Improvement of a Molecular Docking Approach and Its Applications Using QXP^+

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Finding the correct binding mode of highly flexible ligands is a demanding approach in molecular docking studies. With this respect, in some earlier efforts, the docking of these sorts of inhibitors of AChE was not successfully accomplished. For instance E2020, BHG and DECA using QXP^+, FlexX, Auto Dock and G.O.L.D, which is even true for their docking into the ligand-bounded protein. Furthermore, even finding the very final possible binding mode of the ligand that forms the most stable complex with the protein was not confidently obtainable. In this presented work, the difficulties of docking studies on very flexible ligands were addressed by improvement of a consensus method that is based on QXP^+ and local Monte Carlo search algorithm to reduce the conformational search space. The method has been developed using BHG and was successfully applied to other AChE ligands including E2020 and DECA. Although, the procedure has been particularly developed for study and prediction of the binding mode of AChE inhibitors, it was successfully employed for docking the very high flexible inhibitors of other proteins like human Rhinovirus 14, Win52084 (1RUH), and Win51711 (1PIV). The method was also employed for the prediction of binding mode of a few CDK2 inhibitors through docking them into the ligand unbounded proteins as well as into their ligand bounded proteins, while the latter was performed to improve the quality of complexation energy and better scoring of the ligand-protein binding mode to estimate the inhibitory constant of them as a result of molecular docking study.

The method was also used for detailed study on the various AChE inhibitors such as:

- The possible protonation state for the ligand in its complexed state with AChE.
- Definition of the amino acids that are dominantly involved in binding the ligand.
- Importance and influence of particular water molecules on the conformational pose of the ligand in the binding site.
- Selection of particular structural posture of the ligand in the case of PPG with two crystallographicaly possible poses of the ligand in its conformationaly convertible piperidine moiety.
- Prediction of the binding mode of a new derivative of galanthamine and elucidation of its structural details in complex state with docking into a non-complexed protein.
- Study on the possibility of leaving the binding site of AChE through an alternative path way based on “Back door” hypothesis that results finding only one pathway as the most possible one, among four suggested back and side doors.