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Der Pharmacia Lettre, 2014, 6 (3):146-150
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ISSN 0975-5071
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Evaluation of analgesic and anti-inflammatory activity of some 2,5-disubstituted-1,3,4-thiadiazoles

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ABSTRACT

The objective of this study was to investigate the analgesic and anti-inflammatory activity of some synthesized 2-substituted acetamido-5-aryl-1,3,4-thiadiazoles (sixteen compounds). Analgesic activity was determined by using hot wire analgesiometer. The in-vivo anti-inflammatory effects of the thiadiazole compounds were studied in a carageenan induced rat paw edema model. None of the compounds showed any analgesic activity. Some of the compounds showed moderate activity. Results indicate that substitution in the aryl group result in lessening or loss of activity.

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

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INTRODUCTION

The inflammatory process is the response to an injurious stimulus such as infections, physical injuries or due to generation of antibodies. The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury; but in some situations and diseases, the inflammatory response may be exaggerated and sustained without perceptible benefit and even with severe adverse consequences. Irrespective of the initiating stimulus, the classic inflammatory response includes calor (warmth), dolor (pain), rubor (redness), and tumor (swelling)[1]. These responses are the result of increased vascular permeability and vasodilatation which facilitates the access of leucocytes at the damaged region. The leucocytes then remove the stimulus followed by fibrosis. Chemical mediators such as prostaglandins, thromboxanes, prostacyclin and leukotrienes are postulated to play their roles in acute inflammatory response. They have been found essentially in every compartment of body. On the other hand the chronic inflammation involves the mediators like interleukins, interferon and tumor necrosis factor α (TNF–α), and a cytokine that plays a major role in this kind of inflammatory process and whose production is associated with some inflammatory diseases such as rheumatoid arthritis [1,2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used groups of therapeutic agents. However, their everyday and long term use is limited due to the presence of significant adverse side effects such as non-selective NSAIDs cause gastric injury which may result in gastric ulceration, thromboembolic problems and renal side effects. 1,3,4-thiadiazoles are an important class of heterocyclic compounds that correlates with a broad spectrum of biological activities such as anticancer [3-5], antiviral [6], antibacterial [7,8], antioxidant [9,10], antidepressant and anxiolytic [11], anti-tubercular [12,13] and anticonvulsant activities [14-16].

From the in-depth literature review, it was observed that thiadiazole derivatives [17-30] have been reported to have anti inflammatory and analgesic activity with minimal gastrointestinal ulceration and other side effects. Therefore, it was thought useful to carry out the analgesics and anti-inflammatory activity on the synthesized compounds [31-34] having the 1,3,4-thidiazole nucleus with substitution on 2 and 5 position and in continuation of the earlier work [30], to find out their potential as analgesic and anti-inflammatory agents.

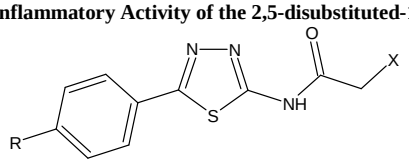
MATERIALS AND METHODS

Albino rats (100-150 g) of either sex were used for determining the analgesic and anti-inflammatory activity of the synthesized compounds in the present study. The dose of the compound 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 with an arrangement for flow 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 up to 4 hours [35].

TABLE 1: Anti-inflammatory Activity of the 2,5-disubstituted-1,3,4-thiadiazoles



Compound No.	R	X	Change in paw volume	% inhibition	log P*#
1	H	Di-*n*-butylamino	0.22 ± 0.03540*	37.14	5.15 ± 0.66
2	H	Di-*iso*- butylamino	0.24 ± 0.02129*	31.42	4.79 ± 0.66
3	H	Piperidin-1-yl	0.26 ± 0.02582*	25.71	3.23 ± 0.66
4	H	4-Methyl piperazin-1-yl	0.36 ± 0.01932	-	1.63 ± 0.68
5	CH_3O	Di-*n*-butylamino	0.27 ± 0.01341	28.57	5.32 ± 0.66
6	CH_3O	Di-*iso*- butylamino	0.32 ± 0.02366	8.57	4.95 ± 0.67
7	CH_3O	Piperidin-1-yl	0.30 ± 0.01788	14.28	3.39 ± 0.67
8	CH_3O	4-Methyl piperazin-1-yl	0.40 ± 0.01460	-	1.80 ± 0.68
9	CH_3	Di-*n*-butylamino	0.24 ± 0.02529*	31.42	5.61 ± 0.66
10	CH_3	Di-*iso*- butylamino	0. 28 ± 0.01932	20.0	5.25 ± 0.66
11	CH_3	Piperidin-1-yl	0.32 ± 0.02732	8.57	3.69 ± 0.66
12	CH_3	4-Methyl piperazin-1-yl	0.38 ± 0.01713	-	2.09 ± 0.68
13	Cl	Di-*n*-butylamino	0.31 ± 0.01342	10.0	5.92 ± 0.66
14	Cl	Di-*iso*- butylamino	0.42 ± 0.01366	-	5.55 ± 0.66
15	Cl	Piperidin-1-yl	0.41 ± 0.01983	-	3.99 ± 0.67
16	Cl	4-Methyl piperazin-1-yl	0.45 ± 0.01527	-	2.40 ± 0.68
		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<0.005) when compared with control; # Carragenan only; *# Calculated by using ACD ChemSketch 12.0 (www.acdlabs.com)*

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 [36,37]. The results were reported in Table-1.

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

Compound 1 showed good anti-inflammatory activity (37 per cent paw oedema inhibition). Compounds 2, 3, 5, 9 and 10 showed moderate anti-inflammatory activity (20-31 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 13) or loss of anti-inflammatory activity (compounds 14, 15 and 16). Although compounds 13, 14 and 15 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.

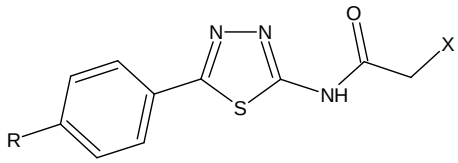


Figure 1: General structure of 2,5-disubstituted -1,3,4-thiadiazoles

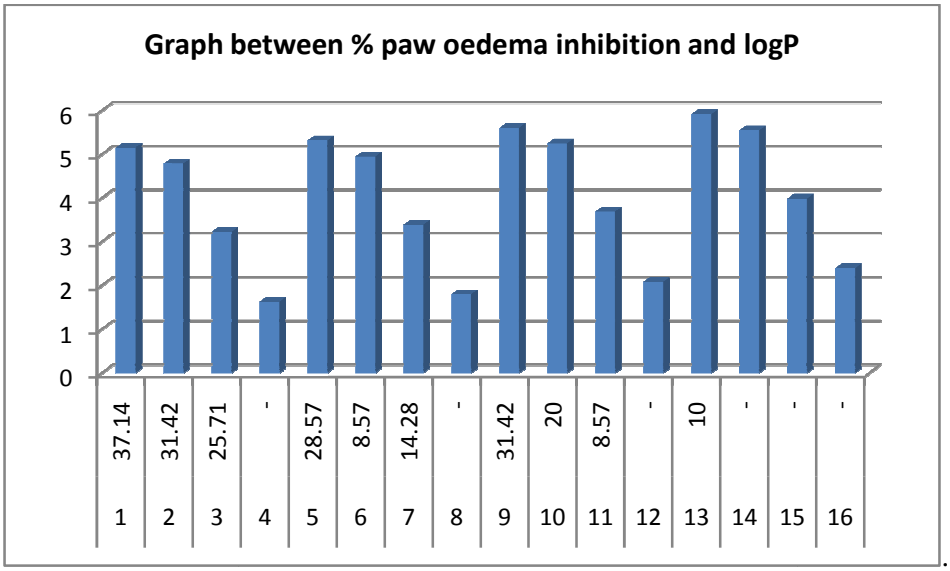


Figure 2a: Graph between % paw oedema inhibition and logP for compounds 1-16 (3D column plot)

Compound 3 has moderate activity that may be due to the presence of rigidity incorporated in the molecule (piperidine ring; metabolic susceptibility decreased). 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.

Piperidine substituted derivatives (3, 11 & 15) are more active as compared to 4-methylpiperazine [more polar group] substituted derivatives (4, 8, 12 & 16). This may be due to the fact that 4-methylpiperazine [more polar group] substituted derivatives (4, 8, 12 & 16) are having lower lipophilicity (Figure 2a & 2b). 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*-butyl amino chain is highly active (37 per cent paw oedema inhibition), due its high lipophilicity. Compound 3 which is a rigid analog of diethyl amino group is also active (≈ 26 per cent paw oedema inhibition). Branched isomer (compound 2) is less active as compared to its normal counterpart (compound 1). Piperidine substituted derivative (more lipophilic) is more active as compared to 4-methylpiperazine substituted derivative (more polar, less lipophilic).

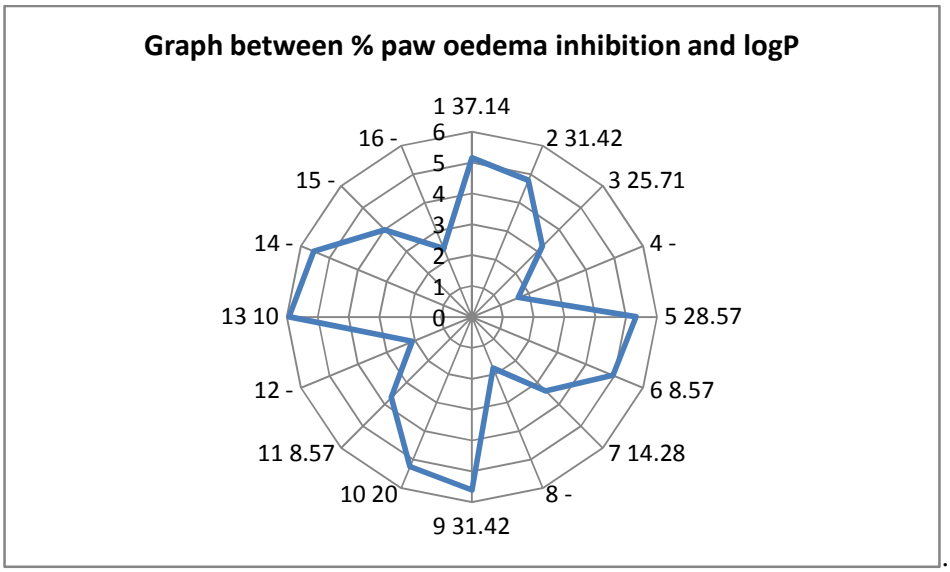


Figure 2b: Graph between % paw oedema inhibition and logP for compounds 1-16 (Radar plot)

CONCLUSION

Evaluation of analgesic and anti-inflammatory activity of some synthesized 2,5-disubstituted-1,3,4-thiadiazoles (sixteen compounds) were done. None of the compounds showed any analgesic activity. Compound 1 showed good anti-inflammatory activity (37 per cent paw oedema inhibition). 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 piperidine derivatives are less active or devoid of biological activity. Di-*n*-butyl amino derivatives are more active. Further work may help in designing and developing more potent selective non acidic NSAIDs.

Acknowledgement
The authors are thankful to Head, Department of Pharmaceutical Sciences, Dr. H.S. Gour Vishwavidyalaya, Sagar (M.P.) for providing necessary facilities. One of the authors, SKJ is grateful to UGC, New Delhi (India) for award of research fellowship during Ph.D. The authors are also thankful to Head, SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur (CG) for moral help and support.

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