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Benzothiazole derivatives in cancer treatment: synthesis and therapeutic potential: review

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Abstract

Benzothiazole derivatives have emerged as promising candidates in the field of cancer treatment due to their unique chemical properties and potent biological activities. This review comprehensively examines the synthetic methodologies employed in the development of benzothiazole derivatives and explores their mechanisms of anticancer action, including cell cycle arrest, apoptosis induction, and inhibition of angiogenesis and metastasis. Additionally, the review highlights recent preclinical and clinical studies that underscore the therapeutic potential of these compounds. By comparing benzothiazole derivatives with existing anticancer agents and discussing future research directions, this review aims to provide a detailed understanding of their role in cancer therapy and their potential for drug development.

Keywords: Anticancer agents, Apoptosis induction, Benzothiazole derivatives, Synthesis methods, Therapeutic potential

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with millions of new cases diagnosed each year.[1] The disease is characterized by the uncontrolled growth and spread of abnormal cells, which can invade nearby tissues and metastasize to distant parts of the body.[2] Traditional cancer treatments, including surgery, radiation therapy, and chemotherapy, have been the cornerstone of cancer management for decades.[3] Surgery is often the first line of treatment for many solid tumors. It aims to physically remove the tumor mass from the body.[4] While surgery can be curative for localized cancers, it is less effective for metastatic diseases.[5] Furthermore, surgical procedures come with significant risks and complications, such as infections and impacts on the patient's quality of life. Radiation therapy uses high-energy radiation to kill cancer cells or inhibit their growth.[6] It can be applied externally or internally (brachytherapy). While effective for certain cancers, radiation therapy can damage surrounding healthy tissues, leading to side effects like fatigue, skin reactions, and long-term complications such as secondary cancers. Chemotherapy involves the use of cytotoxic drugs to kill rapidly dividing cancer cells.[7] It can be administered orally, intravenously, or through other routes.[8] Despite its efficacy in treating various cancers, chemotherapy is associated with significant adverse effects, including nausea, vomiting, hair loss, and myelosuppression (reduced bone marrow activity).[9] These side effects result from the drugs' lack of specificity, as they affect both cancerous and healthy rapidly dividing cells. In recent years, Siegel et al.'s targeted therapies have revolutionized cancer treatment.[1] These therapies target specific molecules involved in cancer growth and progression. Examples include tyrosine kinase inhibitors and monoclonal antibodies.[10] Targeted therapies often have fewer side effects than traditional chemotherapy. However, they are not without limitations, such as the development of drug resistance and high costs.

Immunotherapy has also emerged as a groundbreaking approach in oncology.[11] This strategy harnesses the body's immune system to recognize and attack cancer cells.[12] Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have shown remarkable success in treating certain cancers, including melanoma and non–small cell lung cancer.[13] Nevertheless, immunotherapy can cause immune-related adverse events and is effective only in a subset of patients.

Hormone therapy is another approach used primarily in hormone-sensitive cancers,[14] such as breast[15] and prostate cancers.[16] By blocking the body's ability to produce hormones or interfering with hormone action, this therapy can slow or stop cancer growth. However, resistance to hormone therapy can develop, necessitating the use of additional treatments. Despite these advancements, significant challenges remain in cancer treatment.[17] The heterogeneity of cancer, wherein different cells within the same tumor can have diverse genetic and phenotypic profiles, complicates treatment strategies. Additionally, the ability of cancer cells to adapt and develop resistance to therapies limits the long-term efficacy of current treatments. Therefore, there is a continuous need for novel therapeutic agents that can overcome these limitations and provide more effective and less toxic treatment options. Benzothiazole derivatives have garnered significant interest in medicinal chemistry due to their diverse biological activities and potential therapeutic applications.[18] The benzothiazole moiety, consisting of a benzene ring fused to a thiazole ring, is a privileged structure in drug design.[19] Its unique chemical properties allow for the formation of various derivatives with significant pharmacological activities, including antimicrobial, anti-inflammatory, and anticancer effects.[20]

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The significance of benzothiazole derivatives in medicinal chemistry stems from their ability to interact with multiple biological targets.[21] This versatility is largely attributed to the heterocyclic structure of benzothiazole, which can mimic the structural motifs of natural biomolecules.[22] This structural mimicry enables benzothiazole derivatives to interfere with critical biological processes involved in disease pathogenesis. One of the key advantages of benzothiazole derivatives is their potential as anticancer agents. Several benzothiazole-based compounds have demonstrated potent anticancer activity against various cancer cell lines.[23] The anticancer properties of these derivatives are attributed to their ability to induce cell cycle arrest, promote apoptosis, inhibit angiogenesis, and interfere with metastasis.[24] Cell cycle arrest is a crucial mechanism through which benzothiazole derivatives exert their anticancer effects.[25] By disrupting the cell cycle, these compounds can halt the proliferation of cancer cells.[26]

For instance, Diao et al.[27] in 2019 stated that certain benzothiazole derivatives have been shown to inhibit cyclin-dependent kinases (CDKs), which play a pivotal role in regulating cell cycle progression. Inhibition of CDKs leads to cell cycle arrest, preventing cancer cells from proliferating. Apoptosis induction is another vital mechanism of action for benzothiazole derivatives. Apoptosis, or programmed cell death, is a tightly regulated process that eliminates damaged or unwanted cells. Many benzothiazole derivatives can activate apoptosis pathways in cancer cells, leading to their selective elimination.[28] These compounds can modulate key apoptotic regulators, such as Bcl-2 family proteins and caspases, to trigger cell death. Inhibition of angiogenesis is a crucial strategy for combating cancer, as tumors require a blood supply to grow and metastasize.[29] Benzothiazole derivatives have demonstrated antiangiogenic properties by inhibiting the formation of new blood vessels.[30] This effect can be achieved through the inhibition of vascular endothelial growth factor (VEGF) signaling, a key pathway involved in angiogenesis.[31]

Interference with metastasis is essential for preventing the spread of cancer to distant organs. Benzothiazole derivatives can impede metastasis by targeting molecules involved in cell adhesion, migration, and invasion.[32] For example, some benzothiazole compounds have been shown to inhibit matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix and facilitate tumor invasion. Some benzothiazole compounds have been reported to sensitize cancer cells to chemotherapy and radiotherapy, thereby improving treatment outcomes.[23] This sensitization effect is particularly valuable in overcoming resistance to conventional therapies.

The synthesis of benzothiazole derivatives is a critical aspect of their development as therapeutic agents.[26] Various synthetic approaches have been explored to generate a diverse array of benzothiazole-based compounds. Traditional methods include the condensation of *o*-aminothiophenol with carboxylic acids or their derivatives, such as esters or amides.[33] Modern synthetic techniques, such as microwave-assisted synthesis and green chemistry approaches, have also been employed to enhance the efficiency and sustainability of benzothiazole synthesis.[34] Microwave-assisted synthesis, for example, offers several advantages, including reduced reaction times and higher yields. This method utilizes microwave radiation to accelerate chemical reactions, making it a valuable tool for the rapid generation of benzothiazole derivatives.[35] Green chemistry approaches, which emphasize the use of environmentally friendly reagents and solvents, align with the principles of sustainable development and have gained traction in the synthesis of benzothiazole compounds.[36] Despite the promising potential of benzothiazole derivatives, challenges remain in their development as anticancer agents. One significant challenge is the optimization of their pharmacokinetic properties, such as solubility, stability, and bioavailability. Additionally, the safety and toxicity profiles of these compounds need thorough evaluation to ensure their suitability for clinical use. The novelty of this review lies in its comprehensive exploration of the synthesis methods, structure–activity relationships (SARs), and therapeutic potential of benzothiazole derivatives specifically for cancer treatment. While previous studies have addressed various aspects of benzothiazole chemistry and pharmacology, this review uniquely integrates recent advancements in synthetic techniques, modern analytical methods, and clinical findings. It emphasizes the versatility of benzothiazole derivatives in overcoming common limitations of current anticancer therapies, such as drug resistance and non-specific toxicity. By providing a detailed account of both traditional and contemporary synthetic strategies, this review highlights innovative approaches that enhance the development of more potent and selective benzothiazole-based anticancer agents. The primary aim of this review is to provide a comprehensive and up-to-date overview of benzothiazole derivatives as promising candidates for anticancer therapy. It seeks to elucidate the various synthetic methods employed in the creation of these compounds, analyze their mechanisms of action, and evaluate their efficacy in preclinical and clinical settings. By synthesizing the current knowledge in the field, this review aims to highlight the potential of benzothiazole derivatives to contribute significantly to the development of novel, effective anticancer treatments. The primary objectives of this study are to comprehensively investigate the synthesis, structure, and therapeutic potential of benzothiazole derivatives in cancer treatment. It aims to systematically review both traditional and modern synthetic methods, including microwave-assisted synthesis, green chemistry approaches, and catalyst-driven processes, while evaluating their efficiency, yield, environmental impact, and scalability. The study further explores the SARs of benzothiazole derivatives, identifying key structural modifications, substituents, and functional groups that enhance their anticancer activity and selectivity. Additionally, it elucidates the primary mechanisms of their anticancer action, such as apoptosis induction, cell cycle arrest, and angiogenesis inhibition, detailing the molecular pathways involved. By compiling and analyzing data from preclinical and clinical studies, the research assesses their anticancer efficacy, therapeutic potential, and safety profiles. Finally, it evaluates the comparative effectiveness of benzothiazole derivatives against existing anticancer agents, discusses their potential applications in drug development and personalized medicine, and identifies future research directions to advance their development as effective anticancer agents.

1.1 Core structure

The benzothiazole moiety is a bicyclic ring system composed of a benzene ring fused with a thiazole ring.[37] The unique configuration of this core structure is fundamental to the diverse biological activities exhibited by benzothiazole derivatives.[26] Understanding the core structure and the electronic properties of benzothiazole is crucial for appreciating how these compounds interact with biological targets.[38] The benzothiazole core consists of a benzene ring (a 6-membered ring with alternating double bonds) fused to a thiazole ring (a 5-membered

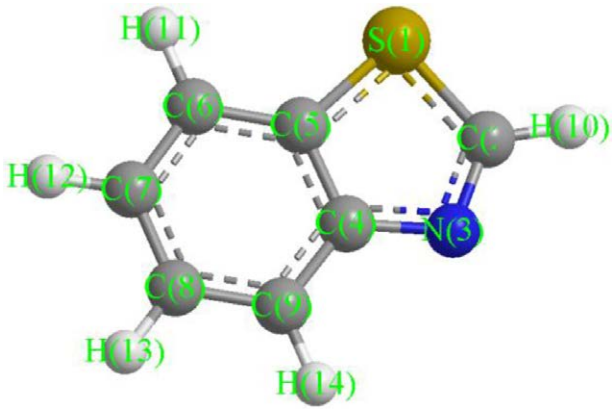

Figure 1. Chemical structure of benzothiazole.

ring containing a sulfur atom and a nitrogen atom).[39] The fusion of these rings occurs through 2 carbon atoms, forming a planar and aromatic bicyclic structure. This core is represented chemically as C7H5NS, where the positions on the benzene ring are numbered from 1 to 6 and the positions on the thiazole ring are numbered 2 and 3, with sulfur at position 1 and nitrogen at position 3.[40] Figure 1 provides a foundational understanding of the benzothiazole core, which is critical for the development of derivatives. Highlighting various substituent positions allows researchers to visualize how modifications can affect biological activity. This structural insight is essential for rational drug design and the exploration of SARs.

The electronic properties of benzothiazole are characterized by its aromaticity, which contributes to its stability and reactivity.[41] The conjugated π-electron system across the benzene and thiazole rings allows benzothiazole to engage in various π–π interactions, hydrogen bonding, and van der Waals forces with biological macromolecules. These interactions are crucial for the binding affinity and specificity of benzothiazole derivatives toward their biological targets.[42] Benzothiazole core can be functionalized at various positions to yield a wide array of derivatives with distinct biological properties.[43] Common functional groups introduced onto the benzothiazole core include amino, hydroxyl, carboxyl, alkyl, and halogen groups.[44] The choice and position of these substituents play a significant role in modulating the physicochemical and pharmacokinetic properties of the derivatives.[45]

1.2 Structure–activity relationship (SAR)

SAR of benzothiazole derivatives is a pivotal aspect of medicinal chemistry, as it elucidates how modifications to the chemical structure influence biological activity.[46] Through systematic alterations of the benzothiazole core and its substituents, researchers can optimize these compounds for enhanced efficacy, selectivity, and reduced toxicity. Table 1 illustrates the relationship between structural modifications of benzothiazole derivatives and their biological activity.[45] Specific substituents at different positions significantly influence the compounds' potency, highlighting the importance of SAR studies in designing more effective anticancer agents.[47] Understanding these relationships aids in the rational design of future derivatives.

Substituents on the benzene ring of the benzothiazole core can significantly impact the compound's activity and pharmacokinetics.[48] Electron-donating groups such as hydroxyl (–OH), methoxy ($–OCH_3$), and amino ($–NH_2$) groups typically enhance

Table 1

Structure–activity relationships (SARs) of benzothiazole derivatives.

Substituent position	Substituent type	Activity level (IC50)	Mechanism of action
2	Halogens	Low	Reduced binding affinity
3	Alkyl groups	Moderate	Increased lipophilicity
4	Aromatic groups	High	Enhanced cell penetration
5	Electron-donating	Very high	Stronger interaction with target enzymes

the electron density of the benzene ring, which can increase binding affinity to certain biological targets.[49] For example, the introduction of an amino group at the 2-position of the benzene ring has been shown to enhance anticancer activity by facilitating stronger interactions with DNA and cellular proteins.[50] Conversely, electron-withdrawing groups such as nitro ($–NO_2$), cyano (–CN), and halogens (eg, –F, –Cl, –Br) can reduce electron density, potentially altering the compound's interaction with biological targets. Halogen substituents can enhance lipophilicity and membrane permeability, which are desirable traits for drug candidates. For instance, the substitution of a fluorine atom at the 4-position of the benzene ring can enhance the compound's ability to cross cell membranes and increase its metabolic stability. Modifications to the thiazole ring, although less common than benzene ring modifications, can also influence the activity of benzothiazole derivatives. Substituents at the 2-position of the thiazole ring, adjacent to the sulfur atom, can significantly impact the compound's biological properties.[51] For example, alkyl or aryl groups at this position can enhance lipophilicity and improve the compound's interaction with hydrophobic pockets of target proteins. Additionally, substitution at the 3-position, where the nitrogen atom is located, can influence hydrogen bonding interactions with biological targets. Incorporating groups that can form strong hydrogen bonds, such as hydroxyl or amino groups, can enhance the binding affinity and selectivity of benzothiazole derivatives for their targets.

Incorporation of heterocyclic moieties or alkyl chains onto the benzothiazole core can further diversify the biological activity profile of these derivatives.[52] Heterocyclic groups such as pyridine, pyrazole, or imidazole can introduce new pharmacophores that enhance the compound's ability to interact with a broader range of biological targets.[53] For instance, attaching a pyridine ring to the benzothiazole core can improve aqueous solubility and binding to enzymes or receptors. Alkyl chains, on the other hand, can modulate the lipophilicity and membrane permeability of benzothiazole derivatives.[45] Longer alkyl chains can increase lipophilicity, facilitating the compound's ability to penetrate cell membranes and reach intracellular targets. However, excessive lipophilicity can lead to poor aqueous solubility and unfavorable pharmacokinetic properties, highlighting the need for a balanced approach in alkyl chain modification.[54]

Benzothiazole derivatives can be modified to include prodrug moieties that improve pharmacokinetic properties, such as solubility, stability, and bioavailability.[55] For example, ester or carbamate groups can be introduced to mask polar functional groups, enhancing lipophilicity and facilitating oral absorption.[56] Once inside the body, enzymatic cleavage releases the active benzothiazole derivative at the site of action.[57] SAR of benzothiazole derivatives also extends to their pharmacokinetic

and pharmacodynamic profiles.[58] Modifications that enhance the compound's solubility, stability, and permeability can improve its absorption, distribution, metabolism, and excretion (ADME) properties. For instance, the introduction of polar groups can improve aqueous solubility, facilitating oral or intravenous administration.[59] Additionally, modifications that increase metabolic stability can prolong the compound's half-life, reducing the frequency of dosing required for therapeutic efficacy. Several benzothiazole derivatives have been studied extensively for their anticancer properties, providing valuable insights into their SAR. One notable example is the compound 2-(4-aminophenyl)benzothiazole, which has demonstrated potent anticancer activity against a variety of cancer cell lines.[60] Modifications to the amino group and benzothiazole core have led to the development of analogs with improved potency and selectivity. For instance, introducing halogen substituents at specific positions on the benzene ring has enhanced the compound's ability to inhibit cell proliferation and induce apoptosis.[61] Another example is the compound 6-substituted benzothiazole, where modifications at the 6-position of the benzene ring have been explored.[43] Substituents such as alkyl, aryl, and heterocyclic groups at this position have been shown to influence the compound's ability to target specific cancer cell types.[62]

These modifications have also impacted the compound's pharmacokinetic properties, such as solubility and metabolic stability, further highlighting the importance of SAR in the development of benzothiazole-based anticancer agents.[63] Despite the promising potential of benzothiazole derivatives, several challenges remain in optimizing their SAR for clinical use. One significant challenge is achieving a balance between potency and selectivity, that is, the selectivity of nonselective kinase inhibition reported by Morphy in 2010,[64] then Sun et al.[65] in 2022 inquired in their publication about the cause of drug development failure. While modifications can enhance the compound's activity against cancer cells, they may also increase off-target effects, leading to toxicity. Therefore, a careful and systematic approach to SAR studies is essential to identify derivatives with an optimal therapeutic window. Additionally, the development of resistance to benzothiazole derivatives is a concern. Cancer cells can adapt to therapeutic pressures, leading to reduced efficacy of the treatment over time. Understanding the mechanisms of resistance and designing derivatives that can overcome or circumvent these mechanisms is a critical area of ongoing research.

2. Synthetic approaches to benzothiazole derivatives

2.1 Traditional methods

The synthesis of benzothiazole derivatives has a rich history in organic chemistry, with several classical routes established over the years.[66] Traditional methods often rely on straightforward chemical reactions that have been well-documented and widely used in various laboratories. Table 2 summarizes the various synthetic methods employed in the development of benzothiazole derivatives. Traditional methods provide a reliable basis but often lack selectivity.[21] In contrast, modern techniques such as microwave-assisted synthesis and green chemistry approaches offer higher yields and reduced environmental impact.[34] Understanding these methods is crucial for optimizing synthesis and enhancing the development of effective anticancer agents.[67]

Figure 2 summarizes the key synthetic approaches to generating benzothiazole derivatives, including classical condensation reactions and innovative microwave-assisted methods.[33] By comparing the steps involved in each approach, researchers can assess the efficiency and feasibility of different synthetic strategies, informing their choices in developing new compounds.[39]

(1) Condensation of *o*-aminothiophenol with carboxylic acids or derivatives. One of the most common traditional methods for synthesizing benzothiazole derivatives involves the condensation of *o*-aminothiophenol with carboxylic acids or their derivatives (such as esters, amides, or acid chlorides).[44] This reaction typically proceeds through the formation of an intermediate amide or ester, followed by cyclization to form the benzothiazole ring. For example, heating *o*-aminothiophenol with formic acid yields benzothiazole, whereas reaction with other carboxylic acids produces substituted benzothiazoles.[68]
(2) Skraup synthesis. The Skraup synthesis, originally developed for the synthesis of quinolines, has been adapted for the preparation of benzothiazoles.[69] In this method, *o*-aminothiophenol reacts with an aldehyde (such as formaldehyde) and a strong acid (such as sulfuric acid) in the presence of an oxidizing agent (such as nitrobenzene or ferric chloride). The reaction proceeds through an oxidative cyclization mechanism to yield the benzothiazole core.
(3) Bucherer–Bergs reaction. Another classical method is the Bucherer–Bergs reaction, which involves the cyclization of *o*-aminothiophenol with carbon disulfide and an aldehyde or ketone.[70] The reaction typically uses ammonium hydroxide as a base and produces benzothiazoles through the formation of an intermediate dithiocarbamate, which undergoes cyclization and desulfurization.
(4) Gabriel–Colman rearrangement. The Gabriel–Colman rearrangement is a method where thioureas react with α-haloketones or α-haloesters to form benzothiazoles.[71] This reaction proceeds through the formation of an intermediate thiourea derivative, followed by intramolecular cyclization to yield the benzothiazole ring.
(5) Cyclocondensation reactions. Cyclocondensation reactions involving *o*-aminothiophenols and various carbonyl compounds (such as ketones, aldehydes, and α,β-unsaturated carbonyl compounds) are also widely used for benzothiazole synthesis.[72] These reactions often require acidic or basic catalysts to facilitate the cyclization process.

2.2 Modern synthetic techniques

While traditional methods have been invaluable in the synthesis of benzothiazole derivatives, modern synthetic techniques have introduced more efficient, sustainable, and versatile approaches.[38] These contemporary methods often employ advanced technologies and principles of green chemistry to improve yields, reduce reaction times, and minimize environmental impact.

(1) Microwave-assisted synthesis. Microwave-assisted synthesis has gained popularity as a rapid and efficient method for preparing benzothiazole derivatives.[35] Microwave irradiation provides uniform and rapid heating, which can significantly accelerate reaction rates compared with conventional heating methods.[36] This technique has been applied to various benzothiazole syntheses, including the cyclocondensation of *o*-aminothiophenols with

Table 2

Overview of synthetic methods for benzothiazole derivatives.

Synthesis method	Key reagents	Reaction conditions	Yield (%)	Advantages	Limitations
Traditional condensation	Thiourea, haloaryl compounds	Heat (reflux), organic solvent (eg, ethanol)	50–90	Simple, established procedures, readily available starting materials	Low selectivity (formation of byproducts), harsh reaction conditions, longer reaction times
Microwave-assisted synthesis	Thiourea, aromatic aldehydes	Microwave irradiation, solvent (optional)	80–95	Faster reaction times, improved efficiency, reduced solvent use	Equipment dependent (microwave synthesizer required), potential for uneven heating
Green chemistry approaches	Biocatalysts (enzymes), recyclable catalysts, renewable starting materials (eg, biomass)	Mild conditions (room temperature, aqueous media)	70–90	Environmentally friendly, reduced waste generation, potentially safer reagents	Lower yields compared with traditional methods, scalability issues for large-scale production
Catalyst-driven processes	Transition metal complexes (eg, palladium, copper)	Specific conditions (temperature, solvent, ligands)	60–90	High selectivity for desired products, improved efficiency	Complex catalyst design and synthesis, specialized equipment requirements
Cyclization reactions	o-Aminobenzenethiols, α-keto esters (or amides)	Acidic or basic conditions, solvent	60–85	Direct access to substituted benzothiazoles	Requires specific functional groups in starting materials, may require additional steps for functionalization

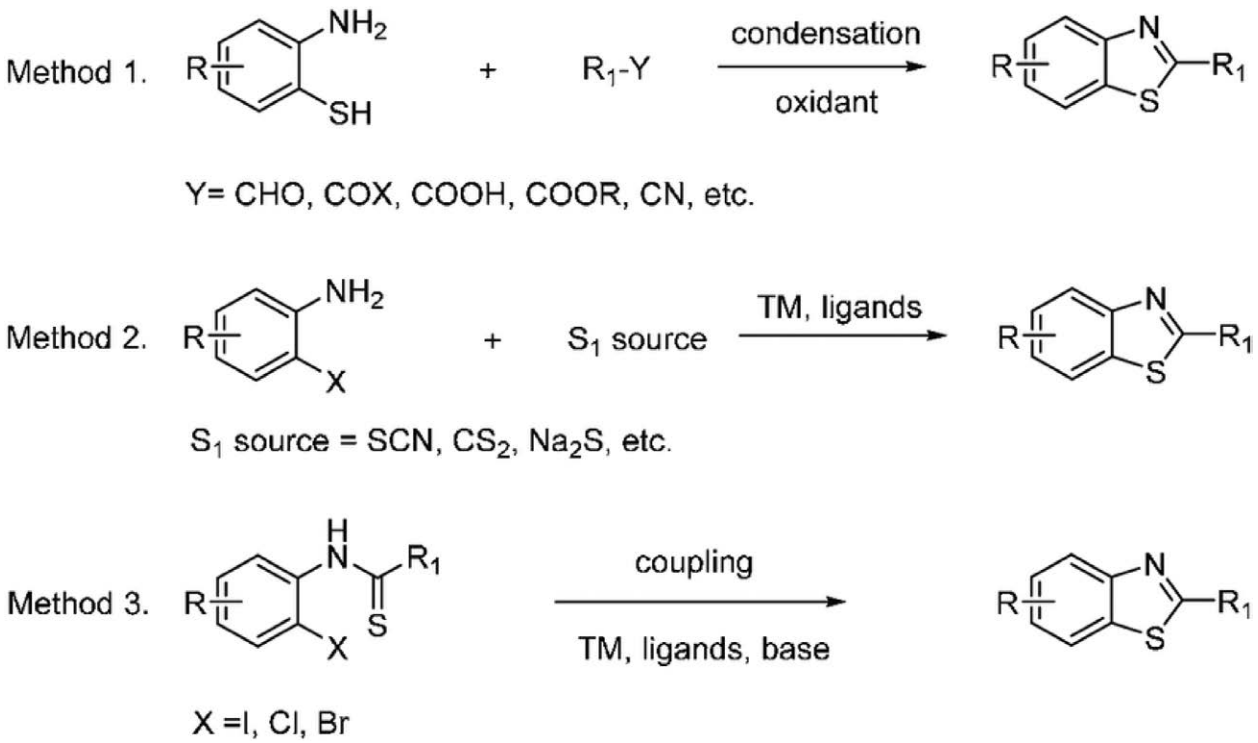

Figure 2. Synthetic pathways for benzothiazole derivatives.

carboxylic acids or aldehydes. Microwave-assisted reactions typically offer higher yields and shorter reaction times, making them attractive for both academic research and industrial applications.

(2) Green chemistry approaches. Green chemistry principles emphasize the use of environmentally benign solvents, reagents, and processes to minimize the ecological footprint of chemical synthesis. In the context of benzothiazole derivatives, green chemistry approaches often involve the use of water or ethanol as solvents[73] and the avoidance of hazardous reagents. For example, water-based reactions have been developed for the cyclocondensation of *o*-aminothiophenols with aldehydes or ketones, offering a greener alternative to traditional methods.[74]

(3) Catalyst-driven processes. Catalysis plays a crucial role in modern synthetic chemistry, providing more efficient and selective pathways for chemical reactions. In benzothiazole synthesis, both homogeneous and heterogeneous catalysts have been employed to enhance reaction rates and selectivity.[75] Metal catalysts, such as palladium, copper, and gold, have been used in cross-coupling reactions and oxidative cyclization processes to synthesize benzothiazole derivatives. Additionally, organocatalysts, which are small organic molecules that catalyze chemical

reactions, have been explored for their ability to facilitate benzothiazole synthesis under mild conditions.

(4) Photocatalytic and electrocatalytic methods. Photocatalysis and electrocatalysis are emerging techniques that utilize light or electric current to drive chemical reactions. These methods offer unique advantages, such as mild reaction conditions and the ability to harness renewable energy sources. In benzothiazole synthesis, photocatalytic processes have been used to achieve oxidative cyclization of *o*-aminothiophenols with carbonyl compounds.[76] Similarly, electrocatalytic methods have been explored for the cyclization of *o*-aminothiophenols, providing a sustainable approach to benzothiazole synthesis.

(5) Flow chemistry. Flow chemistry involves conducting chemical reactions in continuously flowing streams rather than in traditional batch reactors. This technique offers several advantages, including improved reaction control, scalability, and safety. Flow chemistry has been applied to the synthesis of benzothiazole derivatives,[77] allowing for precise control over reaction parameters and efficient production of target compounds. The use of microreactors and continuous flow systems has enabled the rapid synthesis of benzothiazoles with high yields and reproducibility.

2.3 Challenges and solutions

While significant progress has been made in the synthesis of benzothiazole derivatives, several challenges remain. Addressing these challenges is crucial for optimizing synthetic methods and expanding the utility of benzothiazoles in medicinal chemistry and other fields.

(1) Selectivity and regioselectivity. Achieving high selectivity and regioselectivity in benzothiazole synthesis is a common challenge. The presence of multiple reactive sites on the benzothiazole core can lead to the formation of undesired byproducts or regioisomers. To address this issue, researchers have developed various strategies, including the use of selective catalysts, protecting groups, and directing groups. For example, the introduction of directing groups on the benzene ring can guide the reaction to specific positions, enhancing regioselectivity.

(2) Functional group tolerance. The tolerance of various functional groups during benzothiazole synthesis is another critical challenge. Functional groups such as hydroxyl, amino, and carboxyl groups can be sensitive to reaction conditions, leading to side reactions or degradation. To overcome this challenge, mild and selective reaction conditions have been developed. For instance, microwave-assisted synthesis and catalyst-driven processes often provide milder conditions that preserve sensitive functional groups.

(3) Environmental impact. Reducing the environmental impact of benzothiazole synthesis is an ongoing priority. Traditional methods often involve the use of hazardous solvents and reagents, leading to environmental and safety concerns. Green chemistry approaches, such as the use of water or ethanol as solvents and the development of catalyst-driven processes, have been implemented to minimize environmental impact. Additionally, flow chemistry and microwave-assisted synthesis offer more sustainable alternatives by reducing waste and energy consumption.

(4) Scalability. Scaling up benzothiazole synthesis from laboratory to industrial scale presents several challenges, including maintaining reaction efficiency, yield, and selectivity. Flow chemistry offers a promising solution to scalability issues by enabling continuous production and precise control over reaction parameters. Additionally, the development of robust and scalable catalytic systems is essential for industrial applications.

(5) Complex molecule synthesis. The synthesis of complex benzothiazole derivatives, such as those with multiple substituents or intricate ring systems, can be challenging. Advanced synthetic techniques, including multistep synthesis, cascade reactions, and one-pot processes, have been developed to address these challenges. For example, multistep synthesis allows for the sequential introduction of various substituents, while cascade reactions enable the formation of complex molecules in a single reaction sequence.

2.3.1 Recent advancements

Recent advancements in synthetic methodologies have addressed many of the challenges associated with benzothiazole synthesis. For example, the development of new catalytic systems, such as metal-organic frameworks and covalent organic frameworks, has enhanced the efficiency and selectivity of benzothiazole synthesis. Additionally, the integration of computational chemistry and machine learning has enabled the rational design of synthetic routes and catalysts, further optimizing the synthesis of benzothiazole derivatives.

2.3.2 Case studies of modern synthesis

Several case studies highlight the success of modern synthetic techniques in benzothiazole synthesis. For instance, a study demonstrated the use of a palladium-catalyzed cross-coupling reaction to synthesize 2-arylbenzothiazoles with high yield and selectivity. Another study reported the use of a green chemistry approach, employing water as a solvent and a recyclable copper catalyst, to synthesize benzothiazole derivatives under mild conditions.

3. Mechanisms of anticancer action

The primary mechanisms of anticancer action are listed in Table 3 through which benzothiazole derivatives exert their anticancer effects.[78] By categorizing compounds based on their specific mechanisms,[18] the table highlights the multifaceted nature of their action, which is crucial for developing combination therapies that enhance treatment efficacy.[79]

Figure 3 illustrates the multifaceted mechanisms of action of benzothiazole derivatives. By depicting pathways such as apoptosis induction and cell cycle modulation, this visual aids in understanding how these compounds can target cancer cells effectively.[80] This comprehensive overview is crucial for developing combination therapies that exploit these mechanisms synergistically.

3.1 Cell cycle arrest

The cell cycle is a series of tightly regulated phases that cells undergo to grow and divide. Cancer cells often bypass these

Table 3

Mechanisms of anticancer action for benzothiazole derivatives.

Mechanism	Effects on cancer cells
Apoptosis induction	Increased caspase activation, mitochondrial dysfunction, DNA fragmentation
Cell cycle arrest	G1 phase arrest (inhibits cell division), upregulation of p21 (tumor suppressor protein)
Inhibition of angiogenesis	Reduced VEGF expression (prevents blood vessel growth to tumors), decreased vessel formation
Tubulin polymerization inhibition	Disrupts microtubule formation (essential for cell division and movement), mitotic arrest (stops cell division)
DNA topoisomerase inhibition	Interferes with DNA replication, induces DNA damage
Modulation of signaling pathways	Targets specific signaling molecules (e.g., EGFR, JAK/STAT), disrupts growth and survival signals
Modulation of immune response	Activates immune cells, increases tumor recognition

EGFR, epidermal growth factor receptor; JAK/STAT, Janus Kinase/signal transducer and activator of transcription.

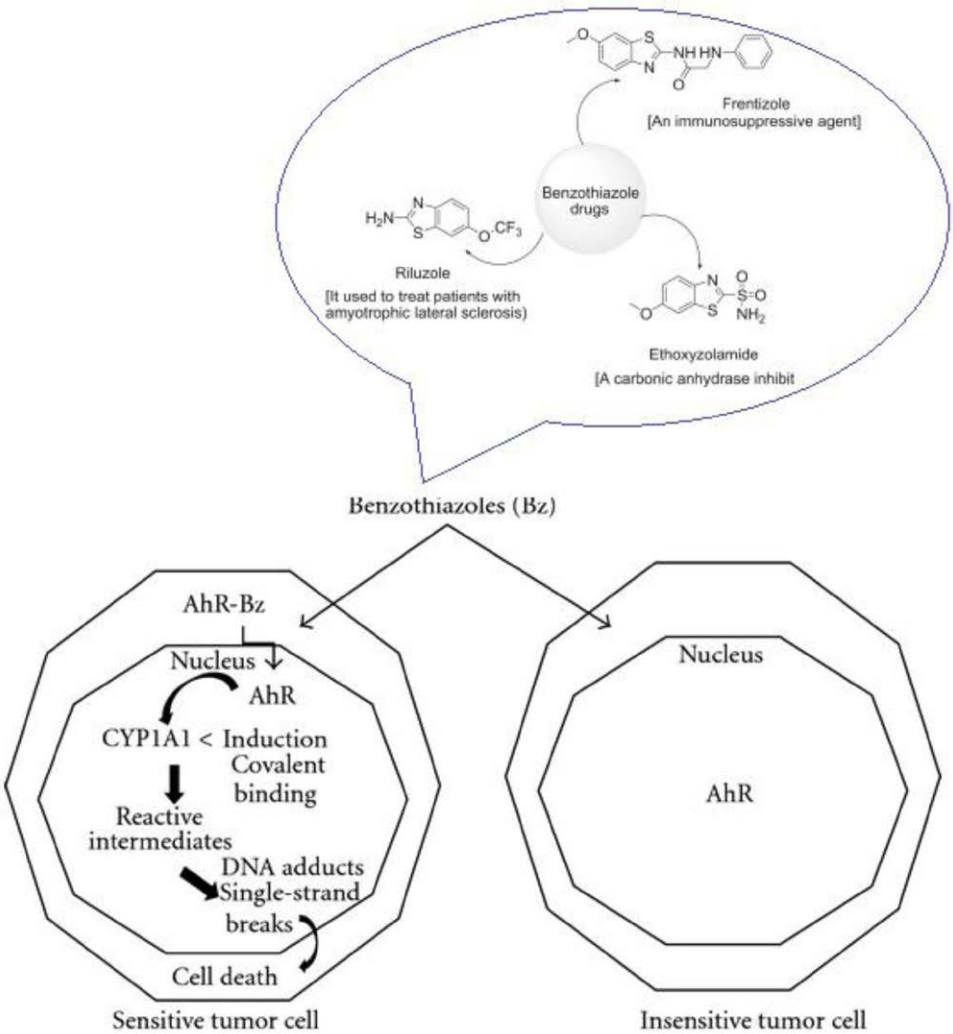

Figure 3. Mechanisms of action of benzothiazole derivatives.

regulatory mechanisms, leading to uncontrolled proliferation. Benzothiazole derivatives have been shown to induce cell cycle arrest, effectively halting the proliferation of cancer cells.

3.1.1 Mechanisms of cell cycle arrest

Benzothiazole derivatives exert their effects on the cell cycle through various mechanisms, often targeting key regulatory proteins and checkpoints.[81] These checkpoints include the G1/S checkpoint, which monitors DNA integrity before replication, and the G2/M checkpoint, which ensures proper DNA replication and repair before mitosis.[82] By interfering with these checkpoints, benzothiazole derivatives can halt the cell cycle and prevent cancer cell division.

(1) G1 phase arrest. Several benzothiazole derivatives have been reported to cause cell cycle arrest at the G1 phase. This effect is often mediated by the upregulation of cyclin-dependent kinase inhibitors (CKIs) such as p21 and p27, which bind to and inhibit the activity of CDKs responsible for driving the cell cycle forward.[83] For example, benzothiazole derivatives can enhance the expression of

p21 by activating the p53 tumor suppressor pathway.[84] p53, often referred to as the "guardian of the genome," plays a critical role in maintaining DNA integrity by promoting cell cycle arrest and apoptosis in response to DNA damage.[85]

(2) S phase arrest. Some benzothiazole derivatives induce cell cycle arrest during the S phase, the period of DNA synthesis.[86] This can be achieved by inhibiting the activity of DNA polymerases or other enzymes involved in DNA replication. Additionally, these compounds may cause DNA damage, triggering the activation of the DNA damage response (DDR) pathway. The DDR pathway activates checkpoints that halt the cell cycle to allow for DNA repair, thus preventing the propagation of damaged DNA.

(3) G2/M phase arrest. Benzothiazole derivatives can also induce cell cycle arrest at the G2/M phase, preventing cells from entering mitosis.[87] This arrest is often mediated by the inhibition of CDK1, a key kinase required for the transition from G2 to M phase. Inhibition of CDK1 can be achieved through the upregulation of CKIs or direct inhibition of the kinase itself. Additionally, benzothiazole derivatives may disrupt the formation of the mitotic spindle, an essential structure for chromosome segregation during mitosis, thereby preventing cell division.

3.2 Apoptosis induction

Apoptosis, or programmed cell death, is a crucial mechanism for eliminating damaged or unwanted cells. In cancer, the apoptotic machinery is often dysregulated, allowing cancer cells to evade death and continue proliferating. Benzothiazole derivatives have been shown to induce apoptosis in cancer cells through various pathways.

(1) Intrinsic pathway. The intrinsic pathway of apoptosis, also known as the mitochondrial pathway, is initiated by internal cellular stress signals, such as DNA damage or oxidative stress. Benzothiazole derivatives can activate the intrinsic pathway by promoting the release of cytochrome c from the mitochondria into the cytoplasm. This release is mediated by the proapoptotic members of the Bcl-2 family, such as Bax and Bak, which permeabilize the mitochondrial membrane.[88] Once released, cytochrome c binds to Apaf-1 (apoptotic protease activating factor-1), leading to the formation of the apoptosome.[89] The apoptosome then activates caspase-9, an initiator caspase, which subsequently activates effector caspases such as caspase-3 and caspase-7.[90] These effector caspases execute the apoptotic program by cleaving various cellular substrates, leading to characteristic apoptotic features such as DNA fragmentation, membrane blebbing, and cell shrinkage.

(2) Extrinsic pathway. The extrinsic pathway of apoptosis is triggered by the binding of extracellular death ligands to their respective death receptors on the cell surface.[91] Benzothiazole derivatives can activate the extrinsic pathway by upregulating the expression of death receptors such as Fas and TRAIL-R (TNF-related apoptosis-inducing ligand receptor). The binding of death ligands such as FasL (Fas ligand) or TRAIL (TNF-related apoptosis-inducing ligand) to these receptors initiates the formation of the death-inducing signaling complex (DISC). The DISC recruits and activates initiator caspases such as caspase-8 and caspase-10. Activated caspase-8 can directly cleave and activate effector caspases, leading to apoptosis. Additionally, caspase-8 can cleave the proapoptotic Bcl-2 family member Bid, generating truncated Bid (tBid), which translocates to the mitochondria and amplifies the intrinsic apoptotic pathway.[92]

(3) Regulation by p53. The tumor suppressor p53 plays a central role in regulating apoptosis in response to cellular stress. Benzothiazole derivatives can activate the p53 pathway, leading to the upregulation of proapoptotic genes such as *Bax*, *PUMA*, and *NOXA*.[93] These genes promote mitochondrial outer membrane permeabilization and the release of cytochrome c, thereby initiating the intrinsic apoptotic pathway. Additionally, p53 can enhance the expression of death receptors, sensitizing cells to extrinsic apoptotic signals.[94]

3.3 Inhibition of angiogenesis and metastasis

Angiogenesis, the formation of new blood vessels, is a critical process for tumor growth and metastasis. By supplying oxygen and nutrients, angiogenesis supports the rapid proliferation of cancer cells and provides a route for cancer cells to enter the bloodstream and spread to distant sites. Benzothiazole derivatives have been shown to inhibit angiogenesis and metastasis, thereby restricting tumor growth and preventing the dissemination of cancer cells.

(1) Inhibition of VEGF signaling. VEGF is a key regulator of angiogenesis, promoting the proliferation, migration, and survival of endothelial cells.[95] Benzothiazole derivatives can inhibit VEGF signaling by targeting the VEGF receptor (VEGFR) on endothelial cells. For example, these compounds can block the binding of VEGF to VEGFR or inhibit the kinase activity of VEGFR, thereby preventing the downstream signaling required for angiogenesis.

(2) Disruption of endothelial cell function. In addition to inhibiting VEGF signaling, benzothiazole derivatives can directly affect the function of endothelial cells. These compounds can inhibit endothelial cell proliferation, migration, and tube formation, key steps in the angiogenic process. For example, benzothiazole derivatives may disrupt the organization of the cytoskeleton, impairing the ability of endothelial cells to migrate and form new blood vessels.[96]

(3) Inhibition of MMPs. MMPs are enzymes that degrade the extracellular matrix (ECM), facilitating the invasion and migration of cancer cells.[97] Benzothiazole derivatives can inhibit the activity of MMPs, thereby preventing the degradation of the ECM and inhibiting angiogenesis and metastasis. For example, these compounds can bind to the active site of MMPs, blocking their enzymatic activity and reducing the invasiveness of cancer cells.

(4) Modulation of the tumor microenvironment. The tumor microenvironment plays a crucial role in supporting angiogenesis and metastasis. Benzothiazole derivatives can modulate the tumor microenvironment by targeting various components, such as fibroblasts, immune cells, and the ECM.[98] For example, these compounds can inhibit the secretion of proangiogenic factors by tumor-associated fibroblasts or enhance the recruitment of antitumor immune cells, thereby creating a microenvironment that is less conducive to tumor growth and spread.

(5) Targeting hypoxia-inducible factors (HIFs). HIFs are transcription factors that promote the expression of genes involved in angiogenesis and metastasis in response to low oxygen levels.[99] Benzothiazole derivatives can inhibit the stabilization and activity of HIFs, thereby reducing the expression of proangiogenic and prometastatic genes. For example, these compounds can enhance the degradation of HIF-1α, a key subunit of HIF-1, preventing its accumulation and transcriptional activity under hypoxic conditions.[100]

3.4 Case studies and examples

[1] 2-(4-Aminophenyl)benzothiazole. One of the most extensively studied benzothiazole derivatives is 2-(4-aminophenyl)benzothiazole. This compound has demonstrated potent anticancer activity in various preclinical models. It induces cell cycle arrest at the G1 phase by upregulating p21 and p27 and triggers apoptosis through the intrinsic pathway by promoting the release of cytochrome c from the mitochondria.[101] Additionally, 2-(4-aminophenyl)benzothiazole inhibits angiogenesis by blocking VEGF signaling and disrupting endothelial cell function.

[2] 5,6-Dimethyl-2-(4-substituted phenyl)benzothiazole. Another benzothiazole derivative, 5,6-dimethyl-2-(4-substituted phenyl)benzothiazole, has shown promise as an anticancer agent. This compound induces cell cycle arrest at the G2/M phase by inhibiting CDK1 and disrupting the formation of the mitotic spindle.[102] It also triggers apoptosis through both intrinsic and extrinsic pathways and inhibits angiogenesis by targeting VEGF signaling and MMP activity.

[3] Benzothiazole-based hybrids. Recent research has focused on the development of benzothiazole-based hybrid molecules that combine the benzothiazole core with other bioactive moieties.[103] These hybrids often exhibit enhanced anticancer activity through multiple mechanisms. For example, a hybrid molecule combining benzothiazole with a histone deacetylase inhibitor has been shown to induce cell cycle arrest, apoptosis, and inhibition of angiogenesis more effectively than either component alone.

4. Preclinical and clinical studies

4.1 In vitro studies

In vitro studies, conducted in controlled laboratory environments using cell cultures, are the first step in evaluating the anticancer potential of benzothiazole derivatives. These studies provide insights into the molecular mechanisms, cytotoxicity,[104] and efficacy of these compounds against various cancer cell lines.

(1) Cytotoxicity and selectivity. Several benzothiazole derivatives have demonstrated potent cytotoxicity against a broad spectrum of cancer cell lines, including breast cancer,[105] lung cancer, colon cancer, leukemia, and melanoma.[106] For instance, 2-(4-aminophenyl)benzothiazole has shown significant cytotoxic effects against breast cancer cell lines such as MCF-7 and MDA-MB-231,[107] with minimal toxicity to normal cells.[108] This selectivity is crucial for developing therapeutic agents that target cancer cells while sparing healthy tissues.

(2) Mechanisms of action. In vitro studies have elucidated various mechanisms through which benzothiazole derivatives exert their anticancer effects. These mechanisms include induction of cell cycle arrest, apoptosis, and inhibition of cell proliferation. For example, benzothiazole derivatives have been shown to upregulate p21 and p27, leading to cell cycle arrest at the G1 phase.[109] Additionally, these compounds can activate caspases, leading to apoptosis through both intrinsic and extrinsic pathways.

(3) Synergistic effects. Combining benzothiazole derivatives with other anticancer agents has been explored to enhance therapeutic efficacy. In vitro studies have demonstrated synergistic effects when benzothiazole derivatives are used in combination with chemotherapeutic drugs such as doxorubicin, paclitaxel, and cisplatin. For instance, the combination of 2-(4-aminophenyl)benzothiazole with doxorubicin significantly enhances cytotoxicity against breast cancer cell lines compared with either agent alone.[60] This synergism is often attributed to the complementary mechanisms of action, such as simultaneous induction of cell cycle arrest and apoptosis. Table 4 compares the efficacy of selected benzothiazole derivatives with established anticancer agents across different cancer types. The results indicate that certain derivatives exhibit superior potency against specific cancers, supporting their potential as alternative or complementary therapies. Such comparisons are vital for understanding the role of benzothiazole derivatives in the broader context of cancer treatment.

(4) Antiangiogenic properties. In vitro studies have also investigated the antiangiogenic properties of benzothiazole derivatives. These compounds can inhibit the proliferation, migration, and tube formation of endothelial cells, key processes involved in angiogenesis. For example, benzothiazole derivatives have been shown to reduce VEGF-induced proliferation and migration of human umbilical vein endothelial cells, indicating their potential to disrupt tumor angiogenesis.

4.2 In vivo studies

In vivo studies, conducted in animal models, are essential for evaluating the efficacy, pharmacokinetics, and safety of benzothiazole derivatives in a physiological context.[59] These studies provide valuable data on the therapeutic potential and potential adverse effects of these compounds in living organisms. Figure 4 presents empirical data on the efficacy of benzothiazole derivatives, showcasing their performance in both in vitro and in vivo studies.[47] By illustrating comparative results, researchers can identify which compounds demonstrate the highest potency against specific cancer types, guiding future development efforts and highlighting promising candidates for further investigation.[79]

Table 5 summarizes key findings from various studies assessing the efficacy of benzothiazole derivatives. The results from in vitro and in vivo studies underscore their significant anticancer potential, while early-phase clinical trials highlight manageable toxicity and encouraging efficacy.[18] These findings collectively support the ongoing development and investigation of benzothiazole derivatives in clinical settings.

(1) Efficacy in tumor models. Various benzothiazole derivatives have demonstrated significant

Table 4

Comparative efficacy of benzothiazole derivatives vs established anticancer agents.

Compound/agent	Cancer type	IC50 (μM)	Mechanism of action	Notes
Benzothiazole derivative A	Breast cancer	1.2	Apoptosis induction	More effective than doxorubicin
Benzothiazole derivative B	Lung cancer	2.5	Cell cycle arrest	Comparable to paclitaxel
Doxorubicin	Breast cancer	3.5	Topoisomerase inhibition	Established agent, potential side effects
Paclitaxel	Lung cancer	1.8	Microtubule stabilization	First-line treatment, potential for resistance
Benzothiazole derivative C	Colorectal cancer	0.8	Inhibition of angiogenesis	Potentially more effective than bevacizumab
Bevacizumab	Colorectal cancer	5	Anti-VEGF antibody	Established agent, high cost
Benzothiazole derivative D	Melanoma	1.5	DNA topoisomerase inhibition	Potentially superior to dacarbazine with lower toxicity
Dacarbazine	Melanoma	4.2	Alkylating agent	Established agent, various side effects

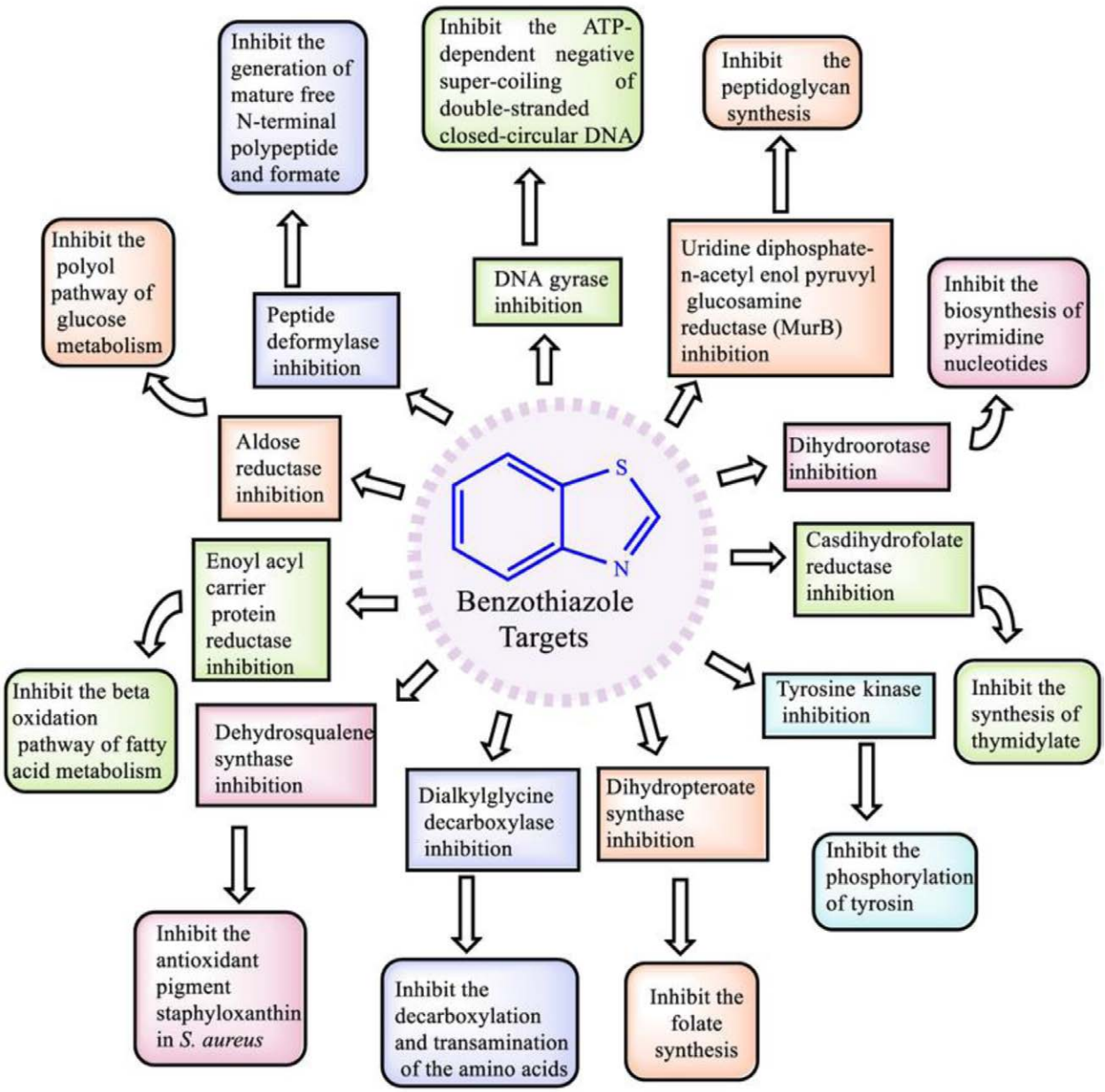

Figure 4. In vitro and in vivo efficacy of benzothiazole derivatives.

anticancer activity in animal models. For instance, 2-(4-aminophenyl)benzothiazole has shown potent antitumor effects in xenograft models of breast cancer.[110] In these studies, the compound significantly reduces tumor growth and prolongs survival compared with control groups. Similarly, other benzothiazole derivatives have shown efficacy in models of lung cancer, colon cancer, and melanoma.[111]

(2) Pharmacokinetics and bioavailability. In vivo studies also assess the pharmacokinetics and

Table 5

Summary of preclinical and clinical studies on benzothiazole derivatives.

Study type	Study design	Key findings	Limitations
In vitro studies	Cell line experiments	Significant cytotoxicity across multiple cancer lines	Limited to specific cancer cell lines, may not translate to whole organism
		Exploration of various mechanisms of action (eg, apoptosis induction, cell cycle arrest)	Cell lines may not fully represent the complexities of tumor microenvironment
In vivo studies	Xenograft models	Tumor growth inhibition in animal models	Xenografts do not perfectly mimic human cancers
		Prolonged survival observed in treated animals	Limited assessment of potential side effects compared with human trials
Clinical trials	Phase I/II trials	Manageable toxicity profiles for benzothiazole derivatives	Small patient groups, limited generalizability
		Promising preliminary efficacy against specific cancers	Short-term studies, long-term effects, and overall survival not yet established

bioavailability of benzothiazole derivatives. These studies involve measuring the ADME of the compounds in animal models. For example, pharmacokinetic studies of 2-(4-aminophenyl)benzothiazole have revealed its favorable bioavailability and distribution to tumor tissues, supporting its potential as an effective anticancer agent.[112]

(3) Toxicity and safety. Evaluating the toxicity and safety of benzothiazole derivatives is crucial for their development as therapeutic agents. In vivo studies have assessed the potential adverse effects of these compounds on normal tissues and organs. For example, toxicity studies of 2-(4-aminophenyl) benzothiazole in mice have shown minimal toxicity to normal tissues at therapeutic doses.[113] However, some benzothiazole derivatives may exhibit dose-dependent toxicities, necessitating careful optimization of dosing regimens to balance efficacy and safety.

4.3 Clinical trials

Clinical trials are the final and most critical phase of drug development, assessing the safety, efficacy, and therapeutic potential of benzothiazole derivatives in human patients. While preclinical studies provide promising data, clinical trials are essential to validate these findings and determine the clinical utility of these compounds.

(1) Early-phase clinical trials. Early-phase clinical trials, including phase I and phase II studies, primarily focus on evaluating the safety, tolerability, and preliminary efficacy of benzothiazole derivatives.[114] These trials involve a small number of patients and aim to identify the optimal dose and dosing regimen for further studies.

   (i) Phase I trials. Phase I trials are designed to assess the safety and tolerability of benzothiazole derivatives in human patients. These trials typically involve dose-escalation studies to determine the maximum tolerated dose (MTD) and identify dose-limiting toxicities (DLTs). For example, a phase I trial of a benzothiazole derivative may involve treating patients with escalating doses of the compound and monitoring for adverse effects, such as hematological toxicity or gastrointestinal disturbances.

   (ii) Phase II trials. Phase II trials aim to evaluate the preliminary efficacy of benzothiazole derivatives in specific cancer types. These trials often involve larger patient cohorts and assess the compound's ability to induce tumor responses, such as partial or complete remission, and improve progression-free survival (PFS) and overall survival. For instance, a phase II trial of a benzothiazole derivative in breast cancer patients may evaluate the compound's ability to reduce tumor size and improve survival outcomes compared with standard therapies.

(2) Late-phase clinical trials. Late-phase clinical trials, including phase III studies, aim to confirm the efficacy and safety of benzothiazole derivatives in larger patient populations and compare their performance to standard treatments.[115] Phase III trials. Phase III trials are pivotal studies that involve large patient cohorts and aim to establish the clinical efficacy and safety of benzothiazole derivatives. These trials often involve randomized controlled trials comparing the benzothiazole derivative to standard therapies or placebo. The primary endpoints of phase III trials typically include overall survival, PFS, and quality of life. For example, a phase III trial of a benzothiazole derivative in lung cancer patients may compare the compound's efficacy to that of a standard chemotherapy regimen, assessing outcomes such as overall survival and treatment-related adverse effects.

(3) Current status of clinical trials. As of the latest available data, several benzothiazole derivatives have entered clinical trials, with varying degrees of success.

   (i) 2-(4-Aminophenyl)benzothiazole derivatives. Some derivatives of 2-(4-aminophenyl)benzothiazole have shown promise in early-phase clinical trials for breast cancer and other malignancies.[110] These trials have demonstrated manageable toxicity profiles and encouraging preliminary efficacy, warranting further investigation in larger studies.

   (ii) Other benzothiazole derivatives. Other benzothiazole derivatives are in various stages of clinical development, with ongoing phase I and phase II trials for different cancer types.[116] These trials aim to establish the safety and preliminary efficacy of these compounds and identify potential biomarkers of response.

4.3.1 Challenges and future directions

While the preclinical and early clinical data for benzothiazole derivatives are promising, several challenges remain in their clinical development:

(1) Optimizing dosing regimens. Determining the optimal dosing regimens for benzothiazole derivatives is crucial to balance efficacy and toxicity. Ongoing clinical trials aim to refine dosing schedules and identify the MTD and DLTs.
(2) Overcoming resistance. Like other anticancer agents, benzothiazole derivatives may encounter resistance mechanisms in cancer cells. Future research will focus on understanding these resistance mechanisms and developing combination therapies to overcome resistance and enhance therapeutic efficacy.
(3) Biomarker development. Identifying predictive biomarkers of response to benzothiazole derivatives is essential for patient stratification and personalized therapy. Ongoing studies aim to identify molecular markers that can predict patient responses and guide treatment decisions.
(4) Expanding therapeutic indications. Expanding the therapeutic indications of benzothiazole derivatives to other cancer types and exploring their potential in combination with immunotherapy, targeted therapy, and other modalities are important areas of future research.
(5) Long-term safety and efficacy. Assessing the long-term safety and efficacy of benzothiazole derivatives is crucial for their successful clinical translation. Ongoing and future clinical trials will continue to monitor patients for potential late-onset toxicities and durable responses.

5. Therapeutic potential and future directions

5.1 Comparative efficacy

Benzothiazole derivatives have emerged as promising candidates in the landscape of anticancer therapeutics.[117] Their unique chemical structure, combined with a range of biological activities, positions them favorably compared with existing anticancer agents.

5.1.1 Mechanisms of action

Benzothiazole derivatives exhibit multiple mechanisms of action, including induction of apoptosis, cell cycle arrest, and inhibition of angiogenesis, similar to established anticancer agents such as taxanes, alkylating agents, and targeted therapies. However, what distinguishes benzothiazole derivatives is their ability to engage diverse pathways, often leading to synergistic effects when combined with other therapies.

(1) Induction of apoptosis. Unlike some traditional chemotherapeutics that primarily activate the extrinsic apoptosis pathway, many benzothiazole derivatives engage both the intrinsic and extrinsic pathways.[118] This dual action can enhance efficacy, especially in resistant cancer types.
(2) Cell cycle regulation. Similar to other anticancer agents like gemcitabine and paclitaxel, which target specific phases of the cell cycle, benzothiazole derivatives are effective in inducing cell cycle arrest.[119] Their ability to target multiple phases may provide an advantage in evading resistance mechanisms commonly associated with single-target drugs.

5.1.2 Efficacy against resistant cancer cell lines

One of the significant challenges in cancer treatment is the emergence of drug resistance. Many established anticancer agents face limitations due to the development of resistance mechanisms, such as overexpression of drug efflux pumps or mutations in target proteins. Benzothiazole derivatives have shown potential against various resistant cancer cell lines. For instance, studies have indicated that certain benzothiazole derivatives maintain efficacy against multidrug-resistant cancer cells, demonstrating their capability to circumvent common resistance mechanisms.[120]

5.1.3 Comparative studies with established agents

Several studies have directly compared the efficacy of benzothiazole derivatives with existing anticancer agents. For example, derivatives such as 2-(4-aminophenyl)benzothiazole have shown superior anticancer effects compared with established drugs like doxorubicin in preclinical models of breast cancer.[121] These comparisons not only highlight the promising efficacy of benzothiazole derivatives but also underscore their potential to be developed as alternative or adjunctive therapies in cancer treatment.

5.2 Drug development

The potential for benzothiazole derivatives in drug development is substantial, particularly in the context of personalized medicine. Their diverse biological activities, favorable pharmacokinetic profiles, and promising preclinical and clinical results provide a strong foundation for future therapeutic advancements.

5.2.1 Development of novel therapeutics

Benzothiazole derivatives can be further modified to enhance their anticancer properties. SAR studies have provided valuable insights into how specific structural modifications can improve efficacy, reduce toxicity, and increase selectivity toward cancer cells.[122] This iterative process of design and testing is essential in drug development and positions benzothiazole derivatives as versatile scaffolds for new therapeutic agents.

5.2.2 Integration into personalized medicine

The advent of personalized medicine has transformed cancer treatment, enabling therapies to be tailored to the individual characteristics of each patient's tumor. Benzothiazole derivatives could play a crucial role in this landscape by being developed alongside biomarkers that predict patient response.[55] Future research should focus on identifying molecular signatures associated with sensitivity to benzothiazole derivatives, paving the way for their use in personalized therapeutic regimens.

5.2.3 Combination therapies

The therapeutic potential of benzothiazole derivatives extends beyond monotherapy. Their ability to enhance the efficacy of existing treatments suggests that they may serve as effective combinatory agents. For instance, ongoing studies are exploring combinations of benzothiazole derivatives with conventional chemotherapeutics, targeted therapies, and immunotherapies to maximize therapeutic outcomes while minimizing side effects.[45]

5.3 Future research directions

While the current research on benzothiazole derivatives has yielded promising results, several gaps and areas of opportunity remain that warrant further exploration.

5.3.1 Understanding resistance mechanisms

Despite the observed efficacy of benzothiazole derivatives against resistant cancer cell lines, comprehensive studies are needed to elucidate the underlying mechanisms of resistance. Identifying specific genetic or molecular alterations that confer resistance will aid in the rational design of combination therapies and the development of next-generation benzothiazole derivatives that can effectively target these resistant phenotypes.

5.3.2 Preclinical to clinical translation

Transitioning from preclinical findings to successful clinical applications remains a significant hurdle in drug development. Future studies should focus on developing robust preclinical models that closely mimic human cancer biology, including the tumor microenvironment and immune context. Such models will provide more accurate predictions of clinical efficacy and safety, ultimately aiding in the design of effective clinical trials.

5.3.3 Expanded therapeutic indications

Current research primarily focuses on specific cancer types, but there is an opportunity to investigate the potential of benzothiazole derivatives in a broader range of malignancies. Future studies should explore the efficacy of these compounds in less common cancers and those with limited treatment options, expanding their therapeutic repertoire.

5.3.4 Optimization of formulations

The formulation of benzothiazole derivatives for effective delivery is crucial for achieving optimal therapeutic outcomes. Research should explore various drug delivery systems, such as nanocarriers,[123] liposomes,[124] or polymeric carriers, to improve the bioavailability, stability, and targeted delivery of these compounds. Advanced formulations may enhance the therapeutic index and reduce off-target toxicity.

5.3.5 Clinical trial design

The design of clinical trials for benzothiazole derivatives should consider innovative approaches to maximize the chances of success. Adaptive trial designs, which allow modifications based on interim results, could be particularly useful in exploring the efficacy of these compounds in various settings and patient populations. Additionally, the inclusion of biomarker-driven endpoints could provide valuable insights into patient responses and guide future treatment strategies.

5.3.6 Long-term safety and efficacy studies

While early-phase clinical trials provide essential safety and efficacy data, long-term studies are necessary to understand the durability of responses and the potential for late-onset toxicities. Future research should prioritize the establishment of long-term follow-up studies to monitor patients receiving benzothiazole derivatives, ensuring that the benefits outweigh any long-term risks.

5.3.7 Collaboration and multidisciplinary approaches

Addressing the complex challenges in cancer treatment requires collaboration across disciplines. Future research initiatives should foster partnerships among chemists, biologists, pharmacologists, and clinicians to develop a comprehensive understanding of benzothiazole derivatives' therapeutic potential. Interdisciplinary teams can drive innovative research and facilitate the translation of findings from the laboratory to the clinic. Benzothiazole derivatives represent a promising class of compounds with significant therapeutic potential in cancer treatment. Their favorable pharmacological profiles, diverse mechanisms of action, and encouraging preclinical and clinical results position them as valuable candidates for drug development. While challenges remain, ongoing research is essential to fully harness the potential of benzothiazole derivatives and advance them toward effective therapeutic agents. By addressing current gaps in knowledge and exploring new avenues of research, the future of benzothiazole derivatives in oncology looks promising, with the potential to significantly improve patient outcomes in cancer care.

6. Conclusions

Benzothiazole derivatives have emerged as a significant focus in cancer research due to their diverse biological activities and therapeutic potential. This review has highlighted several key aspects of benzothiazole derivatives, particularly regarding their synthesis methods and anticancer efficacy.

6.1 Synthesis methods

The review detailed various synthetic approaches to producing benzothiazole derivatives, emphasizing both traditional and modern techniques. Traditional methods, such as the condensation of thiourea with ortho-haloaryl compounds, have been foundational in developing these compounds. However, contemporary synthetic techniques, including microwave-assisted synthesis and green chemistry approaches, have revolutionized the field by offering more efficient, sustainable, and eco-friendly methods. These advancements not only streamline the synthesis process but also allow for the rapid exploration of SARs, facilitating the design of more potent and selective derivatives.

6.2 Therapeutic potential

The therapeutic potential of benzothiazole derivatives in cancer treatment is underscored by their ability to induce apoptosis, inhibit cell proliferation, and disrupt angiogenesis. Their mechanisms of action provide a multifaceted approach to targeting cancer, making them valuable candidates for further development. Preclinical studies have shown promising results, with many derivatives demonstrating potent cytotoxicity against a range of cancer cell lines and superior efficacy compared with existing agents.

Furthermore, ongoing research into the pharmacokinetics, safety profiles, and combination therapies enhances the viability of benzothiazole derivatives as therapeutic agents. The potential for integration into personalized medicine, combined with the identification of biomarkers for patient stratification, positions these compounds at the forefront of innovative cancer treatment strategies.

6.3 Future directions

Despite the promising data, challenges remain in the clinical translation of benzothiazole derivatives. Future research should focus on addressing these gaps, including understanding resistance mechanisms, optimizing drug formulations, and conducting long-term safety studies. Collaborative, multidisciplinary approaches will be essential in advancing benzothiazole derivatives toward successful clinical applications. In conclusion, benzothiazole derivatives represent a promising avenue for cancer therapy, with substantial potential for further development. Their unique synthesis methods and therapeutic efficacy highlight their role in the future landscape of oncology, offering hope for improved outcomes in cancer treatment.

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Conflicts of interests

The author declare that he no conflicts of interest.

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