**Dear Prof. Milos Duran,**

**Editor**

**Journal of the Serbian Chemical Society**

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| **Manuscript ID** | **:** | **6968** |
| **Title** | **:** | **Computational, antimicrobial, DNA binding and anticancer activities of pyrimidine incorporated ligand and its copper(II) and zinc(II) complexes** |

Thank you for your useful comments and suggestions on the improvement of our manuscript. We have modified the manuscript and please find enclosed the revised manuscript entitled **“Computational, antimicrobial, DNA binding and anticancer activities of pyrimidine incorporated ligand and its copper(II) and zinc(II) complexes”** to be considered for publication in the **Journal of the Serbian Chemical Society**.

All the comments of the reviewers are addressed and they are given below,

**Reviewer A**

**Abstract:**

The sentence "The in vitro anticancer properties of L... " is not completed. (The in vitro anticancer properties...were determined).

* **As per reviewer suggestion, the above cited line has been modified.**

**INTRODUCTION**

It is necessary to modulate the text of Introduction with references.

Specifically, pyrimidine derivatives in Reference 2 also showed an antimicrobial activity, not only an antitumor activity. Pyrimidine derivatives in Reference 3 showed an antiamoebic activity not antitumor. Pyrimidine derivatives in Reference 6 showed anti-pneumocystis carinii pneumonia activity. Pyrimidine derivatives in Reference 11 showed an antihyperglycemic activity.

* **As per reviewer suggestion, the necessary modulation has been carried out in the text of Introduction with references.**

**EXPERIMENTAL**

Computational studies:

Change the sentence "its complex were conquered by the program DFT-B3LYP…" by "its complexes were conquered by the B3LYP functional…" (DFT-B3LYP is not program).

* **As per reviewer suggestion, the sentence has been modified.**

It is necessary to specify the methodology for Docking study.

* **As per reviewer suggestion, the methodology for Docking study has been included.**

**RESULTS AND DISCUSSION**

FT-IR spectra

Change 1589 by 1591 cm-1 (for L), 1525 by 1535 cm-1 (for complex 2), and percholrates by perchlorates.

* **As per reviewer suggestion, the typographical error has been changed in our manuscript.**

**Protein-ligand interaction**

The authors conclude that "interaction is validated to be better" and "indicating a better protein-ligand interaction". I think it is correct to argue that interactions are stronger, not better. It is necessary to explain why the Cu, Zn-superoxide dismutase (pdb code:1SPD), erythrocyte catalase (pdb code:1QQW), glutathionine peroxidase (pdb code:2HE3), and estrogen receptor (pdb code:1A52) are selected as target for study of protein-ligand interactions. Whether the binding of tested compounds inhibits the activity of these enzymes/receptor (describe in more detail)?

* **Oxidative stress on normal cells suppresses the common physiological functions such as apoptosis leading to uncontrolled cell growth and division. The docked complex predicted with the strong interactions between the ligand and the antioxidant enzymes. Thus the increased activities of antioxidant enzymes helps in modulating the production of ROS, decreasing oxidative stress mediated DNA damage and thereby reducing cancer progression.**
* **Reference**

**Roy A and Manikkam R (2015).  Cytotoxic impact of costunolide isolated from *Costus speciosus* on breast cancer via differential regulation of cell cycle-An *in-vitro* and *in-silico* approach.  *Phytotheraphy Resaerch.  29(10): 1532-9.***



**DNA binding**

There are two columns with "FREE" descriptor in the header of Table 3 (I assume that the first one refers to free tested compounds and the second one to systems of tested compounds with CT-DNA). It would be helpful to use the different labels for these two columns.

* **As per reviewer suggestion, the labels of two column of table 3 have been changed.**

**Viscosity measurements**

The graph of relative viscosity were described in Figure 5, not 6.

* **As per reviewer suggestion, the figure number has been changed.**

The graphs in Figure 2 and 4 requires a legend.

* **As per reviewer suggestion, the required legends of Figure 2 and 4 have been modified.**

I consider that the results of Anticancer studies should be discussed before the results of DNA binding, Viscosity measurements and Protein-ligand interaction.

* **As per reviewer suggestion, anticancer study has been discussed before the results of DNA Interaction and protein-ligand interaction.**

**REFERENCES**

References 2, 4, 5, 6, 8, 11, 13, 18, 22, 26, 27, 32, 36, 40, 41, and 44 are not correctly formatted**.**

* **As per reviewer suggestion, the cited references have been modified into the required format.**

**Note:** One of new reference has been added under the 25th reference. So, the above cited reference could be called as 26 is **27**; 27 is **28**; 32 is **33**, 36 is **37**, 40 is **41**, 41 is **42** and 44 is **45**.

For better readability, I propose that the phrases (equations) inserted by Equation tool in Electronic absorption spectra, ESR spectra, DNA binding section (equation 1 and 2), be inserted in the main text by Symbol, Superscript and Subscript tools.

* **As per reviewer suggestion, the equation tool has been used to insert the equations in the above said sections of the manuscript.**

**Reviewer B**

Please indicate the page numbers for suggested corrections.

Please, be as specific as possible if major correction by the author(s) is recommended! :

 Sankarganesh and authors of the manuscript: „Computational, antimicrobial, DNA binding and anticancer activities of pyrimidine incorporated ligand and its copper(II) and zinc(II) complexes“, need to put the range of (increasing?) different DNA concentrations and concentration of Tris-HCl buffer in the legend of Fig.2 and Fig 4.

* **As per reviewer suggestion, the legends of Fig.2 and Fig.4 have been improved our manuscript (in page no 11).**

To give measurements and equations used for the determination related to IC50, too.

* **As per reviewer suggestion, the IC50 values determination equation has been included in the required parts of this manuscript. (in page no 5)**

Once again I thank for your valuable comments to clear my mistakes.

Thank you very much for your efforts in handling this manuscript.

Look forward to seeing your reply.

Yours sincerely,

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