

AutoDock Vina

Computational Chemistry Working Group Meet #1

Molecular Docking

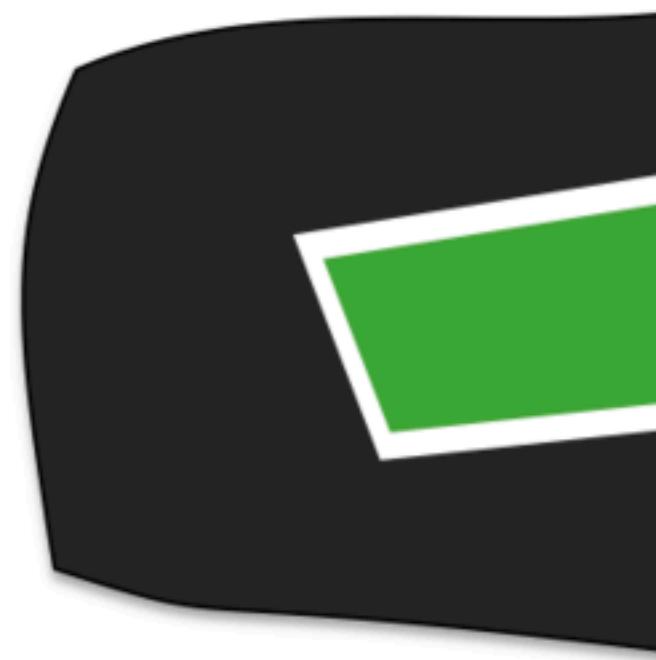
Target



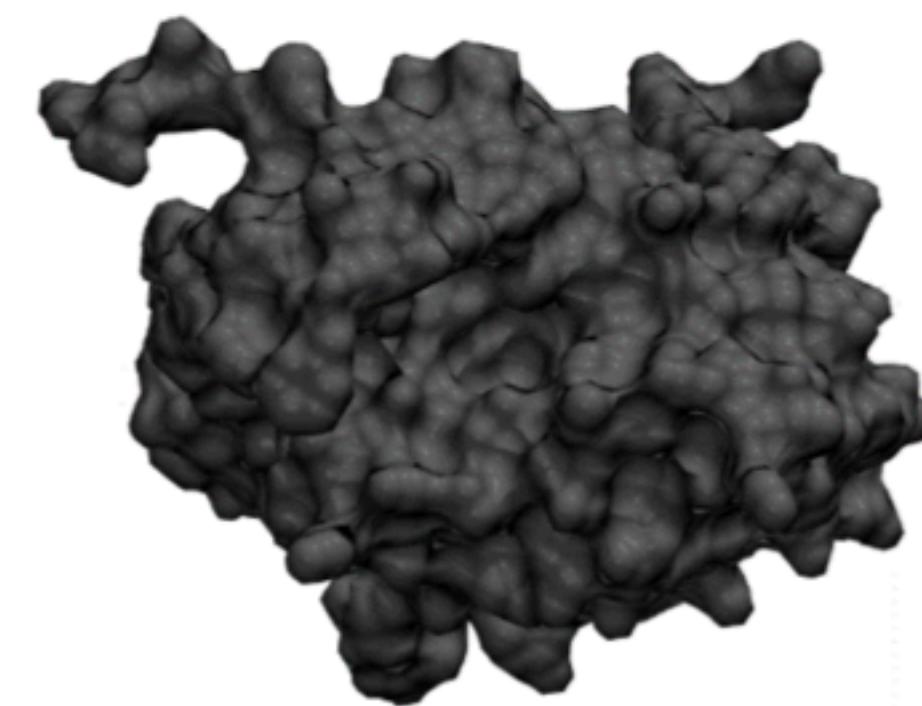
Ligand



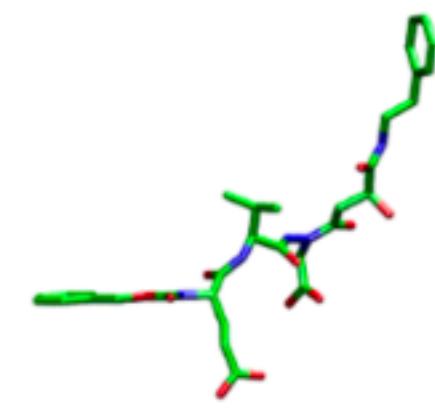
Complex



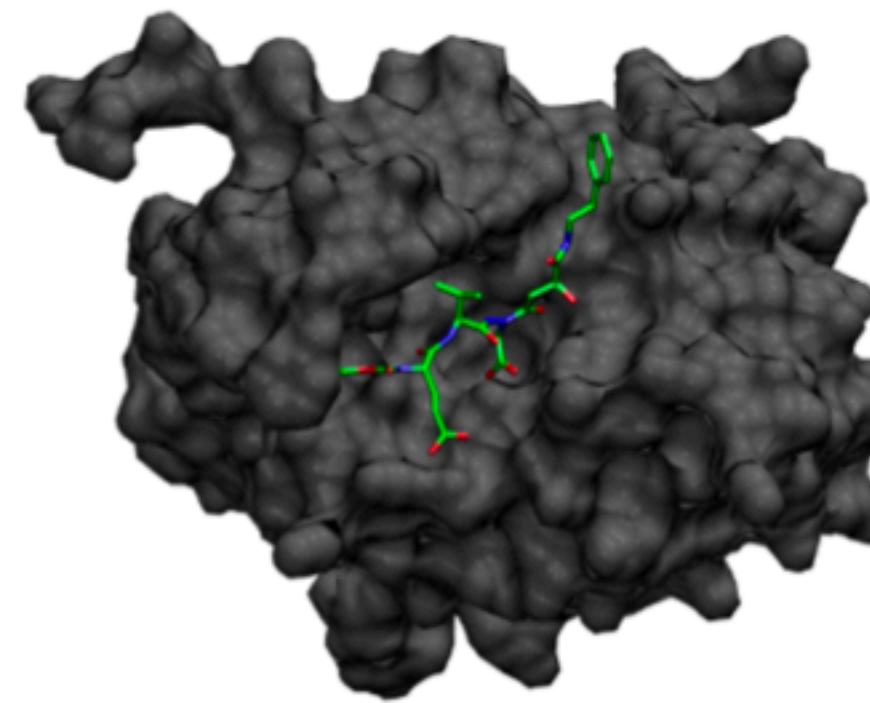
docking

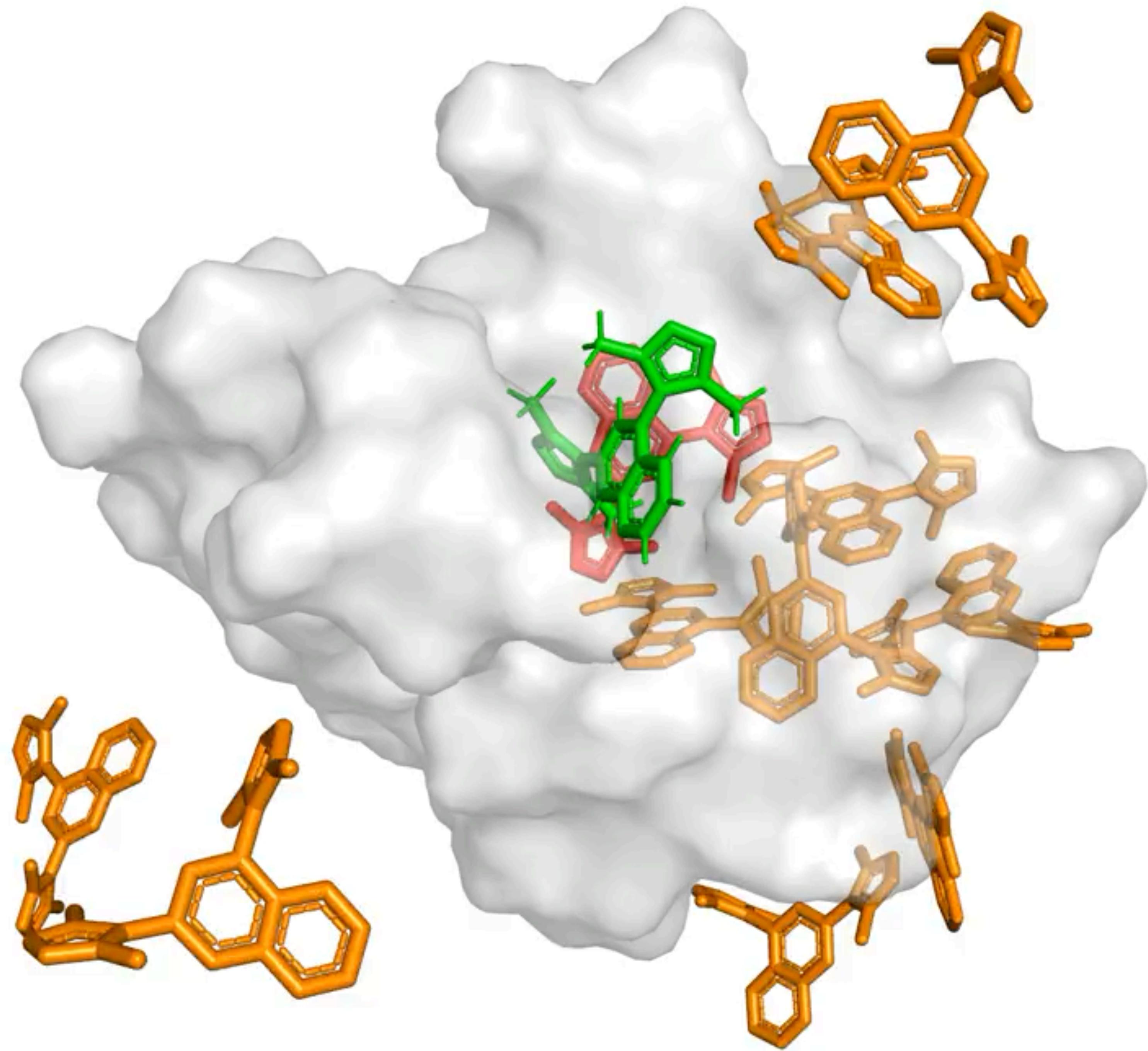


+



docking

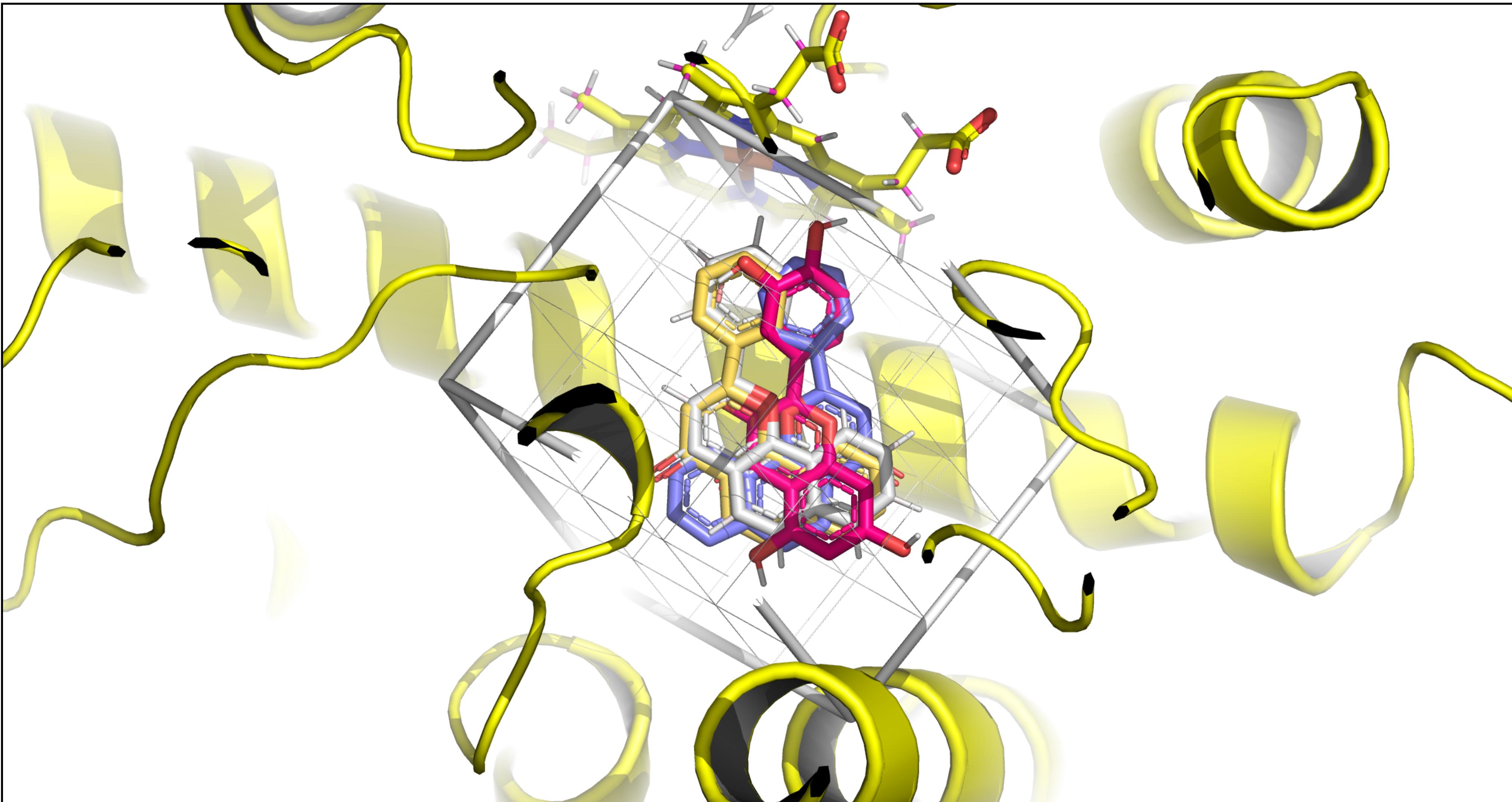




Manas Mahale

Why Dock ?

Predict Bound Conformations & Binding Affinity



Molecular Dynamics with Explicit Solvent

Representational Detail

Molecular Docking

Manas Mahale

Molecular Dynamics with Implicit Solvent

Computational Complexity

Assumptions

Assumption

- Protonation state, Charge distribution in the molecules **DO NOT** change, between bound & unbound states.
- *Much or All receptors are rigid.*
- Covalent lengths, and angles stay constant for the rigid part
- A chosen set of covalent bonds can be *freely rotatable*.

MD vs Docking

Docking is ultimately interested in reproducing chemical potentials, which determine the bound conformation preference and the free energy of binding. It is a *qualitatively* different concept governed not only by the **minima** in the energy profile but also by the **shape of the energy profile**.

Scoring Function

Scoring Function

- Docking programs are **superficially physics-based** systems.
- Superficially physics-based scoring functions **Do Not** necessarily perform better than the alternatives. AutoDock Vina's scoring function is more of “machine learning” than directly physics-based in its nature.
- It is ultimately justified by its performance on test problems rather than by theoretical considerations following some, possibly too strong, approximating assumptions.

Scoring Function

$$c = \sum_{i < j} f_{t_i t_j}(r_{ij})$$

Summation over all of the pairs of atoms that can move relative to each other, excluding 1–4 interactions, i.e., atoms separated by three consecutive covalent bonds.

Here, each atom i is assigned a type t_i , and a symmetric set of interaction functions $f_{t_i t_j}$ of the interatomic distance r_{ij} should be defined.

Scoring Function

$$c = c_{\text{inter}} + c_{\text{intra}}$$

Scoring Function

$$s_1 = g(c_1 - c_{\text{intra}1}) = g(c_{\text{inter}1})$$

s is predicted free energy of binding

Scoring Function

$$s_i = g(c_i - c_{\text{intra}1})$$

s is predicted free energy of binding

Scoring Function

$$f_{titj}(r_{ij}) \equiv h_{titj}(d_{ij})$$

h_{titj} is a weighted sum of *steric interactions*, identical for all atom pairs, *hydrophobic interaction* between hydrophobic atoms, and, where applicable, *hydrogen bonding*.

All interaction functions f_{titj} are cut off at $r_{ij} = 8 \text{ \AA}$

Scoring Function

Conformation-independent function g

$$g(c_{\text{inter}}) = \frac{c_{\text{inter}}}{1 + wN_{\text{rot}}}$$

where N_{rot} is the number of active rotatable bonds between heavy atoms in the ligand and w is the associated weight.

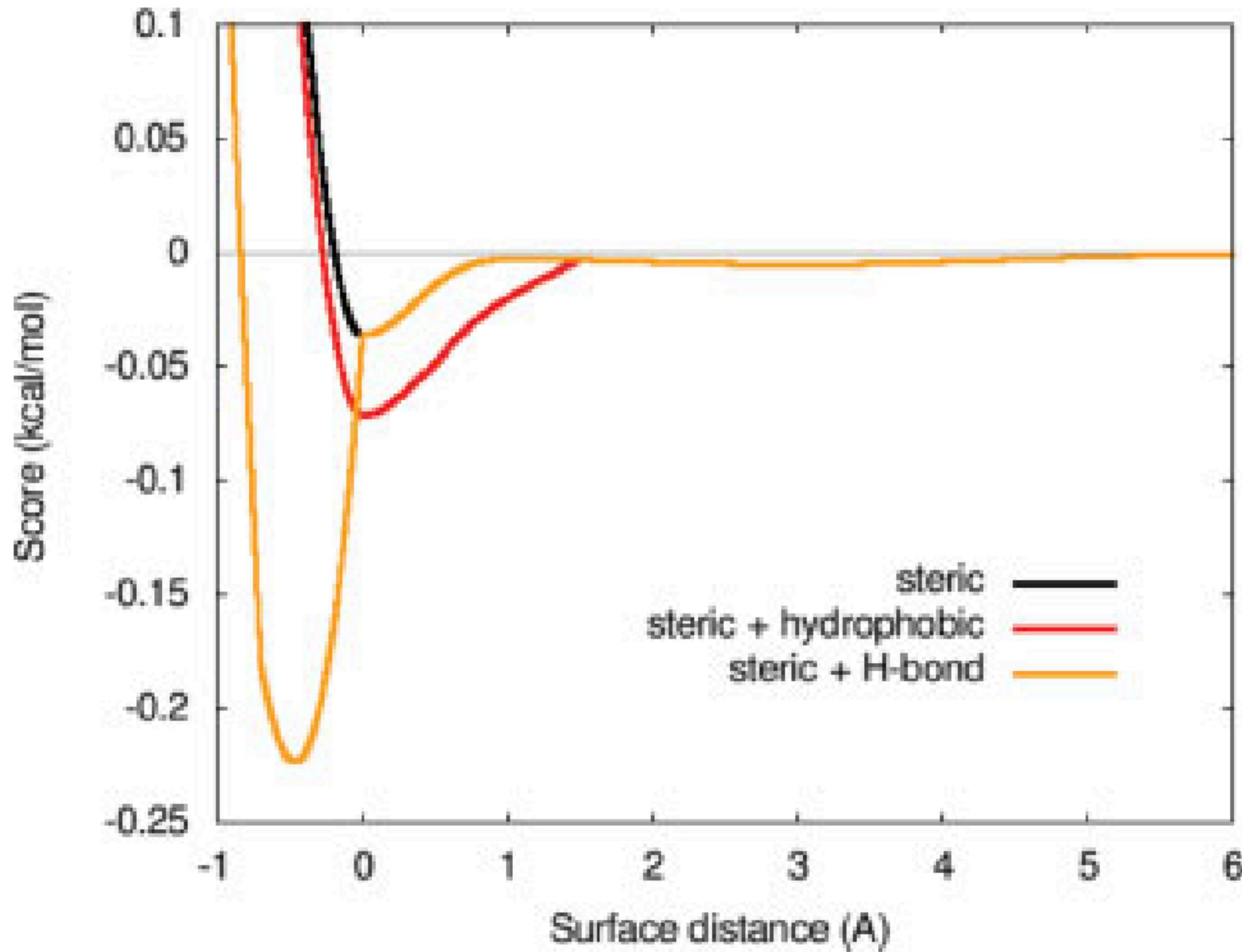


Figure 1. Weighted scoring function term combinations. Steric interactions, steric and hydrophobic interactions, and steric and hydrogen bonding interactions, using weights from Table 1.

Optimization Algorithm



From left to right: **Broyden**, **Fletcher**, **Goldfarb**, and **Shanno**.

Validation and Bias

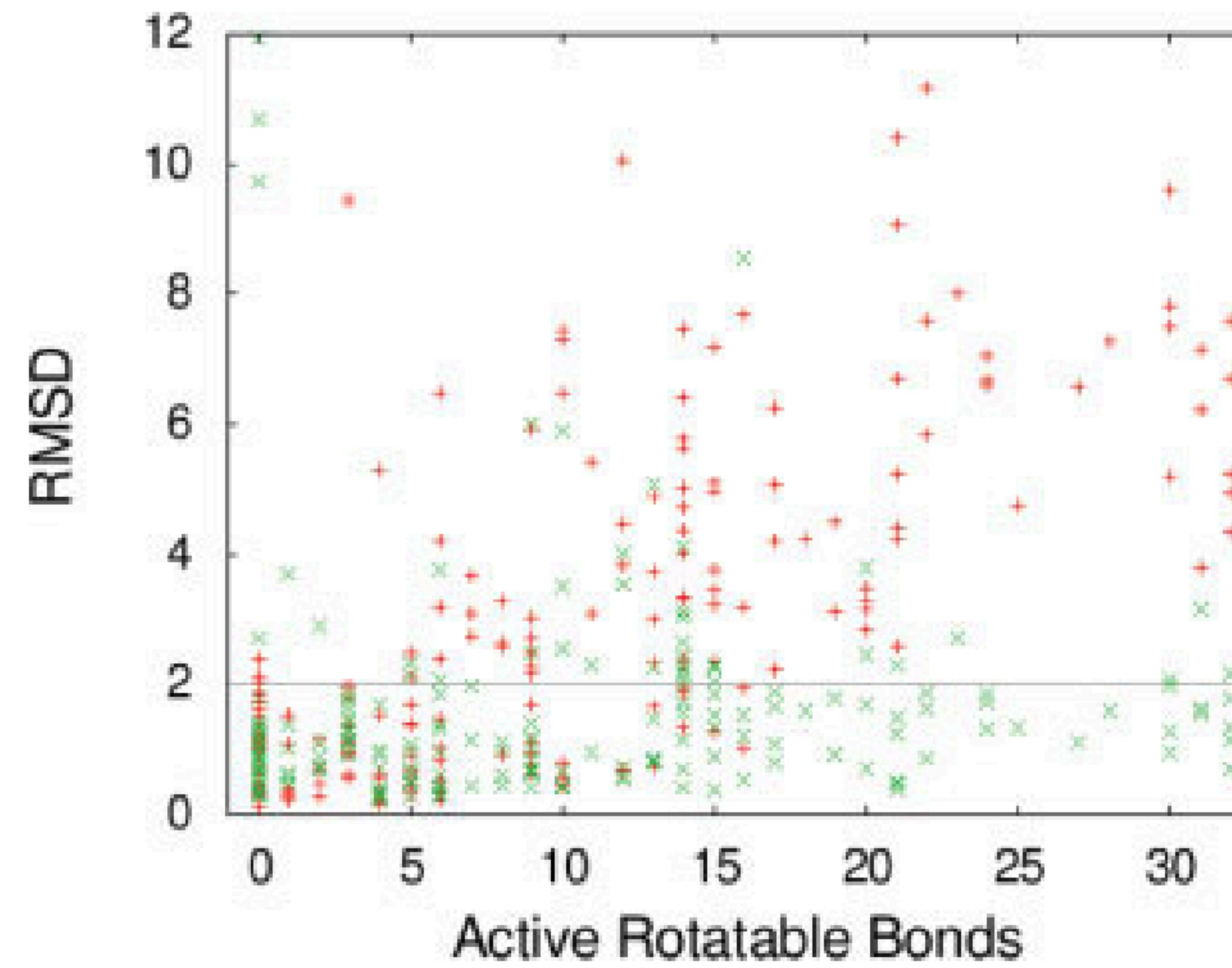
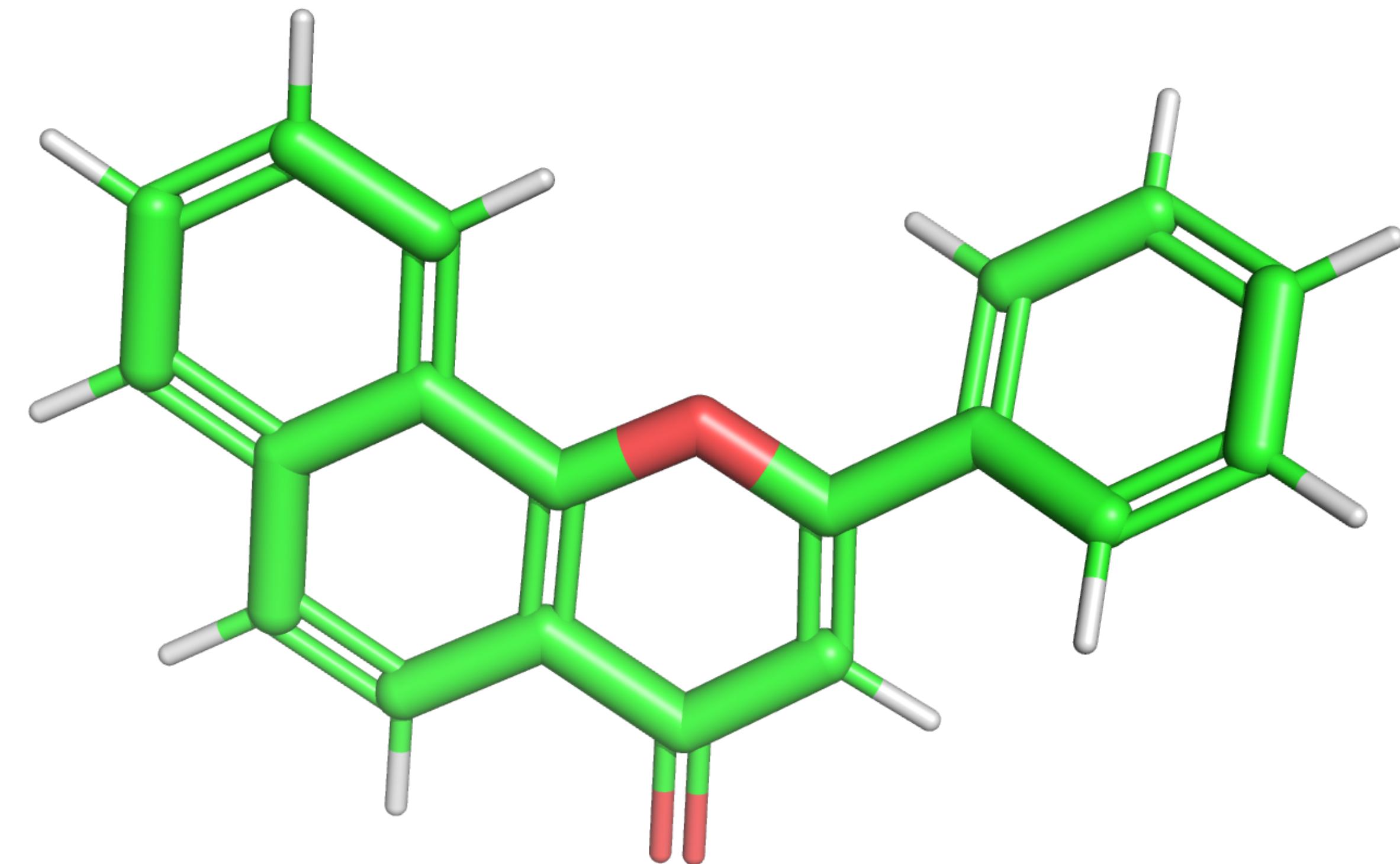


Figure 3. RMSD of the predicted bound ligand conformation from the experimental one. (Red +) Autodock; (Green ×) Vina. Abscissa shows the number of active rotatable bonds.

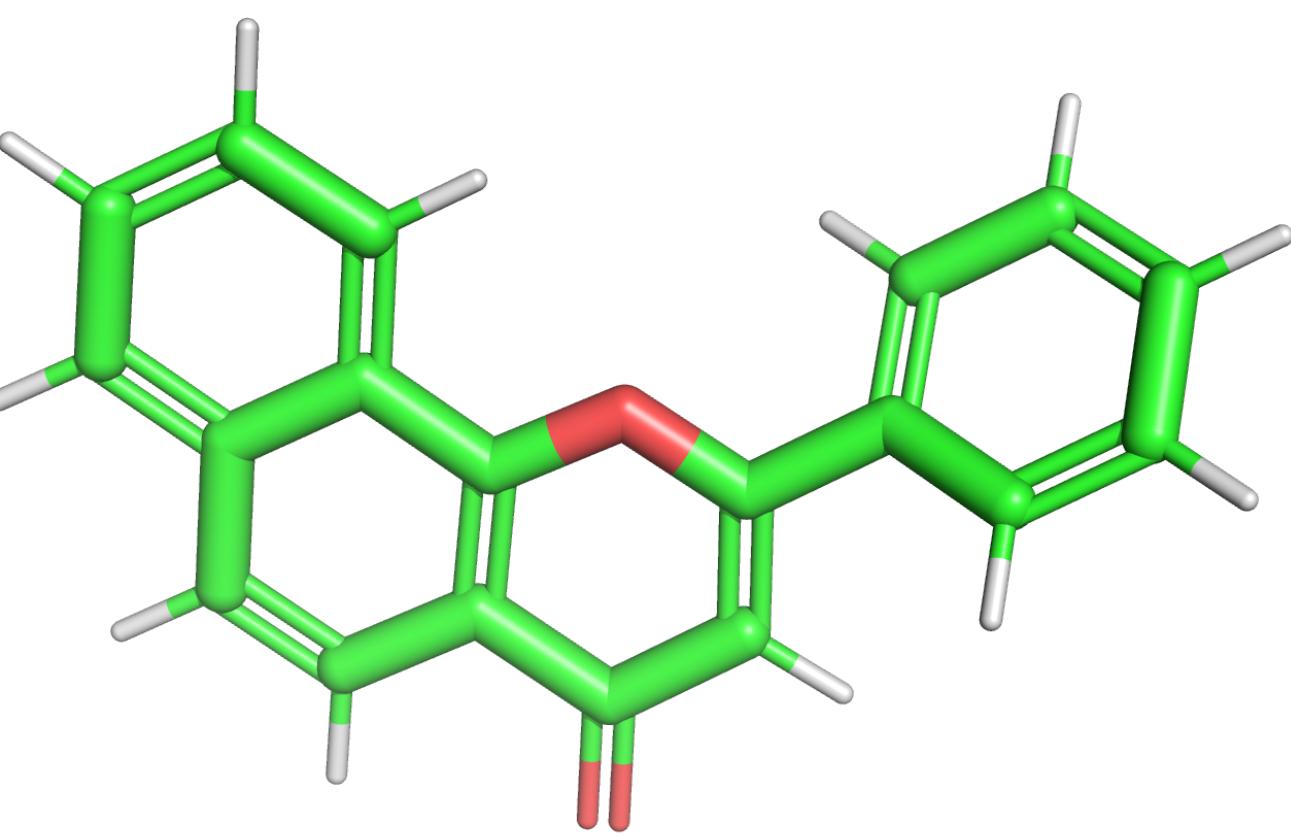
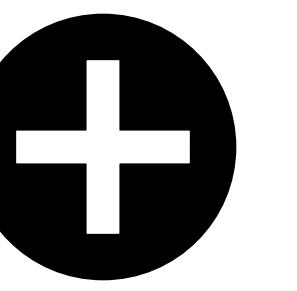
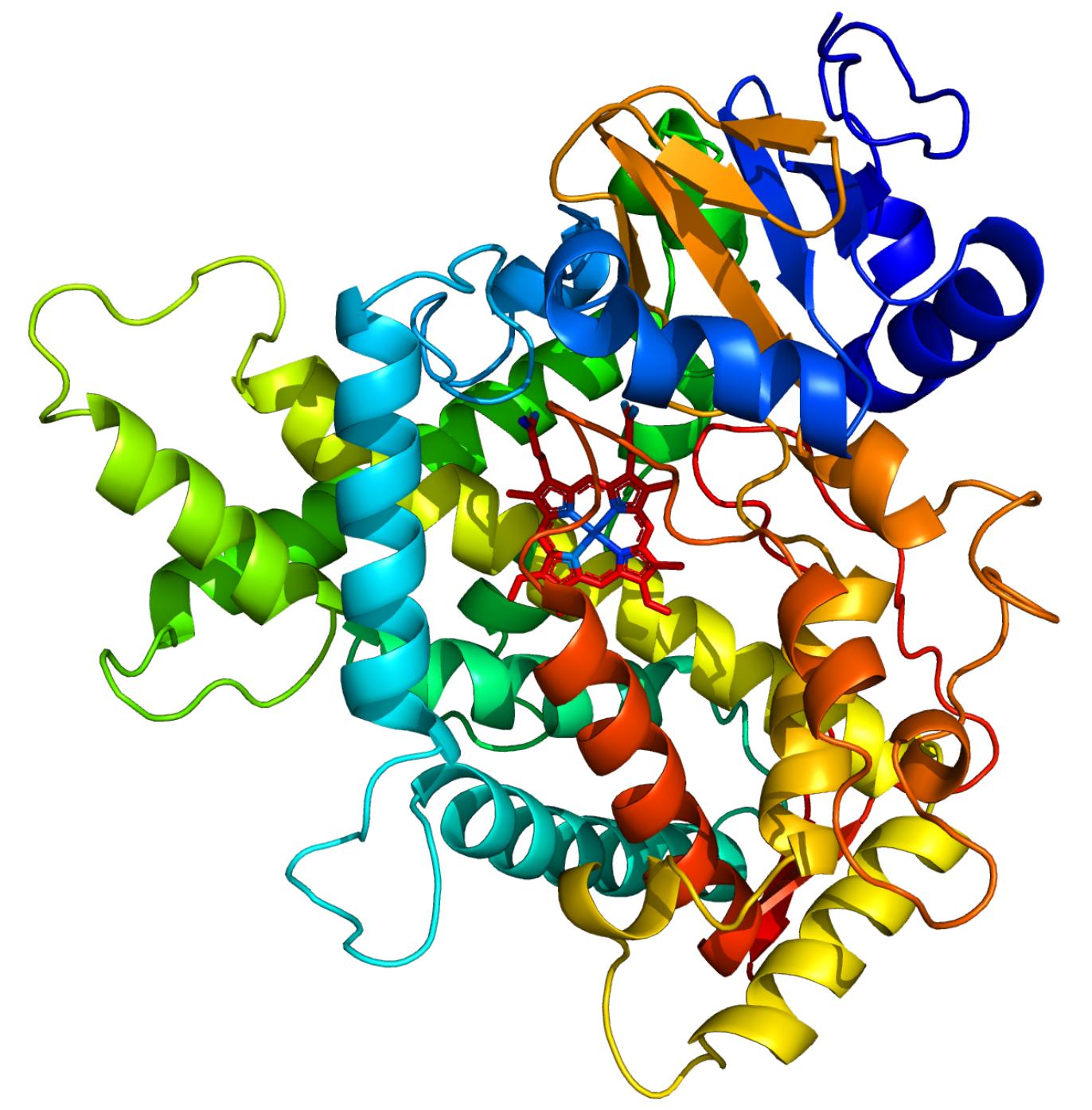
Example

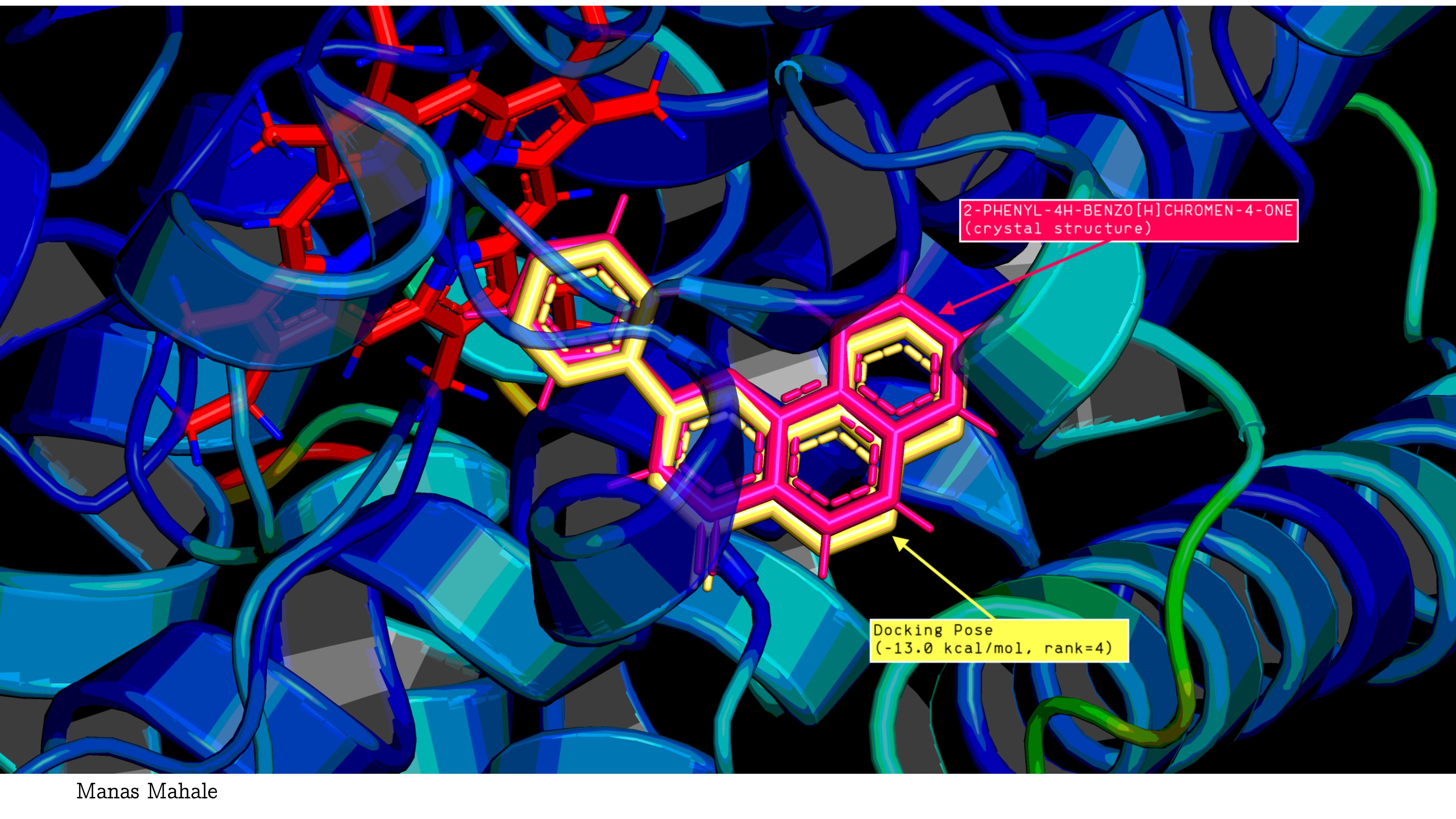


Human Cytochrome P450 1A1 in complex with alpha-naphthoflavone
PDB:4i8v



Ligand : 2-PHENYL-4H-BENZO[H]CHROMEN-4-ONE





2-PHENYL-4H-BENZO[H]CHROMEN-4-ONE
(crystal structure)

Docking Pose
(-13.0 kcal/mol, rank=4)

✖ ⓘ rescoring_lig_BHF.txt



Open withTextEdit

```
#####
# If you used AutoDock Vina in your work, please cite:      #
#                                                               #
# O. Trott, A. J. Olson,                                         #
# AutoDock Vina: improving the speed and accuracy of docking   #
# with a new scoring function, efficient optimization and      #
# multithreading, Journal of Computational Chemistry 31 (2010) #
# 455-461                                                       #
#                                                               #
# DOI 10.1002/jcc.21334                                         #
#                                                               #
# Please see http://vina.scripps.edu for more information.     #
#####
```

Detected 8 CPUs

Reading input ... done.

Setting up the scoring function ... done.

Analyzing the binding site ... done.

Using random seed: -795113930

Performing search ... done.

Refining results ... done.

mode	affinity (kcal/mol)	dist from best mode	
		rmsd l.b.	rmsd u.b.
1	-13.6	0.000	0.000
2	-13.6	0.131	1.083
3	-13.2	1.583	4.015
4	-13.0	1.560	3.876
5	-12.7	1.007	1.734
6	-12.2	1.603	6.064
7	-12.1	1.710	6.133
8	-11.9	1.016	5.924
9	-11.3	1.637	6.253
10	-11.0	1.840	7.114

Writing output ... done.

Fin.

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