner as indomethacin.

The difference in mechanism of action of these compounds is also evident in their anti-ulcer (gastro-protective) effect as shown from the results in Table 2, in which all the compounds show some activity against ulceration induced by 200 mg/kg dose of acetylsalicylic acid. If these agents were acting by the same mechanism, i.e. inhibition of prostaglandin synthesis then, they would rather have increased the number of ulceration but this was the opposite.

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