

# Thermodynamic-based Algorithms for the Optimization of Binding Affinity and Selectivity in Drug Design

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## **Abstract**

The human genome has revealed targets for drug development against a large number of human diseases. In many cases, however, those targets belong to structurally homologous families of proteins (e.g. kinases, proteases, growth factors, blood coagulation factors, etc) and therefore successful drug development requires the ability to bind to their intended target with high affinity and to discriminate unwanted proteins by exhibiting low affinity towards them, i.e. high selectivity. Usually, when active compounds are first identified, they exhibit micromolar or even weaker affinities. To become effective drugs, the binding affinities of those compounds need to be optimized by three or more orders of magnitude. Simultaneously, their selectivity needs to be maximized. This task is not a trivial one if one considers that it needs to be done while satisfying several stringent constraints, e.g. the molecular weight cannot substantially exceed 500Da in order for the molecule to be orally bioavailable; the compound needs to exhibit appropriate membrane permeability, suitable levels of serum binding, viable water solubility, no toxicity, etc.. The simultaneous optimization of binding affinity and selectivity requires an accurate assessment of the contribution of each force (van der Waals, hydrogen bonding, hydrophobicity, etc) to affinity and selectivity and the derivation of the best balance of forces for each specific target. Structure-based thermodynamic algorithms provide effective ways to successfully address this issue.