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A Review on Synthesis and Biological Activities of Oxadiazole Derivatives

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Abstract

Heterocyclic compounds are organic molecules of the cyclic type's compounds with one or more than one heteroatom; such as oxygen, nitrogen or sulphur. They are used as precursors for synthesis of various compounds of pharmaceutical, agrochemicals, paints and dye, food applications. Metal coordinated with heterocyclic compounds are widely used as drugs and in various surgical instruments. Synthetic heterocycles have extensive therapeutic uses such as antibacterial, anticancer, antioxidant and anti-tumor etc. Antibacterial or antibiotics are used to prevent or suppressing bacteria growth. Many heterocyclic compounds such as Doxorubicin, Gefitinib, Nivolumab, Selpercatinib etc., are all FDA approved drugs containing either nitrogen or oxygen heterocyclic moieties. This paper aims to review the synthesis, properties and biological evaluation of oxadiazole heterocyclic compounds that can be further co-ordinated with suitable metal.

Keywords: *Antibacterial Activity, Antioxidant, Heterocyclic Compounds, Oxadiazole*

1.0 Introduction

In our daily life heterocyclic compounds are extremely important. Among them five membered nitrogen and oxygen containing heterocyclic compounds are used extensively for medicinal applications such as anticancer, antitubercular, antifungal, antimicrobial, antiparasitic, anti-inflammatory, antihypertensive, antihistaminic, anti-obesity and other potential medicinal agents[1]. The biological activities of heterocyclic compounds are enhanced through metal co-ordination bonds[2]. Metals such as copper, zinc, iron, magnesium, nickel, cobalt, etc., have been extensively used to increase the stability, bioavailability, and biological properties of heterocyclic compounds[3]. Metal implants and surgical instruments are primary requirement in medical field, and are been used since decade[4]. These surgical instruments are prone to corrosion and to avoid the corrosion organic heterocyclic compounds are used as inhibitors. This review paper high lights the five membered nitrogen and oxygen containing heterocyclic compounds of Oxadiazole and their synthesis, some of their biological activities[6]. Also, various metals complexes of oxadiazoles are also reported in this review article. Oxadiazoles are aromatic heterocyclic compound of the azole family that five membered heterocyclic compounds with two nitrogens

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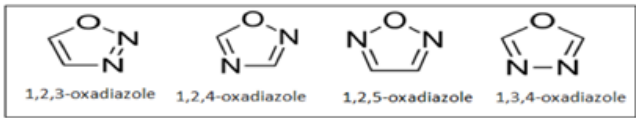


Figure 1. Isomeric structures of oxadiazol.

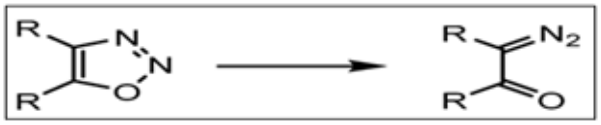


Figure 2. Acyl diazomethane tautomer.

and one oxygen atom. Heterocyclic compounds can also be referred to as furadiazoles. Four isomers of oxadiazole are indicated in the Figure 1. They are 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole (furazan) and1,3,4-oxadiazole[7].

1,2,4-Oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole etc., are the parent core moieties in the FDA approved drugs such as, oxolamine, raltegravir, pleconaril and butalamine[8]. The diazoketone tautomer is formed when the 1,2,3-isomer ring-opens. It is known as a condensed derivative with benzene in solution, along

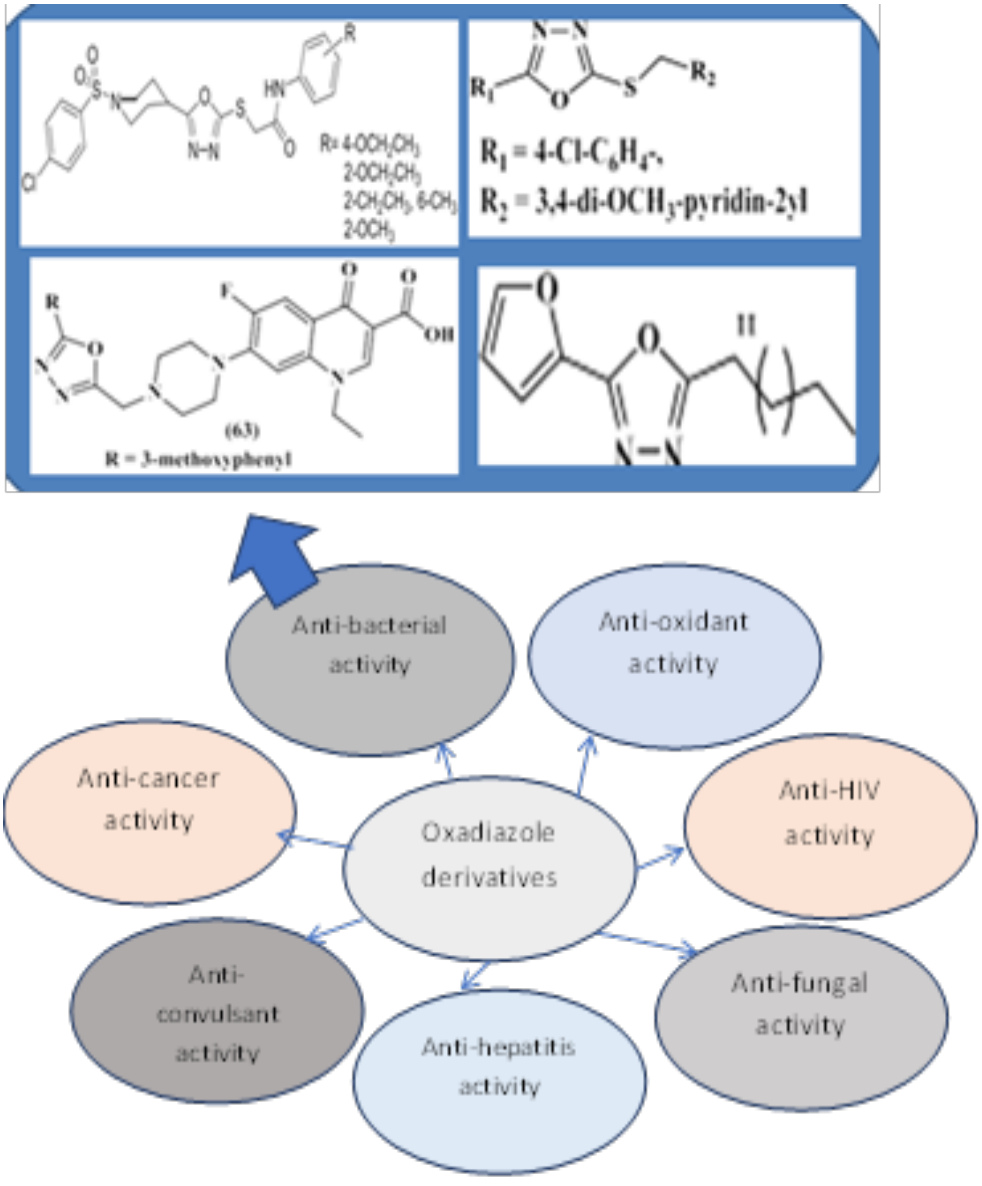


Figure 3. Applications of Oxadiazol.

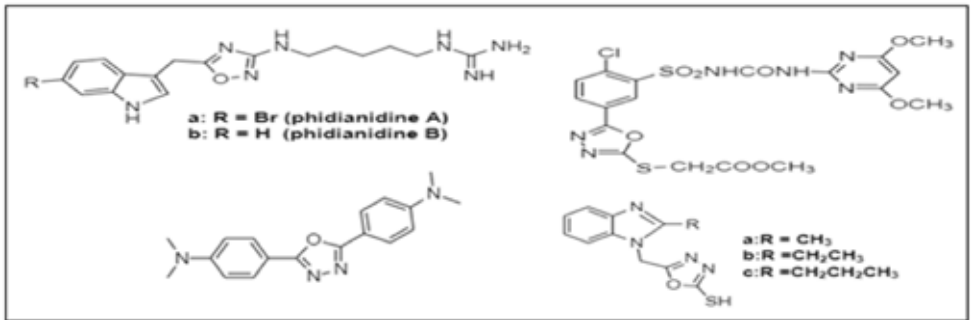


Figure 4. Some of the Oxadiazole derivatives used in medicinal, agricultural and industrial applications.

with mesoionic substances, so it is also called as "sydnones".

Medicinal chemistry has taken considerable advantages of 1,3,4-oxadiazoles and reported to display a broad range of biological activities like antibacterial, hypolipidemic, anti-tubercular, anti-cancer, antifungal, cytotoxic, vasodilatory, anti-inflammatory, analgesic, and ulcerogenic activities[9] (Figure 3).

In addition, oxadiazoles also has greater applications in agricultural and industrial segments. Oxadiazoles with polymer chain containing oxadiazole has been referred as potential ambipolar hosts due to the presence of oxadiazole linkages of phosphorescent light-emitting diodes (Figure 4). Similarly, the oxadiazole-carbazole linkage POC polymer is ir(ppy) as a monomer[10]. Due to this, they obtained composites could show different properties of enhanced light-emitting. These properties could be used to produce Organic Light-Emitting Diode (OLED).

2.0 Physical Properties of 1,3,4-oxadiazole

The liquid form of 1,3,4 oxadiazole having boiling point of approximately 150 °C, and three heteroatoms are capable of forming hydrogen bonds (Table 1). Their 2,5-disubstituted derivatives show no color. In FT-IR spectrum the absorption band at 1640-1650 cm^{-1} corresponds to C=N stretching, and C-O at 1020 cm^{-1}. IN ^{1}HNMR spectrum, peaks at 8.73 ppm in CDCl3. 1,3,4-Oxadiazole is a symmetric, aromatic compound having a resonance energy of 167.4 kJ/mol. 1,3,4-oxadiazole has a refractive index nD of 1.43. Its solubility is dependent on the type of substitution attached[10,11]. Therefore, a molecule with 2,5-dimethyl substitutes is water-soluble, whereas the 2,5-diphenyl substituted counter moiety is less soluble as expected.

Table 1. Characteristics of 1,3,4-oxadiazole

S. N.	Property	Information
1	Molecular weight	70.051 g/mol
2	Molecular formula	$C_2H_2N_2O$
3	Density	1.2 g/cm^3
4	Melting point	-4.26℃
5	Boiling point	150 ℃
6	Flashpoint	62.4 ℃
7	Vapor pressure at 25 ℃	5.0 mmHg
8	Enthalpy of vaporization	31.1 kJ/mol
9	Index refraction	1.416
10	Molar refractivity Platform perceptual analysis	14.7 cm^3

Some of the commercially available drugs containing 1,2,4-oxadiazole includes Fenadiazole (hypnazol is a hypnotic drug), Butalamine (a vasodilator), Pleconaril (suppressesasthmatic symptoms), Proxazole (This drug is used for functional gastrointestinal disorder), Zibotentan (anticancer), Raltegravir (an antiretroviral drug), furamizole (an antibiotic) butyl PBD (a liquid scintillator neutrino, Oxalamine (a suppressant for the cough) and Nesapidil (anti-hypertensive)[12] are as shown in Figure 5.

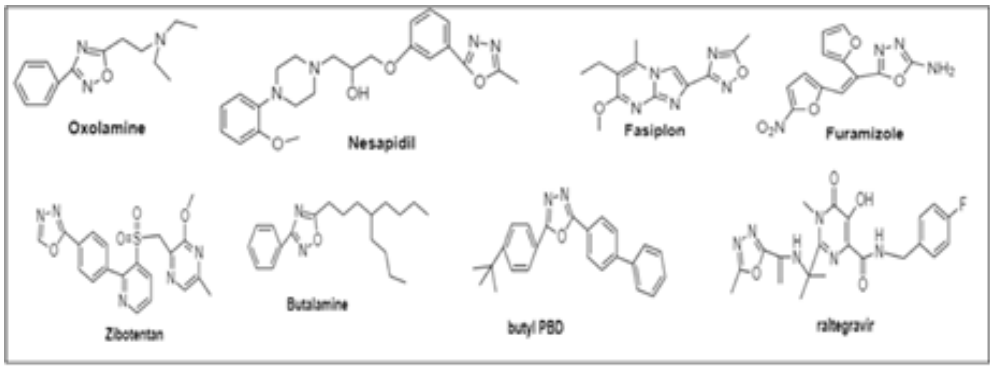
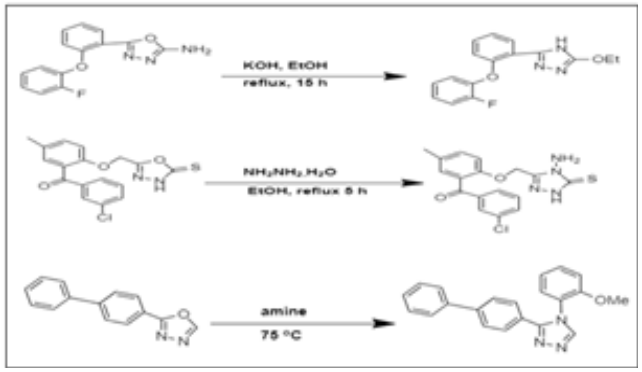


Figure 5. Commercially available drugs containing oxadiazole

3.0 Rearrangement Reaction

According to Almasirad and colleagues, 1,3,4-triazole was produced from 1,3,4-oxadiazole when potassium hydroxide was present (Scheme 1). Similarly, the same transition occurred when amines (2-methoxyphenylamine and 2-methoxybenzylamine) and hydrazine hydrate were present[12-14].



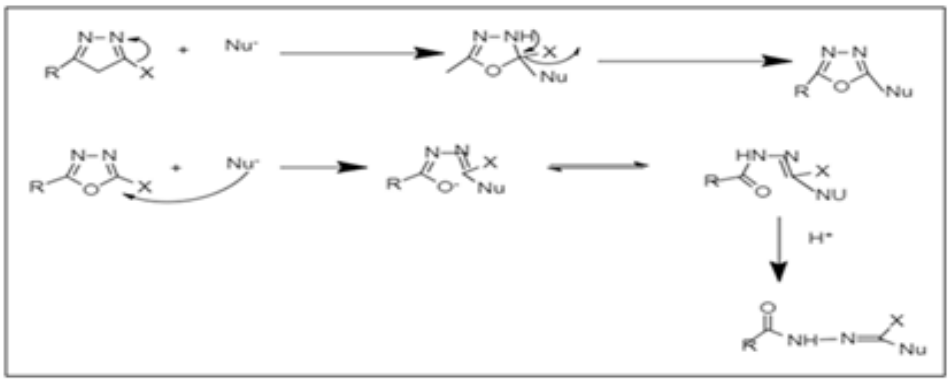
Scheme 1. Rearrangement reactions of 1,3,4-oxadiazoles

4.0 Reactions with Nucleophile

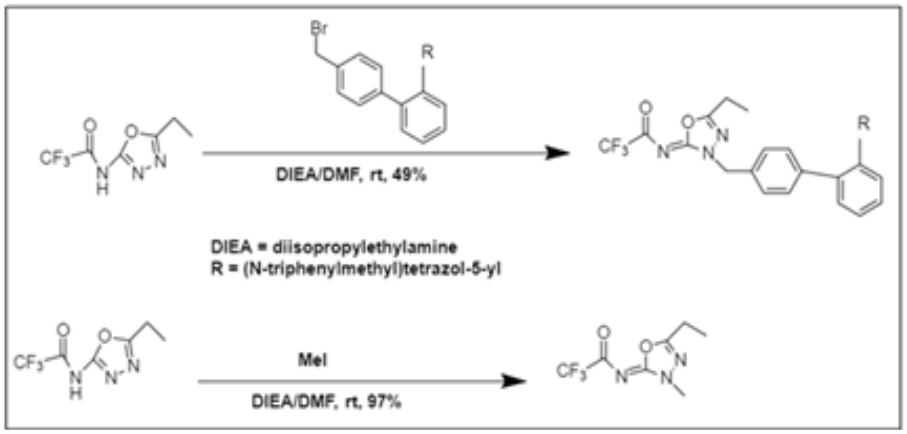
The 2nd or 5th position carbon atoms in 1, 3, 4-oxadiazole ring having lower electron density is prone to undergo nucleophilic attack leading to ring cleavage (Scheme 2). However, the halogen or sulfonyl group present on the 2nd position of carbon of the substituted 1, 3, 4-oxadiazole moiety can be resistant to undergo nucleophilic substitution process[15].

5.0 Nitrogen is Subject to Electrophilic Attack (Electrophilic Assault on Nitrogen)

1,3,4-Oxadiazoles can be made a weak base by increasing the inductive effect by introducing suitable substitution. Alkyl halides and 1,3,4-oxadiazolescan interact to form *N*-alkylation reactions, *endo*-*N*-derivatives were the product produced by alkylating substituted 1,3,4-oxadiazoles[15,16] (Scheme 3).



Scheme 2. Nucleophilic reaction of 1,3,4-oxadiazoles



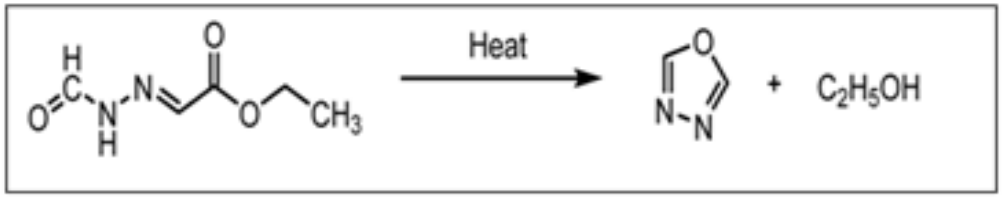
Scheme 3. Electrophilic attack at nitrogen

6.0 Synthesis of Oxadiazole

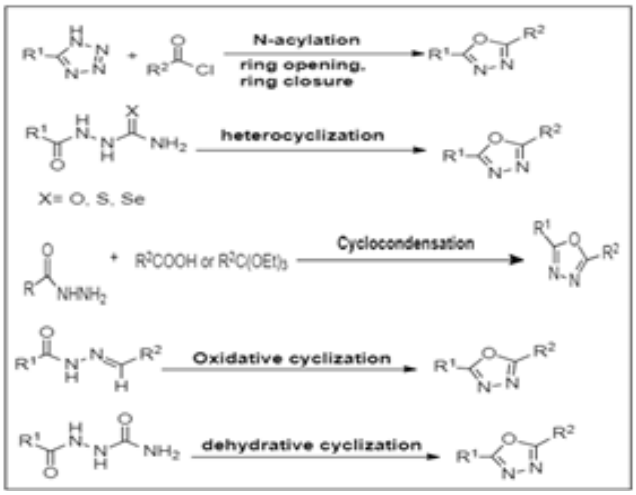
6.1 General Procedure for the Synthesis of 1,3,4-Oxadiazoles

In 1965, Ainsworth reported the first synthesis of 1,3,4-oxadiazole. The synthesis was completed by formyl hydrazine ethyl formate being subjected to thermolysis at atmospheric pressure (Scheme 4).

Schwarzer *et al.,* had proposed a new synthetic route of preheating polyphosphoric acid and phosphorous pentoxide to 100 °C with N,N′-diacylhydrazines or N-acylhydrazones to obtian 1,3,4-oxadiazole (Scheme 5). Several other authors modified the procedure



Scheme 4. Preparation of 1,3,4-oxadiazole by thermolysis



Scheme 5. Some different possible methods for the preparation of 1,3,4-oxadiazoles

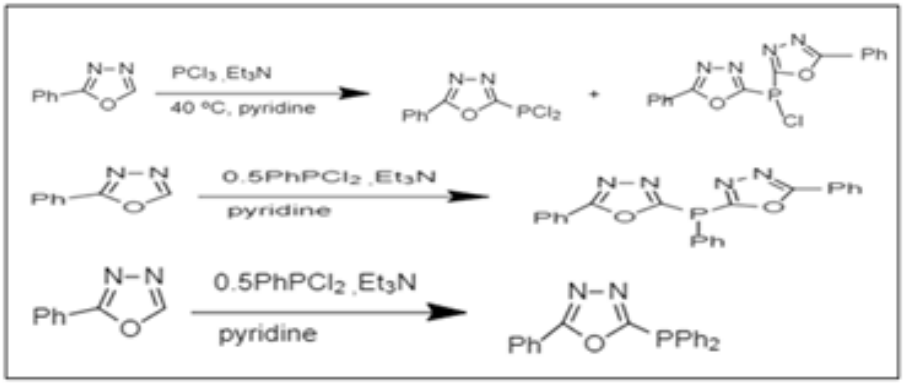
by using different cyclo dehydrating agents[17]. Other possibilities for the synthesis including acylation, that converts 1,2,4-oxadiazole derivatives by opening and closing the tetrazole ring, and heterocyclization of semi carbazides, thio semi-carbazides or selenosemi-carbazides under the influence of UV- radiation.

6.2 1,3,4-oxadiazole Phosphorylation

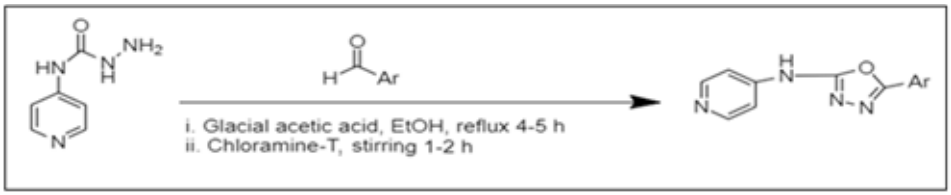
1,3,4-Oxadiazoles were prepared using phosphorus (III) halides in the presence triethylamine[18-20] (Scheme 6).

6.3 Aldehydes and Hydrazides Condensation

To successfully generate 1,3,4-oxadiazoles, chloramine-T was used after glacial acetic acid to carry out the



Scheme 6. Phosphorylation of 1,3,4-oxadiazol



Scheme 7. Oxadiazole is produce through the condensation of an aldehydes and hydrazides

condensation reaction between aldehydes and hydrazides[20,21](Scheme 7).

6.4 Condensation of Hydrazides with Halide

The 1,3,4-oxadiazoles were produced by condensing the hydrazides with 2-chloroacetic acid after being refluxed with substituted halo acetic acid utilizing phosphorus oxychloride as a cyclization agent [21] (Scheme 8)

7.0 Biological Activity

7.1 Antibacterial Activity

Acetamide substituted 1,3,4-oxadiazole derivatives were synthesised and screened against five different bacterial strains (*Salmonella typhi, Escherichia coli, P. aeruginosa, S. aureus* and *Bacillus subtilis*)[22-26].



Scheme 8. Condensation of hydrazides with halide

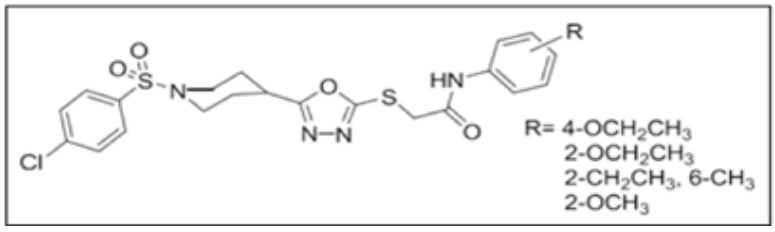


Figure 6.

7.2 Antioxidants Activity

Free radicals can be generated during the chemical process of oxidation, which can then start a chain reaction that damages cells. Antioxidants are molecules that stop other molecules from oxidizing, such as thiol compounds or vitamin C, which can stop these chain reactions and shield cells from damage[26-31]. Some novel 1,3,4-oxadiazole/thiadiazole-2-thiols complexes of organosulfur and organ selenium compounds were synthesized and screened for in vitro antioxidant activity using DPPH free radical.

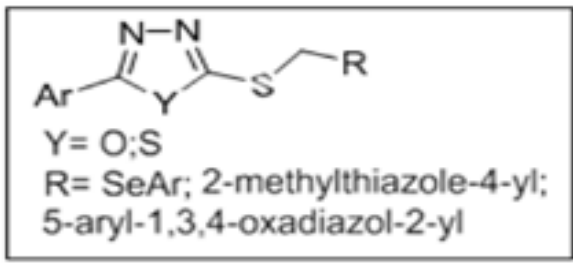


Figure 7.

8.0 Metal-coordinated Heterocyclic Compounds

9.0 Conclusion

In this review, we present the various methods of synthesis of 1,3,4 oxadiazoles and their therapeutical applications such as anti-bacterial, antifungal activity, anti-inflammation, anticancer activities. This review provides the major application of 1,3,4 oxadiazoles in pharmaceutical and gives an insight for the researchers to design more potent 1,3,4 oxadiazoles and metals which can be used to enhance the biological property, bioavailability and stability of the oxadiazole compounds. Metals can be coordinated by substituting various oxygen containing functional groups to increase the solubility, bio-availability, pH stability etc., making the parent moiety more potent.

10.0 References

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Table 2. Metal-coordinated heterocyclic compounds

Sl. No	Metal	Heterocyclic compound	Applications	Reference
1	Nickel	Isatin and coumarin	anticancer activity (Leukemia cancer cell (K-562)	Retnam *et al.*, 2023 [32]
2	CU	Thiosemicarbazones	leukemia cell line (U937)	Serena Montalbano *et al.*, 2023 [33]
3	CU	Oxadiazole	anticancer activity HT-29 (colon)	Ankit Siwach *et al.*, 2020[34]
4	Os	Oxadiazole	HCT-116 lung cancer cell line	Bharat H. Pursuwan *et al.*, 2020[35]
5	Ln	2,2′-bipyridine	MCF-7 (breast cancer	Stefka Ivanova *et al.*, 2023[36]
6	Os	Pyrazol	anticancer activity HCT-116 cell line	Bharat H. Pursuwani *et al.*, 2021[37]

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