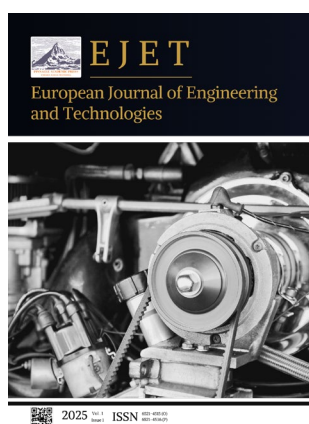




Review **Open Access**

# V-Shaped Ligand-Engineered Copper-Based Coordination Polymers for Urease Inhibition: Design Strategies and Applications

Nolan R. Hayes <sup>1,\*</sup>



<sup>1</sup> University of Portsmouth, Portsmouth, UK

\* Correspondence: Nolan R. Hayes, University of Portsmouth, Portsmouth, UK

**Abstract:** Copper-based coordination polymers (Cu-CPs) regulated by V-shaped auxiliary ligands have emerged as a promising class of urease inhibitors with unique structural features and enhanced bioactivity. This review summarizes recent advances in the design and fabrication of V-shaped ligand-engineered Cu-CPs, emphasizing their structural characteristics and the underlying mechanisms of urease inhibition. The interplay between Cu<sup>2+</sup> centers and ligand environment modulates electronic properties and accessibility, resulting in superior inhibitory performance. Additionally, the environmental applications, stability, and comparative advantages over traditional inhibitors are discussed. Challenges such as synthetic complexity, safety concerns, and scalability are also addressed, alongside future perspectives focusing on degradable and stimuli-responsive CPs and multifunctional designs. This work highlights the potential of V-shaped ligand-regulated Cu-CPs as efficient, environmentally friendly urease inhibitors and their role in advancing sustainable agricultural practices.

**Keywords:** V-shaped ligands; urease inhibition; structure–activity relationship; controlled release; copper coordination polymers (CCP)

Received: 27 July 2025

Revised: 03 August 2025

Accepted: 18 August 2025

Published: 29 August 2025



**Copyright:** © 2025 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Urease is a nickel-containing metalloenzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide. This enzymatic process plays a vital role in nitrogen metabolism in plants and microbes. However, in agricultural systems, uncontrolled urease activity leads to rapid urea degradation, resulting in substantial nitrogen loss through ammonia volatilization, soil alkalization, and reduced fertilizer efficiency. These effects not only compromise crop yield but also contribute to environmental pollution. To mitigate such issues, urease inhibitors have been widely explored and applied in modern agriculture.

Conventional urease inhibitors such as N-(n-butyl) thiophosphoric triamide (NBPT) and phenylphosphorodiamidate (PPD) are known for their initial effectiveness. However, they suffer from limitations including short half-life, thermal instability, and potential phytotoxicity. In this context, the development of more stable, efficient, and environmentally friendly alternatives has become a research priority.

Metal–organic coordination polymers (CPs), especially those based on transition metals, have emerged as promising candidates for urease inhibition due to their highly tunable frameworks, structural diversity, and potential for controlled release. Copper-based CPs (Cu-CPs) have attracted particular interest because of the redox activity and

coordination versatility of  $\text{Cu}^{2+}$  ions, which enable effective interactions with urease through mechanisms such as competitive binding to the active site or steric hindrance [1].

Recent work has shown that introducing V-shaped auxiliary ligands into the synthesis of Cu-CPs can direct the formation of unique low-dimensional architectures, enhancing their urease inhibitory activity [2]. This phenomenon is consistent with broader findings in coordination chemistry, where the design of dual-metal or multi-site catalytic centers has been shown to significantly modulate reaction pathways and product selectivity in electrocatalysis [3].

Moreover, the environmental applicability and stability of these V-shaped ligand-regulated Cu-CPs have been demonstrated in soil-plant systems, where they effectively prolong urease inhibition and reduce nitrogen loss under realistic agricultural conditions [4]. These findings highlight the promise of V-shaped ligand-engineered Cu-CPs as next-generation urease inhibitors with improved efficacy and environmental compatibility.

## 2. Structural Features of V-Shaped Ligand-Regulated Cu-CPs

### 2.1. Basic Structural Characteristics of Copper-Based Coordination Polymers

Copper-based coordination polymers (Cu-CPs) represent a versatile class of metal-organic frameworks formed by the coordination of  $\text{Cu}^{2+}$  ions with organic ligands. The structural diversity of Cu-CPs arises primarily from the variable coordination geometry of copper ions, which commonly exhibit coordination numbers of four to six. Typical geometries include square planar, tetrahedral, and octahedral configurations. These coordination modes enable  $\text{Cu}^{2+}$  to assemble into diverse polymeric networks ranging from one-dimensional chains to two-dimensional layers and three-dimensional frameworks. The dimensionality and topology of the resulting Cu-CPs depend significantly on the coordination environment provided by the ligands and the metal centers. The interplay of these factors dictates not only the crystallographic structure but also the functional properties relevant for applications such as urease inhibition.

### 2.2. Geometric Configuration of V-Shaped Ligands

V-shaped auxiliary ligands are characterized by two donor groups connected via a rigid or semi-rigid backbone that forms an angular conformation typically ranging from  $60^\circ$  to  $120^\circ$ . This geometric constraint plays a crucial role in directing the assembly of coordination polymers. The donor atoms involved are frequently nitrogen, oxygen, or sulfur, which can coordinate with  $\text{Cu}^{2+}$  ions in various modes, including monodentate, bidentate, or bridging coordination. The angular geometry of V-shaped ligands imposes spatial restrictions that favor the formation of extended two-dimensional or one-dimensional structures rather than dense three-dimensional networks. Moreover, the rigidity of the ligand backbone controls the flexibility and stability of the coordination environment, which in turn influences the accessibility of metal sites essential for catalytic or inhibitory activity.

### 2.3. Influence of Ligands on Crystal Dimensionality and Topology

The spatial and electronic characteristics of auxiliary ligands significantly influence the crystal dimensionality and topology of Cu-CPs. V-shaped ligands, due to their fixed angle and donor atom positioning, often induce the formation of low-dimensional architectures such as two-dimensional layers. These ligands limit the possible coordination angles and distances around the  $\text{Cu}^{2+}$  centers, restricting the growth of the network into higher dimensions. This structural control is essential for tuning the porosity, surface area, and active site exposure of the polymer, which are critical parameters for urease inhibition. By contrast, linear or flexible ligands tend to promote denser, three-dimensional frameworks that may limit substrate accessibility.

#### 2.4. Representative Examples of V-Shaped Ligand-Regulated Cu-CPs

Recent experimental studies have successfully demonstrated the synthesis of novel two-dimensional Cu-CPs regulated by V-shaped ligands. For instance, one study synthesized Cu-CP layers with well-defined pore structures and accessible copper centers that exhibited enhanced urease inhibitory activity [1]. The angular ligands directed the assembly of  $\text{Cu}^{2+}$  ions into extended planar networks, facilitating efficient interaction with the enzyme active sites [5]. These examples illustrate the effectiveness of V-shaped ligand design in producing coordination polymers with tailored structures and superior biological functions. The comparison of these materials with other Cu-CPs synthesized using different ligand geometries further highlights the importance of ligand shape in determining activity.

### 3. Urease Inhibition Mechanism of Cu-CPs

#### 3.1. Competitive Binding of $\text{Cu}^{2+}$ with $\text{Ni}^{2+}$ in Urease Active Site

Urease is a metalloenzyme that relies on two nickel ions ( $\text{Ni}^{2+}$ ) coordinated within its active site to catalyze the hydrolysis of urea into ammonia and carbon dioxide. The unique coordination geometry and electronic properties of these  $\text{Ni}^{2+}$  ions are essential for enzymatic activity. Copper ions ( $\text{Cu}^{2+}$ ), possessing similar coordination preferences and ionic radii, can competitively bind to the enzyme's active site or replace  $\text{Ni}^{2+}$  ions, leading to enzyme inhibition [6]. The presence of  $\text{Cu}^{2+}$  alters the metal center environment, causing steric hindrance and electronic perturbations that disrupt substrate binding and catalytic function. This competitive binding mechanism is a primary mode through which Cu-CPs exert urease inhibitory effects, as the  $\text{Cu}^{2+}$  centers effectively interfere with the enzyme's natural catalytic process.

#### 3.2. Influence of Ligand Environment on Electronic Properties

The electronic environment around  $\text{Cu}^{2+}$  centers in Cu-CPs is profoundly affected by the nature of the coordinating ligands. Ligands with electron-donating groups tend to increase the electron density at the copper ion, enhancing its nucleophilicity and binding affinity toward urease active sites. Conversely, electron-withdrawing ligands reduce electron density, potentially weakening these interactions [7]. The ligand environment also influences the coordination strength, redox stability, and overall reactivity of  $\text{Cu}^{2+}$  ions, which are critical factors determining the inhibitory potency and durability.

To summarize the key factors affecting the urease inhibition mechanism related to ligand properties, Table 1 categorizes their roles and effects:

**Table 1.** Effects of Ligand Properties on Urease Inhibition Mechanism by Cu-CPs.

Ligand Property	Effect on $\text{Cu}^{2+}$ Electronic Environment	Impact on Urease Inhibition	Example / Notes
Electron-Donating Groups	Increase electron density on $\text{Cu}^{2+}$	Enhanced binding affinity and stronger inhibition	Amines, pyridine rings
Electron-Withdrawing Groups	Decrease electron density on $\text{Cu}^{2+}$	Weakened binding affinity, reduced inhibition	Nitro, carbonyl groups
Steric Bulk	Limits accessibility to Cu centers	May reduce enzyme binding if too bulky	Bulky alkyl substituents
Ligand Flexibility	Influences coordination geometry	Flexible ligands may reduce structural rigidity	Flexible alkyl chains
Donor Atom Type	Alters coordination strength and mode	N, O, or S donors provide different affinities	N-donors often stronger than O-donors

This overview highlights how careful ligand selection can be used to tune the copper coordination environment, thereby optimizing urease inhibition. Rational design of ligand electronic and steric properties is thus essential for developing Cu-CPs with high efficacy and stability.

### *3.3. Synergistic Effects of Metal Centers and Ligands*

Beyond individual contributions, the synergistic interaction between metal centers and their ligands significantly enhances urease inhibition. The spatial arrangement and coordination geometry influenced by the ligands affect the accessibility and orientation of  $\text{Cu}^{2+}$  ions toward the urease active site [8]. V-shaped auxiliary ligands, in particular, impose specific angles and steric environments that optimize the exposure of copper centers for enzyme interaction. This cooperation ensures that copper ions are both chemically and spatially positioned to effectively bind or block the active site. Additionally, ligands may form secondary interactions such as hydrogen bonding or hydrophobic contacts with enzyme residues, stabilizing the inhibitor–enzyme complex and prolonging inhibition.

### *3.4. Structure-Activity Relationship Analysis*

Correlating the structural parameters of Cu-CPs with their urease inhibition performance reveals valuable insights for rational design. Experimental studies show that Cu-CPs incorporating V-shaped ligands demonstrate superior inhibition compared to those with linear or flexible ligands, highlighting the importance of ligand geometry in functional efficacy [9]. The two-dimensional layered structures formed under V-shaped ligand regulation expose more accessible  $\text{Cu}^{2+}$  sites, facilitating stronger and more effective interactions with the enzyme. Additionally, modifications in ligand electronic properties and polymer dimensionality directly influence inhibition kinetics and durability. Such structure–activity relationship analyses guide the fine-tuning of Cu-CPs for enhanced biological function.

## **4. Environmental Applications and Stability**

### *4.1. Controlled Release and Stability of Cu-CPs in Soil–Plant Systems*

Copper-based coordination polymers (Cu-CPs) exhibit controlled release behavior in agricultural soils, primarily due to their robust metal–ligand frameworks. The strong coordination bonds between  $\text{Cu}^{2+}$  ions and V-shaped ligands enhance the structural integrity of Cu-CPs, minimizing rapid degradation or leaching [10]. This stability ensures a gradual and sustained release of active copper ions, maintaining effective urease inhibition over extended periods. Such controlled release contrasts sharply with small-molecule inhibitors that often suffer from rapid dissipation, limiting their practical application. Furthermore, the stability of Cu-CPs under varying pH and moisture conditions in soil supports their viability in diverse agricultural environments.

### *4.2. Mobility and Environmental Fate of Cu-CPs*

The migration and environmental fate of Cu-CPs in soil are critical for assessing their ecological impact and safety. Due to their polymeric nature and relatively large molecular size, Cu-CPs tend to exhibit limited mobility within the soil matrix. This restricted migration confines their activity to the vicinity of application, reducing risks of copper accumulation in non-target zones. Studies also indicate that Cu-CPs have low bioavailability to soil microorganisms compared to ionic copper salts, potentially mitigating toxic effects on soil biota. Understanding the balance between stability and bioavailability is essential for optimizing both efficacy and environmental safety [11].

#### 4.3. Comparative Evaluation of Cu-CPs and Conventional Urease Inhibitors

Comparing Cu-CPs with traditional urease inhibitors such as N-(n-butyl) thiophosphoric triamide (NBPT) reveals distinct advantages of the former in agricultural application. While NBPT demonstrates rapid urease inhibition, its effectiveness declines sharply within days due to environmental degradation and microbial breakdown. In contrast, Cu-CPs maintain urease suppression for longer durations, reducing the need for frequent re-application. Table 2 summarizes key differences in stability, release profile, environmental mobility, and inhibitory longevity between Cu-CPs and conventional inhibitors.

**Table 2.** Comparison of Cu-CPs and Conventional Urease Inhibitors in Agricultural Application.

Property	Cu-CPs	NBPT and Similar Inhibitors
Release Profile	Controlled, sustained release	Rapid release, short duration
Stability in Soil	High, due to strong metal-ligand bonds	Low, prone to degradation
Environmental Mobility	Low, limited diffusion	Moderate, can leach and migrate
Inhibitory Longevity	Extended (weeks to months)	Short (days)
Toxicity to Soil Biota	Low bioavailability, reduced toxicity	Potential toxicity due to rapid dissociation
Application Frequency	Low, fewer re-applications needed	High, frequent application required

#### 4.4. Agricultural Potential and Practical Considerations

Field and greenhouse experiments have validated the practical benefits of Cu-CPs as urease inhibitors. Their enhanced stability and prolonged activity contribute to improved nitrogen use efficiency, reducing fertilizer losses and environmental pollution. Additionally, Cu-CPs formulated with V-shaped ligands demonstrate good compatibility with crops and soil microbiota, minimizing phytotoxicity risks. Despite these advantages, challenges remain regarding large-scale synthesis, cost-effectiveness, and regulatory approval. Future research should focus on optimizing formulations, assessing long-term environmental impacts, and developing sustainable production methods to facilitate broader agricultural adoption [12].

### 5. Challenges and Future Perspectives

#### 5.1. Synthetic Complexity and Scalability

The synthesis of V-shaped ligand-regulated copper coordination polymers (Cu-CPs) presents considerable challenges in terms of complexity and scalability. Typically, these syntheses require multi-step ligand preparation, strict control of reaction parameters such as temperature, solvent polarity, and stoichiometry, which limits throughput and reproducibility. Moreover, the use of sophisticated ligands with rigid backbones often involves costly precursors and specialized reagents, increasing production costs. Scaling these protocols to industrial levels faces difficulties not only in maintaining product consistency but also in ensuring environmental compliance due to solvent use and waste management. Hence, future work must focus on developing more sustainable, facile, and cost-effective synthetic strategies, potentially leveraging green chemistry principles and continuous flow techniques to enable large-scale manufacture without compromising structural precision or functional performance.



### 5.2. Safety, Toxicity, and Environmental Impact

Although Cu-CPs show promise as efficient urease inhibitors, their comprehensive safety profile remains insufficiently characterized. The fate of copper ions released into the soil matrix, their bioavailability, and accumulation pose potential ecological risks, including phytotoxicity and disruption of beneficial microbial communities essential for soil health. Existing toxicity studies are often limited to short-term laboratory assays, lacking long-term field evaluations under varied environmental conditions. In particular, the impact on soil fauna, aquatic organisms from runoff, and potential bioaccumulation through the food chain require rigorous investigation. Additionally, regulatory frameworks demand standardized ecotoxicological data for environmental risk assessment before widespread application. Addressing these gaps necessitates multidisciplinary research incorporating environmental chemistry, microbiology, and toxicology to establish safe application guidelines and develop formulations minimizing ecological footprints.

### 5.3. Development of Degradable and Stimuli-Responsive CPs

A promising direction to overcome environmental concerns is the design of degradable and stimuli-responsive Cu-CPs. These advanced materials aim to combine effective urease inhibition with environmentally benign degradation pathways, thereby preventing long-term persistence and metal buildup. Stimuli-responsive CPs can modulate release profiles triggered by soil pH changes, moisture levels, or microbial enzyme activity, enabling 'smart' delivery systems that release inhibitors only when needed, increasing efficiency and reducing waste. Table 3 outlines a comparison between conventional Cu-CPs and these next-generation materials, highlighting their enhanced environmental compatibility and functional sophistication. However, incorporating degradability and responsiveness adds complexity to synthesis and may impact material stability and efficacy, necessitating careful balancing in design.

**Table 3.** Comparison of Conventional and Advanced Copper Coordination Polymers.

Feature	Conventional Cu-CPs	Degradable / Stimuli-Responsive CPs
Environmental Persistence	High, chemically stable	Designed for controlled degradation
Release Profile	Passive, sustained release	Active, triggered by environmental stimuli
Synthetic Complexity	Moderate to high	Higher due to additional functional groups
Ecotoxicity Potential	Uncertain, possible accumulation	Reduced via biodegradability and responsiveness
Functional Integration	Primarily urease inhibition	Multifunctional: sensing, responsive release

### 5.4. Multifunctional Design and Future Research Directions

Future research should expand the scope of Cu-CPs toward multifunctionality, integrating urease inhibition with complementary agricultural needs. Incorporating sensing modules could enable in situ monitoring of soil nitrogen or microbial activity, guiding precision agriculture practices. Additionally, engineering CPs with responsive release triggered by environmental cues (e.g., moisture, temperature) would optimize inhibitor efficiency, minimizing overuse and environmental impact. Combining urease inhibitors with nutrient delivery systems or biocontrol agents could generate synergistic effects, enhancing crop productivity and sustainability. To achieve these goals, interdisciplinary approaches combining materials science, agronomy, and environmental sciences are essential. Advances in computational modeling and machine learning can accelerate rational design of Cu-CPs, predicting structure-function relationships to streamline development.

Furthermore, extensive field trials and lifecycle assessments will be crucial to validate performance and safety under real-world conditions, ultimately facilitating commercial translation.

## 6. Conclusion

V-shaped ligand-regulated copper-based coordination polymers (Cu-CPs) represent a novel and promising structural platform for urease inhibition. The unique geometric constraints imposed by V-shaped ligands enable precise control over the coordination environment of  $\text{Cu}^{2+}$  centers, resulting in tailored architectures that enhance interaction with the urease active site. This structural modulation directly correlates with improved inhibitory performance, highlighting the critical role of ligand design in optimizing biological activity.

The comprehensive analysis of structure–activity relationships presented in this review provides valuable theoretical guidance for the rational design of next-generation urease inhibitors. By leveraging the synergy between metal centers and organic ligands, future research can develop Cu-CPs with enhanced potency, stability, and environmental compatibility.

Looking ahead, expanding the application of V-shaped ligand-engineered Cu-CPs towards sustainable agriculture and precision fertilization holds great potential. Integration with controlled-release technologies and multifunctional designs will further advance the development of eco-friendly urease inhibitors, contributing to improved nitrogen utilization efficiency and reduced environmental impact. Overall, these advances align with the global pursuit of greener agricultural practices and resource-efficient crop production.

## References

1. M. Zhang, Y. Li, J. Wang, L. Zhao, H. Liu, and Q. Chen, "Cu-Based Metal–Organic Frameworks Characterized by V-Shaped Ligands and Application to Efficient Separation of  $\text{C}_2\text{H}_2/\text{CO}_2$  and  $\text{C}_2\text{H}_2/\text{CH}_4$ ," *Cryst. Growth Des.*, vol. 25, no. 7, pp. 2002–2012, 2025, doi: 10.1021/acs.cgd.4c01524.
2. M. R. Ramadan, S. E. Mohamed, N. M. Abdel-Rahman, A. H. Aboelnasr, E. M. Yousef, and R. M. Ramadan, "DNA binding and antioxidant activities of novel synthesized Fe (III), Ni (II) and Cu (II) complexes derived from monodentate V-shaped Schiff bases," *J. Transit. Met. Complexes*, vol. 2024, 2024, doi: 10.32371/jtmc/246166.
3. G. Xie, W. Guo, Z. Fang, Z. Duan, X. Lang, D. Liu, G. Mei, Y. Zhai, X. Sun, and X. Lu, "Dual-metal sites drive tandem electrocatalytic  $\text{CO}_2$  to  $\text{C}_2^+$  products," *Angew. Chem.*, vol. 136, no. 47, p. e202412568, 2024, doi: 10.1002/ange.202412568.
4. A. Lena, M. Corti, G. Costabile, S. Pagano, M. Gianneschi, and A. Erba, "Photoactivatable V-Shaped Bifunctional Quinone Methide Precursors as a New Class of Selective G-quadruplex Alkylating Agents," *Chem.–Eur. J.*, vol. 28, no. 35, p. e202200734, 2022, doi: 10.1002/chem.202200734.
5. F. Ding, C. Ma, W. L. Duan, J. Luan, Y. Chen, and T. Sun, "Second auxiliary ligand induced two copper-based coordination polymers and urease inhibition activity," *J. Solid State Chem.*, vol. 331, p. 124537, 2024, doi: 10.1016/j.jssc.2023.124537.
6. J. Zhang, X. Wang, R. Li, H. Zheng, M. Zhu, and Q. Wu, "A highly efficient luminescent MOF-based TNP sensor fabricated by new AIE ligand," *Polyhedron*, vol. 259, p. 117067, 2024, doi: 10.1016/j.poly.2024.117067.
7. J. Ai, Y. Zhao, and Z. Z. Tian, "Two novel coordination polymers based on 'V'-shaped carboxylic acid: synthesis, crystal structure and properties," *J. Mol. Struct.*, vol. 1278, p. 134873, 2023, doi: 10.1016/j.molstruc.2022.134873.
8. F. Ding, N. Su, C. Ma, B. Li, W. L. Duan, and J. Luan, "Fabrication of two novel two-dimensional copper-based coordination polymers regulated by the 'V'-shaped second auxiliary ligands as high-efficiency urease inhibitors," *Inorg. Chem. Commun.*, vol. 170, p. 113319, 2024, doi: 10.1016/j.inoche.2024.113319.
9. W. L. Duan, Y. X. Li, W. Z. Li, J. Luan, H. Zhang, and Q. Sun, "Controllable synthesis of copper-organic frameworks via ligand adjustment for enhanced photo-Fenton-like catalysis," *J. Colloid Interface Sci.*, vol. 646, pp. 107–117, 2023, doi: 10.1016/j.jcis.2023.05.021.
10. S. E. Mohamed, R. M. Ramadan, N. M. El-Khatib, H. M. Saleh, E. A. Aboelenin, and M. A. Abbas, "Design, synthesis, biomedical investigation, DFT calculation and molecular docking of novel Ru(II)-mixed ligand complexes," *J. Biomol. Struct. Dyn.*, vol. 41, no. 4, pp. 1233–1252, 2023, doi: 10.1080/07391102.2021.2017355.
11. L. Zhang, J. Q. Ma, Y. Z. Guo, X. Y. Li, L. Hou, and Y. Y. Wang, "New Co-MOF adsorption material with pharynx-shaped channel and large cavity for record ethylene and propylene purification," *Sci. China Chem.*, vol. 68, no. 3, pp. 967–973, 2025, doi: 10.1007/s11426-024-2271-2.

12. F. Ding, C. Y. Hung, J. K. Whalen, L. Wang, Z. Wei, and L. Zhang *et al.*, "Potential of chemical stabilizers to prolong urease inhibition in the soil–plant system," *J. Plant Nutr. Soil Sci.*, vol. 185, no. 3, pp. 384–390, 2022, doi: 10.1002/jpln.202100314.

**Disclaimer/Publisher's Note:** The views, opinions, and data expressed in all publications are solely those of the individual author(s) and contributor(s) and do not necessarily reflect the views of PAP and/or the editor(s). PAP and/or the editor(s) disclaim any responsibility for any injury to individuals or damage to property arising from the ideas, methods, instructions, or products mentioned in the content.