

Editorial

Metal Complexes Containing Bioactive Ligands: Structure and Biological Evaluation

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Currently, the development of medicinal chemistry depends on naturally occurring scaffolds, as nearly 50% of FDA-approved compounds are related to compounds already present in nature [1]. The metal chelation of bioactive molecules provides an important means of increasing the biological activity of related complexes. In this context, the design of metal-based therapeutics represents a promising strategy to overcome the limitations associated with purely organic drugs, such as poor bioavailability, limited selectivity, and resistance development [2–7]. The incorporation of transition metal ions can significantly modulate redox properties, coordination geometry, and lipophilicity, thereby influencing pharmacokinetics and mechanisms of action [8–12]. Consequently, the rational combination of bioactive ligands with metal centers continues to attract considerable attention, incorporating inorganic chemistry, medicinal chemistry, and computational modeling.

This Special Issue, titled “Metal Complexes Containing Bioactive Ligands: Structure and Biological Evaluation”, was curated to showcase modern synthetic procedures for the chemical modification of bioactive compounds and their transition metal complexes. Research topics also include theoretical methods for elucidating the modification mechanism, compound stability, complexation modes, and interactions, using Density Functional Theory (DFT), Natural Bond Orbital Theory (NBO), and Quantum Theory of Atoms in Molecules (QTAIM). In the following parts, short outlines of the published papers are presented.

A review paper by Mihajlović, Trif, and Živković presents a comprehensive collection of papers regarding the metal complexes with hydroxyflavones and their anticancer and antimicrobial activity [13]. Hydroxyflavones represent a hydroxylated subgroup of flavones, compounds composed of three six-membered rings. These compounds are known for their antioxidant and antimicrobial activity due to their involvement in plant defense mechanisms [14,15]. Furthermore, the literature suggests that cytotoxic effects and antiviral, antidepressant, antiparasitic, and antiallergenic activity are shown by hydroxyflavones [16–21]. The complexation mode of these compounds strongly depends on the number and relative position of hydroxyl groups [22,23]. The reviewed literature suggests that a broad range of biological activities is shown by metal complexes containing hydroxyflavones, such as anticancer, antimicrobial, anti-inflammatory, and antimutagenic action [24]. The authors of the review also propose directions for the future development of these metal-based agents, as solubility in water remains a major challenge.

Yang, Li, and Luo examined the complexation abilities of two-sulfur-containing compounds, namely, diphenylacetyl disulfide and 3,3'-diaminodiphenyl sulfone [25]. Three mononuclear complexes were obtained in one-pot conditions ($[\text{C}_4\text{H}_{18}\text{CuO}_{12}\text{S}_2](\text{I})$, $[\text{C}_{12}\text{H}_{18}\text{N}_4\text{NiO}_{11}\text{S}](\text{II})$ and $[\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2\text{Zn}](\text{III})$). The structures of the compounds were elucidated using X-ray analysis, FTIR, UV-Vis, NMR, and ESI-MS, while the thermal



Received: 2 March 2026

Accepted: 4 March 2026

Published: 5 March 2026

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stability was determined by thermogravimetry. The cytotoxicity measurements were performed against the human cancer cell lines lung cancer A549, liver cancer SMMC-7721, breast cancer MDA-MB-231, and colon cancer SW480. The inhibition rates of complexes II and III were relatively high, around 20% in MDA-MB-231 and SW480.

A research team led by Prof. Jevtovic [26] presented structural, antioxidant, and protein/DNA-binding properties of a sulfate-coordinated Ni(II) complex with a pyridoxal-semicarbazone (PLSC) ligand. In this contribution, the structure of $[\text{Ni}(\text{PLSC})(\text{SO}_4)(\text{H}_2\text{O})_2]$ was solved via X-ray analysis, and the stabilization interactions within the crystallographic structure were described by Hirshfeld surface analysis [27,28]. The structure was later optimized by the B3LYP functional [29] in conjunction with the 6-311++G(d,p) basis set [30] for non-metallic atoms and two pseudopotentials (LanL2DZ and def2-TZVP [31,32]) for Ni in the Gaussian 09 program package [33]. The applicability of the selected level of theory was demonstrated by comparing experimental and theoretical bond lengths and angles. The QTAIM method [34] was used to assess the strength and type of interactions between central metal ions and ligand molecules. The antioxidant activity of the complex towards hydroxyl and ascorbyl radical was examined via electron paramagnetic resonance (EPR) spectroscopy, and the detected activity towards hydroxyl radical was higher than that of ascorbic acid. Interactions with Human Serum Protein (HSA) and DNA were examined using spectrofluorimetric titrations and molecular docking.

The interactions of four ruthenium(II) complexes of the type $[(\eta^6\text{-}p\text{-cymene})\text{RuCl}(\text{dpm})]$, where dpm are hexa-(L3–L5) and meso-substituted (L6) dipyrromethene ligands, were prepared in the contribution by Murillo and coworkers [35]. The structures of these compounds were characterized via MS, FTIR, NMR, UV-VIS, and X-ray crystallography. For the optimization of structure, the authors have employed the B3LYP functional together with DGDZVP basis set for ruthenium atoms [36] and 6-31+G(d,p) basis set for the remaining atoms. The DNA-binding affinity was determined via UV-VIS titration, followed by computational calculations. The highest experimental binding constant was obtained for Ru-3 ($6.5 \pm 0.5 \times 10^{11} \text{ M}^{-1}$), with the binding energy of $-61.8 \text{ kJ mol}^{-1}$. This result was further supported by docking studies and molecular-level interaction analysis.

De Matos and coworkers [37] obtained two Ru(II) polypyridyl complexes, *cis*- $[\text{Ru}(\text{dmbpy})_2\text{Cl}(\text{bpy})](\text{PF}_6)$ (Rubpy) and *cis*- $[\text{Ru}(\text{dmbpy})_2\text{Cl}(\text{bpe})](\text{PF}_6)$ (Rubpe) (dmbpy = 4,4'-Dimethyl-2,2'-dipyridyl, bpy = 4,4'-dipyridyl and bpe = 1,2-bis(4-pyridyl)ethane) that were spectroelectrochemically characterized. This type of complex has been extensively examined due to its lower toxicity, slower ligand exchange and dissociation, strong interactions with proteins and DNA, and cytotoxicity that includes different cancer models [38–40]. In the previous contributions, it was proven that the aromaticity of the terpyridine substituent in the complexes of the type $[\text{Ru}(\text{R-tpy})(\text{LL})\text{Cl}]_n^+$ (R = chloro or 4-chlorophenyl; LL = bidentate ligand) enhances the biological activity [41,42]. The complexes reported by de Matos and coworkers showed strong interactions with the transport proteins, as evidenced by titration experiments. The dominant mechanisms of interaction with DNA included partial intercalation and groove binding. The cellular uptake of the complexes was relatively high in HeLa and MDA-MB-231 cells.

In the paper by Akin-Polat and coworkers [43], six chloro[N-alkyl-N-cinnamyl-benzimidazol-2-yliden]silver(I) complexes were successfully synthesized, in which allyl (3a), methoxymethyl (3b), benzyl (3c), 3-fluorobenzyl (3d), 4-fluorobenzyl (3e), and 4-methyl-benzyl (3f) substituents were present on the benzimidazole ring. The structures were confirmed via MS, FTIR, and NMR, while X-ray crystallography was used to determine the structures of the 3c and 3d complexes. The activity of compounds against trophozoites and cysts of the pathogenic *Acanthamoeba castellanii* strain was investigated, with the following order of activity: 3d > 3c > 3f > 3a > 3b > 3e. High concentrations of compounds

(1000 μM) led to the near-total eradication of protozoa. This is the first contribution in the literature to use silver-*N*-heterocyclic carbene complexes against *Acanthamoeba castellanii*, one of the *Acanthamoeba* spp., free-living amoebae commonly found in soil, freshwater, and air [44,45].

Halevas et al. examined the antioxidant activity of four newly synthesized nickel and cobalt complexes with chrysin in reference [46]. Each of these compounds contained one of the bidentate chelating agents (2,2'-bipyridine and 1,10-phenanthroline), and the structures were verified using physicochemical and crystallographic methods. Chrysin is a flavonoid with two hydroxyl groups at the 5 and 7 carbons [47] and it can be found in plant extracts, propolis, and honey extracts [48,49]. Before these results, only a few other complexes with chrysin had been characterized via X-ray crystallography, such as in [50,51]. The activity of the compounds presented in the Special Issue was tested against the DPPH radical, and dose-dependent antioxidant potential was shown. All four compounds were more active than chrysin, and in general, the nickel complexes had higher antioxidant activity than cobalt complexes. The obtained activity was of the same order of magnitude as for the cobalt complexes containing non-steroidal anti-inflammatory drugs, as another class of bioactive ligands [52].

Mohammed and coworkers [53] published results regarding the synthesis and structural characterization of two ligands containing escitalopram and eugenol/curcumin and their complexes with Mn(II), Co(II), Ni(II), and Cu(II). Eugenol is a phenolic compound that acts as a bidentate ligand with potential antibacterial activity, which is reflected in the damage to the membranes of Gram-negative and Gram-positive bacteria [54]. Escitalopram belongs to the class of selective serotonin reuptake inhibitors (SSRIs), and it has previously been linked to form multifunctional ligands [55]. Curcumin is a naturally occurring compound, obtained from turmeric powder of *Curcuma longa*, with a strong chelating effect towards central transition metal ions [56]. Chemical modifications of bioactive compounds and their conjugation with other active components are expected to enhance therapeutic efficacy [57]. The complexes described in the papers in this Special Issue were characterized via FTIR, UV-Vis, ^1H NMR, elemental analysis, molar conductivity, and magnetic susceptibility. The geometries were optimized using DFT methods. The diffusion method was used to assess the antimicrobial activity of complexes towards *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. Cobalt-containing complexes were the most active due to the increase in co-lipophilicity and improved diffusion through the cell membrane.

The Guest Editor hopes that this Special Issue will serve as a useful resource for researchers in bioinorganic and medicinal inorganic chemistry and encourage further collaborative work towards the development of new metal-based therapeutic and diagnostic approaches.

Data Availability Statement: This article is an Editorial and does not report original research data. No new data were created or analyzed in this study. Data sharing is not applicable.

Acknowledgments: The Guest Editor sincerely thanks all authors for their valuable contributions, the reviewers for their careful and constructive evaluations, and the editorial team of *Inorganics* for their professional support throughout the preparation of this Special Issue.

Conflicts of Interest: The author declares no conflicts of interest.

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