Synthesis and anti-inflammatory activity of fluorinated propanedione derivatives

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A new series of five 1-(2',4'-difluorophenyl)-3-(substituted phenyl)-1,3 propanediones from 2',4'-difluorinated chalcones have been synthesized. All the compounds (20 mg/kg po) possess anti-inflammatory activity, as reflected by their ability to provide protection (70.00 - 93.00%) against carrageenan induced edema in rat paw. Standard indomethacin provided 79.00% protection at the same dose. The safety of these substituted propanediones are reflected by toxicity studies.

Keywords: Difluorinated propanediones, dibromostyryl ketones, chalcones, anti-inflammatory activity, acute toxicity studies

Compounds containing β-diketone unit exhibit anti-inflammatory and anti-mitotic activities1-4. We have previously reported some difluorinated chalcone derivatives as potentially active anti-inflammatory agents5. The presence of fluorine enhances therapeutic efficacy and lipid solubility6,7,8. In view of these observations, five novel propanedione analogues with fluorine substitution in aromatic ring were synthesised. The 2',4'-difluorinated chalcones were synthesised by Claisen Schmidt condensation reaction using variously substituted benzaldehydes and 2',4'-difluoroacetophenone followed by bromination of chalcones to give dibromostyryl ketones. These dibromostyryl ketones were treated with methanolic KOH to synthesise 1-(2',4'-difluorophenyl)-3-(substituted phenyl)-1,3 propanediones. They were evaluated for anti-inflammatory activity using carrageenan induced paw edema model and acute toxicity studies were carried out to determine their safety.

Results and Discussion

Difluorinated chalcones 1a-1e were prepared starting from 2',4'-difluoroacetophenone following the reported procedure5. These compounds were converted to dibromo derivatives 2a-2e, which on treatment with methanolic KOH gave the difluorinated propanediones 3a-3e (Scheme I).

The anti-inflammatory activities of 3a-3e (Table I) were studied in vivo for their percent inhibition of edema in the carrageenan model of inflammation in rats using the method illustrated by Winter et al.9.

The percent inhibition of edema was calculated against the control on the basis of experimental data obtained. Statistical analysis revealed that anti-inflammatory activity of all propanedione derivatives was comparable to standard drug indomethacin with m-bromo substituted compound 3d exhibiting highest inhibition i.e., 93.00%. All the propanedione derivatives exhibited encouraging anti-inflammatory activity. The low toxicity of synthesized compounds was evident from the observation that there was no mortality in mice at doses upto 2000 mg/kg.

A comparison of the anti-inflammatory activities of the difluorinated propanediones and the corresponding chalcones reveal that the propanediones possessed better activity (Figure 1).

Materials and Methods

All melting points were recorded on a Veego VMP-D apparatus and are uncorrected. All solvents were used after distillation. All reactions were monitored by TLC using Merck pre-coated silica gel 60 F254 plates and spots were visualized by observing in UV cabinet under short UV. 2',4'-difluoroacetophenone was synthesized in-house. All other reagents and solvents were purchased from S. D. Fine Chemicals, Mumbai and Lancaster (Germany). IR spectra (KBr) were recorded on a Shimadzu, 8400S FT-IR. Spectrometer and values expressed in cm⁻¹. ¹H NMR spectra were recorded in CDCl₃ on an EL Varian 300 MHz instrument using TMS as an internal reference. Chemical shift values are reported in δ (ppm).

Experimental Section

General method for synthesis of fluorinated chalcones

A series of 2',4'-difluorinated chalcones 1a-1e were prepared by condensing substituted benzaldehydes...
NOTES

365

![Chemical structures](image)

(0.02 moles) and 2',4'-difluoroacetophenone (0.01 moles), using solid sodium hydroxide in ethanol at RT (Scheme I). Five compounds were synthesized viz. 2',4'-difluoro-4-methoxychalcone, 1a; 2',4'-difluoro-4-chlorochalcone, 1b; 2',4'-difluoro-3-nitrochalcone, 1c; 2',4'-difluoro-3-bromochalcone, 1d; 2',4'-difluoro-4-fluorochalcone, 1e. Their synthesis, physical constant and spectral characterization have been reported in an earlier paper 5.

**General method for synthesis of 2',4'-((difluorophenyl)dibromostyrylketones 2a-2e**

2',4'-((Difluorophenyl)styrylketones (0.01 moles) were vigorously stirred for 0.5 hr in chloroform (10 mL) while bromine was added in a dropwise manner. The reaction-mixture was allowed to stand for an hour. The precipitated product was filtered, washed with ether to remove excess of bromine and recrystallised from ethanol.

**Table I — In vivo anti-inflammatory activities of fluorinated propanediones**

<table>
<thead>
<tr>
<th>Compd</th>
<th>Vt-Vo [Mean ± SEM]</th>
<th>% Inhibition of edema at the end of three hours.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>0.09±0.010</td>
<td>79.00*</td>
</tr>
<tr>
<td>3a</td>
<td>0.088±0.017</td>
<td>81.23*</td>
</tr>
<tr>
<td>3b</td>
<td>0.126±0.020</td>
<td>70.00*</td>
</tr>
<tr>
<td>3c</td>
<td>0.090±0.012</td>
<td>79.00*</td>
</tr>
<tr>
<td>3d</td>
<td>0.073±0.008</td>
<td>93.00*</td>
</tr>
<tr>
<td>3e</td>
<td>0.075±0.004</td>
<td>83.30*</td>
</tr>
</tbody>
</table>

Values expressed as Mean ± SEM, n = 6 in each group. *P<0.01 compared with control.

![Graph](image)

Figure 1 — Comparison of anti-inflammatory activities of propanediones and chalcones
2,3-Dibromo-1-(2′,4′-difluorophenyl)-3-(3-bromophenyl)propan-1-one, 2d. Yield 93.10%; m.p. 94°C; IR (KBr): 1689, 1099, 1610, 1213, 1210, 539 cm⁻¹; ¹H NMR (CDCl₃): δ 5.64 (dd, 1H), 5.73 (dd, 1H), 6.99-7.27 (m, 4H), 7.45-7.50 (m, 2H), 8.07-8.15 (m, 1H).

2,3-Dibromo-1-(2′,4′-difluorophenyl)-3-(p-fluorophenyl)propan-1-one, 2e. Yield 62.5%; m.p. 83°C; IR (KBr): 1683, 1000, 1610, 1228, 551 cm⁻¹; ¹H NMR (CDCl₃): δ 5.54 (dd, 1H), 5.71 (dd, 1H), 6.93-7.09 (m, 2H), 7.27-7.32 (m, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.64 (s, 1H), 8.11-8.21 (m, 1H).

General method for synthesis of 1-(2′,4′-difluorophenyl)-3-(substituted phenyl)-1,3-propanediones 3a-3e

A solution of KOH (2.5 g) in methanol (25 mL) was added to a solution of 2′,4′-(difluorophenyl)dibromostyrylketones (0.01 moles) in methanol (200 mL) and the contents were refluxed for 3 hr in a boiling water-bath. The mixture was cooled in an ice bath and the KBr that separated was filtered. The filtrate was acidified with Conc. HCl, diluted with water and refluxed for 2 hr. The contents were cooled and the solid that separated out was filtered washed with water and recrystallised from acetic acid.

1-(2′,4′-Difluorophenyl)-3-(p-methoxyphenyl)propane-1,3-dione, 3a. Yield 76.73%; m.p. 153°C; IR (KBr): 1622, 1595, 1099, 1190 cm⁻¹; ¹H NMR (CDCl₃): δ 3.88 (s, 2H), 3.98 (s, 3H, OCH₃), 6.67 (dd, 1H), 6.81 (dd, 1H), 6.85 (s, 1H), 6.97 (d, 1H), 7.92-8.02 (m, 2H), 8.18 (s, 1H).

1-(2′,4′-Difluorophenyl)-3-(p-chlorophenyl)propane-1,3-dione, 3b. Yield 72.30%; m.p. 102°C; IR (KBr): 1620, 1593, 1093, 1238, 1290 cm⁻¹; ¹H NMR (CDCl₃): δ 3.88 (s, 2H), 6.67 (dd, 1H), 6.81 (dd, 1H), 6.90 (s, 1H), 7.45 (d, 2H), 7.89 (d, 1H), 8.01 (t, 1H).

1-(2′,4′-Difluorophenyl)-3-(3-nitrophenyl)propane-1,3-dione, 3c. Yield 88.42%; m.p. 144°C; IR (KBr): 1605, 1505, 1097, 1210, 1234 cm⁻¹; ¹H NMR (CDCl₃): δ 3.89 (s, 2H), 6.45 (dd, 1H), 6.83 (dd, 1H), 6.98 (s, 1H), 7.68 (t, 1H), 7.99-8.07 (m, 1H), 8.41-8.27 (m, 1H), 8.79 (s, 1H).

1-(2′,4′-Difluorophenyl)-3-(3-bromophenyl)propane-1,3-dione, 3d. Yield 88.57%; m.p. 105°C; IR (KBr): 1616, 1589, 1078, 1238, 1213 cm⁻¹; ¹H NMR (CDCl₃): δ 3.87 (s, 2H), 6.65 (dd, 1H), 6.80 (dd, 1H), 6.86 (s, 1H), 7.11-7.20 (m, 2H), 7.94-8.07 (m, 2H).

1-(2′,4′-Difluorophenyl)-3-(p-fluorophenyl)propane-1,3-dione, 3e. Yield 78.13%; m.p. 93°C; IR (KBr): 1605, 1050, 1097, 1610, 1234 cm⁻¹; ¹H NMR (CDCl₃): δ 3.88 (s, 2H), 6.69 (dd, 1H), 6.82 (dd, 1H), 6.89 (s, 1H), 7.36 (t, 1H), 7.67 (d, 1H), 7.93 (d, 1H), 7.98-8.10 (m, 1H).

Anti-inflammatory activity

Animals

Sprague-Dawley rats (140-200 g) of both sexes were used for the studies. These rats were obtained from the Department of Biopharmaceutics, Haffkine Institute, Mumbai. The animals were divided into groups of six each and fasted for 12 hr before the experiment. The ethical guidelines prescribed for the investigation of animals used in experiments were followed in all tests.

Paw edema induced by carrageenan

Carrageenan (0.1 mL, 1%) was administered into the plantar surface of the right hind paw of the animals. The experimental groups, negative control group (0.5% CMC), and positive control group (20 mg/kg Indomethacin) were given either the control drug or test compounds orally, 1 hr prior to the administration of the carrageenan. Before injection of carrageenan, the average volume (V₀) of the right hind paw of each rat was calculated from 3 readings that did not deviate more than 3%. After injection of the phlogistic agent, the paw volume (Vₜ) was measured after 3 hr with the aid of a plethysmometer. The edema was expressed as an increase in the volume of paw and percentage inhibition of acute edema was obtained as follows:

\[ \% \text{Inhibition} = \left[1 - \left( \frac{\Delta V_{\text{experimental}}}{\Delta V_{\text{control}}} \right) \right] \times 100 \]

where,

\[ \Delta V = V_t - V_0 = \text{Mean paw volume.} \]

Data analysis

Results are presented as mean ± SEM (standard error of mean) of six rats. Statistical analysis were performed using one-way analysis of variance (ANOVA) followed by Dunnett’s test for multiple comparisons, using Graph-pad Software. \( P \) values of \( P < 0.05 \) were taken as significant.

Toxicity study

Acute toxicity of 1-(2′,4′-difluorophenyl)-3-(substituted phenyl)-1,3-propanediones was determined in albino mice with the Staircase method. Each group of 5 animals was fasted for 24 hr prior to the
administration of the test compounds. The test compounds, 3a-3e, were administered orally in doses up to 2000 mg/kg and mice were kept under observation for a period of 24 hr.

**Conclusion**

We prepared newer series of 1-(2',4'-difluorophenyl)-3-(substituted phenyl)-1,3-propanediones. All five compounds synthesized have shown good anti-inflammatory activity in the carrageenan-induced paw edema model. Conversion of the difluorinated chalcones to difluorinated propanediones seems to provide better protection against inflammation.

**References**


