A MINI-REVIEW ON THE ANTIMICROBIAL ACTIVITY AND ANTIVIRAL ACTIVITIES OF BENZOTRIAZOLE DERIVATIVES

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ABSTRACT

Benzotriazole and its derivatives are incredible because of their widespread applications, particularly in the pharmaceutical and agricultural industries. Several synthetic techniques are accessible, including the conventional Pinner reaction, the Sandmeyer reaction, and metal-catalyzed processes, demonstrating the versatility of creating diverse benzotriazole derivatives. This article summarises the synthetic processes and antibacterial characteristics of benzotriazole derivatives. Furthermore, the antibacterial efficacy of benzotriazole derivatives against various infectious organisms, including bacteria, fungi, and viruses, is examined. Benzotriazole compounds have strong antibacterial properties, making them promising candidates for future research in the battle against infectious illnesses. This study summarises the developments of benzotriazole compounds as potential antimicrobial and antiviral activity.

KEYWORDS:
Benzotriazole; antimicrobial activity; antiviral activity; antibacterial.

1. INTRODUCTION

Benzotriazole and its derivatives are gaining popularity because of their many biological properties, which include antiviral, antiproliferative, antibacterial, and antiprotozoal activity[1][4]. The antibacterial activity of benzotriazole derivatives has been extensively studied since the late 1980s, and they are particularly effective against a diverse variety of bacterial strains[1]. One of the most important discoveries in this field is the presence of triazolo[4,5-f]-quinolinone carboxylic acids, which include a benzotriazole moiety. These acids showed effective antibacterial action against Escherichia coli, with MIC values ranging from 12.5 to 25 μg/mL. However, annulations at various positions within the triazole ring might cause a partial or complete loss of antibacterial action [1]. N-acyl-1H-benzotriazole or N-ethyl-1H-benzotriazole acetate derivatives were prepared by combining benzotriazole with thiophene, pyridine, thiadiazol, or pyrazole moieties. Adding a \(-\text{COOMe}\) group to the fifth position of benzotriazole results in compounds with outstanding antibacterial properties (MIC values of 0.25-0.125 μg/ml) [1]. Derivatives of N-acyl-1H-benzotriazole or N-ethyl-1H-benzotriazole acetate have also been synthesized by integrating benzotriazole into thiophene, pyridine, thiadiazol, or pyrazole moiety. Adding a \(-\text{COOMe}\) group to the fifth position of benzotriazole results in compounds with outstanding antibacterial properties (MIC values of 0.25-0.125 μg/ml) [1]. Benzotriazole derivatives have also been involved in 4-oxo-thiazolidines and their 5-arylidene derivatives, producing 5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolidin-4-ones. These compounds were tested against a variety of bacterial species, including Bacillus subtilis, Salmonella typhimurium, Escherichia coli, and...
Bacillus anthracis, and had strong antibacterial activity[1]. In addition to antibacterial action, benzotriazole derivatives have been shown to have antiviral activity against enteroviruses, a major cause of celiac disease[3]. A nested case-control study within a prospective birth cohort found that enterovirus infections may cause celiac disease[3]. Finally, the diversity of benzotriazole derivatives in terms of antibacterial and antiviral activity, as well as their capacity to synthesise diverse functional groups, making them an attractive field of research for the creation of novel medications to battle infectious illnesses. Further research into the SAR of benzotriazole derivatives, as well as the optimisation of their synthesis processes, is required to improve their antibacterial and antiviral properties, as well as to assure their safety and efficacy in clinical applications. [1] [3]. The antimicrobial activity of benzotriazole derivatives demonstrates their tremendous potential as antibacterial agents. Recent research has shown that alternative aryl and heteroaryl substitutions at certain places of the benzotriazole ring improve antibacterial activity against a variety of bacterial species, including E. coli, E. faecalis, S. aureus, P. aeruginosa, and others. Furthermore, the addition of electron-withdrawing and electron-releasing groups at precise places on the benzotriazole ring has been shown to greatly increase antibacterial activity [2].

1.1 | SYNTHESIS

The production and antibacterial activity of benzotriazole have been widely researched and shown beneficial in fighting a variety of illnesses. Benzotriazole derivatives exhibit antibacterial properties against bacteria, fungi, viruses, and parasites. Researchers synthesized numerous benzotriazole compounds and examined their ability to suppress the development of diverse bacteria. The antibacterial activity of benzotriazole derivatives has been extensively researched, and they, like other azole rings, have emerged as one of the most recent active highlights[5]. The discovery and development of antimicrobial medications were important scientific advances in the early twentieth century. Despite the significant investment in antifungal activities of the benzotriazole moiety in antimicrobial medication development, Acanthamoeba Castellani, a protozoan, has been evaluated in vitro using 1H-benzotriazole and its chloro, bromo, and methyl counterparts, as well as their N-alkyl derivatives. According to the findings, chloro-hexedine and 5,6-dibromo-1H-benzotriazole are less effective against protozoa than 5,6-diabromo-1H-benzotriazole and 5,6-dibromo-1H-benzotriazole[8].

![Fig.1 Derivatives of Antimicrobial Benzotriazole](image)
2. BENZOTRIAZONE AS ANTIMICROBIAL AND ANTIVIRAL AGENT

Gangurde et al. described the design, synthesis, and biological assessment of a new series of (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 have been synthesized via a three-component process. The synthesized compound (Fig.2) was evaluated 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. Benzotriazole-pyrazole clubbed thiazole hybrids are bioactive heterocycles. The work most likely entailed the deliberate creation of these hybrid molecules, which combine the structural properties of benzotriazole, pyrazole, and thiazole to produce compounds with potential biological activity [9].

Fig. 2. Benzotriazole derivatives with antimicrobial activity

Ramani et al. applied Autodock 4.2 to perform molecular docking experiments on a new benzotriazole derivative as a strong antibacterial drug against Staphylococcus aureus tyrosyl tRNA synthetase (PDB: 1JIJ). Among all the Benzotriazole derivatives, 2-(1H-1,2,3-Benzotriazol-1-yl)-N-(4-methoxyphenyl)acetamide(Fig.3) is the most effective and demonstrated greatest binding energy (-8.9 K/Cal) and interaction with TYR36, GLY38, ALA39, ASP40, THR42, LEU70, and GLN196[10].

Fig. 3. Benzotriazole derivatives with antimicrobial activity

Aggarwal and Singh investigated the manifestation of antibacterial activity in benzotriazole and its derivatives. The study most likely concentrated on synthesizing and testing benzotriazole compounds to emphasize their efficacy against specific microbial infections. Only a few substances have been identified as active against five or six diseases. In-silico activity was carried out with new benzotriazole compounds. N-(3-(1H-benzo[d][1,2,3]triazol-1-yl)propyl)-2,4-dichloroaniline; 4a; N-(3-(1H-benzo[d][1,2,3]triazol-1-yl)propyl)-2,4-dinitro aniline; 4b; and N-(3-(1H-benzo[d][1,2,3]triazol-1-yl)propyl)-4-methoxyaniline; 4c. The compounds 4(a-c) were effectively docked with protein 4CAW: Aspergillus fumigatus N-myristoyl transferase in combination with myristoyl CoA and a pyrazole sulphonamide ligand via H-bonding, with optimum ligand pose energies of -12.3686 kcal/mol, -10.6038 kcal/mol, and -10.2153 kcal/mol, with docked run times of 16 sec., 9 sec., and 16 sec., respectively. This investigation revealed new insights into the antibacterial action of benzotriazoles [11].
Rokde et al. published an article in Chemistry & Biodiversity on the design, synthesis, and antibacterial characteristics of novel 2-oxo-4-substituted aryl-azetidine benzotriazoles. The study focused on the strategic design and chemical synthesis of these hybrid compounds, which combine the structure of azetidine and benzotriazole to enhance biological activity. Several compounds were synthesized and investigated to discover novel antibacterial agents. These compounds have been evaluated using the agar-cup plate technique. The most effective medication, 4-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)amino)-N-(2-argio-3-methyl-4-oxoaze tidin-1-yl)benzamide (Fig. 5), showed a zone of inhibition of 18±0.09 mm and 19±0.09 mm against E. coli aureus [12].

Singh et al. studied the antibacterial activity of benzotriazole compounds, among which are β-amino alcohols and 1,3-oxazolidines, by cyclization. Molecular docking studies were carried out to determine the binding affinity and the interaction of these prescription drugs with bacterial target proteins, revealing probable mechanisms for activity. Compounds 6a, 6b, and 6c have shown antibacterial activity against Staphylococcus aureus (ATCC25923) with MIC values of 32, 8, and 64 μM, respectively. Compounds 6d, 6e, 6f, 6g, 6h, 6i, 6j, 6k, and 6a, 6b, 6c have no activity against Bacillus subtilis (ATCC6633), with MIC values of 64, 16, 64, 64, 16, and 32, 8, 64 μM, respectively [13].
AL-SHUAAEB and Riyadh Ahmed Atto reported the synthesis of novel coumarin compounds with amino benzotriazole and triazole moieties, as well as their antibacterial properties. The work concentrated on the design and chemical synthesis of these new compounds, which included the biologically active scaffolds of coumarin, amino benzotriazole, and triazole to improve their antibacterial activity. Bacterial resistance has resulted in the production of increasingly powerful, complex coumarin derivatives. When an amine group containing a heterocyclic molecule was inserted into the carboxylic side, the levofloxacin nucleus demonstrated comparable antibacterial efficacy against microbes. The produced compounds in Fig.7 were evaluated for antibacterial activity in vitro against three bacteria (Staphylococcus aureus, Streptococcus aureus, as gram-positive bacteria, and Proteus spp.). As gram-negative bacteria) and two fungi (Aspergillus spp., and Candida spp.) [14]

Khalaf, Ahmed, and Dalaf reported on the synthesis, characterization, and biological assessment of novel compounds including indole, benzotriazole, and thioacetyl chloride. The study includes creating new compounds by combining the bioactive cores of indole and benzotriazole with thioacetyl chloride to build multifunctional molecules with improved biological characteristics. The Biological activity Bacterial compound (Fig.8) indicates a high impact on Bactria (E coli), furthermore, the compound (Fig.8) showed a high effect on Bactria (staphylococcus), and the biological activity fungus for the compound (Fig.8) showed a high effect on fungi (Candida albicans). [15]
Jimoh et al. investigated the biological properties and docking of synthetic benzotriazole and benzimidazole compounds as antibacterial agents. The work covers the development of novel compounds with benzotriazole and benzimidazole moieties to examine their potential antibacterial properties. This study discovered that the synthesized compounds were active against organisms with activity, and docking results revealed that the synthesized compounds had relatively low binding energy when compared to the usual drug used and those previously described. The synthesized molecules were docked against two DNA gyrase, PDB IDs 2XCT and 3ILW. The most active molecule against PDB ID 2XCT and PDB ID 3ILW was 1-butyl-1H-benzotriazole (−13.716). The synthesized compounds showed broad-spectrum antibacterial activity against both gram-positive and gram-negative pathogenic microorganisms. All the compounds were of varying potency; with inhibition zones ranging from 24 to 30 mm and MIC ranging from 25 to 50 μg/mL.

Li et al. studied novel bisamide-decorated benzotriazole compounds, to discover anti-phytopathogenic viral drugs. The study aimed to synthesize novel chemicals and assess their bioactivity against crop-damaging phytopathogenic viruses. The needed molecular docking study was carried out with Tripos SYBYL-X 2.0. The docking analysis results are presented in Table S1. There was an evident interaction between compound Fig.10 and TMV-CP, as evidenced by the high Surflex-Dock scores of 7.66 (the Surflex-Dock scores indicate the -log Kd value) when compared to the antiviral drug ribavirin.

Ibba et al. reported their research in Frontiers in Chemistry, looking into the synthesis, anticancer, and antiviral effects of novel benzotriazole-dicarboxamide derivatives in vitro. The research focuses on the creation of new benzotriazole-dicarboxamide molecules and their possible medicinal applications. The compounds were investigated for their antiviral and anticancer properties. Compounds 11a, 11b, and 11c exhibited antiviral activity against the tested picornaviruses, Coxsackievirus B5, and Poliovirus-1.
Kleoff et al. reported on a scalable synthesis of benzotriazoles using [3+2] cycloaddition of azides and arynes in flow. Because benzotriazole substituted piperidone Fig. 12 has potential antibacterial and antifungal action, we aimed for a quick and scalable synthesis. Using our procedure, we produced Fig. 12 with a 66% yield. To show the scalability of our flow procedure, we synthesized this drug on a gram scale, resulting in a theoretical productivity of 0.33 g/h and a yield of 69% using the same reactor configuration [19].

Fetouh et al. developed a unique, low-cost nanoscience process for producing a silver nanoparticle-activated carbon composite. This mixture was created as a possible antiviral, biocide, and catalyst. The study most likely comprised the composite material's creation and characterization, as well as an evaluation of its antiviral and catalytic properties. While 1-hydroxy-4-nitro-6-trifluoromethyl benzotriazole is used as an antiviral reagent and precursor for various COVID-19 therapy formulations. SNPs@AC composite material exhibited increased biological activity against VERO cells [20].
Piras et al. investigated the preliminary anti-Coxsackie activity of a new 1-[4-(5,6-dimethyl(H)-1H(2H)-benzotriazol-1(2)-yl)phenyl]-3-alkyl(aryl)ureas. The study most likely involves the production of these new urea derivatives and the assessment of their anti-Coxsackie efficacy. Coxsackieviruses are recognized pathogens that cause a variety of human illnesses, including myocarditis, meningitis, and hand, foot, and mouth disease. Compounds Fig.14 (CC50 >100 μM; EC50 = 9 μM) were tested for selectivity of action against various RNA (positive- and negative sense), double-stranded (dsRNA), and DNA viruses. None of them had considerable antiviral activity was determined[21].

![Fig. 14. Benzotriazole derivatives with antiviral activity](image)

Ren et al. studied the synthesis and bioactivity of new benzotriazole compounds as possible antibacterial agents and their interactions with calf thymus DNA. The work most likely consisted of designing and synthesizing novel benzotriazole compounds, which were then tested for antibacterial effectiveness against various microbes. Bioactive testing demonstrated that the new chemical (Fig. 15) exhibited moderate to good antibacterial and antifungal activity against the tested strains compared to the reference drugs chloromycetin, norfloxacin, and fluconazole. The 2,4-chlorophenyl substituted benzotriazole derivative (Fig.15) demonstrated high antibacterial activity against MRSA, with a MIC value of 4 μg/mL, twice as effective as chloromycetin [22].

![Fig. 15. Benzotriazole derivatives with antimicrobial activity](image)

Jamkhandi, C. M., and John Intru Disouza provide the synthesis and antimicrobial assessment of 1H-benzotriazol-1-y1 {[2-hydroxy-5-[(E) phenyldiazenyl] phenyl} methanone. The synthesis most likely required a sequence of chemical processes to mix the starting components and produce the target molecule. When compared to the standard, derivatives 16a and 16b had the strongest antibacterial activity. The compound's structure indicates that it has a benzotriazole ring with a phenyldiazenyl group connected to a phenyl ring. This sort of molecule is known to have antibacterial characteristics, making it a promising candidate for future research in medicine or materials science[23].
3. CONCLUSION

According to the literature, benzotriazole is an important lead chemical substance that is used in a variety of drug discovery and development applications in the pharmaceutical and therapeutic areas. The inclusion of nitrogen enhances its antibacterial action. The many synthetic technologies available demonstrate their diversity and ability to modify structures according to needs. These compounds have potent antibacterial activity and antiviral activity against a wide range of disease species, such as bacteria, fungi, and viruses, making them appealing possibilities for further research in defending against infectious illnesses. As a result, the benzothiazole moiety may be a more appealing alternative for researchers working to find and develop novel drugs with broad pharmacological action. So, the benzothiazole moiety may be a better alternative for researchers for novel drug development with a wide pharmacological activity.

REFERENCES:


