Drug Design

Gerhard Klebe

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Methodology, Concepts, and Mode-of-Action

With 494 Figures and 44 Tables

Springer Reference

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ISBN 978-3-642-17906-8 ISBN 978-3-642-17907-5 (eBook)
ISBN 978-3-642-17908-2 (print and electronic bundle)
DOI 10.1007/978-3-642-17907-5
Springer Heidelberg New York Dordrecht London

This work is based on the second edition of "Wirkstoffdesign", by Gerhard Klebe, published by Spektrum Akademischer Verlag 2009, ISBN: 978-3-8274-2046-6

Library of Congress Control Number: 2013933987

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

The present handbook on drug design builds on the German version first written by Hans-Joachim Böhm, Hugo Kubinyi, and me in 1996. After 12 years of success on the market, the German version of this handbook was entirely rewritten and significantly extended, then by me as the sole author. The new edition particularly considers novel approaches in drug discovery and many successful examples reported in literature on structure-based drug design and mode-of-action analysis. This novel version appeared in 2009 on the German market. Several attempts were made to translate this book into English to make it available to a wider audience. This intention was driven by the fact that the author was repeatedly approached with the question as to why such a successful book is not available in the English language. An analysis of the textbook market made apparent that no similar compendium was (and still is) available covering the same field of interest. Finally, Springer agreed in the translation project, and Dr. Leila Telan, a gifted bilingual medicinal chemist and physician, was found willing to take the task of producing a first draft of a cover-to-cover translation of the German original. This version was corrected, and some chapters extended by the author. The book is meant for students of chemistry, pharmacy, biochemistry, biology, chemical biology, and medicine interested in the design of new active agents and the structural foundations of drug action. But it is also tailored to experts in drug industry who want to obtain a more comprehensive overview of various aspects of the drug discovery process.

Such a book project would not have been possible without the help of many friends and colleagues. First of all, I want to express my sincere thanks to Dr. Leila Telan, Düsseldorf, Germany, who produced the first version of this translation. Her version and the modifications of the author have been carefully proofread by many colleagues in the field. Their help is highly appreciated. Furthermore, I would like to acknowledge the help of Prof. Dr. Hugo Kubinyi, Heidelberg, Germany, who assisted in correcting the first version of the English translation. Particular thanks go to Dr. Simon Cottrell, Cambridge, England, and to Dr. Nathan Kilah, Hobat, Tasmania, Australia, for their excellent and very thorough proofreading of the different chapters. The project was ideally guided by Dr. Daniel Quinones and

Dr. Sylvia Blago, Springer, Heidelberg, Germany. The author is grateful to the publisher for their assistance and technical support in producing the electronic and printed version of this handbook.

Marburg, Germany, May 2013 Gerhard Klebe

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Introduction

Drug design is a science, a technology, and an art all in one. An *invention* is the result of a creative act, and a *discovery* is the detection of an already-existing reality. *Design* encompasses the two processes with emphasis on a targeted approach based on the available knowledge and technology. Furthermore, the creativity and intuition of the researcher play a decisive role.

Drugs are all substances that affect a system by inducing a particular effect. In the context of this book, drugs are substances that exhibit a biochemical or pharmacological effect, in most cases medications, that achieve a therapeutic result in humans.

The idea of rational *drug design* is not new. Organic compounds were prepared more than a century ago with the goal of attaining new medicines. The sedatives chloral hydrate (1869) and urethane (1885), and the antipyretics phenacetin (1888) and acetylsalicylic acid (1897) are early examples of how targeted compounds can be made that have favorable therapeutic properties by starting with a working hypothesis. The fact, that the hypotheses in all four cases were more or less incorrect (► Sects. 2.1, ► 2.2, and ► 3.1) simultaneously demonstrates one of the main problems of drug design.

In the case of the artistic design of a poster or commodity, or, in the case of engineering, the design of an automobile, a computer, or a machine, the result is usually predictable. In contrast, the design of a drug is even today not completely foreseeable. The consequences of the smallest structural changes of a drug on its biological properties and target tissue are too multifaceted and at present too poorly understood.

Until modern times, scientists have worked on the principle of trial and error to find new medicines. By this they derived mostly empirical rules that have contributed to a knowledge base for rational drug design and which has been translated by individual researchers more or less successfully into practice. Today new technologies are available for drug research, for instance, combinatorial chemistry, gene technology, and automated screening methods with high throughput, protein crystallography and fragment screening, virtual screening, and the application of bio- and chemoinformatics.

In many cases the *molecular mechanisms* of the mode of action of medicines are fairly well understood, but in other cases we are at the threshold of comprehension. Many of these mechanisms will be discussed in this book. Progress in protein crystallography and NMR spectroscopy allows the determination of the *three-dimensional structure* of protein–ligand complexes on a routine basis. As is shown in many of the illustrations in this book (for a general explanation of "reading" these illustrations, see the appendix at the end of this book) these structures make a decisive contribution to the targeted design of drugs. 3D structures with up to atomic resolution are known for approximately 550,000 small molecules and more than 85,000 proteins and protein–ligand complexes, and the numbers are increasing exponentially. Methods for the prediction of the 3D structures of small molecules are now mature, and semiempirical and *ab initio* quantum chemical calculations on drugs are now routinely performed. The *sequencing of the human genome* is complete, and the genomes of other organisms are reported nearly every week, including those of important human pathogens. The age of *structural genomics* has begun, and it is only a matter of time before the 3D structures of entire gene families are available. Given enough sequence homology, modeling programs can nowadays achieve an impressive reliability. In the meantime, the composition of entire genomes is being processed with structure-prediction programs. There are already interesting approaches for the *de novo* prediction of 3D protein structures, and the first correct 3D structural predictions have been successfully accomplished.

Structure-based and computer-aided design of new drugs is here to stay in practical drug research. Computer programs serve the search for, modeling of, and targeted design of new drugs. In countless cases these techniques have assisted the discovery and optimization of new drugs. On the other hand, a too-strict and one-sided focus on the computational results bears the danger of losing sight of the available knowledge of the relationship between the chemical structure and biological activity. Another danger is the limited consideration of an active agent only with respect to its interaction with one single target without considering the other essential requirements for a drug, for instance, the *pharmacokinetic and toxicological properties*. In the last decade, intensive research effort has gone into the compilation of empirical guidelines to predict bioavailability, toxicological profiles, and metabolic properties (*ADME parameters*). The ability to predict the metabolic profile for a given xenobiotic by the arsenal of cytochrome P450 enzymes or to predict for each individual patient the metabolic peculiarities is still a dream. Nonetheless, just such an individually adjusted therapy and dosing regime is within the realm of possibilities. It is also conceivable that in the foreseeable future, gene sequencing of each of us will be financially feasible and will require a manageable and justifiable amount of time and effort. This will open entirely new perspectives for drug research. Whether this pushes open the gate to *individualized personal medicines* will be a question of cost. The theme of this book is to introduce the methods required for drug design particularly based on structural and mechanistic evidence. By the use of well-selected examples the route to the discovery and development of new medicines is discussed and will be reflected under the constantly changing conditions.

Drug research is a multidisciplinary field in which chemists, pharmacists, technologists, molecular biologists, biochemists, pharmacologists, toxicologists, and clinicians work together to pave the way for a substance to become a therapeutic. Because of this, the majority of drug developments is done in an *industrial setting*. It is only there that the financial requirements and structural organization are in place to allow a successful cooperation of all disciplines that are necessary to channel the research in the required manner toward a common goal. The fundamentals and future-oriented innovations of drug research are, however, increasingly being established in *academia*. Interestingly, an increasing amount of research activities at the universities have recently been devoted to drug developments for *infectious diseases* and for *diseases that particularly afflict developing countries*, which have been sorely neglected by the profit oriented pharmaceutical industry of the industrialized world. This is even more alarming when we consider that our improved quality of life and prolonged life expectancy are attributable to, above all else, a victory over devastating infectious diseases. We can only hope that *politicians* recognize this situation in time and make the resources and organizational infrastructure available so that the academic research groups can step into the breach in an efficient and goal-oriented way.

The rising *costs of research and development*, an already high standard of health care in many indications, and distinctly increased safety awareness and the concomitant demanding standards of the regulatory authorities have caused the number of new chemical entities (NCE) to steadily decrease over the last decades from 70–100 per year from 1960 to 1969, to 60–70 from 1970 to 1979, to an average of 50 between 1980 and 1989, to 40–45 in the 1990s, and even less in the new millennium. Despite this, there have still been new developments, and distinct progress has been made in the therapy of, for example, psychiatric diseases, arterial hypertension, gastrointestinal ulcers, and leukemia in addition to the broadening of indications for older compounds. Of the blockbusters, a disproportionately large percentage of the drugs were found in the last years by using a rational approach.

The cost of developing and launching a new drug has increased continuously; to date, it is between US $800–$1,600 million. Only large pharmaceutical companies can still afford these costs, with the associated risk of failure in the last phases of clinical trials, or a misjudgment of the therapeutic potential of a new drug.

There is talk nowadays of a *paradigm shift* in pharmaceutical research. In research this refers to the use of *new technologies*; in the market place this refers to a concentration process of *corporate mergers and acquisitions*. The last decade brought about many such “mega-mergers.” Larger and larger sales figures are being achieved by fewer and fewer companies. In parallel to this, a very dynamic and hardly insignificant scene has developed of small- to medium-sized, highly flexible *biotech companies*. The areas of gene technology, combinatorial chemistry, substance profiling, and rational design are particularly well represented in numerous such companies. Larger companies try to outsource their riskier research concepts to these companies and contract their services for everything up to the development of clinical candidates. However, the success of this scene has led to the result that the “good” companies have been swallowed by the “big” companies. Many former

employees of "big pharma" have established their own small companies with an innovative idea. If the idea was good and successful, after a few years these innovators find themselves once again incorporated into the organization of a "big pharma" company.

At the same time the *prescribing practices* in all areas of *health care* have changed. Formerly it was the physician alone, occasionally in consultation with a pharmacist, who was responsible for the pharmacological therapy of the patient. Today cost-cutting measures, "negatives lists," health insurance, the purchasing departments of hospitals and pharmacies, the ubiquitous Internet, and even public opinion influence therapies to an ever larger extent.

The *drug market*, with its US $600 billion, is an extremely attractive market. Furthermore, this market is characterized by dynamic growth, which is decidedly more than in other markets. The best selling drug in 2005, Lipitor® (Sortis® in Europe; atorvastatin) achieved US $12.2 billion in annual sales. Only illegal narcotics like heroin and cocaine have higher sales figures.

Tailored medications – Will the latest technologies really deliver on this promise? What makes drug research so difficult? To use a parable, it is something like playing against an almighty chess computer. The rules are known to both sides, but it is very difficult to comprehend the consequences of each individual move during a complicated middle game. A biological organism is an extremely complicated system. The effect of a drug on the system and the effect of the system on the drug are multifaceted. Every structural change made with the goal of optimizing one particular characteristic simultaneously changes the finely tuned equilibrium of the other characteristics of the drug.

The knowledge of the interplay between the *chemical structure and the biological effect* must be united with the newest technology and results of genetic research to purposefully develop new medicines. It is also necessary to define the range of applications and the limitations of new technologies. Theory and modeling cannot exist detached from experiment. The results of calculations depend strongly on the boundary parameters of the simulation. The results collected at one system are only conditionally transferable to other systems. Only an experienced specialist is in a position to fully exploit the special potential of theoretical approaches. The claims that some software and venture capital companies make, that their results automatically lead to success, should be considered with some skepticism. This book should be helpful in these situations too, to separate the wheat from the chaff and to identifying the *application range* of these method as well as their *limitations*.

This book is about *drug research and the mode of action of medicines*. It is different from classical textbooks on pharmaceutical chemistry in its structure and goals. The principles, methods, and problems associated with the search for new medicines are the themes. Classes of drugs are not discussed, but rather the way that these drugs were discovered and some insights into the structural requirements for their action on a particular target protein. As the title suggests, the book is meant for students of chemistry, pharmacy, biochemistry, biology, and medicine who are interested in the art of designing new medicines and the structural fundamentals of how drugs act on their targets.

In the first section, after an introduction to the history of medicines and the concept of serendipity as an unpredictable but always very successful concept in drug research, examples from classical drug research will be presented. A discussion about the fundamentals of drug action, the ligand–receptor interaction, and the influence of the three-dimensional structure on the efficacy of a drug round the section out. In the second section, the search for lead structures and their optimization and the use of prodrug strategies are introduced. New screening technologies but also the systematic modification of structures by using the concept of bioisosteres and a peptidomimetic approach are discussed. In the third section, experimental and theoretical methods applied in drug research are described. Combinatorial chemistry has afforded access to a wide variety of test substances. Gene technology has produced the target proteins in their pure form, and has helped to characterize these proteins' properties and function from the molecular level to the cellular assembly, all the way to the organism level. It has built a bridge between understanding the effects of a drug therapy on the complex microstructure of a cell and in systems biology of an organism. The spatial structure of proteins and protein–ligand complexes are accessible through NMR spectroscopy and X-ray crystallography. Their structural principles are becoming better understood and are increasingly allowing us access to the binding geometry of the drugs. The computer methods and molecular dynamics simulations of complex conformational analysis have also sharpened our understanding of targeted drug design. The fourth section introduces design techniques such as pharmacophore and receptor modeling, and discusses the methods of, and uses for, quantitative structure–activity relationships (QSAR). Insights into the transport and distribution of drugs in biological systems are given, and different techniques for structure-based design are presented. A drug-design case study from the author's research closes the chapter. The fifth section of this book focuses on the core question of pharmacology: How drugs actually work? Enzymes, receptors, channels, transporters, and surface proteins are divided into individual chapters and discussed as a group of target proteins. The spatial structure of the protein and modes of action are used to elucidate in detail why a drug works and why it must exhibit a particular geometry and structure to work. Exemplarily, the contributions of structure-based and computer-aided design to the discovery of new drugs are presented in these chapters, and other aspects are also shifted into the spotlight.

Because of the concept of this book, many important drugs are not considered or are only fleetingly mentioned. The same is true of receptor theory, pharmacokinetics and metabolism, the basics of gene technology, and statistical methods. The biochemical, molecular biological, and pharmacological fundamentals of the mode of action of drugs, which are important for the understanding of the theme of drug design, are only commented upon in outline form. Other disciplines that are critical for the development of an active substance to a medicine and application to patients, such as pharmaceutical formulations, toxicological testing, and clinical trials, are not themes that are covered in this book.

The selection of examples from therapeutic areas was made subjectively and for didactic reasons based on case studies and to bring other aspects of drug research to

the foreground. A balanced presentation of the methods of drug design and their practical application was attempted. The interested reader does not have to read the book chronologically. If the reader's interest is purely on drugs and their mode of action, then they can also begin with ▶ Chap. 22. There are many cross references in the text to help the reader to find the passages in other parts of the book that are necessary for an exact comprehension of what is being discussed at any given part. The references and literature suggestions that follow cite particularly recommendable monographs and are ordered alphabetically; journals and series on the themes that are discussed in later chapters are not mentioned specifically again.

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