DDT Vol. 9, No. 8 April 2004

Computational Medicinal Chemistry for Drug Discovery

Edited by Patrick Bultinck *et al.*, Marcel Dekker, 2004, New York & Basel, 794 pages, US$195.00. ISBN 0-8247-4774-7

Today, computer-assisted approaches are indispensable prerequisites to support medicinal chemistry programs. Although they were introduced in the late 1950s, their real value was only appreciated following the availability of powerful yet affordable computer technology. Consequently, this field has developed rapidly during the past decade, and computational chemists are now an integral part of multidisciplinary drug discovery teams.

This book covers a range of computational approaches with potential applications in drug discovery. The editors provide theoretical and application-oriented chapters, primarily selected for their relevance to medicinal chemistry. The experts authoring these chapters reflects this balance (40 academic, 17 industry). The book is divided into 27 medium- to high-quality chapters, offering a comprehensive state-of the-art overview of modern computational methods. The selection of topics reflects the complexity of problems that are inherent in this field.

The first few chapters provide information on theoretical methods, namely semi-empirical approaches, wave-function based quantum chemistry, density-functional theory and QM/MM. Of particular interest are those contributions that critically compare molecular mechanics force fields (Chapter 1) and that discuss the accuracy and applicability of quantum chemistry in medicinal chemistry (Chapter 6). Some other chapters, however, lack a discussion of their impact on medicinal chemistry.

Chapter 7 provides a solid and profound review on rules-based 3D structure generation methods, conformational searching and their application in drug discovery. In the following section, these formalisms are extended to describe molecular properties such as electrostatic potential, non-bonded interactions, behaviour in solvent, and reactivity and similarity involving quantum properties. Although the discussions on molecular electrostatic potentials (Chapter 8) and nonbonded interactions (Chapter 9) provide valuable reviews of the field, a detailed discussion of their importance for protein–ligand recognition would have been useful. The discussion relies on calculations only, while concepts in structure-based design, such as the lock-and-key model, receptor shape and functional group complementarity, are missing.

The increasing role of target structures from X-ray crystallography is highlighted by two contributions on methods and caveats in structure-based design. A critical assessment of protein structures highlights several sources of errors in 3D structures (Chapter 15), followed by a comprehensive account of recent developments in docking and scoring (Chapter 16). Unfortunately, an in-depth discussion on the impact of errors and low-resolution structures on design strategies is missing. Furthermore, other structure-based design methods did not find their way into this book, for example, virtual screening, *de novo* design or structure-based optimization.

This section is complemented by an informative review outlining the complexity in pharmacophore elucidation (Chapter 17) with many applications, followed by an account on the success of 3D pharmacophore models for database searching and hit identification (Chapter 18). Chapters on maximal common substructures and molecular descriptors are followed by two excellent contributions on 2D and 3D-QSAR (Chapters 21 and 22), each clearly demonstrating the value and broad application areas of these established and powerful methods. As descriptors and QSAR clearly influenced chemoinformatics, two informative contributions on computational library design and data mining strategies were consequently added at this point.

These chapters clearly account for the fact that the focus of computational medicinal chemistry has shifted from the accurate treatment of single molecules towards processing of larger collection of molecules. At the end of this tour around computational chemistry, the successful design of sialidase inhibitors is shortly discussed, employing different computational approaches for studying protein–ligand complexes (Chapter 27). A critical discussion of similar case studies here would have been useful to illustrate how the diverse collection of tools presented throughout this book could potentially be applied to solve real-life problems in medicinal chemistry. A glossary of important terms in computational chemistry rounds off the text well.

The editors and authors have succeeded in producing a book that integrates basic and application knowledge on computational chemistry in drug discovery and thus illustrates the achievements and caveats on the way towards rational drug design. This book covers a broad range of computational approaches, therefore, most sections touch only briefly on important areas, while other, equally important approaches were missed. Some chapters focus nicely on the general theme outlined in the preface, while others cover it rather broadly and present theoretical approaches without direct medicinal chemistry impact. For important areas, case studies to illustrate the potential and limitations of these technologies and to put the range of methods into perspective would have been desirable. Nevertheless, the density of information, its readability and the selection of research topics make this a recommended reference for graduate students and researchers in the field.

Hans Matter
Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany
e-mail: hans.matter@aventis.com

 PII: S1359-6446(04)03071-5