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# Latest Update on Pharmacological Activities of 1,3,4-Oxadiazole Derivatives

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## Abstract

Heterocyclic compounds have been an interesting area for the study of synthesis and biological activity of novel oxadiazole derivatives for a long time. Heterocyclic compounds possess diverse biological properties that have led to intense study and research of these compounds. One of these compounds 1,3,4-Oxadiazole is a versatile heterocyclic nucleus is a novel molecule which attract the medicinal chemist to search a new therapeutic molecule. 1,3,4-oxadizole exhibited a wide range of biological activities which includes antimicrobial activity, anti-tubercular, anticonvulsant, anti-diabetic, anti-allergic, enzyme inhibitors, anti-HIV activity, antipyretic activity, Immunosuppressive activity, Spasmolytic Activity, antioxidant activity, Anti-Alzheimer's activity cardiovascular acivity, anti-inflammatory, anti-tumor activity, insecticidal activity, CGRP receptor antagonists, anti-anthelmintic activities. Results of various derivatives of different oxadiazole and their substitutions with diverse biological activities are reviewed in present article.

**Keywords:** 1,3,4-oxadiazoles derivatives; Pharmacological activities

## Introduction

Oxadiazole is a five membered heterocycle having two carbons, two nitrogens, one oxygen and two double bonds having general formula $C_2H_2ON_2$. Oxadiazole is considered to be derived from furan by replacement of two methane (-CH=) group by two pyridine type nitrogen (-N=). There are four possible isomers of oxadiazole (1,2, 3, 4) depending on the position of nitrogen atom in the ring and are numbered as shown in Figure 1.

Out of its four possible isomers, 1, 3, 4-oxadiazole is widely exploited for various applications. A Wide variety of substituted 1,3,4-oxadiazoles have attracted considerable attention in the field of drug discovery because of their wide range of pharmacological activities. Oxadiazoles have occupied a specific place in the field of medicinal chemistry due to its wide range of activities [1].

## Anticonvulsant Activity

A series of new 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles was designed and synthesized as anticonvulsant agents. 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 [2] (Figure 2).

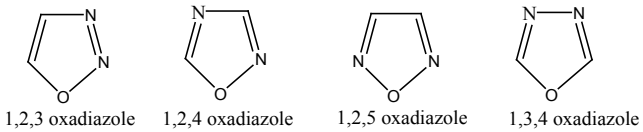


**Figure 1:** Isomers of oxadiazole.

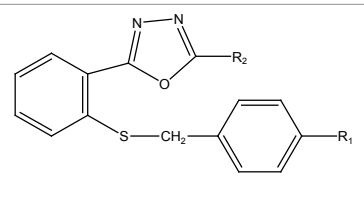


**Figure 2:** 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles derivatives.

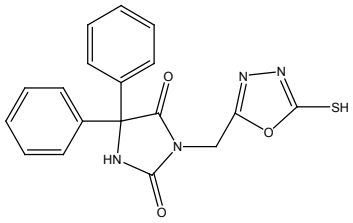

**Figure 3:** 3-[(5-Sulphanyl-1,3,4-oxadiazol-2-yl)methyl]-5,5diphenylimidazolidine-2,4-dione.

Hybrids between phenytoin and thiosemicarbazide, 1,3,4-oxadiazole, 1,3,4-thiadiazole or 1,2,4-triazole were synthesized and tested for anticonvulsant activity. Preliminary anticonvulsant screening was performed using standard maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens in mice. The neurotoxicity was determined applying the rotarod test. Among these compounds 4 showed the highest protection (80%) in the scPTZ test at a dose of 100 mg/kg [3] (Figure 3).

A series of novel 1,3,4-oxadiazole derivatives of phthalimide (4a-j) were prepared in satisfactory yields and evaluated for their anticonvulsant and neurotoxicity studies. All the compounds were active in MES screen and less neurotoxic than phenytoin. Compound 4j having methoxy substitution at para position of the distal aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity [4] (Figure 4).

A series of five membered heterocyclics was synthesized by the reaction between isoniazid and various substituted isothiocyanates

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and was tested for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsometer. Among the synthesized compounds (IIIf) 2-(chlorophenyl)amino-5-(4-pyridyl)-1, 3, 4-oxadiazole were found promising compounds of the series [5] (Figure 5).

The azole pharmacophore is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum anticonvulsant agents. The results revealed that five compounds 17,18 were able to display noticeable anticonvulsant activity in both tests at 100 mg/kg dose level [6] (Figure 6).

## Antimicrobial Activity

Six new 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-thione,2-amino-5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole,5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole 2(3*H*)-one derivatives have been synthesized from 1-and/or 2-naphthol. All the compounds were active against *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans*, and *C. parapsilosis* at 64–256 µg/ml concentration [7] (Figure 7).

A series of new 2-amino 1, 3, 4oxadiazoles were synthesized followed by condensation with various substituted aldehydes to yield their Schiff bases. The synthesized compounds were evaluated for their antimicrobial activity against two Gram positive bacteria two Gram negative bacteria and two fungal species yeast strains. All the synthesized compounds showed good antimicrobial activity [8] (Figure 8).

A series of 3-(5-phenyl-1,3,4-oxadiazole-2-yl)-2-(substituted styryl)-quinazoline-4(3H)-ones 3(a-h) were synthesized by reacting 2-methyl-3-(5-phenyl-1,3,4-oxadiazole-2-yl)-quinazoline-4(3H)-one All the compounds were screened for antibacterial activity by using cup plate method. Out of these compounds unsubstituted styryl compounds showed significant activity [9] (Figure 9).

Synthesized a series of (4E)-4-(2-substituted aryl hydrazono)-1-{4-[(4-acetyl-4,5-dihydro-5-methyl-5-phenyl-1,3,4-oxadiazol-2-yl) aminomethyl] phenyl}-3-methyl-1H-pyrazol-5(4H)-one. Has been found to possess antimicrobial activity [10] (Figure 10).

## Anti-HIV Activity

The newly synthesized compounds were evaluated for their HIV inhibitory activity as reverse transcriptase inhibitors by using microtiter anti-HIV assays with CEM-SS cells or fresh human peripheral blood mononuclear cells. Compound 6b showed the highest activity with an $IC_{50}$ value of 1.44 $\mu$M [11] (Figure 11).

## Insecticide Activity

A series 2-(5-(Trifluoromethyl)pyridyloxylmethyl)-5-aryl-1,3,4-

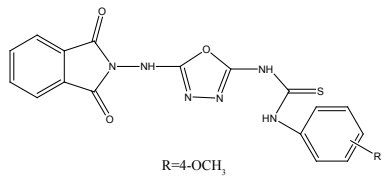



**Figure 4:** 1-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1,3,4-oxadiazol-2-yl}-3-(4-methoxyphen-yl) thiourea.

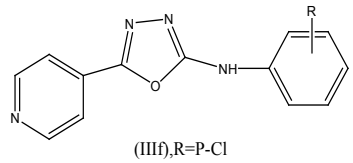



**Figure 5:** 2-(chlorophenyl)amino-5-(4-pyridyl)-1, 3, 4-oxadiazole derivatives.

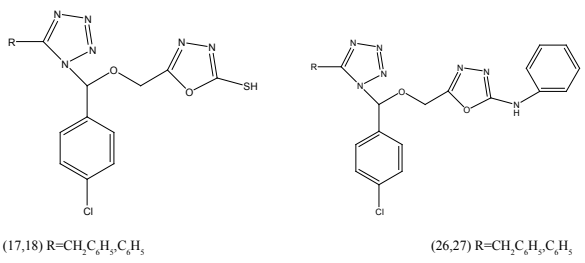



**Figure 6:** 5-{[2-(5-Benzyl-1H-tetrazol-1-yl)-1-(4-chlorophenyl)ethoxy]methyl}-1,3,4-oxadiazole-2-thiol and 5-phenylamino derivatives.

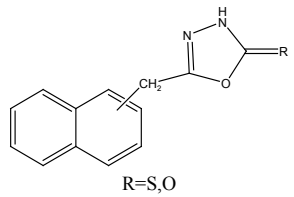



**Figure 7:** 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole derivatives.

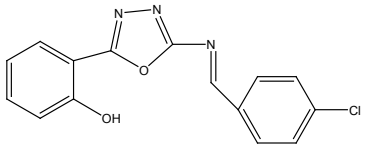


**Figure 8:** 2-(5-{[-(4chlorophenyl)methylidene]amino}-1,3, 4-oxadiazol-2-yl) phenol derivatives.

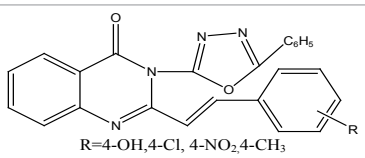



**Figure 9:** 3-(5-phenyl-1,3,4-oxadiazole-2-yl)-2-(substituted styryl)-quinazoline-4(3H)-ones derivatives.

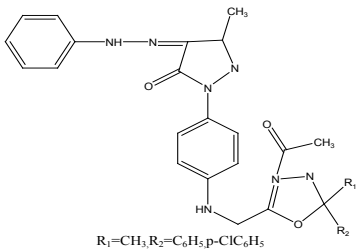



**Figure 10:** Various derivatives of aryl hydrazono and aminomethyl containing oxadiazole.

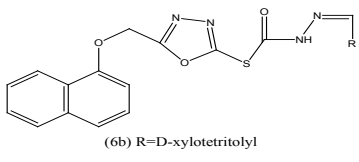
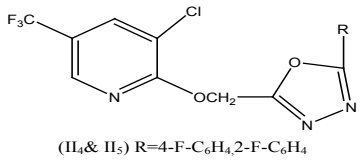



**Figure 11:** hydrazide and imidrazone derivatives containing 1,3,4-oxadiazole.

oxadiazole derivatives. Have been designed and synthesized by four-step synthetic route. All oxadiazole have greater insecticidal activity especially those having flurorine on the benzene ring ($II_4$&$II_5$), exhibited a significant insecticidal activity[12] (Figure 12).

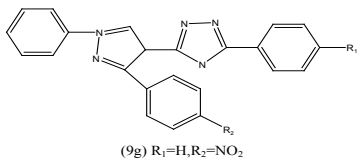
## Anti-inflammatory

A novel series of 2-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazoles were designed and synthesized for selective COX-2 inhibition with potent anti-inflammatory activity. Among the compounds tested, 9g was found to be the most potent inhibitor of COX-2 with $IC_{50}$ of 0.31 μM showing promising degree of anti-inflammatory activity in the carrageenan-induced rat paw edema model with $ED_{50}$ of 74.3 mg/kg [13] (Figure 13).




($II_4$& $II_5$) R=4-F-$C_6H_4$,2-F-$C_6H_4$

**Figure 12:** 2-(5-(Trifluoromethyl)pyridyloxylmethyl)-5-aryl-1,3,4-oxadiazole derivatives.

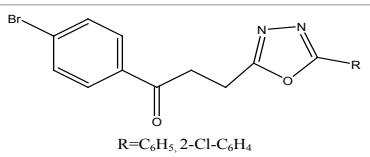



(9g) $R_1$=H,$R_2$=$NO_2$

**Figure 13:** 2-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazole derivatives.

A novel series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles (4a-n) have been synthesized from 3-(4-bromobenzoyl)propionic acid with the aim to get better anti-inflammatory and analgesic agents with minimum or without side effects [14] (Figure 14).

The synthesis of 5-(6-methyl-2-substituted 4-pyrimidinyloxymethyl) -2,3-dihydro-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives and the results of anti-inflammatory activity *in vivo* are described. Most of the tested compounds exhibited anti-inflammatory activity and some of them were more active than acetylsalicylic acid [15] (Figure 15).




R=$C_6H_5$, 2-Cl-$C_6H_4$

**Figure 14:** phenyl substituted-1,3,4-oxadiazole derivatives.

## Anti-Tubercular Activity

A series of 3-[5-pyridine-5-yl] 1, 3, 4-oxadiazole-2-yl] pyridinehas been Synthesized All the synthesized compounds shown to significant anti-tubercular activities. But compound 4g and 4h was found to possess better activity then others. Structure activity relationship and mass fregmentation has also been studied [16] (Figure 16).

Synthesized a series of 2-(4-nitro-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole derivatives. Compound 5e exhibited highest antitubercular activity (0.46 μg/mL) close to that of standard Isoniazid (0.40 μg/mL) [17] (Figure 17).

A series of 1,3,4 oxadiazole derivatives have been synthesized and evaluated for antitubercular activity. All the compounshave shown promising antitubercular activity when compared with the standard drug streptomycine [18] (Figure 18).

A series of 5-aryl-2-thio-1,3,4-oxadiazole derivatives were screened for their anti-mycobacterial activities against Mycobacterium tuberculosis H37Rv. The synthesized compounds 30-37 appeared to be the most active derivatives exhibiting more than 90% inhibition of mycobacterial growth at 12.5 μg/ml [19] (Figure 19).

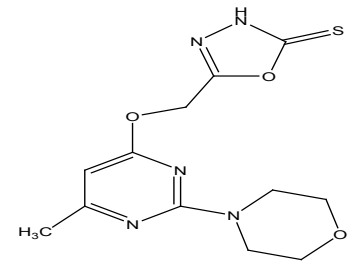
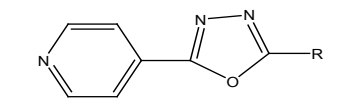



**Figure 15:** 5-(6-methyl-2-substituted-4-pyrimidinyloxymethyl)-2,3-dihydro-1,3,4 oxadiazole-2-thiones.

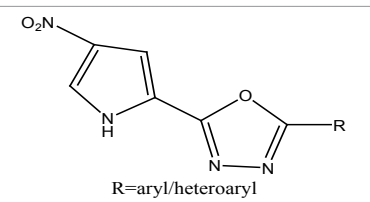
## Cardiovascular Activity

A series of novel substituted imidazole derivatives were synthesized and have been screened *in vivo* for their hypotensive and acute toxicity activities. Out of seventeen compounds eight compounds have shown good hypotensive and bradycardiac responses. Compounds 4c have shown better activity than reference drug clonidine [20] (Figure 20).



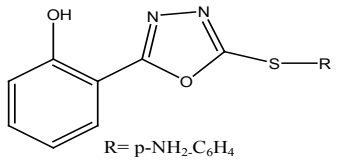

(4g,4h) R=$C_5H_4N$, 2-$NH_2$-$C_6H_4$

**Figure 16:** 3-[5-pyridine-5-yl] 1, 3, 4-oxadiazole-2-yl] pyridine derivatives.




R=aryl/heteroaryl

**Figure 17:** 2-(4-nitro-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole derivatives.




R= p-$NH_2$.$C_6H_4$

**Figure 18:** streptomycine.

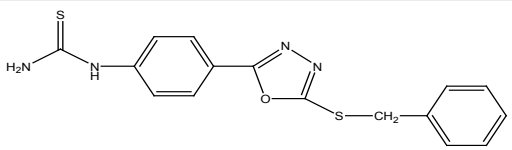
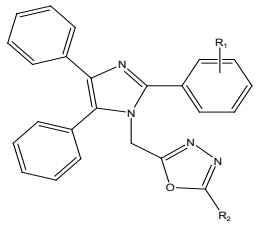



**Figure 19:** 5-aryl-2-thio-1,3,4-oxadiazole derivatives.

Some new (4-[3-acetyl-5-(pyridine-3-yl)-2,3-dihydro-1,3,4-oxadiazole-2-yl]phenyl acetate) derivatives has been found to possess considerable antihypertensive activity [21] (Figure 21).

## Anthelmintic Activity

Various substituted 3-amino-1-(2,4-dinitro phenyl)-5-[(5-substituted-1,3,4-oxadiazol-2-yl)amino]-1-Hpyrazole-4-carboxyamide and (5*E*)-5-[4-(dimethylamino) benzylidene]-3-(5-substituted-1,3,4-oxadiazol-2-yl)-2-phenyl-3,5-di hydro-4*H*-imidazol-4-one containing different functional groups have been synthesised by using different aromatic aldehydes and semicarbazide. All the compounds have been screened for their anthelmintic activity [22] (Figure 22).



(4C) $R_1$=p-N$(CH_3)_2$ ,$R_2$=3$(OCH_3)$.4(OH)-$C_6H_3$

**Figure 20:** Novel substituted imidazole derivatives containing oxadiazole moiety.

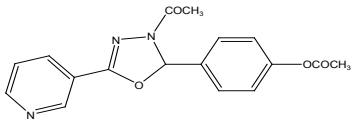
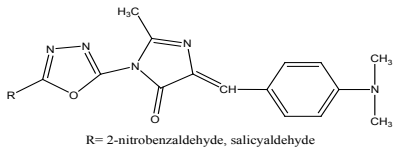
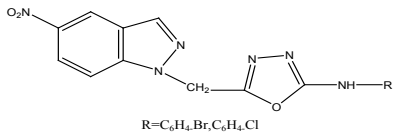


**Figure 21:** various derivatives of pyridine and phenyl acetate containing oxadiazole moiety.



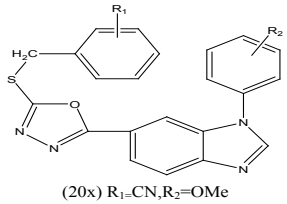
R= 2-nitrobenzaldehyde, salicyaldehyde

**Figure 22:** (5*E*)-5-[4-(dimethylamino) benzylidene]-3-(5-substituted-1,3,4-oxadiazol-2-yl)-2-phenyl-3,5-di hydro-4*H*-imidazol-4-one derivatives.



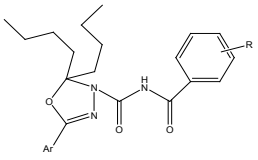
R=$C_6H_4$.Br,$C_6H_4$.Cl

**Figure 23:** 5-nitroindazole derivatives containing-1,3,4-oxadiazoles moeity.



(20x) $R_1$=CN,$R_2$=OMe

**Figure 24:** 3-[({5-[1-(4-Methoxyphenyl)-1H-benzimidazol-6-yl]-1,3,4-oxadiazolyl} sulfanyl)methyl]benzonitrile.



(3a) Ar =p-Cl-$C_6H_4$, R =2,6-2F

(3b) Ar =3,4,5-$(MeO)_3$-$C_6H_2$, R =2,6-2F

**Figure 25:** 1,3,4-oxadiazole-3(2H)-carboxamide derivatives.

## Antipyretic Activity

Synthesized a series of 2-[(5'-nitroindazole-1'-methyl)]-5-(p-bromophenylamino)-1,3,4-oxadiazole derivatives. All synthesized compound showed remarkable antipyretic activity, similar to that of acetylsalicylic acid [23] (Figure 23).

## Anti-Alzheimer's Activity

A series of 3-[({5-[1-(4-Methoxyphenyl)-1H-benzimidazol-6-yl]-1,3,4-oxadiazolyl} sulfanyl)methyl]benzonitrile derivatives has been synthesized. Among these compound 20x showed highly selective and potent GSK-3β inhibitory activity *in vitro* [24] (Figure 24).

## Monoamine Oxidase (MAO) Inhibitors

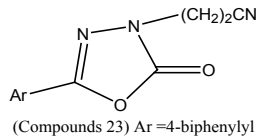
A new series of 1,3,4-oxadiazole-3(2H)-carboxamide derivatives have been synthesized by direct heterocyclization reaction of substituted benzoylisocyanate with various aroylhydrazones as novel monoamine oxidase inhibitors (MAOIs). The preliminary results showed that most of the compounds 3a, 3b have moderate inhibitory activities toward MAO at the concentration of $10^{-5}$-$10^{-3}$ M [25] (Figure 25).

Some new 5-aryl-1,3,4-oxadiazol-2(3H)-one derivatives and sulfur analogues were prepared and evaluated *in vitro* for their inhibitory properties on monoamine oxidase (MAO) types A and B. The most active compounds in these series acted preferentially against MAO B with I&a values in the range of 1.8-0.056 μM. Compounds 23 and its oxadiazolethione analogue 33 were found to act as potent, selective and competitive MAO B inhibitors [26] (Figure 26).

## Anti-tumor Agents

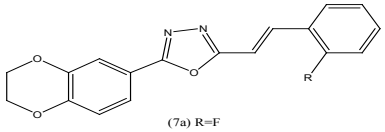
A series of 1,3,4-oxadiazole deriva tives containing 1,4-benzodioxan moiety have been designed, synthesized and evaluated for their antitumor activity. Most of the synthesized compounds were proved to have potent antitumor activity and low toxicity. Among them, compound 7a showed the most potent biological activity against Human Umbilical Vein Endothelial cells [27] (Figure 27).

Recently Some new 3-(2-Methoxyphenylaminomethyl)-5-(2-bromophenyl)-1,3,4-oxadiazoline-2-thione derivatives has been found to possess considerable anti-tumor agents property [28] (Figure 28).



(Compounds 23) Ar =4-biphenylyl

**Figure 26:** 5-aryl-1,3,4-oxadiazol-2(3H)-one derivatives.



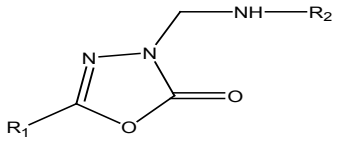
(7a) R=F

**Figure 27:** 1,3,4-oxadiazole deriva tives containing 1,4-benzodioxan moiety.

## Antioxidant Activity

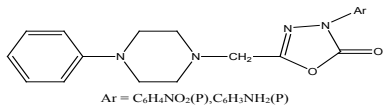
Synthesized A series of new 2-N- phenyl piperazino methylene-4-(4'-amino, 2'-nitro phenyl)-5-mercapto-1,3,4-oxadiazole derivatives. All compounds were screened for their antioxidant activity. Antioxidant activity of methanol solutions of synthesized compounds was determined by Reducing power assay and Hydrogen peroxide scavenging activity at 700 nm and 250 nm respectively [29] (Figure 29).

A series of 3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl azo dyes were synthesized by a multi-step reaction sequence. The synthesized compounds were screened for their antimicrobial and *in vitro* antioxidant properties [30] (Figure 30).



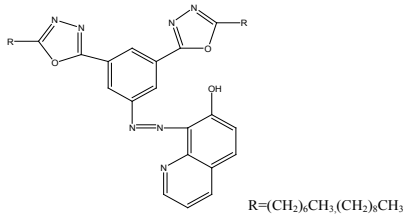

(3q) $R_1$=2-bromophenyl,$R_2$=2-methoxyphenyl

**Figure 28:** 3-(2-Methoxyphenylaminomethyl)-5-(2-bromophenyl)-1,3,4-oxadiazoline-2-thione derivatives.



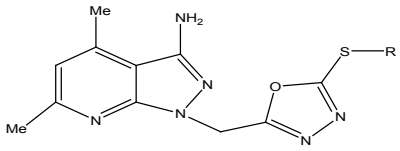

Ar = $C_6H_4NO_2(P)$,$C_6H_3NH_2(P)$

**Figure 29:** 2-N- phenyl piperazino methylene-4-(4'-amino, 2'-nitro phenyl)-5-mercapto-1,3,4-oxadiazole derivatives.



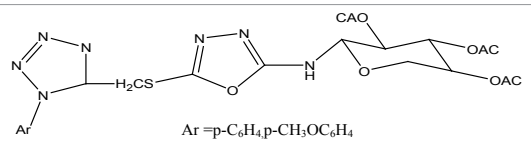

R=$(CH_2)_6CH_3$,$(CH_2)_8CH_3$

**Figure 30:** 3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl azo dyes derivatives.



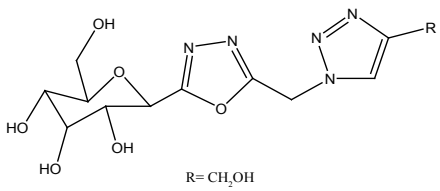

R=Me,$CH_2C_6H_5$

**Figure 31:** 1,3,4 oxadiazole derivatives.




Ar =p-$C_6H_4$,p-$CH_3OC_6H_4$

**Figure 32:** 5-[1-(4-Methoxyphenyl)-1H-tetrazol-5-ylsulfanylmethyl]-N-(2,3,4-tri-O-acetyl-b-D-xylopyranosyl)-1,3,4-oxadiazole-2-amine derivatives.




R= $CH_2OH$

**Figure 33:** 2-(β-D-Glucopyranosyl)-5-(4,-hydroxymethyl-1,2,3-triazol-1,-ylmethyl)-1,3,4-oxadiazole derivatives.

## Anti-Diabetes Activity

Synthesized a series of new 5-(1-aryl-1H-tetrazol-5-ylsulfanylmethyl)-N-(2,3,4-tri-Oacetyl-b-D-xylopyranosyl)-1,3,4-oxadiazole-2-amines derivatives. Some of the synthesized compounds displayed PTP-1B inhibition and microorganism inhibition [32] (Figure 32).

Some synthesis a series of 2-(β-D-Glucopyranosyl)-5-(4,-hydroxymethyl-1,2,3-triazol-1,-ylmethyl)-1,3,4-oxadiazole derivativeshas been also found to possess antidiabetes [33] (Figure 33).

## Spasmolytic Activity

Synthesized a series 2(substituted acetyls-amino-5-alkyl-1,3,4-oxadiazoles derivatives has been found to possess considerable spasmolytic acticity. Compound GK-4 and GK-8 showed non-specific spasmolytic activity [34] (Figure 34).

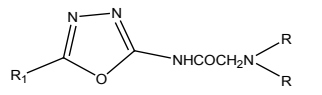
## Immunosuppressive Activity

A new potential lead structure 5-amino-3-methyl-4-[2-(5-amino-1,3,4-oxadiazolo)] isoxazole monohydrate, was synthesized. *In vitro* assays showed that the compound had a potent immunosuppressive activity [35] (Figure 35).

A series of 2-(5-(Benzylthio)-1,3,4-oxadiazol-2-yl)-5-methoxyphenol derivatives derived from 4-methoxysalicylic acid or 4-methylsalicylic acid (6a–6z) have been first synthesized for their potential immunosuppressive activity. Among them, compound 6z displayed the most potent biological activity against lymph node cells [36] (Figure 36).

## Anti-allergic Activity

A new class of sila-substituted 1,3,4-oxadiazoles was synthesized




(GK-4,GK-8) $R_1$=methyl,R=ethyl,$R_1$=ethyl,R= -n-propyl

**Figure 34:** 2(substituted acetyls-amino-5-alkyl-1,3,4-oxadiazoles derivatives.

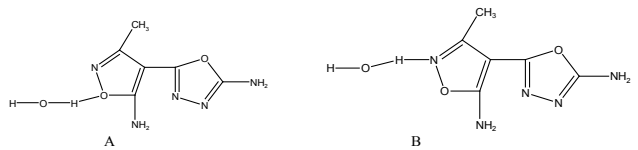
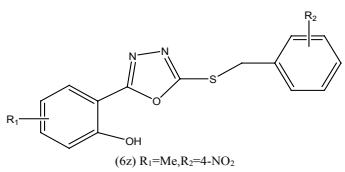



**Figure 35:** Structure (5-amino-3-methyl-4-[2-(5-amino-1,3,4-oxadiazolo)]-isoxazole monohydrate).




(6z) $R_1$=Me,$R_2$=4-$NO_2$

**Figure 36:** 2-(5-(Benzylthio)-1,3,4-oxadiazol-2-yl)-5-methoxyphenol derivatives.

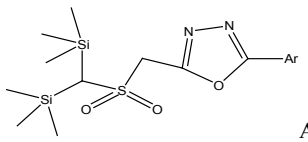



**Figure 37:** 2-((Bis(trimethylsilyl)methylsulfonyl)methyl)-5-phenyl-1,3,4-oxadiazole.

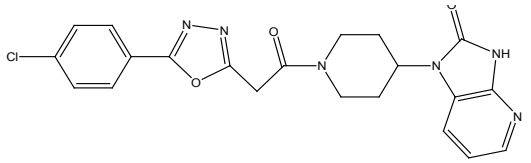



**Figure 38:** 1,3,4 oxadiazole derivatives.

by a convenient synthetic method. Both silathio/silasulfonyl acetic acids were efficiently condensed with benzohydrazides in the presence of phosphorus oxychloride to give sila-substituted 1,3,4-oxadiazoles in high yields. The compounds displayed variable extent of anti-allergic activity on IgE/Ag-stimulated RBL-2H3 cells at 50 and 100 μM concentrations. Compounds having sulfonyl moiety with bis(trimethylsilyl)-1,3,4-oxadiazoles (5a-c) exhibited better anti-allergic activities [37] (Figure 37).

## CGRP receptor Antagonists

A pharmacophore model was built, based on known CGRP receptor antagonists, and this was used to aid the identification of novel leads. Analogues were designed, modelled and synthesized. As a result a novel series of oxadiazole Calcitonin gene-related peptide (CGRP) receptor antagonists has been identified and the subsequent optimisation to enhance both potency and bioavailability is presented [38] (Figure 38).

## Discussion

1,3,4-oxadiazole are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, and as raw material for drug synthesis. the survey of the literature revealed that 1,3,4-oxadiazole is a versatile lead molecules for designing potential bioactive agents, and its derivatives were reported to possess broad-spectrum of pharmacological activities. This review highlights the therapeutic properties of the 1,3,4-oxadiazole ring and found to be promising as it is related to diverse range of pharmacological activities. Thus this paper proves to be significant for further research work on the bioactive oxadiazole ring.

These results revealed that 1,3,4-oxadiazole and substituted electrophilic are the essential pharmacophore for the pharmacological activities.

The existing literature suggested that 1,3,4-oxadiazole is responsible to control the various pathological conditions.

We observed that 1,3,4-oxadiazole derivatives had potent anticonvulsant, antimicrobial, anticancer properties. This ring is the new light to medicinal chemist or scientist to discover new lead target. Because of its high efficacy and lower side effect, this ring may be useful tool of new light for modern anticancer therapy.

## Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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