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Editorial

Bioinorganic Chemistry of Copper: From Biochemistry to Pharmacology

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Copper is an essential trace element found ubiquitously in humans [1,2], plants [3–5], vertebrates and invertebrates [6], and is present in different active sites at innumerous proteins and enzymes [7–11]. In such biological systems, copper enzymes perform functions such as uptake and transport of oxygen; electron transfer in the respiratory chain; catalytic oxidation or reduction of many substrates; antioxidant action; uptake, transport and storage of metal ions, etc. [12,13]. Structurally, copper compounds appear in many configurations, coordinated with simple ligands or biomolecules, in a wide range of arrangements [14]. The two common oxidation states of copper, Cu^{+} and Cu^{2+}, present in biological systems exhibit peculiar properties, with a range of reactivity and nuclearity, forming mono-, bi-, poly-nuclear, or even cluster species. The proteins of copper may have one or many metal ion centers with different spectroscopic signatures and dissimilar activity [15]. On the other hand, copper ions are also involved in neurodegenerative diseases, in which their redox properties play important roles [16–22]. Considering the varying biological roles of copper described above, the development of new copper-containing coordination complexes is an intense topic of research, involving exploration of their pharmacological properties, especially their anticancer activities [23–31].

Consequently, the Bioinorganic Chemistry of copper constitutes a rich and challenging field of investigation, attracting the attention and interest of research groups around the world, as demonstrated by the huge number of files found in literature searches by using copper in combination with a second keyword, such as antibacterial, anticancer, diseases, catalysts, mimics, proteins, spectroscopy, reactivity, etc.

This diversity is clearly demonstrated in this Special Issue of *Inorganics*, 'Bioinorganic Chemistry of Copper', which contains 14 published articles that explore topics such as antiproliferative studies, anticancer agents, anti-inflammatory compounds, potential radioactive imaging diagnosis agents, reactive species related to amyloid peptides, antiparasitic activity, catalytic oxidative activity, and protein mimics.

Potential anticancer agents were reported in most of the published articles. A review about mixed chelate homoleptic or heteroleptic copper(II) complexes, known as Casiopeínas® and already used in clinical tests, was provided by Ruiz-Azuara and coworkers (contribution 1), describing translational medicine criteria to establish a normative process for new drug development.

Batista and coll. (contribution 2) isolated and characterized a series of Cu(I)/PPh_3/naphtoquinone complexes with anticancer properties against diverse tumor cells. Their mode of action also involves reactive oxygen species (ROS) generation, both in the absence (peroxyl radicals) and presence of irradiation (hydroxyl radicals).

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The cytotoxicity of phenylcarboxylate–copper(II) complexes with typical binuclear paddle-wheel arrangements was investigated by Fernandez et al. (contribution 3), who studied their lipophilicity, DNA binding, and cytotoxicity toward metastatic breast adenocarcinoma, lung epithelial carcinoma and cisplatin-resistant ovarian carcinoma cells.

A series of mononuclear copper(II) complexes with ligands containing phenolate and imine moieties was verified by Serre et al. (contribution 4), to act as efficient artificial nucleases, activated by reduction with ascorbate, toward cancer cell lines sensitive or resistant to cisplatin itself, with IC_{50} values much lower than those for cisplatin.

New isothiosemicarbazone–copper(II) complexes with varied structural features were isolated and characterized by different techniques, as reported by Graur et al. (contribution 5), showing antioxidant activity similar to trolox, used as an antioxidant agent in medicine, as well as high antiproliferative activity against cells sensitive to doxorubicin, a standard chemotherapy medication. Additionally, these compounds showed significant antibacterial and antifungal activities.

A strategic combination of bioactive ligands and metals that are already consolidated in the synthesis of metallopharmaceutical agents, allowed Corbi and coll. (contribution 6), to prepare and investigate naproxen (Nap)-based complexes of copper(II) and platinum(II) which showed cytostatic behavior over a set of tumor cells, but no bactericidal activity.

Complexes with other pharmacological activities were also presented. Copper(II) complexes with bi-, tetra-, or pentadentate ligands showing potential anti-inflammatory activity against Rheumatoid Arthritis (RA) were evaluated regarding their diffusion and membrane permeability, as described by Jackson and coll. (contribution 7). Chemical speciation was used to determine the predominant complex in solution at physiological pH. However, no correlation was found between partition coefficient and/or molecular weight and tissue permeability.

Since oxidative stress and metal (especially copper) dyshomeostasis are crucial factors in the pathogenesis of Alzheimer's disease (AD), involving ROS generation, Density Functional Theory (DFT) computations were used by L. Bertini and coll. (contribution 8), to verify a possible mechanism of oxidation through the OH radical propagation toward the phospholipidic membrane.

In another study, Valensin and co-workers (contribution 9) described an active alkaloid lycorine (LYC) capable of suppressing induced amyloid β (Aβ) toxicity in differentiated SH-SY5Y cell lines, likely by binding to the N-terminal region of Aβ via electrostatic interactions, which are favored in the presence of copper ions.

In the work of Portes et al. (contribution 10), copper(II) and zinc(II) compounds with oxindolimine ligands were shown to act as efficient trypanocidal agents against trypomastigote and amastigote forms of the parasites, through the generation of reactive oxygen species (ROS), inducing apoptosis, and probably involving the inhibition of selected parasite proteins. The determined IC_{50} values are lower and selective indexes (LC_{50}/IC_{50}) are higher, after 24 or 48 h incubation, modulated by the metal and the ligand, in comparison to traditional antiparasitic drugs used in clinics, or other metal-based compounds previously reported in the literature.

New penta- and hexadentate ligands containing pyridine moiety were prepared and verified to form stable Cu(I) and Cu(II) complexes, characterized by different methods, as reported by Mirica and coll. (contribution 11). After that, further experiments were performed to verify their potential use in vivo as ^{64}Cu PET imaging agents.

In addition, studies on structure–function relationships, methodologies, and catalysis were reported. Signorella and coll. (contribution 12) described the critical role of the flexibility or rigidity of the ligands in the redox cycle of copper superoxide dismutase (SOD) and therefore in the design of their mimics. A combination of ligand flexibility, total charge, and labile binding sites provided optimized catalytic properties for a *trans*-[Cu(II)N_4-Schiff base] complex in the dismutation of superoxide ions.

Applications of ^{111}Ag perturbed angular correlation (PAC) of γ-ray spectroscopy to elucidate the chemistry of Cu(I) in biological systems were reviewed by V. Karner et al.

(contribution 13). Since monovalent copper ion is isoelectronic with Ag(I) (both closed-shell d10), and both ions share ligand and coordination geometry preferences, the focused spectroscopy is appropriate to investigate the structural aspects of some small blue copper proteins, such as plastocyanin and azurin, involved in electron transport and transfer.

Finally, a catalytic action of copper compounds was reported by J. Isaac et al. (contribution 14) in the study of symmetrical and unsymmetrical dicopper(I) complexes with oxazolines or mixed pyridine–oxazoline coordination moieties that react with O_2 at low temperature to form μ-η^2:η^2 Cu_2:O_2 peroxido species. These may result in C–C coupling products after reaction with a phenolate substrate, with the formation of an intermediary mixed-valence $Cu^{II}Cu^{III}$ species, as indicated by electrochemical and EPR results.

This Special Issue includes a range of examples of copper(I) and copper(II) compounds reactivity, reported by many researcher groups, using distinct strategies to illustrate different aspects of their bioinorganic chemistry.

Conflicts of Interest: The authors declare no conflict of interest.

List of Contributions

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