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Development of Immuno-Modulators: Application of Molecular Dynamics Simulation

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Abstract : The accurate characterization of ligand binding affinity is indispensable for designing molecules with optimized binding affinity. Computational tools help in many directions to predict quantitative correlations between protein-ligand structure and their binding affinities. Molecular dynamics (MD) simulation is a modern state-of-the-art technique to evaluate the underlying basis of ligand-protein interactions by characterizing dynamic and energetic properties during the event. Autoimmune diseases arise from an abnormal immune response of the body against own tissues. The current regimen for the described condition is limited to immune-modulators having compromised pharmacodynamics and pharmacokinetics profiles. One of the key player mediating immunity and tolerance, thus invoking autoimmunity is Interleukin-2; a cytokine influencing the growth of T cells. Molecular dynamics simulation techniques are applied to seek insight into the inhibitory mechanisms of newly synthesized compounds that manifested immunosuppressant potentials during in silico pipeline. In addition to estimation of free energies associated with ligand binding, MD simulation yielded us a great deal of information about ligand-macromolecule interactions to evaluate the pattern of interactions and the molecular basis of inhibition. The present study is a continuum of our efforts to identify interleukin-2 inhibitors of both natural and synthetic origin. Herein, we report molecular dynamics simulation studies of Interluekin-2 complexed with different antagonists previously reported by our group. The study of protein-ligand dynamics enabled us to gain a better understanding of the contribution of different active site residues in ligand binding. The results of the study will be used as the guide to rationalize the fragment based synthesis of drug-like interleukin-2 inhibitors as immune-modulators.

Keywords : immuno-modulators, MD simulation, protein-ligand interaction, structure-based drug design
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