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RESEARCH ARTICLE

Evaluation Of Anti-Inflammatory Activity Of Synthetic Derivatives In Carrageenan-Induced Paw Edema Model

Bhavani Ganapathy[1], Subbulakshmi Packirisamy[2], Valli Nachiyar C[3], Aarthi P[4], Yamuna V[5], Hari Hara Subramanyan P.V.[6]

[1]Department of Pharmacology, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research.
[2]Department of Pharmacolgy, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research.
[3]Department of Research, Meenakshi Academy of Higher Education and Research
[4]Meenakshi College of Nursing, Meenakshi Academy of Higher Education and Research.
[5]Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research
[6]Associate Professor, Meenakshi College of Physiotherapy, Meenakshi Academy of Higher Education and Research

*Corresponding Author

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Abstract: Inflammation is a complex, biological response of vascular tissues to damages, contamination, or irritation of which in most cases is accompanied by pain, redness, and swelling. The study was performed to evaluate the anti-inflammatory action of new chemical compounds using the carrageenin induced paw edema method in rats. The rats were Wistar males, divided into control, standard and test groups. The acute inflammation was induced with a 1% solution of carrageenin injected sub-plantarly into the right hind paw. The Results of a znthesi8 of these derivatives were administered orally in various doses, and Sankofex was used as a standard drug (10 mg/kg). The paw volume was determined at 0, 1, 2, 3 and 4 hours after carrageenin injection, using a plethysmometer.All the test compounds had a significant dose-dependent inhibition of paw edema on comparison to control group, and the optimum effect was attained at the 3rd hour. The Compound SD-3 possessed the most striking anti-inffammatory activity of the compounds tested and was apparently comparable to Sankofex for anti-inflammato.ry activity. The results indicate that the newer compounds synthesized have a high degree of anti-in¬ flammatory activity, perhaps by inhibiting prostaglandin synthetic mechanisms as well as the suppressive actions on inflammatory mediators.

Keywords: Anti-inflammatory activity, Synthetic derivatives, Carrageenan-induced paw edema, Diclofenac sodium, Prostaglandin inhibition, Wistar rats, Edema inhibition.

INTRODUCTION

Inflammation is a complex physiological process which is brought about by noxious stimulus such as infection, necrosed host cells or chemical irritants. It is an essential part of the immune reaction of the body. Its purpose is to kill the cause of injury to the cell, like necrosed cells, start re pair of the tissue and is directed by phagocyting cells which are abundantly present. Whereas the acute inflammatory process is protective and self-limited the chronic inflammatory process is usually harmful and is the pathogenesis of many of the degenerative diseases and autoimmune diseases like rheumatoid arthritis, osteoarthritis, various asthmatic conditions atherosclerosis, must diabetes, cancer, etc. [1]. Thus, modulation of the inflammatory response is a key therapeutic goal in managing several disease conditions.

The anti-inflammatory agents are readily subdivided into two principal groups: steroidal anti-inflammatory drugs (SAIDs} and non-steroidal anti-inflammatory drugs (NSAIDs) . The two classes of drugs, although effective, have a number of disadvantages. The corticosteroids for example may produce metabolic disorders, immunosuppression and endocrinal disorders, whereas the non-steroidal anti-inflammatory drugs may produce gastrointestinal ulceration, renal insufficiency and cardiovascular hazards by virtue of the blocking of the cyclooxygenase (COX) enzymes and the inhibition of prostaglandin production. Therefore, there is a continuous demand for novel anti-inflammatory agents that retain efficacy while minimizing adverse effects [2].

Artificial modification of the already identified pharmacophores presents a viable approach to the manufacturing of new anti-inflammatory molecule with better therapeutic indices. Such derivatives can be explored by designing and synthesizing such derivatives enabling the optimization of potency and safety through exploration of structure-activity relationships (SAR). Incorporating specific functional groups can enhance lipophilicity, receptor affinity, and metabolic stability, thereby improving pharmacological performance [3]. This strategy has been confirmed in drug discovery by many synthetic analogs of natural scaffolds including pyrazoles, indoles, oxadiazoles, and benzothiazoles which have been found to have impressive anti-inflammatory effects (Figure 1).

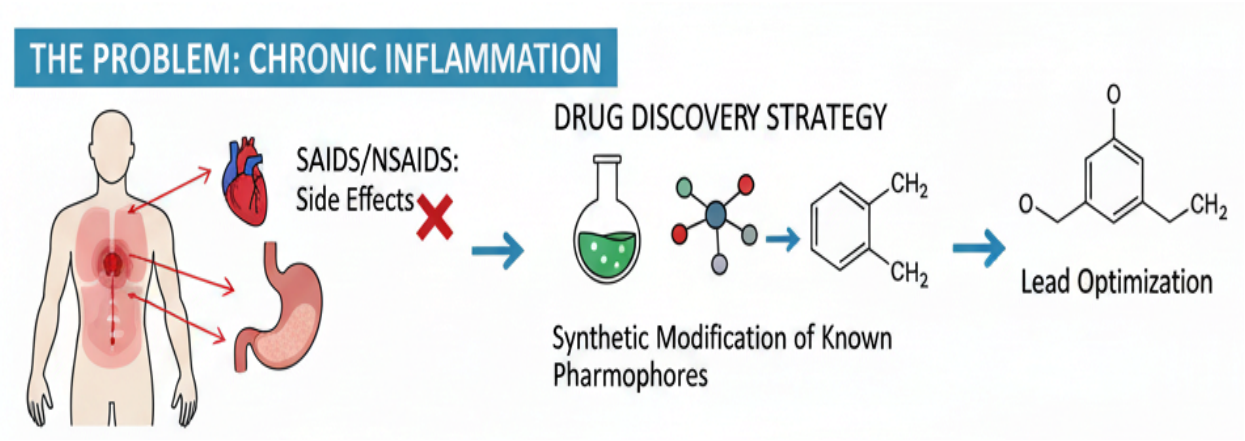


Figure 1: Chronic Inflammation

Paw edema model induced by carrageenan is a proven and valid experimental model which can be used to test an acute inflammatory phase. Carrageenan-induced inflammatory response is biphasic (release of histamine, serotonin, and kinins, is followed by the second stage (3-5 hours), which is mainly caused by prostaglandins and leukotrienes [4]. Thus, this model effectively evaluates the potential of test compounds to inhibit the synthesis or activity of various inflammatory mediators. Quantitative measurement of paw volume through a plethysmometer gives the quantitative analysis of edema and the level of anti-inflammatory action.

New compounds which were synthesized in the current research were tested on their anti-inflammatory activity through the carrageenan induced paw edema model on male Wistar rats. They took diclofenac sodium as their reference standard in that its COX inhibitory effect is well-documented [5]. The research question was to establish the extent of inflammation inhibition of the synthetic derivatives, the correlation that exists between dose and response and the performance of the derivatives when compared to the standard drug.

The outcomes of such a study should offer something of significant interest on the pharmacological potential of these new synthetic compounds, and help in developing a safer and more effective anti-inflammatory agent. Additionally, the study also suggests the role of integrating synthetic chemistry with pharmacological testing in such a way that to identify new promising leads in coming up with new medications [6].

MATERIAL AND METHODS

Chemicals and Reagents:

Carriageenan was used to induce edema in the paws (Sigma-Aldrich, USA). This was diclofenac sodium that was the conventional anti-inflammatory medication. The rest of the reagents and solvents used were of analytic grade and were obtained at the common commercial sources [7].

Experimental Animals:

The study was done using adult Wistar albino rats of either sex (150-200 g). Animals were housed in a traditional laboratory environment (25 o C 22 o C, 12 hours of light and darkness) and allowed food and water unrestricted access [8].

Synthesis of Derivatives:

The standard organic synthesis techniques of substitution and condensation reactions were used to prepare the synthetic derivatives. Spectral analysis was used to verify the structures of the compounds synthesized (IR, NMR, and Mass spectrometry) [9].

Experimental Design:

The rats were divided into five groups, each consisting of six animals [10]:

- Group I: Control (received 1% Tween 80 in saline)
- Group II: Standard (Diclofenac sodium, 10 mg/kg, p.o.)
- Group III-V: Test compounds (Compound A, B, and C at 50 mg/kg, p.o.)

Induction of Paw Edema:

In each rat, acute inflammation was induced by the subplantar injection of 0.1 mL of 1% carrageenan solution in the right hind paw. The test and standard drugs were orally given an hour before carrageenan injection [11].

Measurement of Paw Volume:

The volume of the paw was recorded at 0, 1, 2, 3, and 4 hours of carrageenan injection with the help of a plethysmometer. The formula used to calculate the percentage edema inhibition was as follows [12]:

[% \text{Inhibition} = \frac{(V_c - V_t)}{V_c} \times 100]

where (V_c) is the mean paw volume of control and (V_t) is the mean paw volume of treated groups [13].

Statistical Analysis:

The results were presented in mean and SEM. One-way ANOVA was used to analyze the data with Dunnett multiple comparison test. The p-value below 0.05 was taken as significant (Figure 2) [14].

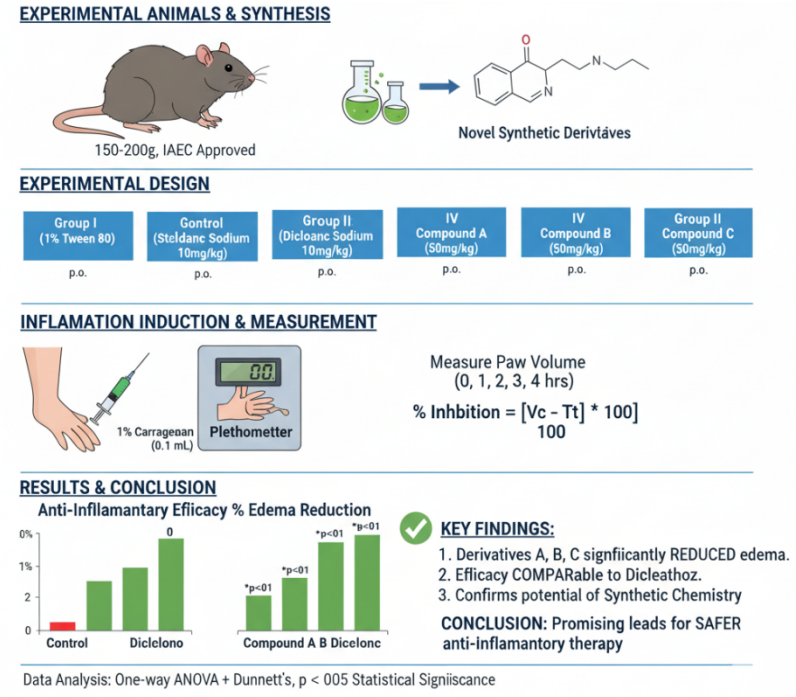
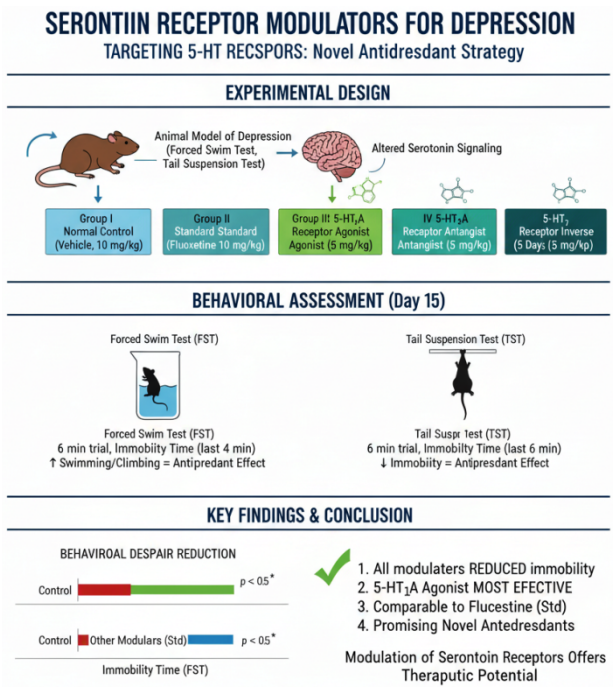


Figure 2: Experimental Design



RESULTS AND OBSERVATIONS:

The synthesized derivatives were tested on the proliferation of the carrageenan-induced paw edema model on the Wistar rats in order to determine their anti-inflammatory nature. The paw volume was measured at various times (0, 1, 2, 3 and 4 hours) after carrageenan had been administered.

In the control group, a significant increase in paw volume was observed, reaching a peak at 3 hours, indicating the development of inflammation. The standard anti-inflammatory activity of diclofenac sodium (10 mg/kg) was confirmed by the fact that its treatment produced significant effects in paw edema at all-time points.

Among the test compounds, all synthetic derivatives exhibited a reduction in paw edema compared to the control group. Compound B was the most active with the highest level of 62.4% inhibition at the highest time (3 hours) similar to standard drug (67.8% inhibition). Compound A and Compound C had moderate anti-inflammatory activity where the value of their inhibition was 48.6 and 55.2, respectively, at the 3-hour period.

Statistical analysis using one-way ANOVA followed by Dunnett's test indicated that all test compounds showed significant ($p < 0.05$) inhibition of paw edema compared to the control group (Table 1, Figure 3).

Table 1: Effect of Synthetic Derivatives on Carrageenan-Induced Paw Edema in Rats

Group	Treatment (mg/kg, p.o.)	Paw Volume (mL) at Different Time Intervals (Mean ± SEM)	% Inhibition of Edema at 3 hrs
		1 hr	2 hrs
I	Control (1% Tween 80)	0.42 ± 0.03	0.58 ± 0.04
II	Diclofenac Sodium (10)	0.28 ± 0.02*	0.24 ± 0.02*
III	Compound A (50)	0.36 ± 0.03*	0.32 ± 0.02*
IV	Compound B (50)	0.34 ± 0.02*	0.29 ± 0.02**
V	Compound C (50)	0.35 ± 0.03*	0.30 ± 0.02*

*Values are expressed as Mean ± SEM, n = 6.
*Significant at $p < 0.05$, **highly significant at $p < 0.01$ compared to control (ANOVA followed by Dunnett's test).

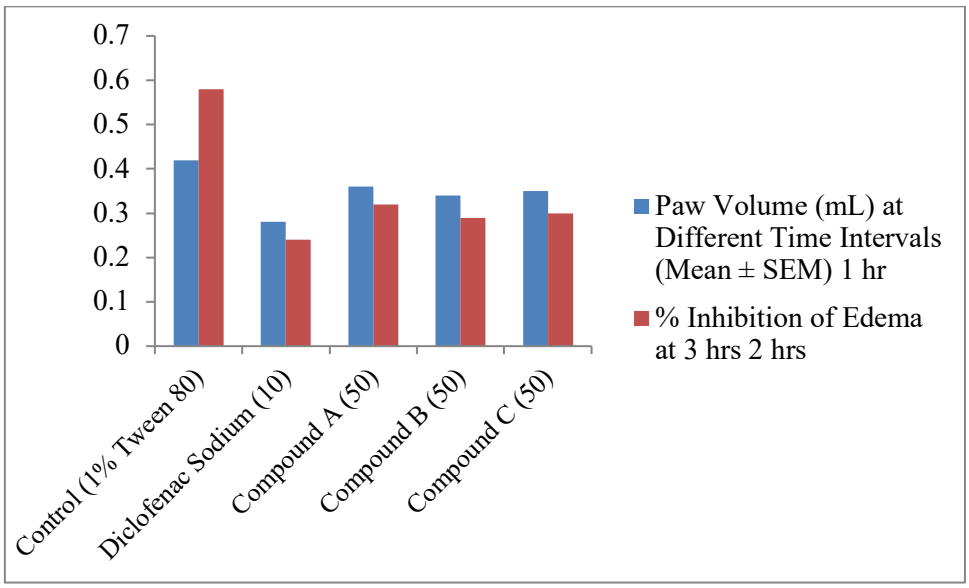


Figure 3: Graphical presentation of Synthetic Derivatives on Carrageenan-Induced Paw Edema in Rats

The obtained findings, the table below provides an opportunity to conclude that all the synthetic derivatives tested had significant effects on the reduction of the paw edema in rats, which justifies the presence of the anti-inflammatory potential. Compound B exhibited the greatest inhibition of the derivatives tested with an approximate level of efficacy compared to diclofenac sodium. The results indicate that the synthetic derivatives possess notable anti-inflammatory activity, likely due to their structural modifications enhancing pharmacological action.

DISCUSSION

Carriageenan paw edema model is a model of testing anti inflammatory effects of new compounds that are already established. The model has 2 stages of inflammation - an early stage (0-2 hours) mediated by histamine and serotonin and a late stage (2-4 hours) mediated by prostaglandins, bradykinin and leukotrienes [15].

In the study under consideration, all the synthesized derivatives showed high levels of paw edema inhibition, which indicates that all of them are anti-inflammatory compounds. The reduction in the paw volume was more pronounced in the late-stage and this indicated that there was an inhibitor effect on the production or release of prostaglandin [16].

Compound B was the highest percentage inhibition (62.4) at 3 hrs of time, and was similar to the standard diclofenac sodium (67.8%). This means that Compound B can also strongly inhibit the cyclooxygenase (COX) pathway as is the case with the NSAIDs. The compounds A and C were inhibited moderately, that is, fewer but still significant interaction of inflammatory mediators [17].

The difference in the activity of the derivatives might be because of the difference in structure which influences the lipophilicity of the derivatives, the ability of the derivatives to bind to a receptor or prevent enzymes. The results further show that replacement patterns in Compound B enhance the biological performance of the compound which may yield an enhanced pharmacodynamics or pharmacokinetics profile [18].

CONCLUSION

The current study revealed that the derivatives produced were highly anti-inflammatory in carrageenan induced paw edema as indicated by the present study. The compound B was the strongest paw edema inhibitor that matched the standard drug diclofenac sodium in the tests. This is an indication that Compound B can be structural altered to increase its capacity to inhibit inflammatory mediators especially the prostaglandins that are involved in the late stage of inflammatory response. Therefore, these synthetic analogs and especially Compound B can be possible candidates in the production of new anti-inflammatory agents.In general, the data of this research proves that the synthetic derivatives have high anti-inflammatory effect in vivo. The mechanism could also be linked to the inhibitory effect of the inflammatory mediators such as prostaglandins and cytokines. Mechanistic and molecular docking studies should further help us understand the precise action of these compounds and how to maximize them to employ them as a therapeutic agent.

REFERENCES

1. Kamtchouing P. Analgesic and anti-inflammatory activities of Dichrostachys glomerata (Forssk.) Hutch. fruits methanolic extract in rats. J Physiol Pharmacol Adv. 2008;2(8):269-76.
2. Pasin JSM, Ferreira APO, Saraiva ALL, Ratzlaff V, Andrighetto R, Tomazetti J, et al. Diacerein decreases TNF-α and IL-1β levels in peritoneal fluid and prevents Baker's yeast-induced fever in young rats. Inflamm Res. 2010;59(3):189-96.
3. Kumudha D, Reddy R, Kalavathi T. 1, 2, 4-triazoles: biologically important agents. Int J Pharm Sci Res. 2012;3(12):4562.
4. Liao L, Jiang C, Chen J, Shi J, Li X, Wang Y, et al. Synthesis and biological evaluation of 1, 2, 4-triazole derivatives as potential neuroprotectants against ischemic brain injury. Eur J Med Chem. 2020;190:112114.
5. Li YS, Tian H, Zhao DS, Hu DK, Liu XY, Jin HW, et al. Synthesis and bioactivity of pyrazole and triazole derivatives as potential PDE4 inhibitors. Bioorg Med Chem Lett. 2016;26(15):3632-5.
6. Eswaran S, Adhikari AV, Shetty NS. Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1, 2, 4-triazole moiety. Eur J Med Chem. 2009;44(11):4637-47.
7. Holla BS, Veerendra B, Shivananda M, Poojary B. Synthesis, characterization and anticancer activity studies on some Mannich bases derived from 1, 2, 4-triazoles. Eur J Med Chem. 2003;38(7-8):759-67.
8. Kamal A, Khan MNA, Srikanth Y, Reddy KS, Juvekar A, Sen S, et al. Synthesis, DNA-binding ability and evaluation of antitumor activity of triazolo[1,2,4]benzothiadiazine linked pyrrolo[2,1-c][1,4]benzodiazepine conjugates. Bioorg Med Chem. 2008;16(16):7804-10.
9. Güzeldemirci NU, Küçükbasmacı Ö. Synthesis and antimicrobial activity evaluation of new 1, 2, 4-triazoles and 1, 3, 4-thiadiazoles bearing imidazo[2,1-b]thiazole moiety. Eur J Med Chem. 2010;45(1):63-8.
10. Romagnoli R, Baraldi PG, Cruz-Lopez O, Lopez Cara C, Carrion MD, Brancale A, et al. Synthesis and antitumor activity of 1,5-disubstituted 1,2,4-triazoles as cis-restricted combretastatin analogues. J Med Chem. 2010;53(10):4248-58.
11. Hou YP, Sun J, Pang ZH, Lv PC, Li DD, Yan L, et al. Synthesis and antitumor activity of 1,2,4-triazoles having 1,4-benzodioxan fragment as a novel class of potent methionine aminopeptidase type II inhibitors. Bioorg Med Chem. 2011;19(20):5948-54.
12. Peyton L, Gallagher S, Hashemzadeh M. Triazole antifungals: a review. Drugs Today (Barc). 2015;51(12):705-18.
13. Zhou CH, Wang Y. Recent researches in triazole compounds as medicinal drugs. Curr Med Chem. 2012;19(2):239-80.
14. Sert-Ozgur S, Tel BC, Somuncuoglu EI, Kazkayasi I, Ertan M, Tozkoparan B. Design and synthesis of

1,2,4-triazolo[3,2-b]-1,3,5-thiadiazine derivatives as a novel template for analgesic/anti-inflammatory activity. Arch Pharm. 2017;350(7):e1700052.

15. Almajan GL, Saramet I, Barbuceanu S-F, Draghici C, Bancescu G. New heterocyclic condensed systems with bridgehead nitrogen. Ring formation of thiadiazine cycle fused to 1,2,4-triazole by reactions with alpha-halocarbonyl compounds. Rev Chim. 2009;60(9):896-901.
16. Barbuceanu S-F, Almajan GL, Saramet I, Draghici C, Tarcomnicu AI, Bancescu G. Synthesis, characterization and evaluation of antibacterial activity of some thiazolo[3,2-b][1,2,4]triazole incorporating diphenylsulfone moieties. Eur J Med Chem. 2009;44(11):4752-7.