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Magn. Reson. Discuss., referee comment RC2
https://doi.org/10.5194/mr-2021-20-RC2, 2021

Comment on mr-2021-20

Anonymous Referee #2

Referee 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-RC2, 2021

Small-molecule inhibitors of the PDZ domain of Dishevelled proteins interrupt Wnt signalling, by Kamdem et al.

The manuscript describes the identification of new small molecule inhibitors of Wnt signalling targeted to Dishevelled proteins and specifically to its PDZ domain. These inhibitors have been optimized using a multistep strategy that combines virtual screening and Structure-aided binding selection including hit validation by NMR titrations and an exhaustive characterization of the interactions using X-ray crystallography. A second generation of sulfonamides compounds was synthesized to expand the molecular diversity and complexes were crystallized to unveil the similarities and differences of the interactions. The authors have also determined the affinities of the best compounds by ITC and performed cell viability assays to measure the cytotoxic effects.

Overall, this is a solid multidisciplinary work that represents a valuable contribution to the complex field of hit to lead optimization. The results are well described, the experiments are documented in detail and the conclusions are supported by the data.

I have only minor recommendations:

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.

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).

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.

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

Equation1 Please correct this equation.