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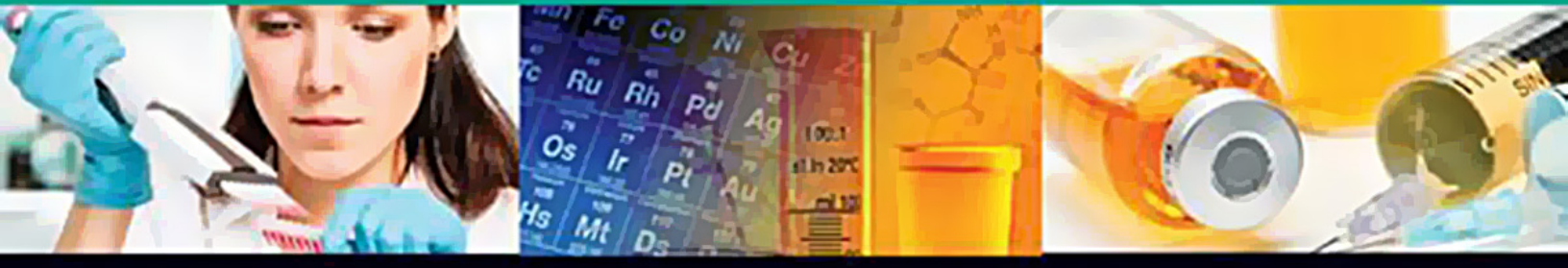
THE PRACTICE OF MEDICINAL CHEMISTRY



FOURTH EDITION

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Foreword

The world's economy depends to a significant extent on our ability to deliver affordable and sustainable healthcare. As such, this new edition of *The Practice of Medicinal Chemistry* plays an important role in educating the next generation of scientists in the area as it goes beyond the simple delivery of new healing drugs to combat disease and illness. It enriches our knowledge and the very understanding of the lives of everyone on the planet. It is truly amazing how the different scientific disciplines can combine in this way to design and make such a wonderful array of functional molecules to serve some of our current needs. Nevertheless, the future presents enormous healthcare challenges that can only be met by appropriate investment and further fundamental scientific discovery. This new edition of *The Practice of Medicinal Chemistry* provides a unique scholarly compilation of the tools, techniques, and methods necessary to begin this journey of discovery, whether in industry or academia.

The book's practical overview differentiates this text from others. It provides a menu of topics that can be consulted individually, while also providing a holistic view covering the history of drug discovery through to the issues of today involving the consumption and production of pharmaceuticals. The process of drug discovery has become a highly complex operation requiring the medicinal chemist to acquire wide-ranging skills from areas such as biology, technology, modelling, delivery, physiochemistry, and synthesis. To pull this together in a single book is a heroic task that these authors have done magnificently.

As our science moves forward toward more biologicals, smaller volume products that are focused on patients, and more sustainable and flexible manufacturing in an ever more regulated environment, we will require new generations of creative individuals. They will need to be ever more innovative, using all the tools our modern society can offer. In particular, big-data mining, tissue sampling and genomic mapping, the "Internet of Things," and wearable health monitors will all be likely components in the armory of the next breed of medicinal chemist.

I regard this expanded textbook as essential reading for all those new to the field. It also provides a quality check for current practitioners in this rapidly evolving environment. The book also does not shy away from providing a future vision of the trends of the discipline. It is written by experts who elegantly convey their passion, experience, and insight for the benefit of all readers.

I therefore welcome this updated and expanded version of *The Practice of Medicinal Chemistry* and believe it provides—as did past editions—the bedrock of our discipline.

Steven V. Ley
Cambridge
http://www.leygroup.ch.cam.ac.uk/

Preface to the Fourth Edition

Bringing a new drug to patients is both a privilege and a challenge fraught with success and failure. A privilege because there can be no greater calling than to alleviate suffering to enable a healthier life.

> Without health, life is not life; it is only a state of languor and suffering—an image of death. ***Buddha***

A challenge fraught with success and failure as no drug makes it from idea to patients without experiencing success and failure.

> Success is not final; failure is not fatal. It is the courage to continue that counts. ***Winston Churchill***

Prof. Camille Wermuth recognized the need to capture in a single volume the essence of the disciplines needed by medicinal chemists, so as to enable those just entering the field or the seasoned professional to keep pace with the ever-changing nature of drug discovery and development. His vision became *The Practice of Medicinal Chemistry*, providing the medicinal chemistry community with access to experts from across the industry and academia who would share their knowledge to educate the community, thereby preparing the community to recognize and seize opportunities as they emerged.

> Fortune favors the prepared mind. ***Louis Pasteur***

The fourth edition has built off the previous editions. It is updated to reflect developments over the last seven years, including five new chapters on topics such as the evaluation of the biological activity of compounds and systems biology. More than seventy experts from ten countries have shared their insights and perspectives on the practice of medicinal chemistry.

The editorial work for the fourth edition has been shared by Camille Wermuth, Pierre Raboisson, Didier Rognan, and Dave Aldous. Odile Blin helped organize and shape how we initiated the fourth edition; we are indebted to her tireless professionalism. The editors wish to express their thanks to Molly M. McLaughlin and the Elsevier Academic Press, who have worked with us to keep this project moving forward.

I believe my final quote—from Jason Calacanis—captures the challenges medicinal chemists face every day.

> You have to have a big vision and take very small steps to get there. You have to be humble as you execute but visionary and gigantic in terms of your aspiration. In the Internet industry, it's not about grand innovation; it's about a lot of little innovations—every day, every week, every month—making something a little bit better. ***Jason Calacanis***

Medicinal chemistry is a highly collaborative and iterative process that has many paths. Being open, collaborative, and humble are qualities that will help you successfully navigate these paths from idea to patient.

Preface to the Third Edition

Like the preceding editions of this book, this third edition treats of the essential elements of medicinal chemistry in a unique volume. It provides a practical overview of the daily problems facing medicinal chemists, from the conception of new molecules through to the production of new drugs and their legal/economic implications. This edition has been updated, expanded and refocused to reflect developments in the past 5 years, including 11 new chapters on topics such as hit identification methodologies and cheminformatics. More than 50 experts in the field from eight different countries, who have benefited from years of practical experience, give personal accounts of both traditional methodologies and the newest discovery and development technologies, providing readers with an insight into medicinal chemistry.

A major change in comparison to the previous editions was the decision to alleviate my editorial burden in sharing it with seven section editors, each being responsible for one of the eight sections of the book. I highly appreciated their positive and efficacious collaboration and express them my warmest thanks (in the alphabetical order) to Michael Bowker, Hugo Kubinyi, John Proudfood, Bryan Reuben, Richard Silverman, David Triggle and Han van de Waterbeemd.

Another change was the decision taken by Elsevier/Academic Press to publish the book in full colors thus rendering it more pleasant and user-friendly. I take this occasion to thank Keri Witman, Pat Gonzales, Kirsten Funk and Renske van Dijk for having successively ensured the editorial development of the book. Taking into account that we had to work with a cohort of about 50 authors, each of them having his personality, his original approach and his main busy professional live, this was not an easy task. I am deeply indebted to my assistant Odile Blin for the way she had mastered, efficiently and with friendliness, all the secretarial work and particularly the contacts with the different authors and with the Elsevier development editors. As for the earlier editions, I also want to express my gratitude to my wife Renée and my daughters Delphine, Joëlle and Séverine for all their encouragements and for sacrificing many hours of family life in order to leave me enough free time to edit this new version of the "Medicinal Chemist's Bible."

My final thoughts go to the future readers of the book, and especially to the newcomers in Medicinal Chemistry having the curiosity to read the preface. I cannot resist giving them some advice for doing good science.

First of all, be open-minded and original. As Schopenhauer noted, the task of the creative mind is "not so much to see what no one has seen yet; but to think what nobody has thought yet, about what everyone sees." A wonderful illustration is found in Peter Hesse's cartoon below.

Second, always keep in mind that the object of Medicinal Chemistry is to synthetize new drugs useful for suffering patients. Like many scientists, medicinal chemists, have to navigate between two tempting reefs. On one side they should avoid doing "NAAR": non-applicable applied research, on the other side they may be attracted by "NFBR": non-fundamental basic search."

Third, convinced as they may be that the neighbors grass is always greener, they may be attracted to start their research in using as a hit a recently published competitor's product. In fact, the published compound may exhibit only a weak activity, therefore be very careful when starting a new program and never forget that the worst thing a medicinal chemist can do is to prepare a me-too of an inactive compound!

Camille G. Wermuth

Preface to the Second Edition

Like the first edition of *The Practice of Medicinal Chemistry* (nicknamed 'The Bible' by medicinal chemists) the second edition is intended primarily for organic chemists beginning a career in drug research. Furthermore, it is a valuable reference source for academic, as well as industrial, medicinal chemists. The general philosophy of the book is to complete the biological progress − Intellectualization at the level of function using the chemical progress Intellectualization at the level of structure (Professor Samuel J. Danishevsky, *Studies in the chemistry and biology of the epothilones and eleutherobins*, Conference given at the XXXIVémes Rencontres Internationales de Chimie Th6rapeutique, Facult6 de Pharmacie, Nantes, 8−10 July, 1998).

The recent results from genomic research have allowed for the identification of a great number of new targets, corresponding to hitherto unknown receptors or to new subtypes of already existing receptors. The massive use of combinatorial chemistry, associated with high throughput screening technologies, has identified thousands of hits for these targets. The present challenge is to develop these hits into usable and useful drug candidates. This book is, therefore, particularly timely as it covers abundantly the subject of drug optimization.

The new edition of the book has been updated, expanded and refocused to reflect developments over the nine years since the first edition was published. Experts in the field have provided personal accounts of both traditional methodologies, and the newest discovery and development technologies, giving us an insight into diverse aspects of medicinal chemistry, usually only gained from years of practical experience.

Like the previous edition, this edition includes a concise introduction covering the definition and history of medicinal chemistry, the measurement of biological activities and the three main phases of drug activity. This is followed by detailed discussions on the discovery of new lead compounds including automated, high throughput screening techniques, combinatorial chemistry and the use of the internet, all of which serve to reduce preclinical development times and, thus, the cost of drugs. Further chapters discuss the optimization of lead compounds in terms of potency, selectivity, and safety; the contribution of genomics; molecular biology and X-ray crystallization to drug discovery and development, including the design of peptidomimetic drugs; and the development of drug-delivery systems, including organ targeting and the preparation of pharmaceutically acceptable salts. The final section covers legal and economic aspects of drug discovery and production, including drug sources, good manufacturing practices, drug nomenclature, patent protection, social-economic implications and the future of the pharmaceutical industry.

I am deeply indebted to all co-authors for their cooperation, for the time they spent writing their respective contributions and for their patience during the editing process. I am very grateful to Didier Rognan, Paola Ciapetti, Bruno Giethlen, Annie Marcincal, Marie-Louise Jung, Jean-Marie Contreras and Patrick Bazzini for their helpful comments.

My thanks go also to the editorial staff of *Academic Press* in London, particularly to Margaret Macdonald and Jacqueline Read. Last but not least, I want to express my gratitude to my wife Renée for all her encouragements and for her comprehensiveness.

Camille G. Wermuth

Preface to the First Edition

The role of chemistry in the manufacture of new drugs, and also of cosmetics and agrochemicals, is essential. It is doubtful, however, whether chemists have been properly trained to design and synthesize new drugs or other bioactive compounds. The majority of medicinal chemists working in the pharmaceutical industry are organic synthetic chemists with little or no background in medicinal chemistry who have to acquire the specific aspects of medicinal chemistry during their early years in the pharmaceutical industry. This book is precisely aimed to be their 'bedside book' at the beginning of their career.

After a concise introduction covering background subject matter, such as the definition and history of medicinal chemistry, the measurement of biological activities and the three main phases of drug activity, the second part of the book discusses the most appropriate approach to *finding a new lead compound or an original working hypothesis*. This most uncertain stage in the development of a new drug is nowadays characterized by high-throughput screening methods, synthesis of combinatorial libraries, data base mining and a return to natural product screening. The core of the book (Parts III to V) considers the *optimization of the lead in terms of potency, selectivity, and safety*. In 'Primary Exploration of Structure-Activity Relationships', the most common operational stratagems are discussed, allowing identification of the portions of the molecule that are important for potency. 'Substituents and functions' deals with the rapid and systematic optimization of the lead compound. 'Spatial Organization, Receptor Mapping and Molecular Modelling' considers the three-dimensional aspects of drug-receptor interactions, giving particular emphasis to the design of peptidomimetic drugs and to the control of the agonist- antagonist transition. Parts VI and VII concentrate on the definition of satisfactory drug-delivery conditions, i.e. means to ensure that the molecule reaches its target organ. Pharmacokinetic properties are improved through adequate chemical modifications, notably prodrug design, obtaining suitable water solubility (of utmost importance in medical practice) and improving organoleptic properties (and thus rendering the drug administration acceptable to the patient). Part VIII, 'Development of New Drugs: Legal and Economic Aspects', constitutes an important area in which chemists are almost wholly self taught following their entry into industry.

This book fills a gap in the available bibliography of medicinal chemistry texts. There is not, to the author-editor's knowledge, any other current work in print which deals with the practical aspects of medicinal chemistry, from conception of molecules to their marketing. In this single volume, all the disparate bits of information which medicinal chemists gather over a career, and generally share by word-of-mouth with their colleagues, but which have never been organized and presented in coherent form in print, are brought together. Traditional approaches are not neglected and are illustrated by modern examples and, conversely, the most recent discovery and development technologies are presented and discussed by specialists. Therefore, *The Practice of Medicinal Chemistry* is exactly the type of book to be recommended as a text or as first reading to a synthetic chemist beginning a career in medicinal chemistry. And, even if primarily aimed at organic chemists entering into pharmaceutical research, all medicinal chemists will derive a great deal from reading the book.

The involvement of a large number of authors presents the risk of a certain lack of cohesiveness and of some overlaps, especially as each chapter is written as an autonomic piece of information. Such a situation was anticipated and accepted, especially for a first edition. It can be defended because each contributor is an expert in his/her field and many of them are 'heavyweights' in medicinal chemistry. In editing the book I have tried to ensure a balanced content and a more-or-less consistent style. However, the temptation to influence the personal views of the authors has been resisted. On the contrary, my objective was to combine a plurality of opinions, and to present and discuss a given topic from different angles. Such as it is, this first edition can still be improved and I am grateful in advance to all colleagues for comments and suggestions for future editions.

Special care has been taken to give complete references and, in general, each compound described has been identified by at least one reference. *For compounds for which no specific literature indication is given, the reader is referred to the Merck Index*.

The cover picture of the book is a reproduction of a copperplate engraving designed for me by the late Charles Gutknecht, who was my secondary school chemistry teacher in Mulhouse. It represents an extract of Brueghel's engraving *The alchemist ruining his family in pursuing his chimera*, surmounted by the aquarius symbol. Represented on the left-hand side is my lucky charm caster oil plant (*Ricinus communis L., Euphorbiaceae*), which was the starting point of the pyridazine chemistry in my laboratory. The historical cascade of events was as follows: cracking of caster oil produces n-heptanal and aldolization of n-heptanal – and, more generally, of any enolisable aldehyde or ketone – with pyruvic acid leads to a-hydroxy-γ-ketonic acids. Finally, the condensation of these keto acids with hydrazine yields pyrodazones. Thus, all our present research on pyridazine derivatives originates from my schoolboy chemistry, when I prepared in my home in Mulhouse n-heptanal and undecylenic acid by cracking caster oil!

Preparing this book was a collective adventure and I am most grateful to all authors for their cooperation and for the time and the effort they spent to write their respective contributions. I appreciate also their patience, especially as the editing process took much more time than initially expected.

I am very grateful to Brad Anderson (University of Utah, Salt Lake city), Jean-Jacques André (Marion Merrell Dow, Strasbourg), Richard Baker (Eli Lilly, Erl Wood, UK), Thomas C. Jones (Sandoz, Basle), Isabelle Morin (Servier, Paris), Bryan Reuben (London South Bank University) and John Topliss (University of Michigan, Ann Arbor) for their invaluable assistance, comments and contributions.

My thanks go also to the editorial staff of Academic Press in London, Particularly to Susan Lord, Nicola Linton and Fran Kingston, to the two copy editors Len Cegielka and Peter Cross, and finally, to the two secretaries of our laboratory, Franqois Herth and Marylse Wernert.

Last but not least, I want to thank my wife Renée for all her encouragement and for sacrificing evenings an Saturday family life over the past year and a half, to allow me to sit before my computer for about 2500 hours!

Camille G. Wermuth

SECTION ONE

General Aspects of Medicinal Chemistry

CHAPTER

1

Medicinal Chemistry: Definitions and Objectives, Drug Activity Phases, Drug Classification Systems

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OUTLINE

Medicinal chemistry remains a challenging science which provides profound satisfaction to its practitioners. It intrigues those of us who like to solve problems posed by nature. It verges increasingly on biochemistry and on all the physical, genetic and chemical riddles in animal physiology which bear on medicine. Medicinal chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases and thereby to contribute to a healthier and happier life. **A Burger** [1]

I. DEFINITIONS AND OBJECTIVES

A. Medicinal Chemistry and Related Disciplines and Terms

A definition of medicinal chemistry was given by a IUPAC specialized commission: "*Medicinal chemistry* concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interests of the medicinal chemist are not restricted to drugs but include bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification, and synthesis of the metabolic products of these drugs and related compounds" [2].

Drugs—natural and synthetic alike—are chemicals used for medicinal purposes. They interact with complex chemical systems of humans or animals. Medicinal chemistry is concerned with this interaction, focusing on the organic and biochemical reactions of drug substances with their targets. This is one aspect of drug chemistry.

Other important aspects are the synthesis and the analysis of drug substances. The two latter aspects together are sometimes called *pharmaceutical chemistry*, but the synthesis of drugs is considered by some people—mainly chemists—to be part of medicinal chemistry, denoting analytical aspects as pharmaceutical chemistry. In German faculties of pharmacy, the literal translations of pharmaceutical and medicinal chemistry—Pharmazeutische and Medizinische Chemie—are used synonymously.

The general study of drugs is called *pharmacy* or *pharmacology*. A common narrower definition of pharmacology concentrates on the fate and effects of a drug in the body. *Clinical chemistry*, a different subject, is concerned with the determination of physiological and pathophysiological parameters in body fluids, such as enzyme activities and metabolites in blood and urine. The term *biopharmacy* has been reserved for the investigation and control of absorption, distribution, metabolism, excretion, and toxicology (ADMET) of drug substances.

Some further terms are more or less synonymous with medicinal chemistry: *(molecular) pharmacochemistry, drug design, selective toxicity*. The French equivalent to medicinal chemistry is chimie thérapeutique, and the German terms are Medizinische/Pharmazeutische Chemie and Arzneimittelforschung.

In academia, medicinal chemistry is a major subject in most pharmacy faculties—both for undergraduates and in research—and in many chemistry faculties. In the pharmaceutical industry, medicinal chemistry is at the heart of the search for new medicines.

The main activities of medicinal chemists are evident in the analysis of their most important scientific journals (e.g., *Journal of Medicinal Chemistry, European Journal of Medicinal Chemistry, Bioorganic and Medicinal Chemistry, ChemMedChem, Archiv der Pharmazie, Arzneimittelforschung, Chemical and Pharmaceutical Bulletin*).

The *objectives of medicinal chemistry* are as easily formulated as they are difficult to achieve: find, develop, and improve drug substances that cure or alleviate diseases (see below, Section I.C.) and understand the causative and accompanying chemical processes (see below, Section III.A).

Medicinal chemistry is an interdisciplinary science covering a particularly wide domain situated at the interface of organic chemistry with life sciences such as biochemistry, pharmacology, molecular biology, genetics, immunology, pharmacokinetics, and toxicology on one side, and chemistry-based disciplines such as physical chemistry, crystallography, spectroscopy, and computer-based techniques of simulation, data analysis, and data visualization on the other side.

B. Drugs and Drug Substances

Drugs are composed of *drug substances* (syn. *active pharmaceutical ingredients, APIs*) and *excipients* (syn. *ancillary substances*). The combination of both is the work of pharmaceutical technology (syn. *galenics*) and denoted a *formulation*.

In 2014, the World Drug Index contained over 80,000 marketed and development drug substances [3]. The United States *Orange Book* listed approx. 3,500 products in 2014, and the United States Pharmacopeia contains monographs of approx. 1,400 small-molecules Active Pharmaceutical Ingredients (APIs) and 160 biologic drug substances [4]. In 2013 in Germany, the "Rote Liste" contained approximately 6,000 drugs in 7,500 formulations representing approximately 2,000 APIs [5]. The WHO Essential Medicines List held approximately 350 drug substances in 2013 that WHO claims sufficient for the treatment of approx. 90 percent of all diseases where drugs are useful [6].

What makes a chemical "drug-like?" Because of the versatility of their molecular targets (see below), there can be no universal characteristic of drug substances. However, since the general structure of the target organisms is identical, generalizations as to drug substance structure are possible for biopharmacy [7,8]. For a chemical to be readily absorbed by the gut and distributed in the body, its size, hydrophilicity/lipophilicity ratio, stability toward acid media and hydrolytical enzymes, etc. have to meet defined physicochemical criteria. A careful analysis of reasons for drug attrition revealed that only 5 percent were caused by pharmacokinetic difficulties, whereas 46 percent were due to insufficient efficacy and 33 percent to adverse reactions in animals or humans [9]. Since both wanted and unwanted effects are due to the biological activity, 79 percent of drug candidates had unpredicted or wrongly predicted sum activities.

Predictions of toxicity from molecular features are still precarious [10–12]. Only rather general rules are for sure; such as avoidance of very reactive functional groups, for example, aldehyde because of oxidative instability and haptene nature; α,β-unsaturated carbonyl compounds and 2-halopyridines because of their unspecific reactivity as electrophiles. Torcetrapib is a typical example of toxicity—or adverse effects—challenges. It was an antiatherosclerotic drug candidate promising to become a blockbuster when in latter phase III of clinical trials, an increased risk of mortality led the company to discontinue its development. It was not clear whether the effects

were caused by the mechanism of action—inhibition of cholesteryl ester transfer protein—some other effect or an interaction with another drug. This is just one instance that "it isn't that simple [and] nothing's obvious and nothing's for certain" in rational drug development [13].

C. Stages of Drug Development

Most drugs were discovered rather than developed [14]. That is why a large number of drug substances are natural products or derivatives thereof. It is a matter of debate if ethnic medicines or nature still hold gems as yet undiscovered by pharmacy [15,16]. Synthetic substance collections ("libraries") have been created through (automated) organic chemistry. The very high number and diversity of natural and synthetic chemical entities is faced with an equally growing number of potential reaction partners (targets) from biochemical and pathophysiological research.

In virtual, biochemical and cell-based testing, compound selections are run against an isolated or physiologically embedded target that may be involved in the disease process [17]. Compounds that exceed a certain threshold value in binding to the target or modulation of some functional signal behind it, are called *hits*. If the identity and purity of the compound and the assay result are confirmed in a multipoint activity determination, the compound rises to the status of *validated hit*. From this one hopes to develop leads. A *lead* is a compound or series of compounds with proven activity and selectivity in a screen and fulfills some drug development criteria such as originality, patentability, and accessibility (by extraction or synthesis). Molecular variation hopefully tunes the physicochemical parameters so that it becomes suitable for ADME. An example of a small optimization algorithm is shown in Figure 1.1.

If the resulting *optimized lead* (*preclinical candidate*) displays no toxicity in cell and animal models, it becomes a *clinical candidate*. If this stands the tests of efficacy and safety in humans and overcomes marketing hurdles, a *new drug entity* will enter the treasure trove of pharmacy. Box 1.1 illustrates that activity is a necessary but not sufficient quality of medicines. There is, of course, no ideal drug in the real world, but one has to find a relative optimum. This often means developing a drug that has a different side-effect profile than drugs marketed for the same therapeutic indication so prescriptions can be tailored to the ways different patients react to a drug.

The role of medicinal chemistry is most prominent in steps one and two of drug development:

1. The discovery step, consisting of the choice of the therapeutic target (biochemical, cellular, or *in vivo* model; see below) and the identification or discovery and production of new active substances interacting with the selected target.
2. The optimization step that deals with the improvement of an active compound. The optimization process primarily takes into account the increase in potency, selectivity, and decrease in toxicity. Its characteristics are the establishment of structure–activity relationships, ideally based on an understanding of the molecular mode of action.

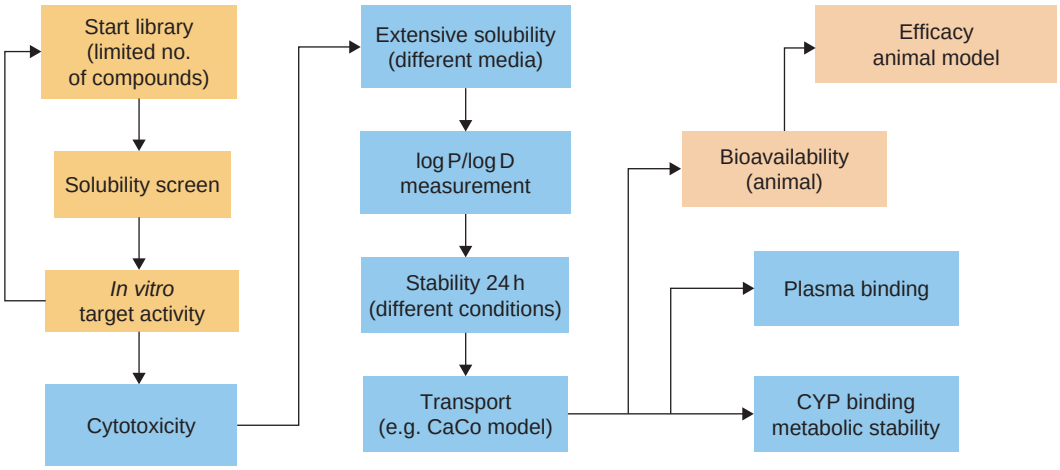

FIGURE 1.1 Example of an optimization algorithm. *Source: Adapted from a presentation by Dr. U. Heiser, Probiodrug AG, Halle, Germany, reproduced with permission.*

3. The formulation step, whose purpose is the continuation of the improvement of the pharmacokinetic properties and the fine-tuning of the pharmaceutic properties of active substances to render them suitable for clinical use. This can consist—to name just a few instances—of the preparation of better absorbed compounds, of sustained release formulations, and of water-soluble derivatives or in the elimination of properties related to the patient's compliance (irritation, painful injection, undesirable organoleptic properties). For an example, see Figure 1.2.

The main tasks of medicinal chemistry consist of the optimization of the following characteristics:

a. Higher affinity and target-intrinsic activation for better clinical activity so the dosage and nonspecific side effects will be as low as possible. There are no examples of drugs that are dosed below 10 mg/day that cause idiosyncratic adverse drug reactions. For drug substances that have to be given in higher doses—i.e., the majority—medicinal chemistry tries to find active derivatives that will be metabolized in a safe way [18]. This includes assaying for inhibition of or reaction with key enzymes of biotransformation, such as oxidases of the cytochrome type, some of which are highly demanded by food constituents and xenobiotics including drug substances [19]. Medicinal chemistry tries to prepare drugs that are not metabolized by bottleneck enzymic pathways [20].

b. Better selectivity, which may lead to a reduction of unwanted side effects. This sometimes entails the assaying of a very high number of other targets; for example, an antidepressive serotonin re-uptake inhibitor has to be tested against all subtypes of serotonin, adrenaline, and dopamine receptors, plus many other key receptors and enzymes.

BOX 1.1

THE IDEAL NEW DRUG SUBSTANCE

- New chemical entity for patentability and registration.
- Maximum four-step synthesis with, for example, no heavy metal catalysts and no environmentally problematic waste; no chromatographic purification steps; purity>99 percent.
- Stable up to 70°C even in humid air and light.
- Solid-state properties (crystalline, not polymorphous, not hygroscopic) that make it a perfect partner for (tablet) compaction.
- Solubility in water sufficient for the production of stable blood-isotonic solutions.
- Oral bioavailability .90 percent with no interindividual variation.
- Very high activity and pharmacokinetic profile enable once-a-day-dosage at 5–10 mg.

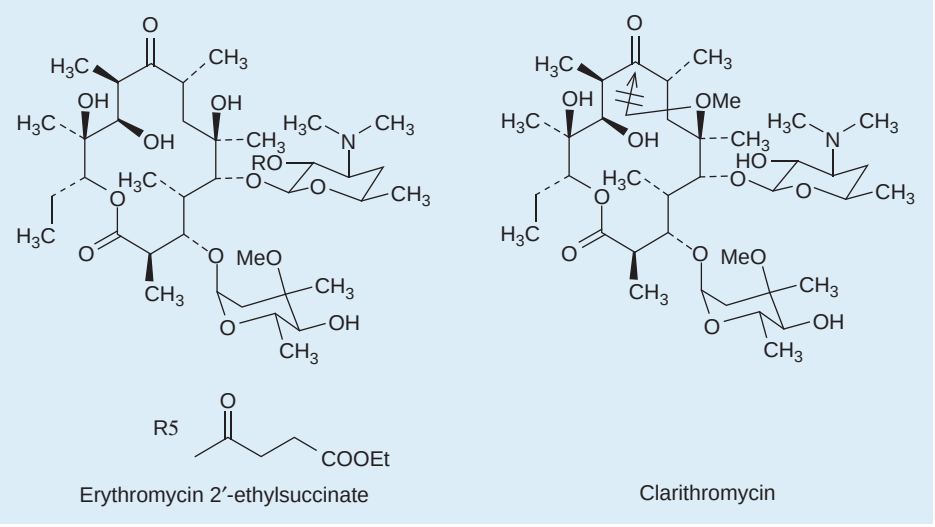

FIGURE 1.2 An example of fine-tuning of pharmacologically active chemicals: Erythromycin 29-ethylsuccinate and clarithromycin are semisynthetic derivatives of the macrolide antiinfective erythromycin. The small molecular change in the former leads to the elimination of bitterness which is important as this class of drugs is often used in pediatrics and administered as a syrup. In the latter, because hemiketal formation is no longer possible (arrow), clarithromycin is stable in the acidic milieu of the stomach (pH 2).