Review Paper:

Pharmacological significance of Oxadiazole scaffold

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Abstract

Heterocycles come under an important branch of organic chemistry that contains at least one atom other than carbon as a part of ring system. The most common hetero atoms that are widely used are nitrogen, oxygen and sulphur. In synthetic organic chemistry, synthesis of heterocyclic compound is of immense interest due to its therapeutic applications and their existence in several natural products like vitamins, hormones, antibiotics and alkaloids. The oxadiazole nucleus is one of the most significant and well known heterocyclic compounds due to its broad range of pharmacological and therapeutic activities like anti-depressant, anti-convulsant, anti-proliferate, anti-fungal, anti-inflammatory, anti-cancer, anti-HIV, insecticidal, anti-miotic, herbicidal, hypoglycemic and muscle relaxant etc.

The wide and potent activities of oxadiazole and their derivatives have established them as pharmacologically significant scaffolds. The basic heterocyclic rings present in the several medicinal agents are 1,2,3-oxadiazole, 1,2,4- oxadiazole, 1,2,5-oxadiazole and 1, 3, 4- oxadiazole. Research has focused on oxadiazole and their derivatives to prove the pharmacological importance of heterocyclic nucleus. The present review will summarize the pharmacological activities reported for oxadiazole derivatives.

Keywords: Five-membered heterocyclic compounds, 1,3,4-oxadiazole, antibacterial activity, anti-inflammatory activity, anti-fungal activity, anticonvulsant activity, antidepressant activity, anti-oxidant activity.

Introduction

Heterocyclic compounds comprising the five membered oxadiazole nucleus possess a diversity of useful therapeutic agents[29,48,53,55]. Oxadiazole is obtained from furan by replacing two methane (-CH=) groups by two pyridine type nitrogen atoms (- N=). Oxadiazoles are cyclic compounds containing one oxygen and two nitrogen atoms in a five-membered ring. Four isomers of oxadiazole nucleus are possible that differ in the 'position of nitrogen atoms' in the nucleus. These are 1,2,3-oxadiazole, 1,2,4- oxadiazole, 1,2,5- oxadiazole and 1, 3, 4- oxadiazole[14,46].

Oxadiazoles are significant aromatic heterocyclic compounds, hold desired electronic and charge-transport properties and we can easily introduce the various functional groups into the structurally rigid oxadiazole ring. These characteristics resulted in the extensive potential applications of oxadiazole based derivatives in the field of medicinal chemistry[25]. Among the isomers of oxadiazole, 1,3,4 oxadiazole is significant because of its notable biological activities and engaged a precise place in the field of medicinal chemistry due to its wide range of activities. Compounds enclosing 1,3,4-oxadiazole structure hold different pharmacological effects which include antibacterial, antifungal, anti-tubercular, anticonvulsant, anti-allergic, anti-inflammatory, cytotoxic and insecticidal activities[4,6,8].

Pharmacological activities

The oxadiazole scaffold is tremendously versatile and has been performed as a clinically potent drug emphasizing the significance of this nucleus. The recent studies have exposed that oxadiazole derivatives have a broad range of pharmacological activities which can be categorized into the following classes:

Anti-bacterial activity: The discovery of antibiotics like penicillin and tetracycline provides the noble way for better health for millions of people around the world. However, nowadays the effectiveness of antimicrobial drugs available in the market is somewhat in doubt in future because microorganisms especially bacteria are becoming resistant to more and more antimicrobial agents. It leads to the discovery of new antimicrobial agents. So today's need is to overcome the resistance to antimicrobials or to treat infections with alternative means. To fulfill this demand, various compounds were synthesized and screened for its antimicrobial activity[22].

In the recent years, much attention has been focused to synthesize heterocyclic compounds comprising of nitrogen atom due to biological and medicinal importance including ontological research. Nitrogen based heterocyclic compounds play an important part in the biochemical processes in living cells. The important aromatic heterocycles are DNA and RNA containing pyrimidine, thymine and purine bases in our body. Most of the enzymes have aromatic heterocycles as major constituents while coenzymes incorporate non-amino acids moieties, most of them are aromatic nitrogen heterocycles. Some important vitamins are constructed on aromatic heterocyclic scaffold[13].

Oxadiazole is an important heterocyclic ring present in variety of biologically active molecules inclusive of fungicidal, bactericidal, anticancer and antitubercular activities etc. Various oxadiazoles have been shown to be

active against a wide range of bacteria such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis* and fungi such as *Candida albicans*, *Candida krusei* and *Candida parapsilosis*. Oxadiazole drug was the first effective chemotherapeutic agent to be employed systematically for the prevention and cure of bacterial infection in the human being[19,26,41,43,45,56].

Aziz-ur-rehman et al[4] have reported the synthesis of 5-substituted-2-((6-chloro-3,4 methylenedioxyphenyl)methyl thio)-1,3,4-oxadiazole derivatives and evaluated their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus typhi* and *Bacillus subtillus*. Among the synthesized derivatives, all the molecules have exhibited adequate antibacterial activity activity against *E. coli*.

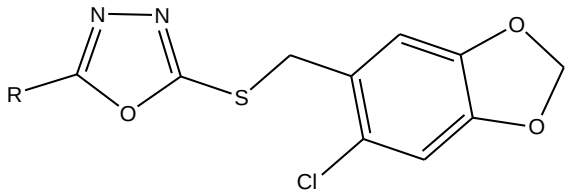


Fig. 1: 5-substituted-2-((6-chloro-3,4 methylenedioxyphenyl)methylthio)-1,3,4-oxadiazole derivatives

Salahuddin et al[49] have reported the synthesis of 1,3,4-oxadiazole bearing 1H-benzimidazole derivatives and evaluated their antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* by agar diffusion technique considering ofloxacin as the reference. From the results of *in vitro* antimicrobial activities, it was revealed that the compounds bearing deactivating group (electron withdrawinggroup like NO_2, Br and Cl) and weakly activating group i.e. CH_3 group were the extreme active against *E. coli* and *S. aureus*.

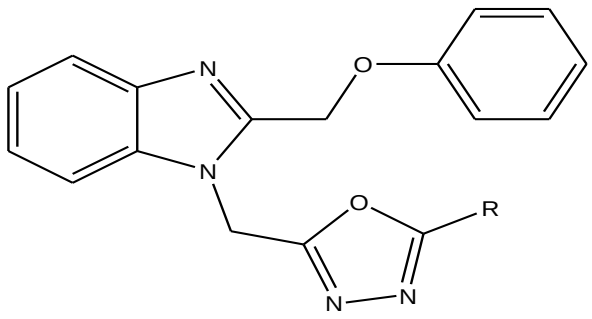


Fig. 2: 2-(phenoxymethyl)-1-[(5-substituted-1,3,4-oxadiazol-2-yl)methyl]-1H-benzimidazole

Aziz-ur-rehman et al[5] have reported the synthesis of N'-substituted-2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylthio) acetohydrazide derivatives and evaluated their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, *Pseudomonas aeruginosa* and *Salmonella typhi*.

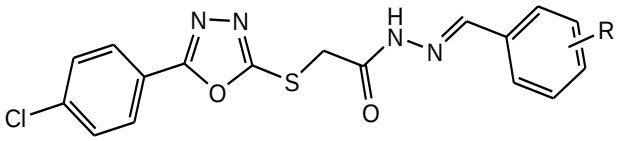


Fig. 3: N'-substituted-2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylthio)acetohydrazide derivatives

Jignesh et al[28] have reported the synthesis and *in vitro* antibacterial activity of new oxoethylthio-1,3,4-oxadiazole derivatives against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, *Salmonella paratyphi A*. Among the synthesized derivatives, it was revealed that some of the derivatives exhibited favourable anti-mycobacterial activity which can be further modeled to exhibit better potency than the standard drugs.

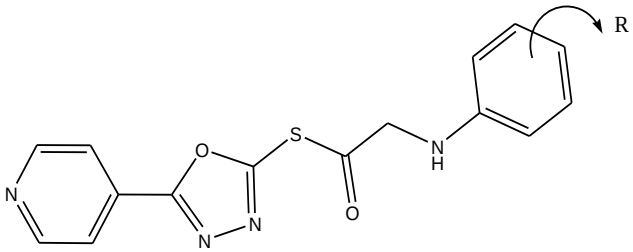


Fig. 4: 2(4-pyridyl)-5[(aryl/heteroarylamino)-1-oxoethyl]thio-1,3,4-oxadiazole

Rai et al[47] have reported the synthesis, characterization and antibacterial activity of 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1H-pyrazol-4-yl]-5-(substituted-phenyl)[1,3,4] oxadiazole against bacteria like *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumonia*. It was reported that dichloro analogs showed similar spectrum of activity than mono fluoro analogs. Unsubstituted analog showed moderate activity against *S.aureus*, *E. coli* and *K. pneumonia* when compared to all other analogs in the series.

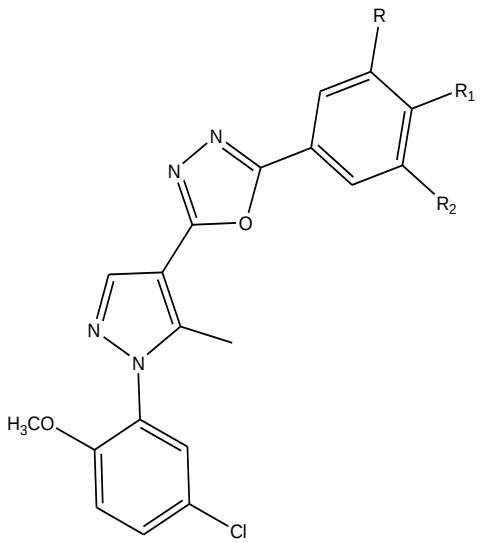


Fig. 5: 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1H-pyrazol-4-yl]-5-(substituted-phenyl)[1,3,4] oxadiazole

Manjunatha et al[40] reported the synthesis and biological evaluation of some 1,3,4- oxadiazole derivatives. They also evaluated antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. It was witnessed that the oxadiazole Mannich bases comprising 4-Cl, 3-Cl ,4-NO_2 and 4-F substituents in aryl piperazine moiety showed very good activity, while these groups were exchanged by 4-OMe and 2-OEt group; there was sharp decrease in the activity. It was reported that Mannich bases having 4-ethoxycarbonylpiperidin-1-ylmethyl,4-nitrophenylpiperazin -4-ylmethyl and 4-fluorophenylpiperazin-4-ylmethyl groups exhibited better activity (73.92%, 75.14% and 75.38%) than the standard drug.

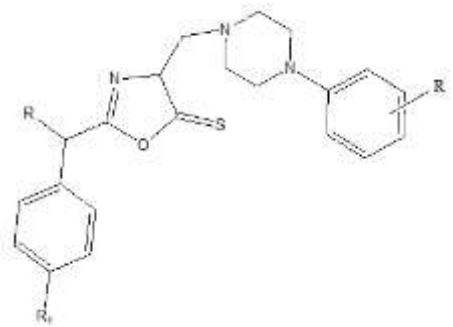


Fig. 6: 1,3,4-oxadiazole Mannich bases

Shridhar et al[52] synthesized a series of 2,5-disubstituted-1,3,4-oxadiazoles. The synthesized compounds were tested for their antimicrobial activity against few microorganisms like *E. coli*, *S. aureus* and *P. aeruginosa* considering commercial antibiotic streptomycin as a reference. It can be reported that the compounds having 2-chlorophenyl substituent on the 5th position of the oxadiazole ring may have a good antimicrobial profile of the compound.

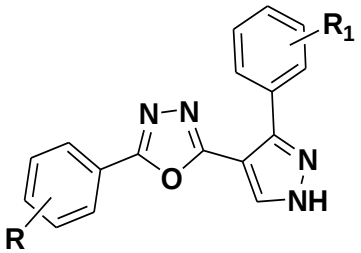


Fig. 7: 2,5-disubstituted-1,3,4-oxadiazoles

Desai et al[16] reported a series of 2-{5-[4-(1-aza-2-(2-thienyl) vinyl) phenyl] (1,3,4-oxadiazol-2-ylthio)}-N-aryl acetamides. The antibacterial activity of the newly synthesized compounds was screened against gram positive bacteria *Staphylococcus aureus* (MTCC 96), *Staphylococcus pyogenes* (MTCC 442) and gram negative bacteria *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688) considering ampicillin as the standard drug. It was reported that the synthesized oxadiazole derivative exhibit a wide range of antimicrobial activity.

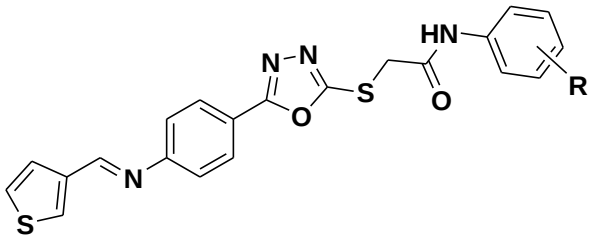


Fig. 8: 2-{5-[4-(1-aza-2-(2-thienyl) vinyl) phenyl] (1,3,4-oxadiazol-2-ylthio)}-N-aryl acetamides

Anti-Inflammatory activity: Inflammation is the local response of living mammalian tissue to injury due to any agent. It is a body defense reaction in order to eliminate or limit the spread of injurious agent. The drugs used as anti-inflammatory come under the class of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are the backbone for the management of pain which arises due to inflammatory diseases. These drugs suppress natural processes that are responsible for inflammation.[3] A number of non-selective non-steroidal anti-inflammatory drugs (NSNS-AIDs) such as indomethacin, ibuprofen, phenyl butazone, oxyphenyl butazone, diclofenac, fenoprofen, caprofen, benoxaprofen, sulindac and aspirin etc. are available in the market[2].

During past decades, compounds bearing heterocyclic nuclei have received much attention due to their chemotherapeutic value in the development of novel anti-inflammatory activities[39]. The oxadiazole chemistry has been developed extensively and is still developing. Presently there are a number of drugs used clinically which comprise oxadiazole moiety in association with various heterocyclic rings[12].

Bansal et al[7] have designed a series of 1,3,4-oxadiazole derivatives by oxidative cyclization of various pyrazolylaldehyde N-acylhydrazones with iodobenzenediacetate (IBD) in dichloromethane by stirring at room temperature for 20-25 min. The synthesized compounds were tested for anti-inflammatory activity considering celecoxib and diclofenac as the reference drugs. Among the compounds tested, some compounds showed promising degree of anti-inflammatory activity with ED50 in the range of 72.6e125.4 mg/kg. ED50s of the reference drugs celecoxib and diclofenac were found to be 81.7 and 110.4 mg/kg respectively[7].

Sahoo et al[10] designed various Schiff base of 1,3,4-oxadiazole analogues and performed anti-inflammatory activity by carrying an induced paw edema method in Wistar rats. It was reported that the compound with hydroxyl substituent at para position of nucleus exhibited maximum anti-inflammatory activity in comparison with F, Cl, Br, OCH_3, NO_2 group on the whole level. It was revealed that the anti-inflammatory activity of the synthesized compound depends on the position of the substituents on the phenyl ring. In case of bromo and chloro derivatives, the activity order is para> meta> ortho.

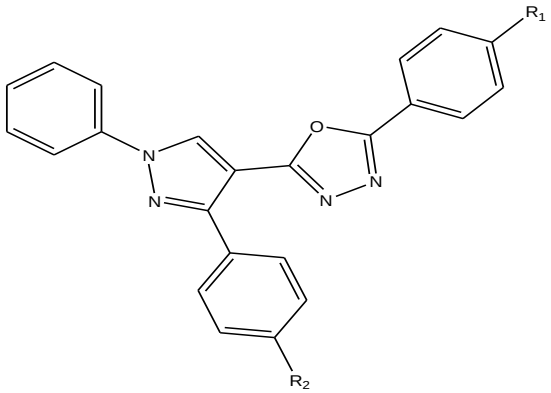


Fig. 9: 2-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazoles

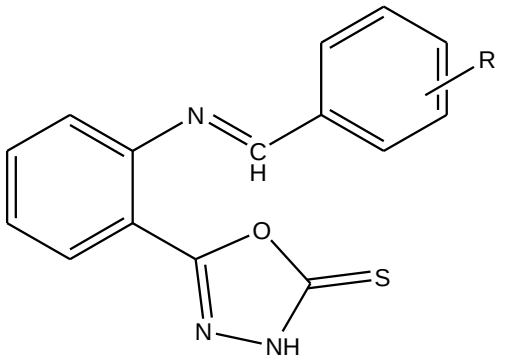


Fig. 10: Schiff base of 1,3,4-oxadiazole analogues

Abd-Ellah et al[1] have reported a novel group of oxadiazole derivatives and performed anti-inflammatory activity with indomethacin as a standard drug tested using an induced rat pawoedema method. Their results showed that the newly synthesized compounds have enhanced anti-inflammatory activities. Among the synthesized compounds, un-substituted phenyl ring exhibited the highest anti-inflammatory activity. Introduction of electron withdrawing group decreased the anti-inflammatory activity from 100% to 86% and the introduction of electron donating group also decreased the anti-inflammatory activity from 100% to 78%.

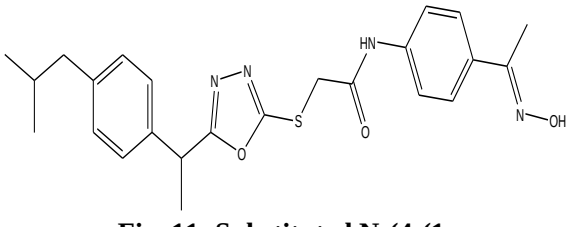


Fig. 11: Substituted N-(4-(1-(hydroxyimino)ethyl)phenyl)-2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio) acetamides

Mane et al[38] have synthesized benzofuran derivatives bearing oxadiazole. Considering diclofenac sodium as standard, all the newly synthesized compounds were screened for anti-inflammatory activity by induced rat paw edema method. Some of the compounds exhibited good anti-inflammatory activity. It was reported that the compounds bearing substituted aniline moiety gave better anti-inflammatory activity compared to unsubstituted aniline. Thus alteration of carboxylic acid functionality to oxadiazole in benzofuran analogs of anthranilic acid provides betteranti-inflammatory activity.

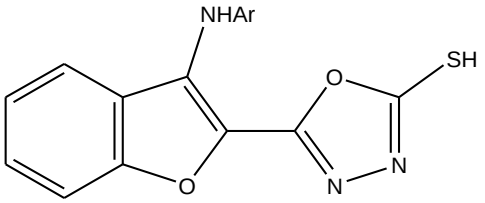


Fig. 12: 5-(3-Arylaminobenzofuran-2-yl)-1, 3, 4-oxadiazole-2-thiol

Iyer et al[27] reported a series of 1,3,4-oxadiazoles derived from benzoxazole. The results revealed that *in vivo* anti-inflammatory activity of synthesized oxadiazole derivatives induced paw edema method showing that the tested compounds showed substantial edema inhibition with a mean value ranging from 21.8 to 70.6% in comparison to 48.5% edema inhibition obtained for the reference drug indomethacin. Among all the tested compounds, oxadiazole ring bearing -C_5H_4N as a substituent exhibited a significant inhibition of edema with mean edema inhibition value of 70.6% underlining that this compound could be considered for further clinical studies to ascertain its potential hit as anti-inflammatory agents.

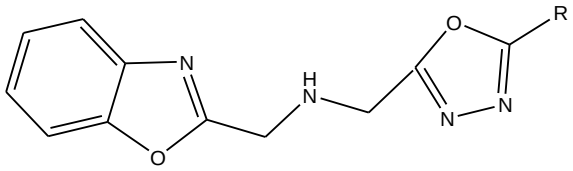


Fig. 13: (benzo[d]oxazol-2-yl)-N-[(5-subtituted-1,3,4-oxadiazol-2-yl)methyl]methanamine

Anti-fungal activity: Farshori et al[21] have reported a solvent-free synthesis of 2,5 disubstituted 1,3,4 oxadiazole from fatty acid hydrazides under solvent-free microwave irradiation. The anti-fungal activities of newly synthesized compounds were determined by disk diffusion method considering greseofulvin as standard drug. It was found to exhibit potent antifungal activities against *C. albicans*, *A. fumigatus* and *P. marneffei* fungal strains. Moderate activity against *T. mentagrophytes* fungal strains was obtained. It was identified that the nature of substituent has a strong influence on the extent of antibacterial and antifungal activities.

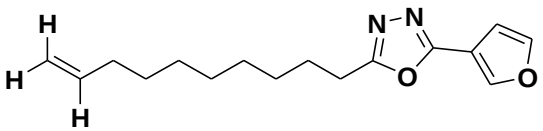


Fig. 14: 2,5-disubstituted-1,3,4-oxadiazoles

Khalilullah et al[33] reported the preparation of 1,3,4-oxadizole derivatives containing 1,4-benzodioxane ring

system from 2,3-dihydro-1,4-benzodioxane-2-carbohydrazide. The synthesized compounds were tested for antifungal activity against *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans* by two fold serial dilution technique. The newly synthesized compounds were found to exhibit better antibacterial and antifungal activities than reference drugs norfloxacin, chloramphenicol and fluconazole against tested strains. Among the synthesized compounds, more lipophilic group at the same position greatly enhanced the antifungal activities.

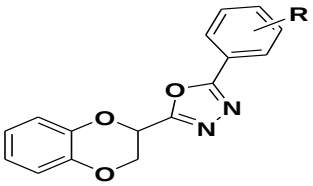


Fig. 15: 1,3,4-oxadizole derivatives containing 1,4-benzodioxane ring system

Desai et al[15] synthesized a series of 3-chloro-1-(aryl)-4-(2-(2-chloro-6-methylquinolin-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)-4-ethyl-azetidin-2-ones. The synthesized oxadiazole derivatives were screened for their antifungal against three different strains like *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatusand*. It was reported that the synthesized compounds possess excellent anti-fungal activity against *C.albicans* and few compounds possess good activity against *A. niger* and *A. clavatus*. The remaining compounds of the entire series possess moderate antifungal activity.

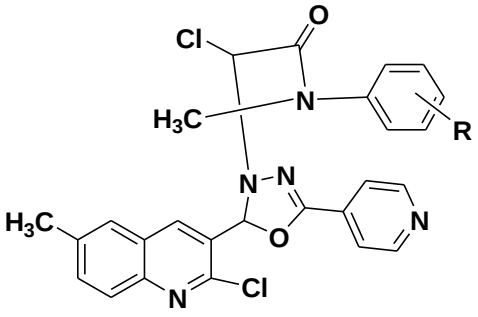


Fig. 16: 3-chloro-1-(aryl)-4-(2-(2-chloro-6-methylquinolin-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)-4-ethyl-azetidin-2-ones

Salimon et al[50] described the synthesis of 2-[5-thiol-1,3,4-oxadiazol-2-yl]-9(10H)-acridone derivatives and all the synthesized derivatives were examined for their antibacterial and antifungal activities by minimum inhibitory concentration (MIC). It was found that the synthesized oxadiazole compounds exhibit a considerable biological activity towards the tested microorganisms.

Structure–activity relationship studies proved the antimicrobial activity of the synthesized compounds based on the presence of the versatile pharmacophore which might increase the lipophilic character of the molecules which facilitates the crossing through the biological membrane of the microorganism and thereby inhibit the growth of microorganisms.

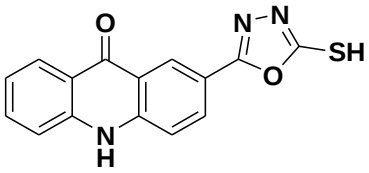


Fig. 17: 2-[5-thiol-1,3,4-oxadiazol-2-yl]-9(10H)-Acridone derivatives

Wani et al[58] synthesized a new series of 2-(4-ethyl-2-pyridyl)-1H-imidazole clubbed 1,3,4-oxadiazole derivatives. The antifungal activity of synthesized compounds against different strains of laboratory and clinically isolated Candida species depends on the presence and position of substituents on the phenyl ring of the 1,3,4-oxadiazole unit. Docking studies revealed that the active compounds closely fit into the active site of the target protein and may well explain their promising activities.

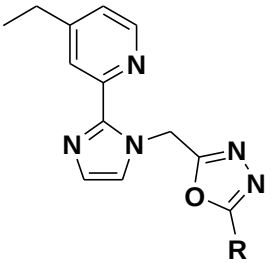


Fig. 18: 2-(4-ethyl-2-pyridyl)-1H-imidazole clubbed 1,3,4-oxadiazole derivatives

Anti-cancer activity: Gudipati et al[24] found a new series of 3-{4-(5-mercapto-1,3,4-oxadiazole-2-yl)phenylimino)-5 or 7-substituted indolin-2-one derivatives by treating 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol with different isatin derivatives. The anticancer activities of all the synthesized derivatives were examined against HeLa cancer cell lines with the help of MTT assay. They were active as growth inhibitors of the test HeLa, IMR-32 and MCF-7 cancer cell lines. It was proved that all the synthesized compounds were found to be the potential anticancer agent.

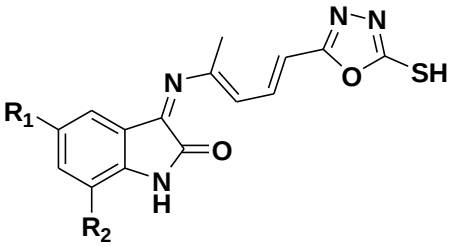


Fig. 19: 3-{4-(5-mercapto-1,3,4-oxadiazole-2-yl) phenylimino)-5 or 7-substituted indolin-2-one

Du et al[20] have synthesized novel 1,3,4-oxadiazole thioether derivatives based on 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole(metronidazole) scaffold and the cytotoxic activities of all the compounds were assessed against three

cancer cell lines. The SAR of the synthesized compounds against human TS indicated that the sort and position of the substituent on the phenyl ring or heterocycle play a vital role. Molecular docking and 3D-QSAR studies supported that 1,3,4-oxadiazole can be selected as dual antitumor/antibacterial agents.

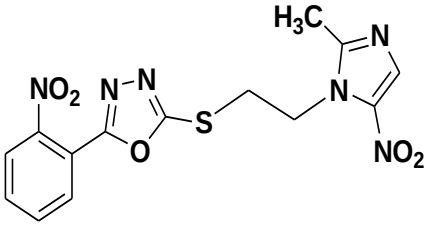


Fig. 20: 2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethylthio)-5-(2-nitrophenyl)-1,3,4-oxadiazole

Zhang et al[60] stated a series of 1,3,4-oxadiazole derivatives bearing benzotriazole moiety and examined for their anticancer activity. The bioactivity assay results showed that the synthesized compounds exhibited the enhanced inhibitory activity for FAK and good potent activity against human breast cancer cell MCF-7. Molecular docking of the most powerful inhibitor into binding site of FAK was done and the results confirmed that the compounds could bind well with the FAK active site. The results offered theoretical basis for advanced structural optimization of 1,3,4-oxadiazole derivatives as FAK inhibitors and showed that the compound was a feasible anticancer agent.

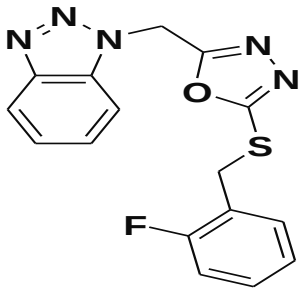


Fig. 21: 1-((5-(2-fluorobenzylthio)-1,3,4-oxadiazol-2-yl) methyl)-1H-benzo[d][1,2,3]triazole

Sambhaji et al[51] used novel multistep synthetic route to design 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-oxadiazole derivatives by using thionicotinamide. All the synthesized derivatives were screened for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Ra (MTB) and *Mycobacterium bovis* BCG. The synthesized compounds have shown low cytotoxicity (CC50: >100 lg/mL) towards four human cancer cell lines.

Molecular docking studies have also been done against mycobacterial enoyl reductase (InhA) enzyme to gain an insight into the binding modes of these molecules and were found to have good binding affinity. It was reported that the 1,3,4-oxadiazoles containing pyridyl and thiazolyl scaffolds offer an attractive lead series for the discovery of novel antitubercular agents.

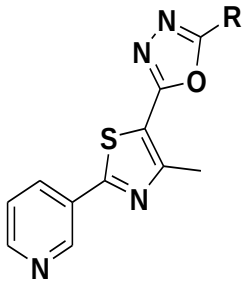


Fig. 22: 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-oxadiazole derivatives

Upare et al[3] reported the synthesis of cinnamic acid derivatives through bioisosteric replacement of terminal carboxylic acid with "oxadiazole". In this study, they approached to synthesize series of cinnamic acid derivatives (styryl oxadiazoles) in good yield by reacting the substituted cinnamic acids with amidoximes. The *in vitro* anti-tubercular activity of synthesized compounds was examined against *Mycobacterium tuberculosis* (Mtb) H37Ra strain. The SAR study has recognized several compounds with mixed anti-tubercular profiles.

Some of the compounds exhibited favourable anti-TB activity against MtbH37Ra. They observed that for anti-tubercular activity of synthesized compounds, electron withdrawing and halogen substituents and increasing chain length i.e. 3rd position of 1,2,4-oxadiazole is most favoured whereas electron donating and bulky substituents are least favoured at the phenyl ring of cinnamic acid.

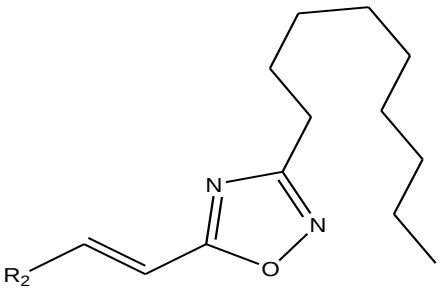


Fig. 23: N'-substituted 3-nonyl-5-((E)-prop-1-enyl)-1,2,4-oxadiazole

Gokhale et al[23] designed molecular hybrids of indole-3-carbinol and 1,3,4-oxadiazole-2-thiols and all the title compounds were screened *in vitro* to prove their antiproliferative and antimicrobial activity. Among the synthesized compounds, three compounds exhibited good anti-proliferative activity with more than 70 % cell growth inhibition against three cancer cell lines, HepG2 (human liver hepatocellular carcinoma), HeLa (humancervix carcinoma) and MCF-7 (human breast carcinoma). Compound with a methoxy group on the benzyl ring showed good inhibition activity.

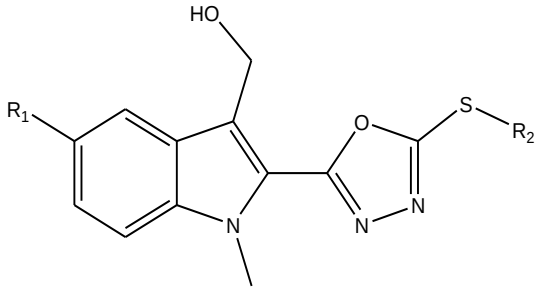


Fig. 24: Disubstituted (1,5-dimethyl-2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-1H-indol-3-yl)methanol

Anticonvulsant and Antidepressant activity: Globally, more than 50 million people were affected by epilepsy which is a chronic non-communicable brain disorder. After cerebrovascular diseases and dementia, epilepsy is one of the most common neurological conditions faced by human beings[35]. Although there is availability of a plethora of antiepileptic drugs (AEDs), their adverse effects resulted in the treatment failure of about 25% of patients[17]. In recent years, it was reported that various 1,3,4 oxadiazole derivatives proved to have potential anticonvulsant [59] and antidepressant activities[30].

Singh et al[9] synthesized a series of based hybrids with significant (60–78%) yields. Considering tiagabine as standard drug, anti-convulsant activity of the synthesized compound was examined using subcutaneous pentylenetetrazol (scPTZ) in mice and MES induced seizure. Among the synthesized compounds, few compounds displayed significant activity against pentylene tetrazole (scPTZ) induced seizures. The derivatives also exhibited noticeable anti-depressant activity, devoid of serotonergic augmentation as assessed using the despair swim test, 5-hydroxytryptophan (5-HTP)-induced head twitch test and learned helplessness test. Among the synthesized nipecotic acid 1,3,4 oxadiazole, compounds bearing electron withdrawing substituent were found to be more potent than the electron releasing group.

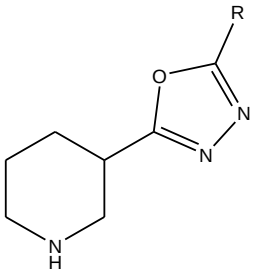


Fig. 25: Nipecotic acid 1,3,4 oxadiazole derivatives

Singh et al[54] designed a series of novel nipecotic acid 1,3,4-oxadiazole hybrids with the intent to increase the lipophilicity of nipecotic acid and its penetration through the blood—brain barrier (BBB). The anticonvulsant activity of the synthesized compounds was examined by using the subcutaneous pentylene tetrazol (scPTZ) test in mice. Some of the compounds exhibited significant protection against scPTZ-induced seizures. The synthesized derivatives also showed good antidepressant activity devoid of serotonergic augmentation as assessed using the despair swim test, 5-hydroxytryptophan (5-HTP)- induced head twitch test and learned helplessness test.

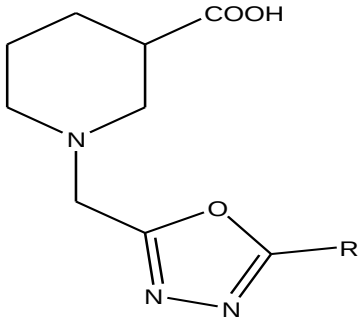


Fig. 26: N'-substituted-1-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)piperidine-3-carboxylic acid

Kashaw et al[31] designed novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones and screened for anticonvulsant, neurotoxicity, sedative-hypnotic and phenobarbitone-induced hypnosis potentiation test**.** The synthesized compound bearing $-CH_3$ and -Cl group exhibited anticonvulsant activity at various doses in one or more test models. The central nervous system (CNS)-depressant activity of the synthesized compound was tested with the help of the forced swim method. It was resolved that the synthesized compounds exhibited better sedative-hypnotic and CNS-depressant activities.

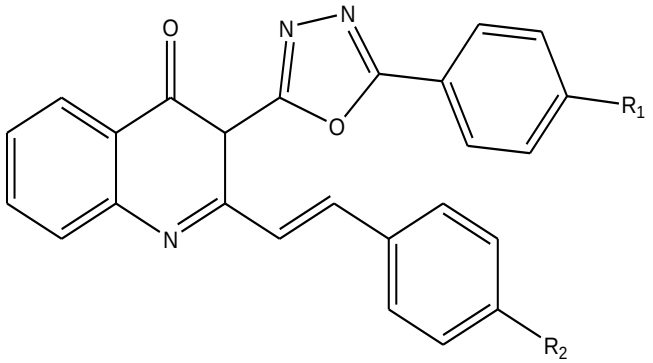


Fig. 27: 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones

Kumudha et al[36] designed a series of new 1,3,4-oxadiazoles and 1,2,4-triazoles from substituted benzohydrazides. The synthesized compounds were screened for anticonvulsant, CNS depressant activity and neurotoxicity. The anticonvulsant activity of the synthesized compound was carried out by both maximal electrical shock method and PTZ animal model using pentylenetetrazole (PTZ) as convulsant. All the tested compounds exhibited moderate to good anticonvulsant in both MESand PTZ tests and very less CNS Depressant activity.

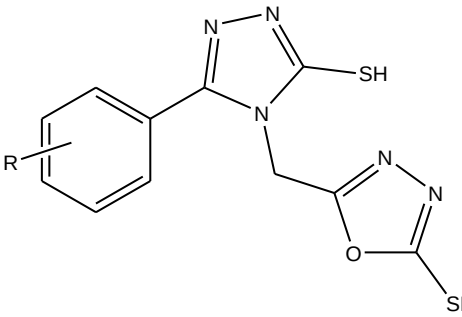


Fig. 28: 4-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-5-phenyl-4H-1,2,4-triazole-3-thiol

Anti-oxidant activity: The biological macromolecules were damaged by the free radicals like superoxide, singlet oxygen, hydroxyl radical produced from the reactive oxygen species (ROS) under oxidative stress and donate the pathogenesis which cause several health problems including cancer, inflammation, atherosclerosis, cardiovascular and neurodegenerative diseases. This can be overcome by utilizing the antioxidants which avert the oxidation of biological substrates, reducing oxidative stress, DNA mutations and malignant alterations. In recent findings, substituted 1,3,4-oxadiazole derivatives have been described to display a wide-ranging spectrum of biological activity[44].

Kotaiah et al[34] conveyed the synthesis of new series of N-substituted phenyl-5-methyl-6-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl) thieno [2,3-d]pyrimidin-4-amine derivatives. By using DPPH, hydrogen peroxide and nitric oxide radical scavenging assays, all the synthesized derivatives were examined for their *in vitro* antioxidant activity. The title compounds bearing electron donating group on both sides of the thienopyrimidine ring improve the anti-oxidant activity and electron withdrawing groups like nitro group decrease the activity.

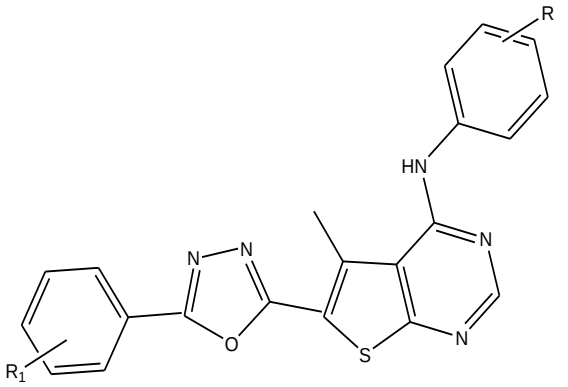


Fig. 29: N-substituted phenyl-5-methyl-6-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)thieno[2,3-d]pyrimidin-4-amine derivatives

Kashid et al[32] designed a series of novel 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives by reacting hydrazide molecule with substituted acids in the presence of $POCl_3$ as an efficient reagent via cyclisation. The title compound exhibited good to moderate antioxidant activity as compared to the standard drug ascorbic acid (IC_{50} = 44.18 µM/mL). The presence of 4-chloro benzene at 5 position of oxadiazole showed better activity as compared to 2- chloro and 3-chloro substituent and also hybrid molecules are powerful as compared to others for DPPH radical scavenging activity [32].

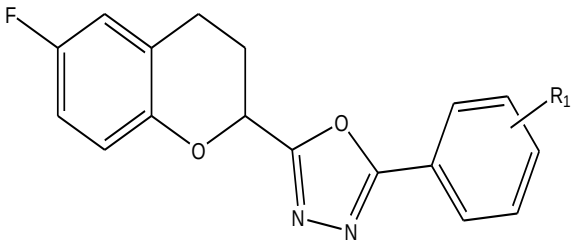


Fig. 30: N'-substituted 2-(6-fluoro-3,4-dihydro-2H-chromen-2-yl)-5-phenyl-1,3,4-oxadiazole

Lakshmi Ranganatha et al[37] utilized multi step reaction to synthesize 2,5disubstituted 1,3,4 oxadiazole analogues containing N-methyl indole and benzophenone moiety. All the synthesized compounds were screened for antioxidant activity via different *in vitro* models such as DPPH, nitric oxide and hydrogen peroxide methods. It was concluded that few of the synthesized compounds are potent in their antioxidant properties. Particularly, the compound bearing one additional oxadiazole ring in between benzophenone and N-methyl indole to be the significant one for revealing antioxidant activity near the standard drug compared to the standard drug ascorbic acid in all the above three methods.

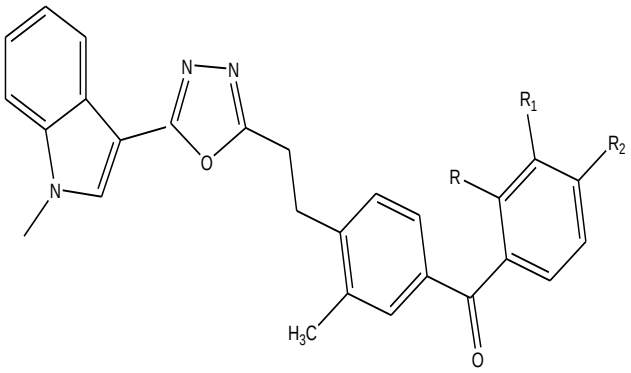


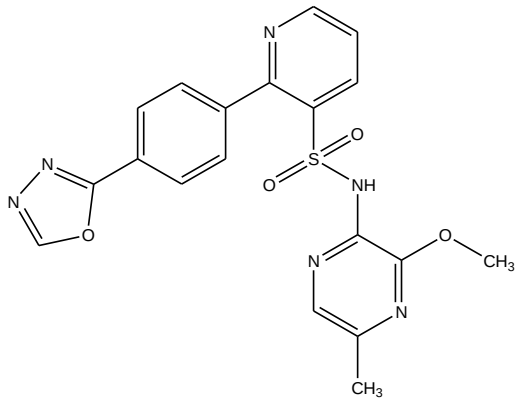
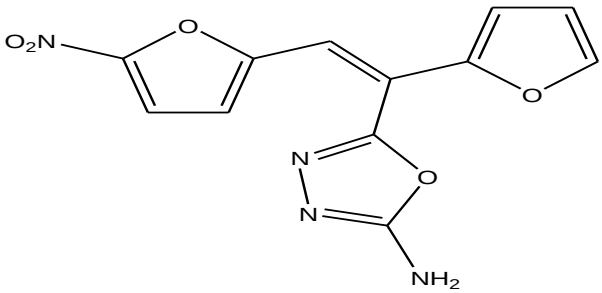
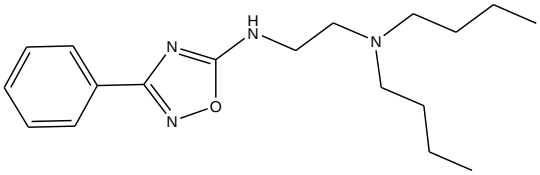
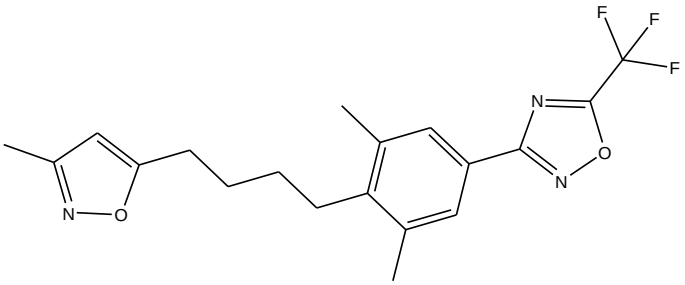
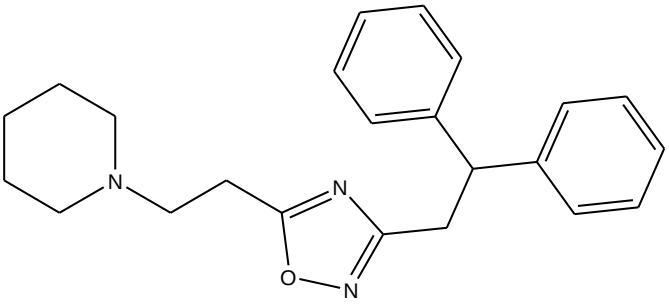
Fig. 31: 2,5disubstituted 1,3,4oxadiazole analogues containing N-methyl indole and benzophenone moiety

Conclusion

The power of the oxadiazole nucleus is manifested from the clinically used drugs. Despite the oxadiazole moiety is important medical agent, there will be future scope in this auspicious moiety as a number of different molecular targets are existing for various 1,2,3-oxadiazole, 1,2,4-oxadiazole,1,2,5- oxadiazole and 1, 3, 4- oxadiazole derivatives.

The facts reported in this manuscript will be beneficial for the futhur study of this scaffold in order to estimate their enhanced biological potential in a better way and for growing further pharmacologically potent medicinal agents for curing various diseases.

Table 1
Some successful oxadiazole based drugs available in clinical therapy[11,18,57,58,60]

Drug	IUPAC name	Structure	Application
Zibotentan	N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide		anti-cancer drug
Furamizole	2-Amino-5-(2-(5-nitro-2-furyl)-1-(2-furyl)-vinyl)-1,3,4-oxadiazole		Anti-microbial agent
Butalamine	N,N-Dibutyl-N'-(3-phenyl-1,2,4-oxadiazol-5-yl)ethane-1,2-diamine		Vasodilator
Pleconaril	3-{3,5-dimethyl-4-[3-(3-methylisoxazol-5-yl)propoxy] phenyl}-5-(trifluoromethyl)-1,2,4-oxadiazole		Antiviral drug
Prenoxdiazine	1-[2-[3-(2,2-diphenylethyl)-1,2,4-oxadiazol-5-yl]ethyl]piperidine		Cough suppresent

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