Reviewer's report

Title: Characterization of ERK Docking Domain Inhibitors that Induce Apoptosis by Targeting Rsk-1 and Caspase-9

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Reviewer: eric chevet

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Major Compulsory Revisions

1) Show data not shown in the present manuscript. In particular fluorescence quenching assays that compare parent molecules to the new compounds.

2) Show cell growth inhibition data in other cancer cell lines.

3) In Figure 3A and B, the legend of the blots is not clearly spelled out in the figure legend. In addition it appears that some compounds (>76.5) decrease endogenous PARP cleavage. How many repeats of the experiments were performed. Quantitation should be carried out.

4) Another apoptosis assay should be performed, for instance AnnexinV/PI staining should be carried out at least for the compounds showing enhancement of PARP cleavage.

5) The poor annotation of the figures should be corrected (for instance the authors should indicate what C, -, and U stand for).

6) In Figure 4, normalization of ERK levels should be performed using ERK antibodies. In addition Figure 4B is not clear at all. A single bar graph should be provided with the dose response for each compound and statistical analysis performed.

7) Figure 5, statistics should be shown

8) Figure 6, same comment as in Figure 4B

9) What is the relevance of Figure 7. The impact of the compounds tested on Rsk and Bad phosphorylation is certainly coherent with enhanced apoptosis and reduced proliferation. In contrast the impact on the ERK5 and Akt pathways just demonstrates the relative specificity of the compounds without bringing any mechanistic insight.

10) The authors propose that the compounds may alter ERK interaction with some of its partners and consequently modify downstream signaling events towards apoptosis which should be clearly demonstrated. Recently, a report in Nature Methods has described the ERK interactome, the authors could certainly use these data to provide an identity map for each compound towards ERK (at least) and then map the downstream events which can result in the induction of apoptosis. It is also important to note that the relevance to cancer is weak in the current version of the manuscript and should consequently be addressed in a
revised version.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interest