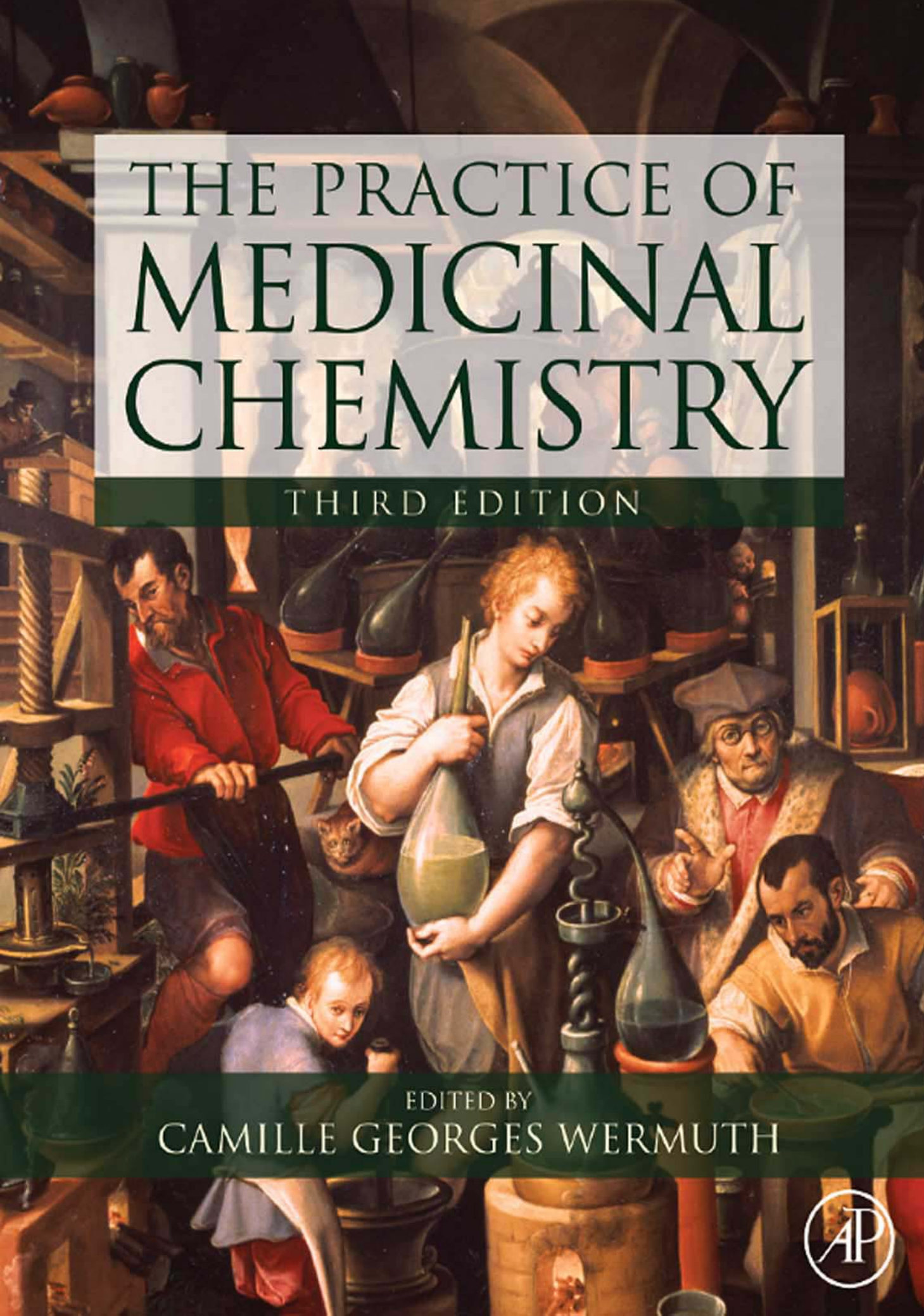
THE PRACTICE OF
MEDICINAL
CHEMISTRY
THIRD EDITION
EDITED BY
CAMILLE GEORGES WERMUTH
AP

The Practice of Medicinal Chemistry

Third edition

This page intentionally left blank

The Practice of Medicinal Chemistry

Third edition

Edited by

Camille Georges Wermuth
Prestwick Chemical Inc.
Illkirch, France

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON • NEW YORK • OXFORD
• PARIS • SAN DIEGO • SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
84 Theobald's Road, London WC1X 8RR, UK

First published 1996
Reprinted 2001
Second edition 2003
Third edition 2008

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-374194-3

For information on all Academic Press publications
visit our web site at www.books.elsevier.com

Typeset by Charon Tec Ltd., A Macmillan Company
(www.macmillansolutions.com)

Printed in China
08 09 10 9 8 7 6 5 4 3 2 1

Contents

Biography xxv

Section Editors xxvii

Contributors xxix

Preface to the First Edition xxxv

Preface to the Second Edition xxxvii

Preface to the Third Edition xxxix

Part I General Aspects of Medicinal Chemistry
Section Editor: Hugo Kubinyi 1

1. A History of Drug Discovery 3
François Chast

I. Introduction 4
- A. The renewal of chemistry 4
- B. The dawn of the organic chemistry crosses the birth of biology 5

II. Two Hundred Years of Drug Discoveries 6
- A. Pain killers: best-sellers and controversies 6
- B. Giving back the heart its youth 10
- C. Fight against microbes and viruses 15
- D. Drugs for immunosuppression 24
- E. Contribution of chemists to the fight against cancer 26
- F. Drugs for endocrine disorders 30
- G. Anti-acid drugs 34
- H. Lipid lowering drugs 35
- I. From neurotransmitters to receptors 37
- J. Drugs of the mind 41

III. Considerations on Recent Trends in Drug Discovery 49
- A. From genetics to DNA technology 49
- B. Hopes and limits for drug hunting 52

References 55

2. Medicinal Chemistry: Definitions and Objectives, Drug Activity Phases, Drug Classification Systems 63
Peter Imming

I. Definitions and Objectives 63
- A. Medicinal chemistry and related disciplines and terms 63
- B. Drugs and drug substances 64
- C. Stages of drug development 64

II. Drug Activity Phases 66
- A. The pharmaceutical phase 66
- B. The pharmacokinetic phase 66

C. The pharmacodynamic phase 67
D. The road to successful drug development? 67
III. Drug Classification Systems 67
A. Classification by target and mechanism of action 68
B. Other classification systems 70
References 71

3. Measurement and Expression of Drug Effects 73
Jean-Pierre Nowicki and Bernard Scatton

I. Introduction 73
II. *In Vitro* Experiments 75
A. Binding studies 75
B. Ligand–receptor interaction-induced functional effects 76
C. Allosteric interaction 78
D. Expression of functional effects for targets other than GPCRS 79
E. Cellular and tissular functional responses 79
III. *Ex Vivo* Experiments 81
IV. *In Vivo* Experiments 82
References 83

4. Molecular Drug Targets 85
Jean-Pierre Gies and Yves Landry

I. Introduction 86
A. How many drug targets for how many drugs? 86
B. From the drug target to the response of the organism 86
C. Drug binding, affinity and selectivity 87
D. Various ligands for a single target 87
II. Enzymes as Drug Targets 88
A. Targeting human enzymes 88
B. Targeting enzymes selective of invading organisms 89
III. Membrane Transporters as Drug Targets 89
A. Established drug targets among membrane transporters 89
B. Progress in the pharmacological control of membrane transporters 89
IV. Voltage-Gated Ion Channels as Drug Targets 90
A. Voltage-gated sodium channels (Na_V channels) 90
B. Voltage-gated calcium channels (Ca_V channels) 91
C. Potassium channels 91
V. Non-Selective Cation Channels as Drug Targets 92
VI. Direct Ligand-Gated Ion Channels (Receptors with Intrinsic Ion Channel) 93
A. P2X-ATP receptors 94
B. Glutamate-activated receptors 94
C. The "Cys-loop receptor superfamily" 95
VII. Receptors with Intrinsic Enzyme Activity 95
A. Receptors with guanylate cyclase activity 95
B. Receptors with serine/threonine kinase activity 96
C. Receptors with tyrosine kinase activity 96
VIII. Receptors Coupled to Various Cytosolic Proteins 97
A. Receptors coupled to the cytosolic tyrosine kinase JAK 97
B. Receptors coupled to the cytosolic Src, Zap70/Syk and Btk tyrosine kinases (immunoreceptors) 97
C. Receptors coupled to the cytosolic serine/threonine kinase IRAK 98
D. Receptors coupled to caspases and to NFκB 98
E. Receptors of the cellular adhesion 99
IX. G-Protein-Coupled Receptors 99
A. How many druggable GPCRs? 100

B. Diversity of G-proteins 101
C. Diversity of GPCR-elicited signaling and related drug targets 101
X. Nuclear Receptors As Drug Targets 103
References 104

5. Drug Targets, Target Identification, Validation and Screening 106
Kenton H. Zavitz, Paul L. Bartel and Adrian N. Hobden

I. Introduction 106
II. Improving the Resolution of Disease Etiology 107
III. Biopharmacuetical Therapies 108
A. Passive immunotherapy 108
IV. Drug Target Identification 109
A. Rare mutations leading to generalized therapies 109
B. Mining the proteome 109
C. Yeast two-hybrid systems 110
D. RNA interference 111
V. Hit-to-Lead 113
A. Cell-based screening 113
B. Intracellular receptors 113
C. Intracellular enzymes 115
D. G-protein-coupled receptors 115
E. Transgenic animals 117
F. Drug metabolism 118
G. Toxicology 118
VI. Clinical Biomarkers 119
VII. Conclusions 119
References 119

Part II Lead Compound Discovery Strategies
Section Editor: John R. Proudfoot 123

6. Strategies in the Search for New Lead Compounds or Original Working Hypotheses 125
Camille G. Wermuth

I. Introduction 125
A. Hits and leads 125
B. The main hit or lead finding strategies 126
II. First Strategy: Analog Design 126
A. Typical examples 126
B. The different categories of analogs 127
C. Pros and cons of analog design 128
III. Second Strategy: Systematic Screening 129
A. Extensive screening 129
B. Random screening 129
C. High-throughput screening 130
D. Screening of synthesis intermediates 131
E. New leads from old drugs: The SOSA approach 132
IV. Third Strategy: Exploitation of Biological Information 134
A. Exploitation of observations made in humans 134
B. Exploitation of observations made in animals 137
C. Exploitation of observations made in the plant kingdom and in microbiology 137
V. Fourth Strategy: Planned Research and Rational Approaches 138
A. L-DOPA and rarkinsonism 138

B. Inhibitors of the ACE 139
C. Discovery of the H2-receptor antagonists 141
VI. Conclusion 142
References 142

7. High-Throughput Screening and Drug Discovery 144
John R. Proudfoot

I. Introduction 144
II. Historical Background 144
III. From Screen to Lead 146
A. Compound collections 146
B. Assays 146
C. Hit-to-lead process 147
IV. Examples of Drugs Derived from Screening Leads 147
A. Reverse transcriptase inhibitors, nevirapine, efavirenz, and delavirdine 148
B. Endothelin antagonists, bosentan, sitaxsentan, edonentan, and ambrisentan 150
C. Raf kinase inhibitor, sorafenib 152
V. Practical Application, Recent Example 152
A. IKK inhibitors 152
VI. Conclusion 154
References 155

8. Natural Products as Pharmaceuticals and Sources for Lead Structures 159
David J. Newman, Gordon M. Cragg and David G. I. Kingston

I. Introduction 159
II. The Importance of Natural Products in Drug Discovery and Development 160
A. The origin of natural products 161
B. The uniqueness of the natural products approach 161
C. The impact of new screening methods 162
III. The Design of an Effective Natural-Products-Based Approach to Drug Discovery 163
A. Acquisition of biomass 163
B. The unexplored potential of microbial diversity 164
C. Extraction 167
D. Screening methods 167
E. Isolation of active compounds 168
F. Structure elucidation 168
G. Further biological assessment 168
H. Procurement of large-scale supplies 168
I. Determination of structure–activity relationships 169
IV. Examples of Natural Products or Analogs as Drugs 169
A. Antihypertensives 169
B. Anticholesterolemics 169
C. Immunosuppressives 171
D. Antibiotics 171
E. Microbial anticancer agents 172
F. Anticancer agents from plants 174
G. Anticancer agents from marine organisms 175
H. Antimalarial agents 177
I. Other natural products 177
V. Future Directions in Natural Products as Drugs and Drug Design Templates 177
A. Introduction 177
B. Combinatorial chemistry 177
C. Natural products as design templates 178
D. Interactions of microbial sources, genomics, and synthetic chemistry 178
VI. Summary 180
References 180

9. Biology Oriented Synthesis and Diversity Oriented Synthesis in Compound Collection Development 187
Kamal Kumar, Stefan Wetzel and Herbert Waldmann

I. Introduction 187
II. Diversity Oriented Synthesis 188
A. DOS: Principles 188
B. DOS of small molecule libraries 188
C. Applications of DOS libraries 192
III. Biology Oriented Synthesis 194
A. Introduction 194
B. The scaffold tree for structural classification of natural products 194
C. Protein structure similarity clustering 199
D. BIOS: The combined application of SCONP and PSSC 202
E. BIOS: Prospects and future directions 205
IV. Conclusion and Outlook 205
References 206

10. *In Silico* Screening: Hit Finding from Database Mining 210
Thierry Langer and Sharon D. Bryant

I. Introduction 210
A. Chemoinformatics in drug discovery 211
B. What is the difference between a hit and a lead structure? 211
C. Data mining using chemoinformatics 212
II. Representation of Chemical Structures 212
A. Structural keys and 1D fingerprints 213
B. Topological descriptors 213
C. 3D descriptors 214
D. Further descriptors 216
III. Data Mining Methods 216
IV. Database Searches 217
A. Distance and similarity searches 217
B. 2D database searches 217
C. 3D database searches 218
V. Applications 218
A. Ligand-based *in silico* screening 218
B. Structure-based *in silico* screening 219
C. Assessing affinity profiles using parallel *in silico* screening 219
D. Example: Parallel pharmacophore-based virtual screening 219
VI. Conclusion and Future Directions 222
References 222

11. Fragment-Based Drug Discovery 228
Bennett T. Farmer and Allen B. Reitz

I. Ligand–Protein Interactions: First Principles 228
A. Binding energy as the sum of the parts 228
B. Historical development 229
C. Ligand efficiency 230
II. Status of Late 1990s Drug Discovery in the Pharmaceutical Industry 230
III. What is FBDD? 231
A. Concept and overview 231
B. Differences between FBDD and HTS/HTL approaches 233
C. The role of the medicinal chemist in FBDD 234

IV. Creation and Analysis of FBDD Libraries 234
A. General evaluation and analysis 234
B. Computational approaches 235
C. Use of primary data: sprouting and merging to create secondary libraries 235
V. Nuclear Magnetic Resonance 235
A. 1D (ligand-based) screening 235
B. Example 236
C. 2D (protein-based) screening 237
VI. X-ray Crystallography 237
A. General principles and limitations 237
B. Examples 238
VII. Other Biophysical and Biochemical Screening Methods 238
A. Substrate activity screening 238
B. *In situ* click chemistry 239
C. SPR spectroscopy 239
D. SAR by mass spectroscopy 239
VIII. Methods for Fragment Hit Follow-Up 239
A. How to best reduce false positives (NMR, MS) and false negatives (X-ray) 239
B. Isothermal and differential titration calorimetry and further secondary analysis 240
IX. Trends for the Future 240
References 241

12. Lead-Likeness and Drug-Likeness 244
Alex Polinsky

I. Introduction 244
II. Assessing "Drug-Likeness" 245
A. Avoiding known threats 245
B. Mimicking known drugs 247
C. Direct property prediction 249
III. Selecting Better Leads: "Lead-Likeness" 250
A. What is a "high-quality" lead compound? 250
B. Designing "lead-like" libraries for biochemical screening 251
IV. Conclusion 253
References 253

13. Web Alert: Using the Internet for Medicinal Chemistry 255
David Cavalla

I. Introduction 255
II. Blogs 256
III. Wikis 257
A. RSS information feeds 257
IV. Compound Information 257
A. Chemspider 257
B. The NIH Roadmap and PubChem 258
C. ChemBank 258
V. Biological Properties of Compounds 258
A. Prediction of biochemical properties 259
B. Molecular datasets 259
C. Information on metabolic properties 260
VI. Drug Information 260
A. DrugBank 260
VII. Physical Chemical Information 261
VIII. Prediction and Calculation of Molecular Properties 261
IX. Chemical Suppliers 263

X. Chemical Synthesis 264
XI. Chemical Software Programs 263
A. Chemical drawing and viewing software 264
B. Various chemoinformatics software 265
C. Datasets for virtual screening 266
XII. Analysis 267
XIII. Chemical Publications 267
A. Journals 267
B. Open access 268
C. Theses 268
XIV. Patent Information 269
A. Japanese patents 270
XV. Toxicology 270
XVI. Metasites and Technology Service Provider Databases 272

Part III Primary Exploration of Structure–Activity Relationships
Section Editor: Camille G. Wermuth 273

14. Molecular Variations in Homologous Series: Vinylogues and Benzologues 275
Camille G. Wermuth

I. Homologous Series 275
A. Definition and classification 275
B. Shapes of the biological response curves 277
C. Results and interpretation 278
II. Vinylogues and Benzologues 283
A. Applications of the vinylogy principle 283
B. Comments 287
References 287

15. Molecular Variations Based on Isosteric Replacements 290
Paola Ciapetti and Bruno Giethlen

I. Introduction 290
II. History: Development of the Isosterism Concept 291
A. The molecular number 291
B. The isosterism concept 292
C. The notion of pseudoatoms and Grimm's hydride displacement law 293
D. Erlenmeyer's expansion of the isosterism concept 293
E. Isoserism criteria: Present conceptions 293
F. The bioisosterism concept: Friedman's and Thornber's definitions 294
III. Currently Encountered Isosteric and Bioisosteric Modifications 294
A. Replacement of univalent atoms or groups 294
B. Interchange of divalent atoms and groups 294
C. Interchange of trivalent atoms and groups 296
D. Ring equivalents 297
E. Groups with similar polar effects: functional equivalents 303
F. Reversal of functional groups 320
IV. Scaffold Hopping 323
A. Successful examples of serendipitous scaffold hopping 323
B. Scaffold hopping and virtual screening 325
V. Analysis of the Modifications Resulting from Isosterism 326
A. Structural parameters 327
B. Electronic parameters 327
C. Solubility parameters 327
D. Anomalies in isosterism 328

VI. Minor Metalloids-Toxic Isosters 330
A. Carbon–silicon bioisosterism 330
B. Carbon–boron isosterism 331
C. Bioisosteries involving selenium 333
References 334

16. Ring Transformations 343
Christophe Morice and Camille G. Wermuth

I. Introduction 343
II. Analogical Approaches 343
A. Analogy by ring opening: open-chain analogs 343
B. Analogy by ring closure 345
C. Other analogies 349
III. Disjunctive Approaches 354
A. Cocaïne-derived local anesthetics 355
B. Morphinic analgesics 355
C. Dopamine autoreceptor agonists 355
D. CCK antagonists 355
IV. Conjunctive Approaches 356
A. Dopaminergic antagonists 356
B. Glutamate NMDA and AMPA receptor antagonists 358
C. Norfloxacin analogs 359
D. Melatonin analogs 360
V. Conclusion 360
References 360

17. Conformational Restriction and/or Steric Hindrance in Medicinal Chemistry 363
André Mann

I. Introduction 363
A. Theoretical points 364
B. On constrainted analogs 366
C. On conformational analysis 367
D. On the natur of Steric effects 368
E. Rigid compounds and bioavailability 368
II. Case studies 368
A. Bradykinin 368
B. Allylic constraints for inducing conformational rigidity 369
C. Diversity-Oriented Synthesis 371
D. Epibatidine bioactive conformation 371
E. Ligands for the Hepatitis C virus 372
F. Nociceptin 374
G. Opioid receptors ligands 374
H. Peptidomimetics for SH2 domains 375
III. Summary and Outlook 377
References 378

18. Homo and Heterodimer Ligands the Twin Drug Approach 380
Jean-Marie Contreras and Wolfgang Sippl

I. Indroduction 380
II. Homodimer and Symmetrical Ligands 383
A. Symmetry in nature 383
B. Homodimers as receptors ligands 383
C. Homodimers as enzyme inhibitors 387

D. Homodimers as DNA ligands 390
E. Homodimers of pharmacological interest 390
III. Heterodimer and Dual Acting Ligands 391
A. Hybrid molecules as ligands of two different receptors 391
B. Hybrids as enzymes inhibitors 394
C. Hybrids acting at one receptor and one enzyme 398
D. Other examples of dual acting drugs 400
IV. Binding Mode Analysis of Identical and Non-identical Twin Drugs 401
A. Identical and non-identical twin drugs interacting with two adjacent binding sites located on the same macromolecule 403
B. Identical twin drugs interacting with two similar binding sites located on different monomers of the same macromolecule 405
C. Identical and non-identical twin drugs interacting with two different binding sites located on different macromolecules 408
V. Conclusion 409
References 410

19. Application Strategies for the Primary Structure–Activity Relationship Exploration 415
Camille G. Wermuth

I. Introduction 415
II. Preliminary Considerations 415
III. Hit Optimization Strategies 416
A. Some information about the target is available 417
B. No information about the target is available 418
C. The predominant objective is potency 418
D. The predominant objective is the establishment of SARs 419
E. The predominant objective consists of analog design 422
IV. Application Rules 422
A. Rule number one: the minor modification rule 422
B. Rule number two: the biological logic rule 423
C. Rule number three: the structural logic's rule 424
D. Rule number four: the right substituent choice 424
E. Rule number five: the easy organic synthesis (EOS) rule 425
F. Rule number six: eliminate the chiral centers! 425
G. Rule number seven: the pharmacological logic rule 426
References 426

Part IV Substituents and Functions: Qualitative and Quantitative Aspects of Structure–Activity Relationships
Section Editor: Han van de Waterbeemd 429

20. Substituent Groups 431
Patrick Bazzini and Camille G. Wermuth

I. Introduction 431
II. Methyl Groups 432
A. Effects on solubility 432
B. Conformational effects 434
C. Electronics effects 435
D. Effects on metabolism 437
E. Extensions to other small alkyl groups 440

III. Effects of Unsaturated Groups 441
A. Vinyl series 442
B. Allylic series 443
C. Acetylenic series 445
D. Cyclenic equivalents of the phenyl ring 447
IV. Effects of Halogenation 448
A. The importance of the halogens in the structure–activity relationship 448
B. Usefulness of the halogens and of cognate functions 451
V. Effects of Hydroxylation 452
A. Effects on solubility 453
B. Effects on the ligand–receptor interaction 453
C. Hydroxylation and metabolism 453
VI. Effects of Thiols and Other Sulfur-Containing Groups 454
A. Drugs containing thiol 454
B. Drugs containing oxidized sulfides 454
C. Drugs containing thiocyanate or thiourea 454
VII. Acidic Functions 456
A. Effects on solubility 456
B. Effects on biological activity 457
VIII. Basic Groups 458
IX. Attachment of Additional Binding Sites 459
A. To increase lipophilicity 459
B. To achieve additional interactions 459
References 460

21. The Role of Functional Groups in Drug–Receptor Interactions 464
Laurent Schaeffer

I. Introduction 464
II. General Principles 464
III. The Importance of the Electrostatic and Steric Match Between Drug and Receptor 465
A. Electrostatic interactions 465
B. Steric interactions 471
C. Enthalpy/entropy compensation 472
IV. The Strengths of Functional Group Contributions to Drug–Receptor Interactions 473
A. Measuring functional group contributions 473
B. The methyl group and other nonpolar substituents 475
C. The hydroxyl group and other hydrogen-bond forming substituents 476
D. Acidic and basic substituents 476
E. Practical applications for the medicinal chemist 476
F. Ligand efficiency 478
V. Cooperative binding 478
References 479

22. Compound Properties and Drug Quality 481
Christopher A. Lipinski

I. Introduction 481
II. Combinatorial Libraries 482
A. Library design for HTS screens 482
B. Experimental synthesis success rate 483
C. Poor solubility and library design 483
D. Importance of the synthesis rate-determining step 483
E. If protocol development is rate determining 484
F. Poor ADME properties – business aspects 484

G. If library production is rate determining 484
H. Relative importance of ADME assays 484
III. Chemistry Control of Intestinal Permeability 484
A. Improving permeability 485
B. Hydrogen bonding and permeability 485
C. Intramolecular hydrogen bonds 485
D. Permeability testing 485
IV. Chemistry Control of Aqueous Solubility 486
A. The definition of poor solubility 486
B. Aqueous solubility and blunt SAR 486
C. Changing the pK_a 486
D. Improving aqueous solubility 487
V. I*n Vitro* Potency and Chemistry Control 487
A. Lead complexity 487
VI. Metabolic stability 488
A. ADME computational models 488
B. Limitations of Caco-2 cell culture 488
C. Poor aqueous solubility and permeability assay noise 489
D. Physiologically-relevant screening concentration 489
VII. Acceptable Solubility Guidelines for Permeability Screens 489
A. Batch-mode solubility prediction 490
References 490

23. Quantitative Approaches to Structure–Activity Relationships 491
Han van de Waterbeemd and Sally Rose

I. Introduction to QSAR 491
II. Brief History and Outlook 492
III. QSAR Methodology 493
A. Descriptors 493
B. Methods for building predictive models 496
C. Global and local models, and consensus modeling 503
D. Time-series behavior and autoQSAR 503
E. Experimental design 504
F. Inverse QSAR and multi-objective optimization 505
IV. Practical Applications 505
A. Limitations and appropriate use 505
B. Examples 506
C. Library design, compound acquisition and profiling 508
D. HTS analysis 509
E. Software 509
References 510

Part V Spatial Organization, Receptor Mapping and Molecular Modeling
Section Editor: David J. Triggle 515

24. Overview: The Search for Biologically Useful Chemical Space 517
David J. Triggle

I. Introduction 517
II. How Big is Chemical Space? 518
III. Biological Space is Extremely Small 518
IV. Limited Biological Space as an Effective Biological Strategy 519
References 520

25. Pharmacological Space 521
Andrew L. Hopkins

I. What is Pharmacological Space? 521
II. Chemical Space 521
A. Drug-like space 522
III. Target Space 524
A. Druggability 525
B. Structure-based druggability 526
C. Degrees of druggability 527
D. Druggable genome 529
VI. Conclusions 531
Acknowledgments 531
References 531

26. Optical Isomerism in Drugs 533
Camille G. Wermuth

I. Introduction 533
II. Experimental Facts and Their Interpretation 533
A. Stereoselectivity in biologically active compounds 533
B. The three-point contact model 535
C. Diastereoisomers 537
D. Stereoselectivity ratios 537
E. Pfeiffer's rule 538
III. Optical Isomerism and Pharmacodynamic Aspects 538
A. Differences in potency and antagonism between two enantiomers 538
B. Differences in the pharmacological profile of two enantiomers 539
IV. Optical Isomerism and Pharmacokinetic Effects 539
A. Isomer effects on absorption and distribution 540
B. Isomer effects on metabolism 540
C. Isomer effects on uptake 541
D. Isomer effects on excretion 541
V. Practical Considerations 541
A. Racemates or enantiomers? 541
B. The distomer counteracts the eutomer 542
C. Racemic switches 542
D. The distomer is metabolized to unwanted or toxic products 542
E. Deletion of the chiral center 543
F. Usefulness of racemic mixtures 543
References 546

27. Multi-Target Drugs: Strategies and Challenges for Medicinal Chemists 549
Richard Morphy and Z. Rankovic

I. Introduction 549
II. Strategies for Lead Generation 551
III. Main Areas of Focus in DML Discovery (1990–2005) 553
A. SERT-plus DMLs for depression 554
B. Dopamine D_2-plus DMLs for schizophrenia 555
C. DMLs targeting the angiotensin system for hypertension 555
D. Histamine H_1-plus DMLs for allergies 558
E. AChE-based DMLs for Alzheimer's disease 559
F. PPAR-based DMLs for metabolic disease 560
G. DMLs that inhibit multiple kinases for treating cancer 560

H. DMLs targeting the arachidonic acid cascade 561
I. Mu-opioid-plus DMLs for treating pain 563
IV. Optimization of the Activity Profile and Wider Selectivity 563
V. The Physicochemical Challenge 565
VI. Summary 568
References 569

28. Pharmacophore Identification and Pseudo-Receptor Modeling 572
Wolfgang Sippl

I. Introduction 572
A. Historical background 573
B. Definitions 573
C. Importance of the pharmacophore concept 574
D. Application of pharmacophores 574
II. Methodology 575
A. Pharmacophore modeling 575
III. Advanced approaches 577
A. Structure-based pharmacophores 577
B. Pseudo-receptor models 579
IV. Application study 580
A. Pharmacophore-based screening for novel histamine H_3-receptor antagonists 580
B. Pharmacophore determination process 581
C. Pharmacophore-based screening of compound libraries 582
V. Conclusions 584
References 584

29. 3D Quantitative Structure–Property Relationships 587
Thierry Langer and Sharon D. Bryant

I. Introduction 587
II. 3D QSAR Workflow 589
III. 3D QSAR: Conformation Analysis and Molecular Superimposition 590
IV. Calculation of 3D Molecular Field Descriptors 591
V. Statistical Tools 592
VI. Alignment Independent 3D QSAR Techniques 592
VII. Validation Of 3D QSAR Models 594
VIII. Applications 594
A. 3D QSAR study on the structural requirements for inhibiting AChE 594
B. 3D QSAR as a tool to determine molecular similarity 597
IX. Conclusions and Future Directions 601
References 601

30. Protein Crystallography and Drug Discovery 605
Jean-Michel Rondeau and Herman Schreuder

I. Presentation 605
II. Historical Background 607
A. The early days of crystallography 607
B. The current state of the art 607
C. Past and present contributions to drug discovery 608
III. Examples 609
A. Aliskiren (Tekturna™, Rasilez™) 609
B. Nilotinib (Tasigna™) 610
IV. Basic Principles and Methods of Protein Crystallography 611
A. Crystallization 611

B. Data collection 615
C. From diffraction intensities to a molecular structure 615
D. Information content and limitations of crystal structures 618
V. Practical Applications 621
A. Target identification, selection and validation 621
B. Hit/lead generation 623
C. Lead optimization 627
References 629

Part VI Chemical Modifications Influencing the Pharmacokinetic Properties
Section Editor: Richard B. Silverman 635

31. Physiological Aspects Determining the Pharmacokinetic Properties of Drugs 637
Koen Boussery, Frans M. Belpaire and Johan Van de Voorde

I. Introduction 637
II. Passage of Drugs Through Biological Barriers 638
A. Transcellular drug transport 638
B. Paracellular drug transport 640
III. Drug Absorption 640
A. Dosage form of the drug 640
B. GI motility and gastric emptying 640
C. GI permeability to the drug 642
D. Perfusion of the GI tract and the first-pass effect 643
IV. Drug Distribution 644
A. Plasma protein binding 644
B. Drug accumulation 645
C. The blood–brain barrier 645
V. Drug Elimination 645
A. Excretion 645
B. Biotransformation 647
VI. Some Pharmacokinetic Parameters and Terminology 648
A. Plasma concentration–time curve 648
B. Volume of distribution 649
C. Clearance 650
D. Elimination half-life ($T_{1/2}$) 651
E. Bioavailability 651
VII. Variability in Pharmacokinetics 652
A. Genetic factors 652
B. Age 652
C. Drug interactions 653
D. Disease state 653
E. Pregnancy 653
Bibliography 654

32. Biotransformation Reactions and their Enzymes 655
Bernard Testa

I. Introduction 655
II. Functionalization Reactions 656
A. Enzymes catalyzing functionalization reactions 657
B. Reactions of carbon oxidation and reduction 660
C. Oxidation and reduction of N- and S-containing moieties 662
D. Reactions of hydration and hydrolysis 663

III. Conjugation Reactions 664
A. Introduction 664
B. Methylation 665
C. Sulfonation 665
D. Glucuronidation 665
E. Acetylation 667
F. Conjugation with coenzyme A and subsequent reactions 668
G. Conjugation reactions of glutathione 669
IV. Biological Factors Influencing Drug Metabolism 671
V. Concluding Remarks 672
References 672

33. Biotransformations Leading to Toxic Metabolites: Chemical Aspects 674
Anne-Christine Macherey and Patrick M. Dansette

I. Historical Background 674
II. Introduction 675
III. Reactions Involved in the Bioactivation Process 676
A. Oxidation 676
B. Oxidative stress 678
C. Reduction 680
D. Substitutions: hydrolysis and conjugation 682
E. Eliminations 683
F. Further biotransformations leading to the ultimate toxicant 683
IV. Examples of Metabolic Conversions Leading to Toxic Metabolites 685
A. Acetaminophen 685
B. Tienilic acid 687
C. Halothane 688
D. Valproic acid 690
E. Troglitazone 691
V. Conclusion 693
References 694

34. Drug Transport Mechanisms and their Impact on the Disposition and Effects of Drugs 697
Jean-Michel Scherrmann

I. Introduction 697
II. Biology and Function of Transporters 698
A. Modes of active transport 698
B. Genes and classification 698
C. Basic structure 699
D. Distributions and properties of transporters in tissues 699
III. Transporters in Drug Disposition 702
A. ABC transporters 702
B. SLC transporters 703
IV. Roles of Transporters in Drug Pharmacokinetics, Pharmacodynamics and Toxicology 705
A. Intestinal absorption 705
B. Liver and hepatic clearance 706
C. Blood barriers and tissue distribution 707
D. Kidney and renal clearance 707
V. Conclusion 709
Acknowledgments 709
References 709

35. Strategies for Enhancing Oral Bioavailability and Brain Penetration 711
Brian C. Shook and Paul F. Jackson

I. Introduction 711
II. Enhancing Oral Bioavailability 711
A. Metabolic stability 711
B. Structural rigidity 712
C. pK_a 713
D. Hydrogen bond interactions 713
E. Miscellaneous 715
III. Enhancing Brain Penetration 715
A. Metabolic stability 715
B. pK_a 716
C. Log P 717
D. Hydrogen bond interactions 718
IV. Conclusion 719
References 719

36. Designing Prodrugs and Bioprecursors 721
Camille G. Wermuth

I. Introduction 721
II. The Different Kinds of Prodrugs 721
A. Definitions and classifications 721
B. The carrier prodrug principle 722
C. The bioprecursor-prodrug principle 723
D. Other categories of prodrugs 724
E. Practical applications of prodrug design 724
III. Carrier Prodrugs: Application Examples 724
A. Improvement of the bioavailability and the biomembrane passage 724
B. Site-specific delivery 728
C. Prolonged duration of action 730
IV. Particular Aspects of Carrier Prodrug Design 731
A. Use of cascade prodrugs 731
B. Codrugs 734
C. Soft drugs 734
D. Carrier prodrugs: conclusion 734
V. Bioprecursor Prodrugs: Application Examples 735
A. Oxidative bioactivations 735
B. Reductive bioactivations 737
C. Mixed bioactivation mechanism 738
D. Reactions without change in the state of oxidation 740
VI. Discussion 740
A. Bioprecursors versus carrier prodrugs 740
B. Existence of mixed-type prodrugs 740
VII. Difficulties and Limitations 741
VIII. Conclusion 742
References 742

Part VII Pharmaceutical and Chemical Means to Solubility and Formulation Problems
Section Editor: Michael J. Bowker 747

37. Preparation of Water-Soluble Compounds through Salt Formation 749
Michael J. Bowker and P. Heinrich Stahl

I. Introduction 749
II. The Solubility of Compounds in Water 750

A. The determination and prediction of solubility 750
B. Ionization of drugs and the importance of pK_a 751
III. Acids and Bases Used in Salt Formation 751
IV. Early salt formation studies 753
A. Choice of salt formers 753
B. Prediction of the pH of the salt in solution 754
C. Search for crystalline salts 755
V. Comparison of Different Crystalline Salts 755
A. Melting point 756
B. Aqueous solubility 756
C. Common ion and indifferent electrolyte effects 758
D. Hygroscopicity 758
E. Solubility in co-solvents (water-miscible solvents) 759
F. Dissolution Rate 759
G. Particle size and crystal morphology 760
H. Polymorphism and pseudopolymorphism 760
I. Chemical stability 761
J. Other properties 761
VI. Implications of Salt Selection on Drug Dosage Forms 762
A. Tablet products 762
B. Hard gelatine capsules 763
C. Parenteral solutions 763
D. Oral solutions 763
E. Suspension formulations 763
F. MDI products 764
G. DPI products 764
H. Soft gelatine capsule formulations 764
I. Emulsions, creams and ointments 764
VII. Conclusion 765
References 765

38. Preparation of Water-Soluble Compounds by Covalent Attachment of Solubilizing Moieties 767
Camille G. Wermuth

I. Introduction 767
II. Solubilization Strategies 768
A. How will the solubilizing moiety be grafted? 768
B. Where will it be grafted? 768
C. What kind of solubilizing chain will be utilized? 768
III. Acidic Solubilizing Chains 769
A. Direct introduction of acidic functions 769
B. Alkylation of OH and NH functions with acidic chains 769
C. Acylation of OH and NH functions with acidic chains 770
IV. Basic Solubilizing Chains 775
A. Direct attachment of a basic residue 775
B. Bioisosteric exchange of a basic functionality 776
C. Development of a water-soluble prodrug of diazepam 776
D. Attachment of the solubilizing moiety to an alcoholic hydroxyl 777
E. Attachment of the solubilizing moiety to an acidic NH function 779
F. Attachment of the solubilizing moiety to a basic NH_2 function 779
G. Attachment of the solubilizing moiety to carboxylic acid functionalities 780
V. Non-ionizable Side Chains 780
A. Glycolyl and glyceryl side chains 780
B. Polyethylene glycol derivatives 781
C. Glucosides and related compounds 781

VI. Concluding Remarks 782
References 783

39. Drug Solubilization with Organic Solvents, or Using Micellar Solutions or Other Colloidal Dispersed Systems 786
Michael J. Bowker and P. Heinrich Stahl

I. Introduction 786
II. Factors Controlling Solubility and Absorption 788
A. The nature of drug substances 788
B. The polarity of the solvent system 788
III. Water–cosolvent systems 789
IV. Solubilization Mediated by Surfactants 793
V. Solubilization by Lipid Vehicles 798
A. Emulsions and microemulsions 798
B. Liposomes 802
VI. Nanoparticles and Other Nanocolloidal Technologies 803
VII. Drug Delivery and Clearance Mechanisms of Nanocolloids 806
VIII. Drug Delivery and Accumulation Using Colloidal Systems for the Treatment of Cancer 807
A. Liposome formulations 807
B. Formulations based on nanoparticles, microparticles and conjugated systems 808
IX. Modification of Drug Toxicity by Nanocolloidal Drug Delivery Systems 808
References 809

40. Improvement of Drug Properties by Cyclodextrins 813
Kaneto Uekama and Fumitoshi Hirayama

I. Introduction 813
II. Pharmaceutically Useful CyDs 813
A. Physicochemical profiles of CyDs 814
B. Biological profiles of CyDs 814
III. Improvement of Drug Properties 816
A. Solubilization 817
B. Stabilization in solution 818
C. Control of solid properties 819
D. Release control 821
E. Enhancement of drug absorption 822
F. Reduction of side-effects 824
G. Use in peptide and protein drugs 826
H. Combined use of CyDs with additives 829
IV. CyD-Based Site-Specific Drug Delivery 831
A. Colon targeting 832
B. Cell targeting 834
C. Brain targeting 835
V. Conclusion 835
References 835

41. Chemical and Physicochemical Approaches to Solve Formulation Problems 841
Camille G. Wermuth

I. Introduction 841
II. Increasing Chemical Stability 841
III. Improved Formulation of Peptides and Proteins 844
IV. Dealing with Mesomorphic Crystalline Forms 845
V. Increasing the Melting Point 846
A. Salt or complex formation 846
B. Covalent derivatives 846

C. Introduction of symmetry 847
VI. Gastrointestinal Irritability and Painful Injections 847
A. Gastrointestinal irritability 847
B. Avoidance of painful injections 848
VII. Suppressing Undesirable Organoleptic Properties 849
A. Odor 849
B. Taste 850
References 852

Part VIII Development of New Drugs: Legal and Economic Aspects
Section Editor: Bryan G. Reuben 855

42. Discover a Drug Substance, Formulate and Develop It to a Product 857
Bruno Galli and Bernard Faller

I. Introduction 857
II. Discover the Drug Substance 857
A. Exploratory research (target finding) 858
B. Early discovery program (lead finding) 858
C. Mature discovery program (lead optimization) 858
D. Research–development interface 859
E. Learning experiences 859
III. Defining Experimental Formulations, The Creative Phase 859
A. Basic thoughts on oral formulation 859
B. What is the purpose of a formulation? 859
C. Suggested sequence of activities prior to start formulation 860
D. Biopharmaceutical classification of compounds 861
E. How do we proceed at a practical level? 861
F. Which formulation principles are used? 862
IV. Pharmaceutical Development in Industry 863
V. Fixing The Quality And Develop The Product in A Regulated Environment 865
References 866

43. Drug Nomenclature 867
R. G. Balocco Mattavelli, J.C. Dong, S. Lasseur and S. Kopp

I. Introduction 867
II. Trade Names and Nonproprietary Names 867
III. Drug Nomenclature 868
A. INNs for pharmaceutical substances 868
B. Common names selected by the International Standards Organization (ISO) 874
IV. Use and Protection of Nonproprietary Names 874
A. Use of nonproprietary names 874
B. Protection of nonproprietary names 874
V. Summary 875
References 875
Annex 875

44. Legal Aspects of Product Protection: What a Medicinal Chemist Should Know about Patent Protection 878
Maria Souleau

I. Introduction 878
A. History of the patent-system prior to 1883 878
B. Main conventions and treaties 879

II. Definition of A Patent – Patent Rights 882
III. Kind of Inventions 882
IV. Subjects of Patents: Basic and Formal Requirements for Filing a Patent 882
A. Basic requirements 882
B. Formal requirements 888
V. Lifetime of Patents 890
VI. Ownership of Patents 890
VII. Infringement of a Patent 890
VIII. Patents as a Source of Information 891
IX. Patenting in the Pharmaceutical Industries 891
X. Conclusion 892
References 892

45. The Consumption and Production of Pharmaceuticals 894
Bryan G. Reuben

I. "Important" Drugs 895
A. The top-earning drugs 895
B. The most widely prescribed drugs 895
C. National differences in prescribing 899
II. Sources of Drugs 902
A. Vegetable sources 902
B. Animal sources 902
C. Biological sources 902
D. Fermentation 903
E. Chemical synthesis 903
III. Manufacture of Drugs 903
A. Good manufacturing practice 904
B. Plant design 904
C. Formulation and packaging–sterile products 905
D. Choice of reagents 906
E. "Green" chemistry 906
F. Downstream processing 907
G. Outsourcing 907
IV. Social and Economic Factors 909
A. Pattern and cost of innovation 909
B. Patents 910
C. Orphan drugs 911
D. Generic pharmaceuticals 912
E. Parallel trade 914
F. Cost containment measures 914
G. Pharmacoeconomics 916
V. The Future of the Pharmaceutical Industry 918
A. Trends in pharmaceuticals 919
B. Conclusion 920
References 920

Index 923

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.

This page intentionally left blank

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.

This page intentionally left blank

Contributors

Raffaella. G. Balocco Mattavelli
Manager of the International Nonproprietary
Names Programme
Quality Assurance & Safety: Medicines
World Health Organization
20, av. Appia
CH-1211, Geneva 27

Paul L. Bartel
Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, UT 84108
USA

Patrick Bazzini
Prestwick Chemical Inc.
Boulevard Gonthier
d'Andernach
67400 Illkirch
France

Frans M. Belpaire
Heymans Institute for Pharmacology
Jeroom Duquesnoylaan 37
9051 Gent
Belgium

Koen Boussery
Laboratory of Medical Biochemistry and Clinical Analysis
Faculty of Pharmaceutical Sciences
Gent University
Harelbekestraat 72
9000 Gent
Belgium

Michael J. Bowker
M.J. Bowker Consulting Ltd.
36, Burses Way
Hutton, Brentwood
Essex CM13 2PS
UK

Sharon D. Bryant
Medicinal Chemistry Group
Laboratory of Pharmacology and Chemistry
National Institute of Environmental Health Sciences
P.O. Box 12233, MD: B3-05
Research Triangle Park, NC 27709
USA

David Cavalla
Arachnova
St. John's Innovation Centre
Cambridge CB4 4WS
UK

François Chast
Pharmacy, Pharmacology, Toxicology Department
Hôtel-Dieu
1, Place du Parvis Notre-Dame
75004 Paris
France

Paola Ciapetti
Head of Medicinal Chemistry
Novalyst Discovery
Boulevard Sébastien Brant BP 30170
F-67405 Illkirch Cedex
France

Jean-Marie Contreras
Prestwick Chemical Inc.
Boulevard Gonthier d'Andernach
67400 Illkirch
France

Gordon M. Cragg
Natural Products Branch
National Cancer Institute
1003 W 7th Street, Suite 206
Frederick, MD 21701
USA

Patrick M. Dansette
Laboratoire de Chimie et Biochimie
Pharmacologiques et Toxicologiques
Université PARIS Descartes
UMR 8601 – CNRS
45, Rue des Saints Pères
F-75270 Paris Cedex 06
France

Ji-Cui Dong
International Nonproprietary Names Programme
Quality Assurance & Safety: Medicines
World Health Organization
20, av. Appia
CH-1211, Geneva 27

Bernard Faller
Novartis Pharma AG
Werk Klybeck
Klybeckstrasse 141
WKL-122.P.33
CH-4057 Basel
Switzerland

Bennett T. Farmer
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
USA

Bruno Galli
Novartis Pharma AG
TRD-PTM WSJ-340-451
Lichtstrasse 35
CH-4056 Basel
Switzerland

Jean-Pierre Gies
Université Louis Pasteur
Faculté de Pharmacie
Equipe de Signalisation Cellulaire
74, Route du Rhin
67401 Illkirch-Cedex,
France

Bruno Giethlen
Prestwick Chemical Inc.
Boulevard Gonthier d'Andernach
67400 Illkirch
France

Fumitoshi Hirayama
Faculty of Pharmaceutical Sciences
Sojo University
4-22-1 Ikeda
Kumamoto 860-0082
Japan

Adrian N. Hobden
Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, UT 84108
USA

Andrew L. Hopkins
Division of Biological Chemistry and Drug Discovery
College of Life Sciences
University of Dundee
Dundee
Scotland DD1 5EH
UK

Peter Imming
Institut für Pharmazie
Martin-Luther-Universitaet Halle-wittenberg Wolfgang-Langenbeck-Str. 4
06120 Halle (Saale) Germany

Paul F. Jackson
Johnson & Johnson
Pharmaceutical R&D, L.L.C.
Welsh McKean Roads
P.O. Box 776
Spring House, PA 19477
USA

David G. I. Kingston
Virginia Polytechnic Institute & State University
Department of Chemistry, M/C 0212
3111 Hahn Hall
West Campus Drive
Blacksburg, VA 24061
USA

Sabine Kopp
Medicines Quality Assurance Programme
Quality Assurance & Safety: Medicines
World Health Organization
20, av. Appia
CH-1211 Geneva 27

Hugo Kubinyi
Donnersbergstrasse 9
67256 Weisenheim am Sand
Germany

Kamal Kumar
Max Planck Institute of Molecular Physiology
Otto-Hahn-Str. 11
D-44227 Dortmund
Germany

Yves Landry
Université Louis Pasteur
Faculté de Pharmacie
Equipe de Signalisation Cellulaire
74, Route du Rhin
67401 Illkirch-Cedex,
France

Thierry Langer
Inte:Ligand GmbH
Clemens Maria Hofbauer-G.6
2344 Maria Enzersdorf
Austria

Institute of Pharmacy
University of Innsbruck
Innrain 52
6020 Innsbruck
Austria

Sophie Lasseur
International Nonproprietary Names Programme
Quality Assurance & Safety: Medicines
World Health Organization
20, av. Appia
CH-1211, Geneva 27

Christopher A. Lipinski
Melior Discovery
10 Conshire Drive
Waterford, CT 06385-4122
USA

Anne-Christine Macherey
Unité de Prévention du Risque Chimique
UPS 831–Bat.11
CNRS
Avenue de la Terrasse
F-91198 Gif sur Yvette Cedex
France

André Mann
Département de Pharmacochimie de la Communication Cellulaire
UMR 7175 LC 1 ULP/CNRS
Faculté de Pharmacie
74 route du Rhin
67401 Illkirch
France

Christophe Morice
Prestwick Chemical Inc.
Boulevard Gonthier
d'Andernach
67400 Illkirch
France

Richard Morphy
Organon Laboratories Ltd.
A part of the Schering Plough Corporation
Newhouse
Lanarkshire
Scotland ML1 5SH
UK

David J. Newman
Natural Products Branch
National Cancer Institute
1003 W 7th Street, Suite 206
Frederick, MD 21701
USA

Jean-Pierre Nowicki
Sanofi-Aventis RD
31, Avenue Paul Vaillant-Couturier
92220 Bagneux
France

Alex Polinsky
Research Technologies
Pfizer Global Research and Development
620 Memorial Drive
Cambridge, MA 02138
USA

John R. Proudfoot
Boehringer Ingelheim
Pharmaceuticals Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
USA

Z. Rankovic
Organon Laboratories Ltd.
A part of the Schering Plough Corporation
Newhouse
Lanarkshire
Scotland ML1 5SH
UK

Allen B. Reitz
Johnson & Johnson
Pharmaceutical Research and Development, LLC
Welsh McKean Rds.
Spring House, PA 19477
USA

Bryan G. Reuben
London South Bank University
24 Claverley Grove
London N3 2DH
UK

Jean-Michel Rondeau
Novartis Pharma AG
Novartis Institutes for BioMedical Research
WSJ-88.8.08A
CH-4056 Basel
Switzerland

Sally Rose
Cresset BioMolecular Discovery Ltd
BioPark Hertfordshire
Broadwater Road
Welwyn Garden City
Herts., AL7 3AX
UK

Bernard Scatton
Sanofi-Aventis RD
31, Avenue Paul Vaillant-Couturier
92220 Bagneux
France

Laurent Schaeffer
Prestwick Chemical Inc.
Boulevard Gonthier
d'Andernach
67400 Illkirch
France

Jean-Michel Scherrmann
INSERM U 705; CNRS 7157
University Paris Descartes and Paris Diderot
Department of Pharmacokinetics Faculty of Pharmacy
4, avenue de l'Observatoire
75006 Paris
France

Herman Schreuder
Aventis Pharma Deutschland GmbH
Building G 6865A
D-65926 Frankfurt am Main
Germany

Brian C. Shook
Johnson & Johnson
Pharmaceutical R&D, L.L.C.
Welsh McKean Roads
P.O. Box 776
Spring House, PA 19477
USA

Richard B. Silverman
Department of Chemistry
Northwestern University
2145, Sheridon Road
Evanston, IL 60208-3113
USA

Wolfgang Sippl
Department of Pharmaceutical Chemistry
Martin-Luther-Universität Halle-Wittenberg
Wolfgang-Langenbeck-Str. 4
06120 Halle (Saale)
Germany

Maria Souleau
Sanofi-Aventis
20, Rue Raymond Aron
92160 Antony
France

P. Heinrich Stahl
Lerchenstrasse 28
79104 Freiburg im Breisgau
Germany

Bernard Testa
Service de Pharmacie, CHUV
Centre Hospitalier Universitaire Vaudois
Rue du Bugnon 46
CH-1011 Lausanne
Switzerland

David J Triggle
SUNY at Buffalo
School of Pharmaceutical Sciences
126 Cooke Hall
Buffalo, NY 14260
USA

Kaneto Uekama
Faculty of Pharmaceutical Sciences
Sojo University
4-22-1 Ikeda
Kumamoto 860-0082
Japan

Johan Van de Voorde
Ghent University
Vascular Research Unit
De Pintelaan 185 – Blok B
9000 Gent
Belgium

Han van de Waterbeemd
AstraZeneca
LG DECS, Global Compound Sciences
Alderley Park, 50S39
Macclesfield
Cheshire SK10 4TG
UK

Herbert Waldmann
Max Planck Institute of Molecular Physiology
Otto-Hahn-Str. 11
D-44227 Dortmund
Germany

Camille G. Wermuth
Prestwick Chemical Inc.
Boulevard Gonthier d'Andernach
67400 Illkirch
France

Stefan Wetzel
Max Planck Institute of Molecular Physiology
Otto-Hahn-Str. 11
D-44227 Dortmund
Germany

Kenton H. Zavitz
Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, UT 84108
USA

This page intentionally left blank

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

This page intentionally left blank

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!

Camille G. Wermuth

This page intentionally left blank

Part I

General Aspects of Medicinal Chemistry

Hugo Kubinyi

Section Editor

This page intentionally left blank

Chapter 1

A History of Drug Discovery

From first steps of chemistry to achievements in molecular pharmacology

François Chast

I. INTRODUCTION
A. The renewal of chemistry
B. The dawn of the organic chemistry crosses the birth of biology
II. TWO HUNDRED YEARS OF DRUG DISCOVERIES
A. Pain killers: best-sellers and controversies
B. Giving back the heart its youth
C. Fight against microbes and viruses
D. Drugs for immunosuppression
E. Contribution of chemists to the fight against cancer
F. Drugs for endocrine disorders
G. Anti-acid drugs
H. Lipid lowering drugs
I. From neurotransmitters to receptors
J. Drugs of the mind
III. CONSIDERATIONS ON RECENT TRENDS IN DRUG DISCOVERY
A. From genetics to DNA technology
B. Hopes and limits for drug hunting
REFERENCES

Le médicament place l'organisme dans des conditions particulières qui en modifient heureusement les procédés physiques et chimiques lorsqu'ils ont été troublés.

Claude Bernard*

During more than 2,000 years, Hippocratic medical tradition weighed on the development of a modern medicine and a renewed approach of the treatment of diseases. The basis for the use of drugs remained founded on empirical theories linked to the equilibrium of body's "humors" consisting in sanguine, melancholic, phlegmatic and choleric. Health and disease were seen as a question of balance or imbalance with foods and herbs classified according to their ability to affect natural homeostasis. Later, during the Middle Ages, Muslim world made significant contributions to medicine and a major medical advance was the founding of many hospitals and university medical schools.

Before the 1800s, pharmacy remained an empiric science, guided by traditional medicine, inherited from "Ancients." Numerous drugs, most of them being prepared with plant extracts, (Figure 1.1) sometimes efficacious, were available. But none of them could respond to a chemical definition of what we call today a drug, except drugs coming from mineral reign.

The technology of making drugs was crude at best: tinctures, poultices, soups, and infusions were made with water- or alcohol-based extracts of freshly ground or dried herbs or animal products such as bone, fat, or even pearls, and sometimes from minerals best left in the ground.[1]

The objective of this first chapter is to offer a presentation of the fabulous history of drug discoveries, from traditional pharmacy emerged from ethnopharmacy, till the recent

*Leçons sur les Effets de Substances Médicamenteuses et Toxiques (1857) deuxième leçon (5 mars 1856), p.38: "Drugs place the body in particular conditions which modify fortunately the physical and chemical processes when they have been disturbed."

FIGURE 1.1 Opium latex flowing out of poppy.

concepts of drug design, production and development, born from molecular genetics and molecular pharmacology.

Of course, it is not possible to describe exhaustively, in such a short chapter, such a complex and diversified history. We made the choice to describe the evolution of few families of drugs as examples of mankind ingenuity and intelligence to make pharmaceutical progress more and more successful in treating or preventing diseases.

I. INTRODUCTION

A. The renewal of chemistry

The 18th century concluded its progress in chemistry with an enthusiastic environment. Joseph Priestley in the United Kingdom, Carl Wilhelm Scheele in Sweden, Antoine Laurent de Lavoisier in France,[2] gave a precise signification to the chemical reactivity and promoted a large number of substances to the statute of chemical reagents. Scheele and Priestley prepared and studied oxygen. Both of them discovered nitrogen as a constituent of air, carbon monoxide, ammonia, and several other gases ; manganese, barium and chlorine; isolated glycerin and many acids, including tartaric, lactic, uric, prussic, citric, and gallic. Lavoisier is generally considered as the founder of modern chemistry as creating the oxygen theory of combustion.[3] He should be known as one of the most astonishing 18th century "men of the Enlightenment," the founder of modern scientific experimental methodology. By formulating the principle of the conservation of mass, he gave a clear differentiation between elements and compounds, something so important for pharmaceutical chemistry. Few years later, Antoine François de Fourcroy, Louis Nicolas Vauquelin, Joseph Louis Proust, Jöns Jakob Berzelius, Louis-Joseph Gay-Lussac, and Humphrey Davy introduced new concepts in chemistry. Those scientists integrated the practical advancements of a new generation of experimenters. All these industrial innovations would have their own impact on other developments in industrial and then medicinal chemistry.[4] At the turn of the 19th century, as the result of a scientific approach, drugs are becoming an industrial item. Claude Louis Berthollet began the industrial exploitation of chlorine (1785). Nicolas Leblanc prepared sodium hydroxide (1789) and then, bleach (1796). Davy performed electrolysis and distinguished between acids and anhydrides. Louis Jacques Thénard prepared hydrogen peroxide and Antoine Jérôme Balard discovered bromide (1826). The growing of therapeutic resources was mainly due to the mastery of chemical or physico-chemical principles proposed by Gay-Lussac and Justus Von Liebig.[5] This chemists' generation, by realizing all these discoveries, established the compost of the therapeutic discoveries of the 19th century. The constitution of chemistry as a scientific discipline found a new turn few decades later by crossing the road of biology which included revolutionary works of Claude Bernard,[6] Rudolph Virchow,[7] and Louis Pasteur.[8] Besides these fundamental sciences, physiology, biochemistry, or microbiology were becoming natural tributaries of the outbreak of pharmacology. Thus, rational treatments were about to be designed on the purpose of new knowledge in various clinical or fundamental fields. After a period characterized by extraction and purification from natural materials (mainly plants), drugs would be synthesized in chemical factories or prepared through biotechnology (fermentation or gene technology) after a rational research, design and development in research laboratories. Whereas the purpose was to isolate active molecules from plants during the first half of the 19th century, the birth of organic chemistry following charcoal and oil industries, progressively led chemists and pharmacists toward organic synthesis performed in what would be called "laboratory" a new concept created by this generation of scientists. Even when those laboratories hosted discoveries like active principles extracted from plants, progresses in drug compounding and packaging made irreversible industrialization processes. At the same time, the economical dimension of growing pharmaceutical industry transformed drugs as strategic items, mainly when it could interfere with military processes, for instance during colonial expeditions.

The "modern" word "*pharmacology*" became more and more often used by physicians after the works of François Magendie (Figure 1.2) in France or Oscar Schmiedeberg in Germany. Progressively a clear dichotomy took place between those two entities. *Materia Medica* considered drugs with a static and conservative view as for their