Structure-Based Ligand Design

edited by Klaus Gubernator and Hans-Joachim Böhm

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Methods and Principles in Medicinal Chemistry

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H. Timmerman

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Preface

Structure-based ligand design is defined as the search for molecules that fit into the binding pocket of a given target and that can form favorable interactions.

During the past few years, structure-based ligand design has gained an increasingly prominent position within medical chemistry. An impressive number of convincing examples have been published which prove the potential of this approach. Two factors underly the increasing importance and effort of structure-based ligand design: on the one hand, new computer programs for conformational analysis, ligand docking, structural alignment and *de novo* design have been developed; and on the other hand, scientific progress in the molecular biology providing the three-dimensional (3D) structure of therapeutically relevant biopolymers.

Despite such unquestionable progress, lead discovery by structure-based ligand design still faces several problems and limitations such as a lack of availability of 3D structures for the important group of membrane-bound receptors, or adequate computational approaches to reflect induced-fit in drug–reactor interactions.

With regard to the prime aim of our series, i.e. to provide practice-oriented information for medicinal chemists, Klaus Gubernator and Hans-Joachim Böhm have subdivided this volume into two parts. The first part comprises a concise introductory chapter, written by the editors, and covering all aspects of the methodological background in this research field. The second part comprises several chapters which summarize some success stories in the field of structure-based ligand design, such as the design of inhibitors of beta-lactamase (by Gubernator et al.), sialidase (by N. Taylor) or HIV-1 reverse transcriptase (by W. Schäfer). Progress in new computational approaches to predict protein–ligand interactions is described by H. J. Böhm.

The editors would like to thank the contributors to this volume for their cooperation. We are sure that scientists entering the field of structure-based ligand design will find in this volume the adequate support for the successful application of lead discovery techniques.

December 1997

Düsseldorf — Raimund Mannhold
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Methods and Principles in Medicinal Chemistry

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Structure-Based Ligand Design

A Personal Foreword

Writing or editing a book about a rapidly evolving area of science is a challenge. Doing this while being involved in real projects every day is even more of a challenge. And changing location and assignment during this exercise (which is true for both editors) adds further hurdles.

We are thus particularly glad to now present a series of real-life stories from practitioners in the field that have been selected to reflect the current status of structure-based design, it's achievements and also it's controversies. These are embedded in review-type methodological chapters and discussions about scope and future perspectives of these approaches.

Our personal summary from writing several chapters and editing others is that structure-based design actually works and it's successes are now well documented. It cannot be applied to every project and the explosion of biostructural information has just started, dramatically broadening the scope of structure-based design in the future. The methodologies exploiting this information are still evolving and there is room for completely new approaches. This makes this field so interesting, in addition to the beauty of the 3D-structure, and makes writing an account or review so rewarding.

We would like to thank the contributors for the nice collaboration that we had. We also would like to acknowledge the continuous high interest of the series editors in this book project and their very valuable comments and suggestions on earlier versions of this work. We would also like to extend our thanks to our employers who fully support these additional activities, and to our families who have suffered from our mental absence for more than one weekend.

Summer 1997

San Diego K. G.
Basel H. J. B.

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K. Gubernator and H. J. Boehm

1.1 Introduction

During the past decade, medicinal chemistry has taken tremendous advantage of the fascinating scientific progress in the field of molecular biology. The three-dimensional (3D) structure determination of biopolymers is one such area which has developed extremely rapidly. As an ever-increasing number of 3D structures is now available, in medicinal chemistry the number of research projects in which the structure of the molecular target is known has rapidly increased. Therefore, there is strong interest both in industry and in academia to develop and apply new approaches that exploit such structural information in the drug discovery process. The purpose of the present volume is to summarize the current state of structure-based design and to present some interesting examples. This should convince the reader that structure-based ligand design has become a mature discipline of medicinal chemistry [1,2].

Structure-based ligand design is based on the observation that drugs bind to clearly defined molecular targets. A strong and selective binding can be obtained from a high structural and chemical complementarity between the macromolecular target and the ligand [3, 4]. Structure-based ligand design may therefore be described as the search for small molecules that fit into the binding site of the target and can form favorable interactions.

1.1.1 From Ligand Design to Drug Discovery

Structure-based design is now actively pursued by sizeable groups in both academic institutions as well as in the research departments of pharmaceutical companies. Very tight collaboration with both synthetic chemists as well as with experimental biologists performing the biological assay has turned out to be a critical success factor. This often results in the dissemination of structural information to all scientists involved in the project and, ideally, the persistent use of that information in the process of inventing new active principles.

Identifying a ligand to a given target is just the first step in the process of discovering a new drug that offers a therapeutic opportunity for the treatment of a disease. A number of further hurdles have to be taken by a compound until it also qualifies as a drug: It needs to be absorbed, transported, stable to metabolization, and distributed to the right compartment. It also has to be non-toxic, free of side effects, and chemically stable in a formulation. Most of these aspects are even more difficult to assess in a rational fashion. The ligand design part of the drug discovery process is therefore just the first step in a multidisciplinary effort that usually requires several rounds of refinement between the identification of an active principle and the selection of a viable drug candidate. Structure-based design can assist this continuous