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: Nathalie Lamarche-Vane

Reviewer’s report:

In this paper, Boston et al. identified novel test compounds that are improved compared to the parent one, called 76. They found that test compounds 76.2, 3, and 4 inhibited proliferation and induced apoptosis in Hela cells. These effects appeared to be through caspase-9 activation and a decrease in Bad phosphorylation. Furthermore, the test compound 76.3 was more potent to inhibit RSK and caspase-9 phosphorylation.

Overall, they identified new specific ERK inhibitors that can inhibit cell proliferation and induce apoptosis in Hela cells through the inhibition of ERK-mediated phosphorylation substrates and pro-apoptotic proteins. This is an interesting study; the data are convincing and well performed with the appropriate controls. However, in some places, statistical data are missing to support the conclusions.

Major compulsory revisions:

1) In fig. 3A, it is mentioned that the PARP cleavage was inhibited with the caspase inhibitor Z-VAD-FMK as data not shown. These data should be presented in the figure.

2) In fig. 4A, the total ERK blot should be shown. In addition, if there is a decrease in ERK phosphorylation by compound 76.2, it does not seem statistically different on the graph and it is not convincing on the blot. This should be clarified.

3) The blots in fig. 4C are not very convincing and do not reflect the graph, in particular for pS136. The authors should show a better blot, and include total Bad in the western blots. In fig 4B, is it really 2-10uM tested?

4) There is no statistics in fig. 5. It should be included. For example, the 2-fold increase in Bad expression with compound 76 (shown in the graph) is not convincing in the blot.

5) The conclusion that compound 76.4 is more potent (see fig 4B and 6B) should be revised. It is clear that 76.3 is the more potent compound but 76.4 seems to behave like 76.2.

6) In general, figure legends are not always well detailed. For example, C and U are not represented in some figure legends.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests