EXPLORATION OF POTENTIAL AND BIOLOGICAL EVALUATION OF NOVEL BENZOTHIAZOLE DERIVATIVES

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Abstract

Benzothiazole, a privileged heterocyclic core, has received significant attention during the past few years due to its rich diversity of biological activities and synthetic utility. The present review presents a comprehensive overview of the recent progress in the design, synthesis, and biological exploration of new benzothiazole derivatives as promising drug candidates. The distinctive combination of a thiazole moiety and a benzene ring confers special pharmacophoric characteristics with the ability to interact with a wide range of biotargets like receptors, enzymes, and nucleic acids. The article starts with a concise overview of structural importance and medicinal significance of the benzothiazole framework, preceded by an extensive account on contemporary design strategies utilized to augment potency and selectivity such as structure-activity relationship (SAR) analysis, bioisosteric replacement, and molecular modeling methods. A number of synthetic routes are discussed, from traditional condensation reactions to newer green chemistry methods like microwave-assisted synthesis, one-pot synthesis, and solvent-free approaches that provide higher yields, reduced reaction times, and environmentally friendly conditions. In the biomedical context, new benzothiazole derivatives have shown strong activity in a wide range of therapeutic fields ranging from antimicrobial, anticancer, and anti-inflammatory activities to antioxidant and antiviral functions. The modes of action are generally explained by DNA intercalation, enzyme inhibition, and receptor binding, as evidenced by molecular docking and QSAR investigations. Particular care is taken for SAR correlations and target-specific design to elucidate how particular substituents affect biological responses. In spite of encouraging preclinical results, limitations like aqueous solubility issues, metabolic instability, and restricted in vivo activity are still hurdles to clinical progress. However, ongoing investigation into benzothiazole derivatives is very promising for the discovery of multi-target therapeutics with enhanced pharmacological properties. This review aspires to act as an invaluable textbook for medicinal chemists, pharmacologists, and researchers dealing with heterocyclic drug design, providing an overview of the rational design of new benzothiazole-based therapeutics.

Keywods: Benzothiazole, Anticancer, Antimicrobial, Heterocyclic compound, Synthetic bioactive compound

1. Introduction

The discovery of new drugs continues to be a continuously evolving challenge in medicinal chemistry, particularly in the context of emerging multidrug resistance and intricate disease pathologies. Among the plethora of heterocyclic templates developed for pharmaceutical applications, benzothiazole, a bicyclic framework composed of a benzene and a thiazole ring, has found itself as a versatile and pharmacologically useful entity. Due to the distinctive electronic disposition and structural hardness, the benzothiazole core has exhibited an extensive range of biological activities such as antimicrobial, anticancer, anti-inflammatory, anticonvulsant, antitubercular, and enzyme inhibitory activity. Historically, benzothiazole derivatives have drawn scientific interest because of their occurrence in both natural and synthetic bioactive compounds. [1] The heteroatoms present in the benzothiazole ring strengthen hydrogen-bonding interactions and allow for binding affinity towards diverse biological targets like enzymes, receptors, and nucleic acids. Additionally, their susceptibility to structural modification makes it possible for designing derivatives with enhanced potency and selectivity. With advancements in structure-activity relationship (SAR) studies, computational modeling, and high-throughput synthesis techniques, researchers have successfully optimized this pharmacophore for targeted drug discovery. A significant concern in modern therapeutics is the rapid evolution of microbial resistance to conventional antibiotics, necessitating the exploration of novel chemical entities with potent antimicrobial properties. Benzothiazole derivatives, through their dual action potential like DNA binding and enzyme inhibition, provide an attractive scaffold for the design of next-generation antimicrobials. [2] Besides, the cytotoxicity evaluation by assays like lactate dehydrogenase (LDH) release also helps in further understanding the mechanism of action and safety profile of these compounds. The present review elaborately points out recent advances in the design strategies, synthetic methodologies, and biological evaluation of new benzothiazole derivatives. [3] It seeks to gather and critically interpret evidence literature on their antimicrobial activity and cytotoxicity, primarily using in vitro models, which sheds light on their potential therapeutics. An insight into how chemical structure relates to biological activity, this article brings into focus the utility of benzothiazole scaffolds as a useful tool in rational drug design and invites further research in this exciting area of medicinal chemistry. [4]

2. Benzothiazole: A Privileged Scaffold

Medicinal chemistry lives and breathes on the ongoing search for heterocyclic scaffolds that can act as central cores for the discovery of new therapeutic agents. Of these, benzothiazole has emerged as a privileged scaffold because of its broad range of biological activities and its potential to act as a chemically diverse and biologically active framework. The "privileged scaffold" is a designation used to describe molecular skeletons that are able to give high affinity and selectivity for various biological targets after suitable functionalization. Benzothiazole qualifies as such and has thus emerged as one of the most investigated heterocyclic systems in contemporary drug research and development. The benzothiazole core is a fused bicyclic ring system consisting of a benzene ring fused with a thiazole unit. The thiazole ring is itself a five-membered planar aromatic ring possessing one

nitrogen and one sulfur atom in positions 1 and 3, respectively. The ring fusion with the benzene ring gives rise to a highly conjugated, planar compound with greater resonance stability. The presence of heteroatoms (N and S) in the ring makes it polarizable and enables the ability to form multiple non-covalent interactions like hydrogen bonding, π-π stacking, and dipole interactions with a variety of biological macromolecules like proteins, nucleic acids, and enzymes. This distinctive electronic environment renders benzothiazole derivatives as suitable candidates for interacting with a variety of biological targets. [5]

2.1 Structural Features and Chemical Properties

The chemical conformation of benzothiazole is one of the main reasons for its biological diversity. The aromatic and planar scaffolding enables it to intercalate into DNA or RNA, and thus it has the potential to be used as an anticancer or antimicrobial drug. The sulfur and nitrogen atoms of the thiazole ring provide hydrogen bond acceptor or donor functions, which increase its binding affinity to biological targets like enzymes (through active site interactions) or receptors (through ligand-receptor recognition). [6]

The scaffold enables multiposition substitution, particularly at positions C-2 and C-6, which are normally the most reactive and the most important for biological interactions. Modifications at these sites can profoundly change lipophilicity, electronic distribution, and steric profile, enabling fine adjustment of pharmacokinetic and pharmacodynamic characteristics. In addition, the benzothiazole ring is rather stable under physiological and conditions of synthesis, enabling a broad variety of chemical modifications such as nucleophilic substitutions, electrophilic aromatic substitutions, acylation, alkylation, and oxidative couplings. Substitution patterns have a significant bearing on the profile of biological activity. [7] As a case in point, the introduction of electron-withdrawing groups like halogens or nitro groups at certain positions will increase antimicrobial activity, whereas electron-donating groups like hydroxyl or methoxy groups could enhance antioxidant activity. The conformational rigidity of the scaffold also enables fixed three-dimensional conformations, which is particularly important in ligand receptor interactions and discriminatory enzyme inhibition. [8]

2.2 Natural and Synthetic Sources

Even though benzothiazole derivatives are mostly recognized from synthetic sources, some naturally occurring molecules share the same heterocyclic aspect. For example, some marine microorganisms, fungal metabolites, and plants have been identified to produce benzothiazole-type moieties as part of their metabolisms or defense mechanisms. Naturally occurring analogs of these compounds usually act as starting points for synthetic modification. Some examples are 2-substituted benzothiazoles isolated from microbial cultures that have antibacterial or antifungal activities. Most biologically active benzothiazole derivatives, however, are obtained synthetically. [9] Synthetic compounds are more desirable in drug research because they can be more easily functionalized, are reproducible, highly pure, and scalable. Various synthetic routes have been optimized to produce complex libraries of benzothiazole analogs for high-throughput biological screening. The possibility to incorporate a broad variety of side chains and substituents on the benzothiazole core renders it an extremely

versatile pharmacophore, and its potential application in diverse therapeutic indications such as oncology, neurology, infectious diseases, and inflammation. [10]

2.3 Drug Development Significance in the Past

The therapeutic potential of benzothiazole derivatives has been exploited for more than a century, first as dyes and industrial chemicals and subsequently evolving towards the pharmaceutical industry. A number of drugs containing benzothiazole have been formulated and marketed for clinical use, and numerous others are under different stages of preclinical and clinical trials. [11] One of the first and most widely recognized compounds is Riluzole, a derivative of benzothiazole employed in the therapy of amyotrophic lateral sclerosis (ALS). It acts mainly through preventing the release of glutamate, blocking voltage-dependent sodium channels, and disrupting intracellular signaling. Another well-documented compound is Ethoxzolamide, a carbonic anhydrase inhibitor employed for its diuretic and antiglaucoma actions. Such compounds illustrate the pharmacological versatility of the benzothiazole ring and justify its potential in targeting various physiological systems. [12] In oncology, many benzothiazole analogs have been synthesized that exhibit high cytotoxic activity against diverse cancer cell lines. Such compounds tend to be active by mechanisms including DNA intercalation, tubulin polymerization inhibition, topoisomerase inhibition, or kinase modulation. In antimicrobial chemotherapy, various 2-substituted benzothiazole analogs have been found to inhibit resistant bacterial and fungal strains, frequently surpassing ordinary antibiotics. [13] The decades-long SAR studies have found that even slight changes in the benzothiazole ring system can cause drastic changes in biological activity. This has encouraged medicinal chemists to keep exploring this scaffold extensively, resulting in the discovery of new derivatives with enhanced potency, selectivity, metabolic stability, and safety profiles. Finally, the benzothiazole core is a chemically stable and biologically privileged pharmacophore that remains at the center of medicinal chemistry efforts towards the design of numerous therapeutic agents. [14] Its structural diversity, combined with its long history in medicinal chemistry, renders it a valuable resource in contemporary drug discovery. The ongoing investigation and optimization of benzothiazole derivatives have vast potential in solving the urgent clinical issues of antimicrobial resistance, cancer therapy, and neurodegenerative diseases, and solidify benzothiazole as a cornerstone scaffold in medicinal and pharmaceutical chemistry. [15]

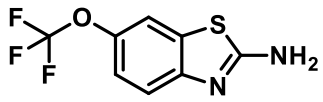
2.4. Few recently developed benzothiazole derivatives

Riluzole

IUPAC Name: 2-amino-6-(trifluoromethoxy)benzothiazole

Riluzole is a benzothiazole derivative used primarily in the treatment of Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disorder characterized by motor neuron degeneration. It was the first FDA-approved drug for ALS and is believed to work by inhibiting presynaptic glutamate release, blocking voltage-gated sodium channels, and interfering with intracellular signal transduction. Its trifluoromethoxy group enhances

lipophilicity and blood-brain barrier (BBB) permeability, making it effective in CNS disorders. It represents a landmark in the use of benzothiazoles for neuroprotective therapy. [16]

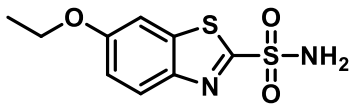


2-amino-6-(trifluoromethoxy)benzothiazole

Ethoxzolamide

IUPAC Name: 6-ethoxy-1,3-benzothiazole-2-sulfonamide

Ethoxzolamide is a carbonic anhydrase inhibitor used in the treatment of glaucoma, epilepsy, and diuretic applications. It inhibits the enzyme carbonic anhydrase, thereby reducing the production of aqueous humor in the eye and controlling intraocular pressure. The presence of the sulfonamide group at position 2 is critical for its enzyme-inhibiting activity. Ethoxzolamide demonstrates the utility of benzothiazole in designing enzyme-targeting agents, especially in the central nervous system and ocular pharmacology. [17]

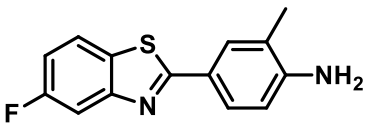


6-ethoxy-1,3-benzothiazole-2-sulfonamide

Phortress (5F-203 / NSC 710305)

IUPAC Name: 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole

Phortress is a novel benzothiazole-based investigational anticancer agent that exhibits selective cytotoxicity against breast, ovarian, and renal cancer cells. Its activity is largely dependent on metabolic activation by cytochrome P450 enzymes, particularly CYP1A1 and CYP1B1, which are overexpressed in certain tumors. Once metabolized, it acts as a DNA-damaging agent, leading to apoptosis in cancer cells. It represents a new class of tumor-targeted prodrugs and highlights the application of benzothiazoles in oncology drug design. [18]

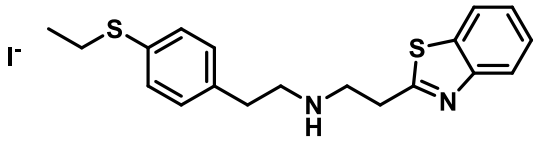


2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole

Dithiazanine Iodide

IUPAC Name: N-[2-[4-(ethylthio)phenyl]ethyl]-2-(benzothiazol-2-yl)ethanamine iodide

Dithiazanine iodide is an anthelmintic drug, particularly used in veterinary medicine for treating heartworm infections in dogs. It belongs to the phenothiazinium class and exhibits cidal activity against microfilariae and adult worms. The compound acts by disrupting energy metabolism and inducing neuromuscular paralysis in helminths. Although it has limited use in human medicine due to its toxicity, it exemplifies the parasiticidal potential of benzothiazole derivatives. [19]

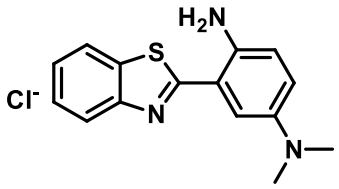


N-[2-[4-(ethylthio)phenyl]ethyl]-2-(benzothiazol-2-yl)ethanamine iodide

Thioflavin T

IUPAC Name: [3-(benzothiazol-2-yl)-N,N-dimethylbenzene-1,4-diamine] chloride

Thioflavin T is a benzothiazole-based fluorescent dye widely used in biochemical and pathological studies for detecting amyloid fibrils, particularly in Alzheimer's disease research. It binds selectively to the β-sheet structures of amyloid plaques and exhibits enhanced fluorescence upon binding. This property is used to monitor amyloid formation in real-time kinetic assays and in histopathological staining. It showcases the application of benzothiazole in molecular diagnostics and imaging. [20]

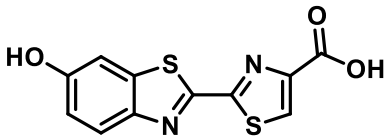


[3-(benzothiazol-2-yl)-N,N-dimethylbenzene-1,4-diamine] chloride

Luciferin (Bioluminescent substrate – Benzothiazole core)

IUPAC Name: 2-(6-hydroxy-2-benzothiazolyl)thiazole-4-carboxylic acid

Luciferin is a naturally occurring benzothiazole derivative used as a substrate by the enzyme luciferase in bioluminescent organisms such as fireflies. Upon oxidation by luciferase in the presence of ATP, oxygen, and magnesium ions, luciferin emits light. This reaction is widely exploited in bioluminescence imaging (BLI) for tracking gene expression, tumor growth, and infection progression in live animals. Luciferin's discovery has revolutionized non-invasive imaging techniques and represents a non-therapeutic but powerful research tool in life sciences. [21]



2-(6-hydroxy-2-benzothiazolyl)thiazole-4-carboxylic acid

3. Reported Pharmacological and Biological Properties of benzothiazoles derivatives

Benzothiazole derivatives have proven to be one of the most potential heterocyclic compounds in the field of drug discovery, with a broad spectrum of pharmacological activities. The intrinsic structural diversity of the benzothiazole nucleus enables it to engage in many biochemical interactions, as both a benzene ring and a thiazole ring are fused to each other. This peculiar combination provides both aromatic stability and the possibility of introducing different functional groups at strategic sites, yielding compounds with wide pharmacological potential. The electron-donating sulfur and nitrogen atoms in the thiazole ring are responsible for hydrogen bonding, π-π interactions, and electrostatic binding with target proteins, thus making benzothiazoles effective ligands for a wide variety of receptors and enzymes. [22] In the past decades, researchers have widely studied benzothiazole analogs to understand their activities in antimicrobial, anticancer, anti-inflammatory, antioxidant, neuroprotective, and antiparasitic treatments. Through both in vitro and in vivo models, these activities have been confirmed, revealing the excellent drug-like character, metabolic stability, and cellular permeability of the scaffold. [23]

Antimicrobial Activity

One of the most important therapeutic uses of benzothiazole derivatives is their antimicrobial activity, especially in the context of increasing antimicrobial resistance around the world. The ring structure plasticity of benzothiazole allows it to be amenable to electron-withdrawing or electron-donating group modification to create very potent antimicrobials. The antimicrobial actions of these compounds are thought to be the result of several mechanisms such as interference with the replication of bacterial DNA, inhibition of essential enzymes in bacteria, disruption of microbial cell membranes, and interference with protein synthesis. [24] Additionally, appending lipophilic moieties or hybridation with other antimicrobial pharmacophores, e.g., azoles, quinolones, or triazoles, has resulted in new benzothiazole-derived antibiotics that exhibit activity against multi-drug-resistant strains. The amphiphilic character of most benzothiazoles also makes them permeate lipid membranes easily, promoting intracellular accumulation and target interaction. [25]

Antibacterial Activity

Benzothiazole derivatives have exhibited great potential against a wide spectrum of bacterial pathogens, including Gram-positive and Gram-negative bacteria. In various studies, 2-substituted benzothiazoles have exhibited strong antibacterial activity against common pathogens such as Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae. Antibacterial activity is generally ascribed to the inhibition of necessary enzymes like DNA gyrase and topoisomerase IV, which are involved in supercoiling and replication of bacterial DNA. Benzothiazole moieties attached with sulfonamide, amide, or Schiff base functionalities have also been found to exhibit increased bacterial inhibition by interfering with the folate

biosynthesis pathway or bacterial cell wall formation. Structural optimization, including halogenation (fluoro, chloro, or bromo substitution) at targeted positions, has been observed to drastically increase antibacterial activity and optimize pharmacokinetic attributes. Over the past few years, workers have also studied benzothiazole-fluoroquinolone hybrids and nanoformulations of benzothiazoles as targeted antibacterial therapies of increased efficacy and lowered toxicity. [26]

Antifungal Activity

Besides antibacterial activity, benzothiazole derivatives have also shown notable antifungal activity. Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans fungal infections have become more challenging to treat because of a restricted number of therapeutic alternatives and increasing resistance. The antifungal activity of benzothiazoles is mainly manifested as disruption of the fungal cell membrane, inhibition of ergosterol biosynthesis, or interference with fungal oxidative phosphorylation. Certain derivatives were found to modify the mitochondrial membrane potential and trigger fungal apoptosis. The incorporation of polar functionality like hydroxyl, amino, or imidazole rings has been found to enhance water solubility and target specificity of these derivatives. Hybrid molecules consisting of benzothiazole with azoles or triazoles have produced highly active antifungal agents with broad antifungal spectrum and low minimum inhibitory concentrations (MIC). The compounds are promising leads for systemic mycotic infections as well as topical applications for cutaneous mycoses. [27]

Antiviral Activity

Though in initial phases of development with respect to antibacterial and antifungal treatments, benzothiazole analogs have also exhibited potential antiviral activity against a number of viruses such as HIV, HCV, and influenza viruses. Antiviral action is usually manifested through viral replication enzyme inhibition like reverse transcriptase, proteases, and RNA-dependent RNA polymerases. Certain benzothiazole analogs have also been found to be of potential use in inhibiting viral entry into host cells through glycoprotein-receptor interference. Strategic positioning of polar functional groups and aromatic systems increases binding affinity of these molecules to active sites of viral enzymes. For example, benzothiazole-imidazole hybrids inhibited HIV-1 reverse transcriptase, and fluorinated benzothiazole analogs proved active against HCV in replicon assays. With good pharmacokinetic profiles and the ready chemical modifiability, benzothiazoles are now intensely researched as scaffolds for next-generation antiviral drugs. [28]

Anticancer Activity

Most certainly the most commonly investigated application of benzothiazole derivatives is their anticancer activity. A great majority of compounds possessing benzothiazole moieties have exhibited cytotoxicity against a range of cancerous cell lines, such as those from breast, lung, colon, liver, and ovarian cancers. These agents exert anticancer activity through various mechanisms: DNA intercalation, topoisomerase I and II inhibition, microtubule dynamic disruption, angiogenesis inhibition, and apoptosis induction through caspase activation. Some benzothiazole derivatives are also kinase inhibitors of EGFR, VEGFR, and CDKs, inhibiting the cell proliferation signaling pathways. [29] One of the earliest is Phortress, a 2-(4-amino-3-methylphenyl)-5-

fluorobenzothiazole, which exhibits selective cytotoxicity against hormone-resistant breast cancer cells through activation by cytochrome P450 enzymes. Further, benzothiazole conjugates with peptides or targeting ligands have demonstrated greater tumor selectivity and less off-target cytotoxicity. In contemporary oncology, benzothiazole derivatives are investigated not just as cytotoxic agents but also as drug carriers, imaging agents, and dual-function theranostic agents. [30]

Anti-inflammatory and Analgesic Activity

Chronic inflammation is at the core of the pathophysiology of numerous diseases, including arthritis, cardiovascular disease, and cancer. Benzothiazole derivatives have demonstrated notable anti-inflammatory activity, and through several mechanisms. Most compounds have shown selective cyclooxygenase-2 (COX-2) inhibition, decreasing the formation of pro-inflammatory prostaglandins without inhibiting COX-1, thus limiting gastrointestinal side effects. Aside from inhibition of COX, some derivatives interfere with the expression of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 and inhibit nuclear factor kappa B (NF-κB) signaling. Derivatives containing sulfonamide or amide moieties have exhibited potent activity in carrageenan-induced paw edema, acetic acid-induced writhing, and formalin-induced pain models. The dual anti-inflammatory and analgesic activity of benzothiazole analogs renders them promising agents for the treatment of pain and inflammatory diseases with a broader margin of safety than conventional NSAIDs. [31]

Antioxidant Activity

Oxidative stress is an integral component of aging, cancer, and neurodegenerative disorders. Antioxidant activity of benzothiazole derivatives is primarily due to free radical scavenging, chelation of pro-oxidant metal ions, and antioxidant enzyme activation capacity. Favorable structures like phenolic OH, methoxy, or amino groups are responsible for increased radical scavenging through electron donation processes. Some of the benzothiazole derivatives have presented considerable activity in in vitro test systems such as DPPH, ABTS, superoxide anion, and hydroxyl radical scavenging. In addition, hybrid molecules of benzothiazole with other antioxidant scaffolds such as coumarins, flavonoids, or hydroxyquinolines have been found to exhibit synergistic activity. In cell culture models, benzothiazole antioxidant compounds have exhibited the ability to inhibit lipid peroxidation, reduce ROS-induced DNA damage, and suppress apoptotic signaling pathways, thus making them potential candidates for cytoprotection and anti-aging therapies. [32]

Anticonvulsant and Neuroprotective Activity

Benzothiazole derivatives also presented excellent potential in the therapy of neurological disorders. Their anticonvulsant action has been established in a variety of animal models, including maximal electroshock seizure (MES) and pentylenetetrazole (PTZ)-induced seizure tests. The anticonvulsant activity is exerted through multiple mechanisms, e.g., modulation of GABAergic transmission, sodium and calcium channel blockade, and facilitation of inhibitory neurotransmission. Benzothiazoles possess neuroprotective activities as well by inhibiting monoamine oxidase (MAO), inhibiting glutamate excitotoxicity, and preventing oxidative neuronal injury. Some of the derivatives have been reported to exhibit efficacy in Alzheimer's disease models,

specifically in inhibiting amyloid-beta aggregation and tau phosphorylation. Benzothiazole-based dye thioflavin T has broad applications as a fluorescent probe to investigate amyloid plaque formation. All these observations indicate that benzothiazole scaffolds can be utilized for the design of multifunctional neurotherapeutics with anticonvulsant, antidepressant, and neuroprotective activities. [33]

Antitubercular and Antimalarial Applications

The worldwide burden of tuberculosis and malaria, especially in developing countries, requires the creation of new chemotherapeutic compounds. Benzothiazole derivatives have been investigated as antitubercular drugs against many enzymes necessary for the survival of Mycobacterium tuberculosis, including enoyl-ACP reductase (InhA), DNA gyrase, and Arabinosyl transferases involved in cell wall biosynthesis. Some benzothiazole-isoniazid hybrids were found to exhibit enhanced efficacy and lower toxicity than isoniazid alone. Conversely, antimalarial action of benzothiazoles is primarily due to their capacity to inhibit heme polymerization, falcipain proteases, and Plasmodium dihydrofolate reductase (DHFR). Substituted benzothiazole-quinoline and benzothiazole-pyrimidine hybrids have shown nanomolar-range IC50 values against Plasmodium falciparum strains, including chloroquine-resistant parasites. Dual-acting molecules provide a platform for developing combination therapies or single molecules with several target actions, essential in curtailing resistance emergence and improving treatment effectiveness. [34]

4. Recent Developments and Patents on Benzothiazole-Based Medicines

The past two decades have seen a phenomenal growth in the synthesis of benzothiazole-based compounds due to their vast range of biological activities and their easy synthetic adaptability. The ongoing progress in medicinal chemistry and computational drug design has made it possible for scientists to fine-tune the structure of benzothiazole derivatives to optimize pharmacodynamic and pharmacokinetic profiles. [35] Evidence for this increasing interest comes not just from the rising number of research publications but also from the considerable number of patents filed and issued worldwide on benzothiazole-derived drugs. All these advances include new synthetic pathways, new pharmacophores, drug delivery systems targeting, hybrid molecules, and theranostic agents. They all highlight the importance of benzothiazole as a privileged scaffold in drug discovery and development. Structurally, current research has also been aimed at the development of benzothiazole hybrids by marrying the core scaffold with other bioactive moieties like quinolines, triazoles, thiazolidinones, pyrazoles, and coumarins. [36] These hybrid compounds are usually synthesized via multicomponent reactions (MCRs), microwave-assisted reactions, and green chemistry methods, which enable quicker and more environmentally friendly synthesis. These approaches improve the multi-targeting activity of benzothiazole derivatives, which is very useful in the case of highly complicated diseases such as cancer, neurodegeneration, and multidrug-resistant infections. For instance, benzothiazole-quinoline hybrids have been patented as effective antimalarial agents because they inhibit Plasmodium enzymes and heme polymerization in a dual manner. Likewise, benzothiazole-triazole conjugates have been found to be beneficial as anticancer agents against tubulin polymerization and topoisomerases, and these have reached preclinical trials. [37] One of the

most effective developments has been in the field of anticancer benzothiazole derivatives, where various compounds have been found to exhibit very high selectivity in cytotoxicity against cancer cells without affecting normal tissues. An example is Phortress (NSC 710305), a prodrug that is metabolized by cytochrome P450 enzymes, specifically CYP1A1 and CYP1B1, overexpressed in some tumor cells. When metabolically activated, Phortress yields a reactive electrophilic species that is DNA-binding and apoptotic. Its mechanism of selective tumor activation has been of interest to drug companies and has resulted in a number of patents dealing with its structure, analogs, formulations, and therapeutic combinations. In addition, the construction of benzothiazole-based fluorescent probes to image cancer and monitor drug delivery has provided new opportunities for theranostic use, in which therapy and diagnosis are combined into one platform. In the field of infectious diseases, recent patents outline benzothiazole derivatives as potent antibacterial, antifungal, and antitubercular agents. Both mono-therapeutic molecules and combination therapies are addressed in these patents. For instance, US and European patents were issued for benzothiazole derivatives of β-lactamase inhibitors to revive the activity of β-lactam antibiotics against resistant bacterial isolates. Patents include benzothiazole-sulfonamide hybrids as InhA enzyme inhibitors of Mycobacterium tuberculosis. The concept of dual-action benzothiazoles, acting on both bacterial membranes and vital metabolic enzymes, has picked up pace in recent decades, especially for infection treatment where resistance has made traditional antibiotics useless. [38]

In the field of central nervous system (CNS) disorders, great progress has been achieved in the synthesis of benzothiazole derivatives for neuroprotective and anticonvulsant purposes. Various patents have been issued for compounds that act on GABA receptors, sodium channels, and also monoamine oxidase (MAO) inhibition. Some such patented series of compounds are benzothiazole riluzole analogs, which possess increased blood-brain barrier permeability, decreased neurotoxicity, and extended activity in epilepsy and ALS models. Moreover, benzothiazole dyes such as Thioflavin T and their analogs have been redesigned to not only bind amyloid but also inhibit amyloid assembly, for which patents exist for their application in the diagnosis and therapy of Alzheimer's. [39] Another significant advance is the use of benzothiazole moieties in nanocarriers and targeted delivery systems. Benzothiazole-functionalized liposomes, dendrimers, and polymeric nanoparticles have demonstrated enhanced drug loading efficiency, controlled release, and target-oriented accumulation in the tumor tissue using patents from Bennett et al. These systems frequently utilize the pH-sensitive or redox-sensitive properties of benzothiazole derivatives to control the release of the drug in pathological tissue. For example, benzothiazole-bearing micelles have been patented for targeted delivery of anticancer drugs such as doxorubicin and paclitaxel with enhanced efficacy to the tumor site, decreasing systemic toxicity and enhancing therapeutic benefits. [40]

Benzothiazole derivatives are being patented more and more in the area of diagnostics as fluorescent imaging probes, notably for identifying amyloid plaques, nucleic acids, and cancer biomarkers. Electron-donating group-

functionalized derivatives exhibit strong fluorescence and strong binding to misfolded proteins as well as nucleic acids. They have been patented for applications in imaging technologies such as PET, MRI, and fluorescence microscopy. These dual-utility molecules not only improve the detection of disease but also provide real-time measures of therapeutic response. Patent applications have also been centered on green and scalable syntheses for benzothiazole derivatives. Microwave reactions, solvent-free conditions, and enzyme catalysis have been patented for synthesizing complex benzothiazole skeletons rapidly and sustainably. This is especially critical in the pharmaceutical sector, where scalability, reproducibility, and sustainability are key for regulatory approval and commercial success. [41]

Regulatory and commercial considerations aside, the international intellectual property (IP) scene mirrors increasing industrial demand for benzothiazole chemistry. patents have been sought in the United States, Europe, Japan, and India, with big shot applicants being pharmaceutical giants like Pfizer, Roche, Sanofi, and a number of biotech startups. These patents not only protect novel molecular entities (NMEs) but also include derivatives, intermediates, synthetic routes, dosage forms, and therapeutic combinations. Numerous benzothiazole compounds are in early-stage clinical trials for uses that span cancer and Alzheimer's through drug-resistant infections and epilepsy, rendering this class a highly active translational research and pharmaceutical investment focus. Recent patenting and breakthroughs involving benzothiazole derivatives are a testament to their pivotal position in discovering novel therapeutic drugs. [42] The tunability, flexibility, and biological compatibility of the scaffold induce ongoing synthesis of multifunctional drugs that address the current issues of selectivity, efficacy, and safety. As computational modelling, high-throughput screening, and bioinformatics tools continue to advance, it is anticipated that the next generation of benzothiazole derivatives will provide even higher promise in both monotherapy and combination therapy scenarios. Further, interdisciplinary incorporation of benzothiazole chemistry with nanotechnology, imaging sciences, and personalized medicine is poised to propel the future of this class towards a new age of smart therapeutics and diagnostic systems. [43]

5. Conclusion

Benzothiazole has solidified itself as a privileged and highly versatile scaffold in medicinal chemistry. The widespread structural diversity of the benzothiazole nucleus—owing to its distinct electronic arrangement, planarity, and heteroatom presence—makes it possible to engage with various biological targets such as enzymes, receptors, and nucleic acids. During the last three decades, there has been enormous advancement in the synthesis and design of benzothiazole derivatives possessing robust and variant biological activities like antimicrobial, anticancer, anti-inflammatory, antioxidant, anticonvulsant, antiviral, antitubercular, and antimalarial activities. Such pharmacological activity, coupled with support from structure-activity relationship (SAR) studies, computational modeling, and in vitro/in vivo biological assays, has highlighted the huge therapeutic potential of this skeleton. Recent studies have been directed not only towards the development of

enhanced bioactivity and selectivity of benzothiazole derivatives but also towards rational design of improved pharmacokinetic and safety profiles. Hybridization with additional bioactive fragments, creation of multi-target directed ligands (MTDLs), and incorporation into nanocarrier systems have broadened the clinical utility of benzothiazoles. Even with their promising biological properties and supportive preclinical results, low water solubility, metabolic instability, and less-than-optimal in vivo activity continue to restrict the full clinical utility of most benzothiazole compounds. However, the recent increase in patent submissions, successful exploration of commercialized drugs such as Riluzole and Ethoxzolamide, and progression of new benzothiazole derivatives such as Phortress to clinical trials reflect the ongoing importance of this scaffold in drug discovery. Additionally, the fusion of benzothiazole chemistry with contemporary tools such as molecular docking, QSAR, high-throughput screening, and green chemistry synthesis protocols guarantees future drugs from benzothiazoles to be more effective, target-specific, and ecologically sound. In summary, benzothiazole is a precious chemical compound for medicinal chemists and pharmaceutical researchers. Its ongoing discovery has great potential for tackling urgent healthcare problems such as antimicrobial resistance, cancer, neurological diseases, and parasitic infections. With combined interdisciplinary strategies and emphasis on clinical translation, benzothiazole derivatives stand to be at the center of the next generation of therapeutic advances.

Submission declaration:

This manuscript has not been published previously and is not being considered for publication elsewhere. The authors confirm that the work is original, and all authors have read and approved the final manuscript for submission.

Declaration of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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