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Exploring Benzotriazoles as Multifunctional Pharmacophores in Contemporary Medicinal Chemistry

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Heterocyclic compounds, which are among the largest and most diverse families of organic compounds, play a crucial role in both chemistry and daily life. Their significance is particularly pronounced in medicinal chemistry, where they are essential for the development of therapeutic agents. One notable heterocyclic compound is benzotriazole, a bicyclic structure composed of a fused benzene ring and three nitrogen atoms. This compound has garnered significant attention due to its wide spectrum of biological and pharmacological activities. Benzotriazole and its derivatives exhibit a broad spectrum of therapeutic effects, demonstrating significant antibacterial, antifungal, anti-inflammatory, and analgesic properties. These compounds are of considerable interest in pharmaceutical research due to their potential to address various health conditions through these versatile biological activities. Additionally, they have shown potential in anticancer therapies, as well as in the treatment of helminthic infections, depression, and oxidative stress. Benzotriazole derivatives have also demonstrated antitubercular, anticorrosive, and plant growth inhibitory activities, highlighting their versatility across various fields.

Keywords: Anticancer; Antifungal; Antimicrobial; Benzotriazole; Fused heterocycles.

Heterocyclic compounds have opened new frontiers in the fields of medicinal and organic chemistry. Among this diverse family, benzotriazole stands out for its remarkable properties, making it a valuable compound in various applications. Its unique structure and functionality offer potential in areas such as corrosion inhibition, material science, and even medicinal chemistry, where it has been explored for its biological activity. Its unique characteristics, such as strong electron-donating ability, versatile group-release capabilities, and role as an anion director, have captured the attention of both chemists and pharmacists alike. Benzotriazole can be readily integrated into molecular structures via several synthetic methods, such as condensation, addition, and substitution reactions.[1-5] The common structure of benzotriazole is shown in Figure 1.

Benzotriazole derivatives possess a wide variety of biological, chemical, and industrial properties, making them useful in many different applications. The compound consists of two fused rings, with the five-membered ring demonstrating tautomerism, a feature that adds to its chemical complexity.[6-10] The physicochemical properties are shown in Table 1.

The literature review indicates that benzotriazole derivatives exhibit activity against

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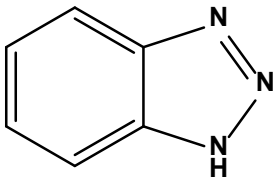
a broad spectrum of target species. This paper specifically focuses on examining benzotriazoles of both biological and industrial relevance, highlighting their most active sites and exploring the related target species. Additionally, it highlights key synthetic methods for these derivatives, and biological response shown.[11-16]

Additionally, they are essential precursors for the production of acid azides, peptides, 3 hydroxymethyl-2,3-dihydrobenzofurans, and 3-hydroxymethylbenzofurans. Two tautomeric forms of benzotriazole exist [17] (Figure 2).

Furthermore, benzotriazole derivatives facilitate the incorporation of radicals from different chemical structures through a number of reactions, such as addition, condensation, and benzo triazolyl alkylation, by acting as precursors for radicals and electron donors. The various biological activities of benzotriazole compounds, which are useful ingredients in choleretic, antibacterial, antifungal, antiprotozoal, antiviral, antioxidant, analgesic, anti-inflammatory, antihyperglycemic, and antiproliferative agents, greatly benefit the pharmaceutical industry. A key technique in modern drug research is protein-ligand or protein-protein docking, which measures the shape and electrostatic interactions of the ligand to predict its orientation when it binds to an enzyme or protein receptor.[18]



1*H*-benzo[*d*][1,2,3]triazole
Chemical Formula: $C_6H_5N_3$

Fig. 1. Structure of Benzotriazole with IUPAC Name.

Synthesis:[19-33]

Scheme-I: Benzotriazoles are synthesized through a cyclocondensation reaction between O-Phenylenediamine (OPD) and sodium nitrite and acetic acid. The method involves heating reagents, leading to the formation of a mono diazonium intermediate from the diamine. This intermediate then undergoes spontaneous cyclization, resulting in the formation of the benzotriazole ring structure as mentioned in figure 3.

Scheme-II: 1, 2, 3-Benzotriazole can be synthesized by directly reacting o-phenylenediamine with nitrous acid figure 4. Another method involves hydrolyzing an acylated or arylated benzotriazole, which is produced by reacting to nitrous acid with a mono-acylated or arylated o-Phenylenediamine. The direct method generally yields higher overall results compared to the multi-step processes.

Scheme-III: Solvent-Free N-Alkylation of Benzotriazole:

A simple and effective method for the highly regioselective N-alkylation of benzotriazole under solvent-free conditions is described in figure 5. This approach employs SiO, , K, CO*f* , and tetrabutylammonium bromide (TBAB) as

Table 1. Physico-chemical Properties of Benzotriazole

Parameter	Value
Molecular Formula	$C_6H_5N_3$
Formula Weight	119.124
Composition	C (60.50%), H (4.23%), N (35.27%)
Molar Refractivity	34.71 ± 0.3 cm³
Molar Volume	88.3 ± 3.0 cm³
Index of Refraction	1.715 ± 0.02
Surface Tension	73.9 ± 3.0 dyne/cm
Density	1.348 ± 0.06 g/cm³
Dielectric Constant	Not available
Polarizability	13.76 ± 0.5 × 10^{-24} cm³

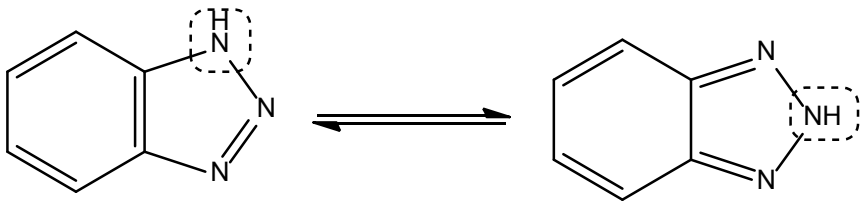


Fig. 2. Tautomeric forms of benzotriazole (1H-1,2,3-benzo-triazole and 2H-1,2,3-benzotriazole).

catalysts, and the reactions are carried out using either thermal or microwave heating. The process produces 1-alkyl benzotriazoles in moderate to high yields, with short reaction times, highlighting its practicality and excellent regioselectivity.

Scheme-IV: The formation of benzotriazoles can be achieved through a reaction involving o-phenylenediamine (benzene-1,2-diamine), sodium nitrite (NaNO,), and acetic acid (CH*f* COOH). When o-phenylenediamine is treated with sodium nitrite in an acidic medium, such as acetic acid, a diazonium ion intermediate is generated. This intermediate then reacts with the nitrogen source to form the benzotriazole structure as depicted in figure 6.

Scheme-V: A diverse range of substituted benzotriazoles was successfully prepared through a [3 + 2] cycloaddition reaction of azides with benzynes as sketch in figure 7. This approach was simple and mild, enabling additional substitutions to take place under the same conditions, as shown in the reaction below.

Pharmacological Characteristic Of Benzatriazole:

The privileged structure of benzotriazole, which is recognized for its broad pharmacological potential. Due to its versatile chemical properties, Benzotriazole is a useful framework for creating new pharmacologically active compounds (figure 8). It is quickly gaining attention in the synthesis of heterocycles and has shown considerable potential in a variety of chemical processes, especially as a synthetic aid. Additionally, benzotriazole and its derivatives exhibit a wide range of pharmacological

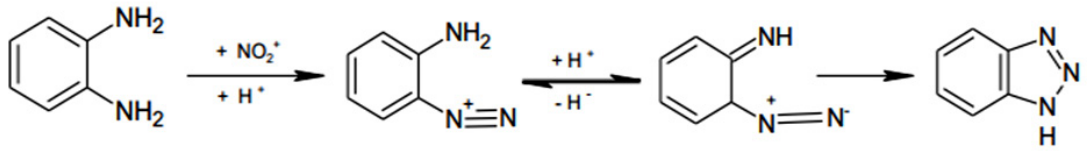


Fig. 3. Benzotriazole synthesis from OPD

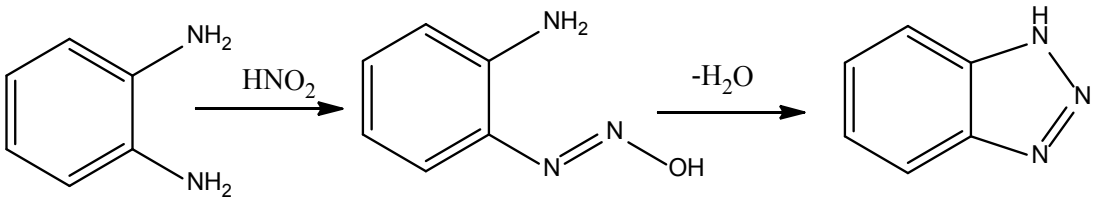


Fig. 4. Synthesis of 1,2,3-benzotriazole

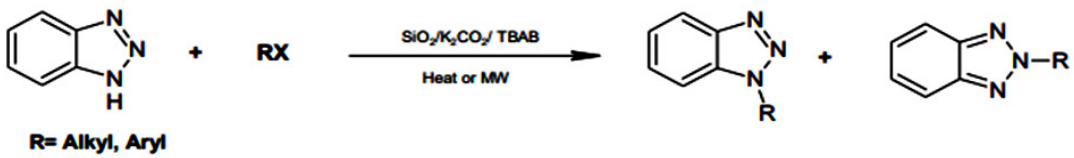


Fig. 5. Solvent free N-alkylation of benzotriazole

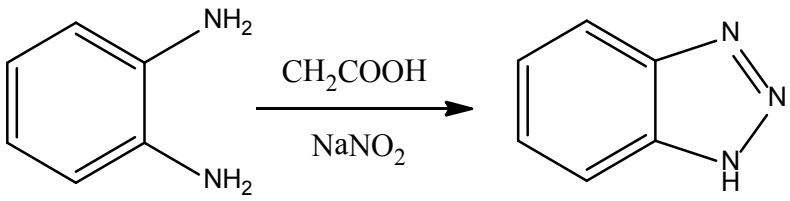


Fig. 6. Synthesis of Benzotriazole in acidic medium

activities, as supported by numerous literature reports, highlighting its importance in medicinal chemistry.

Mechanism of action of benzotriazole

Benzotriazole interacts with lipid bilayers to damage microbial cell membranes, increasing membrane permeability and ultimately causing cell lysis. Additionally, benzotriazole disrupts DNA synthesis and inhibits important enzymes involved in cellular respiration and energy production, among other microbial enzyme systems essential for cell metabolism and reproduction. Additionally, benzotriazole can produce reactive oxygen species in microbial cells, causing oxidative stress and harming DNA and proteins. Benzotriazole is a versatile agent against bacteria, fungus, and other pathogens due to its diverse approach to antimicrobial action. It may find use in a variety of industries, such as medicines, personal care products, and water treatment.[34]

Multifunctional Pharmacophoric Biological Activity:[35-38]

According to recent research conducted between 2020 and 2025, benzotriazole derivatives have emerged as privileged pharmacophores in medicinal chemistry, with significant presentations

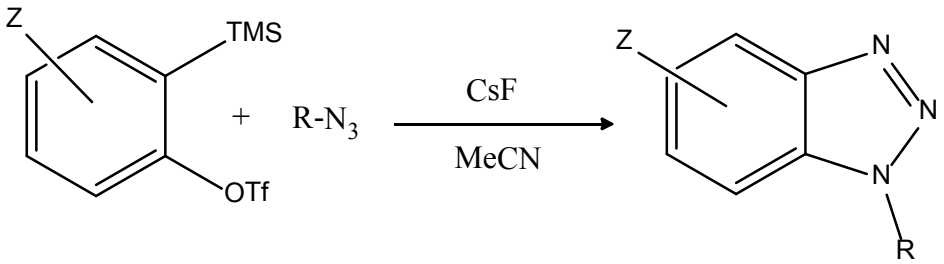


Fig. 7. Cycloaddition reaction of azides for benzotriazole synthesis

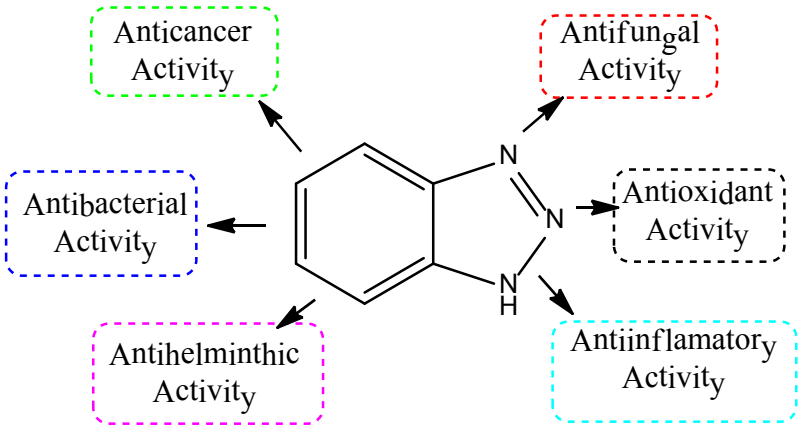


Fig. 8. Various Biological activity of Benzotriazole Scaffold

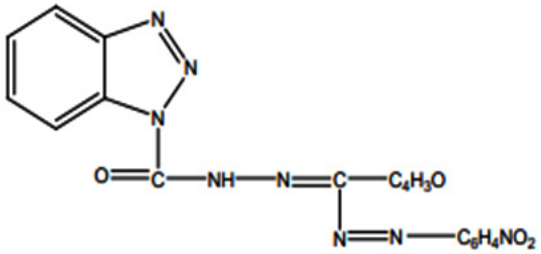
Table 2. Key Trends in chemistry of Benzotriazole

Time Frame	Key Substituents	Key Mechanism
2020-2021	4,5,6,7-Tetrabromobenzotriazole (TBB) and N/C-substituted derivatives	CK2 inhibition, Apoptosis (Prostate/Colon)
2022-2023	N-alkylated/Hybrid derivatives	Cell membrane disruption, FAK inhibition
2024-2025	Metal complexes/Targeted agents	Mitochondria respiration inhibition, Selective cytotoxicity

due to their structural versatility and ability to function as multitarget agents. In 2021–2025, benzotriazole esters were found to be potent, mechanism-based inactivators of the SARS-CoV-2 3CL protease, and in 2024–2025, while recent findings indicate that bumetrizole has emerged as a multifunctional pharmacophore with a primary focus on the substitution leading to inhibition or activation, as indicated in the table 2.

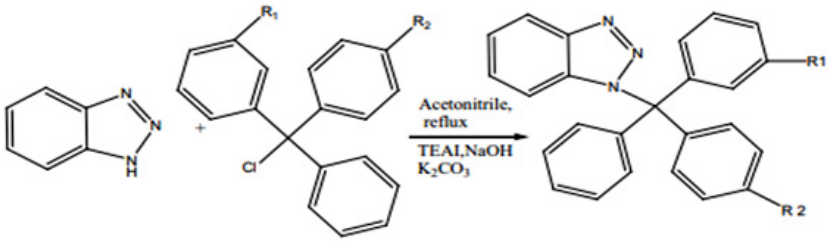
Antifungal activity: Benzotriazoles have demonstrated notable antifungal activity, inhibiting the growth of fungi, which are single-celled, spore-producing organisms. In a study conducted by Sudhir et al [39] synthesizes various benzotriazole derivatives and confirmed for their antifungal properties. These compounds (figure 9) demonstrated notable in vitro effectiveness against *Trichophyton rubrum* and *Epidermophyton floccosum,* which are common dermatophytes causing skin infections.[39]

Rezaei et al[39] have demonstrated that derivatives of 1,2,4-triazole and benzotriazole



1-(1H-benzol(d)[1,2,3]triazole-1-carbonyl)derivative

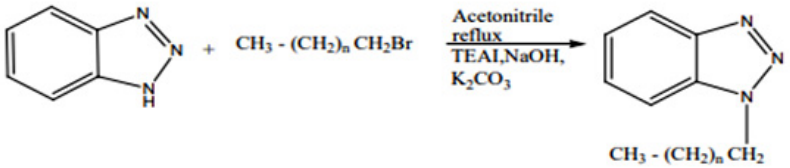
Fig. 9. Carbonyl derivative of benzotriazole



R1=R2=H

R1=H,R2=OCH3

R1=R2=OCH3



(n)=3

(n)=6

Fig. 10. Derivatives of 1,2,4-triazole and benzotriazole

(figure 10) effectively inhibit cytochrome P450 14á-demethylase (14DM) and exhibit significant antifungal activity. Their compounds demonstrated effectiveness against *Microsporum canis, Trichophyton mentagrophytes, Trichophyton rubrum, Epidermophyton floccosum,* and *Candida albicans,* with performance similar to the well-known antifungal's.[40]

Anticancer activity: Benzotriazole derivatives have emerged as promising candidates for anticancer therapy due to their potential to inhibit key cellular pathways involved in tumor progression. In a study conducted by Zhang et al[40] 1,3,4-oxadiazole derivatives incorporating a benzotriazole group were discovered (figure 11) to be effective inhibitors of Focal Adhesion Kinase (FAK), an important protein in cancer cell migration and survival. These compounds demonstrated notable cytotoxic effects against various cancer cell lines, such as the Human Leukemia Jurkat T-cell line, Murine Leukemia L1210 cell line, Estrogen-resistant human breast adenocarcinoma MDA-MB-231 cell line, and Estrogen-sensitive human adenocarcinoma MCF-7 cell line. These findings suggest that benzotriazole-based compounds may represent a novel approach for the development of targeted anticancer therapies.[41]

Swider et al[41] have shown derivatives of 4,5,6,7-tetrabromo-benzotriazole (TBB) figure 12. are strong inhibitors of CK2 (casein kinase 2) activity. CK2 is an important enzyme with multiple subunits, including two catalytic subunits, CK2á and CK2á', and a regulatory dimer, CK2â. Inhibition of any of these subunits has been shown to disrupt CK2's normal function, ultimately inducing cell death. This highlights the therapeutic potential of TBB derivatives figure 13 and 14 in targeting CK2 for cancer treatment and other diseases associated with dysregulated kinase activity.[42]

CK2 plays a crucial role in tumor cells by safeguarding them against apoptosis

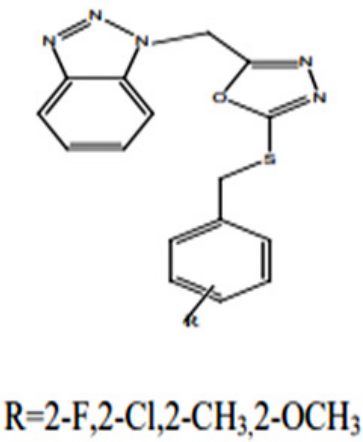


Fig. 11. 1,3,4-oxadiazole derivatives incorporating a benzotriazole scaffold

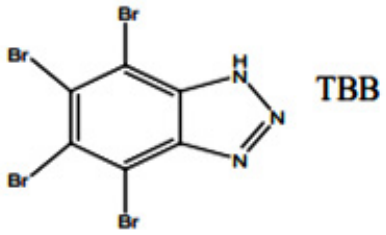


Fig. 12. Derivatives of 4,5,6,7-tetrabromo-benzotriazole

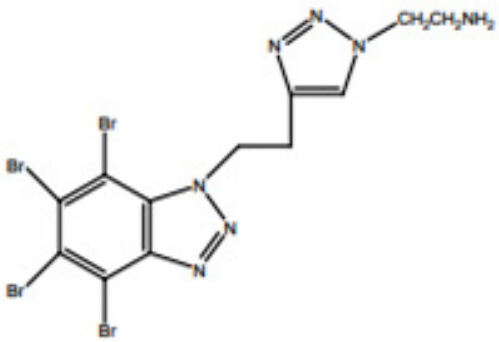


Fig. 13. 2-(4-(2- Perbromo (1-H-Benzo[d] triazole-1-yl) ethyl)-1H,1,2,3 triazole-1-yl) ethanamine.

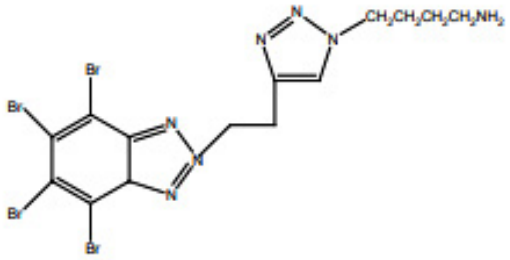


Fig. 14. 4-(4-(2-Perbromo(2-H-Benzo[d]triazole-2-yl) ethyl)-1H,1,2,3-triazole-1-yl)butane-1-amine

(programmed cell death). As a result, inhibiting CK2 activity offers a promising therapeutic strategy for cancer treatment. By disrupting this protective mechanism, CK2 inhibition can sensitize tumor cells to apoptosis, thereby promoting their destruction and potentially improving treatment outcomes.

Antiviral (HIV) activity: Bosque et al[42] have proposed an innovative strategy for curing human immunodeficiency virus by leveraging the action of benzotriazoles figure 15. to reactivate dormant HIV-1. The challenge of latent HIV-1 reservoirs, which persist as a major obstacle to HIV eradication, is addressed through the inhibition of STAT5 SUMOylation. Benzotriazoles specifically block the SUMOylation of phosphorylated STAT5, thereby enhancing its activity and increasing its binding to latent HIV-1 reservoirs. This process reduces the size of these latent reservoirs in primary cells without inducing unwanted cell proliferation. In this context, benzotriazoles act as latency-reversing agents, with STAT5 signalling and SUMOylation emerging as key targets for novel HIV eradication strategies. This approach has shifted the focus of HIV research towards new avenues for "shock and kill" therapies, offering hope for more effective ways to eliminate the virus from the body.[43]

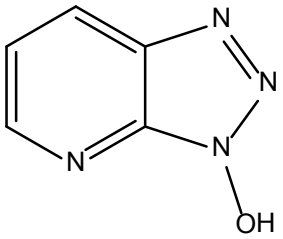
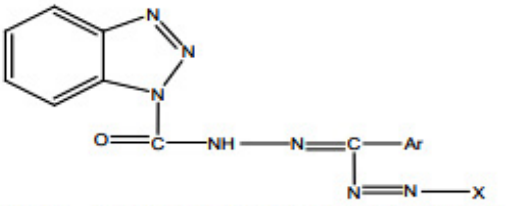


Fig. 15. 1-hydroxy-7-aminobenzotriazole

Anthelmintic activity: Helminth infections have become an increasing concern as a cause of various diseases. In response, Pawar et al[43] synthesized innovative 1,2,3-benzotriazole derivatives figure 16 and evaluated their anthelmintic activity. The compounds were examined against mature *Pheretima posthuma* (earthworms), chosen for their anatomical and physiological similarities to the intestinal roundworm parasites that affect humans. This approach aimed to identify potential new treatments for helminthic infections.[44]

The benzotriazole derivatives containing a nitro group exhibit the most potent anthelmintic activity. Additionally, N-alkylated derivatives of



A.Ar=C_6H_5,X=$C_6H_4NO_2$;B. Ar=C_4H_3O,X=$C_6H_4NO_2$;C.$C_6H_4NO_2$,X=$C_6H_4NO_2$;D. Ar=C_6H_4Cl,X=$C_6H_4NO_2$

Fig. 16. 1,2,3-benzotriazole derivatives

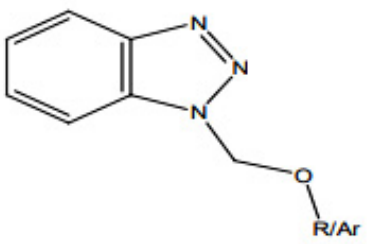
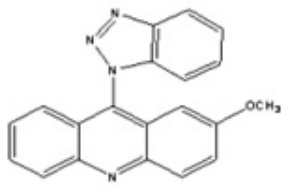


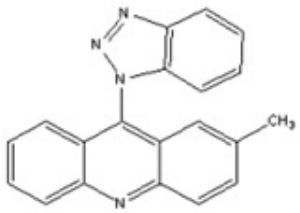
Fig. 17. N-alkylated derivatives of benzotriazole.

benzotriazole figure 17 have also demonstrated significant anthelmintic effects. These compounds have been tested on *Pheretima posthuma* (Indian earthworm) by Sudhir et al[45] showing promising results in their effectiveness against parasitic infestations.[45]

Antimicrobial activity: Heterocyclic compounds have shown significant promise in the treatment of microbial diseases, demonstrating potent antibacterial effects. Among these, acridine derivatives of benzotriazole have been particularly



9-(Benzotriazol-1-yl)-2-methoxy acridine



9-(Benzotriazole-1-yl)-2-methyl acridine

Fig. 18. a) 9-(Benzotrizol-1-yl)-2-methoxy acridine; b) 9-(Benzotrizol-1-yl)-2-methyl acridine

effective, exhibiting strong antibacterial activity against a range of pathogenic bacteria, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, and *Salmonella typhi*, all of which are commonly encountered in clinical infections. These results underscore the potential of acridine-benzotriazole derivatives (figure 18) as promising candidates for the development of novel antibacterial treatments.[46]

Kumar et al[46] synthesized some others derivative of benzotriazole (figure 19) showing antibacterial activities.

These derivatives have been tested for their antibacterial properties against various bacterial strains, including *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, and Salmonella typhi*. Among them, BT1 stands out for its exceptional effectiveness in inhibiting both Gram-positive

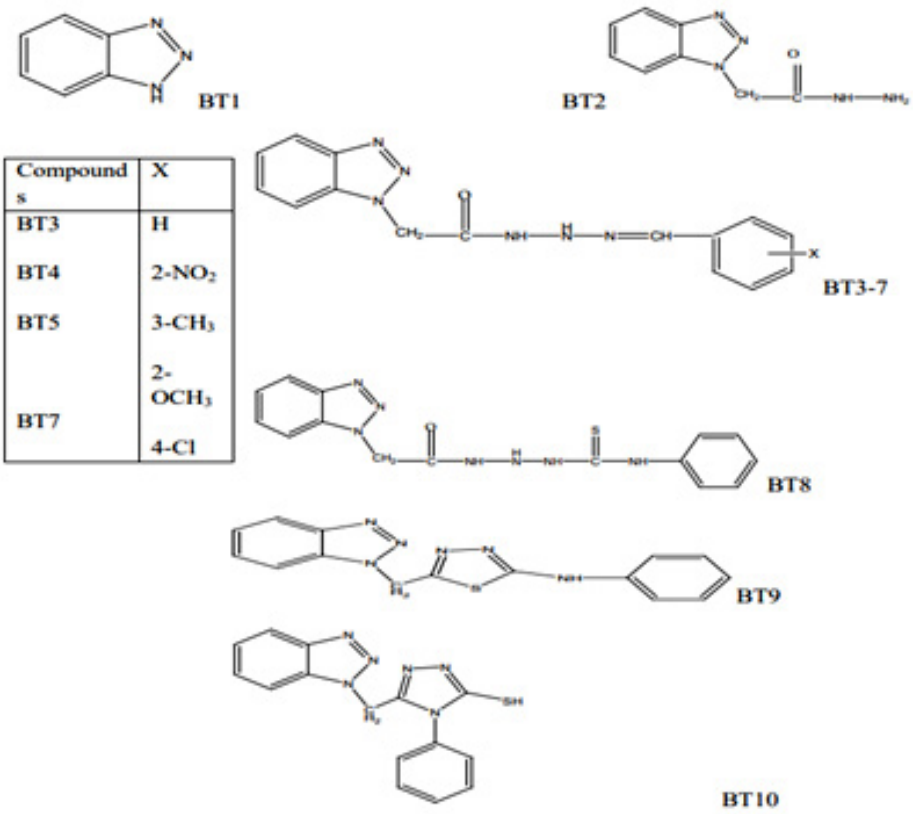


Fig. 19. 2-(1H-benzo[d][1,2,3] triazol-1-yl) acetohydrazide derivative

and Gram-negative bacteria. Likewise, BT1 exhibits considerable antifungal activity against *Candida albicans*, highlighting its broad-spectrum antimicrobial potential.[47]

Antidepressant activity: Benzotriazole derivatives have demonstrated pharmacological activity as anti-serotonergic agents, meaning they inhibit the action of serotonin, a neurotransmitter linked to regulating mood and anxiety. By blocking serotonin's activity, these compounds may help alleviate anxiety symptoms, as serotonin is often involved in the pathophysiology of anxiety disorders.

The research conducted by Caliendo and co-worker explores the anti-serotonergic effects of a range of benzotriazole derivatives, specifically figure 20A and figure 20B, these compounds were evaluated for their potential to modulate serotonin receptors, revealing varying degrees of serotonergic activity. The results suggest that structural modifications to the piperazine and benzotriazole rings influence the anti-serotonergic efficacy, offering valuable insight into the development of selective serotonin receptor modulators.[48-52]

Antioxidant activity: Antioxidants are vital reducing agents that help stabilize free radicals, especially those produced during cellular metabolism. These free radicals, like Reactive Oxygen Species (ROS), can inflict considerable

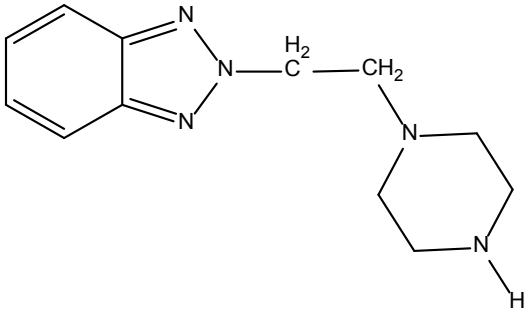


Fig. 20. A: 2-(2-(piperazin-1-yl) ethyl)-2H-benzo[d] [1,2,3] triazole

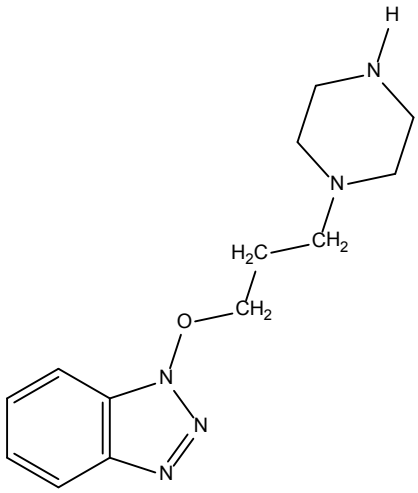


Fig. 20. B: 1-(3-(piperazin-1-yl) propoxy)-1H-benzo[d][1,2,3] triazole

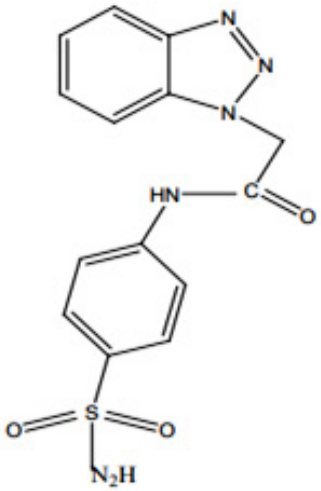


Fig. 21. 2-(1H-benzotriazole-1-yl)-N-(4-Sulfamolyphenyl) acetamide

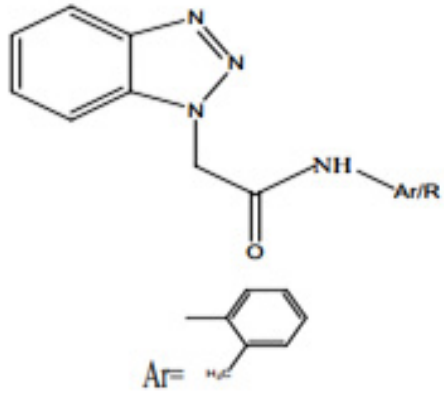


Fig. 22. N-(2-Methylphenyl)-2-(1H-benzotriazol-1-yl) ethanamide.

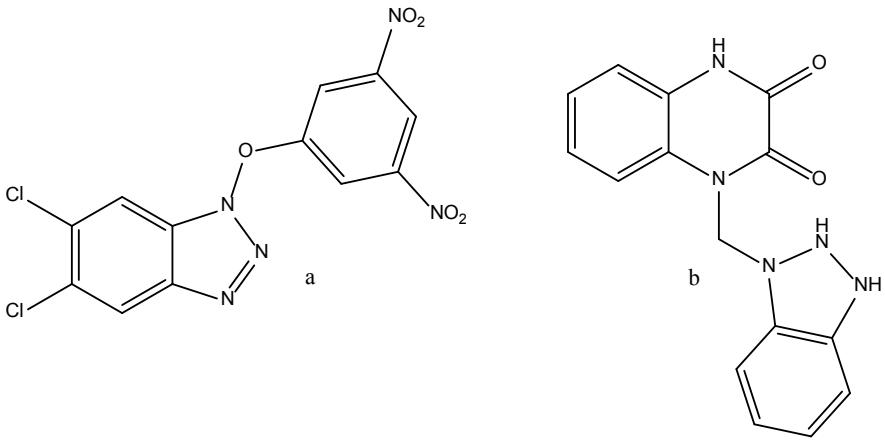


Fig. 23. a) 5,6-dichloro-1-(3,5-dinitrophenoxy)-1H-benzo[d] [1,2,3] triazole; b) 1-((2,3-dihydro-1H-benzo[d] [1,2,3] triazol-1-yl) methyl)

damage to cells and tissues. Antioxidants neutralize these harmful molecules to protect against oxidative stress. Recent studies have shown that benzotriazole derivatives, specifically those of N-phenyl acetamide and carbamic acid (figure 21), exhibit notable antioxidative properties, effectively counteracting the destructive effects of ROS and contributing to cellular protection.[53-58]

Anti-inflammatory activity: Inflammation is a physiological response characterized by symptoms such as swelling and pain, typically occurring when the immune system reacts to injury or the presence of harmful antigens. In this context, Jain and his team [58] have investigated the anti-provocative properties of N-(Alkyl or Aryl)-2-(1H-benzotriazol-1-yl) ethanamide derivatives, which are compounds based on benzotriazole. Their study investigates how these benzotriazole derivatives may exert anti-inflammatory effects, potentially offering new therapeutic avenues for managing inflammation-related conditions.[58-63]

Antituberculosis Activity: The replacement of the benzotriazole with halogen atoms on the phenyl ring has been shown significantly enhance the bioactivity of benzotriazole derivatives. Specifically, chlorine-substituted benzotriazole derivatives exhibit notable anti-mycobacterial activity. Interestingly, when the chlorine atoms on the benzotriazole ring are replaced by other halogens, the anti-mycobacterial activity decreases considerably. Furthermore, the existence of a nitro grouping in the benzyloxy part of the molecule, coupled with a dichloro-substitution on the benzotriazole ring, contributes to a marked increase in biological activity. Dubey and his coworker explored various halogenated and nitro-containing compounds for their potential antituberculosis activity, underscoring the significance of these structural modifications in improving therapeutic efficacy.[64-68]

CONCLUSION

The chemistry, multifunctional role, and pharmacological potential of benzotriazole, a versatile class of bioactive heterocyclic compounds, are highlighted in this review. These molecules exhibit a variety of biological activities, including antibacterial, antiviral, anticancer, antimicrobial, anti-inflammatory, anticonvulsant, analgesic, and antioxidant effects. The electron-rich and conjugated structure of the benzotriazoles are useful scaffolds for drug design.

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