Computational strategies for structure-based lead optimization and analysis of SAR transfer

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The topic of this PhD research is the application of computational chemistry in drug discovery and design. The project was conducted at the *Department* of *Drug Science and Technology* of UniTo and at the *Department of Life Science Informatics* at b-it, University of Bonn. The aim of the thesis is the design of new small molecules effective in cancer therapies as well as the developing of innovative computational methodologies aimed at hit-to-lead and lead optimization. The target of these studies was *human* dihydroorotate dehydrogenase (*h*DHODH), a flavin-dependent mitochondrial enzyme involved in *de novo* pyrimidine biosynthesis. *h*DHODH overexpression has been associated with acute myelogenous leukemia, a disease for which the standard of intensive care has not changed over decades.[ref] In this study, computer-aided lead optimization were carried out on a potent *h*DHODH inhibitor.[1] Structure-based approaches were used to generate working hypotheses to modify further the lead compound and improve its molecular properties. A series of analogues were designed, synthetized and biologically evaluated.[2] Moreover, this doctorate focused also on the identification of new computational strategies for lead-optimization. The exploration of structure-activity relationships (SARs) is central relevance in drug design. In such situations, one would ideally like to build upon priori knowledge, utilize available SAR information, and evaluate the possibility of an "SAR transfer", i.e., the exploration of an alternative chemotype that displays similar SAR characteristics and potency progression. So far, few studies have computationally (and indifferent ways) analyzed SAR transfer events.[3-5] However, currently lacking are structure-based approaches for the assessment and prediction of SAR transfer. In our analysis, we investigated SAR environments with the aid of experimental structures and compound binding data (Fig.1), introducing a computational method for the structure-based identification of SAR transfer events and their systematic assessment.

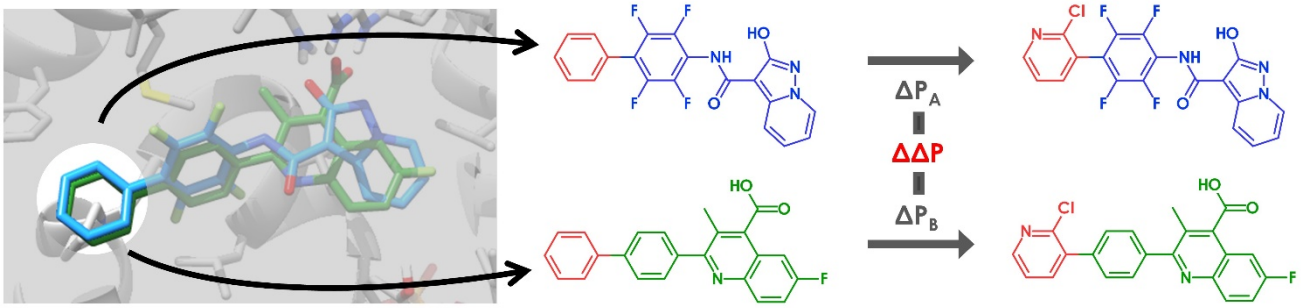

Figure 1: The representation illustrates principles of computational structure-based SAR transfer exploration. On the left, complex X-ray structures of *h*DHODH with two inhibitors are superimposed (PDB ID: 6FMD and 1D3G). The circle highlights a shared phenyl ring. On the right, the two inhibitors are displayed together with corresponding active analogues, red substructure represents the shared fragment. From the ΔP (potency difference) value of each X-ray inhibitor – analogue pair, ΔΔP is determined.

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