Qeios

Peer Review

Review of: "Synthesis, ADME, Toxicity, and In Silico Molecular Docking Study of Novel β-Carboline Derivatives as Potential Inhibitor Anticancer Agents"

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Synthesis, ADME, Toxicity, and In Silico Molecular Docking Study of Novel β-Carboline Derivatives as Potential Inhibitor Anticancer Agents

The title doesn't really make any sense; either they are inhibitors of a specific enzyme (which should then be stated), or they are potential anticancer agents, in which case the word „inhibitor“ should be omitted. The title is not in line with the work.

This short work describes the three-step synthesis of two compounds, 4A and 4B, which are derivatives of heterocycle β-carbolines; however, I would suggest the authors make major revisions and expand this study to obtain more useful results.

Rewrite the abstract since it is confusing and doesn't give the reader sufficient information regarding all the aspects of the manuscript.

Here is a review of each section of this work:

Introduction:

The mentioned eudistomins are not anticancer drugs; this should be corrected since it gives the readers incorrect information. Those are compounds with antiproliferative/anticancer activity. Also, the introduction should include data on their anticancer activity, how strong it is, and whether the mechanism of action was explored.

„Hence, due to these limitations, very few classes of anticancer drugs have been developed[3] „– this sentence seems rather exaggerated; there are a number of novel anticancer agents, and it is one of the

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most developed areas.

„β-carboline derivatives are present in commercially available and widely used[10]“ – this sentence is not finished.

Also, activity in the CNS is very common for the β-carbolines and should be mentioned.

„As part of our ongoing study on bioactive benzimidazoles and their analogs, certain fresh and physiologically active benzimidazoles were previously synthesized[11][12][13][14][15]“ – I'm not sure how this sentence relates to this work. Maybe the authors could explain in more detail this connection.

Results and discussion

The text that describes the scheme is not related to Scheme 1 as it should be. The authors haven't drawn the reaction step that yields compound 1, and therefore, the numbers of the compounds are also incorrect in this paragraph:

„Initially, the starting material L-tryptophan methyl ester (1) undergoes a Pictet-Spengler condensation reaction with the corresponding aldehyde to yield methyl 1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole-3-carboxylate (**2**). The obtained intermediate methyl 1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole-3-carboxylate (1) was subsequently aromatized with I_2 in DMSO at 90 ºC[16], to obtain methyl 1-methyl-9H-pyrido[3,4-b] indole-3-carboxylate (2). The obtained intermediates were subsequently N-alkylated with benzyl bromide in K_2CO_3 and DMF solvent at 65 ºC for 5 h, giving 3A-B (**Scheme 1**).“

Molecular docking

The authors should explain why they chose this specific enzyme, and also the results should be more clearly presented in the text.

„The compound also exhibits the best hydrogen bonds with the essential amino acids.“ – what does it mean „the best hydrogen bonds“? What kind of hydrogen bonds are the best?

Molecular Prediction ADME Parameters and Swiss Target Prediction – the title is completely wrong, please revise; also, SwissADME should be properly cited if used, please see the instructions for the citation on their web page.

The text in this section should be thoroughly revised. I’m not sure if the authors actually understand the results they obtained with this web tool by reading the text.

“Nearly all the molecules demonstrate drug likeness characteristics, adhering to Lipinski's rule with zero violations, and their bioavailability scores are almost identical.“ – there are only two compounds; how can the authors say „nearly all“ – what does this mean?

Table 1. – there is no mention of the compounds, abbreviations are not explained, and it should be more concise.

Toxicity

Also, the text is full of grammatical mistakes; please revise thoroughly.

Figure 4. – the text in the figure is too small, and the explanation is insufficient; please correct.

Figure 5. – the explanation for this image is missing; add it in the text.

Experimental section

Missing – general text, the sources for the chemicals, the instruments used, the (flash) chromatography eluents, the type of silica gel, yields are missing, most of the spectroscopic data is missing (IR, MS), and 1H NMR is given for only one compound, but it is unclear for which one.

Conclusion:

^{1}HNMr, ^{13}CNMR – very suspicious; 13C NMR is mentioned here, but not before. Therefore, I can conclude that the data throughout the manuscript is inconsistent and very difficult to read and evaluate.

Suggestions for the authors:

- Prepare more compounds.
- Perform antiproliferative activity assays for all the prepared compounds.
- Link docking results with the bioactivity data.
- Suggest a possible mechanism of action.
- Increase the consistency of the presented data and add data that is missing.
- Correct all the errors, not only in writing but also in the presentation of the results.
- The experimental section needs special attention – add the missing content.
- NMR spectra should be added for the title compound.

Declarations

Potential competing interests: No potential competing interests to declare.