

# Construction of Biologically Potential Library by Diversity-Oriented Synthesis

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An increasing number of therapeutic targets have been identified due to the rapid advances in genomics and proteomics. This has created a tremendous need to develop more efficient methods for the generation of new chemical entities which can be used as drug leads to modulate various disease targets in chemical biology and medicinal chemistry research. Combinatorial chemistry and high-throughput screening have been utilized in an effort to improve the quality and efficiency of early drug discovery. Although these approaches are highly efficient for creating and screening large numbers of compounds, their hit rates are far from satisfactory. This is often attributed to the lack of structural diversity in combinatorial compound libraries. It is recognized that molecular skeletons are more important than the appendices for high-throughput screening, and a compound library featuring a high degree of structural diversity can effectively increase the occupation of "chemical space", thus improving the hit rates for diverse biological targets in "biological space" [1,2]. Traditionally, combinatorial libraries yield similar molecular skeletons decorated with different substituents, and display narrow diversity in chemical space. Therefore, the library quality (structural diversity) counts more than its quantity (number of compounds) in 'unbiased' screening processes.

The ability to establish compound libraries encompassing a high level of structural diversity, which populate wider areas of chemical space, is one of the key factors required for improving the success of biological screenings. To address this issue, diversity-oriented synthesis (DOS), introduced by Schreiber [3], has emerged as a powerful and efficient tool for generating libraries of complex and diverse molecules. A successful DOS library usually features three types of diversity: substitutional diversity, stereochemical diversity, and most importantly skeletal diversity. In recent years, considerable research has been carried out to increase the structural diversity of compound libraries by DOS methods [4-11]. The dominant strategies include "build/couple/pair (B/C/P)", functional group pairing, reagent-based and substrate-based approaches.

Besides structural diversity, drug-likeness of a DOS library is also a critical issue to improve the success of discovering biologically functional compounds in assays [12,13]. A diverse library which is created with little consideration of drug-likeness properties may be subjected to more absorption, distribution, metabolism, excretion, and toxicity (ADME/T) problems during the drug discovery process. Privileged structures typically exhibit good drug-like properties, and the chemical space around privileged structures is usually rich in biological activity. Incorporation of privileged structural motifs in DOS pathways may lead to the creation of both diversity and drug-likeness in compound libraries. This concept of DOS around privileged structures is termed as "privileged-substructure-based DOS (pDOS)" [14]. Park's laboratory has applied the pDOS concept to construct various polyheterocyclic molecules embedded with benzopyrans, pyrroles, carbohybrids, and acetal-fused pyranopyrones.

Despite these advances, robust strategies for efficient construction of DOS, especially around privileged structures, libraries are still significant and needed. High-quality libraries with both structural

diversity and drug-likeness provide valuable sources to explore new areas of chemical space compared with libraries produced by traditional combinatorial chemistry. As a result, the greater biological diversity is potentially rewarding and should facilitate the lead generation in drug discovery process.

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