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Pharmaceutical Sciences **Review Article……!!!**

OXADIAZOLE AND ITS REACTIVITY: A REVIEW ON CHEMICAL PROPERTIES/ BEHAVIOUR OF OXADIAZOLE NUCLEUS

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KEYWORDS:

Oxadiazole; Chemical Reactivity; pharmacological Activities; Marketed drugs.

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ABSTRACT

Oxadiazole is an aromatic heterocyclic compound that contains an oxygen atom and two nitrogen atoms in a five-membered ring. The molecular formula of Oxadiazole is **C2H2N2O.** Oxadiazole moiety shows pharmacological activities such as anti-tubercular activity, anti-inflammatory, analgesic activities, antiviral activity, anticancer activity, antimicrobial activity, and antioxidant activity. The present review article has discussed the Oxadiazole chemistry, preparation methods, biological activities, and marketed drug having Oxadiazole nucleus with special reference of the various chemical reactivity which gives even more effective derivatives.

INTRODUCTION:

The new era of heterocyclic moieties which are developed in the past few decades plays a very significant role in the treatment of various diseases where **oxadiazole** constitutes an important class for new compounds development. There is the total of four isomers of Oxadiazole are exist among them **1,3,4-oxadiazoles** play a key role in the synthesis of newer medicinal compounds. **Ainsworth** in 1965, for the first time, prepared 1,3,4-Oxadiazole by the thermolysis of ethyl formate, formally hydrazine, at atmospheric pressure. Previously it had common names like oxybiazole, diazoxole, furo(bb')diazole, biozole, and then common names were replaced by the **IUPAC name** 1,3,4-oxadiazole. [1]

The existing isomers of Oxadiazole (Figure 1.6) depending on the position of nitrogen atoms present in the ring namely as 1,2,3- Oxadiazole **(1)**, 1,2,4-oxadiazole **(2),** 1,2,5-oxadiazole **(3),** and 1,3,4-oxadiazole **(4)** but one of them 1,2,3-oxadiazole isomer (1) is unstable ring open to form the diazo ketone tautomer. 1, 3, 4-Oxadiazole is an important isomer among the class of oxadiazoles because of its use in the treatment of various biological activities, such as the proliferation of cells, tuberculosis, allergy, viral diseases, etc. [2] These first four isomeric Oxadiazole was reported by Belgian Workers. [3]

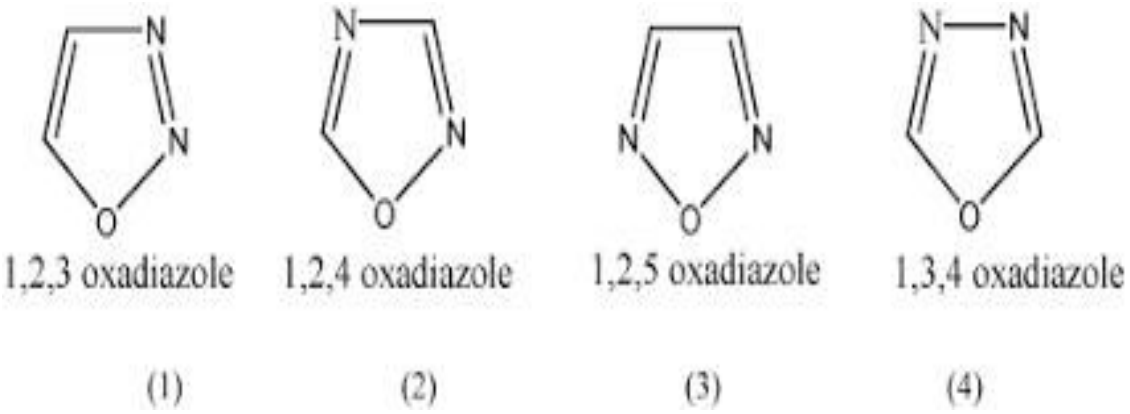


Figure 1 Isomers of oxadiazoles

It was revealed by the data of **Web of Science**, since 2000 the scientific attention of 1, 3, 4-oxadiazoles applications is continuously rising (Figure 2). [4]

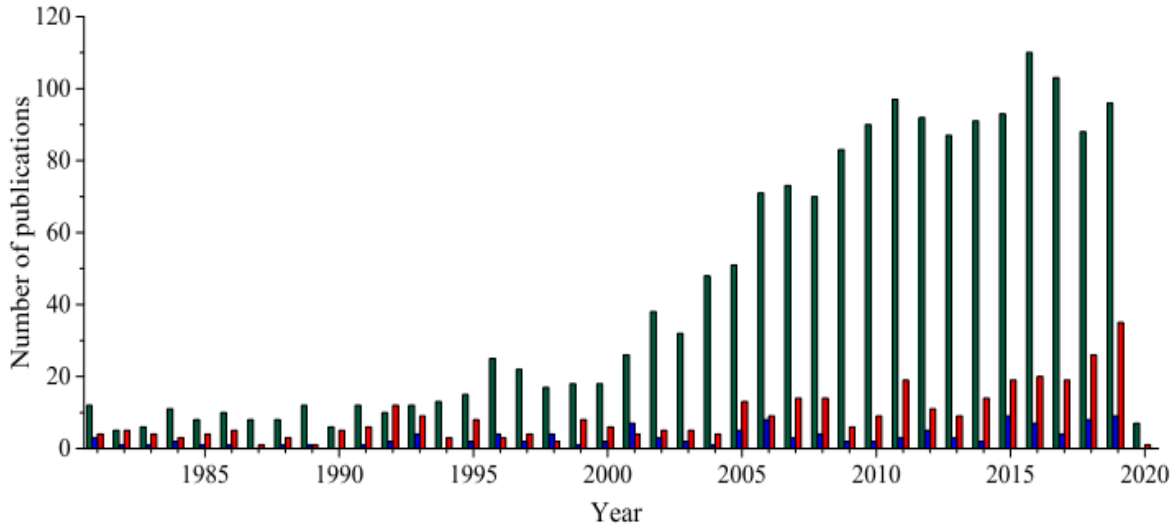


Figure 2 Number of publications containing the keywords: "1, 2, 4-oxadiazole" (red), "1, 2, 5-oxadiazole" (blue), and "1, 3, 4-oxadiazole" (green) in their title since 1980

CHEMISTRY OF OXADIAZOLE

The oxadiazole chemistry has been searched utterly and is still searching. The -N=C-O- linkage can react with the nucleophilic centers of malignant cells and exhibit its biological activity. ln other cases, oxadiazoles have been described as bioisosteres foresters, carboxylic acids, and carboxamides. Through non-covalent interactions, Oxadiazole ensures the connection with targets by using their electronic and charge-transporting properties. Extra heteroatom in Oxadiazole exhibits an inductive effect which makes it a very weak base. The oxadiazole ring shows the character of conjugated diene because the aromaticity of oxadiazole is reduced when the replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) occurs. The carbon atom of the Oxadiazole ring possesses low electron density which leads to difficulty for electrophilic substitutions but if the oxadiazole ring is substituted with electron-releasing groups, the attack of electrophiles occurs at nitrogen. Oxadiazole undergoes nucleophilic substitution with replacement of halogen atom in case of Halogen-substituted Oxadiazole, by nucleophiles. [5]

PREPARATION OF OXADIAZOLE

Various methods for synthesizing Oxadiazole are given below. [5, 1, 6, 7, 8]

1. From substituted acid hydrazide
2. From condensation of 2-thienyl hydrazide
3. From acyl urea
4. From cyclodehydrogenation using phosphorus oxychloride ($POCl_3$)
5. From cyclization of semicarbazid

REACTIVITY OF OXADIAZOLE

The chemical properties or reactivity of Oxadiazole can be defined by the following flow chart (Figure 3). [9, 10, 5]

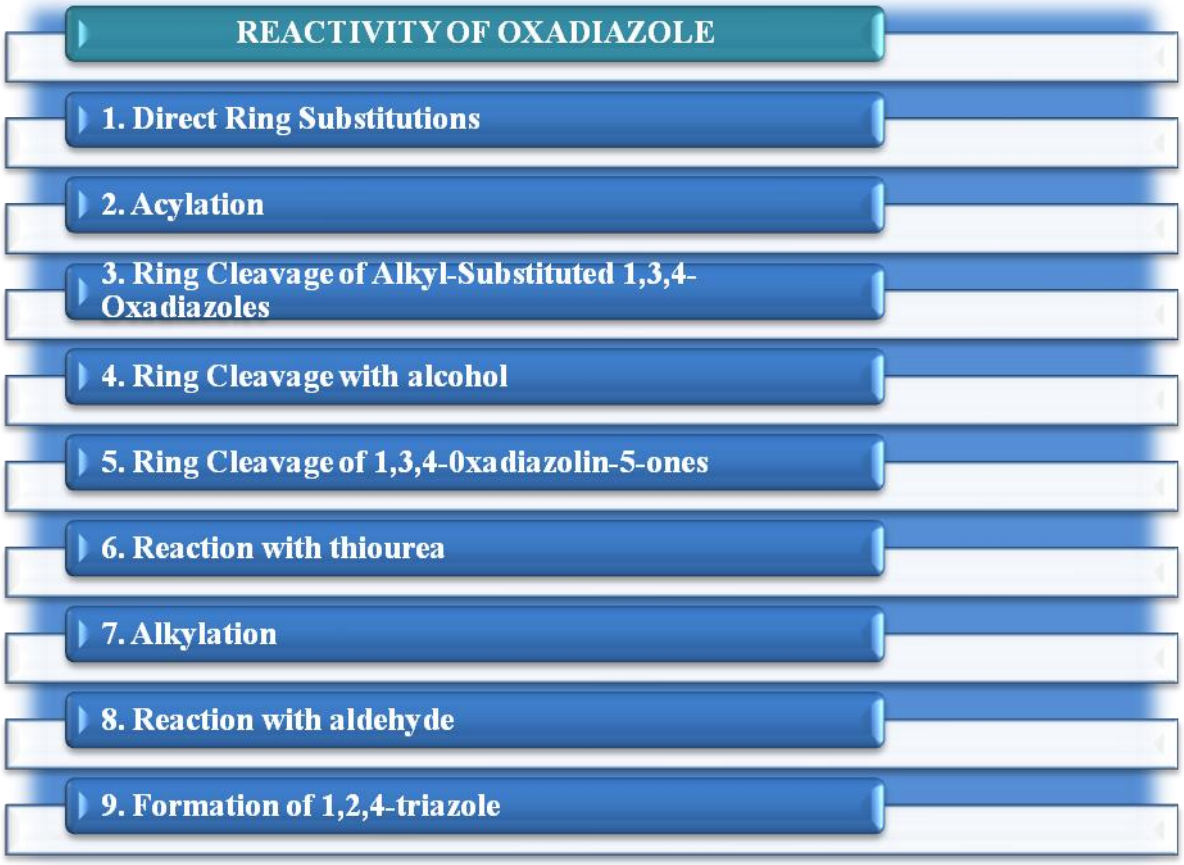
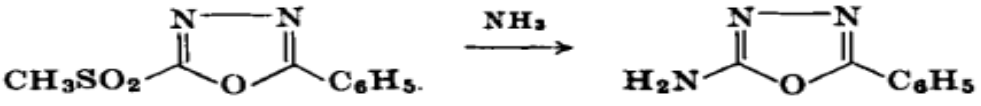


Figure 3 Systemic diagram of Reactivity of Oxadiazole

1. Direct Ring Substitutions

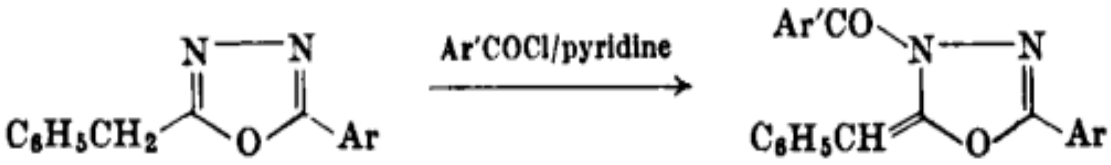
The direct substitution of functional groups into the oxadiazole nucleus is the least possible. For nucleophilic substitution, we have the example of ammonolysis of 2-phenyl-5-methanesulfonyl-l, 3, 4-oxadiazole which gives 2-phenyl-5-amino-l, 3, 4-oxadiazole in less yield (Scheme 1).



(Scheme 1)

2. Acylation

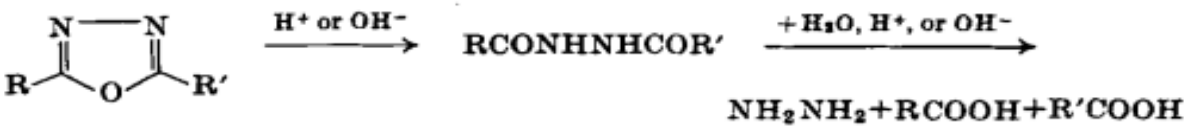
In the presence of aromatic acid chlorides and pyridine 2-benzyl-5- aryl-l, 3, 4-oxadiazole, because of its active methylene group, is acylated into 2-benzylidene-3-aroyl-5-aryl- 1,3,4-oxadiazoline (Scheme 2).



(Scheme 2)

3. Ring Cleavage of Alkyl-Substituted 1, 3, 4- Oxadiazoles

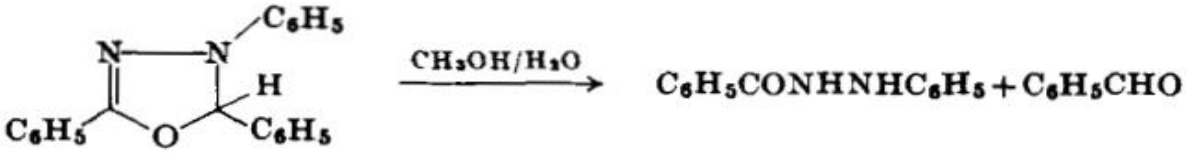
Acidic or basic treatment of the 2, 5-dialkyl-1, 3, 4-oxadiazoles leads ring cleavage and gives the product carboxylic acids and hydrazine or acid hydrazides (Scheme 3).



(Scheme 3)

4. Ring Cleavage with alcohol

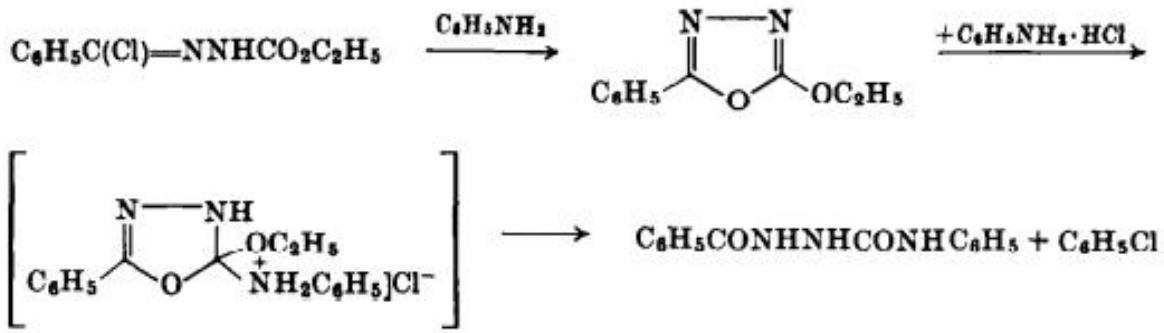
2, 3, 5-Triphenyl-2, 3-dihydro-l,3,4-oxadiazole is treated with boiled aqueous methanol which leads to ring cleavage and gives benzoyl-2-phenylhydrazine and benzaldehyde (Scheme 4).



(Scheme 4)

5. Ring Cleavage of 1, 3, 4-0xadiazolin-5-ones

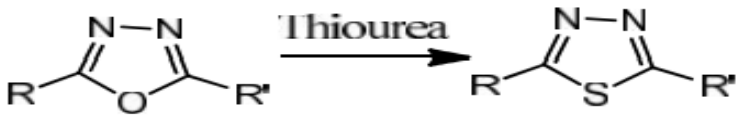
The reaction of aniline to alpha chlorobenzal carbethoxyhydrazone yield 2-phenyl-5-ethoxy-l, 3, 4-oxadiazole which further reacts with aniline hydrochloride, finally gives open-chain phenylsemicarbazide and ethyl chloride (Scheme 5). [9]



(Scheme 5)

6. Reaction with Thiourea

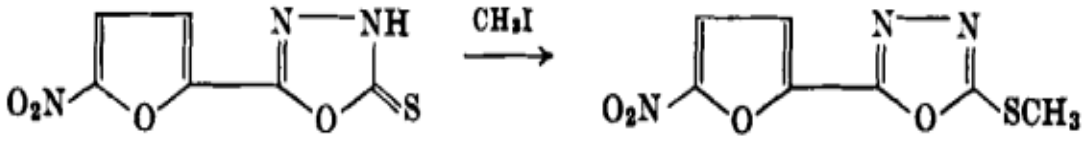
2,5- diaryl- 1,3,4-oxadiazole reacts with thiourea under reflux temperature for 3 to 4 days and gives 2,5-diaryl-1,3,4- thiadiazole, but only 2 to 5% of oxadiazoles gets converted to thiadiazoles (Scheme 6).



(Scheme 6)

7. Alkylation

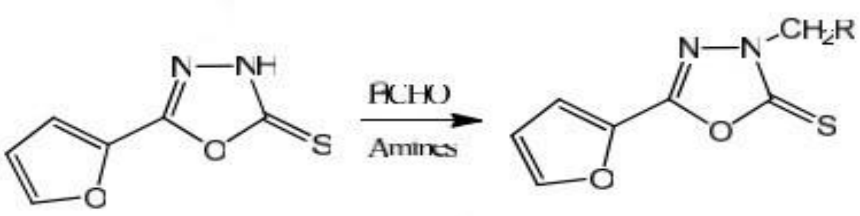
Alkylation can be done by methylation of 2-(2-nitro-5-furyl) 1, 3, 4-oxadiazoline-5-thionein the presence of methyl iodide, and this reaction gives 2-(2-nitro-5-furyl)-5- methylthio-l,3,4-oxadiazole as a product (Scheme 7).



(Scheme 7)

8. Reaction with Aldehyde

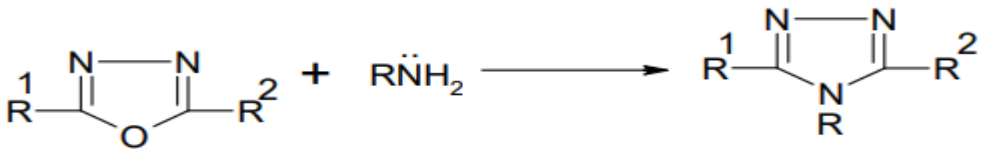
A series of Mannich bases of 5-furan- 2-yl[1,3,4]oxadiazole-2-thiol can be obtained by its reaction with suitably substituted amines and formaldehyde in the presence of ethanol (Scheme 8). [10]



(Scheme 8)

9. Formation of 1, 2, 4-triazole

The formation of hydrazine derivative which may further recyclize to form 1, 2, 4 –triazoles can be obtained by the reaction of alkyl or aryl- 1, 3, 4-oxadiazoles with a nucleophile (Scheme 9). [5]



(Scheme 9)

PHARMACOLOGICAL ACTIVITY OF 1, 3, 4-OXADIAZOLE

1, 3, 4-Oxadiazole heterocyclic ring is one of the most important heterocyclic moieties because of its versatile biological actions. The presences of the ring skeleton exert potential anti-tubercular activity, anti-inflammatory, analgesic activities, antiviral activity, anticancer activity, and antimicrobial activity. It is also reported that 1, 3, 4-oxadiazole bearing fused thiophene derivatives have antioxidant activity. In addition, 1, 3, 4-oxadiazole containing thiazole moiety shows antimicrobial and cytotoxic activities. It was also found that oxadiazole-bearing chromene derivatives have potential antibacterial and antifungal properties. Furthermore, pyridazine derivatives show interesting antifungal activity. Also, phenyl-bearing oxadiazole exerts versatile biological properties, such as antimicrobial and cytotoxic activity and anti-inflammatory activity. The systematic chart compiling the pharmacological activity of 1, 3, 4-oxadiazole derivatives is shown below (Figure 4). [11] - [25]

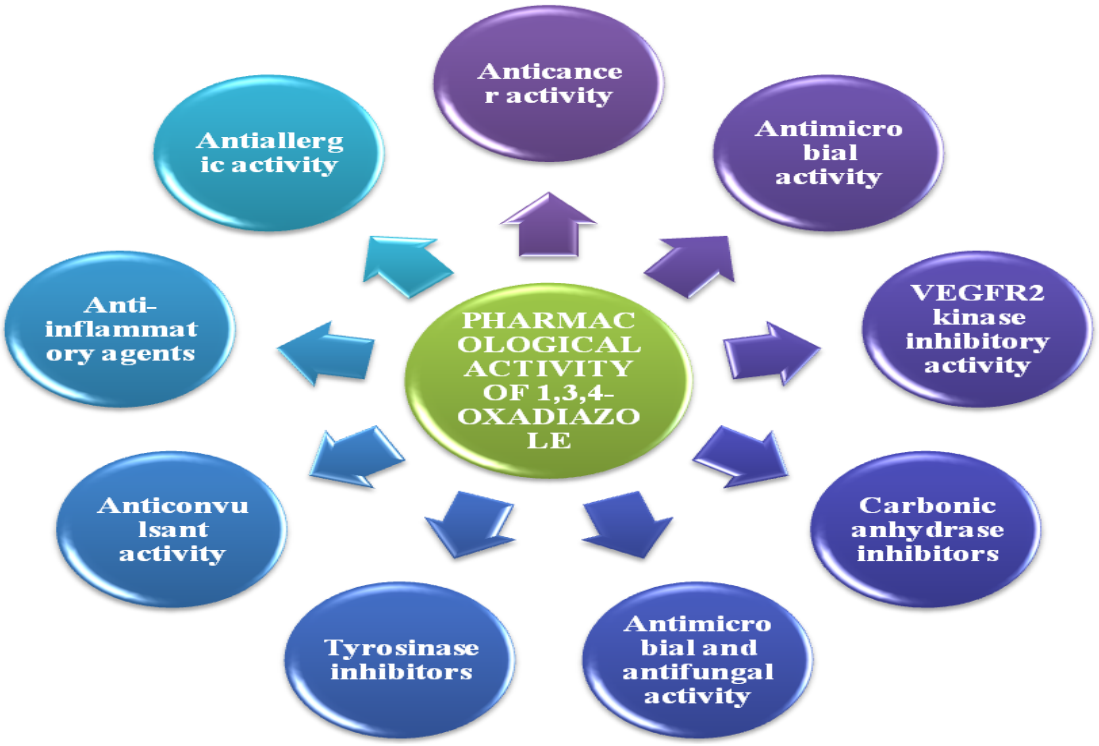
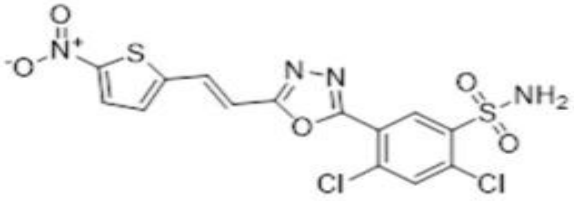
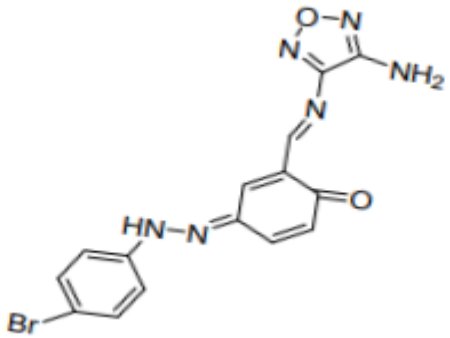
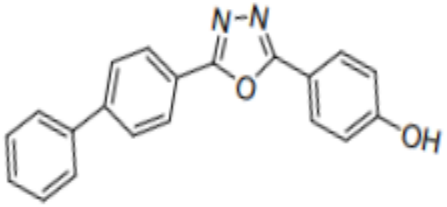
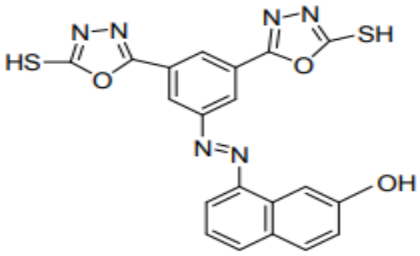
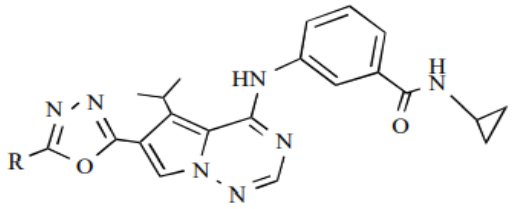
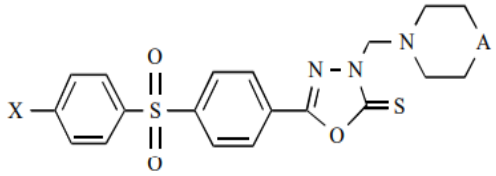
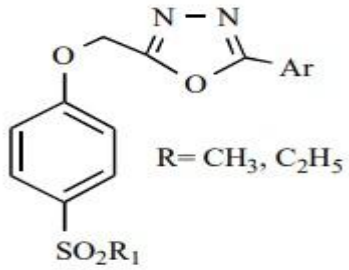
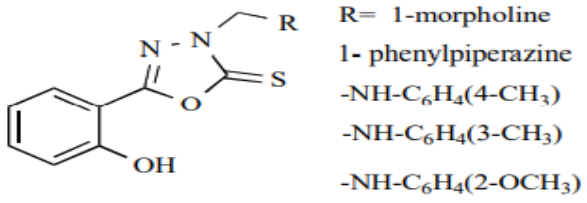
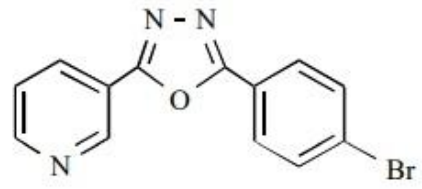
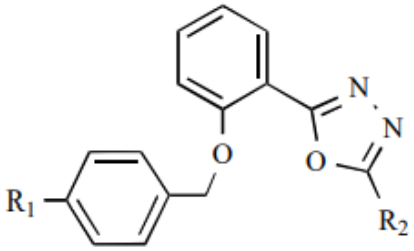
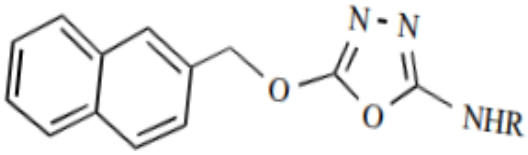
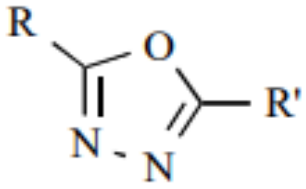
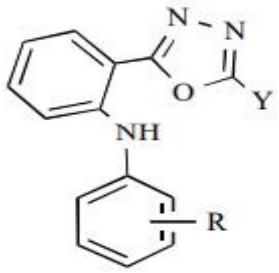
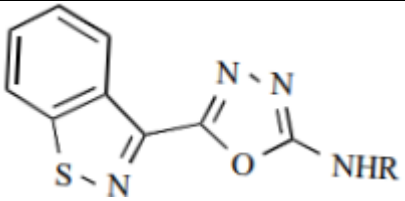


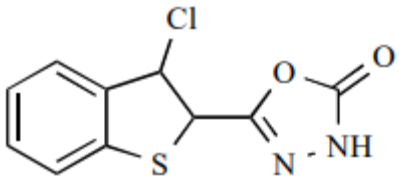
Figure 4 Systemic diagram of pharmacological activity of 1, 3, 4-Oxadiazole

Table 1 Various Pharmacological activity of 1, 3, 4-Oxadiazole

S. NO.	CHEMICAL STRUCTURE AND NAME	PHARMACOLOGICAL ACTIVITY	AUTHOR NAME	YEAR
1.	 5-(2-arylvinyl)-1,3,4-oxadiazol-2-yl) benzene sulfonamides derivatives	Anticancer activity	Szafranski et al [11]	**2020**
2.	 2-((4-amino-1,2,5-oxadiazol-3- ylimino)methyl)-4-(phenyldiazenyl) phenol derivatives	Antimicrobial activity	Kakanejadifard A [12]	**2013**
3.	 5-biphenyl,2-(-4-hydroxy)phenyl,1,3,4-oxadiazoles	Antimicrobial activity	Kumar R [13]	**2013**
4.	 1,3,4-oxadiazole incorporated azo dye derivatives	Antimicrobial activity	Shridhar AH [14]	**2012**

5.	 R=NHMe,$NHMe_2$,$NHCH_2CH_2OH$, $NHCH_2CH_2CH_2NH_2$ N- and O-tethered oxadiazole compounds	Vascular endothelial growth factor receptor-2 (VEGFR2) kinase inhibitory activity	Cai, Zhen-wei [15]	**2008**
6.	 X = H, Cl, Br A = CH_2 , O mercapto-1,3,4-oxadiazole	Carbonic anhydrase inhibitors	Almajan, G. L [16]	**2008**
7.	 2-[(4-alkylthio/alkylsulfonyl-phenoxy) methyl]-5-substituted-1,3,4-oxadiazoles	Antimicrobial and antifungal activity	Karabasan agouda, T [17]	**2007**
8.	 5-(2- hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole2-thione	Anticancer activity	Aboraia, A.S [18]	**2006**
9.	 3 -[5-(4 -bromophenyl)-1,3,4-oxadiazol-2-yl] pyridine	Tyrosinase inhibitors	Khan, M.T.H [19]	**2005**

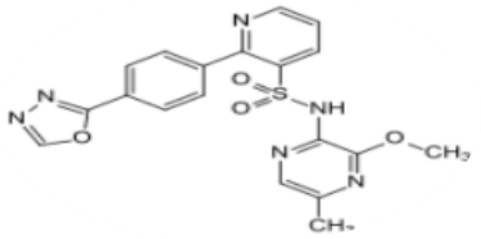
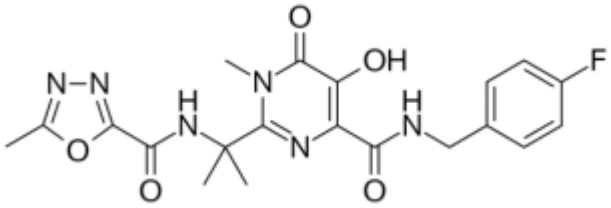
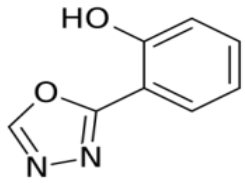
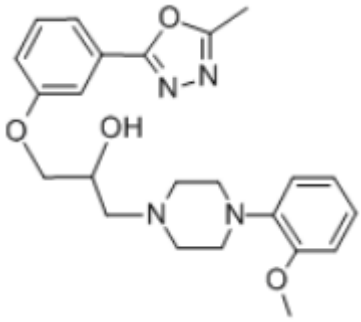
10.	 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles	Anticonvulsant activity	Zarghi, A [20]	**2005**
11.	 R= CH_3 , C_2H_5 , $CH_2 = CH_2$, C_6H_5 2-(2-naphthyloxymethyl)-5-substituted-amino-1,3,4-oxadiazole derivatives	Anti-inflammatory agents	Palaska, E [21]	**2002**
12.	 R = H, o-chloro-phenyl, m-chlorophenyl, p-chlorophenyl, phenyl R' = NH, $NHCOCH_3$ 2-amino-5- substituted-1,3,4-oxadiazoles	Muscle relaxant	Yale, H.L. [22]	**1996**
13.	 2,5 substituted-1,3,4-oxadiazoles	Dual inhibitors of cyclooxygenase and 5-lipoxygenase	Boschelli, D.H. [23]	**1993**
14.	 R = CH_3 , C_2H_5 , C_6H_5 , p-ClC_6H_4 , $CH_3OC_6H_4$ 3-heterocyclyl-1,2-benoisothiazoles having 1,3,4-oxadiazole	Anti-inflammatory agents	Sawhney, S.N [24]	**1993**

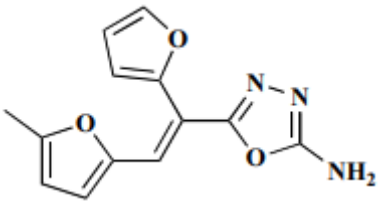
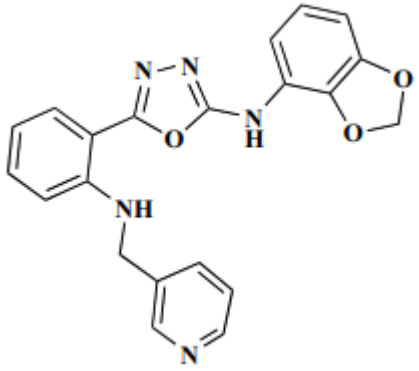
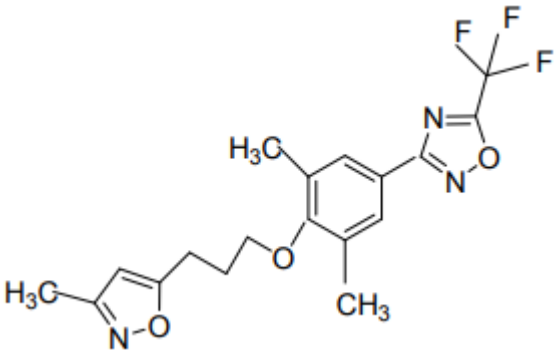
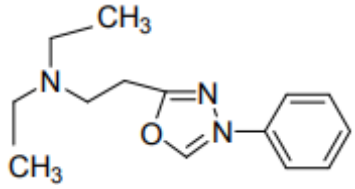
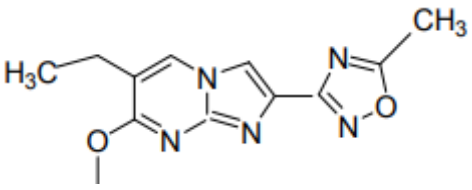
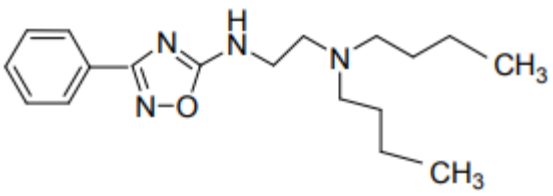
15.	 3-chloro-2-(2,3-dihydro2-oxo-l,3,4-oxadiazol-5-yl)benzo[b]thiophene	Anti allergic activity	Musser, J.H [25]	**1984**

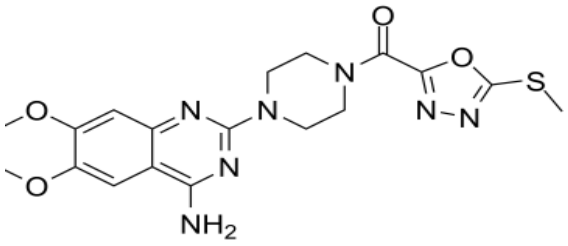
OXADIAZOLE NUCLEUS CONTAINING MARKETED DRUG

Following are the successfully used marketed drugs Containing Oxadiazole Nucleus with their chemical structure and biological activity. [26], [27], [28], [29], [30]

Table 2 Oxadiazole containing marketed drug

S NO.	DRUG	CHEMICAL STRUCTURE	BIOLOGICAL ACTIVITY
1.	**Zebotentan**		**Anticancer drug**
2.	**Raltegravir**		**Anti-HIV drug**
3.	**Fenadizole**		**Hypnotic drug**
4.	**Nesapidil**		**Antihypertensive drug**

5.	**Furamizole**		**Antibiotic**
6.	**ABT-751**		**Tubulin poymerisation inhibitor**
7.	**Pleconaril**		**Antiviral drug**
8.	**Oxolamine**		**Cough supressant**
9.	**Fasiplon**		**Anxiolytic drug**
10.	**Butalamine**		**Vasodialator**

11.	**Tiodazosin**		**Antihypertensive drug**

CONCLUSION

The present study has provided information regarding Oxadiazole nuclei such as its chemical nature, preparation methods, pharmacological activities, and a piece of brief knowledge about how the nucleus reacts with other chemical molecules and provides more diverse derivatives. In order to obtain a more effective derivative, the study provides the various chemical reaction of Oxadiazole moiety which can help the chemist for further new discoveries of Oxadiazole derivative with more effective and safe compounds.

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