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CHEMISTRY, SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 1,3,4-OXADIAZOLE DERIVATIVES: A REVIEW

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ABSTRACT

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. The current review was based on the chemistry, synthesis and pharmacological properties of 1,3,4-oxadiazole derivatives. 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. 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. 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.]. 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. It concluded that 1,3,4-oxadiazole derivatives possesses numerous pharmacological properties including antimicrobial, anti-inflammatory, antibacterial, anticancer, antifungal, tuberculostatic, analgesic, antiviral, antioxidant, insecticidal, anti-parasitic, and blood pressure-lowering. Thus, it is a promising moiety for new novel drug design with broad therapeutic efficacy on various medical conditions.

KEYWORDS: 1,3,4-oxadiazole, synthesis, pharmacological properties, antioxidant, anti-cancer.

INTRODUCTION

Oxadiazoles belong to the group of heterocyclic which consists of a five-membered heterocyclic ring, comprising of one oxygen atom and two nitrogen atoms. The oxadiazole molecule is formed by substituting two carbon atoms in furan with nitrogen atoms of the pyridine type.[1] Oxadiazole compounds provide numerous characteristics that find use across diverse industries. These compounds possess a diverse range of biological activity, allowing them to be utilized in medicine and pharmacology as active agents. For example, they have anti-inflammatory and analgesic, antibacterial, antiviral, antifungal, anticancer, and blood pressure reducing effects.[2] Given the possible biological activity of this molecule, it is also utilized in agriculture as herbicides, insecticides, and plant protection agents to combat diseases caused by bacteria, viruses, and fungi. The oxadiazole groups also possess valuable optical characteristics. The molecule has a 1,2-diazole fragment which functions as an electron withdrawing group. This property makes it highly valuable in a range of conducting systems.[3] Consequently, it is feasible to enhance the quantum yield of fluorescence and enhance the stability of the molecule. Oxadiazole derivatives are utilized in many applications such as organic light emitting diodes, laser dyes, optical brighteners, and scintillators. These molecules are also present in products such as thermal insulation polymers.[4]

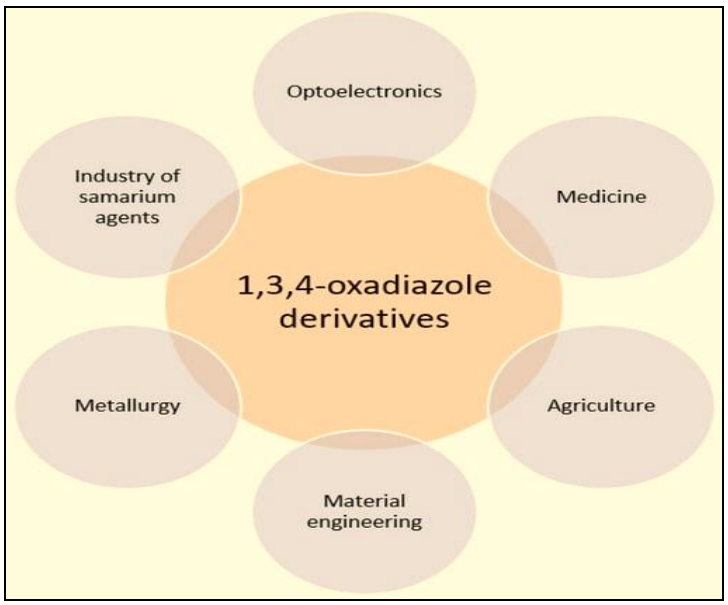


Fig. 1: Applications of 1,3,4-oxadiazole derivatives.

Chemistry of 1,3,4-Oxadiazoles

These compounds consist of a pentagonal heterocyclic ring that includes two nitrogen atoms and one oxygen atom. Oxadiazoles exist in several isomeric forms due to the distinct arrangement of the heteroatoms. Examples of these isomers are 1,3,4-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, and 1,2,5-oxadiazole. Aromatic systems are referred to as azoxins, whereas five-membered cyclic compounds with an equal number of nitrogen and oxygen atoms that have undergone partial reduction are termed furoxanes.[5]

Fig. 2: Isomeric structures of oxadiazoles.

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, as well as in mesoionic substances, so-called "sydnones".[6]

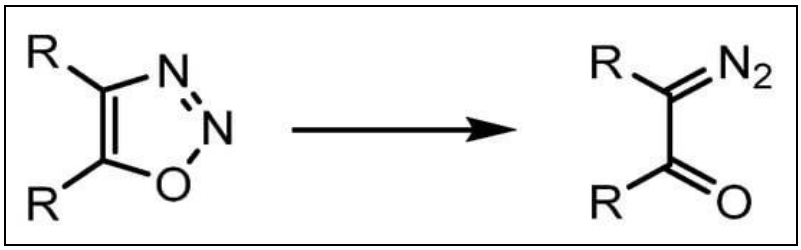


Fig. 3: Acyldiazomethane tautomer.

In contrast to 1,2,3-oxadiazoles, other isomers, namely 1,2,4-oxadiazoles, are Stable from a thermodynamic perspective. Their responsiveness is primarily influenced by their fragrant nature. The 1,2,4-oxadiazoles exhibit a significant propensity for ring rearrangement events due to their relatively low level of aromaticity.[7] Based on the calculations conducted, it was determined that the aromaticity index of the 1,2,4-oxadiazole molecule was lower compared to the furan molecule.[8] X-ray structural spectroscopy (1–4) has identified numerous 1,2,4-oxadiazole derivative structures in recent years. The study has identified the structures suitable for energetic materials[9] and complex compounds containing 1,2,4-oxadiazole derivatives that can bind copper or cobalt cations and exhibit biological activity.[10]

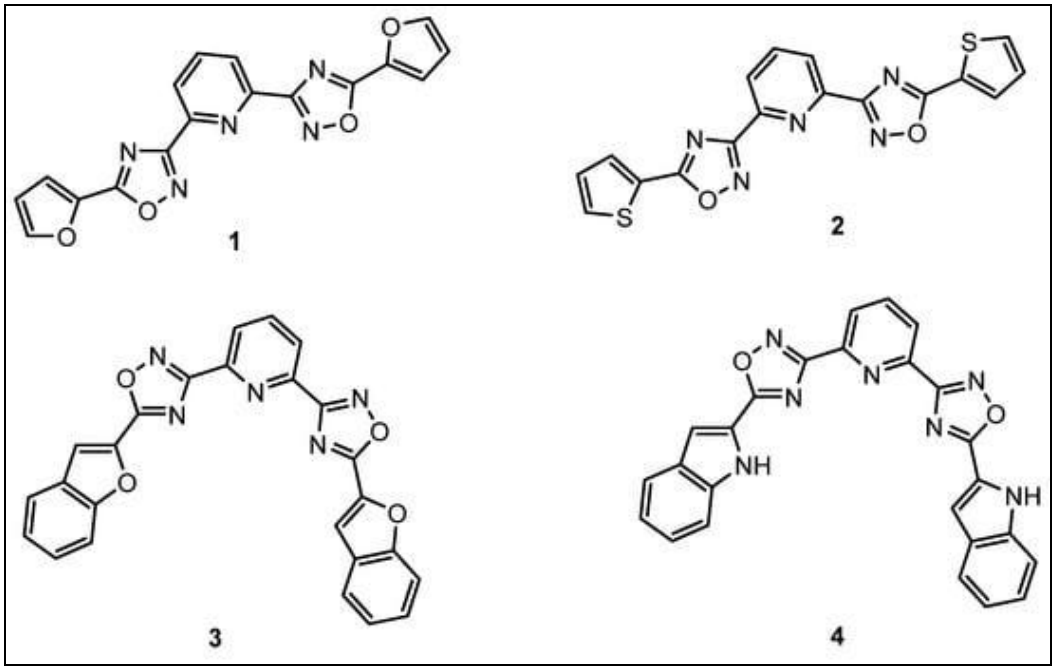


Fig. 4: Different 1,2,4-oxadiazole derivatives (1) 2,6-bis(5-furan-2yl)-1,2,4-oxadiazol-3-yl)pyridine; (2) 2,6-bis(5-(thiophen-2yl)-1,2,4-oxadiazol-3-yl)pyridine; (3) 5-(benzofuran-2-yl)-3-(6-(5-(2,3-dihydrobenzofuran-2yl)-1,2,4-oxadiazol-3-yl)pyridin-2-yl)-1,2,4-oxadiazole; (4) 3-(6-(5-(1H-indol-2-yl)-1,2,4-oxadiazole-3-yl)pyridin-2-yl)-5-(indolin-2-yl)-1,2,4-oxadiazole.

Due to the relatively 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.[11]

Furazan, also known as 1,2,5-Oxadiazole, is an alternative isomeric variation of oxadiazole. The furazan ring is highly prone to fragmentation. For instance, the use of sodium hydroxide in a water-based solution has the capability to fully break apart the heterocyclic ring. Because of their elevated positive enthalpy of formation and dense nature, furazan and its oxides (furoxan) have recently become increasingly popular in the production of high-energy and explosive substances. These molecules enhance the oxygen equilibrium and simultaneously emit nitrogen gas, which is environmentally benign, during decomposition.[12] The unsubstituted 1,3,4-oxadiazole is the most stable isomeric structure among all isomeric oxadiazoles. The fundamental constituent of 1,3,4-oxadiazole is a liquid that has a boiling

point of 150°C. Liquids are also present in lower alkyl derivatives. Aryl substituents greatly enhance the melting and boiling points, particularly in the case of symmetrical derivatives. Introducing alternative functional groups at the 2 and 5 locations of the oxadiazole ring generally decreases the melting and boiling points. The solubility of 1,3,4-oxadiazoles in water is contingent upon the nature of the substituents present on the heterocyclic ring. 1,3,4-Oxadiazole, when it has two methyl groups, is fully soluble in water. However, the solubility is greatly reduced when aryl substituents are present. Oxadiazoles can undergo conversion into other five-membered heterocycles. The application of hydrazine hydrate transforms 1,3,4-oxadiazoles into triazolamines, while thiourea turns the 1,3,4-oxadiazole ring into thiadiazole.[13] Oxadiazoles are a class of chemicals that have the ability to efficiently transport electrons and prevent the movement of electron holes. This activity is exhibited by both low-molecular-weight derivatives and polymers, including dendritic forms.[14] Additionally, the heterocyclic ring exhibits a significant energy difference between its highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) due to the restricted conjugation of π electrons. Due to this, a significant group of chemicals known as 1,3,4-oxadiazole derivatives have been widely utilized in optoelectronics, organic light emitting diodes, and organic photovoltaics. Furthermore, 1,3,4-Oxadiazoles exhibit biological activity, and their derivatives are employed in the fields of medicine, pharmacology, and agriculture.[15]

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.[16]

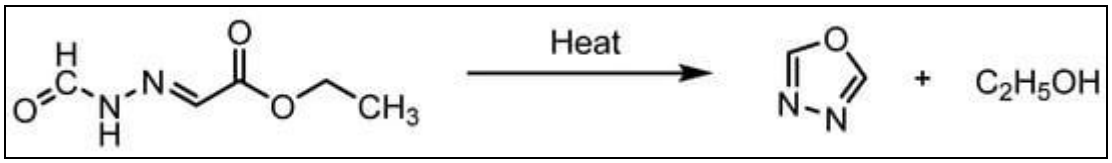


Fig. 5: [Scheme 1] First preparation of 1,3,4-oxadiazole by thermolysis.[16]

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.[17]

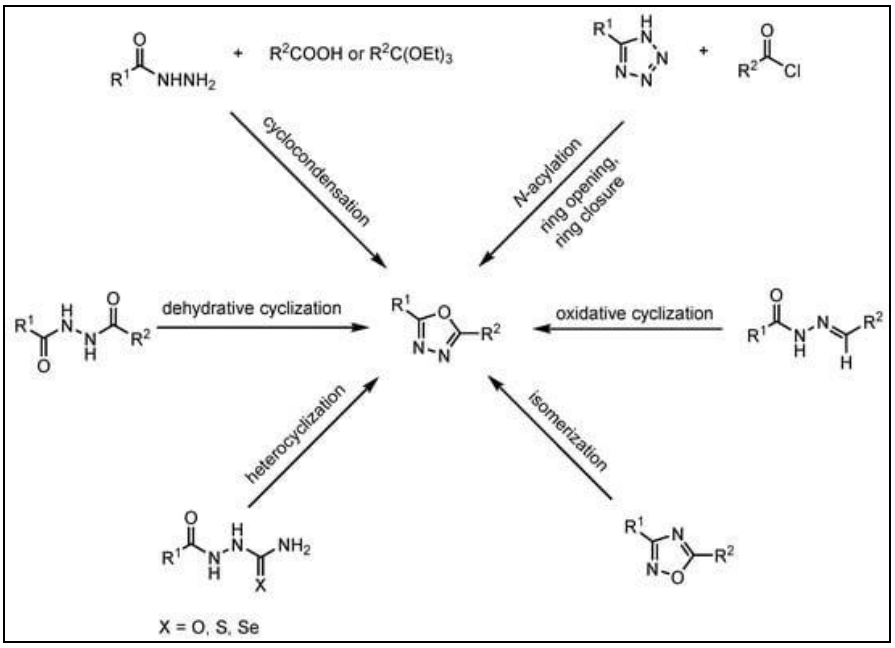


Fig. 6: [Scheme 2] Possible methods for the preparation of 1,3,4-oxadiazoles.

The most popular methods of obtaining 1,3,4-oxadiazole derivatives are based on the use of *N*,*N*′-diacylhydrazines or *N*-acylhydrazones. 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. Other possibilities of synthesis include acylation, subsequent opening and closure of the tetrazole ring[56], conversion of 1,2,4-oxadiazole derivatives under the influence of UV ra-diation and heterocyclization of semicarbazides, thiosemicarbazides or selenosemi-carbazides.[18]

Pharmacological properties of 1,3,4-Oxadiazoles

1,3,4-Oxadiazoles are extensively utilized in agriculture due to their insecticidal, fungicidal, and herbicidal characteristics. An example of a potent herbicide can be created by mixing 1,3,4-oxadiazole with 3,5-dihalophenoxypyridines.(5). The compounds exhibit the anticipated efficacy against Echinochloa cruss-galli, Avena fatua, and Sorgum halepense.[19] A multitude of compounds utilizing the 1,3,4-oxadiazole ring structure have previously received authorization and been successfully brought to market. Among many compounds, we may identify derivatives of metoxadiazone, an insecticide, as well as derivatives of oxadiazone (6), which exhibit herbicidal properties.[20][21]

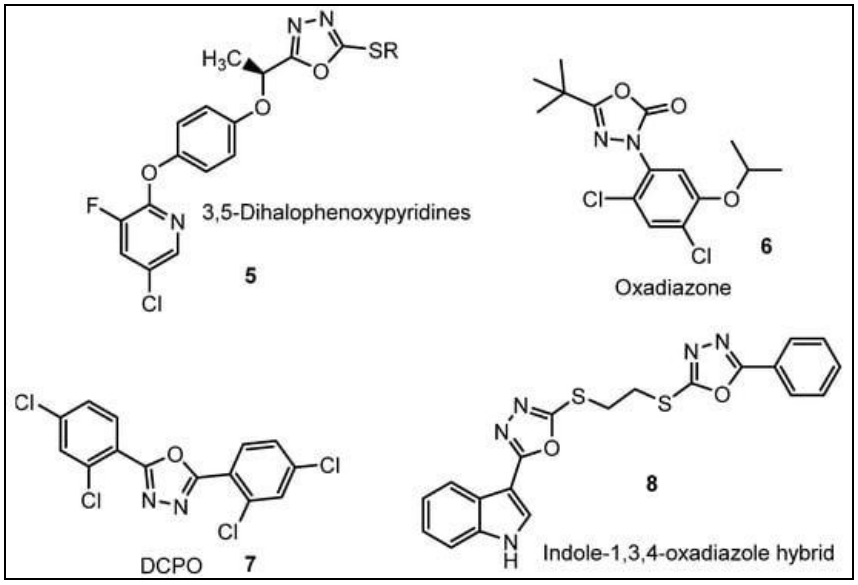


Fig. 7: Compounds with herbicidal, insecticidal, and antibacterial activity.

The compounds that demonstrate insecticidal activity also encompass symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole derivatives (DCPO) (7). These chemicals exhibit potent efficacy against house flies, flies, and leaf rollers.[22] DCPO-based analogs has the unique ability to regulate insect growth and development by disrupting their chitin manufacturing process, distinguishing them from conventional agents in this category. The procedure of suppressing the formation of the outer shell of insects is achieved by interfering with the integration of carbon-labeled N-acetylglucosamine, which plays a crucial role in the production of chitin. Furthermore, DCPO and its analogs has the capability to impede the production of both DNA and insect proteins. Regrettably, their utilization is restricted as a result of their inadequate solubility in polar solvents. Ongoing research is being conducted to enhance the solubility and augment the biological efficacy of.[23]

Antibacterial compounds with a 1,3,4-oxadiazole ring can be effectively utilized in agricultural applications. Xanthomonas oryzae and Ralstonia solanacearum bacteria are responsible for bacterial blight on rice leaves and also have a role in causing bacterial wilt in tobacco. This results in significant devastation and economic loss for farmers worldwide.[24] Indole derivatives with a double 1,3,4-oxadiazole unit (8) have the potential to be effective against Xanthomonas oryzae and Ralstonia solanacearum. Biological investigations have demonstrated that the antibacterial efficacy against these two pathogens was superior to that of the reference sample containing Bismerthiazol (BMT). The effectiveness of the medicines in issue was already significant at extremely low doses, specifically about 100 µg/mL.[25]

Medicinal applications utilize molecules that include the 1,3,4-oxadiazole core and demonstrate biological activity. These molecules are efficient in combating viruses, bacteria, fungi, inflammation, pain, high blood pressure, and cancer.[26] Raltegravir (10) is a highly recognized chemical molecule that has been licensed for therapy and comprises a 1,3,4-oxadiazole moiety. This chemical exhibits potent antiviral properties. Currently, it serves as the main medication for treating HIV infection. The function of this substance relies on inhibiting integrase, which is an enzyme capable of merging viral genetic material with human chromosomes. This stage is seen critical in the complete development of AIDS.[27] The utilization of Raltegravir in the field of medicine has enabled a substantial reduction in the viral activity and expedited its degradation within the human body. Clinical tests have demonstrated that the concentration of virus particles in a volume of one milliliter of blood was reduced to less than 50 copies following administration of Raltegravir. The outcome of this study demonstrated that the use of this medicine was more effective than other treatments that can inhibit the activity of reverse transcriptase. At present, Raltegravir is being testing to determine its impact on concealed viral reservoirs.[28]

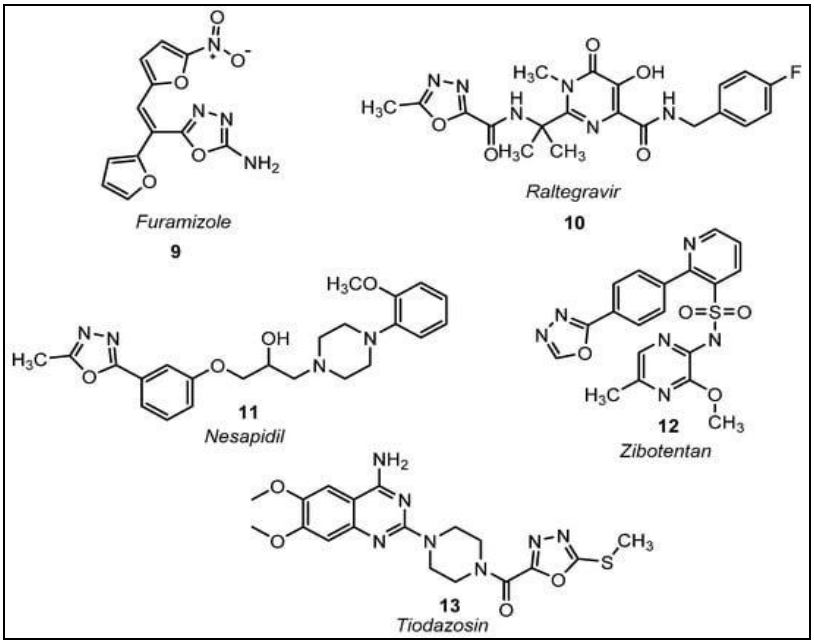
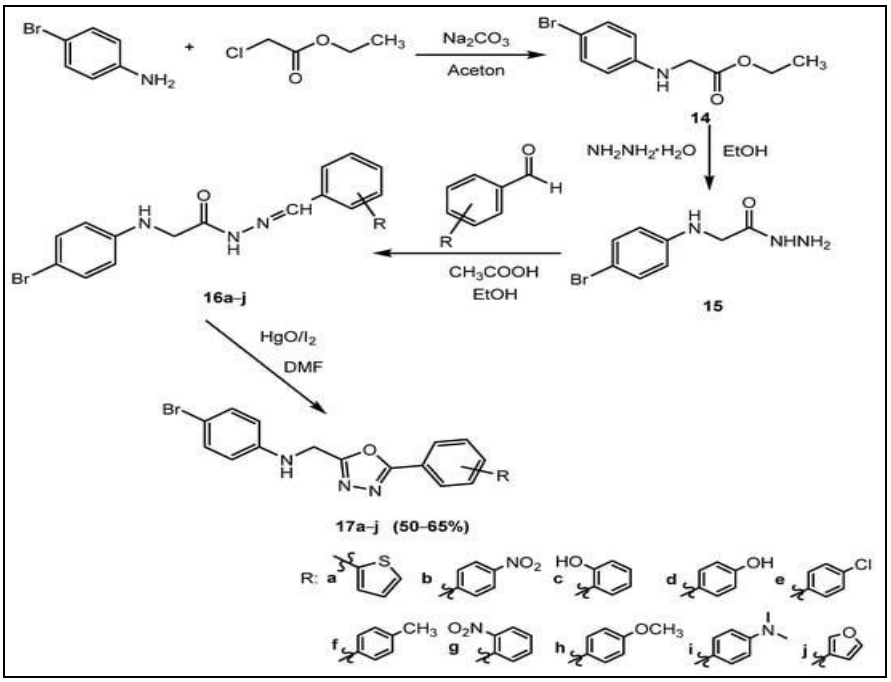


Fig. 8: Various derivatives of 1,3,4-oxadiazole.

Nesapidil (11) is also included among the substances authorized as medicinal products. This chemical is classified as a class IV antiarrhythmic medication. The primary mechanism of action involves the inhibition of calcium ion influx into the cells of the cardiac muscle and the smooth muscles of the blood arteries by directly blocking the calcium channel. This

promotes vasodilation and enhances coronary perfusion. In addition, Nesapidil has the ability to decelerate atrioventricular conduction and sinus rhythm.[29] Zibotentan (12) is a fascinating chemical that has anticancer properties. It is a selective ETA receptor antagonist employed in the management of advanced prostate cancers. Zibotentan works by inhibiting apoptosis and cell growth. At elevated dosages, it can also inhibit angiogenesis in neoplastic tissue.[30] Preclinical investigations have demonstrated that the combination of Zibotentan and Paclitaxel has a synergistic impact, specifically leading to an increase in apoptosis.[70] Ongoing research is being conducted to evaluate the efficacy of this chemotherapeutic agent in treating ovarian and breast cancer.[31]

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.[32]



Scheme 9: Synthesis of aniline derivatives containing 1,3,4-oxadiazole.

Bhat et al. suggested a technique for synthesizing 2-aryl-1,3,4-oxadiazole containing a p-bromophenylaminomethyl group at position 5, utilizing mercury oxide in the presence of iodine. When p-bromoaniline and ethyl chloroacetate are combined, they produce ethyl N-(p-bromophenyl) acetate (14).[33] Subsequently, the ester can be transformed into the equivalent hydrazide (15) by employing hydrazine hydrate. The suitable hydrazone (16a–j) is formed through subsequent treatment with various aryl aldehydes. This hydrazone then undergoes cyclization under the action of mercury oxide and iodine.[34] An advantage of this approach is that it eliminates the requirement to provide heat to the reaction mixture. The substrates undergo complete conversion within 48 hours. The ultimate products can be purified using recrystallization from a mixture of DMF and ethanol in a 1:1 volumetric proportion. The synthesis of a range of 1,3,4-oxadiazole derivatives (17a–j) can be achieved with yields ranging from 50% to 65%.[35]

Aniline derivatives with 1,3,4-oxadiazole moieties were examined for their antibacterial effects against Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, and Escherichia coli, with Amoxicillin serving as the reference medication. During the investigation of antifungal activity, all substances were evaluated in relation to the widely used antifungal drug, Ketoconazole. Furthermore, the biological activity was assessed to determine its anti-inflammatory properties. The 1,3,4-oxadiazole compounds exhibited favorable antibacterial and anti-inflammatory effects, as well as modest antifungal effects. Derivatives 17e, 17f, and 17h exhibited superior antibacterial activity, whereas compounds 17b, 17c, 17d, and 17g had enhanced antifungal activity.[36]

A synthetic route was discovered to produce propan-3-one derivatives with a 1,3,4-oxadiazole core. The crucial cyclization step was the interaction between the carboxylic acid derivative (20) and aromatic acid hydrazide (19a–n) in the presence of phosphoryl oxychloride (POCl3). The initial stage involves the formation of a hydrazide, which subsequently undergoes a cyclization reaction with a cyclodehydrate, such as POCl3. The mixture underwent reflux for an extended period of time. The final compounds (21a–n) were purified by recrystallization from methanol, resulting in yields ranging from 54% to 66%. The previous steps involved the synthesis of acid hydrazide (19a–n) using a conventional method that involves esterification of carboxylic acids followed by hydrazinolysis. The carboxylic acid derivative (20) was synthesized as the second reagent through an electrophilic substitution reaction between bromobenzene and maleic anhydride.[37]

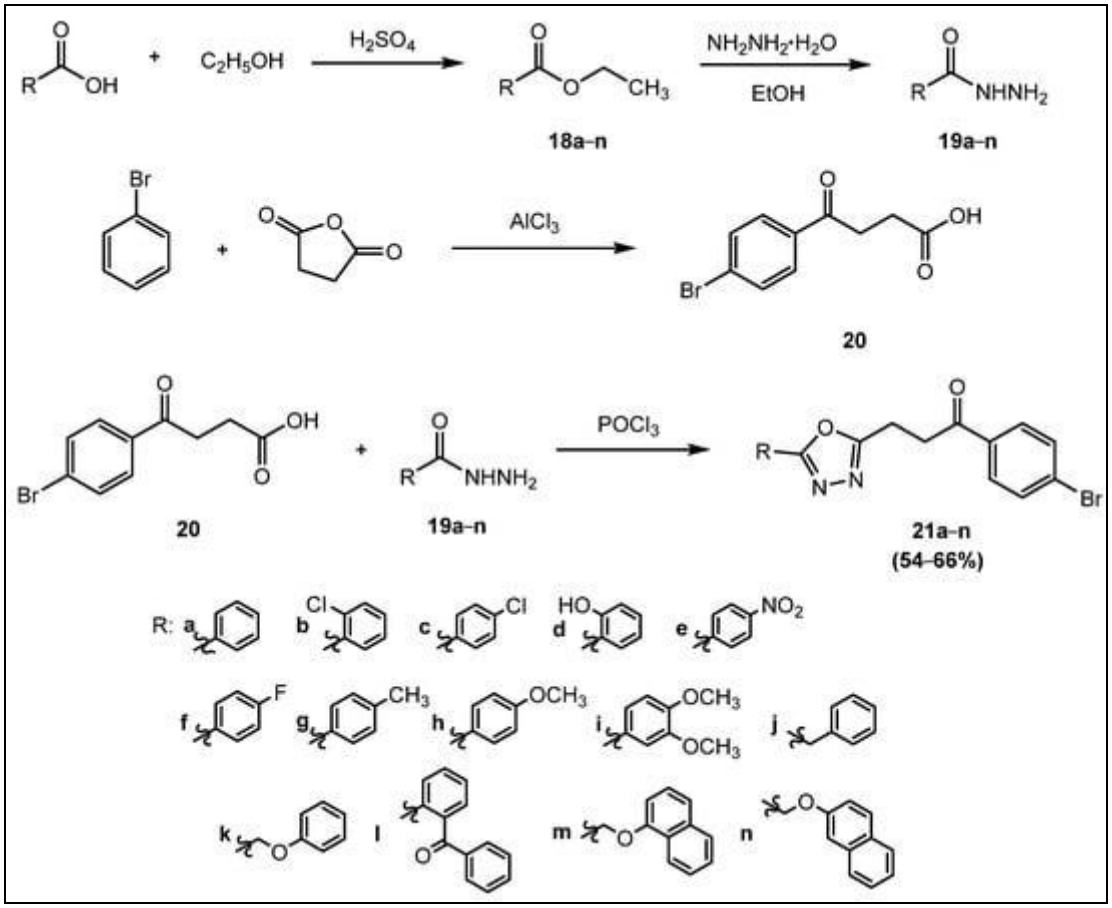


Fig. 10: [Scheme 3] Synthesis of propan-3-one derivatives containing 1,3,4-oxadiazole.

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.[38]

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 carbio-thioamide derivatives (24a–f). The reactants used in this case were iodine dissolved in potassium iodide solution. 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%.[39]

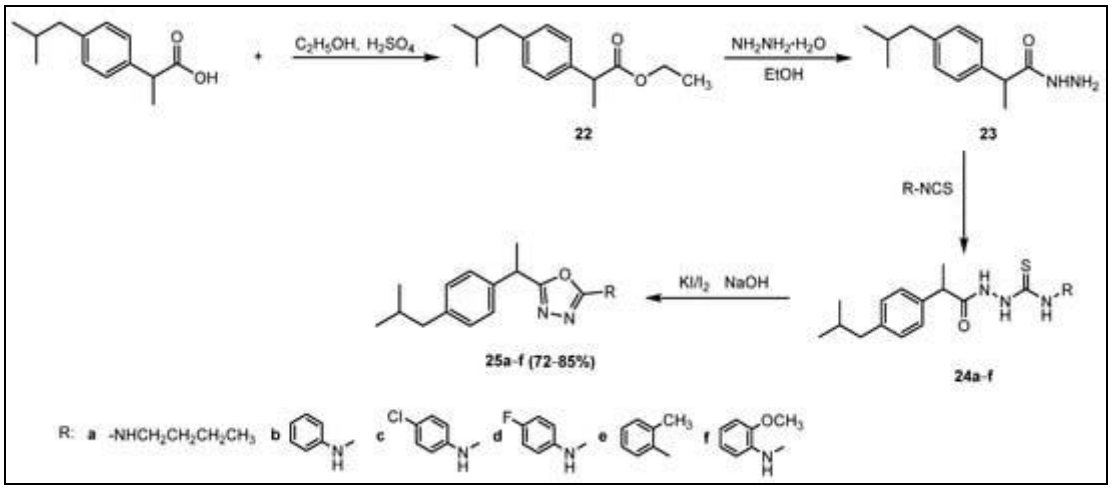


Fig. 11: **Synthesis of 5-[2-(4-*iso*butylphenyl)ethyl]-2-(aryl)-1,3,4-oxadiazole derivatives.**

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%.[40]

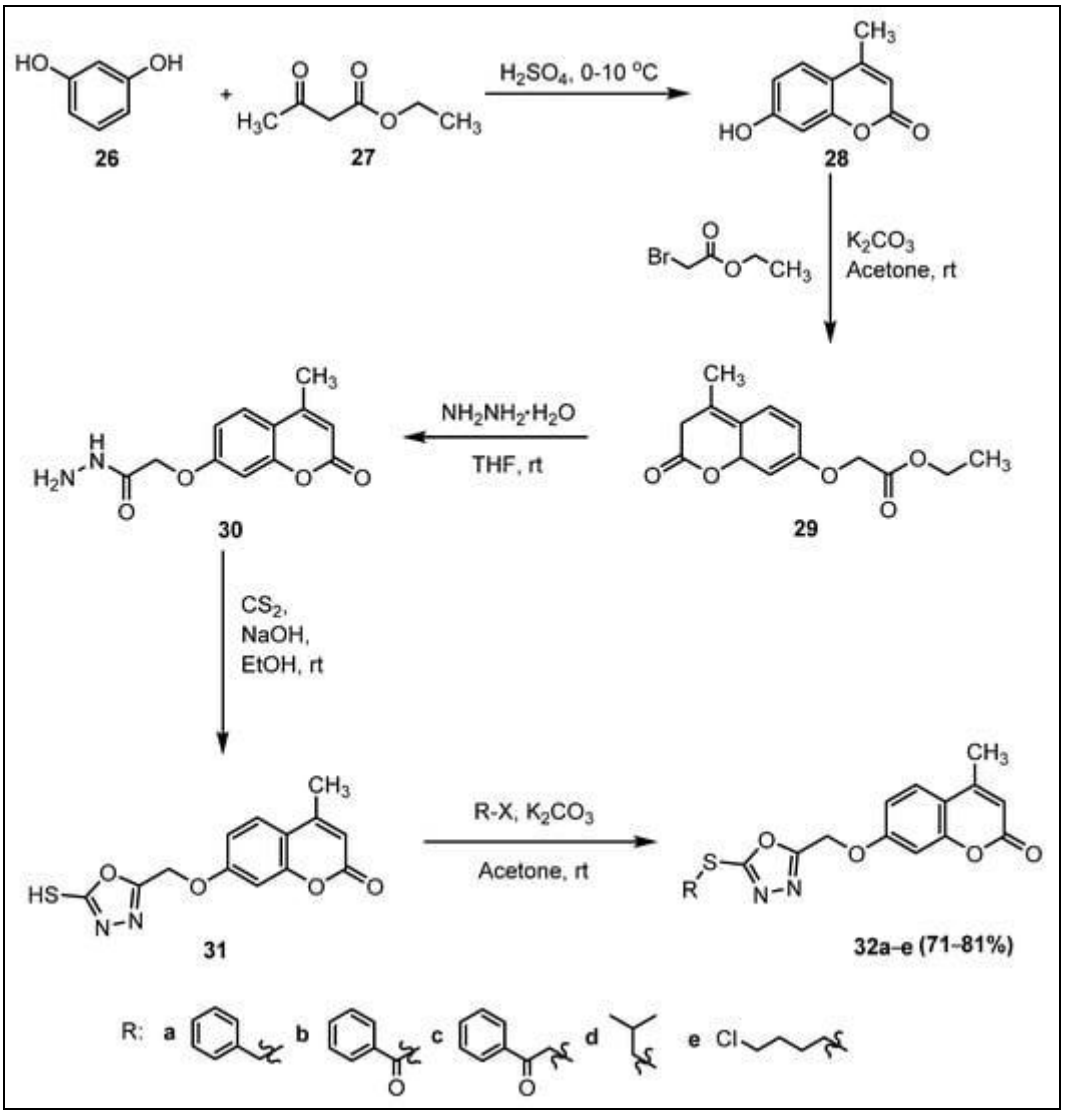


Fig. 12: [Scheme 4] Coumarin derivatives containing 1,3,4-oxadiazole.

Narella et al. proposed the preparation of 1,3,4-oxadiazole derivatives connected to a coumarin core via a methylenoxy linker. 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%. 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.[41]

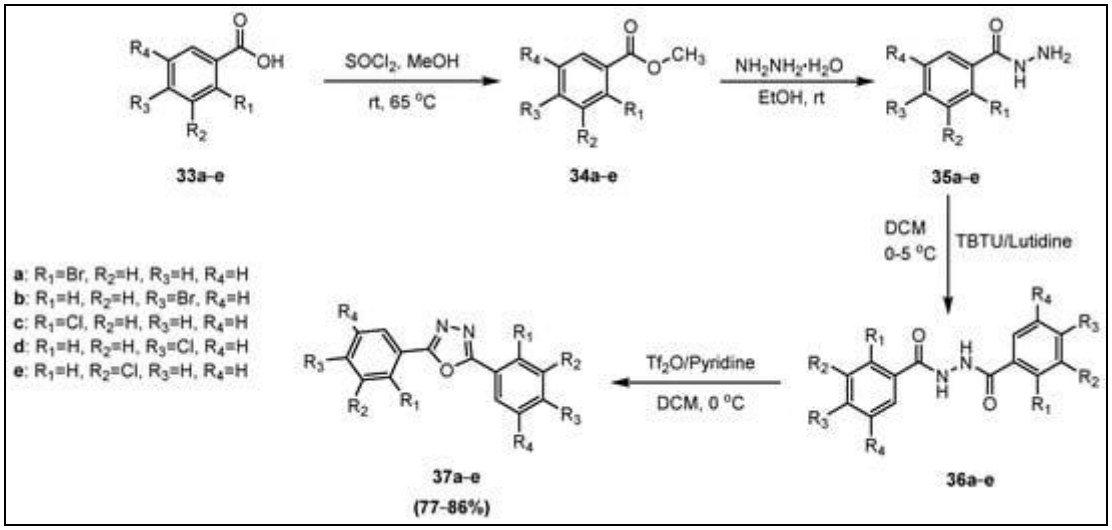


Fig. 13: [Scheme 5] Synthesis of 2,5-bisphenyl-1,3,4-oxadiazole derivatives.

Zabiulla et al. suggested a method for synthesizing 2,5-bisphenyl-1,3,4-oxadiazoles using trifluoromethanesulfonic anhydride as the primary reagent to facilitate the cyclization of N,N′-diacylhydrazines. The necessary diacylhydrazines (36) were synthesized from the substituted benzoic acid (33) by esterifying it with methanol, then treating it with hydrazine hydrate, and finally coupling it with the help of TBTU and lutidine. The compound N,N′-diacylhydrazine (36) at an intermediate stage was dissolved in dichloromethane (DCM), with pyridine serving as the basic catalyst. The reaction mixture was agitated for approximately 3 hours at a temperature of 0 degrees Celsius. The unrefined substances were refined by silica gel column chromatography employing a mobile phase consisting of a hexane and ethyl acetate mixture in a ratio of 9:1. The ultimate goods (37) were acquired with yields varying

from 77 to 86%. An indisputable benefit of this approach is the comparatively brief response time of 3 hours and the avoidance of the necessity to apply heat to the reaction mixture.[42]

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. 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 equimolar 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).

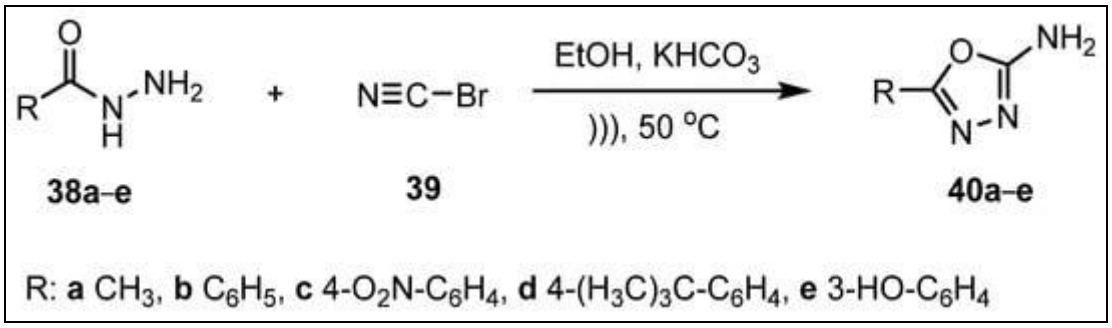


Fig. 14: [Scheme 6] Synthesis of 2-amino-1,3,4-oxadiazole derivatives.

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.

Jasiak et al. proposed two methods of obtaining 2-(2-arylethenyl)-1,3,4-oxadiazole derivatives. 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.[43]

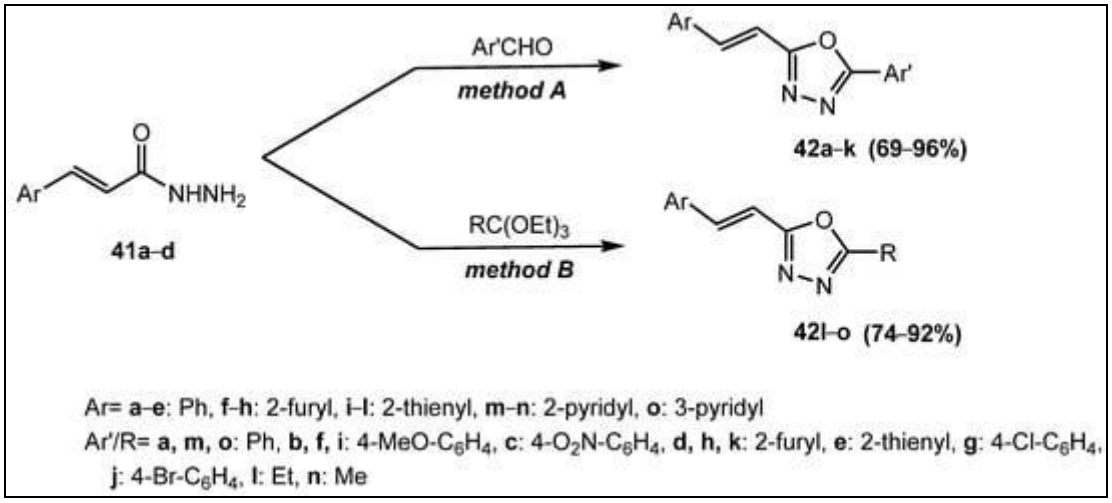


Fig. 15: [Scheme 7] Synthesis of 2-(2-arylethenyl)-1,3,4-oxadiazole derivatives.

CONCLUSION

It concluded that 1,3,4-oxadiazole derivatives possesses numerous pharmacological properties including antimicrobial, anti-inflammatory, antibacterial, anticancer, antifungal, tuberculostatic, analgesic, antiviral, antioxidant, insecticidal, anti-parasitic, and blood pressure-lowering. Thus, it is a promising moiety for new novel drug design with broad therapeutic efficacy on various medical conditions.

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Nil.

CONFLICT OF INTEREST

None.

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