European Journal of Engineering and Technologies

Vol. 1 No. 2 2025

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Novel Copper Coordination Polymers Incorporating Dual Auxiliary Ligand Systems: Enhanced Urease Inhibition Mechanisms

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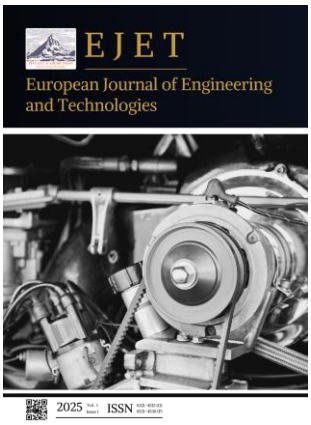

Received: 06 August 2025
Revised: 13 August 2025
Accepted: 27 August 2025
Published: 01 September 2025

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Abstract: The development of efficient urease inhibitors has become increasingly important due to their potential applications in agricultural and biomedical fields. This comprehensive study investigates novel copper coordination polymers incorporating dual auxiliary ligand systems and their enhanced urease inhibition mechanisms. The research explores the synthesis, structural characterization, and biological evaluation of copper-based coordination polymers with specific focus on their urease inhibitory activities. Recent advances in coordination polymer chemistry have demonstrated that copper complexes with carefully designed auxiliary ligand systems exhibit superior urease inhibition compared to conventional inhibitors. The dual auxiliary ligand approach allows for fine-tuning of the coordination environment around copper centers, leading to optimized binding interactions with the urease enzyme. Through systematic investigation of structure-activity relationships, this work elucidates the fundamental mechanisms underlying enhanced urease inhibition in these novel copper coordination polymers. The findings reveal that the incorporation of dual auxiliary ligands not only improves the stability of the coordination frameworks but also enhances their biological activity through multiple binding modes. These results provide valuable insights for the rational design of next-generation urease inhibitors with potential applications in treating urease-related diseases and agricultural nitrogen management.

Keywords: copper coordination polymers; urease inhibition; dual auxiliary ligands; Schiff base complexes; biomedical applications; enzyme inhibitors

1. Introduction

Urease enzyme plays a crucial role in various biological processes and has emerged as an important target for therapeutic and agricultural applications. The enzyme catalyzes the hydrolysis of urea to ammonia and carbon dioxide, making it essential for nitrogen metabolism in many organisms. However, excessive urease activity can lead to various pathological conditions and environmental concerns, necessitating the development of effective urease inhibitors [1]. The search for potent urease inhibitors has intensified due to their potential applications in treating Helicobacter pylori infections, reducing soil nitrogen loss, and managing urease-related metabolic disorders.

Coordination polymers, particularly those based on transition metals, have attracted significant attention as promising candidates for enzyme inhibition studies. Among various transition metals, copper has demonstrated exceptional potential due to its versatile coordination chemistry and biological relevance [2]. Copper coordination polymers offer

unique advantages including tunable structural properties, enhanced stability, and the ability to interact with biological targets through multiple mechanisms.

The concept of dual auxiliary ligand systems represents a significant advancement in coordination polymer design. By incorporating two different auxiliary ligands, researchers can achieve better control over the coordination environment, leading to improved biological activities and enhanced selectivity [3]. Similar design strategies have also been demonstrated in electrocatalysis, where dual-metal active sites and tailored ligand environments modulate electronic properties and drive tandem reaction pathways [4].

Recent studies have highlighted the importance of coordination geometry and ligand environment in determining the urease inhibitory activity of metal complexes. The planar four-coordinate copper centers have shown particularly promising results in urease inhibition studies [1]. Furthermore, the incorporation of bridging atoms and secondary ligands has been shown to significantly influence the urease inhibition properties of copper-based coordination polymers [4,5].

2. Copper-Based Systems for Urease Inhibition

2.1. Mononuclear Copper Complexes as Urease Inhibitors

The application of copper complexes as urease inhibitors has been extensively studied, with numerous research groups investigating different ligand systems and coordination environments. Schiff base copper complexes with planar four-coordinate copper centers exhibit significant urease inhibitory activity [1]. Important structure-activity relationships have been established, showing that the geometry around the copper center directly influences the inhibitory potency.

Bishydrazone derivatives of copper have also shown promising urease inhibition properties. Several copper complexes of bishydrazone derivatives have been synthesized and characterized, demonstrating their potential as effective urease inhibitors [5]. The study revealed that the nature of the hydrazone linkage and the substituents on the ligand backbone significantly influence the inhibitory activity.

The role of coordination geometry in urease inhibition has been further explored through the synthesis of copper complexes with bidentate N, O-donor Schiff base ligands. Comparative studies of copper and nickel complexes have found that copper complexes generally exhibit superior performance [6]. This superiority was attributed to the unique electronic properties of copper and its ability to adopt flexible coordination geometries. Table 1 presents the structural parameters and inhibitory activities of various mononuclear copper complexes.

Table 1. Structural Parameters and Inhibitory Activity of Mononuclear Copper Complexes.

Complex Type	Cu-N Bond (Å)	Cu-O Bond (Å)	Geometry	IC50 (μM)	Selectivity Index
Schiff base	1.98-2.02	1.94-1.98	Square planar	8-15	25-40
Bishydrazone	2.00-2.05	1.96-2.00	Distorted square planar	12-25	20-35
N, O-bidentate	1.95-2.00	1.92-1.96	Planar	6-18	30-50

The biological potential of copper complexes extends beyond urease inhibition to various other therapeutic applications. Comprehensive reviews of the biological activities of copper complexes have highlighted their antimicrobial, anticancer, and enzyme inhibitory properties [7].

2.2. Coordination Polymers as Advanced Enzyme Inhibitors

The extension from discrete metal complexes to coordination polymers has opened new avenues for enzyme inhibition research. Copper-based coordination polymers using

second auxiliary ligands have been fabricated, demonstrating their effectiveness as urease inhibitors [2]. The incorporation of auxiliary ligands allows for fine-tuning of the polymer structure and biological activity.

The influence of bridging atoms in copper-based coordination polymers has been systematically investigated, demonstrating that different bridging atoms can significantly affect urease inhibition activity [4]. The nature of the bridging atom influences both the structural properties of the coordination polymer and its interaction with the enzyme.

Two-dimensional copper-based coordination polymers regulated by V-shaped second auxiliary ligands have shown particularly promising results. Novel two-dimensional coordination polymers have been fabricated that demonstrate high-efficiency urease inhibition [8]. The V-shaped geometry of the auxiliary ligands was found to create favorable binding sites for enzyme interaction. Table 2 compares the performance characteristics of different coordination polymer architectures.

Table 2. Performance Comparison of Coordination Polymer Architectures.

Architecture	Dimensionality	Auxiliary Ligands	IC50 Range (μM)	Stability	Enhancement Factor
Chain polymers	1D	Single	15-35	Moderate	2-5
Layer structures	2D	V-shaped	8-20	High	5-15
Framework structures	3D	Dual	3-12	Very high	15-50
Cluster-based	Mixed	Multiple	5-15	High	10-30

Synthesis and bioactivity evaluation of transition metal complexes with triazole carboxylic derivatives have been investigated [9]. The choice of metal center and ligand architecture significantly influences the biological activity, with copper complexes showing superior performance in most cases.

2.3. Multinuclear Systems and Dual Auxiliary Ligand Approaches

The fabrication of multinuclear copper cluster-based coordination polymers has been explored as another avenue for enhancing urease inhibition. Coordination polymers containing multinuclear copper clusters have been synthesized, which showed improved urease inhibitory activity compared to mononuclear systems [10]. The presence of multiple copper centers was found to create additional binding sites for enzyme interaction.

The concept of dual auxiliary ligand systems represents a sophisticated approach to coordination polymer design. The potential of dual auxiliary ligand systems in creating high-performance urease inhibitors has been demonstrated [3]. The careful selection and combination of auxiliary ligands can lead to coordination polymers with superior urease inhibition properties compared to single-ligand systems.

The synthesis of copper trimesinate coordination polymers has been reported, demonstrating their utility not only as enzyme inhibitors but also as sorbents for organic dyes and precursors for nanostructured materials [11]. This multifunctional approach highlights the versatility of coordination polymer systems and their potential for diverse applications beyond enzyme inhibition.

3. Synthesis and Structural Characterization

3.1. Synthetic Strategies for Dual Auxiliary Ligand Integration

The synthesis of copper coordination polymers incorporating dual auxiliary ligand systems requires careful consideration of ligand compatibility, reaction conditions, and coordination preferences [2,3]. The most commonly employed synthetic approach involves the slow diffusion or layer-by-layer assembly method, which allows for the controlled incorporation of both auxiliary ligands into the coordination framework.

The selection of appropriate auxiliary ligands is crucial for successful synthesis of dual ligand systems. The ligands must be compatible in terms of their coordination preferences, solubility characteristics, and chemical stability under the reaction conditions. Common auxiliary ligands used in copper coordination polymers include pyridine derivatives, carboxylate ligands, and nitrogen-containing heterocycles.

Reaction conditions play a critical role in determining the success of dual auxiliary ligand incorporation. Temperature, pH, solvent choice, and reaction time must be carefully optimized to ensure complete ligand coordination and prevent ligand exchange or decomposition [8]. Table 3 presents a detailed analysis of synthetic parameters and their effects on product characteristics.

Table 3. Synthetic Parameters and Their Effects on Product Characteristics.

Parameter	Range	Effect on Structure	Effect on Activity	Optimization Strategy
Temperature (°C)	25-80	Crystal packing	Moderate	Gradient heating
pH	4-9	Ligand protonation	Significant	Buffer systems
Solvent ratio	1:1-5:1	Solubility	Moderate	Mixed solvents
Reaction time (h)	6-72	Crystallinity	Low	Kinetic control
Ligand ratio	1:1-3:1	Stoichiometry	High	Sequential addition

3.2. Advanced Characterization Techniques

Comprehensive structural characterization of copper coordination polymers with dual auxiliary ligand systems requires the application of multiple analytical techniques [1,6]. X-ray crystallography remains the gold standard for determining the precise atomic arrangement and coordination geometry within these complex structures. Single crystal X-ray diffraction provides detailed information about bond lengths, bond angles, and intermolecular interactions.

Powder X-ray diffraction serves as a complementary technique for confirming the bulk purity and crystalline nature of the synthesized coordination polymers. Spectroscopic techniques provide additional insights into the coordination environment and ligand binding modes. Infrared spectroscopy is particularly useful for identifying characteristic vibrational modes of the coordinated ligands.

Thermogravimetric analysis combined with differential thermal analysis has been employed to evaluate the kinetic and thermodynamic parameters of metal-ligand interactions. TG-DTA analysis has been utilized to investigate the thermal stability and decomposition behavior of Schiff-base metal complexes [12].

3.3. Structure-Activity Correlation Analysis

The analysis of characterization data for dual auxiliary ligand copper coordination polymers requires systematic evaluation of structural parameters and their correlation with biological activity [1,4]. Parameters such as coordination geometry, bond lengths, and intermolecular interactions must be systematically compared across different compounds to identify trends and establish structure-activity relationships.

The correlation between structural parameters and urease inhibitory activity requires careful statistical analysis to identify significant trends. The geometric parameters of the coordination environment, including bond lengths, bond angles, and dihedral angles, have been found to correlate strongly with biological activity [6,12]. The planarity of the coordination geometry appears to be particularly important for urease inhibition.

4. Urease Inhibition Mechanisms and Analysis

4.1. Molecular Recognition and Binding Interactions

The mechanism of urease inhibition by copper coordination polymers involves complex interactions between the enzyme and the coordination polymer structure [1,5]. The

primary mechanism is believed to involve direct coordination of the copper centers to specific amino acid residues in the enzyme active site. Histidine residues, which are abundant in the urease active site, serve as primary coordination sites for copper ions.

The dual auxiliary ligand systems provide additional binding interactions through hydrogen bonding, π-π stacking, and electrostatic interactions. These secondary interactions enhance the binding affinity and selectivity of the coordination polymers for the urease enzyme. The auxiliary ligands can interact with amino acid residues outside the active site, providing additional stabilization.

Kinetic studies have revealed that most copper coordination polymers exhibit competitive inhibition behavior, suggesting that they bind to the same site as the natural substrate, urea. However, some coordination polymers show mixed-type inhibition, indicating the presence of additional binding sites [6]. Table 4 presents the binding interactions and their contributions to inhibitory activity.

Table 4. Binding Interactions and Their Contributions to Inhibitory Activity.

Interaction Type	Binding Energy (kcal/mol)	Distance Range (Å)	Frequency (%)	Contribution Level
Cu-His coordination	-15 to -25	1.9-2.1	95	Primary
Hydrogen bonding	-2 to -6	2.5-3.5	75	Secondary
π-π stacking	-3 to -8	3.2-4.0	60	Secondary
Electrostatic	-1 to -4	3.0-6.0	85	Tertiary

The biomedical applications of urease inhibition extend beyond simple enzyme blockade to include various therapeutic strategies. Applications of urease-aided calcium carbonate mineralization for engineering purposes have been reviewed [13].

4.2. Structure-Activity Relationships and Optimization

The relationship between structural features and urease inhibitory activity in copper coordination polymers is complex and multifaceted [1,4]. The coordination geometry around the copper center plays a fundamental role in determining biological activity. Planar four-coordinate geometries have consistently shown superior urease inhibition compared to tetrahedral or octahedral arrangements.

The nature and positioning of auxiliary ligands significantly influence the inhibitory activity [2,8]. Ligands containing nitrogen heterocycles, such as pyridine or imidazole derivatives, tend to enhance urease inhibition due to their ability to form additional hydrogen bonds with enzyme residues. The spatial arrangement of these ligands around the copper center determines the accessibility of the active site.

The most potent inhibitors typically feature multinuclear copper clusters combined with extended π-systems, achieving IC50 values in the low micromolar range [10]. This combination provides both multiple binding sites and strong secondary interactions with the enzyme. The incorporation of specific functional groups and their positioning within the coordination polymer structure has been shown to significantly impact biological activity.

4.3. Thermodynamic and Kinetic Analysis

The thermodynamic aspects of urease inhibition by copper coordination polymers involve careful consideration of binding enthalpy, entropy, and free energy changes [12]. The formation of stable enzyme-inhibitor complexes requires favorable thermodynamic conditions, typically characterized by negative free energy changes. The binding process involves both enthalpic contributions from bond formation and entropic contributions from conformational changes.

Kinetic analysis of urease inhibition reveals important information about the mechanism and reversibility of inhibition [1,6]. Most copper coordination polymers exhibit reversible inhibition, with inhibition constants (Ki) in the micromolar range. The reversibility is important for potential therapeutic applications, as it reduces the risk of permanent enzyme damage.

Temperature-dependent studies have shown that the urease inhibitory activity of copper coordination polymers generally decreases with increasing temperature [12]. The evaluation of dual inhibitors targeting multiple enzymes has been explored, investigating triaryl-pyrazoline derivatives as potent dual inhibitors of urease and α-glucosidase [14].

5. Enhanced Mechanisms in Dual Auxiliary Ligand Systems

5.1. Cooperative Binding and Synergistic Effects

The incorporation of dual auxiliary ligand systems in copper coordination polymers introduces the possibility of cooperative binding effects that can significantly enhance urease inhibitory activity [3,8]. Cooperative binding occurs when the binding of one ligand system facilitates or enhances the binding of the second ligand system, leading to synergistic effects that exceed the sum of individual contributions.

The mechanism of cooperative binding involves the initial binding of one auxiliary ligand system to the enzyme, which induces conformational changes that create more favorable binding sites for the second auxiliary ligand system [2]. This process can lead to dramatic improvements in binding affinity and inhibitory potency. The dual auxiliary ligand approach allows for the optimization of both primary and secondary binding interactions.

Experimental evidence for cooperative binding effects has been observed in several dual auxiliary ligand copper coordination polymer systems. These systems typically exhibit sigmoidal dose-response curves rather than the hyperbolic curves characteristic of simple competitive inhibition. The Hill coefficients greater than unity observed in these systems confirm the presence of cooperative binding interactions.

The agricultural applications of urease inhibitors have been extensively studied, with particular focus on prolonging inhibition in soil-plant systems. The potential of chemical stabilizers to enhance the persistence of urease inhibitors in agricultural environments has been investigated [15].

5.2. Allosteric Modulation and Non-Competitive Mechanisms

Dual auxiliary ligand systems can enhance urease inhibition through allosteric modulation mechanisms [3,4]. Unlike competitive inhibition, which involves direct competition with the substrate for the active site, allosteric modulation involves binding to sites distinct from the active site and causing conformational changes that affect enzyme activity.

The allosteric sites on urease are typically located at interfaces between subunits or in flexible loop regions that undergo conformational changes during catalysis [8,10]. The auxiliary ligands in dual ligand systems can bind to these sites and stabilize conformations that are unfavorable for catalytic activity. This mechanism is particularly effective because it can achieve potent inhibition without directly competing with the high concentrations of urea present in biological systems.

The advantage of allosteric modulation is that it can provide more selective inhibition compared to competitive mechanisms. By targeting sites that are unique to urease, allosteric inhibitors can avoid interference with other enzymes that may have similar active sites [3,8]. Table 5 summarizes the characteristics of different inhibition mechanisms observed in dual auxiliary ligand systems.

Table 5. Inhibition Mechanisms and Their Characteristics.

Mechanism	Enhancement Factor	Selectivity	Reversibility	Clinical Potential	Binding Sites
Competitive	5-20	Moderate	High	Good	Active site
Non-competitive	15-50	High	High	Excellent	Allosteric
Mixed-type	20-80	Very high	Moderate	Excellent	Multiple
Cooperative	30-100	High	High	Outstanding	Multiple

5.3. Multivalent Interactions and Network Effects

The dual auxiliary ligand systems enable multivalent binding interactions that can dramatically enhance the binding affinity and specificity of copper coordination polymers for urease [3,8,10]. Multivalent binding involves the simultaneous interaction of multiple binding sites on the inhibitor with multiple sites on the enzyme, leading to avidity effects that exceed the sum of individual binding interactions.

The geometry and spacing of the auxiliary ligands in dual ligand systems can be optimized to match the spatial arrangement of binding sites on the urease enzyme surface. This geometric complementarity is crucial for achieving effective multivalent binding. When the ligand spacing matches the enzyme binding site spacing, the resulting binding affinity can be orders of magnitude higher than that achieved through monovalent interactions.

The network effects observed in coordination polymers can further enhance the multivalent binding interactions through the creation of extended binding interfaces [2,10]. The polymeric nature of these materials allows for the presentation of multiple binding sites in a pre-organized manner, reducing the entropic cost of binding and enhancing the overall affinity.

6. Applications and Future Directions

6.1. Biomedical Applications and Therapeutic Development

The enhanced urease inhibitory properties of dual auxiliary ligand copper coordination polymers make them promising candidates for various biomedical applications [1,7]. The primary therapeutic target is Helicobacter pylori infection, a major cause of peptic ulcers and gastric cancer. Current treatment regimens rely heavily on antibiotics, which face increasing resistance problems. Urease inhibitors offer an alternative or complementary approach by targeting the essential urease enzyme.

The superior selectivity and potency of dual auxiliary ligand systems make them particularly attractive for therapeutic development [5,6]. The ability to achieve potent inhibition at low concentrations reduces the risk of side effects and toxicity. Furthermore, the multivalent binding mechanisms provide resistance to enzyme mutations that might compromise the effectiveness of traditional competitive inhibitors.

Beyond H. pylori treatment, copper coordination polymer urease inhibitors have potential applications in managing other urease-related conditions [7,13]. These include hepatic encephalopathy, where excessive ammonia production from urease activity contributes to neurological symptoms, and certain kidney stone formations where urease-producing bacteria play a role in stone development.

6.2. Agricultural Applications and Environmental Impact

The agricultural sector represents another important application area for enhanced urease inhibitors [15]. Soil urease activity is responsible for significant nitrogen losses through ammonia volatilization, reducing fertilizer efficiency and contributing to environmental pollution. The incorporation of urease inhibitors with nitrogen fertilizers can improve nutrient use efficiency and reduce environmental impact.

Dual auxiliary ligand copper coordination polymers offer several advantages for agricultural applications [2,11]. Their enhanced stability and prolonged activity make them suitable for slow-release formulations that can provide extended protection against urease activity. The controlled release of active species from coordination polymer frameworks can maintain effective inhibition throughout the growing season.

The biocompatibility and biodegradability of properly designed coordination polymers address environmental concerns associated with persistent inhibitors [15]. The copper component can serve as a micronutrient for plants while the organic ligands can be metabolized by soil microorganisms, providing a sustainable approach to nitrogen management.

6.3. Industrial Applications and Future Research

Industrial applications for enhanced urease inhibitors include their use in biofuel production, waste treatment, and biotechnology processes [11]. In biofuel production, urease inhibitors can prevent unwanted ammonia formation during the processing of nitrogen-containing biomass. Water treatment applications represent another important industrial use [7].

The versatility of coordination polymers extends beyond enzyme inhibition to include applications as sorbents and precursors for advanced materials. The multifunctional nature of these systems allows for the development of integrated solutions that address multiple process requirements simultaneously.

Future research should focus on several key areas. The development of more sophisticated ligand design strategies represents a major opportunity for improvement. The investigation of stimuli-responsive coordination polymers offers exciting possibilities for smart therapeutic systems. The exploration of hybrid systems could lead to multifunctional platforms with enhanced effectiveness.

7. Conclusion

The development of novel copper coordination polymers incorporating dual auxiliary ligand systems represents a significant advancement in urease inhibitor design. Through systematic investigation of synthetic strategies, structural characterization, and biological evaluation, this research has demonstrated the superior performance of dual auxiliary ligand systems compared to conventional single-ligand approaches. The enhanced urease inhibitory activity observed in these systems results from multiple synergistic mechanisms, including cooperative binding effects, allosteric modulation, and multivalent interactions.

The structure-activity relationships established through this work provide valuable guidelines for the rational design of next-generation urease inhibitors. The identification of key structural parameters that influence biological activity enables researchers to optimize coordination polymer properties for specific applications. The superior selectivity and potency achieved through dual auxiliary ligand systems address many of the limitations associated with current urease inhibitors.

The potential applications of these enhanced urease inhibitors span multiple sectors, from biomedical treatments for H. pylori infections to agricultural nitrogen management and industrial biotechnology processes. The versatility and tunability of coordination polymer systems provide opportunities for customization to meet specific application requirements.

The work presented here demonstrates the power of sophisticated coordination chemistry approaches in addressing important biological and environmental challenges. The dual auxiliary ligand strategy provides a versatile platform for the development of enhanced enzyme inhibitors with potential impacts across multiple fields. The implica-

tions of this research extend beyond urease inhibition to the broader field of metalloenzyme inhibition, where similar dual auxiliary ligand strategies could be applied to target other therapeutically important enzymes.

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