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Rapid screening of anti-inflammatory properties of newly synthesized derivatives of indomethacin

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Anti-inflammatory effects of newly synthesized derivatives of indomethacin with 3-aminospirohydantoins and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione, have been studied. It was found that the compounds tested possess an inhibitory activity on acute inflammation, but not stronger than that of indomethacin. The structure of spirohydantoin residue influences the effects of the new molecules.

Keywords: Inflammation, Indomethacin, 3-aminospirohydantoins, 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione

INTRODUCTION

Non-steroid anti-inflammatory drugs (NSAD) are widely used in therapy of inflammation, fever and pain. The main mode of their action is the inhibition of cyclooxygenase (COX) isoenzimes COX1 and COX2.Thus they suppress the synthesis and reduce the amount of prostaglandins, which increases during inflammation. Irrespective of their numerous side effects the drugs of this group (aspirin, paracetamol, indomethacin, ibuprophen, diclofenac, etc.) are still commonly prescribed in the cases of acute and chronic inflammatory diseases because of their remarkable effectiveness.

Different substituted hydantoins and their derivatives have also revealed various activities, including inhibition of allergy reactions, mediated by serotoninergic, cholinergic, adrenergic, dopaminergic mediatory systems [1 - 6]. Spirohydantoin derivatives are intensively synthesized and studied like drugs for mental diseases such as schizophrenia, anxiety and/or depression [7], antitumor agent [8] and in inflammatory processes of allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis. It was found also that indomethacin shares partly the same mechanism on allergic inflammatory processes as spirohydantoin derivatives [9]. That is why in the present study we tested the possible anti-inflammatory effect of the newly synthesized by Marinov et al. [10] compounds, derivatives of indomethacin with 3-aminospirohydantoins and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione.

EXPERIMENTAL

Materials

The new amides shown in Table 1 were prepared with good yield by interaction of a series of 3-aminospirohydantoins and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione with indomethacin.

Methods

The anti-inflammatory activity of the new compounds was tested on male Wistar rats (160-200g), using a carrageenan-induced paw edema model. Acute inflammation was induced by intraplantar (i.pl.) injection of 0.1 ml λ-carrageenan (CG, 1%, w/v) into the right hind paw. The compounds in a volume of 0.1 ml/100g was administered intraperitoneally (i.p.) 30 min before the induction of the CG-inflammation. The paw volume was measured plethysmographically (Ugo Basile, Italy) before the injection of CG, to obtain a control value, and then every 60 min for a period of 4 hours. Data are expressed as edema rate (%). Values for each group represent the mean +SEM of 5-7 animals. The effects of derivatives, as well as of indomethacin have been compared to that of the control group.

To make the results comparable, we tested the effects of derivatives in equimolar doses, relative to indomethacin 3mg/kg. All compounds investigated, as well as the referent drug indomethacin were suspended with Twin 80 in saline. The rats in the control group were injected only with saline. All

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institutional and national guidelines for care and use of laboratory animals were followed.

Statistics

The data were statistically analyzed by one-way ANOVA (Dunnett post hoc test), $P<0.05$ being accepted as the minimum level of statistical significance of the established differences.

RESULTS AND DISSCUSION

The compounds shown in Table 1 have been tested.

Our study has shown, that most of newly synthesized compounds exert an anti-inflammatory effect, but none of them possesses efficacy, stronger than that of indomethacin. The effects of compounds 1-4 (in which a spirohydantoin residue is incorporated) on acute inflammation are presented on fig 1, 2 and 3. Comp 1 with C5- ring in spirohydantoin moiety did not improve the anti-inflammatory properties of indomethacin. Applied in a concentration, equimolar to 3mg/kg indomethacin, it decreased the paw volume significantly, compared to the control, in the first 120 min of observation, but the effect was not significant to the end of the experiment.

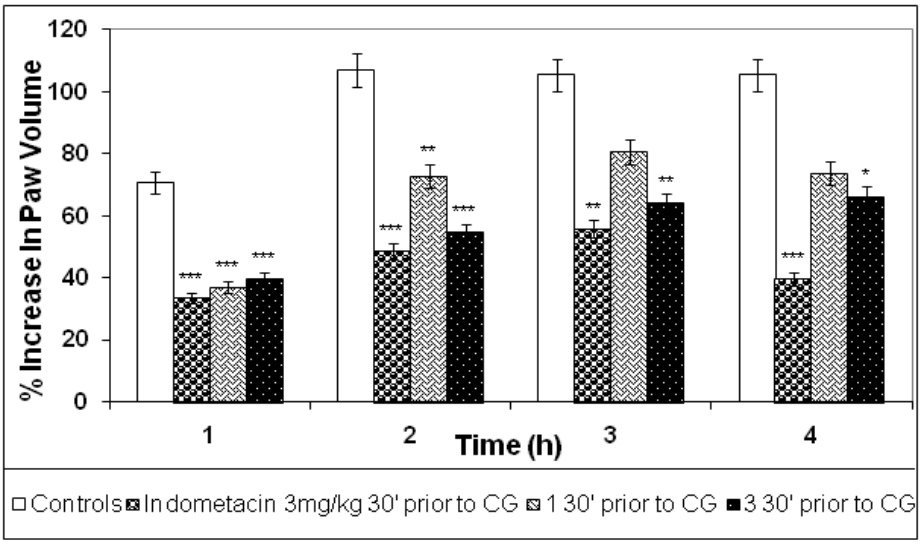


Fig. 1. Anti-inflammatory effect of indomethacin (3 mg/kg) and its derivatives 1 and 3 in doses equimolar to indomethacin, applied 30 min prior to carrageenan (CG).Values represent the mean ± SEM of 6-8 animals. Statistically significant differences versus control with CG *p<0.05; **p<0.01.

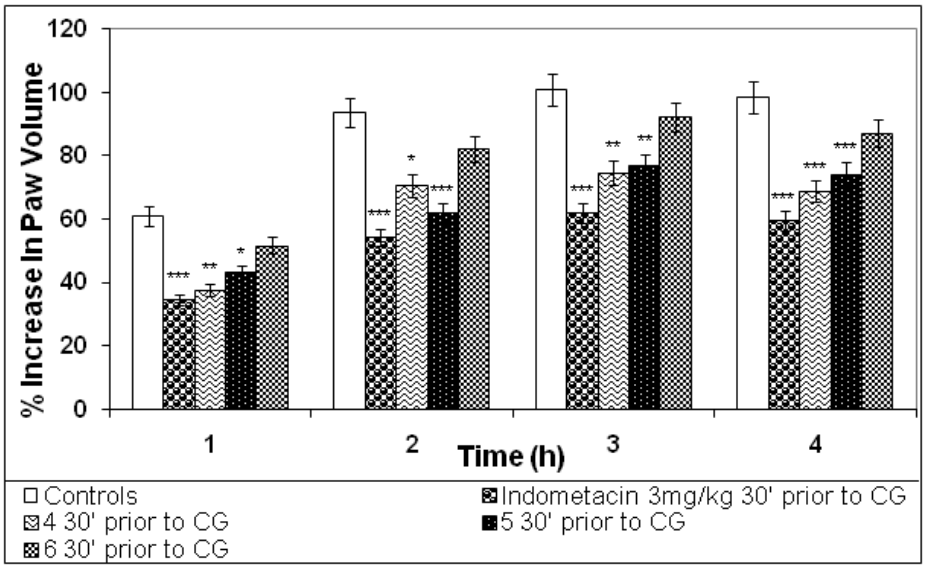
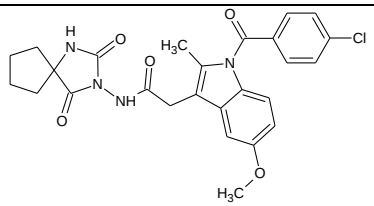
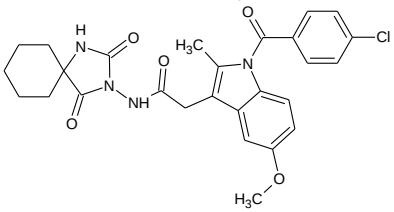
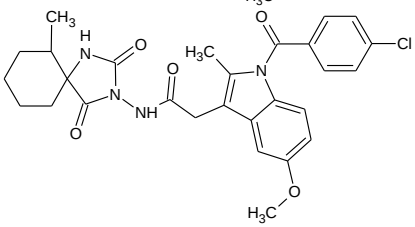
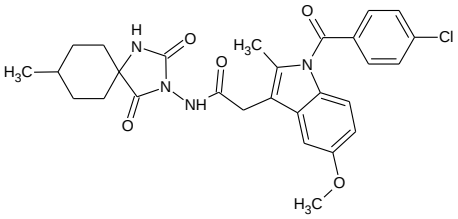
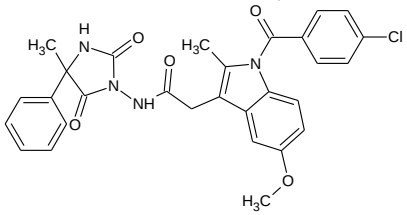
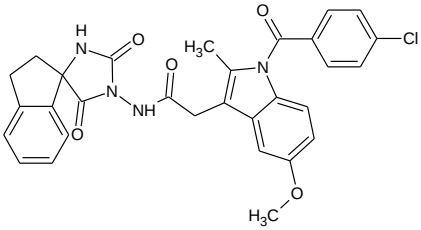
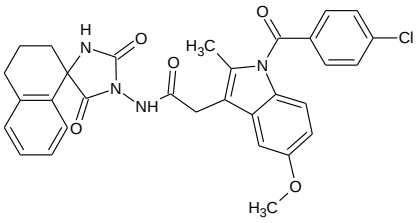
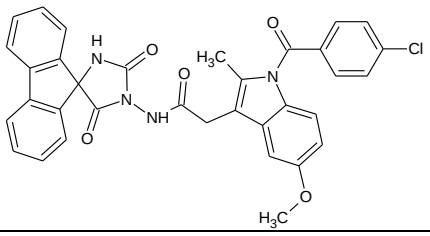


Fig. 2. Anti-inflammatory effect of indomethacin (3 mg/kg) and its derivatives 4, 5 and 6 in doses equimolar to indomethacin, applied 30 min prior to carrageenan (CG).Values represent the mean ± SEM of 6-8 animals. Statistically significant differences versus control with CG *p<0.05; **p<0.01.

Table 1. Structures of new compounds

№ / FW	Structure
1 $C_{26}H_{25}ClN_4O_5$ 508.95	
2 $C_{27}H_{27}ClN_4O_5$ 522.98	
3 $C_{28}H_{29}ClN_4O_5$ 537.01	
4 $C_{28}H_{29}ClN_4O_5$ 537.01	
5 $C_{29}H_{25}ClN_4O_5$ 544.99	
6 $C_{30}H_{25}ClN_4O_5$ 556.99	
7 $C_{31}H_{27}ClN_4O_5$ 571.02	
8 $C_{34}H_{25}ClN_4O_5$ 605.04	

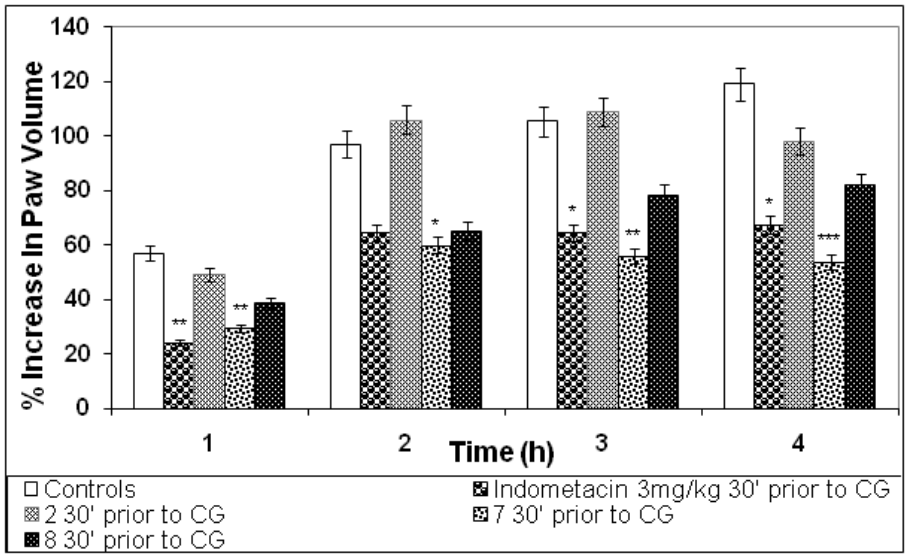


Fig. 3. Anti-inflammatory effect of indomethacin (3 mg/kg) and its derivatives 2, 7 and 8 in doses equimolar to indomethacin, applied 30 min prior to carrageenan (CG).Values represent the mean ± SEM of 6-8 animals. Statistically significant differences versus control with CG *p<0.05; **p<0.01.

The expanding of the ring (C6 instead of C5) in a spirohydantoin residue eliminated completely the anti-inflammatory capacity of the new substance (comp. 2, fig 3). This compound did not affect the increase of rats paw, induced by carrageenan, the rise being comparable to that of the controls (fig 3). However, the experiments have shown that the attachment of a methyl group in the C6 cycle (comp. 3 and 4) recovered the inhibitory potency of derivatives on inflammation and leads to effects, comparable with that of equimolar concentration indomethacin. It was found also that the rate of suppression is irrespective of the position of the methyl group- the percentage of inhibition evoked by the two isomers were very similar during the entire period of observation. It could be suggested that methyl group leads to conformational changes, affecting the activity.

In the second group (5-8) compounds 6 and 8 in dose equivalent to 3mg/kg indomethacin trend to reduce, but not significantly, the increase of inflamed paw volume, while comp.5 and comp.7 inhibited the inflammation as strong as indomethacin.

CONCLUSIONS

The results obtained showed, that most of the tested derivatives of indomethacin with 3-aminospirohydantoins and 3-amino-5-methyl-5-phenylimidazolidine-2,4-dione, poses an anti-inflammatory activity but not stronger than that of indomethacin. The structure of spirohydantoin residue influences the anti-inflammatory activity of the newly synthesized compounds.

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БЪРЗ СКРИНИНГ НА ПРОТИВОВЪЗПАЛИТЕЛНИТЕ СВОЙСТВА НА НОВОСИНТЕЗИРАНИ ПРОИЗВОДНИ НА ИНДОМЕТАЦИН

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(Резюме)

Изследвани са противовъзпалителните ефекти на новосинтезирани производни на индометацин със серия от 3-аминоспирохидантоини и 3-амино-5-метил-5-фенилимидазолидин-2,4-дион. Установено е, че изследваните съединения потискат възпалителния процес, но не по-силно от индометацина. Установена е зависимост между структурата на спирохидантоиновия остатък и проявения ефект.