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Comprehensive Review on the Synthesis, Structural Characterization, and Diverse Biological Applications of Thiazine Derivatives

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Abstract : *Thiazine derivatives are a versatile group of heterocyclic compounds featuring a six-membered ring which includes both nitrogen and Sulfur atoms. This article brings together the latest research concerning the synthetic methods, techniques used for structural characterization, and the wide range of biological properties of these compounds. Synthetic methods for thiazine derivatives have moved from classical, multi-step processes that mainly make use of chalcone and thiourea as starting materials to more modern and efficient approaches such as multicomponent reactions (MCRs), microwave-assisted synthesis, and green, sustainable processes. The catalysts used nowadays go from simple bases like NaOH and KOH to more advanced metal-free systems involving nanoparticles and those activated by visible light, all of which have been designed in order to increase the yields and reduce the environmental impact.*

The structure of these compounds is usually determined by combining a number of spectroscopic techniques, such as FT-IR, 1D and 2D NMR, and mass spectrometry, together with more advanced methods like X-ray diffraction and Density Functional Theory (DFT) calculations when mechanistic and conformational analysis is required. Thiazine derivatives have a wide range of pharmacological activities, such as antimicrobial, antifungal, anticancer, anticonvulsant, antioxidant and antidiabetic effects. Their neuroprotective properties, especially their action as inhibitors of BACE1 in the case of Alzheimer's disease, as well as their application as environmentally friendly pesticides, highlight the growing range of their uses in both medicinal chemistry and industry. This review brings together evidence from a variety of studies to give a thorough account of the present state and future potential of thiazine research.

Key Words: Alzheimer disease, Thiazine derivatives, Green synthesis, Pharmacological activities.

1. INTRODUCTION

Thiazines are six-membered heterocycles composed of four carbon atoms, one nitrogen atom, and one sulfur atom [2], [7]. Several isomeric arrangements are known—most notably 1,2-, 1,3-, and 1,4-thiazine—and these frameworks have become central scaffolds for many biologically active molecules [2], [7], [23], [28]. Among them, 1,3-thiazine has attracted particular attention in medicinal chemistry because the ring tolerates broad structural variation and substituents can be introduced relatively easily [23], [28], [30].

Interest in thiazine derivatives continues to grow worldwide due to their wide-ranging pharmacological profiles, spanning well-established antimicrobial and antifungal activities to newer investigations in cancer, Alzheimer's disease, and viral infections [28], [41], [46], [64]. Earlier synthetic work relied largely on chalcones (α, β-unsaturated ketones) as key intermediates, which are cyclized with thiourea or related reagents [6], [8]. More recently, the toolkit

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has expanded to include alternative approaches designed with atom economy, lower energy input, and improved environmental compatibility in mind [16], [32], [35]. This review surveys these developments in synthesis alongside the biological studies that continue to highlight the therapeutic relevance of the thiazine scaffold.

Synthetic Methodologies for Thiazine Derivatives

Chalcone-Based Synthesis

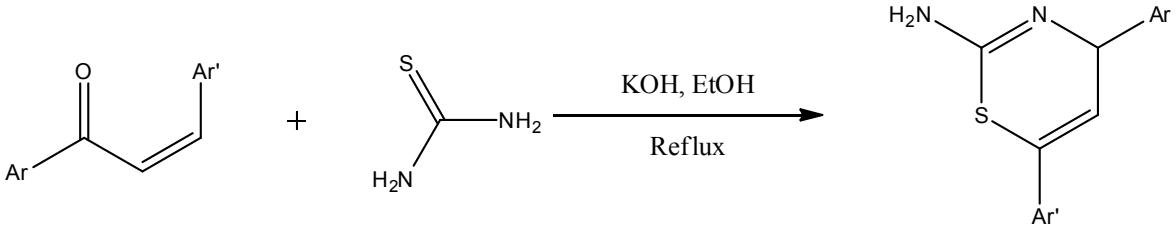


Figure 1. Representative chalcone-thiourea cyclo-condensation used to prepare 4,6-diaryl-1,3-thiazin-2-amine derivatives.

The scheme shows a generic substituted chalcone reacting with thiourea under basic ethanolic conditions and heating /reflux. The exact substituents, reaction time, purification procedure, and yield vary among the reported studies [1], [2], [6], [10]

Cyclocondensation between chalcones and thiourea remains one of the most dependable and frequently used routes to 1,3-thiazine derivatives. Typically, the process begins by generating the chalcone precursor through a Claisen–Schmidt condensation of substituted acetophenones with aromatic aldehydes under basic conditions, commonly using NaOH in methanol or ethanol [2], [7], [8]. In one representative example, chalcones (1 and 2) were treated with thiourea in ethanol in the presence of sodium hydroxide and magnetically stirred for about 12 hours to afford the corresponding thiazine derivatives [2].

Mechanistically, the cyclization is often described as a Michael addition in which the sulfur atom of thiourea attacks the β-carbon of the chalcone, followed by cyclocondensation and a dehydrogenation step that completes formation of the thiazine ring [7], [13]. Variations of this general approach are also common. For instance, chalcones derived from 3-acetyl-2,5-dichlorothiophene can be converted to 6-aryl-4-(2,5-dichlorothiophen-3-yl)-6H-1,3-thiazin-2-amine derivatives by reaction with thiourea in the presence of hydrochloric acid [1]. Across reported studies, reactions are frequently carried out in alcoholic solvents (e.g., ethanol or isopropanol) under reflux, with reaction times ranging from roughly 2.5 to 16 hours [5], [9], [18], [19].

Multicomponent and One-Pot Reactions

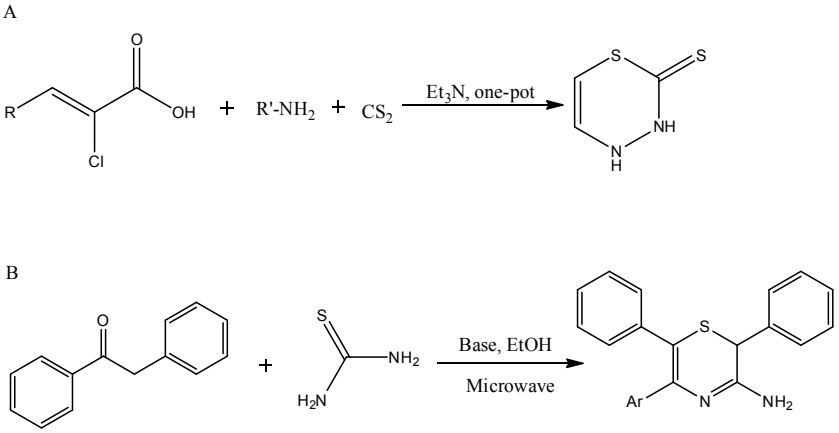


Figure 2. Representative reaction schemes for modern thiazine synthesis.

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(A) A three-component, one-pot rout involving a beta chlorovinyl aldehyde, a primary amine, and carbon disulfide to give a substituted 1,3-thiazine-2-thion. (B) Microwave-assisted cyclocondensation of a substituted chalcone with thiourea to give a 4,6-diaryl-1,3-thiazine-2-amine. Substituents are represented generically because the reported substrate scope and conditions differ between studies [34], [36], [40], [54]

In response to demands for higher efficiency and better alignment with green chemistry, multicomponent reactions (MCRs) and one-pot procedures have become increasingly prominent. By combining three or more readily available starting materials in a single vessel, these strategies can streamline access to structurally complex thiazine frameworks [17], [34], [61].

Three-Component Reactions (3-CR): One practical one-pot 3-CR employs β-chlorovinyl aldehydes, primary amines, and carbon disulfide to produce 1,3-thiazine-2-thiones [36]. A related method proceeds through zwitterion adduct intermediates and can be performed in greener solvents such as acetone, ethanol, or 2-methyl-tetrahydrofuran at room temperature, notably without requiring added catalysts [34].

Sequential C-S Couplings: A greener route to 2-mercapto 5,6-dihydro-4H-1,3-thiazines has been reported via a cascade sequence that combines an intermolecular thiol–isothiocyanate step with an intramolecular thiol–halogen click cyclization [40].

Solvent-Free Strategies: Solvent-free, one-pot access to imidazo[2,1-b][1,3]thiazine derivatives has been achieved using thiohydantoins, aromatic aldehydes, and 5,5-dimethylcyclohexane-1,3-dione, with p-toluenesulfonic acid as the catalyst [39].

Domino Reactions: Rapid entry to functionalized thiazines has also been demonstrated through an iodine-catalyzed, four-component domino synthesis [54].

Green synthesis and sustainable protocols

In recent thiazine chemistry, green principles have increasingly shaped reaction design, with many studies focusing on minimizing hazardous byproducts and reducing energy input [16], [21], [23], [27]. A consistent approach involves switching to safer solvent environments. Water, for instance, has been used as a benign medium for three-component syntheses of functionalized thiazines, providing a simple route with improved environmental compatibility [38]. Ethanol/water (1:1) systems have similarly been employed to facilitate sequential C–S couplings [40]. In addition to these conventional greener solvent choices, Deep Eutectic Solvents (DES) have emerged as sustainable media, including in the synthesis of N-substituted phenothiazines [37]. For 1,4-benzothiazine preparation, many greener protocols also emphasize metal-free catalysis and mild, environmentally acceptable conditions [32]. Collectively, the field has moved toward efficient, low-waste sequences—often combining sequential MCR steps with cyclization—to maintain high yields while limiting waste generation [31].

Microwave- and ultrasound-assisted methods

Beyond solvent and catalyst selection, alternative activation techniques have become prominent because they can significantly reduce reaction times and, in many cases, improve yields compared with conventional heating [10], [23], [65]. Under microwave irradiation, rapid syntheses of 4,6-diphenyl-substituted thiazine derivatives have been achieved from chalcones and thiourea, offering a practical alternative to lengthy reflux conditions [10]. Microwave conditions have also supported the preparation of optically active N-substituted 2-methyl-2H-benzo[b] [1,4]thiazin-3(4H)-ones via a Smiles rearrangement strategy [59]. Ultrasound has been used in parallel as part of greener routes to sulfonamide-containing thiazine derivatives [44], and Baker's yeast-catalyzed syntheses performed under ultrasonication have likewise furnished medicinally relevant heterocycles [45].

Diverse catalytic systems

Optimization of thiazine synthesis spans a wide range of catalytic platforms, from traditional base-promoted reactions to newer metal-free approaches. ZnO nanoparticles have been highlighted as a fast and efficient option for generating thiazine derivatives [24]. Even so, classical basic conditions remain common, with NaOH and KOH frequently used [2], [9]. In more targeted settings—especially within green or MCR-oriented procedures—bases such as potassium

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carbonate (K2CO3) [40] and triethylamine (Et3N) [36] appear regularly. Sodium amide (NaNH2) has also been applied more specifically for alkylation of phenothiazines using chloro-compounds [47].

Acid catalysis is also well represented. Boron trifluoride-diethyl etherate (BF3·OEt2) has enabled room-temperature access to imidazo[2,1-b] [1,3]thiazines [20], while Yb(OTf)3 has been used to promote acid-catalyzed cyclo-condensation in one-pot syntheses of 2-amino-4H-1,3-thiazines [52]. For cyclizing alkylated intermediates, refluxing mixtures of glacial acetic acid and hydrochloric acid (3:1) have likewise been employed [48].

More recent reports emphasize alternative and metal-free catalytic concepts. Visible-light-mediated catalysis without metals has been presented as a strategy for assembling fused six-membered heterocyclic frameworks [31]. Elemental iodine and diiodine have served effectively as catalysts in four-component and cascade multicomponent reactions, enabling formation of thiazines and thiazine imides [53], [54]. DABCO (1,4-diazabicyclo[2.2.2]octane) has supported one-pot preparation of 1,4-benzothiazine derivatives and benzofuran-linked thiazines [49], [55]. Gold catalysis has also been described for 1,3-thiazine synthesis and has been linked to the isolation of uncommon tautomers [60]. Additionally, a task-specific ionic liquid has been applied to promote conjugate hydrothiocyanation of chalcones, a useful precursor transformation for thiazine-related heterocycles [26].

Structural characterization and elucidation

Accurate structural assignment remains central to thiazine research and typically relies on converging spectroscopic evidence. The heterocyclic framework is most commonly confirmed by 1H and 13C NMR; in 1,3-thiazines, diagnostic signals such as methine protons (CH–S) and imine carbons (C=N) are frequently monitored [5], [7]. When substitution patterns complicate interpretation, extended 1D/2D NMR experiments (COSY, HMBC, HSQC) are often required to establish connectivity and validate the proposed structures [1]. FT-IR analysis complements NMR by verifying functional groups, including imine NH, cyclic NH, C=N, and C–S features; for example, thiazine-2-imine hydrochlorides show characteristic IR bands associated with piperidinyl and imino groups [7], [8]. Molecular weight and elemental composition are typically confirmed through HRMS and ESIMS [1], [5], [36], [43], while UV–Vis spectroscopy is used to probe electronic transitions and conjugation within thiazine systems [9], [19].

Advanced analytical and theoretical studies

When definitive three-dimensional confirmation is needed, single-crystal X-ray diffraction remains the primary method for establishing structure and conformational details [20], [36], [47]. Computational tools have become increasingly integrated into these studies, with DFT calculations often used to reinforce experimental findings—whether to clarify mechanistic proposals (including sequential addition–substitution in C–S coupling processes) [40] or to examine the electronic characteristics of 1,3-thiazine scaffolds [30], [63]. Across many reports, TLC continues to be routinely applied for monitoring reactions and assessing product purity [7], [42], [56].

II. DIVERSE BIOLOGICAL AND PHARMACEUTICAL APPLICATIONS

Antimicrobial and antifungal potential

A broad range of thiazine derivatives has been reported to act against pathogenic microorganisms. In antibacterial assays, synthesized 1,3-thiazines have inhibited Gram-positive bacteria such as Staphylococcus aureus and Bacillus subtilis, along with Gram-negative strains including Escherichia coli and Pseudomonas aeruginosa [3], [7], [9]. In some cases, activity against S. aureus surpassed that of reference antibiotics such as Gentamycin [15]. Strong inhibition has also been described for bis-thiazine derivatives tested against S. aureus (MTCC3381) and E. coli (MTCC739) [3], [10]. Antifungal studies commonly report moderate to high activity against Candida albicans and additional strains [1], [7], [20], [42], with enhanced effects often associated with phenolic substituents and particular N,S heteroatom arrangements [9].

Anticancer and antiproliferative activity

Interest in thiazine scaffolds also extends to cancer-related research. 1,3-thiazine derivatives have shown activity across several models, including breast cancer (MCF-7), lung cancer, and prostate cancer (PC3) cell lines [12], [8], [41]. Mechanistic findings include tumor growth inhibition by compounds such as 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-

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thiones [36]. Phenothiazine derivatives used in cancer therapy have been described as proteasome activators that inhibit cell growth [33]. Isochromanone-based thiazines have additionally been reported to inhibit migration of HepG2 cells and to exert antiproliferative effects in A-431 tumor cells [20].

Neurological and anticonvulsant properties

Neurological applications have likewise been investigated. In anticonvulsant evaluations, 1,3-thiazine derivatives originating from 1-acetylnaphthalene produced strong effects in animal models, and 4-fluorophenyl-substituted analogs notably prolonged seizure onset [4]. Similar anticonvulsant performance has been reported for derivatives bearing 3,4,5-trimethoxyphenyl and 4-isopropylphenyl groups [5]. In the context of Alzheimer's disease, 1,3-thiazine scaffolds have been highlighted as BACE1 inhibitors relevant to reducing amyloid-beta accumulation [28], [30]. Schiff base 1,3-thiazines derived from 3-methoxy chalcone have also been examined for anxiolytic potential [56].

Antioxidant, anti-inflammatory, and analgesic effects

Several thiazine families have been assessed for roles in oxidative stress and inflammatory pathways. Some 2-amino-1,3-thiazines demonstrated antioxidant capacity comparable to ascorbic acid [15], and benzothiazine derivatives have been evaluated both for antioxidant properties and acetylcholinesterase inhibition [51]. Anti-inflammatory and analgesic activity is frequently noted for thiazine and benzothiazine derivatives, supporting their consideration as potential alternatives to non-steroidal anti-inflammatory drugs (NSAIDs) [11], [25], [28]. Novel 1,5-benzothiazepine derivatives have also been investigated as potent anti-inflammatory agents [29].

Antiviral and antidiabetic properties

Antiviral screening indicates that thiazine-related scaffolds may act against multiple viral targets. In particular, novel [1,2,4]triazolo[3,4-b] [1,3,4]thiadiazine derivatives showed anti-viral effects against influenza A (H1N1), with compound 2a displaying the highest selectivity index (>300) [43]. Other derivatives have been studied against rabies virus [50] and coronavirus [62]. In metabolic disease research, benzalacetophenone-derived thiazines have been investigated for antidiabetic potential [13], and broader screening discussions have described thiazine and oxazine derivatives as candidates with antidiabetic and antimycobacterial promise [27], [33].

Pesticidal and other industrial applications

Beyond therapeutic relevance, thiazines have been evaluated for agricultural and industrial uses. Chalcone-derived thiazines have been tested as pesticides (anti-dubas) targeting the Cholinesterase enzyme, and sulfur-containing thiazines were reported to outperform oxygen-containing oxazine counterparts [2]. Because acetylcholinesterase inhibition is significant in both pesticide development and neurodegenerative research, 2H-benzo[b] [1,4]thiazin-3(4H)-one derivatives have been designed and assessed as AChE inhibitors with pesticidal and anti-Alzheimer's applications [57], [51]. Certain compounds have also been examined as molluscicides, particularly those combining pyrazole and 1,4-thiazine motifs [22]. In materials chemistry, thiazine scaffolds have been incorporated into new azo dyes for textiles and related applications [14], and they continue to be recognized as versatile building blocks for assembling complex heterocyclic ring systems of industrial importance [58].

III. COMPARATIVE ANALYSIS OF SYNTHETIC ROUTES

Across published work, different synthetic routes reflect practical trade-offs. Classical reflux methods remain dependable and well established, but microwave-assisted protocols can deliver analogous transformations within minutes rather than hours and often improve yields [10], [40], [42], [65]. A similar contrast appears between stepwise chalcone-based routes and one-pot MCR strategies: multi-step sequences allow intermediate chalcones to be isolated and characterized, which can be useful for SAR analysis, whereas one-pot MCR approaches generally save time, reduce solvent use, and align more closely with sustainability aims [17], [34], [39]. Catalyst choice also affects both efficiency and environmental impact; ZnO nanoparticles, metal-free systems such as DABCO or iodine, and visible-light catalysis are frequently preferred in green protocols, while effective conventional bases like NaOH may require additional neutralization and can generate larger waste streams that must be addressed [24], [31], [49], [54].

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IV. LIMITATIONS, RESEARCH GAPS, AND FUTURE DIRECTIONS

Although the field has advanced considerably, several important issues still warrant deeper study. One persistent hurdle is the optimization of green methods: many environmentally friendly protocols have been reported, but adapting and refining them for large-scale industrial production remains difficult [23]. In addition, mechanistic understanding has not kept pace with synthetic output. Detailed mechanistic studies—especially for complex MCRs and nanoparticle-catalyzed reactions—are still relatively limited compared with the number of empirical synthetic reports [40].

A further gap concerns biological validation. Most activity profiles currently rely on in vitro assays, and more rigorous in vivo investigations and clinical trials are needed to confirm the therapeutic promise of these compounds [28]. Selectivity is also a major concern; improving the target specificity of thiazine-based anticancer and antiviral agents to reduce off-target effects remains a critical research need [43]. Looking ahead, future work should expand the diversity of heterocyclic substitutions on the thiazine ring and leverage computational docking studies to design derivatives with stronger binding affinities for defined biological targets [28], [56].

V. CONCLUSION

Research on the synthesis and applications of thiazine derivatives continues to develop rapidly and remains highly active. Synthetic access to these versatile heterocycles has become increasingly efficient, ranging from traditional chalcone-thiourea condensations to modern multicomponent and green approaches. Their broad spectrum of biological activities—including antimicrobial, anticancer, and neuroprotective effects—highlights the thiazine scaffold as a privileged manifold in drug discovery. With the continued integration of sustainable practices and advanced characterization techniques, thiazine derivatives are well positioned to stay at the forefront of medicinal chemistry, offering innovative responses to global health and industrial challenges.

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