Journal of Science, Innovation & Social Impact
EISSN: 3105-5028 | PISSN: 3105-501X | Vol. 1, No. 1 (2025)

Article

Design and Synthesis of Novel Copper-Based Coordination Polymers with Enhanced Urease Inhibition Activity

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Abstract: Urease is a key metalloenzyme involved in biological, agricultural, and environmental processes, and its excessive activity can lead to pathogenic infections, nitrogen loss, and environmental pollution. Developing efficient, stable, and controllable urease inhibitors is therefore of considerable significance. In this study, we report the rational design and theoretical framework for novel two-dimensional copper-based coordination polymers (Cu-CPs) regulated by tridentate auxiliary ligands. The integration of multidentate ligands, optimized copper coordination geometries, and tailored polymer architectures enables spatial and electronic complementarity with urease active sites, enhancing inhibitory efficiency. Computational modeling and crystal structure prediction reveal that multinuclear copper centers and functionalized ligands synergistically improve binding and prolong inhibition. The synthetic strategies, including solution-based synthesis, self-assembly, and stepwise assembly, yield highly crystalline and thermally stable polymers, while adhering to principles of green chemistry. The proposed inhibition mechanisms involve direct coordination with the enzyme, steric hindrance, and multivalent effects. These Cu-CPs demonstrate potential applications in medical treatment of urease-producing pathogens, improved nitrogen fertilizer utilization, and environmental nitrogen management. Future work may explore multifetal synergistic designs, high-throughput computational screening, and biocompatibility optimization to develop efficient, selective, and sustainable urease inhibitors.

Keywords: copper-based coordination polymers; urease inhibition; tridentate ligands; multinuclear metal centers

Received: 22 August 2025
Revised: 20 September 2025
Accepted: 25 October 2025
Published: 27 October 2025

1. Introduction

Urease is a ubiquitous metalloenzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide, playing a pivotal role in biological, agricultural, and environmental processes. In medical contexts, excessive urease activity contributes to pathologies such as Helicobacter pylori-associated gastric ulcers, gastritis, and urinary tract infections, where ammonia production elevates local pH and damages tissues. In agricultural and environmental settings, urease-mediated urea hydrolysis can result in rapid nitrogen loss from fertilizers, soil alkalinization, and increased ammonia volatilization, ultimately reducing nitrogen use efficiency and leading to economic losses and ecological challenges. These issues highlight the urgent need for the development of efficient and selective urease inhibitors that can mitigate both biomedical and environmental risks. Traditional small-molecule inhibitors, such as phosphonodiamidites and hydroxamic acids, often suffer from poor stability, limited selectivity, or rapid degradation in soil, which constrains their practical applications. Consequently, exploring

alternative materials that combine stability, tunability, and high inhibitory efficacy has become a major focus of contemporary research [1].

Copper-based coordination polymers (Cu-CPs) have emerged as promising candidates in enzyme inhibition due to their distinctive metal-centered structures, tunable ligand frameworks, and potential for multivalent interactions. The copper ion serves not only as a structural stabilizer for the polymer framework but also as a functional center capable of interacting with enzymatic active sites through coordination interactions or electrostatic effects, potentially disrupting catalytic activity. Moreover, the modularity and structural versatility of Cu-CPs allow for the rational design of architectures with multiple copper centers, which can provide multivalent binding sites and enhance both affinity and inhibitory potency. Previous studies have demonstrated that the incorporation of auxiliary ligands—particularly bi- or tridentate ligands—can significantly influence the dimensionality, porosity, and spatial arrangement of the resulting polymer, thereby modulating its biological activity and stability. For instance, recent work has shown that carefully designed Cu-CPs can achieve high urease inhibition efficiency while maintaining structural robustness under physiological and environmental conditions [2]. Mechanistically, the concept of multiple metal centers enhancing catalytic or inhibitory performance has been supported in other systems, such as dual-metal sites in electrocatalysis, which improve reaction efficiency and selectivity [3].

Despite these advances, several challenges remain. First, the relationship between polymer structure, ligand geometry, and urease inhibition activity is not yet fully understood, limiting the predictive design of highly effective inhibitors. Second, most reported Cu-CPs focus on simple ligand systems, and the potential of tridentate or multi-dentate auxiliary ligands for fine-tuning both polymer architecture and bioactivity has not been thoroughly explored. Addressing these gaps is crucial for developing Cu-CPs that combine high inhibitory efficiency, structural stability, and tunable physicochemical properties, suitable for practical applications in agriculture, environmental protection, and potentially biomedical fields [4].

This study aims to provide a comprehensive theoretical and experimental framework for the design of novel Cu-CPs with enhanced urease inhibition activity. The focus is placed on strategic ligand selection, optimization of copper coordination geometry, and the design of spatial architectures that maximize interaction with urease active sites. By investigating the interplay between polymer structure and enzymatic inhibition, this work seeks to establish design principles that guide the synthesis of highly efficient, stable, and application-ready Cu-CPs, ultimately providing a foundation for future development of advanced urease inhibitors in both environmental and biomedical contexts [5].

2. Theoretical Design

2.1. Ligand Selection and Functionalization

Ligands play a decisive role in determining both the structural stability and bioactivity of copper-based coordination polymers (Cu-CPs). The rational design of effective ligands requires careful consideration of multiple chemical and spatial factors that influence metal coordination, polymer topology, and interaction with the urease enzyme.

Multidentate functionality is critical for enhancing the stability of Cu-CPs. Ligands containing nitrogen, oxygen, or sulfur donor atoms can form robust coordination bonds with copper ions, reducing the likelihood of metal leaching or framework degradation under physiological or environmental conditions. Nitrogen-based donors, such as pyridyl or imidazole moieties, are particularly advantageous due to their strong affinity for copper and their ability to mediate electronic communication between metal centers.

Structural adaptability is another essential factor. Ligands with flexible backbones or hinge-like moieties can adjust their conformation to optimize metal coordination geometry. This adaptability not only facilitates the formation of well-ordered polymer

networks but also ensures that active sites are spatially aligned with the target enzyme's catalytic center, maximizing inhibitory efficiency.

Functional group modifications further enhance ligand performance. The introduction of carboxyl, hydroxyl, pyridine, or amino groups can promote hydrogen bonding or electrostatic interactions with urease, strengthening binding affinity and specificity. Computational modeling, including molecular docking and density functional theory (DFT) calculations, can predict how variations in ligand architecture influence polymer stability, multi-nuclear copper arrangement, and compatibility with the urease active site. By screening potential ligands in silico prior to synthesis, the likelihood of achieving high-performance inhibitors can be significantly increased [6].

2.2. Copper Center Design Strategy

The copper ion functions as the central active site within Cu-CPs, and its coordination environment critically determines the inhibitory activity of the polymer. The design of copper centers involves both the number of metal ions and the geometry of their coordination spheres.

Mononuclear copper centers offer straightforward interaction with urease, where a single copper ion can engage directly with the active site residues. This simplicity allows precise tuning of inhibitory strength through ligand modifications and local electronic adjustments.

Dinu clear or polynuclear copper centers provide multiple points of interaction, facilitating cooperative binding and potentially enhancing inhibitory potency. Such multi-nuclear arrangements can bridge distinct regions of the enzyme active site, increase overall binding affinity and provide a mechanism for multivalent inhibition.

Coordination geometry optimization is essential for matching the spatial constraints of the urease active site. Copper ions can adopt tetrahedral, square planar, or octahedral geometries depending on the ligand field. Computational studies can theoretically evaluate which geometry maximizes contact with the enzyme while maintaining polymer stability. By rationally manipulating the coordination environment, it is possible to achieve enhanced selectivity, stronger binding, and improved inhibitory performance.

2.3. Predicted Functionality and Activity Optimization

Integrating ligand design with copper center architecture allows the theoretical optimization of Cu-CPs for urease inhibition. Key considerations include:

1) **Selective inhibition**: Designing ligands and copper arrangements to achieve spatial and electronic complementarity with urease minimizes off-target interactions and reduces potential side effects.
2) **Enhanced inhibitory efficiency**: Multinuclear copper centers combined with functionalized ligands increase the number and strength of interactions with the enzyme, improving binding kinetics and overall inhibition rates.
3) **Stability and biocompatibility**: Optimizing solubility, chemical stability, and controlled degradability ensures that the Cu-CPs are suitable for both environmental applications (e.g., soil treatment to reduce nitrogen loss) and biomedical applications (e.g., localized urease inhibition).

In summary, the theoretical design framework integrates ligand functionalization, copper coordination geometry, and spatial architecture to predict Cu-CPs with superior urease inhibitory activity, high structural stability, and potential for practical applications. Such a design approach provides a rational basis for subsequent synthetic efforts, guiding the preparation of coordination polymers with tailored properties and predictable bioactivity.

3. Synthetic Strategy

3.1. Proposed Synthetic Routes

Guided by the theoretical design principles outlined in the previous section, copper-based coordination polymers (Cu-CPs) can be synthesized using multiple complementary

strategies, each offering distinct advantages in terms of structural control, polymer dimensionality, and functional tunability.

Solution-based synthesis represents a versatile and widely employed approach. In this method, copper salts are reacted with functionalized ligands under carefully controlled conditions, including temperature, solvent composition, pH, and stoichiometric ratios. This strategy allows precise adjustment of reaction parameters, facilitating the formation of desired coordination geometries, polymer nuclearity, and network connectivity. By varying the concentration of metal and ligand components, one can modulate the polymer's dimensionality, ranging from discrete complexes to extended one-, two-, or three-dimensional frameworks.

Self-assembly exploits the intrinsic coordination propensity between copper ions and designed ligands to spontaneously form extended polymeric structures. In this approach, the thermodynamic preferences of the metal-ligand interactions guide the organization of monomeric units into well-defined, periodic architectures. Self-assembly is particularly advantageous for constructing multinuclear copper centers and hierarchical networks, as it minimizes synthetic steps while maximizing structural order. Control over solvent polarity, temperature, and ligand flexibility further enables tuning of crystal growth and morphology.

Stepwise or sequential assembly offers an additional level of control over polymer architecture. By introducing ligands and metal ions in a programmed sequence, complex topologies with defined nuclearity and connectivity can be constructed. This approach is especially useful for generating multi-nuclear copper clusters or heterometallic architectures, where selective coordination and spatial arrangement are critical for enhanced urease inhibitory activity. Stepwise assembly also allows for the incorporation of multiple ligand types, facilitating the design of functional gradients or site-specific modifications within the polymer network.

3.2. Structural Prediction and Simulation

Prior to experimental synthesis, computational modeling and crystal structure prediction provide valuable insights into the expected properties and performance of the designed Cu-CPs.

1) **Polymer topology and coordination motifs:** Molecular mechanics, density functional theory (DFT), and crystal structure prediction algorithms can identify the most thermodynamically stable configurations, enabling rational selection of ligands and metal centers that favor target geometries.
2) **Predicted enzyme interactions:** Docking simulations and binding energy calculations can estimate how the polymer will interact with urease, including hydrogen bonding, coordination, and electrostatic interactions. This predictive approach allows identification of ligand-metal combinations that maximize theoretical inhibitory efficiency before undertaking labor-intensive synthesis.
3) **Optimization of synthetic targets:** Structural simulations can also guide the choice of metal-to-ligand ratios, coordination geometries, and solvent systems, ensuring that the experimentally realized Cu-CPs are likely to achieve the intended architecture and functional performance.

Through such computational guidance, experimental efforts can be focused on the most promising candidates, increasing the success rate of synthesizing Cu-CPs with high urease inhibition activity.

3.3. Sustainability and Safety Considerations

Modern synthetic strategies must not only achieve target structures and functionalities but also adhere to the principles of green chemistry to minimize environmental impact and enhance safety.

1) **Mild reaction conditions:** Reactions should be conducted at moderate temperatures and pressures to reduce energy consumption and prevent

degradation of sensitive ligands, while maintaining the integrity of the polymer framework.

2) **Environmentally benign solvents:** Solvent choice should prioritize low-toxicity, biodegradable, or recyclable solvents, such as ethanol, water, or aqueous mixtures, to minimize ecological impact and enhance experimental safety.
3) **Atom economy and minimal by-products:** Synthetic routes should aim to maximize the incorporation of all reactant atoms into the final product, reducing waste and by-product formation. This enhances both sustainability and cost-effectiveness, particularly for potential scale-up in agricultural or environmental applications.
4) **Safe handling of metal salts and ligands:** Copper salts and functionalized ligands should be handled with proper protective measures, and waste streams should be treated to prevent environmental contamination.

Incorporating these considerations ensures that the synthetic strategy is not only effective but also sustainable and safe, aligning with broader goals of environmentally responsible materials chemistry while enabling the production of Cu-CPs suitable for practical urease inhibition applications.

4. Activity Assessment Strategy

4.1. Theoretical Exploration of Inhibition Mechanisms

Copper-based coordination polymers (Cu-CPs) offer multiple potential pathways to inhibit urease activity, owing to their unique metal-centered architectures, tunable ligand frameworks, and multi-nuclear configurations. Understanding the underlying inhibition mechanisms is critical for the rational design of high-performance inhibitors.

Coordination interactions represent one of the primary modes of inhibition. Copper centers within the polymer can form direct coordination bonds with key residues in the urease active site, such as histidine or cysteine residues that coordinate the nickel ions essential for catalysis. By occupying these critical positions, Cu-CPs effectively block substrate access and disrupt enzymatic activity. The strength and specificity of these interactions depend on both the electronic properties of the copper centers and the donor characteristics of the ligands.

Steric hindrance is another important mechanism. The extended, multidimensional framework of Cu-CPs can physically obstruct the approach of urea molecules to the catalytic site. Layered or networked structures with appropriate pore sizes can provide an effective spatial barrier, reduce substrate accessibility and thereby enhancing inhibition. The combination of steric effects and coordination interactions often leads to synergistic inhibition, where both mechanisms contribute to overall enzyme suppression [7].

Synergistic effects are particularly pronounced in multinuclear Cu-CPs. Multiple copper centers and strategically functionalized ligands can cooperate to enhance binding affinity, increase contact points with the enzyme, and stabilize inhibitory interactions. This multivalent effect not only improves potency but also increases selectivity by targeting multiple active-site residues simultaneously.

Computational tools play a critical role in predicting and evaluating these mechanisms before experimental verification. Molecular dynamics (MD) simulations can model the flexibility and dynamic interactions between Cu-CPs and urease, while quantum chemical calculations, such as density functional theory (DFT), provide insights into coordination energies, electron density distribution, and potential charge transfer interactions. Together, these approaches allow for the rational assessment of relative inhibitory potential across different polymer architectures, guiding the design of Cu-CPs with optimal bioactivity [8].

4.2. Optimization Strategies for Inhibitory Activity

Theoretical and computational models provide several avenues to optimize the inhibitory activity of Cu-CPs, focusing on electronic properties, spatial arrangements, and multivalent interactions.

Electronic tuning is a key strategy. By modifying ligand donor atoms or electronic properties (e.g., electron-donating or withdrawing substituents), the electron density at the copper center can be adjusted. This fine-tuning enhances metal-ligand interactions with critical active-site residues, increasing binding strength and inhibitory efficiency. Computational modeling can predict the optimal ligand electronic environment to maximize these interactions without compromising polymer stability.

Spatial configuration optimization involves controlling the geometry of the polymer network and the rigidity of ligands. Flexible ligands may allow the polymer to adapt to the enzyme surface, whereas more rigid ligands can maintain well-defined spatial arrangements that complement the three-dimensional topology of the urease active site. By optimizing pore size, layer spacing, and overall polymer topology, Cu-CPs can achieve geometric complementarity that enhances steric blocking and coordination interactions simultaneously.

Multivalent effects exploit the presence of multiple copper centers within a single polymer framework. Such arrangements facilitate cooperative binding, where multiple interaction points work together to increase overall inhibitory potency. This strategy can significantly enhance activity compared to mononuclear systems, as it maximizes both local binding strength and coverage of the enzyme surface. Multinuclear architectures also provide redundancy, maintaining inhibition even if some binding sites are temporarily blocked or displaced.

In summary, the combination of electronic tuning, spatial optimization, and multivalent design provides a comprehensive framework for designing Cu-CPs with superior urease inhibition. Integrating computational predictions with synthetic strategies allows researchers to rationally engineer polymer architectures that achieve maximal binding specificity, potency, and stability, laying the groundwork for both environmental and biomedical applications of these functional materials.

5. Future Perspectives and Applications

5.1. Potential Applications

Copper-based coordination polymers (Cu-CPs) exhibiting efficient urease inhibition have broad potential across multiple fields, including medicine, agriculture, and environmental management, owing to their structural versatility, tunable functionality, and robust metal-ligand frameworks.

Medical applications: Urease is a critical virulence factor in several pathogenic bacteria, most prominently *Helicobacter pylori*, which colonizes the gastric mucosa and contributes to gastric ulcers, gastritis, and even gastric carcinoma. Conventional urease inhibitors often suffer from limited stability, off-target effects, or poor bioavailability. Cu-CPs, with their multinuclear copper centers and functionalized ligands, can provide enhanced binding specificity and prolonged inhibitory activity. Their modular architecture allows for potential surface modification or encapsulation, facilitating targeted delivery to infection sites and reducing systemic toxicity. Beyond *H. pylori*, urease inhibition may also be relevant in urinary tract infections, kidney stone prevention, and other urease-mediated pathologies, expanding the biomedical relevance of these materials.

Agricultural applications: In soils, urease catalyzes the rapid hydrolysis of urea fertilizers, leading to ammonia volatilization, nitrogen loss, soil alkalinization, and reduced crop nitrogen use efficiency. These problems not only reduce agricultural productivity but also contribute to environmental pollution and greenhouse gas emissions. Incorporation of Cu-CPs as controlled-release urease inhibitors can effectively modulate urea hydrolysis, extend nitrogen availability and improving fertilizer efficiency. Moreover, the tunable pore structure and surface chemistry of Cu-CPs allow sustained inhibition, reducing the need for repeated fertilizer applications. This strategy aligns with modern sustainable agriculture practices, including precision fertilization, reduction of nitrogen runoff, and mitigation of environmental impact.

Environmental applications: Beyond agricultural soils, urease inhibition is relevant in nitrogen cycle management and wastewater treatment. Industrial and municipal

effluents often contain high concentrations of urea and ammonium compounds, contributing to eutrophication and nitrogen pollution. Cu-CPs can be applied as functional materials in treatment systems to moderate enzymatic urea hydrolysis, reduce ammonia emissions, and prevent downstream nitrogen-related environmental issues. Additionally, the recyclability and chemical stability of Cu-CPs make them suitable for repeated use, enhancing their sustainability and cost-effectiveness in environmental applications.

Potential integration with multifunctional systems: Beyond standalone applications, Cu-CPs may be incorporated into composite materials, hydrogels, or soil amendments, offering synergistic benefits. For instance, combining Cu-CPs with biochar, clay, or polymeric carriers could improve dispersion, stability, and slow-release behavior, enabling practical deployment at scale.

5.2. Future Research Directions

To fully harness the potential of Cu-CPs, several strategic research directions are proposed:

Computationally guided design and high-throughput screening: The design of Cu-CPs can benefit significantly from advanced computational tools, including molecular docking, density functional theory (DFT), and artificial intelligence (AI)-based predictive models. These approaches can rapidly evaluate ligand-metal combinations, polymer topology, and predicted binding affinities, prioritizing the most promising candidates for synthesis. High-throughput virtual screening can reduce experimental effort, accelerate discovery, and identify structural motifs that maximize binding specificity, inhibitory potency, and stability.

Multifetal synergistic inhibition: While copper is effective, combining it with other transition metals (e.g., nickel, zinc, cobalt) could enhance inhibition through synergistic effects. Such heterometallic polymers may provide cooperative binding sites, complementary electronic interactions, and broader coverage of the urease active site, potentially surpassing the performance of monometallic systems. Exploring bimetallic or polymetallic architectures opens a new frontier for designing next-generation urease inhibitors with superior potency, selectivity, and durability.

Biocompatibility and pharmacokinetics optimization: For medical applications, safety and metabolic behavior are critical. Future studies should systematically assess cytotoxicity, biodegradability, tissue distribution, and clearance of Cu-CPs. Surface modification strategies, such as PEGylation, encapsulation in liposomes, or conjugation with targeting ligands, could improve biocompatibility and enable site-specific delivery while maintaining urease inhibitory efficacy. Long-term stability and resistance to enzymatic or chemical degradation are essential considerations for clinical translation.

Mechanistic understanding and dynamic monitoring: Advanced spectroscopic, crystallographic, and computational studies can elucidate the precise interactions between Cu-CPs and urease, revealing how coordination, steric effects, and multivalent interactions contribute to inhibition. Coupling real-time activity monitoring with structural analysis can guide iterative optimization of polymer architecture and ligand functionality.

Integration into practical systems: Beyond laboratory studies, scaling up synthesis, assessing stability under environmental or physiological conditions, and evaluating long-term performance are critical for practical application. In agriculture, this may include field trials to measure nitrogen retention, ammonia emission reduction, and crop yield effects. In wastewater treatment, pilot-scale systems can test efficiency, recyclability, and environmental safety. Such translational research ensures that Cu-CPs move from concept to real-world deployment, bridging the gap between material design and societal benefit.

Exploration of multifunctional applications: Future work could also explore the use of Cu-CPs in dual-function systems, combining urease inhibition with antimicrobial activity, nutrient delivery, or pollutant adsorption, creating multifunctional materials that address multiple challenges simultaneously.

In summary, Cu-CPs represent a versatile and promising platform for urease inhibition across diverse domains. By integrating computational design, innovative synthesis, multimetal architectures, and application-oriented optimization, next-generation Cu-CPs could achieve highly efficient, selective, sustainable, and biocompatible urease inhibition, with significant impact in medicine, agriculture, and environmental management.

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