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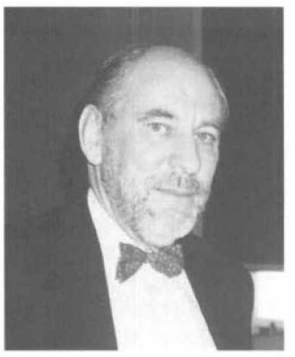
Combinatorial Chemistry: A New Paradigm for Drug Discovery



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For part of the content of the presentation see: *H.M. Geysen, C.D. Wagner, W.M. Bodnar, C.J. Markworth, G.J. Parke, F.J. Schoenen, D.S. Wagner, D.S. Kinder*, 'Isotope or Mass Encoding of Combinatorial Libraries', *Chemistry & Biology* **1996**, *3*, 679.

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Strategy and Tactics in Combinatorial Organic Synthesis. Applications to Drug Discovery

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Abstract. A strategic analysis of various issues which pertain to the enablement of combinatorial organic synthesis to produce libraries of non-polymeric organic molecules is given. Methods and examples of the development of solid-phase organic chemistry and its subsequent application to combinatorial library synthesis for drug discovery is illustrated with successful case studies. The synthetic versatility of resin-bound amino-acid-derived imine intermediates to produces β-sultams and pyridines is shown. Use of natural products as key components for creation of combinatorial libraries is presented using *Rauwolfia* alkaloids and the cephalosporin nucleus as examples.

1. Strategy in Combinatorial Synthesis

A comparison between conventional and combinatorial approaches to drug discovery reveals an apparent discontinuity in the strategies and tactics brought to bear by these respective techniques [1][2]. Though the principles underlying chemical reactions are of course invariant, the practice of combinatorial organic chemistry as it relates to lead discovery diverges markedly from serial compound synthesis. For example, in a conventional medicinal chemistry approach, single compounds of previously specified structure are iteratively synthesized and subjected to biological evaluation. In contrast, the goal of combinatorial chemistry is to create screenable *populations* of molecules. Thus, the potential success of the combinatorial approach is leveraged since extremely large numbers of analogs of a previously specified *substructure* are prepared and screened. The mechanics of developing a combinatorial synthesis also affords distinct advantages. Combinatorial synthesis on solid support greatly simplifies the problem of product isolation, and in contrast to solution-phase synthesis, easily permits use of large numbers of building blocks (BB) and reagent excesses to drive reactions to completion. These factors frequently result in solid-phase synthesis (SPS) providing products in higher yield and purity than the corresponding chemistry in solution! Combinatorial chemical reactions must proceed reliably in the face

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