REVIEWS

Strategy of Drug Design: A Molecular Guide to Biological Activity. By W. P. PURCELL, G. E. BASS, and J. M. CLAYTON. Wiley-Interscience, Wiley, New York, N.Y., 1973. 193 pp. 14.5 × 22.5 cm. Price $9.95.

Comprehensively yet concisely written in a step-by-step manner, this is a very useful book to introduce students, medicinal chemists, and drug designers to the structure–activity relationship study from a mathematical approach. The book consists of six chapters and four appendixes, with an author index and a subject index.

The introductory chapter presents a historical background of the development of various mathematical models. This is followed by three chapters on linear free energy related (extrathermodynamic) models, wherein the Hammett equation, Hansch calculations, Free–Wilson model, among others, are illustrated to correlate physicochemical properties (hydrophobic, steric, electronic, *etc.*) of a given molecule with its biological activity. Two following chapters on *de novo* model present a statistical approach for tabulating and ranking substituent group contributions to biological activity.

While correlations between calculated and observed biological activities in a closely related series of compounds are sometimes successful, the mathematical approach has presently found its usefulness mainly in correlating *in vitro* biological activities (enzyme inhibitory action, for example) and, in a limited extent, predicting semiquantitative and largely qualitative structure–activity relationships. The reason, as the authors wisely point out, is: "... that this approach does not represent a panacea to drug design and that biological systems are not ready to lie quietly while we dissect and probe with neat, mathematical models and laws of physics."

Although a molecule may exert its activity as such *in vitro*, it often undergoes various metabolic changes such as hydrolysis, hydroxylation, cyclization, esterification, reduction, oxidation, and/or ring cleavage, to name just a few. Furthermore, there are factors which can influence metabolism of a given compound or drug, *e.g.*, animal species, strain, age, sex, size of dose, route of administration, presence of other foreign compounds, temperature, time of day, and diet, which are rather difficult to consider and gather in a few equations. The authors very aptly review the efforts made to bring some order to a complex sequence of events by illustrating the nine hydrophobic, eight steric, 54 electronic, and eight miscellaneous parameters for the use in the linear free energy related model. However, for *in vivo* studies, these factors or parameters may not be additive.

Although the development of a few equations with some interesting correlations of experimental results is a far cry from "Drug Design," the mathematical approach is nevertheless a meaningful one which can be used and continuously developed for the study of structure–activity relationships. In this regard, the authors as well as other workers in this field are to be congratulated and encouraged for being involved in this undertaking.

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The Chemistry and Biochemistry of the Sulfhydryl Groups in Amino Acids, Peptides and Proteins. By MENDEL FRIEDMAN. Pergamon Press, Elmsford, NY 10523, 1973. vii + 485 pp. 18 × 26 cm. Price $22.50.

The main focus of the book is the sulfhydryl group (SH). The scientific literature is extensively reported and critical comment is offered. Division of the book is into 16 chapters, each devoted to a particular topic.

The first chapter deals with the pKa and K_a of the SH group in the aminothiol with greatest emphasis on methods used in their determination. A critical evaluation of the methods is offered.

Chapters 2–9 cover a wide variety of reactions of SH groups. Reactions of SH and other groups with transition metals are discussed in the second chapter. The affinity of SH for transition metals is related to the involvement of SH groups and metals in active sites of enzymes and in chelates.

In the next chapter the role of the SH group in protein structure is presented. Major emphasis is placed on the return of protein denatured by reduction of the disulfide bonds to the original structure by oxidation.

Reactions through which SH groups can be eliminated from protein and the products of the reactions are considered in Chapter 5. The importance of these reactions to food, wool, leather, and other technologies is illustrated.

Chapters 6–8 cover reactions through which SH groups may be modified. Chapter 6 deals with organic halides and epoxides. Chapter 7 emphasizes transfer of groups from S to N and S to S. Chapter 8 deals with the mechanisms through which simple thiols can be used to break disulfide bonds in protein. Practical application of the latter reactions are considered, for example, in relation to SH content of flour and bread quality.

Procedures for introducing thiol groups into proteins are discussed in Chapter 9. The primary areas of concern are synthesis of new cysteines, procedures used in thiolation, and methods used to protect SH groups during peptide synthesis.

The use of thiols as radioprotectives with various proposed mechanisms and conflicts is the focus of the next chapter. Consideration is given to factors such as the influence of pH and oxygen.

A number of methods for analysis for SH and S-S content of protein are included in Chapter 11.

Chapter 12 reports on the different reactivities of SH groups in proteins and the relation of enzyme activity and protein structure.

The involvement of SH groups in active sites of enzymes is considered next (Chapter 13). Major emphasis is on methods used to determine reaction mechanisms of SH enzymes.

Chapter 14 outlines several of the known biosynthesis routes for thiols. Involvement of SH in other aspects of metabolism is also discussed. Sulfhydryl groups are involved in certain cases in detoxification reactions. Mechanisms of reaction are considered.

The final chapter of the book is turned to the practical application of SH chemistry to disease and drug action.

The wide variety of topics covered in the book would make it of interest to any serious student of SH chemistry or biochemistry. Although discussion of the literature is often only fragmentary, entry into the literature is provided by extensive references. The critical evaluation of the literature provides insight into problems present in SH research and also points out conflicts which could lead to needed research.

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Frontiers in Catecholamine Research. Proceedings of the Third International Catecholamine Symposium Held at the University of Strasbourg, Strasbourg, France, May 20–25, 1973. Edited by E. USDIN and S. H. SNYDER, Pergamon Press, Elmsford, NY 10523, 1973. 1219 pp. 17.5 × 26 cm. Price $50.00.

This challenging title holds in 1219 pages eight broad topics with 210 papers which were presented at the Third International Catecholamine Symposium in May 1973. "The Impact of Monoamine Research on Drug Development" deals with mechanisms of drug action, *e.g.*, drugs affecting biosynthesis, the amine pump, intraneuronal storage, norepinephrine release, structure of the nerve terminal, receptors, and amine catabolism.