[L4] Integrated Strategy for Lead Optimization based on fragment growing: the DOTS (Diversity Oriented Target-focused Synthesis) approach

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Over the past few decades, hit identification in the pharmaceutical industry and academia has been greatly facilitated by advances in high-throughput screening (HTS) and the design of high-quality chemical libraries. One major hurdle remaining in drug discovery is process automation of hit-to-lead (H2L) optimization. Here, we report a time-efficient and cost-efficient integrated strategy, diversity-oriented target-focused synthesis (DOTS), for H2L optimization and partially automated design of potent chemical probes. DOTS consists of chemical library design and virtual screening coupled with robotic diversity-oriented *de novo* synthesis and an automated *in vitro* evaluation platform. Following hit identification by HTS methodology, the binding mode of the core molecule is usually determined at the atomic level using structural methods such as X-ray crystallography. In DOTS, a focused virtual library is generated by combining an activated fragment corresponding to the substructure binding to the target with a collection of functionalized building blocks using *in silico*-encoded chemical reactions. These reactions are carefully chosen from a list of one-step organic transformations that are relevant in medicinal chemistry and known to give high yields, which greatly limits attrition rates. Target-specific compounds are selected by virtual screening, followed by synthesis and evaluation *in vitro* using robotic platforms. The proof of concept was demonstrated using the optimization of bromodomain inhibitors as a test case, leading to the validation of several compounds with affinity improved by several orders of magnitude. The proposed process can be implemented in academic environments or biotech companies that require process automation.