Review of: "Flavocillin: a potent TrxR and OATP inhibitor"

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Potential competing interests: No potential competing interests to declare.

The manuscript describes Flavocillin as a potential TrxR and OTAPs inhibitor. The topic is relevant, yet a major review is needed.

The structure of the manuscript needs to be improved, for now there is no transparent workflow; the authors mix methods, results and conclusions. The introduction fails to inform readers about the aim of the work, the authors mention there are differences in sequences of TrxR and GrxR in the human and bacteria, yet they do not elaborate if those are relevant in general or even in this manuscript. Predicted properties appear in the conclusions.

Some obtained results are not discussed or are irrelevant to the topic the authors discuss (example: predicted carcinogenicity, fish aquatic toxicity), some are mentioned at least twice in different place (Lipinski rules), some appear without any introduction of their importance in beta-lactam based drug development (oral bioavailability, HI absorption), some results seem like the authors were trying to write a review, not to describe their own experiment.

The text does mention Protox II and SEA obtained results, which are used and also visible in the figure, yet there is no citation nor method description, no citation for Uppsala University results, no citation to some *in vitro* results. Other *in vitro* cited results, if cited, miss the unit (MIC), the comparison of obtained results lacks numbers.

No explanation for EN 1522 and 1537 that appear in the text or why those are relevant to the discussed properties (EN 1522, google results give me only European standard for bullet resistance of for example windows).

Results of in *silico* work are poorly described. I believe it would not be possible to reproduce this experiment by the readers (missing conditions of the in *silico* environment, missing PDB code of used structure into which the authors docked compound, were the compound and the structure prepared somehow before it was docked?). The obtained results are described in a chaotic and superficial way, the authors mention ‘high affinity of -10.1’ but do not mention any other ligand to which it could be compared in order to say that the affinity is improved (the result itself does not give us any new relevant information about the interaction with the target). The work lacks 2D interaction scheme which, I believe, is the most important to address to the readers the matter of the docking performed. Based on such scheme it would be possible to describe interactions between the molecule and the target (the authors mention ammonium salt affinity is higher than the free acid form, and since we don’t know the type of the interaction then this means nothing. If the interaction is ionic then it is true, yet doesn’t bring anything new, since it is common).

Figures are presented poorly. Besides being print screens (I can see your Windows not being activated, which I should

not) they are mentioned in the text but placed at the bottom of the manuscript, which makes it more difficult to read, they also consist of data that are not discussed later in the text. The authors could also work on citations to be uniform.