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Evaluation of Anti-inflammatory activity of acid Hydrazide derivatives

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Abstract

***Plan**: Anti-inflammatory evaluation of acid hydrazide derivatives.*
***Prologue**: Hydrazide derivatives of organic compounds forms a significant group of derivatives which exhibit an array of biological activities like anti-inflammatory, antibacterial, antifungal, anti-neoplastic, antiviral etc. In view of above facts, we hereby reported the anti-inflammatory evaluation of selected most active eight antimicrobial acid (nicotinic acid, naphthalene-1-acetic acid and 2-naphthoxy acetic acid) hydrazide derivatives.*
***Methodology**: The anti-inflammatory activity of reported hydrazide derivatives determined by carrageenan induced paw oedema method and diclofenac sodium as standard drug.*
***Outcome**: Anti-inflammatory activity showed that nicotinic acid hydrazide derivatives with NO_2 substituents at ortho and meta position were the most active ones among the selected hydrazide derivatives, having 35.73% and 37.29%; 25.12% and 34.17% inhibition, at two different doses 20 mg/kg and 50 mg/kg b.w., respectively.*
***Keywords**: Anti-inflammatory, Antimicrobial, Acid hydrazides*

1. Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, fenbuprofen, diclofenac and fenbufen under current clinical usage suffer from a common drawback of gastrointestinal toxicity due to direct contact of free carboxylic group with gastrointestinal mucosa and inhibition of cyclooxygenase enzyme non-selectively [1]. In order to overcome these side effects, most studies are being focused on synthesis and identification of new chemical entities with minimal side effects and excellent anti-inflammatory properties.

Inflammation is known not only as a symptom of great deal of common diseases but also as an early phase of some serious diseases such as cancer, heart vascular diseases, and Alzheimer's dementia. Thus, the discovery of novel anti-inflammatory drugs has been attracting a lot of interests [2]. Hydrazide derivatives have attracted continuing interest over the years because of their wide range of biological activities *viz.* antimicrobial [3], antimycobacterial [4], antitumor [5], anti-inflammatory [6], trypanocidal [7], antiviral [8] and antimalarial activities [9].

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Further, it is well known that microbial infections often produce pain and inflammation. In normal practice, two groups of agents (chemotherapeutic and anti-inflammatory) are prescribed simultaneously. Unfortunately, none of the drugs possesses these two activities in a single component. However, during literature survey studies it was observed that many active antimicrobial agents showed very good anti-inflammatory activity [10-12].

In view of above facts, we hereby reported the anti-inflammatory evaluation of selected most active eight antimicrobial acid (nicotinic acid, naphthalene-1-acetic acid and 2-naphthoxy acetic acid) hydrazide derivatives (Table 1) synthesized during our earlier studies [13-16] and compared their anti-inflammatory activity with standard drug, diclofenac sodium.

2. Experimental

The anti-inflammatory activity of eight newly synthesized [13-16] most active antimicrobial hydrazide derivatives determined by carrageenan induced paw oedema method [16]. Wistar albino rats of either sex weighing 180-250 g were used for the experiment. All the experiments were carried out in accordance with the recommendations of the guidelines for care and use of laboratory animals. The protocol was approved by the Institutional Animal Ethics Committee, CCS HAU, Hisar.

This study was carried out in animal hose of Guru Jambheshwar University of Science and Technology, Hisar. Wistar albino rats were housed in the clean polypropylene cages and kept under room temperature, in 12 h of light-dark cycle. The animals were given standard laboratory diet and water ad libitum. Food was withdrawn 12 h before and during experimental hours. The animals were divided into 18 groups with each group containing 5 animals. A mark was made on the hind paw (left) just below the tibia-tarsal junction, so that every time the paw diameter was measured from a fixed position. The initial paw diameter of each rat was noted by digital vernier calliper.

The 17^{th} group received 0.6% sodium carboxy methyl cellulose and 18^{th} group received diclofenac sodium at a dose of 10 mg/kg body weight. The 1^{st} to 16^{th} groups were administered with the test compounds at a dose 20 mg/kg and 50 mg/kg (suspended in 0.6% CMC). The rats were injected with 0.1 ml of 1% (w/v) carrageenan in the subplantar region of the left hind paw after 30 min of treatment of test compounds. The right paw served as a reference to non-inflamed paw for comparison. The initial paw diameter was measured within 30 s of the injection. The relative increase in paw diameter was measured in control, standard and test compounds at an interval of 0 h, 0.5 h, 1 h, 2 h, 3 h and 4 h after the carrageenan injection.

The difference between the two readings *i.e.* 0 h and 4 h was taken as the diameter of edema; the percentage inhibition (Table 2) of paw edema was calculated using the formula,

$$\textit{Percentage of inhibition of paw edema} = (1-Dt/Dc) \times 100$$

Where Dt and Dc are the diameter of edema for compound treated and control group, respectively.

3. Results and discussion

The chemical structures of most active antimicrobial hydrazide derivatives synthesized in our previous studies [13-16] selected for anti-inflammatory activity study are presented in Table 1 and the results are expressed as % inhibition of oedema over the untreated control group of anti-inflammatory studies are given in Table 2. The tested compounds showed anti-inflammatory activity ranging from 0.31% to 37.29%, whereas standard drug diclofenac sodium showed 38.85 % inhibition after 4 h (Table 2). Nicotinic acid (2-nitro-benzylidene)-hydrazide, **III** and nicotinic acid (3-nitro-benzylidene)-hydrazide, **IV** having NO_2 substituents showed 35.73% and 37.29% inhibition; 25.12% and 34.17%, at two different doses 20 mg/kg and 50 mg/kg b.w., respectively, which is comparable to standard drug diclofenac sodium (10 mg/kg body weight) i.e. 38.85%. Further, (naphthalen-1-yloxy)-acetic acid [1-(2-bromo-4-cyano-phenyl)-ethylidene]-hydrazide, **VI** showed some inhibition (20.90%) at a dose of 50 mg/kg b.w.

Further, it is interesting to note here that the presence of NO_2 and Br groups (compounds **III**, **IV** and **VI**) improved the anti-inflammatory activity of studied hydrazide derivatives. This observation revealed the fact that presence of NO_2 and halo substituents increases the anti-inflammatory potential. This fact is supported by the observations of Manjunatha *et al.* [17].

4. Conclusion

The anti-inflammatory activity of hydrazide derivatives showed that nicotinic acid hydrazides having NO_2 substituents at *ortho* and *meta* position were the most active ones and exhibited anti-inflammatory activity comparable to standard drug diclofenac sodium.

Table- 1: Melting point and chemical structures of most active antimicrobial agents synthesized in previous studies selected for anti-inflammatory activity study [13-16]

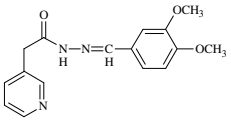
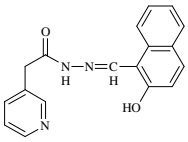
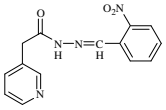
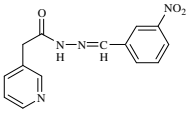
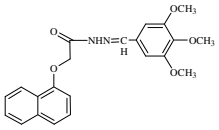
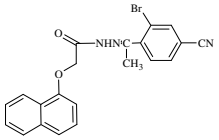
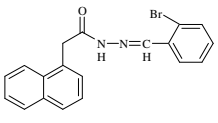
Comp.	*Chemical structure*	*IUPAC name*	*M. P. (^oC)*
I		Pyridin-3-yl-acetic acid (3,4-dimethoxy-benzylidene)-hydrazide	118-121
II		Pyridin-3-yl-acetic acid (2-hydroxy-naphthalen-1-ylmethylene)-hydrazide	231-234
III		Pyridin-3-yl-acetic acid (2-nitro-benzylidene)-hydrazide	178-181
IV		Pyridin-3-yl-acetic acid (3-nitro-benzylidene)-hydrazide	169-172
V		(Naphthalen-1-yloxy)-acetic acid (3,4,5-trimethoxy-benzylidene)-hydrazide	136-139
VI		(Naphthalen-1-yloxy)-acetic acid [1-(2-bromo-4-cyano-phenyl)-ethylidene]-hydrazide	162-165
VII		Naphthalen-1-yl-acetic acid (2-bromo-benzylidene)-hydrazide	193-195

Table- 2: Anti-inflammatory activity data of selected hydrazide derivatives

Comp.	*Dose (mg/Kg)*	*Edema (mm)*						
		0 min	*30 min*	*60 min*	*120 min*	*180 min*	*240 min*	*% inhibition (4 h)*
I	20	3.78 ± 0.01	5.08 ± 0.1	6.47 ± 0.12	6.48 ± 0.08	6.55± 0.07	6.39 ± 0.07	0.31
	50	3.67 ± 0.06	5.05 ± 0.09	6.25 ± 0.07*	6.27 ± 0.08*	6.21 ± 0.06*	6.18 ± 0.04	3.59
II	20	3.7 ± 0.1	5.28 ± 0.19	6.24 ± 0.34	6.61 ± 0.09	6.67 ± 0.05	6.25 ± 0.04	2.50
	50	3.7 ± 0.1	5.24 ± 0.23	6.20 ± 0.32	6.54 ± 0.06	6.60 ± 0.04	6.12 ± 0.08	4.52
III	20	3.64 ± 0.06	5.14 ± 0.02	6.34 ± 0.06*	5.4 ± 0.11*	4.16 ± 0.03*	4.12 ± 0.06*	35.73
	50	3.78 ± 0.06	5.05 ± 0.04	5.92 ± 0.03*	4.63 ± 0.18*	4.05 ± 0.05*	4.02 ± 0.04*	37.29
IV	20	3.79 ± 0.02	5.04 ± 0.04	5.75 ± 0.09*	4.86 ± 0.13*	4.85 ± 0.14*	4.8 ± 0.15*	25.12
	50	3.71 ± 0.09	5.09 ± 0.05	5.41 ± 0.09*	4.41 ± 0.05*	4.25 ± 0.02*	4.22 ± 0.22*	34.17
V	20	3.77 ± 0.12	5.06 ± 0.07	6.53 ± 0.04	6.68 ± 0.05	6.66 ± 0.07	6.21 ± 0.08	3.12
	50	3.48 ± 0.12	4.87 ± 0.2	6.24 ± 0.06	6.58 ± 0.1	6.60 ± 0.05	6.19 ± 0.05	3.43
VI	20	3.92 ± 0.07	5.05 ± 0.3	6.28 ± 0.19	6.59 ± 0.07	6.63 ± 0.08	6.13 ± 0.06	4.37
	50	3.88 ± 0.08	5.12 ± 0.31	5.27 ± 0.11*	5.12 ± 0.06*	5.51 ± 0.08*	5.07 ± 0.08	20.90
VII	20	3.79 ± 0.06	5.38 ± 0.14	6.03 ± 0.25	6.56 ± 0.23	6.71 ± 0.06	6.15 ± 0.07	4.06
	50	3.68 ± 0.09	5.31 ± 0.05	6.02 ± 0.14	6.4 ± 0.08	6.52 ± 0.07	6.14 ± 0.06	4.21
VIII	20	3.83 ± 0.10	5.52 ± 0.06	6.63 ± 0.05	6.52 ± 0.17	6.68 ± 0.04	6.19 ± 0.06	3.43
	50	3.57 ± 0.10	4.86 ± 0.35	6.60 ± 0.12	6.46 ± 0.07	6.58 ± 0.05	6.11 ± 0.12	4.68
Diclofenac (Std.)	10	3.69 ± 0.04	4.95 ± 0.05	5.39 ± .04*	4.22 ± 0.05*	3.94 ± 0.05*	3.92 ± 0.05*	38.85
Control		3.76 ± 0.02	5.15 ± 0.02	6.77 ± 0.03	6.84 ± 0.04	6.85 ± 0.04	6.41 ± 0.03	

*p<0.01 when compared to control group; Values are in Mean ± SEM (n=5); One-way ANOVA followed by Dunnet's t-test; Diclofenac sodium is used as the standard; CMC - Carboxy methyl cellulose as a suspending agent.

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