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Investigating the Antimicrobial Activity of Derivatives of Benzotriazole

Niranjan Sanjay Chaudhari*[1], Mohammad Safwan Akbar Ali Khan[1], Mohammed Fahim Abdul Azim Khan[1], Shaikh Mohd Owais Mohd Azam[1], S P Srinivas Nayak[2]

[1]Pharm D Intern, Department of Pharmacy Practice, Parul Institute of Pharmacy & Research, Parul University, Vadodara, Gujarat, INDIA.

[2]Assistant Professor, Department of Pharmacy Practice, Parul Institute of Pharmacy & Research, Parul University, Vadodara, Gujarat, INDIA.

*Corresponding Author: niranjanchaudhari4@gmail.com

ORCiD

https://orcid.org/0009-0002-3292-6177

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ABSTRACT

Benzotriazole derivatives have emerged as a promising class of compounds with significant antimicrobial activity. This review article delves into the diverse antimicrobial properties of benzotriazole derivatives, focusing on their efficacy against various pathogenic microorganisms. We provide a detailed examination of the chemical structure-activity relationship (SAR) of these derivatives, highlighting how modifications to the benzotriazole core influence their antimicrobial potency. The review synthesizes findings from recent studies that explore the mechanisms of action, spectrum of activity, and potential applications of benzotriazole derivatives in combating bacterial, fungal, and viral infections. Additionally, we discuss the challenges and future directions in optimizing these compounds for clinical use, including issues related to toxicity, stability, and formulation. By consolidating current research and identifying key trends, this article aims to offer a comprehensive resource for researchers and pharmaceutical developers interested in harnessing the antimicrobial potential of benzotriazole derivatives.

Keywords- Benzotriazole, Antimicrobial, Benzene**.**

I. INTRODUCTION

Benzotriazole is a significant class of bicyclic heterocyclic compounds composed of three nitrogen atoms fused with a benzene ring. This structure allows for tautomerism within its five-membered rings. Benzotriazole is particularly relevant in the dairy industry due to its efficacy in inhibiting metal corrosion. The compound is both inexpensive and stable, with a pKa of 8.2, making it acidic and easily soluble in alkaline solutions [1]. It also dissolves readily in organic solvents such as ethanol, benzene, toluene, chloroform, and DMF. The fused benzene ring in benzotriazole creates an extensive conjugated system, facilitating π-π stacking interactions, which are non-covalent attractions between aromatic rings. Additionally, the presence of three nitrogen atoms enables the formation of hydrogen bonds and coordination bonds, making benzotriazole derivatives particularly adept at binding to various enzymes and receptors within biological systems [2]. This capacity for diverse non-covalent interactions underpins the broad spectrum of biological activities exhibited by benzotriazole derivatives. The compound possesses both electron-donating and electron-accepting properties. Benzotriazole has shown significant potential in pharmaceutical applications, particularly in the treatment of various diseases. Triazole derivatives, which include compounds like imidazole, thiazole, carbazole, oxazole, and benzimidazole, play crucial roles in medicinal chemistry and are widely used in clinical settings. As a

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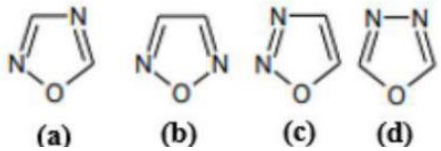
fused aromatic nitrogen-containing heterocyclic compound, benzotriazole and its derivatives have numerous biological and industrial applications, including use as corrosion inhibitors, ultraviolet light stabilizers for polymers, and anti-foggants in photography [3]. Benzotriazole has been explored for a wide range of biological activities, including antibacterial, antiviral, anti-inflammatory, anticonvulsant, enzyme inhibition, DNA cleavage, antifungal, herbicidal, antitubercular, antimicrobial, and antiproliferative effects. The rapid genetic evolution of microorganisms and their increasing resistance to antibiotics has made the development of new therapeutic agents a continuous challenge [4]. This review aims to deliver an in-depth analysis of the antimicrobial properties of benzotriazole derivatives, focusing on their chemical structures, mechanisms of action, and potential therapeutic uses.

II. ANTIMICROBIAL

The compound's growing popularity is largely due to its wide range of biological properties, such as antiviral, antiproliferative, antibacterial, and antiprotozoal activities [5]. The antibacterial properties of benzotriazole derivatives have been extensively studied since the late 1980s, showing efficacy against a wide variety of bacterial strains. Notably, triazolo[4,5-f]-quinolinone carboxylic acids, which contain a benzotriazole moiety, have demonstrated potent antibacterial activity against Escherichia coli, with minimum inhibitory concentrations (MICs) ranging from 12.5 to 25 μg/mL. However, modifications at various positions within the triazole ring can lead to partial or complete loss of antibacterial activity [6]. Derivatives such as N-acyl-1H-benzotriazole or N-ethyl-1H-benzotriazole acetate have been synthesized by incorporating benzotriazole into thiophene, pyridine, thiadiazol, or pyrazole moieties. Adding a -COOMe group to the fifth position of benzotriazole results in compounds with remarkable antibacterial properties, exhibiting MIC values as low as 0.125-0.25 μg/ml. Further, benzotriazole derivatives have been integrated into 4-oxo-thiazolidines and their 5-arylidene derivatives, forming 5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolidin-4-ones, which have shown strong antibacterial activity against species like Bacillus subtilis, Salmonella typhimurium, Escherichia coli, and Bacillus anthracis. Beyond antibacterial effects, benzotriazole derivatives have exhibited antiviral activity against enteroviruses, which are implicated in celiac disease [7]. A nested case-control study within a prospective birth cohort suggested that enterovirus infections could trigger celiac disease. The structural diversity of benzotriazole derivatives, alongside their antibacterial and antiviral activities, positions them as a promising focus for developing new drugs to combat infectious diseases. Further research is needed to refine the structure-activity relationship (SAR) of benzotriazole derivatives and optimize their synthesis processes to enhance their efficacy and safety in clinical applications. Overall, the antimicrobial properties of benzotriazole derivatives underscore their significant potential as antibacterial agents. Recent studies have indicated that altering aryl and heteroaryl substitutions at specific positions on the benzotriazole ring can enhance antibacterial activity against various bacterial species, including E. coli, E. faecalis, S. aureus, and P. aeruginosa. Additionally, introducing electron-withdrawing and electron-donating groups at targeted sites on the benzotriazole ring has been shown to significantly boost antibacterial efficacy [8].

III. CHEMISTRY OF BENZOTRIAZOLE

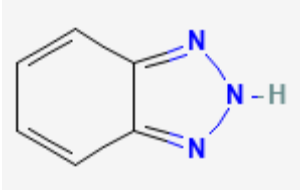
Benzotriazole derivatives are characterized by a large conjugated system that facilitates interactions, with the three nitrogen atoms playing a crucial role in forming coordination bonds with hydrogen and other atoms. This structural feature gives these derivatives a high affinity for various enzymes and receptors, enabling a range of noncovalent interactions and resulting in diverse biological activities. Benzotriazole, an inorganic compound with the formula C6H3, is a heterocyclic nitrogen compound containing three nitrogen atoms, each possessing a lone electron pair. These atoms contribute to the formation of a five-membered ring, which can exist in different tautomeric forms. This compound is also referred to as oxadiazole due to its five-membered ring structure, which includes one oxygen and two nitrogen atoms [19].



1,2,4-oxadiazole (a), 1,2,5- oxadiazole (b), 1,2,3-oxadiazole (c), and 1,3,4- oxadiazole (d)

IV. PHYSIOCHEMICAL PROPERTIES OF BENZOTRIAZOLE [9-10]

Structure:



Chemical Structure: Benzotriazole ($C_6H_5N_3$) features a benzene ring fused with a triazole ring, which imparts distinctive properties to the compound, blending the aromatic stability of the benzene ring with the reactivity of the triazole ring.

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Molecular Weight: Benzotriazole has a molecular weight of around 119.12 g/mol and usually appears as a white to light tan crystalline powder.

Melting Point: enzotriazole has a melting point in the range of 95-99°C, signifying its solid state under standard conditions, while also highlighting its moderate sensitivity to heat.

Boiling Point: The boiling point is relatively high, ranging from 204 to 210°C at standard atmospheric pressure. However, it may decompose prior to reaching this temperature.

Solubility: Benzotriazole exhibits moderate solubility in water, approximately 20 g/L at 20°C, and is highly soluble in organic solvents such as ethanol, methanol, and acetone. Its solubility in water diminishes with a decrease in temperature.

pKa Value: Benzotriazole, with a pKa of approximately 8.2, is a weak acid that can exist in both protonated and deprotonated states depending on the pH of the solution.

Partition Coefficient (Log P): Benzotriazole has a log P value of about 1.44, indicating moderate hydrophobicity and solubility in both aqueous and lipophilic environments.

UV Absorption: Benzotriazole exhibits strong UV absorption, peaking at around 273 nm, makes it effective as a UV stabilizer in various materials.

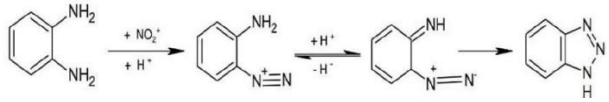
Stability: chemically stable under normal conditions, it can degrade in highly acidic or basic environments. It is resistant to oxidation and remains stable for extended periods when stored correctly.

Reactivity: The triazole ring in benzotriazole is highly reactive, facilitating a range of chemical modifications.

V. SYNTHESIS OF BENZTRIAZOLE

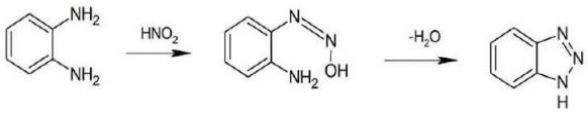
Preparation-1:

Benzotriazoles are synthesized by cyclocondensing o-phenylenediamines with sodium nitrite in acetic acid. The reaction is initiated by heating the reagents together, resulting in the formation of a monodiazonium derivative from the diamine, which then undergoes spontaneous cyclization [16]



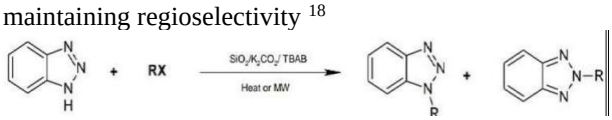
Preparation-2:

Hydrolyzing an acylated or aroylated benzotriazole—previously synthesized by treating the corresponding mono-acylated or aroylated o-phenylenediamine with nitrous acid—yields 1,2,3-benzotriazole directly. This method is more efficient and offers higher overall yields compared to alternative approaches involving multiple intermediate steps [17]

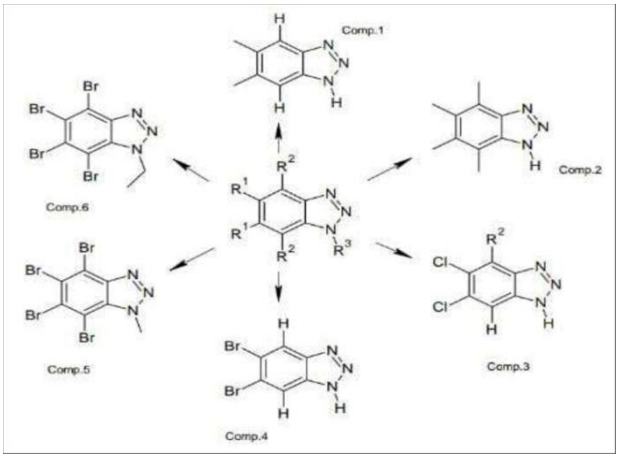


Preparation-3:

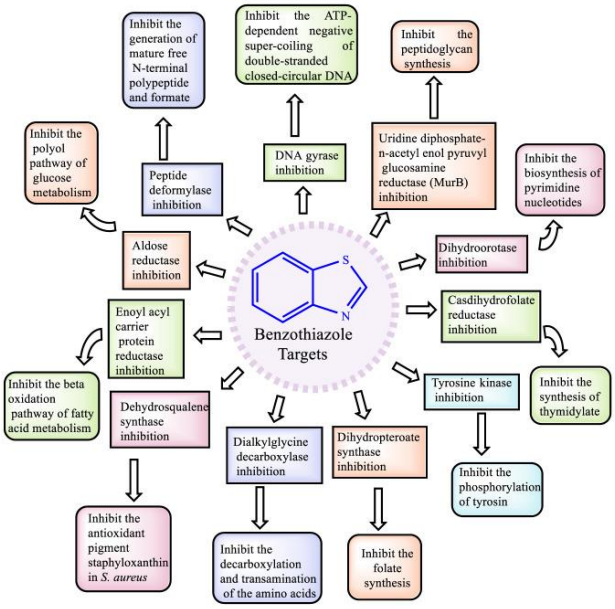
A highly efficient, solvent-free method for N-alkylation of benzotriazole has been developed, utilizing SiO_2, K_2CO_3, and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions. This approach enables the production of 1-alkyl benzotriazoles with rapid reaction times and moderate to high yields, while maintaining regioselectivity [18]



VI. DERIVATIVES OF ANTIMICROBIAL BENZTRIAZOLE [16]



VII. DIFFERENT ANTIBACTERIAL TARGETS OF BENZOTRIAZOLE ACTIVITY [20-23]



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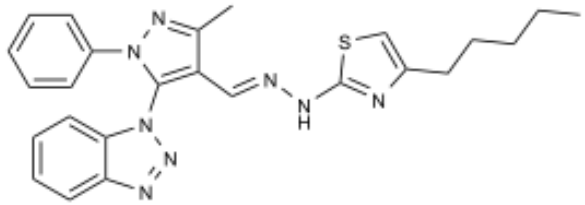
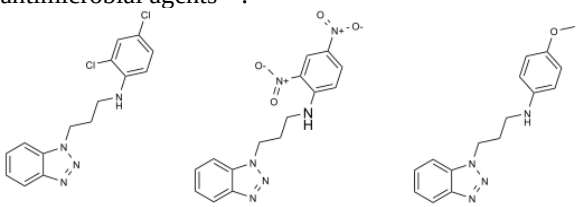
VIII. LITERATURE REVIEW BASED ANTIBACTERIAL ACTIVITY

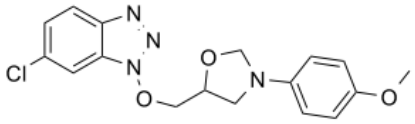
In their 2024 study, Gangurde et al. synthesized a series of novel (E)-2-(2-((5-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazinyl)-4-(aryl)thiazole derivatives through a three-component reaction involving 5-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde, thiosemicarbazide, and various substituted phenacyl bromides. The newly synthesized benzotriazole-pyrazole-thiazole hybrids were characterized using FT-IR, 1H NMR, 13C NMR, and HRMS. These compounds were tested for antibacterial activity against E. coli, B. subtilis, B. megaterium, and S. aureus, as well as antifungal activity against A. niger, A. oryzae, Rhizopus spp., and C. albicans, showing significant activity against all tested strains [11].



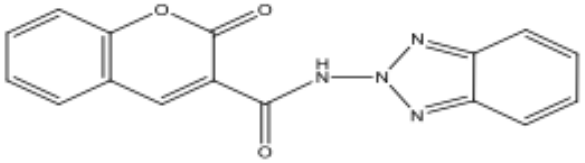
Aggarwal et al. (2023) investigated the antimicrobial properties of various benzotriazole derivatives against Gram-negative bacteria (Pseudomonas aeruginosa, Escherichia coli), Gram-positive bacteria (Bacillus subtilis, Staphylococcus aureus), and fungal strains (Candida albicans, Candida utilis, Aspergillus niger, Aspergillus flavus). The study found that most compounds exhibited moderate to strong antimicrobial activity, with a few effective against up to six pathogens. In silico analysis of benzotriazole derivatives (N-(3-(1H-benzo[d][1,2,3]triazol-1-yl)propyl)-2,4-dichloroaniline; 1a, N-(3-(1H-benzo[d][1,2,3]triazol-1-yl)propyl)-2,4-dinitroaniline; 1b, and N-(3-(1H-benzo[d][1,2,3]triazol-1-yl)propyl)-4-methoxyaniline; 1c) showed successful docking with the Aspergillus fumigatus N-myristoyl transferase protein, with binding energies of -12.3686 kcal/mol, -10.6038 kcal/mol, and -10.2153 kcal/mol, respectively. This research highlights the potential of benzotriazoles as antimicrobial agents [12].



Singh et al. (2023) synthesized a series of benzotriazole-based β-amino alcohols through aminolysis of benzotriazolated epoxides under catalyst- and solvent-free conditions, achieving excellent yields. These β-amino alcohols were further converted into benzotriazole-based oxazolidine derivatives. The compounds were characterized using 1H NMR, 13C NMR, and mass spectrometry. Antimicrobial testing revealed that compounds 4a, 4e, and 5f exhibited activity against Staphylococcus aureus (MICs: 32, 8, and 64 μM, respectively). Additionally, compounds 4a, 4e, 4k, 4i, 4m, 4n, 4o, 5d, 5e, 5f, 5g, and 5h showed significant activity against Bacillus subtilis (MICs ranging from 8 to 64 μM). Molecular docking studies were performed to assess ligand–protein interactions, highlighting the potential of these compounds as antibacterial agents. [13].



AL-SHUAEEB et al. (2023) aimed to design and synthesize novel coumarin derivatives incorporating 2-aminobenzotriazole and 2-amino-5-mercapto-1,3,4-thiadiazole. The study involved synthesizing coumarin-3-carboxylic acid (compound 2), 2-aminobenzotriazole (compound 3), and 2-amino-5-mercapto-1,3,4-thiadiazole (compound 5), followed by coupling these compounds to create the target derivatives. The new compounds were characterized using physicochemical properties, FTIR spectroscopy, and CHNS & O elemental microanalysis conducted in France. The study highlighted that incorporating an amine group from a heterocyclic compound into the carboxylic side of coumarin derivatives yielded significant antimicrobial activity, comparable to levofloxacin [14].



Ibrahim et al. (2021) reported the synthesis, characterization, and biological evaluation of novel indole, benzotriazole, and thioacetyl chloride derivatives. The study involved the preparation of 2-amino-5-mercapto-1,3,4-thiadiazole (M1) through the cyclization of thiosemicarbazide with carbon disulfide and sodium carbonate. This precursor was then reacted with various aromatic aldehydes to form hydrazones (M2-M4). These hydrazones were further reacted with chloroacetyl chloride to yield 5-(substituted benzylidene)amino-2-thioacetyl chloride-1,3,4-thiadiazole derivatives (M5-M7). Additional compounds (M8-M10) and (M11-M13) were synthesized by reacting (M5-M7) with benzotriazole or indole, respectively. The synthesized compounds were characterized using physical properties, FT-IR, and ^{1}H NMR spectroscopy. Biological testing was conducted to assess the antibacterial and antifungal activities of select compounds [15].

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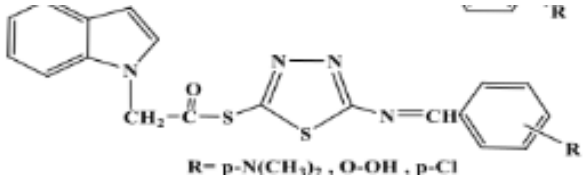

IX. CONCLUSION

Benzotriazole derivatives have gained attention as promising antimicrobial agents due to their ability to disrupt microbial cell membranes, inhibit enzyme functions, and interfere with nucleic acid synthesis. The structural flexibility of benzotriazole enables the design of a broad array of derivatives with enhanced effectiveness and specificity against various pathogens. While significant strides have been made in understanding the antimicrobial mechanisms of these compounds, challenges such as pharmacokinetics, toxicity, and resistance profiles remain. Further research is crucial to ensure their safe and effective clinical application. Additionally, investigating the potential for synergistic effects with existing antibiotics and utilizing advanced synthetic methods to develop novel derivatives could provide new strategies for combating resistant microbial strains. In summary, benzotriazole derivatives hold considerable promise in the development of innovative antimicrobial therapies. Ongoing research is vital to fully realize their therapeutic potential and address the escalating issue of antimicrobial resistance.

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