

The manuscript, 'Complexes of Zinc(II) Chloride with N-Vinyl-, N-Allyl- and N-Propargylimidazoles: Structural, Theoretical and Biological' describes the synthesis and characterisation of a series of zinc(II) complexes with imidazole derivatives, as well as their biological properties. The authors present two new Zn(II) complexes and two that have been previously reported, all of which have been properly characterised, with two being fully characterised through single crystal X-ray data. A broad range of biological assays are included in the manuscript, suggesting that these compounds may exhibit antihypoxic, wound-healing, antifungal and antitumour activity. The methodology applied to synthesise the complexes was straightforward: the organic species were mixed with ZnCl₂ in a 1:2 molar ratio. Overall, these data are of interest given the good biological activity of some compounds, but additional data are required. I therefore recommend major corrections having in view the following aspects:

Major aspects that must be addressed:

1. The manuscript does not provide any experimental data on the stability of the complexes under physiologically relevant conditions. It is unclear from the DFT data whether the complexes retain their structural integrity in solution or undergo ligand exchange prior to exhibiting biological activity. Consequently, ¹H NMR studies over time in D₂O are necessary. The spectra registered in different deuterated solvents do not provide stability data as the authors claim.
2. Biological studies must be conducted in comparison with those of the free ligands and ZnCl₂ respectively. These must also be compared with both antimicrobial and antitumour reference drugs. Without this information, the clinical relevance of the reported MIC or CC₅₀ values cannot be assessed.
3. The cell death mechanism for the most active compounds must be assessed using either LDH release or flow cytometry (Annexin V/PI).
4. Powder X-ray data must be provided and compared with data simulated from single crystal X-rays in order to prove that the bulk species has the same structure as the single crystal, and that the two compounds have the same structure where single crystals were unavailable.
5. The purpose of this study is not clearly explained in the introduction.
6. The thermodynamic parameters were calculated considering both the dissociation reactions:

$$\text{ZnCl}_2\text{L}_2 + 7\text{H}_2\text{O} \rightarrow [\text{ZnClL}_2 \times \text{H}_2\text{O}]^+ + \text{Cl}^- \times 6\text{H}_2\text{O} \quad (2)$$

$$\text{ZnCl}_2\text{L}_2 + \text{H}_2\text{O} \rightarrow \text{ZnCl}_2\text{L} \times \text{H}_2\text{O} + \text{L} \quad (3)$$
however, there is no experimental data in the paper accounting for one of these processes. Moreover, based on the NMR data, the authors conclude that all species are stable in solution.
7. Why were 'anion-independent structures' used in the QSAR study analysis? What are these structures?

Minor aspects that must be addressed:

- The complexes are not of zinc chloride, but of Zn(II). This must therefore be changed throughout the paper. The title must also be changed to mention zinc(II) complexes and imidazole derivatives, since 'N-propargylimidazoles' is not correct as it is a single species.
- The formula of the complexes with the corresponding notations and ligands enumeration must be provided in the abstract. The complexes must be presented as [ZnCl₂L₂] instead of ZnCl₂L₂.

- The Expression „Staphylococcus Aureus, Escherichia Coli, and the yeast-like fungus Candida Albicans” must be corrected as „*Staphylococcus aureus*, *Escherichia coli*, and the yeast-like fungus *Candida albicans*”.
- The oxidation state of zinc must be specified throughout the paper and it can be written as Zn(II).
- The expression 'vital metals' must be changed to 'essential metals'.
- I disagree that zinc should be prioritised for drug development; in my opinion, copper should be prioritised due to its redox properties.
- The sentence “Zinc redox inertness and lack of ligand field stabilisation energy provide important advantages for coordination, allowing it to maintain diverse coordination geometries and complex stability” is incorrect, as Zn(II) complexes are highly reactive precisely as a result of its zero-field stabilisation energy.
- The notation used for the complexes in this work can sometimes be confusing for the reader. For example, the first compound is presented as (1), 1, (ALL-Cl) (1) and (ALL-Cl). Please use the same notation throughout the paper.
- The arrows in Scheme 1 should be replaced with lines, as in modern coordination chemistry bonds are not considered localised.
- The expression 'Chemical shifts of the protons of imidazole cycle were significantly low-field shifted' must be corrected.
- The expression 'short-wavelength region' must be replaced by 'higher wavelength' and angstroms by Å.
- In an enumeration, the unit of measurement must only be presented once at the end (i.e. 80° and 133° instead of 80° and 133°).
- The terms 'antiproliferative' and 'anti-tumour' mean the same thing, so only 'anti-tumour' activities must be preserved.
- In vitro, the name of the microorganisms and N- must be in italics throughout the paper.
- The number of repeated biological experiments must be presented in the experimental section, since the standard deviation is presented in Tables 5 and 6.
- The ml must be replaced by mL throughout the paper.
- The '50% toxic concentration' must be replaced by 'medium toxic concentration'.
- The sentence at lines 392–394 must be modified, as 'metal complexes' appears twice.
- The sentence 'As shown in Table 7, A had the highest predicted probabilities of being anti-atherosclerotic ($P_a = 426, 0.88$) and anti-eczematic ($P_a = 0.84$)' is unintelligible. What compound is A?
- The m.p. must be eliminated from the experimental part, since the complexes decompose at that temperature and do not melt.
- The medium used for compound solubilisation in anti-hypoxic, wound-healing and antitumour experiments must be specified.