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EDITED BY

TOSHIO FUJITA

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Volume 23

QSAR AND DRUG DESIGN: NEW DEVELOPMENTS AND APPLICATIONS

Based on Topics presented at the Annual Japanese (Quantitative) Structure–Activity Relationship Symposium and the Biennial China–Japan Drug Design and Development Conference

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ELSEVIER
Amsterdam – Lausanne – New York – Oxford – Shannon – Tokyo 1995

ELSEVIER SCIENCE B.V.
P.O. Box 1527
1000 BM Amsterdam, The Netherlands

ISBN 0-444-88615-X

This book is printed on acid-free paper.

Printed in The Netherlands

PHARMACOCHEMISTRY LIBRARY – VOLUME 23

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PHARMACOCHEMISTRY LIBRARY, edited by H. Timmerman

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Professor Corwin Hansch

Without his heartfelt encouragements, the editing of this volume would never have been completed.

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PREFACE

In this series of *Pharmacochemistry Library* the preceding volume dealing with the QSAR methodology and related topics is Vol. 16, *QSAR: Rational Approaches to the Design of Bioactive Compounds*, edited by Carlo Silipo and Antonio Vittoria, both of whom unfortunately passed away recently. Volume 16 was published as the Proceedings of the 8th European Symposium on Quantitative Structure–Activity Relationships held in 1990 in Sorrento, Italy. Like the European Symposium, the Japanese Symposium on Structure–Activity Relationships has been organised annually since 1975. A bilateral symposium with Chinese scientists, the "China–Japan Drug Design and Development Conference", has been held biennially since 1989.

This volume, instead of taking the form of Proceedings, is an edited volume based on topics selected from those presented at these symposia. Each chapter is thus more complete than the original presentations and includes consecutive series of the same topic originally presented separately.

The structure–activity relationship (SAR) studies of bioactive compounds seem to have at least two objectives. One is to obtain insight into the pharmacological modes of action and the other is to deduce possible guiding principles for designing analogues with better bioactive profiles. The quantitative approach to the SAR (QSAR), initiated by Corwin Hansch and his co-workers some 35 years ago, opened up new possibilities in the SAR discipline. Because the Hansch QSAR expanded the Hammett-Taft paradigm in physical organic chemistry toward the biomedicinal (re)activity, the mode of action has been illustrated on the (sub)molecular level in many cases. It also revealed the critical importance of the hydrophobicity of the bioactive molecule. Before the advent of the QSAR, the mode of action had remained mostly on the level of discussions in terms of the "lock-and-key" hypothesis. Because the relationships are represented in the form of mathematical correlation equations with physicochemical (electronic, steric, hydrophobic and others when necessary) parameter terms in the QSAR, the bioactivity of non-measured analogues has sometimes been predicted by extrapolating significant parameters and proved after synthesis and biological tests. This can be regarded as the beginning of the quantitative drug design.

Perhaps stimulated by the success of the traditional Hansch QSAR, a number of newer software-based methodologies have been publicized in the SAR and drug design disciplines, supported by the tremendous progress in computer technology in recent years. Among them are those based on theoretical physicochemical and/or molecular orbital calculations, those utilizing molecular modelling and graphics, those managing sophisticated statistical operations and data-base-oriented procedures. Some theoretical calculation softwares do not only deal with the stereo-electronic energy of ligands, but also extend their scope into protein molecules. Thus, the current situation is as if a successful drug design from receptor protein structures could be not entirely impossible.

In this volume topics are covered among almost every procedure and subdiscipline described above. They are categorized into three sections. Section I includes topics illustrating newer methodologies relating to ligand-receptor interactions, molecular graphics and receptor modelling as well as the three-dimensional (Q)SAR examples with the active analogue approach and the comparative molecular field analysis. Note that the last two chapters also use the traditional QSAR to cross-validate the results obtained with the newer procedures. In Section II the hydrophobicity parameters, log P (1-octanol/water), for compound series of medicinal-chemical interest are analysed physico-organic chemically. New procedures for the lead generation using databases of aminoacid sequences and structural evolution patterns, as well as a newer statistical QSAR modification utilizable in cases when the bioactivity potency is represented by ratings, are also placed in this Section. Section III contains the examples based on the traditional Hansch QSAR approach. Two contributions are from China illustrating how to identify the lead structures from folk medicine and how to optimize them in clinical applications. Others in this Section are instructive examples of the Hansch approach for various series of bioactive compounds in rationalizing the potency variations, actual designing the clinical candidates and revealing the (sub)molecular mechanism of action. A variety of methodologies and procedures are presented in this single volume. It is recommended that the readers regard each of the methodologies as complementary to others.

It must be confessed that editing this volume required a much longer period than I had originally expected. Apologies are due to some of the authors if their chapters have become out of date, because the speed of progress in this field is very fast. If there could be something to mitigate the responsibility, it is the fact that most of the chapters dealing with rapidly growing topics describe their methodological philosophy in some detail. With understanding the background way of thinking, further developments can hopefully be caught up without difficulty.

Last but not least, the editor expresses his sincere thanks to Mrs. A. Elzabeth Ichihara for critical correction of the English in most of the original manuscripts.

August 1, 1995
Toshio Fujita,
at Fujitsu Kansai Systems Laboratory

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Three-Dimensional Structure-Based Drug Design, Molecular Modelling and Three-Dimensional QSAR.

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RATIONAL APPROACHES TO COMPUTER DRUG DESIGN BASED ON DRUG–RECEPTOR INTERACTIONS

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ABSTRACT

We have developed two novel methods and computer programs for rational drug design on the basis of drug–receptor interaction. The program GREEN is to perform docking studies efficiently and rationally, when the receptor structure is known. The main features of the program are the real-time estimation of intermolecular interaction energy and the informative visualization of the drug binding site. In addition, many functions help to find approximately the stable positions and conformations of a drug molecule inside the receptor cavity. The other program, RECEPS, is for rational superposition of molecules and for receptor mapping, when the receptor structure is not known. The superposition is performed through the use of spatial grid points and monitored by several goodness-of-fit indices indicating the similarities in physical and chemical properties. Based on the superposed structures, a three-dimensional receptor image can be constructed, which reveals cavity shapes, expected locations and characters of hydrogen-bonding groups, electrostatic potentials of the surface, and other features.

1. INTRODUCTION

For the development of new drugs, a tremendous number of compounds must be synthesized and assayed for biological activities. As the difficulties in synthesizing compounds have decreased with the technical advances of organic synthesis, the efficient design of bio-active molecules has become more and more important. Usually, drug development starts with the selection of a lead compound, and then the structure is modified to obtain better biological response profiles. But, starting from an appropriate lead compound is the key to success. How to find an appropriate lead compound and how to optimize the lead structure efficiently are the central problems of drug development. As yet, however, no general

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methods for solving these problems are available. Indeed, finding new lead compounds is so difficult as compared with optimizing existing lead compounds that they have never been generated artificially.

It has long been desired to design active structures on the basis of logic and calculations, not relying on chance or trial-and-error. Computers have been introduced into drug design for that purpose, and with the remarkable progress of computer technology in the past thirty years, computers have become widely used in drug research for maintaining databases, statistical processing, molecular modeling, theoretical chemical calculation, and so on. Since analyses of the relationships between structures and activities by using computers began more than twenty years ago (1), various approaches have been reported by many researchers. Some of them, however, have fallen by the wayside as our understanding of drug-receptor interactions has deepened.

Drug-Receptor Interactions

It is well known now that a drug molecule exerts its biological activities by binding specifically to a target macromolecule, or receptor, in the body. Dozens of receptor molecules for various hormones and neural transmitters have been isolated and characterized, and their amino acid sequences have been determined. None of the three-dimensional structures of such receptors has been elucidated, whereas those of hundreds of proteins have already been elucidated to atomic resolution by X-ray crystallographic analyses. Some solutions have been obtained for complexes of protein and ligand molecules. These results have provided us with details of molecular recognition by the macromolecule as well as the three-dimensional structure of the macromolecule. Such concrete molecular images have validated the key-and-lock model for drug–receptor interaction, which had been vaguely understood for a long time.

In most of the complexes, ligand molecules are non-covalently bound to proteins. The complexes are stabilized by intermolecular forces such as hydrogen bonds, electrostatic interactions, van der Waals forces, and hydrophobic interactions. The strength of binding, which is represented experimentally by equilibrium constants of binding or dissociation, can be estimated by empirical energy calculations. The sum of the intramolecular and intermolecular energy values is taken as an index for showing

the binding affinity, although the molecular recognition results from the free energy decrease upon complexation between the molecules. Accordingly, the more energetically favorable the interaction of the ligand molecule with the receptor is, the more efficiently the ligand can bind to the target receptor specifically. There are many examples where agonist and antagonist molecules with quite different chemical structures can bind strongly to the same site of the same receptor as the natural bio-active compounds. This fact is well evidenced by a number of crystallographic studies on protein–ligand or enzyme–inhibitor complexes.

It can be seen that it is not the skeletal structure itself but the three-dimensional array of submolecular physical and chemical properties of the ligand molecule that is recognized by proteins. As receptors consist mainly of proteins and the main functions of receptors seem to depend on the protein constituents, the molecular recognition between a receptor and drug is supposed to be very similar to that between an enzyme and substrate. The only difference is that reactions proceed in the case of enzymes, whereas signals are transduced between cells in the case of receptors. Many enzyme inhibitors are used as clinical drugs, in order to maintain biological homeostasis by controlling biochemical reactions or to prevent pathogenic microorganisms from proliferating. In this article, we use the term "receptor" in a broad sense, including not only the pharmacological receptors for hormones and neural transmitters but also enzymes or other globular proteins or nucleic acids.

Methods for Analysis of Structure-Activity Relationships

Various approaches have been proposed for analyzing structure-activity relationships using computers. Among them, there are approaches in which the chemical structural formula is split up into component units. The individual substructural components are regarded as being significant to various extents for the biological activity, and the structure-activity relationships are analyzed assuming that the activity is controlled by combinations of the activity-indices assigned to the individual structural units contained in each structural formula. The activities of a series of compounds are expressed as functions of these indices by linear or non-linear combination methods. These approaches seem to be

just for the analyses, but not effective for understanding molecular recognition by biological macromolecules. Some of the substructures may indeed play important roles in interaction with the receptor. But, they can often be replaced by other groups with similar physical and chemical properties. As stated before, it is not just the existence of the particular structural units but the spatial alignments of physical and chemical properties of the units that are important. It seems to be quite difficult to reconstitute the separated pieces of a structural formula to obtain new molecules in the hope that they will have the same biological activity as the original molecule.

Among approaches based on the physicochemical properties of molecules, Hansch and Fujita's method (2) is excellent. They have developed a method whereby the relationships between structures and activities can be analyzed quantitatively. In this method, biological activities are correlated with various physicochemical properties of substituent groups at specified positions of molecules in a series of derivatives with the same skeletal structure. By regression analyses, the activities of dozens of compounds can be represented by an equation consisting of a linear combination of several physicochemical variables. Usually, the physicochemical properties of substituent groups, such as inductive, resonance, hydrophobic, and other effects, and those of whole molecules, such as the partition coefficient and molar refractivity, are chosen as variables (3), since they make significant contributions to the activity. From the coefficient for each variable term in the equation, we can determine quantitatively the extent of the contribution of each property to the activity. This method is a powerful tool to indicate quantitatively the direction of subsequent structural modifications in order to improve the biological activity. Although the interpretation of the physical meanings of the variables is not always clear, the equation covers a number of interactions between drugs and biological systems. The method has been shown to be useful for performing lead optimization rationally and used worldwide. But, it is necessary to establish different methods for interpreting the structure-activity relationships for molecules with different skeletal structures, and for designing new molecules with different skeletons. For these purposes, efficient methods using three-dimensional structures, based on new concepts, seem to be essential.