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Oxazole and thiazole: A comparative review of their chemistry, synthesis and microbial activity

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Abstract
Oxazole and thiazole are important aromatic five-membered heterocyclic scaffolds containing oxygen–nitrogen and sulfur–nitrogen combinations, respectively. Their compact aromatic frameworks, electronic characteristics, substitution flexibility and ability to participate in molecular interactions make them valuable in synthetic, pharmaceutical and medicinal chemistry. This review presents a comparative account of the chemistry, structural features, physicochemical properties and established synthetic approaches of oxazole and thiazole, with particular emphasis on their microbial activity. Classical oxazole-forming methods such as the Robinson–Gabriel cyclodehydration and van Leusen oxazole synthesis are discussed alongside catalytic, one-pot and multicomponent approaches. For thiazoles, the Hantzsch cyclization and modern diversification strategies are highlighted. Reported microbial activities include antibacterial, antifungal, antimycobacterial and antiprotozoal effects, with activity depending strongly on substitution pattern, molecular size, lipophilicity, electronic character and the presence of complementary pharmacophoric groups. Recent literature also indicates growing interest in thiazole-containing compounds against drug-resistant bacterial strains. The review compares the two heterocycles from a structure–activity perspective and identifies important directions for the design of new antimicrobial candidates.
Keywords: Oxazole; Thiazole; Heterocyclic chemistry; Synthesis; Antimicrobial activity; Antibacterial; Antifungal; Structure–activity relationship.

1. Introduction

Heterocyclic chemistry occupies a central position in modern organic and medicinal chemistry because heteroatoms incorporated into cyclic frameworks can substantially modify polarity, hydrogen-bonding ability, electronic distribution, conformational behavior and interactions with biological targets. Five-membered aromatic heterocycles are particularly valuable because they provide compact and relatively rigid scaffolds that can be diversified at several positions. Among these systems, oxazole and thiazole have received sustained attention in both academic and pharmaceutical research.

Oxazole is a five-membered aromatic ring containing oxygen at position 1 and nitrogen at position 3. Thiazole is the corresponding sulfur-containing analogue, with sulfur at position 1 and nitrogen at position 3. The difference between oxygen and sulfur changes polarizability, size, lipophilicity and electronic properties, and consequently can influence molecular recognition and pharmacological behavior. Both rings occur in natural products and synthetic molecules, and thiazole is also a constituent of thiamine and several bioactive natural products [1–4].

The biological relevance of these heterocycles is particularly important in antimicrobial research. Oxazole- and thiazole-containing molecules have been investigated against a range of bacterial and fungal organisms, while thiazole derivatives have also been explored against mycobacterial and protozoal pathogens. Reported activity is highly compound-dependent and cannot be attributed to the heterocyclic ring alone. The purpose of this review is therefore to provide a comparative, chemistry-focused account of oxazole and thiazole, followed by a focused assessment of their reported microbial activity and the structural features associated with antimicrobial potency.

2. Oxazole

2.1 Structure and aromaticity

Oxazole (C3H3NO) is an aromatic, doubly unsaturated five-membered heterocycle. The ring contains one pyridine-like nitrogen and one oxygen atom separated by carbon. Its aromatic character arises from a six-electron π system involving the two double bonds and one lone pair contribution from oxygen. The heteroatoms influence the electron density of the ring and provide sites for interactions with hydrogen-bond donors and acceptors.

2.2 Physicochemical and chemical characteristics

The oxazole ring is relatively electron deficient compared with many carbocyclic aromatic systems. Substituents can strongly influence its electronic properties, and functionalization can be directed toward positions that are activated by the ring heteroatoms. The ring is sufficiently stable to occur in natural products and pharmaceuticals, while its substitution chemistry permits the preparation of structurally diverse analogues. The balance of rigidity, polarity and aromaticity makes oxazole useful as a scaffold in medicinal chemistry [1,6].

2.3 Important synthetic approaches

Robinson–Gabriel synthesis is a classical route to substituted oxazoles. It involves cyclodehydration of suitable N-acyl-α-aminoketones using dehydrating conditions. Polyphosphoric acid and other dehydrating reagents have been employed, and the reaction is particularly useful for preparing 2,5- and 2,4,5-substituted oxazoles [7].

The van Leusen oxazole synthesis is another important method. It uses tosylmethyl isocyanide (TosMIC) and suitable carbonyl-derived partners under basic conditions to construct the oxazole ring. Reviews have highlighted the versatility of this approach for preparing medicinally relevant oxazole-containing structures [8].

Modern research has expanded oxazole synthesis through catalytic, one-pot and multicomponent reactions. Such methods aim to improve atom economy, substrate scope, reaction efficiency and functional-group tolerance. Recent reviews also emphasize environmentally improved methods and multicomponent strategies as important directions for oxazole synthesis [9,10].

3. Thiazole

3.1 Structure and aromaticity

Thiazole (C3H3NS) is a five-membered aromatic heterocycle containing sulfur and nitrogen. Like oxazole, it possesses a six-electron aromatic π system. The larger, more polarizable sulfur atom gives thiazole a different electronic and lipophilic profile from oxazole. These differences can affect binding interactions, metabolic behavior and the physicochemical properties of substituted derivatives.

3.2 Natural occurrence and chemical importance

Thiazole and thiazole-containing structures occur in biologically important molecules and natural products. Thiazole-containing compounds are found in thiamine, peptides and several natural-product families. The ring has consequently become a recognized pharmacophore in medicinal chemistry and a versatile building block for the construction of heterocyclic libraries [4,11].

3.3 Hantzsch thiazole synthesis

The Hantzsch thiazole synthesis is one of the best-known routes to substituted thiazoles. In a general form, an α-haloketone or related α-halo carbonyl compound reacts with a thioamide, thiourea or related sulfur-containing nucleophile, followed by cyclization and elimination to produce the thiazole ring. The method is valued for its straightforward access to a wide range of substitution patterns [12].

Contemporary thiazole chemistry includes microwave-assisted reactions, multicomponent methods, transition-metal-catalyzed functionalization and other approaches that broaden the accessible chemical space. A 2024 review covering literature from 2017–2022 summarized numerous synthetic strategies together with biological activities of thiazole derivatives [4].

4. Comparative Chemistry Of Oxazole And Thiazole

Property	Oxazole	Thiazole
Ring system	Five-membered aromatic heterocycle	Five-membered aromatic heterocycle
Heteroatoms	O and N	S and N
Molecular formula	C3H3NO	C3H3NS
Key heteroatom	Oxygen; smaller and more electronegative	Sulfur; larger and more polarizable
Aromaticity	Aromatic	Aromatic
Typical synthesis	Robinson–Gabriel; van Leusen; multicomponent routes	Hantzsch; cyclization; modern catalytic routes
Medicinal relevance	Antimicrobial, anti-inflammatory, anticancer and other activities	Antimicrobial, anticancer, antitubercular, antiviral and other activities
Representative drug relevance	Oxaprozin, tafamidis and other oxazole/isoxazole-containing pharmaceuticals	Multiple approved and investigational thiazole-containing agents

5. Chemical Reactions And Functionalization

5.1 Oxazole functionalization

Oxazole derivatives can be diversified by substitution and cross-coupling strategies. Depending on the substitution pattern, functionalization may involve electrophilic or nucleophilic processes, metalation, halogenation and transition-metal-catalyzed coupling. Such transformations are important because medicinal chemistry frequently requires systematic modification of a core scaffold to tune potency, selectivity, solubility and metabolic stability [6,8,9].

5.2 Thiazole functionalization

Thiazole chemistry similarly permits substitution and cross-coupling at positions activated by the heteroaromatic system. Halogenated thiazoles can serve as intermediates in carbon–carbon and carbon–heteroatom bond-forming reactions. The availability of multiple functionalization strategies makes thiazole suitable for library synthesis and structure–activity relationship studies [4,12].

6. Microbial Activity

6.1 Antibacterial activity

Oxazole and thiazole derivatives have been widely investigated as antibacterial agents. Reported studies describe activity against both Gram-positive and Gram-negative bacteria, although the spectrum and potency vary substantially with molecular structure. Thiazole-containing compounds have received particular attention because suitable substitution and hybridization can produce compounds active against difficult bacterial targets, including methicillin-resistant

Staphylococcus aureus (MRSA). Recent reviews emphasize the value of the 1,3-thiazole nucleus in the search for alternatives to conventional antibacterial scaffolds, especially in the context of antimicrobial resistance [4,15,16]. For oxazoles, antibacterial effects have likewise been reported for structurally diverse derivatives, with electron-withdrawing groups, hydrophobic substituents and appropriate heteroaromatic combinations often influencing activity [1].

6.2 Antifungal activity

Antifungal activity has been reported for numerous oxazole and thiazole derivatives. Structural modification around the heteroaromatic ring can alter lipophilicity, membrane interaction and target binding, thereby changing antifungal potency. Thiazole-based compounds in particular have been described as useful scaffolds for the development of broad-spectrum anti-infective candidates [4,17]. Oxazole derivatives have also demonstrated activity in experimental screening against fungal organisms. Because different assays, strains and endpoints are used across studies, direct numerical comparison should be made cautiously.

6.3 Antimycobacterial and antitubercular activity

The thiazole nucleus has attracted sustained interest in antimycobacterial research, including the development of compounds directed against Mycobacterium tuberculosis. Recent literature describes thiazole-containing hybrids and derivatives as promising candidates and emphasizes the importance of systematic structure–activity relationship studies [4,18]. Oxazole-containing molecules have also been investigated in anti-infective research, although the literature is less extensive than for thiazole in some areas. Activity against mycobacteria is strongly influenced by the complete molecular architecture, physicochemical properties and target-specific interactions.

6.4 Antiprotozoal and other microbial activity

Thiazole derivatives have also been reported with antiprotozoal activity, including activity against protozoal pathogens, while related heterocyclic systems have been investigated in broader anti-infective research [17]. Such findings demonstrate that the thiazole and oxazole frameworks can serve as adaptable platforms for antimicrobial discovery. However, promising in-vitro activity does not by itself establish therapeutic usefulness; selectivity, toxicity, pharmacokinetics and reproducibility require further evaluation.

6.5 Factors affecting antimicrobial activity

Antimicrobial potency depends on the complete molecular structure rather than the heterocycle alone. Important variables include substituent electronics, hydrophobicity, hydrogen-bonding capacity, molecular size, steric effects, ionization, conformational restriction and the presence of additional pharmacophores. The position and nature of substituents can alter permeability and target interactions. Consequently, comparative SAR studies are valuable for identifying structural features that improve microbial inhibition while maintaining acceptable physicochemical and safety profiles.

7. Pharmaceutical Importance

Oxazole-containing pharmaceutical structures have attracted particular attention because the ring can provide a compact aromatic pharmacophore while influencing polarity and molecular recognition. A 2025 review of oxazole- and isoxazole-containing pharmaceuticals described more than 20 FDA-approved drugs containing these nuclei, including examples such as tafamidis and oxaprozin [13].

Thiazole is also an established medicinal-chemistry motif. Reviews have documented thiazole-containing marketed drugs as well as compounds in clinical and preclinical development across multiple therapeutic areas [11]. Thiamine provides a prominent biological example of a thiazole-containing natural product-derived system [4,11].

Example	Heterocyclic motif	Relevance
Oxaprozin	Oxazole-containing	Non-steroidal anti-inflammatory drug; cited as an oxazole-containing pharmaceutical [13]
Tafamidis	Oxazole-containing	Pharmaceutical containing an oxazole nucleus; used in transthyretin amyloidosis [13]
Thiamine	Thiazole-containing	Essential vitamin containing a thiazolium/thiazole-related heterocyclic unit [4,11]

8. Structure–Activity Relationship (Sar) For Microbial Activity

SAR studies indicate that antimicrobial activity is determined by the complete molecular architecture. The oxazole or thiazole ring can contribute electronic and hydrogen-bond-accepting characteristics, but additional substituents frequently determine target recognition, membrane permeability and overall potency. Comparative studies therefore need to consider closely related analogues rather than assuming that replacement of oxygen by sulfur will always improve activity.

Useful antimicrobial SAR variables include electron-withdrawing versus electron-donating substituents, hydrogen-bond donor/acceptor count, molecular size, conformational restriction, hydrophobicity, heteroatom placement and the nature of appended aromatic or

heteroaromatic groups. For resistant bacterial pathogens, recent reviews also emphasize rational modification of thiazole-containing structures to improve activity against strains such as MRSA [15,16].

9. Recent Advances In Microbial Research

Recent research trends include the design of thiazole-containing molecules against antimicrobial-resistant bacteria, hybridization of oxazole or thiazole with other pharmacophores, and the use of computational and SAR approaches to prioritize compounds for biological evaluation. Contemporary reviews highlight thiazole as a versatile platform for antimicrobial drug discovery and report increasing attention to resistant organisms and target-directed design [15,16].

Another important direction is the integration of efficient synthesis with biological screening. One-pot, multicomponent, catalytic and microwave-assisted methods can provide rapid access to structurally diverse heterocycles, allowing larger analogue sets to be evaluated. For meaningful comparison, antimicrobial studies should use clearly defined organisms, appropriate controls and standardized susceptibility endpoints whenever possible.

10. Future Perspectives

Future research on oxazole- and thiazole-based antimicrobial agents should emphasize validated biological targets, standardized susceptibility testing, selectivity toward microbial cells over host cells, and reproducible structure–activity relationships. Particular attention is warranted for drug-resistant bacteria and fungal pathogens for which new chemical matter is needed. Combination strategies, heterocycle hybridization, computational design and greener synthetic methods may further expand the accessible chemical space.

For comparative medicinal chemistry, replacing oxygen with sulfur or changing the substitution pattern can be used as a rational strategy to examine how heteroatom identity affects antimicrobial activity, physicochemical properties and target binding. Such bioisosteric comparisons should be supported by experimental data rather than assumed to produce equivalent biological effects.

11. Conclusion

Oxazole and thiazole are important aromatic five-membered heterocycles with substantial value in synthetic and medicinal chemistry. Although they share a related ring architecture, replacement of oxygen by sulfur produces meaningful differences in electronic, steric and physicochemical properties. Classical methods such as Robinson–Gabriel and van Leusen synthesis for oxazoles and Hantzsch synthesis for thiazoles remain important, while catalytic, one-pot and multicomponent methods continue to expand accessible chemical space. Both scaffolds have been investigated for microbial activity, including antibacterial and antifungal effects, while thiazole derivatives have attracted particular attention in antimycobacterial research and against resistant bacterial strains. Continued integration of efficient synthesis, standardized antimicrobial testing, SAR analysis and biological validation is likely to support the development of new oxazole- and thiazole-based antimicrobial candidates.

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13. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this review.

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