ANTIMICROBIAL ACTIVITIES OF 1,3,4-OXADIAZOLE: A REVIEW

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Received on: 08/10/11 Revised on: 30/10/11 Accepted on: 16/11/11

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ABSTRACT

1, 3, 4-Oxadiazole is a highly privileged structure the derivatives of which exhibit a wide range of biological activities including antibacterial, antitubercular, vasodilatory, antifungal, cytotoxic, anti-inflammatory and analgesic, hypolipidemic, anticancer and ulcerogenic activities. Resistance to number of antimicrobial agents among a variety of clinically significant species of bacteria is becoming increasingly important global problem. 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, antimicrobial agents.

INTRODUCTION

Oxadiazole is a five-membered heterocyclic aromatic chemical compound having two carbons, two nitrogen, and one oxygen atoms and two double bonds having general formula C₂H₂O₂N₂. Oxadiazole (Oxazole) is the parent compound for a vast class of heterocyclic compounds. These are azoles with oxygen and Nitrogen. There are four isomers of oxadiazole

![Diagram of Oxadiazole isomers](image)

1,2,4-Oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unstable and reverts to the diazoketone tautomer. The stable oxadiazoles appear in a variety of pharmaceutical drugs including raltegravir, butalamine, oxolamine, and pleconaril.

A large number of oxadiazole derivatives have been prepared and many of these compounds have shown wide spectrum of antimicrobial activity. Some oxadiazoles with different substituent at different location on the heterocyclic ring resulted in fungicidal and bactericidal agents of various potencies. Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene.

The electrophillic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp² carbon atom.

The present manuscript specially emphasizes on chemistry, methods of synthesis and reactivity of 1, 3, 4-oxadiazole and its derivatives.

The common synthetic approaches to oxadiazoles involve cyclization of diacylhydrazines. A variety of reaction conditions influence the cyclization reaction. Typically, the reaction is promoted by heat and anhydrous reagents including thionyl chloride, phosphorous oxychloride, phosphorous pentoxide, triphenylphosphine, and triflic anhydride. Alternative synthetic methods comprise reaction of carboxylic hydrazides with keteneylidene triphenylphosphorane or base-promoted cyclization reaction of trichloroacetic acid hydrazones.

Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules. Out of its four possible isomers, 1, 3, 4-oxadiazole is widely exploited for various applications. A numbers of therapeutic agents such as HIV-integrase inhibitor raltegravir, a nitrofuran antibacterial furamizole, a potent PDF inhibitor BB-83698, antihypertensive agents tiodazosin and nesapidil are based on 1,3,4-oxadiazole moiety.

The 1, 3, 4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The present review attempts to summarize the various routes of synthesis and the reactions of 1, 3, 4-oxadiazole and its derivatives and focus on their biological potential. Literature reveals that 1, 3, 4-Oxadiazole is a highly privileged structure the derivatives of which exhibit a wide range of biological activities including antibacterial, antitubercular, vasodilatory, antifungal, cytotoxic, anti-inflammatory and analgesic, hypolipidemic, anticancer and ulcerogenic activities. Oxadiazole derivatives have been found to possess broad spectrum antimicrobial activity and therefore are useful substractures for further molecular exploration.

ANTIMICROBIAL ACTIVITY

The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists. Resistance to number of antimicrobial agents among a variety of clinically significant species of bacteria is becoming...
increasingly important global problem. The 1,3,4-oxadiazole have shown significant antimicrobial activity against a wide variety of microorganisms like fungi, Gram +ve and Gram –ve bacteria.3

**Ahmed O. Maslat et al** synthesized compounds are: 5,5’-dimercapto-bis-[1,3,4-oxadiazol-2-yl]propane, 5,5’-dimercapto-bis-[1,3,4-oxadiazol-2-yl]butane, 5,5’-dimercapto-bis-[1,3,4-oxadiazol-2-yl]octane and 5,5’-dibenzythio-bis-[1,3,4-oxadiazol-2-yl] butane. Newly synthesized compounds were investigated for their antibacterial, antifungal activities against *S. aureus* and *B. subtilis*.4

![Image 1](image1.png)

**Rakesh Chawla et al** synthesized some new 3-acetyl-5-(3-chloro-1 benzol[b]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles and 2-(3-chloro-1 benzol[b]thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles and was evaluated for Anti- Microbial activity.5

![Image 2](image2.png)

**Farshori et al** synthesized 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4- Oxadiazoles (compound 4) and tested for in vitro antimicrobial activities by disc diffusion method. Among the synthesised compounds, found to be more active against fungal strain i.e *Penicillium marneffei* and was compared with greseofulvin as standard drug.6

![Image 3](image3.png)

**Nitin Bhardwaj et al** have synthesized derivatives of 1,3,4-oxadiazoles by incorporating indole nucleus at one of the two free positions in the oxadiazole ring system. These synthesized compounds evaluated for antimicrobial activity by Punched-hole method against MTCC 441 (*Bacillus subtilis*), MTCC 1430 (*Staphylococcus aureus*), MTCC 424 (*Pseudomonas aeruginosa*), MTCC 1573 (*Escherichia coli*) and MTCC 2546 (*A. niger*) respectively using the standard drugs norfloxacin and fluconazole. The compounds which were active against bacterial strains were effective at a much higher concentration as compared to the standard drug.7

![Image 4](image4.png)

**B. Chandrakantha et al** synthesized a series of new 1,3,4-oxadiazole with 2-fluoro-4-methoxy moiety and are tested for Anti- Microbial activity all synthesized compounds showed significant anti-bacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa*, and anti-fungal activity against *C. Albicans*.8

![Image 5](image5.png)

**Asif Husain et al** have synthesized a novel series of 2-[3-(4-bromophenyl) propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles from 3-(4-bromobenzoyl) propionic acid as starting material in the reaction with different aryl acid hydrazidesin phosphorous oxychloride and screened for antibacterial activity by using Gram positive (*Staphylococcus aureus*) and Gram negative (*Escherichia coli*), and tested for in vitro Antimicrobial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*.9

![Image 6](image6.png)

**M. Shahar Yar et al** synthesized a series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives and was tested for in vitro Anti- Microbial activity. 2-(2 naphthyloxymethyl)-5-phenoxy methyl-1,3,4-oxadiazole exhibited > 90% inhibition among all the synthesized compounds.10

![Image 7](image7.png)
Kumar et al synthesised some novel 2-substituted-5-[isopropylthiazole] clubbed 1,3,4 Oxadiazoles and tested for antimicrobial activity by broth microdilution method. Among the various some improved antibacterial activity against tested Gram-positive bacteria i.e Staphylococcus aureus, Staphylococcus faecalis, Bacillus subtilis and compound having p-methoxy substitution showed excellent antifungal activity against Saccharomyces cerevisiae, Candida tropicalis, Aspergillus Niger. These tested compounds were compared with standard drugs i.e Ciprofloxacin, Norfloxacin, Fluconazole.

H. S. Yathirajan et al have synthesized 2-[(6-bromo-2-naphthyl)oxy]acetoxyhydrazide and various substituted aromatic acids in the presence of POCI3. They also synthesized 5-[(6-bromo-2-naphthyl)oxy]methyl]-1,3,4-oxadiazole-2(3H)-thione using hydrazide, CS2 and KOH. These synthesized compounds were further subjected to Mannich reaction to get a series of Mannich bases. All the newly synthesized compounds were screened for their antimicrobial activity. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate to good inhibition at µg ml-1 in DMSO.

Prakash et al synthesised a series of novel unsymmetrical 2,5-disubstituted 1,3,4- Oxadiazoles and then the final compounds were tested for their antibacterial and antifungal activities. Among the tested compounds, maximum shows antibacterial activity against Staphylococcus aureus and was compared with ciprofloxacin as standard drug.

Manish Kumar Mishra et al synthesized 6 – Methyl – 4 – aryl – 5 - (5- phenyl -1, 3, 4 – oxadiazol -2- yl) -1, 2, 3, 4-tetrahydroprymidine-2(1H)-one. All the derivatives has effect against Streptococcus pneumonia(+ve) and Escheria coli (-ve).

Neeraj Kumar Fuloria et al have made a series new 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanones 2a-e was synthesized by the cyclization of imines 1a-e using acetic anhydride. These products were evaluated for antibacterial and anti-fungal activity against freshly cultured strains of S. aureus (SA) and P. aeruginosa (PA) using sterile nutrient agar media and for antifungal activity against freshly cultured strains of C. albicans (CA) and A. flavus (AF) using sterile sabouraud’s agar medium by the disk diffusion method at a concentration of 2 mg per mL using DMF as solvent. The results were recorded in duplicate using ampicillin and fluconazole at a concentration of 1 mg per mL as standards.

Yan Li et al synthesized fifteen novel (E)-a-(methoxyimino)benzeneacetate derivatives. Bioassays indicated that compounds shows potent fungicidal activity against Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Physalospora piricola and Bipolaris mayelis and showed potent fungicidal activity against R. Solani.

Chen et al synthesized 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives (Compound 22) and tested for their antifungal activity against Gibberella zeae, Botrytis cinerea, Sclerotinia sclerotiorum.
Mojahidul Islam et al synthesized a series of 5-{3′-oxo-6′-(substituted aryl)-2′,3′,4′,5′-tetrahydropyridazin-2′-ylmethyl}-2-substituted 1,3,4-oxadiazole and then final compounds were tested for their antibacterial activity using cup plate method.18

Mohamed Ashraf Ali et al synthesized a series of oxadiazole mannnich bases by reaction between oxadiazole derivatives, dapsone, and appropriate aldehydes and was evaluated against Mycobacterium Tuberculosis. Compound 3-{2-furyl [4-(4{-2-furyl [5-(2-naphthoxy)methyl]-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl] methylamino] phenylsulfonyl} anilino)methyl]-5-(2-naphthoxy)methyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione from all the synthesized compounds have shown best activity against M. Tuberculosis and isoniazid resistant M. Tuberculosis.19

Rai et al synthesized 2-[1-(5-chloro-2-methoxyphenyl)-5-methyl-1H-pyrazol-4-yl]-5- (substitutedphenyl)-1,3,4-oxadiazole and tested for their antibacterial activity. From the tested compounds, compound 10a which is unsubstituted showed significant activity against Bacillus subtilis and moderate activity against Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia. Flourine incorporated in phenyl ring of 1,3,4-oxadiazole showed improved activity against both Gram +ve bacteria i.e Bacillus subtilis, Staphylococcus aureus and Gram –ve bacteria i.e against Escherichia coli, Klebsiella pneumonia. These compounds were compared with Ampicillin as standard drug.22

CONCLUSION
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 variety of microorganisms like fungi, Gram +ve and Gram –ve bacteria. Furamizole is a compound which is based upon 1,3,4-oxadiazole ring and has strong antibacterial activity.

REFERENCES


