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 authors,

This new synthesis is great, as it is very ecofriendly, but nevertheless, I'm afraid that it still lacks novelty at this stage. The products described in the experimental section were recently reported in Appl Organomet Chem. 2024;38:e7305. https://doi.org/10.1002/aoc.7305, as well as the mechanism of the catalytic reaction. Your examples are very similar to the reported ones, with longer times and almost the same yields (or sometimes lower). The advantage of the reaction is the conditions, using easily affordable compounds (not necessary to prepare a catalyst) and the workup (only filtration). NEt_3 has already been used as a catalyst in this kind of reaction (or just as a catalyst)? If yes, cite examples. Have you tried to extend the scope either by using a substituted cyclohexanone or a ketone instead of the aldehyde??

Be careful with the description of your compounds in the experimental section: don't forget to give the nomenclature of each compound, and check the multiplicity of your protons (compound 4a, 5.73 ppm should be a triplet as it is the ethylenic proton with two neighbors; and I don't think that J could be 16 Hz on an aromatic compound.

You could add the numbering to the final product to help the reader (tetrahydronaphthalene numbering linked to the nomenclature).

Scheme table 2, add the number of each compound. For table 1, remove R on the 4 as you only use H, and under each compound, add the numbering too.

In the introduction, MCR is commonly used in green chemistry for its atom economy, fewer purification steps (and less waste), and is more and more used (cite number of MCR publications these last years).

I wouldn't develop a part on heterocyclic chemistry in this article because, for me, tetrahydronaphthalenes are not heterocycles (no heteroatom) but carbocyclic bicyclic compounds. However, it would be interesting to develop these kinds

of compounds: their uses (draw the structures with the motifs, whether it be in medicinal chemistry or other uses), cite the different methods to prepare them, and if the chiral centers can be controlled (and cite examples of compounds).

Instead of developing generalities on cancer, you should develop the 3A8P protein (implications, inhibitors…) and then make a link with tetrahydronaphthalenes.

Could you test some molecules on the 3A8P (or cells surexpressing it) to confirm the theory?

For the molecular docking study, I think you should mention which software you used. Add the reference for Lipinsky. Usually, the octanol/water ratio is expressed as logP, which must be less than 5.

Cell permeability and PHOA were determined using molecular docking or another tool?

You could define the sections of Table 4 (potential energy, RMS…) and cite how they were obtained.

In your figure, show all the interactions (H-bonds, pi stacking, etc.) and be careful with the stereochemistry (I'm not sure you determined an ee for your compounds). Is it the same result with another stereochemistry (or racemic)? In the legend, mention A38P (it's this one and so specific interactions). Do you know a reference inhibitor to compare with and show that your compounds are good? Is it possible to introduce new substituents to allow other bonds and increase their affinity?

The part "comparison of catalyst" should be just after the NEt3 conditions (before the scope) and highlight that you have only to filtrate the precipitate to get the expected compound.