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Evaluation of Anti-Inflammatory Activity of 3-(1-Methoxy Napthalen-2-yl)-5-Phenylisoxazole by Using Passive Anaphylaxis in Rats.

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Abstract: *The structures of newly synthesized compounds were established on the basis of elemental analyses, IR. The newly synthesized heterocyles were characterized based on their chemical properties and spectroscopic data, and were found to difference in the reading prior to and after challenge represents the edema volume and the anti-anaphylactic effect was expressed as the percentage inhibition by using passive paw anaphylaxis in rats. Isoxazole derivatives have been prepared by condensing alpha-naphthol with acetic unhydride respectively. While compounds have been synthesized by the reaction of 3-(1-methoxy napthalen-2-yl)-5-phenylisoxazole.The compounds were screened for their anti-inflammatory activities.*

Keywords: *Isoxazole Derivatives, Anti-Inflammatory Activity, Paw Anaphylaxis.*

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I. Introduction

Inflammation

Inflammation (Latin, īnflammō, "I ignite, set alight") is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants[1]Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process.

Inflammation can be classified as either acute or chronic

Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process[2].

Causes

Burns
Chemical irritants
Frostbite Toxins
Infection by pathogens
Physical injury, blunt or penetrating
Immune reactions due to hypersensitivity
Ionizing radiation
Foreign bodies, including splinters, dirt and debris
Trauma

Table 1. Cardinal signs and symptoms of acute inflammation

Sr.no.	The classic signs and symptoms of acute inflammation:	
1	English	Latin
2	Redness	Rubor*
3	Swelling	Tumor*
4	Heat	Calor*
5	Pain	Dolor*
6	Loss of function	Functiolaesa**

Acute inflammation is a short-term process, usually appearing within a few minutes or hours and ceasing upon the removal of the injurious stimulus[3]. It is characterized by five cardinal signs: [4] The acronym that may be used for this is "PRISH" for Pain, Redness, Immobility (loss of function), Swelling and Heat.

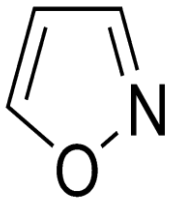
The traditional names for signs of inflammation come from Latin

Dolor (pain)
Calor (heat)
Rubor (redness)
Tumor (swelling)
Functiolaesa (loss of function)[5].

Redness and heat are due to increased blood flow at body core temperature to the inflamed site; swelling is caused by accumulation of fluid; pain is due to release of chemicals that stimulate nerve endings. Loss of function has multiple causes[6].

Drug:Isoxazole derivative have widespread pharmacological activities and are the part of some antifungal agents, anti-microbial and anti-inflammatory agents. As discussed earlier, the agents within azoles class vary importantly in regards to spectrum of activity, pharmacokinetic profiles, and toxicities. So in order to develop a broad-spectrum fungicide, it was an attempt to synthesize and develop newer isoxazole derivatives. Therefore the present investigation was aimed to explore isoxazole molecules as cheaper and safer antifungal, anti-microbial and anti-inflammatory agents. So to make use of their Antifungal, Anti-microbial and Anti-inflammatory agents. Potential; we preferred these two for work.

Isoxazole is a five membered heterocyclic compound having two hetero atoms: oxygen at position 1 and nitrogen at position 2. Claisen first reported an isoxazole (I) for a product from the reaction of 1,3diketone with hydroxylamine hydrochloride.Subsequently a solid foundation for the chemistry of isoxazole was laid down by Claisen and his students. It was shown to possess typical properties of an aromatic system but under certain reaction conditions. Particularly in reducing or basic media, it becomes very highly labile.[7]



The next important contribution to the chemistry of isoxazoles was made by Quelicoin 1945, when he began to study the formation of isoxazoles from nitrile N-oxide and unsaturated compounds.

SYNTHETIC ASPECT Isoxazoles can be prepared by various methods; some of them are described as under.

1. A variety of 3, 5-disubstituted 4-bromo isoxazoles (II) are readily prepared in good to excellent yields under mild reaction conditions.
2. Tayade V. B. et al .have synthesized some new 3,5-diarylisoxazoles from the reaction of 2-aryl acetophenones with hydroxyl amie hydrochloride in presence of alkali.[8]
3. Dawood Kamal etal.have prepared isoxazole derivatives from en amino nitriles[9].
4. Mark Lautens and Ame´lie Roy have constructed isoxazoles (III), were achieved in good yields in a rapid and simple way by using N-acetoacetyl derivatives.
5. Solid phase synthesis of isoxazole derivatives based on amino acids was reported by Lidia De Luca and co-workersin the presence of basic catalyst and dichloromethane used as a solvent. One pot synthesis of polyfunction alize disoxazoles have been synthesized by the reaction of dipyrrolidinium 3,3-dimethyl pentanedinitrile-2,4-dinitronate and acetyl chloride in benzene.[10]
6. Keisuke Suzuki et al.have synthesized functionalized isoxazole derivatives (IV) by cyclo condensation of C-chlorooximes with cyclic 1,3-diketones. [11]

7. Crawley L. S. and Fan Shawe W. J. have prepared isoxazole (V) from α,β-unsaturated carbonyl compounds, hydroxyl amine hydrochloride and KOH in methanol.[12]

8. R. Kalirajan etal., have synthesized and check antimicrobial screening against various gram positive and Gram negative bacteria and anti-fungal activity against various fungal stains compared with standard drug (Ampicillin and Ketoconazole) using solvent control.[13]

Therapeutic Importance

Isoxazole derivatives exhibit various biological activities such as,

1. Antibacterial [11]
3. Anticholestermic[14]
4. Anticancer [15]

5. Anthelmintics[16]
6. Anticonvulsant[17]

Table 2. IR Interpretation of 3-(1-methoxy napthalen-2-yl)-5-phenylisoxazole.

Sr.No.	Wave Number (cm^{-1})	Remark
1	1678	C=N
2	3066	Ar C—H
3	1593	Ar C=C
4	682	C-Cl

Drug profile:
Diclophenac: Diclophenac is Nonsteroidal anti-inflammatory drugs used to relieve the inflammation, swelling, stiffness, and joint pain associated with rheumatoid arthritis, osteoarthritis The exact mechanism of action is not entirely known, but it is thought that the primary mechanism responsible for its anti-inflammatory / antipyretic / analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid.[18]

II. Material & methods

Anti-inflammatory activity
In vivo methods: Passive anaphylaxis in rat
Chemical
Anaphylactic rat serum, Diclophenac sod. (Dcs) , Distilled water.
Animals
Rats (Albino Wistar) - weight around 200-250 g were divided into five groups.
YIP/CPCSEA/IAEC/2011-2012/02dt:-31/03/2012.
Procedure:

- Rats (Albino Wistar)- weight around 200-250 g were divided into five groups

Preparation of Antiserum:

- wistar albino rats of either sex selected randomly were ,injected ,(s.c.) with 0.2 ml of 10 % w/v egg albumin.
- On day 1, 3 and 5. Twenty one days after the first immunization, blood was collected from retro-orbital plexus under light ether anesthesia.
- The collected blood was allowed to clot and serum was separated by centrifugation at 1500 rpm. And The separated serum was stored at -20°C until it was used

Table 3. The treatment schedule

GROUPS	TREATMENT (Before 1hr of injection of serum p.o.)	SENSITIZATION
Control	Distilled water	Left hind paw with 0.1 ml of undiluted serum+ left hind paw with 10µg of egg albumin in 0.1 ml saline
Standard	Diclophenac sod.(20mg/kg)	
Test I	25mg/kg	
Test II	50mg/kg	

- The hind paw volume was measured after 30 minutes by displacement method using mercury column plethysmometer.
- The difference in the reading prior to and after challenge represents the edema volume and the anti-anaphylactic effect was expressed as the percentage inhibition.

III. Result And discussion

The present study was undertaken to synthesis & evaluation of anti-inflammatory activity of 3-(1-methoxy napthalen-2-yl)-5-phenylisoxazole.The aim of present study is to design the new synthetic compound which is more potential. The compounds were also evaluated for their in vivo Anti-inflammatory activity by using paw anaphylaxis in rats method. The hind paw volume was measured by displacement method using mercury column plethysmometer. The difference in the reading prior to and after challenge represents the edema volume and the anti-anaphylactic effect was expressed as the percentage inhibition.

Evaluation:
Statistical analysis by one way ANOVA analysis with dunnett post hoc test
Passive anaphylaxis in rats:
Statistical Analysis by one way ANOVA with Dunnett post hoc test
Values are mean ± SEM, n=6 in each group
Significantly different from control group *P<0.001

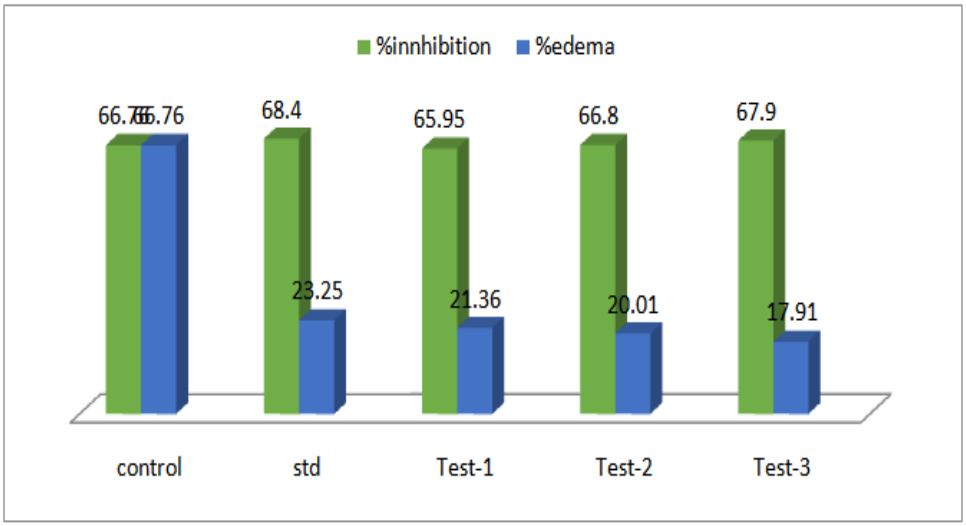


Figure 1: The effect on Passive Paw Anaphylaxis

Table 4. The Anti-inflammatory activity of 3-(1-methoxy napthalen-2-yl)-5 phenylisoxazole

Group	% Inhibition of edema at 60 minutes (Mean±SEM)	% Edema after 60 minutes (Mean±SEM)
Control		66.76±0.36
Standard(Diclofenac)	68.40	23.25±0.076*
Test 1(25mg/kg, p. o.)	65.95	21.36±0.075*
Test 2(50mg/kg, p.o.)	66.8	20.01±0.10*
Test 3(100mg/kg, p.o.)	67.9	17.91±0.11*

IV. Conclusion

The compounds have highly significant activity when compared with standard drug diclophenac, with percentage of inhibition to the inflammatory response ranging from 62% to 75%.Many isoxazole derivatives have been synthesized and evaluated for anti-inflammatory activity. From the limitations of therapeutically available isoxazole containing anti-inflammatory agents.We have synthesized different substituted, 3-(1-methoxy napthalen-2-yl)-5-phenylisoxazole nucleus and condensed them to offer targeted compounds.A new class of isoxazole derivatives 3-(1-methoxy napthalen-2-yl)-5-phenylisoxazole was synthesized and evaluated for antifungal,antimicrobial and antinflammatory activity.

- The logic behind the condensation of alpha-naphthol with acetic anhydride
- In present investigation, there is one asymmetric carbon as shown in structure which will help to increase the selectivity of the compound.
- In most of the antifungal, antimicrobial & anti-inflammatory drugs, long structure is present. The structure is much complex and needs a lengthy synthetic sequence to achieve the final product. This makes bulk drug expensive, which indirectly increases the cost of the treatment, also development of resistance and selectivity are problems associated with it. The generic market dominates the patented drugs in third world countries on the cost of treatment issue. Therefore, producing a simple, inexpensive molecule with more or less identical activity to patented drug molecule has become a need for third world countries.
- The synthesized were screened for the anti-inflammatory activity. The result of this study shows isoxazole derivative3-(1-methoxy napthalen-2-yl)-5-phenylisoxazole are found to be effective in experimental model of paw anaphylaxis.

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