Ligand Binding Study of Carbonic Anhydrase 2

Maurus Schmid, Thomas R. Ward*, Markus Meuwly*

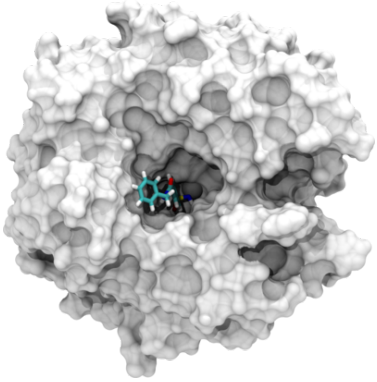
University of Basel, Spitalstrasse 51, 4056 Basel

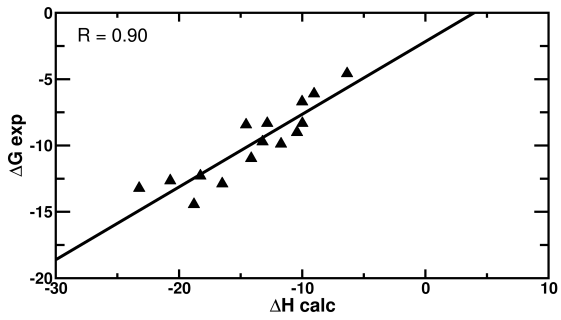
University of Basel, Klingelbergstrasse 80, 4056 Basel

Carbonic anhydrases (CAs) are ubiquitous metalloenzymes that catalyze the reversible hydration of carbon dioxide with remarkable efficiency. CA isoforms are involved in various pathological processes including infections, tumorigenicity, osteoporosis, epilepsy, etc. and CAs have thus been the focus of many biophysical studies of protein-ligand interactions. Today, at least 25 clinically used drugs are known to display pronounced CA inhibitory properties [1].

To design a protein with particular properties, understanding the influence of residues is crucial. In this work we report on a computational strategy that allows predicting strong inhibitors and potentially beneficial mutations of the protein.

The active site of most CAs contains a $Zn(His)_3$ which is essential for catalysis. The carbonic anhydrase protein is ideal for the design of potent and selective inhibitors. Among these, arylsulfonamides, which bind tightly to the Zn ion at physiological pH (down to sub-nM), occupy a place of choice [2].





We report a Molecular Mechanics Generalized Born Solvent Approximation (MMGBSA [3]) study comparing the binding free energy for this important class of inhibitors. 18 of these sulfonamides were investigated. Using this method, not only the total binding free energy, but also the influence of a particular residue can be examined. Thus the effect of mutations on key residues on the binding can be determined.

To validate the simulations, we compare the results with published biophysical data as well as with a simulation using QM/MM simulations with the Self-consistent charge Density-Functional Tight-Binding (SCCDFTB [4]) method. Results show a high (up to $R = 0.90$) correlation between the predicted values and biophysical data.

[1] Supuran, C. T., *Nature reviews. Drug discovery*, **2008**, *7*, 168-181.

[2] Krishnamurthy, V. M.; Kaufman, G. K.; Urbach, A. R.; Gitlin, I.; Gudiksen, K. L.; Weibel, D. B.; Whitesides, G. M. , *Chemical reviews* , **2008**, *108*, 946-1051.

[3] Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T., *Journal of the American Chemical Society,* **1990**, *112*, 6127–6129.

[4] Elstner, M.; Porezag, D.; Jungnickel, G.; Elsner, J.; Haugk, M.; Frauenheim, T.; Suhai, S.; Seifert, G. , *Phys. Rev. B* , **1998**, *58*, 7260-7268.