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Note

Synthesis and anti-inflammatory activity of fluorinated chalcone derivatives

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A series of twelve 2',4'-difluorinated chalcones have been synthesized by Claisen-Schmidt condensation of 2',4'-difluoroacetophenone with appropriately substituted benzaldehydes. These compounds have then been subjected to preliminary anti-inflammatory screening using the carrageenan induced rat paw oedema model. Compounds **1, 7, 10** and **11** have activity comparable to indomethacin at 20 mg kg^{-1} by oral route.

Keywords: Chalcones, 2',4'-difluoroacetophenone, substituted benzaldehydes, Claisen-Schmidt condensation, anti-inflammatory activity

Due to the interesting activity of chalcone derivatives as biological agents, considerable attention has been focused on this class of compounds. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, anticancer, antileishmanial and antitubercular agents[1-6]. Some of these compounds are also known to possess anti-inflammatory and analgesic properties[7-21].

Recently, fluorinated chalcone derivatives have been reported to possess anti-inflammatory activity due to their influence on nitric oxide production[13]. Useful alterations in the biological activity often results from the introduction of fluorine in a molecule, due to altered physicochemical properties[22, 23].

In this study, is described the synthesis and anti-inflammatory evaluation of twelve 2',4'-difluorinated chalcone derivatives.

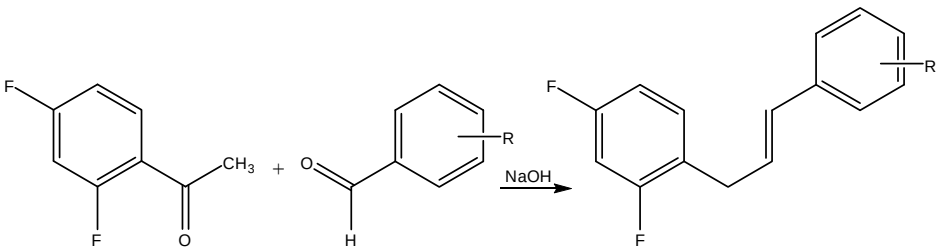
Results and Discussion

The general synthetic plan employed to synthesize the chalcone derivatives used the Claisen-Schmidt condensation, which has been previously reported[15]. A series of 2',4'-difluorinated chalcones **1-12** were prepared by condensing variously substituted benzaldehydes with 2',4'-difluoroacetophenone, using solid sodium hydroxide in ethanol at RT (**Scheme I**). This procedure afforded various chalcone derivatives in good yield and the products were always obtained as the *trans*-alkene (*E*-form) as determined by ^{1}H NMR spectroscopy.

The anti-inflammatory activities of **1-12** (**Table I**) were studied *in-vivo* for their percent inhibition of oedema in the carrageenan model of inflammation in rats using the method illustrated by Winter *et al*[24,25]. The percent inhibition of oedema was calculated against the control on the basis of experimental data obtained. All the fluorinated chalcone derivatives exhibited anti-inflammatory activity. Compounds **1, 7, 10** and **11** showed activity comparable to standard drug indomethacin and the remaining compounds showed lower activity.

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 F_{254} 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 Shimadzu, 8400S FT-



Scheme I

Table I

Compd	V_t-V_0 (Mean ± SEM)	% inhibition of oedema at the end of 3 hr
Indomethacin	0.133 ± 0.012	75.04†
1	0.100 ± 0.003	81.23*†
2	0.400 ± 0.040	24.95*†
3	0.333 ± 0.021	37.52*†
4	0.300 ± 0.019	43.71*†
5	0.230 ± 0.021	56.28*†
6	0.333 ± 0.039	37.52*†
7	0.134 ± 0.009	74.85†
8	0.300 ± 0.008	43.71*†
9	0.267 ± 0.012	49.90*†
10	0.200 ± 0.033	62.47†
11	0.133 ± 0.004	74.85†
12	0.234 ± 0.036	56.09*†

Values expressed as Mean ± SEM, n = 6 in each group
*P<0.05 compared with indomethacin.
†P<0.05 compared with control.

IR spectrometer and values expressed in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ on an EL Varian 300 MHz instrument using TMS as an internal reference. Chemical shift values are reported in δ (ppm).

Experimental Section

Chemistry

General method for synthesis of fluorinated chalcones

These compounds were prepared by stirring a mixture of 2',4'-difluoroacetophenone (0.01 mol), substituted aromatic benzaldehydes (0.02 mol) and solid NaOH pellet (about 100 mg) in 20 mL of 95% ethanol for 0.5 hr. The reaction mixture was then allowed to stand for 1 hr. The precipitated product was filtered and purified by recrystallization from ethanol.

2',4'-difluoro-4-methoxychalcone, 1

Yield 66%; m.p. 84°C; IR (KBr): 1659, 1598, 1191, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.86 (s, 3H, OCH_3), 6.87-7.02 (m, 4H), 7.23-7.30 (m, 1H), 7.59 (d, *J*= 7.8 Hz, 2H), 7.75 (d, *J*= 15.6 Hz, 1H, β-H), 7.88 (q, *J*= 7.8 Hz, 1H, 3'-H).

2',4'-difluoro-3-nitrochalcone, 2

Yield 86%; m.p. 141°C; IR (KBr): 1670, 1612, 1199, 1098 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.91-7.06 (m, 2H), 7.51 (d, *J*=15.6 Hz, 1H, α-H), 7.62 (t, *J*= 8.1 Hz, 1H, 5-H), 7.83 (d, *J*=15.6 Hz, 1H, β-H), 7.91-7.97 (m, 2H), 8.27 (d, *J*= 8.4 Hz, 1H, 4-H), 8.5 (s, 1H, 2-H).

2',4'-difluoro-3,4,5-trimethoxychalcone, 3

Yield 75%; m.p. 97°C; IR (KBr): 1664, 1608, 1190, 1098 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.91 (s, 9H, OCH_3), 6.85 (s, 2H), 6.88-7.07 (m, 2H), 7.24 (m, 1H), 7.68 (d, *J*= 14.7 Hz, 1H, β-H), 7.89 (q, *J*= 6.6 Hz, 1H, 3'-H).

2',4'-difluoro-3,4,5-trimethoxy-2-methylchalcone, 4

Yield 73%; m.p. 88°C; IR (KBr): 1665, 1592, 1192, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.56 (s, 1H, 6-H), 6.86-7.02 (m, 2H), 7.65 (dd, *J*= 15.6 Hz, 1H, α-H), 7.87-7.98 (m, 2H).

2',4'-difluoro-4-chlorochalcone, 5

Yield 74%; m.p. 102°C; IR (KBr): 1658, 1599, 1334 1191, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.98-7.04 (m, 2H), 7.33-7.40 (m, 3H), 7.56 (d, *J*= 8.7Hz, 2H), 7.73 (d, *J*= 15.6 Hz, 1H, β-H), 7.88 (q, *J*= 7.8 Hz, 1H, 3'-H).

2',4'-difluoro-2-nitrochalcone, 6

Yield 65%; m.p. 110°C; IR (KBr): 1659, 1610, 1557, 1197, 1097, 870 cm^{-1}; ^{1} H NMR ($CDCl_3$): δ 6.89-7.06 (m, 2H), 7.26 (dd, *J*= 15.6 Hz, 1H, α-H), 7.58 (t, *J*= 7.8 Hz 1H, 4-H), 7.66-7.76 (m, 2H), 7.92 (q, *J*= 7.5 Hz, 1H, 3'-H), 8.08 (d, *J*= 7.8 Hz, 1H, 3-H), 8.15 (d, *J*= 15.6 Hz, 1H, β-H).

2',4'-difluoro-3-bromochalcone, 7

Yield 82%; m.p. 98°C; IR (KBr): 1666, 1607, 1228, 1191, 1094 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.88-7.05 (m, 2H), 7.30-7.46 (m, 4H), 7.74 (dd, *J*= 9.6 Hz, 1H, 5-H), 7.91 (q, *J*= 8.1 Hz, 1H, 3'-H), 8.17 (d, *J*= 15.9 Hz, 1H, β-H).

2',4'-difluoro-2-chlorochalcone, 8

Yield 64%; m.p. 61°C; IR (KBr): 1659, 1604, 1334, 1199, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.89-7.04 (m, 2H), 7.31 (d, *J*= 7.8 Hz, 2H), 7.38 (dd, *J*= 15.6 Hz, 1H, α-H), 7.54 (d, *J*= 7.8 Hz, 1H, 6-H), 7.69 (d, *J*= 15.6 Hz, 1H, β-H), 7.77 (brs, 1H, 3-H), 7.91 (q, *J*= 8.1 Hz, 1H, 3'-H).

2',4'-difluoro-4-methylchalcone, 9

Yield 61%; m.p. 80°C; IR (KBr): 1664, 1599, 1195, 1099 1cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.4 (s, 3H,

CH_3), 6.87-7.03 (m, 2H), 7.22 (d, *J*= 7.8 Hz, 2H), 7.34 (dd, *J*= 15.6 Hz, 1H, α-H), 7.53 (d, *J*= 7.8 Hz, 2H), 7.75 (d, *J*= 15.6 Hz, 1H, β-H), 7.89 (q, *J*= 7.5 Hz, 1H, 3'-H).

2',4'-difluoro-4-bromochalcone, 10

Yield 79%; m.p. 102°C; IR (KBr): 1664, 1606, 1228, 1192, 1091cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.88-7.04 (m, 2H), 7.38 (dd, *J*= 15.6 Hz, 1H, α-H), 7.49 (d, *J*= 8.4 Hz, 2H), 7.56 (d, *J*= 8.4 Hz, 2H), 7.71 (d, *J*= 15.6 Hz, 1H, β-H), 7.91 (q, *J*= 7.8 Hz, 1H, 3'-H).

2',4'-difluoro-4-fluorochalcone, 11

Yield 66%; m.p. 67°C; IR (KBr): 1662, 1612, 1191, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.88-7.04 (m, 2H), 7.08-7.14 (m, 2H), 7.29-7.34 (dd, *J*= 15.6 Hz, 1H, α-H), 7.60-7.65 (m, 2H), 7.74 (d, *J*= 7.8 Hz, 1H, β-H), 7.90 (q, *J*= 7.8 Hz, 1H, 3'-H).

2',4'-difluoro-4-dimethylaminochalcone, 12

Yield 66%; m.p. 121°C; IR (KBr): 2921, 1659, 1603, 1310, 1187, 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 6H, NMe_2), 6.69 (d, *J*= 9 Hz, 2H), 6.85-6.99 (m, 2H), 7.17 (dd, *J*= 15.6 Hz, 1H, α-H), 7.53 (d, *J*= 9 Hz, 2H), 7.73 (d, *J*= 15.3 Hz, 1H, β-H), 7.85 (q, *J*= 8.1 Hz, 1H, 3'-H).

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 oedema induced by carrageenan

0.1 mL of 1% carrageenan in distilled water 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 ($V_\circ$) 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 (V_t) was measured after 3 hr with the aid of a plethysmometer. The oedema was expressed as an increase in the volume of paw and percentage inhibition of acute oedema was obtained as follows:

$$\% \text{ Inhibition} = [1-(\Delta V_{test}/ \Delta V_{control})] \times 100$$

where,

$\Delta V = V_t - V_0$, V= Mean Paw Volume

Data analysis

Results are presented as mean ± SEM (standard error of mean) of six rats. Statistical analyses 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.

Conclusion

Attempts have been made to prepare a newer series of 2',4'-difluorinated chalcones. Of the twelve compounds, four have shown promising results. However, in order to exploit their therapeutic potential, further extensive studies need to be carried out.

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