WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 11, 289-314. Review Article ISSN 2277–7105

UNDERSTANDING THE CHEMISTRY & PHARMACOLOGY OF BENZOTRIAZOLE IN PHARMACEUTICAL APPLICATIONS

Pratik V. Malvade*, Hemlata S. Bhawar and Vaijanti A. Medge

Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, Maharashtra, India 413736.

Article Received on
04 April 2025,

Revised on 24 April 2025,
Accepted on 14 May 2025

DOI: 10.20959/wjpr202511-36843

***Corresponding Author**
Pratik V. Malvade
Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, Maharashtra, India 413736.

ABSTRACT

Benzotriazole is a bicyclic heterocyclic compound that has important implications in medicinal chemistry due to multiple biological activities. Benzotriazole is characterized by fused benzene and triazole ring having molecular formula $C_6H_5N_3$ and provides unique electronic properties that enhance its stability and reactivity at the same time. Literature showed that wide range of pharmacological activities like antibacterial, anti-inflammatory, and anticancer properties are present with benzotriazole derivatives. Notably, some derivatives showed potent antimicrobial activity against resistant strains such as MRSA. The potential of benzotriazole derivatives to inhibit critical enzymes and modulate biological pathways positions them as promising candidates for drug development. Moreover, advances in synthetic methodologies allowed preparation of novel derivatives with improved efficacy and safety profiles. However, toxicity, bioavailability, and resistance development still continue to pose challenges in the successful application of these compounds at a clinical level. This review integrates existing information with benzotriazole derivatives concerning the synthesis, biological activities, and potential applications as therapeutic agents with its flexibility and importance in the realm of drug design. This review aims to encouragement of further research by exploring structure-activity relationships and recent advances in the field for benzotriazole's therapeutic potential across a number of disease models.

KEYWORDS: Benzotriazole, Heterocyclic Scaffold, Anticancer, anti-inflammatory, Antiviral, Antimicrobial, Drug Development.

INTRODUCTION

Benzotriazole (BZT) is an organic compound.[1] It is a bicyclic heterocyclic that exhibits the fused configuration of benzene ring and triazole ring.[2] Its molecular formula is $C_6H_5N_3$. In the compound benzotriazole, there is a bicyclic structure of a six-membered aromatic ring that is benzene ring fused with triazole ring.[1,2] This has accordingly made it acquire some unique electronic properties for enhancing its stability as well as the reactivity of this compound.[3] Benzotriazole has molecular weight of 119.12 g/mol and has a melting point ranging from 98.5°C to 100°C with a density of about 1.36 g/cm³.[1] This compound is slightly soluble in water, measured as around 2 g per 100 ml, and very soluble in organic solvents.[4] The UV absorbance of benzotriazole at a wavelength of about 286 nm, making it an excellent UV stabilizer for plastics and coatings.[5,6] Its ability to make complexes with metal ions enhances effectiveness as an inhibitor to corrosion, making it even more important in many industrial applications.[7,8]

Benzotriazole has been synthesized in late 1960s; thus, research has focused immensely on their pharmacological potency and its clinical use.[9] Throughout past decades, significant number of benzotriazole derivatives have been designed and screened for wide-range of biological activities such as antibacterial, antihypertensive, and analgesic activity.[10] On the bases of this broad scope of the biological activity has positioned the benzotriazole derivative as lead for further drugs.[10] Some of these derivatives are found to have strong antimicrobial activities against the resistant strains of bacteria, including MRSA, while others are reported to be active against several lines of tumor cells as anticancer agents.[11] More study of these derivatives is leading to newer pharmacological properties that can be used in search of useful therapeutic agents capable of treating several different diseases.[1,4]

Benzotriazole derivatives are reported to have broad-ranging biological activities that might promise some applications in pharmacy. Indeed, from the literature, there is antibacterial activity against not only Gram-positive but also Gram-negative bacteria, also some derivatives show activity against MRSA, a pathogen known for very challenging treatment due to its resistance to antibiotics.[12,13] In addition, it has also been noted that these drugs have antifungal action against some pathogens such as Candida species and Aspergillus species, thereby making them indispensable in clinical cases where opportunistic infections are common.[14,15] Apart from the antimicrobial effects, benzotriazoles also exhibit anti-inflammatory action, where they inhibit critical inflammatory mediators involved in chronic

inflammation and hence can be used in managing diseases like rheumatoid arthritis.[6] Besides, they also contribute positively to cardiovascular health due to promotion of vasodilation and reduction in blood pressure levels.[16]

Benzotriazole derivatives are important in drug discovery process due to pharmacological activities and structural flexibility. Scientists have been investigating new approaches toward the therapeutic management of complex diseases such as cancer, and benzotriazoles are promising templates for developing drugs with better efficacy and safety profiles.[17] Because benzotriazoles can serve as bioisosteres of all functional groups commonly encountered in pharmaceutical agents, medicinal chemists can modulate already developed lead compounds by replacing the less favorable groups with a benzotriazole while keeping or enhancing biological activity.[18]

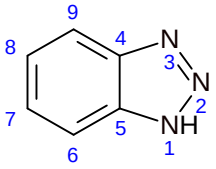
This review shall be a completely integrated summary, combining systematically the synthesis, biological activities, and medicinal use of benzotriazole derivatives, with recent advances made in the field, and seeks to merge contemporary knowledge pertaining to the pharmacological effects of this class of compounds across various disease models via focusing on the analysis of structural changes directed toward enhancing therapeutic effects. The third crucial objective is to look into SAR in respect of benzotriazole derivatives to understand the kind of structural changes would affect the biological activity. This will, in turn allow scientists to develop better drugs that possess higher pharmacokinetic profiles. The review seeks to give insight to the significance of benzotriazole holds in medicinal chemistry and will encourage further research into therapeutic applications.

STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF BENZOTRIAZOLE

The SAR is one of the most crucial principles in medicinal chemistry, considering that it deals with how the chemical structure is related to biological activity.[19] Knowing SAR allows researchers to design better pharmaceuticals through changes in molecular structure, which can make the good properties better and adverse effects worse.[19]

Biological efficiency according to chemical composition

The benzotriazole derivatives have very wide ranges of biological activities highly susceptible to the chemical structure. Even the minute variation in the substituents of the benzotriazole nucleus can result in major activity differences between the compounds for different biological targets.



1*H*-benzotriazole

1. Substituent Effects

Electron-Withdrawing Groups (EWGs): The presence of EWGs, as evidenced by trifluoromethyl groups at specific positions, such as C-2, was found to greatly increase antibacterial activity. For example, trifluoromethyl-substituted analogues were found to possess antibacterial activities comparable to that of established drugs, such as nitrofurantoin.[20,21]

Electron-Donating Groups (EDGs): On the other hand, EDGs can also influence the solubility and bioavailability.[22] The biological fluids' solubility increases with the alkyl or alkoxy-substituted compounds and thus enhances their pharmacokinetic profiles.[23]

Aromatic Systems: The incorporation of additional aromatic rings or heterocycles into the benzotriazole framework can lead to enhanced interactions with target proteins, both through π-π stacking and hydrophobic interactions. This structural modification has been exploited in the synthesis of highly potent anticancer agents.[24]

2. Simple Changes

Such modification of the benzotriazole core might produce derivative compounds with superior biological activities:

- Fused Ring Systems: Some documented studies can demonstrate attaching benzotriazole onto alternative heterocyclic structures significantly alters the mechanism but enhances the efficacy with specific pathogens.[25]
- Alkylation and Acylation: The introduction of alkyl or acyl groups at various positions on the benzotriazole ring can fine-tune the biological activity by affecting lipophilicity and steric hindrance.[26]

3. Methods of computation in SAR research

Advances in computational chemistry have now allowed for the study of SAR through predictive tools that indicate how structural changes will affect biological activity:

Molecular Docking: This tool provides insights into how different benzotriazole derivatives interact with target proteins at an atomic level and what binding affinity and mode of action could be involved.[27]

QSAR models describe the quantitative correlation between chemical structures and biological activities that will enable the identification of important structural characteristics responsible for the desired effects.[27]

SYNTHESIS OF BENZOTRIAZOLE

1. Cyclo-Condensation Reactions

a. Some of the major importance in benzotriazole synthesis relates to its synthesis with the employment of o-phenylenediamines and sodium nitrite.[28] It commonly proceeds starting with diazotization of o-phenylenediamine; under acidic medium, one of the amines is changed over into a diazonium salt with the employment of sodium nitrite. Normally conducted at temperatures around 5-10 °C. The aim of this method was to suppress side reactions. Following diazotization, heating of the reaction mixture serves to facilitate cyclization into benzotriazole. In most of the syntheses involving diazotization as a step, substitution of variables concerning reaction, especially temperature, affects not only yields but purity too.[25]

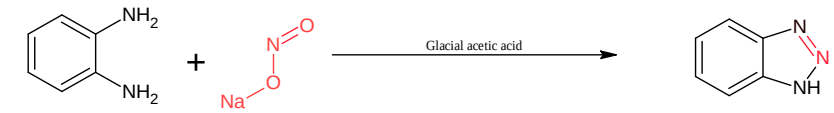
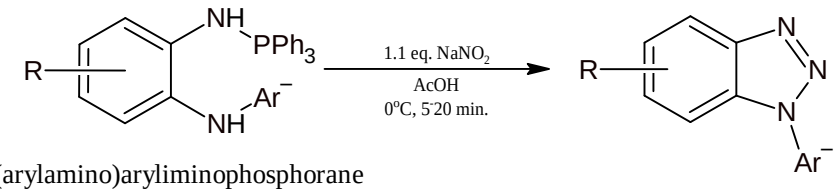


Fig. 1: Cyclo-condensation synthesis of Benzotriazole.

b. The synthesis of benzotriazole using N-Phenyl-2-[(triphenyl-lambda^5-phosphanylidene)amino]aniline involves a multi-step reaction process. Initially, the N-phenyl compound and sodium nitrite reacted in presence of acid to form a diazonium salt.[29] This salt then undergoes cyclization under controlled conditions, typically involving heating and pressure, which facilitates the formation of benzotriazole. The reaction conditions are critical, as they influence the yield and purity of the final product.[29] Following the cyclization, the mixture is cooled, and the pH is adjusted to separate the desired benzotriazole from by-products.

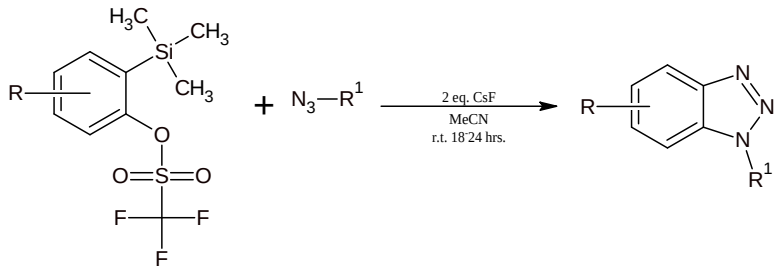


2-(arylamino)aryliminophosphorane

Fig. 2: Cyclo-condensation using N-Phenyl-2-[(triphenyl-lambda^5-phosphanylidene)amino]aniline.

2. [3 + 2] cycloaddition reaction with azides

The synthesis of benzotriazole using 2-(trimethylsilyl)phenyl triflate involves a [3 + 2] cycloaddition reaction with azides.[30] Initially, 2-(trimethylsilyl)phenyl triflate is reacted with azides in the presence of cesium fluoride (CsF), typically in acetonitrile (MeCN) at elevated temperatures.[31] The reaction conditions are optimized for yield, with reports indicating yields of around 60% to 76% depending on the specific azide and experimental setup used. The process effectively generates benzyne intermediates, which then react with azides to form benzotriazoles.[32] This method is noted for its efficiency and compatibility with various functional groups, making it a valuable route in synthetic organic chemistry for producing substituted benzotriazoles.

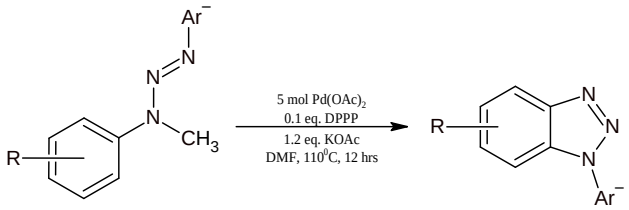


2-(Trimethylsilyl)phenyl Triflate

Fig. 3. [3 + 2] cycloaddition reaction with azides.

3. Diazotization Reaction

Benzotriazole can be synthesized using 1,3-diphenyl-3-methyltriazene through a diazotization reaction.[33] The process begins with the preparation of 1,3-diphenyl-3-methyltriazene, which is then treated with nitrous acid generated from sodium nitrite and an acid, leading to the formation of a diazonium salt.[34] This diazonium salt undergoes cyclization, typically facilitated by heating or under acidic conditions, resulting in the formation of benzotriazole.[33]



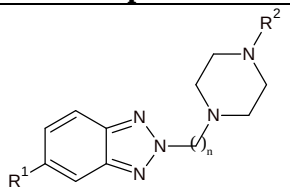
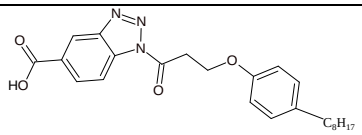
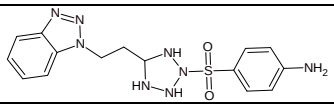
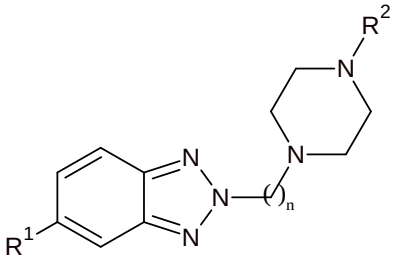
1,3-Diphenyl-3-methyltriazene

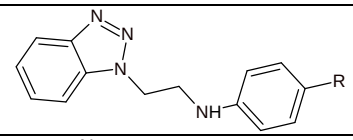
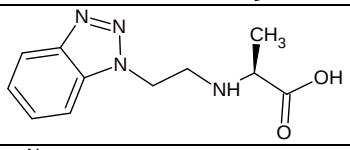
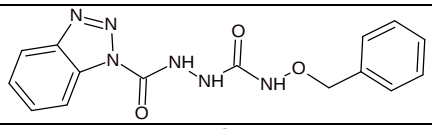
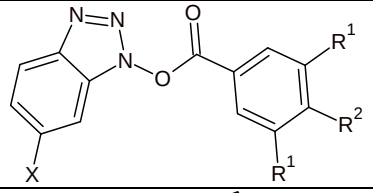
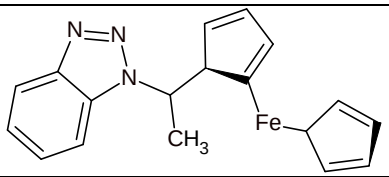
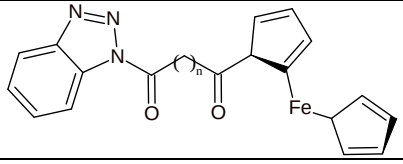
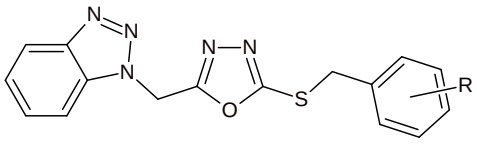
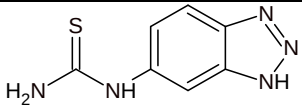
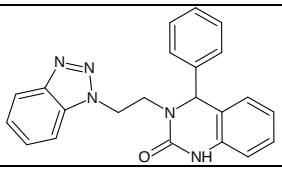
Fig. 4: Benzotriazole through a diazotization reaction.

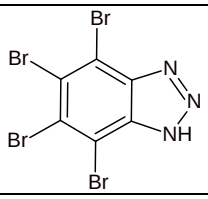
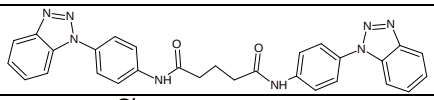
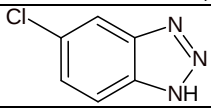
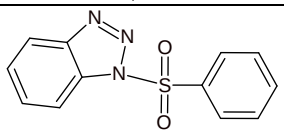
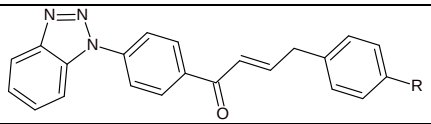
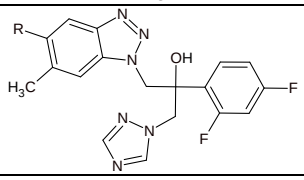
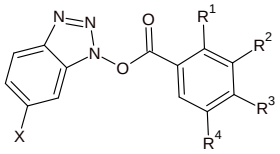
BIOLOGICAL ACTIVITIES OF BENZOTRIAZOLE

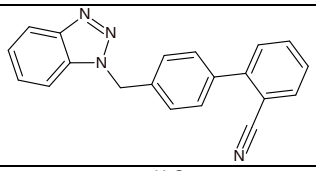
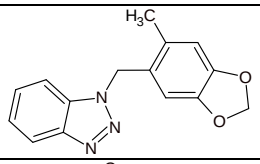
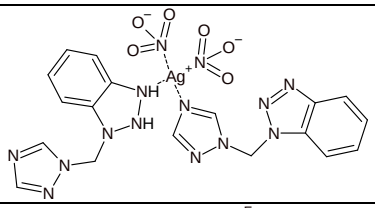
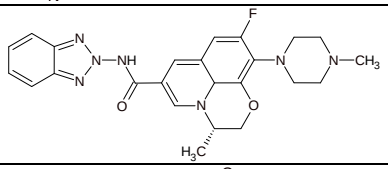
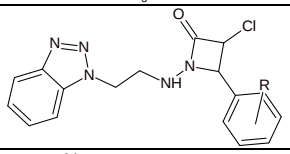
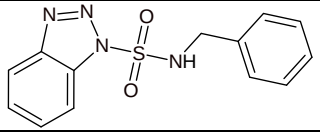
Benzotriazole derivatives have been very well researched concerning their multifaceted biological activities and have gained an important position in a variety of therapeutic conditions.[25] The importance of benzotriazole in medicinal chemistry is evident through its flexibility in the pharmaceutical design process because it has allowed the creation of new drugs for most diseases and disorders. In fact, the already done research continues to study and enhance the biomedical applications of benzotriazole derivatives.[35]

Table 1: Benzotriazole Derivatives having various activities.

Activity	Compounds	Substitutions
Anthelmintic agents.[36,37]		Ar = Ph, X = $C_6H_4NO_2$ Ar = C_4H_3O, X = $C_6H_4NO_2$ Ar = $C_6H_4NO_2$, X = $C_6H_4NO_2$ Ar = C_6H_4Cl, X = $C_6H_4NO_2$
Anti-inflammatory Agents[38]		
		
Antipsychotics[39]		R^1 = OMe, R^2 = Ph, n=2 R^1 = OMe, R^2 = Ph, n=3 R^1 = OMe, R^2 = 2-$MeOC_6H_4$, n=2 R^1 = OMe, R^2 = 3-$MeOC_6H_4$, n=3 R^1 = Cl, R^2 = Ph, n=2 R^1 = Cl, R^2 = Ph, n=3 R^1 = Cl, R^2 = 2-$MeOC_6H_4$, n=2 R^1 = Cl, R^2 = 3-$MeOC_6H_4$, n=3 R^1 = H, R^2 = 2-Pyrimidinyl, n=2 R^1 = H, R^2 = 2-Pyrimidinyl,

		n=3 R^1 = H, R^2 = 2-Pyrimidinyl, n=4 R^1 = H, R^2 = 3-$CF_3C_6H_4$, n=3
Antioxidant[39,40]		R = SO_2NH_2 R = OH
		
		
Anticancer[41,42]		X = H, R^1, R^2 = H X = H, R^1 = H, R^2 = OH
		
		n = 2 n = 3
		R = 2-F R = 2-Cl R = 2-Br R = 2-Me R = 2-OMe R = 2NO_2 R = 3-F R = 3-Cl R = 3-Br R = 3-Me R = 3-OMe R = 3-NO_2 R = 4-F
Antiviral[43,44]		
		

		
		
Antiparasitic[45]		
		
		R = OMe R = Cl
Antifungal[46,47]		R = H R = Me
		X = H, R^1, R^2, R^3, R^4 = H X = H, R^1, R^2, R^4 = H, R^3 = NO_2 X = H, R^1, R^3, R^4 = H, R^2 = NO_2 X = H, R^1 = Cl, R^2, R^3, R^4 = H X = H, R^1, R^2, R^4 = H, R^3 = Cl X = H, R^1, R^3 = H, R^2, R^4 = NO_2 X = H, R^1, R^3, R^4 = H, R^2 = Me X = H, R^1, R^3, R^4 = H, R^2 = OMe X = Cl, R^1, R^2, R^3, R^4 = H X = Cl, R^1 = Me, R^2, R^3, R^4 = H X = Cl, R^1, R^2, R^4 = H, R^3 = NO_2 X = Cl, R^1, R^3, R^4 = H, R^2 = NO_2 X = Cl, R^1 = Cl R^2, R^3, R^4 = H X = Cl, R^1, R^2, R^4 = H, R^3 = Cl

		
		
		
Antibacterial[48,49]		
		R = 4-NO_2 R = 2-NO_2
Protozoan Inhibitor		

A) Antimicrobial Activities

Benzotriazole derivatives exhibit significant antimicrobial activities, making them valuable in combating various pathogens.[50] These compounds have been shown to possess antimicrobial properties, which are critical in development of new therapeutic agents.[51]

1. Antibacterial Activity

Researchers studied the antibacterial activity of benzotriazole analogues, revealing their effectiveness against range of bacterial strains, like *Escherichia coli*.[52] *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.[50] Structural modifications, such as the introduction of electron-withdrawing groups, enhance their antibacterial potency. For instance, triazolo[4,5-f]-quinolinone carboxylic acids containing benzotriazole moiety have given notable antibacterial action.[53,54] Synthesis of 5-halogenomethylsulfonyl-benzotriazoles has been reported, which exhibited excellent antibacterial activity, including MRSA.[55] The MIC values of these compounds were in a comparable range to that of known antibiotics, such as nitrofurantoin. Another series of oxazolidinone derivatives bearing benzotriazoles was found to be active against resistant strains, with MIC values of down to 0.25–0.125 µg/mL.[56]

2. Protozoan Inhibitor

N-benzenesulfonylbenzotriazoles were examined for their promising anti-trypanosomal activity against *Trypanosoma cruzi* with dose-dependent inhibitory effects on epimastigote forms.[57] They are of interest for the treatment of Chagas disease.

3. Antiviral Activity

Benzotriazole derivatives have been used as antiviral compounds against the viral protease necessary for the replication process of viruses. Some compounds were established selective against coxsackievirus B5 (CVB5) with their range, EC50 in the magnitude of 6-52 µM.[58] Unsubstituted benzotriazoles have been described to be selective for the replicase and have an EC50 3 µM for BVDV.[58,59] For example, bis-benzotriazole-dicarboxamide derivatives have been shown to inhibit poliovirus helicase, demonstrating their potential as antiviral agents against picornaviruses.[60]

A. Anticancer Properties

Benzotriazole Derivatives Fused with Quinolone Skeletons Have Improved Anticancer Activities due to Enhanced Interaction with Tubulin and Disruption of Mitosis in Cancer Cells.[41] For instance, some compounds shown remarkable antiproliferative effects against breast cancer (MCF-7), leukemia (HL-60), and colon cancer (HCT-116) cell lines.[61] This compound acts by inhibiting tubulin polymerization and promoting apoptosis through modulation of pro-apoptotic and anti-apoptotic proteins.[62]

a) Vorozole

Vorozole is a triazole-derived competitive aromatase inhibitor, which is involved in biosynthesis of estrogen. It has been investigated clinically as an antineoplastic agent in postmenopausal women with advanced breast cancer.[63] Clinical studies concluded that vorozole markedly lowered plasma estradiol levels by about 90% and produced objective responses in as many as 35% of the patients treated. In phase II studies, clinical efficacy was favorable to aminoglutethimide and megestrol acetate but improved the quality of life than did that of aminoglutethimide.[64] However, being withdrawn from further testing due to lack of significant difference in median survival versus other treatments, vorozole typifies the potential in oncology of benzotriazole derivatives.[65]

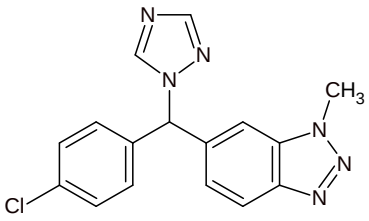


Fig. 5. Structure of Vorozole.

B. Anti-inflammatory and Analgesic Effects

Research indicates that certain benzotriazole compounds can reduce inflammation by inhibiting pro-inflammatory cytokines and enzymes responsible for inflammation.[66] Structural modifications that improved receptor selectivity for anti-inflammatory agents those can depress pro-inflammatory cytokine synthesis with minimal side effects.[67]

Mechanisms Involved in Anti-inflammatory Action

The mechanisms through which benzotriazole derivatives exert anti-inflammatory effects include:

- Inhibition of Cytokine Production: These compounds can suppress production of pro-inflammatory cytokines like TNF-alpha and IL-6.[68]
- Blocking Enzyme Activity: Benzotriazole derivatives may inhibit cyclooxygenase (COX) enzymes that are pivotal in the inflammatory response.[23]
- Modulation of Immune Response: By affecting immune cell signaling pathways, these compounds can help modulate the body's inflammatory response.[69]

PHARMACODYNAMICS: DRUG INTERACTION WITH BIOLOGICAL TARGETS

Pharmacodynamics is the study of the effects that drugs exert on biological systems, with particular emphasis on mechanisms of action and interactions with biological targets, including enzymes and receptors. In this regard, benzotriazole derivatives have emerged as significant compounds, manifesting a wide range of pharmacological activities resulting from their ability to interact with multiple biological targets.

A. Interaction with Enzymes

Benzotriazole derivatives are generally known as enzyme inhibitors, which is an important role in their pharmacological activity. Some benzotriazoles have been found to be inhibitors of CYP51, an enzyme in sterol biosynthesis of fungi.[70] This inhibition is due to impact on the development of antifungal drugs because they affect integrity of fungal cell membrane

and growth capabilities. Molecular docking studies have demonstrated that these compounds can bind to active site of CYP51, showing a substantial decline in fungal viability.[71]

Moreover, some benzotriazole derivatives are mechanism-based inactivators of certain enzymes. They were employed for inhibition of SARS-CoV-1 3CL protease which is important for replication enzymes of the severe acute respiratory syndrome (SARS) virus.[72] With an irreversible covalent complex formation at the active site of such a protease, benzotriazole derivatives are able to strongly inhibit the replication of viruses and may find further applications in developing new antiviral drugs.[72]

B. Interaction with Receptors

In addition to the interaction with enzymes, benzotriazole derivatives interact with various receptors in biological systems. Such interactions can either stimulate or inhibit the activity of the receptors, thus creating a medicinal effect.[73] For example, some benzotriazole compounds have been reported as agonists or antagonists at particular receptors in pain and inflammation pathways.[74]

More importantly, it has been shown that benzotriazole derivatives can modulate ion channels. Specifically, such compounds can affect voltage-gated sodium channels.[75] They may influence neuronal excitability and therefore could potentially offer new therapeutic benefits in diseases like epilepsy or neuropathic pain.[76]

Mechanism of action

The mechanisms through which benzotriazole derivatives exert their pharmacological activity are numerous and complex. These mechanisms may include

- Competitive inhibition: It occurs when other compounds compete with natural substrates that combine to the active site of enzymes.[77]
- Allosteric Modulation: In some of the derivatives, it is bound to other sites than the active site of enzymes or receptors leading through conformational changes to activation or inhibition.[78]
- Covalent Bonding: A few benzotriazole derivatives form covalent bonds with target enzymes, thus causing irreversible inhibition.[79]

LIMITATIONS IN EXISTING RESEARCH

1. Toxicity Problems

Even though benzotriazole derivatives show potential pharmacological properties, their toxicity is still a critical concern. Several reports point out that certain benzotriazole analogs could be toxic to aquatic organisms and hence create a concern related to environmental safety.[1] Humans will experience skin sensitization and several other adverse effects on chronic exposure to these compounds. The potential for toxicity necessitates thorough evaluation during the drug development process, as it can significantly impact the viability of compounds in clinical settings.[80] Furthermore, the toxicological profiles of many benzotriazole derivatives remain underexplored, leading to a gap in knowledge that could hinder their therapeutic application.[81]

2. Bioavailability Challenges

The main critical limitation is the bioavailability of benzotriazole derivatives. Many compounds exhibit poor solubility and permeability, which can limit their absorption and effectiveness when administered.[4] The physicochemical properties of benzotriazoles often pose a challenge in formulation, which requires innovative approaches to enhance solubility and stability.[6] Some strategies include prodrug design, nanoparticle formulation, or the use of solubilizing agents to enhance bioavailability and ensure therapeutic efficacy.

3. Development of Resistance

Developing resistances is an increasing phenomenon to be concerned with in this topic of antimicrobial and antiviral therapies using benzotriazole derivatives.[13] As with a lot of pharmacological products, prolonged use leads the bacteria or viruses to strain and become resistant, affecting previously effective treatments.[13,60] Understanding all those mechanisms that cause resistance help developers create new derivatives that don't have such problems. New approaches to combination therapies or novel delivery systems may offer pathways toward maintaining efficacy against resistant pathogens.[82]

FUTURE RESEARCH PROSPECTIVE

1. New Synthetic Approaches

Given the constraints linked to the benzotriazole derivatives currently in existence, there is a critical demand for new synthetic methods that will provide compounds with superior pharmacological profiles.[83] New developments in synthetic methods have made it possible to generate various benzotriazole derivatives with specific properties. One such development

is copper-free 'click' chemistry, which is very useful for synthesis of substituted benzotriazoles under mild conditions, and this method provides an easy way to construct complex structures with minimal byproducts.[84]

The role of principles of green chemistry in synthesis of benzotriazole derivatives may further sustainability and minimize impact on the environment.[2] Some examples of such methodologies are solvent-free reactions and microwave-assisted synthesis, which could increase the yield and decrease waste at the production level.[37]

2. Potential Therapeutic Applications

The versatility of benzotriazole derivatives promises many more potential therapeutic applications that are not yet being explored. For example, ongoing research into the role of benzotriazole derivatives as inhibitors of specific enzymes involved in cancer metabolism may lead to novel anticancer agents.[61,73] Similarly, investigating their activity against emerging viral pathogens could make benzotriazole derivatives an essential component in antiviral therapy.[58]

Furthermore, their application towards the treatment of neurodegenerative diseases is very exciting research direction.[85] Specific benzotriazole derivatives have been found to be involved in the modulation of neuroinflammatory pathways and protection of neurons from oxidative stress, thus these compounds may be useful for treatment of Alzheimer's and Parkinson's disease.[86]

3. Exploration of New Analogues with Enhanced Efficacy

Analogues with high efficiency must be explored in order to overcome current limitations related to existing benzotriazole compounds. SAR studies would guide the design of novel derivatives through strategies identified on key structural features of SARs, which contribute to improved biological activity while minimizing toxicity.[27]

Research efforts should focus on synthesizing and evaluating a diverse library of benzotriazole derivatives with various substituents and modifications. This approach may uncover compounds with potent activity against resistant strains or those exhibiting favorable pharmacokinetic profiles.[87] Additionally, utilizing high-throughput screening techniques can accelerate the identification of promising candidates for further development.[88]

CONCLUSION

Review interprets the multifaceted role of benzotriazole derivatives in medicinal chemistry, highlighting their diverse biological activities and therapeutic potential. The structural versatility of benzotriazoles allows for the design of novel compounds exhibiting significant antimicrobial, anti-inflammatory, and anticancer properties. Notably, certain derivatives demonstrate remarkable efficacy against resistant pathogens such as MRSA and various cancer cell lines, positioning them as promising candidates for drug development. Despite their potential, challenges related to toxicity and bioavailability must be addressed to facilitate clinical application. The integration of advanced synthetic methodologies has led to improved efficacy and safety profiles for these compounds. Future research should focus on elucidating structure-activity relationships (SAR) to optimize therapeutic outcomes. Ultimately, this review underscores the importance of benzotriazole in drug design and encourages further exploration of its therapeutic applications across various disease models.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

REFERENCES

1. Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. Benzotriazole: A Novel Synthetic Auxiliary. Tetrahedron, **1991**; 47(16): 2683–2732. https://doi.org/10.1016/S0040-4020(01)87080-0.
2. Shah, J. J.; Mohanraj, K. Comparison of Conventional and Microwave-Assisted Synthesis of Benzotriazole Derivatives. Indian J. Pharm. Sci., **2014**; 76(1): 46–53.
3. Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. Benzyne Click Chemistry: Synthesis of Benzotriazoles from Benzynes and Azides. Org. Lett., **2008**; 10(12): 2409–2412. https://doi.org/10.1021/ol800675u.
4. (PDF) Benzotriazole in Medicinal Chemistry. https://www.researchgate.net/publication/279897455_Benzotriazole_in_Medicinal_Chemistry (accessed 2024-12-24).
5. Richards, C. A. J.; McMurray, H. N.; Williams, G. Smart-Release Inhibition of Corrosion Driven Organic Coating Failure on Zinc by Cationic Benzotriazole Based Pigments. Corros. Sci., **2019**; 154: 101–110. https://doi.org/10.1016/j.corsci.2019.04.005.

6. Yeo, J.; Lee, Y. M.; Lee, J.; Park, D.; Kim, K.; Kim, J.; Park, J.; Kim, W. J. Nitric Oxide-Scavenging Nanogel for Treating Rheumatoid Arthritis. Nano Lett., **2019**; 19(10): 6716–6724. https://doi.org/10.1021/acs.nanolett.9b00496.
7. Cliff, N.; Kanouni, M.; Peters, C.; Yaneff, P. V.; Adamsons, K. Use of Reactable Light Stabilizers to Prevent Migration and to Improve Durability of Coatings on Plastic Substrates. JCT Res., **2005**; 2(5): 371–387. https://doi.org/10.1007/s11998-005-0005-y.
8. Mennucci, M. M.; Banczek, E. P.; Rodrigues, P. R. P.; Costa, I. Evaluation of Benzotriazole as Corrosion Inhibitor for Carbon Steel in Simulated Pore Solution. Cem. Concr. Compos, **2009**; 31(6): 418–424. https://doi.org/10.1016/j.cemconcomp.2009.04.005.
9. Wan, J.; Lv, P.-C.; Tian, N.-N.; Zhu, H.-L. Facile Synthesis of Novel Benzotriazole Derivatives and Their Antibacterial Activities. J. Chem. Sci., **2010**; 122(4): 597–606. https://doi.org/10.1007/s12039-010-0094-8.
10. Briguglio, I.; Piras, S.; Corona, P.; Gavini, E.; Nieddu, M.; Boatto, G.; Carta, A. Benzotriazole: An Overview on Its Versatile Biological Behavior. Eur. J. Med. Chem., **2015**; 97: 612–648. https://doi.org/10.1016/j.ejmech.2014.09.089.
11. Al-Omran, F.; El-Khair, A. A.; Mohareb, R. M. Synthesis and Biological Effects of New Derivatives of Benzotriazole as Antimicrobial and Antifungal Agents. J. Heterocycl. Chem., **2002**; 39(5): 877–883. https://doi.org/10.1002/jhet.5570390504.
12. Saleh, S. S.; AL-Salihi, S. Sh.; Mohammed, I. A. Biological Activity Study for Some Heterocyclic Compounds and Their Impact on the Gram Positive and Negative Bacteria. Energy Procedia, **2019**; 157: 296–306. https://doi.org/10.1016/j.egypro.2018.11.194.
13. Xu, Z. 1,2,3-Triazole-Containing Hybrids with Potential Antibacterial Activity against Methicillin-Resistant Staphylococcus Aureus (MRSA). Eur. J. Med. Chem. **2020**, 206, 112686. https://doi.org/10.1016/j.ejmech.2020.112686.
14. Jimoh, T. A.; Oyewale, A. O.; Ibrahim, H.; Habila, J. D.; Arthur, D. E. Some Benzotriazole and Benzimidazole Derivatives as Antifungal Agents for Candida Species: A Molecular Docking Study. Chem. Afr., **2023**; 6(1): 383–391. https://doi.org/10.1007/s42250-022-00498-y.
15. Khabnadideh, S.; Rezaei, Z.; Pakshir, K.; Zomorodian, K.; Ghafari, N. Synthesis and Antifungal Activity of Benzimidazole, Benzotriazole and Aminothiazole Derivatives. Res. Pharm. Sci., **2012**; 7(2): 65–72.
16. Yang, C.; He, S.; Lu, S.; Liao, X.; Song, Y.; Chen, Z.-F.; Zhang, G.; Li, R.; Dong, C.; Qi, Z.; Cai, Z. Pollution Characteristics, Exposure Assessment and Potential Cardiotoxicities

of PM2.5-Bound Benzotriazole and Its Derivatives in Typical Chinese Cities. Sci. Total Environ., **2022**; 809: 151132. https://doi.org/10.1016/j.scitotenv.2021.151132.

17. Zhou, C.-H.; Wang, Y. Recent Researches in Triazole Compounds as Medicinal Drugs. Curr. Med. Chem., **2012**; 19(2): 239–280. https://doi.org/10.2174/092986712803414213.
18. Guan, Q.; Xing, S.; Wang, L.; Zhu, J.; Guo, C.; Xu, C.; Zhao, Q.; Wu, Y.; Chen, Y.; Sun, H. Triazoles in Medicinal Chemistry: Physicochemical Properties, Bioisosterism, and Application. J. Med. Chem., **2024**; 67(10): 7788–7824. https://doi.org/10.1021/acs.jmedchem.4c00652.
19. Gianti, E.; Zauhar, R. J. Chapter 7 - Structure–Activity Relationships and Drug Design. In Remington (Twenty-third Edition); Adejare, A., Ed.; Academic Press, 2021; pp 129–153. https://doi.org/10.1016/B978-0-12-820007-0.00007-6.
20. Peters, S. J.; Patel, K. Electron Distribution in 1,2,3-Benzotriazole and 1,2,3-Triazole Anion Radical Isomers: An EPR and DFT Study. J. Org. Chem., **2021**; 86(21): 14786–14796. https://doi.org/10.1021/acs.joc.1c01584.
21. Wang, X.; Shan, Y.; Mao, H.; Xiao, X.; Wang, N.; Lv, X.; Zhou, L. Selective N–N or N–S Bond Cleavage of 1-Trifluoromethyl Benzotriazoles Enables Divergent Synthesis of 1,2,4-Benzotriazines and Benzotriazoles. Org. Chem. Front, **2023**; 10(20): 5138–5143. https://doi.org/10.1039/D3QO00916E.
22. B, L.; N, K.; T, S. Evaluation of Antidiabetic and Antioxidant Potential of Some Novel Ethoxylated Head of α, β-Unsaturated Ketones. Res. J. Pharm. Technol., **2020**; 13(3): 1397–1402. https://doi.org/10.5958/0974-360X.2020.00256.5.
23. Wang, X.; Du, J.; Zhou, T.; Fang, X.; Yang, H. Novel Benzotriazole-Benzimidazole Metal Complexes: Structure-Activity Relationship, Synthesis, Characterization, and Antidiabetic Activity. J. Mol. Struct., **2023**; 1292: 136141. https://doi.org/10.1016/j.molstruc.2023.136141.
24. Wu, L.; Zhao, X.; Bi, E. Predicting the Effect of Dissolved Humic Acid on Sorption of Benzotriazole to Biochar. Biochar, **2022**; 4(1): 15. https://doi.org/10.1007/s42773-022-00134-5.
25. Bollikolla, H. B.; Boddapati, S. N. M.; Thangamani, S.; Mutchu, B. R.; Alam, M. M.; Hussien, M.; Jonnalagadda, S. B. Advances in Synthesis and Biological Activities of Benzotriazole Analogues: A Micro Review. J. Heterocycl. Chem., **2023**; 60(5): 705–742. https://doi.org/10.1002/jhet.4587.

26. Yu, J.; Singh, A. S.; Yan, G.; Yu, J.; Tiwari, V. K. Recent Developments on Denitrogenative Functionalization of Benzotriazoles. Synthesis, **2020**; 52(24): 3781–3800. https://doi.org/10.1055/s-0040-1707253.
27. D'Souza, S.; Balaji, S.; K V, P. QSAR, Molecular Docking, Molecular Dynamics and MM-GBSA Approach for Identification of Prospective Benzotriazole-Based SARS-CoV 3CL Protease Inhibitors. J. Biomol. Struct. Dyn., **2022**; 40(24): 14247–14261. https://doi.org/10.1080/07391102.2021.2002718.
28. Kale, R. R.; Prasad, V.; Mohapatra, P. P.; Tiwari, V. K. Recent Developments in Benzotriazole Methodology for Construction of Pharmacologically Important Heterocyclic Skeletons. Monatshefte Für Chem. - Chem. Mon., **2010**; 141(11): 1159–1182. https://doi.org/10.1007/s00706-010-0378-1.
29. Łukasik, E.; Wróbel, Z. 2-(Arylamino)Aryliminophosphoranes as Easily Available and Convenient Starting Materials in the Synthesis of 1,2,3-Benzotriazoles. Synlett., **2014**; 25(14): 1987–1990. https://doi.org/10.1055/s-0034-1378448.
30. Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. Benzyne Click Chemistry: Synthesis of Benzotriazoles from Benzynes and Azides. Org. Lett., **2008**; 10(12): 2409–2412. https://doi.org/10.1021/ol800675u.
31. Gundepaka, P.; Kankala, S.; Guguloth, H.; Kotte, S.; Chakilam, V.; Kagga, M.; Vadde, R.; Vasam, C. S. Synthesis of Piperidine Bound 3,4,5-Trisubstituted Isoxazolines Via 1,3-Dipolar Cycloaddition Reactions Catalyzed By N-Heterocyclic Carbene. Asian J. Res. Chem., **2013**; 6(10): 916–919.
32. Guin, A.; Gaykar, R. N.; Bhattacharjee, S.; Biju, A. T. Selective Synthesis of N-H and N-Aryl Benzotriazoles by the [3 + 2] Annulation of Sodium Azide with Arynes. J. Org. Chem., **2019**; 84(19): 12692–12699. https://doi.org/10.1021/acs.joc.9b02198.
33. Zhou, J.; He, J.; Wang, B.; Yang, W.; Ren, H. 1,7-Palladium Migration via C−H Activation, Followed by Intramolecular Amination: Regioselective Synthesis of Benzotriazoles. J. Am. Chem. Soc., **2011**; 133(18): 6868–6870. https://doi.org/10.1021/ja2007438.
34. Naqvi, A.; Shahnawaaz, M.; Rao, A. V.; Seth, D. S. Synthesis and Characterization of Some Azo Compounds. Asian J. Res. Chem., **2010**; 3(2): 428–429.
35. Anjana, V. S.; Kumar, P. M. An Overview on Medicinal Perspective and Biological Behavior of Benzotriazole; Synthetic Study on Its Multifaceted Biological Activities. Int. J. Res. Rev., **2021**; 8(5): 365–378. https://doi.org/10.52403/ijrr.20210546.

36. Pawar, S.; Gorde, P.; Kakde, R. Synthesis of New N1-Substituted Benzotriazoles as Anthelmintic Agents. Arch. Appl. Sci. Res., **2010**.
37. Sudhir, M. S.; Venkata Nadh, R. Evaluation of in Vitro Anthelmintic Activities of Novel 1,2,3 – Benzotriazole Derivatives Synthesized in Ultrasonic and Solvent Free Conditions. J. Pharm. Res., **2013**; 7(1): 47–52. https://doi.org/10.1016/j.jopr.2013.01.004.
38. Drews, A.; Bovens, S.; Roebrock, K.; Sunderkötter, C.; Reinhardt, D.; Schäfers, M.; van der Velde, A.; Schulze Elfringhoff, A.; Fabian, J.; Lehr, M. 1-(5-Carboxyindol-1-Yl)Propan-2-One Inhibitors of Human Cytosolic Phospholipase A2α with Reduced Lipophilicity: Synthesis, Biological Activity, Metabolic Stability, Solubility, Bioavailability, And Topical in Vivo Activity. J. Med. Chem., **2010**; 53(14): 5165–5178. https://doi.org/10.1021/jm1001088.
39. Tomić, M.; Kundaković, M.; Butorović, B.; Janać, B.; Andrić, D.; Roglić, G.; Ignjatović, D.; Kostić-Rajačić, S. Pharmacological Evaluation of Selected Arylpiperazines with Atypical Antipsychotic Potential. Bioorg. Med. Chem. Lett., **2004**; 14(16): 4263–4266. https://doi.org/10.1016/j.bmcl.2004.06.005.
40. Perković, I.; Tršinar, S.; Žanetić, J.; Kralj, M.; Martin-Kleiner, I.; Balzarini, J.; Hadjipavlou-Litina, D.; Katsori, A. M.; Zorc, B. Novel 1-Acyl-4-Substituted Semicarbazide Derivatives of Primaquine - Synthesis, Cytostatic, Antiviral and Antioxidative Studies. J. Enzyme Inhib. Med. Chem., **2013**; 28(3): 601–610. https://doi.org/10.3109/14756366.2012.663366.
41. Zhang, S.; Luo, Y.; He, L.-Q.; Liu, Z.-J.; Jiang, A.-Q.; Yang, Y.-H.; Zhu, H.-L. Synthesis, Biological Evaluation, and Molecular Docking Studies of Novel 1,3,4-Oxadiazole Derivatives Possessing Benzotriazole Moiety as FAK Inhibitors with Anticancer Activity. Bioorg. Med. Chem., **2013**; 21(13): 3723–3729. https://doi.org/10.1016/j.bmc.2013.04.043.
42. Fu, J.; Yang, Y.; Zhang, X.-W.; Mao, W.-J.; Zhang, Z.-M.; Zhu, H.-L. Discovery of 1H-Benzo[d][1,2,3]Triazol-1-Yl 3,4,5-Trimethoxybenzoate as a Potential Antiproliferative Agent by Inhibiting Histone Deacetylase. Bioorg. Med. Chem., **2010**; 18(24): 8457–8462. https://doi.org/10.1016/j.bmc.2010.10.049.
43. Kumar, V.; Malhotra, S. V. Synthesis of Nucleoside-Based Antiviral Drugs in Ionic Liquids. Bioorg. Med. Chem. Lett., **2008**; 18(20): 5640–5642. https://doi.org/10.1016/j.bmcl.2008.08.090.
44. Tonelli, M.; Paglietti, G.; Boido, V.; Sparatore, F.; Marongiu, F.; Marongiu, E.; La Colla, P.; Loddo, R. Antiviral Activity of Benzimidazole Derivatives. I. Antiviral Activity of

1-Substituted-2-[(Benzotriazol-1/2-yl)Methyl]Benzimidazoles. Chem. Biodivers., **2008**; 5(11): 2386–2401. https://doi.org/10.1002/cbdv.200890203.

45. Becerra, M. C.; Guiñazú, N.; Hergert, L. Y.; Pellegrini, A.; Mazzieri, M. R.; Gea, S.; Albesa, I. In Vitro Activity of N-Benzenesulfonylbenzotriazole on Trypanosoma Cruzi Epimastigote and Trypomastigote Forms. Exp. Parasitol., **2012**; 131(1): 57–62. https://doi.org/10.1016/j.exppara.2012.02.028.
46. Črešnar, B.; Petrič, Š. Cytochrome P450 Enzymes in the Fungal Kingdom. Biochim. Biophys. Acta BBA - Proteins Proteomics, **2011**; 1814(1): 29–35. https://doi.org/10.1016/j.bbapap.2010.06.020.
47. Shalini, K.; Kumar, N.; Drabu, S.; Sharma, P. K. Advances in Synthetic Approach to and Antifungal Activity of Triazoles. Beilstein J. Org. Chem., **2011**; 7: 668–677. https://doi.org/10.3762/bjoc.7.79.
48. Zhang, S.-L.; Chang, J.-J.; Damu, G. L. V.; Geng, R.-X.; Zhou, C.-H. Berberine Azoles as Antimicrobial Agents: Synthesis, Biological Evaluation and Their Interactions with Human Serum Albumin. MedChemComm., **2013**; 4(5); 839–846. https://doi.org/10.1039/C3MD00032J.
49. Eustice, D. C.; Feldman, P. A.; Zajac, I.; Slee, A. M. Mechanism of Action of DuP 721: Inhibition of an Early Event during Initiation of Protein Synthesis. Antimicrob. Agents Chemother., **1988**; 32(8): 1218–1222. https://doi.org/10.1128/AAC.32.8.1218.
50. Dhanaraju, M. D.; Gopi, C.; Sastry, V. G. Synthesis and Biological Evaluation of Some 4-(5((1h-Benzo [D][1,2,3]Triazol-1-Yl)Methyl)-1,3,4-Oxadiazol-2yl)-N-Benzylidenebenamine Derivative as a Anti-Microbial and Anti-Convulsant Agents. Asian J. Res. Chem., **2015**; 8(7): 459–465. https://doi.org/10.5958/0974-4150.2015.00075.9.
51. Badeliya, S. N.; Kapupara, P. P.; Chaudhary, A. B. In Silico Analysis of Novel Azetidinone Substituted Benzotriazole and Benzimidazole Derivatives as Plasmodium Falciparum Glutamate Dehydrogenase Inhibitors. Res. J. Pharm. Technol., **2022**; 15(4): 1431–1436. https://doi.org/10.52711/0974-360X.2022.00237.
52. Abraham, N.; Namachivayam, C.; Sundaramoorthy, S. Lactobacillus- An Friendly Bacteria. Int. J. Technol., **2021**; 11(2): 70–77. https://doi.org/10.52711/2231-3915.2021.00010.
53. Dhanaraju, M. D.; Gopi, C.; Sastry, V. G. Synthesis and Biological Evaluation of Some 4-(5((1h-Benzo [D][1,2,3]Triazol-1-Yl)Methyl)-1,3,4-Oxadiazol-2yl)-N-Benzylidenebenamine Derivative as a Anti-Microbial and Anti-Convulsant Agents. Asian J. Res. Chem., **2015**; 8(7): 459–465. https://doi.org/10.5958/0974-4150.2015.00075.9.

54. Nuvole, A.; Sanna, P.; Paglietti, G.; Juliano, C.; Zanetti, S.; Cappuccinelli, P. 1,2,3-Triazolo[4,5-f]Quinolines. II. Preparation and Antimicrobial Evaluation of 6-Ethyl-6,9-Dihydro-1(2)(3)-R-1(2) (3)H-Triazolo [4,5-f]Quinolin-9-One-8-Carboxylic Acids as Anti-Infectives of the Urinary Tract (1). Farm. Soc. Chim. Ital., **1989**; 44(6): 619–632.
55. Ochal, Z.; Bretner, M.; Wolinowska, R.; Tyski, S. Synthesis and in Vitro Antibacterial Activity of 5-Halogenomethylsulfonyl- Benzimidazole and Benzotriazole Derivatives. Med. Chem., **2013**; 9(8): 1129–1136.
56. Santos Fernandes, G. F.; Benito Scarim, C.; Kim, S.-H.; Wu, J.; Castagnolo, D. Oxazolidinones as Versatile Scaffolds in Medicinal Chemistry. RSC Med. Chem., **2023**; 14(5): 823–847. https://doi.org/10.1039/D2MD00415A.
57. Becerra, M. C.; Guiñazú, N.; Hergert, L. Y.; Pellegrini, A.; Mazzieri, M. R.; Gea, S.; Albesa, I. In Vitro Activity of N-Benzenesulfonylbenzotriazole on Trypanosoma Cruzi Epimastigote and Trypomastigote Forms. Exp. Parasitol., **2012**; 131(1): 57–62. https://doi.org/10.1016/j.exppara.2012.02.028.
58. Ibba, R.; Corona, P.; Nonne, F.; Caria, P.; Serreli, G.; Palmas, V.; Riu, F.; Sestito, S.; Nieddu, M.; Loddo, R.; Sanna, G.; Piras, S.; Carta, A. Design, Synthesis, and Antiviral Activities of New Benzotriazole-Based Derivatives. Pharmaceuticals, **2023**; 16(3): 429. https://doi.org/10.3390/ph16030429.
59. Loddo, R.; Novelli, F.; Sparatore, A.; Tasso, B.; Tonelli, M.; Boido, V.; Sparatore, F.; Collu, G.; Delogu, I.; Giliberti, G.; La Colla, P. Antiviral Activity of Benzotriazole Derivatives. 5-[4-(Benzotriazol-2-Yl)Phenoxy]-2,2-Dimethylpentanoic Acids Potently and Selectively Inhibit Coxsackie Virus B5. Bioorg. Med. Chem., **2015**; 23(21): 7024–7034. https://doi.org/10.1016/j.bmc.2015.09.035.
60. Ibba, R.; Piras, S.; Corona, P.; Riu, F.; Loddo, R.; Delogu, I.; Collu, G.; Sanna, G.; Caria, P.; Dettori, T.; Carta, A. Synthesis, Antitumor and Antiviral In Vitro Activities of New Benzotriazole-Dicarboxamide Derivatives. Front. Chem., **2021**; 9. https://doi.org/10.3389/fchem.2021.660424.
61. Pon Matheswari, P.; Ilavarasi Jeyamalar, J.; Iruthayaraj, A.; Ravindran Durai Nayagam, B. Synthesis, Structural, Multitargeted Molecular Docking Analysis of Anti-Cancer, Anti-Tubercular, DNA Interactions of Benzotriazole Based Macrocyclic Ligand. Bioorganic Chem., **2024**; 147: 107361. https://doi.org/10.1016/j.bioorg.2024.107361.
62. Qadri, T.; Aziz, M.; Ali Channar, P.; Abida Ejaz, S.; Hussain, M.; Muhammad Attaullah, H.; Ujan, R.; Hussain, Z.; Zehra, T.; Saeed, A.; R. Shah, M.; A. Ogaly, H.; M. Al-Zahrani, F. A. Synthesis, Biological Evaluation and in Silico Investigations of Benzotriazole

Derivatives as Potential Inhibitors of NIMA Related Kinase. RSC Adv., **2023**; 13(48): 33826–33843. https://doi.org/10.1039/D3RA06149C.

63. Wouters, W.; Van Ginckel, R.; Krekels, M.; Bowden, C.; De Coster, R. Pharmacology of Vorozole. J. Steroid Biochem. Mol. Biol., **1993**; 44(4): 617–621. https://doi.org/10.1016/0960-0760(93)90268-2.
64. Goss, P. E.; Winer, E. P.; Tannock, I. F.; Schwartz on behalf of the North American Vorozole Study Group, L. H. Randomized Phase III Trial Comparing the New Potent and Selective Third-Generation Aromatase Inhibitor Vorozole With Megestrol Acetate in Postmenopausal Advanced Breast Cancer Patients. J. Clin. Oncol., **1999**; 17(1): 52–52. https://doi.org/10.1200/JCO.1999.17.1.52.
65. Goss, P. E. Pre-Clinical and Clinical Review of Vorozole, a New Third Generation Aromatase Inhibitor. Breast Cancer Res. Treat., **1998**; 49(1): S59–S65. https://doi.org/10.1023/A:1006052923468.
66. Rahmani, S. E.; Lahrech, M. Evaluation of the Antioxidant Activity of Some Hydrazone Schiff's Bases Bearing Benzotriazole Moiety. Res. J. Pharm. Technol., **2018**; 11(9): 4104–4107. https://doi.org/10.5958/0974-360X.2018.00754.0.
67. Gupta, K.; Sirbaiya, A. K.; Kumar, V.; Rahman, M. A. Current Perspective of Synthesis of Medicinally Relevant Benzothiazole Based Molecules: Potential for Antimicrobial and Anti-Inflammatory Activities. Mini Rev. Med. Chem., **2022**; 22(14): 1895–1935. https://doi.org/10.2174/1389557522666220217101805.
68. Li, Z.; Liang, X.; Liu, W.; Zhao, Y.; Yang, H.; Li, W.; Adamovsky, O.; Martyniuk, C. J. Elucidating Mechanisms of Immunotoxicity by Benzotriazole Ultraviolet Stabilizers in Zebrafish (Danio Rerio): Implication of the AHR-IL17/IL22 Immune Pathway. Environ. Pollut., **2020**; 262: 114291. https://doi.org/10.1016/j.envpol.2020.114291.
69. Guo, Z.; Li, H.; Yu, W.; Ren, Y.; Zhu, Z. Insights into the Effect of Benzotriazoles in Liver Using Integrated Metabolomic and Transcriptomic Analysis. Environ. Int., **2024**; 187: 108716. https://doi.org/10.1016/j.envint.2024.108716.
70. Singh, A.; Singh, K.; Sharma, A.; Kaur, K.; Chadha, R.; Bedi, P. M. S. Recent Advances in Antifungal Drug Development Targeting Lanosterol 14α-Demethylase (CYP51): A Comprehensive Review with Structural and Molecular Insights. Chem. Biol. Drug Des., **2023**; 102(3): 606–639. https://doi.org/10.1111/cbdd.14266.
71. Lebouvier, N.; Pagniez, F.; Na, Y. M.; Shi, D.; Pinson, P.; Marchivie, M.; Guillon, J.; Hakki, T.; Bernhardt, R.; Yee, S. W.; Simons, C.; Lézé, M.-P.; Hartmann, R. W.; Mularoni, A.; Le Baut, G.; Krimm, I.; Abagyan, R.; Le Pape, P.; Le Borgne, M. Synthesis,

Optimization, Antifungal Activity, Selectivity, and CYP51 Binding of New 2-Aryl-3-Azolyl-1-Indolyl-Propan-2-Ols. Pharmaceuticals, **2020**; 13(8): 186. https://doi.org/10.3390/ph13080186.

72. Hooper, A.; Macdonald, J. D.; Reilly, B.; Maw, J.; Wirrick, A. P.; Han, S. H.; Lindsey, A. A.; Rico, E. G.; Romigh, T.; Goins, C. M.; Wang, N. S.; Stauffer, S. R. SARS-CoV-2 3CL-Protease Inhibitors Derived from ML300: Investigation of P1 and Replacements of the 1,2,3-Benzotriazole. Med. Chem. Res., **2023**; 32(7): 1383–1390. https://doi.org/10.1007/s00044-023-03108-9.
73. He, S.; Xiao, H.; Luo, S.; Li, X.; Zhang, J.-D.; Ren, X.-M.; Yang, Y.; Xie, X.-D.; Zhou, Y.-Y.; Yin, Y.-L.; Luo, L.; Cao, L.-Y. Benzotriazole Ultraviolet Stabilizers Promote Breast Cancer Cell Proliferation via Activating Estrogen-Related Receptors α and γ at Human-Relevant Levels. Environ. Sci. Technol., **2022**: 56(4): 2466–2475. https://doi.org/10.1021/acs.est.1c03446.
74. Sparatore, F.; Sparatore, A. 3,3-Disubstituted 3,4-Dihydro-1,2,4-Benzotriazines: Chemistry, Biological Activity, and Affinity to Sigma Receptors. Molecules, **2024**; 29(1): 132. https://doi.org/10.3390/molecules29010132.
75. Uesaka, T.; Ishitani, T.; Sawada, R.; Maeda, T.; Yagi, S. Fluorescent 2-Phenyl-2H-Benzotriazole Dyes with Intramolecular N–H···N Hydrogen Bonding: Synthesis and Modulation of Fluorescence Properties by Proton-Donating Substituents. Dyes Pigments, **2020**; 183: 108672. https://doi.org/10.1016/j.dyepig.2020.108672.
76. Paprocki, D.; Winiewska-Szajewska, M.; Speina, E.; Kucharczyk, R.; Poznański, J. 5,6-Diiodo-1H-Benzotriazole: New TBBt Analogue That Minutely Affects Mitochondrial Activity. Sci. Rep., **2021**; 11(1): 23701. https://doi.org/10.1038/s41598-021-03136-8.
77. Kasperowicz, S.; Marzec, E.; Maciejewska, A. M.; Trzybiński, D.; Bretner, M.; Woźniak, K.; Poznański, J.; Mieczkowska, K. A Competition between Hydrophobic and Electrostatic Interactions in Protein–Ligand Systems. Binding of Heterogeneously Halogenated Benzotriazoles by the Catalytic Subunit of Human Protein Kinase CK2. IUBMB Life, **2020**; 72(6): 1211–1219. https://doi.org/10.1002/iub.2271.
78. Szabó, G.; Erdélyi, P.; Kolok, S.; Vastag, M.; Halász, A. S.; Kis-Varga, I.; Lévay, G. I.; Béni, Z.; Kóti, J.; Greiner, I.; Keserű, G. M. Fragment-Based Optimization of Dihydropyrazino-Benzimidazolones as Metabotropic Glutamate Receptor-2 Positive Allosteric Modulators against Migraine. J. Med. Chem., **2021**; 64(12): 8607–8620. https://doi.org/10.1021/acs.jmedchem.1c00563.

79. Khodiev, M. Kh.; Holikulov, U. A.; Issaoui, N.; Al-Dossary, O. M.; Bousiakoug, L. G.; Lavrik, N. L. Estimation of Electrostatic and Covalent Contributions to the Enthalpy of H-Bond Formation in H-Complexes of 1,2,3-Benzotriazole with Proton-Acceptor Molecules by IR Spectroscopy and DFT Calculations. J. King Saud Univ. - Sci., **2023**; 35(3): 102530. https://doi.org/10.1016/j.jksus.2022.102530.
80. Wouters, W.; Snoeck, E.; De Coster, R. Vorozole, a Specific Non-Steroidal Aromatase Inhibitor. Breast Cancer Res. Treat., **1994**; 30(1): 89–94. https://doi.org/10.1007/BF00682743.
81. Bajaj, K.; Sakhuja, R. Benzotriazole: Much More Than Just Synthetic Heterocyclic Chemistry. In The Chemistry of Benzotriazole Derivatives: A Tribute to Alan Roy Katritzky; Monbaliu, J.-C. M., Ed.; Springer International Publishing: Cham., 2016; pp 235–283. https://doi.org/10.1007/7081_2015_198.
82. Gattinoni, C.; Tsaousis, P.; Euaruksakul, C.; Price, R.; Duncan, D. A.; Pascal, T.; Prendergast, D.; Held, G.; Michaelides, A. Adsorption Behavior of Organic Molecules: A Study of Benzotriazole on Cu(111) with Spectroscopic and Theoretical Methods. Langmuir, **2019**; 35(4): 882–893. https://doi.org/10.1021/acs.langmuir.8b03528.
83. Rachwal, S.; Katritzky, A. R. 5.01 - 1,2,3-Triazoles. In Comprehensive Heterocyclic Chemistry III; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; pp 1–158. https://doi.org/10.1016/B978-008044992-0.00501-0.
84. Loukopoulos, E.; Abdul-Sada, A.; Csire, G.; Kállay, C.; Brookfield, A.; Tizzard, G. J.; Coles, S. J.; Lykakis, I. N.; Kostakis, G. E. Copper(II)-Benzotriazole Coordination Compounds in Click Chemistry: A Diagnostic Reactivity Study. Dalton Trans., **2018**; 47(31): 10491–10508. https://doi.org/10.1039/C8DT01256C.
85. Ramirez, E.; Ganegamage, S. K.; Elbatrawy, A. A.; Alnakhala, H.; Shimanaka, K.; Tripathi, A.; Min, S.; Rochet, J.-C.; Dettmer, U.; Fortin, J. S. 5-Nitro-1,2-Benzothiazol-3-Amine and N-Ethyl-1-[(Ethylcarbamoyl)(5-Nitro-1,2-Benzothiazol-3-Yl)Amino]Formamide Modulate α-Synuclein and Tau Aggregation. ACS Omega, **2023**; 8(22): 20102–20115. https://doi.org/10.1021/acsomega.3c02668.
86. Rosales Hernández, M. C.; Olvera-Valdez, M.; Velazquez Toledano, J.; Mendieta Wejebe, J. E.; Fragoso Morales, L. G.; Cruz, A. Exploring the Benzazoles Derivatives as Pharmacophores for AChE, BACE1, and as Anti-Aβ Aggregation to Find Multitarget Compounds against Alzheimer's Disease. Molecules, **2024**; 29(19): 4780. https://doi.org/10.3390/molecules29194780.

87. Dorababu, A. Pharmacology Profile of Recently Developed Multi-Functional Azoles; SAR-Based Predictive Structural Modification. ChemistrySelect, **2020**; 5(22): 6730–6758. https://doi.org/10.1002/slct.202000294.
88. Castañeda-Monsalve, V.; Fröhlich, L.-F.; Haange, S.-B.; Homsi, M. N.; Rolle-Kampczyk, U.; Fu, Q.; von Bergen, M.; Jehmlich, N. High-Throughput Screening of the Effects of 90 Xenobiotics on the Simplified Human Gut Microbiota Model (SIHUMIx): A Metaproteomic and Metabolomic Study. Front. Microbiol., **2024**; 15. https://doi.org/10.3389/fmicb.2024.1349367.