



1,3,4-Oxadiazole: A Comprehensive Review of its Chemistry, Synthetic Strategies, Pharmacological activities, and diverse applications

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ABSTRACT :

1,3,4-oxadiazole heterocycle is a five-membered aromatic ring with two nitrogen atoms and one oxygen atom, derived conceptually from furan by substitution of two methylene groups ($=CH-$) with two pyridine-type nitrogen ($=N-$) atoms. This heterocycle has been drawing much attention due to its unusual range of biological activities, its role as a bioisostere of ester and amide groups in drug design, and its usage in materials science and agriculture. This review consolidates the current knowledge of the structural properties of 1,3,4-oxadiazole, its major synthetic routes (cyclodehydration of diacylhydrazines and oxidative cyclization of hydrazones) and its biological profile in anticancer, antimicrobial, antitubercular, antiviral, anti-inflammatory, antiparasitic, and current green-chemistry approaches to its synthesis.

Keywords: 1,3,4-Oxadiazole, Synthetic strategies, Pharmacological activities, Medicinal chemistry, Bioisosterism.

1. INTRODUCTION

Oxadiazoles are five-membered heteroaromatic rings with two carbon atoms, two nitrogen atoms, and one oxygen atom and have four regioisomeric forms [2]. Among the four isomers, 1,3,4-oxadiazole and 1,2,4-oxadiazole are more prominent and well-known due to their extensive range of significant chemical and biological properties [1]. Figure 1 below shows the four isomers alongside the ring numbering of the atoms in the rings with the 1,3,4 isomer being emphasized due to its centrality in the current review.



Figure 1: Isomeric forms of Oxadiazole

Oxadiazoles are common motifs in drug-like molecules and are frequently used as bioisosteric replacements for ester and amide functionalities [2]. A systematic comparison of matched pairs in the AstraZeneca compound collection revealed that, in almost all cases, the 1,3,4-oxadiazole isomer has an order of magnitude lower lipophilicity (log D) than its 1,2,4-isomeric partner, and significant differences also tend to favor the 1,3,4-isomer in terms of metabolic stability, hERG inhibition, and aqueous solubility [2]. These differences can be explained by the intrinsically different charge distributions (such as dipole moments) of the two regioisomers [2]. In short, the 1,3,4-oxadiazole ring is more polar and less fat-soluble than its 1,2,4-isomer, which normally means better water solubility and less accumulation in fatty tissues [2]. Molecular modeling studies further show that introducing the 1,3,4-oxadiazole ring into drug candidates can change their polarity, flexibility and metabolic stability, and the ring can act as a hydrogen-bond acceptor [3]. The ring's pyridine-type nitrogen atoms facilitate the molecule's binding to various enzymes and receptors through weak but numerous interactions, eliciting a wide range of biological effects [4].

There are several marketed drugs containing the 1,3,4-oxadiazole nucleus, one of which is the nitrofuran derivative furamizole, which has a pronounced antibacterial effect; the antiviral drug raltegravir; and the anti-arrhythmic drug nesapidil [1]. Other drugs containing the 1,3,4-oxadiazole nucleus are tiodazosin and zibotentan [5], as well as the clinically approved drugs pleconaril and oxolamine [4]. Table 1 presents these examples of marketed drugs containing the 1,3,4-oxadiazole nucleus along with their therapeutic uses.

DRUG	THERAPEUTIC USE
Raltegravir	HIV-1 integrase inhibitor; first of its class
Furamizole	Nitrofuran antibacterial agent
Tiodazosin	Antihypertensive agent
Nesapidil	Anti-arrhythmic therapy
Zibotentan	Anticancer agent
Pleconaril	Clinically approved, oxadiazole core
Oxolamine	Clinically approved, oxadiazole core

Table 1: Marketed drugs containing the 1,3,4-oxadiazole nucleus

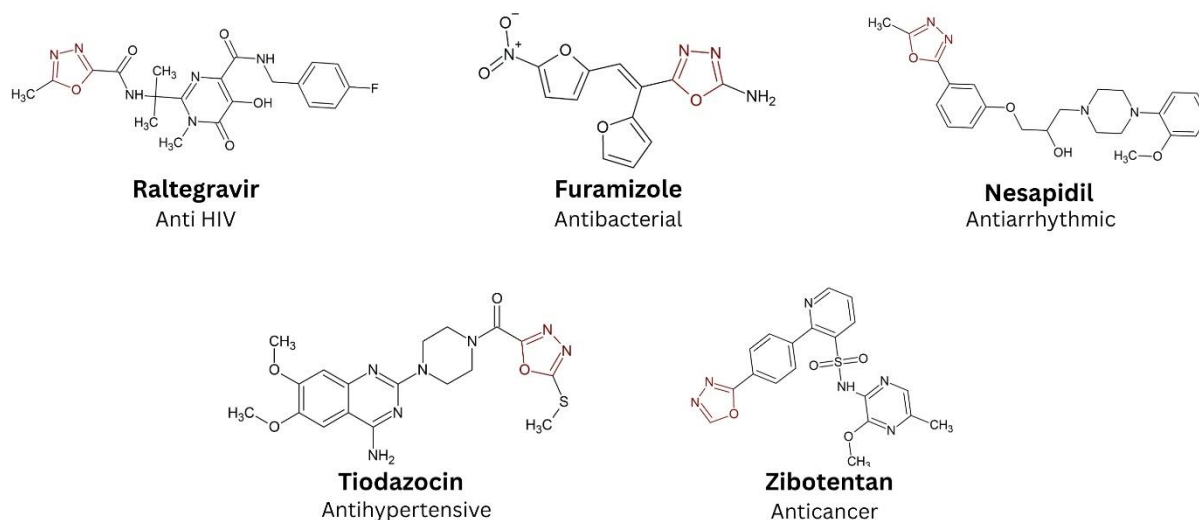


Figure 2: some marketed drugs that containing 1,3,4-oxadiazole nucleus

2. STRUCTURAL CHEMISTRY AND PHYSICOCHEMICAL PROPERTIES

The oxadiazole molecule consists of two nitrogen atoms and one oxygen atom, which together form a five-membered ring of heterocyclic structure [6]. The heterocyclic ring system 1,3,4-oxadiazole nucleus possesses the an $-N=C-O-$ linkage as a characteristic group, which has been extensively utilized in the field of drug discovery [7]. The substituents at positions 2 and 5 of the ring offer the possibility to link a hydrophobic (lipophilic) group as an anchoring element for drug design [7]. In medicinal chemistry practice, this implies that nearly any desired substituent may be introduced at these positions and the behavior of a drug-like molecule will be adjusted accordingly [7].

Compared with the other oxadiazole isomers, 1,3,4-oxadiazoles exhibit better thermal stability, metabolic stability, aqueous solubility, and lower lipophilicity [5]. The ring's high photoluminescent quantum yield, excellent thermal and chemical stability, and the presence of potential coordination (nitrogen and oxygen donor atom) sites make these molecules prominent choices for metal-ion sensors [8]. 2,5-Disubstituted-1,3,4-oxadiazole derivatives

have also been used as electron-conducting and hole-blocking materials in organic electronics, owing to the electron-deficient character and good electron-transport properties of the oxadiazole ring [9].

3. SYNTHETIC STRATEGIES

The principal synthetic routes to 1,3,4-oxadiazoles are summarized in Figure 3. Each route is described in detail below.

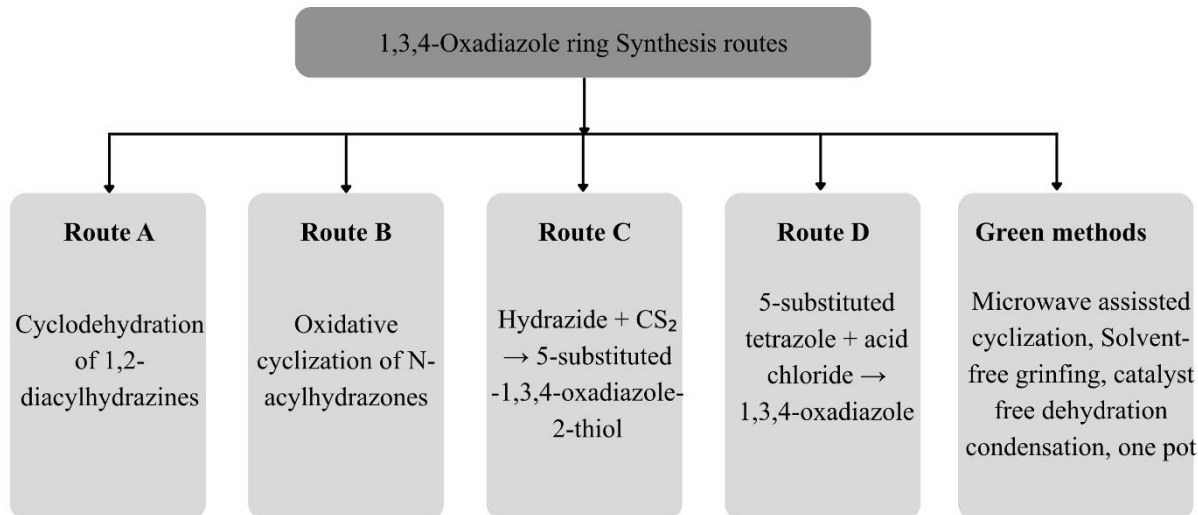


Figure 3: Overview of the principle synthetic routes to 1,3,4-oxadiazole and emerging green methods.

3.1 Cyclodehydration of diacylhydrazines

This is the most typical approach. The reaction begins with 1,2-diacylhydrazines, which are formed by combining two acid hydrazide fragments [9]. These hydrazines are then exposed to a dehydrating agent (a chemical that eliminates water), resulting in the two fragments closing into a ring and forming the 1,3,4-oxadiazole [10, 9]. Typical dehydrating agents include thionyl chloride, polyphosphoric acid, phosphorus pentoxide, acetic anhydride, phosphorus oxychloride, and sulfuric acid [10, 9]. On the other hand, acid hydrazides can also react directly with acid chlorides or carboxylic acids to yield the same product [11]. This method is preferred since the starting materials (hydrazides, hydrazines and hydrazones) are available and inexpensive [9], but the reaction conditions are often severe and require long periods of incubation [9].

3.2 Oxidative cyclization of N-acylhydrazones

In this route, the starting materials are hydrazide-hydrazones, which are obtained by condensing (joining together) a carboxylic acid hydrazide with an appropriate aldehyde [9]. The hydrazone is then treated with an oxidizing agent, which induces an internal cyclization (the formation of a ring) to close the ring and yield the 1,3,4-oxadiazole [9]. Typical oxidants include potassium permanganate in acetone, bromine in acetic acid, Pb_3O_4 , and chloramine-T [9]. Alternative oxidants include transition metal oxidants (Pb, Mn, Fe, Ce, Cu), trichloroisocyanuric acid, iodobenzene diacetate, Dess-Martin periodinane, and electrochemical methods [9]. A recent and effective variant makes use of iodosobenzene and boron trifluoride etherate, which reacts with aromatic aldehyde N-acylhydrazones at room temperature to yield 2,5-disubstituted-1,3,4-oxadiazoles in mild to good yields [9].

3.3 Reaction with Carbon disulfide and related reagents

5-Substituted-1,3,4-oxadiazole-2-thiols (that is, oxadiazoles bearing a sulfur-containing thiol group at position 2) can commonly be prepared by reaction of acid hydrazides with carbon disulfide [11]. This approach is significant because the resulting thiol group is a convenient group for subsequent chemical modification, allowing chemists to attach a wide variety of substituents to the sulfur atom [11].

3.4 Tetrazole and multicomponent approaches

A contemporary approach allows conversion of 5-substituted tetrazoles with carboxylic acid chlorides into 1,3,4-oxadiazoles [11]. Irradiation with microwave energy enabled reaction of 5-phenyl-1H-tetrazole with terephthaloyl chloride to give a bis-oxadiazole product with 81.6% yield versus only 15.5% under conventional heating at 100 °C for 12 hours [11]. In more recent work, multicomponent strategies making use of (N-isocyanoimino)triphenylphosphorane (NIITP) as a three-atom C-N-N source have been developed allowing for the post-functionalization of drug-like

amides and carboxylic acids [12]. The reaction of carboxylic acids with NIITP is also listed amongst the common synthetic routes for preparing 1,3,4-oxadiazole analogues [11].

3.5 Green and microwave assisted methods

Traditional methods commonly employ acid hydrazides and dehydrating agents such as phosphorus oxychloride, but yield low amounts of product and generate dangerous byproducts [13]. However, green chemistry methods, such as solvent-free processes, microwave-assisted synthesis, and non-toxic catalysts, have been shown to increase efficiency, lower energy consumption, and give higher yields with lower hazardous byproducts [13]. Microwave irradiation allows for these reactions to be simple, rapid, high yielding, and avoid chromatographic purification [14]. One-pot synthesis of 2-amino-1,3,4-oxadiazoles from isothiocyanates and hydrazides in the presence of tert-butyl hydroperoxide in water under microwave irradiation gives products in high yields (85-98%) [15]. Microwave mediated synthesis is one of the innovative green techniques highlighted in recent reviews [16]. Table 2 highlights these methods by comparing them side by side.

ROUTE	STARTING MATERIALS	TYPICAL REAGENTS	ADVANTAGES	LIMITATIONS
Cyclodehydration	1,2-diacylhydrazines	SOCl_2 , POCl_3 , P_2O_5 , PPA, Ac_2O , H_2SO_4	Scalable, readily available starting materials	Harsh conditions, long reaction times
Oxidative cyclization	N-acylhydrazones	KMnO_4 , Br_2/AcOH , Pb_3O_4 , chloramine-T, $(\text{PhIO})_n/\text{BF}_3 \cdot \text{Et}_2\text{O}$	Mild conditions possible	Toxic metal oxidants in some variants
CS_2-mediated	Acid hydrazides	CS_2/KOH	Access to 2-thiol derivatives for further derivatization	Multi-step
Tetrazole route	5-substituted tetrazoles, acid chlorides	Microwave or conventional heating	High yields (81.6% under MW)	Limited substrate scope
NIITP multicomponent	Tertiary amides, carboxylic acids, NIITP	Vaska's complex, TMDS	Late-stage functionalization of drug-like molecules	Specialized reagent
Green methods	Various hydrazides/isothiocyanates	MW irradiation, solvent-free, water, TBHP	85-98% yields, eco-friendly, shorter times	Requires specialized equipment

Table 2: Comparison of principle synthetic routes to 1,3,4-oxadiazoles

4. BIOLOGICAL ACTIVITIES

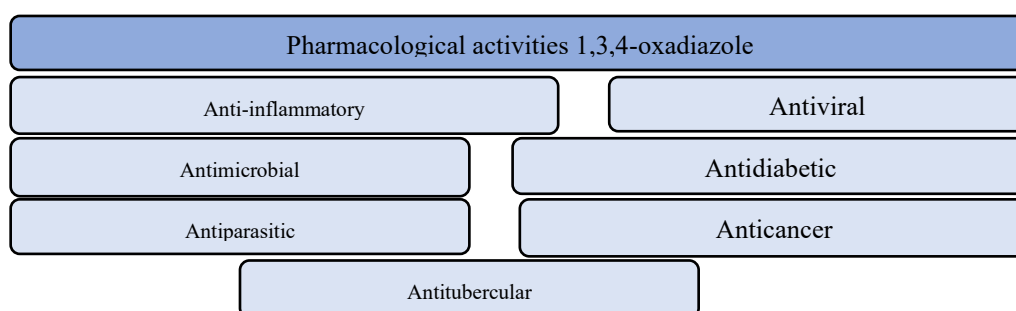


Figure 4: Pharmacological activities of 1,3,4-oxadiazole

4.1 Anticancer activity

The anti-cancer potential of 1,3,4-oxadiazoles has been reviewed in detail, and their derivatives have demonstrated anti-proliferative activity through the inhibition of various growth factors, enzymes, and kinases [17]. In most of the publications reviewed, the most active derivatives of 1,3,4-oxadiazole have had better efficacy than reference drugs [17]. Mechanistically, the hybridization of 1,3,4-oxadiazole with other anti-cancer pharmacophores inhibited various enzymes including thymidylate synthase, HDAC, topoisomerase II, telomerase, and thymidine phosphorylase [18].

Representative examples include novel unsymmetrical 1,3,4-oxadiazoles where the most active agent, compound 2j, has shown high potency against human cancer cells with IC_{50} values ranging from 0.05 to 1.7 μ M and caused G₂/M arrest of the cell cycle with a strong apoptotic response [19]. Lipophilic 1,3,4-oxadiazoles that were coupled to alkylated piperazine with 10-14 carbon chain moieties gave IC_{50} values of 1.6 to 3.55 μ M for the 4T1 mammary carcinoma cell line and up to 3.9 μ M for CT26 colon cancer cells, with a selectivity index up to 19 [20]. In simple terms, these compounds kill cancer cells at very low concentrations while leaving healthy cells relatively unharmed [19, 20].

4.2 Antimicrobial

The worldwide development of antimicrobial resistance drives scientists to find new compounds against which microbes would be sensitive, and many new structures that contain the 1,3,4-oxadiazole ring have exhibited antibacterial, antitubercular, antifungal, antiprotozoal, and antiviral activities [23]. In many publications, the activity of new 1,3,4-oxadiazole compounds is higher than the activity of already known antibiotics and other antimicrobial agents [23]. The presence of the 1,3,4-oxadiazole group in antimicrobial agents can change their polarity and flexibility, which largely improves biological activities through hydrogen-bond, steric, electrostatic, and hydrophobic interactions with target sites [24]. The molecular targets of 1,3,4-oxadiazoles as antimicrobial agents include enoyl reductase (InhA) and 14- α -demethylase of the mycobacterial cell; GlcN-6-P synthase, thymidylate synthase, peptide deformylase, RNA polymerase, and dehydrosqualene synthase of bacterial strains; and the ergosterol biosynthesis pathway, P450-14- α -demethylase, and protein-N-myristoyltransferase of fungal strains [24].

4.3 Antitubercular activity

Several series of 1,3,4-oxadiazoles have been developed as antitubercular drugs against *Mycobacterium tuberculosis*. 5-Substituted-2-[(3,5-dinitrobenzyl)sulfanyl]-1,3,4-oxadiazoles showed outstanding in vitro activity against *M. tuberculosis* and six multidrug-resistant clinical isolates, and minimum inhibitory concentration values were as low as 0.03 μ M [25]. These compounds showed highly selective antimycobacterial effects with no activity against other bacteria or fungi tested, and they showed low in vitro toxicities in four proliferating mammalian cell lines [25] and in isolated primary human hepatocytes [25]. A 2-mercapto-1,3,4-oxadiazole lead (compound 8j) showed a MIC of 0.6 μ g/mL against *M. tuberculosis* H37Rv, was not toxic to CHO-K1 cells with a selectivity index of 39, and showed activity against a pre-extensively drug-resistant clinical isolate [26].

4.4 Antiviral and anti-HIV activity

1,3,4-Oxadiazole is described as a privileged structure that confers on its derivatives a wide and potent range of biological functions, including antiviral activities, such as anti-HIV, anti-HCV, anti-HBV and anti-HSV [3]. Molecular modelling and pharmacokinetic studies suggest that the introduction of the 1,3,4-oxadiazole ring into inhibitors may alter the polarity, flexibility and metabolic stability, and the ring can act as a hydrogen-bond acceptor, and thus can be a valuable isosteric substituent of amide or ester groups in antiviral drug design [3].

4.5 Anti-inflammatory and analgesic activity

Literature from 2005 to 2016 is rich with reports of synthesized 1,3,4-oxadiazoles designed to possess substantial anti-inflammatory and analgesic activity with a lesser degree of adverse effects, including derivatives of existing NSAIDs [27]. This is significant because the typical NSAIDs, such as ibuprofen and indomethacin, are associated with a high risk of side effects, for example, ulcers; oxadiazole derivatives of these drugs are designed to mitigate this issue [27].

4.6 Antidiabetic activity

Oxadiazole derivatives can be considered promising hits in antidiabetic drug discovery field since they are able to modulate peroxisome proliferator-activated receptor gamma, α -glucosidase, α -amylase and glycogen synthase kinase 3 beta, key regulators of glucose homeostasis and insulin signaling [28].

4.7 Antiparasitic activity

Oxadiazole 2-oxides that were identified from a quantitative high-throughput screen as inhibitors of the parasite enzyme thioredoxin glutathione reductase (TGR) with low micromolar to low nanomolar activities were shown to cure infected mice of multiple schistosome stages upon treatment with 4-phenyl-1,2,5-oxadiazole-3-carbonitrile-2-oxide [53]. This type of activity was linked to nitric oxide donation [53], while structure/mechanism studies elucidated the pharmacophore and connected the ability of oxadiazole 2-oxide to donate NO with its inhibitory activity against TGR [54]. Previously, it was reported that 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles represent a novel class of antimalarial agents with activity in mice infected with *Plasmodium berghei* [55]. More recently, a pan-active 1,3,4-oxadiazole antiparasitic compound (24) has been described, which demonstrated low micromolar IC₅₀ values against *Trypanosoma brucei* and *Leishmania promastigotes* and amastigotes with nanomolar IC₅₀ against *Plasmodium falciparum* and high selectivity for the parasite over mammalian cells [56].

5. APPLICATIONS BEYOND MEDICINE

5.1 Materials science and optoelectronics

Oxadiazole derivatives are among the most promising electron-conducting/hole-blocking materials for organic light-emitting devices [9]. 2,5-Disubstituted-1,3,4-oxadiazole derivatives are appropriate electron-conducting and hole-blocking materials, as the oxadiazole ring is electron-deficient and has good electron-transporting properties [9]. What is more, their high photoluminescent quantum yield, chemical and thermal stability, and the availability of the potential coordination site (the nitrogen and oxygen donor atoms) make them attractive molecular building blocks for metal-ion sensors [8].

5.2 Fluorescent chemosensors

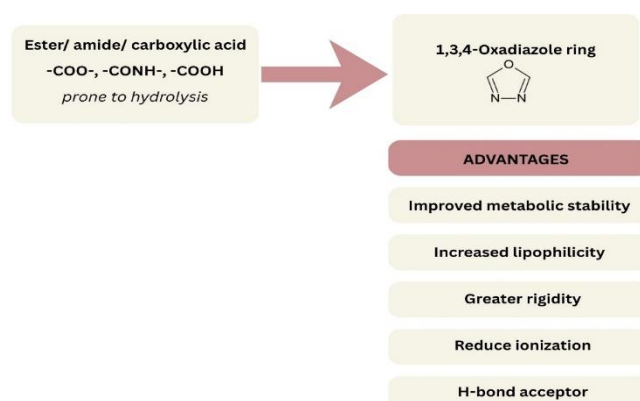
A thiophene-substituted 1,3,4-oxadiazole derivative acts as a turn-off fluorescence chemosensor for Fe²⁺ and a turn-on for Ni²⁺ and Cu²⁺ with limits of detection in the order of 0.5-3 μM [8]. A calix[4]crown-based 1,3,4-oxadiazole is selectively quenched by Cu²⁺ via a photo-induced electron transfer mechanism and acts as an on-off switchable fluorescent chemosensor triggered by metal ion exchange [8]. This happens because the ring of the oxadiazole contains nitrogen and oxygen atoms that can bind metal ions, modulating (changing) the fluorescence of the compound [8].

PROBE SCAFFOLD	TARGET ION	DETECTION LIMIT	KEY PROPERTY
Thiophene-substituted TTO	Fe ²⁺ (off), Ni ²⁺ and Cu ²⁺ (on)	0.5-3 μM	1:1 binding stoichiometry
Oxadiazole-based OFF-ON	Zn ²⁺	Not reported	Living-cell imaging
Double oxadiazole-BAPTA salt	Cd ²⁺	20 nM	Living-cell imaging in MCF-7
Ratiometric oxadiazole probe	Ca ²⁺	Not reported	202 nm Stokes shift; 490/582 nm
Calix[4]crown oxadiazole	Cu ²⁺	Not reported	On-off switchable via PET
Tricyclic heterocyclic probe	Pd ²⁺	3.97 x 10 ⁻⁹ M	Water-soluble; fast response

Table 3: Representative 1,3,4-oxadiazole fluorescent chemosensors and their targets

6. Bioisosterism and drug design considerations

Figure 5: Bioisosteric replacement of ester/ amide/ carboxylic acid groups by the 1,3,4-oxadiazole ring and its principal advantages



The 1,3,4-oxadiazole nucleus is a bioisostere of carboxylic acid, ester and amide groups which contributes to pharmacological activity by engaging in hydrogen-bonding interactions with receptors[4]. Bioisosteres are groups of atoms or substituents that are capable of mimicking or replacing another group of atoms in a drug (while retaining its effect); the 1,3,4-oxadiazole ring replaces the ester or amide group and is more resistant to hydrolysis (breaking down by water)[4]. The 1,3,4-oxadiazole ring is a bioisostere of amide and ester functions, imparting favorable physicochemical properties including increased metabolic stability and lipophilicity as well as hydrogen bonding potential[28].

The bioisosteric substitution has to be used wisely. Raltegravir, which contains a 1,3,4-oxadiazole ring was found to undergo ring cleavage at pH 1.0 and 13.0 in vitro and thus reduced anti-HIV activity of the drug; cyclodextrins can protect it from such pH effects[2]. This example demonstrates that although 1,3,4-oxadiazoles are generally hydrolytically stable analogs of esters and amides they can undergo degradation at extreme pH[2].

CONCLUSION

1,3,4-Oxadiazole is a privileged five-membered heterocycle that finds its place in medicinal chemistry, agrochemistry, corrosion science, and optoelectronics due to its combination of metabolic stability, hydrogen bond capacity, favorable lipophilicity profile compared to the 1,2,4- isomer, and potential for synthesis under both classical and green conditions. This heterocycle is present in a number of marketed drugs (raltegravir, furamizole, tiadazosin, nesapidil, zibotentan, pleconaril and oxolamine) and has ongoing SAR-driven drug discovery efforts for anticancer, antimicrobial, antitubercular, antiviral, anti-inflammatory, anticonvulsant, antidiabetic and antiparasitic agents. Thus, 1,3,4-oxadiazole will continue to play a significant role in drug discovery in the years to come. The 30 references cited in this article provide a good foundation for any researcher starting in this area of heterocyclic chemistry.

Conflict of interest

The authors declare that they have no known financial, commercial, or personal conflicts of interest that could have influenced the work reported in this review article. All authors confirm that the research was conducted independently and that no external organization or individual had any role that could bias the content or conclusions of this manuscript.

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