Activin Receptor Type IIA Protein Kinase Inhibitors: Free Energy Calculations and Ligand Binding

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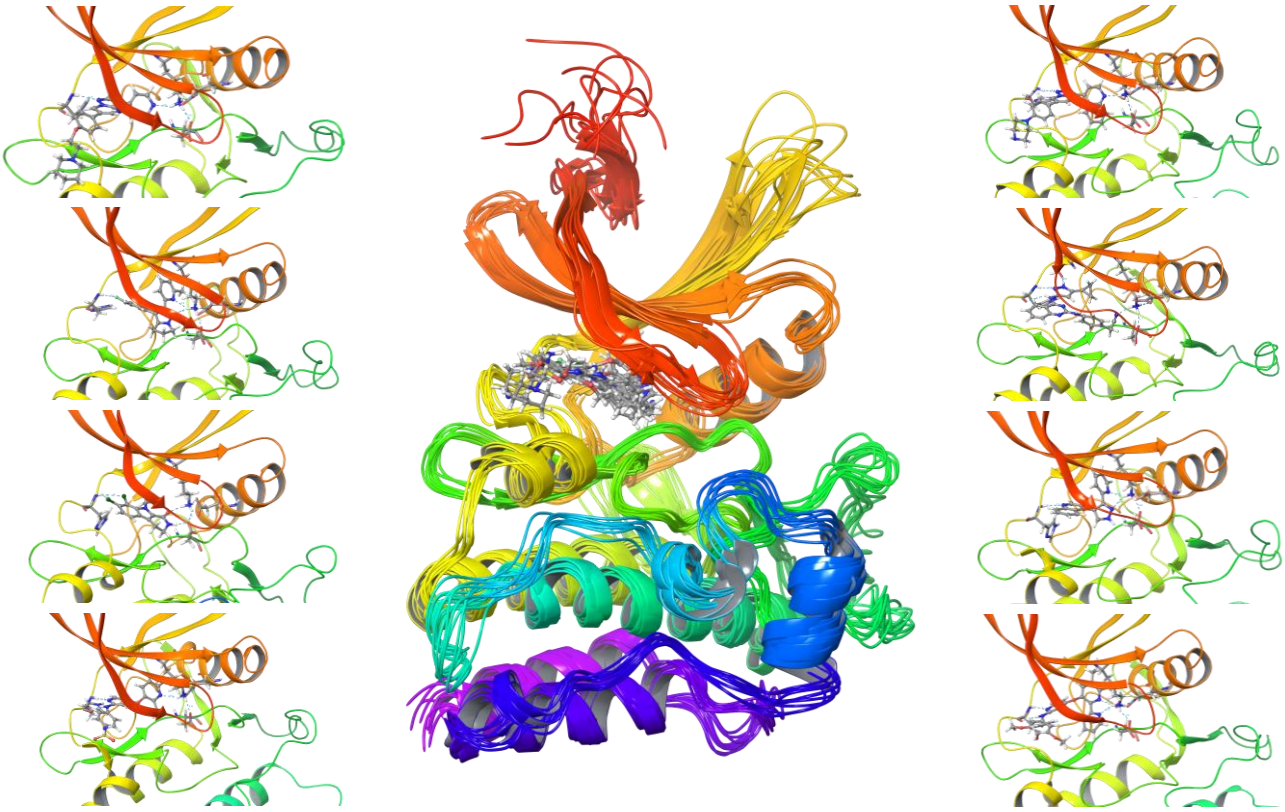

In the present research, we reviewed the use of Molecular Mechanics combined with Poisson-Boltzmann and Generalized Born Surface Area (MM-PB(GB)/SA), as well as the Linear Interaction Energy (LIE) method, for calculating ligand binding free energies. With an aim towards better understanding a variety of biological functions, including muscle growth and bone formation as well as viability and adhesion of prostatic epithelial cells, Dorsomorphin (K_D = 58 nM), LDN-193189 (K_D = 14 nM), and seven other ligands [1] were investigated as Activin Receptor Type IIA Protein Kinase (ActRIIA) [2] ATP-binding site inhibitors. Due to the lack of experimental structural information for the binding of these ligands, 10 ns Molecular Dynamics (MD) simulations in explicit water using Amber 14 software package were performed for each receptor-inhibitor complex.

[1] Horbelt, D. et al. *J. Biol. Chem*. **2015**, *290*, 3390.
[2] Han, S. et al. *Protein Sci.* **2007**, *16*, 2272.