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Review Article

Insight into the Synthesis Approaches of Oxadiazole and its Derivatives, Focuses on their Pharmacological Activities

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ABSTRACT

Oxadiazoles and their derivatives represent a significant class of organic compounds, wielding profound implications in both the realms of medicinal science and heterocyclic rings housing oxygen and nitrogen atoms, has garnered attention owing to their multifaceted. Pharmacological potential. The diverse array of biological activities exhibited by oxadiazole derivatives spans antimicrobial, anti-inflammatory, anti-cancer and anti-viral effects. Beyond medicinal applications, these compounds showcase utility in agriculture, with their herbicidal, insecticidal and fungicidal properties enabling their role as effective plant protection agents. Researchers have been focusing on the synthesis and exploration of these compounds for their potential in drug development. This review article is an in-depth exploration of diverse synthetic methodologies for oxadiazole and its derivatives while highlighting their associated pharmacological activities. It offers valuable insights into this class of compounds' versatile chemistry and potential therapeutic applications.

Keywords: Oxadiazole, Oxadiazole Derivative, Synthesis, Biological Activity.

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INTRODUCTION

Oxadiazole is an organic compound having a five-membered ring composed of two Carbon (C) molecules, one Oxygen (O) molecule and two Nitrogen (N) molecules. The nomenclature "oxadiazole" originates from the inclusion of one oxygen (-oxa) and two nitrogen (-diazole) atoms within its ring structure. Within the realm of organic chemistry, oxadiazoles hold significance and find diverse applications in medicinal chemistry, materials science and agriculture.[1] Due to their heightened stability in biological environments, oxadiazole rings are commonly employed as a structural motif in drug development. They serve as a bio-isosteric substitute for functional groups containing carbonyls, such as esters, amides, carbamates, acid chlorides and hydroxamic esters.[2-4] These have recently attracted the attention of numerous research organizations due to their capacity to serve as suitable bio-isosteric exchange options for functional groups including carbonyl. The continual rise in the number of specialists can be used to gauge their level of excitement.[5-7]

Oxadiazole-related molecules come in various forms and chemists have synthesized numerous compounds with this core structure, each with its own set of properties and potential applications. Here are some examples of various oxadiazole derivatives such as 1,2,4-oxadiazole, 1,2,5-oxadiazole, benzoxadiazine, thiazole-oxadiazoles, pyrazole-oxadiazoles and oxadiazoles polymers.[8,9] These are just a few examples of the many oxadiazole corollaries that have been produced synthetically and explored for various purposes in chemistry, materials science, pharmaceuticals and agriculture. The unique properties of oxadiazoles and their derivatives make them valuable in a broad spectrum of applications.[10] Considering the potential of oxadiazole moiety in the future lots of study is required in this subject. Oxadiazole moiety holds significant promise and potential in the field of drug discovery.

Chemistry of oxadiazole

Oxadiazoles, a distinctive class of heterocyclic bio scaffolds, serve as pivotal motifs in drug-like compounds. These structures are characterized by a five-membered ring housing an oxygen atom along with two nitrogen atoms and the positional arrangement of these atoms delineates the isomeric nature as either 1,2,4-oxadiazole or 1,2,5-oxadiazole. The unique arrangement

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of oxygen and nitrogen atoms imparts distinct characteristics to the two main isomers, emphasizing their structural diversity. A noteworthy feature is the classification of oxadiazole derivatives into four isomers (1,2,3,4). Categorization depends on the positioning of nitrogen atoms within the ring, with each isomer being assigned a specific number.[11,12] The inherent weak basicity of oxadiazole arises from the inductive effect exerted by the additional heteroatom, establishing its reluctance to accept protons.[13] In the context of reactivity, the replacement of the -CH= groups in furan with pyridine-type nitrogen atoms (-N=) results in a diminished aromaticity of the oxadiazole ring. This alteration imparts characteristics reminiscent of a conjugated diene. The electron-withdrawing impact of the nitrogen atom, evident in the comparatively low electron concentration on the carbon atom, renders electrophilic substitutions within the oxadiazole ring exceptionally challenging. Despite this, oxadiazoles showcase remarkable versatility in organic synthesis, participating in various cross-coupling reactions such as Suzuki-Miyaura and Stille coupling. Additionally, they engage in reactions like Williamson ether synthesis, Friedel-Crafts Acylation and Hantzsch synthesis.[14,15] The diverse reactivity positions oxadiazoles as valuable building blocks in organic synthesis, with derivatives exhibiting promising pharmacological activities. While oxadiazole rings typically exhibit robust resistance against nucleophilic attacks, halogen-substituted oxadiazoles display a propensity for nucleophilic substitution, wherein nucleophiles replace the halogen atoms.[16] This nuanced reactivity further accentuates the multifaceted role of oxadiazoles in the realm of chemical transformations these are the examples of four derivatives of oxadiazoles given in Figure 1.[17,18]

Various Synthetic Approach of Oxadiazole Derivatives

Oxadiazole, offers diverse synthetic pathways. Scientists worked to delve into several prevalent techniques employed for the synthesis of oxadiazoles.[19]

Rakesh R. Somani *et al.* (2011) worked on the oxidative cyclo-dehydrogenation process of Schiff's bases derived from 2-phenyl-3-semicarbazidoindole **(5)**, conducted in the presence of ferric chloride in acetic acid, resulted in the formation of substituted-3-(5'-phenyl-oxadiazolyl)-amino indole **(6)** depicted in Figure 2.[20,21]

Ansari *et al.* (2009) worked on 2-substituted-1H-benzimidazole as the initial material and a nucleophilic substitution reaction was executed by combining o-phenylenediamine **(7)** with carboxylic acid. This process led to the formation of a compound **(8)**. Subsequently, **(8)** underwent nucleophilic substitution, yielding ethyl (2-substituted-1H-benzimidazol-1-yl) acetate **(9)**. The structural confirmation of compound **(9)** was accomplished through analysis using Infrared Spectroscopy (IR), proton Nuclear Magnetic Resonance (1H NMR) and elemental analysis. The subsequent step involved the transformation of compound **(9)** into compound **(10)** upon treatment with hydrazine hydrate. Employing phosphoryl chloride, compound **(10)** was subjected to reactions with diverse aliphatic or aromatic carboxylic acids, resulting in the production of the final product, compound **(11)** as shown in Figure 3.[22]

Bostrom *et al* (2014). was worked on $CHCl_3$ and the corresponding acyl hydrazide **(12)** were combined and then dropwise additions of the chloride of thionyl were made. After 20 hr of reflux heating, the mixture produced a translucent liquid extracted in a vacuum. Following vacuum distillation, the product was purified using chromatography by column.[23] Similar products are formed by similar types of reactants with the phenol and pyridine substituents and give products as **(13)** **(15)** and **(17)** as depicted in Figure 4.[24]

Bhat *et al.* (2022) suggested that the utilization of mercury oxide in the presence of iodine to produce 2-aryl-.1,3,4-oxadiazole that has been aligned at the position of 5 by the p-bromo-phenylamino methyl group. Ethyl-(p-bromophenol) acetate **(20)** is produced by mixing p-bromoaniline **(18)** and ethylene chloroacetate **(19)**. After that, employing hydrazine hydrate, the ester created

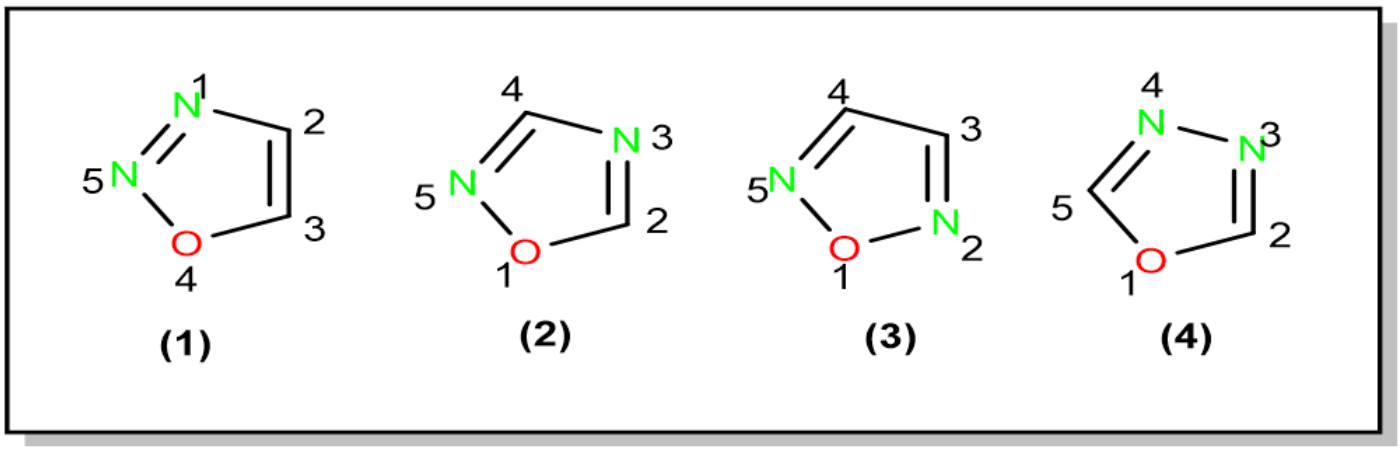


Figure 1: These are four different isomers of (1) oxadiazole:1,2,3-oxadiazole, (2) 1,2,4-oxadiazole (3)1,2,5-oxadiazole (4)1,3,5-oxadiazole.

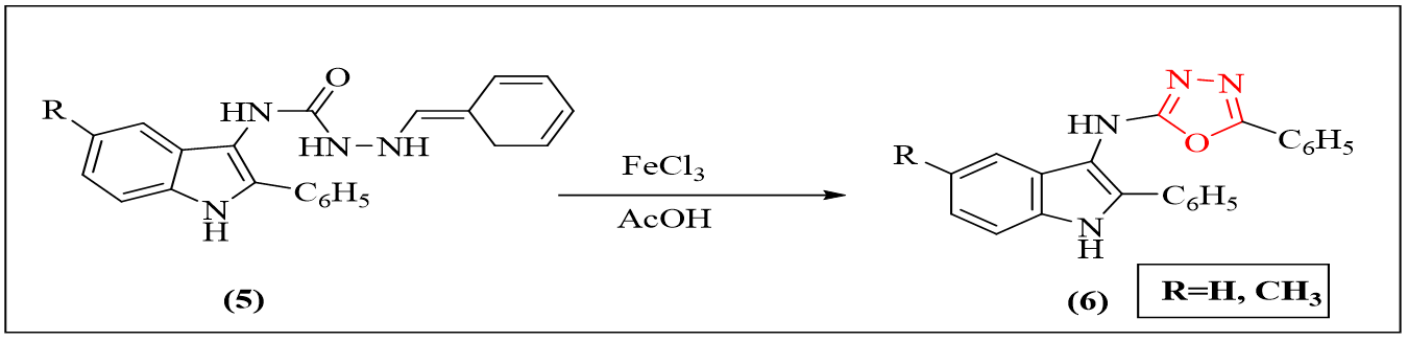


Figure 2: Preparation of 1,3,4-oxadiazole analogues using Schiff's bases.

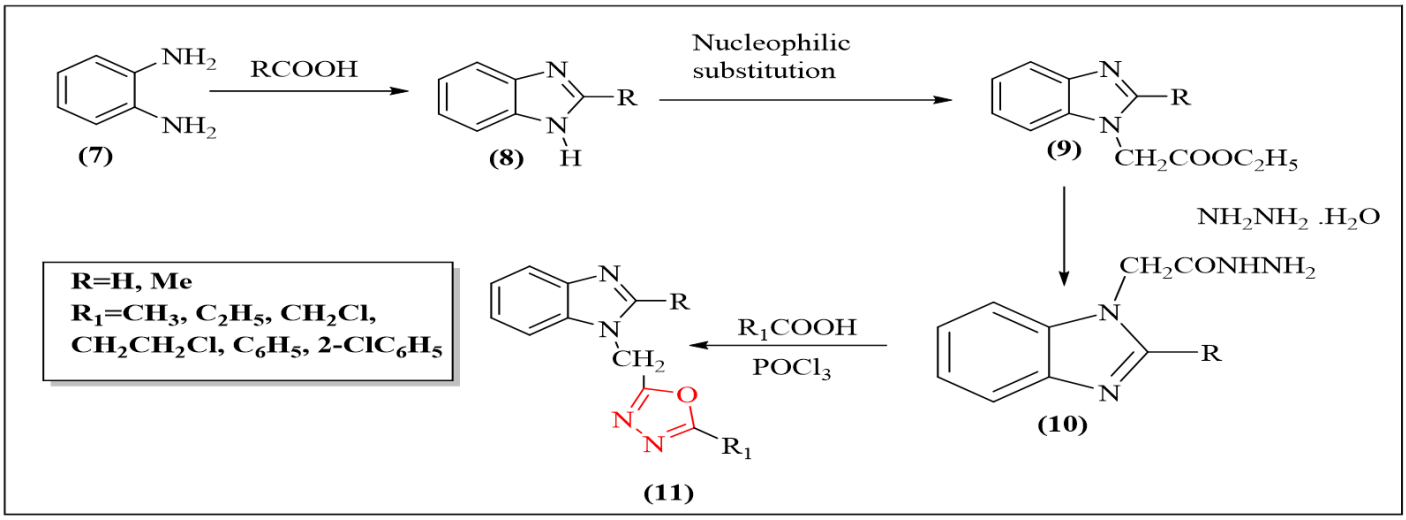


Figure 3: Synthesis of oxadiazole derivatives.

may be changed into the corresponding hydrazide **(21)**. The suitable hydrazone **(22)** is formed after further reaction with a variety of aryl aldehydes and it then undergoes a ring-forming reaction under a combination of mercury oxide and iodine. Recrystallization done via DMF: Methanol at a 2:2 volume ratio can purify the end products. Thus, with yields of 50-65%, a sequence of 1,3,4-oxadiazole derivative **(23)** may be produced shown in Figure 5.[25]

Khanum *et al.* (2022) suggested using microwave radiation to create 5-(2-aroyl) aryloxymethyl-,2-phenyl-1,3,4-oxadiazole derivatives **(26)**. Using hydrazine mixed in ethanol, a cyclization process was conducted on the previously produced using a conventional approach. Benzoic acid, clay and hydrazide were combined during the primary synthesis stage using a vortex mixer. After the extraction method compound **(26)** were produced with a yield of 60-80% using un-modified household microwave oven at 60% power for around 15 min depicted in Figure 6.[26]

Sahin *et al.* (2002) was prepared1-/2-Naphthyloxyacetic acid hydrazide **(28)** was synthesized through the esterification of 1-/2-naphthol with ethyl bromoacetate **(27)** in the presence of anhydrous potassium carbonate in dry acetone. The subsequent step involved refluxing the obtained product with hydrazine hydrate in absolute ethanol, resulting in the formation of 1-/2-naphthyloxyacetic acid hydrazide **(28)**.[27,28] The synthesis continued with the combination of acid hydrazides and carbon disulfide, leading to the creation of 1,3,4-oxadiazole-2(3H)-thiones **(29)**. Further, the reaction of hydrazide with cyanogen bromide in an alkaline solution resulted in the production of 2-amino-1,3,4-oxadiazole derivatives **(30)**.[29,30] Additionally, the reaction of hydrazides with CDI in a mixture of triethylamine (TEA) led to the synthesis of 1,3,4-oxadiazol-2(3H)-one **(31)** compound depicted in Figure 7.[31,32]

Kowalewska *et al.* (2022) was worked on oxadiazole moiety containing furan molecules that were synthesized using an ultrasonic-assisted synthetic method.[33] In accordance with the synthetic procedure outlined by Kowalewska *et al*, the generation of ethyl benzofuran-2-carboxylate **(36)** was achieved through a multistep approach. This involved the interaction between bromo-substituted salicylaldehyde **(34)** and ethyl chloroacetate in the presence of KOH, depicted in Figure 8.[34]

Rana *et al.* (2023) worked and examined the preparation of numerous novel 2-substituted.1,3,4-oxadiazoles via creatinine. By reacting creatinine with ethyl chloroacetate and two alkyl halides to make compounds **(40)**, an ester of creatinine was created. Following that, compounds **(40)** combined with semi-carbazide hydrochloride to create hydrazide derivatives

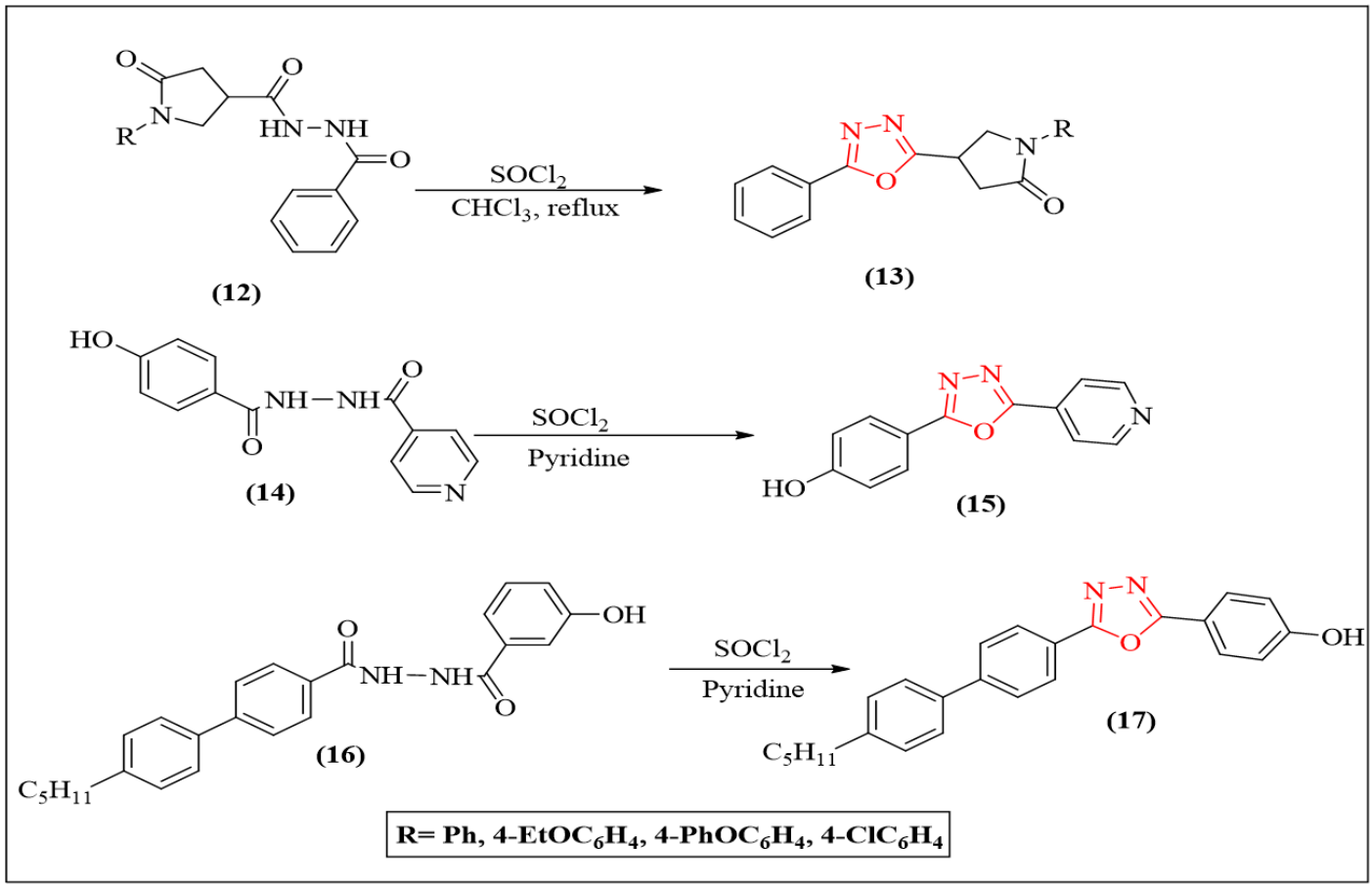


Figure 4: Preparation of 2,5-disubstituted.1,3,4-oxadiazoles.

(41). After cyclizing these hydrazides with 5% sodium hydroxide, 1,3,4.-oxadiazole derivatives **(42)** were created. These substances react to form Schiff bases **(42)** when they encounter aromatic aldehydes. Ultimately, Schiff bases were reacted with different reagents to generate derivatives on position 2 of diazetidine **(43)** with β-lactam **(44)** from. 1,3,4-oxadiazoles as shown in Figure 9.[35,36]

Sahoo *et al.* (2014) enumerated a collection of distinct schiff's imines of 1,3,4-oxadiazole analogues reported by Sahoo *et al* as depicted in Figure 10. green chemistry concepts are applied in the synthesis of these molecules, reaction of 1-(pyridine-4-yl) ethen-1-amine **(45)** in presence of potassium-o-ethyl dithiocarbonate at 80°C which formed compound **(46)** which tautomerism with compound **(47)** and at resultant formed substituted 1,3,4-oxadiazole derivative **(48)** in presence of 37% formaldehyde, dimethylformamide easily soluble in ethanol.[37]

Sasmita et al (2023) worked to generate compound **(56)**, respectively, firstly heated a Homogeneous quantity of. 5-chloro-4-nitrobenzo1,2,5oxadiazole **(51)** with 4-Amino-substituted phenylboronic acid vinyl cyclohexanol ester **(52)** in DMF at 80°C for 2 hr. Then, substrates **(56)** were stirred via 4-(amino-methyl) phenylboronic acid pinacol ester **(53)** (2.0 equivalent) in the presence of sodium tertiary butoxide (1.2-1.5 equivalent) in DMF under nitrogen-rich environment at room temperature (30 °C) for 15 hr to create derivatives **(56)**. To create a hybrid **(58)**, **(51) and (54)** were further reacted with 4-hydroxyphenyl boronic acid pinacol ester compound **(58)** (2.0 equivalent) in the presence of triethylamine (Et_3N) (1.0 equivalent) in acetonitrile under a nitrogen-rich environment at ambient temperature (30°C) for 15 hr. **(59)** was similar as depicted in Figure11.[38]

Srivastav *et al.* (2011) worked on the synthesis of oxadiazole with an imidazole moiety was achieved through a microwave-assisted method in the absence of solvents as shown in Figure 12.[39]

Ali *et al.* (2014) synthesize N-Benzyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-1-(1H-pyrrol-2- yl)methanamine **(75)** via one-pot reaction of benzylamine **(71)**, pyrrole-2-carbaldehyde **(72)**, (N-isocyanimino)triphenylphosphorane **(73)** and benzoic acid **(74)** in the presence of dichloromethane. This reaction occurs within 15hr at room temperature with 85% yield Figure 13.[40]

Adil *et al* (2019) worked on a collection of 5-{3-'oxo-6'-(substituted aryl)-2,3,4,5-tetrahydropyriidazin-2yl, methyl}-2-substituted 1,3,4-oxadiazoles **(81)** derivatives were created 1,3,4-diazoles that are 2-substituted with the proper aromatic hydrocarbon B-aroyl propanoic acid **(77)** is produced when succinic anhydride is combined with $AlCl_3$. The related acid cycles into an intermediate

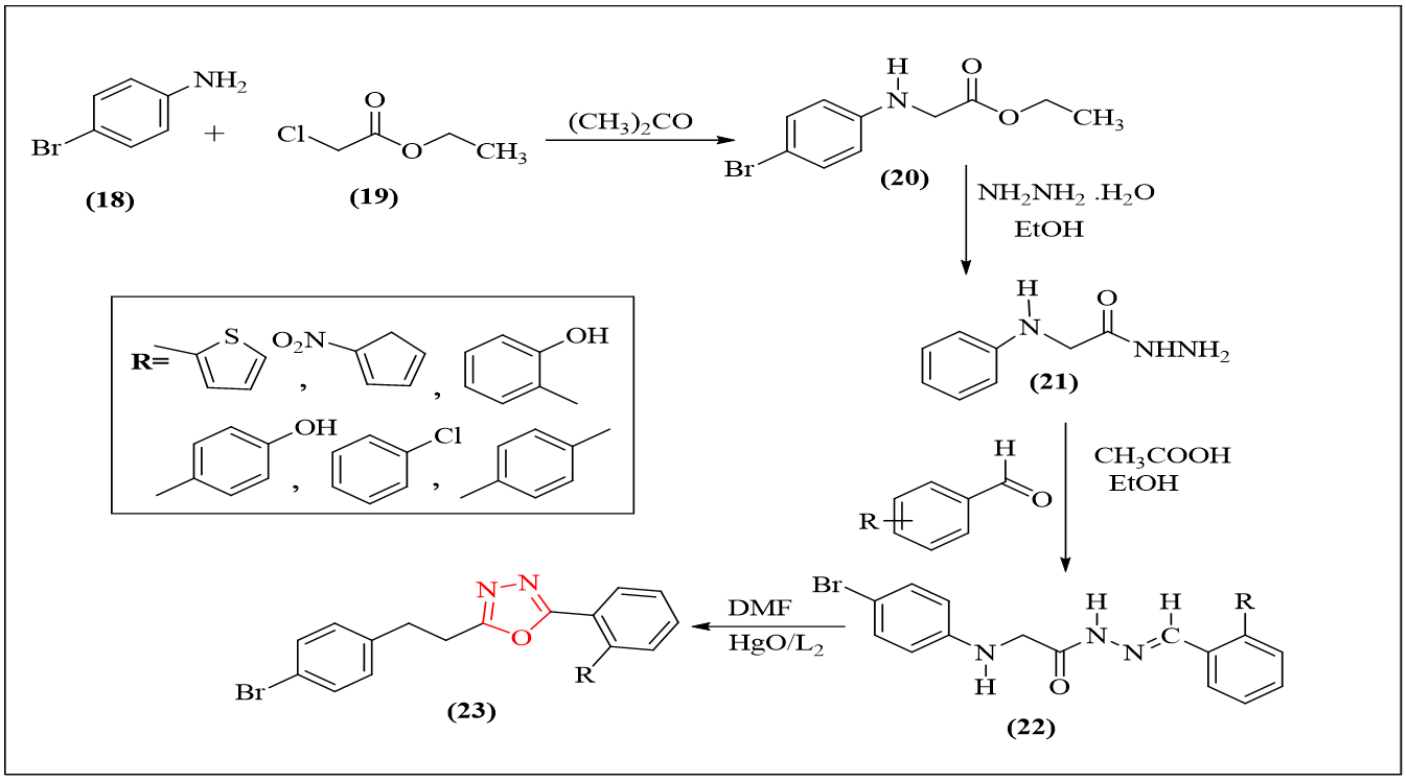


Figure 5: Preparation of 1,3,4-oxadiazole compounds from p-bromoaniline.

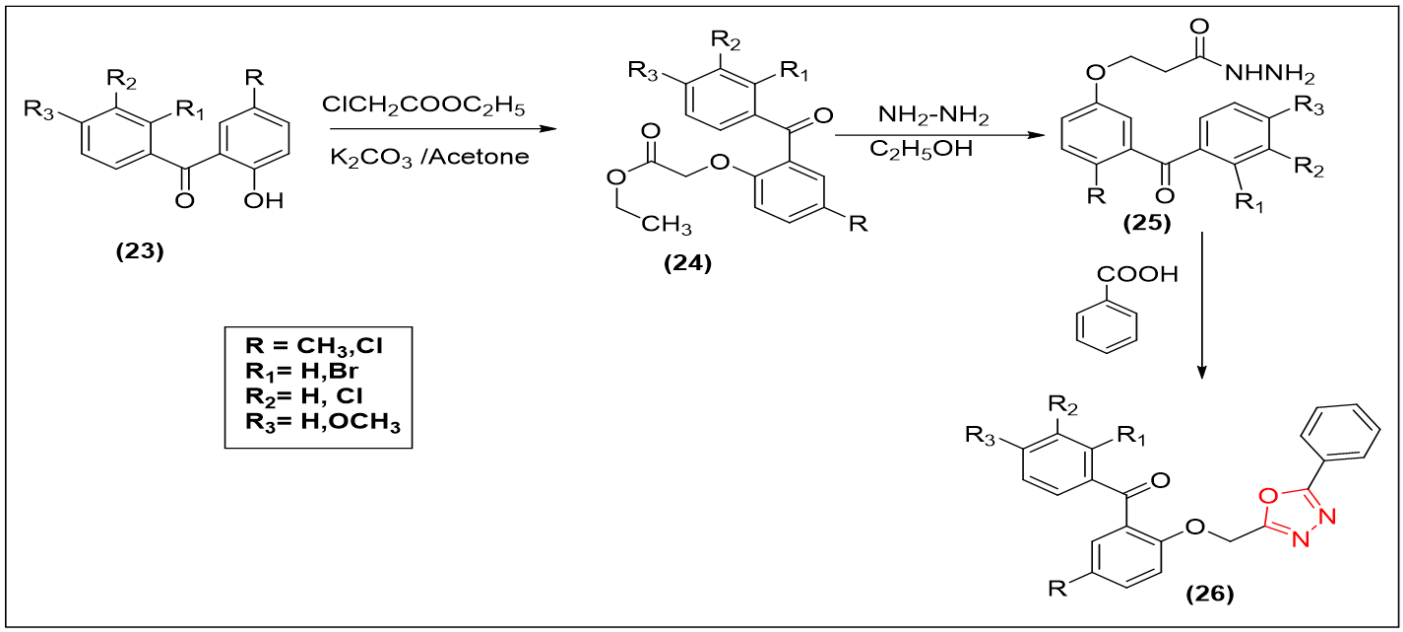


Figure 6: Preparation of 2-(2-aroyl)-aryloxymethyl-2-phenyl-1,3,4-oxadiazole derivatives.

(78) form of pyridazines. This intermediate was transformed to 1,3,4 Oxadiazoles by reaction with ethyl bromo acetate to produce aceto-hydrazides **(79)** which formed end product **(81)** depicted in Figure 14.[41]

Sathyanarayana *et al.* (2022) lists the series of reactions that go into making the title compounds. Two approaches have been employed for the synthesis of derivatives of 1,3,4-oxadiazole. One method uses alternative aldehydes and the other method uses different acetophenones. The esterification product of 2,5-bis(2,2,2-trifluoromethoxy) benzoic acid yielded the crucial intermediate, 2,5-bis(trifluoro-ethoxy) ethyl benzene benzo hydrazide **(84)**. Several hydrazone compounds **(85)** were created by condensing different aldehydes/acetophenones via 2,5-ditrifluoroethoxybenzohydrazide. After adding acetic anhydride to the obtained hydrazones, 1-{5-[2,5-bis(2,2,2-tri

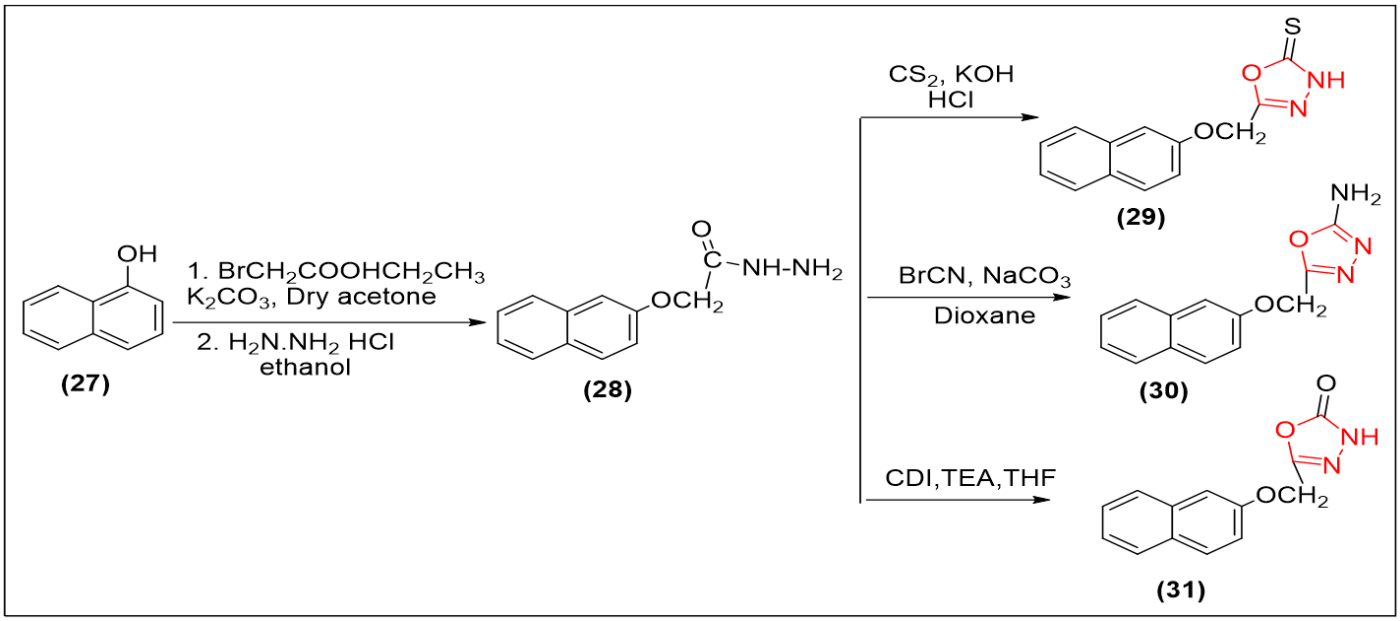


Figure 7: Synthesis of 1-/2-naphthyloxyacetic acid hydrazide.

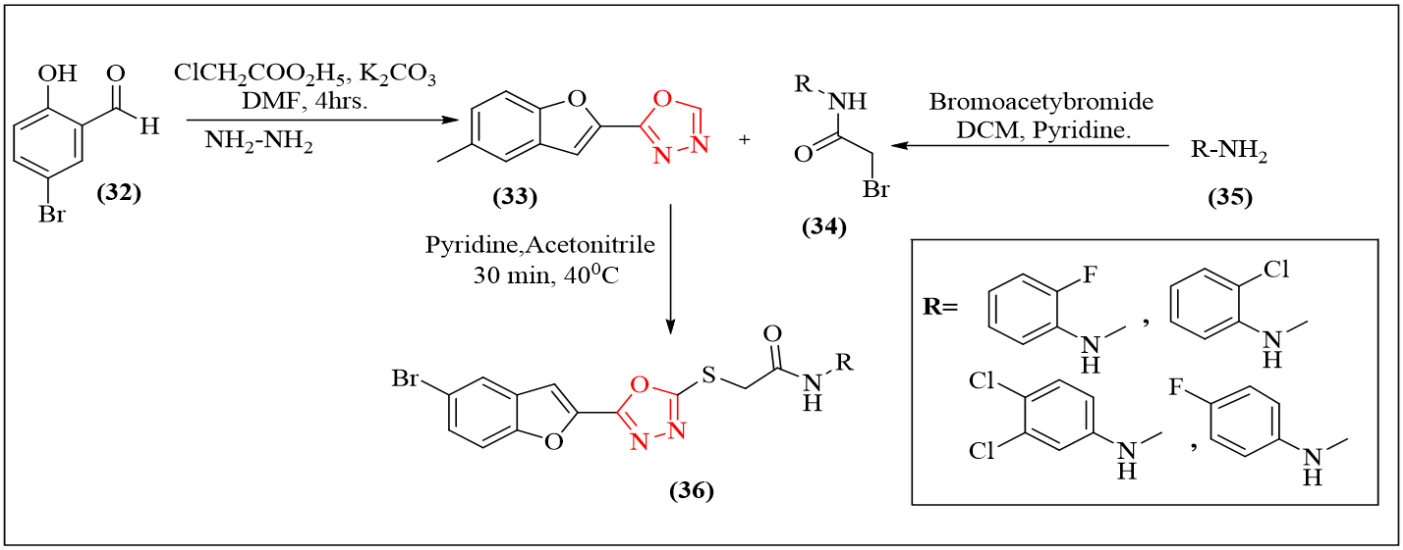


Figure 8: Synthesis of S-alkylated furan-oxadiazole derivatives (36) was carried out with the assistance of ultrasonic conditions.

fluoromethyl) phenyl] was produced. 1-{5-[2,5-bis(2,2,2-trifl uoroethoxy) phenyl] and 1,3,4-oxadiazol-3(2H)-yl} ethenone **(85)** and 3-Oxadiazol-3(2 methyl)-ethenone **(86)** as depicted in Figure 15.[42]

Seung *et al.* (2013) synthesized N-benzyl-5-phenyl-1,3,4-oxadiazol-2-amine **(88)**, when thio-semicarbazide derivative **(87)** undergoes de-sulfurative cyclization reaction proceed by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide with hydrochloride (EDC.HCl) in the presence of dimethyl sulfoxide at 60°C. This reaction is occurred within 2hr gives 100% yield Figure 16.[43]

Amer *et al.* (2018) worked on a procedure outlined in **[44]** involving the synthesis of 2-(4-nitro phenoxy) aceto-hydrazide **(91)** through the reaction of p-nitrophenol **(89)** with ethyl chloroacetate in the presence of potassium hydroxide in presence of pot to create. After carbonating to produce ester derivative **(92)**, hydrate hydrazine is reacted to produce 5-((4-nitrophenoxy) methyl)-1,3,4-oxadiazole-2-thiol **(93)** via cyclization of hydrazide by KOH, carbon disulfide and ethanol was heated for 10 hr under reflux. And further proceed the reaction for the formation of final products Ethyl 2-(5-(4-nitrophenoxy) methyl)-1,3,4-oxadiazol-2-yl)thioacetate-hydrazide **(94)** as depicted in Figure 17.[44]

Suman Bala *et al.* (2014) conducted research involving utilizing a versatile starting material for synthesizing 1,3,4-oxadiazole derivatives. In reaction anisole **(95)** react with dihydrofuran-2,5-dione **(96)** in presence of anhydrous

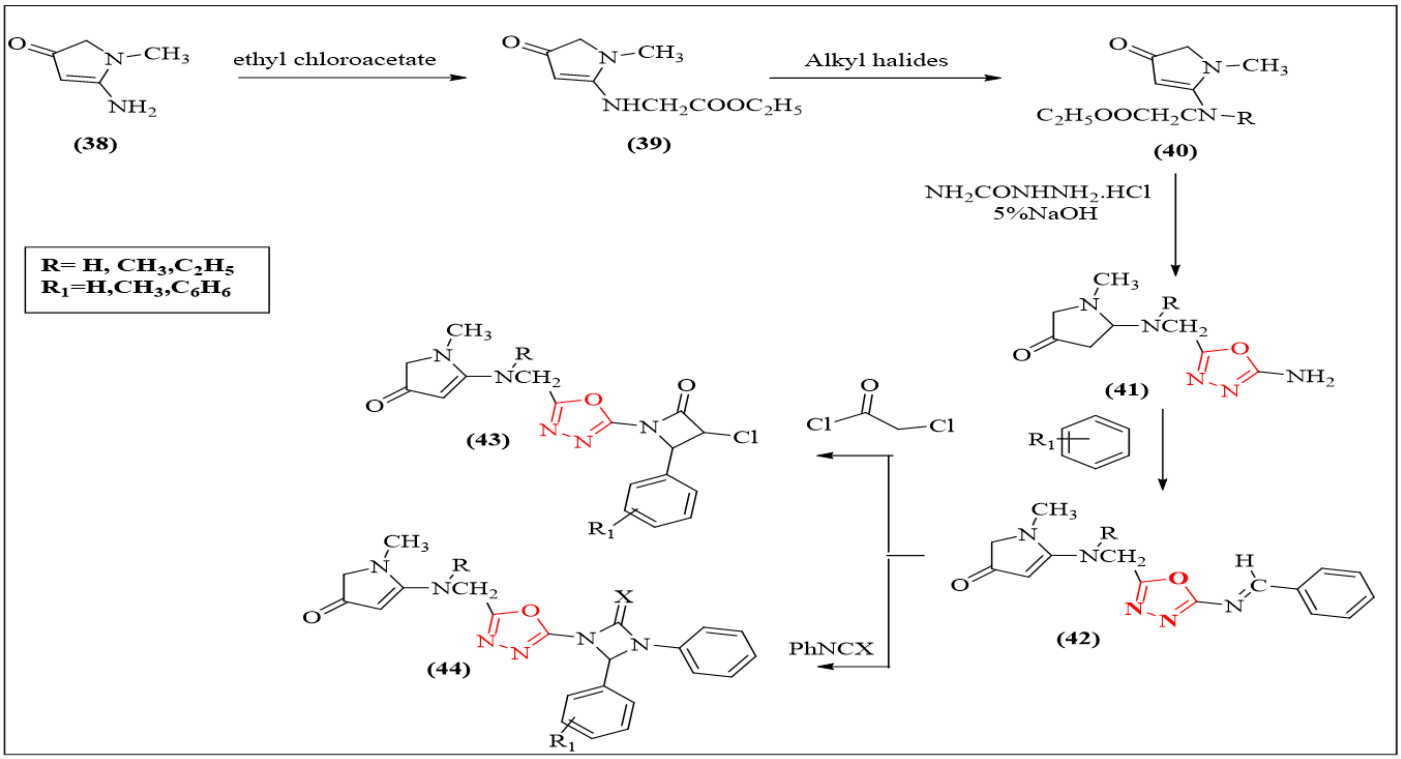


Figure 9: Preparation of phenyl isocyanate, phenyl isothiocyanate and chloro-acetyl chloride.

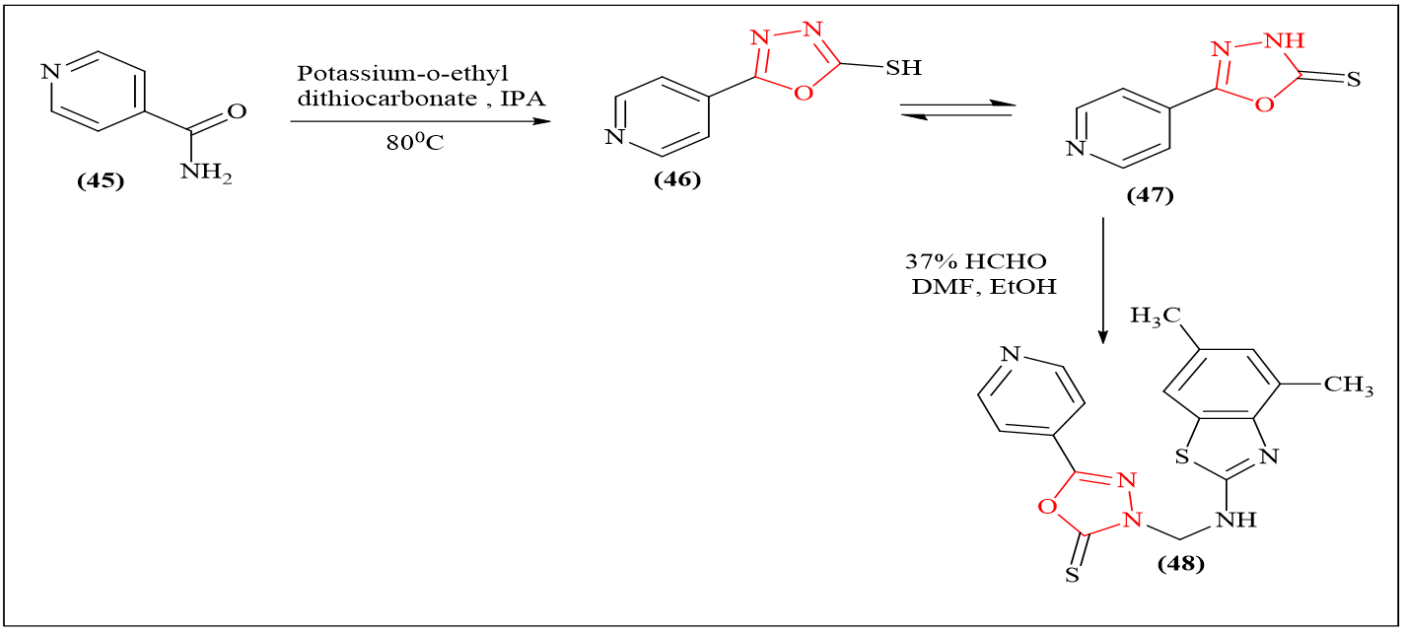


Figure 10: Enumerated a collection of 1,3,4-oxadiazole derivatives (48).

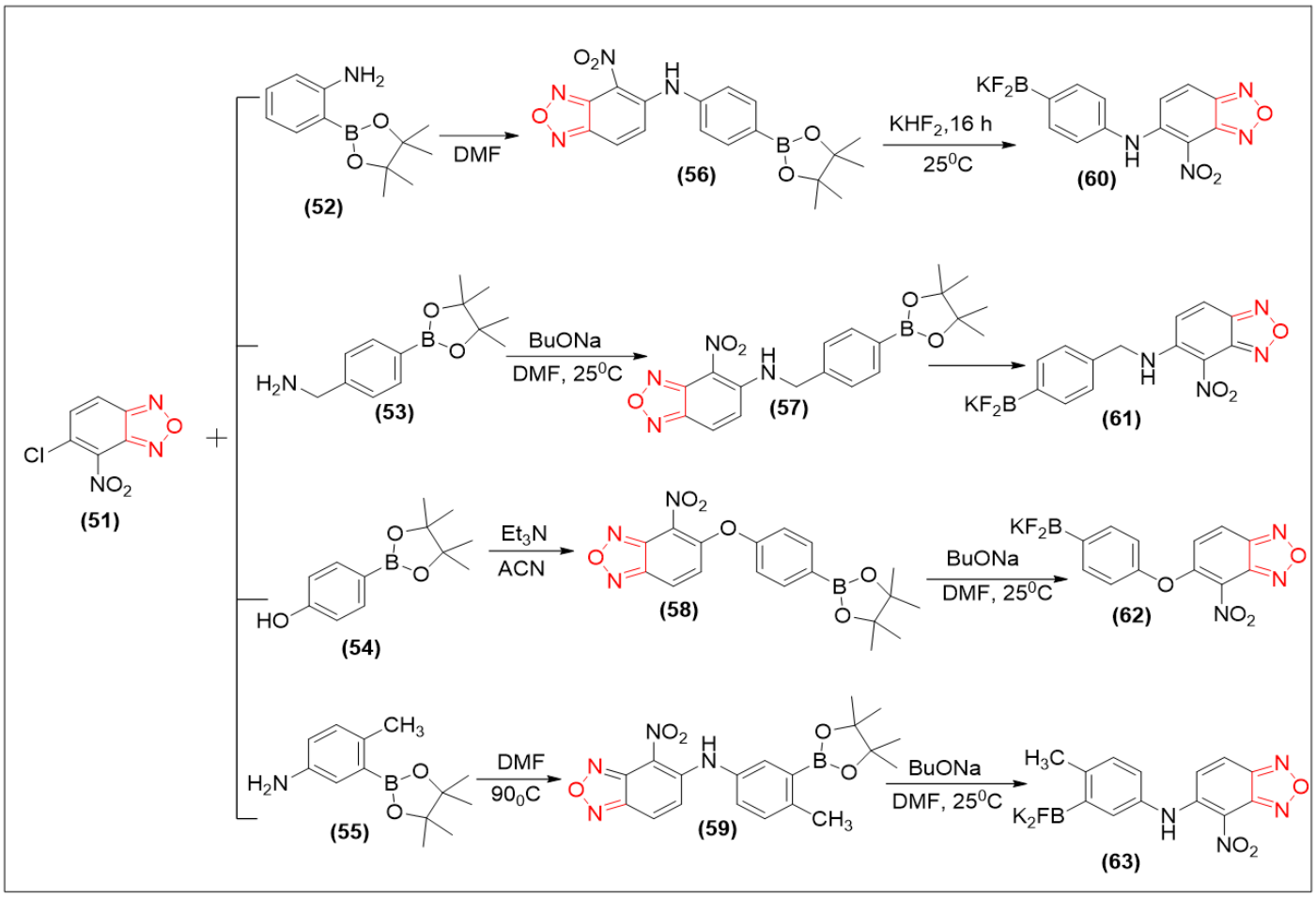


Figure 11: General synthetic scheme of boron-based compounds.

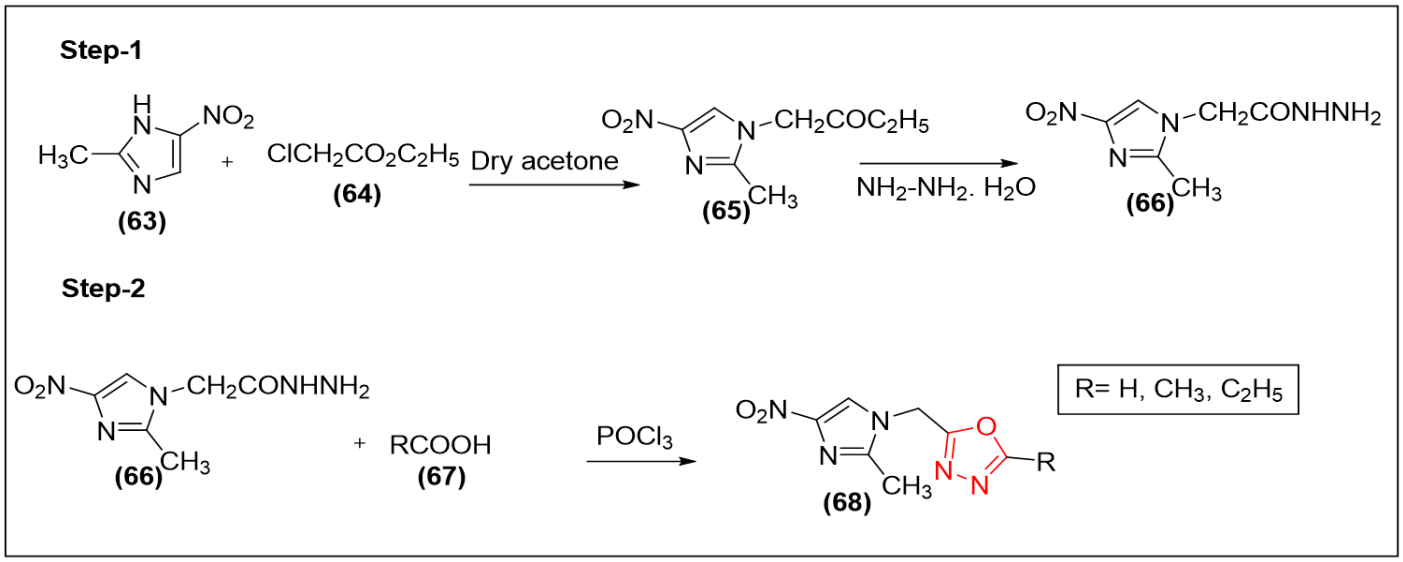


Figure 12: Preparation of 1,3,4-oxadiazole containing imidazole ring.

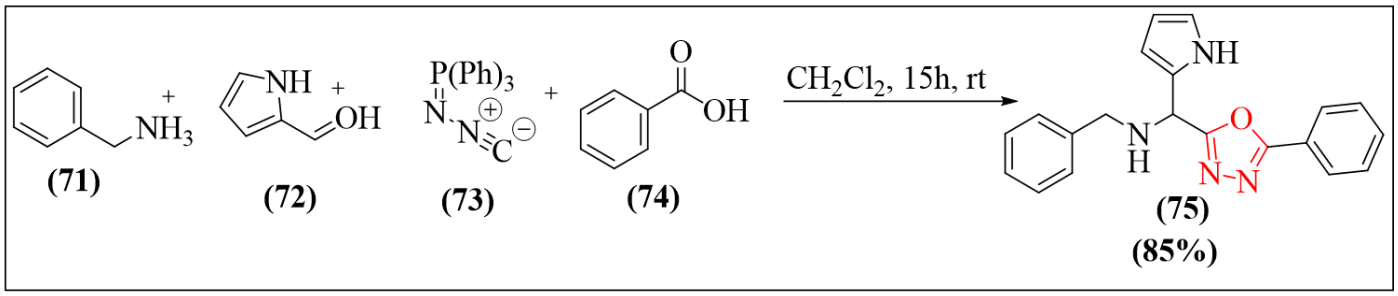


Figure 13: One-pot synthesis of 1,3,4-oxadiazole in the presence of dichloromethane..

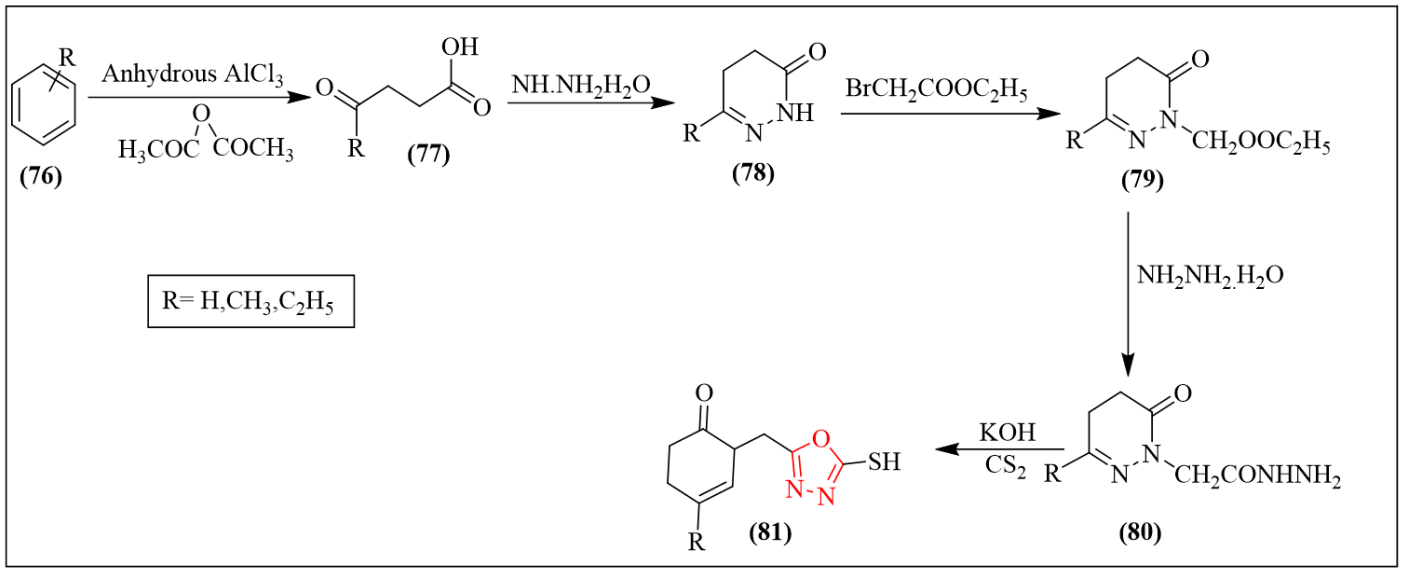


Figure 14: 1,3,4-Oxadiazoles are synthesise by combining hydrazides with aroyl propanoic acid.

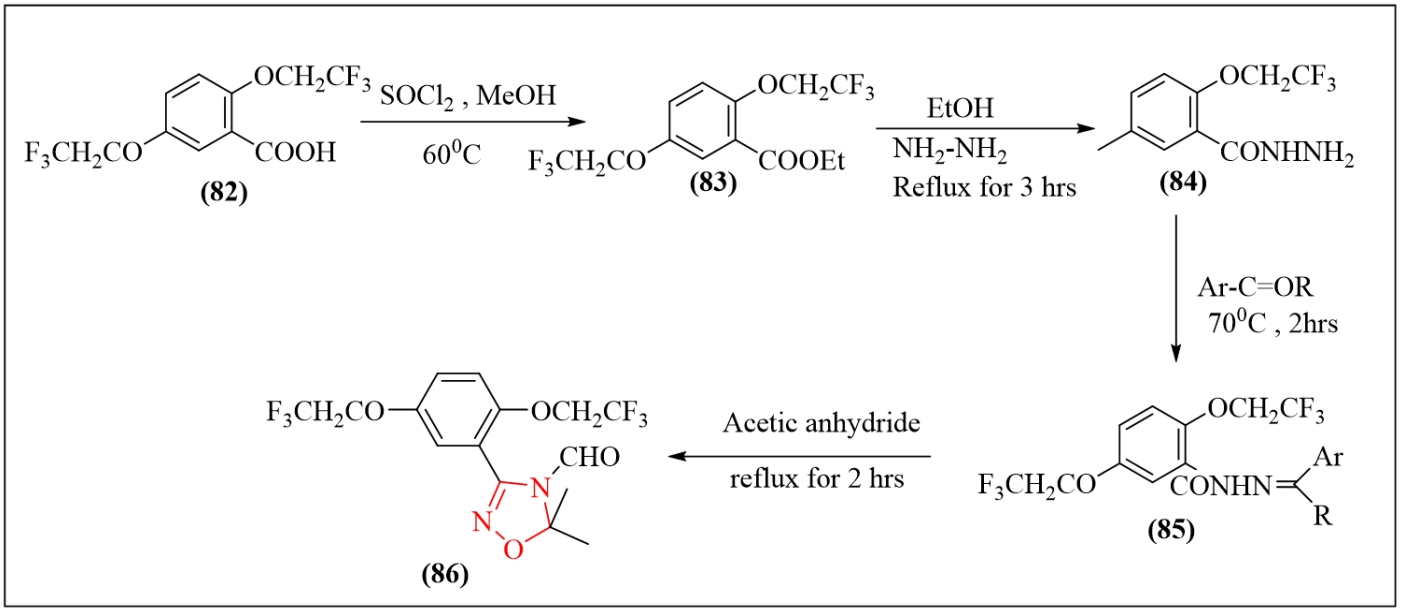


Figure 15: Synthetic route for the compounds.

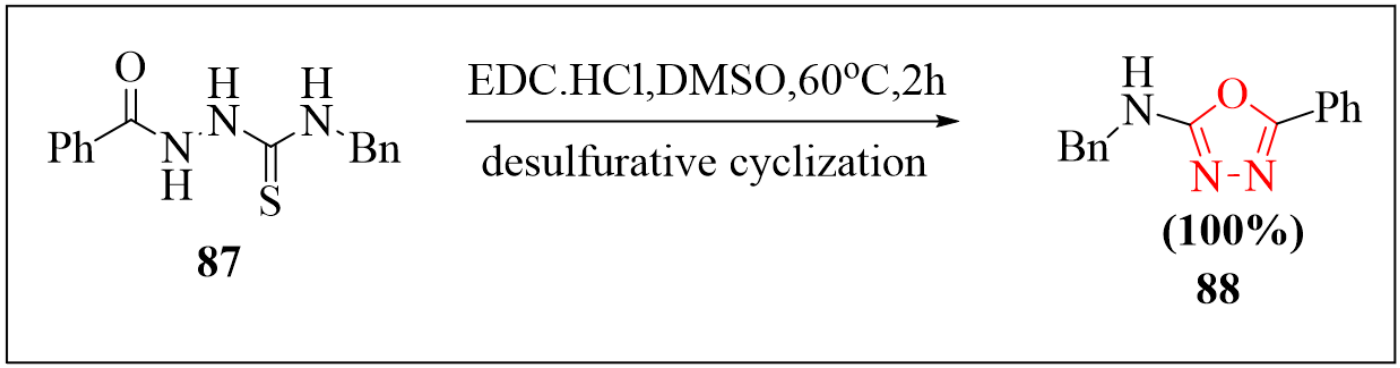


Figure 16: Synthesis of 1,3,4-oxadiazole from thiosemi-carbazide.

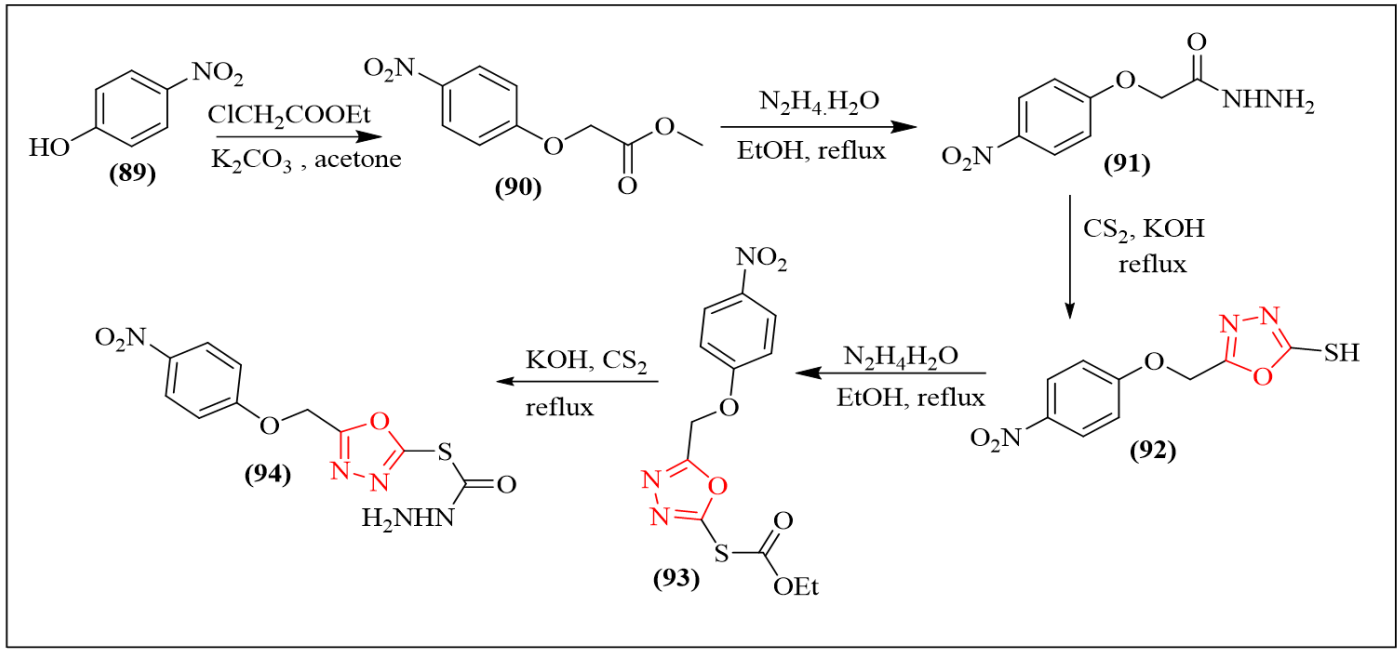


Figure 17: Synthesis of oxadiazoles derivative from nitrophenols.

$AlCl_3$ also called Fischer esterification, converting substituted aromatic acids into 4-(4-methoxyphenyl)-4-oxobutanoic acid **(97)**. Subsequently, these esters underwent further reaction with $POCl_3$, leading to the formation of the respective oxadiazole derivatives compounds **(98)** Figure 18.[45]

Desai *et al.* (2021) used a reasoned method to create a novel sequence oxadiazole derivatives were exposed to microwave induction (MWI). Using the MTT colorimetric assay, the synthesized compounds were assessed for their *in vitro* antimicrobial activity against bacterial, fungal activity. Compounds **(103)** showed the strongest antibacterial activity of all the compounds examined; on the other hand, compounds **(103)** proved to be the most successful antifungal agents. In reaction1-(1H-Benzoimidazol-1-yl)-ethanol reacted with benzo-hydrazide compound with (1:1) ethane in presence of 1,4-dioxane and formed compound **(101)** further compound **(101)** reacted with acetic anhydride and formed compound **(102)** react with 4- chlorobenzaldehyde in presence of KOH as catalyst and ethanol used as solvent resultant formed compound **(103)** further substitution in compound **(103)** formed series of oxadiazole derivatives represented in **Figure 19.**[46]

Khan *et al.* (2003) Carbethoxymethoxy-4-methylcoumarin (7-methyl) **(106)** prepared via 7-hydroxy-4-methylcoumarin **(104)** in combination with chloroethyl acetate **(105)** were mixed in dehydrated acetone and combined with potassium carbonate was added for 10 hr, the reaction mixture underwent reflux. When the reactions have been accomplished, after removing K_2CO_3, the filtrate evaporated until it was completely dry. After adding cold water to the residue thus created, a solid mass was produced. To produce a colourless flake, it was washed, rinsed with water and then precipitated from ethanol. Further, the reaction of compound **(106)** with ethanol hydrazine hydrate was mixed and for 3 hr, the reaction amalgamation refluxed and formed 4-Methylcoumarinyl-7-oxyacetic hydrazide **(107)** and 4-Methyl-7-(5-phenyl-1,3,4-oxadiazol-2-ylmethoxy) chromen-2-one **(108)**. The mixture of methanol and cyanogen

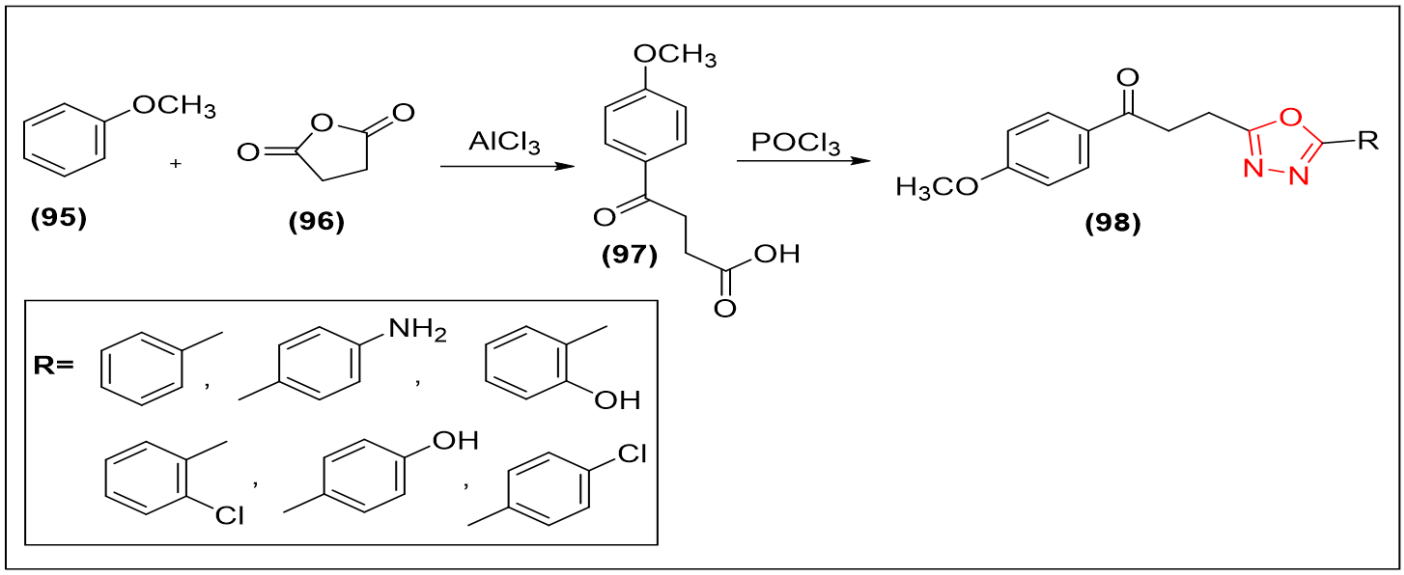


Figure 18: Preparation of 1,3,4-oxadiazole derivative.

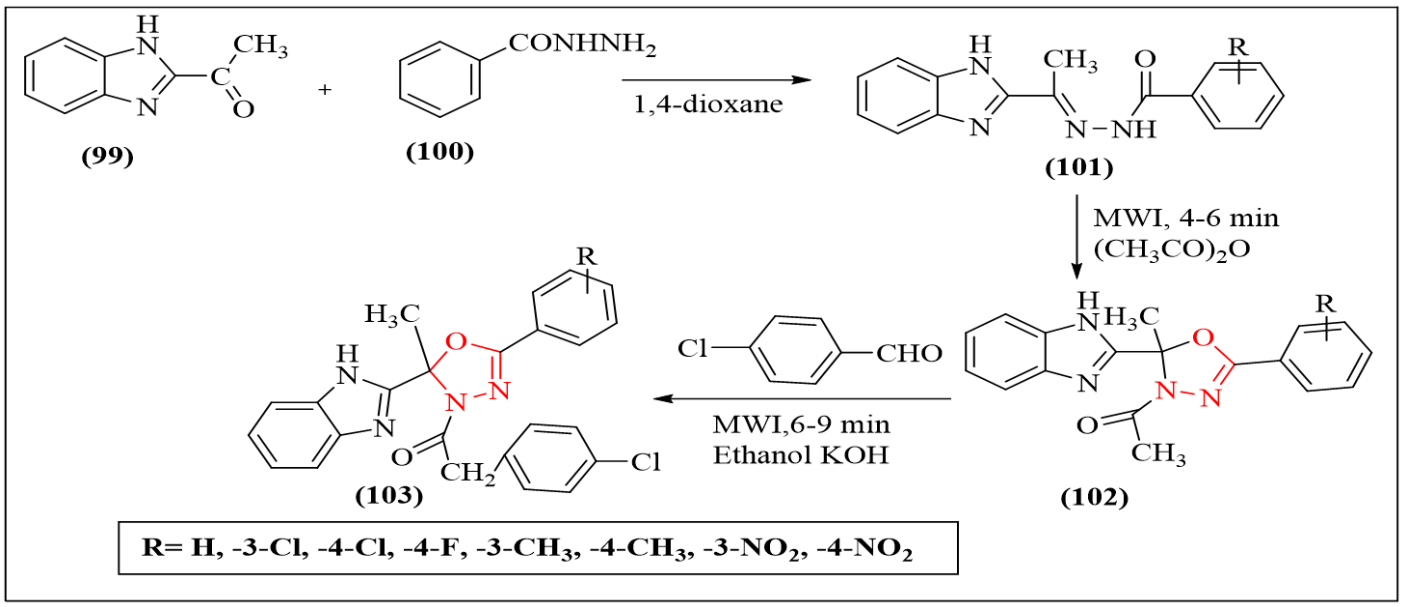


Figure 19: Synthetic route for the synthesis of oxadiazole derivatives.

bromide was mixed, until 2 hr the reaction mixture was heated vigorously while under reflux and formed compound **(109)** and **(110)** as depicted in Figure 20.[47,48]

Ali *et al.* (2021) synthesised 2-(3-Fluorophenyl)-1,3,4-oxadiazole **(113)**, when benzoic acid derivatives **(111)** react with (N-isocyanimino) triphenyl phosphorane **(112)** under goes intramolecular aza-wittig–type cyclization reaction in the presence of chloroform which is act as solvent. This reaction occurs at room temperature within 12hr with yield 82.2% Figure 21.[49,50]

Teslenko *et al.* (2022). presented a modern one-pot method for the preparation of 1,2,4-oxadiazole derivatives **(117)**, **(118)** Via the reaction (Z)-N'-hydroxy-4-methyl-1 ,2,5-oxadiazole-3-carboximidamide **(114)** with 4-methoxybenzaldehyde **(115)** in presence of Scandium tri-fluoromethanesulfonate at room temperature formed 5-(4-methoxyphenyl)-3-(4-methyl-1,2,5-oxadiazol-3-yl)-4,5-dihydro-1,2,4-oxadiazole **(116)**.[51-53] MnO_2 in acetic acid used as oxidant to formed final product 4-methyl-1,2,5-oxadiazole-3-carboxamide **(118)** and 3-(4-methyl-1,2,5-oxadiazol-3-yl)-5-(p-tolyl)-4,5-dihydro-1,2,4-oxadiazole **(119)** as end product shown in Figure 22.[54,55]

Telehoiu *et al.* (2019). Worked on the reaction in the presence of concentrated sulfuric acid, the reaction of carbazolyl propionic acid **(119)** with methanol yields methyl (2RS)-2-(6-chloro-9H-carbazol-2-yl)-propanoate;(carprofen methyl ester) **(124).** Carprofen hydrazides also known as

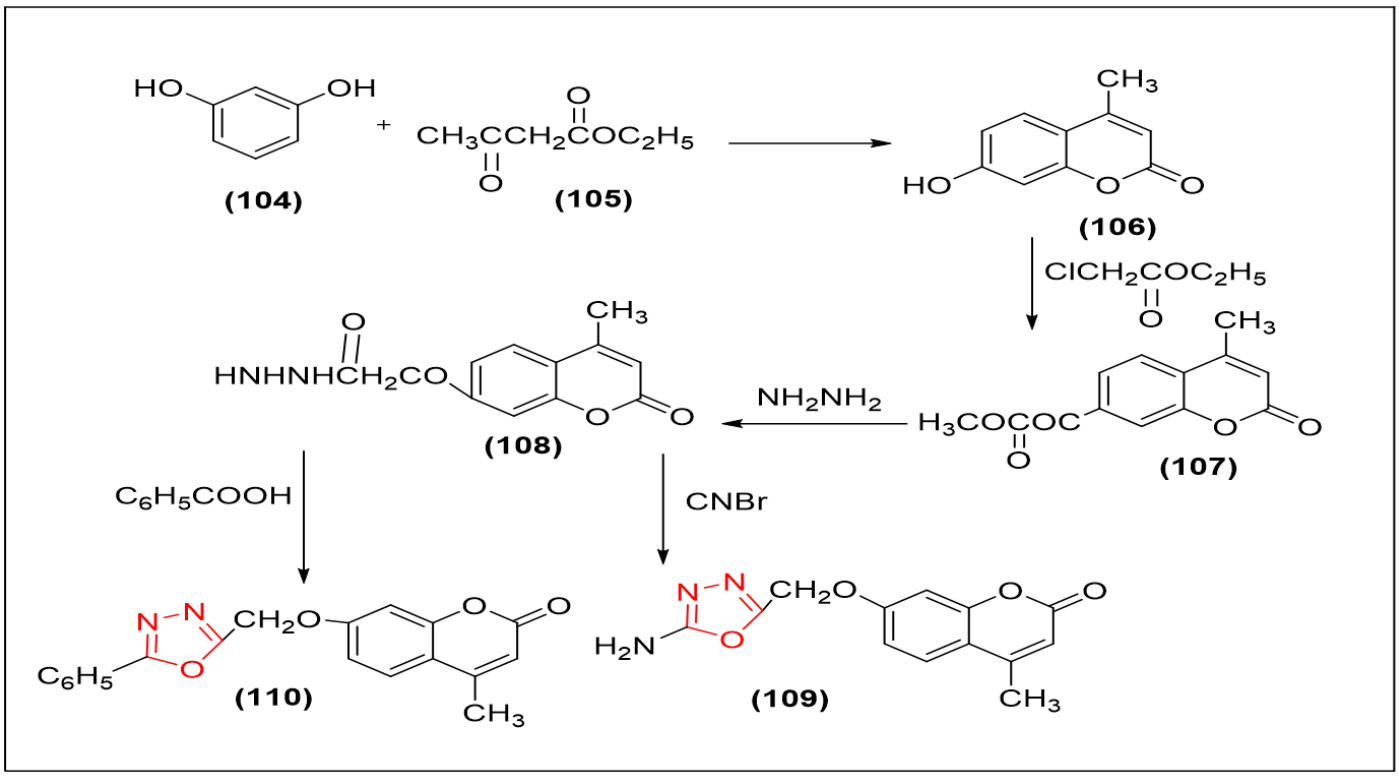


Figure 20: Synthesis of 4-Methyl-7-(5-phenyl-1,3,4-oxadiazol-2-ylmethoxy) chromen-2-one and 4-Methyl-7-(S-amino-1,3,4-oxadiazol-2-ylmethoxy) comarin-2-one.

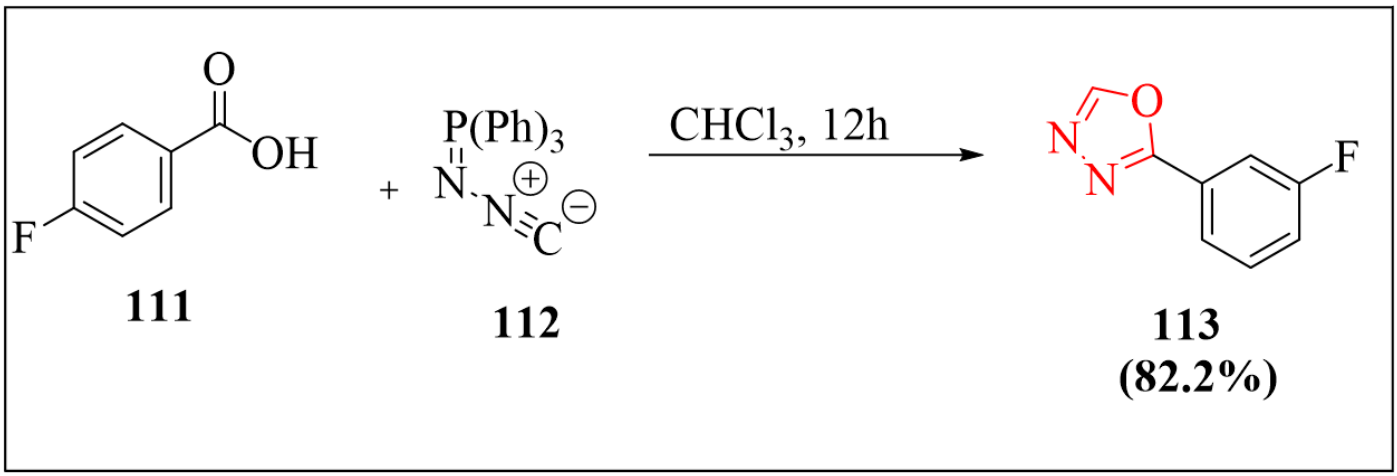


Figure 21: Synthesis of 1,3,4-oxadiazole from the reaction between isocyaniamino and carboxylic acid compound.

'(2RS)-2-(6-chloro-9H-carbazol-2-yl)-propane hydrazide, was produced when reacted with hydrazine hydrate in ethanol during refluxing **(121).**[56,57] The Di halogenated hydrazine **(122)** was prepared by stirring the carprofen hydrazide **(123)** and the acyl chloride was reacted at room temperature using anhydrous pyridine.[58,59] For the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles **(124)** the associated acyl-hydrazide was heated in the water bath with phosphorus chloride oxide. By reacting isoniazid with phosphorus oxychloride, we were also able to obtain compound **(124)** starting from carprofen.[60,61] as depicted in Figure 23.

Remarkable Biological Activities of Oxadiazole

Oxadiazole plays a crucial role because of its biological efficacy and its application in diverse products, including industrial materials, pharmaceutical and medical products, agricultural and so on and

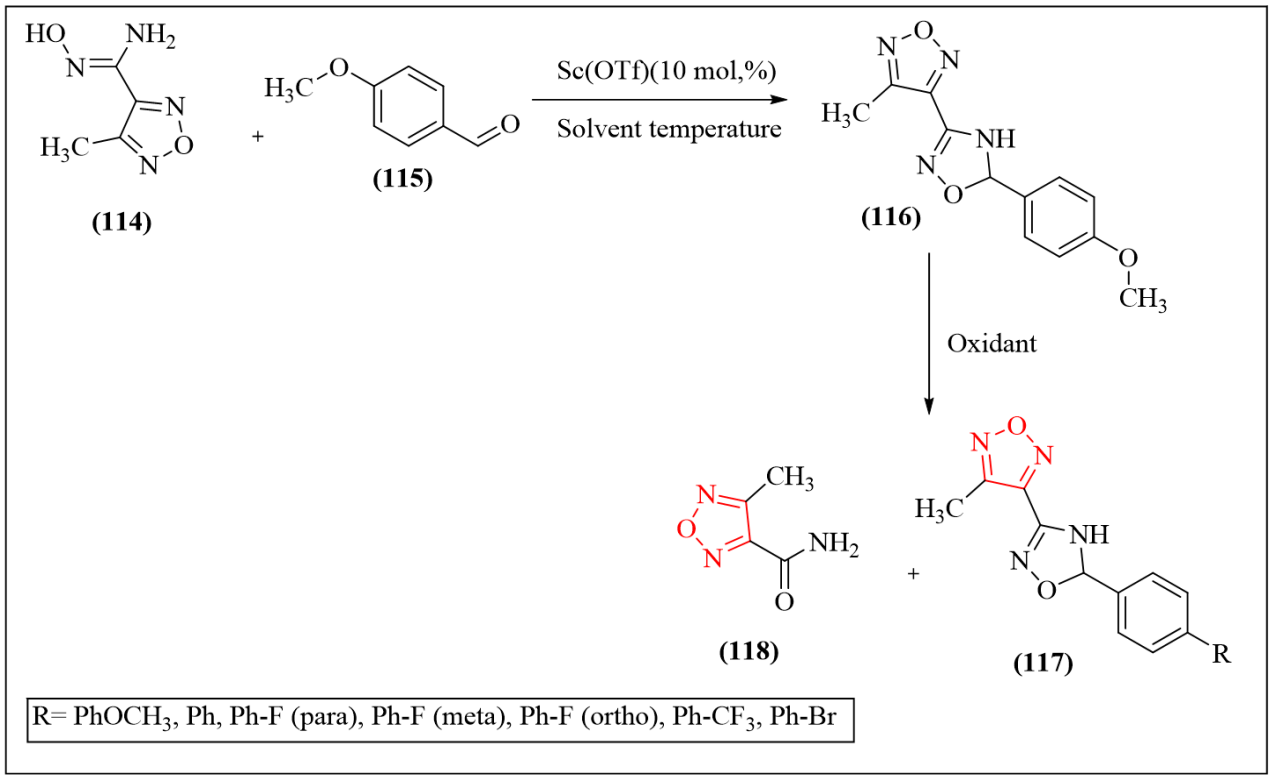


Figure 22: Synthesis route for 1,2,4-oxadiazole.

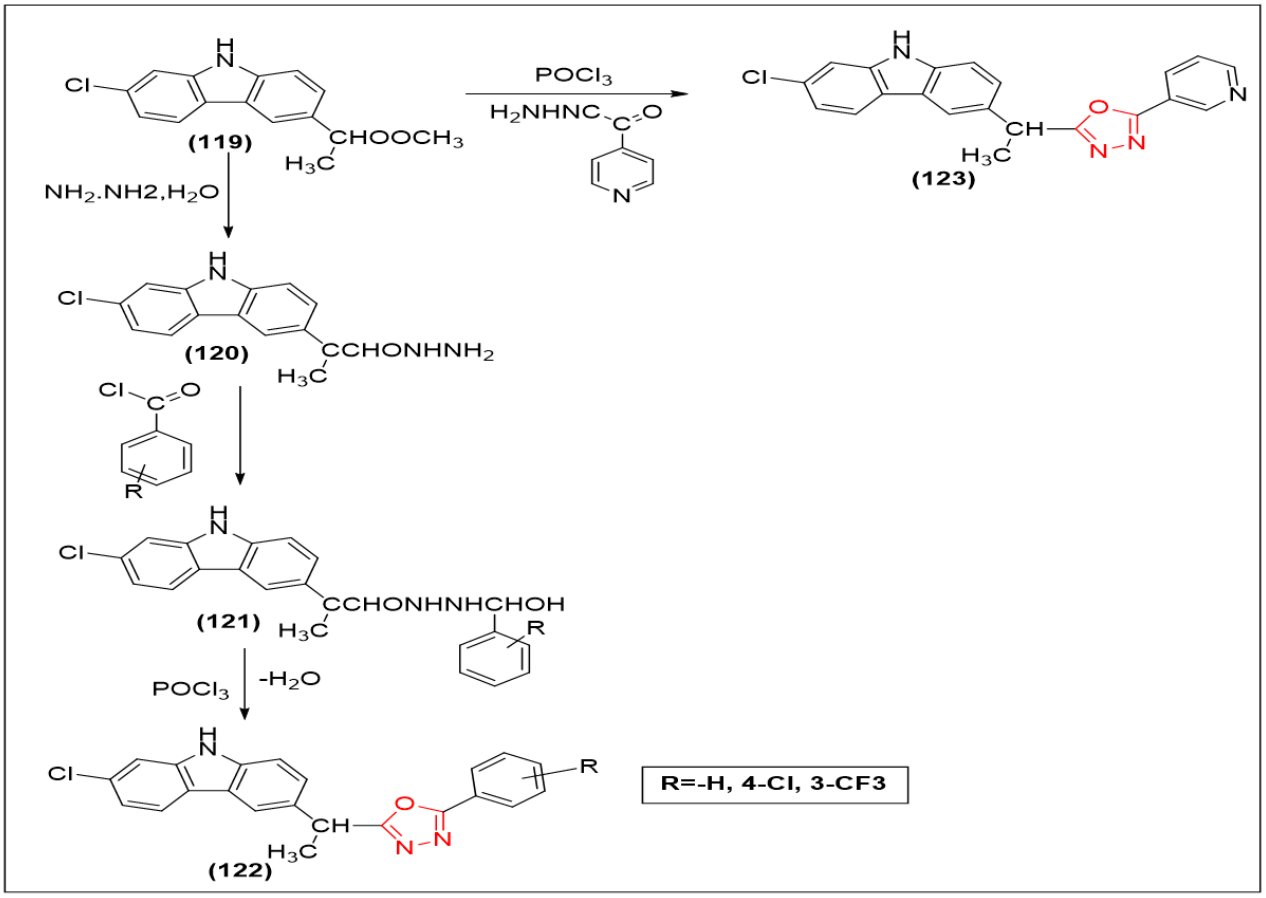


Figure 23: Preparation for the novel 2,5-disubstituted-1,3,4-oxadiazole5-disubstituted-1,3,4-oxadiazole.

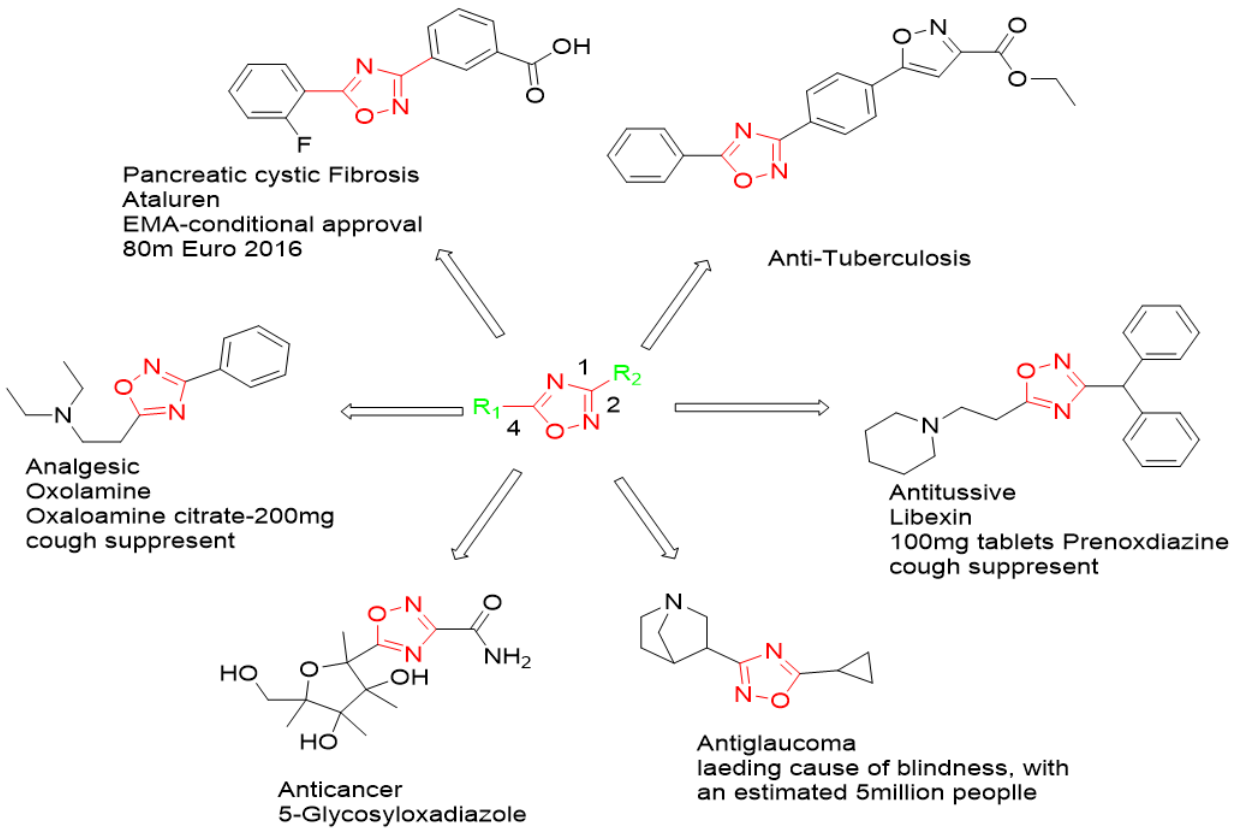
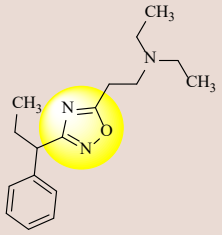
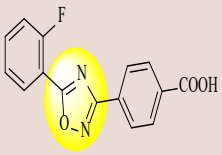
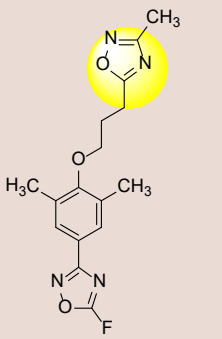
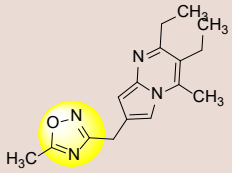
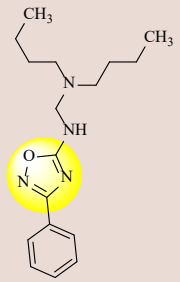
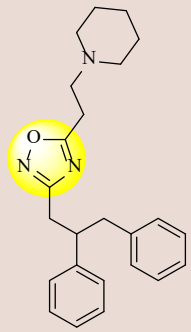
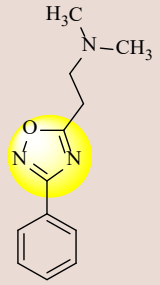


Figure 24: Remarkable biological activities of 1,3,4-Oxadiazole.

Table 1: Pharmacological efficacy of commercially available drugs containing the 1,2,4-oxadiazole nucleus.

Drugs	Structure of drugs	IUPAC Name	Receptor action	Biological activity	References
Proxazole.		N,N-diethyl-2-,[3-(1-phenylpropyl)-1,2,4-oxadiazol-5-yl]ethanamine	H-1antagonist	Gastrointestinal disorders / renal hypertension	64,65
Ataluren.		3-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]benzoic acid	Biliverdin IX-beta reductase	Progressive muscle degeneration	66-69
Pleconaril.		3-[3,5-dimethyl-4-[3-(3-methyl-1,2-oxazol-5-yl) propoxy]phenyl]-5-(trifluo-romethyl)-1,2,4-oxadiazole,	Capsid inhibitor	Anti-viral	70-75

Drugs	Structure of drugs	IUPAC Name	Receptor action	Biological activity	References
Fasiplon.		3-(6-ethyl-7-methoxy-5-methylimidazo[1,2-a]pyrimidin-2-yl)-5-methyl-1,2,4-oxadiazole.	GABA receptor positive allosteric modulators	Anticarcinogenic	76-78
Butalamine.		N',N'-dibutyl-N-(3-phenyl-1,2,4-oxadiazol-5-yl) ethane-1,2-diamine,	Alpha-2 adrengeric Receptor`	Vasodilatory agents for peripheral circulation	79
Prenoxdiazine.		3-(2,2-diphenylethyl)-5-(2-piperidin-1-ylethyl)-1,2,4-oxadiazole.	Desensitizing the pulmonary stretch receptors	Respiratory sedatives	80
Oxolamine		N,N-diethyl-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethanamine.	Suppress the lung and bronchial receptors	Antitussive	81

the biological activity of oxadiazole derivative has shown in Figure 24.[62,63] products and many more. There are several derivatives of oxadiazole with varying substituents and these derivatives can exhibit a huge range of biological activities. Here are various biological activities associated with oxadiazole compounds like antimicrobial, anti-inflammatory, anti-cancer, antioxidant, antiviral, anticonvulsant and neuroprotective activity as shown in Figure 2. It's important to note that the specific biological activity of an oxadiazole derivative depends on its chemical structure, including the nature and position of substituents. Applications for the derivatives of oxadiazoles in medicinal and synthetic chemistry are numerous. 1,2,4-oxadiazole or 1,3,4-oxadiazole is a considerable class of chemicals for the creation of new pharmaceuticals. The core structure of 1,2,4-oxadiazole is found in numerous drugs available in the market, as illustrated in Table 1.[62] According to reports, 1,3,4 oxadiazole's aryl and alkyl halide analogues have superior biological activity when compared to derivatives of unsubstituted oxadiazole. The center of as Table 2 illustrates, oxadiazole is an ingredient in numerous marketed medications. The nitrogen-atom-attached pyridine ring of,1,3,4-Oxadiazole serves as an efficient binding site for a variety of receptors and enzymes trigger a wide range of pharmacological effects.

Due to their diverse applications, the study of 1,3,4-oxadiazole and its derivatives has substantially increased in the last few years.[98] The PubChem database contains 1,198 literature (1,163 articles and 35 reviews) reports and 1,018 patents on 1,3,4-oxadiazole from 2014 to 2023. 1,3,4-oxadiazole and their derivatives can be prepared by several synthesis protocols, by obeying the principle of green chemistry.[99,100] All the recently granted Patents on 1,3,4-oxadiazole and its derivatives given in Table 3.

Table 2: Pharmacological efficacy of commercially available drugs containing the 1,3,4-oxadiazole nucleus.

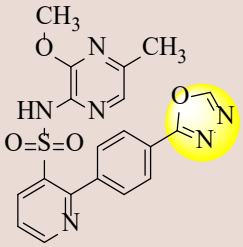
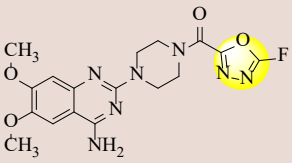
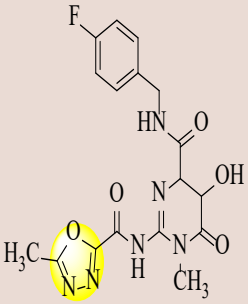
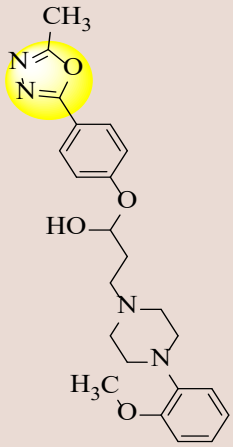
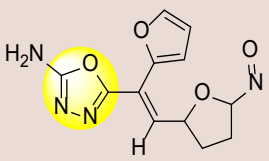
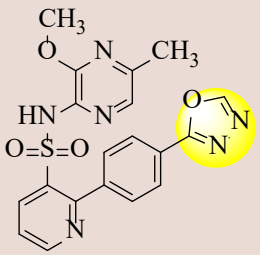
Drugs	Structure of drugs	IUPAC Name	Receptor action	Pharmacological uses	References
Zibotentan.		N-(3-methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl) phenyl]pyridine-3-sulfonamide.	ETB receptor/	Anticarcinogenic activity	82,83
Tiodazosin.		[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-(5-methylsulfanyl-1,3,4-oxadiazol-2-yl)methAnone	Alpha blocker	Antihypertensive`	84,85
Raltegravir		N-[2-[4-[(4-fluorophenyl)methylcarbamoyl]-5-hydroxy-1-methyl-6-oxopyrimidin-2-yl]propan-2-yl]-5-methyl-1,3,4-oxadiazole-2-carboxamide	HIV-1 RNAs and human polymerase	AIDS therapy	86-88
Nesapidil.		1-[4-(2-methoxyphenyl) pi-perazin-1-yl]-3-[3-(5-methyl-1,3,4-oxadiazol-2-yl) phenoxy]propan-2-ol	ETA receptor antagonist	Calcium entry blockers with vasodilatory effects	89
Furamizole		5-[(E)-1-(furan-2-yl)-2-(5-nitrofuran-2-yl)ethenyl]-1,3,4-oxadiazol-2-amine	ETA receptor antagonist	Antimicrobial	90-93
Dapagliflozin		N-(3-methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl) phenyl]pyridine-3-sulfonamide	Sodium-glucose co-transporter 2 (SGLT2) inhibitors Top of Form Bottom of Form	Endothelin related diseases	94-97

Table 3: Recently granted Patents on 1,3,4-oxadiazole and its derivatives.

Sl. No.	Patent number	Patent date	Inventors	Description
1.	US-11542254-B2.[101]	03 January 2023	Ji Haitao, Zhang Min	Synthesis and application of 4-substituted benzoylpiperazine-1-substituted carbonyls and its derivatives and protein-protein interaction dysfunction using the compounds and compositions.
2.	CA-2915486-C.[102]	03 January 2023	Cruce Christopher J, Giardello Michael A, Conley Brian L, Stephen Anthony R.	Manufacture and compositions of thermal insulation materials and use of Ring Opening Metathesis Polymerization polymers (ROMP polymers).
3.	US-11534442-B2.[103]	27 December 2022	Reaume Andrew G, Cong Weina, Greenway Frank, Coulter Ann.	It provides compositions and comprising a lyn kinase activator and TRPM8 agonist and methods of reducing blood glucose levels, weight gain and so on.
4.	US-11535592-B2.[104]	27 December 2022	Garneau-Tsodikova Sylvie, Gonzalez Octavio Alberto.	Method and composition of antimicrobial compounds and methods for the control of Porphyromonas gingivalis.
5.	US-11535608-B2 El.[105]	27 December 2022	El-Deiry Wafik S, Tian Xiaobing.	Composition, reactivation Prodigiosin analogs follows p53 pathway and mutation in breast cancer and so on.
6.	US-11530210-B2.[106]	20 December 2022	Hiscox Afton,Stenne Brice, Chrovian Christa, Gelin Christine, Samant Andrew, Letavic Michael A, Dvorak Curt.	Composition and modulation method of substituted pyrazolo-pyridines as GluN2B receptor ligands and treatment of disease states, disorders.
7.	CA-2915817-C.[107]	13 December 2022	Vankayalapati Hariprasad, Sorna Venkataswamy, Warner Steve L, Bearss David J, Sharma Sunil, Stephens Bret.	Invention the compound substituted (e)-n'-(1-phenylethylidene) benzohydrazide analogs and treatment of a disorder of uncontrolled cellular proliferation in a mammal.
8.	CA-3013000-C.[108]	13 December 2022	Charrier Jean-Damien, Durrant Steven, Kay David, Knegtel Ronald, Maccormick Somhairle, Mortimore Michael, O'donnell Michael, Pinder Joanne, Reaper Philip Michael, Rutherford Alistair, Virani Anisa Nizarali, Young Stephen.	Invention of pyrazine compounds useful as inhibitors of ATR protein kinase and methods of treating of various diseases, the study of intracellular signal transduction pathway.
9.	US-11524010-B2.[109]	13 December 2022	Augelli-Szafran Corinne E, Moukha-Chafiq Omar, Suto Mark J, Shalev Anath, Thielen Lance, Chen Junqin, Jing Gu.	Compositions of substituted quinazoline sulfonamides as Thioredoxin Interacting Protein (TXNIP) inhibitors and that lower hepatic glucose production and methods of identifying, making and using of them.
10.	US-11518824-B2.[110]	06 December 2022	Mihan Shahram, Gregorius Heike, Fraaije Volker, Mulhaupt Rolf, Zhong Fan.	A nano platelet gibbsite treated with compound of formula (ORa)3Si-Rb or of formula Rc-COOH hydrocarbons radical is used as a catalyst support.

CONCLUSION

In conclusion, the exploration of various synthetic approaches to oxadiazole and its derivatives has significantly enriched our understanding of the chemical landscape, offering a diverse array of methods for their preparation. This versatility in synthetic strategies not only enhances the accessibility of oxadiazole derivatives but also allows for the fine-tuning of their structures, enabling the creation of compounds with tailored properties. The remarkable biological activities exhibited by oxadiazole derivatives across a spectrum of applications, including antimicrobial, anticancer, anti-inflammatory, antiviral activities, antipyretic activities, anticonvulsant activity and analgesic activity underscore their potential as valuable candidates in medicinal chemistry. These findings highlight the importance of continued research into the structure-activity relationships of oxadiazole derivatives, paving the way for the development of novel and more potent therapeutic agents. As we delve deeper into the biological activities of oxadiazole derivatives, it becomes evident that these compounds hold great promise in addressing various health challenges. The synergy between synthetic methodologies and biological investigations provides a solid foundation for future advancements in drug discovery and development. This review also includes the potential of both 1,2,4-oxadiazole and 1,3,4-oxadiazole nuclei as promising frameworks for drug development has been underscored in this study drug like pleconaril used as an anti-viral commonly used as 1,2,4-oxadiazole derivative similarly, drug-like proxazole, ataluren, etc. Nesapidil as a calcium entry blocker with vasodilatory effects used as a potent 1,3,4-oxadiazole derivative, other examples are zibotentan, raltegravir, etc. The article highlights that compounds based on these structures demonstrate significant efficacy across a spectrum of biological activities, ranging from the treatment of inflammation, cancer, diabetes, hypertension and insomnia, to Alzheimer's disease, ulcer and CNS stimulants. Also demonstrate the various synthetic approaches for preparation of 1,2,4-oxadiazole and 1,3,4-oxadiazole derivatives. The research presented herein elucidates novel synthetic pathways for both 1,2,4-oxadiazole and 1,3,4-oxadiazole derivatives, unveiling their biological activities, which hold promise for the creation of innovative drugs. The Reacher working ongoing efforts to uncover new synthetic routes and elucidate the intricacies of their biological mechanisms position oxadiazole derivatives as key players in the quest for innovative pharmaceuticals. In summary, the comprehensive insights gained from the study of synthetic approaches to oxadiazole and its derivatives, coupled with their remarkable biological activities, not only contribute to the ever-expanding chemical knowledge but also hold significant implications for the development of therapeutically relevant compounds with diverse application.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NMR: Nuclear Magnetic Resonance; **IR:** Infrared; **DMF:** Di Methyl Formamide; **TEA:** Triethanolamine; **MWI:** Microwave Induction; **ETB:** Receptor: Endothelin Receptor Type B; **AIDS:** Acquired immunodeficiency syndrome.

SUMMARY

Oxadiazole is a molecular organic compound with a heterocyclic ring composed of carbon, oxygen and nitrogen atoms. Regardless of their better stability in biological contexts, oxadiazole rings suggest substantial biological activity, addressing issues such as infectious diseases and chronic disorders in medicinal chemistry. The key objective of this review is to explore several synthetic approaches associated with oxadiazole and its derivatives and also how they function in the body. The different reactions position oxadiazole as a valuable building block in chemical synthesis, with derivatives showing appealing medicinal properties. The many synthetic procedures, such as Suzuki-Miyaura, Stille coupling 3+2] cycloaddition process and many other methods employed for the synthesis of oxadiazole through diverse schemes, have been thoroughly examined. This review also concisely linked the pharmacological activities of new oxadiazole and its derivatives, including prenoxdiazine, dapagliflozin, nesapidil, pleconaril and so on. This study underlines the significance it is to carrying out additional research on the structure-activity interactions of oxadiazole derivatives in order to create new and improved medicinal medicines.

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contain. a 4-memb. Heterocycl. Ring. V3 Five-memb. Rings with One Heteroat. together with their Benzo and other Carbocycl.-fused Deriv. V4 Five-member. Rings with Two Heteroat., each with their Fused Carbocycl. Deriv. 2008 (pp. 1-13718). Elsevier. https://doi.org/10.1016/C2009-1-28335-3.

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