Book Reviews

Fragment-Based Approaches in Drug Discovery. Edited by Wolfgang Jahnke and Daniel A. Erlanson. Wiley-VCH Verlag, Weinheim, Germany. 2006. xxii + 369 pp. 17 × 25 cm. ISBN 35273129919. $190.00.

An active molecule is more than its parts and pieces and Fragment-Based Approaches in Drug Discovery attempts to dissect druglike compounds into smaller pieces or fragments, a proper combination of which can lead to other novel high-affinity ligands.

This book is Volume 34 in the highly respected series Methods and Principles in Medicinal Chemistry, edited by R. Mannhold, H. Kubinyi, and G. Folkers, and it is a worthy member of the series. The field of fragment-based approaches to drug discovery has emerged over the past 10 years, and it is an area of both industrial and academic interest.

The individual contributors to the book are drawn primarily from industry, but academia is well represented. The book consists of three main sections. Chapters 1−7 describe the background and computational approaches. Chapters 8−14 cover the experimental methods and applications, and Chapters 15 and 16 describe related and emerging fields in chemistry that have the potential to transform fragment-based drug discovery.

Chapter 1 provides a comprehensive discussion of the concept and theory of the fragment-based approach and how one can narrow the number of synthetically possible compounds to manageable proportions. It also posits that with small fragments one will obtain higher hit rates (albeit of much less potency) with very small compounds rather than with more complex molecules and that by appropriate combination of these fragments, novel high-affinity ligands may be discovered. Chapter 2 reviews the concept and application of multivalency, which is the intellectual sibling to fragment-based approaches and sets the stage for fragment-based approaches to drug discovery.

The quality of a fragment library, as for other types of potential drug library, is critical for its success, and the design of fragment libraries is discussed in Chapter 5 in terms of chemical space, druglikeness, and data mining. In Chapter 6 the authors attempt to dissect existing drugs into their component parts and they conclude that there are considerable differences between oral and injectable drugs and between the implications for the choice of fragments in a screening collection. In Chapter 7 the multicopy simultaneous search program is presented. This is a powerful approach to fragment-based drug discovery and for its use in ligand design.

In the second part of the book, Chapter 8 provides a comprehensive review of NMR-based approaches to fragment assembly, and in addition it provides some specific examples. The original "SAR by NMR" approach is reviewed in Chapter 9, which also cites a number of successes of application of this method, as well as providing a useful reminder of the limitations of these strategies.

The application of X-ray crystallography to fragment-based drug design and the process by which it is used is discussed in Chapters 10 and 11. Chapter 12 reviews the potential synergies resulting from marrying the NMR and X-ray crystallographic techniques. Case studies are provided to illustrate the use of these powerful methods to advance medicinal chemistry programs. Use of mass spectrometry to identify fragments is described in Chapter 13, together with an example of its application.

Chapters 15 and 16 are introductions to emerging research areas that are tangential to fragment-based drug discovery. There are two recent areas of synthesis: click chemistry (which was introduced in 2001 and is a modular approach inspired by nature using a highly reliable set of reactions) and dynamic combinatorial chemistry (which is based on the implementation of dynamic assembly and recognition processes).

Overall, the book is a good attempt to provide in one volume many aspects of this emerging field and it presents a wealth of information on topics that are difficult to find elsewhere. It is a worthwhile reference book for those scientists who are interested in new developments and new tools to aid in the ongoing quest for new and better drugs. However, although it may be read with interest by a typical medicinal chemist, I believe that it will be more appreciated by the computer-modeling community.

Jan W. F. Wasley

Simpharma LLC
1, Stone Fence Lane
Guilford, Connecticut 06437

JM078010Z

10.1021/jm078010z