Molecular docking study on the interaction of LU AF64280 and LU AF33241 with PDE2A

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Abstract: The phosphodiesterase (PDE) family of proteins are important regulators of signal transduction, which they achieve by controlling the secondary messengers cyclic AMP (cAMP) and cyclic GMP (cGMP). cAMP and cGMP are involved in many critical intracellular processes such as gene transcription, kinase activation, signal transduction in learning and memory, and channel function as secondary messengers. The involvement of PDEs in neuronal communication has made them important therapeutic targets.(1) Phosphodiesterase-2A (PDE2A) is a potential therapeutic target for treatment of Alzheimer's disease and pulmonary hypertension. However, most of the current PDE2A inhibitors have moderate selectivity over other PDEs. Phosphodiesterase-2 (PDE2) is a key enzyme catalyzing hydrolysis of both cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) that serve as intracellular second messengers. PDE2 has been recognized as an attractive drug target, and selective inhibitors of PDE2 are expected to be promising candidates for the memory enhancer, antidepressant, and anxiolytic agent.(2)

Using the X-ray crystal structure of PDE2A (from PDB ID: 4C1I), we investigated the binding modes of a range of promising inhibitors based on the known PDE2A 2 inhibitors (LU AF64280 and LU AF33241) to PDE2A.Lu AF64280 represents a novel tool compound for selective PDE2A inhibition that substantiates a critical role of this enzyme in cognitive processes under normal and pathological conditions.(3).The 3D structures were prepared using the Hyperchem software. Water molecules of crystallization were removed from the complex and then the protein structure was prepared for docking: All hydrogens were added and after determining the Kolman united atom charges, nonpolar hydrogens were merged into their corresponding carbons using AutoDock Tools. Inhibitors were docked based on the docking studies using the AutoDock Vina, a protein-compound docking program. The result showed that there is a good agreement between the experimental inhibitory activity and the docking score.

Keywords: Phosphodiesterases 2 A; inhibitors; molecular docking; schizophrenia

References:

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