A Comprehensive Review on 1,3,4-oxadiazole Derivatives

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ABSTRACT
Furadiazole or 1,3,4-oxadiazole is a five membered heterocyclic nucleus and it is derived from the furan ring by replacement of two methane group (-CH=) by pyridine type nitrogen. 1,3,4-oxadiazole derivatives have a number of biological activities like antibacterial, antifungal, anti-inflammatory, anti-cancer, genotoxic, hypolipidemic, cytotoxic, ulcerogenic activities etc. Antimicrobial agents are clinically useful agents against significant species of bacteria which is having global problem. In this review we have collected information about the 1,3,4-oxadiazole nucleus and its antimicrobial activity for further research and development. Oxadiazoles are formed by cyclization of diazoketone tautomers which is influenced by the different reaction conditions maintained.

Keywords: Oxadiazole, antimicrobial activity, antimicrobial agents.

INTRODUCTION
Oxadiazoles form an important class of heterocyclic aromatic compounds of azole family with extensive medicinal properties.

\[
\begin{align*}
(1) & \quad \text{N} \quad \text{N} \\
(2) & \quad \text{N} \quad \text{N} \\
(3) & \quad \text{N} \quad \text{N} \\
(4) & \quad \text{N} \quad \text{N}
\end{align*}
\]

It can exist in four isomeric forms i.e., 1,2,3-oxadiazole (1), 1,2,4-oxadiazole (2), 1,2,5-oxadiazole (3) and 1,3,4-oxadiazole (4).

The isomers 1,2 and 3 are unstable and ring opening reaction occurs to form diazoketone tautomer. It is similar to furan and formed by replacing two pyridine type nitrogen(-N=). This will reduce the aromaticity of oxadiazole ring, and make it a weak base due to inductive effect of extra heteroatom. Oxadiazole ring is seen in different variations of pharmaceutical medicines like butalamine, oxalamine, raltegravir, pleconaril and fasiplon. Electrophilic substitution reaction in oxadiazole ring is very difficult to perform at carbon position due to the low density of electrons on carbon atom which can be allocated to the electron withdrawal of pyridine type nitrogen. The 1,3,4-oxadiazole undergoes electrophilic substitution reactions on electron rich nitrogen. It improves reactivity if the oxadiazole ring is substituted with electron-releasing groups. Halogen-substituted oxadiazoles undergo nucleophilic substitution reaction with replacement of halogen by nucleophiles. The 1,3,4-oxadiazole moiety possesses good pharmacokinetic properties due to presence of -N=C-O- group which increases its lipophilicity and thus capacity to reach the target. Moreover, 2,5-disubstituted 1,3,4-oxadiazoles are also found to exhibit better structures for the antimicrobial and antifungal properties compared to the standard drugs.

Antimicrobial Activity
1,3,4-oxadiazole derivatives have been investigated for antibacterial, antioxidant, anticonvulsant, analgesic, anti-inflammatory, antiemetic, antimicrobial, antifungal and host of other biological activities. Oxadiazole derivatives possess broad spectrum antimicrobial activity. A number of methods have been reported for synthesis of 1,3,4-oxadiazoles. The most common method is reaction between acid hydrazides (or hydrazine) with acid chlorides (or carboxylic acids) followed by direct cyclization of diacylhydrazines using a variety of dehydrating agents like phosphorus oxychloride, Thionyl chloride, Phosphorus pentoxide.

Mohd Amir et al. (2011), synthesized a series of 2-[(5-diphenylmethyl-1,3,4-oxadiazoles-2-yl) sulfanyl-N-(substituted phenyl)-acetamides as antiinflammatory agents using paw edema model in wister rats. Halogen substituted derivatives in aryl ring showed significant anti-inflammatory activity.

\[
\begin{align*}
(5) & \quad \text{O} \quad \text{S} \quad \text{NH} \\
(6) & \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{Cl}
\end{align*}
\]

In the year 2007, he synthesized derivatives of 2-substituted aryl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4-oxadiazole for anti-inflammatory and ulcerogenicity using pylorus ligation method.
Mudasir R Bandy et al (2010) was successful in synthesizing 5-(alkenyl)-2-amino-1,3,4-oxadiazoles and 2-(alkenyl)-5-phenyl-1,3,4 oxadiazole. These compounds obtained were screened for antibacterial and antifungal activities. These compounds revealed broad spectrum of activity and showed promising results.8

![Structure 7](image7.png)  
![Structure 8](image8.png)

Dhansay Dewangan et al (2010) explored 2,5-disubstituted-1,3,4-oxadiazole derivative for analgesic and anti-inflammatory activity by acetic acid induced method and carrageenan induced rat paw edema respectively.

![Structure 9](image9.png)  
![Structure 10](image10.png)

Compound 9, 10

| a | 2-OH-C6H4 |
| b | 4-OCH3-C6H4 |
| c | 3-OCH3, 4-OH-C6H4 |
| d | 2-C6H5O |
| e | -C6H5 |
| f | -C6H4 |
| g | -C6H4N |
| h | 2-NH2-C6H4 |
| i | 4-NH2-C6H4 |
| j | 2-COOH-C6H4 |

Analgesic activity was shown by 9b, 10f, and 10j while significant anti-inflammatory activity was seen in 9c, 10g, 10j.9

Rakesh Chawla et al (2010) synthesizes 3-acetyl-5-(3-chloro-1-benzo[b] thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles and 2-(3-chloro-1-benzo[b] thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles to investigate for antimicrobial activity.10

![Structure 11](image11.png)

Farshori et al (2010) synthesized and also investigated compounds for antimicrobial and antifungal activity. He synthesized 5-alkenyl/hydroxyl-alkenyl-2-phenyl amine-1,3,4-oxadiazole derivatives.11

![Structure 12](image12.png)

B. Chandrakantha et al (2010) tested a series of 1,3,4-oxadiazole derivatives with 2-fluoro-4-methoxy which has been synthesized for antimicrobial activity against Escherichia coli and Pseudomonas aeruginosa, and antifungal activity against C. Albicans.12

Kumar et al (2010) synthesized some novel 1,3,4-oxadiazoles derivatives using 2-substituted-5-[isopropylthiazole] and investigated them for antibacterial and antifungal activity. The standard drugs used were ciprofloxacin, norfloxacin, and fluconazole.13

![Structure 13](image13.png)

![Structure 14](image14.png)

![Structure 15](image15.png)
H. S. Yathirajan et al. (2010) synthesized 2-[(6-bromo-2-naphthyl)oxy] acetoxyhydrazide derivatives of 1,3,4-oxadiazole using manich reaction for antimicrobial activity.\(^{14}\)

Prakash et al. (2010) synthesized novel unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles for antibacterial and antifungal activities. The compounds were compared with ciprofloxacin as standard drug.\(^{15}\)

Manish Kumar Mishra et al. (2010) synthesized 6-methyl-4-aryl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-one. The derivatives were effective against gram +ve (Streptococcus pneumonia) and gram –ve (E.coli) bacteria.\(^{16}\)

Nitin Bhardwaj et al. (2009) was successful in synthesizing indole substituted 1,3,4-oxadiazoles and evaluated them for antimicrobial activity using norfloxacin and fluconazole as standards. The compounds were found to be effective at higher concentrations with respect to standard drug.\(^{17}\)

Neeraj Kumar Fuloria et al. (2009) synthesized novel compounds series of 1-(2-aryl-5-phenethyl-1,3,4-oxadiazole-3(2H)-yl)ethanones and evaluated them for antibacterial and antifungal activity. The results were compared against ampicillin and fluconazole.\(^{18}\)

Asif Husain et al. (2009) investigated antibacterial activity in both Gram +ve (Staphylococcus aureus) and Gram-ve (E.coli) bacteria by synthesizing a novel series of 2-{3-[4-bromophenyl]propan-3-one}-5-(substituted phenyl)1,3,4-oxadiazoles.\(^{19}\)

Rakesh Saini et al. (2009) investigated 2,5-disubstituted -1,3,4-oxadiazole derivatives for anti-bacterial activity against E.coli and S.aureus. The ortho-chloro benzene substituted derivative was found to be most effective.\(^{20}\)

Rai et al. (2009) tested antibacterial activity on 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1H-pyrazol-4-yl]-5-
(substituted phenyl)-1,3,4-oxadiazole using Ampicillin as standard.\(^{21}\)

Karthikeyan \textit{et al} (2008) tested 2,4-dichloro-5-fluorophenyl containing oxadiazoles for antimicrobial and antifungal activity.\(^{22}\)

Liu \textit{et al} (2008) investigated sulfoxide derivatives of trimethoxy phenyl-1,3,4-oxadiazole for antifungal activity.\(^{23}\)

Shashikant V Bhandari \textit{et al} (2008) studied anti-inflammatory activity and ulcerogenicity of 5-[2-(2,6-dichloroaniline)benzyl]2-mercapto-1,3,4 oxadiazole.\(^{24}\)

Mohammed zareef \textit{et al} (2008) synthesized 5-substituted-2-mercapto-1,3,4-oxadiazoles derivatives to screen them for anti-microbial and antifungal activity using agar well diffusion method and agar plate technique respectively. The corresponding S-esters and S-amides were also synthesized. The meta chloro benzene of S-esters was found to exhibit moderate activity.\(^{25}\)

Shaharyar \textit{et al} (2007), synthesized some novel 1,3,4-oxadiazole derivatives as an anti-tubercular drugs. The compound 2-(2'naphthyl oxymethyl)-5 phenoxymethyl 1,3,4-oxadiazole showed highest activity among the synthesized derivatives\(^{26}\)

Mohamed Ashraf Ali \textit{et al} (2007) investigated oxadiazole derivatives formed using mannich reaction between 1,3,4-oxadiazole, dapsone and aldehydes for antitubercular activity. Compound 3-[2-furyl][4(4-[2-furyl][5-(2-naphthyl oxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazole-3yl]
methylamino]phenyl sulfonyl]-anilino methyl]-5-(2-naphthyl oxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione have shown good activity.\(^{27}\)
Yan Li et al. (2006) synthesized novel (E)-a-(methoxyimino)-benzeneacetate derivatives to evaluate fungicidal activity against Rhizoctonia solani, Botrytis cinerea, Gibberella zeae et al. It shows potent fungicidal activity against R. Solani.28

Mojahidul Islam et al. (2006) synthesized novel series of 5- {3’-oxy-6’- (substitutedaryl)-2’,3’,4’,5’- tetrahydropyridazin-2(1H)methyl)-2-substituted 1,3,4-oxadiazole for antibacterial activity.29

Ahmed O. Maslat et al. (2002) synthesized mercapto derivatives to investigate their antibacterial and antifungal property against S. aureus and B. subtilis. They synthesized 5,5’-dimercapto-bis [1,3,4-oxadiazole-2-yl] propane; 5,5’-dimercapto-bis-[1,3,4-oxadiazole-2-yl] butane; 5,5’-dimercapto-bis[1,3,4-oxadiazole-2-yl] soxane and 5,5’-dibenzyl thio-bis-[1,3,4-oxadiazole-2-yl] butane.31

**CONCLUSION**

This review highlights the broad spectrum of antimicrobial activity associated with 1,3,4-oxadiazoles along with anti-inflamatory, anti-tumour, analgesic, anti-convulsant, antioxidant, anti-viral activity and a host of other activities. This puts impetus on the need to explore 1,3,4-oxadiazole moiety for further research and screening.

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