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Benzotriazole: An overview of its versatile biological behaviour

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Abstract

A cyclic compound or ring structure that has atoms of more than one element (such as sulfur, oxygen, or nitrogen) in its ring, is called a heterocyclic compound. Benzotriazole is a type of heterocyclic compound that has nitrogen in it. It has three nitrogen atoms at the 1st, 2nd, and 3rd positions of the ring. Each nitrogen atom has a lone pair of electrons that is not shared with other atoms. This makes the five-membered ring have many medicinal effects, such as killing or stopping the growth of microbes, protozoa, fungi, worms, and mycobacteria; preventing nausea, fighting viruses, tumours, bacteria, and inflammation; protecting cells from damage; blocking protein kinase; activating PARP; and inhibiting histone acetylase.

1. Introduction

Heterocyclic compounds are ring-shaped structures, composed of carbon and at least one other element, such as oxygen, nitrogen, or sulfur.

Benzo-fused azoles are organic heterocyclic substances with a cyclic structure that includes three nitrogen atoms and a fused benzene ring, exhibiting diverse biological activities (Figure 1). Derivatives of benzotriazoles serve various purposes, functioning as plastics, rubber, chemical fibres, photo stabilizers, radioprotectors, and corrosion inhibitors (Afroz Patan *et al.,* 2023). They also play a crucial role as precursors in the synthesis of peptides, acid azides, 3-hydroxymethyl-2,3-dihydrobenzofurans, and 3-hydroxymethylbenzofurans (Anjana *et al.,* 2021). Benzotriazole has two tautomeric forms (Figure 2). Additionally, benzotriazole derivatives act as electron donors and serve as precursors for radicals, facilitating their incorporation from distinct chemical structures through a variety of processes, including addition, condensation, and benzotriazolylalkylation (Indumathy *et al.,* 2023).

The pharmaceutical field greatly benefits from the diverse biological activities of benzotriazole, compounds, which serve as valuable components in choleretic, antibacterial, antifungal, antiprotozoal, antiviral, antioxidant, analgesic, anti-inflammatory, antihyperglycemia, and antiproliferative agents (Ranjeeta Verma *et al.,* 2022).

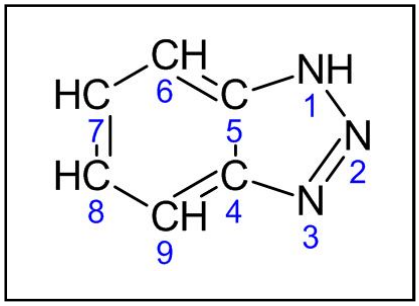

Figure 1: Benzotriazole.

Protein-ligand or protein-protein docking is a crucial tool in current drug development for predicting the orientation of the ligand when it binds to a protein receptor or enzyme by quantifying its shape and electrostatic interactions. Along with coulombic interactions and the creation of hydrogen bonds, van der Waals interactions are also significant. A docking score, which indicates the possibility for binding, roughly represents the sum of all these interactions.

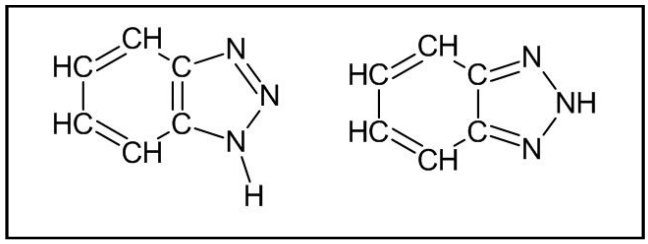

Figure 2: Tautomeric forms of benzotriazole (1*H*-1,2,3-benzotriazole and 2*H*-1,2,3-benzotriazole).

1.1 Mechanism of action of benztriazole

Modes of action involves disrupting microbial cell membranes by interacting with lipid bilayers, leading to increased membrane

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permeability and eventual cell lysis. Benzotriazole also interferes with microbial enzyme systems crucial for cell metabolism and replication, such as disrupting DNA synthesis and inhibiting key enzymes involved in cellular respiration and energy production. Furthermore, benzotriazole can generate reactive oxygen species within microbial cells, inducing oxidative stress and damaging cellular components like proteins and DNA. This multifaceted approach to antimicrobial activity makes benzotriazole a versatile agent against bacteria, fungi, and other pathogens, with potential applications in various industries, including pharmaceuticals, personal care products, and water treatment.

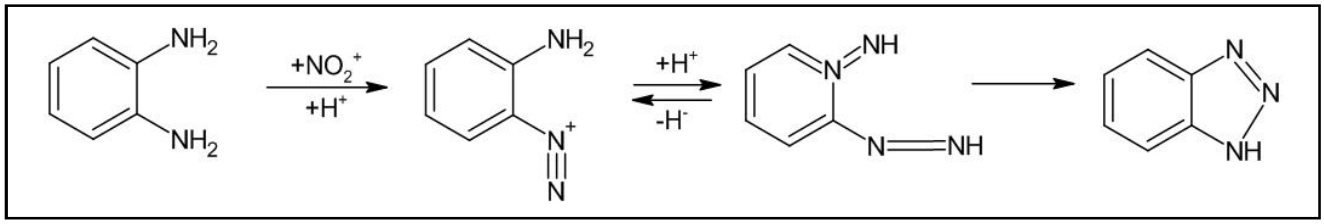
Table 1: Profile of benzotriazole

S.No.	Properties	Values
1	Molecular formula	$C_6H_5N_3$
2	Molecular weight	119.13
3	miLogP	1.29
4	TPSA	41.58
5	Natoms	9
6	Count of acceptors of hydrogen bonds	2
7	Count of donors of hydrogen bonds	1

2. Synthesis

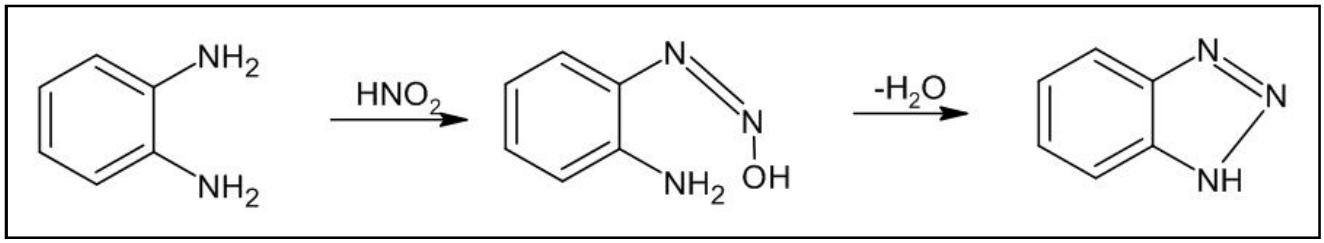
2.1 Scheme-I

Benzotriazoles are produced through the cyclocondensation of o-phenylenediamines with sodium nitrite in acetic acid. The process involves heating the reagents together. The diamine is transformed into the mono-diazonium derivative, which then undergoes spontaneous cyclization.



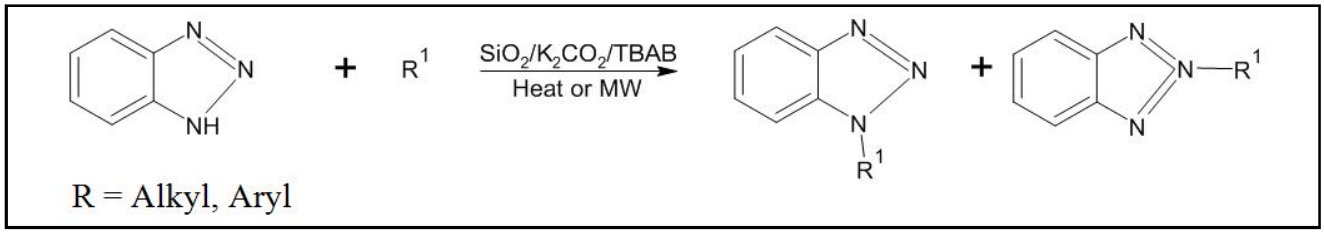
2.2 Scheme-II

Describes the direct preparation of 1,2,3-benzotriazole through two main routes. Firstly, it is synthesized directly by subjecting nitrous acid to o-phenylenediamine. Secondly, it is obtained through the hydrolysis of an acylated or arylated benzotriazole, previously formed by treating nitrous acid with the corresponding monoacylated or arylated o-phenylenediamine. This direct approach yields higher overall yields compared to methods involving multiple intermediate steps.



2.3 Scheme-III

The N-alkylation of benzotriazole can be efficiently and selectively achieved under solvent-free conditions using a straightforward method. The process involves the use of SiO_2, K_2CO_3, and tetrabutylammonium bromide (TBAB) under both thermal and microwave conditions. This technique results in the regioselective formation of 1-alkyl benzotriazoles with moderate to high yields and in a short duration.



3. Benzotriazole and its pharmacological activities

The pharmacological properties of benzotriazole include antimicrobial, antifungal, anti-inflammatory, antioxidant, anthelminthic, antibacterial and anticancer activity (Figure 3) (Afroz Patan *et al.,* 2023). Marketed drugs of benzotriazole: vorozole, alizapride.

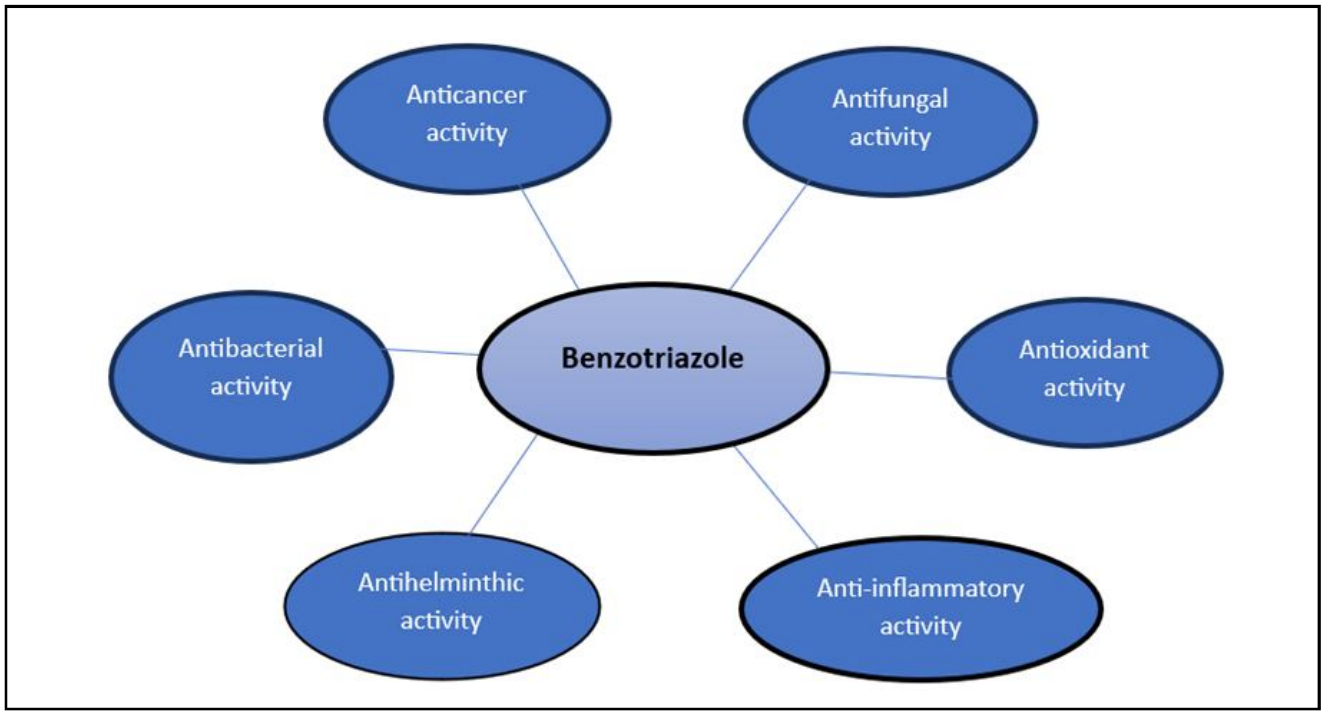
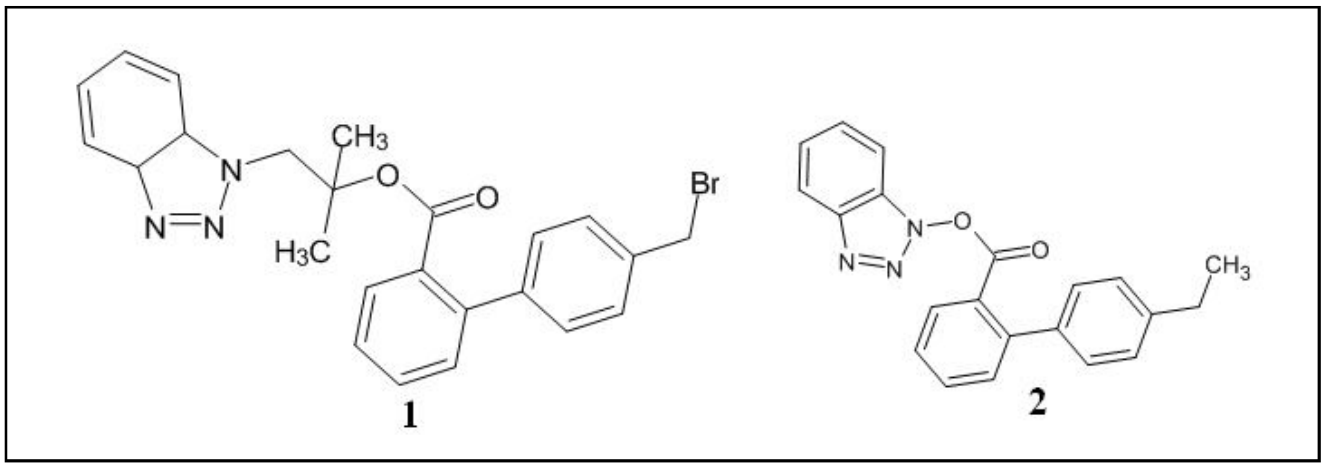


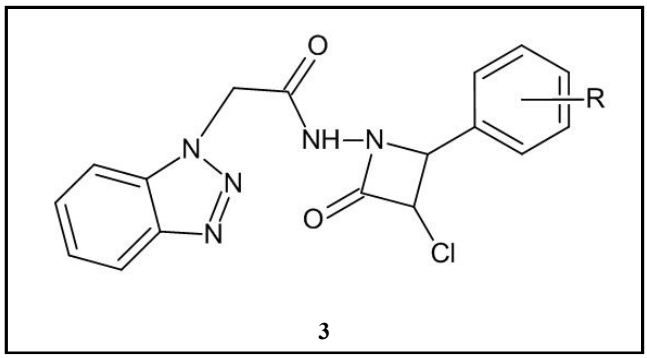
Figure 3: Various pharmacological activities of benzotriazole.

3.1 Antimicrobial activity of benzotriazole nucleus

Microwave-assisted solvent-free synthesis of n-alkyl benzotriazole derivatives and their antimicrobial Studies was researched by Raghu Ningegowda *et al.* (2009). Many new N-alkylated benzotriazole derivatives with pharmaceutically relevant substituted biphenyl and benzyl halides were synthesized to further elucidate the structural activity connection between the chemistry and antibacterial activity. The synthesised compound's *in vitro* antibacterial activities were evaluated by testing them against a panel of susceptible and resistant Gram-positive and Gram-negative bacteria using MIC deter-mination. It is noteworthy to notice that compounds 1 and 2 showed double the antibacterial activity.

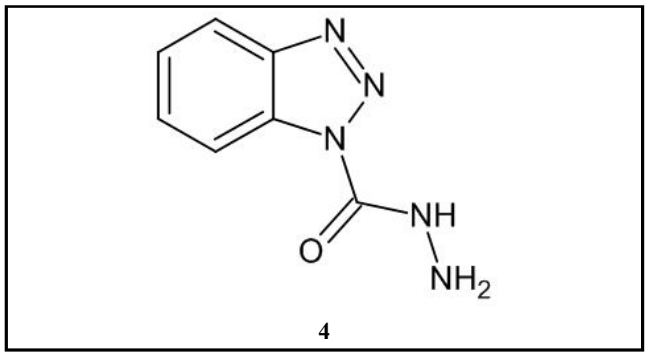


A study was conducted by Ranza Elrayess *et al.* (2013) on the synthesis and antimicrobial activities of novel derivatives of benzotriazole and benzimidazole that include the β-lactam moiety. A new class of β-lactam-containing compounds, such as benzotriazole and benzimidazole, has been created. The study used analytical and spectral data to describe freshly produced chemicals. The compounds were tested *in vitro* for antibacterial activity against several Gram-positive and Gram-negative bacteria and *Candida albicans* strains. Compound **3** exhibited strong antibacterial activity; however, none demonstrated anticandida action. The work emphasizes the significance of knowing the β-lactam moiety in benzimidazole and benzotriazole derivatives for their possible antibacterial activities.



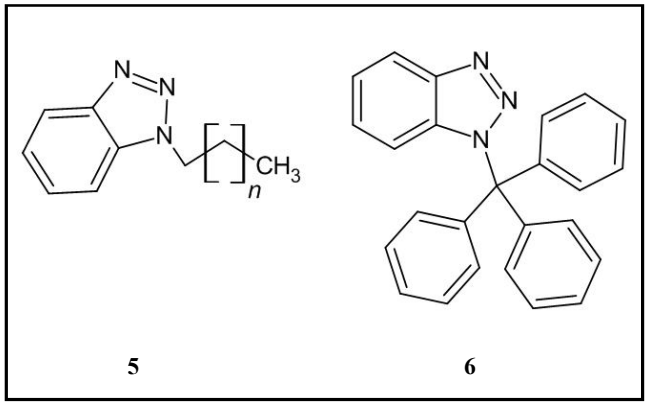
3

Mahesh Chand *et al.* (2018) investigated the synthesis, antibacterial, and antioxidant properties of hybrid compounds combining benzotriazole and 1,2,4-triazole. Eleven novel 1,2,4-triazolyl benzotriazoles were synthesized by using 1-(hydrazinyl carbonyl-methyl)-1H-benzotriazole as a powerful intermediary. The compounds were characterized using mass spectrometry, ^{1}H NMR, ^{13}C NMR, and infrared spectra. Their antibacterial effectiveness *in vitro* against four fungal strains and seven bacterial strains was evaluated. Compounds **4** were more effective than miconazole against the *Aspergillus niger* strain and exhibited equivalent antibacterial activity against *Klebsiella pneumonia*.



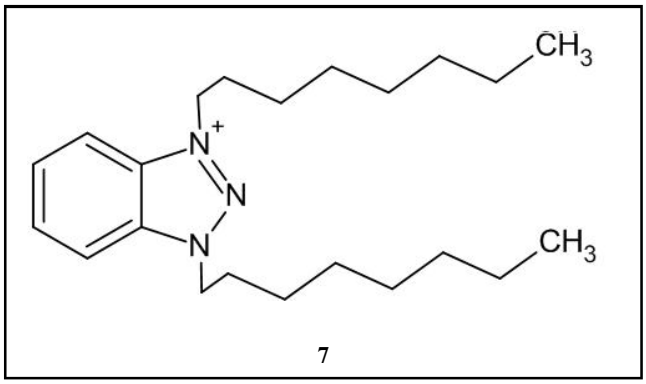
4

Zahra Rezaei *et al.* (2009) investigated the design, synthesis, and antifungal properties of triazole and benzotriazole compounds. A series of novel benzo triazole derivatives are synthesised as cytochrome P450 14a-demethylase (14DM) inhibitors. The chemical structures of the newly discovered compounds were verified using elemental and spectral (^{1}H NMR, ^{13}C NMR, and Mass) analysis. Compounds 5 and 6 were created by building a virtual library of compounds and docking them to the enzyme's active site. They were also shown to be active *in vitro* against *C. albicans*.



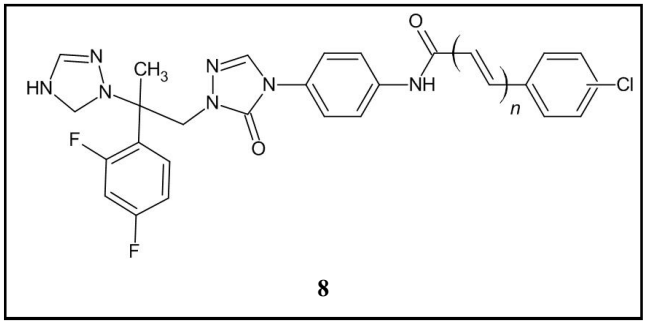
5 **6**

Tajudeen Jimoh *et al.* (2022) conducted a molecular docking study on certain benzotriazole and benzimidazole derivatives used as antifungal agents against candida species. The synthesized chemicals were evaluated *in vitro* against several fungi. The generated compounds were matched with CYP51, a member of the cytochrome P450 family 51 sub-family A (PDB ID: 5JLC), to determine the best conformation and orientation for maximizing and minimizing energy. MICs ranged from 25 to 50 g/ml, and inhibitory zones from 24 to 37 mm, indicating that seven benzotriazole and benzimidazole derivatives had diverse degrees of efficacy against various species of Candida. During the molecular docking experiment, compounds that were synthesized with target CYP51 are classified as members of the cytochrome P450 family 51 sub-family A (PDB ID: 5JLC). A docking value of -22.73 was marginally lower than that of the conventional medicine, fluconazole, when 1,3-dioctyl-1H-benzimidazol-3-ium was docked with CYP 51 and PDB ID: 5JLC. According to the p-value of 0.018099, which is less than 0.05, derived from an ANOVA analysis of the zone of inhibition, compound 5 was shown to be the most active against the Candida species. Compound **7**, 1,3-dioctyl-1H-benzimidazol-3-ium, was shown to have the greatest antifungal activity against *C. stellatoidea*.



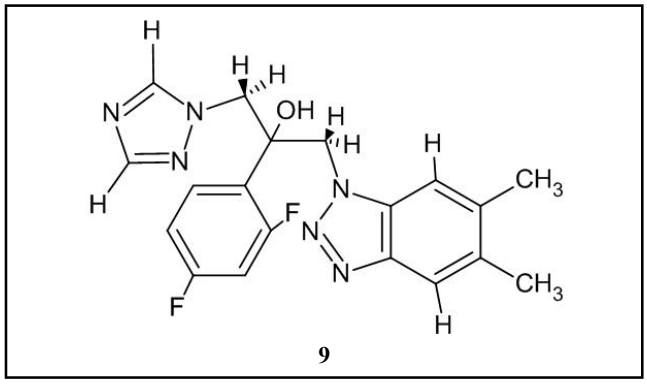
7

Yongwei Jiang *et al.* (2011) investigated the synthesis, molecular docking, and *in vitro* assessment of novel triazole derivatives as antifungal drugs. Based on the active site of lanosterol 14a-demethylase from *C. albicans* (CACYP51), a series of 1-(2-(2,4-fluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl)-1H-1,2,4-triazol-5(4H)-one derivatives were synthesized as fluconazole analogues. *In vitro*, substance **8** had some degree of action against eight human pathogenic fungi, and several of them exhibited better antifungal activity against *C. albicans* than the reference medication fluconazole. Flexible molecular docking was used to analyze the structure-activity relationships (SARs) of the target molecules. The suggested chemicals interact with CACYP51 by hydrogen bonding, van der Waals, and hydrophobic interactions.



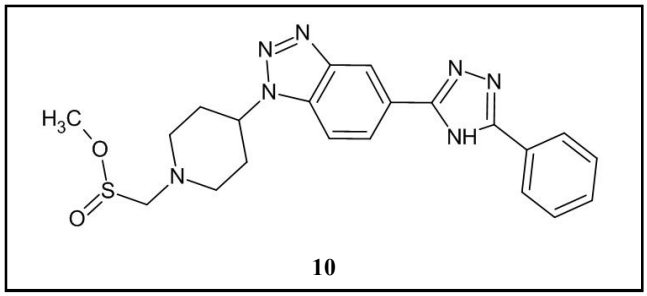
8

The design, synthesis, and antifungal activity of 5(6)-substituted benzotriazoles were investigated by Pallav Patel *et al.* (2010). To identify inhibitors that are effective against both Candida and Aspergillus spp., a series of 5(6)-(un) substituted benzotriazole analogues, designated by compounds 3a–3h and 3b–3f, were prepared using crystalline oxirane intermediate 1 that has previously been synthesized in our lab. Each medication's inhibitory action against several Aspergillus and Candida species was evaluated. With MICs ranging from 1.6 mg/ml to 25 mg/ml and 12.5 mg/ml to 25 mg/ml, respectively, the five compounds which are derivatives of 5,6-dimethylbenzotriazol-2-yl, 5-chlorobenzotriazol-1-yl, and 6-methylbenzotriazol-1-yl (**9**) showed strong antifungal activity against *A. niger* and Candida spp. This work covers the design, synthesis, regioisomer characterization (using COSY and NOESY 2D-NMR spectroscopy and single molecule X-ray crystallography), antifungal evaluation, molecular docking, and structure-activity relationships of the various 5(6)-(un)substituted benzotriazole analogues.



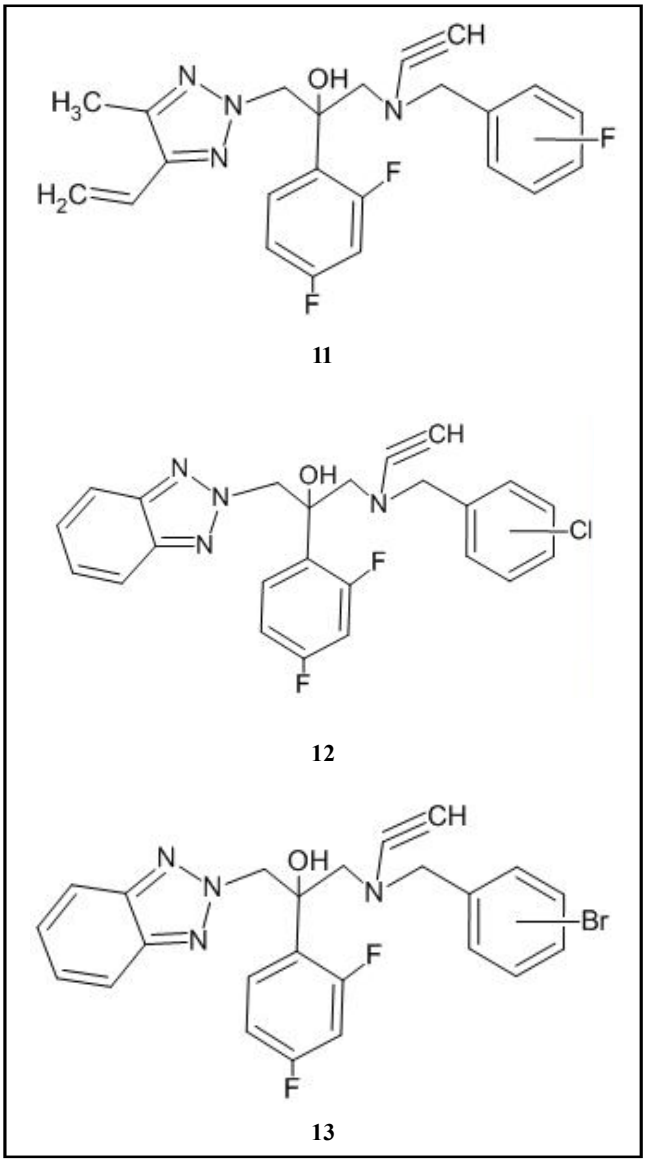
9

The synthesis, docking study, and antifungal activity of many new 1,2,4-triazoles were investigated by Jaiprakash Sangshetti *et al.* (2011). Using ZrO-Cl2•8H_2O as a catalyst, it has been reported how to synthesise a novel series of 1,2,4-triazoles containing 1,2,3-triazoles and piperidine rings in ethanol. Between 80 and 85% of the yields were obtained. To evaluate the *in vitro* antifungal activity of each of the generated compounds, the standard agar technique was employed. Following a docking study, the newly synthesized compound **10** was shown to all bind identically to the active site of the fungal enzyme P450 cytochrome lanosterol 14a-demethylase.



10

Zhongjun Guan *et al.* (2010) investigated the biological evaluation, molecular docking, and synthesis of novel triazole derivatives as antifungal agents. Compounds 1av and 2af represent twenty-eight novel triazole derivatives that have been synthesized for application in structure-activity relationship studies as antifungal agents. To construct the compounds, the fluconazole structure and the molecular modelling of the cytochrome P450 14a demethylase (CYP51) active site were utilized. For the first time, all of them are being reported. Their chemical structures are characterized by elemental analysis, LCMS, ^{13}C NMR, and ^{1}H NMR. The antifungal activity has been evaluated in vitro using minimum inhibitory concentrations, or MICs. Compound 11 showed higher efficacy than fluconazole (FCZ) against nearly all investigated fungi, except *A. fumigatus*.



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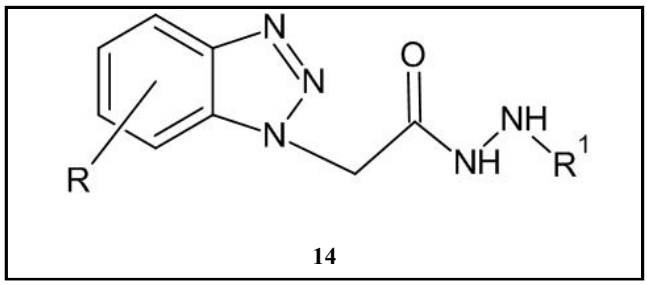
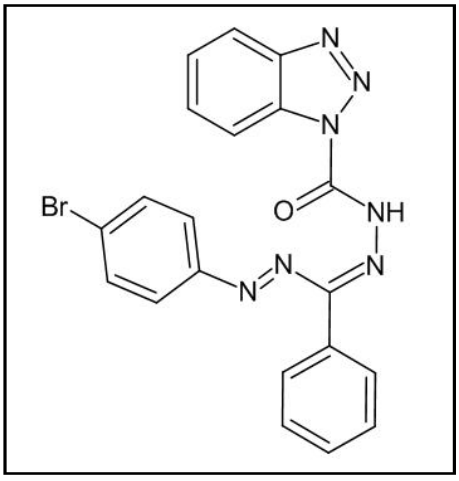
13

Suma *et al.* (2012) investigated the production and antibacterial properties of many novel 1, 2, and 3 benzotriazole derivatives that include moieties of pyrazolidinedione. The goal of this study was to create substituted benzotriazole derivatives with moieties of pyrazilidin-3,5dione. The compounds underwent diazotization, anhydrous potassium carbonate and ethyl chloroacetate treatment, and diethyl propanedioate condensing. Elements analysis, mass spectroscopy, ^{1}H-NMR, and infrared spectroscopy were used to describe the compounds. The cup plate diffusion technique was utilized to assess the antibacterial activity. Comparing the compounds 14 to ciprofloxacin and amoxicillin, they demonstrated strong antibacterial action against *Proteus vulgaris,* as well as antifungal efficacy against *A. niger* and *C. albicans*.



14

The antibacterial activity of several more recent 1,2,3-benzotriazole compounds produced by ultrasonication in solvent-free conditions was investigated by Muvvala *et al.* (2014). The chemical and pharmaceutical industries are placing an increasing amount of emphasis on reducing waste from conventional synthetic procedures. This effort involved the synthesis of new 1,2,3-benzotriazole compounds using ultrasonication and no solvents. The resulting chemicals were separated and described using spectral analysis. The antibacterial qualities of these compounds were evaluated against a variety of bacterial strains using the paper disc diffusion method. Some of the compounds 15 that were created showed remarkable effectiveness against a variety of bacteria.



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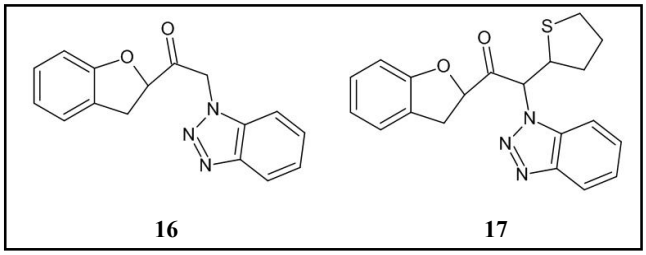
3.2 Anti-inflammatory activity of benzotriazole nucleus

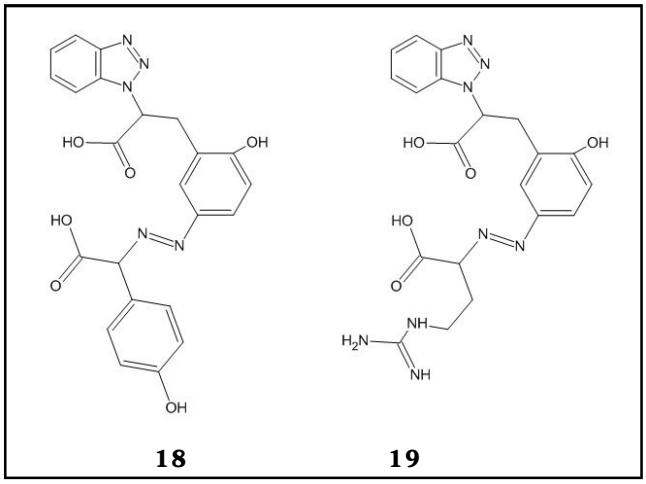
The synthesis and pharmacological assessment of many new benzotriazole derivatives containing pyrazolidinedione moieties were investigated by Suma *et al.* (2012). The effort aims to create novel benzotriazole compounds containing pyrazolidine dione moieties using refluxation, stirring, alkylation, and diazotization processes. For the n=8 derivatives, IR, ^{1}H NMR, and mass spectrum analysis were employed. With a percentage yield ranging from 71.43% to 88.06%, the compounds demonstrated significant analgesic and anti-inflammatory activities *in vivo* when compared to tramadol and indomethacin. To ensure purity, TLC was employed after the components were evaluated.

Kamal M. Dawood *et al.* (2006) investigated the synthesis, anticonvulsant, and anti-inflammatory properties of several novel heterocycles based on benzotriazole and benzofuran. By combining 2-bromoacetylbenzofuran with 1H-benzotriazole, 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)ethanone was created. The proper thioacetanilide derivatives were then produced by this ethanone's reaction with phenylisothiocyanate. Hydrazonoyl chlorides were used to treat the later ethanone and thioacetanilide derivatives to yield the appropriate pyrazole and 1,3,4-thiadiazole derivatives. Thiophene and thiazole derivatives were produced via the reaction between the derivative of thioacetanilide and α-haloketones and α-halodiketones, respectively. It was shown that the newly synthesized compounds **16** and **17** functioned as selective COX-2 inhibitors, with anticonvulsant and anti-inflammatory qualities.



16 17

Jamkhandi *et al.* (2015) investigated the synthesis, characterisation, and qsar assessment of derivatives of benzotriazolyl-3-{5-(carboxymethyl) diazenyl] -2-hydroxyphenyl prop-2-enoic acid. Derivatives of -2-hydroxyphenylprop-2-enoic acid synthesized by the diazonium coupling method are benzotriazol-1-yl-3-{5-[(E)-(carboxymethyl) diazenyl]. Through the intermediate molecule (2E)-2-(1H-benzotriazol-1-yl)-3-(2-hydroxyphenyl) propenoic acid, the diazonium coupling process with various amino acids yielded the five derivatives, spanning from Ie to Ve. Mass spectrum data, TLC, IR, NMR, and physical and chemical properties were used to characterize the generated derivatives. The potential of each derivative to lower inflammation was examined *in vitro*. To explore the quantitative structural activity relationship (qsar), a collection of response factors, including *in vitro* anti-inflammatory activity data, and predictor variables, including physicochemical qualities, were employed. According to the results, the derivatives **18** and **19** showed a noticeably high percentage of protein precipitation inhibition when compared to the standard.

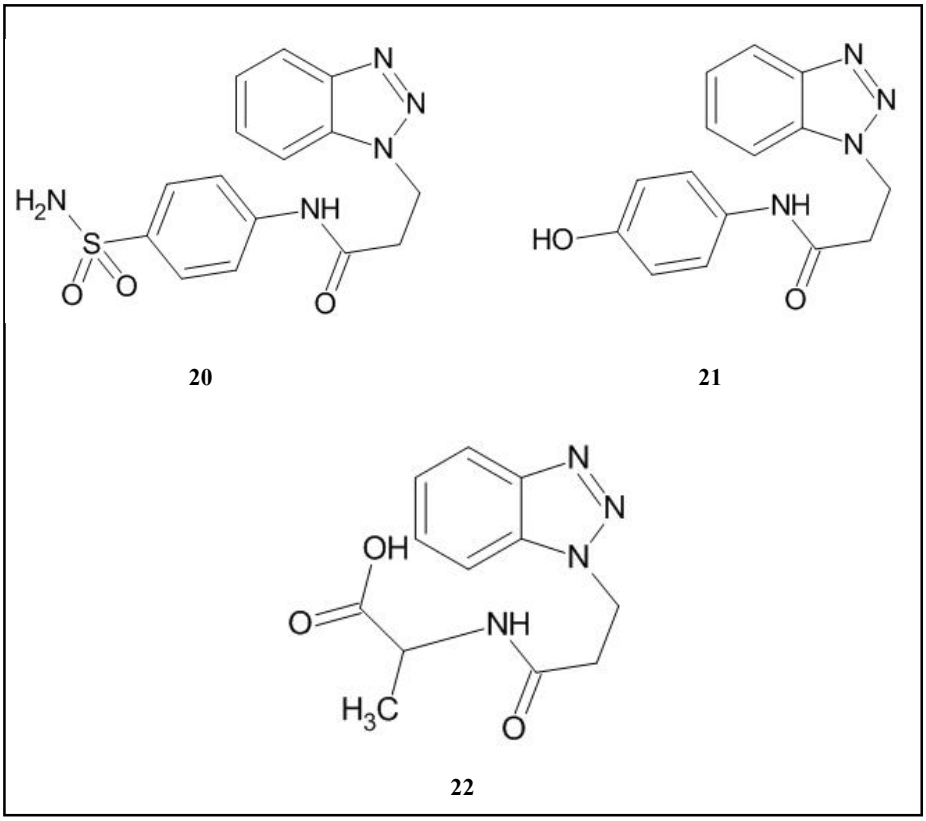


18 19

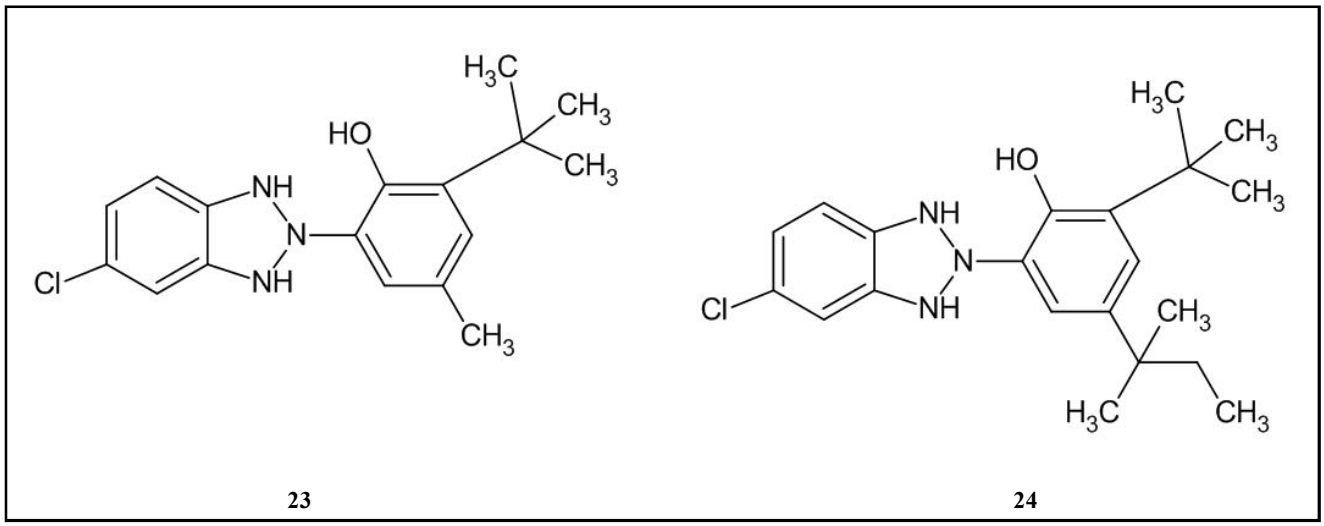
3.3 Antioxidant activity of benzotriazole nucleus

The assessment of antioxidant activity for some benzotriazole substitutes with n-phenylacetamide and acetylcarbamic acid derivatives was conducted by Jamkhandi *et al.* (2013). The antioxidant capabilities of ten benzotriazole compounds that have been replaced

with acetylcarbamic acid and N-phenylacetamide were investigated. The compounds were prepared and screened for antioxidant activity using the griess reaction test method. The compounds 20, 21, and 22 had the highest level of antioxidant activity, whilst the remaining derivatives displayed moderate activity. The data were expressed statistically.

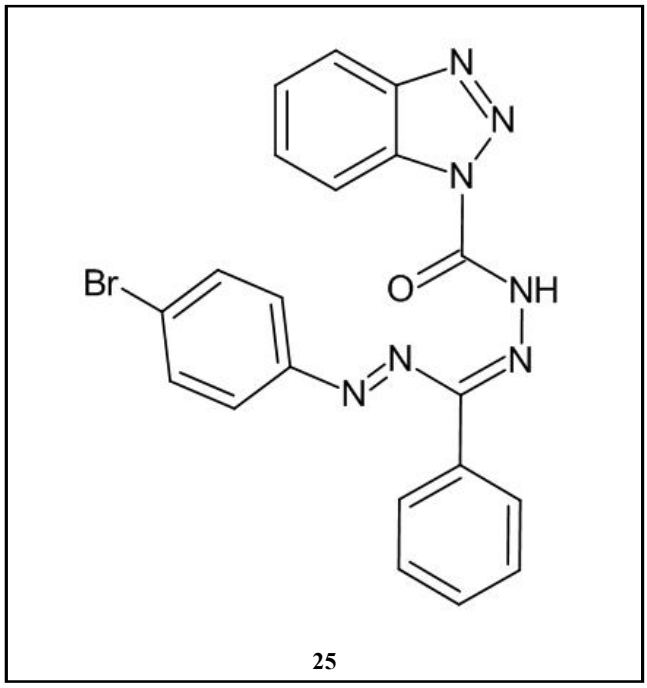


In plastic marine trash, Manviri Rani *et al.* (2017) investigated the antioxidants and benzotriazole-type UV stabilizers in their novel goods. In plastics, antioxidants and ultraviolet stabilizers (UVSs) are the most often used additives to prolong the life of polymeric materials. More and more people are becoming aware of the ways that plastic marine debris and microplastics might introduce or spread dangerous substances that could harm marine life and the ecosystem. Yet, not much is understood about the chemicals involved in plastic, particularly the additional compounds. Examined the UVSs and antioxidants in plastic garbage (23) that were collected from beaches and the corresponding new plastic items that were sold in markets (24) that were associated with food, fishing, and general usage to determine the extent of plastic pollution they were exposed to. Antioxidants were more abundant in plastic trash and new plastics than in UVSs, suggesting that antioxidants are used more frequently than UVSs.



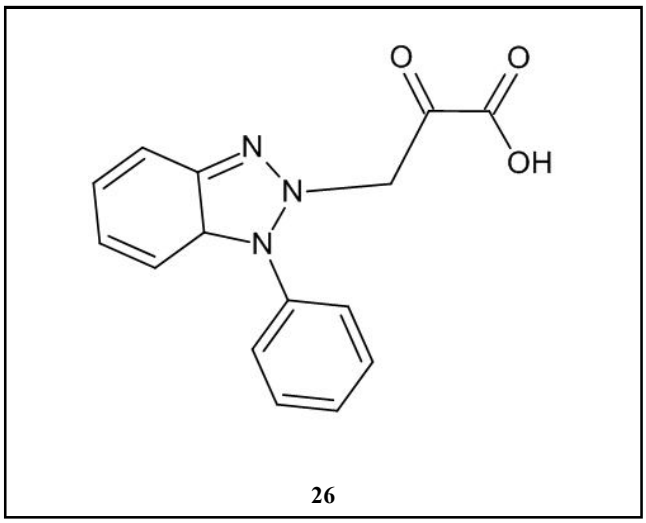
3.4 Antihelminthic activity of benzotriazole nucleus

The evaluation of the in vitro anthelmintic activity of new 1,2,3-benzotriazole derivatives synthesized in ultrasonic and solvent-free conditions was conducted by Sudhir *et al.* (2013). The anthelmintic action of compounds of benzotriazole. The novel 1,2,3-benzotriazole compounds' anthelmintic effectiveness by ultrasonication in a solvent-free environment. Newer derivatives were produced in an ultrasonic environment without the use of solvents, using "1H benzo[d][1,2,3]triazole" as the starting material. The resulting chemicals were identified and characterized using spectrum studies and melting points. All of the more recent 1,2,3-benzotriazole compounds made *via* solvent-free ultrasonic activation showed moderate to good yields, ranging from 71 to 82%. The data interpretation of the spectrum values to standard values verified the structures of the produced substances. Out of the sixteen synthetic derivatives, four compounds exhibited anthelmintic action in a dose-dependent manner, resulting in the shortest duration of paralysis and death at varying derivative concentrations. Compound **25** may have better action since it has an extra p-nitrophenyl substituent attached to the cyano group.



25

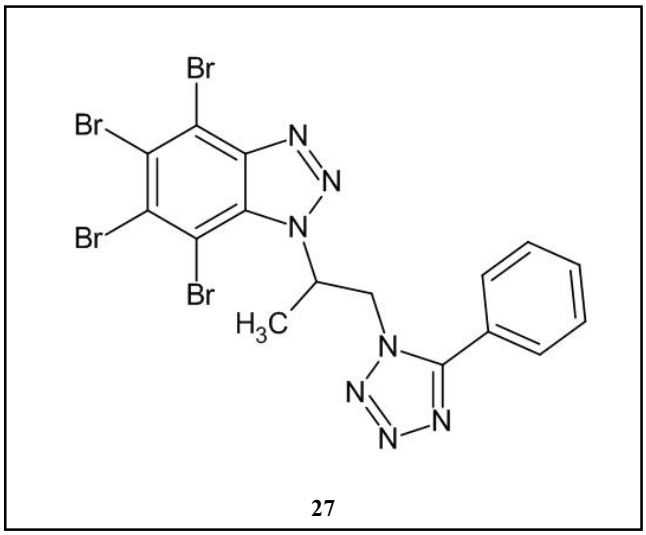
Renata Paprocka *et al.* (2022) an evaluation of the anti-inflammatory and anthelmintic effects of 1,2,4-triazole derivatives. In the process of searching for new nematicides, we examined many 1,2,4-triazole derivatives 9-22 that were generated by combining itaconic anhydride with N-(3)-substituted amidrazones. In two sets of compounds, 9-16 and 17-22, the double bond on the methacrylic acid molecule was located differently. The anti-inflammatory qualities of derivatives 12 and 19 as well as the toxicity of derivatives 9-22 were tested using peripheral blood mononuclear cells (PBMC). In PBMC cells induced by phytohemagglutinin, the antiproliferative activity of compounds 12 and 19-22 was assessed cytometrically. Compound 26 had the highest anti-inflammatory effect. Compounds 12 and 14 have the potential to be effective anthelmintic medication candidates since they showed more anthelmintic activity than albendazole.



26

3.5 Anticancer activity of benzotriazole nucleus

The synthesis of polybrominated benzotriazole and benzimidazole derivatives with a tetrazole ring and their cytotoxic action were investigated by Edyta Lukowska-Chojnacka *et al.* (2016). Numerous new benzimidazole and benzotriazole derivatives with a tetrazole moiety were produced by N-alkylating 5-aryltetrazole with 4,5,6,7-tetrabromo1-(3-chloropropyl)-1H-benzimidazole and 4,5,6,7-tetrabromo.2-a, 3-chloropropyl-2H-benzotriazole. The majority of the derivatives of 2,5-disubstituted tetrazole were generated by the regioselective procedure. All synthesised compounds were evaluated for their cytotoxicity on human recombinant casein kinase 2 alpha subunit (rhCK2a) and human T-cell lymphoblast (CCRF-CEM) and breast cancer (MCF-7) cell lines. The results have shown that several of the synthesized compounds (27) exhibited substantial cytotoxicity at micromolar doses (Shobhit Srivastava *et al.* 2022).



27

4. Discussion

Azoles, including benzotriazole derivatives, constitute a significant class of heterocyclic compounds. The imidazole ring, a common structural motif in azoles, confers biological activity. Triazoles, derived from slight modifications of the imidazole ring, exhibit improved activities and fewer adverse effects. Benzotriazole

derivatives have been extensively investigated due to their diverse biological effects. Benzotriazoles exhibit antimicrobial properties against bacteria, fungi, and parasites. Structure-activity relationship (SAR) studies enhance our understanding of their mode of action. Some benzotriazole derivatives show promise as antitumor agents. Their mechanisms of action and potential for cancer therapy warrant further exploration. Continued research on benzotriazole derivatives is essential. Exploring novel applications, optimizing SAR, and uncovering additional biological effects are crucial. Collaborations between medicinal chemists, pharmacologists, and clinicians will drive progress. In summary, benzotriazole derivatives occupy a significant place in biomedical research, offering a versatile array of biological properties. Their potential impact on antimicrobial therapy, cancer treatment, and metabolic regulation makes them an exciting area of study.

5. Conclusion

This nucleus appears to be a particularly attractive scaffold in drug discovery and development procedures since benzotriazoles are a class of bioactive heterocyclic compounds that demonstrate a wide range of biological activities. Because of their bioactivities against bacteria, fungi, inflammation, and cancer, substituted benzotriazole derivatives are widely employed in medicine. This article provides a review of several bioactivities. To gain more insight into the relationship between the target and through the use of these techniques, novel benzotriazole compounds for various purposes were investigated, providing researchers with improved ideas now underway. Researchers in medicinal chemistry may find it easier to choose the right nucleus and functions when constructing benzotriazole hybrids that are effective against a range of disorders if they conduct additional research and clinical trials to examine additional pharmacological activities, their interactions, and the degree of toxicity with other compounds. According to this review, it may be possible to synthesise a lead product that uses benzotriazole as a tagging molecule to create novel benzotriazole chemical entities with promising biological properties.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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