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Synthesis and anti-inflammatory activity of three nitro chalcones ☆

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ABSTRACT

The aim of this study was to synthesize three nitro substituted chalcones and to evaluate their anti-inflammatory activity in the model of carrageenan induced edema in rats. The nitro chalcone were prepared by aldol condensation using of mechanical agitation and environmentally friendly solvents with 72–73% yields in approximately 2 h. The three structures were evaluated on biological activity at dose of 200 mg/kg and they showed anti-inflammatory protective effect by both oral and intraperitoneal administration, this effect was time dependent.

Chalcones are part of the selected group of chemical compounds associated with diverse pharmacological activities. The chalcone structure has been reported in compounds with anti-inflamatory, anti-ulcerative, antibacterial, antifungal and antimalarial activities among others.[1–5]

Chalcones and their derivatives are polyphenolic compounds of the flavonoids family. They have been found in many plants as metabolic precursors of other flavonoids and isoflavonoids.[6] It is noteworthy to mention that the presence of chalcones have been reported in plants traditionally employed for therapeutical purposes.[7,8]

From a synthetic point of view, there is a great interest for the development of structural analogues of chalcones.[8] The Claisen–Schmidt condensation between acetophenone derivatives with benzaldehyde derivatives, with both acid and basic catalysis has been by far the leading reaction employed for these compounds, as shown in Figure 1.[9]

Furthermore, the synthesis of new chalcone analogues is growing nowadays, because of the potential anti-inflammatory activities they may exhibit, which make them attractive candidates for the treatment of chronic diseases which involve inflammatory processes, for example, *diabetes mellitus*.[10]

On behalf of this, the objectives of this work were to synthesize three nitro-substituted chalcones and to evaluate their anti-inflammatory activity in the carrageenan induced paw edema model in rat.

The synthesis of the three nitro-chalcones was conducted by the Claisen–Schmidt condensation between 2′-nitroacetophenone (**1**), 3′-nitroacetophenone (**2**) and 4′-nitroacetophenone (**3**) and benzaldehyde (4), this reaction was promoted wit sodium hydroxide (NAOH) according to previously reported procedure[11] (Fig. 2).

All the reagents were analytical-reagent grade and were used without further purification. The general procedure started with the preparation of a solution of NaOH (6.7 mmol) in water (6 mL). This solution was cooled at 0 °C with an ice bath, and ethanol (10 mL) was slowly added, the reaction flask was then removed from the ice bath and set at room temperature before the slow addition of the corresponding acetophenone (10 mmol) after this, benzaldehyde (10 mmol) was slowly added to the reaction mixture, which was left at room temperature with mechanical agitation for 2 h, afterwards the reaction mixture was cooled at 0 °C for 24 h. The solid products were filtrated from the crude mixture, washed with cold water and recrystallized with a dichloromethane/ethanol mixture. The crystals thus obtained were dried at 70 °C and properly stored at room temperature prior their physicochemical and spectroscopic characterizations and the determination of their anti-inflammatory activity. The chalcones prepared with this procedure were: (*E*)-1-(2′-nitrophenyl)-3-phenylprop-2-en-1-one (2′-nitrochalcone) (**5**); (*E*)-1-(3′-nitrophenyl)-3-phenylprop-2-en-1-one (3′-nitrochalcone) (**6**) and (*E*)-1-(4′-nitrophenyl)-3-phenylprop-2-en-1-one (4′-nitrochalcone) (**7**).

The three chalcones were obtained in good yields (>75%). All of them were solids and they were poorly soluble in water and highly

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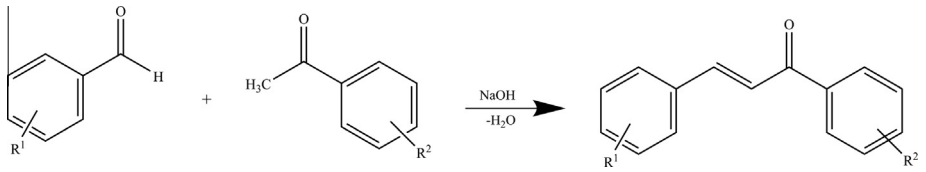

Figure 1. Claisen–Schmidt condensation employed for the synthesis of chalcones.

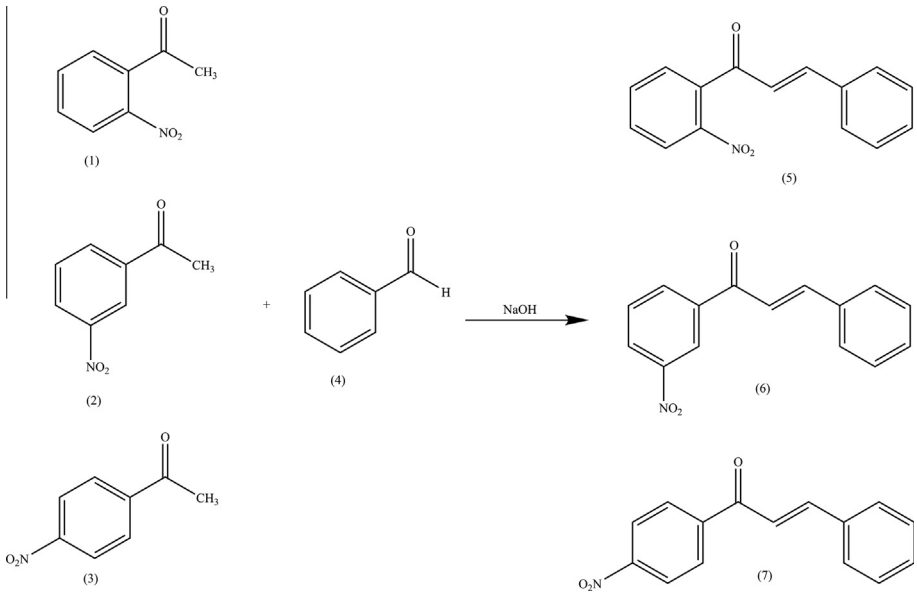

Figure 2. Synthesis of the three nitro-sustituted chalcones. (**1**) 2′-Nitroacetophenone; (**2**) 3′-nitroacetophenone; (**3**) 4′-nitroacetophenone; (**4**) benzaldehyde; (**5**) 2′-nitrochalcone; (**6**) 3′-nitrochalcone; (**7**) 4′-nitrochalcone.

soluble in dimethylsulfoxide (DMSO). The UV–Vis spectra showed the expected maximum absorbance wavelengths, whereas the IR spectra bands were in agreement with the functional groups expected in the structures. The ^{1}H NMR coupling constants for the alquene protons, showed that the stereochemistry around the double bond was (*E*) in the three compounds. The assignment of the ^{13}C NMR spectra confirmed the structures (Supplementary data). The evaluation of the anti-inflammatory effect of the three chalcones was assayed by the carrageenan induced paw edema in rat.[12]

First, it was assayed the temporal evolution of the inflammatory activity of carrageenan: 2 groups of 6 male Wistar rats (180–220 g) were employed. At $t = 0$, the volume of the right hind paw was measured. After this, one group was applied via intraplantar (i.pl.) in the right hind paw with a single dose (50 μL) of carrageenan at 0.3% in saline solution 0.9%. The second group served as control and was applied i.pl. in the right hind paw with a single dose (50 μL) of saline solution 0.9%. The volume of the right hind paw of the 12 specimens was measured every hour for 7 h. Each measurement was made in triplicate with a pletismometer (Ugo Basile 7140). The i.pl. application of carrageenan in the right hind paw of the rats derived into an edema development from a basal value of 1.1 ± 0.01 mL to a maximum of 1.9 ± 0.04 mL which was presented 3 h after the administration of carrageenan. The control group showed a basal volume of 1.1 ± 0.01 mL and there were no statistical significance differences (p <0.05) in the volume of the control group along the 7 h of the experiment (Fig. 3). When the volumes of the carrageenan and control groups were compared, statistical significance differences (p <0.05) were found.

The anti-inflammatory protective effect of the three chalcones (**5**–**7**) was evaluated at a single dose of 200 mg kg^{-1}, the vehicle employed was DMSO. To perform this test, an arrangement of 7

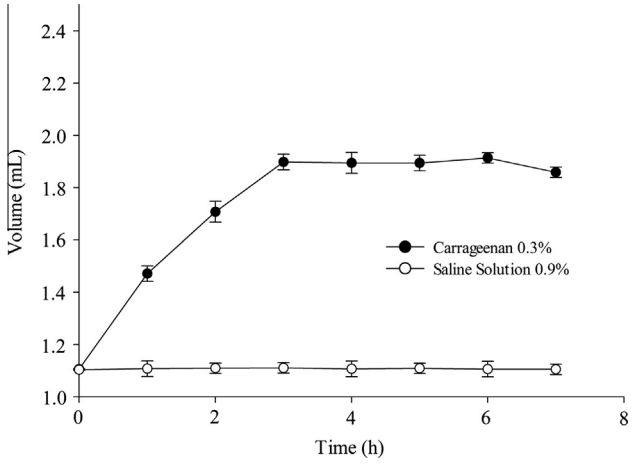

Figure 3. Time course of the volume of the right rear paw of the rat: a rise of the volume after the i.pl. application of carrageenan 0.3% is shown. Each point represents average ± standard error (n = 6).

groups, each of them with 6 rats, was made. Three of these groups received their corresponding chalcone by oral administration (p.o.), while other three received their corresponding chalcone by intraperitoneal injection (ip). The seventh group was the control and only received the vehicle p.o. Meloxicam (**8**) was employed as a reference drug: a group of 6 rats received p.o. a single dose (10 mg kg^{-1}) of the reference.[13] After this administrations, a single dose of carrageenan 0.3% vas applied i.pl. in the right hind paw of each specimen, in a similar way as described above. The volume of