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Future Frontiers in Diversity-Oriented Synthesis

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The late 1980's to mid-1990's ushered exciting developments in pharmaceutical research worldwide. With innovative tools and techniques provided by combinatorial chemistry and molecular biology, a tremendous amount of effort and money was invested into the application of highly efficient high-throughput screening (HTS) technologies that could screen thousands of compounds at a time [1,2]. However, medicinal chemists were confronted with the painful realization that the chemical space was too vast to be fully explored. The understanding emerged that library size was not paramount, and that the diversity of molecules in the library is a critical determinant for the success of any screening campaign [3]. Early combinatorial libraries sacrificed diversity in order to accommodate facile reaction and purification methodologies, resulting in the production of collections of compounds that lacked structural complexity.

Diversity-oriented synthesis (DOS) is a strategy that aims to tackle the issue of the colossal chemical space within the constraints of finite time and resources. Given that shape complementarity is the fundamental basis by which Nature processes and directs cellular information, it should be desirable for chemical libraries to contain compounds with a diverse range of molecular architectures, particularly if the exact nature of the target is not known [4]. To achieve this, DOS aims to utilize chemical reactions to generate a variety of different molecular scaffolds, upon which peripheral functional decorations can be attached. Indeed, it has been recognized that the diversity of the central scaffold is one of the most important determinants of structural diversity, with libraries containing a small number of compounds based around multiple scaffolds being superior to those with larger numbers of molecules based on a single scaffold [5]. Since the seminal presentation of the DOS concept by Schreiber over a decade ago [6], the field of DOS and its applications has expanded at a remarkable rate.

Organic synthetic methodologies lie at the heart of DOS, as they allow the fabrication of complex molecular scaffolds from more simple starting materials. A few synthetic strategies have attracted particular attention for use in DOS due to their versatility. In a multi-component reaction (MCR), several building blocks are appended together to generate a larger scaffold with multiple points of diversity [7]. Recently, Cerulli et al. have employed the Ugi multi-component reaction to generate structurally diverse polyfunctionalizedpyrrolidines from a chiral cyclic imine, two enantiomerically pure isocyanides and various carboxylic acids [8]. Cycloaddition reactions, including the well-known "click" reactions, can generate diverse cyclic and heterocyclic scaffolds with a high degree of structural and stereochemical complexity [9]. For example, Tan et al. have recently reported the first 1,3-dipolar cycloaddition of electron-deficient alkynes with isatin-based azomethineylides, generating a diverse variety of spiro-oxindole-based 2,5-dihydropyrroles [10]. Ring-closing metathesis can furnish rings of a wide range of sizes [11], and Ascic et al. have recently utilised this technique to generate various 5- and 7-membered heterocycles and cyclic animals from amino alcohols with alkene substituents [12]. Additionally, an overarching framework that has been employed in DOS is the so-called build/couple/pair (B/C/P) approach presented *Nielsen and Schreiber* [13]. In the "build" step, stereochemically diverse building blocks are synthesized, which are combined in the "couple" phase to yield multiple stereoisomeric combinations of a larger structure. In the final "pair" stage, the molecule can be transformed into distinct scaffolds through the use of a variety of different cyclisation reactions.

Towards the future, we envisage that DOS will continue to contribute to the discovery of new synthetic methodologies that can be used for scaffold generation. With persistent improvement in scaffold diversity in compound libraries, a greater proportion of the chemical space can be efficiently explored. Additionally, practitioners of DOS may find synergy with other disciplines in chemistry and biology to enhance the success of an integrated drug discovery program. In a recent study, Hung et al. have applied DOS principles to fragment-based drug discovery (FBDD) in order to generate sp^3-rich fragments with increased complexity and three-dimensional character [14]. If the structure of the biological target is known, structure-based or ligand-based virtual screening techniques could guide the synthesis of scaffolds towards those that might be expected to show activity. Finally, the very nature of DOS encourages a greater application of phenotypic screening, a technique that has been somewhat neglected in the pharmaceutical industry in favor of target-based approaches, as a plethora of both known and unknown biological processes can be simultaneously interrogated by the powerful structural diversity of molecules generated by DOS. Given the innovative studies in DOS that have been reported over the last few years, we believe that organic chemistry will continue to play a central role in the development and maturation of this exciting field.

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