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Synthesis, Characterization and Evaluation of In Vivo Anti-Inflammatory Activity of N-Substituted-1, 3, 4-Oxadiazole Derivatives

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ABSTRACT

The new series oxadiazole derivatives were prepared by reacting aromatic carboxylic acids. In the present work 10 different 5-substituted-1, 3, 4-oxadiazole -2-amine derivatives (3a -i) were synthesized. Substituted carboxylic acid is converted into substituted ethyl benzoate by esterification. Different ethyl benzoate is converted into different aroyl hydrazide by treating with hydrazine hydrate. The different aroyl hydrazide is converted 5-substituted-1, 3, 4-oxadiazole-2-amine derivatives by treating with cyanogen bromide. Confirmation of the chemical structure of the synthesized compounds was substantiated by TLC, IR, 1H NMR, and MS spectroscopy. In present study, a series of 1, 3, 4-oxadiazole derivatives(3a- i)were evaluated for in vivo anti-inflammatory activity by carrageenan induced paw edema method.
The results of anti-inflammatory evaluation revealed that compounds 3c, 3e and3i exhibited significant anti-inflammatory activity at a dose of 25 mg kg-1 compared to indomethacin used as the reference standard. The anti-inflammatory activity investigation highlights that the synthesized compound 3e could be considered for further clinical studies.

Keywords : Anti-Inflammatory, Oxadiazole, Aroyl Hydrazide

I. INTRODUCTION

1, 3, 4-oxadiazole are an important class of heterocyclic compound with wide range of biological activities. The chemistry of heteroangement demonstrate in cyclic compounds has been an interesting field of study for long time. The synthesis of novel Oxadiazole belongs to group of heterocyclic compounds that exhibit a wide range of biological activities . A lot of compounds containing such an arrangement demonstrate strong antibacterial, anticonvulsant, anticancer, fungicidal inhibition of tyrosinase and cathepsin K. In the organic synthesis. The five-membered 1, 3, 4-oxadiazole heterocycles are also useful intermediates in organic synthesis and widely employed as electron sporting and hole-blocking materials. Oxadiazole based molecular assemblies are an interesting and continuously developing area of research. These compounds demonstrate interesting luminescent properties, emitting blue to green light with high quantum efficiency depending on the substituents attached to the oxadiazole ring. Given facile synthesis and the possibility of appending different π-conjugated groups new oxadiazole derivatives are intensively investigated for biomedical applications.

Non-steroidal anti-inflammatory drugs (NSAID`S)are widely used for treating of pain and inflammation, thus being first line drugs for the treatment of arthritis. Osteoarthritis and other clinical condition associated pain and inflammation. Longterm clinical use of NSAIDS are associated with dyspepsia, gastro duodenal ulcers, gastritis bleeding and nephrotoxicity.

Table 1 : synthesized 1, 3, 4-oxadiazole derivatives from benzoic acid and its derivatives

Sr. No.	Compounds
1.	5-phenyl-1, 3, 4-oxadiazole-2 amine(a)
2.	5-(2-hydroxy phenyl)-1, 3, 4-oxadiazole-2 amine(b)
3.	5-(2-chlorophenyl)-1, 3, 4-oxadiazole-2 amine(c)
4.	5-(4-amino phenyl)-1, 3, 4-oxadiazole-2 amine(d)
5.	5-(4-chlorophenyl)-1, 3, 4-oxadiazole-2 amine(e)
6.	5-(2-amino phenyl)-1, 3, 4-oxadiazole-2 amine(f)
7.	5-(4-nitro phenyl)1, 3, 4-oxadiazole-2 amine(g)
8.	5-(2, 3-dihydroxy phenyl)-1, 3, 4-oxadiazole-2 amine(h)
9.	5-(2-nitrophenyl)-1, 3, 4-oxadiazole-2 amine(i)
10.	5-(3, 4, 5-trihydroxy phenyl)-1, 3, 4-oxadiazole-2 amine(j)

II. EXPERIMENTAL

2. 1. MATERIALS AND METHODS:

All chemicals and solvent procured from commercial sources, purified and dried using standard procedures from literature whenever required the reagents were purchased fromResearch lab, Mumbai . and issued from store department of Rajarambapu College of Pharmacy, Kasegaon. And solvents were purified by distillation and residual water was removed. The test compounds 1, 3, 4-oxadiazole derivatives 3a-3j were synthesized in our laboratory. Meltingpoint of synthesized compounds was determined by open capillary tubes. IR spectra were recorded using KBr disc on JASCO FTIR-4600. Mass spectra were recorded on QP 2010 Shimadzu. H1NMR spectra were performed in CDCl3 solution using Bruker 300MHz, using DMSO as solvent. The test compound was synthesized by the following procedure

Mass spectra were recorded on QP 2010 Shimadzu.

Synthesis of ethyl -4-nitrobenzoate:

Sub. ethyl benzoate was prepared by dissolving 0. 01mole of p-nitro benzoic acid in absolute ethanol (20 ml). carboxylic acid group is esterified with ethanol and the reaction is processed by refluxing the mixture for 3-5 hours by adding few drops of H_2SO_4, which is act as a catalyst. The final product was obtained as precipitated form which was continued for the next step preparation.

Synthesis of 4-nitrobenzohydrazide:

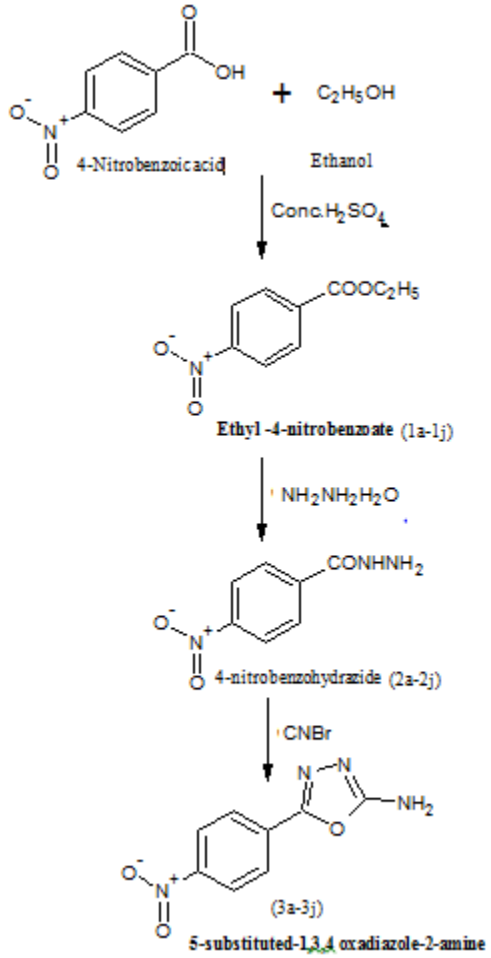
The mixture of compound 1 (0. 01mol)and 0. 02 Mol 99% hydrazine hydrate was refluxed for 5-6 hours. The reaction mixture was cooled. The solid precipitate was obtained. Dried and recrystallized from ethanol. The completion of reaction was monitored by Thin Layer Chromatography and Infrared Spectrophotometer.

Yield=68% ;Melting point=200-202 ^{0}C.

Synthesis of 5-substituted-1, 3, 4 oxadiazole-2-amine:

To a solution of the 4-nitrobenzohydrazide (0. 01 mol) in ethanol (20 ml), and cynogenbromide (1. 05g)were added, and the reaction mixture was refluxed and continuously stirring (around 6 h). The residue was dissolved in water and then made basic with sodium bicarbonate solution. The precipitate was filtered off, dried, and crystallized from ethanol, room temp for

overnight. The mixture was poured into cold water, filtered, dried and crystallized from ethanol. The completion of reaction was monitored by Thin Layer Chromatography and Infrared Spectrophotometer.



2. 2. AnimalsUsed :

AnimalsWistar rats (100–120 g) of either sex used in this study were purchased from the Animal House of the National Institute of Biosciences, pune. The animals were maintained under standard laboratory conditions (12 h light/dark cycles at 22 ± 2◦C) and fed standard rodent pellets (National Institute of Biosciences, pune, Maharashtra) and water. The protocol was approved by the Committee For The Purpose Of Control and Supervision of Experiments on Animals (Reg. No. 1290/PO/Re/S/09/CPCSEA 16/03/19.)

2. 2. 1 ACUTE TOXICITY STUDY

Acute toxicity studies were performed to estimate the median lethal dose (LD50) value of the synthesized compounds 3a-3j as per the OECD guidelines (TG420) and the testing dose for the newly synthesized compounds on the animal for the in vivo anti-inflammatory activity was fixed. The LD50 of the 1, 3, 4-oxadiazoles 3a-3j were determined as per reported method.

2. 2. 2. ANTI-INFLAMMATORY EVALUATION

Anti-inflammatory activity was evaluated by carrageenan-induced paw edema test using group of Wistar rats weighing 100-120gm each and 2 rats per group as standard, test and control. The hind paw edema was induced in each rat by the sub-plantar injection of 0. 1mL of carrageenan suspension (1. 0% w/v in 0. 9% saline) 1 h after the administration of the test compounds and standard drug orally. The linear paw circumference was measured immediately before injection and at 30 min interval for 4 h using the cotton thread method. Anti-inflammatory activity is determined by evaluating the reduction in edema size and determining % inhibition of edema. A reduction in edema when compared with control and an increase % inhibition in the treated groups is an indication of anti-inflammatory activity.

$$\%\text{inhibition} = (a\text{-}x/b\text{-}y) \times 100$$

Where, x is the mean of paw volume of rats in the test group before administration of carrageenan and/or test compounds or reference drug, **a** is the mean paw volume of rats after the administration of carrageenan in the test group, **b** is the mean paw volume of rats after the administration of carrageenan in the control group, **y** is the mean paw volume of rats before the administration of carrageenan in the control group. The mean % inhibition of Diclofenac and tested compound at 25 mg kg^{-1} concentration was compared with control and repeated measures ANOVA with Dennett's test.

III. RESULTS AND DISCUSSION

3. 1. IN VIVO ANTI-INFLAMMATORY EVALUATION OF THE TEST COMPOUNDS(3A-3J):

The compounds 3a-3j at a dose 25 mg $kg^{-1}$was evaluated for in vivo anti-inflammatory activity by carrageenan induced paw edema method. Diclofenac a 25 mg $kg^{-1}$was used as reference standard and CMC as control. The result of anti-inflammatory screening at the end of four hours the administration of carrageenan showed that compounds 3a-3j exhibited edema reduction14. 5 to 72. 3%, in comparison to standard Diclofenac, which showed an edema reduction of about 50. 01%.

Compounds with aryl/heteroaryl substitution at position C5 of the oxadiazole moiety, compounds 3e (4-chlorophenyl), 3f (2-amino phenyl), 3h (2, 3-dihydroxy phenyl), exhibited superior anti-inflammatory efficacy than that of Diclofenac with an edema reduction ranging from 58. 5 to 68. 3%. compound 3g (4-nitro phenyl) was most potent of all other 1, 3, 4-oxadiazole compounds in the present series with an edema reduction of 72. 3%.
Compound 3a proved to be the major exception of all the tested compounds showing edema reduction only 14. 5%, whereas compounds 3c and 3d exhibited edema reduction 29. 5 and 21. 7% respectively. The anti-inflammatory results highlight the importance of aryl/heteroaryl as substituent at position 5 of the oxadiazole moiety as possible reason for the anti-inflammatory efficacy.

The percentage inhibition of inflammation by the test compounds at dose 25 mg kg^{-1} at the end of four hours' time intervals expressed in table 2.

Table 2 : In vivo anti-inflammatory activity of the test compounds at 25 mg kg^{-1} by carrageenan induced paw edema method.

Sr. No.	Compound	Percentage protection
1.	3a	14. 5
2.	3b	35. 7
3.	3c	29. 5
4.	3d	21. 7
5.	3e	58. 5
6.	3f	63. 9
7.	3g	72. 3
8.	3h	68. 3
9.	3i	51. 2
10.	3j	47. 1
11.	Diclofenac	60. 5

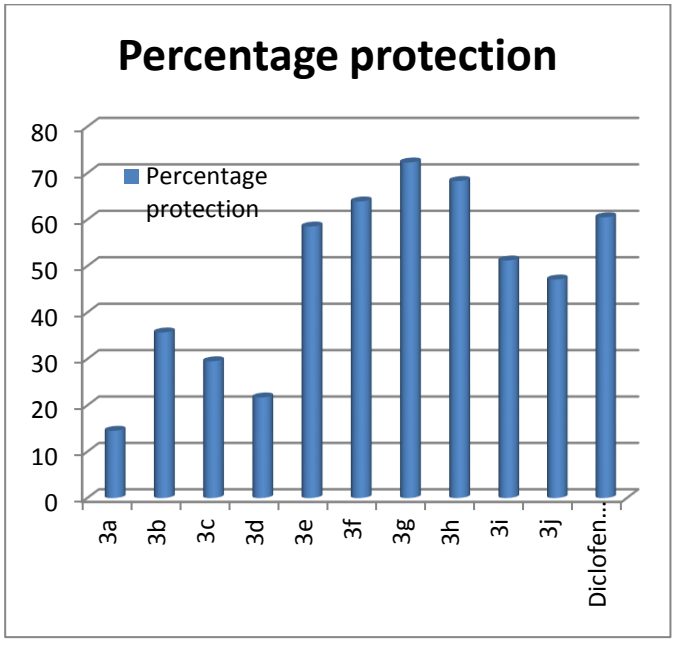


Fig. 1. Percentage protection of derived compounds

IV. CONCLUSION

The pharmacological evaluation of the 1, 3, 4-oxadiazole derivatives 3a-3j, for in vivo anti-

inflammatory efficacy have produced promising results. The in vivo anti-inflammatory activity was evaluated by carrageenan induced paw edema method at a dose 25 mg kg-1 and the result were encouraging. The anti-inflammatory activity data indicated that the 1, 3, 4-oxadiazole derivatives 3g, 3f and 3h could be considered as possible hit as therapeutic agents. It can be concluded that compounds 3g, 3f and 3h certainly holds great promise towards good active leads in medicinal chemistry. A further investigation to explore the molecular mechanics is in progress.

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