

1, 3, 4-OXADIAZOLE AND THEIR PHARMACOLOGICAL PROPERTIES: A REVIEW

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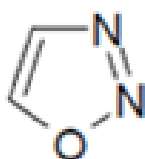
ABSTRACT

Oxadiazole is a five member heterocyclic ring contains two nitrogen and one oxygen atom. The presence of 1,3,4 oxadiazole structures in different types of compounds is increasing their biological effect. Oxadiazole nucleus has emerged as one of the potential pharmacophore responsible for various biological properties. This interesting group of compound has many biological activities such as antimicrobial, anti-inflammatory, antitubercular, anticonvulsant, anticancer, anti-HIV, hypoglycemic and genotoxic.

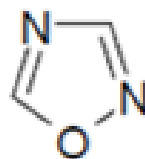
KEYWORDS: 1, 3, 4-Oxadiazole, Oxadiazole, Antimicrobial, Anti-inflammatory, Anticonvulsant, Anticancer.

INTRODUCTION

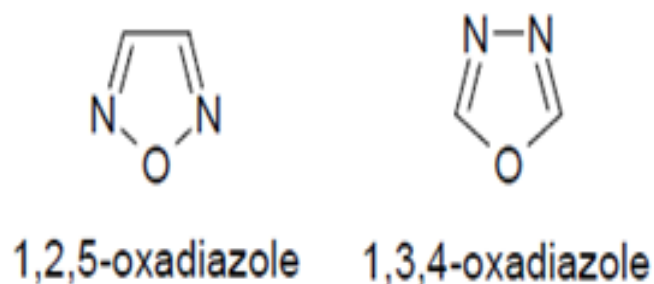
Compounds having a five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles or in the older literature furadiazoles. Four types of oxadiazole are known namely 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles. Out of these 1, 3, 4-oxadiazoles are found to be most potent biologically. The compounds containing oxadiazole ring are exhibit different pharmacological activities.



1,2,3-oxadiazole



1,2,4-oxadiazole

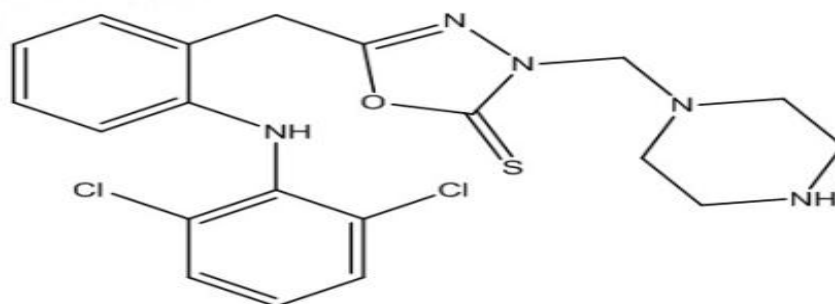


Anti-inflammatory activity

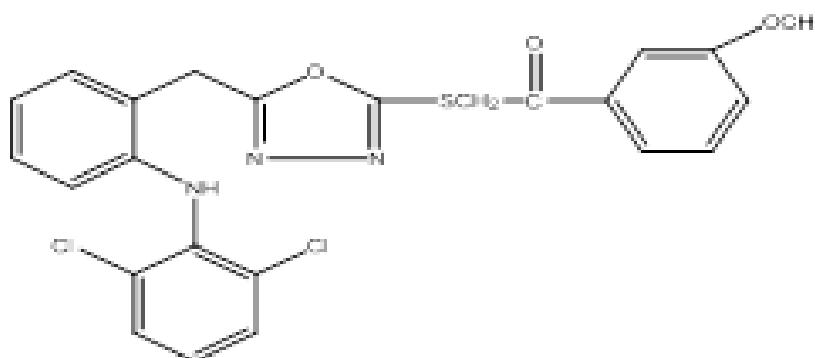
Non-steroidal anti-inflammatory drugs (NSAIDs) are the most preferred class of drugs in use for the treatment of various pathological conditions such as pain, fever, inflammatory diseases and rheumatoid arthritis.^[1] The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting the enzyme Cyclooxygenases (COXs) and thromboxane synthase with a varying degree of selectivity.^[2] It is well known that COX exists in two isoforms, COX-1 and COX-2, which are regulated differently. COX-1 provides cytoprotection in the gastrointestinal (GI) tract whereas inducible COX-2 mediates inflammation.^[3] COX-2 is an attractive target for medicinal chemists as it is expressed only in few normal tissues and is greatly upregulated in inflamed tissues as well as many premalignant and malignant tumors. Since, most of the NSAIDs in the market show greater selectivity for COX-1 than COX-2^[4] chronic use of NSAIDs, including Diclofenac may elicit appreciable gastro-intestinal (GI) irritation, bleeding and ulceration.^[5] The GI damage from NSAIDs is generally attributed to two factors, local irritation by the carboxylic acid moiety, common to most NSAIDs and (topical effect) decreased tissue prostaglandin production, which undermines the physiological role of cytoprotective prostaglandins in maintaining the GI health and homeostasis.^[6] 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, cardiac vascular diseases and Alzheimer's dementia. Therefore, the challenge still exists for the pharmaceutical industry to develop, effective anti-inflammatory agents with enhanced safety profile. It has been reported in literature that certain compounds bearing oxadiazole nucleus possess significant anti-inflammatory activity with reduced ulcerogenic effect.^[7-9]

Mahesh B Palker, Anuj Singhai *et al.*, reported synthesis, pharmacological screening and *in silico* studies of new class of diclofenac analogues as a promising anti-inflammatory agents.

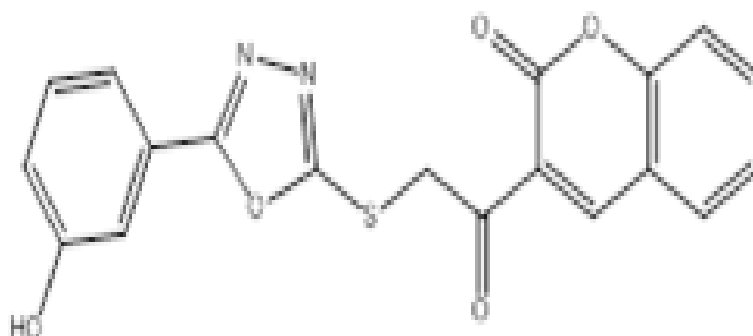
Among the series different compounds exhibited good anti inflammatory activity and less side effect as compared to diclofenac.^[10]



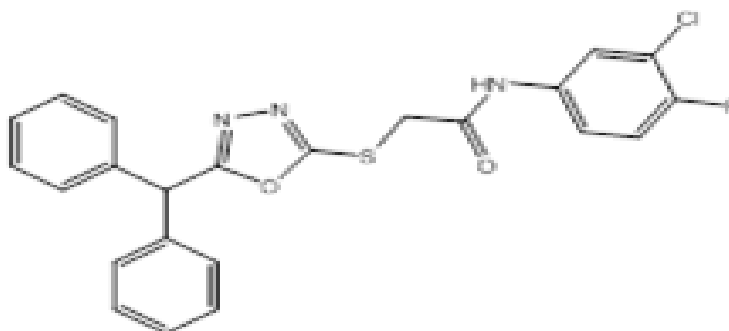
Bhandari SV *et al.*, synthesized novel 3-substituted phenacyl-1,3,4-oxadiazol-2-thiol and schiff bases of diclofenac as nonulcerogenic derivatives and evaluated them for anti-inflammatory, analgesic and ulcerogenic activity in the carrageenin induced rat paw edema model. Among the series different compounds exhibited very significant anti-inflammatory activity.^[11]



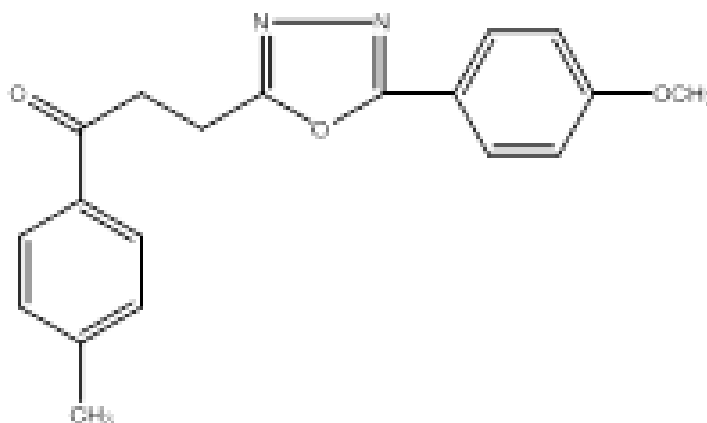
Ingale N *et al.*, reported synthesis and evaluation of anti-inflammatory and analgesic activity of 3-[(5substituted-1,3,4-oxadiazole-2yl-thio)acetyl]-2H-chromen-2-ones. Among the series some compounds was shown good anti inflammatory activity by carrageenan induced rat paw edema method.^[12]



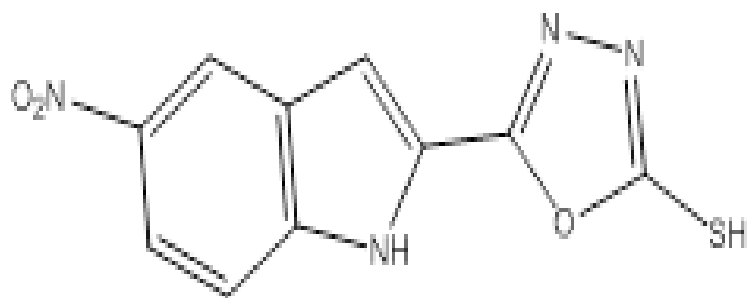
Mohammad A *et al.*, reported the synthesis of 1, 3, 4-oxadiazole derivatives of aryl acetic acid and screened for their anti inflammatory and analgesic activities. Among the series following compound exhibited good anti inflammatory activity in carrageenan induced rat paw edema method.^[13]



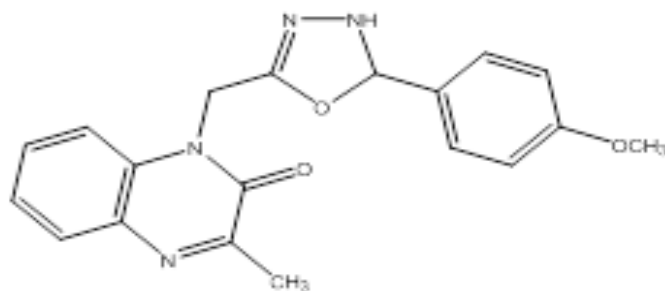
Akhter M *et al.*, reported the synthesis of 2,5-disubstituted-1,3,4 oxadiazoles from aroylpropionic acid and screened for their anti-inflammatory and analgesic activities. Among the series following compound exhibited good anti inflammatory activity in carrageenan induced rat paw edema method.^[14]



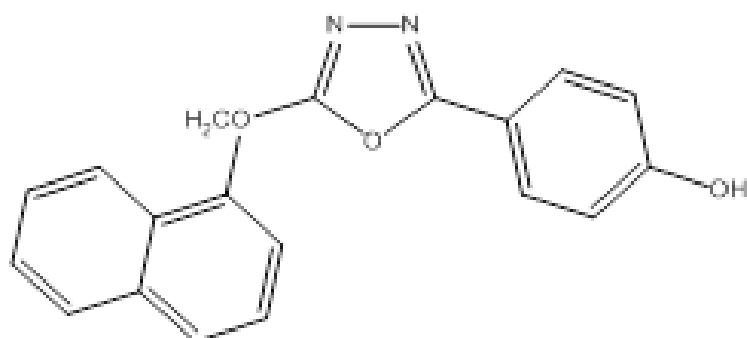
Narayana B *et al.*, reported synthesis of heterocycles derived from substituted indole-2-carbohydrazides and screened for their anti inflammatory activity. Among the series following compound exhibited good anti inflammatory activity in carrageenan induced rat paw edema method.^[15]



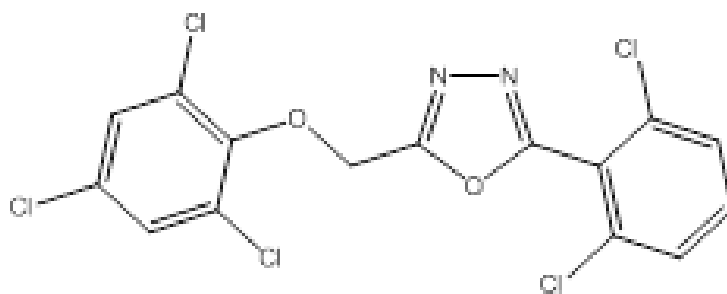
Wagle S *et al.*, reported synthesis of some new 2-(3-methyl-7-substituted-2-oxoquinoxaliny)-5-(aryl)-1,3,4-oxadiazole as potential non-steroidal anti-inflammatory and analgesic agent. Among the series following compound exhibited good anti inflammatory and analgesic activity in carrageenan induced rat paw edema method and hot plate method respectively.^[16]



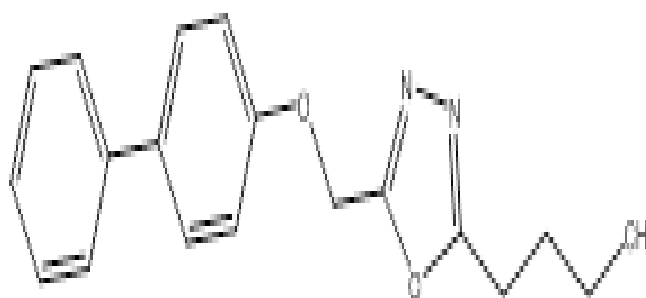
Rajak H *et al.*, reported synthesis of some novel oxadiazole and oxadiazoline analogues for their anti-inflammatory activity. Among the series following compound exhibited good anti inflammatory activity in carrageenan induced rat paw edema method.^[17]



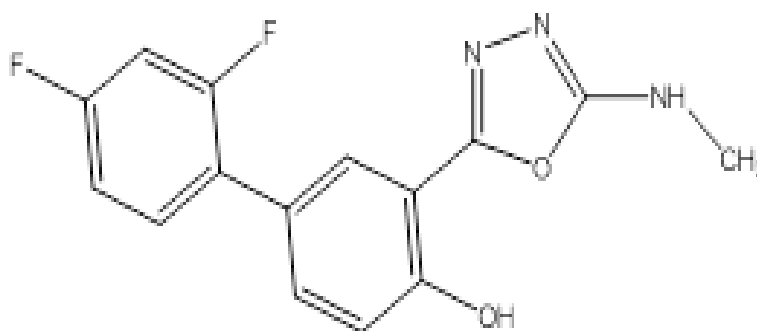
Mohd A *et al.*, reported synthesis of some 1,3,4-oxadiazole derivatives as potential anti-inflammatory agent. Among the series following compound exhibited good anti inflammatory activity in carrageenan induced rat paw edema method.^[18]



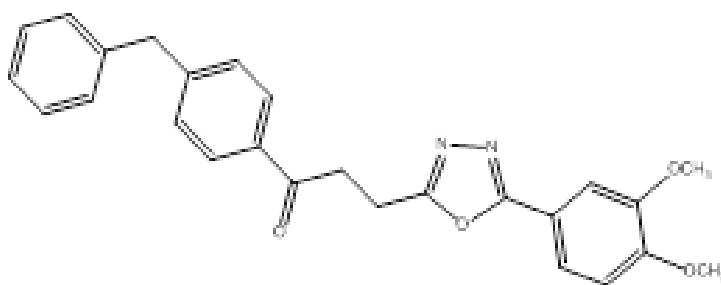
Kumar H *et al.*, reported synthesis of 1,3,4-oxadiazole derivatives and screened for their anti-inflammatory and analgesic activities. Among the series following compound exhibited good anti inflammatory activity in carrageenan induced rat paw edema method.^[19]



Kucukguzel SG *et al.*, reported synthesis of some novel heterocyclic compounds derived from diflunisal hydrazide as potential anti-infective and anti-inflammatory agents. Among the series following compound exhibited good anti inflammatory activity.^[20]

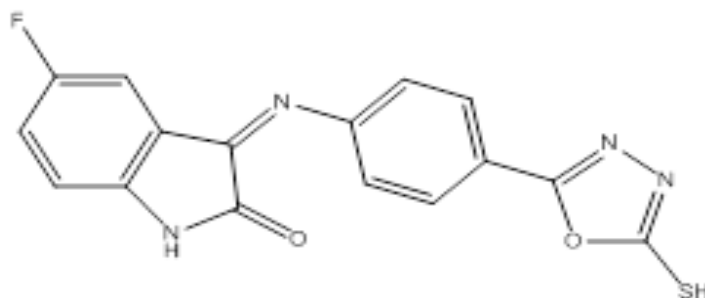


Husain A *et al.*, reported synthesis and biological evaluation of β - aroyl propionic acid based 1,3,4-oxadiazoles and tested for anti-inflammatory, analgesic, lipid peroxidation, ulcerogenic and antibacterial activity. The compound has shown very good anti-inflammatory activity.^[21]

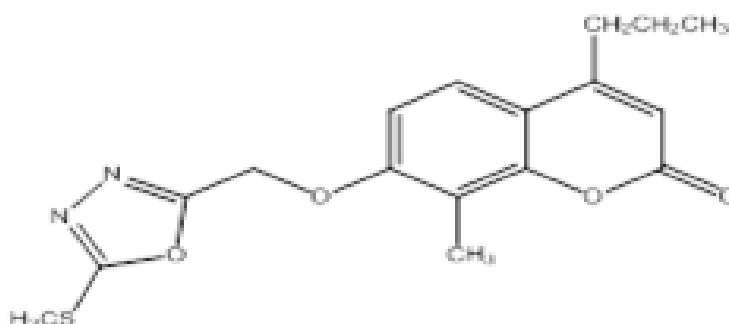


Anticancer activity

Gudipati R *et al.*, reported synthesis, characterization and anticancer activity of certain 3{4-(mercapto-1, 3, 4-oxadiazole-2-yl)phenylimino}indolin-2-one derivatives. The anticancer activity of all the synthesized compounds was evaluated against HeLa, IMR-32, MCF-7 cancer cell lines using MTT method. Among the series following compound showed good anticancer activity.^[22]

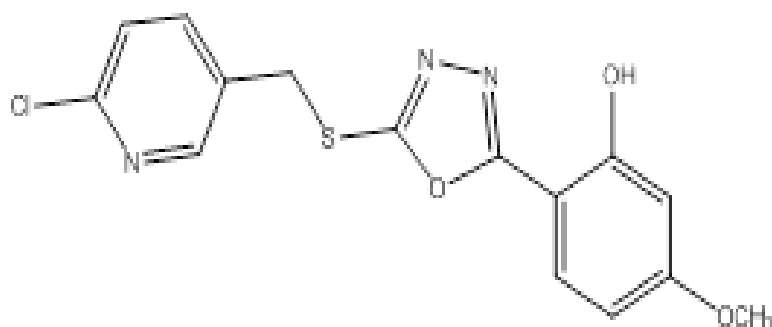


Magda MF *et al.*, reported synthesis and docking studies of novel benzopyran-2-ones as promising anticancer agents. Among the series following compound exhibited good anticancer activity.^[23]

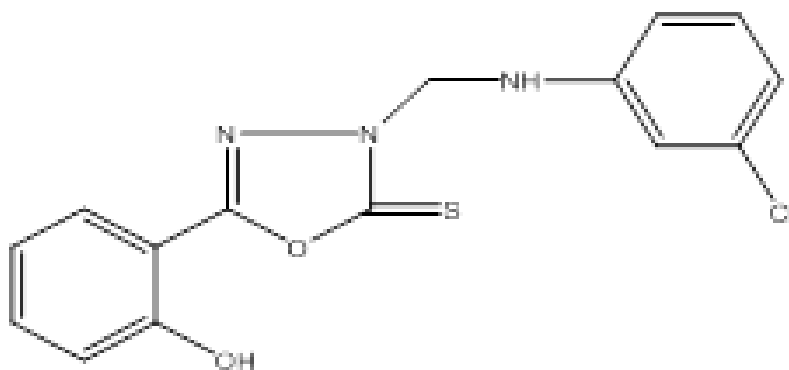


Zheng QZ *et al.*, reported synthesis, biological evaluation and molecular docking studies of 2-chloropyridine derivatives possessing 1,3,4-oxadiazole moiety as potential antitumor agents. All the synthesized derivatives were evaluated for their ability to antiproliferative activity

against gastric cell SGC-7901 and showed good antiproliferative activity. Among the series following compound showed good antiproliferative activity.^[24]



Aboraia AS *et al.*, reported novel 5-(2-hydroxyphenyl)-3-substituted-2, 3-dihydro-1,3,4-oxadiazole-2-thione derivatives as promising anticancer agents. Among the series following compound exhibited good anticancer activity.^[25]



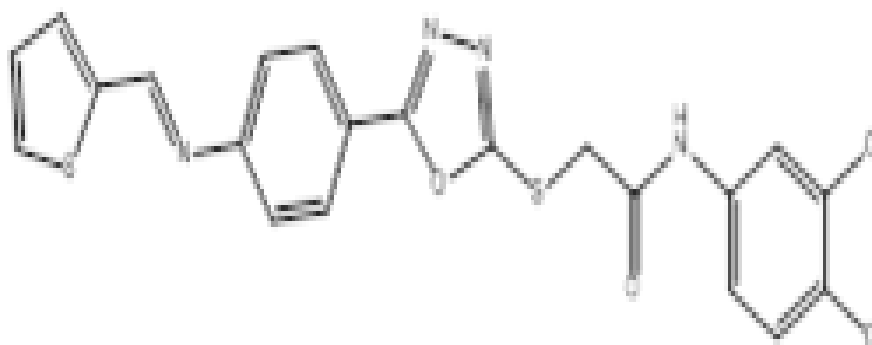
Antimicrobial activity

Infectious diseases are remaining a serious threat to public health, rapid resistance development by the microorganisms is recognized from the beginning. The resistance development among major pathogens makes antimicrobials more and more ineffective. The resistance is developed by bacteria due to bacterial enzymes, transfer of genetic material, acquired resistance and poor prescribing and utilization of antimicrobial in practice.^[26,27]

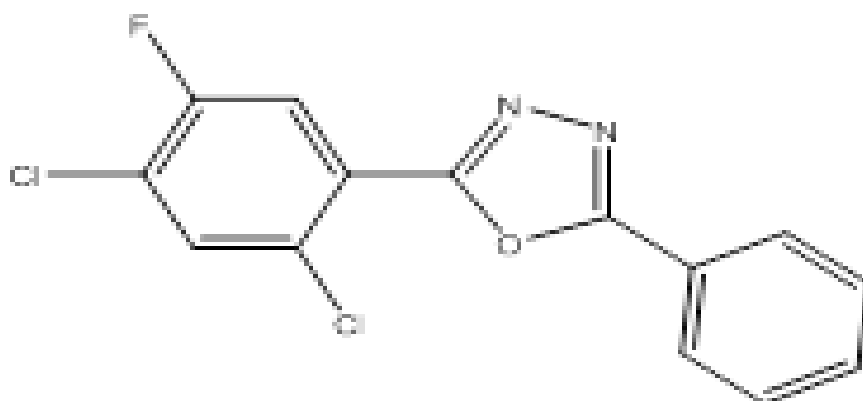
The incidence of multidrug-resistant pathogenic bacteria is increasing. One additional reason for developing new antibiotics is related to their own toxicity. As with other therapeutic agents, the use of antibiotics may also cause side effects in patients. These include mild reactions such as upset stomach, vomiting, and diarrhoea (cephalosporins, macrolides, penicillins and tetracyclines), rash, other mild and severe allergic reactions (cephalosporins and penicillins), sensitivity to sunlight (tetracyclines), nervousness, tremors and seizures

(quinolones). Some side effects are more severe and depending on the antibiotic, may disrupt the hearing function (aminoglycosides), kidneys (aminoglycosides and polypeptides) or liver (rifampin). To counteract the resistance produced by microbes there is a need to invent new drugs, which are more safe and effective.^[28-29] A large number of medicines which have been discovered belong to a major class of heterocycles containing nitrogen, oxygen and sulphur. Biological activities of these heterocycles has helped the medicinal chemist to plan, organize and implement newer approaches towards the discovery of new drugs.^[30-31]

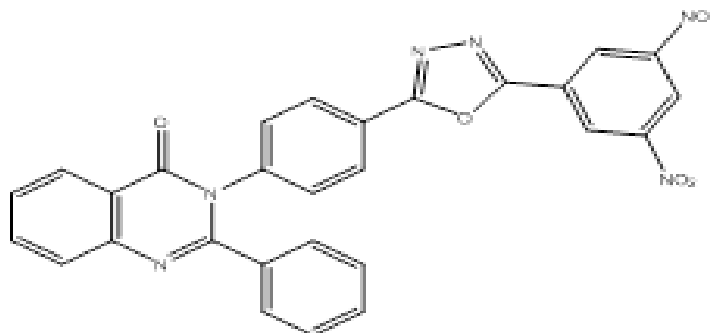
Desai NC *et al.* reported synthesis and antimicrobial screening of 1, 3, 4-oxadiazole and clubbed thiophene derivatives. All the synthesized compounds were evaluated for antibacterial and antifungal activities. Among the synthesized compounds, the following compound showed good antibacterial and antifungal activity.^[32]



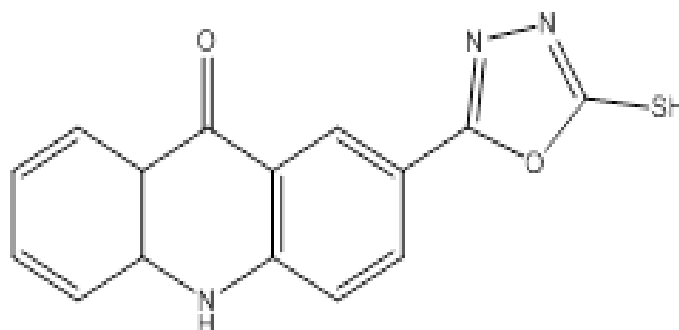
Jha KK *et al.*, reported synthesis and biological evaluation of 1,3,4-oxadiazoles. The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (MTCC 443), *Staphylococcus epidermidis* (ATCC12228) and *Staphylococcus aureus* (ATCC25923) bacterial strains by disc diffusion method. Among the synthesized compounds, the following compound showed good antibacterial activity.^[33]



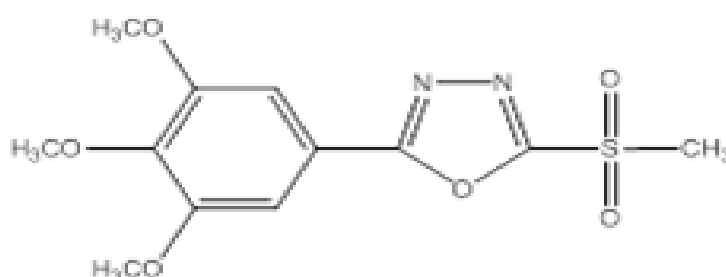
Sah P et al., reported synthesis and *in vitro* biological evaluation of some quinazolin substituted pyrazoles, pyrazolones and 1,3,4-oxadiazoles. The antibacterial activity of compounds was evaluated by disc diffusion method. Among the synthesized compounds, the following compound showed good antibacterial activity.^[34]



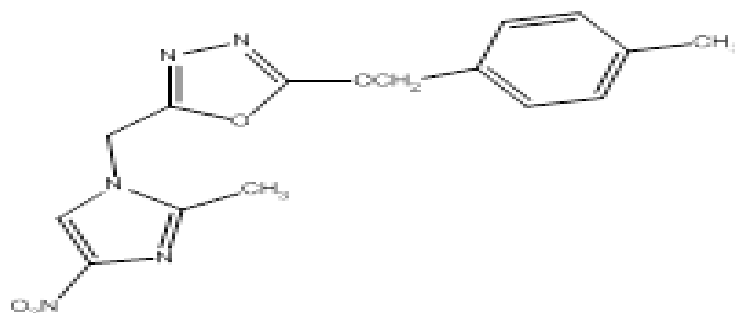
Salimon J et al., reported synthesis and pharmacological evaluation of 9(10H)-acridone bearing 1,3,4-oxadiazole derivatives as antimicrobial agent. All the newly synthesized compounds were evaluated for their *in vitro* antibacterial activity against *Staphylococcus aureus*, *Streptococcus viridans* and *Escherichia coli*. by disc diffusion method. Among the synthesized compounds, the following compound has shown good antibacterial activity.^[35]



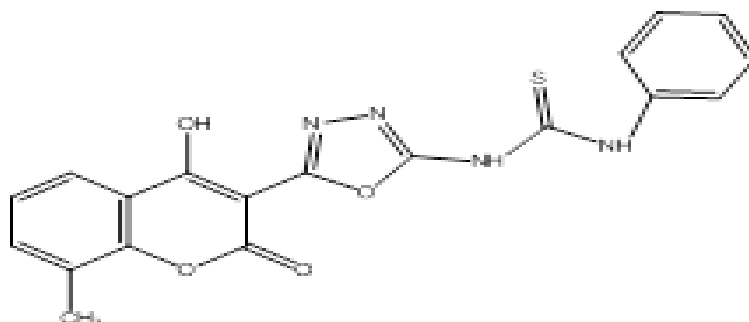
Cai-Jun Chen et al., reported synthesis and antifungal activity of 1,3,4-oxadiazole derivatives. All the newly synthesized compounds were evaluated for their *in vitro* antifungal activity. Among the series following compound exhibited good antifungal activity.^[36]



Frank PV *et al.*, reported solvent-free microwave-assisted synthesis of oxadiazole containing imidazole moiety. All the synthesized compounds were evaluated for antibacterial and antifungal activities. Among the synthesized compounds, the following compound showed good antibacterial and antifungal activity.^[37]

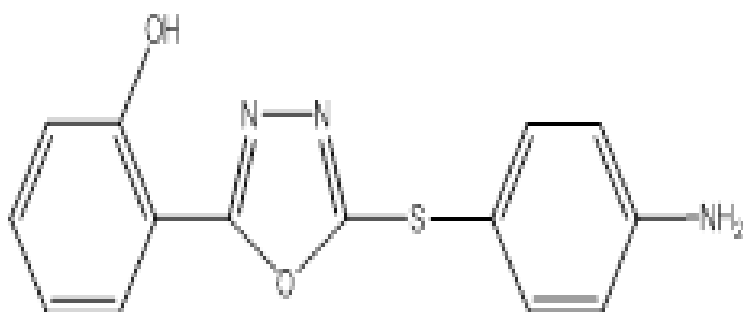


Mulwad VV *et al.*, reported synthesis and antibacterial activity of 2,5 disubstituted-1,3,4-oxadiazole derivatives. All the newly synthesized compounds were evaluated for their *in vitro* antibacterial activity. Among the synthesized compounds, the following compound showed good antibacterial and antifungal activity.^[38]

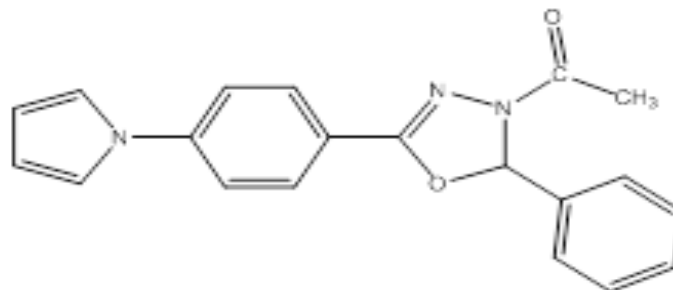


Antitubercular activity

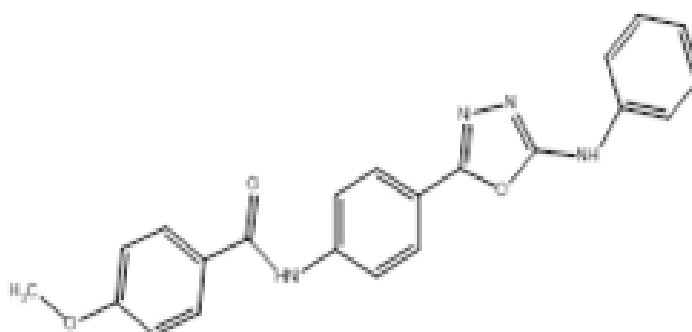
Pattan SR *et al.*, reported synthesis and evaluation of some novel substituted 1,3,4-oxadiazole and pyrazole derivatives for antitubercular activity. Among the series compound exhibited good antitubercular activity by middle brook 7H9 agar medium against H₃₇Rv strain.^[39]



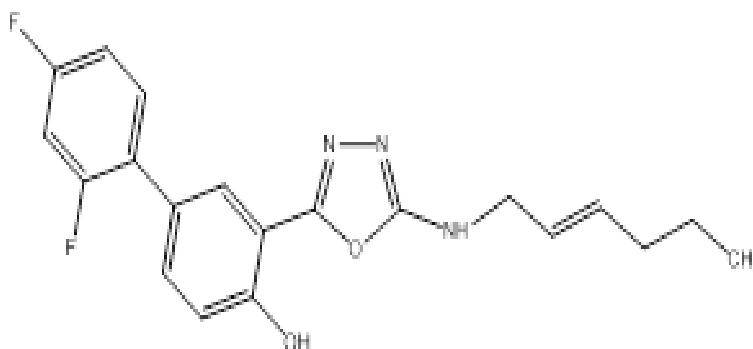
Joshi SD et al., reported synthesis of some new 1,3,4-oxadiazole derivatives and screened them for their antitubercular activity. Among the series following compound showed good antitubercular activity.^[40]



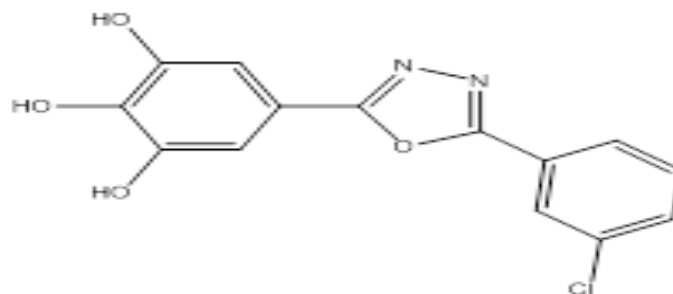
Kucukguzel SG et al., reported synthesis, characterization and biological activity of novel 4-thiazolidinones, 1,3,4-oxadiazoles and some related compounds. The synthesized compounds were screened for antitubercular activity. Among the series following compound showed good antitubercular activity.^[41]



Kucukguzel G et al., reported synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. These compounds screened for anti-TB activity against *Mycobacterium tuberculosis* H37Rv. The following compound showed good antitubercular activity.^[42]

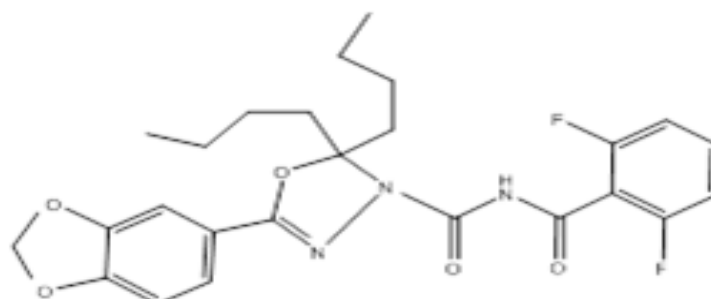


Arunkumar S *et al.*, reported synthesis characterization and biological evaluation of some novel 2,5 disubstituted-1,3,4-oxadiazole derivatives of gallic acid. All synthesized compounds were subjected to antimicrobial, anti-fungal and anti-tubercular activity. The antitubercular activity was observed at concentrations 100 μ g/ml on *Mycobacterium tuberculosis*. Among the synthesized compounds the following compound showed good antitubercular activity.^[43]

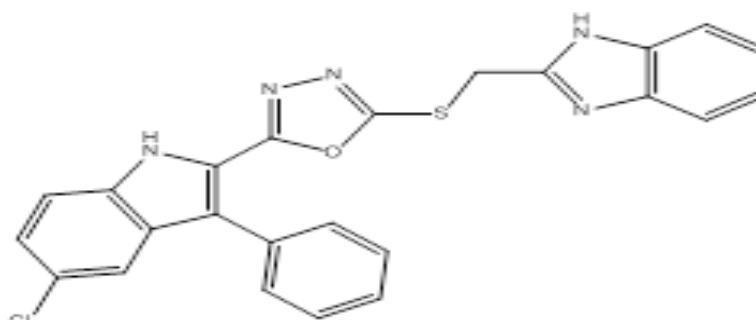


Miscellaneous activities

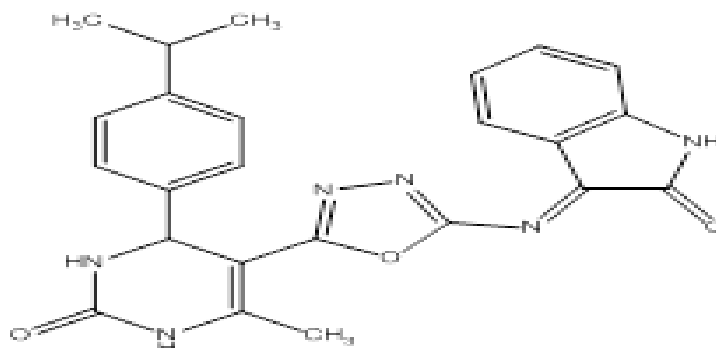
Shaoyong K *et al.*, reported synthesis of 1,3,4-oxadiazole derivative. The newly synthesized compounds were evaluated for their MAO inhibitory activity by kynuramine fluorimetric assay method. The following compound was most potent of the series.^[44]



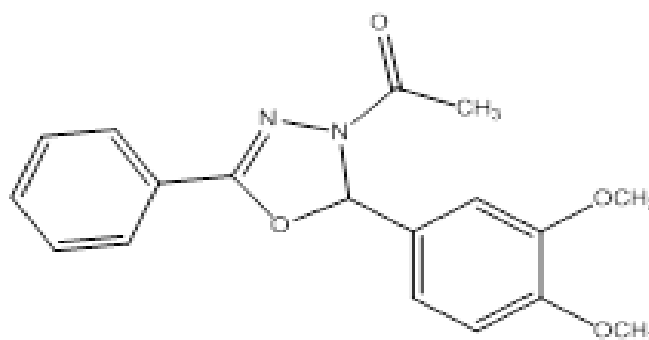
Manjunath SY *et al.*, reported synthesis and anthelmintic activity of triheterocycles: [5-(5''substituted-3''-phenylidol-2''-yl)-1,3,4-oxadiazol-2''-yl thiomethyl] benzimidazoles. Among the series following compound showed good anthelmintic activity.^[45]



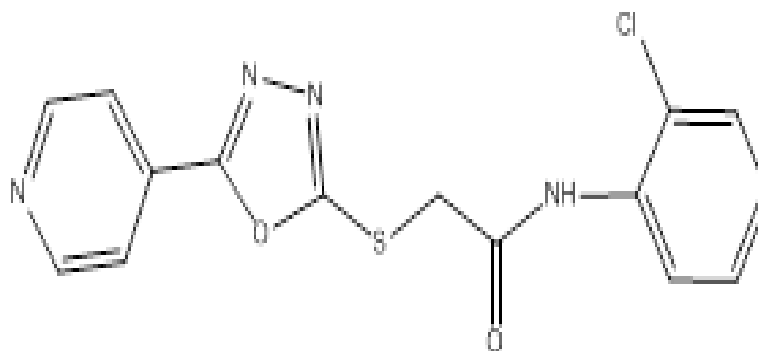
Georg S *et al.*, reported synthesis and biological evaluation of some 1,3,4-oxadiazole derivatives. Among the series following compound showed the good free radical scavenging activity.^[46]



Aanandhi MV *et al.*, reported synthesis and In-vitro antioxidant activity of substituted-1,3,4-oxadiazole derivatives. Among the synthesized compounds the following compound showed good antioxidant activity.^[47]



Rajasekaran S *et al.*, reported microwave assisted synthesis of some 5-pyridyl-2-[(N-substitutedphenyl) thioacetamido]-1,3,4-oxadiazoles as antibacterial and antioxidant agents. Among the synthesized compounds the following compound showed good antioxidant activity.^[48]



CONCLUSION

Above mentioned research work on 1,3,4-oxadiazole confirms the activities of oxadiazole as lead for development of new and more potent compounds possessing excellent biological activities. Oxadiazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and Biological conditions.

Acknowledgement

I express my humble thanks to all our friends for their guidance in searching various articles and journals for completing this review. I would like to express my sincere regards to my wife Palak, Son Harsh and entire family.

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