Book Reviews

Exploiting Chemical Diversity for Drug Discovery. Edited by Paul A. Bartlett and Michael Entzeroth. RSC Publishing, The Royal Society of Chemistry, Cambridge, U.K. 2006. xxiv + 420 pp. 16 × 24 cm. ISBN 0-85404-842-1. £119.95.

The discovery of a new drug candidate and its identification as a useful therapeutic entity is a complex, multistep process involving diverse scientific disciplines. A major objective of pharmaceutical research has been to improve this drug discovery process in order to make it faster, more efficient, and productive. Accordingly, during the past 50 years the concepts and approaches to the discovery and development of new drug products have undergone many changes. Because only about 1 in every 10 000 compounds synthesized for evaluation as a potential therapeutic agent survived as a marketed product, in the 1980s pharmaceutical research efforts began to be directed toward technologies such as combinatorial chemistry, large compound library screening, high-throughput screening, etc. that enabled faster evaluation of larger numbers of compounds. These efforts, however, did not result in the anticipated increase in new drug products. In 2002, only 17 new chemical entities, an historical low, were approved by the United States Food and Drug Administration, and this number increased only slightly to 21 in 2003. About 40% of the new therapeutic candidates selected on the basis of potency and selectivity failed because of their pharmacokinetic, physicochemical, and toxicological properties. In an effort to increase the probability for the clinical success of new drug candidates, new strategies have been developed. This volume describes a diverse group of recent changes that have occurred in both chemistry and screening in an effort to enhance the discovery of new therapeutic agents.

The first eight chapters are directed toward a variety of methods that have been developed more quickly to obtain candidates of good quality for screening for potential therapeutic utility. Chapter 1 illustrates, with numerous examples, the use of polymer-assisted solution-phase synthesis and automation to expedite the synthesis of biologically active compounds. Chapter 2 describes various approaches, e.g., microwave, sonochemical, and fluorous phase techniques, employed to accelerate synthesis and isolation of new drug candidates. The next four chapters deal with chemical libraries for screening. Chapter 3 considers the combinatorial biosynthesis of new polyketides related to natural polyketide drugs, e.g., erythromycin, tetracycline, daunorubicin, rapamycin, lovastatin, etc. Chapter 4 describes various strategies for the targeted design, i.e., the use of druglike scaffolds, e.g., benzodiazepinones, for the preparation of new compound libraries via combinatorial chemistry methods. Chapter 5 reviews compound collections that are available for drug discovery and some methods for optimizing selection of compounds for screening. Quantitative estimation of the extent of differential features and properties within a compound collection, i.e., chemical diversity, is the topic of Chapter 6. Chapter 7 considers the evolution of high-throughput screening methods from the early large-diversity combinatorial libraries to more specific target-oriented libraries. An overview of approaches to the identification of biologically active peptides and methods for transforming them into small molecules or peptidomimetics is presented in Chapter 8.

The next five chapters deal with operational developments in screening and high-throughput assays. The application of "miniaturization" and "parallel processing" in the development of high-density well plates and microassays for high-throughput experiments in pharmaceutical research is considered in Chapter 9. The rapidly expanding applications of fluorescence detection technologies in the high-throughput screening of chemical libraries are considered in Chapter 10.

The increasingly important use of genetically engineered cell-based assays in drug discovery is the subject of Chapter 11. New screening technologies involving NMR have become valuable tools in drug discovery. These are reviewed in Chapter 12. Methods and applications of various chemical microarrays in screening are the topic of Chapter 13.

The final four chapters deal with various technologies that promote sound evaluation of side effects, pharmacokinetics, toxicity, etc. that may increase the probability of success in developing drug candidates. Chapter 14 considers various methods for assessing the selectivity of lead compounds. The application of in vitro methods, as well as physicochemical and pharmacokinetic values, in the selection of drug candidates is the focus of Chapter 15. The use of in silico, i.e., computational or computer-assisted, methods as predictors of in vivo absorption, distribution, metabolism, excretion, and toxicological properties of drug candidates is the subject of Chapter 16. The final chapter deals with high content screening, which is a microscopy-based screening in which pictures of cells in culture are viewed in order to deduce the biological effect of chemicals in the cellular environment.

Each chapter contains a comprehensive and up-to-date list of references as recent as 2005. The book concludes with an adequate subject index. Written by 39 academic and industrial experts from a variety of scientific disciplines, Exploiting Chemical Diversity for Drug Discovery provides an excellent introduction to evolving methodologies in the drug discovery process. It will be of interest as a reference resource and an excellent overview for medicinal chemists and all others involved in the drug discovery process.

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