**Review on Dissertation Thesis of**

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# Computational Studies of Interactions of Small Molecules with Their Biological Targets

The main theme of the presented thesis is the usage of quantum chemistry for the molecular docking and prediction of the octanol/water partition coefficients (logP) of small drug-like molecules. Dissertation thesis is written at a good level of English with few typos. The introduction presents drug design, non-covalent interactions and theoretical chemistry, while the thesis focuses on two research topics – the prediction of binding interactions with cyclin-dependent kinase 2 and the prediction of lipophilicity of neuroactive steroids with the use of quantum chemistry methods. The thesis spans over more than 100 pages and it is well-sourced with more than 160 references. The candidate already published 10 impact peer-reviewed papers (1 first author in *ChemPhysChem*) and already collected over 63 citations.

The first topic shows the successful drug design projects describing the use of newly developed QM-based scoring methodology. Furthermore, the author shows the fragmentation analysis able to distinguish the relative importance of individual substitution groups. This type of analysis is sought for by experimentalists as it can in principle lead further synthesis efforts. However, the comparison with several established docking methods (e.g. Vina, or Autodock) of the tested QM-based docking approach and the detailed performance benchmarking of the individual terms in the scoring function is lacking.

The second topics shows several papers with the lipophilicity predictions of neurosteroids linking their activity towards NMDA receptor. Especially the last paper shows interesting trend that higher lipophilicity means also higher activity of the compounds. However, there is no clear explanation of the mechanism of this observed trend, nor whether it is valid for only a limited set of pharmacophores. Moreover, predicted lipophilicity measures were not validated against each other nor against the experiment, but it is worth notice that COSMO-based prediction showed superior performance in the last SAMPL6 logP prediction challenge (Isik M et al, *JCAMD* (2019). doi:10.1007/s10822-019-00271-3).

Despite these few omissions, I **recommend the acceptation** of the submitted thesis as a part of the procedure of awarding the Ph.D. degree as it is pushing the state-of-the-art in the docking studies towards better accuracy. I have several questions on the candidate listed on the following page.

In Olomouc, 28. 2. 2020

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**Questions:**

1. Why the addition of additional terms lowers the correlation of $\Delta G'_{bind}$ to $\Delta G_{exp}$? Which term causes the biggest mismatch? Would $\Delta G_{conf}$ (protein) term be stabilizing or destabilizing the complex?

2. Can you show and comment on the effect of the substitutions at positions a-h on a simple 2D depiction of the proposed inhibitors? Visual description of these positions is missing in the thesis.

3. On several occasions (p.7, p.72) you specify that "The calculated logP was estimated on the basis of the change in the molecular conformation related to the transfer between n-octanol and water". How does logP relate to the conformation?

4. Explain the mechanism behind the correlation between all $\Delta G_{solv}$ and $\Delta G_{exp}$ values presented in the thesis. Why docking was not used to predict $\Delta G_{bind}$ that was correlated with $\Delta G_{exp}$ similarly as in the CDK2 studies?