Molecular Dynamics Simulations and Virtual Screening to Identify Potent Inhibitors of Human Asparagine Synthetase.

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Asparagine amidohydrolase (ASNase), which catalyzes the hydrolysis of asparagine to aspartate and ammonia, has been used in a wide range to treat acute lymphoblastic leukemia (ALL) *(1)*. Correlation between ASNase resistance and the up-regulation of glutamine-dependent asparagine synthetase (ASNS) has been reported *(2)*. The spread of an *L*-asparagine amidohydrolase(ASNase)-resistant MOLT-4 leukemia cell line (MOLT-4R) was suppressed by an adenylated sulfoximine transition-state analogue , which inhibits human asparagine synthetase (hASNS) *(3)*. Therefore, discovering potent lead inhibitors for ASNS is important in order to discover drugs that can treat acute lymphoblastic leukemia (ALL). In this study, molecular dynamics simulations of ASNS in complex with the reaction intermediate, β-aspartyl-AMP were performed. The results provide information about important active site residues and important protein ligand interactions especially there is no crystal structure of ASNS- β-aspartyl-AMP complex. The simulated model was further used in the docking and virtual screening of NCI database and the potential hits will be also presented.

References

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