frontiers | Frontiers in Chemical Biology

TYPE Perspective
PUBLISHED 15 January 2026
DOI 10.3389/fchbi.2026.1764819

OPEN ACCESS

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RECEIVED 10 December 2025
REVISED 07 January 2026
ACCEPTED 07 January 2026
PUBLISHED 15 January 2026

CITATION
Chiaverini L, Ciccone L, Marrone A, Famlonga L, Piroddu D, Tonali N, Tolbatov I, Gailer J, Marzo T, Messori L and La Mendola D (2026) From simple to complex: multiscale modeling of metal-mediated protein interactions to uncover mechanistic insights into the action of inorganic drugs.
Front. Chem. Biol. 5:1764819.
doi: 10.3389/fchbi.2026.1764819

From simple to complex: multiscale modeling of metal-mediated protein interactions to uncover mechanistic insights into the action of inorganic drugs

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This Perspective article explores the crucial role of computational and experimental models in protein metalation studies which is at the heart of advancing inorganic medicinal drugs. The intricate world of protein-inorganic drug interactions poses a significant challenge to computational and experimental characterisation. Indeed, the vast conformational landscapes and dynamic behaviours of proteins demand sophisticated modelling strategies to accurately predict drug behaviour and mechanism of action. Using selected examples, this article demonstrates how research progresses from simple models to increasingly complex systems, thereby facilitating the acquisition of comprehensive mechanistic insights. An effective and pragmatic strategy for navigating this complexity is to deliberately use simple models as steppingstones towards understanding more intricate protein metalation phenomena. This hierarchical modelling paradigm enables researchers to systematically develop an understanding of processes ranging from fundamental atomic interactions to the entire protein-drug dynamic, balancing computational and experimental feasibility with deep mechanistic insight.

KEYWORDS

DFT, metallodrugs, plasma studies, protein metalation, SEC-ICP, X-ray crystallography

1 Introduction

The so-called protein metalation process, i.e., the process by which inorganic drugs coordinate with a protein side chain to form an adduct, is widely recognised as being highly relevant for predicting the biological activity of inorganic drugs, including their function and toxicity (Lee et al., 2017; Merlino et al., 2017; Loreto et al., 2020; Steel and Hartinger, 2020). In this context, simplified models are crucial for current bioinorganic and metalation studies. These simplified systems may consist of molecular models of amino acids with

specific functional groups, isolated amino acids, or proteins that do not represent the actual biological targets of the drugs. Instead, they act as versatile surrogate systems whose interactions with inorganic drugs provide mechanistic information that can be generalized to real biological targets. Their versatility also lies in the fact that they can be investigated using a wide range of experimental and computational techniques, and they are considerably more accessible and cost-effective than complex biological environments. Given the intrinsic complexity of biological systems, even when considering the cell alone, the adoption of such simplified models represents a practical and effective strategy to extract mechanistic insights that would otherwise be difficult to obtain. However, these models should primarily serve as efficient time-saving tools to guide the selection of the most promising molecules for more complex experiments.

In this way, their predictive capability should help to streamline the research process by reducing reliance on costly procedures and minimising the unnecessary use of animal testing. Computationally, the article details a hierarchical approach to modelling protein–metallodrug interactions (Bellotti et al., 2023). Initially, simplified models, such as those representing the side chains of metalated residues and their immediate neighbours, are employed to represent the protein environment, thereby reducing computational costs. This is followed by the inclusion of the protein backbone close to the metalation site for a more complete representation. The highest level of computational modeling involves studying the entire protein, including its conformational dynamics. However, even these full-protein studies are inherently models, as they rely on approximations, simplified force fields, and limited sampling of the vast conformational landscape, thus providing an idealized representation of the biological reality (Kim et al., 2025). Experimentally, specific examples are used, some of which are from our experience, to illustrate the use of diverse model systems. This includes studies on isolated amino acids or their molecular models to investigate the reactivity towards specific residues.

Furthermore, the article will showcase the use of small, well-characterized model proteins such as hen egg-white lysozyme (HEWL), bovine pancreatic ribonuclease (RNase A), and cytochrome c (cyt c). These serve as tractable systems to elucidate fundamental protein metalation processes. The discussion will then extend to larger proteins that are more biologically relevant yet still 'model' proteins, such as Human Serum Albumin (HSA) and carbonic anhydrase (CA), which provide insights closer to *in vivo* conditions while maintaining experimental manageability (Vitali et al., 2025). Next, we move to present some underexplored protein target relevant in Alzheimer's disease (AD). It involves Aβ aggregation promoted by metal dyshomeostasis, a process in which Cu, Zn and Fe modulate peptide misfolding and oxidative stress. Transthyretin (TTR), a bona fide biological target with proven neuroprotective activity, binds Aβ and mitigates its aggregation, a mechanism further influenced by metal ions such as Cu^{2+}. Understanding how TTR, Aβ and metal ions interact is therefore essential for guiding the rational design of metal-active therapeutics for AD. Finally, we introduce the reader to an innovative analytical approach that, by taking advantage of the previously obtained mechanistic information through the aforementioned models, allows the study of inorganic medicinal entities in real biological fluids (Chiaverini et al., 2025).

The advantages and limitations of these complementary computational and experimental modelling strategies are discussed through their careful integration, demonstrating their synergistic power in predicting drug behaviour and mechanism of action. Ultimately, the importance of this multilevel modelling strategy for designing improved next-generation metallodrugs with enhanced efficacy and reduced propensity for resistance is emphasised.

2 Computational modeling integrated with experimental evidence

To address the phenomenon of metalation from a computational perspective, the usage of a multilevel approach is often a necessity in order to reduce the computational burden. At the smallest scale, this strategy is built on the utilization of simplified models, such as isolated side chains of metalated residues and sometimes the inclusion of their immediate chemical neighbors (Tolbatov and Marrone, 2022c; Tolbatov and Marrone, 2022b). This initial level of modeling offers a computationally inexpensive yet highly effective means to represent the localized protein environment around the metalation site. It allows for the precise investigation of specific chemical interactions, bond formation, thermodynamics and kinetics of the studied metalation reactions, which would be otherwise prohibitively expensive or complex to isolate within a full protein context. All of this evidence can be effectively combined with experimental findings. The modelling complexity can then be increased progressively by incorporating segments of the protein backbone adjacent to the metalation site to provide a more complete representation of the local structural and electronic environment. The culmination of this hierarchical approach involves studying the entire protein, including its intrinsic conformational dynamics, using advanced techniques like classical molecular dynamics simulations. Even at this highest level, however, these full-protein studies remain models, relying on approximations, simplified force fields, and limited sampling of the vast conformational landscape, thus inherently providing an idealized representation of biological reality. The strength of this multiscale methodology lies in its ability to extract critical mechanistic insights from simplified systems and gradually integrate them into more complex biological contexts (Czapla-Masztafiak et al., 2017). Again, also at the highest level theoretical and multiple experimental approaches can be conveniently combined so that to produce reliable information for the mechanistic interpretation (Ferraro and Merlino, 2025).

2.1 Case study 1: multilevel investigation of SARS-CoV-2 nsp13 protein metalation. From experimental evidence to mechanistic information

The investigation into the structural reshaping of the SARS-CoV-2 nsp13 protein by bismuth (III) ions exemplifies the utility of a multilevel computational strategy that leverages simple models

(Tolbatov et al., 2022). Non-structural protein 13 (nsp13) helicase is a crucial component of the SARS-CoV-2 viral machinery and can be conveniently expressed and studied as a potential target for inorganic molecules bearing different metal centres, including bismuth. In fact, the nsp13 helicase activity can be decreased by Bi^{3+} ions replacing Zn^{2+} in its zinc-finger metal centers (Shu et al., 2020; Yuan et al., 2020). *In vitro* studies demonstrated that RBC inhibited both the ATPase (IC_{50} = 0.69 μM) and DNA-unwinding (IC_{50} = 0.70 μM) functions of the SARS-CoV-2 helicase via an irreversible displacement of zinc(II) ions from the enzyme by bismuth (III) ions. *In vivo*, the use of RBC in a golden Syrian hamster model resulted in a complete suppression of viral replication, leading to decreased viral loads in both the upper (nasal turbinate) and lower (lung) respiratory tracts. This therapeutic treatment also relieved virus-associated pneumonia and remarkably diminished the expression of pro-inflammatory cytokines.

To understand the atomistic details of this process and its functional implications, a comprehensive computational approach was adopted (Figure 1), combining density functional theory (DFT) calculations with classical molecular dynamics (MD) simulations (Amber03 force field (Duan et al., 2003)) and molecular interaction field (MIF) analyses using the ATOMIF tool (Tolbatov et al., 2022).

This computational approach was built upon significant experimental evidence demonstrating the potent antiviral activity of bismuth (III) compounds. Notably, a study by Yuan et al. identified ranitidine bismuth citrate (RBC) as a potent anti-SARS-CoV-2 agent, both *in vitro* and *in vivo*. This drug showed low cytotoxicity and a high selectivity index of 975 in infected cells (Yuan et al., 2020).

At the most fundamental level, DFT calculations (using the ωB97X functional (Chai and Head-Gordon, 2008) with def2SVP and def2TZVP basis sets (Andrae et al., 1990; Weigend and Ahlrichs, 2005) were employed to characterize the potential energy surface of the Zn^{2+}/Bi^{3+} substitution, utilizing the C-PCM implicit solvation model (Barone and Cossi, 1998) to account for the aqueous environment. These thermodynamic studies quantified the relative binding affinities of the metal ions and evaluated the specific protonation states of the coordinating cysteine residues. In this context, these calculations implicitly utilized simplified models of the zinc-finger binding sites, focusing on the metal ion and its immediate coordinating Cys and His amino acid side chains. By modeling the stepwise replacement of the native metal, the study provided the energetic basis for the irreversible displacement of Zn^{2+} observed experimentally. This level of modeling, involving small, precisely defined chemical systems, is critical for obtaining highly accurate quantum mechanical insights into the energetics and local bond rearrangements that define the initial metalation event.

Moving to higher levels of modeling, the insights gained from the initial DFT studies on simplified metal-binding sites were crucial for developing accurate cationic dummy atom (CDA) models for Zn^{2+} and Bi^{3+} ions. By accounting for the specific hemi-directed coordination geometry of Bi^{3+} resulting from its $6s^2$ lone pair, these CDA models effectively captured the coordination geometry and charge distribution of the metal centers within a classical force field framework. This implementation allowed for the next stage of

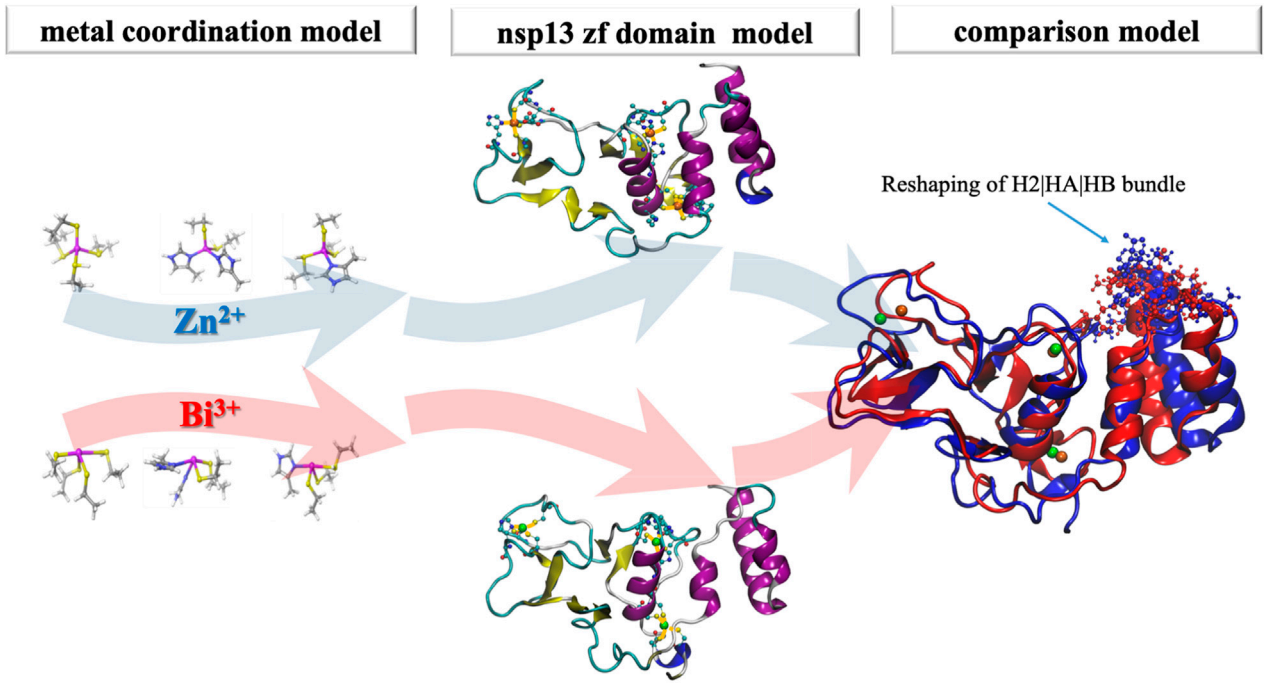

FIGURE 1
Multilayered modeling of protein metalation: different levels of simplification allow to gain comprehensive insights into protein metalation. Left: A detailed atomic-level DFT representation of a metal ion coordinated by one or two relevant amino acid side chains from the nsp13 zinc finger. Middle: intermediate model with a representation of the nsp13 ZBD, highlighting the metal centers and their coordination environment at MD level. Right: structural reshaping and torsion in the H2|HA|HB bundle induced by the Zn^{2+}/Bi^{3+} exchange.

investigation: molecular dynamics simulations of the entire zinc-binding domain (ZBD) of nsp13. This intermediate level of modeling enabled the study of structural modifications induced by the Zn^{2+}/Bi^{3+} exchange within the context of the full ZBD, including its secondary structural elements (alpha-helices and beta-sheets) and their conformational dynamics. Furthermore, the highest level of modeling extended to examining the interaction of nsp13 with nsp12, a key partner in the viral replication and transcription complex (Adedeji et al., 2012; Jia et al., 2019; Chen et al., 2020). This was achieved by superimposing the simulated nsp13 ZBD conformations onto experimentally characterized cryo-electron microscopy structures of the nsp13-nsp12 complex, allowing for the analysis of how metal exchange in nsp13 might affect its crucial protein-protein interactions.

This multilayered computational approach yielded significant insights into the mechanism of nsp13 impairment by Bi^{3+} ions. The DFT calculations confirmed that Bi^{3+} can indeed replace Zn^{2+} and induce structural modifications in the zinc-binding domain, particularly affecting the protonation states and coordination geometries of the coordinating residues. The subsequent MD simulations, utilizing the refined CDA models, revealed that the Bi^{3+} substitution leads to appreciable structural reshaping of the nsp13 ZBD, including a slight torsion of the H2|HA|HB bundle and localized conformational changes. Crucially, the molecular interaction field (MIF) analyses, performed using the ATOMIF tool, identified a specific hydrophobic region near the ZF2 site whose extent decreased upon Bi^{3+} binding. This region was then precisely correlated with the interaction interface between nsp13 and nsp12, suggesting that the Zn^{2+}/Bi^{3+} exchange weakens this critical protein-protein interaction. These findings provide an atomistic rationale for the observed antiviral activity of Bi^{3+} salts and highlight the disruption of the nsp13-nsp12 interaction as a plausible therapeutic strategy against SARS-CoV-2.

2.2 Case study 2: computational and experimental investigations of diruthenium and dirhodium paddlewheel complexes

Recent computational and experimental studies have focused on elucidating the kinetics and thermodynamics of the reactions between dirhodium and diruthenium paddlewheel tetraacetate complexes and nucleophilic sites in proteins (Tolbatov and Marrone, 2022a; Tolbatov and Marrone, 2022b). The dinuclear complexes, $Rh_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2$, $Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)Cl$, and $[Ru_2(\mu\text{-}O_2CCH_3)_4(H_2O)_2]^+$, have drawn significant attention as perspective anticancer drugs due to their robust carcinostatic properties (Erck et al., 1974; De Oliveira Silva, 2010; Hanif-Ur-Rehman et al., 2016; Hrdina, 2021; Tolbatov et al., 2023). Understanding their precise mode of action, particularly how they interact with and metalate biological targets like proteins and DNA/RNA nucleobases, is paramount for their development into effective therapeutics. This has led to numerous computational and experimental investigations aimed at elucidating these intricate mechanisms (Tolbatov et al., 2023; Tolbatov et al., 2024; Tolbatov et al., 2025).

Computational (Tolbatov and Marrone, 2022a; 2022b) and experimental (Santos et al., 2012; Messori et al., 2014) studies strategically employ simplified models to investigate the fundamental reactivity of these complexes. The computational investigations were carried out using the range-corrected density functional ωB97X with def2-quality basis sets (def2SVP/def2TZVP) and the IEFPCM solvation model (Tomasi et al., 1999). Rather than modelling the full complexity of a protein, research begins by focusing on substituting ligands on metal complexes with isolated nucleophilic groups that mimic protein side chains (Figure 2). The thermodynamic studies quantified the binding affinity by calculating the Gibbs free energy of substitution for various residues, while the kinetic studies mapped the potential energy surface to identify the

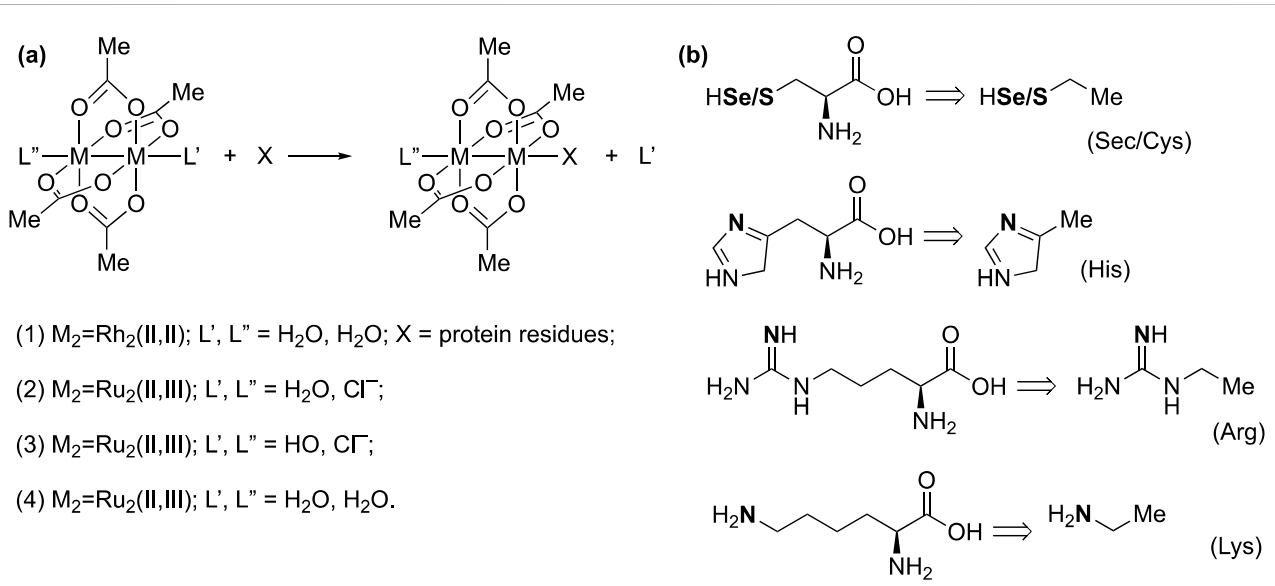

FIGURE 2
(a) Attack of a protein residue by the dimetal paddlewheel complex, resulting in the substitution of the axial ligand with the protein residue.
(b) Simplified models of selected protein residues, the metalated atom is in bold.

activation barriers associated with axial ligand exchange. This approach, which accurately captures the local chemical environment, allows for the acquisition of key information on energetics and local bond rearrangements.

By identifying an interchange mechanism involving a distorted penta-coordinated transition state, these studies provided a clear atomistic picture of how the metal-metal bond influences the labilization of the leaving group. Although the main focus was on simplified side-chain models, these studies implicitly considered an additional level of modelling by examining how the overall solution environment and pH influence reactivity and selectivity. For instance, the kinetic study (Tolbatov and Marrone, 2022a) explicitly investigated the hydroxo form of the diruthenium complex, $[Ru_2(\mu\text{-}O_2CCH_3)_4(OH)Cl]^-$, which is prevalent at higher pH values, and analyzed how pH impacts chloride substitution. This demonstrates the importance of the broader biological context and how environmental factors can modulate the reactivity of these metallodrugs, extending the utility of the simplified models to predict behavior under varying physiological conditions. The thermodynamic study (Tolbatov and Marrone, 2022b) also discusses how factors like bulk exposure and pH influence the prevalence and accessibility of various nucleophilic residues in a protein -for example, Arg and Lys at higher pH, or buried Cys/Sec residues (where Sec denotes selenocysteine)- further integrating environmental considerations into the interpretation of simplified model results.

In summary, these two computational studies provide critical insights into the reactivity and selectivity of dirhodium and diruthenium paddlewheel complexes. By employing DFT with simplified models of protein residue side chains, we were able to precisely determine the thermodynamics (binding affinity and preferences) and kinetics (reaction barriers and rates) of axial ligand substitution. By identifying an interchange mechanism involving a distorted penta-coordinated transition state, the thermodynamic study (Tolbatov and Marrone, 2022b) revealed that while both dirhodium and diruthenium complexes react favorably with many protein nucleophiles, specific preferences emerge under different conditions, with Sec and His identified as particularly suitable targets. The kinetic study (Tolbatov and Marrone, 2022a) further refined this understanding by exploring reaction barriers, showing that water substitution is generally kinetically favored, but chloride substitution in hydroxo forms of diruthenium complexes can offer enhanced selectivity towards specific residues like Cys and Sec at higher pH. The analysis of transition state geometries also provided valuable information on how steric hindrance from future ligand modifications could be leveraged to improve selectivity. This comprehensive, multiscale approach, starting from highly simplified models and progressively incorporating environmental factors, is instrumental in guiding the rational design of next-generation metallodrugs with enhanced efficacy and targeted action.

A clear example of this is the experimental work by Santos et al. (Santos et al., 2012). This study used the tetrakis (acetato) chloridodiruthenium (II,III) complex as a soluble prototype to investigate its reactivity with the simple amino acids glycine, cysteine, histidine, and tryptophan. The results revealed that the paddlewheel framework remained stable during the axial ligand substitution reactions and was mostly preserved in the presence of the amino acids. This simple model approach was shown to be highly predictive when the same complex was later investigated in a more complex biological system. In a subsequent experimental study on hen egg-white lysozyme (HEWL) (Messori et al., 2014), it was found that the complex forms a stable metal-protein adduct with the diruthenium core conserved. Unlike the previously studied amino acid models, which only showed axial ligand substitution, this study revealed the concomitant release of two of the four bridging equatorial acetate ligands from each diruthenium center upon binding to the protein. Specifically, X-ray diffraction analysis confirmed that two diruthenium moieties bind to the protein at residues Asp101 and Asp119, highlighting the displacement of the bridging acetate ligands by bidentate aspartate residues.

This progression from simple experimental models (amino acids) to more complex ones (a full protein) mirrors the multilevel computational approach. By starting with simplified models and progressively incorporating more complex biological and environmental factors, it is possible to systematically build a complete understanding from fundamental atomic interactions to the entire protein-drug dynamics. This comprehensive, multiscale strategy is instrumental in guiding the rational design of next-generation metallodrugs with enhanced efficacy and targeted action.

2.3 Case study 3: a joint computational-experimental perspective on the anticancer properties of the auranofin analog $Au(PEt_3)I$

Auranofin (AF) is an FDA-approved gold-based drug, but its iodide analog, $Au(PEt_3)I$ (AF-I), has shown even more promising anticancer properties, including potent *in vitro* cytotoxic activity against ovarian and colorectal cancer and the ability to induce rapid tumor remission in a mouse model (Marzo et al., 2019). To understand the reasons for this enhanced activity, an integrated approach using both computational and experimental models of increasing complexity was employed (Tolbatov et al., 2020).

Computational studies using simplified models were conducted to gain a deeper understanding of the binding mechanism. The theoretical investigations were carried out at the DFT level using the B3LYP functional (Becke, 1993) and the LACVP** basis set (Bochevarov et al., 2013) to calculate the reaction pathways of iodide displacement by various amino acid side chains, incorporating the Poisson–Boltzmann continuum solvent method (Im et al., 1998) to account for implicit solvation. These thermodynamic and kinetic studies evaluated the Gibbs free energy of adduct formation and the corresponding activation barriers for the ligand exchange process. By comparing the energetic profiles of AF and AF-I, the calculations highlighted how the high trans influence of the iodide ligand modulates the labilization of metal-ligand bonds. This provided a mechanistic explanation for the unique reactivity profiles observed in these iodide-based complexes.

In parallel, simple experimental models to investigate the reactivity of AF-I were exploited. Using a multi-technique approach including NMR, IR, and ESI mass spectrometry, it was studied how AF-I and AF interact with relevant amino acid residues: histidine, methionine, cysteine, and Sec. The results showed that while AF-I did not react significantly with His or Met, it readily

formed adducts by displacing the iodide ligand and binding to the thiol group of cysteine and the selenol group of Sec. This approach provided key insights into the drug's binding preferences and reactivity at a fundamental, molecular level.

The insights gained from these simple models were then used to understand the drug's activity within more complex biological systems. The study confirms that the true pharmacophore is the $[Au(PEt_3)]^+$ cation, which is believed to be released from AF-I and capable of binding to key cellular targets. Indeed, the drug exerts its pharmacological effects through interaction with non-genomic targets such as the protein thioredoxin reductase (Tolbatov et al., 2020). The combined experimental and theoretical results from the simple models contributed to a more comprehensive understanding of the reactivity and activation mechanisms of the drug in the presence of biological targets. This integrated approach helped to shed light on the mechanistic basis for the enhanced antitumor activity of AF-I compared to AF.

3 From solid-state analysis to complex biological matrices: expanding insights into metallodrug behavior

3.1 Solid-state analysis a tool to inspire innovative metallodrugs for Alzheimer's diseases

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and neuropathological hallmarks that include extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles, and neuronal loss. According to the amyloid cascade hypothesis, an imbalance between Aβ production and clearance initiates a sequence of molecular events leading to neurotoxicity and inflammation (Behl, 2024).

Aβ peptides, generated through the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases, display a strong tendency to aggregate, a process that is central to AD pathology (Zhou et al., 2011). Growing evidence indicates that metal ion dyshomeostasis plays a crucial role in modulating Aβ aggregation and toxicity. Transition metals such as copper (Cu), iron (Fe), and zinc (Zn), which are essential for normal brain function, are found at abnormally high concentrations in amyloid plaques and are known to interact directly with Aβ peptides (Arena et al., 2012; Hureau, 2012; Borghesani et al., 2018; Stefaniak and Bal, 2019). Cu^+ and Cu^{2+} bind specific histidine residues of Aβ, forming coordination complexes that can alter peptide conformation and aggregation pathways (Brzyska et al., 2009; Abelein et al., 2022). The redox activity of Cu and Fe further promotes the generation of reactive oxygen species (ROS), contributing to oxidative stress and neuronal damage, while Zn can either inhibit or accelerate Aβ aggregation depending on its local concentration (Tõugu et al., 2011).

Metal ions also influence protein-protein interactions relevant to AD. A notable example is transthyretin (TTR), a transport protein with neuroprotective properties that can bind Aβ and inhibit its fibrillization. Importantly, recent studies have shown that the TTR-Aβ interaction is metal-dependent, occurring in the presence of Cu^{2+}, which appears to modulate the conformation of both proteins and enable binding (Ciccone et al., 2018). These findings highlight the role of metal ions not only in Aβ aggregation but also in regulating protective molecular interactions.

Given the involvement of metals in AD pathology, metal chelation has emerged as a potential therapeutic strategy aimed at restoring metal homeostasis and reducing oxidative stress. Compounds such as clioquinol and PBT2 have been investigated in clinical trials to modulate metal–Aβ interactions (Xing et al., 2025). However, despite strong conceptual support, no metal chelators have yet been approved for AD treatment. Major challenges include achieving blood–brain barrier permeability, avoiding depletion of essential metal ions, and selectively targeting pathogenic metal–Aβ complexes without disrupting physiological metalloproteins. These limitations underscore the need for a deeper understanding of metal trafficking and coordination chemistry in the AD brain to enable the rational design of effective metal-targeted therapies.

3.2 Future perspectives and new insights into the role of metals in AD

An emerging perspective that could inspire future therapeutic design is the integration of TTR-helix-derived analogues (Shi et al., 2023) with a purposely mild metal-chelating functionality (Ciccone et al., 2023). TTR helices have already demonstrated the ability to interact with Aβ and attenuate its aggregation, and several studies highlight how metal ions-particularly Cu^{2+}-can stabilize the natural TTR-Aβ interaction. Building on this concept, one could envisage next-generation analogues equipped with a low-affinity chelator that does not sequester physiological metals indiscriminately but instead becomes functionally engaged only within the TTR-helix-Cu-Aβ interface. In this framework, the chelator would act as a facilitator of the metal-bridged interaction rather than as a classical metal scavenger, thereby enhancing the analogue's affinity for Aβ while more closely mimicking the native mode of TTR action. Such a strategy, by exploiting situational and interaction-driven chelation, offers a promising avenue for designing molecules that reinforce the protective role of TTR against Aβ aggregation without perturbing broader metal homeostasis.

The clarity gained at the solid-state level now serves as a foundation for extending these studies into more complex cellular models, where the interplay among TTR, Aβ, and metal ions can be examined under physiologically relevant conditions. Such translation from structural insight to biological systems is essential for elucidating the true physiological role of TTR-mediated metal chelation and for understanding its mechanism of action, ultimately guiding the rational development of innovative metallodrugs for Alzheimer's disease.

4 Effective translation of novel metal complexes to advance clinical cancer therapy

Despite their proven clinical success, metal-based anticancer drugs still represent only a small fraction of approved chemotherapeutics. Advancing novel mono- and bimetallic

complexes (MBCs) from the laboratory to the clinic therefore remains a major challenge in medicinal inorganic chemistry. While many newly synthesized complexes display promising cytotoxicity and selectivity *in vitro*, successful clinical translation critically depends on their pharmacological behavior under physiological conditions. In contrast to most small organic drugs, MBCs are often prone to hydrolysis and ligand exchange reactions in the bloodstream, processes that can compromise efficacy and induce severe side effects, including nephrotoxicity and neurotoxicity (Oun et al., 2018). Consequently, adequate stability in blood plasma is a prerequisite for ensuring that metal complexes reach their intended target tissues intact following intravenous administration.

To address this issue, bioanalytical approaches capable of probing the fate of metallodrugs in blood plasma have proven invaluable. In particular, hyphenated size-exclusion chromatography coupled to inductively coupled plasma atomic emission spectroscopy (SEC–ICP-AES; Size-Exclusion Chromatography coupled with Inductively Coupled Plasma-Atomic Emission Spectroscopy) enables the real-time monitoring of metal-containing species and their interactions with plasma proteins. This methodology was originally developed to profile endogenous Cu-, Fe-, and Zn-containing plasma proteins (Manley et al., 2009) and was subsequently adapted to investigate the plasma stability and metabolism of platinum-based anticancer drugs. Comparative studies on cisplatin and carboplatin revealed markedly different hydrolysis rates, with cisplatin undergoing more rapid degradation while forming similar platinum–protein adducts, highlighting the importance of plasma stability for translational success (Sooriyaarachchi et al., 2011; Sooriyaarachchi et al., 2016).

The same bioanalytical strategy has been successfully applied to evaluate the behavior of novel bimetallic anticancer complexes in blood plasma. For example, studies on the bimetallic complex Titanocref provided direct experimental evidence that the intact compound can persist in circulation and reach target tissues following intravenous administration, thereby supporting its advancement toward preclinical evaluation (Sarpong-Kumankomah et al., 2020). Collectively, these findings underscore the critical role of plasma stability assessments in guiding the rational selection of metal-based drug candidates with realistic translational potential.

5 Conclusion

This perspective outlines a multiscale strategy that demonstrates how the deliberate integration of simplified and increasingly complex computational and experimental models enables a deeper mechanistic understanding of protein metalation, which is a central process in the action of inorganic drugs. It is inherently challenging to understand the multiple reaction patterns that metallo(id)-based drugs undergo in the biological milieu, given that numerous biomolecules can serve as potential binding partners. For this reason, simplified systems, including minimal models, amino acids and isolated proteins, are essential for understanding reactivity, selectivity and structural effects. While these models inevitably lack the full complexity of real biological environments, thereby limiting the direct interpretation of mechanistic pathways, carefully controlled experimental and computational conditions have been shown to reliably capture key features of the protein metalation process (Merlino, 2021). Such insights can then be generalized to systems of progressively higher biological relevance.

The issue of predictability is often raised, as simplified models can behave in a case-specific manner and may not always produce an exact response from real biological targets. However, these limitations can be effectively mitigated by integrating multiple complementary techniques and progressively increasing the level of biological complexity. Indeed, several studies illustrate how information extracted from reduced models can successfully guide the interpretation of complex cellular responses and illuminate therapeutic mechanisms. This is the case for instance of oxaliplatin. It was demonstrated in 2014–2015 using simple model proteins, that its reactivity is substantially different from cisplatin and carboplatin (Messori et al., 2015). A few years later, in 2017, Lippard and coworkers confirmed a completely different mechanism of action of oxaliplatin that does rely on DNA-independet mechanisms, evidence that was anticipated with the above-mentioned studies (Bruno et al., 2017).

Crucially, the transition from model systems to bona fide biological targets exemplified by the metal-mediated interactions among Aβ, Cu^{2+}, and the neuroprotective protein transthyretin, highlights the power of this hierarchical approach for addressing unmet medical needs such as Alzheimer's disease. Likewise, advanced bioanalytical strategies for probing metallodrug stability and metabolism in plasma help to bridge the remaining gap between mechanistic studies and translational success, enabling the identification of metal-based complexes with true clinical potential.

Overall, embracing a multilevel modeling paradigm is essential for modern medicinal inorganic chemistry. By strategically combining computational accuracy, experimental tractability, and biological relevance, this approach accelerates discovery, enhances mechanistic clarity, increases predictive power, and paves the way for next generation metallodrugs with improved efficacy, safety, and translational viability.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LoC: Writing – review and editing, Writing – original draft, Methodology. LiC: Conceptualization, Writing – review and editing, Writing – original draft. AM: Writing – review and editing, Writing – original draft. LF: Writing – original draft, Writing – review and editing. DP: Writing – original draft, Writing – review and editing. NT: Writing – original draft, Writing – review and editing. IT: Writing – original draft, Writing – review and editing. JG: Writing – review and editing, Methodology, Writing – original draft. TM: Writing – review and editing, Conceptualization, Writing – original draft, Supervision. LM: Writing – review and editing. DL: Writing – review and editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. LM thanks MIUR PRIN2022 (Project Code: 2022JMFC3X, "Protein Metalation by Anticancer Metal-based Drugs"). TM thanks Ministero Italiano dell'Università e della Ricerca (MUR) under the program PRIN 2022-Progetti di Rilevante Interesse Nazionale, project code: 2022ALJRPL "Biocompatible nanostructures for the chemotherapy treatment of prostate cancer". JG greatly acknowledges funding from Alberta Innovates Health Solutions (AIHS, grant 201000689), a VPR Catalyst Grant (grant 116412850] and a MITACS scholarship to LoC.

Acknowledgements

We are grateful to all the colleagues whose insightful discussions were essential to the development of this paper.

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