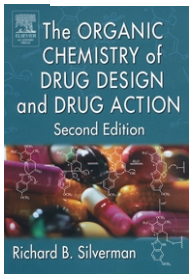

The Organic Chemistry of Drug Design and Drug Action

Richard B. Silverman, Second Edition, Elsevier Academic Press, US$77.95, 617 pages, ISBN 0-12-643732-7

It is estimated that the volume of scientific knowledge doubles approximately every seven years. Hence, it could be argued that the publication of this comprehensively updated edition of Silverman's *The Organic Chemistry of Drug Design and Drug Action* could be somewhat overdue. Was it worth the wait? Well, the resounding answer is yes!

Like the first edition, this text is directed towards graduates who are embarking on a career in medicinal chemistry in the discovery laboratory. However, the scope of this treatise is far greater. Silverman continues to blur the edges between chemistry and pharmacology in a manner that is incontrovertibly relevant to the discipline of drug design and development.

Whereas the format of the second edition mirrors that of the first edition, the author has adapted many of the references to demonstrate current practice within the pharmaceutical industry. This is exemplified with a detailed abundance of recent new drug applications (NDAs) that are suitably described and are likely to be recognised by many of the readership. Many of these new citations highlight the recent progress made in this area from both a chemical and pharmacodynamic perspective (chapter 3). Indeed, the author has gone to great lengths to ensure that a particular drug and its mode of action are never presented in isolation. Undeniably, recent advances in the dissemination of pharmaceutically relevant information, such as the increased population of sequences in gene and protein databases, have furthered efforts to amalgamate aspects of chemistry and pharmacodynamics. In addition, the recent explosion in purification methodologies has rendered enzymes as more attractive and economically viable targets. To this end, chapters 4 and 5 are dedicated to important new enzyme targets and enzyme inhibitors, and there is deference to the many relatively new therapeutic administrations in this area. Included within the varied notable examples are the lead discovery of a lopinavir and ritonavir co-formulation for the treatment of HIV infection and the design of hypocholesterolemic agents such as lovastatin.

Silverman also fundamentally recognises the perpetual struggle that is faced by pharmaceutical companies to bridge the widening innovation deficit through the application of new chemistries. Advances in directed library design, screening methodologies and assay throughput are all acknowledged in the battle to meet aggressive new chemical entity (NCE) quotas. Furthermore, the text is underpinned with numerous current statistics that not only demonstrate past and current trends within the industry, but also hint towards future directions. Evidence for this seamless evolution of countless emerging techniques provides the reader with a full understanding of the complex process that is modern drug design and development.

The author has also meticulously directed his review towards all areas of interaction between drugs and bio-organisms, including metabolism. Chapter 7 is dedicated to the issues that are associated with the biofunctionalisation, conjugation and clearance of drugs in terms of their inherent activity and the activity of secondary products and metabolites. The essential role of radiolabelled NCEs is acknowledged within any drug absorption, distribution, metabolism, excretion and toxicity (ADMET) programme, as is the role of the superfamilies of enzymes that are involved in the elimination pathways. As a result of the need for increased selectivity, another area that is given credence is that of prodrugs and drug delivery systems. Once again, Silverman has updated the text to reflect recent examples that bear relevance to the pharmacopoeia of today.

Summary

Overall, this compendium does not detail the organic synthesis of pharmaceutically active compounds – it is instead a rational discussion of the effective design and functionalisation of chemical space in the search for new druggable entities. Thus, although this volume details many chemical structures and cascades, the organic synthesis of these molecules is taken as a baseline requirement. It is the mode of action of these NCEs that interests this particular readership, and this is graphically described at the molecular level.

Irrespective of the discovery programme that is adopted within any screening laboratory, organic chemistry will play a major role. It is predicted that only 5% of the available chemical space (10^{60} molecules) has currently been harnessed, and with the continuous onslaught of new indications this text offers a timely update on progress in this area. Beyond the many hundreds of current references that support each chapter, the author also provides a range of questions that are aimed to stretch the more erudite enthusiast.

With the continued pressure on the industry to meet targets and to bridge the innovation gap, progress in drug design is rapid and continuous, and the third edition of the text is eagerly anticipated. It can only be imagined how Silverman will reflect, perhaps in another seven or so years, on the current innovations, screening trends and new drug approvals.

Michael E. Cooper
GE Healthcare
Biosciences, Discovery Systems
The Maynard Centre
Cardiff
UK CF14 7YT
e-mail: michael.e.cooper@ge.com

 PII: S1359-6446(04)03199-X