25 years of small molecule optimization at Novartis: A retrospective analysis of chemical series evolution

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In early drug discovery, optimization of small molecules with respect to safety and biological activity is an important task to deliver drug candidates with highest chances of success in subsequent clinical trials. Typically, analyses have focused on the comparison of approved and failed drug candidates or have investigated the association of structural and measured properties with clinical outcomes. However, the actual optimization process is barely characterized, mainly due to missing annotations about chemical series that have been worked on in past projects.

In this contribution, we report a reconstruction of ~3000 chemical series from our Novartis in-house compound database. We present modifications made to the previously published protocol for automated chemical series identification [1, 2], which allowed application to datasets with more than 100k compounds. Based on our reconstruction we characterize the determined series and their connections with each other.

Using the registration dates of the compounds, we further characterized the evolution of chemical properties over time. Determination of active optimization phases allowed us to trace both structural and ADMET properties during optimization of the molecules. Our analysis revealed multiple patterns, which are repeatedly observed in the reconstructed series. We investigate the influence of the chemists on the observed trends and quantify the extent to which the respective ADMET properties can be improved over time.

References:

[1] F. Kruger *et al.* Automated Identification of Chemical Series: Classifying like a Medicinal Chemist*. J. Chem. Inf. Model. 2020, 60, 6, 2888–2902*

[2] M. Beckers *et al*. *manuscript in preparation*, 2022