Molecular Modeling study of DOT1L for discovery of new potent inhibitors, drugs for acute leukemias: A Virtual Screening, Molecular Docking, ADME & Tox study

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ABSTRACT

Mixed lineage leukemia (MLL) is an aggressive form of leukemia that affects both infants and adults and typically carries a poor prognosis. The underlying genetic defect is a chromosomal translocation that fuses the MLL gene to a variety of partners, and the resulting oncogenic fusion proteins gain the ability to interact with at least 3 known protein complexes, one of which contains DOT1L, a histone methyltransferase that catalyzes the methylation of histone H3 (H3K79). As DOT1L is essential for leukemic transformation, small-molecule inhibitors of DOT1L function are an attractive therapeutic target for this type of leukemia.

As per the previous researches show anti-cancer activity of Pyrazolone we have presumed that derivates of this moeity can be good inhibitor for DOT1L. With the help of virtual screening and molecular docking approach using Lamarckian Genetic Algorithm we have performed the binding mode of derivates of Pyrazolone with DOT1L.

The study involved virtual screening of 6000 molecules on the basis of structure similarity of Pyrazolone from different chemical databases. Molecular docking using Lamarckian Genetic Algorithm was carried out for these ligands and the result gave binding energies which were in the range of -11.18 kcal/mol to -1.25 kcal/mol. The top molecules were selected on the basis of minimum binding energy and protein-ligand complex was created. They were then visualized using UCSF chimera for H-bond interaction between ligand and active site residues of DOT1L which resulted in finding intricate atomic scale properties between ligand and residues PHE 223, ASP 161 and GLU 186. The top molecules then were run for in-silico ADMET and druglikeness properties in which we got promising results. Further in-vitro and in-vivo study is required on these molecules to test the inhibition of DOT1L.