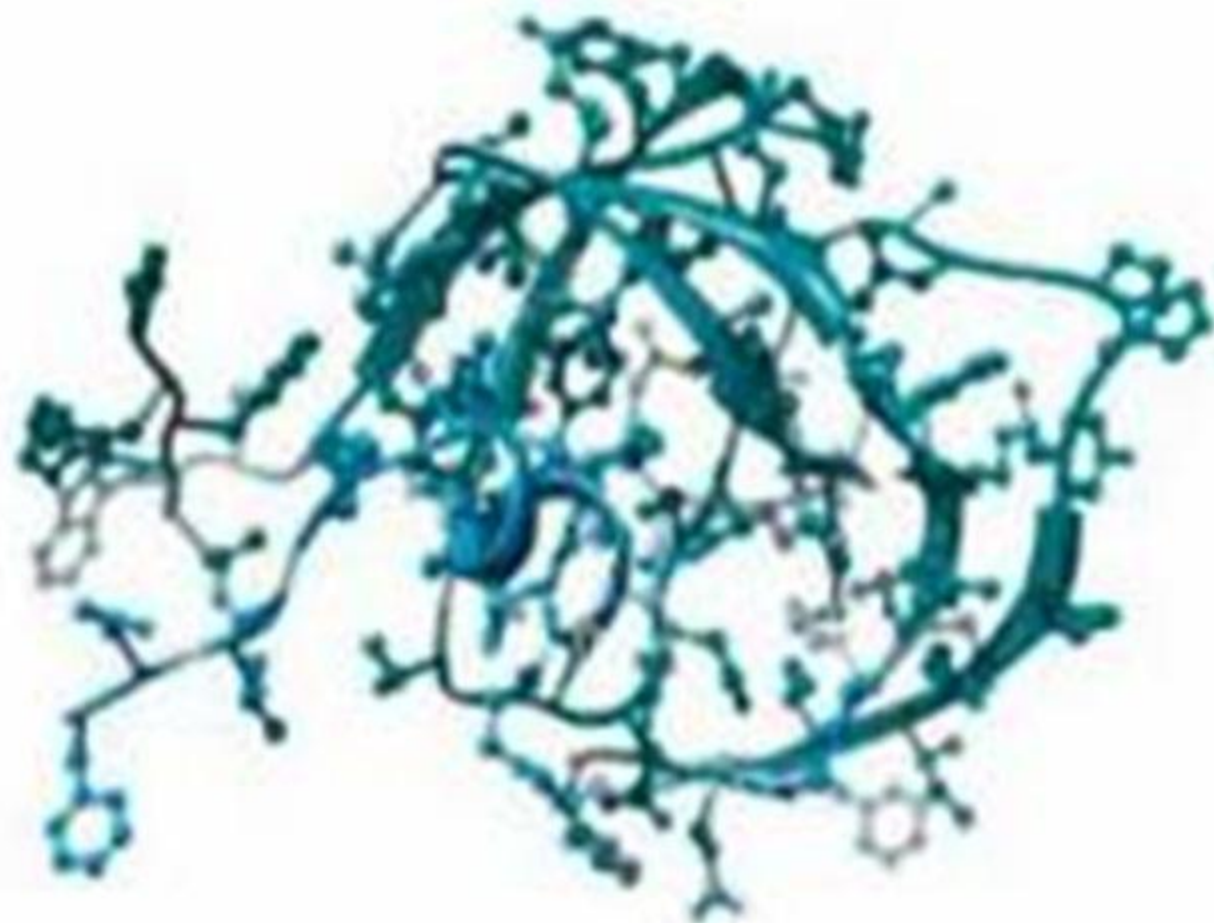


OXFORD

An Introduction to  
**Medicinal  
Chemistry**

FOURTH EDITION



Graham L. Patrick

An Introduction to

# Medicinal Chemistry

FOURTH EDITION

Graham L. Patrick

With a chapter on COMBINATORIAL AND PARALLEL SYNTHESIS  
co-authored by **John Spencer**

OXFORD  
UNIVERSITY PRESS

**OXFORD**

UNIVERSITY PRESS

Great Clarendon Street, Oxford OX2 6DP

Oxford University Press is a department of the University of Oxford.

It furthers the University's objective of excellence in research,  
scholarship, and education by publishing worldwide in

Oxford New York

Auckland Cape Town Dares Salaam Hong Kong Karachi

Kuala Lumpur Madrid Melbourne Mexico City Nairobi

New Delhi Shanghai Taipei Toronto

With offices in

Argentina Austria Brazil Chile Czech Republic France Greece

Guatemala Hungary Italy Japan Poland Portugal Singapore

South Korea Switzerland Thailand Turkey Ukraine Vietnam

Oxford is a registered trade mark of Oxford University Press in the UK  
and in certain other countries

Published in the United States

by Oxford University Press Inc., New York

© Graham L. Patrick 2009

The moral rights of the author have been asserted

Database right Oxford University Press (maker)

First published 2009

All rights reserved. No part of this publication may be reproduced,  
stored in a retrieval system, or transmitted, in any form or by any  
means, without the prior permission in writing of Oxford University  
Press, or as expressly permitted by law, or under terms agreed with the  
appropriate reprographics rights organization. Enquiries concerning  
reproduction outside the scope of the above should be sent to the Rights  
Department, Oxford University Press, at the address above

You must not circulate this book in any other binding or cover  
and you must impose the same condition on any acquirer

British Library Cataloguing in Publication Data

Data available

Library of Congress Cataloging in Publication Data

Data available

Typeset by Macmillan Publishing Solutions

Printed in Great Britain

on acid-free paper by Ashford Colour Press, Gosport, Hampshire

ISBN 978-0-19-923447-9

1 3 5 7 9 10 8 6 4 2

# Preface

This text is aimed at undergraduates and postgraduates who have a basic grounding in chemistry and are studying a module or degree in medicinal chemistry. It attempts to convey, in a readable and interesting style, an understanding about drug design and the molecular mechanisms by which drugs act in the body. In so doing, it highlights the importance of medicinal chemistry in all our lives and the fascination of working in a field which overlaps the disciplines of chemistry, biochemistry, physiology, microbiology, cell biology, and pharmacology. Consequently, the book is of particular interest to students who might be considering a future career in the pharmaceutical industry.

Following the success of the first three editions, as well as useful feedback from readers, there has been some reorganization and updating of chapters. Some case studies that were embedded in chapters now stand alone, and a couple of new case studies have been introduced that cover the statins and the antimalarial agent artemisinin.

Following the introductory chapter, the book is divided into five parts:

- Part A contains six chapters that cover the structure and function of important drug targets such as receptors, enzymes, and nucleic acids. Students with a strong background in biochemistry will already know this material, but may find these chapters a useful revision of the essential points.
- Part B covers pharmacodynamics in chapters 7–10, and pharmacokinetics in chapter 11. Pharmacodynamics is the study of how drugs interact with their molecular targets, and the consequences of those interactions. Pharmacokinetics relates to the issues involved in a drug reaching its target in the first place.
- Part C covers the general principles and strategies involved in discovering and designing new drugs and developing them for the marketplace.
- Part D looks at particular ‘tools of the trade’, which are invaluable in drug design—QSAR, combinatorial synthesis, and computer aided design.
- Part E covers a selection of specific topics within medicinal chemistry—antibacterial, antiviral and anti-cancer agents, cholinergics and anticholinesterases, adrenergics, opioid analgesics, and antiulcer agents. To some extent, those chapters reflect the changing emphasis in medicinal chemistry research. Antibacterial agents, cholinergics, adrenergics, and opioids have long histories, and much of the early development of these drugs relied heavily on random variations of lead compounds on a trial and error basis. This approach was wasteful but it led to the recognition of various design strategies which could be used in a more rational approach to drug design. The development of the antiulcer drug cimetidine (chapter 25) represents one of the early examples of the rational approach to medicinal chemistry. However, the real revolution in drug design resulted from giant advances made in molecular biology and genetics, which have provided a detailed understanding of drug targets and how they function at the molecular level. This, allied to the use of molecular modelling and X-ray crystallography, has revolutionized drug design. The development of protease inhibitors as antiviral agents (chapter 20) is a prime example of the modern approach.

G. L. P.  
Dec 2008

# About the book

The fourth edition of *An Introduction to Medicinal Chemistry* and its accompanying Online Resource Centre contains many learning features. This section illustrates each of these learning features and explains how they will help you to understand this fascinating subject.

## Emboldened key words

Terminology is emboldened and defined in a glossary at the end of the book, helping you to become familiar with the language of medicinal chemistry.

## Boxes

Boxes are used to present in-depth material and to explore how the concepts of medicinal chemistry are applied in practice. Boxes are grouped into three themes, General Interest, Synthesis, and Clinical Correlation. See page xix for a full list.

## Key points

Summaries at the end of major sections within chapters highlight and summarize key concepts and provide a basis for revision.

## Questions

End-of-chapter questions allow you to test your understanding and apply concepts presented in the chapter.

## Further reading

Selected references allow you easily to research those topics that are of particular interest to you.

## Appendices

The appendices include an index of drug names and their corresponding trade names, and an extensive glossary.

the surface of the macromolecule allowing the drug to sink into the body of the larger molecule. Some drugs react with the binding site and become permanently attached via a covalent bond that has a bond strength of 200–400 kJ mol<sup>-1</sup>. However, most drugs interact through weaker forms of interaction known as **intermolecular bonds**. These include electrostatic or ionic bonds, hydrogen bonds, van der Waals interactions, dipole-dipole interactions and hydrophobic interactions. (It is also possible for these interactions to take place *within* a molecule, in which case they are called **intramolecular**

with 'visiting' drugs. The specific regions where this takes place are known as **binding regions**. The study of how drugs interact with their targets through binding interactions is known as **pharmacodynamics**. Let us now consider the types of intermolecular bond that are possible.

### 1.3 Intermolecular bonding forces

There are several types of intermolecular bonding interactions, which differ in their bond strengths. The number

### BOX 12.8 Click chemistry *in situ*

A femtomolar inhibitor for the acetylcholinesterase enzyme was obtained by fragment self-assembly within the active site of the enzyme. One of the molecular fragments contained an azide group while the other contained an alkyne group. In the presence of the enzyme, both fragments were bound to the active site, and were positioned close enough to each other for an irreversible 1,3 dipolar cycloaddition to take place, forming the inhibitor *in situ*. This type of reaction has been called 'click chemistry *in situ*'.

The diagram illustrates the 1,3-dipolar cycloaddition reaction between an azide (H<sub>2</sub>N-CH<sub>2</sub>-N<sub>2</sub>) and an alkyne (R-C≡C-H). The reaction is catalyzed by an enzyme, forming a 1,2,3-triazole ring system (H<sub>2</sub>N-CH<sub>2</sub>-N-CH<sub>2</sub>-C(R)=C-H).

### KEY POINTS

- Strategies designed to target drugs to particular cells or tissues are likely to lead to safer drugs with fewer side effects.
- Drugs can be linked to amino acids or nucleic acid bases to target them against fast-growing and rapidly dividing cells.
- Drugs can be targeted to the gastrointestinal tract by making them ionized or highly polar such that they cannot cross the gut wall.
- The central nervous system side effects of peripherally act-

absorbed into the blood supply, but it is also important to ensure that any groups that are cleaved from the molecule are non-toxic.

### 14.6.1 Prodrugs to improve membrane permeability

#### 14.6.1.1 Esters as prodrugs

Prodrugs have proved very useful in temporarily masking an 'awkward' functional group which is important to

### QUESTIONS

1. Proflavine is a topical antibacterial agent that intercalates bacterial DNA and was used to treat wounded soldiers in the Far East during the Second World War. What role (if any) is played by the tricyclic ring and the primary amino groups? The drug cannot be used systemically. Suggest why this is the case.

Proflavine

adenine was synthesized early on in the evolution of life when the Earth's atmosphere consisted of gases such as hydrogen cyanide and methane. It has also been possible to synthesize adenine from hydrogen cyanide. Consider the structure of adenine and identify how cyanide molecules might act as the building blocks for this molecule.

4. The genetic code involves three nucleic acid bases coding

### FURTHER READING

Berg, C., Neumeier, K., and Kirkpatrick, P. (2003) Teriparatide. *Nature Reviews Drug Discovery*, **2**, 257–258.

Burke, M. (2002) Pharms market. *Chemistry in Britain*, June, 30–32 (antibiotics).

Duncan, R. (2003) The dawning era of polymer therapeutics. *Nature Reviews Drug Discovery*, **2**, 347–360.

Ezzell, C. (2011) Magic bullets fly again. *Scientific American*, October 29–31 (antibiotics).

Matthews, T., et al. (2004) Enfuvirtide: the first therapy to inhibit the entry of HIV-1 into host CD4 lymphocytes. *Nature Reviews Drug Discovery*, **3**, 215–225.

Moreland, L., Bate, G., and Kirkpatrick, P. (2006) Abatacept. *Nature Reviews Drug Discovery*, **5**, 185–186.

Opalinska, J. B., and Gewirtz, A. M. (2002) Nucleic-acid therapeutics: basic principles and recent applications. *Nature Reviews Drug Discovery*, **1**, 503–514.

## Appendix 3

### Statistical data for QSAR

To illustrate how statistical terms such as  $\bar{y}$ ,  $s$ , and  $F$  are derived and interpreted, the following numerical data will be used. There are 6 compounds in the study ( $n = 6$ ).  $Y_{ij}$  is the logarithm of the observed activity for each of the compounds and  $X$  is a physicochemical parameter. The QSAR equation and the calculated activity is  $Y_{ij} = Y_{ij} - Y_{ij}$  (Fig. A3.1). This is then squared and the values are added together to give the sum of the squares ( $SS_{ij}$ ).

$SS_{\text{res}}$  is a measure of how much the experimental activity varies from the mean of all the experimental activities and

# About the Online Resource Centre

Online Resource Centres provide students and lecturers with ready-to-use teaching and learning resources. They are free-of-charge, designed to complement the textbook, and offer additional materials that are suited to electronic delivery.

Many of these resources can be downloaded and can be fully customized, allowing them to be incorporated into your institution's existing virtual learning environment.

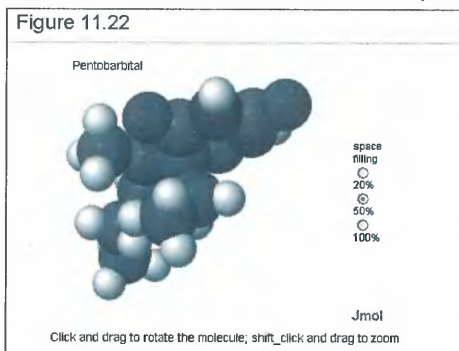
You will find this material at: [www.oxfordtextbooks.co.uk/orc/patrick4e/](http://www.oxfordtextbooks.co.uk/orc/patrick4e/)

The screenshot shows the Oxford University Press Online Resource Centre interface. At the top, it displays the book title 'Patrick: An Introduction to Medicinal Chemistry, 4e'. Below this, there are sections for 'Student resources' and 'Lecturer resources'. The 'Student resources' section includes '3D rotatable structures', 'Multiple choice questions and answers', and 'Links to articles cited in the book'. The 'Lecturer resources' section includes 'PowerPoint slides', 'Answers to end-of-chapter questions', and 'Test bank'. There are also links for 'About the book', 'Sample Content', and 'Keep me updated about this site'.

## Student resources

### Rotatable 3D structures

Fully interactive 3D models of selected molecules in the book help you to visualize them. All models kindly generated by Dr James Keeler, University of Cambridge.



### Online quiz

A range of multiple-choice questions for each chapter, to check your understanding, or for use as a revision tool.

### Hyperlinked bibliography

Direct links to online articles cited in the book.\*

### Updates

Six-monthly updates to the content in the fourth edition, focusing on fast-moving research areas.

## Lecturer resources

### Test Bank

A bank of multiple choice questions, which can be downloaded and customized for your teaching.

### Answers

Answers to end-of-chapter questions.

### Figures from the book

All of the figures from the textbook are available to download electronically for use in lectures and handouts.

### PowerPoint slides

PowerPoint slides are provided to help teach selected topics from the book.

\*Institutional subscription required for full text access

# Acknowledgements

The author and Oxford University Press would like to thank the following people who have given advice on the various editions of this textbook:

Dr Lee Banting, School of Pharmacy and Biomedical Sciences, University of Portsmouth, UK

Dr Don Green, Department of Health and Human Sciences, London Metropolitan University, UK

Dr Mike Southern, Department of Chemistry, Trinity College, University of Dublin, Ireland

Professor Mikael Elofsson, Department of Chemistry, Umeå University, Sweden

Dr Ed Moret, Faculty of Pharmaceutical Sciences, Utrecht University, The Netherlands

Professor John Nielsen, Department of Natural Sciences, University of Copenhagen, Denmark

Professor H. Timmerman, Department of Medicinal Chemistry, Vrije Universiteit, Amsterdam, The Netherlands

Professor Nouri Neamati, School of Pharmacy, University of Southern California, USA

Professor Kristina Luthman, Department of Chemistry, Gothenburg University, Sweden

Professor Taleb Altel, College of Pharmacy, University of Sharjah, United Arab Emirates

Professor Dirk Rijkers, Faculty of Pharmaceutical Sciences, Utrecht University, The Netherlands

Dr Sushama Dandekar, Department of Chemistry, University of North Texas, USA

Dr John Spencer, Medway School of Science, University of Greenwich, UK

Dr Angeline Kanagasooriam, School of Physical Sciences, University of Kent at Canterbury, UK

Dr A. Ganesan, School of Chemistry, University of Southampton, UK

Dr Rachel Dickins, Department of Chemistry, University of Durham, UK

Dr Gerd Wagner, School of Chemical Sciences and Pharmacy, University of East Anglia, UK

Dr Colin Fishwick, School of Chemistry, University of Leeds, UK

Professor Paul O'Neil, Department of Chemistry, University of Liverpool, UK

Professor Trond Ulven, Department of Chemistry, University of Southern Denmark, Denmark

Professor Jennifer Powers, Department of Chemistry and Biochemistry, Kennesaw State University, USA

Professor Joanne Kehlbeck, Department of Chemistry, Union College, USA

Dr Robert Sindelar, Faculty of Pharmaceutical Sciences, University of British Columbia, Canada

Professor John Carran, Department of Chemistry, Queen's University, Canada

Professor Anne Johnson, Department of Chemistry and Biology, Ryerson University, Canada

Dr Jane Hanrahan, Faculty of Pharmacy, University of Sydney, Australia

Dr Echel Forbes, School of Science and Engineering, University of West of Scotland

The author would like to express his gratitude to Dr John Spencer of the University of Greenwich for coauthoring chapter 16, on Combinatorial Synthesis, and for feedback during writing. Much appreciation is due to Nahoum Anthony and Dr Rachel Clark of the Strathclyde Institute for Pharmaceutical and Biomedical Sciences at the University of Strathclyde, for their assistance with creating Figures 2.9, Box 8.2, Figures 1 and 3, Figures 17.1, 17.11, 17.47, 20.16, 20.23, 20.52, and 20.53 from pdb files, some of which were obtained from the RSCB Protein Data Bank. Dr James Keeler of the Department of Chemistry, University of Cambridge kindly generated the molecular models that appear on the books Online Resource Centre. Thanks also to Dr Stephen Bromidge of Glaxo-SmithKline for permitting the description of his work on selective 5-HT<sub>2C</sub> antagonists, and for providing many of the diagrams for that case study. Finally, many thanks to Cambridge Scientific, Oxford Molecular, and Tripos for their advice and assistance in the writing of chapter 17.

# Brief contents

List of Boxes	xix	
Acronyms and Abbreviations	xxi	
1 Drugs and drug targets: an overview	1	
<b>PART A Drug targets</b>		
2 Proteins: structure and function	17	
3 Enzymes: structure and function	30	
4 Receptors: structure and function	42	
5 Receptors and signal transduction	58	
6 Nucleic acids: structure and function	71	
<b>PART B Pharmacodynamics and pharmacokinetics</b>		
7 Enzymes as drug targets	87	
8 Receptors as drug targets	101	
9 Nucleic acids as drug targets	119	
10 Miscellaneous drug targets	135	
11 Pharmacokinetics and related topics	152	
■ Case study 1: Statins	177	
<b>PART C Drug discovery, design, and development</b>		
12 Drug discovery: finding a lead	187	
13 Drug design: optimizing target interactions	212	
14 Drug design: optimizing access to the target	242	
15 Getting the drug to market	268	
■ Case study 2: The design of ACE inhibitors	285	
■ Case study 3: Artemisinin and related antimalarial drugs	292	
■ Case study 4: The design of oxamniquine	298	
<b>PART D Tools of the trade</b>		
16 Combinatorial and parallel synthesis	307	
17 Computers in medicinal chemistry	332	
18 Quantitative structure–activity relationships (QSAR)	377	
■ Case study 5: design of a thymidylate synthase inhibitor	403	
■ Case study 6: Design of a serotonin antagonist as a possible anxiolytic agent	407	
<b>PART E Selected topics in medicinal chemistry</b>		
19 Antibacterial agents	421	
20 Antiviral agents	475	
21 Anticancer agents	519	
22 Cholinergics, anticholinergics, and anticholinesterases	579	
23 Drugs acting on the adrenergic nervous system	609	
24 Opioid analgesics	632	
25 Antiulcer agents	653	
■ Case study 7: Current research into antidepressant agents	683	
Appendix 1 Essential amino acids	689	
Appendix 2 The standard genetic code	690	
Appendix 3 Statistical data for QSAR	691	
Appendix 4 The action of nerves	694	
Appendix 5 Microorganisms	698	
Appendix 6 Drugs and their trade names	700	
Glossary	707	
General further reading	725	
Index	727	



# Detailed contents

List of Boxes	xix	3.3 The active site of an enzyme	31
Acronyms and Abbreviations	xxi	3.4 Substrate binding at an active site	32
<b>1 Drugs and drug targets: an overview</b>	<b>1</b>	3.5 The catalytic role of enzymes	33
1.1 What is a drug?	1	3.5.1 Binding interactions	33
1.2 Drug targets	3	3.5.2 Acid–base catalysis	34
1.2.1 Cell structure	3	3.5.3 Nucleophilic groups	34
1.2.2 Drug targets at the molecular level	4	3.5.4 Cofactors	35
1.3 Intermolecular bonding forces	5	3.5.5 Naming and classification of enzymes	36
1.3.1 Electrostatic or ionic bonds	5	3.5.6 Genetic polymorphism and enzymes	36
1.3.2 Hydrogen bonds	6	3.6 Regulation of enzymes	36
1.3.3 Van der Waals interactions	8	Box 3.1 The external control of enzymes by nitric oxide	38
1.3.4 Dipole–dipole and ion–dipole interactions	9	3.7 Isozymes	39
1.3.5 Repulsive interactions	9	3.8 Enzyme kinetics: the Michaelis–Menten equation	39
1.3.6 The role of water and hydrophobic interactions	10		
1.4 Pharmacokinetic issues and medicines	11	<b>4 Receptors: structure and function</b>	<b>42</b>
1.5 Classification of drugs	11	4.1 Role of the receptor	42
1.6 Naming of drugs and medicines	12	4.2 Neurotransmitters and hormones	42
		4.3 Receptor types and subtypes	45
		4.4 Receptor activation	45
		4.5 How does the binding site change shape?	45
		4.6 Ion channel receptors	47
		4.6.1 General principles	47
		4.6.2 Structure	48
		4.6.3 Gating	49
		4.6.4 Ligand-gated and voltage-gated ion channels	49
		4.7 G-Protein-coupled receptors	50
		4.7.1 General principles	50
		4.7.2 Structure	51
		4.7.3 The rhodopsin-like family of G-protein- coupled receptors	52
		4.8 Kinase-linked receptors	53
		4.8.1 General principles	53
		4.8.2 Structure of tyrosine kinase receptors	54
		4.8.3 Activation mechanism for tyrosine kinase receptors	54
		4.8.4 Tyrosine kinase-linked receptors	55
		4.9 Intracellular receptors	56
		4.10 Regulation of receptor activity	56
		4.11 Genetic polymorphism and receptors	57
		<b>5 Receptors and signal transduction</b>	<b>58</b>
		5.1 Signal transduction pathways for G-protein- coupled receptors	58
		5.1.1 Interaction of the receptor–ligand complex with G-proteins	58
		5.1.2 Signal transduction pathways involving the $\alpha$ -subunit	59
<b>2 Proteins: structure and function</b>	<b>17</b>		
2.1 Primary structure of proteins	17		
2.2 Secondary structure of proteins	18		
2.2.1 The $\alpha$ -helix	18		
2.2.2 The $\beta$ -pleated sheet	18		
2.2.3 The $\beta$ -turn	18		
2.3 Tertiary structure of proteins	19		
2.3.1 Covalent bonds: disulfide links	21		
2.3.2 Ionic or electrostatic bonds	21		
2.3.3 Hydrogen bonds	21		
2.3.4 Van der Waals and hydrophobic interactions	22		
2.3.5 Relative importance of bonding interactions	23		
2.3.6 Role of the planar peptide bond	23		
2.4 Quaternary structure of proteins	23		
2.5 Translation and post-translational modifications	25		
2.6 Proteomics	26		
2.7 Protein function	26		
2.7.1 Structural proteins	27		
2.7.2 Transport proteins	27		
2.7.3 Enzymes and receptors	27		
2.7.4 Miscellaneous proteins and protein–protein interactions	28		
<b>3 Enzymes: structure and function</b>	<b>30</b>		
3.1 Enzymes as catalysts	30		
3.2 How do enzymes lower activation energies?	31		

5.2	Signal transduction involving G-proteins and adenylyate cyclase	60	7.5	Suicide substrates	92
5.2.1	Activation of adenylyate cyclase by the $\alpha_s$ -subunit	60	Box 7.3	Suicide substrates	94
5.2.2	Activation of protein kinase A	60	7.6	Isozyme selectivity of inhibitors	94
5.2.3	G <sub>i</sub> -Protein	61	Box 7.4	Designing drugs to be isozyme selective	95
5.2.4	General points about the signalling cascade involving cyclic AMP	62	7.7	Medicinal uses of enzyme inhibitors	95
5.2.5	Role of the $\beta\gamma$ -dimer	63	7.7.1	Enzyme inhibitors used against microorganisms	95
5.2.6	Phosphorylation	63	7.7.2	Enzyme inhibitors used against viruses	96
5.3	Signal transduction involving G-proteins and phospholipase C	64	7.7.3	Enzyme inhibitors used against the body's own enzymes	96
5.3.1	G-protein effect on phospholipase C	64	Box 7.5	Action of toxins on enzymes	97
5.3.2	Action of the secondary messenger—diacylglycerol	65	7.8	Enzyme kinetics	98
5.3.3	Action of the secondary messenger—inositol triphosphate	65	7.8.1	Lineweaver–Burk plots	98
5.3.4	Resynthesis of phosphatidylinositol diphosphate	66	7.8.2	Comparison of inhibitors	99
5.4	Signal transduction involving kinase-linked receptors	67	<b>8 Receptors as drug targets</b>	<b>101</b>	
5.4.1	Activation of signalling proteins and enzymes	67	8.1	Introduction	101
5.4.2	Small G-proteins	68	8.2	The design of agonists	101
5.4.3	Activation of guanylate cyclase by kinase receptors	69	8.2.1	Binding groups	101
<b>6 Nucleic acids: structure and function</b>	<b>71</b>		8.2.2	Position of the binding groups	102
6.1	Structure of DNA	71	8.2.3	Size and shape	104
6.1.1	Primary structure of DNA	71	8.2.4	Pharmacodynamics and pharmacokinetics	104
6.1.2	Secondary structure of DNA	71	8.2.5	Examples of agonists	104
6.1.3	Tertiary structure of DNA	74	8.2.6	Allosteric modulators	105
6.1.4	Chromatins	76	8.3	The design of antagonists	105
6.1.5	Genetic polymorphism and personalized medicine	76	8.3.1	Antagonists acting at the binding site	105
6.2	Ribonucleic acid and protein synthesis	76	Box 8.1	Antagonists as molecular labels	107
6.2.1	Structure of RNA	76	Box 8.2	Oestradiol and the oestrogen receptor	108
6.2.2	Transcription and translation	77	8.3.2	Antagonists acting outwith the binding site	110
6.2.3	Small nuclear RNA	79	8.4	Partial agonists	110
6.3	Genetic illnesses	80	8.5	Inverse agonists	111
6.4	Molecular biology and genetic engineering	81	8.6	Desensitization and sensitization	111
			8.7	Tolerance and dependence	113
			8.8	Receptor types and subtypes	113
			8.9	Affinity, efficacy, and potency	115
			<b>9 Nucleic acids as drug targets</b>	<b>119</b>	
			9.1	Intercalating drugs acting on DNA	119
			9.2	Topoisomerase poisons: non-intercalating	121
			9.3	Alkylating and metallating agents	123
			9.3.1	Nitrogen mustards	123
			9.3.2	Nitrosoureas	124
			9.3.3	Busulfan	125
			9.3.4	Cisplatin	125
			9.3.5	Dacarbazine and procarbazine	126
			9.3.6	Mitomycin C	127
			9.4	Chain cutters	128
			9.5	Chain terminators	129
			9.6	Control of gene transcription	130
			9.7	Agents that act on RNA	131
			9.7.1	Agents that bind to ribosomes	131
			9.7.2	Antisense therapy	131

## **PART B Pharmacodynamics and pharmacokinetics**

### **7 Enzymes as drug targets**

**87**

7.1	Inhibitors acting at the active site of an enzyme	87
7.1.1	Reversible inhibitors	87
Box 7.1	A cure for antifreeze poisoning	88
7.1.2	Irreversible inhibitors	89
7.2	Inhibitors acting at allosteric binding sites	89
Box 7.2	Irreversible inhibition for the treatment of obesity	90
7.3	Uncompetitive and non-competitive inhibitors	90
7.4	Transition-state analogues: renin inhibitors	91

## xii Detailed Contents

<b>10 Miscellaneous drug targets</b>	<b>135</b>		
10.1 Transport proteins as drug targets	135	11.7 Drug dosing	170
10.2 Structural proteins as drug targets	135	11.7.1 Drug half-life	171
10.2.1 Viral structural proteins as drug targets	135	11.7.2 Steady-state concentration	171
10.2.2 Tubulin as a drug target	135	11.7.3 Drug tolerance	171
Box 10.1 Antidepressant drugs acting on transport proteins	136	11.7.4 Bioavailability	172
10.3 Biosynthetic building blocks as drug targets	138	11.8 Formulation	172
10.4 Biosynthetic processes as drug targets: chain terminators	139	11.9 Drug delivery	172
10.5 Protein–protein interactions	139	■ Case study 1: Statins	177
Box 10.2 Targeting transcription factor–coactivator interactions	140		
10.6 Lipids as a drug target	143	<b>PART C Drug discovery, design and development</b>	
10.6.1 ‘Tunnelling molecules’	144	<b>12 Drug discovery: finding a lead</b>	<b>187</b>
10.6.2 Ion carriers	146	12.1 Choosing a disease	187
10.7 Carbohydrates as drug targets	147	12.2 Choosing a drug target	187
10.7.1 Glycomics	147	12.2.1 Drug targets	187
10.7.2 Antigens and antibodies	148	12.2.2 Discovering drug targets	187
Box 10.3 Glycosphingolipids	149	Box 12.1 Recently discovered target: the caspases	188
		12.2.3 Target specificity and selectivity between species	189
<b>11 Pharmacokinetics and related topics</b>	<b>152</b>	12.2.4 Target specificity and selectivity within the body	189
11.1 Pharmacodynamics and pharmacokinetics	152	12.2.5 Targeting drugs to specific organs and tissues	190
11.2 Drug absorption	152	12.2.6 Pitfalls	190
11.3 Drug distribution	154	Box 12.2 Pitfalls in choosing particular targets	190
11.3.1 Distribution round the blood supply	154	12.2.7 Multi-target drugs	191
11.3.2 Distribution to tissues	154	Box 12.3 Early tests for potential toxicity	191
11.3.3 Distribution to cells	155	12.3 Identifying a bioassay	192
11.3.4 Other distribution factors	155	12.3.1 Choice of bioassay	192
11.3.5 Blood–brain barrier	155	12.3.2 <i>In vitro</i> tests	193
11.3.6 Placental barrier	155	12.3.3 <i>In vivo</i> tests	193
11.3.7 Drug–drug interactions	156	12.3.4 Test validity	194
11.4 Drug metabolism	156	12.3.5 High-throughput screening	194
11.4.1 Phase I and phase II metabolism	156	12.3.6 Screening by NMR	194
11.4.2 Phase I transformations catalysed by cytochrome P450 enzymes	157	12.3.7 Affinity screening	195
11.4.3 Phase I transformations catalysed by flavin-containing monooxygenases	160	12.3.8 Surface plasmon resonance	195
11.4.4 Phase I transformations catalysed by other enzymes	160	12.3.9 Scintillation proximity assay	196
11.4.5 Phase II transformations	160	12.3.10 Isothermal titration calorimetry	196
11.4.6 Metabolic stability	163	12.3.11 Virtual screening	196
Box 11.1 Metabolism of an antiviral agent	164	12.4 Finding a lead compound	197
11.4.7 The first pass effect	166	12.4.1 Screening of natural products	197
11.5 Drug excretion	166	12.4.2 Medical folklore	199
11.6 Drug administration	167	12.4.3 Screening synthetic compound ‘libraries’	200
11.6.1 Oral administration	167	12.4.4 Existing drugs	200
11.6.2 Absorption through mucous membranes	168	12.4.5 Starting from the natural ligand or modulator	202
11.6.3 Rectal administration	168	Box 12.4 Selective optimization of side activities (SOSA)	202
11.6.4 Topical administration	168	Box 12.5 Natural ligands as lead compounds	204
11.6.5 Inhalation	168	12.4.6 Combinatorial and parallel synthesis	204
11.6.6 Injection	169		
11.6.7 Implants	169		

12.4.7	Computer-aided design of lead compounds	204		
12.4.8	Serendipity and the prepared mind	205		
Box 12.6	Examples of serendipity	205		
12.4.9	Computerized searching of structural databases	206		
12.4.10	Fragment-based lead discovery	206		
Box 12.7	Use of NMR spectroscopy in finding lead components	207		
Box 12.8	Click chemistry <i>in situ</i>	208		
12.4.11	Properties of lead compounds	209		
12.5	Isolation and purification	209		
12.6	Structure determination	209		
12.7	Herbal medicine	210		
<b>13</b>	<b>Drug design: optimizing target interactions</b>	<b>212</b>		
13.1	Structure–activity relationships	212		
13.1.1	Binding role of alcohols and phenols	213		
13.1.2	Binding role of aromatic rings	214		
13.1.3	Binding role of alkenes	215		
13.1.4	Binding role of ketones and aldehydes	215		
13.1.5	Binding role of amines	215		
13.1.6	Binding role of amides	216		
13.1.7	Binding role of quaternary ammonium salts	218		
13.1.8	Binding role of carboxylic acids	218		
13.1.9	Binding role of esters	218		
13.1.10	Binding role of alkyl and aryl halides	219		
13.1.11	Binding role of thiols and ethers	220		
13.1.12	Binding role of other functional groups	220		
13.1.13	Binding role of alkyl groups and the carbon skeleton	220		
13.1.14	Binding role of heterocycles	220		
13.1.15	Isosteres	222		
13.1.16	Testing procedures	222		
13.2	Identification of a pharmacophore	223		
13.3	Drug optimization: strategies in drug design	225		
13.3.1	Variation of substituents	225		
13.3.2	Extension of the structure	227		
Box 13.1	Use of extension tactics	228		
13.3.3	Chain extension/contraction	228		
13.3.4	Ring expansion/contraction	228		
13.3.5	Ring variations	229		
13.3.6	Ring fusions	230		
13.3.7	Isosteres and bioisosteres	230		
13.3.8	Simplification of the structure	232		
Box 13.2	Simplification	233		
13.3.9	Rigidification of the structure	234		
Box 13.3	Rigidification tactics in drug design	236		
13.3.10	Conformational blockers	237		
13.3.11	Structure-based drug design and molecular modelling	237		
13.3.12	Drug design by NMR	238		
13.3.13	The elements of luck and inspiration	238		
Box 13.4	A slice of luck	239		
<b>14</b>	<b>Drug design: optimizing access to the target</b>	<b>242</b>		
14.1	Optimizing hydrophobic/hydrophilic properties	242		
14.1.1	Variation of alkyl or acyl substituents to vary polarity	243		
14.1.2	Varying polar functional groups to vary polarity	243		
14.1.3	Variation of <i>N</i> -alkyl substituents to vary $pK_a$	244		
14.1.4	Variation of aromatic substituents to vary $pK_a$	244		
14.1.5	Bioisosteres for polar groups	244		
Box 14.1	Use of bioisosteres to increase absorption	245		
14.2	Making drugs more resistant to chemical and enzymatic degradation	245		
14.2.1	Steric shields	245		
14.2.2	Electronic effects of bioisosteres	245		
14.2.3	Stereoelectronic modifications	246		
14.2.4	Metabolic blockers	246		
14.2.5	Removal or replacement of susceptible metabolic groups	247		
14.2.6	Group shifts	247		
14.2.7	Ring variation and ring substituents	248		
14.3	Making drugs less resistant to drug metabolism	249		
14.3.1	Introducing metabolically susceptible groups	249		
14.3.2	Self-destruct drugs	249		
Box 14.2	Shortening the lifetime of a drug	250		
14.4	Targeting drugs	250		
14.4.1	Targeting tumour cells: ‘search and destroy’ drugs	251		
14.4.2	Targeting gastrointestinal infections	251		
14.4.3	Targeting peripheral regions rather than the central nervous system	251		
14.5	Reducing toxicity	251		
14.6	Prodrugs	252		
14.6.1	Prodrugs to improve membrane permeability	252		
Box 14.3	Varying esters in prodrugs	253		
14.6.2	Prodrugs to prolong drug activity	254		
14.6.3	Prodrugs masking drug toxicity and side effects	255		
Box 14.4	Prodrugs masking toxicity and side effects	255		
14.6.4	Prodrugs to lower water solubility	256		
14.6.5	Prodrugs to improve water solubility	256		
Box 14.5	Prodrugs to improve water solubility	256		
14.6.6	Prodrugs used in the targeting of drugs	257		
14.6.7	Prodrugs to increase chemical stability	257		
14.6.8	Prodrugs activated by external influence (sleeping agents)	257		
14.7	Drug alliances	258		
14.7.1	‘Sentry’ drugs	258		
14.7.2	Localizing a drug’s area of activity	259		
14.7.3	Increasing absorption	259		
14.8	Endogenous compounds as drugs	259		
14.8.1	Neurotransmitters	259		
14.8.2	Natural hormones, peptides and proteins as drugs	260		
14.8.3	Antibodies as drugs	261		

## xiv Detailed Contents

14.9 Peptides and peptidomimetics in drug design	262	16.7.4 Substituent variation	323
14.9.1 Peptidomimetics	262	16.7.5 Designing compound libraries for lead optimization	323
14.9.2 Peptide drugs	264	16.7.6 Computer-designed libraries	323
14.10 Oligonucleotides as drugs	264	16.8 Testing for activity	323
<b>15 Getting the drug to market</b>	<b>268</b>	16.8.1 High throughput screening	323
15.1 Preclinical and clinical trials	268	16.8.2 Screening 'on bead' or 'off bead'	324
15.1.1 Toxicity testing	268	16.9 Parallel synthesis	324
15.1.2 Drug metabolism studies	270	16.9.1 Solid phase extraction	325
Box 15.1 Drug metabolism studies and drug design	270	16.9.2 Use of resins in solution phase organic synthesis (SPOS)	326
15.1.3 Pharmacology, formulation, and stability tests	271	16.9.3 Reagents attached to solid support: catch and release	327
15.1.4 Clinical trials	271	16.9.4 Microwave technology	328
15.2 Patenting and regulatory affairs	274	16.9.5 Microfluidics in parallel synthesis	329
15.2.1 Patents	274	<b>17 Computers in medicinal chemistry</b>	<b>332</b>
15.2.2 Regulatory affairs	276	17.1 Molecular and quantum mechanics	332
15.3 Chemical and process development	278	17.1.1 Molecular mechanics	332
15.3.1 Chemical development	278	17.1.2 Quantum mechanics	332
Box 15.2 Synthesis of ebalzotan	279	17.1.3 Choice of method	333
15.3.2 Process development	279	17.2 Drawing chemical structures	333
15.3.3 Choice of drug candidate	280	17.3 3D structures	333
Box 15.3 Synthesis of ICI D7114	280	17.4 Energy minimization	334
15.3.4 Natural products	281	Box 17.1 Energy minimizing apomorphine	334
■ <b>Case study 2: The design of ACE inhibitors</b>	<b>285</b>	17.5 Viewing 3D molecules	335
■ <b>Case study 3: Artemisinin and related antimalarial drugs</b>	<b>292</b>	17.6 Molecular dimensions	335
■ <b>Case study 4: The design of oxamniquine</b>	<b>298</b>	17.7 Molecular properties	336
		17.7.1 Partial charges	336
		17.7.2 Molecular electrostatic potentials	337
		17.7.3 Molecular orbitals	338
		Box 17.2 Study of HOMO and LUMO orbitals	339
		17.7.4 Spectroscopic transitions	339
		17.7.5 Use of grids in measuring molecular properties	339
		17.8 Conformational analysis	341
		17.8.1 Local and global energy minima	341
		17.8.2 Molecular dynamics	341
		17.8.3 Stepwise bond rotation	342
		Box 17.3 Finding conformations of cyclic structures by molecular dynamics	343
		17.8.4 Monte Carlo and the Metropolis method	343
		17.8.5 Genetic and evolutionary algorithms	345
		17.9 Structure comparisons and overlays	346
		17.10 Identifying the active conformation	347
		17.10.1 X-ray crystallography	347
		17.10.2 Comparison of rigid and non-rigid ligands	348
		Box 17.4 Identification of an active conformation	348
		17.11 3D pharmacophore identification	350
		17.11.1 X-ray crystallography	350
		17.11.2 Structural comparison of active compounds	350
		17.11.3 Automatic identification of pharmacophores	350
		17.12 Docking procedures	352
		17.12.1 Manual docking	352

## PART D Tools of the trade

### 16 Combinatorial and parallel synthesis 307

16.1 Combinatorial and parallel synthesis in medicinal chemistry projects	307
16.2 Solid phase techniques	308
16.2.1 The solid support	308
16.2.2 The anchor/linker	310
16.2.3 Protecting groups and synthetic strategy	311
16.3 The mix and split method in combinatorial synthesis	312
16.4 Structure determination of the active compound(s)	313
16.4.1 Tagging	313
16.4.2 Photolithography	315
16.5 Examples of combinatorial synthesis	316
16.6 Dynamic combinatorial synthesis	318
Box 16.1 Dynamic combinatorial synthesis of vancomycin dimers	319
16.7 Planning and designing a combinatorial synthesis	320
16.7.1 'Spider-like' scaffolds	320
16.7.2 Designing 'drug like' molecules	321
16.7.3 Scaffolds	321
Box 16.2 Examples of scaffolds	322

17.12.2 Automatic docking	352	18.10.6 Case Study: inhibitors of tubulin polymerization	400
17.12.3 Defining the molecular surface of a binding site	352	■ <b>Case study 5: Design of a thymidylate synthase inhibitor</b>	403
17.12.4 Rigid docking by shape complementarity	353	■ <b>Case study 6: Design of a serotonin antagonist as a possible anxiolytic agent</b>	407
17.12.5 Use of grids in docking programs	356		
17.12.6 Rigid docking by matching hydrogen bonding groups	356		
17.12.7 Rigid docking of flexible ligands: the FLOG program	357		
17.12.8 Docking of flexible ligands: anchor and grow programs	357		
17.12.9 Docking of flexible ligands: simulated annealing and genetic algorithms	361		
17.13 Automated screening of databases for lead compounds	362		
17.14 Protein mapping	362		
17.14.1 Constructing a model protein: homology modelling	362		
17.14.2 Constructing a binding site: hypothetical pseudoreceptors	363		
Box 17.5 Constructing a receptor map	364		
17.15 <i>De novo</i> design	365		
17.15.1 General principles of <i>de novo</i> design	365		
17.15.2 Automated <i>de novo</i> design	366		
17.16 Planning a combinatorial synthesis	373		
17.17 Database handling	374		
<b>18 Quantitative structure-activity relationships (QSAR)</b>	<b>377</b>		
18.1 Graphs and equations	377		
18.2 Physicochemical properties	378		
18.2.1 Hydrophobicity	379		
Box 18.1 Altering log <i>P</i> to remove central nervous system side effects	381		
18.2.2 Electronic effects	382		
Box 18.2 Insecticidal activity of diethyl phenyl phosphates	384		
18.2.3 Steric factors	384		
18.2.4 Other physicochemical parameters	385		
18.3 Hansch equation	385		
Box 18.3 Hansch equation for a series of antimalarial compounds	386		
18.4 Craig plot	387		
18.5 Topliss scheme	388		
18.6 Bioisosteres	390		
18.7 Free–Wilson approach	390		
18.8 Planning a QSAR study	391		
18.9 Case Study	391		
18.10 3D QSAR	394		
18.10.1 Defining steric and electrostatic fields	394		
18.10.2 Relating shape and electronic distribution to biological activity	395		
18.10.3 Advantages of CoMFA over traditional QSAR	397		
18.10.4 Potential problems of CoMFA	397		
18.10.5 Other 3D QSAR methods	398		
		<b>PART E Selected topics in medicinal chemistry</b>	
		<b>19 Antibacterial agents</b>	<b>421</b>
		19.1 History of antibacterial agents	421
		19.2 The bacterial cell	423
		19.3 Mechanisms of antibacterial action	423
		19.4 Antibacterial agents that act against cell metabolism (antimetabolites)	424
		19.4.1 Sulfonamides	424
		Box 19.1 Sulfonamide analogues with reduced toxicity	425
		Box 19.2 Treatment of intestinal infections	426
		19.4.2 Examples of other antimetabolites	428
		19.5 Antibacterial agents that inhibit cell wall synthesis	429
		19.5.1 Penicillins	429
		Box 19.3 Clinical properties of benzylpenicillin and phenoxymethylpenicillin	431
		Box 19.4 <i>Pseudomonas aeruginosa</i>	434
		Box 19.5 The isoxazolyl penicillins	440
		Box 19.6 Clinical aspects of $\beta$ -lactamase-resistant penicillins	440
		Box 19.7 Ampicillin prodrugs	442
		Box 19.8 Clinical aspects of broad-spectrum penicillins	444
		19.5.2 Cephalosporins	444
		Box 19.9 Synthesis of 3-methylated cephalosporins	448
		Box 19.10 Clinical aspects of cephalosporins	450
		19.5.3 Other $\beta$ -lactam antibiotics	450
		19.5.4 $\beta$ -Lactamase inhibitors	451
		Box 19.11 Clinical aspects of miscellaneous $\beta$ -lactam antibiotics	452
		19.5.5 Other drugs that act on bacterial cell wall biosynthesis	454
		Box 19.12 Clinical aspects of cycloserine, bacitracin and vancomycin	458
		19.6 Antibacterial agents that act on the plasma membrane structure	459
		19.6.1 Valinomycin and gramicidin A	459
		19.6.2 Polymyxin B	459
		19.6.3 Killer nanotubes	459
		19.6.4 Cyclic lipopeptides	459
		Box 19.13 Clinical aspects of drugs acting on the plasma membrane	460
		19.7 Antibacterial agents that impair protein synthesis: translation	460
		19.7.1 Aminoglycosides	460
		Box 19.14 Clinical aspects of aminoglycosides	462

## xvi Detailed Contents

19.7.2 Tetracyclines	462	20.8 Antiviral drugs acting against RNA viruses: flu virus	503
19.7.3 Chloramphenicol	462	20.8.1 Structure and life cycle of the influenza virus	503
19.7.4 Macrolides	462	20.8.2 Ion channel disrupters: adamantanes	505
Box 19.15 Clinical aspects of tetracyclines and chloramphenicol	463	20.8.3 Neuraminidase inhibitors	506
19.7.5 Lincosamides	464	20.9 Antiviral drugs acting against RNA viruses: cold virus	514
19.7.6 Streptogramins	464	20.10 Broad-spectrum antiviral agents	515
19.7.7 Oxazolidinones	465	20.10.1 Agents acting against cytidine triphosphate synthetase	515
Box 19.16 Clinical aspects of macrolides, lincosamides, streptogramins and oxazolidinones	465	20.10.2 Agents acting against S-adenosylhomocysteine hydrolase	516
19.8 Agents that act on nucleic acid transcription and replication	466	20.10.3 Ribavirin (or virazole)	516
19.8.1 Quinolones and fluoroquinolones	466	20.10.4 Interferons	516
Box 19.17 Synthesis of ciproxacillin	467	20.10.5 Antibodies and ribozomes	516
Box 19.18 Clinical aspects of quinolones and fluoroquinolones	467	20.11 Bioterrorism and smallpox	517
19.8.2 Aminoacridines	468	<b>21 Anticancer agents</b>	<b>519</b>
19.8.3 Rifamycins	468	21.1 Cancer: an introduction	519
19.8.4 Nitroimidazoles and nitrofurantoin	468	21.1.1 Definitions	519
19.9 Miscellaneous agents	468	21.1.2 Causes of cancer	519
Box 19.19 Clinical aspects of rifamycins and miscellaneous agents	469	21.1.3 Genetic faults leading to cancer: proto-oncogenes and oncogenes	519
19.10 Drug resistance	469	21.1.4 Abnormal signalling pathways	520
19.10.1 Drug resistance by mutation	470	21.1.5 Insensitivity to growth-inhibitory signals	521
19.10.2 Drug resistance by genetic transfer	470	21.1.6 Abnormalities in cell cycle regulation	521
19.10.3 Other factors affecting drug resistance	470	21.1.7 Apoptosis and the p53 protein	522
19.10.4 The way ahead	471	21.1.8 Telomeres	524
Box 19.20 Organoarsenicals as antiparasitic drugs	473	21.1.9 Angiogenesis	525
<b>20 Antiviral agents</b>	<b>475</b>	21.1.10 Tissue invasion and metastasis	526
20.1 Viruses and viral diseases	475	21.1.11 Treatment of cancer	526
20.2 Structure of viruses	475	21.1.12 Resistance	528
20.3 Life cycle of viruses	476	21.2 Drugs acting directly on nucleic acids	529
20.4 Vaccination	477	21.2.1 Intercalating agents	529
20.5 Antiviral drugs: general principles	478	Box 21.1 Clinical aspects of intercalating agents	530
20.6 Antiviral drugs used against DNA viruses	479	21.2.2 Non-intercalating agents that inhibit the action of topoisomerase enzymes on DNA	531
20.6.1 Inhibitors of viral DNA polymerase	479	Box 21.2 Clinical aspects of non-intercalating agents inhibiting the action of topoisomerase enzymes on DNA	531
Box 20.1 Clinical aspects of viral DNA polymerase inhibitors	482	21.2.3 Alkylating and metallating agents	532
20.6.2 Inhibitors of tubulin polymerization	482	Box 21.3 Clinical aspects of alkylating and metallating agents	534
20.6.3 Antisense therapy	482	21.2.4 Chain cutters	535
20.7 Antiviral drugs acting against RNA viruses: HIV	483	21.2.5 Antisense therapy	535
20.7.1 Structure and life cycle of HIV	483	21.3 Drugs acting on enzymes: antimetabolites	535
20.7.2 Antiviral therapy against HIV	484	21.3.1 Dihydrofolate reductase inhibitors	535
Box 20.2 Clinical aspects of antiviral drugs used against HIV	485	21.3.2 Inhibitors of thymidylate synthase	536
20.7.3 Inhibitors of viral reverse transcriptase	485	Box 21.4 Clinical aspects of antimetabolites	538
20.7.4 Protease inhibitors	487	21.3.3 Inhibitors of ribonucleotide reductase	538
Box 20.3 Clinical aspects of reverse transcriptase inhibitors	488	21.3.4 Inhibitors of adenosine deaminase	539
20.7.5 Inhibitors of other targets	500	21.3.5 Inhibitors of DNA polymerases	539
Box 20.4 Clinical aspects of protease inhibitors	501	21.3.6 Purine antagonists	540
		21.4 Hormone-based therapies	540
		21.4.1 Glucocorticoids, oestrogens, progestins and androgens	540

21.4.2	LHRH Agonists	541	22.2.2	Autonomic motor nervous system	581
21.4.3	Antioestrogens	541	22.2.3	Enteric system	581
21.4.4	Antiandrogens	542	22.3	Neurotransmitters	581
21.4.5	Aromatase inhibitors	542	22.4	Actions of the peripheral nervous system	582
21.5	Drugs acting on structural proteins	543	22.5	Cholinergic system	582
Box 21.5	Clinical aspects of hormone-based therapies	544	22.5.1	Cholinergic signalling system	582
21.5.1	Agents that inhibit tubulin polymerization	544	22.5.2	Presynaptic control systems	583
21.5.2	Agents that inhibit tubulin depolymerization	546	22.5.3	Cotransmitters	583
Box 21.6	Clinical aspects of drugs acting on structural proteins	547	22.6	Agonists at the cholinergic receptor	584
21.6	Inhibitors of signalling pathways	547	22.7	Acetylcholine: structure, SAR, and receptor binding	585
21.6.1	Inhibition of farnesyl transferase and the Ras protein	547	22.8	Instability of acetylcholine	587
Box 21.7	Development of a non-peptide farnesyl transferase inhibitor	551	22.9	Design of acetylcholine analogues	587
21.6.2	Protein kinase inhibitors	551	22.9.1	Steric shields	587
Box 21.8	General synthesis of gefitinib and related analogues	554	22.9.2	Electronic effects	588
Box 21.9	General synthesis of imatinib and analogues	556	22.9.3	Combining steric and electronic effects	589
Box 21.10	Design of sorafenib	561	22.10	Clinical uses for cholinergic agonists	589
Box 21.11	Clinical aspects of kinase inhibitors	562	22.10.1	Muscarinic agonists	589
21.7	Miscellaneous enzyme inhibitors	563	22.10.2	Nicotinic agonists	589
21.7.1	Matrix metalloproteinase inhibitors	563	22.11	Antagonists of the muscarinic cholinergic receptor	590
21.7.2	Cyclooxygenase 2 inhibitors	565	22.11.1	Actions and uses of muscarinic antagonists	590
21.7.3	Proteasome inhibitors	565	22.11.2	Muscarinic antagonists	590
21.7.4	Histone deacetylase inhibitors	566	Box 22.1	Photoaffinity labelling	593
21.7.5	Other enzyme targets	566	22.12	Antagonists of the nicotinic cholinergic receptor	594
21.8	Miscellaneous anticancer agents	567	22.12.1	Applications of nicotinic antagonists	594
21.8.1	Synthetic agents	567	22.12.2	Nicotinic antagonists	594
21.8.2	Natural products	568	22.13	Receptor structures	598
21.8.3	Protein therapy	569	22.14	Anticholinesterases and acetylcholinesterase	599
21.8.4	Modulation of transcription factor–coactivator interactions	569	22.14.1	Effect of anticholinesterases	599
21.9	Antibodies, antibody conjugates, and gene therapy	570	22.14.2	Structure of the acetylcholinesterase enzyme	599
21.9.1	Monoclonal antibodies	570	22.14.3	Active site of acetylcholinesterase	599
Box 21.12	Clinical aspects of antibodies and antibody–drug conjugates	570	22.15	Anticholinesterase drugs	601
21.9.2	Antibody–drug conjugates	571	22.15.1	Carbamates	601
21.9.3	Antibody–directed enzyme prodrug therapy (ADEPT)	572	22.15.2	Organophosphorus compounds	603
Box 21.13	Gemtuzumab: an antibody–drug conjugate	573	22.16	Pralidoxime: an organophosphate antidote	605
21.9.4	Antibody-directed abzyme prodrug therapy (ADAPT)	574	22.17	Anticholinesterases as ‘smart drugs’	606
21.9.5	Gene-directed enzyme prodrug therapy (GDEPT)	574	Box 22.2	Mosses play it smart	607
21.9.6	Other forms of gene therapy	575	<b>23</b>	<b>Drugs acting on the adrenergic nervous system</b>	<b>609</b>
21.10	Photodynamic therapy	575	23.1	Adrenergic nervous system	609
<b>22</b>	<b>Cholinergics, anticholinergics, and anticholinesterases</b>	<b>579</b>	23.1.1	Peripheral nervous system	609
22.1	Peripheral nervous system	579	23.1.2	Central nervous system	609
22.2	Motor nerves of the peripheral nervous system	580	23.2	Adrenergic receptors	609
22.2.1	Somatic motor nervous system	580	23.2.1	Types of adrenergic receptor	609
			23.2.2	Distribution of receptors	610
			Box 23.1	Clinical aspects of adrenergic agents	611
			23.3	Endogenous agonists for the adrenergic receptors	611
			23.4	Biosynthesis of catecholamines	611
			23.5	Metabolism of catecholamines	612
			23.6	Neurotransmission	612



## xviii Detailed Contents

23.6.1 Neurotransmission process	612	Box 24.5 Comparison of opioids and their effects on opioid receptors	649
23.6.2 Cotransmitters	612	24.8.2 Analogues of enkephalins	649
23.6.3 Presynaptic receptors and control	613	24.8.3 Inhibitors of peptidases	650
23.7 Drug targets	614	24.8.4 Endogenous morphine	650
23.8 Adrenergic binding site	614	24.9 The future	651
23.9 Structure–activity relationships	615	<b>25 Antiulcer agents</b>	<b>653</b>
23.9.1 Important binding groups on catecholamines	615	25.1 Peptic ulcers	653
23.9.2 Selectivity for $\alpha$ - versus $\beta$ -adrenoreceptors	616	25.1.1 Definition	653
23.10 Adrenergic agonists	617	25.1.2 Causes	653
23.10.1 General adrenergic agonists	617	25.1.3 Treatment	653
23.10.2 $\alpha_1$ -, $\alpha_2$ -, $\beta_1$ - and $\beta_3$ -Agonists	617	25.1.4 Gastric acid release	653
23.10.3 $\beta_2$ -Agonists and the treatment of asthma	618	25.2 $H_2$ Antagonists	654
Box 23.2 Synthesis of salbutamol	619	25.2.1 Histamine and histamine receptors	655
23.11 Adrenergic receptor antagonists	620	25.2.2 Searching for a lead	656
23.11.1 General $\alpha/\beta$ -blockers	620	25.2.3 Developing the lead: a chelation bonding theory	659
23.11.2 $\alpha$ -Blockers	620	25.2.4 From partial agonist to antagonist: the development of burimamide	660
23.11.3 $\beta$ -Blockers as cardiovascular drugs	621	25.2.5 Development of metiamide	661
Box 23.3 Synthesis of aryloxypropanolamines	623	25.2.6 Development of cimetidine	664
Box 23.4 Clinical aspects of $\beta$ -blockers	623	25.2.7 Cimetidine	665
23.12 Other drugs affecting adrenergic transmission	626	Box 25.1 Synthesis of cimetidine	666
23.12.1 Drugs that affect the biosynthesis of adrenergics	626	25.2.8 Further studies of cimetidine analogues	667
23.12.2 Drugs inhibiting the uptake of noradrenaline into storage vesicles	627	25.2.9 Further $H_2$ antagonists	670
23.12.3 Release of noradrenaline from storage vesicles	627	25.2.10 Comparison of $H_1$ and $H_2$ antagonists	672
23.12.4 Reuptake inhibitors of noradrenaline into presynaptic neurons	627	25.2.11 $H_2$ Receptors and $H_2$ antagonists	673
23.12.5 Inhibition of metabolic enzymes	629	25.3 Proton pump inhibitors	673
23.12.6 Antagonists of the $\alpha_2$ -adrenoceptor	630	25.3.1 Parietal cells and the proton pump	673
<b>24 Opioid analgesics</b>	<b>632</b>	25.3.2 Proton pump inhibitors	674
24.1 History of opium	632	25.3.3 Mechanism of inhibition	675
24.2 The active principle: morphine	633	25.3.4 Metabolism of proton pump inhibitors	676
24.2.1 Isolation of morphine	633	25.3.5 Design of omeprazole and esomeprazole	676
24.2.2 Structure and properties	633	Box 25.2 Synthesis of omeprazole and esomeprazole	679
Box 24.1 Clinical aspects of morphine	634	25.3.6 Other proton pump inhibitors	679
24.3 Structure–activity relationships	634	25.4 <i>Helicobacter pylori</i> and the use of antibacterial agents	680
24.4 Molecular target for morphine: opioid receptors	636	25.4.1 Treatment	680
24.5 Morphine: pharmacodynamics and pharmacokinetics	636	25.5 Traditional and herbal medicines	681
24.6 Morphine analogues	638	<b>■ Case Study 7: Current research into antidepressant agents</b>	<b>683</b>
24.6.1 Variation of substituents	638	APPENDIX 1 Essential amino acids	689
Box 24.2 Synthesis of <i>N</i> -alkylated morphine analogues	639	APPENDIX 2 The standard genetic code	690
24.6.2 Drug extension	639	APPENDIX 3 Statistical data for QSAR	691
24.6.3 Simplification or drug dissection	640	APPENDIX 4 The action of nerves	694
24.6.4 Rigidification	644	APPENDIX 5 Microorganisms	698
Box 24.3 Opioids as antidiarrhoeal agents	644	APPENDIX 6 Drugs and their trade names	700
Box 24.4 Synthesis of the oripavines	645	GLOSSARY	707
24.7 Agonists and antagonists	646	GENERAL FURTHER READING	725
24.8 Endogenous opioid peptides and opioids	648	INDEX	727
24.8.1 Endogenous opioid peptides	648		

# List of boxes

## General interest

3.1	The external control of enzymes by nitric oxide	38	18.3	Hansch equation for a series of antimalarial compounds	386
7.1	A cure for antifreeze poisoning	88	19.1	Sulfonamide analogues with reduced toxicity	425
7.2	Irreversible inhibition for the treatment of obesity	90	19.2	Treatment of intestinal infections	426
7.3	Suicide substrates	94	19.5	The isoxazolyl penicillins	440
7.4	Designing drugs to be isozyme selective	95	19.7	Ampicillin prodrugs	442
7.5	Action of toxins on enzymes	97	19.20	Organoarsenicals as antiparasitic drugs	473
8.1	Antagonists as molecular labels	107	21.7	Development of a non-peptide farnesyl transferase inhibitor	551
8.2	Oestradiol and the oestrogen receptor	108	21.10	Design of sorafenib	561
10.1	Antidepressant drugs acting on transport proteins	136	21.13	Gemtuzumab: an antibody–drug conjugate	573
10.2	Targeting transcription factor–cofactor interactions	140	22.1	Photoaffinity labelling	593
10.3	Glycosphingolipids	149	22.2	Mosses play it smart	607
11.1	Metabolism of an antiviral agent	164	24.3	Opioids as antidiarrhoeal agents	644
12.1	Recently discovered targets: the caspases	188			
12.2	Pitfalls in choosing particular targets	190	<b>Synthesis</b>		
12.3	Early tests for potential toxicity	191	15.2	Synthesis of ebalzotan	279
12.4	Selective optimization of side activities (SOSA)	202	15.3	Synthesis of ICI D7114	280
12.5	Natural ligands as lead compounds	204	16.1	Dynamic combinatorial synthesis of vancomycin dimers	319
12.6	Examples of serendipity	205	19.9	Synthesis of 3-methylated cephalosporins	448
12.7	Use of NMR spectroscopy in finding lead compounds	207	19.17	Synthesis of ciprofloxacin	467
12.8	Click chemistry <i>in situ</i>	208	21.8	General synthesis of gefitinib and related analogues	554
13.1	Use of extension tactics	228	21.9	General synthesis of imatinib and analogues	556
13.2	Simplification	233	23.2	Synthesis of salbutamol	619
13.3	Rigidification tactics in drug design	236	23.3	Synthesis of aryloxypropanolamines	623
13.4	A slice of luck	239	24.2	Synthesis of <i>N</i> -alkylated morphine analogues	639
14.1	Use of bioisosteres to increase absorption	245	24.4	Synthesis of the oripavines	645
14.2	Shortening the lifetime of a drug	250	25.1	Synthesis of cimetidine	666
14.3	Varying esters in prodrugs	253	25.2	Synthesis of omeprazole and esomeprazole	679
14.4	Prodrugs masking toxicity and side effects	255	CS2.1	Synthesis of captopril and enalaprilate	290
14.5	Prodrugs to improve water solubility	256	CS4.1	Synthesis of oxamniquine	302
15.1	Drug metabolism studies and drug design	270			
16.2	Examples of scaffolds	322	<b>Clinical correlation</b>		
17.1	Energy minimizing apomorphine	334	19.3	Clinical properties of benzylpenicillin and phenoxymethylpenicillin	431
17.2	Study of HOMO and LUMO orbitals	339	19.4	<i>Pseudomonas aeruginosa</i>	434
17.3	Finding conformations of cyclic structures by molecular dynamics	343	19.6	Clinical aspects of $\beta$ -lactamase-resistant penicillins	440
17.4	Identification of an active conformation	348	19.8	Clinical aspects of broad-spectrum penicillins	444
17.5	Constructing a receptor map	364			
18.1	Altering log <i>P</i> to remove central nervous system side effects	381			
18.2	Insecticidal activity of diethyl phenyl phosphates	384			

## xx List of boxes

19.10	Clinical aspects of cephalosporins	450	21.2	Clinical aspects of non-intercalating agents inhibiting the action of topoisomerase enzymes on DNA	531
19.11	Clinical aspects of miscellaneous $\beta$ -lactam antibiotics	452	21.3	Clinical aspects of alkylating and metallating agents	534
19.12	Clinical aspects of cycloserine, bacitracin and vancomycin	458	21.4	Clinical aspects of antimetabolites	537
19.13	Clinical aspects of drugs acting on the plasma membrane	460	21.5	Clinical aspects of hormone-based therapies	544
19.14	Clinical aspects of aminoglycosides	462	21.6	Clinical aspects of drugs acting on structural proteins	547
19.15	Clinical aspects of tetracyclines and chloramphenicol	463	21.11	Clinical aspects of kinase inhibitors	562
19.16	Clinical aspects of macrolides, lincosamides, streptogramins and oxazolidinones	465	21.12	Clinical aspects of antibodies and antibody–drug conjugates	570
19.18	Clinical aspects of quinolones and fluoroquinolones	468	23.1	Clinical aspects of adrenergic agents	611
19.19	Clinical aspects of rifamycins and miscellaneous agents	469	23.4	Clinical aspects of $\beta$ -blockers	623
20.1	Clinical aspects of viral DNA polymerase inhibitors	482	24.1	Clinical aspects of morphine	634
20.2	Clinical aspects of antiviral drugs used against HIV	485	24.5	Comparison of opioids and their effects on opioid receptors	649
20.3	Clinical aspects of reverse transcriptase inhibitors	488	CS3.1	Clinical properties of artemisinin and analogues	296
20.4	Clinical aspects of protease inhibitors	501			
21.1	Clinical aspects of intercalating agents	530			

## Acronyms and abbreviations

ACE	angiotensin-converting enzyme	GABA	$\gamma$ -aminobutyric acid
ADAPT	antibody-directed abzyme prodrug therapy	GAP	GTPase activating protein
ADEPT	antibody-directed enzyme prodrug therapy	GCP	Good Clinical Practice
ADH	alcohol dehydrogenase	GDEPT	gene-directed enzyme prodrug therapy
AIC	5-aminoimidazole-4-carboxamide	GEF	guanine nucleotide exchange factors
AIDS	acquired immune deficiency syndrome	GGTase	geranylgeranyltransferase
AML	acute myeloid leukaemia	GH	growth hormone
AMP	adenosine 5'-monophosphate	GIT	gastrointestinal tract
ATP	adenosine 5'-triphosphate	GLP	Good Laboratory Practice
AUC	area under the curve	GMP	Good Manufacturing Practice
CCK	cholecystokinin	GnRH	gonadotrophin-releasing hormone
CDKs	cyclin-dependent kinases	HA	haemagglutinin
cGMP	cyclic GMP	HAART	highly active antiretroviral therapy
CKIs	cyclin-dependent kinase inhibitors	HAMA	human anti-mouse antibodies
CML	chronic myeloid leukaemia	HIV	human immunodeficiency virus
CMV	cytomegalovirus	HOMO	highest occupied molecular orbital
CNS	central nervous system	HPLC	high-performance liquid chromatography
COMT	catechol <i>O</i> -methyltransferase	HPMA	<i>N</i> -(2-hydroxypropyl)methacrylamide
COX	cyclooxygenase	HRV	human rhinoviruses
CSD	Cambridge Structural Database	HTS	high-throughput screening
CYP	enzymes that constitute the cytochrome P450 family	IGF-1R	insulin growth factor 1 receptor
DG	diacylglycerol	IND	Investigational Exemption to a New Drug Application
DHFR	dihydrofolate reductase	IP <sub>3</sub>	inositol triphosphate
DNA	deoxyribonucleic acid	IPER	International Preliminary Examination Report
dTMP	deoxythymidine monophosphate	IRB	Institutional Review Board
dUMP	deoxyuridine monophosphate	ISR	International Search Report
EC <sub>50</sub>	concentration of drug required to produce 50% of the maximum possible effect	K <sub>M</sub>	Michaelis constant
EGF	epidermal growth factor	LH	luteinizing hormone
EMA	European Agency for the Evaluation of Medicinal Products	LHRH	luteinizing hormone-releasing hormones
EPC	European Patent Convention	LUMO	lowest unoccupied molecular orbital
EPO	European Patent Office	MAA	Marketing Authorization Application
FDA	US Food and Drug Administration	MAB	monoclonal antibody
FGF	fibroblast growth factor	MAO	monoamine oxidase
FGF-R	fibroblast growth factor receptor	MAOI	monoamine oxidase inhibitor
FH <sub>4</sub>	tetrahydrofolate	MAP	mitogen-activated protein
FPGS	folylpolyglutamate synthetase	MAPK	mitogen-activated protein kinases
FPP	farnesyl diphosphate	MDR	multidrug resistance
FT	farnesyl transferase	MEP	molecular electrostatic potential
FTI	farnesyl transferase inhibitor	MMP	matrix metalloproteinase
		MMPI	matrix metalloproteinase inhibitor

## xxii Acronyms and abbreviations

NA	neuraminidase or noradrenaline	PLS	partial least squares
NAD <sup>+</sup> /NADH	nicotinamide adenine dinucleotide	PPI	proton pump inhibitor
NAG	<i>N</i> -acetylglucosamine	PPTs	pyridinium 4-toluenesulfonate
NAM	<i>N</i> -acetylmuramic acid	QSAR	quantitative structure–activity relationship
NCE	new chemical entity	RES	reticuloendothelial system
NDA	New Drug Application	RFC	reduced folate carrier
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate	RMSD	root mean square distance
NME	new molecular entity	RNA	ribonucleic acid
NMR	nuclear magnetic resonance	SAR	structure–activity relationships
NNRTIs	non-nucleoside reverse transcriptase inhibitors	SCAL	safety-catch acid-labile linker
NO	nitric oxide	SCF	stem cell factor
NRTI	nucleoside reverse transcriptase inhibitor	SCID	severe combined immunodeficiency disease
NSAID	non-steroidal anti-inflammatory drug	SOP	standard operating procedure
NVOC	nitroveratryloxycarbonyl	SPA	scintillation proximity assay
PABA	<i>p</i> -aminobenzoic acid	SPR	surface plasmon resonance
PBP	penicillin binding protein	TB	tuberculosis
PCP	phencyclidine, otherwise known as ‘angel dust’	TFA	trifluoroacetic acid
PCT	Patent Cooperation Treaty	TGF- $\alpha$	transforming growth factor $\alpha$
PDB	Protein Data Bank	TGF- $\beta$	transforming growth factor $\beta$
PDGF	platelet-derived growth factor	THF	tetrahydrofuran
PDGF-R	platelet-derived growth factor receptor	TM	transmembrane
PDT	photodynamic therapy	TNF	tumour necrosis factor
PEG	polyethylene glycol	TNF-R	tumour necrosis factor receptor
PIP <sub>2</sub>	phosphatidylinositol diphosphate	TNT	trinitrotoluene
PI	protease inhibitor	TRAIL	TNF-related apoptosis-inducing ligand
PKA	protein kinase A	VEGF	vascular endothelial growth factor
PKB	protein kinase B	VEGF-R	vascular endothelial growth factor receptor
PKC	protein kinase C	VIP	vasoactive intestinal peptide
PLC	phospholipase C	VOC-Cl	vinylloxycarbonyl chloride
		VRE	vancomycin-resistant enterococci
		VZV	varicella-zoster viruses