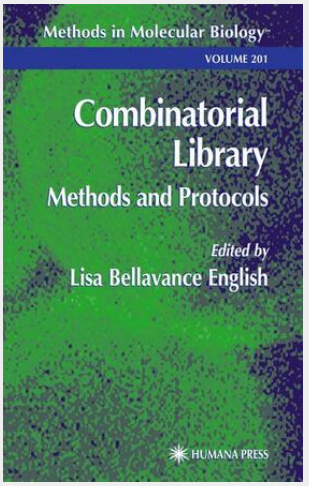
English

Combinatorial Library

Methods and Protocols



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The continued successes of large- and small-scale genome sequencing projects are increasing the number of genomic targets available for drug d- covery at an exponential rate. In addition, a better understanding of molecular mechanisms—such as apoptosis, signal transduction, telomere control of ch- mosomes, cytoskeletal development, modulation of stress-related proteins, and cell surface display of antigens by the major histocompatibility complex m- ecules—has improved the probability of identifying the most promising genomic targets to counteract disease. As a result, developing and optimizing lead candidates for these targets and rapidly moving them into clinical trials is now a critical juncture in pharmaceutical research. Recent advances in com- natorial library synthesis, purification, and analysis techniques are not only increasing the numbers of compounds that can be tested against each specific genomic target, but are also speeding and improving the overall processes of lead discovery and optimization. There are two main approaches to combinatorial library production: p- allel chemical synthesis and split-and-mix chemical synthesis. These approaches can utilize solid- or solution-based synthetic methods, alone or in combination, although the majority of combinatorial library synthesis is still done on solid support. In a parallel synthesis, all the products are assembled separately in their own reaction vessels or microtiter plates. The array of rows and columns enables researchers to organize the building blocks to be c- bined, and provides an easy way to identify compounds in a particular well.

By significantly increasing the number of targets available for drug discovery, the Human Genome and Proteome projects have made the use of combinatorial libraries essential to developing and optimizing drug candidate molecules more rapidly. Lisa English and a panel of expert researchers have collected in Combinatorial Library Methods and Protocols a novel series of computational and laboratory methods for the design, synthesis, quality control, screening, and purification of combinatorial libraries. Here the reader will find cutting-edge techniques for the preparation of encoded combinatorial libraries, for the synthesis of DNA-binding polyamides, and for combinatorial receptors. There are also state-of-the-art methods for computational library design, quality control by mass spectrometry, and structure verification using 1D and 2D NMR. A variety of well-known computational approaches are provided to meet the information management challenge of multiple biological assays. Each readily reproducible technique includes detailed step-by-step instructions and helpful notes on troubleshooting and avoiding pitfalls. Timely and highly practical, Combinatorial Library Methods and Protocols makes available for all drug discovery researchers all the powerful combinatorial chemistry tools that are increasing the number of candidate compounds and speeding the process of drug discovery and development today.