Book Reviews

Annual Review of Pharmacology and Toxicology. Volume 49. Edited by Arthur K. Cho, Terrence F. Blaschke, Paul A. Insel, and Horace H. Loh. Annual Reviews Inc., Palo Alto, CA. 2009. x + 470 pp. 18.5 × 24 cm. ISBN 978-0-8243-0449-2. $84.00.

This is the 49th volume of this review series. A variety of timely topics is covered in 19 reviews written by experts working in their respective fields. The reviews offer perspective and updates covering a broad range of individual topics in pharmacology and toxicology. Each individual review will be of value to medicinal chemists working in the scientific areas directly related to the given review topic. Select reviews that more directly address significant aspects of drug design/discovery and are thus likely to be of more direct interest to medicinal chemists and those involved in drug discovery include: (1) Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics; (2) Lipid Mediators in Health and Disease: Enzymes and Receptors as Therapeutic Targets for the Regulation of Immunity and Inflammation; (3) Small-Molecule Inhibitors of the MDM2-p53 Protein−Protein Interaction to Reactivate p53 Function: A Novel Approach for Cancer Therapy; (4) Epigenics, DNA Methylation, and Chromatin Modifying Drugs; (5) The COXIB Experience: A Look in the Rearview Mirror; (6) Immunodrugs: Therapeutic VLP-Based Vaccines for Chronic Diseases; (7) Topical Microbicides to Prevent HIV: Clinical Drug Development Challenges; (8) Emerging Pharmacology: Inhibitors of Human Immunodeficiency Virus Integration; (9) Mycobacterial Subversion of Chemotherapeutic Reagents and Host Defense Tactics: Challenges in Tuberculosis Drug Development.

All reviews are cohesive and informative. The subject index is complete and thorough. Citations for most reviews are substantial and current. The present volume is a welcome addition to this long-standing series, providing concise summaries of advances in Pharmacology and Toxicology. It is noteworthy that this book, as well as additional Annual Reviews series, is located online at www.annualreviews.org.

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JM9004384

10.1021/jm9004384

Chemoinformatics Approaches to Virtual Screening. Edited by Alexander Varnek and Alexander Tropsha. Royal Society of Chemistry, Cambridge, U.K. 2008. ix + 342 pp. 16 × 24 cm. ISBN 9780854041442. £89.95.

This aptly named book covers the burgeoning field of virtual screening in a comprehensive and up-to-date manner. In addition to appealing to the chemoinformatics and computational chemistry specialist, this book can give medicinal chemists the background they need to make productive use of these methodologies. The 10 chapters cover structure representation and comparison (fragment descriptors, topological and 3D pharmacophores, molecular similarity analysis, molecular field topology analysis); data analysis and model building (probabilistic approaches in activity prediction, fragment-based de novo design); and applications (ADME/Tox prediction, compound library design, integrated chemo- and bioinformatics approaches).

I was struck by the assertion in Chapter 1 that chemoinformatics is a branch of theoretical chemistry with its own representation of molecules. Whereas quantum chemistry considers molecules as ensembles of electrons and nuclei and whereas molecular mechanics/dynamics considers molecules as collections of atoms and bonds and the classical forces between them, "chemoinformatics represents molecules as objects in a chemical space defined by molecular descriptors". The question, of course, is which descriptors (out of the thousands that exist) are relevant for describing and predicting a molecule's physical and biological properties. As this monograph makes clear, while there is no single method that works in all cases, a number of methods have proven to be useful and predictive.

The first chapter presents a summary of the various (mostly 2D) fragment descriptors, including supramolecular fragments used to classify reactions, how they are calculated, stored in a computer, and managed, and how they are used in virtual screening and in silico design applications.

The second chapter reviews "topological pharmacophores". Such 2D pharmacophoric patterns require "aligning" common features of 2D chemical structures, and several methods of doing so are reviewed, along with methods of generating topological pharmacophore fingerprints for use in similarity search or virtual screening applications. The chapter includes a critical review of both 3D and topological pharmacophore applications, and both methods are shown to be useful.

Chapter 3 covers classical 3D pharmacophore-based virtual screening in some detail. Pharmacophore features and representations are discussed, as are methods for aligning molecules and pharmacophores. Ligand-based pharmacophore models are discussed, as are structure-based pharmacophores (utilizing the structure of the ligand receptor). There is a nice discussion of techniques to validate a pharmacophore model for virtual screening, and use of these methods in conjunction with other screening methods such as drug−receptor "docking". An interesting application of a database of pharmacophores for profiling compounds' multiple activities is reviewed.

Chapter 4 reviews molecular similarity analysis in virtual screening. This is based on the "similarity-property principle" that molecules with globally similar structures tend to exhibit similar biological activities, and the variety of properties used to measure similarity is discussed. Every experienced medicinal chemist knows that some analogue series have a broad structure−activity relationship curve, while others have a "discontinuous" SAR curve where an apparent minor structural change can alter potency by several orders of magnitude. The chapter lists several examples of these varying "activity landscapes": factor Xa inhibitors show a "continuous" SAR landscape with similar binding orientations and local SARs, while ribonuclease A inhibitors show a discontinuous SAR landscape with two different binding modes. Attempts to quantify these differences in SAR landscapes are reviewed, especially Bajorath's SAR Index (SARI). The SARI allowed division of 16 reference series into three classes of SAR: continuous, heterogeneous, and discontinuous. These categorizations could be quite useful to medicinal chemists in trying to decide when to abandon elaboration of a series that is not achieving the desired activity.

Chapter 5 reviews molecular field topology analysis. In a topological version of 3D comparative molecular field analysis, the authors' method builds a molecular supergraph that aligns all of the chemical structures, develops a descriptor matrix that is used for partial least-squares regression building of a structure−activity correlation, and uses the correlation for virtual screening.

Chapter 6 details a probabilistic approach to predicting biological activities. The chapter begins by reviewing the problems with describing biological activities in the literature, difficulties in determining dose−effect relationships, and errors and inaccuracies in activity data points in most databases. The chapter builds compound training sets, derives activity probability models, and presents an evaluation of performance on test sets.

Chapter 7 reviews fragment-based de novo design of druglike molecules. Receptor-based design builds inhibitors of target receptors, while ligand-based design builds compound libraries similar to a lead structure. Techniques for building molecules from fragments and multiple methods for scoring the designs are reviewed.

Chapter 8 presents the argument that, in general, ADME/Tox prediction methods are still too unreliable for anything but qualitative use. The "rule of five" is lauded as an alert system for "druggability" of compounds. The chapter discusses the availability of data sets and accuracy of predictive models for other properties: aqueous solubility, human intestinal absorption, drug distribution including blood−brain barrier permeability, and plasma protein binding. The chapter addresses methods to estimate the applicability domain of the predictive models and takes the position that, with the current paucity of reliable experimental data and lack of consideration of applicability domain, most ADME/Tox models are of limited practical value for virtual screening.

Chapter 9 reviews principles and applications of compound library design. Combinatorial vs cherry-picking libraries is discussed. Similarity-guided design and diversity-based design of libraries as well as pharmacophore-guided, QSAR-based, and protein structure-based methods for compound library design are discussed.

Chapter 10 considers integrated chemo- and bioinformatics approaches to virtual screening. Given the public availability of large compound collections, academics as well as other researchers can use virtual screening techniques to find likely active compounds.

Despite the multiauthored format, this book presents a logical flow of subjects and it possesses a unity appropriate for a monograph. The technical concepts are presented clearly and in sufficient detail to allow appreciation of their utility; real-world drug discovery examples are often given, and many chapters point out limitations of the approaches and they make suggestions for further development. There are few typographical errors, references are reasonably up to date, and there is an extensive subject index.

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JM900346B

10.1021/jm900346b