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PHARMACOLOGICAL EVALUATION OF 2-PYRAZOLINE DERIVATIVES AS ANTI- INFLAMMATORY AGENTS

Pharma

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ABSTRACT

Pyrazolines are prominent nitrogen-containing heterocyclic compounds and many pyrazoline derivatives have found their clinical application as NSAIDs. Side effects caused by selective NSAIDs always create a need for further investigation and studies of some newer anti-inflammatory agents for various clinical conditions. Out of the studied compounds, 1-(3-(2-(1H-indol-3-yl)vinyl)-5-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one was observed to have significant anti-inflammatory activity which can be beneficial after further investigation and derivatization.

KEYWORDS

2-pyrazolines, anti- inflammatory, paw edema method.

INTRODUCTION

Biological transformation of arachidonic acid (AA) into a variety of inflammatory mediators occurs through two metabolic pathways, cyclooxygenase, and lipoxygenase. Cyclooxygenases lead to the production of cytoprotective Prostaglandins (PGs), thromboxanes (TXA2) and prostacyclin (PGI2) whereas lipoxygenases have been observed to produce leukotrienes (LTs) and also catalyze the oxidation of lipoproteins (LDL, HDL) to atherogenic forms [1,2]. Cyclooxygenase enzymes exist in different isoforms such as constitutive COX-1, induced COX-2 and COX-3 [3,4]. Various inflammatory diseases, allergic reaction [5-7] and neo-angiogenesis [8,9] exhibit high expression of above-mentioned inflammatory mediators. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most important class of widely used therapeutics for the treatment of inflammation and pain. The principle pharmacological effects of NSAIDs arise from their inhibition of cyclooxygenases (COXs) which control the conversion of arachidonic acid to prostaglandins and thromboxanes [10-12]. The discovery of the second isoform of cyclooxygenase, known as COX-2 has opened a new line of research based on the assumption that pathological prostaglandins (PGs) are produced by the inducible isoform COX-2 while physiological PGs are produced by constitutive isoform COX-1 [13]. The side effects of the classical NSAIDs such as gastrointestinal (GI) irritation, bleeding and ulceration are due to high COX-1 versus COX-2 selectivity, and due to their acidity also [14]. In view of this, it is highly desirable to separate the therapeutic effects of anti-inflammatory drugs from their side effects. Thus, decreasing acidity and increasing the specificity for COX-2 over COX-1 could provide new COX-2 inhibitors with fewer risks [15-18]. A high level of selective COX-2 inhibition represents, therefore, a therapeutic strategy to alleviate pain and inflammation without the untoward GI toxicity due to COX-1 inhibition. Therefore, selective COX-2 inhibitors (coxibs) with better safety profile have been marketed as a new generation of NSAIDs [19,20]. But careful prospective examination of cox inhibitors has revealed unexpected cardiovascular adverse effect [21]. Therefore, development of novel compounds having anti-inflammatory activity as well as improved safety profile is still a requirement of time.

Medicinal chemists have carried out considerable research on pyrazoline derivatives due to their diverse therapeutic applications extending from central nervous system applications to antimicrobials. The most predominant biological activity is observed for the anti-inflammatory activity. Literature survey revealed that many pyrazoline derivatives have found their clinical application as NSAIDS. Antipyrine, *2,3-dimethyl-1-phenyl-3-pyrazolin-5-one*, was the first pyrazolone derivative used in the management of pain and inflammation. It should be noted that, number of drugs are in market containing pyrazole/pyrazoline/pyrazolidine moieties have been used for various treatments, e.g. Celecoxib, Famprofazone, Deracoxib, Sulfinpyrazone, Apixaban, Allopurinol, Rimonabant, Ruxolitinib, Sulfaphenazole, and Phenazone, Felcobuzone, Mefobutazone, Morazone, and Ramifenazone. In addition, some of the derivatives are under pre-clinical studies, e.g. SLV-330 and E-6087. Phenylbutazone and its potent metabolite oxyphenbutazone, a prototype of pyrazolinedione NSAIDs, are potent anti-inflammatory agents. However, their use became restricted due to their GI side effects. Feprazone, the 4-(methylbutenyl)-analogue, is comparable to phenylbutazone in efficacy, but with less side effects on GI tract. Several related pyrazolidine-3,5- diones, pyrazolin-3-ones and pyrazolin-5-ones are also available as NSAIDs; examples are felcobuzone, mefobutazone, morazone, famprofazone, and ramifenazone [22]. Besides these many pyrazoline derivatives are also reported in literature as having potent anti-inflammatory activity. In view of these observations and in continuation of our research work on the pyrazoline derivatives, we report here the anti-inflammatory profile of some synthesized pyrazoline derivatives.

METHOD

This study was done following the procedure of Winter et al. Wistar rats (200.0 ± 20.0 g) were used in the study and animals were allowed free access to food and water under a 12h/12h light/dark cycle with the room temperature maintained at 25 ± 1 C and relative humidity of 40-60%. The rats were randomly divided into three groups (control, drug treated, and standard, group of six animals each). The control group was given with normal saline: tween 80 (95:5) whereas the standard group was administered with Diclofenac Sodium 10 mg/kg and the test groups received the synthesized compounds at the dose of 50 mg/kg orally 1h before the carrageenan injection.

A freshly prepared suspension of carrageenan (1% in 0.9% saline) (0.05 ml) was injected under the planter region of the right hind paw of each rat.

Test compounds and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1 h before the carrageenan injection and the paw volume of each rat was measured after 1 h, 2h, 3h, and 4h of administration of carrageenan by using Plethysmometer (Model 7140, Ugo Basile, Italy). The study protocols were approved by the Ethics Committee (Regn. No. -2005/PO/RcBT/S/18/CPCSEA). The anti-inflammatory activity was expressed as percentage inhibition of edema volume in treated animals in comparison with the control group.

%Inhibition of edema = $[(V_c - V_t)/V_c] \times 100$

Where, V_c and V_t are the volumes of edema for the control and drug-treated animal groups, respectively [23].

RESULTS AND DISCUSSION

The paw volume of each rat was measured after 1 h, 2h, 3h, and 4h of administration of carrageenan by using Plethysmometer which were injected with test and standard compounds 1 h before the carrageenan injection. The anti-inflammatory activity was expressed as percentage inhibition of edema volume.

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Table 1 Structure Of Pyrazoline Derivatives Used For Study Of Anti-inflammatory Activity

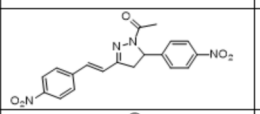
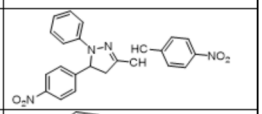
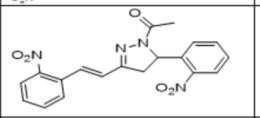
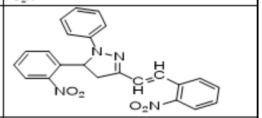
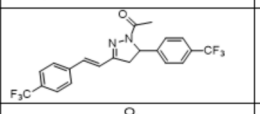
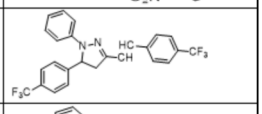
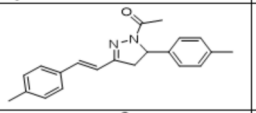
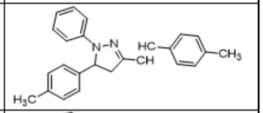
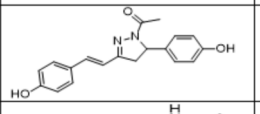
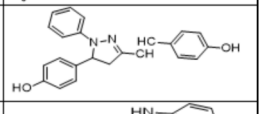
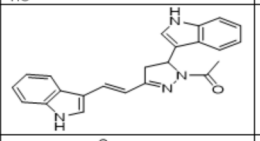
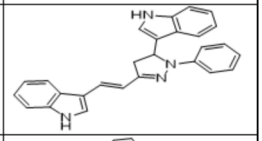
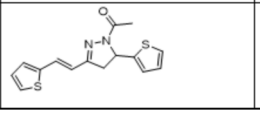
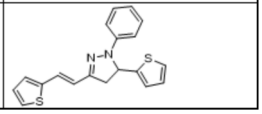
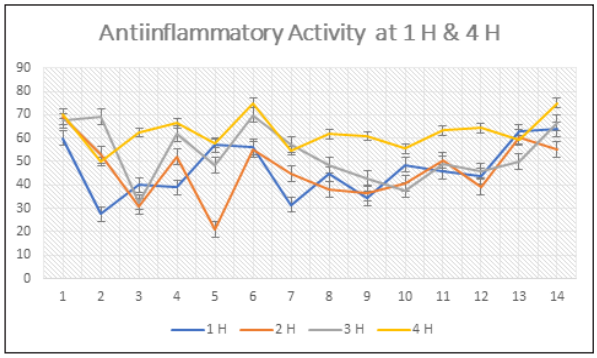
Comp. No	Structure	Comp. No	Structure
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 2 Anti-inflammatory Activity of compounds 1-14

Paw edema volume Mean Swelling Volume (in mL) ± SEM (% inhibition of edema)								
Comp. No	**1 h**	**% age Inhibition**	**2h**	**% age Inhibition**	**3h**	**% age Inhibition**	**4h**	**% age Inhibition**
1	0.42±0.0058	60	0.38±0.0065	69.105	0.41±0.0120	67.460	0.38±0.0078	70.312
2	0.76±0.0065	27.619	0.58±0.0045	52.845	0.39±0.0060	69.047	0.64±0.0060	50
3	0.63±0.0060	40	0.85±0.0058	30.894	0.85±0.0056	32.539	0.48±0.0065	62.5
4	0.64±0.0045	39.047	0.59±0.0060	52.032	0.48±0.0060	61.904	0.43±0.0120	66.406
5	0.45±0.0065	57.142	0.97±0.0120	21.138	0.65±0.0058	48.412	0.54±0.0037	57.812
6	0.46±0.0045	56.190	0.55±0.0111	55.284	0.38±0.0065	69.841	0.32±0.0045	75
7	0.72±0.0056	31.428	0.68±0.0037	44.715	0.54±0.0058	57.142	0.58±0.0060	54.687
8	0.58±0.0051	44.761	0.76±0.0045	38.211	0.65±0.0032	48.412	0.49±0.0092	61.718
9	0.69±0.0092	34.285	0.78±0.0051	36.585	0.72±0.0049	42.857	0.50±0.0045	60.937
10	0.54±0.0066	48.571	0.73±0.0051	40.650	0.86±0.0037	37.746	0.57±0.0081	55.468
11	0.55±0.0149	47.619	0.65±0.0060	47.154	0.77±0.0066	38.888	0.43±0.0037	66.410
12	0.57±0.0066	45.714	0.61±0.0081	50.406	0.64±0.0149	49.206	0.47±0.0060	63.281
13	0.59±0.0081	43.809	0.75±0.0051	39.024	0.68±0.0037	46.031	0.45±0.0149	64.843
14	0.39±0.0066	62.857	0.49±0.0037	60.162	0.63±0.0051	50	0.52	59.375
Control	1.05	-	1.23	-	1.26	-	1.28±0.0060	-
Standard	0.38±0.0078	63.809	0.55±0.0056	55.284	0.42±0.0078	66.666	0.32±0.0111	75

Statistical Analysis: All the results were expressed as mean ± Standard Error Mean (SEM). Statistical analysis was done by using one way ANOVA and critical range for significance difference between two groups of observations was taken as *p<0.05, **p<0.01, compared with control.



The maximum reduction in the inflammation was observed at 120 min after administration of different compounds. The onset of action was found to be 30 min. In case of compound **1**, the maximum percent inhibition in inflammation was observed at 4 h (70.312%). The percentage inhibition of inflammation compounds **4** (66.406 %), **6** (75 %), **11** (66.410 %), **12** (63.281 %) & **13** (64.843%) also was found to be significantly good and comparable relative to the standard compound. Anti-inflammatory activity of compounds **3** (62.5 %), **8** (61.718 %), **9** (60.937 %) and **14** (59.375 %) was observed to be of intermediate level relative to the standard compound whereas activity of compounds 2,5,7 and 10 was observed to be less remarkable than the standard compounds.

CONCLUSION

The present work describes the investigation of anti-inflammatory activity of various pyrazoline derivatives. It was interesting to note that three pyrazoline derivatives 6, 1 and 11 were found to have significant anti-inflammatory activity. Out of these compounds, compound **6** *1-(3-(2-(1H-indol-3-yl)vinyl)-5-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one* has emerged as the lead compound, which showed maximum anti-inflammatory activity. Thus, the compound 6 represents a fruitful matrix for development of a new anti-inflammatory agent that would deserve further investigation and derivatization.

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