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Study of analgesic and anti-inflammatory activity of some 2-substituted acetamido-5-aryl-1,3,4-thiadiazoles

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ABSTRACT

Study of analgesic and anti-inflammatory activity of some synthesized 2-substituted acetamido-5-aryl-1,3,4-thiadiazoles (sixteen compounds) were done. None of the compounds showed any analgesic activity. One of the compound [1/4a1] showed anti-inflammatory activity comparable with the standard drug. Some of the compounds showed moderate activity. Results indicate that substitution in the aryl group result in reduction or loss of activity.

Keywords: 2, 5-disubstituted -1,3,4-thiadiazoles, analgesic and anti-inflammatory activity

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INTRODUCTION

Inflammation is caused by living tissues when subjected to injury. Living tissues respond to the injury in complex way, depending on its rigorousness. A local response is often associated with inflammation and the damage tissues go through changes to allow the entry of plasma and phagocyte cells at the place of injury. This early local response is called acute inflammation which is a short-term response that usually results in healing. The mechanism involves in the course of action showed that leukocytes gain access to the damaged region, removing the stimulus and repairing the tissues. If acute inflammation persists for a longer period, it changes into chronic inflammation. Chronic inflammation is a prolonged, deregulated response that involves active inflammation, tissue destruction and attempts at tissue repair. To overcome the challenges of inflammatory disorders, several classes of anti-inflammatory drugs have been used. These include non-steroidal anti-inflammatory drugs (NSAIDs), Immuno Selective Anti-Inflammatory Derivatives (ImSAIDs), corticosteroids etc., [1].

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used medications worldwide for the treatment of pain and inflammation. Their everyday and long-term administration is limited due to their gastrointestinal and renal side effects. In order to minimize these side effects, there is increased focus on developing non-steroidal anti-inflammatory drugs without the acidic group (carboxylic moiety). From the in-depth literature review, it was observed that thiadiazole derivatives [2-31] have been reported to have anti inflammatory and analgesic activity with minimal gastrointestinal ulceration and other side effects. Therefore, it was thought worthwhile to carry out the analgesics and anti-inflammatory activity on the synthesized compounds [32-34] having the 1,3,4-thidiazole nucleus with substitution on 2 and 5 position in order to find out their potential as analgesic and anti-inflammatory agents.

MATERIALS AND METHODS

In the present study of analgesic and anti-inflammatory activity of the synthesized compounds, albino rats (100-150 g) of either sex were used. The dose of the drug taken was 100 mg/kg body weight. Administration of the compounds was oral in all the studies. For the pharmacological evaluation, the compounds were suspended in water using Tween 80 as a suspending agent. For all the studies, animals were divided into groups of 4 animals. The control group received the calculated amount of normal saline. All the experiments were carried out at room temperature.

Analgesic Activity

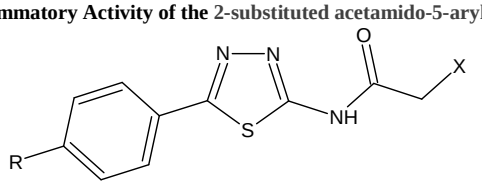
Analgesic activity was determined by using hot wire Analgesiometer provided with an arrangement for circulation of cold water to avoid over heating of the area surrounding the wire. The rats were then put into a rat holder individually with the tail protruding out of the hole. The tail was then kept on the hot wire of the instrument in such a way that it did not touch the wire. It is presumed that on feeling pain, the rat would withdraw its tail. The reaction time was noted before the administration of drug, which served as a control reading. The animals of various groups were then given the synthesized compounds. The reaction time was noted after the administration of the drug at hourly intervals upto 4 hours [35, 36].

Anti-inflammatory Activity

Carageenan induced rat paw edema method was used in the present study. Initially right hind paw volume of different groups of rats was measured by the plethysmometer. The suspension was administered orally by means of a curved cannula.

Albino rats weighing (100-150 grams) were divided into the different groups, each having five animals. Each rat was weighed and the compounds were administered according to their body weight. After the lapse of 30 minutes, 0.1 ml of 1 % carageenan suspension was injected under the planter aponeurosis of the right hind paw of albino rats. The right hind paw volume was again measured after 3 hours by means of a plethysmometer. For the control group, only carageenan solution was injected into the right hind paw of each rat and the paw volume was measured by means of plethysmometer [37-42]. The results were reported in table-1.

Table-1: Anti-inflammatory Activity of the 2-substituted acetamido-5-aryl-1,3,4-thiadiazoles



S. No.	Compound entry	R	X	Change in paw volume (mL) ± SEM	% oedema inhibition	log P#
1	4a1	H	Di-n-propylamino	0.18 ± 0.02921**	48.57	4.09 ± 0.66
2	4a2	H	Di-iso- propylamino	0.26 ± 0.02607	25.71	3.72 ± 0.66
3	4a3	H	Pyrrolidine	0.20 ± 0.03346*	42.85	2.66 ± 0.66
4	4a4	H	2-Pyrrolidinone	0.30 ± 0.03651	14.28	1.51 ± 0.69
5	4b1	CH_3O	Di-n-propylamino	0.24 ± 0.02633*	28.57	4.26 ± 0.66
6	4b2	CH_3O	Di-iso- propylamino	0.32 ± 0.02422	8.57	3.89 ± 0.67
7	4b3	CH_3O	Pyrrolidine	0.36 ± 0.02580	-	2.83 ± 0.67
8	4b4	CH_3O	2-Pyrrolidinone	0.36 ± 0.02065	-	1.67 ± 0.69
9	4c1	CH_3	Di-n-propylamino	0.24 ± 0.01932*	30.0	4.55 ± 0.66
10	4c2	CH_3	Di-iso- propylamino	0.30 ± 0.01461	14.28	4.18 ± 0.66
11	4c3	CH_3	Pyrrolidine	0.25 ± 0.02113*	28.57	3.12 ± 0.66
12	4c4	CH_3	2-Pyrrolidinone	0.33 ± 0.01770	5.71	1.97 ± 0.69
13	4d1	Cl	Di-n-propylamino	0.47 ± 0.01770	-	4.86 ± 0.66
14	4d2	Cl	Di-iso- propylamino	0.50 ± 0.01788	-	4.49 ± 0.66
15	4d3	Cl	Pyrrolidine	0.24 ± 0.02065*	31.42	3.43 ± 0.67
16	4d4	Cl	2-Pyrrolidinone	0.38 ± 0.01862	-	2.27 ± 0.69
			Control	0.35 ± 0.03087		
			Phenyl butazone (Standard drug)	0.16 ± 0.02390***	54.28	

** The difference is statistically significant (P<0.05) when compared with control; ** The difference is statistically significant (P<0.02) when compared with control; *** The difference is statistically significant (P<0.005) when compared with control; # Carragenan only; *# Calculated by using ACD ChemSketch 12.0 (www.acdlabs.com)*

RESULTS AND DISCUSSION

Analgesic Activity

None of the compounds gave any analgesic effect; this indicates that the synthesized compounds do not have any potential for analgesic activity.

Anti-inflammatory Activity

So far as anti-inflammatory activity is concerned, compounds 1 and 3 showed good anti-inflammatory activity (43 & 49 per cent paw oedema inhibition). Compounds 2, 5, 11 and 15 also showed moderate anti-inflammatory activity (25-31 per cent paw oedema inhibition). Rest of the compounds do not showed any activity or low activity.

Results indicate that *p*-Chloro substitution in the aromatic ring (at position 5 of 1,3,4-thiadiazole ring) results in reduction (compound 15) or loss of anti-inflammatory activity (compounds 13, 14 and 16). Although these compounds are more lipophilic (higher logP value) but devoid of biological activity, this may be due to the presence of electron withdrawing group in the aryl ring which is not favorable. Compound 15 has moderate activity that may be due to the presence of rigidity incorporated in the molecule (pyrrolidine ring; metabolic susceptibility decresed). In compounds where X is N, N-dialkyl amino group are more active than heterocyclic group (Figure 1). As compared to di-*n*-alkyl amino derivatives, di-*iso*-alkyl amino derivatives are less active (compound 2, 6, 10) or not active (compound 14) indicating that branching result in reduction or loss of activity. The may be due to the more metabolic susceptibility of branched isomers as compared to normal isomers.

Pyrrolidine substituted derivatives (3, 11 & 15) are more active as compared to 2-pyrrolidinone [more polar group] substituted derivatives (4, 8, 12 & 16). Overall substitution in phenyl aromatic ring at 2 position of 1,3,4-thiadiazole ring by methoxy (CH_3O), methyl (CH_3) and chloro (Cl) result in lesser activity (compound 5-16) as compared to unsubstituted derivatives (compound 1-4). Among the unsubstituted derivatives (compound 1-4), compound 1 having di-*n*-propyl amino chain is highly active (≈ 49 per cent paw oedema inhibition), due its high lipophilicity. Compound 3 which is a rigid analog of diethyl amino group is also active (≈ 43 per cent paw oedema inhibition) whereas branched isomer (compound 2) and 2-pyrrolidinone derivative are showing lower activity.

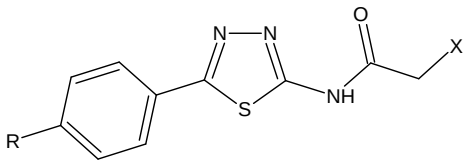


Figure 1: General structure of 2-substituted acetamido-5-aryl-1,3,4-thiadiazoles

CONCLUSION

Analgesic and anti-inflammatory activity of some synthesized 2-substituted acetamido-5-aryl-1,3,4-thiadiazoles (sixteen compounds) were done. None of the compounds showed any analgesic activity. Compound (2) showed anti-inflammatory activity comparable with the standard drug although it is slightly less. Some of the compounds showed moderate activity. Results indicate the potential of these compounds as anti-inflammatory agents which are non-acidic and non steroidal. Substitution in the aryl group at 5-position of 1,3,4-thiadiazole nucleus result in reduction or loss of activity. Branched isomer and 2-pyrrolidinone derivatives are less active or devoid of biological activity. Di-*n*-propyl amino derivatives are more active. Further work may help in designing and developing more potent selective non acidic NSAIDs.

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