Heterocyclic compounds are indispensable structural units for both the chemists and the biochemists. 1,3,4-Oxadiazole derivatives have been extensively studied owing to their wide spectrum of biological activities. The present review article covers the active compounds having oxadiazole ring with fused heterocycles which possess interesting biological activities such as anti-inflammatory, analgesic, antimicrobial, anti-convulsant, anti-proliferative, antimycobacterial, anti-protozoal, anti-diabetic, anthelmintics and MAO enzyme inhibitors. Results of various derivatives of different oxadiazole and their substitutions with diverse biological activities are reviewed in present article.

KEY WORDS
1,3,4-oxadiazole derivatives, biological activities

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INTRODUCTION

Oxadiazoles are five membered ring system containing two carbon atoms, two nitrogen atoms and one oxygen atom. Depending upon the position of N-atom in the heterocyclic ring, oxadiazoles may be divided into four types.

![Diagram of oxadiazole structures]

Of all the possible isomers, 1, 3, 4-oxadiazole has been found to posses appreciable biological activities [1-5]. The 1, 3, 4-oxadiazole isomer of oxadiazole series and its dihydro derivatives provide a bulk of literature on oxadiazole. A glance at the standard reference work shows that more studies have been carried out on the 1, 3, 4-oxadiazole than all other isomers combined. Therefore, a considerable research has been focused on this nucleus.

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 electrophilic 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. Literature survey reveals that the oxadiazoles undergoes number of reactions such as electrophilic substitution, nucleophilic substitution, thermal and photochemical [6]. This has been exploited in the preparation of oxadiazole therapeutic molecules for various applications. In this view an attempt has been made to review the biological activities of oxadiazoles.

PREPARATION OF OXADIAZOLES

Thiosemicarbazides

2-Amino-5-substituted-1,3,4-oxadiazoles (1) can be conveniently prepared from 1-benzoyl-thiosemicarbazide by cyclization with lead oxide [7].

![Scheme 1]

Thiosemicarbazides are also cyclised in the presence of mercuric oxide to give 2-amino-5-substituted-1,3,4-oxadiazole (2) [8].

![Scheme 2]
Hydrazines

Hydrazones are oxidatively cyclized by lead tetraacetate \[^9\] to give the corresponding disubstituted -1,3,4-oxadiazole (3).

\[
\text{R-CH=NNH-OR'} \xrightarrow{\text{Pb(OAc)}_4} \text{N-N}=\text{O}
\]

\((3)\)

Scheme 3

Acid Hydrazides

Acid hydrazides are cyclized with carbon disulfide in the presence of pyridine or alkali hydroxide to give 2-mercapto-1,3,4-oxadiazole (4) \[^10\].

\[
\text{R-CO-NH-NH}_2 + \text{CS}_2 \xrightarrow{\text{KOH/Pyridine}} \text{N-N}=\text{S}
\]

\((4)\)

Scheme 4

Aryl acid hydrazides are cyclized with ortho-esters to give 2-aryl-1,3,4-oxadiazole (5) \[^11\].

\[
\text{Ar-CO-NH-NH}_2 \xrightarrow{\text{CH}_2(\text{OC}_2\text{H}_5)_2} \text{N-N}
\]

\((5)\)

Scheme 5

BIOLOGICAL PROFILE

Oxadizoles possess various biological activities which are given hereunder:

Anti-inflammatory activity

Burbuliene et al \[^12\] synthesized and evaluated 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanyl methyl]-3\(H\)-1,3,4-oxadiazole-2-thiones for their in vivo anti-inflammatory activity. Compound (6) was found to be more active than standard ibuprofen. In search of novel compounds, Kumar et al \[^13\] also synthesized a series of substituted 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives (7) by cyclisation of carboxylic group of biphenyl-4-yloxy acetic acid in various reaction conditions. The target compounds was pharmacologically evaluated for their anti-inflammatory potential. Khan \[^14\] and Saxena et al \[^15\] synthesized 2-(coumarin-3-yl)-5-aryl-1,3,4-oxadiazole derivatives (8) and 5-[2-ylidene phenyl]-1,3,4-oxadiazole-2(3\(H\)) thione (9) respectively. All the oxadiazole derivatives were evaluated for their ability to inhibit carrageenan induced rat paw edema and showed good to moderate anti-inflammatory activity.
Analgesic activity

Jayashankar et al \cite{16} synthesized a series of novel ether-linked bis (heterocycle)s (10) via [3 + 2]-cycloaddition reaction of nitrile oxide with allyl alcohol followed by intramolecular 1,3-diploar cycloaddition reaction of nitrile imine with carbonyl group and showed good analgesic activity. Bhandari et al \cite{17} synthesized and screened a series of S- substituted phenacyl 1,3,4-oxadiazoles (11) derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid). These compounds were tested \textit{in vivo} for their analgesic activity. Eight new compounds, out of 18, were found to have significant analgesic activity in the acetic acid induced writhing model with no ulcerogenicity. Gilani et al \cite{18} synthesized a series of 1,3,4-oxadiazole (12a–g) derivatives of isoniazid in satisfactory yield and pharmacologically evaluated for their analgesic activity by known experimental models. Further, Akhter et al \cite{19} reported synthesis and analgesic activity of various aroylpropionic acid derivatives containing 1,3,4-oxadiazole nucleus (13a–i). The study showed that the cyclization of carboxylic group of aroylpropionic acids into an oxadiazole nucleus resulted in compounds having good analgesic effects with reduced gastric irritation.

\begin{align*}
R = a: & \text{C}_6\text{H}_5 \\
b: & 2-\text{C}_6\text{H}_4\text{Cl}
\end{align*}

\begin{align*}
R = & \text{H}, 4-\text{CH}_3, 2,4-(\text{CH}_3)_2 \\
R' = & [\text{H}; 2-\text{Cl}; 4-\text{Cl}; 4-\text{NO}_2]
\end{align*}
Antimicrobial activity

Chandrakantha et al \[20\] synthesized a new series of 1,3,4-oxadiazoles bearing 2-flouro-4-methoxy phenyl moiety (14) and their antimicrobial studies were performed. Few of the compounds showed significant antimicrobial activity. Joshi et al \[21\] synthesized a novel series of compounds (15) derived from 5-substituted-2-thiol-1,3,4-oxadiazoles. Compounds were evaluated for their preliminary in vitro antibacterial activity against some gram-positive and gram-negative bacteria. Some compounds showed very good antibacterial activity. Liu et al also \[22\] synthesized a series of novel sulfoxide derivatives containing 1,3,4-oxadiazole moiety and evaluated their antifungal activity. The bioassay results showed that the compound (16) possess high antifungal activity. El-eman et al \[23\] synthesized 5-(1-adamantyl)-2-substituted thio-1,3,4-oxadiazole. All the synthesized compounds were tested for in vitro activities against certain strains of gram positive and gram negative bacteria and the yeast like pathogenic fungus Candida albicans. Compound (17) was found as the most active derivatives particularly against gram positive bacteria.

\[
\begin{align*}
\text{R}= & \text{Substituted acid} \\
\text{R} = & \text{C}_6\text{H}_5; 2,6-\text{Cl}_2\text{C}_6\text{H}_3
\end{align*}
\]

Anticonvulsant activity

Lankau et al \[24\] synthesized a series of 3- and 5-aryl-1,2,4-oxadiazole derivatives and evaluated their anticonvulsant activity in a variety of models. These 1,2,4-oxadiazoles exhibit considerable activity in both pentylenetetrazole (PTZ) and maximal electroshock seizure.
(MES) models. Compound (18) was protective in the PTZ model in rats with an oral ED₅₀ of 25.5 mg/kg and in the MES model in rats with an oral ED₅₀ of 14.6 mg/kg. Neurotoxicity (rotarod) was observed with an ED₅₀ of 335 mg/kg. Gilani et al [25] synthesized a series of isoniazid incorporated derivatives of 1,3,4-oxadiazoles (19a-h) and found that all the compounds were active in MES and a majority of compounds were active in ScPTZ test. Zarghi et al [26] synthesized new 1,3,4-oxadiazoles (20) as anticonvulsant agents. Electroshock and pentylenetetrazole-induced lethal convulsion test showed that the induction of an amino group in position 2 of 1,3,4-oxadiazole ring had the best anticonvulsant activity.

Zarghi et al [27] synthesized a series of 2-substituted-5-(benzyloxyphenyl)-1,3,4-oxadiazoles (21) and evaluated their anticonvulsant activity both in PTZ and MES models. They proposed that anticonvulsant effect was mediated through benzodiazepine receptors mechanism. Almasirad et al [28] synthesized a new series of 2-substituted-5-[2-(2-fluorophenoxy) phenyl]-1,3,4-oxadiazoles and screened for their anticonvulsant activity. Compound (22) showed considerable anticonvulsant activity both in PTZ and MES models. The effect was supposed to be mediated by the benzodiazepine receptors and other unknown mechanism, respectively.

\[
\text{(18)}
\]

\[
\text{(19a-h)}
\]

\[
\text{(20)}
\]

\[
\text{(21)}
\]

\[
\text{(22)}
\]

**Anti-proliferative activity**

Ouyang et al [29] synthesized derivatives of oxadiazoles and evaluated their ability to inhibit tubulin polymerization and to arrest mitotic division of tumor cells. Among the synthesized compounds, 23 showed potent activity. Padmavathi et al [30] synthesized a new class of 1,3,4-oxadiazoles from acid hydrazides on treatment with different carboxylic acids.
in the presence of phosphorus oxychloride. Compound 24 exhibited maximum cytotoxicity. Aboriaa et al. synthesized a series of 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives and 13 of them were selected by the National Cancer Institute (NCI) and evaluated for their in vitro anticancer activity. These compounds have been selected for a full anticancer screening against a 60-cell panel assay where they showed non-selective broad spectrum and promising activity against all cancer cell lines. Compounds 25 and 26 proved to be the active members in this study compared to 5-fluorouracil and cyclophosphamide as reference drugs, respectively. Compounds 25 and 26 were identified as promising lead compounds. Gudipati et al. synthesized a series of 5- or 7-substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin-2-one by treating 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol with different isatin derivatives. All the synthesized derivatives were screened for anticancer activity against HeLa cancer cell lines using MTT assay. All the synthetic compounds produced a dose dependant inhibition of growth of the cells. The IC$_{50}$ values of all the synthetic test compounds were found between 10.64 and 33.62 μM. The potency (IC$_{50}$ values) of anticancer activity of compounds 27 was comparable with that of known anticancer agent, cisplatin. Among the synthesized 2-indolinones, compounds 27 with halogen atom (electron withdrawing groups) at C5 position showed the most potent activity. These results indicate that C5 substituted derivatives may be useful leads for anticancer drug development in the future. Kumar et al. developed a facile, convenient and high yielding method and synthesized a series of novel 5-(3'-indolyl)-2-(substituted)-1,3,4-oxadiazoles from readily available starting materials and screened for their in vitro anticancer activity against various human cancer cell lines. Compounds 28a, 28b and 28c exhibited potent cytotoxicity (IC$_{50}$~1 μM) and selectivity against human cancer cell lines.
Anti-mycobacterial activity

Mallikarjuna\(^{[34]}\) and Joshi et al\(^{[35]}\) synthesized a series of 4-isopropylthiazole-2-carbohydrazide analogs, derived clubbed oxadiazole-thiazole derivatives\(^{(29)}\) and 4-pyrrol-1-yl benzoic acid hydrazide analogs \(^{(30)}\). The synthesized compounds were evaluated for their preliminary \textit{in vitro} anti-tubercular activity against \textit{Mycobacterium tuberculosis} H\(_{37}\)R\(_{v}\) strain by broth dilution assay method. Some compounds showed very good anti-tubercular activity. Further, Ahsan et al\(^{[36]}\) synthesized a series of 1,5-dimethyl-2-phenyl-4-\{[5-aryl-1,3,4-oxadiazol-2-yl]methyl\}amino\}-1,2-dihydro-3\(H\)-pyrazol-3-one after molecular properties prediction by Molinspiration and MolSoft software. Among the compounds synthesized, compound \(^{(31)}\) was found to be active with MICs, 0.78 \(\mu\)M and 1.52 \(\mu\)M against MTB and INHR-TB, respectively.

\begin{center}
\begin{tabular}{ccc}
\(R_1\) & \(R_2\) & \(R\) \\
F & H & a 4-pyridyl \\
Cl & H & b 3-pyridyl \\
Br & H & c 4-BnO-3-CH\(_3\)OC\(_6\)H\(_3\) \\
\end{tabular}
\end{center}

\textbf{Anti/protozoal}

Ishii et al\(^{[37]}\) synthesized a series of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives \(^{(32)}\) and screened for their \textit{in vitro} activity against \textit{Trypanosoma cruzi}. The bioactivity was expressed as fifty-percent inhibitory concentration (IC\(_{50}\)) of
parasite population growth for *T. cruzi*. A molecular modeling approach was performed to establish qualitative relationships regarding the biological data and the compounds physicochemical properties. The 5-(4-CO$_2$CH$_3$Ph) derivatives was the most active compounds for *T. cruzi* (IC$_{50}$ = 7.91 lM). Durust et al. synthesized a series of novel oxadiazolyl pyrrolo triazole diones (33a-k). These novel heterocyclic compounds were investigated for their *in vitro* anti-protozoal activity and results found to be good.

![Chemical structure](image)

\( R = -C_2H_3O_2 \)

\( R = \)

- a: H
- b: Cl
- c: Br
- d: F
- e: CH$_3$
- f: I
- g: NO$_2$
- h: OCH$_3$
- i: SCH$_3$
- j: CF$_3$
- k: N(CH$_3$)$_2$

### Anti-diabetic

Shingalapur et al. synthesized a series of 1,3,4-oxadiazoles 34(a–j) containing 2-mercapto benzimidazole moiety and screened for *in vivo* antidiabetic activity using Oral Glucose Tolerance Test (OGTT). Some of the compounds showed excellent antidiabetic activity and also pharmacophore derived from active molecules suggested that presence of –OH group was a common feature in all active compounds. Zou et al. synthesized a series of furoxan-based nitric oxide-releasing chrysin derivatives (35). Pharmacological assays indicated that all chrysin derivatives exhibited *in vitro* inhibitory activities against aldose reductase and advanced glycation end-product formation. Some chrysin derivatives were also found to increase the glucose consumption of HepG2 cells. Furthermore, the compounds released a low amount of NO in the presence of L-cysteine (range from 0.20% to 1.89%). This hybrid furoxan-based NO donor chrysin derivatives offer a mutual prodrug design concept for the development of therapeutic or preventive agents for vascular complications due to diabetes.
R= Halogenated Aryl or Heterocyclic Ring

**Anthelmintics**

Bharathi et al \[^{41}\] synthesized 1,3,4-oxadiazole derivatives (36) by refluxing the mixture of aldehyde with semicarbazide hydrochloride in ethanol using sodium acetate as a catalyst. The newly synthesized compounds were tested for its anthelmintic activity. The results showed that the synthesized compounds showed good activity.

\[
\begin{align*}
&\text{R=CH}_8\text{H}_8\text{O}_3, \text{C}_9\text{H}_{10}\text{O}_3, \text{C}_7\text{H}_6\text{O}, \text{C}_7\text{H}_6\text{O}_2, \text{C}_7\text{H}_5\text{NO}_3, \text{C}_9\text{H} \\
&\end{align*}
\]

**MAO enzyme inhibitors**

Shaoyong et al \[^{42}\] synthesized a new series of 1,3,4-oxadiazole-3(2H)-carboxamide derivatives (37) by direct heterocyclization reaction of substituted benzoilisocyanate with various aroylhydrazones as novel monoamine oxidase inhibitors (MAOIs). The newly synthesized compounds were evaluated for their MAO inhibitory activity by Kynuramine Fluorimetric assay method. The preliminary results showed that most of the compounds have moderate inhibitory activities toward MAO at the concentration of $10^{-5}$–$10^{-3}$ M providing a novel class of lead compounds with potential MAO inhibitions for further optimization.

**4. CONCLUSION**

Oxadiazoles belongs to an important class of heterocyclic compounds and exhibits a wide range of biological properties. Few methods for the synthesis of oxadiazole have been reported. Thus by studying all the derivatives showing variety of activities it can be
concluded that oxadiazole ring have been explored in past years and is still be used for future development of new drugs against many more pathological conditions.

Acknowledgments

The authors are thankful to the Principal, KIET School of Pharmacy for motivation. Authors are also thankful to KIET library and NISCAIR, New Delhi for providing the literature.
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