Principles, Software, Tools, and Applications in Drug Discovery

Combinatorial Library Design and Evaluation

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Combinatorial chemistry and library design are relatively new fields, and this is one of the first books published to cover them. Combinatorial library use is now common in the drug discovery industry, and is moving into use in other fields.

However, there is still disagreement regarding the best techniques to use, and especially in how to balance the need for chemical diversity with the need for drug-like characteristics. This volume discusses not only the historical development of many commonly used techniques, but also describes state of the art methods still in development. The early chapters especially give extensive historical reviews and include large numbers of specific examples and references. The combination makes this a valuable resource for researchers and students getting started with combinatorial library design.

Both editors of this 648-page, hardcover book currently work for Amgen, Inc. Each received a Ph.D. in India, then did post-doctoral work in the United States before moving to Amgen. The individual chapters were written by more than 50 scientists from 22 companies, universities and research institutes in the United States and Europe. The 5 main sections and 20 included chapters are described in more detail below.

The first chapter is a thorough introduction, entitled 'Library Design Concepts and Implementation Strategies', giving a medicinal chemists' view of combinatorial library design. It discusses the various possible goals of combinatorial libraries, advantages and disadvantages of solid phase organic synthesis vs. solution phase synthesis, and library construction strategies (parallel vs. pooled synthesis). Compound design within various library types is also explained — combinatorial libraries (managing diversity and molecular properties), discovery libraries (where synthetic efficiency, diversity and lead quality are the guiding factors), targeted libraries (less molecular diversity, clustered around a particular structure) and optimization libraries (primarily used to improve pharmacokinetic properties). This well-researched chapter has many examples of actual libraries and strategies employed by various pharmaceutical companies, as well as 150 references for further investigation.

The second section is entitled 'Design Principles', and contains chapters that discuss the various design methods being used in drug discovery today. The chapters include:

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Each chapter contains a wealth of background information on that technique in general, not just how it applies to combinatorial libraries. The first chapter in this section gives a detailed history of pharmacophore development, the stages of drug discovery when the concept is the most useful, and them moves on to the use of pharmacophores in library design. Also included are specific examples of libraries that have used these techniques. Chapter 3 talks about 1-D and 2-D QSAR, and begins with an exhaustive historical overview and background, as well as methods to distinguish drug-like and non drug-like molecules. An extensive table listing successful applications of QSAR, and another listing QSAR software and sources will prove a useful reference.

Chapter 4 moves on to 3-D QSAR, and discusses building a model of the receptor, as well as features required in the ligand. The next chapter moves on to discuss two ligand docking systems — methotrexate/dihydrofolate reductase and cyclodextrin glycosyltransferase-maltose. The first is a common success story in ligand–protein docking algorithms, and the later is a common failure. By examining how they are treated with different methods, the advantages and disadvantages of various approaches are elucidated. Chapter 6 gives background on structure-based computer-aided drug design methods, with a detailed description of the continuum electrostatic approach (as developed by the author of this chapter) for docking small to medium sized fragments, as well as detailed descriptions of application to a specific example. The final chapter in this section talks about classical QSAR methods and scoring functions, and gives specific recommendations on using estimates of binding affinity and predictions of distribution, metabolism and other pharmacokinetic properties to reduce the number of iterations required in the drug discovery cycle.

Part 3 of this book is entitled 'Current Methods and Software Tools', and contains chapters describing various software tools currently available for library design. The chapters are:

- Knowledge-Based Approaches for the Design of Small Molecule Libraries for Drug Discovery
- Drug-Likeness Profiles of Chemical Libraries
- Tools for Designing Diverse, Drug-Like, Cost-Effective Combinatorial Libraries
- Relative and Absolute Diversity Analysis of Combinatorial Libraries
- Rational Combinatorial Library Design and Database Mining Using Inverse QSAR Approach
- Dissimilarity-Based Compound Selection for Library Design
- Pharmacophore-Based Approaches to Combinatorial Library Design
- High-Throughput Conformational Sampling and Fuzzy Similarity Metrics: A Novel Approach to Similarity Searching and Focused Combinatorial Library Design and Its Role in the Drug Discovery Laboratory

Chapter 8 reviews developments in drug database analysis, to try to

arrive at a concensus on what the characteristics of a drug-like molecule are, and an automated way to select groups of compounds that balance diversity and drugability, (DURGA algorithm). The next chapter briefly describes methods that have been developed by three separate groups (Gilet & Bradshaw, Ajay, *et al.*, and Sadowski & Kubinyi) to recognize and rank the druglikeness of chemical compounds, using information implicitly available in databases of drugs and general chemicals. Chapter 10 discusses software available from MSI (now known as Accelerys, Inc.) to address library development factors of diversity/similarity selection, druglikeness, cost-effectiveness and time constraints, and how they can be combined to produce a set of criteria that can be simultaneously applied to select a synthesis subset from a virtual library. Chapter 11 discusses a broad range of molecular descriptors and the (dis)similarity measures used with them, including substructural keys and hashed fingerprints, atom pairs and topological torsions, connectivity indices and BCUT descriptors, estimated physical properties, and pharmacophore triplets and tetrads. The following chapter describes the inverse QSAR method, or the use of QSAR models for rational design of targeted chemical libraries and database mining.

Chapter 13 moves on to computational methods used to ensure coverage of the largest possible expanse of chemical space in the search for bioactive molecules, especially through the use of various dissimilarity-based compound selection methods, and in particular the SELECT algorithm developed by the authors of this chapter (Gillet & Willett). Chapter 14 describes methods for library development based on the pharmacophore, to incorporate 3-D information without requiring computationally intensive molecular superposition. The final chapter in this section discusses a method for the buildup and exploitation of a virtual library of chemically feasible compounds, using fuzzy mathematics. The authors postulate that since the "similar compounds have similar activities" hypothesis is imprecise, it does not rigorous mathematical treatment is not required in its implementation.

The final section of this book deals with the applications of library design in the industrial setting, and includes:

- Applications of Cell-Based Diversity Methods to Combinatorial Library Design
- Structure Based Combinatorial Library Design and Screening: Applications of the Multiple Copy Simultaneous Search (MCSS) Method
- Genetic Algorithm-Directed Lead Generation
- Enhancement of the Drug Discovery Process by Integration of Structure-Based Drug Design and Combinatorial Synthesis
- Design of Structural Combinatorial Libraries that Mimic Biological Motifs

Chapter 16 discusses a property-based reagent/synthon selection tool, intended for use by the bench chemist to design diverse libraries. By analysing the clustering patterns of active compounds, insight is gained into potentially useful descriptors and methods for library development. The next chapter discusses fragment positioning methods (methods that determine energetically favorable binding positions for various functional groups or fragments) and their use in combinatorial library design. It also talks about the specifics of the MCSS method and its use to design structure based peptide, small organic compound and large focused libraries, and the use of MCSS-generated theoretical pharmacophores for database and virtual library screening. Chapter 18 moves on to library generation methods developed using adaptive learning (genetic) algorithms.

The penultimate chapter describes, using several specific examples, the use of structure-based design in conjunction with combinatorial chemistry, to reduce the number of compounds in a library while

increasing the production of active molecules. The final chapter talks about the design of libraries whose compounds mimic biological motifs — especially a specific method for small cyclic analogs of protein loops, and the use of screening results to develop computational models that reasonably separate active compounds from inactives.

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