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Oxadiazole Derivatives: A Comprehensive Review of Their Chemistry, Synthesis, and Pharmacological Potential

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A B S T R A C T

Heterocyclic compounds are circular in shape having at least one N, S or O atom in place of carbon (other atoms boron, silicon etc can also take part). They have a significant role as part of natural biological compounds as well as synthesized derivatives. This study is taken from several research as well as review articles, book chapters, reports from Google scholar, PubMed, NIH, Research Gate, Academia, WHO's official website. Oxadiazole derivatives represent a crucial class of nitrogen-containing heterocyclic compounds with broad applications in medicinal, pharmaceutical, and polymer chemistry. Among their four isomeric forms 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazoles the 1,2,4- and 1,3,4-isomers are of particular interest due to their chemical stability, aqueous solubility, and strong pharmacological profiles. These scaffolds exhibit diverse biological activities, including antibacterial, antifungal, antiviral, anticancer, antitubercular, anti-inflammatory, and anticonvulsant properties. Their utility is further highlighted by their presence in approved drugs such as raltegravir and investigational candidates like ataluren and zibotentan. The electron-deficient nature of the oxadiazole ring, attributed to multiple heteroatoms, enhances its metabolic stability and allows for functionalization via nucleophilic substitution, especially in halogenated derivatives. Strategic substitution with electron-withdrawing groups (e.g., p-NO_2, p-Cl) has been shown to enhance biological activity through improved pharmacokinetic and pharmacodynamic properties. Various synthetic methodologies, from classical approaches to green chemistry techniques, have enabled efficient production of oxadiazole derivatives. Given their structural diversity, chemical resilience, and potent bioactivity, oxadiazole compounds continue to offer significant potential for drug discovery and therapeutic innovation. This review highlights their synthesis, structural characteristics, and multifaceted pharmacological applications, supporting their continued exploration in modern medicinal chemistry.

Keywords: Heterocycle, Oxadiazole, Bioactivities, Pharmacological profiling, Synthesis.

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INTRODUCTION

A subset of organic chemistry is heterocyclic compounds which are circular in shape with at least a nitrogen, sulphur or oxygen atom in place of one carbon. In addition, atoms like boron, silicon, and phosphorus can also take part in forming five or six membered fused rings systems (Kumar *et al.*, 2024). The importance of these structures is they make up a bulk of many biologically relevant substances like nucleotides (DNA and RNA), haemoglobin, chlorophyll and some vitamins (Khot *et al.*, 2025). Due to the variety of their structure and wide range of biological activity, the significance of heterocyclic compounds extends across medicine, agrochemistry, and veterinary medicine. For instance, triazine containing compounds has been used as

antibacterial agents, herbicides, urinary antiseptics, and as anti-inflammatories (Ghosh *et al.,* 2024). Additionally, derivative compounds of oxadiazole are acknowledged for their numerous therapeutic characteristics, for example, antiviral, antifungal, antibacterial, and anthelmintic effects. They also function as copolymers, corrosion blockers, developers, sanitizers, antioxidants, and colorants (Kamala *et al.,* 2024). They act as pathways to generate different organic compounds. Some natural compounds such as alkaloids (e.g., vinblastine, morphine, reserpine) and antibiotics like cephalosporin and penicillin, contain a heterocyclic structure.

Medicinal chemistry merges chemistry with health issues by striving to comprehend prevalent diseases (Wess *et al*., 2024) and their treatments, while heterocyclic compounds play a crucial part in this field (Jampilek *et al.,* 2019). Medicinal chemistry is based on conventional fields such as organic chemistry, biology, and specific branches of physics (Eyube *et al.,* 2024). This branch of modern chemistry started when scientists across the globe focused on isolating and refining active compounds from the tissues of both plants and animals, along with microorganisms and the by-products generated from their fermentation processes (Mouneir *et al.,* 2022). Pyridine (C_5H_5N), pyrrole (C_4H_5N), furan (C_4H_4O), and thiophene (C_4H_4S) are the most famous simple heterocyclic compounds. Structurally, pyridine is made up of a benzene-like aromatic ring with nitrogen substitution (Varshney *et al.,* 2023), whereas the others are made up of a five-membered cyclic structure differing only in their heteroatom (N, O, or S) (Landge *et al.,* 2024). These heterocyclic compounds usually possess functional groups that may be integrated into their ring or linked as substituent groups. To elucidate, the basic N-atoms may present within the ring as part of ring structure or as amino groups. This resilience makes these compounds able to imitate or behave as functional groups in many chemical and biological processes. The tetrazole ring is often served as bioisostere because of its structure and acidic character in relation to carboxylic acids. The tetrazole ring which consists of four Nitrogen atoms has large charge distribution which increase metabolic stability and bioavailability (Uppadhayay *et al*., 2022).

Health issues are enhancing at a dangerous rate and have become a major clinical affair (Filip *et al*., 2022). In a recent time, pharmaceutical chemistry experts have been trying to develop new drugs which cause no safety issues and can effectively resolve these clinical concerns (Fernendes *et al.,* 2022). The curiosity of medicinal and pharmaceutical chemists has been attracted efficiently by nitrogen-containing heterocyclic compounds and especially those compounds which contain oxadiazole groups because of their multiple therapeutic effects and efficacy (Ruan *et al.,* 2022). Oxadiazoles, as a subclass of heterocyclic compounds, possess a unique five-membered ring structure composed of two nitrogen (N) atoms, one oxygen (O) atom and two carbon (C) atoms (Atmaram *et al.,* 2022). Such compounds are also called by other names, like azoximes, oxybiazoles, biozoles, diazoxoles, furadiazoles and furoxans (Kumar *et al.,* 2022). The synthesis of oxadiazoles was first time reported by Ainsworth in 1965 via thermolysis reaction of some hydrazine derivatives (Saxena *et al.,* 2019). The empirical formula of oxadiazoles is $C_2H_2ON_2$ and their molecular weight is 70.05 g/mol. They are well known due to their heat stability and water solubility, showing resonance energy close to 167.4 kJ/mol (Vaghani *et al.,* 2021; Kumar *et al*., 2023; Murmu *et al.,* 2024). Substitution at position 2 of the ring has been shown to further enhance their heat stability (Zhang *et al.,* 2022). The 3D arrangement of N-atoms in oxadiazole ring produces four distinct isomers 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazole (Figure 1) (Du *et al.,* 2021). The 1,3,4-oxadiazole moiety has evolved as therapeutically rich structure, with its broad-spectrum biological activity making it important in field of modern drug discovery and development. Structurally, these compounds can be observed as derivatives of furan in which two methylene (-CH2-) are substituted with N-atoms, a modification that minimize the aromatic property of the ring and give it conjugated diene-like character (Atmaram *et al*., 2022). Moreover, the presence of heteroatom imparts weak basicity into the molecule through inductive effects. Hydrogen atoms on the ring are liable to nucleophilic substitution, further enhancing the synthetic and functional versatility of compounds (Banik *et al*., 2021).

Oxadiazole derivatives attracted researchers in material and polymer science fields because of their distinct attributes (Liu *et al.,* 2024). In recent nine years, there have been about 646 patent applications of oxadiazole derivatives are submitted. This shows the significance of oxadiazoles in scientific community (Anjanayya *et al.,* 2024). Currently ataluren and zibotentan which are oxadiazole-containing drugs are in the last-stage clinical trials (Jadhav *et al.,* 2021). The antiviral drug, raltegravir (used for HIV treatment) is solely medication available in market that contains oxadiazole (Mohammad *et al.,* 2022). In the present, use of oxadiazoles is increasing in various therapeutic areas, such as diabetes, overweight, inflammation, cancer and infection (Hassan *et al*., 2022). Oxadiazole moiety has been offering multiple uses in drug

development initiatives. Adding them to the pharmacophore has been manifested to increase ligand binding in several ways. It is rigid aromatic linker that has the same therapeutic effect as carbamates, amides and esters and can join a wide range of substituents (Ruan et al., 2022). Oxadiazoles display regioisomerism, with the most studied and utilized isomers being 1,2,4-, 1,3,4- and 1,2,5-oxadiazoles (Wang *et al.,* 2023), as illustrated in Figure 2. In the meanwhile, these isomers are widely researched and have found various pharmaceutical applications, the 1,2,3-oxadizole isomer is significantly unstable and less frequently explored (Du *et al.,* 2021). The synthesis and functionalization of oxadiazole derivatives have been a long-standing area of interest because of their multiple bioactivities. 1,3,4-oxadiazole derivatives possess a significant spectrum of therapeutic effects, including antimicrobial effects against bacteria, fungi and tubercular pathogens and significant antiviral activity against Human Immune deficiency Virus (HIV). They are also effective in CNS disorders via monoamine oxidase (MAO) inhibition, metabolic conditions by anti-diabetic effect and tyrosine inhibition, and oncology applications with significant anticancer effect. Especially their potent inhibition of cathepsin K is very important (Figure 2) (Wang *et al.,* 2022). The oxadiazole nucleus is present in most commercially marketed antihypertensive medications, including tiodazosin and nesapidil, and antibiotics, like furamizole (Figure 2) (Desai *et al.,* 2022).

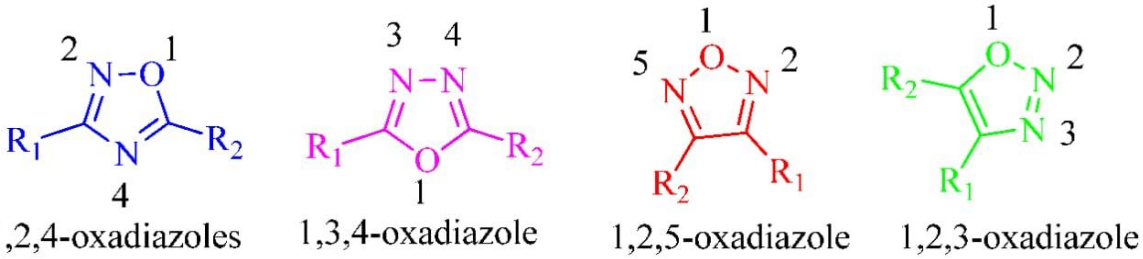


Figure 1: Four different possible isomers of oxadiazole.

The reason for the lower frequency of the 1,2,5-regioisomer is that its side chains R1 and R2 are orientated differently from those of the other two isomers. Although having varied regioisomeric configurations, oxadiazoles always have the same R1 and R2 side chains (Mohammad *et al.,* 2022). These side chains' locations are therefore rather comparable. It is anticipated that matching pairings will form bonds similarly because they have the same general molecular structures. Oxadiazoles' remarkable hydrogen bond acceptor qualities and their regioisomers' unique hydrocarbon bonding potentials have been demonstrated (Hernández-López *et al.,* 2022).

Chemistry of oxadiazole

Oxadiazole exhibits minimal basic character, consequence of electron-withdrawing effects from multiple heteroatoms within its ring structure. (Desai *et al*., 2022). When two vinylene (-CH=) groups in the furan precursor are replaced by imine-like nitrogen atoms (-N=), the aromatic character of the resulting oxadiazole ring is significantly diminished, giving it properties more consistent with a conjugated diene system (Liu *et al.,* 2025). Electrophilic substitution at the carbon atoms of the oxadiazole ring is generally unfavourable, as these positions have low electron density, a result of the electron-withdrawing nature of the nitrogen atoms (Qadr *et al.,* 2021). However, when the oxadiazole ring bears electron-donating substituents, electrophiles may instead target the nitrogen atoms in the ring (Banik *et al.,* 2022). While the oxadiazole ring typically shows resistance to nucleophilic attack, nucleophilic substitution reactions can still occur at positions where halogen atoms are present, behaving similarly to reactions at aliphatic sp^2 carbon centre (John *et al.,* 2021).

Synthesis of 1,2,4-oxadiazole derivatives

Several efficient methodologies are used for the synthesis of 1,2,4-oxadiazole derivatives, showcasing significant progress in heterocyclic chemistry. A simple method is reported in which N-hydroxyacetimidoyl chloride is reacted with methyl acetimidate in the presence of Toluene (a). A common approach involves condensation reactions, as demonstrated by Adib et al., who achieved high yields 92–97% of 3,5-disubstituted 1,2,4-oxadiazole derivatives using a solvent-free, microwave-assisted synthesis involving hydroxylamine, nitriles, and aldehydes (b). Poulain et al. introduced an alternative route based on uranium activation, reacting amidoximes with carboxylic acids to afford oxadiazoles in 66–96% yield. TBTU effectively activates carboxyl groups for O-acylation reactions, even with sterically hindered acids (c) (Poonam *et al*., 2022). Another

method involved stepwise thermal condensation of arylcarbonyl chloride derivatives with N-hydroxybenzamidines in dioxane under reflux and controlled heating, followed by precipitation and isolation of the product (d) (Vaidya *et al.*, 2020). In a multistep synthetic protocol, substituted o-hydroxybenzoic acids and o-hydroxybenzamides were first reacted in xylene with thionyl chloride and catalytic pyridine at 140°C to yield intermediates, which upon refluxing with hydroxylamine hydrochloride and triethylamine in ethanol produced the final oxadiazole derivatives after recrystallization (e) (Shi *et al.*, 2021). These diverse strategies highlight the versatility and adaptability of 1,2,4-oxadiazole synthesis under both classical and modern reaction conditions (Figure 3).

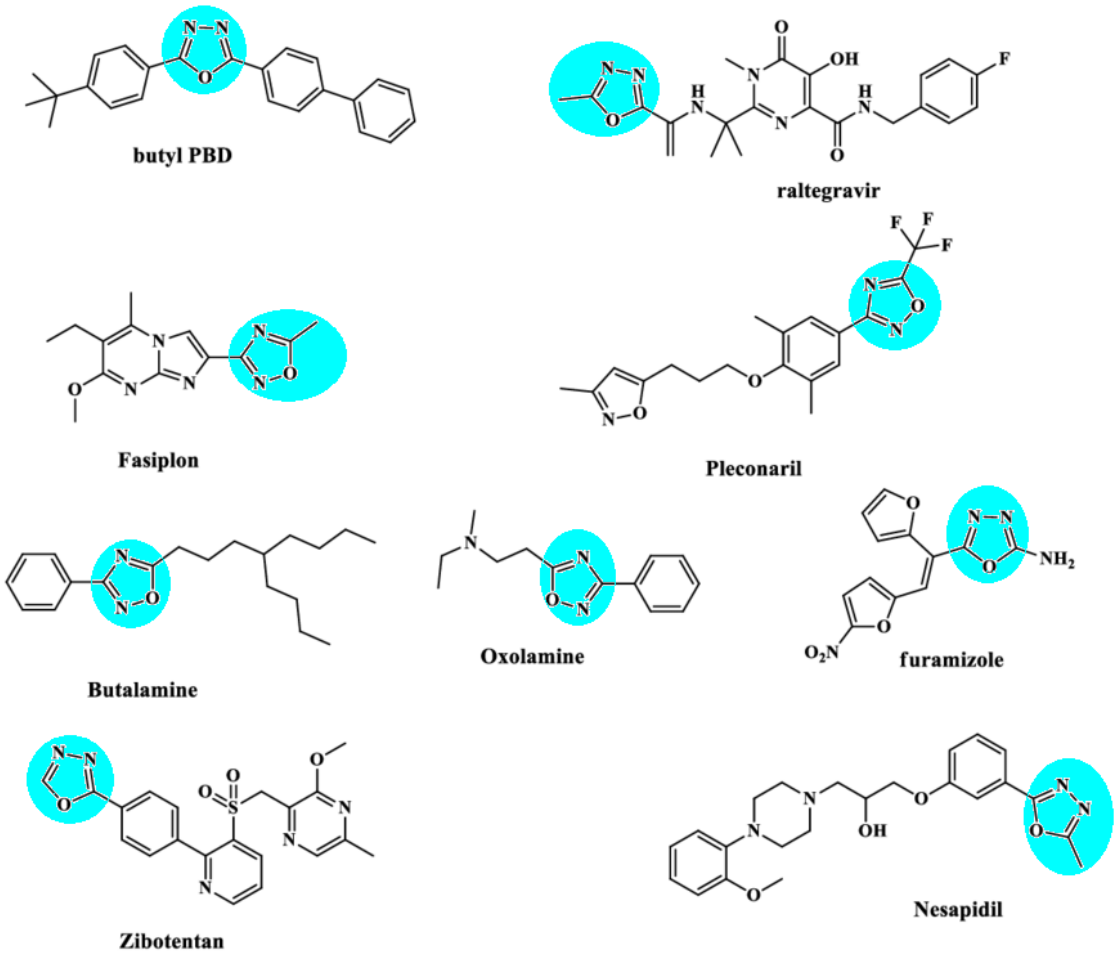
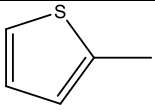


Figure 2: Commercially available different drugs containing oxadiazole ring.

Table 1: Detail of substituents R_1 and R_2.

Sr. No	R_1	R_2
a		-CH3
b	$-CH_3$	$-NH_2$
c	Benzene	=O
d	$-CH_3$	Benzene
e	$-CH_3$	$-NH_2$

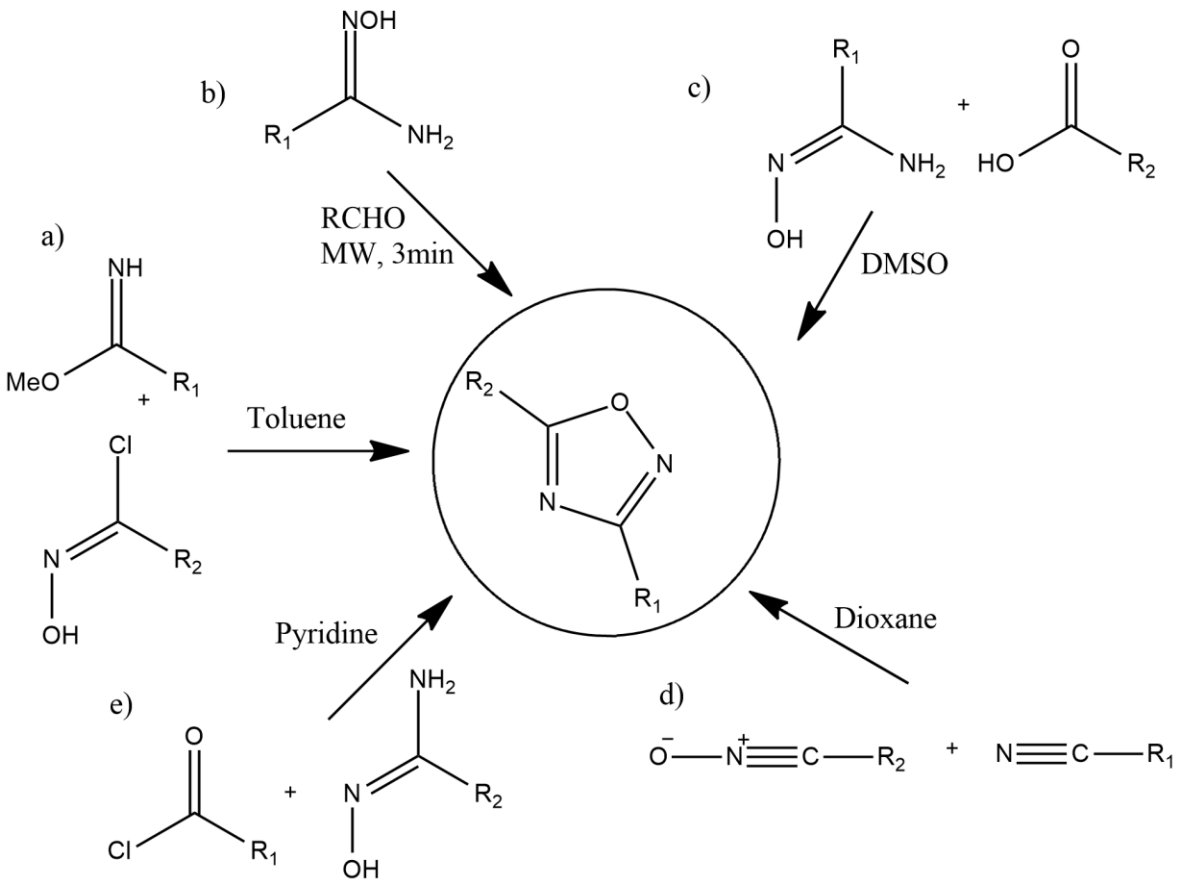


Figure 3: Several methodologies for the synthesis of 1,2,4-oxadiazole derivatives.

Synthesis of 1,3,4-oxadiazole derivatives

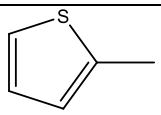
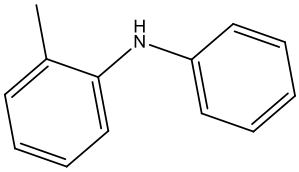
Several synthetic strategies are developed for the preparation of 1,3,4-oxadiazole derivatives, each offering unique advantages in terms of efficiency, selectivity, or reaction conditions. M.A. Elborai et al. reported a convenient and rapid method for synthesizing 2-amino-5-(2'-thienyl)-1,3,4-oxadiazole via the condensation of 2-thienyl hydrazide with cyanogen bromide (CNBr), a procedure widely cited in literature for the synthesis of amino-substituted oxadiazoles due to its simplicity and short reaction time (a). H. Singh and his co-workers synthesized 5-oxo-1,3,4-oxadiazoline compounds bearing 2-arylmethyl substituents from acylureas using bromine in sodium hydroxide, demonstrating an effective halogenation-based approach (b). Additionally, D.H. Boschelli et al. developed a method for preparing substituted aryl 1,3,4-oxadiazolones by reacting CDI with TEA in tetrahydrofuran (THF), showcasing the utility of CDI as a coupling agent in heterocycle construction (c). A widely used classical method involves the cyclodehydrogenation of alkyl hydrazides with substituted aromatic acids in the presence of phosphorus oxychloride, affording 2-alkyl-5-aryl-1,3,4-oxadiazoles in good yields (d) (Somani *et al.,* 2011). Furthermore, 1,3,4-oxadiazol-2-amines have been prepared by oxidative ring closure of semicarbazone precursors under ultrasonic conditions using N-bromosuccinimide (NBS) and sodium acetate, providing a greener and efficient alternative for ring closure (e) (Poonam *et al.,* 2022). These diverse methodologies underscore the versatility of 1,3,4-oxadiazole synthesis and its adaptability to various structural requirements and reaction conditions (Figure 4).

Synthesis of 1,2,5-oxadiazole derivatives

The synthesis of 1,2,5-oxadiazole derivatives has been explored through a range of methodologies that emphasize efficiency, selectivity, and safety. One classical method involves the dehydration-induced ring closure of bisoximes using metal hydroxides at high temperatures (>100 °C), producing the oxadiazole ring through a vigorous heating process (a) (Poonam *et al.,* 2022). Freitas et al. (2023) introduced a particularly simple and efficient strategy involving the cyclodehydration of nitroketoximes to yield 1,2,5-oxadiazole-N-oxides, providing a straightforward entry into N-oxide derivatives (b). Deng et al. (2021) further

expanded the synthetic landscape by reporting a metal-free tandem cyclization of arylketimines with nitro compounds to generate 1,2,5-oxadiazole-fused quinolines, showing the potential for complex fused ring systems under mild conditions (c). In a distinct approach, Makhova's group developed a chemo-selective N-nitration protocol converting 3-methyl-1,2,4-triazole to bis(triazolyl)oxadiazole-N-oxide using hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) and sodium nitrite ($NaNO_2$), showing functional group compatibility and regioselectivity (d) (Kumar *et al.,* 2023). Neel and Zhao et al. developed a safer and more tolerant route employing 1,1'-carbonyldiimidazole (CDI) to synthesize 3,4-disubstituted 1,2,5-oxadiazoles from bisoxime precursors at room temperature. This approach proceeds in two steps: hydroxylamine addition to cyanooximes to form bisoximes in situ, followed by CDI-induced cyclodehydration, affording oxadiazoles in yields ranging from 56–85% (e) (de Freitas Filho *et al.,* 2023). Collectively, these methods underscore the growing versatility in constructing 1,2,5-oxadiazole scaffolds with potential for multiple application in heterocyclic and medicinal chemistry (Figure 5).

Table 2: Detail of substituents R_1 and R_2.

Sr. No	R_1	R_2
a		$-NH_2$
b	$-CH_3$	=O
c		=O
d	$-CH_3$	Benzene
e	$-CH_3$	$-NH_2$

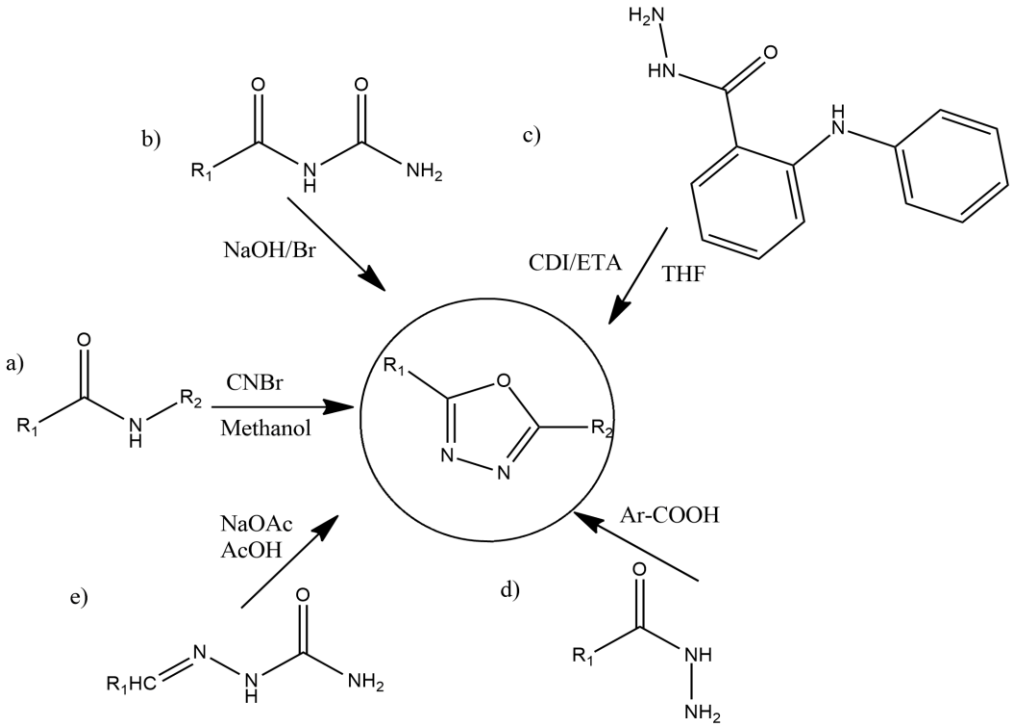


Figure 4: Several methodologies for the synthesis of 1,3,4-oxadiazole derivatives.

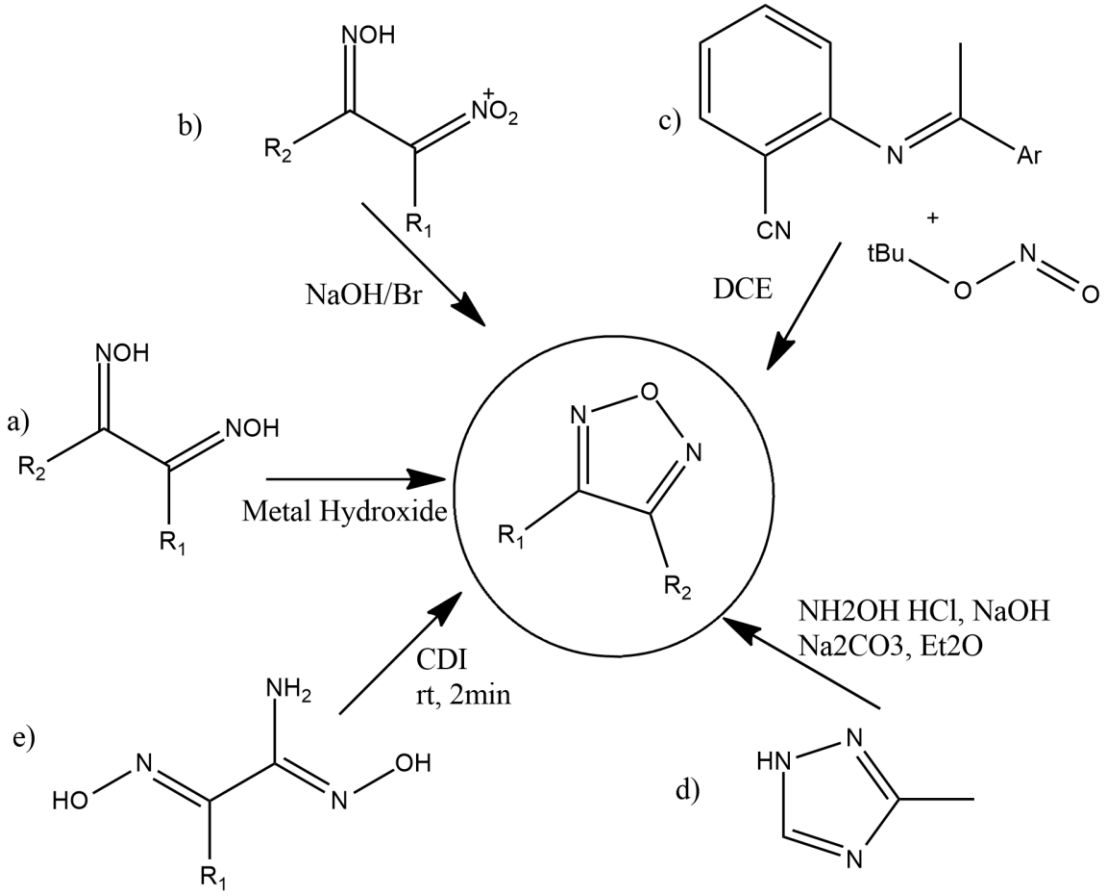


Figure 5: Several methodologies for the synthesis of 1,2,4-oxadiazole derivatives.

Table 3: Detail of substituents R_1 and R_2.

Sr. No	R_1	R_2
a	$-CH_3$	$-NH_2$
b	$-CH_3$	Benzene
c	Benzene	=O
d	$-CH_3$	Benzene
e	$-CH_3$	$-NH_2$

Biological activities of oxadiazole derivatives

As we know, oxadiazole is gaining attention from medicinal chemists because of its pharmacological activities and utilization as a preferred moiety in drug discovery for a variety of therapeutic purposes (Kumar et al. 2011). The oxadiazole ring shows activity because of its hydrophilic and electron-donating characteristics, yet metabolic stability is provided by its chemical and thermal resistance. According to Saunders et al. 1988; Patani and Voie et al. 1996, as bio-isosteric substitutes in drug design, ester, amide and acidic compound; 1,2,4-oxadiazoles are commonly used to describe the metabolic liabilities associated with them.

Drugs based on 1,2,4-oxadiazole have shown good properties in a few clinical trials. reports the 1,2,4-oxadiazole scaffolds incorporating commercially available medications, highlighting their importance in the field of pharmaceutical chemistry (Kleeman et al. 2001). Oxolamine **1** primarily has anti-inflammatory and anti-tussive properties. Libexin exhibits anti-tussive activity. Cystic fibrosis is treated with ataluren (Bora et al. 2014). Selkirk et al. (2014) reported that 1,2,4-oxadiazole moiety interacts and blocks many receptors such as 5-HT 1 B/D (5-hydroxytryptamine 1B/D). 1,2,5-oxadiazole contain many therapeutic characteristics such as antitubercular, antitumoral, anti-tussive and anti-inflammatory (Figure 6).

Anti-Tubercular activity

Parikh et al. (2020) described substituted 1,2,4-oxadiazoles as strong anti-TB drugs as they show antitubercular properties against Mycobacterium tuberculosis (H37Rv) in the in vitro experiment. The drug, Ethionamide is the second line treatment for MDR-TB (Multi Drug Resistant-Tuberculosis) but its adverse effects are reported. Shruthi et al. (2016) suggested a design approach after creating compounds of Benzimidazole-oxadiazole hybrid as anti-TB drug [73].

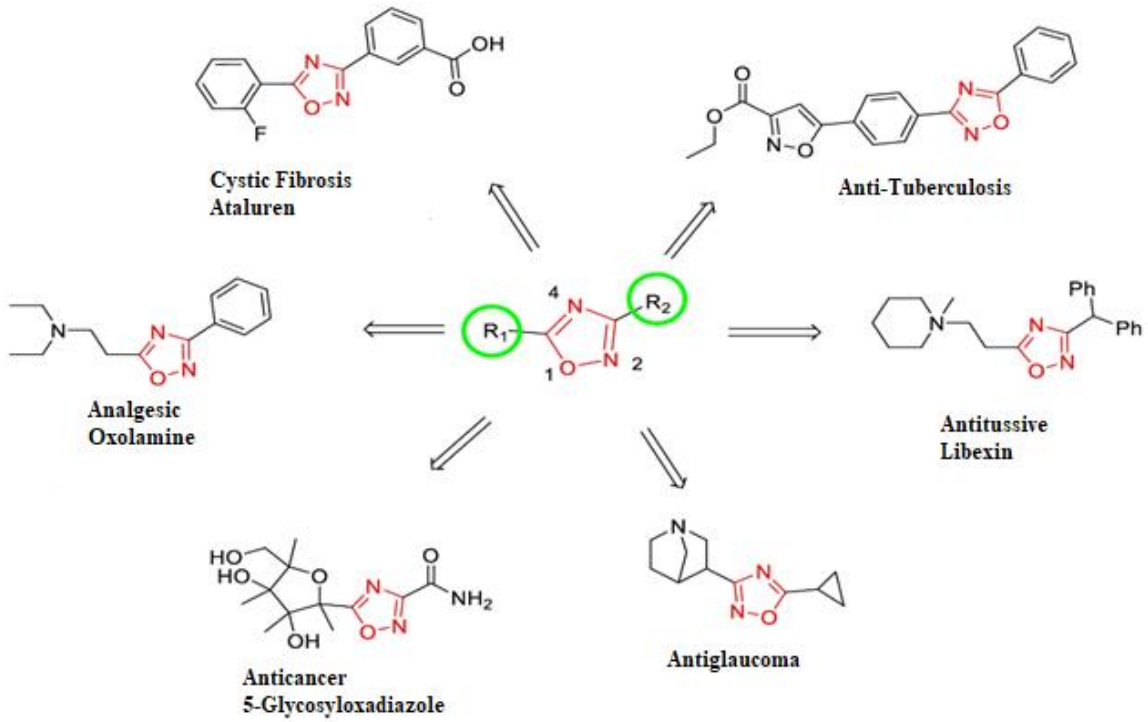


Figure 6: Commercially available drugs containing 1,2,4-oxadiazole nucleus.

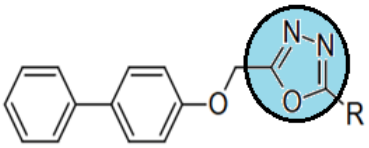
Anticancer activity

Kala et al. (2020) designed and developed 1,2,4-oxadiazole compounds with quinoline derivatives and screened them for their anticancer property against Etoposide (have therapeutic effects against multiple types of cancer such as lung cancer, testicular cancer, lymphoma and non-lymphocytic leukemia etc). Etoposide is usually used for testicular cancer, in combination with different drugs i-e Bleomycin. Some of the synthesized compounds show comparatively more activity than Etoposide. To develop new derivatives in which 1,2,4-oxadiazole replace the central imidazole ring as primary change and explore their Structure Activity relationship, Cascioferro et al. (2019) worked on structural changes made onnortopsentin (an alkaloid). The compounds show positive results when tested against human cell lines. Cai et al. (2015a, b) reported synthesis of different analogues of 1,2,4-oxadiazoles such as 2-aminobenzamide, hydroxamate and trifluoromethyl ketones. To evaluate the effect of this modification, the amide group in vorinostat was replaced with 1,2,4-oxadiazole as a bioisosteric substitute. Testing revealed that most of these new compounds had more potent activity against human acute myeloid leukemia U937 cells compared to A549 and NCI-H661 lung cancer cell lines. Additionally, Atmaram et al. (2022) synthesized various 2-aminobenzamide and hydroxamate derivatives containing 1,2,4-oxadiazole following optimization efforts on the standard drug Entinostat.

Anti-Inflammatory Activity

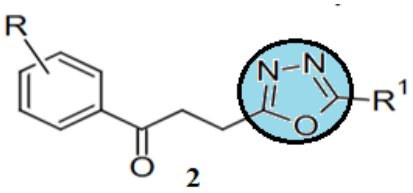
1,3,4-oxadiazole derivatives were developed and checked their ability to reduce inflammation by using technique named as carrageenan-induced rat paw edema test. The compound **1** was checked as a lead compound with protective effect on lipid peroxidation, lower ulcerogenic rate and high anti-potential. Inflammatory activity contained by compound and reference drug was 81.81% and 79.54%

respectively.



1

Anti-inflammatory activity of many derivatives of aroylpropanoic acid with oxadiazole moiety **2** was checked after their synthesis. Results showed that some compounds possessed analgesic and anti-inflammatory characteristics, the same as ibuprofen and they were also safe (Kamboj *et al.*, 2010).

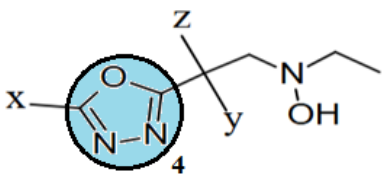


2

Mullican H.D et al. (2014) synthesized a series of 5-[2-(3,5-dimethoxy-4-hydroxyphenyl)ethyl]-1,3,4-oxadiazoles having aim of discovering bifunctional inhibitors of cyclooxygenase and 5-lipooxygenase possessing better pharmacokinetic characteristics. Carrageenan rat paw edema technique was used to test the compounds. The result showed compounds have good anti-inflammatory property. A series of 1,3,4-oxadiazole derivatives of biphenyl-4-yloxyaceticacid was synthesized by Harish kumar et al. (2016) and tested for their ability to reduce inflammation. Results revealed that the compounds had strong anti-inflammatory property (Martin *et al*., 2013).

Antimicrobial Activity

Many steps are involved in synthesis of 1,3,4-oxadiazole-2(3H)-thiones and their S-alkyl derivatives **3**. Different techniques such as IR, NMR and LCMS were utilized to test these compounds for analgesic and antibacterial activity and few of them gave strong positive results. Antibiotic activity of substituted 5-indole-1,3,4-oxadiazole was investigated. Some compounds show positive activity against different types of bacteria such as 1,3,4-oxadiazole derivatives **4** showed activity against *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* while activity was showed against *S. aureus* by 2-phenyl 5-indole-1,3,4-oxadiazole.



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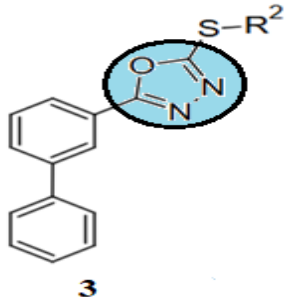
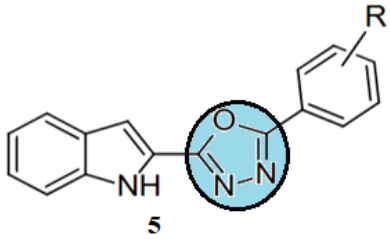


3

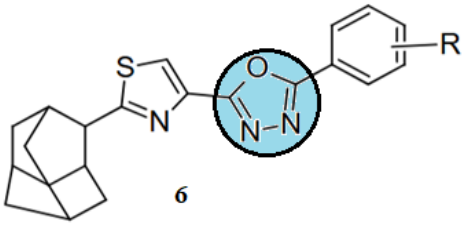
The compounds such as 3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl)-2-subtituted phenyl-2,3-dihydro-1,3,4-oxadiazoles **5** were synthesized and investigated for antibacterial characteristics against different bacteria i-e *B. subtilis*, *S. aureus* and *E. coli* alongwith antifungal properties against *C. albicans* and *A. niger*. These compounds showed mild antifungal but strong antibacterial properties; some of them even showed stronger effect against *S. aureus* and *B. subtilis* than Ciprofloxacin.



5

Anticancer activity

Several drugs are available in clinical setting for anti-tumor activity. Several 1,3,4-oxadiazole derivatives **6** are used against cancer due to having antitumoral properties. ß-carboline derivatives are most important compounds having broad spectrum of anticancer characteristics at GI_{50} as well as TGI levels. In-vitro anti proliferative property of 1,3,4-oxadiazole derivatives with different aryl groups were tested using a wide range of human tumor -derived cells and they showed positive results.

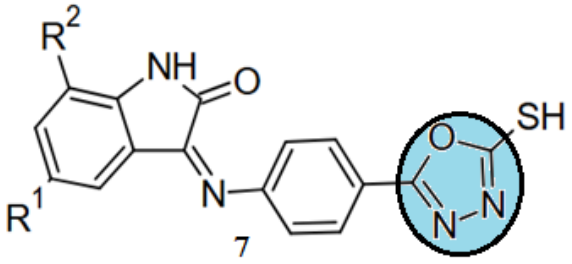


6

A lot of 1,3,4-oxadiazole derivatives were developed and investigated for having anticancer activity against HeLa cancer cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. All of them blocked cell proliferation in a dose-dependent way. One of these compounds showed to have an IC_{50} value the same as

a most popular anticancer drug, Cisplatin (Kamboj et al., 2010).

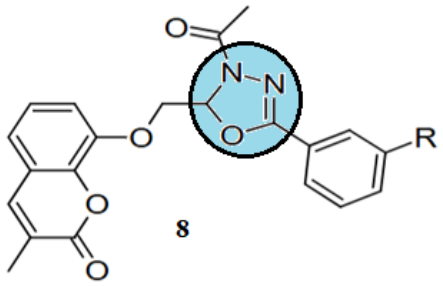
By utilizing cyclocondensation phenomenon of 1-(4-hydroxyphenyl)-2-aroylhydrazines with thiophosgene Loetchutiant et al. (2018) synthesized a new series of 5-(substituted aryl)-3-(4-hydroxyphenyl)-1,3,4-oxadiazole-2-(3H)-thiones **7**. Anti-proliferative activity of the resulting compounds was assessed against microbes. The span of their IC_{50} values was 24mM-94mM and they showed anticancer activity comparable with genistein and epigenin. Ouyang et al. (2020) synthesized and described various 1,3,4-oxadiazole derivatives for having property to block tubulin polymerization and disrupt mitosis in cancer cells. Effective action was shown by one of these compounds. Results of its in-vitro studies revealed that at minute (ng) concentration, it inhibits mitotic cycle in squamous cell tumors and breast cancer along with the cells that are multi-drug-resistant. Quin-Zhong Zheng et al. (2022) worked on the synthesis of a 1,3,4-oxadiazole nucleus containing series of 2-chloropyridine derivatives. The synthetic compounds showed superior growth-inhibitory effects on SGC-7901 gastric cancer cells compared to the standard treatment (Martin *et al.,* 2013).



7

Antioxidant Activity

With the use of microwave and traditional techniques, 5-pyridyl-2-[(N substituted phenyl) thioacetamido]-1,3,4-oxadiazoles **8** were developed and their in-vitro antioxidant property was also tested by utilizing DPPH free radicals scavenging assay. According to the result, the molecule containing 2-chloro substitution has suppressed 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical.

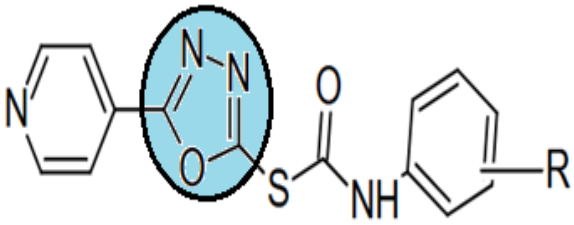


8

The synthesized oxadiazole-based molecules, bearing substituted phenyl and coumarin moieties, for example, 3-acetyl-2-(substituted phenyl-5-(4-methylcoumarinyl-7-oxymethyl)-2,3-dihydro 1,3,4-oxadiazoles were tested for their antioxidant characteristics. Results of diphenylpicryl hydrazyl assay reported more than 50% antioxidant property in hydrogen and methyl containing derivatives.

Anticonvulsant Activity

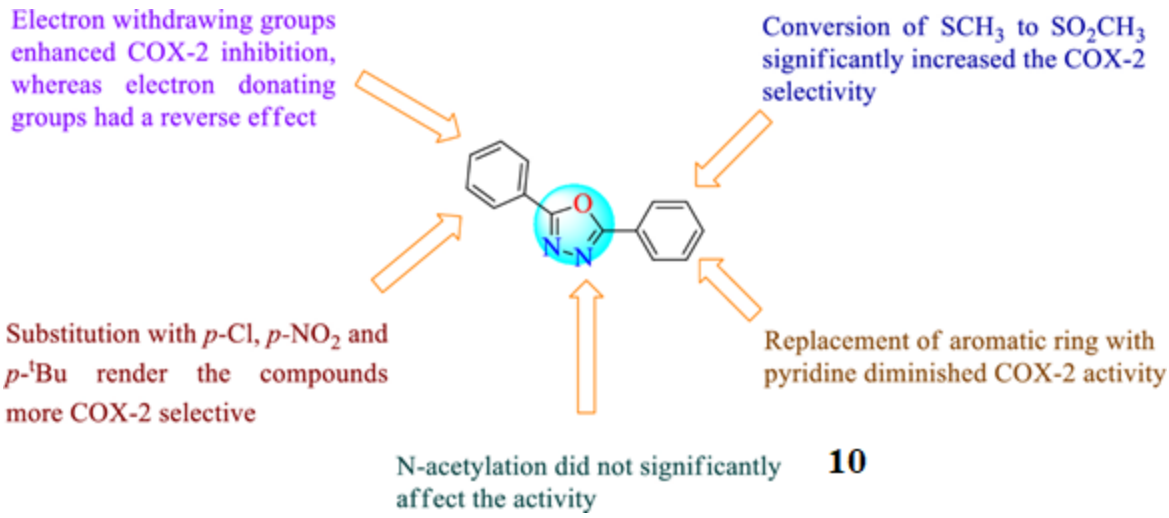
Epilepsy is a neurological condition of spontaneous, abnormal and sporadic electrical activity in the brain. From the past 20 years, even though new epileptic drugs have been available for use in clinical field, the subcutaneous pentylenetetrazol and Maximum Electroshock tests are most common epilepsy models used to describe the anticonvulsant characteristics. The work was done on the synthesis of a series of oxadiazole derivatives coupled with pyridine **9** and their neurotoxic potential and seizure-suppressing properties were described. One of these compounds showed potent activity in Maximal Electroshock Seizure test (a widely used preclinical method in anticonvulsant drug design to assess the potential of a drug to prevent or reduce the severity of seizures, also known as MES-Test) and according to results it was comparatively less toxic than Phenytoin which is a reference drug (Kamboj *et al.,* 2010).



9

Structure Activity Relationship

By substituting phenyl ring with many substituents including p-NO_2 and p-Cl, its structure activity is raised. Another method to enhance the therapeutic effect is transformation of the methyl-thio (–SCH_3) group into methyl-sulfonyl (–SO_2CH_3) group. The potency can be lowered by removing phenyl and pyridine ring from structure **10**. On the other hand, the presence of an acetyl group on the N-atom of the oxadiazole structure showed no effect. It is reported that novel compounds having several pharmacological properties and high pharmacokinetic characteristics, could be developed by using 2,5-disubtituted 1,3,4-oxadiazole scaffold (Siwach *et al.,* 2020).



DISCUSSION

Heterocyclic compounds, especially those containing nitrogen atoms in their rings, have significant activities in pharmaceuticals, agrochemicals and veterinary medicine. They are also part of many biological relevant molecules such as nucleotides, hemoglobin and chlorophyll etc. The structural flexibility and varied substituent patterns on heterocyclic rings increase the potential for fine-tuning the compounds for specific therapeutic outcomes (Ali et al., 2025). Among the nitrogen containing heterocyclic compounds, isatin and oxadiazole derivatives have a unique place in medicinal chemistry (Abbasi et al., 2021). In the research of new biological compounds, scientists found the oxadiazole ring-containing compounds very significant in the field of pharmaceutical chemistry as well as polymer chemistry. There are four important derivatives based on 3-dimensional arrangement of nitrogen atoms in oxadiazole ring: 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazole. They are well known due to their heat stability and water solubility properties. Oxadiazole ring containing drugs are available in market (raltegravir) as well as many of them are in last stage clinical trials (ataluren, zibotentan etc). All isomers except 1,2,3-oxadizole (which is unstable and less frequently explored) have potent therapeutic characteristics such as antitussive, antibacterial, antiviral, antifungal, anticancer, antitubercular, antioxidant, anti-inflammatory and anticonvulsant etc. The oxadiazole nucleus is present in many commercially available antihypertensive drugs such as tiodazosin, nesapidil and antibiotics such as furamizole etc.

Oxadiazole contain negligible basic characters due to electron-withdrawing effects from multiple heteroatoms within its ring structure. The oxadiazole ring usually shows resistance to nucleophilic attack but nucleophilic substitution reactions can still occur at positions where halogen atoms are present, behaving similarly to reactions at aliphatic sp^2 carbon centre. There are some methods by using which, the activity of these derivatives can be enhanced such as by substituting phenyl ring with many substituents including p-NO_2 and p-Cl. Oxadiazole derivatives were synthesized firstly in 1965 by Ainsworth and now there are several methods (methods of synthesis for each derivative are reported above) that are used currently to obtain high yield of oxadiazole derivatives.

Furthermore, oxadiazole derivatives show remarkable chemical resilience, withstanding metabolic degradation better than many other heterocyclic counterparts. This contributes to prolonged plasma half-life and reduced dosing frequency, both favourable attributes in pharmacotherapy. Despite being resistant to nucleophilic attack due to the electron-deficient nature of the ring, the presence of halogen substituents can activate certain positions toward nucleophilic aromatic substitution, facilitating selective functionalization and enabling further structural diversification.

Another notable aspect is their potential application beyond traditional pharmaceuticals, such as in polymer chemistry, material sciences, and diagnostic agents, due to their photo stability, fluorescence properties, and ability to act as ligands in coordination chemistry. However, in the biomedical field, their primary impact lies in targeted therapy, especially for diseases requiring selective receptor modulation or enzyme inhibition—such as cancer, tuberculosis, and drug-resistant infections. Further, in vitro enzyme inhibition assays revealed that these heterocyclic hybrids have potential inhibitory action.

In summary, oxadiazole derivatives continue to be an area of rich scientific inquiry due to their chemical robustness, functional flexibility, and therapeutic promise. The growing number of patents (>646 in recent years) reflects the high level of research interest and industrial application. With ongoing developments in synthetic chemistry, molecular modeling, and pharmacological screening, oxadiazole-based compounds are well-positioned to serve as lead structures in the development of next-generation drugs. Future research should focus on in-depth mechanistic studies, in vivo evaluations, and optimization of ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, which will further define their role in clinical settings.

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