medicinal research series volume 12

MODERN DRUG RESEARCH

Paths to Better and Safer Drugs

edited by
Yvonne Connolly Martin
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Paths to Better and Safer Drugs

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Additional Volumes in Preparation

We dedicate this book to Professor Corwin Hansch in gratitude for all that he has contributed to the world of drug research. Many readers of this book will recognize that a quarter of a century ago his new approaches heralded the age of rational drug design: they were developed and applied to ultimately influence each of the disciplines covered in this book. However, his contributions are not limited to scientific ones. Two of us had the opportunity to work directly with Corwin and learn by example how to make science exciting and rewarding. His enthusiasm for research, his energetic pursuit of creative and useful answers to scientific questions even in the face of seemingly impossible odds, and his open-mindedness to new ideas are characteristics that all scientists would do well to emulate.

About the Series

This series of monographs was conceived by the late Dr. Fred Schueler of Tulane University. His untimely death came prior to the completion of the first volumes of the series, and his friend and very able colleague, Dr. Alfred Burger of the University of Virginia, took on the task of editing the first three volumes of the series. Dr. Burger's heavy responsibilities forced him to withdraw from further active participation with the series, and the next three volumes were selected from books already under contract to Marcel Dekker, Inc., with Dr. Gary Grunewald of the University of Kansas as Consulting Editor. At this point an Editorial Advisory Board was selected and Grunewald became the Series Editor. The traditions established under the leadership of Schueler and Burger will be continued.

It is hoped that books for the series will serve a useful role in the areas of medicinal chemistry, chemical pharmacology, and biochemistry. It is the intent of the Editor and the Editorial Advisory Board that books selected for the series should be timely and fill a definite need in the general areas mentioned. We welcome suggestions for future monographs in the series.

Gary L. Grunewald

Preface

A new era is dawning in drug research. New ways of developing better and safer drugs are becoming apparent. Major changes are taking place both in how and which chemical compounds are tested for their therapeutic usefulness and in the possibilities for interpreting biological effects at the molecular level.

This new era has arisen partly from the exciting advances in the scientific knowledge of the molecular basis of bodily functions and of how these functions change in illness. Technological innovations, particularly in the fields of molecular and structural biology and computer technology, are making significant contributions to modern drug research. Furthermore, the substantial advances in the capabilities of theoretical and synthetic chemistry, as well as macromolecular structure determination by X-ray diffraction and nuclear magnetic resonance spectroscopy, have led to an increasing understanding of the interactions of active substances with their biological target molecules. Because of the progress in all of these fields, it is now sometimes possible to study in atomic detail the binding sites for ligands on DNA, enzymes, and other proteins such as antibodies. In such cases, the variation of the affinity within a series of test compounds can be interpreted in the light of how the individual molecules fit into the macromolecular binding site.

The most dramatic advance of modern biology is undoubtedly that of genetic engineering. With these techniques scientists can now produce large quantities of specific DNA, RNA, or protein molecules; molecules that form the structural and functional basis of living things. Furthermore, specific changes can be made to these molecules to probe the effect of such changes in structure on changes in function. As a consequence of these and related developments in biochemistry, the strategies and experimental methods used in the search for new drugs are changing fundamentally. Where once testing of potential new drugs started with studies in organ or whole-animal preparations, such tests are now often secondary to biochemical tests.

Technological advances in polymers, on the other hand, provide a vital basis for innovation in pharmaceutical dosage forms that are safer and more convenient for the patient or that expand the types of molecules suitable for therapeutic use.

However, it is not only scientific and technical developments that are changing the face of drug research: the research and development environment at pharmaceutical companies has also experienced change. Special disciplines no longer stand alone as independent units; research and development processes now center around collaboration within interdisciplinary project groups. Better and safer drugs will be discovered and developed by a close collaboration of pharmacologists, biochemists, molecular biologists, medicinal and theoretical chemists, toxicologists, pharmacists, and physicians.

What are the therapeutic challenges for which new drugs are needed? Bacterial infections, once the plague of mankind, have now been largely abated. We can now treat the symptoms of many other common

diseases such as cardiovascular, metabolic, respiratory, and mental illnesses. However, the chief goal of future drug research must be the search for a cure or prevention of these diseases. Moreover, drugs must be developed for diseases for which no drug treatment has yet been successful: diseases of the immunological system; viral infections, especially AIDS; malignant tumors; and diseases of the central nervous system, especially Alzheimer's disease. Successful cure of these diseases will not only prolong life but improve the quality of life as well.

Because of the revolutionary changes taking place, we decided to organize a book that outlines the scientific, technical, organizational, and social context of current and future drug research. It is designed to give readers an insight into the possibilities of this field and help those currently involved in it gain an insight into the complexity of the various disciplines. We expect that at least parts of this book will prove useful for courses in medicinal chemistry or those that touch on matters associated with the research and development of drugs.

To accomplish these goals we chose authors who have worked many years in the field of their contribution, applying their research to create newly marketed drugs. Their knowledge and experience give the chapters a flavor of the excitement and hard work involved in drug research. Additionally, the authors have thought carefully about the practical application of the various new technologies and sometimes sound a cautionary note not obvious to someone more distant from the problem.

For didactic reasons we divided the book into three parts. Chapters 1-5 describe the modern scientific basis, Chapters 6-9 describe the strategic

aspects, and Chapter 10 describes the social environment of modern drug research. We included Chapter 10 because we are convinced that without the basic approval of society, which appears to be decreasing in some countries, the huge financial commitment for the development of revolutionary new drugs would not be possible. Furthermore, Chapter 10 discusses the appropriate corporate culture to foster creative drug research and development.

We appreciate the patience of the authors who carefully worked over their chapters and listened to our comments to make them a part of a coherent picture. We also are indebted to Mrs. Gudrun Schwaar for valuable organizational assistance and to Miss Diana Schlichthaerle for drawing the chemical formulae.

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