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Review Article

ANTIMICROBIAL ACTIVITY OF 1, 3, 4-OXADIAZOLES: A REVIEW

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This review provides readers with an overview of their broad spectrum of pharmacological activities for 1, 3, 4-oxadiazole derivatives, and as reported over the past years. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists. This Review has basic information about 1, 3, 4-oxadiazole and its antimicrobial activity work for further development in this field.

Keywords: 1, 3, 4-oxadiazole, Antimicrobial activity, Review

INTRODUCTION

Oxadiazole is a heterocyclic aromatic compound of molecular formula $C_2H_2N_2O$. It is a five membered ring consisting of 2 nitrogen atoms, 2 carbon atoms, 1 oxygen atom and 2 double bonds which shows antimicrobial, anticancer, anti-inflammatory and antioxidant activities etc. . This review article has summarized vital information on antimicrobial activity of 1, 3, 4-oxadiazole heterocyclic nucleus to provide effective antimicrobial drugs by solving the problem of microbial resistance towards currently used antibiotics. 1, 3, 4-Oxadiazole is a well known heterocyclic nucleus because of its broad spectrum of pharmacological activities especially potent antimicrobial activities. There are 4 isomers of oxadiazole as shown in the Figures below.


1,2,3 oxadiazole


1,2,4 oxadiazole


1,2,5 oxadiazole


1,3,4 oxadiazole

Oxadiazole shows inductive effect because of the presence of heteroatom in the ring and thus it is considered to be a weak base. It consists of 2 pyridine like nitrogen, due to which it exhibits conjugate diene type character. Electrophillic substitution at carbon is very difficult in this case due to less electron density which is mainly due to the presence of pyridine like nitrogen in the ring that shows electron withdrawal effect.

Due to the presence of two pyridine type nitrogen, the aromaticity will be removed. Many studies on comparison between 1, 2, 4- and 1, 3, 4-oxadiazole pairs shows that, in all cases,1, 3, 4-oxadiazole isomer shows lower magnitude lipophilicity as compared to its isomeric partner.

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Other differences involve metabolic stability, hERG inhibition, and aqueous solubility. All these studies favoured the 1, 3, 4-oxadiazole isomers. The difference in profile between the 1, 2, 4 and 1, 3, 4 regioisomers can be rationalized by their intrinsically different charge distributions. The 1, 3, 4-oxadiazole undergoes number of reactions including electrophillic substitution, nucleophilic substitution, thermal and photochemical.

2, 5-disubstituted-1,3,4-oxadiazole drivatives are colorless substances. Replacement of an alkyl residue by an aryl radical considerably raises the melting and boiling points. Usually the asymmetrical 1,3,4-oxadiazole derivatives melt and boil at lower temperature than the symmetrical compounds.

The solubility of oxadiazoles in water varies with the substituents present: 2, 5-dimethyl-1, 3, 4- oxadiazole is miscible with water in all proportions whereas the solubility of 2, 5-diphenyl-1, 3, 4-oxadiazole in water is less.

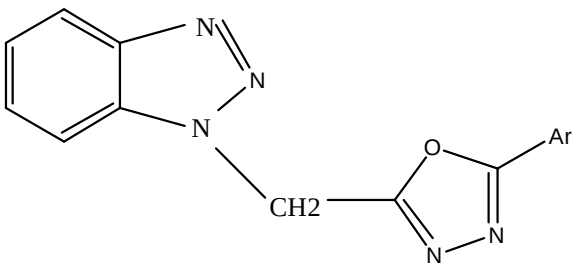
Electrophilic introduction of functional groups (for example nitro or sulphuric acid groups) into the nucleus is unusual. Electrophilic substitution occurs in aryl substituent. Halogenations is also difficult, but 2, 5-diaryl-1, 3, 4-oxadiazoles, afford complexes with halogens. A range of acylation and alkylation reactions of hydroxyl, thio and amino-1, 3, 4-oxadiazoles occur at the ring nitrogen .

Nucleophilic substitution reactions are uncommon. Many of nucleophilic reagents cause ring cleavage, depending upon the electron density at C-2 and C-5. Generally aryl substituted 1, 3, 4- oxadiazoles are less sensitive to acid than the alkyl substituted derivatives.

An antimicrobial is an agent that kills microorganisms or inhibits their growth. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria and antifungal are used against fungi. They can also be classified according to their function. Agents that kill microbes are called microbicidal, while those that merely inhibit their growth are called biostatic. The use of antimicrobial medicines to treat infection is known as antimicrobial chemotherapy, while the use of antimicrobial medicines to prevent infection is known as antimicrobial prophylaxis.

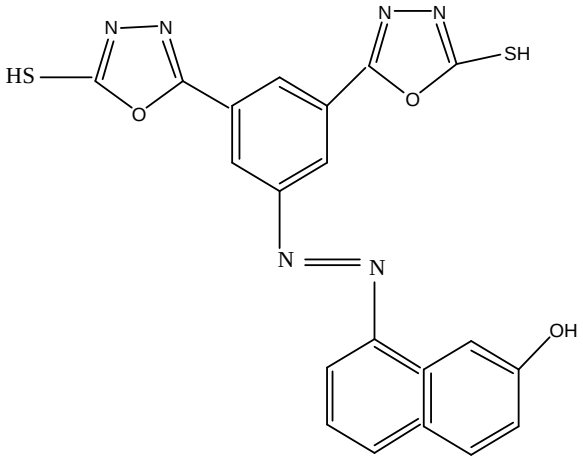
The most recent literature survey on antimicrobial potential of novel 1,3,4 -oxadiazole derivatives has been presented in this section as given below:

Arvind K. Singh *et al.* Synthesis of (ethyl 2-(1H Benzo [d] [1, 2, 3] triazole –1 – yl] acetate) and (2H – benzo [d] [1, 2, 3] triazole – 1 – yl ace to hydrazine) along with their derivatives has been done. The Antimicrobial activity of the synthesized compounds was evaluated, on Streptococcus *aurous* and Esteria *coli.* The present investigation deals with the synthesized compounds possessing good antimicrobial activity.

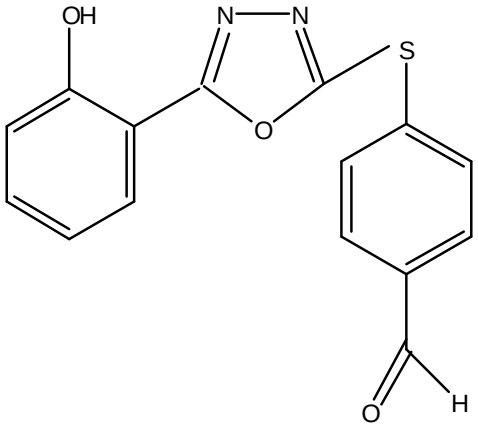


Shridhar *et al* synthesized 1,3,4-oxadiazole incorporated azo dye derivatives (2) and evaluated their antimicrobial activity. The antimicrobial activity of newly synthesized compounds was determined by well plate method in nutrient agar (antibacterial activity) and

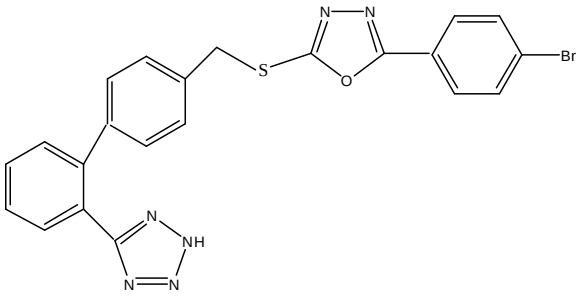
Sabouraud dextrose agar (antifungal activity). *E. coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhi*, were used to investigate the antibacterial activities and *Pseudomonas Aeruginosa, Candida albicans, Candida parapsilosis,* were used to investigate the antifungal activities. One compound showed maximum inhibitory activity against *Pseudomonas aureginosa* and *Candida parapsilosis* at MIC 2.5 mg/ml. Antibacterial drug Ampicillin and antifungal drug Fluconazole were used as standard drug.



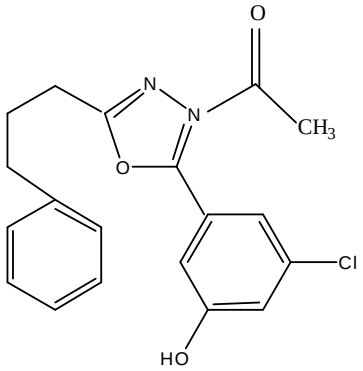
Parikh *et al.* synthesized a novel series of 4-((5-2-hydroxyphenyl)-1,3,4-oxadiazol-2 yl)sufanyl)benzaldehyde derivatives and screened for antimicrobial activity byfilter paper disc method. Stains used were *Staphylococcus aureus*, *Pseudomonas aeruginosa, Bacillus subtillis, Escherichia coli* for the antibacterial activity and for the antifungal activity fungi *Candida albicans.* Ciprofloxacin and Ampicillin as standard antibacterial drug and Ketoconazole and Fluconazole as standard antifungal drug were used. From the result it was found that some compounds showed excellent antibacterial activity against *P. aeruginosa* whereas other compounds displayed better antibacterial activity against *B. subtilis*.



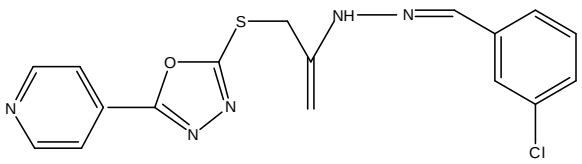
Jun-Shu *et al.* synthesized the series of several new 5-[4'-(5-phenyl-1,3,4-oxadiazole-2-yl-sulfonylmethyl)-biphenyl-2-yl]- tetrazole derivatives and these compounds were evaluated for their antimicrobial activity against *B. subtilis* and *E. coli* at the concentration of 100ìg/ml in nutrient agar media. These compounds demonstrated significant antimicrobial activities as compared with standard drug.



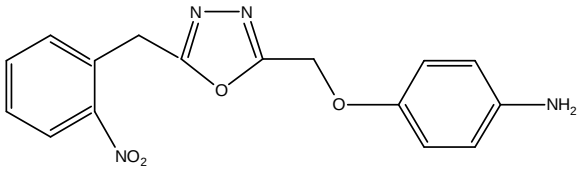
Fuloria *et al*. synthesized a new series 1-(2-aryl-5-phenethyl-1, 3, 4-oxadiazole-3(2*H*)-yl)-ethanones and investigated for their antimicrobial activities. These newly synthesizedcompounds showed good antibacterial activity against the stains of micro-organisms like *S. aureus, P. aeruginosa* as compared with standard drug.



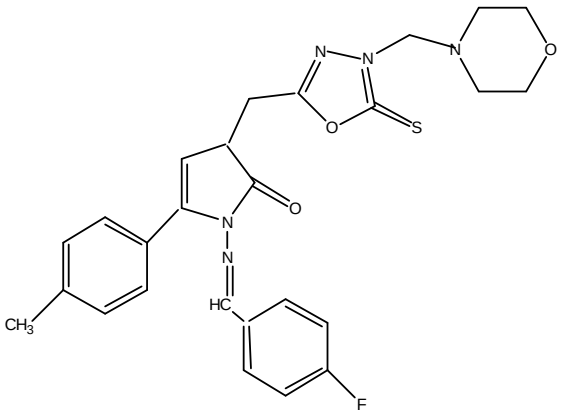
Somani *et al.* synthesized A novel series of 2-(3-chlorobenzylidene)-1-(1-(5-(pyridine-4-yl)-1, 3, 4-oxadiazol-2-ylthio) prop-2-en-2 yl)hydrazine derivatives and evaluated for their antimicrobial activity. The *in vitro* antibacterial activity against *S. aureus* and *E. coli* was determined by cup-plate method by using Ampicillin as standard drug. The *in vitro* antifungal activity of titled compounds was carried out against *C. albicans* and *A. niger* by using Fluconazole as standard drug. The tests were repeated thrice to confirm the findings that the some compounds exhibited good antibacterial activities against *S. aureus* while some compounds were effective against *E. coli*. One compound was found to be the most potent against *C. albicans* and two compounds were more active as antifungal agents against *A. niger* on comparision with standard drug.



Patel *et al.* synthesized 4-thiazolidinone incorporated 1, 3, 4-oxadiazoles and screened them for their antibacterial and antifungal *in vitro* activity against *E. coli*, *P.aeruginosa*, *S. aureus*, *S. pyogenes*, *C.albicans, A. niger*, *A. clavatus* respectively by using broth microdilution method. Minimum inhibitory concentration was determined and compared with standard drugs Ampicillin and Griseofulvin. Some compounds showed good antimicrobial activity and other compounds depicted moderate activity.

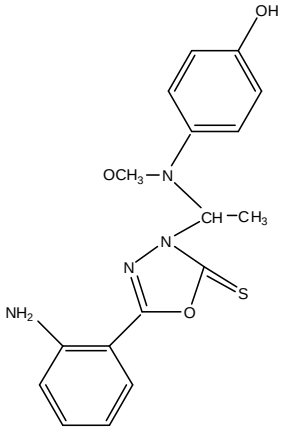


Demirbas *et al.* synthesized 2-(5-mercapto)-1, 3, 4-oxadiazol-2-ylmethyl-1, 2, 4-triazol-3-one derivatives. The antimicrobial effects of the substances were tested quantitatively in their respective broth media by using double dilution and the Minimal Inhibition Concentration (MIC) values were determined. Ampicillin and fluconazole were used as standard antibacterial and antifungal drugs, respectively. Few compounds displayed good to moderate antimicrobial activity .

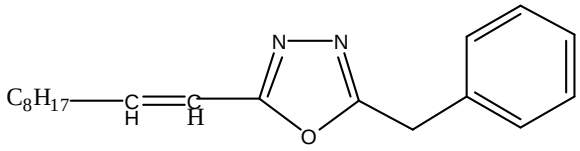


Kanthiah *et al.* synthesized (2-aminophenyl)-1, 3, 4-oxadiazole-2(3*H*)-thione derivatives and screened for their antimicrobial activities. Gram positive microorganisms such as *Staphylococcus aureus*, *Streptococcus pyogenes*, Gram negative microorganisms such as *Escherchia coli*,

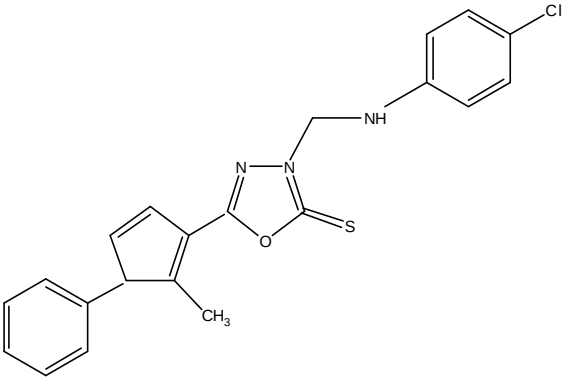
*Klebsiellaaerogenes*and fungus *Candida albicans* were used for antibacterial studies. The disc diffusion method was used to evaluate antimicrobial activities. Compounds at a concentration of 100 μg/ml showed good antibacterial and antifungal activitiesagainst all the tested microorganisms. Amikacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activities respectively.



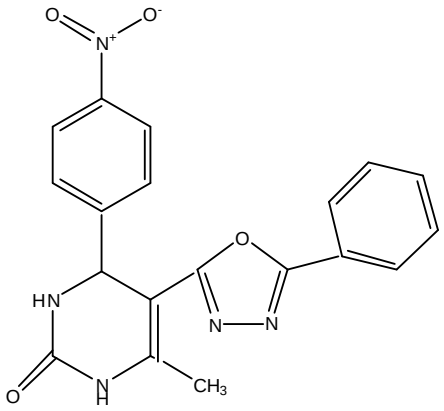
Farshori *et al.* synthesized 5-alkenyl/ hydroxyalkenyl-2-phenylamine-1, 3, 4-Oxadiazoles and tested for their *in vitro* antimicrobial activities by disc diffusion method. Among the synthesized compounds, some compounds were found to be active against fungal stain i.e *Penicillium marneffei* and was compared with Griseofulvin as standard drug whereas other compounds were found to be active against bacterial stains like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Klebsiella pneumoniae* and were compared with Chloramphenicol as standard drug.



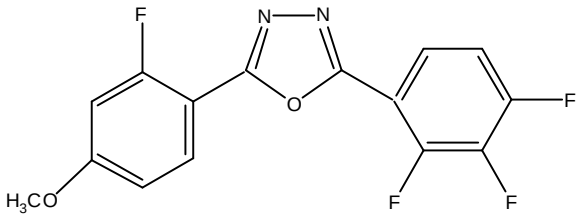
Reddy *et al.* synthesized 4-fluoroanilinomethyl, 4-chloroanilinomethyl, 2-trifluoromethylanilinomethyl-oxadiazole derivatives. The synthesized compounds were evaluated for their antibacterial activity against three representative Gram positive bacteria *Bacillus subtilis, Bacillus sphaericus*, *Staphylococcus aureus* and three Gram negative bacteria *Pseudomonas aeruginosa*, *Klobsinella aerogenes* and *Chromobacterium violaceum*. In addition, these compounds were also screened for their antifungal activity against four fungal microorganisms *Candida albicans*, *Aspergillus fumigatus, Trichophyto rubrum* and *Trichophyton mentagrophytes*. Most of the compounds showed excellent antimicrobial activities when compared with their respective standard drugs.



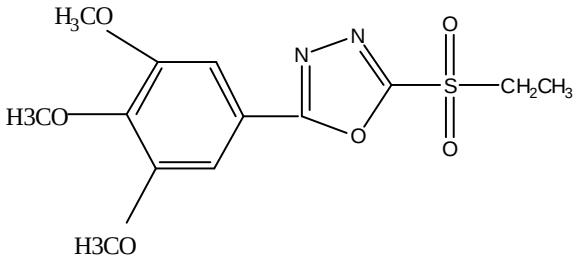
Mishra *et al.* synthesized A series of 3, 4-dihydro-6-methy-4-(4-nitrophenyl)-5-(5-pheny-1, 3, 4-oxadiazol-2-yl) pyrimidin-2-(1*H*)-one derivatives and tested for their antimicrobial activity by cup and plate method. Some compounds showed promising antibacterial activity against gram positive bacteria *Streptococcus pneumonia* and other compounds displayed promising antibacterial activity against gram positive bacteria *Escherichia coli* as compared to standard drugs Ofloxacin and Levofloxacin.



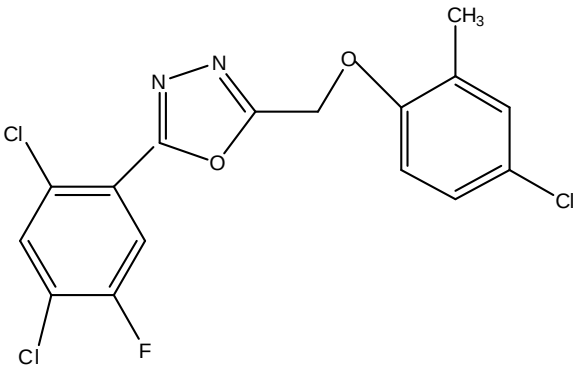
Chandrakantha *et al.* synthesized some novel 1, 3, 4-oxadiazole derivatives bearing 2-flouro-4-methoxy phenyl moiety and screened for antimicrobial activity through serial dilution method. Amongst the various compounds synthesized, two compounds showed excellent antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* and other compounds displayed excellent antifungal activity against *Candida albicans*. Compounds tested for antibacterial activity were compared with standard drug Furacin and for antifungal activity standard drug was Flucanazole.



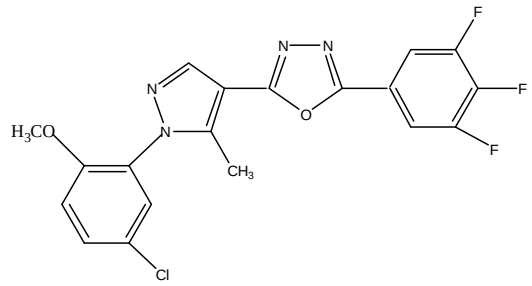
Chen *et al.* synthesized 5-(3, 4, 5-trimethoxyphenyl)-2-sulfonyl-1, 3, 4-oxadiazole derivatives and investigated for their antifungal activity against *Gibberellazeae, Botrytis cinerea, Sclerotiniasclerotiorum*. Amongst the tested compounds, two compounds depicted promising antifungal activities when compared with standard drug Hymexazol.



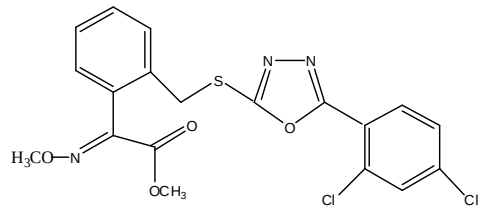
Karthikeyan *et al.* synthesized 2, 4-dichloro-5-flourophenyl containing oxadiazoles and then final compounds were demonstrated for their antimicrobial activity. Few compounds displayed good inhibition against *Staphylococcus aureus*, *Escherichia coli* when compared with standard drug Ciprofloxacian. Some other compounds also showed good inhibition aganist all the fungal stains *Candida albicans*, *Aspergillus fumigatus* and *Penicillium marneffei* when compared with standard drug Greseofluvin.



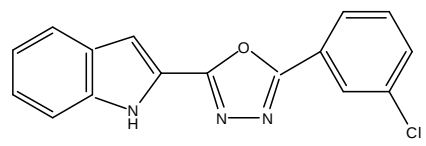
Rai *et al.* synthesized a novel series of 2-[1-(5-chloro-2-methoxyphenyl)-5-methyl-1*H*-pyrazol-4-yl]-5- (substitutedphenyl)-1, 3, 4-oxadiazole derivatives and invesigated for their antibaterial activity. From the tested compounds, few compounds showed significant activity against *Bacillus subtilis* and *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumonia*. These compounds were compared with Ampicillin as standard drug.



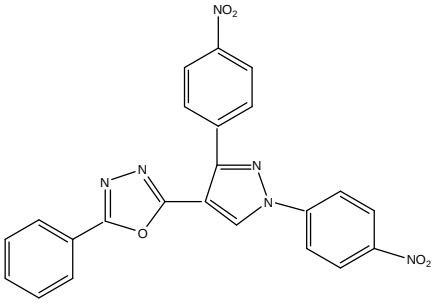
Li *et al.* synthesized (E)-α-(metheoxyimino)-benzeneacetate derivatives containing 1, 3, 4-Oxadiazole ring and investigated for their fungicidal activities. All of the compounds exhibited significant fungicidal activities against *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibbereapers zeae*, *Physalospora piricola* and *Bipolaris mayclis* when compared with standard drug.



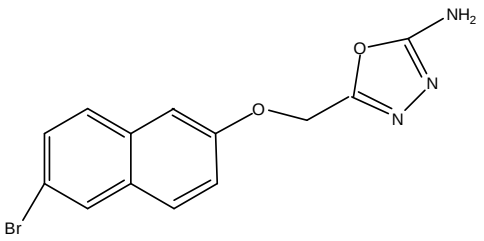
Bhardwaj *et al.* synthesized a novel series of 2-(5-(3-chlorophenyl)-1, 3, 4-oxadiazol-2-yl)-1*H*-indole derivatives and demonstrated for their antimicrobial activity on different stains. Out of total of compounds synthesized, three compounds were found to be active against bacterial stains like *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* whereas none of the compound was found to be effective against fungal stains. Standard Drugs used for comparision of antimicrobial activities were Norfloxacin and Fluconazole.



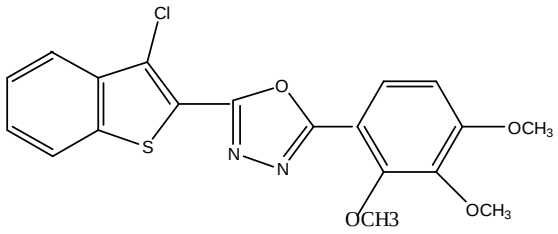
Prakash *et al.* synthesized a series of novel unsymmetrical2[1, 3-bis(4-nitrophenyl)-1*H*-pyrazol-4-yl)-5-phenyl-1, 3, 4- oxadiazoles and tested for their antibacterial and antifungal activities. Amongst the tested compounds, two compounds depicted most potent antibacterial activity against *Staphylococcus aureus* and was compared with ciprofloxacin asstandard drug. Two compounds displayed maximum inhibition against both of the fungi *Aspergillus niger* and *Aspergillus flavus* when compared with Fluconazole as standard drug.



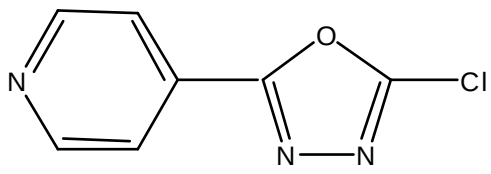
Mayekar *et al* synthesized a series of new 5-amino, 2-(-5-bromo) naphthalene) carboxalate, 1, 3, 4-oxadiazole derivatives having 6-bromonaphthalene moiety. The antimicrobial activities of title compounds were examined against two gram positive bacteria (*S. aureus*, *S. pyogenes*), two gram negative bacteria (*E. coli*, *P. aeruginosa*) and three fungi (*C. albicans*, *A. niger*, *A. clavatus*) by using the broth microdilution method. Some of the tested compounds displayed significant antimicrobial activities when compared with their respective standard drugs.



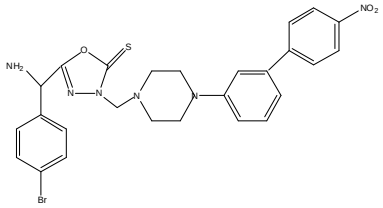
Ansari *et al.* synthesized some new 3-acetyl-5-(3-chloro-1-benzo[*b*]thiophen-2-yl)-2-substituted phenyl-2, 3- dihydro-1, 3, 4-oxadiazoles (22) and evaluated for their antimicrobial activities. All the compounds were screened for their antibacterial activities against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans* and *Asperigillus niger.* Some compounds exhibited significant antibacterial and moderate antifungal activities on comparision with their respective standard drugs.



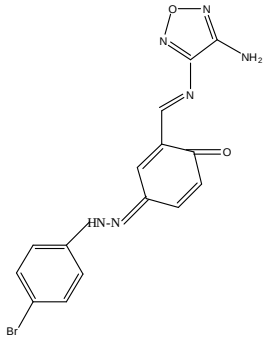
Dewangan *et al.* synthesized novel derivatives of 4-(5-chloro-1, 3, 4-oxadiazole-2-yl) pyridine and evaluated for antimicrobial activities. The antimicrobial activities of title compounds were examined against two gram positive bacteria (*S. aureus*, *S. pyogenes*), two gram negative bacteria (*E. coli*, *P. aeruginosa*) and three fungi (*C. albicans*, *A. niger*, *A. clavatus*) using the broth microdilution method. Some derivatives exhibited excellent antimicrobial activities on comparision with their respective standard drugs.



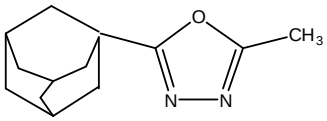
Prakash *et al.* synthesized a novel series of 5-(amino(4-bromophenyl)methyl)-3-((4-phenylpiperazin-1-yl)methyl)-1, 3, 4-oxadiazole-2(3*H*) thiones. The newly synthesized compounds were invesigated for their antimicrobial activities. Microbial stains used for antibacterial activity were *Staphylococcus aureus, Bacillus subtilis, Escherichiacoli* and *Pseudomonas aeruginosa* and for antifungal activity *Candida albicans* and *Asperigillus niger.* Few compounds showed good antimicrobial activity on comparision with standard drug Norfloxin.



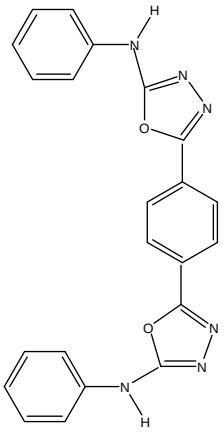
Kakanejadifard *et al.* synthesized some novel 2-((4-amino-1, 2, 5-oxadiazol-3- ylimino)methyl)-4-(phenyldiazenyl) phenol derivatives and evaluated their antimicrobial activities. The synthesized compounds were screened for their *in vitro* antimicrobial activity against both Gram-positive (*Staphylococcus aureus* and *Bacillus cereuss*) and Gram negative (*Escherichia coli* and *Klebsiella pneumonia*) bacteria by using disc diffusion method. The antibacterial activity was reported as the minimum inhibitory concentration (MIC) in mg/ml. One compound showed the most potent antimicrobial activity with MIC value of 57 mg/ml against *S. aureus* and *B. cereuss* as compared with standard drug.



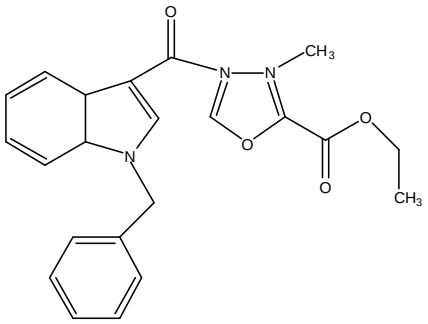
Kadi *et al.* synthesized a novel series of 2-(1-adamantylamino)-5-substituted-1, 3, 4-oxadiazole derivatives and screened their antimicrobial activity.The primary screening was carried out using the agar disc diffusion method using Muller Hinton agar medium. Antimicrobial activity of compounds was compared with antibacterial drug Ampicillin and the antifungal drug Clotrimazole against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeuroginosa* and *Candida albicans.* Some compounds depicted good to moderate antimicrobial activity relative to standard drug.



Shaker *et al.* synthesizedN-phenyl-5-(-4-(5-phenylamino-1, 3, 4-oxadiazol-2-yl) phenyl)-1, 3, 4-oxadiazol-2-amine and examined their antimicrobial activity. Gram-negative bacteria (*Seratia*), gram-positive bacteria (*Bacillus cereus*), as well as two different fungi, *Fusarium monoiliforum* and *Aspergillus flavus* were used for this purpose. Some compounds showed good antimicrobial activity whereas other compounds displayed moderate antimicrobial activity as compared with standard drug.

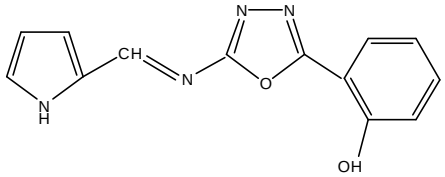


Rahman *et al.* synthesized compounds some new (3a,7a-dihydro-1*H*-indol-3-yl) (4-methyl- 1, 3, 4-oxadiazolidin-3-yl) methanone derivatives and screened *in vitro* for their antimicrobial activities against four stains of bacteria (*Staphylococcus aureus, Serratia marcescens, Streptococcus, Pseudomonas aeruginosa*) and two species of fungi (*Aspergillu sparasitcus, Penicillium oxalicum*) using the filter paper disc method. Most of the compounds exhibited considerable activities against two bacterial species, *Serratia marcescens* and *Streptococcus*. Some compounds exhibited a moderate activity against *Staphylococcus aureus*. All the screened compounds were inactive against *Pseudomonas aeruginosa.* Some compounds showed moderate antibacterial activity against *Penicillium oxalicum*.



Nazk Mohammed Aziz *et al.* synthesized new metal complexes of the ligand (HL) 2-[1H-Pyrrol-2-ylimino methyl]-5-phenyl-1, 3, 4-oxadiazol with the metal ions Co(II), Ni(II) and Cu(II), were prepared in alcoholic medium. The Schiff bases were condensed by using [Pyrrolcarboxaldehyde] with [2-amino-5-(phenyl-1, 3, 4-oxadiazole] in alcoholice medium. As the Schiff baseprepared was tridentate ligand, it was used for forming complexes with Co+2, Ni+2, Cu +2 and Zn+2 ions of type M (HL)2. All the synthesized Schiff base and their metal complexes were characterized

by FTIR Spectroscopy, Electronic Spectroscopy, Elemental Analysis, Magnetic Susceptibility Measurements, Thermal Analysis, *1H*-NMR Spectra, and Mass Spectra. The antimicrobial activity of these compounds was determined by the agar diffusion method. These types of bacteria *Staphylococcus aureus*, *Escherishia coli*, *Pseudononas aeroginosa* and *Cndida albicans* were used to show the biological activities of the ligand and its complexes.



CONCLUSION

Various oxadiazole derivatives have been placed a successfully used antimicrobial drugs in clinical practic. This review has highlighted the use of Oxadiazole derivatives having antimicrobial activity. The 1, 3, 4-oxadiazole have shown significant antimicrobial activity against a wide . . . . . **.** In conclusion we arrive at the postulate that 1, 3, 4-oxadiazole has anti microbial activity . And important antimicrobial drug is Furazolidone.

Furazolidone is a nitrofuran antibacterial agent. It is marketed by Roberts Laboratories under the brand name Furoxone and by GlaxoSmithKline as Dependal-M. Diafuron, medaron. Furazolidone as antimicrobial is used to treat diarrhea or enteritis caused by bacteria and protozoa including traveler's diarrhea, food poisoning, typhoid fever, cholera, salmonella infections, and giardiasis.

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