

Combinatorial Library

Methods and Protocols

The continued successes of large- and small-scale genome sequencing projects are increasing the number of genomic targets available for drug discovery at an exponential rate. In addition, a better understanding of molecular mechanisms—such as apoptosis, signal transduction, telomere control of chromosomes, cytoskeletal development, modulation of stress-related proteins, and cell surface display of antigens by the major histocompatibility complex molecules—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 combinatorial 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: parallel 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 combined, and provides an easy way to identify compounds in a particular well.

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160,49 €

149,99 € (zzgl. MwSt.)

Lieferfrist: bis zu 10 Tage

Artikelnummer: 9780896039803

Medium: Buch

ISBN: 978-0-89603-980-3

Verlag: Humana

Erscheinungstermin: 22.08.2002

Sprache(n): Englisch

Auflage: 2002

Serie: Methods in Molecular Biology

Produktform: Gebunden

Gewicht: 1670 g

Seiten: 383

Format (B x H): 157 x 235 mm

