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MEETING ABSTRACTS

ASSESSMENT OF SCORING FUNCTIONS FOR AChE-LIGAND INTERACTIONS

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Computer-aided drug design is based on molecular modelling which includes two steps; molecular docking accompanied by scoring docked poses. Molecular docking fits the right molecular "key" to a known receptor "lock" by optimizing the atomic coordinates of a ligand to adapt its 3D structure in such a way to accommodate the binding into the receptor. The second step is the determination of a good fit between the ligand "key" and receptor "lock" using a function that correctly prioritizes the docked ligand poses and predicts their binding affinities by taking into account molecular interactions between the ligand, protein and solvent.

The 68 crystal structures of complexes between acetylcholinesterase (AChE, EC 3.1.1.7) and its ligands, deposited in PDB, were analysed by scoring the functions: LigScore1, LigScore2, PLP1, PLP2, Jain, PMF and PMF04. The scores derived from scoring functions were correlated with an inhibition constant for each ligand (Ki or IC_{50}) in a broad range 10^{-3} – 10^{-12} M. Scores were also correlated with other computational properties as the number of rotational bonds, number of H-bond donor or acceptor atoms, molecular complexity index and topological polar surface area. The linear correlation between the scores derived from the scoring function and matching pKi data resulted in the highest r value for the PLP2 function, r = 0.77, with 10% of the slope error. The LigScore1 function resulted in the lowest r value of 0.47 with 23% of the slope error. The PLP2 scoring function is a good candidate in drug discovery related to AChE, although with a higher number of crystal structures of AChE complexes and reliable kinetic data, a better scoring function could be developed.

Keywords: AChE; drug discovery; scoring function; inhibition constant