Opportunities and challenges for free energy calculations in drug design

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Free energy calculations have become a powerful addition to the computational chemist's toolbox to support structure-based drug design in hit-to-lead and lead optimization stages of drug discovery projects. Methodological advances, the availability of less expensive large computational resources and automated workflows have opened up the possibility to apply the technology in an industry context at large scale. In 2016, we started a large initiative at Merck KGaA to thoroughly investigate the potential of free energy calculations for compound optimization and to define best practices for using this technology. Here, we present prospective data from using FEP+ in 10 drug active discovery projects at Merck KGaA over the course of three years and compare this performance to results obtained on a new, challenging benchmark of five pharmaceutically relevant targets. We further discuss opportunities and challenges and highlight use cases and conditions that can maximize the impact of the method.

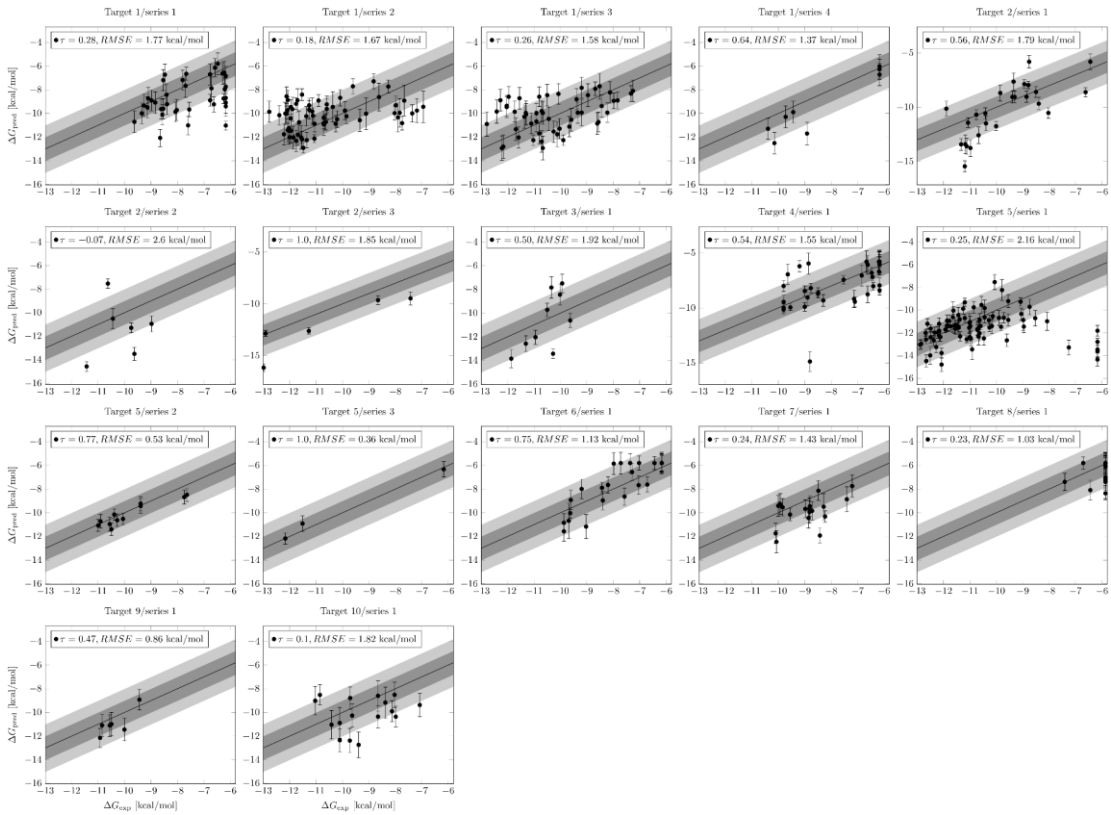

Figure 1 *Prospective accuracy for FEP+ on 17 chemical series from 10 in-house drug discovery projects.*

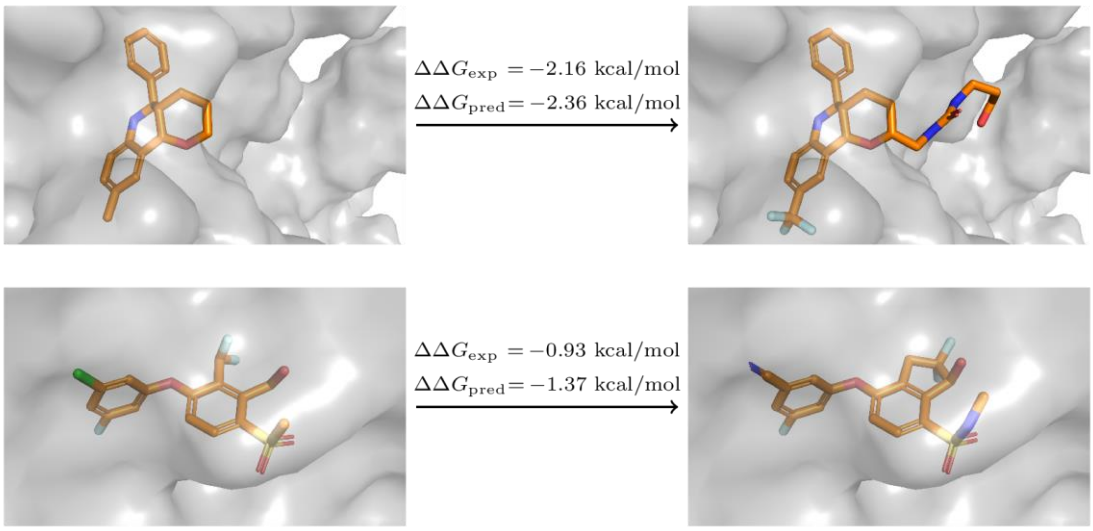

Figure 2 *Examples of challenging transformations from a large, public benchmark correctly predicted by FEP.*