Current Chemistry Letters 14 (2025) 299–322

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

Benzotriazole and its derivatives: A comprehensive review of its synthesis, activities and applications

Monika R. Kshatriya[a] and Jinal A. Gajjar[a*]

[a]*Jeel Goswami College of Science & Research, Monark University, Vahelal, Ahmedabad, Gujarat, India*

C H R O N I C L E

Article history:
Received August 3, 2024
Received in revised form
September 16, 2024
Accepted November 5, 2024
Available online
November 5, 2024

Keywords:
Benzotriazole
Toxicity
Antimicrobial
Antiviral
Anticancer
Drug Resistance

A B S T R A C T

Benzotriazole, commonly referred to as BTAH, has garnered significant interest across several scientific disciplines due to its outstanding characteristics and wide-ranging applications. This document provides a concise overview of benzotriazole and its use in challenging corrosion scenarios. Furthermore, we emphasize the versatility of this molecule and the extensive research commitment associated with it. This thorough analysis examines the synthesis of benzotriazoles and their derivatives in-depth and encapsulates the numerous methods involved. Additionally, we conducted a thorough analysis of toxicity studies and the pertinent implications of benzotriazoles on human health, marine life, and the ecosystem. Our purpose is to provide readers with a thorough understanding of the potential dangers of this chemical by undertaking an extensive examination of associated risks and bad effects. During this review, we emphasize significant research discoveries and trends, offering useful insights into the current status of benzotriazole research and its future potential. The development of such research advances from 2010 to 2024.

1. Introduction

Benzotriazole derivatives are nitrogen-containing heterocycles that exhibit a broad spectrum of biological and pharmacological actions, including antibacterial, antifungal, anticancer, anti-inflammatory, and analgesic characteristics. [1-3] Benzotriazole has attracted considerable attention across several scientific fields due to its varied usage and distinctive chemical structure. It is categorized as a heterocyclic aromatic molecule, integrating a benzene ring with a triazole ring, which confers critical attributes such as elevated thermal stability, UV absorbance, and corrosion resistance. [4-6] Bioactivity is a general characteristic attribute of nitrogen-containing five-membered heterocycles, including compounds such as pyrroles, pyrazolines, azoles, oxazoles, triazoles, and others. These heterocycles exhibit a wide range of biological and pharmacological activities due to their unique electronic properties and structural stability, making them highly relevant in medicinal chemistry and drug design.[7-12] Furthermore, the pharmaceutical activity of nitrogen-containing five-membered heterocycles can be significantly enhanced by the presence of nitro groups within the molecules. This structural modification has been recently confirmed as an effective way to increase the bioactivity of these compounds, providing additional pathways for drug development and therapeutic applications.[13-15]

Benzotriazole is used for corrosion inhibition, polymer photo stabilization, medicinal chemistry, and electrochemical sensing. It is widely used as a corrosion inhibitor, creating a protective coating on metal surfaces to avert harm. Its corrosion-inhibiting characteristics are esteemed in industries like aerospace, automotive, and oil and gas. [16-20]

Benzotriazole and its derivatives function as UV absorbers, protecting polymers and coatings from UV radiation damage; hence, they are essential in UV-sensitive applications such as coatings and epoxy resins. Their distinctive structure

* Corresponding author
E-mail address jinalg112@gmail.com (J. A. Gajjar)

doi: 10.5267/j.ccl.2024.11.004

has prompted investigations into the creation of innovative therapeutic agents, owing to their varied biological activities and potential uses across several domains. [21–22] Extensive research has investigated the synthesis and functionalization of benzotriazole derivatives, aiming to enhance their characteristics for targeted applications, including corrosion inhibition, photo stabilization, and medicinal usage.[23-25]

Understanding the toxicological characteristics of benzotriazole is essential for evaluating its safety for human health and environmental effects. Benzotriazole, with its multifunctional properties, continues to be a central element of innovation in materials science, corrosion protection, and medicinal chemistry. [26–28] There are two tautomeric forms of benzotriazole (BTAH) that are made when protons move between nitrogen atoms **(Fig. 1, Forms A and B)**[29]. As early as 1860, Zonin studied azoxybenzene nitration. This led to the discovery of 2-phenylbenzotriazole-1-oxide, which was written about by Werner and Stastny in 1899.[30-31] In recent years, benzotriazole-derived compounds have been developed for applications in chemical synthesis, materials science, water treatment, and corrosion inhibition.[32-34] Considering the global increase in cancer mortality rates, with the World Health Organization documenting 9.6 million deaths and 18.1 million cases per year, especially in poorer nations, benzotriazole derivatives represent a significant basis for the development of novel treatments. [35]

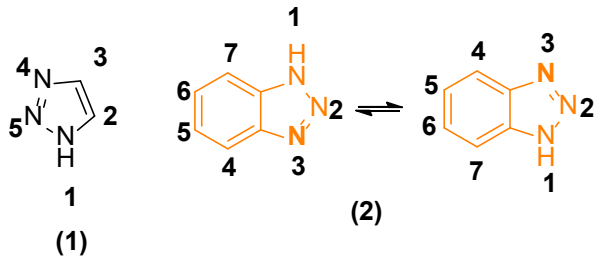


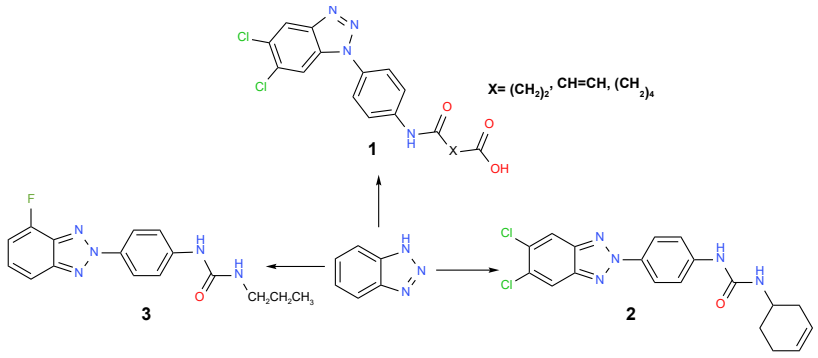
Fig. 1. The two tautomeric forms in Hbta

2. Biological Activities of Benzotriazole Derivatives

Benzotriazole compounds have diverse biological actions, including antiviral, antifungal, anticancer, antitubercular, and antioxidative properties. This section elucidates instances of essential chemicals and their distinct biological functions.

2.1. Benzotriazole as an Antiviral Agent

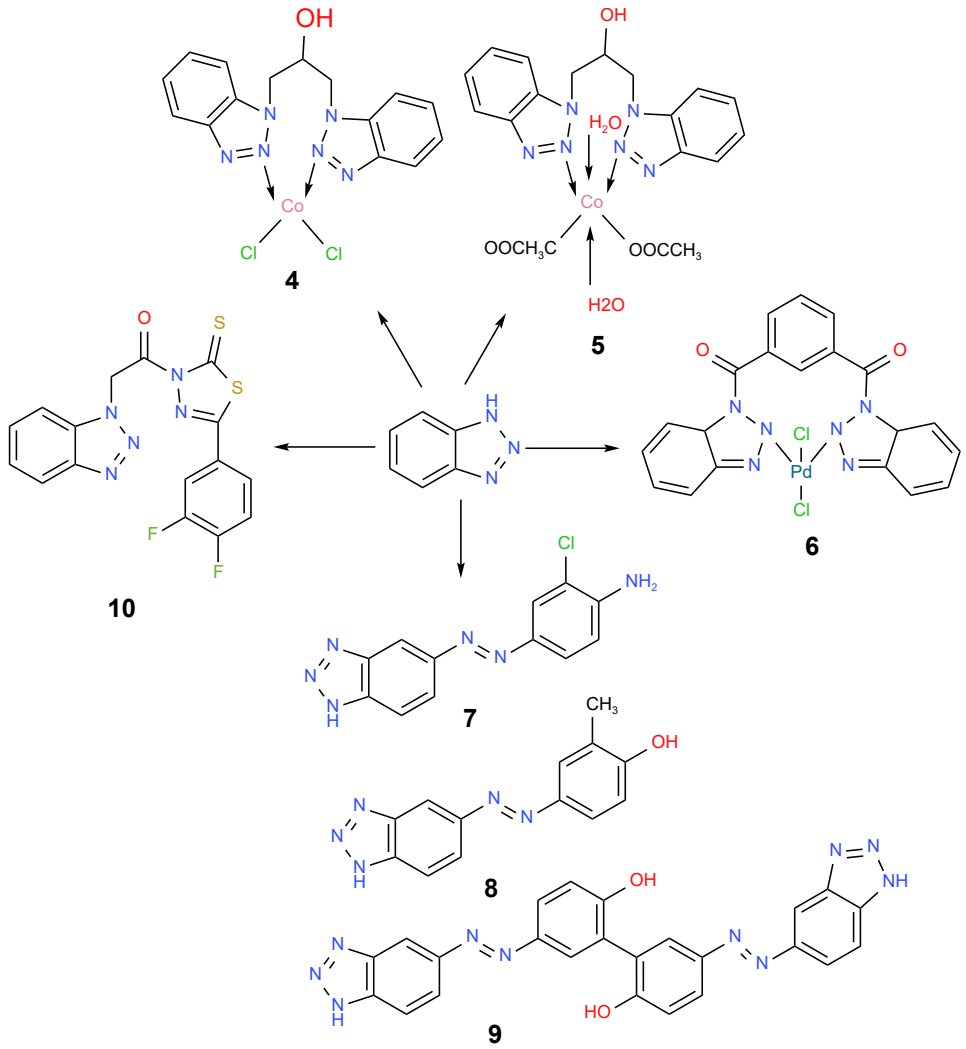
Research on benzotriazole-derived compounds has shown many potential antiviral medicines. Ibba et al. identified compounds including (Compound 1)[36] *2-(1H-benzo[d][1,2,3]triazol-1-yl)acetamide*, which showed strong antiviral activity against *Coxsackievirus B5*, with an MIC of 13 µM. This chemical obstructs viral replication by targeting viral RNA polymerase, offering a potential basis for the advancement of antiviral treatments. *N-(4-fluoro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)phenyl)Pivala- mide* (Compound 2)[37] demonstrated significant suppression of the *Seoul virus* (SEOV) entrance mechanism, exhibiting a minimum inhibitory concentration (MIC) of 4 µM. This chemical demonstrated significant effectiveness in a cell-based experiment and has potential as a targeted antiviral drug. *5-(1H-benzo[d][1,2,3]triazol-1-yl)-1H-tetrazole* (*Compound 3)*[38] was very good at killing *Poliovirus-1*, with an MIC of 9 µM. The method entails the interruption of viral entrance and reproduction, demonstrating its extensive antiviral efficacy. **Scheme 1** shows how these benzotriazole-based antiviral medicines are made, with clear labels on each molecule to make them easy to find and help with further research.



Scheme 1. The Antiviral activity of Benzotriazole derivatives

2.2. Benzotriazole as an antifungal agent

Benzotriazole derivatives demonstrate antifungal activity as well. Co (II) complexes with benzotriazole ligands, namely *N-(benzotriazole-1-yl)acetohydrazide* (Compound 4)[39], exhibited considerable antifungal activity, exceeding that of free ligands against *Candida albicans* and *Aspergillus niger*. A palladium complex benzotriazole derivative (Compound 5)[40] demonstrated a minimum inhibitory concentration (MIC) of 16 µg/mL against *Aspergillus niger*. Furthermore, the *2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide-Co(II)* complex (Compound 6)[41] showed significant antifungal activity, effectively inhibiting many fungal species, including Candida Alicante. Compound *2-(5-bromo-1H-benzo[d][1,2,3]triazol-1-yl)acetamide* (Compound 7), *N-(4-methoxybenzylidene)-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* (Compound 8) *and 3-(1H-benzo[d][1,2,3]triazol-1-yl)propanoic acid-Co(II) complex* (Compound 9) exhibited significant antifungal activity against *Aspergillus niger* and *Candida species* at several doses[42]. Additionally, the *N-(4-chlorobenzyl)-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetamide* (Compound 10)[43] demonstrates potent antifungal activity, significantly suppressing fungal proliferation at low minimum inhibitory concentration (MIC) values against various pathogenic fungi. **Scheme 2** delineates these antifungal drugs' synthesis pathways and reaction mechanisms, with each molecule appropriately cited for clarity.

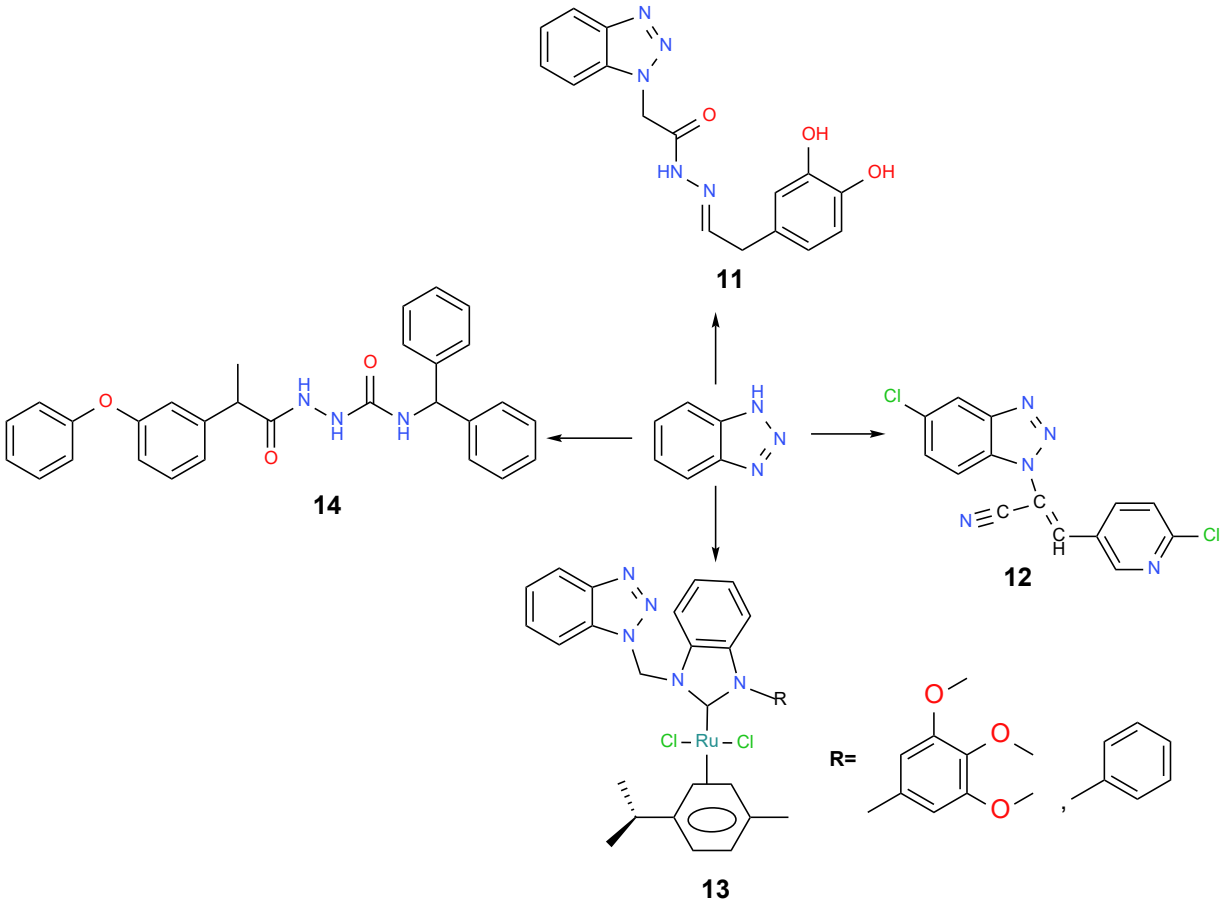


Scheme 2. The Antifungal activity of Benzotriazole derivatives

2.3. Benzotriazole as an antineoplastic agent

Benzotriazole derivatives have shown significant potential as antineoplastic (anticancer) agents, with several compounds demonstrating strong cytotoxic effects against various cancer cell lines. *2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(3,4,5-trimethoxybenzylidene)acetohydrazide* (Compound 11)[44] exhibited notable cytotoxicity across a range of cancer cell lines, with a minimum inhibitory concentration (MIC) of 29 µg/mL, particularly effective against breast and colorectal cancer cells. *N'-(2-hydroxy-3-methoxybenzylidene)-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* (Compound 12)[45] showed selective potency against stomach cancer cell lines, with a MIC ranging from 3.04 to 5.47 µg/mL, highlighting its potential for targeted anticancer therapy. Additionally, the *ruthenium(II)-coordinated 2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide complex* (Compound 13)[46] demonstrated a MIC of 200 µg/mL against *Caco-2* colorectal cancer cells, showing cytotoxic effects comparable to cisplatin while maintaining low toxicity against non-cancerous cells, which

suggests a favourable therapeutic index. Finally, *N-benzyl-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetamide* (Compound 14)[47] exhibited significant antiproliferative activity against breast and prostate cancer cell lines, with a MIC of 25 µg/mL, positioning it as a promising candidate for further anticancer research. **Scheme 3** provides the synthetic routes for these benzotriazole-based antineoplastic agents.



Scheme 3. The Anticancer activity of Benzotriazole derivatives

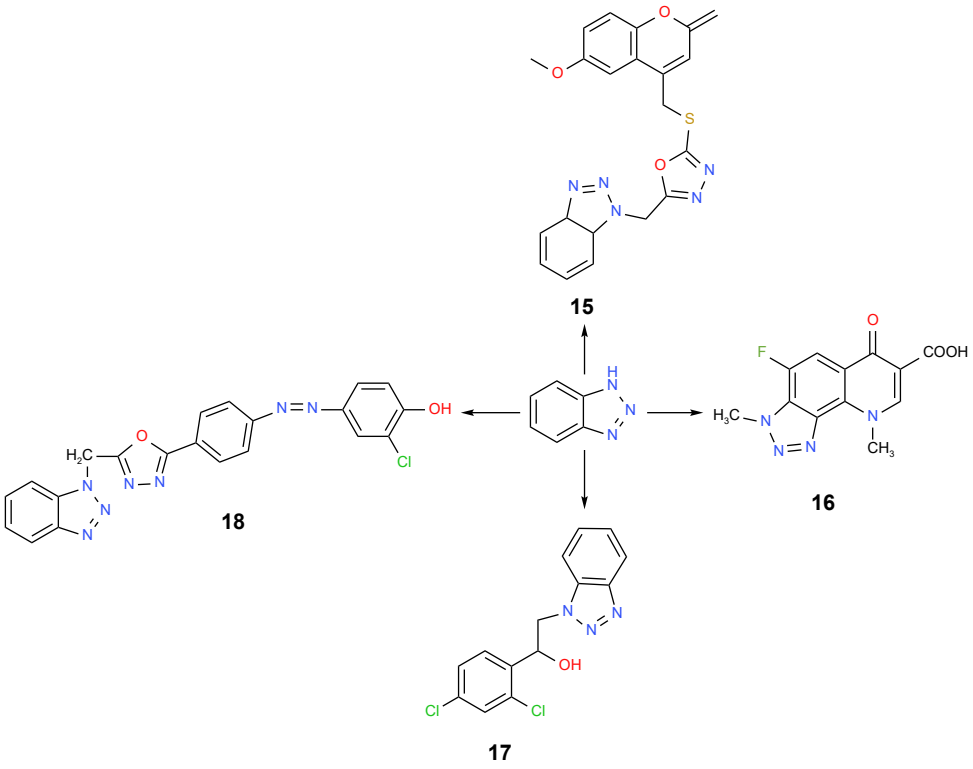
2.4. Benzotriazole as an antitubercular agent

Benzotriazole derivatives have surfaced as viable contenders in combating Mycobacterium tuberculosis (Mtb), particularly in tackling drug-resistant strains. Numerous drugs have demonstrated significant antitubercular efficacy, as evidenced by their minimum inhibitory concentration (MIC) values. *2-(1H-benzo[d][1,2,3]triazol-1-yl)thioacetamide* (Compound 15)[48], which is, showed strong activity against the Mtb H37Rv strain, with an MIC of 15.5 µg/mL. This makes it a promising candidate for further development in antitubercular therapies. *N'-(4-fluorobenzylidene)-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* (Compound 16)[49] effectively blocked Mycobacterium TB, with an MIC of 57.9 µg/mL, suggesting that it could be used as a moderately effective antitubercular agent. Additionally, (Compound 17)[38] *3-(1H-benzo[d][1,2,3]triazol-1-yl)phenylacetamide* showed a minimum inhibitory concentration (MIC) of 16 µg/mL against the Mtb H37Rv strain, indicating strong action that could be improved for better results. Finally, *N-benzyl-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetamide* (Compound 18)[50] showed great antibacterial activity against many bacterial strains, including Mtb, with a MIC of 21 µg/mL, suggesting that it could be used to fight a wide range of microbes. **Scheme 4** shows how to make antitubercular chemicals from benzotriazoles. Each product is clearly labelled to make further research and progress easier.

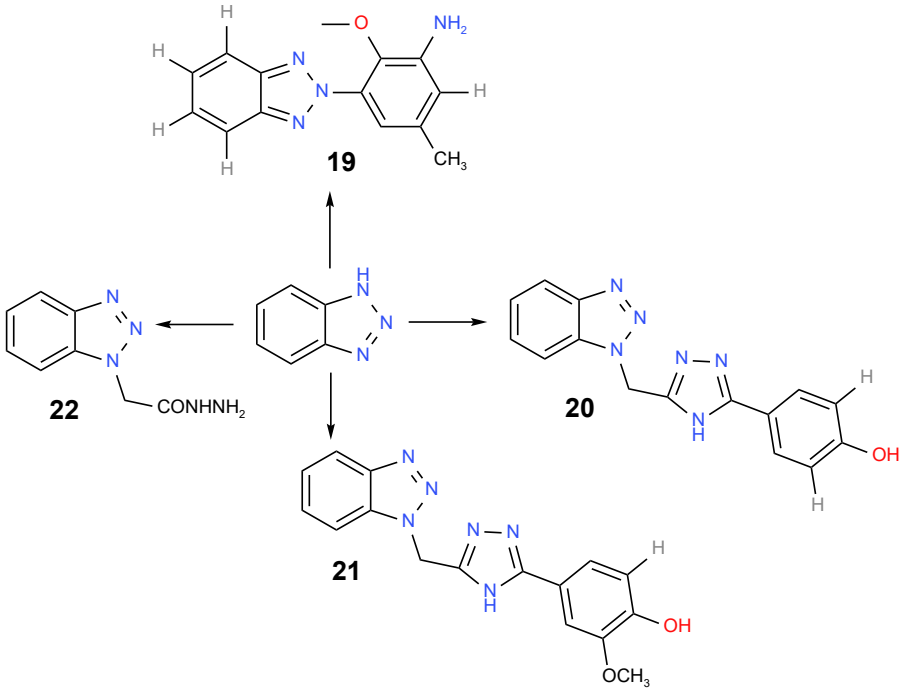
2.5. Benzotriazole as an antioxidant

Benzotriazole compounds have significant antioxidative capabilities, aiding in the neutralization of free radicals associated with aging and other illnesses. Radical scavenging experiments have recognized numerous substances for their potent antioxidant properties, measured by their minimum inhibitory concentration (MIC) values. PBT1, or *2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(3,4,5-trimethoxybenzylidene)acetohydrazide,* (Compound 19)[51] was the tested compound that showed the highest antioxidant activity. Its minimum inhibitory concentration (MIC) was 98.52 µg/mL, which suggests that it could be used in treatments for oxidative stress. (Compound 20) *N'-(2-hydroxy-3-methoxybenzylidene)-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* showed strong antioxidant activity, with a MIC of 84.97 µg/mL, making it a

possible treatment for diseases connected to oxidative damage. *N'-(4-hydroxy-3,5-dimethoxybenzylidene)-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* (Compound 21) showed antioxidative properties with a minimum inhibitory concentration of 92.22 µg/mL. It had a lot of free radical scavenging potential and could be used to fight inflammation or ageing. In the end, *N-(4-chlorobenzyl)-2-(1H-benzo[d][1,2,3]triazol-1-yl)acetamide* (Compound 22) showed strong antioxidant properties, with a MIC of 53.19 µg/mL.[52] This made it a very good antioxidant that could be used in medicine. In **Scheme 5**, the steps for making these antioxidant benzotriazole derivatives are shown. Each molecule is clearly labeled to make further research and use easier.



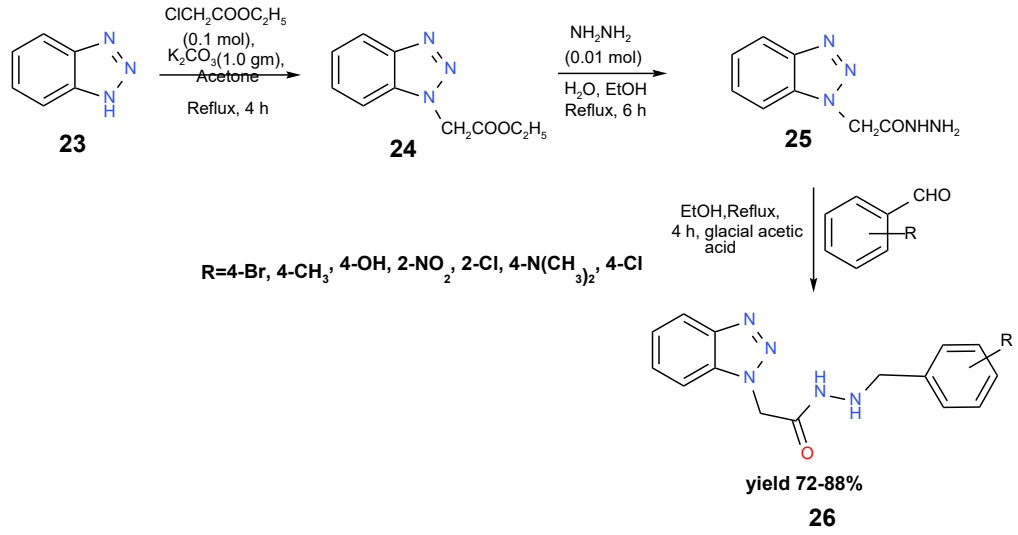
Scheme 4. The antitubercular activity of Benzotriazole derivatives



Scheme 5. The antioxidative activity of Benzotriazole derivatives

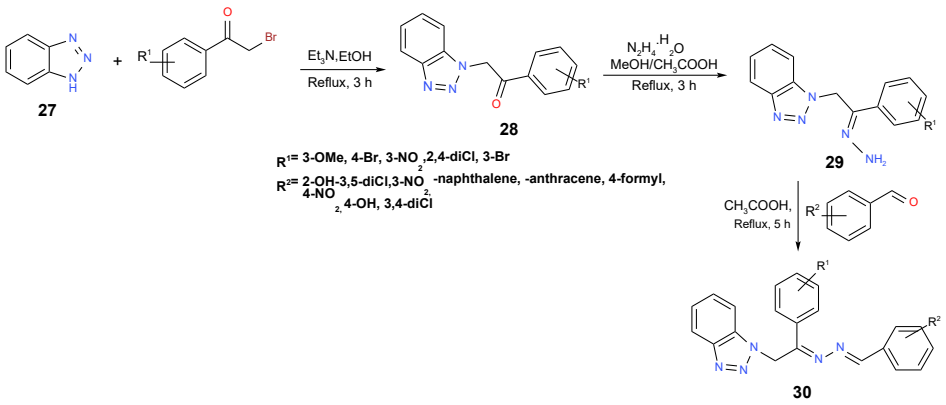
3. Reactions and Synthesis of Benzotriazole Derivatives

A convenient and efficient 4-step synthesis of Schiff bases *2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(substituted benzylidene)acetohydrazide* demonstrated by Rahmani Salah Eddin et al. **(See Scheme 6)** [42]. the synthesis begins with the preparation of benzotriazole ethyl acetate (compound 24) from benzotriazole (compound 23) via a nucleophilic substitution reaction. This step involves the use of chloroethyl acetic acid and potassium carbonate as a base, with acetone as the solvent. The second step consists of the hydrazinolysis of the ester group in benzotriazole ethyl acetate (compound 24), where hydrazine hydrate reacts with benzotriazole ethyl acetate to produce *2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* (compound 25). The final step is a condensation reaction where an equal amount of substituted aromatic aldehydes is added to *2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* (compound 25), forming Schiff bases (compound 26). The results showed that all the compounds exhibit significant antioxidant activity. The Compounds substituted with electron-donating groups like methoxy and hydroxyl showed higher antioxidant activity.[53]



Scheme 6. The Synthesis of *2-(1H-Benzo[d][1,2,3]Triazol-1-yl)-N'-(Substituted Benzylidene)Acetohydrazide*

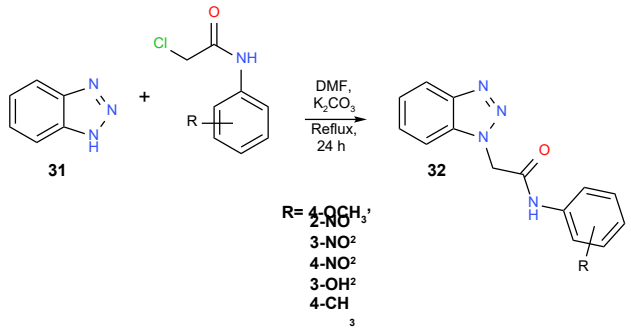
Khan et al. have developed a way for the synthesis, in vitro α-glucosidase inhibition, and molecular docking examination of the benzotriazole-based bis-Schiff base derivatives The synthesis starts with the reaction between benzotriazole (compound 27) and substituted phenacyl bromide in the presence of triethylamine and ethanol, forming compound 28. This step is a typical nucleophilic substitution where the benzotriazole acts as the nucleophile, attacking the electrophilic carbon in the phenacyl bromide. The next step involves the reaction of compound 28 with hydrazine hydrate in a methanol/acetic acid mixture, yielding compound 29. This process involves the substitution of the bromine atom with a hydrazone group, again showcasing a nucleophilic substitution reaction. In the final step, compound 29 undergoes a condensation reaction with an aldehyde (R_2CHO) in the presence of acetic acid, leading to the formation of the bis-Schiff base derivative (compound 30). This step is a classic example of Schiff base formation, where the primary amine reacts with the aldehyde to form an imine bond. the observation found that numerous of the compounds exhibited sturdy α-glucosidase inhibitory interest, with IC50 values within the micromolar range. Molecular docking research was additionally accomplished to analyse the binding interactions between the compounds and the α-glucosidase enzyme. The results of the docking studies had been in exact settlement with the data on in vitro α-glucosidase inhibitory activity. **(See Scheme 7).**[54]



Scheme 7. The Synthesis of benzotriazole-based bis-Schiff base analogs

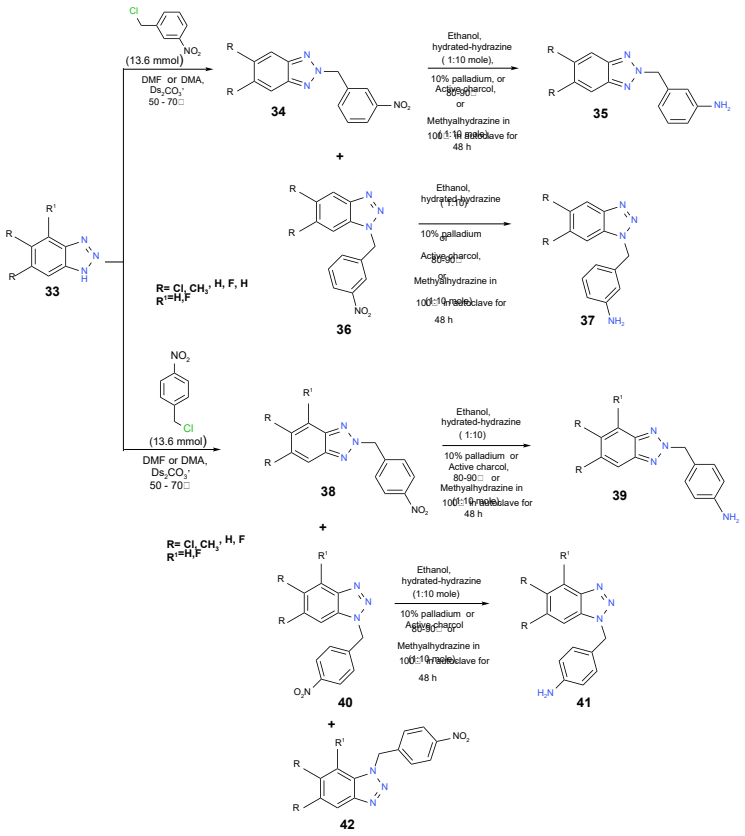
Bashir et al. investigated the reaction of Benzotriazole (compound 31) reacts with 2-chloro-N-(substituted phenyl) acetamide (compound 32). This step involves a nucleophilic substitution where the nitrogen atom in benzotriazole attacks

the electrophilic carbon in 2-chloro-N-(substituted phenyl) acetamide, leading to the displacement of the chlorine atom. The reaction produces the final product, *2-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(substituted phenyl)acetamide* (compound 32), under reflux conditions in DMF with potassium carbonate (K_2CO_3) as a base. The synthesized benzotriazole derivatives are characterized using various analytical techniques such as IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry, confirming their structures. The compounds exhibit a broad spectrum of biological activities, including antibacterial, antifungal, antiviral, anti-inflammatory, antihypertensive, and analgesic properties. **(See Scheme 8).** [55]



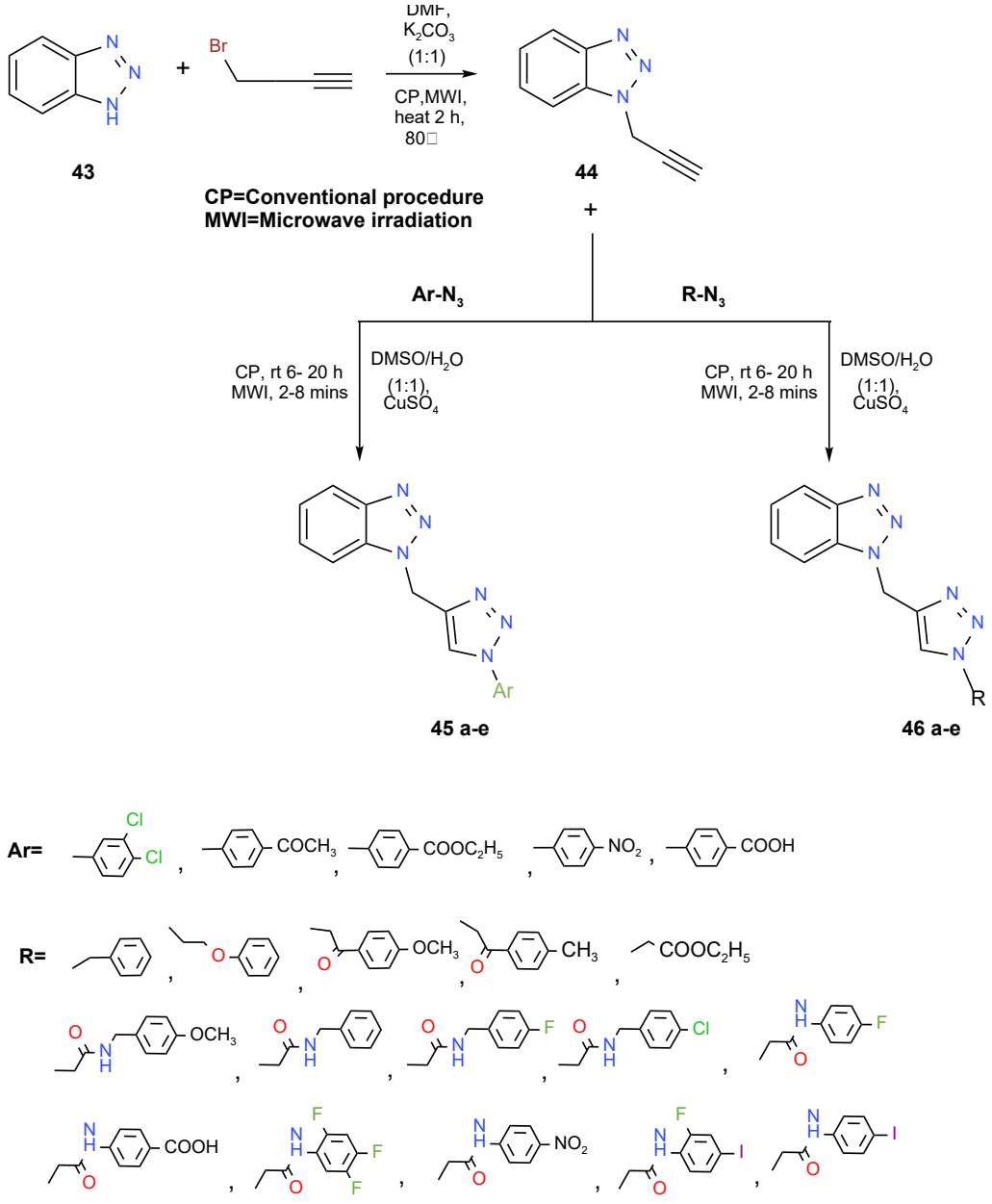
Scheme 8. The Synthesis of 2-(1H-benzo[d]1,2,3–triazole-1-yl)– N-(substituted phenyl) acetamide

Ibba et al. developed an effective method for producing *benzo[d][1,2,3]triazol-1(2)-yl derivatives* as potential antiviral agents. Benzotriazole derivatives (compound 33) are reacted to form nitro-substituted intermediates (compounds 34,35,36,37,38). These nitro intermediates undergo reduction, using either methylhydrazine or hydrated hydrazine in the presence of palladium on activated carbon. This reduction process converts the nitro groups to amines, leading to the formation of the final compounds (compounds 39, 40, 41, 42). The reduction is catalysed by palladium on activated carbon (10% Pd/C), a common catalyst for hydrogenation reactions. Ethanol is used as the solvent, and the reaction is conducted under autoclave conditions at elevated temperatures (80–90°C), which facilitates the hydrogenation process. The synthesized amine derivatives (compounds 39, 40, 41, 42) are investigated for their biological activity, particularly as antiviral agents. Among them, compound *N-(4-((4-fluoro-1H-benzo[d][1,2,3]triazol-1-yl)methyl)phenyl)pivalamide* exhibits promising activity against *coxsackievirus B5*. **(See Scheme-9).**[56]



Scheme 9. The Synthesis of new antivirals, a notable number of benzo[d][1,2,3]triazol-1(2)-yl d

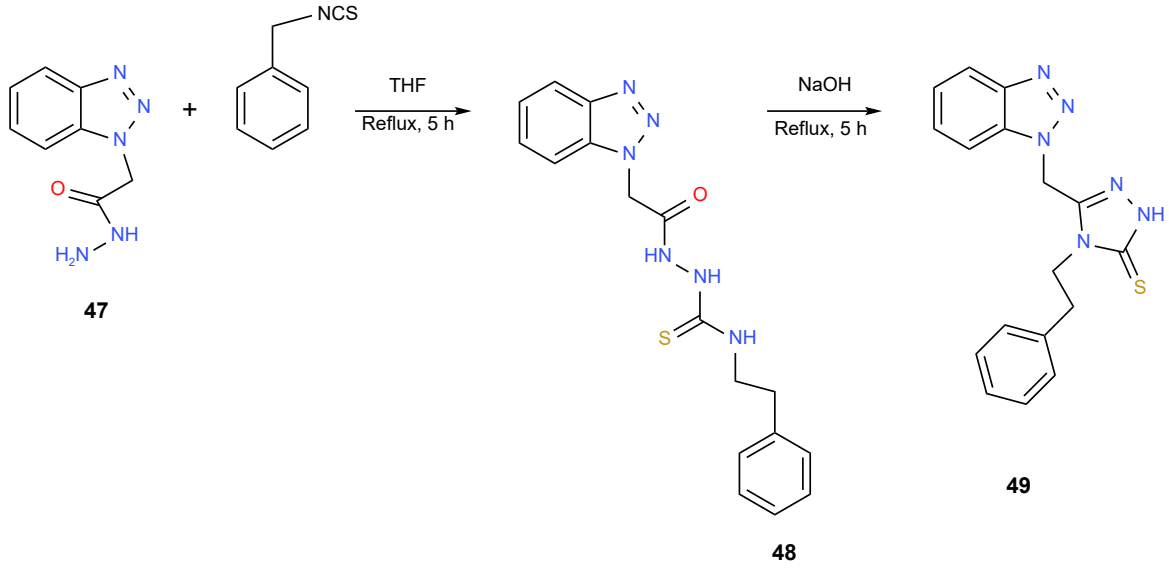
Shaya Yahya et al. described the synthesis of benzotriazole-1,2,3-triazole derivatives with potential anti-cancer interest. The synthesis begins with the reaction of Benzotriazole (compound 43) with propargyl bromide, yielding an intermediate acetylene derivative (compound 44) via alkylation. This acetylene derivative (44) is then subjected to a Cu(I)-catalyzed 1,3-dipolar cycloaddition ("click" reaction) in the presence of DMSO and water, leading to the formation of triazole-containing derivatives (45a-g, 46a-g). The traditional method involves refluxing the reaction mixture for around 6 hours, yielding the products in 80-83%. Microwave irradiation significantly reduces the reaction time to just 2-6 minutes while achieving higher yields (88-90%). The comparison between the conventional and microwave-assisted methods indicates that microwave-assisted synthesis is more energy-efficient and time-saving, with better yields, demonstrating it as an effective strategy for synthesizing benzotriazole derivatives. The synthesized benzotriazole derivatives (45a-g, 46a-g) are of interest due to their potential anti-cancer properties, showcasing the importance of efficient synthesis methods **(Scheme 10)**.[57]



Scheme 10. The synthesis series of novel benzotriazole1,2,3-triazole.

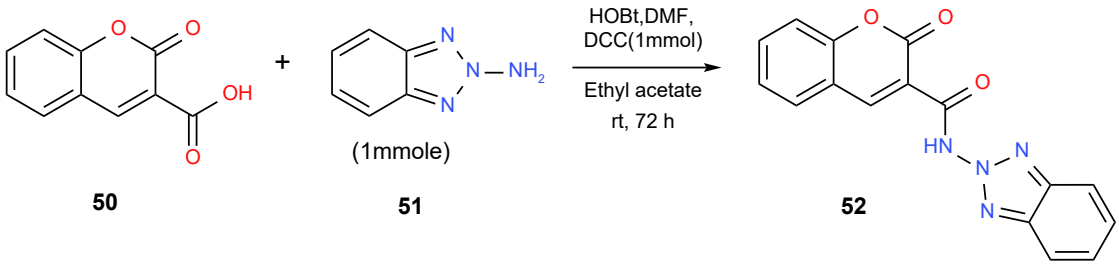
Karagoz and co-workers give the synthetic pathway here involves the reaction of a hydrazide (compound 47) with an isothiocyanate. Isothiocyanates are commonly used in organic synthesis for creating thiourea derivatives and related compounds. This reaction likely proceeds through a nucleophilic attack on the isothiocyanate carbon, forming a thiourea intermediate (compound 48). After the formation of the thiourea intermediate (compound 48), the reaction undergoes base-mediated cyclization under the influence of sodium hydroxide (NaOH). This step typically involves the deprotonation of the intermediate, leading to intramolecular cyclization and the formation of the final product (compound 49). The reaction employs a strategy of ring closure, where the intermediate compound undergoes cyclization to form the triazole and benzotriazole ring systems within the product (compound 49). This type of ring closure is often key in building heterocyclic

frameworks. The synthesis is carried out under reflux in tetrahydrofuran (THF) for 5 hours. Reflux is a common technique in organic synthesis to maintain the reaction at the solvent's boiling point, ensuring that the reaction proceeds efficiently. **(See Scheme-11)**.[58]



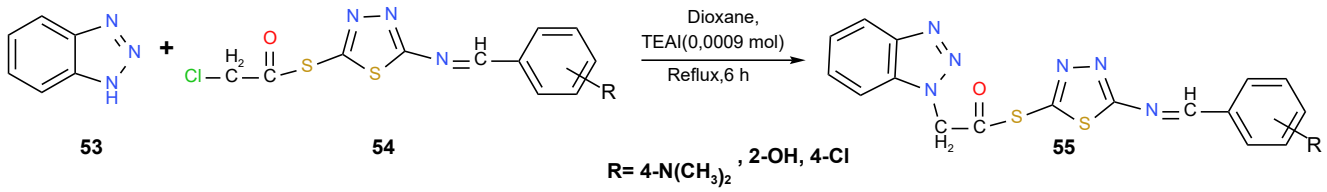
Scheme 11. The Synthetic of (BPT)

Riyadh Ahmed effectively synthesized compound, *N-(2H-Benzo[d][1,2,3]triazol-2-yl)-2-oxo-2H-chromene-3-carboxamide* The key reaction strategy involves the formation of an amide bond between the carboxylic acid group of 2-oxo-2H-chromene-3-carboxylic acid (compound 50) and the amine group of 2-amino benzotriazole (compound 51). This type of coupling reaction is commonly employed in organic synthesis to link amino groups with carboxylic acids. DCC is used as a coupling reagent in this synthesis. DCC activates the carboxylic acid, making it more reactive towards nucleophilic attack by the amine group. This is a standard method in peptide synthesis and other applications requiring amide bond formation. The reaction also involves HOBt, which is used to suppress side reactions and increase the yield of the desired product. HOBt stabilizes the intermediate, leading to more efficient amide bond formation. The reaction is carried out at room temperature (rt) for 72 hours. The extended reaction time allows for the completion of the coupling process under mild conditions, which is often desirable for sensitive or complex molecules The product (compound 52) features a heterocyclic amide, a structure that is significant in medicinal chemistry due to its potential biological activity. The coupling reaction strategy employed here is specifically geared toward constructing this type of heterocyclic structure. **Scheme-12.**[59]



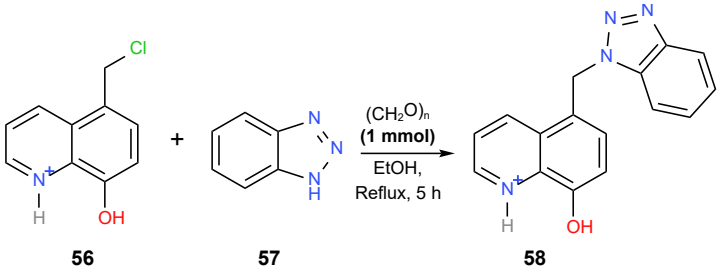
Scheme 12. The synthesis of *N-(2H-benzo[d][1,2,3]triazol-2-yl) -2-oxo-2H-chromene-3-carboxamide*

Aziz Ibrahim successfully synthesized benzotriazole derivatives in this strategy, a primary aromatic amine is converted into a diazonium salt, which serves as a versatile intermediate for various substitution reactions. Diazotization is particularly useful in introducing aryl groups or forming azo compounds in benzotriazole derivatives. This approach involves the cycloaddition of azides with alkynes to form triazoles, a type of heterocycle that is closely related to benzotriazoles. Azide cycloaddition, often referred to as "click chemistry," is a reliable and efficient method for synthesizing triazole-containing derivatives. Metal-catalyzed C-H activation is a powerful strategy for directly functionalizing C-H bonds in benzotriazoles. This methodology allows for the formation of new C-C, C-N, or C-O bonds, enabling the introduction of various functional groups into the benzotriazole core. The specific synthesis of benzotriazole derivatives described in the text involves the formation of thioester bonds. In this methodology, benzotriazole (53) is reacted with thioacetyl chloride (54) in the presence of dry dioxane and triethylamine (TEA), leading to the formation of thioester-linked derivatives (55). This approach is significant for its role in enhancing the antibacterial activity of the synthesized compounds. **(Scheme-13)**.[60]



Scheme 13. The Synthesis of Benzotriazole derivatives

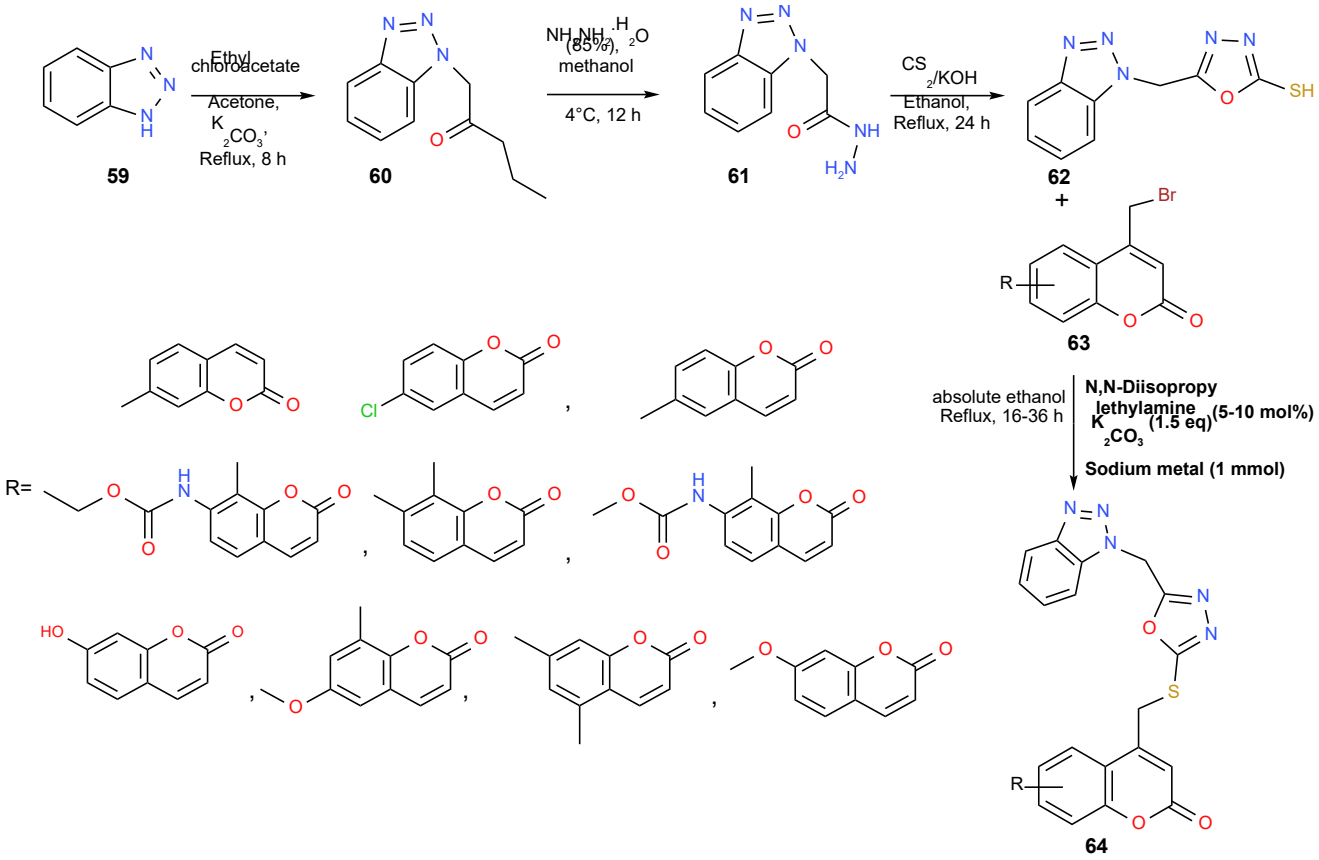
Banacer Himmi and his co-workers gave the synthesis depicted in the reaction involves a Mannich reaction, which is a classical three-component reaction where an aldehyde (in this case, paraformaldehyde) reacts with a compound containing an active hydrogen atom (quinoline derivative 56) and an amine (benzotriazole 57). The Mannich reaction is well-known for its ability to form carbon-nitrogen bonds, which are essential in the construction of complex nitrogen-containing heterocycles such as quinoline derivatives. Benzotriazole (57) is used in this synthesis as a reactant to introduce a nitrogen-rich moiety into the quinoline framework. Benzotriazole-based reactions are highly versatile and are commonly employed in the synthesis of various heterocyclic compounds due to their stability and reactivity. The reaction is carried out under reflux conditions in ethanol (EtOH) for 5 hours, which is a typical procedure to ensure the reaction goes to completion by maintaining the temperature and solvent under a controlled state. The resulting product, compound (58) a quinoline derivative (DD2), is obtained with a yield of 30%. The structure of the compound is characterized using spectroscopic methods and single-crystal X-ray diffraction, which provides detailed information about the molecular structure. Additionally, molecular docking studies are employed to investigate the potential activity of DD2 against SARS-CoV-2 targets, demonstrating its relevance in antiviral research. **(Scheme-14)**.[61]



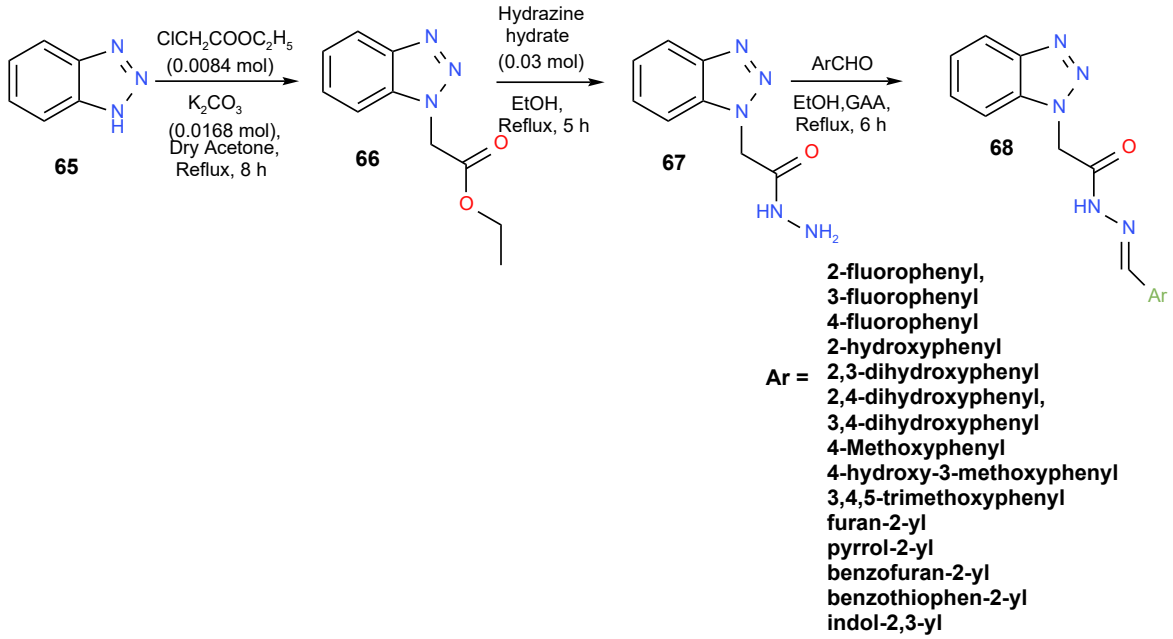
Scheme 14. The Synthesis of, (DD2) derivative

Ambekar et al. reported the synthesis of coumarin derivatives containing a new 1,3,4-oxadiazoles benzotriazole moiety The synthesis begins with benzotriazole (59) reacting with ethyl chloroacetate to produce an ester intermediate (60) via esterification. This intermediate is then subjected to hydrazinolysis using hydrazine hydrate in methanol at 4°C, forming the hydrazide (61). These two steps are crucial for introducing the hydrazide functionality, which serves as a precursor for subsequent heterocyclic ring formation. The hydrazide (61) undergoes cyclization with carbon disulfide in the presence of potassium hydroxide and ethanol, leading to the formation of the 1,3,4-oxadiazole ring (62). This strategy is commonly used to synthesize oxadiazole-containing compounds, which are known for their wide range of biological activities. The next step involves coupling the oxadiazole-containing compound (62) with 4-bromomethyl coumarins (63). This step combines the oxadiazole-benzotriazole moiety with a coumarin structure, which is known for its various pharmacological properties. The reaction is carried out under reflux conditions using either N, N-diisopropylethylamine, potassium carbonate or sodium metal as the base in absolute ethanol, leading to the final product (64) with yields ranging from 75% to 34%. Throughout the synthesis, several steps involve reflux conditions and the use of different bases like potassium carbonate, sodium metal, or N, N-diisopropylethylamine to facilitate the reactions. These conditions ensure complete reaction and high yields of the desired products. The final compounds (64), with different R-substituted groups, show significant antimycobacterial activity against the *Mycobacterium tuberculosis* H37Rv strain at low micromolar doses. This demonstrates the potential of these coumarin derivatives in drug development for tuberculosis treatment. **Scheme 15**.[62]

Smaa E. Kassab et al. studied a new class of compounds called *2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(2,3,4-substituted)derivatives* **(Scheme-16)**.[63] The compound *ethyl2-(1H-benzo[d][1,2,3]triazol-1-yl)(66) acetate* made by using benzotriazole (65) reacted with ethyl chloroacetate in the presence of anhydrous potassium carbonate. Intermediate was reacted with hydrazine hydrate to form *2-(1H-benzo[d][1,2,3,]triazo-1-yl)acetohydrazide* (67) compound. By combining this intermediate with various types of aldehydes, and glacial acrylic acid (GAA) the researchers were able to obtain the final product *2-(1H-benzo[d][1,2,3]triazo-1-yl)-(2,3,4-substituted)* (68) with excessive yields. Each synthesized molecule was evaluated by the NCI (USA) for its potential anticancer activity below DTP. The study's objective was to evaluate the compounds' anticancer activity against specific cancer cell lines and identify any inhibitory effects against FAK and Pyk2, leading to apoptosis.



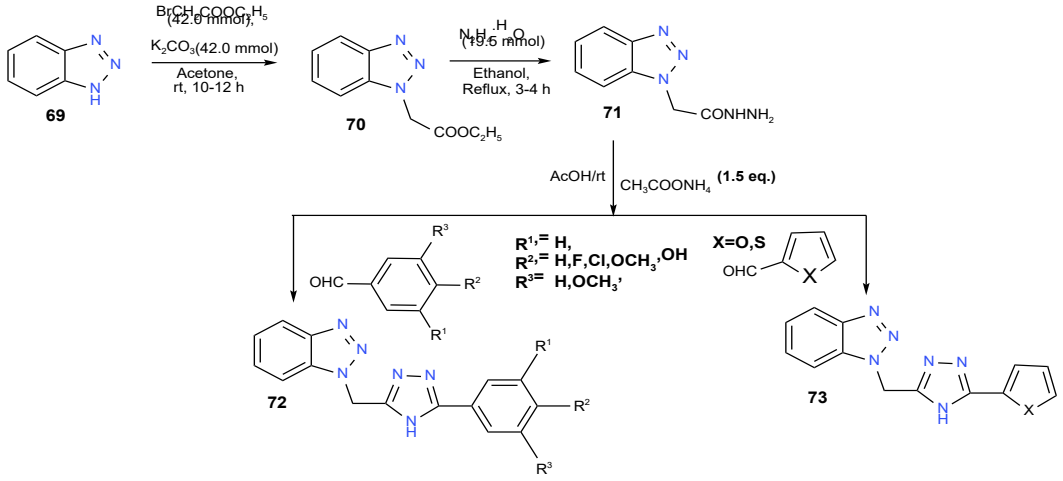
Scheme 15. The Synthesis of 1,3,4-oxadiazoles containing benzotriazole and coumarin moiety



Scheme 16. The Synthesis of *2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(2,3,4-substituted)* derivatives.

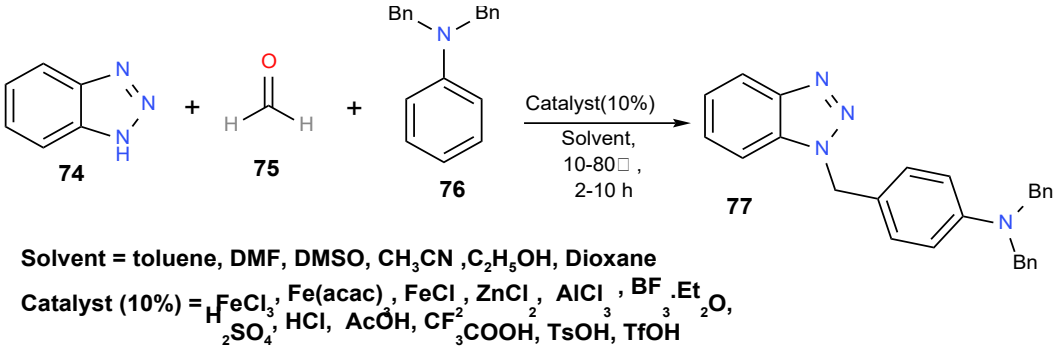
Subhash Chand Jain and his team have developed a novel approach for synthesizing 1,2,4-triazolyl benzotriazoles with high yield, as described in **Scheme-17.**[64] The method involves employing benzotriazole (69) in the presence of ethyl bromoacetate to yield *1-(methoxycarbonyl methyl)-1H-benzotriazole* (70), which is then refluxed with hydrazine hydrate to produce *1-(hydrazinylcarbonylmethyl)-1H-benzotriazole* (71). The corresponding triazolyl benzotriazoles (72, 73) were obtained after reacting (71) with various substituted aromatic aldehydes. The compounds were extensively characterized by

using various spectral techniques ^{1}H NMR, ^{13}C NMR, and mass and they were found to have promising antimicrobial, antifungal, and antioxidant activities. Particularly, compounds with -OH and/or -OCH_3 groups in the phenyl ring exhibited elevated antimicrobial activity. Compound 68 shows the demonstrated good antifungal activity[53].



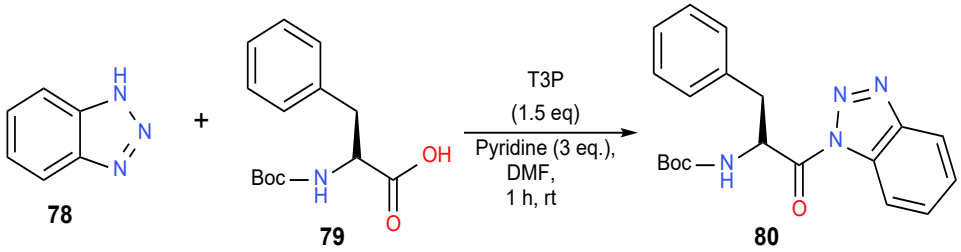
Scheme 17. The Synthesis of 1,2,4-triazolebenzotriazoles.

Xingdong Wang and colleagues developed a new method for the synthesis of N-alkyl benzotriazoles (77) using a one-pot reaction of benzotriazoles (74) with aldehydes (75), and tertiary anilines (76) in the presence of various catalysts, thereby obtaining the final compounds in higher yield (77) **(Scheme-18).**[65] This method is efficient, regioselective, and environmentally friendly, with good tolerance to functional groups and easily accessible starting materials. The protocol is suitable for drug development and can be carried out without inert gas, producing water as the only by-product. The mechanistic studies indicated that azaquinzole methide was probably involved as an intermediate in this transformation. A gram-scale reaction was successfully carried out.



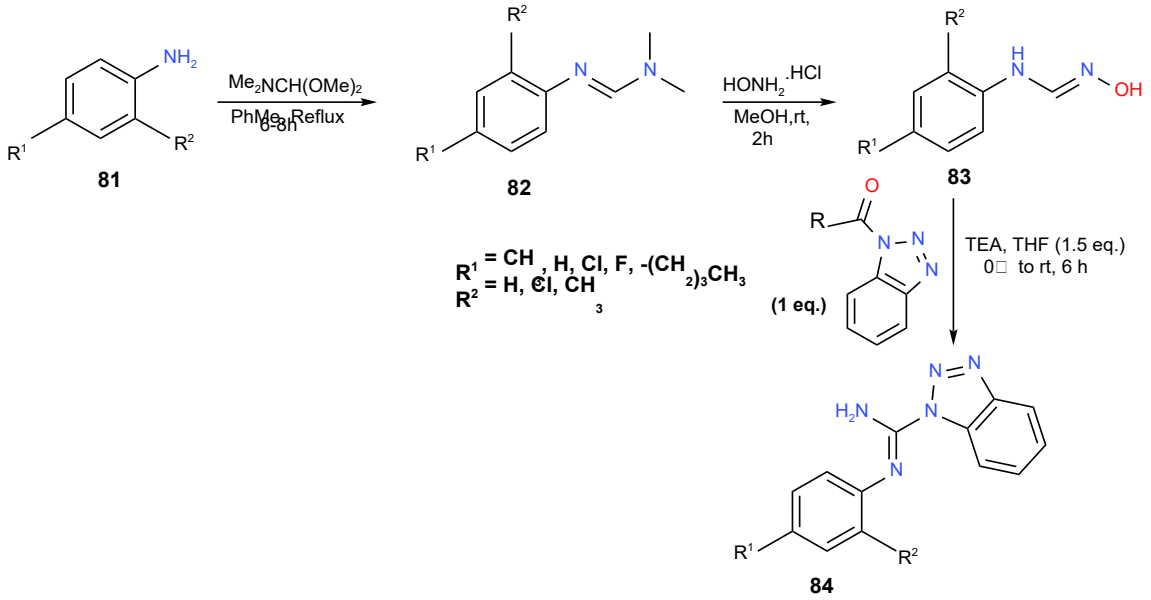
Scheme 18. One-Pot Synthesis of N-Alkyl Benzotriazoles.

Guillaume Laconde and co-workers have synthesized N-acyl-benzotriazole amino acid derivatives **(Scheme-19).**[66] The synthesis of N-acyl-benzotriazole amino acid derivatives was carried out in a one-pot procedure. The compound (80) was produced by a reaction between the amino acid (79) and benzotriazole (78) with T3P (Propane phosphonic acid anhydride), DMF as a solvent, and pyridine as a base. In the one-pot method, T3P can synthesize various N-acyl-benzotriazole amino acid derivatives, including those with acid-sensitive protecting groups. N-acyl-benzotriazole amino acid derivatives have a wide range of uses. Using the highly sensitive trityl group can avoid the need for tedious purification and more toxic reagents. In addition, T3P was used for the synthesis of biotin and N-Fmoc polyethylene glycol derivatives.



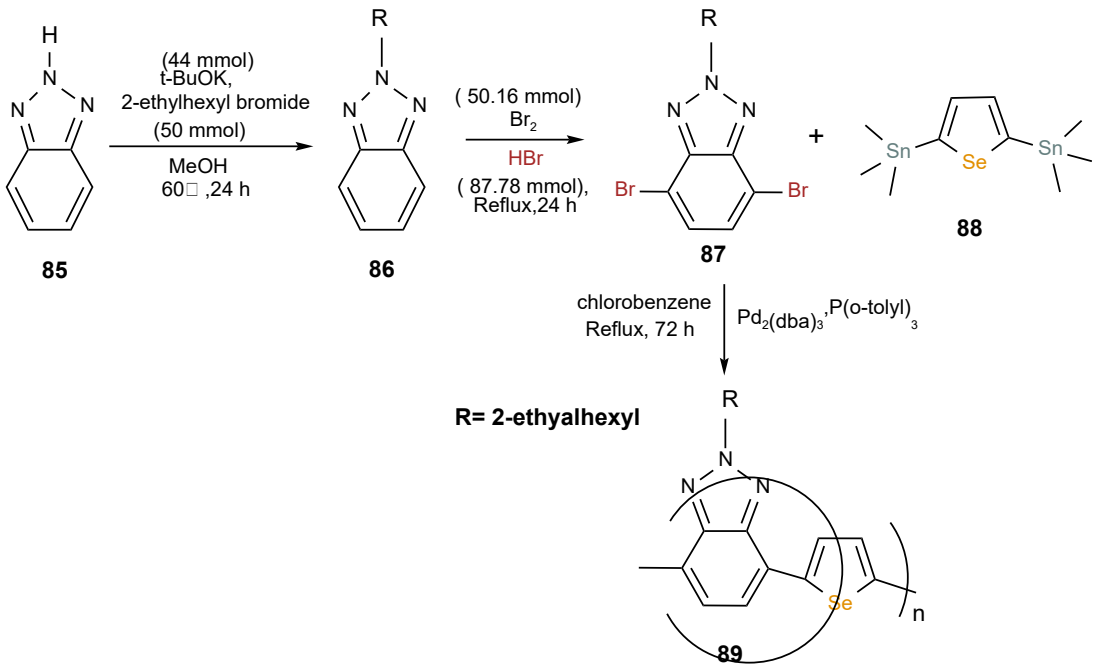
Scheme 19. The synthesis of N-acyl-benzotriazole amino acid derivatives

Researchers led by Riham M. Bokhtia created a novel class of 1H-benzotriazole-1-carboximidamide derivatives. They treated substituted anilines (81) with N, N-dimethyldimethylacetyl to obtain (E)-N'-(substituted phenyl)-N, N-dimethylimidamides (82) which were further reacted with hydroxylamine hydrochloride in the presence of methanol to obtain oxime intermediate (83) with a fair yield. The final product *1H*-benzotriazole-1-carboximidamides (84) was synthesized from the oximes intermediate (83) **(Scheme-20).**[67] The structure of the obtained compound was further confirmed and investigated by X-ray and DFT studies. In this study, the author explored the use of acyl benzotriazoles as the source of benzotriazole. When using aminoacyl benzotriazole instead of aryl benzotriazole, it obtained a higher yield.



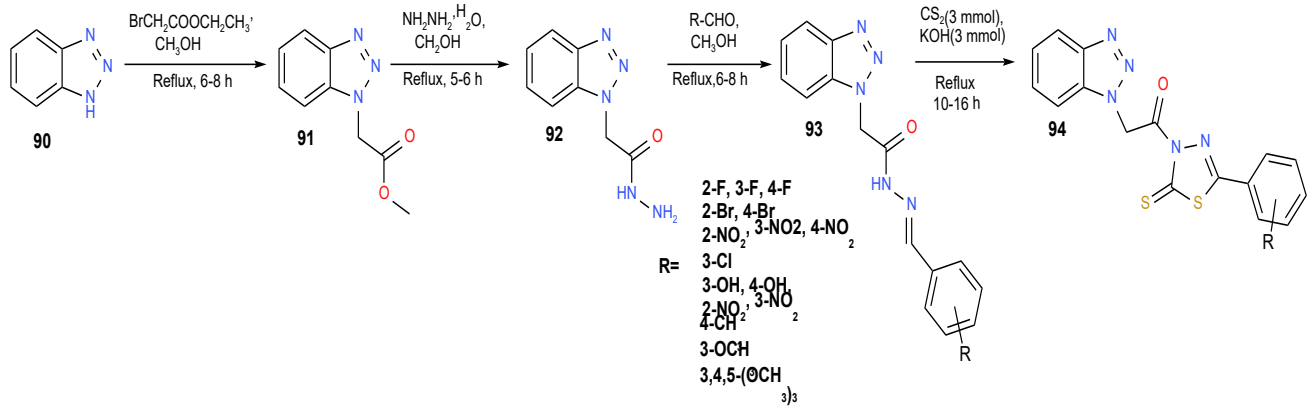
Scheme 20. The Synthesis of *1H-benzotriazole-1-carboximidamides*

Eunbyuel Lee and their team synthesized a new polymer called *poly(4,7-(2-ethylhexyl)-2H-benzo[d][1,2,3]triazole-alt-5,5'-selenophene*)(P(BTz-Se)) using a Stille coupling reaction. To create the polymer, they first reacted 1,2,3-benzotriazole (85) with 2-ethylhexyl bromide and potassium tert-butoxide in methanol to obtain *2H-(2-ethylhexyl)-benzotriazole* (86) which further reacted with bromine and hydrobromic acid under reflux condition to get *4,7-dibromo-2H-(2-ethylhexyl)-benzotriazole* (87). The intermediate (87) further reacted with *2,5-bis(trimethylstannyl)selenophene* (88) using triphenylphosphine as catalysts to obtain the final product P(BTz-Se) (89) **(Scheme-21).**[68] The hole mobility of P(BTz-Se) was six times higher than the reported hole mobility of a BTz-thiophene copolymer, making it a promising candidate for use in organic field-effect transistors and other optoelectronic devices.



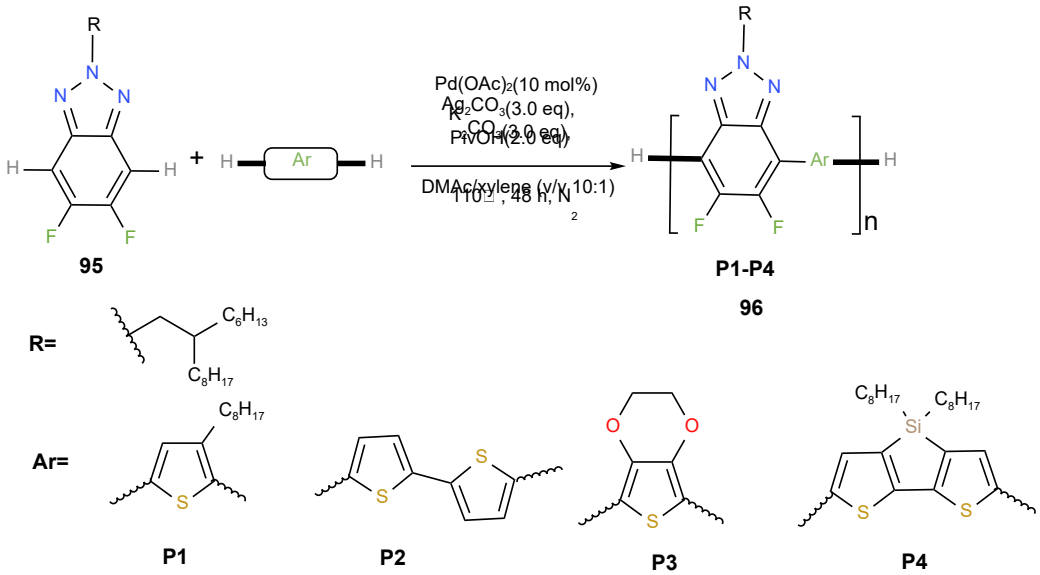
Scheme 21. Synthesis of *4,7-dibromo-2H-(2-ethylhexyl)-benzotriazole*

Godhani and his team have successfully synthesized novel derivatives of benzotriazole-substituted 1,3,4-thiadiazole-2(*3H*)-thiones using a specific reaction sequence **(Scheme-22).**[69] The process began by esterifying benzotriazole (90) with ethyl bromoacetate, which resulted in the appropriate ester (91). The ester was then hydrazinolysis with hydrazine hydrate in ethanol to create *2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide* (92). Following the reaction, the hydrazide was condensed with aromatic aldehydes in ethanol to form Schiff base derivatives (93). The Schiff bases were then cyclized with CS_2 in alcoholic KOH, resulting in the formation of *2(1H-benzo[d][1,2,3]triazol-1-yl)-1-(5-(aryl)-2-thioxo-1,3,4-thiadiazol-3(2H)-yl)ethan-1-one derivatives* (94) in high yield. These derivatives exhibited promising biological activity against various bacterial and fungal strains, along with anti-inflammatory and anti-spasmodic properties. Among the 15 compounds, substituted three compounds 3-F, 4-F, and 3-NO_2 showed promising antifungal activities.



Scheme 22. The synthesis of *2-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(5-(aryl)-2-thioxo-1,3,4-thiadiazol-3(2H)-yl)ethan-1-one.*

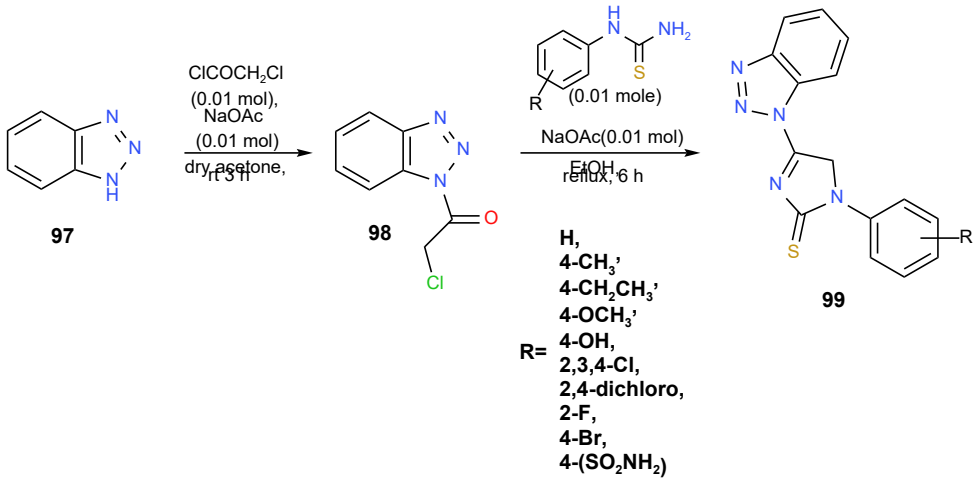
Han et al. have developed a new synthetic procedure for π-conjugated polymers containing benzotriazole units (96 **P1-P4**) Using a palladium-catalyzed direct C-H cross-coupling polycondensation technique, the research team produced four distinct π-conjugated polymers (96). These polymers were created by combining several thiophene derivatives **(Scheme-23)**[70] with 5,6-difluorobenzotriazole (95). The produced compounds demonstrated strong thermal stability and good solubility in common organic solvents, according to the results. With a maximum external quantum efficiency of up to 6.2%, the polymers also demonstrated encouraging electroluminescent characteristics.



Scheme 23. The Synthesis of π-conjugated polymers containing benzotriazole units

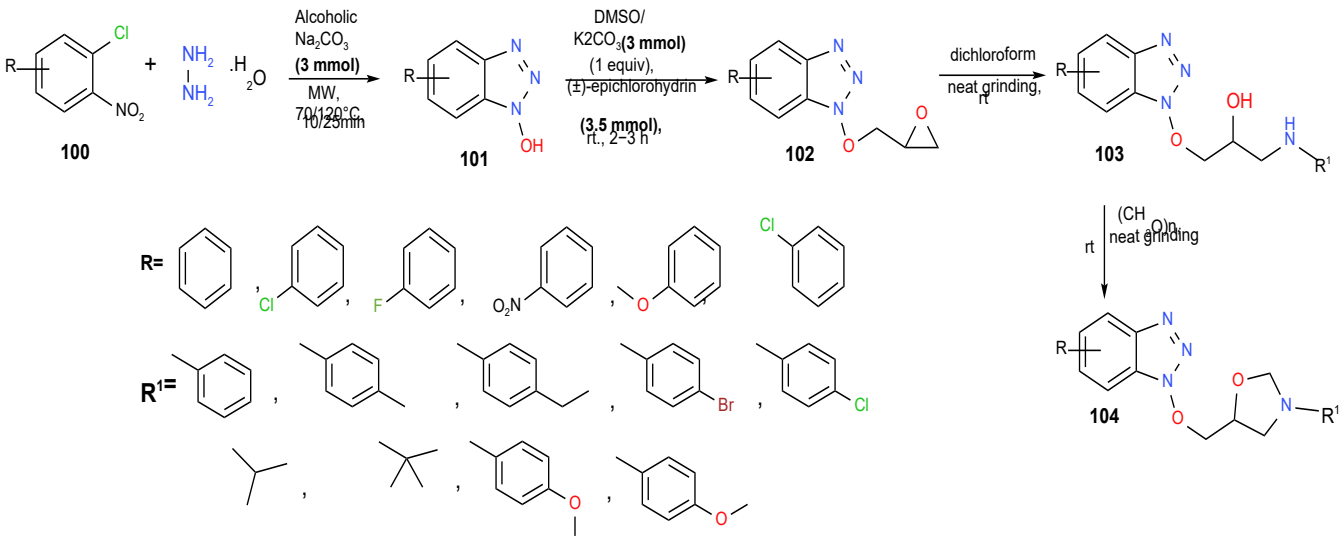
Khayyat et al. have synthesized several benzotriazole derivatives and evaluated their ability to inhibit the development of human cancer cells. Researchers produced *1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-chloroethan-1-one* (98) by reacting benzotriazole (97) with sodium acetate and chloroacetic acid chloride. The final product, benzotriazole imidazole-thione derivatives (99) was obtained by combining (97) with thiourea derivatives **(Scheme-24).**[71] The research team assessed the efficacy of these compounds against many human cancer cell lines, such as HCT-116 (colorectal cancer), HL-60 (human promyelocytic leukemia), and MCF-7 (breast cancer). Compound functionalized with 2,4-$(Cl)_2$ was shown to be the most

effective against cancer cell lines, such as MCF-7, HL-60, and HCT-116, with IC50 values of 3.57, 0.40, and 2.63 µM, respectively.



Scheme 24. The Synthesis of benzotriazoloimidazol-thione derivatives.

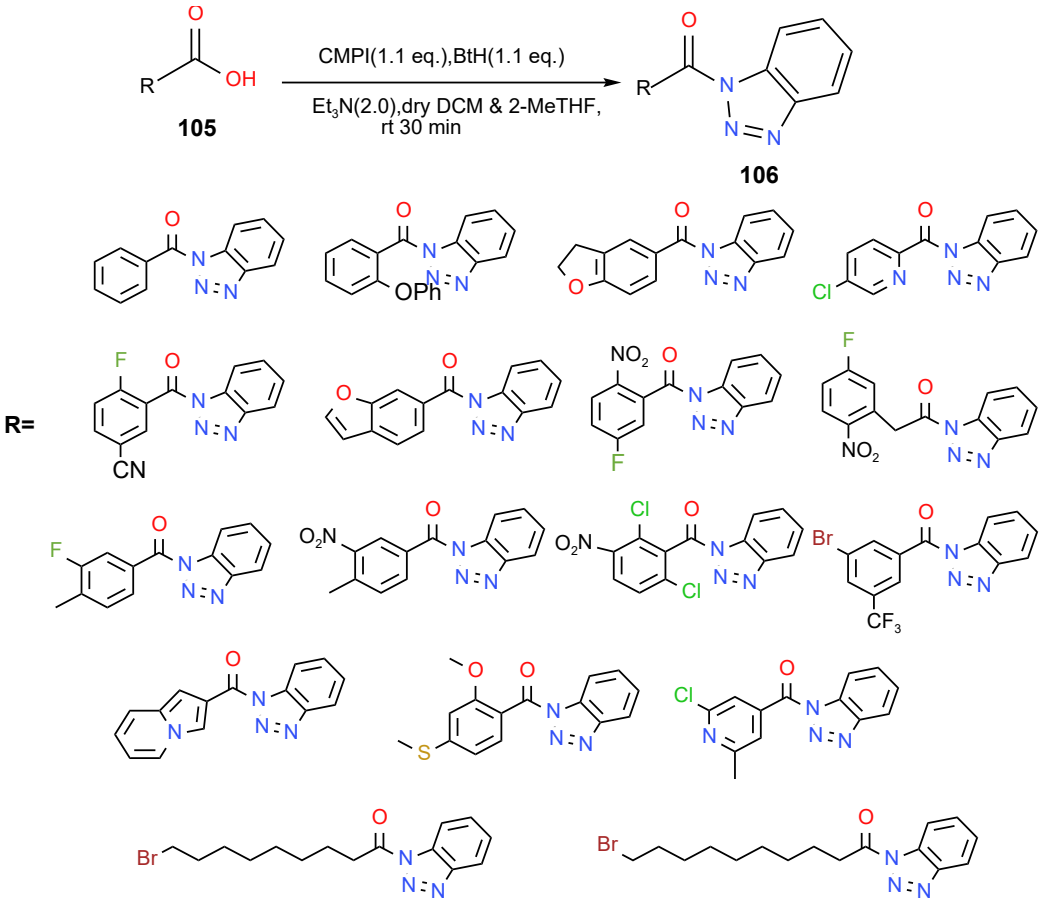
Singh et al. present the antibacterial properties of a category of β-amino alcohols. The synthesis starts with benzotriazole-derived β-amino alcohols (Compound 101). A process called ammonolysis turns benzotriazole epoxides into the β-amino alcohol intermediate during the formation of this molecule. The β-amino alcohol (101) is then cyclized in a one-pot procedure to get 1,3-oxazolidine (Compound 102). This phase needs neither a catalyst nor a solvent, hence streamlining the synthesis process and improving efficiency. The process occurs via intramolecular condensation, resulting in the production of the oxazolidine ring. The intermediate compound 103, undergoes further functional group changes. These alterations may entail the incorporation of certain substituents to enhance the biological activity of the final molecules. Compound 104 is made in the last step. It is a modified 1,3-oxazolidine derived from benzotriazole that is more stable and may have antibacterial properties. Spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, and mass spectrometry thoroughly characterize the substance, thereby validating the structure and purity of the synthesized product. We evaluated the compounds' antibacterial activities using microtiter plates. The antibacterial activity results indicated that the compounds 104 substituted with Benzine, bromo, and choro exhibited efficacy against the *Staphylococcus aureus* strain. **(Scheme-25).**[72]



Scheme 25. The Synthesis of benzotriazole-based β-amino alcohol and corresponding1,3-oxazolidines

Pandey et al. developed the Mukaiyama reagent and used an innovative and effective process to synthesize N-acyl-benzotriazoles. This practical method allows the high-yield production of a variety of N-acyl-benzotriazoles (105) in mild conditions. The reaction between benzotriazole and carboxylic acid (106) occurs because 2-chloro-1-methylpyridinium iodide enhances the carboxylic acids group's ability to interact with benzotriazole **(Scheme-26).**[73] N-acyl benzotriazoles are widely used in peptide synthesis, pharmaceutical chemistry, and materials research, among other areas. Using 2-methoxyfene as the solvent makes this method inexpensive and environmentally friendly, without the need for column purification. It was found that the method is trustworthy for a wide range of carboxylic acid substrates including aliphatic,

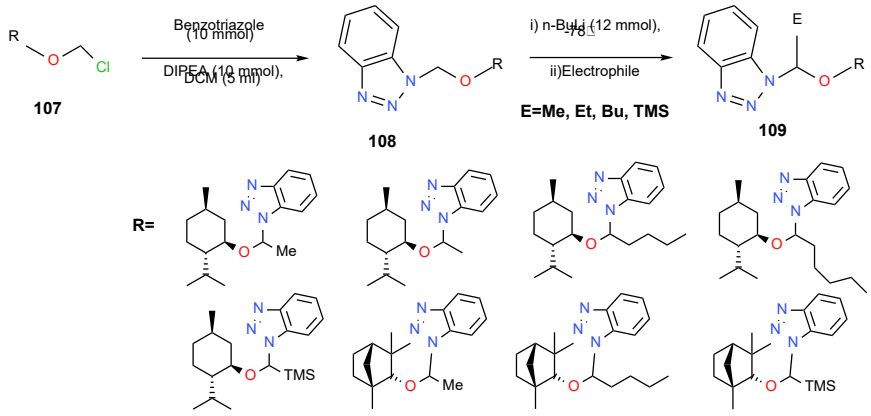
aromatic, and heterocyclic carboxylic acids with different substitutions, and can achieve high yields of N-acyl benzotriazoles in milligram to gram scale.



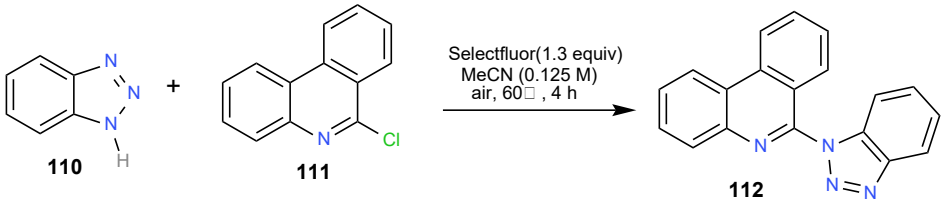
Scheme 26. The Synthesis of N-acyl-benzotriazole using Mukaiyama reagent

Cheema et al. investigated how well different benzotriazole-derived α-substituted hemiaminal ethers could stop cholinesterase from working. The synthesis starts with benzotriazole-substituted α-hydroxy ketones or aldehydes (Compound 107). A condensation reaction between benzotriazole and α-hydroxy ketones or aldehydes makes this molecule, which is the main substrate. This reaction creates a hemiaminal intermediate. Compound 107 subsequently conducts a nucleophilic substitution reaction. This step involves benzotriazole reacting with the right electrophilic reagent, like an alkyl or aryl halide, while a base is present. This creates an α-substituted hemiaminal intermediate (Compound 108). This reaction incorporates an α-substituent into the hemiaminal ether, enhancing stability and establishing the requisite structural framework. The intermediate compound (108) undergoes cyclization to produce the final benzotriazole-derived, α-substituted hemiaminal ether (Compound 109). This step may need further reaction conditions, like moderate heating or the use of a catalyst, to promote ring closure. The resultant product, (Compound 109), possesses a hemiaminal ether structure, characterized by increased stability and possible dual inhibitory action against enzymes such as *acetylcholinesterase* and *butyrylcholinesterase*. The synthesized compounds (107–109) are characterized by spectroscopic methods, including ^{1}H NMR, ^{13}C NMR, and mass spectrometry, to verify their structures and ascertain purity. The study showed that all the compounds that were made could stop both *acetylcholinesterase* (AChE) and *butyrylcholinesterase* (BChE) from working in the lab. The compounds with an optically active (R)-methyl group had markedly more activity than their comparable racemic mixes. **(Scheme 27).**[74]

Akulov, A. A. et al. describe a novel method for directly functionalizing phenanthridine with a benzotriazole residue to generate a C–N bond **(Scheme 28).**[75] The approach comprises a one-step synthesis of 1,2,3-triazolyl-substituted phenanthridine (112) by direct C-N coupling of commercially available unsubstituted phenanthridine (111) and 1H-benzotriazole (110). The reaction, carried out in the presence of Select fluor as an oxidant and MeCN as a solvent, yields *6-(1H-benzotriazol-1-yl)phenanthridine* (112) a useful substrate for further chemical transformations. The obtained product is separated and purified using chromatography. The creation of novel synthesis techniques for phenanthridine derivatives is critical for their usage as fluorescence probes and other applications.

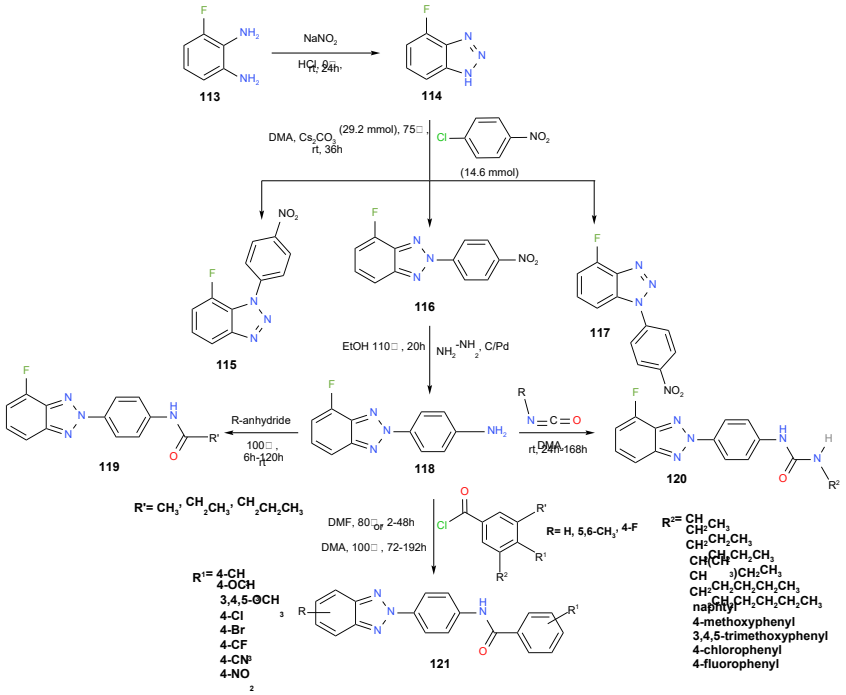


Scheme 27. The Synthesis of α-substitedbenzotraiazole-based hemiaminal ethers.



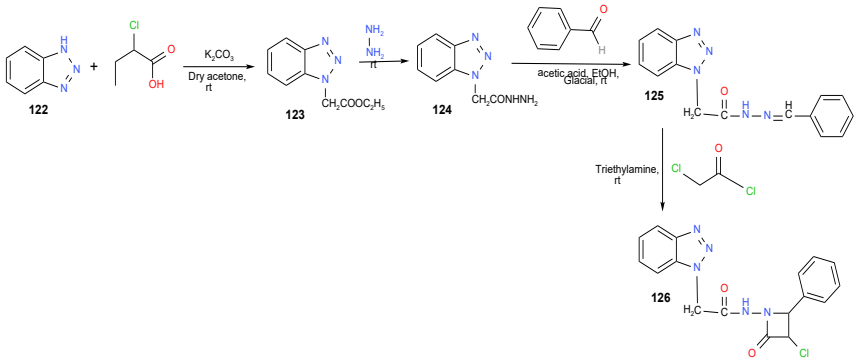
Scheme-28. The synthesis of *6-(1H-Benzo[d][1,2,3]triazol-1-yl)phenanthridine*

Corona, Paola, et al. explore the antiviral potential of benzotriazole-based compounds. **Scheme 29**[76] illustrates several reactions that can be utilized to produce derivatives of benzotriazoles. The first step in the synthesis process typically involves creating an intermediate (115, 116, 117). This can be achieved by combining an azide (113) with 4-fluoro-1H-benzo[d][1–3] triazole (114) in the presence of a 1-chloro-4-nitrobenzene catalyst. The intermediate can then be cyclized to form the desired benzotriazole derivative (118, 119, 120,121). By changing the reaction conditions or using different starting materials, the resulting substituents on the benzotriazole ring can be transformed. These substituents can significantly impact the compound's biological activity, as demonstrated in this investigation. Compounds with slight modifications on the 4-position of the ring, like the addition of a fluorine atom, displayed superior antiviral effects against enteroviruses. Furthermore, the substitution of the amide group with an alkyl-urea group further enhanced the compounds' antiviral properties.



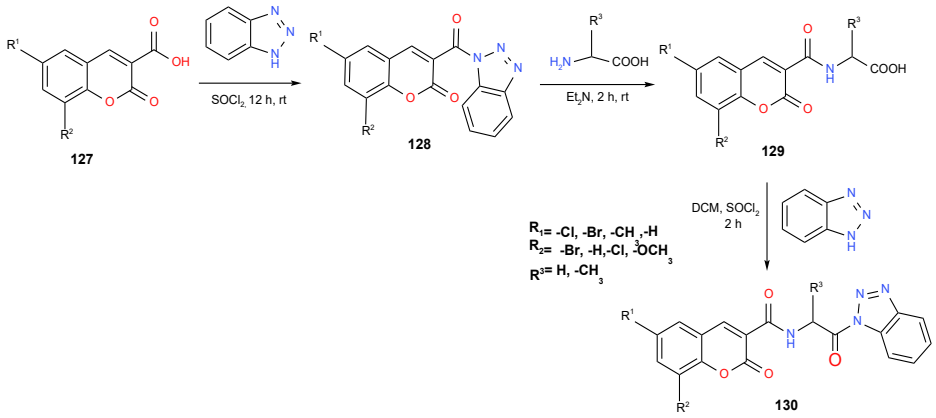
Scheme 29. The synthesis of benzotriazole derivatives.

Anwar, Saleem, et al. give the procedure for the synthesis of Benzotriazole-based azetidinone derivatives in **scheme-30.**[77] The process initiates with benzotriazole (122) and ethyl chloroacetate, which react in the presence of potassium carbonate (K_2CO_3) in dry acetone to produce intermediates (123,124). Subsequently, this intermediate is treated with hydrazine in acetic acid and ethanol to yield the product (125). This product is then utilized with chloroacetic chloride in the presence of triethylamine to obtain the desired azetidinone derivatives as the resulting product (126). These compounds exhibit potential for various pharmaceutical and medical applications. Following synthesis, the compounds underwent characterization using diverse spectroscopic techniques, including IR and ^{1}H NMR spectroscopy. Additionally, the compounds were evaluated for their antioxidant and antiurolithiatic activities through in vitro assays, encompassing radical scavenging assays and assessment of calcium oxalate crystal formation in urine.



Scheme 30. The synthesis of benzotriazole azotidinone derivatives

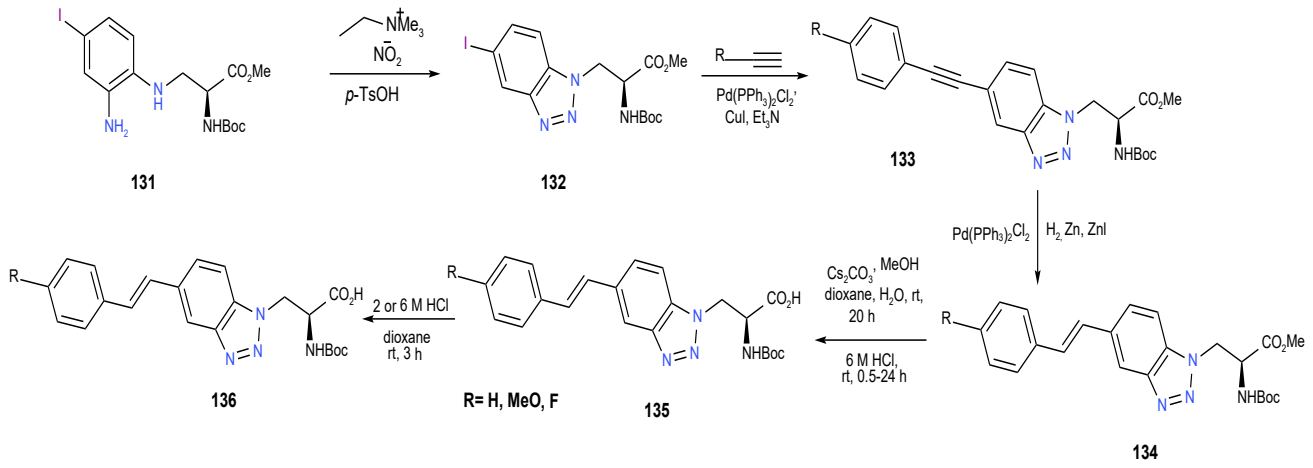
B.B. et al. synthesize innovative coumarin-amino acid-benzotriazole compounds and evaluate their inhibitory efficacy against acetylcholinesterase, urease, and lipase enzymes. The pathway in **scheme 31**[78] starts with the activation of benzotriazole. In this phase, benzotriazole has a reaction with thionyl chloride ($SOCl_2$) in the presence of a solvent such as dichloromethane (DCM). Thionyl chloride chlorinates benzotriazole, enhancing its reactivity for subsequent coupling processes. The active intermediate, referred to as Compound 128, In the subsequent phase, Compound 128 is conjugated with a chosen amino acid (such as glycine or alanine) to incorporate the amino acid moiety into the structure. This reaction transpires in the presence of a base, commonly triethylamine (TEA), which promotes the nucleophilic substitution of the amino acid on the activated benzotriazole. This process yields Compound 129, an intermediate comprising benzotriazole and an amino acid. Compound 129 is then treated with a coumarin derivative. The coumarin moiety is included via a condensation process, in which the benzotriazole-amino acid intermediate (129) establishes a link with the coumarin molecule. This phase entails heating or moderate catalysis to promote the reaction, yielding Compound 130, which now incorporates the coumarin-amino acid-benzotriazole framework. In the concluding phase, Compound 130 undergoes purification, generally via recrystallization or chromatography, to produce the final coumarin-amino acid-benzotriazole conjugate (Compound 130). This molecule, which proficiently integrates the benzotriazole, amino acid, and coumarin moieties, is further characterized using spectroscopic techniques including ^{1}H NMR, ^{13}C NMR, and mass spectrometry to verify its structure and purity. Following synthesis and characterization, Compound 130 may be assessed for its biological activity, namely as an inhibitor of enzymes such as acetylcholinesterase, urease, and lipase. The promise of this compound as an enzyme inhibitor arises from the structural contributions of each component: benzotriazole for biological activity, amino acid for targeting, and coumarin for improved binding affinity.



Scheme 31. Synthetic pathways for the synthesis of coumarin-amino acid-benzotriazole conjugates.

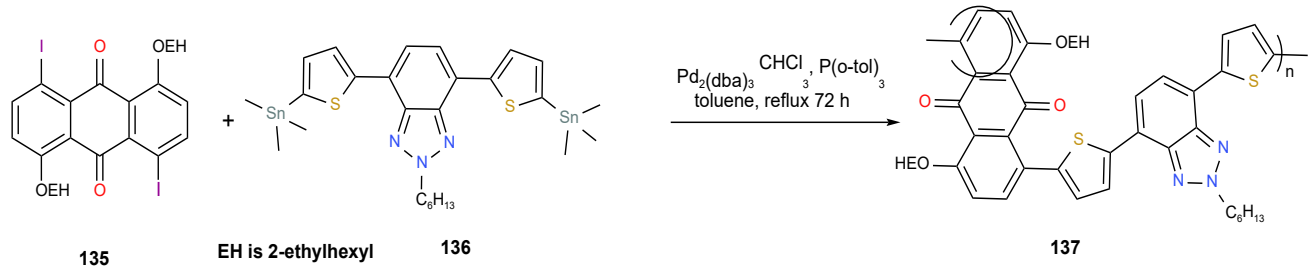
Riley et al. investigate the glowing features and creation of α-amino acids derived from benzotriazole that are mixed with alkynyl and alkenyl groups. The synthetic pathway in **Scheme 32**[79] starts with an α-amino acid derivative (Compound 131). When the first substance is changed, it can add the benzotriazole moiety because it has a functional group (like an amine or carboxylic acid). the amino acid derivative for its compatibility with benzotriazole, which allows it to function as a foundation for future processes. Diazotization of the amino group in Compound 131 leads to the formation of a diazonium salt (Compound 132). In this step, a nitro-sating agent (often sodium nitrite and hydrochloric acid) is used on the amino acid derivative to change the amine group into a diazonium group. This diazonium salt functions as a reactive intermediate capable of promoting cyclization with benzotriazole.

Compound 132 subsequently undergoes intramolecular cyclization to provide the benzotriazole unit (Compound 133). The cyclization process involves the diazonium group interacting with a nearby nucleophilic site, resulting in the fusion of a triazole ring with the benzene ring, thereby finalizing the benzotriazole structure within the amino acid framework. During this phase, a palladium-catalyzed coupling process functionalizes the amino acid containing benzotriazole (Compound 134) with an alkenyl moiety. An unsaturated side chain is added by alkenylation, which increases the compound's structural variety and possible biological activity. Bis(triphenylphosphine)palladium(II) dichloride, copper iodide, and an alkenyl halide are often used as catalysts in this reaction. The alkenyl-fused benzotriazole (Compound 135) undergoes hydrogenation to get the saturated derivative (Compound 136). This reaction converts the alkenyl group into an alkyl chain, increasing the stability of the product. Commonly, we employ palladium on carbon (Pd/C) as the hydrogenation catalyst, which facilitates the reaction under moderate conditions to selectively saturate the alkenyl group. Spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, and mass spectrometry characterize Compound 136.



Scheme 32. Synthesis of Alkenyl-Fused Benzotriazole-Derived α-Amino Acids

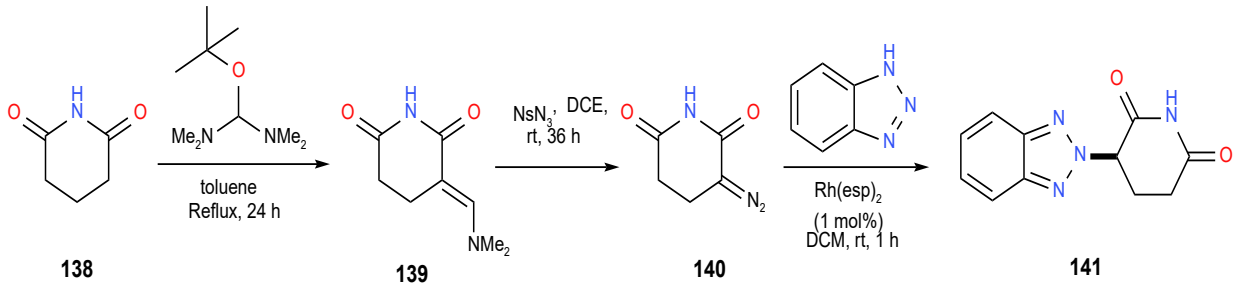
Ghosh, Nani Gopal, and colleagues explain the photocatalytic production of hydrogen peroxide (H_2O_2) with thiophene-coupled benzotriazole and anthraquinone-based D-A-type polymer nanoparticles. **Scheme 33**[80] begins with the utilization of thiophene-coupled benzotriazole (136) and anthraquinone-based D-A-type polymer nanoparticles (135) as photocatalysts for H_2O_2 production (137). Photocatalysis happens when exposed to visible light radiation. The researchers measured H_2O_2 creation by measuring the amount of H_2O_2 produced per milligram of nanoparticles. The research intends to increase the efficiency of H_2O_2 production for various applications. The study also examines a range of characterization methods, including particle size-dependent examinations, gas chromatography (GC), and comparisons to other situations.



Scheme 33. Synthetic route for the PAQBTz polymer through the Stille coupling polycondensation.

Krasavin, Mikhail, et al. describe how to create a thalidomide analog known as "benzotriazole thalidomide" via a novel synthetic technique **(Scheme 34).**[81] The scientists found a way to substitute thalidomide's phthalimide core with benzotriazole to improve its ability to engage E3 ligases in proteolysis-targeting chimeras (PROTACs). Bredereck's reagent

was used for modifying commercial glutamine (138), specifically (dimethylamino)methylenation at the α-position. This procedure introduced a dimethylamino-methylene group into the glutamine core, resulting in a product (139). Compound (139) then performed a Regitz diazo transfer reaction with 4-nitrophenylsulfonyl azide (NsN_3). This technique yielded a previously unknown substance, 3-diazopiperidine-2,6-dione (140), in high yield. The next step was to activate compound (140) using Rh(II)espionate(bis[rhodium(*a, a, a',a*'-tetramethyl-1,3-benzenedipropionic acid)]). This activated compound (140) reacted with benzotriazole to yield the desired benzotriazole thalidomide (141) in excellent yield and complete regioselectivity.



Scheme 34. Synthesis of 'benzotriazole thalidomide'

3. Conclusions

Benzotriazoles and its derivatives are important heterocyclic compounds with a broad spectrum of pharmacological activities, including anticancer, antimicrobial, and anti-inflammatory effects. They are also used as ligands in the catalysis of transition metals and as materials in electronics and photonics. Despite the importance of benzotriazole and its derivatives, many existing synthesis methods are inefficient, uneconomical, and harmful to the environment. Therefore, new, environmentally friendly, efficient, and economical methods for the large-scale production of benzotriazole and its derivatives need to be developed. In this review, most of the methods described in the literature for the synthesis of benzotriazole and its derivatives have been compiled. The review also highlights the need for new synthetic methods that address the challenges of existing methods.

Acknowledgements

The authors are thankful to the Department of Chemistry, Monark University, Dehgam, Gujarat for providing all necessary facilities.

References

1. Zeng, H., Prato, S., Fasoli, E., Mariani, E., & Tatti, E. (**2020**). Low temperature magnetic behavior of benzotriazole molecules. *Phys. Chem. Chem. Phys.*, 22, 4200-4207.
2. McConville, L., Law, G., & Long, J. (**2021**). Benzotriazole derivatives in corrosion inhibition: A critical review. *Prog. Org. Coat.*, 158, 106295.
3. Singh, P., & Gu, M. (**2021**). Electrochemical and surface investigation on benzotriazole-functionalized materials. *Electrochim. Acta*, 390, 138857.
4. Wang, L., Zhang, Y., & Zhang, X. (**2019**). Corrosion protection of copper by benzotriazole derivatives. *Corros. Sci.*, 158, 108092.
5. Finsgar, M. (**2019**). Recent advances in the application of benzotriazole as a corrosion inhibitor. *Corros. Eng. Sci. Technol.*, 54(5), 343-355.
6. Meier, P., & Klinsch, C. (**2020**). Comprehensive analysis of benzotriazole derivatives in chemical applications. *Appl. Sci.*, 10(11), 3879.
7. Sumran, G.; Jain, N.; Kumar, P.; Aggarwal, R. Trifluoromethyl-β-dicarbonyls as versatile synthons in synthesis of heterocycles. *Chem. Eur. J.* **2024**, *30* (11), e202303599.
8. Garg, A.; Bhalla, A. Environmental-benign pathways for the synthesis of medicinally relevant heterocycles. In *Green Approaches in Medicinal Chemistry for Sustainable Drug Design*; Elsevier, 2024; pp. 361–396.
9. Kushwaha, P.; Rashi; Bhardwaj, A.; Khan, D. Synthetic approaches toward imidazo-fused heterocycles: a comprehensive review. *J. Heterocycl. Chem.* **2024**.
10. Li, J.; Dong, Z.; Zhao, C. Recent progress for the construction of eight-membered nitrogen-heterocycles. *New J. Chem.* **2024**.
11. Bendi, A.; Yadav, P.; Saini, K.; Singh Bhathiwal, A.; Raghav, N. A comprehensive examination of heterocyclic scaffold chemistry for antitubercular activity. *Chem. Biodivers.* **2024**, e202400067.

12. Beigiazaraghbelagh, P.; Poursattar Marjani, A. Carbon-based catalysts: advances in synthesizing N-heterocyclic compounds using graphene family and graphite oxide. *Res. Chem. Intermed.* **2024**, *50* (2), 485–531.
13. Sadowski, M.; Kula, K. Unexpected course of reaction between (1E, 3E)-1,4-dinitro-1,3-butadiene and N-methyl azomethine ylide—a comprehensive experimental and quantum-chemical study. *Molecules* **2024**, *29* (21), 5066.
14. Sadowski, M.; Dresler, E.; Zawadzińska, K.; Wróblewska, A.; Jasiński, R. Syn-propanethial S-oxide as an available natural building block for the preparation of nitro-functionalized, sulfur-containing five-membered heterocycles: an MEDT study. *Molecules* **2024**, *29* (20), 4892.
15. Aute, D.; Parhad, A.; Vikhe, V.; Uphad, B.; Gadhave, A. Aluminized polyborate catalyzed efficient solvent-free synthesis of 1,8-dioxo-decahydroacridines via Hantzsch condensation. *Curr. Chem. Lett.* **2024**, *13* (2), 417–424.
16. Cho, Y., Kang, M., & Kim, J. (**2020**). Effects of benzotriazole on copper corrosion in chloride media. *Corros. Sci.*, 173, 108760.
17. Xu, Q., Chen, M., & Ren, Q. (**2018**). Electrochemical and surface study of benzotriazole films. *J. Appl. Electrochem.*, 48(8), 853-860.
18. Sun, J., Lu, L., & Han, H. (**2019**). Synthesis and application of benzotriazole-functionalized materials. *Chem. Eng. J.*, 365, 1-10.
19. Yan, W., & Yin, J. (**2021**). Advanced applications of benzotriazole as a corrosion inhibitor. *Appl. Surf. Sci.*, 563, 150255.
20. Igarashi, M., Saito, R., & Matsumoto, T. (**2019**). Influence of benzotriazole on the localized corrosion of copper. *Electrochim. Acta*, 318, 556-562.
21. Balta, P., & Scott, R. (**2018**). A review on the electrochemical behavior of benzotriazole. *Electrochim. Acta*, 289, 243-253.
22. Choudhury, K., & Nandi, A. (**2020**). Benzotriazole as a corrosion inhibitor in acidic media. *Arab. J. Chem.*, 13(10), 7548-7562.
23. Roy, D., Mukherjee, S., & Das, S. (**2019**). Electrochemical analysis of benzotriazole-coated metals. *J. Chem. Eng.*, 66(4), 1224-1231.
24. Prabhu, R., & Ananda, S. (**2020**). Corrosion inhibition and surface protection studies of benzotriazole derivatives. *J. Mol. Liq.*, 310, 113235.
25. Hussein, A., & Haridy, R. (**2019**). Electrochemical properties of benzotriazole in various pH environments. *J. Electrochem. Soc.*, 166(10), 613-619.
26. Hernandez, M., Torres, T., & Morales, P. (**2020**). Benzotriazole derivatives as efficient corrosion inhibitors. *Corros. Sci.*, 177, 108928.
27. Reddy, P., & Chandra, A. (**2021**). Application of benzotriazole in advanced materials. *Appl. Sci.*, 11(2), 387.
28. Li, T., Zhao, Y., & Guo, Z. (**2019**). Enhanced performance of benzotriazole in corrosive environments. *Corros. Eng. Sci. Technol.*, 54(2), 98-106.
29. Xie, L., Yang, Y., & Zhu, Q. (**2018**). Chemical and electrochemical insights on benzotriazole coating behavior. *J. Phys. Chem. C*, 122(14), 7334-7343.
30. Kumar, A., Mishra, R., & Sharma, S. (**2019**). An overview of benzotriazole derivatives for corrosion protection. *Prog. Org. Coat.*, 134, 124-130.
31. Ibon, A., Cossío, F.P., Elguero, J., Fresno, N., Hernandez-Folgado, L., García-Granda, S., Menéndez-Taboada, L., Pérez-Fernández, R., Reviriego, F., & Vázquez-Viñuela, L. (**2013**). Reaction of NH-indazoles with 1-fluoro-2,4-dinitrobenzene: Unusual formation of benzotriazole-N-oxides. *New J. Chem.*, 37, 1756-1763.
32. Lee, Y.H., Hong, M.S., Ko, S.J., & Kim, J.G. (**2021**). Effect of benzotriazole on localized corrosion of copper. *Materials*, 14(11), 2722.
33. Liu, L., Shuang, L., Qi, Y., Wu, X., & Xie, J. (**2020**). Corrosion inhibition behavior of benzotriazole derivatives on copper. *Anti-Corros. Methods Mater.*, 67(4), 123-129.
34. Youssef, Y.M., Ahmed, N.M., Nosier, S.A., Farag, H.A., & Abdel-Aziz, M.H. (**2020**). Utilizing benzotriazole for corrosion protection in metals under flow conditions. *Chem. Pap.*, 74(8), 3395-3408.
35. Paoletti, N., & Supuran, C.T. (**2024**). Benzothiazole derivatives in antitumor agents. *Arch. Pharm.*, 357(6), e200059.
36. Ibba, R., Piras, S., Corona, P., Riu, F., Loddo, R., Delogu, I., Collu, G., Sanna, G., Caria, P., Dettori, T., & Carta, A. (**2021**). Synthesis, antitumor, and antiviral activities of new benzotriazole-dicarboxamide derivatives. *Front. Chem.*, 9, 660424.
37. Sanna, G., Piras, S., Madeddu, S., Busonera, B., Klempa, B., Corona, P., Ibba, R., Murineddu, G., Carta, A., & Loddo, R. (**2020**). 5,6-Dichloro-2-phenyl-benzotriazoles: Potent inhibitors of orthohantavirus. *Viruses*, 12(1), 122.
38. Corona, P., Piras, S., Ibba, R., Riu, F., Murineddu, G., Sanna, G., Madeddu, S., Delogu, I., Loddo, R., & Carta, A. (**2020**). Antiviral activity of benzotriazole-based derivatives. *Open Med. Chem. J.*, 14(1), 9-15.
39. Murcia-Galán, R.A., Durán, S.M., Leal-Pinto, S.M., Roa-Cordero, M.V., Vargas, J.D., Herrera, L.V., Muñoz-Castro, A., MacLeod-Carey, D., Naranjo, T.W., Rodríguez-Kessler, P.L., & Hurtado, J.J. (**2023**). Antifungal activity of Co(II) and Cu(II) complexes containing 1,3-bis(benzotriazol-1-yl)-propan-2-ol on fluconazole-resistant *Candida* species. *BMC Chem.*, 17(1), 135.
40. Rivera, J.P., de Becerra, E.G., De la Vega Quintero, G.P., Hernández, C.V., & De la Parra Morales, A.F. (**2019**). Benzotriazole derivatives palladium complex: Synthesis, characterization, antifungal, and catalytic activity. *Sci. Technica*, 24(1), 104-112.
41. Lv, M., Ma, J., Li, Q., & Xu, H. (**2018**). Discovery of benzotriazole-azo-phenol/aniline derivatives as antifungal agents. *Bioorg. Med. Chem. Lett.*, 28(2), 181-187.

42. Godhani, D.R., Mulani, V.B., Mehta, J.P., & Kukadiya, N.B. (**2018**). Synthesis and antimicrobial evaluation of benzotriazole-substituted 1,3,4-thiadiazoles. *World Sci. News*, (100), 51-60.
43. Kassab, A.E., & Hassan, R.A. (**2018**). Novel benzotriazole N-acylarylhydrazone hybrids: Design, synthesis, and anticancer activity. *Bioorg. Chem.*, 80, 531-544.
44. Li, Q., Liu, G., Wang, N., Yin, H., & Li, Z. (**2020**). Synthesis and anticancer activity of benzotriazole derivatives. *J. Heterocycl. Chem.*, 57(3), 1220-1227.
45. Onar, G., Gürses, C., Karataş, M.O., Balcıoğlu, S., Akbay, N., Özdemir, N., Ateş, B., & Alıcı, B. (**2019**). Palladium(II) and ruthenium(II) complexes of benzotriazole-functionalized N-heterocyclic carbenes: Cytotoxicity, antimicrobial, and DNA interaction studies. *J. Organomet. Chem.*, 886, 48-56.
46. Perković, I., Butula, I., Kralj, M., Martin-Kleiner, I., Balzarini, J., Hadjipavlou-Litina, D., Katsori, A.M., & Zorc, B. (**2012**). Novel NSAID carbamoylcarbazides as potential anticancer agents. *Eur. J. Med. Chem.*, 51, 227-238.
47. Ambekar, S.P., Mohan, C.D., Shirahatti, A., Kumar, M.K., Rangappa, S., Mohan, S., Basappa, Kotresh, O., & Rangappa, K.S. (**2018**). Synthesis of coumarin-benzotriazole hybrids and evaluation of anti-tubercular activity. *Lett. Org. Chem.*, 15(1), 23-31.
48. Carta, A., Bua, A., Corona, P., Piras, S., Briguglio, I., Molicotti, P., Zanetti, S., Laurini, E., Aulic, S., Fermeglia, M., & Pricl, S. (**2019**). Design, synthesis, and antitubercular activity of 4-alkoxy-triazoloquinolones. *Eur. J. Med. Chem.*, 161, 399-415.
49. Kim, S., Cho, S.N., Oh, T., & Kim, P. (**2012**). Design and synthesis of 1H-1,2,3-triazoles derived from econazole as antitubercular agents. *Bioorg. Med. Chem. Lett.*, 22(22), 6844-6847.
50. Gopi, C., Dhanaraju, M.D., & Sastry, V.G. (**2015**). Synthesis and antimicrobial evaluation of benzotriazole-based oxadiazole derivatives. *Glob. J. Pharmacol.*, 9(3), 246-250.
51. Tasheh, N.S., Fouegue, A.D.T., & Ghogomu, J.N. (**2021**). Antioxidant and UV absorption properties of benzotriazole derivatives via DFT/TD-DFT. *Comp. Chem.*, 9(3), 161-196.
52. Chand, M., Kaushik, R., & Jain, S.C. (**2018**). Synthesis and activities of hybrid molecules with benzotriazole and 1,2,4-triazole. *Turk. J. Chem.*, 42(6), 1663-1677.
53. Rahmani, S.E., & Lahrech, M. (**2018**). Evaluation of antioxidant activity of Schiff bases bearing benzotriazole moiety. *Res. J. Pharm. Technol.*, 11(9), 4104-4107.
54. Khan, I., Rehman, W., Rahim, F., Hussain, R., Khan, S., Fazil, S., Rasheed, L., Taha, M., Shah, S.A.A., Abdellattif, M.H., & Farghaly, T.A. (**2022**). Synthesis and α-glucosidase inhibitory activity of benzotriazole-based bis-Schiff bases. *Pharmaceuticals*, 16(1), 17.
55. Hashim, G., Bashir, H., & Abdalfarg, N.A. (**2023**). Reactions of dichloro-N-(substituted phenyl) acetamide with benzotriazole. *Sirte Univ. Sci. J.*, 13(1), 71-77.
56. Ibba, R., Corona, P., Nonne, F., Caria, P., Serreli, G., Palmas, V., Riu, F., Sestito, S., Nieddu, M., Loddo, R., & Sanna, G. (**2023**). Design and antiviral activities of new benzotriazole derivatives. *Pharmaceuticals*, 16(3), 429.
57. Alraqa, S.Y., Alharbi, K., Aljuhani, A., Rezki, N., Aouad, M.R., & Ali, I. (**2021**). Benzotriazole-triazole hybrids: DNA binding, docking, and anticancer studies. *J. Mol. Struct.*, 1225, 129192.
58. Karagöz, Z., Oguz, U.I., & Genç, M. (**2023**). Synthesis, solvatochromic analysis, and theoretical studies of benzotriazole derivatives. *Bitlis Eren Univ. Sci. J.*, 12(2), 568-577.
59. John, W., Buratai, L.B., Biu, A.A., Badau, S.J., & Onyiche, T.E. (**2023**). Application of benzotriazole in medical science. *Kanem J. Med. Sci.*, 17(1), 45-50.
60. Abbas, H.H., & Abood, Z.H. (**2023**). Microwave synthesis and antibacterial assay of 1,3-thiazolidin-4-one derivatives. *AIP Conf. Proc.*, 2977, 129-135.
61. Himmi, B., Brandán, S.A., Sert, Y., Kawther, A.A., Dege, N., Cinar, E.B., El Louzi, A., Bougrin, K., & Karrouchi, K. (**2023**). A quinoline-benzotriazole derivative: Synthesis, crystal structure and characterization by using spectroscopic, DFT, and molecular docking methods. *Results Chem.*, 5, 100916.
62. Ambekar, S.P., Mohan, C.D., Shirahatti, A., Kumar, M.K., Rangappa, S., Mohan, S., Basappa, Kotresh, O., & Rangappa, K.S. (**2018**). Synthesis of coumarin-benzotriazole hybrids and evaluation of their anti-tubercular activity. *Lett. Org. Chem.*, 15(1), 23-31.
63. Kassab, A.E., & Hassan, R.A. (**2018**). Novel benzotriazole N-acylarylhydrazone hybrids: Design, synthesis, anticancer activity, effects on cell cycle profile, caspase-3 mediated apoptosis, and FAK inhibition. *Bioorg. Chem.*, 80, 531-544.
64. Chand, M., Kaushik, R., & Jain, S.C. (**2018**). Synthesis and antimicrobial and antioxidant activities of hybrid molecules containing benzotriazole and 1,2,4-triazole. *Turk. J. Chem.*, 42(6), 1663-1677.
65. Yuan, Y.G., Wang, J.L., Zhang, Y.X., Li, L., Reza, A.M.M.T., & Gurunathan, S. (**2023**). Biogenesis, composition, and potential therapeutic applications of mesenchymal stem cell-derived exosomes in various diseases. *Int. J. Nanomedicine*, 18, 3177-3210.
66. Laconde, G., Amblard, M., & Martinez, J. (**2019**). A simple and versatile method to synthesize N-acyl-benzotriazoles. *Tetrahedron Lett.*, 60(4), 341-343.
67. Bokhtia, R.M., Panda, S.S., Girgis, A.S., Pillai, G.G., Ibrahim, T.S., Shalaby, E.M., Gigli, L., Abdel-Aal, E.H., & Al-Mahmoudy, A.M. (**2020**). Efficient synthesis and computational studies of useful guanylating agents: 1H-benzotriazole-1-carboximidamides. *ChemistrySelect*, 5(44), 13963-13968.
68. Lee, E., Shin, W., Bae, O., Kim, F.S., & Hwang, Y.J. (**2019**). Synthesis and characterization of a highly crystalline benzotriazole-selenophene copolymer semiconductor. *Polymer*, 184, 121856.

69. Godhani, D.R., Mulani, V.B., Mehta, J.P., & Kukadiya, N.B. (**2018**). Synthesis and antimicrobial evolution of some new benzotriazole-substituted 1,3,4-thiadiazoles. *World Sci. News*, (100), 51-60.
70. Han, D., Li, J., Zhang, Q., He, Z., Wu, Z., Chu, J., & Lu, Y. (**2021**). Synthesis of π-conjugated polymers containing benzotriazole units via palladium-catalyzed direct CH cross-coupling polycondensation for OLEDs applications. *Polymers*, 13(2), 254.
71. Khayyat, A.N., Mohamed, K.O., Malebari, A.M., & El-Malah, A. (**2021**). Design, synthesis, and antiproliferative activities of novel substituted imidazole-thione linked benzotriazole derivatives. *Molecules*, 26(19), 5983.
72. Al-Jibori, S.A., Al-Doori, L.A., Al-Janabi, A.S., Alheety, M.A., Akbaş, H., & Karadag, A. (**2020**). Novel Hg(II) and Pd(II) benzotriazole (Hbta) complexes: Synthesis, characterization, X-ray crystal structure of [Pd(PPh3)(μ-bta)Cl]2·DMSO and thermodynamic study of their H2 storage. *J. Mol. Struct.*, 1207, 127832.
73. Singh, N., Abrol, V., Parihar, S., Kumar, S., Khanum, G., Mir, J.M., Dar, A.A., Jaglan, S., Sillanpää, M., & Al-Farraj, S. (**2023**). Design, synthesis, molecular docking, and in vitro antibacterial evaluation of benzotriazole-based β-amino alcohols and their corresponding 1,3-oxazolidines. *ACS Omega*, 8(44), 41960-41968.
74. Baddam, S.R., Kalagara, S., Ganta, S., Ponnuru, V.S., Vudari, B., & Allamf, A.R. (**2023**). Expedient method for acylation of amines, alcohols, and thiols using trimethylsilyl acetate. *ARKIVOC*, 2023(8), S1-S32.
75. Cheema, Z.M., Nisar, M., Gondal, H.Y., Alhussain, S.A., Zaki, M.E., & Coldham, I. (**2023**). New benzotriazole-derived α-substituted hemiaminal ethers with enhanced cholinesterase inhibition activity: Synthesis, structural, and biological evaluations. *J. Saudi Chem. Soc.*, 27(6), 101746.
76. Anwar, S., Singh, V., Nirala, R.K., Prabha, S., Athar, F., Kumar, S., & Thakur, S.C. (**2023**). Synthesis of benzotriazole-based azetidinone derivatives and their evaluation on calcium oxalate crystallization. *Korean J. Physiol. Pharmacol.*, 27(4), 552-563.
77. Akulov, A.A., Pershin, A.A., Kopchuk, D.S., Varaksin, M.V., Zyryanov, G.V., & Chupakhin, O.N. (**2023**). Direct cross-dehydrogenative C–N coupling of phenanthridine with 1H-benzotriazole. *Russ. J. Org. Chem.*, 59(7), 1255-1259.
78. Menteşe, E., Çalışkan, N., Sökmen, B.B., & Akyüz, G. (**2024**). Synthesis and biological evaluation of coumarin-amino acid-benzotriazole conjugates. *Russ. J. Bioorg. Chem.*, 50(1), 191-200.
79. Riley, L.M., Mclay, T.N., & Sutherland, A. (**2023**). Synthesis and fluorescent properties of alkynyl- and alkenyl-fused benzotriazole-derived α-amino acids. *J. Org. Chem.*, 88(4), 2453-2463.
80. Ghosh, N.G., Sarkar, A., Sanke, D.M., Karmakar, H.S., & Zade, S.S. (**2023**). Photocatalytic H2O2 production by thiophene-coupled benzotriazole and anthraquinone-based D–A-type polymer nanoparticles. *Macromol. Rapid Commun.*, 44(14), 2300013.
81. Krasavin, M., Bubyrev, A., Kazantsev, A., Heim, C., Maiwald, S., Zhukovsky, D., Dar'in, D., Hartmann, M.D., & Bunev, A. (**2022**). Replacing the phthalimide core in thalidomide with benzotriazole. *J. Enzyme Inhib. Med. Chem.*, 37(1), 527-530.