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Review

Synthesis and Biological Activity of 1,3,4-Oxadiazoles Used in Medicine and Agriculture

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Abstract: Biologically active compounds play a key role in the fight against diseases affecting both human and animal living organisms, as well as plants. Finding out about new molecules with a potential biological effect, not yet described in the literature, is one of the most important aspects in the development of medicine and agriculture. Compounds showing desirable biological activity include heterocyclic moieties such as 1,3,4-oxadiazoles. The oxadiazole molecule is composed of two nitrogen atoms and one oxygen atom, forming a five-membered heterocyclic ring. Structures of this type have been successfully used in the treatment of various diseases in humans and animals, and play an important role in modern agriculture. It has been proven that many oxadiazole derivatives exhibit antibacterial, antiviral, blood pressure lowering, antifungal, antineoplastic, anticancer, antioxidant, anti-inflammatory and analgesic properties. In addition, compounds based on 1,3,4-oxadiazole can act as plant protection agents due to their herbicidal, insecticidal and fungicidal activity. Due to the constantly growing interest in heterocyclic systems of this nature, new methods of obtaining complex structures containing oxadiazole rings are sought. This article discusses various methods of synthesis of 1,3,4-oxadiazole derivatives exhibiting biological activity. Based on these techniques, these compounds could be used in the future in medicine and agriculture.

Keywords: 1,3,4-oxadiazoles; medicine; agriculture; biological activity; synthesis

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1. Introduction

Many plants are at risk of attack by phytopathogenic types of fungus. Diseases caused by these types of microorganisms can cause considerable damage [1]. Invasions of these pathogens also create the possibility of competition for valuable nutrients and disturb the normal metabolic balance of plants. As a result, various consequences may be observed in the development and growth of the plant. The most common diseases caused by attacks by pathogens include etiolation and necrosis [2]. Additionally, it is common for several types of microorganisms to attack simultaneously. In this way, it is possible to intensify the negative effects on the plant organism [3]. The problems associated with this type of infection have a significant impact on the quality and yield of the harvested crop, leading to large economic losses [4]. Unfortunately, the frequent or improper use of traditional pesticides contributes to the development of specific fungal resistance, thus making it difficult to effectively fight infections [5]. The search for new, safer, and more efficient plant protection products has become a priority for many research teams around the world. New compounds capable of selectively attacking a given pathogen using unique mechanisms of action, or by turning off microbial resistance, are highly desirable.

Increasing antimicrobial resistance is also a global problem in medicine, placing a significant burden on healthcare sectors as well as increasing morbidity and mortality worldwide. According to estimates published by the WHO, 13 million people suffer from fungal diseases, of which 1.6 million die each year due to serious fungal infections such as cryptococcosis invasive candidiasis, invasive aspergillosis and their chronic forms, as well

as pneumocystosis [6]. The irrational use of antimicrobials in the clinical and veterinary sectors has led to the selection, spread, and evolution of multidrug-resistant microorganisms. To overcome this problem, combinational therapies that combine several antimicrobial substances are widely used in the pharmaceutical industry. However, high toxicity is often observed, and drug–drug interactions cannot always be effectively predicted. Therefore, the development and synthesis of polyactive compounds which selectively and simultaneously target several pathogens can help in the fight against antimicrobial resistance. A literature study revealed that complex 1,3,4-oxadiazole derivatives are valuable compounds in this respect. These molecules are widely used in the production of many biopharmaceutical substances, showing a wide range of biological activities [7].

Oxadiazoles belong to the group of heterocyclic compounds which contains one oxygen and two nitrogen atoms, forming a five-membered heterocyclic ring. The oxadiazole molecule is derived from furan, where two carbon atoms are replaced by nitrogen atoms of the pyridine type. Oxadiazole molecules have many properties that are used in various industries. These compounds exhibit a wide spectrum of biological activity, which makes it possible to apply them in medicine and pharmacology as active agents, e.g., with anti-inflammatory and analgesic [8], antimicrobial [9], antiviral [10], antifungal [11], antitumor [12] and blood pressure lowering properties [13]. The antimicrobial properties of 1,3,4-oxadiazoles were the subject of a recent review [14]. Due to the potential biological activity of this type of compound, they are also used in agriculture as herbicides, insecticides and plant protection agents against diseases caused by bacteria, viruses and fungi. The oxadiazole moieties also have valuable optical properties. The 1,2-diazole fragment present in the molecule acts as an electron withdrawing group, so it is widely used in various types of conducting systems [15]. It is therefore possible to increase the quantum yield of fluorescence and improve the stability of the molecule. For this reason, oxadiazole derivatives are used as organic light emitting diodes, laser dyes, optical brighteners and scintillators [15–17]. These molecules can be also found in materials such as thermal insulation polymers (Figure 1) [18].

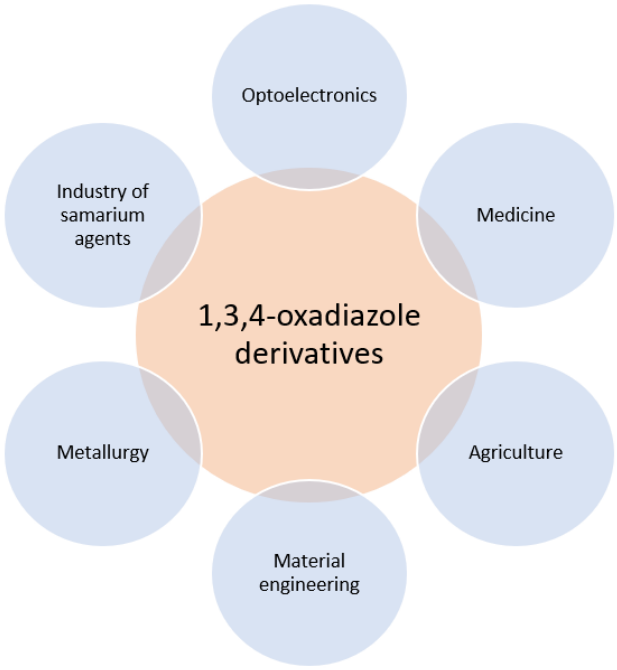


Figure 1. Possible applications of 1,3,4-oxadiazole derivatives.

2. Chemistry of Oxadiazoles

These compounds are composed of a five-membered heterocyclic ring containing two nitrogen atoms and one oxygen atom. Due to the different arrangement of the het-ero-

atoms, oxadiazoles exist in different isomeric forms, e.g., 1,3,4-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole and 1,2,5-oxadiazole (Figure 2). Aromatic systems are so-called azoxins, while five-membered cyclic molecules with the same number of nitrogen and oxygen atoms that have been partially reduced are known as furoxanes [19].

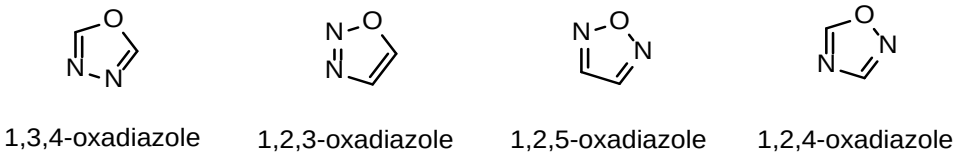


Figure 2. Isomeric structures of oxadiazoles [20].

Given the presence of and open ring, i.e., the diazo-ketone tautomer, 1,2,3-oxadiazole is an extremely unstable structure. It was known as a condensed derivative with benzene in solution [21], as well as in mesoionic substances, so-called "sydnones" (Figure 3) [22].

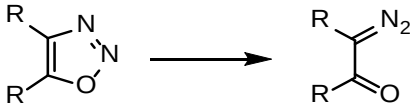


Figure 3. Acyldiazomethane tautomer [21].

In contrast to 1,2,3-oxadiazoles, other isomers, namely 1,2,4-oxadiazoles, are thermodynamically stable. Their reactivity is mainly influenced by their aromaticity. The high reactivity to ring rearrangement reactions is attributed to the relatively low aromaticity of 1,2,4-oxadiazoles [23,24]. On the basis of the performed calculations, it was found that the aromaticity index for 1,2,4-oxadiazole was lower than for the furan molecule [25]. In recent years, many 1,2,4-oxadiazole derivate structures have been detected using X-ray structure spectroscopy (1–4) [26,27]. The structures that can be used in energetic materials [28] and complex compounds based on 1,2,4-oxadiazole derivatives that can bind copper or cobalt cations, and have biological activity, have been determined [29–31] (Figure 4).

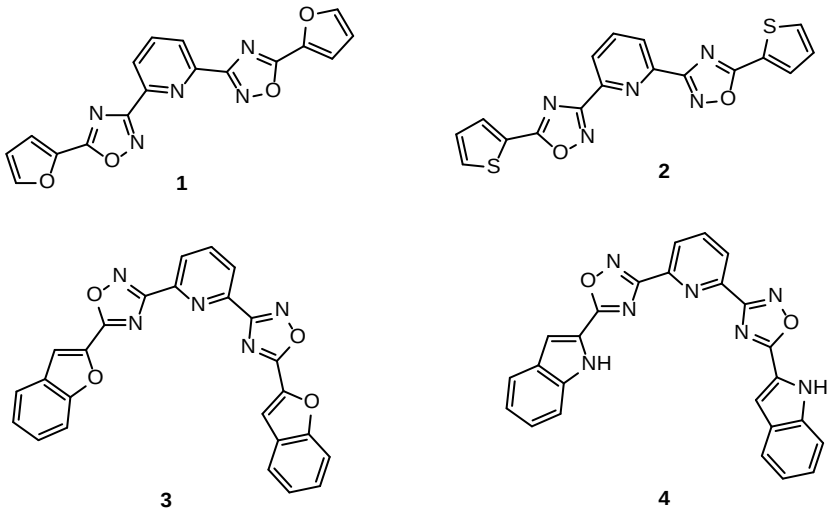


Figure 4. Examples of compounds based on 1,2,4-oxadiazole units (**1**) 2,6-bis(5-furan-2yl)-1,2,4-oxadiazol-3-yl)pyridine; (**2**) 2,6-bis(5-(thiophen-2yl)-1,2,4-oxadiazol-3-yl)pyridine; (**3**) 5-(benzofuran-2-yl)-3-(6-(5-(2,3-dihydrobenzofuran-2yl)-1,2,4-oxadiazol-3-yl)pyridin-2-yl)-1,2,4-oxadiazole; (**4**) 3-(6-(5-(1H-indol-2-yl)-1,2,4-oxadiazole-3-yl)pyridin-2-yl)-5-(indolin-2-yl)-1,2,4-oxadiazole [27].

Due to the realtively low aromaticity and high susceptibility of the O–N bond to reduction, 1,2,4-oxadiazoles are investigated for the possibility of rearrangement into other

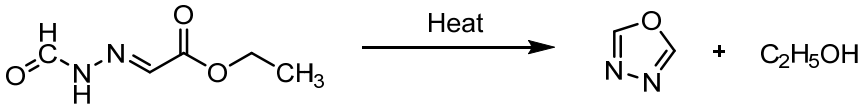
heterocyclic compounds. Moreover, the nitrogen and carbon atoms present in the molecule are characterized by nucleophilic and electrophilic characteristics, while the entire ring has the properties of an electron withdrawing group, which leads to increased reactivity of the attached substituents [27,32,33].

Colloquially called furazan, 1,2,5-Oxadiazole is another isomeric form of oxadiazole. The furazan ring is very susceptible to breaking. For example, the presence of sodium hydroxide in aqueous solution is able to completely cleave the heterocyclic ring [34]. Due to its high positive enthlapy of formation and high density, furazan and their oxides (furoxan) have recently gained popularity in the synthesis of high-energy and explosive materials. These compounds improve the oxygen balance and also release nitrogen gas, which is harmless to the environment, during decomposition [35].

The most stable isomeric structure among all isomeric oxadiazoles is unsubstituted 1,3,4-oxadiazole. The basic unit of 1,3,4-oxadiazole is a liquid with a boiling point of 150 °C. Lower alkyl derivatives are also liquids. Aryl substituents significantly increase melting and boiling points, especially in the case of symmetrical derivatives. Substitution with different functional groups at the 2 and 5 positions of the oxadiazole ring typically lowers the melting and boiling points. The solubility of 1,3,4-oxadiazoles in water is determined by the type of substituents on the heterocyclic ring. With two methyl groups, 1,3,4-Oxadiazole is completely soluble in water, while aryl substituents lower the solubility significantly. Oxadiazoles can be converted to other five-membered heterocycles: the use of hydrazine hydrate converts 1,3,4-oxadiazoles to triazolamines, while thiourea converts the 1,3,4-oxadiazole ring to the thiadiazole [36–38]. Oxadiazoles belong to a group of compounds capable of transporting electrons efficiently and blocking electron holes. Such activity is demonstrated by both low-molecular-weight derivatives as well as polymers and dendritic forms [39–41]. They also have a wide energy gap between the HOMO and LUMO orbitals due to the limited conjugation of π electrons in the heterocyclic ring [42]. For this reason many 1,3,4-oxadiazole derivatives constitute an important class of compounds that have been used successfully in optoelectronics, organic light emitting diodes and organic photovoltaics [43–48]. Additionally, 1,3,4-Oxadiazoles possess biological activity, and their derivatives are used in medicine and pharmacology, as well as in agriculture [49].

3. General Methods for the Synthesis of 1,3,4-Oxadiazoles

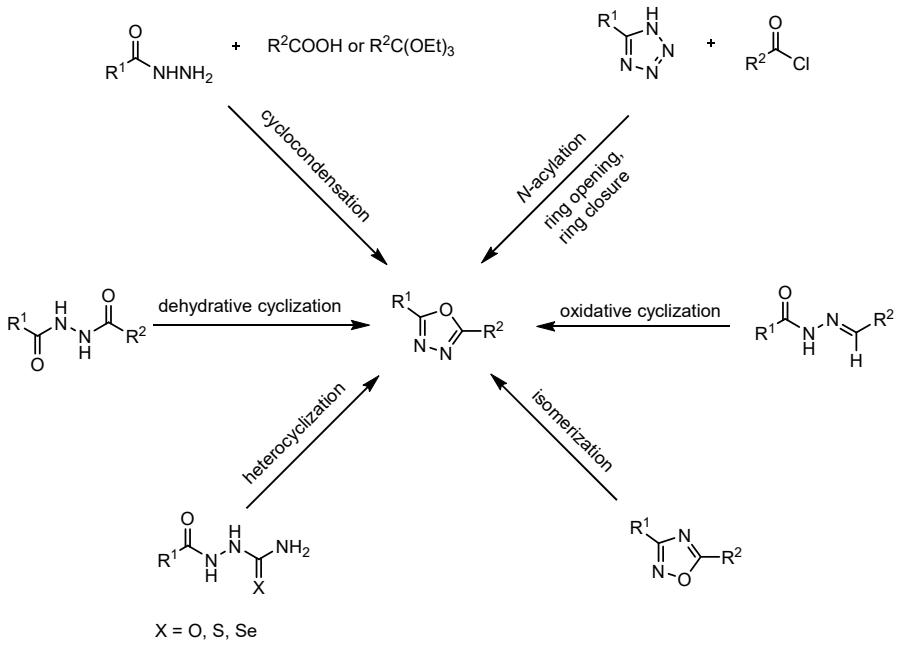
The preparation of unsubstituted 1,3,4-oxadiazole was first described by Ainsworth in 1965. The synthesis was carried out by applying thermolysis at atmospheric pressure to formylhydrazone ethylformate (Scheme 1) [50,51].



Scheme 1. First preparation of 1,3,4-oxadiazole by thermolysis [51].

Basic unsubstituted 1,3,4-oxadiazole can be obtained using the simplest *N*,*N*′-diformylhydrazine in a reaction with phosphorus pentoxide in the presence of polyphosphoric acid. The synthesis technique proposed by Schwarzer et al. is based on preheating the polyphosphoric acid to a temperature of about 100 °C in the first step and then adding P_2O_5. Hydrazine can then be added to the mixture. The reaction is carried out at elevated temperature for several hours. Unsubstituted 1,3,4-oxadiazole thus obtained can then be neutralized with sodium bicarbonate [52]. The most popular methods of obtaining 1,3,4-oxadiazole derivatives are based on the use of *N*,*N*′-diacylhydrazines or *N*-acylhydrazones (Scheme 2). The most frequently used cyclodehydrating agents for *N*,*N*′-diacylhydrazines are polyphosphoric acid (PPA) [53], H_2SO_4 [54], $POCl_3$ [55], $SOCl_2$ [56], $(CF_3SO_2)_2O$ [57], P_2O_5 [58], $BF_3{\cdot}OEt_2$ [59] or Burgess reagent [60]. In addition, it is possible to obtain 1,3,4-oxadiazole derivatives by oxidative cyclization of *N*-acylhydrazones with oxidizing substances such as ceric ammonium nitrate (CAN) [36], Br_2 [61], $KMnO_4$ [62], PbO_2 [63],

chloramine T [64], DDQ [65], or hypervalent iodine reagents [66,67]. One-pot syntheses of oxadiazole groups from acid hydrazides with carboxylic acids and ortho-esters in the presence of an acid catalyst are also described in the literature [68–71]. Other possibilities of synthesis include acylation, subsequent opening and closure of the tetrazole ring [72], conversion of 1,2,4-oxadiazole derivatives under the influence of UV ra-diation [73], and heterocyclization of semicarbazides, thiosemicarbazides or selenosemi-carbazides [74–76].



Scheme 2. Possible methods for the preparation of 1,3,4-oxadiazoles [77].

4. 1,3,4-Oxadiazoles Used Commercially in Agriculture and Medicine

Due to their insecticidal, fungicidal and herbicidal properties, 1,3,4-Oxadiazoles are widely used in agriculture. For example, an effective herbicide may be obtained by combining 1,3,4-oxadiazole with 3,5-dihalophenoxypyridines (**5**) (Figure 5). These compounds show the expected activity against *Echinochloa cruss-galli*, *Avena fatua* and *Sorgum halepense* [78]. Many compounds based on the 1,3,4-oxadiazole ring have already been authorized and commercialized. Among others, we can distinguish derivatives of metoxadiazone, which is an insecticide, or oxadiazone (**6**) derivatives, showing herbicidal activity [79–81].

The compounds exhibiting insecticidal activity also include symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole derivatives (DCPO) (**7**) (Figure 5). Such compounds show strong activity against house flies, flies and leaf rollers [82]. Analogs based on the DCPO structure, unlike traditional agents of this type, are able to control the process of growth and development of insects by interfering with their chitin biosynthesis process. The process of inhibiting the structure of the external shell of insects is based on the interference with the incorporation of carbon-labeled *N*-acetylglucosamine, which is active in the synthesis of chitin. Additionally, DCPO and its analogs are able to inhibit the synthesis of both DNA and insect proteins. Unfortunately, due to their poor solubility in polar solvents, their use is limited. Research is ongoing to improve their solubility and increase their biological effectiveness [83].

Compounds having a 1,3,4-oxadiazole ring with antibacterial activity can be used successfully in agriculture. The bacteria *Xanthomonas oryzae* and *Ralstonia solanacearum* cause bacterial blight on rice leaves and contribute to bacterial wilt in tobacco. This causes enormous damage and loss to farmers around the world [84]. Indole derivatives containing a double 1,3,4-oxadiazole unit (**8**) may be be effective against *Xanthomonas oryzae* and *Ralstonia solanacearum*. Biological studies have shown that the antimicrobial activity against

these two pathogens was greater than that of the reference sample with *Bismerthiazol* (BMT). The efficacy of the agents in question was already high at very low concentrations, i.e., around 100 μg/mL [85].

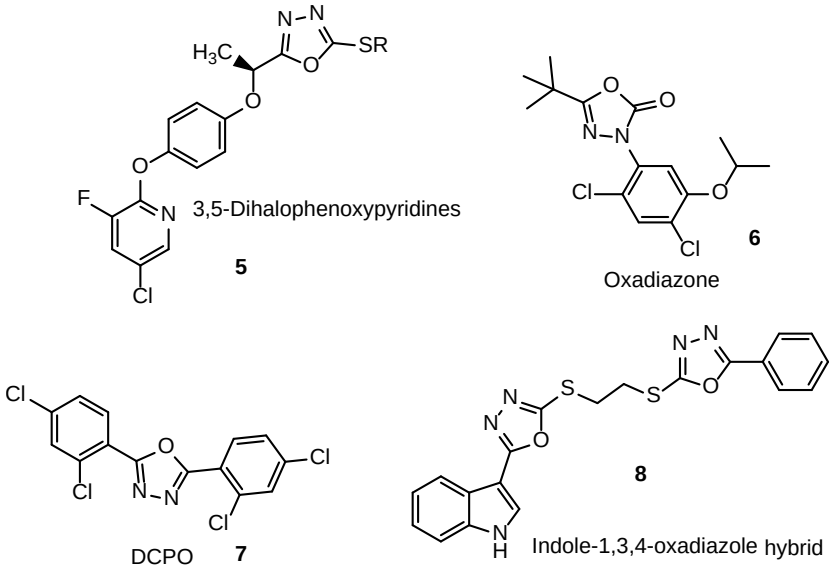


Figure 5. Compounds with herbicidal, insecticidal, and antibacterial activity: 3,5-dihalophenoxypyridines [78], oxadiazone [86], 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole (DCPO) [87], and indole-1,3,4-oxadiazole hybrid [85].

Molecules containing the 1,3,4-oxadiazole core and exhibiting biological activity are used in medicine as effective antiviral, antibacterial, antifungal, anti-inflammatory, analgesic, blood pressure-lowering and anticancer agents (Figure 6) [88,89]. *Raltegravir* (**10**) is one of the most recognized chemical compounds approved for therapy that contains a 1,3,4-oxadiazole moiety. This substance has a strong antiviral effect. It is currently used as the primary drug in the treatment of HIV infection. Its activity is based on the inhibition of integrase—an enzyme that can integrate viral genetic material with human chromosomes. This stage is considered crucial in the entire pathogenesis of AIDS [90]. The use of *Raltegravir* in medicine made it possible to significantly reduce the dynamics of the virus and accelerate its decomposition in the human body. Clinical studies have shown that the viral load in one ml of blood was below 50 copies after taking *Raltegravir*. This result turned out to be superior to the use of other drugs capable of blocking reverse transcriptase. Currently, *Raltegravir* is being tested for its effects on hidden viral reservoirs [91].

Nesapidil (**11**) is also included among the substances authorized as medicinal products. It is a compound belonging to the IV class of antiarrhythmic drugs. Its principle of operation is to block the calcium channel by directly inhibiting the influx of calcium ions to the cells of the heart muscle and the smooth muscles of the blood vessels. This increases blood flow and relieves coronary vasoconstriction. Additionally, *Nesapidil* helps to slow AV conduction and sinus rhythm [92].

An interesting compound with anticancer activity is *Zibotentan* (**12**). It is a specific ETA receptor antagonist used in the treatment of severe prostate tumors. The mechanism of action of *Zibotentan* is based on the inhibition of apoptosis and cell proliferation. At higher concentrations, it is also able to stop the growth of blood vessels within neoplastic tissue [93]. It has been proven in preclinical studies that the combination of *Zibotentan* and *Paclitaxel* exhibits a synergistic effect; in particular, it increases apoptosis [94]. Research is ongoing on the effectiveness of this chemotherapeutic in terms of its use against ovarian and breast cancer [95].

An example of a medicinal preparation used in cases of cardiovascular diseases is *Thiodiazosin* (**13**). This compound includes a quinazoline structure and a 1,3,4-oxadiazole

core. It has antihypertensive activity. The mechanism of action is based on blocking adrenergic receptors, leading to the relaxation of vascular smooth muscles and the inhibition of the secretion of norepinephrine secreted from the adrenal glands. *Thiodazosin* is used as a first line treatment when there is a need to treat cardiovascular disease related to hypertension. An additional benefit of *Thiodazosin* is its prolonged half-life in blood plasma compared to another drug with a similar effect—*Prazosin*. As a result, the therapeutic concentration of the drug in the blood is prolonged, extending its action in vivo [96].

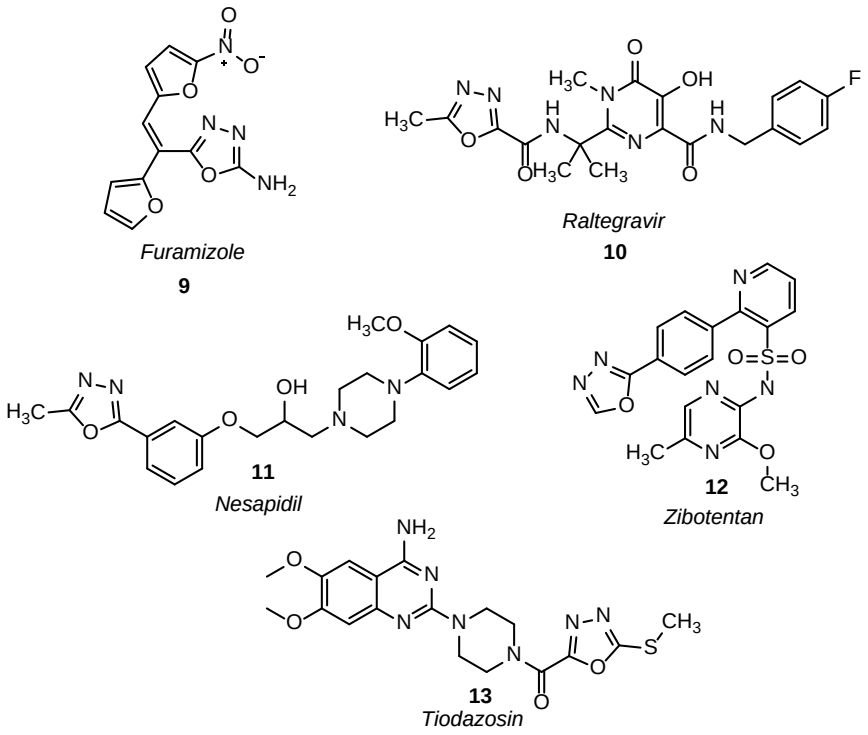


Figure 6. Compounds based on 1,3,4-oxadiazole used in medicine: Furamizole [97], Raltegravir [98], Nesapidil [99], Zibotentan [95], Thiodazosin [97].

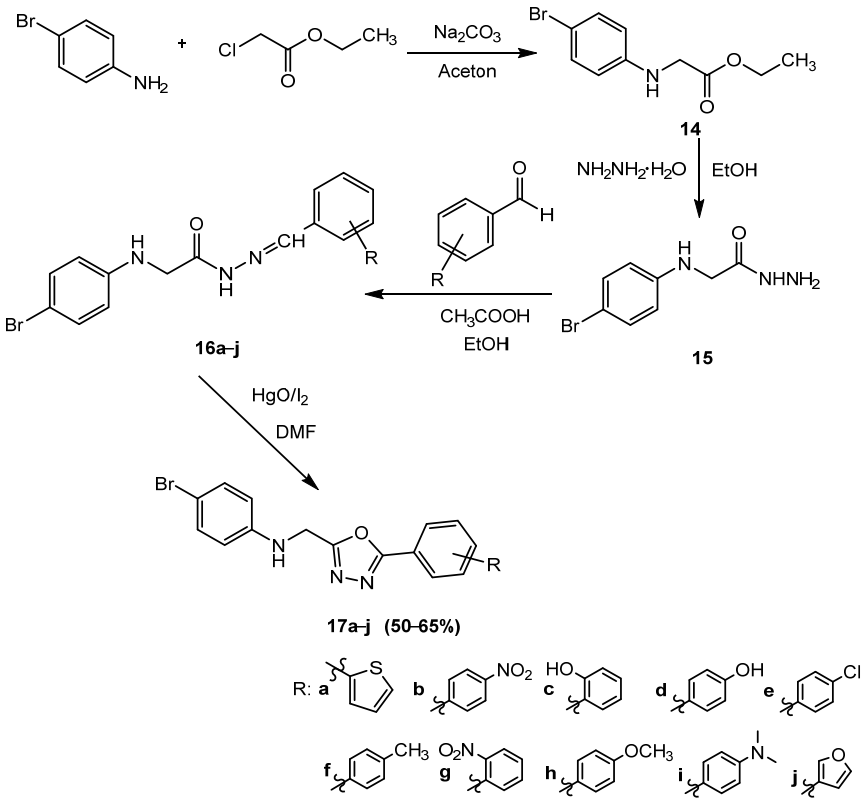
Another compound used in medicine is 2-amino-5-[2-(5-nitro-2-furyl)-1-(2-furyl)-vinyl]-1,3,4-oxadiazole, commonly known as *Furamizole* (**9**). This molecule is a derivative of nitrofuran, which has strong antibacterial activity [20].

5. Investigation of the Synthesis of New, Biologically Active 1,3,4-Oxadiazoles

Bhat et al. proposed a method for the preparation of 2-aryl-1,3,4-oxadiazole substituted at position 5 with a *p*-bromophenylaminomethyl group by using mercury oxide in the presence of iodine. The use of *p*-bromoaniline and ethyl chloroacetate yields ethyl *N*-(*p*-bromophenyl) acetate (**14**). Then, the ester produced may be converted to the corresponding hydrazide (**15**) using hydrazine hydrate. Subsequent treatment with a range of aryl aldehydes results in formation of the appropriate hydrazone (**16a–j**) which undergo cyclization under the influence of mercury oxide and iodine (Scheme 3). The advantage of this method is that there is no need to heat the reaction mixture. The substrates are completely converted after 48 h. The final products may be purified by recrystallization from DMF:ethanol in a 1:1 volume ratio. A series of 1,3,4-oxadiazole derivatives (**17a–j**) may be thus obtained with yields of 50–65% [100].

Aniline derivatives containing 1,3,4-oxadiazole moieties have been tested for antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* using *Amoxicillin* as a standard drug. In the studies of antifungal activity, all compounds were compared with the popular antifungal agent, Ketoconazole. In addition, biological activity was tested for anti-inflammatory effects. The described 1,3,4-oxadiazole

derivatives showed good antibacterial and anti-inflammatory activity, and moderate antifungal activity. Derivatives **17e**, **17f**, and **17h** showed better antibacterial activity, while compounds **17b**, **17c**, **17d**, and **17g** showed better antifungal activity [100].

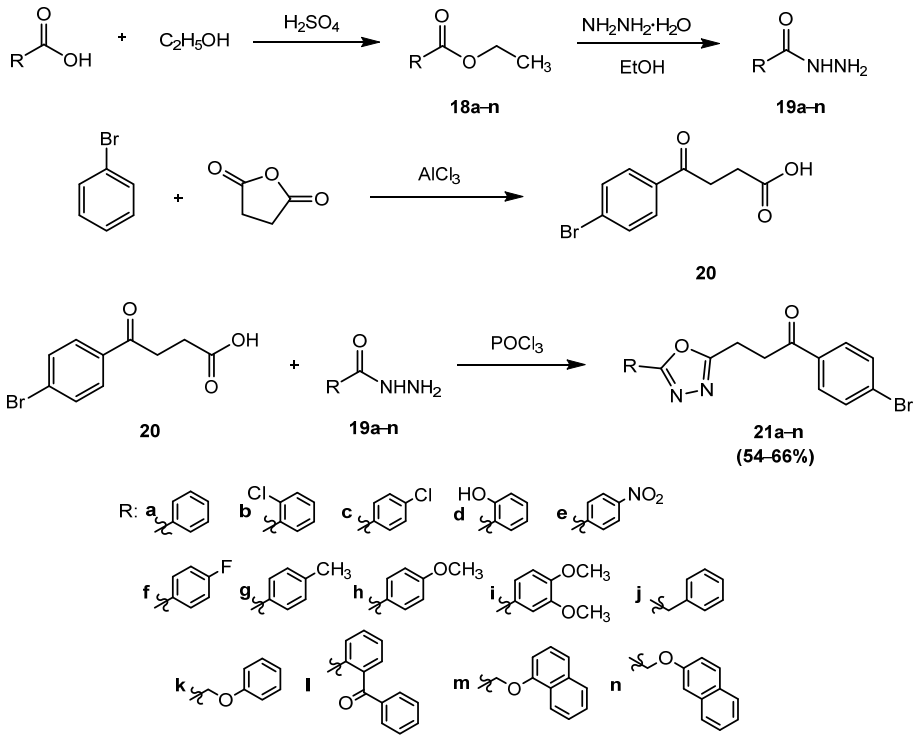


Scheme 3. Synthesis of aniline derivatives containing 1,3,4-oxadiazole groups [100].

Husain et al. developed a synthetic path yielding the corresponding propan-3-one derivatives containing a 1,3,4-oxadiazole core (Scheme 4). The essential cyclization step consisted of carrying out the reaction between the carboxylic acid derivative (**20**) and aromatic acid hydrazide (**19a–n**) in the presence of phosphoryl oxychloride ($POCl_3$). In the first step, a hydrazide is formed, which then undergoes a cyclization reaction with a cyclodehydrate such as $POCl_3$. The reaction mixture was heated to reflux for several hours. Final compounds (**21a–n**) were purified by recrystallization from methanol with yields varying from 54 to 66%. The preceding stages included the formation of acid hydrazide (**19a–n**) according to a standard procedure consisting of esterification of carboxylic acids and hydrazinolysis. The second reagent, carboxylic acid derivative (**20**), was prepared via electrophilic substitution reaction from bromobenzene and maleic anhydride [101].

All 2-[3-(4-bromophenyl)propan-3-one]-5-phenyl-1,3,4-oxadiazole (**21a–n**) derivatives products were tested for their anti-inflammatory effect. Their activity was checked in vivo in rats by inducing paw swelling with carrageenan. The obtained results were compared with the standard drug used in the treatment of this type of disease, *Indomethacin*. The 2-[3-(4-bromophenyl)propan-3-one]-5-phenyl-1,3,4-oxadiazole derivatives (**21a–n**) all showed an anti-inflammatory effect ranging from about 33 to 62%. Derivatives **21c** and **21i** showed the strongest activity, with efficiencies of 59.5% and 61.9%, respectively. This effect was comparable to that of Indomethacin, which showed an activity of 64.3% at the same dose (20 mg/kg body weight). These studies confirmed that the presence of 3,4-dimethoxyphenyl, 4-chlorophenyl or the 5-position substitution of the oxadiazole ring improves the anti-inflammatory activity. Some of the derivatives have also been tested for their analgesic effect based on commercially used *Acetylsalicylic acid*. Compounds **21b**, **21c**, **21e**, **21f** and **21i** showed analgesic activity ranging from about 44 to 71%, while

Acetylsalicylic acid showed an analgesic activity of 63.2%. An analysis showed that the most effective were the derivatives containing halogen substituents attached to the 5 position of the oxadiazole ring [101].



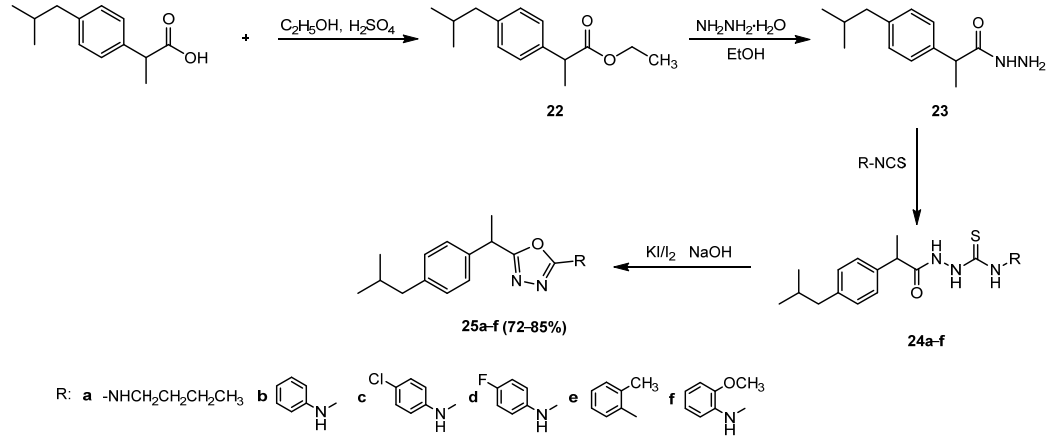
Scheme 4. Synthesis of propan-3-one derivatives containing 1,3,4-oxadiazole groups [101].

The synthesis of 1,3,4-oxadiazoles proposed by Amir et al., leading to the preparation of extended *Ibuprofen* derivatives, is based on a cyclization reaction starting from carbiothioamide derivatives (**24a–f**). The reactants used in this case were iodine dissolved in potassium iodide solution (Scheme 5). For this purpose, the carbiothioamide derivatives (**24a–f**) prepared in advance from acid hydrazide (**23**) and the appropriate isothiocyanate were suspended in ethanol and dissolved with the addition of aqueous sodium hydroxide. Iodine in a 5% potassium iodide solution was then gradually added to the mixture until the iodine color was maintained at room temperature. In the next step, the mixture was heated to reflux for about 5 h. The advantages of this method of obtaining 1,3,4-oxadiazole derivatives are undoubtedly the lack of the need to use hazardous cyclodehydration compounds and the high yield of the final products. Ibuprofen derivatives containing 1,3,4-oxadiazole groups as solids were purified by recrystallization from ethanol. The desired final structures (**25a–f**) were obtained with yields of 72–85% [49].

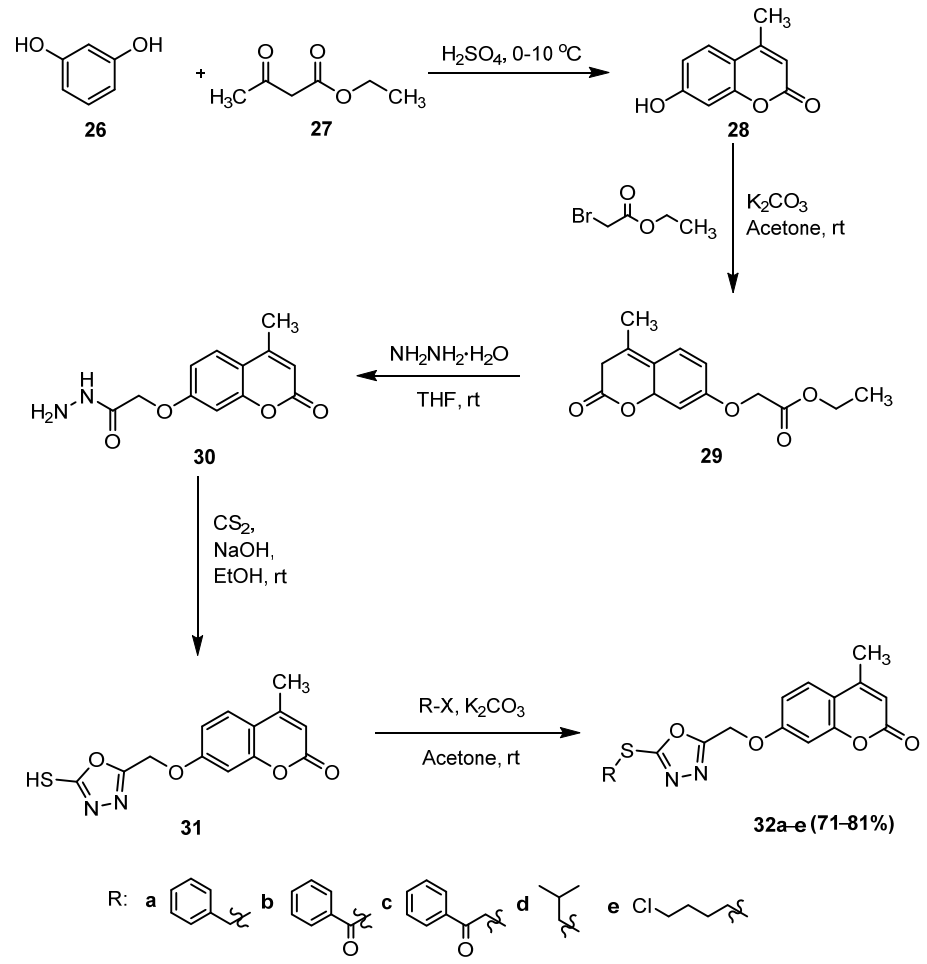
The obtained products in the form of 5-[2-(4-*iso*butylphenyl)ethyl]-2-(aryl)-1,3,4-oxadiazole derivatives (**25a–f**) were tested for their anti-inflammatory activity. A carrageenan solution was injected into groups of six rats. One of the groups was treated as a control. The remaining rats were treated with the tested pre-therapy at doses of 70 mg/kg body weight. The reference point of the test substances was standard *Ibuprofen*, which showed an anti-inflammatory effect of 92% four hours after administration. Derivative **25a** showed the strongest activity (86%). This compound was also tested for application as a painkiller, obtaining the desired activity at a level of 73%. The *Ibuprofen* standard showed an analgesic effect equal to 83.5% [49].

Narella et al. proposed the preparation of 1,3,4-oxadiazole derivatives connected to a coumarin core via a methylenoxy linker (Scheme 6). The starting coumarin fragment was prepared from resorcinol (**26**) and ethyl acetoacetate (**27**). Then, it was treated with ethyl bromoacetate, yielding an extended coumarin-bearing ester, which was converted to the appropriate hydrazide (**30**) under the influence of hydrazine hydrate. Such hydrazides

underwent cyclization in the presence of carbon disulfide and ethanol. The process of obtaining oxadiazole (**31**) was carried out in the presence of a base such as sodium hydroxide. The reaction mixture was heated to reflux overnight with stirring. Due to the use of a base during the synthesis, the mixture then had to be acidified with HCl solution. The obtained precipitate products were purified by recrystallization from ethanol. The advantage of using CS_2 as a cyclizing reagent is undoubtedly the high yield of 1,3,4-oxadiazole derivatives, i.e., 71–81% [102].



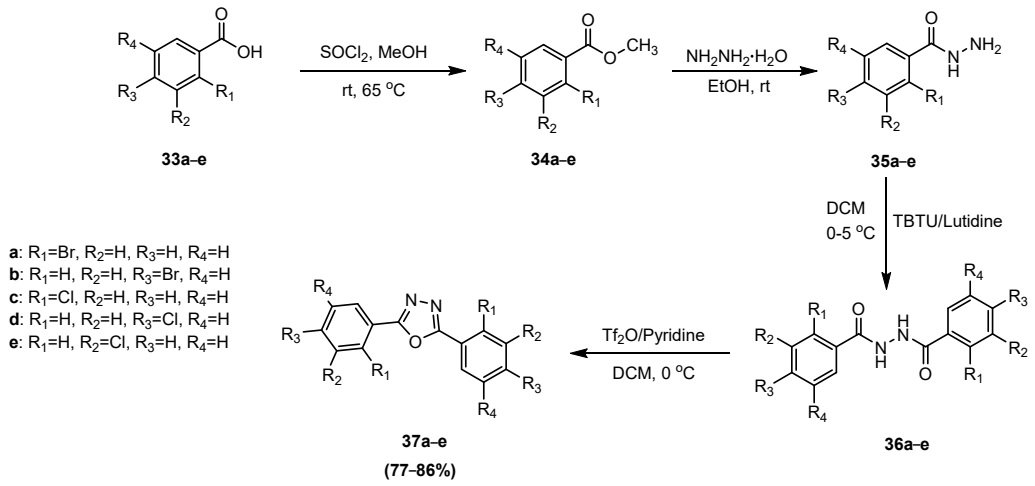
Scheme 5. Synthesis of 5-[2-(4-*iso*butylphenyl)ethyl]-2-(aryl)-1,3,4-oxadiazole derivatives [49].



Scheme 6. Preparation of coumarin derivatives containing 1,3,4-oxadiazole core [102].

The obtained derivatives were tested against the four isoforms of carbonic anhydrase hCA. In comparative tests, *Acetazolamide* was used as the standard drug. None of the compounds obtained showed the potential to inhibit the cytosolic isoforms hCA I or hCA II. Significant blocking against the hCA XII transmembrane isoform was shown in all the molecules obtained, while against hCA IX, the inhibition was variable. Consequently, coumarin–oxadiazole hybrids were found to be selective inhibitors of two carbonic anhydrase enzymes directly related to tumors. The derivative **32b** appears to be the most promising compound and may be used in the future for the treatment of neoplastic diseases [102].

The synthesis of 2,5-bisphenyl-1,3,4-oxadiazoles proposed by Zabiulla et al. is based on the use of trifluoromethanesulfonic anhydride as the main reagent responsible for carrying out the cyclization of *N*,*N*′-diacylhydrazines (Scheme 7). The essential diacylhydrazines (**36**) were prepared from the substituted benzoic acid (**33**), which were esterified with methanol, then treated with hydrazine hydrate and finally coupled under the influence of TBTU and lutidine. The intermediate *N*,*N*′-diacylhydrazine (**36**) was dissolved in dichloromethane (DCM), and pyridine was used as the basic catalyst. The reaction mixture was stirred for approximately 3 h at 0 °C. The crude products were purified by silica gel column chromatography using a mixture of hexane and ethyl acetate (9:1) as the mobile phase. The final products (**37**) were obtained with yields ranging from 77 to 86%. The undoubted advantage of this method is the relatively short reaction time of 3 h and avoiding the need to heat the reaction mixture [103].

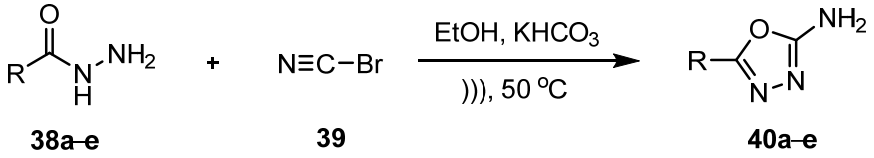


Scheme 7. Synthesis of 2,5-bisphenyl-1,3,4-oxadiazole derivatives [103].

The obtained derivatives were tested for antibacterial and antifungal activity against Gram-positive bacteria (*Bacillus cereus*, *Staphylococcus aureus*, *Staphylococcus aureus* (MRSA), *Enterobacter aerogenes* and *Mi-crococcus luteus*), Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumonia*, *Proteus vulgaris*, *Salmonella typhimurium*, *Salmonella paratyphi B*) and fungi (*Botrytis cinerea*, *Candida krusei*, *Candida albicans*, *Fusarium moniliforme*, *Malassesia pachydermatis*, *Aspergillus niger*, *Fusarium solani*, *Colletotrichum gloeosporioides*, *Aspergillus flavus*, *Candida parapsilosis*). The tests were performed using the disc diffusion method. Streptomycin, a standard antibacterial drug, was used as a reference for this purpose. The highest activity was observed for compound **5a**, which had two ortho bromo groups on two different aromatic rings directly attached to the 1,3,4-oxadiazole moiety. The remaining compounds showed moderate antibacterial activity. For antifungal studies, Ketoconazole, a standard drug for the treatment of disease caused by pathogenic fungi, was used as a reference compound. In this study, derivative **37a** also showed the strongest activity [103].

Beyzaei et al. developed an ultrasound-assisted method for the synthesis of 2-amino-1,3,4-oxadiazole derivatives substituted with aryl and methyl groups at position 5 (Scheme 8). The substrates for this type of reaction were various hydrazide derivatives (**38a–e**) bearing alkyl and aryl substituents and cyanogen bromine (**39**) added in an equimo-

lar amount. It was also necessary to use a base—potassium bicarbonate. The presence of the base had a positive effect on the efficiency of the reaction by neutralizing the evolved hydrogen bromide, which could react with the hydrazide. Anhydrous ethanol was used as a solvent. The reaction mixture was subjected to an ultrasonic bath at 50 °C. The formed oxadiazole derivatives were washed with water and dried to give pure final products. The undoubted advantage of using ultrasonic prilling is the reduction of the synthesis time to several hours and the high yield of the desired 1,3,4-oxadiazole derivatives (**40a–e**) [104].



38a–e **39** **40a–e**

R: **a** CH_3, **b** C_6H_5, **c** 4-O_2N-C_6H_4, **d** 4-$(H_3C)_3C$-C_6H_4, **e** 3-HO-C_6H_4

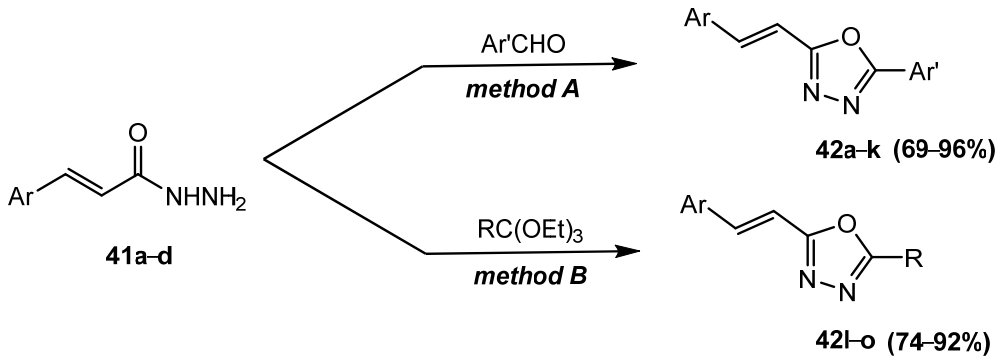
Scheme 8. Synthesis of 2-amino-1,3,4-oxadiazole derivatives [104].

The obtained 2-amino-1,3,4-oxadiazole derivatives were tested for their antioxidant activity. The tests were carried out against 2,2,-diphenyl-1-picrylhydrazyl (DPPH). Effects were calculated as IC_{50} values. *Ascorbic acid* (*Vitamin C*) IC_{50} 0.022 mM was used as a reference substance. All obtained final products, except derivative **40d**, showed antioxidant activity. The strongest properties were exhibited by derivative **40c**; this was attributed to the presence of a nitro group, which is capable of withdrawing electrons and deactivating the phenyl ring [104].

Jasiak et al. proposed two methods of obtaining 2-(2-arylethenyl)-1,3,4-oxadiazole derivatives (Scheme 9). The first was based on the use of the appropriate 3-arylacrylhydrazides (**41a–d**) and an aromatic aldehyde which were reacted with *p*-toluenesulfonic acid (*p*-TsOH), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of dry toluene. The reaction mixture was heated to reflux until the starting hydrazide was completely consumed. The obtained final products were purified by silica gel column chromatography (benzene:EtOAc 3:1) to give the 2-(2-arylethenyl)-1,3,4-oxadiazole derivatives (**42a–k**) with 69–96% yields. The second method was based on dissolving the 3-arylacrylhydrazide in a mixture of the appropriate triethyl orthoester and glacial acetic acid. The reaction mixture was held at reflux until the substrate disappeared completely. The crude products were purified by recrystallization from benzene/hexane to give the final products (**42l–o**) with 74–92% yields. The advantages of using these methods for the preparation of 1,3,4-oxadiazole include a reaction time of 3–7 h and high yields of the final products [105].

The obtained 2-(2-arylethenyl)-1,3,4-oxadiazole derivatives were tested in vitro for their antibacterial and antifungal activity using the broth microdilution method in accordance with the standards of the European Committee on Antimicrobial Susceptibility Testing (ECAST) and the Clinical and Laboratory Standards Institute (CLSI). Tests were performed against Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 43300, *Staphylococcus aureus* ATC 6538, *Staphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 10876 *Micrococcus luteus* ATCC 10240), Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 12453, *Bordetella bronchiseptica* ATCC 4617, *Salmonella typhimurium* ATCC 14028, *Pseudomonas aeruginosa* ATCC 9027) and fungi (*Candida albicans* ATCC 2091, *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019). Commercially available *Ciprofloxacin* with antimicrobial activity and *Fluconazole* with antifungal activity were used as reference compounds. The studies showed that the obtained compounds **42a–f**, **h–j** and **n–o** did not exhibit an inhibitory effect on the growth of all bacterial strains. The broadest spectrum of antibacterial activity was shown by the derivative of 5-ethyl-2-[2-(2-thienyl)ethenyl]- 1,3,4-oxadiazole (**41l**). The remaining compounds, i.e., **42g**, **42k**, and **42m**, showed moderate antibacterial activity against Gram-positive and Gram-negative bacteria.

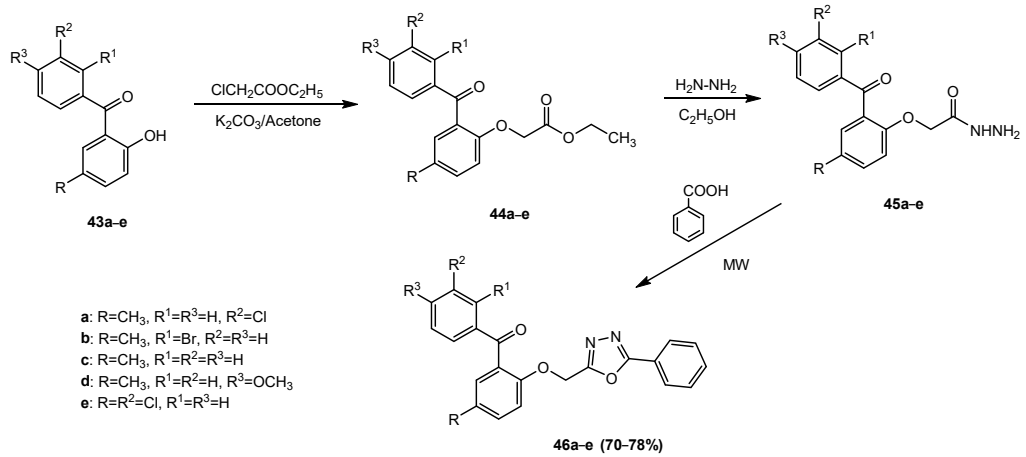
In the studies devoted to antifungal activity, compound **41l** showed the best activity against all *Candda* spp. Compounds **42f** and **42m** showed mild activity against some of the tested *Candida* spp. species. The remaining oxadiazoles were inactive [105].



Ar= **a–e**: Ph, **f–h**: 2-furyl, **i–l**: 2-thienyl, **m–n**: 2-pyridyl, **o**: 3-pyridyl
Ar'/R= **a, m, o**: Ph, **b, f, i**: 4-MeO-C_6H_4, **c**: 4-O_2N-C_6H_4, **d, h, k**: 2-furyl, **e**: 2-thienyl, **g**: 4-Cl-C_6H_4, **j**: 4-Br-C_6H_4, **l**: Et, **n**: Me

Scheme 9. Synthesis of 2-(2-arylethenyl)-1,3,4-oxadiazole derivatives [105].

Khanum et al. proposed a method for the synthesis of 5-(2-aroyl)aryloxymethyl-2-phenyl-1,3,4-oxadiazole derivatives with the use of microwave radiation. The cyclization reaction was carried out on the previously obtained hydrazide derivatives (**45a–e**), obtained by a standard procedure using hydrazine dissolved in ethanol (Scheme 10). The main synthesis step was performed using benzoic acid and clay, which were mixed with the hydrazide by means of a vortex mixer. The prepared mixture was irradiated in an unmodified domestic microwave oven at 50% power for about 10 min. After extraction, pure 5-(2-aroyl)aryloxymethyl-2-phenyl-1,3,4-oxadiazole derivatives (**46a–e**) were obtained with a yield of 70–78%. The advantage of this method is the fast reaction time and the limited use of organic solvents [106].

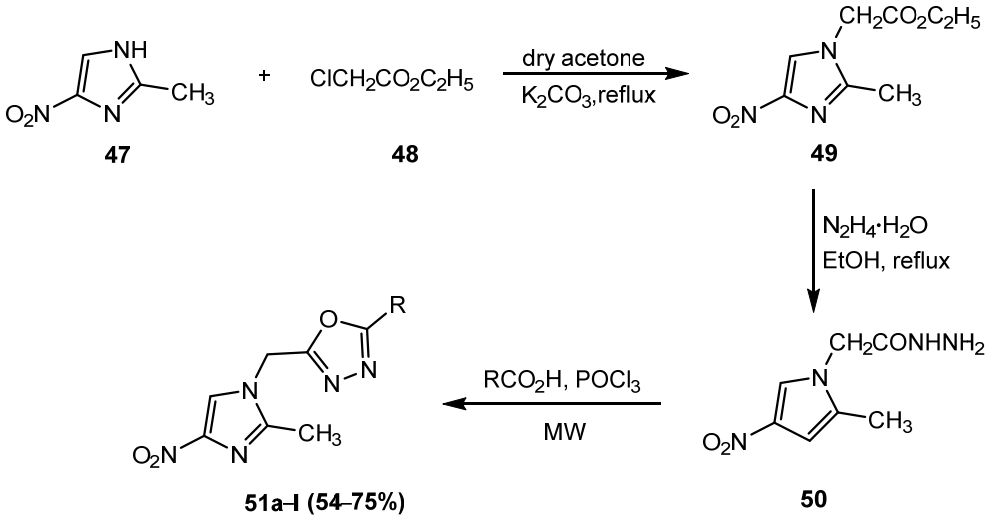


Scheme 10. Synthesis of 2-(2-aroyl)aryloxymethyl-2-phenyl-1,3,4-oxadiazole derivatives [106].

The activity of 5-(2-Aroyl)aryloxymethyl-2-phenyl-1,3,4-oxadiazole derivatives was tested against the downy mildew pathogen (*Sclerospora graminicola*) in Pearl Millet (*Pennisetum glaucum*). Initial phytotoxicity studies were also conducted by assessing seed germination and seedling vigour. An analysis of the inhibitory effect on mold growth was carried out by treating with nonphytotoxic concentrations of 5-(2-aroyl)aryloxymethyl-2-phenyl-1,3,4-oxadiazole derivatives for about 6 h before sowing in pots containing a mixture

of soil, sand and manure inoculated with 40,000 zoospor/mL of pathogen. *Metalaxyl-M* was used as a reference compound—a widely used substance for the prevention of downy mildew. The research showed that none of the 5-(2-aroyl)aryloxymethyl-2-phenyl-1,3,4-oxadiazole derivatives was phytotoxic for Pearl Millet seeds. The prevalence of downy mildew in seeds treated with 1 g/kg of seeds of compound **46a** was 65% under greenhouse conditions and 48% under field conditions. The control sample treated with sterile distilled water and methanol was 92% infected. The remaining compounds (**46b–e**) showed no activity against downy mildew [106].

Another example of the use of microwave radiation in the synthesis of 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole derivatives (Scheme 11) was presented by Frank et al. In carrying out the cyclization reaction, the substrate in the form of 2-methyl-4-nitro-1-imidazoacethydrazide (**50**), obtained in a two-step sequence of transformations starting from 2-methyl-4-nitro-imidazole (**47**), was used. In the first step, imidazole was reacted with ethylchloroacetate (**48**) in dry acetone against potassium carbonate to give imidazole acetate (**49**), which was reacted with hydrazine hydrate. The main stage of the synthesis, with the use of microwave radiation, was carried out with carboxylic acid derivatives and phosphorus oxychloride. The acid/hydrazide mixture was ground, a few drops of $POCl_3$ were added and the mixture was reacted in a 160 W microwave oven for about 5 min. The obtained crude products were purified by recrystallization from ethanol:DMF to give the final 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole derivatives (**51a–l**) with a yield of 54–75%. The advantages of using microwave radiation include the fast reaction time and the absence of organic solvents [107].



5a: R=C_6H_6 **5g**: R=2-C_4H_3O
5b: R=4-$CH_3C_6H_4$ **5h**: R=C_6H_5-OCH_2
5c: R=4-$OCH_3C_6H_4$ **5i**: R=4-CH_3-C_6H_4-OCH_2
5d: R=4-ClC_6H_4 **5j**: R=2-CH_3-C_6H_4-OCH_2
5e: R=2-$CH_3C_6H_4$ **5k**: R=4-Cl-C_6H_4-OCH_2
5f: R=C_5H_4N **5l**: R=4-Cl-2-CH_3-C_6H_3-OCH_2

Scheme 11. Synthesis of 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole derivatives [107].

The obtained 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole derivatives were tested for antibacterial activity against four strains of bacteria, i.e., *Staphylococcus aureus* (G+), *Klebsiella pneumoniae* (G−), *Escherichia coli* (G−) and *Pseudomonas aeruginosa* (G−), and antifungal activity against *Aspergillus flavus*, *A. fumigatus*, *Penicillium*, *Trichophyton*, by the cup-plate method. Among the tested compounds, derivatives **51e**, and **51l** showed good activity against *E. coli*, *P. aeruginosa*, and *K. pneumoniae* bacteria, and moderate activity

against S. aureus. Moreover, derivative **51h** showed good activity against *E. coli*, and *P. aeruginosa*. Compound **51j** also showed moderate potency against *S. aureus*. When tested for antifungal activity, the **51d** molecule showed good potency against all fungi. Compound **51f** showed great activity against *A. flavus*, and *Penicillium*. Additionally, **51j** showed effective potency against *A. fumigatus*, and moderate activity against *Trichophyton*. Compounds **51g** and **51i** were moderately active against *Penicillium*, and *Trichophyton*. Studies related to the anti-inflammatory effects of 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazole derivatives were also carried out. For this purpose, the Winter method was used, which is based on the induction of edema with formalin. Rat paw volume was measured with a Buttle apparatus. Studies confirmed that all compounds exhibited anti-inflammatory effects at doses of 50 mg/kg body weight. The anti-inflammatory effects of derivatives **51b**, **51c**, and **51d** were comparable to that of *Indomethacin* at doses of 1–5 mg/kg [107].

6. Conclusions

Five-membered heterocyclic compounds, which are 1,3,4-oxadiazole derivatives, are the basic building blocks of many compounds exhibiting biological activities which are desirable both in medicine and agriculture. Research on the strength of these biological activities has confirmed the assumptions that many systems of this type could be used in treatments against various types of pathogens. The need to discover new compounds with antibacterial, antifungal, anti-inflammatory or analgesic properties has prompted many teams to research the development of new synthetic pathways of the aforementioned compounds. The other branch of intensive study on 1,3,4-oxadiazole drugs includes structure modifications and functionalizations of currently used medicines and pesticides. The introduction of new substituents and the formation of new hybrid materials with other biologically active molecules may influence the solubility of potential drug molecules, thereby increasing bioavailability and effectiveness. Interest in the structures of substances based on oxadiazoles is growing year by year, thus expanding the library of biologically active compounds that could be used in the future in treatments for humans and animals or to prevent the occurrence of diseases in plants.

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