Biologically Active 2,5-Disubstituted-1,3,4-Oxadiazoles

Harish Rajak1*, Murli Dhar Kharya2 and Pradeep Mishra3
1Medicinal Chemistry Division, SLT Institute of Pharmaceutical Sciences, Guru Ghasidas University, Bilaspur-495 009 (CG) INDIA.
2Natural Product Research Laboratory, Department of Pharmaceutical Sciences, Dr. H. S, Gour University, Sagar-470 003 (MP) INDIA.
3GLA Institute of Pharmaceutical Research, Mathura-281 406 (MP) INDIA.

ABSTRACT: There are vast numbers of pharmacologically active heterocyclic compounds in regular clinical use. The presence of heterocyclic structures in diverse types of compounds is strongly indicative of the profound effects such structure exerts on physiologic activity, and recognition of this is abundantly reflected in efforts to find useful synthetic drugs. The 1,3,4-oxadiazole nucleus has emerged as one of the potential pharmacophore responsible for diverse pharmacological properties. Medical Literature is flooded with reports of a variety of biological activities of 2,5-Disubstituted-1,3,4-oxadiazoles. The present work is an attempt to summarize and enlist the various reports published on biologically active 2,5-disubstituted-1,3,4-oxadiazoles.

KEYWORDS: 1,3,4-oxadiazoles, anti-inflammatory activity, hypoglycemic activity, anticonvulsant activity, antiallergic activity, antimicrobial activity, anticancer activity.

Introduction

Compounds having a five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles and in the older literature were known furadiazoles. Four types of oxadiazoles are known, namely 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles. Out of these 1,3,4-oxadiazoles are found to be most potent, biologically.

Much attention has been paid to 1,3,4-oxadiazole derivatives in recent years, because they display anti-inflammatory, hypoglycemic, anticonvulsant, antimicrobial and other activities. A literature summary of biologically active 1,3,4-oxadiazoles is presented in this review.

NSAIDs (Non-steroidal anti-inflammatory drugs) are widely used for the treatment of pain, fever and inflammation particularly arthritis. NSAIDs reduce the inflammation and pain associated with arthritis by blocking metabolism of arachidonic acid by the enzyme cyclooxygenase (CO) and thereby the production of prostaglandins. In chronic use of NSAID’s, one of the prominent side effects is formation of gastric ulcers. This adverse effect may be attenuated in the presence of an inhibitor of 5-lipoxygenase (5-LO). 1,3,4-oxadiazoles found to possess anti-inflammatory properties by virtue of dual mechanism, i.e., inhibit both CO and LO reducing the gastric ulcer formation (Palomer AT et al., 2002; Warner TD et al., 1999; Smith CJ et al., 1998).

Some 1,3,4-oxadiazole derivatives have found to exert their anti-inflammatory effect via cyclooxygenase and 5-lipoxygenase inhibitory activity (Kramer et al. 1993).
One of the important factors responsible for GI damage is local irritation by carboxylic acid moiety. On the other hand, it has been reported in literature that compounds bearing 1,3,4-oxadiazole nucleus possess significant anti-inflammatory activity. Replacement of the carboxylic acid group of diclofenac with 1,3,4-oxadiazole nucleus in novel compounds, resulted in appreciable anti-inflammatory activity in carrageenan-induced rat paw edema test (Amir et al., 2004).

Some new 2-thio-3-(substituted-aminomethyl)-5-(3,5-dinitrophenyl)-1,3,4-oxadiazoles has been found to possess considerable anti-inflammatory property (Nigam et al., 1992).

With the aim of discovering dual inhibitors of 5-lipoxygenase (LO) and cyclooxygenase (CO) with improved pharmacokinetic properties, a series of 5-(6-methyl-2-substituted-4-pyrimidyloxymethyl)-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives exhibited anti-inflammatory activity and some of them were more active than acetylsalicylic acid (Jakubkienė et al., 2003).

The replacement of carboxylic acid functionality of several fenamates (N-arylanthranilic acid) with 1,3,4-oxadizole nucleus resulted in dual inhibitors of CO and LO when tested in an intact rat basophilic leukemia (RBL-1) cell line. These heterocyclic analogs of ibufenamic acid are also active in carrageenan-induced rat foot pad edema (CFE), a model of acute inflammation (Boschelli et al., 1993).

A number of 2-(2-naphthyloxymethyl)-5-substituted amino-1,3,4-oxadiazoles were synthesized for their anti-inflammatory activity (Palaska E et al., 2002).

The anti-inflammatory evaluation of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)sulfanylmethyl]-1,3,4-oxadiazole-2-thiones revealed that some of these derivative were much more potent than ibuprofen (Burbuliene NM et al., 2004).

Most of the compounds of series 5-(6-methyl-2-substituted-4-pyrimidyloxymethyl)-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives exhibited anti-inflammatory activity and some of them were more active than acetylsalicylic acid (Jakubkienė et al., 2003).
Some 5-(4-pyridyl)-4-(substituted methyl)-1,3,4-oxadiazoline-2-thione hydrochloride has also been found to possess anti-inflammatory activity (Singh et al., 1986).

Potent anti-inflammatory activity has been reported in 2-(substituted aryl)-5-(substituted phenyl)-1,3,4-oxadiazoles (Kumar et al., 1987).

Some 3-pentadecylphenol derivatives containing the 1,3,4-oxadiazole nucleus have been found to exhibit good anti-inflammatory activity (Ramalingam T and Sattur PB, 1990; Ramalingam T and Sattur PB, 1987).

Anti-inflammatory potential of substituted oxadiazoles i.e., 2-aryl amino-5-(4-biphenoxymethyl)-1,3,4-oxadiazoles was reflected in their ability to provide 36 to 76% protection in carrageenan-induced rat paw edema method (Raman et al., 1983, 1989).

A series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives were also evaluated for their anti-inflammatory activity (Omar et al., 1996).

Two novel series of compounds i.e., 1,3,4-oxadiazole and oxadiazoline analogues were synthesized for their potential anti-inflammatory activity, using the carrageenan-induced rat paw edema method and cotton pellet-induced granuloma method. Some compounds demonstrated marked anti-inflammatory activity. They concluded that in general, all oxadiazoles have greater anti-inflammatory activity than their corresponding oxadiazoline analogues (Rajak et al., 2007).

Besides above studies, several other research groups have also reported anti-inflammatory properties in oxadiazole compounds (Kishore et al., 1975; Saxena et al., 1992; Schrier DJ et al., 1994; Sawhney SN and Gupta A, 1991; Nargund LVG et al., 1994; Tozkoparan B et al., 2000; Kalsi et al., 1988; Najer et al., 1966).

**Hypoglycemic Activity**

Some novel oxadiazole derivatives have also been synthesized to discover hypoglycemic agents (Hanna et al., 1995).
Some 2-arylamino-5-(2-naphthoxyethyl)-1,3,4-oxadiazole derivatives have exhibited considerable oral hypoglycemic activity (Hussain et al., 1986).

A series of 1,3,4-oxadiazole analogues, i.e., 2-arylamino-3-{3-aryl-4-oxaquinozolin-2-yl(methylamino)phenyl}-1,3,4-oxadiazoles have been found to possess oral hypoglycemic activity (Husain MK and Jamali MR, 1988).

A series of 2,5-disubstituted 1,3,4-oxadiazoles derivatives with different substituents were synthesized for their hypoglycemic activity (Girges MM, 1994).

Two other research groups, also reported hypoglycemic activities in oxadiazoles (O’neal et al., 1962; Hokfelt et al., 1962).

Anticonvulsant Activity

A novel series of 2-substituted amino-5-aryl-1,3,4-oxadiazole derivatives were synthesized for their anticonvulsant properties (Omar AMME and Aboulwafa OM, 1984).

Some 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazole derivatives were synthesized and evaluated as anticonvulsant agents (Zarghi et al., 2005).

In this study, Electroshock and Pentylene tetrazole-induced lethal convulsion tests showed that the introduction of an amino group in position 2 of 1,3,4-oxadiazole ring and a fluoro substituent at para position of benzylthio moiety had the best anticonvulsant activity.

Some Mannich bases like 5-{3,4-methylenedioxyphenyl}-3-arylaminomethyl-1,3,4-oxadiazole-2-thiones, were synthesized for their anticonvulsant properties (Choudhary et al., 1978).

Some of the compounds, i.e., 2-substituted-5-{2-[2-fluorophenoxy]phenyl}-1,3,4-oxadiazoles and -1,2,4-triazoles showed considerable anticonvulsant activity in PTZ and MES models (Almasirad A et al., 2004).
Some of compounds of a novel series of 2-[(2-alkoxy-3-methoxyphenyl) methyl]-5-arylamino-1,3,4-oxadiazoles were found to possess significant anticonvulsant activity (Tsitsa P et al., 1989).

A new series of 2-substituted-5-[2-(2-halobenzyloxy)phenyl]-1,3,4-oxadiazoles were designed and synthesized for their anticonvulsant activity. Electroshock and pentyleneetrazole-induced lethal convolution tests showed that the introduction of an amino group at position 2 of 1,3,4-oxadiazole ring and a fluoro substituent at ortho position of benzyloxy moiety had the best anticonvulsant activity. They also reported that anticonvulsant effect of studied oxadiazoles is mediated through benzodiazepine receptors (Zarghi et al., 2008).

The anticonvulsant properties were also reported in structurally diverse 2,5-disubstituted-oxadiazoles (Singh HH et al., 1973).

**Enzyme inhibitors**

The monoamine oxidase, pyruvate oxidase and succinate dehydrogenase inhibitory properties were reported in some 3-arylaminomethyl-5-(2-hydroxy-3,5-dibromophenyl)-1, 3, 4-oxadiazole-2-thiones (Soni et al., 1982).

The monoamine oxidase inhibitory property was studied in some 5-aryl-3-(2-cyanoalkyl)-1,3,4-oxadiazol-2(3H)-ones and 5-aryl-3-(2-cyanoethyl)-1,3,4-oxadiazol-2(3H)-thiones (Mazouz et al., 1990; Mazouz et al., 1993).

**Antiallergic Activity**

The in-vitro serotonin-3-antagonist activities were found positive in some new 1,3,4-oxadiazole-2-thione derivatives (Pramanik SS and Mukherjee A., 1998).

The H2-antagonistic activity of N, N'-1,3,4-oxadiazole-2, 5-diamines has been reported (Kramer VI and Schunack W., 1986).

**Antimicrobial Activity**

Over the last few decades, the rapid emergence of drug resistance in the treatment of infectious diseases emphasizes worldwide need for novel antimicrobial agents. So present scenario greatly demands newer, safer and effective antimicrobial agents that will overcome this problem. A number of researchers have reported antimicrobial activities in 1,3,4-oxadiazoles.

A series of 2- amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazoles were screened for their antibacterial activity. In this study, some of the compounds shown significant results (Sherman WR, 1961).
A series of 5-substituted 1,3,4-oxadiazole-2-thiones have been synthesized for their antibacterial properties (Dighe VS et al., 1963; Wildersmith AE et al., 1962).

The tuberculostatic and leprostatic properties in a series of 5-(4-pyridyl)-1,3,4-oxadiazole-2-thione, and 5-(4-pyridyl)-1,3, 4-oxadiazole-2-one were reported (Wildersmith AE, 1964).

12 Two aryloxyaryl methyl-1,3,4-oxadiazoles derivatives were designed and synthesized for screening against A. niger and H. oryzae and were found to possess moderate to fairly good antifungal activity (Sharma RS and Bahel SC, 1982).

With the aim of discovering antibacterial compounds, some 2-phenylamino-5-(β-aryl ethyl)-1,3,4-oxadiazoles were synthesized and evaluated for antimicrobial properties (Andotra et al., 1986).

The Mannich bases, sulphides and disulphides of 1,3,4-oxadiazole-2-thiones had exhibited antifungal activity (Tewari et al., 1991). The antimicrobial activity has been reported in 5-aryl-2-[N-(5-nitrofurfurylidene)] and 5-aryl-2-(N-thiocarbamoylamino)-1,3,4-oxadiazoles (Kapoor et al., 1991).
A series of N-alkylated-2-amino-1,3,4-oxadiazoles were synthesized for their antimitotic activity (Rai KML and Linganna N, 2000).

\[
\begin{align*}
\text{R} & \text{N} - \text{O} - \text{N} \quad \text{(CH}_2\text{)}\text{Br} \\
\text{N} & \text{O} - \text{N} \quad \text{(CH}_2\text{)}\text{Br}
\end{align*}
\]

Antitubercular activity in 2,5-disubstituted 1,3,4-oxadiazole derivatives was reported (Chaudhari et al., 1995).

\[
\begin{align*}
\text{R} & \text{N} - \text{S} - \text{R} \\
\text{O} & \text{N} - \text{N} - \text{NH} \quad \text{CH}_3 \\
\text{H} & \\
\end{align*}
\]

A series of 5-(4'-acetamidophenoxy)methyl)-2-mercaptoacetyl-N-arylureido-1,3,4-oxadiazole derivatives were found to possess antiviral and bactericidal activities (Shukla et al., 1980).

\[
\begin{align*}
\text{Ac} & \text{N} - \text{H} - \text{O} \quad \text{CH}_2 - \text{S} - \text{R} \\
\text{R} = & \text{CH}_2 \text{CONHCONH} \text{R}
\end{align*}
\]

A series of 2-aryl/aralkyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazoles were synthesized and exhibited fungicidal activity on antifungal evaluations (Dutta et al., 1986).

\[
\begin{align*}
\text{Cl} & \text{Cl} \\
\text{O} & \text{N} - \text{Cl} - \text{N} - \text{Ar}
\end{align*}
\]

Antibacterial activity in 5-(benzothiazole-2-ylthiomethyl)-2-phenylamino-1,3,4-oxadiazole, 5-benzothiazole-2-ylthiomethyl)-2-amino-1,3,4-oxadiazole and 5-(benzothiazole-2-ylthiomethyl)-1,3,4-oxadiazole-2-thione has been reported (Radha Rani et al., 1990).

\[
\begin{align*}
\text{O} & \text{N} \quad \text{S} - \text{CH}_2 - \text{N} - \text{H}
\end{align*}
\]

A series of novel 5-(1-2-naphthoxy)methyl)-1,3,4-oxadiazole-2(3H)-thione, 2-amino-5-(1-2-naphthoxy)methyl)-1,3,4-oxadiazole-2(3H)-one derivatives were synthesized for their antimicrobial activity. All the compounds were active against S. aureus, E. coli, P. aeruginosa, C. albicans and C. parapsilosis at concentration 64-256 µg/mL (Sahin et al., 2002).

The antimicrobial and anti-HIV-1 activity (using XTT assay) of certain 5-(1-adamantyl)-2-substitutedthio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted antimethyl-1,3,4-oxadiazolines-2-thiones was evaluated (El-Emam AA et al., 2004).

\[
\begin{align*}
\text{O} & \text{N} \quad \text{S} - \text{CH}_2 - \text{N} - \text{H}
\end{align*}
\]

A series of novel 5-(1-2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3H)-thione, 2-amino-5-(1-2-naphthoxy)methyl)-1,3,4-oxadiazole, 4-oxadiazole, 5-(1-2-naphthoxy)methyl)-1,3,4-oxadiazole-2(3H)-one derivatives were synthesized for their antimicrobial activity. All the compounds were active against S. aureus, E. coli, P. aeruginosa, C. albicans and C. parapsilosis at concentration 64-256 µg/mL (Sahin et al., 2002).

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\[
\begin{align*}
\text{O} & \text{N} \quad \text{S} - \text{CH}_2 - \text{N} - \text{H}
\end{align*}
\]

The antimicrobial activity of a new series of 2-{4-[2-(5-ethylpyridin-2-yl) ethoxy]phenyl}-5-substituted-1,3,4-oxadiazoles was reported (Gaonkar SL et al., 2006).

\[
\begin{align*}
\text{N} & \text{O} \quad \text{S} - \text{CH}_2 - \text{N} - \text{H}
\end{align*}
\]

Bis-1,3,4-oxadiazole derivatives were found to possess antibacterial, antifungal and genotoxic activities (Maslat et al., 2002).
Antibacterial and antiamebic activities were reported in a series of structurally simple 1,3,4-oxadiazoles (Kachroo PL et al. 1990).

Certain new 1,3,4-oxadiazole derivatives having mercapto and carboxymethylthio moieties were reported. Among these, some of the oxadiazoles were found to possess good antimicrobial activity as compared to standard drug norfloxacin (Dabhi TP et al., 1992).

The fungicidal activity was reported in a series of diheterocyclic compounds containing 1,2,4-triazolo[1,5-a]pyrimidine and 1,3,4-oxadiazole rings (Liu Z et al., 2001).

In an investigation, new N'-aryl-N 3-2-p-chlorophenyl-1,3,4-oxadiazol-5-ylacylureas were synthesized and evaluated for their antimicrobial potential (Mehta L and Parekh H, 1988).

Sixteen new 3-aryliminomethyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thiones and six 3-alkyl aryl/alkyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thiones were synthesized for their fungicidal activity against Curvularia verruciformis and Alternaria tenuis (Nath SC, 1984).
Some 2,5-disubstituted-1,3,4-oxadiazoles were synthesized and screened for anti-tubercular activity against *M. tuberculosis* H$_3$Rv (Macaev F et al., 2005).

Fifteen novel (E)-α-(methoxyimino)-benzene acetate derivatives containing 1,3,4-oxadiazole nucleus were found to possess potent fungicidal activity against *R. Solani* than Kresoxim-methyl (Li Y et al., 2006).

Antimicrobial and anti-inflammatory activities were reported in novel 2-substituted-5-(1-adamantyl)-1,3,4-oxadiazoles and 2-substituted-5-(1-adamantyl)-1,3,4-thiadiazoles. Several derivatives showed good to moderate antibacterial activity particularly against the tested Gram-positive bacteria *Bacillus subtilis* and marked antifungal activity against *Candida albicans* (Kadi AA et al. 2007).

Insecticidal Activity
1,3,4-oxadiazole is among very few pharmacophores known for its insecticidal activity. A novel series of 2-fluorophenyl-5-aryl/cyclopropyl-1,3,4-oxadiazoles were evaluated for their insecticidal potential (Shi W et al., 2000).

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Mannich bases derived from substituted oxadiazole-2-thiones were found to possess insecticidal activity. These compounds were also screened for antimicrobial properties (Sengupta AK et al. 1979).

The insecticidal activity of a number of substituted 1,3,4-oxadiazoles derived from 2-chloropyridine-5-acetic acid were reported (Holla BS et al., 2004).

Eight 2-(5-(trifluoromethyl)-pyridyloxymethyl)-1,3,4-oxadiazoles were designed and synthesized for their insecticidal activity. Two of these oxadiazoles exhibited significant insecticidal activity on armyworm, *Leucania separate walker* at 500 mg/L (Cao S et al., 2002).

Insecticidal activity was also reported in structurally diverse analogues of 2,5-disubstituted-1,3,4-oxadiazoles (Sengupta A K and Singh B, 1979).

Fourteen new 2,5-disubstituted-1,3,4-oxadiazoles, namely (i) six 2-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl]-5-substituted-1,3,4-oxadiazoles and (ii) eight 2-substituted-phenoxy-methyl-5-substituted-aryl-1,3,4-oxadiazoles, were synthesized for their insect growth regulatory activity against second-instar larvae of armyworm (*Pseudaletia separata* Walker). Two of these compounds showed good insecticidal activity, with LC(50) values of 14.33 and 15.85 μg/mL, respectively (Shi W et al., 2001).

**Anticancer Activity**

A series of 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives were evaluated for their in-vitro anticancer activity, where seven out of twenty two synthesized compounds displayed high anticancer activity, in the primary assay. These seven oxadiazole compounds were 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. As a result of 60-cell panel assay two oxadiazole compounds were identified as promising lead compounds (Aboraia AS et al., 2006).

**Other Activities**

A novel series 1-[3,3-diphenyl-3-(2-alkyl-1,3,4-oxadiazol-5-y] propyl] cycloalkylamines were found to possess antidiarrheal activity (Adelstein GW et al., 1976).
Some 2-(β-arylethyl)-5-phenylamino-1,3,4-oxadiazoles were synthesized for their in-vitro amoebicidal activity against *E. histolytica*. These compounds exhibited very mild to moderate amoebicidal activity as compared with the standard drug metronidazole (Andotra CS et al., 1989).

A series of new 2,5-disubstituted-1,3,4-oxadiazoles carrying 1,2-diarylethyl/aryloxyalkyl moieties at 2-position and phenyl, amino, mercapto, thioacetic acid or ethyl thioacetate groups at 5 position exhibited CNS depressant activity in experimental animals (Ramalingam T et al., 1981).

The antidepressant property has also been reported in indolmethyl-1,3,4-oxadiazoles (Misra U et al., 1996).

A combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues for their tyrosinase inhibitory activity was reported (Khan MTH et al., 2005). The structure-activity relationship among the library compounds was also discussed. Tyrosinase (Polyphenol oxidase) is known to be a key enzyme for melanin biosynthesis in plants and animals. Therefore, tyrosinase inhibitors should be clinically useful for the treatment of some dermatological disorders associated with melanin hyper pigmentation and also important in cosmetics for whitening and depigmentation after sunburn.

Coumarin derivatives as well as oxadiazole derivatives were reported to possess anthelmintic properties. The compounds were designed in such a manner so as to contain these two pharmacophores in a single structure i.e., 3-(substituted amino-(-NR'R''methyl)-5-(4-methyl-7-coumarinyl oxymethyl-1,3,4-oxadiazolin-2-thione. Later compounds were found to possess excellent anthelmintic properties (Husain MI and Shukla MK, 1978).

The replacement of carboxamide group of antiarrrhythmic 4-dialkylamino-2,2-diarybutyramide analogs by oxadiazole moiety resulted in a considerable decrease in antiarrrhythmic activity (Adelstein GW, 1973).

Current treatments for chronic hepatitis B virus (HBV) infection include the use of interferon-α and of nucleoside analogs lamivudine, adefovir and entecavir. Besides this recently, anti-hepatitis B virus activities in oxadiazoles has been reported (Tan TMC et al., 2006). 1-{2-[5-(1-Benzene sulfonyl-propyl)-[1,3,4]oxadiazol-2-yl-sulfanyl]-ethyl}-4-(2-methoxy-phenyl)-piperazine was found to inhibit the expression of the viral antigens, HBsAg and HBeAg in a concentration-dependent manner with no cytotoxic effects and without any effects on the expression of viral transcripts. The inhibition of virion production was found comparable to that of lamivudine and EC50 values of 1.63 and 2.96 μM were obtained for one of oxadiazole derivatives and lamivudine, respectively.

A series of novel N-[5-(4-substituted) phenyl-1,3,4-oxadiazol-2-yl]-2-(substituted)-acetamides were designed and synthesized for their local anesthetic activity (Rajak H et al., 2008).


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