



Second Edition

*The Practice of*  
**MEDICINAL  
CHEMISTRY**

*Edited by* CAMILLE GEORGES WERMUTH





# Contents

---

<b>Biography</b>	viii
<b>Contributors</b>	ix
<b>Foreword</b>	xi
<b>Preface to the First Edition</b>	xiii
<b>Preface to the Second Edition</b>	xv
<b>Part I General Aspects of Medicinal Chemistry</b>	
1 A brief history of drugs: from plant extracts to DNA technology <i>François Chast</i>	1
2 Medicinal chemistry: definition and objectives, the three main phases of drug activity, drug and disease classifications <i>Camille G. Wermuth</i>	29
3 Measurement and expression of drug effects <i>Jean-Paul Kan</i>	41
4 Drug targets: molecular mechanisms of drug action <i>Jean-Pierre Gies and Yves Landry</i>	51
<b>Part II Lead Compound Discovery Strategies</b>	
5 Strategies in the search for new lead compounds or original working hypotheses <i>Camille G. Wermuth</i>	67
6 Natural products as pharmaceuticals and sources for lead structures <i>David Newman, Gordon Cragg and David Kingston</i>	91
7 Basics of combinatorial chemistry <i>Cécile Vanier and Alain Wagner</i>	111
8 The contribution of molecular biology to drug discovery <i>Kenton H. Zavitz and Adrian N. Hobden</i>	121
9 Electronic screening: lead finding from database mining <i>Lothar Terfloth and Johann Gasteiger</i>	131
10 High-speed chemistry libraries: assessment of drug-likeness <i>Alexander Polinsky</i>	147
11 Web alert—using the internet for medicinal chemistry <i>David Cavalla</i>	159

**Part III Primary Exploration of Structure–Activity Relationships**

12	Molecular variations in homologous series: vinylogues and benzologues <i>Camille G. Wermuth</i>	173
13	Molecular variations based on isosteric replacements <i>Camille G. Wermuth</i>	189
14	Conformational restrictions and/or steric hindrance in medical chemistry <i>Camille G. Wermuth</i>	215
15	Conformational restriction and/or steric hindrance in medicinal chemistry <i>André Mann</i>	233
16	Identical and non-identical twin drugs <i>Jean-Marie Contreras and Jean-Jacques Bourguignon</i>	251
17	Optical isomerism in drugs <i>Camille G. Wermuth</i>	275
18	Application strategies for the primary structure–activity relationship exploration <i>Camille G. Wermuth</i>	289

**Part IV Substituents and Functions: Qualitative and Quantitative Aspects of Structure–Activity Relationships**

19	Specific substituent groups <i>Camille G. Wermuth</i>	301
20	The role of functional groups in drug–receptor interactions <i>Peter Andrews</i>	327
21	Compound properties and drug quality <i>Christopher A. Lipinski</i>	341
22	Quantitative approaches to structure–activity relationships <i>Han van de Waterbeemd and Sally Rose</i>	351

**Part V Spatial Organization, Receptor Mapping and Molecular Modeling.**

23	Stereochemical aspects of drug action I: conformational restriction, steric hindrance and hydrophobic collapse <i>Daniel H. Rich</i>	371
24	Pharmacophore identification and receptor mapping <i>Hans-Dieter Höltje</i>	387
25	Three-dimensional quantitative structure–property relationships <i>Gabriele Cruciani</i>	405
26	Protein crystallography and drug discovery <i>Jean-Michel Rondeau and Herman Schreuder</i>	417
27	Protein homology modelling and drug discovery <i>Tom Blundell and Charlotte Deane</i>	445
28	The transition from agonist to antagonist activity: symmetry and other considerations <i>David J. Triggle</i>	459
29	Design of peptidomimetics <i>Hiroshi Nakanishi and Michaël Kahn</i>	477

**Part VI Chemical Modifications Influencing the Pharmacokinetic Properties**

30	The fate of xenobiotics in living organisms <i>Franz Belpaire and Marc G. Bogaert</i>	501
31	Biotransformation reactions <i>Jacques Magdalou, Sylvie Fournel-Gigleux, Bernard Testa and Mohamed Ouzzine</i>	517
32	Chemical mechanisms of toxicity: basic knowledge for designing safer drugs <i>Anne-Christine Macherey and Patrick M. Dansette</i>	545
33	Designing prodrugs and bioprecursors <i>Camille G. Wermuth</i>	561
34	Macromolecular carriers for drug targeting <i>Etienne H. Schacht, Katleen De Winne, Katty Hoste and Stefan vansteenkiste</i>	587

**Part VII Pharmaceutical and Chemical Formulation Problems**

35	Preparation of water-soluble compounds through salt formation <i>P. Heinrich Stahl</i>	601
36	Preparation of water-soluble compounds by covalent attachment of solubilizing moieties <i>Camille G. Wermuth</i>	617
37	Drug solubilization with organic solvents, or using micellar solutions or other colloidal dispersed systems <i>P. Heinrich Stahl</i>	631
38	Improvement of drug properties by cyclodextrins <i>Kaneto Uekama and Fumitoshi Hirayama</i>	649
39	Chemical and physicochemical solutions to formulation problems <i>Camille G. Wermuth</i>	675

**Part VIII Development of New Drugs: Legal and Economic Aspects**

40	Discover a drug substance, formulate and develop it to a product <i>Bruno Galli and Bernard Faller</i>	687
41	Drug nomenclature <i>Sabine Kopp-Kubel</i>	697
42	Legal aspects of product protection — what a medicinal chemist should know about patent protection <i>Maria Souleau</i>	707
43	The consumption and production of pharmaceuticals <i>Bryan G. Reuben</i>	723

<b>Index</b>	751
--------------	-----