Modern Methods of Drug Discovery

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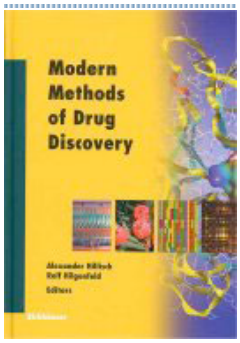

This concise volume offers a broad overview of the newest techniques being used in pharmaceutical research today.

Many of these techniques have only been developed in the last 10–15 years and continue to evolve rapidly. This book skims the surface of a wide variety of techniques, aiming for breadth, not depth, of coverage.

The specific methods described in this volume include proteomics, bioinformatics, high-throughput screening techniques, natural products, combinatorial chemistry, molecular diversity, compound library design, protein 3D-structures, NMR-based screening, 3D QSAR in modern drug design, physicochemical concepts, and computer-aided prediction of drug toxicity and metabolism.

Each chapter focuses on a specific area, beginning with a brief introduction, often describing the historical problems that lead to the development of that method. The chapter itself then delves into the details of the method, including which techniques are most appropriate for particular situations. Where appropriate, both computational and experimental methods are described.

A number of both black and white and colour illustrations, as well as extensive citations to the peer-reviewed literature, provide a solid foundation for further research into any of the techniques.

This slim volume boasts 28 contributors from pharmaceutical companies and academic institutions, 10 in the United States and the remainder throughout Europe.

The book does have some shortcomings. Several of the chapters would have benefited from more careful editing, most likely being written by non-native English speakers. More web sites as references, instead of just peer-reviewed literature, would have kept the book from becoming outdated as quickly. A discussion of how the various techniques can be used together would have been valuable, but was perhaps outside the focus of this volume.

This volume would be a valuable asset to anyone who needs a quick introduction to the wide variety of methods being using in drug discovery today, especially students or other newcomers to the drug discovery field. The individual chapters are discussed in more detail below.

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Chapter 1 is 'Modern methods of drug discovery: An introduction', an overview of the drug discovery process, describing the various phases along the drug discovery pipeline and the economics of drug discovery.

It discusses where in the process the various techniques that are discussed in later chapters fit. At the outset it is made clear that none of these methods are a magic cure-all that will instantly shave years off the drug discovery cycle, but instead are complementary tools with different strengths and weaknesses, which must be applied appropriately and synergistically.

The first technique described is 'Proteomics', which includes technologies for protein mapping (separating, distinguishing and quantifying the proteins present in individual samples), and techniques for identifying specific proteins and characterizing their complete structure and functional role.

The main protein mapping technology in use today is two-dimensional polyacrylamide gel electrophoresis (2D-PAGE), which can resolve up to 2000 proteins on a single gel — significantly better than other separation techniques, but still not the 6000 proteins expressed by typical tissues.

The use of mass spectrometry (MS) and genomics-derived sequence databases for protein characterization is briefly discussed, as are new directions such as HPLC and capillary electrophoresis for separation, proteomic diagnostics, and target discovery and validation.

Bioinformatics is discussed next, as a "theoretical, computer-based science dedicated to the extrapolation of biological knowledge from biological information". Bioinformatics today is mainly the filtering and assessing of likely drug target candidates, especially targets derived from genomic applications. Genomics produces huge numbers of sequences, but those genetic sequences must be examined to identify the regions of similarity and/or identity and thus of possible pharmaceutical interest.

A wide variety of methods have been developed for conducting sequence comparisons (mainly pairwise methods and profile methods) as well as for scoring the matches, and the most important of these are discussed.

Biological databases, including sequence databases, domain databases, structural classification databases, comparison, mutation and bibliographic databases are described. Gene characterization (the prediction of reading frames and exons from sequence) and EST (expressed sequence tag) clustering are also discussed briefly, as are protein structure prediction and metabolic simulation.

Chapter 4 discusses the rapidly developing and highly automated field of high-throughput screening (HTS) techniques. Newer developments such as miniaturization, parallel processing, μHTS and chip technologies are discussed in detail.

Logistical challenges in the implementation of an HTS program, sample sourcing, and storage are discussed, along with plating technologies, detection methods and chip technologies. Photos of the mechanical systems being described add visual interest.

Almost 1/3 of all drugs (and clinical candidates) are natural products, and the next chapter describes how natural products can be used for lead identification.

The historical review that begins this chapter lists many of natural products, their sources, and their use as a source of structural diversity. The Natural Products Pool that has been formed for industrial drug discovery purposes is also described.

Chapter 6 focuses on a specific type of combinatorial chemistry,

libraries built from amino acids and short peptides. Combinatorial chemistry has gained rapid acceptance by both industry and academia, for its ability to rapidly produce a large number of structurally similar molecules.

Two synthetic methods — divide, couple and recombine (DCR) and reagent mixture — are discussed. Deconvolution methods, used to identify the individual active compounds in a mixed batch, including iterative deconvolution, positional scanning deconvolution and tagging are also described. The final section describes a specific example of work with peptidomimetic libraries formed by chemical transformation of existing peptide libraries.

The quantitation of molecular diversity is one of the most interesting problems in chemistry today. Diversity calculations are used to develop appropriate selection strategies and allow synthesis of the smallest number of compounds possible, while still covering a significant portion of structure space and retaining drug-like qualities. Various descriptors and methods of using them are discussed in chapter 7, 'Computational approaches towards the quantification of molecular diversity and design of compound libraries'.

A number of descriptors derived from 2D, 3D, and alternative methods are discussed. In addition, numerous ways to select compounds based on their diversity, including maximum dissimilarity, cluster analysis, and cell-based analysis, are described. Descriptor validation methods are used to measure the effectiveness of particular descriptors for particular targets, and can also be applied to combinatorial libraries.

'The role of protein 3D-structures in the drug discovery process', includes descriptions of both how protein structures are determined (X-ray crystallography, NMR spectroscopy, and comparative modelling) as well as success stories, where 3D protein structures were used in the development of marketed pharmaceuticals.

The next chapter discusses the use of NMR as a screening technique for ligand binding, including both advantages and disadvantages. Structure–Activity Relationship (SAR) by NMR and ligand-based methods (dynamic, relaxation, diffusion and combination) are discussed, along with recent advances and specific examples. Special attention is given to designing compound libraries for use with NMR screening.

'Structure-based design of combinatorial libraries' talks about the use of pre-existing information to drive the design of directed libraries and maximize the number of active compounds in libraries of 100–1000 molecules. Where there is a known SAR for the target, similarity searching, binary QSAR or pharmacophore discovery with 3D database searching are the primary techniques.

A review of recent 3D database searching in lead discovery, the traditional method, is presented. A highly detailed description of 3D database searching as it is used in combinatorial design follows, including specific software and structure examples.

While QSAR has long been used to predict biological activities from physical properties, the designing of new compounds using QSAR has proven much more difficult. '3D QSAR in modern drug design' describes both 3D grid and psuedo-3D methods that do not require molecular alignment.

Proper molecular alignment is one of the most critical aspects of QSAR, and is described in some detail, along with specific examples demonstrating the wide variety of 3D QSAR techniques currently available.

Chapter 12 is 'Physicochemical concepts in drug design', which include solubility, lipophilicity, absorption, and other physiochemical properties which play a large role in the ultimate success or failure of a

new drug. Both experimental and computational approaches to measuring or predicting these properties are discussed, as well as several specific examples where a specific physiochemical property is correlated with activity in a particular system.

The final chapter discusses 'Computer-aided prediction of drug toxicity and metabolism'. Common toxocological assays are discussed, then the bulk of the chapter discusses computer-aided methods to predict toxicity and metabolism, developed as alternatives to the expensive and time-consuming in-vivo assays. This chapter includes URLs for many of the programs discussed.

Opinions expressed here are those of the reviewer and not necessarily those of Elsevier.

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