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Theoretical binding efficiencies in bioactive molecular design: a case study on BACE-1 inhibitors

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Background and Aims: Beta site amyloid precursor protein cleaving enzyme-1 (BACE-1) is an important membrane associated protein responsible for formation of amyloid plaques causing alzheimer. Peptidic/non-peptidic inhibitors of this key protease have been developed up to now. Small molecule BACE-1 inhibitors have been considered due to the pharmacokinetic problems of peptidic inhibitors. In this study, small molecule BACE-1 inhibitors were subjected to dissection analysis and constitutional fragments considering atom type, hybridization, and bond order were generated. These simplified structures were assessed in terms of binding to the BACE-1 active site through a validated docking procedure.
Methods: Autodock4.2 program was applied to conduct a docking simulation method. All the preprocessing steps for ligands and receptor were performed by AutoDock Tools and What IF server.
Results: Isophthalamide scaffold was found to be an appropriate scaffold for further bioactive molecular modifications. Other following efficient scaffolds contained arylpiperazine, imidazolidinone, pyrimidinone and benzoimidazole. The ways these findings might be beneficial to guide rational bioactive molecular development strategies were suggested.
Conclusions: Shape-based dissection analysis was applied to dissect BACE-1 inhibiting structures. The classification route was followed by a fragment-based docking strategy to rank the structural features of BACE-1 inhibitors. Our case study confirmed that evaluation of the ligand-receptor interactions on the basis of ligand binding efficiency indices rather than the mere free energy of binding could be a helpful strategy in recognizing potential candidates for further bioactive molecular design. Moreover; various efficiency parameters of simplified BACE-1 inhibiting structures obtained on the basis of docking calculation were in good agreement with each other. Our case study re-consolidated that designing larger structures may require special attention toward efficiency indices incorporating MW rather than number of heavy atoms. This technique leads to more realistic view at the individual atom participations in binding to the receptor.

Keywords: Alzheimer; Dissection analysis; Docking; Binding efficiency