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In vitro antioxidant and *in vivo* anti-inflammatory activity of 1,3,4-Oxadiazole derivatives

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ABSTRACT

In the present study, a series of 1,3,4-oxadiazole derivatives (4a-4k) were evaluated for *in vitro* antioxidant property by DPPH radical scavenging assay method and *in vivo* anti-inflammatory activity by carrageenan induced paw edema method. The title compounds 4a-4k exhibited significant antioxidant efficacy ranging from 36 to 82 % and the results of anti-inflammatory evaluation revealed that compounds 4j, 4g and 4d exhibited significant anti-inflammatory activity of 68, 64 and 62%, respectively 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 4j could be considered for further clinical studies to ascertain its possible hit as anti-inflammatory agents.

1. INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAID's) are widely used for the management of pain and inflammation, thus being first line drugs for the treatment of arthritis, osteoarthritis and other clinical condition associated pain and inflammation [1]. Long term clinical use of NSAID's are associated with dyspepsia, gastroduodenal ulcers, gastritis bleeding and nephrotoxicity [2,3].

Gastrointestinal damages, which are the prominent side effects of NSAID's are usually attributed to the local irritation caused by the interaction between carboxylic acid group present in NSAID's (diclofenac, ibuprofen, indomethacin, mefenamic acid and many more) and the mucosal cells [4]. Literature studies on NSAID's highlights investigation on modification of the carboxylic acid group with other functional moieties like ester [5], amide [6] and also conversion to five member heterocycles [7,8] which efficiently reduces the risk of gastic ulceration without loss of anti-inflammatory efficacy.

Inhibition of 5-lipoxygenase (5-LO's) has been reported to be helpful in attenuating the formation of gastric ulcer during the long term therapy of NSAID's [9]. Literature studies on 1,3,4-oxadiazoles as anti-inflammatory agents highlighted their importance in inhibiting 5-LO's, thus reducing gastric ulcer formation, apart from suppressing prostaglandin anabolism from arachidonic acid by inhibiting cycloxygenase (COX) enzyme, thus indicating its importance as anti-inflammatory agent being nonulcerogenic nature [10, 11]. Hence, 1,3,4-oxadiazoles have been widely explored for its anti-inflammatory property [12-15].

1,3,4-oxadiazole being an toxophoric moiety (N-C-O), highlighting its importance as a potential biodynamic molecule [16], has been widely explored for its biological activities like anticonvulsant [17], antidepressant [18], anticancer [19], analgesic [20], antibacterial [21], antifungal [22], antimycobacterial [23], anthelmintic [14], hypoglycemic [24] and antiangiogenic [25] etc.

Similarly, numerous 1.3.4-oxadizole derivatives are in clinical use as therapeutic agents. Therapeutic agents such as HIV-integrase inhibitor *(Raltegravir)*, antibacterial agent *(Furamizole)*, antihypertensive agent *(Tiodazosin)* and anti arrhythmic agent *(Nesapidil)* are designed on 1,3,4-oxadiazole moiety (Fig. 1).

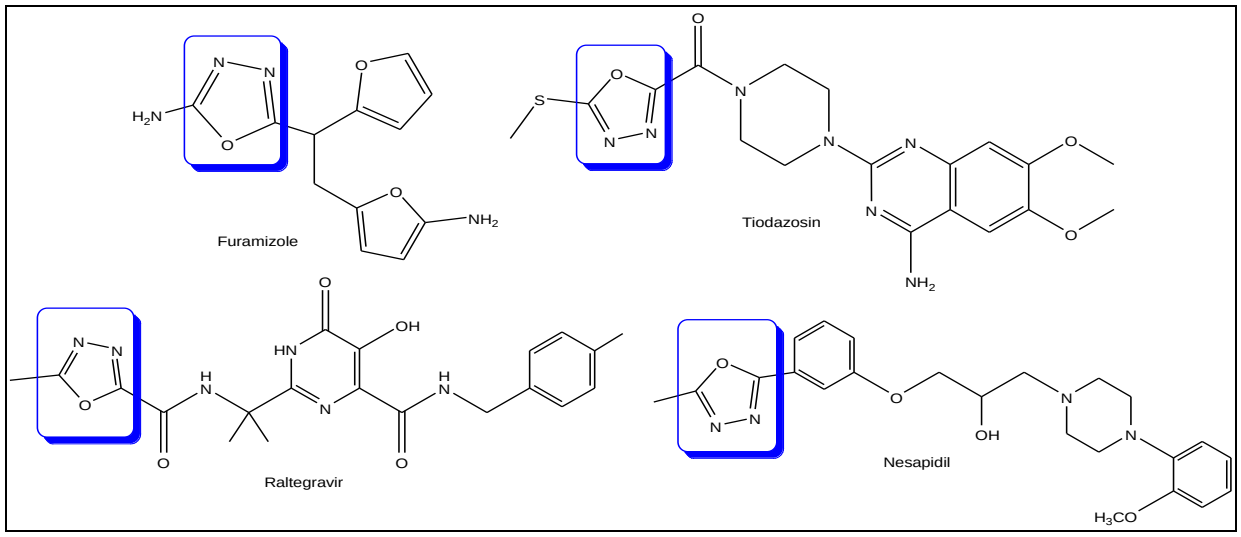

Fig. 1: 1,3,4-Oxadiazole derivatives in clinical use

In our previous study, we had reported the synthesis and characterization of 1,3,4-oxadiaozle derivatives **4a-4k** (Fig. 2), from (1*H*-benzo[*d*]imidazol-2-yl)methanamine [26]. Wherein, *N*-[(1*H*-benzo[*d*]imidazol-2-yl)methyl](5-substituted-1,3,4-oxadiazol-2-yl)methanamine; **4a-4j** (Table 1) were prepared from nucleophilic addition of aryl/heteroaryl/aliphatic carboxylic acids with 2-[(1*H*-benzo[*d*]imidazol-2-yl)methylamino]acetohydrazide in presence of phosphorous oxychloride. The acetohydrazide derivative was prepared by condensation of ethyl 2-[(1*H*-benzo[*d*]imidazol-2-yl)methylamino]acetate with hydrazine monohydrate. The ester derivative was prepared by *N*-alkylation of (1*H*-benzo[*d*]imidazol-2-yl)methanamine with ethyl 2-chloroacetate in the presence of anhydrous potassium carbonate. The compound 5-{[(1*H*-benzo[*d*]imidazol-2-yl)methylamino]methyl}-1,3,4-oxadiazole-2-thiol **(4k)** was prepared by condensation of the acetohydrazide with carbon disulphide and potassium hydroxide.

In continuation of the work, in our present investigation, we herein report the *in vitro* antioxidant property and *in vivo* anti-inflammatory efficacy of these eleven 1,3,4-oxadiazole derivatives **4a-4k**.

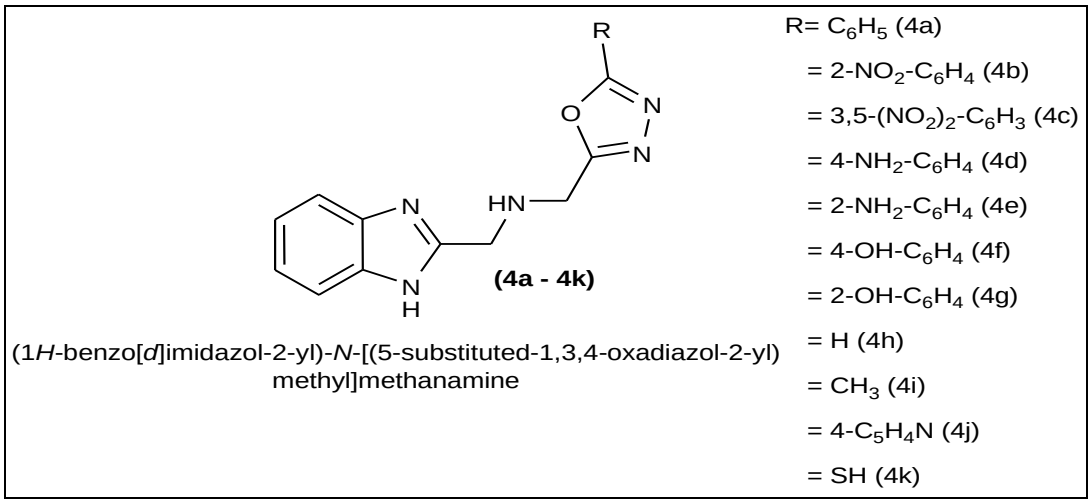

Fig 2: Synthesized 1,3,4-oxadiazole derivative from benzimidazole 4a-4k

Table 1: Synthesized 1,3,4-oxadiazole derivatives from benzimidazole 4a-4k

Sl. No.	Compound
1.	*N*-[(1*H*-benzo[*d*]imidazol-2-yl)methyl](5-phenyl-1,3,4-oxadiazol-2-yl)methanamine (4a)
2.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl]methanamine (4b)
3.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl)methyl]methanamine (4c)
4.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl)methyl]methanamine (4d)
5.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-(2-aminophenyl)-1,3,4-oxadiazol-2-yl)methyl]methanamine (4e)
6.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)methyl]methanamine (4f)
7.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)methyl]methanamine (4g)
8.	*N*-[(1,3,4-oxadiazol-2-yl)methyl](1*H*-benzo[*d*]imidazol-2-yl)methanamine (4h)
9.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]methanamine (4i)
10.	(1*H*-benzo[*d*]imidazol-2-yl)-*N*-[(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)methyl]methanamine (4j)
11.	5-{[(1*H*-benzo[*d*]imidazol-2-yl)methylamino]methyl}-1,3,4-oxadiazole-2-thiol (4k)

2. EXPERIMENTAL SECTION

2.1. Materials and methods

The chemicals used were purchased from Fluka chemicals, Mumbai, India, and the solvents were purified by distillation and residual water was removed. The test compounds 1,3,4-oxzdiazole derivatives 4a-4k were synthesized in our laboratory.

2.1.1. *In vitro* antioxidant activity

The *in vitro* antioxidant activity was carried out by DPPH radical scavenging assay method with suitable modification [27]. In brief, the assay was carried out using UV spectrophotometer at 517 nm. To the 2 mL solution of synthesized compounds (0.1 µM), 2 mL DPPH solution (25 µM) was added into the test tube. The solution was incubated at 37 °C for 30 min and the absorbance of each solution was measured at 517 nm against the reagent blank solution. The ascorbic acid (0.1 µM) was used as the reference antioxidant. The experimental values summarized for DPPH radical scavenging assays are expressed as the mean ± standard error of mean (m ± SEM). The percent free radical scavenging activity was calculated by the formula given below.

$$\%\ Scavenging = \frac{Control\ absorbance - Test\ absorbance}{Control\ absorbance} \times 100$$

2.2. Pharmacology

All the animal experimental procedures and protocols adapted in the study were reviewed and approved by the Institutional Animal Ethics Committee. The experimental procedures and protocols were in accordance with the guidelines of the CPCSEA, Ministry of Forests and Environment, Govt. of India. The animals were obtained from the JSS Medical college, Mysore, India, and were maintained in colony cages at 25 ± 2°C, relative humidity of 45-55%, under a 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use and they were deprived of food 12 h prior to experiment and only water was allowed *ad libitum*.

2.2.1. Acute toxicity studies

Acute toxicity studies were performed to estimate the median lethal dose (LD50) value of the synthesized compounds 4a-4k as per the OECD guidelines (TG 420) and the testing dose for the

newly synthesized compounds on the animal model for the *in vivo* anti inflammatory activity was fixed. The LD50 of the 1,3,4-oxadizoles 4a-4k were determined as per the reported method.

2.2.2. Anti-inflammatory evaluation

Anti-inflammatory activity was evaluated by carrageenan-induced paw edema test using groups of albino rats weighing 100-120 g each and 6 rats per group, as per the reported method [13]. The animals were injected with 0.1 mL of carrageenan (1% solution in normal saline) in the plantar tissue of the right hind paw. The first group received only 0.5% carboxymethylcellulose (CMC) orally and served as untreated control. The test groups received compounds suspended in 0.5% CMC orally at a dose of 25 mg kg^{-1} one hour prior to carrageenan injection. While the positive control group received 25 mg kg^{-1} indomethacin suspended in 0.5% CMC, orally one hour before carrageenan injection.

Four hours after carrageenan administration, the paw volumes (mL) were measured using the mercury displacement technique with the help of a plethysmograph. The percent inhibition of paw edema was calculated by using the following formula.

$$\%\ Inhibition = \left(\frac{a - x}{b - y}\right) \times 100$$

Where ***x*** is the mean paw volume of rats in the test group before the 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 (reference drug/ test compound treated), ***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 percent inhibition of indomethacin and tested compounds at 25 mg kg^{-1} concentrations was compared with control using the repeated measures ANOVA with Dunnet's test.

3. RESULTS AND DISCUSSION

3.1. *In vitro* antioxidant evaluation

The 1,3,4-oxadiazole derivatives (4a-4k) were evaluated for their free radical scavenging activity by DPPH radical assay method using ascorbic acid as standard. The compounds 4a-4k exhibited

significant scavenging activity ranging from 36 to 82% in comparison to 89% antioxidant activity obtained for the reference drug, ascorbic acid.

Compounds 4f (4-hydroxy phenyl) exhibited potent antioxidant efficacy of 82%, which can be attributed to the phenolic hydroxy group substitution at position C4 of the phenyl moiety. Similarly, other compounds 4k (mercapto), 4g (2-hydroxy phenyl), 4j (pyridine-4-yl), 4d (4-amino phenyl) and 4e (2-amino phenyl) exhibited substantial antioxidant property of 79.4, 76.6, 76.1, 68.6 and 61.4 %, respectively. The radical scavenging activity highlighted the importance of polar group substitution at the ortho/para position of the phenyl moiety at position C5 of 1,3,4-oxadizole molecule. The antioxidant results measured by DPPH radical assay methods are given in Table 2.

Table 2: *In vitro* antioxidant activity for the test compounds 4a-4k

Sl. No.	Compound	*Percentage free radical scavenging activity
1.	4a	54.87 ± 2.54
2.	4b	36.13 ± 1.84
3.	4c	41.42 ± 3.12
4.	4d	68.64 ± 2.17
5.	4e	61.42 ± 1.76
6.	4f	82.42 ± 1.34
7.	4g	76.67 ± 1.27
8.	4h	51.31 ± 2.04
9.	4i	42.61 ± 1.34
10.	4j	76.11 ± 1.47
11.	4k	79.42 ± 3.09
12.	Ascorbic Acid	89.17 ± 1.86

*Results are expressed as the mean values from three independent experiments ± SEM.

3.2. *In vivo* anti-inflammatory evaluation of the test compounds 4a-4k:

The compounds 4a-4k at a dose of 25 mg kg^{-1} were evaluated for *in vivo* anti-inflammatory activity by carrageenan induced paw edema method. Indomethacin at 25 mg kg^{-1} was used as reference standard and CMC as control. The result of the anti-inflammatory screening at the end of four hours after the administration of carrageenan showed that compounds 4a-4k exhibited edema reduction of 12.6 to 68.7%, in comparison to standard indomethacin, which showed an edema reduction of about 48.2%.

Interestingly, compounds with aryl/hetroaryl substitution at position C5 of the oxadiazole moiety (4a-4g and 4j) in the present series exhibited significant anti-inflammatory efficacy ranging from 29.6 to 68.7% edema reduction.

Among compounds with aryl/hetroaryl substitution at position C5 of the oxadiazole moiety, compounds 4d (4-amino phenyl), 4e (2-amino phenyl), 4f (4-hydroxy phenyl) and 4g (2-hydroxy phenyl) exhibited superior anti-inflammatory efficacy than that of indomethacin with an edema reduction ranging from 56.9 to 64.5%. Compound 4j (pyridin-4-yl) was the most potent of all the other 1,3,4-oxadiazole compounds in the present series with an edema reduction of 68.7%. While, compounds with nitrophenyl substitution, namely 4b (2-nitrophenyl) and 4c (3,5-dinitrophenyl), exhibited diminished activity in comparison to the other compounds 4a, 4d, 4e, 4f, 4g and 4j with aryl/hetroaryl substitution, with edema reduction of only 29.6 and 37.5 %, respectively.

Compound 4h proved to be the major exception of all the tested compounds showing edema reduction of only 12.6%, whereas compounds 4k and 4i exhibited edema reduction of 26.4 and 19.2%, respectively. The anti-inflammatory results highlight the importance of aryl/hetroaryl as substituent at position 5 of the oxadiazole moiety as possible reason for the anti-inflammatory efficacy.

The statistical analysis of the anti-inflammatory data by Dunnet's test revealed that compounds 4a-4k exhibited significant ($P< 0.001$) anti-inflammatory activity compared to control. The percentage inhibition of inflammation by the test compounds at dose of 25mg kg^{-1} at the end of four hours time intervals are expressed as m ± SEM. in Table 3.

Table 3: *In vivo* anti-inflammatory activity of the test compounds at 25 mg kg^{-1} by carrageenan induced paw edema method at the end 4 h

Sl. No.	Compound	[a,b]Percentage Protection
1.	4a	47.25 ± 0.72***
2.	4b	29.64 ± 1.14***
3.	4c	37.49 ± 1.16***
4.	4d	62.19 ± 2.07***
5.	4e	58.43 ± 2.16***
6.	4f	56.92 ± 2.10***
7.	4g	64.46 ± 1.15***
8.	4h	12.61 ± 0.79***
9.	4i	19.28 ± 0.91***
10.	4j	68.72 ± 1.87***
11.	4k	26.45 ± 1.32***
12.	Indomethacin	48.72 ± 1.61***

[a] Results are expressed as the mean values from three independent experiments ± SEM.

[b] Data was analyzed by Dunnet's test. n = 3; (***) equals P<0.001

4. CONCLUSION

The pharmacological evaluation of the 1,3,4-oxadiazoles derivatives 4a-4k, for *in vitro* antioxidant property and *in vivo* anti inflammatory efficacy have produced promising results. The result of *in vitro* antioxidant activity correlates the importance of antioxidant property with respect to edema inhibition as seen in case of anti-inflammatory screening. The *in vivo* anti-inflammatory activity was evaluated by carrageenan induced paw edema method at a dose of 25 mg kg^{-1} and the results were encouraging. The anti-inflammatory activity data indicated that the 1,3,4-oxadizole derivatives 4j, 4g and 4d could be considered as possible hit as therapeutic agents. It can be concluded that compounds 4j, 4g and 4d 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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