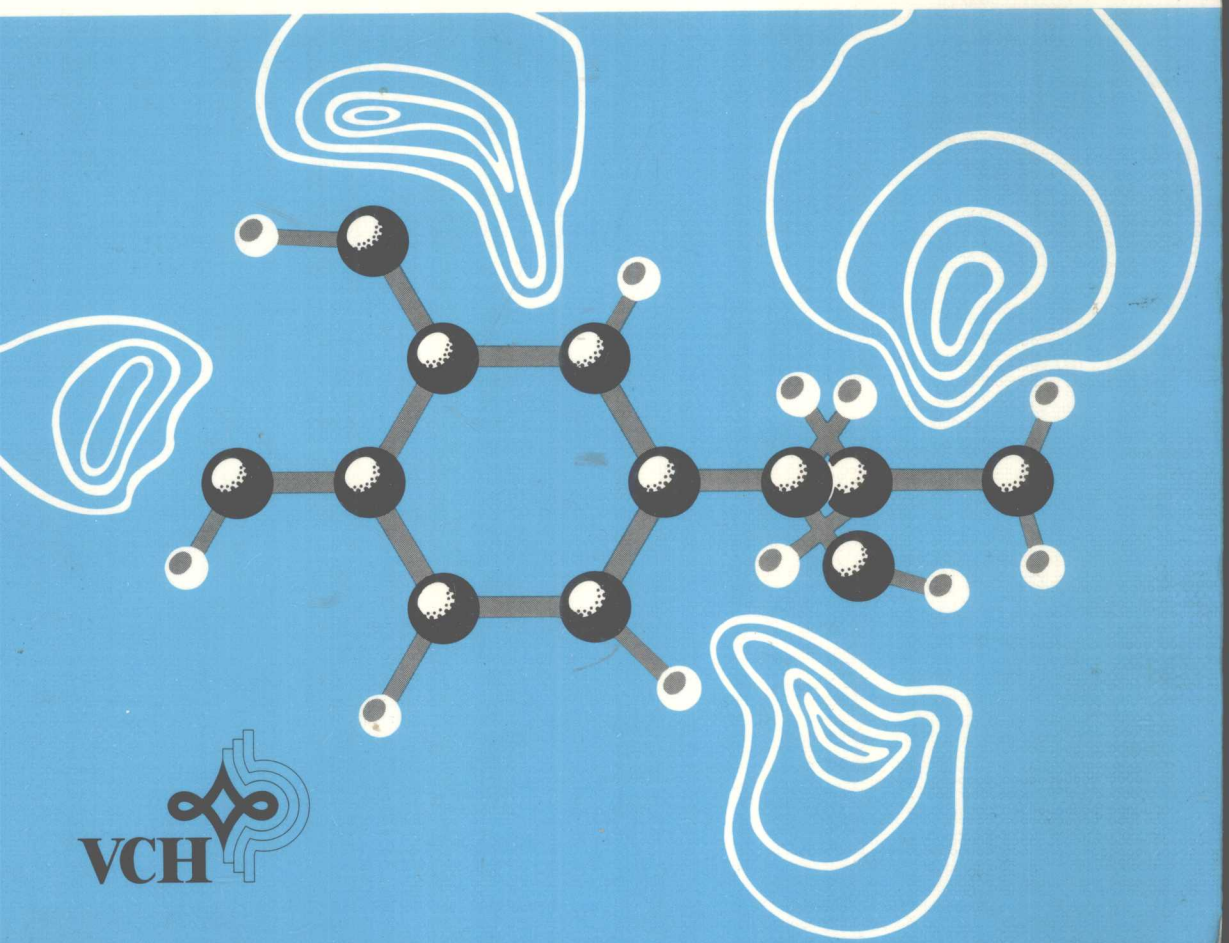
QSAR and Strategies in the Design of Bioactive Compounds

edited by J. K. Seydel



VCH

QSAR and Strategies in the Design of Bioactive Compounds

Proceedings of the Fifth European Symposium on Quantitative Structure-Activity Relationships Bad Segeberg 1984

edited by
J. K. Seydel

Prof. Dr. J. K. Seydel
Institut für Experimentelle Biologie und Medizin
Forschungsinstitut Borstel
Parkallee 1–42
D-2061 Borstel
Federal Republic of Germany

Library of Congress Card No. 85-2408

Deutsche Bibliothek Cataloguing-in-Publication Data

QSAR and strategies in the design of bioactive compounds: proceedings of the 5th European Symposium on Quantitative Structure Activity Relationships, Bad Segeberg 1984/ed. by J. K. Seydel. – Weinheim; Deerfield Beach, FL: VCH, 1985.
ISBN 3-527-26306-3 (Weinheim)
ISBN 0-89573-433-8 (Deerfield Beach, FL)

NE: Seydel, Joachim K. [Hrsg.]; European Symposium on Quantitative Structure Activity Relationships <05, 1984, Segeberg>

Printing: Weihert-Druck GmbH, D-6100 Darmstadt
Bookbinding: Wilhelm Osswald + Co., D-6730 Neustadt/Weinstr.
Printed in the Federal Republic of Germany

J. K. Seydel

QSAR and Strategies in the Design of Bioactive Compounds

Proceedings of the 5th European Symposium on Quantitative
Structure-Activity Relationships
17.–21. September 1984, Bad Segeberg, Federal Republic of Germany

Distribution:
VCH Verlagsgesellschaft, P.O. Box 1260/1280, D-6940 Weinheim
(Federal Republic of Germany)
USA and Canada: VCH Publishers, 303 N.W. 12th Avenue, Deerfield Beach,
FL 33442-1705 (USA)

ISBN 3-527-26306-3 (VCH Verlagsgesellschaft) ISBN 0-89573-433-8 (VCH Publishers)

Preface

After the preceeding meetings on the same subject at Prague in 1973, Suhl 1976, Budapest 1979 and Bath 1982, the 5th European Symposium on QSAR was held from September 17.–21. 1984 at Bad Segeberg, Federal Republic of Germany.
The organizers were glad to welcome 150 delegates and accompanying persons from 20 nations, the majority from the European countries (125), 20 from the United States, 3 from Japan and 2 from India.

The Organizing Committee has tried to set a frame and stage for the presentation and discussion of new research work in the more and more extending field of methods used in drug development.

For this purpose six major topics have been chosen, each introduced by an invited speaker in a plenary lecture, followed by 3–4 contributed papers. Main emphasis has also been put on the poster presentations, covering 3 important areas in QSAR. Special poster discussion sessions guided by a chairman were held for each of the 3 poster subjects. In addition, the Organizing Committee decided to include the poster material into the proceedings of the symposium. The 6 topics discussed in the lectures were:

Methods in QSAR
QSAR-Parameters
Molecular Modelling
Application of QSAR Analysis in Medicinal Chemistry
Application of QSAR Analysis in Pharmacokinetics
Application of QSAR Analysis in Agrochemistry

The 3 poster sessions were on Methods and Parameters, on Application of QSAR in Medicinal Chemistry and Pharmacokinetics and on Application of QSAR in Agrochemistry and Environmental Safety. QSAR covers a wide range of disciplines, tools and ideas. It is my hope that this is reflected in a comprehensive manner in these proceedings.

In the opening lecture special attention was paid to problems involved at the left hand side of QSAR equations, the biological activity data, and the risk implied in their interpretation. Besides the classical LFER-approach, which still is the most applied method, much emphasis has been put on the evaluation of new or better structural parameters and especially on possibilities to consider configuration and conformation of drug molecules and the dynamics involved in the receptor interaction. The progressive development of computer graphics in combination with X-ray analysis of substrate but also of receptor molecules has opened new dimensions in drug research. There seems to be no way back to the "old style". Molecular shape analysis, distance geometry and, calculation of conformation and interaction energies will gain more and more influence. Multivariate analysis by powerful statistical methods as principal components analysis, partial least squares and canonical correlation analysis will be especially helpful to analyse large data sets of biological activity data, obtained in various biological systems and complex pharmacokinetic data. These methods will furthermore be helpful to analyse environmental toxicity data of chemicals of various classes. QSAR may finally lead to a better selection of suitable test systems and reduction of animal studies.

For these reasons we have chosen the title "QSAR and Strategies in Design of Bioactive Compounds" for this volume of the proceedings.

The aim of the methods discussed is not only to optimize within known series of drugs and to generate new leads, but also to guide our thinking so that a practical goal is reached: a better understanding of drug action mechanisms and by this a more rational drug design.

Gradually over the years the focus of QSAR has changed from purely academic to being more and more practical. This is also expressed in the number of contributions to this symposium and the number of delegates from industry.

Finally it is my pleasure to express my sincere thanks to the Organizing Committees for their great help, encouragement, guidance and enthusiasm and to the pharmaceutical industry and various institutions for their financial support. My thanks are going also to the delegates and participants for their wonderful cooperation.

J. K. Seydel
Organizing Secretary

Borstel, Sept. 1984

Scientific Organizing Committee:
Dr. V. Austel
Dr. W. Draber
Prof. Dr. H.-D. Höltje
Doz. Dr. H. Kubinyi
Dr. E. Möller
Prof. Dr. J. K. Seydel
Dr. K.-J. Schaper

Local Organizing Committee:
Mr. R. Bartels
Dr. L. Bock
Mrs. I. Bouchain
Mr. H.-P. Cordes
Mr. V. Grote
Mrs. B. Kunz
Mrs. M. Nendza
Mrs. F. Seydel
Mrs. H. Theiler
Dr. K. Visser
Mrs. E. Wempe

Contents

Session III
Molecular Modelling
Chairman: C. Hansch

Session IV
Application of QSAR Analysis in Medicinal Chemistry
Chairman: J.G. Topliss

Session V
Application of QSAR Analysis in Pharmacokinetics
Chairman: H. Kubinyi

Poster Session III
QSAR in Agrochemistry and in Environmental Safety
Chairman: P. Moser

Papers

Opening Lecture

To which Extent Can Receptor Events be Extrapolated from Drug-Induced Responses?

Heinz Lüllmann, Albrecht Ziegler

Department of Pharmacology, University of Kiel,
Hospitalstraße, D-2300 Kiel, W.-Germany

ABSTRACT

An essential aspect of QSAR is to extrapolate on receptor events (occupation, rate constants) from biological dose response curves which provide apparent constants such as ED_{50}-values, intrinsic activities,and slope factors. The difficulties of this approach will be discussed and illustrated by examples taken from work on muscular tissues. The informations obtainable from tissue-response relations and dose-response-curves are considered.

The basis of any investigation into structure-activity relationships is the assumption that drug-molecules interact with specific chemical structures of living matter thus resulting in functional alterations (KAHN, 1976). An interaction of this kind can be considered to obey the law of mass action:

$$[A] + [R] \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} [AR]$$

$$K_D = \frac{k_{-1}}{k_{+1}}$$

A	drug molecules
R	binding sites
K_D	dissociation constant
k_{+1} k_{-1}	rate constants

and thus can be characterized by half maximal saturation (K_D) and the rate constants (k_{+1}, k_{-1}). These essential values for evaluating structure-activity relationships are expected from studies undertaken with living matter such as bacteria, isolated cells,

intact organs, experimental animals or even human beings. The unsurmountable dilemma, however, at present is that pharmacologists (microbiologist, clinicians) cannot provide direct informations on the concentration of AR nor on the rate constants because only the consequences of AR formation, i.e. the biological responses are measurable. In the following we shall, therefore, discuss the reservations which have to be made when drug effects are considered to directly reflect receptor events. Within this large field we shall restrict ourselves to plasmalemmal receptors whose occupation induces alterations of muscular tissues. We should like to discuss three aspects: 1) time-response relations; 2) concentration-response relations; 3) functional state and responses.

1. Time-response relations

Upon administration of a drug, its equilibrium effect is achieved with a certain time course. An example is given in Fig. 1, raising the question: which process governs the rate of the response. The rate-limiting process can considered to be either the disposition of the drug (diffusion within the extracellular space), the drug-receptor-interaction, or the transformation of AR formation into the biological response.
As demonstrated in Fig.1 the time course of the effect and that of drug uptake by the tissue differ considerably in this particular case. Here, the uptake should reflect the filling of the biophase and the saturation of the receptors. The obvious discrepancy between the rates of the two processes indicates that the receptor occupation is not linearly related to the biological response.
If the drug administration is so much retarded that disposition is not any longer rate limiting, similar time courses of the concentration of the drug in the biophase and of the mechanical response might be observed (Fig.2, lower panel).

This holds true only if the final drug concentration is far away from maximum effective concentrations. However, even under these conditions dissociation between the time course of the response and that of drug concentration in the biophase can be observed (Fig.2, upper panel).

Several possibilities exist to explain the difference between the response pattern of the two smooth muscle preparations, one of it is that in taenia coli two processes are initiated by the drug-