Volume: 5 Issue: 7 Pages: 06-10

A Review on Recent Progress in the Synthetic Methodologies and Biological Significance of Thiazole-Containing Schiff Base Ligands and their Metal Complexes

[*1] Dr. AS Tekale

[*1] Research Laboratory, Department of Chemistry, Shivaji Mahavidyalaya, Udgir, Latur, Maharashtra, India.

Article Info.
E-ISSN: 2583-6528
Impact Factor (QJIF): 8.4
Peer Reviewed Journal
Available online:
www.alladvancejournal.com

Received: 08/June/2026
Accepted: 03/July/2026

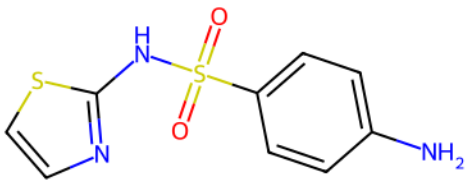
***Corresponding Author**
Dr. AS Tekale
Research Laboratory, Department of Chemistry, Shivaji Mahavidyalaya, Udgir, Latur, Maharashtra, India.

Abstract
Thiazole-containing Schiff bases occupy a privileged position at the interface of heterocyclic, coordination, and medicinal chemistry. The union of an electron-rich, aromatic 1,3-thiazole ring (C_3H_3NS) with a reactive azomethine (–CH=N–) linkage yields ligands that are synthetically accessible, structurally tunable, and able to chelate a wide range of transition-metal ions through N, O, and S donor atoms. This review summarizes recent progress in the rational design and synthesis of thiazole-derived Schiff base ligands, the growing adoption of green and energy-efficient protocols (microwave, ultrasound, mechanochemical, and nanocatalytic routes), the coordination behaviour of these ligands toward first-row transition metals, and the analytical and computational toolbox used to characterize them. The biological significance of the resulting compounds—antibacterial, antifungal, anticancer, antioxidant, anti-inflammatory, and antidiabetic activities—is discussed alongside the mechanistic rationale (Tweedy's chelation theory, DNA binding and cleavage, enzyme inhibition, and ROS generation). Structure–activity relationships and the increasing role of DFT, molecular docking, molecular dynamics, and ADMET prediction are highlighted, and current challenges and future directions are outlined.

Keywords: Thiazole; Schiff base; azomethine; transition-metal complexes; chelation theory; antimicrobial; anticancer; antioxidant; green synthesis; molecular docking

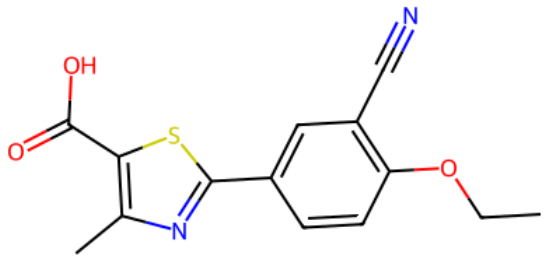
1. Introduction

Heterocyclic scaffolds bearing both nitrogen and sulfur are among the most exploited frameworks in drug discovery. The 1,3-thiazole ring—a five-membered aromatic heterocycle with nitrogen at position 3 and sulfur at position 1—is a recurring motif in natural products and marketed medicines. It is present in thiamine (vitamin B1), in the β-lactam antibiotic penicillin, and in clinically important agents such as sulfathiazole, febuxostat, ritonavir, and dabrafenib. The ring is aromatic (a 6 π-electron system), planar, and metabolically robust, and its 2-, 4-, and 5-positions can be functionalized to tune electronic and steric properties.



Sulfathiazole

Two representative thiazole-containing drugs are shown below to illustrate the pharmacological relevance of the ring.



Febuxostat

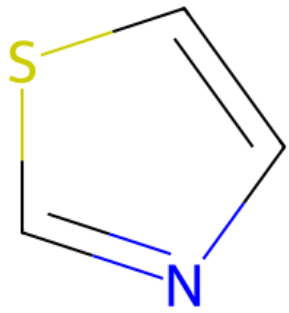
Fig 1: Sulfathiazole (antibacterial, top) and febuxostat (xanthine-oxidase inhibitor, bottom).

Schiff bases—condensation products of primary amines with aldehydes or ketones—were first described by Hugo Schiff in 1864 and are defined by the azomethine (imine) linkage, R–CH=N–R′. The lone pair on the imine nitrogen makes these compounds excellent ligands, and their ease of preparation, structural diversity, and thermodynamic stability have made them central to coordination chemistry.

Combining the two motifs gives thiazole-containing Schiff bases, in which a thiazole unit is tethered to an azomethine group. Most commonly, commercially available 2-aminothiazole (or a substituted analogue) is condensed with an aromatic or heteroaromatic aldehyde; the complementary route condenses a thiazole-carbaldehyde with an amine. The resulting ligands often outperform simpler Schiff bases because the thiazole ring contributes an additional donor atom, extended π-conjugation, and favourable lipophilicity. Crucially, on coordination to a metal ion these ligands frequently display markedly enhanced biological activity relative to the free ligand—an observation that continues to drive the field. This review brings together recent developments in their synthesis, coordination chemistry, characterization, and pharmacological evaluation.

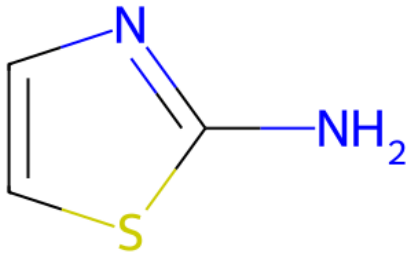
2. The Thiazole Nucleus

Thiazole (molecular formula C_3H_3NS; molar mass 85.13 g mol^{-1}) is an aromatic 1,3-azole. The conventional numbering places sulfur at position 1, the ring carbon between the two heteroatoms at position 2, nitrogen at position 3, and the two remaining carbons at positions 4 and 5. Position 2 is the most electrophilic ring carbon and is the site of the amino group in 2-aminothiazole, the key precursor used throughout this review.



1,3-Thiazole (C3H3NS)

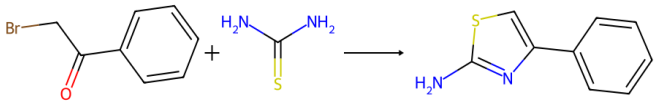
Fig 2: The 1,3-thiazole ring with conventional atom numbering.



2-Aminothiazole (C3H4N2S)

Fig 3: 2-Aminothiazole ($C_3H_4N_2S$), the principal building block for the Schiff bases discussed here.

The classical entry to the ring is the Hantzsch thiazole synthesis, a cyclocondensation of an α-halocarbonyl compound with a thioamide or thiourea. When thiourea is used, the product is a 2-aminothiazole. For example, phenacyl bromide (2-bromo-1-phenylethan-1-one) reacts with thiourea to give 2-amino-4-phenylthiazole, with elimination of HBr and water:



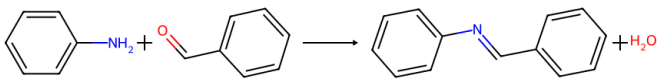
Scheme 1: Hantzsch synthesis of 2-amino-4-phenylthiazole from phenacyl bromide and thiourea (byproducts: HBr, H_2O).

3. Schiff Bases and the Azomethine Linkage

A Schiff base forms by nucleophilic addition of a primary amine to a carbonyl carbon, giving a carbinolamine (hemiaminal) that dehydrates to the C=N product. The overall condensation is:

$$R–NH_2 + R′–CHO \rightarrow R–N=CH–R′ + H_2O$$

The reaction is reversible and mildly acid-catalyzed; removal of water (azeotropically or with a desiccant) drives it to completion. A representative example is the condensation of aniline with benzaldehyde to give N-benzylideneaniline:

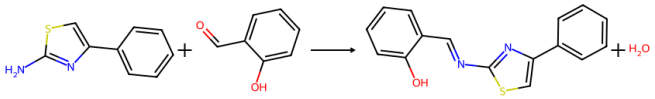


Scheme 2: General Schiff base condensation, illustrated with aniline and benzaldehyde.

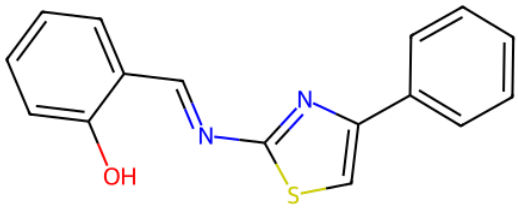
Conjugation with aromatic rings and intramolecular hydrogen bonding—for instance from an ortho-hydroxyl group in salicylaldehyde-derived systems—stabilize the azomethine and typically lock the molecule into the E configuration. In 2-aminothiazolyl Schiff bases the exocyclic nitrogen is conjugated with the ring, so these compounds can be regarded as existing between amino–imine and imino–enamine tautomeric forms; this tautomeric character influences both the donor strength of the azomethine nitrogen and the observed biological behaviour.

4. Design of Thiazole-Containing Schiff Base Ligands

A prototypical ligand is obtained by condensing 2-amino-4-phenylthiazole with salicylaldehyde to give (E)-2-(((4-phenylthiazol-2-yl)imino)methyl)phenol, abbreviated HL ($C_{16}H_{12}N_2OS$):



Scheme 3: Synthesis of the model ligand HL from 2-amino-4-phenylthiazole and salicylaldehyde.



HL: (E)-2-(((4-phenylthiazol-2-yl)imino)methyl)phenol

Fig 4: Ligand HL. The azomethine nitrogen and the phenolic oxygen provide an N,O chelating pocket; the thiazole ring nitrogen offers an optional third donor.

Three Recurring Design Families Dominate the Recent Literature

- **Salicylaldehyde-type ligands** (2-aminothiazole + salicylaldehyde or a substituted 2-hydroxyaldehyde), giving an N,O-donor set with a chelatable phenolic oxygen.
- **Bis-thiazole/symmetric ligands**, in which two thiazole–azomethine arms are joined through a central spacer, offering multidentate coordination pockets and extended planarity favourable for DNA intercalation.
- **Hybrid and hydrazone systems**, where the thiazole is fused with a second pharmacophore (quinoline, coumarin, thiophene, fluorene, benzothiazole) or linked through a hydrazinecarboxamide/thiosemicarbazone bridge to introduce extra N and S donors and additional biological targets.

5. Synthetic Strategies: Conventional and Green

The workhorse method remains reflux of equimolar amine and aldehyde in ethanol or methanol, sometimes with a catalytic drop of glacial acetic acid, for 2–8 h; the product usually precipitates on cooling and is recrystallized. Although reliable, this route is slow, energy-intensive, and solvent-heavy. Recent work has therefore emphasized greener protocols, summarized in Table 1.

Method	Typical time	Key advantage	Representative use
Conventional reflux (EtOH/MeOH, cat. AcOH)	2–8 h	Simple, reliable	General Schiff base formation
Microwave irradiation	sec–min	Large rate acceleration, cleaner products, higher yields	2-Aminothiazole Schiff bases and their chelates
Ultrasound (sonochemistry)	10–40 min	Improved crystallinity, milder conditions	Bis-thiazole Schiff bases
Mechanochemical grinding/ball milling	min	Solvent-free, minimal waste	Solid-state condensations
ZnO-nanoparticle catalysis	min–h	Recyclable benign catalyst, high yields	Thiazole-based Schiff bases
Aqueous/ionic-liquid/DES media	varies	Environmentally responsible media	Green condensations

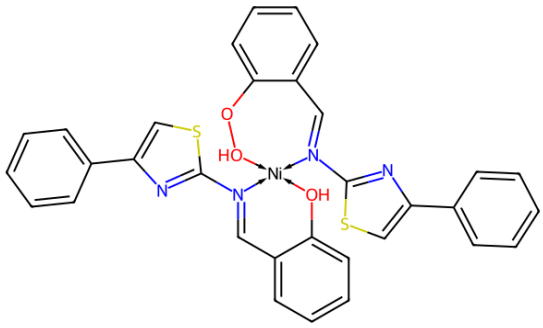
These advances shorten reaction times from hours to minutes, raise yields, and reduce solvent consumption, aligning thiazole Schiff base chemistry with the principles of green chemistry.

6. Coordination Behaviour

Thiazole Schiff bases bind principally through the azomethine nitrogen, supplemented by donor atoms carried on the aldehyde or amine fragment. Depending on the ligand, common donor sets include N,O (phenolate oxygen), N,N (ring or additional imine nitrogen), N,S (thiol/thione sulfur), and tridentate O,N,S or N,N,O arrangements. Coordination frequently involves deprotonation of a phenolic –OH, so many complexes are neutral. For the model ligand HL, complex formation with a divalent metal proceeds according to:

$$2\ HL\ +\ M^{2+}\ \rightarrow\ [M(L)_2]\ +\ 2\ H^{+}$$

Where
M^{2+} = Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+}, etc. The salicylaldimine unit forms a stable six-membered chelate ring (M–O–C–C–C=N), and the resulting bis-chelate complex is illustrated schematically below.



[Ni(L)2] bis(N,O-chelate)

Fig 5: Schematic of a neutral bis-chelate complex, $[M(L)_2]$ (M = Ni shown), formed by two N,O-bound ligand units. Dative bonds denote coordinate bonding to the metal.

Reported geometries span square-planar, tetrahedral, square-pyramidal, and octahedral, according to the metal ion and ligand denticity. First-row transition ions dominate because they are cheaper and less toxic than platinum-group metals, an important consideration for the development of metal-based drugs.

7. Characterization Toolbox

A convergent set of techniques establishes structure and bonding. Table 2 lists the most diagnostic observations.

Technique	Diagnostic observation for thiazole Schiff bases/complexes
FT-IR	ν(C=N) azomethine near 1600–1620 cm^{-1}; shift to lower frequency on N-coordination; loss of phenolic ν(O–H) on deprotonation; new ν(M–N) ~450–500 and ν(M–O) ~520–560 cm^{-1}
$^{1}H/^{13}C$ NMR	Azomethine –CH=N– singlet near δ 8.2–8.9 ppm (^{1}H) and δ ~160–162 ppm (^{13}C); H-bonded phenolic OH near δ 12–13 ppm
UV–Vis	Intraligand π→π*/n→π* bands; d–d and charge-transfer bands report geometry in complexes
Magnetic susceptibility	μ_eff indicates spin state/geometry (e.g. ~1.7–2.0 B.M. for Cu(II); ~4.7–5.2 B.M. for high-spin Co(II); diamagnetic for Zn(II))
Molar conductance	Distinguishes electrolytes from neutral (non-electrolyte) complexes
EPR/ESR	g-values and coordination environment for Cu(II) and VO(IV)
TGA/DTA	Thermal stability; lattice vs. coordinated water
ESI-MS/HRMS	Molecular-ion confirmation of ligand and complex composition
XRD/DFT	Definitive geometry (single-crystal XRD); optimized structures, HOMO–LUMO gaps and MEP maps (DFT, commonly B3LYP)

8. Biological Importance

8.1 Antibacterial and Antifungal Activity

Thiazole Schiff bases and their complexes are consistently active against Gram-positive and Gram-negative bacteria and against pathogenic fungi (Candida, Aspergillus, Fusarium). A recurring finding is that metal complexes are more potent than the parent ligand. This is rationalized by Tweedy's chelation theory and Overton's concept of cell permeability: on chelation, the positive charge of the metal ion is partially delocalized over the donor atoms, lowering polarity and increasing the lipophilic character of the complex. The more lipophilic complex penetrates the microbial lipid membrane more readily, disrupting respiration and blocking protein synthesis. Electron-withdrawing substituents (–NO2, halogen) on the aldehyde-derived aromatic ring frequently enhance antibacterial potency.

8.2 Anticancer Activity

These complexes have been screened against human tumour cell lines including breast (MCF-7), liver (HepG2), lung (A549, H1299), colorectal (HCT116), and cervical (HeLa), often against doxorubicin, adriamycin, or cisplatin as reference drugs. Copper(II) and zinc(II) complexes in particular have shown cytotoxicity approaching or exceeding standard drugs in specific systems. Interest is amplified by the search for alternatives to cisplatin that avoid its cost, resistance, and dose-limiting toxicity. Proposed mechanisms include DNA binding (intercalation, groove binding, or electrostatic interaction), DNA cleavage by redox-active Cu(II) complexes via reactive oxygen species, inhibition of enzymes/receptors such as topoisomerases or EGFR tyrosine kinase, and induction of apoptosis.

8.3 Antioxidant Activity

Radical-scavenging capacity is routinely assessed by the DPPH, ABTS, and FRAP assays. Ligands bearing phenolic hydroxyl groups and their complexes can rival or exceed standards such as ascorbic acid, and the response often correlates with the presence and position of electron-donating (hydroxyl, methoxy) groups.

8.4 Other Activities

The scaffold also underpins reported anti-inflammatory, antidiabetic (α-amylase and α-glucosidase inhibition), antitubercular, antimalarial, antiviral, and enzyme-inhibitory (urease, carbonic anhydrase, cholinesterase) activities, reflecting the broad pharmacological reach of the thiazole–azomethine combination.

9. Representative Systems from the Recent Literature

Table 3 collects a few representative thiazole Schiff base systems and their reported activities to illustrate the breadth of the field.

Ligand type/system	Metal(s)	Principal reported activity
2-Aminothiazole + substituted benzaldehydes	Co, Ni, Cu, Zn	Antibacterial, antifungal, antioxidant
Thiazole–salicylaldehyde (N,O)	Cu, Ni, Co, Zn	Antifungal, DNA binding/cleavage, antioxidant
Bis-thiazole Schiff bases	— (organic)	Antibacterial, antifungal, DPPH scavenging; docking + MD
Thiazole–quinoline hydrazinecarboxamide	Cu, Co, Ni	Antimicrobial, DNA cleavage, cytotoxicity
Thiophene–thiazole hybrids	— (organic)	Antimicrobial, antioxidant; ADMET + docking + MD
Benzothiazole Schiff bases	3d metals	Anticancer (A549, H1299), DNA binding; DFT

Note. The entries above are illustrative of compound classes and activity types; consult the primary references for exact structures, conditions, and quantitative data.

10. Structure–Activity Relationships

Several general trends recur, though exceptions are common and system-dependent:

- **The Identity of the Metal ION:** strongly modulates activity; Cu(II) complexes are frequently the most potent antibacterial and cytotoxic agents, attributed to favourable redox chemistry and geometry.
- **Electron-withdrawing Substituents:** (–NO2, –Cl, –Br) on the aldehyde aromatic ring tend to boost antimicrobial and antiproliferative potency.
- **Electron-donating/Phenolic Groups:** (–OH, –OCH3) tend to enhance antioxidant activity.
- **Increased Lipophilicity:** (through complexation or lipophilic substituents) improves membrane penetration up to an optimum, beyond which poor solubility limits activity.
- **Extended Conjugation and Planarity:** As in bis-thiazole and fused-heterocycle hybrids, favour DNA intercalation and often improve cytotoxicity.

11. Computational Approaches

Computation is now integral rather than supplementary. DFT furnishes optimized geometries, frontier-orbital energies, global reactivity descriptors, and molecular electrostatic potentials that rationalize spectra and reactivity. Molecular docking predicts binding modes and affinities against validated targets—bacterial DNA gyrase B (PDB 6F86), EGFR tyrosine kinase (PDB 1XKK), and others—guiding SAR. Molecular dynamics simulations (typically tens of nanoseconds) assess the stability of ligand–protein complexes under near-physiological conditions, while ADMET/Swiss ADME profiling screens drug-likeness early. Together these methods create a design–synthesize–test–model loop that accelerates discovery.

12. Challenges and Future Perspectives

Despite steady progress, several issues limit translation. Many reports stop at in-vitro screening without pharmacokinetic or in-vivo validation. Crystals suitable for single-crystal XRD are often unavailable, so geometries are inferred rather than proven. Solubility and stability under physiological conditions are frequently under-characterized, and mechanistic claims sometimes rest on a single technique. Priorities include standardized biological assays with proper controls, more single-crystal structures, deeper mechanistic and target-identification studies, assessment of selectivity toward diseased over normal cells, and continued adoption of green synthesis for scalability and sustainability. Hybrid ligands that fuse thiazole–azomethine cores with complementary pharmacophores, and complexes of underexplored or biocompatible metals, are especially promising directions.

Conclusion

Thiazole-containing Schiff base ligands and their metal complexes remain a vibrant and productive research area. Their modular, increasingly green synthesis, their rich and tunable coordination chemistry, and their broad, often metal-enhanced biological profiles make them attractive candidates for antimicrobial, anticancer, and antioxidant applications. As synthetic, analytical, and computational methods continue to converge, the rational design of thiazole Schiff base metal drugs with defined mechanisms and improved selectivity appears both achievable and worthwhile.

References

1. Lemilemu F, Bitew M, Demissie TB, Eswaramoorthy R, Endale M. Synthesis, antibacterial and antioxidant activities of thiazole-based Schiff base derivatives: a combined experimental and computational study. BMC Chemistry. 2021; 15:67. doi:10.1186/s13065-021-00791-w
2. Malik MA, Dar OA, Gull P, Wani MY, Hashmi AA. Heterocyclic Schiff base transition metal complexes in antimicrobial and anticancer chemotherapy. Med Chem Comm. 2018; 9:409-436. doi:10.1039/c7md00526a
3. Varshney A, Mishra AP. *et al*. Synthesis, spectral characterization, computational studies, antifungal, DNA interaction, antioxidant and fluorescence property of a novel thiazole Schiff base ligand and its metal chelates. Spectrochimica Acta Part A. 2023; 297:122765. doi:10.1016/j.saa.2023.122765
4. Narasimhamurthy KH, Swaroop TR, Rangappa KS. A review on progress of thiazole derivatives as potential anti-inflammatory agents. European Journal of Medicinal Chemistry Reports. 2024; 12:100225.
5. Vigato PA, Tamburini S. The challenge of cyclic and acyclic Schiff bases and related derivatives. Coordination Chemistry Reviews. 2004; 248:1717-2128.
6. Abu-Dief AM. *et al*. Transition-metal complexes with benzothiazole-based Schiff base ligands: synthesis, DFT, docking and antifungal/anticancer studies. *Journal of Molecular Structure*. 2019; 1183:302–315.
7. Bryndal I, Stolarczyk M, Mikołajczyk A. *et al*. Pyrimidine Schiff bases: synthesis, structural characterization and recent studies on biological activities. International Journal of Molecular Sciences. 2024; 25:2076. doi:10.3390/ijms25042076
8. Mahmood K, Hashmi W, Ismail H, Mirza B. Synthesis, DNA binding and antibacterial activity of metal(II) complexes of a benzimidazole Schiff base. Polyhedron. 2018; 157:326–334.