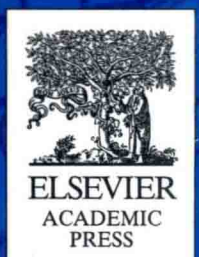
Second Edition

The Practice of MEDICINAL CHEMISTRY

Edited by CAMILLE GEORGES WERMUTH



The Practice of Medicinal Chemistry

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Edited by

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Laboratoire de Pharmacochimie Moléculaire, Faculté de Pharmacie,
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Biography

Camille-Georges Wermuth PhD, Prof. and Founder of Prestwick Chemical, was Professor of Organic Chemistry and Medicinal Chemistry at the Faculty of Pharmacy, Louis Pasteur University, Strasbourg, France from 1969 to 2002. He became interested in Medicinal Chemistry during his two years of military service in the French Navy at the "Centre d'Etudes Physio-biologiques Appliquées à la Marine" in Toulon. During this time he worked under the supervision of Dr Henri Laborit, the scientist who invented artificial hibernation and discovered chlorpromazine.

Professor Wermuths' main research themes focus on the chemistry and the pharmacology of pyridazine derivatives. The 3-aminopyridazine pharmacophore, in particular, allowed him to accede to an impressive variety of biological activities, including antidepressant and anticonvulsant molecules; inhibitors of enzymes such as mono-amine-oxidases, phosphodiesterases and acetylcholinesterase; ligands for neuro-receptors: GABA-A receptor antagonists, serotonine 5-HT_3 receptor antagonists, dopaminergic and muscarinic agonists. More recently, in collaboration with the scientists of the Sanofi Company, he developed potent antagonists of the 41 amino-acid neuropeptide CRF (corticotrophin-releasing factor) which regulates the release of ACTH and thus the synthesis of corticoids in the adrenal glands. Professor Wermuth has also, in collaboration with Professor Jean-Charles Schwartz and Doctor Pierre Sokoloff (INSERM, Paris), developed selective ligands of the newly discovered dopamine D_3 receptor. After a three-year exploratory phase, this research has led to nanomolar partial agonists which may prove useful in the treatment of the cocaine-withdrawal syndrome.

Besides about 300 scientific papers and about 60 patents, Professor Wermuth is co-author or editor of several books including; *Pharmacologie Moléculaire*, Masson & Cie, Paris; *Médicaments Organiques de Synthèse*, Masson & Cie, Paris; *Medicinal Chemistry for the Twenty-first Century*, Blackwell Scientific Publications, Oxford; *Trends in QSAR and Molecular Modeling*, ESCOM, Leyden, two editions of *The Practice of Medicinal Chemistry*, Academic Press, London and *The Handbook of Pharmaceutical Salts, Properties Selection and Use*, Wiley-VCH.

Professor Wermuth was awarded the Charles Mentzer Prize of the Société Française de Chimie Thérapeutique in 1984, the Léon Velluz Prize of the French Academy of Science in 1995, the Prix de l'Ordre des Pharmaciens 1998 by the French Academy of Pharmacy and the Carl Mannich Prize of the German Pharmaceutical Society in 2000. He is Corresponding Member of the German Pharmaceutical Society and was nominated Commandeur des Palmes Académiques in 1995. He has been President of the Medicinal Chemistry Section of the International Union of Pure and Applied Chemistry (IUPAC) from 1988 to 1992 and from January 1998 to January 2000 was President of the IUPAC Division on Chemistry and Human Health.

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Foreword

It is a privilege to write a Foreword to *The Practice of Medicinal Chemistry* written by a distinguished group of contributors. It is also a privilege because this book will be read by medicinal chemists from diverse backgrounds, interests and expertise. What these scientists share is a chosen career in medicinal chemistry, surely one of the most satisfying, because it is dedicated to improving mankind's quality of life and also because it provides an intellectually satisfying environment.

The eight general topics discussed insightfully in forty-three chapters of this textbook were wisely selected and do indeed describe medicinal chemistry as it is practiced today. This Foreword does not analyze or summarize these chapters, but offers instead some personal reflections which, it is hoped, have some relevance to the volume.

Modern medicinal chemistry began in the 1950s when organic chemists began to apply newly developed steric and electronic concepts to an understanding of the structure-activity relationships of the steroids. During the second half of the twentieth century, chemistry and biology made possible the discovery of a steady stream of important new medicines. Chemistry contributed to these discoveries through impactful advances in both theory and practice of this art/science. Notable examples include invaluable advances in physical measurements, computational techniques, inorganic catalysis, stereochemical control of synthesis and the application of physical organic chemical concepts, typified by the transition state analog principle, to enzyme inhibitor design. At the same time, biology continued to contribute through the discoveries of new concepts and understanding at a rate that may well be termed explosive.

Specifically, in 1953 Watson and Crick had proposed the double-helical structure of DNA, and suggested that the sequence of nucleotide units in DNA carries encoded genetic information that determines the amino acid sequence of proteins. These discoveries proved to be a revolutionary event in biology with a profound impact on the vitality of all biomedical research. In the early 1970s, biochemical research made possible the application by Herbert W. Boyer of this new understanding to the introduction of recombinant DNA research, a new technology. This in turn led to the Boyer and Cohen collaboration on prokaryotic and eukaryotic DNA research, early cloning successes, and the founding of Genentech, Inc. in 1976. The beginning of the successful commercialization of the recombinant DNA technology by Boyer and Robert A. Swanson thus occurred twenty-three years after the discovery of the double-helix. The early (and subsequent) successes of Genentech, Inc. amply validated DNA technology as an industrial enterprise. Biotechnology became a household word and with it the search for new biotechnology came to be accepted as a desirable end in itself.

During the 1970s, target validation became an important consideration in the selection of therapeutic programs explored by the pharmaceutical industry. In the strictest sense this strategy holds that intervention in any particular biochemical or pharmacological pathway has been fully validated only if it has been shown to work in human subjects. Any research program that does not pass this definitive test is therefore thought to be a 'long shot.' In practice, this leads to the conclusion that a conservative portfolio of an organization's research programs should strike some appropriate balance between 'validated' and 'long shot' targets. In recent years successful use of antibodies in neutralizing a target protein or other substance has come to be accepted as adequate validation; this is also the case for another validated technology, the use of 'knock-out' or 'knock-in' mice.

At the end of the twentieth century there was every reason to expect that the flow of new drugs from the laboratory stages, *via* clinical trials, to the expected regulatory approval would continue to accelerate. As this book goes to press, the pipelines of both the pharmaceutical industry and of the biotechnology companies are, however, relatively dry. This is at the very time when spectacular advances in biology such as genomics and proteomics seemed to have laid the basis for the discovery of many new breakthrough drugs.

Surprisingly, there has been relatively little discussion of the causes of this paradoxical state of affairs. It is believed by some that the growing impact of marketing departments on the choice of clinical targets may have played a role in bringing about this disappointing state of affairs. Perhaps so, but it seems prudent to suggest that scientific decisions originating within the research organizations themselves may also deserve scrutiny (see below).

The unexpectedly dry pipelines of the industry raise the interesting question of whether it might be wise for any company to also 'validate' *new technologies* on a modest scale before they are extensively embraced by any organization. Two examples serve to illustrate this concern. In the 1980s the recognition that 'rational design' of enzyme inhibitors is a fruitful approach to drug discovery, led to the belief that knowing the tertiary structure of the active sites of such enzyme targets would greatly facilitate the discovery process. Significant time and effort was invested in this approach by several companies before it was recognized that the X-ray structure of the *uninhibited* enzyme is likely to be misleading, because the important role of water molecules and of conformational effects on molecular recognition was not appreciated.

More importantly, the extensive early commitment by the pharmaceutical industry to the use of combinatorial chemistry as the principal source of new chemical entities for lead discovery may be an even more serious issue. Combinatorial chemistry has proven to be an effective tool for lead optimization, but its use as the principal source of compounds for screening for lead discovery has been problematic. At the present time, very few – if any – compounds that are approved drugs or that are in Phase III clinical trials, are thought to owe their existence solely to leads generated by combinatorial chemistry. If this assessment is indeed a valid one, the extensive reliance by the industry on this unvalidated technology may well have contributed to the current disappointing status of the pipelines. For combinatorial chemistry to become a useful source of compounds for lead discovery, two requirements must be met. (1) The successive reactions must proceed sufficiently well to afford the expected final product in good yield. This requirement has generally been met. (2) It is equally important, however, that the chosen synthetic targets incorporate sufficient complexity to have a good chance that some of them will become true leads. The bar for this second objective may often have been lowered too much in order to achieve the first requirement – the desired purity. There is reason to hope that now-a-days both requirements are being met, but only time will tell.

On the other hand, a change in tactics in lead optimization has allowed for huge advances, especially in the discovery of ligands for G-protein coupled receptors. As their first objective, medicinal chemists used to seek to optimize *in vitro* potency. Given the hydrophobic nature of many of these receptors, it is not surprising that the most potent compounds to emerge from this tactic proved to be equally hydrophobic, and thus to display poor pharmacokinetic properties. Attempts to deal with this matter in the so-called 'endgame' more often than not proved to be futile. The program had thus become a victim of the 'hydrophobic trap.' By the end of the twentieth century we had learned to appreciate that measurements or calculations that relate to solubility, and thus to oral bioavailability such as log P and polar molecular surface properties, should guide the synthetic program from the very beginning.

I shall close this Foreword by returning to the theme of medicinal chemists in the service of humanity and illustrate it with two examples: the first relates to AIDS. In the mid-1980s, the human immunodeficiency virus (HIV) had been identified as the cause of AIDS. By 1996 medicinal chemists, in collaboration with biologists, had discovered reverse transcriptase inhibitors and later HIV protease inhibitors, which were combined to provide cocktails of therapy. Various regimes of what was termed 'highly active antiretroviral therapy' (HAART) reduced the viral load below detection levels — an enormous advance. Today there are sixteen approved drugs against AIDS which include seven nucleoside reverse transcriptase inhibitors (NRTIs), three non-nucleoside inhibitors of these enzymes (NNRTIs) and six protease inhibitors (PIs). These medicines thus represent an enormous step forward, although they have failed to eliminate the virus entirely from patients, resulting in the need to continue these therapies, along with their considerable side effects, for life. Resistance to these anti-AIDS medications represents an even more serious challenge, as is our inability to make anti-AIDS therapy readily available to patients in developing nations.

In contrast, the drug Mectizan has all but eliminated another dreaded disease, river blindness, in both Latin America and in West Africa. In other parts of Africa where progress varies on a country-by-country basis, success has been less dramatic. Surely there is every reason for medicinal chemists to be proud of this drug, first discovered and developed as an animal health anthelmintic, and which ultimately proved to have a far more glorious role to play in human medicine. Almost miraculously, oral administration of this drug is required only three times a year, an enormous plus in an environment where patient compliance is so poor. It should be a source of great pride and satisfaction to all medicinal chemists, whether working in the pharmaceutical industry or in other organizations, that at the time of writing Merck & Co., Inc. continues to donate 150 million tablets annually to patients in the developing world.

Looking to the future, great challenges remain including cancer, AIDS and — as life expectancy increases — Alzheimer's disease. It is exciting to contemplate that in the twenty-first century medicinal chemists will, in addition, become increasingly successful in using small molecules to block undesired protein–protein interactions. It is surely the hope of the scientists who have contributed to this book that *The Practice of Medicinal Chemistry* will become a much-consulted adjunct to the medicinal chemists in their search for the drugs of the future.

Ralph Hirschmann
Philadelphia, Pennsylvania

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 (South Bank University, London) 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, François 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

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 Thérapeutique, Faculté 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 pre-clinical 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

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PART I

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