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Thiazole-Containing Schiff Base Ligands and Their Transition-Metal Complexes: Design, Synthesis, Coordination Chemistry, and Biological Importance

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Abstract
Schiff bases derived from the 1,3-thiazole nucleus constitute one of the most versatile ligand families in modern coordination and medicinal chemistry. The fusion of an aromatic, electron-rich, sulfur- and nitrogen-bearing heterocycle with a readily formed azomethine (–CH=N–) linkage yields compounds that are inexpensive to prepare, structurally programmable, and able to chelate essentially the entire first transition series through nitrogen, oxygen, and sulfur donors. This review provides a comprehensive account of the field. We begin with the structure and synthesis of the thiazole ring and the mechanism of azomethine formation, then present a systematic classification of thiazole Schiff bases by their synthetic origin, denticity, and hybrid architecture. Synthetic methodologies are surveyed with emphasis on green and energy-efficient routes (microwave, ultrasonic, mechanochemical, nanocatalytic, and alternative-media techniques) and their green-chemistry metrics. The coordination behaviour of these ligands—donor sets, denticity, geometry, and complex stability—is discussed alongside the full analytical toolbox used for characterization. The core of the review examines biological importance in depth: antibacterial, antifungal, anticancer, antioxidant, anti-inflammatory, antidiabetic, antitubercular, antimalarial, antiviral, and enzyme-inhibitory activities, each with its mechanistic rationale and representative examples. Structure–activity relationships, non-biological applications (chemosensing, catalysis, corrosion inhibition, and materials), in-silico methods (DFT, docking, molecular dynamics, ADMET), and toxicity considerations are also treated. We close with the principal challenges and future directions for the field.

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

1. Introduction

1.1 Historical Background

The imine (azomethine) functional group was first reported by Hugo Schiff in 1864, and compounds bearing the R–CH=N–R′ motif have carried his name ever since. Their utility as ligands became apparent early in the twentieth century, and salen and salophen complexes are now textbook examples of Schiff base coordination chemistry. The thiazole ring, in turn, has a distinguished pharmacological pedigree: it is the reactive core of thiamine (vitamin B1), the fused ring of penicillin, and a component of numerous marketed drugs including sulfathiazole, febuxostat, ritonavir, dasatinib, and dabrafenib. Merging these two privileged structures produces the subject of this review.

1.2 Scope

This review integrates the chemistry (structure, synthesis, coordination) and the applications (chiefly biological, but also analytical and material) of thiazole-containing Schiff bases and their metal complexes, with an emphasis on advances of the last decade. Our aim is to provide both the newcomer and the specialist with a coherent, mechanistically grounded overview.

2. The Thiazole Nucleus

2.1 Structure and Properties

Thiazole (C_3H_3NS; M = 85.13 g mol^{-1}) is a five-membered, planar, aromatic 1,3-azole containing a "pyridine-like" nitrogen at position 3 and a divalent sulfur at position 1. Its 6

π-electron aromatic sextet arises from the two ring double bonds plus a lone pair on sulfur. The ring is amphoteric: N-3 is weakly basic and nucleophilic, whereas C-2 is the most electrophilic carbon and the usual site of the amino substituent in 2-aminothiazole. This ambivalent electronic character underlies both the coordinating ability and the biological versatility of thiazole derivatives.

Fig 1: 1,3-Thiazole with conventional numbering (S-1, C-2, N-3, C-4, C-5).

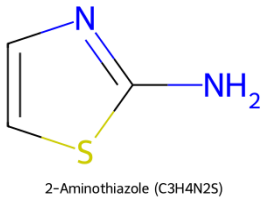
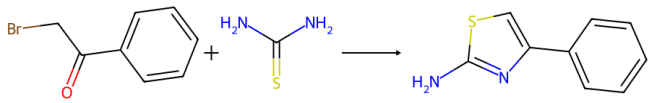


Fig 2: 2-Aminothiazole, the principal amine building block for thiazole Schiff bases.

2.2 Synthesis of the Ring

The dominant preparative route is the Hantzsch thiazole synthesis, the cyclocondensation of an α-halocarbonyl compound with a thioamide or thiourea; thiourea delivers 2-aminothiazoles directly. Alternative methods include the Cook–Heilbron synthesis (from α-aminonitriles) and the Gabriel synthesis (from acylaminoketones). The Hantzsch route to 2-amino-4-phenylthiazole is shown below.

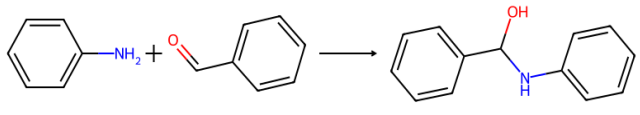


Scheme 1: Hantzsch synthesis of 2-amino-4-phenylthiazole (byproducts: HBr, H_2O).

3. Formation of the Azomethine Linkage

3.1 Mechanism

Imine formation is a two-stage, acid-catalyzed, reversible process. In the first stage the amine nitrogen adds to the carbonyl carbon to give a tetrahedral carbinolamine (hemiaminal):



Scheme 2: Stage 1—nucleophilic addition of the amine to the aldehyde gives the carbinolamine (hemiaminal).

In the second stage the carbinolamine loses water—acid-catalyzed, via an iminium ion—to furnish the azomethine:

Scheme 3: Stage 2—acid-catalyzed dehydration gives the Schiff base (illustrated for aniline + benzaldehyde).

3.2 Factors Affecting Formation and Stability

Because both steps are reversible, imine yield is governed by equilibrium. Removing water (azeotropically, with molecular sieves, or with a desiccant) drives condensation forward. The reaction rate is bell-shaped in pH: too little acid slows dehydration, whereas too much protonates the amine and suppresses nucleophilic addition. Conjugation with aromatic rings, and intramolecular hydrogen bonding (as from an ortho-hydroxyl in salicylaldehyde systems), stabilize the product and typically enforce the E configuration. In 2-aminothiazolyl systems the exocyclic nitrogen conjugates with the ring, giving amino–imine/imino–enamine tautomerism that modulates donor strength.

4. Classification of Thiazole-Containing Schiff Bases

4.1 By Synthetic Origin

Two complementary routes dominate. In the first, 2-aminothiazole (or a substituted analogue) supplies the amine and is condensed with an aldehyde such as salicylaldehyde. In the second, a thiazole-carbaldehyde supplies the carbonyl and is condensed with a primary amine:

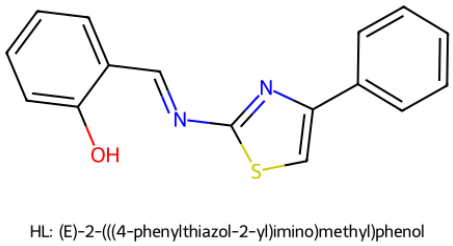
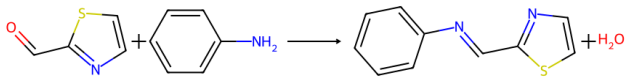


Figure 3: 2-Aminothiazole route: the model ligand HL from salicylaldehyde + 2-amino-4-phenylthiazole (N,O donor).

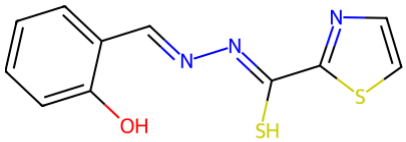


Scheme 4: Carbaldehyde route: thiazole-2-carbaldehyde + a primary amine → thiazolyl Schiff base + H_2O.

4.2 By denticity and Donor Set

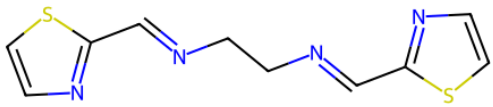
Thiazole Schiff bases span the full range from monodentate to polydentate, as summarized in Table 1.

Denticity	Typical donor set	Representative architecture
Bidentate	N,O or N,N or N,S	2-Aminothiazole + salicylaldehyde (N,O); simple thiazolyl imines (N,N)
Tridentate	O,N,S/N,N,O/N,N,S	Thiazolyl thiosemicarbazones; ortho-functionalized salicylaldimines
Tetradentate	N4/N2O2	Bis-thiazole (salen-type) ligands from a diamine + 2 carbaldehyde units
Polydentate/ macrocyclic	mixed	Template-synthesized macrocycles incorporating thiazole



Representative O,N,S tridentate thiazole ligand

Fig 4: A representative O,N,S tridentate thiazole ligand; the added sulfur donor favours softer metal ions.

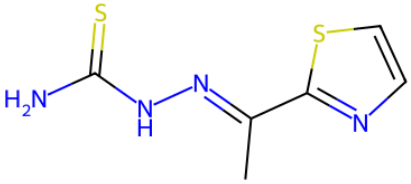


Bis-thiazole Schiff base (tetradentate N4)

Fig 5: A tetradentate bis-thiazole (salen-type) Schiff base formed from a diamine and two thiazole-2-carbaldehyde units.

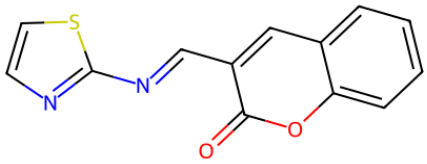
4.3 Hybrid and Specialized Systems

A major recent trend fuses the thiazole–azomethine core with a second pharmacophore or introduces additional donor atoms through a hydrazone or thiosemicarbazone bridge. These hybrids combine complementary biological targets and often improve potency and selectivity.



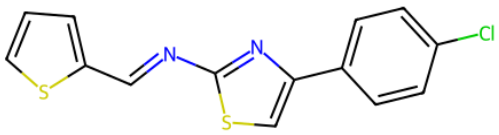
Thiazolyl thiosemicarbazone (N,N,S donor)

Fig 6: A thiazolyl thiosemicarbazone (N,N,S donor), a widely studied hybrid class.



Coumarin–thiazole hybrid Schiff base

Fig 7: A coumarin–thiazole hybrid Schiff base, combining two bioactive scaffolds.



Thiophene–thiazole hybrid

Fig 8: A thiophene–thiazole hybrid, extending conjugation and sulfur content.

5. Synthetic Methodologies

5.1 Conventional Condensation

The classical method refluxes equimolar amine and aldehyde in ethanol or methanol, often with a catalytic drop of glacial acetic acid, for 2–8 h; the product usually precipitates on cooling and is recrystallized. Metal complexes are prepared by treating the ligand with a metal(II) salt, frequently after mild base addition to deprotonate a phenolic hydroxyl.

5.2 Green and Energy-efficient Routes

Recent work strongly favours greener protocols that cut time, energy, and solvent use, summarized in Table 2.

Method	Typical time	Principal advantage
Conventional reflux	2–8 h	Simple and reliable
Microwave irradiation	seconds–minutes	Dramatic rate acceleration, higher yields, cleaner products
Ultrasonication	10–40 min	Cavitation-driven mixing, improved crystallinity
Mechanochemical grinding/ball milling	minutes	Solvent-free, minimal waste
Nanocatalysis (e.g. ZnO NPs)	minutes–hours	Recyclable benign catalyst, high yields
Aqueous/ionic-liquid/DES media	variable	Environmentally responsible reaction media

5.3 Green-chemistry Metrics

Beyond yield, modern reports increasingly quantify sustainability using atom economy, E-factor (mass of waste per mass of product), and process mass intensity. Condensations are inherently atom-economical—water is the only stoichiometric byproduct—so solvent choice and energy input dominate the environmental footprint; this is precisely where microwave, ultrasonic, and solvent-free methods deliver their gains.

6. Coordination Chemistry

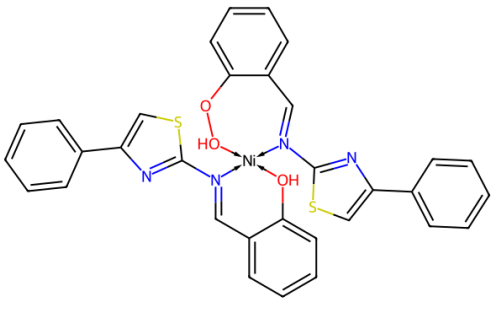
6.1 Donor Atoms, Denticity, and Geometry

Coordination almost always involves the azomethine nitrogen, supplemented by donors from the aldehyde or amine fragment: a phenolate oxygen (after deprotonation), the ring or a second imine nitrogen, or a thiol/thione sulfur. According to hard–soft acid–base considerations, N,O sets favour harder ions (Fe, Mn, VO, Cr), whereas sulfur-containing sets stabilize softer ions (Cu, Ni, Pd, Pt). Reported geometries include square-planar, tetrahedral, square-pyramidal, trigonal-bipyramidal, and octahedral, dictated by the metal, ligand denticity, and any co-ligands or water.

6.2 Complex Formation

For a monobasic bidentate ligand HL, neutral bis-chelate complexes typically form with loss of the phenolic proton:

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



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

Fig 9: A neutral bis-chelate complex $[M(L)_2]$ with two N,O-bound ligand units (M = Ni shown).

Low molar conductance confirms the non-electrolytic nature of such neutral complexes, while magnetic moments and electronic spectra establish spin state and geometry.

7. Characterization Techniques

A convergent battery of techniques establishes structure and bonding; the most diagnostic observations are collected in Table 3.

Technique	Diagnostic observation
Elemental (CHNS) & ESI-MS/HRMS	Stoichiometry and molecular-ion confirmation
FT-IR	ν(C=N) ~1600–1620 cm^{-1}, shifting lower on N-coordination; loss of phenolic ν(O–H); new ν(M–N) ~450–500, ν(M–O) ~520–560 cm^{-1}
^{1}H/ ^{13}C NMR	Azomethine CH ~δ 8.2–8.9 ppm (^{1}H) and ~δ 160–162 ppm (^{13}C); H-bonded OH ~δ 12–13 ppm
UV–Vis	Intraligand π→π*/n→π*; d–d and LMCT/MLCT bands report geometry
Magnetic susceptibility	μ_eff → spin state and geometry
Molar conductance	Electrolyte vs. neutral (non-electrolyte) complex
EPR (Cu, VO)	g-values, geometry, covalency (g∥ > g⊥ pattern)
TGA/DTA	Thermal stability; lattice vs. coordinated water
Single-crystal XRD & Hirshfeld	Definitive geometry; quantified intermolecular contacts
DFT (B3LYP)	Optimized geometry, HOMO–LUMO, reactivity descriptors, MEP

8. Biological Importance

8.1 Antibacterial Activity and the Chelation Mechanism

Thiazole Schiff bases are broadly active against Gram-positive (e.g. S. aureus, B. subtilis) and Gram-negative (e.g. E. coli, P. aeruginosa) bacteria, and their metal complexes are frequently more potent than the free ligands. The standard explanation combines Overton's cell-permeability concept with Tweedy's chelation theory: on chelation, the metal's positive charge is partially delocalized over the donor atoms, lowering polarity and raising lipophilicity. The more lipophilic complex traverses the microbial lipid membrane more readily and interferes with respiration, protein synthesis, and DNA processes. Potency commonly tracks with electron-withdrawing substituents on the aldehyde ring and with the choice of metal (Cu(II) is often most active).

8.2 Antifungal Activity

Activity against Candida albicans, Aspergillus niger, and Fusarium species is widely documented, again often enhanced on complexation. Mechanistically, interference with ergosterol biosynthesis and fungal membrane integrity is implicated, paralleling the antibacterial rationale.

8.3 Anticancer Activity

Cytotoxicity has been demonstrated against numerous human tumour lines—MCF-7 (breast), HepG2 (liver), A549 (lung), HCT116 (colon), and HeLa (cervical)—with doxorubicin or cisplatin as references, and interest is heightened by the search for non-platinum metallodrugs. Proposed mechanisms include: (i) DNA binding by intercalation, groove binding, or electrostatic interaction, quantified by binding constants from UV–Vis and fluorescence titration; (ii) oxidative DNA cleavage by redox-active Cu(II) complexes via ROS; (iii) inhibition of enzymes and receptors such as topoisomerases and EGFR tyrosine kinase; and (iv) induction of apoptosis through mitochondrial and caspase pathways.

8.4 Antioxidant Activity

Radical-scavenging capacity is assayed by DPPH, ABTS, and FRAP methods. Ligands bearing phenolic hydroxyls and their complexes can approach or exceed ascorbic acid, with the response tracking electron-donating (–OH, –OCH3) substitution and, for complexes, the redox activity of the metal centre.

8.5 Anti-inflammatory and Analgesic Activity

Several thiazole Schiff bases inhibit cyclooxygenase and pro-inflammatory mediators, and thiazole is a recognized scaffold in anti-inflammatory drug design, motivating continued exploration of Schiff base derivatives.

8.6 Antidiabetic Activity

Inhibition of the carbohydrate-hydrolyzing enzymes α-amylase and α-glucosidase is a common antidiabetic readout; thiazole Schiff bases and their complexes have shown promising in-vitro inhibition, sometimes rivalling acarbose.

8.7 Antitubercular, Antimalarial, and Antiviral Activity

Reports of activity against Mycobacterium tuberculosis, Plasmodium species, and various viruses underscore the breadth of the scaffold, though these areas remain comparatively less developed and merit deeper mechanistic study.

8.8 Enzyme Inhibition

Beyond the enzymes noted above, thiazole Schiff bases inhibit urease, carbonic anhydrase, and cholinesterases (with implications for Alzheimer's disease), often supported by docking that places the scaffold in the active-site cleft.

Table 4 collects representative classes and their principal reported activities.

System/class	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 (N4) Schiff bases	—/3d metals	Antibacterial, antifungal, DPPH scavenging
Thiazolyl thiosemicarbazones (N,N,S)	Cu,Ni,Pd	Anticancer, antimicrobial, DNA cleavage
Coumarin–/thiophene–thiazole hybrids	—/3d metals	Antimicrobial, antioxidant, enzyme inhibition
Benzothiazole Schiff bases	3d metals	Anticancer (A549, H1299), DNA binding

9. Structure–Activity Relationships

Recurring, though system-dependent, trends include:

- **Metal Identity:** Cu(II) complexes are frequently the most potent antibacterial and cytotoxic agents (favourable redox chemistry and geometry).
- **Electron-withdrawing Groups:** (–NO2, –Cl, –Br) on the aldehyde aromatic ring generally enhance antimicrobial and ant proliferative potency.
- **Electron-donating/phenolic Groups:** (–OH, –OCH3) enhance antioxidant activity.
- **Lipophilicity:** complexation and lipophilic substituents improve membrane penetration up to an optimum, beyond which solubility limits activity.
- **Planarity and Conjugation:** extended, planar systems (bis-thiazole, fused hybrids) favour DNA intercalation and often improve cytotoxicity.
- **Denticity and Donor Set:** added S donors tune selectivity toward softer metals and can sharpen enzyme inhibition.

10. Non-Biological Applications

The same features that make thiazole Schiff bases good ligands support applications beyond medicine. As chemosensors, their metal complexes show colorimetric or fluorimetric responses to selected cations and anions. As catalysts, transition-metal Schiff base complexes mediate oxidation, epoxidation, and C–C coupling reactions. Their strong adsorption on metal surfaces—through N, O, and S lone pairs and π-systems—makes many derivatives effective corrosion inhibitors for mild steel in acidic media. Extended-conjugation systems are also of interest for nonlinear-optical and luminescent materials.

11. Computational and In-Silico Methods

Computation is now integral to the field. DFT (commonly B3LYP with 6-31G(d,p)/LANL2DZ) yields optimized geometries, frontier-orbital energies, MEP maps, and global reactivity descriptors—electronegativity $\chi = (I+A)/2$, hardness $\eta = (I-A)/2$, and electrophilicity $\omega = \chi^2/2\eta$—that rationalize both spectra and reactivity. Molecular docking predicts binding modes against targets such as DNA gyrase B (PDB 6F86), EGFR (PDB 1XKK), and B-DNA (PDB 1BNA); molecular dynamics probes complex stability over tens of nanoseconds; and ADMET/SwissADME profiling screens drug-likeness early, forming a design–synthesize–test–model loop.

12. Toxicity and Drug-Likeness

Realistic development requires attention to selectivity (activity against diseased versus normal cells), aqueous solubility, metabolic stability, and metal-ion toxicity. In-silico ADMET filters (Lipinski and Veber rules, predicted hepatotoxicity and hERG liability) are useful early screens, but must be complemented by experimental cytotoxicity against non-cancerous cell lines and, ultimately, in-vivo evaluation.

13. Challenges and Future Perspectives

Despite a large and growing literature, several gaps limit translation. Many studies stop at in-vitro screening without pharmacokinetic or in-vivo validation; single-crystal structures are frequently unavailable, so geometries are inferred; solubility and physiological stability are under-reported; and mechanistic claims sometimes rest on a single technique. Priorities include standardized, well-controlled bioassays; more definitive structural data; deeper target identification; explicit selectivity assessment; and continued adoption of green, scalable synthesis. Rationally designed hybrids and complexes of biocompatible or underexplored metals are especially promising.

Conclusion

Thiazole-containing Schiff base ligands and their transition-metal complexes remain a remarkably fertile research area. Their modular and increasingly green synthesis, versatile and tunable coordination chemistry, and broad, often metal-enhanced biological activity position them as strong candidates for antimicrobial, anticancer, and antioxidant applications, with useful roles in sensing, catalysis, and materials besides. As synthetic, structural, and computational methods continue to converge, the rational design of thiazole Schiff base metal compounds with defined mechanisms and improved selectivity is an attainable and worthwhile goal.

References

1. Schiff H. Mittheilungen aus dem Universitätslaboratorium in Pisa: eine neue Reihe organischer Basen. Annalen der Chemie und Pharmacie. 1864; 131:118–119.
2. Vigato PA, Tamburini S. The challenge of cyclic and acyclic Schiff bases and related derivatives. Coordination Chemistry Reviews. 2004; 248:1717–2128.
3. Malik MA, Dar OA, Gull P, Wani MY, Hashmi AA. Heterocyclic Schiff base transition metal complexes in antimicrobial and anticancer chemotherapy. MedChemComm. 2018; 9:409-436. doi:10.1039/c7md00526a
4. 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
5. 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
6. 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.
7. Abu-Dief AM. *et al*. Transition-metal complexes with benzothiazole-based Schiff base ligands: synthesis, DFT, DNA binding, docking and anticancer studies. *Journal of Molecular Structure*. 2019; 1183:302–315.
8. Wolfe A, Shimer GH, Meehan T. Polycyclic aromatic hydrocarbons physically intercalate into duplex regions of denatured DNA. Biochemistry. 1987; 26:6392-6396.
9. Trott O., Olson A. J. AutoDock Vina: improving the speed and accuracy of docking. Journal of Computational Chemistry. 2010; 31:455–461.
10. Kajal A, Bala S, Kamboj S, Sharma N, Saini V. Schiff bases: a versatile pharmacophore. J*ournal of Catalysts.* 2013, 893512.
11. Chohan ZH. *et al*. Metal-based antibacterial and antifungal agents: synthesis, characterization and biological evaluation of thiazole-derived Schiff bases and their complexes. *Journal of Enzyme Inhibition and Medicinal Chemistry.* 2006; 21:95–103.
12. 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
13. 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.
14. Prakash A, Adhikari D. Application of Schiff bases and their metal complexes—a review. International Journal of ChemTech Research. 2011; 3:1891–1896.
15. Rudrapal M., De B. Chemistry and biological importance of heterocyclic Schiff bases. *International Research Journal of Pure and Applied Chemistry*. 2013; 3:232–249.