REVIEWER 1

The authors of the manuscript "Synthesis, biological evaluation and docking studies of chalcone and flavone analogs as antioxidants and acetylcholinesterase inhibitors" described the synthesis and biological evaluation of series of chalcone and flavone derivatives. The manuscript was really well written. Length of the paper is acceptable and data were excellent presented in tables and figures. Although some minor corrections must be included.

1) The authors must enhanced the discussion in the synthetic part as well as in the biological part.

R: In response to the petition made by the reviewer, it was decided to add in section 3.1 information concerning the yields obtained for the synthesized compounds and the pros of the employed methodologies, resulting as it follows:

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<td>The substituted 2-hydroxychalcones 2a-2k were prepared by the Claisen-Schmidt condensation of the respective substituted benzaldehyde 1a-1k (1 eq) and 2-hydroxyacetophenone (1 eq) in presence of NaOH in ethanol/water at room temperature by the known literature method (Scheme 1) [35]. The oxidative cyclization of 2-hydroxychalcones 2a-2k to flavones 3a-3k was performed using the classical iodine (1 mmol) in DMSO (Scheme 1) system [36].</td>
<td>Chalcones are usually synthesized by condensation reactions with acid or basic catalysis, even though recently there has been appearing a great number of new procedures for the synthesis of these molecules due to the great interest on their biological properties. Claisen-Schmidt reaction with basic conditions is the most widely synthesis reported in the literature, because of the easily process and efficiency in the product formation [35]. The substituted 2-hydroxychalcones 2a-2k were prepared by the Claisen-Schmidt condensation of the respective substituted benzaldehyde 1a-1k (1 eq) and 2-hydroxyacetophenone (1 eq) in presence of NaOH in ethanol/water at room temperature by the known literature method (Scheme 1) [36]. This methodology allowed the obtention of eleven compounds with moderate to high yields, between 40-97%, being the highest one the yield for compound 2h. The oxidative cyclization of 2-hydroxychalcones 2a-2k to flavones 3a-3k was performed using the classical iodine (1 mmol) in DMSO (Scheme 1) system. This method is particularly useful in flavone synthesis starting from 2-hydroxychalcones as it has been observed the iodine does not give secondary reactions despite the high temperature employed [37]. The corresponding flavones were successfully synthesized with yields between 40-85%.</td>
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2) In the same sense, there are several times that some of the compounds i.e. 2a, 3a, 3b.. etc, had been evaluated as antioxidants/acetylcholinesterase inhibitors

Searching for the mentioned articles by the reviewer, one of them (Tavares et al.) also analyzes inhibition of AChE and antioxidant activity, but the evaluation is from extracts of plants from Portugal. We consider we cannot compare the results from this article to the ones we got, because in one hand we are dealing with plant extracts (a combination of several different molecules) and in the other one synthesized organic compounds. In that article, Tavares et al. do mention flavonoids can be responsible for such biological activities, but being this not isolated while being evaluated, comparison with our molecules is not appropriate.

Of the compounds we are reporting, two of them (3e and 3h) have been also synthesized and evaluated as AChE inhibitors, by Singh et al.; the reported IC50 values differ from our results, having them lower ones which indicate a better activity. As their methodological procedure for the inhibition of AChE have significant differences between the employed in our study, these differences could be expected. Interestingly, they mention as us the importance of methoxyl groups in the flavone B ring to improve the AChE inhibition, and also amongst the better results there are compounds with nitro groups in the same ring. This account that, despite numerical differences, the conclusions withdrawn from the structure requirements for this activity are similar to the ones we got.

As the articles mentioned by the reviewer can not be fully compared with our work, we consider that is not necessary to include them in the Discussion section.


3) If there is a newly synthesized derivative, the authors must highlight.

**R:** Through our literature search, we have not found information regarding the synthesized compounds 2d and 3d; nonetheless we did not mention them in the manuscript as new compounds, as we can not be completely certain of their conditions as new molecules.

4) I missed the NMR data for the compound 3d??

**R:** In response to the question made by the reviewer, due to lack of solubility of the molecule 3d in different deuterated solvents, NMR analysis was not possible, however this was the exception in the whole series of synthesized flavones, as the rest of them were corroborated with 1H and 13C, and even in some cases with bidimensional experiments. This indicates us that the employed methodology for flavone synthesis was successful; in addition to this, precursor chalcone (2d) structure was spectroscopically corroborated, therefore we could expect the cyclization to the corresponding compound 3d to be successful, just as the rest of chalcone to flavone conversion proceeded. Beside that, for compound 3d we have mass spectrometry and infrared spectroscopy, and the results are in accordance to the expected product.