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An insight into binding of oxime-dipeptides at peripheral anionic site as anticholinesterase and reactivator of irreversibly inhibited-ache

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Neuropathological cascades leading to Alzheimer's disease led to development of acetylcholinesterase (AChE) inhibitors due to reduce cholinergic transmission. Hence, in an aim to probe potential ligands which can bind at peripheral anionic site (PAS) of AChE and antidotes against inhibition due to irreversible inhibitors, computationally structure-based approach has been exploited in this work for new pyridoxime-dipeptide analogues. We have combined molecular dynamics simulations with flexible ligand docking approach to determine binding specificity of AChE (PDB entry: 2WHP) towards 2-amino-3-pyridoxime dipeptides. PAS residues are found to be responsible for oxime dipeptides binding along with nearby residues such as Ser293, Tyr337 and Ala204. The docking results depicted complementary multivalent interactions along with good binding affinity (docking score of 12.454). Molecular dynamic study uncovered dynamic behavior of 2-amino-3-pyridoxime-(Arg-Asn) within the active site and exposed its mobile nature and competence to form strong long range order contacts towards active site residues to approach inhibited serine residue and facilitated via hydrogen bonding with water molecules along with slow and large movements of adjacent residues. In an effort to evaluate the complete potential surface profile, 2-amino-3-pyridoxime induced reactivation pathway of sarin-serine adduct has been investigated by the DFT approach at the MO6 / 6-311G (d, p) level along with the Poisson-Boltzmann (PB) solvation model and found to be of relatively low energy barrier.

Biography

Nidhi Chadha is pursuing Ph.D. under the joint supervision in Division of Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences and Department of Chemistry, University of Delhi. She holds an M.Sc in Physical Chemistry and has more than 2 year experience in Computational Science which includes various levels of calculations in the area of drug designing in experimental and theoretical calculations.

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