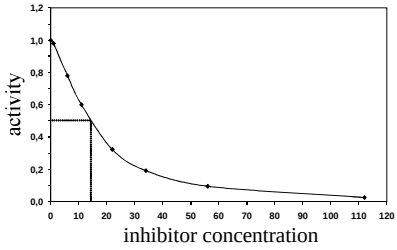
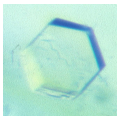
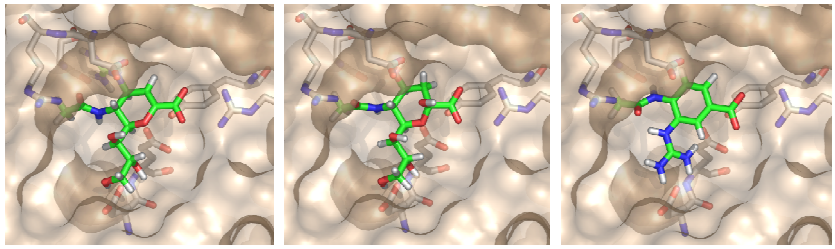
Binding measurements





Crystal, NMR or modeled structures
of complexes of receptor and ligand



Binding free energy
(or biological activity)

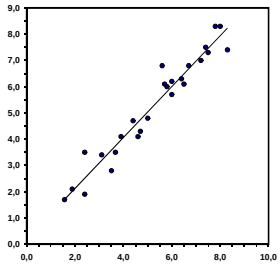
$$\Delta G = \sum_{i=1}^{n} \omega_i \, \Delta u_i^{rep} + C$$

Energy minimize all models

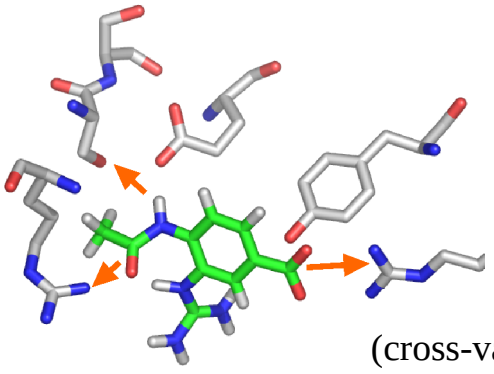
Calculate ligand-receptor binding energy
for each complex

ΔU= intermolecular interaction energy
+ changes in bonded and nonbonded energies
of the receptor and the ligands

Partition ΔU of the receptor and the ligand
into several components on basis of location
in the complex and physicochemical properties

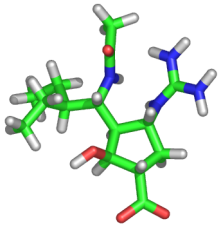


Correlate different components of binding energy ΔU with
ΔG/activity values by Partial Least Squares



Identify important interactions
for determining ΔG/activity

Validate model
(cross-validation, scrambled/random ΔG values)



Predict modified compounds

Synthesize new ligands or mutants