Computer-Guided Efficient Discovery of Potent Enzyme Inhibitors

Jorgensen, William L.
Department of Chemistry, Yale University, New Haven, CT 06520-8107 USA

Drug discovery is being pursued through computer-aided design, synthesis, biological assaying, and crystallography.[1-4] Lead identification features *de novo* design with the ligand growing program *BOMB* or virtual screening. Emphasis is placed on optimization of the resultant hits to yield potent, drug-like inhibitors. Monte Carlo/free-energy perturbation (FEP) simulations are often executed to identify the most promising choices for substituents on rings, heterocycles, and linking groups. The illustrated applications center on the design of inhibitors targeting HIV-1 reverse transcriptase, macrophage migration inhibitory factor, and JAK2 kinase. Micromolar leads have been rapidly advanced to low nanomolar inhibitors, and numerous crystal structures for protein-inhibitor complexes have been obtained. Development and use of fluorescence polarization assays provide direct binding data. Key computational issues are considered including force fields, atomic charge models, conformational sampling, computation of absolute free energies of binding, and unbinding pathways from metadynamics.

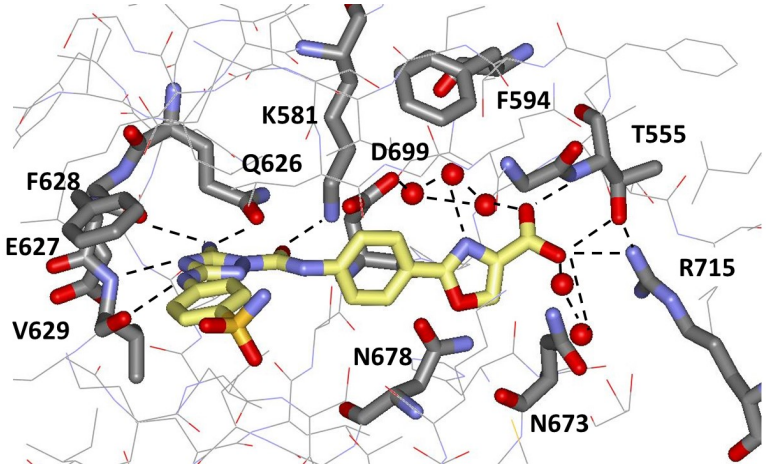

Figure 1. *Rendering from a 2.03-Å crystal structure for a complex with JAK2 JH2 (PDB ID 6OCC). Red spheres represent oxygen atoms of localized water molecules. Carbon atoms of the ligand are in yellow.*

References

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