Review Article

Recent Advances in Medicinal Chemistry with Benzothiazole-Based Compounds: An *In-Depth* Review

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ABSTRACT

Among the many natural ingredients and pharmacological drugs that contain heterocyclic compounds, benzothiazole (BTA), and its derivatives stand out as particularly significant. BTA analogs provide a great deal of structural diversity, which has been helpful in the quest for new therapeutic drugs, and BTA itself displays a variety of pharmacological features. Because each BTA derivative has its own unique set of pharmacological effects, it is clear that this class of chemicals is intriguing. Medicinal chemistry based on BTAs is a hot subject right now, with lots of new research and discoveries happening in the field. In particular, there are a plethora of BTA-based compounds that have found widespread clinical use as highly effective medications for a wide range of disorders. Current developments of BTA-based compounds in medicinal chemistry as anticancer, antibacterial, antifungal, anti-inflammatory, analgesic, anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, antileishmanial, antihistaminic, antimalarial, and other medicinal agents are presented in this work systematically and thoroughly. More effective diagnostic agents, pathologic probes, and BTA-based medications that are both active and less toxic, can be rationally designed, according to the authors of this review study.

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Content

1. Introduction

Heterocyclic compounds represent the largest and most diverse category within the realm of organic compounds [1-5]. The current knowledge base encompasses an extensive array of these compounds, and their numbers continue to grow rapidly owing to prolific synthetic research and expanding synthetic applications. The ubiquity of heterocyclic compounds extends their influence across various scientific domains, including medicinal chemistry, biochemistry, and numerous other scientific disciplines. This review aims to comprehensively explore the recently synthesized or naturally extracted biologically active heterocyclic compounds, which span a spectrum of applications such as antifungal, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, antiallergic, herbicidal, and anticancer agents. The ever-growing repertoire of heterocyclic compounds and their diverse functionalities underscore their significance and potential contributions

across a multitude of scientific and therapeutic endeavors.

Biologically active heterocyclic compounds form an expansive and noteworthy category of molecules, appealing to a wide range of medicinal chemists because of the diverse pharmacological effects they exhibit [6]. This review delves into the current landscape of research on these compounds, highlighting their diverse structural compositions, mechanisms of action, and potential therapeutic applications.

Molecules with at least one heteroatom are called heterocyclic compounds, typically nitrogen, oxygen, or sulfur, although other heteroatoms are also prevalent, and are distinguished from carbocyclic compounds, which consist solely of carbon atoms forming a ring structure. This class of compounds holds a crucial status among organic compounds, finding widespread application in various biological fields due to their efficacy across a spectrum of illnesses. Fundamental biological molecules, including DNA, RNA, chlorophyll, hemoglobin, vitamins, and others, incorporate heterocyclic rings as integral components of their structure. The extensive utility of heterocyclic compounds extends to medicinal applications, where they play pivotal roles in the treatment of common diseases.

In numerous medical conditions, heterocyclic compounds exhibit notable therapeutic effects. Some examples of these compounds include triazine derivatives with anti-inflammatory, urinary antiseptic, and antibacterial properties. Antimicrobial, antifungal, antiviral, and anthelmintic activities are only a few of the many biological functions shown by benzimidazole derivatives [7-18].

An increasingly important area of study, medicinal chemistry bridges the gap between the chemical and medical sciences. The process has its roots in the first attempts to extract useful chemicals from many sources, including the tissues of plants and animals, microbes, and the byproducts of their fermentation. By bringing together traditional areas of chemistry (especially organic chemistry), biology, and even some physics, this multidisciplinary discipline investigates common ailments and their treatments.

The literature review underscores the significant role that heterocyclic compounds occupy in medicinal chemistry. Their diverse applications, ranging from antimicrobial activities to therapeutic interventions for various diseases, highlight the paramount importance of continued research and exploration within this field. The incessant discovery of novel heterocyclic compounds and their potential in addressing medical challenges positions them as essential players in advancing healthcare solutions.

In medical chemistry, heterocycles are crucial, because they are present in many biomolecules, including enzymes, vitamins, natural products, and biologically active chemicals. These chemicals have a wide range of pharmacological effects, including those against fungal infections, inflammation, bacteria, antioxidants, seizures, allergies, herbicides, HIV, diabetes, cancer, and insects. The wide-ranging presence of heterocycles in both medicinal and biological contexts underscores their significance as versatile and impactful components within the field of chemistry and life sciences.

2. Structural Diversity

Heterocyclic compounds, recognized by the presence of at least one non-carbon atom (typically nitrogen, oxygen, or sulfur) within the ring structure, showcase an impressive array of structural diversity. This diversity facilitates a wide spectrum of interactions with biological macromolecules, including proteins and nucleic acids. Common heterocyclic rings encompass pyridines, pyrimidines, imidazoles, thiazoles, and oxazoles, among others.

2.1 Pharmacological activities

The pharmacological activities of biologically active heterocyclic compounds span a broad spectrum, encompassing antimicrobial, anticancer, anti-inflammatory, antiviral, and antiparasitic effects. The presence of heteroatoms within the ring structure often contributes to specific biological interactions, rendering these compounds appealing candidates for drug development.

2.1.1 Antimicrobial activity

Heterocyclic compounds showcase potent antimicrobial properties against bacteria, fungi, and viruses. Examples such as quinolones, imidazoles, and triazoles have found practical applications in treating various infectious diseases. Antifungal medications, also known as substances or drugs, are employed to combat fungal infections, particularly those commonly found on the skin, hair, and nails. Among the prevalent fungal infections are conditions like ringworm and athlete's foot. The mechanism of action of antifungal medicines involves two primary approaches. Initially, these medications may induce cell death in fungal cells by interfering with the substances present in the cell membrane, resulting in the leakage of cell components. Secondly, antifungal drugs can impede the growth and reproduction of fungal cells.

2.1.2 Anticancer activity

Numerous heterocyclic compounds exhibit remarkable anticancer activities by disrupting cellular processes like DNA replication and repair. Compounds like purines, pyrimidines, and indoles have demonstrated promise as potential anticancer agents.

2.1.3 Anti-inflammatory and analgesic activity

Specific heterocyclic compounds, especially those incorporating nitrogen or sulfur in their ring structures, manifest anti-inflammatory and analgesic properties. These compounds often act by modulating enzymes involved in inflammatory pathways.

2.2 Mode of action

Comprehending the mode of action of biologically active heterocyclic compounds is crucial for their rational design and optimization. Many of these compounds target specific biomolecules such as enzymes, receptors, or nucleic acids, thereby modulating cellular processes. Notably, kinase inhibitors with heterocyclic cores have emerged as a prominent class of drugs for treating various diseases, including cancer.

2.3 Therapeutic potential

The therapeutic potential of biologically active heterocyclic compounds spans a diverse range of medical conditions. Their versatility enables the design of compounds with specific target selectivity, thereby reducing side effects and enhancing therapeutic efficacy. Ongoing research aims to explore new heterocyclic scaffolds and optimize existing ones to improve drug candidates.

Biologically active heterocyclic compounds represent a dynamic and promising field in medicinal chemistry. Their structural diversity, coupled with a broad spectrum of pharmacological activities, positions them as crucial players in drug discovery and development. The ongoing research efforts in this field hold the promise of uncovering novel therapeutic agents for various medical conditions, ultimately contributing to advancements in healthcare.

3. Benzothiazole

A wide variety of natural goods and pharmacological medications contain benzothiazole or one of its derivatives, making it a very important heterocyclic molecule. In example, benzothiazole displays a broad range of pharmacological effects, and the structural diversity produced by its analogs is a boon to the search for new therapeutic medicines. The extensive range of pharmacological activities displayed by individual benzothiazole derivatives underscores the unquestionable interest in this compound series. Benzothiazole medicinal chemistry is a dynamic and ever-evolving discipline thanks to the continuous study and improvements in the industry.

Notably, numerous benzothiazole-based compounds have transitioned from research endeavors to practical applications, being extensively utilized as clinical drugs with high therapeutic efficacy across various disease types. The present advancements of benzothiazole-based molecules within the vast domain of medicinal chemistry are thoroughly examined in this comprehensive review. Analgesic, anti-inflammatory, anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, antileishmanial, antihistaminic,

antimalarial, and other therapeutic agent activities are being investigated for these compounds.

This review aims to provide a thorough overview, offering valuable insights into the diverse applications of benzothiazole-based compounds in medicinal chemistry. By encapsulating their multifaceted roles and therapeutic potentials, it is anticipated that this study will stimulate novel ideas for the rational design of more potent and less toxic benzothiazole-based drugs. In addition, it aspires to contribute to the development of more effective diagnostic agents and pathological probes, thereby fostering advancements in the field of medicinal research.

4. Current Developments of Benzothiazole-Based Molecules in Medicinal Chemistry

An emerging issue in medicinal chemistry, the idea of favored structures has recently come to light as a successful technique for novel drug discovery. For the purpose of designing and synthesizing targeted compounds efficiently and within appropriate time periods, benzothiazoles (BTAs) are attractive sources of core scaffolds and capping fragments due to their innate affinity for distinct biological receptors. This unique family of compounds with named structures can bind to several receptors with great affinity. Medicinal chemists can use these molecules to their advantage to find physiologically active drugs quickly and consistently across many therapeutic domains [19-26].

Both in the life sciences and in many industrial domains related to fine and special chemistry, heterocycles containing nitrogen and sulfur are indispensable. In this study, we find BTAs, a class of medicinal chemicals with a wide range of biological effects. With its entire planarity, the BTA ring system is defined as the fusion of a benzene ring to the 4,5-positions of a thiazole ring (Figure 1). Sulfur is at the head of the pack when it comes to the numerical order of the BTA ring locations.

While BTAs are not frequently encountered in marine or terrestrial natural compounds, they are integral components of structures such as firefly luciferin and contribute to the aroma of tea leaves and cranberries. Furthermore, fungi like *Aspergillus clavatus* and *Polyporus frondosus* produce BTAs as flavor compounds. Anticancer, antimicrobial, anticonvulsant, antiviral, antitubercular, antimalarial, analgesic, anti-inflammatory, antidiabetic, and fungicidal properties are just a few of the many biological activities that have kept BTA derivatives in the spotlight. Benzothiazole derivatives have recently been investigated for their possible use as tools in neurodegenerative disease diagnostics, as inhibitors of stearoyl-coenzyme A desaturase and orexin and LTD4 receptors, as well as histamine H2 antagonists, appetite suppressants, and selective fatty acid amide hydrolase inhibitors. Furthermore, they serve as precursors for dyes [18], play a role in plant protection [27], function as imaging agents for β-amyloid plaques [28], and act as sensitizers in photography [29].

As heterocyclic compounds, derivatives of benzothiazole (BTA) find application across diverse realms of chemical research, including polymer chemistry [30,31], dye synthesis [32,33], and pharmaceuticals [34]. As sensitizing dyes, BTA salts have a history of usage in silver photography [35].

As shown in Figure 2 [36], a substantial group of xenobiotics created worldwide for a variety of uses consists of 2-substituted BTA derivatives, which are a notable subset of this family. Benzothiazole is the most basic compound in this class, and it kills fungus [37].

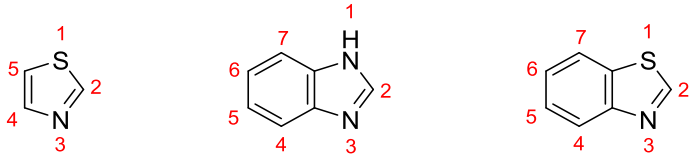

Figure 1. Structures of thiazole, benzo[*d*]imidazole, and benzo[*d*]thiazole

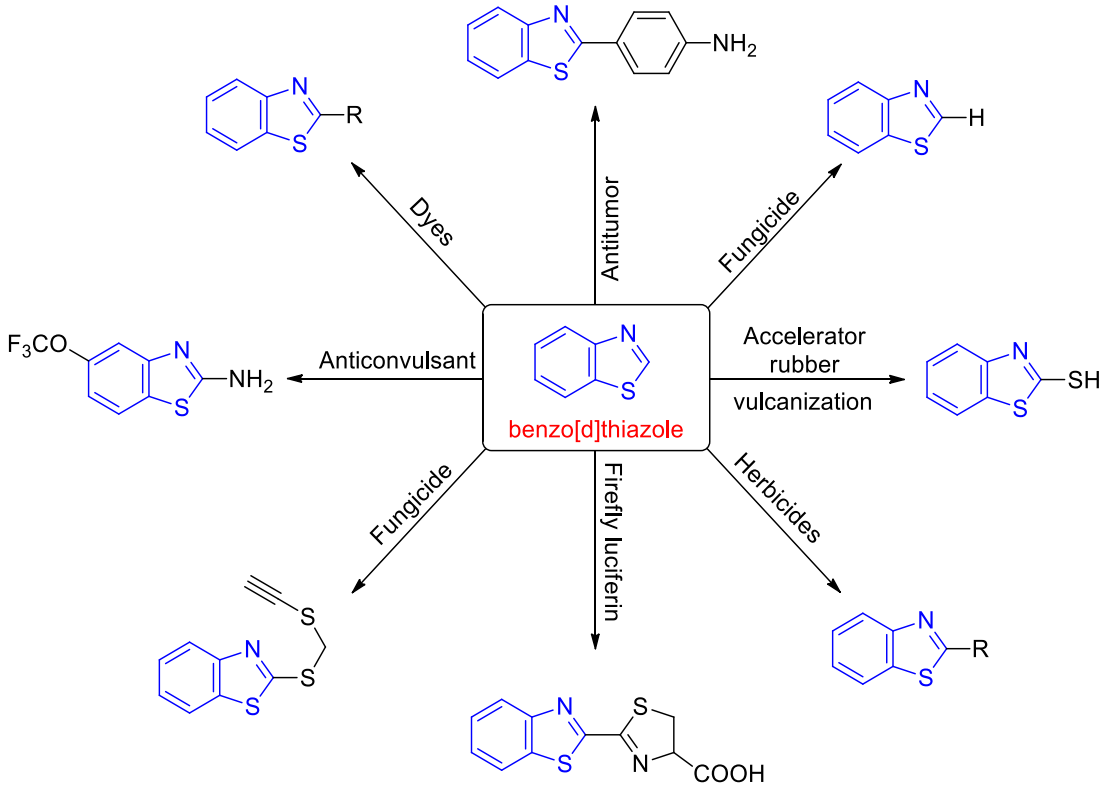

Figure 2. Benzothiazole, a multifunctional nucleus

Different chemicals with unique uses belong to the class of 2-substituted BTA derivatives. As an active component in commercially marketed formulae such as Tribunal and Ormet, methabenzthiazuron (MBTU) operates as a herbicide in winter corn crops [38]. The pulp and paper sector also uses it as a slimicide [39]. The production of several dispersed azo dyes involves 2-aminobenzothiazole [40]. Rhone-Poulenc (Rilutek) sells the anti-ALS medication riluzole (2-amino-6-trifluoromethoxybenzothiazole) [40], and 2-(4-aminophenyl)benzothiazole has anticancer effects [41]. An elastic and flexible cross-linked material can be produced by using BTA derivatives to catalyze the development of sulfide links (reticulation) between unsaturated elastomeric polymers. Rubber accelerator 2-Mercaptobenzothiazole (MBT/BTSH) is used in the production of tires and other specialized goods [42].

The BTA ring system is considered a special structure because of the wide variety of biological consequences linked to it. Although there are publications that focus on the BTA nucleus's anti-inflammatory and antitumor properties, there are also reports that include all of the activities related to the benzothiazole nucleus [43]. However, there has been no published thorough report on the different activities of compounds based on BTA. Besides expanding the scope of biological activity and structure-activity relationship (SAR) research, the principal goals of BTA syntheses include the synthesis of more varied and complex bioactive chemicals for use in other applications, like dye manufacturing. Therefore, both synthetic organic chemists and biologists are becoming more interested in the synthesis of BTA derivatives [44].

Numerous synthetic approaches have been adopted and recorded for 2-substituted benzothiazole (BTA), which was initially synthesized in 1887 by A. W. Hofmann, due to its varied action and uncomplicated cyclization mechanism [45]. Conventional approaches to build the BTA structure include 2-aminothiophenol condensation reactions with a variety of substrates, such as esters, carboxylic acids [45], substituted nitriles, or aldehydes [46]. Nevertheless, there are obstacles to this method, especially when it comes to creating 2-

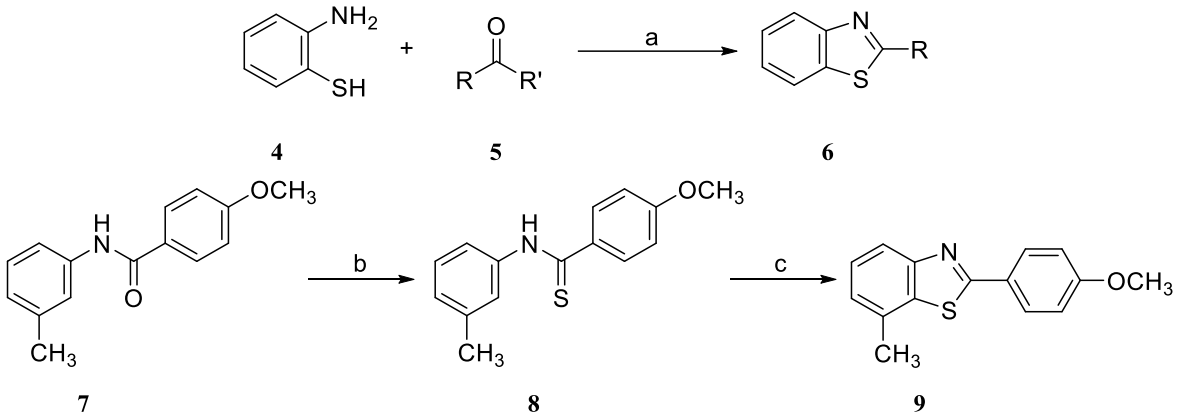

Figure 3. General approach for the synthesis of benzothiazole; Where, R´ = Aldehyde, orthoester, acid, nitrile, imidate, lactone, or anhydride groups. Reagents **(a)** Strong acids/ oxidative reagents/ milder reagents/ other catalysts; Reagent (b) LR, C_6H_5Cl, Reflux, 65% c) NaOH, $K_3Fe(CN)_6$

aminothiophenols with substituents that are easily oxidizable. The thiobenzanilide (**7**) cyclization by Jacobson is another famous route for BTA production [47,48]. Other broad approaches include condensation of 2-aminothiophenol and aromatic aldehydes using different conditions [49,50].

Preparation of BTA derivatives has been successfully accomplished by a number of catalysts, as shown in Figure 3. These include (pmIm)Br [51], I_2 [52], $ZrOCl_2.8H_2O$ [53], TMSCl [54], H_2O [55], PCC [56], CAN [57], nanoceria (CeO_2) [58], cyanide [59], boron trifluoride etherate [60], mesoporous CdS nanospheres [61], silica-supported nano-copper(II) oxide [62], and many more.

5. Pharmacological Effects of the Benzothiazole Analogues

Because of its widespread use in therapeutic medication, benzothiazole (BTA) and its analogues are highly esteemed pharmacophores and structures in medicinal chemistry. In light of this significance, the present review offers a thorough examination of the current advancements in medicinal chemistry centered around benzothiazole, encompassing discussions on strategies and structure-activity relationships (SAR).

5.1 BTA as an antimicrobial agent

The pursuit of enhanced treatment options through the discovery and development of novel antimicrobial drugs has been a primary objective for scientists. In recent decades, the escalating prevalence of multi-drug-resistant microorganisms has become a critical global concern. The pressing need to tackle this worldwide problem is highlighted by the fact that numerous clinically important bacterial species have developed resistance to multiple antimicrobial treatments, such as β-lactam antibiotics, macrolides, quinolones, and vancomycin. A class of chemicals known as benzothiazole (BTA) derivatives continue to be very powerful against microorganisms, even though there have been many attempts to develop new structural models for better antimicrobials. Consequently, they serve as valuable substructures for further exploration in molecular studies.

Numerous studies have demonstrated the significant potential of BTA derivatives as antimicrobial agents. For example, Soni *et al.* synthesized Schiff bases of BTA-triazole conjugates, and exhibited noteworthy antibacterial and antifungal activities. Sulfonamide-containing BTAs, evaluated *in vitro*, displayed good antimicrobial properties. In addition, BTA-pyrimidine derivatives, BTA-thiazolidin-4-one derivatives, and BTA-quinoline compounds have shown promising results in inhibiting the growth of various bacterial and fungal strains.

The synthesized BTA derivatives encompass diverse structural modifications to enhance their antimicrobial activity. For example, it has been demonstrated that the antibacterial and antifungal activity can be enhanced by inserting

electron-withdrawing groups like fluorine, chlorine, and nitro at certain places on the BTA ring. Furthermore, studies exploring hybrid molecules incorporating BTA with different pharmacophores have revealed potent antimicrobial and antifungal activities.

The research efforts in this field underscore the ongoing quest for effective antimicrobial agents and the potential of BTA derivatives to contribute significantly to this endeavor. The structures of various BTA derivatives (compounds **10**, **11**, and **12**) with antimicrobial properties are illustrated in Figure 4.

5.2 BTA as anticancer agents

On a global scale, cancer is a major concern since it is the second biggest killer, after heart disorders [63]. It stands as a severe threat to human health, attracting considerable attention worldwide. Research efforts have been extensive in developing effective anti-cancer therapeutics, using a mix of chemotherapy, radiation treatment, and surgical procedures. To increase the sensitivity of tumor cells to lethal medications, researchers have been concentrating on finding new tumor-specific therapies that are less likely to cross-resist and limit cancer cell migration selectively.

Researchers have probed into many different areas of cancer biology in their quest to find medications with these kinds of effects. Many efforts have been made to alter the BTA nucleus in order to increase its anticancer properties, as BTA derivatives have recently become a center of attention in this field of study. These changes have produced numerous molecules with various pharmacological properties. Mainly, in the 60 human cancer cell lines screened by the National Cancer Institute (NCI) [64], imidazobenzothiazoles, polymerized BTAs, and other substituted BTAs like 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX610 or compound **13**) (Figure 5) showed potent and selective antitumor effects *in vitro*. These cell lines include colon, non-small cell

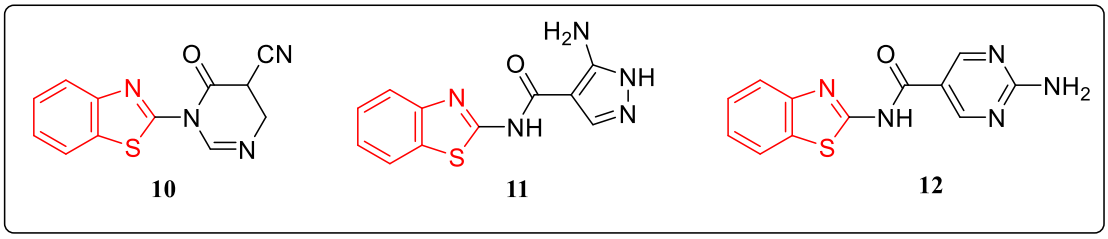

Figure 4. Benzothiazole as an antimicrobial agent

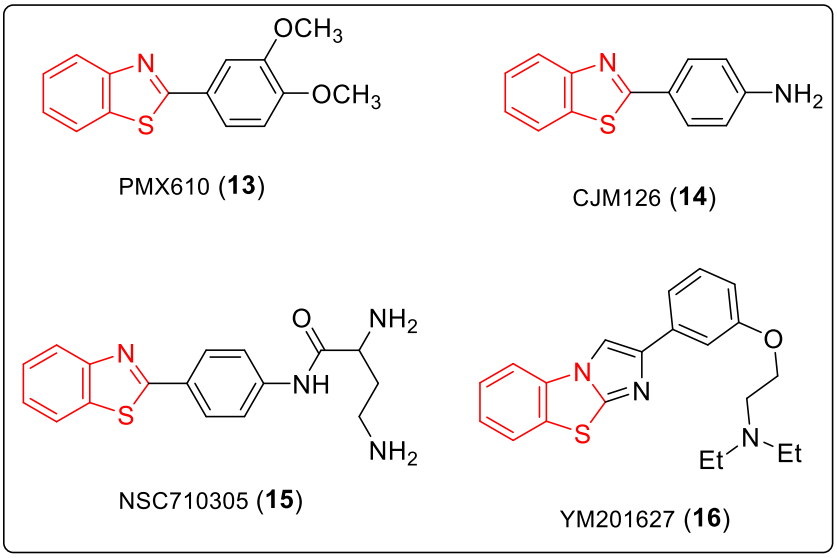

Figure 5. Some chemotherapy drugs based on benzothiazole used in clinical trials

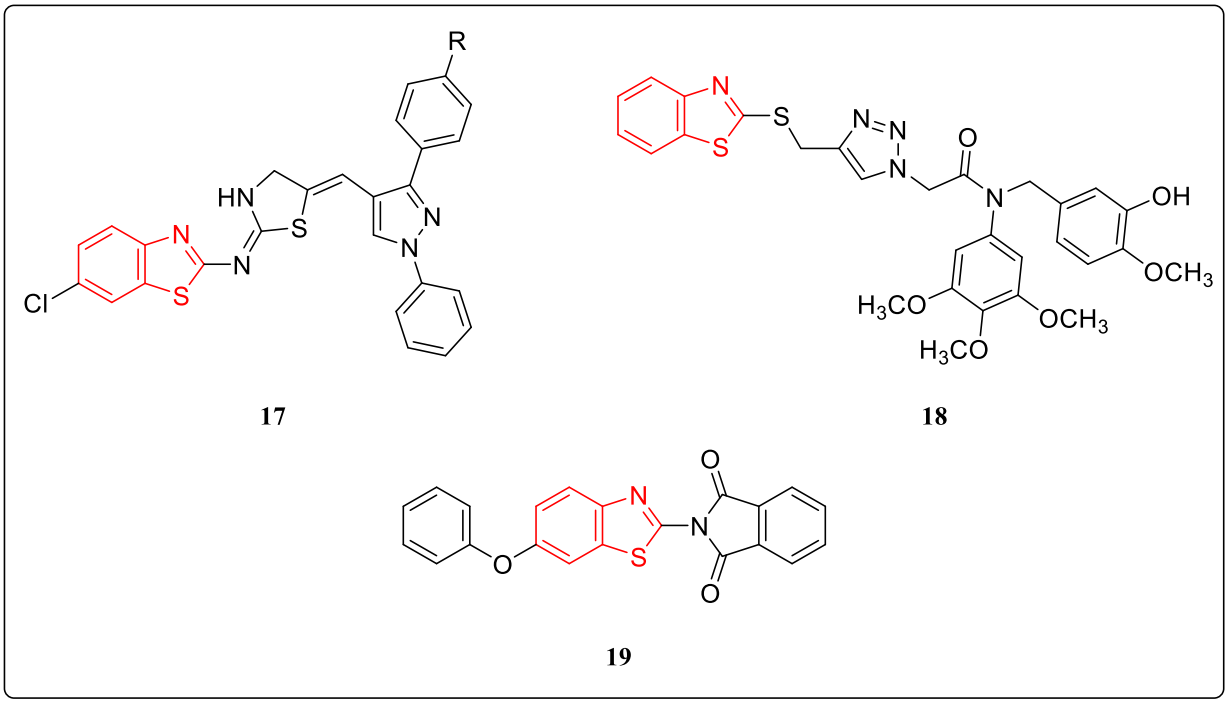

Figure 6. Developed as anticancer drugs

lung, and breast subpanels. When tested on cancer cell lines, they showed impressive anticancer activity as well [65]. 2-(4-Aminophenyl)-BTA (CJM126) (compound **14**) and its analogues constitute a new family of anticancer medicines with a mechanistic approach [66,67]. In addition, there has been an ongoing push to create novel BTA-based anticancer drugs that target specific enzymes or receptors like topoisomerases, microtubules, cytochrome P450, RAF kinases, farnesyltransferase, DNA, and transforming growth factor-b. Figure 6 shows that these molecules **17**, **18**, and **19** have a lot of hopes as anticancer medications that could circumvent the many problems with existing clinical medicines.

5.3 BTA as an anti-inflammatory and analgesic agent

As an offensive mechanism, inflammation triggers changes in the body's physiology that reduce tissue damage and get rid of harmful infections. The process is a complicated series of cellular and modular events that include dilatation of arterioles, venules, and capillaries; increased permeability of blood vessels; exudation of plasma protein-containing fluids; and migration of white blood cells into the area of inflammation. However, conditions including psoriasis, multiple sclerosis, retinitis, inflammatory bowel illnesses, osteoarthritis, rheumatoid arthritis, and atherosclerosis are brought on by chronic inflammation, which significantly increases the risk of morbidity and mortality [68].

There are a number of approaches to the research and development of novel NSAIDs [69]. BTA compounds have shown promise as analgesics and anti-inflammatory agents. An example would be the remarkable anti-inflammatory and analgesic effects of BTA conjugated with spiroindoline, which were produced by Kumar *et al.* [70]. At 100 mg/kg, the 5-chloroindolylbenzothiazole derivative [70] inhibited edema by 72.2% and was the most effective anti-inflammatory agent, while the 7-chloroindolylbenzothiazole derivative was the most effective analgesic agent, with a percentage of 69.2%. Research into the structure-activity relationship (SAR) has shown that the oxadiazole ring and bromo substituents increase the anti-inflammatory and analgesic effects [70].

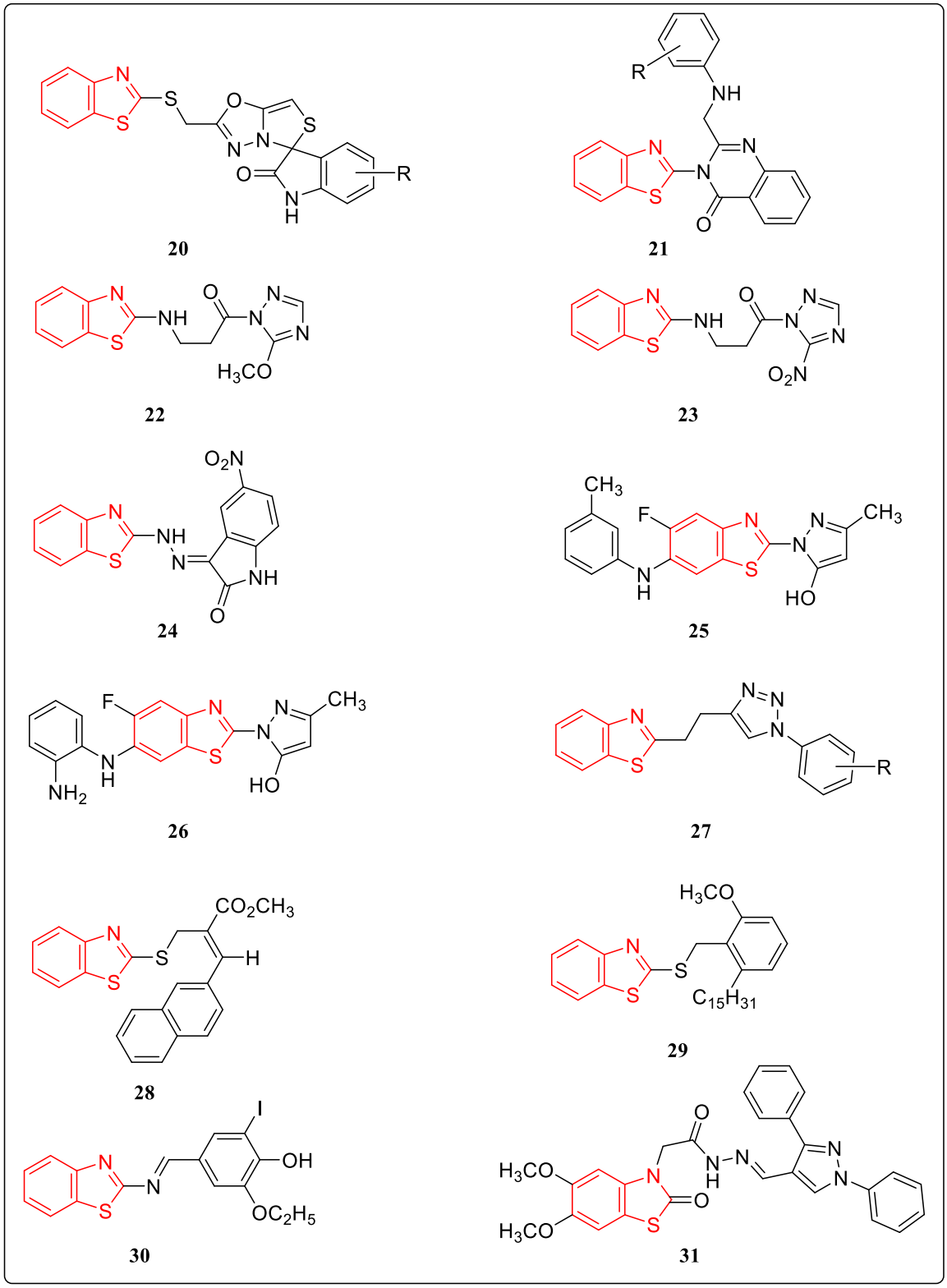

Figure 7. The anti-inflammatory and analgesic properties of benzothiazole

Compounds **20** and **21** conjugated with quinazolines-BTA showed a substantial decrease in edema volume, and the compounds as a whole showed good anti-inflammatory activity. The analgesic and anti-inflammatory properties of compounds **22** and **23** were so

impressive that they outperformed conventional medications like aspirin and naproxen. These compounds were derived from BTA and were synthesized using Mannich bases. The presence of electron-releasing groups, such as OCH_3 on C6 of the BTA ring and C5 of the triazole ring, in compounds has been found to have beneficial effects on inflammation and pain [71].

The anti-inflammatory action was good for the BTA-isatin conjugate molecule **24** and the 6-fluorobenzothiazole-pyrazole conjugated moiety (compounds **25** and **26**). Click-synthesized bis-heterocycles containing 2-mercaptobenzothiazole and 1,2,3-triazoles exhibited anti-inflammatory solid effects, with compound **27** showing potent selective inhibition of COX-2. Compound **28** showed anti-inflammatory action at micromolar doses when the thio-substituted BTA analogs were used as COX-2 inhibitors [72,73]. Alkoxy-BTA derivatives, such as compound **29**, showed high selectivity towards COX-2 inhibition [74]. Benzothiazolyl Schiff bases, including compound **30**, exhibited anti-inflammatory activity *in vivo*, while BTA bearing different heterocycles, for example, Schiff's base of BTA with diphenyl pyrazole nucleus (compound **31**), shown anti-inflammatory and antinociceptive effects simultaneously [75,76]. In Figure 7, the structures of BTA are shown as agents that can reduce inflammation and pain.

5.4 BTA as anti-HIV agents

In the contemporary period, acquired HIV (human immunodeficiency virus) stands as a formidable disorder, and a completely successful chemotherapy for its treatment remains elusive. More than 20 antiretroviral medications are currently available for the treatment of HIV infection, and many of these agents work by blocking enzymes that are essential to the virus's life cycle [77]. The current treatment for HIV-1, the virus that causes AIDS, includes six types of drugs: PIs, NRTIs/NtRTIs, NNRTIs, PIs/NtRTIs, PIs/NRTIs, FIs/CRIs, and INIs, which are designed to block cell entry [78]. Unfortunately, owing to side effects and the rise of drug-resistant virus strains, the current medications on the market only provide temporary or limited clinical advantages [79]. As a result, researchers are presently concentrating on finding new anti-HIV drugs that have different structures and different ways of working.

The integration of benzothiazoles (BTAs), which are crucial pharmacologic heterocyclic nuclei, into various heterocyclic templates has demonstrated strong anti-HIV action. Some of the compounds synthesized by Nagarajan *et al.* (series of compound **32** shown in Figure 8) showed strong anti-HIV effects, and they claimed that these BTA sulfonamides inhibited HIV-1. An improvement in the inhibitors' potency and antiviral activity was observed when the t-butyl urea moiety was replaced with benzothiazole sulfonamide [80]. Delmas *et al.* conducted in vitro assessments of antileishmanial and anti-HIV properties after preparing several BTA-acridinone derivatives. The addition of a 6-amino BTA group to the 2-amino chain or a 6-nitro BTA group to the 4-amino chain increased the antileishmanial activity, as demonstrated by two derivatives **33** and **34** that showed substantial selective antileishmanial activity [81]. Vicini *et al.* tested the antiviral efficacy of synthesized BTA-Schiff bases against HIV-1 in vitro. Among the benzo[d]isothiazole derivatives, compound **35** stood out for its antiproliferative action against skin melanoma and breast adenocarcinoma cells, in addition to inhibiting the proliferation of leukemia cell lines [82].

Anti-HIV activity was assessed by synthesizing BTA-coumarin conjugates. One of the

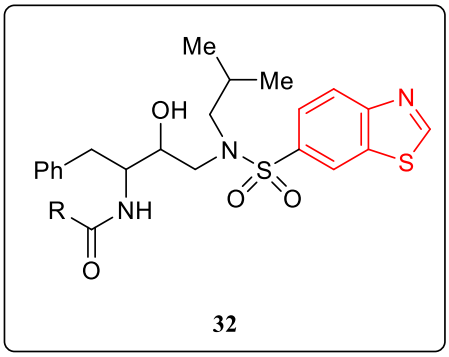

Figure 8. Benzothiazole as anti-HIV agent

compounds **36** were shown to have strong anti-HIV effects on HIV-1 cells that were in their wild-type form. According to structure-activity relationship (SAR) study, methyl substitution reduced biological potential, whereas OH substitution increased anti-HIV activity, which is influenced by hydrogen bonding [83].

Antiviral activity against HIV-1 strains was assessed by synthesizing BTA-piperazinyl derivatives. Compounds **37** and **38** demonstrated strong anti-HIV-1 and anti-HIV-2 activity, and SAR suggested that adding a vinyl group to the N1 position enhanced the selective anti-HIV activity [84,85].

The anti-HIV-1 RT inhibiting activity of synthetic BTA-thiazolidine derivatives was evaluated. With halogen substitution (Cl, F) at positions 4 or 6 of the benzyl ring of the BTA moiety exhibiting high inhibitory activity, halogen-substituted derivatives **39** and **40** emerged as the most active compounds [86]. **Figure 9** shows the structures of BTA that are anti-HIV agents.

5.5 BTA as antioxidant agents

Safeguarding health is one of the primary functions of antioxidant chemicals found in diet.

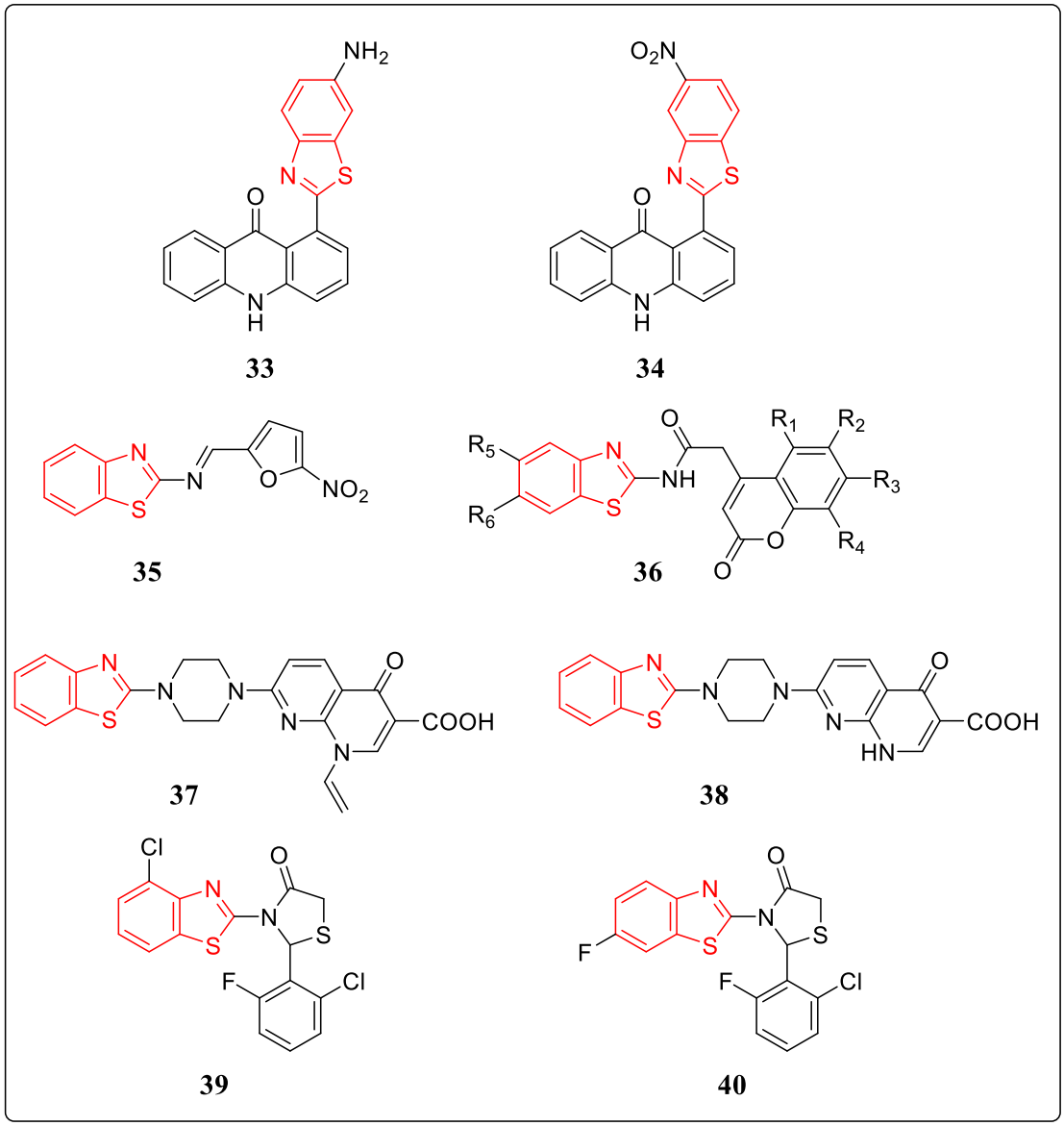

Figure 9. Benzothiazole as anti-HIV agents

Antioxidants, according to scientific research, can reduce the risk of chronic diseases like cancer and heart disease by effectively capturing free radicals. An abundance of oxygen species and highly reactive free radicals in biological systems pose a concern because they can damage DNA, lipids, proteins, or nucleic acids, which can lead to degenerative illnesses. Inhibiting oxidative processes that cause degenerative diseases, antioxidant chemicals such as polyphenols, flavonoids, and phenolic acids neutralize free radicals such as peroxides, hydroperoxides, and lipid peroxyls [87].

The synthesis and evaluation of antioxidant properties of spiro[benzothiazole-indol] conjugates were reported by Karali et al. In terms of antioxidant activity, compound **41** with methyl substitution was the most effective. When spiroindolinones had methyl or halogen groups substituted, their antioxidant capabilities improved; however, when trifluoromethoxy or nitro groups were substituted, the antioxidant activity was diminished [88]. Using the ferric reducing antioxidant power (FRAP) method, Tzanova and colleagues evaluated the in vitro antioxidant activity of a variety of 5-hydroxybenzoyl-benzothiazolone derivatives. With low cytotoxicity and the ability to inhibit reactive oxygen species formation by tert-butyl hydroperoxide (tBHP) in three cell lines, compound **42** showed 1.5 times greater antioxidant activity than Trolox [89]. Thiosulfonic acids containing amino BTA were characterized by Cressier and colleagues, who also tested their antioxidant properties by scavenging free radicals using DPPH or ABTS. Compound **43** in particular among the thiosulfonic acid compounds showed substantial antioxidant characteristics, almost 50% stronger than the gold standard medication WR-2721 [90].

The antioxidant properties of BTA-thiazolidinedione-2-acetamides were tested after their synthesis. Compound **44** showed promising properties in scavenging DPPH radicals, inhibiting lipid peroxidation, and stabilizing the membrane of erythrocytes. A further analogue, 6-methoxy-benzothiazole-2-amine (**45**), showed remarkable inhibitory efficacy against IL-1b. Chemicals that have nitro or methoxy groups attached to the BTA core show anti-inflammatory and antioxidant properties [91]. 2-Hydrazino BTA was prepared and tested for antioxidant properties by Suresh *et al.* The antioxidant activity of all the compounds was excellent, but compounds **46** & **47** exhibited the greatest percentage of free radical scavenging activity [92]. The antioxidant activity of bis-benzothiazole-pyrazoline derivatives was reported and assessed. When a phenyl ring with electron-donating characteristics (in compound **48**) was located at the fourth position, the antioxidant activity was amplified by the presence of a pyrazoline ring in conjunction with two BTA nuclei [93].

The DPPH and ABTS radical scavenging capabilities of coumarin-benzothiazoline derivatives were evaluated after their synthesis. The inclusion of eOH in the coumarin ring enhanced the free radical scavenging activity of the compound **49**, which demonstrated substantial scavenging activity overall [94]. The antioxidant activity of pyrazolyl-BTA derivative **50** was good, and the effects of compounds with trihydroxy substituents were particularly strong [95]. The antioxidant activity against DPPH, ABTS, and FRAP techniques was good when measured using the Mannich bases of the BTA-pyrazole compound **51** [96]. The molecule showed remarkable antioxidant capabilities when it was linked to the para position of the N-methylbenzenamine ring with an electron-withdrawing group [97].

Antioxidant and cytoprotective activities, such as DPPH radical scavenging and superoxide anion production inhibition, were investigated in BTA hydrazone derivatives. The compound **53** worked well at scavenging superoxide anion, while the catechol derivative **52** was most effective at DPPH radicals. Two intriguing compounds exhibited enhanced antioxidant activity due to the phenolic frame and *N*-methylbenzothiazole hydrazone moiety [98]. As antioxidant agents, BTA are shown in Figure 10 by their structures.

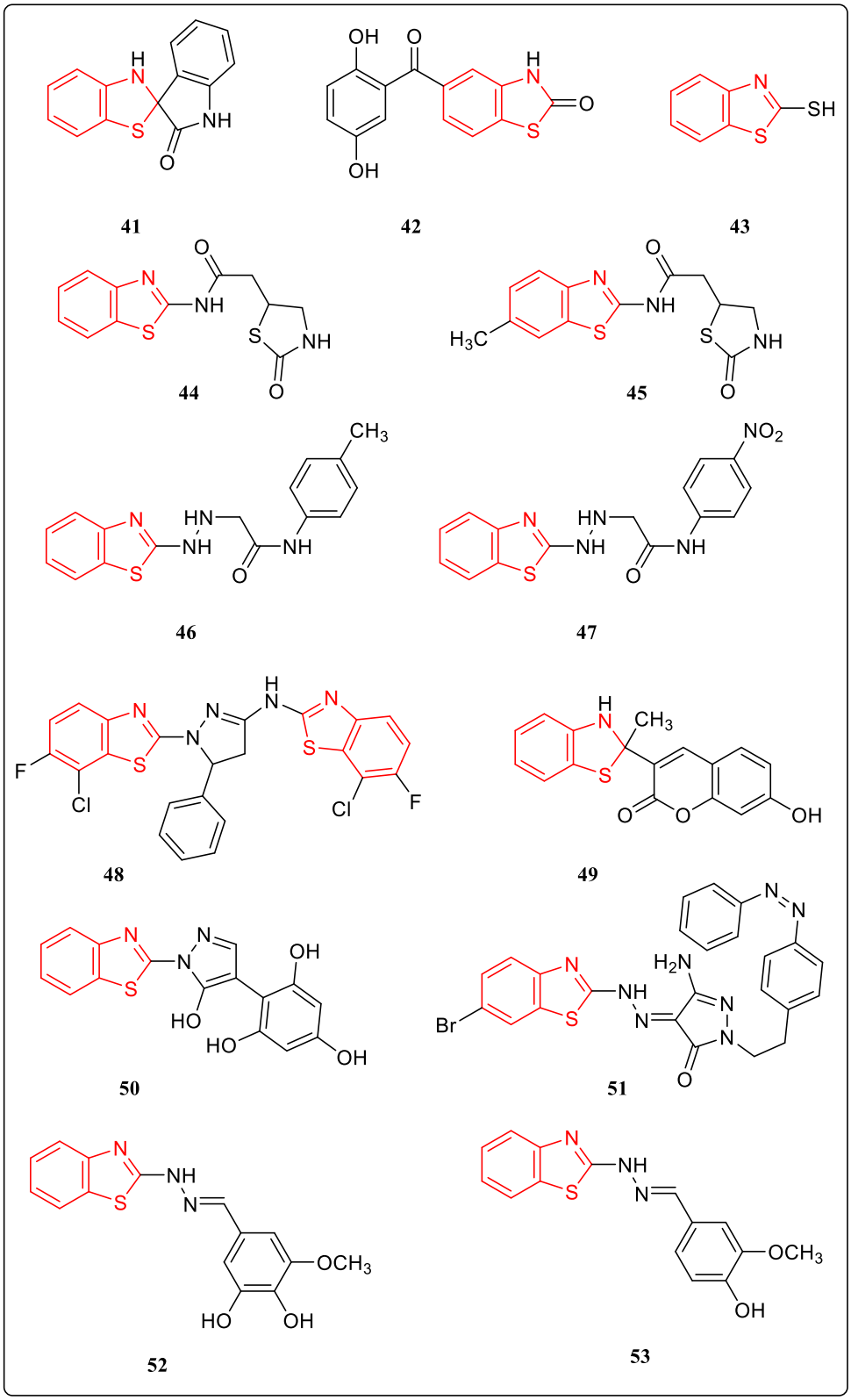

Figure 10. Benzothiazole as antioxidant agents

5.6 BTA as antitubercular agents

As one of the infectious diseases with the highest fatality rates worldwide, tuberculosis (TB) has made a dramatic comeback in recent decades, despite widespread belief to the contrary. Mycobacterium tuberculosis (Mtb) is the causative agent of most tuberculosis (TB) infections; nevertheless, it has a lethal synergy with the human immunodeficiency virus (HIV), which causes a large proportion of HIV-infected people to die from Mtb's aggressiveness. Two primary methods for creating new tuberculosis medications are investigating new structures that the TB organism has never seen before, especially in cases of multi-drug resistant TB, and synthesizing analogs, alterations, or derivatives of current compounds to improve tuberculosis treatment [99]. Figures 11 and 12 shows the BTA structures, which are antitubercular drugs.

A group of researchers led by Huang synthesized BTA-isoxazole carboxamide derivatives that showed antitubercular and anti-protozoal effects against four different protozoan parasites and Mtb H37Rv. Micromolar doses (1.4 and 1.9 mM, respectively) of compounds **54** and **55** inhibited Mtb growth, indicating strong action. The anti-tubercular rhodesiense effects of hydroxamate compound **56** were encouraging. Substituted amino acid esters and tiny dimethylamino groups produced compounds with strong anti-TB action, and various substitutions at the southern amide site were well-tolerated [100].

Rajani *et al.* synthesized analogs conjugated with BTA, triazole, and pyridine, and tested their antitubercular and antibacterial activities against Mtb H37Rv and other microbes *in vitro*. Compound **60** outperformed rifampicin in its anti-TB action, whereas compounds **57**, **58**, and **59** all showed promising antibacterial potential. The antibacterial potential of compounds with nitro, methyl, or halogen substituents was encouraging, whereas the antifungal activity of compounds with methyl substituent was superior [101].

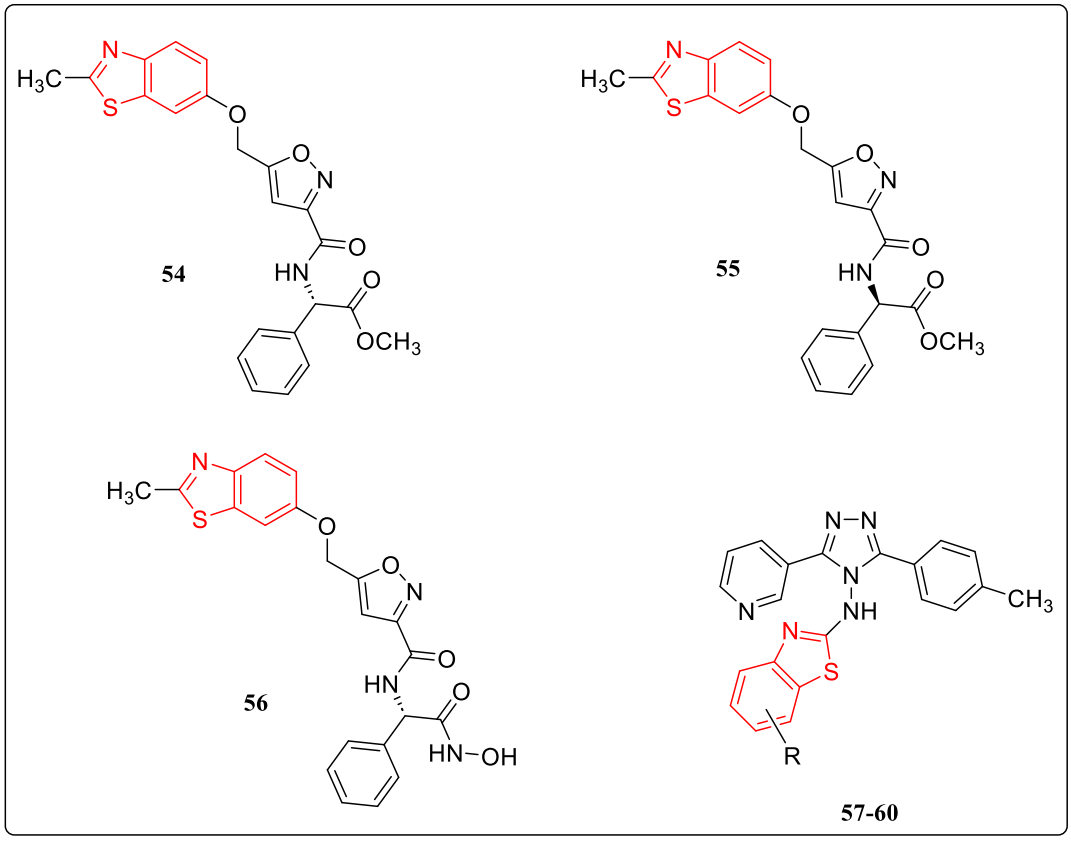

Figure 11. Benzothiazole as antitubercular agents

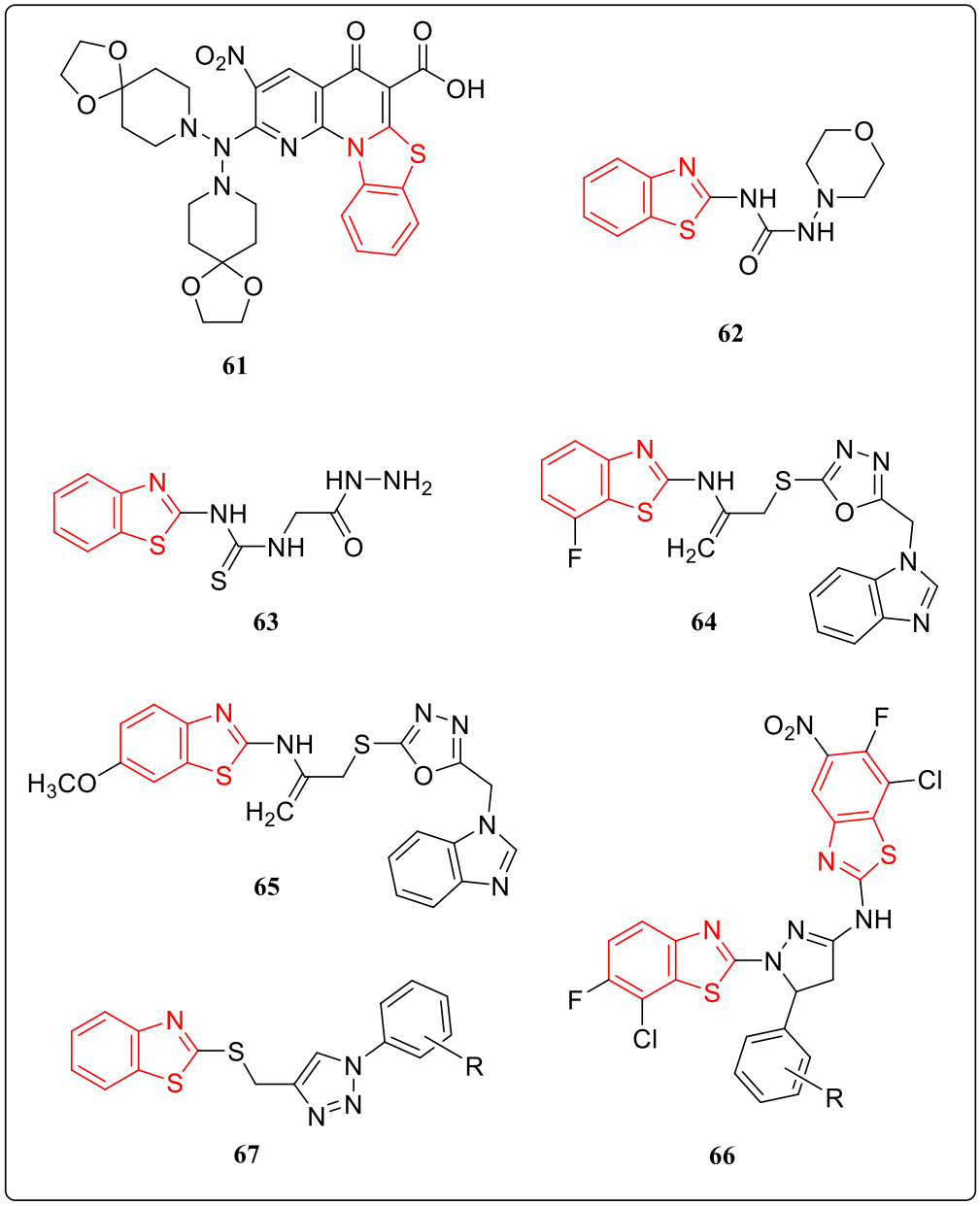

Figure 12. Benzothiazole as antitubercular agents

A series of derivatives of benzothiazolo-naphthyridone were prepared and tested for their anti-TB effects against Mtb H37Rv and MDR-TB in both laboratory and animal studies. The most effective compound in vitro was compound **61**, which had MIC values of 0.19 mM against Mtb and 0.04 mM against MDR-TB, respectively. Compound **61** drastically reduced the mycobacterial burden in spleen and lung tissues, offering substantial protection in the in vivo animal model. The anti-TB activity was carboxylic acid higher in the piperidine-substituted analogs, but they were also cytotoxic [101].

Abdel-Rahman *et al.* synthesized BTA-urea and thiourea compounds and tested their anti-TB, antibacterial, and *in vitro* cytotoxic effects. Compound **62** inhibited tuberculosis development by 37% and was antimicrobial against *E. coli*, whereas compound **63** was as effective as ampicillin against *Staphylococcus aureus* [102].

To test its efficacy against Mtb H37Rv, researchers created BTA variants that contained a diphenyl ether group. Adding halogen substituents to the 2-(2-(4-aryloxybenzylidene) hydrazinyl)benzothiazole ring improved its anti-TB action, however adding methyl, methoxy, or nitro groups to the 6-position on the ring reduced its activity [103]. When tested against Mtb H37Rv, benzimidazole-oxadiazole-BTA conjugates were effective in preventing tuberculosis. The minimum inhibitory concentration (MIC) against Mycobacterium H37Rv was 12.5 mg/mL for compound **64** carrying fluorine and compound **65** carrying methoxy groups on the BTA. Tubercular potency was improved due to the inclusion of halogen atoms, alkoxy, and cyano substituents [104].

To test their potential anti-TB effects against the Mtb H37Rv strain in vitro, researchers created fluoronitrobenzothiazolo-pyrazoline regioisomers and put them through their paces. In comparison to the gold standard medicine pyrazinamide and streptomycin, compound **66** demonstrated complete inhibition at 25 mg/mL. Antitubercular action was improved in compounds that had nitro groups at position 5 of the BTA ring and in compounds that had electron-donating substituents in the aromatic ring [105].

The Mtb H37Rv strain was used to test the anti-TB activity of triazole and 2-Mercaptobenzothiazole conjugates. The H37Rv strain was unable to develop in the presence of compound **67** at 8 mg/mL. Possible active components include aromatic ring chloro and nitro alterations [105].

The anti-TB activity of *N*-Benzothiazolyl acetamide-based analogs was evaluated utilizing the BACTEC MGIT and L.J.MIC techniques. In comparison to the gold standard medication pyrazinamide, analogs based on N-benzothiazole acetamide showed the strongest inhibition (99%) against Mtb H37Rv at constant concentration levels [106].

5.7 BTA as antidiabetic agents

Chronic hyperglycemia is the characteristic of diabetes mellitus, a metabolic condition that can have various causes [107]. Insulin resistance, insufficient insulin secretion, excessive glucose synthesis by the liver, or glucose intolerance are the common causes of non-insulin-dependent diabetes mellitus (NIDDM). Global diabetes prevalence was estimated at 171 million in 2000 and is predicted to reach 366 million by 2030, according to estimates [108]. Diabetic complications include retinopathy, nephropathy, and neuropathy, which manifest as microvascular damage in vital tissues. It lowers quality of life, increases risk of macrovascular consequences (such as ischemic heart disease, stroke, and peripheral vascular disease), shortens life expectancy, and causes substantial morbidity from certain microvascular complications of diabetes [108].

To test the efficacy of BTA-thiazolidinediones on the peroxisome proliferator-activated receptor-gamma (PPARg), Jeon *et al.* created conjugates with exocyclic nitrogens that had alkyl chains of varying lengths. The most effective PPARg agonist was found to be compound **68**, which had methyl substituted on the exocyclic nitrogen. Researchers found that BTA-thiazolidinediones had a stronger inhibitory effect on NO generation and less PPARg activation when their N-alkyl substituents were longer [109].

In order to test the *in vivo* antidiabetic effect of BTA sulfonamide derivatives, Navarrete-Vazquez and colleagues used a rat model of non-insulin-dependent diabetes mellitus. Among the derivatives of **69**, compounds with a methoxy group at BTA ring position 5 showed the most potent anti-diabetic actions [110].

A streptozotocin-induced diabetic rat model was used to assess BTA derivatives for in vivo hypoglycemic activity after their synthesis. In diabetic rats, compound **70** had a more pronounced effect on reducing blood glucose levels, reaching a maximal effect at 100 mg/kg b.w. The presence of a heterocyclic morpholine in the compound **70** may contribute to its maximum glucose-lowering effects [111]. Researchers tested BTA-phenylpropone compounds for their ability to inhibit α-amylase, glucosidase, and protease. The chemical compound **71** demonstrated its ability to inhibit α-amylase with an IC_{50} value of 15.87 mM. In addition, it displayed outstanding

glucosidase activity with an IC_{50} value of 18.04 mM and murine liver glucosidase inhibition with an IC_{50} value of 15.74 mM [112]. It was found that BTA-butanamide derivatives inhibited dipeptidyl peptidase IV (DPP-IV). The DPP-IV inhibitory action of compounds was found to be quite strong, especially those bearing a 6-substituted BTA group. When given to ICR mice orally, the metabolically stable compound **72** inhibited DPP-IV and decreased blood glucose excursion in an oral glucose tolerance test (OGTT). An increase in the inhibitory effects of DPP-IV was observed in compounds having 5 or 6 substituents and a substituted benzothiazolyl group, according to SAR studies [113].

A new class of antidiabetic medications may target the AMP-activated protein kinase (AMPK). In vitro, compound **73** increased glucose absorption by 2.5-fold compared to cells fed with a vehicle and by 1.1-fold compared to PT-1, indicating potential antidiabetic effects [114].

In the fight against type 2 diabetes mellitus, one famous therapeutic target is protein tyrosine phosphatase 1B, or PTP1B. In their study, Navarrete-Vazquez *et al.* synthesized 2-arylsulfonylaminobenzothiazole derivatives and tested their ability to inhibit protein tyrosine phosphatase-1D (PTP-1D). The PTP-1D inhibitory action was substantial for a number of drugs, especially those containing nitro groups at positions 4 and 5 of the sulphonamide function. Compound **74** was the most effective mixed-type PTP-1D inhibitor and reduced plasma glucose concentration 7 hours after intragastric injection, demonstrating anti-hyperglycemic effects in a rat model of type 2 diabetes mellitus [115].

At concentrations below 1 micromolar, benzothiazol-2-oxoacetate derivatives showed potent inhibitory action against protein tyrosine phosphatase 1B (PTP-1B). With an activity level two to four times higher than compound **74**, compound **75** showed the most promise as a reversible and non-slow-binding mixed-type inhibitor of PTP-1B [116].

To determine whether or not they might inhibit protein tyrosine phosphatase 1B (PTP1B), Sparks *et al.* created (S)-IZD derivatives that contained BTA-benzimidazole. The compound exhibited potent inhibitory action against PTP1B. By exchanging the BTA and benzimidazole, these compounds were able to significantly increase their effectiveness as reversible, competitive, and powerful PTP1B inhibitors [117].

To create aldose reductase inhibitors, BTA-indole-*N*-alkanoic acid was manufactured. The aldose reductase enzyme was inhibited by compound **77** with an IC_{50} of 5 μM, whereas the related enzyme aldehyde reductase, which is involved in the detoxification of reactive aldehydes, was 5400 times less active. In the 5-day STZ-induced diabetes rat model, it reduced levels of nerve and lens sorbitol with ED_{50}s of 1.9 and 4.5 mg/kg/d po, respectively [118]. Figure 13 shows the BTA structures, which are antidiabetic drugs.

5.8 BTA as antimalarial agents

Worldwide, 216 million people were infected with malaria in 2010, with 655,000 losing their lives as a direct consequence. A kid dies from the disease every minute in sub-Saharan Africa, where it is most common [119]. The urgent requirement for new antimalarial medications is highlighted by the fast evolution of resistance to first-line antimalarials [120]. One useful strategy in drug research is to use existing antimalarials as jumping off points [121].

The antimalarial effects of a class of rhodacyanines were tested *in vitro* against the chloroquine-resistant strain of Plasmodium falciparum K1 and *in vivo* against Plasmodium berghei in mice by Takasu *et al.* The antimalarial effects of rhodacyanines, which include a BTA moiety, were very encouraging. At doses of 25 mg/kg/d (ip) [122], these compounds showed substantial *in vivo* action, suppressing parasitemia to an extent of about 89%. The same lab has developed a number of novel rhodacyanine dyes with heterocyclic linkages of varying types. There was notable selective toxicity and significant antimalarial activity in compound **81**. Research on the structure-activity relationship (SAR) has shown that the rhodacyanine skeleton is crucial for potent action and that a balance between the hydrophilicity and hydrophobicity of molecules is important for effectiveness [123].

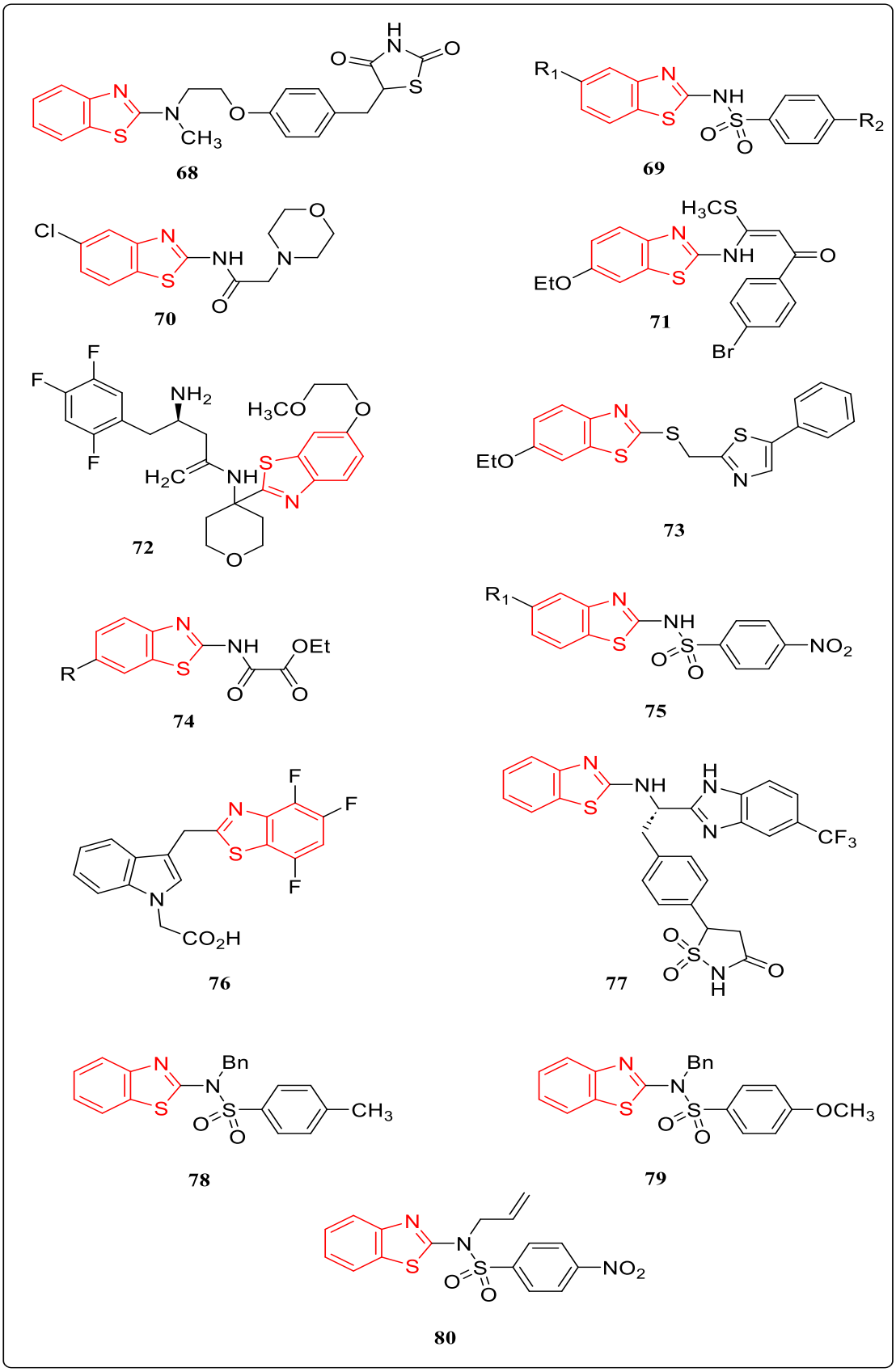

Figure 13. Benzothiazole as antidiabetic agents

Two chloroquine-resistant P. falciparum strains, K1 and W2, were used to assess the antiplasmodial activity of BTA-pyridine analogs of amodiaquine that were produced. With IC_{50} values between 7 and 22 nM, BTA analogs (compounds **82-84**) showed remarkable efficacy against both strains. The BTA analog (bi) presented the least danger of cross-resistance among these analogues, which were all rather low [124].

The antiprotozoal activity against *P. falciparum* K1, *Trypanosoma cruzi*, *T. brucei rhodesiense*, and *L. donovani* were assessed in vitro by Ge *et al.*, who produced cyanine dyes replaced with BTA groups. A number of trimethine cyanines with benzothiazolyl groups were highly active against both Plasmodium falciparum and Trypanosoma cruzi. Trimethine cyanines that have been fluorinated (compounds **85** & **86**) showed promising antimalarial effects. According to SAR research, the antimalarial effects of trimethine cyanines were mediated via the fluorinated benzothiazolyl groups. With an IC_{50} of 0.008 mM, compound **87** showed promise as a treatment for Chagas disease, which has no fully effective or safe option at the moment [125].

In order to block falcipain, a cysteine protease produced by the malaria parasite Plasmodium falciparum, researchers created and tested non-peptidic active analogs from the triazole and BTA class. Both hemoglobinases (FP-2 and FP-3) were inhibited by compounds **88** and **89** containing protonated amines. Interestingly, these same compounds also showed activity against homologous mammalian cysteine proteases that did not have corresponding polar residues, indicating that these residues may not be as important when designing selective inhibitors against FPs [126]. Antimalarial BTA structures are displayed in Figure 14.

5.9 BTA as antidepressants agents

Recurring periods of major symptoms such as disinterest in enjoyable activities, feelings of worthlessness, fluctuations in energy levels, and thoughts of suicide characterize depression, a severe and possibly fatal condition [127]. The National Institute of Mental Health (NIMH) reports that 9.5% of adults in the United States experience major depressive disorder in any given year, which translates to almost 19 million people. Disorders such as bipolar disorder, dysthymic disorder, and severe depressive disorder fall under this category [128]. Medications that alleviate depression are the mainstay of treatment.

To screen for antidepressant properties, researchers synthesized BTA-2,3-dihydrobenzo[b][1,4]dioxine derivatives and measured their binding affinities at the 5-HT1A and $5\text{-}HT_{2A}$ receptors. The tests they used included the forced swimming test (FST) and the tail suspension test (TST). The $5\text{-}HT_{1A}$ receptor and the $5\text{-}HT_{2A}$ receptor showed moderate binding affinities for compound **90**, which is joined by an amide bond in its carbon chain, at 76-94 μM and 87-113 μM, respectively. When attached to a two-carbon side chain, the BTA derivative bp showed a little increase in affinity for the $5\text{-}HT_{2A}$ receptor, with a Ki value of 90 μM compared to 113 μM. To find a potential new antidepressant, compound bp is now being used as a screening method [129].

Separately, Zhu *et a*l. suggested BTA-based drugs as novel antidepressants after reporting that they inhibited both the 5HT1A receptor and the serotonin transporter (SERT). Somewhat promising as dual-acting drugs, compounds **90** and **91** showed modest binding affinity at both the 5HT1A receptor and the SERT site. Likewise, the 5HT2C receptor, the norepinephrine transporter (NET), and the dopamine transporter (DAT) all showed minimal affinity for the compound **90** [130]. As antidepressant drugs, BTA are shown in Figure 15 by their structures.

5.10 Miscellaneous activities of BTA

In addition to the mentioned applications, BTA derivatives demonstrate potential in various medical fields, including anti-infective, antimosquito, antimitotic, diuretic, and anti-Parkinsonian agents, as discussed in this section. Spinacia oleracea L. (spinach) chloroplasts were used to test the inhibitory effects of N-substituted 2-amino BTAs, which

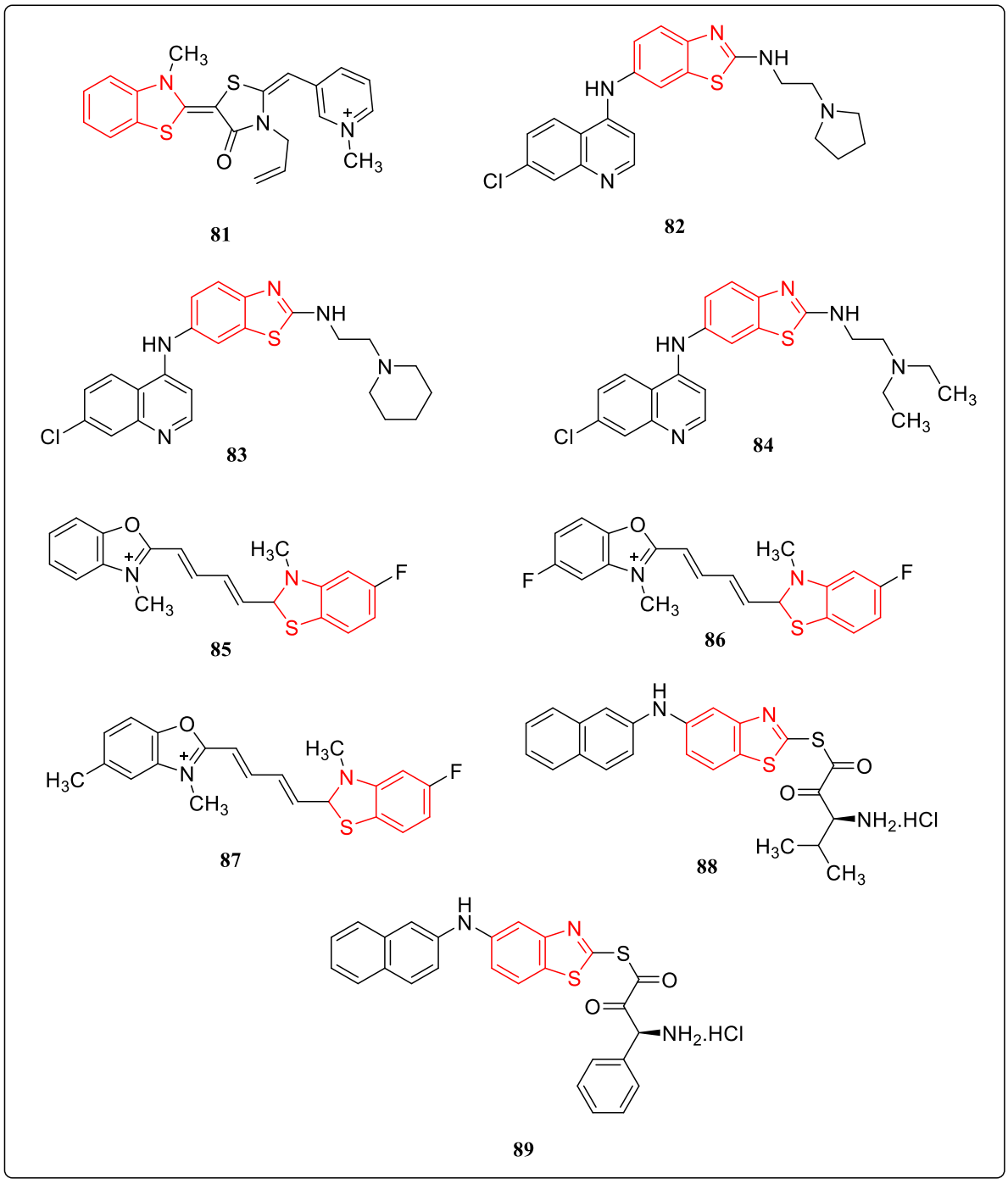

Figure 14. Benzothiazole as antimalarial agents

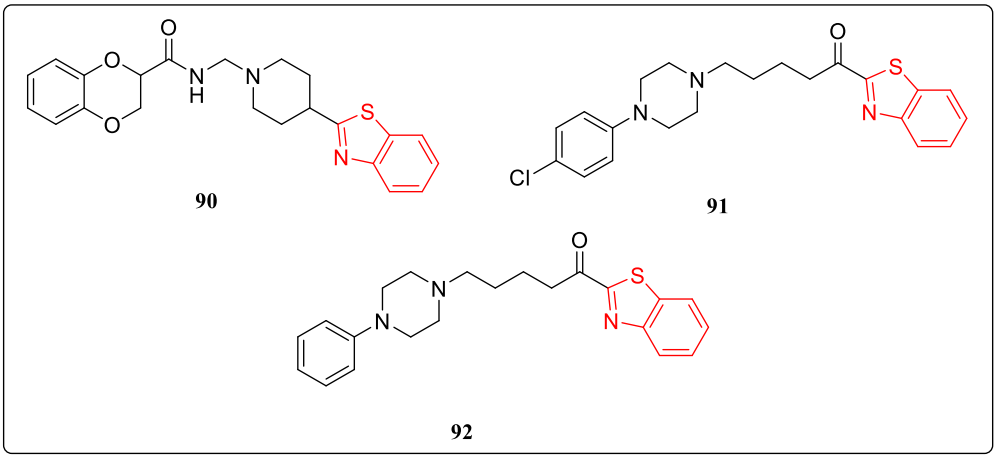

Figure 15. Benzothiazole as antidepressant agents

were produced by Fajkusova *et al.* In addition, antimicrobial, antifungal, and antimycobacterial actions were assessed in vitro. 2-phenylacetylaminobenzothiazole (**93**), outperformed the gold standard, 3-(3,4-dichlorophenyl)-1,1-dimethylurea, in terms of PET inhibition. The antimycobacterial activity of this chemical against *Mycobacterium kansasii* was likewise relatively high. In comparison to the gold standard, phenoxymethylpenicillin, compounds **93** and **94** showed significant activity against Candida albicans and methicillin-resistant Staphylococcus aureus. The importance of the amide/carbamate group is demonstrated by the fact that structure-activity relationship (SAR) investigations reveal that amides exhibit less biological activity compared to carboxamides or carbamates. High herbicidal or anti-infective activity requires the replacement of a bulky group or a long alkyl chain for an amide moiety [131].

The antimosquito capabilities of synthetic substituted-BTA analogs were tested against *Anopheles arabiensis*, including their ability to repel, kill insects, and kill larvae. The maximum repellent action was shown by analogs of the BTA family, while analogue **95** was on par with the positive control compound *N,N*-diethyl-meta-toluamide (DEET). After one day of exposure, the adulticidal activity of mosquitoes was between eleven percent to fifty-five percent [132].

A number of amines were introduced to the dithiocarbamate side chain during the synthesis of BTA dithiocarbamate and chalcone dithiocarbamate derivatives, and their antimitotic action was tested. With an IC_{50} of 1.52 mM, the molecule containing 2-aminobenzothiazole as a side chain showed the most encouraging antimitotic efficacy [133].

Anti-Parkinsonian drugs were synthesized by Azam and colleagues from BTA-urea derivatives. The catalepsy in mice caused by haloperidol could be alleviated by some of the substances tested. Derivatives of phenyl with furfuryl (compound **96**) and 2-and/or 3-methoxy (compound **97**) substituents emerged as powerful medicines that inhibit parkinsonism. SAR investigations showed that an analog with a halogen substitution in the phenyl ring and a 2-chloro, 5-trifluoromethyl substituent had moderate or less effective anti-Parkinsonian efficacy [134].

The diuretic efficacy of biphenylbenzothiazole-2-carboxamide derivatives was assessed after their synthesis. With a diuretic effect of 2.8, compound **98** was 1.75 times more powerful than acetazolamide, and it increased urine output by more than 300% when compared to the control. Urinary excretion was greatly enhanced by substituting electron-withdrawing groups (Cl, F, and Br) at position 6 of the BTA ring structure [135]. Figure 16 shows the structural representation of BTA as other therapeutic drugs.

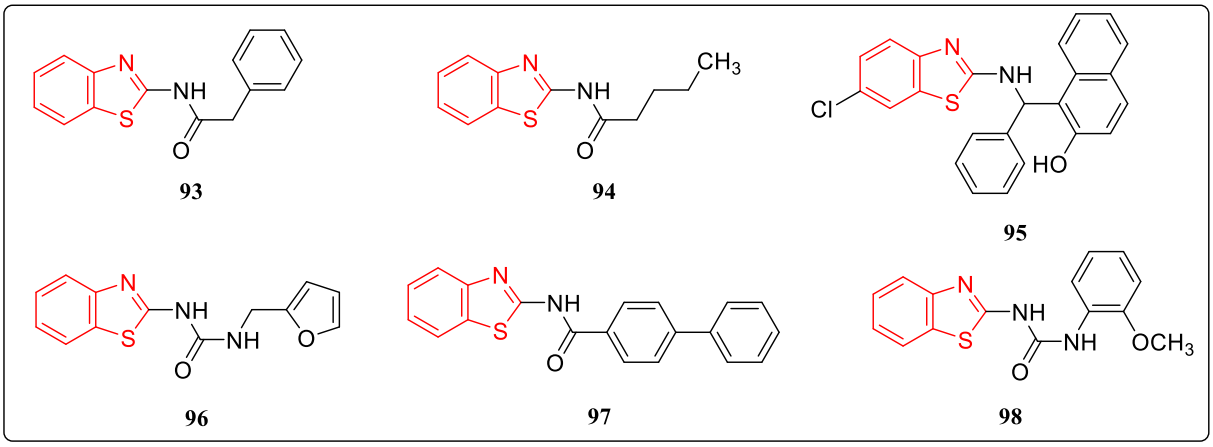

Figure 16. Benzothiazole as other medicinal agents

The preceding discussions unequivocally demonstrate the pivotal role of the structural BTA ring in medicinal chemistry, making it a remarkably active area of research. A significant amount of work has gone into medicinal chemistry based on BTA, and there have been several remarkable accomplishments that demonstrate the great promise of BTA-based molecules as diagnostic tools and medicinal medications. It is worth mentioning that numerous compounds derived from BTA have been developed, marketed, and utilized in various clinical applications. These compounds include agents that fight cancer, infections, fungal infections, inflammation, pain, HIV, seizures, tuberculosis, diabetes, leishmanial infections, and histamine. These chemicals are highly effective in preventing and treating a wide range of disorders, and they are also biocompatible, have high bioavailability, and demonstrate minimal toxicity.

As a whole, these findings demonstrate that BTA derivatives have endless medical applications. It is exciting to note that research and development efforts are actively pursuing a growing variety of BTA derivatives as potential clinical therapeutic candidates.

The potential interaction between the intriguing BTA moiety and many molecular targets opens up a wide range of possibilities. We hope that future research utilizing this framework will lead to more promising outcomes in the medical field. We hope that this data will inspire new synthetic methodologies, better compounds with better biological characteristics, and more exact targeting.

6. Conclusion

Among the many fused heterocyclic compounds, benzothiazoles have received the greatest research attention. They can play a variety of roles in various pathophysiological situations. Due to its enormous biological significance, a variety of synthetic techniques have been used to create effective drug candidates that incorporate this potent scaffold with a variety of substitutions. The anticancer, antihyperglycemic, antiprotozoal, antiviral, and antibacterial properties of benzothiazole derivatives have piqued the interest of researchers for quite some time. This article demonstrates the present function of benzothiazoles in medicinal chemistry by discussing results from SAR investigations and the binding conformation of these heterocycles with different targets. With the help of this knowledge, new, diversified benzothiazoles compounds can be prepared to treat pathophysiological disorders that are currently difficult to treat.

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