Rapid Exploration of Synthetically Tractable Chemical Space for Hit-To-Lead & Lead Optimization

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In the effort to find new drug molecules, vast amounts of compounds are screened *in silico* for potential drug candidates. However, despite the huge number of molecules in the compound libraries used for these computational analyses, they constitute only a very tiny fraction of the chemical space of all drug-like compounds [1, 2]. Due to the enormous size of the drug-like chemical space consisting of up to more than 10^{60} molecules [1, 3], it is highly desirable to focus *in silico* analyses on cleverly selected, structurally diverse, synthesizable drug-like compounds. Especially in the hit-to-lead and lead optimization stages of the drug design process, it would be beneficial to be able to rapidly ideate synthetically tractable, chemically diverse compounds based on the structure of a hit or lead molecule.

Schrödinger's Pathfinder module for reaction based enumeration can, based on a provided "target" molecule, easily generate data sets of sensible and synthetically accessible compounds for computational drug design campaigns. Reaction based enumeration combines rapid enumeration with the functionality of Pathfinder identifying possible routes to desired targets. It is a synthetically aware enumeration tool enabling the user to prepare large compound libraries with significant diversity for the exploration of different R-groups and cores in the later optimization phases of the drug design process.

A study in which reaction based enumeration was combined with docking, multi-parameter optimization, FEP+ binding free energy calculations and active learning [4] showed that this enumeration tool can be useful for exploring a larger chemical space than conventional Structure Activity Relationship (SAR) studies and for identifying synthetically accessible compounds with better properties and potency. Therefore, this new enumeration tool may facilitate the rapid discovery of new drug compounds from the so far unexplored chemical space.

[1] R. S. Bohacek, C. McMartin, W. C. Guida, *Medicinal research reviews*, **1996**, 16, 3-50.
[2] T. Hoffmann, M. Gastreich, *Drug Discovery Today*, **2019**, *24*, 1148-1156.
[3] P. Kirkpatrick, C. Ellis, *Nature*, **2004**, 432, 824-828.
[4] K. D. Konze, P. H. Bos, M. K. Dahlgren, K. Leswing, I. Tubert-Brohman, A. Bortolato, B. Robbason, R. Abel, S. Bhat, *J. Chem. Inf. Model*, **2019**, 59, 3782-3793.