Review of: "Design and Molecular Screening of Various Compounds by Molecular Docking as BACE-1 Inhibitors"

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Potential competing interests: No potential competing interests to declare.

1. The article shows good use of in-silico techniques.
2. In your abstract and Aim and Objective section, you have mentioned donepezil, which is an acetylcholinesterase inhibitor. Why did you take this specific inhibitor as a standard drug for BACE-1 inhibition screening? While there are drugs with known inhibition activity against the BACE-1 enzyme, why not take one of them as a standard?
3. Both Figure 1 and 2 have been taken from other published articles without citing them. Have you obtained permission from the authors before using those figures in your article? http://www.cell-stress.com/researcharticles/alzheimers-disease-amyloid-based-pathogenesis-and-potential-therapies/ and https://www.semanticscholar.org/paper/Dropping-the-BACE%3A-beta-secretase-(BACE1)-as-an-Read-Suphioglu/25e141cf2f66f00a793608a420c97948306fbd3c/figure/0
4. In Figure 17B, it is claimed in the text that the compound forms interactions with Asp32 and Asp228. However, Figure 17B shows no evidence of any type of interaction. Moreover, the compound is showing some unfavorable interactions with the protein which may cause a steric shift in the orientation of the molecule. This issue has not been addressed in the manuscript.
5. A large section of the manuscript is concerning donepezil, which is a known acetylcholinesterase inhibitor and is currently in use for the treatment of dementia due to AD. You are comparing the results of a known ACh inhibitor with BACE-1 activity. How would you justify the in-vivo activity of the compound?
6. Proper references are not given on many instances. Moreover, on many occasions, no reference is given. For example, “The neuroprotective effect of baicalein may be due to the increase in the number of dopaminergic neurons and is caused by anti-apoptotic mechanisms of baicalein,” no proper reference is given here. The reference article you cited is “Synthesis of some new 5-substituted-2-((6-chloro-3,4-methylenedioxyphenyl)methylthio)-1,3,4-oxadiazole derivatives as suitable antibacterial inhibitors,” which does not explain the antioxidant and anti-apoptotic effects of the compound. The manuscript is littered with these examples where no proper reference is given.
7. For potent inhibition of the BACE-1 enzyme, at least one of the amino residues of the catalytic dyad needs to make significant interactions (preferably hydrogen bond or ionic interactions) with the ligand. However, in this manuscript, none of the ligands is showing any interaction with the most important amino acid residues of the active site. The most important amino acid residues of the catalytic site are ASP32, ASP228, PHE108, TRP76, TYR71, ILE118, ILE126, and ARG235, and only one ligand in your manuscript showed some interaction with a few of them, which is not addressed in the discussion and conclusion section.

8. In the results and discussion section, there are hardly any references to support your findings. Some of the original data you took from other sources do not have any reference. Moreover, the whole section has only one reference.
9. There are many instances where a ligand is showing an unfavorable interaction with the key amino acid residues. This is not addressed in the manuscript on how it may affect the overall stability of the docked complex.
10. The manuscript claims the failure of **Lanabecestat, Atabecestat, Verubecestat, Elenbacestat, and Umibecestat. However, no reference was provided for such claims.**
11. Molecular docking alone is not sufficient to support the bold claims of the manuscript. The authors need to conduct extensive MD simulation studies and extensive in-silico ADMET profiling to support the claims of the manuscript.