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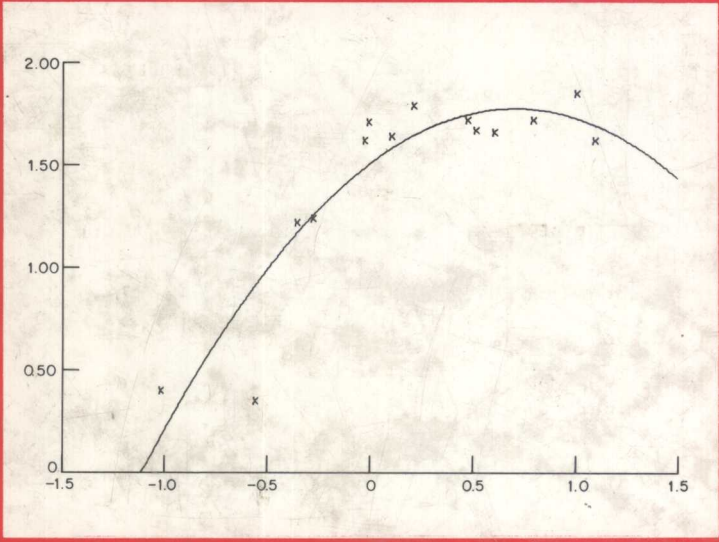
volume 8



Yvonne Connolly Martin

QUANTITATIVE DRUG DESIGN

A Critical Introduction

Quantitative Drug Design

A Critical Introduction

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INTRODUCTION TO 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

My enthusiasm for writing this book arose from my experiences as a referee of manuscripts for the Journal of Medicinal Chemistry as well as from the unreliability of predictions of drug potency which I have made. Examination of the faults made in logic, statistics, or interpretation of quantitative structure-activity relationships by myself or others has made me aware of some of the traps into which one can fall in the execution of such studies.

The objective of this book is to provide a self-study guide for workers unfamiliar with the various methods used in quantitative drug design. Since particular attention will be paid for the standards of quality work, the reader should learn enough to be able to do publishable analyses. I fully realize that in setting such guidelines my own shortcomings become obvious. I hope that readers will inform me of their criticisms.

The references in any book of this type provide the reader with an entrance to the literature on the various topics. In order that the reader becomes familiar with the individuals involved, I have used the complete first name of authors when that is provided in the original article. The title and inclusive page numbers of the article are included for convenience. The majority of the text for this book was completed in early 1976; important new references up to the first six months of 1977 were added where possible.

PREFACE

There are many people who have helped me in my study of structure-activity relationships. Corwin Hansch enthusiastically helped me to learn the methods which he introduced to medicinal chemistry; Julius Taylor in 1960 taught me the importance of physical properties to drug activity and in 1966 badgered me into trying multiple regression analysis on some pargyline data we had; Ronald Wiegand had such faith in the potential usefulness of the extrathermodynamic approach that he supported its application at Abbott when others were highly critical. I am also grateful to those who read part or all of the manuscript and who offered helpful criticism: Paul Craig, William Dunn III, Rainer Franke, Gary Grunewald, James Hackbarth, Corwin Hansch, Al Leo, and Julius Taylor. Willard Bass encouraged and helped me compose the manuscript on the Abbott DEC-10 computer. Arlene Davidson was a great help in this task and also in spotting typographical errors. My most staunch supporter is my husband; it is he who convinced me to write this book and supported the effort with labor of his own at home.

Yvonne Connolly Martin

CONTENTS

Chapter 1

INTRODUCTION AND OVERVIEW OF DRUG DESIGN PROBLEMS

I. SCIENTIFIC FOUNDATIONS OF MODERN DRUG DESIGN METHODS

The techniques involved in the rational design of biologically active molecules have been broadened by the availability of many new instruments and techniques. For example, computers can now do the calculations which could only be contemplated as recently as twenty years ago. This book will discuss primarily those techniques of drug design on which the impact of computers has been largest. That is, the Hansch, extrathermodynamic, or linear free energy and the Free-Wilson or de novo methods are treated in most detail because these methods have been widely used. For example, reviews of these methods have been written by Hansch (1973), Neely (1973), and Purcell et al., (1973) among others. There is also a book of 15 chapters entitled "Biological Correlations--The Hansch Approach", edited by R. F. Gould (1972). Although Purcell et al., treat the subject briefly, no one has described in detail how one

actually applies these methods. In addition, some space is devoted to pattern recognition which is in the beginning stages as far as drug design is concerned. Conformational methods are covered briefly. The design of enzyme inhibitors -- active-site-directed irreversible inhibitors, transition state analogs, and k_{cat} inhibitors -- is also discussed. These methods compliment the extrathermodynamic approach and offer much promise for the future.

The practice of reliable drug design draws upon a knowledge of aspects of several disciplines; physical and organic chemistry, statistics, pharmacology, and biochemistry are perhaps the most important. The success of any one individual or team of individuals in this task depends upon how well they can integrate these diverse disciplines. For example, predictions based on careful experimental quantification of the physical properties of a series of drugs will be incorrect if the proper statistical evaluation of the relationship between these properties and potency have not been used. Alternatively, brilliant calculations on faulty data are likewise faulty. Thus serious workers will always be alert for gaps in their knowledge of the subjects on which drug design are based.

In view of the fact that quantitative drug design derives from many areas, this book will provide references to the key literature on these subjects. Thus physical organic chemistry works written by physical organic chemists will be cited, for statistics, work by statisticians, etc. In this manner, the new worker will be at once in touch with the knowledge basis of the drug design methods. Subjects which are central to the methods or which have not been reviewed elsewhere are treated in more detail than those for which adequate reviews are available.

The chapters in this book are designed to teach the reader how to apply modern drug design methods. It is a how-to-do-it book. Topics are treated in such a manner that they should be understandable by readers with a modern undergraduate training in chemistry. Each subject will be treated in enough detail that a careful student could apply the method, properly, to their own

data. Readers who do not intend to apply these methods, but merely want to be able to evaluate other workers' applications, should have developed a critical facility by the time they finish the study of this book.

Standards for quality work are an integral part of the discussions. For example, for which types of analogs can one reliably calculate a lipid-water partition coefficient? For which analogs are such calculations unreliable? What precautions apply to the accurate determination of partition coefficients or pKa's? How does one decide if a computer program is suitable for these purposes? What are the important statistical criteria for a successful regression analysis? Can data points be dropped from an analysis? How well should a structure activity equation fit a set of data, and conversely when is an equation an over fit of data? These same standards can be applied to the evaluation of the work of others.

The words "drug design" are used instead of "structure-activity relationships" to emphasize that the end result of the application of the various methods should not be a rationalization of existing data, but rather a prediction of new data. Conclusions which have predictive power are much more useful than those which merely summarize a set of observations.

"Drug" is used throughout in its broadest sense, that is as any biologically active compound which is not normally found in the organism, or which is administered in amounts which produce abnormally high levels in the body. By this definition, a pesticide is a drug; so is a natural hormone administered in large doses.

II. TOPICS COVERED

The book is arranged as follows: Chapter 1 includes an introduction to the discipline of drug design. What are its scientific origins? How do scientists go about trying to discover a drug? Chapter 2 is an overview of the extrathermodynamic and Free-Wilson methods. These chapters are intended to acquaint

readers unfamiliar with medicinal chemistry with the type of topics which will be discussed in later chapters.

Chapter 3 is a review of the noncovalent forces between molecules. It is these forces which determine the specificity and often the strength of the interaction between a drug and its receptor. The calculation of physical properties of molecules which can be related to these forces is discussed in Chapter 4. These topics are important to the whole issue of reliability.

Desirable characteristics of the biological data and methods of transformation of raw data into potency values are covered in Chapter 5. These topics are important to understand--more than one expert at linear free-energy calculations has made an error in the calculation of the relative potency of analogs.

The mathematical form of the relationship between potency and physical properties is the subject of Chapter 6. Particular emphasis is given to the complex relationships between potency, partition coefficient, and fraction ionized. Both the empirical Hansch equations and model-based equations are included. These subjects have only recently attracted attention (Martin and Hackbarth, 1976); they have not been reviewed elsewhere.

Chapter 7 contains an introduction to the statistics of multiple linear regression. The characteristics of an acceptable regression analysis computer program, the steps one should follow in the first examination of a set of data, pitfalls and special techniques in regression analysis, and distinctive characteristics of the application of nonlinear regression are discussed in Chapter 8.

Chapter 9 is a detailed illustration of the introductory material with a series of esters of erythromycin. This step-by-step explanation should be a useful guide for readers who have never attempted a regression analysis. Some of the tables are copies of the actual computer printouts from this data.

Statistical methods other than regression analysis are reviewed in Chapter 10. These have not received wide attention, but they can be used in situations in which regression analysis is inappropriate.

Chapter 11 consists of considerations in the design and termination of synthesis in a series. These in general are nonmathematical applications of the concepts covered earlier. This chapter may be of special use to those readers who do not intend to become experts in the calculations of the extrathermodynamic approach, but who do want to apply some of the concepts to their own work.

Chapter 12 consists of several case studies of the actual application of the extrathermodynamic approach to problems in the drug industry. These are meant to illustrate by example points dealt with previously, and also to give the reader a feeling for the strengths and weakness of the extrathermodynamic method.

The Free-Wilson method is covered in Chapter 13. The data on the erythromycin esters is again used as an example to allow comparison between this and the linear free energy approach.

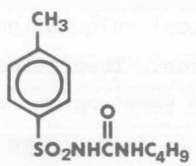
Finally, Chapter 14 provides a brief introduction to design of enzyme inhibitors and the consideration of conformation as a basis for the design of analogs. The design of enzyme inhibitors has been the focus of real advances in recent years. The methods discussed appear to be useful in appropriate cases. The consideration of the three-dimensional shape of the molecule has been one aspect of planning analogs for many years. Recent advances include the calculation of the conformation by potential energy and quantum chemical calculations and measurement of it by nuclear magnetic resonance. Theoretical considerations of the importance of low-energy barriers are even more recent. The conformational approach to drug design may also be evaluated by observations of small-molecule/large-molecule interactions in the crystal state.

Appendix I contains a summary of the important equations used or derived in the text. Appendix II is a list of values of substituent constants for a large number of substituents. Appendix III is a brief introduction to Wisswesser Line Notation. Appendix IV provides information on purchasing computer programs and data banks discussed in the text.

III. STEPS IN DRUG DESIGN

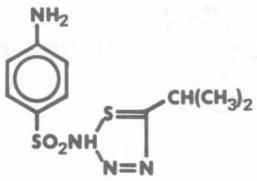
There are several separate steps in the design of a synthetic compound to be used as a drug. These are presented from a slightly different point of view by Biel and Martin (1971). Examples are found in the books edited by Ariens (1971-1976) and by Burger (1970). Each particular step uses a different type and quality of information. The various "rational" approaches to drug design are in general more applicable to one or another of these steps. The stages are briefly described for the newcomer to the field.

After the definition of the type of biological properties the sought-after compound should have, the first step in the discovery of a drug of novel structure is to find a "lead" compound. This is usually a molecule with demonstrable but weak activity of the desired type. An important source of lead compounds is "random" screening. This means simply that many compounds of varied structural types are tested at a high dose in an appropriate biological test. A second rich source for leads is in the observed side effects in animals or man of known drugs. The oral antidiabetic agents, of which tolbutamide (I) is an example, were



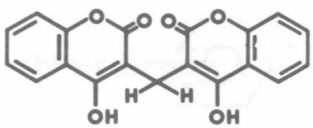
I

discovered by careful molecular modification of a sulfa drug (II) which showed lowering of blood glucose as a side effect (Grunwald,



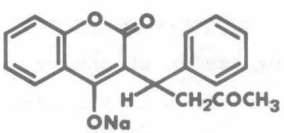
II

1970). A third source of leads for new drugs is found in natural products. For example, the structure of the natural anticoagulant, bishydroxycoumarin (III), led to the synthesis of a distant analog,



III

the widely used anticoagulant drug warfarin (IV) (Cutting, 1969).



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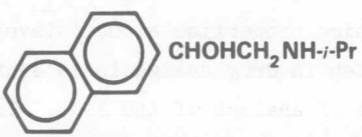
A fourth source of leads is the structure of natural body substances. Pronethalol (V) was designed to antagonize the effects



V

of norepinephrine (VI) (Barrett, 1972). Also, enzyme inhibitors are often designed from the structure of substrates. For example, the monoamine oxidase inhibitor pargyline (VII) is an analog of the substrate, benzylamine (VIII) (Martin et al., 1975).