

Review of: "A Novel One-Pot Three-Component Approach to Orthoaminocarbonitrile Tetrahydronaphthalenes Using Triethylamine (Et₃N) 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.

The authors claim easy and fast access to highly substituted tetrahydro-naphthalenes. The scope of the reaction was tested with different benzaldehyde substrates and shown to be fairly generally applicable in the variation of the nature of substituents on the benzaldehyde. The reaction has a remarkably easy workup with high yields.

The reaction products were investigated *in silico* for their usefulness as antagonists for 3A8P protein, Tiam1, and Tiam2 (Tiam1/2), which are guanine nucleotide-exchange factors that possess the PH-CC-Ex (pleckstrin homology, coiled coil, and extra) region that mediates binding to plasma membranes and signaling proteins in the activation of Rac GTPases. The authors claim potential hits to manipulate Tiam.

The paper is written in understandable English. However, no supplementary data was given, so the evaluation of the purity of the compounds made is impossible to judge, particularly given the very simple workup and the high yields.

P1: "Environmentally friendly method": please indicate why this method is particularly green (e.g., add PMI or other green chemistry KPIs) and compare to existing methods.

P1: No indication was given of the significance of the target 3A8P for this study.

P2: Goals of green chemistry: please cite Anastas, Paul T.; Warner, John C. (1998). Green chemistry: theory and practice. Oxford [England]; New York: Oxford University Press. ISBN 9780198502340.

P2: "and simple work methods": not necessarily

P3: "The type and size of the heterocyclic compounds, together with the substituted groups on them, can affect the physicochemical properties of the medicinal compound." Is redundant and should be taken out once.

P3: "Tetrahydronaphthalene is a heterocyclic compound": wrong statement

P3: "Important pharmacophore in medicinal chemistry": it is of minor importance

P5: "3 mL of ethanol": 30:1 is highly diluted and not along green chemistry principles

P8: The mechanism does not explain why predominantly mixed condensation products were found, e.g., the benzaldehyde-benzaldehyde or the cyclohexane-cyclohexane adduct.

P9: Lipinski, please cite

P9: Lipinski's rules are rules, not laws

P11: Picture is unclear. What are the spatial distances between the atoms? AA are depicted as spheres only

P12: "Leads to the inactivation of this protein and produces beneficial effects during cancer treatment": there is no deeper argument than the fit *in silico* to make this statement. Unsupported.

Citations 25, 26, 42, and 43: why is this cited as a,b,c, etc., although only one reference is given?