Comments

The present manuscript screen the possible inhibitors of mushroom tyrosinase. The manuscript is well written and the findings are interesting. Therefore, article can be consider for publication after revision.

- The manuscript title "Identification of new tyrosinase inhibitors with shape-based virtual screening" is just emphasize on *in-silico* based study, whereas authors also performed *in-vitro* experiments. Therefore, manuscript title must be rephrased. Moreover, add few studies such as (Eur. J. Med. Chem. 141: 273-281; DOI: 10.1007/s12539-016-0171-x; Comput Biol Chem. 2017 Jun; 68:131-142; Chem Biodivers. 2017 Sep;14(9); Drug Des Devel Ther, 2017, 11:2029-2046; Bioorg Chem, 2017, 74:187-196) in introduction part.
- Authors used Neorauflavane as a template, is it possible to use Kojic acid and Arbutine as a template for screening as you used in *in-vitro* experiment as a positive control.
- Author did not discuss about size of protein structure, domain and binding pocket. I would suggest to make one graphical image of all inhibitors or your potent inhibitor against tyrosinase to show binding pocket and ligand conformation.
- Authors did not discuss how many conformations he selected in docking experiments and on what basis he selected best pose of among all either just energy value or binding interaction pattern. In docking figure authors did not mentioned the binding distances of interactions. Moreover, authors claims "One hydroxyl established a hydrogen bond with the side chain of Asn260, while the other hydroxyl interacted with the copper ion" in docking results. However, it's not clear from graphics either it is hydrogen bond or some other type of interaction. In discovery studio mostly the hydrogen bonds are represented by green dotted lines. Moreover, authors did not mentioned docking energy value for 5186-0429 in the results part.
- Moreover, I would suggest (if possible) to run MD simulation using any software to check the stability of target protein.
- For *in-vitro* analysis Table 1, Authors only mentioned IC_{50} value for 5186-0429, however, it's better to calculate IC_{50} values for all other compounds in μM. It would help in comparison amongst all screened compounds with control.

- In MM section, authors mentioned “Vmax and Km values (for Michaelis-Menten kinetics) were obtained with Graph Pad Prism 5.0 from the nonlinear regression of substrate-velocity curves”. However we could not found Vmax and Km values in manuscript file. Moreover, also provide K*i* value *(Ki is the EI dissociation constant).*
- Authors used two substrate (L-Tyro and L-Dopa) for inhibition purpose as mentioned in MM section, while in kinetic study only L-Dopa was used to generate Lineweaver-Burk plots. Therefore, I would suggest to use both substrates and make separate graphs for both substrate.
- Furthermore, I would suggest (if possible) to use Zebrafish model for melanin quantification along with toxicity assay for your most active compound.