

Magn. Reson. Discuss., author comment AC4
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Reply on RC2

Nestor Kamdem et al.

Author 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-AC4>, 2021

Introduction: Perhaps the authors can rearrange some paragraphs to simplify the background description for the non-specialist reader. It could start with the description of Dishevelled proteins (line 56) and their modular composition (please cite some references describing the DIX and the DEP domain structures). Then, it can describe the PDZ structures, their binding properties and why they became targets for drug design to treat several diseases. The authors could also mention a couple of recent reviews describing the advances in the design of peptides and small molecule modulators of PDZ domains and the logic behind this new work.

We change the introduction as requested and include more literature regarding the design of PDZ domain inhibitors, including peptidomimetics, in particular by including a very nice review from the Strømgaard group. We discuss the scope of our work more explicitly in light of the existing data.

Results: The definition of the PDZ binding site is shown as Figure S8. The authors could consider moving this figure to the main figures (New Figure 1 panel A) and label the red and blue spheres with Dishevelled residues. Having this representation next to the complexes will facilitate the description of the binding cavity in the structures (New Figure 1 remaining panels).

Regarding the result section, we will change Figure 1 as requested by transferring the back bone cartoon shown in Figure S8 into Figure 1A, citing it in the virtual screening and NMR section.

Data presentation: The authors should include an overlay of the corresponding data points (as dot plots) in Figure 2 (Bar charts), Figure S4 and Figure S5, and please, add the n number and define the error bars (e.g. SD, SEM) in the figure legends.

We improve the data representation by including of course the definition of the error bars in the figure legends of the various plots and the n numbers. Since the other two referees were ok with the presentation of the data, suggesting even that the paper is actually quite well written, we do not plan so far to change the bar charts in Fig. 2. We think they represent the data quite clearly.

Figure S1: Please use monospaced fonts to ensure that the sequences are aligned.

Figure S1 will of course be changed to monospaced fonts (courier, as it was before), and checked before submission whether the format is kept.

Equation1 Please correct this equation.

Of course, we will correct equation 1.