

## Comment on mr-2021-20

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Community comment on "Small-molecule inhibitors of the PDZ domain of Dishevelled proteins interrupt Wnt signalling" by Nestor Kamdem et al., Magn. Reson. Discuss., <https://doi.org/10.5194/mr-2021-20-CC1>, 2021

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The Dishevelled is an important biological target. In this manuscript, the authors report several novel small molecule inhibitors of the Dishevelled PDZ domain. This study expands the toolbox available to the scientific community to dissect the structure and function of Dishevelled. Those small molecules also have the potential to be further developed as a therapeutic reagent. Therefore, I would be interested in reading the manuscript as a published paper.

However, based on an ITC study, the authors state that "Surprisingly, CBC-322338/3289-8625 showed very low affinity, with a  $K_d$  above 400  $\mu\text{M}$  (assumed to be the threshold for our ITC assay), which was larger than the originally reported value (10.6  $\pm$  1.7) (Grandy 2009)". Compound 3289-8625 was discovered in my laboratory back in 2009. It is not appropriate for the authors to make such a statement without further verification because it is well documented and well understood that not every protein-ligand interaction could be detected and measured by ITC. Our study used a competition binding assay to determine the binding affinity of the compound to the PDZ domain. If the authors wish to dispute our result, they should repeat our study or explain why they think the method we used is incorrect.

The authors also cite a paper by Hori et al. saying the value they obtained is "closer to the value found by Hori et al. (Hori 2018) (954  $\pm$  403  $\mu\text{M}$ )". It is misleading. In the paper by Hori et al., compound 3289-8625 was used as the positive control. Also, it is well known that, in general, binding affinity measured by chemical shift perturbation is different from the value measured by other methods. If that was not known by the authors before, they should know by now. It is interesting to notice that, in the manuscript, the authors report the binding affinities measured by only NMR or ITC, but not both. They should report both values even the data do not agree with each other. Back to the compound 3289-8625, I imagine that the authors must have the compound's binding affinity data to the Dishevelled 1 PDZ domain and Dishevelled 3 PDZ domain, respectively, measured by NMR. If they do, they should report the data. If they don't, I would like to see why they did not conduct the study.