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Benzotriazole Heterocycles Progress in Design, Synthesis and Drug Development

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ABSTRACT: Benzotriazole (BTA) has emerged as a privileged heterocyclic scaffold in medicinal chemistry, owing to its favourable physicochemical properties, structural versatility, and wide-ranging biological activities. Recent advancements in the design and development of benzotriazole derivatives have been driven by innovative synthetic methodologies, including green chemistry approaches, metal catalyzed reactions, and click chemistry, which have enabled the efficient and selective functionalization of the BTA core. These developments have led to the identification of novel BTA-based compounds with significant therapeutic potential, particularly as antifungal, anticancer, antiviral, antimicrobial, anti-inflammatory, and acetylcholinesterase inhibiting agents. Despite challenges related to metabolic stability, solubility, and environmental persistence, recent strategies including prodrug development, molecular hybridization, and targeted drug delivery systems have improved the pharmacokinetic and pharmacodynamic profiles of BTA derivatives. Collectively, these advances underscore the continued relevance and promise of benzotriazole as a core structure in drug discovery and development.

Keywords: Benzotriazole, Hybridization, Click Chemistry, Antifungal, Acetylcholinesterase inhibitor.

INTRODUCTION

Benzotriazole (BTA) is an aromatic heterocyclic compound that has been widely popular in organic as well as inorganic chemistry. It belongs in the general category of azoles, along with other well-known heterocyclic molecules such as pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole and tetrazole[1]. BTA contains a benzene ring that is fused with a five-membered aromatic ring which incorporates the 1,2,3-triazole moiety[2]. Since the proton in this moiety can easily relocate between the nitrogen atoms, BTA can exist in two tautomeric forms, 1H- and 2H-benzotriazole[3].

The triazole family of molecules has become more interesting recently because of their widespread application in farming and manufacturing. Benzotriazole and its derivatives are really useful in medicine chemistry. One of the most important synthetic techniques in drug discovery[4] is adding the benzotriazole core. Encouragement from the great therapeutic characteristics of the connected compounds has spurred medical chemists to create many new chemotherapeutic drugs[5]. Organic compounds including sulfur and nitrogen, as well as their metal complexes, display a broad spectrum of biological activities including antitumor, antibacterial, antifungal, and antiviral properties[6].

In the manufacture of plastics, rubber, and chemical fibre's[7], benzotriazoles are sometimes used as corrosion inhibitors, radiation protectors, and photo stabilizers. Moreover, benzotriazole is essential as a precursor in the production of peptides, acid azides, and 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans. It helps to coupling amino acids in peptide formation and is employed in the production of acid azides as well as other heterocyclic compounds[8].

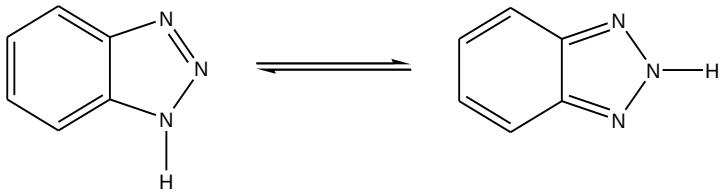
There are two isomeric forms of N-substituted benzotriazoles exist: 1H- and 2H-. Generally observed, in solid and solution phases the 1H-substituted form prevails whereas in the gas phase the 2H-tautomer's share grows. Still, the energy difference between the two isomers is small[9]. Furthermore, using N, N-dimethyl amino-propiophenone hydrochlorides and benzotriazole, respectively, amine exchange reactions have recently produced benzotriazoles carrying Manich bases[10].

Benzotriazole derivatives have exhibited broad-spectrum antibacterial action in addition to their possible anticancer properties. Recent research found that BTA derivatives are effective against Gram-positive as well as Gram-negative bacteria as well as fungal pathogens[11]. Benzotriazole derivatives functionalized with halogens or alkyl groups have been shown to disturb bacterial cell membranes, which causes cell lysis and death. These molecules show especially good promise in the battle against antibiotic-resistant organisms, where traditional antibiotics have shown somewhat reduced efficacy[12]. Moreover, BTA derivatives have shown antifungal action, making them possible candidates for the cure of fungal infections in immunodeficient patients[13].

OVERVIEW OF BENZOTRIAZOLE DERIVATIVES

With the chemical composition C6H5N3, benzotriazole is a heterocyclic molecule containing nitrogen that is remarkably flexible and finds great use in medicinal chemistry because of its broad spectrum of biological effects. These include antibacterial, antifungal, antiviral, anti-inflammatory, antihyperglycemic, antihypertensive, anticancer, and analgesic actions[14]. With its structural framework shown in seven medicines, it is regarded as a useful support for creating novel bioactive chemicals and drug candidates[15]. Furthermore, benzotriazole based chemistry facilitates the synthesis of tri-substituted 1,3,5-triazine from metformin in a metal-free, cost-efficient,

and ecologically friendly fashion. Among other advantages, this technique provides high yields, great product purity, and shorter reaction times[16]. Furthermore, assisting in target identification and the development of covalent inhibitors, benzotriazole chemistry has been critical in producing affinity labelling probes allowing for selective and quick protein modification. Benzotriazole is composed of two fused rings (Fig. 1). The five-membered ring can exist in two tautomeric forms 1H and 2H; derivatives can result from either tautomer[17].



1H Benzotriazole 2H Benzotriazole

Fig. (1) Tautomeric forms of Benzotriazole

PROPERTIES OF BENZOTRIAZOLE

Benzotriazole displays a broad spectrum of characteristics in several fields. In material science, it is used to improve the mechanical properties of ceramic coatings by increasing hardness and strength while lowering friction coefficients[18]. Studies on Benzotriazole derivatives have also concentrated on their effects on geometric parameters, dipole moments, and reactivity, with chlorinated derivatives showing greater electrophilicity[19]. Additionally, Benzotriazole has been employed in the creation of conjugated polymers, resulting in changes in fluorescence emission and enhanced fluorescence quantum efficiency, thus supporting novel fluorescence sensing mechanisms based on photoinduced electron transfer[20]. Moreover, Benzotriazole is employed in corrosion inhibitors with derivatives having hydrophobic shielding layers and enhanced adsorption capacity; their high effectiveness and heat resistance make them useful across several industries[21].

Table 1: Physical Properties of Benzotriazole

Physical Properties	
Chemical formula	$C_6H_5N_3$
Molar mass	119.127 g·mol^{-1}
Appearance	White solid
Density	1.36 g/ml
Melting point	97-99°C (212 °F; 373 K)
Boiling point	204 °C (662 °F; 623 K)
Solubility in water	20 g/L

SYNTHETIC METHOD OF BENZOTRIAZOLE

Benzotriazole can be created using several techniques as described in the supplied research background. Originally noted in 1980 as a synthetic assistant in organic chemistry, benzotriazole Later it has been used to produce various monocyclic and bicyclic heterocycles, which present difficulties during preparation using other methods. Benzotriazole is a very adaptable synthetic helper with a great number of alluring qualities. There are many different ways Benzotriazole may be made[22].

Scheme I

Alexandra A. Ageshina, et al. present a new general synthetic approach to N-unsubstituted BTA from *ortho* metalated aryl azides. A unique feature of our approach is the unprecedented *in situ* transformation of 2-azidophenyllithium into an *N*-lithium derivative of an unsubstituted benzotriazole. The halogen-lithium exchange with *n*-BuLi or *t*-BuLi in THF at –80 °C for 2h turned out to be more successful. Although application of *n*-BuLi was accompanied by formation of intensely coloured side products, treatment of the reaction mixture with dilute hydrochloric acid resulted in the 66% yield of the benzotriazole[23].

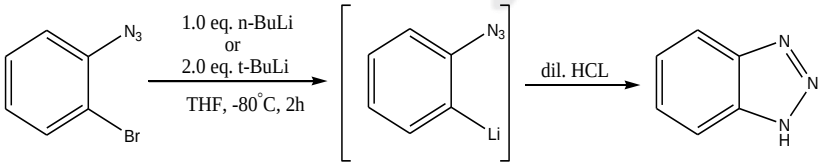


Fig (2) formation of benzotriazole through ortho metalated aryl azides

Scheme II

Khalafi A et al. synthesized 1,2,3-Benzotriazole has been prepared directly by the action of nitrous acid on o-phenylenediamine and by the hydrolysis of an acylated or arylated benzotriazole which has been previously prepared by the action of nitrous acid on the

corresponding mono acylated or arylated o-phenylenediamine. The above procedure is the direct method and gives better over-all yields than the methods involving several intermediate steps[24].

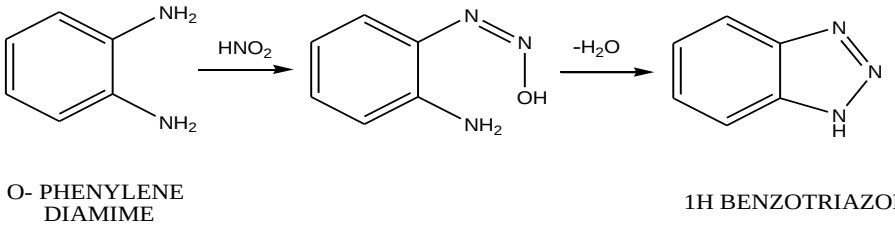


Fig (3) formation of benzotriazole through o- phenylenediamine

Scheme III

K. P. Namdev et al. synthesized N-alkylated Benzotriazole under Solvent-Free Conditions. An efficient, simple and solvent-free method for highly regioselective N-alkylation of benzotriazole in the presence of SiO2, K2CO3 and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions has been described. In this method, 1-alkyl benzotriazoles were obtained regio selectively in moderate to high yields and short reaction times[25].

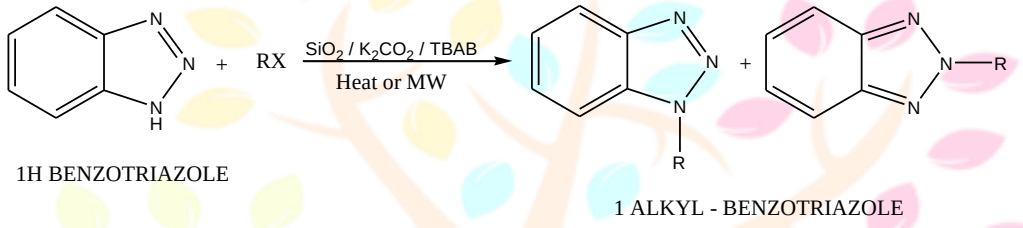
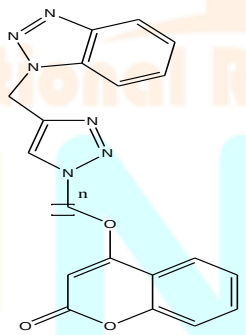
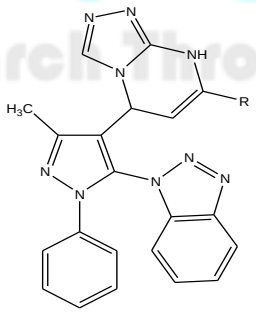
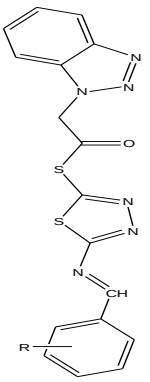
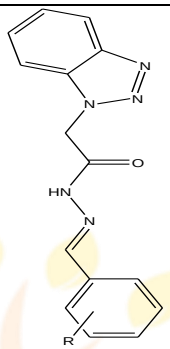
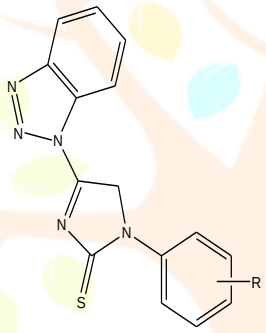
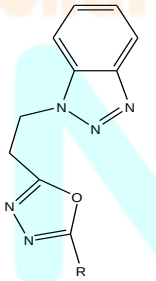
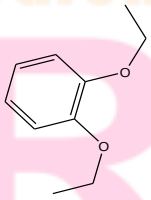
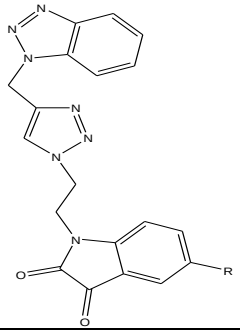
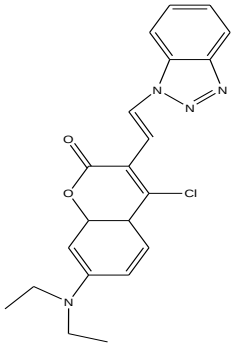
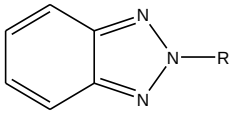
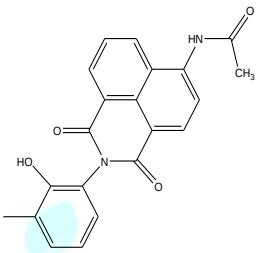
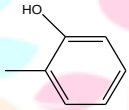
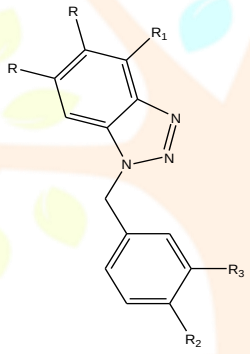
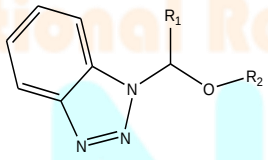
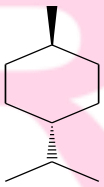
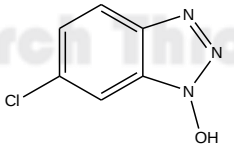
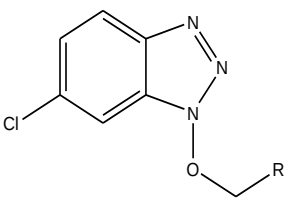
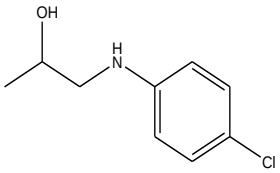


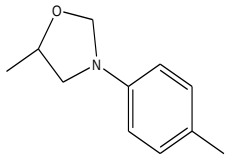
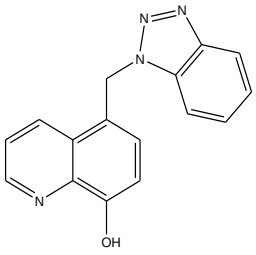
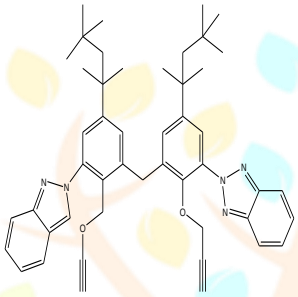
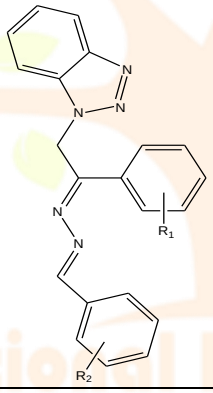
Fig (4) N alkylation of benzotriazole

Table 2: PHARMACOLOGICALCTIVITY

S.NO.	AUTHOR	COMPOUND	DERIVATIVE	ACTIVITIES
1.	A. Singh, S. Sharma, S. Arora at el. (2020)		n a) 2 b) 3 c) 4 d) 5 6	ACETYLCHOLINESTERASE & AMYLOID AGGREGATION [26]
2.	V. Pogaku, R. Krishnan, S. Basavoju et al. (2021)		Alpha-Glucosidase Inhibition R= 4-F.C_6H_4, 4-Cl.C_6H_4, 3-NO_2.C_6H_4 Anti-Cancer R= 4-Et.C_6H_4, 4-OCH_3.C_6H_4, 4-OC_2H_5.C_6H_4, 4-Cl.C_6H_4 Anti- Oxidant R = 4-OC_2H_5.C_6H_4, 4-Cl.C_6H_4, 2-C_4H_3O	ANTI-DIABETIC, ANTI-CANCER & ANTIOXIDANT [27]

3.	Darda' Aziz Ibrahim, S. D. Khalaf, N. Abd Al-Salam Ahmed et al. (2021)		a) R = p-$N(CH_3)_2$, b) o-OH, c) p- Cl	ANTIBACTERIAL& ANTIFUNGAL [28]
3.	K. Rani, C. Kaur, P. Sharma et al. (2021)		a) R = H, b) R = 2-Cl, c) R = 4-OCH_3, d) R = 3,4-OCH_3 e) R = 4-OH, f) R = 4-$N(CH_3)2$	ANTIBACTERIAL[29]
4.	A. Khayyat, K. Mohamed, A. Malebari et al. (2021)		a) R=H, b) R=4-CH_3 c) R=4-C_2H_5 d) R= 4-OCH_3 e) R= 4-OH f) R= 4-CI g) R= 2-CI h) R=3-CI i) R= 2,4-$(CI)_2$ j) R= 2-F k) R=4-Br R=4-(SO_2NH_2)	ANTICANCER & ANTIPROLIFERATIV E[30]
5.	A. Mermer, M. Volkan Bulbul, S. M. Kalender et al. (2022)			ANTI-TUMOR[31]
6.	A. Singh, K. Kaur, H. Kaur at al. (2022)		n = 3 > 2 > 1 R = F > Cl > Br > CH_3 > I > H	ANTIFUNGAL[32]

7.	S. Li, S. Fang, X. Song et al. (2022)			FLUROESXENT PROBE FOR HOMOCYSTIENE DETECTION[33]
8.	T. Uesaka, T. Ishitani, T. Shimeno et al. (2022)		a)  b) 	UV- ABSORBERS[34]
9.	R. Ibba, P. Corona, F. Nonne et al. (2023)		a) R = F, R_1 = H, R_2 = NH_2 b) R = H, R_1 = F, R_2 = $NHCO(CH_3)_3C$, R_3 = H c) R = H, R = H, R_2 = H, R_3 = NHCO-3,4,5-$OCH_3.C_6H_4$ l) R = H, R_1 = H, R_2 = H, R_3 = Cl	ANTIVIRAL[35]
10.	Z. Maqsood Cheema et al. (2023)		R_1 = i = CH_3, ii = C_2H_5, iii = Butyl, iv = pentyl, v = TMS R_2 = 	ACETYLCHOLIN ESTERASE & BUTYLCHOLINE STERASE INHIBITOR [36]
11.	X. Deng, Z. Cao, C. Li et al. (2023)			PHOTOLUMIUMINE SCENCE[37]
12.	N. Singh, V. Abrol, S. Parihar et al. (2023)		R=  R=	ANTIMICROBIAL[38]

				
13.	B. Himmi, S. Brandan, Y. Sert et al. (2023)		a) R = CH_3, b) R = C_2H_5OH, c) R = C_2H_5Cl, d) R = C_3H_7	ANTIVIRAL[39]
14.	T. Qadri, M. Aziz, P. Channar et al. (2023)			ANTICANCER& NEK 7 INHIBITOR[40]
15.	I. Khan, W. Rehman, F. Rahim, R. Hussain et al. (2023)		a) $R_1 = OCH_3$, R_2 = 2-OH, 3,5- Cl b) R_1 = 4- Br, $R_2 = 3\text{-}NO_2$ c) R_1 = 4- Br, R_2 = 2-OH, 3,5- Cl d) R_1 = 4- Br, $R_2 = 4\text{-}NO_2$ e) $R_1 = 3\text{-}NO_2$, R_2 = 2-OH, 3,5- Cl f) R_1 = 4-Br, R_2 = 4-OH, g) R_1 = 2,4-Cl, $R_2 = 4\text{-}NO_2$	ALPHA-GLUCOSIDASE INHIBITOR[41]

Structural Features of Benzotriazole

Benzotriazole is a fused heterocyclic compound made of a 1,2,3-triazole ring and a benzene ring. With the 1H-form being the most prevalent, it comes in two tautomeric shapes: 1H- and 2H-benzotriazole. Because of its stability and flexibility in medicinal chemistry, the molecule is used as a framework for several drug research projects. Several structural benefits of benzotriazoles, including planarity, hydrogen bonding ability, and π-stacking interactions, help to explain their wide range of biological activities. These characteristics let them engage successfully with biological targets including receptors and enzymes[42].

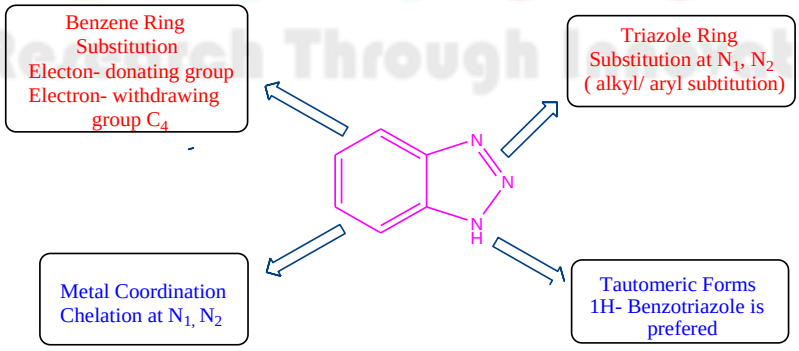


Fig (6) Structural Features of Benzotriazole

1) Planarity

Although there can be minor variations from perfect planarity depending on the particular molecule and its environment, the structure usually keeps a comparatively flat shape; the benzotriazole ring system is commonly regarded as essentially planar. According National Institutes of Health (NIH).gov, studies have indicated that the benzotriazole ring can deviate from planarity, with maximum deviations ranging from 0.0069 (15) Å to 0.027 (16) Å. Further indications of planarity are the dihedral angles between the benzotriazole plane and other neighbouring planes, such as the benzene ring. For instance, little departure from coplanarity is indicated by a dihedral angle of 13.16 (4) ° between the benzotriazole ring and the benzene ring[43].

2) Hydrogen Bonding Capabilities

Benzotriazole can engage in different kinds of hydrogen bonding, intra- and intermolecularly, depending on the particular structure and substitutions. Two nitrogen atoms in benzotriazole can function as hydrogen bond donors or acceptors (N-H). This lets the molecule create powerful hydrogen bonds with other functional groups in the target, amino acids in proteins, or water molecules[44].

- **Intermolecular Bonding:** Benzotriazoles with an N-H group in intermolecular bonding can function as hydrogen bond donors, engaging with oxygen atoms on other molecules or even within the same molecules. Other compounds with acidic hydrogens (e.g., water, alcohols) may accept hydrogen bonds from the nitrogen atoms in the benzotriazole ring. Weak C-H...N or C-H...O hydrogen bonds can also include those in the benzotriazole ring[45].
- **Intramolecular Hydrogen Bonding:** Benzotriazole derivatives with suitable substituents (X) can form intramolecular hydrogen bonds, where the N-H group interacts with a lone pair of electrons on an atom within the same molecule. N-unsubstituted benzotriazoles can exhibit tautomerism, where the proton can be located on different nitrogen atoms, influencing the hydrogen bonding interactions.
- Example- 5,6-Dinitro-1H-benzotriazole: Studies on this compound show that water molecules form hydrogen bonds with the dinitro groups and the N-H of the benzotriazole, contributing to the overall crystal structure[46].

3) π-stacking Interactions

Benzotriazole's structure, which is a benzene ring fused to a triazole ring, facilitates π-π stacking interactions due to its conjugated system. These interactions occur between the aromatic rings of benzotriazole molecules, influencing their crystal packing and other molecular interactions[47]. The benzene ring's connection to triazole, benzotriazole, differs from other triazole derivatives because it has a more considerable conjugated structure to establish π–π stacking interactions. The three nitrogen atoms of benzotriazole easily form hydrogen bonds and coordination bonds. Noncovalent interactions include electrostatic forces, hydrogen bonding, halogen bonding, π-interactions including C-H_n-A (A = O, N, S, X), π-π stacking, cation-π, anion-π, and lone pair-π[48].

4) Bioactivity features

The benzotriazole ring is a versatile scaffold for drug design, meaning it can be modified with different functional groups to create derivatives with various biological activities, including antifungal, antimicrobial, anti-inflammatory, and anticancer properties, is a key feature that makes it valuable in medicinal chemistry. The benzotriazole ring system and its capacity to interact with several biological targets account for this wide bioactivity[49].

Ring System: Benzotriazoles are heterocyclic organic compounds possessing a ring structure. A benzene ring fused with the triazole ring offer a strong planar structure with a wide spectrum of biological activity and easy modification capability[50].

Target Binding and Inhibition: Benzotriazoles' capacity to form hydrogen bonds and stacking interactions helps them bind firmly and effectively to biological targets. goals include enzymes and receptors. This binding makes benzotriazoles effective inhibitors by slowing down the target's activity[51].

Drug Design: The structural elements of benzotriazole make it a useful template for creating new pharmaceuticals. Adding functional groups or changing the benzotriazole core allows researchers to adjust the medicine's binding affinity and specificity for a certain target[52].

Metal Complexation: Benzotriazole forms compounds easily with several metals, especially cobalt, copper, and zinc. Frequently stable, these compounds are employed in corrosion prevention, analytical chemistry, and even as mimics of antioxidant enzymes. Benzotriazole's nitrogen atoms serve as electron donors, therefore enabling interaction with metal ions and so explaining its capacity to form complexes with metals. With iron, copper, cobalt, palladium, and zinc among others, benzotriazole can create several complexes with other metals. The kind of complicated formed depends on the metal, the nearby environment, and the presence of other ligands[53].

Recent Advancement in Benzotriazole Derivatives

In recent years, heterocyclic compounds, analogous, and derivatives have attracted strong interest due to their useful biological and pharmacological properties. The small and simple benzotriazole nucleus is present in compounds aimed at evaluating new entities that possess anti-microbial, antitumor, antitubercular, anti-convulsant, anti-depressant, antimalarial, anti-fungal and anti-inflammatory activities. benzotriazoles display a broad range of biological activities and are found in many potent. Many examples which we came across the literature survey implies that derivatives of benzotriazole can be prepared by bringing necessary modifications in this structure for obtaining the novel compounds which have a broad spectrum of activity against diseases/pathogens[54].

Recent research indicates that benzotriazole derivatives show promise as antifungal agents, particularly against Candida albicans. Studies have explored the use of benzotriazole-based compounds with isatin, pyrazole, and other functional groups, demonstrating their ability to inhibit fungal growth and biofilm formation. Molecular docking and dynamic studies have further highlighted the potential of these compounds to interact with fungal enzymes like sterol 14α-demethylase. The newly synthesized benzotriazole-pyrazole clubbed thiazole hybrids were characterized by FT-IR, 1H NMR, 13C NMR and HRMS methods. The synthesized compounds were screened for antibacterial activity against E. coli, B. subtilis, B. megaterium, and S. aureus and antifungal activity against A. Niger, A. oryzae, Rhizopus spp., and C. albicans[55].

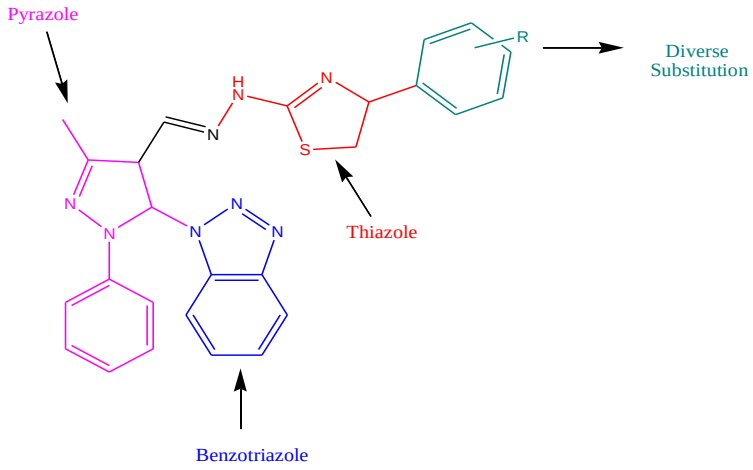


Fig (7): 2-(2-(5-(1H-benzo [d] [1,2,3] triazol-1-yl)-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene) hydrazinyl)-4-(aryl)thiazole

N-acyl benzotriazoles (Ac-BT) have found important applications in modern organic synthesis. This is mainly because that Ac-BT represents a class of mild and selective acylation reagents that outperform the other acid derivatives for the synthesis of peptides or peptidomimetics[56].

Coupling reactions play a crucial role in drug development enabling the rapid expansion of structure–activity relationships (SARs) during drug discovery programs to identify a clinical candidate and simplify subsequent drug development processes. In recent years, benzotriazole and its derivatives have been used as ligands in metal catalyzed coupling reactions. It emphasizes the advances in the utilization of benzotriazole as a ligand in a diverse range of C-C, C-N, C-O, and C-S coupling reactions[57].
Benzotriazoles ultraviolet stabilizers (BUVs) are considered as emerging environmental contaminants, even though they have been around us for almost six decades. During recent years, they received a lot of attention as an emerging pollutant because of their potential hazardous impacts on human health and biota[58]. BUVs are used as additives in polymers, paints, and several industrial and household products to protect them against the harmful effects of UV radiation[59].

Future Perspective and Challenges

Benzotriazole derivatives offer a promising platform for drug discovery due to their diverse biological activities, but challenges remain in optimizing their efficacy and minimizing toxicity. Future research should focus on synthesizing novel benzotriazole derivatives with improved therapeutic profiles, elucidating their mechanisms of action, and assessing their in vivo efficacy and safety[60]. Furthermore, benzotriazole compounds could bind with different metal ions to produce benzotriazole-containing metal complexes, which may possess the bioactivities of both benzotriazole derivatives themselves and supramolecular agents, thus possibly exerting double action mechanisms to overcome drug resistances. For the above reasons, benzotriazole moiety has been commonly employed to construct innovative drug molecules[61].

Challenges

a) Toxicological Concerns: Some benzotriazole compounds have shown potential for environmental and biological toxicity. Their persistence in biological systems and potential for bioaccumulation pose risks that limit their therapeutic use, especially in chronic treatment regime[62].
b) Metabolic Instability: Benzotriazole rings can undergo metabolic transformations that may lead to inactive or toxic metabolites. Understanding and predicting these metabolic pathways is critical but remains complex due to the variability in enzyme systems across individuals[63].
c) Synthetic Complexity: While benzotriazole can be synthesized relatively easily, functionalization at specific positions for optimal drug activity often requires multi-step synthesis with limited yield This may lengthen and raise the price of drug development[64].
d) Target Specificity: Benzotriazole medications are meant to connect with particular biological molecules or cellular pathways rather than influencing the whole body, thus show a great level of target specificity. Because it targets only the affected cells or tissues, this specificity is essential for creating safe and efficient treatments as it reduces adverse effects[65].
e) Regulatory and Environmental Scrutiny: Because of their extensive application in many goods and their possible impact, benzotriazole medications especially benzotriazole ultraviolet stabilizers (BUVSs) are under ever more stringent regulatory and environmental review. environmental effects. Concerns arise about their bioaccumulation, longevity, and possible toxicity to ecosystems and people[66].

Future Perspective

a) Structure-Based Drug Design (SBDD): For benzotriazole medicines, structure-based medication design (SBDD) uses the known 3D structure of a target protein to create novel benzotriazole-based compounds that can effectively Modify and interact with the target protein's activity; this strategy uses computer techniques including virtual screening, molecular docking, and dynamics simulations to find possible drug candidates foresee their binding affinity and action.[67].
b) Prodrug Strategies: To overcome solubility and bioavailability issues, benzotriazole-based drugs can be developed as prodrugs that become active upon metabolic transformation in the body. Prodrugs can accomplish appropriate solubility, increase permeability, provide site-specific targeting (i.e., to organs, tissues, enzymes, or transporters), overcome rapid drug metabolism, decrease toxicity, or provide better patient compliance, all with the aim to provide optimal drug therapy and outcome approach can also help reduce toxicity[68].

c) Hybrid Molecule Design: Benzotriazole moieties can be combined with other pharmacophores to create hybrid compounds that exhibit synergistic effects, enhanced potency, or multi-target action, particularly useful in complex diseases like cancer or neurodegenerative disorders[32].

d) Green Chemistry and Safer Synthesis: Advances in green chemistry may allow for more sustainable and safer synthesis routes for benzotriazole derivatives. These methods focus on minimizing waste, reducing energy consumption, and utilizing environmentally friendly reagents and reaction conditions, minimizing and improving yield[69].

e) Targeting New Biological Pathways: Continued research into novel disease mechanisms, such as epigenetic regulation and protein-protein interactions, may reveal new therapeutic opportunities for benzotriazole scaffolds. Benzotriazole-based drugs are being developed to target new biological pathways by leveraging the versatile biological behaviour of benzotriazole derivatives[70]. These compounds can act as electron donors, radical precursors, and participate in various chemical reactions like addition, condensation, and benzotriazole alkylation. Benzotriazole derivatives have been shown to exhibit a wide range of biological activities, making them valuable components in various pharmaceutical applications[22].

f) Nano-formulation and Drug Delivery: Incorporation of benzotriazole-based drugs into nano carriers (liposomes, nanoparticles, etc.) may enhance the specificity of drug delivery. By modifying their surface properties, these nano capsules can be designed to recognize and bind to target cells, allowing for targeted delivery, control release profiles, and improve therapeutic indices, especially for poorly soluble compounds[71].

This reduces the exposure of healthy tissues to the drug, thereby minimizing side effects. In medicinal chemistry, weak noncovalent interactions play a vital role in the development of active and more selective ligands. Deep benzotriazole cavitand-based dimeric nano capsules can act as excellent hosts for small drug molecules[72].

CONCLUSION

Benzotriazole derivatives have emerged as a valuable class of compounds in modern drug design due to their versatile chemical structure and broad spectrum of biological activities. Recent developments in computational modelling, structure-activity relationship research, and synthetic techniques have greatly spread along the development of BTA-based medicines. Treatment for several illnesses, including cancer, viral infections, inflammation, and microbial resistance, has been shown potential in these derivatives. Though there are some problems like metabolic stability and environmental issues, continuing research improves their pharmacological characteristics via creative techniques including molecular hybridization, prodrug synthesis, and nanotechnology-based delivery systems. Benzotriazole is still an intriguing framework with much potential in pharmaceutical development and research.

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