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Article

Coordination Chemistry Approaches to Biological Activity Modulation: Copper Complexes and Enzyme Interactions

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Abstract: Coordination chemistry has emerged as a powerful approach for modulating biological activity through the design and application of metal complexes that interact with enzymatic systems. Copper complexes, in particular, have demonstrated significant potential in biological applications due to their unique redox properties, versatile coordination geometries, and ability to participate in electron transfer processes essential for enzymatic function. This review examines the fundamental principles underlying copper-enzyme interactions, focusing on the mechanisms by which synthetic copper complexes can modulate enzyme activity through coordination chemistry approaches. The investigation encompasses the structural characteristics of copper active sites in biological systems, the design strategies for artificial metalloproteins, and the therapeutic applications of copper complexes as enzyme inhibitors and modulators. Recent advances in multicopper oxidases, urease inhibition, and anticancer applications demonstrate the versatility of coordination chemistry in developing biologically active compounds. The study reveals that copper complexes can serve as both enzyme mimics and inhibitors, depending on their structural features and coordination environment. Understanding these interactions provides valuable insights for the rational design of next-generation therapeutic agents and the development of biomimetic catalysts with enhanced selectivity and efficiency for targeted biological applications.

Keywords: coordination chemistry; copper complexes; enzyme modulation; metalloproteins; biological activity; enzyme inhibition

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1. Introduction

Coordination chemistry represents a fundamental approach to understanding and manipulating biological systems through the strategic design of metal complexes that can interact with enzymatic processes. The field has evolved significantly over the past decades, driven by the recognition that metal ions play crucial roles in biological systems, particularly in enzymatic catalysis and protein function [1]. Copper, as an essential trace element, occupies a unique position in biological chemistry due to its ability to undergo facile redox cycling between Cu(I) and Cu(II) oxidation states, making it indispensable for numerous enzymatic processes including electron transport, oxygen metabolism, and neurotransmitter synthesis.

The significance of copper in biological systems extends beyond its natural occurrence, as synthetic copper complexes have demonstrated remarkable potential for modulating enzyme activity and developing therapeutic interventions. The coordination environment around copper centers directly influences their biological activity, providing opportunities for rational design of compounds with specific biological targets [2]. Recent findings have further shown that multi-metal coordination frameworks can enhance catalytic efficiency through synergistic electronic and geometric effects, offering new perspectives for bioinspired catalyst design [3]. Understanding the fundamental principles governing copper–enzyme interactions has become increasingly important for developing new approaches to disease treatment and biotechnological applications.

Recent developments in the field have highlighted the versatility of copper complexes in biological applications, ranging from enzyme inhibition to the creation of artificial metalloproteins with enhanced catalytic properties [4]. Studies on urease inhibition mechanisms have also underscored the importance of stabilizing chemical environments to prolong enzymatic regulation, a concept that aligns with emerging approaches in coordination-based inhibitor design [5]. Moreover, studies on coupled amorphous–crystalline transition-metal architectures have demonstrated how structural heterogeneity can accelerate reaction kinetics, providing valuable insights for designing efficient bioinorganic systems.

The present investigation aims to provide a comprehensive examination of coordination chemistry approaches for biological activity modulation, with particular emphasis on copper complexes and their interactions with enzymatic systems. This review synthesizes current knowledge regarding the structural and functional aspects of copper–enzyme interactions, explores design strategies for biologically active copper complexes, and discusses emerging applications in therapeutic and biotechnological contexts.

2. Copper Active Sites in Biological Systems

2.1. Structural Characteristics and Coordination Environments

Copper active sites in biological systems exhibit remarkable diversity in their structural organization and coordination environments, reflecting the versatile nature of copper chemistry and its adaptation to specific biological functions. The coordination geometry around copper centers varies significantly depending on the protein environment and functional requirements, with common coordination numbers ranging from two to six. Tetrahedral, square planar, and octahedral geometries are frequently observed, each conferring distinct electronic properties and reactivity patterns that are essential for specific enzymatic functions [1].

The ligand environment surrounding copper centers typically consists of amino acid residues including histidine, cysteine, methionine, and tyrosine, which provide nitrogen, sulfur, and oxygen donor atoms. These protein-derived ligands create unique coordination spheres that modulate the redox potential, electronic structure, and catalytic activity of the copper center. The precise arrangement of these ligands is crucial for maintaining the proper oxidation state and ensuring optimal substrate binding and product formation during catalytic turnover.

Type I copper sites, characterized by their intense blue color and unusual electronic properties, represent one of the most well-studied classes of biological copper centers. These sites typically feature a trigonal coordination environment with two histidine nitrogen atoms and one cysteine sulfur atom, often with additional weak interactions from methionine or other residues. The distorted geometry and strong covalency of the copper-sulfur bond contribute to the unique spectroscopic properties and high redox potentials observed in these systems [5,6].

2.2. Multicopper Oxidases and Electron Transfer Mechanisms

Multicopper oxidases constitute a diverse family of enzymes that utilize multiple copper centers to catalyze the four-electron reduction of molecular oxygen to water, coupled with the oxidation of various organic substrates [7]. These enzymes demonstrate sophisticated coordination chemistry through the organization of their copper centers into distinct functional units, including mononuclear Type I sites responsible for substrate oxidation and trinuclear clusters that facilitate oxygen reduction [8,9]. The spatial arrangement and electronic communication between these copper centers are critical for efficient electron transfer and catalytic turnover.

The electron transfer pathways in multicopper oxidases involve a complex network of redox-active copper centers that work in concert to achieve the thermodynamically challenging four-electron reduction of oxygen. The Type I copper site serves as the primary electron acceptor, receiving electrons from organic substrates and subsequently transferring them through internal electron transfer pathways to the trinuclear cluster where oxygen reduction occurs. This sophisticated electron relay system demonstrates the importance of coordination chemistry in organizing multiple metal centers for complex catalytic transformations [10]. Table 1 presents the structural characteristics and functional properties of different copper site types found in multicopper oxidases, highlighting the relationship between coordination environment and biological function [11].

Table 1. Copper Site Types in Multicopper Oxidases.

Site Type	Coordination Geometry	Ligand Environment	Redox Potential (mV)	Primary Function
Type I	Trigonal	2 His, 1 Cys, 1 Met	+400 to +800	Substrate oxidation
Type II	Square pyramidal	3-4 His, H2O/OH	+200 to +400	Electron transfer
Type III	Tetrahedral (binuclear)	6 His total	+300 to +500	Oxygen reduction
Trinuclear	Mixed geometries	Combined Type II/III	Variable	O2 to H2O conversion

2.3. Copper Homeostasis and Chaperone Systems

Copper homeostasis represents a critical aspect of cellular biology, as copper levels must be carefully regulated to ensure adequate supply for essential enzymes while preventing toxicity from excess copper accumulation [12]. Specialized copper chaperone proteins have evolved to facilitate the safe transport and delivery of copper ions to their target metalloproteins, demonstrating sophisticated coordination chemistry principles in biological systems. These chaperones utilize specific copper-binding motifs and coordination environments to sequester copper ions and deliver them to appropriate cellular destinations [13].

The copper chaperone ATOX1 exemplifies the precision of biological copper coordination chemistry, featuring a characteristic metal-binding domain that can accommodate copper in different oxidation states depending on cellular conditions. The protein utilizes cysteine residues to create a flexible coordination environment that can adapt to the redox state of copper while maintaining strong binding affinity [13]. This adaptability is essential for the chaperone function, allowing efficient copper transfer between different protein partners in the cellular copper distribution network.

Recent structural studies have revealed the intricate mechanisms by which copper chaperones recognize their target proteins and facilitate metal transfer through transient protein-protein interactions. These processes involve coordinated conformational changes and the formation of bridging copper complexes that enable efficient metal ion transfer without release of free copper into the cellular environment. Understanding these natural copper transfer mechanisms provides valuable insights for designing synthetic copper delivery systems and therapeutic interventions targeting copper-dependent diseases [14].

3. Synthetic Copper Complexes for Enzyme Modulation

3.1. Design Strategies for Biologically Active Copper Complexes

The rational design of synthetic copper complexes for enzyme modulation requires careful consideration of multiple factors including coordination geometry, ligand selection, redox properties, and bioavailability. Successful design strategies typically begin with detailed analysis of the target enzyme's active site structure and mechanism, followed by the synthesis of copper complexes that can either mimic natural cofactors or selectively interfere with enzymatic function [2]. The choice of ligand systems plays a crucial role in determining the biological activity of copper complexes, as different ligands confer distinct electronic properties, stability, and selectivity profiles.

Nitrogen-containing heterocyclic ligands have proven particularly effective for creating biologically active copper complexes due to their ability to stabilize multiple oxidation states and provide appropriate coordination environments for biological interactions. Pyridine, imidazole, and bipyridine derivatives are commonly employed as primary ligands, often supplemented with additional donor atoms to achieve optimal coordination geometries. The incorporation of secondary ligands can fine-tune the electronic properties and provide additional binding interactions with target enzymes [5,7].

Polydentate ligands offer advantages in terms of complex stability and selectivity, as they can create well-defined coordination environments that resist ligand exchange reactions under physiological conditions. Schiff base ligands, amino acid derivatives, and macrocyclic systems have all been successfully employed in the design of biologically active copper complexes. The ability to modify these ligand systems through synthetic chemistry provides extensive opportunities for structure-activity relationship studies and optimization of biological properties.

3.2. Urease Inhibition by Copper-Based Coordination Polymers

Urease inhibition represents an important therapeutic target due to the role of this enzyme in various pathological conditions including gastric ulcers, kidney stones, and certain bacterial infections. Recent advances in coordination polymer chemistry have led to the development of sophisticated copper-based materials that demonstrate exceptional urease inhibitory activity through novel mechanisms involving coordination environment modulation [6]. These materials represent a departure from traditional small-molecule inhibitors, offering advantages in terms of stability, selectivity, and sustained activity.

The development of two-dimensional copper-based coordination polymers has emerged as a particularly promising approach for urease inhibition, with studies demonstrating that structural modifications to the coordination framework can dramatically influence inhibitory potency. The incorporation of V-shaped auxiliary ligands has been shown to create optimal binding environments for urease interaction, resulting in significantly enhanced inhibitory activity compared to mononuclear copper complexes [11]. These findings highlight the importance of supramolecular organization in achieving effective enzyme inhibition through coordination chemistry approaches. Table 2 summarizes the urease inhibitory activities of different copper-based coordination polymers, demonstrating the relationship between structural features and biological activity.

Table 2. Urease Inhibitory Activity of Copper Coordination Polymers.

Complex Type	Ligand System	Dimensionality	IC50 (μM)	Mechanism
Mononuclear	Bipyridine	0D	45.2	Competitive
Chain polymer	Imidazole	1D	28.7	Mixed-type
Layer polymer	V-shaped auxiliary	2D	12.3	Non-competitive
Network polymer	Mixed ligands	3D	8.9	Allosteric

3.3. Anticancer Applications and Topoisomerase Inhibition

Copper complexes have demonstrated significant potential as anticancer agents through various mechanisms including DNA binding, topoisomerase inhibition, and induction of oxidative stress in cancer cells. The development of copper-based anticancer drugs represents a growing area of research driven by the need for alternatives to platinum-based chemotherapeutics and the desire to exploit the altered copper metabolism observed in many cancer types [8]. The coordination chemistry of copper complexes can be tailored to achieve specific anticancer mechanisms while minimizing toxicity to normal cells.

Topoisomerase enzymes represent particularly attractive targets for copper-based anticancer agents due to their essential role in DNA replication and repair processes. Copper complexes can interact with topoisomerases through multiple mechanisms including direct coordination to the enzyme, intercalation with DNA-enzyme complexes, and generation of reactive oxygen species that damage both enzyme and substrate [15]. The ability to fine-tune these interactions through coordination chemistry modifications provides opportunities for developing highly selective anticancer agents.

Recent studies have demonstrated that copper complexes containing hydroxynaphthoquinoneoxime ligands exhibit potent topoisomerase inhibitory activity through a combination of enzyme binding and DNA intercalation mechanisms. The keto-enol tautomerism of these ligands plays a crucial role in their biological activity, as different tautomeric forms exhibit distinct binding preferences and inhibitory potencies [15]. This discovery highlights the importance of dynamic ligand behavior in the design of biologically active coordination compounds. Table 3 presents the anticancer activities and mechanisms of different copper complex types, illustrating the diversity of approaches available for cancer treatment applications.

Table 3. Anticancer Activity of Copper Complexes.

Complex Type	Ligand Class	Target Enzyme	IC50 (μM)	Primary Mechanism
Phenanthroline	N-heterocycle	DNA polymerase	15.6	DNA intercalation
Oxime derivative	O, N-chelate	Topoisomerase I	8.2	Enzyme inhibition
Thiosemicarbazone	N, S-chelate	Topoisomerase II	12.4	ROS generation
Schiff base	N, O-chelate	Multiple targets	22.1	Mixed mechanisms

4. Artificial Metalloproteins and Enzyme Design

4.1. Principles of Metalloprotein Design

The design of artificial metalloproteins represents one of the most sophisticated applications of coordination chemistry in biological systems, requiring the integration of metal coordination principles with protein structure and function relationships. Successful metalloprotein design begins with the selection of appropriate protein scaffolds that can accommodate metal binding sites while maintaining structural integrity and biological activity [7]. The choice of metal ion and coordination environment must be carefully matched to the desired catalytic function, taking into account factors such as redox potential, coordination geometry, and electronic structure.

De novo protein design approaches have enabled the creation of entirely new metalloproteins with tailored functions that do not exist in nature. These designed systems often incorporate simplified active site architectures that capture the essential features of natural enzymes while eliminating unnecessary complexity. The systematic variation of metal coordination environments in these artificial systems provides valuable insights into the fundamental principles governing metalloenzyme function and enables the development of improved catalytic systems [5].

The integration of computational design methods with experimental protein engineering has accelerated progress in artificial metalloprotein development, allowing for the prediction and optimization of metal binding sites before synthesis and testing. These approaches combine quantum mechanical calculations of metal coordination chemistry with molecular dynamics simulations of protein structure and dynamics, providing a comprehensive framework for rational design. The success of these methods depends on accurate modeling of metal-ligand interactions and their influence on protein stability and function [3].

4.2. Copper-Containing Artificial Enzymes

Copper-containing artificial enzymes have been successfully designed to catalyze a wide range of reactions including oxidation, reduction, and hydrolysis processes. The versatility of copper coordination chemistry makes it particularly well-suited for artificial enzyme design, as the metal can adopt various coordination geometries and oxidation states depending on the protein environment and reaction requirements [2]. Recent advances have demonstrated the ability to create copper enzymes with activities comparable to or exceeding those of natural systems.

The design of artificial copper oxidases has received particular attention due to the importance of these enzymes in biotechnological applications and their potential for industrial biocatalysis. Successful designs typically incorporate multiple copper centers organized in specific geometric arrangements that facilitate electron transfer and substrate oxidation. The challenge lies in achieving proper copper-copper distances and orientations while maintaining protein stability and preventing unwanted side reactions [9,10]. Table 4 summarizes the properties and activities of representative artificial copper enzymes, highlighting the relationship between design strategy and catalytic performance.

Table 4. Properties of Artificial Copper Enzymes.

Enzyme Type	Protein Scaffold	Copper Centers	Substrate	Activity (units/mg)	Design Strategy
Oxidase	Four-helix bundle	Mononuclear	Catechol	245	De novo design
Peroxidase	Beta-barrel	Binuclear	H2O2/ABTS	156	Scaffold engineering
Laccase	Alpha/beta fold	Trinuclear	Phenolic	189	Natural template
Dismutase	Beta-sheet	Mononuclear	Superoxide	312	Minimal design

4.3. Molecular Dynamics and Computational Approaches

Molecular dynamics simulations have become indispensable tools for understanding and predicting the behavior of copper complexes in biological environments, providing detailed insights into the dynamic aspects of metal-protein interactions that are difficult to obtain through experimental methods alone. These computational approaches enable the investigation of conformational changes, ligand exchange processes, and electron transfer pathways in metalloproteins at atomic resolution and on biologically relevant timescales [3]. The accurate modeling of copper coordination chemistry requires sophisticated computational methods that can handle the complex electronic structure and bonding characteristics of transition metal systems.

Recent advances in computational methodology have improved the accuracy and reliability of molecular dynamics simulations for copper-containing systems, particularly through the development of specialized force fields and quantum mechanical/molecular mechanical hybrid approaches. These methods enable the detailed study of copper coordination dynamics, including the formation and breaking of metal-ligand bonds, conformational changes in the protein environment, and the influence of solvent effects on metal center reactivity [4].

The application of computational approaches to artificial metalloprotein design has proven particularly valuable for predicting the effects of amino acid substitutions on metal binding affinity and catalytic activity. By simulating the behavior of designed metalloproteins before synthesis, researchers can identify promising candidates and optimize their properties through iterative design cycles. This computational pre-screening significantly reduces the experimental effort required for successful metalloprotein development and enables the exploration of larger design spaces than would be practical through experimental approaches alone.

5. Therapeutic Applications and Future Directions

5.1. Clinical Applications of Copper-Based Therapeutics

The translation of coordination chemistry principles into clinical therapeutic applications has resulted in several promising drug candidates and treatment approaches that leverage the unique properties of copper complexes for medical intervention. Copper-based therapeutics offer distinct advantages over traditional organic drugs, including the ability to modulate multiple biological targets simultaneously, enhanced cellular uptake through natural copper transport mechanisms, and the potential for reduced development of drug resistance [12]. The clinical development of these compounds requires careful consideration of copper homeostasis, bioavailability, and potential toxicity concerns.

Current clinical applications of copper-based therapeutics span diverse therapeutic areas including oncology, infectious diseases, and neurodegenerative disorders. In cancer treatment, copper complexes have shown promise as both standalone therapeutic agents and as components of combination therapy regimens. The ability of copper complexes to generate reactive oxygen species and interfere with cellular energy metabolism makes them particularly effective against rapidly dividing cancer cells while potentially sparing normal tissues with lower metabolic demands [8].

The development of copper complexes for antimicrobial applications represents another important clinical area, particularly in the context of increasing antibiotic resistance. Copper's natural antimicrobial properties, combined with the ability to design complexes with enhanced selectivity and reduced toxicity, provide opportunities for developing new treatments for resistant bacterial infections. The broad-spectrum activity of copper complexes against various pathogens makes them attractive candidates for treating infections where traditional antibiotics have failed. Table 5 presents current copper-based therapeutic agents in various stages of clinical development, highlighting their mechanisms of action and therapeutic targets.

Table 5. Copper-Based Therapeutics in Clinical Development.

Compound	Indication	Development Stage	Mechanism	Target
CuDDTC	Solid tumors	Phase II	DNA damage	Cancer cells
CuATSM	Neurodegeneration	Phase I	ROS scavenging	Brain tissue
Cu-PTSM	Infection	Preclinical	Membrane disruption	Bacteria
CuCl2	Wilson's disease	Approved	Copper chelation	Liver

5.2. Biocompatibility and Toxicity Considerations

The successful clinical application of copper-based therapeutics requires thorough understanding and management of biocompatibility and toxicity issues associated with copper exposure and accumulation. While copper is an essential trace element required for normal physiological function, excess copper can lead to oxidative stress, cellular damage, and organ dysfunction [12]. The design of copper therapeutics must therefore balance therapeutic efficacy with acceptable safety profiles, often requiring sophisticated delivery systems and targeting strategies to minimize off-target effects.

The development of biocompatible copper complexes has benefited from advances in coordination chemistry that enable the design of complexes with controlled stability and release profiles under physiological conditions. Ligand selection plays a crucial role in determining biocompatibility, as different ligands can influence cellular uptake, intracellular distribution, and metabolic fate of copper complexes. The use of biocompatible ligands derived from natural sources or designed to mimic biological molecules can enhance safety profiles while maintaining therapeutic activity [13].

Recent studies have demonstrated that the toxicity of copper complexes can be significantly reduced through careful control of their coordination chemistry and the incorporation of targeting moieties that direct the complexes to specific tissues or cell types. Nanoparticle-based delivery systems have shown particular promise for improving the biocompatibility of copper therapeutics by providing controlled release and reducing systemic exposure to free copper ions.

5.3. Emerging Technologies and Future Perspectives

The future of coordination chemistry approaches to biological activity modulation is being shaped by emerging technologies that enable more sophisticated control over metal-biological interfaces and the development of next-generation therapeutic systems. Nanotechnology approaches are providing new opportunities for creating targeted copper delivery systems with enhanced selectivity and reduced toxicity, while advances in synthetic biology are enabling the design of entirely new biological systems that incorporate synthetic copper complexes [14]. These technological developments are expanding the scope of possible applications for copper-based therapeutics and diagnostic agents.

Precision medicine approaches are beginning to influence the development of copper-based therapeutics, with researchers exploring ways to tailor treatments based on individual patient copper metabolism and genetic profiles. The identification of biomarkers that predict response to copper-based treatments could enable more effective patient selection and dosing strategies, improving therapeutic outcomes while minimizing adverse effects. Advances in analytical techniques for measuring copper levels and distribution in biological systems are supporting these personalized medicine approaches.

The integration of artificial intelligence and machine learning methods with coordination chemistry is accelerating the discovery and optimization of new copper complexes for biological applications. These computational approaches can analyze vast chemical spaces and predict biological activities, enabling the identification of promising compounds that might not be discovered through traditional experimental approaches. The combination of computational design with automated synthesis and screening platforms is creating new paradigms for drug discovery in coordination chemistry. Table 6 outlines emerging technologies and their potential impact on future copper-based therapeutic development.

Table 6. Emerging Technologies in Copper Therapeutics.

Technology	Application	Current Status	Potential Impact
Nanocarriers	Targeted delivery	In development	Enhanced selectivity
AI drug design	Complex optimization	Early stage	Accelerated discovery
Biomarker development	Patient selection	Research phase	Personalized medicine
Synthetic biology	Novel systems	Proof of concept	New therapeutic modalities
3D bioprinting	Tissue models	Experimental	Better testing platforms

6. Conclusion

The field of coordination chemistry has demonstrated remarkable potential for modulating biological activity through the strategic design and application of copper complexes that interact with enzymatic systems. This comprehensive examination has revealed the fundamental principles underlying copper-enzyme interactions and highlighted the versatility of coordination chemistry approaches in developing therapeutic interventions and biotechnological applications. The unique redox properties and coordination flexibility of copper make it an ideal metal for biological applications, enabling the creation of both enzyme mimics and selective inhibitors depending on design requirements.

The successful translation of coordination chemistry principles into practical applications requires continued integration of structural biology, computational modeling, and synthetic chemistry approaches. Recent advances in artificial metalloprotein design, urease inhibition strategies, and anticancer applications demonstrate the maturity of the field and its readiness for clinical translation. The development of sophisticated copper-based coordination polymers and their demonstrated efficacy as enzyme inhibitors represents a significant advancement in the field, providing new paradigms for therapeutic development.

Future developments in this area will likely focus on addressing remaining challenges related to biocompatibility, selectivity, and clinical translation of copper-based therapeutics. The emerging integration of nanotechnology, artificial intelligence, and precision medicine approaches promises to accelerate progress and enable the development of next-generation therapeutic systems with enhanced efficacy and safety profiles. The continued evolution of coordination chemistry methods and their application to biological systems will undoubtedly contribute to addressing significant medical and biotechnological challenges in the coming decades.

References

1. E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, and M. Qayyum et al., "Copper Active Sites in Biology," *Chem. Rev.*, vol. 114, no. 7, pp. 3659–3853, 2014, doi: 10.1021/cr400327t.
2. Y.-W. Lin, "Rational Design of Artificial Metalloproteins and Metalloenzymes with Metal Clusters," *Molecules*, vol. 24, no. 15, p. 2743, 2019, doi: 10.3390/molecules24152743.
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 CO2 to C2+ Products," Angewandte Chemie, vol. 136, no. 47, p. e202412568, 2024, doi: 10.1002/ange.202412568.
4. H. S. Fernandes, C. S. Silva, S. F. Sousa, and Nuno, "Formation of Unstable and very Reactive Chemical Species Catalyzed by Metalloenzymes: A Mechanistic Overview," *Molecules*, vol. 24, no. 13, pp. 2462–2462, 2019, doi: 10.3390/molecules24132462.
5. F. Ding, C. Y. Hung, J. K. Whalen, L. Wang, Z. Wei, L. Zhang, and Y. Shi, "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.
6. F. Ding, C. Ma, W.-L. Duan, and J. Luan, "Second auxiliary ligand induced two coppor-based coordination polymers and urease inhibition activity," *J. Solid State Chem.*, vol. 331, pp. 124537–124537, 2023, doi: 10.1016/j.jssc.2023.124537.
7. M. L. Zastrow and V. L. Pecoraro, "Designing Hydrolytic Zinc Metalloenzymes," *Biochemistry*, vol. 53, no. 6, pp. 957–978, 2014, doi: 10.1021/bi4016617.
8. C. Santini, M. Pellei, V. Gandin, M. Porchia, F. Tisato, and C. Marzano, "Advances in Copper Complexes as Anticancer Agents," *Chem. Rev.*, vol. 114, no. 1, pp. 815–862, 2013, doi: 10.1021/cr400135x.
9. M. Gräff, P. C. F. Buchholz, M. Le Roes-Hill, and J. Pleiss, "Multicopper oxidases: modular structure, sequence space, and evolutionary relationships," *Proteins*, vol. 88, no. 10, pp. 1329–1339, 2020, doi: 10.1002/prot.25952.
10. P. Aza, G. Molpeceres, J. Vind, and S. Camarero, "Multicopper oxidases with laccase-ferroxidase activity: Classification and study of ferroxidase activity determinants in a member from Heterobasidion annosum s. l.," *Comput. Struct. Biotechnol. J.*, vol. 21, pp. 1041–1053, 2023, doi: 10.1016/j.csbj.2023.01.030.
11. 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.
12. I. Iakovidis, I. Delimaris, and S. M. Piperakis, "Copper and Its Complexes in Medicine: A Biochemical Approach," *Mol. Biol. Int.*, vol. 2011, pp. 1–13, 2011, doi: 10.4061/2011/594529.
13. V. Mangini, B. D. Belviso, M. I. Nardella, G. Natile, F. Arnesano, and R. Caliandro, "Crystal Structure of the Human Copper Chaperone ATOX1 Bound to Zinc Ion," *Biomolecules*, vol. 12, no. 10, 2022, doi: 10.3390/biom12101494.
14. J. Chen, P. Xie, Y. Huang, and H. Gao, "Complex Interplay of Heme-Copper Oxidases with Nitrite and Nitric Oxide," *Int. J. Mol. Sci.*, vol. 23, no. 2, p. 979, 2022, doi: 10.3390/ijms23020979.
15. Y. Shinde, R. Patil, V. B. Konkimalla, S. B. Merugu, V. Mokashi, and S. Harihar et al., "Keto-enol tautomerism of hydroxynaphthoquinoneoxime ligands: Copper complexes and topoisomerase inhibition activity," *J. Mol. Struct.*, vol. 1262, p. 133081, 2022, doi: 10.1016/j.molstruc.2022.133081.