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BOOK REVIEW

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The BP is one the worlds Big Five pharmacopoeias and is widely used throughout the world. Even in countries where it is not official (e.g. the United States) it is often used by the pharmaceutical industry as a most useful reference book. For example, the infra-red reference spectra which are found in volume two are often consulted.

The process of European harmonization continues and the titles of the monographs for many drug substances have a five sided star which indicates that the monographs are edited versions of E.P. monographs.

There is much of interest within this B.P., which becomes official 1 December 1993, ranging from the discussion of outliers and analytical philosophy to a consideration of production methods for biologicals. However, for this reviewer who was trained using the 1953 BP there was some sadness in reading the list of monographs which have been deleted. It was like reading the obituaries of old friends. Can Catechu really have expired? Has Lobelia reached the end of the road? How sad to see Sulphapyridine depart!

The 1993 BP has a wealth of information and will be widely used in many parts of the world as either an official compendium or as valuable reference source.

C.T. Rhodes

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BOOK REVIEW

Nucleic Acid Targeted Drug Design

Editors: C. L. Propst and Thomas J. Perun

Published by Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016
1992

644 pages, bound, illustrated
Price $165.00

This book is the second drug design treatise assembled by the editors. The first, "Computer-Aided Drug Design", was aimed specifically at protein targets and was published in 1989. The present treatise is very well-written and follows the same organization as their first book, *i.e.*, it is split into a two section "Methods" (Chapters 2-6) and "Applications" (Chapters 7-13) format. The editors have selected an excellent cast of contributors who concentrate on structure based drug design techniques and the therapeutic agents so designed to be used against targeted nucleic acids.

The editors introduce the reader to this fascinating subject and point out how therapeutic agents can and do interact with nucleic acids, either by intercalation, through covalent bonds, or in the case of DNA binding noncovalently to the major or minor groove. The first chapter in the applications section, Chapter 2, discusses the use of X-ray crystallography (the best way to get static, 3-D information) and NMR spectroscopy (a powerful technique in elucidating 3-D structural information in solution). The authors point out how each technique has advanced to its present state-of-the-art form, outline problems encountered in both areas in data collection and assignment, and discuss software available for refinement of data. A word of caution, this chapter, as well as several in the application section, relies heavily on the readers knowledge of the specific subject matter and jargon. It could be rough going for the novice! Chapter 3 focuses on molecular modeling techniques and theoretical investigations on drugs, *e.g.*, acridine and mitomycin C, that act on DNA/RNA. The author highlights computational software now available and emphasizes many, at best, are qualitative in their semi-predictive powers. Chapter 4 concentrates on the qualitative aspects of sequence specificity which is dependent on the molecular mechanism of how drugs interact with DNA. This includes drugs that either nick (strand scission), alkylate (strand break), or covalently bind to DNA. This chapter explores how to map binding sites of drugs which do not leave a permanent record by "footprinting" analysis. DNA-intercalating ligand molecular modeling is the subject of Chapter 5. Such studies enable investigators to understand the

molecular mechanisms of binding. A combination of techniques are used to develop QSARs that can predict biological actions of the drugs in question. Chapter 6 deals with specific proteins involved in sequence-DNA recognition and the feasiblity of trying to mimick their interactions with synthetic agents. The strategy of drug design in this area is complementary to the antisense oligonucleotide approach for inactivating mRNA. Also, included in this chapter is an excellent discussion on DNA-binding proteins which are categorized in the leucine zipper, helix-turn-helix, homeobox, and zinc-finger domains.

The remaining chapters concentrate on application of the methodology covered in chapters 2-6. The subject of Chapter 7 is groove binders. The information of how a drug or protein binds to the major or minor groove of DNA is covered. A section on drug-recognition patterns and future strategies is extremely interesting and demonstrates how various types of bonds and structural changes play a role in binding of the agent to DNA and possible future drug design. The topic of Chapter 8 centers on the pyrrole[1,4]benzodiazepine antibiotics, primarily tomaymycin, and how they covalently bind to DNA. The authors show how a combination of high-field NMR, fluorescence, and molecular modeling techniques were used to determine how tomaymycin binds to DNA. The combination of techniques allowed one to determine the place and site of binding of tomaymycin as well as its orientation with respect to DNA. This chapter illustrates nicely how the techniques and methodology described in the first section of book can be employed by investigators to solve an intricate scientific problem. Chapter 9 highlights the fascinating role of quinolones on the bacterial enzyme DNA gyrase, a topoisomerase, and explores future drug design of these agents. A thorough review of the active quinolones starting with nalidixic acid through the second generation analogs is furnished and their subsequent development as a result of the discovery of DNA gyrase is provided. Methods used for establishing the mechanism of action of these drugs are described and how information gathered from these techniques, as well as molecular modeling, led to a new series of potential agents. Chapter 10 complements Chapter 4. It looks at drugs with an enediyne motif that bind in the minor groove of DNA and cause strand scission due to a diradical process. The chemistry, biochemistry, and clinical utility of these drugs are featured. This chapter provides the reader with a detailed, up-to-date view of this unique class of drugs. The possible design of new enediynes based on energy factors and transition state theory is covered. Chapter 11 focuses on aminoalkanamide substituted anthracene-9,10-diones and certain phenylquinoline-8-carboxamides, two classes of drugs which are intercalating agents. Theoretical and molecular modeling studies presented in the chapter suggested the 2,6-disubstituted anthracene-9,10-diones should be active and have affinity for DNA. These predicitons were borne out by experimental binding studies. Similar results are presented for the phenylquinoline-8-carboxamides. The authors caution the reader that although the examples they chose correlated well, molecular modeling does not take into consideration factors like drug absorption, transport, or metabolism, all of which can upset the applecart. The topic of Chapter 12 is catalytic RNAs (ribozymes) and their future in the treatment of human diseases. The authors examine gene regulation by natural and artificial antisense RNAs. They describe how information gathered through experimentation can be used to design target specific drugs that may block different steps required in gene expression. Problems which might be

encountered with this class of drugs are discussed as well as possible methods of delivery. I liken Chapter 13 to the frosting on a fine cake. It covers code blockers for duplex DNA and RNAs (antisense DNAs). The hurdles, *e.g.*, stability, permeability into the cell, specificity, metabolism, and elimination, one must overcome to make deliverable, cost-efficient future drugs are discussed.

Chemical modifications and strategies involved in the preparation of these oligonucleotides are thoroughly covered. There is, also, a very interesting section on aptamers and their bright future as therapeutics.

In conclusion, this book is well worth its price and not to expensive for inclusion in personal collections. The information presented is up-to-date and well-referenced. In fact, many of the contributors point out current reviews in their particular subject area that would help the reader better understand the material discussed. Like its predecessor, this book is indispensable.

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