

# **GREEN SYNTHESIS OF METAL COMPLEXES OF THIAZOLE-BASED SCHIFF BASES: A REVIEW**

## **Abstract**

Green synthesis methods for the production of metal complexes, including those of thiazole-based Schiff bases, have gained significant attention. This review focused on the green synthesis approaches for the synthesis of metal complexes of thiazole-based Schiff bases. The synthetic techniques include: Microwave-assisted synthesis, plant-mediated synthesis, microbial synthesis, solvent-free reactions, and biocatalysis. The advantages of this greener synthesis over conventional methods of synthesis were also considered. The challenges, limitations and future perspectives of the greener alternatives were looked at.

**Keywords:** Green synthesis, thiazole-based Schiff bases, microwave-assisted synthesis, mechanochemical synthesis, nanoparticles.

## 1.0 Introduction

Thiazole-based Schiff bases are formed through the reaction of thiazole derivatives with carbonyl compounds (aldehydes or ketones) and primary amines, resulting in the formation of imines characterized by the general structure  $RR'C=NR''$  where the groups R, R', and R'' may be alkyl, aryl, cycloalkyl, or heterocyclic radicals which may or not be substituted. The bases were first synthesized by a German chemist, Hugo Schiff in 1956, from whom their name was coined. The thiazole moiety, a five-membered aromatic ring containing sulfur and nitrogen, contributes unique electronic properties that enhance the biological activity of these compounds. Thiazole-based Schiff bases exhibit a wide range of pharmacological effects, including: Antibacterial, antifungal, antioxidant, and Anticancer (Nagesh *et al.*, 2015; Prakash *et al.*, 2014). The biological activities of these compounds are often attributed to their ability to interact with cellular components. For instance, the nitrogen atom in the imine group can form hydrogen bonds with active sites in enzymes or DNA, disrupting normal cellular processes and leading to antimicrobial or anticancer effects.

### 1.1 Importance in pharmaceutical applications

Thiazole-based Schiff bases exhibit potent antimicrobial properties against a wide range of bacteria and fungi. Their ability to inhibit the growth of resistant strains makes them valuable in the fight against infectious diseases. Aminothiazole is one of the most widely distributed substituted thiazole derivatives found in approved drugs and natural products (Wan *et al.*, 2021; Elsadeket *et al.*, 2021). The benzothiazole nucleus is among the most widely studied fused-thiazole derivatives (Asif and Imran, 2021). Some of the drugs that are currently available and have the thiazole nucleus include; amiphenazole, used in opiate or barbiturate overdose; Famotidine and nizatidine for the treatment of gastric ulcer and gastro-esophageal reflux; Ritonavir for the treatment of human immunodeficiency virus (HIV); Abafungin for dermatomycoses; Cefdinir, a broad-spectrum semi-synthetic antibiotic; Meloxicam and sudoxicam, as non-steroidal anti-inflammatory drugs (NSAIDs) [Fatima *et al.*, 2021; Petrou *et ai.*, 2021; Jain *et al.*, 2018).

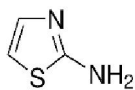


Figure 1: Aminothiazole

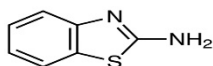


Figure 2: Aminobenzothiazole

The structural versatility of thiazole-based Schiff bases allows for the modification and optimization of their pharmacological properties. This versatility is essential for drug development, as it enables the design of compounds tailored to target specific biological pathways or disease mechanisms effectively.

## 1.2 Metal Complexes and Their Significance

Metal complexes possess distinct electronic configurations and molecular geometries that organic compounds alone cannot achieve. This remarkable trait allows their interaction with biological molecules in exceptional ways. The ability of metal ions to coordinate with various ligands enables the formation of complex structures that can selectively engage with enzyme targets or other biomolecules. This property is particularly useful for designing drugs that can act as catalysts or photoactivatable agents. Also, the redox behavior of metal ions can introduce oxidative stress in cancer cells, providing novel mechanisms for anticancer therapy (Liu *et al.*, 2021).

Metal complexes can operate through various mechanisms that enhance their therapeutic efficacy. These complexes can interact with DNA, proteins, and other cellular components leading to alterations in cellular processes that are critical for disease progression (Liu *et al.*, 2021). For example, organometallic complexes have been designed as selective protein kinase inhibitors (Patel *et al.*, 2021). The structural diversity provided by metal coordination can increase the binding affinity of these compounds to their biological targets, improving their effectiveness as drugs (Dudev and Lim, 2014).

## 1.3 Metal Ions in Enhancing the Properties of Schiff Bases.

Metal ions play a crucial role in enhancing the properties of Schiff bases, significantly impacting their biological activities and potential applications in medicinal chemistry. They contribute to the enhancement of Schiff base properties by stabilizing various oxidation states, allowing Schiff bases to form stable metal complexes (Hashmi *et al.*, 2023)). This stabilization is essential for maintaining the integrity of the complex during biological interactions, which can enhance the overall efficacy of the compound.

The coordination of metal ions with Schiff bases often results in enhanced biological properties compared to the free ligands. For instance, metal complexes have demonstrated improved antimicrobial, anticancer, and antioxidant activities. The presence of metal ions can facilitate interactions with biological targets such as enzymes and DNA, leading to increased potency against pathogens and cancer cells (El-Gammalet *et al.*, (2021).

Metal complexes can exhibit different mechanisms of action than their uncoordinated counterparts. For example, they may induce oxidative stress in target cells through the generation of reactive oxygen species (ROS), which can lead to apoptosis in cancer cells or inhibit microbial growth. This alteration in mechanism is crucial for developing effective therapeutic agents.

The introduction of metal ions can improve the solubility and stability of Schiff base complexes in biological environments. This is particularly important for drug formulation, as higher solubility can lead to better bioavailability and therapeutic outcomes.

Metal complexes derived from Schiff bases often exhibit significant catalytic activity in various chemical reactions. The metal ion can act as a catalyst, facilitating reactions that would be less efficient with organic compounds alone. This property is utilized not only in medicinal chemistry but also in industrial applications.

In addition to biological applications, metal coordination can enhance the optoelectronic properties of Schiff bases, making them suitable for use in solar cells and other electronic devices. The interaction between the metal ion and the ligand can improve charge transport and light absorption capabilities.

## **2.0 Advantages of Green Synthesis**

Green synthesis is driven by several critical factors that address environmental, health, and economic concerns. The importance of adopting green synthesis methods include but, not limited to the following:

**2.1 Reduction of Hazardous Waste:** Traditional chemical synthesis often generates toxic by-products and waste that can harm ecosystems and human health. Green synthesis minimizes or eliminates hazardous waste through eco-friendly processes that either degrade into harmless substances or can be reused.

**2.2 Lower Pollution Levels:** By reducing the release of harmful chemicals into air and water, green synthesis contributes to cleaner environments. This is crucial for protecting biodiversity and maintaining healthy ecosystems.

**2.3 Safer Chemicals:** Green synthesis methods typically utilize non-toxic materials and processes, leading to safer consumer products. This reduces exposure to harmful substances for both workers in the chemical industry and end-users.

**2.4 Cleaner Production Processes:** The adoption of green chemistry principles leads to safer manufacturing environments, decreasing the likelihood of accidents such as fires or explosions due to the reduced use of hazardous chemicals.

**2.5 Cost-Effectiveness:** Green synthesis often results in higher yields with less feedstock and fewer synthetic steps, which can lower production costs. This efficiency allows for faster manufacturing processes and increased plant capacity.

**2.6 Resource Utilization:** Utilizing waste materials as feedstocks not only reduces costs but also promotes sustainability by minimizing reliance on virgin resources. This approach can lead to innovative recycling methods and reduced environmental impact.

**2.7 Renewable Resources:** Many green synthesis methods leverage renewable biological materials (e.g., plant extracts, microorganisms) as reducing agents or stabilizers, making the process more sustainable compared to traditional methods that rely on non-renewable resources.

**2.8 Adaptability to Climate Change:** As environmental challenges intensify, green synthesis provides a pathway for developing sustainable practices that align with global efforts to combat climate change and reduce carbon footprints.

**2.9 Improved Stability and Efficacy:** Green synthesized products often exhibit enhanced stability and performance in applications such as drug delivery, catalysis, and environmental remediation. The use of natural stabilizers can lead to more effective formulations with fewer side effects.

### 3.0 Green Synthesis Methods

#### 3.1 Microwave-Assisted Synthesis

Microwaves fall between radio and infrared frequencies (from around 0.3 to 300 GHz). Prior to 1980s and early 1990, microwave irradiation was used rarely to assist in laboratory syntheses. The first published reports on the use of microwave (MW) irradiation to carry out organic chemical transformation was by the group of Gedye (1986) and Giguere *et al.* (1986).

The use of MW irradiation has become increasingly widespread and has been applied in the synthesis of heterocycles, multicomponent organic syntheses (Martina *et al.*, 2021) and metal-catalysed synthetic procedures (Erdelyi and Gogoll, 2001; Nilsson *et al.*, 2006), characterized by the formation of a single product in high yield, the elimination of by-products, atom economy, the use of mild reaction conditions, water compatibility, and the use of simple purification processes (Barge *et al.*, 2011; Xiong *et al.*, 2012;Rathi *et al.*, 2015;Baqi, 2021)

The real advantages of MW irradiation come to fore in reactions of heat-sensitive biological molecules such as carbohydrates, nucleosides, peptides, proteins, and peptoids; butalsopolymerase chain reaction, trypsin digestion, and solid-phase peptide synthesis [Hayes, 2004; Alcazar *et al.*, 2007). The method allows an efficient energy transfer to these molecules instead of rapidly heating them to high temperatures, decreasing the risk of loss of activity or degradation (Collins, 2010).

MW irradiation offer some distinct advantages in material synthesis because of the possibility of selective and homogenous heating of the reactants. This minimizes thermal gradients and provides uniform nucleation and growth conditions that favour the formation of more uniform nano/materials in terms of size distribution, nucleation, crystal growth processes e.t.c. [Kitchen

*et al.*, 2014; Thomas-Hillman *et al.*, 2018; Dabrowska *et al.*, 2018; Sharma and Das, 2019; Singh *et al.*, 2019; Kumar *et al.*, 2020)

### **Thiazole-based Schiff bases synthesized using microwave irradiation.**

Schiff base derived from o-vanillin with 6-(trifluoromethoxy)benzothiazole and its metal complexes with VO(II), ZrO(II) (1:2 M:L ratio), Cr(III), Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Hg(II) (1:1 M:L ratio) were synthesized by Ajbaniet *al.* (2015) using MW radiation (110 W for 1 min). The authors claimed that microwave-assisted syntheses is a much easier, convenient, quicker and eco-friendly method, without recourse to comparison with other synthetic methods.

5-bromosalicylaldehyde was reacted with 2-amino-5-nitrothiazole, and 4-dimethylaminobenzaldehyde with 2-amino-3-hydroxypyridine via both traditional heating and microwave-assisted synthesis to form two Schiff bases, as reported by Mishra and Jain (2010). The two methods were also applied to the formation of the Cr(III), Co(II), Ni(II), and Cu(II) complexes of the ligands. The ethanolic mixtures of the organic reagents, refluxed for 3–4 h, gave the desired ligands in 70–72% yield, whereas the reagents irradiated for 4–5 min in an MW oven gave 87–88% of the same ligands. A similar behavior was observed in the synthesis of the complexes. Ethanolic mixtures of metal ions and Schiff bases in a 1:2 (M:L) ratio refluxed for 6–10 h yielded 60–70% of the complexes, whereas the MW irradiation was completed in a shorter time (7–10 min) to give a yield of 77–84% [Mishra and Jain, 2010].

E; Guesmi *et al.* (2024) synthesized Novel thiazole-derived Schiff bases via thermal as well as microwave-assisted condensation of 2,4-dihydroxybenzaldehyde and aminothiazole derivatives in an ethanolic solution containing catalytic amounts of acetic acid. The structures of the Schiff bases were elucidated by spectroscopic methods and elemental analyses. The efficiency of these compounds in corrosion inhibition was evaluated for mild steel in H<sub>2</sub>SO<sub>4</sub> solution using electrochemical techniques. The mechanism of adsorption was suggested based on the Temkin adsorption isotherm, and was found to follow mixed mode of adsorption, with the chemical mode is the prevailing as revealed from the free energy change values. Quantum chemical calculations demonstrated that the high electron density on the Schiff bases molecule contributes

to a high corrosion inhibition efficiency. Additionally, the addition of an electron donor group on the thiazole ring enhanced the molecule's adsorption ability on the mild steel surface.

### 3.2 Solvent-Free Reactions

The major objective of solvent-free reactions is to simplify and accommodate in a modern way the classical procedures with the aim of keeping pollution effects to a minimum, together with a reduction in energy and raw materials consumption. Solvent-free techniques hold a strategic position as solvents are very often toxic, expensive, problematic to use and to remove. Solvent-free techniques represent a clean, economical, efficient and safe procedure which can lead to substantial savings in money, time and products. They can be efficiently coupled to non-classical methods of activation that include ultrasound and microwaves.

Three types of solvent-free reactions are considered:

#### **Reactions on Solid Mineral Supports**

Reactants are first impregnated as neat liquids onto solid supports such as alumina, silicas and clays or via their solutions in an adequate organic solvent and further solvent removal in the case of solids. The reaction may involve heating, and byproducts are simply removed by elution with diethyl ether or dichloromethane.

#### **Reactions Without any Solvent, Support, or Catalyst**

These heterogeneous reactions are performed between neat reactants in quasi-equivalent amounts without any adduct. For solid-liquid mixtures, the reaction involves either solubilization of solid in the liquid phase or adsorption of liquid on the solid surface as an interfacial reaction. Mechanochemical synthesis is one of the most interesting green chemistry methods that falls under this category of solvent-free synthesis, due to the reduction in reaction time and mainly the zero or drastically less amount of solvent in the reaction.

#### **Solid-Liquid Phase Transfer Catalysis (PTC)**

This type of solvent-free reaction occurs between neat reactants in quasi-equivalent amounts in the presence of a catalytic quantity of tetraalkylammonium salts or cation complexing agents.

#### **Solvent-free synthesis of metal complexes of thiazole-based Schiff bases.**



There is paucity of literature with regards to the synthesis of metal complexes of thiazole-based Schiff bases but, Vite-Morales *et al.* (2024) reported the synthesis of three Schiff bases derived from 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine, with yields greater than 74%, via the mechanochemical synthesis (grinding of the reactants in a ball mill), without the use of solvents during the reaction and in a shorter time than conventional synthesis. The products were confirmed through FTIR and NMR spectroscopies and mass spectrometry. By <sup>1</sup>H NMR, the signals are identified at 10.11 ppm of the indole proton for Th-In, that of the imine proton at 8.72, 8.38, and 8.75 ppm for Th-In, Th-Qn, and Th-TPA respectively, integrating for the number of protons corresponding to each structure. The FTIR spectra confirmed the appearance of the C = N band corresponding to the formation of the imine at 1631, 1714, and 1636 cm<sup>-1</sup> for Th-In, Th-Qn, and Th-TPA, respectively. Finally, the mass spectra corroborate the expected molecular mass of the synthesized compounds (Vite-Morales *et al.*, 2024).

### 3.3 Biocatalysis

**Biocatalysis** is the use of either a single enzyme (also when provided as crude preparation) or combinations of different enzymes in one pot for the transformation of any well-defined organic compound.

The main steps of a general catalytic cycle are (i) binding of substrate(s), (ii) activation of substrate(s), (iii) stabilization of transition state(s), and (iv) product release (Table 1). The substrate binding relies on several interactions between the enzyme and the substrate, which are required for the precise positioning of the reaction partners to each other in 3D space in a productive way.

Early biocatalytic methods for the preparation of optically pure alcohols and amines (Choi *et al.*, 2015) mainly involved hydrolases (especially lipases and esterases) and have been applied in synthesis on small and industrial scales (Faber, 2018; Bornscheuer and Kazlauskas, 2005; Angajala *et al.*, 2016). In addition to the well-established hydrolases, further types of enzymes are commonly applied in synthesis, including alcohol dehydrogenases (performing the stereoselective reduction of carbonyls) (Hollmann *et al.*, 2020; An *et al.*, 2019; Payeret *et al.*, 2019) transaminases (TAs), imine reductases (IREDs), and reductive aminases (RedAm's) (catalyzing reductive aminations) (Fuchset *et al.*, 2015; Schrittwieser *et al.*, 2015; Ghislieri and Turner, 2014).

The biocatalytic transesterification or hydrolysis of esters represents a standard method to produce molecules with high optical purity and is frequently used in the synthesis of active pharmaceutical ingredients (APIs) (Patel, 2018; Seddigi, *et al.*, 2017; Sunet *et al.*, 2018).

### **Synthesis of thiazole-based Schiff bases using biocatalysts**

The literature searches showed no reports of such synthesis indicating a research gap.

#### **3.4 Nanoparticle-Assisted Synthesis**

Nanoparticles are atoms, molecules or compounds with sizes in the range of 1-100 nanometer (nm). This miniature size thus imparts unique physical and chemical properties to them. They could be metals, oxides, semiconductors, polymers or lipids. They are synthesized in many ways: laser ablation/sputtering; hydrothermal/sol-gel, and by using microorganisms, plants or biomolecules. They have wide applications in medicine (drug delivery, imaging and diagnostics), cosmetics, environmental remediation (water pollution and purification).

Recently the use of ZnO nanoparticles as green catalyst has gained momentum due to their ability to transport electron and their high stability, non-toxicity and recycling properties (Zezelew *et al.*, 2022).

#### **Nanoparticles-assisted synthesis of thiazole-based Schiff base metal complexes.**

There is scarce literature on the synthesis of metal complexes of thiazole-based Schiff bases via nanoparticle-assisted. However, there is a report by Lamilemu *et al.* (2021) for the synthesis of thiazole-based Schiff bases assisted by ZnO nanoparticles. Acetophenone thiazole and p-nitrobenzaldehyde; and p-nitroacetophenone thiazole and p-nitrobenzaldehyde were mixed in absolute ethanol and refluxed for 4 h in the presence of 15% ZnO nanoparticles load at 78 °C. One of the synthesized compounds showed good activities towards Gram-negative *E. coli* and Gram-positive *S. aureus*, respectively, compared to amoxicillin. The binding affinity of the synthesized compounds against DNA gyrase B is within  $-7.5$  to  $-6.0$  kcal/mol, compared to amoxicillin ( $-6.1$  kcal/mol). In silico cytotoxicity predictions showed that the synthesized compounds Lethal Dose (LD50) value are class three ( $50 \leq LD50 \leq 300$ ), indicating that the compounds could be categorized under toxic class. Density functional theory calculations

showed that the synthesized compounds have small band gap energies ranging from 1.795 to 2.242 eV, demonstrating that the compounds have good reactivities.

## **4.0 Challenges and Future Perspectives**

### **4.1 Limitations in Green Synthesis Approaches**

Green synthesis approaches are limited by issues of scalability, reproducibility and economic factors.

At the laboratory-level, reactions are easily controlled to achieve the desired outcome. Scaling-up these reactions to industrial-level scale maybe extremely difficult due to complexity in equipment design, heat and mass transfer, as well as ensuring efficient mixing and agitation in large-scale reactors, such as microwaves reactors (in microwave-assisted synthesis) and ball mills (in mechanochemical synthesis).

In terms of reproducibility of results or outcomes, green synthesis is prone to challenges. Inconsistency in reaction conditions such as small changes in temperature, pressure, reaction time (as in microwave irradiation) or rate of grinding (in mechanochemical synthesis) can adversely affect the reproducibility of outcomes. Other factors include the inconsistency in reporting and lack of standardization of synthesis protocols which may hinder comparison and replication. Likewise, the inadequate documentation of experimental procedures, conditions and results can make reproducing the outcome challenging.

Economically, green synthesis may be expensive due to the use of specialized equipment, solvents and catalysts. The availability of some of the green materials such as extracts, enzymes, and catalysts may be limited.

### **4.2 Future Research Directions**

The unavailability of literature and scanty information with regards to the use of biocatalysts and nanoparticles in the synthesis of metal complexes of thiazole-based Schiff bases, respectively, is a glaring pointer to a research gap in these areas.

In the near future, optimization of green synthesis protocols and prediction of reaction outcomes by integrating artificial intelligence (AI) and machine learning (ML) will be a game-changer.

The exploration of Deep Eutectic Solvents (DESs) as alternative green solvents for the synthesis of various metal complexes is another area of research to be explored.

## 5.0 Conclusion

Green approaches in synthesis have greater advantages over traditional methods of synthesis due to the 12 lofty goals of green chemistry. Green approaches in the synthesis of metal complexes of thiazole-based Schiff bases are a virgin area of research. Synthesis by microwave irradiation and mechanochemical synthesis have been used in the synthesis of these Schiff bases with remarkable success. These Schiff bases and their complexes have not yet been synthesized via biocatalysis (enzymes), but could be in the near future due to the rapid advancement in instrument technology and biotechnology.

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