Chemistry-driven Hit-to-Lead Optimization

Guided by Structure-based Approaches

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For several decades, hit identification for drug discovery has been facilitated by developments in both fragment-based and high-throughput screening technologies. However, a major bottleneck in drug discovery projects continues to be the optimization of primary hits from screening campaigns to derive lead compounds. Computational chemistry or molecular modeling can play an important role during this hit-to-lead (H2L) stage by both suggesting putative optimizations and decreasing the number of compounds to be experimentally synthesized and evaluated [1]. However, it is also crucial to consider the synthesis accessibility of these virtually designed compounds.

Here, we report two chemistry-driven structure-guided methodologies to support the H2L stage. First, the Diversity-Oriented-Target-focused-Synthesis (DOTS) approach was designed for generic computer-aided H2L optimization mimicking either growing or linking strategies from fragment-based drug discovery [2]. This approach was validated using the development of high nanomolar bromodomain inhibitors starting from a low affinity fragment.

The DOTS approach has then been expanded to focus on covalent modifiers [3]. This new method called CovaDOTS can be described as a specific case of linking strategy that is suited for the design of covalent inhibitors starting from a non-covalent ligand. Indeed, the covalent mode of action can be described as a specific case of linking, where suitable linkers are sought to fuse a bound organic compound with a nucleophilic protein side chain. The proof of concept of CovaDOTS was successfully established using three retrospective study cases in which known non-covalent inhibitors have been converted to covalent inhibitors.

Bibliography:

[1] Hoffer, L.; Muller, C. et al. Mol Inform, 2018, 37
[2] Hoffer, L.; Voitovich, Y. V. et al. J Med Chem, 2018, 61, 5719-5732.
[3] Hoffer, L.; Saez-Ayala, M. et al. J Chem Inf Model, 2019, 59, 1472-1485