Book review

Combinatorial Chemistry

by Nick Terrett, Oxford University Press, 1998. £25.00 (200 pages, hardback)
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Combinatorial chemistry has become an integral part of pharmaceutical research in both lead identification and optimization. The creation of large libraries using automated systems for lead generation typically remains the domain of the specialist group. However, for lead optimization targets, a sound knowledge and understanding of the principals of combinatorial chemistry, parallel-array synthesis and solid-phase techniques are important to allow the selection of the best approaches to specific problems. All medicinal chemists need to establish and maintain this understanding, and this has led to a proliferation of research papers, reviews, annual series and, more recently, handbooks and books devoted to the subject. So is another book on combinatorial chemistry necessary, and what can this book add to the understanding of the practicing scientist?

Concise summation of the field

Nick Terrett has been involved in the development of combinatorial chemistry at Pfizer for many years, and this involvement and his insight into the practicalities of combinatorial chemistry and its use in lead optimization has allowed him to produce a clear and concise summation of the field, without becoming too heavily entrenched in speciality areas. This book provides a valuable entry point into understanding both the development of and the practicalities of using the techniques in research today. The development of combinatorial chemistry out of solid-phase peptide synthesis is well documented in this book, and the subsequent development of less and less peptide-like oligomeric libraries describes an elegant story of the movement of the field towards the small molecule arena of drug discovery. During this section, some reference to failed approaches and grand 'universal' libraries that were envisaged by many groups yet failed to deliver on their promise might have served to illustrate the rapid change that has occurred in this field. The discussions on the value and merits of solution- and solid-phase approaches, the use of tagging techniques and the illustration of examples in the pharmaceutical field provide a well balanced view on the need to apply the correct solution to each problem that few experts in the field could question. One specific section worthy of further comment is the discussion on linkers, which is well structured, easy to read and easy to use as a reference point. The focus on functional group rather than specific linker or resin provides a comfortable feel to chemists used to dealing with similar approaches for protecting-group strategies and functional-group manipulations. Finally, the abbreviation list at the start of the book is extremely valuable. In a field where many practitioners invent new verbs and nouns as well as acronyms and abbreviations this listing is valuable both when reading this book and for general reference when reading other works.

There are a few omissions that could have lent further value to this book. A section on the practical aspects of solid-phase chemistry would have been useful, given that most universities are only now beginning to add solid-phase synthesis to their teaching programmes. The techniques of reaction monitoring are well discussed, though the omission of describing Fmoc number counts to follow loading and reaction profiles on solid-phase chemistry is surprising. The practicalities and problems of bead handling associated with single-bead screening and tagging procedures could have merited some comment. For readers interested in areas mentioned only in passing (phage display, continuous flow synthesis), leading references would have been beneficial. Finally, the book would have benefited from some photographic illustrations, especially when describing resins and other equipment and phases used in solid-phase synthesis.

The final conclusions drawn by the author are ones that I, and many others, will share whole-heartedly. Combinatorial chemistry provides a range of tools that can be applied to the real challenges of drug discovery. Once the integration of these tools is entrenched into the process, then the proliferation of papers and conferences on this field will begin to abate, because the successes will be reported in the mainstream medicinal chemistry journals and conferences. Until that time there is a need for well-written introductions for new practitioners in the field and for good reference material for those who have contributed to the developments – this book provides both.

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