Book review

Combinatorial Chemistry and Molecular Diversity in Drug Discovery

edited by Eric M. Gordon and James F. Kerwin, Jr, Wiley–Liss, 1998. £25.50 (516 pages, hardback) ISBN 0-471-15518-7

Making new drugs is a long, complex and expensive undertaking. It costs an average of $500 million and takes 15 years for each new drug to reach the market. In the competition to find the breakthrough product, reducing the cost and the time for drug discovery is a major objective.

With combinatorial chemistry, millions of compounds can be produced simultaneously, and in most cases by automated procedures. The synthesis of such compound libraries, with the evolution of this field from peptide and other natural bio-oligomer libraries to heterocyclic and small organic molecule libraries, is a cost-effective approach for the pharmaceutical industry to search for novel bioactive lead structures. Today, combinatorial chemistry and molecular diversity (CCMD) has advanced to include library strategies, design principles, scaffold design, solid-phase methods, encoding, spatial-separation paradigms and quality control issues.

This book provides an overview of the broad and exploding field of CCMD. It comprises 27 chapters written by experienced scientists largely from the pharmaceutical and biotechnology industries, but also from academia, who contribute in their own specific area of expertise. The chapters are organized into six parts:

- Introduction to combinatorial chemistry and molecular diversity
- Small molecules libraries
- Automation, analytical and computational methods
- Biological diversity
- Screening
- Combinatorial drug screening and development

The first chapter gives an historical overview of the developing field of molecular diversity from both biological sources and from chemical synthesis. Advances in biological methods have included manipulation of microorganisms, DNA synthesis, cloning and sequencing, phage-display libraries and peptides-on-plasmid techniques.

The second chapter is particularly useful; it describes the strategic principles that led to the design of a library, not only its synthesis but also its evaluation in terms of rational design and its implications for screening. Combinatorial chemistry approaches require an interdisciplinary research environment, involving chemistry, biology, engineering, informatics and other fields such as instrumentation. The important fact outlined here is that some effort is now required for the registration of libraries, for the screening of information and for the quantification of diversity. New tools of database management need to emerge.

The following 300 pages of the book review the state of the art in combinatorial chemistry including peptide and oligonucleotide libraries and small organic molecules libraries with heterocyclic pharmacophores, building block collections and a large variety of scaffolds and cyclic templates. These sections are essentially devoted to chemical methods used to obtain such libraries and to the analytical tools available for their evaluation and quality control. Chemical reactions are indicated, with useful comments and some examples of their application.

One section is devoted to the screening of combinatorial libraries produced by parallel, mix-and-split or random incorporation synthesis. The different approaches and technologies are described. The main strategy in the analysis of libraries, such as labelling by fluorescent or radioactive dyes or tags, spatial encoding and the powerful gel-permeation method, are now routine high-throughput screening (HTS) procedures based on 96-well microplate and robotic liquid-handling technology. Nevertheless, signposts to the future indicate that to identify novel lead molecules rapidly, compound screening *in silico* will become a dominant feature.

This book is as broad as has yet been published in the field of CCMD and is a significant survey of the research areas into which the combinatorial chemistry field has recently spread. It would be a reference volume for newcomers to the field and those who are involved in drug discovery and it should benefit anyone who wishes to review this technology platform. The main research areas and approaches of CCMD are described and well documented by full schemes, figures and tables. Every chapter includes literature references for further in-depth reading, and ends with the future directions of the area overviewed. This is an interesting feature because of the rapid rate of progress in applying and developing combinatorial technologies. With the unceasing discovery of new tools in library synthesis and evaluation, and of new concepts in measuring and quantifying molecular diversity, the applications of CCMD will continue to play a fundamental role in healthcare research.

One major highlight of the book is to position CCMD as an essential tool for rational drug discovery, instead of as a mere frame for exploiting HTS, as it was in the early 1990s. The book's only weakness is that the computational techniques for analysis of diversity are scarcely represented, in spite of the fact that such virtual combinatorial chemistry tools are seen as the future of CCMD. Overall, the book is certainly a good reference document, although perhaps more so for those who want to learn more about the domain of CCMD than for the experts within it.

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