Recognition of Gleevec by Src-family Kinases

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Tyrosine kinases are attractive drug targets for curing certain types of cancers. Gleevec, a well-known cancer therapeutic agent, is sufficient to inhibit several tyrosine kinases with good efficacy, including Abl and c-Kit kinases. But it shows less or weak potency to inhibit homologous tyrosine kinases, such as Lck and c-Src kinases. Because the features of the binding sites are highly conserved in Abl and c-Kit as well as in Lck and c-Src, the binding specificity of Gleevec cannot be explained solely based from structural differences. Here, molecular dynamics free energy perturbation (FEP/MD) simulations have been performed to compute the absolute binding free energies of Gleevec to Abl, c- Kit, Lck, and c-Src in explicit water solvent to elucidate the main factors dominating Gleevec’s binding recognition and diverse specificity to the kinases. The calculated absolute binding free energies are in good agreement with experiment. The computations provide a strong physical basis to suggest structural-based drug design for inhibitors of the tyrosine kinases.