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Research Article

Synthesis and Anti-Inflammatory Activity of Some -5-Ethoxy-2-Mercapto Benzimidazole Derivatives

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ABSTRACT
This article includes a description of new series of 5-ethoxy-2-mercapto benzimidazole derivatives, synthesized and evaluated for the anti-inflammatory activity; the synthesis involved the reaction of the parent nucleus (5-ethoxy-2-mercapto benzimidazole) with different *p*-phenacyl bromide substituents. All the newly synthesized compounds were screened for their anti-inflammatory activity by egg albumin-induced rat hind paw edema method.

Keywords: Anti-inflammatory, benzimidazole derivatives, 5-ethoxy-2-mercapto benzimidazole, synthesis.

INTRODUCTION

Inflammation is part of the complex biological response of body tissue to harmful stimuli like pathogens, irritants or damaged cells. It can be classified into either acute and chronic inflammation[1].

Acute inflammation is usually of sudden onset and short duration following the injury of tissues. The classical signs of inflammation are heat, redness, swelling, pain, and loss of function[2]. There were three main processes that may occur in such type of inflammation[3]: there an increase in the blood flow due to dilation of arterioles that supplying the region; an increase in capillaries' permeability which may allow fluid and blood proteins to pass into the interstitial spaces; and migration of neutrophils and few macrophages out of the venules and into interstitial spaces. Chemical mediators such as histamine, serotonin (5-HT), kinins and prostanoids can mediate an acute inflammation induced by phlogistic agents including egg albumin[4]. The phases of inflammation involve a primary phase that is mediated by histamine and 5-HT (up to 2 hours); an intermediate phase involving the activity of bradykinin, and a late phase that involves the synthesis of prostanoid by cyclooxygenase (COX) enzyme[5]. Aromatic heterocycles are precious synthetic moieties for the preparation of new compounds with definite biological, pharmacological and materials properties[6]. Benzimidazole ring system is an important pharmacophore in medicinal chemistry and modern drug discovery[7]. Benzimidazoles have attracted the interest of various research groups, especially since it has been reported that the influence of the substitution at 1, 2 and 5-position is very vital for their pharmacological effect[8]. 2-Mercapto benzimidazole derivatives, exhibited a wide variety of interesting biological activities such as antihistamine[9], anti-viral[10], anti-protozoal[11], anti-mycobacterial[12], anti-fungal[13], anti-convulsant[14], anti-diabetic[15], anxiolytic[16], analgesic[17],and chemo-preventive effect[18]. Thus, the aim of this work was to *in vivo* screen the newly-synthesized 5-ethoxy-2-mercapto benzimidazole derivatives**, 1-4** as anti-inflammatory agents, by hind paw edema method, utilizing diclofenac sodium as a standard drug.

MATERIALS AND METHODS

Chemicals

All the chemicals used for the synthesis, and the analytical data (IR, ^{1}HNMR, and Elemental analysis)] micro were illustrated by our research team in article [19].

Pharmacology

In vivo anti-inflammatory activity

In vivo, acute anti-inflammatory effects of some of the chemically synthesized compounds, [1(5-ethoxy-2-mercapto benzimidazole)-2-(*p*-substituted phenyl)-ethanone] derivatives, **1-4** were evaluated in egg albumin-induced paw edema in rats. The decrease in paw thickness is the basis of screening the newly synthesized compounds for their anti-inflammatory activity. The study was approved by the Scientific and the Ethical Committees of the College of Pharmacy, Baghdad University.

Thirty-six albino rats of both sexes, weighing 180-220g were utilized. The animals were obtained from the Animal House of the College of Pharmacy, University of Baghdad. They were kept under conditions of controlled temperature and humidity and light/ dark cycle, and fed commercial pellets and tap water *ad libitum*. Rats were randomly classified into 6 groups (6 rats each) as follows:

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Table 1: Effect of prior treatment with various compounds against egg albumin-induced acute inflammation compared to -group I [control (dimethyl sulfoxide (DMSO)], and group II (diclofenac sodium 10mg/kg)-treated animals. Percent inhibition (%) compared to control (group I).

Group	Mean increase in paw thickness (mm)				Percent (%) of inhibition			
	30min	90min	150min	210min	30min	90min	150min	210min
Group I Control (DMSO)	5.88± 0.16	5.68± 0.1	5.18± 0.12	5.02± 0.12	----	-----	-----	------
Group II Diclofenac sodium 10mg/kg	5.69± 0.13*A	5.36± 0.18*A	4.9± 0.19*A	4.54± 0.19*A	3.23	6.17	5.5	10.16
Group III (comp.1)	5.95± 0.1*C	5.67± 0.07*C	5.11± 0.1*C	4.88± 0.08*C	---------	0.17	1.35	2.79
Group IV (comp.2)	6.12± 0.17*B	5.89± 0.13*B	5.51± 0.18*B	5.08± 0.12*B	---------	----------	--------	----------
Group V (comp.3)	6.09± 0.16B	5.66± 0.18*D	5.2± 0.11D	5.09± 0.18D	------	0.35	--------	----------
Group VI (comp.4)	6.34*± 0.08D	5.58*± 0.15*E	5.28± 0.09*D	4.95± 0.09*E	---------	1.76	--------	1.39

- Data were expressed as mean ± SEM.
- * $P<0.05$: significant difference compared to control group.
- Values with non-identical subscripts capital letters (A, B, C, D and E) among different groups are considered significantly different ($P<0.05$) in each time column.
- Percent inhibition (%) compared to control (group I).
- Group I= (dimethylsulfoxide=DMSO) (appropriate ml volume according to the body weight of each rat) 30 min prior to (0.05ml) egg albumin.
- Group II= Diclofenac sodium (10mg/kg) 30 min prior to (0.05ml) egg albumin.
- Groups III-VI= [10mg/kg doses of the tested compounds (1, 2, 3, and 4) comparable to the reference drug (diclofenac sodium) 30 min prior to (0.05ml) egg albumin.
- Number of animals= 6/ group.

Group I: According to the body weight of the animal, they intraperitoneally injected with an appropriate volume of dimethylsulfoxide (DMSO). This group served as control.

Group II: Rats intraperitoneally injected with 10mg/kg diclofenac sodium as a standard drug.

Groups III-IV-V-VI: Six rats/group treated with the tested compounds 1-4, respectively. The dose of each test compound was comparable to that of standard drug, and each of the tested compounds was intraperitoneally injected to animals.

Thirty minutes post treatment with control, standard drug or each of the tested compounds, inflammation was induced by injecting 0.05 ml of undiluted fresh egg albumin into the subplantar surface of the left hind paw. The volume of edema produced was measured in millimeters before, and 30 min, 90 min 150 and 210 min after induction of inflammation using a digitalized vernier caliper.

The ability of either diclofenac or each of the tested compounds to suppress paw inflammation was expressed as a percentage of inhibition of paw edema according to the following equation[20]:

Percentage of inhibition (%) = 100X [(1- (x/y)] Where,

X= mean increase in paw volume or thickness of treated rats of each (group II, III, IV, V, or VI).

Y= mean increase in paw volume or thickness of group I rats.

Statistical Analysis

The results were expressed as the mean ± S.E.M. Analysis of data was carried out using one-way analysis of variance (ANOVA) followed by Student's t-test. Differences in mean were considered to be significant when $P< 0.05$.

RESULTS AND DISCUSSION

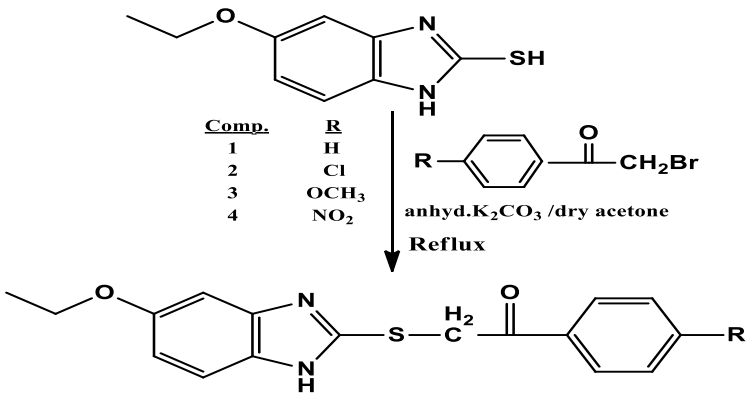
Chemistry

The 5-ethoxy-2-mercapto benzimidazole derivatives were synthesized by the S-Alkylation of the starting material with different *para*-substituted phenacyl bromides to form the title compounds 1-4 (scheme 1).

In-vivo anti-inflammatory activity:

Acute inflammation can be induced in rats paw by an irritant agent such as egg albumin. Such method is widely utilized for screening the ability of anti-inflammatory agents to reduce local edema induced in rats [21].

The anti-inflammatory activity of the four tested compounds [1(4-substituted)-2-[5ethoxy-1*H*-



Scheme1: Synthesis of 5-ethoxy-2-mercapto-benzimidazole derivatives[19].

benzo[*d*]imidazole-2yl)thio)ethanone derivatives,1-4 has been evaluated in comparison with DMSO (control group) and 10mg/kg diclofenac sodium (group II).

The standard drug (diclofenac sodium) produced significant reduction (P<0.05) in rats paw edema in comparison to control group (DMSO); where, the percents of inhibition were 3.23, 6.17, 5.5, and 10.16 % over 30, 90, 120, and 150 minutes periods respectively, as shown in the table (1).

Concerning the test compound phenacyl 2-MBI (compound 1), (group III-treated rats), the intended compound produced significant increase (P<0.05) in rats paw edema at 30, 90, 120 and 150min periods compared to diclofenac sodium. Additionally, such compound produced significant increase (P<0.05) in rats paw edema at 30min time period but significant decrease (P<0.05) in paw edema at 90, 150, and 210 min compared to control group. The percent of edema inhibition were observed at 90, 150, and 210min (although it can be considered as slight inhibition when compared to groups of rats treated with the standard drug, diclofenac sodium) as shown in the table (1).

The compound *p*-chlorophenacyl-2-MBI derivative, (compound 2), (group IV-treated rats) produced a significant increase in paw edema compared to standard drug and control (P<0.05); in other word, its ability to decrease rats paw edema over the tested periods (30, 90, 120, and 150 minutes) was not observed. Table (1)

Concerning *p*-methoxy phenacyl 2-MBI derivative (compound 3),(group V-treated rats), such compound produced a significant increase (P<0.05) in rats paw edema at all time periods compared to diclofenac sodium, but a significant decrease in paw edema (P<0.05) at 90 min period compared to control group. Table (1).

Regarding the compound *p*-nitro phenacyl 2-MBI (compound 4), (group VI-treated rats), such compound produced a significant increase (P<0.05) in rats paw edema at all time periods compared to diclofenac sodium. In contrast, a significant reduction in rats paw edema (P<0.05) with a slight percent inhibition in rats paw edema were observed at 90, and 210 minutes compared to control (DMSO) group. Table (1)

CONCLUSION

From the results of this study, it can be concluded that different [1(4-substituted)-2-[5-ethoxy-1*H*-benzo[*d*]imidazole-2yl)thio) ethanone derivatives, 1-4, were synthesized and possessed weak anti-inflammatory activity compared to diclofenac. For future work, we are planning to perform dose-response curve for the tested compounds against inflammation induced by egg albumin.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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