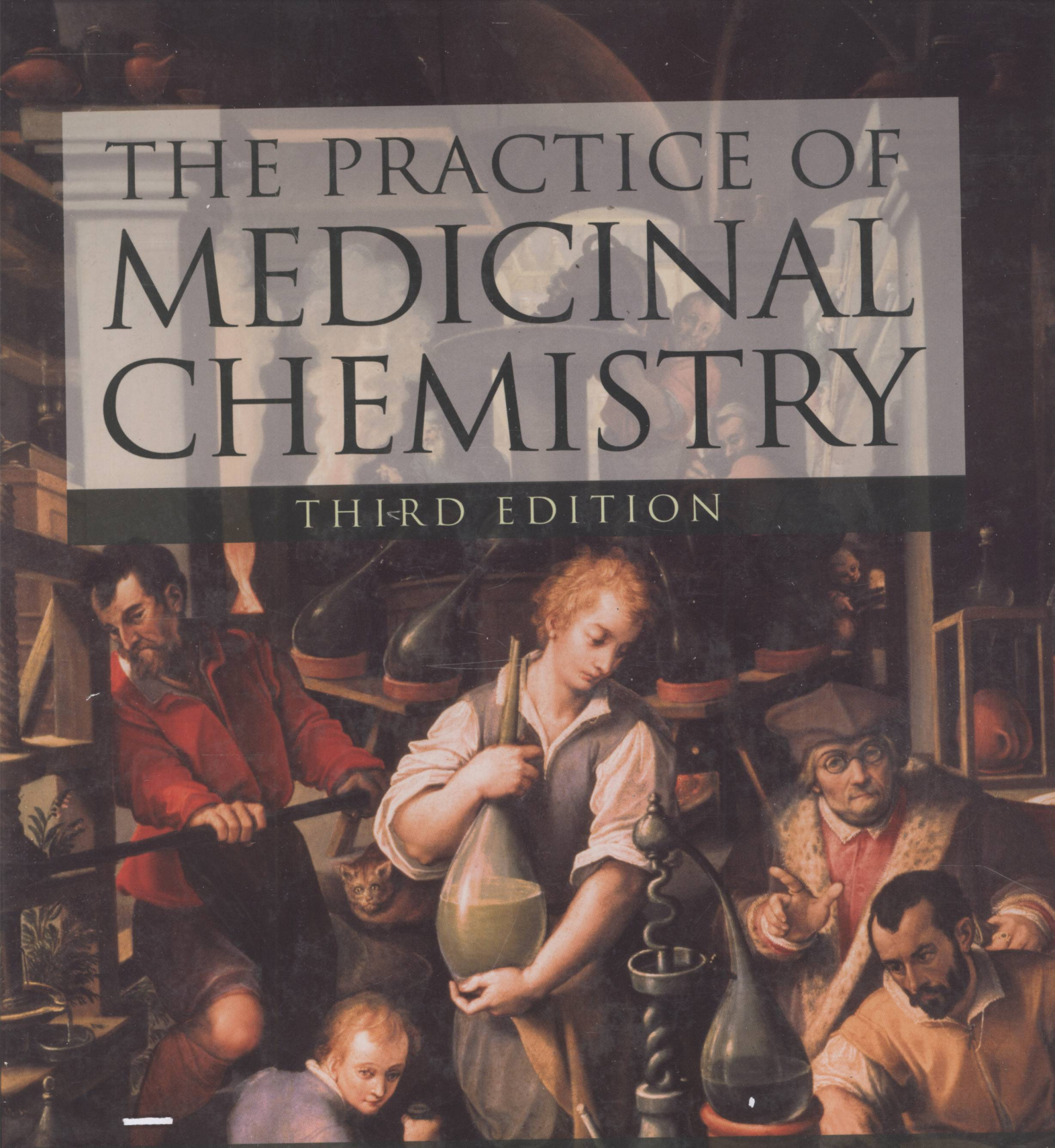
THE PRACTICE OF MEDICINAL CHEMISTRY

THIRD EDITION



EDITED BY

CAMILLE GEORGES WERMUTH

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The Practice of Medicinal Chemistry

Third edition

Edited by

Camille Georges Wermuth
Prestwick Chemical Inc.
Illkirch, France

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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.

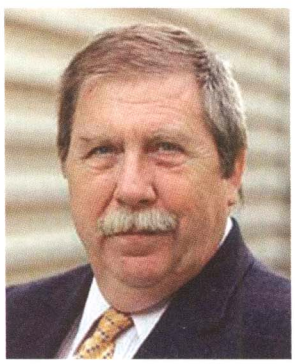
Professor Wermuths' main research themes focus on the chemistry and the pharmacology of pyridazine derivatives. The 3-aminopyridazine pharmacophore, in particular, allowed him to accede to an impressive variety of biological activities, including antidepressant and anticonvulsant molecules; inhibitors 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 80 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.

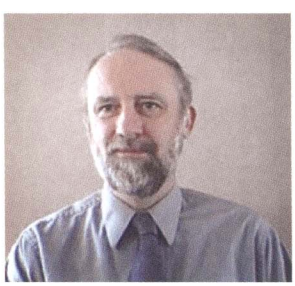
Professor Wermuth was awarded the Charles Mentzer Prize of the Société Française de Chimie Thérapeutique in 1984, the Léon Velluz Prize of the French Academy of Science in 1995, the Prix de l'Ordre des Pharmaciens 1998 by the French Academy of Pharmacy and the Carl Mannich Prize of the German Pharmaceutical 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.

Section Editors

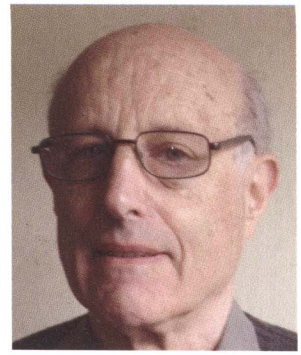
Michael J. Bowker studied chemistry and received his doctorate in Organic Chemistry from the University of Leeds, UK. After 5 years working for a multinational polymer company, he moved to May & Baker Ltd., a UK subsidiary of Rhône-Poulenc Santé (now Sanofi-Aventis). He was a Director of Analytical Chemistry for about 15 years and, more recently, Director of Preformulation at Aventis Pharma Ltd. He has been intimately involved in preformulation and solid-state activities, on a worldwide basis for more than 15 years. He has published several research papers and one chapter for a book on pharmaceutical salts and is currently a Director of M. J. Bowker Consulting Limited, a small company undertaking consultancy in salt selection, polymorph selection and pharmaceutical preformulation.



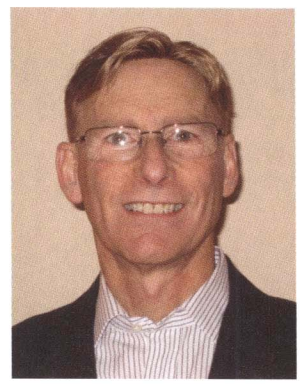
Hugo Kubinyi is a Medicinal Chemist with 35 years of industrial experience in drug design, molecular modeling, protein crystallography and combinatorial chemistry, in Knoll and BASF AG, Ludwigshafen. He is a Professor of Pharmaceutical Chemistry at the University of Heidelberg, former Chair of The QSAR and Modelling Society and IUPAC Fellow. From his scientific work resulted more than 100 publications and seven books on QSAR, drug design, chemogenomics, and drug discovery technologies.



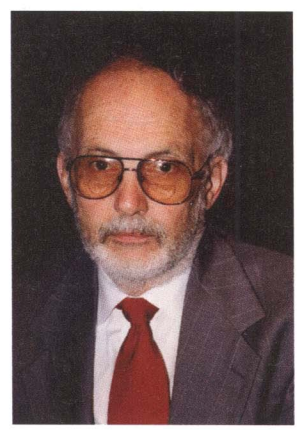
John R. Proudfoot received his Ph.D. from University College Dublin, Ireland in 1981 working with Professor Dervilla Donnelly. He completed post doctoral studies with Professor Carl Djerassi at Stanford University and Professor John Cashman at the University of California San Francisco. In 1987, he joined Boehringer Ingelheim and is presently a Distinguished Scientist in the medicinal chemistry department.



Bryan G. Reuben is Professor Emeritus of Chemical Technology at London South Bank University. He has written widely on the technology and economics of the chemical and pharmaceutical industries. His most recent experimental work was on hydrogen–deuterium exchange in protonated peptides and on the downstream processing of nisin.



Richard B. Silverman is the John Evans Professor of Chemistry at Northwestern University. He has published 240 research articles, holds 38 domestic and foreign patents, has written four books, and is the inventor of Lyrica™ (pregabalin), marketed worldwide by Pfizer for refractory epilepsy, neuropathic pain, fibromyalgia, and (in Europe) for generalized anxiety disorder.



David J. Triggle is a SUNY Disinguished Professor and the University Professor State University of New York at Buffalo. Educated in United Kingdom and Canada in physical and organic chemistry he has served a variety roles at Buffalo including Dean of the School of Pharmacy and University Provost. His work has been principally in the area of the chemical pharmacology of drug–receptor and drug–ion channel interactions. He is the author and editor of some 30 books and several hundred publications.

Han van de Waterbeemd studied organic and medicinal chemistry and got his PhD at the University of Leiden. After his academic years at the University of Lausanne with Bernard Testa he worked for 20 years in the pharmaceutical industry for Roche, Pfizer and AstraZeneca. His research interests are in optimizing compound quality using measured and predicted physicochemical and DMPK properties. He contributed to 145 research papers and book chapters, and (co-)edited 13 books.

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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

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 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

Preface to the Third Edition

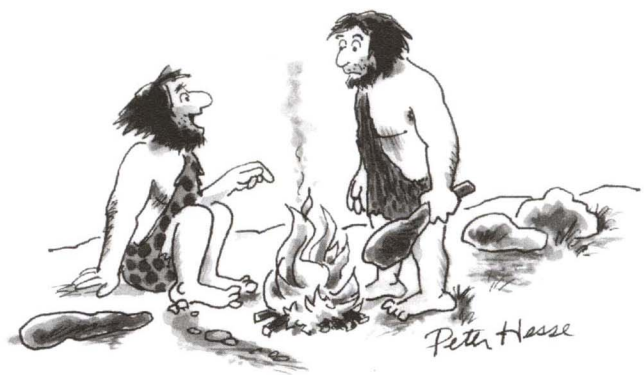
Like the preceding editions of this book, this third edition treats of the essential elements of medicinal chemistry in a unique volume. It provides a practical overview of the daily problems facing medicinal chemists, from the conception of new molecules through to the production of new drugs and their 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.



"IT'S CALLED FIRE... IT RECYCLES WOOD."

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!

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