Date: 7th October 16 05:02:10
Last Sent: 7th October 16 05:02:10
Triggered By: Redacted
BCC: Redacted
Subject: Scientific Reports: Decision letter for SREP-16-33069
Message: ** Please ensure you delete the link to your author homepage in this e-mail if you wish to forward it to your coauthors **

Dear Prof Wahab,

Your manuscript entitled "Potential New H1N1 Neuraminidase Inhibitors from Ferulic Acid and Vanillin: Molecular Modelling, Synthesis and in Vitro Assay" has now been reviewed and the reviewer comments are appended below. You will see that, while they find your work of interest, they have raised points that need to be addressed by a major revision.

We therefore invite you to revise and resubmit your manuscript, taking into account the points raised. At the same time, we ask that you ensure your manuscript complies with our format requirements explained in full at http://www.nature.com/srep/authors/submit.html.

Please use the following link to submit a revised paper and a point-by-point response to the referees:
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** This url links to your confidential homepage and associated information about manuscripts you may have submitted or be reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage first **

We hope to receive your revised paper within four weeks. If you cannot send it within this time, please let us know so that we can close your file. In this event, we will still be happy to reconsider your paper at a later date as long as you haven’t submitted similar or related work elsewhere in the meantime.

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We look forward to hearing from you soon.

Best regards,

Cheryl Ingram-Smith
Editorial Board Member
Scientific Reports

Reviewer comments:

Reviewer #1 (Technical Comments to the Author):

There is unfortunately an apparent disconnection between the enzymatic activities/neuraminidase (moderate, high micromolar) and the antiviral activities in the antiviral assay (low micro/sub micro values). The authors should try to ascertain what is the MoA of the compounds, as probably it won't be related to Neuraminidase inhibition.

Other than that, the article is well written, and the reported structures would be of interest for the scientific community.

Reviewer #1 (Remarks to the Author):

There is unfortunately an apparent disconnection between the enzymatic activities/neuraminidase (moderate, high micromolar) and the antiviral activities in the antiviral assay (low micro/sub micro values). The authors should try to ascertain what is the MoA of the compounds, as probably it won't be related to Neuraminidase inhibition; as such, the conclusions are too generic/unspecific.

Reviewer #2 (Remarks to the Author):

Comments and questions to authors
In this work, neuraminidase inhibitors have been designed and tested against influenza virus subtype H1N1 using in silico and in vitro techniques. The authors found that some ferulic acid (FA) and vanillin (VN) derivatives might possibly use as guideline and/or starting template for further drug development. This manuscript could be published after revision according to the comments and suggestion as follow;
1. In introduction part, authors described about interesting scaffold of FA and its planar aromatic. I was wondering about ‘this favorable entropy generally increase ligand-receptor binding affinity….’. Please clarify this sentence for general readers.
2. Protein preparation for molecular docking and description how to calculate the binding free energy calculation should be added.
3. The design of FA derivatives is based on the structure of commercial drugs OTV, ZNV, etc. (Results of molecular modelling part). Please clarify this point for general readers, this part is quite hard to follow.
4. As the authors determine the IC50 value of each compound, have the authors approximated the binding free energy from this value? And is it in consistent with that obtained from molecular docking? The calculated and experimental binding free energies should be compared and discussed.
5. As a result of NA-VN docking, it showed that VN bound outside the active site, thus it would be better if the authors could deeply examine the source of this

phenomenon. Since VN molecule is quite small, it would easily embedded in the NA active site. In addition, why the binding free energy values of OTV and ZNR in pages 6 and 8 are different?
6. As Page 7 (lines 10-12), the authors mentioned that the hydrogen bonds have been formed to stabilize MY7 and MY8 in Fig. 4. Both ligands also formed hydrogen bond with E277 (as the authors mentioned); however it seems quite far from the side chain of the ligands. These contexts are contrast to themselves. Besides, all designed inhibitors lose interaction with R292, one of important residues for drug binding.
7. Chemical structures in Fig. 2 should be presented in the active form. The assignment of protonation state is very important. As some derivatives (e.g. MY7, MY8, etc.) contained the guanidinium group, same as that of ZNR (Fig. 3), however their protonation states are different as shown in Fig. 4. This must be carefully checked and corrected.
8. In page 8, you refer to entropy 'This might be due to increased in the entropy as MY6…'. Since this work does not calculate the entropy change, it should avoid this keyword.
9. Conclusion then should be added.
10. Language and content must be checked and corrected before publication.

Editorial Board Member comments:

Although problems were noted, the reviews are overall favorable. Please read and address the reviewers' comments carefully, and indicate how each comment was addressed in a point-by-point response.