Gerhard Klebe

Drug Design

Methodology, Concepts, and Mode-of-Action

Springer Reference

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With 494 Figures and 44 Tables

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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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Nature
Nature Reviews Drug Discovery
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Pharmacochemistry Library
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Quantitative Structure-Activity Relationships
Reviews in Computational Chemistry
Science
Scientific American
Trends in Pharmacological Sciences

Nowadays the Internet, discussion platforms, and the tremendously valuable tool of Wikipedia are available to everyone and provide access to an enormous source of information.

Part I

Fundamentals in Drug Research

This colored copper plate engraving from arguably the most beautiful plant book, the *Hortus Eystettensis* by Basilius Besler, Eichstätt, 1613, shows the squill, *Scilla alba* (modern name: *Urginea maritima L.*). This plant was known to the ancient Egyptians, Greeks, and Romans as a remedy for many ailments, but especially dropsy (today: congestive heart failure). It was venerated faithfully as general defense against harm. It was not until our century that the active components of squill, the glycosides scillaren, and proscillaridin were isolated in their pure form, and a derivative with improved bioavailability, meproscillarin (Clift®), was available for pharmaceutical therapy.

Drug Research: Yesterday, Today, and Tomorrow

1

The targeted route to medicines is an old dream of humanity. Even the alchemists sought after the *Elixir*, the *Arcanum* that was meant to heal all disease. It still has not been found today. On the contrary, drug therapy has become even more complicated as our knowledge of the different disease etiologies has become more complex.

Nonetheless, the **success of drug research** is impressive. For hundreds of years, alcohol, opium, and solanaceae alkaloids (from thorn apples) were the only preparatory measures for surgery. Today general anesthesia, neuroleptanalgesia, and local anesthetics allow absolutely pain-free surgical and dental procedures to be carried out. Until this century, plagues and infectious diseases have killed more people than all wars. Today, thanks to hygiene, vaccines, chemotherapeutics, and antibiotics, these diseases have been suppressed, at least in industrialized countries. The dangerously increasing numbers of therapy-resistant bacterial and viral pathogens (e.g., tuberculosis) have presented new problems and make the development of new medications urgently necessary. The H_2-receptor inhibitors and proton-pump inhibitors have drastically reduced the number of surgical procedures to treat gastric and duodenal ulcers. Combinations of these inhibitors with antibiotics have brought even more advances in that it allows a causal therapy (▶ Sect. 3.5). Cardiovascular diseases, diabetes, and psychiatric diseases (diseases of the central nervous system, CNS) are treated mostly symptomatically, that is, the cause of the disease is not addressed, but rather the negative effects of the disease on the organism. Often the therapy is limited to slowing the progression of these diseases or increasing the quality of life. Synthetic corticosteroids have lead to significant pain reduction and retardation of the pathological bone degeneration associated with chronic inflammatory diseases (e.g., rheumatoid and chronic polyarthritis). The spectrum of cancer therapy ranges from healing, particularly in combination with surgical and radiation therapy, all the way to complete failure of all therapeutic measures.

The **history of drug research** can be divided into several sequential phases:

- the beginning, when empirical methods were the only source of new medicines,
- targeted isolation of active compounds from plants,

G. Klebe, *Drug Design*, DOI 10.1007/978-3-642-17907-5_1,

- the beginning of a systematic search for new synthetic materials with biological effects and the introduction of animal models as surrogates for patients,
- the use of molecular and other *in vitro* test systems as precise models and as a replacement for animal experiments,
- the introduction of experimental and theoretical methods such as protein crystallography, molecular modeling, and quantitative structure–activity relationships for the targeted structure-based and computer-supported design of drugs, and
- the discoveries of new targets and the validation of their therapeutic value through genomic, transcriptomic, and proteomic analysis, knock-in and knock-out animal models, and gene silencing with siRNA.

Each preceding phase loses its importance with the arrival of the next phase. Interestingly, in modern drug research individual phases run in the opposite direction. That is, first a target structure is discovered in the sequenced genome of an organism and its function is modulated to validate it as a candidate for drug therapy. Then the structure-based and computer-aided design of an active substance is undertaken in close cooperation with multiple *in vitro* tests to clarify the activity and the activity spectrum. Next, the animal experiments substantiate the clinical relevance, and in the final step clinical trials confirm a test substance's suitability as a medicine for patients.

1.1 It All Began with Traditional Medicines

The beginnings of drug therapy can be found in traditional medicines. The narcotic effect of the milk of the poppy, the use of autumn crocus (*Colchicum autumnale*) for gout, and the diuretic effect of squill (*Urginia maritime*) for dropsy (today: congestive heart failure) have been known since antiquity. The dried herbs and extracts from these and other plants have served as the most important source of medicines for more than 5,000 years. The oldest written records of these uses are from 3000 BC.

Around 1550 BC the ancient Egyptian *Papyrus Ebers* listed approximately 800 prescriptions, of which many contained additional rituals to invoke the help of the gods. The five-volume book *De Materia Medica* of Dioskurides (Greek physician, first century AD) is the most scientifically rigorous work of antiquity. It contains descriptions of 800 medicinal plants, 100 animal products, and 90 minerals. Its influence reached into the late Arabic medicine and the early modern age.

The most famous medicine of antiquity was undoubtedly Theriac. Its precursor, Mithridatum, served the King of Pontus, Mithridates VI (120–63 BC) as an antidote for poisonings of all kinds. Theriac can be traced to Andromachus, the private physician of the emperor Nero, and originally contained 64 ingredients. This preparation remained very widespread even into the eighteenth century. It was prepared in many variations with up to 100 ingredients. In some cities it was even prepared under state control to ensure that none of the ingredients were left out! Its use evolved into a panacea for all diseases. In addition, every imaginable wonder

drug was in use, some examples include rain worm oil, unicorn powder, gastric calculus stones, human cranium powder (Lat. *Cranium*, skull), mummy dust, and many more.

Traditional Chinese medicine was very advanced even in ancient times. A special feature of their formulation was, and is, the circumstances responsible for the effect of four different qualities. The chief (*jun*) is the carrier of the effect, the adjutant (*chen*) supports the effect or induces a different effect. The assistant (*zuo*) can also support the main effect or can serve to ameliorate side effects, and one or more messengers (*shi*) moderate the desired effect. The Chinese Pen-Ts'ao school (first and second century AD), whose goal it was to live for as long as possible without aging (!), recommended the following dosing regime:

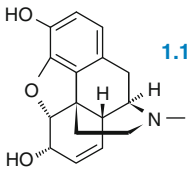
> *When treating a disease with a medicine, if a strong effect is desired, one should begin with a dose that is not larger than a grain of millet. If the disease is healed, no more medicine should be given. If the disease is not healed, the dose should be doubled. If that does not heal the disease, the dose should be increased tenfold. When the disease is healed, the therapy should always be discontinued.*

The Chinese *Materia Medica* published by Li Shizhen in 1590 is made up of 52 volumes. It contains almost 1,900 medical principles, plants, insects, animals, and minerals incorporated into 10,000 detailed recipes for their preparation. The *Chinese Pharmacopeia* from 1990 contains only two volumes. One of those volumes contains 784 traditional medicines; the other contains 967 medications from "Western" medicine.

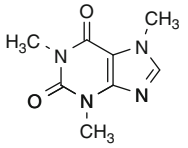
Paracelsus (born Theophrastus Bombastus von Hohenheim; 1493/1494–1541) made a great breakthrough for scientific medical research. He understood the human to be a "chemical laboratory" and held the ingredients of drugs themselves, the *Quinta essentia*, responsible for their healing effects. Despite this, up until the beginning of the nineteenth century all therapeutic principles were based on either extracts from plant, animal ingredients, or minerals; only in the most seldom cases were pure organic compounds used. That changed fundamentally with the advent of organic chemistry. The great age of natural products from plants (for examples see **1.1**–**1.9**, Fig. 1.1), and the active substances that were derived from them had begun. Premature hopes that were invested in some of these substances around the turn of the previous century, for example in heroin (▶ Sect. 3.3), or cocaine (▶ Sect. 3.4), were very quickly squelched, but natural products from plants established the fundamentals for, and form an exceedingly large part of our modern pharmacy. Natural products and their analogues and derivatives are also well represented among the best-selling drugs today.

1.2 Animal Experiments as a Starting Point for Drug Research

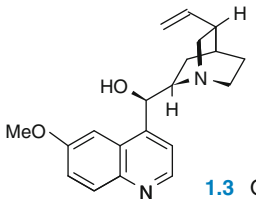
The wealth of experience gained by traditional medicine is based on many thousands of years of sometimes accidental, sometimes intentional observations of their therapeutic effects on humans. Planned investigations on animals were relatively seldom. The biophysical experiment of Luigi Galvani, an anatomy professor in



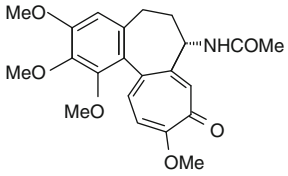
1.1 Morphine



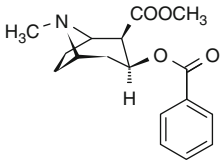
1.2 Caffeine



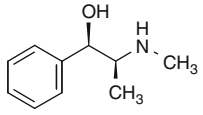
1.3 Quinine



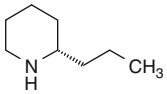
1.4 Colchicine



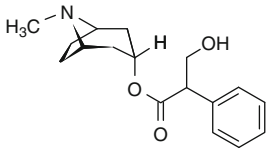
1.5 Cocaine



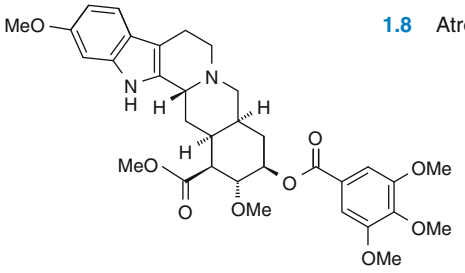
1.6 Ephedrine



1.7 Coniine



1.8 Atropine (racemate)



1.9 Reserpine

Fig. 1.1 Many important natural products were isolated in the nineteenth century, and a few were synthesized. Morphine **1.1** was isolated from opium by Friedrich Wilhelm Adam Sertürner in 1806, caffeine **1.2** was isolated from coffee, and quinine **1.3** was isolated from cinchona bark by Friedlieb Runge in 1819. Quinine was discovered independently by Pierre Joseph Pelletier and Joseph Bienaimé Caventou, who one year later isolated colchicine **1.4** from autumn crocus. Cocaine **1.5** was extracted from coca leaves by Albert Niemann in 1860, and ephedrine **1.6** was extracted from the Chinese plant Ma Huang (*Ephedra vulgaris*) by Nagayoshi Nagai. In 1886 the first alkaloid, coniine **1.7**, which is found in hemlock, was synthesized by Albert Ladenburg; in 1901 atropine **1.8** from Deadly Nightshade was synthesized by Richard Willstätter. Reserpine **1.9**, from *Rauwolfia serpentina* was first prepared in the middle of the twentieth century, and its structure was elucidated.

Bologna, which was first described in his book *De viribus electricitatis in motu musculari* in 1791, has become famous. In 1780 his students had already observed how frog thighs would twitch when the nerve was dissected and if a static electricity generator was simultaneously in use, such devices were standard laboratory equipment in many laboratories at the time. He wanted to demonstrate in standardized experiments whether the twitching was also caused by thunderstorms. He hung the legs on an iron window grill with a copper hook — they twitched simply upon contact with the grill. The voltage difference between the two metals was enough to stimulate the nerve, even without an electrical discharge.

The systematic investigation of the biological effects in animals of plant extracts, animal venoms, and synthetic substances began in the next-to-last century. In 1847 the first pharmacology department was founded at the Imperial University in Dorpat (today: Tartu, Estonia). The famous pharmacologist, Sir James W. Black, who developed the first β-blocker (an antihypertensive, ▶ Sect. 29.3) at ICI, and later took part in the development of the first H_2 antagonists (see gastrointestinal ulcer medications, ▶ Sect. 3.5) at Smith, Kline & French, compared pharmacological testing to a prism: what pharmacologists see in their substances' properties directly depends on the model that was used to test the substances.

Just as a prism would, the models distort our vision in different ways. There is no such thing as a depressed rabbit or a schizophrenic rat. Even if there were such animals, they would not be able to share their subjective perceptions and emotions with us. Gene-modified animals (▶ Sect. 12.5), such as the Alzheimer mouse, are also approximations of reality that have been distorted through a different prism, to use Black's analogy. This actuality is often underestimated in industrial practices. Scientists tend to optimize their experiments on a particular, isolated model. In doing so, many factors and characteristics that are essential for a medicine, for instance the selectivity or bioavailability, are inadequately considered.

There is no way out of this dilemma. We need simple *in vitro* models (Sect. 1.5) to be able to test large series of potentially active compounds, and we need the animal models to correlate the data and to make predictions about the therapeutic effects on humans. In the past, therapeutic progress was preferentially achieved when a new *in vivo* or *in vitro* pharmacological model was available for a new effect (see the H_2 receptor antagonists, ▶ Sect. 3.5).

Typical mistakes in the selection of models and interpretation and comparison of experimental results arise from different modes of application and the correlation of results obtained in different species of animals. It does not make sense to optimize the therapeutic range of a substance in one species, and the toxicology in another. Further, comparing effects after a fixed dose, without determining an effective dose also distorts the results because very strong and weak substances fall outside the measurement range. Measuring the effect strictly according to a schedule is also questionable because neither the latency period, that is the time before an effect is seen, nor the time of maximum biological effect are recorded. In whole-animal models, auxiliary medications are usually applied, which can also influence the experimental results. Anesthetized animals often give entirely different results than conscious animals.

1.3 The Battle Against Infectious Disease

Plagues and infectious diseases, and at the top of this list are malaria and tuberculosis, have killed more people over the ages than all of the wars in the history of humanity. Twenty-two million people died during the first wave of the 1918 influenza ("Spanish flu"). Up until the middle of the twentieth century, millions of people died every year of malaria, and unfortunately, today these numbers are shooting up again (▶ Sect. 3.2). Until the turn of the twentieth century, ipecac (*Psychotria ipecacuanha*) and cinchona (*Cinchona officinalis* L.) were the only therapeutic approaches to this disease. The impressive successes in the fight against plagues came in large part from the last 80 years of drug research. We have the sulfonamides (▶ Sect. 2.3) and their combinations with dihydrofolatereductase inhibitors (▶ Sect. 27.2), the antibiotics (▶ Sects. 2.4, ▶ 6.4, and ▶ 32.6), and the synthetic tuberculostatic medicines (▶ Sect. 6.5) to thank for this. When Selman A. Waksman (1888–1973) received the Nobel Prize for the discovery of streptomycin (▶ Sect. 6.4), a little girl congratulated him with a bouquet of flowers. She was the first patient with meningeal tuberculosis to be healed with streptomycin. Today we cannot appreciate the atmosphere in a tuberculosis hospital from our own experience, rather solely from Thomas Mann's *The Magic Mountain* (German: *Zauberberg*).

However, the infectious diseases, including tuberculosis, are on the advance again. In the past many antibiotics were too broadly used. This and the spread of resistant pathogens in hospitals have led to the situation that many cases are only treatable with very specific antibiotics. If resistance develops to these antibiotics, all of our weapons are dull. New viral infections are looming. Before the advent of the immune disease AIDS (**a**cquired **i**mmune **d**eficiency **s**yndrome) there were very few cases of pneumonia from the fungus *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*), nowadays the numbers have increased tremendously. This type of pneumonia is the primary cause of death of AIDS patients and immunosupressed patients after organ transplantation. A great effort has been made to find drugs for AIDS and its complications. On the other hand, many widespread tropical diseases, for instance malaria and Chagas disease, have been inadequately researched, and expanding resistance to the currently available medications represents an increasing worldwide problem. Because these diseases are rampant in parts of the world where people lack the economic resources to finance chemotherapy, more and more pharmaceutical companies have withdrawn from these research areas for financial reasons. The chances of recovering the development costs from this social stratum are poor. Here the global politics must establish some structure so that these people are able to benefit from the technological progress made by modern drug research. An example of this is the Bill and Melinda Gates Foundation, which is dedicated to the treatment and eradication of diseases around the entire world, but with particular emphasis on developing countries. Improved hygiene has also helped to reduce the risk of infection, for instance traumatic fever or Shigella dysentery (discussed in ▶ Chap. 21, "A Case

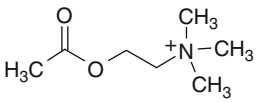
Study: Structure-Based Inhibitor Design for tRNA-Guanine Transglycosylase"). Above all else, it was the vaccines that contributed to the eradication of many infectious diseases. Now as before, hopes rest on new and combined vaccines for the prevention of AIDS, malaria, and gastrointestinal ulcers, the latter of which we now know to be caused by the bacteria *Helicobacter pylori* (▶ Sect. 3.5).

1.4 Biological Concepts in Drug Research

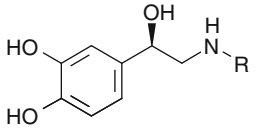
Acetylcholine **1.10** (Fig. 1.2), which was synthesized in 1869 by Adolf v. Bayer, is a **neurotransmitter**, that is, a transfer agent for nerve impulses. In 1921 Otto Loewi, a pharmacologist, proved its biological effect in an elegant experiment. Two isolated frog hearts were perfused with the same solution. The vagal nerve of one of the hearts was stimulated, leading to a slowing of the heart rate, a so-called bradycardia. Shortly afterward, the second heart also began to beat more slowly, which was a clear indication of a *humoral* (Lat. *humor*, *umor*, fluid) signal transfer. Soon after that acetylcholine was recognized as the responsible "Vagus Stoff". Acetylcholine is itself not usable as a therapeutic because it is metabolized too quickly by acetylcholine esterases (▶ Sect. 23.7).

In 1901 Thomas Bell Aldrich (1861–1938) and Jokichi Takamine isolated the first human hormone, adrenaline **1.11** (Fig. 1.2). This hormone and its *N*-desmethyl derivative, noradrenaline **1.12** (Fig. 1.2), are produced in a central location, the adrenal glands, and are released under stress conditions into the entire system with the exceptions of the CNS and the placenta, which have their own barriers against most polar compounds. These substances cause different reactions in different parts of the organism, where they react with the relevant receptors. The specificity is poor, and a plethora of pharmacodynamic effects result: pulse and blood pressure rise, and the organism is prepared for "flight" – which has been an exceedingly important function over the course of evolution.

Noradrenaline and adrenaline (also called norepinephrine and epinephrine, respectively) are also neurotransmitters (▶ Sect. 29.3), just like acetylcholine, the biogenic amines **1.13–1.15**, the amino acids **1.16–1.19**, and peptides, such as **1.20** and **1.21** (Fig. 1.2). Neurotransmitters are produced locally in the nerve cells, stored, and upon stimulation of the nerve, released. After interaction with **receptors** on the neighboring nerve cell, they are quickly metabolized or taken up again by the same neuron that released them. Depending on the name of the neurotransmitter, one speaks of the adrenergic, cholinergic, and dopaminergic (etc.) systems. The effect that adrenaline invokes is referred to as adrenergic, and an antagonist to this system is called antiadrenergic. However, this nomenclature is not always strictly adhered to. It is common to see combinations of the name of the neurotransmitter with the term **agonist** or **antagonist**, or sometimes blocker instead of antagonist, for instance a dopamine agonist, a histamine antagonist, or a β-blocker for antagonists of β-adrenergic receptors. A plethora of drugs have arisen from the structural variations of neurotransmitters.

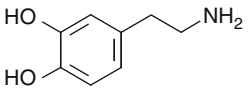


1.10 Acetylcholine

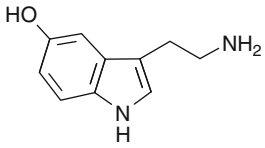


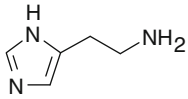
1.11 Adrenaline, R = CH_3

1.12 Noradrenaline, R = H



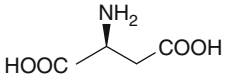
1.13 Dopamine



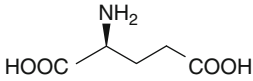


1.14 Histamine

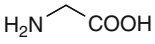
1.15 Serotonin



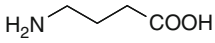
1.16 Aspartic acid



1.17 Glutamic acid



1.18 Glycine



1.19 γ-Aminobutyric acid

Tyr-Gly-Gly-Phe-Met **1.20** Met-Enkephalin

Tyr-Gly-Gly-Phe-Leu **1.21** Leu-Enkephalin

Fig. 1.2 The natural hormones und neurotransmitters acetylcholine **1.10**, adrenaline **1.11**, noradrenaline **1.12**, dopamine **1.13**, histamine **1.14**, and serotonin **1.15**, the excitatory amino acids glutamic acid **1.16** and aspartic acid **1.17**, the inhibitory amino acid glycine **1.18** and γ-aminobutyric acid (GABA) **1.19**, and several peptides, such as the enkephalins **1.20** and **1.21**, substance P and others serve as lead structures for drugs for a variety of cardiovascular and CNS diseases (see ▶ Chaps. 3, "Classical Drug Research"; ▶ 29, "Agonists and Antagonists of Membrane-Bound Receptors"; and ▶ 30, "Ligands for Channels, Pores, and Transporters").

At the end of the 1920s the steroid hormones were isolated, and their structures were determined in short order (▶ Sect. 28.5). Altogether the discoveries of the mid-twentieth century heralded the "golden age" of drug research. The systematic variation of the principles responsible for biological activity and our increasing knowledge of the mode of action has led to the synthesis of enzyme inhibitors, receptor agonists and antagonists, which together with natural product derivatives from plants makes up the largest part of our modern pharmacy.

1.5 *In Vitro* Models and Molecular Test Systems

Around 40 years ago, we began to think about testing substances in simple *in vitro* models. With these models biological testing takes place in test tubes rather than animals. There are many compelling reasons to avoid animal experiments. They increasingly provoke public criticism and are time and cost intensive. In the beginning cell culture models were preferentially employed, for example tumor cell cultures for testing cytostatic therapies, or embryonic chicken heart cells for cardio-active compounds. Later these were joined by receptor-binding studies. The first molecular test models were enzyme-inhibitor assays in which the inhibitory activity of a molecule could be evaluated on one particular target protein in the absence of interfering side effects (▶ Chap. 7, "Screening Technologies for Lead Structure Discovery"). With the progress of gene technology methods (▶ Chap. 12, "Gene Technology in Drug Research"), not only is the preparation of the enzyme simplified, but also receptor-binding studies can be carried out on standardized materials. Today it is possible to achieve an exact evaluation of the entire activity spectrum of any substance on any enzyme, receptors of all types and subtypes, ion channels, and transporters. In the meantime, in industrial drug discovery this procedure has become routine. Before biological screening begins, the following questions have to be answered: what therapeutic goal should be achieved and is this goal achievable? Therapeutic concepts are established based on the pathophysiology and the causes of its alteration. Regulatory interventions with drugs should re-establish the normal physiological conditions as closely as possible. In doing so, a distinct problem occurs. Nature works on two orthogonal principles: the specificity of the mode of action and an accentuated spa separation of effects; the compartmentalization. Adrenaline that is produced in the adrenal glands works on the entire body except for the brain. If it is released there, it works only in the synapse between two nerve cells. As far as the specificity goes, the chemists can beat nature most of the time, but they fail when it comes to spatial separation by a wide margin.

Through the progress made in gene technology (▶ Chap. 12, "Gene Technology in Drug Research") we can investigate active substances much more exactly than before; but by using isolated enzymes and binding studies we are a long way away from the reality of animal models, and even further away from humans. In analogy to the difference between an animal experiment and an isolated-organ experiment, a well-established correlation between the results obtained in cell culture and an *in vitro* test and the desired therapeutic effect is a prerequisite to successfully using the *in vitro* model. The quantitative relationship between different biological effects (▶ Chap. 18, "Quantitative Structure–Activity Relationships") establishes the connection between animal models and humans.

One modern researcher stands out in the area of CNS-active compounds especially, but also in areas of cardiovascular-active compounds and antihistamines. Paul Janssen (1926–2003) was the director of the company Janssen Pharmaceuticals in Beerse, Belgium. In the years after World War II, his company discovered over 70 new active substances, carried out the preclinical and clinical

development, and established them as therapies. In doing so, his company established itself as the most successful in pharmaceutical history. His recipe for success was not a secret. Paul Janssen was a master of structural variation, a Beethoven of drug discovery. The systematic combination of pharmacologically interesting structural fragments, and the elegant evaluation of receptor-binding studies, *in vitro* models, and animal experiments were the foundation of his successes.

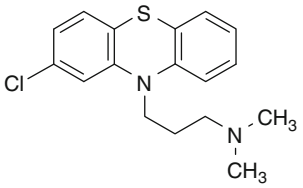
1.6 The Successful Therapy of Psychiatric Illness

Up until the middle of the last century psychiatric hospitals were purely custodial care facilities; they were almost indistinguishable from prisons in terms of the restriction of personal freedom of the individual. The discovery of neuroleptics, antidepressants, anticonvulsives, and sedatives revolutionized psychiatry. Typical examples of this class of drugs are depicted in Fig. 1.3. With the repertoire of drugs that are available today, schizophrenia, chronic anxiety, and depression preponderate open-ward psychiatry. Many patients can be treated in an ambulatory setting. In 1933 Manfred Sakel (1901–1957), who worked at the psychiatric university hospital in Vienna, noticed that when schizophrenics were given insulin to stimulate their appetites, they became calmer. Encouraged by this result, he increased the dose to the point of hypoglycemic coma, which is a form of deep unconsciousness induced by too little blood sugar. Insulin shock, pentetrazole, and electroshock became the standard treatment over the next two decades for psychotic illness, an impressive and frightening proof of the absence of therapeutic alternatives.

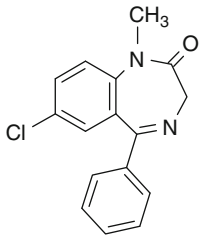
This situation changed in the 1950s with the discovery of reserpine **1.9** (Fig. 1.1, Sect. 1.1), a herbal natural product. This substance exerts its effect by emptying the reserves of the neurotransmitters noradrenaline, serotonin, and dopamine in nerve cells. Reserpine was the first substance to display a prominent neuroleptic effect, that is, it is sedating and calming, and it was the first compound to be used for psychotic illness, for which the biological effect could be explained by a mode of action. In addition, reserpine was used as an antihypertensive medication. Because of its very broad and unspecific effect it is rarely used today for psychiatric illness or arterial hypertension.

The role of dopamine **1.13** (Fig. 1.2, Sect. 1.4) in the etiology of schizophrenia became clear with the discovery of chlorpromazine **1.22** (Fig 1.3, ▶ Sects. 8.5 and ▶ 19.10), a substance that showed a favorable clinical effect. In contrast to the unspecific reserpine, chlorpromazine is a pure dopamine antagonist. The application of chlorpromazine and analogous tricyclic neuroleptics caused symptoms that occur in Parkinson's disease. This was the first indication that an endogenous dopamine deficiency is the cause of that disease.

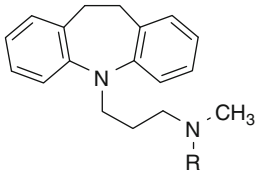
Chlordiazepoxide (Librium®, ▶ Sect. 2.7), the first tranquilizer of the group of benzodiazepines, was found by accident. Only one year after its introduction and for many years after that, the chemically closely related medication diazepam **1.23** (Valium®, Fig. 1.3) was the worldwide best-selling drug. The Rolling Stones



1.22 Chlorpromazine

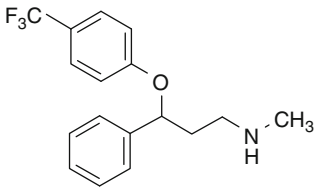


1.23 Diazepam



1.24 Imipramine, R = CH_3

1.25 Desipramine, R = H



1.26 Fluoxetine

Fig. 1.3 A revolution in the therapy of psychiatric illness was brought about by the discovery of potent neuroleptics such as chlorpromazine **1.22**, tranquilizers such as diazepam **1.23**, and antidepressants such as imipramine **1.24**. For the first time, these compounds allowed a purposeful treatment of schizophrenia, chronic anxiety, and depression. Examples of newer antidepressants with specific modes of action on transport systems (▶ Sect. 4.6) for noradrenaline and serotonin are desipramine **1.25** and fluoxetine **1.26**, respectively.

commemorated it in their multifaceted song "*Mother's Little Helper*." Many companies started grandly endowed synthetic programs, and chemists and pharmacologists applied their entire arsenal of methods. Their success justified their efforts. Substances with different modes of action resulted: further tranquilizers, sedatives, hypnotics, and even antagonists. Even today the benzodiazepines (▶ Sect. 30.5) belong to the most popular and widespread medications.

The first antidepressant, iproniazid (▶ Sects. 6.7 and ▶ 27.8) was also an accidental discovery. It works by inhibiting the metabolism of the biogenic amines dopamine, serotonin, noradrenaline, and adrenaline by inhibiting the enzyme monoamino oxidase (▶ Sect. 27.8). In addition to other severe side effects, the first unspecific representatives caused hypertensive crises, and when taken with certain foods a few fatalities occurred. Tyramine, a substance found in cheese, wine, and beer (therefore the term "*cheese effect*") was not duly metabolized. This caused a life-threatening rise in noradrenaline, a hormone that raises blood pressure.

The antidepressant imipramine **1.24** (Fig. 1.3, ▶ Sect. 8.5) resulted from the synthesis of analogues of chlorpromazine. Interestingly and despite its close structural relationship, it is not a neuroleptic but rather it works in the opposite way. It blocks the transporter for noradrenaline and serotonin, and this prevents the

reuptake of these neurotransmitters from the synaptic gap. Desipramine **1.25** and fluoxetine **1.26** are even more selective in that they inhibit only the noradrenaline or the serotonin transporter of nerve cells.

1.7 Modeling and Computer-Aided Design

An extremely capable tool is available for modeling the properties and reactions of molecules, and particularly their intermolecular interactions: the computer. In addition to processing complex numerical problems, it is the translation of the results into color graphics that exceedingly accommodates the human ability to grasp pictures faster and more easily than text or columns of numbers. That is not a surprise. Our brains process text sequentially, but pictures are comprehended in parallel. X-ray crystallography and multidimensional NMR spectroscopic techniques (▶ Chap. 13, "Experimental Methods of Structure Determination") contribute to our understanding of molecules as much as quantum mechanical and force field calculations (▶ Chap. 15, "Molecular Modeling").

Is molecular modeling an invention of modern times? Yes and No. Friedrich August Kekulé (1829–1896) supposedly derived his cyclic structure for benzene from a vision of a snake that circled upon itself and bit its own tail (incidentally, the snake *Uroborus* is an age-old alchemist symbol). This now-famous dream may be, however, traced to a memory of the book *Constitutionsformeln der Organischen Chemie* by the Austrian schoolteacher Joseph Loschmidt (1821–1895; Fig. 1.4). Loschmidt admittedly would take pleasure in contemplating pictures of models that are quite similar to his own. More and more today we place the three-dimensional structure, the steric dimensions, and the electronic qualities of molecules in the foreground. Advances in theoretical organic chemistry and X-ray crystallography have made this possible. The first structure-based design was carried out on hemoglobin, the red blood pigment, in the research group of Peter Goodford. Hemoglobin's affinity for oxygen is modulated by so-called allosteric effector molecules that bind in the core of the tetrameric protein. From the three-dimensional structure he deduced simple dialdehydes and their bisulfite addition products. These substances bind to hemoglobin in the predicted way and shift the oxygen-binding curve in the expected direction.

The first drug developed by using a structure-based approach is the antihypertensive agent captopril, an angiotensin-converting enzyme (ACE) inhibitor (▶ Sect. 25.4). Although the lead structure was a snake venom, the decisive breakthrough was made after modeling the binding site. For this, the binding site of carboxypeptidase, another zinc protease, was used because its three-dimensional structure was known at the time.

The road to a new drug is difficult and tedious. A nested overview of the interplay between the different methods and disciplines from a modern point of view is illustrated in the scheme in Fig. 1.5. In the last few years molecular modeling (▶ Chap. 15, "Molecular Modeling") and particularly the modeling of ligand–receptor interactions (▶ Chap. 4, "Protein–Ligand Interactions as the Basis

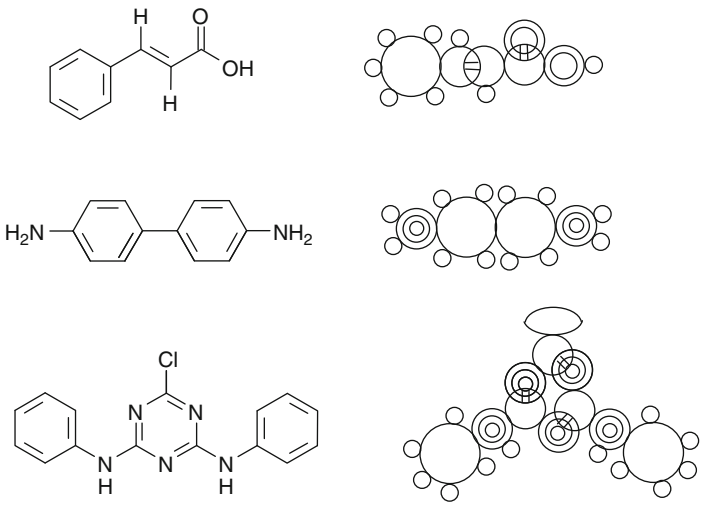


Fig. 1.4 Loschmidt's book *Constitutionsformeln der Organischen Chemie* (1861) contains structures that anticipate both the formulation of the benzene ring as well as the modern modeling structure. Kekulé must have known about this book because he disparaged it in a letter to Emil Erlenmeyer in January 1862 in that he referred to it as "*Confusionsformeln*." Loschmidt did not become famous for his book, but rather because he carried out an experiment in 1865 that determined the number of molecules in a mole to be 6.02×10^{23}, a constant that was later to be named after him.

for Drug Action"), have gained importance. Although modeling is employed predominantly for the targeted structure modification of lead compounds, it is also suitable for the structure-based and computer-aided design of drugs (▶ Chap. 20, "Protein Modeling and Structure-Based Drug Design") and lead structure discovery (▶ Sect. 7.6). Examples of these approaches are given in ▶ Chaps. 23, "Inhibitors of Hydrolases with an Acyl–Enzyme Intermediate"; ▶ 24, "Aspartic Protease Inhibitors"; ▶ 25, "Inhibitors of Hydrolyzing Metalloenzymes"; ▶ 26, "Transferase Inhibitors"; ▶ 27, "Oxidoreductase Inhibitors"; ▶ 28, "Agonists and Antagonists of Nuclear Receptors"; ▶ 29, "Agonists and Antagonists of Membrane-Bound Receptors"; ▶ 30, "Ligands for Channels, Pores, and Transporters"; ▶ 31, "Ligands for Surface Receptors"; ▶ 32, "Biologicals: Peptides, Proteins, Nucleotides, and Macrolides as Drugs".

In addition to modeling and computer-aided design, structure–activity relationship analysis (▶ Chap. 18, "Quantitative Structure–Activity Relationships") has contributed to the understanding of the correlation between the chemical structure of compounds and their biological effects. By using these methods, the influence of lipophilic, electronic, and steric factors on the variation of the biological activity, transport, and distribution of drugs in biological systems could be systematized for the first time on statistically significant foundations.

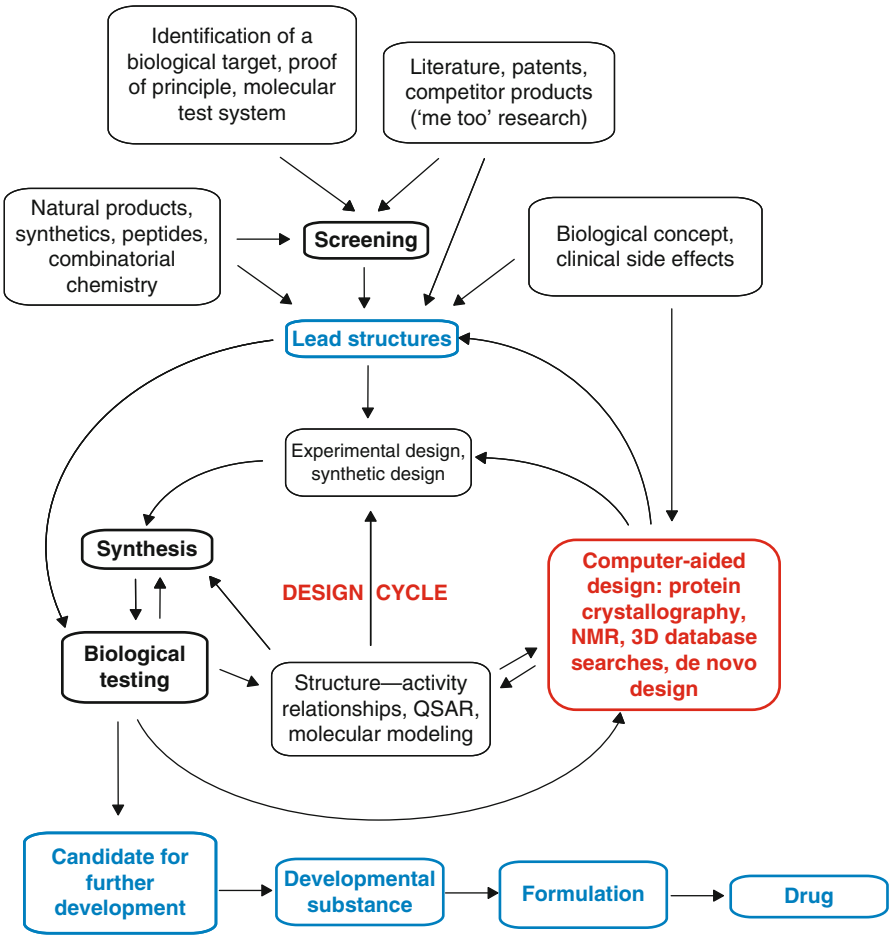


Fig. 1.5 The way to a drug is long. The upper part of the figure shows routes to lead structures. The middle part describes the design cycle, which in practically all cases must be repeatedly reiterated. Each of these phases is described in detail in the following chapters. The result of iterative optimization is candidates for further development such as preclinical and toxicological studies. It is from these studies that the actual candidates are selected. Formulation, clinical trials, and registration then lead to a new medicine. The last phases are not presented in this book.

1.8 The Results of Drug Research and the Drug Market

The development of different methods in drug research has already been described in the last section. Table 1.1 gives a short historical overview of the most prominent results.

Table 1.1 Important milestones in drug research

Year	Substance	Indication/Mode of action
1806	Morphine	Hypnotic
1875	Salicylic acid	Anti-inflammatory
1884	Cocaine	Stimulant, local anesthetic
1888	Phenacetin	Analgetic and antipyretic
1889	Acetylsalicylic acid	Analgetic and antipyretic
1903	Barbiturate	Sedative
1909	Arsphenamin	Anti-syphilitic
1921	Procaine	Local anesthetic
1922	Insulin	Antidiabetic
1928	Estrone	Female sex hormone
1928	Penicillin	Antibiotic
1935	Sulfamidochrysoidine	Bacteriostatic
1944	Streptomycin	Antibiotic
1945	Chloroquine	Antimalarial
1952	Chlorpromazine	Neuroleptic
1956	Tolbutamide	Oral antidiabetic
1960	Chlordiazepoxide	Tranquilizer
1962	Verapamil	Calcium channel blocker
1963	Propranolol	Antihypertensive (β-blocker)
1964	Furosemide	Diuretic
1971	L-DOPA	Parkinson's disease
1973	Tamoxifen	Breast cancer (estrogen receptor antagonist)
1975	Nifedipine	Calcium channel blocker
1976	Cimetidine	Gastrointestinal ulcer (H_2 blocker)
1981	Captopril	Antihypertensive (ACE inhibitor)
1981	Ranitidine	Gastrointestinal ulcer (H_2 blocker)
1983	Ciclosporin A	Immunosuppressant
1984	Enalapril	Antihypertensive (ACE inhibitor)
1985	Mefloquine	Antimalarial
1986	Fluoxetine	Antidepressant (5-HT-transport inhibitor)
1987	Artemisinin	Antimalarial
1987	Lovastatin	Cholesterol biosynthesis inhibitor
1988	Omeprazole	Gastrointestinal ulcer (H^+/K^+-ATPase inhibitor)
1990	Ondansetron	Antiemetic (5-HT_3 blocker)
1991	Sumatriptan	Migraine (5-$HT_{1B,D}$ agonist)
1993	Risperidone	Antipsychotic (D_2/5-HT_2-blocker)
1994	Famciclovir	Antiviral/herpes (DNA polymerase inhibitor)
1995	Losartan	Arterial hypertension (ATII antagonist)
1995	Dorzolamide	Glaucoma (carboanhydrase inhibitor)
1996	Saquinavir	HIV protease inhibitor
1996	Ritonavir	HIV protease inhibitor
1996	Indinavir	HIV Protease inhibitor
1996	Nevirapine	HIV reverse transcriptase inhibitor

(*continued*)

Table 1.1 (continued)

Year	Substance	Indication/Mode of action
1997	Sibutramine	Obesity (*uptake* inhibitor)
1997	Orlistat	Obesity (lipase inhibitor)
1997	Tolcapon	Parkinson's disease (COMT inhibitor)
1998	Sildenafil	Erectile dysfunction (PDE5 inhibitor)
1998	Montelukast	Broncholytic (leukotriene receptor antagonist)
1999	Infliximab	Antirheumatic (TNFα antagonist)
2000	Celecoxib	Analgesic (COX-2 inhibitor)
2000	Verteporfin	Macular degeneration (photodynamic therapy)
2001	Imatinib	Acute myeloid leukemia (kinase inhibitor)
2002	Boscutan	Arterial hypertension (endothelin-1 receptor antagonist)
2002	Aprepitant	Antiemetic (neurokinin receptor antagonist)
2003	Enfuvirtid	HIV fusion inhibitor (oligopeptide)
2004	Ximelagatran	Coagulation inhibitor (thrombin inhibitor)
2004	Bortezomib	Multiple myeloma (proteasome inhibitor)
2005	Bevacizumab	Cytostatic (angiogenese inhibitor)
2006	Natalizumab	Multiple sclerosis (monoclonal antibody; integrin inhibitor)
2006	Aliskiren	Antihypertensive (renin inhibitor)
2007	Maraviroc	HIV fusion inhibitor (CCR5 antagonist)
2007	Sitagliptin	Type-II diabetes (DPPVI inhibitor)
2008	Raltegravir	HIV integrase inhibitor
2009	Rivaroxaban	Oral Anticoagulant (FXa inhibitor)
2010	Mifamurtide	Drug against Osteosarcoma (bone cancer)
2011	Fingolimod	Immunomodulating drug (multiple sclerosis treatment)

The assessment of the **efficacy and safety** of a drug has reached an extraordinarily high standard today. To some extent this development is a bystander in our goal of finding new medicines, but it is also a hindrance. Acetylsalicylic acid (Aspirin®) is without any doubt a valuable drug. Today this compound would have great difficulty to pass clinical trials. Acetylsalicylic acid is an irreversible enzyme inhibitor, it has relatively weak efficacy, it causes gastric bleeding in high doses, and it has a very short biological half-life. Each of these problems would be a profound argument against its continued development today. It probably would have already failed in screening. In a risk–benefit analysis however, it is better than most of the alternatives. Where is the problem? It probably lies in the analytical–deterministic mindset that dominates science, and therefore also drug research. It is often overlooked that such an approach deals with a system as complicated and complex as a human, to whom we apply a drug therapy, cannot always be adequately addressed by all means.

Despite public healthcare systems that constitute a barrier between the supplier and the consumer, the drug market, with worldwide sales of more than US$880 billion, has strong competition. Two forces affect this market: the state of science