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RELEVANCE AND PROSPECTS OF SEARCHING FOR DRUGS WITH ANXIOLYTIC ACTIVITY BASED ON SYNTHETIC ACTIVE SUBSTANCES CONTAINING 1,3,4-OXADIAZOLE RING

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ABSTRACT

Derivatives of oxadiazole or furadiazole rings are known to be a significant family of heterocyclic compounds. Oxadiazole is a five-membered heterocyclic ring with two carbons, one oxygen atom, two nitrogen atoms, and two double bonds. They are made from furan by substituting two nitrogen (-N =) atoms for two methylene groups (= CH). By substituting these groups in the furan ring, the aromaticity was decreased to the point where conjugated diene character is evident. There were four distinct oxadiazole isomers that were known to exist: 1,2,4-oxadiazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole. 1,3,4-thiadiazole's chemistry is one of the most intriguing scaffolds for creating novel therapeutic compounds because of its many pharmacological properties. Numerous changes have been made to the thiadiazole ring, which has demonstrated that it is more powerful and highly useful for a variety of biological functions with a less hazardous structure. Numerous medications on the market have a 1,3,4-thiadiazole ring in their composition. We attempted to gather the recently synthesized 1,3,4-thiadiazole derivatives with significant pharmacological value since 2014 in this review study. New several phenyl-1,3,4-oxadiazole compounds were previously created as BZD receptor agonists. The pharmacological effects of new

substances were assessed in this investigation. The sedative-hypnotic, anxiolytic, and amnesic effects of the compounds were assessed using the pentobarbital-induced loss of righting reflex, increased plus maze, open-field locomotor activity, and passive avoidance test, respectively. This, in turn, is a prelude to promising results, such as the search, research and implementation of substances with low toxic anxiolytic activity with high activity based on substances with this base.

Introduction. The number of health issues was growing daily and had reached the highest level of clinical concern. Medicinal chemists have recently been searching for novel medications that can be utilized to treat these severe clinical issues in a safe manner. Many heterocyclic compounds are being used in clinical settings to treat infectious diseases. The most prevalent heterocyclic compounds have fused rings with five or six members and contain heteroatoms such as nitrogen, oxygen, and sulfur. Phosphorus, silicon, and boron atoms can occasionally be employed as heteroatoms. Researchers studying medical and pharmaceutical chemistry are interested in heterocyclic molecules with nitrogen atoms, such as oxadiazole moieties. Because of its many biological activities, the 1,3,4-oxadiazole heterocyclic ring is one of the most significant heterocyclic moieties [1,2,3,]. These are furan derivatives where two nitrogen atoms have been added in place of two methylene groups. The oxadiazole ring that results from replacing these two methylene groups with two nitrogen atoms has conjugated diene character and is less aromatic. Because of the inductive effect, another heteroatom serves as a weak base for the oxadiazole. In a nucleophilic substitution reaction, nucleophiles took the place of hydrogen atoms. Numerous therapeutic activities, including antibacterial, anticonvulsant, antitumor, hypoglycemic, antipyretic, anti-tubercular, antiviral, immunosuppressive, spasmolytic, antioxidant, anti-inflammatory, insecticidal, central nervous system stimulant, ant amoebic, antiemetic, antidepressant, anthelmintic, vasodilator, antimycotic, antiallergic, anti-Alzheimer, ulcerogenic, and antihypertensive properties are among the various isomers of 1,3,4-oxadiazole, according to published research [4,5,6]. We have examined many oxadiazole derivatives with urea, amide, and sulphonamide groups in order to look into their antioxidant, antiviral, anticancer, antibacterial, and antitubercular properties. Their strong pharmacological effects may be due to the toxophoric -N = C-O connection in the 1,3,4-oxadiazole ring. Substituted 1,3,4-oxadiazoles are most interesting from a pharmacological standpoint. The derivatives of 2,5-disubstituted-1,3,4-oxadiazoles are stable; in particular, 2,5-diaryl-1,3,4-oxadiazoles are more stable than their 2,5-dialkyl counterparts. One of the biggest issues facing the world today is drug resistance, and one of the most intriguing research topics nowadays is the need to create new molecules to address this issue [7,8,9]. Numerous biological activities, including antimicrobial, anticonvulsant, anticancer, antiviral, anti-tuberculosis, anti-inflammatory and analgesic, diuretic, anti-diabetic, anti-depressant, anti-ulcer, anti-malarial, anti-leishmanicidal, anti-influenza, anti-hypolipidemic, anti-hyperlipidemia, and antihypertensive properties, are exhibited by the well-known and significant heterocyclic nucleus of thiadiazole. A hydrogen binding domain, two nitrogen atoms, and a sulfur atom make up the five-membered heterocyclic ring known as thiadiazole. Emil Fischer made the discovery in 1882, and two chemists, Kuh and Freund, detailed its characteristics. It

comes in four isomeric forms: 1,2,4-thiadiazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, and 1,2,5-thiadiazole. It is sometimes referred to as 3,4-dioxythiophene, 4-azathiazole [10,11,12]. This is due in part to the fact that they can be utilized as bio-isosteric substitutes in medication design and, in contrast to other isomers, are resistant to heat and chemicals. Since we have made this a primary research focus, we are examining the structural alterations of several oxadiazole and thiadiazole derivatives, with a focus on the anti-tubercular and anticancer pharmacological actions documented throughout the past five years. In this review paper, the latest developments in the significant biological isomers 1,3,4-thiadiazol will be thoroughly examined and analyzed. Future research will have a fantastic place to start with this [13,14,15].

The goal of this review article is to conduct a comprehensive investigation and analysis of the latest developments in the significant biological isomers 1,3,4-thiadiazol. This will be an excellent starting point for further investigation.

Heterocyclic compounds are important in medical chemistry (figure 1). Heterocyclic compounds continue to produce new therapeutic medicines because of their wide range of pharmacological actions. The ability of the heterocycles to bind with different enzymes, either to the active sites or to enzyme pocket structures, through a variety of intramolecular interactions, including hydrogen bonding, van der Waals and hydrophobic forces, and metallic coordination bonds, accounts for their biological activity and makes them a crucial scaffold in medicinal chemistry. The family of heterocycles, which are essential to living cells, includes a vast array of naturally occurring compounds, including purine bases, pyrimidines, hemoglobin, chlorophyll, and enzyme co-factors. They are practically necessary at every stage of several biochemical and life-sustaining processes. In the pharmaceutical and agrochemical industries, heterocyclic compounds—particularly those with nitrogen, sulfur, and oxygen heteroatoms—are the most significant class of molecules. In fact, heterocycles make up around 60% of the pharmacological ingredients. Many biologically active compounds contain five-membered heterocycles that contain nitrogen, oxygen, or sulfur[1,2,3,4]. Examples of these heterocycles include oxazolidine, isoxazolidine, oxazole, isoxazole, thiazolidine, isothiazolidine, thiazole, isothiazole, oxadiazole, and thiadiazole. These heterocycles are significant structural motifs. The pharmaceutical industry is very interested in these heterocycles because they represent the fundamental building blocks of many medications. These two isomers have the potential to play a crucial role in the pharmacological industry due to their excellent chemical and thermal strength. To make our literature evaluation as thorough as possible, we made an effort to cover a lot of relevant research articles. To keep it current, we added the most recent articles. This review paper aims to perform a thorough investigation and analysis and offer a thorough report in the form of a technical discussion and even data in the form of figures. All things considered, this will be a fantastic place to start for further study in this area [5,7,11].

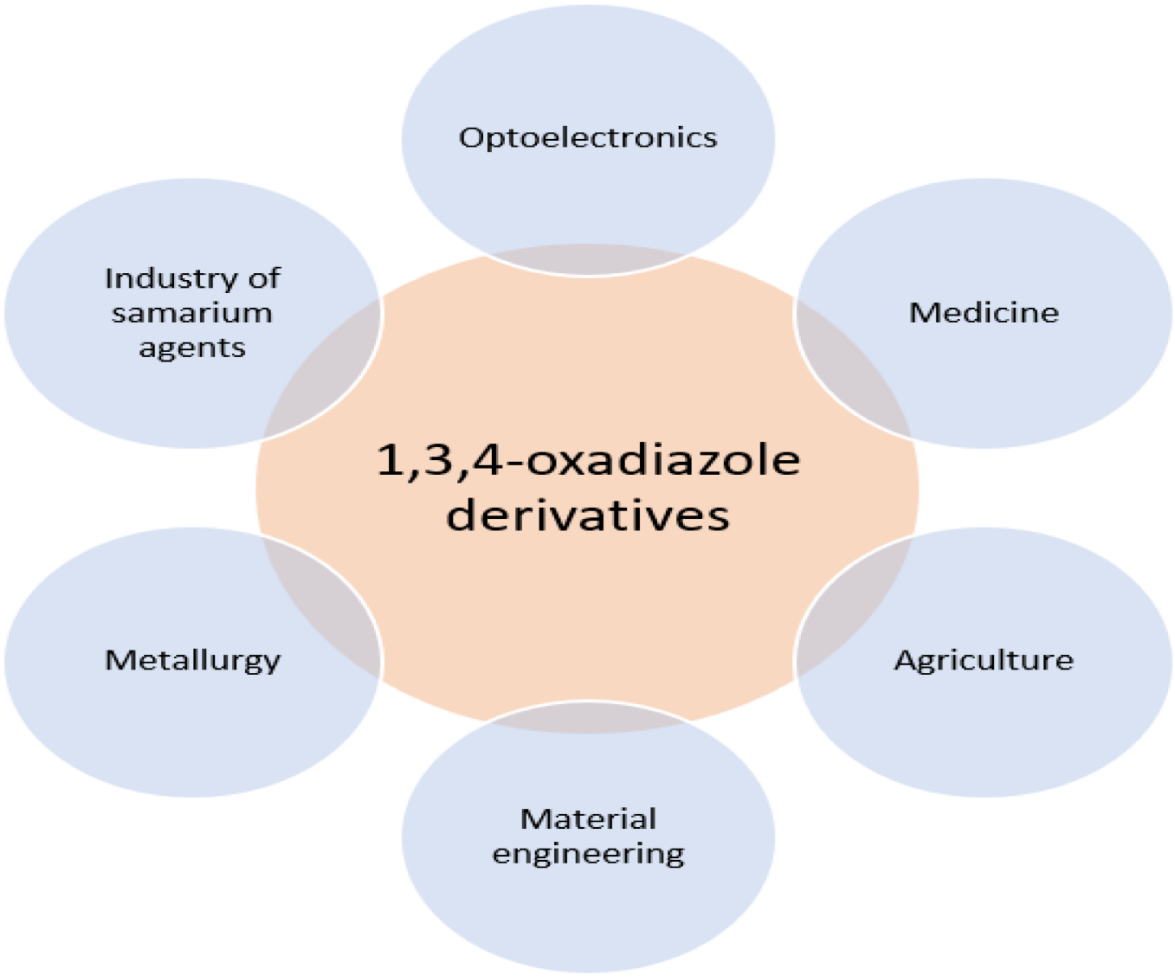

Figure 1. Potential uses for compounds of 1,3,4-oxadiazole [17].

For a long time, the synthesis and biological activity of new oxadiazole derivatives have been studied in the intriguing field of heterocyclic molecules. Because of their varied biological characteristics, heterocyclic compounds have been the subject of extensive study and investigation. Among these substances One innovative molecule that draws medicinal chemists looking for a new therapeutic molecule is 1,3,4-Oxadiazole, which has a flexible heterocyclic nucleus. Numerous biological activities were demonstrated by 1,3,4-oxadizole, including antimicrobial, anti-tubercular, anticonvulsant, antidiabetic, anti-allergic, enzyme inhibitory, anti-HIV, antipyretic, immunosuppressive, spasmolytic, antioxidant, anti-Alzheimer's, cardiovascular, anti-inflammatory, anti-tumor, insecticidal, CGRP receptor antagonist, and anti-anthelmintic properties. The current study reviews the results of several oxadiazole compounds and their substitutions with a range of biological functions [1,7,18,19]. ***Activity of Anticonvulsants.*** As anticonvulsant drugs, a number of novel 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles were created and produced. The addition of an amino group at position 2 of the 1,3,4-oxadiazole ring and a fluoro substituent at the para position of the benzylthio moiety provided the best anticonvulsant action, according to convulsion testing. Phenytoin-thiosemicarbazide, 1,3,4-oxadiazole, 1,3,4-thiadiazole, or 1,2,4-triazole hybrids were created and their anticonvulsant properties evaluated. Standard maximum electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screenings were used to screen mice for anticonvulsants in a preliminary manner. The rotarod test was used to determine the neurotoxicity. At a dose of 100 mg/kg, compound

4 demonstrated the best protection (80%) in the scPTZ test [11-15]. ***Activities to Prevent Alzheimer's.*** [5-[1-(4-Methoxyphenyl)-1H-benzimidazol-6-yl] Derivatives of 1,3,4-oxadiazolyl sulfanyl)methyl benzoonitrile have been produced. In vitro, compound 20x exhibited strong and highly specific GSK-3β inhibitory action. By directly heterocyclizing substituted benzoylisocyanate with different aroylhydrazones, a new set of 1,3,4-oxadiazole-3(2H)-carboxamide derivatives has been created as novel monoamine oxidase inhibitors (MAOIs). According to the preliminary findings, at a concentration of 10-5-10-3 M, the majority of the compounds 3a and 3b exhibit mild inhibitory actions toward MAO [16,17,18]. ***Synthesis of Antioxidant Activity*** Derivatives of 2-N-phenyl piperazino methylene-4- (4'-amino, 2'-nitro phenyl)-5-mercapto-1,3,4-oxadiazole. The antioxidant activity of each molecule was examined. The reducing power assay and hydrogen peroxide scavenging activity at 700 nm and 250 nm, respectively, were used to measure the antioxidant activity of methanol solutions of produced compounds. Through a multi-step reaction process, a number of 3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl azo dyes were created. The produced compounds' antibacterial and in vitro antioxidant qualities were examined [10,11,12].

1,3,4-Oxadiazole Derivatives' Antibacterial Activity. Scientists are now using well-known quinolone antibacterial medications as the foundation for structural modifications. Nalidixic acid was a pharmacophore moiety for structural alteration according to a number of writers. A thiosemicarbazide/acidcarbazide chain or thioxo-1,2,4-triazole/1,3,4-oxadiazole connected to quinoxaline was used in place of the carboxylic group. Compared to the reference medications (ciprofloxacin and amoxicillin), the compound containing 1,3,4-oxadiazole had greater or equivalent effectiveness against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The novel derivatives also exhibited antitubercular properties. Additionally, synthetic nalidixic acid derivatives substitute the isosteric 1,3,4-oxadiazole ring for the carboxylic group. Even more potent than the standard nalidixic acid was the activity of the most active derivatives 2a–b and 3a–b against certain bacterial strains, including Gram-positive strains *S. aureus* and *Bacillus cereus* and Gram-negative strains *Escherichia coli, Klebsiella pneumoniae* and *P. aeruginosa* [14,15,16,17]. A group of scientists under the direction of Guo created a novel class of norfloxacin derivatives with a 1,3,4-oxadiazole ring in 2019. It is evident from examining the data above that there are two ways in which quinolone antibacterial medication adjustments are carried out. As a bioisosteric structure, the 1,3,4-oxadiazole ring takes the role of the carboxylic moiety in nalidixic acid. For fluoroquinolones (ciprofloxacin/norfloxacin), a methylene linker comes before the 1,3,4-oxadiazole molecule is added at the piperazine substituent. The activity of the derivatives is frequently increased by halogen or methyl substituents on the aromatic ring [1,4,7].

In therapeutic practice, benzodiazepines (BZDs) are frequently used as muscle relaxants, hypnotics, anxiolytics, and anticonvulsants. They do, however, have certain negative effects, such as memory issues. We are searching for ligands with less side effects as we continue our study on novel benzodiazepine ligands. Four new 2-phenoxy phenyl-1,3,4-oxadiazole compounds were previously created as BZD receptor agonists. The pharmacological effects of new substances were assessed in this investigation. The sedative-hypnotic, anxiolytic, and amnesic effects of the compounds were assessed using the pentobarbital-induced loss of righting reflex, increased plus maze, open-field locomotor activity, and passive avoidance test, respectively. The findings showed that the new compounds containing NH2, SH, and SCH3 substituents at the oxadiazole ring's 2-

position considerably lengthen the righting reflex time [7-13]. None of the derivatives enhanced open arm time or open arm entry in the elevated plus maze test, suggesting that they had no anxiolytic effects. Furthermore, the mice's step-down latencies were unaffected by the new chemicals. The fact that flumazenil dramatically decreased these drugs' hypnotic action demonstrated that BZD receptors mediate this effect [17,18,19]. This in turn serves as a precursor to encouraging outcomes, such as the identification, investigation, and use of compounds with high activity and low harmful anxiolytic action based on molecules with this base.

Discussion. Health issues were growing daily and eventually reached the highest level of clinical concern. In order to treat these severe clinical issues, medicinal chemists have recently started searching for novel medications that may be administered safely. To treat infectious diseases, many heterocyclic chemicals are used in clinical settings. Heterocyclic compounds of pharmacological significance are essential in the fight against diseases that impact plants, animals, and humans. One of the most crucial elements in the advancement of agriculture, medicine, and other related fields is discovering novel compounds with possible biological effects that have not yet been documented in the literature. Compounds with heterocyclic moiety, such 1,3,4-oxadiazoles, have favorable biological activity. Heterocyclic compounds with five or six fused rings and heteroatoms of nitrogen, oxygen, and sulfur are the most prevalent. Heteroatoms such as silicon, phosphorus, and boron can occasionally be employed. In medical and pharmaceutical chemistry, chemists are interested in heterocyclic molecules with nitrogen atoms, such as oxadiazole moieties for example[1,9,10,17]. Of them, 1,3,4-oxadiazoles and 1,2,4-oxadiazoles are more well-known and have been the subject of more investigation because of their diverse chemical and biological characteristics. 1,3,4-oxadiazoles are now crucial synthons in the creation of novel medications. According to published research, the 1,3,4-oxadiazole derivatives exhibit a range of biological activities, including antibacterial, anti-mycobacterial, anticancer, antiviral, and antioxidant properties. The 1,3,4-oxadiazole ring is present in a variety of commercially marketed medications, including the antiviral medication Raltegravir, the nitrofuran derivative Furamizole, which has potent antibacterial properties, and the anti-arrhythmic medication Nesapidil. The pharmacological properties and different synthesis pathways for 2, 5-disubstituted 1,3,4-oxadiazole and its derivatives were compiled in this review. Because 1,3,4-oxadiazoles has so many pharmacological actions, its chemistry makes it one of the most intriguing scaffolds for creating novel therapeutic compounds [3,4,11,12]. The oxadiazoles ring has undergone a number of changes that have demonstrated its increased potency and effectiveness for a variety of biological functions, along with its less hazardous scaffold. The structure of a number of commercially available medications includes a 1,3,4- oxadiazoles ring. In this review study, we have tried to assemble the recently synthesized 1,3,4- oxadiazoles derivatives bearing substantial pharmacological relevance since 2014. The necessity to synthesize novel chemicals has emerged as one of the most intriguing research areas in order to address drug resistance, one of the key issues facing the world today. One of the most well-known and significant heterocyclic nuclei, thiadiazole has a wide range of biological activities, including antimicrobial, anticonvulsant, anticancer, antiviral, anti-tuberculosis, anti-inflammatory and analgesic, diuretic, anti-diabetic, anti-depressant, anti-ulcer, anti-malarial, anti-leishmanicidal, anti-influenza, anti-hypolipidemic, anti-hyperlipidemia, and antihypertensive (Figure 2).

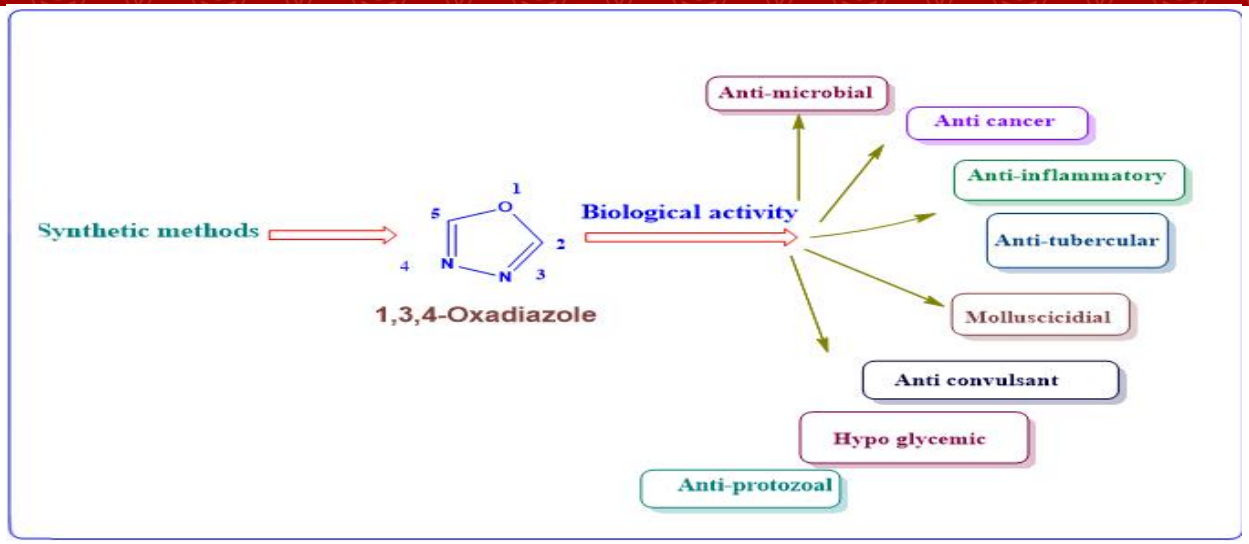

Figure 2. A Brief Overview of Methods for the Synthesis of 1,3,4-Oxadiazole Derivatives and Their Biological Activities [18].

Oxadiazoles is a heterocyclic ring with five members that includes two nitrogen atoms, a sulfur atom, and a hydrogen binding domain. Two chemists, Kuh and Freund, detailed its features after Emil Fischer made the discovery in 1882. It is commonly referred to as 3,4-dioxythiophene, 4-azathiazole, and comes in four isomeric forms: 1,2,4-oxadiazoles, 1,2,3- oxadiazoles, 1,3,4- oxadiazoles, and 1,2,5- oxadiazoles [16,17,18,19].

Conclusions. We have compiled the many pharmacological actions of compounds containing 1,3,4-oxadiazole in this review article. According to this study, molecules containing 1,3,4-oxadiazole can be produced using a variety of synthetic pathways, and the resulting derivatives have a broad range of biological activities, including antioxidant, anticancer, antitubercular, antibacterial, and antiviral properties. The usefulness of 1,3,4-oxadiazole as templates for additional modification or derivatization to create more potent physiologically active compounds was established by this review paper.

1,3,4-oxadiazole is a synthetically flexible substrate that can be employed as a raw material for medication synthesis as well as for the synthesis of a wide range of heterocyclic compounds. 1,3,4-oxadiazole is a flexible lead molecule for creating possible bioactive compounds, according to the literature review, and its derivatives have been shown to have a wide range of pharmacological actions. The 1,3,4-oxadiazole ring's therapeutic qualities are highlighted in this review, and it is considered to be promising due to its relationship to a wide spectrum of pharmacological actions. As a result, this discovery is important for future studies on the bioactive oxadiazole ring.

These findings demonstrated that the two most important pharmacophores for the pharmacological actions are 1,3,4-oxadiazole and substituted electrophilic.

Pharmacological significance may be associated with molecules possessing 1,3,4-oxadiazole ring configurations. It has been suggested that certain organic compounds have therapeutic value. This mini-review provides a brief summary of various approaches for synthesizing physiologically significant 1,3,4-oxadiazole ring compounds. A brief review is also given of the title compounds' antimicrobial, anticancer, anti-inflammatory, anti-tubercular, molluscicidal, hypoglycemic, anticonvulsant, and antiprotozoal properties.

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