Review of: "Synthesis of 1, 2-Disubstituted Benzimidazoles at Ambient Temperature Catalyzed by 1-Methylimidazolium Tetraflouroborate ([Hmim] BF_4) and Investigating Their Anti-ovarian Cancer Properties Through Molecular Docking Studies and Calculations"

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Potential competing interests: No potential competing interests to declare.

Comments to the Authors

Recommendation: major revision

The manuscript titled: "*Synthesis of 1,2-Disubstituted Benzimidazoles at Ambient Temperature Catalyzed by 1-Methylimidazolium Tetrafluoroborate ([Hmim] BF_4) and Investigating Their Anti-ovarian Cancer Properties Through Molecular Docking Studies and Calculations*" by Abdulhamid Dehghani and his team explores. The condensation ring-closing reaction between benzaldehyde and o-phenylenediamine (OPD) was used to successfully synthesize 1,2 derivatives of benzimidazole (**3a-l**). The reaction was carried out with the support of methylimidazolium tetrafluoroborate ([Hmim]BF_4) as a catalyst in the solvent system (EtOH - H_2O). The yield achieved was 85% in a reaction time of 0.16 hours. Twelve 1,2 derivatives of benzimidazole (**3a-l**) were also synthesized under similar conditions, with a yield of 63 - 95% in a very short time (0.11 - 0.44 hours). All products were structurally determined through melting point, ^1H, and ^{13}C NMR spectra. With the help of computational chemistry and drug design, the anti-ovarian cancer properties of (**3a-l**) were investigated. It was found that compound **3j** (a representative substance) is bound to the agonist at the active site of the 6LAD protein, leading to the inactivation of this protein and producing beneficial effects in the treatment of ovarian cancer.

The article presents the following advantages:

A study was conducted on sample **3a** with a fixed amount of [Hmim]BF_4 catalyst at 10 mol % while changing the solvent, temperature, and reaction time. The melting points of the synthetic products (**3a-l**) were compared with reference documents. Additionally, molecular assembly calculations were carried out to determine the number of donor and acceptor hydrogen bonds, cell permeability (QPPCaco), water solubility, dock score, and docking energy of the synthesized compounds.

Some of the notices:

1. Methods: The methods are described in sufficient detail to understand the methods used. However, more appropriate

statistical tests should be applied to ensure the certainty of the results.

2. Results: The results or data presented are directly or publicly available according to the standards of the field. However, additions and corrections are needed.

- The article abstract should include more specific data about the results.

- To make the article more concise, some paragraphs in the introduction should be omitted.

- When writing about the applications of ionic liquids in condensation ring-closing reactions that produce similar benzimidazole derivatives, it is more worthwhile.

- Which ovarian cancer treatment drugs contain a benzimidazole framework?

- There are errors in the formula. The author should redraw the structural formula of **3a**, removing the R group.

- Should supplement the color of isolated products.

- The author has not proposed the mechanism of benzimidazole condensation ring-closing reaction using [Hmim]BF_4 catalyst.

- Reaction time should be in minutes. If we calculate time in hours like now, 0.16 h means 9.6 minutes.

- What is your room temperature? 20 or 25^{0}C?

- How can the derived mixture ratio be checked? If the author isolated each substance, the NMR spectrum of **4a** has not been presented (as proof).

- There are errors in the formula. The author should redraw the structural formula of **3a**, removing the R group.

- There is a significant difference between the melting points of the author's 3g product and the references.

- Lipinski's rule or Lee Pinsky’s rule?

- Note that a paragraph was copied again.

- Tables 3, 4, and 5 contain errors in the substances listed as (**3a-l**) or (**4a-l**). It has to be confirmed clearly.

- As shown in Figures 2 and 3, the author's tests suggest that the 3j coupling is the most effective between the ligand and the receptor (note: understand from the author's current presentation way). However, it's worth noting that despite this, the substance with the largest negative docking energy value among the substances (**3a-l**) isn't **3j**, as per the results presented in Table 5.

- Among the substances (**3a-l**), compound **3f** has the largest negative docking energy value. However, there is no data or results to compare with **3j**, and it is unclear what the interaction between the ligand and its receptor is.

- In the comparison of different catalysts presented in Table 6, it was found that phosphoric acid performed the best with a

shorter reaction time and a simpler solvent. Considering the price, it is likely that [Hmim]BF_4 is not cheaper than phosphoric acid. To fully evaluate the green chemistry criteria from an economic standpoint, the [Hmim]BF_4 catalyst must also be reviewed.

- The author's conclusion lacks specific data and is filled with emotional assessments.

- There isn't sufficient evidence to reach such a conclusion.

3. Interpretation: Please rewrite the abstract to accurately reflect the content of the entire article, focusing on the novelty of the results achieved concisely. Moreover, revise the author's writing style to encompass the entire article. Should rewrite your conclusion.

4. Ethics: In my opinion, the design, data presentation, and citation of the study complied with QEIOS's standard ethical principles and were consistent with the journal's editorial policies as stated.

Finally, there are some typos and grammar errors. Please check all text. Some errors are on all the pages and are dominated by articles and tenses.

(Please check the attachment file: QEIOS - Synthesis of 1, 2-Disubstituted Benzimidazoles at Ambient Temperature (fixed spelling errors))