International Conference on
"Recent Trends in Structural Bioinformatics and Computer Aided Drug Design"
[ICSBCADD'2019]
11th - 13th December, 2019

In silico Lead Optimization via Rapid Exploration of Synthetically Tractable Chemical Space using Schrödinger's Molecular Design Platform

Thomas Steinbrecher

Schrödinger GmbH, Q7 23, 68161 Mannheim, Germany
E-mail: thomas.steinbrecher@schrodinger.com

Improving or maintaining the potency of lead compounds, while simultaneously optimizing multiple other properties required for safety and biological efficacy, is a primary objective of lead optimization in small molecule drug discovery. A series of computational techniques have recently become available to aid in these tasks. We will discuss how predictive free energy calculations, synthesis-aware compound enumeration and next-generation machine learning techniques can rapidly accelerate the identification, under realistic conditions, of chemical matter that fulfils appropriate property constraints.

Specifically, we will recount how enumeration, FEP+ binding free energy calculations and Deep Chem machine learning models have been combined to rapidly generate and profile a library of novel compounds, based on commercially available building blocks, to explore both R-group and core-hopping modifications of an initial CDK2 inhibitor. The entire workflow provides a library of high-affinity, novel CDK2 inhibitors at a high enough throughput to positively impact pharmaceutical industry project timelines. Surprisingly, only a small fraction of the suggested cores had existing matches in Binding DB, despite featuring typical kinase hinge binding features and being achievable by straightforward synthesis. This indicates that exhaustive mining of easily accessible chemical space is typically not done in drug discovery today, even in a highly explored target class like kinases.

Beyond that, we will explore recent advances in applied free energy calculations and their impact on drug discovery programs. Overall, it appears that the combination of the complementary computational techniques in a single technology platform offers huge synergistic effects. We will present evidence that a true *de novo* computational design solution benefiting from these advances is now feasible.