

# A review of benzotriazole derivatives: versatile scaffolds for advancing therapeutics in medicinal chemistry

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## Abstract

Benzotriazole (BtH) is recognized as a versatile heterocyclic scaffold that plays an increasingly vital role in modern drug discovery owing to its broad pharmacological potential and structural flexibility. Although BtH was first synthesized in the 19<sup>th</sup> century, recent advances in synthetic and medicinal chemistry have revitalized interest in BtH and its derivatives for developing multifunctional therapeutics. This review addresses current challenges and opportunities in BtH chemistry by integrating progress in sustainable synthesis, structure–activity relationship (SAR) analyses, and therapeutic applications. The discussion encompasses green methodologies, such as microwave-assisted, ultrasound-assisted, flow, and electrosynthesis techniques, that improve atom economy, reduce waste, and enhance energy efficiency. It also highlights how structural modifications, including halogenation, heterocyclic fusion, and metal complexation, influence biological activity and target selectivity. BtH derivatives exhibit significant antimicrobial, antiviral, anticancer, antioxidant, and enzyme-inhibitory properties, as well as other potential in neuroprotective and anti-inflammatory therapies. However, limited *in vivo* evaluation, lack of standardized bioassay protocols, and scalability challenges in sustainable synthesis remain key research gaps. Overall, this review synthesizes contemporary developments from 2020–2026, demonstrating that BtH serves as a privileged pharmacophore capable of engaging diverse biological targets. By consolidating mechanistic insights and eco-efficient synthesis strategies, the work provides a foundation for designing next-generation BtH-based drug candidates and advancing sustainable medicinal chemistry.

## Key findings

- Benzotriazole derivatives exhibit diverse pharmacological activities including antimicrobial, anticancer, antiviral, antioxidant, and enzyme-inhibitory effects.
- Green methodologies, including microwave-assisted, ultrasound-assisted, flow-based, and electrosynthesis techniques, improve atom economy, efficiency, and sustainability.
- Structural modifications such as halogenation, heterocyclic fusion, and metal complexation significantly influence biological potency and selectivity.
- Structure–activity relationship (SAR) studies reveal that electronic and steric factors govern target binding and therapeutic efficacy.

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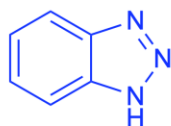


## 1. Introduction

Benzotriazole (BtH), a benzo-fused azole, is a heterocyclic organic compound composed of a five-membered ring containing three nitrogen atoms fused with a benzene ring. It has emerged as a pivotal scaffold in modern drug discovery due to its diverse biological activities and broad range of applications (Figure 1). First synthesized in the 19th century, BtH has gained increasing importance owing to its structural versatility and potential for designing novel therapeutic agents. This heterocyclic framework is valued not only for its flexibility but also for its wide spectrum of biological properties, which have facilitated the discovery of new drugs targeting various diseases. Consequently, extensive research has focused on developing innovative synthetic routes and exploring the biological potential of BtH derivatives, underscoring its enduring relevance in medicinal chemistry [1].

As a multitarget pharmacophore, BtH provides a unique platform for designing compounds with diverse pharmacological profiles, including antimicrobial, anticancer, antiviral, and antioxidant activities. Its derivatives exhibit notable inhibitory effects against a wide range of pathogens and display potent anticancer activity across multiple tumor models, establishing BtH as a valuable lead structure in drug development [2,3]. Moreover, the ability of BtH-based compounds to interact with multiple biological targets enhances their therapeutic efficacy while mitigating the risk of resistance development—a major challenge in current medical treatments [2].

In line with contemporary research priorities, increasing attention has been directed toward green and sustainable approaches for synthesizing BtH derivatives. Current efforts emphasize the development of environmentally benign protocols that improve efficiency while minimizing waste and ecological impact, in accordance with the principles of sustainable chemistry [4–7]. This paradigm shift toward greener methodologies not only ensures regulatory compliance but also reflects the broader scientific commitment to sustainable and responsible drug innovation.



Composition: C(60.50%) H(4.23%) N (35.27%)

Density:  $1.35 \pm 0.06 \text{ g/cm}^3$

Dielectric Constant: Not available

Formula Weight: 119.12

Index of Refraction:  $1.72 \pm 0.02$

Molar Refractivity:  $34.71 \pm 0.30 \text{ cm}^3$

Molar Volume:  $88.30 \pm 3.00 \text{ cm}^3$

Molecular Formula:  $\text{C}_6\text{H}_5\text{N}_3$

Polarizability:  $13.76 \pm 0.50 \cdot 10^{-24} \text{ cm}^3$

Surface Tension:  $73.90 \pm 3.00 \text{ dyne/cm}$

**Figure 1** Structure and general properties of BtH.

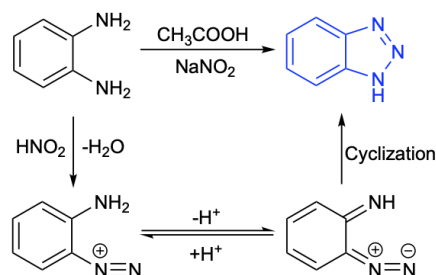
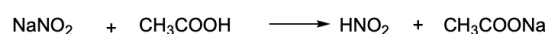
Accordingly, this review provides a comprehensive overview of recent advances in benzotriazole research (2020–2026), emphasizing innovative synthetic methodologies, structure–activity relationship (SAR) trends, and emerging therapeutic insights. By consolidating the latest strategies for synthesizing and evaluating BtH derivatives, this work seeks to bridge existing knowledge gaps and stimulate further exploration in benzotriazole chemistry, thereby reaffirming its role as a vital scaffold in drug discovery and development.

## 2. Advances in synthetic methodologies of benzotriazole derivatives

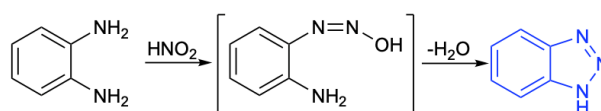
### 2.1. Classical and conventional synthetic routes

The diazotization of *o*-phenylenediamine (1,2-phenylenediamine) with sodium nitrite in the presence of acetic acid remains the most classical and widely employed route for BtH synthesis. In this process, one amino group of the diamine is diazotized to form a monodiazonium intermediate, which subsequently undergoes intramolecular cyclization to yield BtH under mild acidic conditions [8–11] (Scheme 1a).

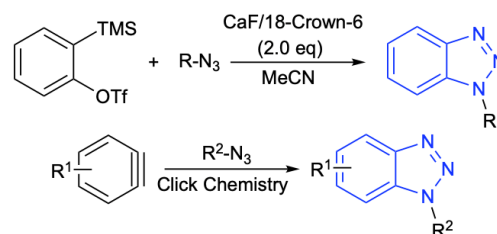
#### a) Diazotization



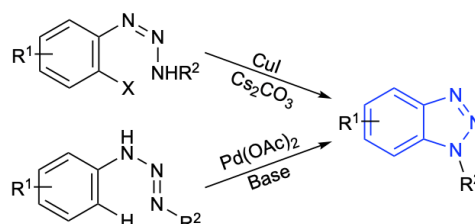
#### b) Hydrolysis of *o*-phenylenediamine



#### c) [3+2] Cycloaddition



#### d) Metal-assisted intramolecular *N*-arylation



**Scheme 1** Classical and conventional synthetic routes of BtH.

An alternative traditional method involves the hydrolysis of acylated or aroylated *o*-phenylenediamine derivatives, prepared via the action of nitrous acid on monoacylated precursors. Direct hydrolysis produces BtH with higher purity and yield compared to multistep protocols [9] (Scheme 1b).

Another classical yet mechanistically distinct route is the [3+2] cycloaddition of arynes with organic azides, which affords substituted BtHs under fluoride-promoted or copper-catalyzed conditions. Arynes generated from *o*-(trimethylsilyl)aryl triflates react efficiently with azides to construct the BtH framework [1,8] (Scheme 1c).

Additionally, the metal-assisted intramolecular *N*-arylation of 2-chloro-1,2,3-BtHs offers a conventional extension, yielding *N*-substituted BtHs via CuI/Cs<sub>2</sub>CO<sub>3</sub>- or Pd-catalyzed Buchwald–Hartwig coupling reactions [1] (Scheme 1d).

Despite their efficiency, scalability, and mechanistic simplicity, these classical diazotization and cyclization pathways often rely on stoichiometric reagents, strong mineral acids, and multistep isolations that generate significant waste and limit environmental compatibility. Although aryne–azide cycloaddition and metal-assisted *N*-arylation have improved structural diversity and regioselectivity, they still depend on toxic solvents, elevated temperatures, and heavy-metal catalysts—factors misaligned with the principles of green chemistry. Consequently, recent research has increasingly focused on sustainable and process-intensified strategies, including microwave-assisted, electro-synthesis, and flow-based systems, which enhance atom economy, minimize hazardous reagents, and improve overall energy efficiency. These innovations are reshaping benzotriazole synthesis toward a more sustainable and environmentally responsible framework.

## 2.2. Green and sustainable methods

The transition from traditional multistep BtH synthesis to environmentally responsible and energy-efficient processes has accelerated in the past decade. Among these, microwave-assisted, ultrasound-assisted, flow-based, and electrochemical approaches stand out for their ability to reduce waste, energy demand, and hazardous reagents, while enhancing scalability and yield.

Microwave-assisted synthesis is particularly recognized for its energy efficiency, drastically shortened reaction times, and ability to operate under solvent-free conditions. This technique employs microwave radiation to directly heat the reaction mixture, leading to enhanced reaction rates, improved selectivity, and minimized thermal degradation of sensitive intermediates. Verma and Singh (2020) [4] demonstrated that microwave heating significantly shortens reaction times and reduces solvent usage in the synthesis of nitrogen-heterocyclic frameworks, including BtH derivatives. They synthesized four BtH derivatives—1-(chloromethyl)-1*H*-BtH (**2**), *N*-(benzo[*e*][1,2,4]-triazin-4(3*H*)-ylmethyl)benzenamine (**4a**), 1-((1*H*-benzo-

[*d*][1,2,3]-triazol-1-yl)methyl)hydrazine (**4b**), and 1-((1*H*-benzo[*d*][1,2,3]-triazol-1-yl)methyl)phenylhydrazine (**4c**), under solvent-free conditions, achieving lower energy input and higher selectivity due to localized superheating and uniform energy distribution. The authors emphasized that such approaches align with several of the 12 Principles of Green Chemistry, notably waste prevention, safer solvent use, and energy efficiency (Scheme 2a). Similarly, Alraqa et al. (2021) [5] reported the microwave-assisted synthesis of BtH-1,2,3-triazole hybrids (**8**). Microwave assistance reduces reaction times and energy use across several BtH transformations. In BtH-1,2,3-triazole “click” libraries, switching from conventional heating (6–12 h, ~80–86% yields) to microwave irradiation (4–8 min, ~89–95% yields) consistently accelerated synthesis with yield gains. Likewise, microwave-assisted propargylation of BtH provided the alkyne intermediate (**6**) in near-quantitative yield in minutes (Scheme 2a). In a separate application space, microwave-assisted routes have been used to build bioactive BtH hybrids (**9–12**); these routes compare favorably to conventional methods [12] (Scheme 2a).

Mermer et al. (2022) [13] reported a green and efficient synthesis of BtH-oxadiazole hybrid compounds (**15**) using ultrasound sonication (US) as an environmentally friendly alternative to conventional reflux conditions. The synthetic route involved the condensation of BtH hydrazide intermediates with substituted benzoic acids in phosphoryl chloride, followed by intramolecular cyclization to form the oxadiazole ring. Compared with the classical reflux method (10–16 h), the ultrasound-assisted approach significantly reduced reaction time to 4–6 h and enhanced yields by nearly threefold, demonstrating marked improvements in energy efficiency and resource utilization. Optimal conditions were achieved at 35 °C and 40 kHz, affording yields up to 87% with minimal solvent use and no need for chromatographic purification (Scheme 2b). This work exemplifies the integration of sonochemical technology into heterocyclic synthesis, aligning closely with the principles of green chemistry by minimizing energy input, reaction duration, and byproduct formation. Overall, the study highlights how ultrasonic irradiation can facilitate cleaner and more sustainable transformations of BtH derivatives, providing a scalable route for generating medicinally relevant hybrid frameworks.

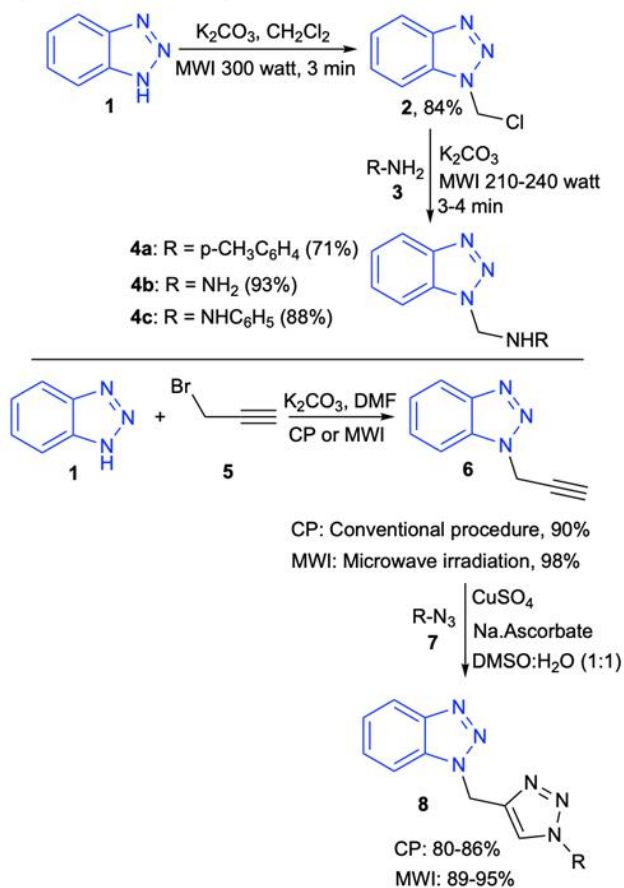
Flow chemistry represents another major advance in sustainable BtH production. Kleoff et al. (2021) [14] reported a metal-free [3+2] cycloaddition between in situ-generated arynes and azides in a continuous-flow microreactor, achieving complete conversion in only 8 minutes at 50 °C. This process safely generated functionalized BtHs (**17**) on gram scale while minimizing the accumulation of reactive azides and improving heat dissipation, thereby enhancing both yield (up to 74%) and operator safety (Scheme 2c).

Electrosynthesis offers yet another sustainable alternative by employing electron-driven oxidation and coupling reactions that minimize the need for metal catalysts and hazardous

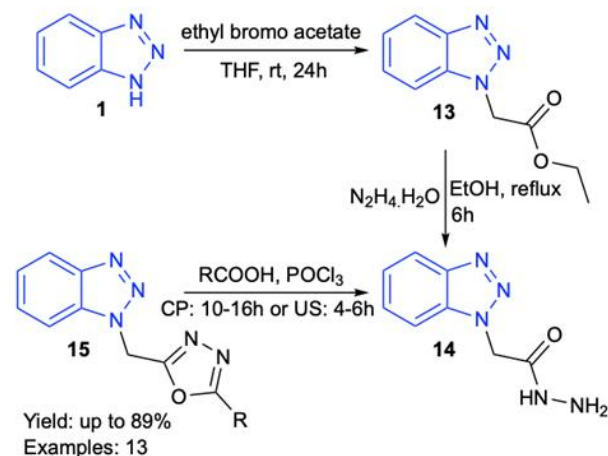
reagents. This approach uses electricity as a clean redox agent, replacing traditional stoichiometric oxidants and significantly reducing chemical waste. Feng et al. (2022) [6] developed an

*N*-hydroxyphthalimide (NHPI)-mediated anodic oxidation of aldehydes with BtH to afford *N*-acylBtHs (**19**) in up to 87% yield under mild, oxidant-free conditions.

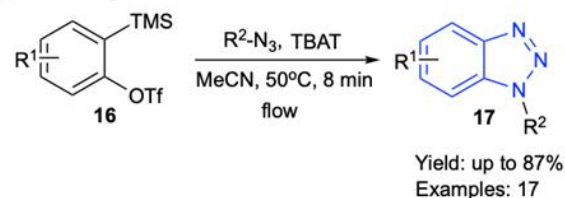
#### a) Microwave-assisted synthesis



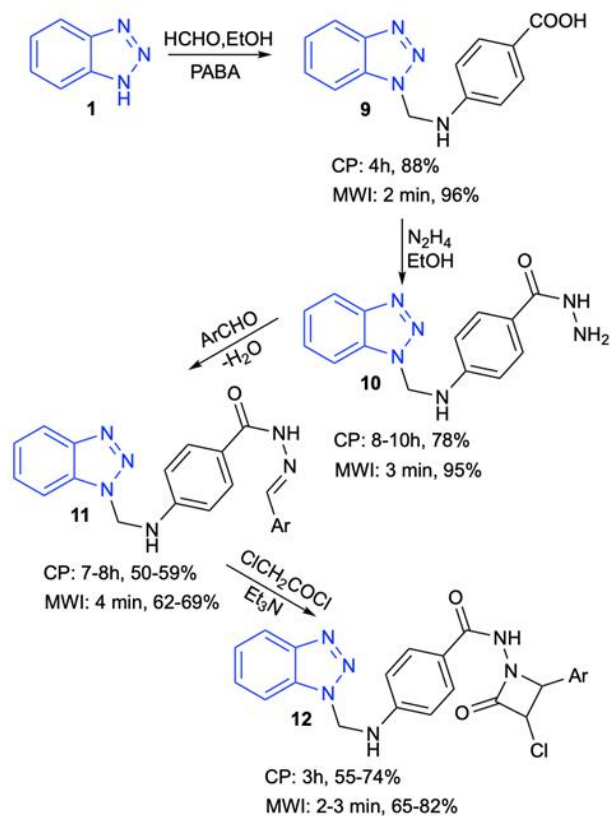
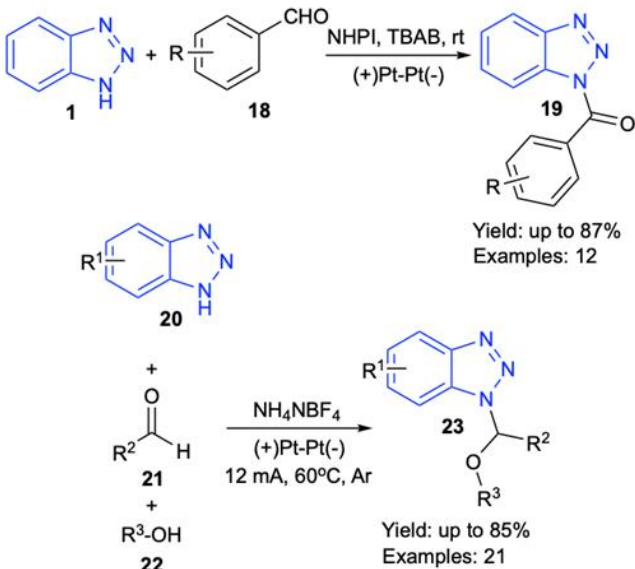
#### b) Ultrasound-assisted synthesis



#### c) Scalable synthesis in flow



#### d) Electrosyntheses



**Scheme 2** Green and sustainable methods of BtH synthesis.

The key phthalimido-*N*-oxy radical (PINO) intermediate enabled selective oxidation while avoiding toxic chlorinating agents (Scheme 2d). Building upon this work, Liu et al. (2023) [7] achieved a three-component electrochemical coupling of BtHs, aldehydes, and alcohols to produce *N*-( $\alpha$ -alkoxyalkyl)BtHs (**23**) in up to 85% yield using  $n\text{Bu}_4\text{NBF}_4$  as electrolyte and platinum electrodes. This undivided-cell system operated without external acids or oxidants, exemplifying an atom-economical and scalable electrosynthesis methodology (Scheme 2d).

Collectively, these green methodologies—microwave-assisted synthesis, ultrasound-assisted, flow-based processing, and electrosynthesis—have transformed BtH synthesis into a safer, cleaner, and more controllable process.

Microwave heating provides rapid energy transfer and minimizes solvent use; flow chemistry enables continuous, scalable, and waste-reduced production, and electrosynthesis achieves redox transformations without hazardous oxidants. Together, these innovations reduce environmental impact, enhance process efficiency, and expand the synthetic versatility of BtH chemistry, paving the way for the sustainable development of functionalized benzotriazole frameworks.

### 2.3. Functionalization and structural diversification

Benzotriazoles (BtHs) are nitrogen-containing heterocycles that have attracted significant attention in medicinal chemistry due to their diverse biological activities and therapeutic potential. Their unique triazole-fused structure allows extensive functionalization, enhancing pharmacological properties and broadening their applications. The BtH core provides a modular and chemically versatile platform whose nitrogen-rich structure supports diverse functionalization. This section highlights contemporary synthetic strategies that extend the chemical space of BtH derivatives—through halogenation, acylation, heterocyclic fusion, and metal coordination—to improve physicochemical stability and fine-tune pharmacological properties.

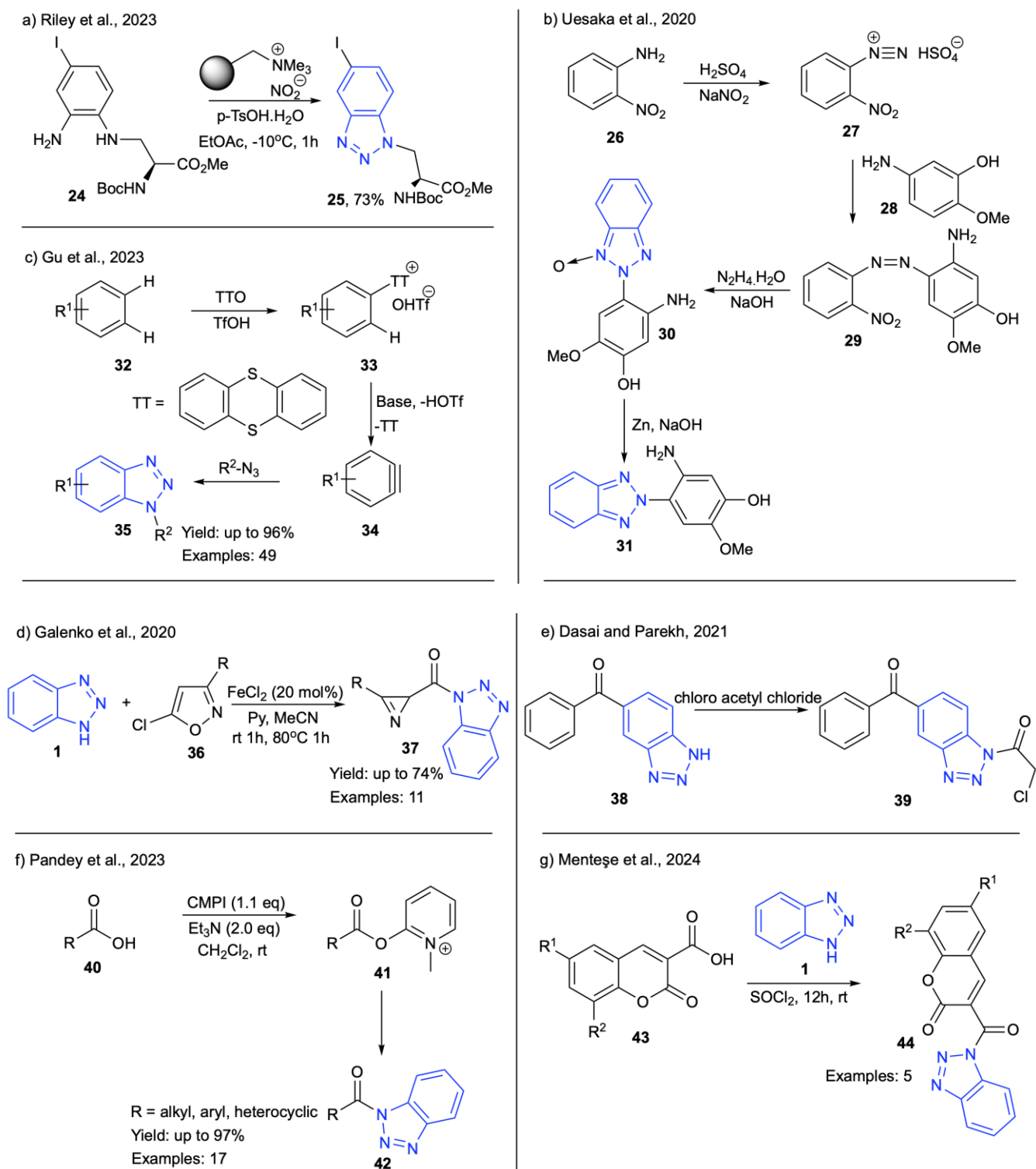
Riley and co-workers (2023) [15] developed a modular synthesis of 5-iodoBtH derivatives as precursors to fluorescent  $\alpha$ -amino acids mimicking *L*-tryptophan. The strategy involved nucleophilic aromatic substitution between 2-fluoro-5-iodonitrobenzene and a 3-aminoalanine derivative, followed by chemoselective nitro reduction with zinc/acetic acid and mild one-pot diazotization–cyclization using polymer-supported nitrite and *p*-toluenesulfonic acid, yielding 5-iodoBtH (**25**) in 73%. This modern adaptation of classical diazotization offers a versatile one-pot route to functionalized BtH chromophores with tunable electronic properties and broad potential in photophysical and biological applications (Scheme 3a).

Uesaka et al. (2020) [16] demonstrated a related approach involving diazonium salt formation from sodium nitrite in dilute sulfuric acid, followed by coupling with substituted phenols to afford arylazo intermediates that

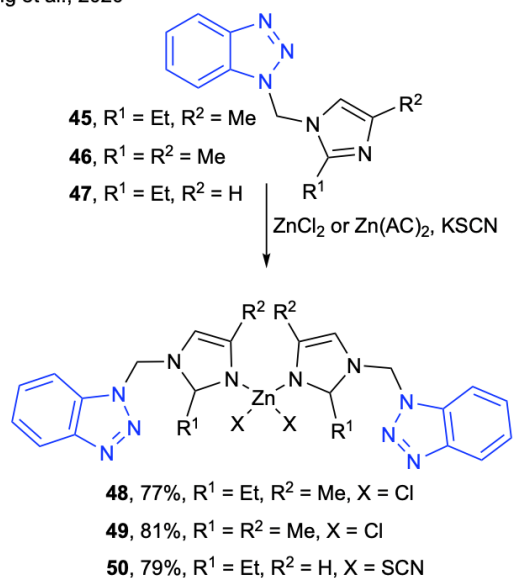
cyclized into BtH derivatives (**31**) (Scheme 3b). Similarly, Gu et al. (2023) [17] introduced a [3+2] cycloaddition using aryl sulfonium salts as aryne precursors reacting with azides. This reaction, noted for high atom economy and functional group tolerance, efficiently generated *N*-substituted BtHs (**35**) in good yields, suitable for scale-up (Scheme 3c).

*N*-AcylBtHs represent a stable, neutral class of acylating agents widely applied in the synthesis of pharmacologically relevant scaffolds. Their chemical stability and selectivity make them superior to traditional acid chlorides, enabling clean acylations without side products or diacylation [18]. Over the recent years, *N*-acylBtH synthesis has evolved from classical acyl chloride coupling to modern catalytic and reagent-controlled methods emphasizing safety, selectivity, and sustainability. Galenko et al. (2020) [19] reported an Fe(II)-catalyzed isomerization of isoxazoles followed by BtH acylation to afford functionalized *N*-acylBtHs (**37**) (Scheme 3d). Desai and Parekh (2021) [20,21] utilized BtH-activated acyl halides for amino acid coupling, generating amide-type ligands (**39**) under mild, base-assisted conditions (Scheme 3e). Pandey et al. (2023) [22] established a Mukaiyama reagent-mediated (**41**), chromatography-free route with excellent atom economy, marking a major step toward sustainable BtH chemistry (Scheme 3f). Complementarily, Menteşe et al. (2024) [23] demonstrated the biological versatility of *N*-acylBtH intermediates through  $\text{SOCl}_2$ -mediated couplings that yielded multifunctional bioactive conjugates (**44**) (Scheme 3g).

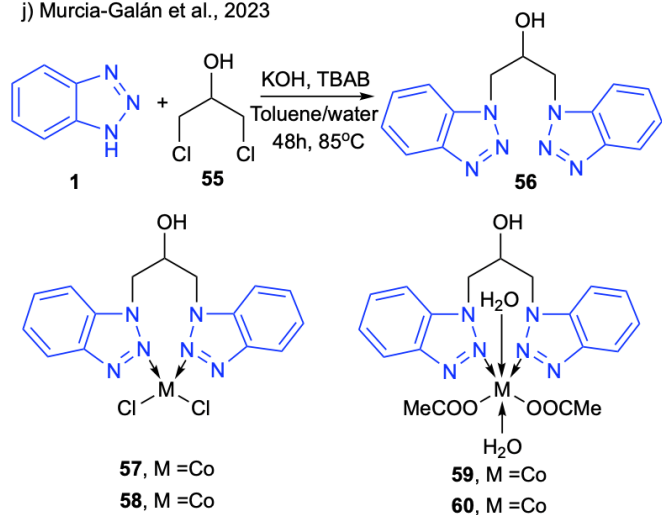
BtH and its derivatives also serve as versatile ligands in coordination chemistry due to their nitrogen-rich triazole ring, which offers multiple coordination sites (N1, N2, N3) for binding transition metals such as Zn(II), Cu(II), Co(II), Ni(II), Mn(II), and Ag(I). These interactions produce stable mono- or polynuclear architectures with notable biological activity. Ling et al. (2020) [24] synthesized three Zn(II)-BtH-imidazole complexes (**48–50**) exhibiting tetrahedral geometry, luminescence, and strong  $\alpha$ -amylase inhibition, indicating insulin-mimetic potential (Scheme 4h). Desai and Parekh (2021) [20,21] prepared Co(II), Ni(II), Cu(II), Zn(II), and Mn(II) complexes using amino acid- and anthranilic acid-derived *N*-acylBtH ligands (**51** and **52**), forming thermally stable octahedral chelates (**53** and **54**) with significant antibacterial and antifungal activity (Scheme 3i). Murcia-Galán et al. (2023) [25] synthesized Co(II) and Cu(II) complexes with 1,3-bis(benzotriazol-1-yl)propan-2-ol ligands, yielding air-stable solids with confirmed M–N/O coordination (**57–60**) and potent antifungal and antibiofilm effects against fluconazole-resistant *Candida* species (MIC = 15.6–125  $\mu\text{g mL}^{-1}$ ) (Scheme 3j). More recently, Elzein et al. (2025) [26] developed five Ag(I) complexes of 1-heteroaryl BtH ligands (**64–68**); notably, the 1-(2-pyridyl)BtH triflate complex (**65**) exhibited strong antimicrobial potency via controlled  $\text{Ag}^+$  release and chelation-enhanced membrane disruption (Scheme 3k).



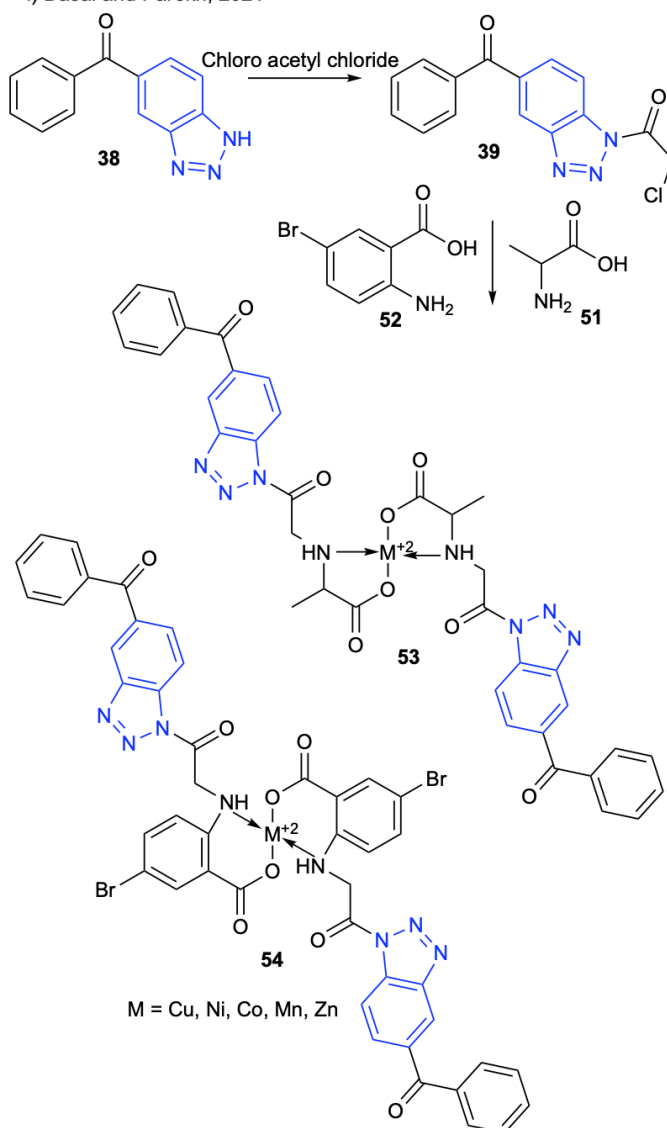
h) Ling et al., 2020



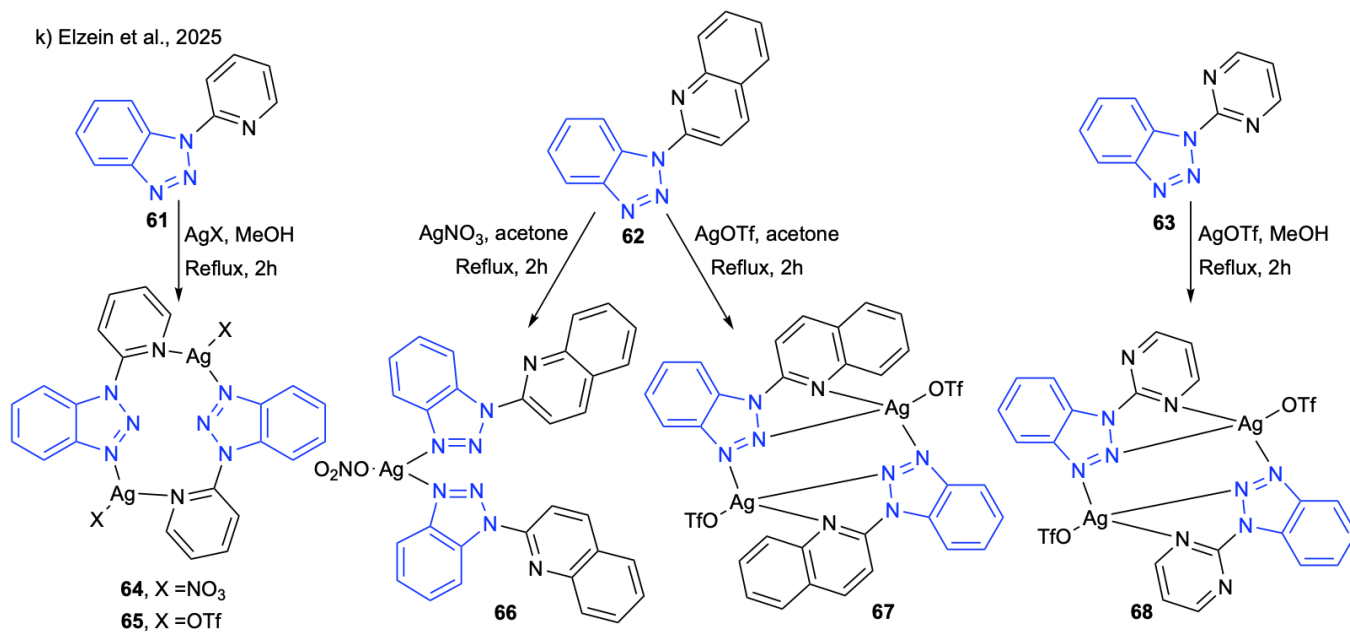
j) Murcia-Galán et al., 2023



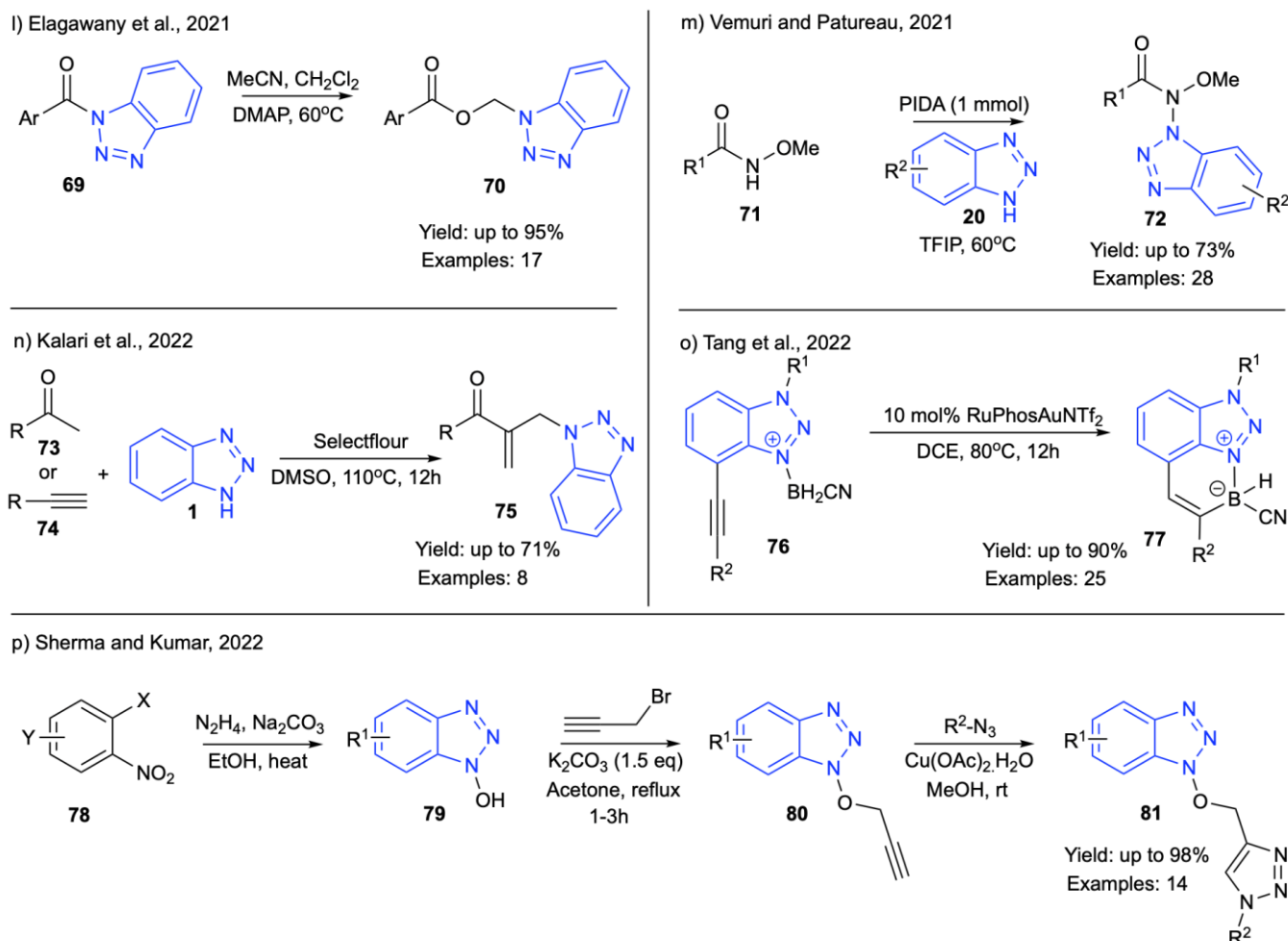
i) Dasai and Parekh, 2021



k) Elzein et al., 2025



Scheme 3 Functionalization and structural diversification of BtH (Cont.).



**Scheme 3** Functionalization and structural diversification of BtH (Cont.).

Collectively, these studies highlight BtH-based metal complexes as a sustainable platform that bridges coordination and medicinal inorganic chemistry, combining structural stability with biological functionality.

Recent advances have increasingly focused on sustainable strategies for structural diversification through innovative bond-forming methodologies. Elagawany et al. (2021) [27] reported a  $\text{CH}_2$  insertion using dichloromethane as a one-carbon synthon to convert *N*-acylBtHs (**69**) into benzotriazolyl alkyl esters (**70**) in up to 95% yield, demonstrating a solvent-activated C–C bond-forming process (Scheme 3l). Vemuri and Patureau (2021) [28] achieved the first intermolecular cross-dehydrogenative N–N coupling of methoxyamides (**71**) with BtHs using (diacetoxyiodo)benzene in hexafluoroisopropanol (HFIP), forming N–N-linked heterocycles (**72**) under mild, oxidant-controlled conditions (Scheme 4m). Kalari et al. (2022) [29] developed a Selectfluor-mediated, transition-metal-free route to  $\beta$ -acyl allyl BtHs (**75**) via DMSO-assisted multicomponent coupling that forms multiple C–C and C–N bonds simultaneously, with DMSO serving as a dual  $\text{CH}_2/\text{CO}$  donor (Scheme 3n). Tang et al. (2022) [30] designed a gold-catalyzed alkyne hydroboration using polymeric  $(\text{BH}_2\text{CN})_n$  to yield four-coordinate BtH–borane (BTAB) complexes (**77**) in up to 90% yield, displaying tunable fluorescence and high chemical stability

(Scheme 3o). Sharma and Kumar (2022) [31] developed a clean, regioselective  $\text{Cu}(\text{OAc})_2$ -catalyzed azide–alkyne “click” synthesis of BtH–triazole conjugates. BtH alkynes reacted with aryl azides in methanol at room temperature to afford 1,4-disubstituted-1,2,3-triazoles (**81**) in 34–98% yield, with excellent atom economy and no chromatographic purification required. This scalable and sustainable process provides an efficient route for BtH structural diversification, yielding multifunctional heterocyclic frameworks of biological relevance (Scheme 3p).

In summary, the expanding field of BtH functionalization reflects its transformation from a classical heterocycle into a highly adaptable and multifunctional molecular platform. From early diazotization and acylation methods to modern catalytic, reagent-controlled, and solvent-mediated protocols, BtH synthesis now achieves superior selectivity, sustainability, and structural diversity. Contemporary methodologies enable the precise formation of C–C, C–N, N–N, and N–B bonds, producing advanced derivatives with tailored physicochemical and biological properties. The development of *N*-acylBtHs, metal–BtH coordination complexes, and borane-linked chromophores exemplifies BtH’s versatility in bridging organic, inorganic, and materials chemistry. Collectively, these innovations expand the synthetic toolbox and deepen understanding of how structural

modifications govern reactivity and biological performance—insights further explored in the next section on Structure–Activity Relationships (SAR) and Mechanistic Insights.

### 3. Structure–activity relationship (SAR) and mechanistic insights

In medicinal chemistry, the design and synthesis of BtH derivatives must be strategically aligned with their biological activities to maximize therapeutic efficacy. Structural modifications—such as the introduction of electron-donating or electron-withdrawing groups, halogenation, alkylation, heterocyclic fusion, and metal complexation—play a pivotal role in modulating the pharmacological effectiveness of BtH-based compounds.

#### 3.1. Impact of electron-donating and electron-withdrawing groups

**Electron-Withdrawing Groups (EWGs):** The incorporation of electron-withdrawing substituents, such as trifluoromethyl groups at specific positions (e.g., C-2), has been shown to significantly enhance antibacterial activity. These groups can increase the affinity of BtH derivatives for their biological targets by stabilizing the active conformation of the molecule during enzyme or receptor interactions [32].

**Electron-Donating Groups (EDGs):** Conversely, electron-donating substituents such as alkyl or alkoxy groups improve solubility and bioavailability within biological systems. Enhanced solubility often leads to more favorable pharmacokinetic profiles, thereby improving the therapeutic performance of BtH derivatives [11].

#### 3.2. Additional modifications and their effects

**Halogenation:** The strategic introduction of halogens (fluorine, chlorine, or bromine) can fine-tune lipophilicity and modulate biological activity. Halogen atoms alter both the steric and electronic properties of BtH derivatives, often enhancing binding affinity to target biomolecules [33].

**Alkylation and Acylation:** Substitution with alkyl or acyl groups at different ring positions can optimize biological activity by modifying steric bulk and hydrophobicity, thereby influencing drug–receptor interactions and membrane permeability [34].

**Heterocyclic Fusion:** The fusion of additional heterocyclic rings can facilitate  $\pi$ – $\pi$  stacking and hydrophobic

interactions with biological targets, leading to derivatives with enhanced potency, particularly against drug-resistant pathogens [1,35].

**Metal Complexation:** Coordination with metals—most notably silver(I)—introduces new electronic and redox features that can markedly increase antimicrobial potency. Metal–BtH complexes also open avenues for developing hybrid therapeutic agents that integrate organic and inorganic pharmacophores [26].

#### 3.3. Mechanistic rationale

The enhancement of biological activity by these structural modifications can be attributed to multiple interaction pathways:

**$\pi$ – $\pi$  Stacking:** The presence of additional aromatic or heterocyclic rings promotes  $\pi$ – $\pi$  interactions with protein residues, improving molecular recognition and binding strength [35].

**Hydrogen Bonding:** Substituents that increase hydrogen-bonding capability, particularly at nitrogen or oxygen sites within the BtH framework, stabilize enzyme–inhibitor complexes and reinforce target engagement [33].

**Enzyme Inhibition Pathways:** BtH-based inhibitors, such as those targeting SARS-CoV-2 protease, illustrate how precise structural tailoring can modulate specific enzymatic processes and suppress viral replication through competitive inhibition [33].

Comprehensive SAR studies have revealed that subtle structural variations within the BtH core profoundly influence pharmacological behavior (Table 1). The interplay between electron-donating and electron-withdrawing groups governs both the electronic environment and physicochemical properties essential for target binding and bioavailability. Meanwhile, modifications such as halogenation, alkylation, and heterocyclic fusion enhance lipophilicity, metabolic stability, and receptor selectivity, while metal complexation introduces new redox and coordination features that expand therapeutic potential. Mechanistically, these improvements arise from synergistic effects involving  $\pi$ – $\pi$  stacking, hydrogen bonding, and enzyme–ligand interactions that strengthen molecular recognition and inhibition at active sites. Collectively, these insights establish a rational framework for designing next-generation BtH derivatives with optimized efficacy, selectivity, and sustainability for diverse pharmacological applications.

**Table 1** Comparative SAR summary.

Modification type	Structure examples	Observed activity
EWG Addition	Trifluoromethyl substituted BtHs	Increased antibacterial activity
EDG Optimization	Alkoxy-substituted BtHs	Enhanced solubility and efficacy
Halogenation	Halogenated BtH derivatives	Improved binding affinity
Alkylation and Acylation	2-oxo-4-substituted azetidine derivatives	Promising antimicrobial activity
Heterocyclic Fusion	BtH derivatives with fused rings	Enhanced target interaction
Metal Complexation	Silver(I) complexes with BtH	Increased antimicrobial potency

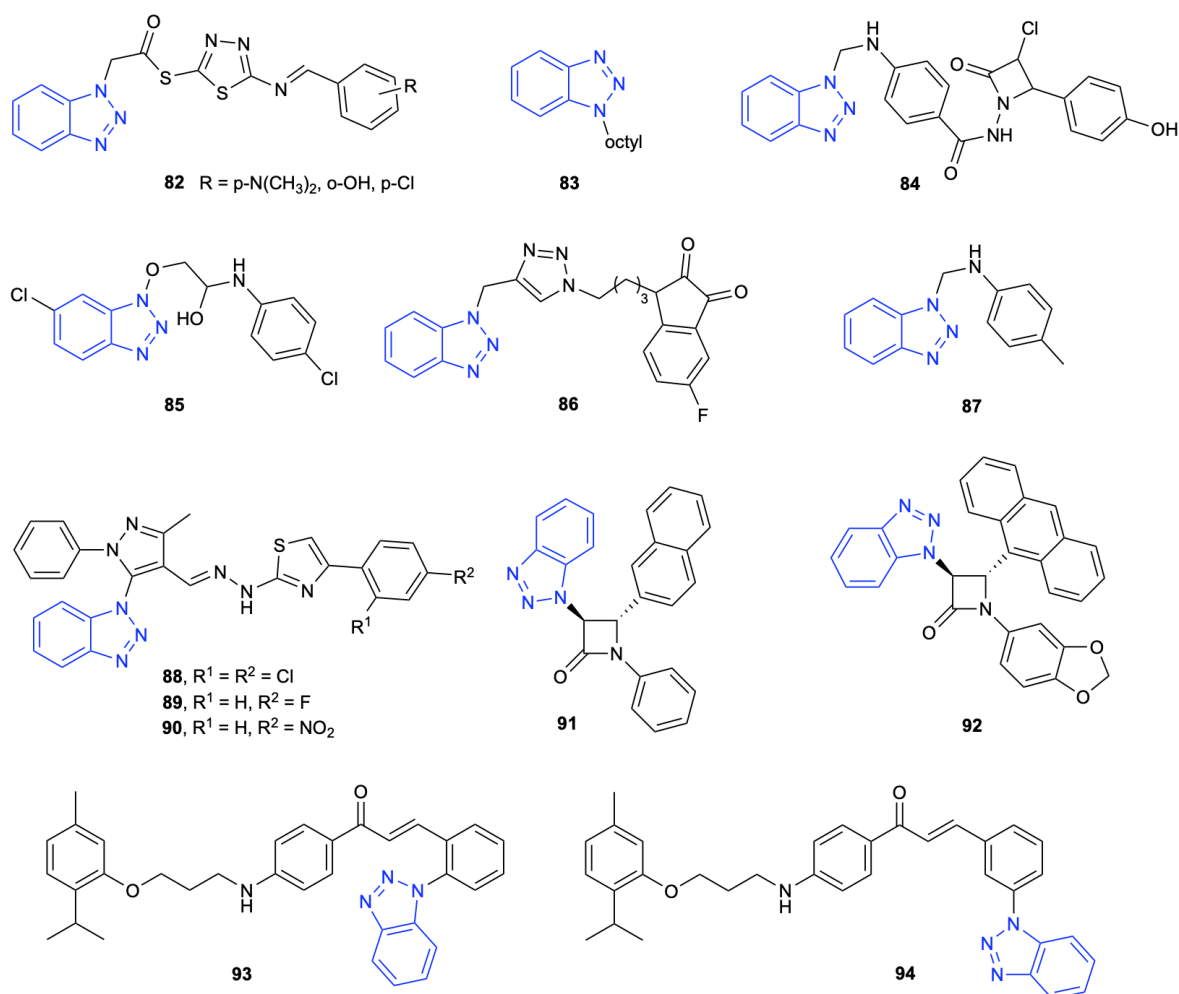
## 4. Pharmacological activities of benzotriazole derivatives

### 4.1. Antifungal and antimicrobial activity

Microbial infections caused by bacteria such as *Staphylococcus aureus* and *Escherichia coli* and fungi including *Candida* and *Aspergillus* species remain among the most persistent and life-threatening global health challenges. The rapid emergence of antibiotic- and azole-resistant strains, coupled with limited therapeutic options, underscores the urgent need for new chemotypes that exhibit enhanced potency and reduced resistance potential. BtH-based scaffolds have emerged as promising frameworks owing to their nitrogen-rich aromatic structure, which enables hydrogen bonding,  $\pi$ - $\pi$  stacking, and metal coordination with biological targets. Recent studies (2020–2025) have explored innovative structural diversification strategies—including hybridization with  $\beta$ -lactams, chalcones, triazoles, thiazoles, metal complexes, and other heterocycles—to optimize antimicrobial and antifungal efficacy, bioavailability, and target selectivity.

Desai and Parekh (2021) [20,21] synthesized *N*-acylBtH ligands and their Cu(II), Co(II), Ni(II), Zn(II), and Mn(II) complexes (**53** and **54**), which displayed strong

antibacterial and antifungal activities. Among these, Cu(II) complexes exhibited the greatest inhibition against various bacteria (*B. Subtilis*, *S. aureus*, *S. typhi* and *E. coli*) and fungi (*P. expansum*, *A. niger* and *Nigrosporas* sp.), highlighting the role of metal–ligand coordination in enhancing lipophilicity and membrane permeability (Figure 2 and Table 2). Ibrahim et al. (2021) [36] prepared BtH-thiadiazole hybrids (**82**) through multistep cyclization and condensation, achieving broad-spectrum antibacterial effects against both Gram-positive and Gram-negative bacteria. Incorporation of electron-withdrawing substituents proved critical for improving bacterial membrane penetration (Figure 2 and Table 2). Jimoh et al. (2022) [37,38] synthesized quaternized BtH-benzimidazole salts, with compound **83** exhibiting remarkable antifungal activity against *Candida stellatoidea* (MIC = 6.25  $\mu\text{g mL}^{-1}$ ; MFC = 25  $\mu\text{g mL}^{-1}$ ; ZOI = 31 mm) and potent antibacterial effects against MRSA and *E. coli* through a membrane-disruptive cationic mechanism (Figure 2 and Table 2). Rokde et al. (2023) [12] reported BtH-azetidinone hybrids via microwave-assisted Staudinger  $\beta$ -lactam formation, where the most active analogue (**84**) produced inhibition zones of 18–19 mm against *E. coli* and *S. aureus*, confirming the synergistic antibacterial effect of  $\beta$ -lactam–BtH hybridization (Figure 2 and Table 2).



**Figure 2** Chemical structures of BtH derivatives exhibiting antifungal and antimicrobial activities.

**Table 2** Antifungal and antimicrobial activity of BtH derivatives.

Compound	Structure type	Substituent / key moiety	Main target	Activity	Ref.
53 and 54	Metal complex	Cu(II) chelate of <i>N</i> -acyl-BtH	Bacteria ( <i>B. Subtilis</i> , <i>S. aureus</i> , <i>S. typhi</i> and <i>E. coli</i> ) Fungi ( <i>P. expansum</i> , <i>A. niger</i> and <i>Nigrosporas</i> sp.)	Inhibition zone: up to 38 mm	20,21
82	Hybrid	Functionalized-aryl	Bacteria ( <i>E. coli</i> and <i>S. aureus</i> ) Fungi ( <i>C. albicans</i> and <i>C. tropicalis</i> )	Inhibition zone: up to 43 mm	36
83	Alkyl BtH	Octyl BtH	<i>C. stellatoidea</i>	MIC = 6.25 $\mu\text{g mL}^{-1}$ ; MFC = 25 $\mu\text{g mL}^{-1}$ ; ZOI = 31 mm	37,38
84	$\beta$ -Lactam hybrid	-OH-substituted aryl	<i>E. coli</i> and <i>S. aureus</i>	Inhibition zones: 18–19 mm	12
85	$\beta$ -Amino alcohol	-OH, -NH (polar)	<i>S. aureus</i>	MIC = 8 $\mu\text{M}$	39
86	Isatin-BtH hybrid	Triazole linker	<i>C. albicans</i>	MIC = 3.9 $\mu\text{M}$ ; MFC = 7.8 $\mu\text{M}$	40
87	Amine-BtH	Methyl-substituted aryl	Bacteria ( <i>B. Subtilis</i> , and <i>E. coli</i> ) Fungi ( <i>A. niger</i> )	Inhibition zone: up to 16 mm	41
88-90	BtH-Pyrazole-Thiazole	2,4-Cl / 4-F / 4-NO <sub>2</sub>	Bacteria ( <i>E. coli</i> , <i>B. subtilis</i> , <i>B. megaterium</i> and <i>S. aureus</i> ) Fungi ( <i>A. niger</i> , <i>A. oryzae</i> , <i>Rhizophus</i> spp. and <i>C. albicans</i> )	MIC = 15.63–62.5 $\mu\text{g mL}^{-1}$	2
91 and 92	BtH- $\beta$ -Lactam	Naphthyl / Anthracenyl	<i>P. falciparum</i>	IC <sub>50</sub> = 9.73 and 5.56 $\mu\text{M}$	42
65	Ag(I)-BtH	1-(2-pyridyl), triflate	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. epidermidis</i> and <i>S. aureus</i>	MIC = 55.9–118.8 $\mu\text{M}$	26
93 and 94	BtH-Chalcone	o- or m-BtH position	<i>C. albicans</i> and <i>C. mycoderma</i>	MIC = 12.91 and 14.72 $\mu\text{g mL}^{-1}$	43

Note: IC<sub>50</sub> = half-maximal inhibitory concentration; MIC = minimum inhibitory concentration; ZOI = zone of inhibition; MFC = minimum fungicidal concentration.

Singh et al. (2023) [39] synthesized  $\beta$ -amino alcohol and oxazolidine derivatives of BtH under solvent- and catalyst-free conditions, achieving MIC values as low as 8  $\mu\text{M}$  against *S. aureus*. The strong activity was attributed to the polar -OH and -NH groups (**85**) enhancing hydrogen bonding with microbial enzymes (Figure 2 and Table 2). In a related study, Singh et al. (2023) [40] designed isatin-BtH click hybrids via CuAAC reactions, with compound **86** demonstrating potent antifungal activity against *Candida albicans* (MIC = 3.9  $\mu\text{M}$ ; MFC = 7.8  $\mu\text{M}$ ) (Figure 2 and Table 2). Subsequently, Singh et al. (2024) [41] employed microwave-assisted synthesis to produce novel BtH scaffolds with significant antibacterial and antifungal activities—compound **87** exhibited inhibition zones up to 16 mm against *B. subtilis*, *E. coli*, and *A. niger* (Figure 2 and Table 2).

Gangurde et al. (2024) [2] developed BtH-pyrazole-thiazole hybrids via multicomponent condensation, yielding compounds **88** (2,4-Cl), **89** (4-F), and **90** (4-NO<sub>2</sub>) with potent antibacterial and antifungal properties (MIC = 15.63–62.5  $\mu\text{g mL}^{-1}$ ). Electron-withdrawing substituents enhanced activity by improving hydrophobic and electronic interactions with microbial enzymes (Figure 2 and Table 2).

Aye et al. (2024) [42] synthesized BtH- $\beta$ -lactam hybrids via diastereoselective ketene-imine cycloaddition; compounds **91** (naphthyl) and **92** (anthracenyl) exhibited potent biological activity (IC<sub>50</sub> = 9.73 and 5.56  $\mu\text{M}$ , respectively), attributed to extensive aromatic stacking within the active site (Figure 2 and Table 2). Elzein et al. (2025) [26] reported Ag(I)-BtH complexes, among which complex **65** containing a 1-(2-pyridyl)BtH ligand displayed excellent antibacterial activity against *P. aeruginosa*, *E. coli*, *S. epidermidis* and *S. aureus* (MIC 55.9–118.8  $\mu\text{M}$ ). This was facilitated by controlled Ag<sup>+</sup> release and *N*-donor stabilization of the metal center (Figure 2 and Table 2). Kumari and Kumar (2025) [43] synthesized BtH-chalcone hybrids through Claisen-Schmidt condensation followed by intramolecular cyclization. Compounds **93** and **94** showed potent antifungal activity against *C. albicans* and *C. mycoderma* (MIC = 12.91 and 14.72  $\mu\text{g mL}^{-1}$ ), outperforming fluconazole (Figure 2 and Table 2).

Collectively, these studies demonstrate clear structure-activity trends across BtH derivatives. Electron-withdrawing substituents (Cl, F, NO<sub>2</sub>) enhance lipophilicity and facilitate membrane penetration, strengthening  $\pi$ - $\pi$  and halogen-bond interactions with microbial enzymes.

Heterocyclic fusion (e.g., thiadiazole, thiazole, chalcone, and  $\beta$ -lactam motifs) increases conjugation and molecular rigidity, improving binding affinity and redox potential. Metal complexation, particularly with Cu(II) and Ag(I), enhances antimicrobial activity through controlled ion release and enzyme denaturation. Furthermore, green synthetic approaches—including microwave irradiation, solvent-free protocols, and click chemistry—enable rapid and sustainable access to bioactive scaffolds. Together, these advances establish BtH-based frameworks as multifunctional, broad-spectrum antimicrobial and antifungal agents with tunable physicochemical and biological properties, providing a robust foundation for future anti-infective drug discovery.

#### 4.2. Antiviral activity

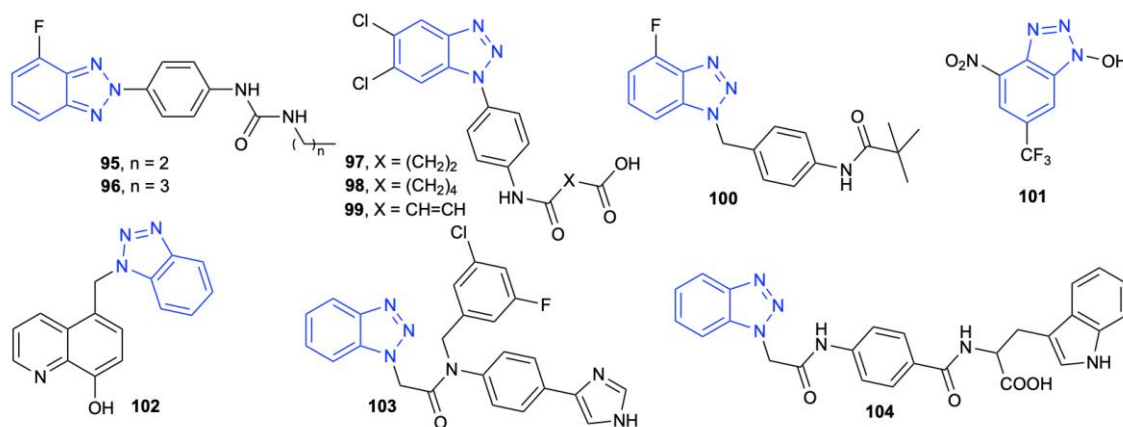
Viral infections caused by pathogens such as SARS-CoV-2, Coxsackievirus, Poliovirus, Hepatitis A virus (HAV), and Tobacco Mosaic Virus (TMV) remain serious global health challenges due to high mutation rates and increasing antiviral resistance. Despite major advances in vaccine development, the need for small-molecule antivirals with broad-spectrum efficacy and specific viral enzyme inhibition remains urgent. BtH derivatives have recently emerged as promising antiviral scaffolds because their versatile heteroaromatic structure enables strong hydrogen bonding,  $\pi$ - $\pi$  stacking, and metal coordination with viral enzyme residues. Functionalization through amide, urea, bisamide, and metal-ligand frameworks allow precise modulation of physicochemical and biological properties, resulting in potent inhibition of viral proteases, helicases, and coat proteins.

Corona et al. (2020) [44] first identified BtH amide and urea derivatives (compounds **95** and **96**) as potent inhibitors of Coxsackievirus B5 and Poliovirus Sb-1, achieving  $EC_{50}$  values of 5.5–6.9  $\mu$ M (Figure 3 and Table 3). Ibba et al. (2021) [45] expanded on this work by designing bis-BtH-dicarboxamide analogues targeting Picornavirus helicase, yielding  $EC_{50}$  = 9–13  $\mu$ M for mono-substituted acidic derivatives (**97–99**) (Figure 3 and Table 3). Later, in 2023 [46], optimized BtH amide derivatives such as compound **100** blocked Coxsackievirus attachment during early replication

( $EC_{50}$  = 12.4  $\mu$ M) (Figure 3 and Table 3). D'Souza et al. (2021) [47] combined QSAR modeling, molecular docking, and dynamics simulations to design BtH-based SARS-CoV 3CL protease inhibitors, predicting strong binding to catalytic residues Cys145 and Glu166—key to proteolytic cleavage during viral replication.

Fetouh et al. (2022) [48] developed an eco-friendly approach by synthesizing 1-hydroxy-4-nitro-6-trifluoromethyl BtH (**101**) embedded in a silver-nanoparticle-activated carbon composite (SNPs@AC), which achieved 96.7 % inhibition of hepatitis A virus (HAV) at 78  $\mu$ g mL<sup>-1</sup>. This result demonstrated a nanocomposite-driven antiviral mechanism via redox activation (Figure 3 and Table 3). Himmi et al. (2023) [49] reported a quinoline-BtH hybrid (**102**) exhibiting superior docking affinity for SARS-CoV-2 3CL protease ( $\Delta G$  = -9.7 kcal mol<sup>-1</sup>) compared to hydroxychloroquine and remdesivir analogues (Figure 3 and Table 3). In parallel, Hooper et al. (2023) [33] optimized the ML300 BtH scaffold to yield derivative **103** with  $IC_{50}$  = 41 nM representing some of the most potent non-covalent SARS-CoV-2 main protease inhibitors to date (Figure 3 and Table 3). Li et al. (2024) [50] further explored bisamide- and heteroaryl-functionalized BtHs, reporting compound **104** with remarkable anti-tobacco mosaic virus (TMV) activity ( $EC_{50}$  = 157.6  $\mu$ g mL<sup>-1</sup>), inhibiting coat protein assembly ( $K_d$  = 0.7  $\mu$ M) and outperforming ribavirin ( $EC_{50}$  = 442.1  $\mu$ g mL<sup>-1</sup>) (Figure 3 and Table 3).

BtH derivatives exhibit strong antiviral activity through scaffold-dependent mechanisms. Electron-withdrawing substituents (e.g., CF<sub>3</sub>, Cl) and amide/urea linkages enhance hydrogen bonding with viral proteases, while hybridization with heterocycles (e.g., quinoline, bisamide) increases planarity and  $\pi$ - $\pi$  stacking, thereby strengthening enzyme binding. Incorporation of metals (Ag, Cu) or nanocomposite matrices introduces redox-mediated viral inactivation pathways. Collectively, structural fine-tuning—particularly at the triazole nitrogen and amide positions—enhances viral target affinity and selectivity, positioning BtHs as next-generation broad-spectrum antiviral scaffolds with promising therapeutic potential.



**Figure 3** Chemical structures of BtH derivatives exhibiting antiviral activities.

**Table 3** Antiviral activity of BtH derivatives.

Compound	Structure type	Viral target	Activity	Key mechanism/interaction	Ref.
<b>95 and 96</b>	BtH amide / urea	Coxsackievirus B5, Poliovirus Sb-1	EC <sub>50</sub> values of 5.5-6.9 μM	Alkyl chains linked to urea nitrogen	44
<b>97-99</b>	mono-substituted acidic BtH	Poliovirus-1 helicase	EC <sub>50</sub> = 9-13 μM	Mono-substituted acidic	45
<b>100</b>	BtH amide	Coxsackievirus B5	EC <sub>50</sub> = 12.4 μM	Viral attachment inhibition	46
<b>101</b>	BtH-Ag composite	hepatitis A. virus	96.7% inhibition at 78 μg mL <sup>-1</sup>	Blocking the cell-virus interaction	48
<b>102</b>	Quinoline-BtH hybrid	SARS-CoV-2 3CL protease	ΔG = -9.7 kcal mol <sup>-1</sup>	π-π stacking and hydrogen bonding	49
<b>103</b>	BtH ML300 analogs	SARS-CoV-2 3CL protease	IC <sub>50</sub> = 41 nM	Non-covalent inhibition, His163 binding	33
<b>104</b>	Bisamide-BtH	Tobacco Mosaic Virus	EC <sub>50</sub> = 157.6 μg mL <sup>-1</sup>	Coat protein assembly inhibition	50

Note: EC<sub>50</sub> = half-maximal effective concentration; IC<sub>50</sub> = half-maximal inhibitory concentration.

### 4.3. Anticancer activity

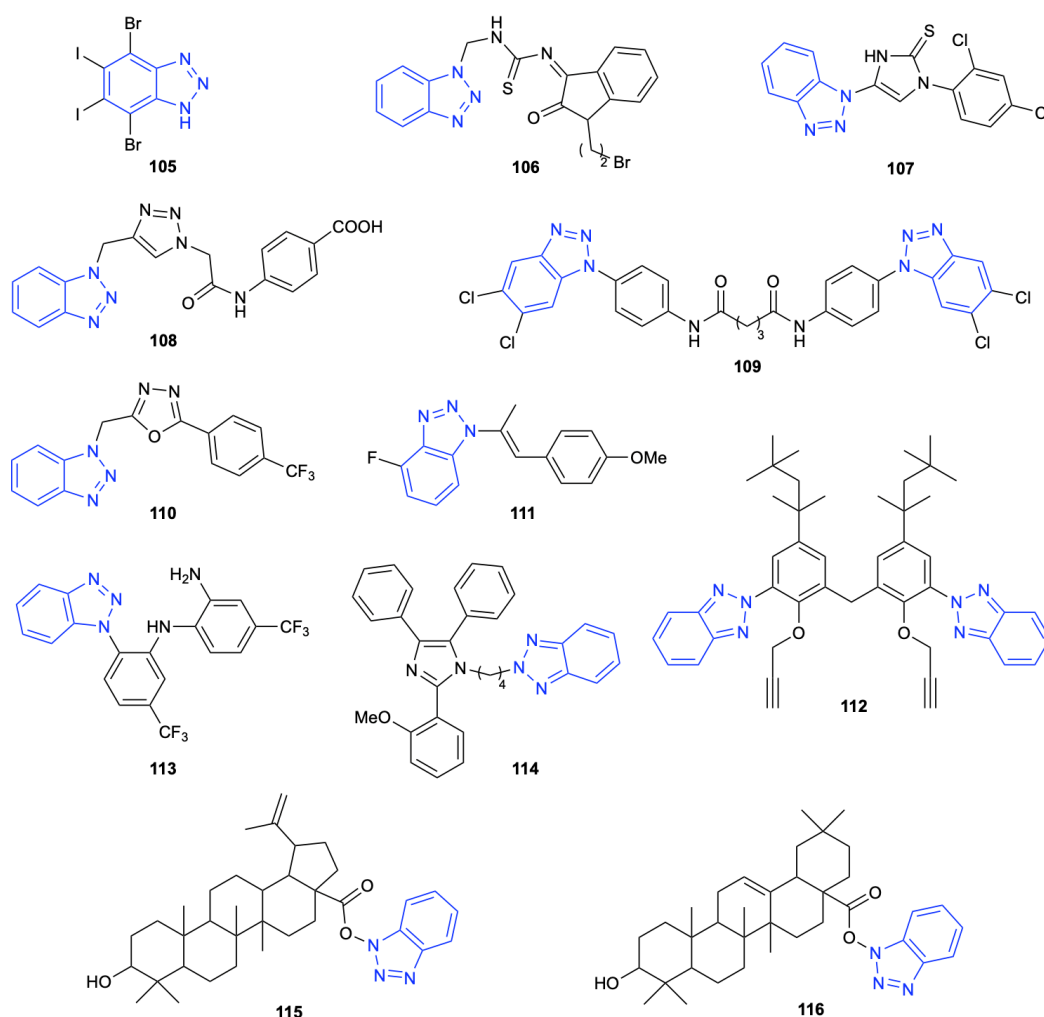
Cancer remains one of the leading causes of global mortality, and resistance to conventional therapies combined with toxicity toward normal cells continues to drive the search for more selective and multifunctional agents. BtH-based scaffolds have attracted significant attention owing to their structural stability, ease of derivatization, and capacity to form strong π-π stacking and hydrogen-bonding interactions with key biomolecular targets such as protein kinase CK2, EGFR, microtubules, and DNA. Recent studies (2020-2026) have explored structural diversification through halogenation, hybridization with pharmacophores (e.g., imidazole, triazole, oxadiazole, benzimidazole), and metal coordination to enhance selectivity, bioavailability, and cytotoxic potency.

Marzec et al. (2020) [51] reported iodinated BtH (**105**) as potent inhibitors of protein kinase CK2, a pro-survival enzyme overexpressed in multiple malignancies. The introduction of iodine enhanced hydrophobic and halogen-bonding interactions at the kinase hinge region, improving potency and stability relative to brominated analogues (Figure 4 and Table 4). Rajesh Kumar et al. (2020) [52] synthesized isatin-imidazole-BtH hybrids via one-pot multicomponent reactions, where **106** exhibited cytotoxicity against MCF-7 breast cancer cells (IC<sub>50</sub> = 2.88 μM) (Figure 4 and Table 4). Khayyat et al. (2021) [53] developed BtH-imidazole-thione hybrids that disrupted microtubule polymerization; notably, **107** displayed submicromolar cytotoxicity (IC<sub>50</sub> = 0.40, 2.63 and 3.57 μM on HL-60, HCT-116 and MCF-7, respectively), inducing G<sub>2</sub>/M arrest and apoptosis through tubulin inhibition (Figure 4 and Table 4). Similarly, Paprocki et al. (2021) [54] synthesized 5,6-diiodo- and 5,6-diiodo-4,7-dibromo-BtHs **105** that retained strong CK2 inhibition (IC<sub>50</sub> = 0.23 μM) comparable to tetrabromoBtH (IC<sub>50</sub> = 0.49 μM) but with reduced mitochondrial toxicity (Figure 4 and Table 4).

Alraqa et al. (2021) [5] designed BtH-1,2,3-triazole hybrids via Cu(I)-catalyzed click chemistry; **108** inhibited

A549 and H1299 lung carcinoma cells by up to 92% and exhibited strong DNA-binding affinity ( $K_b = 10.1 \cdot 10^5 \text{ M}^{-1}$ ). Ibba et al. (2021) [45] introduced bis-BtH-dicarboxamide derivatives (e.g., **109**) with dual antiviral and antiproliferative activity, triggering apoptosis in SK-MES1 lung carcinoma cells (CC<sub>50</sub> = 6.80 μM) (Figure 4 and Table 4). Mermer et al. (2022) [13] synthesized BtH-oxadiazole hybrids via ultrasound-assisted protocols; **110** exhibited antiproliferative activity against PANC-1 pancreatic cells (IC<sub>50</sub> = 87.8 μM) by targeting DDR1 and PDEδ kinases (Figure 4 and Table 4). Riu et al. (2022) [55] reported 4'-fluoro-BtH-acrylonitrile derivatives, where compound **111** demonstrated exceptional potency (IC<sub>50</sub> ≈ 0.1 μM) against HeLa and MCF-7 cells through microtubule destabilization and synergistic action with doxorubicin in resistant melanoma (Figure 4 and Table 4). Qadri et al. (2023) [56] synthesized a bisBtH derivative, **112**, via alkylation of 6,6'-methylenebis(benzotriazolylphenol) with propargyl bromide. Compound **112** showed strong cytotoxicity against MCF-7 (GI<sub>50</sub> = 4.04 μM) and HeLa (GI<sub>50</sub> = 6.08 μM) while remaining non-toxic to normal Vero cells. Molecular docking revealed high binding affinity toward NEK2 (-10.5 kcal mol<sup>-1</sup>), TP53 (-9.5 kcal mol<sup>-1</sup>), and NF-κB (-8.8 kcal mol<sup>-1</sup>), confirming a multitarget inhibition profile (Figure 4 and Table 4).

Aleksandrova et al. (2024) [57] synthesized *N*-aryl BtH-benzimidazole hybrids, among which diphenylamine-linked derivatives **113** exhibited strong cytotoxicity against various cell lines (SH-SY5Y, A549, MCF-7, SW-480 and Hek-293; IC<sub>50</sub> = 22.43-26.28 μM) and inhibited cancer cell migration, indicating dual antimetastatic and antioxidant potential (Figure 4 and Table 4). Finally, Kumar et al. (2026) [58] prepared imidazole-BtH hybrids; compound **114** displayed notable cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cells (IC<sub>50</sub> = 29 μM). Docking and mechanistic studies confirmed EGFR binding at Thr830, leading to apoptosis and G<sub>1</sub>/S-phase arrest (Figure 4 and Table 4).



**Figure 4** Chemical structures of BtH derivatives exhibiting anticancer activities.

**Table 4** Anticancer activity of BtH derivatives.

Compound	Structure type	Target / cell line	Activity	Key mechanism/interaction	Ref.
105	Halogenated BtH	CK2 kinase	Thermodynamic contribution	Halogen bonding, hydrophobic stabilization	51
106	Isatin-thione-BtH	MCF-7	IC <sub>50</sub> = 2.88 μM	COX-2/PI3K inhibition	52
107	BtH-imidazole-thione	HL-60, HCT-116 and MCF-7	IC <sub>50</sub> = 0.40, 2.63 and 3.57 μM	Tubulin inhibition, G <sub>2</sub> /M arrest	53
105	Halogenated BT	CK2	IC <sub>50</sub> = 0.23 μM	Reduced mitochondrial toxicity	54
108	BtH-1,2,3-triazole	A549 and H1299	92% inhibition	DNA minor groove binding	5
109	Bis-BtH-dicarboxamide	SK-MES1	CC <sub>50</sub> = 6.80 μM	Apoptosis induction	45
110	BtH-oxadiazole	PANC-1	IC <sub>50</sub> = 87.8 μM	DDR1/PDEδ inhibition	13
111	BtH-acrylonitrile	HeLa and MCF-7	IC <sub>50</sub> ≈ 0.1 μM	Microtubule destabilization	55
112	Bispropargyloxy-BtH	MCF-7 and HeLa	GI <sub>50</sub> = 4.04 and 6.08 μM	π-π stacking and hydrogen-bonding	56
113	N-Aryl-BtH	SH-SY5Y, A549, MCF-7, SW-480 and Hek-293	IC <sub>50</sub> = 22.43-26.28 μM	Suppress the migration activity of tumor cells	57
114	Imidazole-BtH hybrid	MCF-7 and MDA-MB-231	IC <sub>50</sub> = 29 μM	EGFR inhibition, apoptosis	58
115 and 116	Triterpenic acid-BtH ester	A375	ΔG ≈ -9.0 to -9.4 kcal/mol	Apoptosis	59

Note: IC<sub>50</sub> = half-maximal inhibitory concentration; CC<sub>50</sub> = 50% cytotoxicity concentration; GI<sub>50</sub> = concentration for 50% of maximal inhibition of cell proliferation.

Mioc et al. (2022) [59] synthesized 1-hydroxyBtH (HOBt) esters of betulinic (BA), oleanolic (OA), and ursolic (UA) acids via esterification at the C-28 position. In A375 melanoma cells, these derivatives significantly reduced cell viability and mitochondrial respiration (routine, OXPHOS, and ETS capacities) while sparing normal HaCaT keratinocytes. Among them, **115** and **116** exhibited the strongest cytotoxicity, inducing apoptosis through downregulation of Bcl-2 and upregulation of Bax. Molecular docking studies confirmed enhanced Bcl-2 binding affinities ( $\Delta G \approx -9.0$  to  $-9.4$  kcal/mol) compared with the parent triterpenic acids (Figure 4 and Table 4).

Structure–activity relationship (SAR) analysis indicates that halogen substitution (I, F) enhances binding to kinase and tubulin targets through strengthened hydrophobic and halogen-bonding interactions. Fusion with heterocycles such as imidazole, triazole, and oxadiazole increases  $\pi$ – $\pi$  stacking and hydrogen-bond formation with DNA and enzyme residues, thereby amplifying antiproliferative potency. Electron-withdrawing groups and diphenylamine linkers further optimize cytotoxic and antioxidant profiles, while conjugation with isatin or triterpenic acids imparts dual apoptotic and antimetastatic activity.

#### 4.4. Antioxidant and enzyme-inhibitory activity

Oxidative stress, caused by excessive reactive oxygen species (ROS) and enzymatic dysregulation, plays a central role in the progression of metabolic, cardiovascular, and inflammatory diseases. Enzymes such as  $\alpha$ -glucosidase,  $\alpha$ -amylase, urease, and lipase are key regulators of glucose metabolism, urea hydrolysis, and lipid processing—making them crucial therapeutic targets in diabetes, gastric disorders, and obesity-related conditions. BtH-based compounds, owing to their  $\pi$ -conjugated system, hydrogen-bond donor/acceptor functionality, and metal coordination capability, have emerged as promising multifunctional scaffolds with both radical-scavenging and enzyme-inhibitory properties. Recent studies (2020–2025) have demonstrated that structural tuning through hybridization, metal complexation, and strategic substitution can effectively optimize redox potential, selectivity, and overall bioactivity.

Ling et al. (2020) [24] synthesized Zn(II)–BtH–imidazole complexes—[Zn(emimb)<sub>2</sub>Cl<sub>2</sub>] (**48**), [Zn(dmimb)<sub>2</sub>Cl<sub>2</sub>] (**49**), and [Zn(bmem)<sub>2</sub>(SCN)<sub>2</sub>] (**50**)—which exhibited enhanced  $\alpha$ -amylase inhibition ( $IC_{50} = 1.69$ – $5.97$   $\mu\text{g mL}^{-1}$ ) and notable DPPH radical-scavenging activity ( $IC_{50} = 11.59$   $\mu\text{g mL}^{-1}$ ), attributed to synergistic Zn<sup>2+</sup>–ligand redox effects (Figure 5 and Table 5). Anwar et al. (2023) [60] developed azetidinone–BtH hybrids (**117** and **118**) that showed strong antioxidant activity ( $IC_{50} = 25.32$ – $28.37$   $\mu\text{M}$ ) and inhibition of calcium oxalate crystallization, linked to hydrogen donation and metal chelation (Figure 5 and Table 5). Wang and co-workers [61] synthesized four novel Cu(II)/Zn(II) benzotriazole–benzimidazole complexes. The  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory assays identified complexes **119** and **120** as the most

potent ( $IC_{50} = 1.29$ – $4.69$  mM for  $\alpha$ -amylase and  $0.75$ – $1.63$   $\mu\text{M}$  for  $\alpha$ -glucosidase), surpassing acarbose in enzyme inhibition. These compounds also significantly improved glucose uptake in insulin-resistant HepG2 cells, confirming their antidiabetic potential (Figure 5 and Table 5). Khan et al. (2023) [62] reported BtH bis-Schiff bases as potent  $\alpha$ -glucosidase inhibitors, with compound **121** ( $IC_{50} = 1.10$   $\mu\text{M}$ ) surpassing acarbose ( $IC_{50} = 10.3$   $\mu\text{M}$ ), likely due to electron-withdrawing groups that enhanced hydrogen-bonding interactions within the enzyme's active site (Figure 5 and Table 5). Similarly, Hayat et al. (2025) [63] synthesized Schiff base BtHs, where top compounds (**122**–**125**) exhibited  $\alpha$ -glucosidase inhibition with  $IC_{50}$  values of  $2.2$ – $4.7$   $\mu\text{M}$ . Their activity was influenced by the position, nature, number, and electronic effects of the substituents attached to the phenyl ring (Figure 5 and Table 5). Menteşe et al. (2024) [23] prepared coumarin–amino acid–BtH conjugates that demonstrated exceptional urease (**126**,  $IC_{50} = 0.038$   $\mu\text{M}$ ) and lipase (**127**,  $IC_{50} = 0.101$   $\mu\text{M}$ ) inhibition, attributed to the electronic effects of substituents on the phenyl ring (Figure 5 and Table 5). Aleksandrova et al. (2024) [57] synthesized *N*-aryl BtH–diphenylamine derivatives, among which compounds **128**–**130** effectively inhibited lipid peroxidation (LPO) initiated by ferrous ions, with  $IC_{50}$  values of  $1.11$ – $2.40$   $\mu\text{M}$ . Their activity was up to 29 times higher than that of Trolox, indicating that these compounds exert a markedly stronger antioxidant effect even at much lower concentrations. (Figure 5 and Table 5). Complementarily, Gangurde et al. (2024) [2] reported BtH–pyrazole–thiazole hybrids exhibiting strong DPPH radical-scavenging activity (up to 76%), particularly compound **90**.

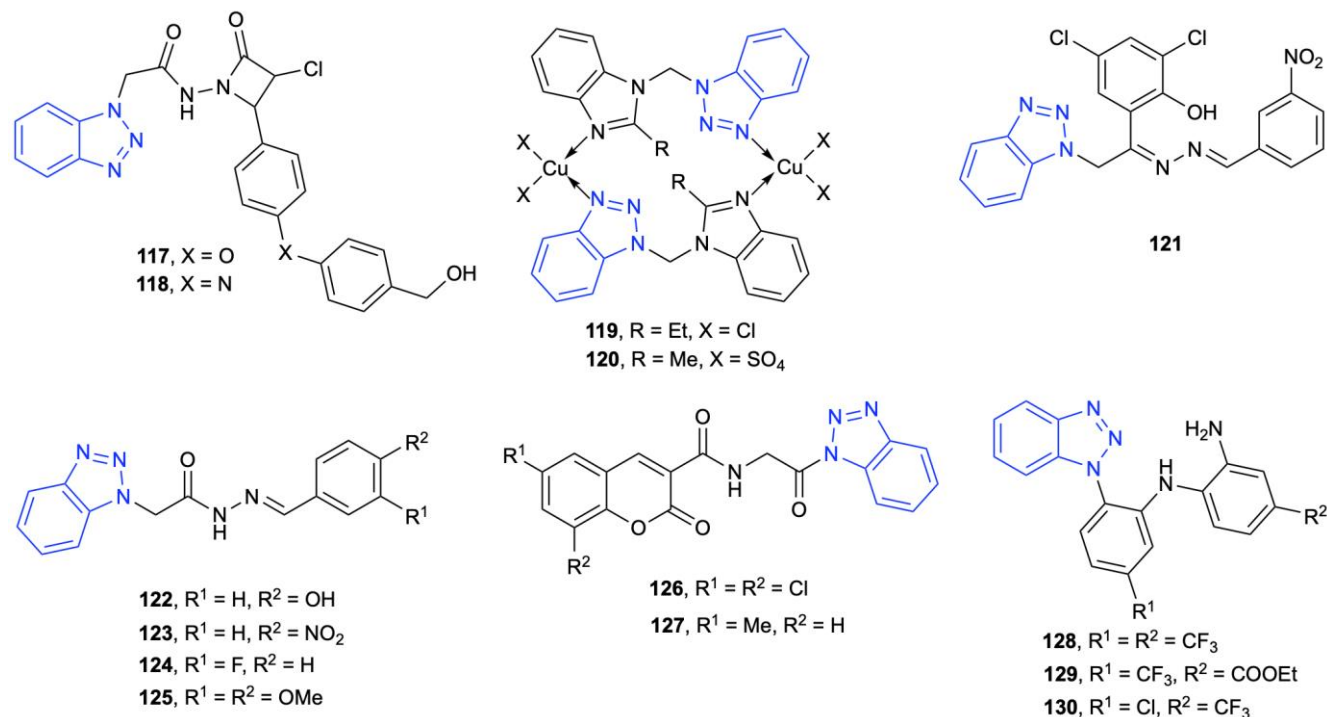
Overall, structure–activity relationship (SAR) analysis reveals that electron-donating groups (–OH, –OCH<sub>3</sub>, –NH<sub>2</sub>) enhance antioxidant performance through resonance-stabilized radical neutralization, whereas electron-withdrawing groups (–Cl, –NO<sub>2</sub>, –CF<sub>3</sub>) improve enzyme inhibition by strengthening dipole–dipole and hydrogen-bonding interactions. Metal complexation, particularly with Zn<sup>2+</sup> and Cu<sup>2+</sup>, and heterocyclic hybridization (imidazole) further amplify redox efficiency and binding strength through cooperative electronic effects. Incorporation of pharmacophores such as coumarin, benzimidazole, and amino acids generates multifunctional BtH frameworks exhibiting both antioxidant and enzyme-inhibitory activities. Collectively, these findings demonstrate that fine-tuning the electronic and structural features of BtH scaffolds—via conjugation, coordination chemistry, and targeted substitution—enables the development of potent, selective, and sustainable therapeutic candidates for combating oxidative and metabolic disorders.

#### 4.5. Antitubercular activities

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), remains one of the world's deadliest infectious diseases. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has severely

undermined current treatment efficacy. Prolonged therapy, drug-induced toxicity, and poor patient compliance further emphasize the urgent need for novel scaffolds with improved selectivity, potency, and reduced resistance potential. BtH derivatives have recently emerged as potent antimicrobial candidates owing to their nitrogen-rich aromatic structure, which facilitates  $\pi$ - $\pi$  stacking, hydrogen

bonding, and lipophilic interactions within enzyme active sites. Notably, hybridization of BtH with pharmacophores such as oxadiazole and hydrazone has proven particularly effective in enhancing lipophilicity, redox stability, and enzymatic affinity, resulting in strong activity against *M. tuberculosis* H37Rv.



**Figure 5** Chemical structures of BtH derivatives exhibiting antioxidant and enzyme-inhibitory activities.

**Table 5** Antioxidant and enzyme-inhibitory activity of BtH derivatives.

Compound	Structure type	Target / assay	Activity	Key mechanism/interaction	Ref.
48-50	Zn(II)-BtH-imidazole complex	$\alpha$ -Amylase / DPPH	$\alpha$ -amylase inhibition (IC <sub>50</sub> = 1.69-5.97 $\mu$ g mL <sup>-1</sup> ) and DPPH activity (IC <sub>50</sub> = 11.59 $\mu$ g mL <sup>-1</sup> )	Zn-assisted electron transfer; metal-ligand synergy	24
117 and 118	Azetidinone-BtH hybrid	DPPH / CaOx inhibition	IC <sub>50</sub> = 25.32-28.37 $\mu$ M	H-donation + metal chelation	60
119 and 120	Cu(II) BtH-benzimidazole complex	$\alpha$ -amylase and $\alpha$ -glucosidase	IC <sub>50</sub> = 1.29-4.69 mM for $\alpha$ -amylase and 0.75-1.63 $\mu$ M for $\alpha$ -glucosidase	Cu-assisted redox-active in enzyme interaction	61
121	BtH bis-Schiff bases	$\alpha$ -glucosidase	IC <sub>50</sub> = 1.10 $\mu$ M	EWG substitution enhances binding The position, nature, number, and electronic effects of the substituents attached to the phenyl ring	62
122-125	Schiff base BtH	$\alpha$ -glucosidase	IC <sub>50</sub> = 2.2-4.7 $\mu$ M	Electronic effects of substituents on the phenyl ring Decrease malondialdehyde level in the system	63
126 and 127	Coumarin-AA-BtH	Lipase / Urease	IC <sub>50</sub> = 0.038 and 0.101 $\mu$ M	Electronic effects of substituents on the phenyl ring Decrease malondialdehyde level in the system	23
128-130	N-aryl BtH-diphenylamine	Lipid peroxidation	IC <sub>50</sub> = 1.11-2.40 $\mu$ M	EWG at para-position	57
90	BtH-pyrazole-thiazole hybrid	DPPH	up to 76% scavenging		2

Note: IC<sub>50</sub> = half-maximal inhibitory concentration.

Pandya et al. (2020) [64] synthesized a series of BtH-oxadiazole-hydrazone hybrids via multistep condensation involving benzoylBtH, hydrazine hydrate, and substituted aromatic aldehydes. Antimycobacterial evaluation using the microplate Alamar Blue assay (MABA) revealed that compounds **131-134** exhibited potent activity against *M. tuberculosis* H37Rv, with MIC values of  $6.25 \mu\text{g mL}^{-1}$  (up to 99% inhibition)—surpassing standard reference drugs. Incorporation of electron-donating groups (-OH, -NMe<sub>2</sub>) enhanced lipophilicity and molecular polarity, thereby improving cell wall penetration and enzyme-ligand interactions (Figure 6 and Table 6). Similarly, Jayaseelan et al. (2025) [65] designed BtH-fused oxadiazole derivatives (**135-138**) through oxidative cyclization, achieving comparable inhibitory activity (sensitive at  $50\text{--}100 \mu\text{g mL}^{-1}$ ). Among these, compounds **137** (p-OH-C<sub>6</sub>H<sub>4</sub>) and **138** (o-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>) showed the highest potency (sensitive at  $1.6 \mu\text{g mL}^{-1}$ ) and exhibited strong docking affinities (-11.9 to -12.8 kcal/mol) toward enoyl-acyl carrier protein reductase (InhA)—a key enzyme in mycolic acid biosynthesis. Nitro and hydroxy substituents contributed to enhanced hydrogen-bonding and hydrophobic interactions, stabilizing ligand binding within the InhA catalytic pocket (Figure 6 and Table 6).

Collectively, these studies demonstrate that substitution pattern and electronic effects play a decisive role in modulating antitubercular activity. Compounds bearing electron-donating groups (-OH, -NMe<sub>2</sub>) exhibited superior potency due to improved hydrogen-bond formation and membrane permeability, while electron-withdrawing group (-NO<sub>2</sub>) strengthened enzyme-ligand stabilization via dipolar and  $\pi\text{-}\pi$  stacking interactions. The BtH-oxadiazole-hydrazone framework provided a rigid, conjugated system that enhanced electron delocalization and redox balance, favoring

stable interactions with the InhA active site. Additionally, aromatic substituents optimized lipophilicity and bioavailability, leading to efficient inhibition of *M. tuberculosis* growth. Overall, these findings highlight BtH-based oxadiazole and hydrazone hybrids as promising lead candidates for next-generation antitubercular agents capable of overcoming resistance through multi-target binding and high metabolic stability.

#### 4.6. Other activities

Beyond antimicrobial and anticancer applications, BtH derivatives exhibit emerging biological roles in neuroprotection, anti-inflammation, and metabolic regulation. The following section surveys representative examples from 2020–2025 to illustrate how structural tuning enables multitarget therapeutic potential. BtH derivatives have expanded far beyond their traditional antimicrobial and anticancer roles, exhibiting promising activity against neurodegenerative and inflammatory. Their multifunctional behavior arises from the electron-rich triazole ring, which enables hydrogen bonding,  $\pi\text{-}\pi$  stacking, and metal chelation—properties that facilitate interaction with diverse biological targets such as acetylcholinesterase (AChE), butyrylcholinesterase (BChE), cyclooxygenase-2 (COX-2), and matrix metalloproteinase-13 (MMP-13). Recent studies (2020–2025) highlight BtH-based hybrids as strong candidates for multitarget therapy addressing oxidative stress and neuroinflammation. The following section presents representative examples illustrating how structural modification of BtH scaffolds enhances their potential in neuroprotective and anti-inflammatory.

**Neuroprotective activity.** Several BtH-based hybrids have shown potent anti-Alzheimer's activity through cholinesterase inhibition and amyloid aggregation control.

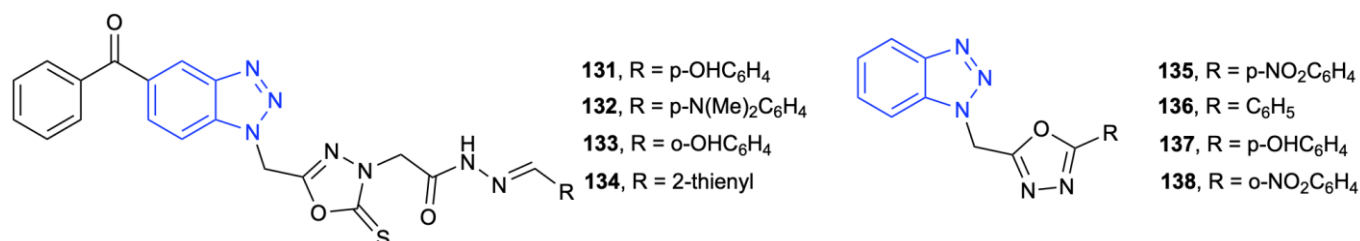


Figure 6 Chemical structures of BtH derivatives exhibiting antitubercular activities.

Table 6 antitubercular activity of BtH derivatives.

Compound	Structure type	Target / assay	Activity	Key mechanism/interaction	Ref.
<b>131-134</b>	BtH-oxadiazole-hydrazone hybrid	<i>M. tuberculosis</i> H37Rv	MIC values of $6.25 \mu\text{g mL}^{-1}$ (up to 99% inhibition)	EDGs enhanced cell wall penetration and enzyme-ligand interactions	64
<b>135-138</b>	BtH-fused oxadiazole	<i>M. tuberculosis</i> H37Rv	sensitive at $1.6 \mu\text{g mL}^{-1}$ , InhA docking -11.9 to -12.8 kcal/mol	NO <sub>2</sub> and OH enhanced hydrogen-bonding and hydrophobic interactions, stabilizing ligand binding	65

Note: MIC = minimum inhibitory concentration.

Cheema et al. (2023) [66] synthesized  $\alpha$ -substituted hemiaminal ether BtHs, where compound **139** (menthyl-butyl) demonstrated strong AChE inhibition ( $IC_{50} = 44.03$  nM), while **140** (menthyl-methyl) was most effective against BChE ( $IC_{50} = 80.74$  nM), underscoring the influence of bulky chiral alkoxy groups on enzyme selectivity (Figure 7 and Table 7). Singh et al. (2020) [67] developed coumarin-BtH hybrids, with compound **141** exhibiting remarkable AChE inhibition ( $IC_{50} = 0.059$   $\mu$ M) and prevention of  $Cu^{2+}$ -induced amyloid aggregation, suggesting both symptomatic and disease-modifying potential (Figure 7 and Table 7). Likewise, Menteşe et al. (2024) [23] synthesized coumarin-amino acid-BtH conjugates, with compound **139** achieving extraordinary AChE inhibition ( $IC_{50} = 0.003$   $\mu$ M) through dual binding at the catalytic and peripheral anionic sites (Figure 7 and Table 7).

**Anti-inflammatory activity.** BtH-based molecules also display potent inhibition of enzymes associated with arthritis and osteoarthritis. Zapico et al. (2021) [68] reported a water-soluble BtH-MMP-13 inhibitor (compound **143**) with exceptional potency ( $IC_{50} = 0.65$  nM), effectively suppressing collagen degradation with high selectivity (Figure 7 and Table 7). Metri et al. (2024) [69] designed BtH-benzamide analogues, identifying compound **144** as the most effective anti-arthritis (77% inhibition at 500  $\mu$ g) and COX-2 inhibitor (73% inhibition at 500  $\mu$ g), providing significant protection in protein-denaturation assays. (Figure 7 and Table 7).

Across therapeutic domains, the BtH core functions as a privileged scaffold fine-tuned by strategic substitution

and heterocyclic fusion. Electron-donating substituents favor AChE through enhanced hydrogen bonding and  $\pi$ - $\pi$  stacking, while electron-withdrawing groups increase anti-inflammatory selectivity via polar or metal-binding interactions. Hybrid architectures incorporating coumarin, amino acid fragment enable multitarget engagement, balancing lipophilicity and polarity for improved bioavailability. Collectively, these findings highlight the multifunctional nature of BtH scaffolds. By optimizing electronic and steric parameters, researchers have developed derivatives capable of simultaneous enzyme inhibition, antioxidant activity, and anti-inflammatory modulation—reinforcing BtH's role as a versatile framework for integrated therapeutic design.

## 5. Limitations

Despite the substantial progress achieved in BtH research, several limitations and challenges remain. Most studies have primarily focused on *in vitro* biological assays, whereas *in vivo* pharmacokinetic, toxicological, and metabolic evaluations are comparatively limited. This gap in translational data restricts the advancement of BtH-based compounds toward clinical application. Furthermore, although a wide range of structural derivatives has been developed, the absence of standardized evaluation protocols often hampers direct comparison of biological results and the establishment of consistent structure-activity relationships (SARs).

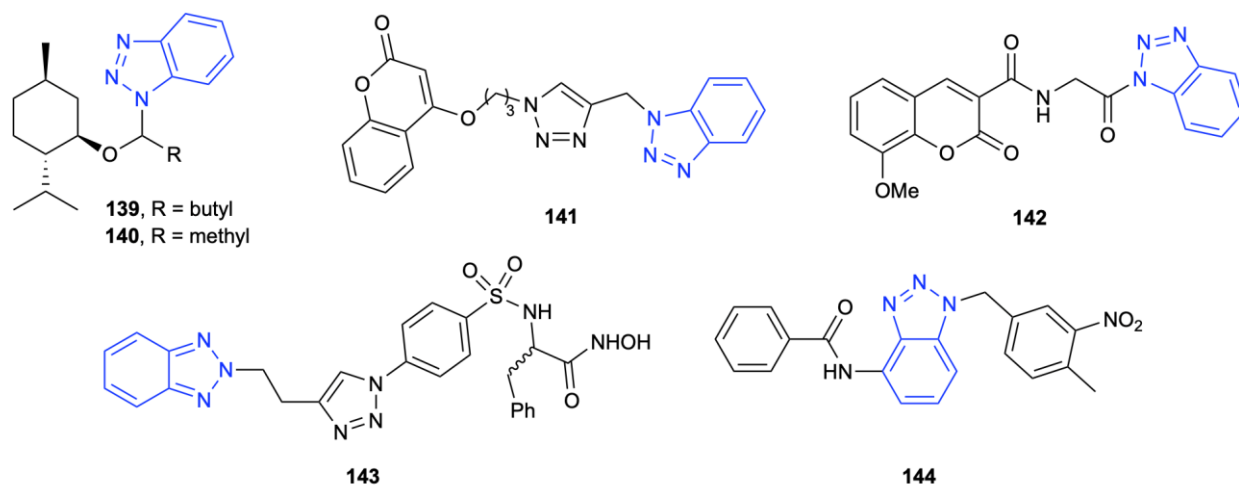


Figure 7 Chemical structures of BtH derivatives exhibiting other activities.

Table 7 Other activity of BtH derivatives.

Compound	Structure Type	Activity	Target	Potency	Reference
<b>139</b> and <b>140</b>	BtH-based hybrid	Anti-Alzheimer	AChE / BChE	$IC_{50} = 44.03$ and $80.74$ nM	66
<b>141</b>	coumarin-BtH hybrid	Anti-Alzheimer	AChE, $A\beta$ aggregation	$IC_{50} = 0.059$ $\mu$ M	67
<b>142</b>	coumarin-amino acid-BtH conjugate	Anti-Alzheimer	AChE	$IC_{50} = 0.003$ $\mu$ M	23
<b>143</b>	Water-soluble BtH scaffold	Anti-inflammatory	MMP-13	$IC_{50} = 0.65$ nM	68
<b>144</b>	BtH-benzamide	Anti-inflammatory	COX-2	73% inhibition at 500 $\mu$ g	69

Note:  $IC_{50}$  = half-maximal inhibitory concentration.

In the synthetic domain, scalability and cost-efficiency continue to pose challenges despite the introduction of green and sustainable approaches such as microwave-assisted, ultrasound-assisted, flow, and electrocatalysis methods. The occasional reliance on toxic solvents, reagents, and catalysts in some synthetic routes remains at odds with the principles of sustainable chemistry. In addition, mechanistic insights into the molecular interactions of BtH derivatives are often based on computational docking studies with limited biochemical or biophysical validation, highlighting the need for deeper experimental elucidation of binding mechanisms.

Future research should therefore prioritize *in vivo* validation of promising derivatives, comprehensive SAR-QSAR modeling using unified datasets, and the refinement of atom-economical, environmentally benign synthetic routes. Expanding interdisciplinary collaborations that integrate medicinal chemistry, pharmacology, and computational biology will be essential to overcome current bottlenecks. Addressing these challenges will enhance the therapeutic relevance of BtH scaffolds and facilitate their sustainable, clinically viable development.

## 6. Conclusions

Benzotriazole (BtH) and its derivatives have proven to be privileged scaffolds in medicinal chemistry owing to their exceptional structural flexibility, broad spectrum of biological activities, and ease of functionalization. Over the past decade, remarkable advances in synthesis—from classical diazotization to innovative green methodologies such as microwave-assisted, ultrasound-assisted, electrocatalysis, and flow-based systems—have enabled the efficient and sustainable preparation of diverse BtH frameworks. Structural diversification through halogenation, heterocyclic fusion, acylation, and metal complexation has yielded potent candidates exhibiting antimicrobial, antiviral, anticancer, antioxidant, enzyme-inhibitory, antitubercular, and neuroprotective activities. Collectively, these findings highlight that subtle electronic and steric modifications can profoundly influence pharmacological performance through enhanced  $\pi$ - $\pi$  stacking, hydrogen bonding, and metal coordination at biological targets.

Despite these advances, the translation of BtH-based molecules into clinically viable drugs remains challenging. Limited *in vivo* evaluation, lack of standardized biological screening, and scalability constraints in sustainable synthesis continue to impede broader application. Moving forward, the integration of green chemistry principles with computational modeling, high-throughput biological screening, and *in vivo* validation will be crucial for the rational design of next-generation BtH derivatives. The convergence of synthetic innovation, mechanistic insight, and sustainability will further strengthen BtH's position

as a cornerstone scaffold for multifunctional therapeutics, guiding future research toward safer, more effective, and environmentally responsible drug discovery.

## Supplementary materials

No supplementary materials are available.

## Data availability statement

Data sharing is not applicable to this article, as no new data were generated or analyzed.

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None.

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## Conflict of interest

The authors declare no conflict of interest.

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multicomponent reactions.



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