Life Sciences 225 (2019) 133

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

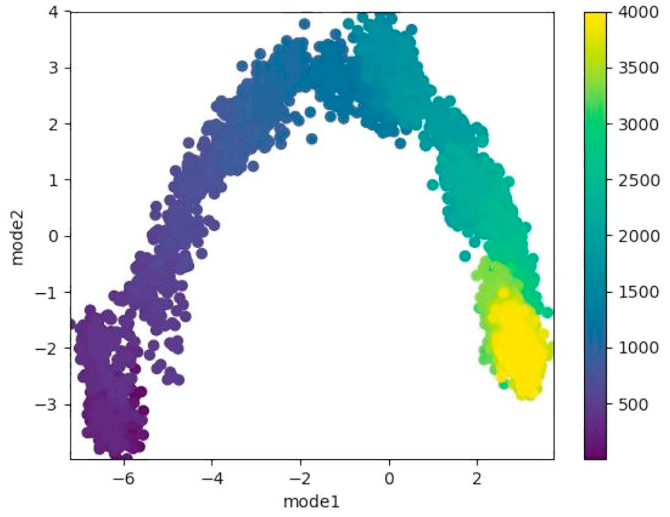
Response to the Questions on Triazoles Binding SMO☆

Dear Prof Wold,

We do appreciate Dr. Kozielewicz's comment which will improve our work.

First, in order to clarify it, we agree to use the names those are more commonly accepted by the people in this field (CRD for cysteine-rich domain and TMD for transmembrane domain).

Second, our goal for this research is to investigate whether or not the ITZ and its analogues can bind on the extracellular region CRD. Thus, it is reasonable propose that the neither the lipid bilayer nor BRIL part are critical to the ligand binding. In order to prove our thought, we did another MD simulation that without the BRIL domain and considering the missing part in SMO. It turns out that the binding free energy between SMO and ITZ is **38.6** kcal/mol, which is very close to our publish data. Plus, we did analyze the whole motion of the protein, and motion of the TMD domain (dPCA result is shown below) has a similar behavior as the one in Fig. 3(b).



The dPCA result of ITZ-SMO transmembrane domain (TMD, which is NTD in the publish data). It is also reasonable to consider the influence of the membrane to the motion of SMO. However, due to the cost of the calculation and the goal of this research, we did not consider the membrane. The computation work is supported by NSFC China (No. 81501726) and Jiangsu NSF (BK20150069).

Best regards,
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☆ Triazoles bind the C-terminal domain of SMO: Illustration by docking and 9 molecular dynamics simulations the binding between SMO and triazoles.

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https://doi.org/10.1016/j.lfs.2019.03.076

Available online 02 April 2019