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RECENT ADVANCE IN ANALGESIC AND ANTIINFLAMMATORY ACTIVITY OF OXADIAZOLE DERIVATIVES

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ABSTRACT

Oxadiazoles are an important class of bioactive and industrially important organic compounds. Steroids and non-steroidal antiinflammatory drugs are globally used for reducing inflammation in the body. 1,3,4-Oxadiazoles are five membered heterocyclic compounds, containing one oxygen and two nitrogen atoms. Literature indicates that compounds containing this nucleus have wide range of pharmacological activities include anti-inflammatory, antimicrobial, analgesic, anti-HIV, antiparkinsonian, antiproliferative, anticonvulsant, antimalarial, antihypertensive, antioxidant, antitubercular, sedative-hypnotic, hypoglycemic etc. Oxadiazoles are also used as photosensitizers, lipid peroxidation inhibitor, genotoxic, spasmolytic, diuretic, antiemetic, hypnotic, sedative, hypotensive, hypoglycemic, nematocidal, amoebicidal agents and plays an important role in agricultural chemistry. Researchers have designed a variety of novel compounds with a means of preventing or minimizing the adverse effects of drugs which cause some serious gastric problems, and risks of complications regarding potential cardiovascular hazards of cyclooxygenase inhibitors. The review represents a broad view on the analgesic and anti-inflammatory activity possessed by compounds having 1,3,4-oxadiazole nucleus.

KEYWORDS

Oxadiazole, Analgesic, Anti-inflammatory, Ulcer and NSAIDs.

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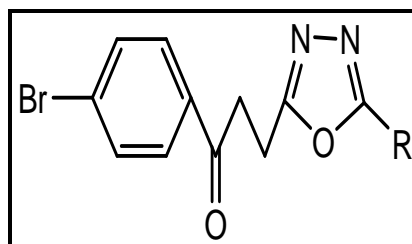
INTRODUCTION

Oxadiazoles are five-membered heterocyclic systems containing one oxygen and two nitrogen atoms, in literature also known as furadiazoles. 1,3,4-Oxadiazole and their synthetic derivatives have diverse pharmacological activities such as anti-inflammatory¹, antimicrobial²⁻⁶, analgesic⁷, antipyretic⁸, anti-HIV⁹, antiproliferative¹⁰⁻¹², anticonvulsant¹³, antihypertensive¹⁴, antioxidant¹⁵, antitubercular¹⁶⁻¹⁷, genotoxic¹⁸, muscle relaxant¹⁹, antipsychotic²⁰ and antidiabetic²¹⁻²² activities etc.

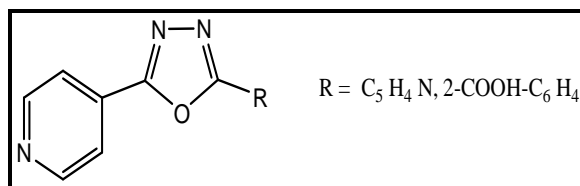
NSAIDs are found for clinical use globally, due to their good anti-inflammatory, analgesic and antipyretic effects. NSAIDs in comparison to analgesic and anti-inflammatory drugs are used as an important tool for the clinician. Anti-inflammatory drugs inhibit both COX-1 and COX-2, but COX-1 is inhibited more eagerly than COX-2. COX-1 inhibition causes side effects (related to gastrointestinal and cardiovascular) and COX-2 inhibition is responsible for therapeutic effects. NSAIDs are particularly used for reducing pain and inflammation in osteoarthritis, rheumatoid arthritis, and arthritis of systemic lupus erythematosus, psoriasis and other seronegative spondyloarthropathies. These agents block metabolism of arachidonic acid through the enzyme cyclooxygenase, and therefore, the production of prostaglandins. NSAIDs are associated with side effects such as; formation of gastric ulcers, including lesions of the gastric, duodenal, intestinal mucosa and dyspepsia, due to the presence of free carboxylic acid. The chronic use of NSAIDs for a long time induces ulcer in the range of 15-30%. 1,3,4-Oxadiazoles have been designed for reducing the gastric ulcer formation because of their enzyme inhibiting properties for both cyclooxygenase and 5-lipoxygenase. Some novel compounds have designed by replacement of the carboxylic acid group with 1,3,4-oxadiazole nucleus have resulted in a significant anti-inflammatory activity.

Analgesic and Anti-Inflammatory Activity

Dhansay Dewangan *et al.*, Synthesized some of the Novel 2, 5- Disubstituted 1, 3, 4-Oxadiazoles and evaluated as analgesic and anti-inflammatory activities. All the synthesized compounds shown significant analgesic and anti-inflammatory activities²³.

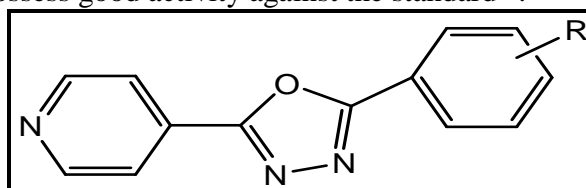


R = C₆H₅ -, 2-ClC₆H₄ -, 4-ClC₆H₄ -, 2-HOC₆H₄ -, 4-NO₂C₆H₄ -, 4-FC₆H₄ -, 4-CH₃C₆H₄ -, 4-OCH₃C₆H₄ -, 3,4-(OCH₃)₂C₆H₃ -, C₆H₅CH₂ -, C₆H₅OCH₂ -, 2-C₆H₅COC₆H₄ -, 1-C₁₀H₇OCH₂ -, 2-C₁₀H₇OCH₂ -

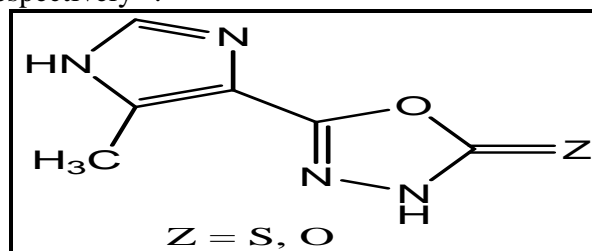


R = C₅H₄N, 2-COOH-C₆H₄

Biju C R *et al.*, worked on the Design and Microwave-assisted Synthesis of 1,3,4-Oxadiazole derivatives and screened for analgesic and anti-inflammatory activities. Almost all the compounds possess good activity against the standard²⁴.



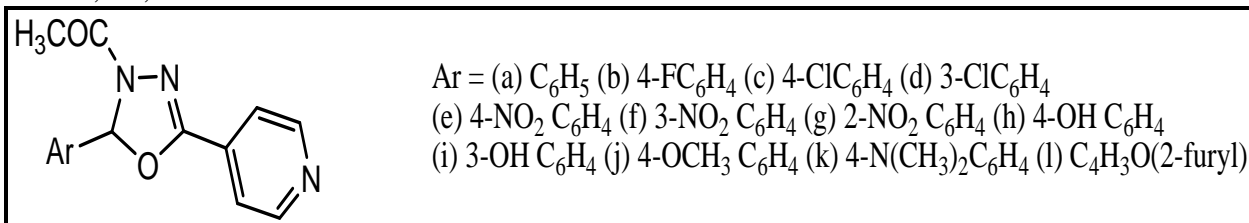
Almasirad *et al.*, Synthesized new methylimidazolyl-1,3,4-oxadiazoles and 1,2,4-triazoles. The analgesic and anti-inflammatory profile of the synthesized compounds were evaluated by writhing and carrageenan induced rat paw edema tests respectively²⁵.



A. Husain and M. Ajmal, Synthesized novel 1,3,4-oxadiazole derivatives. Title compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic and antibacterial activities. A fair number of compounds were found to have significant anti-inflammatory and analgesic activities, while a few compounds showed appreciable antibacterial activity. The newly synthesized compounds showed very low ulcerogenic action²⁶.

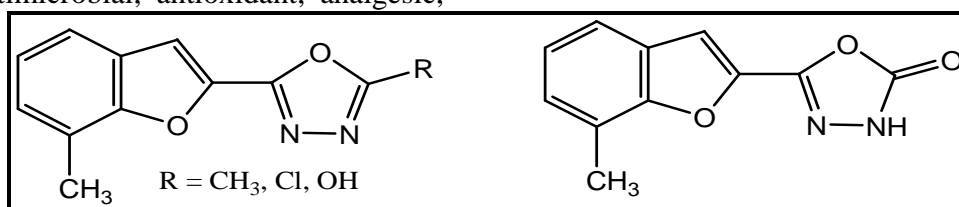
Sudhir Bhardwaj *et al*, worked on the Microwave assisted synthesis and pharmacological evaluation of some 1, 3, 4-oxadiazole derivatives. The

synthesized compounds were screened for antimicrobial, analgesic and anti-inflammatory activities²⁷.



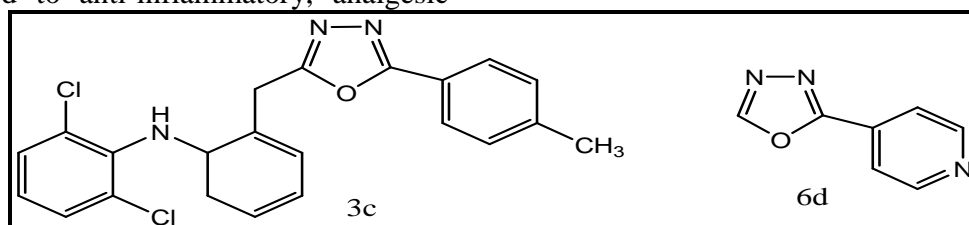
K. M. Basavaraja *et al*, synthesized some of the new oxadiazole and pyrazole derivatives incorporating benzofuran moiety, these have been screened for antimicrobial, antioxidant, analgesic,

anti-inflammatory and antipyretic activities. Compounds 5 and 7 exhibited encouraging results and remaining exhibited moderate activity²⁸.



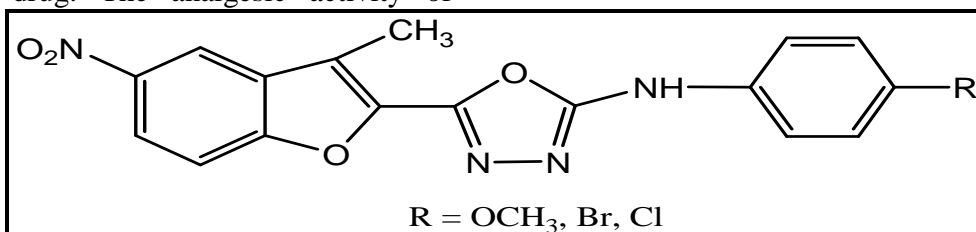
R. R. Somani *et al*, worked on the Synthesis and Evaluation of Anti-inflammatory, Analgesic and Ulcerogenic Potential of NSAIDs Bearing 1,3,4-Oxadiazole Scaffold. These compounds were further subjected to anti-inflammatory, analgesic

and acute ulcerogenic activity. Compound 3c and 6d exhibited good antiinflammatory activity and compounds 3c, 3e, 6c, 6d, 6e were found to be non ulcerogenic²⁹.



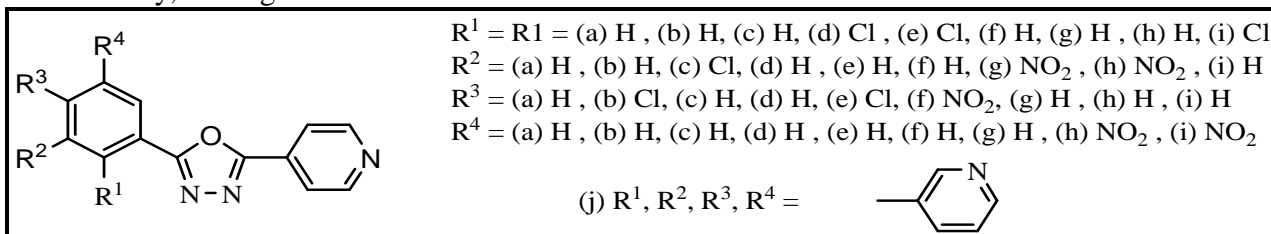
K. M. Basavaraja worked on the Analgesic and anti-inflammatory activity of 3-methoxy-5-nitro-2-(1',3',4'-oxadiazolyl,1',3',4'-thiadiazolyl and 1',2',4'-triazolyl)benzofurans. The title compounds have shown encouraging analgesic activity. Their analgesic potency has been found to be equal to that of a standard drug. The analgesic activity of

remaining compounds is found to be moderate. The anti-inflammatory activity results indicate that some compounds are equally active and comparable with standard phenylbutazone. Other compounds have been found to be either moderately or poorly active³⁰.



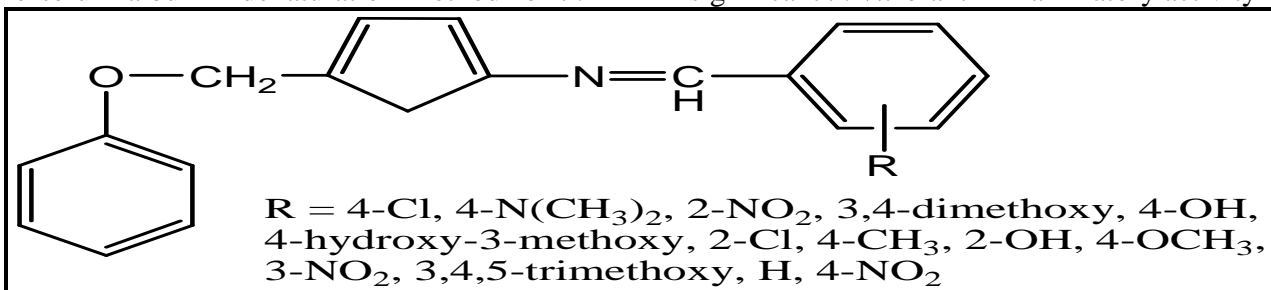
Khusboo Jain *et al.*, worked on the Microwave assisted synthesis and pharmacological evaluation of some 4-(5-(substituted phenyl)-1,3,4-oxadiazol-2-yl) pyridine. Compounds were evaluated for their anti-inflammatory, analgesic and antimicrobial

activities. Some of the compounds were found to have significant anti-inflammatory and analgesic activities, while a few compounds showed appreciable³¹.



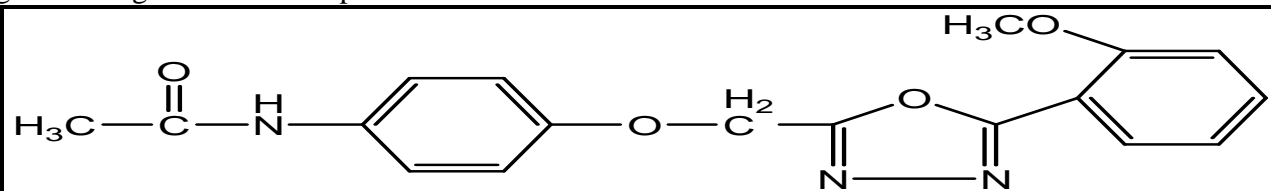
Satyendra Deka *et al.*, Synthesized some novel oxadiazoles and evaluated using inhibition of bovine serum albumin denaturation method for *in-*

vitro anti-inflammatory activity. Compound SBM-4d, SBM-4f, SBM-4h and SBM-4i have shown significant *in-vitro* anti-inflammatory activity³².



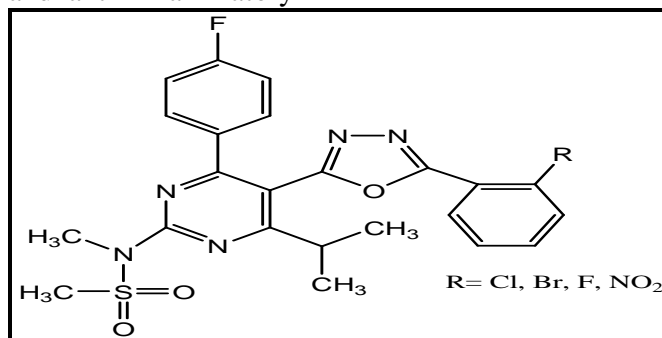
Ilango K *et al.*, Synthesized 2, 5-Disubstituted-1,3,4-oxadiazoles. The titled compounds were screened for *in vivo* anti-inflammatory activity using the carrageenan-induced paw edema method.

A few of them manifested promising activity when compared with the standard drug Diclofenac sodium³³.



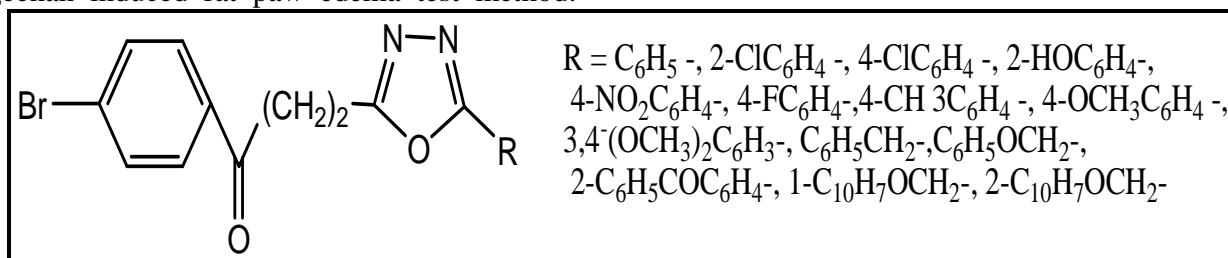
Rajgopal H.Udupi *et al.*, Synthesized a series of pyrimidine substituted 1,3,4-oxadiazole derivatives. The synthesized compounds were evaluated for their *in vitro* antimicrobial and anti-inflammatory

activity. Some of the newly synthesized compounds showed good antimicrobial and anti-inflammatory activities³⁴.



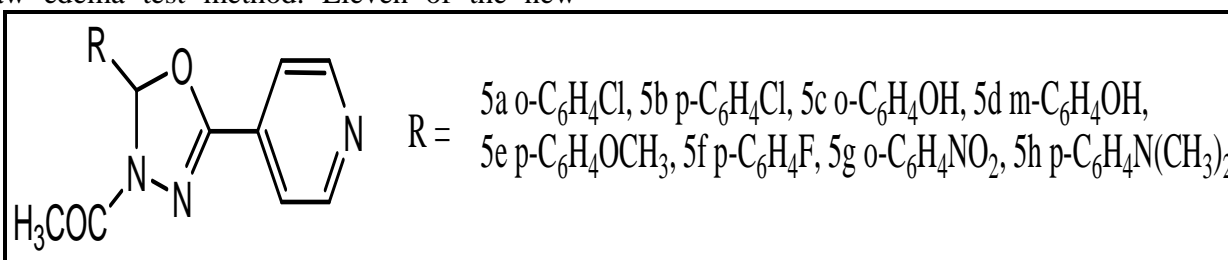
Arvind K. Singh *et al.*, Synthesized some of 1, 3, 4-Oxadiazole derivatives, All compounds were evaluated for their anti-inflammatory activity by the carrageenan induced rat paw edema test method.

The compounds possessing potent anti-inflammatory activity were further tested for their analgesic, ulcerogenic and antioxidant activities³⁵.



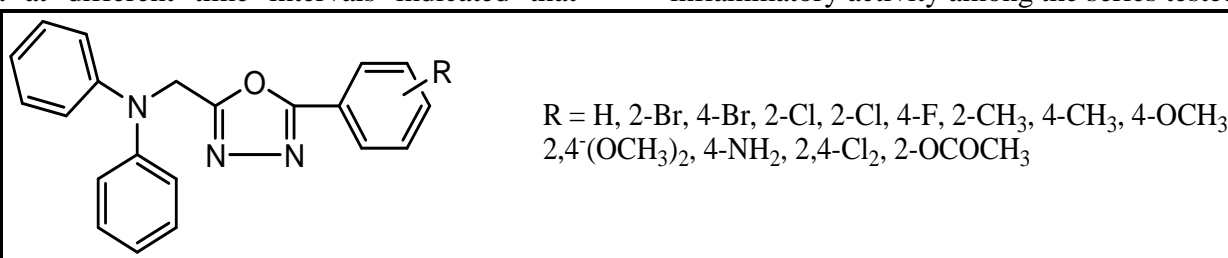
Sadaf J. Gilani *et al.*, Synthesized the Thiazolidin-4-one, azetidin-2-one and 1,3,4-oxadiazole derivatives of isonicotinic acid hydrazide. All compounds were evaluated for their anti-inflammatory activity by the carrageenan-induced rat paw edema test method. Eleven of the new

compounds, out of 32, showed very good anti-inflammatory activity in the carrageenan-induced rat paw edema test, with significant analgesic activity in the tail immersion method together with negligible ulcerogenic action³⁶.



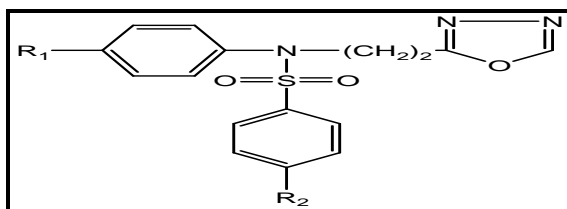
Mohammad Shaquiquzzaman *et al.*, Synthesized some of the new 2-(substituted-phenyl)-5-(N,N-diphenylaminomethyl)-1,3,4-oxadiazoles. The compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation actions. The percentage inhibition in edema at different time intervals indicated that

compounds 8, 11, 12, 14 and 15 exhibited good anti-inflammatory potential. The results illustrate that 2-(2-acetoxyphenyl)-5-(N,N-diphenylaminomethyl)-1,3,4-oxadiazole (15) and 2-(3,4-dimethoxyphenyl)-5-(N,N-diphenylaminomethyl)-1,3,4-oxadiazole (12) showed best anti-inflammatory activity among the series tested³⁷.



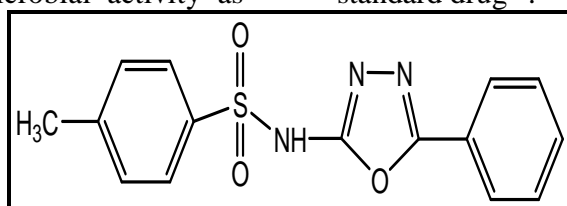
Shobha R. Desai *et al.*, worked on the Synthesis and Pharmacological Activities of Some New 5-Substituted-2-mercapto-1,3,4-oxadiazoles. Only two compounds 4b (73%) and 4e (54%), have shown moderate antituberculosis activity. All the compounds have shown moderate anti-inflammatory

activity and least ulcerogenicity. Most of the compounds have shown significant analgesic activity (64.20-120.72%) in comparison with the standard, Aspirin (49.39%) In the MES method, however only compound 4a, exhibited a protection of 33.33%, and others failed to protect³⁸.



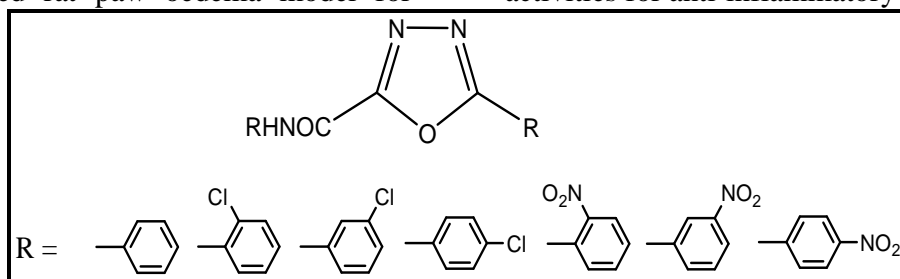
Pal *et al*, worked on the Synthesis, characterization and evaluation of substituted oxadiazole and thiadiazole derivatives. All the compounds show good pharmacological activities. Compounds IVa and IVb exhibited good antimicrobial activity and IVc, IVd showed moderate microbial activity as

compared with a standard drug ofloxacin. Compounds VIb and VIc exhibited good anti-inflammatory activity as compared with standard drug diclofenac-30, while VIc shows good analgesic activity in comparison to aspirin used as standard drug³⁹.



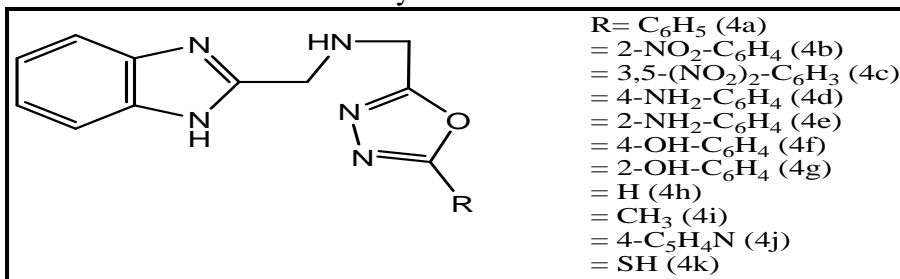
Arvind Kumar Singh *et al*, Synthesized some of the 1, 3,4 -oxadiazole derivatives. These compounds were tested for their anti-inflammatory activity determined by rat paw oedema method. All synthesized derivatives were determined by the carrageenan induced rat paw oedema model for

Anti-inflammatory activity. The entire compound gives good response for anti-inflammatory activity for this activity indomethacin was used as standard drug and compared to new synthesized drugs. Some New Synthesized drugs have to shown better activities for anti-inflammatory⁴⁰.



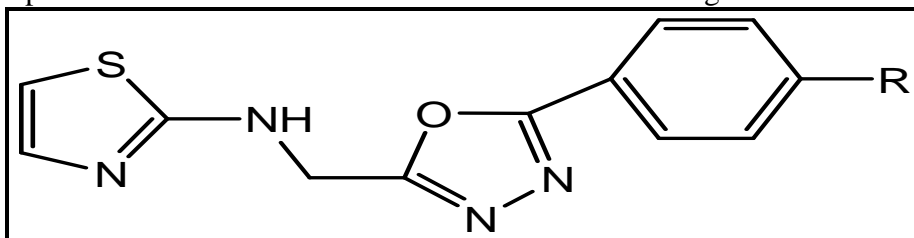
B. Vishwanathan and B.M. Gurupadayya, worked on the *In-vitro* antioxidant and *in-vivo* anti-inflammatory activity of 1,3,4-Oxadiazole derivatives. The title compounds 4a-4k exhibited significant antioxidant efficacy ranging from 36 to 82 % and the results of anti-inflammatory

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 standard⁴¹.



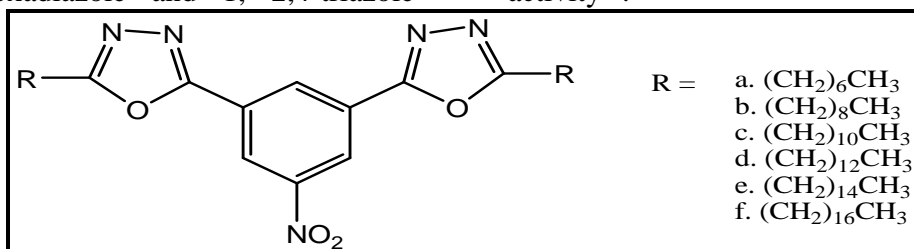
Jisha Shamsudeen, worked on the Synthesis and Evaluation of Anti-inflammatory Activity of Novel Derivatives of 2-Aminothiazole and Oxadiazole, The synthesised compounds were screened for their

anti-inflammatory and anti-microbial potential. Among those compounds 4a and 4b have shown anti-inflammatory activity while compounds 4d and 4e has shown significant anti-microbial activity⁴².



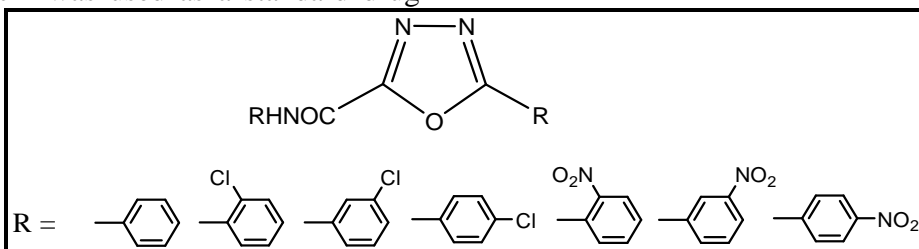
J. Keshavayya *et al.*, worked on the Synthesis, characterization and pharmacological studies of novel bis 1,3,4-oxadiazole and 1, 2,4-triazole

derivatives. Newly synthesized compound displayed potent antibacterial and antinociceptive activity⁴³.



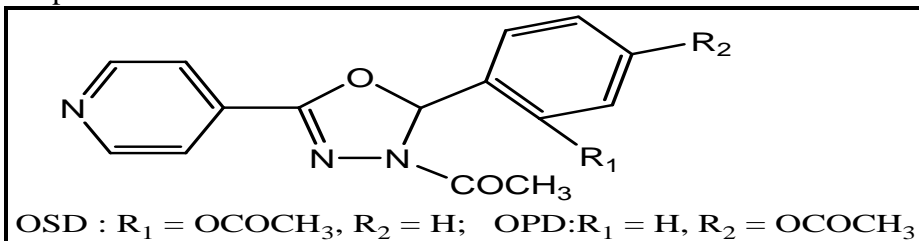
Kumar Singh A *et al.*, worked on the Synthesis, Characterization and Anti-Inflammatory Activity of Some 1,3,4-Oxadiazole Derivatives. For this activity, indometacin was used as a standard drug

and compared to new synthesized drugs. Some new synthesized drugs have shown better activities for the anti-inflammation⁴⁴.



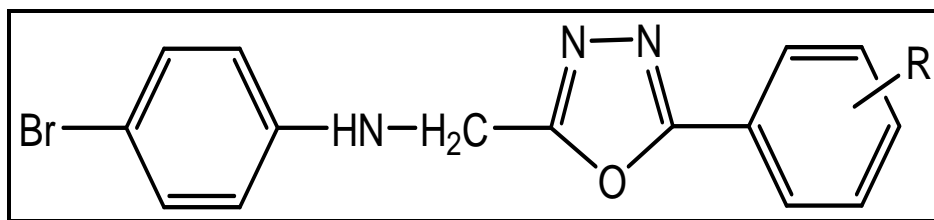
Durga shiva prasad, *et al* Synthesized the Novel 2,5-disubstituted-1,3,4-oxadiazoles. OSD was the better of the two compounds in *in-vivo* models of

inflammation. The o-phenol substitution at position 2 of oxadiazole ring in OSD may be responsible for its better in vivo anti-inflammatory activity⁴⁵.



Bhat, *et al* worked on the Synthesis, characterization and biological activity studies of 1,3,4-oxadiazole analogs. The newly synthesized compounds were screened for antibacterial,

antifungal and anti-inflammatory activities. Some of the compounds showed remarkable antibacterial, antifungal and anti-inflammatory activities⁴⁶.



CONCLUSION

The oxadiazole ring is an important pharmacophore in modern drug discovery. In recent years, attention has increasingly been given to the synthesis of oxadiazole derivatives as a source of anti-inflammatory agents. This review article mainly focused on potent anti-inflammatory activity of 1,3,4-oxadiazoles with lesser side-effects, which has global therapeutic and clinical importance. 1,3,4-Oxadiazole derivatives also show various important pharmacological activities and are widely used for preparation of medicinal active compounds. This activity is exploited for awaking the safe use of this important chemical moiety with minimal or no ulcerogenic activity in future. This summarized study would be useful for the researchers working in this field.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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