Research Paper

Recent Advances in Sulfur-Containing Heterocyclic Compounds: Synthesis, Structural Classification, and Biological Activities: A Comprehensive Review

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ABSTRACT

Heterocycles containing sulfur are one of the most significant types of diverse, pharmaceutical compounds in modern medicinal chemistry. The percentage of all approved medicines by the FDA that are made up of heterocycles containing sulfur has grown from 10% to 20% from the years 2020 to 2024. This article will supply extensive systematic listings of all sulfur-containing heterocycles, class by ring size (e.g., 5-membered [thiazoles, thiophenes, thiadiazoles]; 6-membered [thiazines]; fused bicyclic [benzothiazoles, dibenzothiophenes]) as well as by the number of heteroatoms in each ring system, saturation of each ring system, with very recent synthetic evaluations of synthetic methods employed through several of the most common processes to make these compounds, including both traditional methods (e.g., Hantzsch thiazole synthesis, Gewald reaction) and newer techniques (e.g., microwave-assisted synthesis, "green" synthesis, one-pot multicomponent reactions, transition metal-catalyzed cyclizations like Pd, Cu, etc.) to prepare compounds of interest that have been reported to contain biological activity from 2019-2024. This systematic review will provide an overview of the classes of biological activity (e.g., antimicrobial, anticancer, anti-inflammatory, antiviral, and antioxidant) produced by benzothiazole-thiazolidinone hybrid (and related) compounds and thiadiazole-based covalent inhibitors and thiazole-based anti-cancer compounds based on methods of medicinal chemistry (i.e., structure-activity relationship). Based on the evidence compiled herein, benzothiazole-thiazolidinone hybrids, thiadiazole-based covalent inhibitors, and thiadiazole derivatives are very valuable chemical scaffolds in all these areas. The major impediments to using these compounds in drugs are their synthetic limitations, toxicity, and lack of drug-likeness; however, researchers are working towards utilizing modern technologies for designing targeted covalent inhibitors as well as solubility, reactivity, stability, and low-cost manufacturing methods to facilitate the development of sulfur heterocycles as an important chemical scaffold for developing the next generation of therapeutics.

Keywords: Sulfur heterocycles; Thiazole; Benzothiazole; Thiadiazole; Gewald reaction; Hantzsch synthesis; Antimicrobial; Anticancer; Green synthesis.

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Introduction

One of the most crucial heteroatoms used in drug discovery today is sulfur. Its importance lies in its distinct chemical properties that lend to a wide range of pharmacological benefits: sulfur can exist in many different oxidation states, form a variety of types of bonds, and therefore make many drugs more stable than they otherwise would be, improve their solubility, and thus have a positive impact on both pharmacokinetics and pharmacodynamics [1]. The use of sulfur as a heteroatom in pharmaceutical creation has a long and successful history, as evidenced by the discovery of penicillin, an example of an early revolutionary antibiotic that was found to contain a sulfur atom as part of its

thiazolidine ring [2]. In the years since the introduction of penicillin, this trend has continued on a steady basis – more than 300 FDA-registered drugs made from sulfur have demonstrated various forms of biological activity and numerous possibilities for therapy and there has been an increase in the number of newly FDA-registered drugs that incorporated sulfur between 2020 and 2024, as it went from 10% to 20% of registered drugs as measured by the year (2020: 11%; 2024: 20%) [3].

There is a great deal of variability in the three-dimensional structure of compounds that contain sulfur atoms; therefore, the various types of sulfur-containing scaffolds have an increased utility in therapeutics because of their diverse structural characteristics. There are many different types of sulfur-containing functional groups, including thiols, sulfides, disulfides, sulfones, sulfoxides, sulfonic acid, sulfonamide, sulfate esters, especially thioketones, thioelestters, and thienothiazoles [4]. The FDA has issued drug approval for 3 groups of compounds containing sulfur, including sulfonamides, sulfides, and sulfones [3]. Furthermore, as a result of their diverse pharmacological actions and means of action, sulfur-heterocyclic compounds have become an important class of bioactive compounds in the field of drug discovery. As a result of having several pharmacological activities, sulfur-heterocyclic compounds work by inhibiting the growth or development of microorganisms and modulating the host immune response mechanisms [5].

The fields of medicinal chemistry and pharmaceutical sciences hold heterocycles at the core of both disciplines. Synthetic drugs, from the inception of the pharmaceutical industry, have been developed using the heterocyclic rings contained in natural products, including alkaloids, vitamins, antibiotics, and peptides, as guiding blueprints; therefore, the heterocyclic scaffold is considered a cornerstone of the future drug discovery process, and approximately 85% of all bioactive molecules contain heterocyclic moieties [6]. An analysis conducted on the most recently approved small-molecule drugs demonstrates this phenomenon. Fluorine or N-aromatic heterocycles were included in 23 of the thirty small-molecule novel chemical entities that were approved by the FDA in 2024 (77%); this pattern is comparable with previous years (2022 and 2023) [7].

Numerous intrinsic characteristics contribute to the pharmacological benefits of drugs developed from heterocycles. Ongoing development using heterocyclics opens the door for additional therapeutic and quality-of-life opportunities for patients. The literature is replete with numerous studies and publications addressing the benefits and benefits they present in the development of new therapeutic agents.[8] . One of the classes where increased focus has been directed toward new applications is that of S-heterocycles over the past several years, following extensive efforts made with respect to using N-heterocycles in medicinal chemistry, and researchers have begun to synthesize new S-heterocycles with a clearly demonstrable higher medicinal value than previous N-heterocycles, while also providing a lower toxicity profile. [9]. The size of the heterocyclic ring system will also influence how the S-heterocycle will demonstrate pharmacological activity; smaller rings (3– and 4-member) will provide unique reactivity and characteristics that will facilitate potent pharmacological activity, while making

use of larger rings (6– and 7-member) will yield greater structural stability and more favorable interactions with biological targets. [5].

Sulfur heterocycles have impacted many therapeutic classes. β-lactams, found in the class of penicillin, are examples of early sulfur incorporation in medicine due to their link with the five-membered thiazolidine ring (the penam system). Regarding medications for acid-related gastrointestinal disorders, the proton pump inhibitors esomeprazole (Nexium®) and omeprazole (Prilosec®) contain sulfoxides, making them some of the most widely used sulfonyl late in medicine. [10]. The oncology drugs dabrafenib, dasatinib, ixabepilone, and epothilone all have been shown to possess a thiazole backbone. [11] Recently, tovorafenib, a fluorinated version of the thiazole, has been granted expedited approval by the FDA for the treatment of children with low-grade gliomas containing mutations in BRAF. Taylor and Francis Online, the FDA approved Quizartinib (Vanflyta®) in July 2023 as a new treatment option for adults who have a new acute myeloid leukaemia diagnosis due to being FLT3 (type - iD) positive. There are many other five and six-membered sulfur heterocycles (thiazole, thiadiazole, thiazolidinedione, thiphene, thiopyran, benzothazole, benzothiophene, and phenothiazine) with different methods of cytotoxicity, like inhibiting tyrosine kinases, topoisomerases 1 & 2, tubulin polymerisation, cyclooxygenase, and DNA replication; as well as inhibition of PI3K/Akt and Raf/MEK/ERK signal transduction systems. [12].

Despite the remarkable therapeutic breadth of sulfur-containing heterocyclic compounds, no single comprehensive resource currently integrates their synthetic advances, structural classification across ring sizes, and the full spectrum of biological activities reported in recent literature. The present review therefore aims to provide a systematic and updated account of sulfur-containing heterocyclic compounds with particular emphasis on: (i) the principal synthetic strategies used to construct key scaffolds ranging from three- to seven-membered sulfur rings; (ii) a structural classification that encompasses monocyclic, fused bicyclic, and polycyclic sulfur-containing ring systems; and (iii) the diverse biological activities antimicrobial, anticancer, antidiabetic, anti-inflammatory, antiviral, and antihypertensive reported for these scaffolds, supported by structure–activity relationship (SAR) analyses. By consolidating recent advances from 2019 to 2024, this review is intended to serve as a resource for medicinal chemists and pharmaceutical researchers engaged in the rational design of next-generation sulfur-based therapeutic agents.

3. Classification of Sulfur-Containing Heterocycles

Sulfur-containing heterocycles exhibit many structural types, and an orderly classification will create the parameters needed to assess the ease of making these types of compounds, their physical and chemical properties, and their biological activity. Sulfur-containing heterocycles can be rationally categorized based on three complementary criteria: the size of the ring, the types and combinations of heteroatoms present in rings, and the level of saturation (aromatic or non-aromatic).

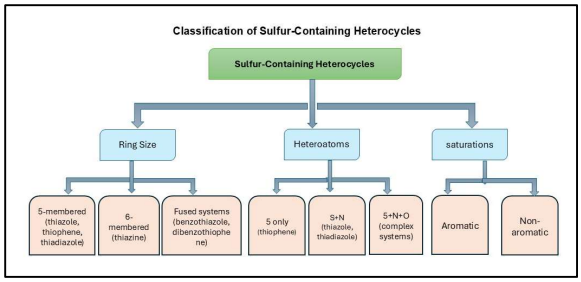


Figure 1 Classification of Sulfur-Containing Heterocycles

3.1. Based on ring size

3.1.1. 5-membered: thiazole, thiophene, thiadiazole

In medicinal chemistry, five-membered sulfur heterocycle rings are the most exploited pharmacologically of all heterocycles. The most common heterocycles in this class are thiophene, thiazole, and thiadiazole, with the three having unique structural and electronic properties that confer their individual biological activity profiles. [13].

3.1.1.1 Thiazole

5-membered aromatic heterocyclic compound with S in position 1, N in position 3. Because of the unique way in which N and S are positioned in the thiazole ring, the π electrons can move freely from one of the bonds in the ring to another through the bonds of the thiazole ring, providing for aromatic properties. Because of the aromatic properties of this ring, there are numerous reactive sites where donor-acceptor, nucleophile/electrophile, or oxidative types of reactions can take place. Substances that contain this ring structure, when entering living systems, may activate or inhibit biochemical pathways and/or enzymes, and stimulate and/or inhibit receptor proteins [11]. The thiazole scaffold has been incorporated into many of the pharmaceutical products found on the market today, with evidence supporting thiazole being a ubiquitous motif in many pharmacologically relevant drug molecules, such as lurasidone, sulfathiazole, ritonavir, and many others, and the scientific community very much acknowledges that this series of compounds has many biological properties. [14]. Thiazole derivatives have been the subject of pharmaceutical research and development for many years, with continuing success over the last few decades due to the many biological properties associated with thiazole derivatives (anticancer, antibacterial, antifungal, anti-HIV, antiulcer, anti-inflammatory, etc.), and there are currently a significant number of thiazole-based pharmaceutical products in the marketplace. [15].

3.1.1.2 Thiophene

A five-membered ring with one sulfur atom per ring makes up the aromatic heterocycle thiophene. It is frequently referred to as the "wonder heterocycle" because of its broad range of biological activities, which include anticancer, antibacterial, antioxidant, and anti-inflammatory/antiallergic properties. It is derived from the Greek words theion, meaning sulfur, and phaino, meaning to shine. [16]. There are 4 thiophene-containing drugs approved by the United States Food and Drug Administration (FDA) in the past ten years, resulting in 26 thiophene-derived drugs being classified into different pharmacological categories. [17]. The unique anticancer properties of thiophenes can be attributed to their ability to bind to multiple cancer-specific proteins based on their substitution pattern and substitution position. Numerous thiophene derivatives have been shown to possess anticancer properties and utilize a variety of signal transduction pathways involved in cancer. There is a growing interest among researchers in developing and/or synthesizing new thiophene derivatives

through the alteration of the substituent groups. [15].

3.1.1.3 Thiadiazole

Thiadiazole (C2H2N4S), with its characteristic five-membered ring, which has one sulphur atom and two nitrogen atoms, exists in four isomers (1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-thiadiazole). Compounds containing this thiadiazole moiety can readily cross biological membranes, interact powerfully with biological targets, and display a wide range of biological activities due to the mesoionic nature of the thiadiazole. [18]. The 1,3,4-thiadiazole derivatives exhibit metabolic stability and bioavailability; as such, this is the most favorable moiety with a variety of therapeutic actions, including anticancer, antiviral, anti-inflammatory, antidiabetic, and antidepressant activities due to their high degree of aromaticity, in vivo stability, and lack of toxicity when administered. [19]. RSC Cuttings Publishing. Another advantage of 1,3,4-thiadiazole is that it can serve as a bioisostere of pyrimidine, which extends its use in drug design. Thiadiazoles demonstrate biological activity based on their capabilities to bind to a wide variety of target molecules through numerous mechanisms, including hydrogen bonding, van der Waals' forces, hydrophobic forces, and metallic coordination bonds. Amongst the thiadiazole isomers, 1,3,4-thiadiazole derivatives represent the most promising group with respect to their antitumor potential. [20].

3.1.2 6-membered: Thiazine

Thiazine is an important six-member heterocyclic compound with one nitrogen atom and one sulfur atom. Three isomer forms of thiazine relate to position: 1,2 (thiazine), 1,3 (thiazine), and 1,4 (thiazine). Because of its various biological functions, thiazine has become an extremely important heterocyclic compound. It has been shown to include many pharmacological effects such as antileukemic, antimycobacterial, anti-inflammatory, sedative, hypnotic, anti-influenza, antituberculosis, inhibition of melanogenesis, inhibition of BACE1 (potential anti-Alzheimer's), neuroprotective, and anticonvulsant activities [21]. Most notable of thiazine's clinical applications is acetazolamide and the thiazine pharmacophore prevention of BACE1 (JNJ - 54861911), which was studied further and proceeded to Phase 2b-3 clinical trials for Alzheimer's disease. A well-known drug that contains a core structure of the heterocyclic compound thiazine is cephalosporin, one of the most prescribed types of antibiotics in the world; it has a core structure of 3,6-dihydro-2H-1,3-thiazine [22]. Structural variations of thiazine through alkyl, aryl, and heteroaryl substituents in multiple positions on the ring of thiazines continue to provide opportunities for the development of new bioactive agents. The wide-ranging pharmacological properties and pharmaceutical application of thiazine derivatives will continue to represent a significant opportunity when generating the next generation of medicinally active compounds [23].

3.1.3 Fused systems: benzothiazole, dibenzothiophene

Incorporating sulfur into ring fusion creates much more complex structures and provides a wider range of pharmacological activity than a single cycle alone. The addition of a carbocyclic or heterocyclic to a sulfur-containing ring helps make the molecule more planar, allows for more efficient π–π stacking of the rings, and usually increases binding to the target [24].

3.1.3.1 Benzothiazole

Benzothiazole (BT) is a bicyclic structure consisting of a benzene ring fused to a thiazole at positions 4 and 5, respectively; it contains both sulfur (S) and nitrogen (N) atoms. BT derivatives have gained considerable relevance due to their various biological activities, as many BT derivatives have shown versatile biological activity, creating a structure that can provide multiple types of compound classes when compared to other heterocycles, which contain only carbon and/or nitrogen atoms. With their nitrogen- and sulfur-containing fused heterocyclic skeleton, BT represents a diverse range of pharmacological activities, such as anticancer, antibiotic (antimicrobial), anti-inflammatory, antidiabetic, neuroprotective, and clinical diagnostic agent activity. [25]. Some of the approved and investigational clinical drugs possessing this heterocyclic skeleton include BT-based agents such as flutemetamol for the diagnosis of Alzheimer's dementia, riluzole for the treatment of ALS, and quizartinib for the treatment of AML – all of which illustrate a wide variety of BT-based therapeutic agents and demonstrate the potential of BT for several different types of medical applications. [26]. At the structural level, the 2-aminobenzothiazole moiety has been shown to possess both hydrogen-bond forming (i.e., H-bond donor and H-bond acceptor) capabilities and the ability to form chalcogen bonds; therefore, the compound may interact through various modalities (e.g., π-π stacking and van der Waals contacts) to produce binding interactions with target protein residues that can result in inhibitory mechanisms of action. [27].

3.1.3.2 Dibenzothiophene

The chemical benzothiophene (benzo[b]thiophene) is comprised of a fused bifunctional ring system—the thiophene (a single five-membered) ring fused to benzene (a single six-membered) ring. A dibenzothiophene compound has an additional six-membered fused benzene to create a three-dimensional structure [28]. As a sulfur-substituted heterocycle, benzothiophene is used in medicinal and biological sciences because they are highly soluble, minimally toxic, and, by extension, shows high bioavailability. The fused 6-membered aromatic ring and thiophenic unit serve as an excellent basis for the development of biologically active compounds that exhibit a multitude of biological/pharmacological activities, such as (but not limited to) antimicrobials, cancer therapeutics, antiinflammatories, antioxidants, antimalarials, antidiabetic agents, and enzyme inhibitors. Springer Group Polycyclic structures make up most structures found in Natural Products, Pharmaceuticals, Fertilizers, and Advanced Materials [29]. Polycyclic Heterocycles, such as dibenzofuran, dibenzothiophene, and carbazole, are just a few of many functionalized Heterocycles that are very ubiquitous and have been the focus of significant research given their vast number of biological applications. Many dibenzothiophene derivatives have been shown to exhibit anticancer activity by affecting cell cycle progression and inducing apoptotic cell death in numerous cancer cell lines [29].

3.2. Based on heteroatoms

A second and complementary classification system considers the other heteroatoms in the sulfur-containing ring system, because they have an important effect on the electronic nature, hydrogen bonding ability, and the target interaction profile of the compound.

3.2.1 S only (thiophene)

Thiophene represents the first member of the simplest group of sulfur heterocyclic compounds, having only sulfur present as the heteroatom in the ring. Thiophene and its derivatives have been identified as key compounds in medicine, primarily due to their potential therapeutic applications, including antimalarial, antimicrobial, antimycobacterial, antidepressant, anticonvulsant, antiviral, anticancer, antihypertensive, anti-inflammatory, and antioxidant activities. Consequently, a multitude of target entities for the discovery of novel classes of physiologically active chemicals have been made available by thiophene and its derivatives. [30] Thiophene's vast number of possible pharmacological outcomes is attributed to its electron-rich nature, thus allowing for π-interactions with enzymatic binding sites and DNA, as well as the ease with which one can functionalize the 2- and 3-positions of thiophene. Moreover, various thiophene-based agents demonstrate the versatility of thiophene as an antibacterial compound, including, but not limited to, monomeric thiophene-based heterocycles, such as pyridines, azoles, diazines, and azepines; aminothiophenes; and thiophene carboxamide-based compounds have demonstrated antimicrobial action. [31]

3.2.2 S + N (thiazole, thiadiazole)

The combination of sulfur (S) and nitrogen (N) in one heterocyclic ring structure is one of the best-known and most useful pharmacological structural motifs in the field of medicine. Some examples of these S+N combination structures are thiazoles (including thiadiazoles, thiazines, benzothiazoles, and their reduced analogs), which have both S and N atoms located within a common 5-membered ring. Chemistry associated with the co-existence of both aromatic and aliphatic S and N within the same molecular structure generates a unique, diverse opportunity for the formation of hydrogen in biological systems, as well as interactions with metals and other small molecules [32]. The thiadiazoles are members of a larger class called "nitrogen-sulfur compounds" which are very commonly found as the building blocks of many biologically active compounds, as well as intermediate handling agents for pharmaceutical compounds in the laboratory; 1,3,4-thiadiazoles have been shown to have a variety of biological activities attributed either partly to the presence of the N=S=C= moiety, or in other studies to the highly aromatic nature of the 5-membered ring [33]. "Thiazolidinones" (the primary nitrogen-sulfur (N/S) heterocyclic molecule) have long been recognized as one of the "privileged pharmacophores" in modern medicinal chemistry, due in part to their association with several FDA-approved drugs and their involvement with some therapeutic targets [34]. "Thiazolidinone" structures contain properties that allow them to exhibit strong N/S heteroatom interactions and have good pharmacokinetic properties (e.g., lipophilicity) associated with their azole ring system; these properties have helped many drug compounds (and pharmaceutical drug formulations) reach their pharmacological target tissues via transmembrane diffusion, thereby improving biological response attributes associated with specific drug targets [35].

3.2.3 S + N + O (complex systems)

Heterocyclic structures containing sulfur, nitrogen, and oxygen heteroatoms can be very molecularly elaborate when fused or hybridized together to form fused or

hybrid ring systems as well; the polarity characteristics of these compounds vary greatly with respect to one another and further add to their diversity by creating larger networks of hydrogen bonds. For example, derivatives of thiazolidinedione (TZD), which have become a major focus of pharmaceutical development, represent many significant contributions to this category of sulfur-containing heterocycles as they exhibit a broad range of pharmacological properties and biological activity against many clinically important targets and are used repeatedly by pharmaceutical researchers as a scaffold in drug development. [36]. Hybrid S+N+O scaffolds, such as triazolothiadiazines (where the triazole is fused to thiadiazole and contains both triazole- and thiadiazole-bound oxo functionalities), represent an additional significant source of hybrid S+N+O scaffolds with significant relevance for cancer drug development and have demonstrated significant antiproliferative activity in large-scale screening of triazolothiadiazoles and triazolothiadiazines. [37] In general, the presence of oxygen within sulfur/nitrogen heterocyclic frameworks alters the electronic density, polarity, and metabolic stability of the rings of these systems, thus creating inherently desirable properties for the development of rational drug design.

3.3. Based on saturation

3.3.1 Aromatic

Thiazole's characteristics for this purpose are similar to that of thiophene and 1,2,3-triazole as its shape/size/conformation/configuration is an average of these docked compounds; the mass spectra of thiazole indicate its aromatic character by the presence of abundant molecular ions, and the thermodynamic data suggests that thiazole self-associates in a liquid state while also being completely soluble in water at room temperature. Aromatic systems (e.g., benzothiazole) benefit from the characteristics provided by the fusion of a benzene ring yielding a greater degree of planarity and π-stacking; therefore, benzothiazole has become attractive to medicinal and synthetic chemists because its fused heterocyclic framework offers a broad array of biological activities including, but not limited to, anticancer, antiinflammatory, antibacterial, antiviral, antimalarial, and anticonvulsant [38]. In the class of fused benzo-thiophene-based compounds, benzo[b] thiophene-based compounds uniquely display not only exceptional chemical properties and biological activities, but also superior pharmacological properties, as well as exhibiting a high degree of metabolic stability; therefore, the unique hybrid structure formed when fused produces a core component for the synthesis of fused heterocyclic compounds with widespread applications [39].

Non-aromatic

Thiazolidine is a five-membered ring that contains one nitrogen and one sulfur atom (C_3H_7NS). It is an effective medicinal and pharmaceutical compound because of its many derivatives with similar medicinal or pharmaceutical activity, including those that provide the basis for the development of probes used in preclinical and clinical settings. The various thiazolidine derivatives possess unique and valuable properties, particularly resulting from their sulfur atom and the ability to exist in multiple conformations; as a result, thiazolidine derivatives contain a great deal of structural diversity. There are many different types of thiazolidine derivatives available for use in research and development; because of

this, many thiazolidines have gained popularity among researchers in both organic synthesis and medicinal chemistry [40]. Additionally, thiazolidines can act as a "bridge" between these two disciplines by enabling researchers to discover new compounds that could potentially be beneficial as drug candidates. The recent emergence of thiazolidines as an important class of compounds to researchers has led to increased interest in their use in the development of new compounds with potential therapeutic activity[41]. In addition to being useful around drug discovery, thiazolidines possess a wide variety of other biological activities, including but not limited to: anticancer, anticonvulsant, antimicrobial, and neuroprotective, as well as having many other biological properties, making thiazolidines very desirable as a chemical structure. Thus, thiazolidines are an important class of compounds for both researchers and pharmaceutical companies. The thiazolidine-2,4-dione (TZD) group of compounds has therapeutic significance as they lack an aromatic ring and are one of the most therapeutically relevant classes of S-heterocycles. The various members of the glitazone class of drugs for diabetes mellitus are all based on the pharmacologic PPARγ agonistic properties of this important class. The only commercially available aldose reductase inhibitor currently permitted in China/India/Japan is epalrestat, a carboxylic acid (as represented by the thiazolidinone chemical structure with a 2-thioxo-4-thiazolidine). This shows that non-aromatic thiazolidinone pharmacophores can be used as therapeutically effective medications [42]. Moreover, the highly privileged non aromatic sulfur-containing ring systems can be utilized in also facilitating multiple mechanisms of action to interact with their respective biological targets through their unique chemistry; such as, thiazolidinone-based entities with their many chemical pathways are known to provide various therapeutic benefits including, but not limited to, antibacterial, anticancer, anti-inflammation, anti-diabetes and neuroprotective mechanisms of action via various biological pathways involving the interactions at PPAR-γ, NF-κB, COX enzymes and DNA topoisomerase targets[43].

4. Synthetic Strategies (Core Section)

Sulfur-containing heterocyclic compounds represent one of the most pharmaceutically significant classes of organic molecules, encompassing scaffolds such as thiophene, thiazole, benzothiazole, thiadiazole, thienothiazole, thiirane, and thietane. For many decades, S-heterocycles have maintained their status as an important part of FDA-approved drugs and medicinally active compounds, and with the exhaustive exploration of nitrogen heterocycles, researchers have increasingly shifted their interest toward S-heterocycles[44] .

4.1 Classical Methods

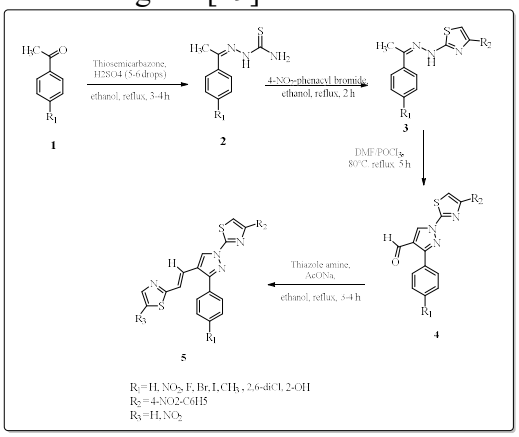
Sulfur-containing heterocycles are still widely produced using classic synthetic methods because of their ease of operation and scalability.

4.1.1 Hantzsch thiazole synthesis

The Hantzsch thiazole synthesis was introduced in 1887 by the German chemist Arthur Hantzsch. It has been proven to be a good way to make the thiazole ring system, and it is still used today. The thiazole was first discovered by Hantzsch and Weber in 1887[45] The thiazole has some properties of pyridine

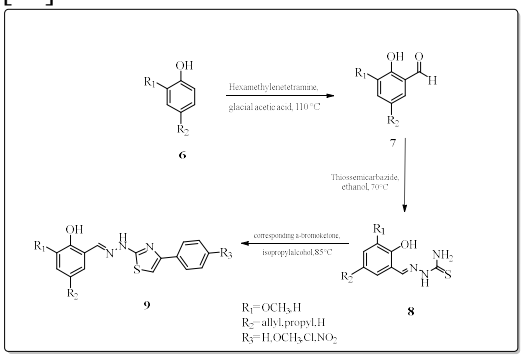
and pyrimidine. The thiazole nucleus is an important part of vitamin B_1, which is also called thiamine [46]. The Hantzsch thiazole synthesis is defined by the combination of α-haloketones with thioamides or thioureas, in which the sulfur atom is very good at attracting molecules, which makes the reaction feasible and completed by a multistep mechanism [47] There were some concerning problems with this Hantzsch thiazole synthesis, such as the reaction taking a long time, the very low yields, and the harsh reaction conditions. These problems have been solved with new methods. For example, we can use microwave conditions to help the reaction, we can go for solvent-free synthesis, and we can use catalytic approaches.[45] The thiazole scaffold is still very interesting to researchers. The Hantzsch thiazole synthesis is used in pharmaceuticals, natural products, and functional organic materials. This shows that the Hantzsch thiazole synthesis is still very important in chemistry today [48]

Bansal et al. synthesized several thiazole-pyrazole compounds efficiently. The synthesis pathway begins with the reaction of thiosemicarbazone with substituted acetophenones **1** in the presence of ethanol and acid to synthesize a para-substituted acetophenone thiosemicarbazone **2**. Additionally, p-NO2-phenacyl bromide in ethanol was used to synthesize Hantzsch thiazoles **3**. This was followed by a Vilsmeier-Haack cyclization reaction utilizing DMF/POCl3 as reagents to produce substituted carbaldehydes **4**. Some thiazole-pyrazole compounds 5 were later produced by refluxing suitable substituted aminothiazoles with carbaldehydes in ethanol and fused sodium acetate. Depending on the substituent added, the yields ranged from modest to good [49]



Scheme 1. Synthesis of thiazole clubbed pyrazole derivatives.

Folquitto et al.[50] Formyl eugenol and formyl dihydro eugenol **7** were first prepared using the well-known Duff reaction to start the synthesis [51] These formylated compounds were then reacted with two commercially available aldehydes, vanillin and salicylaldehyde, in ethanol under heating conditions to create the thiosemicarbazones **8** [52] Lastly, the target thiazole derivatives **9** were produced by reacting thiosemicarbazones **8** with different α-bromoketones in isopropanol under heat [53]



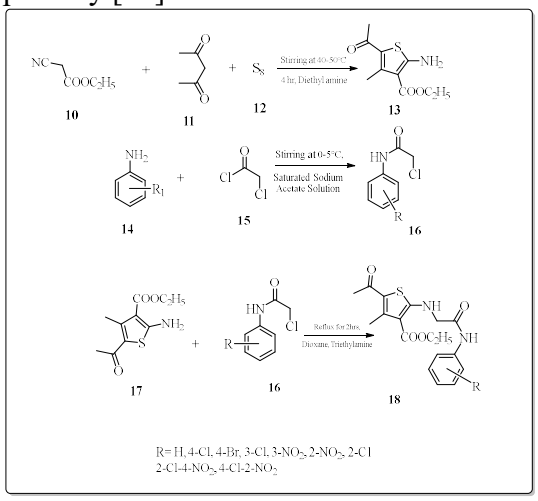
Scheme 2. Synthesis of new thiazole compounds by Hantzsch thiazole synthesis.

4.1.2 Gewald reaction (thiophene synthesis)

The Gewald Reaction involves a reaction of an α-cyano ester and either an aldehyde or a ketone between elemental sulfur and a basic compound to produce a

polysubstituted 2-aminothiophene. Karl Gewald is credited with the development of the reaction [54] This synthesis has been used extensively since it was first published in 1961, becoming widely accepted and used throughout the years following that period due to its ability to provide substituted 2-aminothiophenes, through multiple reagents being supplied as well as under mild conditions [55] Mechanistically, comprehensive DFT computational studies have established that the reaction is initiated by a Knoevenagel-Cope condensation, followed by the opening of elemental sulfur, leading to polysulfide intermediates, which ultimately undergo intramolecular cyclization to furnish the 2-aminothiophene product Over the years, classical limitations of the reaction have been addressed through modern modifications, including microwave-assisted protocols, solvent-free mechanochemical approaches, and aqueous-phase green methodologies, affording the desired products in yields of 75–98% [56] In drug discovery, 2-aminothiophenes occupy a special position owing to their structural simplicity, availability, and broad biological properties, including antimicrobial, anti-inflammatory, antifungal, antioxidant, and antidiabetic activities, and they serve as key scaffolds in top-selling drugs such as olanzapine and tinoridine.

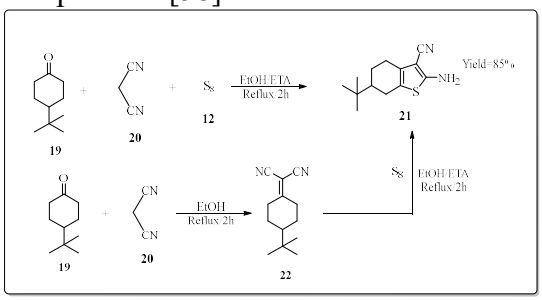
Mishra et al. describe a three-step synthesis of a series of hybrid amide compounds **18** based on 2-aminothiophenes. In step one, ethyl cyanoacetate **10**, acetylacetone **11**, and elemental sulfur S_8 **12** undergo a multi-component Gewald reaction in which Knoevenagel condensation, incorporation of sulfur, and cyclization-aromatization occur to yield a derivative of polysubstituted 2-aminothiophene **13**. In step two, chloroacetyl chloride **15** is used to N-acylate substituted aniline **14**, which produces the N-aryl-2-chloroacetamide intermediates **16**. In step three, the exocyclic -NH_2 group of compounds four reacts with the α-chloro carbon of each intermediate compound **16** by nucleophilic substitution to create a -$NHCH_2$- linkage that connects the thiophene scaffold to the arylacetamide arm, providing access to the final hybrids **18**. The only difference among the compounds is in the terminal aryl substituent (R), providing an opportunity for a systematic SAR study to determine how the electronic properties and steric hindrance of the aryl substituted compounds affect their anticancer potency [57]



Scheme 3. Synthesis of a new thiophene compound by the Gewald reaction.

Balamon et al. used a two-path Gewald reaction for making bicyclic 2-amino-4,5,6,7-tetrahydrobenzob [b]thiophene-3-carbonitrile **21** with a tert-butyl substituent. Using the upper path, all reactions, i.e., Knoevenagel condensation, incorporation of sulfur, cyclization, and the final step to convert to the aromatic ring, occur in one vessel, giving an overall yield of 85% of

compound **21**. 4-tert-butylcyclohexanone **19** is used with malononitrile **20** and elemental sulfur **S8** in ethanol/ethanolamine (ETA) and refluxed for 2 hours. The second method (the bottom pathway) consists of two steps. The ketone **19** and malononitrile **20** undergo a Knoevenagel condensation in refluxing ethanol for 3 hours to produce the intermediate compound **22**. This intermediate is then reacted with elemental sulfur **S8** in a separate reaction (ethanol/ETA at reflux for 2 hours) to complete the cyclization-aromatization sequence, thereby producing the same compound 1 [58]



Scheme 4. Two-pathed synthetic procedure of thiophene-carbonitrile by Gewald reaction.

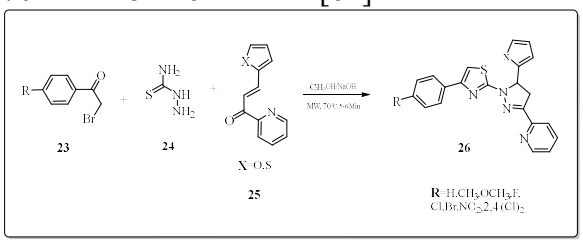
4.2 Modern Synthetic Approaches

Modern synthetic strategies have shifted toward greener, more efficient methodologies now provide diverse sulfur heterocycles with improved atom economy and selectivity for the formation of new and recent sulfur-containing heterocycles.

4.2.1 Microwave-assisted synthesis

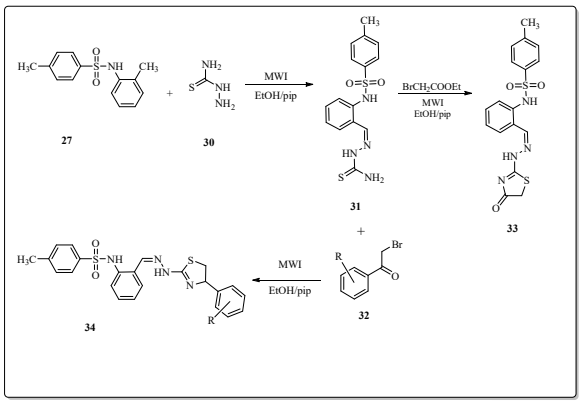
The importance of sulfur-containing heterocyclic compounds for biomedical and material science applications has driven a surge in microwave (MW)-assisted synthetic methods, whose supreme advantage lies in the extraordinary acceleration of reaction rates under unconventional conditions [59] MW-assisted synthesis offers fast, high-yield protocols with milder conditions and reduced environmental impact through solvent-free procedures, making purification more manageable compared to conventional approaches [60].

Mamidala et al. established a single-step, microwave-mediated process for the synthesis of several furan hybrids intended as powerful anticancer drugs, **26**, with remarkable yields. The multicomponent synthesis produced the required compounds by cyclizing phenacyl bromide **23** with thiosemicarbazide **24** and then reacting chalcone **25** with a catalytic quantity of sodium hydroxide (NaOH) in ethanol at 70 °C for 5 to 6 minutes [61]



Scheme 5. Synthetic procedure for sulfur-containing furan hybrids by microwave-assisted reaction.

Alrayes et al. demonstrated that N-{2-[(carbamothioylhydrazono)methyl]phenyl}-4-methylbenzene sulfonamide **31** was created in high yield (92%) by condensing N-(2 formylphenyl)-4-methylbenzenesulfonamide **27** with thiosemicarbazide **30** in the presence of piperidine as a catalyst under microwave irradiation (MWI). Cyclization of **31** with some active methyl bromoacetate or phenacyl bromide derivatives **32** via MWI produced the corresponding thiazole derivatives **33** and **34** [62].

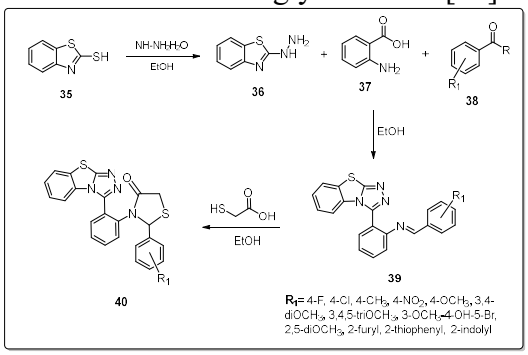


Scheme 6. Synthetic pathway for the synthesis of sulfonamide-sulfur-containing heterocycle by microwave-assisted reaction.

4.2.2 Green chemistry methods

The synthesis of sulfur-containing heterocyclic compounds poses a major challenge for organic chemists, particularly in the context of green chemistry principles; recent work has focused on employing green solvents such as water, ionic liquids, deep eutectic solvents (DES), glycerol, and polyethylene glycol for five-, six-, and seven-membered S-heterocyclic ring systems[63, 64]. Representative catalyst-free aqueous reactions have afforded 2-aminothiophenes, 2-aminothiazoles, benzothiazoles, dithiocoumarins, and thiadiazoles with yields reaching 75–98%, where high medium polarization causes spontaneous product precipitation and facilitates isolation[65] In a recent sustainable approach employing bio-based catalysts, including plant extracts and enzymatic systems, a range of nitrogen- and sulfur-containing heterocycles were synthesized under mild aqueous and solvent-free conditions, achieving excellent reaction yields of 78–93% with high atom economy and low E-factors[64] .

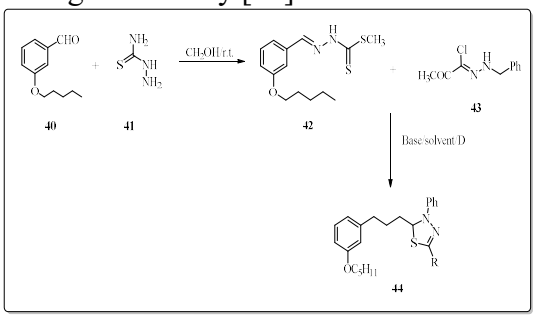
Dwivedi et al. demonstrated that the starting material for the broad synthesis pathway of benzothiazolo[2,3-c][1,2,4]triazole derivatives 4a–l is 2-hydrazinobenzothiazole **36**, which was initially made using the described technique [66]. First, 2-hydrazinobenzothiazole **36** was produced by refluxing a combination of 2-mercaptobenzothiazole **35** and hydrazine hydrate in ethanol. Benzothiazole–thiazole derivatives were obtained by treating a mixture of 2-hydrazinobenzothiazole **36**, anthranilic acid **37**, and several aromatic/heteroaromatic aldehydes **38** under reflux conditions using a one-pot method. As shown in Scheme 1, the desired thiazolidinone-appended benzothiazolo[2,3-c][1,2,4]triazole compounds **40** were created by combining synthesized benzothiazole–triazoles **39** with thioglycolic acid [67].



Scheme 7. Synthesis of benzothiazole-triazole and thiazolidinone-appended benzothiazole-triazole hybrids.

Alhadhrami et el. show how to make a new type of molecule, hydrazonothiadiazole hybrid scaffolds, in a simple way that takes only two steps. Firstly, the starting materials, 3-(pentyloxy)benzaldehyde **40** and methyl hydrazine carbodithioate **41,** are combined by reacting the two together in methanol at room temperature to form the intermediate hydrazone carbodithioate **42** through the process of nucleophilic addition-elimination [68]The new chemical structure has a stable C=N (hydrazone) bond with the removal of water as a byproduct, and was made

under mild, environmentally friendly conditions that did not require the use of harsh chemicals or catalysts to produce it [69]. Then the intermediate developed **42**, undergoes a cyclocondensation reaction with hydrazonoyl chlorine **43** under basic and heated conditions through either an S-alkylation followed by intramolecular ring closure (with the expulsion of CH_3SH) or through a [3+2] dipolar cycloaddition between an in-situ generated nitrilimine and the C=S bond of **42** resulting in the formation of the five membered thiadiazole ring in **44** and the conversion of the intermediate into a compound that exhibits pharmacological properties associated with the compounds that have been shown to have antitumor, antimicrobial and enzyme inhibiting biological activity [70]

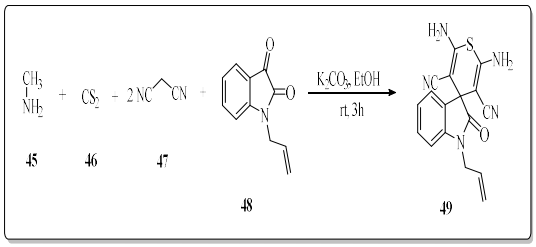


Scheme 8. Synthesis of Hydrazono [1,3,4]thiadiazole by green chemistry methods.

4.2.3 One-pot multicomponent reactions

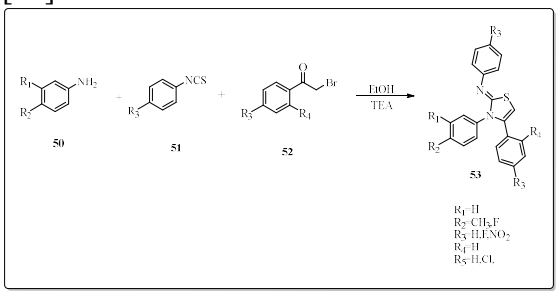
Multicomponent reactions (MCRs) have emerged as a transformative approach in organic synthesis, whereby multiple reactants are combined in a single reaction vessel to create structurally complex products with high atom economy, reduced waste, and minimal operational steps [71] A recent comprehensive review covering 2010 to 2024 examined magnetically recoverable catalysts for one-pot multicomponent synthesis of heterocyclic organosulfur compounds, demonstrating significant enhancements in reaction yields, selectivity, and catalyst recyclability directly aligning chemical synthesis with green chemistry principles [71]. In a specific example, a hydrotalcite–lanthanum nanocatalyst (HT-La) efficiently catalyzed the one-pot three-component condensation of benzaldehyde, malononitrile, and thiophenol for the synthesis of 2-amino-3,5-dicyano-6-sulfanyl pyridine derivatives, with the nanocatalyst demonstrating reusability over several cycles with only moderate activity loss [72].

Moghaddam et el. first examined the reactions of methylamine **45**, carbon disulfide **46**, malononitrile **47**, and 1-allylindoline-2,3-dione **48**. To obtain the corresponding 1-allyl-20,60 diamino-2-oxospiro[indoline-3,40-thiopyran]-30,50-dicarbonitrile **49** in high yield, a mixture of 1 (0.6 mmol), 2 (0.7 mmol), and **48** (0.57 mmol) was added in the presence of K2CO3 and stirred for an additional three hours. The ideal reaction conditions were then reached by screening several bases and solvents. First, the impact of various bases on the reaction was examined. Various reaction solvents were also evaluated for improved outcomes. EtOH was determined to be appropriate for the model reaction and was chosen as both a green and an effective solvent in this process. Overall, at 25 °C and 3 hours of stirring, K2CO3 as the catalyst and EtOH as the solvent produced the greatest results [73]



Scheme 9. Synthetic pathway of thiopyran-dicarbonitrile by One-pot multicomponent reactions.

Mermer et el. created several new compounds that consist of thiazole linked to imine. The compounds 4(a-j) were created by using a Multicomponent reaction that brought 3 chemical elements together at once. The three elements are a substituted aniline **50**, substituted phenacyl bromide **52**, and the Aryl isothiocyanate **51**. In the reaction scheme shown below, the reaction occurs using aniline (the first portion of the reaction scheme showed that the substituted phenyl group on the aniline, R1[2,6-dimethyl], is an aryl isothiocyanate (with R3), and substituted phenacyl bromide (R4/R5). Since there was some worry about how to carry out reactions, by looking at the properties of the reactants based upon previously studied benzoic acid, to figure out what would yield the highest yield from the reaction to generate the final products. Before finalizing the variable conditions for the reaction, options must be evaluated for solvents and bases to carry out the reactions. We examined KOH, NaOH, K2CO3, NaHCO3, and TEA as bases using toluidine and phenyl isothiocyanate and phenacyl bromide to finally see that TEA provided the highest yield (77%) of target products. After testing methanol and other solvents, we finally determined that ethanol would prove to be the optimal solvent to provide maximum yield from these reactions. The final optimized set of conditions is as follows: Ethanol, TEA base, with 120-minute reaction time produced thiazole-imine derivatives **53** with good yields, with diverse substitution patterns (2,6-dimethyl) for each product derivative [74]



Scheme 10. Synthetic pathway of thiazole-imine by One-pot multicomponent reactions.

4.3 Metal-Catalyzed Synthesis

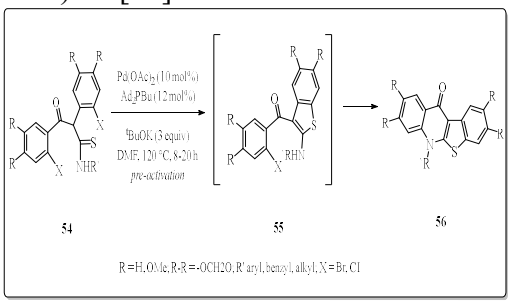
Transition metal-catalyzed reactions have emerged as one of the most powerful strategies for the construction of sulfur-containing heterocyclic frameworks, offering superior selectivity, mild reaction conditions, and broad functional group tolerance compared to classical stoichiometric approaches Among the transition metals explored, palladium and copper have dominated this field owing to their unique ability to activate carbon-sulfur bonds through well-defined oxidative addition, transmetalation, and reductive elimination pathways, enabling efficient access to therapeutically important scaffolds such as benzothiazoles, thiophenes, benzothiophenes, and thiazolines [75].

4.3.1 Pd-catalyzed coupling

Palladium-catalyzed coupling of thiols with aryl halides and pseudo-halides remains one of the most important methods in the synthesis of thioethers and sulfur-containing heterocyclic scaffolds, exploiting diverse mechanistic pathways including oxidative addition, transmetalation, and reductive elimination under mild, well-controlled conditions Sulfur-directed palladium-catalyzed cascade C–H activation and

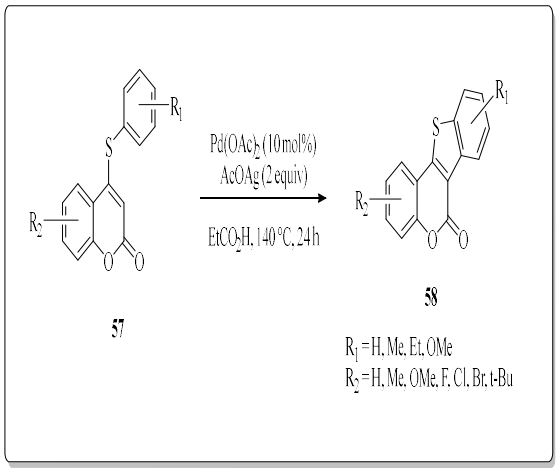
cyclization with alkynes has emerged as a particularly powerful strategy, with the research significance of this approach lying in maintaining a balance between activating and poisoning the catalyst while capitalizing on the diverse and novel properties of the resulting scaffolds [76]. Recent notable advances include Pd(II)-catalyzed oxidative C–H functionalization and annulation of substituted substrates, and a Rh(III)-catalyzed C–H activation/intramolecular annulation for the synthesis of fused sulfur-containing isochromeno-benzothiazine scaffolds, demonstrating the breadth of noble-metal catalysis in this domain [77].

Janni et el. have discovered a double cyclization process (S-cyclization followed by N-cyclization). Starting from N-substituted 2,3-bis(2-halo phenyl)-3-oxopropanethioamides **54**, (2-aminobenzo[b]thio phen-3-yl)(2-halophenyl)methanones **55** (from P(0)-catalyzed S-cyclization) were created as intermediates. These were subsequently transformed in situ by Pd(0) N-cyclization into the ultimately isolated tetracyclic compounds (6-substituted benzo[4,5]thieno[2,3-b]quinolin-11(6H)-ones) **56** [78]



Scheme 11. Synthetic pathway of thieno-quinolinones by Pd-catalyzed coupling.

Zhang et el. reported in 2019 that 4-(phenyl thio)-2H-chromen-2-ones **57** was converted into 6H-benzo[4,5]thieno[3,2-c]chromen-6-ones **58** using Ag2CO3 as an oxidant and Pd(OAc)2 as a catalyst [79].



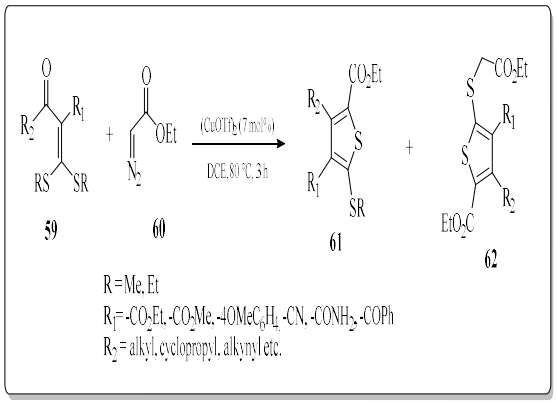
Scheme 12. Synthetic pathway of thieno-chromenones by Pd-catalyzed coupling.

4.3.2 Cu-catalyzed cyclization

Copper-catalyzed cyclization reactions are increasingly becoming a focus in contemporary synthetic organic chemistry due to copper's (Cu) unique redox capabilities (Cu(0)/Cu(I)/Cu(II)), extended earth abundance, affordable price, and environmentally friendly nature as compared with precious metals [80]. Copper's ability to effect both two-electron and one-electron transfer systems results in multiple potential mechanisms of action, including radical development, Lewis's acid activations and bond formation between C and heteroatoms, and thus, copper provides a unique approach to the building of both carbocyclic and heterocyclic frameworks [81]. Enhanced enantioselectivity and functionality tolerance achieved using newly developed ligands (including bisoxazoline-type ligands and phenanthroline-type ligands) has allowed synthetic access to chiral heterocycles – including nitrogen, oxygen, and sulphur-containing heterocycles – important in medicinal chemistry [82, 83]. By combining copper catalysis and visible-light photoredox strategies, the synthetic

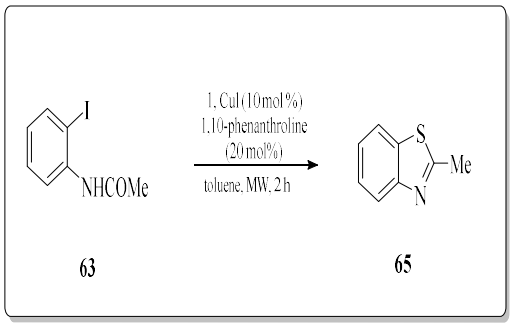
potential has been further enhanced through radical-mediated cyclizations that can be performed at mild reaction conditions [84]; in addition, the formation of intramolecular C–N bonds using copper catalysis allows for a wide range of substrates and a high degree of regioselectivity [81]. Collectively, all these advances have made copper catalysis a powerful and sustainable platform for cyclization chemistry, with numerous uses in the fields of natural products synthesis, drug discovery, and materials science [80] [81]

Sun et el. create poly-substituted thiophenes; they have effectively used Cu(OTf)2 in a domino reaction between diazo compounds 60 and acyclic ketene (S,S)-acetals 59. When copper catalysts were investigated, it was discovered that Cu(OTf)2 was superior to other Cu(II) salts and that the reaction proceeded best in DCE. DMF, THF, and CH_3CN were found to be unsuitable for this reaction. The poly-substituted thiophenes **61** and **62** were discovered to be the predominant and minor products, respectively, when the R_1 group in **59** was CO_2Me, CO_2Et, and 4-$OMeC_6H_4$. However, the tandem reaction produced the exclusive poly-substituted thiophenes **61** in moderate to good yields when the R_1 group was substituted for -CN, -COPh, and -CONH2. [85]



Scheme 13. Synthetic pathway of poly-substituted thiophenes by Cu-catalyzed cyclization.

Silvia et al. tried to separate 2-methylbenzothiazole (14) in the reaction mixture in 50% as the sole reaction product after a combination of **63** and 1, CuI (10 mol %), 1,10-phenanthroline (20 mol%) in a 1:1.5 ratio was heated for two hours under microwave radiation to speed up the ring-closure reaction. The yield of **65** (57%) is not considerably increased by increasing the amount of 1 (13:1 in a 1:3 ratio). [86]



Scheme 14. Synthetic pathway of benzothiazole by Cu-catalyzed cyclization.

4.4 Cyclization Strategies

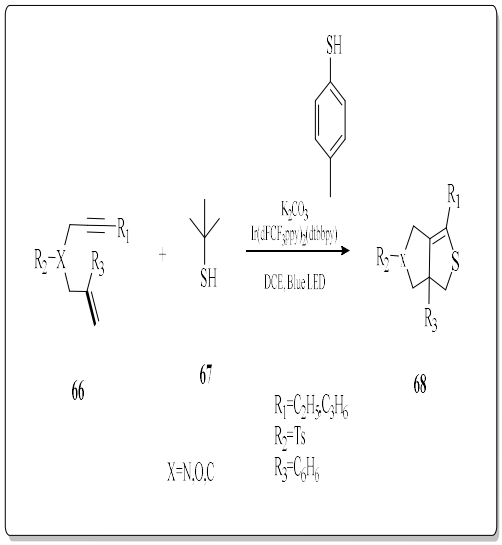
The cyclization of compounds gives rise to many different types of compounds. Transition metals used for catalysis, when performing cyclization, allow us to form both carbocycles and heterocycles in a stereoselective manner, whilst allowing us to activate and perform selective reactions with organic materials, using a variety of methods such as transition metal-catalyzed reactions [87]Using

heterocycles in products has been growing exponentially because of their prevalence in nature and in drug development; it has also been estimated that they account for most registered organic compounds [88]Cyclization can be accomplished in several ways using transition-metal catalysts (i.e., palladium (Pd), copper (Cu), Gold (Au), Rhodium (Rh), and cobalt (Co)) to facilitate the formation of intramolecular C–C bonds and/or intramolecular C–N, C–O, and/or C–S bonds with a very high degree of regioselectivity and stereoselectivity when utilizing these catalysts [1, 2]. Recently, photoredox-mediated radical-polar crossover cyclizations have changed the way we synthesize things by providing very mild conditions and being very compatible with a variety of functional groups [89]In recent years, visible-light-induced cyclization strategies involving nitrogen-centered radicals have also made remarkable progress across transition-metal-catalyzed, metal-free, and photoinduced systems [90]. Collectively, these advances have established cyclization chemistry as a cornerstone of modern synthesis, with broad applications in drug discovery, natural product synthesis, and materials science [91, 92].

4.4.1 Intramolecular cyclization

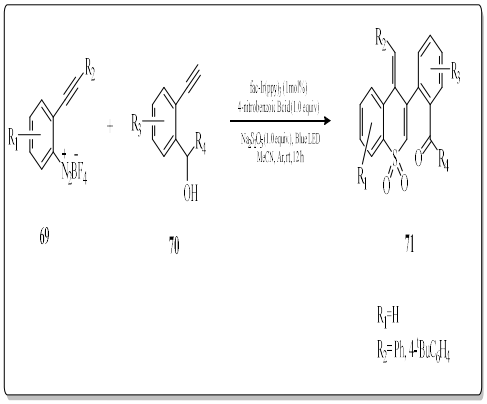
One of the most effective and resource-efficient methods for producing structurally diverse types of both carbocyclic and heterocyclic ring systems in current organic synthesis is through an intramolecular cyclization reaction. Using transition metals as catalysts to promote intramolecular cyclization, it is possible to create stereoselective syntheses of complex frameworks from organic compounds with the potential for selective functionalization or modification under mild conditions. Unlike intermolecular approaches, intramolecular cyclizations benefit from favorable entropic factors and proximity-driven reactivity, often proceeding with high regio- and stereoselectivity. Palladium-catalyzed intramolecular C–H functionalization has further demonstrated the power of this approach by eliminating the need for pre-functionalized substrates [93]. Metal-free intramolecular cyclization strategies have also gained significant traction, offering broad functional group tolerance for the synthesis of pharmaceutically important heterocycles such as indoles [94]. Recently, mild metal-free cyclizations have enabled efficient assembly of diverse N–O heterocycles ranging from 4- to 8-membered rings with yields up to 95% [95]. ACS Publications. Furthermore, Lewis's acid-catalyzed Lewis's hydroamination cascades have extended intramolecular cyclization to privileged scaffolds such as pyrroles and benzo-fused indoles [96]. ACS Publications. Collectively, these strategies have established intramolecular cyclization as a cornerstone of heterocyclic synthesis with broad applications in drug discovery and natural product synthesis [97].

Meng et al. The substrate is 1,6-enyne1a (0.1 mmol, 1.0 equiv.) **66**, the reagent is tert-butyl thiol **67** (0.2 mmol, 2.0 equiv.), the base is K2CO3 (0.2 mmol, 2.0 equiv.), the additive is p-toluene thiol, and Ir [(dFCF3ppy)2(dtbpy)] The intended product **68** is obtained in 97% NMR yield and 95% isolated yield when PF6 is used as a photosensitizer in di chloroethane (DCE) (5.0mL) and exposed to a 30W blue LED for 12 hours.[98]



Scheme 15. Synthetic pathway of sulfur containing hetrocycle by Intramolecular cyclization.

Jiang et al. show a visible-light photoredox-catalyzed cascade cyclization between aryl(alkynyl)iodonium tetrafluoroborate salts **69** and propargylic alcohols **70** to afford thiochromenone derivatives **71**. Using *fac*-Ir(ppy)$_3$ (1.0 mol%) as the photocatalyst under blue LED irradiation, 4-nitrobenzoic acid (1.0 equiv) as a mild oxidant, and $Na_2S_2O_3$ (1.0 equiv) as both a sulfur source and reductant in acetonitrile under argon at room temperature over 12 hours, the reaction proceeds via single-electron transfer (SET) from the excited Ir(III)* to the electrophilic iodonium salt, generating a reactive alkynyl radical that adds to the alkyne of the propargylic alcohol partner, followed by intramolecular C–S bond-forming cyclization to construct the six-membered sulfur-containing ring, ultimately delivering the thiochromenone scaffold **71** bearing an exocyclic alkene [99].



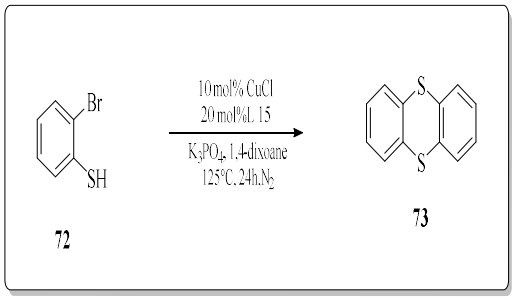
Scheme 16. Synthetic pathway of the thiochromenone scaffold bearing an exocyclic alkene by Intramolecular cyclization.

4.4.2 Intermolecular cyclization

Intermolecular cyclization reactions have emerged as a highly versatile strategy in modern synthetic chemistry, enabling the construction of diverse carbocyclic and heterocyclic frameworks by reacting two or more distinct molecular components. Transition metal complexes have revolutionized this area by activating and selectively functionalizing organic substrates, facilitating the rapid assembly of complex cyclic structures otherwise challenging to construct through conventional methods. Unlike intramolecular approaches, intermolecular cyclizations offer greater flexibility in substrate design and allow simultaneous incorporation of multiple structural fragments into the final ring system. Cycloadditions, being inherently intermolecular in nature, are generally more amenable to convergent synthetic strategies, offering distinct advantages in terms of atom economy and synthetic efficiency [100]. Multicomponent intermolecular cyclization reactions using alkynyl aldehydes have served as privileged strategies for constructing a broad spectrum of N-, O-, and S-heterocycles under metal-catalyzed, metal-free, and visible-light-mediated systems [101]. Pyridinium and

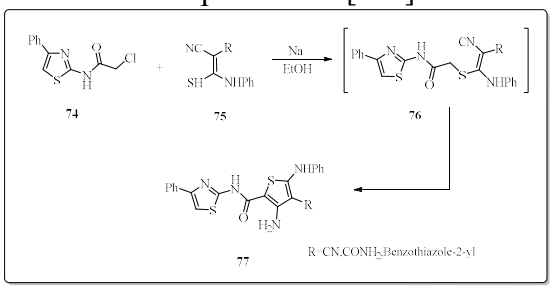
quinolinium 1,4-zwitterions have also been successfully employed as versatile intermolecular blocks in the synthesis of three- to eight-membered heterocycles of relevance to natural products and drug design [102]. Furthermore, visible-light-driven intermolecular cycloadditions have opened new avenues for the synthesis of four-membered ring systems under mild and sustainable conditions Collectively, these advances have established intermolecular cyclization as an indispensable tool in heterocyclic synthesis with broad applications in pharmaceuticals and materials science [103].

Ruiting et al. The copper-catalyzed Ullmann-style reaction shown here involves the coupling of 2-bromothiophenol **72** into dibenzodithiin **73**, which is a symmetric six-membered heterocycle with two sulfanes (sulfur atoms), by way of two successive intermolecular C(sp^2)–S bond formations, once where the thiol of one molecule couples to the aryl bromide of another by way of an Ullmann-type reaction and a second C–S bond that occurs either intermolecularly in order to close the six-membered dithiin ring; the initial intermolecular process is completed by CuCl (10%), which functions as a Cu(I) catalyst, L15 (20%) that stabilizes the activation of the active copper species and lowers the energy of activation required for the coupling process and K_3PO_4, which is an inorganic base used to deprotonate the thiol and to drive the coupling reaction; the reaction for 1,4-dioxane is performed at 125°C for 24 hours in a nitrogen atmosphere in order to prevent the oxidation of the thiol and the copper catalyst, delivering the symmetric dibenzodithiin **73** product through the efficient C–S bond formation consistent with a ligand-assisted Ullmann cross-coupling procedure [104].



Scheme 17. Synthetic pathway of dibenzodithiin by Intermolecular cyclization.

ABDEL-LATIF et al. stated that Compound **74** undergoes cyclocondensation with 3-mercapto-3-phenylamino-acrylonitrile derivatives **75** when sodium ethoxide is present. The corresponding 3-amino 5-phenylamino-2-(4-phenylthiazol-2-yl-carbamoyl)-4 substituted thiophene derivatives **77** were produced. Nucleophilic attack of the thiol function could result in the sulfide intermediate **74**, which could then undergo intramolecular cyclization through nucleophilic addition of the methylene group to the activated nitrile to produce the corresponding 3-amino-4-substituted-thiophenes **77**. [105]



Scheme 18. Synthetic pathway of substituted-thiophenes by Intermolecular cyclization.

5. Biological Activities (Highly Important Section)

Modern medicinal chemistry holds sulfur-containing heterocyclic compounds in high esteem due to their important roles in pharmacological activities. Some of their diverse

pharmacological activity profiles can be attributed to the electronic nature of the sulfur atom, making this atom capable of engaging in hydrophobic interactions, coordinating with metal centers, and forming covalent bonds with biological targets [106]. The sub-sections throughout this article present a systematic, compound-specific organization of biological activity reported recently, verifying that each compound mentioned in the narrative has been included in the form of a summary table.

5.1 Antimicrobial Activity

Antimicrobial resistance represents one of the most critical global health threats of the 21st century, and sulfur-containing heterocycles have emerged as productive scaffolds for addressing this challenge. The most intensively investigated classes include thiazoles, thiadiazoles, benzothiazoles, and their fused or hybrid analogs, all of which exploit the sulfur and nitrogen atoms for key interactions with bacterial enzymes and fungal target proteins [107].

The benzimidazole-thiadiazole hybrid compounds are the strongest representatives of benzimidazole derivatives. A study conducted in 2024 synthesized and tested 9 different hybrids for their antibacterial and antifungal properties against 8 bacterial strains and 3 fungi. Two of these compounds, **5f** and **5h**, were found to be very potent against Pseudomonas and Candida albicans (MIC=3.90 μg/mL), like Voriconazole, but twice as effective as Fluconazole. In addition, both compounds have excellent antibacterial properties against Enterococcus faecalis (ATCC 2942; MIC=3.90 μg/mL). A molecular dock of compound **5h** (substituted with 4-methoxyphenyl) showed that the compound has three hydrophobic interactions with His377 and Tyr1188 and one hydrogen bond with Tyr132 at the active site of the 14α-demethylase enzyme, verifying its proposed mechanism of action as an antifungal agent. [108]

The disulfide scaffold inspired by allicin provides an alternate & novel means to create antimicrobials. A collection of disulfides (heterocycles) with pyridine, pyrimidine, thiophene, thiazole, benzothiazole, & quinoline motifs was designed & produced based on the biological activity of the allicin disulfide compound. Of these, the most promising antifungal compound in vitro against M. fructicola was compound **S8** (a thiazole disulfide) with an effective concentration 50 (EC50) of 5.92 μg/mL. Subsequent vivo testing showed that **S8** had similar curative properties & an increased level of protection compared to thiophanate methyl (the standard), when applied at a rate of 200 μg/mL. Mechanistic assays demonstrated that **S8** inhibited hyphal growth at both time & dose response and compromised the membrane integrity of the hyphae. [109]

For antibacterial sulfonamide hybrids, benzimidazole, indazole, benzothiazole, and thiazole-bearing sulfonamide derivatives have proven effective. In a broth dilution screening, molecules were found highly active (MIC values 50–3.1 μg/mL) against *B. cereus*, *S. aureus*, *E. coli*, and *P. aeruginosa*, with the highest potency recorded against *E. coli*. A notable synergistic effect was observed in fractional inhibitory concentration (FIC) determination, where test compounds in combination with reference drugs chloramphenicol or sulfamethoxazole showed 4–32-fold enhancement in potency. [110]

Benzothiazole–thiazole hybrid compounds also represent a significant

advance in broad-spectrum antimicrobials. A series of benzothiazole-thiazole hybrids **4a–4f** was evaluated against Gram-positive (*S. aureus*, *B. subtilis*, *E. faecalis*), Gram-negative (*E. coli*, *P. aeruginosa*), and fungal strains (*A. niger*, *A. oryzae*, *C. albicans*, Rhizopus sp.) as well as the slow-growing pathogen *Mycobacterium tuberculosis*, using Kirby–Bauer disk diffusion and REMA assays. [111]

A parallel study explored a structurally distinct series of benzimidazole-1,3,4-thiadiazoles. Compounds **4f** and **4i** with MIC values of less than 0.97 µg/mL were found most effective against *E. coli*, while showing the best antifungal activity with MIC = 1.95 µg/mL against *C. albicans* — demonstrating that the benzimidazole-thiadiazole pharmacophore combination yields broad-spectrum potency [112]

Compound No.	**Assay**	**Target Organism**	**Key Result (MIC/ EC 50)**	**Reference**
5f (Benzimidazole-thiadiazole)	MTT/MIC (broth dilution)	*C. albicans*; *E. faecalis*	MIC = 3.90 µg/mL (both); = voriconazole; 2×> fluconazole	[108]
5h (4-OCH₃-phenyl-benzimidazole-thiadiazole)	MTT/MIC; molecular docking	*C. albicans*; *E. faecalis*; 14-α demethylase	MIC = 3.90 µg/mL; H-bond with Tyr 132; ΔE = 3.417 eV (most reactive)	[108]
S8 (Thiazole-disulfide)	*EC50; in vivo bioassay*	MIC (*E. coli*) < 0.97 µg/mL; MIC (*C. albicans*) = 1.95 µg/mL	EC50 = 5.92 µg/mL; curative = thiophanate methyl at 200 µg/mL	[109]

Sulfonamide-heterocyclic series	Broth dilution + FIC	*E. coli* (most potent), *S. aureus*, *P. aeruginosa*	MIC = 3.1–50 µg/mL; FIC 4–32× potentiation with chloramphenicol	[110]
4a–4f (Benzothiazole-thiazole hybrids)	Kirby–Bauer + REMA	*S. aureus, E. coli, M. tuberculosis, C. albicans*	Broad-spectrum; REMA MIC 0.97–500 µg/mL range	[111]
4f, 4i (Benzimidazole-thiadiazoles)	Broth MIC	*E. coli; C. albicans*	MIC (*E. coli*) < 0.97 µg/mL; MIC (*C. albicans*) = 1.95 µg/mL	[112]

5.2 Anticancer Activity

Cancer remains the second leading cause of mortality worldwide,[113] and sulfur-containing heterocycles have demonstrated exceptional anticancer versatility by inhibiting diverse oncological targets: tyrosine kinases, CDKs, VEGFR-2, EGFR, and topoisomerases. The key scaffold classes include thiazolidinones, thiadiazoles, benzothiazoles, and their hybrids [114]

Evaluating cancer cytotoxicity on a wide variety of cell lines, the thiazolidinone and thiadiazole derivatives of the organic compound 4-(4-acetamidophenyl)thiosemicarbazide recently made a great impact in the study of new medications. 6-Thiazolidinone compounds were specifically tested on MCF-7 breast cancer cells (note: their IC50 concentrations of 6.70±0.5µM for compound **6c** and 7.51±0.8µM for compound **6e** are very near the reference drug, doxorubicin, with an IC50∼of 4.17±0.2µM). The incorporation of molecular docking procedures using the PDB code (from the protein data bank) of a molecular target with accession number 1DLS further examines the potential use of a molecule to treat cancer [115]

The benzothiazole studies looked at three kinds of 2-aminobenzothiazole hybrids. These benzothiazole hybrids were made up of thiadiazole aryl urea, cyanothiouracil, and thiazolidine-2,4-dione. The results of the benzothiazole studies showed that benzothiazole compound 4a was very potent. This benzothiazole compound 4a had thiazolidine-2,4-dione in it. The IC50

values of benzothiazole compound 4a were 5.61, 7.92, and 3.84 μM against the HCT-116, HepG-2, and MCF-7 cell lines that were tested. The benzothiazole compound 8a was also looked at. This benzothiazole compound 8a had cyanothiouracil in it. Was methyl-substituted. Benzothiazole compound 8a was the effective cyanothiouracil analog that was tested. The IC50 values of benzothiazole compound 8a were between 10.86 and 18.10 μM, against the HCT-116, HepG-2, and MCF-7 cell lines that were used in the test. Compounds 4a, 4e, and 8a clearly caused apoptosis and cell cycle arrest in MCF-7 cells at the S phase (**4a** and **4a**) and G1/S phase (8a). Compound **4a** showed substantial VEGFR-2 inhibition with an IC50 of 91 nM, which is consistent with the cytotoxic action, compared to sorafenib's 53 nM [116].

VEGFR-2 inhibitors that are thiadiazole based were designed and evaluated as 2,3-dihydro-1,3,4-the studies were conducted on Compound **11a**, the most potent and selective of this class of compounds, which has demonstrated anticancer activity with IC50 (MCF-7 9.49μm, HepG-2 12.89μm) greater than 3 (selective index) over WI-38 normal human cells; Compound **11a** also show comparable inhibition of VEGFR-2 enzymatic activity (IC50=0.055 μm) to Sorafenib. It is further indicated via flow cytometry that Compound **11a** induces >70% apoptosis and results in S phase and G2/M phase cell cycle arrest, while ELISA studies demonstrate that Compound **11a** activates the mitochondrial pathway of apoptosis [117]

When developing an imidazo(thiazolo)lone-thiazolidinone based EGFR series, **4c** (imidazo(thiazolo)lone-thiazolidinone) was identified to be a potent inhibitor of EGFR kinase activity (IC50 = 18.35 ± 1.25 μM) relative to erlotinib (IC50 = 6.12 ± 0.92 μM) & had superior antitumor efficacy (IC50 = 10.74 ± 0.40 μM) against A549 cells than erlotinib. The results of molecular docking, 100ns MD simulations & MMGBSA calculations support that compound **4c** displayed a long-lasting duration of interaction (96% & 97%) at the EGFR binding site, like erlotinib. [118]

A thiazole derivative incorporating a dimethylaniline moiety also demonstrated notable hepatocellular carcinoma activity. Thiazole derivative **2** (4-methyl-substituted thiazole-dimethylaniline hybrid) showed equipotent activity (IC50 = 1.2 μM) against the HepG-2 cell line, matching doxorubicin (IC50 = 1.1 μM), while exhibiting only 80% inhibition against MDA-MB-231. Molecular docking into CDK1/CyclinB1/CKS2 (PDB ID: 4y72) supported the inhibitory mechanism of action [119].

Compound No.	**Assay**	**Target Organism**	**Key Result (MIC/EC50)**	**Reference**
6c (Thiazolidinone)	MCF-7 (br	CDK/PDB 1DLS docking	IC50 = 6.70 ± 0.5 μ	[115]

	east)		M (≈ doxorubicin 4.17)	
6e (Thiazolidinone)	MCF-7 (breast)	CDK/PDB 1DLS docking	IC50 = 7.51 ± 0.8 μM (≈ doxorubicin 4.17)	[115]
4a (Benzothiazole-thiazolidine-2,4-dione)	HCT-116, HepG-2, MCF-7	VEGFR-2 (IC50 = 91 nM); apoptosis + S-phase arrest	IC50 = 5.61 / 7.92 / 3.84 μM	[116]
11a (2,3-dihydro-thiadiazole)	MCF-7, HepG-2	VEGFR-2 (IC50 = 0.055 μM); apoptosis + S/G2 M arrest	9 (MCF-7), 12.89 (HepG-2) μM; SI > 3	[117]
4c (Imidazothiazole-thiazolidinone)	A549 (lung), MCF-7	EGFR kinase (IC50 = 18.35 μM)	IC50 (A549) = 10.74 ± 0.40 μM	[118]
2 (Thiazole-dimethylaniline)	HepG-2 (liver)	CDK1/CyclinB1/CKS2	IC50 = 1.2 μM ≈ doxorubicin (1.1 μM)	[119]

5.3 Anti-inflammatory Activity

Chronic inflammation mediated via the cyclooxygenase (COX) pathway underpins conditions ranging from arthritis to cardiovascular disease and cancer [120]. The structural features of thiazole, benzothiazole, thiazolidinone, and thiophene scaffolds make them naturally suited to occupying the secondary hydrophobic pocket of the COX-2 active site, enabling high selectivity over COX-1[121].

A diphenyl-amino thiazole compound **3b** (R = Me) exhibited the highest COX-2 inhibitory activity (IC50 = 0.09 μM, SI = 61.66), comparable to etoricoxib (IC50 = 0.07 μM, SI = 91.28). Docking simulations showed that the carbonyl group was involved in a hydrogen-bond interaction with His351, while the diphenyl-amino moieties oriented within the hydrophobic pocket through amino acids His90, Thr94, Pro514, Asp515, Pro191, Tyr355, Gly354, Gln192, and Ser353 [122].

According to the same systematic review, compounds with a benzo[d]thiazole structure were also shown as selective COX-2 inhibitors. The benzo[d]thiazole analogs (4) were determined to be very potent, selective COX-2 inhibitors with IC50 values ranging from 0.28 to 0.77μM and SI values between 7.2 and 18.6 and demonstrated appreciable anti-inflammatory activity when evaluated in vivo (inhibition of edema = 1.95–94.6%). Compound 4a, the benzyloxy analog containing a meta-fluorine on the phenyl ring, had the highest activity (IC50 = 0.28 μM, SI = 18.6) and was like celecoxib in terms of both IC50 (0.27 μM) and SI (19.7) [122].

A new series of dual COX/5-LOX inhibitor compounds, which include both in vitro and in vivo studies were created by utilizing the 2-priority green building block-based methodology within the synthesis of the thiazole and thiazolidiene compound series. Compound 6l, which is identified as the most potent of the dual COX-2/5-LOX inhibitor compounds, has been demonstrated as a selective dual inhibitor by exhibiting very low IC50 values of 0.09 from the COX-2 enzyme and 0.38 from the 5-LOX enzyme. In vivo evaluation of the anti-inflammatory properties of **6l** was confirmed in the carrageenan-induced model by demonstrating a 60.82% reduction in edema of the paw in Wistar rats. Furthermore, the anti-inflammatory activity of **6l** is supported by the use of qRT-PCR in the assessment of gene expression of COX-2 and 5-LOX that exhibits a marked downregulation, along with reduced levels of PGE2 and LTB4 found in the paw tissue assayed [123].

A total of seven new thiazole compounds were assessed for their ability to inhibit COX-2 as part of an independent study of new thiazole compounds that are structurally similar to one of the blocks used in the synthesis of (4-(4-chlorothiophen-2-yl) thiazol-2-amine). The seven thiazole compound inhibitors (5a-5g) demonstrated strong inhibitory activity compared to Celecoxib (IC50=0.05 μM), ranging from 0.76 μM (5g) to ≤9.01 μM (5a, 5c), an order of magnitude. The best selective inhibitors, as defined by SI values of 42, 112, and 124, respectively, were 5b, 5d, and 5e. Compound **5d** exhibited the greatest 5-LOX inhibitory activity (IC50 = 23.08 μM), approximately 50% less than zileuton's potency as a reference compound. Molecular docking analysis of compound **5d** demonstrated π–sulfur interactions with Tyr355 and Phe518 through the sulfur of the thiazole and thiophene rings, supporting its dual inhibitory pharmacology [124].

There was a significant thiazolylhydrazine methyl sulfone-based COX-2 inhibitor featured in a recent comprehensive review. Compound **34** is a thiazolylhydrazine methyl sulfone-based analogue that had a meta-hydroxyl substituent and displayed significant/consistent COX-2 selectivity (IC50 = 0.140 ± 0.006 μmol/L; SI > 714.28), comparable to celecoxib (IC50 = 0.132 ± 0.005 μmol/L) [125].
Compounds **35 – 37** from a thiazolyl-aminothiazole-pyrimidine-carbonitrile hybrid series had respective IC50 values of 1.17, 1.13, and 1.03 μmol/L and displayed good and selective COX-2 selectivities and SI values of 5.78, 7.84, and 8.21, respectively, in relation to celecoxib. Additionally, these compounds produced up to 90%, 94%, and 86% of meloxicam in vivo anti-inflammatory activities 4 hours post-dosing, with an overall superior gastric safety profile[126].

Compound No.	**Assay**	**Target Organism**	**Key Result (MIC/EC50)**	**Reference**
3b (Diphenyl-amino thiazole)	In vitro COX-1/COX-2 EIA	COX-2; H-bond with His351, hydrophobic with His90, Thr94, Tyr355	IC50 = 0.09 μM, SI = 61.66 (≈ etoricoxib)	[122]
4a (Benzyloxy-fluorobenzothiazole)	In vitro COX-2 EIA + in vivo	COX-2 selective	IC50 = 0.28 μM, SI = 18.6 (≈ celecoxib 0.27 μM)	[122]
6l (Thiazole-thiophenyl dual	In vitro COX	Dual COX-	IC50(COX-2) =	[123]

inhibitor)	-2/5-LOX + in vivo carrageenan	2/5-LOX; ↓ COX-2 & 5-LOX gene expression	0.09 μM; IC50(5-LOX) = 0.38 μM; edema ↓ 60.82 %	
5d (Chlorothiophen-thiazol-2-amine)	In vitro COX-1/COX-2/5-LOX	COX-2 + 5-LOX; π-S interaction with Tyr355, Phe518	IC50(COX-2) = 0.76 μM, SI = 112; IC50(5-LOX) = 23.08 μM	[124]
5b, 5e	In vi	Sele	SI =	[1
(Chlorothiophen-thiazol series)	tro COX-2 EIA	ctive COX-2	42 (**5b**), 124 (**5e**); IC50 in 0.76–9.01 μM range	24]
34 (Thiazolyl-hydrazine-sulfonyl)	In vitro COX-2 EIA (EIA kit)	Selective COX-2 (similar binding to celecoxib)	IC50 = 0.140 μM; SI > 714.28	[125]
35–37 (Thiazole-pyrimidine carbonitrile)	In vitro COX-2 EI	Selective COX-2; ga	IC50 = 1.03–1.17 μM; ed	[126]

	A + in vi v o e d e m a	str ic sa fe ty > m el ox ic a m	em a ↓ 86 – 94 % vs. me lox ica m	

5.4 Antiviral Activity

Unmatched activity in antiviral drug research was sparked by the COVID-19 pandemic [127]. One class of compounds that has emerged as a strong candidate to fight against the main protease (Mpro/3CLpro) of SARS-CoV-2, the virus causing COVID-19, is sulfur-containing heterocycles, most notably thiadiazoles, thiazolidinones, and diverse benzothiazole derivatives [128]

A systematic screening of the benzothiazole-thiazolidinone series identified five inhibitors of SARS-CoV-2 Mpro with 0.01-34.4 μM IC50 values out of fifteen derivatives evaluated. The most potent of these compounds was **k3**, a hybrid of 6-CN-benzothiazol-2-yl-phenyl-thiazolidin-4-one with an extraordinarily low IC50 value of 0.010 μM resulting from the influence of 6-cyano substitution on the benzothiazole ring and 2-Cl and 6-F substitution on the benzene ring, which form interactions with key catalytic residues, Cys145 and Glu166, of Mpro. Structure-activity analyses confirmed the greater potencies of the 3-(benzo[d]thiazol-2-yl)-2-phenyl-substituted thiazolidin-4-one (**c1, k3, n2**) over 1,3,4-thiadiazol-based thiazolidinones, as demonstrated by **c1**'s IC50 value of 4.736 μM [129].

A novel covalent warhead (2,3,5-substituted [1,2,4]thiadiazoles) for Mpro was developed. Ren's team has made an extensive examination of several nonmimetic covalent inhibitors to Mpro based on their 2,3,5-substituted [1,2,4]thiadiazole structures. The data show that the most effective analog (compound **6a**) had an IC50 value of 0.193 μM in an FRET protease assay (Table 1). Additionally, calculations of the frontier molecular orbitals (FMOs) and molecular electrostatic potential (MEP) for 6a suggest that the 2,3,5-substituted [1,2,4]thiadiazole may serve as a covalent warhead and thereby provide additional Mpro inhibitory activity due to the increasing electronegativity of the thiadiazole moiety [130].

The 2-sulfoxyl-1,3,4-oxadiazole scaffold yielded a structurally distinct class of covalent 3CLpro inhibitors. Among a series of heteroaromatic sulfones and sulfoxides designed and prepared as covalent SARS-CoV-2 3CLpro inhibitors, compound **D6** (a sulfoxide bearing the 2-sulfonyl-1,3,4-oxadiazole scaffold) demonstrated potent irreversible inhibitory activity (IC50 = 0.030 μM) against SARS-CoV-2 3CLpro, along with favorable selectivity toward host cysteine proteases cathepsin B and L. The inhibitory mechanism involves covalent bond formation with Cys145 in the 3CLpro active site via nucleophilic aromatic substitution [131].

In the thiadiazole-sulfamoylphenyl series, spiro-N-(4-sulfamoylphenyl)-1,3,4-thiadiazole carboxamide derivatives were synthesized and evaluated in silico. Newly designed compound **H** was subjected to in silico studies against coronavirus, yielding EC50 = 7.1 mM against SARS-CoV-2 and IC50 = 29.0 mM against SARS-CoV-2 Mpro. The two 2-aminothiadiazole compounds **CoViTris2022 I** and

ChloViD2022 J showed significant binding for the coronaviral-2 polymerase/exoribonuclease with the four principal RNA nucleotides, while compound **L** exhibited a particularly high binding capacity of −9.1 kcal/mol toward the target enzyme [132].

Two novel thiazole carboxylate derivatives were also evaluated for SARS-CoV-2 Mpro binding through structural and computational studies, with ethyl 5-((4-fluorophenyl)carbamoyl)-thiazole-4-carboxylate **2b** and ethyl 5-(p-tolylcarbamoyl)thiazole-4-carboxylate **6b** identified as promising candidates through DFT and molecular docking at the Mpro active site (PDB: 6LU7) [133].

Compound No.	**Assay**	**Target Organism**	**Key Result (MIC/EC50)**	**Reference**
k3 (6-CN-Benzothiazolyl-thiazolidinone)	FRET protease assay	SARS-CoV-2 Mpro; Cys145+Glu166	IC50 = 0.010 μM (surpasses GC376)	[129]
cl (Benzothiazol-2-yl-phenyl-thiazolidinone)	FRET protease assay	SARS-CoV-2 Mpro	IC50 = 4.736 μM	[129]
6a ([1,2,4]Thiadiazole covalent inhibitor)	FRET protease assay + FMO/MEP analysis	SARS-CoV-2 Mpro (covalent warhead)	IC50 = 0.193 μM	[130]

	ysis	head)		
D6 (Sulfoxide-oxadiazole)	Enzymatic 3CLpro assay + dilution experiment	SARS-CoV-2 3CLpro; covalent via Cys145 NAS	IC50 = 0.030 μM (irreversible)	[131]
H (Spiro-thiadiazole-sulfa	In silico (PDB	SARS-CoV	EC50 = 7.1 mM (S	[132]

moyl)	6LU7 docking + ADMET)	-2Mpro	ARS-CoV-2); IC50 = 29.0 mM (Mpro)	
2b (Thiazole carboxylate)	Molecular docking (PDB 6LU7) + DFT	SARS-CoV-2Mpro	Favorable Mpro binding profile; confirmed by DFT/crystal structure	[133]

5.5 Antioxidant Activity

Oxidative stress arising from imbalances between reactive oxygen species (ROS) generation and antioxidant defense is a mechanistic root cause of cancer, neurodegeneration, cardiovascular disease, and accelerated aging [134]. Sulfur-containing heterocycles scavenge free radicals through hydrogen atom transfer (HAT), single-electron transfer (SET), and metal chelation mechanisms, with the sulfur atom and associated conjugated systems playing central roles in electron donation [135].

The studies aimed at evaluating the radical scavenging activity of the series of benzothiazole–monoterpenoid hybrids using two different assays: DPPH and ABTS, and provided very useful SAR data. The results demonstrated that the best examples of radical-scavenging activity using the ABTS method were the hybrids of thymol, **4a** (IC50 = 133.70 ± 10 μM) and **4b** (IC50 = 157.50 ± 10 μM). However, DPPH scavenging activity is much worse for these hybrids (IC50 > 1000 μM), meaning that the hybrids used for ABTS display scaffold-dependent selectivity for the ABTS radical cation versus the DPPH neutral radical [136].

Thiophene-based Gewald synthesis derivatives offered multi-activity antioxidant profiles. Among a series of ethyl-2-(substituted benzylideneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate derivatives, compounds **S4** and **S6** exhibited excellent DPPH antioxidant activity with IC50 values of 48.45 and 45.33 μg/mL, respectively, comparing favorably with ascorbic acid as the standard. The same series also showed significant antibacterial activity, with compound S1 being the most potent antibacterial agent (MIC = 0.81 μM/mL against S. aureus, B. subtilis, E. coli, and Salmonella typhi) [137].

Lastly, the imidazo[2,1-b][1,3,4]thiadiazoles were evaluated for antioxidant and cholinesterase-inhibiting activities. Compound **20aa** was the most potent inhibitor of cholinesterases tested in this study (AChE IC50 = 0.75 μM; BChE IC50 = 4.11 μM; SI = 5.48). It exhibited about 5 times the activity against AChE and 4 times the activity against BChE compared to galantamine. The radical scavenging activity of these compounds was also demonstrated using a DPPH assay, demonstrating the multifunctional nature of the imidazothiadiazole chemistry[138].

Compound No.	**Assay**	**Target Organism**	**Key Result (MIC/EC50)**	**Reference**
4a (Thymol-benzothiazole hybrid	ABTS radical cation decolorization	Radical cation decolorization	IC50 = 133.70 ± 10	[136]

			µM (ABTS); DPPH IC50 > 10000 µM	
4b (Thymol-benzothiazole hybrid)	ABTS radical cation	Radical cation decolorization	IC50 = 157.50 ± 10 µM (ABTS)	[136]
S4 (Tetrahydrobenzothiophene-carboxylate	DPPH radical scavenging	HAT: benzylidene-electron donor contribution	IC50 = 548.45 µg/mL (< ascorbic acid reference	[137]
S6 (Tetrahydrobenzothiophene-carboxylate)	DPPH radical scaven	HAT: benzylidene-electron do	IC50 = 548.45 µg/m	[137]

	ging	nor contribution	L (< ascorbic acid reference)	
20aa (Imidazo[2,1-b]thiadiazole)	DPPH + cholinesterase inhibition	Antioxidant + dual ChEI (multifunctional)	AChEI C50 = 0.75 μM; BChEI C50 = 4.11 μM; DPPH active	[138]

6. Structure–Activity Relationship (SAR)

6.1. Benzothiazole-Thiazole Disulfide Hybrid

The core scaffold comprises a benzothiazole-thiazole disulfide hybrid with three sulfur atoms that enable H-bonding (Arg326, Gln7/CYP450), π–π stacking, and hydrophobic contacts at enzyme active sites, while the –CH_2–S– linker provides conformational flexibility. Regarding R group substitution, electron-withdrawing groups proved superior; meta-NO_2 delivered the best potency (MIC 3.90 μg/mL), and para-Cl/F maintained strong activity with favorable binding-pocket interactions. In contrast, electron-donating groups such as –CH_3 showed the weakest activity (MIC 125–250 μg/mL), while –OCH_3 offered only moderate and selective activity due to reduced polarity and weaker enzyme binding. In terms of lipophilicity, halogens (–Cl, –Br) provided an optimal balance between membrane permeation and target engagement, whereas –NO_2, despite high docking scores, showed limited cellular

uptake, and –OCH_3 may favor fungal selectivity via CYP450 fitting [111].

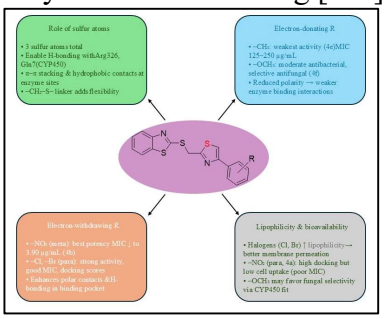


Figure 2 Structure-activity relationship of Benzothiazole-Thiazole Disulfide Hybrid

6.2. Sulfanilamide-Isoxazole Hybrid

The core scaffold is a sulfanilamide-isoxazole hybrid where the SO_2 bridge connecting the aniline (A) and isoxazole (B) units acts as the central pharmacophore. The S=O dipoles function as H-bond acceptors for key residues Arg68 and Arg254, forming 2–4 hydrogen bonds at distances of 2.5–3.1 Å, making the sulfonamide linkage indispensable for target engagement. Concerning electron-withdrawing effects, the –NO_2 series (c) demonstrated the highest activity with optimal H-bonding, –Cl (b series) showed intermediate activity aided by halogen bonding interactions, while –CH_3 (a series) proved the weakest as electron-donating groups reduced binding engagement. Regarding halogen position, the 5,6-diBr + 2-Cl benzimidazole combination (compounds 7a/7c) delivered the highest overall activity, where Br at positions 5,6 contributed hydrophobic contacts and halogen bonding. In contrast, Cl at position 2 enabled π-stacking interactions with Arg68. In terms of lipophilicity and ADMET, compounds maintained logP values of 2.0–4.8, satisfying Lipinski's Ro5, with intestinal absorption exceeding 90%. Br/Cl substitution increased logP, favoring membrane permeation, while –NO_2 increased polarity, directing compounds toward DHPS enzyme targeting [110].

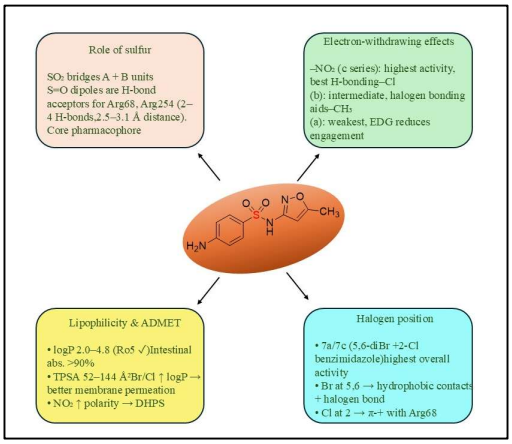


Figure 3 Structure-activity relationship of Sulfanilamide-Isoxazole Hybrid

6.3. Heterocyclic Disulfide (Allicin-Inspired) Scaffold

The core scaffold consists of a heterocyclic disulfide (–S–S–) system connecting a nitrogen-containing ring to an alkyl/aryl R group. The –S–S– bond is the essential pharmacophore, reacting with enzyme cysteine residues, disrupting membrane integrity and causing cellular content leakage, with both sulfur atoms being indispensable for activity. Among heterocyclic rings, pyridine and pyrimidine delivered the best combined antifungal and antibacterial activity, followed by thiazole (moderate), while thiophene, benzothiazole, and quinoline progressively reduced potency, indicating nitrogen-rich, simpler heterocycles are strongly preferred. Regarding R group substitution, small alkyl chains (allyl, n-propyl) conferred the highest potency (S5: MIC_{90} = 1.56 μg/mL), whereas bulky/branched alkyl and halogenated aryl groups (4-F, 4-Cl) showed progressively inferior activity. In terms of lipophilicity, small alkyl chains maintained optimal membrane permeation, while excess bulk or aromaticity led to over-lipophilicity and

poor bioavailability, as confirmed by the good in vivo efficacy of S5 and S8 [109].

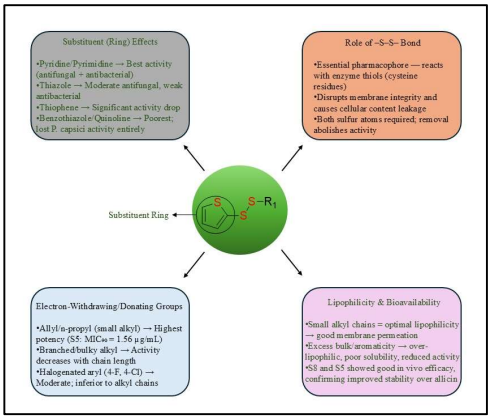


Figure 4 Structure-activity relationship of Heterocyclic Disulfide (Allicin-Inspired) Scaffold

7. Mechanism of Action

Sulfur-containing heterocycles get their biopotency from three separate molecular mechanisms acting together - enzyme inhibition, binding to proteins, and affecting DNA - but they involve one mechanism occurring independently. The sections below will discuss how each of these three mechanisms works together to provide biopotency in terms of antimicrobial, anticancer, anti-inflammatory, antiviral, and antioxidant properties. The antimicrobial mechanisms of sulfur-based heterocycles can be thought of as a multi-pronged approach to destroying important processes in bacteria; these mechanisms work synergistically to provide an extremely effective means of defeating bacteria. These three mechanisms of action occur in an orderly sequence: binding to proteins disrupts cell structure; inhibiting enzymes disrupts biosynthesis; and interacting with DNA delivers lethal damage to the genome.

7.1 Enzyme inhibition

According to current knowledge of the clinical validation of enzymatic targets, DNA gyrase (or topoisomerase II), topoisomerase IV, and dihydrofolate reductase (DHFR) are the most established enzymatic targets against sulfur heterocycles for the treatment of infections.

Fluoroquinolone/Topoisomerase inhibitors are broad-spectrum antibiotics that act on some bacterial strains and are used to treat many different types of infections; by intercalating into the topoisomerase–DNA cleavage complex through bound DNA, fluoroquinolones and other topoisomerase inhibitors stabilise the complex.

Thiazole and thiadiazoles are competitive inhibitors of the ATPase GyrB domain and therefore bind to the adenine nucleotide binding pocket to prevent ATP hydrolysis and strand passage by the enzyme. Additionally, the DHFR inhibitory activity of sulfonamides-permeable sulfonamide-containing sulfur heterocycles prevents the regeneration of tetrahydrofolate. The co-administration of DHPS and DHFR inhibitors has enhanced the thermodynamic properties of the combination in contrast to the potency of each as bacteriostatic agents, producing a bactericidal effect; thus, dual inhibition is a valuable approach for treating methicillin-resistant Staphylococcus aureus (MRSA) and Pneumocystis carinii infections in immunocompromised individuals. [141].

7.1.1 DNA gyrase

Prokaryotes need DNA gyrases to survive; therefore, DNA gyrases are type II topoisomerases that have an A2B2 (heterotetrameric) structure. The catalytic tyrosine (Tyr122 in E. coli) of the GyrA subunit results in a transient break in both strands of DNA. The GyrB subunit utilizes the ATPase domain to generate

energy via the hydrolysis of ATP, which will then allow the passage of strands through the GyrB subunit. Heterocycles such as thiazole, thiadiazole, and benzothiazole can contain substituents (hydroxyl, carboxamide, or urea) that will bind to the allosteric ATP-binding pocket of GyrB. The ethyl urea moiety represents an important structural element that can generate two significant interactions with the conserved aspartate residue of the adenine-binding region of DNA gyrase and has been exploited by several different groups in the development of novel topoisomerase inhibitors. Following the confirmation of novobiocin as a topoisomerase inhibitor, many subsequent GyrB/ParE inhibitors have been produced using structurally conserved motifs. PubMed Central Moreover, ethyl urea was identified as a key motif capable of establishing two important interactions with a conserved aspartate residue in the adenine binding region of the DNA gyrase. This motif was then used by others to design new inhibitors of topoisomerases; validation of novobiocin as a topoisomerase inhibitor led to many different GyrB/ParE inhibitors designed around conserved motifs. [142].

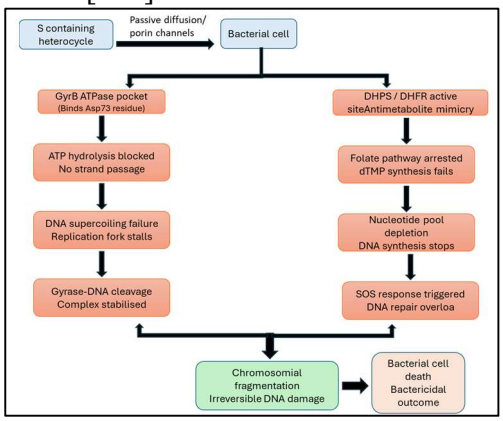


Figure 5 TMP-SMX-Induced Thymineless Death Pathway.

7.1.2 Dihydrofolate Reductase (DHFR) and DHPS Inhibition

DNA gyrase uses negative supercoiling to introduce supercoils into the DNA, topoisomerase IV has been shown to decatenate (uncoil) DNA and relax positive supercoiling, and theoretically, type I topoisomerases could be good targets for drug development; however, the only type of drugs approved by the FDA that target bacterial topoisomerases are type II topoisomerase inhibitors [142].

7.2. DNA interaction

The primary factor for DNA interaction is gyrase. However, inhibiting gyrase with enzymes can cause DNA damage (through trapping cleavage complexes), and certain sulfur-containing heterocyclic compounds can bind directly to bacterial DNA. Aromatic thiazole and benzothiazole compounds with planar characteristics can intercalate between DNA base pairs at right angles to the axis of the DNA helix (also referred to as 'stacking'), with significant π -electronic overlap with adjacent base pairs. Intercalator bases, molecules that can 'stack' on top of one another perpendicular to the DNA backbone, and do not form covalent bonds or break hydrogen bonds between DNA bases; thus, the only known forces providing stability to the intercalator/DNA complex are Van der Waals, hydrogen-bonding, hydrophobic, and charge transfer forces [143]. As a result, these intercalators result in elongation and unwinding of the double-stranded DNA molecule, which then inhibits translocation of DNA polymerase III, RNA polymerase, and ultimately inhibits both the processes of replication and transcription required for a bacterium to proliferate.

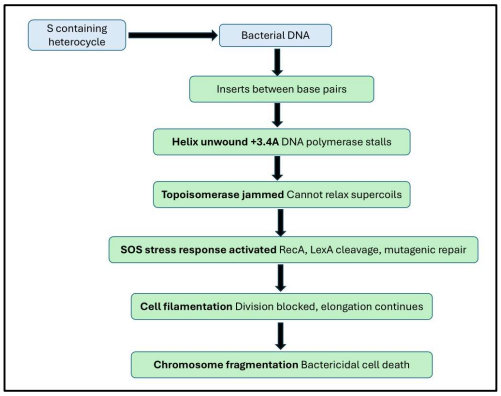


Figure 6 Thymineless Death via DNA Intercalation and SOS Response.

Planar and aromatic sulfur-containing heterocyclic compounds, especially fused bicyclic rings such as benzothiazole and benzothiophene, and thieno-pyrimidines, insert perpendicular into adjacent base pairs in DNA through π–π stacking interactions. For the drug to fit, it must have a planar aromatic surface that is complementary to the shape and size of a base pair (approximately 340 pm^2). The drug then slides between the two stacked bases while not disrupting the Watson-Crick hydrogen bonds. There are three primary mechanisms for drugs to interact with DNA: electrostatic interactions, intercalation between base pairs and binding to either the minor or major grooves of DNA; therefore, planar heterocyclic ligands with a scaffold structure similar to that of purine bases have a high binding affinity for DNA, and the azomethine function of the Schiff base derived from benzothiazole is responsible for its antimicrobial actions. The intercalation of drugs into bacterial DNA has severe and multiple mechanical effects: the drug extends the double helical structure of DNA about 3.4 Å for each intercalated molecule, which increases the twisting angle of adjacent base pairs, resulting in local unwinding of the double helix. The altered topology of DNA (a) inhibits the processivity of DNA polymerase III at a replication fork, (b) blocks the movement of RNA polymerase along the template strand, and (c) blocks the ability of topoisomerases to perform strand passage [144].

7.3 Protein binding

The sulfur heterocycles bind to PBPs via a covalent bond to the active serine residue. Thus, they demonstrate that the β-lactam ring fused with a thiazolidine ring mimics the D-Ala–D-Ala end of the peptide chain accessory component, resulting in the irreversible formation of a covalent bond to an acyl group with the PBP and subsequent failure to create a cell wall. Traditional antibiotics work by targeting specific substances or mechanisms to disrupt the above processes (i.e., inhibition of the creation of a cell wall – administered as penicillins and cephalosporins, leading to bacterial cell lysis; inhibition of the direct formation of proteins by binding to ribosomes of the bacterium, such as tetracyclines; breaking down a key metabolic pathway, sulfonamide disrupting the growth of bacteria) [145]. Thiazole ringed structures, due to their electron richness and ability to coordinate with metal ions, inhibit the normal functioning of a metalloenzyme by acting as a cofactor. Therefore, even if a bacterium develops resistance against one target through mutation, it cannot develop resistance to all three target pathways at the same time. Thus, the emergence of bacterial resistance to multi-target sulfur heterocycles has been reduced.

The transpeptidase enzymes are proteins that work within a cell's membrane to finish constructing the peptidoglycan layer of the bacterial wall. They do this by linking two adjacent peptides by creating a bond between their respective amino acids. The location of the bond is between the last amino acid (5th position) of a

stem peptide and the amino group (6th position) of the adjacent stem peptide.

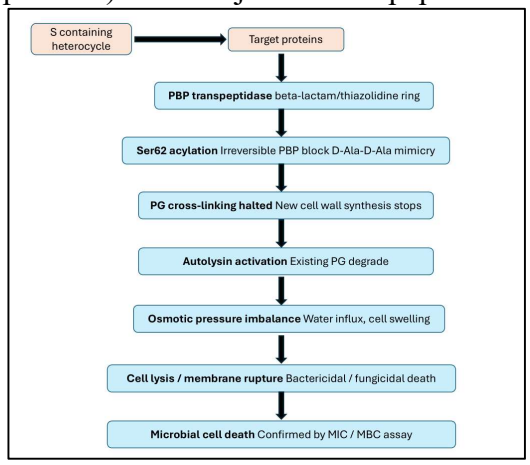


Figure 7 β-Lactam Mechanism via PBP Inhibition and Lysis.

The D-Ala–D-Ala dipeptide on the terminal end of the final stem peptide forms a covalent crosslink via transpeptidation between peptidoglycan and penicillin-binding protein (PBP) at the active site. After binding the D-Ala of the terminal peptide, the penultimate D-Ala is then removed to create a covalent acyl-enzyme intermediate between the hydroxyl group of a serine residue located within the active site of PBP (E. coli PBP2 Ser62) and the terminal dipeptide D-Ala. The need for this intermediate is so that the carbonyl oxygen from the acyl-enzyme may interact with an adjacent ε-amino group of a diaminopimelic acid (DAP) in order to create the 4–3 cross-linkage which gives mechanical strength to the peptidoglycan. Transpeptidation is specifically inhibited by β-lactam antibiotics, which bind to the active serine of the penicillin-binding protein (e.g. PBP2) and create an acyl-enzyme complex by nucleophilic addition to the terminal D-Ala–D-Ala when ppb is involved in transpeptidation. The resulting acyl-enzyme complex does not go on to undergo transpeptidation, as the D-Ala–D-Ala is inversely placed through D-Ala loss. The covalent nature of the link between PPB2 and the acyl-enzyme leads to the failure of β-lactam to replace D-Ala–D-Ala and results in the weakening of the peptidoglycan, resulting in cell lysis [146].

8. Challenges and Future Perspectives

8.1 Synthetic Limitations

While progress has been made, significant challenges still exist in the synthesis of heterocyclic compounds containing sulfur; this includes methods used to synthesize thiazoles, such as the Hantzsch thiazole synthesis and Gewald reaction, which are relatively slow and require extreme conditions with low yields. Although there have been some successes with variations using microwaves or solvent-free reactions, these methods have not been universally successful across all classes of substrates. Catalytic methods employing palladium and copper have demonstrated the ability to synthesize heterocycles rapidly, but there are limitations, e.g., catalyst costs, sensitivity of the catalyst to different functional groups, and enantioselectivity for producing chiral sulfur heterocycles. The synthesis of three-membered and four-membered cyclic systems (e.g., thiiranes and thietanes) is still very challenging because of ring strain and high reactivity. Finally, scaling up green chemistry protocols from the laboratory to the manufacturing level carries the risk of reproducibility and purity issues, along with the additional concern of cost; affordable materials will likely need to be used to create these types of products in a manufacturing setting.

8.2 Toxicity Issues

Though the sulfur atom has advantages for pharmacological use, it brings with it significant toxicity hazards. CYP450-

bioconverted thiophene ring can produce reactive electrophiles that are potential intermediates and react with proteins; this mechanism may also play a role in inducing immune-mediated toxicities. Thiazolidinediones, which help to treat Diabetes Mellitus in people, have been associated with numerous side effects, including, but not limited to, hepatotoxicity and Cardiovascular Events (e.g., troglitazone is no longer marketed after many years of use). The risk of hypersensitivity reactions and crystalluria in patients taking sulfonamides is significant, whereas disulfides typically have poor stability in reducing environments. Therefore, there is a significant gap between in vitro potency and in vivo safety for many thiadiazole and benzothiazole derivatives, indicating the necessity for the earlier incorporation of hERG liability, reactive metabolite trapping, and mitochondrial toxicity assessments in the lead optimization process.

8.3 Drug-Likeness Challenges

Developing effective drug candidates from sulfur heterocyclic compounds that have biological activity often presents challenges because of poor physical and chemical characteristics. Fusion of polycyclic materials tends to increase molecular weight and lipophilicity, causing lower oral bioavailability and higher non-specific protein binding. The thiophene ring is highly susceptible to cytochrome P450-mediated oxidative metabolism, and the sulfide linker can undergo either S-oxidation or S-dealkylation, changing the pharmacodynamic activity. A continual requirement of creating beneficial ADMET properties while establishing isoform selectivity, like COX-2 versus COX-1 or VEGFR-2 versus other related kinases, is an ongoing optimization issue in developing structures. Many neuroprotective therapies require such drug candidates to be able to penetrate through the blood-brain barrier, and a balance in lipophilicity can often not be achieved within the sulfur heterocycles present in chemical space.

8.4 Future Research Directions

The convergence of computational innovations and rational molecular design will enable the future of drug discovery for sulfur-containing heterocycles. The use of artificial intelligence, machine learning, and structure-activity relationship (SAR) in thiazole, thiadiazole, and benzothiazole scaffold optimization will lead to faster identification of potential drug candidates with enhanced ADMET properties and a concomitant reduction in the number of compounds that fail late in development. Additionally, further substantiation of the covalent warhead capability of thiadiazoles and sulfoxide/oxadiazole derivatives against SARS-CoV-2 3CLpro provides a strong rationale for utilizing sulfur electrophilic characteristics across various oxidation states and ring structures, primarily against targets containing cysteine as a nucleophile. For example, hybridization of rationally designed scaffolds that target multiple pairs of dual enzymes (e.g., COX-2/5-LOX; VEGFR-2/CDK; AChE/BChE) in one framework will be instrumental in addressing multiple factors involved in the pathophysiology of cancer, neurodegeneration, and infectious diseases.

The introduction of continuous flow chemistry platforms for producing sulfur heterocycles will improve the scalability, safety, and reproducibility of these compounds in combination with intense research on new antimicrobial scaffolds targeted at GyrB ATPase, bacterial cell

membrane integrity, and DNA gyrase as part of the global response to antimicrobial resistance. Synergistic combinations are an excellent option for immediate action. The low use of sulfur heterocycles against neglected tropical diseases and new RNA viruses means they are a priority for broad-spectrum drug development and responses to future pandemics.

9. Conclusion

The most promising scaffolds that have been identified include benzothiazole-thiazolidinone hybrids that exhibit extremely potent antiviral activity against SARS-CoV-2 Mpro; thiazole derivatives being evaluated for their broad applicability in anticancer, antimicrobial, and covalent inhibition; and thiazoles, which continue to show exceptional flexibility regarding COX-2 inhibition, CDK-mediated anticancer activity, and multitarget anti-inflammatory activities as scaffolds. Benzothiazole-derivative scaffolds have a clinical translation focus; riluzole and quizartinib, approved drugs, have provided significant support. Thiazolidinedione scaffolds have a continuing role as privileged pharmacophores for drug design aimed at both diabetes and cancer. Given the improved synthetic accessibility via sustainable methodologies and the availability of computational tools to navigate SARs more accurately, sulfur-containing heterocyclic compounds have great potential to generate the next wave of therapeutic agents to address the world's most pressing and unmet medical needs.

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