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Chompound contaning oxadiazole derivatives and their potential therapeutic uses.

[1] Neha Sahu*

1Research Scholar, Department of Chemistry School of Basic & Applied Sciences, Lingaya's Vidyapeeth, Faridabad, Haryana.

Faridabad, Haryana

[2] Rizwan Arif

2Assistant Professor, Department of Chemistry School of Basic & Applied Sciences, Lingaya's Vidyapeeth, Faridabad, Haryana

Corresponding author: Neha Sahu

E- mail: nehasahu082018@gmail.com

REVIEW ARTICLE

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ABSTRACT

Derivatives of oxadiazole or furadi azole rings constitute a significant class of heterocyclic substances. Oxadiazole is a heterocyclic, five-membered ring with two carbons, one oxygen atom, two nitrogen atoms, and two double bonds. They are produced by substituting two nitrogen (-N =) atoms for two methylene groups (= CH) in furan. The furan ring's aromaticity was significantly decreased by substituting these groups, resulting in a conjugated diene character. 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. Because of their extensive spectrum of chemical and biological

properties, 1,3,4-oxadiazoles and 1,2,4-oxadiazoles are among the ones that researchers are more familiar with and have explored in greater detail. 1,3,4-oxadiazoles are now widely used as synthons in the creation of novel medications. According to published research, the 1,3,4-oxadiazole nucleus derivatives exhibit a range of biological actions, including antioxidant, antiviral, anticancer, antibacterial, and antimycobacterial properties. Commercially accessible medications with a 1,3,4-oxadiazole ring include Furamizole, a nitrofuran derivative with potent antibacterial action, Raltegravir, an antiviral medication, and Nesapidil, a medication used in anti-arrhythmic therapy. The pharmacological activity and different types of synthesis methods for 2, 5-disubstituted 1,3,4-oxadiazole and its related compounds were summarized in this research. The severity and reality of pathogenic bacterial antibiotic resistance necessitate the quick development of novel antimicrobial medications. The main quality control technique in bacteria for recovering ribosomes stopped during translation is trans-translation. Trans-translation is a promising target for new antibiotics or for enhancing the actions of protein synthesis inhibitors that are currently in use because it is missing in eukaryotes but required to prevent ribosomal stalling and is therefore crucial for bacterial survival.

INTRODUCTION

Health issues were becoming more and more serious clinical issues every day. Medicinal chemists have been searching for novel medications that can be used safely to address these grave clinical issues. Many heterocyclic substances are used in clinical practice to treat infectious diseases. Health issues were becoming more and more serious clinical issues every day. Medicinal chemists have been searching for novel medications that can be used safely to address these grave clinical issues. Many heterocyclic substances are used in clinical practice to treat infectious diseases.The most prevalent heterocyclic compounds are those with five or six fused rings and heteroatoms of nitrogen, oxygen, or sulfur. Heteroatoms can occasionally be made of silicon, phosphorus, and boron atoms.Researchers in the domains of medical and pharmaceutical chemistry are interested in heterocyclic molecules with nitrogen atoms, such as oxadiazole moieties [1].

Oxadiazole is the name for a heterocyclic five-member ring that has one oxygen atom, two carbon atoms, two nitrogen atoms, and two double bonds. Other names for this kind of ring system include furadiazole, biozole, oxybiazole, furoximes, and furoxans. Ainsworth produced oxadiazole for the first time in 1965 by thermolyzing hydrazine. It is soluble in water and has the chemical formula C2H2ON2. Its molecular mass is 70.05 g/mol.The predicted resonance energy of oxadiazoles, which are thermally stable molecules, is 167.4 kJ/mol. The substitution at the second position increases the thermal stability of oxadiazoles [2].

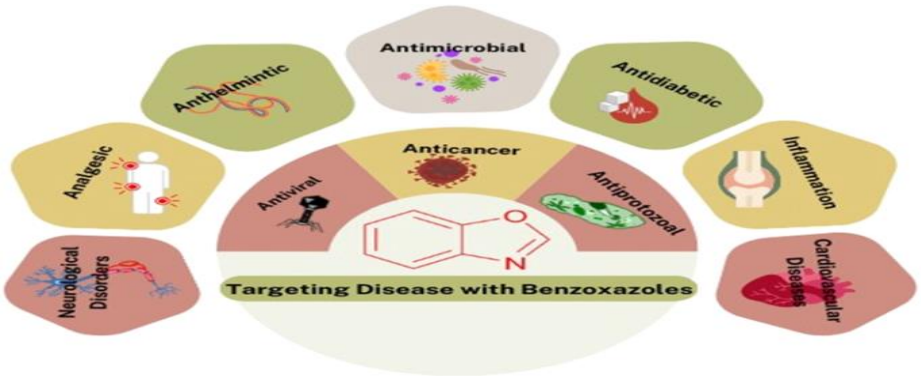

Figure shows: Benzoxazole has so many biological uses, it is a desirable scaffold in medicinal chemistry.

Because of its diverse range of biological activities, the 1,3,4-oxadiazole heterocyclic ring is one of the most significant heterocyclic moieties. These are furan derivatives where two nitrogen atoms have been added in place of two methylene groups. The oxadiazole ring that results from substituting these two methylene groups with two nitrogen atoms has conjugated diene property and loses its aromaticity. The inductive effect causes a second heteroatom to act as a weak base for the oxadiazole. Nucleophiles, which are present in nucleophilic substitution reactions, took the place of hydrogen atoms [3].

Numerous commercially accessible medications with a 1,3,4-oxadiazole ring exist, such as Furamizole, a nitrofuran derivative with potent antibacterial properties. Anti-arrhythmic therapy uses the medications Nesapidil and Raltegravir, which are antiviral drugs. Zibotentan, an FDA-approved anticancer drug, is a 1,3,4-oxadiazole nucleus that contains the most exclusive derivatives on the market. Tiodazosin is a medication used to treat hypertension. The pharmacological activity and different synthesis pathways for 2,5-disubstituted 1,3,4-Oxadiazole and its related compounds throughout the last ten years (2005–2020) were summarized in this review [4].

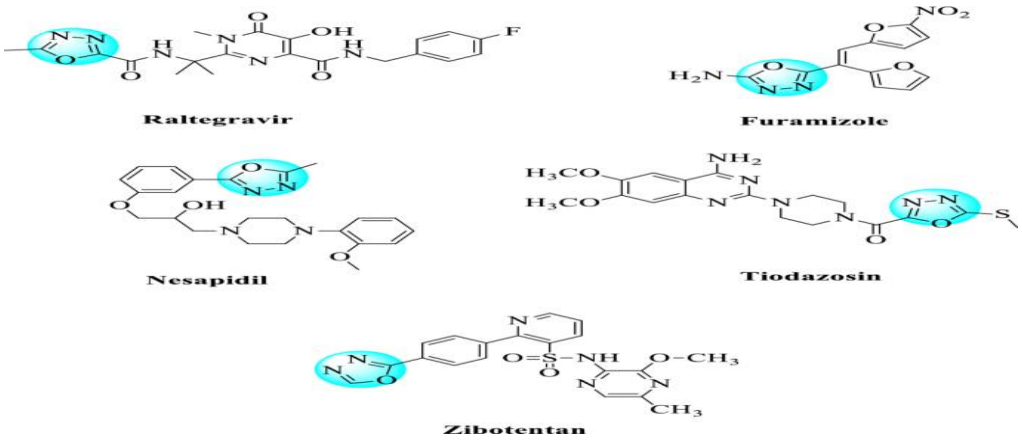

Figure shows: Medications that are sold commercially and have the nucleus of 1,3,4-oxadiazole.

Relationship between 1,3,4-oxadiazole derivatives' structure and activity

The 1,3,4-oxadiazole structure–activity relationship is shown in (Fig. 4). The activity is further increased by substituting other substituents for the phenyl ring, such as p-Cl, p-NO2, and p-tBu. The action is further enhanced by the transformation of the methylthio group into the methyl-sulfonyl group. The activity is reduced when the pyridine ring is substituted for the phenyl ring. The activity was not considerably impacted by the presence of an acetyl group on the oxadiazole ring's nitrogen atom [39]. Therefore, we postulated that the 2,5-disubstituted 1,3,4-oxadiazole scaffold may result in novel powerful drugs with enhanced pharmacokinetic properties and a broad biological activity profile, based on the aforementioned results [5].

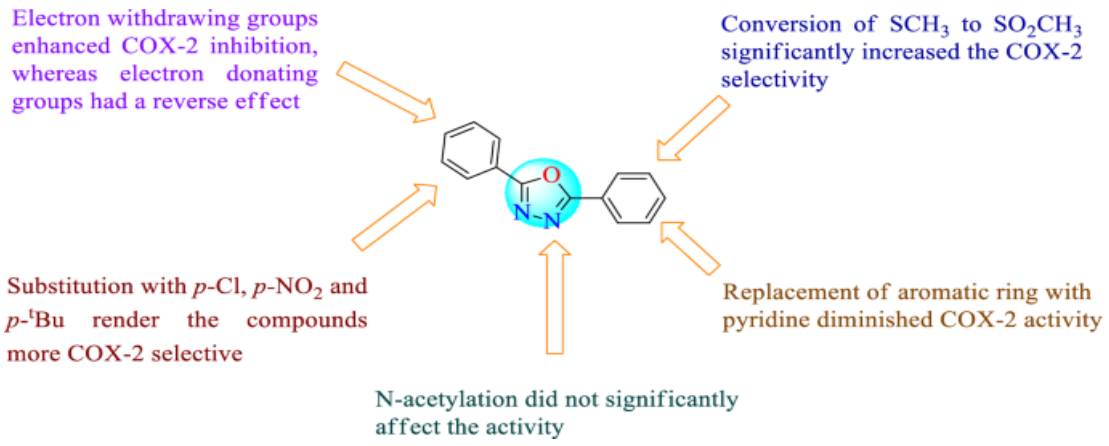

Figure shows: 1,3,4-Oxadiazole's structure–activity relationship

Pharmacological characteristics of a few derivatives of oxadiazole

Better anticonvulsant action is shown by compound N-(4 chlorophenyl) amino-5-(4-pyridyl)-1,3,4-oxadiazole, which has an electron-withdrawing group. Comparing compounds having 3, 4-dimethoxy and p-methoxy groups to reference drugs, the former have more antibacterial potential and the latter have increased anti-inflammatory action [5].

Tamoxifen is available under numerous brand names, including Genox, Tamifen, and Nolvadex. For more than 40 years, this medication has been utilized as a Selective Estrogen-Receptor Modulator (SERM) in the early treatment and prevention of hormone-dependent breast cancer. Regretfully, prolonged use of SERMs during treatment frequently resulted in a host of unfavorable side effects, including blood clots, strokes, cataracts, bone loss, mood swings, depression, increased risk of heart attack and failure, decreased libido, and an increased risk of cancer recurrence or even the development of new ones, including uterine and endometrial. The continued research and development of tamoxifen derivatives is therefore still extremely important [6].

Ponatinib is a multi-targeted tyrosine-kinase inhibitor used to treat chronic myelogenous leukemia. Han M. et al. synthesized a novel class of compounds as analogues of Ponatinib, whose clinical application was suspended in 2013 due to potentially fatal blood clots and numerous other side effects, such as hypertension, headaches, fatigue, abdominal pain, and dry skin. The employed approach involved substituting the alkynyl linker between the benzamide and imidazopirydazine moiety found in the Ponatinib

structure with distinct heterocycle rings consisting of three members: 1,2,4-oxadiazole, 1,3,4-oxadiazole, and oxazole. Throughout the study, the enzyme-linked immunosorbent assay (ELISA) showed the highest activity for 1,2,4-oxadiazole-Ponatinib analogs [7].

LITERATURE

Anti-Insomnia Substances

A health disturbance known as insomnia is linked to inadequate or poor sleep duration. It typically manifests as a loss of sleep, difficulty concentrating, difficulty learning, negative mood, irritability, and occasionally even as a risk factor for heart disease, hypertension, dementia, or melancholy. According to estimates, up to 70% of adults worldwide suffer from sleeplessness, making it a serious public health issue. GABA antagonists were the mainstay of treatment for insomnia for many years, but the increased risk of addiction and worsened mood the following day prompted the development of new anti-insomniac medications. Orexin A and B neuropeptides were discovered in 1998, and since then, their antagonists, such as lemborexant and almorexant, have advanced to clinical trials. Suvorexant, the first Dual-Orexin Receptor Antagonist (DORA) for the treatment of insomnia, was approved by the FDA in 2014 and is marketed under the Belsomra brand. More stronger molecules with a better pharmacological profile and safety are still needed, though, as common side effects include muscle weakness, strange nightmares, sleepwalking, and somnolence the next morning [8].

Agents Antimicrobial

Over 1400 distinct species of microorganisms, including bacteria, viruses, protozoa, fungus, and helminthes, have been identified in literature to date. These organisms can cause illnesses in humans that frequently result in death. Remarkably, hardly 20 of them—mostly bacteria—are in charge of almost two thirds of the fatal instances. In high-developed nations, the number of estimated infections-related deaths has been steadily declining, from 16 million in 1990 to roughly 15 million in 2050, with projections of 13 million. However, a great deal of suffering remains among individuals due to a variety of illnesses, including diarrhea, malaria, HIV/AIDS, pneumonia, and tuberculosis. Finding novel, efficient antibacterial/antiviral medications and developing cutting-edge therapies are two problems of utmost importance given the various pandemic dangers facing Europe and the rest of the world, including the recent infections with the SARS-CoV-2 virus that causes COVID-19 [9].

Agents Anti- Allodynic

Neuropathic pain is a major global issue. These days, anticonvulsants, opioids, and antidepressants with a tricyclic structure are utilized to manage chronic pain. However, some of them are not always helpful and can have serious negative side effects during long-term treatment, including potentially fatal addiction and abuse. Sigma receptors (σ1 and σ2), which were mistakenly characterized as opioid receptors at first (even though their exact role is still unknown), have been discovered as possible targets for the treatment of drug-resistant cancers and illnesses affecting the central nervous system (CNS)[10].

Drug-resistant cancers and illnesses affecting the central nervous system (CNS) may benefit by targeting sigma receptors (σ1 and σ2), which were mistakenly classified as opioid receptors at first (though their exact role is still unknown[11]).

Agents Anti-Inflammatory

The intricate and normal biological reaction of bodily tissues to wounds and diseases is called inflammation. Its action is predicated on the removal of early cell injuries, the removal of necrotic cells or damaged bodily tissues, and the acceleration of healing. However, unchecked inflammation can cause a number of illnesses, such as rheumatoid arthritis, diabetic neuropathy, inflammatory bowel disease, osteoarthritis, and tumor initiation and progression[12].

The most widely used analgesics and anti-inflammatory medications are called non-steroidal anti-inflammatory drugs (NSAIDs), and they work by inhibiting cyclooxygenases. It's interesting to note that in vivo experiments using the carrageenan-induced rat paw edema assay demonstrated significantly greater effectiveness than that of ibuprofen [13].

Additional Biological Processes

The CNS's control of dopamine, serotonin, and glutamate release is greatly influenced by kappa-opioid receptors. Recent research has indicated that KOR may be involved in a variety of neuropsychiatric or neurological disorders, such as epilepsy, addictions, alcoholism, depression, schizophrenia, and anxiety. As a result, medicinal chemists have been interested in the development of novel, effective KOR antagonists with high selectivity and medication-like profiles[14].

METHEDOLOGY.

Creation of Benzoxazoles

Traditionally, carbonyl chemicals such aldehydes, ketones, carboxylic acids, esters, and acyl chlorides are used to condense 2-aminophenols to create benzoxazoles. Several techniques, such as (i) solution-phase, (ii) solid-phase, and (iii) green synthesis, have been used to achieve their synthesis. The benzoxazole nucleus has also been produced under a variety of reaction circumstances[15].

While certain procedures/environments are benign, others could need the use of dangerous solvents and/or unfavorable reaction circumstances. But as Soni et al. thoroughly detail, each approach has unique benefits with regard to yield, efficiency, and environmental factors. Since the biological uses of benzoxazoles are the main focus of this review, various synthesis procedures for them are briefly described in this section[16].

Topoisomerases of DNA

Enzymes known as DNA topoisomerases are involved in DNA relaxing and supercoiling, two processes that are crucial to DNA topology. The genome of a cell must be compressed into the nucleus due to DNA compaction. Thus, it is supercoiled in a way that prevents knots and tensions with the aid of the enzyme topoisomerase. The two primary categories of topoisomerases are type I and type II [17]

While topoisomerase-II simultaneously breaks and uncoils both strands to permit unrestricted rotation, topoisomerase-I breaks one strand of the double helix at its end and causes it to rotate around the other intact strand. Recombination, transcription, chromatin remodeling, and DNA replication all depend on these

processes. Thus, one useful tactic in the fight against cancer is to target and inhibit DNA topoisomerase [18].

In 2021, Karatas and colleagues produced novel antitumour medicines that specifically target human DNA topoisomerase enzymes. The compounds with the best inhibitory effect against DNA topoisomerases were 5-nitro-2-(4-butylphenyl)benzoxazole 2 and 2-(4-butylphenyl) oxazolo[4,5-b]pyridine. The two substances were found to be more successful in inhibiting topoisomerases than etoposide, the standard medication, but they were ineffective when tested on human epithelial cervix adenocarcinomas, human epithelial colorectal adenocarmas, human lung cancers, and human breast cancers[19].

Benzoxazoles as medicines that inhibit protozoa

In tropical nations, protozoan infections are common and significantly affect public health. Among these illnesses are human African trypanosomiasis, which is brought on by several Trypanosoma species, leishmaniasis, which is linked to Leishmania species, and malaria, which is brought on by Plasmodium species. The quest for novel and more potent medications has persisted throughout history, particularly in light of the threat posed by drug-resistant infections. It's interesting to note that substances with the benzoxazole scaffold have been identified as active agents against diseases caused by protozoa, which could support ongoing efforts to discover a cure[20].

CONCLUSION

The 1,2,4-Oxadiazole nucleus and its derivatives appear to provide a favorable framework for the identification and creation of medications with significant bioactivities. The aforementioned considerations have demonstrated that a number of 1,2,4-oxadiazole-based compounds may play a major role in the synthesis of novel drugs that may be effective in treating conditions such as cancer, inflammation, sleeplessness, Alzheimer's disease, and abuse or addiction. The chemicals discussed in this research have significant potential for the creation of new medications because some of them are appropriate for clinical trials and are now undergoing review**.** Furthermore, one of them just started phase I clinical studies. The increasing fascination with this group of substances is driving researchers to create novel, eco-friendly, and productive synthesis techniques. Mechanochemochemistry is one of the newest synthetic methods. Grinding and milling are two effective methods for the quick, solvent-free, and clean synthesis of a wide range of physiologically active chemicals. These reactions, which are typically carried out in a mortar grinder or mixer ball mill, are very valuable because they may improve substrate conversion, reduce or eliminate the need for solvents, or even yield products that weren't possible to achieve with the earlier techniques.

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