



Universidad Tecnológica de Ciudad Juárez

Departamento de Mantenimiento Industrial y
Nanotecnología

04/25/2023

Mr. Keith Yang
Assistant Editor
Pharmaceuticals

Dear Mr. Yang:

On Augst 20 2024, I received from Dr. Federica Centofanti an invitation for a possible contribution to the special issue " Biological and Pharmacological Research on Indole-3-Carbinol (I3C) and Its Derivatives ". in attachment, please find a "Letter" explaining, point by point, the details of the revisions and our responses to the referees' comments, this in addition to the corrected version of the manuscript entitled: "Theoretical-cheminformatic study of four indolyphytoquinones, prospective anticancer candidates" by Edgar Daniel Moyers-Montoya, María Jazmín Castañeda-Muñoz, Daniel Marquez-Olivas, René Miranda-Ruvalcaba, Carlos Alberto Martínez-Pérez, Perla E. García-Casillas, Wilber Montejó-López, María Inés Nicolás-Vázquez and René Gerardo Escobedo-González.

I hope you now find it suitable for a possible publication

Sincerely yours

Dr. René Gerardo Escobedo González

Reviewer 1

- a) **Reviewer:** In the Introduction section, the authors should better outline their goal for the reader. Why did they choose model compounds like TQ, DMQ, DHQ, DMMQ for further modifications?

Us: Done, please review the modified manuscript

- b) **Reviewer:** Quinones, considered to be among the most potent pharmacophores their molecular mechanisms of cytotoxicity have been extensively studied, I find this lacking in the text and literature attachments. In addition, what are the biological activities, metabolic and physicochemical properties of indolylquinones known from the literature?

Us: Done, please review the modified manuscript

Please pay attention to this part of the text, where you can get confused with the authors' designation of compounds:

- c) **Reviewer:** Line 84-85 can be written differently: the targets evaluated are derivatives thymoquinone (TQ), 2,6-dimethoxy-1,4- benzoquinone (DMQ), 2,3-dimethoxy-5-methyl-*p*-benzoquinone (DHQ), and 2,5-dihydroxy-1,4-benzoquinone (DMMQ) referred to as IA-ID in Scheme 1, respectively. Please correct Scheme 1 to make it more readable, separate more clearly the group of benzoquinone compounds from IA-ID compounds. IB does not have a signature in this scheme.

Us: Done, we correct figure 1.

- d) **Reviewer:** Many quinones exhibit poor bioavailability and low solubility in aqueous systems, which hinders their in vivo systemic application and reduces their therapeutic value. In the Results and discussion section of the paper, I am missing a comparison of the starting properties of quinones with the tested compounds (IC50, lipophilicity, bioavailability, etc.). There is no commentary on whether the authors' proposed modifications were accurate or not.

Us: Done, We have attended to the request

- e) **Reviewer:** There are numerous editorial errors in the text: inadequate font, improper use of lowercase/uppercase letters, and incorrect use of punctuation marks. I note that these items should be corrected to improve readability and compliance with the editorial requirements of the journal. (e.g., line 122, 185, table 1, line 298, table 6, table 5).

Us: Done, we correct the errors.

Reviewer 2

- a) **Reviewer:** There is no clearly substantiated idea of choosing these four 3-indolylquinones from a hypothetical series containing tens of thousands of substances containing this motif. Why these four?

Us: Done, We have improved the explanation of why quinones are evaluated

- b) **Reviewer:** These compounds were not even synthesized for simple lipophilicity studies, not to mention more specialized extended tests for biological activity in vitro and in vivo.

Us: The importance of this type of theoretical studies is explained in the manuscript. Please review the manuscript.

Reviewer 3

- a) **Reviewer:** Abstract – does not give a clear idea of the results obtained by the authors. In addition, the last 2 sentences need to be formulated differently.

Us: Done, the abstract was improved, please review the manuscript.

- b) **Reviewer:** The introduction consists of chaotic and unfounded insertions of various information from literary sources, which in no way help to understand the relevance of the study. It is necessary to clearly formulate the originality of the work. Why did the authors choose these molecules? Why are indolylquinones important, what role does this residue play in the manifestation of activity? What is the activity of the original quinones shown in Scheme 1? How important is the approach used by the authors (in silico) to obtain information related to their biological, metabolic activity and physicochemical properties?

Us: Done, the introduction and outline have been improved, please review the manuscript. Furthermore, further explanation is given of the importance of in silico studies.

- c) **Reviewer:** Scheme 1 – should be called Figure 1, because the figure does not show any reactions. In

addition, the title contains errors and the numbering of the compounds is not indicated everywhere

Us: Done, the word scheme was changed to figure.

- c) **Reviewer:** Line 50-52 – a literary source?

Us: Done, the reference was added

- d) **Reviewer:** Line 53-55 is an unclear sentence

Us: done, the sentence has been rewritten

- e) **Reviewer:** Results and discussion – it is not entirely clear why the authors keep returning to their previous study (literature reference 11). If for comparison, then this should be formulated more clearly, especially since a whole section and table 3 are devoted to the previously described compounds.

Us: The results section was modified to indicate comparisons with similar compounds.

- f) **Reviewer:** Line 203-204 – what literature data supports this statement?

Us: Done, the corresponding reference was added

- g) **Reviewer:** Conclusions – do not correspond to the presented evidence and arguments. The authors state that the purpose of their study is to provide recommendations based on the results of a theoretical-computational chemoinformatic contribution of four indolylquinones, accomplishing information related to their biological, metabolic activity and physicochemical properties; however, in seven lines of conclusions, there is no summary of these recommendations. In addition, the conclusions should contain the authors' conclusions on the future prospects of the results obtained, which is also missing.

Us: done, the conclusions were modified

Reviewer 4

- a) **Reviewer:** There is no written which computer program is used for DFT calculations. The applied program should be highlighted and cited correctly.

Us: The implemented program was appropriately highlighted and cited.

- b) **Reviewer:** What label letters a, b, c and d in the superscript in Table 1?

Us: Finished, the label letters a, b, c and d were explained.

- c) **Reviewer:** There are a lot of typo errors:

- Line 45: There is no blank space between 30 and the parentheses, 30[1,2].
- Line 52: Two In (... In In this sense...). After parentheses should be full stop.
- Line 64: Excess empty space in the: to recommend
- The title of Scheme 1, line 91, after a comma should be empty space (TQ,DMQ, ...)
- Line 122: There misses parentheses ([21;...)
- Line 189: It is written IE-II. What is II? I believe it should be IH.
- Line 298: The title of Table 6 should start with the capital letter I.
- Lines 346, 365, 369, 373: There is somewhere the excess empty space, and somewhere it misses.
- Table 9, Toxicity, Eye corrosion for molecule IB, there is written 9898, it should be 0.9898.
- Tables 1 and 6: The used font should be uniformed with the font used in the rest of the text.

Us: Done, the comments were addressed