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The use of combi chem, high-speed analog chemistry and HTS in drug discovery ▼

Over the past decade, research groups in both the pharmaceutical industry and academia have used combi chem and high-speed analog chemistry (HSAC) as tools in the drug discovery process. When coupled with HTS, these approaches have led to the discovery of a significant number of lead structures, clinical candidates and marketed compounds. In a recent issue of *Drug Discovery Today* [1], a timely review describes the use of combinatorial chemistry to discover active matter at signal transduction targets.

Although the review focuses on one strategy (comb chem), I believe that it is necessary to re-emphasize the distinction between combi chem and HSAC. These are distinct chemical synthesis strategies; however, the terms describing them are sometimes used interchangeably. The field of combi chem has focused on the preparation of a limited number of the 10^{100}–10^{200} potential structures that can be made that do not violate the Lipinski 'rule of five' [2]. Variations of this combinatorial strategy include 'diversity oriented synthesis' approaches. Although compounds with excellent potency and specificity can be made, combi chem approaches have typically resulted in libraries of compounds with high logP values, low hit rates and poor ADME characteristics [2,3]. These liabilities truly become magnified (and highly costly) in moving from HTS hits to clinical candidates, where optimized ADME properties are crucial.

By contrast, HSAC focuses on the synthesis of compounds around a common scaffold. When the scaffold is chosen correctly, these densely populated analog expansions typically result in libraries of compounds with better hit rates and good ADME/Tox characteristics. Moreover, analogs derived from carefully chosen 'preferred' scaffolds with demonstrated good 'drug-like' properties would be predicted to have a better chance of delivering a clinical development candidate in a timely and more cost efficient fashion. For example, analogs based on the benzodiazepine template (a 'preferred' scaffold), have resulted in compounds with activities against GPCR, ligand-gated ion channel and kinase targets [4,5]. An inherent benefit of the HSAC approach is that most of the resulting compounds already possess good drug-like properties. Therefore, it should require less time and resources to bring an HTS hit to a clinical development candidate.

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