Review of: "A Novel One-Pot Three-Component Approach to Orthoaminocarbonitrile Tetrahydronaphthalenes Using Triethylamine (Et_3N) as a Highly Efficient and Homogeneous Catalyst Under Mild Conditions and Investigating Its Anti-cancer Properties Through Molecular Docking Studies and Calculations"

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Potential competing interests: No potential competing interests to declare.

Review manuscript ID #: Qeios URQ6FQ entitled: “A Novel One-Pot Three-Component Approach to Orthoaminocarbonitrile Tetrahydronaphthalenes Using Triethylamine (Et_3N) as a Highly Efficient and Homogeneous Catalyst Under Mild Conditions and Investigating Its Anti-cancer Properties Through Molecular Docking Studies and Calculations". Authors reported an environmentally benign method for the synthesis of ortho-aminocarbonitrile tetrahydronaphthalene derivatives by multicomponent reactions of benzaldehydes, cyclohexanone, and malononitrile. The anti-cancer properties of these compounds were studied only by computational chemistry methods.

The actual form of the work does not significantly advance the understanding or development in this field. The manuscript does not meet the required standards. It is poor as far as chemistry or anticancer prediction and, therefore, should be rejected.

More specific comments:

- The title is too long and should be made more concise. I suggest: “A Novel One-Pot Three-Component Approach to Orthoaminocarbonitrile Tetrahydronaphthalenes and Investigation of their Anti-cancer Properties Through Molecular Docking Studies." The title conveniently represents the actual study, although spelling and chemical formula mistakes have been noticed: Et_3N should be corrected to Et_3N (3 should be written as a subscript). Please remove the underscore from the chemical formula of the amine. Further, “its” should be corrected to “their.”
- In general, the idea of this research lacks novelty: The article is based on the report of well-known reactions while investigating the effect of changing the reaction conditions. It is very similar to a previous manuscript already submitted by the authors as far as the methodology is concerned. In addition, the docking investigational study is still poor and elementary and should be supported by work conducted on a plausible biological target, as several mechanisms could be involved in activity. It requires major modification to solidify the design as anticancer agents that should be interpreted into activity. The major part of the manuscript is based on theoretical studies that should be backed with biological testing. Derivatives have been previously synthesized, and I wonder if they were tested for such properties.

The manuscript requires extensive discussion to reach reasonable conclusions about the anti-cancer properties.

- English language should be checked all over the manuscript and corrected. There are language, typographical, spelling, and grammatical mistakes.
- On the other hand, the manuscript contains information that can be omitted without affecting the normal sequence of the work.
- Introduction section should be more concise, avoiding unnecessary information and details, and should be revised properly. Many chemistry pieces of information are elementary and should not be mentioned.
- For all synthesized compounds, IUPAC nomenclatures should be cited.
- Synthesized compounds have been characterized and compared with previous references. ^{1}H NMR data were provided for the synthesized compounds, but values should be assigned to the particular protons.
- Again, as reported in their previous paper, authors committed a mistake in reporting the Lipinski rule of 5, which has been wrongly cited as Lee Pinsky. The rule of 5 is a fact and should be explained to a minimum.
- The legends of tables 3 and 4 also wrongly describe the content of the tables, except for the dock scores and docking energies. The tables are representing ADME properties of synthesized molecules.
- Docking scores are reported but lack units (Kcal/mol), while RMSD energy scores values are not reported at all. They should be added.
- In the docking section, please report the method for ligand preparation as well as the docking protocol. The reader should understand the protocol of the docking study that should be reproducible.
- Provide more details on the specific amino acids and binding pockets targeted in the molecular docking studies.
- The authors should mention the distance criteria that determine the H-bond and hydrophobic interactions, since the hydrogen bonding distance ensures the adequacy of optimum hydrogen bonding.