Abstract No: *ASRS 10*

COMPUTATIONAL STUDY ON HDAC ENZYME INHIBITORS FOR ANTI-CANCER THERAPY

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Histone deacetylases (HDACs) regulate the expression and activity of numerous proteins involved in both cancer initiation and cancer progression**.** In 2006, the US Food and Drug Administration (FDA) approved the use of a histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA, marketed by Merck as Zolinza). Current study implies that selecting the best ligands for further development as drug candidates cannot rely only on docking studies. Combination of docking and molecular dynamic simulations provides best results. Molecular docking was carried out using GROMACS4.5.5 tool to identify HDAC competitive inhibitors to human HDAC1 enzyme and thereby recognize potential anti-cancer agents for cancer treatment. Stability of the enzyme-ligand complexes were studied using Molecular Dynamics (MD) simulations. Changes in microscopic properties of atoms such as atomic positions, velocities and energy are calculated in this study. MD simulations are intensively applied to the study HDAC protein-ligand such as SAHA, Scriptaid, TSA and Valproic acid interactions were calculated using Hex. Root mean square deviation (RMSD) between non-hydrogen atoms of the ligand in the original crystal structure and the same in the docked complex such as HDAC-SAHA, HDAC-Scriptaid, HDAC-TSA, and HDAC-Valproic acid were analyzed by xmgrace. The RMSD of the enzyme bound to TSA was fairly deviated from the RMSD of the enzyme bound to SAHA during the simulation time from 0ps to ~60000ps however overall variation of RMSDs are compatible. The radius of gyration is a good indicator to identify compactness or folding of a biological macromolecule. The Scriptaid and TSA also show a similar compactness of the enzyme as of SAHA. The fluctuation pattern shown by solvent accessible surface area of enzymes bound to ligands, Scriptaid and TSA represent somewhat similar behavior to that of enzyme-SAHA complex, average values and standard deviations were calculated at 60000ps time intervals to obtain a better comparison. From these data observer can draw conclusions about the system being studied.

Keywords: *Histone deacetylases (HDACs), Molecular docking, Scriptaid, Suberoylanilidehydroxamic acid (SAHA), Trichostatin A (TSA) and Valproic Acid.*

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