Development and validation of MM-(GB)SA models for predicting the biological activity of sirtuin inhibitors

Berin Karaman[1] and Wolfgang Sippl[1]

[1] Department of Pharmaceutical Chemistry, Martin-Luther University Halle-Wittenberg

Silent information regulator 2 (Sir2) proteins, also named sirtuins (SIRTs), are NAD+ dependent histone deacetylases distributed in lifeforms ranging from prokaryotes to eukaryotic organisms. To date seven sirtuin subtypes have been identified in humans; SIRT1-7 that share a highly conserved catalytic NAD+/acetyl-lysine binding site. Human sirtuins SIRT1-3 represent interesting targets related to the treatment of age related diseases, neurological disorders (like Parkinson`s and Alzheimer`s diseases), metabolic syndromes (such as diabetes and obesity), viral diseases and cancer [1, 2]. Most of the sirtuin modulators that have been identified so far show limited potency and/or isoform selectivity. Therefore, the development of potent and specific inhibitors of sirtuins might help to evaluate their pharmacological potential for several diseases and exploiting their functions in cellular processes.
In order to rapidly screen large compound databases, docking-based virtual screening (VS) approaches have been used to predict the binding strength of ligands. However, current scoring functions show a poor correlation with biological data and more rigorous methods are in need. In this study, we present an MM-(GB)SA approach that can be used as an effective post-docking filter tool to enrich VS results and prioritize hits for further biological testing.

[1] W. Stünkel , R. M. Campbell, *J Biomol Screen*, **2011**, *16*, 1153-1169.

[2] F. Zhang, S. Wang, L. Gan, P. S. Vosler, Y. Gao, M. J. Zigmond, J. Chen, *Prog Neurobiol*, **2011**, *95*, 373-395.