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.

Dear Editor,

The article 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’’ seems interesting for people working in the field. The authors investigated the effect of triethylamine as an effective catalyst for the synthesis of a wide range of structurally diverse orthoaminocarbonitrile tetrahydronaphthalenes via a three-component one-pot reaction; additionally, the anti-cancer properties of these compounds were investigated through molecular docking calculations. However, there are some concerns:

The title is too long, and it should be shortened.

The abstract is written in very general terms. There should be more discussion of results and statistical evaluation information.

It states that ‘’All the synthesized compounds bind to an agonist at the active site of the 3A8P protein, which leads to the inactivation of this protein’’. However, 3A8P is a guanine nucleotide-exchange factor that possesses the PH-CC-Ex region that mediates binding to plasma membranes and signaling proteins in the activation of Rac GTPases. If this protein is inactivated, signal transduction cannot be passed into the cell, and it does not exhibit anticancer activity. So, this part should be reinterpreted. I think instead of developing generalities on cancer, you should develop the 3A8P protein (implications, inhibitors, etc.) and then make a link with tetrahydronaphthalenes.

The introduction is written in very general terms. The literature information was very unnecessary. They should focus more on orthoaminocarbonitrile tetrahydronaphthalenes and their anticancer mechanism.

Although the method is well-written, it is incomplete. The authors need to explain the nomenclature of the compounds.

The experimental section is far inadequate and should be completed. At the top of page 5, it should be cyclohexanone, not cyclohexanon. If some of them are novel, MS should be used to prove their structure; if they are known, references to spectral data should be given. The IR spectrum of the synthesized compound should be added. They need to describe clearly the docking protocol, including software versions, and a detailed analysis of ligand-protein interactions.

For the molecular docking study, the results are not clear. Your figures show all the interactions such as H-bonds, pi stacking, etc., and I'm not sure you determined your compound's interactions. All figures must have a white background.

I think cell permeability can be determined using different methods. For example, flow cytometry (with the Annexin V method) and confocal fluorescence microscopy (with a fluorescent dye) methods can be suitable for determining cell permeability.

The discussion is very poor. They should discuss more about the results of docking targeting anticancer activity. The references are old; new ones should be added.

The text is well-written; however, a few typographical and grammatical errors should be corrected. For example, on page 3, 4th paragraph, line 10, 'recent years' not 'these years'; page 4, third paragraph, 'received' not 'prepared'; page 3, line 2, 'ideal' not 'idea,' etc.

Best Regards,