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Editorial: New developments in bioinorganic and bioorganic chemistry

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Editorial on the Research Topic
New developments in bioinorganic and bioorganic chemistry

This editorial initiative, led by Prof. Isabel Correia and Prof. Sylvia M. Draper, Specialty Chief Editors of the Bioinorganic Chemistry section, and Prof. Debbie Crans, Field Chief Editor of the journal, aimed to showcase the latest findings in the exciting fields of bioinorganic and bioorganic chemistry. These dynamic and interconnected fields bridge molecular design and biological mechanisms, offering new solutions to complex health challenges.

The research topic exemplifies this progress, focusing on innovative strategies to address cancer, bacterial and fungal infections, and parasitic diseases, most of which demonstrate the shared role of metal-based compounds and redox modulation, in advancing therapeutic approaches in bioinorganic and bioorganic chemistry. Such developments highlight the critical role of interdisciplinary approaches in shaping and reshaping the landscape of medicinal chemistry. In this editorial we will briefly describe the area before focusing on the advances reported in the manuscripts included in this special issue.

The report from Slappendel et al. investigates acylfulvenes as inhibitors of thioredoxin (Trx), a critical enzyme regulating cellular redox balance. Acylfulvenes (AFs) are semi-synthetic derivatives of illudin S (a natural product from the mushroom *Omphalotus illudens*) and are known for their cytotoxic properties and DNA-alkylating activity. Indeed, hydroxymethylacylfulvene (HMAF) has been evaluated for treating various cancers by selectively targeting tumor cells through DNA alkylation. However, the electrophilic intermediates formed during activation can interact with other cellular nucleophiles, and are important considerations to understanding the activity and selectivity of acylfulvenes.

Cancer cells often exhibit dysregulation of the Trx system, making it a compelling target for cancer therapy. This article from Slappendel et al. provides evidence that acylfulvenes, particularly HMAF, can inhibit Trx by covalently modifying its active site cysteines. The disruption of Trx activity and the alteration of its nuclear distribution in cancer cells underscores the dual mechanism of AFs: DNA alkylation and Trx inhibition. This combination highlights the potential of AFs to selectively target tumor cells. The study further compares the reactivity of illudin S, AF, and HMAF with Trx, demonstrating their different binding and inhibition abilities with HMAF exhibiting the strongest effects. Additionally, the impact of Trx system modulation on chemotherapeutic outcomes and the superior therapeutic index of HMAF compared to illudin S and AF were explored. The

findings position Trx as a key cellular target and acylfulvenes as valuable agents in cancer therapy.

The mini review by Kozieł et al. explored the underexplored potential of manganese complexes as anticancer, antibacterial, and antifungal agents compared to metallodrugs based on exogenous metal ions such as Pt, Pd, Au, and Ru, or endogenous Cu. The review highlights the unique properties of Mn complexes, including their redox activity, coordination versatility, and tunable ligand frameworks, and demonstrates how these can be exploited in the design of metallodrugs with tailored reactivity and selectivity. It explores the evolving panorama of Mn-based therapies and their significance in addressing multidrug resistance and other emerging global health challenges.

The review demonstrated how Mn complexes typically induce intracellular reactive oxygen species (ROS), causing oxidative stress due to the physiologically accessible oxidation states of Mn. Manganese-based drugs are discussed as promising tools in combating antimicrobial resistance, a pressing global health crisis aggravated by the overuse and misuse of traditional antibiotics. Selected examples demonstrate how these complexes target essential bacterial components like membranes and enzymes through the catalytic generation of ROS, and disrupt bacterial defense mechanisms while minimizing the development of resistance. Additionally, the review highlights recent studies on the antifungal activity of Mn complexes, further showcasing their versatility as therapeutic agents.

Parasitic diseases such as Chagas disease and Leishmaniasis are caused by closely related trypanosomatid protozoan parasites. These rely on insect vectors for transmission and predominantly affect marginalized populations where they pose significant public health challenges and may be co-endemic in certain regions. The World Health Organization classifies them as neglected tropical diseases, largely due to socio-economic factors that limit pharmaceutical interest.

The work of Scalese et al. stems from their ongoing search for metallodrugs based on vanadium for the treatment of Chagas disease and Leishmaniasis. In this work, the team presents heteroleptic oxidovanadium (IV) complexes containing two bidentate bioactive ligands: an 8-hydroxyquinoline derivative and 2-mercaptopyridine N-oxide (mpo). Among them, [V^{IV}O(L2-H)(mpo)], featuring a 5-chloro-7-iodo-8-hydroxyquinoline ligand, demonstrated selective activity against *Trypanosoma cruzi* trypomastigotes. The compound's mechanism of action - including oxidative stress induction and NADH-fumarate reductase inhibition - highlights its potential as a targeted antiparasitic agent. Metallomic analysis revealed preferential accumulation of the compound in the soluble protein fraction, with only small amounts localized in the DNA fraction, thereby excluding DNA as a primary target. The study underscores the promise for further development by elucidating the selective toxicity and vanadium uptake of this compound in mammalian cells.

The study by Carosella et al. delves into the activation mechanism of urease in *Helicobacter pylori*. This is a bacterium that uses a nickel-dependent enzyme to colonize the acidic environment of the human stomach. Urease activation requires the incorporation of Ni ions into its active site, a process facilitated by accessory proteins including UreD. The researchers employed an integrated approach combining evolutionary coupling analysis, site-directed mutagenesis, in-cell enzymatic assays, and computational docking to elucidate the interaction surface between urease and UreD. Their findings provide a detailed map of functional contacts essential for urease activation, offering potential targets for antimicrobial strategies aimed at inhibiting urease activity by disrupting these critical protein-protein interactions.

The study demonstrates the power of combining computational prediction with experimental validation. By identifying key interaction sites between urease and its accessory protein UreD, the researchers successfully provide molecular insight into the molecular features that hamper *H. pylori* colonization by targeting urease activation. Such targeted interventions could be instrumental in treating infections caused by ureolytic pathogens, thereby addressing a significant public health concern. The work further demonstrates the importance of understanding metalloenzyme activation mechanisms and highlights how detailed molecular insights can help in the design of inhibitors that disrupt essential protein interactions, paving the way for innovative treatments against persistent bacterial infections.

In summary these four articles highlight the strategic use of redox dynamics, metalloenzyme inhibition, and metal-based chemistry. They show how disrupting Trx in cancer cells, harnessing Mn's redox versatility, inducing oxidative stress in parasitic pathogens, and targeting urease activation in *H. pylori* can enhance therapeutic efficacy. The versatility of metal complex design in these examples provides opportunities to tune biological activity and highlights the importance of bioinorganic and bioorganic chemistry in modern drug discovery. Building on these findings, future research should focus on optimizing the pharmacological profiles of new and modified molecules. Expanding preclinical evaluations will be crucial to validate their efficacy and safety. Additionally, exploring synergies between redox modulation, metalloenzyme inhibition, and other therapeutic strategies will open new frontiers in disease management.

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